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Design, Synthesis, and Application of an Optimized Monofluorinated Aliphatic Label for Peptide Studies by Solid-State ^{19}F NMR Spectroscopy

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Abstract: *A conformationally restricted monofluorinated α-amino acid, (3-fluorobicyclo[1.1.1]pentyl)glycine (F-Bpg), was designed as a label for the structural analysis of membrane-bound peptides by solid-state ^{19}F NMR spectroscopy. The compound was synthesized and validated as a ^{19}F label for replacing natural aliphatic α-amino acids. Calculations suggested that F-Bpg is similar to Leu/Ile in terms of size and lipophilicity. The ^{19}F NMR label was incorporated into the membrane-active antimicrobial peptide PGLa and provided information on the structure of the peptide in a lipid bilayer.*

The structural analysis of membrane-active peptides embedded in lipid model bilayers under quasi-native conditions or in native biomembranes has considerably advanced owing to the use of fluorine-labeled analogues in combination with ^{19}F NMR spectroscopy. The large gyromagnetic ratio of the ^{19}F nucleus, its spin of $^1/_2$, the absence of any biological background, and the high sensitivity of ^{19}F NMR chemical shifts to the local environment render this approach advantageous over other NMR labeling strategies.[1] The conformation, alignment in membranes, and dynamic behavior of various membrane-bound peptides have been determined with this approach at near-atomic resolution.[2] Fluorine-substituted amino acids that are to be used as ^{19}F labels in this approach have to meet several strict criteria: 1) They must be conformationally rigid so that the ^{19}F reporter group is placed in a well-defined position relative to the peptide backbone; 2) they must be compatible with the standard procedures of solid-phase peptide synthesis (SPPS); and 3) they must not perturb the native structure and function of the peptide. These criteria exclude almost all known fluorinated α-amino acids,[3] mostly owing to their conformational flexibility.

Over the past decade, we have designed, synthesized, and explored various CF_3-substituted labels (Figure 1a) as analogues of aminoisobutyric acid (**1**),[4] alanine/valine/leucine/isoleucine (**2**),[5,6] proline (**3**),[7,8] serine (**4**),[9a] and phenylalanine (**5**).[9b] Monofluorinated labels, however, that are capable of delivering the same orientational information as the CF_3-substituted ones, and would be even superior[11d] in measurements of intra- and intermolecular distances have received far less attention.[10–13] All monofluorinated labels (**6**–**8**) that have been used in the past have serious drawbacks (Figure 1b). For instance, amino acid **6**[10] is conformationally flexible, making the structural interpretation of NMR parameters ambiguous. In compounds **7** and **8**, the position of the ^{19}F atom is well fixed, but **7**[11] undergoes extensive racemization

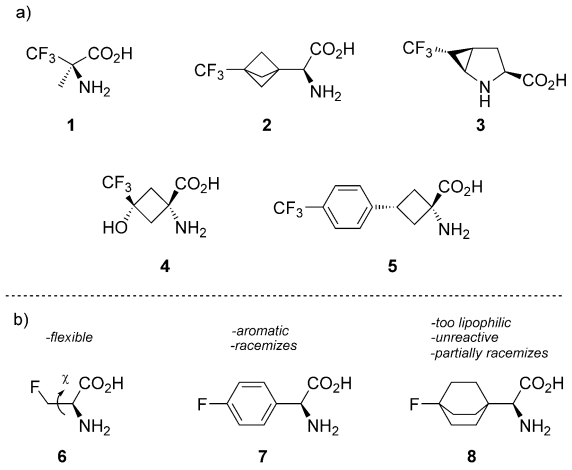

Figure 1. Selected known a) CF_3 and b) F labels employed in structural peptide studies by solid-state ^{19}F NMR spectroscopy.[8]

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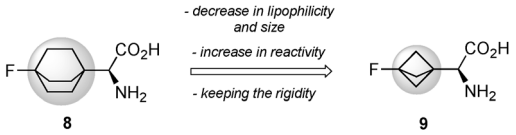
during peptide synthesis, and replacing aliphatic amino acids (Ala, Val, Ile, Leu) with the aromatic compound **7** may perturb the structure and function of peptides. The use of **8** suffers from the reduced reactivity of the amino acid, and it is also much more lipophilic and bulkier than natural aliphatic amino acids.[12]

Herein, we report on the rational design, synthesis, and application of a novel monofluorinated aliphatic amino acid, (3-fluorobicyclo[1.1.1]pentyl)glycine (F-Bpg, **9**). It avoids the problems associated with the use of **6**–**8** for the determination of interatomic distances in membrane-active peptides by solid-state ^{19}F NMR spectroscopy.

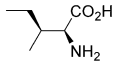
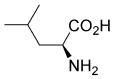
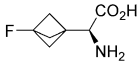
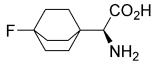
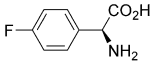
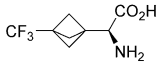
We designed the target structure **9** by analyzing the advantages and disadvantages of the monofluorinated label **8**.[12] We replaced the central core in **8** by the smaller, but nonetheless conformationally rigid bicyclo[1.1.1]pentyl skeleton (Scheme 1). Given the reduced size of the side chain, we expected that **9** should be more reactive than **8** in SPPS. Calculations (Table 1) indeed confirmed that the designed amino acid **9** is more similar to natural Leu/Ile than all other ^{19}F labels in terms of size and lipophilicity (criterion 3).

We started the synthesis of **9** from dibromide **10**, from which the diacid **12**[15] was readily prepared in several steps via propellane **11** following literature procedures (Scheme 2).[16,17] However, the transformation of one carboxyl group in **12** into a fluorine atom with XeF_2 under various

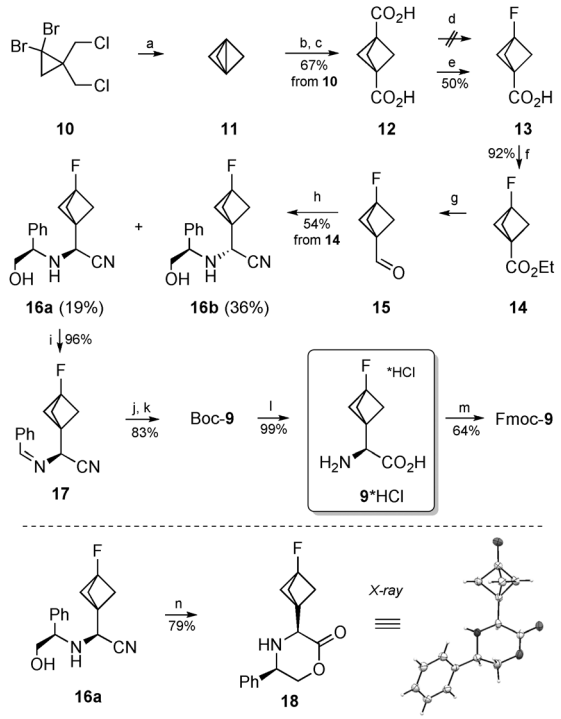


Scheme 1. Design of an optimized ^{19}F NMR label (**9**) for replacing aliphatic α-amino acids in membrane-bound peptides.

Table 1: Calculated properties of amino acids.[14]

Molecule		SASA[a] [Å^2]	Volume[b] [Å^3]	$Q\log P_{o/w}$[c]
Ala		263	372	−3.0
Val		310	474	−1.7
Ile		339	529	−1.5
Leu		345	536	−1.5
9		343	539	−1.5
8		375	644	−0.9
7		385	619	−1.0
2		383	623	−0.8

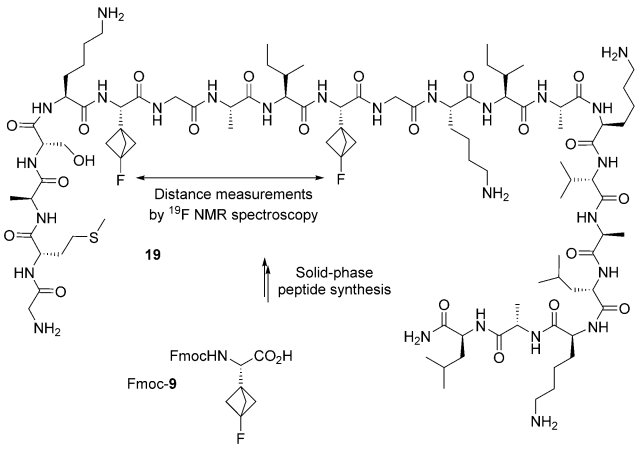
[a] Total solvent-accessible surface area. [b] Total solvent-accessible volume. [c] Octanol/water partition coefficient.



Scheme 2. Synthesis of **9**. Reagents and conditions: a) MeLi (2.1 equiv), pentane/Et_2O, −78 °C; b) butane-2,3-dione, *hν*, −5 °C; c) NaOH (16.5 equiv), Br_2 (7.5 equiv), dioxane/H_2O, 0 °C, 2 h; then RT, 12 h; d) XeF_2 (1.5 equiv), CH_2Cl_2, 0 °C; e) Selectfluor (1.8 equiv), $AgNO_3$ (0.2 equiv), H_2O, 55 °C, 12 h; f) 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI, 1.3 equiv), DIPEA (1.4 equiv), DMAP (0.2 equiv), EtOH (2.0 equiv), CH_2Cl_2, RT, 12 h; g) DIBAL-H (1.2 equiv), toluene, −78 °C, 2 h; h) (*R*)-2-phenylglycinol (1.2 equiv), Me_3SiCN (3.0 equiv), MeOH, 12 h; i) $Pb(OAc)_4$ (1.5 equiv), CH_2Cl_2/MeOH (1:1), 0 °C, 15 min; j) 6 N HCl, reflux, 24 h; k) Boc_2O (3.0 equiv), K_2CO_3 (3.0 equiv), H_2O/THF (1:1), RT, 12 h; l) HCl/dioxane, Et_2O, RT, 12 h; m) Na_2CO_3 (5.0 equiv), FmocCl (1.1 equiv), dioxane/H_2O (2:3), 0 °C, 0.5 h; then RT, 12 h; n) HCl/dioxane, RT, 12 h.

conditions[12] afforded only complex mixtures.[18] Fortunately, Li and co-workers have recently reported a method for the decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor/$AgNO_3$.[19] Inspired by this method, we found that using 1.8 equiv of Selectfluor provided acid **13** in 50% yield,[20,21] which was then smoothly converted into ester **14** in 92% yield. Reduction of **14** with DIBAL-H at −78 °C resulted in the volatile aldehyde **15**, which was used without isolation in the next step, a Strecker-type reaction with (*R*)-α-phenylglycinol as the chiral auxiliary.[22] The diastereomeric products **16a** and **16b** were separated by column chromatography. Oxidative cleavage of the chiral auxiliary in **16a** with $Pb(OAc)_4$ in CH_2Cl_2 smoothly gave imine **17**. Finally, acid hydrolysis of **17**, followed by treatment with Boc_2O/K_2CO_3, afforded the Boc-protected amino acid Boc-**9** in 83% yield. Cleavage of the *N*-Boc group gave the target amino acid **9**·HCl as a white solid. Treatment with FmocCl/Na_2CO_3 then gave Fmoc-**9**. The *S* configuration of the newly formed stereocenter was confirmed by X-ray analysis of derivative **18** (Scheme 2).[23]

To evaluate the practical applicability of the novel amino acid **9** as a ^{19}F NMR label for peptide studies, we incorporated it into the antimicrobial peptide PGLa from the skin of *Xenopus laevis* (GMASKAGAIAGKIAKVALKAL-NH_2)[24] with established α-helical structure and a well-characterized membrane-bound alignment.[25] We synthesized the doubly labeled peptide **19** (GMASK**9**GAI**9**GKIAKVALKAL-NH_2) in which the residues Ala^6 and Ala^{10} were replaced by **9** (Scheme 3) to assess the potential of the label in detecting the



Scheme 3. SPPS of the PGLa analogue **19** with two ^{19}F labels **9**.

F–F contacts. We choose this labeling strategy because it would allow for a direct comparison of our results with previous ^{19}F–^{19}F distance measurements on the same peptide.[11b] Notably, amino acid **9** was readily incorporated into the polypeptide under the standard conditions of manual SPPS. Degradation, low reactivity, or racemization of **9** were not observed, in contrast to the previously tested labels **7** and **8** (criterion 2).[11b,12]

Solid-state ^{19}F NMR spectroscopy of the peptide reconstituted in 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) bilayers gave the expected two ^{19}F resonances (Figure 2). Circular dichroism (CD) spectroscopy of the labeled peptide showed that its α-helical character was slightly decreased compared to the wild-type peptide (Figure 3). This is probably due to the replacement of two amino acids in the peptide as well as the glycine residues next to the labels, which led to a destabilization of the helix near the labeled sites. However, the CD spectra confirmed that the labeled peptide was still mostly α-helical in a membrane-mimicking environment. Like the parent PGLa, the doubly labeled peptide underwent a structural transition from a random coil to an α-helix in micelles or when titrated with trifluoroethanol (TFE). Most importantly, while showing reduced activity, the peptide remained antimicrobial (Table 2).

We validated the use of the proposed label for ^{19}F–^{19}F distance measurements using the centerband only detection of exchange (CODEX) experiment [26] to study the behavior of labeled PGLa reconstituted into frozen DMPC/DMPG (3:1; DMPG = 1,2-dimyristoyl-*sn*-glycero-3-phospho-(1′-*rac*-glycerol)) bilayers (see the Supporting Information for details of the sample preparation). In this experiment, spin exchange leads to a decrease in intensity if the spins are close in space, which was observed in our case (Figure 4). The intramolecular ^{19}F–^{19}F distance was estimated to be approximately 8.0 ± 1.0 Å, which compared well with the previously obtained

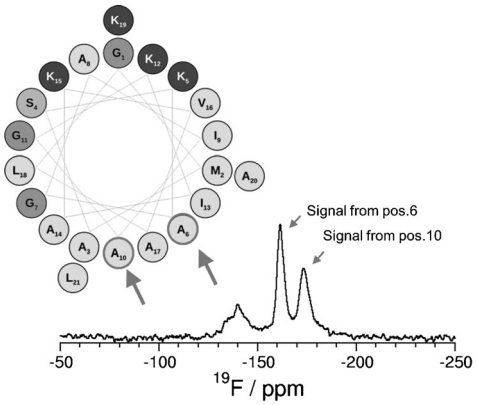


Figure 2. Helical wheel representation of PGLa and the positions where substitution with **9** led to peptide **19**. Static solid-state ^{19}F NMR spectrum of **19** in oriented DMPC bilayers (peptide/lipid = 1:100, 35 °C).

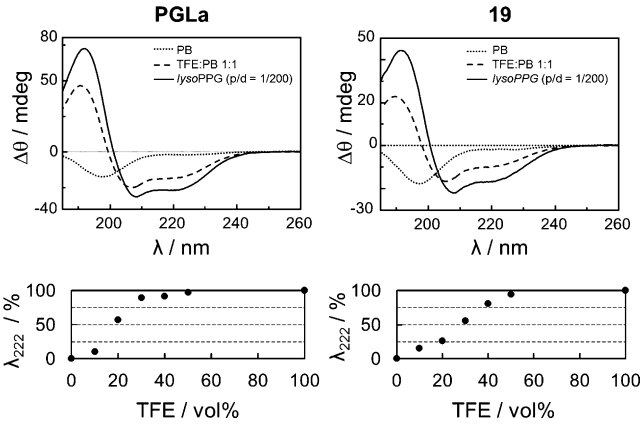


Figure 3. CD spectroscopic analysis of the doubly labeled peptide demonstrates the compatibility of label **9** with helical structures. Top left: CD spectra of PGLa in aqueous environments (10 mM phosphate buffer, pH 7.4, 25 °C: dotted line; 50%TFE: dashed line) and in the presence of negatively charged lipid micelles (solid line, with 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphatidylglycerol as the lipid. p/d = peptide/lipid molar ratio. Top right: **19** under the same conditions. Conformational transitions for PGLa (bottom left) and **19** (bottom right) upon titration with TFE. The transition from a random coil to an α-helix was observed as a change in the CD intensity at 222 nm. The intensity at 0% TFE was taken as 0 and the intensity at 100% TFE as 100.

Table 2: Antimicrobial activity (MIC, μg mL^{-1}) of PGLa and **19**.

Bacterial strain	PGLa	**19**
E. coli DSM 1103	64	128
S. aureus DSM 1104	32	128

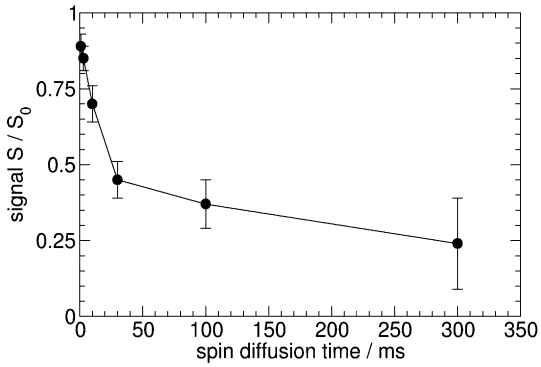


Figure 4. ^{19}F signal decay obtained in the CODEX experiment for spin diffusion as a function of time, indicating the proximity of the two ^{19}F labels. A distance of about 8.0 ± 1.0 Å was obtained from the decay as described in the Supporting Information. The asymptotic value of the normalized intensity of $< 1/2$ indicates the presence of intermolecular couplings, in addition to the intramolecular coupling between the two labels. Conditions: **19** in DMPC/DMPG, peptide/lipid = 1:40, −15 °C.

distance between two ^{19}F labels **7** at the same positions (6.6 ± 0.3 Å)[25] and the expected distance of 7.5–8.0 Å assuming an ideal helix. The slightly longer distance obtained in our experiment might be due to partial distortion of the α-helix caused by the label as observed by CD spectroscopy. Nevertheless, this experiment confirmed the practical utility of **9** as a label to measure interspin distances.

In conclusion, we have designed, synthesized, and validated the monofluorinated α-amino acid **9** as a label for the structural analysis of membrane-bound peptides by solid-state ^{19}F NMR spectroscopy. Amino acid **9** was found to be very similar to leucine and isoleucine in terms of size and lipophilicity. It was smoothly incorporated into the membrane-active antimicrobial peptide PGLa at two positions, and was used for intramolecular distance measurements. Importantly, amino acid **9** possessed none of the drawbacks of the previously used monofluorinated labels **6**–**8**. Therefore, we believe that the new ^{19}F label will soon find wide application in peptide studies.

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Keywords: amino acids · fluorine · peptides · propellanes · solid-state NMR spectroscopy

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Communications

Amino Acids

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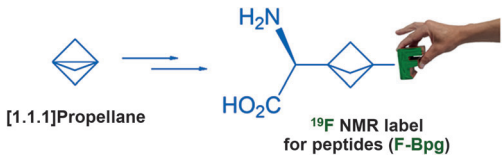
Design, Synthesis, and Application of an Optimized Monofluorinated Aliphatic Label for Peptide Studies by Solid-State ^{19}F NMR Spectroscopy



A conformationally restricted monofluorinated α-amino acid was synthesized and used as a ^{19}F label to replace aliphatic amino acids in peptides. Its incorporation into the membrane-active antimicrobial peptide PGLa demonstrated its applicability for peptide structure analysis and distance measurements by ^{19}F NMR spectroscopy.

