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The Ugi reaction with 2-substituted cyclic imines. Synthesis of substituted proline and homoproline derivatives

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Abstract—The Ugi three-component reaction with 2-substituted five-, six-, and seven-membered cyclic imines was investigated. The reaction opens a new route to substituted proline and homoproline derivatives. It was shown that the method is efficient for the one-step preparation of seminatural dipeptides containing natural amino acid residues, and fragments of substituted proline or pipecolinic acid. The scope and limitation of the approach are discussed.

1. Introduction

Unnatural non-proteinogenic α-amino acids are important substances for different areas of chemistry, biology and material science.[1] They have a wide biological activity and hence numerous medicinal applications. The replacement of natural amino acids in peptides with non-proteinogenic derivatives has become an important goal in synthetic organic chemistry because their incorporation into biologically relevant peptides may influence their properties dramatically.[2] The synthesis of proline peptidomimetics that mimic natural dipeptides is very attractive.[3] Proline is the most conformationally restricted amino acid. The proline residue plays an important role in protein secondary structure, and in many biological processes such as protein folding and protein recognition.[4] Proline isomerism can influence the receptor function of neurotransmitter-gated ion channels.[5] Substituted proline analogues were developed in order to constrain and control the peptide backbone in reverse turn motifs[6] or to alter the imide cis/trans ratio.[7] Pipecolinic acid (homoproline) is abundant in many natural products such as immunosuppressants or cyclic peptides with antifungal activity.[8] Pipecolinic acid residues accelerate the rate of cis–trans imide isomerism, and observe a higher preference for *cis*-imide bonds on the N-terminal of pipecolinic acid in comparison to proline residues.[8] Synthesis of 2-substituted proline or homoproline derivatives and their incorporation into natural peptides is an important goal for peptide chemistry.

Keywords: Ugi reaction; Multicomponent reaction; Imine; Amino acid; Isocyanide; Proline; Homoproline; Peptide.
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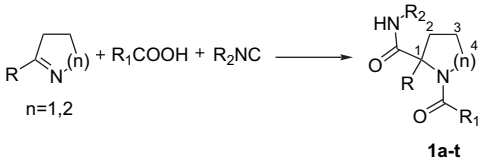
2. Results and discussion

Among the methods for the multicomponent synthesis of peptides or amino acids, the Ugi reaction is one of the most popular.[9] The Ugi reaction with non-substituted five- and six-membered cyclic aldimines was recently reported.[10] The use of 2-substituted cyclic ketimines in the Ugi MCR can give a short and very attractive synthesis of substituted proline derivatives and their higher six- and seven-membered analogues. This article is devoted in investigating the possibility of 2-substituted cyclic imines participating in the Ugi MCR (Scheme 1).



Scheme 1.

Starting cyclic imines with various aliphatic or aromatic substituents in the α-position can be easily prepared according to literature procedure from cheap, commercially available starting materials.[11] This can open broad possibilities for the syntheses of a variety of cyclic amino acid derivatives.

We decided to investigate the synthetic scope and limitations of the approach. Influence of the acid, isocyanide, and imine components on the yield of target cyclic amino acid was studied for this aim. We proposed that the structure of starting cyclic ketimines could most significantly affect the reaction path due to the considerable difference in the

Table 1. Influence of acid component on reaction time and yield (R=Me and R_2=Bn)

Entry	R_1	Product	pK_a	Reaction time (d)	Yield (%)
1	CH_3	—	4.75	5	0
2	Ph	**1a**	4.20	5	50
3	CH_2Cl	**1b**	2.85	3	80
4	$CHCl_2$	**1c**	1.48	3	73
5	CCl_3	**1d**	0.7	2.5	78
6	CF_3	**1e**	0.23	2	83

conformation behavior of five-, six-, and seven-membered nitrogen heterocycles.[12]

A model imine (2-methyl pyrroline) and benzylisocyanide were chosen to study the influence of the acid. We found that target amides of 2-methylproline can be prepared generally in good yield (Scheme 1, Table 1). However, the acidity of the carboxylic acid affects significantly the reaction time. The best result was observed in the case of trifluoroacetic acid TFA. In this case the reaction proceeds in reasonable time at room temperature to give the target amide in 83% yield. Another reason to use TFA is the possibility of subsequent deprotection of the amino acid nitrogen under mild conditions.[13] Acetic acid did not give any Ugi product.

The reaction is of general type. No restrictions on the structure of the isocyanide component were found (using model reaction with methyl pyrroline and TFA). As a rule, various isocyanides having alkyl and aryl substituents or ester groups gave substituted amides of 2-methylproline in high yields (Table 2).

It was found that the effect of the structure of the 2-substituted imine on the reaction path is much more important. Using a model benzylisocyanide and trifluoroacetic acid, we have investigated the relationship between the structure of substituents in the 2-position of the imine and the yield of the Ugi type product (Table 3). Imines with alkyl substituent react smoothly. Even in the case of sterically hindered 2-*tert*-butylpyrroline the target amide can be prepared in almost quantitative yield, however more prolonged reaction time was necessary. A very unusual result was observed in the case of 2-phenylpyrroline and other arylsubstituted imines. Instead of formation of the Ugi product the reaction is directed mainly to the trifluoroacylation of the imine. 2-Phenyl proline derivative **1n** is minor product in this case. For example, in the case of the 2-phenylpyrroline–TFA–benzylisocyanide system, the target Ugi amide was isolated in only 7% yield. We believe that the main reasons for the

Table 2. Influence of isocyanide component on the reaction (R=Me and R_1=CF_3)

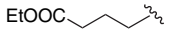
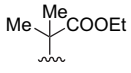
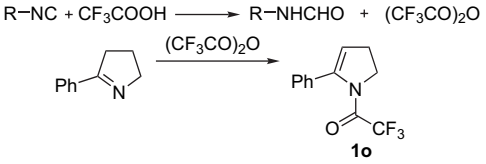
Entry	R_2	Product	Yield (%)
7	Bn	**1e**	83
8	4-Br–Ph	**1f**	72
9		**1g**	85
10		**1h**	50

Table 3. Influence of imine component on reaction time and yield (R_1=CF_3 and R_2=Bn)

Entry	R	Product	Reaction time (d)	Yield (%)
11	Me	**1e**	2	83
12	Bn	**1i**	3	45
13	Bu	**1j**	3	95
14	*i*-Pr	**1k**	4	60
15	Cyclopentyl	**1l**	4	50
16	*t*-Bu	**1m**	6	95
17	Ph	**1n**	5	7

formation of **1o** are the lower acidity of 2-phenylpyrroline compared to 2-alkylsubstituted pyrrolines, the lower electrophilicity of intermediate iminium salt, and finally, the possibility of conjugation of the enamide double bond with the phenyl ring in **1o**. The isocyanide behaves very interestingly in this reaction as a dehydrating agent to form trifluoroacetic anhydride, TFAA, from TFA.[14] The final step of this sequence is trifluoroacylation of 2-phenylpyrroline by TFAA to give enamide **1p** in 65% yield (Scheme 2). Our attempts to perform this reaction with other acids also gave the same results.

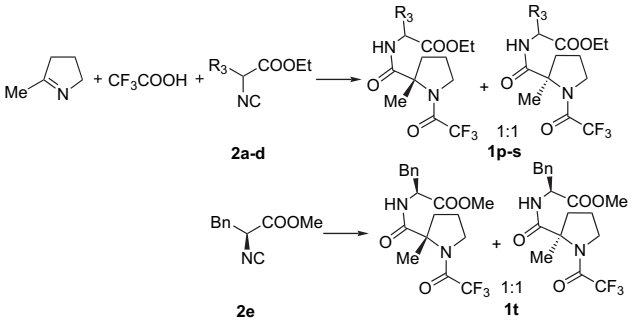


Scheme 2.

We have demonstrated that Ugi multicomponent reaction with 2-alkyl pyrrolines is a general approach to construct derivatives of 2-substituted proline, with a broad variety of such products prepared using this very simple procedure. In the case of isocyanides prepared from protected natural amino acids, this method opens a new route to seminatural dipeptides containing 2-substituted proline (as the acid building block) and a natural amino acid residue (as the amine building block). A crucial step in this synthesis is the preparation of a dipeptide with orthogonal protecting groups at each end. This opens up the possibility for the subsequent selective synthesis of tripeptides and longer peptides.

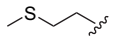
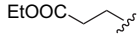
Usually no stereoinduction is observed in the case of chiral isocyanides in Ugi reactions in contrast to the Passerini reaction.[15] However, we proposed that the fixed conformation of cyclic imines could influence the possibility of a diastereoselective Ugi reaction with chiral isocyanides. Chiral isocyanide **2e** was prepared from L-phenylalanine by a literature procedure.[16]

We demonstrated that the method works for the one-step synthesis of some seminatural orthogonally protected dipeptides in good yield. Unfortunately, no induction was observed, and the reaction give a mixture of two diastereomers in a 1/1 ratio in the case of chiral isocyanide **2e**, and four diastereomers in the case of racemic isocyanides **2a–d** (by ^{1}H NMR spectroscopy) (Scheme 3). The results of the reaction of model 2-methyl pyrroline and TFA with various isocyanides **2a–e** are given in Table 4.

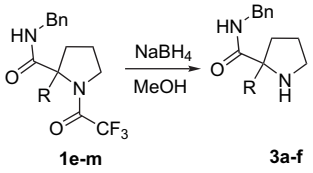


Scheme 3.

Table 4. Ugi reaction with isocyanide derivatives of natural amino acids

Entry	R_3	Product	Yield, %
18	Me	**1p**	65
19	Bn	**1q**	55
20		**1r**	52
21		**1s**	56

The possibility of selective deprotection was shown. Deprotection of **1e–m** results in N-unsubstituted amides **3a–f** (Scheme 4). The N-cleavage of trifluoroacetyl group was carried out under mild conditions in excellent yield (Table 5).

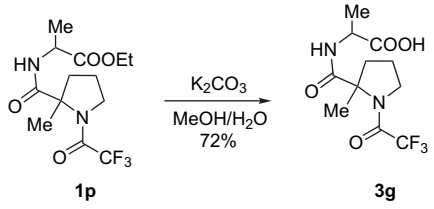


Scheme 4.

Table 5. Cleavage of TFA group

Entry	R	Product	Yield (%)
22	Me	**3a**	80
23	Bn	**3b**	90
24	Bu	**3c**	82
25	*i*-Pr	**3d**	81
26	Cyclopentyl	**3e**	83
27	*t*-Bu	**3f**	77

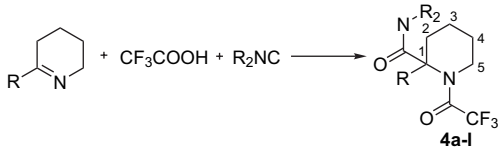
Similarly, the use of aq methanol/K_2CO_3 solution permits selective deprotection of the ester moiety to give the unprotected carboxylic acid (Scheme 5).



Scheme 5.

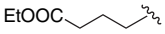
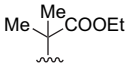
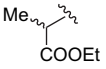
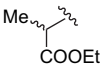
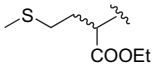
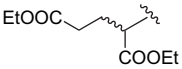
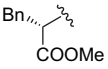
In addition to the 20 common natural amino acids there are a number of rare amino acids as which occur structural fragments of some natural products. Therefore, development of an effective synthesis of higher analogs of proline having six- and seven-membered rings is important. Pipecolinic acid (also known as homoproline) is a proline analogue, which contains a six-membered ring. It is found in several important natural products such as the immunosuppressant FK506, rapamycin, and cyclic peptides with antifungal activity.[8]

The Ugi reaction works is very well both in the case of 2-alkyl and 2-phenylpiperideines in contrast to the reaction with 2-aryl pyrrolines. As a result, a number of pipecolinic acid derivatives can be prepared using the same approach. Probably the difference in the reactivity of 2-substituted pyrrolines and 2-substituted piperideines in the Ugi reaction can be explained by the conformational peculiarities of five- and six-membered rings. In the case of pyrrolines the formation of enamides is more preferable due to lowering of vicinal interactions.[17] We found that it was also possible to synthesize orthogonally protected dipeptides containing a 2-substituted pipecolinic acid moiety (Scheme 6). In general no restriction for this synthesis was found and yields were generally high. Similarly to the reaction with chiral isocyanide **2e** for 2-substituted pyrrolines, the Ugi reaction with 6-ring imine (2-phenylpiperideine) is not diastereoselective, giving both diastereomers in a 1/1 ratio (Table 6, entry 36).



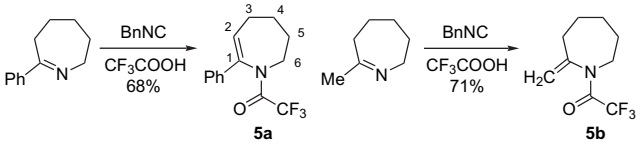
Scheme 6.

Table 6. Ugi synthesis of homoproline derivatives

Entry	R	R_2	Product	Yield (%)
28	Bu	Bn	**4a**	84
29	Ph	Bn	**4b**	79
30	Ph		**4c**	67
31	Ph		**4d**	71
32	Bu		**4e**	
32	Ph		**4f**	72
33	Ph		**4g** and **4h**[a]	84
34	Ph		**4i**	68
35	Ph		**4j**	69
36	Ph		**4k** and **4l**	84

[a] Mixture of two pairs of diastereomers in a 1:1 ratio was isolated.

We found that in the case of Ugi reactions with imines containing a seven-membered ring, no formation of the target amino acid derivatives was observed. Similarly to the reaction of 2-aryl pyrrolines only the formation of enamides take place both in the case of 2-phenyl and 2-methyl imines. Both reactions give the enamide as the only reaction product. In the case of 2-methylazepine, unpredictable elimination to form enamide **5b** having an exocyclic double bond was observed. These results confirmed that conformational peculiarities of five-, six-, and seven-membered cyclic imines are very important in the Ugi reaction. We demonstrated that only in the case of five- and six-membered 2-substituted imines the formation of 2-substituted proline and homoproline derivatives is possible (Scheme 7).



Scheme 7.

3. Conclusion

Thus, we have investigated the reaction of 2-substituted cyclic imines in Ugi reaction conditions. The reaction permits preparation of substituted proline and homoproline derivatives. It was shown that the method is efficient for the one-step preparation of seminatural dipeptides containing natural amino acid residues and fragments of substituted proline or pipecolinic acid. The significant difference in the reactivity of five-, six-, and seven-membered cyclic ketimines was demonstrated.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker VRX-400 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Deuterated solvent peaks were used as internal references: deutero-chloroform at 2.25 and 77.00 ppm and deutero-DMSO at 2.50 and 39.50 ppm. The IR spectra were measured using a UR-20 spectrometer. TLC was performed using 25 DC-Alufolien Kieselgel 60 F_{254} (Merck). Fluka Silica gel 60 (0.063–0.200 mm) was used for column chromatography. Commercial reagents and solvents were generally used as received.

4.2. General procedure for the Ugi reaction

The appropriate imine (1.1 mmol) and carboxylic acid (1 mmol) were dissolved in abs CH_2Cl_2 (2 ml). The isocyanide (1.0 mmol) was added and the solution was stirred for the appropriate time at room temperature. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography (hexane/ethyl-acetate, 1:1).

4.2.1. 1-Benzoyl-*N*-benzyl-2-methylprolinamide (1a). Yield 50%, white solid, mp 87–88 °C [Found: C, 74.62; H, 6.66. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88%]; ν_{max} (Nujol) 2880, 1660, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.7 (1H, br, N*H*), 7.30–7.45 (5H, m, COPh), 7.20–7.35 (5H, m, Ph), 4.5 (2H, d, *J* 5.7 Hz, C*H*$_2$Ph), 3.40–3.55 (2H, m, *H*-4), 2.67–2.77 (1H, m, *H*-2), 1.85–1.92 (1H, m, *H*-2), 1.75–1.85 (2H, m, *H*-3), 1.80 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 174.75, 167.35, 137.15, 136.70, 131.28, 128.65, 127.40, 126.66, 126.16, 69.40, 48.57 (m), 43.61, 38.31, 23.77, 21.06.

4.2.2. *N*-Benzyl-1-(chloroacetyl)-2-methylprolinamide (1b). Yield 80%, colorless oil [Found: C, 61.36; H, 6.86. $C_{15}H_{19}ClN_2O_2$ requires C, 61.12; H, 6.50%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (liquid film) 2870, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.5 (1H, br, N*H*), 7.20–7.35 (5H, m, Ph), 4.41 and 4.45 (2H, both d, *J* 5.6 Hz, C*H*$_2$Ph), 4.03 (2H, d, *J* 1.5 Hz, C*H*$_2$Cl), 3.60–3.75 (2H, m, *H*-4), 2.51–2.63 (1H, m, *H*-2), 1.9–2.05 (1H, m, *H*-2), 1.71–1.93 (2H, m, *H*-3), 1.67 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.9, 165.78, 138.19, 128.43, 127.19, 68.72, 48.81 (m), 43.48, 42.90, 38.54, 23.36, 21.82.

4.2.3. *N*-Benzyl-1-(dichloroacetyl)-2-methylprolinamide (1c). Yield 73%, white solid, mp 107–108 °C [Found: C, 55.01; H, 5.72. $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54.72; H, 5.51%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2870, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.33 (5H, m, Ph), 6.8 (1H, br, N*H*), 6.13 (1H, s, C*H*Cl$_2$), 4.43 (2H, d, *J* 5.3 Hz, C*H*$_2$Ph), 3.71–3.86 (2H, m, *H*-4), 2.50–2.63 (1H, m, *H*-2), 1.95–2.05 (1H, m, *H*-2), 1.75–1.87 (2H, m, *H*-3), 1.70 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.51, 162.47, 138.06, 128.54, 127.32, 127.23, 69.45, 66.15, 48.85 (m), 43.67, 38.38, 23.62, 21.54.

4.2.4. *N*-Benzyl-2-methyl-1-(trichloroacetyl)prolinamide (1d). Yield 78%, white solid, mp 111–112 °C [Found: C, 49.40; H, 5.08. $C_{15}H_{17}Cl_3N_2O_2$ requires C, 49.54; H, 4.71%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (Nujol) 2900, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (5H, m, Ph), 6.6 (1H, br, N*H*), 4.44 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.70–3.85 (2H, m, *H*-4), 2.40–2.50 (1H, m, *H*-2), 1.93–2.08 (2H, m, *H*-2 and *H*-3), 1.77–1.84 (1H, m, *H*-3), 1.70 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.47, 158.70, 138.02, 128.62, 127.55, 127.39, 93.58, 70.37, 51.31 (m), 43.83, 38.56, 24.61, 20.88.

4.2.5. *N*-Benzyl-2-methyl-1-(trifluoroacetyl)prolinamide (1e). Yield 83%, white solid, mp 94–95 °C [Found: C, 57.27; H, 5.72. $C_{15}H_{17}F_3N_2O_2$ requires C, 57.32; H, 5.45%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2880, 1680, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (5H, m, Ph), 6.65 (1H, br, N*H*), 4.42 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.70–3.85 (2H, m, *H*-4), 2.40–2.50 (1H, m, *H*-2), 1.93–2.08 (2H, m, *H*-2 and *H*-3), 1.77–1.84 (1H, m, *H*-3), 1.66 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 171.95, 155.65 (q, *J* 36.6), 137.99, 128.59, 127.34, 116.0 (q, *J* 288.4), 69.46, 48.57 (m), 43.71, 38.31, 23.87, 21.06.

4.2.6. *N*-(4-Bromophenyl)-2-methyl-1-(trifluoroacetyl)-prolinamide (1f). Yield 72%, white solid, mp 119–120 °C [Found: C, 44.50; H, 3.47. $C_{14}H_{14}BrF_3N_2O_2$ requires C, 44.35; H, 3.72%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 2900, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$)

8.3 (1H, br, N*H*), 7.48 (2H, d, *J* 8.6 Hz, *m*-Ph), 6.95 (2H, d, *J* 8.6 Hz, *o*-Ph), 3.32–3.38 (2H, m, *H*-4), 2.53–2.60 (2H, m, *H*-2), 1.83–1.89 (2H, m, *H*-3), 1.73 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 166.72, 154.54 (q, *J* 36.8), 135.71, 130.63, 125.42, 124.05, 116.2 (q, *J* 288.3), 77.62, 49.21 (m), 38.99, 23.96, 21.50.

4.2.7. Ethyl 4-{[2-methyl-1-(trifluoroacetyl)prolyl]amino}-butanoate (1g). Yield 85%, colorless oil [Found: C, 49.39; H, 6.20. $C_{14}H_{21}F_3N_2O_4$ requires C, 49.70; H, 6.26%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2950, 1720, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.7 (1H, br, N*H*), 4.07 (2H, q, *J* 7 Hz, $COOCH_2Me$), 3.67–3.85 (2H, m, *H*-4), 3.26 (2H, q, *J* 5.6 Hz, $CH_2CH_2CH_2COOCH_2CH_3$), 2.30–2.42 (3H, m, *H*-2 and $CH_2CH_2CH_2COOCH_2Me$), 1.90–2.07 (2H, m, *H*-2 and *H*-3), 1.73–1.85 (3H, m, *H*-3 and $CH_2CH_2CH_2COOCH_2Me$), 1.63 (3H, s, *Me*), 1.20 (3H, t, *J* 7.1 Hz, CH_2Me); δ_C (400 MHz, $CDCl_3$) 173.69, 172.12, 155.52 (q, *J* 36.6), 115.2 (q, *J* 288.6), 69.44, 60.44, 48.52 (m), 39.47, 38.40, 31.76, 24.98, 23.83, 20.96, 14.04.

4.2.8. Ethyl 2-methyl-1-(trifluoroacetyl)prolyl-2-methyl-alaninate (1h). Yield 50%, white solid, mp 65–66 °C [Found: C, 50.01; H, 6.30. $C_{14}H_{21}F_3N_2O_4$ requires C, 49.70; H, 6.26%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2930, 1750, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9 (1H, br, N*H*), 4.15 (2H, q, *J* 7.1 Hz, $COOCH_2Me$), 3.67–3.85 (2H, m, *H*-4), 2.4–2.48 (1H, m, *H*-2), 1.91–2.12 (2H, m, *H*-2 and *H*-3), 1.70–1.80 (1H, m, *H*-3), 1.65 (3H, s, *Me*), 1.44 (6H, s, CMe_2), 1.22 (3H, t, *J* 7.1 Hz, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 174.51, 170.99, 155.66 (q, *J* 36.7), 115.2 (q, *J* 288.3), 69.70, 61.46, 56.68, 48.62 (m), 38.12, 24.38, 24.18, 23.81, 21.11, 13.94.

4.2.9. *N*,2-Dibenzyl-1-(trifluoroacetyl)prolinamide (1i). Yield 45%, white solid, mp 89–90 °C [Found: C, 64.59; H, 5.42. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2910, 1680, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.38 (8H, m, Ph and Ph), 7.07 (2H, dd, *J* 2.2, *J* 5.7 Hz, *o*-Ph), 6.9 (1H, br, N*H*), 4.42–4.55 (2H, m, $NHCH_2Ph$), 3.65–3.75 (2H, m, *H*-4), 3.10–3.20 (2H, m, CH_2Ph), 2.35–2.47 (1H, m, *H*-2), 2.03–2.10 (1H, m, *H*-2), 1.70–1.85 (1H, m, *H*-3), 1.32–1.44 (1H, m, *H*-3); δ_C (400 MHz, $CDCl_3$) 172.03, 155.65 (q, *J* 36.6), 138.60, 137.99, 130.33, 128.59, 127.50, 127.34, 126.88, 116.0 (q, *J* 288.4), 70.55, 48.57 (m), 43.70, 39.07, 23.95.

4.2.10. *N*-Benzyl-2-butyl-1-(trifluoroacetyl)prolinamide (1j). Yield 95%, white solid, mp 84–85 °C [Found: C, 60.34; H, 6.62. $C_{18}H_{23}F_3N_2O_2$ requires C, 60.66; H, 6.50%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (Nujol) 2890, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.40 (5H, m, Ph), 4.33–4.57 (2H, m, CH_2Ph), 3.85–3.93 (1H, m, *H*-4), 3.57–3.62 (1H, m, *H*-4), 2.65–2.73 (1H, m, *H*-2), 2.10–2.25 (2H, m, $CH_2CH_2CH_2CH_3$), 1.91–2.02 (2H, m, *H*-2 and *H*-3), 1.75–1.85 (1H, m, *H*-3), 1.05–1.35 (4H, m, $CH_2CH_2CH_2CH_3$), 0.86 (3H, t, $CH_2CH_2CH_2Me$); δ_C (400 MHz, $CDCl_3$) 171.79, 156.53 (q, *J* 36.6), 138.20, 128.58, 127.27, 116.0 (q, *J* 288.4), 74.21, 48.57 (m), 43.66, 34.53, 33.46, 26.10, 23.69, 22.63, 13.80.

4.2.11. *N*-Benzyl-2-isopropyl-1-(trifluoroacetyl)prolinamide (1k). Yield 60%, colorless oil [Found: C, 59.85; H, 6.40. $C_{17}H_{21}F_3N_2O_2$ requires C, 59.64; H, 6.18%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (liquid film) 2950, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, N*H*), 7.22–7.35 (5H, m, Ph), 4.53–4.60 (1H, m, CH_2Ph), 4.32–4.40 (1H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.50–3.58 (1H, m, *H*-4), 3.13–3.23 (1H, m, *H*-2), 2.77–2.83 (1H, m, *H*-2), 1.86–2.03 (2H, m, *H*-3), 1.65–1.73 (1H, m, C*H*), 0.87 (3H, d, *J* 7 Hz, *Me*), 0.83 (3H, d, *J* 7 Hz, *Me*); δ_C (400 MHz, $CDCl_3$) 171.32, 157.65 (q, *J* 36.6), 138.37, 128.54, 127.21, 127.18, 116.53 (q, *J* 288.4), 79.85, 49.99 (m), 43.64, 29.23, 27.38, 23.47, 17.63, 16.18.

4.2.12. *N*-Benzyl-2-cyclopentyl-1-(trifluoroacetyl)prolinamide (1l). Yield 50%, white solid, mp 88–89 °C [Found: C, 62.12; H, 6.44.$C_{19}H_{23}F_3N_2O_2$ requires C, 61.95; H, 6.29%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2920, 1690, 1630 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.9 (1H, br, N*H*), 7.22–7.35 (5H, m, Ph), 4.53–4.60 (1H, m, CH_2Ph), 4.32–4.40 (1H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.50–3.58 (1H, m, *H*-4), 3.30–3.58 (1H, m, *H*-2), 2.82–2.87 (1H, m, *H*-2), 1.90–2.00 (2H, m, *H*-3), 1.52–1.75 (7H, m, cpt), 1.20–1.35 (2H, m, cpt); δ_C (400 MHz, $CDCl_3$) 171.88, 157.06 (q, *J* 36.6), 138.35, 128.54, 127.16, 116.3 (q, *J* 288.4), 78.32, 49.92 (m), 43.63, 41.40, 29.14, 28.71, 27.06, 26.55, 25.37, 23.38.

4.2.13. *N*-Benzyl-2-*tert*-butyl-1-(trifluoroacetyl)prolinamide (1m). Yield 95%, white solid, mp 85–86 °C [Found: C, 60.40; H, 6.72. $C_{18}H_{23}F_3N_2O_2$ requires C, 60.66; H, 6.50%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 2910, 1680, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.8 (1H, br, N*H*), 7.20–7.33 (5H, m, Ph), 4.43–4.51 (2H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.45–3.55 (1H, m, *H*-4), 2.87–2.95 (1H, m, *H*-2), 1.83–1.93 (2H, m, *H*-2 and *H*-3), 1.53–1.65 (1H, m, *H*-3), 1.13 (9H, s, *t*-Bu); δ_C (400 MHz, $CDCl_3$) 171.56, 158.66 (q, *J* 36.9), 138.09, 128.59, 127.53, 127.27, 116.7 (q, *J* 288.1), 84.32, 50.99 (m), 43.98, 38.39, 34.88, 27.84, 23.27.

4.2.14. *N*-Benzyl-2-phenyl-1-(trifluoroacetyl)prolinamide (1n). Yield 7%, white solid, mp 100–101 °C [Found: C, 63.43; H, 5.09. $C_{20}H_{19}F_3N_2O_2$ requires C, 63.82; H, 5.09%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 3000, 1690, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.18–7.33 (8H, m, Ph and Ph), 7.07–7.12 (2H, m, Ph), 4.50–4.57 (2H, m, CH_2Ph), 4.35–4.43 (1H, m, CH_2Ph), 3.97–4.05 (1H, m, *H*-4), 3.87–3.97 (1H, m, *H*-4), 3.10–3.20 (1H, m, *H*-2), 1.86–2.05 (3H, m, *H*-2 and *H*-3); δ_C (400 MHz, $CDCl_3$) 170.34, 156.56 (q, *J* 36.3), 138.06, 137.89, 128.75, 128.57, 127.93, 127.45, 127.29, 125.50, 116.0 (q, *J* 288.6), 77.11, 49.37 (m), 44.11, 40.75, 24.28.

4.2.15. Ethyl 2-methyl-1-(trifluoroacetyl)prolylalaninate (1p), mixture of diastereomers, ratio 1:1. Yield 65%, white solid, mp 69–70 °C [Found: C, 47.83; H, 6.12. $C_{13}H_{19}F_3N_2O_4$ requires C, 48.15; H, 5.91%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2920, 1740, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.7, 6.8 (1H, br, N*H*), 4.48 (1H, m, C*H*), 4.17–4.25 (2H, m, $COOCH_2CH_3$), 3.70–3.87 (2H, m, *H*-4), 2.37–2.48 (1H, m, *H*-2), 1.91–2.10 (2H, m, *H*-2 and *H*-3), 1.76–1.85 (1H, m, *H*-3), 1.68,

1.59 (3H, s, *Me*), 1.38 (3H, m, CH*Me*), 1.25–1.27 (3H, m, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 172.81, 172.76, 171.55, 171.42, 155.97 (q, *J* 36.7), 116.0 (q, *J* 288.3), 69.58, 69.16, 61.49, 61.46, 53.40, 53.24, 48.63 (m), 38.33, 38.24, 23.94, 23.78, 21.10, 20.94, 14.02, 14.00.

4.2.16. Ethyl 2-methyl-1-(trifluoroacetyl)prolylphenylalaninate (1q), mixture of diastereomers, ratio 1:1. Yield 55%, white solid, mp 66–67 °C [Found: C, 56.64; H, 5.45. $C_{19}H_{23}F_3N_2O_4$ requires C, 56.99; H, 5.79%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2940, 1740, 1710, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.07–7.30 (5H, m, Ph), 6.6, 6.5 (1H, br, N*H*), 4.83 (1H, m, C*H*), 4.17 (2H, q, *J* 7.1 Hz, $COOCH_2CH_3$), 3.65–3.80 (2H, m, *H*-4), 3.05–3.20 (2H, m, CH_2Ph), 2.30–2.40 (1H, m, *H*-2), 1.83–2.01 (2H, m, *H*-2 and *H*-3), 1.72–1.83 (1H, m, *H*-3), 1.65, 1.62 (3H, s, *Me*), 1.25 (t, *J* 7.1 Hz, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 171.46, 171.43, 171.26, 171.19, 155.97 (q, *J* 36.7), 135.88, 135.72, 129.37, 129.29, 128.46, 129.39, 127.05, 126.99, 116.0 (q, *J* 288.3), 69.52, 69.46, 61.47, 53.40, 53.24, 48.49 (m), 38.41, 38.15, 37.76, 37.66, 23.67, 21.06, 20.91, 13.99.

4.2.17. Ethyl 2-methyl-1-(trifluoroacetyl)prolylmethioninate (1r), mixture of diastereomers, ratio 1:1. Yield 52%, yellow oil [Found: C, 46.83; H, 6.15. $C_{15}H_{23}F_3N_2O_4S$ requires C, 46.87; H, 6.03%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2980, 1730, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9, 7.0 (1H, br, N*H*), 4.63 (1H, m, C*H*), 4.17 (2H, m, CH_2CH_3), 3.70–3.90 (2H, m, *H*-4), 2.35–2.60 (3H, m, *H*-2, $CH_2CH_2SCH_3$), 2.12–2.20 (1H, m, *H*-2), 2.09, 2.08 (3H, s, SCH_3), 1.94–2.06 (3H, m, *H*-3, CH_2CH_2SMe), 1.80–1.88 (1H, m, *H*-3), 1.68, 1.69 (3H, s, *Me*), 1.27–1.35 (3H, m, CH_2Me); δ_C (400 MHz, $CDCl_3$) 171.71, 171.69, 171.58, 155.60 (q, *J* 36.7), 116.5 (q, *J* 288.5), 69.45, 69.99, 61.54, 52.06, 51.95, 48.44 (m), 38.37, 38.16, 31.04, 30.76, 29.78, 29.75, 23.87, 23.70, 20.79, 20.71, 15.24, 13.93.

4.2.18. Diethyl 2-methyl-1-(trifluoroacetyl)prolylglutamate (1s), mixture of diastereomers, ratio 1:1. Yield 56%, yellow oil [Found: C, 49.48; H, 6.04. $C_{17}H_{25}F_3N_2O_6$ requires C, 49.75; H, 6.14%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2990, 1730, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9, 7.1 (1H, br, N*H*), 4.50 (1H, m, C*H*), 4.07–4.22 (4H, m, $COOCH_2CH_3$ and $COOCH_2CH_3$), 3.70–3.92 (2H, m, *H*-4), 2.32–2.46 (3H, m, *H*-2, CH_2CH_2COOEt), 2.12–2.25 (1H, m, *H*-2), 1.93–2.10 (3H, m, H-3 and CH_2CH_2COOEt), 1.80–1.90 (1H, m, *H*-3), 1.68, 1.67 (3H, s, *Me*), 1.20–1.27 (6H, m, $COOCH_2Me$ and $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 173.43, 173.37, 172.07, 172.01, 171.60, 157.5 (q, *J* 36.5), 116.0 (q, *J* 288.6), 69.52, 68.99, 61.54, 60.71, 52.45, 52.32, 48.50 (m, C-4), 38.60, 38.37, 30.21, 30.18, 26.33, 26.50, 23.95, 23.76, 20.86, 20.79, 14.05, 14.03.

4.2.19. Methyl 2-methyl-1-(trifluoroacetyl)prolyl-L-phenylalaninate (1t), mixture of diastereomers, ratio 1:1. Yield 55%, colorless oil, crystallizes on standing [Found: C, 55.90; H, 5.60. $C_{18}H_{21}F_3N_2O_4$ requires C, 55.96; H, 5.48%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2940, 1740, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.07–7.30 (5H, m, Ph), 6.6, 6.5 (1H, br, N*H*), 4.83–4.88 (1H, m, C*H*), 3.65–3.80 (5H, m, *H*-4, COO*Me*), 3.05–3.20 (2H, m, CH_2Ph), 2.27–2.42 (1H, m, *H*-2), 1.85–2.00 (2H, m, *H*-2 and *H*-3), 1.72–1.83 (1H, m, *H*-3), 1.65, 1.63 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 171.82, 171.73, 171.55, 155.97 (q, *J* 36.7), 135.79, 135.64, 129.37, 129.26, 128.58, 129.52, 127.18, 126.11, 116.0 (q, *J* 288.3), 69.49, 69.43, 53.38, 53.19, 48.54 (m, C-4), 38.44, 38.16, 37.78, 37.65, 23.74, 21.09, 20.90.

4.3. General procedure for deprotection 1e–m

The appropriate amides **1e**–**m** (0.5 mmol) were dissolved in abs MeOH (5 ml). The $NaBH_4$ (0.25 mmol) was added and the solution was stirred for the appropriate time at room temperature. The solvent was removed in vacuo and the resulting crude residue was treated with 2 ml of 2 M aq K_2CO_3. Product was extracted with ethyl-acetate (3×10 ml), dried over K_2CO_3, and evaporate in vacuo.

4.3.1. *N*-Benzyl-2-methylprolinamide (3a). Yield 80%, yellow oil [Found: C, 71.20; H, 8.48. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31%]; R_f (2% NH_3(aq)/CH_3CN) 0.6; ν_{max} (liquid film) 2960, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, t, *J* 5.9 Hz, CH_2Ph), 3.03–3.10 (1H, m, *H*-4), 2.77–2.83 (1H, m, *H*-4), 2.25–2.37 (1H, m, *H*-2), 1.60–1.80 (3H, m, *H*-2 and *H*-3), 1.43 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 177.24, 138.84, 128.47, 127.32, 127.06, 66.50, 47.03, 42.96, 37.61, 26.47, 25.94.

4.3.2. *N*,2-Dibenzylprolinamide (3b). Yield 90%, yellow oil [Found: C, 77.77; H, 7.23. $C_{19}H_{22}N_2O$ requires C, 77.52; H, 7.53%]; R_f (2% NH_3(aq)/CH_3CN) 0.6; ν_{max} (liquid film) 2960, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.0 (1H, br, CON*H*), 7.05–7.35 (10H, m, Ph and Ph), 4.27–4.45 (2H, m, $PhCH_2NH$), 3.67 (1H, d, *J* 13.3 Hz, CH_2Ph), 2.97–3.05 (1H, m, *H*-4), 2.82–2.88 (1H, m, *H*-4), 2.70 (1H, d, *J* 13.3 Hz, $PhCH_2$), 2.23–2.30 (1H, m, H-2), 1.83–1.92 (2H, m, *H*-2 and *H*-3), 1.67–1.80 (1H, m, *H*-3); δ_C (400 MHz, $CDCl_3$) 176.12, 138.55, 137.08, 127.79, 128.41, 127.44, 127.03, 126.70, 70.01, 46.53, 43.49, 43.03, 37.11, 25.61.

4.3.3. *N*-Benzyl-2-butylprolinamide (3c). Yield 82%, yellow oil [Found: C, 73.62; H, 8.95. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2980, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.4 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, d, *J* 6 Hz, CH_2Ph), 2.96–3.05 (1H, m, *H*-4), 2.75–2.82 (1H, m, *H*-4), 2.20–2.27 (1H, m, *H*-2), 1.96–2.04 (1H, m, *H*-2), 1.60–1.73 (3H, m, *H*-3 and $CH_2CH_2CH_2Me$), 1.43–1.50 (1H, m, $CH_2CH_2CH_2Me$), 1.15–1.30 (4H, m, $CH_2CH_2CH_2Me$), 0.85 (3H, t, *J* 7 Hz, *Me*); δ_C (400 MHz, $CDCl_3$) 176.59, 138.89, 128.46, 127.44, 127.08, 69.94, 47.04, 43.04, 38.99, 36.92, 27.06, 26.09, 22.96, 13.88.

4.3.4. *N*-Benzyl-2-isopropylprolinamide (3d). Yield 81%, yellow oil [Found: C, 73.13; H, 8.95. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2950, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, d, *J* 5.9 Hz, CH_2Ph), 2.94–3.03 (1H, m, *H*-4), 2.73–2.80 (1H, m, *H*-4), 2.13–2.27 (2H, m, *H*-2 and C*H*), 1.60–1.76 (3H, m, *H*-2 and *H*-3), 0.89 (6H, m, *Me* and *Me*); δ_C (400 MHz,

$CDCl_3$) 176.33, 138.82, 128.55, 127.39, 126.96, 73.09, 47.21, 42.89, 34.64, 34.59, 26.33, 18.69, 16.99.

4.3.5. *N*-Benzyl-2-cyclopentylprolinamide (3e). Yield 83%, yellow oil [Found: C, 75.13; H, 8.98. $C_{17}H_{24}N_2O$ requires C, 74.96; H, 8.88%]; R_f (2% NH_3(aq)/CH_3CN) 0.7; ν_{max} (liquid film) 2980, 2780 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.23–7.38 (5H, m, Ph), 4.30–4.40 (2H, m, C*H*$_2$Ph), 2.92–3.01 (1H, m, *H*-4), 2.75–2.81 (1H, m, *H*-4), 2.42–2.51 (1H, m, *H*-2), 2.20–2.30 (1H, m, *H*-2), 1.45–1.76 (9H, m, C*H*, *H*-3 and cpt), 1.15–1.35 (2H, m, cpt); δ_C (400 MHz, $CDCl_3$) 176.56, 138.77, 128.43, 127.55, 126.88, 71.56, 47.17, 45.74, 42.76, 34.78, 26.37, 27.06, 26.52, 25.40.

4.3.6. *N*-Benzyl-2-*tert*-butylprolinamide (3f). Yield 77%, yellow oil [Found: C, 73.62; H, 8.95. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2960, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.5 (1H, br, CONH), 7.22–7.35 (5H, m, Ph), 4.40 (2H, m, C*H*$_2$Ph), 2.94–3.0 (1H, m, *H*-4), 2.75–2.85 (1H, m, *H*-4), 2.24–2.33 (1H, m, *H*-2), 1.60–1.80 (3H, m, *H*-2 and *H*-3), 1.04 (9H, s, *t*-Bu); δ_C (400 MHz, $CDCl_3$) 175.74, 138.95, 128.44, 127.56, 127.03, 75.73, 47.05, 43.16, 35.87, 31.19, 26.43, 26.28.

4.3.7. 2-Methyl-1-(trifluoroacetyl)prolylalanine (3g), mixture of isomers. To a stirred solution of amide **1p** 157 mg (0.5 mmol) in a mixture of MeOH/H_2O (1:1, 5 ml), 69 mg (0.25 mmol) K_2CO_3 was added and the solution was stirred for 24 h at room temperature. The solvent was removed in vacuo and the resulting crude residue was treated with 0.2 ml of 50% aq CF_3COOH and product was extracted with ethyl-acetate (3×5 ml) and evaporated in vacuo to yield 72% **3g** as yellow oil [Found: C, 44.65; H, 5.12. $C_{11}H_{15}F_3N_2O_4$ requires C, 44.60; H, 5.10%]; R_f (5% MeOH/CH_3CN) 0.7; ν_{max} (liquid film) 2950, 1690 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.90, 7.85 (1H, s, N*H*), 4.15–4.25 (1H, m, CH), 3.65–3.85 (2H, m, H-4), 2.03–2.15 (1H, m, H-2), 1.81–2.00 (3H, m, *H*-2 and *H*-3), 1.59, 1.48 (3H, s, *Me*), 1.20–2.30 (3H, m, *Me*CH); δ_C (400 MHz, DMSO-d_6) 174.18, 174.13, 171.37, 171.25, 153.95 (q, *J* 36.4), 116.12 (q, *J* 288.4), 68.89, 68.77, 48.21, 47.85, 38.07, 38.01, 23.37, 20.29, 19.99, 17.03, 16.67.

4.3.8. *N*-Benzyl-2-butyl-1-(trifluoroacetyl)piperidine-2-carboxamide (4a). Yield 84%, white solid, mp 91–29 °C [Found: C, 62.00; H, 6.90. $C_{19}H_{25}F_3N_2O_2$ requires C, 61.61; H, 6.80%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (Nujol) 2970, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.37 (5H, m, Ph), 6.10 (1H, br, N*H*), 4.46 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.60–3.70 (1H, m, *H*-5), 3.39–3.49 (1H, m, *H*-5), 2.42–2.52 (1H, m, *H*-2), 1.95–2.06 (1H, m, *H*-2), 1.60–1.90 (6H, m, *H*-3 and C*H*$_2$CH$_2$CH$_2$CH$_3$ and CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.22–1.39 (3H, m, CH$_2$CH$_2$C*H*$_2$CH$_3$ and *H*-4), 1.09–1.20 (1H, m, *H*-4), 0.87 (3H, t, *J* 7.0 Hz, CH$_2$CH$_2$CH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 171.98, 155.75 (q, *J* 36.4), 138.25, 128.71, 127.60, 127.45, 116.0 (q, *J* 288.6), 66.65, 43.82, 42.71 (m), 34.35, 30.48 (C-2), 25.99, 22.85, 21.97, 16.55, 13.94.

4.3.9. *N*-Benzyl-2-phenyl-1-(trifluoroacetyl)piperidine-2-carboxamide (4b). Yield 79%, white solid, mp 99–100 °C [Found: C, 64.65; H, 5.42. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (Nujol) 2960, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.05–7.35 (10H, m, Ph and Ph), 5.8 (1H, br, NH), 4.37–4.45 (1H, m, PhCH_2), 4.22–4.27 (1H, m, PhCH_2), 3.73–3.83 (1H, m, H-5), 3.23–3.30 (1H, m, H-5), 2.55–2.64 (1H, m, H-2), 2.23–2.32 (1H, m, H-2), 1.67–1.83 (2H, m, H-3), 1.52–1.63 (1H, m, H-4), 1.26–1.40 (1H, m, H-4); δ_C (400 MHz, $CDCl_3$) 171.16, 158.13 (q, *J* 36.6), 138.31, 133.66, 129.66, 128.81, 128.72, 127.60, 127.51, 127.40, 117.0 (q, *J* 288.6), 70.40, 44.29, 43.65 (m), 34.68, 23.53, 18.66.

4.3.10. Ethyl 4-({[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}amino)butanoate (4c). Yield 67%, colorless oil [Found: C, 57.60; H, 6.16. $C_{20}H_{25}F_3N_2O_4$ requires C, 57.96; H, 6.08%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2990, 1720, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.47 (3H, m, Ph), 7.22–7.27 (2H, m, Ph), 5.6 (1H, br, N*H*), 4.05 (2H, q, *J* 7.1 Hz, COOC*H*$_2$CH$_3$), 3.78–3.88 (1H, m, *H*-5), 3.23–3.32 (1H, m, *H*-5), 3.16–3.23 (2H, q, *J* 6.3 Hz, C*H*$_2$CH$_2$CH$_2$COOEt), 2.58–2.67 (1H, m, *H*-2), 2.27–2.34 (1H, m, *H*-2), 2.24 (2H, t, *J* 7.1, CH$_2$CH$_2$C*H*$_2$COOEt), 1.55–1.85 (5H, m, *H*-3 and CH$_2$C*H*$_2$CH$_2$COOEt and *H*-4), 1.21–1.45 (1H, m, *H*-4), 1.19 (3H, t, *J* 7.1 Hz, COOCH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.84, 170.66, 157.38 (q, *J* 35.9), 136.06, 129.12, 128.14, 126.95,115.6 (q, *J* 289.1), 69.81, 60.03, 43.03 (m), 39.08, 33.85, 31.17, 23.92, 23.00, 18.09, 13.84.

4.3.11. Ethyl 2-methyl-*N*-{[2-phenyl-1-(trifluoroacetyl)-piperidin-2-yl]carbonyl}alaninate (4d). Yield 71%, colorless oil [Found: C, 57.77; H, 6.15. $C_{20}H_{25}F_3N_2O_4$ requires C, 57.96; H, 6.08%]; R_f (50% EtOAc/hexane) 0.6; ν_{max} (liquid film) 2980, 1710, 1700, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.43 (5H, m, Ph), 6.4 (1H, br, N*H*), 4.07–4.19 (2H, m, COOC*H*$_2$CH$_3$), 3.72–3.85 (1H, m, *H*-5), 3.37–3.45 (1H, m, *H*-5), 2.51–2.60 (1H, m, *H*-2), 1.17–2.24 (1H, m, *H*-2), 1.74–1.88 (2H, m, *H*-3), 1.58–1.7 (2H, m, *H*-4), 1.50 (3H, s, CMe*Me*), 1.42 (3H, s, C*Me*Me), 1.22 (3H, t, *J* 7.1 Hz, COOCH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 174.20, 169.52, 157.85 (q, *J* 35.9), 134.14, 129.11, 128.11, 126.73, 117.7 (q, *J* 289.1), 70.08, 61.31, 56.59, 43.36, 34.77, 24.50, 23.75, 23.14, 18.32, 13.98.

4.3.12. Ethyl *N*-{[2-butyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}alaninate (4e), mixture of diastereomers, ratio 1:1. Yield 78%, white solid, mp 83–84 °C [Found: C, 53.50; H, 7.16. $C_{17}H_{27}F_3N_2O_4$ requires C, 53.68; H, 7.15%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (Nujol) 2980, 1740, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.47, 6.33 (1H, br, N*H*), 4.46–4.57 (1H, m, C*H*), 4.12–4.25 (2H, m, COOC*H*$_2$CH$_3$), 3.65–3.75 (1H, m, *H*-5), 3.33–3.47 (1H, m, *H*-5), 2.33–2.50 (1H, m, *H*-2), 1.95–2.10 (1H, m, *H*-2), 1.60–1.90 (7H, m, *H*-3, *H*-2, C*H*$_2$CH$_2$CH$_2$Me and CH$_2$C*H*$_2$CH$_2$Me), 1.35–1.45 (3H, m, *Me*), 1.30–1.35 (2H, m, CH$_2$CH$_2$C*H*$_2$Me), 1.27–1.30 (3H, t, *J* 7.6 Hz, COOCH$_2$*Me*), 1.05–1.17 (1H, m, *H*-4), 0.85–0.93 (3H, m, CH$_2$CH$_2$CH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 173.11, 171.50, 171.37, 157.38 (q, *J* 35.9), 115.7 (q, *J* 289.1), 66.69, 66.04, 61.53, 48.47, 48.28, 42.68, 42.32, 33.87, 33.67, 30.32, 30.10, 25.88, 22.86, 22.01, 21.69, 18.30, 18.27, 16.52, 16.16, 14.07, 13.98.

4.3.13. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}alaninate (4f), mixture of diastereomers, ratio 1:1. Yield 72%, white solid, mp 96–97 °C [Found: C, 57.05; H, 5.51. $C_{19}H_{23}F_3N_2O_4$ requires C, 56.99; H, 5.79%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.50 (5H, m, Ph), 5.9, 6.4 (1H, br, N*H*), 4.41–4.52 (1H, m, C*H*), 4.10 (2H, q, *J* 7.1 Hz, COOCH_2Me), 3.75–3.90 (1H, m, *H*-5), 3.21–3.42 (1H, m, *H*-5), 2.52–2.64 (1H, m, *H*-2), 2.20–2.40 (1H, m, *H*-2), 1.72–1.87 (2H, m, *H*-3), 1.55–1.69 (1H, m, *H*-4), 1.38–1.52 (1H, m, *H*-4), 1.15–1.4 (6H, m, *Me*, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.76, 172.43, 170.32, 169.98, 157.8 (q, *J* 36.0), 136.79, 135.68, 129.45, 129.20, 128.37, 128.28, 127.31, 127.78, 116.8 (q, *J* 289.2), 69.86, 61.38, 61.26, 48.74, 48.67, 43.61, 43.18 (m), 34.52, 34.07, 23.43, 23.14, 18.66, 18.18, 18.06, 17.59, 14.04, 13.94.

4.3.14. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}phenylalaninate (4g and 4h). Yield 84%, ratio of the diastereomers 1:1.

Diastereomer 1: white solid, mp 96–97 °C [Found: C, 63.05; H, 5.61. $C_{25}H_{27}F_3N_2O_4$ requires C, 63.02; H, 5.71%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.41 (6H, m, Ph and Ph), 6.78–7.01 (4H, m, Ph), 6.2 (1H, br, N*H*), 4.68–4.75 (1H, m, C*H*), 4.00 (2H, q, *J* 7.1 Hz, $COOCH_2CH_3$), 3.63–3.75 (1H, m, *H*-5), 3.25–3.35 (1H, m, *H*-5), 3.15–3.23 (1H, m, CH_2Ph), 2.73–2.85 (1H, m, CH_2Ph), 2.33–2.45 (1H, m, *H*-2), 2.03–2.12 (1H, m, *H*-2), 1.60–1.75 (2H, m, *H*-3), 1.45–1.60 (1H, m, *H*-4), 1.23–1.38 (1H, m, *H*-4), 1.19 (3H, t, *J* 7.1 Hz, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 170.98, 170.13, 156.5 (q, *J* 35.9), 136.41, 136.17, 129.30, 129.10, 128.28, 128.15, 126.73, 126.66, 116.5 (q, *J* 289.2), 69.87, 61.42, 53.57, 43.53 (m), 37.55, 34.52, 23.44, 18.65, 13.94.

Diastereomer 2: white solid, mp 112–113 °C [Found: C, 63.12; H, 5.67. $C_{25}H_{27}F_3N_2O_4$ requires C, 63.02; H, 5.71%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (3H, m, Ph), 7.15–7.20 (2H, m, Ph), 6.91–7.05 (3H, m, Ph), 6.76–6.83 (2H, Ph), 5.90 (1H, br, N*H*), 4.70–4.80 (1H, m, C*H*), 4.01 (2H, q, *J* 7.1 Hz, COOCH_2Me), 3.63–3.74 (1H, m, *H*-5), 3.12–3.21 (1H, m, *H*-5), 2.70–2.97 (2H, m, CH_2Ph), 2.40–2.50 (1H, m, *H*-2), 2.20–2.38 (1H, m, *H*-2), 1.62–1.75 (2H, m, *H*-3), 1.43–1.57 (1H, m, *H*-4), 1.23–1.35 (1H, m, *H*-4), 1.1 (3H, t, *J* 7.1 Hz, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 171.03, 170.22, 156.6 (q, *J* 35.9), 136.50, 136.21, 129.33, 129.09, 128.28, 128.13, 126.68, 126.65, 116.4 (q, *J* 289.2), 69.89, 61.43, 53.61, 43.49 (m), 37.56, 34.52, 23.47, 18.44, 13.97.

4.3.15. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}methioninate (4i), mixture of diastereomers, ratio 1:1. Yield 68%, yellow oil [Found: C, 54.50; H, 5.55. $C_{21}H_{27}F_3N_2O_4S$ requires C, 54.77; H, 5.91%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2990, 1730, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.50 (5H, m, Ph), 6.4, 6.2 (1H, br, N*H*), 4.52–4.67 (1H, m, C*H*), 4.07–4.15 (2H, m, COOCH_2Me), 3.75–3.90 (1H, m, *H*-5), 3.21–3.40 (1H, m, *H*-5), 2.50–2.60 (1H, m, *H*-2), 2.32–2.48 (3H, m, *H*-2 and $CH_2CH_2SCH_3$), 2.15–2.29 (2H, m, C$H_2$$CH_2$SMe), 1.95–2.03 (3H, s, CH_2CH_2S*Me*), 1.67–1.83 (2H, m, *H*-3), 1.52–1.63 (1H, m, *H*-4), 1.26–1.40 (1H, m, *H*-4), 1.15–1.25 (3H, m, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 174.20, 169.52, 158.00 (q, *J* 35.9), 137.14, 129.11, 128.11, 126.73, 116.5 (q, *J* 289.3), 70.08, 61.31, 56.89, 42.36 (m), 34.77, 24.50, 23.75, 23.14, 22.88, 18.32 (C-3), 13.98.

4.3.16. Diethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}glutamate (4j), mixture of diastereomers, ratio 1:1. Yield 69%, yellow oil [Found: C, 56.50; H, 6.05. $C_{23}H_{29}F_3N_2O_6$ requires C, 56.78; H, 6.01%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2990, 1720, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.50 (5H, m, Ph), 6.4, 6.1 (1H, br, N*H*), 4.47–4.56 (1H, m, C*H*), 4.00–4.17 (4H, m, $COOCH_2CH_3$ and $COOCH_2CH_3$), 3.77–3.90 (1H, m, *H*-5), 3.24–3.40 (1H, m, *H*-5), 2.50–2.60 (1H, m, *H*-2), 2.20–2.44 (3H, m, *H*-2 and CH_2CH_2COOEt), 2.13–2.18 (2H, m, CH_2CH_2COOEt), 1.73–1.90 (2H, m, *H*-3), 1.56–1.67 (1H, m, *H*-4), 1.34–1.50 (1H, m, *H*-4), 1.15–1.28 (6H, m, $CH_2CH_2COOCH_2$*Me* and $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.30, 172.49, 171.53, 171.13, 170.62, 170.28, 157.53 (q, *J* 35.9), 136.40, 135.58, 129.33, 129.18, 128.45, 128.30, 127.23, 126.80, 116.3 (q, *J* 289.7), 69.77, 69.73, 61.46, 61.32, 60.43, 60.28, 52.14, 50.00, 43.47, 43.02 (m), 34.35, 34.00, 29.93, 27.03, 26.63, 23.35, 23.02, 18.50, 18.03, 13.94.

4.3.17. Methyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}-L-phenylalaninate (4k and 4l). Yield 84%, ratio of the diastereomers 1:1.

Diastereomer 1: colorless oil, crystallizes on standing [Found: C, 62.35; H, 5.45. $C_{24}H_{25}F_3N_2O_4$ requires C, 62.33; H, 5.45%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.2–7.34 (6H, m, Ph and Ph), 6.98–7.05 (4H, m, Ph), 6.2 (1H, br, N*H*), 4.78–4.85 (1H, m, C*H*), 3.72–3.82 (1H, m, *H*-5), 3.65 (3H, s, COO*Me*), 3.3–3.4 (1H, m, *H*-5), 3.15–3.23 (1H, m, CH_2Ph), 2.9–2.97 (1H, m, CH_2Ph), 2.42–2.53 (1H, m, *H*-2), 2.08–2.18 (1H, m, *H*-2), 1.70–1.85 (2H, m, *H*-3), 1.58–1.69 (1H, m, *H*-4), 1.34–1.44 (1H, m, *H*-4); δ_C (400 MHz, $CDCl_3$) 171.50, 170.19, 156.5 (q, *J* 35.9), 136.36, 136.03, 129.17, 129.08, 128.33, 128.13, 126.85, 126.66, 116.4 (q, *J* 289.1), 69.80, 53.44, 52.22, 43.50 (m), 37.44, 34.48, 23.38, 18.58.

Diastereomer 2: colorless oil, crystallizes on standing [Found: C, 62.30; H, 5.48. $C_{24}H_{25}F_3N_2O_4$ requires C, 62.33; H, 5.45%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30–7.42 (3H, m, Ph), 7.21–7.27 (2H, m, Ph), 7.05–7.14 (3H, m, Ph), 6.84–6.90 (2H, m, Ph), 6.0 (1H, br, N*H*), 4.82–4.89 (1H, m, C*H*), 3.71–3.80 (1H, m, *H*-5), 3.65 (3H, s, *Me*), 3.2–3.29 (1H, m, *H*-5), 2.95–3.08 (2H, m, CH_2Ph), 2.46–2.56 (1H, m, *H*-2), 2.28–2.35 (1H, m, *H*-2), 1.65–1.82 (2H, m, *H*-3), 1.54–1.65 (1H, m, *H*-4), 1.31–1.42 (1H, m, *H*-4); δ_C (400 MHz, $CDCl_3$) 171.54, 169.90, 157.00 (q, *J* 36.0), 135.76, 135.43, 129.30, 128.91, 128.39, 127.05, 126.71, 116.5 (q, *J* 289.1), 69.84, 53.01, 51.99, 43.50 (m), 37.19, 34.13, 23.15, 18.34.

4.3.18. 7-Phenyl-1-(trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-azepine (5a). Yield 68%, yellow oil [Found: C, 62.33; H,

5.34. $C_{14}H_{14}F_3NO$ requires C, 62.54; H, 5.24%]; R_f (30% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1690, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.40 (5H, m, Ph), 6.45 (1H, m, C*H*), 4.4–4.7 (2H, m, *H*-6), 2.3–2.4 (2H, m, *H*-3), 1.80–2.13 (3H, m, *H*-4, *H*-5), 1.31–1.45 (1H, m, *H*-5); δ_C (400 MHz, $CDCl_3$) 154.5 (q, *J* 36.1), 142.51, 136.50, 128.67, 128.33, 127.30, 124.09, 115.9 (q, *J* 289.1), 48.80, 28.66, 26.59, 23.72.

4.3.19. 2-Methylene-1-(trifluoroacetyl)azepane (5b). Yield 71%, yellow oil [Found: C, 52.23; H, 5.74. $C_9H_{12}F_3NO$ requires C, 52.17; H, 5.84%]; ν_{max} (liquid film) 1690, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.15 (1H, s, H*H*C=C), 5.03 (1H, s, *H*HC=C), 3.57–3.68 (2H, m, *H*-6), 2.40–2.50 (2H, m, *H*-2), 1.71–1.81 (2H, m, *H*-3), 1.55–1.69 (4H, m, *H*-4 and *H*-5); δ_C (400 MHz, $CDCl_3$) 155.6 (q, *J* 36.3), 138.15, 116.90 (q, *J* 289.1), 109.82, 48.56, 34.29, 28.13, 26.08, 23.65.

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References and notes

1. Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197–4212.
2. (a) Willims, M.; Kowaluk, E. A.; Arneric, S. P. *J. Med. Chem.* **1999**, *42*, 1481–1500; (b) Dutta, A. S. *Drugs Future* **1988**, *13*, 43–44; (c) Dutta, A. S. *Drugs Future* **1988**, *13*, 761–762; (d) Patane, M. A.; DiPardo, R. M.; Price, R. A. P.; Chang, R. S. L.; Ransom, R. W.; O'Malley, S. S.; Di Salvo, J.; Block, M. G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2495–2500; (e) Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553–5566; (f) Huruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397; (g) Roy, R. S.; Balarm, P. *J. Pept. Res.* **2004**, *63*, 279–289.
3. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
4. Voet, D.; Voet, J.; Pratt, C. *Fundamentals of Biochemistry*; Wiley: New York, NY, 1999; pp 127–128.
5. Lummis, S. C. R.; Beene, D. L.; Lee, L. W.; Lester, H. A.; Brodhurst, R. W.; Dougherty, D. A. *Nature* **2005**, 248–252.
6. (a) Soth, M.; Nowick, J. S. *J. Org. Chem.* **1999**, *64*, 276–281; (b) Hanessian, S.; Blanco, M. J.; Paleo, M. R.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786–8793.
7. (a) Dumy, P.; Keller, M.; Ryan, D. E.; Rohwedder, B.; Wohr, T.; Mutter, M. *J. Am. Chem. Soc.* **1997**, *119*, 918–925; (b) Beausoleil, E.; Sharma, R.; Michnick, S. W.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 6572–6578; (c) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902–12908; (d) Delaney, N. G.; Madison, V. *J. Am. Chem. Soc.* **1982**, *104*, 6635–6641; (e) Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 5927–5937; (f) Grathwohl, C.; Wuthrich, K. *Biopolymers* **1981**, *20*, 2623–2633.
8. Wu, W. J.; Raleigh, D. R. *J. Org. Chem.* **1998**, *63*, 6689–6698.
9. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
10. (a) Flanagan, D. M.; Joullie, M. M. *Synth. Commun.* **1989**, *19*, 1–12; (b) Bowers, M. M.; Carroll, P.; Joullie, M. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 857–865; (c) Hatam, M.; Tehranfar, D.; Martens, J. *Synthesis* **1994**, 619–623; (d) Groger, H.; Hatam, M.; Martens, J. *Tetrahedron* **1995**, *51*, 7173–7180; (e) Zychlinski, A.; Ugi, I. *Heterocycles* **1998**, *49*, 29–32; (f) Maison, W.; Lutzen, A.; Kosten, M.; Schlemminger, I.; Westerho, O.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3515–3525; (g) Maison, W.; Lutzen, A.; Kosten, M.; Schlemminger, I.; Westerho, O.; Saak, W.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1867–1871; (h) Schlemminger, I.; Janknecht, H. H.; Maison, W.; Saak, W.; Martens, J. *Tetrahedron Lett.* **2000**, *41*, 7289–7292; (i) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637–6640; (j) Chapman, T. M.; Davies, L. G.; Gu, B.; Block, T. M.; Scopes, D. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. M.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506–507; (k) Timmer, M.; Risseeuw, M.; Verdoes, M.; Filippov, D.; Plaisier, J.; Van der Marel, G.; Overkleeft, H.; Van Boom, J. *Tetrahedron: Asymmetry* **2005**, *16*, 177–185.
11. (a) Hua, D.; Miao, S.; Bharathi, N.; Katsuhira, T.; Bravo, A. *J. Org. Chem.* **1990**, *55*, 3682–3684; (b) Haslego, M.; Maryanoff, C.; Scott, L.; Sorgi, K. *Heterocycles* **1993**, *35*, 643–647.
12. (a) Juaristi, E. *Conformational Behavior of Six-membered Rings*; VCH: New York, NY, 1995; pp 159–196; (b) Glass, R. *Conformational Analysis of Medium-sized Heterocycles*; VCH: New York, NY, 1988; pp 98–106.
13. Kocienski, P. *Protecting Groups*; Georg Thieme: Stuttgard: New York, NY, 1994; pp 190–191.
14. Ugi, I. *Isonitrile Chemistry*; Academic: New York, NY, and London, 1971; 73–74.
15. Zhu, J.; Bienayme, H. *Multicomponent Reaction*; Wiley-VCH: Weinheim, 2005; pp 1–33.
16. Giesemann, G.; Von Hinrichs, E.; Ugi, I. *J. Chem. Res.* **1982**, 79.
17. Eliel, E.; Wilen, S.; Mander, L. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994; 758–759.