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The Synthesis and Characterization of a Pentafluorosulfanylated Peptide

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Dedicated to Professor George A. Olah on the occasion of his 85th birthday

Keywords: Amino acids / Peptides / Fluorinated substituents / Conformation analysis / Helical structures

The design and synthesis of pentafluorosulfanyl-containing heptad amino acid sequence was described. The three-dimensional conformation of the peptide was investigated by using CYANA (combined assignment and dynamics algorithm for NMR applications) and the integrated autoassignment. This study shows that the one of the diastereomers assumed a very tight coiled conformation in [D_6]DMSO where both pentafluorosulfanyl groups assumed a synclinal relationship. The propensity of the protected heptapeptide to form such a tight coil and of the pentafluorosulfanyl groups to align so uniformly is suggestive of the utility of pentafluorosulfanylated amino acids in promoting conformational control.

Introduction

The pentafluorosulfanyl (SF_5) group has attracted significant attention as a fluorine-containing substituent.[1] To date, the utility of this totally novel functional group has been largely restricted to applications as an aromatic substituent.[2] Combined with the unique octahedral geometry around sulfur, the steric and electronic effects of pentafluorosulfanylation can profoundly modify the properties of molecules into which the substituent has been introduced.[3] The effects of SF_5 group in peptide chemistry remain unknown because of the paucity of available SF_5-containing amino acids and the lack of methods for the direct introduction of a SF_5 moiety to a peptide. To illustrate the stability of the SF_5 group in common synthetic transformations and to assess the influence of the substituent on peptide conformations, a heptapeptide containing an SF_5-substituted amino acid has been prepared.

Extensive fluorination is known to dramatically influence both the reactivity and conformation of amino acids.[4] Most commonly analogs of leucine and valine have been prepared that contain one or two trifluoromethyl replacements for the methyl parts of the terminal isopropyl groups, or alternatively, three to six omega fluorines were introduced. The effect of fluorination has long been thought to increase the lipophobicity of the side chain.[5] However, the hydrophobic properties of the trifluoromethyl group may have a greater effect than lipophobicity or specific fluorine–fluorine interactions.[5a,6] It has also been shown that electrostatic effects involving side chain interactions with a peptide core may diminish the energetic accessibility of some conformations.[7]

These influences have been widely employed in the design of peptides that assume an α-helical conformation. The consequent coiled-coil interactions have been used to study the effect of fluorination on protein-protein interactions. As the core of the coiled-coil should be occupied by hydrophobic amino acids,[8] fluorination of the side chains of those core residues have been shown to confer a general increase in the thermodynamic stability of the coiled-coil.[6a,6b,7b,9] While incorporation of fluorinated analogues of leucine, isoleucine or valine at the core of coiled-coil heptad repeat led to enhanced thermal stability, there are exceptions. It has been found that some fluorinated amino acids exhibit a reduced propensity to form an α-helix in comparison with hydrocarbon analogues.[10] Neither the effect of the pentafluorosulfanyl group on an amino acid or the influence of this substituent on the conformation of peptides has previously been disclosed.

Results and Discussion

A simple SF_5-containing heptapeptide was prepared based on design principles established for de novo synthesis of novel coiled-coil structures.[8,11] An SF_5-containing amino acid derived from allyl glycine (SF_5-substituted norvaline derivative, SF_5NVa) was introduced at the first and fifth position of a heptapeptide sequence (SF_5NVa-Glu-Ser-Lys-SF_5NVa-Lys-Glu or SF_5NV-E-S-K-SF_5NV-K-E) (Figure 1). Conceptually, SF_5NVa introduces a pentafluorosulfanyl group that could yield a hydrophobic interaction in

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the folded state. We assumed that an appropriately designed heptad sequence might tend to assume a coiled conformation with the SF_5-bearing side chains on one side of the coil.

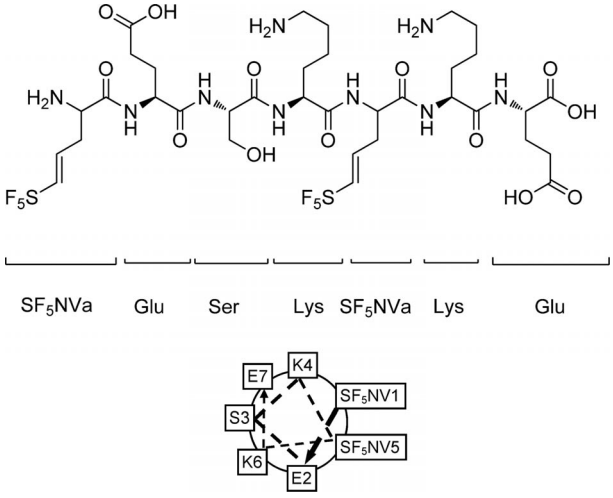


Figure 1. The SF_5-containing heptapeptide (SF_5NVa-Glu-Ser-Lys-SF_5NVa-Lys-Glu or SF_5NV-E-S-K-SF_5NV-K-E) and a coiled representation showing the pentafluorosulfanyl groups in close proximity.

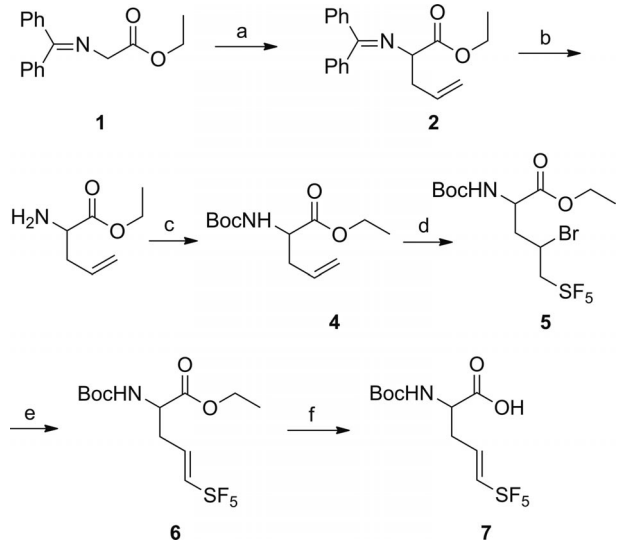
The preparation of the heptad was divided into three steps: (i) the synthesis of (2*RS*)-SF_5NVa; (ii) the syntheses of the *N*-terminal fragment [(2*RS*)-SF_5NVa-Glu-Ser-Lys] and the *C*-terminal fragment [(2*RS*)-SF_5NVa-Lys-Glu]; and (iii) the coupling of these two fragments to give the peptide.

To prepare Boc-protected SF_5NVa (**7**) (Scheme 1), commercially available **1** was transformed to protected amino acid **2** by first deprotonation with LDA and alkylation with allyl bromide.

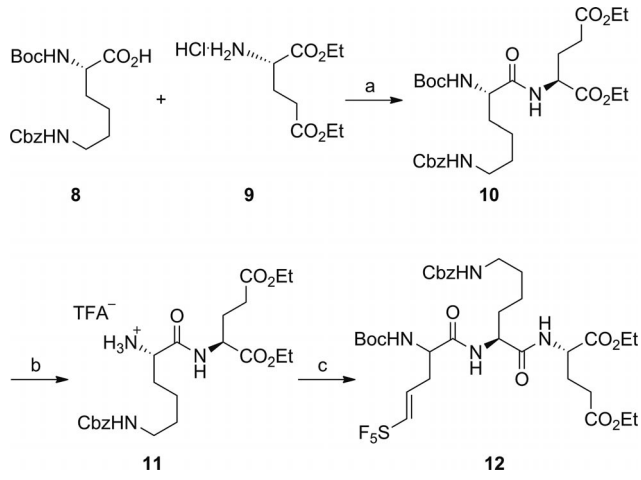
Deprotection with citric acid (15%) gave amine **3** which was protected with Boc anhydride. The SF_5 group was introduced by Et_3B-promoted addition of SF_5Br (0.5 M–1 M in CCl_3F) to the double bond in 85% yield. Dehydrobromination using DBU yielded compound **6** quantitatively. Saponification of **6** with NaOH in ethanol provided **7** in good yield.

The dipeptide **10** required for the *C*-terminal fragment (SF_5NVa-Lys-Glu), was synthesized in 77% yield using peptide coupling with EDC in CH_2Cl_2. Boc deprotection of **10** with trifluoroacetic acid in dichloromethane[12] formed the TFA salt **11**. After drying in vacuo, the resulting TFA salt was used without further purification. Synthesis of the *C*-terminal fragment **12** (SF_5NVa-Lys-Glu) was completed in 80% yield using EDC in dichloromethane for coupling. The SF_5 amino acid **7** required the addition of a small amount of DMF as a co-solvent to improve solubility in reactions with **11** (Scheme 2).

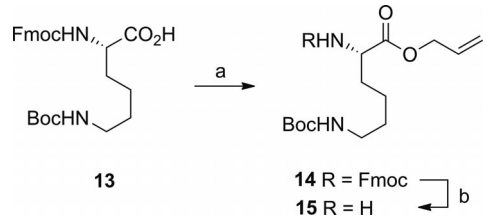
The synthesis of the *N*-terminal fragment (SF_5NVa-Glu-Ser-Lys) began with Fmoc-Boc-protected lysine **13**. The carboxylic acid residue was protected with an allyl group to yield **14** (96%). The deprotection of Fmoc group was carried out using 20% piperidine in dichloromethane to yield a colorless liquid (94%) (Scheme 3).[13]



Scheme 1. Synthesis of SF_5-containing amino acid SF_5NVa. a) 1. LDA, 2. allylbromide, –78 °C to 0 °C, 4 h, 95%; b) citric acid (15%), THF, room temp., 11 h, 70%; c) $(Boc)_2O$, DCM, room temp., 3 h, 82%; d) SF_5Br (1.3 equiv., 0.5 M–1 M in CCl_3F), Et_3B, 0 °C, 10 min, 85%; e) DBU, benzene, room temp., 30 min, 96%; f) NaOH (1 N in H_2O), EtOH, 0 °C to room temp., 13 h, 98%.



Scheme 2. The synthesis of C-terminal fragment. a) Et_3N, HOBt, EDC·HCl, DCM, 0 °C to room temp., 16 h, 77%; b) TFA, DCM, 0 °C to room temp.; c) 7, Et_3N, HOBt, EDC·HCl, DCM, DMF, 0 °C to room temp., 16 h, 80%.



Scheme 3. The protection of carboxylic acid group. a) allyl bromide, DIPEA, MeCN, 96%; b) 20% piperidine, DCM, 0 °C to room temp., 94%.

The coupling reaction[14] of deprotected lysine **15** and protected serine **16** was successfully effected in good yield (90%) to form dipeptide **17** (Scheme 4).

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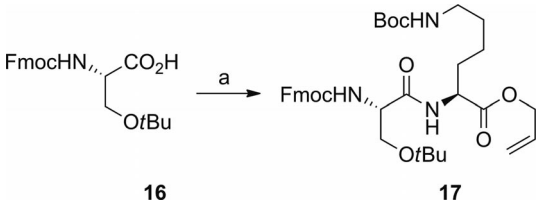
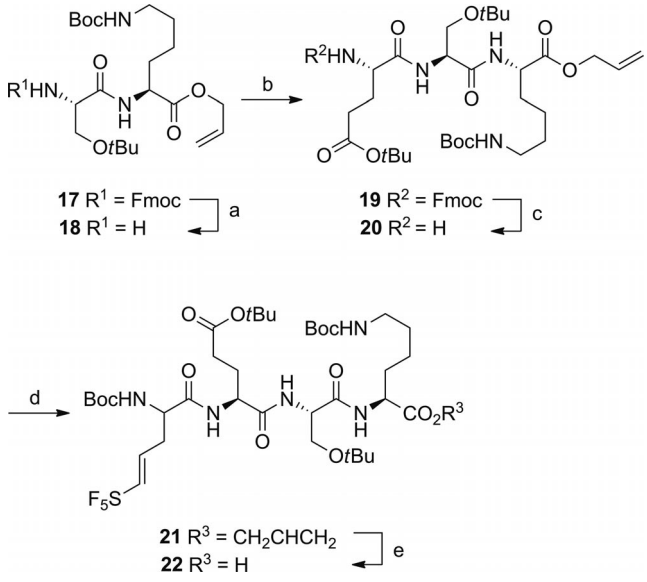


Scheme 4. The coupling reaction of **15** and **16**. a) **15**, NMM, HOBt, EDC·HCl, THF, 0 °C to room temp./15 h, 90%.

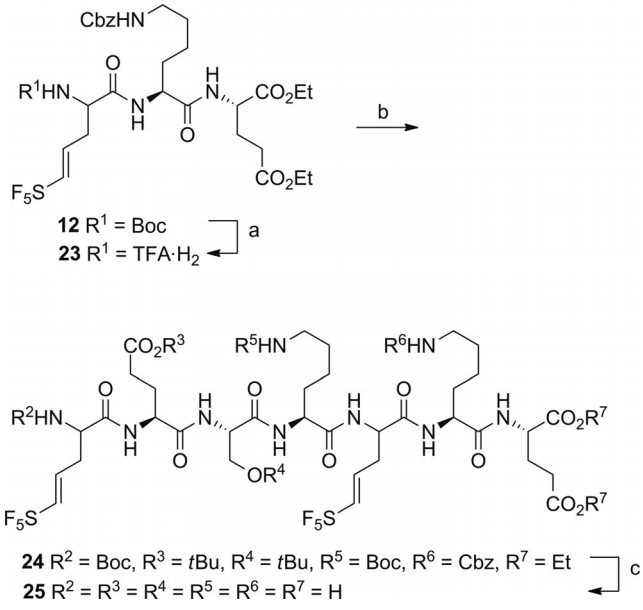
Fmoc deprotection of dipeptide **17** was effected with 20% piperidine in dichloromethane at 0 °C, yielding deprotected dipeptide **18** in 76%. The dipeptide and Fmoc-protected glutamic acid were coupled over 12 h, to give the tripeptide **19** (Glu-Ser-Lys) in 81% yield. The Fmoc protecting group of tripeptide **19** was removed in 92% yield. Then, coupling of deprotected tripeptide and Boc-protected pentafluorosulfanyl amino acid **7** was conducted over 4 h to form the *N*-terminal fragment **21** (SF_5NVa-Glu-Ser-Lys) (Scheme 5).



Scheme 5. The synthesis of *N*-terminal fragment. a) 20% piperidine, DCM, 0 °C to room temp., 76%; b) $HO_2CCH(NHFmoc)$-$CH_2CH_2CO_2tBu$, NMM, HOBt, EDC·HCl, THF, 0 °C to room temp., 12 h, 81%; c) 20% piperidine, DCM, 0 °C to room temp., 92%; d) **7**, NMM, HOBt, EDC·HCl, THF, 0 °C to room temp., 4 h, 93%; e) *N*-ethylaniline, $(Ph_3P)_4Pd$, THF, room temp., 91%.

Prior to coupling *N*-terminal fragment **22** and *C*-terminal fragment **12**, the allyl group protection of **21** was removed using *N*-ethylaniline and tetrakis(triphenylphosphane)palladium(0) in THF at room temperature in 91% yield (Scheme 5).[13,15]

The Boc group was removed from tripeptide **12** to enable the peptide coupling as well. The protected heptad **24** was prepared from **22** and TFA tripeptide salt **23**, under the usual conditions for 4 h. The protected heptad **24** was formed in 88% crude yield (Scheme 6). The final deprotection of the heptad was carried out with TFA, but the purification of the desired product was not successful (Scheme 6).



Scheme 6. The coupling reaction of *N*-terminal fragment with *C*-terminal fragment. a) TFA, DCM, 0 °C to room temp.; b) **22**, NMM, HOBt, EDC·HCl, THF, 0 °C to room temp., 4 h, 88% (crude); c) TFA.

The protected heptad **24** (Figure 2) was characterized by ^{1}H-NMR spectroscopy. The three-dimensional structure of the protected heptad was investigated using CYANA (combined assignment and dynamics algorithm for NMR applications, see: http://www.las.jp/products/cyana/eg/index.html) and the integrated autoassignment module CANDID.[16] CARA (computer-aided resonance assignment, see: http://www.nmr.ch) was used to generate CYANA data input from NOESY NMR spectroscopic data.

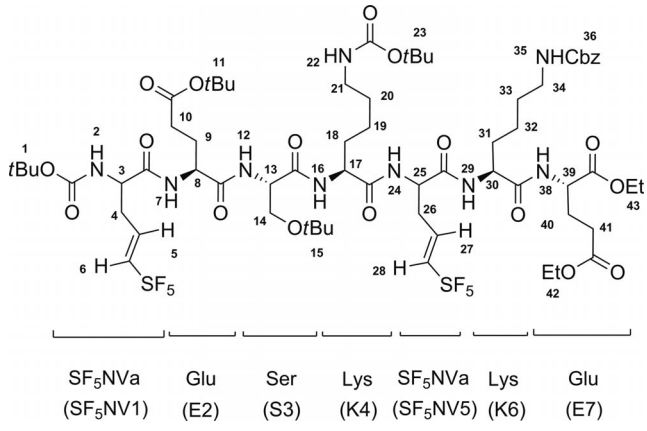


Figure 2. Proton numbering for NMR spectra analyses.

One-dimensional ^{1}H, ^{19}FNMR, and two-dimensional COSY, NOESY, and TOCSY spectra of the heptad were acquired in [D_6]DMSO for the initial NOE (nuclear Overhauser effect) cross-peak assignments and unambiguous as-

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signments of the individual resonances. NOE peaks were used in the structure calculations. An expansion of the amide group region of the NOESY spectrum is shown in Figure 3. Glu (E2) and Lys (K4) were assigned to a pair of NH cross-peaks by analysis of the NOESY and TOCSY NMR spectroscopic data of diastereomeric mixture **24** (Figure 2). In the amide region of the NOESY ([D_6]DMSO), the two sets of NH NOEs labelled E2 (resonances 7a and b, Figure 2) and K4 (resonances 16a and b, Figure 2) are shown. Since SF_5NVa was prepared as a racemate, the four possible diastereomeric combinations of the heptad, such as (7a, 16a), (7a, 16b), (7b, 16a), and (7b, 16b), necessarily were examined. For the structure fitting, it was necessary to substitute the two SF_5NVa residues by leucine (L1, L5) and to remove the protecting groups to accommodate the limitations of the software.

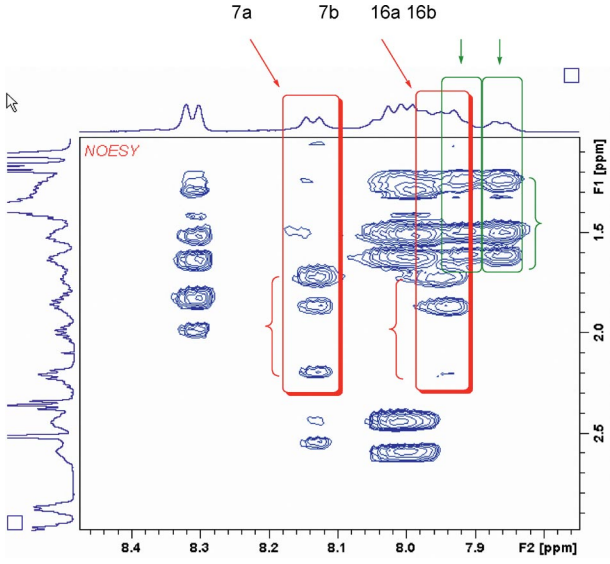

Figure 3. Expansion of the amide resonance region in the NOESY of **24**.

Four possible diastereomeric heptad structures were generated using CYANA and the integrated autoassignment module CANDID. The chemical shift identification tolerance was set to 0.020 ppm in both proton dimensions. Initial NOE cross-peaks were manually assigned in the NMR view of CARA. A total number of 100 structures were generated per CANDID round with 10,000 torsion angle dynamics (TAD) steps in the CYANA annealing protocol. The final number of both manual and CANDID assigned NOE cross-peaks used in structural determination was 154. The 20 lowest-energy structures in the final CANDID round were retained as an ensemble representation of the family of generated structures. A single structure, the most stable among the best 20 structures in each case, was chosen to represent the heptad.

The lowest-energy structures of heptad A [L1-E2(7a)-S3-K4(16a)-L5-K6-E7], B [L1-E2(7a)-S3-K4(16b)-L5-K6-E7], C [L1-E2(7b)-S3-K4(16a)-L5-K6-E7], and D [L1-E2(7b)-S3-K4(16b)-L5-K6-E7] are shown in Figure 4. Heptads A, C, and D show the right-handed helix conformation although the three structures were not fit precisely to an α-helix. Heptad B had a stretched right-handed helix structure. Heptad D [L1-E2 (7b)-S3-K4(16b)-L5-K6-E7] was the best fit for an α-helix in comparison with literature values (Figure 4).

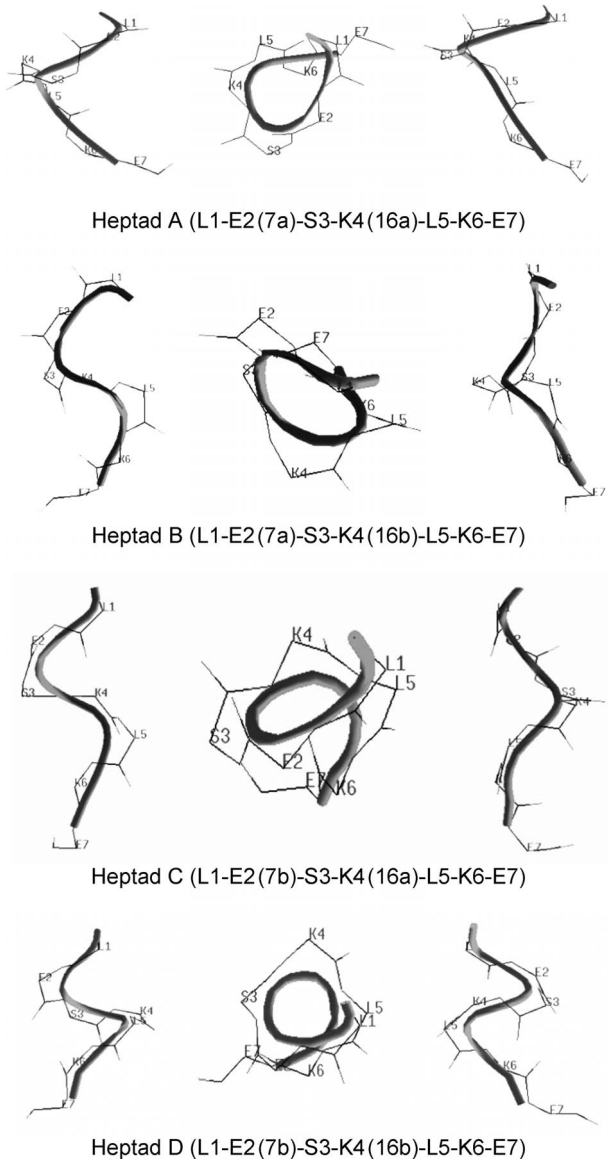

Figure 4. NMR-derived structures of heptads (A, B, C, and D). The four lowest energy conformers obtained from the NOE-constrained simulated annealing. These structures are shown from up and both sides. The *N*-terminal end is at the top and the carbonyl oxygens point down. For clarity, all side chains and hydrogens are omitted. A seven-stranded ribbon (yellow) has been added to trace the helical backbone. The SF_5NVa residues have been substituted by leucine to accommodate software limitations.

The peptide backbone of a helix can be stabilized by intramolecular hydrogen bond between the N–H group of an amino acid and the C=O group of an amino acid four residues earlier. The α-helix conformations therefore yield a consecutive series of strong to medium NOEs between adjacent amide protons, NN(i, i + 1), between amide and α-protons in the same residue, αN(i, i), and between β-protons

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and amide protons in adjacent residues, βN(i, i + 1), medium to weak for the relation between αN(i, i + 1), αN(i, i + 2), αN(i, i + 3), αβ(i, i + 3), and weak interactions for the NN(i, i + 2) and αN(i, i + 4) (see part A of Figure 5).[17]

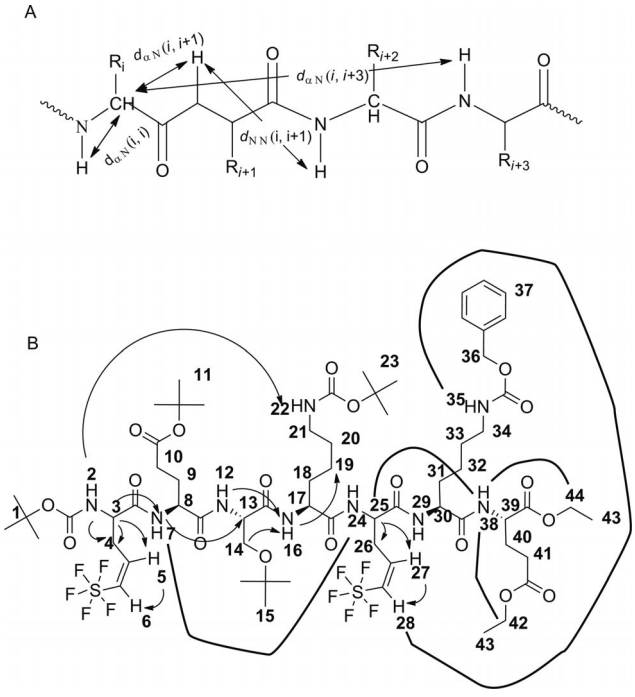

Figure 5. A. Notation for ^{1}H–^{1}H distances in polypeptide chains; B. NOE relationships for **24** detected in [D$_6$]DMSO.

In an analysis of heptad D (Figure 5, B) when compared with the literature values for ^{1}H–^{1}H distances [$d_{\alpha N}(i, i + 4)$ = 4.2 Å, $d_{\alpha N}(i, i + 3)$ = 3.4 Å, $d_{\alpha\beta}(i, i + 3)$ = 2.5–4.4 Å], both the ^{1}H–^{1}H distances $d_{\alpha N}(i, i + 4)$ (4.53 Å) in heptad D and the ^{1}H–^{1}H distances $d_{\alpha N}(i, i + 3)$ (4.73 Å) are longer. ^{1}H–^{1}H distances $d_{\alpha\beta}(i, i + 3)$ were not found in this model structure. Overall, the information obtained from the sequential NOE connectivities suggested that the structure for heptad D is closer to an α-helix than a 3_{10} helix ($i + 3 \rightarrow i$ hydrogen bonding) or π-helix ($i + 5 \rightarrow i$ hydrogen bonding).[18] The $d_{\alpha N}$ (i, i + 4) connectivity observed would be expected only for an α-helical conformation. With only a heptad, the putative assignments cannot assure a complete α-helix but are rather indicative only of a more tightly coiled conformation. Based upon spectroscopic data, the heptad D structure has a slightly larger diameter helix when compared to an α-helix. For the final structure representation of original heptad (SF$_5$NVa-Glu-Ser-Lys-SF$_5$NVa-Lys-Glu), the NMR-derived structure of modified heptad D, in which leucines (L1, L5) are replaced with SF$_5$NVa (SF$_5$NV1, SF$_5$NV5), is shown in Figure 6.

In contrast with the above analysis in [D$_6$]DMSO, where one diastereomer of the protected synthetic heptad (Figure 6) was found to form a coil with the SF$_5$NVa groups extending away from the peptide backbone in a synclinal orientation, in CDCl$_3$, profound changes in NOE relationships was strongly suggestive of **24** assuming a less ordered

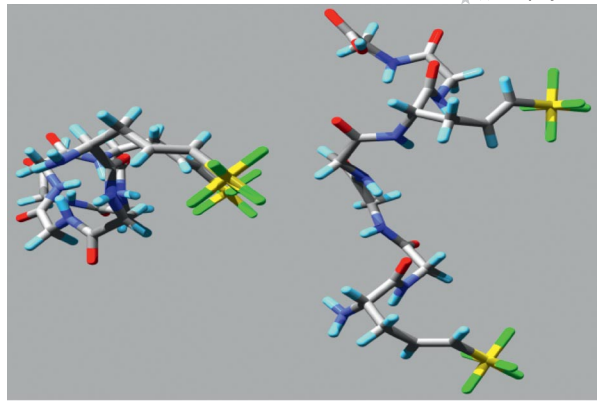

Figure 6. NMR-derived structure of modified heptad D in which leucines (L1, L5) were replaced with SF$_5$NVa (SF$_5$NV1, SF$_5$NV5). These structures are shown from bottom and side. The *N*-terminal end is in the foreground and at the bottom, respectively. For clarity, the side chains with the exception of SF$_5$NVa are omitted.

conformation. Apparently the less polar environment mitigated the intramolecular propensity of the SF$_5$ groups to associate in polar DMSO. These findings suggest that incorporation of selectively introduced SF$_5$NVa residues would be predicted to influence both the quaternary and tertiary structure of longer peptides, especially when those peptides were in a highly polar aqueous environment.

Conclusions

A pentafluorosulfanylated aliphatic amino acid, (*E*)-(*RS*)-2-(*tert*-butoxycarbonylamino)-5-(pentafluorosulfanyl)pent-4-enoic acid (**7**), SF$_5$NVa, was prepared via the addition of pentafluorosulfanyl bromide to a protected allyl glycine intermediate.

The heptad amino acid sequence [Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-(2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu-(Et)-OEt] was prepared via conventional synthetic manipulations. The SF$_5$ group showed good stability towards general organic transformations, polypeptide protection and deprotection reactions and peptide coupling conditions.

Characterization of the peptide conformation by NMR spectroscopy is reported in this work. The three-dimensional conformation of the protected heptad, designed to form an α-helix, was reported using CYANA and the integrated autoassignment module CANDID. Figure 4 shows possible NMR-derived structures of heptads (A, B, C, and D). As anticipated with the heptad, Figure 6 reveals a helical structure close to an ideal α-helix in dimensions. This investigation reveals that an SF$_5$ group can be introduced into a polypeptide and have a potent effect on overall polypeptide structure.

Experimental Section

General: Thin-layer chromatography was performed with silica gel F$_{254}$ (Merck) as the adsorbent on 0.2 mm thick, plastic-backed plates. The chromatograms were visualized under UV (254 nm) or

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by staining with a $KMnO_4$ aqueous solution followed by heating. Column chromatography was performed using silica gel 60 (70–230 mesh, Merck). MALDI-TOF mass spectra was measured on a Bruker Ultraflex III MALDI/TOF/TOF.

NMR Experiments: ^1H, ^{13}C and ^{19}F-NMR spectra were recorded on a Varian Gemini-300 MHz NMR spectrometer at 300, 75.43 and 282.20 MHz respectively or a Bruker Avance-400 MHz NMR spectrometer at 400, 100 and 376 MHz, respectively. The chemical shifts of ^1H and ^{13}C-NMR are reported relative to the residual signal of $CDCl_3$. ^{19}F-NMR spectra are reported relative to the resonance assigned to $CFCl_3$. For the COSY, TOCSY and NOESY 2048×128, 8192×480 and 2048×480 data points were collected, respectively. The number of transients collected for each experiment was 16 for COSY and 48 for TOCSY and NOESY. The spectral width was 14, 8 and 12 ppm, respectively. The relaxation delay for the COSY was 1.48 and 1 s for both TOCSY and NOESY. The NOESY mixing time was 250 ms.

Ethyl 2-(Diphenylmethyleneamino)pent-4-enoate (2): To a solution of *N*,*N*-diisopropylamine (2.2 mL, 16 mmol) in THF (30 mL) was added *n*BuLi (6.3 mL, 16 mmol) slowly at 0 °C. The mixture was stirred for 30 min after addition was complete. Ethyl 2-(diphenylmethyleneamino)acetate (4.0 g, 15 mmol) was added to the reaction mixture at –78 °C. The mixture was stirred for 1 h after addition was complete, and then added allyl bromide (1.9 g, 16 mmol). After stirring for an additional hour, the temperature of the reaction mixture was allowed to slowly increase to 0 °C. The reaction mixture was quenched with water and then extracted with ethyl acetate. The organic layer was separated and the aqueous layer washed with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and then concentrated. The product was obtained in 95% crude yield (4.4 g).

Ethyl (*RS*)-2-Aminopent-4-enoate (3): A 15% solution of citric acid (40 mL) was added to the monoalkylated Schiff base **2** (2.2 g, 7.2 mmol) in THF (40 mL) at room temperature and then was allowed to stir for 11 h. Acid-base work up with 10% HCl, satd. $NaHCO_3$ solution and dichloromethane gave the crude product in 70% yield (0.77 g). The purity of the product was sufficient to proceed to the next step without further purification.

Ethyl (*RS*)-2-(*tert*-Butoxycarbonylamino)pent-4-enoate (4): To a solution of the amine compound **3** (2.2 g, 15 mmol) in dichloromethane (30 mL) was added Et_3N (4.66 g, 46.0 mmol) and di-*tert*-butyl dicarbonate (4.04 g, 18.5 mmol) at room temp. which was then allowed to stir for 3 h. The reaction mixture was quenched with water and then extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography to afford 3.07 g of a colorless liquid (82% yield).

Ethyl (2*RS*,4*RS*)-4-Bromo-2-(*tert*-butoxycarbonylamino)-5-(pentafluorosulfanyl)hexanoate (5): To 7.8 mL of an 0.55 M solution of pentafluorosulfanyl bromide (0.89 g, 4.3 mmol) in CCl_3F was added an 1 M solution of triethylborane in hexane (0.33 mL, 0.33 mmol) followed by the slow addition of Boc-protected amino acid **4** (0.80 g, 3.3 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The reaction mixture was quenched with satd. $NaHCO_3$ solution and then extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography to afford the diastereoisomer mixture of colorless liquid (1.26 g, 85% yield). The diastereoisomeric mixture was used without further purification.

Ethyl (*RS*)-2-(*tert*-Butoxycarbonylamino)-5-(pentafluorosulfanyl)-hex-4-enoate (6): To a solution of **5** (1.25 g, 2.78 mmol) in benzene (10 mL) was added DBU (0.51 g, 3.33 mmol) and then stirred for 30 min at room temperature. The reaction mixture was quenched with water and then extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered and then concentrated. The crude product was purified by flash chromatography to afford 0.99 g of a colorless liquid (96% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.49–6.35 (m, 2 H), 5.23 (d, J = 6.9 Hz, 1 H), 4.45–4.38 (m, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 2.73–2.63 (m, 1 H), 2.55–2.45 (m, 1 H), 1.40 (s, 9 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 82.6 (quintet, $^2J_{SF\text{-}SF4}$ = 150.4 Hz, 1 F, axial SF), 62.0 (d, J = 148.7 Hz, 4 F, equatorial SF) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 155.0, 142.9 (t, J = 19.8 Hz), 133.6 (t, J = 7.0 Hz), 80.3, 61.9, 52.2, 34.1, 28.2, 14.0 ppm. $C_{12}H_{20}F_5NO_4S$ (369.34): calcd. C 39.02, H 5.46; found C 39.28, H 5.62.

(*RS*)-2-(*tert*-Butoxycarbonylamino)-5-pentafluorosulfanylhex-4-enoic Acid [Boc-(2*RS*)-SF_5NVa] (7): To a solution of **6** (0.30 g, 0.81 mmol) in ethanol was added 1 N NaOH solution (0.97 mL) and then stirred for 13 h at room temperature. The reaction mixture was washed with dichloromethane and then the solution acidified (pH 3) with 1 N HCl. The acidic solution was extracted with dichloromethane in three portions. The combined organic layers were dried with $MgSO_4$, filtered and then concentrated. The crude product was purified by flash chromatography to afford 0.27 g of a colorless liquid (98% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.45 (br. s, 1 H), 6.54–6.38 (m, 2 H), 5.19 (br. s, 1 H), 4.58–4.54 (m, 1 H), 2.84–2.67 (m, 1 H), 2.59–2.49 (m, 1 H), 1.43 (s, 9 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 82.3 (quintet, $^2J_{SF\text{-}SF4}$ = 150.3 Hz, 1 F, axial SF), 61.9 (d, J = 149.2 Hz, 4 F, equatorial SF) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ = 175.1, 155.2, 143.3 (t, J = 19.7 Hz), 133.2 (t, J = 7.4 Hz), 80.9, 52.1, 33.7, 28.2 ppm. $C_{10}H_{16}F_5NO_4S$ (341.29): calcd. C 35.16, H 4.73; found C 35.23, H 4.80.

Boc-Lys(Cbz)-Glu(Et)-OEt (10): The hydrochloride of Glu(Et)-OEt (**9**) (0.50 g, 2.1 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. This solution was treated with Et_3N (1.16 g, 11.5 mmol), 1-hydroxybenzotriazole (HOBt) (0.34 g, 2.51 mmol), a solution of the Boc-Lys(Cbz) (**8**) (0.80 g, 2.1 mmol) in CH_2Cl_2 (10 mL), and 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDC·HCl) (0.48 g, 2.5 mmol). The mixture was warmed to room temperature, and stirring was continued for 16 h with exclusion of light. Subsequent dilution with $CHCl_3$ was followed by thorough washing with 1 M HCl solution in three portions, satd. aq. $NaHCO_3$ in two portions and brine solution. The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford 0.91 g of a white solid (77% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.08 (m, 6 H), 5.50 (s, 2 H), 4.94 (s, 2 H), 4.47–4.38 (m, 1 H), 4.09–3.87 (m, 5 H), 3.03 (br. s, 2 H), 2.32–2.16 (m, 2 H), 2.10–1.98 (m, 1 H), 1.90–1.75 (m, 1 H), 1.72–1.59 (m, 1 H), 1.56–1.44 (m, 1 H), 1.43–1.32 (m, 2 H), 1.29 (m, 10 H), 1.08 (t, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 172.1, 171.2, 156.3, 155.3, 136.4, 128.0, 127.6, 127.5, 79.2, 66.0, 61.1, 60.2, 53.8, 53.2, 51.2, 40.0, 31.6, 29.8, 28.9, 27.9, 27.1, 26.6, 21.9, 13.7, 13.6 ppm.

TFA·Lys(Cbz)-Glu(Et)-OEt (11): Boc-protected amino acid **10** (0.45 g, 0.79 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. An equal volume of TFA was added, and the mixture was warmed to room temp., and stirring continued for 1.5 h. Concentration under reduced pressure, co-evaporation with CH_2Cl_2, and drying of the residue under high vacuum yielded the crude TFA salt, which was used without further purification.

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Boc-(2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu(Et)-OEt (12): Crude dipeptide **11** (0.044 g, 0.79 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. This solution was treated with Et_3N (0.44 g, 4.4 mmol), HOBt (0.14 g, 1.0 mmol), a solution of the Boc-(2*RS*)-SF$_5$NVa-OH (**7**) (0.27 g, 0.79 mmol) in CH_2Cl_2 (5 mL), and DMF (1.5 mL) and EDC·HCl (0.20 g, 1.0 mmol). The mixture was warmed to room temp., and stirring was continued for 16 h with exclusion of light. Subsequent dilution with $CHCl_3$ was followed by thorough washing with 1 M HCl solution in three portions, satd. aq. $NaHCO_3$ in two portions and brine solution. The organic phase was dried with $MgSO_4$, filtered and then concentrated under reduced pressure. The crude product was purified by flash chromatography to afford 0.50 g of a mixture of diastereomers as a white solid (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 7.05–6.87 (m, 2 H), 6.53–6.34 (m, 2 H), 5.39–5.26 (m, 1 H), 5.19–4.98 (m, 3 H), 4.54–4.46 (m, 1 H), 4.46–4.37 (m, 1 H), 4.37–4.25 (m, 1 H), 4.18–4.02 (m, 4 H), 3.21–3.07 (m, 2 H), 2.77–2.62 (m, 1 H), 2.51–2.24 (m, 3 H), 2.21–2.08 (m, 1 H), 2.03–1.91 (m, 1 H), 1.90–1.75 (m, 2 H), 1.72–1.59 (m, 1 H), 1.57–1.44 (m, 2 H), 1.40 (m, 10 H), 1.25–1.17 (m, 6 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 82.7 (quintet, 1 F, $^2J_{SF\text{-}SF4}$ = 149.7 Hz, axial SF), 62.0 (d, J = 149.3 Hz, 4 F, equatorial SF) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 172.8, 171.3, 171.2, 171.1, 170.81, 170.77, 170.1, 170.0, 156.5, 156.4, 155.1, 142.9 (m, J = 19.7 Hz), 142.7 (m, J = 19.8 Hz), 136.3, 136.2, 133.7 (m, J = 7.4 Hz), 128.2, 127.7, 80.3, 66.4, 66.3, 61.4, 60.61, 60.56, 52.6, 51.7, 39.8, 33.3, 31.4, 30.04, 29.99, 28.8, 27.9, 26.4, 21.7, 21.4, 13.7 ppm.

Fmoc-Lys(Boc)-*O*-Allyl (14): To a solution of acetonitrile (10 mL) and allyl bromide (12 mL) was added Fmoc-Lys(Boc)-OH (**13**) (2.3 g, 5.0 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.8 mL, 10 mmol) and then stirred for 4 h at 40 °C. The reaction mixture was concentrated to half volume. Subsequent dilution with ethyl acetate was followed by a thorough washing with 1 M HCl solution in three portions, aq. $NaHCO_3$ (half saturated) in two portions and then brine solution. The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford 2.44 g of a pale yellow solid (96% yield).

Lys(Boc)-*O*-Allyl (15): To Fmoc-Lys(Boc)-*O*-Allyl (**14**) (2.19 g, 4.31 mmol) was added 20% piperidine in CH_2Cl_2 (10.4 mL) at 0 °C. After 30 min stirring at room temperature, toluene (10 mL) was added and volatiles were removed under vacuum. The residue was purified by flash chromatography to afford 1.16 g of a colorless liquid (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.27 (ddt, J = 17.14, 1.46, 1.3 Hz, 1 H), 5.20 (ddt, J = 10.43, 1.8, 1.2 Hz, 1 H), 4.56 (ddd, J = 5.85, 1.4, 1.7 Hz, 2 H) 3.42 (m, 2 H), 3.08 (m, 2 H), 1.84 (m, 2 H), 1.72 (m, 2 H), 1.57 (m, 2 H), 1.4 (m, 2 H),1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 155.9, 131.9, 118.6, 78.9, 65.4, 54.3, 40.2, 34.3, 29.7, 28.3, 22.8 ppm.

Fmoc-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (17): The Lys(Boc)-*O*-Allyl (**15**) (0.36 g, 1.3 mmol) was dissolved in THF (13 mL) and cooled to 0 °C. This solution was treated with the Fmoc-Ser(*t*Bu)-OH **16** (0.46 g, 1.2 mmol), HOBt (1-hydroxybenzotriazole) (0.20 g, 1.5 mmol), EDC·HCl (0.29 g, 1.5 mmol), *N*-methylmorpholine (0.25 g, 2.5 mmol). The mixture was warmed to room temp., and stirring was continued for 15 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 0.74 g of a colorless liquid (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.27 (m, 8 H), 5.88 (m, 1 H), 5.31 (d, J = 16.5 Hz, 1 H), 5.24 (d, J = 10.9 Hz, 1 H), 4.60 (m 1 H), 4.38 (d, J = 8 Hz, 2 H), 4.21 (t, J = 7 Hz, 1 H), 3.81 (dd, J = 8, 4 Hz, 2 H), 3.37 (t, J = 8 Hz, 1 H), 3.07 (dt, J = 7, 2 Hz, 2 H), 1.92–1.82 (m, 2 H), 1.75–1.65 (m, 2 H), 1.53–1.44 (m, 2 H), 1.41 (s, 9 H), 1.21 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.2, 155.9, 143.9, 143.7, 141.3, 131.5, 127.7, 127.0, 125.1, 119.9, 119.0, 79.1, 77.2, 74.3, 67.1, 65.9, 61.7, 54.2, 52.2, 47.1, 32.1, 29.5, 28.4, 27.3, 22.4 ppm.

Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (18): To Fmoc-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (**17**) (0.45 g, 0.69 mmol) was added 20% piperidine in CH_2Cl_2 (4 mL) at 0 °C. After 30 min stirring at room temp., toluene (10 mL) was added and volatiles were removed under vacuum. The residue was purified by flash chromatography to afford 0.23 g of a pale yellow liquid (76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (br. s, 2 H), 5.78 (m, 1 H), 5.21 (d, J = 16.8 Hz, 1 H), 5.12 (d, J = 10.4 Hz, 1 H), 4.74 (t, J = 6 Hz, 1 H), 4.50 (d, J = 8.6 Hz, 2 H), 4.46 (dd, J = 8.0, 2.8 Hz, 1 H), 3.44–3.37 (m, 1 H), 2.86 (m, 1 H), 1.87 (br. s, 2 H), 1.80–1.70 (m, 2 H), 1.63–1.52 (m, 2 H), 1.30 (s, 9 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 171.7, 155.7, 131.4, 118.5, 78.6, 73.1, 65.5, 63.6, 54.9, 51.5, 40.0, 32.0, 29.2, 28.2, 27.2, 22.2 ppm.

Fmoc-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (19): The Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (**18**) (0.19 g, 0.43 mmol) was dissolved in THF (7 mL) and cooled to 0 °C. This solution was treated successively with the Fmoc-Glu(*t*Bu)-OH (0.17 g, 0.41 mmol), HOBt (0.12 g, 0.86 mmol), EDC·HCl (0.17 g, 0.86 mmol), *N*-methylmorpholine (0.13 g, 1.3 mmol). The mixture was warmed to room temp., and stirring was continued for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 0.29 g of a colorless liquid (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.21 (m, J = 8 Hz), 7.03 (d, J = 6 Hz, 1 H), 5.87 (m, 1 H), 5.30 (dq, J = 17.3, 1.32 Hz, 1 H), 5.22 (dq, J = 10.4, 6.2 Hz, 1 H), 4.59 (d, J = 6 Hz, 1 H), 4.56 (m, 1 H), 4.44 (m, 1 H), 4.40–4.28 (m, 2 H), 4.25–4.16 (m, 1 H), 3.81 (dd, J = 8.1, 4.0 Hz 1 H), 3.38 (t, J = 7.6 Hz 1 H), 3.00 (t, J = 6.9 Hz 2 H), 2.54–2.30 (m, 2 H), 2.18–2.08 (m, 2 H), 2.02–1.90 (m, 2 H), 1.89–1.77 (m, 2 H), 1.72–1.60 (m, 2 H), 1.44 (s, 9 H), 1.41 (s, 9 H), 1.17 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 171.5, 171.2, 169.9, 156.3, 156.0, 143.8, 141.3, 131.6, 127.7, 127.1, 125.1, 120.0, 118.9, 81.2, 79.2, 77.2, 74.2, 67.3, 65.8, 61.1, 54.8, 53.2, 53.1, 52.2, 47.1, 40.4, 32.0, 29.4, 28.4, 28.1, 27.4, 22.4 ppm.

Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (20): To Fmoc-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (**19**) (0.32 g, 0.38 mmol) was added 20% piperidine in CH_2Cl_2 (4 mL) at 0 °C. After 30 min stirring at room temperature, toluene (10 mL) was added and volatiles were removed under vacuum. The residue was purified by flash chromatography to afford 0.22 g of a colorless liquid (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.8 (d, 1 H), 7.30 (d, 1 H), 5.78 (m, 1 H), 5.21 (dd, J = 17, 1.32 Hz, 1 H), 5.14 (dt, J = 10.4 Hz, 1.21 1 H), 4.71 (t, 1 H), 4.51 (d, 2 H), 4.47 (m, 2 H), 4.34 (m, 2 H), 3.65 (dd, 1 H), 3.47–3.26 (m, 2 H), 2.96 (q, 2 H), 2.32–2.21 (m, 2 H), 2.04–1.94 (m, 1 H),1.93–1.67 (m, 2 H), 1.67–1.55 (m, 2 H), 1.32 (s, 9 H), 1.31 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.39, 172.46, 171.48, 170.08, 155.78, 131.37, 118.67, 80.29, 78.70, 73.88, 65.60, 61.15, 54.42, 52.57, 52.00, 39.97, 31.75, 31.63, 29.94, 29.24, 28.21, 27.85, 27.17, 22.21 ppm.

Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (21): The Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (**20**) (0.21 g, 0.34 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. This solution was treated with the Boc-(2*RS*)-SF$_5$NVa-OH (**7**) (0.12 g, 0.34 mmol), HOBt (0.055 g, 0.41 mmol), EDC·HCl (0.079 g, 0.41 mmol), *N*-methylmorpholine (0.069 g, 0.68 mmol). The mixture was warmed to room temp., and stirring was continued for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was

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purified by flash chromatography to afford 0.30 g of a mixture of diastereomers as a colorless liquid (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49–6.31 (m, 1 H), 5.85–5.73 (m, 1 H), 5.22 (dq, J = 16.9, 1.37 Hz, 1 H), 5.14 (dq, J = 10.32, 1.03 Hz, 1 H), 4.51 (d, J = 5.6 Hz, 2 H), 4.47–4.37 (m, 1 H), 4.35–4.26 (m, 1 H), 4.22–4.15 (m, 1 H), 3.63–3.55 (m, 1 H), 3.46–3.39 (m, 1 H), 3.36 (br. s, 2 H), 3.26 (p, J = 1.56 Hz, 1 H), 3.02–2.91 (m, 2 H), 2.64–2.54 (m, 1 H), 2.42–2.30 (m, 1 H), 2.24 (t, J = 7.23 Hz,2 H), 2.03–1.91 (m, 1 H), 1.98–1.69 (m, 2 H), 1.66–1.54 (m, 1 H), 1.34 (s, 9 H), 1.33 (s, 9 H), 1.32 (s, 9 H), 1.09 (s, 9 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 82.72 (q, $^2J_{SF\text{-}SF4}$ = 150 Hz, 1 F, axial SF), 82.65 (q, $^2J_{SF\text{-}SF4}$ = 149.7 Hz, 1 F, axial SF), 61.76 (d, J = 149.4 Hz, 4 F, equatorial SF), 61.78 (d, J = 148.1 Hz, 4 F, equatorial SF) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 171.50, 171.48, 170.9, 170.0, 156.3, 155.5, 142.7, 142.7, 134.08, 134.07, 131.4, 118.7, 81.1, 81.0, 80.3, 79.2, 77.2, 74.0, 74.0, 65.7, 61.0, 52.7, 52.6, 52.0, 49.5, 49.3, 49.1, 48.9, 48.7, 48.5, 48.3, 33.6, 31.7, 31.6, 31.39, 31.35, 29.5, 29.1, 28.2, 28.0, 27.76, 27.75, 27.1, 27.0, 22.3 ppm.

Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-OH (22): To a solution of Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-*O*-Allyl (**21**) (0.176 g, 0.188 mmol) in THF (6 mL) at room temp. was added tetrakis(triphenylphosphane)palladium(0) (0.044 g, 0.038 mmol) and *N*-ethylaniline (0.228 g, 1.88 mmol). After stirring for 32 min at room temp., dilution with ethyl acetate was followed by a thorough washing with aq. saturated NH_4Cl solution. The water layer was extracted with ethyl acetate in three portions. The combined organic layer was dried with $MgSO_4$, filtered and then concentrated under reduced pressure. The crude product was purified by flash chromatography to afford 0.154 g of a white solid (91% yield).

(2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu(Et)-OEt (23): Boc-(2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu(Et)-OEt (**12**) (0.085 mg, 0.095 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C. An equal volume of TFA was added, and the mixture was warmed to room temp., and stirring continued for 1.5 h. Concentration under reduced pressure, co-evaporation with CH_2Cl_2, and drying of the residue under high vacuum yielded the crude TFA salt, which was used without further purification.

Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-(2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu(Et)-OEt (24): The (2*RS*)-SF$_5$NVa-Lys(Cbz)-Glu(Et)-OEt (**23**) (0.040 g, 0.05 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. This solution was treated with the Boc-(2*RS*)-SF$_5$NVa-Glu(*t*Bu)-Ser(*t*Bu)-Lys(Boc)-OH (**22**) (0.046 g, 0.051 mmol), HOBt (1-hydroxybenzotriazole) (0.009 g, 0.06 mmol), EDC·HCl (0.012 g, 0.062 mmol), *N*-methylmorpholine (0.026 g, 0.26 mmol). The mixture was warmed to room temp., and stirring was continued for 6.5 h. Subsequent dilution with $CHCl_3$ was followed by a thorough washing with 1 M HCl solution in three portions, satd. aq. $NaHCO_3$ in two portions and brine solution. The organic phase was dried with $MgSO_4$, filtered and then concentrated under reduced pressure. The product was obtained in 88% crude yield (0.070 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (m, 1 H), 8.18 (d, J = 7 Hz, 1 H), 8.03–7.93 (m, 3 H), 7.79 (d, J = 6.6 Hz, 1 H), 7.37–7.26 (m, 5 H), 7.12 (t, J = 5.6 Hz, 1 H), 7.05–6.95 (m, 1 H), 6.91–6.75 (m, 2 H), 6.60 (d, J = 6.1 Hz, 1 H), 6.62–6.50 (m, 2 H), 5.0 (s, 2 H), 4.51–4.42 (m, 1 H), 4.37–4.29 (m, 2 H), 4.29–4.21 (m, 3 H), 4.21–4.13 (m, 1 H), 4.11 (m, 2 H), 3.54–3.44 (m, 2 H), 3.02–2.99 (m, 2 H), 2.92–2.84 (m, 2 H), 2.66–2.55 (m, 2 H), 2.48–2.39 (m, 2 H), 2.34 (t, J = 7.5 Hz, 2 H), 2.21 (t, J = 7.5 Hz, 2 H), 2.06–1.82 (m, 2 H), 1.87–1.71 (m, 2 H), 1.7–1.58 (m, 2 H), 1.58–1.46 (m, 2 H), 1.45–1.22 (m, 4 H), 1.40–1.37 (s, 9 H), 1.37 (s, 9 H), 1.13–1.07 (apparent s, 9 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm. HRMS (MALDI-TOF): calcd. for [M + Na]$^+$ $C_{65}H_{103}F_{10}N_9NaO_{19}S_2$: 1590.6550, found 1590.6553.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra are available for key intermediates and TOCSY and NOESY data for the final product.

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[1] a) M. Salwiczek, S. Samsonov, T. Vagt, E. Nyakatura, E. Fleige, J. Numata, H. Colfen, M. T. Pisabarro, B. Koksch, *Chem. Eur. J.* **2009**, *15*, 7628–7636; b) D. Lentz, K. Seppelt, in: *Chemistry of Hypervalent Compounds* (Ed.: K.-y. Akiba), Wiley-VCH, New York, **1999**, pp. 295–325; c) R. W. Winter, R. A. Dodean, G. L. Gard, *ACS Symp., Ser.* **2005**, *911*, 87–118; d) G. L. Gard, *Chim. Oggi* **2009**, *27*, 10–13.

[2] J. T. Welch, in: *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*, vol. 5 (Eds.: V. Gouverneur, K. Mueller), Imperial College Press Co., **2012**, pp. 171–204.

[3] P. Kirsch, G.-V. Röschenthaler, *ACS Symp., Ser.* **2007**, *949*, 221–243.

[4] M. Salwiczek, E. Nyakatura, U. I. M. Gerling, S. Ye, B. Koksch, *Chem. Soc. Rev.* **2012**, *41*, 2135–2171.

[5] a) A. Niemz, D. A. Tirrell, *J. Am. Chem. Soc.* **2001**, *123*, 7407–7413; b) B. Bilgicer, X. Xing, K. Kumar, *J. Am. Chem. Soc.* **2001**, *123*, 11815–11816; c) B. Bilgicer, K. Kumar, *Tetrahedron* **2002**, *58*, 4105–4112.

[6] a) H.-Y. Lee, K.-H. Lee, H. M. Al-Hashimi, E. N. G. Marsh, *J. Am. Chem. Soc.* **2006**, *128*, 337–343; b) K.-H. Lee, H.-Y. Lee, M. M. Slutsky, J. T. Anderson, E. N. G. Marsh, *Biochemistry* **2004**, *43*, 16277–16284; c) T. Arai, T. Imachi, T. Kato, H. I. Ogawa, T. Fujimoto, N. Nishino, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1383–1389; d) M. Salwiczek, B. Koksch, *ChemBioChem* **2009**, *10*, 2867–2870; e) T. Arai, T. Imachi, T. Kato, N. Nishino, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 439–445.

[7] a) S. S. Pendley, Y. B. Yu, T. E. Cheatham III, *Proteins Struct., Funct., Bioinf. Proteins* **2009**, *74*, 612–629; b) C. Jäckel, M. Salwiczek, B. Koksch, *Angew. Chem.* **2006**, *118*, 4305; *Angew. Chem. Int. Ed.* **2006**, *45*, 4198–4203; c) C. Jaeckel, W. Seufert, S. Thust, B. Koksch, *ChemBioChem* **2004**, *5*, 717–720.

[8] J. M. Mason, K. M. Arndt, *ChemBioChem* **2004**, *5*, 170–176.

[9] a) Y. Tang, G. Ghirlanda, W. A. Petka, T. Nakajima, W. F. DeGrado, D. A. Tirrell, *Angew. Chem.* **2001**, *113*, 1542; *Angew. Chem. Int. Ed.* **2001**, *40*, 1494–1496; b) S. Son, I. C. Tanrikulu, D. A. Tirrell, *ChemBioChem* **2006**, *7*, 1251–1257; c) B. C. Buer, R. de la Salud-Bea, H. M. Al Hashimi, E. N. G. Marsh, *Biochemistry* **2009**, *48*, 10810–10817; d) J. K. Montclare, S. Son, G. A. Clark, K. Kumar, D. A. Tirrell, *ChemBioChem* **2009**, *10*, 84–86; e) B. Bilgicer, A. Fichera, K. Kumar, *J. Am. Chem. Soc.* **2001**, *123*, 4393–4399; f) Y. Tang, D. A. Tirrell, *J. Am. Chem. Soc.* **2001**, *123*, 11089–11090.

[10] H.-P. Chiu, Y. Suzuki, D. Gullickson, R. Ahmad, B. Kokona, R. Fairman, R. P. Cheng, *J. Am. Chem. Soc.* **2006**, *128*, 15556–15557.

[11] a) M. Salwiczek, T. Vagt, B. Koksch, in: *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Blackwell Publishing, **2009**, pp. 391–409; b) B. Apostolovic, M. Danial, H.-A. Klok, *Chem. Soc. Rev.* **2010**, *39*, 3541–3575; c) H. Robson Marsden, A. Kros, *Angew. Chem.* **2010**, *122*, 3050; *Angew. Chem. Int. Ed.* **2010**, *49*, 2988–3005; d) A. L. Boyle, D. N.

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Woolfson, *Chem. Soc. Rev.* **2011**, *40*, 4295–4306; e) N. R. Zaccai, B. Chi, A. R. Thomson, A. L. Boyle, G. J. Bartlett, M. Bruning, N. Linden, R. B. Sessions, P. J. Booth, R. L. Brady, D. N. Woolfson, *Nat. Chem. Biol.* **2011**, *7*, 935–941.

[12] D. Seebach, T. Sifferlen, D. J. Bierbaum, M. Rueping, B. Jaun, B. Schweizer, J. Schaefer, A. K. Mehta, R. D. O'Connor, B. H. Meier, M. Ernst, A. Glättli, *Helv. Chim. Acta* **2002**, *85*, 2877–2917.

[13] R. Hamzavi, F. Dolle, B. Tavitian, O. Dahl, P. E. Nielsen, *Bioconjugate Chem.* **2003**, *14*, 941–954.

[14] a) Z. Chen, J. Deng, T. Ye, *Arkivoc* **2003**, *vii*, 268–285; b) H. Tamiaki, T. Obata, Y. Azefu, K. Toma, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 733–738.

[15] S. K. George, T. Schwientek, B. Holm, C. A. Reis, H. Clausen, J. Kihlberg, *J. Am. Chem. Soc.* **2001**, *123*, 11117–11125.

[16] a) P. Güntert, in: *Methods in Molecular Biology*, vol. 278, **2004**, pp. 353–378; b) P. Guntert, *Prog. Nucl. Mag. Res. Sp.* **2003**, *43*, 105–125; c) P. Güntert, in: *BioNMR in Drug Research*, Wiley-VCH, **2003**, pp. 39–66; d) C. Mumenthaler, P. Güntert, W. Braun, K. Wüthrich, *J. Biomol. NMR* **1997**, *10*, 351–362; e) P. Guntert, in: *Protein NMR Spectroscopy: Practical Techniques and Applications*, John Wiley & Sons, **2011**, pp. 159–192; f) T. Ikeya, J.-G. Jee, Y. Shigemitsu, J. Hamatsu, M. Mishima, Y. Ito, M. Kainosho, P. Güntert, *J. Biomol. NMR* **2011**, *50*, 137–146.

[17] a) K. Wüthrich, in: *NMR of Proteins and Nucleic Acids*, **1986**; b) D. G. Reid, in: *Methods in Molecular Biology*, vol. 60, **1997**.

[18] N. Sewald, H.-D. Jakubke, in: *Peptides: Chemistry and Biology*, Wiley-VCH, **2002**.

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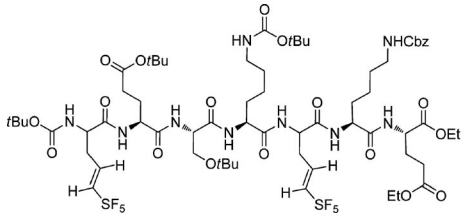

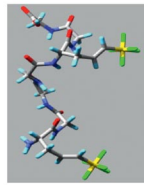

The design and synthesis of pentafluorosulfanyl-containing heptad amino acid sequence was described. The investigation of the peptide conformation shows that the one of the diastereomers assumed a very tight coiled conformation in [D_6]DMSO where both pentafluorosulfanyl groups assumed a synclinal relationship. The propensity of the protected heptapeptide to form such a tight coil and of the pentafluorosulfanyl groups to align so uniformly is suggestive of the utility of pentafluorosulfanylated amino acids in promoting conformational control.

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