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The Passerini Reaction with CF_3-Carbonyl Compounds – Multicomponent Approach to Trifluoromethyl Depsipeptides

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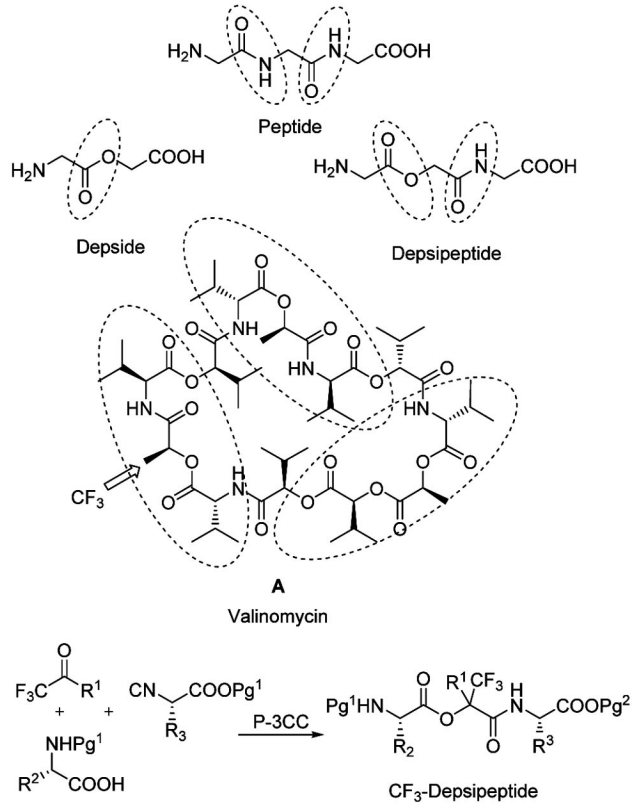
The first detailed investigation of the Paserini reaction with CF_3-carbonyl compounds is reported. The reaction provides a new approach to trifluorolactic acid derivatives and CF_3-substituted depsipeptides. The method is promising for the synthesis of chiral trifluoromethyl depsipeptides, i.e. orthogonally protected building blocks for incorporation into naturally occurring depsipeptides.

Introduction

Depsides and depsipeptides are interesting classes of biopolymers that have recently received much attention.[1] These polymeric compounds are analogues of peptides: depsides are composed of hydroxy acids linked by ester bonds, and depsipeptides are formed by hydroxy and amino acids linked together by ester and amide bonds. In general, depsipeptides are peptides bearing a COO group instead of a CONH group (Scheme 1). Naturally occurring depsipeptides show promising biological activities, including antibacterial, antiviral, antifungal and anti-inflammatory properties.[2] However, their greatest future therapeutic potential is in cancer treatment.[3] Additionally, amide-to-ester substitutions in the backbone of peptides were found to be a useful tool for evaluating the role of protein hydrogen bonding.[4] Furthermore, depsipeptides can serve as branching units for building dendrimers[5] and can function as nonviral vectors for drug delivery.[6]

The Passerini, three-component condensation (P-3CC), which is the reaction of an isocyanide, a carbonyl compound and a carboxylic acid, is experiencing a growing interest owing to its efficiency in the synthesis of diverse products.[7] It is arguably the best method for producing α-acyloxy amides in a highly convergent manner and the most convergent approach to depsipeptides.[8]

The modification of peptides and proteins by the incorporation of α-trifluoromethyl- (α-Tfm-) substituted amino acids has attracted considerable attention[9] due to the unique stereoelectronic properties of the trifluoromethyl group.[10] Consequently, α-Tfm depsipeptides could become interesting candidates for medicinal chemistry. Recently, the synthesis of a CF_3-depsides, based on OH insertion of CF_3-substituted metal carbenoid into the carboxylic group of *N*-protected amino acids, was described.[11]



Scheme 1. Synthesis of CF_3-depsipeptides.

The enhanced carbonyl activity of polyfluoro carbonyl compounds[12] allowed us to propose that their use in isocyanide-based, multicomponent reactions can result in a straightforward approach to fluorinated amino acids building blocks. Recently, we have shown that imines of CF_3-

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carbonyl compounds are effective precursors for the Ugi reaction,[13] and we proposed that CF_3-carbonyl compounds can be very interesting partners for the P-3CC. To the best of our knowledge, CF_3-carbonyl compounds have not been systematically investigated in the Passerini reaction. Previously, only a few selected examples of the Passerini reaction with hexafluoroacetone and trifluoromethyl ketones were described.[14]

In this paper, we report the detailed investigation of the Passerini reaction with CF_3-carbonyl compounds that provides a new approach to trifluorolactic acid derivatives and CF_3-substituted depsipeptides—convenient trifluoromethyl building blocks for incorporation into naturally occurring depsipeptides (Scheme 1). Valinomycin (**A**), a symmetric cyclodepsipeptide isolated from *Streptomyces fuivissimus*, is formed by three repeating units of depsipeptide D-Val-L-Lac-D-Val connected by D-hydroxyisovaleric acid.[15] Valinomycin shows excellent K^+/Na^+ selectivity, acts as an ion-conducting antibiotic and allows uncontrolled movement of ions across the cell membrane.[16] Unfortunately, it shows no selective toxicity for bacterial cells over mammalian cells and is, therefore, useless as a therapeutic agent.[17] The incorporation of fluorinated fragments into valinomycin can improve its medicinal properties. Our suggested protocol can be an effective synthesis of fluorinated depsipeptide building blocks for incorporation into naturally occurred depsipeptides.

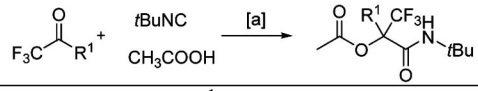
Results and Discussion

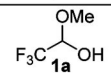
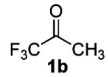
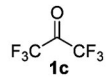
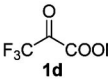
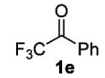
Trifluoroacetaldehyde (fluoral) methyl hemiacetal (**1a**) is the most convenient and commercially available form of gaseous trifluoroacetaldehyde (b.p. –18.8 to –17.5 °C). We have found that **1a** readily reacts in the Passerini reaction with acetic acid and *tert*-butyl isocyanide (*t*BuNC) to give the product **2a** in 93% yield (Table 1, Entry 1). We tested other CF_3-carbonyl compounds in the model reaction. CF_3-ketones **1b**–**d** reacted smoothly (Table 1, Entries 2–4). We found trifluoroacetophenone (**1e**) to be less reactive (Table 1, Entry 5), possibly due to the lower electrophilicity of the carbonyl group and increased steric hindrance. Commercially available aqueous hexafluoroacetone ($CF_3COCF_3 \times 1.5\,H_2O$) failed to react, while anhydrous hexafluoroacetone gave the product in high yield (Table 1, Entry 3).[14a]

We next investigated the influence of the acid component on the model reaction of fluoral hemiacetal and *t*BuNC (Table 2). Acetic and benzoic acid led to the corresponding products in good yields. *N*-protected, chiral, amino acids gave no stereoinduction and led to the corresponding depsides **2h**,**i** in good yields as mixtures of diastereomers (*dr* ≈ 1:1).

Formic and trifluoroacetic acids gave directly trifluoroacetic amide **2g** with a free hydroxy group after column chromatograhy due to a facile deprotection of the trifluoroacetyl- or formyl-lactic amides during the work-up.[7,18] This seems to be useful for subsequent fictionalization of the OH group, as in, for example, ester formation. Moreover, amides of α-(trifluoromethyl)lactic acid were found to be inhibitors of PDHKs (Pyruvate Dehydrogenase Kinases).[19]

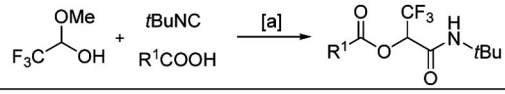
Table 1. CF_3-carbonyl compounds in the Passerini reaction.

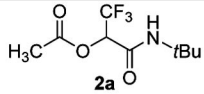
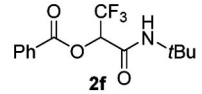
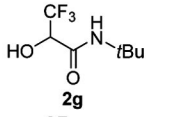
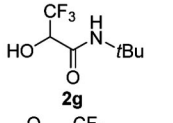
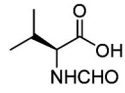
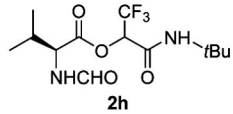
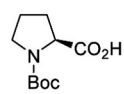
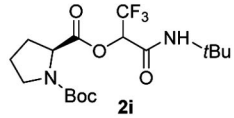


Entry	Carbonyl compound	R^1	Product	Reaction time, d	% Yield
1	 **1a**	H	**2a**	1	93
2	 **1b**	CH_3	**2b**	1	87
3[b]	 **1c**	CF_3	**2c**	1	68
4	 **1d**	COOMe	**2d**	2	67
5	 **1e**	Ph	**2e**	2	53

[a] CH_2Cl_2, –20 °C to room temp. [b] Gaseous **1c** was condensed into the mixture of carboxylic acid and isocyanide at –40 °C.

Table 2. Influence of the carboxylic component.

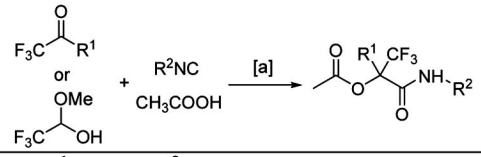


Entry	Acid	Product	% Yield
1	CH_3COOH	 **2a**	93
2	PhCOOH	 **2f**	60
3[b]	HCOOH	 **2g**	82
4[b]	CF_3COOH	 **2g**	53
5[c]		 **2h**	54
6[c]		 **2i**	84

[a] CH_2Cl_2, –20 °C to room temp., 24 h. [b] After column chromatography. [c] *dr* ≈ 1:1.

We have investigated the influence of the isocyanide on the yield of Passerini reaction. Aliphatic, aromatic and sterically hindered isocyanides reacted straightforwardly. In general, the structure of the isocyanide did not affect the reaction outcome significantly, except for the less reactive trifluoroacetone (Table 3, Entry 10).

Table 3. Synthesis of trifluorolactic amides.



Entry	R^1	R^2	Product	% Yield
1	H	*t*Bu	**2a**	93
2	H	4-$MeOC_6H_4CH_2$	**3b**	84
3	H	4-EtC_6H_4	**3c**	83
4	CH_3	4-EtC_6H_4	**3d**	48
5	Ph	4-$MeOC_6H_4CH_2$	**3e**	61
6	COOMe	4-$MeOC_6H_4CH_2$	**3f**	96
7	COOMe	4-EtC_6H_4	**3g**	40
8[b]	H		**3h**	66
9[b]	CH_3		**3i**	33
10[b]	Ph	COOEt	**3j**	14
11[b]	COOMe		**3k**	78

[a] CH_2Cl_2, –20 °C to room temp., 24 h. [b] *dr* ≈ 1:1.

Consequently, we have demonstrated that the Passerini reaction with CF_3-carbonyl compounds is a general approach to a broad variety of α-Tfm-substituted hydroxy acid derivatives. It should be noted that compounds **3a**–**c** are amides of trifluorolactic acid (CF_3-hydroxyacetic acid), which were found to be effective precursors for the synthesis of liquid crystals.[20]

The Passerini reaction with CF_3-carbonyl compounds, isocyanoacetic acid derivatives **4a**,**b** and *N*-protected amino acids opens a new multicomponent, one-step route to orthogonally protected depsipeptides containing natural amino acid residues and α-Tfm-substituted hydroxy acid fragments (Table 4). We have synthesized a number of various CF_3-depsipeptides in high yields. Unfortunately, we observed no stereoinduction, and we isolated products **5b**–**d** as a mixture of diastereomeric pairs (*dr* ≈ 1:1). Protected amino acids were ineffective chiral auxiliaries in the Passerini reaction, which is in agreement with literature data.[21]

Previously, Ostaszewski et al. reported that chiral isocyanoacetates can undergo racemization in the Passerini reaction.[22] Recently, we have developed new nonracemizable isocyanoacetates with an *ortho*-ester protective group OBO for multicomponent reactions.[23] We decided to use the chiral isocyanide **4c**, fluoral **1a** and Boc-D-valine for the synthesis of chiral depsipeptide unit D-Val-L-trifluoroLac-D-Val (Scheme 2).

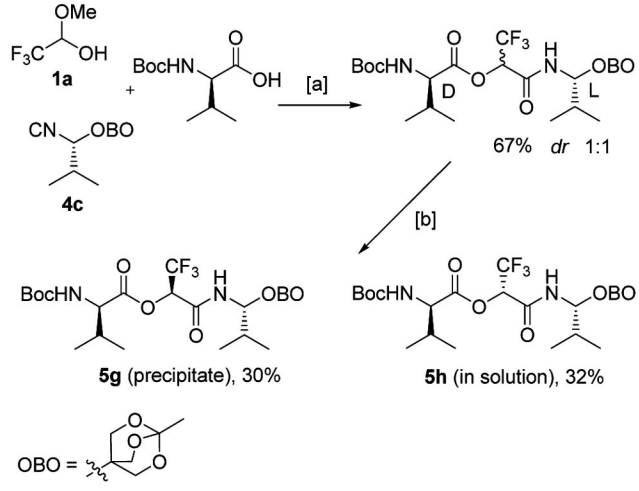
Unfortunately, we observed no stereoinduction under the influence of two chiral components and found the diastereomeric ratio of **5g**/**5h** to be ca. 1:1. However, the mixture of isomers **5g**,**h** can be easily separated by crystallization. The absence of stereoinduction cannot be caused by racemization of the product under the reaction conditions.[24] We have found that depsipeptide **5g** fully retains its absolute configuration in presence of both piperidine (2 equiv., 24 h), and DBU (1.4 equiv., 30 min).[25]

We confirmed the absolute configuration of **5g** by X-ray analysis (unfortunately, due to the low quality of the crystals formed, the necessary number of reflections have not been collected).[26] Nevertheless, the X-ray picture confirmed the assigned configuration of diastereomer **5g**. The

Table 4. Synthesis of CF_3-depsipeptides.

Entry	R^1	R^2	Pg	Isocyanide	Product	% Yield
1	H	H	Boc	**4a**	**5a**	62
2	H	H	Boc	**4b**	**5b**[b]	55
3	H	*i*Pr	Boc	**4a**	**5c**[b]	58
4[c]	H	*i*Pr	Cbz	**4b**	**5d**[b]	58
5	CH_3	H	Boc	**4a**	**5e**	35
6	CF_3	H	Boc	**4a**	**5f**	64

[a] CH_2Cl_2, room temp., 24 h. [b] *dr* ≈ 1:1. [c] THF was used as solvent.



Scheme 2. [a] CH_2Cl_2, room temp., 24 h. [b] Crystallisation: petroleum ether/$CHCl_3$.

fact that both diastereomers can be separated easily is an advantage for the further synthesis of CF_3-substituted valinomycin. The suggested approach can be effective for the preparation of other diastereopure depsipeptides.

Conclusions

In conclusion, the first example of the Passerini reaction with fluoral methyl hemiacetal was described. A number of CF_3-carbonyl compounds were tested in the Passerini condition. The scope and limitations of the reaction were discussed. A novel approach to trifluorolactic acid derivatives and trifluoromethyl-depsipeptides was described. OBO-protected chiral isocyanoacetate was successfully employed in the synthesis of a diastereopure depsipeptide for incorporation into valinomycin. The method is promising for the synthesis of chiral α-Tfm depsipeptides.

Experimental Section

General Procedure for the Passerini Reaction: Isocyanide (1 mmol) was added to a mixture of carbonyl compound (1 mmol) and carboxylic acid (1 mmol) in CH_2Cl_2 (10 mL) at –20 °C. The mixture was stirred for 12 or 24 h, concentrated, and the product was isolated by column chromatography (if needed).

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoroethyl Acetate (2a): Yield 93% (220 mg, 0.93 mmol). White solid m.p. 120–122 °C. R_f (hexanes/EtOAc, 2:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 9 H, *t*Bu), 2.24 (s, 3 H, $COCH_3$), 5.43 (q, $J_{H,F}$ = 7.32 Hz, 1 H, $CHCF_3$), 5.8 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.9 (O*C*OCH$_3$), 160.3 (CONH), 121.4 (q, J = 281.7 Hz, CF_3), 70.0 (q, J = 32.0 Hz, *C*HCF$_3$), 52.2 [*C*(CH$_3$)$_3$], 28.4 [C(*C*H$_3$)$_3$], 20.4 (OCO*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –70.6 (d, J = 7.1 Hz, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3310 (CO*NH*), 1760 (*CO*NH), 1680 (*CO*CH$_3$) cm^{-1}. $C_9H_{14}F_3NO_3$ (241.21): calcd. C 44.81, H 5.85; found C 44.70, H 5.88.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoro-1-methylethyl Acetate (2b): Gaseous hexafluoroacetone (15 mmol) was bubbled[27] through the solution of acetic acid (10 mmol) and *t*BuNC (10 mmol) in CH_2Cl_2 (50 mL) at –40 °C. The reaction stood overnight at room temp., after which it was concentrated, and the solid residue was washed with hexanes; yield 87% (220 mg, 0.87 mmol). White solid, m.p. 93–94 °C. R_f (hexanes/EtOAc, 2:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.60 (s, 1 H, NH), 2.15 (s, 3 H, $OCOCH_3$), 1.78 (s, 3 H, CF_3CCH_3), 1.33 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.8 (O*C*OCH$_3$), 162.7 (CONH), 123.1 (q, J = 283.2 Hz, CF_3), 73.6 [m, *C*(CF$_3$)CH$_3$], 52.0 [*C*(CH$_3$)$_3$], 28.1 [C(*C*H$_3$)$_3$], 21.2 (OCO*C*H$_3$), 15.6 (*C*H$_3$CF$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –82.6 (s, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3380 (CO*NH*), 1690 (*CO*NH), 1675 (*CO*CH$_3$) cm^{-1}. $C_{10}H_{16}F_3NO_3$ (255.23): calcd. C 47.06, H 6.32; found C 47.10, H 6.28.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoro-1-(trifluoromethyl)ethyl Acetate (2c): Yield 68% (210 mg, 0.68 mmol). White solid, m.p. 79–80 °C. R_f (hexanes/EtOAc, 2:1) = 0.85. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.5 (br. s, 1 H, NH), 2.23 (s, 3 H, CH_3), 1.35 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.0 (O*C*OCH$_3$); 155.9 (*C*ONH); 120.5 (q, J = 288.5 Hz, CF_3), 53.2 [*C*(CH$_3$)$_3$], 28.1 [C(*C*H$_3$)$_3$], 20.5 (OCO*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –73.0 (s, 2 CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3380 (CO*NH*), 1800 (*CO*NH), 1770 (*CO*Me) cm^{-1}. $C_{10}H_{13}F_6NO_3$ (309.21): calcd. C 38.84, H 4.24; found C 39.04, H 4.12.

Methyl 2-(Acetyloxy)-2-[(*tert*-Butylamino)carbonyl]-3,3,3-trifluoropropanoate (2d): Yield 67% (200 mg, 0.67 mmol). White solid, m.p. 43–45 °C. R_f (hexanes/EtOAc, 2:1) = 0.55. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.7 (br. s, 1 H, N*H*), 3.84 (s, 3 H, $COOCH_3$), 2.24 (s, 3 H, $OCOCH_3$), 1.36 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.8 (*C*OCH$_3$), 165.4 (*C*OCO$_2$CH$_3$), 156.9 (*C*ONH*t*Bu), 120.7 (q, J = 286.2 Hz, CF_3); 79.2 [q, J = 30.0 Hz, *C*(CF$_3$)CO$_2$CH$_3$], 54.2 (COO*C*H$_3$), 52.4[*C*(CH$_3$)$_3$], 28.1 [C(*C*H$_3$)$_3$], 20.2 (OCO*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.05 (s, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3385 (CO*NH*), 1740 (*CO*NH), 1715 (*CO*CH$_3$) cm^{-1}. $C_{11}H_{16}F_3NO_5$ (299.24): calcd. C 44.35, H 5.38; found C 44.15, H 5.39.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoro-1-phenylethyl Acetate (2e): Yield 53% (170 mg, 0.53 mmol). White solid, m.p. 86–87 °C. R_f (hexanes/EtOAc, 2:1) = 0.55. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.50–7.58 (m, 2 H, Ar*H*); 7.36–7.47 (m, 3 H, Ar*H*), 5.9 (br. s, 1 H, N*H*), 2.29 (s, 3 H, $OCOCH_3$), 1.34 [s, 9 H, NHC(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.8 (O*C*OCH$_3$), 162.7 (*C*ONH), 131.2 (Ar*C*), 129.6 (Ar*C*H), 128.4 (Ar*C*H), 127.2 (Ar*C*H), 122.6 (q, J = 285.4 Hz, CF_3), 83.5 [m, *C*(CF$_3$)Ph], 52.2 [*C*(CH$_3$)$_3$], 28.2 [C(*C*H$_3$)$_3$], 21.3 (OCO*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.1 (s, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3370 (CO*NH*), 1760 (*CO*NH), 1710 (*CO*CH$_3$) cm^{-1}. $C_{15}H_{18}F_3NO_3$ (317.30): calcd. C 56.78, H 5.72; found C 56.70, H 5.88.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoroethyl Benzoate (2f): Yield 60% (180 mg, 0.6 mmol). White solid, m.p. 159–160 °C. R_f (hexanes/EtOAc, 2:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.10 (d, J = 7.20 Hz, 2 H, Ar*H*), 7.66 (t, J = 7.47 Hz, 1 H, Ar*H*), 7.51 (t, J = 7.76 Hz, 2 H, Ar*H*), 6.0 (br. s, 1 H, N*H*), 5.67 (q, J = 7.08 Hz, 1 H, $CHCF_3$); 1.37 [s, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.8 (O*C*OPh), 160.4 (*C*ONH), 134.4, 130.1, 128.8, 127.7 (Ar*C*H), 122.1 (q, J = 281.7 Hz, CF_3), 70.4 (q, J = 31.5 Hz, *C*HCF$_3$), 52.2 [*C*(CH$_3$)$_3$], 28.4 [C(*C*H$_3$)$_3$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.8 (d, J = 6.9 Hz) ppm. IR (nujol): $\tilde{\nu}$ = 3320 (CO*NH*), 1740 (*CO*NH), 1680 (*CO*Ph) cm^{-1}. $C_{14}H_{16}F_3NO_3$ (303.28): calcd. C 55.44, H 5.32; found C 55.63, H 5.37.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoroethyl Formate (2g): Yield 82% (162 mg, 0.82 mmol). White solid, m.p. 105–107 °C. R_f (hexanes/EtOAc, 2:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.17 (s, 1 H, OH), 5.9 (br. s, 1 H, N*H*), 5.55 (q, J = 6.8 Hz, 1 H, $CHCF_3$), 1.37 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.6 (*C*ONH), 157.4 (H*C*O), 121.5 (q, J = 281.8 Hz, CF_3), 69.3 (q, J = 32.2 Hz, *C*HCF$_3$), 52.4 [*C*(CH$_3$)$_3$], 28.3 [C(*C*H$_3$)$_3$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.7 (d, J = 6.9 Hz, 3 F, CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3400 (*OH*), 3320 (CO*NH*), 1750 (*CO*NH) cm^{-1}. $C_7H_{12}F_3NO_3$ (215.17): calcd. C 42.21, H 6.07; found C 42.33, H 6.30.

1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoroethyl *N*-Formyl-L-valinate (2h, ≈ 1:1 mixture of diastereomers): Yield 54% (176 mg, 0.54 mmol). White solid, m.p. 152–154 °C. R_f (hexanes/EtOAc, 1:1) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.32, 8.16 (s, 1 H, NHC*H*O), 7.07–7.09 (m, 1 H, N*H*CHO), 6.71, 6.55 [s, 1 H, N*H*C(CH$_3$)$_3$], 5.45, 5.39 (q, J = 7.1 Hz, 1 H, $CHCF_3$), 4.45–4.53, 4.25–4.33 (m, 1 H, NHC*H*i*Pr*), 2.23–2.33, 2.05–2.17 [m, 1 H, C*H*(CH$_3$)$_2$], 1.33, 1.31 [s, 9 H, C(CH$_3$)$_3$], 0.90–1.05 [m, 6 H, CH(CH$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.6,

168.4 (O*C*OCH*i*Pr), 162.4, 161.9 (*C*ONH*t*Bu), 160.5, 160.3 (NH*C*HO), 121.6, 121.7 (q, J = 281.4 Hz, CF_3), 70.1 (m, *C*HCF$_3$), 57.4, 56.6 (*C*HNHCHO), 52.4 [*C*(CH$_3$)$_3$]; 29.9, 30.2 [*C*H(CH$_3$)$_2$]; 28.1 [C(*C*H$_3$)$_3$]; 18.8, 18.5, 18.2, 17.3 [CH(*C*H$_3$)$_2$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –73.9 (d, J = 7.2 Hz, 0.74 CF_3), –74.32 (d, J = 6.9 Hz, 0.37 CF_3), –74.35 (d, J = 7.2 Hz, 0.52 CF_3), –74.43 (d, J = 6.9 Hz, 0.36 CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3340 (CO*NH*), 1755 (*CO*NH), 1710 (NH*CHO*) cm^{-1}. $C_{13}H_{21}F_3N_2O_4$ (326.31): calcd. C 47.85, H 6.49; found C 47.99, H 6.73.

1-*tert*-Butyltyl 2-{1-[(*tert*-Butylamino)carbonyl]-2,2,2-trifluoroethyl} (2S)-Pyrrolidine-1,2-dicarboxylate (2i, ca. 1:1 mixture of diastereomers): Yield 84% (330 mg, 0.84 mmol). Colorless oil. R_f (hexanes/EtOAc, 1:1) = 0.75. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.2, 6.8 (br. s, 1 H, N*H*t*Bu*), 5.50, 5.25 (q, J = 7.3 Hz, CHCF$_3$), 4.43–4.46, 4.27–4.31 (m, 1 H, CHCOO), 3.39–3.52 (m, 2 H, C*H*$_2$NBoc), 1.84–2.30 (m, 4 H, C*H*$_2$C*H*$_2$), 1.47, 1.43 (s, 9 H, *tBu*OOC), 1.36–1.39 (m, 9 H, *tBu*NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.3, 169.8 (*C*OO), 160.5, 160.4 (*C*ONH*t*Bu), 155.1, 154.3 (*C*OO*t*Bu), 121.8, 121.7 (q, J = 281.0 Hz, CF_3), 80.4, 80.2 [COO*C*(CH$_3$)$_2$], 71.5, 69.5 (q, J = 30.7 Hz), 58.6, 58.6 (*C*HCOO), 52.1, 52.0 [CONH*C*(CH$_3$)$_3$], 46.6, 46.5 (CH$_2$CH$_2$*C*H$_2$N), 30.1, 29.6 (*C*H$_2$CH$_2$CH$_2$N), 28.14, 28.09 [NHC(*C*H$_3$)$_3$], 28.05, 28.03 [COOC(*C*H$_3$)$_3$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.5 (d, J = 7.3 Hz, 0.45 CF_3), –77.1 (d, J = 7.3 Hz, 0.55 CF_3) ppm. $C_{17}H_{27}F_3N_2O_5$ (396.40): calcd. C 51.51, H 6.87; found C 51.80, H 6.88.

2,2,2-Trifluoro-1-{[(4-methoxybenzyl)amino]carbonyl}ethyl Acetate (3b): Yield 84% (162 mg, 0.53 mmol). White solid, m.p. 84–85 °C. R_f (hexanes/EtOAc, 2:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.15 (d, J = 8.7 Hz, 2 H, Ar*H*), 6.84 (d, J = 8.7 Hz, 2 H, Ar*H*), 6.6 (br. s, 1 H, N*H*), 5.56 (q, J = 7.1, Hz, 1 H, CHCF$_3$), 4.30–4.46 (m, 2 H, NHC*H*$_2$Ph), 3.78 (s, 3 H, PhOC*H*$_3$), 2.19 (s, 3 H, OCOCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.1 (O*C*OCH$_3$), 161.4 (*C*ONH), 159.2 (Ar*C*), 137.4 (Ar*C*), 128.9 (Ar*C*H), 121.7 (q, J = 281.0 Hz, CF_3), 114.1 (Ar*C*H), 69.9 (q, J = 32.2 Hz, *C*HCF$_3$), 55.1 (O*C*H$_3$), 43.0 (NH*C*H$_2$), 20.1 (OCO*C*H$_3$) ppm. IR (nujol): $\tilde{\nu}$ = 3300 (CO*NH*), 1760 (*CO*NH), 1680 (*CO*CH$_3$) cm^{-1}. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.95 (d, J = 7.2 Hz, CF_3) ppm. $C_{13}H_{14}F_3NO_4$ (305.25): calcd. C 51.15, H 4.62; found C 51.05, H 6.66.

1-{[(4-Ethylphenyl)amino]carbonyl}-2,2,2-trifluoroethyl acetate (3c): Yield 83% (240 mg, 0.83 mmol). Green solid, m.p. 113–114 °C. R_f (hexanes/EtOAc, 2:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.9 (br. s, 1 H, NH), 7.40 (d, J = 8.3 Hz, 2 H, Ar*H*), 7.15 (d, J = 8.3 Hz, 2 H, Ar*H*), 5.69 (q, J = 6.90 Hz, 1 H, CHCF$_3$), 2.62 (q, J = 7.6 Hz, 2 H, PhC*H*$_2$CH$_3$), 2.28 (s, 3 H, OCOCH$_3$), 1.21 (t, J = 7.6 Hz, 3 H, PhCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.1 (O*C*OCH$_3$), 159.5 (*C*ONH), 141.8 (Ar*C*), 133.7 (Ar*C*), 128.4 (Ar*C*H), 121.7 (q, J = 281.8 Hz, CF_3), 120.7 (Ar*C*H), 70.5 (q, J = 32.9 Hz, *C*HCF$_3$), 28.3 (Ph*C*H$_2$CH$_3$), 20.2 (OCO*C*H$_3$), 15.5 (PhCH$_2$*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –73.40 (d, J = 7.0 Hz) ppm. IR (nujol): $\tilde{\nu}$ = 3385 (CO*NH*), 1770 (*CO*NH), 1680 (*CO*CH$_3$) cm^{-1}. $C_{13}H_{14}F_3NO_3$ (289.25): calcd. C 53.98, H 4.88; found C 53.78, H 4.92.

1-{[(4-Ethylphenyl)amino]carbonyl}-2,2,2-trifluoro-1-methylethyl Acetate (3d): Yield 48% (145 mg, 0.48 mmol). Green solid, m.p. 110–112 °C. R_f (hexanes/EtOAc, 2:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.5 (br. s, 1 H, NH), 7.37 (d, J = 8.4 Hz, 2 H, Ar*H*), 7.15 (d, J = 8.4 Hz, 2 H, Ar*H*), 2.61 (q, J = 7.6 Hz, 2 H, PhC*H*$_2$CH$_3$), 2.18 (s, 3 H, OCOCH$_3$), 1.91 (3 H, CH$_3$CCF$_3$), 1.20 (t, J = 7.6 Hz, 3 H, PhCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.1 (O*C*OCH$_3$), 162.0 (*C*ONH), 141.5 (Ar*C*), 134.0 (Ar*C*), 128.4 (Ar*C*H), 123.1 (q, J = 284.0 Hz, CF_3), 120.9 (Ar*C*H), 81.0 (q, J = 30.0 Hz, CH$_3$*C*CF$_3$), 28.3 (Ph*C*H$_2$CH$_3$), 21.1 (OCO*C*H$_3$), 15.8 (PhCH$_2$*C*H$_3$), 15.6 (*C*H$_3$CCF$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.75 (d, J = 1.0 Hz, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3345 (CO*NH*), 1730 (*CO*NH), 1695 (*CO*OCH$_3$) cm^{-1}. $C_{14}H_{16}F_3NO_3$ (303.28): calcd. C 55.44, H 5.32; found C 55.22, H 5.06.

2,2,2-Trifluoro-1-{[(4-methoxybenzyl)amino]carbonyl}-1-phenylethyl Acetate (3e): Yield 61% (232 mg, 0.61 mmol). Colorless oil. R_f (hexanes/EtOAc, 2:1) = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.55 (d, J = 4.52 Hz, 2 H, Ar*H*), 7.40 (s, 3 H, Ar*H*), 7.16 (d, J = 8.2 Hz, 2 H, Ar*H*), 6.85 (d, J = 8.2 Hz, 2 H, Ar*H*), 6.4 (br. s, 1 H, NH), 4.33–4.43 (m, 2 H, NHC*H*$_2$Ph), 3.78 (s, 3 H, PhOCH$_3$), 3.77 (s, 3 H, OCH$_3$), 2.25 (s, 3 H, COCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.9 (O*C*OCH$_3$), 163.8 (*C*ONH), 159.1 (Ar*C*), 130.9 (Ar*C*), 129.6 (Ar*C*H), 129.2 (Ar*C*), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 127.2 (Ar*C*H), 114.1 (Ar*C*H), 122.6 (q, J = 285.4 Hz, CF_3), 83.2 (m, *C*CF$_3$), 55.2 (PhO*C*H$_3$), 43.4 (*C*H$_2$), 21.2 (OCO*C*H$_3$) ppm. IR (film): $\tilde{\nu}$ = 3380 (CO*NH*), 1760 (*CO*NH), 1730 (*CO*CH$_3$) cm^{-1}. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.3 (s, CF_3) ppm. $C_{19}H_{18}F_3NO_4$ (381.35): calcd. C 59.84, H 4.76; found C 59.74, H 4.74.

Methyl 2-(Acetyloxy)-3,3,3-trifluoro-2-{[(4-methoxybenzyl)amino]carbonyl}propanoate (3f): Yield 96% (350 mg, 0.96 mmol). White solid, m.p. 82–84 °C. R_f (hexanes/EtOAc, 2:1) = 0.55. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.2 (s, 1 H, NH), 7.17 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.85 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.46 (d, J = 5.6 Hz, 2 H, NHC*H*$_2$), 3.82 (s, 3 H, COOCH$_3$), 3.76 (s, 3 H, PhOCH$_3$), 2.26 (s, 3 H, OCOCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.0 (*C*OCH$_3$), 165.0 (*C*OOCH$_3$), 159.1 (Ar*C*), 158.7 (*C*ONH), 128.9 (Ar*C*), 128.7 (Ar*C*H), 121.6 (q, J = 286.1 Hz, CF_3), 114.1 (Ar*C*H), 79.2 (m, *C*CF$_3$), 55.2 (ArO*C*H$_3$), 54.3 (COO*C*H$_3$), 43.8 (*C*H$_2$Ar), 20.1 (OCO*C*H$_3$) ppm. IR (nujol): $\tilde{\nu}$ = 3400 (CO*NH*), 1760 (*CO*NH), 1685 (*CO*OCH$_3$) cm^{-1}. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –77.2 (s, CF_3) ppm. $C_{15}H_{16}F_3NO_6$ (363.29): calcd. C 49.59, H 4.44; found C 49.71, H 4.50.

Methyl 2-(Acetyloxy)-2-{[(4-ethylphenyl)amino]carbonyl}-3,3,3-trifluoropropanoate (3g): Yield 40% (140 mg, 0.4 mmol). Green oil. R_f (hexanes/EtOAc, 2:1) = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.8 (br. s, 1 H, NH), 7.48 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.18 (d, J = 8.0 Hz, 2 H, ArH), 3.9 (s, 3 H, COOCH$_3$), 2.62 (q, J = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 2.29 (s, 3 H, OCOCH$_3$), 1.21 (t, J = 7.6, Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.8 (*C*OCH$_3$), 165.6 (*C*OOCH$_3$), 156.2 (*C*ONH), 141.5 (Ar*C*), 134.2 (Ar*C*), 128.3 (Ar*C*H), 121.2 (q, J = 286.2 Hz, CF_3), 120.4 (Ar*C*H), 78.6 (m, *C*CF$_3$), 54.5 (COO*C*H$_3$), 28.2 (*C*H$_2$CH$_3$), 19.9 (OCO*C*H$_3$), 15.5 (CH$_2$*C*H$_3$) ppm. IR (film): $\tilde{\nu}$ = 3400 (CO*NH*), 1780 (*CO*NH), 1680 (*CO*OCH$_3$) cm^{-1}. $C_{15}H_{16}F_3NO_5$ (347.28): calcd. C 51.88, H 4.64; found C 52.04, H 4.80.

Ethyl *N*-[2-(Acetyloxy)-3,3,3-trifluoropropanoyl]alaninate (3h, ca. 1:1 mixture of diastereomers): Yield 66% (188 mg, 0.66 mmol). White solid, m.p. 78–80 °C. R_f (hexanes/EtoAc, 1:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.9 (br. s, 1 H, N*H*), 5.58 (m, 1 H, CHCF$_3$), 4.55 (m, 1 H, NHC*H*CH$_3$), 4.21 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 2.24 (s, 3 H, OCOC*H*$_3$), 1.39–1.46 (m, 3 H, NHCHC*H*$_3$), 1.27 (s, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.1 (O*C*OCH$_3$), 168.0 (*C*OOEt), 160.9 (*C*ONH), 123.1 (q, J = 281.7 Hz, *C*F$_3$), 69.9 (m, *C*HCF$_3$), 61.9 (O*C*H$_2$CH$_3$), 48.3 (NH*C*HCH$_3$), 20.2, 20.1 (OCO*C*H$_3$), 18.1, 18.0 (NHCH*C*H$_3$), 14.0, 13.9 (OCH$_2$*C*H$_3$) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.9, –77.11 (d, J = 6.9 Hz, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3390 (CO*NH*), 1750 (*CO*NH), 1670 (*CO*-

OCH_3) cm^{-1}. $C_{10}H_{14}F_3NO_5$ (285.22): calcd. C 42.11, H 4.95; found C 42.34, H 5.01.

Ethyl *N*-[2-(Acetyloxy)-3,3,3-trifluoro-2-methylpropanoyl]alaninate (3i, ca. 1:1 mixture of diastereomers): Yield 33% (100 mg, 0.33 mmol). White solid, m.p. 79–81 °C. R_f (hexanes/EtOAc, 1:1) = 0.8. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.6 (br. s, 1 H, NH), 4.48–4.56 (m, 1 H, NHC*H*CH_3), 4.23–4.14 (m, 2 H, OC*H*$_2CH_3$), 2.15, 2.13 (s, 3 H, $OCOCH_3$), 1.80 (s, 3 H, CH_3CCF_3), 1.38 (m, 3 H, NHCHC*H*$_3$), 1.25 (t, J = 7.13 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.2 ($OCOCH_3$), 167.9 (*C*OOEt), 163.3 (*C*ONH), 122.9 (q, J = 284.0 Hz, CF_3), 80.5 [m, *C*(CF_3)CH_3], 61.7 (OCH_2CH_3), 48.6 (NH*C*HCH$_3$), 21.0, 20.9 ($OCOCH_3$), 18.1, 17.7 (NHCH*C*H$_3$), 15.7, 15.5 (CH_3CCF_3), 13.9, 13.8 (OCH_2CH_3) ppm. IR (nujol): $\tilde{\nu}$ = 3420 (CO*NH*), 1770 (*CO*NH), 1690 (*CO*CH_3) cm^{-1}. $C_{11}H_{16}F_3NO_5$ (299.24): calcd. C 44.15, H 5.39; found C 44.36, H 5.44.

Ethyl *N*-[2-(Acetyloxy)-3,3,3-trifluoro-2-phenylpropanoyl]alaninate (3j, ca. 1:1 mixture of diastereomers): Yield 14% (51 mg, 0.14 mmol). Yellow oil. R_f (hexanes/EtoAc, 1:1) = 0.8. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.60 m (2 H, Ar*H*), 7.50–7.39 (m, 3 H, Ar*H*), 6.8 (br. s, 1 H, NH), 4.54–4.70 (m, 1 H, NHC*H*), 4.13–4.25 (m, 2 H, OCH_2CH_3), 2.31, 2.29 (s, 3 H, $COCH_3$), 1.35–1.45 (m, 3 H, NHCHC*H*$_3$), 1.19–1.30 (m, 3 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (*C*OCH_3), 167.7 (*C*ONH), 163.9 (*C*OOEt), 130.9 (Ar*C*), 129.6 (Ar*C*H), 128.4 (Ar*C*H), 127.2 (Ar*C*H), 122.4 (q, J = 285.8 Hz, CF_3), 81.4 (m, *C*CF_3Ph), 61.8 ($COOCH_2CH_3$), 48.6 (NH*C*HCH$_3$), 21.2 (OC-O*C*H$_3$), 17.9 (NHCH*C*H$_3$), 14.0 ($COOCH_2CH_3$) ppm. IR (film): $\tilde{\nu}$ = 3400 (CO*NH*), 1780 (*CO*NH), 1750 (*CO*OEt), 1700 (*CO*CH_3) cm^{-1}. $C_{16}H_{18}F_3NO_5$ (361.31): calcd. C 53.19, H 5.02; found C 53.50, H 5.41.

Ethyl *N*-[2-(Acetyloxy)-3,3,3-trifluoro-2-(methoxycarbonyl)propanoyl]alaninate (3k, ca. 1:1 mixture of diastereomers): Yield 78% (267 mg, 0.78 mmol). Yellow oil. R_f (hexanes/EtoAc, 1:1) = 0.8. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.6, 8.3 (br. s, 1 H, N*H*), 4.53 (sept, J = 7.1 Hz, 1 H, NHC*H*), 4.12–4.30 (m, 2 H, $OCOCH_2CH_3$), 3.86 (3 H, $COOCH_3$), 2.24 (s, 3 H, $OCOCH_3$), 1.40–1.50 (m, 3 H, NHCHC*H*$_3$), 1.23–1.31 (m, 3 H, $OCOCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.7, 171.6 (*C*OOEt), 168.8, 168.6 (*C*OCH_3), 164.7, 164.4 (*C*OOCH_3), 158.1, 158.0 (*C*ONH), 122.5, 122.3 (q, J = 281.2 Hz, *C*F_3), 78.4 (*C*CF_3), 61.7, 61.2 (OCH_2CH_3), 54.4 ($COOCH_3$), 49.3 (NH*C*H), 20.1, 20.0 ($OCOCH_3$), 17.7, 17.6 (NHCH*C*H$_3$), 14.0, 13.9 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –77.2, –77.4 (s, CF_3) ppm. IR (film): $\tilde{\nu}$ = 3380 (CO*NH*), 1750 (*CO*NH), 1660 (*CO*OCH_3) cm^{-1}. $C_{12}H_{16}F_3NO_7$ (343.25): calcd. C 41.99, H 4.70; found C 42.20, H 4.87.

Ethyl 2,2-Dimethyl-4,7,10-trioxo-9-(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5a): Yield 62% (240 mg, 0.62 mmol). White solid, m.p. 129–130. R_f (hexanes/EtOAc, 1:1) = 0.8. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.4 (m, 1 H, CON*H*), 5.18 (q, J = 6.8 Hz, 1 H, $CHCF_3$), 5.2 (br. s, 1 H, N*H*Boc), 4.20 (q, J = 7.1 Hz, 2 H, $OCOCH_2CH_3$), 3.95–4.15 (m, 4 H, CH_2, CH_2); 1.44 s [9 H, $C(CH_3)_3$], 1.27 (t, J = 7.1 Hz, 3 H, $OCOCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.7 (*C*OCH_2NH), 167.9 (*C*OOEt), 162.1 (CF_3CONH), 156.7 (O*C*O*t*Bu), 121.5 (q, J = 281.0 Hz, CF_3), 80.8 [*C*(CH_3)$_3$], 70.2 (q, J = 32.2 Hz, *C*HCF_3), 61.5 (OCH_2CH_3), 42.3 (*C*H_2NHBoc), 41.2 (NH*C*HCO_2Et), 28.1 [C(*C*H$_3$)$_3$], 13.8 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.3, –77.4 (s, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3370 (CO*NH*), 1760 (*CO*NH), 1710 (*CO*CH_3), 1690 (*CO*OEt) cm^{-1}. $C_{14}H_{21}F_3N_2O_7$ (386.32): calcd. C 43.53, H 5.48; found C 43.86, H 5.82.

Ethyl 2,2,12-Trimethyl-4,7,10-trioxo-9-(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5b, ca. 1:1 mixture of diastereomers): Yield 55% (220 mg, 0.55 mmol). White solid, m.p. 50–51 °C. R_f (hexanes/EtOAc, 1:1) = 0.7. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.61–7.68 (m, 1 H, CON*H*), 5.50–5.56 (m, 1 H, $CHCF_3$), 4.44–4.51 (m, 1 H, C*H*CH_3), 3.90–4.20 (m, 4 H, C*H*$_2$NHBoc, CO-O*C*H$_2CH_3$), 1.39, 1.40 [s, 9 H, $C(CH_3)_3$], 1.20–1.29 (m, 6 H, CHC*H*$_3$ and $OCOCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.9, 171.8 (*C*OOEt), 167.8, 167.7 (O*C*OCH_2NH), 161.3 (CF_3CONH), 156.6, 156.5 (O*C*O*t*Bu), 121.3 (q, J = 281 Hz, CF_3), 80.8, 80.7 [*C*(CH_3)$_3$], 70.5 (m, *C*HCF_3), 61.7, 61.6 (OCH_2CH_3), 48.5, 48.4 (NH*C*HCH_3), 42.4, 42.3 (*C*H_2NHBoc), 28.1 [C(*C*H$_3$)$_3$], 17.8, 17.7 (NHCH*C*H$_3$); 13.9 13.8 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.7 (d, J = 6.9 Hz, 0.34 CF_3), –76.8 (d, J = 7.2 Hz, 0.31 CF_3), –79.7 (d, J = 7.2 Hz, 0.19 CF_3), –79.7 (d, J = 7.2 Hz, 0.16 CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3375 (CO*NH*), 1720 (*CO*NH), 1680 (*CO*O*t*Bu), 1680 (*CO*OEt) cm^{-1}. $C_{15}H_{23}F_3N_2O_7$ (400.35): calcd. C 45.00, H 5.79; found C 45.25, H 5.55.

Ethyl (6*S*)-6-Isopropyl-2,2-dimethyl-4,7,10-trioxo-9-(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5c, ca. 1:1 mixture of diastereomers): Yield 58% (249 mg, 0.58 mmol). Colorless oil. R_f (hexanes/EtOAc, 1:1) = 0.7. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.6, 7.5 (m, 1 H, CON*H*i*Pr), 5.62–5.72, 5.42–5.55 (m, 1 H, $CHCF_3$), 4.90–5.08 (m, 1 H, COC*H*i*Pr), 4.00–4.52 (m, 4 H, CH_2, CH_2), 1.95–2.40 [m, 1 H, C*H*(CH_3)$_2$], 1.43, 1.39 [s, 9 H, $C(CH_3)_3$], 1.18–1.28 (m, 3 H, $OCOCH_2CH_3$), 0.84–1.07 [m, 6 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.9, 174.7 (*C*ONH), 171.7, 171.6 (O*C*OCH*i*Pr), 161.5, 161.1 (*C*OOEt), 156.0, 155.9 (O*C*O*t*Bu), 121.5 (q, J = 281 Hz CF_3), 81.0, 80.8 [*C*(CH_3)$_3$], 69.3 (q, J = 32.0 Hz, *C*HCF_3), 61.5, 61.4 (OCH_2CH_3), 60.0, 59.9 (*C*H*i*Pr), 48.5, 48.4 (NH*C*H_2CO_2Et), 30.1 (CH_3CHCH_3), 28.2, 28.1 [C(*C*H$_3$)$_3$], 19.1, 19.0, 18.6, 18.5, 17.4, 17.3, 17.2, 17.0 (CH_3CHCH_3); 14.0, 13.9 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.7 (d, J = 7.2 Hz, 0.25 CF_3), –76.1 (d, J = 7.2 Hz, 0.25 CF_3), –76.7 (d, J = 7.2 Hz, 0.27 CF_3), –76.8 (d, J = 7.2 Hz, 0.23 CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3340 (CO*NH*), 1780 (*CO*NH), 1700 (*CO*CH_3), 1680 (*CO*OEt) cm^{-1}. $C_{17}H_{27}F_3N_2O_7$ (428.40): calcd. C 47.66, H 6.35; found C 47.80, H 5.49.

Ethyl (6S)-6-Isopropyl-12-methyl-2,2-dimethyl-4,7,10-trioxo-9-(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5d, ca. 1:1 mixture of diastereomers): The reaction was performed in THF; yield 58% (277 mg, 0.58 mmol). Colorless oil. R_f (hexanes/EtOAc, 1:1) = 0.7. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.6, 7.4 (br. s, 1 H, CONH), 7.25–7.39 (m, 5 H, Ar*H*), 5.5–5.75 (m, 2 H, N*H*CBz, $CHCF_3$), 5.00–5.20 (m, 2 H, CH_2Ph), 4.31–4.40, 4.15–4.25 (m, 1 H, C*H*i*Pr), 4.10–4.18 (m, 2 H, O*C*H_2CH_3), 3.84–4.06 (m, C*H*CH_3), 2.10–2.40 [m, 1 H, C*H*(CH_3)$_2$], 1.15–1.35 (m, 6 H, NHCHC*H*$_3$, OCH_2CH_3), 0.95–1.08 [m, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.3 (CONH), 169.1, 168.7 (O*C*O-CH*i*Pr), 161.6, 161.5 (*C*OOEt), 157.2, 156.6 (O*C*O*t*Bu), 135.8, 135.7, (Ar*C*), 128.6, 128.3, 128.0, 127.9 (Ar*C*H), 121.5 (q, J = 281 Hz, CF_3), 70.1 (m, *C*HCF_3), 67.4, (O*C*H_2Ph), 61.5 (CO-O*C*H_2CH_3), 60.0, 59.4 (*C*H*i*Pr), 30.3, 30.1 (CH_3CHCH_3), 19.0, 18.6 (CH*C*H$_3$), 18.1, 17.2 (CH*C*H$_3$), 13.9 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –76.3 (d, J = 7.2 Hz, 0.5 CF_3), –76.6 (d, J = 6.5 Hz, 0.5 CF_3) ppm. IR (film): $\tilde{\nu}$ = 3360 (CO*NH*), 1750 (*CO*NH), 1700 (*CO*OCH_2Ph), 1680 (*CO*OEt) cm^{-1}. $C_{21}H_{27}F_3N_2O_7$ (476.44): calcd. C 52.94, H 5.71; found C 53.20, H 5.99.

Ethyl 2,2,9-Trimethyl-4,7,10-trioxo-9-(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5e): Yield 35% (155 mg, 0.35 mmol).

Yellow oil. R_f (hexanes/EtOAc, 1:1) = 0.75. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.4 (1 H, CONH), 5.27 (br. s, 1 H, NHBoc), 3.80–4.23 (m, 6 H, $CO_2CH_2CH_3$, CH_2NHBoc, CH_2CO_2Et), 1.87 (s, 3 H, CH_3CF_3), 1.45 [s, 9 H, $C(CH_3)_3$], 1.24 (t, J = 7.3 Hz, 3 H, $OCOCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.9 ($OCOCH_2NH$), 167.4 ($COOEt$), 164.1 (CF_3CONH), 156.7 ($OCOtBu$), 122.9 (q, J = 284.0 Hz, CF_3), 81.0 [$C(CH_3)_3$], 71.4 (m, $CHCF_3$), 61.4 (OCH_2CH_3), 43.3 (CH_2NHBoc), 41.7 ($NHCH_2CO_2Et$), 28.2 [$C(CH_3)_3$], 15.9 (CF_3CH_3), 14.0 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –82.5 (s, CF_3) ppm. IR (film): $\tilde{\nu}$ = 3380 (CO*NH*), 1775 (*CO*NH), 1700 (*COO*tBu), 1680 (*CO*OEt) cm^{-1}. $C_{18}H_{29}F_3N_2O_7$ (442.43): calcd. C 48.87, H 6.61; found C 48.90, H 6.80.

Ethyl 2,2-Dimethyl-4,7,10-trioxo-9,9-bis(trifluoromethyl)-3,8-dioxa-5,11-diazatridecan-13-oate (5f): Compound 5f was obtained according to the procedure for **2b**; yield 64% (268 mg, 0.64 mmol). White solid, m.p. 132–134 °C. R_f (hexanes/EtOAc, 1:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.3 (br. s, 1 H, CON*H*), 5.2 (br. s, 1 H, N*H*Boc), 4.16–4.34 (m, 4 H, $CO_2CH_2CH_3$, CH_2NHBoc), 3.53–4.70 (m, 2 H, CH_2CO_2Et), 1.39 [s, 9 H, $C(CH_3)_3$], 1.29 (t, J = 7.2 Hz, 3 H, $OCOCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.5 ($OCOCH_2NH$), 169.3 (*C*OOEt), 159.8 (CF_3CONH), 157.0 ($OCOtBu$), 121.2 (q, J = 280 Hz, CF_3, CF_3), 81.0 [$C(CH_3)_3$], 79.1 [m, $C(CF_3)_2$], 62.8 (OCH_2CH_3), 44.9 (CH_2NHBoc), 42.7 ($NHCH_2CO_2Et$), 28.0 [$C(CH_3)_3$], 13.9 (OCH_2CH_3) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.7 (q, J = 8.9 Hz, 1.5 F, 0.5 CF_3), –75.2 (q, J = 8.9 Hz, 1.5 F, 0.5 CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3370 (CO*NH*), 1790 (*CO*NH), 1720 (*COO*tBu), 1680 (*CO*OEt) cm^{-1}. $C_{18}H_{26}F_6N_2O_7$ (496.40): calcd. C 43.55, H 5.28; found C 43.74, H 5.18.

Synthesis of Chiral Depsipeptides 5g,h: Isocyanide (992 mg, 4.7 mmol) was added to a mixture of **1a** (611 mg, 4.7 mmol), and Boc-D-Valine (1030 mg, 4.7 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 24 h at room temp., concentrated, and the **5g/5h** mixture of diastereomers (1660 mg, 3.1 mmol, 67%) was isolated by column chromatography (hexanes/EtOAc, 3:1). The solid residue was crystallized from petroleum ether/chloroform (10:1). After the material was cooled to –20 °C, compound **5g** precipitated. The filtrate was concentrated and purified by column chromatography (hexanes/EtOAc, 3:1) to afford **5h** (790, mg, 32%). The precipitate of **5g** was crystallized from the same solvent and gave pure product (750 mg, 30%).

5g: Yield 30% (750 mg). White solid, m.p. 105–107 °C. R_f (hexanes/EtOAc, 2:1) = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.41 (d, J = 9.6 Hz, 1 H, N*H*Boc), 5.67 (q, J = 6.8 Hz, 1 H, $CHCF_3$), 4.99 (d, J = 8.6 Hz, 1 H, N*H*), 4.32–4.41 (m, 1 H, CH*i*Pr), 4.05 (dd, J = 3.3, 6.6 Hz, 1 H, CH*i*Pr), 3.80–3.90 [m, 6 H, $C(OCH_2)_3$], 2.13–2.30 [m, 2 H, $CH(CH_3)_2$, $CH(CH_3)_2$], 1.43 [s, 9 H, $C(CH_3)_3$], 1.03 (d, J = 6.8 Hz, 3 H, CH_3), 0.84–0.96 (m, 9 H, 3 CH_3), 0.76 [s, 3 H, $(OCH_2)_3CCH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.6 (*C*OO), 161.3 (CONH), 154.9 (*C*ONHBoc), 121.6 (J = 281.2 Hz, CF_3), 108.1 [$C(OCH_2)_3$], 80.1 [$C(CH_3)_3$], 72.4 [$C(OCH_2)_3$], 70.3 (q, J = 32.2 Hz, $CHCF_3$), 58.5 (*CH*iPr), 57.1 (*CH*iPr), 30.8 [$CH(CH_3)_2$], 30.5 [$(OCH_2)_3CCH_3$], 28.2 [$C(CH_3)_3$], 27.7 [$CH(CH_3)_2$], 20.8 (CH_3), 19.0 (CH_3), 17.1 (CH_3), 16.9 (CH_3), 14.1 [$(OCH_2)_3CCH_3$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.4 (d, J = 7.0 Hz, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3340 (CO*NH*), 1710 (*CO*NH), 1690 (*COO*tBu) cm^{-1}. $[\alpha]_D^{20}$ = –23.55 (c = 0.025, MeOH). ESI-MS (*m*/*z*): calcd. for $C_{23}H_{37}F_3N_2O_8Na$ [M^+] 549.2400; found 549.2399.

5h: Yield 32% (790 mg). White solid, m.p. 105–107 °C. R_f (hexanes/EtOAc, 2:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.39 (d, J = 10.1 Hz, 1 H, N*H*Boc), 5.53 (q, J = 6.8 Hz, 1 H, $CHCF_3$), 4.94 (d, J = 8.8 Hz, 1 H, N*H*), 4.31–4.39 (m, 1 H, CH*i*Pr), 4.10 (dd, J = 3.8, 6.3 Hz, 1 H, CH*i*Pr), 3.85 [s, 6 H, $C(OCH_2)_3$], 2.55–2.33 [m, 1 H, $CH(CH_3)_2$], 2.11–2.21 [m, 1 H, $CH(CH_3)_2$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.03 (d, J = 6.8 Hz, 3 H, CH_3), 0.93 (d, J = 6.8 Hz, 3 H, CH_3), 0.80–0.90 (m, 6 H, 2 CH_3), 0.78 [s, 3 H, $(OCH_2)_3CCH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.7 (*C*OO), 161.1 (CONH), 155.7 (*C*ONHBoc), 121.6 (J = 281.0 Hz, CF_3), 108.1 [$C(OCH_2)_3$], 80.2 [$C(CH_3)_3$], 72.3 [$C(OCH_2)_3$], 70.8 (q, J = 32.9 Hz, $CHCF_3$), 58.5 (*CH*iPr), 57.0 (*CH*iPr), 30.7 [$CH(CH_3)_2$], 30.42 [$(OCH_2)_3CCH_3$], 28.0 [$C(CH_3)_3$], 27.5 [$CH(CH_3)_2$], 20.7 (CH_3), 20.0 (CH_3), 17.1 (CH_3), 16.9 (CH_3), 14.1 [$(OCH_2)_3CCH_3$] ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$, 25 °C): δ = –74.2 (d, J = 6.9 Hz, CF_3) ppm. IR (nujol): $\tilde{\nu}$ = 3340 (CO*NH*), 1710 (*CO*NH), 1690 (*COO*tBu) cm^{-1}. $[\alpha]_D^{20}$ = –5.63 (c = 0.025, MeOH). ESI-MS (*m*/*z*): calcd. for $C_{23}H_{37}F_3N_2NaO_8$ [M^+] 549.2400, found 549.2398.

Supporting Information (see also the footnote on the first page of this article): General information, X-ray analysis of **5g**, racemization experiment details and copies of NMR spectra of all compounds.

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[1] C. E. Ballard, H. Yu, B. Wang, *Curr. Med. Chem.* **2002**, *9*, 471–498.
[2] a) Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482; b) F. Sarabia, S. Chammaa, A. Sánchez Ruiz, L. Martín Ortiz, F. J. López Herrera, *Curr. Med. Chem.* **2004**, *11*, 1309–1332.
[3] a) E. Hamel, D. G. Covell, *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 19–53.
[4] a) D. Seebach, Y. R. Mahajan, R. Senthilkumar, M. Rueping, B. Jaun, *Chem. Commun.* **2002**, 1598–1599; b) S. Aravinda, N. Shamala, C. Das, P. Balaram, *Biopolymers* **2002**, *64*, 255–267; c) T. S. Haque, J. C. Little, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 6975–6985; d) X. Yang, M. Wang, M. C. Fitzgerald, *Bioorg. Chem.* **2004**, *32*, 438–449; e) E. T. Powers, S. Deechongkit, J. W. Kelly, *Adv. Protein Chem.* **2006**, *73*, 39–78.
[5] J. Kress, A. Rosner, A. Hirsch, *Chem. Eur. J.* **2000**, *6*, 247–257.
[6] K. E. Uhrich, S. M. Cannizzaro, R. S. Langer, K. M. Shakesheff, *Chem. Rev.* **1999**, *99*, 3181–3198.
[7] L. Banfi, R. Riva, *The Passerini Reaction*, in: *Organic Reactions* (Eds.: L. E. Overman, R. Adams), vol. 65, John Wiley & Sons, New York, **2005**.
[8] U. Fetzer, I. Ugi, *Justus Liebigs Ann. Chem.* **1962**, *659*, 184–189.
[9] a) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727–1739; b) X.-L. Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711–6745; c) A. Sutherland, C. L. Willis, *Nat. Prod. Reports* **2000**, *17*, 621–631.
[10] a) S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko, *Tetrahedron* **2007**, *63*, 7753–7808; b) C. Jäckel, B. Koksch, *Eur. J. Org. Chem.* **2005**, 4483–4503; c) M. Zanda, *New J. Chem.* **2004**, *28*, 1401–1411.
[11] D. V. Vorob'eva, I. D. Titanyuk, I. P. Beletskaya, S. N. Osipov, *Mendeleev Commun.* **2005**, *15*, 222–223.
[12] a) *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS Symp., Ser. 911, Washington, D. C., **2005**; b) P. Kirsch, in: *Modern Fluoroorganic Chemistry. Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.
[13] a) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Tetrahedron* **2008**, *64*, 11706–11712; b) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova,

G.-V. Röschenthaler, V. G. Nenajdenko, *Synlett* **2009**, 403–406.
[14] a) W. Middleton, D. England, G. Krespan, *J. Org. Chem.* **1967**, *32*, 948–950; b) M. Barker, D. Demaine, D. House, G. Inglis, M. Johnston, H. Jones, S. Macdonald, L. Mclay, S. Shanahan, P. Skone, M. Vinader, *Non-steroidal inflammation inhibitors*, WO 2004071389.
[15] B. Dietrich, P. Viout, J.-M. Lehn, in: *Macrocyclic Chemistry*, VCH, Weinheim, **1993**.
[16] a) W. L. Duax, J. F. Griffin, D. A. Langs, G. D. Smith, P. Grochulski, V. Pletnen, V. Ivanov, *Biopolymers (Pept. Sci.)* **1996**, *40*, 141–155; b) R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen, *Chem. Rev.* **1985**, *85*, 271–339.
[17] G. L. Patrick, in: *Introduction to Medicinal Chemistry*, Oxford University Press Inc., Oxford New York, **2001**, pp. 420–423.
[18] a) T. Ziegler, H.-J. Kaisers, R. Schlömer, C. Koch, *Tetrahedron* **1999**, *55*, 8397–8408; b) J. E. Semple, T. D. Owens, K. Nguyen, O. E. Levy, *Org. Lett.* **2000**, *2*, 2769–2772.
[19] G. R. Bebernitz, T. D. Aicher, J. L. Stanton, J. Gao, S. S. Shetty, D. C. Knorr, R. J. Strohschein, J. Tan, L. J. Brand, C. Liu, W. H. Wang, C. C. Vinluan, E. L. Kaplan, C. J. Dragland, D. DelGrande, A. Islam, R. J. Lozito, X. Liu, W. M. Maniara, W. R. Mann, *J. Med. Chem.* **2000**, *43*, 2248–2257.
[20] F. Masatoshi, S. Shinichi, *Optically active trifluorolactic acid derivative and liquid crystal composition*, US 5665270.
[21] D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.
[22] S. Berłożecki, W. Szymański, R. Ostaszewski, *Tetrahedron* **2008**, *64*, 9780–9783.
[23] A. G. Zhdanko, V. G. Nenajdenko, *J. Org. Chem.* **2009**, *74*, 884–887.
[24] For racemisation of depsipeptides see: O. Kuisle, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1999**, *64*, 8063–8075.
[25] See Supporting Information for more details.
[26] X-ray analysis of **5g** is discussed in the Supporting Information.
[27] Hexafluoroacetone hydrate was dehydrated by heating with sulfuric acid (concentrated) according to the literature procedure. See, for example: Y. Guo, K. Fujiwara, K. Uneyama, *Org. Lett.* **2006**, *8*, 827–829.

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