Synthesis of Chiral α-Trifluoromethyl α,α-Disubstituted α-Amino Acids and Conformational Analysis of L-Leu-Based Peptides with (*R*)- or (*S*)-α-Trifluoromethylalanine

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Abstract: Various racemic α-trifluoromethyl α,α-disubstituted α-amino acids were synthesized by the reaction of methyl 3,3,3-trifluoropyruvate imines with Grignard reagents. The optical resolution of racemates using (*R*)-1,1'-bi-2-naphthol {(*R*)-BINOL} esters gave optically active α-trifluoromethylated α,α-disubstituted α-amino acids, such as α-trifluoromethylalanine (αCF$_3$Ala), α-trifluoromethylleucine (αCF$_3$Leu), and α-trifluoromethylphenylalanine (αCF$_3$Phe). The optically active (*R*)- or (*S*)-αCF$_3$Ala was incorporated into the L-Leu-based pentapeptides, and their preferred conformation in solution and in the crystal state was studied by Fourier transform infrared (FT-IR) absorption, nuclear Overhauser effect spectroscopy (NOESY) NMR, and circular dichroism (CD) spectra, as well as X-ray crystallographic analysis. Both L-Leu-based peptides with (*R*)- or (*S*)-αCF$_3$Ala formed right-handed 3$_{10}$-helical structures. Both peptide-backbones at the N-terminal residues 1-3 were very similar, but the ϕ and ψ torsion angles of residues 4 and 5 between peptides with (*R*)- or (*S*)- αCF$_3$Ala were different.

Introduction

α,α-Disubstituted α-amino acids (dAAs) are non-proteinogenic α-amino acids, in which the α-hydrogen atom is replaced with an alkyl substituent.[1] It is known that the incorporation of achiral dAAs, such as dimethylglycine (αMeAla, Aib), diethylglycine (Deg), and cyclic amino acids (Ac$_n$c), into peptides induces stable secondary structures such as α-helix, 3$_{10}$-helix, and planar conformations.[2] Furthermore, chiral dAAs such as α-methylated dAAs, α-ethylated dAAs, and chiral cyclic dAAs have been reported, and their homo- and heteropeptides preferentially formed right-handed (*P*) or left-handed (*M*) helical structures, or fully planar C$_5$-conformations.[3,4]

α-Trifluoromethyl (αCF$_3$) dAAs have been designed instead of αMedAAs because hydrogen can be isosterically replaced with fluorine from the point of medicinal chemistry. The CF$_3$ group is one of the most hydrophobic substituents, with polarization effects on neighboring groups, and acts as an electron donor for hydrogen bonding. Thus, peptides with αCF$_3$dAAs would be good candidates for screening of lead compounds in drug development, and chiral αCF$_3$dAAs have become attractive synthetic targets.[5]

The synthesis of chiral αCF$_3$dAAs has already been reported, but there are few different types of optically active αCF$_3$dAAs and their applicability is limited.[6] For example, Zanda *et al.* used optically active N-sulfinyl imine for stereoselective synthesis of α-trifluoromethyl α-amino acids but dr and ee values were varied by alkyl substituents due to the epimerization of imine moieties during the reaction.[6b] Herein, we synthesized racemic αCF$_3$dAAs using Burger's methods,[7] resolved racemic αCF$_3$dAAs using an (*R*)-1,1'-bi-2-naphthol {(*R*)-BINOL} as chiral esters, and studied the preferred structures of L-Leu-based pentapeptides with (*R*)- or (*S*)- α-trifluoromethylalanine (αCF$_3$Ala).[3h]

Results and Discussion

Methyl 2-(benzyloxycarbonylimino)- and 2-(*t*-butoxycarbonylimino)-3,3,3-trifluoropyruvates **3** were prepared from methyl 3,3,3-trifluoropyruvate **1** via addition of Cbz- or Boc-primary carbamate and subsequent dehydration, according to Burger's methods (Scheme 1).[7] Reaction of imines **3** with Grignard reagents at -78 ºC afforded Boc- and Cbz-protected αCF$_3$dAA methyl esters **4**-**8**, as shown in Table 1. The Grignard addition reactions of Cbz-protected **3** gave Cbz-protected αCF$_3$dAA methyl esters, such as Cbz-αCF$_3$Ala-OMe **4**, Cbz-αCF$_3$Val-OMe **6**, and Cbz-αCF$_3$Leu-OMe **7** in 72-93% isolated yields (entries 1-5). The reactions of Boc-protected **3** also produced Boc-protected αCF$_3$dAA methyl esters Boc-**4**-**8** in good yields, except for Boc-αCF$_3$Val-OMe **6** (entries 6-10). In the reaction of ^{i}PrMgCl, the steric hindrance between Boc and ^{i}Pr groups may decrease the isolated yield of Boc-**6** to 58%.

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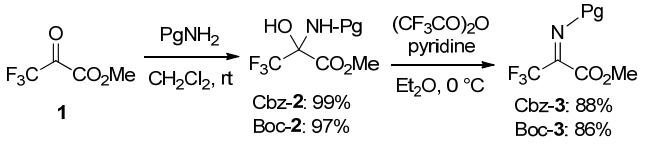
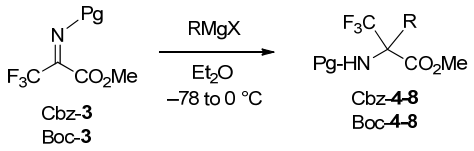


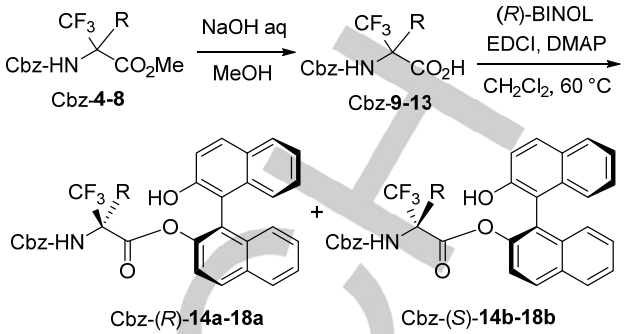
Scheme 1. Synthesis of Cbz- and Boc-protected imines **3**.

Table 1. The 1,2-addition reactions of Grignard reagents to imines **3**.



Entry	Pg	R	X	Products: Yield (%)
1	Cbz	Me	Br	Cbz-**4**: 93
2	Cbz	Et	Cl	Cbz-**5**: 79
3	Cbz	^{i}Pr	Cl	Cbz-**6**: 80
4	Cbz	^{i}Bu	Br	Cbz-**7**: 72
5	Cbz	$PhCH_2$	Cl	Cbz-**8**: 78
6	Boc	Me	Br	Boc-**4**: 87
7	Boc	Et	Cl	Boc-**5**: 85
8	Boc	^{i}Pr	Cl	Boc-**6**: 58
9	Boc	^{i}Bu	Br	Boc-**7**: 84
10	Boc	$PhCH_2$	Cl	Boc-**8**: 82

The optical resolutions of racemic αCF_3dAAs were performed via (*R*)-BINOL ester derivatives, and separation of their diastereo-isomers by chromatography.[8] After alkaline hydrolysis of methyl esters in **4-8**, the resulting carboxylic acids **9-13** were converted into (*R*)-BINOL esters using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (Scheme 2). Although the diastereo-isomers of Boc-αCF_3dAA (*R*)-BINOL esters could not be separated by chromatography, fortunately, the diastereo-isomers of five Cbz-αCF_3dAA (*R*)-BINOL esters **14-18** could be separated by column chromatography on silica gel or preparative TLC.



Scheme 2. Synthesis of (*R*)-BINOL esters of Cbz-CF_3dAAs. Compounds **4**, **9**, and **14**: R = Me; **5**, **10**, and **15**: R = Et; **6**, **11**, and **16**: R = ^{i}Pr; **7**, **12**, and **17**: R = ^{i}Bu; **8**, **13**, and **18**: R = $PhCH_2$.

The separated (*S*)- and (*R*)-Cbz-αCF_3dAA (*R*)-BINOL esters were hydrolyzed under alkaline conditions into (*S*)- and (*R*)-Cbz-αCF_3dAA acids, respectively. The Cbz-protecting group in Cbz-**9-13** was removed by hydrogenolysis using H_2/10% Pd-C, and αCF_3dAA·HCl salt was obtained by treatment with methanolic HCl. Comparing these specific rotation signs with the reported values, the absolute configurations were determined.[6] Figure 1 shows structures of optically active (*S*)-αCF_3dAAs. The (*R*)-BINOL esters of (*S*)-αCF_3dAAs were less polar than those of (*R*)-ones, except for the (*R*)-BINOL ester of (*S*)-α-trifluoromethylleucine (αCF_3Leu), which was more polar.

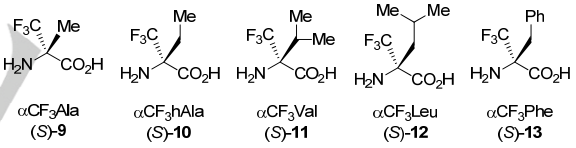
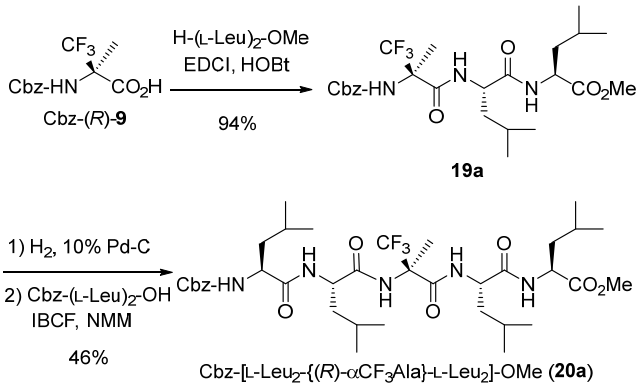


Figure 1. Structures of synthesized chiral αCF_3dAAs.

L-Leu-based peptide sequence could provide useful information regarding the effect of CF_3 moiety by comparing with Aib-containing L-Leu peptides, which were previously synthesized.[9] L-Leu-based pentapeptides **20** with (*R*)- or (*S*)-αCF_3Ala were prepared by the solution-phase method, as follows: The Cbz-{(*R*)-αCF_3Ala} **9** was coupled with a dipeptide amine H-(L-Leu-L-Leu)-OMe using EDCI and 1-hydroxybenzotriazole (HOBt) in CH_2Cl_2 to give the tripeptide **19a** in 94% isolated yield. Deprotection of the Cbz-protecting group in **19a** by H_2/10% Pd-C and subsequent coupling with Cbz-(L-Leu-L-Leu)-OH using isobutyl chloroformate (IBCF) and *N*-methylmorpholine (NMM) gave the pentapeptide **20a** with (*R*)-αCF_3Ala in 46% isolated yield (Scheme 3). The pentapeptide **20b** with (*S*)-αCF_3Ala was similarly prepared.



Scheme 3. Synthesis of L-Leu-based pentapeptide **20a** with (*R*)-αCF$_3$Ala.

The preferred conformations of L-Leu-based peptides **20a** and **20b** were studied in solution and in the crystalline state. The nuclear Overhauser effect spectroscopy (NOESY) NMR spectrum of **20a** in $CDCl_3$ solution only showed the d_{NN} correlations between N(*i*)-H and N(*i*+1)-H (*i* = 1,2), together with the $d_{\alpha 1N3}$ correlation. On the other hand, that of **20b** showed the complete series of sequential d_{NN} correlations between N(*i*)-H and N(*i*+1)-H (*i* = 1~4), accompanied by the $d_{\alpha 1N3}$ correlation. These correlations suggested the helical structure of **20b** with (*S*)-αCF$_3$Ala (Figure 2).

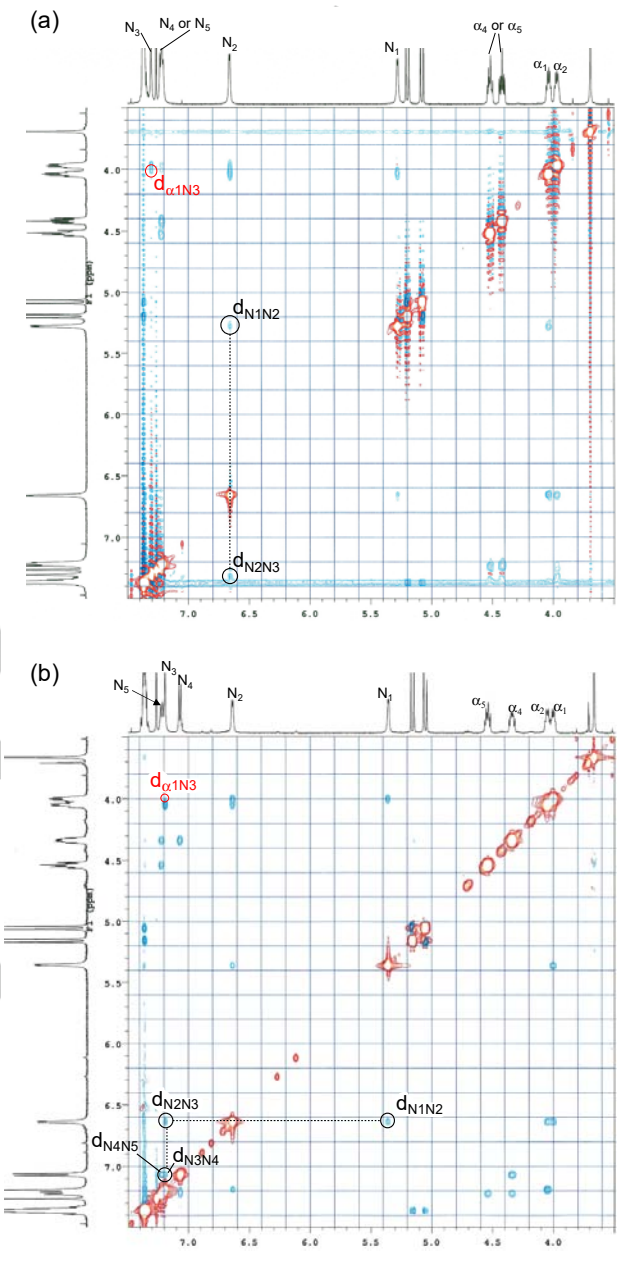


Figure 2. The NOESY NMR spectra of **20a** (a) and **20b** (b).

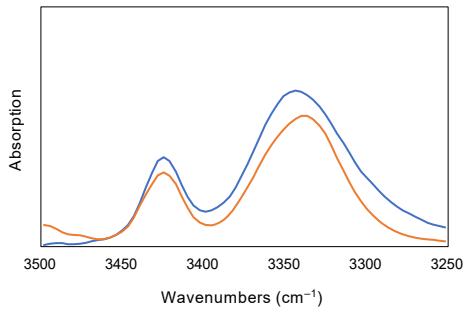


Figure 3. The FT-IR absorption spectra of peptides **20a** (blue) and **20b** (orange) in $CDCl_3$ (Peptide concentration: 5 mM).

The Fourier transform infrared (FT-IR) absorption spectra in the N-H stretching region of peptides **20a** and **20b** both showed weak bands in the 3440-3420 cm^{-1} region, which corresponded to hydrogen bond-free, solvated N-H groups. Furthermore, they showed strong bands in the 3350-3330 cm^{-1} region, which are assigned as hydrogen bonded N-H groups. These FT-IR absorption spectra are similar to those of helical peptides (Figure 3).[10]

The circular dichroism (CD) spectra of **20a** and **20b** were measured in 2,2,2-trifluoroethanol solution. However, the CD spectra did not give any characteristic maxima for secondary structures because the length of peptides may be too short to analyze the preferred conformation by CD spectra.[11]

Recrystallizations of peptides **20a** from MeOH/H_2O, and **20b** from $CHCl_3$/*n*-hexane gave crystals suitable for X-ray crystallographic analysis. Figure 4 shows superimposed structures of peptides **20a** with (*R*)-αCF_3Ala and **20b** with (*S*)-αCF_3Ala.

The structure of **20a** with (*R*)-αCF_3Ala was solved in a monoclinic $P2_1$ space group to show a right-handed 3_{10}-helical structure in the asymmetric unit. The average ϕ and ψ torsion angles of residues 1-4 were –63.9° and –28.5°, respectively, which agree with those of an ideal right-handed 3_{10}-helix (-60°, -30°),[12] although those of residue 5 were different, –128.0° and –116.4°, respectively. The intramolecular hydrogen bonds of N(*i*+3)-H···O=C(*i*) (*i* = 0~2) type (3_{10}-helix) and N(5)-H···O=C(1) type (α-helix) were observed. Thus, N(5)-H was bound by bifurcated hydrogen bonds to O(1)=C(1) and O(2)=C(2).

In the orthorhombic $P2_12_12_1$ space group of peptide **20b**, a right-handed 3_{10}-helical structure existed together with two chloroform molecules. The average ϕ and ψ torsion angles of residues 1-3 were –50.9° and –33.6°, respectively, which are those of a right-handed helix. However, those of residue 4 (–105.5° and +6.4°), respectively and residue 5 (–112.7° and –82.5°), respectively were distorted. In the crystal, the intramolecular hydrogen bonds of N(*i*+3)-H···O=C(*i*) (*i* = 0~2) type (3_{10}-helix) were formed.

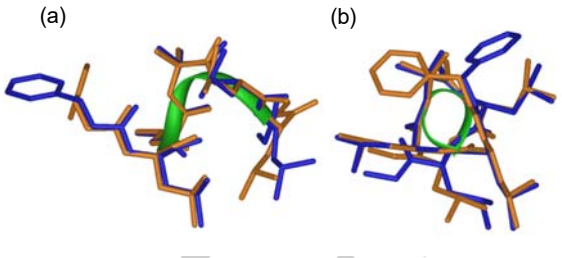


Figure 4. Superimposed structures of peptides **20a** (blue) and **20b** (orange). (a) side view; (b) top view.

The conformational analysis of L-Leu-based peptides **20a** and **20b** revealed that both peptides on the whole formed right-handed (*P*) 3_{10}-helical structures. These results may be attributed to the property of αCF_3Ala is to form a helical structure, like Aib, and the property of L-Leu is to form right-handedness. Especially, the 3_{10}-helical conformations at the amino acid residues (1-3) well-matched; however, the conformations at the C-terminal residues (4 and 5) of **20a** and **20b** were different.[13] The structure of chiral $ClCH_2CO$-(αCF_3Ala) based on X-ray crystallographic analysis has already been reported.[14] However, here we demonstrated for the first time the structural differences of L-Leu-based peptides incorporating (*R*)- or (*S*)-αCF_3Ala by X-ray crystallographic analysis. The hydrophobicity and electro-negativity of the CF_3 group in (*R*)- and (*S*)-αCF_3Ala residues (3) differently affected the C-terminal and penultimate residues (4 and 5) in **20a** and **20b**, and their structures may be different, although the effects of crystal packing and recrystallizing solvents cannot be excluded.

Conclusions

We synthesized varying optically active αCF_3dAAs by optical resolution using (*R*)-BINOL esters, and incorporated (*R*)- and (*S*)-αCF_3Ala into the L-Leu-based peptides Cbz-[L-Leu-L-Leu-{(*R*)- or (*S*)-αCF_3Ala}-L-Leu-L-Leu]-OMe. X-ray crystallographic analysis revealed that the pentapeptides with (*R*)- or (*S*)-αCF_3Ala both formed similar right-handed 3_{10}-helical conformations, but with different structures at the C-terminal and penultimate residues (4 and 5) in the crystalline state. The CF_3 substituent has a hydrophobic property and an electron-withdrawing effect, and is often shown in drug structures. Thus, the αCF_3dAAs and their conformational property of peptides may be invaluable to design peptide-based drug candidates.[15] Further studies on peptides possessing other αCF_3dAAs are in progress.

Deposition Numbers CCDC 2016233 (for **20a**), and 2016232 (for **20b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and

Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information Summary

Supporting information includes the experimental section, X-ray crystallographic data, CD spectra, calculation, and the spectroscopic data of compounds.

Acknowledgments

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Keywords: amino acid • conformation • helix • peptide • trifluoromethyl

Reference

[1] a) F. Ehrlich, A. Wendel, *Biochem. Z.* **1908**, *8*, 438-466; b) K. Pfister 3rd., W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk, E. F. Rogers, *J. Am. Chem. Soc.* **1955**, *77*, 697-700; c) G. W. Kenner, R. C. Sheppard, *Nature* **1958**, *181*, 48-48; d) M. T. Leplawy, D. S. Jones, G. W. Kenner, R. C. Sheppard, *Tetrahedron* **1960**, *11*, 39-51; e) H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, *30*, 238-264; f) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517-3599; g) C. Cativiela, M. Ordóñez, *Tetrahedron: Asymmetry* **2009**, *20*, 1-63; h) C. Cativiela, M. Ordóñez, J. L. Viveros-Ceballos, *Tetrahedron* **2020**, *76*, 130875.

[2] a) E. Benedetti, V. Barone, A. Bavoso, B. Di Blasio, F. Lelj, V. Pavone, C. Pedone, G. M. Bonora, C. Toniolo, M. T. Leplawy, K. Kaczmarek, A. Redlinski, *Biopolymers* **1988**, *27*, 357-371; b) C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, V. Barone, F. Lelj, M. T. Leplawy, K. Kaczmarek, A. Redlinski, *Biopolymers* **1988**, *27*, 373-379; c) I. L. Karle, P. Balaram, *Biochemistry* **1990**, *29*, 6747-6756; d) E. Benedetti, *Biopolymers (Pept. Sci.)* **1996**, *40*, 3-44; e) M. Tanaka, N. Imawaka, M. Kurihara, H. Suemune, *Helv. Chim. Acta* **1999**, *82*, 494-510; f) R. Gessmann, H. Brückner, K. Petratos, *J. Pept. Sci.* **2003**, *9*, 753-762; g) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349-358; h) C. Peggion, M. Crisma, C. Toniolo, F. Formaggio, *Tetrahedron* **2012**, *68*, 4429-4433; i) F. Formaggio, M. Crisma, G. Ballano, C. Peggion, M. Venanzi, C. Toniolo, *Org. Biomol. Chem.* **2012**, *10*, 2413-2421.

[3] a) B. Jaun, M. Tanaka, P. Seiler, F. N. M. Kühnle, C. Braun, D. Seebach, *Liebigs Ann./Recueil* **1997,** 1697-1710; b) N. Imawaka, M. Tanaka, H. Suemune, *Helv. Chim. Acta* **2000**, *83*, 2823-2835; c) M. Tanaka, S. Nishimura, M. Oba, Y. Demizu, M. Kurihara, H. Suemune, *Chem. Eur. J.* **2003**, *9*, 3082-3090; d) M. Tanaka, Y. Demizu, M. Doi, M. Kurihara, H. Suemune, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5360-5363; e) M. Tanaka, K. Anan, Y. Demizu, M. Kurihara, M. Doi, H. Suemune, *J. Am. Chem. Soc.* **2005**, *127*, 11570-11571; f) M. Nagano, M. Doi, M. Kurihara, H. Suemune, M. Tanaka, *Org. Lett.* **2010**, *12*, 3564-3566; g) R. Eto, M. Oba, A. Ueda, T. Uku, M. Doi, Y. Matsuo, T. Tanaka, Y. Demizu, M. Kurihara, M. Tanaka, *Chem. Eur. J.* **2017**, *23*, 18120-18124; h) Y. Koba, A. Ueda, M. Oba, M. Doi, Y. Demizu, M. Kurihara, M. Tanaka, *ChemistrySelect* **2017**, *2*, 8108-8114; i) Y. Koba, A. Ueda, M. Oba, M. Doi, T. Kato, Y. Demizu, M. Tanaka, *Org. Lett.* **2018**, *20*, 7830-7834.

[4] a) M. Crisma, A. Moretto, C. Peggion L. Panella, B. Kaptein, Q. B. Broxterman, F. Formaggio, C. Toniolo, *Amino Acids* **2011**, *41*, 629-641; b) M. Crisma, M. De Zotti, F. Formaggio, C. Peggion, A. Moretto, C. Toniolo, *J. Pept. Sci.* **2015**, *21*, 148-177; c) M. Crisma, C. Toniolo, Biopolymers *(Pept. Sci.)* **2015**, *104*, 46-64.

[5] C. Jäckel, B. Koksch, *Eur. J. Org. Chem.* **2005**, 4483-4503.

[6] a) P. Bravo, S. Capelli, S. V. Meille, F. Viani, M. Zanda, *Tetrahedron: Asymmetry* **1994**, *5*, 2009-2018; b) A. Asensio, P. Bravo, M. Crucianelli, A. Farina, S. Fustero, J. G. Soler, S. V. Meille, W. Panzeri, F. Viani, A. Volonterio, M. Zanda, *Eur. J. Org. Chem.* **2001**, 1449-1458; c) F. Huguenot, T. Brigaud, *J. Org. Chem.* **2006**, *71*, 7075-7078; d) J. Yang, Q.-Q. Min, Y. He, X. Zhang, *Tetrahedron Lett.* **2011**, *52*, 4675-4677; e) E. Devillers, J. Pytkowicz, E. Chelain, T. Brigaud, *Amino Acids* **2016**, *48*, 1457-1468.

[7] a) K. Burger, E. Hoess, K. Gaa, *Chem. Ztg*. **1989**, *113*, 243-247; b) K. Burger, C. Schierlinger, W. Hollweck, K. Mütze, *Liebigs Ann. Chem.* **1994**, 399-406; c) N. Sewald, W. Hollweck, K. Mütze, C. Schierlinger, L. C. Seymour, K. Gaa, K. Burger, B. Koksch, H. D. Jakubke, *Amino Acids* **1995**, *8*, 187-194; d) S. N. Osipov, A. S. Golubev, N. Sewald, T. Michel, A. F. Kolomiets, A. V. Fokin, K. Burger, *J. Org. Chem.* **1996**, *61*, 7521-7528.

[8] M. Oba, A. Shimabukuro, M. Ono, M. Doi, M. Tanaka, *Tetrahedron: Asymmetry* **2013**, *24*, 464-467.

[9] Y. Demizu, M. Tanaka, M. Nagano, M. Kurihara, M. Doi, T. Maruyama, Y. Suemune, *Chem. Pharm. Bull.* **2007**, *55*, 840-842.

[10] a) C. Toniolo, G. M. Bonora, V. Barone, A. Bavoso, E. Benedetti, B. Di Blasio, P. Grimaldi, F. Lelj, V. Pavone, C. Pedone, *Macromolecules* **1985**, *18*, 895–902; b) Y. Demizu, M. Doi, M. Kurihara, H. Okuda, M. Nagano, H. Suemune, M. Tanaka, *Org. Biomol. Chem.* **2011**, *9*, 3303-3312.

[11] See supporting information for CD spectra.

[12] a) C. Toniolo, E. Benedetti, *Trends Biochem. Sci.* **1991**, *16*, 350-353. b) R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas.* **1994**, *113*, 1-19. c) L. Pal, G. Basu, P. Chakrabarti, *Proteins: Struct. Funct. Genet.* **2002**, *48*, 571-579. d) C. Toniolo, M. Crisma, F. Formaggio, C. Peggion, Q. B. Broxterman, B. Kaptein, *Biopolymers (Pept. Sci.)* **2004**, *76*, 162-176.

[13] We calculated the conformation of peptides Cbz-[L-Leu-L-Leu-{(*R*)- & (*S*)-αCF$_3$Ala}-L-Leu-L-Leu]-OMe **20a** and **20b** by MacroModel 10.0 (OPLS2005, H_2O, 20,000 calculation), starting from the X-ray crystallographic structures. By restricted calculation, a right-handed (*P*) 3_{10}-helix of Cbz-[L-Leu-L-Leu-(*S*)-αCF$_3$Ala-L-Leu-L-Leu]-OMe **20b** was more stable than that of Cbz-[L-Leu-L-Leu-(*R*)-αCF$_3$Ala-L-Leu-L-Leu]-OMe **20a** by *ca.* 2.5 kcal/mol.

[14] J. W. Keller, C. S. Day, *Acta Cryst.* **1984**, *C40*, 1224-1226.

[15] a) D. Maisch, P. Wadhwani, S. Afonin, C. Böttcher, B. Koksch, A. S. Ulrich, *J. Am. Chem. Soc.* **2009**, *131*, 15596-15597; b) A. Botz, V. Gasparik, E. Devilers, A. R. F. Hoffmann, L. Caillon, E. Chelain, O. Lequin, T. Brigaud, L. Khemtemourian, *Biopolymers* **2015**, *104*, 601-610; c) C. Gadais, E. Devillers, V. Gasparik, E. Chelain, J. Pytkowicz, T. Brigaud, *ChemBioChem* **2018**, *19*, 1026-1030.

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Layout 1:

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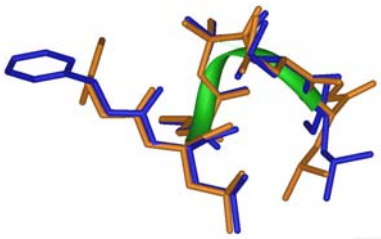
Various α-trifluoromethyl α,α-disubstituted α-amino acids were synthesized by the reaction of methyl 3,3,3-trifluoropyruvate imines with Grignard reagents, and the optical resolution of racemates using (*R*)-1,1'-bi-2-naphthol {(*R*)-BINOL} esters. X-ray crystallographic analysis revealed that L-Leu-based pentapeptides with (*R*)- or (*S*)-α-trifluoromethylalanine (αCF_3Ala) both formed similar right-handed 3_{10}-helical structures at the N-terminal residues 1-3, but with different ϕ and ψ torsion angles of residues 4 and 5.



Helical structures*

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Synthesis of Chiral α-Trifluoromethyl α,α-Disubstituted α-Amino Acids and Conformational Analysis of L-Leu-Based Peptides with (*R*)- or (*S*)-α-Trifluoromethylalanine

*one or two words that highlight the emphasis of the paper or the field of the study