Stereoselective Preparation of 3-Amino-2-fluoro Carboxylic Acid Derivatives, and Their Incorporation in Tetrahydropyrimidin-4(1*H*)-ones, and in Open-Chain and Cyclic *β*-Peptides

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The preparation of (2*S*,3*S*)- and (2*R*,3*S*)-2-fluoro and of (3*S*)-2,2-difluoro-3-amino carboxylic acid derivatives, **1**–**3**, from alanine, valine, leucine, threonine, and β^3h-alanine (*Schemes 1* and *2*, *Table*) is described. The stereochemical course of (diethylamino)sulfur trifluoride (DAST) reactions with *N*,*N*-dibenzyl-2-amino-3-hydroxy and 3-amino-2-hydroxy carboxylic acid esters is discussed (*Fig. 1*). The fluoro-*β*-amino acid residues have been incorporated into pyrimidinones (**11**–**13**; *Fig. 2*) and into cyclic *β*-tri- and *β*-tetrapeptides **17**–**19** and **21**–**23** (*Scheme 3*) with rigid skeletons, so that reliable structural data (bond lengths, bond angles, and *Karplus* parameters) can be obtained. *β*-Hexapeptides Boc[(2*S*)-β^3hXaa(*α*F)]$_6$OBn and Boc[β^3hXaa(*α*,*α*F$_2$)]$_6$-OBn, **24**–**26**, with the side chains of Ala, Val, and Leu, have been synthesized (*Scheme 4*), and their CD spectra (*Fig. 3*) are discussed. Most compounds and many intermediates are fully characterized by IR- and ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy, by MS spectrometry, and by elemental analyses, $[\alpha]_D$ and melting-point values.

1. Introduction. – The effect of backbone substitution **A** by F-atom(s) (or other heteroatoms) of a peptide consisting of proteinogenic *α*-amino acids cannot be studied due to hydrolytic instability[4]). In constrast, F-substituted *β*- and *γ*-amino acid derivatives **B** [1][3–6] and **C** [7] are stable. For incorporation of 3-amino-2-fluoro and 3-amino-2,2-difluoro acid moieties into *β*-peptides **D**-F and **D**-F$_2$, or for syntheses of *β*-peptides **E**-F and **E**-F$_2$ bearing F-atom in each residue, we needed an access to configurationally pure building blocks of type **1**, **2**, and **3** with *N*-Boc protection for solution synthesis [4] and *N*-Fmoc protection for solid-phase peptide synthesis [5].

One aim of the present paper is to describe the preparation of such *α*-fluoro-*β*-amino acid derivatives in full detail[5]), and to discuss some mechanistic aspects. A

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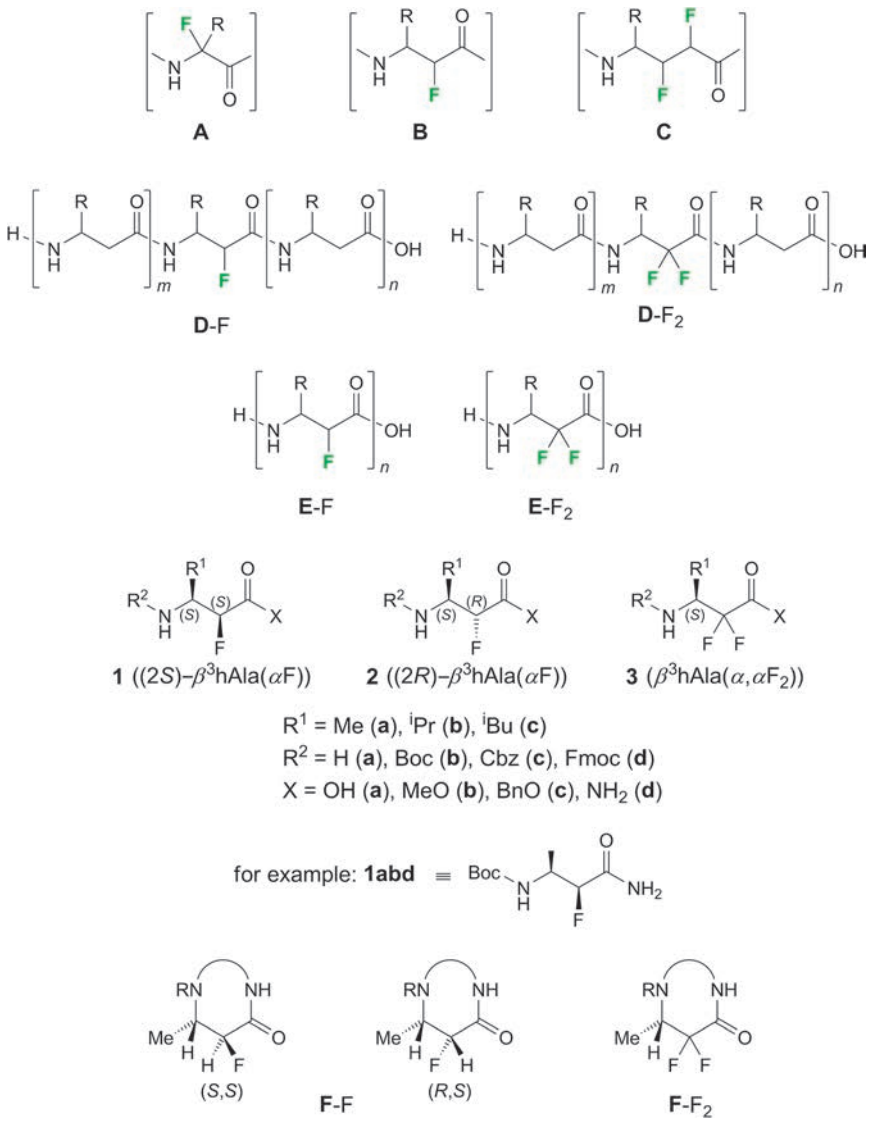
[3]) Part of the Master Thesis (Diplomarbeit) of *C. N.*, ETH Zürich, 2002/2003.

[4]) See the discussion in [1]. For a *γ*,*γ*-difluoro-*δ*-amino acid, see [2].

[5]) Only the preparation of the alanine-derived compounds **1**–**3**, R^1 = Me, has been described in full detail [4]. For the NMR-structural analyses of four peptides with a central fluoro- or difluoro-substituted building block, see: [1][5][6]. Polyfluorinated peptides of type **E**-F and **E**-F$_2$ are mentioned in a preliminary communication [3], and in the hitherto unpublished master thesis of *C. Noti* (see *Footnote 3*). For determination of proteolytic stabilities of F-substituted *β*-peptides, see [4].



second purpose is to present cyclic and macrocyclic F-substituted β-amino acid derivatives **F**-F and **F**-F_2, which fulfill the following stringent requirements: *i*) they should be crystalline (for X-ray analysis) and *ii*) they are likely to have the same conformation in solution (for NMR analysis) and in the solid state; this would provide experimental data (*Karplus* parameters) for the interpretation of NMR spectra and for comparison with structures calculated by *ab initio* or molecular-dynamics methods[6]).

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[6]) It turned out that both the NMR analysis and the MD calculation of F-substituted β-peptides gave confusing results, due to lack of reliable parameters [5][6][8].

2. Preparation of the F-Substituted *β*-Amino Acid Derivatives 1–3. – We have chosen three stereospecific methods for the introduction of F-substituents, all starting from natural *α*-amino acids alanine, valine, leucine, and threonine[7]). The F-atoms were introduced nucleophilically with (diethylamino)sulfur trifluoride (DAST; 'F^-') [9] and electrophilically with $(PhSO_2)_2NF$ ('F^+') [9b][10].

The 'work-horse' route (*Scheme 1*) started from the aldehydes **4a**–**4c** [11] obtained by *N*,*N*-dibenzylation and CO_2H reduction of the corresponding amino acids. *Reetz*'s diastereoselective non-chelation-controlled (BF_3) and chelation-controlled ($TiCl_4$) cyanohydrin reaction with Me_3SiCN (→ **5a**–**5c**) [12] was followed by the *Pinner* reaction with aqueous workup to give the 3-amino-2-hydroxy carboxyclic acid esters **6a**–**6c**, treatment of which with DAST led to mixtures of the constitutional isomers **7** and iso-**7** with higher regioselectivities in the *l*-series of compounds (*i.e.*, **6** → **7**) than in the *u*-series (*i.e.*, *epi*-**6** → *epi*-**7**; see mechanistic discussion in *Sect. 3*). For the preparation of the geminal difluoro-*β*-amino acid esters, a 'cheaper' non-diastereoselective version of the cyanohydrin reaction was used [13] (*Scheme 1*; lower part). *Swern* oxidation of the mixture of diastereoisomers **6**/*epi*-**6** to the *α*-keto esters and *in situ* treatment with DAST provided the difluoro esters **8** in enantiomerically pure form[8]).

For preparation of the butanoate derivative *epi*-**7a**, there is a shorter route (*Scheme 2*, *a*) [15]: the *N*,*N*-dibenzylthreonine benzyl ester (**9**) undergoes a fluorinating rearrangement when treated with DAST to give *epi*-**7a**Bn of (2*R*,3*S*)-configuration as the major product. As with the other mixtures of isomers **7**/iso-**7** (*Scheme 1*, upper part) chromatographic separation from the 'direct' substitution product iso-*epi*-**7a**Bn and isolation of the pure *α*-fluoro-*β*-amino acid ester *epi*-**7a**Bn was straightforward.

Finally, the methyl Boc- and Cbz-(*S*,*S*)-3-amino-2-fluorobutanoates, **1abb** and **1acb**, are accessible by direct fluorination [16] of the corresponding doubly lithiated [17] β^3hAla derivatives with $(PhSO_2)_2NF$ (*Scheme 2*, *b*).

Having established the preparation of the 3-amino-*N*,*N*-dibenzyl-2-fluoro- and -2,2-difluoro-alkanoates **7** and **8**, only simple functional-group manipulations were needed to arrive at the desired building blocks **1**–**3** for peptide synthesis. The reagents and solvents used are collected in the *Table*, together with the starting materials and products of the various conversions. The absolute configurations of compounds **1**–**3** follow from the use of (*S*)- or L-*α*-amino acid starting materials, the relative configurations are deduced from an X-ray crystal structure (bottom part of the *Table*), from NMR data and by analogy[9]).

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[7]) Since these amino acids are all available in both enantiomeric forms, the enantiomers of the compounds reported herein will be accessible by exactly the same methodology.

[8]) Purification of the keto esters by chromatography turned out to lead to partial racemization. The *in situ* procedure led to the *N*-Boc-amino-difluoro carboxylic acids **3aba**, **3bba**, and **3cba** with er > 97:3, > 99:1, and > 98:2, respectively, as derived from HPLC on chiral column material of precursor esters. For previous preparations of *α*,*α*-difluoro-*β*-amino acid derivatives, see [14a,b]. For a comprehensive review on the methods of synthesis of geminal difluoro methylene compounds, see [14c].

[9]) The NMR-structural analyses [1][5][6] of *β*-hepta- and *β*-tridecapeptides of type **D**-F and **D**-F_2 with central F- or F_2-*β*-amino acid residues **1**, **2**, and **3** (R^1 = Me, R^2, Y = $(\beta hXaa)_n$) provide further support for the correctness of the *relative* and *absolute* configurational assignment of these building blocks.

Scheme 1. *Conversion of the Ala-, Val-, Leu-Derived (S)-Dibenzylamino Aldehydes* **4** *to the Mono- and Difluoro-Substituted β-Amino Acid Esters* **7** *and* **8**. The OH/F replacement with DAST (**6** → **7**) occurs with retention of configuration. The migratory fluorination, in which the F-atom winds up at C(3) (replacing NBn_2) and the amino group at C(2) (replacing OH), takes place with inversion of configuration on both centers (**6** → iso-**7**).

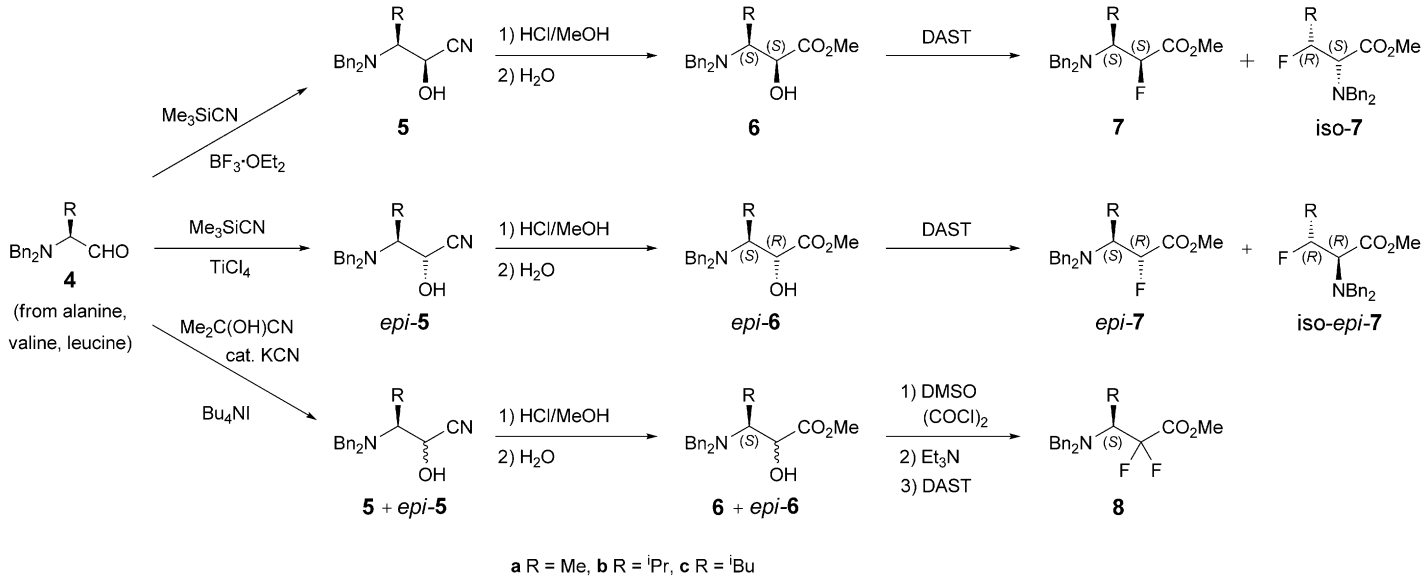
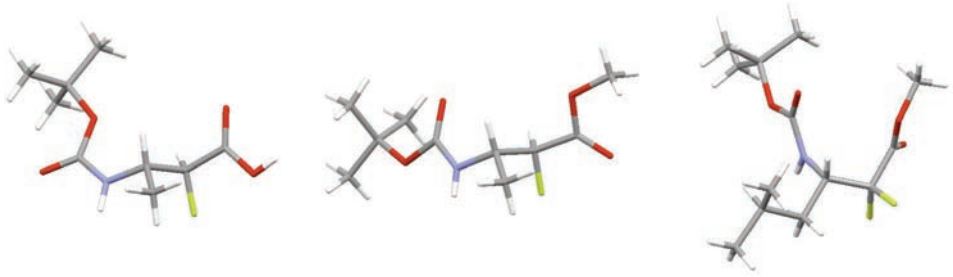


Table. *Reagents Used for the Functional-Group Manipulations to Convert the Primary Products* **7** *and* **8** *of Fluorination to the Starting Materials* **1**–**3**. Interconversions of compounds of type **1** and **2** are also included in this *Table*. For the specification with the letters **a**, **b**, **c**, **d**, see the *Formulae* in the *Introduction*. The X-ray data for compounds **1aba**, **1abb**, and **3cbb** have been deposited with the *Cambridge Crystallographic Data Centre*.

Starting material of type **1**, **2**, **3**, **7**, **8** → [1) LiOH, EtOH/H_2O; 2) H_2, Pd/C, MeOH; 3) Boc_2O, Et_3N, MeOH; 4) CbzCl, Et_3N, MeOH; 5) BnBr, Cs_2CO_3, DMF; 6) EtOCOCl/Et_3N, NH_3, THF; 7) TFA/CH_2Cl_2] → Product of type **1**, **2**, **3**

Starting material	Reaction conditions	Product	Starting material	Reaction conditions	Product
7a	*1*, *2*, *3*	**1aba**	**1abb**	*1*	**1aba**
7b	*1*, *2*, *3*	**1bba**	**1acb**	*1*	**1aca**
7c	*1*, *2*, *3*	**1cba**	**1cba**	*5*	**1cbc**
epi-**7a**	*1*, *2*, *3*	**2aba**	**2cba**	*5*	**2cbc**
epi-**7a**Bn	*2*, *3*	**2aba**	**3cba**	*5*	**3cbc**
epi-**7a**Bn	*2*, *4*	**2aca**	**1aca**	*6*, *2*	**1aad**
epi-**7b**	*1*, *2*, *3*	**2bba**	**2aca**	*6*, *2*	**2aad**
epi-**7c**	*1*, *2*, *3*	**2cba**	**3aca**	*6*, *2*	**3aad**
8a	*1*, *2*, *3*	**3aba**	**1cbc**	*7*	**1cac**
8a	*1*, *2*, *4*	**3aca**	**2cbc**	*7*	**2cac**
8b	*2*, *3*	**3bbb**	**3cbc**	*7*	**3cac**
8c	*2*, *3*	**3cbb**	**3bbb**	*1*	**3bba**
			3cbb	*1*	**3cba**

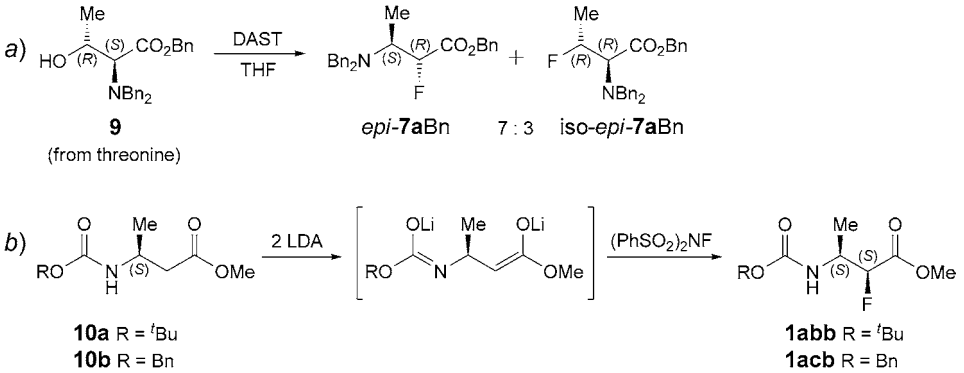


1aba CCDC-840442 **1abb** CCDC-840443 **3cbb** CCDC-840445

Before describing the use of the fluorinated β-amino acids for tetrahydropyrimidinone and peptide synthesis, some comments about the mechanistic course of the DAST reaction are appropriate.

3. Stereo- and Regiochemical Course of the DAST Reactions 6 → 7. – As we can see from *Schemes 1* and *2*,*a*, the desired β-amino-α-fluoro-acid esters **7** are formed with

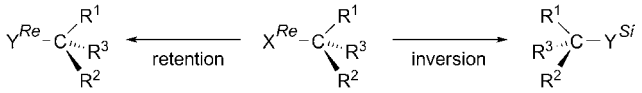
Scheme 2. *Alternative Routes to α-Fluoro-β-amino Acid Derivatives. a*) Treatment of an *N,N*-dibenzylthreonine ester with DAST, and *b*) direct electrophilic fluorination of an *N*-carbamoyl-β-amino acid ester through a doubly lithiated species.

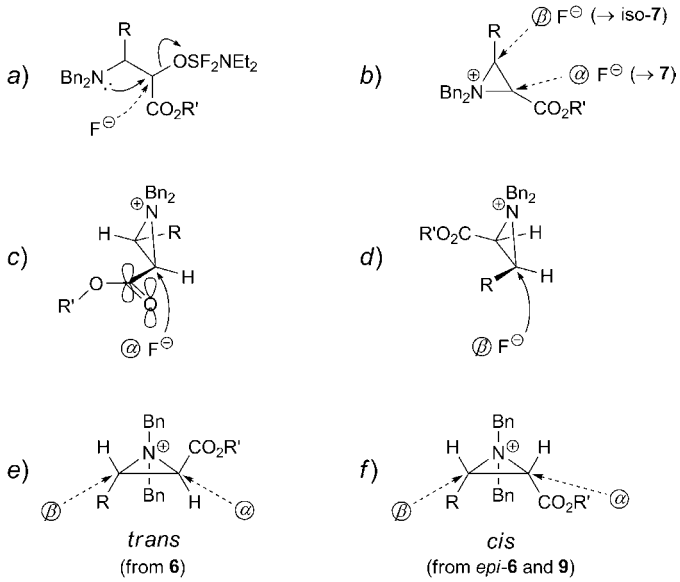


retention of configuration[10]), when we start from the β-amino-α-hydroxy-acid esters **6**, and with inversion on both stereogenic centers, when we start from the α-amino-β-hydroxy ester **9**. The isomeric α-amino-β-fluoro carboxylic acid esters iso-**7** and iso-*epi*-**7** are formed with inversion on both centers and with retention on the F-substituted C-atom, respectively. This, at first sight, somewhat confusing stereochemical outcome is caused by the intermediacy of *N,N*-dibenzylaziridinium ions [15a,b], as outlined in *Fig. 1,b–f*. Both, the ring closure to, and the ring opening of the three-membered ring occur with an S_N2-type inversion of configuration, and the regiochemical course is determined by the relative rates of C–N bond cleavage next to the ester group and next to the substituent R on the three-membered ring. As can be seen from the table in *Fig. 1*, the carbonyl-assisted opening of the aziridinium ring is preferred in the *trans*-substituted series, while there is a delicate dependence on the type of substituent in the *cis*-series of aziridinium intermediates. Concomitantly, the yields of the desired β-amino-α-fluoro-acid derivatives of (2*R*,3*S*)-configuration (*epi*-**7**) are lower than those of the (*S*,*S*)-isomers **7**.

4. Tetrahydropyrimidin-4(1*H*)ones and Cyclo-β-peptides Containing the F-Substituted Amino Acid Residues of 1a, 2a, and 3a. – As mentioned in the *Introduction*, there is lack of structural and NMR data for F-substituted carbonyl compounds. To correlate X-ray-crystal solid-state structures with NMR-solution structures, the compounds should have rigid skeletons. Thus, we turned to previous work on non-fluorinated β-amino acid derivatives, which had been shown to have a high degree of crystallinity, and which had structures that are likely not to be subject to dynamic conformational equilibrations on

[10]) Note that the *CIP* convention may not be useful for assigning retention or inversion of configuration because priority orders may change. A useful test is to assign whether the new substituent is located in the same or in the opposite half-space of the stereogenic center as compared to the replaced substituent:





R	R'	Ⓐ/Ⓑ (7/iso-7)	Ⓐ/Ⓑ (*epi*-7/iso-*epi*-7)	Yield [%] 7	*epi*-7
H	Bn	99 : 1[a])	–	90	–
Me	Me	91 : 9	52 : 48	85	37
Me	Bn	–	73 : 27	–	60
^{i}Bu	Me	94 : 6	66 : 34	85	45
^{i}Pr	Me	97 : 3	97 : 3	72	60

[a]) Taken from [15a].

Fig. 1. *Steric and regiochemical course of the DAST reactions with dibenzylamino hydroxy esters* **6** *and* **9**. *a*) Reaction with DAST converts the OH group to a leaving group, which is not replaced intermolecularly by F^- but intramolecularly by Bn_2N. *b*) The resulting aziridinium ion can react with F^- in the α-carbonyl (α) or in the β-carbonyl position (β). *c*) In the *trans*-substituted aziridinium ring, an S_N2-assisting conformation of the ester group is possible (high regioselectivity of α attack). *d*) In the *cis*-substituted aziridinium ring, there are three substituents on the same face of the three-membered ring, which causes steric hinderence of the S_N2-assisting ester-group conformation, allowing for competing ring-opening (β) next to the R group (poor regioselectivity (*epi*-**7**/iso-*epi*-**7**)). *e*) and *f*) *trans*- and *cis*-aziridinium-ion intermediates, relative rates of ring opening, and yields of purified products **7** and *epi*-**7**. The high selectivity of formation of *epi*-**7b** through as *cis*-aziridinium ion might be due to a kind of neopentyl effect: a Me group of the ^{i}Pr-substituent blocks the S_N2 trajectory of the attacking F^- nucleophile, thus favoring the ring opening next to the ester group.

the NMR time-scale. These were hexahydropyrimidin-4-ones **G** [18], and cyclo-β-tri- and -tetrapeptides **H** [19] and **I**, respectively [20][11]) (*Fig. 2*).

*Tetrahydropyrimidin-4(1*H*)-ones* **11**–**13**. Thus, we treated the amino acid amides **1aad**, **2aad**, and **3aad** with pivalaldehyde in refluxing CH_2Cl_2 (with azeotropic removal

[11]) These cyclo-β-peptides assemble to stacks in the solid state. A cyclo-β-tripeptide has recently been used to construct a mimic of CD40L with a K_D value of 2.4 nM [21].

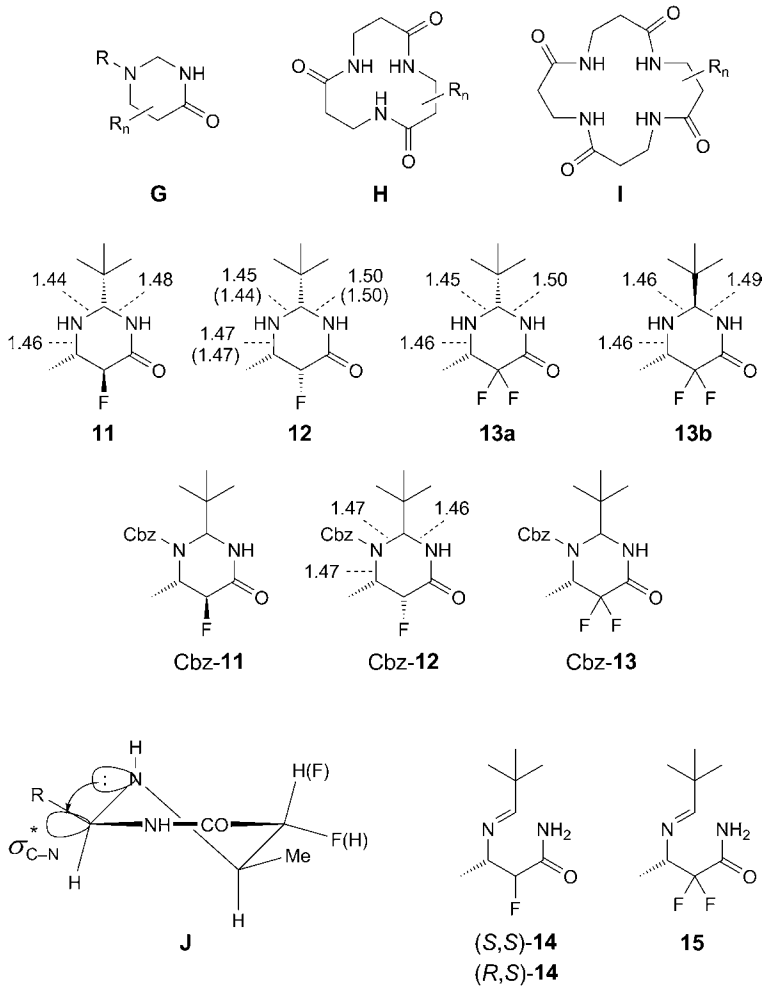


Fig. 2. *Cyclic derivatives* **G**, **H**, *and* **I** *of β-amino acids and F-substituted tetrahydro-pyrimidinones* **11**–**13**. The numbers in the formulae of **11**–**13** are bond distances in Å, determined by X-ray crystal-structure analysis[13]). For **12**, two sets of bond lengths are given, since there are two different conformations in the crystal unit cell of this compound. Presentation **J** indicates the $n_N \rightarrow \sigma^*(C–N)$ interaction facilitating ring opening to the imino amides **14** and **15**.

of H_2O), which led to the tetrahydropyrimidin-4(1*H*)-ones **11**, **12**, and **13**, respectively (*Fig. 2*). The yields of purified, crystalline products were moderate or low (52, 43, and 16%, resp.), which was, at least partially, due to their lability: when dissolved in a protic solvent such as MeOH, they underwent ring opening to yield imino amides **14** and **15** (NMR-tube experiment). Especially the F_2-substituted compounds of type **13** are prone to undergo this isomerization. The *cis*- and *trans*-isomers **13a** and **13b** co-crystallized in a 1:1 ratio and could not be separated. The crystals of **12** contain two conformers in the unit cell. Benzyloxycarbonylation of the tetrahydropyrimidin-4(1*H*)-

ones **11**–**13** gave more stable[12]) derivatives Cbz-**11**, Cbz-**12**, and Cbz-**13**, respectively. X-Ray crystal structures[13]) of compounds **11**–**13** exhibit pronounced pyramidalization of the amino *N*(5) (Δ between 0.30 and 0.44 Å), such that the virtual lone-pair lobe is *antiperiplanar* to the C(6)–N(1) bond, with concomitant bond-length shortening and lengthening. In the Cbz derivatives, the N(5)-atom is, of course, sp^2-hybridized, and the bond lengths (in Cbz-**12**) are more or less normal[14]). The instability of tetrahydropyrimidin-4(1*H*)-ones is clearly caused by a stereoelectronic effect ($n_N \rightarrow \sigma^*(C–N)$), as indicated by the presentation **J** in *Fig. 2*.

Cyclo-β-tripeptides **17**–**19**. The synthesis was accomplished according to traditional protocols (*Scheme 3*). Coupling of the *N*-Boc-fluoro-amino acids with the dipeptide ester H-βGly-βGly-OMe using HBTU/NMM[15]) furnished the *N*-Boc-β-tripeptides **16a**–**16c** in high yields. There are numerous approaches for the cyclization of peptides, many with miserable yields. The route *via* pentafluorophenyl esters, as developed by *U. Schmidt et al.* [24], was the method of choice, as it had been successfully employed for β-peptides before [19b,d]: transesterification of **16a**–**16c** to the active esters, Boc-deprotection, and slow addition (*via* syringe pump) of solutions of the resulting TFA salts of the tripeptide pentafluorophenyl esters to a dilute (3.3 mM) solution of *Hünig* base (DIPEA in MeCN, 70°) gave the cyclo-β-tripeptides **17**–**19** in good overall yields (*Scheme 3*, left). Like the non-fluorinated analogs [19b,c], the cyclization products are insoluble in essentially all common solvents and precipitated from the hot, dilute reaction mixture, to be isolated by simple filtration. NMR Spectra were recorded in a mixture of $CDCl_3$ and TFA.

Cyclo-β-tetrapeptides **21**–**23**. In an attempt to prepare cyclo-β-dipeptides consisting of one F-substituted residue and one β-Gly moiety, we prepared the *N*-Boc-protected peptide methyl esters **20a**–**20c**. By the same procedure as for the tripeptides, the dipeptide pentafluoro-phenyl esters were prepared, and their solutions were added to the *Hünig*-base solution (MeCN, 70°). To our surprise[16]), the cyclo-β-tetrapeptides

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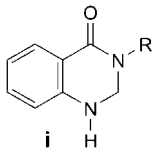
[12]) The F_2-substituted Cbz-**13** was still quite unstable and could be isolated in only 6% yield as an oil (see *Exper. Part*). We had noticed the instability of such hydro-pyrimidinones with non-F-substituted derivatives before [18f].

[13]) The crystal structures of the heterocycles **11**–**13** of type **G** and of the cyclo-β-tri- and -tetrapeptides **H** and **I** will be published separately, together with detailed NMR analyses and *ab initio* calculations [22].

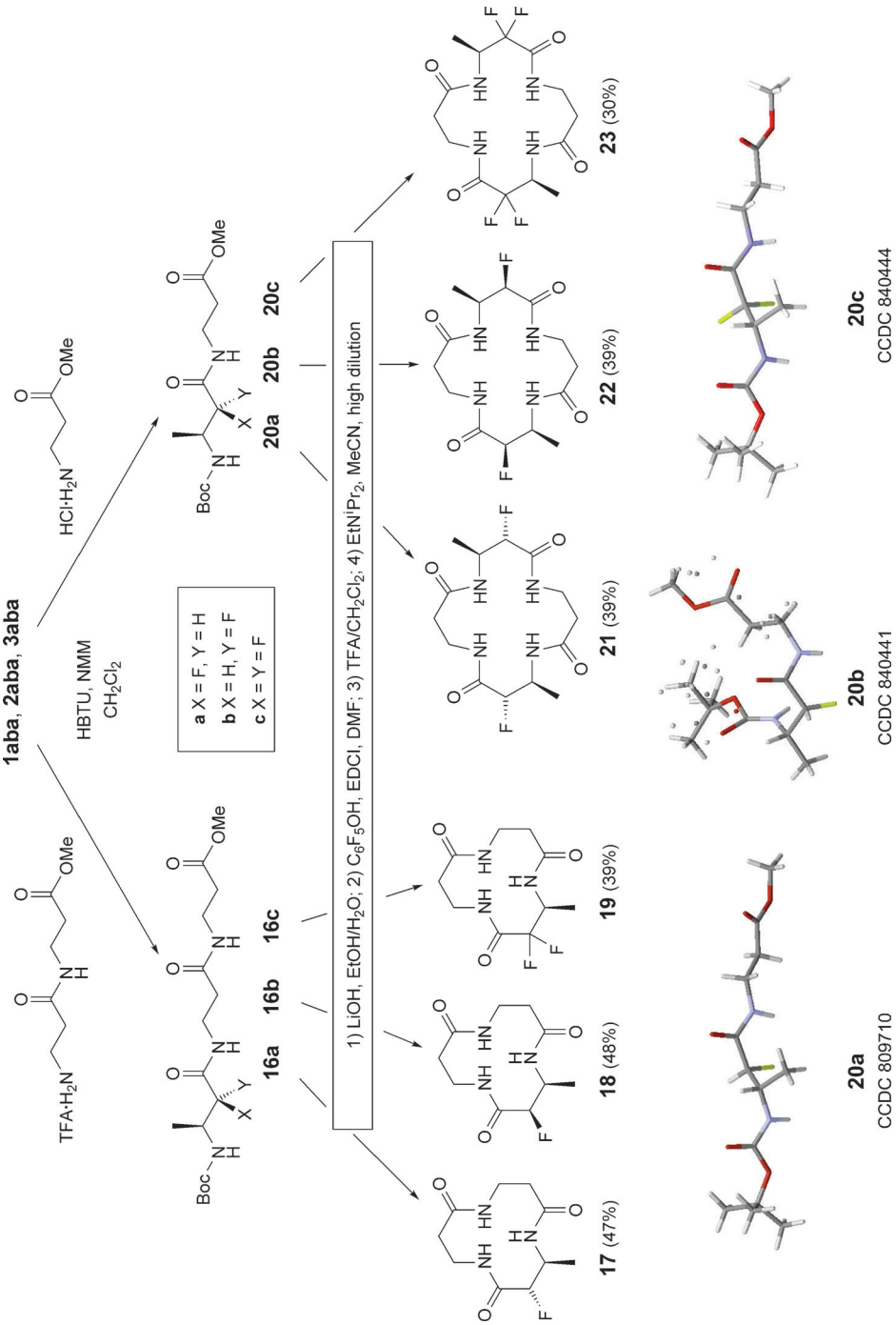
[14]) The dihydrobenzopyrimidin-1(1*H*)-ones of type **i** are also somewhat unstable. In crystal structures, their N(1)-atom is, however, only slightly or not at all pyramidalized (π-conjugation is stronger than $n \rightarrow \sigma^*$ interaction) [23].



i

[15]) For abbreviations not specified in the *Schemes*, *Table*, and *Figures*, see introduction of the *Exper. Part*.

[16]) A 'reverse' case was reported by *Vilarrasa* and co-workers, who tried to prepare a cyclo-β-tetrapeptide under the same conditions and were disappointed to obtain the eight-membered ring of a cyclo-β-dipeptide [20b].



Scheme 3. *Synthesis of F-Substituted Cyclo-β-tripeptides* **17**–**19** *and Cyclo-β-tetrapeptides* **21**–**23**, *and X-Ray Crystal Structures of the Linear Precursors* **20a**–**20c**. Overall yields of conversions from the open-chain *N*-Boc-protected peptide esters **16** and **20** are given. The X-ray data for compounds **20b** and **20c** have been deposited with the *Cambridge Crystallographic Data Centre*. The structure of **20a** has been published in [6]; parts of the structure of **20b** are disordered.

21–**23** were isolated in acceptable yields (30–40%; *Scheme 3*, right). Again, these cyclic peptides have high melting points and poor solubilities in common organic solvents, like the non-fluorinated counterparts [19d][20c], and as with those, we were not able to prepare suitable single crystals for conventional X-ray analyses.

There are ongoing attempts to determine the structures of some of the F-substituted cyclo-β-peptides **17**–**19** and **21**–**23** by powder-diffraction techniques[13]), a method that had been successful with the simple (β^3hAla)$_4$ derivatives [20c].

5. Synthesis and Spectroscopic Characterization of β-Hexapeptides 24–26 with F-Substitution in Each Residue. – From the NMR analyses of β-peptides containing a single, central fluoro- or difluoro-β-amino acid residue **1**, **2**, or **3** [1][5][6], we would expect that a β-hexapeptide **24b**, built of (*S*,*S*)-2-fluoro-βhVal, -βhAla, and -βhLeu residues does not fold to an (*M*)-3_{14}-helix [25]. The isomeric hexapeptide **25b** with the corresponding (2*R*,3*S*)-fluoro-amino acid building blocks, on the other hand, could fold to an (*M*)-helix, with axial disposition [25] of an F-atom in each residue. For the hexapeptide **26b**, with two geminal F-atoms in each amino acid moiety of the (βhVal-βhAla-βhLeu)$_2$ chain, a weaker tendency for folding to the 3_{14}-helix must be envisaged [6].

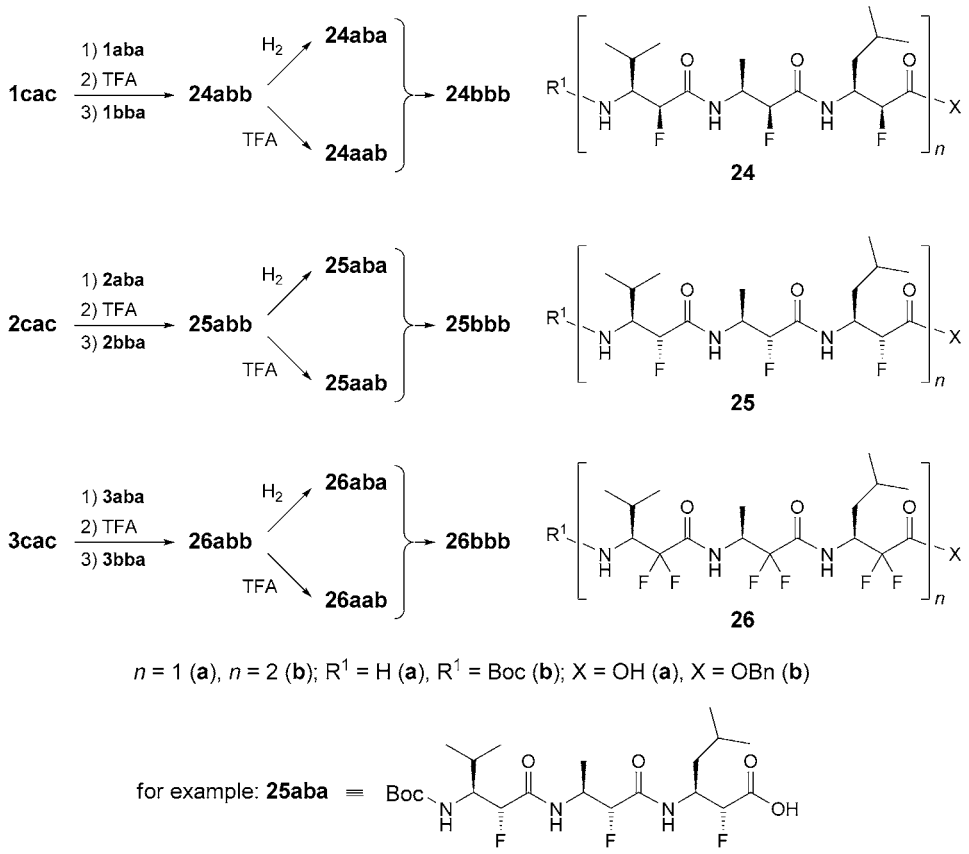
Synthesis. The assembly of the three F-substituted β-hexapeptides **24b**–**26b** was performed as outlined in *Scheme 4*, by using a classical solution-phase Boc strategy for the coupling (with NMM/HOBt/EDC or NMM/HATU[15]), and a C-terminal benzyl ester group. After attaching the βhAla and βhVal units to the βhLeu-benzyl esters (*i.e.*, **1cac**, **2cac**, **3cac**), the tripeptide derivatives **25abb**–**26abb** were divided into two portions, one to be Boc-deprotected (TFA in CH_2Cl_2), the other one to be debenzylated (H_2/Pd-C in MeOH).

Fragment coupling of the two trimers gave the terminally protected hexapeptides **24bbb**–**26bbb**, which were investigated as such or after deprotection to **24baa**–**26baa**, respectively. Most intermediates and final products of these syntheses were characterized by melting points, $[\alpha]_D$ values, ^{1}H-, ^{13}C-, ^{19}F-NMR, MS, IR, CD spectroscopy, and elemental analyses (see *Exper. Part*).

CD and NMR Spectra. In our work on β-peptides, we have preferentially used MeOH as solvent for CD and NMR recordings; it turned out that some of the fluoro-hexapeptide derivatives are poorly soluble in this solvent. For the high dilution (0.2 nM) of solutions for recording CD spectra, the solubility in MeOH was sufficient, but for NMR recordings, we had to turn to more polar solvents such as (D_6)DMSO (H-bond destroying) or CF_3CD_2OD (TFE, favoring secondary-structure formation).

The *CD spectra* of the hexapeptide **24bbb**, consisting of *like*-fluoro-β-amino acid residues in hexafluoro-isopropanol ($(CF_3)_2CHOH$; HF^{i}PrOH), of the *unlike*-isomer **25bbb** and its deprotected form **25baa** (in MeOH, TFE, and HF^{i}PrOH), and of the hexapeptide **26bbb** with geminal difluoro groups and its unprotected form **26baa** (in the same solvents) are shown in *Fig. 3*, *a*, *b*, and *c*, respectively. The peptide consisting of (*S*,*S*)-building blocks exhibits two strong *Cotton* effects (θ *ca.* 80,000) at 213 (positive) and 195 nm (negative) in HF^{i}PrOH; due to lack of comparison, it is impossible to interpret this spectrum. If we compare the CD spectra of the hexapeptide derivatives with one F-atom per amino acid unit and (2*R*,3*S*)-configuration (*Fig. 3*,*b*) and with two F-atoms per amino acid unit (*Fig. 3*,*c*) in the standard solvent MeOH, we would

Scheme 4. *Synthesis of the β-Tri- and β-Hexapeptide Derivatives* **24a**–**26a** *and* **24b**–**26b**, *Respectively, with One or Two F-Sustituents in Each Amino Acid Residue.* The syntheses were carried out by coupling in solution using the Boc strategy. For details, see the *Exper. Part*.



conclude that there is no secondary structure in the first case (weak extrema) and an unknown structure in the second case (strong maxima of θ up to 100,000 near 220 and 215 nm)[17]). There are two surprises in the CD spectra.

i) In the fluorinated alcohols as solvents, the unprotected β-hexapeptide **25baa** with (*R*,*S*)-building blocks exhibits a CD pattern, which *'the experts in the area'* would associate with a left-handed 3_{14}-helix (minimum, albeit weak, near 215, and intensive maximum near 195 nm; *Fig. 3*,*b*); such a helix would have *all* F-atoms in the thermodynamically more stable axial disposition (with antiperiplanar arrangement of F- and carbonyl O-atom, *i.e.*, F–C–C=O dihedral angle of 180° [6]). The terminally protected form **25bbb** has a more or less flat CD pattern near zero in all three solvents (*Fig.3*,*b*).

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17) A typical CD spectrum of a β-peptide folding to a 3_{14}-helix shows a strong *negative Cotton* effect near 215 nm [25].

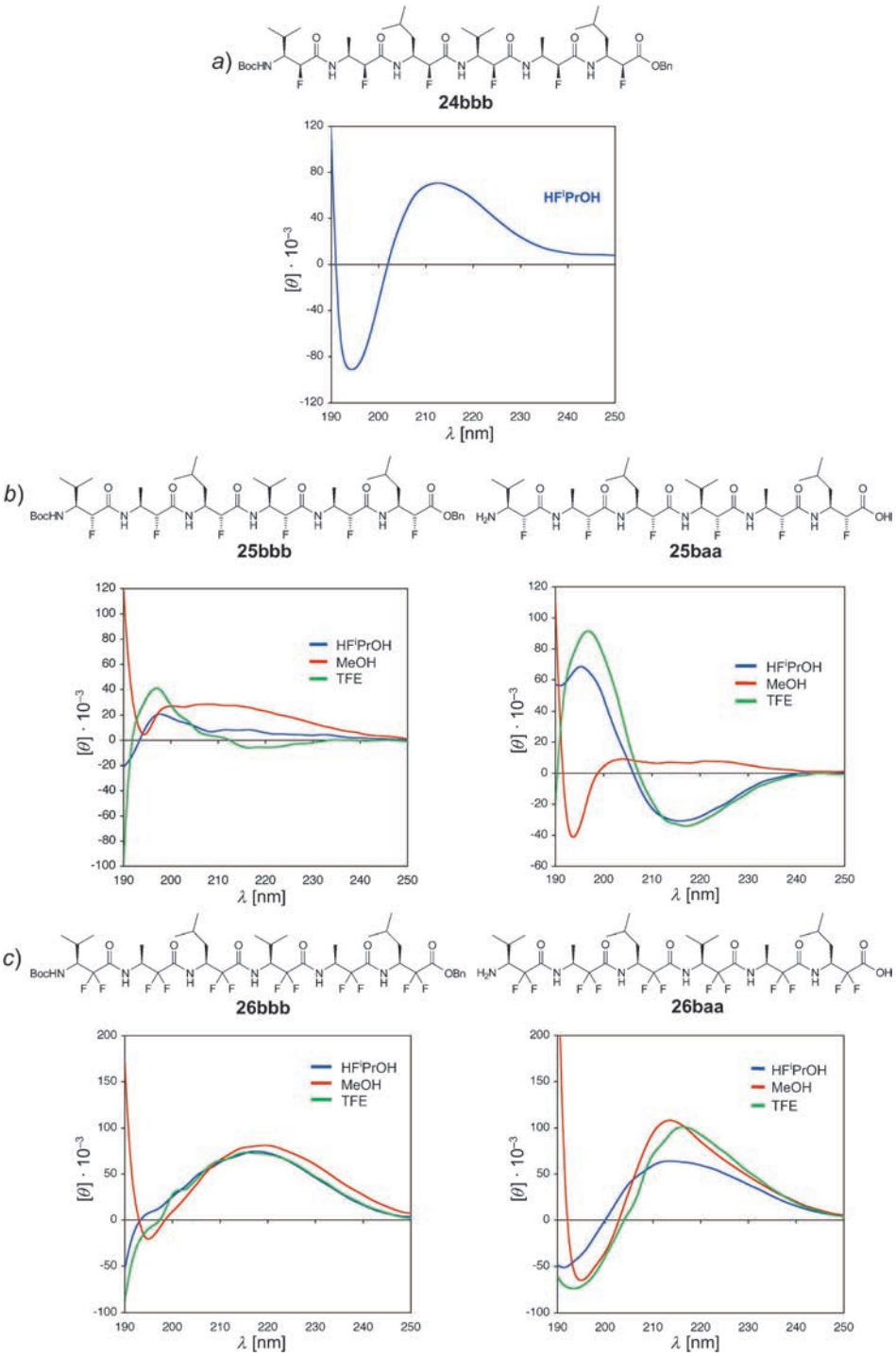

Fig. 3. *CD Spectra of the β-hexapeptide derivatives with one or two F substituents in each residue*

ii) The β-hexapeptides with geminal difluoro substitution in each residue give rise to CD spectra, which are almost superimposable with those for the protected form **26bbb** (*Fig. 3,c*), and quite similar to those for the unprotected form **26baa** in all three solvents (*Fig. 3,c*), meaning that – in first approximation – the secondary-structure-inducing fluorinated solvents do not change the backbone conformation, as compared to MeOH.

Caveat: Suggestions, made in this section, about possible structures of the fluorinated hexapeptides must be taken with due care: we have reiterated that the CD spectra of β-peptides can be deceiving, to say the least [25][26].

NMR Spectra of the hexafluoro- and dodecafluoro-β-hexapeptides with and without terminal protection (*N*-Boc, OBn) were recorded with solutions in CF_3CD_2OD/TFA, CD_3OH, or (D_6)DMSO (see *Fig. 4*); they are described in the *Exper. Part*; an interpretation will have to wait for our detailed NMR-structural analyses with the parameters determined from the cyclic compounds.

6. Conclusions and Outlook. – Configurationally uniform mono- and difluoro-β-amino acid derivatives and peptides with and without N- and/or C-terminal protections have been successfully prepared by known methods. The intermediacy of *N,N*-dibenzyl-aziridinium ions in the DAST reaction of vicinal amino-hydroxy-substituted C-chains has been confirmed. The regioselectivity of S_N2-type ring opening of these three-membered rings has been shown to be subject to intriguing, subtle substitution effects. The expected crystallinity of cyclic derivatives of the fluorinated β-amino acids has come true. The tetrahydropyrimidin-4(1*H*)-ones readily form suitable single crystals, for X-ray structure determination. The cyclic β-tri- and β-tetrapeptides could be purified to give correct elemental analyses, but are poorly soluble, so that we have to resort to – ongoing – powder X-ray diffraction measurements in a synchroton beam. The results of the X-ray-structural investigations will be reported separately, together with full NMR-structural analyses and computational results. The multiply F-substituted β-peptides have, so far, resisted all attempts of structure determination, due to poor solubility in common solvents and to lack of reliable *Karplus* parameters. With the data collected from the cyclic derivatives, we are now in the process of making another attempt. The CD spectra of these linear β-hexapeptides, as reported herein, can be merely considered as 'fingerprints', and the discussed similarities of CD patterns with those of β-peptides of known structure may be accidental.

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Experimental Part

1. *General. Abbreviations:* β-hAa: β-Homoamino acid, Bn: benzyl, Boc: (*tert*-butoxy)carbonyl, Boc_2O: di(*tert*-butyl) dicarbonate, DAST: (diethylamino)sulfur trifluoride, EtN^iPr_2 (*Hünig* base): ethyl(diisopropyl)amine, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, FC: flash chromatography, HATU: *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate, HF^iPrOH: 1,1,1,3,3,3-hexafluoropropan-2-ol, HBTU: *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetra-

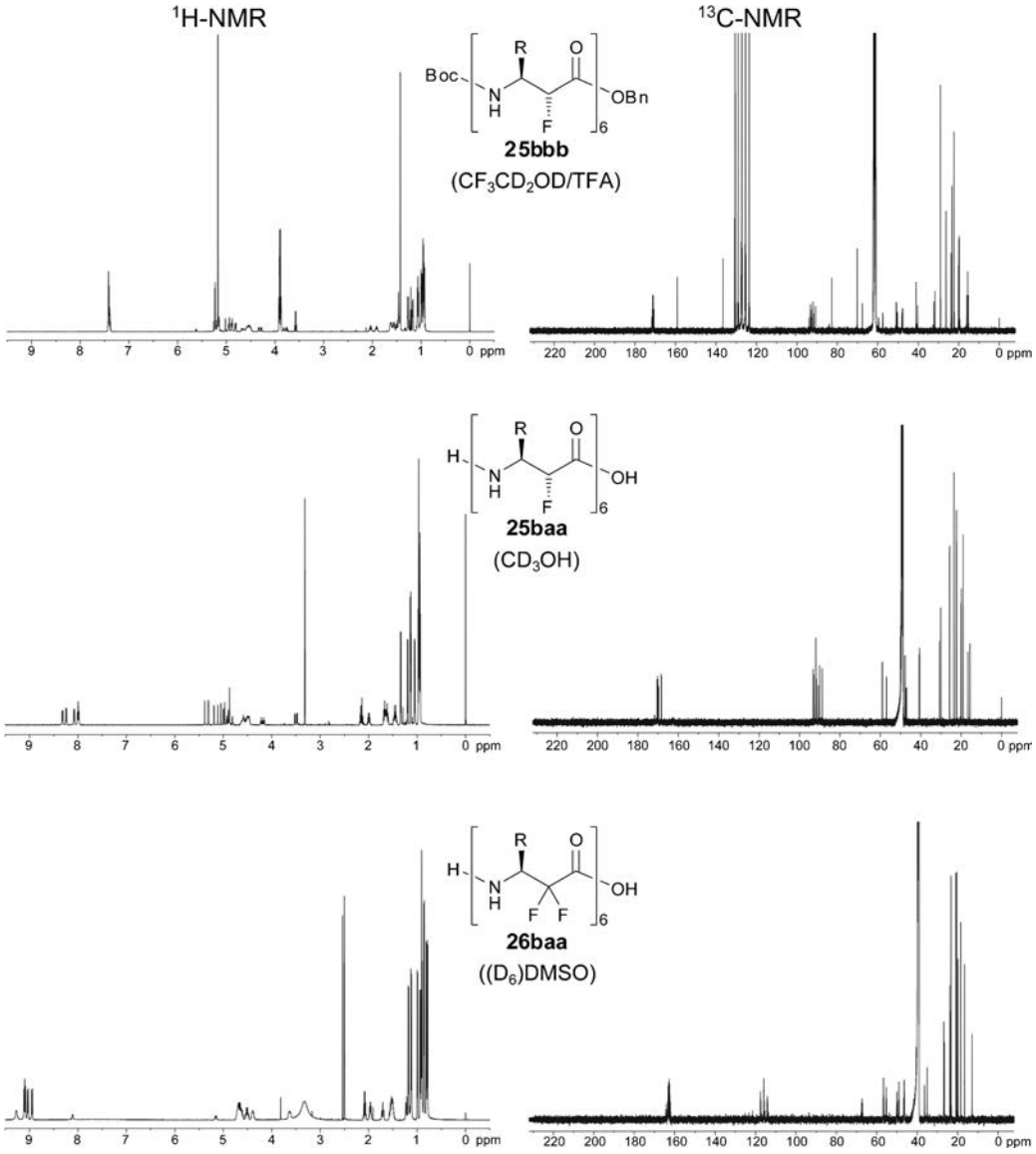


Fig. 4. *^{1}H- and ^{13}C-NMR Spectra of the hexapeptide derivatives* **25bbb**, **25baa**, *and* **26baa**. For ^{1}H- and ^{19}F-NMR spectra of **24bbb** and for the ^{19}F-NMR spectra of **26bbb**, see the *Exper. Part*. For **25bbbb**, ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra are described in the *Exper. Part*.

methyluronium hexafluorophosphate, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum (0.01 – 0.1 Torr), NMM: 4-methylmorpholine, NFSI: *N*-fluorobenzene-sulfonimide, TFA: trifluoroacetic acid, TFE: 2,2,2-trifluoroethanol.

DMSO and Et_3N were distilled over CaH_2 and stored over 4-Å molecular sieves. Solvents for FC and workup procedures were distilled over *Sikkon* (anh. $CaSO_4$; *Fluka*). α-Amino acids were purchased from

Bachem, *Senn*, or *Degussa*. Dry THF was distilled from sodium and benzophenone; dry CH_2Cl_2 was distilled from CaH_2. All moisture-sensitive reactions were carried out under a positive pressure of N_2 or Ar in oven-dried glassware (140°). All other reagents and solvents were used as received from *Fluka* or *Aldrich*. Sat. HCl/MeOH soln. was prepared by bubbling anh. HCl gas into MeOH at 0° (ice bath). Aldehydes **4b** and **4c** [11], cyanohydrins **5b** and **5c** [12], alanine derivatives **1aba**, **2aba**, **3aba**, **6a**, *epi*-**6a**, and **7a** [4] were synthesized according to published procedures.

TLC: *Merck* silica gel *60 F_{254}* plates; detection with UV light or by dipping into a soln. of ninhydrin (0.6 g), AcOH (2 ml), H_2O (13 ml), and BuOH (285 ml), or a soln. of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 ml), and H_2O (940 ml), followed by heating. FC: *Fluka* silica gel *60* (40–63 μm); at *ca.* 0.3 bar. Anal. RP-HPLC: *Knauer* HPLC system *K 1000*, pump type *64*, *EuroChrom 2000* integration package, degaser, UV detector *K 2000* (variable-wavelength monitor), *Macherey-Nagel C_8* column (*Nucleosil 100-5 C_8* (250 × 4 mm)); at 220 nm. Prep. RP-HPLC: *Knauer* HPLC system, pump type *64*, programmer *50*, UV detector (variable-wavelength monitor), *Macherey-Nagel C_8* column (*Nucleosil 100-7 C_8* (250 × 21 mm)); at 220 nm. M.p.: *Büchi 510* apparatus; uncorrected. Optical rotations ($[\alpha]_D^{r.t.}$): *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell) at r.t.; the solvent and the concentration (g/100 ml) are given in the procedures. CD Spectra: *Jasco J-710* spectrophotometer, recording from 190 to 250 nm at 20°; 1-mm rectangular cell; average of five scans, corrected for the baseline; peptide concentration, 0.2 mM; band width, 1.0 nm; resolution, 0.2 nm; sensitivity, 100 mdeg; response, 0.5 s; speed, 20 nm/min.; molar ellipticity $[\theta]$ in deg cm^2 mol^{-1} (λ in nm); smoothing by *Jasco* softwares). IR Spectra: *Perkin-Elmer 782* spectrophotometer. NMR spectra: *Bruker AMX 600* (^{1}H: 600 and ^{13}C: 150.9 MHz), *AMX 500* (^{1}H: 500 and ^{13}C: 125 MHz), *AMX 400* (^{1}H: 400 and ^{13}C: 100 MHz), or *AV-400* (^{1}H: 400, ^{13}C: 100, and ^{19}F: at 376 MHz), or *Varian Gemini 300* (^{1}H: 300, ^{13}C: 75, and ^{19}F: 282 MHz); chemical shifts δ in ppm and coupling constants J in Hz. HR-MS: *IonSpec Ultima 4.7* (HR-ESI-MS and HR-MALDI-MS) or *Bruker Reflex* (MALDI-TOF-MS) spectrometer; in m/z (% of basis peak). Elemental analyses: performed in the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

2. *General Procedures 1–14* (*GP 1–14*). *Fluorination of β-Homoalanine Methyl Esters: GP 1.* A soln. of BuLi (1.6M hexane, 2.2 equiv.) was added to a soln. of $^iPr_2NH$ (2.2 equiv.) in THF (0.5M) at −78° under Ar. The mixture was stirred for 1 h at −78°, then a soln. of the *N*-Boc- or *N*-Cbz-amino acid ester (1 equiv.) in THF (0.5M) was added. The mixture was stirred for 1 h at −78° and then a soln. of NFSI (2.5 equiv.) in THF (1M) was added dropwise *via* syringe. The resulting yellow mixture was stirred for 2.5 h at −78° and for 2 h at 0°. Sat. NH_4Cl was added, and the aq. layer was extracted with CH_2Cl_2 (3 ×). The combined org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by FC.

Fluorination Reactions with DAST: GP 2. All reactions were performed in PET flasks under N_2. To a soln. of the appropriate starting material (1 equiv.) in CH_2Cl_2 (2 ml/mmol), DAST (1.5–3 equiv.) was slowly added at 0° (ice bath) or r.t. The mixture was stirred at 0° or r.t. for 3–6 h, poured into H_2O, cautiously neutralized by the addition of solid K_2CO_3, and extracted with Et_2O (2 ×). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by FC.

Methyl Ester Hydrolysis: GP 3. A mixture of the methyl ester (1 equiv.) and $LiOH \cdot H_2O$ (3 equiv.) in EtOH/H_2O 2 : 1 (4 ml/mmol) was well stirred for 1 h at r.t., cooled to 0° (ice bath), and neutralized by the addition of 1M HCl. The mixture was diluted with H_2O and extracted with AcOEt or CH_2Cl_2 (3 ×). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. The crude product was used without further purification.

Benzyl Hydrogenolysis: GP 4. To a soln. of the Bn-protected compound in MeOH (10 ml/mmol), a cat. amount of Pd/C (10%, 30 mg per equiv. of Bn group) was added. The apparatus was evacuated and flushed three times with H_2, and the mixture was vigourously stirred for 12–24 h. The catalyst was filtered off through *Celite*, washed several times with MeOH, and the combined org. layers were evaporated. The crude product was used without further purification.

Boc Protection: GP 5. To a soln. of the amine or the TFA salt (1 equiv.) in MeOH (3 ml/mmol), Boc_2O (1.5 equiv.) and Et_3N (3–5 equiv.) were added. The mixture was stirred at r.t. for 12 h, concentrated under reduced pressure, dissolved in AcOEt and washed successively with 0.5M HCl, sat.

K_2CO_3, and brine. The org. layer was dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by FC.

Benzyl Ester Formation: GP 6. According to the procedure described in [27], a mixture of the carboxylic acid (1 equiv.) and dry Cs_2CO_3 (1 equiv.) in DMF (3 ml/mmol) was stirred for 10 min at r.t., and treated with BnBr (1.2 equiv.). After stirring for 12 h at r.t., the mixture was diluted with AcOEt and washed successively with 1M HCl (2×), sat. K_2CO_3, and brine. The org. layer was dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by FC.

Non-Stereoselective Preparation of Cyanohydrins: GP 7. In analogy to the procedure described in [13], a vigorously stirred, biphasic soln. of the dibenzylamino aldehyde (1 equiv.) in hexane/H_2O 3:1 (1.5 ml/mmol) was treated with acetone cyanohydrin (=2-hydroxy-2-methylpropanenitrile; 1.5 equiv.) at r.t. After stirring for 5 min, cat. amounts of KCN (0.03 equiv.) and Bu_4NI (0.01 equiv.) were added. The mixture was stirred at r.t. for 2 h, poured into H_2O, and extracted with Et_2O (3×). The combined org. phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude epimeric mixture of cyanohydrins was used without further purification.

Methanolysis of Cyanohydrins: GP 8. A soln. of the cyanohydrin (1 equiv.) in sat. HCl/MeOH (5–10 ml/mmol) was stirred at r.t. for 12 h, concentrated under reduced pressure, poured into H_2O, cautiously neutralized by the addition of solid K_2CO_3, and extracted with AcOEt (3×). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by FC.

Oxidation of α-Hydroxy Esters to α-Keto Esters: GP 9. A dry three-necked round-bottom flask, equipped with a magnetic stirrer and a dropping funnel, was charged with anh. CH_2Cl_2 (7.5 ml/mmol) under N_2. After cooling to −78° (dry ice/acetone bath), oxalyl chloride (1.2 equiv.) and anh. DMSO (2 equiv.) were added dropwise, so that the temp. did not exceed −65°. The mixture was stirred at −78° for 10 min, treated with a soln. of the appropriate methyl ester (1 equiv.) in CH_2Cl_2 (1 ml/mmol), and stirred for additional 1.5 h at −78°. After addition of dry Et_3N (4 equiv.), the mixture was allowed to warm to r.t. over 0.5 h, whereupon H_2O (4 ml/mmol) was added. The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (3×). The combined org. phases were washed with 1% HCl, 5% $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated. The crude keto esters are immedially used for the DAST reactions without prior purification.

*Preparation of 6-Alkyl-2-(*tert*-butyl)tetrahydropyrimidin-4(1*H*)-ones: GP 10.* At −20°, 1 equiv. of the *N*-Cbz-protected *β*-amino acid was dissolved in THF, and 1.2 equiv. of Et_3N and ethyl chloroformate were added. The resulting colorless suspension was cooled below −50°, and *via* a needle NH_3 gas was bubbled in for 1 h. After another 3 h, the solvent was removed by rotary evaporation. To the colorless solid, H_2O was added, and the resulting suspension was filtered and washed with H_2O and Et_2O. The isolated powder was dried for 12 h under h.v., then suspended in MeOH, and 10% Pd/C was added. After 12 h under H_2 (balloon), the Pd/C was filtered off (*Celite*), MeOH was evaporated, and the obtained *β*-amino acid amide was dissolved in CH_2Cl_2, 2 equiv. of pivalaldehyde was added, and the mixture was heated under reflux in an inverse *Dean–Stark* trap for 12 h. The solvent was removed, and the isolated crude product was purified by FC and/or recrystallization.

*Cbz Protection of Tetrahydropyrimidin-4(1*H*)-ones: GP 11. N,O*-Bis(trimethylsilyl)acetamide (1.5 equiv.) was added to a soln. of the corresponding tetrahydropyrimidin-4(1*H*)-one, **11**–**13**, in CH_2Cl_2 at r.t. After 1 h, the mixture was cooled to 0° and Cbz chloride (1.3 equiv.) was added. After 20 h at 0°, sat. $NaHCO_3$ was added, and the aq. layer was extracted with CH_2Cl_2 (3×). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. The crude products were purified by FC.

Peptide Coupling: GP 12. GP 12a. With HBTU. A soln. of the ammonium salt of the amino acid ester or peptide ester (1 equiv.) in CH_2Cl_2 was cooled to 0°, treated successively with the appropriate carboxylic acid (1 equiv.), NMM (3 equiv.), and HBTU (1.2 equiv.), and stirred for 12 h at r.t. The mixture was diluted with AcOH, and washed with aq. HCl (1M), sat. K_2CO_3, and brine. The org. phase was dried ($MgSO_4$), filtered, evaporated, and the obtained crude product was purified by FC.

GP 12b. With EDC/HOBt. A soln. of the amino acid or peptide ester, or its TFA salt (1 equiv.) in CH_2Cl_2 (3 ml/mmol) was cooled to −10°, treated successively with a soln. of the appropriate acid (1 equiv.) in CH_2Cl_2 or THF (3 ml/mmol), NMM (3–5 equiv.), HOBt (1.2 equiv.) and EDC·HCl (1.2 equiv.), and stirred at −10° for 12 h. The mixture was diluted with AcOEt, washed with 1M HCl (3×),

sat. K_2CO_3 (3 ×), and brine. The org. layer was dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by FC.

GP 12c. With HATU. A soln. of the amino acid or peptide ester, or its TFA salt (1 equiv.) in CH_2Cl_2 or DMF (6 ml/mmol) was cooled to 0°, treated successively with the appropriate acid (1 equiv.), NMM (3–5 equiv.), and HATU (1.2 equiv.), and stirred at r.t. for 12 h. The mixture was diluted with AcOEt, washed with 1M HCl (3 ×), sat. K_2CO_3 (3 ×), and brine. The org. layer was dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by FC.

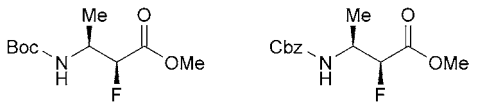
GP 12d. With HATU, Forming an Insoluble Peptide. The peptide-coupling reaction was performed according to *GP 12c*, but during the reaction the formed peptide precipitated. The mixture was evaporated, and the residue was stirred in AcOEt for 10 min. The resulting suspension was centrifuged, and the solid was stirred successively in AcOEt (2 ×) and MeOH/H_2O 1:1 (3 ×) for 10 min each. After the final centrifugation, the product was dried under h.v. for 12 h.

Cyclization of Oligopeptides: GP 13. A soln. of the unprotected peptide in DMF (0.4M) was treated at r.t. with pentafluorophenol (1 equiv.) and EDCI (1 equiv.). After 16 h, the mixture was evaporated, and the residue was dissolved in $CHCl_3$. The resulting soln. was washed successively with 1M aq. HCl and brine. The org. phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (0.5M) and an equal volume of TFA was added at 0°. The mixture was stirred for 1 h at 0° and for 1 h at r.t. The solvent was evaporated, and the residue was dissolved in toluene and evaporated twice. The obtained residue was dissolved in MeCN (0.025M) and slowly added (over 4 h) to a soln. of *Hünig*'s base (EtN^iPr_2) in MeCN (3.3 mM) at 70° (bath temp.) with a syringe pump. The resulting precipitate was filtered, washed, and dried under h.v.

Boc Deprotection: GP 14. GP 14a. A soln. of the *N*-Boc-protected compound in CH_2Cl_2 (3 ml/mmol) was cooled to 0° (ice bath), treated with TFA (3 ml/mmol), and stirred at 0° for 1.5 h. After concentration under reduced pressure, the TFA salt was dried under h.v. for 2 h and used without further purification.

GP 14b. After Boc deprotection according to *GP 14a*, the TFA salt was dissolved in AcOEt, washed with sat. K_2CO_3 (2 ×), dried ($MgSO_4$), filtered, and evaporated. The resulting amine was used without further purification.

3. *Preparation of the Fluorinated β-Amino Acid Derivatives* **1**–**3**, **7**, *and* **8**. 3.1. *By Enolate Fluorination* (*Scheme 2*, *b*). *Methyl (2*S*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-fluorobutanoate* (**1abb**). Fluorination of Boc-hAla-methyl ester (1.87 g, 8.63 mmol; prepared from Boc-Ala [28]) was performed according to *GP 1*. Purification by FC (CH_2Cl_2/AcOEt 98:2) afforded **1abb** (1.38 g, 68%). Pale yellow oil, which crystallized by scratching. Recrystallization gave colorless needles. M.p. 66–68° (hexane/Et_2O). $[\alpha]^{28}_D = -1.9$ ($c = 1.0$, MeOH). IR: 3369*m*, 3252*w*, 2983*w*, 2944*w*, 1758*s*, 1686*s*, 1510*s*, 1440*m*, 1388*m*, 1366*m*, 1338*m*, 1275*m*, 1247*m*, 1225*s*, 1164*s*, 1135*m*, 1112*s*, 1061*s*, 1008*s*, 980*m*, 938*w*, 921*w*, 877*m*, 849*m*, 783*m*, 750*m*, 696*w*, 675*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16 (*dd*, *J* = 7.0, 0.7, Me); 1.46 (*s*, 3 Me); 3.82 (*s*, Me); 4.12–4.40 (*m*, NCH); 4.79 (br. *s*, NH); 5.05 (*dd*, *J* = 49.4, 2.2, CFH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.2 (*d*, *J* = 5.2, Me); 22.3 (3 Me); 47.8 (*d*, *J* = 19.7, NCH); 52.5 (Me); 80.0 (*C*Me$_3$); 90.2 (*d*, *J* = 188.2, FCH); 154.9 (CO); 168.2 (*d*, *J* = 24.0, FC*C*O). ^{19}F-NMR (280 MHz, $CDCl_3$): 40.6 (*dd*, *J* = 49.0, 26.9, 1 F). Anal. calc. for $C_{10}H_{18}FNO_4$ (235.25): C 51.06, H 7.71, N 5.95; found: C 51.04, H 7.54, N 6.15.

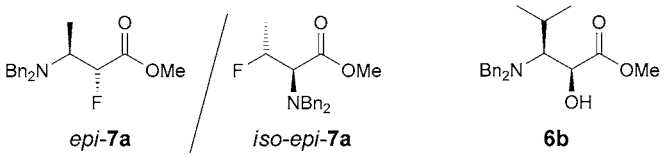


1abb **1acb**

*Methyl (2*S*,3*S*)-3-{[(Benzyloxy)carbonyl]amino}-2-fluorobutanoate* (**1acb**). Fluorination of Cbz-hAla methyl ester (5.03 g, 20.0 mmol, prepared from Cbz-Ala [28]) was performed according to *GP 1*. Purification by FC (CH_2Cl_2/AcOEt 98:2) afforded **1acb** (3.83 g, 71%). Pale yellow oil, which crystallized by scratching. Recrystallization gave colorless needles. M.p. 52–53° (hexane/Et_2O). $[\alpha]^{28}_D = +3.7$ ($c = 1.0$, MeOH). IR: 3330*m*, 3068*w*, 3038*w*, 2992*w*, 2961*w*, 2896*w*, 2852*w*, 1759*s*, 1682*s*, 1652*m*, 1527*s*,

1466*m*, 1454*m*, 1437*m*, 1390*w*, 1381*w*, 1334*m*, 1276*s*, 1258*m*, 1228*s*, 1140*m*, 1113*s*, 1068*m*, 1013*s*, 983*m*, 941*m*, 912*m*, 860*w*, 840*m*, 785*m*, 751*s*, 730*m*, 696*s*, 671*m*, 655*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (*d*, *J* = 6.9, Me); 3.81 (*s*, Me); 4.12–4.40 (*m*, NCH); 4.92–5.17 (*m*, NH, FCH, PhCH_2); 7.27–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.3 (*d*, *J* = 5.3, Me); 48.3 (*d*, *J* = 20.4, NCH); 52.6 (Me); 67.1 (Ph*C*H$_2$); 90.0 (*d*, *J* = 188.5, FCH); 128.2 (CH); 128.3 (CH); 128.6 (CH); 136.2 (CH); 155.4 (CO); 168.0 (*d*, *J* = 23.7, FC*C*O). ^{19}F-NMR (282 MHz, $CDCl_3$): 41.0 (*dd*, *J* = 49.0, 26.7, 1 F). Anal. calc. for $C_{13}H_{16}FNO_4$ (269.27): C 66.84, H 8.56, N 4.10; found: C 66.57, H 8.46, N 4.11.

3.2. *By the Cyanohydrin Route* (*Scheme 1*). 3.2.1. *Monofluorinated Ala-Derived Compounds. Methyl (2*R*,3*S*)-3-(Dibenzylamino)-2-fluorobutanoate* (*epi*-**7a**) *and Methyl (2*R*,3*R*)-2-(Dibenzylamino)-3-fluorobutanoate* (iso-*epi*-**7a**). The methyl ester *epi*-**6a** [4] (2.04 g, 6.51 mmol) was dissolved in CH_2Cl_2 (13 ml) and fluorinated with DAST (1.3 ml, 8.70 mmol) at 0° for 3 h according to *GP 2*. FC (pentane/Et_2O 9:1) yielded *epi*-**7a** (753 mg, 37%) and iso-*epi*-**7a** (690 mg, 34%).

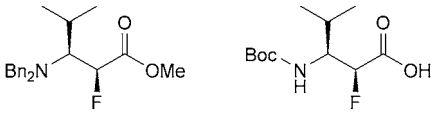


Data of epi-**7a**. Light yellow oil. R_f (pentane/Et_2O 5:1) 0.41. $[\alpha]_D^{r.t.} = +27.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3570*w*, 3064*w*, 3032*m*, 2954*w*, 2841*w*, 2810*w*, 1762*s*, 1602*w*, 1495*m*, 1453*m*, 1439*m*, 1382*m*, 1358*m*, 1298*m*, 1171*s*, 1137*w*, 1106*m*, 1074*w*, 1025*s*, 948*w*, 911*w*, 832*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.27 (*dd*, *J* = 0.6, 7.0, Me); 3.29 (*ddq*, *J* = 3.8, 7.0, 31.8, NCH); 3.33 (*d*, *J* = 13.4, 2 PhC*H*H′); 3.63 (*s*, MeO); 3.90 (*d*, *J* = 13.4, 2 PhCH*H*′); 4.84 (*dd*, *J* = 3.8, 49.1, CHF); 7.19–7.32 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 8.0 (*d*, *J* = 4.4), 51.9 (Me); 53.9 (*d*, *J* = 18.4, CH); 55.0 (CH_2); 94.2 (*d*, *J* = 189.2), 127.0, 128.1, 129.1 (CH); 139.6, 169.0 (*d*, *J* = 25.6) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −200.4 (*dd*, *J* = 32.0, 49.1, CHF). HR-MALDI-MS: 338.2 (11, $[M+Na]^+$), 316.2 (100, $[M+H]^+$), 314.2 (5), 296.2 (4), 268.2 (5), 224.1 (9), 158.1 (8). Anal. calc. for $C_{19}H_{22}FNO_2$ (315.39): C 72.36, H 7.03, N 4.44; found: C 72.51, H 7.08, N 4.35.

Data of iso-epi-**7a**. Light yellow oil. R_f (pentane/Et_2O 5:1) 0.52. $[\alpha]_D^{r.t.} = -104.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3063*w*, 3008*m*, 2953*m*, 2845*w*, 1729*s*, 1602*w*, 1495*m*, 1454*m*, 1435*w*, 1383*w*, 1359*w*, 1277*w*, 1162*s*, 1115*w*, 1074*m*, 1024*m*, 990*w*, 939*w*, 877*w*, 843*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.35 (*dd*, *J* = 6.3, 24.0, Me); 3.37 (*dd*, *J* = 5.7, 23.7, NCH); 3.77 (*d*, *J* = 14.0, 2 PhC*H*H′); 3.78 (*s*, MeO); 4.06 (*d*, *J* = 14.0, 2 PhCH*H*′); 5.12 (*ddq*, *J* = 5.8, 6.3, 47.9, CHF); 7.21–7.40 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.3 (*d*, *J* = 22.4), 51.4 (Me); 55.6 (CH_2); 64.9 (*d*, *J* = 19.6), 89.7 (*d*, *J* = 173.2), 127.1, 128.3, 128.8 (CH); 139.5, 171.0 (*d*, *J* = 6.7) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −181.8 (*dquint.*, *J* = 23.5, 48.0, CHF). HR-MALDI-MS: 338.2 (13, $[M+Na]^+$), 316.2 (100, $[M+H]^+$), 314.2 (15), 296.2 (7), 238.2 (14), 224.1 (28), 158.1 (8). Anal. calc. for $C_{19}H_{22}FNO_2$ (315.39): C 72.36, H 7.03, N 4.44; found: C 72.43, H 7.12, N 4.45

3.2.2. *Monofluorinated Val-Derived Compounds. Methyl (2*S*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-methylpentanoate* (**6b**). The cyanohydrin **5b** [12] (12.74 g, 41.3 mmol) was treated with a sat. HCl/MeOH soln. (210 ml) according to *GP 8*. FC (AcOEt/hexane 1:9 → 3:7) yielded **6b** (8.61 g, 61%). Light yellow oil. R_f (CH_2Cl_2) 0.19. $[\alpha]_D^{r.t.} = -0.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3532*w*, 3064*w*, 2955*m*, 2873*w*, 2802*w*, 1728*s*, 1602*w*, 1494*m*, 1453*m*, 1366*w*, 1272*m*, 1137*m*, 1089*m*, 1028*w*, 990*w*, 967*w*, 913*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.6, Me); 1.02 (*d*, *J* = 6.7, Me); 2.18–2.31 (*m*, Me_2C*H*); 2.74 (*dd*, *J* = 1.5, 10.2, NCH); 2.99 (*d*, *J* = 4.6, OH); 3.40 (*d*, *J* = 13.9, 2 PhC*H*H′); 3.72 (*s*, MeO); 3.95 (*d*, *J* = 13.9, 2 PhCH*H*′); 4.59 (*dd*, *J* = 1.5, 4.6, C*H*OH); 7.20–7.38 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.8, 21.5 (Me); 26.3 (CH); 52.5 (Me); 54.8 (CH_2); 66.5, 67.4, 126.9, 128.1, 129.2 (CH); 139.9, 176.7 (C). HR-MALDI-MS: 364.2 (9, $[M+Na]^+$), 342.2 (100, $[M+H]^+$), 252.2 (23). Anal. calc. for $C_{21}H_{27}NO_3$ (341.44): C 73.87, H 7.97, N 4.10; found: C 74.08, H 7.81, N 4.30.

*Methyl (2*S*,3*S*)-3-(Dibenzylamino)-2-fluoro-4-methylpentanoate* (**7b**). Compound **6b** (3.84 g, 11.25 mmol) was dissolved in CH_2Cl_2 (22 ml) and fluorinated with DAST (2.2 ml, 16.9 mmol) at 0° for 3 h, according to *GP 2*. FC (pentane/Et_2O 10:1) yielded **7b** (2.78 g, 72%). Yellow oil. R_f (pentane/Et_2O 10:1) 0.35. $[\alpha]_D^{r.t.} = -15.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3066*w*, 3032*m*, 2956*m*, 2803*w*, 1758*s*, 1602*w*,

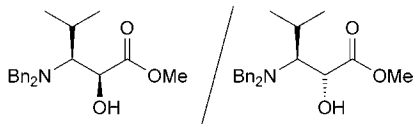


7b **1bba**

1494*m*, 1476*w*, 1453*m*, 1438*m*, 1366*w*, 1287*s*, 1136*m*, 1116*m*, 1084*s*, 1016*m*, 992*w*, 968*w*, 912*w*, 867*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80 (*d*, *J* = 6.6, Me); 1.00 (*d*, *J* = 6.7, Me); 2.13–2.26 (*m*, Me_2CH); 2.89 (*ddd*, *J* = 1.0, 9.9, 29.2, NCH); 3.34 (*d*, *J* = 13.8, 2 PhC*H*H′); 3.75 (*s*, MeO); 3.96 (*d*, *J* = 13.8, 2 PhCH*H*′); 5.37 (*d*, *J* = 48.3, CHF); 7.22–7.38 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.3, 21.3 (Me); 26.3 (*d*, *J* = 5.0, CH); 52.3 (Me); 54.6 (CH_2); 66.0 (*d*, *J* = 18.9), 86.3 (*d*, *J* = 195.3), 127.1, 128.2, 129.2 (CH); 139.2, 171.3 (*d*, *J* = 23.1) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −201.9 (*dd*, *J* = 28.8, 48.0, CHF). HR-MALDI-MS: 366.2 (1, $[M+Na]^+$), 344.2 (18, $[M+H]^+$), 300.1 (6), 252.2 (27). Anal. calc. for $C_{21}H_{26}FNO_2$ (343.44): C 73.44, H 7.63, N 4.08; found: C 73.30, H 7.47, N 4.01.

*(2*S*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-fluoro-4-methylpentanoic Acid* (**1bba**). Compound **7b** (2.77 g, 8.06 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (1.02 g, 24.2 mmol) in $EtOH/H_2O$ (30 ml, 2:1) according to *GP 3*, the carboxylic acid was dissolved in MeOH (80 ml) and hydrogenolyzed according to *GP 4*, and Boc-protected with Boc_2O (2.0 g, 9.17 mmol) and Et_3N (3.2 ml, 22.9 mmol) in MeOH (28 ml) according to *GP 5*. FC (CH_2Cl_2/MeOH/AcOH 100:3:0.1 → 100:5:0.2) yielded the carboxylic acid **1bba** (1.62 g, 80% over 3 steps). Colorless solid. M.p. 133–134°. R_f (CH_2Cl_2/MeOH/AcOH 100:5:1) 0.25. $[\alpha]_D^{rt.} = -5.8$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3447*m*, 3011*w*, 2980*m*, 2933*w*, 1749*m*, 1712*s*, 1503*s*, 1456*w*, 1393*w*, 1369*m*, 1161*s*, 1128*w*, 1098*w*, 1041*w*, 999*w*, 868*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.94 (*d*, *J* = 6.8, Me); 0.96 (*d*, *J* = 6.8, Me); 1.44 (*s*, *t*-Bu); 1.93–2.02 (*m*, Me_2CH); 3.91 (*td*, *J* = 5.5, 21.5, NCH); 4.89 (*dd*, *J* = 5.1, 48.7, CHF). ^{13}C-NMR (100 MHz, CD_3OD): 18.2, 20.5, 28.8 (Me); 30.0 (*d*, *J* = 2.6), 57.9 (*d*, *J* = 21.2) (CH); 80.4 (C); 91.2 (*d*, *J* = 186.9) (CH); 158.3, 172.1 (*d*, *J* = 23.1) (C). ^{19}F-NMR (282 MHz, CD_3OD): −199.7 (*dd*, *J* = 21.3, 49.1, CHF). HR-ESI-MS: 565.2 (23), 543.2 (90, $[2M+2\,Na]^+$), 521.3 (59, $[2M+Na]^+$), 294.1 (23), 272.1 (100, $[M+Na]^+$), 216.1 (14). Anal. calc. for $C_{11}H_{20}FNO_4$ (249.28): C 53.00, H 8.09, N 5.62; found: C 53.04, H 7.86, N 5.44.

*Methyl (2*S/R*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-methylpentanoate* (**6b**/*epi*-**6b**). A soln. of freshly prepared **4b** [11] (16.2 g, 57.5 mmol) in hexane/H_2O (115 ml, 3:1) was treated with acetone cyanohydrin (7.85 ml, 86.3 mmol), KCN (112.2 mg, 1.7 mmol), and Bu_4NI (148.7 mg, 0.4 mmol) according to *GP 7*. The crude epimeric mixture of cyanohydrins was treated with a sat. HCl/MeOH soln. (290 ml) according to *GP 8*. FC (hexane/AcOEt 98:2 → 7:3) yielded **6b**/*epi*-**6b** (15.5 g, 79% over 2 steps). Yellow oil. R_f (hexane/AcOEt 7:3) 0.46. The mixture could be separated by a further FC (hexane/AcOEt 95:5) to yielding pure **6b** and *epi*-**6b**. The ^{1}H- and ^{13}C-NMR data for **6b** ((2*R*,3*S*)) were in accordance with those described above.

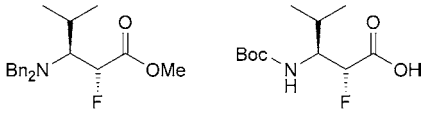


6b *epi*-**6b**

Data of epi-**6b** ((2*S*,3*S*)). Light yellow oil. R_f (pentane/Et_2O 3:2) 0.42. $[\alpha]_D^{rt.} = -15.6$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3600*w*, 3527*w*, 3067*w*, 3008*m*, 2961*m*, 2872*w*, 1949*w*, 1887*w*, 1815*w*, 1731*s*, 1494*w*, 1453*m*, 1389*w*, 1269*s*, 1146*m*, 1076*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06 (*d*, *J* = 6.5, Me); 1.16 (*d*, *J* = 6.5, Me); 2.35–2.47 (*m*, Me_2CH); 2.82 (*dd*, *J* = 3.3, 8.6, NCH); 3.22 (br. *s*, OH); 3.44 (*s*, MeO); 3.75 (*d*, *J* = 13.4, 2 PhC*H*H′); 3.99 (*d*, *J* = 13.7, 2 PhCH*H*′); 4.33 (*d*, *J* = 3.1, C*H*OH); 7.20–7.38 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.5, 22.9 (Me); 28.1 (CH); 52.3 (Me); 56.4 (CH_2); 65.4, 72.6, 126.7, 128.0, 129.1 (CH); 140.1, 175.4 (C). HR-MALDI-MS: 364.2 (16, $[M+Na]^+$), 342.2 (100, $[M+H]^+$), 328.2 (11),

321.2 (26), 291.2 (19), 266.2 (70), 252.2 (49). Anal. calc. for $C_{21}H_{27}NO_3$ (341.44): C 73.87, H 7.97, N 4.10; found: C 73.85, H 7.84, N 4.20.

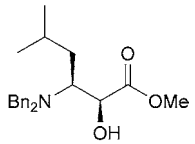
*Methyl (2*R*,3*S*)-3-(Dibenzylamino)-2-fluoro-4-methylpentanoate* (*epi*-**7b**). Compound *epi*-**6b** (911 mg, 2.67 mmol) was dissolved in CH_2Cl_2 (6 ml) and fluorinated with DAST (525 µl, 4.00 mmol) at 0° for 3 h, according to *GP 2*. FC (pentane/Et_2O 99:1 → 97:3) yielded *epi*-**7b** (551 mg, 60%). Yellow oil. R_f (pentane/Et_2O 10:1) 0.21. $[\alpha]_D^{r.t.} = -22.8$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3065*w*, 3032*m*, 2955*s*, 2851*w*, 1760*s*, 1602*w*, 1494*m*, 1476*w*, 1453*s*, 1390*w*, 1359*m*, 1294*m*, 1144*s*, 1116*m*, 1073*s*, 1016*m*, 979*w*, 949*w*, 911*w*, 835*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.02 (*d*, $J = 6.6$, Me); 1.12 (*d*, $J = 6.8$, Me); 2.29–2.37 (*m*, Me_2CH); 2.88 (*ddd*, $J = 2.6$, 9.0, 34.0, NCH); 3.63 (*s*, MeO); 3.81 (*d*, $J = 13.6$, 2 PhC*H*H′); 3.85 (*d*, $J = 13.6$, 2 PhCH*H*′); 5.15 (*dd*, $J = 2.6$, 47.9, CHF); 7.19–7.30 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.2, 22.1 (Me); 27.8 (*d*, $J = 1.8$, CH); 52.0 (Me); 55.6 (CH_2); 64.5 (*d*, $J = 18.0$), 91.1 (*d*, $J = 189.6$), 126.9, 128.1, 129.4 (CH); 140.0, 170.2 (*d*, $J = 25.3$) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −202.1 (*dd*, $J = 34.2$, 48.0, CHF). HR-MALDI-MS: 366.2 (5, $[M + Na]^+$), 344.2 (71, $[M + H]^+$), 324.2 (12), 252.2 (100), 126.1 (7). Anal. calc. for $C_{21}H_{26}FNO_2$ (343.44): C 73.44, H 7.63, N 4.08; found: C 73.49, H 7.59, N 4.20.



epi-**7b** **2bba**

*(2*R*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-fluoro-4-methylpentanoic Acid* (**2bba**). Compound *epi*-**7b** (472 mg, 1.37 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (173 mg, 4.12 mmol) in $EtOH/H_2O$ (7.5 ml, 2:1) according to *GP 3*, the carboxylic acid was dissolved in MeOH (15 ml), hydrogenolyzed according to *GP 4*, and Boc-protected with Boc_2O (354 mg, 1.64 mmol) and Et_3N (570 µl, 4.1 mmol) in MeOH (5 ml) according to *GP 5*. FC (hexane/AcOEt 2:1 + 2% AcOH) yielded **2bba** (293 mg, 85% over 3 steps). Light yellow solid. M.p. 70–73°. R_f (CH_2Cl_2/MeOH/AcOH 100:5:1) 0.27. $[\alpha]_D^{r.t.} = -35.8$ ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$): 3440*m*, 3026*w*, 2979*m*, 2923*w*, 1754*w*, 1713*s*, 1505*s*, 1456*w*, 1393*w*, 1369*m*, 1310*w*, 1161*s*, 1077*w*, 1045*w*, 904*w*, 861*w*. ^{1}H-NMR (300 MHz, CD_3OD): 0.97 (*d*, $J = 6.8$, Me); 1.03 (*d*, $J = 6.5$, Me); 1.42 (*s*, *t*-Bu); 1.83–1.95 (*m*, Me_2CH); 3.80 (*ddd*, $J = 1.9$, 8.7, 30.2, NCH); 5.13 (*dd*, $J = 1.9$, 48.2, CHF). ^{13}C-NMR (75 MHz, CD_3OD): 18.4, 18.8, 27.5 (Me); 30.1, 57.8 (*d*, $J = 18.9$) (CH); 79.0 (C); 88.5 (*d*, $J = 185.6$, CH); 156.9, 177.9 (C). ^{19}F-NMR (282 MHz, CD_3OD): −203.2 (*dd*, $J = 29.9$, 48.0, CHF). HR-ESI-MS: 565.2 (27), 543.2 (14, $[2M + 2\,Na]^+$), 294.1 (100), 272.1 (33, $[M + Na]^+$). Anal. calc. for $C_{11}H_{20}FNO_4$ (249.28): C 53.00, H 8.09, N 5.62; found: C 52.96, H 7.96, N 5.43.

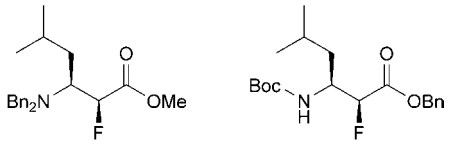
3.2.3. *Monofluorinated Leu-Derived Compounds. Methyl (2*S*,3*S*)-3-(Dibenzylamino)-2-hydroxy-5-methylhexanoate* (**6c**). The cyanohydrin **5c** [12] (4.43 g, 13.8 mmol) was treated with a sat. HCl/MeOH soln. (70 ml) according to *GP 8*. FC (AcOEt/hexane 1:9 → 3:7) yielded **6c** (4.20 g, 86%). Light yellow oil. R_f (pentane/Et_2O 4:1) 0.23. $[\alpha]_D^{r.t.} = +10.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3528*w*, 3032*w*, 2956*m*, 2869*w*, 2810*w*, 1729*s*, 1602*w*, 1494*m*, 1453*m*, 1366*w*, 1268*m*, 1137*w*, 1089*m*, 1071*m*, 966*w*, 905*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*d*, $J = 6.5$, Me); 0.84 (*d*, $J = 6.7$, Me); 0.92 (*ddd*, $J = 4.9$, 8.4, 13.7, 1 H, CH_2CH); 1.67 (*ddd*, $J = 5.0$, 8.8, 14.0, 1 H, CH_2CH); 1.74–1.80 (*m*, Me_2CH); 3.04–3.08 (*m*, NCH); 3.05 (*d*, $J = 6.8$, OH); 3.50 (*d*, $J = 13.8$, 2 PhC*H*H′); 3.71 (*s*, MeO); 3.86 (*d*, $J = 13.8$, 2 PhCH*H*′); 4.61 (*dd*, $J = 2.4$, 6.7,



6c

C*H*OH); 7.20–7.35 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.7, 23.4 (Me); 24.2 (CH); 35.0 (CH_2); 52.4 (Me); 54.5 (CH_2); 57.9, 69.3, 127.0, 128.2, 129.1 (CH); 140.0, 175.6 (C). HR-MALDI-MS: 378.2 (6, $[M+Na]^+$), 356.2 (100, $[M+H]^+$), 266.2 (50). Anal. calc. for $C_{22}H_{29}NO_3$ (355.48): C 74.33, H 8.22, N 3.94; found: C 74.15, H 8.08, N 4.02.

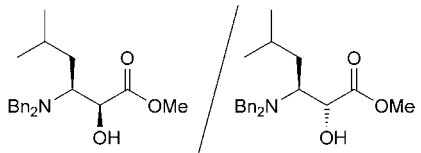
*Methyl (2*S*,3*S*)-3-(Dibenzylamino)-2-fluoro-5-methylhexanoate* (**7c**). Compound **6c** (325 mg, 0.91 mmol) was dissolved in CH_2Cl_2 (2 ml) and fluorinated with DAST (180 µl, 1.37 mmol) at 0° for 3 h, according to *GP 2*. FC (pentane/Et_2O 99:1 → 97:3) yielded **7c** (277 mg, 85%). Light yellow oil. R_f (pentane/Et_2O 10:1) 0.24. $[\alpha]^{rt}_D = -6.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3065*w*, 3032*w*, 2956*m*, 2869*w*, 2806*w*, 1756*s*, 1603*w*, 1495*m*, 1454*m*, 1439*m*, 1367*m*, 1285*s*, 1162*w*, 1138*w*, 1086*w*, 1070*m*, 1017*w*, 967*w*, 907*w*, 868*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.44 (*d*, *J* = 6.4, Me); 0.84 (*d*, *J* = 6.6, Me); 0.96–1.03 (*m*, 1 H, C*H*$_2$CH); 1.74–1.84 (*m*, Me_2C*H*, 1 H of C*H*$_2$CH); 3.16 (*dddd*, *J* = 1.8, 3.8, 9.7, 31.3, NCH); 3.44 (*d*, *J* = 13.8, 2 PhC*H*H′), 3.74 (*s*, MeO); 3.94 (*d*, *J* = 13.8, 2 PhCH*H*′); 5.42 (*dd*, *J* = 1.8, 50.3, CHF); 7.21–7.35 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.1, 23.6 (Me); 24.0, 35.2 (*d*, *J* = 4.0) (CH); 52.3 (Me); 54.2, 54.3 (CH_2); 57.3 (*d*, *J* = 19.1), 88.0 (*d*, *J* = 191.7), 127.1, 128.2, 129.1 (CH); 139.5, 170.2 (*d*, *J* = 24.0) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −201.6 (*dd*, *J* = 30.9, 50.2, CHF). HR-MALDI-MS: 397.0 (7, $[M+K]^+$), 380.2 (12, $[M+Na]^+$), 358.2 (100, $[M+H]^+$), 354.1 (26), 338.2 (17), 280.2 (45), 266.2 (60). Anal. calc. for $C_{22}H_{28}FNO_2$ (357.47): C 73.92, H 7.89, N 3.92; found: C 73.80, H 7.73, N 3.96.



7c **1cbc**

*Benzyl (2*S*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-fluoro-5-methylhexanoate* (**1cbc**). Compound **7c** (4.13 g, 11.55 mmol) was hydrolyzed with LiOH · H_2O (1.45 g, 34.65 mmol) in EtOH/H_2O (45 ml, 2:1) according to *GP 3*; the obtained carboxylic acid was dissolved in MeOH (115 ml) and hydrogenolyzed according to *GP 4*, and Boc-protected with Boc_2O (3.02 g, 13.86 mmol) and Et_3N (4.87 ml, 34.65 mmol) in MeOH (35 ml) according to *GP 5*. The resulting acid **1cba** was dissolved in DMF (35 ml) and treated with Cs_2CO_3 (3.78 g, 11.6 mmol) and BnBr (1.66 ml, 13.9 mmol) according to *GP 6*. FC (pentane/Et_2O 7:1) yielded **1cbc** (3.43 g, 84% over 4 steps). Colorless oil. R_f (pentane/AcOEt 9:1) 0.44. $[\alpha]^{rt}_D = -18.2$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 3036*w*, 2964*m*, 2872*w*, 1759*m*, 1708*s*, 1503*s*, 1456*w*, 1390*w*, 1369*m*, 1164*s*, 1128*w*, 1103*w*, 1046*w*, 908*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.75 (*d*, *J* = 6.5, Me); 0.83 (*d*, *J* = 6.7, Me); 0.96 (*ddd*, *J* = 3.1, 10.0, 13.3, 1 H, C*H*$_2$CH); 1.39–1.46 (*m*, 1 H, C*H*$_2$CH); 1.44 (*s*, *t*-Bu); 1.54–1.59 (*m*, Me_2C*H*); 4.09–4.22 (*m*, NCH); 4.59 (*d*, *J* = 9.1, BocN*H*); 5.06 (*dd*, *J* = 2.6, 49.2, CHF); 5.15 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$); 5.32 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$); 7.33–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.1, 23.4 (Me); 24.4 (CH); 28.3 (Me); 37.4 (*d*, *J* = 3.3, CH_2); 50.3 (*d*, *J* = 19.7, CH); 67.3 (CH_2); 79.9 (C); 90.6 (*d*, *J* = 187.5), 128.7, 128.8, 128.9 (CH); 134.9, 155.2, 167.6 (*d*, *J* = 24.2) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −199.0 (*dd*, *J* = 26.7, 48.0, CHF). HR-MALDI-MS: 392.2 (7, $[M+K]^+$), 376.2 (100, $[M+Na]^+$), 344.2 (12), 320.1 (60), 300.1 (18), 254.2 (48). Anal. calc. for $C_{19}H_{28}FNO_4$ (353.43): C 64.57, H 7.98, N 3.96; found: C 64.51, H 7.82, N 3.91.

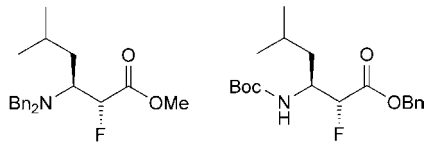
*Methyl (2*S/R*,3*S*)-3-(Dibenzylamino)-2-hydroxy-5-methylhexanoate* (**6c**/*epi*-**6c**). A soln. of freshly prepared **4c** [11] (5.6 g, 19.1 mmol) in hexane/H_2O (40 ml, 3:1) was treated with acetone cyanohydrin (2.6 ml, 28.7 mmol), KCN (40.0 mg, 0.6 mmol), and Bu_4NI (47.0 mg, 0.2 mmol) according to *GP 7*. The crude epimeric mixture of cyanohydrins was treated with a sat. HCl/MeOH soln. (100 ml) according to *GP 8*. FC (pentane/Et_2O 4:1) yielded **6c**/*epi*-**6c** (7.12 g, 78% over 2 steps). Yellow oil. R_f (pentane/Et_2O 4:1) 0.23. Both epimers could be separated by a further FC (hexane/AcOEt 95:5) yielding pure **6c** and *epi*-**6c**. The ^{1}H- and ^{13}C-NMR data for **6c** ((2*R*,3*S*)) were in accordance with those described above.



6c *epi*-**6c**

Data of epi-**6c** ((2*S*,3*S*)). Light yellow oil. R_f (pentane/Et_2O 3:2) 0.43. $[\alpha]_D^{rt.} = +43.7$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3520*w*, 3008*w*, 2957*s*, 1731*s*, 1495*m*, 1454*m*, 1366*w*, 1269*m*, 1155*m*, 1092*m*, 1028*w*, 973*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.5$, Me); 1.00 (*d*, $J = 6.2$, Me); 1.48–1.58 (*m*, 1 H, CH_2CH); 1.60–1.69 (*m*, 1 H, CH_2CH); 1.77–1.86 (*m*, Me_2CH); 3.00–3.08 (*m*, NCH); 3.36 (*d*, $J = 13.7$, 2 PhC*H*H′); 3.48 (*s*, MeO); 3.95 (*d*, $J = 13.4$, 2 PhCH*H*′); 4.18 (*d*, $J = 4.1$, C*H*OH); 7.19–7.39 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.1, 24.1 (Me); 25.5 (CH); 32.8 (CH_2); 52.4 (Me); 55.6 (CH_2); 57.2, 73.2, 126.8, 128.1, 129.1 (CH); 139.9, 174.9 (C). HR-MALDI-MS: 378.2 (9, $[M + Na]^+$), 356.2 (100, $[M + H]^+$), 266.2 (60), 178.1 (9), 176.1 (8).

*Methyl (2*R*,3*S*)-3-(Dibenzylamino)-2-fluoro-5-methylhexanoate* (*epi*-**7c**). Compound *epi*-**6c** (2.42 g, 6.80 mmol) was dissolved in CH_2Cl_2 (14 ml) and fluorinated with DAST (1.34 ml, 10.21 mmol) at 0° for 3 h, according to *GP 2*. FC (pentane/Et_2O 99:1 → 96:4) yielded *epi*-**7c** (1.09 g, 45%). Light yellow solid. M.p. 62–63°. R_f (pentane/Et_2O 10:1) 0.31. $[\alpha]_D^{rt.} = +31.7$ ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$): 3064*w*, 3032*w*, 2957*s*, 2870*w*, 2810*w*, 1762*s*, 1603*w*, 1495*m*, 1454*m*, 1439*w*, 1361*w*, 1304*m*, 1158*m*, 1076*m*, 1029*w*, 1001*w*, 972*w*, 938*w*, 911*w*, 887*w*, 831*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89 (*d*, $J = 6.4$, Me); 0.92 (*d*, $J = 6.4$, Me); 1.50–1.76 (*m*, Me_2CH_2CH); 3.15 (*tdd*, $J = 4.0$, 10.2, 31.4, NCH); 3.40 (*d*, $J = 13.4$, 2 PhC*H*H′); 3.61 (*s*, MeO); 3.87 (*d*, $J = 10.3$, 2 PhCH*H*′); 4.97 (*dd*, $J = 3.6$, 49.0, CHF); 7.19–7.31 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.0, 23.7 (Me); 25.0 (CH); 31.9 (*d*, $J = 3.3$, CH_2); 51.9 (Me); 55.0, 55.1 (CH_2); 56.5 (*d*, $J = 18.1$), 91.9 (*d*, $J = 188.8$), 126.9, 128.1, 129.3 (CH); 139.7, 169.4 (*d*, $J = 25.6$) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −202.6 (*dd*, $J = 31.0$, 48.0, CHF). HR-MALDI-MS: 358.2 (22, $[M + H]^+$), 338.2 (62), 278.2 (19), 266.2 (100). Anal. calc. for $C_{22}H_{28}FNO_2$ (357.47): C 73.92, H 7.89, N 3.92; found: C 73.87, H 8.13, N 4.08.

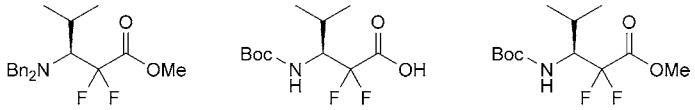


epi-**7c** **2cbc**

*Benzyl (2*R*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-fluoro-5-methylhexanoate* (**2cbc**). Compound *epi*-**7c** (940 mg, 2.63 mmol) was hydrolyzed with LiOH·H_2O (331 mg, 7.89 mmol) in EtOH/H_2O 2:1 (10 ml) according to *GP 3*, the carboxylic acid was dissolved in MeOH (26 ml) and hydrogenolyzed according to *GP 4*, and Boc-protected with Boc_2O (707 mg, 3.24 mmol) and Et_3N (1.13 ml, 8.10 mmol) in MeOH (15 ml) according to *GP 5*. The resulting acid **2cba** was dissolved in DMF (8 ml), and treated with Cs_2CO_3 (968 mg, 3.0 mmol) and BnBr (385 µl, 3.24 mmol) according to *GP 6*. FC (pentane/Et_2O 9:1) yielded **2cbc** (861 mg, 92% over 4 steps). Colorless solid. M.p. 80–82°. R_f (pentane/AcOEt 9:1) 0.42. $[\alpha]_D^{rt.} = -37.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3439*m*, 3009*w*, 2962*m*, 2923*w*, 2872*w*, 1759*s*, 1709*s*, 1503*s*, 1456*w*, 1392*w*, 1368*m*, 1331*w*, 1164*s*, 1135*w*, 1083*m*, 1052*w*, 949*w*, 913*w*, 867*w*, 850*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.5$, 2 Me); 1.36–1.50 (*m*, CH_2CH); 1.42 (*s*, *t*-Bu); 1.62–1.72 (*m*, Me_2CH); 4.20–4.33 (*m*, NCH); 4.66 (*d*, $J = 10.0$, BocN*H*); 4.89 (*dd*, $J = 1.9$, 47.9, CHF); 5.11 (*d*, $J = 12.0$, 1 H, PhCH_2); 5.27 (*d*, $J = 12.0$, 1 H, PhCH_2); 7.32–7.42 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.0, 22.9 (Me); 24.7 (CH); 28.3 (Me); 40.3 (CH_2); 50.3 (*d*, $J = 20.4$, CH); 67.5 (CH_2); 79.7 (C); 89.7 (*d*, $J = 187.4$), 128.6, 128.7, 128.7 (CH); 135.0, 155.2, 168.1 (*d*, $J = 25.2$) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −204.1 (*dd*, $J = 26.7$, 48.0,

CHF). HR-MALDI-MS: 376.2 (51, $[M+Na]^+$), 320.1 (34). Anal. calc. for $C_{19}H_{28}FNO_4$ (353.43): C 64.57, H 7.98, N 3.96, F 5.38; found: C 64.77, H 7.81, N 3.90, F 5.37.

3.2.4. *Difluoro-Substituted Val- and Leu-Derived Compounds. Methyl (3*S*)-3-(Dibenzylamino)-2,2-difluoro-4-methylpentanoate* (**8b**). The mixture **6b**/*epi*-**6b** (5.1 g, 14.9 mmol) was oxidized with oxalyl chloride (1.5 ml, 17.9 mmol) and DMSO (2.1 ml, 29.8 mmol) according to *GP 9*. The resulting crude keto ester was dissolved in CH_2Cl_2 (26 ml) and fluorinated with DAST (5.5 ml, 44.7 mmol) at r.t. for 6 h, according to *GP 2*. FC (pentane/Et_2O 95:5) yielded **8b** (3.4 g, 64% over 2 steps). Light yellow oil. R_f (pentane/Et_2O 95:5) 0.31. $[\alpha]_D^{r.t.} = -2.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3005*m*, 2954*m*, 2841*w*, 1959*w*, 1769*s*, 1708*s*, 1600*w*, 1492*w*, 1451*m*, 1440*w*, 1415*w*, 1359*s*, 1303*m*, 1281*w*, 1164*w*, 1118*s*, 1087*m*, 1067*s*, 1041*m*, 979*w*, 913*w*, 841*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.96 (*d*, *J* = 6.7, Me); 1.06 (*d*, *J* = 6.9, Me); 2.13–2.19 (*m*, Me_2CH); 3.17–3.25 (*ddd*, *J* = 7.0, 14.6, 16.9, NCH); 3.69 (*s*, MeO); 3.81 (*d*, *J* = 13.4, 2 PhC*H*H′); 3.89 (*d*, *J* = 13.4, 2 PhCH*H*′); 7.21–7.31 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.9, 22.5 (Me); 26.7 (*d*, *J* = 2.0, CH); 53.1 (Me); 55.2 (CH_2); 63.6 (*dd*, *J* = 18.4, 22.8, CH); 119.4 (*dd*, *J* = 256.7, 262.1, C); 127.1, 128.2, 129.5 (CH); 139.3, 165.1 (*t*, *J* = 32.8) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −105.3 (*dd*, *J* = 17.1, 265.7, 1 F, CF_2); −108.9 (*dd*, *J* = 14.9, 264.6, 1 F, CF_2). HR-MALDI-MS: 397.0 (15), 375.0 (21, $[M+Na]^+$), 362.2 (69, $[M+H]^+$), 360.2 (34), 266.2 (70), 252.2 (38). Anal. calc. for $C_{21}H_{25}F_2NO_2$ (361.43): C 69.79, H 6.97, N 3.88, F 10.51; found: C 69.81, H 7.01, N 3.84, F 10.39.



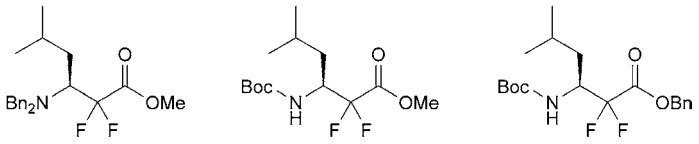
8b **3bba** **3bbb**

*(3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2,2-difluoro-4-methylpentanoic Acid* (**3bba**). Compound **8b** (847 mg, 3.0 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (379 mg, 9.0 mmol) in EtOH/H_2O 2:1 (12 ml) according to *GP 3*. The resulting acid **3bba** (790 mg, 98%) was used without further purification. Colorless solid. M.p. 115–116°. $[\alpha]_D^{r.t.} = -49.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3446*m*, 3026*w*, 2982*m*, 2933*w*, 1760*m*, 1717*s*, 1506*s*, 1394*w*, 1369*m*, 1310*w*, 1160*s*, 1092*w*, 1041*w*, 1005*w*, 873*m*. ^{1}H-NMR (300 MHz, CD_3OD): 0.94 (*d*, *J* = 6.8, Me); 0.98 (*d*, *J* = 6.8, Me); 1.44 (*s*, *t*-Bu); 2.01–2.09 (*m*, Me_2CH); 4.11 (*ddd*, *J* = 5.0, 13.1, 17.4, BocNHC*H*). ^{13}C-NMR (75 MHz, CD_3OD): 17.6, 20.6, 28.4 (Me); 28.7, 57.8 (*t*, *J* = 22.0) (CH); 80.2, 116.5 (*t*, *J* = 253.9), 157.8, 166.0 (*t*, *J* = 31.7) (C). ^{19}F-NMR (282 MHz, CD_3OD): −111.1 (*dd*, *J* = 12.8, 254.0, 1 F, CF_2); −112.6 (*dd*, *J* = 17.1, 255.0, 1 F, CF_2). HR-ESI-MS: 613.3 (7, $[2M+2K]^+$), 579.2 (12, $[2M+2Na]^+$), 557.2 (100, $[2M+Na]^+$), 370.1 (15), 290.1 (64, $[M+Na]^+$), 234.1 (7), 212.1 (13).

*Methyl (3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2,2-difluoro-4-methylpentanoate* (**3bbb**). The hydrogenolysis of **8b** (2.0 g, 5.5 mmol) was performed in presence of Boc_2O (1.8 g, 8.2 mmol) in MeOH (90 ml) according to *GP 4*. FC (pentane/Et_2O 95:5) yielded **3bbb** (1.3 g, 83%). Colorless solid. R_f (pentane/Et_2O 95:5) 0.16. M.p. 48–49°. $[\alpha]_D^{r.t.} = -19.8$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3446*m*, 2974*m*, 2882*w*, 1769*s*, 1713*s*, 1497*s*, 1446*w*, 1395*w*, 1369*s*, 1308*m*, 1159*s*, 1092*w*, 1056*m*, 1005*w*, 979*w*, 867*w*, 836*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.95 (*d*, *J* = 6.8, Me); 1.01 (*d*, *J* = 6.8, Me); 1.44 (*s*, *t*-Bu); 2.09–2.16 (*m*, Me_2CH); 3.86 (*s*, MeO); 4.14–4.23 (*m*, NCH); 4.68 (*d*, *J* = 10.5, BocN*H*). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.1, 20.5 (Me); 27.1 (CH); 28.2, 53.4 (Me); 56.5 (*dd*, *J* = 21.7, 26.4, CH); 80.2, 115.2 (*t*, *J* = 257.1), 155.4, 164.1 (*t*, *J* = 31.2) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −111.8 (*dd*, *J* = 8.5, 257.2, 1 F, CF_2); −116.8 (*dd*, *J* = 21.3, 257.2, 1 F, CF_2). HR-ESI-MS: 585.3 (39, $[2M+Na]^+$), 320.1 (9, $[M+K]^+$), 304.1 (100, $[M+Na]^+$). Anal. calc. for $C_{12}H_{21}F_2NO_4$ (281.30): C 51.24, H 7.52, N 4.98, F 13.51; found: C 51.41, H 7.46, N 5.14, F 13.51.

*Methyl (3*S*)-3-(Dibenzylamino)-2,2-difluoro-5-methylhexanoate* (**8c**). Mixture **6c**/*epi*-**6c** (5.3 g, 15.0 mmol) was oxidized with oxalyl chloride (1.6 ml, 18.0 mmol) and DMSO (2.1 ml, 30.0 mmol) according to *GP 9*. The resulting crude keto ester was dissolved in CH_2Cl_2 (30 ml) and fluorinated with DAST (5.5 ml, 45.0 mmol) at r.t. for 6 h, according to *GP 2*. FC (pentane/CH_2Cl_2 95:5) yielded **8c** (3.7 g, 65% over 2 steps). Colorless solid. R_f (pentane/CH_2Cl_2 95:5) 0.16. M.p. 60°. $[\alpha]_D^{r.t.} = +14.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3087*w*, 3032*w*, 2958*m*, 2869*m*, 1767*s*, 1603*w*, 1496*w*, 1454*m*, 1440*w*, 1380*w*, 1313*m*, 1117*s*, 1062*s*, 1028*w*, 966*w*, 917*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.75 (*d*, *J* = 6.5, Me); 0.93 (*d*, *J* = 6.6,

Me); 1.45–1.63 (*m*, CH_2CH); 1.79–1.88 (*m*, Me_2C*H*); 3.31–3.42 (*m*, NCH); 3.56 (*d*, *J* = 13.4, 2 PhC*H*H′); 3.68 (*s*, MeO); 3.82 (*d*, *J* = 13.4, 2 PhCH*H*′); 7.20–7.32 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.6, 22.8 (Me); 24.9 (CH); 32.6 (*d*, *J* = 2.5, CH_2); 52.9 (Me); 54.6 (CH_2); 57.0 (*dd*, *J* = 20.4, 25.0, CH); 118.7 (*t*, *J* = 258.0, C); 127.1, 128.2, 129.4 (CH); 139.2, 164.8 (*dd*, *J* = 30.9, 34.0) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −103.7 (*dd*, *J* = 11.7, 255.0, 1 F, CF_2); −114.2 (*dd*, *J* = 23.5, 254.0, 1 F, CF_2). HR-MALDI-MS: 413.3 (10, $[M+K]^+$), 398.2 (22, $[M+Na]^+$), 376.2 (100, $[M+H]^+$), 284.2 (11), 266.2 (15), 181.1 (17). Anal. calc. for $C_{22}H_{27}F_2NO_2$ (375.46): C 70.38, H 7.25, N 3.73; found: C 70.43, H 7.40, N 3.72.



8c **3cbb** **3cbc**

*Methyl (3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2,2-difluoro-5-methylhexanoate* (**3cbb**). The hydrogenolysis of **8c** (1.6 g, 4.2 mmol) was performed in presence of Boc_2O (1.3 g, 6.2 mmol) in MeOH (70 ml) according to *GP 4*. FC (pentane/Et_2O 19:1) yielded **3cbb** (1.3 g, 95%). Colorless solid. R_f (pentane/Et_2O 19:1) 0.17. M.p. 77°. $[\alpha]_D^{rt} = -39.6$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3436*w*, 2964*m*, 2872*w*, 1769*s*, 1713*s*, 1503*s*, 1441*w*, 1390*w*, 1369*m*, 1308*w*, 1159*s*, 1072*m*, 1046*w*, 1021*w*, 959*w*, 877*w*, 846*w*, 826*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.93 (*d*, *J* = 6.5, Me); 0.96 (*d*, *J* = 6.7, Me); 1.42 (*s*, *t*-Bu); 1.36–1.46 (*m*, CH_2CH); 1.67–1.74 (*m*, Me_2C*H*); 3.86 (*s*, MeO); 4.25–4.35 (*m*, NCH); 4.51 (*d*, *J* = 10.0, BocN*H*). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.2, 23.5 (Me); 24.3 (CH); 28.2 (Me); 36.3 (CH_2); 51.2 (*dd*, *J* = 23.4, 27.4, CH); 53.4 (Me); 80.2, 114.7 (*t*, *J* = 254.3), 155.1, 163.9 (*dd*, *J* = 31.3, 33.5) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −103.7 (*dd*, *J* = 11.7, 254.0, 1 F, CF_2); −114.2 (*dd*, *J* = 18.1, 254.0, 1 F, CF_2). HR-ESI-MS: 660.9 (4), 613.3 (100, $[2M+Na]^+$), 318.1 (53, $[M+Na]^+$), 306.6 (5), 214.8 (3), 209.5 (4), 156.2 (4). Anal. calc. for $C_{13}H_{23}F_2NO_4$ (295.33): C 52.87, H 7.85, N 4.74; found: C 52.86, H 7.65, N 4.79.

*Benzyl (3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2,2-difluoro-5-methylhexanoate* (**3cbc**). Compound **3cbb** (1.13 g, 4.02 mmol) was hydrolyzed with LiOH · H_2O (506 mg, 12.6 mmol) in EtOH/H_2O 2:1 (15 ml) according to *GP 3*. The resulting carboxylic acid **3cba** was dissolved in DMF (12 ml) and treated with Cs_2CO_3 (1.31 g, 4.02 mmol) and BnBr (570 µl, 4.82 mmol) according to *GP 6*. FC (pentane/Et_2O 19:1) yielded **3cbc** (1.40 g, 96% over 2 steps). Colorless solid. M.p. 47°. R_f (pentane/Et_2O 19:1) 0.20. $[\alpha]_D^{rt} = -18.6$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3436*m*, 3026*w*, 2954*m*, 2861*w*, 1764*s*, 1713*s*, 1503*s*, 1456*m*, 1390*w*, 1369*s*, 1303*w*, 1267*w*, 1159*s*, 1072*s*, 1046*m*, 1026*w*, 954*w*, 908*w*, 877*w*, 846*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87 (*d*, *J* = 6.5, Me); 0.91 (*d*, *J* = 6.7, Me); 1.31–1.37 (*m*, CH_2CH); 1.43 (*s*, *t*-Bu); 1.64–1.72 (*m*, Me_2C*H*); 4.23–4.39 (*m*, NCH); 4.51 (*d*, *J* = 10.3, BocN*H*); 5.19 (*d*, *J* = 12.0, 1 H, $PhCH_2$); 5.32 (*d*, *J* = 12.0, 1 H, PhCH_2); 7.34–7.47 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.2, 23.4 (Me); 24.3 (CH); 28.2 (Me); 36.6 (CH_2); 51.2 (*t*, *J* = 26.3, CH); 68.5 (CH_2); 80.2, 114.7 (*t*, *J* = 255.9) (C); 128.7, 128.8 (CH); 134.2, 155.1, 163.3 (*t*, *J* = 31.8) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −116.7 (*dd*, *J* = 11.7, 254.0, 1 F, CF_2); −118.8 (*dd*, *J* = 14.9, 252.9, 1 F, CF_2). HR-ESI-MS: 765.4 (18, $[2M+Na]^+$), 410.2 (21, $[M+K]^+$), 394.2 (100, $[M+Na]^+$). Anal. calc. for $C_{19}H_{27}F_2NO_4$ (371.42): C 61.44, H 7.33, N 3.77, F 10.23; found: C 61.36, H 7.16, N 3.69, F 10.26.

4. *Preparation of the Fluorinated Tetrahydropyrimidin-4(1*H*)-ones* **11**–**13** (*Fig. 2*). *(2*S*,5*S*,6*S*)-2-(*tert*-Butyl)-5-fluorotetrahydro-6-methylpyrimidin-4(1*H*)-ones* (**11**). According to *GP 10*, aminobutanoic acid **1aca** (1.82 g, 7.13 mmol) was converted to the corresponding Cbz-protected amino acid amide **1acd** (1.11 g, 61% yield), and subsequent hydrogenation (1.00 g, 3.93 mmol) gave the *β*-amino acid amide **1aad** (470 mg, quant.). Amide **1aad** (60.0 mg, 0.50 mmol) was treated with pivalaldehyde to afford crude **11** as colorless solid. Recrystallization of this crude product from hexane/AcOEt afforded **11** (81.1 mg, 86% yield). Colorless solid. A second recrystallization gave colorless prisms. M.p. 131–132° (hexane/AcOEt). $[\alpha]_D^{26} = +21.0$ (*c* = 1.0, $CHCl_3$). IR: 3318*w*, 3243*m*, 3107*w*, 2967*m*, 2954*m*, 2914*m*, 2871*m*, 1681*s*, 1660*s*, 1478*s*, 1454*m*, 1438*m*, 1417*m*, 1403*m*, 1381*w*, 1365*m*, 1330*m*, 1300*m*, 1284*m*, 1250*m*, 1207*w*, 1152*m*, 1134*m*, 1100*m*, 1056*s*, 1039*s*, 1017*m*, 965*m*, 937*w*, 904*w*, 874*w*, 805*m*, 763*s*, 686*s*, 635*m*. ^{1}H-NMR (400 MHz,

$CDCl_3$): 0.96 (*s*, 3 Me); 1.33 (*d*, *J* = 6.3, Me); 3.07–3.19 (*m*, NCH); 4.08 (*d*, *J* = 7.0, NCHN); 4.26 (*dd*, *J* = 48.3, 10.0, CFH); 6.17 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.6 (Me); 24.8 (3 Me); 34.2 (*t*-Bu); 51.7 (*d*, *J* = 21.9, NCH); 75.5 (NCHN); 88.9 (*d*, *J* = 189.9, FCH); 168.9 (*d*, *J* = 20.5, CF*C*O). ^{19}F-NMR (376 MHz, $CDCl_3$): −198.5 (*dd*, *J* = 48.4, 5.5, F). Anal. calc. for $C_9H_{17}FN_2O$ (188.24): C 57.42, H 9.10, N 14.88; found: C 57.40, H 9.28, N 14.87.

*Benzyl (2*S/R*,5*S*,6*S*)-2-(*tert-*Butyl)-5-fluorotetrahydro-6-methyl-4-oxopyrimidine-1(2*H*)-carboxylate* (Cbz-**11**). According to *GP 11*, **11** (100 mg, 0.53 mmol) was dissolved in CH_2Cl_2 (1.0 ml), and treated with *N*,*O*-bis(trimethylsilyl)acetamide (0.20 ml, 0.80 mmol) and Cbz-Cl (0.10 ml, 0.69 mmol). FC (CH_2Cl_2/AcOEt 9:1 → 3:1) yielded Cbz-**11** (66.7 mg, 39%). Colorless oil. $[\alpha]^{24}_D = +35.6$ (*c* = 0.77, $CHCl_3$). IR: 3228*w*, 2961*w*, 2911*w*, 2879*w*, 1688*s*, 1483*w*, 1456*w*, 1391*m*, 1318*s*, 1291*s*, 1198*m*, 1160*w*, 1120*w*, 1076*m*, 1038*s*, 1019*m*, 967*w*, 898*w*, 774*m*, 736*m*, 697*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00 (*s*, 3 Me); 1.56 (*d*, *J* = 6.3, Me); 4.20–4.36 (*m*, NCH); 4.90 (*dd*, *J* = 48.2, 8.6, CFH); 5.18 (*s*, PhCH_2); 5.38–5.40 (*s*, NCHN); 7.10 (*s*, NH); 7.31–7.41 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.4 (Me); 26.5 (3 Me); 38.6 (*t*-Bu); 53.6 (*d*, *J* = 29.6, NCH); 68.5 (Ph*C*H_2), 72.9 (NCHN); 86.4 (*d*, *J* = 180.1, FCH); 128.2 (arom. C); 128.4 (arom. C); 128.7 (arom. C); 135.6 (arom. C); 152.0 (CO); 167.2 (*d*, *J* = 20.2, CF*C*O). ^{19}F-NMR (280 MHz, $CDCl_3$): −195.5 (*dd*, *J* = 47.7, 22.6, F). ESI-MS: 323.1758 ([*M* + H]$^+$, $C_{17}H_{24}FN_2O_3^+$; calc. 323.1765 (err. 2.3 ppm)). Anal. calc. for $C_{17}H_{23}FN_2O_3$: C 63.34, H 7.19, N 8.69; found: C 63.08, H 7.28, N 8.40.

*(2*S*,5*R*,6*S*)-2-(*tert-*Butyl)-5-fluorotetrahydro-6-methylpyrimidin-4(1*H*)-ones* (**12**). According to *GP 10*, aminobutanoic acid **2aca** (1.80 g, 7.05 mmol) was converted to the corresponding Cbz-protected amino acid amide **2acd** (1.16 g, 65% yield), and subsequent hydrogenation (1.00 g, 3.93 mmol) gave the β-amino acid amide **2aad** (467 mg, 99% yield). Amide **2aad** (240 mg, 2.00 mmol) was treated with pivalaldehyde to give crude **12** as white solid. Purification by FC (CH_2Cl_2/AcOEt 1:1) afforded **12** (251 mg, 67% yield). Colorless solid. Crystallization gave colorless prisms. M.p. 141–142° (hexane/AcOEt). $[\alpha]^{26}_D = +116.6$ (*c* = 1.0, $CHCl_3$). IR: 3321*w*, 3294*w*, 3252*w*, 3193*w*, 3069*w*, 2982*w*, 2950*w*, 2910*w*, 2876*w*, 1671*s*, 1483*m*, 1454*m*, 1411*w*, 1374*m*, 1340*m*, 1287*w*, 1278*w*, 1261*w*, 1234*w*, 1214*w*, 1172*w*, 1144*m*, 1103*w*, 1078*m*, 1049*w*, 1014*w*, 993*m*, 982*m*, 952*m*, 938*m*, 904*w*, 884*w*, 869*w*, 834*m*, 819*s*, 798*m*, 711*m*, 688*m*, 661*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (*s*, 3 Me); 1.29 (*dd*, *J* = 6.8, 1.2, Me); 1.42 (br. *s*, NH); 2.94–3.12 (*m*, NCH); 4.01 (*d*, *J* = 7.0, NCHN); 4.52 (*ddd*, *J* = 48.4, 1.8, 0.7, CFH); 6.63 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.9 (*d*, *J* = 7.9, Me); 25.0 (3 Me); 34.2 (Me_3*C*); 51.6 (*d*, *J* = 21.0, NCH); 76.2 (NCHN); 87.8 (*d*, *J* = 174.5, FCH); 166.9 (*d*, *J* = 19.1, CF*C*O). ^{19}F-NMR (376 MHz, $CDCl_3$): 46.7 (*ddd*, *J* = 48.5, 30.1, 4.3, 1 F). Anal. calc. for $C_9H_{17}FN_2O$ (188.24): C 57.42, H 9.10, N 14.88; found: C 57.16, H 9.07, N 14.68.

*Benzyl (2*S/R*,5*R*,6*S*)-2-(*tert-*Butyl)-5-fluorotetrahydro-6-methyl-4-oxopyrimidine-1(2*H*)-carboxylate* (Cbz-**12**). According to *GP 11*, **12** (100 mg, 0.53 mmol) was dissolved in CH_2Cl_2 (1.0 ml), and treated with *N*,*O*-bis(trimethylsilyl)acetamide (0.20 ml, 0.80 mmol) and Cbz-Cl (0.10 ml, 0.69 mmol). FC (CH_2Cl_2/AcOEt 3:1) yielded Cbz-**12** (58.1 mg, 34% yield). Crystallization gave colorless prisms. M.p. 124–125° (Et_2O). $[\alpha]^{24}_D = -62.9$ (*c* = 1.0, $CHCl_3$). IR: 3197*w*, 3121*w*, 3086*w*, 2989*w*, 2961*w*, 2900*w*, 1704*m*, 1677*s*, 1475*w*, 1466*w*, 1458*w*, 1417*m*, 1399*m*, 1390*m*, 1329*m*, 1311*s*, 1299*s*, 1282*s*, 1216*w*, 1193*w*, 1084*s*, 1063*m*, 1046*s*, 970*w*, 942*w*, 899*w*, 870*w*, 814*w*, 774*m*, 750*s*, 700*s*, 630*w*, 611*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.01 (*s*, 3 Me); 1.35 (*dd*, *J* = 7.2, 2.5, Me); 4.72 (*dd*, *J* = 48.1, 6.4, CFH); 5.05–5.15 (*m*, NCH); 5.20–5.21 (*m*, PhCH_2); 5.39 (*s*, NCHN); 6.41 (*s*, NH); 7.35–7.42 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.9 (Me); 26.6 (3 Me); 37.3 (Me_3*C*); 51.7 (*d*, *J* = 23.5, NCH); 68.6 (Ph*C*H_2), 72.5 (NCHN); 84.0 (*d*, *J* = 192.9, FCH); 128.3 (arom. C); 128.6 (arom. C); 128.7 (arom. C); 135.5 (arom. C); 156.6 (CO); 166.8 (*d*, *J* = 20.8, CF*C*O). ^{19}F-NMR (376 MHz, $CDCl_3$): −198.8 (*d*, *J* = 48.5, 1 F). ESI-MS: 323.1766 ([*M* + H]$^+$, $C_{17}H_{24}FN_2O_3^+$; calc. 323.1765 (err. −0.2 ppm)); 345.1585 ([*M* + Na]$^+$, $C_{17}H_{23}FN_2NaO_3^+$; calc. 345.1585 (err., 0.0 ppm)). Anal. calc. for $C_{17}H_{23}FN_2O_3$: C 63.34, H 7.19, N 8.69; found: C 63.09, H 7.12, N 8.65.

*(2*R/S*,6*S*)-2-(*tert-*Butyl)-5,5-difluorotetrahydro-6-methylpyrimidin-4(1*H*)-ones* (**13a**/**13b**). According to *GP 10* aminobutanoic acid **3aca** (1.40 g, 5.12 mmol) was converted to the corresponding Cbz-protected amino acid amide **3acd** (930 mg, 67% yield), and subsequent hydrogenation (800 mg, 2.94 mmol) gave the β-amino acid amide **3aad** (405 mg, quant.). Amide **3aad** (200 mg, 1.45 mmol) was treated with pivalaldehyde to give crude **13a**/**13b** as white solid. Purification by FC (hexane/AcOEt 7:3,

hexane/acetone 85:15) afforded **13a**/**13b** (73.1 mg, 24%; dr 3:1). Colorless solid. Crystallization gave colorless prisms (1:1 diastereoisomeric co-crystal). M.p. 110–113° (hexane/AcOEt). $[\alpha]^{20}_{D} = -3.1$ ($c = 1$, $CHCl_3$). IR: 3321*w*, 3294*w*, 3252*w*, 3193*w*, 3069*w*, 2982*w*, 2950*w*, 2910*w*, 2876*w*, 1671*s*, 1483*m*, 1454*m*, 1411*w*, 1374*m*, 1340*m*, 1287*w*, 1278*w*, 1261*w*, 1234*w*, 1214*w*, 1172*w*, 1144*m*, 1103*w*, 1078*m*, 1049*w*, 1014*w*, 993*m*, 982*m*, 952*m*, 938*m*, 904*w*, 884*w*, 869*w*, 834*m*, 819*s*, 798*m*, 711*m*, 688*m*, 661*m*. ^{1}H-NMR (400 MHz, $CDCl_3$; *: minor isomer): 0.98 (*s*, 3 Me); 0.99 (*s*, 3 Me*); 1.29 (*d*, $J = 5.4$, Me*); 1.30 (*d*, $J = 6.6$, Me); 1.59–1.65 (*m*, NH); 2.16–2.24 (*m*, NH*); 3.10–3.26 (*m*, NCH); 3.44–3.54 (*m*, NCH*); 4.08–4.14 (*m*, NCHN, NCHN*); 6.13 (br. *s*, NH); 6.24 (br. *s*, NH). ^{19}F-NMR (280 MHz, $CDCl_3$): −104.3 (*ddd*, $J =$ 277.5, 13.9, 3.9, 1 F*); −120.2 (*dd*, $J = 280.4$, 17.9, 1 F); −121.4 (*ddd*, $J = 280.3$, 6.6, 2.1, 1 F); −123.8 (*d*, $J = 275.9$, 1 F*).

*Benzyl (2*S*/*R*,6*S*)-2-(*tert*-Butyl)-5,5-difluorotetrahydro-6-methyl-4-oxopyrimidine-1(2*H*)-carboxylate* (Cbz-**13**). According to *GP 11*, **13** (150 mg, 0.73 mmol) was dissolved in CH_2Cl_2 (1.4 ml), and treated with *N*,*O*-bis(trimethylsilyl)acetamide (0.27 ml, 1.09 mmol) and Cbz-Cl (0.13 ml, 0.95 mmol). FC (CH_2Cl_2/Et_2O 97:3) yielded Cbz-**13** (15.1 mg, 6%). Colorless oil. IR: 3236*w*, 2960*w*, 2875*w*, 1760*w*, 1693*s*, 1483*m*, 1455*w*, 1403*w*, 1373*w*, 1331*w*, 1296*w*, 1284*w*, 1199*s*, 1152*m*, 1104*m*, 1071*m*, 1029*w*, 1003*m*, 937*w*, 910*w*, 805*m*, 774*m*, 747*m*, 697*s*, 653*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.00 (*s*, 3 Me); 1.32 (*d*, $J = 6.6$, Me); 3.21 (*ddq*, $J = 19.1$, 12.7, 6.4, NCH); 4.13 (*dd*, $J = 11.9$, 3.4, NCHN); 5.20 (*s*, PhCH_2); 7.35–7.44 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.1 (Me); 24.9 (3 Me); 34.2 (Me_3C); 53.3 (*t*, $J = 24.5$, NCH); 67.9 (PhCH_2), 75.7 (NCHN); 110.8 (*t*, $J = 247.0$, CF_2); 128.1 (arom. C); 128.4 (arom. C); 128.7 (arom. C); 134.9 (arom. C); 151.8 (CO); 163.6 (*t*, $J = 29.8$, CF*C*O). ^{19}F-NMR (280 MHz, $CDCl_3$): −120.5 (*dd*, $J = 282.2$, 17.8, 1 F); −121.7 (*ddd*, $J = 282.2$, 6.9, 1.9, 1 F). ESI-MS: 341.1684 ($[M+H]^+$, $C_{17}H_{23}F_2N_2O_3^+$; calc. 341.1671 (err., −3.7 ppm)).

5. *Preparation of the Fluorinated Cyclo-β-tripeptides* **17**–**19** (*Scheme 3*, left). 5.1. *(*S,S*)-Isomer* **17** *from* **16a**. *Boc-(2*S*,3*S*)-β^{2,3}-hAla(α-F)-hGly-hGly-OMe* (**16a**). According to *GP 12a* amino fluoro acid **1aba** (700 mg, 3.16 mmol) was converted to the corresponding tripeptide. Purification by FC (hexane/acetone 7:3 → 1:1) afforded **16a** (821 mg, 69%). Colorless solid. Crystallization gave colorless prisms. M.p. 155–156° (CH_2Cl_2/Et_2O). $[\alpha]^{20}_{D} = -22.6$ ($c = 1.0$, MeOH). IR: 3350*m*, 3282*m*, 3086*w*, 2977*w*, 2951*w*, 1734*m*, 1689*s*, 1655*s*, 1640*s*, 1554*m*, 1530*s*, 1442*m*, 1387*m*, 1367*m*, 1337*m*, 1311*m*, 1271*m*, 1250*m*, 1171*s*, 1111*m*, 1062*m*, 990*m*, 926*w*, 883*m*, 850*w*, 806*w*, 781*w*, 749*m*, 708*m*, 643*m*, 616*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.11 (*dd*, $J = 7.0$, 0.5, Me); 1.46 (*s*, 3 Me); 2.43 (*td*, $J = 6.7$, 0.5, CH_2); 2.55 (*t*, $J = 6.6$, CH_2); 3.45 (*t*, $J = 6.6$, NCH_2); 3.47–3.56 (*m*, NCH_2); 3.70 (*s*, Me); 4.12 (*dqd*, $J = 27.3$, 7.0, 3.0, NCH); 4.90 (*dd*, $J = 49.7$, 3.0, FCH). ^{13}C-NMR (100 MHz, CD_3OD): 12.6 (*d*, $J = 5.7$, Me); 27.3 (3 Me); 33.3 (CH_2); 34.89 (CH_2); 34.93 (CH_2); 35.3 (CH_2); 49.2 (*d*, $J = 20.5$, NCH); 50.8 (Me); 79.0 (Me_3C); 92.3 (*d*, $J = 190.6$, FCH); 156.0 (CO); 168.8 (*d*, $J = 20.0$, CF*C*O); 172.3 (CO); 172.4 (CO). ^{19}F-NMR (280 MHz, CD_3OD): −203.7 (*dd*, $J = 49.5$, 27.2, 1 F). Anal. calc. for $C_{16}H_{28}FN_3O_6$ (377.41): C 50.92, H 7.48, N 11.13; found: C 50.96, H 7.44, N 10.99.

*Cyclo[(2*S*,3*S*)-β^{2,3}-hAla(α-F)-hGly-hGly]* (**17**). According to *GP 3*, **16a** (480 mg, 1.27 mmol) was converted to the corresponding carboxylic acid (443 mg, 96% yield). According to *GP 13*, the carboxylic acid (363 mg, 1.00 mmol) was converted to the pentafluorophenyl ester (471 mg, 89% yield), subsequent removal of the Boc group (400 mg, 0.756 mmol) afforded the TFA salt, which was converted (by treatment with $^iPr_2NEt$ in MeCN) to **17** (148 mg, 80%). Colorless solid. M.p. 299–300° (dec., MeCN). IR: 3388*m*, 3102*w*, 2973*w*, 2949*w*, 2876*w*, 1662*s*, 1646*s*, 1565*s*, 1544*s*, 1454*m*, 1446*m*, 1377*m*, 1351*w*, 1312*w*, 1270*m*, 1237*m*, 1200*m*, 1157*w*, 1133*m*, 1098*m*, 1069*s*, 1029*s*, 1009*m*, 988*w*, 923*w*, 880*w*, 864*w*, 736*m*, 713*m*, 671*s*, 609*m*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.49 (*d*, $J = 7.4$, Me); 2.52–2.64 (*m*, 2 C*H*H); 2.72 (*dt*, $J = 14.0$, 3.6, 1 H, CH_2); 3.06 (*ddd*, $J = 14.6$, 11.8, 5.6, 1 H, CH_2); 3.29–3.44 (*m*, 2 NC*H*H); 3.76 (*ddd*, $J = 14.1$, 5.4, 2.6, 1 H, NCH_2); 4.20–4.27 (*m*, 1 H, NCH_2); 4.58 (*dq*, $J = 21.6$, 7.3, NCH); 4.98 (*d*, $J = 48.6$, FCH). ^{19}F-NMR (280 MHz, $CDCl_3$ + TFA): −179.3 (*dd*, $J = 48.2$, 21.2, 1 F). ESI-MS: 246.1241 ($[M+H]^+$, $C_{10}H_{16}FN_3NaO_3^+$; calc. 246.1248 (err., 3.0 ppm)).

5.2. *(*R,S*)-Isomer* **18** *from* **16b**. *Boc-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-hGly-hGly-OMe* (**16b**). According to *GP 12a*, amino fluoro acid **2aba** (1.19 g, 5.40 mmol) was converted to the corresponding tripeptide. Purification by FC (hexane/acetone 7:3 → 1:1) afforded **16b** (1.51 g, 74%) as colorless solid. Recrystallization gave colorless solid. M.p. 117–118° (CH_2Cl_2/Et_2O). $[\alpha]^{20}_{D} = +22.2$ ($c = 1.0$, MeOH). IR: 3336*m*, 3312*m*, 3089*w*, 2973*w*, 2936*w*, 1732*m*, 1686*s*, 1656*s*, 1640*s*, 1526*s*, 1439*m*, 1366*m*, 1354*m*, 1326*m*,

1284*m*, 1247*m*, 1200*m*, 1164*s*, 1104*m*, 1056*m*, 1028*m*, 993*m*, 921*w*, 889*w*, 851*w*, 782*w*, 653*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.24 (*d*, *J* = 7.0, Me); 1.44 (*s*, 3 Me); 2.34–2.48 (*m*, CH_2); 2.56 (*t*, *J* = 6.7, CH_2); 3.42–3.56 (*m*, 2 NCH_2); 3.70 (*s*, Me); 4.08–4.22 (*m*, NCH); 4.80 (*dd*, *J* = 47.7, 3.0, FCH). ^{13}C-NMR (100 MHz, CD_3OD): 15.8 (Me); 27.3 (3 Me); 33.3 (CH_2); 35.0 (CH_2); 35.1 (CH_2); 35.4 (CH_2); 47.5 (*d*, *J* = 20.4, NCH); 50.8 (Me); 79.0 (Me_3*C*); 92.5 (*d*, *J* = 189.4, FCH); 156.0 (CO); 169.1 (*d*, *J* = 21.1, CF*C*O); 172.3 (CO); 172.5 (CO). ^{19}F-NMR (376 MHz, CD_3OD): 46.7 (*dd*, *J* = 47.7, 24.9, 1 F). Anal. calc. for $C_{16}H_{28}FN_3O_6$ (377.41): C 50.92, H 7.48, N 11.13; found: C 51.01, H 7.47, N 10.94.

*Cyclo[(2*R*,3*S*)-β^{2,3}-hAla(α-F)-hGly-hGly]* (**18**). According to *GP 3*, **16b** (1.00 g, 2.65 mmol) was converted to the corresponding carboxylic acid (955 mg, 99%). According to *GP 13*, the carboxylic acid (850 mg, 2.34 mmol) was converted to the pentafluorophenyl ester (1.09 g, 88%), subsequent removal of the Boc group (250 mg, 0.472 mmol) afforded the TFA salt, which was converted (by treatment with EtN^iPr_2 in MeCN) to **18** (74.8 mg, 75%). Colorless solid. M.p. 305° (dec., MeCN). IR: 3329*m*, 3284*m*, 3098*w*, 2971*w*, 2929*w*, 2871*w*, 1670*s*, 1663*s*, 1648*s*, 1550*s*, 1452*m*, 1435*m*, 1371*w*, 1347*m*, 1303*m*, 1275*m*, 1243*m*, 1199*m*, 1187*m*, 1164*w*, 1119*m*, 1094*m*, 1083*m*, 1066*w*, 1056*w*, 1013*m*, 991*m*, 960*w*, 924*w*, 886*w*, 866*w*, 788*w*, 738*m*, 686*s*, 670*m*, 632*m*, 616*m*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.38 (*d*, *J* = 7.0, Me); 2.54 (*ddd*, *J* = 13.8, 5.3, 1.8, 1 H, CH_2); 2.64 (*dt*, *J* = 15.2, 6.2, 1 H, CH_2); 2.82 (*ddd*, *J* = 13.8, 12.1, 6.1, 1 H, CH_2); 3.06 (*ddd*, *J* = 15.2, 8.1, 5.6, 1 H, CH_2); 3.30–3.47 (*m*, 2 NC*H*H); 3.70–3.79 (*m*, 1 H, NCH_2); 3.89–4.00 (*m*, 1 H, NCH_2); 4.67–4.89 (*m*, NCH); 5.01 (*dd*, *J* = 47.5, 1.6, FCH); 6.81 (*d*, *J* = 9.3, NH); 7.35 (br. *s*, NH); 7.78 (br. *s*, NH). ^{19}F-NMR (280 MHz, $CDCl_3$ + TFA): −204.4 (*ddd*, *J* = 47.3, 32.2, 3.7, 1 F). ESI-MS: 268.1067 ($[M+H]^+$, $C_{10}H_{16}FN_3NaO_3^+$; calc. 268.1068 (err., 0.5 ppm)).

5.3. *Difluoro Derivative* **19** *from* **16c**. *Boc-(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-hGly-hGly-OMe* (**16c**). According to *GP 12a*, amino fluoro acid **3aba** (1.00 g, 4.18 mmol) was converted to the corresponding tripeptide. Purification by FC (CH_2Cl_2/acetone 8:2) afforded **16c** (1.21 g, 73%) as colorless solid. Recrystallization gave colorless prisms. M.p. 151–152° (CH_2Cl_2/Et_2O). $[\alpha]_D^{28} = +16.3$ (*c* = 1.0, MeOH). IR: 3345*m*, 3289*m*, 3092*w*, 2975*w*, 2951*w*, 1735*m*, 1693*s*, 1677*m*, 1641*m*, 1533*s*, 1442*m*, 1388*w*, 1367*m*, 1341*m*, 1314*m*, 1269*m*, 1253*m*, 1198*m*, 1172*s*, 1152*m*, 1128*w*, 1105*m*, 1078*m*, 1059*m*, 1044*m*, 1009*m*, 997*m*, 925*w*, 887*w*, 870*w*, 851*m*, 787*w*, 754*w*, 709*m*, 642*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.21 (*d*, *J* = 7.0, Me); 1.45 (*s*, 3 Me); 2.37–2.50 (*m*, CH_2); 2.56 (*t*, *J* = 6.7, CH_2); 3.44–3.58 (*m*, 2 NCH_2); 3.69 (*s*, Me); 4.23–4.35 (*m*, NCH). ^{13}C-NMR (100 MHz, CD_3OD): 12.6 (Me); 27.3 (3 Me); 33.2 (CH_2); 34.7 (CH_2); 34.9 (CH_2); 35.8 (CH_2); 48.3 (*t*, *J* = 26.1, NCH); 50.8 (Me); 79.3 (Me_3*C*); 116.0 (*t*, *J* = 255.7, CF_2); 156.0 (CO); 164.2 (*t*, *J* = 28.8, CF*C*O); 172.1 (CO); 172.4 (CO). ^{19}F-NMR (376 MHz, CD_3OD): −117.5 (*dd*, *J* = 251.1, 11.0, 1 F); −119.9 (*dd*, *J* = 251.1, 15.1, 1 F). Anal. calc. for $C_{16}H_{27}F_2N_3O_6$ (395.40): C 48.60, H 6.88, N 10.63; found: C 48.71, H 6.89, N 10.53.

*Cyclo[(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-hGly-hGly]* (**19**). According to *GP 3*, **16c** (800 mg, 1.84 mmol) was converted to the corresponding carboxylic acid (770 mg, quant.). According to *GP 13*, the carboxylic acid (700 mg, 1.84 mmol) was converted to the pentafluorophenyl ester (880 mg, 87%), subsequent removal of the Boc group (660 mg, 1.21 mmol) afforded the TFA salt, which was converted (by treatment with EtN^iPr_2 in MeCN) to **19** (194 mg, 61%). Colorless solid. M.p. 297–299° (dec., MeCN). IR: 3307*m*, 3264*m*, 3098*w*, 2986*w*, 2945*w*, 1685*w*, 1664*s*, 1640*s*, 1556*s*, 1538*s*, 1446*m*, 1435*m*, 1372*m*, 1346*w*, 1317*w*, 1278*m*, 1249*m*, 1200*s*, 1185*s*, 1161*m*, 1146*s*, 1118*s*, 1092*m*, 1070*s*, 1023*m*, 1011*m*, 977*m*, 976*w*, 919*w*, 890*w*, 861*w*, 834*w*, 778*w*, 704*m*, 678*s*, 654*s*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.36 (*d*, *J* = 6.9, Me); 2.56 (*ddd*, *J* = 14.2, 5.2, 2.0, 1 H, CH_2); 2.62–2.87 (*m*, 2 C*H*H); 3.03 (*ddd*, *J* = 15.3, 7.2, 5.4, 1 H, CH_2); 3.40–3.57 (*m*, 2 NC*H*H); 3.68–3.77 (*m*, 1 H, NCH_2); 3.90–4.02 (*m*, 1 H, NCH_2); 4.76–4.96 (*m*, NCH); 6.90 (*d*, *J* = 10.2, NH); 7.53 (br. *s*, NH); 7.82 (br. *s*, NH). ^{19}F-NMR (280 MHz, $CDCl_3$ + TFA): −109.9 (*d*, *J* = 256.2, 1 F); −126.5 (*d*, *J* = 256.2, 21.9, 1 F). ESI-MS: 264.1153 ($[M+H]^+$, $C_{10}H_{16}F_2N_3O_3^+$; calc. 264.1154 (err. 0.6 ppm)).

6. *Preparation of the Di- and Tetrafluoro-cyclo-β-tetrapeptides* **21**–**23** (*Scheme 3*, right). 6.1. *(*S*,*S*,*S*,*S*)-Isomer* **21** *from Boc-Dipeptide Ester* **20a**. *Boc-(2*S*,3*S*)-β^{2,3}-hAla(α-F)-hGly-OMe* (**20a**). According to *GP 12a*, amino fluoro acid **1aba** (2.21 g, 10.0 mmol) was converted to the corresponding dipeptide **20a**. Purification by FC (hexane/AcOEt 65:35 → 6:4) afforded **20a** (2.36 g, 77%). Colorless solid. Recrystallization gave colorless prisms. M.p. 114–115° (CH_2Cl_2/Et_2O). $[\alpha]_D^{20} = -33.0$ (*c* = 1.0, MeOH). IR: 3355*m*, 2990*w*, 2942*w*, 1733*s*, 1687*s*, 1657*s*, 1550*m*, 1521*s*, 1446*m*, 1427*w*, 1396*w*, 1367*w*, 1333*m*, 1299*w*, 1268*m*, 1250*s*, 1203*m*, 1182*s*, 1162*s*, 1110*m*, 1084*m*, 1061*s*, 993*m*, 964*w*, 934*w*, 880*m*, 847*w*,

807*w*, 779*m*, 748*m*, 703*m*, 639*m*, 611*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.11 (*d*, *J* = 7.0, Me); 1.45 (*s*, 3 Me); 2.58 (*t*, *J* = 6.1, CH_2); 3.54–3.65 (*m*, NCH_2); 3.71 (*s*, Me); 4.20–4.40 (*m*, NCH); 4.76 (br. *s*, NH); 4.97 (*dd*, *J* = 50.1, 2.2, FCH); 6.88 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.2 (*d*, *J* = 5.3, Me); 28.3 (3 Me); 33.7 (CH_2); 34.4 (CH_2); 47.7 (*d*, *J* = 20.4, NCH); 51.9 (Me); 79.8 (Me_3C); 93.0 (*d*, *J* = 190.6, FCH); 154.8 (CO); 167.4 (*d*, *J* = 19.1, CF*C*O); 172.6 (CO). ^{19}F-NMR (376 MHz, $CDCl_3$): −196.2 (*dd*, *J* = 46.5, 18.0, 1 F). Anal. calc. for $C_{13}H_{23}FN_2O_5$ (306.33): C 50.97, H 7.57, N 9.14; found: C 50.94, H 7.51, N 9.06.

*Cyclo[(2*S*,3*S*)-β^{2,3}-hAla(α-F)-hGly]$_2$* (**21**). According to *GP 3*, **20a** (1.60 g, 5.22 mmol) was converted to the corresponding carboxylic acid (1.46 g, 95%). According to *GP 13*, the carboxylic acid (1.00 g, 3.42 mmol) was converted to the pentafluorophenyl ester (1.43 mg, 91% yield), subsequent removal of the Boc group (458 mg, 1.00 mmol) afforded the TFA salt, which was converted (by treatment with $^iPr_2NEt$ in MeCN) to **21** (203 mg, 58%). Colorless solid. M.p. 249° (dec., MeCN). IR: 3299*m*, 3093*w*, 3059*w*, 2971*w*, 2961*w*, 2941*w*, 1658*s*, 1561*m*, 1541*s*, 1473*w*, 1449*w*, 1425*m*, 1394*w*, 1380*m*, 1353*w*, 1336*m*, 1276*w*, 1242*w*, 1223*m*, 1203*m*, 1159*m*, 1121*m*, 1083*m*, 1036*m*, 999*w*, 963*w*, 941*w*, 923*w*, 887*w*, 811*w*, 769*w*, 635*m*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.44 (*d*, *J* = 7.3, Me); 2.30 (*ddd*, *J* = 16.7, 12.0, 3.4, 1 H, CH_2); 2.63 (*dt*, *J* = 17.0, 3.1, 1 H, CH_2); 3.42–3.53 (*m*, 1 H, NCH_2); 3.81–3.90 (*m*, 1 H, NCH_2); 4.57–4.74 (*m*, NCH); 4.89 (*dd*, *J* = 46.8, 2.1, FCH); 7.00 (*dd*, *J* = 9.5, 0.3, NH); 7.75 (br. *s*, NH). ^{19}F-NMR (376 MHz, $CDCl_3$ + TFA): −182.7 (*ddd*, *J* = 46.5, 19.5, 3.9, 1 F). ESI-MS: 349.1687 ($[M+H]^+$, $C_{14}H_{23}F_2N_4O_4^+$; calc. 349.1682 (err. −1.3 ppm)).

6.2. *(*R,S,R,S*)-Isomer* **22** *from* **20b**. *Boc-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-hGly-OMe* (**20b**). According to *GP 12a*, amino fluoro acid **2aba** (1.00 g, 4.52 mmol) was converted to **20b**. Purification by FC (hexane/AcOEt 65:35 → 6:4) afforded **20b** (1.08 g, 78%). Colorless solid. Recrystallization gave colorless needles. M.p. 82–83° (CH_2Cl_2/Et_2O). $[\alpha]^{28}_D = +13.9$ (*c* = 1.0, MeOH). IR: 3336*m*, 3330*m*, 2981*w*, 2940*w*, 1739*s*, 1682*s*, 1658*s*, 1548*m*, 1522*s*, 1440*m*, 1390*w*, 1367*m*, 1351*m*, 1320*m*, 1267*m*, 1250*s*, 1195*s*, 1164*s*, 1121*w*, 1096*m*, 1073*w*, 1055*m*, 1033*m*, 987*m*, 942*w*, 887*m*, 846*m*, 814*m*, 781*w*, 758*w*, 742*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.18 (*d*, *J* = 6.7, Me); 1.44 (*s*, 3 Me); 2.58 (*td*, *J* = 6.1, 1.7, CH_2); 3.59 (*q*, *J* = 6.0, NCH_2); 3.72 (*s*, Me); 4.20–4.33 (*m*, NCH); 4.83 (*dd*, *J* = 47.1, 1.8, FCH); 5.17 (*d*, *J* = 8.6, NH); 6.90 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.0 (Me); 28.3 (3 Me); 33.7 (CH_2); 34.4 (CH_2); 47.0 (*d*, *J* = 22.3, NCH); 51.9 (Me); 79.6 (Me_3C); 91.6 (*d*, *J* = 190.8, FCH); 154.9 (CO); 168.4 (*d*, *J* = 19.9, CF*C*O); 172.6 (CO). ^{19}F-NMR (376 MHz, $CDCl_3$): −196.1 (*dd*, *J* = 47.1, 18.0, 1 F). Anal. calc. for $C_{13}H_{23}FN_2O_5$ (306.33): C 50.97, H 7.57, N 9.14; found: C 50.89, H 7.49, N 9.05.

*Cyclo[(2*S*,3*S*)-β^{2,3}-hAla(α-F)-hGly]$_2$* (**22**). According to *GP 3*, **20b** (1.70 g, 5.55 mmol) was converted to the corresponding carboxylic acid (1.57 g, 97%). According to *GP 13*, the carboxylic acid (1.07 g, 3.66 mmol) was converted to the pentafluorophenyl ester (1.45 g, 86% yield), subsequent removal of the Boc group (458 mg, 1.00 mmol) afforded the TFA salt, which was cyclized by treatment with $^iPr_2NEt$ in MeCN to give **22** (206 mg, 59%). Colorless solid. M.p. 295–296° (dec., MeCN). IR: 3394*w*, 3325*m*, 3298*m*, 3049*w*, 2974*w*, 2950*w*, 2879*w*, 1654*s*, 1567*m*, 1539*s*, 1444*m*, 1416*m*, 1382*w*, 1349*w*, 1316*m*, 1299*w*, 1283*w*, 1254*m*, 1211*m*, 1166*w*, 1112*m*, 1091*m*, 1079*m*, 1052*w*, 1037*w*, 1024*w*, 986*m*, 964*m*, 924*w*, 868*w*, 831*w*, 771*w*, 750*w*, 690*m*, 667*m*, 632*m*, 611*m*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.31 (*d*, *J* = 6.9, Me); 2.46 (*ddd*, *J* = 16.2, 8.4, 3.2, 1 H, CH_2); 2.77 (*ddd*, *J* = 16.2, 8.2, 3.1, 1 H, CH_2); 3.24–3.37 (*m*, 1 H, NCH_2); 3.60–3.74 (*m*, 1 H, NCH_2); 4.13–4.32 (*m*, NCH); 5.05 (*dd*, *J* = 46.7, 1.9, FCH); 7.91 (br. *s*, NH); 8.12 (*d*, *J* = 8.0, NH). ^{19}F-NMR (280 MHz, $CDCl_3$ + TFA): 40.1 (*dd*, *J* = 46.6, 31.8, 1 F). ESI-MS: 349.1672 ($[M+H]^+$, $C_{14}H_{23}F_2N_4O_4^+$; calc. 349.1682 (err. −1.3 ppm)).

6.3. *Tetrafluoro-cyclo-β-tetrapeptide* **23** *from* **20c**. *Boc-(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-hGly-OMe* (**20c**). According to *GP 12a*, amino fluoro acid **3aba** (1.00 g, 4.18 mmol) was converted to **20c**. Purification by FC (CH_2Cl_2/acetone 8:2) afforded **20c** (952 mg, 71%). Colorless solid. Recrystallization gave colorless prisms. M.p. 115–116° (CH_2Cl_2/Et_2O). $[\alpha]^{28}_D = +8.7$ (*c* = 1.0, MeOH). IR: 3354*m*, 2987*m*, 2955*w*, 1732*m*, 1688*s*, 1671*m*, 1550*m*, 1523*s*, 1446*m*, 1428*w*, 1397*m*, 1368*m*, 1335*m*, 1314*m*, 1253*m*, 1204*m*, 1180*s*, 1157*s*, 1092*w*, 1076*m*, 1056*m*, 1026*m*, 1010*m*, 994*m*, 927*w*, 892*m*, 862*w*, 845*m*, 782*w*, 774*w*, 740*w*, 710*m*, 632*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.21 (*d*, *J* = 7.1, Me); 1.45 (*s*, 3 Me); 2.54–2.66 (*m*, CH_2); 3.46–3.58 (*m*, NCH_2); 3.70 (*s*, Me); 4.30 (*ddq*, *J* = 14.6, 11.5, 7.2, FCH). ^{13}C-NMR (100 MHz, CD_3OD): 12.6 (Me); 27.3 (3 Me); 32.8 (CH_2); 35.1 (CH_2); 48.2 (*t*, *J* = 25.6, NCH); 50.9 (Me); 79.2 (Me_3C); 116.1 (*t*, *J* = 255.5, FCH); 156.0 (CO); 164.2 (*t*, *J* = 28.8, CF*C*O); 172.1 (CO). ^{19}F-NMR (376 MHz, CD_3OD): −117.5 (*dd*,

J = 251.5, 11.3, 1 F); −119.9 (*dd*, J = 251.5, 15.0, 1 F). ESI-MS: 349.1672 ([M + H]$^+$, $C_{14}H_{23}F_2N_4O_4^+$; calc. 349.1682 (err. +0.7 ppm)). Anal. calc. for $C_{13}H_{22}F_2N_2O_5$ (324.32): C 48.14, H 6.84, N 8.64; found: C 48.18, H 6.63, N 8.44.

*Cyclo[(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-hGly]$_2$* (**23**). According to *GP 3*, **20c** (430 mg, 1.33 mmol) was converted to the corresponding carboxylic acid (406 mg, 97%). According to *GP 13*, the carboxylic acid (400 mg, 1.29 mmol) was converted to the pentafluorophenyl ester (570 mg, 93% yield), subsequent removal of the Boc group (570 mg, 1.20 mmol) afforded the TFA salt, which was cyclized by treatment with EtN^{i}Pr$_2$ in MeCN to give **23** (218 mg, 47%). Colorless solid. M.p. 300° (dec., MeCN). IR: 3292*m*, 3077*w*, 2989*w*, 2950*w*, 1679*s*, 1651*s*, 1539*s*, 1451*m*, 1415*w*, 1385*w*, 1351*w*, 1305*w*, 1267*w*, 1242*w*, 1198*m*, 1169*m*, 1145*s*, 1112*m*, 1074*m*, 1006*m*, 914*w*, 871*w*, 840*w*, 801*w*, 720*m*, 705*m*, 689*m*. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA): 1.31 (*d*, J = 6.9, Me); 2.46 (*ddd*, J = 16.2, 8.4, 3.2, 1 H, CH_2); 2.77 (*ddd*, J = 16.2, 8.2, 3.1, 1 H, CH_2); 3.24–3.37 (*m*, 1 H, NCH_2); 3.60–3.74 (*m*, 1 H, NCH_2); 4.13–4.32 (*m*, NCH); 5.05 (*dd*, J = 46.7, 1.9, FCH); 7.91 (br. *s*, NH); 8.12 (*d*, J = 8.0, NH). ^{19}F-NMR (280 MHz, $CDCl_3$ + TFA): 40.1 (*dd*, J = 46.6, 31.8, 1 F). ESI-MS: 385.1499 ([M + H]$^+$, $C_{14}H_{21}F_4N_4O_4^+$; calc. 385.1493 (err., −1.3 ppm)).

7. *Synthesis of the Hexapeptide Derivatives* **24**–**26** *by Coupling in Solution* (*Scheme 4*). 7.1. *The Boc-Hexapeptide Benzyl Ester* **24bbb**, *Consisting of (*S,S*)-Residues* **1**. *Boc-(2*S*,3*S*)-β^{2,3}-hAla(α-F)-(2*S*,3*S*)-β^{2,3}-hLeu(α-F)-OBn* (dipeptide derivative from **1cac** and **1aba**). The benzyl ester **1cbc** (198 mg, 0.56 mmol) was Boc-deprotected according to *GP 14a*. The resulting TFA salt (**1cac** · TFA) was dissolved in CH_2Cl_2 (5 ml) and treated with the acid **1aba** (124 mg, 0.56 mmol), NMM (310 µl, 2.8 mmol), HOBt (91 mg, 0.67 mmol), and EDC · HCl (128 mg, 0.67 mmol) according to *GP 12b*. FC (CH_2Cl_2/MeOH 100:1) yielded the corresponding dipeptide (173 mg, 68%). Colorless solid. M.p. 148–150°. $[\alpha]_D^{r.t.}$ = −40.2 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 3436*m*, 2964*m*, 2923*w*, 2872*w*, 1759*m*, 1713*s*, 1528*w*, 1503*s*, 1456*m*, 1369*m*, 1333*w*, 1277*w*, 1164*s*, 1128*w*, 1082*w*, 1062*w*, 1031*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.73 (*d*, J = 6.5, Me); 0.83 (*d*, J = 6.6, Me); 1.00 (*ddd*, J = 3.2, 10.2, 13.8, 1 H, C*H*$_2$CH); 1.12 (*d*, J = 6.9, Me); 1.45 (*s*, *t*-Bu); 1.45–1.58 (*m*, CH*H′*C*H*); 4.28–4.36 (*m*, NCH); 4.48–4.60 (*m*, NCH); 4.64 (br. *s*, BocN*H*); 4.99 (*dd*, J = 2.3, 50.0, CHF); 5.02 (*dd*, J = 2.9, 49.1, CHF); 5.16 (*d*, J = 11.9, 1 H, PhC*H*$_2$); 5.35 (*d*, J = 11.9, 1 H, PhC*H*$_2$); 6.36 (br. *s*, NH); 7.33–7.41 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.5, 20.7, 23.4 (Me); 24.4 (CH); 28.3 (Me); 36.7 (*d*, J = 3.3, CH_2); 47.7 (*d*, J = 22.1), 48.3 (*d*, J = 19.9) (CH); 67.5 (CH_2); 79.9 (C); 89.9 (*d*, J = 188.8), 93.1 (*d*, J = 190.7), 128.7, 128.9, 129.0 (CH); 134.7, 154.7, 167.0 (*d*, J = 24.1), 167.3 (*d*, J = 19.2) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −202.8 (*dd*, J = 28.8, 49.1, CHF); −204.6 (*dd*, J = 26.7, 49.1, CHF). HR-MALDI-MS: 495.2 (2, [M + K]$^+$), 479.2 (61, [M + Na]$^+$), 423.2 (8), 403.2 (11), 379.2 (32, [M + Na − Boc]$^+$), 357.2 (100, [M + H − Boc]$^+$), 339.2 (6). Anal. calc. for $C_{23}H_{34}F_2N_2O_5$ (456.53): C 60.51, H 7.51, N 6.14; found: C 60.62, H 7.60, N 6.18.

*Boc-(2*S*,3*S*)-β^{2,3}-hVal(α-F)-(2*S*,3*S*)-β^{2,3}-hAla(α-F)-(2*S*,3*S*)-β^{2,3}-hLeu(α-F)-OBn* (**24abb**). The dipeptide derivative (363 mg, 0.79 mmol) described above was Boc-deprotected according to *GP 14a*. The resulting TFA salt was dissolved in CH_2Cl_2 (4 ml) and treated with the acid **1bba** (200 mg, 0.80 mmol), NMM (440 µl, 4.0 mmol), HOBt (129 mg, 0.95 mmol), and EDC · HCl (183 mg, 0.95 mmol) according to *GP 12b*. FC (CH_2Cl_2/MeOH 100:5) yielded **24abb** (407 mg, 84%). Colorless solid. R_f (CH_2Cl_2/MeOH 200:3) 0.36. M.p. 189–190°. $[\alpha]_D^{r.t.}$ = −49.9 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 3432*s*, 3008*w*, 2966*s*, 2874*w*, 1760*m*, 1694*s*, 1522*s*, 1497*s*, 1456*w*, 1392*w*, 1368*m*, 1292*w*, 1161*s*, 1127*m*, 1082*w*, 1030*w*, 995*w*, 968*w*, 903*w*, 868*w*, 826*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.73 (*d*, J = 6.5, Me); 0.84 (*d*, J = 6.6, Me); 0.93 (*dd*, J = 0.9, 6.8, Me); 1.00 (*d*, J = 6.7, Me); 0.99–1.06 (*m*, 1 H, C*H*$_2$); 1.19 (*d*, J = 7.0, Me); 1.44 (*s*, *t*-Bu); 1.44–1.57 (*m*, 1 H, C*H*$_2$CH); 1.98–2.01 (*m*, Me$_2$C*H*); 3.94–4.03 (*m*, BocNHC*H*); 4.51–4.71 (*m*, 2 NCH, BocN*H*); 4.94 (*dd*, J = 4.1, 48.9, CHF); 4.99 (*dd*, J = 2.5, 49.8, CHF); 5.02 (*dd*, J = 3.0, 49.0, CHF); 5.17 (*d*, J = 11.9, 1 H, PhC*H*$_2$); 5.34 (*d*, J = 11.9, 1 H, PhC*H*$_2$); 6.42 (br. *d*, J = 5.8, NH); 6.47 (br. *d*, J = 4.9, NH); 7.33–7.41 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.1, 17.9, 20.2, 20.8 (Me); 23.3 (CH); 24.5, 28.3 (Me); 29.6 (*d*, J = 3.2, CH); 36.8 (CH_2); 46.0 (*d*, J = 19.5), 48.5 (*d*, J = 20.0), 56.9 (*d*, J = 20.9) (CH); 67.5 (CH_2); 79.8 (C); 89.9 (*d*, J = 188.8), 92.4 (*d*, J = 191.3), 128.8, 128.9, 129.0 (CH); 134.7, 155.7, 166.9 (*d*, J = 19.3), 167.0 (*d*, J = 23.8), 167.3 (*d*, J = 19.5) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −193.0 (*dd*, J = 25.6, 49.1, CHF); −202.7 (*dd*, J = 28.8, 49.1, CHF); −204.2 (*dd*, J = 26.7, 49.1, CHF). HR-MALDI-MS: 626.3 (3, [M + K]$^+$), 610.3 (32, [M + Na]$^+$), 554.2 (8), 534.2 (13), 510.3 (8, [M + Na − Boc]$^+$), 488.3 (100, [M + H − Boc]$^+$), 470.2 (8). Anal. calc. for $C_{29}H_{44}F_3N_3O_6$ (587.68): C 59.27, H 7.55, N 7.15; found: C 59.17, H 7.34, N 7.16.

*Boc-(2*S*,3*S*)-β²,³-hVal(α-F)-(2*S*,3*S*)-β²,³-hAla(α-F)-(2*S*,3*S*)-β²,³-hLeu(α-F)-(2*S*,3*S*)-β²,³-hVal(α-F)-(2*S*,3*S*)-β²,³-hAla(α-F)-(2*S*,3*S*)-β²,³-hLeu(α-F)-OBn* (**24bbb**). Compound **24abb** (120 mg, 0.20 mmol) was hydrogenolyzed according to *GP 4* to yield the corresponding acid **24aba** (103 mg, quant.). Another sample of **24abb** (71 mg, 0.12 μmol) was Boc-deprotected according to *GP 14b*. The resulting TFA salt of **24aab** (60 mg, 0.12 mmol) was dissolved in DMF (3 ml) and treated with **24aba** (61 mg, 0.12 mmol), NMM (40 μl, 0.37 mmol), and HATU (56 mg, 0.15 mmol), and the hexapeptide was isolated according to *GP 12d*. Drying under h.v. yielded **24bbb** (96 mg, 80%). Colorless solid. M.p. >260° (dec.). ^{1}H-NMR (300 MHz, (D_6)DMSO): 0.65 (*d*, *J* = 6.5, Me); 0.75–0.90 (*m*, 7 Me); 1.01–1.15 (*m*, 2 C*H*H′CH); 1.02 (*d*, *J* = 7.2, Me); 1.04 (*d*, *J* = 7.5, Me); 1.43–1.49 (*m*, 2 Me_2C*H*); 1.66–1.82 (*m*, 2 CH*H*′CH); 1.84–1.94 (*m*, 2 Me_2C*H*); 3.78–3.85 (*m*, BocNHC*H*); 4.12–4.48 (*m*, 5 NCH); 4.79 (*dd*, *J* = 5.9, 48.6, CHF); 4.83 (*dd*, *J* = 2.8, 49.8, CHF); 4.86 (*dd*, *J* = 3.1, 49.8, CHF); 4.87 (*dd*, *J* = 2.8, 49.5, CHF); 4.94 (*dd*, *J* = 5.9, 47.6, CHF); 5.06 (*dd*, *J* = 3.7, 48.6, CHF); 5.15 (*d*, *J* = 12.1, 1 H, $PhCH_2$); 5.26 (*d*, *J* = 12.1, 1 H, $PhCH_2$); 6.65 (*d*, *J* = 9.7, NH); 7.36–7.40 (*m*, 5 arom. H); 7.97 (*d*, *J* = 8.7, NH); 8.27 (*d*, *J* = 7.8, NH); 8.33 (*d*, *J* = 8.7, NH); 8.37 (*d*, *J* = 8.1, NH); 8.45 (*d*, *J* = 8.7, NH). ^{19}F-NMR (282 MHz, (D_6)DMSO): −192.4 (*dd*, *J* = 16.0, 47.0, CHF); −193.3 (*dd*, *J* = 19.1, 48.0, CHF); −199.4 (*dd*, *J* = 26.7, 49.1, CHF); −200.3 (*dd*, *J* = 25.6, 49.1, CHF); −201.0 (*dd*, *J* = 26.7, 48.0, CHF); −202.1 (*dd*, *J* = 27.7, 49.1, CHF). HR-MALDI-MS: 989.5 (100, [*M* + Na]$^+$), 969.5 (9), 933.5 (8), 913.4 (16), 889.5 (35, [*M* + Na − Boc]$^+$), 869.5 (41), 867.5 (74, [*M* + H − Boc]$^+$), 847.5 (30), 827.5 (20), 758.4 (12), 738.4 (5), 586.4 (8).

7.2. *The Boc-Hexapeptide Benzyl Ester* **25bbb** *and the Unprotected Hexapeptide* **25baa**, *Consisting of (*R,S*)-Residues* **2**. *Boc-(2*R*,3*S*)-β²,³-hAla(α-F)-(2*R*,3*S*)-β²,³-hLeu(α-F)-OBn* (dipeptide derivative from **2cac** and **2aba**).The benzyl ester **2cbc** (431 mg, 1.22 mmol) was Boc-deprotected according to *GP 14b*. The resulting TFA salt of **2cac** was dissolved in CH_2Cl_2 (3 ml) and treated with **2aba** (270 mg, 1.22 mmol), NMM (400 μl, 3.7 mmol), and HATU (557 mg, 1.46 mmol) according to *GP 12c*. FC (hexane/AcOEt 3:1) yielded the corresponding dipeptide (460 mg, 82%). Colorless solid. M.p. 92–93°. $[\alpha]_D^{r.t.} = -31.0$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3429*m*, 3008*w*, 2962*m*, 2923*w*, 2872*w*, 1761*m*, 1707*s*, 1862*w*, 1528*w*, 1501*s*, 1455*m*, 1391*w*, 1368*m*, 1341*m*, 1296*w*, 1165*s*, 1128*w*, 1086*m*, 1044*w*, 1030*w*, 847*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.93 (*d*, *J* = 6.7, 2 Me); 1.11 (*d*, *J* = 6.7, Me); 1.42 (*s*, *t*-Bu); 1.45–1.49 (*m*, CH_2CH); 1.55–1.63 (*m*, Me_2C*H*); 4.15–4.28 (*m*, BocNHC*H*); 4.64 (*qd*, *J* = 8.2, 24.1, NCH); 4.86 (*dd*, *J* = 3.5, 47.0, CHF); 4.91 (*dd*, *J* = 2.2, 47.2, CHF); 5.12 (br. *s*, BocN*H*); 5.15 (*d*, *J* = 12.0, 1 H, $PhCH_2$); 5.23 (*d*, *J* = 12.0, 1 H, $PhCH_2$); 6.41 (*dd*, *J* = 4.2, 9.6, NH); 7.34–7.42 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.5, 21.9, 22.9 (Me); 24.7 (CH); 28.3 (Me); 39.8 (CH_2); 46.8 (*d*, *J* = 25.5), 48.3 (*d*, *J* = 21.1) (CH); 67.7 (CH_2); 79.7 (C); 89.1 (*d*, *J* = 189.3), 91.3 (*d*, *J* = 192.4), 128.7, 128.8, 128.9 (CH); 134.7, 155.0, 167.5 (*d*, *J* = 25.1), 168.0 (*d*, *J* = 18.6) (C). ^{19}F-NMR (282 MHz, $CDCl_3$): −194.4 (*dd*, *J* = 14.9, 45.9, CHF); −230.6 (*dd*, *J* = 24.5, 48.0, CHF). HR-MALDI-MS: 479.2 (46, [*M* + Na]$^+$), 357.2 (100, [*M* + H − Boc]$^+$). Anal. calc. for $C_{23}H_{34}F_2N_2O_5$ (456.53): C 60.51, H 7.51, N 6.14; found: C 60.55, H 7.73, N 6.27.

*Boc-(2*R*,3*S*)-β²,³-hVal(α-F)-(2*R*,3*S*)-β²,³-hAla(α-F)-(2*R*,3*S*)-β²,³-hLeu(α-F)-OBn* (**25abb**). The dipeptide derivative (402 mg, 0.88 mmol) described above was Boc-deprotected according to *GP 14b*. The resulting TFA salt was dissolved in DMF/CH_2Cl_2 (1:1, 6 ml), and treated with the acid **2bba** (200 mg, 0.80 mmol), NMM (290 μl, 2.64 mmol), and HATU (402 mg, 1.06 mmol) according to *GP 12c*. FC (CH_2Cl_2/AcOEt 95:5) yielded **25abb** (467 mg, 90%). Colorless solid. R_f (CH_2Cl_2/AcOEt 9:1) 0.22. M.p. 158–159°. $[\alpha]_D^{r.t.} = -37.1$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3430*m*, 3008*w*, 2966*m*, 2923*w*, 2875*w*, 1761*m*, 1716*s*, 1682*s*, 1521*s*, 1456*w*, 1391*w*, 1368*m*, 1298*w*, 1169*m*, 1135*w*, 1085*m*, 1044*m*, 902*w*, 863*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.89 (*d*, *J* = 6.5, Me); 0.93 (*d*, *J* = 6.6, Me); 0.97 (*d*, *J* = 6.7, Me); 1.04 (*d*, *J* = 6.7, Me); 1.19 (*d*, *J* = 6.9, Me); 1.39–1.44 (*m*, 1 H, CH_2CH); 1.40 (*s*, *t*-Bu); 1.60–1.65 (*m*, Me_2C*H*); 1.67–1.72 (*m*, 1 H, CH_2CH); 1.85–1.92 (*m*, Me_2C*H*); 3.80 (*ddd*, *J* = 2.0, 8.6, 32.4, BocNHC*H*); 4.39–4.48 (*m*, NCH); 4.53–4.60 (*m*, NCH); 4.79 (*dd*, *J* = 4.8, 47.6, CHF); 5.02 (*dd*, *J* = 2.6, 48.5, CHF); 5.06 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.18 (*dd*, *J* = 2.1, 47.8, CHF); 5.21 (*d*, *J* = 12.1, 1 H, PhCH_2); 6.48 (*d*, *J* = 10.2, NH); 7.31–7.44 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, CD_3OD): 15.8 (*d*, *J* = 2.9), 19.6, 20.0, 21.9, 23.4 (Me); 25.8 (CH); 28.8 (Me); 31.5 (*d*, *J* = 2.8, CH); 40.2 (CH_2); 47.3 (*d*, *J* = 23.0), 50.1 (*d*, *J* = 20.2), 58.8 (*d*, *J* = 18.5) (CH); 68.6 (CH_2); 80.2 (C); 90.8 (*d*, *J* = 187.0), 91.9 (*d*, *J* = 186.9), 93.2 (*d*, *J* = 191.3), 129.6, 129.6, 129.8 (CH); 136.7, 158.1, 169.5 (*d*, *J* = 25.4), 170.1 (*d*, *J* = 21.1), 170.5 (*d*, *J* = 21.5) (C). ^{19}F-NMR (282 MHz, CD_3OD): −193.6 (*dd*, *J* = 18.1, 48.0, CHF); −202.1 (*dd*, *J* = 25.6, 48.0, CHF); −203.3 (*dd*, *J* = 32.0, 48.0, CHF). HR-MALDI-MS: 626.3 (3, [*M* + K]$^+$), 610.3 (100, [*M* + Na]$^+$), 554.2 (51), 510.3 (22, [*M* + Na − Boc]$^+$),

488.3 (50, [M + H – Boc]$^+$), 379.2 (7). Anal. calc. for $C_{29}H_{44}F_3N_3O_6$ (587.68): C 59.27, H 7.55, N 7.15; found: C 59.43, H 7.65, N 7.14.

*Boc-(2*R*,3*S*)-β^{2,3}-hVal(α-F)-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-(2*R*,3*S*)-β^{2,3}-hLeu(α-F)-(2*R*,3*S*)-β^{2,3}-hVal(α-F)-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-(2*R*,3*S*)-β^{2,3}-hLeu(α-F)-OBn* (**25bbb**). Compound **25abb** (117.5 mg, 0.2 µmol) was hydrogenolyzed according to *GP 4* to yield the corresponding acid **25aba** (99.5 mg, quant.). Another sample of **25abb** (120 mg, 0.2 µmol) was Boc-deprotected according to *GP 14b*. The resulting amine **25aab** (105 mg, 0.20 mmol) was dissolved in DMF/CH_2Cl_2 1:1 (3 ml) and treated with **25aba** (99.5 mg, 0.20 mmol), NMM (70 µl, 0.60 mmol), and HATU (93 mg, 0.25 mmol), according to *GP 12c*. FC ($CHCl_3$/TFE 98:2 → 95:5) yielded **25bbb** (118 mg, 60%). Colorless solid. M.p. 234–236°. R_f ($CHCl_3$/TFE 9:1) 0.25. For ^{1}H- and ^{13}C-NMR spectra, see also *Fig. 4*. ^{1}H-NMR (600 MHz, (D_3)TFE/TFA): 0.93–1.01 (*m*, 6 Me); 1.06 (*t*, *J* = 7.2, 2 Me); 1.17 (*d*, *J* = 6.7, Me); 1.27 (*d*, *J* = 6.9, Me); 1.43 (*s*, *t*-Bu); 1.44–1.63 (*m*, 2 C*H*$_2$CH, 2 Me$_2$C*H*); 1.89–1.93 (*m*, Me$_2$C*H*); 2.01–2.07 (*m*, Me$_2$C*H*); 3.73–3.82 (*m*, BocNHC*H*); 4.30 (*dd*, *J* = 8.2, 30.1, NCH); 4.49–4.69 (*m*, 4 NCH); 4.84 (*d*, *J* = 4.2, 46.8, CHF); 4.86 (*d*, *J* = 3.5, 46.7, CHF); 4.91 (*d*, *J* = 4.0, 46.3, CHF); 4.98 (*d*, *J* = 2.8, 47.1, CHF); 5.19 (*td*, *J* = 2.5, 46.4, 2 CHF); 5.23 (*d*, *J* = 12.1, PhC*H*$_2$); 7.37–7.43 (*m*, 5 arom. H). ^{13}C-NMR (150 MHz, (D_3)TFE/TFA): 15.2, 15.6, 16.0, 19.7, 19.8, 19.9, 20.1, 22.3, 23.3, 23.8 (Me); 26.3, 28.9 (CH); 29.1 (Me); 31.7, 32.2 (CH); 40.3, 41.1 (CH_2); 47.7 (*d*, *J* = 25.6), 48.0 (*d*, *J* = 23.5), 50.3 (*d*, *J* = 23.2), 50.9 (*d*, *J* = 20.6), 57.4 (*d*, *J* = 18.9), 59.8 (*d*, *J* = 19.0) (CH); 70.2 (CH_2); 82.7 (C); 91.4 (*d*, *J* = 187.3), 92.3 (*d*, *J* = 190.2), 92.4 (*d*, *J* = 189.9), 92.6 (*d*, *J* = 183.0), 92.7 (*d*, *J* = 183.9), 93.3 (*d*, *J* = 191.8), 128.8, 129.3, 129.4 (CH); 126.5, 159.1, 170.7 (*d*, *J* = 20.7), 171.1 (*d*, *J* = 20.1), 171.2 (*d*, *J* = 20.9), 171.3 (*d*, *J* = 25.2), 171.6 (*d*, *J* = 21.5) (C). ^{19}F-NMR (282 MHz, (D_6)DMSO): – 190.9 (*m*, 2 CHF); – 191.5 (*dd*, *J* = 18.1, 48.0, CHF); – 197.0 (*dd*, *J* = 26.7, 47.0, CHF); – 198.3 (*dd*, *J* = 27.7, 48.0, CHF); – 199.8 (*dd*, *J* = 25.6, 47.0, CHF). HR-MALDI-MS: 1005.5 (4, [M + K]$^+$), 989.5 (75, [M + Na]$^+$), 889.5 (35, [M + Na – Boc]$^+$), 867.5 (100, [M + H – Boc]$^+$), 849.5 (3), 758.4 (5), 488.3 (13).

*TFA · H-(2*R*,3*S*)-β^{2,3}-hVal(α-F)-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-(2*R*,3*S*)-β^{2,3}-hLeu(α-F)-(2*R*,3*S*)-β^{2,3}-hVal-(α-F)-(2*R*,3*S*)-β^{2,3}-hAla(α-F)-(2*R*,3*S*)-β^{2,3}-hLeu(α-F)-OH* (**25baa**). **25bbb** (35 mg, 36 µmol) was hydrogenolyzed according to *GP 4* and Boc-deprotected according to *GP 14a*. The crude product was purified by prep. RP-HPLC (MeCN/H_2O + 0.1% TFA 5:95 → 60:40 (in 25 min) → 90:10 (in 5 min) at a flow rate of 18 ml/min) and lyophilized to yield **25baa** (TFA salt; 14.4 mg, 45%). Colorless foam. For ^{1}H- and ^{13}C-NMR spectra, see *Fig. 4*. HR-MALDI-MS: 821 (5), 799 (15, [M + Na]$^+$), 777 (100, [M + H]$^+$), 759 (5), 543 (3).

7.3. *The Boc-Hexapeptide Benzyl Ester* **26bbb** *and the Unprotected Hexapeptide* **26baa**, *Consisting of 2,2-Difluoro-β-amino Acid Residues* **3**. *Boc-(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-(3*S*)-β^{2,2,3}-hLeu(α,α-F$_2$)-OBn* (dipeptide derived from **3cac** and **3aba**). The benzyl ester **3cbc** (500 mg, 1.4 mmol) was Boc-deprotected according to *GP 14b*. The resulting TFA salt of **3cac** (365 mg, 1.35 mmol) was dissolved in DMF (9 ml), and treated with the acid **3aba** (322 mg, 1.35 mmol), NMM (450 µl, 4.04 mmol), and HATU (614 mg, 1.62 mmol) according to *GP 12c*. FC (hexane/AcOEt 98:2 → 9:1) yielded the corresponding dipeptide (423 mg, 64%). Colorless solid. M.p. 132°. R_f (hexane/AcOEt 4:1) 0.38. $[\alpha]_D^{r.t.} = +10.7$ (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 3426*m*, 3005*w*, 2964*m*, 2933*w*, 2872*w*, 1764*m*, 1713*s*, 1508*s*, 1456*m*, 1364*m*, 1308*w*, 1164*s*, 1092*m*, 1061*m*, 1031*w*, 908*w*, 861*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.84 (*d*, *J* = 6.5, Me); 0.89 (*d*, *J* = 6.7, Me); 1.21 (*d*, *J* = 7.0, Me); 1.31–1.45 (*m*, C*H*$_2$CH); 1.44 (*s*, *t*-Bu); 1.54–1.62 (*m*, Me$_2$C*H*); 4.33–4.41 (*m*, NCH); 4.68 (*pd*, *J* = 3.1, 11.6, NCH); 4.92 (br. *s*, BocN*H*); 5.24 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$); 5.33 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$); 6.40 (*d*, *J* = 10.0, NH); 7.36–7.41 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8, 21.0, 23.3 (Me); 24.2 (CH); 28.3 (Me); 36.4 (CH_2); 48.8 (*t*, *J* = 26.0), 49.8 (*t*, *J* = 24.9) (CH); 68.9 (CH_2); 80.2, 113.9 (*t*, *J* = 256.4), 115.8 (*t*, *J* = 257.6) (C); 128.8, 128.9, 129.1 (CH); 133.8, 154.9, 162.6 (*t*, *J* = 32.2), 163.5 (*t*, *J* = 30.0) (C). ^{19}F-NMR (282 MHz, CD_3OD): – 113.0 (*dd*, *J* = 12.8, 254.0, 1 F, CF_2); – 114.7 (*dd*, *J* = 12.8, 252.9, 1 F, CF_2); – 115.3 (*dd*, *J* = 12.8, 252.9, 1 F, CF_2); – 116.2 (*dd*, *J* = 12.8, 252.9, 1 F, CF_2). HR-MALDI-MS: 531.2 (8, [M + K]$^+$), 515.2 (100, [M + Na]$^+$), 459.2 (76, [M + Na – isobutylene]$^+$), 415.2 (47, [M + Na – Boc]$^+$), 393.2 (89, [M + H – Boc]$^+$). Anal. calc. for $C_{23}H_{32}F_4N_2O_5$ (492.51): C 56.09, H 6.55, N 5.69, F 15.43; found: C 56.17, H 6.68, N 5.61, F 15.42.

*Boc-(3*S*)-β^{2,2,3}-hVal(α,α-F$_2$)-(3*S*)-β^{2,2,3}-hAla(α,α-F$_2$)-(3*S*)-β^{2,2,3}-hLeu(α,α-F$_2$)-OBn* (**26abb**). The dipeptide derivative described above (284 mg, 0.57 mmol) was Boc-deprotected according to *GP 14b*. The resulting TFA salt was dissolved in DMF (4 ml), and treated with the acid **3bba** (152 mg, 0.57 mmol),

NMM (190 µl, 1.70 mmol), and HATU (259 mg, 0.68 mmol) according to *GP 12c*. FC (hexane/AcOEt 95:5 → 8:2) yielded **26abb** (270 mg, 73%). Colorless solid. M.p. 122–124°. R_f (hexane/AcOEt 4:1) 0.38. $[\alpha]^{r.t.}_{D} = +13.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3426*m*, 3261*w*, 3036*w*, 2964*m*, 2875*w*, 1767*s*, 1713*s*, 1525*s*, 1504*s*, 1456*m*, 1392*m*, 1369*m*, 1308*m*, 1158*s*, 1087*m*, 1006*w*, 903*w*, 872*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.79 (*d*, *J* = 6.6, Me); 0.89 (*d*, *J* = 6.7, Me); 0.94 (*d*, *J* = 6.8, Me); 0.98 (*d*, *J* = 6.7, Me); 1.22 (*d*, *J* = 7.0, Me); 1.19–1.26 (*m*, 1 H, CH_2CH); 1.43 (*s*, *t*-Bu); 1.52–1.61 (*m*, Me_2CH); 1.68 (*ddd*, *J* = 3.8, 12.1, 15.7, 1 H, CH_2CH); 2.03–2.10 (*m*, Me_2CH); 4.16 (*ddd*, *J* = 4.6, 11.5, 18.7, $CHCF_2$); 4.59–4.69 (*m*, 2 $CHCF_2$); 5.23 (*d*, *J* = 11.9, 1 H, $PhCH_2$); 5.34 (*d*, *J* = 11.9, 1 H, $PhCH_2$); 7.35–7.44 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, CD_3OD): 13.7, 17.9, 21.0, 21.1, 23.7 (Me); 25.4 (CH); 28.7 (Me); 28.8 (CH); 36.0 (CH_2); 51.3 (*t*, *J* = 23.1), 58.1 (*t*, *J* = 25.3) (CH); 69.9 (CH_2); 80.7, 115.7 (*t*, *J* = 255.5), 117.0 (*t*, *J* = 256.1), 118.2 (*t*, *J* = 257.1) (C); 129.8, 130.0, 130.1 (CH); 135.9, 158.3, 164.1 (*t*, *J* = 32.1), 165.6 (*t*, *J* = 28.9), 165.8 (*t*, *J* = 29.0) (C). ^{19}F-NMR (282 MHz, CD_3OD): −110.6 (*dd*, *J* = 11.7, 252.9, 1 F, CF_2); −110.8 (*dd*, *J* = 9.6, 254.0, 1 F, CF_2); −113.3 (*dd*, *J* = 18.7, 252.9, 1 F, CF_2); −113.4 (*dd*, *J* = 13.4, 254.0, 1 F, CF_2); −115.2 (*dd*, *J* = 12.8, 252.9, 1 F, CF_2); −118.1 (*dd*, *J* = 16.6, 252.9, 1 F, CF_2). HR-MALDI-MS: 680.3 (2, $[M+K]^+$), 664.3 (52, $[M+Na]^+$), 608.2 (81, $[M+Na-\text{isobutylene}]^+$), 564.2 (54, $[M+Na-Boc]^+$), 542.2 (100, $[M+H-Boc]^+$), 524.2 (6), 466.2 (7), 303.1 (8). Anal. calc. for $C_{29}H_{41}F_6N_3O_6$ (641.65): C 54.28, H 6.44, N 6.55, F 17.77; found: C 54.08, H 6.57, N 6.56, F 17.75.

Boc-(3S)-β^{2,2,3}-hVal(α,α-F$_2$)-(3S)-β^{2,2,3}-hAla(α,α-F$_2$)-(3S)-β^{2,2,3}-hLeu(α,α-F$_2$)-(3S)-β^{2,2,3}-hVal(α,α-F$_2$)-(3S)-β^{2,2,3}-hAla(α,α-F$_2$)-(3S)-β^{2,2,3}-hLeu(α,α-F$_2$)-OBn (**26bbb**). Compound **26abb** (145 mg, 0.226 µmol) was C-terminally deprotected by hydrogenolysis according to *GP 4* to yield the corresponding acid **26aba** (107 mg, 86%). Another sample of **26abb** (125 mg, 0.194 µmol) was Boc-deprotected according to *GP 14b*. The resulting TFA salt of **26aab** (105 mg, 0.194 mmol) was dissolved in DMF (3 ml), and treated with the acid **26aba** (107 mg, 0.194 mmol), NMM (57 µl, 0.52 mmol), and HATU (88 mg, 0.23 mmol) according to *GP 12c*. The crude product was purified by prep. RP-HPLC ($MeCN/H_2O$ + 0.1% TFA 10:90 → 55:45 (in 2 min) → 67:33 (in 23 min) → 90:10 (in 2 min) at a flow rate of 18 ml/min) and lyophilized to yield **26bbb** (72 mg, 38%). Colorless solid. M.p. 208–210°. ^{19}F-NMR (282 MHz, CD_3OD): −109.1 (*dd*, *J* = 13.9, 257.2, C*F*F′); −109.3 (*dd*, *J* = 8.5, 254.0, 1 F, CF_2); −110.6 (*dd*, *J* = 11.7, 252.9, 1 F, CF_2); −110.7 (*dd*, *J* = 13.9, 257.2, 1 F, CF_2); −111.2 (*dd*, *J* = 9.6, 252.9, 1 F, CF_2); −111.9 (*dd*, *J* = 10.7, 254.0, 1 F, CF_2); −112.4 (*dd*, *J* = 14.9, 256.1, 1 F, CF_2); −113.3 (*dd*, *J* = 12.8, 252.9, 1 F, CF_2); −115.3 (*dd*, *J* = 12.8, 254.0, 1 F, CF_2); −117.0 (*dd*, *J* = 17.1, 252.9, 1 F, CF_2); −117.1 (*dd*, *J* = 16.0, 255.0, 1 F, CF_2); −117.6 (*dd*, *J* = 16.0, 252.9, 1 F, CF_2). HR-MALDI-MS: 1097 (6, $[M+Na]^+$), 1041 (28, $[M+Na-\text{isobutylene}]^+$), 1013 (13), 997 (100, $[M+Na-Boc]^+$), 975 (6, $[M+H-Boc]^+$), 957 (15), 921 (8), 848 (6).

TFA · H-(3S)-β^{2,2,3}-hVal(α,α-F$_2$)-(3S)-β^{2,2,3}-hAla(α,α-F$_2$)-(3S)-β^{2,2,3}-hLeu(α,α-F$_2$)-(3S)-β^{2,2,3}-hVal-(α,α-F$_2$)-(3S)-β^{2,2,3}-hAla(α,α-F$_2$)-(3S)-β^{2,2,3}-hLeu(α,α-F$_2$)-OH (**26baa**). Compound **26bbb** (14 mg, 13 µmol) was hydrogenolyzed according to *GP 4* and Boc-deprotected according to *GP 14a*. The crude product was dissolved in hexafluoropropan-2-ol and precipitated by the addition of $MeOH/H_2O$ 1:1. After filtration, the solid was washed (3 ×) with $MeOH/H_2O$ 1:1 and dried under h.v. for 12 h to yield **26baa** (TFA salt; 11.9 mg, 91%). Colorless solid. For ^{1}H- and ^{13}C-NMR spectra, see *Fig. 4*. HR-MALDI-MS: 929 (11), 907 (38, $[M+Na]^+$), 885 (100, $[M+H]^+$), 410 (15).

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