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New Fluorinated Peptidomimetics through Tandem Aza-Michael Addition to α-Trifluoromethyl Acrylamide Acceptors: Synthesis and Conformational Study in Solid State and Solution[#]

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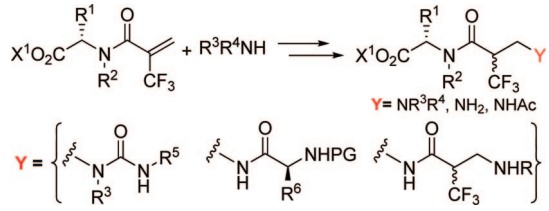

A range of partially modified retro (PMR) ψ[$NHCH_2$] peptide mimetics containing a hydrolytically stable $CH_2CH(CF_3)CO$ unit have been synthesized. The first kind of peptidomimetics is obtained from the highly efficient aza-Michael addition of different amines to α-trifluoromethyl acrylamide acceptors. Subsequent deprotection of the amino group furnishes the key common intermediate for the synthesis of other families of peptidomimetics: dipeptides, tripeptides, peptidomimetics containing a urea moiety, and structures containing two units of α-trifluoromethyl-β^2-alanine. Finally, a conformational study of several of the newly synthesized peptidomimetics, performed with the aid of X-ray analysis and NMR techniques, shows a β-turn-like conformation for the structures both in the solid state and in solution.

Introduction

Peptides are essential components of living organisms, acting as hormones, neurotransmitters, and neuromodulators. As such, they exert an essential influence on basic functions including metabolism, reproduction, respiration, and immune defense.[1] Nevertheless, the use of peptides in drug development is limited due to their low metabolic stability in vivo and their poor bioavailability.[2] One strategy to circumvent these drawbacks is to modify the peptide structure in such a way that the metabolic stability may be enhanced. Various alterations can be performed at any point on the peptide chain in order to obtain peptidomimetics: amino acids can be deleted, added, or replaced by other natural or non-natural amino acids; synthetic scaffolds can substitute for all or part of the peptide backbone; cyclizations can be performed to increase the rigidity of the molecules, and finally, peptide bond surrogate units X, usually represented as ψ(X), can be used instead of the peptidic bond (X instead of CO−NH).[1,3] Another common strategy is the inversion of the

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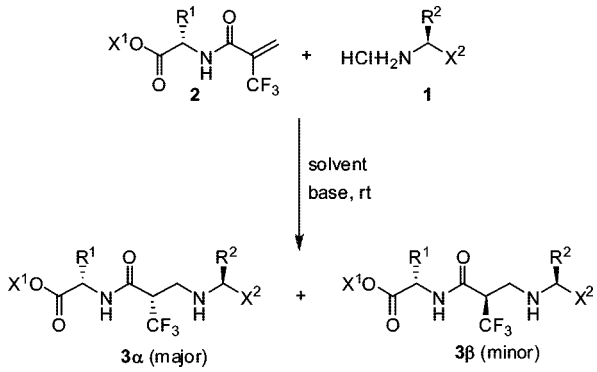
SCHEME 1. Stereoselective Aza-Michael Addition of Nitrogen Nucleophiles 1 to *N*-(α-Trifluoromethyl)acryloyl-α-amino Esters 2

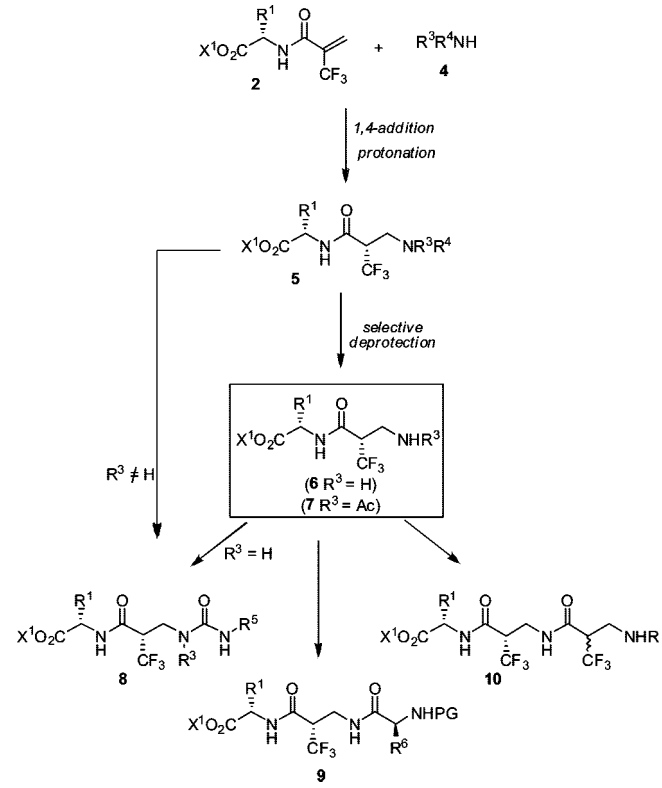


peptide bonds (NH−CO instead of CO−NH). While inverting all the bonds generates retropeptides, reversing one or more (but not all) of the peptide bonds leads to partially modified retropeptides (PMR)[1,4,5] Although retropeptides generally have a higher resistance to hydrolysis than their peptide analogues, there are enzymes that easily hydrolyze the retropeptide bond. One possible approach to avoid proteolytic degradation of both peptide and retropeptide bonds is to replace them with hydrolytically stable groups. Several fluorinated groupings, for example, are able to substitute the peptide bond and remain stable in the presence of hydrolytic enzymes.[5,6]

In previous papers, we have reported on the synthesis of partially modified retro (PMR) $\psi[NHCH_2]$ peptide mimetics containing a chemically stable and stereodefined $CH_2CH(CF_3)CO$ unit that can be considered to be a substitute for a trifluoroalanine.[7] The key step for the synthesis of such compounds is a tandem diastereoselective aza-Michael addition−enolate protonation of nitrogen nucleophiles **1** to *N*-trifluorometacryloyl α-amino esters **2** (Scheme 1). The reaction proceeds with very high diastereoselectivity (up to 42:1), but is highly dependent on various experimental factors such as the type of solvent and base used in the reaction as well as the particular R^1 and R^2 substituents present. The most important factor, however, seems to be the presence of carbonyl groups in both starting materials **1** and **2**. It is important to point out that no reaction is observed unless a trifluoromethyl group is present in the Michael acceptor **2**.

In the present paper, we extend this methodology to the synthesis of a class of related peptidomimetics containing a

SCHEME 2. Synthesis of Peptidomimetics Containing Trifluoroalanine



trifluoroalanine unit. We first obtained peptidomimetics **5** through addition of several different amines **4** to the Michael acceptor **2**.[8] Subsequent deprotection led to the key common intermediate **6**, which can either give rise to acetylated peptidomimetics **7** or react with different substrates to furnish peptidomimetics **8**, which contain a urea moiety, tripeptides **9**, and systems **10**, which contain two units of α-trifluoromethyl-β^2-alanine (Scheme 2).

β-Turns are, together with α-helices and β-sheets, the most important structural elements of peptides and proteins from both structural and functional points of view. These secondary structures play an essential role in globular proteins and are involved in many of the molecular recognition events in biological systems.[9] Therefore, it is important to consider the conformation adopted by a given peptidomimetic. With this in mind, we report herein on several X-ray and NMR studies performed in order to analyze the tendency of these compounds to adopt turn-like conformations both in the solid state and in solution.

Results and Discussion

Addition of Amines 4 to Michael acceptor 2. We began by investigating the effects of different solvents, bases, and temperatures on the diastereoselectivity of the process, employing **2a** and benzylamine **4a** as model systems. The first conclusion we reached was that the reaction is quite simple, efficient, and very fast (30 min) in comparison to other aza-

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SCHEME 3. Synthesis of Peptidomimetics 5

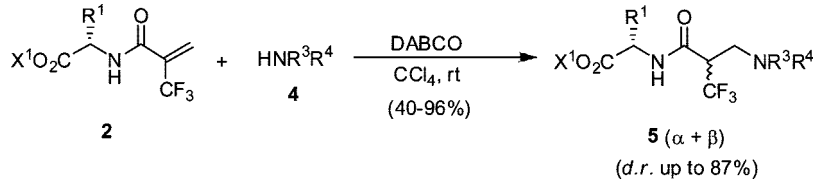


TABLE 1. Aza-Michael Reaction of 2 with Aliphatic Amines 4[a]

entry	2	4	X^1	R^1	R^3	R^4	product	dr (α/β)[b]	yield[c] (%)
1	**2a**	**4a**	Bn	*i*-Pr	Bn	H	**5a**	13:1	87
2[d]	**2b**	**4a**	*t*-Bu	*i*-Pr	Bn	H	**5b**	8:1	95
3	**2a**	**4b**	Bn	*i*-Pr	allyl	H	**5c**	10:1	68
4	**2b**	**4b**	*t*-Bu	*i*-Pr	allyl	H	**5d**	5:1	70
5	**2a**	**4c**	Bn	*i*-Pr	*p*-$FC_6H_4CH_2$	H	**5e**	14:1	69
6	**2a**	**4d**	Bn	*i*-Pr	(*R*)-CH(Me)Ph	H	**5f**	6:1	90
7	**2a**	**4e**	Bn	*i*-Pr	(*S*)-CH(Me)Ph	H	**5g**	10:1	75
8[d]	**2b**	**4e**	*t*-Bu	*i*-Pr	(*S*)-CH(Me)Ph	H	**5h**	8:1	64
9	**2a**	**4f**	Bn	*i*-Pr	*p*-$MeOC_6H_4CH_2$	H	**5i**	10:1	74
10	**2a**	**4g**	Bn	*i*-Pr	Bn	Bn	**5j**	2:1	80
11	**2b**	**4g**	*t*-Bu	*i*-Pr	Bn	Bn	**5k**	2:1	90
12[d]	**2b**	**4h**	*t*-Bu	*i*-Pr	(*S*)-CH(Me)$C_{10}H_7$	H	**5l**	6:1	84
13	**2c**	**4a**	Bn	Bn	Bn	H	**5m**	4:1	80
14	**2d**	**4a**	*t*-Bu	Me	Bn	H	**5n**	5:1	81
15	**2e**	**4a**	*t*-Bu	*i*-Bu	Bn	H	**5o**	7:1	96

[a] The reaction was carried out on a 1 mmol scale. Amine **4** (1 equiv) and DABCO (1 equiv) were added to a solution of the Michael acceptor **2** (1 equiv) in CCl_4 (10 mL) and stirred at rt for 30 min. [b] Determined with the aid of ^{19}F NMR spectroscopic analysis. [c] Overall yield of purified diastereoisomeric mixture. [d] Results taken from ref 7c.

Michael reactions.[10] The best results were obtained when the reaction was performed at room temperature with CCl_4 as a solvent and 1 equiv of DABCO as a base (87% yield and 13:1 dr).[7] To study the scope of the reaction, several different amines **4** were added to Michael acceptors **2** under these optimal conditions (Scheme 3, Table 1).

Unlike the addition of amino esters **1** to Michael acceptors **2**, in which the nature of the X^1 group has no significant influence on the diastereoselectivity of the process,[7a] in this case, the influence of the X^1 group was quite remarkable, being higher when X^1 = Bn than when X^1 = *t*-Bu (entry 1 vs 2, 3 vs 4, and 7 vs 8; Table 1). The R^1 side chain of acceptors **2** also had a marked influence; thus, better stereocontrol was obtained when a bulkier R^1 group was present. This latter trend can be observed by comparing **5a** (R^1 = *i*-Pr, entry 1, Table 1) with **5m** (R^1 = Bn, entry 13, Table 1) or **5b** (R^1 = *i*-Pr, entry 2, Table 1) with **5n** (R^1 = Me, entry 14, Table 1) and **5o** (R^1 = *i*-Bu, entry 15, Table 1). With regard to the effect of the amine structure on the reaction, higher selectivity was obtained with primary amines than with secondary ones; in fact, use of the latter resulted in a dramatic drop in the diastereoselectivity as can be seen, for example, in the comparison between **5a** vs **5j** (entries 1 and 10, Table 1) or between **5b** vs **5k** (entries 2 and 11, Table 1). Moreover, like the aza-Michael addition of α-amino esters to acceptors **2**,[7a] (*S*)-amines produced the products with higher diastereoselectivity (matched pair) than (*R*)-amines (mismatched pair) (entry 7 vs entry 6, Table 1). Finally, substitution at the benzyl group of benzylamines (entries 1, 5, and 9, Table 1) was found to have only a minor effect.

The configuration of the major diastereoisomer **5hα** was determined with the aid of X-ray diffraction analysis while the configurations of the other major diastereoisomers were assigned by means of analogy. Suitable monocrystals of **5hα** were obtained through recrystallization from *n*-hexane; the X-ray diffraction analysis revealed an *S* configuration of the new stereocenter (Figure 1). The crystal consists of two independent molecules in the asymmetric unit, both presenting a β-turn-like secondary structure. The two molecules of the asymmetric unit are related to each other through hydrogen bonds N−H···O=C and N−H···F and connected to the molecules of neighboring asymmetric units by two hydrogen bonds N−H···O=C, thus generating an infinite zigzag chain.[11]

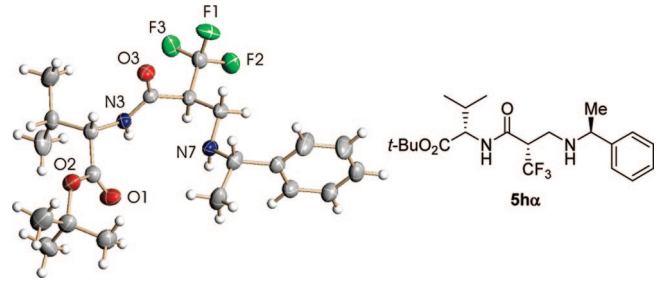
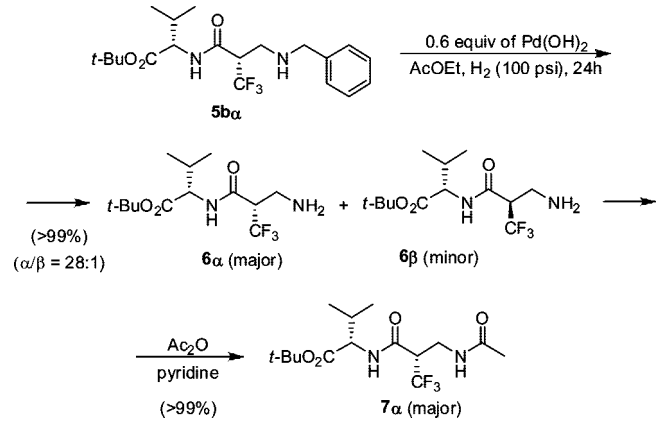


FIGURE 1. X-ray structure of **5hα**.

Deprotection of 5b To Afford Key Intermediate 6. The obvious, most direct way to synthesize the unprotected amine **6** (Scheme 4) is to perform the reaction between Michael acceptors **2** and ammonia. However, when we tried this approach, it failed completely, resulting in the formation of a complex mixture in which products derived from double addition were identified. We therefore decided to undertake the selective deprotection of compounds **5**. Even though the best diastereoselectivities were obtained when X^1 = Bn, we chose **5b** (X^1 = *t*-Bu) for the synthesis of intermediate **6** and,

SCHEME 4. Synthesis of Peptidomimetics 6 and 7



(10) α-Substituted acrylamide acceptors are often unreactive as aza-Michael acceptors. In fact, a substrate similar to compound **2** but with a methyl instead of a trifluoromethyl group is completely unreactive in the kind of addition that we are describing in this paper; only starting material is recovered from the reaction. Therefore, the extraordinary reactivity of adduct **2a** is due to the presence of the electron-withdrawing CF_3 group (see ref 7c). A similar behavior is observed in the case of other aza-Michael reactions with 4-substituted acceptors (see ref 5).

(11) For more details about the packing of the crystal, see the Supporting Information.

consequently, for the different families of peptidomimetics **7**−**10**. The reason for this choice was that it allowed for the selective deprotection of the amine moiety while keeping the carboxylic acid protected. Although this step seemed to be straightforward at first, it turned out to be a complicated reaction. Our initial attempts to carry out the hydrogenolysis of **5** with different catalysts [$Pd(OH)_2$, Pd/C, PtO_2, $PdCl_2$], at different H_2 pressures, and with different solvents and reaction times were thus unsuccessful, resulting in either no reaction or very poor conversions. Finally, using stoichiometric amounts of $Pd(OH)_2$ in AcOEt under atmospheric pressure of H_2, we were able to obtain the deprotected product **6** in quantitative yields (Scheme 4). We managed to reduce the catalyst loading to 0.6 equiv by increasing the H_2 pressure to 100 psi and still obtain a quantitative yield of **6**; however, further efforts to reduce the catalyst loading resulted in a dramatic drop in yield and sometimes in no reaction. Some degree of epimerization (<4%) for the stereocenter containing the CF_3 group was observed. Acetylated dipeptide **7** was easily prepared by treating **6** with Ac_2O in pyridine (Scheme 4). The major diastereoisomer, **7α**, was easily separated with the aid of column chromatography and then employed to confirm the configuration. It was also used in the conformational analyses involving X-ray and NMR techniques (see Figure 2).

Synthesis of Urea-Substituted Peptidomimetics 8. As stated above, various moieties have been used to replace the amide bond in the peptide structure, among them, the urea group.[12] For example, ureas have been included in the structure of some enzymatic inhibitorsD[13] and used to induce a reorganization of the peptide structure through bidimensional turns.[14] The synthesis of PMR $\psi[NHCH_2]$ ureas that contain an α-trifluoromethyl-β^2-alanine **8** can be carried out starting from both secondary amine **5** and primary amine **6**. Indeed, these urea-containing pseudopeptides were obtained in good to excellent yields through reaction with the corresponding isocyanate in dry CH_2Cl_2 at 0 °C in only 30 min (Scheme 5, Table 2).

We also investigated the scope of the reaction, which proceeds efficiently with both primary amines **6** (entries 1−4, Table 2) and secondary amines **5** (entries 5−7, Table 2). A selection of aromatic (entries 1 and 2, Table 2), linear aliphatic (entries 3, 5 and 6, Table 2), and branched aliphatic (entries 4 and 7, Table 2) isocyanates **11** gave the expected products in high yields. It is important to note that this method is also suitable for the use of isocyanates derived from an α-amino ester. In particular, the reaction between **5b** and the isocyanate derived from the *tert*-butyl ester of valine gave the pseudotripeptide **8g** (entry 7, Table 2) in excellent yield. In this way, the direction of the chain of the retropeptide can be restored, and at the same time, the peptide chain can be extended.

SCHEME 5. Preparation of Urea-Containing Peptidomimetics 8

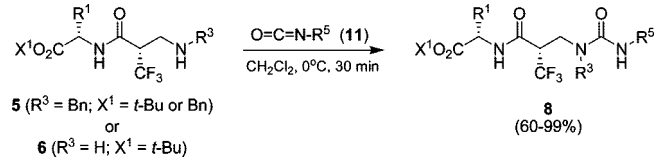


TABLE 2. Synthesis of Urea-Peptidomimetics 8[a]

entry	product	X^1	R^1	R^3	R^5	yield[b] (%)
1	**8a**	*t*-Bu	*i*-Pr	H	*p*-F-C_6H_4	90
2	**8b**	*t*-Bu	*i*-Pr	H	*p*-MeO-C_6H_4	60
3	**8c**	*t*-Bu	*i*-Pr	H	Et	94
4	**8d**	*t*-Bu	*i*-Pr	H	(*R*)-CH(Me)Ph	99
5	**8e**	*t*-Bu	*i*-Pr	Bn	CH_2CO_2Et	85
6	**8f**	Bn	Bn	Bn	Et	95
7	**8g**	*t*-Bu	*i*-Pr	Bn	(*S*)-CH(*i*-Pr)CO_2*t*-Bu	91

[a] When the starting material is **6** (R^3 = H), a mixture of both diastereoisomers α/β (28:1) is employed for the reaction, although, only the major one is shown in Scheme 5. All the ureas obtained as a diastereoisomeric mixture could be separated by flash chromatography. [b] Overall yield of purified diastereoisomeric mixture.

In addition to the synthesis of urea peptidomimetics described above, a symmetric urea peptidomimetic **8h** was prepared starting with **6** and isocyanate **11**. The latter was, in turn, obtained from **6** upon treatment with triphosgene and $NaHCO_3$. The symmetric tetrapeptide was obtained in 69% overall yield in both steps. One noteworthy feature of this synthesis is that **8h** has a C2 axis of symmetry (Scheme 6).

Synthesis of Peptidomimetics 9 and 10. The coupling of *N*-protected α-amino acids and **6** was carried out in the presence of TMP, HATU, and HOAt to give tripeptides **9** in good yields (Scheme 7).[15,16] The chosen α-amino acids were phenylglycine and glycine.

Bis-trifluoromethylated peptidomimetics **10** were obtained in two steps from intermediate **6**. The first step involved the reaction of **6** with (α-trifluoromethyl)acryloyl chloride **12**.[17] This reaction led to a new Michael acceptor **13** in high yield, which was then reacted with the appropriate nitrogen nucleophiles (Scheme 8).

Two different representative nitrogen nucleophiles were chosen for the aza-Michael reaction: an amine (benzylamine) and an α-amino ester (valine *tert*-butyl ester hydrochloride). Thus, the new Michael acceptor **13** was treated with the corresponding nitrogen nucleophile under the same conditions described above for the aza-Michael reaction of **2** with amines (DABCO, CCl_4, rt). The expected products were obtained, but with a dramatic drop in the diastereoselectivity as compared to the equivalent aza-Michael reactions between the same nucleophiles with Michael acceptor **2b** (Nu = NH_2CH_2Ph: 2:1 vs 8:1; Nu = $NH_2CH[CH(CH_3)_2]$-*t*-$BuCO_2$: 4:1 vs 38:1) (Scheme 9). Although this result was somewhat disappointing, it was not completely unexpected since the main cause for asymmetric induction in **2b** (the stereocenter of the amino acid grouping) is more distant from the newly formed stereocenter.[7c]

Secondary Structure of Peptidomimetics Containing a Trifluoroalanine Unit. Structural studies for a series of peptidomimetics containing a trifluoroalanine unit were carried out in order to analyze their backbone secondary structure. The

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(14) (a) Nowick, J. S.; Abdi, M.; Bellamo, K. A.; Love, J. A.; Martínez, E. J.; Noronha, G.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 89–99. (b) Nowick, J. S.; Holmes, D. L.; Macking, G.; Noronha, G.; Shaka, A. J.; Smith, E. M. *J. Am. Chem. Soc.* **1996**, *118*, 1066–1072. (c) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 2764–2765.

(15) A mixture of both diastereoisomers **6α/β** (96:4) is employed for the reaction, although only the major one is shown in Scheme 7.

(16) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266.

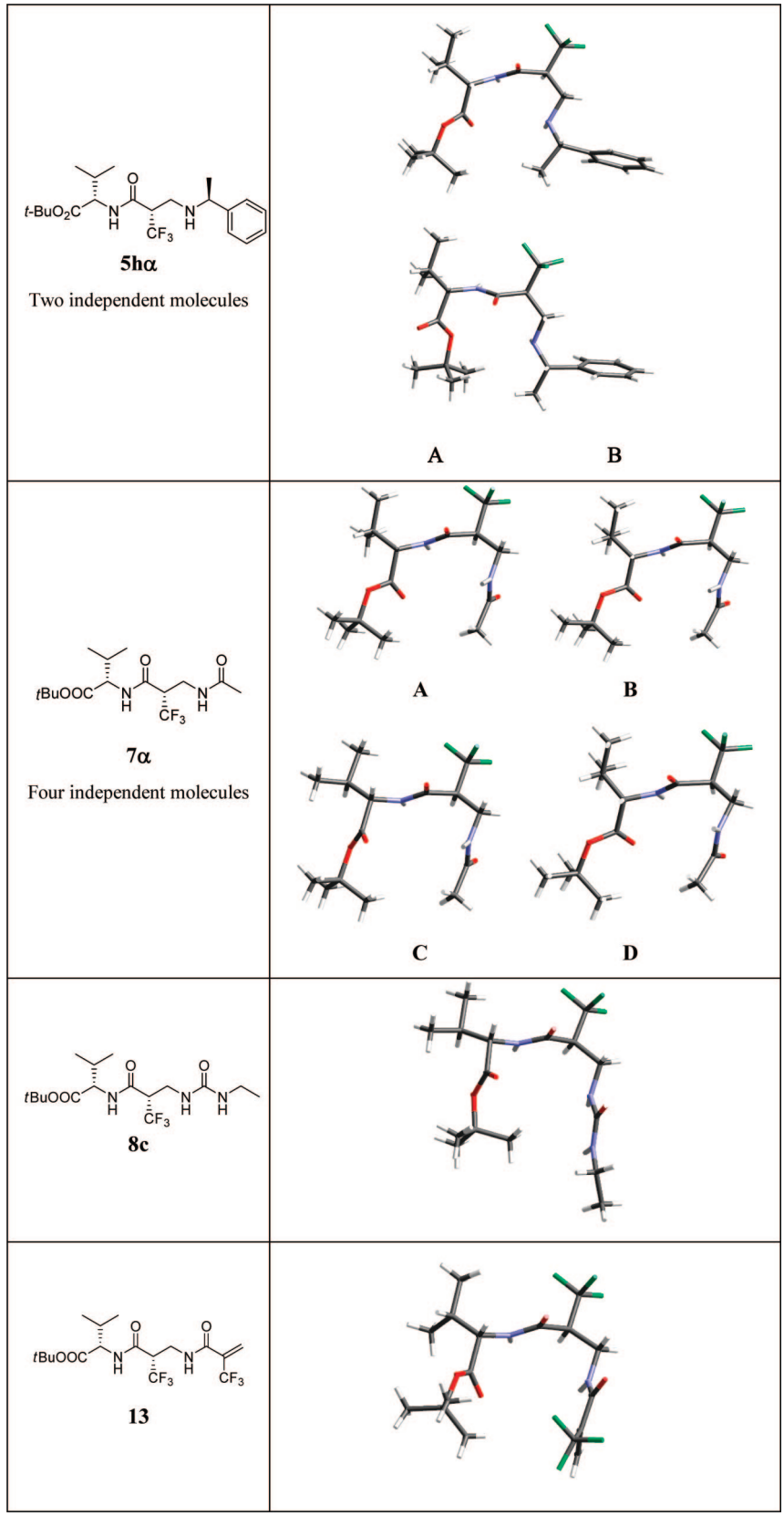
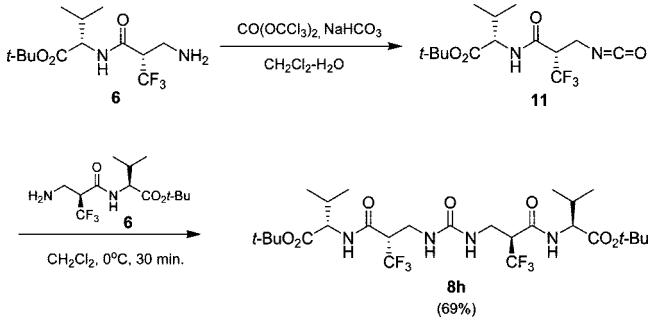


FIGURE 2. X-ray plot of trifluoroalanine-containing peptidomimetic backbone for **5hα**, **7α**, **8c**, and **13** (red oxygen, blue nitrogen, green fluorine, gray carbon, and white hydrogen atoms).

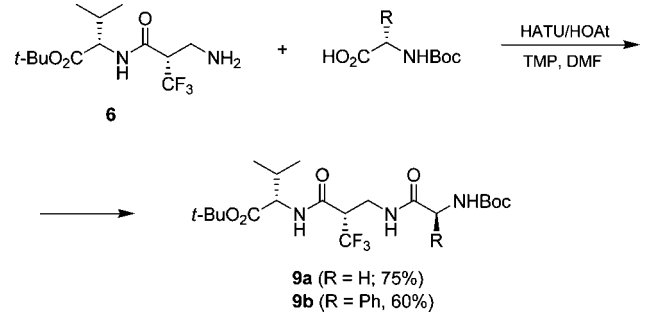
single-crystal X-ray structure of compounds **5hα**, **7α**, **8c**, and **13** were thus determined.[18] The results showed that one (**8c**, **13**), two (**5hα**), and four (**7α**) independent molecules are present in the crystal structure asymmetric unit. The molecular structure for all the independent molecules of compounds **5hα**, **7α**, **8c**, and **13** show a β-turn-like, nine-membered folding pattern,

SCHEME 6. Synthesis of Symmetric Urea-Containing Tetrapeptide 8h[a]

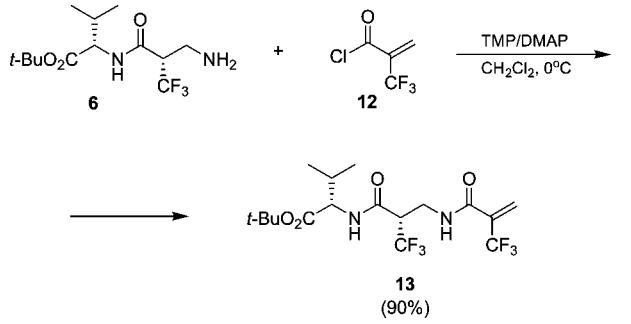


[a] A 28:1 diastereomeric mixture for compound **6** was used as starting material. Compound **8h** consisted of a 26:3:3:1 mixture of diastereomers, only the major of which is shown.

SCHEME 7. Coupling of 6 with *N*-Protected α-Amino Acids



SCHEME 8. Preparation of Michael Acceptor 13

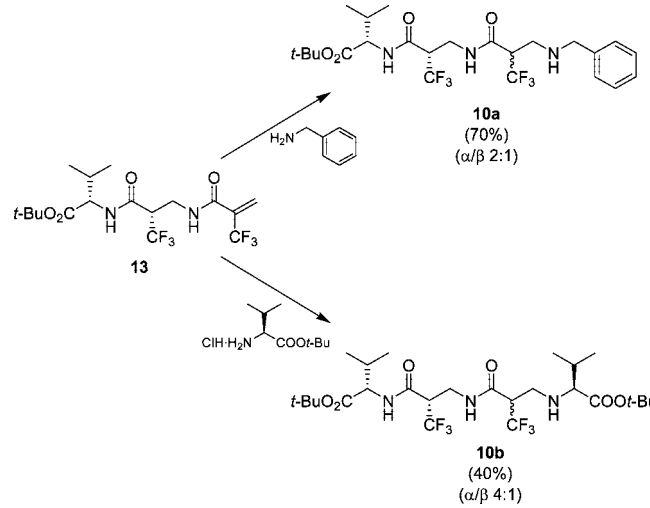


although no intramolecular hydrogen bonding was observed in the crystal structure (Figure 2).

Several examples of related PMR-peptides, such as triamide **14**[19] and PMR ψ[NHCH(CF_3)]Gly peptides **15**,[5] with β-turn-like, nine-membered conformation have been previously reported. These have all been found to have intramolecular N−H···O=C hydrogen bonds in the solid state (Figure 3).

Canonical β-turns are constituted of four amino acid residues and are characterized by a sudden change in the direction of

SCHEME 9. Aza-Michael Addition of Nitrogen Nucleophiles to 13



the peptidic chain. Canonical β-turns involve a 10-membered ring with a hydrogen bond between the backbone CO(i) and the backbone NH(i + 3).[20] The simplest and most abundant β-turns, those of type I and type II, can be characterized by the ϕ and ψ torsion angles of the two residues, i+1 and i+2, in the middle of the turn (Figure 4a).[21] Although β-turns are mostly stabilized by hydrogen bonds, it is not clear that such hydrogen bonds are necessary for the appearance of β-turns.[21b] A distance criterion has been established, according to which the $C_i^{\alpha}-C_{i+3}^{\alpha}$ distance must be shorter than 7 Å.[22] Therefore, typical parameters studied for canonical C10 β-turns are the dihedral angles ϕ_{i+1}, ψ_{i+1}, ϕ_{i+2}, and ψ_{i+2} and the $C_i^{\alpha}-C_{i+3}^{\alpha}$ distance.

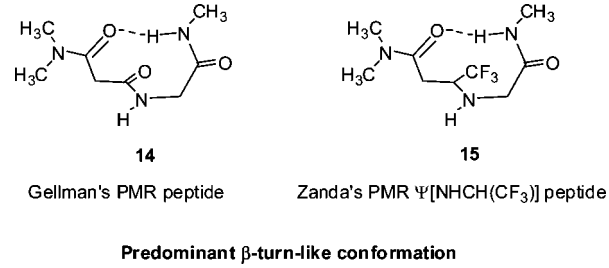


FIGURE 3. Conformation of Gellman's and Zanda's PMR-peptides.

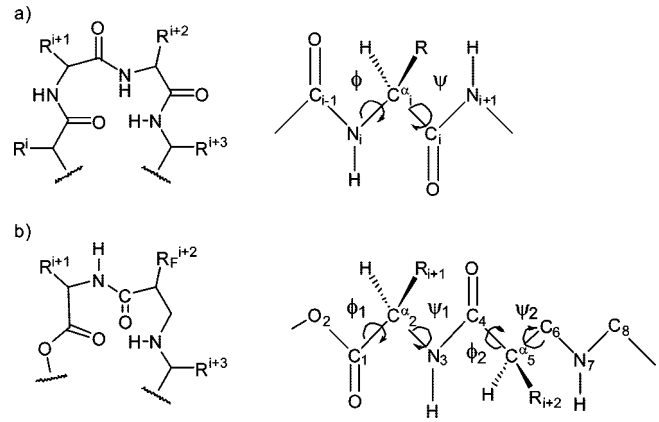


FIGURE 4. (a) C_{10} β-turn motif and typical backbone torsion angles ϕ ($C_{i-1}-N_i-C^{\alpha}{}_i-C_i$) and ψ ($N_i-C^{\alpha}{}_i-C_i-N_{i+1}$) in a simple peptide model. (b) C_9 β-turn-like motif and backbone torsion angles ϕ_1 ($O_2-C_1-C^{\alpha}{}_2-N_3$), ψ_1 ($C_1-C^{\alpha}{}_2-N_3-C_4$), ϕ_2 ($N_3-C_4-C^{\alpha}{}_5-C_6$), and ψ_2 ($C_4-C^{\alpha}{}_5-C_6-N_7$) in trifluoroalanine-containing peptidomimetics.

(17) For the preparation of (α-trifluoromethyl)acryloyl chloride **12**, see: (a) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y.; Taguchi, T.; Iitaka, Y. *J. Org. Chem.* **1991**, *56*, 1718–1725. (b) Yamakazi, T.; Ichige, T.; Takei, S.; Kawashita, S.; Kitazume, T.; Kubota, T. *Org. Lett.* **2001**, *3*, 2915–2918.

(18) For more details about the crystal structure determination, see the Supporting Information.

(19) (a) Gellman, S. H.; Adams, B. R.; Dado, G. P. *J. Am. Chem. Soc.* **1990**, *112*, 460–461. (b) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630–8632. (c) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164–1173. (d) Liang, G.-B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994–3995. (e) Dado, G. P.; Desper, J. M.; Holmgren, S. K.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4834–4843. (f) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228–4245.

TABLE 3. O(2)···C(8) Distance (Å) and ϕ_1 ($O_2-C_1-C^{\alpha}{}_2-N_3$), ψ_1 ($C_1-C^{\alpha}{}_2-N_3-C_4$), ϕ_2 ($N_3-C_4-C^{\alpha}{}_5-C_6$), and ψ_2 ($C_4-C^{\alpha}{}_5-C_6-N_7$) Torsion Angles (deg) for All Independent Molecules of Peptidomimetics 5hα, 7α, 8c, and 13[a]

			torsion angles in residue $i+1$		torsion angles in residue $i+2$	
entry	product	O(2)···C(8) distance	ϕ_1	ψ_1	ϕ_2	ψ_2
1	**5hαA**	5.7014(26)	159.83(15)	−118.84(18)	−114.91(17)	58.45(20)
2	**5hαB**	5.0325(25)	−21.43(22)	−81.73(20)	−138.29(16)	65.34(20)
3	**7αA**	5.6487(56)	164.97(41)	−113.15(46)	−129.74(39)	52.64(45)
4	**7αB**	5.5476(62)	168.12(36)	−120.73(44)	−124.47(40)	45.72(46)
5	**7αC**	5.1404(56)	−81.87(44)	−101.74(47)	−128.99(40)	55.91(44)
6	**7αD**	5.4147(59)	165.69(39)	−131.66(44)	−126.11(41)	38.66(50)
7	**8c**	5.2277(30)	−77.54(22)	−86.94(23)	−128.65(21)	74.50(22)
8	**13**	5.4156(90)	146.57(81)	−109.88(85)	−126.71(65)	58.47(74)

[a] The O(2)···C(8) distance found for all independent molecules of compounds **5hα**, **7α**, **8c**, and **13** is within the 5.03−5.70 Å range. This is in good agreement with a corresponding $C_i^{\alpha}\cdots C_{i+3}^{\alpha}$ distance being shorter than 7 Å, which is the distance criterion for β-turns. The ψ_1, ϕ_2, and ψ_2 torsion angles determined for all the molecules are in the range of -106 ± 25, -127 ± 12, and $52 \pm 13°$, respectively. These values are not within the range defined for type I and type II β-turns for the ϕ and ψ torsion angles of the two residues, $i+1$ and $i+2$, in the middle of the turn [type I: $\phi_{i+1} = -60 \pm 30°$, $\psi_{i+1} = -30 \pm 30°$, $\phi_{i+2} = -90 \pm 30°$, $\psi_{i+2} = 0 \pm 50°$; type II: $\phi_{i+1} = -60 \pm 30°$, $\psi_{i+1} = +120 \pm 30°$, $\phi_{i+2} = +80 \pm 30°$, $\psi_{i+2} = 0 \pm 50°$]. However, the β-turn-like folded peptidomimetic torsion angle sequence $\psi_1 \cdot \phi_2 \cdot \psi_2$ is similar to a retro-inverso type II β-turn torsion angle sequence $(-\phi_{i+2}) \cdot (-\psi_{i+>1}) \cdot (-\phi_{i+1})$. The values found for the ϕ_1 torsion angle [$157 \pm 11°$ (**5hα**A, **7α**A, **7α**B, **7α**D), $-80 \pm 3°$ (**7α**C, **8c**), and -21.5 ± 0.1 (**5hα**B)] do not fit in a retro-inverso type II torsion angle sequence. Since the ϕ_1 torsion angle is not involved in the 9-membered, β-turn-like conformation present in compounds **5hα**, **7α**, **8c**, and **13**, it will therefore not be expected to correspond to the $(-\Psi_{i+2})$ torsion angle present in a C_{10} β-turn.

TABLE 4. Hydrogen Bond Lengths (Å) and Angles (deg) for Trifluoroalanine-Containing Peptidomimetics 5hα, 7α, 8c, and 13

compd		X···Y	H···Y	X−H···Y
5hα	N7A−H7A···F	3.749(2)	2.907(18)	168(2)
	N7−H7···O1A[i]	3.152(2)	2.288(17)	172(2)
7α	N7A−H7A···O3D	2.874(5)	2.07(2)	168(5)
	N7B−H7B···O1C	3.067(5)	2.25(2)	171(5)
	N7C−H7C···O3B	2.928(5)	2.13(2)	173(5)
	N7D−H7D···O3A	2.833(5)	2.10(3)	150(5)
8c	N7−H7···O3[i]	2.989(3)	2.25(2)	147(2)
	N7−H7···O1[i]	3.124(3)	2.58(2)	124(2)
13	N7−H7···O2[i]	2.831(7)	2.33(6)	150(9)

[a] Symmetry operators: **5hα** (i: $x-1, y, z$), **7α** (i: $x-1, y, z$; ii: $x+1, y, z$), **8c** (i: $-x+1, y+{}^1/_2, -z$), 13 (i: $-x+2, y+{}^1/_2, -z+2$).

The corresponding torsion angles of the two residues $i+1$ and $i+2$ for the analysis of the β-turn-like nine-membered folding pattern found for the backbone of compounds **5hα**, **7α**, **8c**, and **13** are ϕ_1 ($O_2-C_1-C^{\alpha}{}_2-N_3$), ψ_1 ($C_1-C^{\alpha}{}_2-N_3-C_4$), ϕ_2 ($N_3-C_4-C^{\alpha}{}_5-C_6$), and ψ_2 ($C_4-C^{\alpha}{}_5-C_6-N_7$) (Figure 4b). The O(2)···C(8) distance would correspond to the $C_i^{\alpha}\cdots C_{i+3}^{\alpha}$ distance if we take into account that in the reported peptidomimetics, O(2) corresponds to C_i^{α} in a typical peptidic sequence (Figure 4b). These parameters have all been determined from single-crystal X-ray diffraction data (Table 3).

In all the crystal structures reported, the N(7)−H moiety is involved in the 3D intermolecular hydrogen bonding network rather than in an intramolecular N−H···O=C hydrogen bond (Table 4). The hydrogen bonding scheme for the four independent molecules of compound **7α** is shown in Figure 5. This means that the β-turn-like conformation found in all the independent molecular structures of **5hα**, **7α**, **8c**, and **13** is inherent to the peptidomimetic backbone primary structure and does not depend on the intramolecular hydrogen bond formation.

Compound **7α** was selected to confirm the conformation of these new peptidomimetics in solution. The temperature dependence of NMR chemical shifts for amide protons that do not form strong hydrogen bonds with a given solvent, e.g., $CDCl_3$, provide valuable information about the formation of hydrogen bonds.[23] Peptide NH protons that either have no hydrogen bonds or are strongly hydrogen bonded exhibit little temperature dependence ($\Delta\delta/\Delta T \leq 2.6$) while protons in equilibrium between hydrogen-bonded and non hydrogen-bonded states display a high temperature dependence ($\Delta\delta/\Delta T \geq 2.6$).[24] We thus performed ^{1}H NMR ($CDCl_3$) experiments using a 3 mM solution of **7α** at different temperatures. The notably high $\Delta\delta/\Delta T$ value for both H_a and H_b protons (8.39 and 21.60, respectively) indicate that they are in equilibrium between hydrogen-bonded and non-hydrogen-bonded states (Figure 6). To determine whether the hydrogen-bonded state was due to an intra- or intermolecular interaction, ^{1}H NMR analysis of **7α** under concentrated conditions (300 mM) was carried out.

For both H_a and H_b, the chemical shift moved downfield with the variation being quite remarkable (0.49 ppm and 1.13 ppm, respectively), a result that indicates that intermolecular hydrogen bonds are involved. This variation in chemical shifts to downfield regions for the concentrated samples as compared to the diluted ones was observed for all the temperature ranges studied. The $\Delta\delta/\Delta T$ value for both H_a and H_b protons was very high at this concentration (12.50 and 18.75, respectively), confirming the equilibrium between the two states (Figure 6).

Finally, in order to discard the possibility of intramolecular interactions and thereby confirm the existence of the intermolecular hydrogen bonds, the chemical shift of protons H_a and H_b upon the addition of MeOD, a competitive solvent for hydrogen bond formation, was measured (Figure 7). Amide protons with intramolecular hydrogen bonds exchange much more slowly with the solvent than those with intermolecular hydrogen bonds and thus the chemical shift should not change significantly in the former case. The considerable increase of

(20) For some leading references, see, for example: (a) Sibanda, B. L.; Thornton, J. M. *Nature* **1985**, *316*, 170–174. (b) Wilmot, C. M.; Thornton, J. M. *J. Mol. Biol.* **1988**, *203*, 221–232. (c) Sibanda, B. L.; Thornton, J. M. *J. Mol. Biol.* **1993**, *229*, 428–447. (d) Mattos, C.; Petsko, G. A.; Karplus, M. *J. Mol. Biol.* **1994**, *238*, 733–747. (e) Gunasekaran, K.; Ramakrishnan, C.; Balaram, P. *Protein Eng.* **1997**, *10*, 1131–1141. (f) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806–1816.

(21) See, for example: (a) Rai, R.; Vasudev, P. G.; Ananda, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem.—Eur. J.* **2007**, *13*, 5917. (b) Czinki, E.; Császár, A. G.; Perczel, A. *Chem.—Eur. J.* **2003**, *9*, 1182. (c) Wipf, P.; Henninger, T. C.; Gelb, S. J. *J. Org. Chem.* **1998**, *63*, 6088.

(22) (a) Levitt, M. *J. Mol. Biol.* **1976**, *104*, 59. (b) Chou, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1993**, *229*, 428–447.

(23) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 389–400.

(24) $\Delta\delta/\Delta T$ values are given in ppb/K.

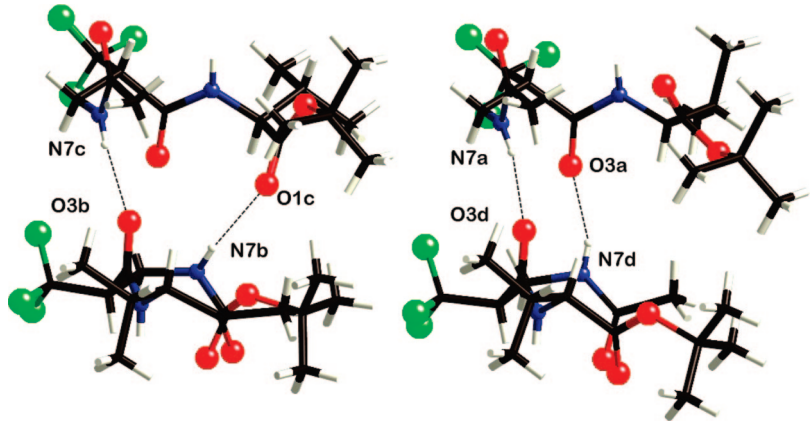
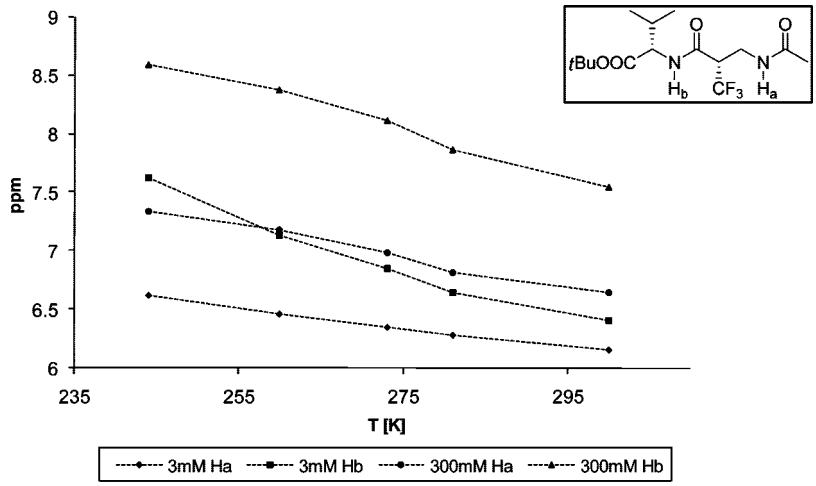


FIGURE 5. Hydrogen-bonding scheme for the four independent molecules of compound **7α**.



	$\Delta\delta NH_a/\Delta T$	$\Delta\delta NH_b/\Delta T$
3mM	8.39	21.60
300mM	12.5	18.7

FIGURE 6. Temperature dependence of amide protons NH_a and NH_b of **7α** at concentrations of 3 mM and 300 mM.

the chemical shift values found in the ^1H NMR experiments upon the successive addition of MeOD thus implies the absence of intramolecular hydrogen bonds.

Taken together, these results suggest the formation of intermolecular hydrogen bonds for **7α**. These results are in complete agreement with the X-ray diffraction analysis of the compound's crystal structure, in which further evidence of these intermolecular hydrogen bonds can be found (see Table 4).

Conclusion

In this paper, we have described the synthesis of several families of α-trifluoromethyl-β^2-alanine unit-containing peptidomimetics. First, the synthesis of peptidomimetics **5** by means of a stereoselective aza-Michael addition of amines to the fluorinated Michael acceptor **2** proceeds very efficiently in comparison with other similar reactions; in fact, similar substrates without a trifluoromethyl group do not react at all under the conditions used here. Hydrogenolysis of *N*-benzyl-protected amine **5b** gives *N*-free peptidomimetic **6**, which was then used as an intermediate for the synthesis of other peptidomimetics: PMR $\psi[NHCH_2]$ urea peptides containing an α-trifluoromethyl-β^2-alanine **8**, PMR $\psi[NHCH_2]$ tripeptides containing an α-trifluoromethyl-β^2-alanine **9**, and PMR $\psi[NHCH_2]$ containing two α-trifluoromethyl-β^2-alanine units **10**.

The backbone conformation for some selected trifluoroalanine-containing peptidomimetics has been analyzed through single-crystal X-ray diffraction and NMR techniques. It was observed that trifluoroalanine-containing PMR $\psi[NHCH_2]$ peptides provide a preorganized β-turn-like conformation backbone even though no intramolecular hydrogen bonding was observed in either solid state or solution. This type of peptidomimetics could thus be used to induce β-turn-like conformations and to promote β-hairpin formation.

Experimental Section

General Method. The reactions were carried out under nitrogen atmosphere unless otherwise indicated. The solvents were purified prior to use: CH_2Cl_2 and CCl_4 were distilled from calcium hydride. Benzylamine was distilled before use. All reagents were used as received unless otherwise stated. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm E. Merk precoated silica gel plates. Visualization was carried out with UV light, aqueous ceric ammonium molybdate solution, or potassium permanganate stain. Flash column chromatography was performed

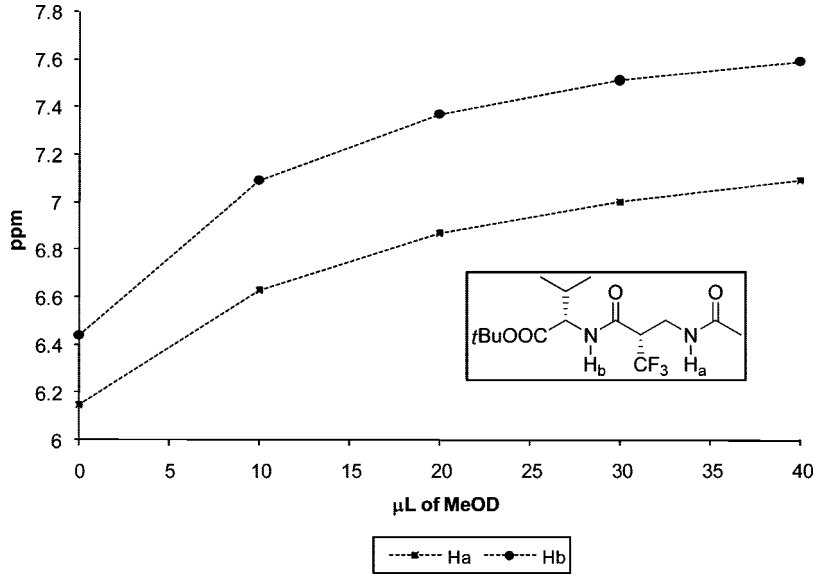


FIGURE 7. Chemical shift dependence of amide protons NH_a and NH_b of **7α** upon addition of MeOD.

with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). Melting points were measured with a "Cambridge Instrument" apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 300 MHz Bruker and 400 MHz Bruker Advance spectrometers. Chemical shifts (δ) are given in ppm. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. High-resolution mass spectra measurements were carried out on a VGmAutospec instrument (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service.

General Procedure for the Synthesis of Peptidomimetics 5. Amine **4** (0.2 mmol) was added to a solution of Michael acceptor **2** (0.2 mmol) and DABCO (0.2 mmol) in CCl_4 (4 mL) at 0 °C. The reaction mixture was stirred at this temperature until TLC revealed total consumption of the starting material (30 min). The solvent was removed under vacuum, yielding a diastereoisomeric mixture of **5α/5*β***. Major diastereoisomer **5α** was separated in most cases by means of flash chromatography (*n*-hexane/ethyl acetate) on deactivated silica gel (2% Et_3N in *n*-hexane) and later, when necessary, washed with *n*-hexane to yield a white solid.

(*S*)-*tert*-Butyl 2-(*S*+*R*)-[2-(allylaminomethyl)-3,3,3-trifluoropropanamido]-3-methylbutanoate (5bα/5b*β*). Total yield 95%. Major diastereoisomer **5bα**: mp 94−96 °C; $[\alpha]^{25}_D = +1.9$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H), 1.39 (s, 9H), 2.08−2.18 (m, 1H), 2.41 (br, 1H), 2.92−2.98 (m, 1H), 3.14−3.23 (m, 2H), 3.74−3.83 (m, 2H), 4.39 (dd, $J_1 = 8.4$ Hz; $J_2 = 4.3$ Hz; 1H), 7.22−7.27 (m, 5H), 7.55 ppm (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.5 (CH_3), 18.9 (CH_3), 27.9 (CH_3), 31.1 (CH), 45.0 (C_q, ^3J(C,F) = 2.8 Hz), 50.5 (C_q, ^2J(C,F) = 25.2 Hz), 53.9 (CH_2), 57.8 (CH), 82.1 (C), 124.6 (C_q, ^1J(C,F) = 280.0 Hz), 127.4 (CH), 128.1 (CH), 128.5 (CH), 138.7 (C), 165.5 (C_q, ^3J(C,F) = 2.2 Hz), 170.0 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -66.7$ ppm (d, J(H,F) = 9.2 Hz, 3F); HRMS *m*/*z* calcd for $C_{20}H_{29}F_3N_2O_5$ 402.2130, found 402.2218 $[M]^+$.

Synthesis of the Intermediate 6: (*S*)-*tert*-Butyl 2-[2-(Aminomethyl)-3,3,3-trifluoropropanamido]-3-methylbutanoate (6). Pearlman catalyst $Pd(OH)_2$ (60%) was added to a solution of **5b** (0.7 mmol) in AcOEt (30 mL). This mixture was stirred for 24 h under H_2 atmosphere (100 psi) and then was filtered through Celite. The solvent was removed under vacuum to obtain a diastereoisomeric mixture **6α/6*β*** (28:1). Total yield >99%. Data were taken from the 28:1 mixture. Major diastereoisomer **6α**: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.86$ (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 1.40 (s, 9H), 2.09−2.20 (m, 1H), 2.64 (br, 2H), 3.07−3.10 (m, 1H), 3.17−3.30 (m, 2H), 4.40 (dd, $J_1 = 8.2$ Hz; $J_2 = 4.5$ Hz; 1H), 7.53 ppm (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 16.4 (CH_3), 17.9 (CH_3), 26.9 (CH_3), 29.9 (CH), 37.2 (C_q, ^3J(C,F) = 2.3 Hz), 51.1 (C_q, ^2J(C,F) = 25.3 Hz), 57.0 (CH), 81.3 (C), 123.5 (C_q, ^1J(C,*F* = 280.5 Hz), 164.6 (C_q, ^3J(C,F) = 2.3 Hz), 170.0 (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -66.8$ ppm (d, J(H,F) = 8.2 Hz, 3F); HRMS *m*/*z* calcd for $C_{13}H_{23}F_3N_2O_3$ 312.1660, found 312.1619 $[M]^+$.

Synthesis of 7: (2*S*)-2-[(2*S*)-2-(Acetylaminomethyl)-3,3,3-trifluoropropanamido]-3-methylbutanoate (7). Acetic anhydride (2.14 mmol, 0.2 mL) and pyridine (2.14 mmol, 0.17 mL) were added to a solution of **6** (0.54 mmol, 0.169 mg) in CH_2Cl_2 (12 mL) and stirred at room temperature for 12 h. The reaction mixture was quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, and the solvents were removed under reduced pressure to obtain a white solid, which was then purified by recrystallization. Yield >99%. Major diastereoisomer **7α**: mp 202−204 °C; $[\alpha]^{25}_D = +101.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.85$ (d, $J = 6.9$, 3H), 0.89 (d, J = 6.8, 3H), 1.40 (s, 9H), 1.91 (s, 3H), 2.12−2.20 (m, 1H), 3.34−3.55 (m, 2H), 3.83−3.91 (m, 1H), 4.37 (dd, $J_1 = 8.3$, J_2 = 4.5, 1H), 6.31 (sa, 1H), 6.92 (d, $J = 8.3$, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 17.4$ (CH_3), 18.9 (CH_3), 22.9 (CH_3), 27.9 (CH), 30.5 (CH_3), 36.3 (C_q, $^3J_{CF} = 3.5$), 49.5 (C_q, $^2J_{CF} = 26.4$), 58.2 (CH), 82.1 (C), 124.0 (C_q, $^1J_{CF} = 266.8$), 165.8 (C_q, $^3J_{CF} = 1.7$), 170.9 (C), 171.2 (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -67.5$ ppm (d, J(H,F) = 7.2 Hz, 3F); HRMS *m*/*z* calcd for $C_{15}H_{25}F_3N_2O_4 \cdot HCl$ 355.1844, found 355.1812 $[M]^+$.

General Procedure for the Synthesis of Isocyanates 11g and 11h.[25] A saturated solution of $NaHCO_3$ (5 mL) and a solution of triphosgene (0.32 mmol) in CH_2Cl_2 (1 mL) were added to a solution of the *tert*-butyl ester of valine (0.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the isocyanate was formed (20 min), the organic layer of the reaction was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvents were removed under reduced pressure to yield the crude product, which was employed in the next reaction with no further purification.

General Procedure for the Synthesis of Urea-Substituted Peptidomimetics 8. Isocyanate **11** (0.54 mmol) was added to a solution of **6** (0.54 mmol) in CH_2Cl_2 (3 mL) under N_2 atmosphere. The reaction mixture was stirred until TLC revealed total consumption

of the starting material (30 min). The solvent was removed under vacuum to yield a diastereoisomeric mixture of **8α/8*β***. Major diastereoisomer **8α** was separated through purification with the aid of recrystallization or flash chromatography on silica gel as stationary phase.

(*S*)-*tert*-Butyl 2-(*S*+*R*)-2-[(3-Ethylureidomethyl)-3,3,3-trifluoropropanamido]-3-methylbutanoate (8c). Total yield 94%. Major diastereoisomer **8cα**: mp 204−206 °C; $[\alpha]^{25}_D = +53.5$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, CD_3COCD_3) $\delta = 0.95$ (d, $J = 4.6$, 3H), 0.97 (d, $J = 4.6$, 3H), 1.06 (t, $J = 7.3$, 3H), 1.47 (s, 9H), 2.14−2.22 (m, 1H), 3.11−3.19 (m, 2H), 3.42−3.49 (m, 1H), 3.64−3.76 (m, 2H), 4.36 (dd, $J_1 = 6.6$, $J_2 = 5.4$, 1H), 5.60 (br, 1H), 5.71 (br, 1H), 8.00 ppm (br, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) $\delta = 15.8$ (CH_3), 17.8 (CH_3), 19.3 (CH_3), 28.1 (CH_3), 31.6 (CH), 35.3 (CH_2), 37.8 (C_q, ^3J(C,F) = 1.8 Hz), 50.1 (C_q, ^2J(C,F) = 23.7 Hz), 58.9 (CH), 81.9 (C), 125.9 (C_q, ^1J(C,F) = 277.8 Hz), 166.2 (C), 166.2 (C_q, ^3J(C,F) = 3.0 Hz), 171.3 (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -67.4$ ppm (d, J (H,F) = 8.2 Hz, 3F); HRMS *m*/*z* calcd for $C_{16}H_{28}F_3N_3O_4$ 383.2031, found 383.2082 $[M]^+$.

General Procedure for the Synthesis of Peptidomimetics 9. *sym*-Collidine (1.10 mmol), HOAt (0.22 mmol), and HATU (0.22 mmol) were added to a solution of **6** (0.22 mmol) and the corresponding *N*-protected α-amino acid (0.28 mmol) in anhydrous DMF (2.5 mL). The reaction mixture was stirred overnight, quenched with HCl 1 N (6 mL), and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, and then the solvents were removed under reduced pressure to obtain a diastereoisomeric mixture of **9α/9*β***. The crude reaction mixture was subjected to flash chromatography (*n*-hexane/ethyl acetate 6:1) to afford the major diastereoisomer **9α.**

[6*S*,10(*S*+*R*),13*S*)-*tert*-Butyl 13-Isopropyl-2,2-dimethyl-4,7,11-trioxo-6-phenyl-10-(trifluoromethyl)-3-oxa-5,8,12-triazatetradecan-14-oate (9b). Total yield 60%. Major diastereoisomer **9bα** obtained as a white solid: mp 174−177 °C; $[\alpha]^{25}_D = +100.9$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.90$ (d, $J = 6.0$ Hz, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 1.36 (br, 9H), 1.44 (s, 9H), 2.09−2.22 (m, 1H), 3.14−3.20 (m, 2H), 4.01−4.06 (m, 1H), 4.32 (dd, $J_1 = 8.3$ Hz, $J_2 = 5.5$ Hz, 1H), 5.0 (d, $J = 6.2$ Hz, 1H), 5.45 (d, $J = 4.9$ Hz, 1H), 7.13−7.15 (m, 2H), 7.26−7.34 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 18.1$ (CH_3), 19.1 (CH_3), 28.0 (CH_3), 28.2 (CH_3), 29.7 (CH), 37.2 (CH_2), 49.8 (C_q, ^2J(C,F) = 27.2 Hz), 59.1 (CH), 59.4 (CH), 80.5 (C), 82.7 (C), 123.7 (C_q, ^1J(C,F) = 280.0 Hz), 127.4 (CH), 129.0 (CH), 129.3 (CH), 136.1 (C), 155.7 (C), 166.7 (C), 171.5 (C), 172.4 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -67.6$ ppm (d, J(H,F) = 6.1 Hz, 3F); HRMS *m*/*z* calcd for $C_{26}H_{38}F_3N_3O_6$ 546.2790, found 546.2872 $[M + 1]^+$.

Synthesis of Michael Acceptor 13: (*S*)-*tert*-Butyl 3-Methyl-2-(*S*+*R*)-3,3,3-trifluoro-2-[(2-(trifluoromethyl)acrylamido)methyl]propanamido butanoate (13). To a solution of **6** (0.72 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere at 0 °C were added *sym*-collidine (1.44 mmol) and a solution of (α-trifluoromethyl)acryloyl chloride **12** (1.44 mmol) in CH_2Cl_2 (5 mL) followed by a catalytic amount of DMAP. The reaction mixture was stirred until TLC revealed total consumption of the starting material (2 h). The reaction was quenched with NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with HCl 1 M (3 × 10 mL) and dried over anhydrous sodium sulfate, and the solvent was then removed under reduced pressure to obtain the crude product. Purification through flash chromatography (*n*-hexane/ethyl acetate 8:1) afforded the pure product **13** as a white solid: yield 90%; mp 185−189 °C; $[\alpha]^{25}_D = +71.4$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.82$ (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 1.39 (s, 9H), 2.08−2.18 (m, 1H), 3.34−3.47 (m, 1H), 3.63−3.72 (m, 1H), 3.84−3.92 (m, 1H), 4.39 (dd, $J_1 = 8.7$ Hz, $J_2 = 4.5$ Hz, 1H), 6.17 (q, $J_{HF} = 1.14$ Hz, 1H), 6.35 (q, $J = 8.5$ Hz, 1H), 6.43 (q, $J_{HF} = 1.5$ Hz, 1H), 6.71 ppm (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ =17.2 (CH_3), 18.7 (CH_3), 27.9 (CH_3), 30.9 (CH), 36.3 (C_q, ^3J(C,F) = 2.9 Hz), 49.3 (C_q, ^2J(C,F) = 26.4 Hz), 57.9 (CH), 82.5 (C), 121.8 (C_q, ^1J(C,F) = 272.5 Hz), 123.9 (C_q, ^1J(C,F) = 280.5 Hz), 129.0 (C_q, ^3J(C,F) = 5.2 Hz), 133.7 (C_q, ^2J(C,F) = 31.0 Hz), 161.5 (C), 164.7 (C_q, ^3J(C,F) = 2.3 Hz), 170.4 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -64.6$ (s, 3F), −67.1 (d, J(H,F) = 9.3 Hz, 3F); HRMS *m*/*z* calcd for $C_{17}H_{24}F_6N_2O_4$ 435.1718, found 435.1799 $[M + 1]^+$.

General Procedure for the Synthesis of Bis-trifluoromethylated Peptidomimetics 10. To a solution of **13** (0.10 mmol) in CCl_4 (3 mL) under nitrogen atmosphere at 0 °C were added DABCO (0.10 mmol) and then the nitrogenated nucleophile (0.10 mmol). The reaction mixture was stirred until TLC revealed total consumption of the starting material (2 h). The solvent was then removed under vacuum. The crude reaction mixture was subjected to flash chromatography (*n*-hexane/ethyl acetate 6:1) to obtain the product as a diastereomeric mixture (**10α/10*β***).

(*S*)-*tert*-Butyl 2-{(*S*)-2-[(*S*+*R*)-2-(benzylaminomethyl)-3,3,3-trifluoropropanamidomethyl]-3,3,3-trifluoropropanamido}-3-methylbutanoate (10a). The mixture of **10aα/10a*β*** 2:1 was not separable by FC: total yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.80$ (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 1.38 (s, 9H), 1.59 (br, 1H), 2.06−2.14 (m, 1H), 2.85−2.90 (m, 1H), 2.95−3.05 (m, 1H), 3.08−3.16 (m, 1H), 3.29−3.38 (m, 1H), 3.46−3.56 (m, 1H), 3.69−3.71 (m, 2H), 3.82−3.89 (m, 1H), 4.36 (dd, $J_1 = 8.5$ Hz, $J_2 = 4.6$ Hz, 1H), 6.36 (d, $J = 8.5$ Hz, 1H), 7.19−7.30 (m, 5H), 7.95 ppm (t, $J = 5.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 17.4$ (CH_3), 18.8 (CH_3), 27.9 (CH_3), 30.9 (CH), 36.1 (C_q, ^3J(C,F) = 2.9 Hz); 44.6 (CH_2); 49.7 (C_q, ^2J(C,F) = 25.8 Hz); 50.2 (C_q, ^2J(C,F) = 25.3 Hz), 53.6 (CH_2), 58.0 (CH), 82.5 (C), 123.9 (C_q, ^1J(C,F) = 280.5 Hz), 124.5 (C_q, ^1J(C,F) = 271.3 Hz), 127.5 (CH), 128.1 (CH), 128.6 (CH), 138.7 (C), 165.0 (C_q, ^3J(C,F) = 2.3), 166.3 (C_q, $^3J_{CF}$ = 2.3 Hz), 170.9 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta = -66.7$ (d, J(H,F) = 8.6 Hz, 3F), −67.4 ppm (d, J(H,F) = 7.8 Hz, 3F); HRMS *m*/*z* calcd for $C_{24}H_{33}F_6N_3O_4$ 542.2453, found 542.2471 $[M + 1]^+$.

Single-Crystal X-ray Diffraction. Crystals were grown by means of slow evaporation of *n*-hexane (**5hα**), *n*-hexane/$CHCl_3$ (**7α**), acetone (**8c**), or *n*-hexane/CH_2Cl_2 (**13**) solutions. Crystals suitable for X-ray diffraction were measured at 100(2) K (**13**) or 150(2) K (**5hα**, **7α**, and **8c**) on a Nonius-Kappa CCD diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) and a ω scan mode. Crystal structures were solved with direct methods, and all non-hydrogen atoms were refined anisotropically on F^2 (program SHELXL-97).[26] The hydrogen atoms of the NH groups were located in a difference Fourier synthesis and refined with restrained N−H bond lengths. The methyl groups for compounds **5hα**, **7α**, and **8c** were refined as *rigid*. Other hydrogen atoms were included using a *riding* model. For compound **13**, the *t*-Bu group is disordered over two positions; the disordered atoms were refined isotropically. The absolute structure could not be determined by means of anomalous dispersion effects.[27] The programs use neutral atom scattering factors, $\Delta f'$ and $\Delta f''$, and absorption coefficients from *International Tables for Crystallography*.[28] **Crystal data for compound 5hα:** colorless prism, 0.45 × 0.20 × 0.16 mm size, orthorhombic, $P2_12_12_1$, $a = 9.668(19)$ Å, $b = 20.336(4)$ Å, $c = 23.189(5)$ Å, $V = 4559.4(16)$ Å^3, $Z = 8$, $D_c = 1.213$ g cm^{-3}, $2\theta_{max} = 54.96°$, 34939 reflections collected of which 5747 were independent ($R_{int} = 0.045$), 547 refined parameters, $R_1[I > 2\sigma(I)] = 0.0345$, wR_2(all data) = 0.0789. **Crystal data for compound 7α:** colorless prism, 0.36 × 0.12 × 0.04 mm size, triclinic, $P1$, $a = 9.5958(19)$ Å, $b = 12.452(3)$ Å, $c = 15.882(3)$ Å, $\alpha = 90.36(3)$, $\beta = 92.27(3)$, $\gamma = 98.29(3)°$, $V = 1876.2(7)$ Å^3, $Z = 4$, $D_c = 1.255$ g cm^{-3}, $2\theta_{max} = 55.76°$, 8912 reflections collected of which 4747 were independent ($R_{int} = 0.094$), 913 refined parameters, $R_1[I > 2\sigma(I)] = 0.0648$, wR_2(all data) = 0.1325. **Crystal data for**

(25) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S. L. *J. Org. Chem.* **1996**, *61*, 3929–3934.
(26) *SHELXL-97*: Sheldrick, G. M., University of Göttingen: Germany, 1997.
(27) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.

compound 8c: colorless lath, 0.45 × 0.09 × 0.03 mm size, monoclinic, $P2_1$, $a = 10.503(2)$ Å, $b = 9.1652(18)$ Å, $c = 10.804(2)$ Å, $\beta = 92.64(3)°$, $V = 1038(4)$ Å3, $Z = 2$, $D_c = 1.226$ gcm^{-3}, $2\theta_{max} = 52.74°$, 7646 reflections collected of which 4230 were independent ($R_{int} = 0.059$), 253 refined parameters, $R_1[I > 2\sigma(I)] = 0.0440$, wR_2(all data) = 0.0904. **Crystal data for compound 13:** colorless spike, 0.58 × 0.12 × 0.08 mm size, monoclinic, $P2_1$, $a = 10.504(2)$ Å, $b = 9.4224(19)$ Å, $c = 11.523(2)$ Å, $\beta = 110.52(3)°$, $V = 1068.1(4)$ Å^3, $Z = 2$, $D_c = 1.351$ g cm^{-3}, $2\theta_{max} = 52.74°$, 4203 reflections collected of which 2297 were independent ($R_{int} = 0.040$), 278 refined parameters, $R_1[I > 2\sigma(I)] = 0.0802$, wR_2(all data) = 0.2420.

CCDC-706798 and CCDC-706801 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(28) *International Tables for Crystallography*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C, Tables 6.1.1.4 (pp 500−502), 4.2.6.8 (pp 219−222), and 4.2.4.2 (pp 193−199).

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds. Details about the packing of the crystal structure of compounds **5hα**, **7α**, **8c**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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