EurJOC

European Journal of Organic Chemistry

Chemistry Europe

European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202100804

Link to VoR: https://doi.org/10.1002/ejoc.202100804

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Fluorine-labelled Spiro[3.3]heptane-Derived Building Blocks: Is Single Fluorine the Best?

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Dedicated to 130th anniversary of Organic Chemistry Department, Chemical Faculty, Taras Shevchenko National University of Kyiv

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Abstract: The reliable methodology for constructing 6-fluoro-spiro[3.3]heptane scaffold is developed. A vast library of 2-mono- and 2,2-difunctionallized 6-fluoro-spiro[3.3]heptane-derived building blocks were obtained in a multigram scale (up to 302 g) though the convergent synthetic strategy. This class of compounds was designed for medicinal chemistry as fluorine-labelled conformationally restricted isosteres of cyclohexane framework. The structure was confirmed by X-ray diffraction study and the physicochemical properties (acidity, lipophilicity and water solubility) were characterized. Finally, the generation of virtual compound libraries using the LLAMA software showed that the monofluorinated spiro[3.3]heptane-derived building blocks demonstrated the highest propensity to populate the lead-like chemical space as compared to non- and difluorinated counterparts, as well as cyclohexane derivatives, while retaining similar three-dimensionality features.

Introduction

Site-selective fluorine introduction has emerged as an important tool not only in modern medicinal chemistry intended for endowing the molecules with unique physiological properties (*e.g.* altering the lipophilicity, protecting against oxidative metabolism, functional group mimesis *etc.*)[1–6] but also for the preparation of fluorine-labelled building blocks widely used in spectroscopic structural studies.[7–9] For instance, incorporation of ^{19}F-labelled amino acids into membrane-active peptides allows their deeper study under natural conditions in lipid bilayers by solid-state ^{19}F NMR spectroscopy technique.[10–13]
An efficient ^{19}F label must meet several criteria: (a) to be conformationally constrained to place the ^{19}F reporter in a well-defined position; (b) to be compatible with the synthesis of the target molecule; (c) not to change structure and function of the target molecule.[11] Meanwhile, introducing the fluorine atom proximal to functional group into flexible building blocks can alter the conformational preferences of the target system because of the structural features contributing to a *gauche* effect between these key moieties.[14–17] This issue can be addressed with conformationally rigid sp^3-enriched building blocks bearing fluorine atom (label) at the outward position. At the same time, monofluorinated cycloalkane derivatives do not meet the above requirements because of interconversion between isoenergetic (or close in energy) conformers.[18] Besides, their synthesis requires specific approaches in order to control stereochemistry as well as unique techniques for the separation of the corresponding diastereomers. These obstacles could be circumvented by exploiting the spirocyclic scaffolds[19–22] that have been proven to be 3D-shaped isosteres of cycloalkanes.
In this regard, spiro[3.3]heptane scaffold can be considered as a close isostere and conformationally restricted surrogate of cyclohexane motif (Figure 1, A).[23] This is also true for the heteroatom-substituted systems (Figure 1, B).[24,25] Biological evaluation of drug-like molecules bearing heteroatom-substituted azaspiro[3.3]heptane framework instead of piperidine, piperazine, morpholine, or thiomorpholine units revealed significantly improved pharmacological profile of the modified compounds. Specifically, this allowed retaining biological activity and increasing aqueous solubility, hydrophilicity, and metabolic stability.[24]

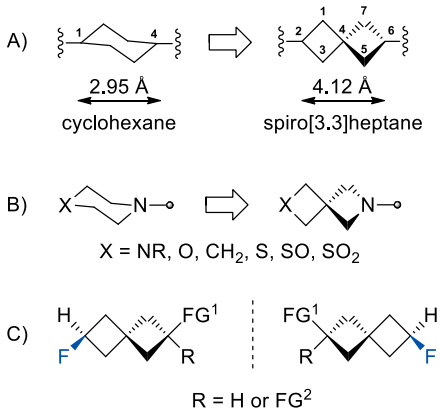
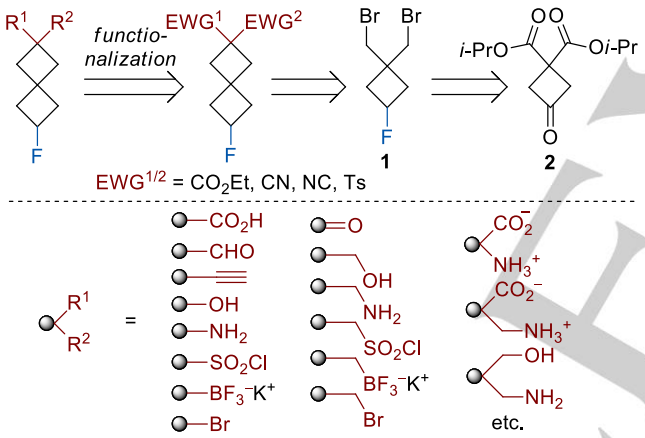


Figure 1. Spirocyclic isosteres of saturated carbo- and heterocyclic six-membered rings

Taking into account all of the above, we propose 6-fluoro-spiro[3.3]heptane scaffold as the conformationally rigid analogue

of 4-fluorocyclohexane ring bearing definitely located fluorine atom (label) at the outward position. An important feature of the spirocyclic framework that also might be beneficial is attributed to its (a)symmetry. While 1-substituted 4-fluorocyclohexanes are often available as difficult-to-separate diastereomeric mixtures,[26] 2-(di)substituted 6-fluorospiro[3.3]heptanes exist as enantiomeric pairs due to their axial chirality (Figure 1, C).

As an extension of our previous works on 5,5- and 6,6-difluorinated spiro[3.3]heptane building blocks,[27,28] herein we report the results of our synthetic, physico-chemical, and chemoinformatic studies on 2-substituted 6-fluorospiro[3.3]heptanes, as well as the synthesis of a series of the corresponding mono- and bifunctional building blocks derived from this scaffold. To the best of our knowledge, this class of compounds have not been presented in the literature. Therefore, we envisaged a convergent synthetic strategy based on utilization of the key intermediate – 1,1-bis(bromomethyl)-3-fluorocyclobutane (**1**). The latter compound can be prepared in four steps from well-documented diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**2**).[29–31] Following the convergent retrosynthetic strategy, several 2,2-difunctionallized 6-fluorospiro[3.3]heptanes can be prepared from **1**, that in turn can be convenient common precursors for a large series of 6-fluorospiro[3.3]heptane-derived building blocks. (Scheme 1).

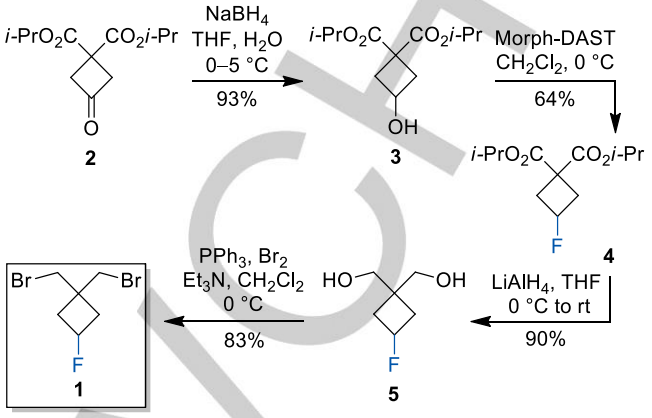


Scheme 1. Retrosynthetic disconnection of 6-fluorospiro[3.3]heptane-derived building blocks

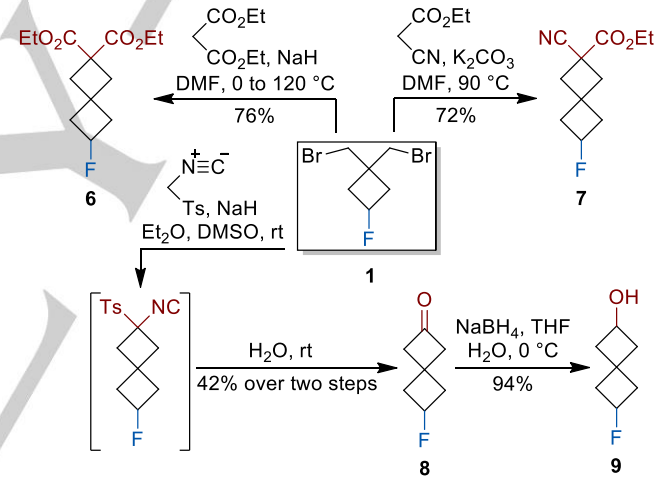
Results and Discussion

Following the above retrosynthetic plan, we subjected diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**2**) to reduction with $NaBH_4$ and further deoxofluorination with Morph-DAST (Scheme 2). Thus obtained 3-fluorocyclobutane dicarboxylate **4** (60% yield over two steps) was converted into the corresponding diol **5** (90% yield) upon the action of $LiAlH_4$. The next deoxobromination under the modified Appel reaction conditions afforded target dibromide **1** in 83% yield. Notably, nearly 500 g of **1** could be obtained from a single run of the described synthetic sequence.

Next, dibromo derivative **1** was used as 1,3-dielectrophile to alkylate several functionalized active methylene compounds, namely, diethyl malonate, ethyl cyanoacetate, and tosylmethyl isocianide (TosMIC). Consequently, corresponding diester **6** (76% yield), cyano ester **7** (72% yield), and ketone **8** (42% yield) were obtained (Scheme 3). In turn, the latter compound was subjected to $NaBH_4$-mediated reduction that afforded alcohol **9** in 94% yield.

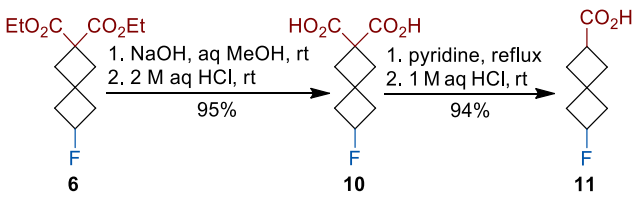


Scheme 2. Synthesis of key intermediate **1**



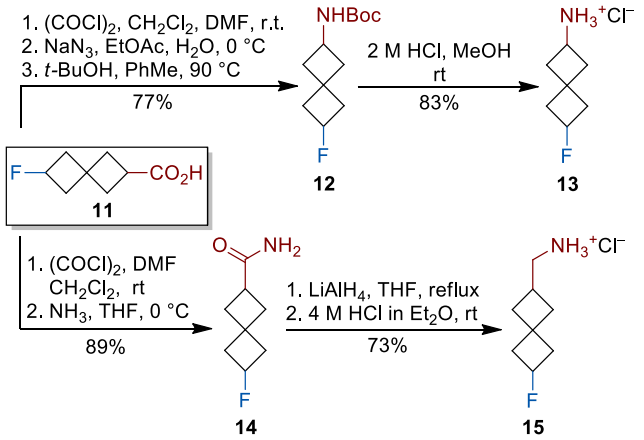
Scheme 3. Synthesis of 6-fluorospiro[3.3]heptane-derived common synthetic precursors

With the set of these compounds in hands, we were able to vastly expand the chemical space of available 2-(di)functionalized 6-fluorospiro[3.3]heptane building blocks. At first, the exhaustive saponification of diester **6** gave corresponding dicarboxylic acid **10** (95% yield), which was transformed into carboxylic acid **11** (94% yield) upon thermal decarboxylation in pyridine (Scheme 4).



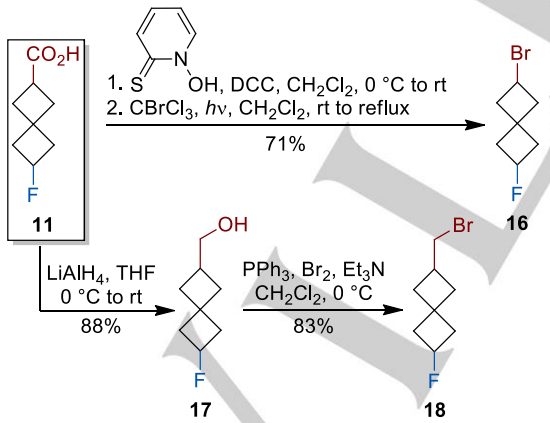
Scheme 4. Synthesis of carboxylic acid **11**

Carboxylic acid **11** was an entry point to nearly all the monofunctionalized building blocks described below. Thus, following a modified Curtius protocol the corresponding *N*-Boc-protected amine **12** was obtained in 77% yield (Scheme 5). Further acid-promoted deprotection afforded amine hydrochloride **13** (83% yield) (Scheme 5). Alternatively, carboxylic acid **11** was converted into amide **14** (89% yield); the following $LiAlH_4$-promoted reduction gave adjacent homologous amine **15** that was also isolated as a hydrochloride in 73% yield.



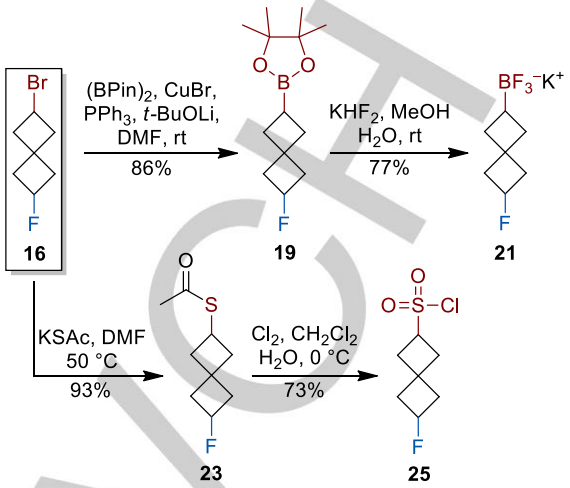
Scheme 5. Synthesis of homologous amine hydrochlorides **13** and **15**

In a similar way, carboxylic acid **11** was transformed into two homologous bromides **16** and **18**. The former one was obtained in 71% yield adopting the Barton decarboxylative bromination method. Meanwhile, the latter one was accessed via a modified Appel deoxobromination of alcohol **17** in 83% yield, obtained from **11** and $LiAlH_4$ in 88% yield (Scheme 6).



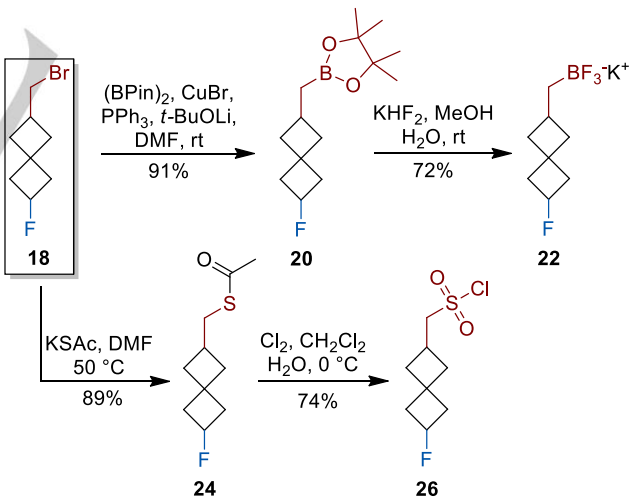
Scheme 6. Synthesis of homologous bromides **16** and **18**

In their turn, bromides **16** and **18** pave the way to another homologous series of supremely versatile organoboron and organosulfur building blocks.[32–38] In particular, pinacolborolane functionality was installed through $Cu(PPh_3)Br$-catalyzed reaction of above bromides with bis(pinacolato)diboron and *t*-BuOLi (Schemes 7 and 8). Thus obtained pinacolates **19** and **20** (86% and 91% yields, respectively) were readily converted into the corresponding trifluoroborates **21** (77% yield) and **22** (72% yield).



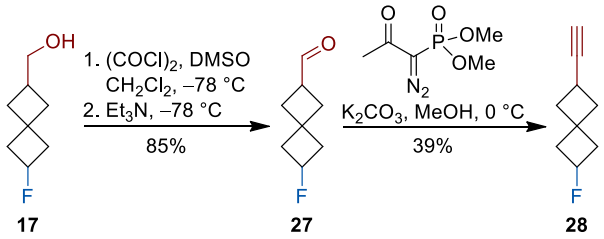
Scheme 7. Synthesis of trifluoroborate **21** and sulfonyl chloride **25**

On the other hand, bromides **16** and **18** were susceptible to nucleophilic substitution with KSAc to form the corresponding thioacetates **23** (93% yield) and **24** (89% yield). The final-stage oxidative chlorination under typical conditions (Cl_2, CH_2Cl_2, water, 0 °C) provided homologous sulfonyl chlorides **25** (73% yield) and **26** (74% yield) in a straightforward manner (Schemes 7 and 8).



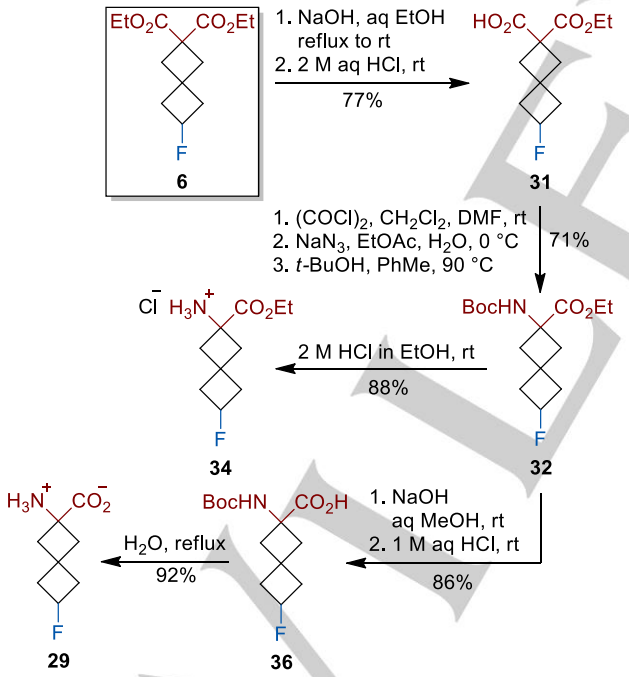
Scheme 8. Synthesis of trifluoroborate **22** and sulfonyl chloride **26**

The synthetic utility of alcohol **17** was also demonstrated by the preparation of aldehyde **27** (85% yield) through the Swern oxidation procedure and subsequent Seyferth–Gilbert homologation with the Ohira–Bestmann reagent[39,40] that gave alkyne **28**, albeit in moderate yield (39%), partially due to the product volatility (Scheme 9).



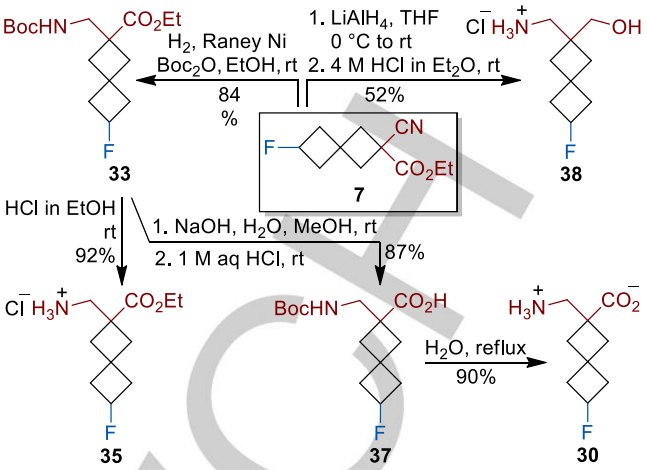
Scheme 9. The synthesis of aldehyde **27** and alkyne **28**

Finally, synthesis of two homologous amino acids **29** and **30**, as well as a small set of their monoprotected derivatives was succeeded. In this way, *N*-Boc-protected amino acid ester **32** (71% yield) resulted from Curtius rearrangement of monoester **31** (obtained from diester **6** in 77% yield, Scheme 10), whereas its closest homologue **33** (84% yield) was provided by Raney Ni-catalyzed hydrogenation of cyano ester **7** in the presence of Boc_2O (Scheme 11). Further, they were both deprotected with ethanolic HCl to give amino ester hydrochlorides **34** (88% yield, Scheme 10) and **35** (92% yield, Scheme 11) as well as saponified into the corresponding *N*-Boc-protected amino acids **36** (86% yield, Scheme 10) and **37** (87% yield, Scheme 11). Ultimately, these Boc-protected amino acids **36** and **37** were processed into target amino acids **29** (92% yield, Scheme 10) and **30** (90% yield, Scheme 11) by simple refluxing in aqueous media.



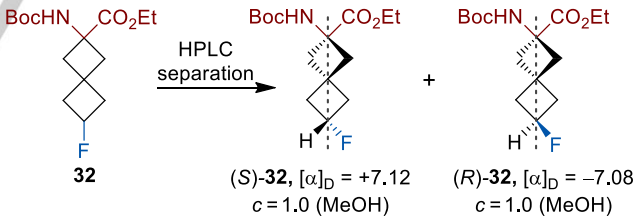
Scheme 10. Synthesis of amino acid **29** and its monoprotected derivatives

Apart from that, cyano ester **7** was a suitable precursor of amino alcohol **38** that was isolated as hydrochloride in 52% yield after $LiAlH_4$-mediated reduction procedure (Scheme 11).



Scheme 11. Synthesis of amino acid **30**, its monoprotected derivatives, and amino alcohol **38**

To further demonstrate the feasibility of creating advanced fluorine-labelled spiro[3.3]heptane-derived building blocks for the needs of bioorganic and medicinal chemistry, we have put some efforts to the preparation of enantiomerically pure derivatives. To our delight, chiral-stationary-phase HPLC separation of racemic *N*-Boc-protected amino ester **32** afforded the corresponding single enantiomers (Scheme 12). To establish their absolute configuration, one of these products was treated with 2 M HCl in 1,4-dioxane and then subjected to slow crystallization from EtOAc. According to the results of X-Ray diffraction study, (*R*) configuration could be assigned to corresponding derivative **34**·H_2O (Figure 2). These derivatives are rare examples of enantiopure compounds where the axial chirality is defined merely by the H/F difference.[41]



Scheme 12. Separation of enantimeric *N*-Boc-amino esters **32** (chiral axis is shown by blue dotted line)

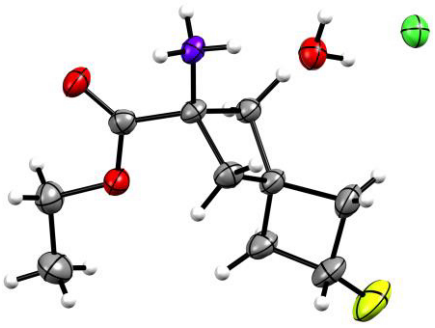


Figure 2. Molecular structure of (*R*)-**34**·H_2O according to X-ray diffraction study

Physicochemical properties. With an eye of more integrated study of the discussed building blocks, we evaluated the impact of the fluorinated carbon chain at the C-6 position of the 2-functionalized spiro[3.3]heptane scaffold on their physico-chemical properties, particularly, acidity/basicity, lipophilicity, and aqueous solubility. We have limited this part of the work with the study of carboxylic acids **11**, **39**, **40** and amine hydrochlorides **13**, **41**, **42** (Figure 3).

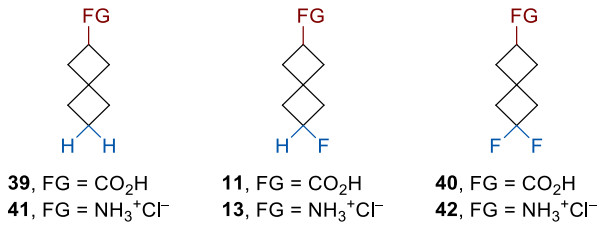


Figure 3. Model building blocks used to study the physico-chemical properties

It was found that within the studied series, the pK_a values varied in an expected manner. Thus, subsequent introducing the fluorine atoms increased acidity by 0.20 (**11**) and 0.04 (**40**) pK_a units for the carboxylic acids, and by 0.40 (**13**) and 0.23 (**42**) for the amine hydrochlorides as compared to their non-fluorinated counterparts (Figure 4). Notably, the observed correlation did not follow a general rule of thumb established previously for acyclic fluorinated amines (ΔpK_a ~ –0.1 per each ε-F).[42] Specifically, each fluorine atom introduced into the spiro[3.3]heptane scaffold exerted a stronger basicity-lowering effect, as much as it was expected. This correlates with the results obtained for the δ-fluorinates acyclic aliphatic amines (ΔpK_a ~ –0.3) and can be explained by more efficient inductive transmission of electronic polarization from the fluorine atoms to the amino group through the rigid spirocyclic scaffold.

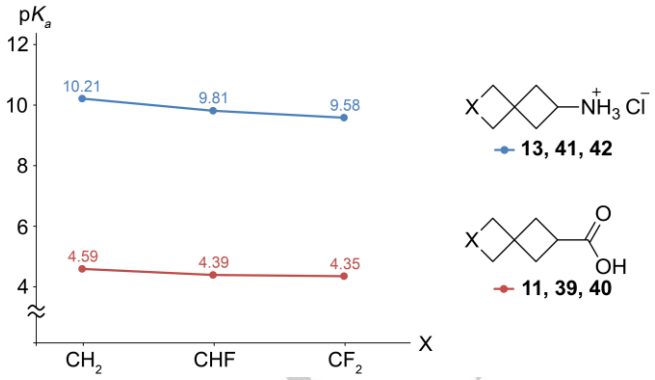
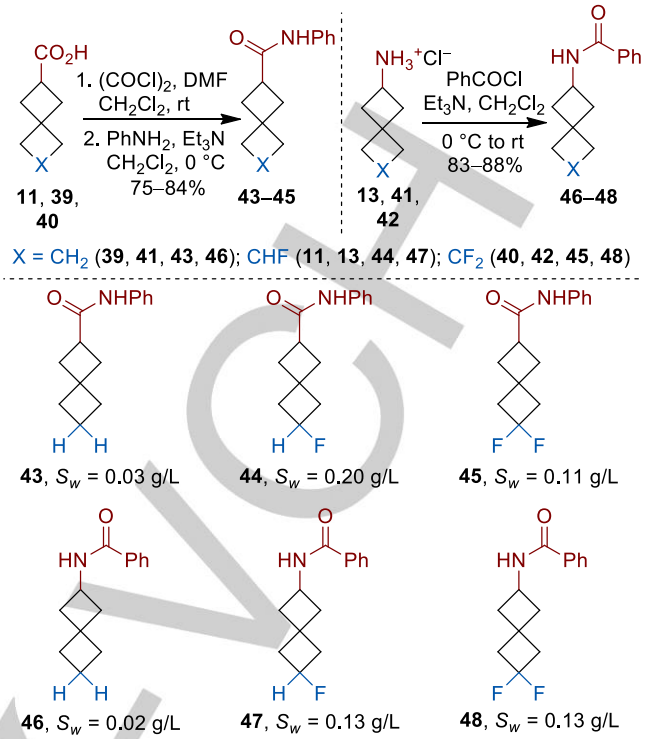


Figure 4. Measured pK_a values (23 °C) for carboxylic acids **11**, **39**, **40** and amine hydrochlorides **13**, **41**, **42**

To evaluate the effect of the fluorinated methylene unit on the aqueous solubility and lipophilicity of 2-functionallized spiro[3.3]heptane derivatives, carboxylic acids **11**, **39**, **40** were converted into anilides **43**–**45**, while amines **13**, **41**, **42** were transformed into the corresponding benzamides **46**–**48** (Scheme 13).



Scheme 13. Synthesis and aqueous solubility (S_w, 23 °C) of model derivatives **43**–**48**

Interestingly, within the series of anilides **43**–**45** and benzamides **46**–**48** the measured Log*P* values varied in a non-monotonic manner. Thus, monofluorinated anilide **44** and its isomer **47** were characterized by the smallest log*P* values (2.69 and 2.39, respectively), while their nonfluorinated counterparts **43** and **46** had almost identical values of logP (3.27 and 3.26, respectively). The measured lipophilicity of *gem*-difluorinated representatives **45** and **48** showed the intermediate log*P* values (2.93 and 2.53, respectively) within the studied series (Figure 5). In general, these results correlate with the trends reported in the literature for the acyclic counterparts.[42]

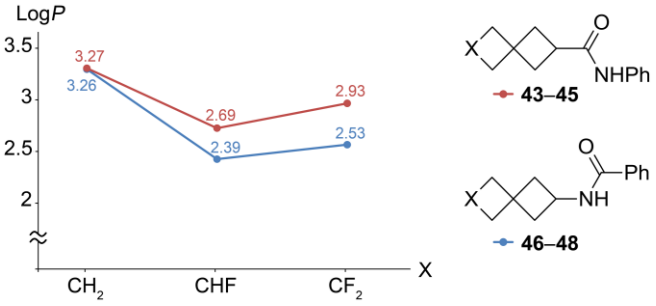


Figure 5. Measured Log*P* values (23 °C) for benzamides **43–45** and anilides **46–48**

Finally, aqueous solubility (S_w) within both the anilide and benzamide series correlated with their hydrophilicity: introducing the fluorine atoms increased the solubility in all cases (Scheme 13).

Exit vector plot (EVP) analysis[43–45] of mono- and difluorinated spiro[3.3]-heptane scaffolds (simulated from X-Ray data obtained for (*R*)-**34**) showed that exit vectors representing the polar functional groups attached to the bicyclic ring system are further from the "colinear" orientation for the case of monofluorinated derivative (Figure 6). This is apparent from the values of φ_2 angle which is larger for this derivative. Such orientation might be one of the factors responsible for somewhat higher polarity of the monofluorinated spiro[3.3]heptanes.

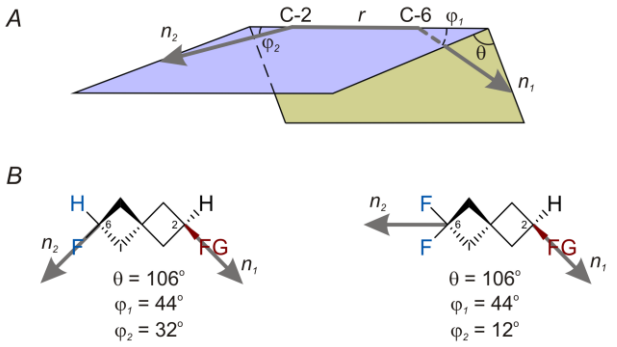


Figure 6. (A) Definition of exit vector plot (EVP) parameters *r*, θ, φ_1, and φ_2 (*B*) Exit vector analysis of mono- and gem-difluorinated spiro[3.3]heptanes

Virtual library generation. To further explore the potential of the synthesized compounds for medicinal chemistry, we have evaluated the building blocks shown in Figure 3 and compared them to the parent cyclohexane derivatives (*i.e.* cyclohexane-carboxylic acid and cyclohexanamine) using a LLAMA tool developed by Nelson and co-workers.[46] The key feature of their method is the so-called lead-likeness penalty (LLP) that assesses the compound compliance with the lead-likeness criteria according to its physico-chemical properties (*i.e.* heavy (non-hydrogen) atom count, ALog*P*, number of aromatic rings, and an undesirable functional group filter).[47,48] The LLP values start with zero (for the 'perfect' lead-like compounds) and increase as more and more features of the lead-likeness definition by Churcher and co-workers[49] are violated.

It was found that the library generated from 6-fluorospiro[3.3]-heptane-derived building blocks had the lowest mean lead-likeness penalty (LLP) among all the compound series studied (Table 1). 92% and 53% of this library members fit the lead-like chemical space as defined by "rule-of-four" (MW < 400, Log*P* < 4)[50] and rigorous Churcher's rules (MW = 200…350, Log*P* = –1…3),[49] respectively (Figure 7, *A*). The three-dimensionality of all the four libraries was similar, as illustrated by the average F*sp*^{3} and plane of best fit (PBF) values (Table 1), as well as principal moment of inertia (PMI) plot describing the overall molecular shape (Figure 76, *B*).

Table 1. LLAMA analysis of fluorinated spiro[3.3]heptane scaffolds and their non-fluorinated analogues

Building blocks[a]	Library size	Lead-likeness penalty (LLP)[b]	F*sp*^{3}[b,c]	Plane of best fit (PBF), Å[b,c]
FG	285	1.58	0.622	0.99
F, FG	285	1.48	0.622	1.00
F, F, FG	182	1.77	0.654	1.01
FG	285	1.70	0.599	1.04

[a] FG = CO_2H or NH_2 [b] Mean values over the corresponding libraries are given [c] Fraction of sp^3-hybrid carbon atoms [d] Plane of best fit, the mean atomic distance from a theoretical plane that passes through the molecule, configured in such a way as to minimize the value

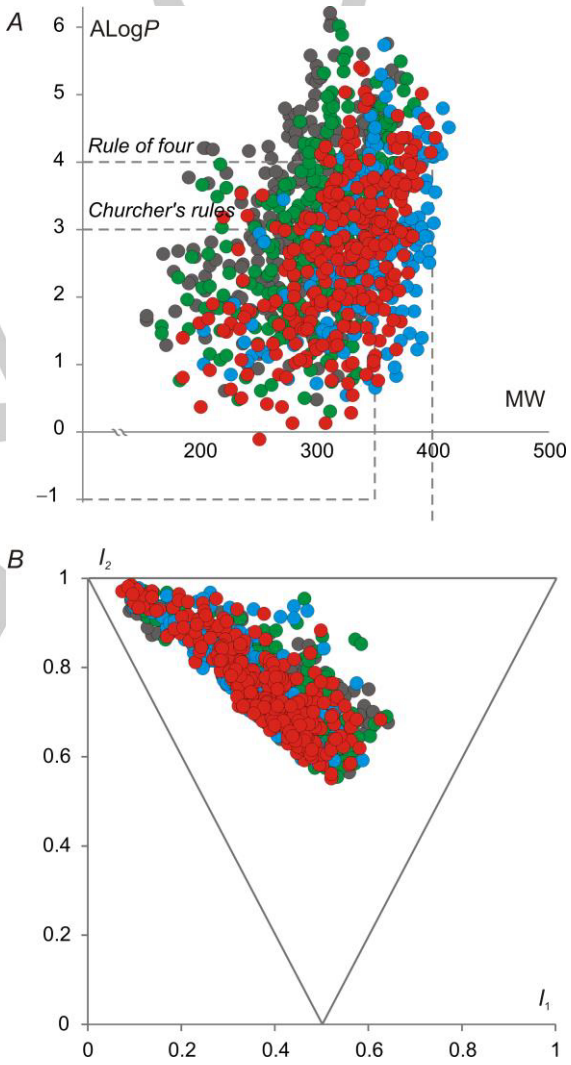


Figure 7. LLAMA-based virtual libraries generated from fluorinated spiro[3.3]heptane scaffolds and their non-fluorinated analogues: (*A*) MW – ALog*P* plot; (*B*) principal moment of inertia (PMI) plot. Data point colors refer to derivatives of: green – parent spiro[3.3]heptane; red – 6-fluorospiro[3.3]heptane; blue – 6,6-difluorospiro[3.3]heptane; grey – cyclohexane

Conclusion

A convenient methodology to construct 6-fluoro-spiro[3.3]heptane scaffold was developed. Following the convergent synthetic strategy starting from the single key precursor – 1,1-bis(bromo-

methyl)-3-fluorocyclobutane (**1**) – a considerable variety of 2-mono- and 2,2-difunctionalized 6-fluorospiro[3.3]heptane-derived building blocks was prepared in fewest possible steps at multigram scale (33 representatives, up to 302 g). The described procedures are readily scaled up and can be modified for introducing other functional groups. Moreover, a possibility to obtain the title compounds as pure enantiomers with rarely occurring subtype of axial chirality (caused merely by the H/F difference) was demonstrated.

The pK_a values within the studied series of spiro[3.3]heptane-derived carboxylic acids **11**, **39**, **40** and amines **13**, **41**, **42** varied in an expected manner (*i.e.* decreased upon increasing the degree of fluorination); however, the fluorine atom(s) had much stronger impact on the acidity/basicity as compared to the acyclic ε-fluorinated analogs. At the same time, the lipophilicity followed a non-monotonic pattern: $CH_2 \geq CF_2 > CHF$, which is consistent with the literature data for the acyclic counterparts. Also, the fluorination increased aqueous solubility of the corresponding spiro[3.3]heptane derivatives. These effects likely arise from the relative spatial position of the functional group and the fluorine atom(s), as well as concerted electronic polarization within the rigid spiro[3.3]heptane scaffold.

Virtual library construction using the LLAMA tool showed that the monofluorinated spiro[3.3]heptane-derived building blocks demonstrated the highest propensity to populate the lead-like chemical space as compared to non-[27,51,52] and difluorinated[28] counterparts, as well as simple cyclohexane derivatives, while retaining similar three-dimensionality features. Considering all the above, the title compounds are indeed promising advanced chemotypes for early drug discovery and ^{19}F-labelling studies, and they should find their application in these or related areas in the nearest future.

Experimental Section

The solvents were purified according to the standard procedures.[53] 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}, and ^{19}F{^{1}H} NMR spectra were recorded on an 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, and 470 MHz for ^{19}F), 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)). HRMS analyses were conducted on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Lipophilicity was measured as the logarithm of the distribution coefficient between *n*-octanol and water using shake-flask method; analytical HPLC was used to establish the concentrations in both phases after the partitioning. CCDC deposition number for the structure of (*R*)-**34**·H_2O is 2093380. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Diisopropyl 3-hydroxycyclobutane-1,1-dicarboxylate (3): Diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**2**) (1.0 kg, 4.13 mol) was dissolved in THF (5.0 L) followed by addition of water (500 mL) and the resulting mixture was cooled to 0 °C. Then $NaBH_4$ (94.2 g, 2.48 mol) was added portionwise, maintaining the internal temperature below 5 °C. Thus obtained mixture was allowed to react with stirring at above temperature for 1 h. After, saturated aq. NH_4Cl (4 L) was added, the obtained mixture was extracted with EtOAc (3 L). The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure to give the title compound **3** as colorless liquid. The product was pure enough to be used without further purification. Yield 941 g, 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.07 (sept, *J* = 6.2 Hz, 2H), 4.38 (p, *J* = 7.0 Hz, 1H), 2.91–2.81 (m, 2H), 2.49–2.38 (m, 2H), 1.99 (br. s, 1H), 1.25 (d, *J* = 6.2 Hz, 12H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 170.6, 68.6, 61.9, 45.6, 39.6, 21.0 ppm; MS (EI): *m/z* = 185 [M – C_3H_7O]$^+$; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{12}H_{20}O_5Na$: 267.1208, found: 267.1201.

Diisopropyl 3-fluorocyclobutane-1,1-dicarboxylate (4): Morph-DAST (842 g, 4.81 mol) was added dropwise to the stirred ice-cold solution of diisopropyl 3-hydroxycyclobutane-1,1-dicarboxylate (**3**) (941 g, 3.85 mol) in CH_2Cl_2 (5 L) maintaining the internal temperature below 5 °C. Then it was allowed to equilibrate to rt and left to react with stirring for 40 h. After, the reaction mixture was slowly poured into stirred saturated aq. K_2CO_3 (5 L) (*Caution:* Gas evolution!). The organic layer was separated, dried (Na_2SO_4), evaporated at reduced pressure, and distilled *in vacuo* to give the title compound **4** as colorless liquid. Yield 604 g, 64%; b.p. 60–65 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21–4.98 (m, 3H), 2.94–2.83 (m, 2H), 2.80–2.65 (m, 2H), 1.26 (d, *J* = 2.8 Hz, 6H), 1.25 (d, *J* = 2.8 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 170.3 (d, *J* = 133.4 Hz), 82.3 (d, *J* = 210.5 Hz), 69.3 (d, *J* = 33.1 Hz), 45.2 (d, *J* = 15.2 Hz), 38.1 (d, *J* = 23.6 Hz), 21.5 (d, *J* = 2.9 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –166.9 ppm; MS (EI): *m/z* = 187 [M – C_3H_7O]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{12}H_{20}FO_4$: 247.1345, found: 247.1334.

(3-Fluorocyclobutane-1,1-diyl)dimethanol (5): Diisopropyl 3-fluorocyclobutane-1,1-dicarboxylate (**4**) (604 g, 2.45 mol) was added dropwise to the stirred ice-cold suspension of $LiAlH_4$ (112 g, 2.95 mol) in THF (4.5 L). Then it was allowed to equilibrate to rt and left to react with stirring for 16 h. After, the reaction mixture was quenched upon cooling by sequential dropwise addition of water (112 mL), 50% aq. NaOH (112 g, 61 mL), and water (336 mL) again. Thus obtained mixture was allowed to stir for 15 min, the precipitate formed was filtered off, washed with THF (500 mL), and the filtrate was evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (2 L), dried (Na_2SO_4), and evaporated at reduced pressure to give the title compound **5** as yellowish crystals. Yield 296 g, 90%; m.p. 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (dquint, *J* = 55.3, 6.3 Hz, 1H), 3.78 (s, 2H), 3.69 (s, 2H), 2.39–2.30 (m, 2H), 2.30 (br. s, 2H), 2.15–1.97 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 84.2 (d, *J* = 207.9 Hz), 68.8 (d, *J* = 234.5 Hz), 36.0 (d, *J* = 11.7 Hz), 34.7 (d, *J* = 21.0 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –167.8 ppm; MS (EI): *m/z* = 85 [M – CH_2O – H_2O]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_6H_{12}FO_2$: 135.0821, found: 135.0816.

1,1-Bis(bromomethyl)-3-fluorocyclobutane (1): Br_2 (791 g, 255 mL, 4.94 mol) was added dropwise to the stirred ice-cold solution of Ph_3P (1.3 kg, 4.95 mol) in CH_2Cl_2 (4 L) maintaining the internal temperature below 10 °C. Thus obtained suspension was left to stir at 0 °C for 45 min followed by addition of Et_3N (502 g, 691 mL, 4.96 mol) and further stirring at above temperature for 15 min. Next, the solution of (3-fluorocyclobutane-1,1-diyl)dimethanol (**5**) (296.2 g, 2.21 mol) in CH_2Cl_2 (250 mL) was added dropwise at 0 °C. Then it was allowed to warm to rt and left to react with stirring for 16 h. After, the reaction mixture was slowly diluted with water (4 L), the organic layer was separated, washed with saturated aq. Na_2CO_3 (2.5 L), dried (Na_2SO_4), and evaporated at reduced pressure. The remainder was triturated with hexane (5 L) and filtered, while precipitate was washed with hexane (2 × 500 mL). The combined filtrate was evaporated at reduced pressure and the residue was distilled *in vacuo* to give the title compound **1** as colorless liquid. Yield 479 g, 83%; b.p. 56–57 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16–4.94 (m, 1H), 3.71 (s, 2H), 3.60 (s, 2H), 2.56–2.42 (m, 2H), 2.32–2.17 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 82.0 (d, *J* = 206.9 Hz), 40.4 (d, *J* = 144.9 Hz), 38.2 (d, *J* = 22.1 Hz), 37.1 (d, *J* = 11.2 Hz)

ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –171.4 ppm; MS (EI): *m/z* = 214 $[M - C_2H_3F]^+$; elemental analysis calcd. (%) for $C_6H_9Br_2F$: C 27.72, H 3.49; found: C 27.99, H 3.85.

Diethyl 6-fluorospiro[3.3]heptane-2,2-dicarboxylate (6): Diethyl malonate (517 g, 3.23 mol) was added dropwise to the stirred ice-cold suspension of NaH (60% dispersion in mineral oil, 128 г, 3.2 mol) in DMF (2 L) and the obtained mixture was left to stir for 1 h. Then it was gradually heated to 60 °C followed by addition of 1,1-bis(bromomethyl)-3-fluorocyclobutane (**1**) (400 g, 1.54 mol). After, the reaction mixture was slowly heated to 120 °C and stirred at this temperature for 16 h. Then it was allowed to warm to rt, diluted with water (3 L), and extracted with *t*-BuOMe (3 L). The organic layer was washed with water (2 × 2 L), dried (Na_2SO_4), evaporated at reduced pressure, and the residue was distilled *in vacuo* to give the title compound **6** as colorless liquid. Yield 302 g, 76%; b.p. 81–82 °C (1 mBar); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.90 (dquint, *J* = 55.7, 6.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 4H), 2.63 (s, 2H), 2.59 (s, 2H), 2.55–2.42 (m, 2H), 2.34–2.15 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 171.5, 83.3 (d, *J* = 211.7 Hz), 61.5, 49.1, 43.6 (d, *J* = 20.0 Hz), 40.7 (d, *J* = 30.7 Hz), 29.4 (d, *J* = 16.8 Hz), 14.0 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.9 ppm; MS (EI): *m/z* = 258 $[M]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}FO_4$: 259.1346, found: 259.1336.

Ethyl 2-cyano-6-fluorospiro[3.3]heptane-2-carboxylate (7): 1,1-Bis(bromomethyl)-3-fluorocyclobutane (**1**) (150 g, 577 mmol) and ethyl cyanoacetate (67.9 g, 600 mmol) were dissolved in DMF (700 mL) followed by addition of K_2CO_3 (200 g, 1.45 mol). The resulting mixture was gradually heated to 90 °C and stirred at this temperature for 16 h. Then it was allowed to warm to rt, diluted with water (1 L), and extracted with EtOAc (1.2 L). The organic layer was washed with water (2 × 600 mL), dried (Na_2SO_4), evaporated at reduced pressure, and the residue was distilled *in vacuo* to give the title compound **7** as colorless liquid. Yield 87.3 g, 72%; b.p. 69–70 °C (1 mBar); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.94 (dquint, *J* = 55.4, 6.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.87–2.61 (m, 5H), 2.61–2.49 (m, 1H), 2.49–2.22 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 168.4, 120.0, 83.1 (d, *J* = 211.4 Hz), 63.0, 43.7 (d, *J* = 20.8 Hz), 43.2 (d, *J* = 20.8 Hz), 42.9, 35.9, 31.0 (d, *J* = 16.3 Hz), 13.9 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –170.4 ppm; MS (EI): *m/z* = 165 $[M - C_2H_3F]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{15}FNO_2$: 212.1087, found: 212.1078.

6-Fluorospiro[3.3]heptan-2-one (8): NaH (60% dispersion in mineral oil, 86 g, 2.15 mol) was added to the solution of 1,1-bis(bromomethyl)-3-fluorocyclobutane (**1**) (160 g, 615 mmol) in a mixture of DMSO (960 mL) and Et_2O (600 mL) followed by dropwise addition of the solution of TosMIC (324 g, 1.66 mol) in a mixture of DMSO (640 mL) and Et_2O (200 mL) maintaining the temperature below 20 °C. Thus obtained mixture was left to react with stirring for 2 h; then it was diluted with water (2 L) and extracted with EtOAc (2 L). The organic layer was washed with water (2 × 1.5 L), dried (Na_2SO_4), and evaporated at reduced pressure. Obtained brown viscous residue was distilled *in vacuo* to give the title compound **8** as colorless liquid. Yield 33.0 g, 42%; b.p. 30–31 °C (1 mBar); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.06 (dquint, *J* = 55.5, 6.7 Hz, 1H), 3.18 (d, *J* = 3.8 Hz, 2H), 3.10 (d, *J* = 3.8 Hz, 2H), 2.70–2.42 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 206.1, 83.0 (d, *J* = 212.5 Hz), 58.7 (d, *J* = 32.5 Hz), 42.5 (d, *J* = 20.6 Hz), 24.3 (d, *J* = 17.7 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.8 ppm; MS (EI): *m/z* = 100 $[M - CO]^+$ (100), 128 $[M]^+$ (5); elemental analysis calcd. (%) for C_7H_9FO: C 65.61, H 7.08; found: C 65.33, H 7.37.

6-Fluorospiro[3.3]heptan-2-ol (9): 6-Fluorospiro[3.3]heptan-2-one (**8**) (16 g, 125 mmol) was dissolved in THF (100 mL) followed by addition of water (10 mL) and the resulting mixture was cooled to 0 °C. Then $NaBH_4$ (2.85 g, 75 mmol) was added portionwise and the resulting mixture was stirred at above temperature for 1 h. After, saturated aq. NH_4Cl (150 mL) was added, the obtained mixture was extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **9** as colorless liquid. Yield 15.2 g, 94%; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.92 (dquint, *J* = 55.7, 6.8 Hz, 1H), 4.23 (quint, *J* = 7.4 Hz, 1H), 2.47–2.31 (m, 4H), 2.31–2.13 (m, 2H), 2.02 (dd, *J* = 12.0, 7.4 Hz, 1H), 1.94 (dd, *J* = 12.0, 7.4 Hz, 1H), 1.76 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 83.5 (d, *J* = 212.3 Hz), 62.9, 44.8 (d, *J* = 30.5 Hz), 42.7 (d, *J* = 19.6 Hz), 42.4 (d, *J* = 19.6 Hz), 25.1 (d, *J* = 17.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –168.6 ppm; MS (EI): *m/z* = 84 $[M - C_2H_3F]^+$; elemental analysis calcd. (%) for $C_7H_{11}FO$: C 64.59, H 8.52; found: C 64.45, H 8.33.

6-Fluorospiro[3.3]heptane-2,2-dicarboxylic acid (10): Diethyl 6-fluorospiro[3.3]heptane-2,2-dicarboxylate (**6**) (300 g, 1.16 mol) was added to the solution of NaOH (186 g, 4.65 mol) in water (2 L) and MeOH (500 mL) and the resulting solution was stirred at rt for 16 h. Then MeOH was evaporated at reduced pressure, the remaining aqueous solution was acidified with 2 M aq. HCl to pH = 2, and extracted with EtOAc (2 × 800 mL). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was triturated with hexane (500 mL), filtered and washed with hexane (25 mL) to give the title compound **10** as colorless crystals. Yield 224 g, 95%; m.p. 190–192 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.69 (s, 2H), 4.91 (dquint, *J* = 55.9, 6.5 Hz, 1H), 2.46 (s, 2H), 2.44 (s, 2H), 2.44–2.35 (m, 2H), 2.19–2.04 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ = 173.1, 83.6 (d, *J* = 209.8 Hz), 49.0, 43.6 (d, *J* = 19.5 Hz), 40.7 (d, *J* = 19.5 Hz), 29.1 (d, *J* = 17.0 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = – 167.8 ppm; MS (EI): *m/z* = 112 $[M - 2CO_2H]^+$; HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_9H_{10}FO_4$: 201.0563, found: 201.0568.

6-Fluorospiro[3.3]heptane-2-carboxylic acid (11): 6-Fluorospiro[3.3]heptane-2,2-dicarboxylic acid (**10**) (220 g, 1.09 mol) was dissolved in pyridine (2 L) and the resulting solution was refluxed with stirring for 16 h. Then it was evaporated at reduced pressure, diluted with water (1 L), acidified with 1M aq. HCl to pH 2, and extracted with EtOAc (2 × 1 L). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **11** as yellowish crystals. Yield 162 g, 94%; m.p. 65–67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 11.36 (br. s, 1H), 4.92 (dquint, *J* = 55.6, 6.7 Hz, 1H), 3.10 (p, *J* = 8.5 Hz, 1H), 2.53 (dq, *J* = 12.8, 6.7 Hz, 1H), 2.47–2.38 (m, 2H), 2.37–2.10 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 181.5, 83.5 (d, *J* = 212.1 Hz), 43.4 (d, *J* = 19.8 Hz), 43.1 (d, *J* = 19.8 Hz), 37.1 (d, *J* = 29.3 Hz), 33.5, 31.1 (d, *J* = 16.8 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.8 ppm; MS (EI): *m/z* = 112 $[M - CO - H_2O]^+$; HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_8H_{10}FO_2$: 157.0665, found: 157.0667.

***tert*-Butyl (6-fluorospiro[3.3]heptan-2-yl)carbamate (12):** 6-Fluorospiro[3.3]heptane-2-carboxylic acid (**11**) (45 g, 285 mmol) was dissolved in a mixture of CH_2Cl_2 (400 mL) and DMF (1 mL) followed by dropwise addition of $(COCl)_2$ (45.2 g, 30.5 mL, 356 mmol). The resulting solution was stirred at rt for 2 h and evaporated at reduced pressure. Thus obtained crude acid chloride was dissolved in EtOAc (200 mL) and cooled to 0 °C followed by dropwise addition of a solution of NaN_3 (55.5 g, 854 mmol) in water (350 mL) maintaining the above temperature. The reaction mixture was stirred at 0 °C for an additional 1 h and extracted with EtOAc (2 × 200 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to a half of initial volume at reduced pressure and external temperature below 30 °C. This solution was added dropwise to hot (90 °C) mixture of *t*-BuOH (220 mL) and PhMe (400 mL) and thus obtained reaction mixture was stirred at above temperature for an additional 40 h. Then it was evaporated at reduced pressure to give the title compound **12** as colorless powder. Yield 50.3 g, 77%; m.p. 102–105 °C; mixtures of Boc-rotamers were observed by NMR spectroscopy; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.87 (dquint, *J* = 55.7, 6.6 Hz, 1H), 2.51–2.40 (m, 1H), 4.60 (br. s, 1H), 2.40–2.23 (m, 3H), 2.23–2.07 (m, 2H), 1.89 (t, *J* = 10.1 Hz, 1H), 1.81 (t, *J* = 10.1 Hz, 1H), 1.40 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 154.9, 83.8 (d, *J* = 212.5 Hz), 79.4, 43.1 (d, *J* = 3.6 Hz), 43.0 (d, *J* = 20.0 Hz), 42.6 (d, *J* = 20.0 Hz), 41.8, 28.4, 27.8 (d, *J* = 17.5 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –

169.0 ppm; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{12}H_{20}FNNaO_2$: 252.1375, found: 252.1369.

6-Fluorospiro[3.3]heptan-2-amine hydrochloride (13): *tert*-Butyl (6-fluorospiro[3.3]heptan-2-yl)carbamate (**12**) (40 g, 174 mmol) was added portionwise to the stirred 2M HCl in MeOH (400 mL) and thus obtained mixture was additionally stirred for 2 h. Then it was evaporated at reduced pressure, triturated with EtOAc (200 mL), and filtered to give the title compound **13** as colorless powder. Yield 23.8 g, 83%; m.p. 232–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (s, 3H), 4.93 (dquint, *J* = 55.8, 6.7 Hz, 1H), 2.49–2.43 (m, 1H), 2.38–2.30 (m, 1H), 2.29–2.20 (m, 4H), 2.20–2.13 (m, 2H), 2.12–2.06 (m, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 83.4 (d, *J* = 210.2 Hz), 42.4 (d, *J* = 19.7 Hz), 42.2 (d, *J* = 19.7 Hz), 40.6, 38.7 (d, *J* = 8.0 Hz), 28.1 (d, *J* = 17.6 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –167.4 ppm; MS (APCI): *m/z* = 130 [M + H]$^+$; HRMS (ESI) *m/z* [M + H] calcd for $C_7H_{13}FN$: 130.1032, found: 130.1025.

6-Fluorospiro[3.3]heptane-2-carboxamide (14): 6-Fluorospiro[3.3]heptane-2-carboxylic acid (**11**) (25 g, 158 mmol) was dissolved in a mixture of CH_2Cl_2 (250 mL) and DMF (0.5 mL) followed by dropwise addition of $(COCl)_2$ (24.1 g, 16.3 mL, 190 mmol). The resulting solution was stirred at rt for 2 h and evaporated at reduced pressure. Thus obtained crude acid chloride was dissolved in THF (250 mL) and cooled to 0 °C followed by bubbling gaseous NH_3 through the reaction mixture for 30 min maintaining the above temperature. Then it was left to stir for 2 h and allowed to equilibrate to rt. The precipitate formed was filtered off, washed with THF (50 mL) and the filtrate was evaporated at reduced pressure to give the title compound **14** as beige powder. Yield 22.1 g, 89%; m.p. 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (br. s, 1H), 5.35 (br. s, 1H), 4.92 (dquint, *J* = 55.6, 6.7 Hz, 1H), 2.97 (p, *J* = 8.5 Hz, 1H), 2.61–2.47 (m, 1H), 2.46–2.29 (m, 3H), 2.32–2.11 (m, 4H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 177.0, 83.6 (d, *J* = 212.0 Hz), 43.5 (d, *J* = 19.7 Hz), 42.9 (d, *J* = 19.7 Hz), 37.3 (d, *J* = 9.2 Hz), 34.6, 30.7 (d, *J* = 16.9 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.7 ppm; MS (EI): *m/z* = 111 [M – C_2H_3F]$^+$ (100), 157 [M]$^+$ (9); HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_8H_{13}FNO$: 158.0981, found: 158.0969.

(6-Fluorospiro[3.3]heptan-2-yl)methanamine hydrochloride (15): A solution of 6-fluorospiro[3.3]heptane-2-carboxamide (**14**) (22.1 g, 141 mmol) in THF (100 mL) was added dropwise to a stirred boiling suspension of $LiAlH_4$ (10.6 g, 280 mmol) in THF (400 mL) and the resulting mixture was refluxed with stirring for 2 h. Then it was allowed to warm to rt and stirred for an additional 16 h. After, the reaction mixture was quenched upon cooling by sequential dropwise addition of water (10 mL), 50% aq. NaOH (10 g), and water (30 mL) again. Thus obtained mixture was allowed to stir for 15 min, the precipitate formed was filtered off, washed with THF (2 × 50 mL), and the filtrate was evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. Thus obtained residue was dissolved in Et_2O (150 mL) followed by addition of 4 M HCl in Et_2O (20 mL). The precipitate formed was filtered and washed with a minimal amount of Et_2O to give the title compound **15** as beige powder. Yield 18.6 g, 73%; m.p. 190–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.93 (br. s, 3H), 4.92 (dquint, *J* = 55.8, 6.8 Hz, 1H), 2.77 (p, *J* = 6.0 Hz, 2H), 2.49–2.36 (m, 2H), 2.36–2.27 (m, 1H), 2.19–1.99 (m, 4H), 1.89–1.75 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 83.5 (d, *J* = 210.6 Hz), 43.6, 43.2 (d, *J* = 19.2 Hz), 42.9 (d, *J* = 19.1 Hz), 37.4 (d, *J* = 6.8 Hz), 30.1 (d, *J* = 16.4 Hz), 28.0 ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –167.3 ppm; MS (APCI): *m/z* = 144 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_8H_{15}FN$: 144.1189, found: 144.1184.

2-Bromo-6-fluorospiro[3.3]heptane (16): 1-Hydroxypyridine-2(1*H*)-thione (61.9 g, 487 mmol) was added to the stirred solution of 6-fluorospiro[3.3]heptane-2-carboxylic acid (**11**) (70 r, 443 mmol) in CH_2Cl_2 (700 mL) and the resulting solution was cooled to 0 °C. Next, DCC (100 g, 487 mmol) was added dropwise and obtained reaction mixture was allowed to stir in the dark at rt for 16 h. The formed precipitate was filtered off and washed with CH_2Cl_2 (150 mL). The combined filtrate was evaporated at reduced pressure to the half of initial volume (ca. 400 mL). After, $CBrCl_3$ (264 g, 1.33 mol) was added and the obtained mixture was irradiated with daylight lamp upon stirring and reflux for 2 h. Finally, it was evaporated at reduced pressure and the residue was distilled *in vacuo* to give the title compound **16** as colorless liquid. Yield 60.9 g, 71%; b.p. 30–32 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.92 (dquint, *J* = 55.5, 6.8 Hz, 1H), 4.38 (p, *J* = 7.8 Hz, 1H), 2.78–2.62 (m, 2H), 2.62–2.42 (m, 4H), 2.41–2.14 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 83.2 (d, *J* = 212.4 Hz), 46.7 (d, *J* = 6.0 Hz), 42.9 (d, *J* = 20.1 Hz), 42.3 (d, *J* = 20.1 Hz), 37.1, 31.5 (d, *J* = 16.6 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.4 ppm; MS (EI): *m/z* = 145/147 [M – C_2H_3F]$^+$; elemental analysis calcd. (%) for $C_7H_{10}BrF$: C 43.55, H 5.22; found: C 43.66, H 5.37.

(6-Fluorospiro[3.3]heptan-2-yl)methanol (17): 6-Fluorospiro[3.3]heptane-2-carboxylic acid (**11**) (150 g, 948 mmol) was added dropwise to the stirred ice-cold suspension of $LiAlH_4$ (36.1 g, 950 mmol) in THF (1.4 L). Then it was allowed to warm to rt and left to react with stirring for 16 h. After, the reaction mixture was quenched upon cooling by sequential dropwise addition of water (36 mL), 50% aq. NaOH (36 g, 20 mL), and water (110 mL) again. Thus obtained mixture was allowed to stir for 15 min, the precipitate formed was filtered off, washed with THF (2 × 150 mL), and the filtrate was evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (1 L), dried (Na_2SO_4), and evaporated at reduced pressure to give the title compound **17** as colorless liquid. Yield 121 g, 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (dquint, *J* = 55.8, 6.7 Hz, 1H), 3.58 (dd, *J* = 6.7, 2.3 Hz, 2H), 2.55–2.30 (m, 2H), 2.29–2.04 (m, 4H), 1.89–1.75 (m, 2H), 1.42 (s, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 83.8 (d, *J* = 212.3 Hz), 67.0, 44.0 (d, *J* = 19.2 Hz), 43.7 (d, *J* = 19.2 Hz), 36.7 (d, *J* = 30.8 Hz), 32.4, 30.7 (d, *J* = 16.7 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.3 ppm; MS (EI): *m/z* = 106 [M – H_2O – HF]$^+$; elemental analysis calcd. (%) for $C_8H_{13}FO$: C 66.64, H 9.09; found: C 66.31, H 9.11.

2-(Bromomethyl)-6-fluorospiro[3.3]heptane (18): Br_2 (86.2 g, 27.8 mL, 539 mmol) was added dropwise to the stirred ice-cold solution of Ph_3P (142 g, 541 mmol) in CH_2Cl_2 (700 mL) maintaining the internal temperature below 10 °C. Thus obtained suspension was stirred at 0 °C for 45 min, Et_3N (55.2 g, 76 mL, 545 mmol) was added, and the mixture was stirred at above temperature for 15 min. Next, the solution of (6-fluorospiro[3.3]heptan-2-yl)methanol (**17**) (65 g, 451 mmol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C. Then the mixture was allowed to warm to rt and stirred for 16 h. After, the reaction mixture was slowly diluted with water (1 L), the organic layer was separated, washed with saturated aq. Na_2CO_3 (500 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The remainder was triturated with hexane (500 mL) and filtered, while precipitate was washed with hexane (2 × 50 mL). The combined filtrate was evaporated at reduced pressure and the residue was distilled *in vacuo* to give the title compound **18** as colorless liquid. Yield 77.5 g, 83%; b.p. 45–46 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (dquint, *J* = 55.7, 6.8 Hz, 1H), 3.39 (d, *J* = 7.6 Hz, 2H), 2.62 (hept, *J* = 7.6 Hz, 1H), 2.56–2.45 (m, 1H), 2.42–2.30 (m, 1H), 2.30–2.10 (m, 4H), 1.91–1.73 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 83.2 (d, *J* = 212.5 Hz), 43.3 (d, *J* = 19.5 Hz), 42.9 (d, *J* = 19.5 Hz), 39.0 (d, *J* = 31.9 Hz), 38.4, 32.4, 29.0 (d, *J* = 16.8 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.4 ppm; MS (EI): *m/z* = 159/161 [M – C_2H_3F]$^+$; elemental analysis calcd. (%) for $C_8H_{12}BrF$: C 46.40, H 5.84; found: C 46.16, H 5.87.

General procedure for the preparation of pinacol boronates 19 and 20: The corresponding bromide **16**, **18** (155 mmol) was dissolved in DMF (300 mL) followed by sequential addition of *t*-BuOLi (24.9 g, 311 mmol), $(BPin)_2$ (47.4 g, 187 mmol), Ph_3P (5.3 g, 20.2 mmol), and CuBr (2.26 g, 15.8 mmol) under Ar atmosphere maintaining internal temperature below 30 °C (*Caution:* Exothermic reaction!). Thus obtained mixture was stirred for 16 h; then it was diluted with EtOAc (300 mL) and filtered through silica gel. The filtrate was washed with water (1 × 500 mL and 2 × 150 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue

was subjected to silica gel column chromatography (EtOAc – hexane 1:15) affording the title compound **19**, **20** as colorless liquid.

2-(6-Fluorospiro[3.3]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19): from 2-bromo-6-fluorospiro[3.3]heptane (**16**) (30 g, 155 mmol), *t*-BuOLi (24.9 g, 311 mmol), $(BPin)_2$ (47.4 g, 187 mmol), Ph_3P (5.3 r, 20.2 mmol), and CuBr (2.26 g, 15.8 mmol). Yield 32.1 g, 86%, R_f 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (dquint, *J* = 55.8, 6.8 Hz, 1H), 2.55–2.34 (m, 2H), 2.26–1.95 (m, 6H), 1.80 (p, *J* = 8.1 Hz, 1H), 1.26 (s, 12H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 83.9 (d, *J* = 212.2 Hz), 83.1, 43.6 (d, *J* = 19.2 Hz), 43.5 (d, *J* = 19.2 Hz), 35.9 (d, *J* = 24.7 Hz), 34.0 (d, *J* = 16.4 Hz), 24.7, 12.6 (br. s) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.6 ppm; MS (EI): *m/z* = 220 $[M – HF]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{13}H_{23}BFO_2$: 241.1775, found: 241.1768.

2-((6-Fluorospiro[3.3]heptan-2-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20): from 2-(bromomethyl)-6-fluorospiro[3.3]heptane (**18**) (35 g, 169 mmol), *t*-BuOLi (27 g, 337 mmol), $(BPin)_2$ (51 g, 201 mmol), Ph_3P (5.76 g, 22 mmol), and CuBr (2.45 g, 17 mmol). Yield 37.8 g, 91%, R_f 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (dquint, *J* = 56.0, 6.9 Hz, 1H), 2.54–2.44 (m, 1H), 2.38 (hept, *J* = 8.9 Hz, 1H), 2.33–2.23 (m, 1H), 2.23–2.04 (m, 4H), 1.78–1.54 (m, 2H), 1.24 (s, 12H), 0.92 (d, *J* = 7.9 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 84.2 (d, *J* = 212.4 Hz), 82.9, 43.8 (d, *J* = 19.1 Hz), 43.3 (d, *J* = 19.1 Hz), 42.8 (d, *J* = 14.1 Hz), 30.2 (d, *J* = 16.8 Hz), 27.0, 24.8, 19.2 (br. s) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –168.9 ppm; MS (EI): *m/z* = 170 $[M – C_6H_{12}]^+$; HRMS (ESI) *m/z* $[M + NH_4]^+$ calcd for $C_{14}H_{28}BFNO_2$: 272.2197, found: 272.2194.

General procedure for the preparation of potassium trifluoroborates 21 and 22: The corresponding pinacol boronate **19**, **20** (117 mmol) was dissolved in MeOH (200 mL) followed by addition of a solution of KHF_2 (45.5 g, 583 mmol) in water (100 mL). Thus obtained mixture was stirred at rt for 16 h and evaporated at reduced pressure. The residue was triturated with EtOAc (200 mL), filtered, and washed with EtOAc (3 × 100 mL). The combined filtrate was evaporated at reduced pressure to give the title compound **21**, **22** as colorless powder.

Potassium trifluoro(6-fluorospiro[3.3]heptan-2-yl)borate (21): from 2-(6-fluorospiro[3.3]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**19**) (28.0 g, 117 mmol). Yield 19.8 g, 77%; m.p. > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.80 (dquint, *J* = 56.0, 7.0 Hz, 1H), 2.44–2.30 (m, 1H), 2.28–2.14 (m, 1H), 2.03–1.76 (m, 2H), 1.79–1.56 (m, 4H), 1.13–0.93 (m, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 84.4 (d, *J* = 211.2 Hz), 44.8 (d, *J* = 18.0 Hz), 43.9 (d, *J* = 18.0 Hz), 36.6 (d, *J* = 5.8 Hz), 32.6 (d, *J* = 15.4 Hz), 20.5 (br. s) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –144.2, –166.5 ppm; MS (APCI): *m/z* = 203 $[M –K–3F+2OH+HCO_2]^-$; HRMS (ESI) *m/z* $[M]^-$ calcd for $C_7H_{10}BF_4$: 181.0812, found: 181.0814.

Potassium trifluoro((6-fluorospiro[3.3]heptan-2-yl)methyl)borate (22): from 2-((6-fluorospiro[3.3]heptan-2-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**20**) (32.0 g, 126 mmol). Yield 21.1 g, 72%; m.p. > 230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.85 (dquint, *J* = 56.0, 6.7 Hz, 1H), 2.39 (dq, *J* = 12.5, 6.7 Hz, 1H), 2.19 (dq, *J* = 12.5, 6.7 Hz, 1H), 2.14–2.02 (m, 1H), 2.00–1.89 (m, 4H), 1.60–1.41 (m, 2H), 0.09 (p, *J* = 6.6 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 84.3 (d, *J* = 211.4 Hz), 44.13 (d, *J* = 28.3 Hz), 44.07 (d, *J* = 18.1 Hz), 43.50 (d, *J* = 18.1 Hz), 30.3 (d, *J* = 16.1 Hz), 29.4, 29.0 (br. s) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –136.0, –166.3 ppm; MS (APCI): *m/z* = 217 $[M –K–3F+2OH+HCO_2]^-$; HRMS (ESI) *m/z* $[M]^-$ calcd for $C_8H_{12}BF_4$: 195.0968, found: 195.0971.

General Procedure for the Preparation of Ethanethioates 23 and 24: The corresponding bromide **16**, **18** (129 mmol) was dissolved in DMF (125 mL), KSAc (29.5 g, 258 mmol) was added, and the resulting mixture was stirred at 50 °C for 16 h. Then it was cooled to rt, diluted with water (250 mL), and extracted with *t*-BuOMe (250 mL). The organic layer was washed with water (2 × 150 mL), dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **23**, **24** as yellow liquid.

***S*-(6-Fluorospiro[3.3]heptan-2-yl) ethanethioate (23):** from 2-bromo-6-fluorospiro[3.3]heptane (**16**) (25 g, 129 mmol). Yield 22.6 g, 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (dquint, *J* = 55.6, 6.7 Hz, 1H), 3.98 (p, *J* = 8.3 Hz, 1H), 2.63–2.45 (m, 3H), 2.46–2.29 (m, 2H), 2.28 (s, 3H), 2.25–2.04 (m, 3H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 195.8, 83.6 (d, *J* = 212.5 Hz), 43.2 (d, *J* = 19.8 Hz), 43.1 (d, *J* = 19.8 Hz), 42.1 (d, *J* = 33.1 Hz), 32.2, 31.8 (d, *J* = 16.8 Hz), 30.4 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.5 ppm; MS (EI): *m/z* = 145 $[M – CH_3CO]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_9H_{14}FOS$: 189.0749, found: 189.0741.

***S*-((6-Fluorospiro[3.3]heptan-2-yl)methyl) ethanethioate (24):** from 2-(bromomethyl)-6-fluorospiro[3.3]heptane (**18**) (25 g, 121 mmol). Yield 21.7 g, 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (dquint, *J* = 55.7, 6.8 Hz, 1H), 2.93 (d, *J* = 7.5 Hz, 2H), 2.54–2.35 (m, 3H), 2.34 (s, 3H), 2.26–2.06 (m, 4H), 1.83–1.67 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 195.3, 83.4 (d, *J* = 212.5 Hz), 43.2 (d, *J* = 19.4 Hz), 42.9 (d, *J* = 19.4 Hz), 39.2 (d, *J* = 16.7 Hz), 34.5, 30.2, 29.8, 29.6 (d, *J* = 16.7 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.2 ppm; MS (EI): *m/z* = 159 $[M – CH_3CO]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{10}H_{16}FOS$: 203.0906, found: 203.0907.

General Procedure for the Preparation of Sulfonyl Chlorides 25 and 26: The corresponding ethanethioate **23**, **24** (117 mmol) was added to a stirred mixture of CH_2Cl_2 (200 mL) and water (200 mL) and the resulting emulsion was cooled to 0 °C. Then Cl_2 was bubbled through the stirred reaction mixture maintaining the above temperature until it became yellow green (ca. 30 min). After, the reaction mixture was allowed to warm to 10 °C, the organic layer was separated, washed with water (2 × 150 mL), dried (Na_2SO_4), and evaporated at reduced pressure to give the title compound **24**, **26** as yellow liquid.

6-Fluorospiro[3.3]heptane-2-sulfonyl chloride (25): from *S*-(6-fluorospiro[3.3]heptan-2-yl) ethanethioate (**23**) (22.- g, 117 mmol). Yield 18.1 g, 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (dquint, *J* = 55.3, 6.5 Hz, 1H), 4.34 (p, *J* = 8.1 Hz, 1H), 2.85–2.72 (m, 2H), 2.64–2.51 (m, 4H), 2.41–2.30 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 82.5 (d, *J* = 212.0 Hz), 62.8, 42.72 (d, *J* = 20.6 Hz), 42.68 (d, *J* = 20.6 Hz), 36.6 (d, *J* = 26.7 Hz), 29.6 (d, *J* = 16.4 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –170.4 ppm; MS (APCI): *m/z* = 193 $[M – H]^-$ (for the corresponding sulfonic acid); elemental analysis calcd. (%) for $C_7H_{10}ClFO_2S$: C 39.54, H 4.74, S 15.08; found: C 39.15, H 4.91, S 15.31.

(6-Fluorospiro[3.3]heptan-2-yl)methanesulfonyl chloride (26): from *S*-((6-fluorospiro[3.3]heptan-2-yl)methyl) ethanethioate (**24**) (21 g, 104 mmol). Yield 17.3 g, 74%.; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (dquint, *J* = 55.6, 6.8 Hz, 1H), 3.76 (d, *J* = 7.2 Hz, 2H), 2.97 (hept, *J* = 8.1 Hz, 1H), 2.67–2.52 (m, 1H), 2.44–2.30 (m, 3H), 2.30–2.14 (m, 2H), 2.11–1.92 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 83.0 (d, *J* = 212.4 Hz), 70.1, 42.8 (d, *J* = 20.0 Hz), 42.4 (d, *J* = 20.0 Hz), 39.4 (d, *J* = 21.6 Hz), 31.1 (d, *J* = 16.8 Hz), 25.7 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.7 ppm; MS (APCI): *m/z* = 207 $[M – H]^-$ (for the corresponding sulfonic acid); elemental analysis calcd. (%) for $C_8H_{12}ClFO_2S$: C 42.39, H 5.34, S 14.14; found: C 42.22, H 5.52, S 14.30.

6-Fluorospiro[3.3]heptane-2-carbaldehyde (27): $(COCl)_2$ (47.6 g, 32.2 mL, 375 mmol) was added dropwise to cold (–78 °C) solution of DMSO (58.5 g, 53.2 mL, 749 mmol) in CH_2Cl_2 (900 mL) maintaining the temperature below –70 °C, and the resulting mixture was stirred at above temperature for 15 min. Then the solution of (6-fluorospiro[3.3]heptan-2-yl)methanol (**17**) (45 g, 312 mmol) in CH_2Cl_2 (100 mL) was added dropwise at –78 °C and thus obtained mixture was stirred at above temperature for 30 min. Next, Et_3N (126 g, 174 mL, 1.25 mol) was added, and the reaction mixture was warmed to 0 °C. Finally, water (500 mL) was added, the organic layer was separated, washed with saturated aq. Na_2CO_3 (200 mL) and brine (200 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **27** as colorless liquid. Yield 37.7 g, 85%; b.p. 45–46 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 4.92 (dquint, *J* =

55.6, 6.7 Hz, 1H), 3.13 (p, *J* = 9.0 Hz, 1H), 2.60–2.46 (m, 1H), 2.45–2.09 (m, 7H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 201.4, 82.9 (d, *J* = 212.3 Hz), 43.2 (d, *J* = 19.8 Hz), 42.8 (d, *J* = 19.8 Hz), 40.6, 33.8 (d, *J* = 17.0 Hz), 30.9 (d, *J* = 16.9 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.9 ppm; MS (EI): *m/z* = 96 $[M - C_2H_3F]^+$; HRMS (ESI) *m/z* $[M + NH_4]^+$ calcd for $C_8H_{15}NFO$: 160.1137, found: 160.1114.

2-Ethynyl-6-fluorospiro[3.3]heptane (28): K_2CO_3 (73 g, 528 mmol) was dispersed in MeOH (200 mL) followed by addition of 6-fluorospiro[3.3]heptane-2-carbaldehyde (**27**) (25 g, 176 mmol). Thus obtained mixture was cooled to 0 °C, and the Ohira-Bestmann reagent (39.2 г, 204 mmol) was slowly added. The reaction mixture was allowed to warm to rt and stirred for 1 h. Then it was diluted with water (500 mL) and extracted with hexane (400 mL). The organic layer was washed with water (300 mL), dried (Na_2SO_4), and evaporated at reduced pressure. Thus obtained residue was distilled *in vacuo* to give the title compound **28** as colorless oil. Yield 9.6 g, 39%; b.p. 60–61 °C (28 mBar); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.90 (dquint, *J* = 55.7, 6.7 Hz, 1H), 2.94 (pd, *J* = 8.3, 2.5 Hz, 1H), 2.56–2.39 (m, 2H), 2.40–2.28 (m, 2H), 2.28–2.08 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 87.3, 83.1 (d, *J* = 212.4 Hz), 68.5, 42.8 (d, *J* = 19.7 Hz), 42.7 (d, *J* = 19.7 Hz), 40.9 (d, *J* = 16.0 Hz), 31.3 (d, *J* = 16.9 Hz), 19.7 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.6 ppm; MS (EI): *m/z* = 92 $[M - C_2H_3F]^+$; elemental analysis calcd. (%) for $C_9H_{11}F$: C 78.23, H 8.02; found: C 78.22, H 7.71.

2-(Ethoxycarbonyl)-6-fluorospiro[3.3]heptane-2-carboxylic acid (31): A solution of diethyl 6-fluorospiro[3.3]heptane-2,2-dicarboxylate (**6**) (125 g, 484 mmol) in a mixture of EtOH (600 mL) and water (300 mL) was brought to boil followed by dropwise addition of a solution of NaOH (18.4 g, 460 mmol) in water (300 mL) at reflux within 1 h. Then it was allowed to equilibrate to rt and left to stir for 16 h. EtOH was evaporated at reduced pressure, the remaining aqueous solution was diluted with water (500 mL) and extracted with *t*-BuOMe (500 mL). The aqueous layer was separated, acidified with 2M aq. HCl to pH 3, and extracted with EtOAc (2 × 300 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **31** as yellowish oil. Yield 86 g, 77%; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.91 (dquint, *J* = 55.6, 6.5 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.72–2.67 (m, 2H), 2.67–2.62 (m, 2H), 2.57–2.46 (m, 2H), 2.35–2.20 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (154 MHz, $CDCl_3$): δ = 177.1, 171.2, 83.2 (d, *J* = 211.5 Hz), 61.9, 48.9, 43.7 (d, *J* = 8.9 Hz), 43.6 (d, *J* = 8.9 Hz), 40.9 (d, *J* = 29.0 Hz), 29.5 (d, *J* = 16.6 Hz), 13.96 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –170.1 ppm; MS (EI): *m/z* = 166 $[M - CO_2 - HF]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{16}FO_4$: 231.1033, found: 231.1023.

Ethyl 2-((*tert*-butoxycarbonyl)amino)-6-fluorospiro[3.3]heptane-2-carboxylate (32): 2-(Ethoxycarbonyl)-6-fluorospiro[3.3]heptane-2-carboxylic acid (**31**) (75 g, 326 mmol) was dissolved in a mixture of CH_2Cl_2 (800 mL) and DMF (1 mL) followed by dropwise addition of $(COCl)_2$ (50 g, 33.8 mL, 394 mmol). The resulting solution was stirred at rt for 2 h and evaporated at reduced pressure. Thus obtained crude acid chloride was dissolved in EtOAc (260 mL) and cooled to 0 °C followed by dropwise addition of a solution of NaN_3 (63.6 g, 978 mmol) in water (400 mL) maintaining the above temperature. The reaction mixture was allowed to stir at 0 °C for an additional 1 h and extracted with EtOAc (2 × 250 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to a half of initial volume at reduced pressure and external temperature below 30 °C. This solution was added dropwise to hot (90 °C) mixture of *t*-BuOH (250 mL) and PhMe (500 mL) and thus obtained reaction mixture was stirred at above temperature for an additional 40 h. Then it was evaporated at reduced pressure to give the crude product which was subjected to silica gel column chromatography (hexane – EtOAc 6:1, R_f 0.46) affording the title compound **32** as colorless crystals. Yield 70.1 g, 71%; m.p. 53–55 °C; mixtures of Boc-rotamers were observed by NMR spectroscopy; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.12 (br. s, 1H), 4.92 (dquint, *J* = 55.7, 6.7 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.73–2.64 (m, 4H), 2.64–2.49 (m, 2H), 2.51–2.35 (m, 2H), 2.37–2.24 (m, 2H), 1.44 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 173.6, 154.8, 83.7 (d, *J* = 211.1 Hz), 79.8, 61.4, 54.8, 44.3 (d, *J* = 20.0 Hz), 43.8 (d, *J* = 20.0 Hz), 43.4 (br. s), 28.30 (d, *J* = 17.5 Hz), 28.27, 14.1 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.7 ppm; MS (APCI): *m/z* = 202 $[M - CO_2 - C_4H_8 + H]^+$; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{24}FNNaO_4$: 324.1587, found: 324.1578.
A sample of **32** (200 mg) was subjected to chiral stationary phase HPLC separation (Chiralpak AS-H 250×4.6 mm, 5 μm column, gradient elution with hexane – *i*-PrOH (90 to 10 v/v), 0.6 mL/min). (*S*)-**32**: 85 mg, 42%; colorless oil; t_R = 13.7 min; $[\alpha]_D^{20}$ = +7.12 (c = 1.0 in MeOH). (*R*)-**32:** 85 mg, 42%; colorless oil; t_R = 17.2 min; $[\alpha]_D^{20}$ = –7.08 (c = 1.0 in MeOH). Spectral data for the enantiomers were in accordance with those for the racemic mixture.

Ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-6-fluorospiro[3.3]heptane-2-carboxylate (33): Ethyl 2-cyano-6-fluorospiro[3.3]heptane-2-carboxylate (**7**) (75 g, 355 mmol) and Boc_2O (107 g, 492 mmol) were dissolved in EtOH (500 mL) followed by addition of freshly prepared Raney-Ni (15 g). The reaction mixture was loaded in an autoclave and hydrogenated at 50 Bar for 64 h. Then it was filtered and evaporated at reduced pressure to give the crude product, which was subjected to silica gel column chromatography (hexane – EtOAc 6:1, R_f 0.54) affording the title compound **33** as colorless oil. Yield 94.4 g, 84%; mixtures of Boc-rotamers were observed by NMR spectroscopy; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.92 (br. s, 1H), 4.91 (dquint, *J* = 55.7, 6.7 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.53–3.35 (m, 2H), 2.68–2.56 (m, 1H), 2.56–2.39 (m, 3H), 2.39–2.16 (m, 2H), 2.13–2.00 (m, 2H), 1.45 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 175.2, 155.8, 83.1 (d, *J* = 211.6 Hz), 78.8, 60.4, 45.4, 44.0 (d, *J* = 19.8 Hz), 43.7 (d, *J* = 19.8 Hz), 43.3, 39.8 and 39.7, 28.4 (d, *J* = 16.7 Hz), 27.9, 13.7 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –169.5 ppm; MS (APCI): *m/z* = 216 $[M - CO_2 - C_4H_8 + H]^+$; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{26}FNNaO_4$: 338.1744, found: 338.1735.

General procedure for the Preparation of Amino Acid Ester Hydrochlorides 34 and 35: The corresponding Boc-protected ester **32**, **33** (8.5 mmol) was added to 2M ethanolic HCl (25 mL) and the resulting mixture was stirred for 2 h. Then it was evaporated at reduced pressure, the residue was triturated with Et_2O (20 mL) and filtered to give the title compound **34**, **35** as colorless powder.

Ethyl 2-amino-6-fluorospiro[3.3]heptane-2-carboxylate hydrochloride (34): from ethyl 2-((*tert*-butoxycarbonyl)amino)-6-fluorospiro[3.3]heptane-2-carboxylate (**32**) (2.5 g, 8.3 mmol). Yield 1.74 g, 88%; m.p. 127–129 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.82 (s, 3H), 4.94 (dquint, *J* = 56.8, 5.9 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.70–2.51 (m, 6H), 2.32–2.11 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.2, 83.7 (d, *J* = 208.6 Hz), 62.3, 53.3, 43.8 (d, *J* = 19.7 Hz), 43.6 (d, *J* = 19.7 Hz), 41.6 (d, *J* = 18.6 Hz), 27.8 (d, *J* = 17.5 Hz), 14.2 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –168.2 ppm; MS (APCI): *m/z* = 202 $[M + H]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{10}H_{17}FNO_2$: 202.1243, found: 202.1237.

Ethyl 2-(aminomethyl)-6-fluorospiro[3.3]heptane-2-carboxylate hydrochloride (35): from ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-6-fluorospiro[3.3]heptane-2-carboxylate (**33**) (25 g, 79.3 mmol). Yield 18.3 g, 92%; b.p. 98–101 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.18 (s, 3H), 4.93 (dquint, *J* = 55.8, 6.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.08 (s, 2H), 2.62–2.51 (m, 2H), 2.42–2.33 (m, 2H), 2.31–2.07 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 174.0, 83.8 (d, *J* = 209.6 Hz), 61.4, 44.03 (d, *J* = 20.0 Hz), 43.85 (d, *J* = 20.0 Hz), 43.88, 41.8, 40.0, 28.8 (d, *J* = 16.4 Hz), 14.3 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –167.6 ppm; MS (APCI): *m/z* = 216 $[M + H]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{19}FNO_2$: 216.1400, found: 216.1391.

General procedure for the preparation of Boc-protected amino acids 36 and 37: The corresponding Boc-protected ester **32**, **33** (99.5 mmol) was added to the solution of NaOH (12 g, 300 mmol) in a mixture of water (150 mL) and MeOH (150 mL) and the resulting mixture was

allowed to stir at rt for 16 h. Then MeOH was evaporated at reduced pressure, the remaining aqueous solution was acidified with 1M aq. HCl to pH 3, and extracted with EtOAc (2 × 200 mL). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was triturated with hexane (100 mL), filtered and washed with hexane (7 mL) to give the title compound **36**, **37** as colorless powder.

2-((*tert*-Butoxycarbonyl)amino)-6-fluorospiro[3.3]heptane-2-carboxylic acid (36): from ethyl 2-((*tert*-butoxycarbonyl)amino)-6-fluorospiro[3.3]heptane-2-carboxylate (**32**) (30 g, 99.5 mmol). Yield 23.4 g, 86%; m.p. 159–160 °C; mixtures of Boc-rotamers were observed by NMR spectroscopy; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (br. s, 1H), 4.93 (dquint, *J* = 55.6, 6.7 Hz, 1H), 2.84–2.71 (m, 2H), 2.66–2.47 (m, 2H), 2.42–2.16 (m, 4H), 1.45 (s, 9H) ppm; ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ = 175.9 and 175.4, 155.1 and 154.7, 83.8 (d, *J* = 209.8 Hz), 78.5 and 78.3, 54.6 and 54.3, 44.2 (d, *J* = 19.2 Hz), 43.7 (d, *J* = 19.2 Hz), 43.0 (d, *J* = 12.1 Hz), 28.7, 28.4 (d, *J* = 14.7 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.8 ppm; MS (APCI): *m/z* = 174 [M – CO_2 – C_4H_8 + H]$^+$; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{13}H_{20}FNNaO_4$: 296.1274, found: 296.1264.

2-(((*tert*-Butoxycarbonyl)amino)methyl)-6-fluorospiro[3.3]heptane-2-carboxylic acid (37): from ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-6-fluorospiro[3.3]heptane-2-carboxylate (**33**) (35 g, 111 mmol). Yield 27.7 g, 87%; m.p. 121–123 °C; mixtures of Boc-rotamers were observed by NMR spectroscopy; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (br. s, 1H), 4.93 (dquint, *J* = 56.5, 6.4 Hz, 1H), 3.57–3.36 (m, 2H), 2.77–2.43 (m, 4H), 2.42–2.19 (m, 2H), 2.18–1.98 (m, 2H), 1.49 (s, 9H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 181.7 and 179.7, 157.8 and 156.4, 83.5 (d, *J* = 211.9 Hz), 81.3 and 79.5, 46.9 and 45.4, 44.5 (d, *J* = 19.4 Hz), 44.1 (d, *J* = 19.4 Hz), 43.7, 40.1 and 40.0, 28.9 (d, *J* = 16.8 Hz), 28.4 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –169.5 ppm; MS (APCI): *m/z* = 286 [M – H]$^-$; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{14}H_{22}FNNaO_4$: 310.1430, found: 310.1420.

General procedure for the preparation of amino acids 29 and 30: The corresponding Boc-protected amino acid **36**, **37** (36.5 mmol) was dispersed in water (100 mL) and the resulting mixture was stirred at reflux for 40 h. Then it was evaporated at reduced pressure, the residue was triturated with MeCN (50 mL), filtered, and washed with MeCN (2 × 25 mL) to give the title compound **29**, **30** as colorless powder.

2-Amino-6-fluorospiro[3.3]heptane-2-carboxylic acid (29): from 2-((*tert*-butoxycarbonyl)amino)-6-fluorospiro[3.3]heptane-2-carboxylic acid (**36**) (10 g, 36.5 mmol). Yield 5.83 g, 92%; m.p. 242–245 °C; ^{1}H NMR (400 MHz, D_2O): δ = 4.86 (dquint, *J* = 56.4, 6.8 Hz, 1H), 2.59–2.46 (m, 3H), 2.44–2.33 (m, 1H), 2.28 (t, *J* = 13.8 Hz, 2H), 2.24–2.09 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, D_2O): δ = 176.2, 84.3 (d, *J* = 205.7 Hz), 54.6, 42.8 (d, *J* = 20.5 Hz), 42.6 (d, *J* = 20.5 Hz), 41.1 (d, *J* = 50.1 Hz), 26.6 (d, *J* = 18.3 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, D_2O): δ = –168.9 ppm; MS (APCI): *m/z* = 174 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_8H_{13}FNO_2$: 174.0930, found: 174.0921.

2-(Aminomethyl)-6-fluorospiro[3.3]heptane-2-carboxylic acid (30): from 2-(((*tert*-butoxycarbonyl)amino)methyl)-6-fluorospiro[3.3]heptane-2-carboxylic acid (**37**) (10 g, 34.8 mmol). Yield 5.87 g, 90%; m.p. 225–227 °C; ^{1}H NMR (400 MHz, D_2O): δ = 4.87 (dquint, *J* = 56.5, 6.8 Hz, 1H), 3.08 (s, 2H), 2.49–2.27 (m, 4H), 2.23–2.02 (m, 2H), 2.02–1.85 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, D_2O): δ = 181.6, 84.5 (d, *J* = 206.5 Hz), 45.1, 43.1 (d, *J* = 19.0 Hz), 42.8 (d, *J* = 19.0 Hz), 41.7, 39.7 (d, *J* = 11.3 Hz), 27.4 (d, *J* = 18.0 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, D_2O): δ = –167.8 ppm; MS (APCI): *m/z* = 188 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_9H_{15}FNO_2$: 188.1087, found: 188.1079.

(2-(Aminomethyl)-6-fluorospiro[3.3]heptan-2-yl)methanol (38): Ethyl 2-cyano-6-fluorospiro[3.3]heptane-2-carboxylate (**7**) (10 g, 47.1 mmol) was added to the stirred suspension of $LiAlH_4$ (1.8 g, 47.3 mmol) in THF (70 mL) at 0 °C. Then it was allowed to warm to rt and left to react with stirring for 16 h. After, the reaction mixture was quenched upon cooling by sequential dropwise addition of water (1.8 mL), 50% aq. NaOH (1.8 g, 1 mL), and water (5.4 mL) again. The resulting mixture was allowed to stir for 15 min, the precipitate formed was filtered off, washed with THF (2 × 15 mL), and the filtrate was evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was dissolved in Et_2O (100 mL) followed by addition of 4M HCl in Et_2O (15 mL). The precipitate formed was filtered and washed with a minimal amount of Et_2O to give the title compound **38** as colorless powder. Yield 5.18 g, 52%; m.p. 138–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.91 (s, 3H), 5.07 (t, *J* = 5.4 Hz, 1H), 4.91 (dquint, *J* = 56.0, 6.8 Hz, 1H), 3.39 (s, 2H), 2.82 (s, 2H), 2.42 (p, *J* = 6.8 Hz, 2H), 2.20–2.04 (m, 2H), 2.01–1.90 (m, 2H), 1.90–1.78 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 83.9 (d, *J* = 210.3 Hz), 65.5, 44.69, 44.72 (d, *J* = 19.0 Hz), 44.37 (d, *J* = 19.0 Hz), 39.2 (d, *J* = 17.2 Hz), 37.8, 28.0 (d, *J* = 16.2 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –166.9 ppm; MS (APCI): *m/z* = 174 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_9H_{17}FNO$: 174.1294, found: 174.1286.

General procedure for the preparation of *N*-phenyl carboxamides 43–45: The corresponding carboxylic acid **11**, **39**, **40** (6.32 mmol) was dissolved in CH_2Cl_2 (20 mL) followed by addition of DMF (0.02 mL) and $(COCl)_2$ (970 mg, 0.66 mL, 7.64 mmol). The resulting mixture was stirred at rt for 3 h and evaporated at reduced pressure. Thus obtained crude acyl chloride was dissolved in CH_2Cl_2 (5 mL) and added dropwise to cold (0 °C) solution of $PhNH_2$ (620 mg, 0.62 mL, 6.66 mmol) and Et_3N (958 mg, 1.32 mL, 9.47 mmol) in CH_2Cl_2 (20 mL), maintaining the above temperature. Then it was allowed to warm to rt and left to react with stirring for 16 h. After, the reaction mixture was successively washed with water (25 mL) and saturated aq. Na_2CO_3 (20 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was triturated with hexane (10 mL) and filtered to give the title compound **43**–**45** as colorless powder.

***N*-Phenylspiro[3.3]heptane-2-carboxamide (43):** from spiro[3.3]heptane-2-carboxylic acid (**39**) (886 mg, 6.32 mmol). Yield 1.14 g, 84%; m.p. 125–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.71 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 1H), 3.05 (p, *J* = 7.4 Hz, 1H), 2.23–2.08 (m, 4H), 2.03 (t, *J* = 7.4 Hz, 2H), 1.88 (t, *J* = 7.4 Hz, 2H), 1.77 (p, *J* = 7.4 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 172.7, 139.4, 128.6, 122.8, 119.0, 37.3, 34.8, 34.4, 33.9, 15.9 ppm; MS (APCI): *m/z* = 216 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{14}H_{18}NO$: 216.1388, found: 216.1379.

6-Fluoro-*N*-phenylspiro[3.3]heptane-2-carboxamide (44): from 6-fluorospiro[3.3]heptane-2-carboxylic acid (**11**) (1 g, 6.32 mmol). Yield 1.17 g, 79%; m.p. 106–108 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.74 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 4.95 (dquint, *J* = 55.9, 6.6 Hz, 1H), 3.11 (p, *J* = 8.3 Hz, 1H), 2.43–1.97 (m, 8H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 172.0, 137.4, 128.5, 123.7, 119.2, 83.2 (d, *J* = 212.1 Hz), 43.1 (d, *J* = 20.0 Hz), 42.49 (d, *J* = 20.0 Hz), 36.8 (d, *J* = 5.8 Hz), 35.8, 30.3 (d, *J* = 16.5 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –167.5 ppm; MS (APCI): *m/z* = 234 [M + H]$^+$; MS (APCI): *m/z* = 234 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{14}H_{17}FNO$: 234.1294, found: 234.1284.

6,6-Difluoro-*N*-phenylspiro[3.3]heptane-2-carboxamide (45): from 6,6-difluorospiro[3.3]heptane-2-carboxylic acid (**40**) (1.11 g, 6.32 mmol). Yield 1.19 g, 75%; m.p. 117–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.01 (t, *J* = 7.7 Hz, 1H), 3.15 (p, *J* = 9.2 Hz, 1H), 2.67 (t, *J* = 12.5 Hz, 2H), 2.54 (t, *J* = 12.5 Hz, 2H), 2.35 (t, *J* = 9.2 Hz, 2H), 2.26 (t, *J* = 9.2 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ = 172.7, 139.7, 129.1, 123.4, 120.7 (t, *J* = 279.3 Hz), 119.5, 47.3 (t, *J* = 21.2 Hz), 46.6 (t, *J* = 21.2 Hz), 36.5, 34.9, 28.8 (t, *J* = 9.2 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –89.5 ppm; MS (APCI): *m/z* = 252 [M + H]$^+$; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{14}H_{16}F_2NO$: 252.1199, found: 252.1190.

General Procedure for the Preparation of Benzamides 46–48: The corresponding amine hydrochloride **13**, **41**, **42** (6.04 mmol) was dissolved in CH_2Cl_2 (20 mL) followed by addition of Et_3N (1.52 g, 2.09 mL, 15 mmol) and the resulting mixture was cooled to 0 °C. Then PhCOCl (0.89 g, 0.74 mL, 6.33 mmol) was added dropwise and thus obtained reaction mixture was stirred at rt for 16h. Then it was successively washed with water (25 mL) and saturated aq. Na_2CO_3 (20 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was triturated with hexane (10 mL) and filtered to give the title compound **46**–**48** as colorless powder.

***N*-(Spiro[3.3]heptan-2-yl)benzamide (46):** from spiro[3.3]heptan-2-amine hydrochloride (**41**) (890 mg, 6.04 mmol). Yield 1.08 g, 83%; m.p. 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 6.31 (br. s, 1H), 4.45 (h, *J* = 8.1 Hz, 1H), 2.52 (td, *J* = 8.1, 3.2 Hz, 2H), 2.08 (t, *J* = 7.3 Hz, 2H), 2.00–1.78 (m, 6H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 166.2, 134.2, 130.8, 128.0, 126.4, 43.0, 40.4, 37.1, 34.3, 33.8, 16.3 ppm; MS (APCI): *m/z* = 216 $[M + H]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO$: 216.1388, found: 216.1385.

***N*-(6-Fluorospiro[3.3]heptan-2-yl)benzamide (47):** from 6-fluorospiro[3.3]heptan-2-amine hydrochloride (**13**) (1 g, 6.04 mmol). Yield 1.2 g, 85%; m.p. 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 6.50 (br. s, 1H), 4.88 (dquint, *J* = 55.5, 7.0 Hz, 1H), 4.46 (h, *J* = 8.1 Hz, 1H), 2.56–2.35 (m, 3H), 2.35–2.10 (m, 3H), 2.04 (t, *J* = 10.2 Hz, 1H), 1.95 (t, *J* = 10.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 166.8, 134.4, 131.4, 128.5, 126.9, 83.8 (d, *J* = 212.4 Hz), 43.0 (d, *J* = 19.8 Hz), 42.8, 42.6 (d, *J* = 19.8 Hz), 41.2, 28.3 (d, *J* = 16.9 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –166.8 ppm; MS (APCI): *m/z* = 234 $[M + H]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}FNO$: 234.1294, found: 234.1284.

***N*-(6,6-Difluorospiro[3.3]heptan-2-yl)benzamide (48):** from 6,6-difluorospiro[3.3]heptan-2-amine hydrochloride (**42**) (1.11 g, 6.04 mmol). Yield 1.34 g, 88%; m.p. 134–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.60 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 4.37 (h, *J* = 8.2 Hz, 1H), 2.69 (t, *J* = 13.3 Hz, 2H), 2.57 (t, *J* = 13.3 Hz, 2H), 2.41 (td, *J* = 8.2, 3.0 Hz, 2H), 2.25 (td, *J* = 8.2, 3.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ = 165.9, 134.8, 131.5, 128.6, 127.7, 120.8 (t, *J* = 279.3 Hz), 47.0 (t, *J* = 21.2 Hz), 46.2 (t, *J* = 21.2 Hz), 41.6, 26.2 (t, *J* = 9.5 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –89.5 ppm; MS (APCI): *m/z* = 252 $[M + H]^+$; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{16}F_2NO$: 252.1199, found: 252.1189.

Acknowledgements

The work was funded by Enamine Ldt. Additional funding from Ministry of Education and Science of Ukraine, Grants No. 19BF037-03 (A.V.D. and O.O.G.) and 21BF037-01M (A.V.C. and O.O.G) is also acknowledged. The authors thank Dr. Eduard Rusanov for X-Ray diffraction studies, Mr. Artem Skreminskiy for LogP measurements, Ms. Olga Kovalenko and Ms. Margaryta Bolgova for pK_a titrations, Dr. Olesya Volovenko and Ms. Iryna Pugach for chiral stationary phase HPLC separation, and Prof. Andrey A. Tolmachev for his encouragement and support.

Keywords: Building blocks • Convergent synthesis • Organofluorine compounds • Small rings • Spiro compounds

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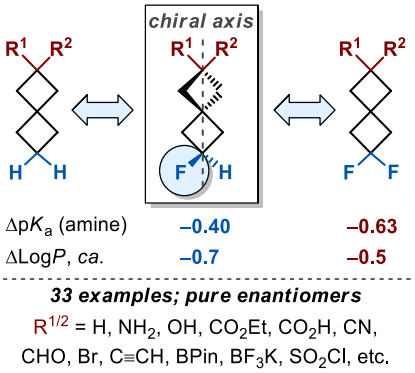
10.1002/ejoc.202100804

Fluorinated spirocycles



The convergent synthesis of a series of mono- and bifunctional 6-fluoro-spiro[3.3]heptanes – advanced fluorine-labelled conformationally rigid building blocks for medicinal chemistry – is developed. The target products were obtained on a multigram scale (up to 302 g), characterized (p*Ka*, Log*P*, and S_w), and assessed with the lead-likeness criteria.

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