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α N–O turn induced by fluorinated α-aminoxy diamide: synthesis and conformational studies

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ABSTRACT

Two α-aminoxy diamides with fluorinated side chains were synthesized. Their secondary structures characterization was carried out by ^{1}H NMR, and IR spectrometries as well as X-ray crystallography studies. α N–O turn secondary structures are adopted insusceptibly by side-chain-fluorinated α-aminoxy residues. Thus the fluorinated α-aminoxy diamide can be a potential residue as a biological tracer to be incorporated into aminoxy peptides.

1. Introduction

For several decades, organofluorine chemistry has been an important area of organic chemistry, especially in the synthesis of fluorinated biologically active molecules such as peptidomimetics and drug candidates, and realizing their functions in biosystems (such as molecular recognition of enzymes).[1] Fluorine atom, as a bioisostere, has been widely used to replace a hydrogen atom or hydroxyl group of leading compounds, for example, to design pharmaceutical and bioactive molecules.[2] In addition, because of its extremely rare existence in biological molecules, the fluorine atom has been used as a biological tracer and mechanistic probe in ^{19}F NMR spectroscopy for investigation of protein folding pathways, the structures and properties of enzymes, and the like.[1d,3]

α-Aminoxy peptides (a kind of peptidomimetic foldamers[4] composed of α-aminoxy acids),[5] which have predictable secondary structures depending on the chirality of residues but not the side chains, have been found to have several bioactive applications, such as anion receptors and channels.[6] Bioactive peptidomimetics design was of particular interest to us. We intended to introduce one fluorine atom into the side chain of α-aminoxy acid residue, and expected that the designed compound would adopt an α N–O turn (which features an eight-membered-ring with an intramolecular hydrogen bond between adjacent residues of α-aminoxy peptide, Fig. 1)[7] with no disturbance of the fluorine atom due to its very weak hydrogen bond acceptor property.[8] Thus the residue has the opportunity to be incorporated into aminoxy peptide as a biological tracer. Hereinafter, we report the synthesis of two α-aminoxy diamides **1** and **2** (Fig. 2) with fluoroethyl and fluoropropyl side chains, respectively, and characterization of their secondary structures.

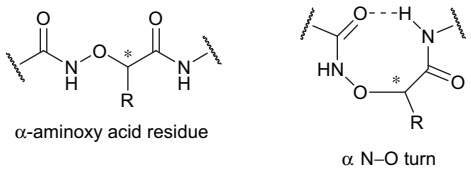

Figure 1. α-Aminoxy acid and α N–O turn.

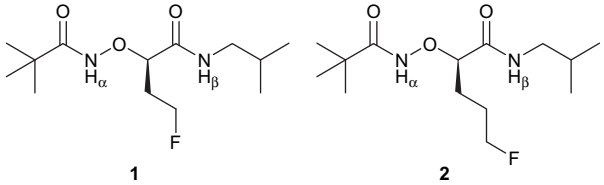

Figure 2. Fluorinated α-aminoxy diamides **1** and **2**.

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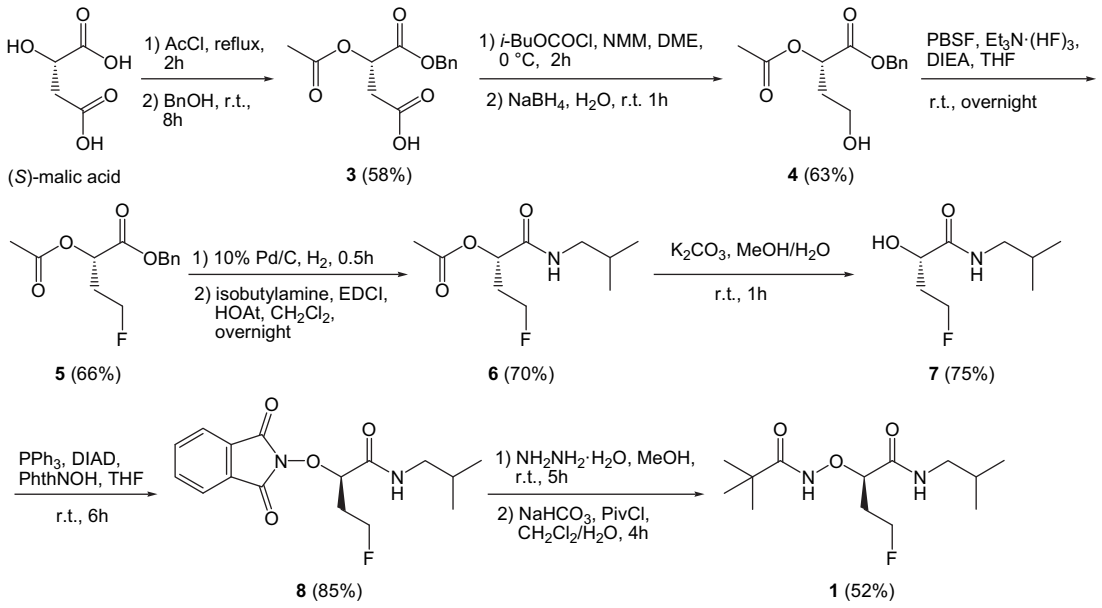
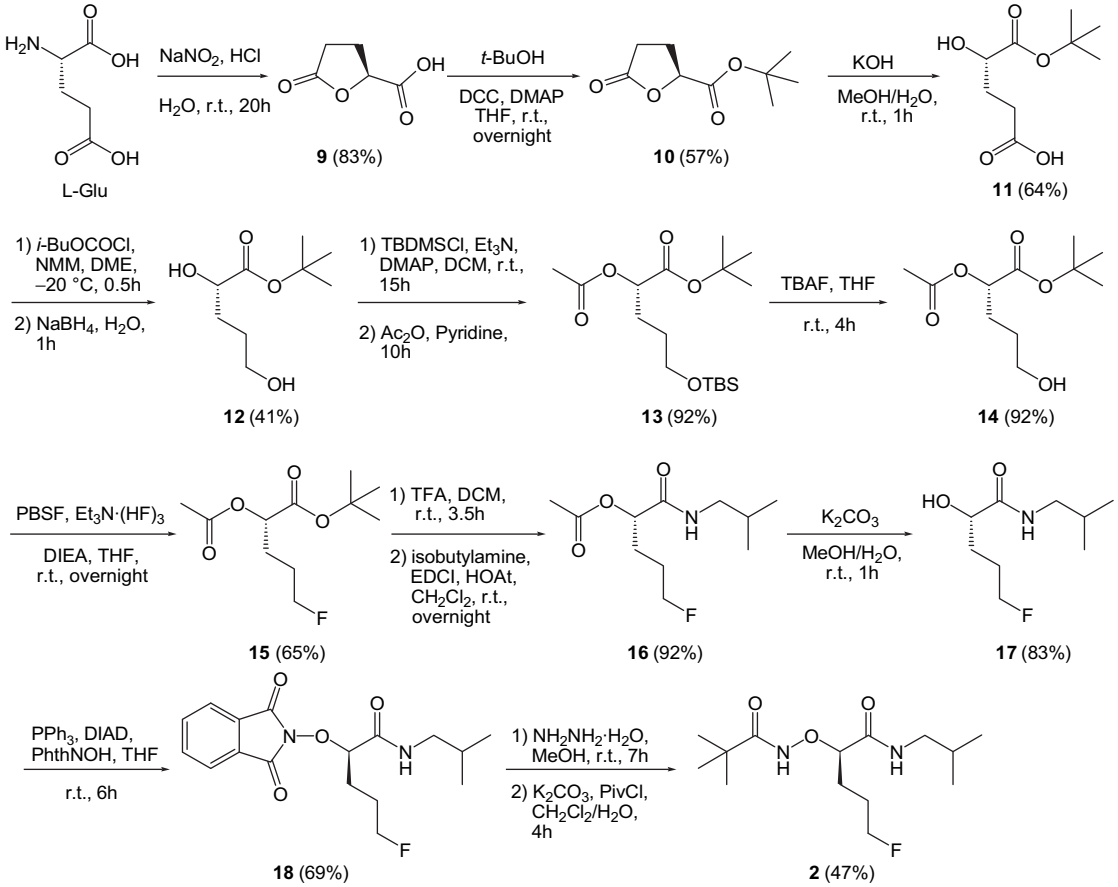


Scheme 1. Synthesis of fluoroethyl side-chained α-aminoxy acid monomer **1**.

2. Results and discussion

2.1. Synthesis of fluorinated α-aminoxy diamides

As shown in Schemes 1 and 2, fluorinated α-aminoxy diamides **1** and **2** were synthesized from (*S*)-malic acid and L-glutamic acid, respectively.[9] The key step for introducing the fluorine atom was to substitute the hydroxy group with a fluorine atom using perfluorobutanesulphonyl fluoride (PBSF) in the presence of $Et_3N\cdot(HF)_3$ and diisopropyl ethyl amine (DIEA).[10] Conventional protection/deprotection, Mitsunobu reaction, and coupling reaction were involved to introduce the N–O segment and build up the amide bond.[11,12] When introducing the N–O bond by Mitsunobu reaction of compound **7** or **17** to produce compound **8** or **18**,



Scheme 2. Synthesis of fluoropropyl side-chained α-aminoxy acid monomer **2**.

separately, the configuration at the α-carbon was inversed via an S_N2 mechanism.[11]

2.2. Conformational studies

*2.2.1. ^1H NMR dilution and titration studies of diamides **1** and **2**.* ^1H NMR dilution (Fig. 3) and titration (Fig. 4) studies of diamides **1** and **2** were carried out firstly. Generally, the chemical shift of the proton on the nitrogen atom varied with the concentration of the sample and the solvent. At high concentration (e.g., 200 mM), an intermolecular hydrogen bond between the N*H* proton and the carbonyl oxygen atom is formed, which induced a strong downfield chemical shift of N*H* protons in ^1H NMR spectra similar to that of intramolecular hydrogen bonded N*H* protons. But at low concentration (1.56–5 mM), almost no intermolecular hydrogen bond is formed. Thus both intermolecular and intramolecular hydrogen-bonded N*H* protons showed downfield shifts at 200 mM in $CDCl_3$, but only intramolecular hydrogen-bonded N*H* protons showed downfield shifts at 1.56 mM concentration. It is the chemical shifts of the solvent accessible N*H*s (non-intramolecular hydrogen-bonded) that significantly upfield shifted upon dilution from 200 mM to 1.56 mM in $CDCl_3$. Moreover, adding the strong hydrogen bond acceptor DMSO-d_6, which can form hydrogen bonds with N*H* protons, to a sample at low concentration in $CDCl_3$ induced a downfield chemical shift of the solvent accessible N*H* protons. Table 1 summarises the results of the ^1H NMR studies of diamides **1** and **2**, including the chemical shifts of N*H*s at low concentration in non-hydrogen bonded solvent, dilution studies with gradual dilution of the sample from 200 mM to 1.56 mM in $CDCl_3$, and titration studies carried out by adding 5 μl aliquots of DMSO-d_6 to a 5 mM sample solution in $CDCl_3$. Normally, non hydrogen-bonded general amide N*H* has chemical shift ca. 6.5 ppm at low concentration.[13] The non-hydrogen-bonded aminoxy amide N*H* has chemical shift ca. δ 8.5–9.0 ppm.[12] At a concentration of 1.56 mM in $CDCl_3$, the chemical shifts of N-terminal aminoxy amide NH_αs are ca. 8.5 ppm, while those of *C*-terminal general amide NH_βs are downfield (δ=8.43 ppm for compound **1** and 8.24 ppm for compound **2**). Dilution studies showed that the chemical shifts of NH_αs apparently moved upfield, whereas the chemical shifts of NH_βs changed very little, upon dilution with $CDCl_3$. The DMSO-d_6 titration study indicated that the NH_αs at the N-terminus had a dramatic downfield shift, whereas NH_βs at the *C*-terminus showed little change upon addition of DMSO-d_6. These ^1H NMR studies suggest

Table 1
Chemical shifts of amide and aminoxy amide protons of **1** and **2** at 25 °C and their chemical shift changes (Δδ) in ^1H NMR dilution (dilu.) and DMSO-d_6 titration (DMSO) studies

Compound	NH_α (ppm)			NH_β (ppm)		
	δ[a]	Δδ[b] (dilu.)	Δδ[c] (DMSO)	δ[a]	Δδ[b] (dilu.)	Δδ[c] (DMSO)
1	8.56	0.73	2.04	8.43	0.07	0.12
2	8.45	0.76	1.84	8.24	0.13	0.05

[a] The value of δ refers to the chemical shift observed in the ^1H NMR spectrum of the indicated compound in $CDCl_3$ at a concentration of 1.56 mM.
[b] The values of Δδ were calculated according to the expression δ_{NH} (200 mM)−δ_{NH} (1.56 mM).
[c] The values of Δδ were calculated according to the expression δ_{NH} (5 mM in $CDCl_3$/7% DMSO-d_6)−δ_{NH} (5 mM in $CDCl_3$).

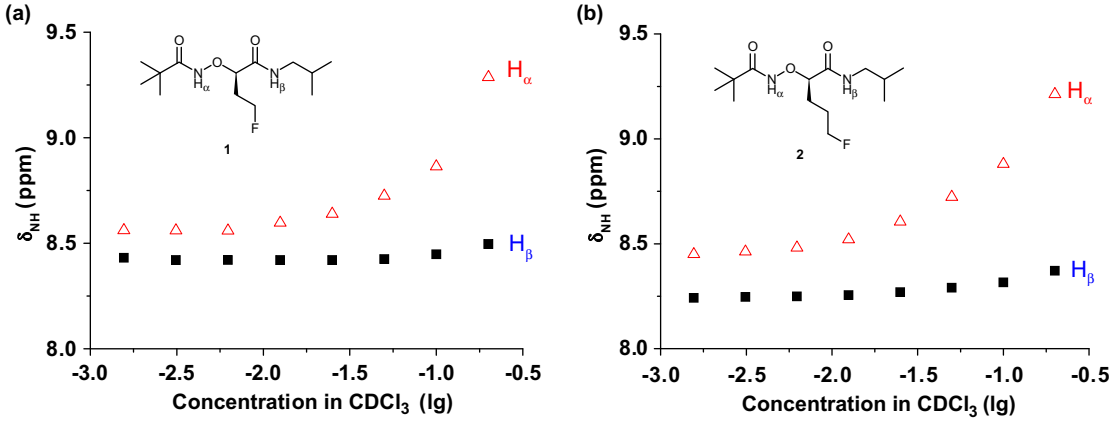


Figure 3. The correlation between the chemical shift and concentration's logarithm of NH in amide functional group of compounds **1** and **2**.

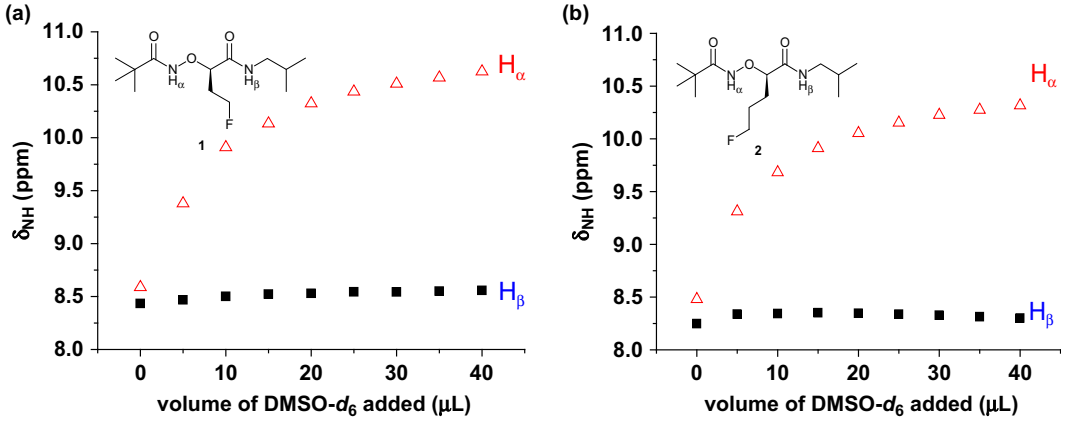


Figure 4. The correlation between the chemical shift of NH (in amide group of compounds **1** and **2**) and quantity of DMSO-d_6 added.

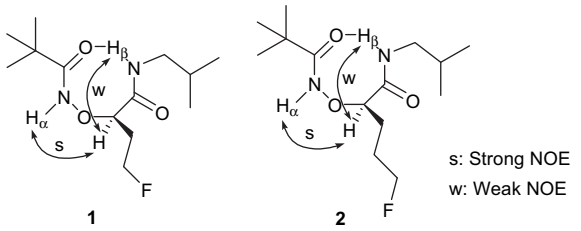


Figure 5. The NOE effects review of compounds **1** and **2** according to their 2D NOESY spectra (5 mM in $CDCl_3$ at 25 °C).

that the N-terminus N*H* protons (H_α) of diamides **1** and **2** are solvent accessible, whereas the *C*-terminus protons (H_β) are intramolecularly hydrogen bonded.

2.2.2. 2D NOESY studies. Nuclear Overhauser effect spectroscopy (2D NOESY) of compounds **1** and **2** (5 mM in $CDCl_3$) at 25 °C showed strong nuclear Overhauser effects (NOEs) between NH_α and C$_\alpha H$, but weak NOEs between NH_β and C$_\alpha H$, indicating that compounds **1** and **2** adopted a folded structure (Fig. 5), which is the same as previously reported D-α-aminoxy peptides.[14] This indicated that the conformation of diamides **1** and **2** in organic solvent does not change with introduction of fluorine atom into the side chain.

2.2.3. FTIR spectra studies. FTIR spectra of the N–H stretch region of compounds **1** and **2** at 2 mM concentration in CH_2Cl_2 are shown in Figure 6. For compound **1**, the band at 3381 cm^{-1} corresponds to the non hydrogen-bonded aminoxy N–H_α at the N-terminus. The bands in the region of 3305 cm^{-1} were assigned to the stretching bands of the hydrogen-bonded amide N–H_β at the *C*-terminus.[7] For compound **2**, similar results were obtained. The band at 3379 cm^{-1} corresponds to the non hydrogen-bonded aminoxy N–H_α, whereas absorptions in the region of 3305 cm^{-1} were assigned to an intramolecular hydrogen-bonded amide N–H_β at the *C*-terminus. Both compounds **1** and **2** have a weak absorption in the region of 3423 cm^{-1}, which can be assigned to non hydrogen-bonded general amide N–H_β stretching. This suggests that the α-aminoxy diamides **1** and **2** adopted predominantly the intramolecular eight-membered-ring hydrogen-bonded conformations in the organic solvent.

2.2.4. X-ray diffraction analysis. X-ray diffraction analysis of compound **1** disclosed the conformation of fluorinated α-aminoxy amide in the solid state (Figs. 7 and 8). An intramolecular eight-membered-ring hydrogen bond is clearly formed between the *C*-terminal general amide NH_β proton and the N-terminal aminoxy amide carbonyl oxygen ($NH_{i+2}\cdots O{=}C_i$, distance 2.30 Å), so that an α N–O turn is formed. The *C*-terminal general amide NH_β proton is also hydrogen-bonded to the N–O oxygen atom with a distance of 2.36 Å. This intramolecular five-membered-ring hydrogen bond is

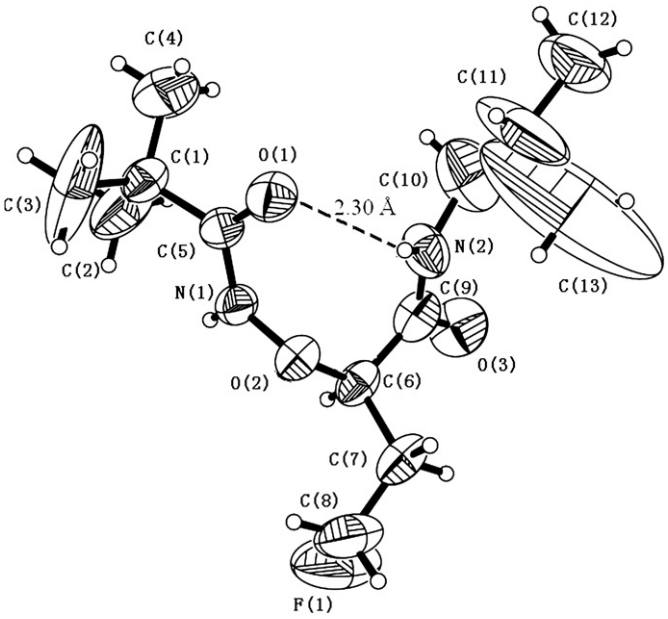


Figure 7. ORTEP structure of compound **1** with atom labels and intramolecular hydrogen bond.

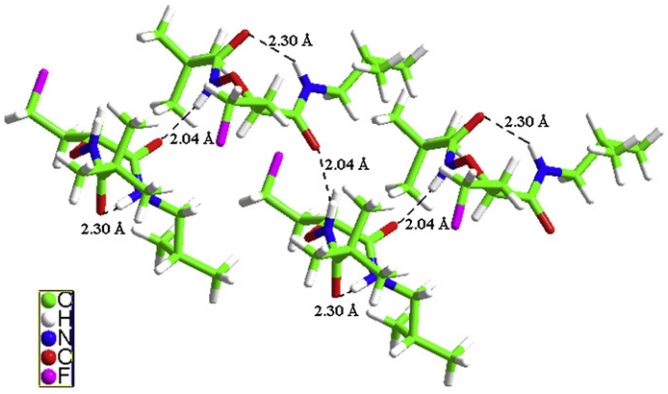


Figure 8. Structure of compound **1** with intra- and intermolecular hydrogen bonds.

also a stabilising factor in the secondary structure formed by fluorinated aminoxy amide. The side chain of the fluoroethyl group is almost anti to the N–O bond with dihedral angle $\angle NOC_\alpha C_S$= 162.57°. The chirality of the α N–O turn is also determined by the configuration of the α-carbon. For this D-aminoxy acid monomer, a right-handed α N–O turn is adopted (dihedral angle $\angle NOC_\alpha C_O$= 75.28°). The distance between the N-terminal aminoxy amide NH_α

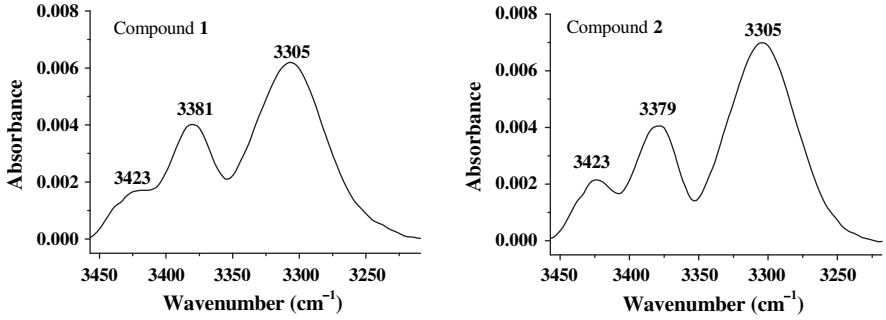


Figure 6. FTIR spectra of the N–H stretch region of compounds **1** and **2** at a 2 mM in CH_2Cl_2.

proton and $C_\alpha H$ is shorter (O–NH_α…HC_α, distance 2.36 Å) than that between the *C*-terminal general amide NH_β proton and α-H (NH_β…HC_α, distance 3.29 Å). This is in accordance with the 2D NOESY result that a strong NOE was observed in NH_i…H_iC_α but a weak NOE in NH_{i+1}…H_iC_α. The conformation of fluorinated α-aminoxy amide in the solid state is very similar to that in organic solvent. The crystal structure of compound **1** indicates that the incorporated fluorine atom has no effect on the adoption of the α N–O turn. As shown in Figure 8, the fluorine atom on the side chain does not form intra- or intermolecular hydrogen bonds with N*H* protons.

3. Conclusions

In conclusion, α-aminoxy diamides with fluorinated side-chains adopt the stable secondary structure of α N–O turn, while the fluorine atom at the end of the side chain does not form a hydrogen bond with general amide and aminoxy amide N*H* protons. This result suggests that the fluorinated side chain α-aminoxy residues can be incorporated into peptides without disarranging the backbone structure, but acting as a potential biological tracer in biological studies of aminoxy foldamers.

4. Experimental section

4.1. General

*4.1.1. (R)-2-(N-Pivalylamidoxy)-4-fluoro-N-isobutylbutanamide (**1**).* White solid; mp 82.5 °C; R_f=0.34 (EtOAc:hexane=1:2); $[\alpha]^{20}_D$+10.4° (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.29 (1H, br s, NH_α), 8.50 (1H, br s, NH_β), 4.76–4.53 (2H, m, $^2J_{HF}$=46.9 Hz, CH_2F), 4.38 (1H, dd, *J*=8.8, 3.4 Hz, α-H), 3.14–3.03 (m, 2H), 2.47–2.30 (m, 1H), 2.16–2.00 (m, 1H), 1.88–1.77 (m, 1H), 1.21 (9H, s, *t*-Bu), 0.92 (3H, d, *J*=6.3 Hz, Me), 0.91 (3H, d, *J*=6.3 Hz, Me) ppm; ^{13}C NMR & DEPT (100 MHz, $CDCl_3$): δ=178.5 (C=O), 170.4 (C=O), 83.4 (CH), 80.8 (CH_2, d, *J*=164.0 Hz), 46.8 (CH_2), 38.1 (C), 32.7 (CH_2, d, *J*=20.0 Hz), 28.5 (CH), 27.1 (CH_3), 20.2 (CH_3) ppm; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ=−130.1 ppm; IR (CH_2Cl_2) 3234, 2961, 1651 cm^{-1}; HRMS (ESI) for $C_{13}H_{26}FN_2O_3$ (M^++H): calcd 277.1928, found 277.1916.

*4.1.2. (R)-5-Fluoro-2-(N-Pivalylamidoxy)-N-isobutylpentanamide (**2**).* White solid; mp 89.0 °C; R_f=0.35 (EtOAc:hexane=1:2); $[\alpha]^{20}_D$+41.1° (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.78 (1H, s, NH_α), 8.31 (1H, br s, NH_β), 4.62–4.41 (2H, m, $^2J_{HF}$=47.4 Hz, CH_2F), 4.27 (1H, dd, *J*=7.8, 4.4 Hz, α-H), 3.15–3.01 (2H, m, NCH_2), 2.10–1.78 (5H, m, –CH_2CH_2– & CHMe$_2$), 1.20 (9H, s, *t*-Bu), 0.92 (3H, d, *J*=6.4 Hz, Me); 0.91 (3H, d, *J*=6.4 Hz, Me) ppm; ^{13}C NMR & DEPT (100 MHz, $CDCl_3$): δ=178.5 (C=O), 170.6 (C=O), 86.4 (CH), 84.2 (CH_2, d, *J*=163.1 Hz), 46.7 (CH_2), 38.2 (C), 28.5 (CH), 28.1 (CH_2, d, *J*=4.8 Hz), 27.2 (CH_3), 26.4 (CH_2, d, *J*=20.0 Hz), 20.2 (CH_3) ppm; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ=−133.5 ppm; IR (CH_2Cl_2) 3264, 2961, 1656, 1553 cm^{-1}; HRMS (ESI) for $C_{14}H_{27}FN_2O_3$ (M^++H): calcd 291.2084, found 291.2069.

Acknowledgements

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Supplementary data

Synthetic schemes and characterization data of **1**–**2** and intermediates; copies of IR spectra of **1** and **2**; crystallographic data of **1**. The supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.09.113.

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