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Synthesis of α,α-Difluoro-β-amino Esters or *gem*-Difluoro-β-lactams as Potential Metallocarboxypeptidase Inhibitors

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The synthesis of *gem*-difluorinated β-lactams and *gem*-difluorinated β-amino acids, each possessing a potential basic functional group, from ethyl bromodifluoroacetate and either imines (for β-lactams) or *N*-(α-aminoalkyl)benzotriazoles (for β-amino esters) was investigated. A series of these compounds were used for the design of novel metallocarboxypeptidase inhibitors. *N*-Alkylation and *N*-acylation of these two versatile scaffolds were carried out, leading to the expected targets in moderate to good yields.

Introduction

Introduction of fluorine atoms into bioorganic and bioactive molecules often induces modifications of chemical, physical, and biological properties and as a consequence leads to the generation of novel and potent biological, pharmacological, and chemotherapeutic agents.[1–3] The strength of the C–F bond (485.6 kJ mol^{-1}) confers relative stability against metabolic transformations.[4] Furthermore, the small nature of the steric perturbations produced in the molecule, because of the relative homology of the van der Waals radii of H (1.20 Å) and F (1.47 Å), usually allows them to enter metabolic pathways similarly to the corresponding non-fluorinated compounds. The replacement of hydrogen by fluorine does alter the properties of molecules, however, affecting the basicity or acidity of neighboring groups, lipophilicity/hydrophobicity, hydrogen bonding, dipole moment, and overall reactivity and stability. As a result, a large number of physiologically active compounds and therapeutic agents containing strategically located fluorine atoms are currently widely used or in development.[5]

In the past decade, increasing work has been devoted to the study of nonnatural foldamers and sequence-specific oligomers that mimic various aspects of the folding, organization, and function of polypeptides or biological polymers.[6] In particular, β-amino acids are recognized as pharmacologically important compounds,[7,8] since β-peptides are able to adopt stable and well-organized conformations.[9] Such building blocks provide useful scaffolds for the design of functional mimics of natural proteinic structures. Furthermore, β-peptides are stable to proteolytic degradation in vitro and in vivo,[10] which represents an important advantage over natural peptides and proteins. Moreover, β-amino acids also play key roles in medicinal chemistry as, for example, precursors of pharmacologically important β-lactam antibiotics[11] and components of biologically active unnatural oligopeptides.[12]

Because of the exciting benefits of fluorine substitution and the importance of amino acids in biochemical functions, the area of fluorine-containing amino acids (FAAs) is expanding rapidly, taking a major place in the family of nonnatural amino acids.[13] FAAs are known to show antibacterial activity, to act as proteinase inhibitors, and to exhibit promising properties as candidates for peptide modification.[14] Given the biomedicinal and synthetic potential reported for β-amino acids, and the biological influence of fluorine substitution in the β-position relative to the amino group, it is not surprising that considerable efforts have been devoted to the development of efficient syntheses of *gem*-difluoromethylene compounds,[15] and more specifically of α,α-difluoro-β-amino acids. Replacement of various functional groups by a *gem*-difluoromethylene group has generated potent transition-state-type inhibitors.[16] Several α,α-difluoro-β-amino acids[17] or *gem*-difluorinated peptides[18] have been synthesized and tested as potent competitive serine protease inhibitors or [^{18}F]-radiolabeled markers.[19] The *gem*-difluoromethylene/methylene transposition in the "western" β-amino acid moiety of the naturally

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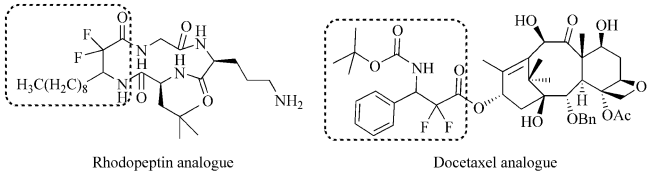
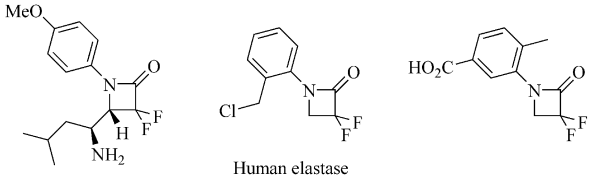
occurring antifungal cyclic tetrapeptide rhodopeptin results in improved activity and novel physical properties (Scheme 1).[20] Incorporation of fluorinated β-amino acids in the side chain of analogues of Docetaxel (Taxotere®) was investigated to improve the cytotoxicity of this chemotherapy drug (Scheme 1).[21] The introduction of a β-amino acid bearing one or two fluorine atoms in its 2-position into a β-peptide chain induces an alteration of the neighboring electronic environment without incurring steric constraints. Such modifications improve stability against enzymatic degradations and can beneficially influence the biological activity.[22]



Scheme 1. Examples of introduction of β-amino acid moieties into bioactive compounds.

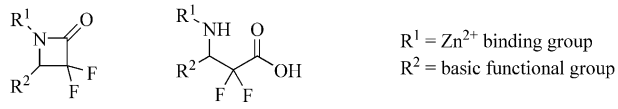
The azetidin-2-one (β-lactam) skeleton has attracted significant interest among synthetic and medicinal chemists, mainly because it is the core of natural and nonnatural antibiotics. Great efforts have been dedicated to the synthesis of new types of β-lactams to address the bacterial resistance of some of these drugs.[23] To tackle this growing problem, the introduction of fluorine, in particular of the difluoromethylene moiety, into the azetidinone structure has been suggested because of the unique changes produced in physiochemical, and consequently biological, behavior. 3,3-Difluoroazetidin-2-ones have been already synthesized, and some of them have demonstrated potential biological activities[18a,24] (Scheme 2) or have turned out to be versatile synthetic intermediates and useful building blocks.[25,26] The growing interest in 3,3-difluoroazetidines[27] is illustrated by their potential therapeutic inhibitory activity towards dipeptidyl peptidase-IV for the antihyperglycaemic treatment of type 2 diabetes.[28]



Scheme 2. Examples of bioactive 3,3-difluoroazetidin-2-ones.

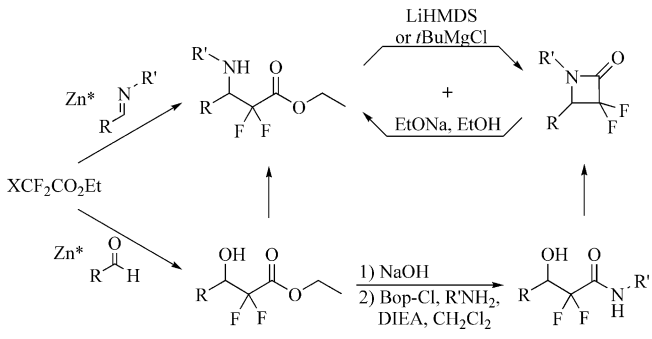
The importance and usefulness of β-lactams as versatile synthetic intermediates has also been widely recognized with the development of the "β-lactam synthon method"[29] for the preparation of various amino acids, peptides, peptidomimetics, human cytomegalovirus protease inhibitors based on activated carbonyl groups,[30] cholesterol absorption inhibitors,[31] and other types of compounds of biological and medicinal interest.

In the course of a medicinal chemistry program devoted to the synthesis of basic metallocarboxypeptidase inhibitors, we were interested in small and original molecules. In this study we report the synthesis and functionalization of α,α-difluoro-β-amino acid and 3,3-difluoroazetidin-2-one templates. Our strategy was based on the salt bridge interactions between the *C*-terminal carboxylate of the substrate and the basic residues of the active site of the carboxypeptidase. 3,3-Difluoroazetidin-2-ones can be regarded as the masked forms of *gem*-difluoroacetyl functional groups, and have turned out to be prodrugs for the corresponding β-amino acids. Since a metalloprotease substrate requires a zinc-binding group (ZBG) for coordination with the catalytic zinc atom of the active site, it was decided to use the neutral thiol moiety and the carboxylic acid function as ZBG. We were therefore interested in molecules of small size and high water solubility possessing a carboxylate or a thiol as zinc-chelating group and a basic functional group. β-Substituted α,α-difluoro-β-amino acids and 3,3-difluoroazetidin-2-ones are attractive scaffolds for the design of novel metallocarboxypeptidase inhibitors (Scheme 3).



Scheme 3. Design of potent metallocarboxypeptidase inhibitors.

Several general methodologies for the syntheses of the 3,3-difluoroazetidin-2-one and α,α-difluoro-β-amino ester skeletons have been developed. Among them, Reformatsky-type reactions[32] with ethyl halodifluoroacetate are usually applied either with carbonyl compounds or with imines, thus leading to β-hydroxy esters and β-amino ester/β-lactam mixtures,[33] respectively (Scheme 4). In the first case, the pathways mainly involve either a two-step strategy with conversion of the formed 2,2-difluoro-3-hydroxy esters into the desired 2,2-difluoro-3-hydroxypropionamides[21a,26,34] or hydroxamates,[18a] followed by internal N1–C4 cyclization or the replacement of a hydroxy group by different nucleophiles[21a,35] under Mitsunobu conditions. In the second case, condensation of the appropriate Reformatsky reagents derived from ethyl bromodifluoroacetate with aldimines or synthetic equivalents can lead, depending on the



Scheme 4. General strategies directed towards the production of 3,3-difluoroazetidin-2-ones and α,α-difluoro-β-amino esters through Gilman–Speeter and Reformatsky reactions.

reaction conditions and/or the substitution of the substrate, either to the β-amino ester or 3,3-difluoroazetidin-2-one derivatives or to mixtures of these two products (these are difficult to separate in most cases).[18b,34c,36] The Gilman–Speeter reaction, also called ester-imine condensation, has emerged as a powerful approach for the synthesis of *gem*-difluoro-β-amino carbonyl compounds, mainly in their racemic forms, but also in the enantiomerically pure series.[25b–25d,37]

We recently disclosed the stereoselective and chemoselective preparation of 3,3-difluoroazetidin-2-ones and α,α-difluoro-β-amino acids.[38] The key transformation is the addition, with high levels of stereoselectivity (up to 98%), of the organozinc reagent derived from ethyl bromodifluoroacetate to chiral 1,3-oxazolidines or aldimines derived from aliphatic and aromatic aldehydes, and either (*R*)-phenylglycinol or (*R*)-methoxyphenylglycinol.

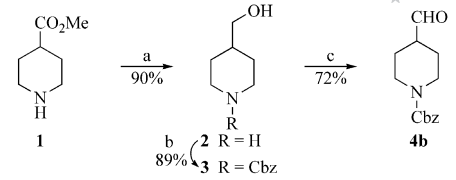
To extend the usefulness of this type of reaction in the synthesis of biologically active compounds, we now report our results relating to the straightforward and chemoselective synthesis of β-lactams and β-amino esters derived from several aldehydes bearing basic functional groups. We have also investigated the introduction of thiol and carboxylate zinc-binding groups in good to excellent yields by *N*-alkylation of β-lactams and *N*-acylation of β-amino esters.

Results and Discussion

To develop original compounds as novel metallocarboxypeptidase inhibitors, we prepared a series of β-lactams and β-amino esters substituted (R^2, Scheme 3) with protected or unprotected basic groups [namely pyridin-3-yl, pyridin-4-yl, piperidin-4-yl, and 4-(aminomethyl)benzyl groups]. Such functional groups can be introduced by use of the corresponding aldehydes.

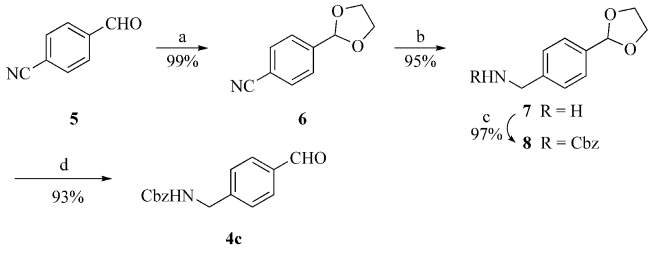
Preparation of Starting Aldehydes

The Cbz-protected piperidine-4-carbaldehyde **4b** was prepared by the synthetic route outlined in Scheme 5. Reduction of commercially available methyl isonipecotate (**1**) with $LiAlH_4$ in THF gave **2** in 90% yield.[39] The protection of (piperidin-4-yl)methanol as its Cbz derivative followed by Swern oxidation afforded aldehyde **4b** in 58% overall yield.[40]



Scheme 5. (a) $LiAlH_4$, THF, room temp.; (b) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, room temp.; (c) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2, –60 °C → room temp.

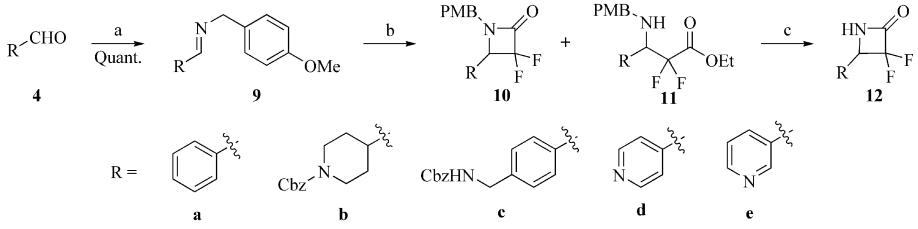
Cbz-protected 4-(aminomethyl)benzaldehyde derivative **4c** was prepared from 4-cyanobenzaldehyde (**5**) in a four-step sequence as shown in Scheme 6. Formation of dioxolane-type acetal **6** was followed by the reduction of the cyano group.[41] The primary amine **7** was converted into the corresponding *N*-Cbz-protected amine and was then subjected to mild acidic conditions to remove the acetal in 93% yield.[42]



Scheme 6. (a) Ethylene glycol, PTSA, toluene, reflux; (b) $LiAlH_4$, THF, 0 °C → 65 °C; (c) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, room temp.; (d) AcOH, H_2O, room temp.

Synthesis of *gem*-Difluoro-β-lactams and -β-amino Esters

Racemic *N*-deprotected 3,3-difluoroazetidin-2-ones can be efficiently prepared in a three-step route based on Gilman–Speeter reactions between the Reformatsky reagent derived from ethyl bromodifluoroacetate and the appropriate aldimines (Scheme 7). (*p*-Methoxybenzyl)amine was used, because the PMB protecting group can be easily removed under mild conditions. The imines were easily prepared by condensation of the appropriate arene-, heterocycle-, and alkanecarbaldehydes **4a**–**e** and (*p*-methoxybenzyl)-amine in CH_2Cl_2 in the presence of $MgSO_4$, and were isolated quantitatively without further purification. Compounds **9a**–**e** were treated with ethyl bromodifluoroacetate (2 equiv.) in the presence of freshly activated Zn dust in



Scheme 7. Synthesis of 3,3-difluoroazetidin-2-ones. (a) $MgSO_4$, *p*-$MeOC_6H_4CH_2NH_2$, CH_2Cl_2, room temp.; (b) $BrZnCF_2CO_2Et$, THF, reflux; (c) CAN, CH_3CN, H_2O, 0 °C.

THF at reflux over 2 h, leading to the expected products in high yields. In situ activation of zinc, performed with dibromoethane and chlorotrimethylsilane at room temp., and preparation of the organozinc reagent prior to the addition of the aldimine led to higher yields under milder conditions.[43] The results are summarized in Table 1. The difluoroazetidin-2-ones **10** were the major or the only isolated products except in the case of **9c**, in which a particular result was observed (Table 1, Entry 3): a 1:1 β-lactam **10c**/β-amino ester **11c** ratio was obtained in good overall yield. As previously described by our group,[38b] the presence of a primary carbamate greatly disfavored the cyclization step. Pyridine derivatives **9d** and **9e** each gave 10% yields of α,α-difluoro-β-amino esters **11d** and **11e**, which could not be eliminated after purification on silica gel by flash chromatography. Nevertheless, this noncyclized byproduct was degraded during the oxidative debenzylation step. Deprotection was then carried out by a classical procedure with 3 equiv. of ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water in a 9:1 ratio, leading to racemic azetidin-2-ones **12a**–**e** in moderate to good yields.[44]

Table 1. Preparation of azetidin-2-ones **10** and **12**.

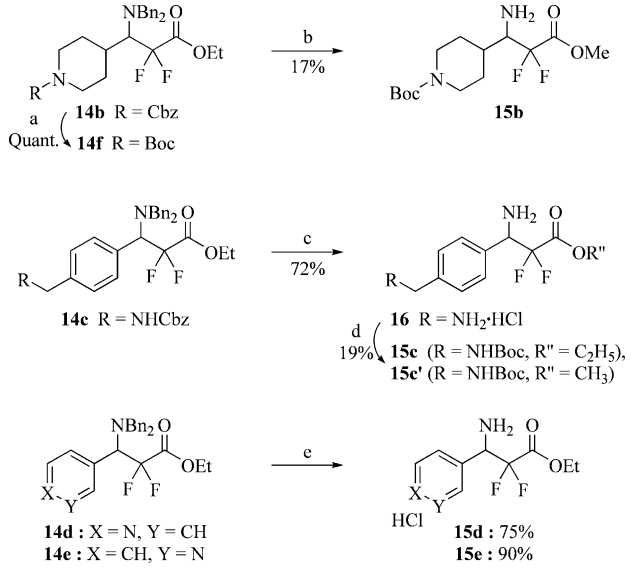
Entry	Starting aldehyde	Yield **10** + **11** [%][a]	Ratio **10**/**11** [%][b]	Yield **12** [%][c]
1	**4a**	74	100:0	83[d]
2	**4b**	70	100:0	38
3	**4c**	72	52:48[e]	43
4	**4d**	85[f]	89:11[g]	62[h]
5	**4e**	86[f]	90:10[g]	49[h]

[a] Global isolated yield. [b] Ratios determined by ^{19}F NMR spectroscopy. [c] Isolated yield from β-lactam **10**. [d] See ref.[38a] for full characterization. [e] The two products can be separated on silica gel. [f] See ref.[37b] for full characterization of this product. [g] Not separable by silica gel flash chromatography. [h] See ref.[38b] for full characterization.

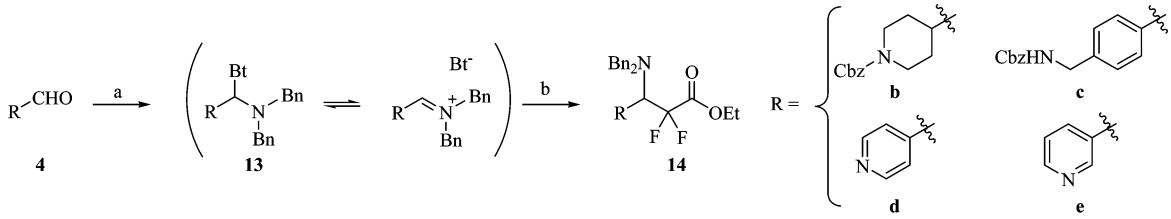
As we were looking for an efficient and short way to prepare β-amino ester derivatives in a selective manner, we decided to investigate Katritzky's procedure,[36c] using the ethyl bromodifluoroacetate zinc derivative and *N*-(α-aminoalkyl)benzotriazoles for the preparation of α,α-difluoro-β-amino esters.

N-(α-Aminoalkyl)benzotriazoles **13** (Scheme 8), easily prepared from dibenzylamine, benzotriazole, and aldehydes **4b**–**e**, were used without purification as iminium salt precursors in Katritzky's methodology.[45] To our delight, benzotriazole-mediated aminoalkylations provided protected α,α-difluorinated β-amino esters **14b**–**e** in high yields through Reformatsky reactions with ethyl bromofluoroacetate, activated zinc, and trimethylsilyl chloride in THF at reflux.

We then turned our attention to the conversion of dibenzylated amines into primary amines by catalytic hydrogenolysis (Scheme 9). Selective removal of benzyl protecting groups from **14b** was achieved by a two-step route. Hydrogenolysis of the Cbz group followed by in situ Boc protection gave **14f** in quantitative yield. Debenzylation of the tertiary amine by hydrogenolysis in the presence of Pearlman's catalyst in ethanol or in a mixture of ethanol and ethyl acetate was inefficient, and a complex mixture of products was obtained, due to transcarbamoylation. Other conditions such as catalytic transfer hydrogenation with cyclohexene turned out to be inefficient in our case.[46] Hydrogenolysis of the two benzyl protecting groups was finally carried out with the following combination: H_2 (1 bar)/Pearlman's catalyst/EtOH/MeOH/room temp. to afford the β-amino ester **15b** in 17% yield.



Scheme 9. (a) H_2 (1 bar), Boc_2O, Pd/C, EtOH, 40 °C; (b) H_2, $Pd(OH)_2$/C, EtOH/MeOH, 40 °C; (c) H_2 (1 bar), Pd/C, EtOH, AcOEt, HCl/*i*PrOH (6 N), 40 °C; (d) Boc_2O (1 equiv.), Et_3N, CH_2Cl_2, room temp.; (e) H_2 (1 bar), Pd/C, EtOH, HCl/*i*PrOH (6 N), room temp.



14	b	c	d	e
Yield [%][a]	83	60	82	81

[a] Global isolated yield from aldehydes **4**.

Scheme 8. Synthesis of β-branched ethyl 3-(dibenzylamino)-2,2-difluoropropanoates. (a) Bn_2NH, BtH, EtOH, 78 °C; (b) $BrZnCF_2CO_2Et$, TMSCl, THF, 67 °C.

Removal of the benzyl functional groups in **14c** was achieved by hydrogenolysis [Pearlman's catalyst, H_2 (1 bar), EtOH, AcOEt, HCl/*i*PrOH 6 N, 40 °C] to afford diamine **16** as a monochloride salt (72%). Selective protection with Boc_2O (1 equiv.) was tentatively carried out in a conventional manner but was not selective enough, so **15c** (and its methyl analog **15c′** obtained by transesterification of **15c** during the purification process due the presence of methanol in the eluent composition) was isolated in only 19% yield. Cleavage of the benzyl groups in **14d** and **14e** was best achieved by hydrogenolysis in the presence of Pd/C catalyst under 1 bar of hydrogen in EtOH and HCl/*i*PrOH (6 N) to afford **15d** and **15e** in excellent yields.

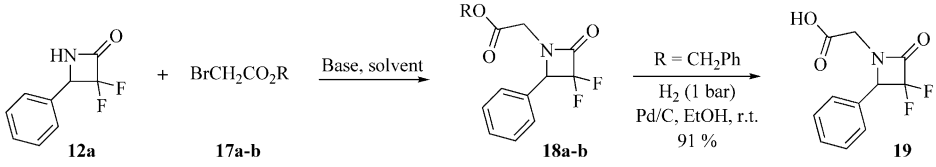
N-Alkylation of *gem*-Difluorinated β-Lactams

N-Alkylation of β-lactams **12a**–**e**, as required for the preparation of potential metallocarboxypeptidase inhibitors, was then investigated. A review of the literature revealed that *N*-alkylation of *N*-unsubstituted β-lactams was not consistently efficient.[47] Strong bases (such as NaH,[48] $NaNH_2$, *t*BuOK,[49] *n*BuLi,[50] or LiHMDS[51]) have been employed with basic scaffolds, but such basic conditions induce either polymerization of azetidin-2-ones or epimerization of chiral centers (especially at C-3). Alkylation under less basic conditions have been described either with organic non-nucleophilic bases such as Et_3N or DIEA or with inorganic bases (K_2CO_3 in acetone,[52] Cs_2CO_3 in MeCN,[53] CsF in DMF,[54] Ag_2O in MeCN[55]). These milder conditions were compatible with various functionalities and prevented potential epimerization. However, only highly reactive electrophiles gave satisfactory levels of conversion and yields, probably because of the low nucleophilicity of the nitrogen atom. Good yields can be obtained by phase-transfer catalysis methodology (KOH/nBu$_4$NBr/THF) as described by Reuschling et al.,[56] despite the risks of side reactions or nucleophilic opening of the β-lactam ring.

In order to find the best conditions for alkylation, we first turned our attention to the introduction of the carboxylate moiety with bromoacetate esters (**17a**: R = methyl, **17b**: R = benzyl). The required side chain can be introduced by base-mediated alkylation of the nitrogen atom in a 1-unsubstituted 3,3-difluoroazetidin-2-one. To the best of our knowledge, only one example of such a strategy has been reported. De Kimpe[57] described the synthesis of *N*-substituted *gem*-difluorinated azetidinones under phase-transfer conditions.

The *N*-alkylation of model β-lactam **12a** was therefore carefully optimized by varying the electrophile, the base, and experimental conditions (Scheme 10, Table 2). Extensive experimentation showed that numerous sets of conditions were either unsuccessful or gave inconsistent results. Treatment with strong bases such as NaH or LDA proved to be inefficient. Attempts with KOH in homogeneous or heterogeneous systems induced complete β-lactam degradation. Functionalization of **12a** under the phase-transfer conditions described by De Kimpe[57] turned out to be inefficient in our case. Whereas Hünig's base caused rapid degradation and triethylamine gave low levels of conversion, treatment of β-lactam **12a** with methyl or benzyl bromoacetates, and tetramethylguanidine in the presence of TBAI (tetrabutylammonium iodide) provided the *N*-substituted azetidin-2-ones **18a** and **18b** in excellent yields (Table 2, Entries 5–6).

In order to introduce a sulfhydryl group as a Zn-chelating function, we then applied these conditions to *S*-(3-bromopropyl)thioacetate.[58] Unfortunately, none of these experimental conditions allowed access to the corresponding *N*-substituted β-lactam, due to the poor electrophilicity of this alkylating agent. We next examined deprotection of **18a** and **18b** in order to obtain functionalized *N*-substituted lactams. Compound **18a** was subjected to various sets of acidic or basic conditions in order to carry out saponification. In most cases, we observed rapid degradation of the β-lactam skeleton. However, when benzyl ester **18b** was subjected to hydrogenolysis conditions (H_2, Pd/C), we were pleased to observe the formation of 2-oxoazetidin-1-ylacetic acid **19** in 91% yield.



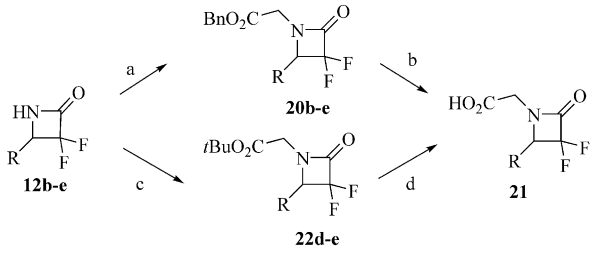
Scheme 10. Synthesis of *N*-substituted azetidin-2-ones.

Table 2. Optimization of the *N*-alkylation step.

Entry	Base [equiv.]	$BrCH_2CO_2R$ [equiv.]	Solvent	Temperature	Time [h]	**18**, yield [%]
1	*t*BuOK (1.6)	**17a** (1.5)	THF	0 °C → room temp.	20	**18a**, 37[a]
2[b]	KOH (2)	**17a** (1.5)	THF	room temp.	20	**18a**, 50[c]
3	CsF (10)	**17a** (3)	DMF	room temp.	72	**18a**, 10[c]
4	Et_3N (1)	**17a** (10)	THF	room temp.	14	**18a**, 20[c]
5[b]	TMG[d] (2)	**17a** (10)	THF	room temp.	6	**18a**, quantitative
6[b]	TMG[d] (2)	**17b** (10)	THF	room temp.	18	**18b**, 91[a]

[a] Isolated yields. [b] Addition of 0.5 equiv. of TBAI. [c] Conversion determined by ^{19}F NMR relative to **12a**. [d] 1,1,3,3-Tetramethylguanidine.

This synthetic strategy was then applied to several highly functionalized 3,3-difluoroazetidin-2-ones (Scheme 11). With this goal, we performed alkylation of β-lactams **12b**–**e** with benzyl bromoacetate **17b** under previously optimized conditions, to provide **20b**–**e** in moderate to excellent yields (Table 3).



Scheme 11. (a) $BrCH_2CO_2Bn$, TMG, TBAI, MeCN, room temp.; (b) H_2, Pd/C, EtOH, room temp.; (c) $BrCH_2CO_2tBu$, TMG, TBAI, MeCN, room temp.; (d) TFA, CH_2Cl_2, 0 °C.

Table 3. Syntheses of functionalized 3,3-difluoroazetidinones.

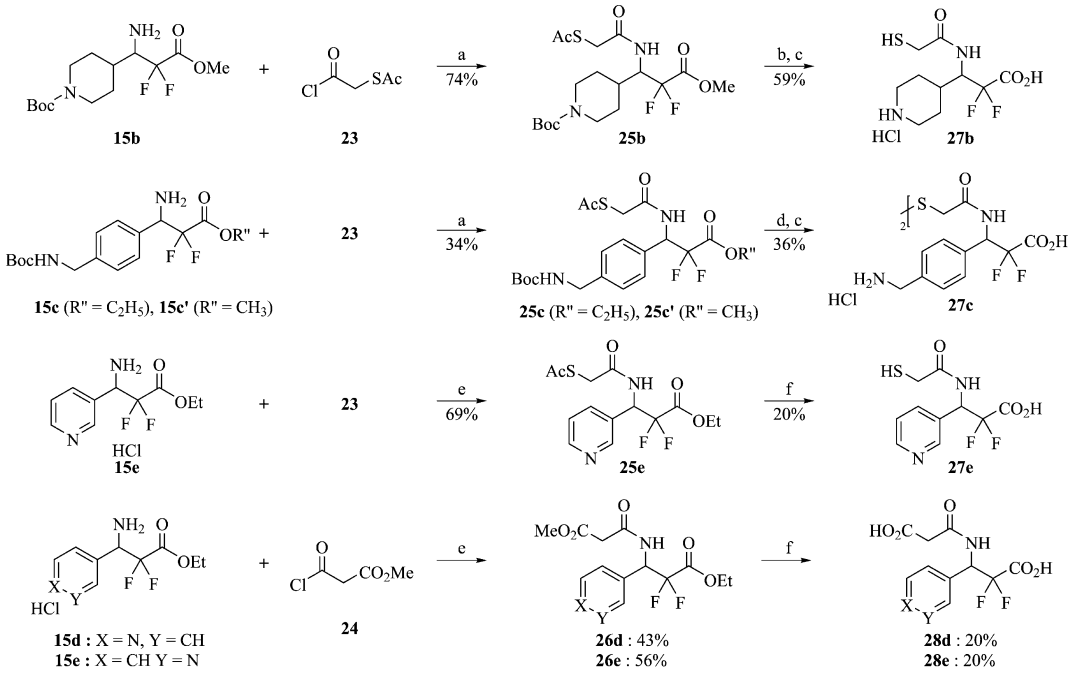
Entry	Substrate	Alkylation agent [equiv.]	R	**20** or **22**, yield [%][a]	**21**, yield[%][b]
1	**12b**	**17b** (37)	Bn	**20b**, 30	**21b**, 50
2	**12c**	**17b** (11)	Bn	**20c**, 95	**21c**, 25
3	**12d**	**17b** (1.1)	Bn	**20d**, 29	n.r.[c]
4	**12e**	**17b** (1.1)	Bn	**20e**, 50	n.r.[c]
5	**12d**	**17c** (1.1)[d]	*t*Bu	**22d**, 47	**21d**, 44[e]
6	**12e**	**17c** (1.1)[d]	*t*Bu	**22e**, 50	**21e**, 56[e]

[a] Isolated yield. [b] Isolated yield after purification by gel permeation chromatography. [c] No reaction under atmospheric pressure of hydrogen, and higher pressure induced the slow formation of unidentified compounds. [d] Use of NaI (1 equiv.) instead of TBAI. [e] Partial degradation: formation of β-amino acids produced by cleavage of the N–C(O) bond in the β-lactam intermediate by water during purification.

In the case of pyridinyl derivatives (**12d** and **12e**), 1 equiv. of benzyl bromoacetate was used in order to minimize alkylation of the pyridine ring. Treatment of **20b** and **20c** with hydrogen in the presence of Pd/C resulted in removal of the *N*-Cbz protecting group and the labile benzyl ester to afford amino acids **21b** and **21c** (Scheme 11). Unexpected partial degradation occurred during hydrogenolysis of **20c**, leading to the cleavage of the N1–C4 bond of the β-lactam ring and the isolation of the corresponding amido acid. Disappointingly, removal of the benzyl ester protecting groups from compounds **20d** and **20e** with Pd/C hydrogenation systems turned out to be ineffective, whereas higher pressures of hydrogen induced side reactions. To circumvent this problem, we investigated the synthesis of *tert*-butyl esters that could be used to facilitate deprotection of the carboxylate. Subsequent treatment of azetidin-2-ones **12d** and **12e** with *tert*-butyl bromoacetate (**17c**) and TMG in MeCN afforded *N*-alkylated products (**22d** and **22e**) in 50% yield. Acidic deprotection (50% TFA/CH_2Cl_2) of these compounds afforded the acids, which were purified by gel permeation chromatography to recover β-lactams **21d** and **21e** in 44% and 56% yields, respectively.

N-Acylation of *gem*-Difluorinated β-Amino Acids

In an effort to synthesize novel potential metallocarboxypeptidase inhibitors, we decided to develop a family of sulfhydryl acids containing basic groups. We envisioned the preparation of these targets by *N*-acylation of the β-amino



Scheme 12. (a) DIEA, DMAP, CH_2Cl_2, room temp.; (b) 50% TFA, CH_2Cl_2, 0 °C; (c) NaOH, H_2O, MeOH, room temp.; (d) $HCl_{(g)}$, MeOH, room temp.; (e) Et_3N, DMAP, CH_2Cl_2, room temp.; (f) LiOH, H_2O, MeOH, THF, 0 °C.

acids derived from α,α-difluorinated β-amino esters **15b**–**e**, since these molecules are highly useful synthetic intermediates for the insertion of zinc-binding groups. We were interested in the introduction of thiol and carboxylate functionalities.

This strategy thus required the use of a highly reactive electrophile in order to overcome the rather low reactivity of the deactivated amine due to the inductive effect of the neighboring CF_2 moiety.

Keeping the aforementioned goals in mind, we decided to use acyl chlorides bearing masked sulfhydryl or carboxylic functions. Starting from mercaptoacetic acid, we therefore prepared (acetylsulfanyl)acetic acid (**23**; Scheme 12) by acetylation with Ac_2O and Et_3N, followed by the action of oxalyl chloride in CH_2Cl_2 at room temperature, in 43% overall yield.[59] Commercially available methyl malonyl chloride (**24**) proved to be an excellent starting material for the introduction of a carboxyl group.

The synthesis of the series of sulfhydryl acids **27** was carried out by starting from the appropriately substituted *gem*-difluorinated β-amino esters **15b**–**e** (Scheme 12). Addition of (acetylthio)acetyl chloride (**23**) in the presence of catalytic DMAP gave the acylated compounds **25b**–**e** in moderate to good yields. The thioester **25b** was then converted into the thiol **27b** by Boc deprotection with 50% TFA/CH_2Cl_2 followed by basic deprotection with aqueous NaOH in 59% yield. Removal of the protecting groups of **25c** and **25c′** with methanolic HCl followed by treatment with aqueous NaOH gave disulfide **27c** in moderate yield. In addition to rapid and unavoidable oxidation of thiol functionality, the amide bond proved to be particularly weak, and, as a consequence, the corresponding β-amino acid was isolated in only 20% yield. Deprotection of **25e** with aqueous LiOH afforded **27e**.

With an effective sequence to hand, a similar route was used for diacid compounds **28d** and **28e**, but methyl malonyl chloride (**24**) was used instead of **23**. Treatment with triethylamine in CH_2Cl_2 resulted in acylation to give diesters **26d** and **26e** in good yields, and these were then hydrolyzed to diacids. Unfortunately, due to an arduous purification, the yields of **28d** and **28e** were only 20%.

Conclusions

We succeeded in the synthesis of the target molecules displaying specific features in the course of our medicinal program devoted to the synthesis of basic metallocarbopeptidase inhibitors. A general synthetic route, in the racemic series, of various *gem*-difluoro-β-lactams and -β-amino esters, possessing different basic groups, has been successfully developed. *N*-Alkylation of *gem*-difluoro-β-lactams and *N*-acylation of *gem*-difluoro-β-amino esters were carried out, leading, in moderate to good yields, to the expected potential basic metallocarbopeptidase inhibitors.

Experimental Section

Abbreviations: AcOH = acetic acid; Boc = *tert*-butoxycarbonyl; BopCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride; BtH = 1*H*-benzotriazole; CAN = ceric ammonium nitrate; Cbz = benzyloxycarbonyl; CH_2Cl_2 = dichloromethane; CI = chemical ionization; DIEA = *N*,*N*-diisopropylethylamine; DMAP = 4-(dimethylamino)-pyridine; DMF = dimethyl formamide; DMSO = dimethyl sulfoxide; EI = electron impact ionization; ESI = electrospray ionization; EtOAc = ethyl acetate; FAAs = fluorine-containing amino acids. IR = infrared; LDA = lithium diisopropylamide; LiHMDS = lithium hexamethyldisilazide; MeCN = acetonitrile; MeOH = methanol; MS = mass spectrometry; NMR = nuclear magnetic resonance; PMB = *p*-methoxybenzyl; PTSA = *p*-toluenesulfonic acid; TBAI = tetrabutylammonium iodide; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography; TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine; TMSCl = chlorotrimethylsilane; ZBG = zinc-binding group; Zn* = activated zinc dust.

General: Unless otherwise mentioned, all the reagents were purchased from commercial sources and used as received. All glassware was dried in an oven at 100 °C prior to use. THF was distilled from sodium/benzophenone ketyl under nitrogen prior to use. Dichloromethane (CH_2Cl_2) was distilled under nitrogen from P_2O_5 prior to use. DMSO and MeCN were distilled under nitrogen from CaH_2, and DMF from BaO. NMR spectra were recorded with a Bruker DXP 300 instrument. ^{1}H NMR chemical shifts (300.13 MHz) are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (δ = 0 ppm) in $CDCl_3$. ^{13}C NMR chemical shifts (75.47 MHz) are expressed in parts per million downfield from $CDCl_3$ as internal standard (δ = 77.16 ppm). ^{19}F NMR chemical shifts (282.40 MHz) are expressed in parts per million downfield from $CFCl_3$ as internal standard (δ = 0 ppm). Coupling constants *J* are reported in Hertz. Abbreviations used for peak multiplicity are: br.: broad; s: singlet; d: doublet; t: triplet; q: quadruplet; m: multiplet. Progress of the reactions was monitored by TLC on Merck silica gel plates (thickness 0.2 mm with fluorescence indicator $60F_{250}$). Flash column chromatography purifications were carried out on 40–63 mesh silica gel 60A by "flash" methodology. Silica TLC plates were visualized under UV light, by use of a solution of phosphomolybdic acid in ethanol (10%) followed by heating, or by use of a solution of aqueous alkaline potassium permanganate (1 N) and heating. Values of R_f were measured after an elution of 6 cm. Infrared (IR) spectra were recorded with a Perkin–Elmer 1420 instrument. Absorption bands are reported in cm^{-1}. Elemental analyses were performed with a Carlo Erba 1106 instrument. Melting points are uncorrected. Mass spectra were performed with a Thermofinnigan Navigator 2.1 instrument for electrospray or with a JEOL AX500 instrument (isobutane, 200 eV) for CI. HRMS measurements were performed with a JEOL AX500 spectrometer.

Starting Materials: All substrate imines were readily synthesized by condensation of the appropriate aldehyde with (*p*-methoxybenzyl)-amine according to the following procedure. Anhydrous $MgSO_4$ (2 g) and the appropriate aldehyde (1 equiv.) were added at ambient temperature to a solution of the corresponding amine (10 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 12 h. The solids were filtered by suction, and the filtrate was washed with CH_2Cl_2 (2 × 20 mL). The corresponding imine was recovered quantitatively after concentration under reduced pressure, and was used without purification. Activated zinc was prepared by stirring a quantity of zinc dust in dilute hydrochloric acid for about 5 min. The zinc was then filtered off, washed neutral with deionized water, with ethanol, with acetone, and with diethyl ether, and dried at 100 °C under vacuum.[32a] All *N*,*N*-disubstituted 1*H*-benzotriazolylamines were synthesized according to the following general procedure. Dibenzylamine (3.21 g, 30 mmol) and the appropriate aldehyde (30 mmol, 1 equiv.) were successively added to

a solution of 1*H*-benzotriazole (3.57 g, 30 mmol, 1 equiv.) dissolved in a minimum amount of ethanol (ca. 5 mL). The mixture was heated at reflux for 4 h in the presence of dried molecular sieves (3 Å, 1 g), and then stirred at room temp. for 12 h. After removal of molecular sieves by suction filtration through a pad of Celite and concentration of the filtrate under vacuum, the obtained solid could be recrystallized from ethanol.

(Piperidin-4-yl)methanol (2): A solution of methyl isonipecotate (**1**, 10 mL, 74 mmol) in anhydrous THF (80 mL) was slowly added under argon to an ice-cooled suspension of $LiAlH_4$ (3.5 g, 92.2 mmol, 1.25 equiv.) in anhydrous THF (250 mL). After the visible gas evolution had ceased, the mixture was left standing at room temp. for 20 h. After treatment with water (4 mL), aqueous NaOH solution (1 N, 4 mL), and water (8 mL), and stirring with diethyl ether (200 mL) for 30 min, the slurry was filtered and washed with diethyl ether (2 × 100 mL). The organic fraction was dried with $MgSO_4$, and the solvents were removed under vacuum to afford the title compound as a colorless oil; yield 7.67 g (90%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 3.42 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 3.05 (dt, $^3J_{H,H}$ = 3, $^2J_{H,H}$ = 12 Hz, 2 H), 2.56 (td, $^3J_{H,H}$ = 2.5, $^2J_{H,H}$ = 12 Hz, 2 H), 2.15 (br. s, 2 H), 1.75–1.65 (m, 2 H), 1.65–1.50 (m, 1 H), 1.10 (ddd, $^3J_{H,H}$ = 4, $^3J_{H,H}$ = 13, $^2J_{H,H}$ = 25 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 68.3, 46.6, 39.4, 30.2 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3368, 1634, 1039 cm^{-1}. MS (EI+): *m*/*z* (%) = 115.0 [M]$^+$. $C_6H_{13}NO$ (115.18): calcd. C 62.57, H 11.38, N 12.16; found C 62.09, H 11.44, N 12.28.

Benzyl 4-(Hydroxymethyl)piperidine-1-carboxylate (3): Amine **2** (7.67 mmol, 66.6 mmol) was dissolved in CH_2Cl_2 (230 mL) at 0 °C. A solution of Na_2CO_3 (32 g, 302 mmol, 4.5 equiv.) in water (230 mL) was added. Benzyloxycarbonyl chloride (10 mL, 72 mmol, 1.1 equiv.) was added dropwise. After the system had been stirred at room temp. for 12 h, ice-cold water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, filtered, dried with $MgSO_4$, and concentrated in vacuo to give the crude material. Silica gel flash column chromatography [CH_2Cl_2/EtOAc (8:2 to 6:4) as eluent] gave pure **3** as a colorless oil; yield 14.78 g (89%); TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.39. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.45–7.35 (m, 5 H), 5.19 (s, 2 H), 4.35–4.20 (m, 2 H), 3.55 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 2.90–2.80 (m, 2 H), 1.85–1.75 (m, 2 H), 1.75–1.65 (m, 1 H), 1.30–1.15 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 155.2, 136.7, 128.4, 127.9, 127.7, 67.3, 66.9, 43.8, 38.6, 28.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3432, 1697, 1439, 1247, 1215, 1038 cm^{-1}. MS (EI+): *m*/*z* = 249 [M]$^{+\cdot}$, 204, 158, 142, 91. $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45, H 7.68, N 5.62; found C 67.90, H 7.57, N 5.14.

1-(Benzyloxycarbonyl)piperidine-4-carboxaldehyde (4b): A stirred solution of freshly distilled DMSO (13.3 mL, 187.3 mmol, 4.5 equiv.) in anhydrous CH_2Cl_2 (70 mL) was cooled to –78 °C. A solution of oxalyl chloride (5.3 mL, 61.8 mmol, 1.5 equiv.) in dry CH_2Cl_2 (10 mL) was then added dropwise, and stirring was continued for 30 min. Next, a solution of alcohol **3** (10.4 g, 41.7 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise over 15 min, and the resultant slurry was stirred at –78 °C for 30 min. *N*,*N*-Diisopropylethylamine (36.1 mL, 217.9 mmol, 5.25 equiv.) was added, and the resultant slurry was stirred at –60 °C for an additional 30 min. The mixture was allowed to warm to room temp. overnight. A solution of NaH_2PO_4 (7.5 g, 64.1 mmol, 1.5 equiv.) in water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). The organic phases were washed with aqueous HCl (1 N, 100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), and were then dried with anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residual product was purified by chromatography on a silica gel column [cyclohexane/EtOAc (9:1 to 6:4) as eluent] to give **4b** as a colorless oil; yield 7.42 g (72%); TLC: silica gel (cyclohexane/EtOAc, 6:4), R_f = 0.38. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 9.64 (s, 1 H), 7.35–7.30 (m, 5 H), 5.10 (s, 2 H), 4.10–3.95 (m, 2 H), 3.00 (dt, $^3J_{H,H}$ = 2.5, $^2J_{H,H}$ = 13 Hz, 2 H), 2.45–2.35 (m, 1 H), 1.95–1.85 (m, 2 H), 1.56 (ddd, $^3J_{H,H}$ = 4, $^3J_{H,H}$ = 11, $^2J_{H,H}$ = 24 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 202.7, 128.5, 128.0, 127.9, 67.1, 47.7, 43.0, 25.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1728, 1698, 1278, 1225 cm^{-1}. $C_{14}H_{17}NO_3$ (247.30): calcd. C 68.00, H 6.93, N 5.66; found C 67.15, H 6.57, N 5.55.

4-(1,3-Dioxolan-2-yl)benzonitrile (6): 4-Cyanobenzaldehyde (**5**, 15 g, 114.4 mmol) was placed in a round flask together with ethyleneglycol (11.5 mL, 206 mmol, 1.8 equiv.), dry toluene (300 mL), and *p*-toluenesulfonic acid as catalyst (1.5 g, 8.7 mmol, 8% with respect to **5**). The solution was heated at reflux in a Dean–Stark apparatus with water trap for 18 h. It was then neutralized with saturated aqueous $NaHCO_3$ solution (100 mL), and the phases were separated. The aqueous layer was extracted with toluene (3 × 50 mL), and the combined organic layers were collected, dried with $MgSO_4$, and filtered. The toluene solution was concentrated under reduced pressure, and the title compound **6** was obtained as a pale yellow solid; yield 20.04 g (99%); m.p. 160 °C (dec.). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.63 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.54 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.80 (s, 1 H), 4.10–3.95 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 142.9, 132.0, 127.0, 118.4, 112.7, 102.2, 65.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2230, 1085, 942 cm^{-1}. MS (EI+): *m*/*z* = 175 [M]$^{+\cdot}$, 144, 130, 103, 73, 51. $C_{10}H_9NO_2$ (175.19): calcd. C 68.56, H 5.18, N 8.00; found C 68.08, H 4.88, N 7.59.

4-(1,3-Dioxolan-2-yl)benzylamine (7): A solution of nitrile **6** (10.6 g, 60.5 mmol) in anhydrous THF (40 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (5.1 g, 127.7 mmol, 2 equiv.) in anhydrous THF (200 mL). The reaction mixture was allowed to warm to room temp., heated at reflux for 4 h, and stirred at room temp. for 12 h. The mixture was then recooled in an ice bath, and diethyl ether was added (200 mL). The mixture was then carefully quenched with water (5 mL), aqueous NaOH solution (1 N, 5 mL), and a second portion of water (10 mL). After 30 min, the white suspension was filtered through a pad of Celite, and concentrated in vacuo to give amine **7** as a yellow oil; yield 10.3 g (95%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.42 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.30 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.77 (s, 1 H), 4.10–4.05 (m, 2 H), 4.05–3.95 (m, 2 H), 3.84 (s, 2 H), 1.58 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 144.3, 136.3, 127.0, 126.6, 103.6, 65.2, 46.2 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3667, 1616, 1081, 943 cm^{-1}. $C_{10}H_{13}NO_2$ (179.22): calcd. C 67.02, H 7.31, N 7.82; found C 66.84, H 7.71, N 7.59.

Benzyl [4-(1,3-Dioxolan-2-yl)benzyl]carbamate (8): A solution of sodium carbonate (19.6 g, 185 mmol, 4 equiv.) in water (60 mL) was added to a solution of amine **7** (8.14 g, 45.4 mmol) in CH_2Cl_2 (140 mL). Benzyl chloroformate (6.5 mL, 45.7 mmol, 1 equiv.) was added dropwise at 0 °C and with stirring. After having been stirred at room temp. for 12 h, the reaction mixture was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were further washed with water (100 mL), saturated aqueous NH_4Cl solution (50 mL), and brine (50 mL), and dried with anhydrous $MgSO_4$. After concentration, **8** was obtained as a pale yellow solid; yield 13.8 g (97%); m.p. 145 °C; TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.25. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.39 (d, $^3J_{H,H}$ = 14.5 Hz, 2 H), 7.35–7.30 (m, 5 H), 7.29 (d, $^3J_{H,H}$ = 14.5 Hz, 2 H), 5.78 (s, 1 H), 5.11 (s, 3 H), 4.37 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 4.15–3.95 (2 × m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 156.4,

139.4, 137.2, 136.4, 128.5, 128.1, 127.5, 126.7, 103.4, 66.9, 65.3, 44.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3280, 1681, 1554, 1260, 1077, 941 cm^{-1}. $C_{18}H_{19}NO_4$ (313.36): calcd. C 69.00, H 6.11, N 4.47; found C 69.14, H 6.29, N 4.41.

Benzyl (4-Formylbenzyl)carbamate (4c): A solution of acetal **8** (13.9 g, 43.9 mmol) in aqueous AcOH (50%, 140 mL) was stirred at room temp. for 12 h. After concentration, flash column chromatography [cyclohexane/EtOAc (9:1 to 6:4) as eluent] gave aldehyde **4c** as a colorless solid; yield 11.0 g (93%); m.p. 68 °C; TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.49. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 9.97 (s, 1 H), 7.82 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.42 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.35–7.30 (m, 5 H), 5.23 (br. s, 1 H), 5.13 (s, 2 H), 4.44 (d, $^3J_{H,H}$ = 6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 191.8, 156.4, 145.4, 136.2, 135.6, 130.1, 128.6, 128.3, 128.2, 127.5, 67.1, 44.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3304, 1682, 1609, 1529, 1253, 1207, 1052 cm^{-1}. $C_{16}H_{15}NO_3$ (269.30): calcd. C 71.36, H 5.61, N 5.20; found C 71.09, H 5.72, N 5.14.

General Procedure for 10b–e. Benzyl 4-[3,3-Difluoro-1-(4-methoxybenzyl)-4-oxoazetidin-2-yl]piperidine-1-carboxylate (10b): A dry, 60-mL Schlenk tube was charged with a suspension of freshly acid-washed zinc dust (4.75 g, 72.7 mmol, 6 equiv.) in anhydrous THF (19 mL) under argon. Chlorotrimethylsilane (460 μL, 5 mol-%) and 1,2-dibromoethane (315 μL, 5 mol-%) were added to the suspension. The mixture was stirred at room temp. for 10 min. Controlled addition of a solution of ethyl bromodifluoroacetate (5 g, 24.6 mmol, 2.05 equiv.) in anhydrous THF (5 mL) was performed with a syringe. A temperature of ca. 50 °C was maintained during the addition (self-heating). After the end of the addition, the reaction mixture was stirred at room temp. for 10 min. A solution of the corresponding imine **9b** (12.1 mmol) in anhydrous THF (8 mL) was added. The reaction mixture was then heated to reflux for 2 h. The reaction mixture was cooled to room temp. and quenched by addition of saturated aqueous NH_4Cl solution (10 mL). After filtration, the aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated under vacuum. The crude product was then purified by flash chromatography on silica gel [cyclohexane/EtOAc (95:5 to 70:30) as eluent] to afford β-lactam **10b** as a yellow oil; yield 3.76 g (70%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.35–7.30 (m, 5 H), 7.10 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 6.87 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 5.09 (s, 2 H), 4.88 (d, $^2J_{H,H}$ = 15 Hz, 1 H), 4.30–4.05 (m, 2 H), 4.03 (dd, J = 2.5, $^2J_{H,H}$ = 15 Hz, 1 H), 3.78 (s, 3 H), 3.55–3.45 (m, 1 H), 2.80–2.60 (m, 2 H), 1.90–1.80 (m, 1 H), 1.70–1.60 (m, 2 H), 1.25–1.10 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 161.4 (t, $^2J_{C,F}$ = 30.5 Hz), 159.6, 155.0, 136.5, 129.5, 128.5, 128.0, 127.9, 125.3, 120.8 (dd, $^1J_{C,F}$ = 285.5, $^1J_{C,F}$ = 291.5 Hz), 114.5, 68.1 (dd, $^2J_{C,F}$ = 22, $^2J_{C,F}$ = 24 Hz), 67.1, 55.2, 45.7, 43.3, 36.0, 28.2 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.5 (d, $^2J_{F,F}$ = 236.5 Hz), –123.6 (dd, $^3J_{F,H}$ = 73, $^2J_{F,F}$ = 236.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1787, 1698, 1514, 1434, 1301, 1249, 1225, 1061, 699 cm^{-1}. $C_{24}H_{26}F_2N_2O_4$ (444.48): calcd. C 64.85, H 5.90, N 6.30; found C 64.99, H 6.03, N 6.09.

Benzyl {4-[3,3-Difluoro-1-(4-methoxybenzyl)-4-oxoazetidin-2-yl]-benzyl}carbamate (10c) and Benzyl 4-{2-(Ethoxycarbonyl)-2,2-difluoro-1-[(4-methoxybenzyl)amino]ethyl}benzylcarbamate (11c): These compounds were prepared according to the above General Procedure, from aldehyde **4c** (1.37 g, 5.1 mmol), (*p*-methoxybenzyl)amine (0.70 g, 5.1 mmol), activated zinc dust (2 g, 30.6 mmol), ethyl bromodifluoroacetate (2.12 g, 10.4 mmol), and anhydrous acetonitrile (16 mL). The crude product was purified by silica gel column chromatography [cyclohexane/EtOAc (85:15 to 70:30) as eluent] to give the β-lactam **10c** as a colorless oil and the β-amino ester **11c** as a white solid; yield 0.89 g and 0.90 g (72% global yield).

β-Lactam 10c: TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.35. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.35–7.25 (m, 7 H), 7.17 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.00 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 6.81 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 5.22 (br. s, 1 H), 5.13 (s, 2 H), 4.86 (d, $^2J_{H,H}$ = 14 Hz, 1 H), 4.65 (dd, $^3J_{H,F}$ = 1.5, $^3J_{H,F}$ = 7 Hz, 1 H), 4.39 (m, 2 H), 3.79 (d, $^2J_{H,H}$ = 14 Hz, 1 H), 3.77 (s, 3 H) ppm. ^{13}C ($CDCl_3$, 75.4 MHz): δ = 160.7 (t, $^2J_{C,F}$ = 30.5 Hz), 159.6, 156.7, 140.5, 137.1, 136.4, 130.9, 129.5, 129.2, 128.5, 128.2, 128.1, 127.7, 120.4 (t, $^1J_{C,F}$ = 292 Hz), 114.4, 67.4 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 26.5 Hz), 66.9, 55.3, 44.6, 43.6 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.8 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 223 Hz), –121.9 (d, $^2J_{F,F}$ = 223 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3340, 1787, 1718, 1612, 1514, 1302, 1249, 1201, 1034 cm^{-1}. $C_{26}H_{24}F_2N_2O_4$ (466.49): calcd. C 66.94, H 5.19, N 6.01; found C 66.88, H 5.45, N 5.91.

β-Amino Ester 11c: M.p. 106 °C; TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.45. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.35–7.25 (m, 9 H), 7.09 (d, $^3J_{H,H}$ = 7 Hz, 2 H), 6.81 (d, $^3J_{H,H}$ = 7 Hz, 2 H), 5.13 (br. s, 2 H), 4.40 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 4.25 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 4.18 (dd, $^3J_{H,F}$ = 6.5, $^3J_{H,F}$ = 21 Hz, 1 H), 3.77 (s, 3 H), 3.69 (d, $^2J_{H,H}$ = 13 Hz, 1 H), 3.42 (d, $^2J_{H,H}$ = 13 Hz, 1 H), 2.07 (br. s, 1 H), 1.26 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 163.9 (dd, $^2J_{C,F}$ = 30.5, $^2J_{C,F}$ = 34 Hz), 158.8, 156.4, 139.0, 136.4, 133.4, 130.9, 129.5, 129.2, 128.5, 128.2, 128.1, 127.7, 115.1 (dd, $^1J_{C,F}$ = 253.5, $^1J_{C,F}$ = 257 Hz), 113.7, 66.9, 62.8, 62.5 (dd, $^2J_{C,F}$ = 21, $^2J_{C,F}$ = 27 Hz), 55.2, 49.9, 44.7, 13.9 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –108.6 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 257 Hz), –121.0 (dd, $^3J_{F,H}$ = 21.5, $^2J_{F,F}$ = 223 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3334 1769, 1703, 1612, 1303, 1250, 1210, 1072, 699 cm^{-1}. $C_{28}H_{30}F_2N_2O_5$ (512.56): calcd. C 65.61, H 5.90, N 5.47; found C 65.13, H 5.55, N 5.38.

3,3-Difluoro-1-(4-methoxybenzyl)-4-phenylazetidin-2-one (10a): Preparation, description, and spectroscopic data for this compound have already been reported in ref.[38a]

3,3-Difluoro-1-(4-methoxybenzyl)-4-(pyridin-4-yl)azetidin-2-one (10d) and Ethyl 2,2-Difluoro-3-[(4-methoxybenzyl)amino]-3-(pyridin-4-yl)propanoate (11d): Preparation, description, and spectroscopic data for these compounds have already been reported in ref.[38b]

3,3-Difluoro-1-(4-methoxybenzyl)-4-(pyridin-3-yl)azetidin-2-one (10e) and Ethyl 2,2-Difluoro-3-(4-methoxybenzylamino)-3-(pyridin-3-yl)propanoate (11e): Preparation, description and spectroscopic data of these compounds have already been reported in ref.[38b]

General Procedure for 12b–e. *rac*-Benzyl 4-(3,3-Difluoro-4-oxoazetidin-2-yl)piperidine-1-carboxylate (12b): CAN (7 g, 12.7 mmol, 3.6 equiv.) was added in small portions at 0 °C to *N*-protected β-lactam **10b** (1.56 g, 3.5 mmol) in a mixture of CH_3CN/H_2O (9:1, 22 mL). After 20 min at 0 °C and 6 h at room temp., the mixture was poured into water (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with $NaHCO_3$ (5%, 100 mL), Na_2SO_3 (10%, 100 mL), $NaHCO_3$ (5%, 100 mL), and finally brine (50 mL). After concentration and flash column chromatography [CH_2Cl_2/EtOAc (95:5 to 80:20) as eluent] the desired racemic product **12b** was obtained as an orange oil; yield 0.43 g (38%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.40–7.30 (m, 5 H), 5.10 (s, 2 H), 5.02 (br. s, 1 H), 4.30–4.10 (m, 2 H), 3.62 (t, $^3J_{H,H}$ = 9, $^3J_{H,F}$ = 9 Hz, 1 H), 2.90–2.70 (m, 2 H), 1.70–1.50 (m, 3 H), 1.30–1.10 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 161.1 (t, $^2J_{C,F}$ = 31 Hz), 155.3, 136.4, 128.5, 128.1,

127.9, 121.5 (dd, $^1J_{C,F}$ = 287.5, $^1J_{C,F}$ = 291 Hz), 67.4, 66.2 (dd, $^2J_{C,F}$ = 23, $^2J_{C,F}$ = 24 Hz), 43.3 and 43.1, 35.9, 27.9 and 27.6 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.2 (d, $^2J_{F,F}$ = 239 Hz), –125.4 (dd, $^3J_{F,H}$ = 40, $^2J_{F,F}$ = 239 Hz) ppm.

***rac*-Benzyl 4-(3,3-Difluoro-4-oxoazetidin-2-yl)benzylcarbamate (12c):** This compound was prepared from **10c** according to the same procedure as employed for **12b**, from β-lactam **10c** (4.3 g, 9.2 mmol) and CAN (15.2 g, 27.7 mmol, 3 equiv.) in a mixture of CH_3CN/H_2O (9:1, 170 mL). Chromatography [CH_2Cl_2/EtOAc (95:5 to 85:15) as eluent] gave pure racemic **12c** as a white solid; yield 1.37 g (43%); TLC: silica gel (CH_2Cl_2/EtOAc, 9:1), R_f= 0.52. ^{1}H NMR (CD_3OD, 300.3 MHz): δ = 7.40–7.25 (m, 9 H), 5.10 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7.5 Hz, 1 H), 5.09 (s, 2 H), 4.32 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 163.4 (t, $^2J_{C,F}$ = 30 Hz), 159.0, 141.8, 138.2, 133.0, 129.4, 129.0, 128.8, 128.6, 128.2, 122.8 (t, $^1J_{C,F}$ = 292 Hz), 67.5, 65.5 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 26 Hz), 45.1 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –116.6 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 222.5 Hz), –122.9 (d, $^2J_{F,F}$ = 222.5 Hz) ppm.

***rac*-3,3-Difluoro-4-(pyridin-4-yl)azetidin-2-one (12d):** This compound was prepared from the mixture of **10d** and **11d** according to the same procedure as employed for **12b**, from β-lactam **10d** (1.2 g, 3.95 mmol) and CAN (6.5 g, 11.85 mmol, 3 equiv.) in a mixture of CH_3CN/H_2O (9:1, 55 mL). Chromatography [CH_2Cl_2/MeOH/NH_4OH (95:5:0.5 to 80:20:2) as eluent] gave pure racemic **12d** as a pale beige solid; yield 0.45 g (62%); m.p. 160 °C (dec.); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.44. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 10.32 (t, J = 12.5 Hz, 1 H), 8.98 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 8.01 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 5.69 (dd, $^3J_{H,F}$ = 1.5, $^3J_{H,F}$ = 7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 160.3 (t, $^2J_{C,F}$ = 29.5 Hz), 151.0, 144.3, 124.9, 121.8 (t, $^1J_{C,F}$ = 294.5 Hz), 62.5 (dd, $^2J_{C,F}$ = 22.5, $^2J_{C,F}$ = 26 Hz) ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –112.7 (ddd, $^3J_{F,H}$ = 7, $^4J_{F,H}$ = 13.5, $^2J_{F,F}$ = 219.5 Hz), –118.7 (dd, $^4J_{F,H}$ = 11.5, $^2J_{F,F}$ = 219.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3079, 1813, 1384, 718 cm^{-1}. MS (CI+): m/z = 185 [M + H]$^+$, 173, 159, 145, 93.

***rac*-3,3-Difluoro-4-(pyridin-3-yl)azetidin-2-one (12e):** This compound was prepared from the mixture of **10e** and **11e** according to the same procedure as employed for **12b**, from β-lactam **10e** (12.6 g, 41.4 mmol) and CAN (68 g, 124 mmol, 3 equiv.) in a mixture of CH_3CN/H_2O (9:1, 550 mL). Chromatography [CH_2Cl_2/MeOH/NH_4OH (95:5:0.5 to 80:20:2) as eluent] gave pure racemic **12e** as a brown viscous oil; yield 3.74 g (49%); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 95:5:0.5), R_f = 0.25. ^{1}H NMR (CD_3OD, 300.3 MHz): δ = 8.70–8.65 (m, 2 H), 8.02 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.66 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 8 Hz, 1 H), 5.35 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7 Hz, 1 H) ppm. ^{1}H NMR ([D$_6$]DMSO, 300.3 MHz): δ = 10.04 (t, $^4J_{H,F}$ = 12 Hz, 1 H), 8.65–8.60 (m, 2 H), 7.86 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.53 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 8 Hz, 1 H), 5.42 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 75.4 MHz): δ = 162.8 (t, $^2J_{C,F}$ = 30 Hz), 150.1, 148.3, 138.1, 131.8, 125.8, 125.6 (t, $^1J_{C,F}$ = 294.5 Hz), 63.3 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 26.5 Hz) ppm. ^{19}F NMR (CD_3OD, 288.3 MHz): δ = –116.4 (dd, $^3J_{F,H}$ = 6.5, $^2J_{F,F}$ = 228 Hz), –122.5 (d, $^2J_{F,F}$ = 228 Hz) ppm. ^{19}F NMR ([D$_6$]DMSO, 288.3 MHz): δ = –114.2 (ddd, $^3J_{F,H}$ = 7.5, $^4J_{F,H}$ = 14, $^2J_{F,F}$ = 223 Hz), –120.3 (ddd, $^3J_{F,H}$ = 2, $^4J_{F,H}$ = 12, $^2J_{F,F}$ = 223 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3079, 1813, 1384, 718 cm^{-1}. MS (CI+): m/z = 185 [M + H]$^+$, 165, 142, 100, 91.

General Procedure for 14b–e. *rac*-Benzyl 4-[1-(Dibenzylamino)-2-(ethoxycarbonyl)-2,2-difluoroethyl]piperidine-1-carboxylate (14b): The *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13b** was prepared according to the above General Procedure; dibenzylamine (0.79 g, 4 mmol) and aldehyde **4b** (1 g, 4.05 mmol, 1 equiv.) were successively added to a solution of 1*H*-benzotriazole (0.48 g, 4 mmol, 1 equiv.) dissolved in dry ethanol (1 mL). The mixture was heated at reflux for 4 h in the presence of dried molecular sieves (3 Å, 0.5 g) and was then stirred at room temp. for 12 h. After removal of molecular sieves by suction filtration and concentration of the filtrate under vacuum, the obtained solid could be recrystallized from ethanol. Chlorotrimethylsilane (1.1 mL, 8.6 mmol, 2.2 equiv.) was added to a suspension of activated zinc dust (0.79 g, 12 mmol, 3 equiv.) in anhydrous THF (10 mL), stirred in a dry Schlenk tube under argon, followed 10 min later by ethyl bromodifluoroacetate (1.83 g, 9 mmol, 2.2 equiv.). After 10 min, a solution of **13b** (4 mmol) in anhydrous THF (4 mL) was added dropwise. After 3 h at 60 °C, the mixture was cooled, poured into saturated aqueous $NaHCO_3$ solution (20 mL), and then filtered through Celite. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 60 mL). The organic layers were combined and washed with brine (40 mL), and were then dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product was chromatographed [cyclohexane/EtOAc (95:5 to 80:20) as eluent] to give pure ester **14b** as a yellow oil; yield 1.88 g (83%; 2 steps). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.25–7.10 (m, 15 H), 4.96 (br. s, 2 H), 4.11 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 4.10–3.90 (m, 2 H), 3.79 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 3.72 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 3.25–3.05 (m, 1 H), 2.65–2.50 (m, 2 H), 1.95–1.85 (m, 1 H), 1.85–1.70 (m, 1 H), 1.50–1.40 (m, 1 H), 1.17 (t, $^3J_{H,H}$ = 7 Hz, 3 H), 1.10–1.00 (m, 1 H), 0.90–0.85 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 164.3 (t, $^2J_{C,F}$ = 32 Hz), 155.0, 139.0, 136.8, 129.4, 128.4, 128.2, 127.9, 127.8, 127.2, 119.0 (t, $^1J_{C,F}$ = 260 Hz), 67.0, 62.9, 62.2 (t, $^2J_{C,F}$ = 20 Hz), 55.0, 44.2 and 43.8, 35.3, 30.4 and 28.8, 13.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –102.1 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 259 Hz), –113.7 (dd, $^3J_{F,H}$ = 24.5, $^2J_{F,F}$ = 259 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1787, 1698, 1514, 1434, 1249, 1225, 1061, 699 cm^{-1}. $C_{32}H_{36}F_2N_2O_4$ (550.65): calcd. C 69.80, H 6.59, N 5.09; found C 69.22, H 6.71, N 4.97.

***rac*-Benzyl 4-[1-(Dibenzylamino)-2-(ethoxycarbonyl)-2,2-difluoroethyl]benzylcarbamate (14c):** The *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13c** was prepared according to the same procedure as employed for **14b**; dibenzylamine (5.13 g, 26 mmol) and aldehyde **4c** (7 g, 26 mmol, 1 equiv.) were successively added to a solution of 1*H*-benzotriazole (3.1 g, 26 mmol, 1 equiv.) dissolved in dry ethanol (5 mL). The mixture was heated at reflux for 4 h in the presence of dried molecular sieves (3 Å, 2 g), and was then stirred at room temp. for 12 h. After removal of molecular sieves by suction filtration and concentration of the filtrate under vacuum, the obtained solid could be recrystallized from ethanol. Racemic β-amino ester **14c** was obtained from *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13c** according to the procedure already described for the conversion of **13b** into **14b**, with activated zinc dust (6.3 g, 96.4 mmol, 4 equiv.), chlorotrimethylsilane (3.7 mL, 28.9 mmol, 1.2 equiv.), and ethyl bromodifluoroacetate (10.7 g, 52.9 mmol, 2.2 equiv.) in anhydrous THF (95 mL). Chromatography [cyclohexane/EtOAc (97:3 to 80:20) as eluent] gave pure ester **14c** as a white solid; yield 8.93 g (60%; 2 steps); TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.58. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.40–7.10 (m, 15 H), 5.13 (s, 3 H), 4.41 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 4.31 (dd, $^3J_{H,F}$ = 8, $^3J_{H,F}$ = 26 Hz, 1 H), 4.30 (q, $^3J_{H,H}$ = 7 Hz, 1 H), 4.01 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 3.99 (q, $^3J_{H,H}$ = 7 Hz, 1 H), 3.06 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 1.12 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 163.9 (dd, $^2J_{C,F}$ = 30, $^2J_{C,F}$ = 34 Hz), 156.5, 139.0, 138.7, 136.4, 131.3, 129.1, 128.5, 128.3, 128.1, 127.3, 127.2, 117.1 (dd, $^1J_{C,F}$ = 253, $^1J_{C,F}$ = 259.5 Hz), 66.9, 63.3 (dd, $^2J_{C,F}$ = 19.5, $^2J_{C,F}$ = 28.5 Hz), 62.8, 54.9, 44.7, 13.6 ppm. ^{19}F NMR

(CDCl$_3$, 288.3 MHz): δ = –102.0 (d, $^2J_{F,F}$ = 262 Hz), –113.8 (d, $^2J_{F,F}$ = 262 Hz) ppm.

***rac*-Ethyl 3-(Dibenzylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (14d):** The *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13d** was prepared according to the same procedure as employed for **14b**; dibenzylamine (8.37 g, 42.4 mmol) and pyridine-4-carbaldehyde (**4d**, 5 g, 46.7 mmol, 1.1 equiv.) were successively added to a solution of 1*H*-benzotriazole (5.06 g, 42.5 mmol, 1 equiv.) dissolved in dry ethanol (5 mL). The mixture was heated at reflux for 4 h in the presence of dried molecular sieves (3 Å, 4 g), and was then stirred at room temp. for 12 h. After removal of molecular sieves by suction filtration and concentration of the filtrate under vacuum, the obtained solid could be recrystallized from ethanol. Racemic β-amino ester **14d** was obtained from *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13d** by the procedure already described for the conversion of **13b** to **14b**, from iminium salt **13d** (9 g, 22.2 mmol), activated zinc dust (3 g, 45.9 mmol, 2 equiv.), chlorotrimethylsilane (3.5 mL, 27.4 mmol, 1.2 equiv.), and ethyl bromodifluoroacetate (6.75 g, 33.3 mmol, 1.5 equiv.) in anhydrous THF (7 mL). Chromatography [cyclohexane/EtOAc (95:5 to 70:30) as eluent] gave pure ester **14d** as a pale yellow solid; yield 7.47 g (82%; 2 steps); m.p. 93 °C; TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.30. ^{1}H NMR (CDCl$_3$, 300.3 MHz): δ = 8.69 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 7.35–7.20 (m, 12 H), 4.45–4.30 (m, 2 H), 4.04 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 3.10 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H), 1.18 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ = 163.3 (dd, $^2J_{C,F}$ = 29.5, $^2J_{C,F}$ = 34 Hz), 149.6, 139.5, 138.0, 129.1, 128.4, 127.5, 125.7, 116.6 (dd, $^1J_{C,F}$ = 255, $^1J_{C,F}$ = 261 Hz), 63.1, 62.7 (dd, $^2J_{C,F}$ = 19.5, $^2J_{C,F}$ = 28.5 Hz), 54.9, 13.6 ppm. ^{19}F NMR (CDCl$_3$, 288.3 MHz): δ = –102.1 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 259 Hz), –113.7 (dd, $^3J_{F,H}$ = 24.5, $^2J_{F,F}$ = 259 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1770, 1293, 1204, 1066, 700 cm^{-1}. $C_{24}H_{24}F_2N_2O_2$ (410.47): calcd. C 70.23, H 5.89, N 6.82; found C 69.91, H 6.02, N 6.46.

***rac*-Ethyl 3-(Dibenzylamino)-2,2-difluoro-3-(pyridin-3-yl)propanoate (15e):** The *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13e** was prepared according to the same procedure as employed for **14b**; dibenzylamine (16.74 g, 84.9 mmol) and pyridine-3-carbaldehyde (**4e**, 10 g, 93.4 mmol, 1.1 equiv.) were successively added to a solution of 1*H*-benzotriazole (10.11 g, 84.9 mmol, 1 equiv.) dissolved in dry ethanol (15 mL). The mixture was heated at reflux for 4 h in the presence of dried molecular sieves (3 Å, 6 g), and then stirred at room temp. for 12 h. After removal of molecular sieves by suction filtration and concentration of the filtrate under vacuum, the obtained solid could be recrystallized from ethanol. Racemic β-amino ester **14e** was obtained from *N*,*N*-disubstituted 1*H*-benzotriazolylamine **13e** according to the procedure already described for the conversion of **13b** into **14b**, from iminium salt **13e** (9 g, 22.2 mmol), activated zinc dust (3 g, 45.9 mmol, 2 equiv.), chlorotrimethylsilane (3.5 mL, 27.4 mmol, 1.2 equiv.), and ethyl bromodifluoroacetate (6.75 g, 33.3 mmol, 1.5 equiv.) in anhydrous THF (7 mL). Chromatography [cyclohexane/EtOAc (9:1 to 7:3) as eluent] gave pure ester **14e** as a yellow oil; yield 7.35 g (81%); TLC: silica gel (cyclohexane/EtOAc, 7:3), R_f = 0.42. ^{1}H NMR (CDCl$_3$, 300.3 MHz): δ = 8.62 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 5 Hz, 1 H), 8.55 (d, $^4J_{H,H}$ = 2 Hz, 1 H), 7.81 (dt, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.35 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 8 Hz, 1 H), 7.30–7.20 (m, 10 H), 4.37 (dd, $^3J_{H,F}$ = 8, $^3J_{H,F}$ = 9 Hz, 1 H), 4.30 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 4.00 (d, $^2J_{H,H}$ = 13 Hz, 2 H), 3.03 (d, $^2J_{H,H}$ = 13 Hz, 2 H), 1.26 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ = 163.5 (dd, $^2J_{C,F}$ = 30, $^2J_{C,F}$ = 34 Hz), 151.9, 150.0, 138.1, 137.9, 129.2, 128.4, 127.5, 126.3, 123.4, 120.3 (t, $^1J_{C,F}$ = 290 Hz), 63.0, 61.6 (dd, $^2J_{C,F}$ = 19.5, $^2J_{C,F}$ = 29.5 Hz), 54.9, 13.7 ppm. ^{19}F NMR (CDCl$_3$, 288.3 MHz): δ = –101.5 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 257 Hz), –113.6 (dd, $^3J_{F,H}$ = 25, $^2J_{F,F}$ = 257 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1770, 1292, 1204, 1064, 700 cm^{-1}. $C_{24}H_{24}F_2N_2O_2$ (410.47): calcd. C 70.23, H 5.89, N 6.82; found C 69.95, H 5.83, N 6.75.

***rac-tert*-Butyl 4-[1-(Dibenzylamino)-2-(ethoxycarbonyl)-2,2-difluoroethyl]piperidine-1-carboxylate (14f):** A solution of racemic β-amino ester **14b** (10 g, 17.8 mmol) and Boc$_2$O (4.3 g, 19.7 mmol, 1.1 equiv.) in EtOH (80 mL) was added to a suspension of palladium on charcoal 10% (1 g) in EtOH (10 mL). The mixture was hydrogenated at atmospheric pressure and 40 °C until no starting material could be observed by TLC (ca. 48 h), filtered through Celite, and concentrated. The crude oil was crystallized from diethyl ether and, after filtration and drying, the pure β-amino ester **14f** was obtained as a white solid; yield 9.19 g (quant.); m.p. 124 °C; TLC: silica gel (cyclohexane/EtOAc, 8:2), R_f = 0.55. ^{1}H NMR (CDCl$_3$, 300.3 MHz): δ = 7.30–7.15 (m, 10 H), 4.25–4.05 (m, 2 H), 4.05–3.90 (m, 2 H), 3.80 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H), 3.73 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H), 3.20 (td, $^3J_{H,H}$ = 7.5, $^3J_{H,F}$ = 7.5, $^3J_{H,F}$ = 23 Hz, 1 H), 2.60–2.45 (m, 2 H), 2.00–1.85 (m, 1 H), 1.85–1.70 (m, 1 H), 1.50–1.40 (m, 1 H), 1.24 (t, $^3J_{H,H}$ = 7 Hz, 3 H), 1.15–1.00 (m, 1 H), 1.00–0.85 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ = 164.4 (t, $^2J_{C,F}$ = 32 Hz), 154.6, 139.0, 129.4, 128.2, 127.2, 119.0 (t, $^1J_{C,F}$ = 260 Hz), 79.4, 62.9, 62.3 (t, $^2J_{C,F}$ = 20 Hz), 55.1, 43.8, 35.4, 30.5 and 28.9, 28.4, 13.8 ppm. ^{19}F NMR (CDCl$_3$, 288.3 MHz): δ = –106.1 (d, $^2J_{F,F}$ = 250 Hz), –107.2 (dd, $^3J_{F,H}$ = 11.5, $^2J_{F,F}$ = 250 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1773, 1695, 1295, 1210, 1176, 1063, 700 cm^{-1}.

***rac-tert*-Butyl 4-[1-Amino-2,2-difluoro-2-(methoxycarbonyl)ethyl]-piperidine-1-carboxylate (15b):** A solution of dibenzylamine **14f** (7.15 g, 13.8 mmol) was added to a suspension of Pearlman's catalyst (palladium hydroxide 20% on activated charcoal, 0.5 g) in ethanol (80 mL). The reaction mixture was stirred at 40 °C under hydrogen (1 bar) for 48 h. The catalyst was filtered off and washed with ethanol (2 × 20 mL). The combined organic layers were concentrated, and the residue was chromatographed on silica gel [cyclohexane/EtOAc + 0.5% Et$_3$N (95:5 to 70:30) as eluent] to give **15b** as a yellow oil; yield 0.76 g (17%). ^{1}H NMR (CDCl$_3$, 300.3 MHz): δ = 4.25–4.00 (m, 2 H), 3.87 (s, 3 H), 3.08 (ddd, $^3J_{H,H}$ = 4, $^3J_{H,F}$ = 10.5, $^3J_{H,F}$ = 18 Hz, 1 H), 2.75–2.55 (m, 2 H), 1.80–1.65 (m, 1 H), 1.42 (s, 9 H), 1.60–1.20 (m, 4 H) ppm. ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ = 164.7 (d, $^2J_{C,F}$ = 32, $^2J_{C,F}$ = 33 Hz), 154.6, 116.7 (t, $^1J_{C,F}$ = 255 Hz), 79.4, 57.5 (t, $^2J_{C,F}$ = 23 Hz), 53.3, 43.7, 36.5, 28.4, 29.4 and 26.4 ppm. ^{19}F NMR (CDCl$_3$, 288.3 MHz): δ = –111.2 (dd, J = 115, $^2J_{F,F}$ = 263 Hz), –117.0 (dd, $^3J_{F,H}$ = 11, $^2J_{F,F}$ = 263 Hz) ppm.

***rac*-Ethyl 3-Amino-3-[4-(aminomethyl)phenyl]-2,2-difluoropropanoate Hydrochloride (16):** A solution of *N*-protected β-amino ester **14c** (10.94 g, 18.1 mmol) in EtOAc (30 mL) was added to a suspension of palladium on charcoal (10%, 0.5 g) in ethanol (30 mL), followed by the addition of HCl (5 N)/*i*PrOH (15 mL). The mixture was hydrogenated at atmospheric pressure and 40 °C until no starting material could be observed by TLC (ca. 3 d), filtered through a pad of Celite, washed with ethanol (2 × 25 mL), and concentrated. The hydrochloride salt of β-amino ester **16** was obtained as a hygroscopic white solid; yield 3.84 g (72%). ^{1}H NMR (CD$_3$OD, 300.3 MHz): δ = 7.60–7.40 (m, 4 H), 5.16 (dd, $^3J_{H,F}$ = 7.5, $^3J_{H,F}$ = 19 Hz, 1 H), 4.07 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 4.03 (s, 2 H), 1.04 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (CD$_3$OD, 75.4 MHz): δ = 161.8 (t, $^2J_{C,F}$ = 24 Hz), 137.4, 131.1, 130.9, 114.2 (t, $^1J_{C,F}$ = 259 Hz), 65.3, 57.3 (dd, $^2J_{C,F}$ = 22.5, $^2J_{C,F}$ = 24.5 Hz), 43.7, 14.1 ppm. ^{19}F NMR (CD$_3$OD, 288.3 MHz): δ = –108.7 (dd, $^3J_{F,H}$ = 6.5, $^2J_{F,F}$ = 260 Hz), –120.1 (dd, $^3J_{F,H}$ = 18.5, $^2J_{F,F}$ = 260 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3401, 1778, 1596–1519, 1315, 1200, 1128–1100, 1056 cm^{-1}.

***rac*-Benzyl 4-[1-Amino-2-(ethoxycarbonyl)-2,2-difluoroethyl]benzylcarbamate (15c) and *rac*-Benzyl 4-[1-Amino-2,2-difluoro-2-(methoxycarbonyl)ethyl]benzylcarbamate (15c′):** A solution of amine hydrochloride **17** (4 g, 13.6 mmol), triethylamine (4.15 mL, 30 mmol, 2.2 equiv.), Boc_2O (2.97 g, 13.6 mmol, 1 equiv.), and DMAP as catalyst (20 mg, 1 mol-%) was stirred at room temp. for 24 h. The mixture was poured into saturated aqueous NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried with $MgSO_4$ and concentrated before purification by flash chromatography on silica gel [CH_2Cl_2/MeOH (98:2 to 96:4) as eluent] to afford the mixture of β-amino esters **15c** and **15c′** as a pale yellow oil; yield 0.91 g (19%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.35–7.15 (m, 8 H), 4.85 (br. s, 2 H), 4.43 (dd, $^3J_{H,F}$ = 11.5, $^3J_{H,F}$ = 14.5 Hz, 2 H), 4.28 (d, $^3J_{H,H}$ = 6 Hz, 4 H), 4.23 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 3.65 (s, 3 H), 1.76 (br. s, 2 H), 1.43 (br. s, 18 H), 1.22 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 165.0 (t, $^1J_{C,F}$ = 33 Hz), 155.9, 139.6, 135.2, 128.2, 127.6, 79.6, 62.9, 58.1 (t, $^2J_{C,F}$ = 23.5 Hz), 53.3, 44.2, 28.5, 28.4, 13.9 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.4 (dd, $^3J_{F,H}$ = 12, $^2J_{F,F}$ = 261 Hz), –117.8 (dd, $^3J_{F,H}$ = 16.5, $^2J_{F,F}$ = 261 Hz) ppm (ethyl β-amino ester); δ = –113.4 (dd, $^3J_{F,H}$ = 11 Hz, $^2J_{F,F}$ = 261 Hz), –117.3 (dd, $^3J_{F,H}$ = 16 Hz, $^2J_{F,F}$ = 261 Hz) ppm (methyl β-amino ester). IR (KBr): $\tilde{\nu}_{max}$ = 3340, 1767, 1698, 1516, 1367, 1276, 1252, 1170, 1073, 758 cm^{-1}.

***rac*-Ethyl 3-Amino-2,2-difluoro-3-(pyridin-4-yl)propanoate Hydrochloride (15d):** A solution of *N*-protected β-amino ester **14d** (7.45 g, 18.1 mmol) in ethanol (30 mL) was added to a suspension of palladium on charcoal (10%, 1 g) in ethanol (15 mL), followed by the addition of HCl (5 N)/*i*PrOH (15 mL). The mixture was hydrogenated at atmospheric pressure and 40 °C until no starting material could be observed by TLC (ca. 3 d), filtered through a pad of Celite, washed with ethanol (2 × 25 mL), and concentrated. The hydrochloride salt of β-amino ester **16d** was obtained as a hygroscopic white solid; yield 3.62 g (75%); m.p. 190 °C (dec.); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.70. ^{1}H NMR ([D$_6$]-DMSO, 300.3 MHz): δ = 8.91 (d, $^3J_{H,F}$ = 6 Hz, 2 H), 7.97 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 5.59 (dd, $^3J_{H,F}$ = 11.5, $^3J_{H,F}$ = 15 Hz, 1 H), 5.3–4.3 (br. s, 3 H), 4.28 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 1.18 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.4 MHz): δ = 160.5 (t, $^2J_{C,F}$ = 30.5 Hz), 146.6, 143.3, 126.0, 112.5 (t, $^1J_{C,F}$ = 258 Hz), 64.6, 54.3 (t, $^2J_{C,F}$ = 24.5 Hz), 13.6 ppm. ^{19}F NMR ([D$_6$]DMSO, 288.3 MHz): δ = –109.5 (dd, $^3J_{F,H}$ = 11, $^2J_{F,F}$ = 259 Hz), –112.5 (dd, $^3J_{F,H}$ = 15, $^2J_{F,F}$ = 259 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3399, 2790, 1778, 1640–1616–1529, 1318, 1223, 1071 cm^{-1}.

***rac*-Ethyl 3-Amino-2,2-difluoro-3-(pyridin-4-yl)propanoate Hydrochloride (15e):** This compound was prepared from *N*,*N*-dibenzyl β-amino ester **14e** according to the same procedure as employed for **15d**, from *N*-protected β-amino ester **14e** (2.9 g, 7.05 mmol), palladium on charcoal (10%, 0.17 g), HCl (5 N)/*i*PrOH (3 mL) in ethanol (10 mL). The hydrochloride salt of β-amino ester **15e** was obtained as a white, viscous oil; yield 1.69 g (90%); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.70. ^{1}H NMR (CD_3OD, 300.3 MHz): δ = 9.14 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 9.08 (br. s, 1 H), 8.75 (m, 1 H), 8.21 (m, 1 H), 5.80 (dd, $^3J_{H,F}$ = 8, $^3J_{H,F}$ = 9 Hz, 1 H), 4.42 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 1.34 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (CD_3OD, 75.4 MHz): δ = 165.0 (t, $^2J_{C,F}$ = 30.5 Hz), 147.3, 146.1, 145.6, 130.3, 128.5, 113.5 (dd, $^1J_{C,F}$ = 259.5, $^1J_{C,F}$ = 261.5 Hz), 65.9, 54.8 (t, $^2J_{C,F}$ = 24.5 Hz), 14.0 ppm. ^{19}F NMR (CD_3OD, 288.3 MHz): δ = –110.4 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 275 Hz), –116.4 (dd, $^3J_{F,H}$ = 16.5, $^2J_{F,F}$ = 275 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3401, 1769, 1668, 1318, 1210, 1072 cm^{-1}.

***rac*-Methyl 2-(3,3-Difluoro-2-oxo-4-phenylazetidin-1-yl)acetate (18a):** A solution of azetidin-2-one **12a** (2.3 g, 12.6 mmol), nBu$_4$NI (2.3 g, 6.3 mmol, 0.5 equiv.), and methyl bromoacetate (**17a**, 15 mL, 158 mmol, 12.5 equiv.) in anhydrous acetonitrile (17 mL) was treated dropwise with 1,1,3,3-tetramethylguanidine (2.9 g, 25.1 mmol, 2 equiv.). The mixture was stirred at room temp. for 12 h. The solvent was evaporated to dryness, and the residue was chromatographed on silica gel [cyclohexane/EtOAc (95:5 to 70:30) as eluent] to give β-lactam **18a** as an opalescent oil; yield 3.21 g (quant.); TLC: silica gel (cyclohexane/EtOAc, 8:2), R_f = 0.35. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.43 (m, 3 H), 7.28 (m, 2 H), 5.25 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7.5 Hz, 1 H), 4.49 (d, $^3J_{H,H}$ = 18 Hz, 1 H), 3.73 (s, 3 H), 3.61 (dd, J = 2, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 167.2, 161.2 (t, $^2J_{C,F}$ = 31 Hz), 130.0, 129.6, 129.1, 128.0, 120.9 (t, $^1J_{C,F}$ = 291 Hz), 69.2 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27 Hz), 52.7, 40.7 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –116.9 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 225 Hz), –124.6 (d, $^2J_{F,F}$ = 225 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1799, 1750, 1323, 1208, 1131, 1068, 703 cm^{-1}. $C_{12}H_{11}F_2NO_3$ (255.22): calcd. C 56.47, H 4.34, N 5.49; found C 56.46, H 4.75, N 5.21.

***rac*-Benzyl 2-(3,3-Difluoro-2-oxo-4-phenylazetidin-1-yl)acetate (18b):** This compound was prepared from racemic β-lactam **12a** according to the procedure already described for the conversion of **12a** into **18a**, from azetidin-2-one **12a** (2 g, 10.9 mmol), nBu$_4$NI (2 g, 5.4 mmol, 0.5 equiv.), benzyl bromoacetate (**17b**, 17.35 mL, 109 mmol, 10 equiv.), and 1,1,3,3-tetramethylguanidine (2.5 g, 21.7 mmol, 2 equiv.) in anhydrous acetonitrile (10 mL). Chromatography on silica gel [cyclohexane/EtOAc (10:0 to 8:2) as eluent] gave β-lactam **18b** as a colorless oil; yield 3.28 g (91%); TLC: silica gel (cyclohexane/EtOAc, 8:2), R_f = 0.41. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.40–7.15 (m, 10 H), 5.17 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7 Hz, 1 H), 5.11 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.05 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 4.46 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.58 (d, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 166.8, 161.4 (t, $^2J_{C,F}$ = 31 Hz), 134.7, 130.2, 129.7, 129.3, 128.9, 128.8, 128.7, 128.2, 121.0 (dd, $^1J_{C,F}$ = 289, $^1J_{C,F}$ = 292 Hz), 69.4 (dd, $^2J_{C,F}$ = 24.5, $^2J_{C,F}$ = 27 Hz), 67.9, 41.1 (t, J = 30 Hz) ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.1 (d, $^2J_{F,F}$ = 225.5 Hz), –121.8 (d, $^2J_{F,F}$ = 225.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1798, 1747, 1323, 1201, 1067, 701 cm^{-1}.

***rac*-2-(3,3-Difluoro-2-oxo-4-phenylazetidin-1-yl)acetic Acid (19):** β-Lactam **18b** (3.31 g, 10 mmol) was dissolved in ethanol (60 mL), and palladium on charcoal (10%, 0.2 g) was added. The mixture was first placed under nitrogen and subsequently under hydrogen (hydrogen balloon, 1 bar). After the system had been stirred at room temp. for 24 h, the hydrogen gas was removed with the aid of a nitrogen flow. The catalyst was filtered off through a pad of Celite and washed with ethanol (2 × 20 mL). The solvent was evaporated in vacuo. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 500:500:10) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the title compound **20** as a white solid; yield 3.28 g (91%); m.p. 162 °C. ^{1}H NMR (CD_3OD, 300.3 MHz): δ = 7.50–7.45 (m, 3 H), 7.40–7.35 (m, 2 H), 5.34 (dd, $^3J_{H,F}$ = 2, $^3J_{H,F}$ = 7.5 Hz, 1 H), 4.45 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.74 (dd, J = 1, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C (CD_3OD, 75.4 MHz): δ = 170.0, 162.8 (t, $^2J_{C,F}$ = 31 Hz), 131.4, 130.9, 130.1, 129.2, 122.4 (t, $^1J_{C,F}$ = 290 Hz), 70.5 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27 Hz), 42.1 ppm. ^{19}F NMR (CD_3OD, 288.3 MHz): δ = –104.2 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 225 Hz), –121.9 (d, $^2J_{F,F}$ = 225 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3044, 1791, 1718, 1323, 1243, 701 cm^{-1}. MS (CI+): m/z = 242 [M + H]$^+$, 198, 154, 140, 102, 93. HRMS (CI+): calcd. for $C_{11}H_9F_2NO_3$ 242.0629; found 242.0626. $C_{11}H_9F_2NO_3$ (241.20): calcd. C 54.78, H 3.76, N 5.81; found C 54.82, H 3.58, N 5.78.

Benzyl *rac*-4-{1-[(Benzyloxycarbonyl)methyl]-3,3-difluoro-4-oxoazetidin-2-yl}piperidine-1-carboxylate (20b): This compound was prepared from racemic β-lactam **12a** according to the procedure already described for the conversion of **12a** into **18b**, from azetidin-2-one **12b** (0.56 g, 1.7 mmol), nBu$_4$NI (0.3 g, 0.8 mmol, 0.5 equiv.), benzyl bromoacetate (**17b**, 10 mL, 63 mmol, 37 equiv.), and 1,1,3,3-tetramethylguanidine (0.39 g, 3.4 mmol, 2 equiv.) in anhydrous acetonitrile (10 mL). Chromatography on silica gel [cyclohexane/EtOAc (95:5 to 80:20) as eluent] gave β-lactam **20b** as an orange oil; yield 0.24 g (30%); TLC: silica gel (cyclohexane/EtOAc, 8:2), R_f = 0.40. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.40–7.25 (m, 10 H), 5.20 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.15 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.10 (s, 2 H), 4.43 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 4.30–4.05 (m, 2 H), 3.96 (dt, $^3J_{H,F}$ = 2.5, $^3J_{H,H}$ = $^3J_{H,F}$ = 11 Hz, 1 H), 3.87 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 2.85–2.60 (m, 2 H), 2.00–1.85 (m, 1 H), 1.75–1.65 (m, 1 H), 1.60–1.45 (m, 1 H), 1.30–1.10 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 166.6, 161.2 (t, $^2J_{C,F}$ = 31 Hz), 155.0, 136.5, 134.5, 128.9, 128.7, 128.6, 128.5, 128.1, 127.9, 69.8 (dd, $^2J_{C,F}$ = 22, $^2J_{C,F}$ = 25 Hz), 67.8, 67.2, 43.3, 43.2 and 43.1, 35.7, 28.1 and 27.6 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –113.5 (dd, $^3J_{F,H}$ = 8, $^2J_{F,F}$ = 234 Hz), –114.5 (dd, $^3J_{F,H}$ = 21, $^2J_{F,F}$ = 234 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1798, 1747, 1323, 1201, 1067, 701 cm^{-1}.

Benzyl *rac*-[2-(4-{[(Benzyloxycarbonyl)amino]methyl}phenyl)-3,3-difluoro-4-oxoazetidin-1-yl]acetate (20c): This compound was prepared from racemic β-lactam **12c** according to the procedure already described for conversion of **12a** into **18b**, from azetidin-2-one **12c** (1.28 g, 3.7 mmol), nBu$_4$NI (1.38 g, 3.7 mmol, 1 equiv.), benzyl bromoacetate (**17b**, 9.2 g, 40 mmol, 10.8 equiv.), and 1,1,3,3-tetramethylguanidine (0.84 g, 7.3 mmol, 2 equiv.) in anhydrous acetonitrile (80 mL). Chromatography on silica gel [CH_2Cl_2/EtOAc (100:0 to 98:2) as eluent] gave β-lactam **20c** as a colorless oil; yield 1.74 g (95%); TLC: silica gel (CH_2Cl_2/EtOAc, 95:5), R_f = 0.75. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.40–7.25 (m, 12 H), 7.21 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.21 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7.5 Hz, 1 H), 5.17 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.12 (br. s, 3 H), 5.10 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H), 4.50 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 4.38 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 3.61 (dd, J = 1.5, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 166.5, 161.1 (t, $^2J_{C,F}$ = 31 Hz), 156.4, 140.7, 136.2, 134.5, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 120.8 (t, $^1J_{C,F}$ = 291 Hz), 68.9 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 26.5 Hz), 67.7, 66.9, 44.5, 40.9 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.1 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 225 Hz), –121.8 (d, $^2J_{F,F}$ = 225 Hz) ppm. $C_{27}H_{24}F_2N_2O_5$ (494.50): calcd. C 65.58, H 4.89, N 5.67; found C 65.97, H 5.06, N 5.57.

***rac*-Benzyl 2-[3,3-Difluoro-2-oxo-4-(pyridin-4-yl)azetidin-1-yl]acetate (20d):** This compound was prepared from racemic β-lactam **12d** according to the procedure already described for the conversion of **12a** into **18b**, from azetidin-2-one **12d** (5.15 g, 28 mmol), nBu$_4$NI (10.3 g, 29.7 mmol, 1 equiv.), benzyl bromoacetate (**17b**, 7 g, 30.6 mmol, 1.1 equiv.), and 1,1,3,3-tetramethylguanidine (6.4 g, 55.6 mmol, 2 equiv.) in anhydrous acetonitrile (150 mL). Chromatography on silica gel [CH_2Cl_2/MeOH/NH_4OH (99.5:0.5:0.05 to 98:2:0.2) as eluent] gave β-lactam **20d** as a pale yellow oil; yield 2.70 g (29%); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 97:3:0.3), R_f = 0.73. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.66 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 7.40–7.25 (m, 5 H), 7.18 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 5.22 (dd, $^3J_{H,F}$ = 2, $^3J_{H,F}$ = 7 Hz, 1 H), 5.17 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.11 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 4.54 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.67 (dd, J = 1.5, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 166.3, 160.7 (t, $^2J_{C,F}$ = 31 Hz), 150.6, 138.8, 134.3, 128.9, 128.7, 128.5, 122.5, 120.7 (dd, $^1J_{C,F}$ = 291, $^1J_{C,F}$ = 293 Hz), 68.0 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 27 Hz), 67.9, 41.3 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –113.3 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 225.5 Hz), –120.6 (d, $^2J_{F,F}$ = 225.5 Hz) ppm. MS (EI+): m/z = 332 [M]$^{+\cdot}$, 281, 232, 198, 169, 141, 91, 65.

***rac*-Benzyl 2-[3,3-Difluoro-2-oxo-4-(pyridin-3-yl)azetidin-1-yl]acetate (20e):** This compound was prepared from racemic β-lactam **12e** according to the procedure already described for the conversion of **12a** into **18b**, from azetidin-2-one **12e** (0.5 g, 2.7 mmol), nBu$_4$NI (0.5 g, 3.3 mmol, 1.2 equiv.), benzyl bromoacetate (**17b**, 0.68 g, 3.0 mmol, 1.1 equiv.), and 1,1,3,3-tetramethylguanidine (0.62 g, 5.4 mmol, 2 equiv.) in anhydrous acetonitrile (50 mL). Chromatography on silica gel [CH_2Cl_2/MeOH/NH_4OH (99.5:0.5:0.05 to 98:2:0.2) as eluent] gave β-lactam **20e** as a pale yellow oil; yield 0.45 g (50%); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 98:2:0.2), R_f = 0.48. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.65 (d, $^3J_{H,H}$ = 4 Hz, 1 H), 8.49 (s, 1 H), 7.61 (dd, $^4J_{H,H}$ = 1, $^3J_{H,H}$ = 8 Hz, 1 H), 7.4–7.2 (m, 6 H), 5.26 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7 Hz, 1 H), 5.17 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 5.11 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 4.49 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.63 (dd, J = 1.5, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 166.3, 160.8 (t, $^2J_{C,F}$ = 30.5 Hz), 151.3, 149.6, 135.6, 134.3, 128.8, 128.7, 128.5, 124.6, 123.8, 120.8 (t, $^1J_{C,F}$ = 292 Hz), 67.9, 67.0 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27 Hz), 41.1 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –113.8 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 226 Hz), –121.2 (d, $^2J_{F,F}$ = 226 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1800, 1747, 1312, 1206, 1067, 699 cm^{-1}.

***rac-tert*-Butyl 2-[3,3-Difluoro-2-oxo-4-(pyridin-4-yl)azetidin-1-yl]-acetate (22d):** This compound was prepared from racemic β-lactam **12d** according to the procedure already described for the conversion of **12a** into **18b**, from azetidin-2-one **12d** (1.9 g, 10.3 mmol), NaI (1.8 g, 12 mmol, 1.15 equiv.), *tert*-butyl bromoacetate (**17c**, 2 g, 10.3 mmol, 1 equiv.), and 1,1,3,3-tetramethylguanidine (2.37 g, 20.6 mmol, 2 equiv.) in anhydrous acetonitrile (100 mL). Chromatography on silica gel [CH_2Cl_2/MeOH/NH_4OH (99:1:0.1 to 98:2:0.2) as eluent] gave β-lactam **22d** as a brown oil; yield 1.44 g (47%).

***rac-tert*-Butyl 2-[3,3-Difluoro-2-oxo-4-(pyridin-3-yl)azetidin-1-yl]-acetate (22e):** This compound was prepared from racemic β-lactam **12e** according to the procedure already described for the conversion of **12a** into **18b**, from azetidin-2-one **12e** (0.65 g, 3.5 mmol), NaI (0.6 g, 4 mmol, 1.15 equiv.), *tert*-butyl bromoacetate (**17c**, 0.69 g, 3.5 mmol, 1 equiv.), and 1,1,3,3-tetramethylguanidine (0.81 g, 7 mmol, 2 equiv.) in anhydrous acetonitrile (50 mL). Chromatography on silica gel [CH_2Cl_2/MeOH/NH_4OH (99.5:0.5:0.05 to 98:2:0.2) as eluent] gave β-lactam **22e** as a pale yellow solid; yield 0.52 g (50%); m.p. 85 °C; TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 95:5:0.5), R_f = 0.75. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.65 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 8.54 (s, 1 H), 7.63 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.36 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 8 Hz, 1 H), 5.25 (dd, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 7 Hz, 1 H), 4.33 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.47 (dd, J = 1, $^2J_{H,H}$ = 18 Hz, 1 H), 1.39 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 165.4, 160.8 (t, $^2J_{C,F}$ = 31 Hz), 151.3, 149.6, 135.5, 125.9, 123.8, 120.8 (t, $^1J_{C,F}$ = 291.5 Hz), 83.6, 66.9 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 27 Hz), 41.8, 27.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –114.1 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 225.5 Hz), –121.3 (d, $^2J_{F,F}$ = 225.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1797, 1733, 1416, 1374, 1315, 1248, 1166, 1066, 720 cm^{-1}. $C_{14}H_{16}F_2N_2O_3$ (298.29): calcd. C 56.37, H 5.41, N 9.39; found C 56.45, H 5.45, N 9.46.

***rac*-2-[3,3-Difluoro-2-oxo-4-(piperidin-4-yl)azetidin-1-yl]acetic Acid Hydrochloride (21b):** β-Lactam **20b** (0.23 g, 0.5 mmol) was dissolved in ethanol (5 mL), and Pd/C (10%, 50 mg) was added. The mixture was first placed under nitrogen and subsequently under hydrogen (hydrogen balloon, 1 bar). After the mixture had been stirred at room temp. for 24 h, the hydrogen gas was removed with the aid of a nitrogen flow. The catalyst was filtered off through a

pad of Celite, and washed with ethanol (2 × 10 mL). The solvent was evaporated in vacuo. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 100:100:2) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **21b** as a pale yellow lyophilizate; yield: 70 mg (50%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 4.13 (dt, $^3J_{H,F}$ = 2.5, $^3J_{H,F}$ = 9 Hz, 1 H), 4.06 (d, $^2J_{H,H}$ = 17.5 Hz, 1 H), 3.82 (d, $^2J_{H,H}$ = 17.5 Hz, 1 H), 3.45–3.35 (m, 2 H), 3.00–2.85 (m, 2 H), 2.30–2.10 (m, 1 H), 2.00–1.85 (m, 2 H), 1.65–1.45 (m, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 174.0, 163.6 (t, $^2J_{C,F}$ = 30.5 Hz), 120.5 (t, $^1J_{C,F}$ = 290 Hz), 70.5 (dd, $^2J_{C,F}$ = 22, $^2J_{C,F}$ = 24.5 Hz), 49.8, 44.2 and 44.1, 33.6, 25.5 and 24.6 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –115.2 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 232.5 Hz), –125.3 (d, $^2J_{F,F}$ = 232.5 Hz) ppm. MS (ESI–): *m*/*z* = 247.0 [M – H]$^-$, 183.0.

***rac*-2-{2-[4-(Aminomethyl)phenyl]-3,3-difluoro-4-oxoazetidin-1-yl}-acetic Acid Hydrochloride (21c):** This compound was prepared from racemic β-lactam **20c** according to the procedure already described for the conversion of **20b** into **21b**, from azetidin-2-one **20c** (1.71 g, 3.4 mmol) and Pd/C (10%, 0.2 g) in methanol (60 mL). The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 500:500:10) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **21c** as a white lyophilizate; yield 0.26 g (25%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 7.65 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.61 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.58 (dd, $^3J_{H,F}$ = 2, $^3J_{H,F}$ = 7 Hz, 1 H), 4.58 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 4.32 (s, 2 H), 4.04 (d, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 170.9, 163.4 (t, $^2J_{C,F}$ = 31 Hz), 134.8, 130.8, 129.7, 129.4, 120.3 (t, $^1J_{C,F}$ = 288 Hz), 69.4 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 26.5 Hz), 43.0, 42.3 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –115.8 (dd, $^3J_{F,H}$ = 6.5, $^2J_{F,F}$ = 225.5 Hz), –123.0 (d, $^2J_{F,F}$ = 225.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3042, 1752, 1518, 1412, 1220 cm^{-1}. MS (ESI+): *m*/*z* = 292.9 [M + Na]$^+$, 270.9 [M + H]$^+$, 254.0 [M + H – NH_3]$^+$.

2-{3-[4-(Aminomethyl)phenyl]-2,2-difluoropropanamido}acetic Acid: The hydrogenolysis deprotection step of **20c** into **21c** was accompanied by partial degradation. The corresponding hydrochloride salt was isolated from the steric exclusion chromatography as a white lyophilizate; yield 105 mg (10%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 7.40–7.35 (m, 4 H), 4.14 (s, 2 H), 3.91 (s, 2 H), 3.43 (dt, $^3J_{H,H}$ = 3, $^3J_{H,F}$ = 16.5 Hz, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 172.6, 166.6 (t, $^2J_{C,F}$ = 30 Hz), 132.6, 132.3, 131.5, 129.3, 117.4 (t, $^1J_{C,F}$ = 252 Hz), 43.0, 41.1, 40.2 (t, $^2J_{C,F}$ = 24.5 Hz) ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –106.4 (t, $^2J_{F,F}$ = 16.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3330, 2038, 1697, 1551, 1407, 1230, 902, 770 cm^{-1}. MS (ESI+): *m*/*z* = 294.9 [M + Na]$^+$, 273.0 [M + H]$^+$, 256.0 [M + H – NH_3]$^+$.

***rac*-2-[3,3-Difluoro-2-oxo-4-(pyridin-4-yl)azetidin-1-yl]acetic Acid Hydrochloride (21d):** TFA (6 mL) was added to a solution of azetidin-2-one **22d** (1.44 g, 4.85 mmol) in wet CH_2Cl_2 (8 mL). The mixture was stirred at 0 °C for 1 h. After concentration, the crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 500:500:10) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the trifluoroacetate salt of the title compound **21c** as a pale yellow lyophilizate; yield 0.76 g (44%). ^{1}H NMR (CD_3OD, 300.3 MHz): δ = 7.65 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.61 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.58 (dd, $^3J_{H,F}$ = 2, $^3J_{H,F}$ = 7 Hz, 1 H), 4.58 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 4.32 (s, 2 H), 4.04 (d, $^2J_{H,H}$ = 18 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 75.4 MHz): δ = 169.8, 164.1 (t, $^2J_{C,F}$ = 30.5 Hz), 152.4, 144.4, 127.4, 122.3 (t, $^1J_{C,F}$ = 293 Hz), 68.9 (dd, $^2J_{C,F}$ = 23, $^2J_{C,F}$ = 27 Hz), 43.3 ppm. ^{19}F NMR (CD_3OD, 288.3 MHz): δ = –77.9 (CF_3), –115.6 (dd, $^3J_{F,H}$ = 7.5, $^2J_{F,F}$ = 224 Hz), –121.6 (d, $^2J_{F,F}$ = 224 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3422, 2350, 1801, 1730, 1643, 1420, 1324, 1193, 720 cm^{-1}. MS (ESI+): *m*/*z* = 242.9 [M + H]$^+$.

***rac*-3-[(Carboxymethyl)amino]-2,2-difluoro-3-(pyridin-4-yl)propanoic Acid Hydrochloride:** The trifluoroacetate form of the product of nucleophilic ring-opening was obtained during the TFA deprotection step of **22d**, after isolation from the steric exclusion chromatography as a white lyophilizate; yield 200 mg (11%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.89 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 8.19 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 5.32 (dd, $^3J_{H,F}$ = 8.5, $^3J_{H,F}$ = 15 Hz, 1 H), 3.80 (s, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 170.3, 165.8 (t, $^2J_{C,F}$ = 26 Hz), 149.8, 142.6, 128.4, 114.0 (t, $^1J_{C,F}$ = 261 Hz), 62.6 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 26 Hz), 47.5 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –77.9 (CF_3), –108.3 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 254.5 Hz), –112.4 (dd, $^3J_{F,H}$ = 15, $^2J_{F,F}$ = 254.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3412, 1740, 1644, 1510, 1407, 1295, 1243, 1194 cm^{-1}. MS (ESI+): *m*/*z* = 260.9 [M + H]$^+$.

***rac*-2-[3,3-Difluoro-2-oxo-4-(pyridin-3-yl)azetidin-1-yl]acetic Acid Hydrochloride (21e):** TFA (2.5 mL) was added to a solution of azetidin-2-one **22e** (0.3 g, 1 mmol) in wet CH_2Cl_2 (2.5 mL). The mixture was stirred at 0 °C for 1 h. After concentration, the crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 200:200:4) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **21e** as a pale yellow lyophilizate; yield 0.16 g (56%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.97 (s, 1 H), 8.85 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H), 8.76 (d, $^2J_{H,H}$ = 7.5 Hz, 1 H), 8.15 (t, $^3J_{H,H}$ = 6.5 Hz, 1 H), 5.74 (dd, $^3J_{H,F}$ = 2, $^3J_{H,F}$ = 6.5 Hz, 1 H), 4.45 (d, $^2J_{H,H}$ = 18.5 Hz, 1 H), 4.05 (d, $^2J_{H,H}$ = 18.5 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 170.5, 166.0 (t, $^2J_{C,F}$ = 23.5 Hz), 147.4, 142.6, 141.9, 131.7, 128.0, 66.6 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 27 Hz), 42.8 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –115.2 (dd, $^3J_{F,H}$ = 6.5, $^2J_{F,F}$ = 226.5 Hz), –125.5 (d, $^2J_{F,F}$ = 226.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3412, 1802, 1736, 1637, 1400, 1313, 1203 cm^{-1}. MS (ESI+): *m*/*z* = 242.9 [M + H]$^+$.

***rac*-3-[(Carboxymethyl)amino]-2,2-difluoro-3-(pyridin-4-yl)propanoic Acid Hydrochloride:** The hydrochloride form of the product of nucleophilic ring-opening was obtained during the TFA deprotection step of **22e**, after isolation from the steric exclusion chromatography as a pale yellow lyophilizate; yield 130 mg (44%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.98 (s, 1 H), 8.92 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 8.76 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.18 (dd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 8 Hz, 1 H), 5.36 (dd, $^3J_{H,F}$ = 8, $^3J_{H,F}$ = 16 Hz, 1 H), 3.84 (s, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 169.9, 165.7 (t, $^2J_{C,F}$ = 25 Hz), 147.8, 143.7, 142.8, 129.9, 128.5, 114.0 (t, $^1J_{C,F}$ = 260 Hz), 60.8 (dd, $^2J_{C,F}$ = 23.5, $^2J_{C,F}$ = 26 Hz), 47.3 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –108.3 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 256 Hz), –113.0 (dd, $^3J_{F,H}$ = 16, $^2J_{F,F}$ = 256 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3416, 1740, 1637, 1406, 1297, 1196 cm^{-1}. MS (ESI+): *m*/*z* = 282.9 [M + Na]$^+$, 260.9 [M + H]$^+$. MS (ESI–): 258.7 [M – H]$^-$.

(Acetylsulfanyl)acetyl Chloride (23): Acetic anhydride (30 mL, 317 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of mercaptoacetic acid (20 mL, 287 mmol), triethylamine (80 mL, 569 mmol, 2 equiv.), and DMAP as catalyst (100 mg) in anhydrous MeCN (200 mL). The mixture was stirred at room temp. for 18 h. The reaction was quenched with water (20 mL). The solvent was

evaporated to dryness, and the residue was taken up in CH_2Cl_2 (200 mL). The organic layer was washed with water (2 × 100 mL), and extracted with aqueous NaOH solution (1 N, 100 mL). The aqueous layer was washed with diethyl ether (100 mL), acidified to pH = 1 by the addition of aqueous HCl solution (4 N), and extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was distilled under reduced pressure (1 Torr), and the fraction boiling between 118 and 122 °C was collected to afford pure (acetylsulfanyl)acetic acid as a pale yellow oil; yield 25.03 g (65%). ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 10.17 (br. s, 1 H), 4.09 (s, 2 H), 2.38 (s, 3 H) ppm. ^{13}C ($CDCl_3$, 75.4 MHz): δ = 193.9, 174.7, 31.3, 30.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3450, 1697 cm^{-1}. $C_4H_6O_3S$ (134.15): calcd. C 35.81, H 4.51, S 23.90; found C 36.02, H 4.99, S 23.59. Oxalyl chloride (7.5 mL, 88.4 mmol, 1.5 equiv.) was added dropwise at 0 °C over 1 h to a solution of acid (8 g, 59.6 mmol) and DMF (0.6 mL, 7.7 mmol) in anhydrous CH_2Cl_2 (100 mL). The mixture was stirred at room temp. for 12 h, and the solvents were evaporated to dryness. The crude oil was distilled at 7 mbar to give pure acyl chloride **23** as an orange oil; yield 6.10 g (67%); b.p. 62 °C. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 4.15 (s, 2 H), 2.40 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 192.9, 169.6, 42.4, 30.4 ppm.

***rac*-*tert*-Butyl 4-[1-{[(Acetylsulfanyl)acetyl]amino}-2,2-difluoro-2-(methoxycarbonyl)ethyl]piperidine-1-carboxylate (25b):** A solution of acyl chloride **23** (0.75 g, 4.9 mmol, 2.05 equiv.) in anhydrous CH_2Cl_2 (3 mL) was added under nitrogen to a solution of β-amino ester **15b** (0.79 g, 2.4 mmol) in anhydrous CH_2Cl_2 (5 mL). *N*,*N*-Diisopropylethylamine (0.87 mL, 5 mmol, 2.1 equiv.) was then added dropwise to the solution at 0 °C, and the mixture was stirred at room temp. for 12 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 × 80 mL). The combined extracts were dried with anhydrous $MgSO_4$, and the solvent was evaporated to give a crude oily product. This was subjected to column chromatography [CH_2Cl_2/EtOAc (90:10 to 75:25) as eluent] to afford pure amide **25b** as a yellow oil; yield 0.78 g (74%); TLC: silica gel (CH_2Cl_2/EtOAc, 7:3), R_f = 0.78. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 6.59 (d, $^3J_{H,H}$ = 10 Hz, 1 H), 4.55–4.40 (m, 1 H), 4.15–3.95 (m, 2 H), 3.77 (s, 3 H), 3.49 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H), 3.43 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H), 2.70–2.50 (m, 2 H), 1.95–1.80 (m, 1 H), 1.36 (s, 9 H), 1.7–1.2 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 196.2, 168.5, 163.1 (dd, $^2J_{C,F}$ = 31, $^2J_{C,F}$ = 33.5 Hz), 154.4, 114.5 (t, $^1J_{C,F}$ = 257 Hz), 79.4, 53.9 (dd, $^2J_{C,F}$ = 22.5, $^2J_{C,F}$ = 27 Hz), 53.5, 43.2, 35.3, 32.6, 30.0, 29.1, 28.2, 26.6 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –109.7 (dd, $^3J_{F,H}$ = 6, $^2J_{F,F}$ = 265 Hz), –115.6 (dd, $^3J_{F,H}$ = 18.5, $^2J_{F,F}$ = 265 Hz) ppm.

***rac*-Ethyl 3-{[(Acetylsulfanyl)acetyl]amino}-3-(4-{[(*tert*-butoxycarbonyl)amino]methyl}phenyl)-2,2-difluoropropionate (25c) and *rac*-Methyl 3-{[(Acetylsulfanyl)acetyl]amino}-3-(4-{[(*tert*-butoxycarbonyl)amino]methyl}phenyl)-2,2-difluoropropionate (25c′):** Racemic β-amino ester **25c** and its methyl ester derivative **25c′** were obtained from β-amino ester **15c** and its methyl ester derivative **15c′** (mixture of ethyl and methyl esters) according to the procedure already described for the conversion of **15b** into **25b**, from **15c** and **15c′** (0.91 g, 2.6 mmol), DMAP (50 mg), *N*,*N*-diisopropylethylamine (0.5 mL, 2.9 mmol, 1.2 equiv.), and acyl chloride **23** (0.79 g, 5.1 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (13 mL). The crude product was chromatographed on silica gel [CH_2Cl_2/EtOAc (95:5 to 90:10) as eluent] to afford **25c** as a yellow oil; yield 0.42 g (34%).

Ethyl Ester 25c: 51%. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.30–7.15 (m, 5 H), 5.58 (td, $^3J_{H,F}$ = 2.5, $^3J_{H,H}$ = $^3J_{H,F}$ = 9.5 Hz, 1 H), 4.86 (br. s, 1 H), 4.28 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 4.23 (2 × q, $^3J_{H,H}$ = 7 Hz, 2 H), 3.53 (m, 2 H), 2.41 (s, 3 H), 1.43 (s, 9 H), 1.25 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C ($CDCl_3$, 75.4 MHz): δ = 196.6, 167.9, 162.8 (t, $^2J_{C,F}$ = 25 Hz), 155.9, 140.1, 131.5, 128.5, 127.7, 117.0 (t, $^2J_{C,F}$ = 258 Hz), 79.6, 63.3, 55.0 (t, $^2J_{C,F}$ = 24 Hz), 32.8, 30.2, 28.4, 13.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –111.8 (dd, $^3J_{F,H}$ = 9.5, $^2J_{F,F}$ = 258 Hz), –115.6 (dd, $^3J_{F,H}$ = 17, $^2J_{F,F}$ = 258 Hz) ppm.

Methyl Ester 25c′: 49%. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 7.30–7.15 (m, 5 H), 5.63 (td, $^3J_{H,F}$ = 2.5, $^3J_{H,H}$ = $^3J_{H,F}$ = 9.5 Hz, 1 H), 4.86 (br. s, 1 H), 4.28 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 3.79 (s, 3 H), 3.53 (m, 2 H), 2.41 (s, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 196.5, 167.8, 162.9 (t, $^2J_{C,F}$ = 25 Hz), 155.9, 140.1, 131.5, 128.5, 127.6, 117.0 (t, $^2J_{C,F}$ = 258 Hz), 79.6, 55.0 (t, $^2J_{C,F}$ = 24 Hz), 53.6, 32.8, 30.2, 28.4, 13.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –111.3 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 259 Hz), –115.2 (dd, $^3J_{F,H}$ = 17, $^2J_{F,F}$ = 259 Hz) ppm.

***rac*-Ethyl 3-{[(Acetylsulfanyl)acetyl]amino}-2,2-difluoro-3-(pyridin-3-yl)propionate (25e):** Racemic β-amino ester **25e** was obtained from β-amino ester **15e** according to the procedure already described for the conversion of **15b** into **25b**, from **15e** (1 g, 3.75 mmol), DMAP (50 mg), triethylamine (1.8 mL, 12.8 mmol, 3.4 equiv.), and acyl chloride **23** (0.73 g, 4.8 mmol, 1.25 equiv.) in anhydrous CH_2Cl_2 (10 mL). The crude product was chromatographed on silica gel [CH_2Cl_2/MeOH/NH_4OH (98:2:0.2 to 96:4:0.4) as eluent] to afford **25e** as a yellow solid; yield 0.90 g (69%); m.p. 117 °C; TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.43. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.60 (d, $^3J_{H,H}$ = 1.5 Hz, 1 H), 8.58 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.66 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.40 (br. d, $^3J_{H,H}$ = 9.5 Hz, 1 H), 7.29 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 7.5 Hz, 1 H), 5.70 (m, 1 H), 4.26 (dq, J = 1.5, $^3J_{H,H}$ = 7 Hz, 2 H), 3.57 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.50 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 2.40 (s, 3 H), 1.27 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 196.7, 168.0, 162.2 (dd, $^2J_{C,F}$ = 31, $^2J_{C,F}$ = 32.5 Hz), 150.3, 149.6, 135.8, 128.8, 123.5, 113.2 (t, $^1J_{C,F}$ = 257.5 Hz), 63.6, 53.2 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27.5 Hz), 32.7, 30.2, 13.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –110.7 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 261 Hz), –115.7 (dd, $^3J_{F,H}$ = 18.5, $^2J_{F,F}$ = 261 Hz) ppm.

***rac*-2,2-Difluoro-3-[(mercaptoacetyl)amino]-3-(piperidin-4-yl)-propionic Acid (27b):** TFA (10 mL) and water (1 mL) were added to a solution of amide **25b** (0.78 g, 2.4 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at 0 °C for 1 h. After concentration, the crude product was dissolved in a mixture of MeOH/H_2O (1:3, 40 mL) and treated with aqueous NaOH solution (2 N) until pH = 9 was reached. The reaction mixture was stirred at 0 °C for 12 h. Most of the solvents were evaporated, and the mixture was washed with diethyl ether (30 mL) and acidified with aqueous HCl solution (1 N) until pH = 1 was reached. The aqueous phase was washed with diethyl ether (30 mL), and lyophilized. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 500:500:10) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **27b** as a yellow lyophilizate; yield 0.45 g (59%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 4.46 (dt, $^3J_{H,F}$ = 5.5, $^3J_{H,H}$ = $^3J_{H,F}$ = 14.5 Hz, 1 H), 3.35–3.45 (m, 2 H), 3.26 (s, 2 H), 2.90–3.05 (m, 2 H), 2.05–2.20 (m, 1 H), 1.95–2.05 (m, 2 H), 1.45–1.65 (m, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 172.5, 166.0 (t, $^2J_{C,F}$ = 28 Hz), 113.8 (t, $^1J_{C,F}$ = 257 Hz), 52.3 (t, $^2J_{C,F}$ = 24.5 Hz), 41.5 and 41.4, 31.2, 25.0, 21.8 and 21.7 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –110.1 (dd, $^3J_{F,H}$ = 14.5, $^2J_{F,F}$ = 249.5 Hz), –111.0 (dd, $^3J_{F,H}$ = 14.5, $^2J_{F,F}$ = 249.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3390, 2496, 1756, 1666, 1545, 1422, 1202, 959, 682 cm^{-1}. MS (ESI+): m/z = 304.9 [M + Na]$^+$, 283.0 [M + H]$^+$.

***rac*-3-[4-(Aminomethyl)phenyl]-3-[({[({1-[4-(aminomethyl)phenyl]-2-carboxy-2,2-difluoroethyl}carbamoyl)methyl]disulfanyl}acetyl)-amino]-2,2-difluoropropionic Acid (27c):** Anhydrous HCl was bubbled through a solution of the mixture of β-amino ester **25c** and its methyl ester derivative **25c′** (0.42 g, 0.9 mmol) in anhydrous MeOH for 10 min. The resulting solution was then stirred at room temp. for 3 h and concentrated. The resulting yellow oil was dissolved in a mixture of MeOH/THF (1:1, 20 mL) and treated with aqueous NaOH (2 N) solution until pH = 9 was reached. The reaction mixture was stirred at room temp. for 12 h, poured into water (30 mL), washed with diethyl ether (30 mL), and acidified with aqueous HCl (1 N) until pH = 1 was reached. The aqueous phase was washed with diethyl ether (30 mL), and lyophilized. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 500:500:10) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **27c** as a pale yellow lyophilizate; yield 0.10 g (36%). ^{1}H NMR (D_2O, 300.3 MHz): δ (pair of diastereomers) = 7.45–7.35 (m, 8 H), 5.53 (dd, $^3J_{H,F}$ = 13, $^3J_{H,F}$ = 15.5 Hz, 2 H), 4.08 (s, 2 H), 4.05 (s, 2 H), 3.34 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H), 3.31 (s, 2 H), 3.24 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ (pair of diastereomers) = 171.8, 167.4 (t, $^2J_{C,F}$ = 28.5 Hz), 134.3, 133.8, 129.5, 129.4, 115.2 (t, $^1J_{C,F}$ = 257 Hz), 56.0 (t, $^2J_{C,F}$ = 24.5 Hz), 42.9, 41.1 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ (pair of diastereomers) = –111.6 (dd, $^3J_{F,H}$ = 12.5, $^2J_{F,F}$ = 250.5 Hz), –111.8 (dd, $^3J_{F,H}$ = 13, $^2J_{F,F}$ = 250.5 Hz), –114.3 (dd, $^3J_{F,H}$ = 16, $^2J_{F,F}$ = 250.5 Hz), –114.5 (dd, $^3J_{F,H}$ = 16, $^2J_{F,F}$ = 250.5 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3500–3000, 1753, 1656, 1543, 1420, 1190, 971, 685 cm^{-1}. MS (ESI+): *m*/*z* = 628.9 [M + Na]$^+$, 607.0 [M + H]$^+$, 589.8 [M + H – NH_3]$^+$.

***rac*-3-Amino-3-[4-(aminomethyl)phenyl]-2,2-difluoropropanoic Acid Hydrochloride:** The hydrochloride form of the product of amide bond cleavage was obtained during the NaOH deprotection step of **25c**, after isolation by steric exclusion chromatography, as a white lyophilizate; yield 50 mg (20%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 7.51 (s, 4 H), 5.05 (dd, $^3J_{H,F}$ = 6, $^3J_{H,F}$ = 9 Hz, 1 H), 4.19 (s, 2 H) ppm. ^{1}H NMR ([D_6]DMSO, 300.3 MHz): δ = 9.43 (br. s, 1 H), 8.70 (br. s, 3 H), 7.57 (s, 4 H), 5.09 (dd, $^3J_{H,F}$ = 10, $^3J_{H,F}$ = 16 Hz, 1 H), 4.01 (s, 2 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 166.5 (t, $^2J_{C,F}$ = 26 Hz), 135.2, 130.0, 129.8, 129.4, 114.6 (dd, $^1J_{C,F}$ = 257.5, $^1J_{C,F}$ = 261 Hz), 57.0 (dd, $^2J_{C,F}$ = 22.5, $^2J_{C,F}$ = 26 Hz), 42.9 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –107.8 (dd, $^3J_{F,H}$ = 5.5, $^2J_{F,F}$ = 245 Hz), –117.4 (dd, $^3J_{F,H}$ = 18.5, $^2J_{F,F}$ = 245 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3020, 2044, 1682, 1592, 1410, 1217, 817 cm^{-1}. MS (ESI+): *m*/*z* = 253.0 [M + Na]$^+$, 231.0 [M + H]$^+$, 214.0 [M + H – NH_3]$^+$.

***rac*-2,2-Difluoro-3-[(mercaptoacetyl)amino]-3-(pyridin-3-yl)propionic Acid (27e):** A solution of amide **25e** (0.9 g, 2.6 mmol) in a mixture of MeOH/THF/H_2O (1:1:1, 18 mL) was treated with an aqueous LiOH solution (1 N, 7 mL). The reaction mixture was stirred at 0 °C for 12 h. Most of the solvents were evaporated, and the mixture was washed with diethyl ether (30 mL) and acidified with aqueous HCl solution (1 N) until pH = 1 was reached. The aqueous phase was washed with diethyl ether (30 mL) and lyophilized. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 200:200:4) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **27e** as a white lyophilizate; yield 0.16 g (20%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.82 (s, 1 H), 8.65 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 8.52 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.95 (dd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 8 Hz, 1 H), 5.70 (dd, $^3J_{H,F}$ = 11, $^3J_{H,F}$ = 15.5 Hz, 1 H), 3.17 (d, $^2J_{H,H}$ = 15 Hz, 1 H), 3.11 (d, $^2J_{H,H}$ = 15 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 174.1, 165.3 (dd, $^2J_{C,F}$ = 26, $^2J_{C,F}$ = 27 Hz), 147.0, 142.0, 141.2, 134.5, 127.9, 114.2 (dd, $^1J_{C,F}$ = 256, $^1J_{C,F}$ = 261 Hz), 53.4 (dd, $^2J_{C,F}$ = 25.5, $^2J_{C,F}$ = 28 Hz), 27.2 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –111.4 (d, $^2J_{F,F}$ = 256 Hz), –112.6 (d, $^2J_{F,F}$ = 256 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3404, 2360, 1756, 1669, 1547, 1409, 1325, 1194, 682 cm^{-1}. MS (ESI–): *m*/*z* = 275.0 [M – H]$^-$, 190.9, 117.0.

***rac*-Ethyl 2,2-Difluoro-3-[3-methoxy-3-oxopropanoyl)amino]-3-(pyridin-4-yl)propanoate (26d):** A solution of methyl malonyl chloride (**24**, 0.7 mL, 6.05 mmol, 1.6 equiv.) in anhydrous CH_2Cl_2 (3 mL) was added under nitrogen to a solution of β-amino ester **15d** (1 g, 3.75 mmol) in anhydrous CH_2Cl_2 (12 mL). *N*,*N*-Diisopropylethylamine (1.7 mL, 9.85 mmol, 2.6 equiv.) was then added dropwise to the solution at 0 °C, and the mixture was stirred at room temp. for 12 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL), and the mixture was extracted with CH_2Cl_2 (2 × 80 mL). The combined extracts were dried with anhydrous $MgSO_4$, and the solvent was evaporated to give a crude oily product. This was subjected to column chromatography [CH_2Cl_2/MeOH/NH_4OH (98:2:0.2 to 96:4:0.4) as eluent] to afford pure amide **26d** as a brown oil; yield 0.53 g (43%); TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.49. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.61 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 8.54 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H), 8.30 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 5.75 (dt, $^3J_{H,F}$ = 9.5, $^3J_{H,F}$ = 16 Hz, 1 H), 4.26 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 3.76 (s, 3 H), 3.42 (d, $^2J_{H,H}$ = 18.5 Hz, 1 H), 3.34 (d, $^2J_{H,H}$ = 18.5 Hz, 1 H), 1.25 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 169.8, 164.8, 162.2 (t, $^2J_{C,F}$ = 31 Hz), 150.2, 141.8, 123.1, 113.1 (t, $^1J_{C,F}$ = 258 Hz), 63.6, 54.2 (dd, $^2J_{C,F}$ = 24.5, $^2J_{C,F}$ = 26 Hz), 52.7, 40.0, 13.7 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –110.7 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 262 Hz), –114.5 (dd, $^3J_{F,H}$ = 16, $^2J_{F,F}$ = 262 Hz) ppm.

***rac*-Ethyl 2,2-Difluoro-3-[3-methoxy-3-oxopropanoyl)amino]-3-(pyridin-3-yl)propanoate (26e):** Racemic β-amino ester **26e** was obtained from β-amino ester **15e** according to the procedure already described for the conversion of **15d** into **26d**, with β-amino ester **15e** (1.04 g, 3.9 mmol), methyl malonyl chloride (**24**, 0.7 mL, 6.05 mmol, 1.5 equiv.), and *N*,*N*-diisopropylethylamine (1.7 mL, 9.85 mmol, 2.5 equiv.) in anhydrous CH_2Cl_2 (10 mL). Chromatography [CH_2Cl_2/MeOH/NH_4OH (99:1:0.1 to 96:4:0.4) as eluent] gave pure amide **26e** as a yellow oil; yield 0.72 g (56%). TLC: silica gel (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), R_f = 0.5. ^{1}H NMR ($CDCl_3$, 300.3 MHz): δ = 8.63 (d, $^4J_{H,H}$ = 2 Hz, 1 H), 8.55 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 5 Hz, 1 H), 8.50 (br. d, $^3J_{H,H}$ = 10 Hz, 1 H), 7.72 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.31 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 7.5 Hz, 1 H), 5.79 (dt, $^3J_{H,F}$ = 10, $^3J_{H,F}$ = 16 Hz, 1 H), 4.26 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 3.76 (s, 3 H), 3.40 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 3.33 (d, $^2J_{H,H}$ = 18 Hz, 1 H), 1.26 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 169.9, 164.6, 162.3 (dd, $^2J_{C,F}$ = 31, $^2J_{C,F}$ = 32.5 Hz), 150.3, 149.7, 135.8, 129.0, 123.6, 113.3 (t, $^1J_{C,F}$ = 257 Hz), 63.6, 53.1 (dd, $^2J_{C,F}$ = 25, $^2J_{C,F}$ = 27 Hz), 52.7, 40.0, 13.8 ppm. ^{19}F NMR ($CDCl_3$, 288.3 MHz): δ = –110.7 (dd, $^3J_{F,H}$ = 8.5, $^2J_{F,F}$ = 262 Hz), –114.5 (dd, $^3J_{F,H}$ = 16, $^2J_{F,F}$ = 262 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3293, 1770, 1748, 1671, 1550, 1330, 1292, 1203, 1133, 1073, 713 cm^{-1}.

***rac*-3-[(Carboxyacetyl)amino]-2,2-difluoro-3-(pyridin-4-yl)propanoic Acid (28d):** A solution of amide **26d** (0.54 g, 1.6 mmol) in a mixture of MeOH/H_2O (1:1, 10 mL) was treated with aqueous NaOH solution (1 N, 1.65 mL, 1 equiv.). The reaction mixture was stirred at room temp. for 2 h. Most of the solvent was evaporated, and the mixture was washed with diethyl ether (2 × 30 mL) and acidified with aqueous HCl solution (1 N) until pH = 1 was reached. The aqueous phase was washed with diethyl ether (30 mL) and

lyophilized. The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 200:200:4) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **28d** as a yellow lyophilizate; yield 93 mg (20%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.78 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 8.10 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H), 5.80 (t, $^3J_{H,F}$ = 13 Hz, 1 H), 3.56 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 3.47 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 75.4 MHz): δ = 169.0, 166.3, 163.4 (t, $^2J_{C,F}$ = 31 Hz), 154.9, 141.7, 127.1, 113.7 (t, $^1J_{C,F}$ = 255.5 Hz), 56.0 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27.5 Hz), 42.0 ppm. ^{19}F NMR (D_2O, 288.3 MHz): δ = –110.9 (dd, $^3J_{F,H}$ = 13, $^2J_{F,F}$ = 256 Hz), –111.8 (dd, $^2J_{F,F}$ = 13, $^2J_{F,F}$ = 256 Hz) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3404, 2360, 1756, 1669, 1547, 1409, 1325, 1194, 682 cm^{-1}. MS (ESI+): *m*/*z* = 288.9 [M + H]$^+$.

***rac*-3-[(Carboxyacetyl)amino]-2,2-difluoro-3-(pyridin-3-yl)propanoic Acid (28e):** Racemic β-amino acid **28e** was obtained from β-amino ester **26e** according to the procedure already described for the conversion of **26d** into **28d**, from β-amino ester **26e** (0.65 g, 1.95 mmol) and an aqueous LiOH solution (1 N, 6 mL, 6 mmol, 3 equiv.) in a mixture of MeOH/THF/H_2O (1:1:1, 18 mL). The crude product was purified by steric exclusion chromatography on a column of Biogel P2 (Bio-Rad) with MeCN/H_2O/HCl (1 N, 200:200:4) as the solvent. Fractions containing only product were pooled, and the solvent was removed under vacuum. Lyophilization yielded the hydrochloride salt of the title compound **28e** as a white lyophilizate; yield 112 mg (20%). ^{1}H NMR (D_2O, 300.3 MHz): δ = 8.82 (s, 1 H), 8.75 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 8.62 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 8.06 (dd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 8.5 Hz, 1 H), 5.79 (t, $^3J_{H,F}$ = 13 Hz, 1 H), 3.50 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 3.41 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H) ppm. ^{1}H NMR ([D$_6$]DMSO, 300.3 MHz): δ = 9.39 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H), 8.86 (s, 1 H), 8.76 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 8.26 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.78 (dd, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 8 Hz, 1 H), 5.84 (dt, $^3J_{H,H}$ = $^3J_{H,F}$ = 10, $^3J_{H,F}$ = 18 Hz, 1 H), 3.32 (d, $^2J_{H,H}$ = 15.5 Hz, 1 H), 3.25 (d, $^2J_{H,H}$ = 15.5 Hz, 1 H) ppm. ^{13}C ([D$_6$]DMSO, 75.4 MHz): δ = 169.0, 166.3, 163.4 (t, $^2J_{C,F}$ = 31 Hz), 145.1, 144.5, 142.8, 132.9, 126.2, 113.7 (t, $^1J_{C,F}$ = 255.5 Hz), 52.0 (dd, $^2J_{C,F}$ = 24, $^2J_{C,F}$ = 27.5 Hz), 42.6 ppm. ^{19}F NMR ([D$_6$]DMSO, 288.3 MHz): δ = –109.8 (dd, $^3J_{F,H}$ = 9.5, $^2J_{F,F}$ = 254.5 Hz), –114.6 (dd, $^2J_{F,F}$ = 19, $^2J_{F,F}$ = 254.5 Hz) ppm. MS (ESI+): *m*/*z* = 310.9 [M + Na]$^+$, 288.9 [M + H]$^+$. $C_{11}H_{10}F_2N_2O_5$·HCl (324.67): C 40.69, H 3.42, N 8.63; found C 40.64, H 3.37, N 8.66.

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