Design and synthesis of N-nonpolar nucleobase dipeptides: application of the Ugi reaction for the preparation of dipeptides having fluoroarylalkyl groups appended to the nitrogen atom

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A single-step one-pot synthesis based on the Ugi four-component condensation of previously unknown dipeptides, **2**, **3**, **4** and **5**, having a fluoroaromatic group appended to the nitrogen atom, is described. The series of dipeptides produced here can be viewed as nonpolar nucleobase dipeptides since the difluorotoluene nucleoside **1** is a well known nonpolar analogue of natural thymidine. A mixture of N-protected amino acids **7**, fluorophenethylamines **6**, isocyanides **8**, and acetone or paraformaldehyde are stirred in methanol in the presence of 3 Å molecular sieves to furnish the *N*-fluoroarylethyl-Aib- or -Gly-containing dipeptides **2** or **3**, in moderate yields. The dipeptides **2d** and **3b**, having a cyclohex-1-enamide moiety, are deprotected readily with 3 M HCl in THF to afford the free dipeptides in high yields. The *N*-fluoroarylmethyl-Aib- or -Gly-containing β-alanyl dipeptides **4** or **5**, designed based on the structure of 2′,5′-linked isoDNA, are also synthesized in a similar fashion to the preparation of **2**, in moderate to good yields as both protected and free dipeptides.

Introduction

Difluorotoluene nucleoside **1** has been developed as a nonpolar shape mimic for natural thymidine and it has been intensively used as a probe of the biological noncovalent interactions of oligonucleotides.[1] To everyone's great surprise, **1** serves as a template for DNA synthesis even though it lacks standard polar hydrogen bonding. These reports, along with our continuing interest in the study of fluorine-containing amino acids/peptides,[2] have prompted us to synthesize *N*-difluorotolylethyl dipeptides **2** as N-nonpolar nucleobase peptides (Fig. 1).

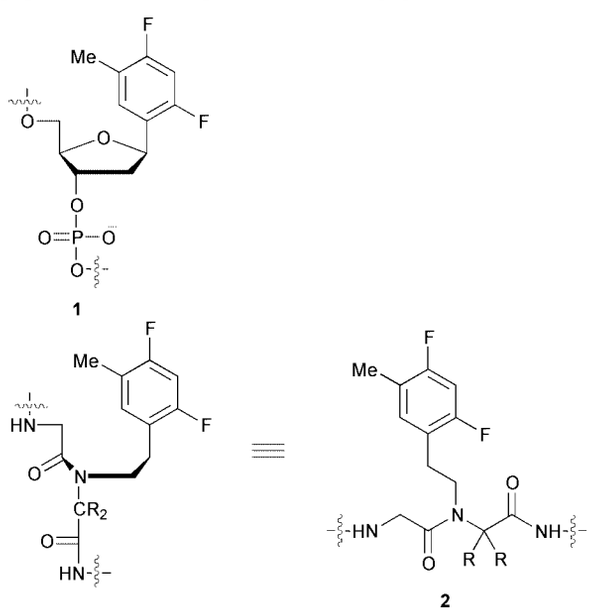
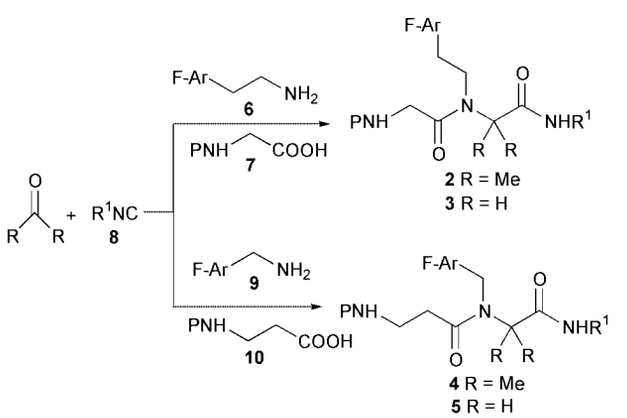


Fig. 1

The incorporation of a fluoroaryl moiety would be expected to confer significant changes in the secondary structure of the peptides due to the strong stacking effects of the fluoroaromatic rings,[3] now functioning as nucleobase surrogates. Moreover, the introduction of a fluorine atom into amino acids and peptides[4] should, in general, induce interesting new chemical and physiological properties.[5] In an earlier communication,[6] we briefly described a single-step synthesis of previously unknown N-nonpolar nucleobase dipeptides **2** that consists of Gly and Aib, substituted with fluoroarylalkyl pendent groups, using the Ugi four-component condensation [Aib: α-aminoisobutyric acid, 2-methylalanine, Ala(2-Me)]. We now delineate full details of our work, including an extension to the synthesis of a series of N-nonpolar nucleobase dipeptides **3**, **4** and **5** consisting of Gly–Gly, βAla–Aib, and βAla–Gly backbones, respectively (Scheme 1).



F-Ar: fluoroaryl; P= Z, Boc; R^1= Bu^t, 1-cyclohexenyl, CH_2COOEt

Scheme 1 Synthesis of N-nonpolar nucleobase dipeptides **2**–**5** by the Ugi four-component condensation.

Results and discussion

Design and synthesis of nonpolar nucleobase dipeptides 2 and 3 based on a Gly–Aib or Gly–Gly framework

In recent years the synthesis of heterocyclic substituted non-proteinogenic amino acids and peptides,[7] especially those

Table 1 Synthesis of nonpolar nucleobase dipeptides **2** [Gly–Aib(*N*-fluoroarylethyl)][a]

Entry	Glycine **7**[b]	F–Ar–$CH_2CH_2NH_2$ **6**	CNR^1 **8**	Product **2**	Yield (%)[c]
1	**7a**	*p*-Fluorophenethylamine **6a**	$CNBu^t$ **8a**	**2a**	42
2	**7a**	2,4-Difluorophenethylamine **6b**	$CNBu^t$ **8a**	**2b**	51
3	**7a**	2,4-Difluorophenethylamine **6b**	$CNCH_2COOEt$ **8b**	**2c**	42
4	**7b**	2,4-Difluorophenethylamine **6b**	CN-cyclohex-1-nyl **8c**	**2d**	45
5	**7a**	*ar*-Pentafluorophenethylamine **6c**	$CNBu^t$ **8a**	**2e**	45
6	**7a**	*ar*-Pentafluorophenethylamine **6c**	$CNCH_2COOEt$ **8b**	**2f**	51
7	**7a**	2,4-Difluoro-5-methylphenethylamine **6d**	$CNBu^t$ **8a**	**2g**	43

[a] The Ugi reaction was performed using glycines **7** ($ProtNHCH_2COOH$), amines **6** (F–Ar–$CH_2CH_2NH_2$), isocyanides **8** (CNR^1) and acetone in MeOH to give dipeptides **2** (see Scheme 1). [b] **7a**: $ZNHCH_2COOH$, **7b**: $BocNHCH_2COOH$. [c] Yields were based on the amines **6** employed.

amino acids with nucleobases on the side chains,[8] has received much attention. This synthetic activity stems from the biological activity of such analogues, their use as probes to study amino acid–nucleobase interactions, and their utility as peptide (or polyamide) nucleic acids (PNAs),[9] peptoid nucleic acids,[10] aminopentanoic acid nucleobases (APNs)[11] or several analogues of PNA.[12]

The dipeptides **2** were designed, based on the structure of difluorotoluene nucleoside **1**, as nonpolar nucleobase peptides. The preparation of the target compounds **2** undoubtedly could be accomplished by conventional peptide-synthesis procedures. However, this would require multi-step syntheses. The Ugi four-component coupling reaction has recently been shown to be a powerful method for the synthesis of amino acids, peptides and nucleobase-peptide chimaeras.[13,14] We applied the method to the preparation of our dipeptides substituted with fluoroarylethyl pendent groups. Three components for performing the Ugi reaction, *i.e.*, oxo compounds, isocyanides and amino acids, are readily available. The key fluoroarylethylamines **6** were prepared as follows: The fluorophenylacetonitriles **11a**–**c** were reduced by the treatment with aluminium trichloride and lithium aluminium hydride in THF[15] to give the corresponding amines **6a**–**c** in 50–70% yield. The amine **6d** containing the 2,4-difluorotoluene moiety as a steric mimic for thymine was prepared from 5-bromo-2,4-difluorotoluene **12** as follows: Treatment of **12** with Mg, followed by formylation with *N*,*N*-dimethylformamide (DMF),[16] gave the aldehyde **13** in 45% yield, which was then converted into nitroalkene **14** *via* nitroaldol reaction using nitromethane (53% yield) and subsequent dehydration by methanesulfonyl chloride[16] in 61% yield. The product **14** was reduced by the action of lithium aluminium hydride in THF–Et_2O[17] to give 2,4-difluoro-5-methylphenethylamine **6d** in 63% yield (Scheme 2).

The key Ugi reaction was very easy to execute and the desired protected dipeptides **2** were obtained in a single-step one-pot procedure (Scheme 1 and Table 1). Table 1 shows the results of the Ugi reaction using acetone as an oxo compound. The reactions proceeded with moderate yields for a variety of different substituted isocyanides **8** and fluoroarylethylamines **6** to furnish fluoroaromatically pendented dipeptides **2** with an *N*-substituted Aib fragment. When $CNCH_2COOEt$ **8b** was used for the reaction, corresponding tripeptides **2c** and **2f** were obtained (entries 3 and 6). It is interesting to note that 1-iso cyanocyclohexene **8c** was also used in the Ugi reaction to lead to dipeptides having a cyclohexenamide moiety which can be converted to a variety of functional groups (Table 1, entry 4).[18] Since the *N*-alkyl-Aib moiety is known to stabilize helical conformations of mother peptides,[19] the introduction of the resulting dipeptides, Gly–Aib **2**, into oligopeptides would be interesting.

The Ugi reaction was next performed with formaldehyde instead of acetone in order to prepare *N*-fluoroarylethyl dipeptides **3** based on the Gly–Gly framework. *N*-Boc-glycine **7b** was treated with *p*-fluorophenethylamine **6a**, *tert*-butyl isocyanide **8a** and paraformaldehyde in methanol to furnish N-nonpolar nucleobase dipeptide **3a** in 41% yield. The dipeptide **3b** was obtained by a similar treatment of *N*-Boc-glycine **7b** with 2,4-difluoro-5-methylphenethylamine **6d**, 1-isocyanocyclohexene **8c** and paraformaldehyde in 40% yield (Fig. 2).

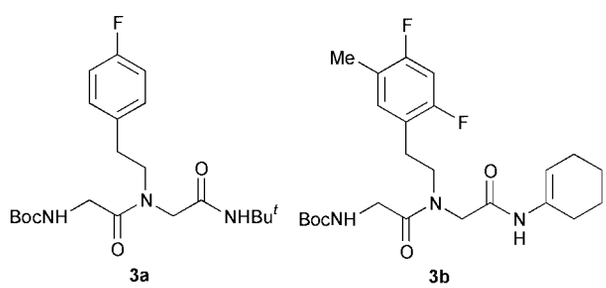


Fig. 2 Dipeptides **3** consisting of a Gly-Gly framework.

N-Fluoroarylethyl dipeptides **2d** (Table 1, entry 4) and **3b** (Fig. 2), each having a cyclohexenamide moiety, were converted to the corresponding free dipeptides **2h** and **3c** in 100% and 91% yield, respectively, by treatment with 3 M HCl in THF (Fig. 3).

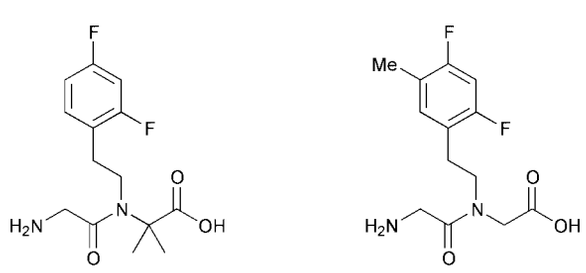
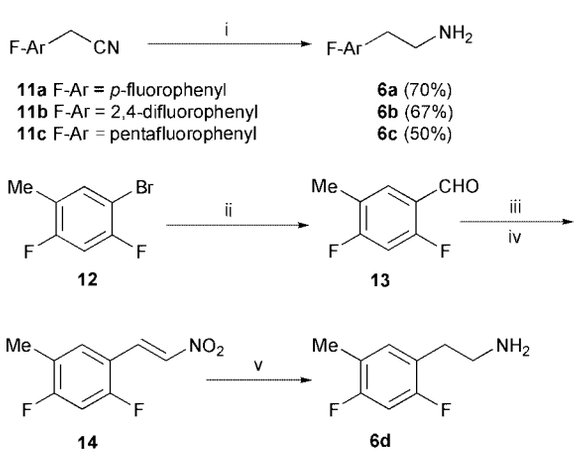


Fig. 3



Scheme 2 *Reagents and conditions (and yields)*: i, $AlCl_3$, $LiAlH_4$, THF, 0 °C (50–70%); ii, Mg, DMF, THF, 0 °C (45%); iii, $MeNO_2$, KOH–MeOH (53%); iv, MsCl, Et_3N CH_2Cl_2 (61%); v, $LiAlH_4$, THF–Et_2O, reflux (63%).

Finally we briefly show the additional utility of the method for a single-step synthesis of peptoid nucleic acid derivatives. Peptoid nucleic acids have been obtained by interchanging the positions of backbone CH_2 and side-chain CO groups of PNAs (Fig. 4). In contrast to PNAs, peptoid nucleic acids have

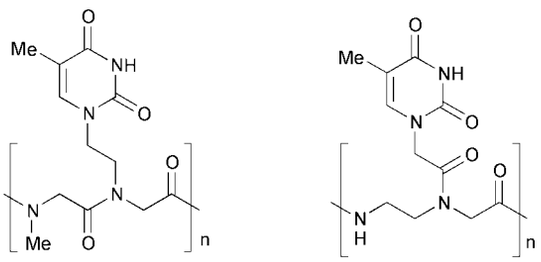
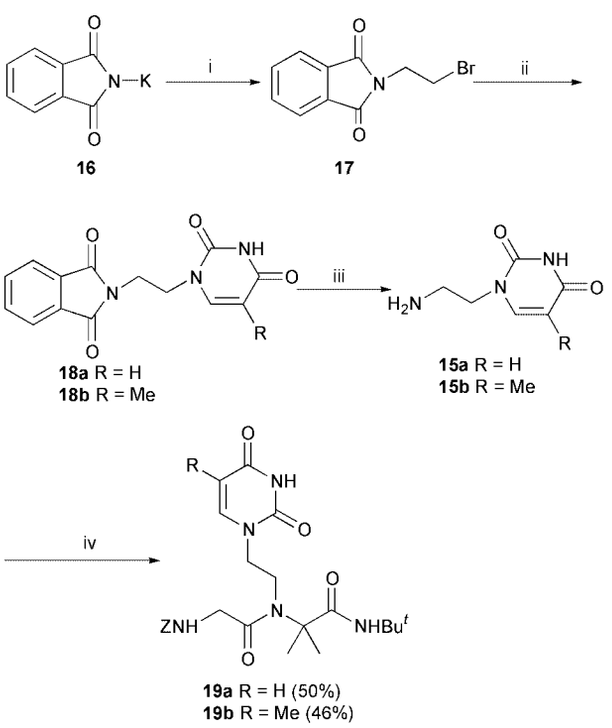


Fig. 4 Structures of peptoid nucleic acid and peptide nucleic acid (PNA).

not attracted much attention. However it has been recently found that a peptoid nucleic acid having thymine as the base is hybridized with DNA and the relative stability of the duplex is higher than that of DNA/DNA.[10]

Since peptoid nucleic acids are prepared by a conventional stepwise procedure,[10] we performed the preparation of the derivatives using our one-pot method. The nucleobase ethyleneamines **15a**,**b** used for the Ugi reaction were prepared as follows: Potassium phthalimide **16** was converted into the bromide **17** by treating with 1,2-dibromoethane in 73% yield. Then **17** was coupled with uracil or thymine in DMSO to give the respective compound **18a**,**b** in 65–66% yield. Compounds **18a**,**b** were converted to the corresponding amines **15a**,**b** by reduction with *n*-butylamine in methanol[20] in high yields.

One-pot preparation of peptoid nucleic acid derivatives was achieved by the Ugi four-component condensation of the amines **15a**,**b** with Z-glycine **7a**, acetone and *tert*-butyl isocyanide **8a** to furnish peptoid nucleic acid monomer derivatives **19a**,**b**, in 50% and 46% yield, respectively (Scheme 3).



Scheme 3 *Reagents and conditions (and yields)*: i, 1,2-dibromoethane, DMF, rt (73%); ii, uracil or thymine, DMSO, K_2CO_3, rt [66% (R = H), 65% (R = Me)]; iii, *n*-butylamine, MeOH, reflux [74% (R = H), 80% (R = Me)]; iv, $ZNHCH_2COOH$ **7a**, $CNBu^t$ **8a**, acetone, MeOH, MS 3 Å, −78 °C; then rt, 1 week.

Design and synthesis of nonpolar nucleobase dipeptides 4, 5 based on a βAla–Aib or βAla–Gly framework

One of the recent modifications of DNA structure is 2′,5′-linked isoDNA where the connecting phosphodiester is linked *via* a 2′,5′ linkage of 3′-deoxyriboses instead of the 3′,5′ linkage of 2′-deoxyriboses of natural DNA.[21] IsoDNA **20** has recently drawn much interest from researchers due to its ability to form a heteroduplex with RNA that is as stable as the comparable normal DNA/RNA duplexes.[21]

We next focused our attention to try to synthesize β-alanyl dipeptides **4**, substituted with fluoroarylmethyl pendent groups, by the Ugi reaction, which products were designed based on the structure of isoDNA **20** (Fig. 5). Constituent elements of **4** are a

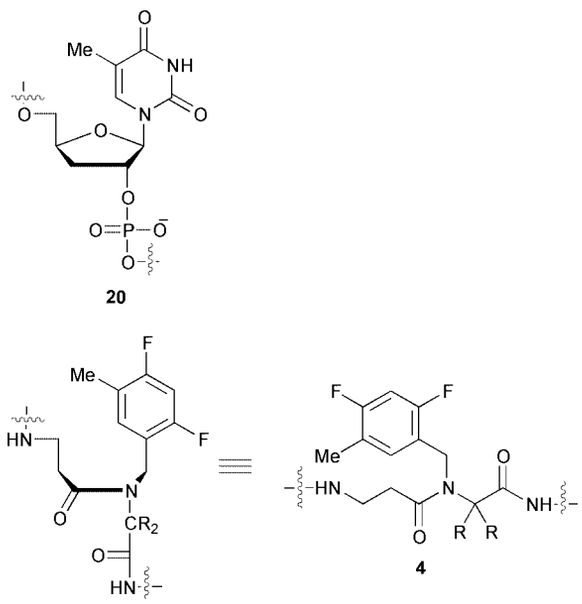


Fig. 5

β-alanine, an α-amino acid, and a fluoroarylmethyl unit. This arrangement was chosen because of the seven-atom spacing that can be found between the nucleobases in 2′,5′-linked isoDNA, and because the optimal number of bonds between the nucleobases and the backbone was found to be one.

The fluorobenzylamines **9** for the Ugi reaction were obtained as follows: *p*-Fluorobenzylamine **9a** and 2,4-difluorobenzylamine **9b** are commercially available and, *ar*-pentafluorobenzylamine **9c** was readily prepared by refluxing pentafluorobenzonitrile **21** with BH_3·THF complex in THF.[22] 2,4-Difluoro-5-methylbenzylamine **9d** was prepared from 5-bromo-2,4-difluorotoluene **12** in two steps. The bromo difluorotoluene **12** was converted into the corresponding cyanide **22** by treatment with copper(I) cyanide in DMF at 160 °C then[23] in 50% yield. The cyanide **22** was reduced to **9d** under refluxing with BH_3·THF complex in THF[22] in 67% yield (Scheme 4).

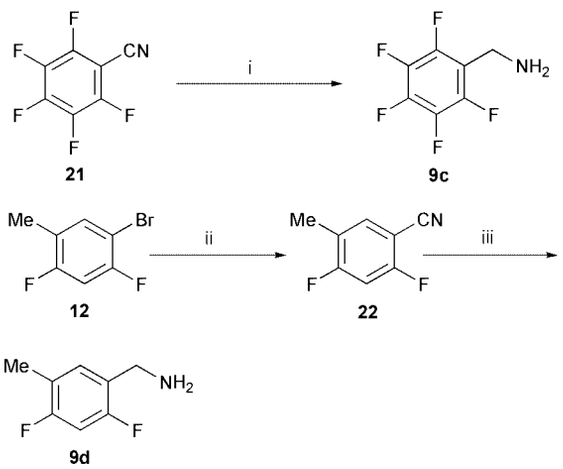
The Ugi condensation of the four components, fluorobenzylamines **9a**–**d**, *N*-protected β-alanines **10**, acetone, and isocyanides **8** successfully produced the target dipeptides, βAla–Aib(*N*-fluoroarylmethyl) **4a**–**f** in a single step, in 43–66% yield (Scheme 1 and Table 2). There is little difference between the yields of the compounds in the βAla–Aib series and those in the Gly–Aib series (Table 1 and Table 2). A variety of fluorobenzylamines **9**, including **9d** as a thymine isostere, were incorporated to produce dipeptides **4a**,**b**,**d**–**f** and tripeptide **4c** in a single step.

Finally dipeptides **5** based on the βAla–Gly framework were synthesized. Boc–βAla–Gly(*N*-*p*-fluorophenylmethyl)-NBu^t **5a** was prepared from the coupling of *N*-Boc-β-alanine **10b** with *p*-fluorobenzylamine **9a**, *tert*-butyl isocyanide **8a**, and paraformaldehyde in 45% yield. The dipeptide **5b** was also prepared

Table 2 Synthesis of nonpolar nucleobase dipeptides **4** [βAla–Aib(*N*-fluoroarylmethyl)][a]

Entry	β-Alanines **10**[b]	F–Ar–CH_2NH_2 **9**	CNR[1] **8**	Product **4**	Yield (%)[c]
1	**10a**	*p*-Fluorobenzylamine **9a**	CNBu[t] **8a**	**4a**	59
2	**10a**	2,4-Difluorobenzylamine **9b**	CNBu[t] **8a**	**4b**	66
3	**10a**	2,4-Difluorobenzylamine **9b**	$CNCH_2COOEt$ **8b**	**4c**	44
4	**10b**	2,4-Difluorobenzylamine **9b**	CN-cyclohex-1-enyl **8c**	**4d**	43
5	**10a**	*ar*-Pentafluorobenzylamine **9c**	CNBu[t] **8a**	**4e**	43
6	**10a**	2,4-Difluoro-5-methylbenzylamine **9d**	CNBu[t] **8a**	**4f**	43

[a] The Ugi reaction was performed using β-alanines **10** ($ProtNHCH_2CH_2COOH$), amines **9** (F–Ar–CH_2NH_2), isocyanides **8** (CNR^1) in MeOH to give dipeptides **4** (see Scheme 1). [b] **10a**: $ZNHCH_2CH_2COOH$, **10b**: $BocNHCH_2CH_2COOH$. [c] Yields were based on the amines **9** employed.



Scheme 4 *Reagents and conditions (and yields)*: i, BH_3·THF complex, THF, reflux; then 2.6 M HCl, reflux (98%); ii, CuCN, DMF, 160 °C (50%); iii, BH_3·THF complex, THF, reflux; then 2.6 M HCl, reflux (67%).

by a similar treatment of *N*-Boc-β-alanine **10b**, 2,4-difluoro-5-methylbenzylamine **9d**, 1-isocyanocyclohexene **8c** and paraformaldehyde in 41% yield (Fig. 6).

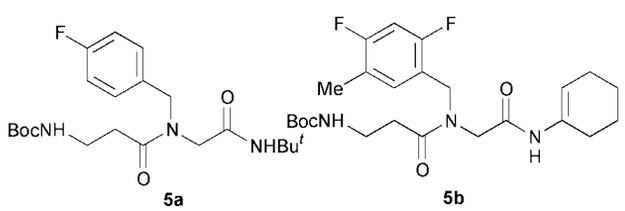


Fig. 6 Dipeptides **5** consisting of a βAla-Gly framework.

Both βAla–Aib **4d** (Table 2, entry 4) and βAla–Gly **5b** (Fig. 6), which have the cyclohex-1-enamide moiety, were deprotected under acidic conditions to give free dipeptides **4g** and **5c** in 96% and 92% yields (Fig. 7).

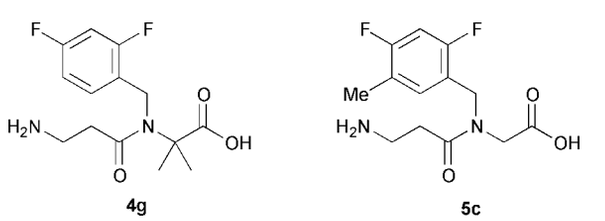


Fig. 7

Conclusion

We have demonstrated a single-step synthesis of a series of dipeptides, having fluoroaromatic groups appended to the nitrogen atom as isosteric replacements for thymine, by Ugi reaction. The peptides are regarded to be N-nonpolar nucleobase dipeptides. Of particular note to our method is its applicability to those peptides containing a variety of amino acids (not only α- and β-, but also χ-amino acids) attached to a diverse series of fluoroarylalkyl groups. Incorporation of species **2**, **3**, **4** and **5** into oligopeptides are now under investigation. In addition, we plan to extend application of this reaction for the synthesis of nonpolar peptoid nucleic acids.†

Experimental

Melting points were recorded on a Yanagimoto micro-melting apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 1600 spectrometer. ^1H NMR spectra were measured as solutions in $CDCl_3$, CD_3OD or D_2O and chemical shifts are expressed in ppm relative to internal Me_4Si (δ 0.00) and were recorded on a JEOL GX-270 (270 MHz) spectrometer. ^{19}F NMR spectra were measured with $CFCl_3$ as an internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ-values.

The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. *J*-Values are given in Hz. ^{13}C NMR spectra were recorded at 125.76, 75.46 and 68 MHz using Unity plus 500, Varian Gemini 300 and JEOL GX-270 instruments. Chemical shifts are quoted in δ_C/ppm and are referenced to $CDCl_3$. Electron ionization (EI) mass spectra were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC (PLC) were performed on BW-200 (Fuji Silysia) and Kieselgel 60 (Merck, art. 7748), respectively. All reactions were carried out under a dry N_2 atmosphere. Unless otherwise noted, reagents were added by syringe. MeOH was distilled from CaO immediately prior to use.

General procedure for the preparation of amines 6a–c

First the reducing agent was prepared by adding a solution of aluminium chloride (1.47 g, 11.0 mmol) in THF (15 ml) to a stirred suspension of lithium aluminium hydride (0.417 g, 11.0 mmol) in THF (10 ml) with stirring for 5 min. To this mixture was added a fluorophenylacetonitrile **11a**–**c** (1.00 g) at 0 °C and stirred for 1 h. The reaction was quenched by adding ice–water (30 ml). The phases were separated and the aqueous phase was extracted twice with diethyl ether (50 ml × 2), diluted with aq. ammonia (50 ml), and stirred for an additional 20 min. The precipitate formed was filtered off and the phases were separated. This treatment was repeated twice. The organic phases were combined and extracted with 3 M HCl to trap the free amine. The aqueous portion was made alkaline with 1 M NaOH solution and extracted with diethyl ether (50 ml). The extract was dried over Na_2SO_4 and evaporated to give the corresponding amine **6a**–**c** in 50–70% yield, which were used for the Ugi reaction without further purification.

***p*-Fluorophenethylamine 6a.**[24] Prepared by following the general procedure from **11a** (1.00 g, 7.31 mmol) as a yellow oil

† We have accomplished the synthesis of nonpolar peptide nucleic acids[2d] but the synthesis of nonpolar peptoid nucleic acid has not yet done. The framework of **2** and **3** is as same as that of peptoid nucleic acids. However it lacks a methyl group on the glycyl nitrogen atom. Therefore the peptides **2** and **3** are not considered to be nonpolar peptoid nucleic acids as they are.

(729 mg, 70%); ν_{max} (neat)/cm^{-1} 3436, 3003, 1603, 1511, 1385, 1230, 1158, 1098, 1018; δ_H ($CDCl_3$) 2.71 (2H, br t, *J* 6.9, CH_2CH$_2$N), 2.93 (2H, br t, *J* 6.9, CH$_2$CH_2N), 6.96 (2H, m, ArH), 7.15 (2H, m, ArH); δ_F ($CDCl_3$) −117.8 (m); *m*/*z* (EI) 140 (M^+ + 1), 139 (M^+), 122 (M^+ − NH_3); HRMS Found: M^+, 139.0819. $C_8H_{10}FN$ requires *M*, 139.0797.

2,4-Difluorophenethylamine 6b.[25] Prepared by following the general procedure from **11b** (1.00 g, 6.53 mmol) as a yellow oil (694 mg, 67%); ν_{max} (neat)/cm^{-1} 3435, 3294, 2999, 1504, 1138, 965; δ_H ($CDCl_3$) 2.73 (2H, br t, *J* 6.9, CH_2CH$_2$N), 2.91 (2H, br t, *J* 6.9, CH$_2$CH_2N), 6.81 (2H, m, ArH), 7.18 (1H, m, ArH); δ_F ($CDCl_3$) −114.6 (m), −115.7 (br q, *J* 7.8); *m*/*z* (EI) 157 (M^+), 156 (M^+ − 1), 140 (M^+ − NH_3); HRMS Found: M^+, 157.0694. $C_8H_9F_2N$ requires *M*, 157.0703.

***ar*-Pentafluorophenethylamine 6c.**[26] Prepared by following the general procedure from **11c** (1.00 g, 4.82 mmol) as a yellow oil (510 mg, 50%); ν_{max} (neat)/cm^{-1} 3422, 2969, 1504, 1247, 1121, 1083, 960; δ_H ($CDCl_3$) 2.82 (2H, br t, *J* 6.5, CH_2CH$_2$N), 2.96 (2H, br t, *J* 6.5, CH$_2$CH_2N); δ_F ($CDCl_3$) −144.1 (dd, *J* 6.8, 15.2), −157.5 (t, *J* 10.7), −163.2 (td, *J* 7.6, 13.2); *m*/*z* (EI) 211 (M^+), 210 (M^+ − 1), 194 (M^+ − NH_3); HRMS Found: M^+, 211.0374. $C_8H_6F_5N$ requires *M*, 211.0395.

Preparation of 2,4-difluoro-5-methylphenethylamine 6d

2,4-Difluroro-5-methylbenzaldehyde 13. A solution of **12**[1a] (5.0 g, 24.3 mmol) in THF (20 ml) was added to magnesium turnings (641 mg, 26.7 mmol) in THF (20 ml) under nitrogen at such a rate to maintain reflux. The reaction was initiated by the addition of a few crystals of iodine with occasional warming. After formation of Grignard reagent by stirring at room temperature for about 1 h, a mixture of freshly distilled DMF (1.87 ml, 24.3 mmol) and THF (10 ml) was added to the stirred mixture at 0 °C during 5 min. The mixture was stirred on the ice-bath for 45 min and then at room temperature for 4 h. A simple work-up according to the literature procedure[16] and subsequent purification by column chromatography on silica gel (hexane–ethyl acetate 8 : 2) afforded aldehyde **13** (2.40 g, 45%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2931, 2861, 1692 (CHO), 1491, 1266, 1175, 849; δ_H ($CDCl_3$) 2.27 (3H, s, ArCH_3), 6.85 (1H, t, *J* 9.6, ArH), 7.72 (1H, t, *J* 8.1, ArH), 10.24 (1H, s, CHO); δ_F ($CDCl_3$) −101.6 (m), −122.4 (m); *m*/*z* (EI) 156 (M^+), 155 (M^+ − 1); HRMS Found: (M^+ − 1), 155.0139. $C_8H_5F_2O$ requires *m*/*z*, 155.0139.

2,4-Difluoro-5-methyl-β-nitrostyrene 14. A mixture of **13** (2.4 g, 15.5 mmol) and nitromethane (7.40 ml, 137 mmol) was stirred under nitrogen and treated with 3 M methanolic KOH until pH 8 was attained. After being stirred for 1 h the solution was acidified to pH 4 with concentrated sulfuric acid. The mixture was added to water (50 ml) and extracted with diethyl ether (50 ml × 2). The extracts were combined and successively washed with saturated aq. sodium hydrogen carbonate (20 ml) and brine (10 ml), and dried over Na_2SO_4. Concentration under reduced pressure followed by column chromatography on silica gel (hexane–ethyl acetate 8 : 2) afforded the nitro alcohol intermediate (1.76 g, 53%).

The nitro alcohol intermediate (1.76 g, 8.11 mmol) and mesyl chloride (0.690 ml, 8.92 mmol) were stirred under nitrogen in dichloromethane (15 ml). Triethylamine (2.26 ml, 16.2 mmol) was added during 5 min and the reaction mixture was boiled gently and then stirred for 1.5 h at room temperature. After work-up according to the literature procedure,[16] concentration under reduced pressure followed by column chromatography on silica gel (hexane–ethyl acetate 9 : 1) furnished nitro alkene **14** (1.0 g, 61%) as a yellowish solid; ν_{max} (neat)/cm^{-1} 2932, 1637, 1515, 1347, 1105, 967; δ_H ($CDCl_3$) 2.28 (3H, s, ArCH_3), 6.89 (1H, t, *J* 9.8, ArH), 7.34 (1H, t, *J* 8.1, ArH), 7.66 (1H, d, *J* 13.8, CH=C*H*NO$_2$), 7.98 (1H, d, *J* 13.8, C*H*=CHNO$_2$); δ_F ($CDCl_3$) −105.4 (q, *J* 9.2), −109.4 (q, *J* 10.1); *m*/*z* (EI) 199 (M^+); HRMS Found M^+, 199.0424. $C_9H_7F_2NO_2$ requires *M*, 199.0445.

2,4-Difluoro-5-methylphenethylamine 6d. A solution of **14** (500 mg, 2.51 mmol) in anhydrous THF (8 ml) was added dropwise to a well-stirred suspension of $LiAlH_4$ (286 mg, 7.53 mmol) in anhydrous diethyl ether (10 ml), and the mixture was refluxed for 4 h. Excess of $LiAlH_4$ was destroyed by the dropwise addition of water (2 ml) and 15% NaOH solution (5 ml). The combined filtrate was concentrated to dryness under reduced pressure and oily amine **6d** (273 mg, 63%) was obtained which was used for the Ugi reaction without further purification; ν_{max} (neat)/cm^{-1} 3664, 3009, 2932, 1578, 1494, 1179, 958; δ_H ($CDCl_3$) 2.21 (3H, s, ArCH_3), 2.71 (2H, br t, *J* 6.4, CH_2CH$_2$N), 2.92 (2H, br t, *J* 6.4, CH$_2$CH_2N), 6.73 (1H, m, ArH), 6.93 (1H, m, ArH); δ_F ($CDCl_3$) −113.7 (q, *J* 7.8), −115.1 (q, *J* 7.8); *m*/*z* (EI) 171 (M^+); HRMS Found: M^+, 171.0860. $C_9H_{11}F_2N$ requires *M*, 171.0860.

Typical experimental procedure for the preparation of dipeptides 2 by the Ugi four-component condensation reaction: *N*-Benzyloxycarbonylglycyl-*N*-(4-fluorophenylethyl)-2-methylalanine (*N*-*tert*-butyl)amide 2a [Z-Gly-Aib(*N*-4-fluorophenylethyl)-NBu^t]

The amine **6a** (200 mg, 1.52 mmol) and acetone (176 mg, 3.04 mmol) were dissolved in distilled methanol (10 ml) in a flask containing molecular sieves 3 Å, dried previously for at least half an hour. The mixture was stirred for 1 h and then N-protected amino acid **7a** (635 mg, 3.04 mmol) was added directly into the flask in one portion. A solution of *tert*-butyl isocyanide **8a** (252 mg, 3.04 mmol) in methanol (1 ml) was added to the flask at −78 °C in one portion. The resulting solution was stirred at room temperature for 1 week. When the reaction was complete by TLC (5–10% MeOH in CH_2Cl_2), the reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel BW200, eluting with 0–5% methanol in CH_2Cl_2 gradient to give **2a** (301 mg, 42%) as a colourless solid; mp 83–84 °C (from ethyl acetate–hexane) (Found: C, 65.93; N, 8.84; H, 7.20. Calc. for $C_{26}H_{34}FN_3O_4$: C, 66.22; N, 8.91; H, 7.27%); ν_{max} (neat)/cm^{-1} 3410, 3337, 1715, 1663, 1510; δ_H ($CDCl_3$) 1.29 (9H, s, Bu^t), 1.55 (6H, s, Me$_2$C<), 2.93 (2H, br t, *J* 8.2, CH_2CH$_2$N), 3.48 (2H, br t, *J* 8.2, CH$_2$CH_2N), 4.04 (2H, d, *J* 4.3, CH$_2$CON), 5.11 (2H, s, PhCH_2), 5.46 (1H, br s, NH), 5.74 (1H, br s, NH), 6.99 (2H, t, *J* 8.5, ArH), 7.18 (2H, m, ArH), 7.29 (5H, m, ArH); δ_F ($CDCl_3$) −117.2 (m); δ_C (75.45 MHz; $CDCl_3$) 24.83 [C(*C*H$_3$)$_2$], 28.82 [C(*C*H$_3$)$_3$], 37.07 (CH$_2$), 43.74 (CH$_2$), 45.61 (CH$_2$), 51.26 [*C*(CH$_3$)$_3$], 63.23 [*C*(CH$_3$)$_2$], 67.08 (CH$_2$), 115.88 (d, $^2J_{C,F}$ 21.8, F–Ar–CH), 128.05, 128.18, 128.57 (each s, 5 × Ar–CH), 130.05 (d, $^3J_{C,F}$ 8.5, F–Ar–CH), 133.39 (d, $^4J_{C,F}$ 3.7, F–Ar–C), 136.43 (Ar–C, *ipso*), 156.33 (C=O), 161.84 (d, $^1J_{C,F}$ 244.0, Ar–C–F), 168.25 (C=O), 173.40 (C=O); *m*/*z* (EI) 471 (M^+); HRMS Found: M^+, 471.2552. $C_{26}H_{34}FN_3O_4$ requires *M*, 471.2570.

***N*-Benzyloxycarbonylglycyl-*N*-(2,4-difluorophenylethyl)-2-methyalanine (*N*-*tert*-butyl)amide 2b [Z-Gly-Aib(*N*-2,4-difluorophenylethyl)-NBu^t].** Condensation of **6b** (160 mg, 1.02 mmol), acetone (147 mg, 2.53 mmol), **7a** (531 mg, 2.54 mmol) and **8a** (211 mg, 2.54 mmol) gave **2b** (250 mg, 51%) as a white solid; mp 89–90 °C (from ethyl acetate–hexane) (Found: C, 63.42; N, 8.25; H, 6.72. Calc. for $C_{26}H_{33}F_2N_3O_4$: C, 63.79; N, 8.58; H, 6.79%); ν_{max} (neat)/cm^{-1} 3415, 3322, 1715, 1664, 1507; δ_H ($CDCl_3$) 1.32 (9H, s, Bu^t), 1.54 (6H, s, Me$_2$C<), 2.96 (2H, br t, *J* 7.9, CH_2CH$_2$N), 3.48 (2H, br t, *J* 7.9, CH$_2$CH_2N), 4.09 (2H, d, *J* 5.4, CH$_2$CON), 5.12 (2H, s, PhCH_2), 5.45 (1H, br s, NH), 5.71 (1H, br s, NH), 6.82 (2H, m, ArH), 7.18 (1H, m, ArH), 7.35 (5H, m, ArH); δ_F ($CDCl_3$) −111.5 (br quintet, *J* 7.3), −114.1 (br q, *J* 8.3); δ_C (68 MHz; $CDCl_3$) 24.48 [C(*C*H$_3$)$_2$], 28.53 [C(*C*H$_3$)$_3$], 31.12 (CH$_2$), 43.42 (CH$_2$), 43.73 (CH$_2$), 51.01]

$C(CH_3)_3$], 63.04 [$C(CH_3)_2$], 68.86 (CH_2), 104.13 (t, ^2J 25.7, F–Ar–CH), 111.65 (dd, $^2J_{C,F}$ 21.2, $^4J_{C,F}$ 3.8, F–Ar–CH), 120.19 (dd, $^2J_{C,F}$ 16.2, $^4J_{C,F}$ 3.8, F–Ar–C), 127.97, 128.07, 128.47 (each s, 5 × Ar–CH), 131.46 (dd, $^3J_{C,F}$ 9.5, $^3J_{C,F}$ 6.7, F–Ar–CH), 136.39 (Ar–C, *ipso*), 156.32 (C=O), 161.09 (dd, $^1J_{C,F}$ 247.0, $^3J_{C,F}$ 11.7, Ar–C–F), 162.12 (dd, $^1J_{C,F}$ 247.0, $^3J_{C,F}$ 11.7, Ar–C–F), 168.42 (C=O), 173.39 (C=O); *m*/*z* (EI) 489 (M^+); HRMS Found: M^+, 489.2393. $C_{26}H_{33}F_2N_3O_4$ requires *M*, 489.2416.

[*N*-Benzyloxycarbonylglycyl-*N*-(2,4-difluorophenylethyl)-2-methylalanyl]glycine ethyl ester 2c [Z-Gly-Aib(*N*-2,4-difluorophenylethyl)-Gly-OEt]. Condensation of **6b** (200 mg, 1.27 mmol), acetone (147 mg, 2.54 mmol), **7a** (532 mg, 2.54 mmol) and **8b** (288 mg, 2.54 mmol) gave **2c** (280 mg, 42%) as an oil; ν_{max} (neat)/cm^{-1} 3194, 3077, 1626, 1506, 1457; δ_H ($CDCl_3$) 1.29 (3H, t,*J* 7.1, OCH_2CH_3), 1.61 (6H, s, $Me_2C<$), 2.99 (2H, br t, *J* 7.8, CH_2CH_2N), 3.51 (2H, br t, *J* 7.8, CH_2CH_2N), 3.99 (2H, d, *J* 2.7, CH_2CON), 4.11 (2H, d, *J* 2.7, NCH_2CO), 4.21 (2H, q, *J* 7.2, OCH_2CH_3), 5.11 (2H, s, $PhCH_2$), 5.71 (1H, br s, NH), 6.22 (1H, br s, NH), 6.84 (2H, m, ArH), 7.22 (1H, m, ArH), 7.34 (5H, m, ArH); δ_F ($CDCl_3$) −111.5 (br quintet, *J* 7.4), −114.2 (br q, *J* 8.3); *m*/*z* (EI) 519 (M^+); HRMS Found: M^+ 519.2258. $C_{26}H_{31}F_2N_3O_6$ requires *M*, 519.2275.

***N*-*tert*-Butoxycarbonylglycyl-*N*-(2,4-difluorophenylethyl)-2-methylalanine (*N*-cyclohex-1-enyl)amide 2d [Boc-Gly-Aib(*N*-2,4-difluorophenylethyl)-*N*(cyclohex-1-enyl)].** Condensation of **6b** (200 mg, 1.27 mmol), acetone (147 mg, 2.54 mmol), **7b** (444 mg, 2.54 mmol) and **8c** (272 mg, 2.54 mmol) gave **2d** (275 mg, 45%) as a colourless oil; ν_{max} (neat)/cm^{-1} 3423, 3010, 1702, 1505, 1425, 854; δ_H ($CDCl_3$) 1.43 (9H, s, Bu^t), 1.59 (6H, s, $Me_2C<$), 1.69 (4H, m, CH_2 × 2), 2.13 (4H, m, CH_2 × 2), 2.97 (2H, br t, *J* 8.2, CH_2CH_2N), 3.49 (2H, br t, *J* 8.2, CH_2CH_2N), 4.03 (2H, d, *J* 4.3, CH_2CON), 5.47 (1H, br s, NH), 6.04 (1H, br s, CH=C<), 6.55 (1H, br s, NH), 6.85 (2H, m, ArH), 7.19 (1H, m, ArH); δ_F ($CDCl_3$) −111.2 (m), −113.6 (m); *m*/*z* (EI) 479 (M^+); HRMS Found: M^+, 479.1515. $C_{25}H_{35}N_3F_2O_4$ requires *M*, 479.1526.

***N*-Benzyloxycarbonylglycyl-*N*-(pentafluorophenylethyl)-2-methylalanine (*N*-*tert*-butyl)amide 2e [Z-Gly-Aib(*N*-pentafluorophenylethyl)-NBu^t].** Condensation of **6c** (200 mg. 0.947 mmol), acetone (110 mg, 1.89 mmol), **7a** (394 mg, 1.89 mmol) and **8a** (157 mg, 1.89 mmol) gave **2e** (235 mg, 45%) as a white solid; mp 64–65 °C (from ethyl acetate–hexane) (Found: C, 57.40; N, 7.54; H, 5.59. Calc. for $C_{26}H_{30}F_5N_3O_4$: C, 57.45; N, 7.73; H, 5.56%); ν_{max} (neat)/cm^{-1} 3378, 3317, 1735, 1659, 1510; δ_H ($CDCl_3$) 1.33 (9H, s, Bu^t), 1.55 (6H, s, $Me_2C<$), 3.09 (2H, br t, *J* 8.2, CH_2CH_2N), 3.47 (2H, br t, *J* 8.2, CH_2CH_2N), 4.11 (2H, d, *J* 4.6, CH_2CON), 5.12 (2H, s, $PhCH_2$), 5.46 (1H, br s, NH), 5.66 (1H, br s, NH), 7.34 (5H, m, ArH); δ_F ($CDCl_3$) −143.7 (dd, *J* 7.3, 22.3), −155.88 (t, *J* 20.3), −161.6 (td, *J* 7.5, 21.7); δ_C (68 MHz; $CDCl_3$) 14.16 (CH_2), 24.99 [$C(CH_3)_2$], 28.51 [$C(CH_3)_3$], 42.28 (CH_2), 43.30 (CH_2), 51.12 [$C(CH_3)_3$], 63.06 [$C(CH_3)_2$], 66.91 (CH_2), 110.5 (m, Ar–C–F), 127.99, 128.08, 128.46 (each s, 5 × Ar–CH), 137.5 (dm, $^1J_{C,F}$ 254.0, Ar–C–F), 136.33 (Ar–C, *ipso*), 140.28 (dm, $^1J_{C,F}$ 254.0, Ar–C–F), 145.10 (dm, $^1J_{C,F}$ 257.0, F–Ar–C), 156.31 (C=O), 168.55 (C=O), 173.24 (C=O); *m*/*z* (EI) 543 (M^+); HRMS Found: M^+, 543.1118. $C_{26}H_{30}F_5N_3O_4$ requires *M*, 543.1141.

[*N*-Benzyloxycarbonylglycyl-*N*-(pentafluorophenylethyl)-2-methylalanyl]glycine ethyl ester 2f [Z-Gly-Aib(*N*-pentafluorophenylethyl)-Gly-OEt]. Condensation of **6c** (200 mg, 0.947) mmol), acetone (110 mg. 1.89 mmol), **7a** (394 mg, 1.89 mmol) and **8b** (214 mg, 1.89 mmol) gave **2f** (280 mg, 51%) as a white solid; mp 64–65 °C (from ethyl acetate–hexane); ν_{max} (neat)/cm^{-1} 3333, 2986, 1726, 1663, 1506; δ_H ($CDCl_3$) 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.61 (6H, s, $Me_2C<$), 3.09 (2H, br t, *J* 8.0, CH_2CH_2N), 3.51 (2H, br t, *J* 8.0, CH_2CH_2N), 3.98 (2H, d, *J* 4.8, CH_2CON), 4.14 (2H, br d, *J* 4.8, $NHCH_2CO$), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 5.10 (2H, s, $PhCH_2$), 5.78 (1H, br s, NH), 6.36 (1H, br s, NH), 7.33 (5H, m, ArH); δ_F ($CDCl_3$) −139.1 (dd, *J* 8.3, 22.0), −150.8 (t, *J* 20.8), −157.1 (td, *J* 13.9, 21.0); *m*/*z* (EI) 573 (M^+), 553 (M^+ − HF); HRMS Found: M^+ 573.1924. $C_{26}H_{28}F_5N_3O_6$ requires *M*, 573.1950.

***N*-Benzyloxycarbonylglycyl-*N*-(2,4-difluoro-5-methylphenylethyl)-(2-methylalanine *N*-*tert*-butyl)amide 2g [Z-Gly-Aib(*N*-2,4-difluoro-5-methylphenylethyl)-NBu^t].** Condensation of **6d** (200 mg, 1.16 mmol), acetone (134 mg, 2.32 mmol), **7a** (540 mg, 2.58 mmol) and **8a** (214 mg, 2.58 mmol) gave **2g** (255 mg, 43%) as a colourless oil; ν_{max} (neat)/cm^{-1} 3425, 3328, 1746, 1673, 1528, 1452; δ_H ($CDCl_3$) 1.27 (9H, s, Bu^t), 1.34 (6H, s, $Me_2C<$), 1.62 (3H, s, $ArCH_3$), 2.48 (2H, br t, *J* 5.0, CH_2CH_2N), 3.47 (2H, br t, *J* 5.0, CH_2CH_2N), 4.54 (2H, br s, CH_2CON), 5.08 (2H, s, $PhCH_2$), 5.44 (1H, br s, NH), 5.52 (1H, br s, NH), 6.82 (1H, m, ArH), 7.34 (5H, m, ArH), 7.71 (1H, m, ArH); δ_F ($CDCl_3$) −111.7 (br quintet, *J* 6.9), −115.2 (br q, *J* 8.6); *m*/*z* (EI) 506 (M^+ + 3), 503 (M^+); HRMS Found: (M^+ + 3), 506.2835. $C_{27}H_{38}F_2N_3O_4$ requires *m*/*z*, 506.2830.

***N*-*tert*-Butoxycarbonylglycyl-*N*-(4-fluorophenylethyl)glycine (*N*-*tert*-butyl)amide 3a [Boc-Gly-Gly(*N*-4-fluorophenylethyl)-NBu^t].** Condensation of **6a** (200 mg, 1.43 mmol), paraformaldehyde (515 mg, 2.86 mmol), **7b** (500 mg, 2.86 mmol) and **8a** (237 mg, 2.86 mmol) yielded **3a** (240 mg, 41%) as a yellow oily mixture of rotamers; ν_{max}(neat)/cm^{-1} 3423, 3330, 3071, 2976, 1663, 1511, 1231, 1098; δ_H ($CDCl_3$) 1.25, 1.27 (total 9H, each s, Bu^{t}N), 1.33, 1.37 (total 9H, each s, Bu^{t}O), 2.81 (2H, br t, *J* 7.3, NCH_2CH_2), 3.47 (2H, br t, *J* 7.3, NCH_2CH_2), 3.60, 3.76 (total 2H, each s, $>NCH_2CO$), 3.80 (2H, br s, $NHCH_2CO$), 5.26, 5.71 (total 1H, each br s, NH), 5.65, 6.01 (total 1H, each br s, NH), 6.92 (2H, m ArH), 7.06 (2H, m, ArH); δ_F ($CDCl_3$) −117.2 (m); δ_C (68 MHz; $CDCl_3$) 28.30 [$NC(CH_3)_3$], 28.63 [$OC(CH_3)_3$], 33.85, 33.97 (each s, CH_2), 41.84, 42.20 (each s, CH_2), 49.79, 50.47 (each s, CH_2), 51.36, 51.72 [each s, $NC(CH_3)_3$], 51.99, 52.12 (each s, CH_2), 79.85 [$OC(CH_3)_3$], 115.55 (m, F–Ar–CH), 130.20 (m, F–Ar–CH), 133.14 (F–Ar–C), 155.75 (C=O), 161.84 (d, $^1J_{C,F}$ 245.0, Ar–C–F), 166.26, 167.71 (each s, C=O), 169.42, 169.54 (each s, C=O); *m*/*z* (EI) 410 (M^+ + 1), 409 (M^+), 354 [(M^+ + 1) − Bu^t]; HRMS Found: M^+, 409.2379. $C_{21}H_{32}FN_3O_4$ requires *M*, 409.2377.

***N*-*tert*-Butoxycarbonylglycyl-*N*-(2,4-difluoro-5-methylphenylethyl)glycine (*N*-cyclohex-1-enyl)amide 3b [Boc-Gly-Gly(*N*-2,4-difluoro-5-methylphenylethyl)-N(cyclohex-1-enyl)].** Condensation of **6d** (200 mg, 1.16 mmol), paraformaldehyde (418 mg, 2.32 mmol), amino acid **7b** (404 mg, 2.32 mmol) and **8c** (248 mg, 2.32 mmol) gave **3b** (216 mg, 40%) as a yellow oily mixture of rotamers; ν_{max} (neat)/cm^{-1} 3423, 3318, 3017, 1682, 1508, 1369, 846; δ_H ($CDCl_3$) 1.44 (9H, s, Bu^{t}O), 1.65–2.26 (8H, m, CH_2 × 4), 2.21 (3H, s, $ArCH_3$), 2.89 (2H, m, CH_2CH_2N), 3.55 (2H, m, CH_2CH_2N), 3.79 (2H, m, NCH_2CO), 3.92 (2H, br s, CH_2CON), 5.28 (1H, br s), 5.41 (1H, br s), 6.08 (1H, br s), 6.79 (1H, m, ArH), 6.96 (1H, m, ArH); δ_F ($CDCl_3$) −117.1 (m), −119.4 (m); *m*/*z* (EI) 465 (M^+); HRMS Found: M^+, 465.2460. $C_{24}H_{33}F_2N_3O_4$ requires *M*, 465.2439.

***N*′-(2,4-Difluorophenylethyl)-*N*-glycyl-2-methylalanine 2h [Gly-Aib(*N*-2,4-difluorophenylethyl)].** To a solution of **2d** (30.0 mg, 0.062 mmol)) in THF (3 ml) was added 3 M HCl (2 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated *in vacuo* and dissolved in water (10 ml). Then it was extracted with diethyl ether (50 ml). The aqueous portion was taken and evaporated with subsequent freeze drying to obtain **2h** (19 mg, 100%) as a yellow oily mixture of rotamers; δ_H (D_2O) 1.42, 1.44 (total 6H, each s,

$Me_2C<$), 2.86 (2H, br t, *J* 8.1, CH_2CH_2N), 3.44 (2H, br t, *J* 8.1, CH_2CH_2N), 3.86 (2H, br d, *J* 8.9, CH_2CON), 6.85 (2H, m, ArH), 7.21 (1H, m, ArH); δ_F (D_2O) −108.1 (m), −110.5 (m); *m*/*z* (EI) 300.13 (M^+).

***N′*-(2,4-Difluoro-5-methylphenylethyl)-*N*-glycylglycine 3c [Gly-Gly(*N*-2,4-difluoro-5-methylphenylethyl)].** To a solution of **3b** (20.0 mg, 0.04 mmol) in THF (4 ml) was added 3 M HCl (3 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated in *vacuo* and the residue was dissolved in water (5 ml). Then it was extracted with diethyl ether (20 ml). The aqueous portion was taken and on evaporation with subsequent freeze drying gave **3c** (11.2 mg, 91%) as a yellow oily mixture of rotamers; δ_H (D_2O) 2.27 (3H, s, $ArCH_3$), 2.79 (2H, m, CH_2CH_2N), 3.52 (2H, m, CH_2CH_2N), 3.64, 3.80 (total 2H, each s, NCH_2CO), 3.96, 4.01 (total 2H, each s, NH_2CH_2CO), 6.86 (1H, m, ArH), 7.11 (1H, m, ArH); δ_F (D_2O) −120.5 (m), −124.7 (m); *m*/*z* (EI) 286 (M^+); HRMS Found: M^+, 286.1131. $C_{13}H_{16}F_2N_2O_3$ requires *M*, 286.1111.

Preparation of amines 15a and 15b

***N*-(2-Bromoethyl)phthalimide 17.** To a well-stirred solution of potassium phthalimide **16** (5.00 g, 27.0 mmol) in DMF (10 ml) was added 1,2-dibromoethane (6.91 ml, 81.0 mmol) and the reaction mixture was stirred overnight under nitrogen. After the completion of the reaction by TLC, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (200 ml) and extracted with water (100 ml × 2). The organic portion was washed successively with saturated aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford **17** (5.0 g, 73%) as a white crystalline solid; mp 220–221 °C (from dichloromethane–hexane) (Found: C, 47.42; N, 5.47; H, 3.18. Calc. for $C_{10}H_8BrNO_2$: C, 47.27; N, 5.51; H, 3.17%); ν_{max} (KBr)/cm^{-1} 3003, 2998, 1710, 1227, 923, 863; δ_H ($CDCl_3$) 3.62 (2H, t, *J* 6.6, NCH_2CH_2), 4.13 (2H, t, *J* 6.6, NCH_2CH_2), 7.26 (2H, m, ArH), 7.89 (2H, m, ArH); HRMS Found: M^+, 253.9850. $C_{10}H_8{}^{79}BrNO_2$ requires *M*, 253.9817; and Found: M^+, 255.9785. $C_{10}H_8{}^{81}BrNO_2$ requires *M*, 255.9796.

1-(2-Phthalimidoethyl)uracil 18a. Uracil (5.00 g, 45.0 mmol) was dissolved in DMSO (100 ml) and then treated with K_2CO_3 (5.50 g, 40 mmol) and **17** (5.20 g, 20.5 mmol) for 12 h at room temperature. After the precipitate had been filtered off, the filtrate was concentrated under reduced pressure to a viscous yellowish liquid. The liquid was diluted with dichloromethane (100 ml) and extracted with water (50 ml). The water layer was also back-extracted with dichloromethane (50 ml). The combined organic layers were concentrated at reduced pressure and the resulting oil was dissolved in a small volume of dichloromethane and induced to crystallize with hexane to obtain **18a** (3.86 g, 66%) as a white powder; mp 234–235 °C (from dichloromethane–hexane) (Found: C, 58.59; N, 14.56; H, 3.98. Calc. for $C_{14}H_{11}N_3O_4$: C, 58.95; N, 14.73; H, 3.89%); ν_{max} (KBr)/cm^{-1} 3595, 3492, 3164, 3096, 1769, 1717, 1458; δ_H (5% CD_3OD in $CDCl_3$) 3.54 (4H, br s, NCH_2CH_2N), 5.49 (1H, d, *J* 7.8, uracil 5-H), 7.04 (1H, d, *J* 7.8, uracil 6-H), 7.68 (2H, m, ArH), 7.85 (2H, m, ArH); *m*/*z* (EI) 285 (M^+); HRMS Found: M^+, 285.0453. $C_{14}H_{11}N_3O_4$ requires *M*, 285.0453.

1-(2-Phthalimidoethyl)thymine 18b. Thymine (5.00 g, 39.5 mmol) was alkylated with **17** (5.20 g, 20.5 mmol) in a manner similar to the preparation of **18a** to obtain **18b** (4.0 g, 65%) as a white solid; mp 229–230 °C (from dichloromethane–hexane); ν_{max} (KBr)/cm^{-1} 3464, 3168 (NH), 2292, 1773, 1712 (C=O), 1391, 1184, 875; δ_H (5% CD_3OD in $CDCl_3$) 2.46 (3H, s, 5-CH_3), 3.89–4.20 (4H, m, NCH_2CH_2N), 6.83 (1H, br s, thymine 6-H), 7.65 (4H, m, ArH); *m*/*z* (EI) 299 (M^+); HRMS Found: M^+, 299.0877. $C_{15}H_{13}N_3O_4$ requires *M*, 299.0906.

1-(2-Aminoethyl)uracil 15a. Compound **18a** (1.00 g, 3.50 mmol) was treated with a solution of *n*-butylamine–methanol (1 : 4; v/v) at reflux for 2 days. The reaction mixture was concentrated to dryness and then dissolved in 0.5 M HCl (50 ml). After extraction with diethyl ether (50 ml), the aqueous portion was evaporated under reduced pressure. The residue was dissolved in benzene–methanol (1 : 1) to form an azeotropic mixture, which was evaporated. A solid mass was formed, which was recrystallized from a mixture of MeOH–diethylether–chloroform to obtain **15a** (400 mg, 74%) as a off-white powder; ν_{max} (KBr)/cm^{-1} 3391, 3093, 1966, 1669, 1569, 1458, 1170, 1085; δ_H (CD_3OD) 2.81 (2H, br t, *J* 7.3, $CH_2CH_2NH_2$), 4.05 (2H, br t, *J* 5.2, $>NCH_2CH_2$), 5.60 (1H, d, *J* 7.6, uracil 5-H), 7.52 (1H, d, *J* 7.6, uracil 6-H); *m*/*z* (EI) 155 (M^+), 154 ($M^+ - 1$); HRMS Found: M^+, 155.0632. $C_6H_9N_3O_2$ requires *M*, 155.0655.

1-(2-Aminoethyl)thymine 15b. Compound **18b** (1.00 g, 3.30 mmol) was treated with a solution of *n*-butylamine–methanol (1 : 4; v/v) in a manner analogous to the preparation of **15a**. A similar work-up and recrystallization procedure gave **15b** (450 mg, 80%) as a white powder; ν_{max} (KBr)/cm^{-1} 3852, 3796, 1716, 1473, 1355, 913, 808; δ_H (CD_3OD) 1.88 (1H, s, thymine 5-CH_3), 2.91 (2H, t, *J* 5.5, $CH_2CH_2NH_2$), 4.03 (2H, t, *J* 5.5, $>NCH_2CH_2$), 7.35 (1H, br s, thymine 6-H); *m*/*z* (EI) 169 (M^+), 152 ($M^+ - NH_3$); HRMS Found: ($M^+ - NH_3$), 152.0521. $C_7H_8N_2O_2$ requires *m*/*z*, 152.0552.

***N*-Benzyloxycarbonylglycyl-*N′*-[2(uracil-1-yl)ethyl]-2-methylalanine (*N*-*tert*-butyl)amide 19a {Z-Gly-Aib[*N*-(uracil-1-yl)-ethyl]-NBu^t}.** Condensation of **18a** (200 mg, 1.29 mmol), acetone (149 mg, 2.58 mmol), **7a** (540 mg, 2.58 mmol) and **8a** (214 mg, 2.58 mmol) yielded **19a** (320 mg, 50%) as a white solid; mp 84–85 °C (from ethyl acetate–hexane); ν_{max} (neat)/cm^{-1} 3343, 2978, 1675, 1518, 1455; δ_H ($CDCl_3$) 1.34 (9H, s, Bu^t), 1.52 (6H, s, $Me_2C<$), 3.64 (2H, br s, NCH_2CH_2N), 3.98 (4H, br s, NCH_2CH_2N + CH_2CON), 5.09 (2H, s, $PhCH_2$), 5.61 (2H, br s, NH × 2), 5.71 (1H, d, *J* 7.8, NC*H*=CHCO), 7.34 (5H, m, ArH), 7.47 (1H, d, *J* 7.8, NCH=C*H*CO), 8.33 (1H, br s, CONHCO); *m*/*z* (EI) 487 (M^+); HRMS Found: M^+, 487.2436. $C_{24}H_{33}N_5O_6$ requires *M*, 487.2442.

***N*-Benzyloxycarbonylglycyl-*N*-[2-(thymin-1-yl)ethyl]-2-methylalanine (*N*-*tert*-butyl)amide 19b {Z-Gly-Aib[*N*-(thymin-1-yl)ethyl]-NBu^t}.** Condensation of **18b** (200 mg, 1.18 mmol), acetone (139 mg, 2.36 mmol), **7a** (491 mg, 2.36 mmol) and **8a** (196 mg, 2.36 mmol) gave **19b** (275 mg, 46%) as a white solid; mp 46–47 °C (from ethyl acetate–hexane); ν_{max} (neat)/cm^{-1} 3499, 3385, 1715, 1699, 1499; δ_H ($CDCl_3$) 1.33 (9H, s, Bu^t), 1.51 (6H, s, $Me_2C<$), 1.91 (3H, s, $CH=CCH_3$), 3.61 (2H, br s, NCH_2CH_2N), 3.96 (2H, br s, NCH_2CH_2N), 3.99 (2H, d, *J* 4.5, CH_2CON), 5.09 (2H, s, $PhCH_2$), 5.61 (1H, br s, NH), 5.73 (1H, br s, NH), 7.31 (5H, m, ArH), 7.34 (1H, br s, >N–C*H*=CMe), 8.99 (1H, br s, CONHCO); *m*/*z* (EI) 502 ($M^+ + 1$), 501 (M^+); HRMS Found: M^+, 501.2575. $C_{25}H_{35}N_5O_9$ requires *M*, 501.2587.

ar-Pentafluorobenzylamine 9c[27]

To a stirred solution of **21** (100 mg, 0.518 mmol) in anhydrous THF (8 ml) was added BH_3·THF (1 M; 2.5 ml, 2.50 mmol) carefully. The resultant solution was stirred and heated to reflux for 10 h. After the mixture had cooled, 2.6 M HCl (10 ml) was carefully added and heating was continued at reflux for 30 min. The resultant solution was evaporated *in vacuo*. The residue obtained was dissolved in 2.6 M HCl (10 ml) and extracted with diethyl ether (20 ml). The aqueous portion was made alkaline with 1 M aq. NaOH up to pH 10–11 and was again extracted with diethyl ether (100 ml); this extract was washed with brine, dried over Na_2SO_4, and concentrated to give **9c** (105 mg, 98%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3395, 2965, 1504, 1171, 1119,

991; δ_H ($CDCl_3$) 3.96 (2H, br s, ArCH_2); δ_F ($CDCl_3$) −145.9 (dd, *J* 9.1, 22.1), −156.6 (t, *J* 20.8), −162.5 (td, *J* 8.4, 22.1); *m/z* (EI) 197 (M^+), 196 ($M^+ - 1$); HRMS Found: M^+, 197.0256. $C_7H_4F_5N$ requires *M*, 197.0264.

Preparation of 2,4-difluoro-5-methylbenzylamine 9d

2,4-Difluoro-5-methylbenzonitrile 22. To a well-stirred solution of **12** (900 mg, 4.34 mmol) in dry DMF (40 ml) was added copper(I) cyanide (487 mg, 5.43 mmol) in one portion and the mixture was heated at 160 °C for 3 h. Then the reaction mixture was cooled and poured into water (20 ml), whereupon 20% aq. $FeCl_3$ (9 ml) was added. The mixture was extracted with diethyl ether (100 ml × 2) and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (1–2% ethyl acetate–hexane) to afford **22** (335 mg, 50%) as a white solid; mp 55–56 °C (from ethyl acetate–hexane) (Found: C, 62.80; N, 8.96; H, 3.11. Calc. for $C_8H_5F_2N$: C, 62.75; N, 9.15; H, 3.29%); ν_{max} (KBr)/cm^{-1} 3054, 2939, 2232, 1603, 1535, 1089, 1004, 903; δ_H ($CDCl_3$) 2.28 (3H, s, ArCH_3), 6.92 (1H, t, *J* 9.1, ArH), 7.47 (1H, *J* 7.5, ArH); δ_F ($CDCl_3$) −101.7 (q, *J* 8.8), −106.7 (q, *J* 8.8); *m/z* (EI) 153 (M^+), 126 (M^+ − HCN); HRMS Found: M^+, 153.0365. $C_8H_5F_2N$ requires *M*, 153.039.

2,4-Difluoro-5-methylbenzylamine 9d. Compound **22** (100 mg, 0.613 mmol) was converted to the corresponding oily amine **9d** (65.0 mg, 67%) by a single-step reduction with BH_3·THF (1 M; 2.5 ml, 2.50 mmol) in dry THF (8 ml) by a procedure similar to the preparation of **9c**; ν_{max} (neat)/cm^{-1} 3378, 3293, 3081, 2932, 1613, 1503, 1087, 889; δ_H ($CDCl_3$) 2.17 (3H, s, ArCH_3), 3.78 (2H, br s, ArCH_2), 6.68 (1H, t, *J* 9.8, ArH), 7.06 (1H, t, *J* 8.5, ArH); δ_F ($CDCl_3$) −111.7 (br quintet, *J* 7.5), −115.2 (br q, *J* 8.7); *m/z* (EI) 157 (M^+), 156 ($M^+ - 1$); HRMS Found: M^+, 157.0698. $C_8H_9F_2N$ requires *M*, 157.0703.

Preparation of dipeptides 4

***N*-(Benzyloxycarbonyl-β-alanyl)-*N*-(4-fluorobenzyl)-2-methylalanine (*N*-*tert*-butyl)amide 4a [Z-βAla-Aib(*N*-4-fluorobenzyl)-NBu^t].** Condensation of **9a** (200 mg, 1.65 mmol), acetone (191 mg, 3.30 mmol)), **10a** (736 mg, 3.30 mmol) and **8a** (274 mg, 3.30 mmol) yielded **4a** (460 mg, 59%) as a white solid; mp 74–75 °C (from ethyl acetate–hexane) (Found: C, 65.74; N, 8.64; H, 7.31. Calc. for $C_{26}H_{34}FN_3O_4$: C, 66.22; N, 8.91; H, 7.27%); ν_{max} (neat)/cm^{-1} 3433, 3341, 1712, 1664, 1511; δ_H ($CDCl_3$) 1.32 (9H, s, Bu^t), 1.37 (6H, s, $Me_2C<$), 2.51 (2H, br t, *J* 5.5, CH_2CH_2N), 3.47 (2H, br q, *J* 5.5, CH_2CH_2N), 4.53 (2H, s, ArCH_2N), 5.08 (2H, s, PhCH_2), 5.44 (1H, br s, NH), 5.58 (1H, br s, NH), 7.03 (2H, t, *J* 8.6, ArH), 7.34 (7H, m, ArH); δ_F ($CDCl_3$) −115.5 (m); δ_C (68 MHz; $CDCl_3$) 24.58 [C(CH_3)$_2$], 28.73 [C(CH_3)$_3$], 34.73 (CH_2), 37.22 (CH_2), 46.82 (CH_2), 51.16 [C(CH_3)$_3$], 63.18 [C(CH_3)$_2$], 66.63 (CH_2), 115.90 (d, $^2J_{C,F}$ 21.8 F–Ar–CH), 127.61 (d, $^3J_{C,F}$ 8.1, F–Ar–CH), 127.94, 128.43 (each s, 5 × Ar–CH), 133.89 (d, $^4J_{C,F}$ 3.2, F–Ar–C), 136.68 (Ar–C, *ipso*), 156.38 (C=O), 162.01 (d, $^1J_{C,F}$ 245.0, Ar–C–F), 172.61 (C=O), 173.72 (C=O); *m/z* (EI) 471 (M^+); HRMS Found: M^+, 471.2543. $C_{26}H_{34}FN_3O_4$ requires *M*, 471.2533.

***N*-(Benzyloxycarbonyl-β-alanyl)-*N*-(2,4-difl uorobenzyl)-2-methylalanine (*N*-*tert*-butyl)amide 4b [Z-βAla-Aib(*N*-2,4-difluorobenzyl)-NBu^t].** Condensation of **9b** (200 mg, 1.39 mmol), acetone (161 mg, 2.78 mmol), **10a** (620 mg, 2.78 mmol) and **8a** (231 mg, 2.78 mmol) gave **4b** (450 mg, 66%) as a white solid; mp 73–74 °C (from ethyl acetate–hexane) (Found: C, 63.58; N, 8.56; H, 6.88. Calc. for $C_{26}H_{33}F_2N_3O_4$: C, 63.29; N, 8.58; H, 6.79%); ν_{max} (neat)/cm^{-1} 3435, 3339, 1714, 1659, 1509; δ_H ($CDCl_3$) 1.34 (9H, s, Bu^t), 1.37 (6H, s, $Me_2C<$), 2.48 (2H, br t, *J* 5.5, CH_2CH_2N), 3.47 (2H, br q, *J* 5.5, CH_2CH_2N), 4.54 (2H, br s, ArCH_2N), 5.08 (2H, s, PhCH_2), 5.44 (1H, br s, NH), 5.53 (1H, br s, NH), 6.83 (2H, m, ArH), 7.34 (5H, m, ArH), 7.71 (1H, m, ArH); δ_F ($CDCl_3$) −111.7 (quintet, *J* 7.6), −115.2 (q, *J* 8.7); δ_C (68 MHz; $CDCl_3$) 24.14 [C(CH_3)$_2$], 28.55 [C(CH_3)$_3$], 34.40 (CH_2), 37.01 (CH_2), 41.04 (CH_2), 51.02 [C(CH_3)$_3$], 62.86 [C(CH_3)$_2$], 66.45 (CH_2), 103.91 (t, $^2J_{C,F}$ 25.5, F–Ar–CH), 111.88 (dd, $^2J_{C,F}$ 21.2, $^4J_{C,F}$ 3.5, F–Ar–CH), 121.23 (dd, $^2J_{C,F}$ 14.0, $^4J_{C,F}$ 3.5, F–Ar–C), 127.94, 127.98, 128.45 (each s, 5 × Ar–CH), 129.19 (dd, $^3J_{C,F}$ 9.5, $^3J_{C,F}$ 5.6, F–Ar–CH), 136.69 (Ar–C, *ipso*), 156.37 (C=O), 159.55 (dd, $^1J_{C,F}$ 248.0, $^3J_{C,F}$ 11.7, Ar–C–F), 162.23 (dd, $^1J_{C,F}$ 248, $^3J_{C,F}$ 11.7, Ar–C–F), 172.69 (C=O), 173.64 (C=O); *m/z* (EI) 489 (M^+); HRMS Found; M^+, 489.2457. $C_{26}H_{33}F_2N_3O_4$ requires *M*, 489.2475.

***N*-(Benzyloxycarbonyl-β-alanyl)-*N*-(2,4-difluorobenzyl)-2-methylalanylglycine ethyl ester 4c [Z-βAla-Aib(*N*-2,4-difluorobenzyl)-Gly-OEt].** Condensation of **9b** (200 mg, 1.39 mmol), acetone (161 mg, 2.78 mmol), **10a** (523 mg, 2.78 mmol) and **8b** (314 mg, 2.78 mmol) gave **4c** (320 mg, 44%) as a white solid; mp 89–90 °C (from ethyl acetate–hexane) (Found: C, 59.91; N, 7.87; H, 5.90. Calc. for $C_{26}H_{31}F_2N_3O_6$: C, 60.11; N, 8.09; H, 6.01%); ν_{max} (neat)/cm^{-1} 3353, 2986, 1712, 1661, 1509; δ_H ($CDCl_3$) 1.26 (3H, t, *J* 6.9, OCH$_2$CH_3), 1.44 (6H, s, $Me_2C<$), 2.51 (2H, br t, *J* 5.4, CH_2CH_2N), 3.47 (2H, br q, *J* 5.4, CH_2CH_2N), 4.04 (2H, d, *J* 5.1, NHCH_2CO), 4.19 (2H, q, *J* 6.9, OCH_2CH$_3$), 4.56 (2H, s, ArCH_2N), 5.07 (2H, s, PhCH_2), 5.61 (1H, br s, NH), 6.21 (1H, br s, NH), 6.85 (2H, m, ArH), 7.31 (5H, m, ArH), 7.75 (1H, m, ArH); δ_F ($CDCl_3$) −111.6 (br quintet, *J* 7.3), −115.1 (br q, *J* 9.1); *m/z* (EI) 519 (M^+); HRMS Found: M^+, 519.2160. $C_{26}H_{31}F_2N_3O_6$ requires *M*, 519.2181.

***N*-(*tert*-Butoxycarbony-β-alanyl)-*N*-(2,4-difluorobenzyl)-2-methylalanine (*N*-cyclohex-1-enyl)amide 4d [Boc-βAla-Aib(*N*-2,4-difluorobenzyl)-N(cyclohex-1-enyl)].** Condensation of **9b** (200 mg, 1.39 mmol), acetone (162 mg, 2.79 mmol), **10b** (624 mg, 2.79 mmol) and **8c** (299 mg, 2.79 mmol) gave **4d** (290 mg, 43%) as a colourless oil; ν_{max} (neat)/cm^{-1} 3448, 3187, 1692, 1656, 1504, 853; δ_H ($CDCl_3$) 1.42 (9H, s, Bu^t), 1.44 (6H, s, $Me_2C<$), 1.68 (4H, m, CH_2 × 2), 2.13 (4H, m, CH_2 × 2), 2.47 (2H, br t, *J* 5.5, CH_2CH_2N), 3.38 (2H, br q, *J* 5.5, CH_2CH_2N), 4.57 (2H, s, ArCH_2N), 5.22 (1H, br s, NH), 6.05 (1H, br s, CH=C<), 6.54 (1H, br s, NH), 6.84 (2H, m, ArH), 7.81 (1H, m, ArH); δ_F ($CDCl_3$) −111.7 (m), −115.2 (m); *m/z* (EI) 479 (M^+), 422 (M^+ − Bu^t); HRMS Found: M^+, 479.2539. $C_{25}H_{35}N_3F_2O_4$ requires *M*, 479.2563.

***N*-(Benzyloxycarbonyl-β-alanyl)-*N*-(pentafluorobenzyl)-2-methylalanine (*N*-*tert*-butyl)amide 4e [Z-βAla-Aib(*N*-pentafluorobenzyl)-NBu^t].** Condensation of **9c** (200 mg, 1.01 mmol), acetone (117 mg, 2.02 mmol), **10a** (451 mg, 2.02 mmol) and **8a** (168 mg, 2.02 mmol) gave **4e** (240 mg, 43%) as a white, solid mixture of rotamers; mp 86–87 °C (from ethyl acetate–hexane) (Found: C, 57.24; N, 7.59; H, 5.56. Calc. for $C_{24}H_{30}F_5N_3O_4$: C, 57.45; N, 7.73; H, 5.56%); ν_{max} (neat)/cm^{-1} 3437, 3346, 1714, 1660, 1508; δ_H ($CDCl_3$) 1.27 (9H, s, Bu^t), 1.36 (6H, s, $Me_2C<$), 2.68 (2H, br t, *J* 5.5, CH_2CH_2N), 3.52 (2H, br q, *J* 5.5, CH_2CH_2N), 4.54, 4.73 (total 2H, each br s, ArCH_2N), 5.09 (2H, s, PhCH_2), 5.43, 5.47 (total 1H, each br s, NH), 5.55 (1H, br s, NH), 7.33 (5H, m, ArH); δ_F ($CDCl_3$) −143.3 (dd, *J* 7.8, 22.0), −155.7 (t, *J* 20.1), −161.7 (td, *J* 9.9, 22.1); δ_c (68 MHz; $CDCl_3$) 24.05, 24.11 [each s, C(CH_3)$_2$], 28.39, 28.54 [each s, C(CH_3)$_3$], 34.31, 34.98 (each s, CH_2), 37.05, 37.07 (each s, CH_2), 37.92, 40.53 (each s, CH_2), 50.91, 51.20 [each s, C(CH_3)$_3$], 62.74, 63.56 [each s, C(CH_3)$_2$], 66.54 (CH_2), 111.9 (m, Ar–C–F), 127.94, 127.98, 128.42 (each s, 5 × Ar–CH), 136.58 (Ar–C, *ipso*), 137.88 (dm, $^1J_{C,F}$ 253.0, Ar–C–F), 140.28 (dm, $^1J_{C,F}$ 252.0, Ar–C–F), 145.09 (dm, $^1J_{C,F}$ 253.0, F–Ar–C), 156.46 (C=O), 172.97 (C=O), 173.38 (C=O); *m/z* (EI) 543 (M^+), 542 ($M^+ - 1$); HRMS Found; M^+, 543.2198. $C_{24}H_{30}F_5N_3O_4$ requires *M*, 543.2239.

***N*-(Benzyloxycarbonyl-β-alanyl)-*N*-(2,4-difluoro-5-methylbenzyl)-2-methylalanine (*N*-*tert*-butyl)amide 4f [Z-βAla-Aib-(*N*-2,4-difluoro-5-methylbenzyl)-NBu^t].** Condensation of **9d** (200 mg, 1.27 mmol), acetone (147 mg, 2.54 mmol), **10a** (567 mg, 2.54 mmol) and **8a** (211 mg, 2.54 mmol) gave **4f** (265 mg, 43%) as a white solid; mp 120–121 °C (from ethyl acetate–hexane); ν_{max} (neat)/cm^{-1} 3433, 3327, 1713, 1663, 1510; δ_H ($CDCl_3$) 1.32 (9H, s, Bu^t), 1.37 (6H, s, Me_2C<), 2.22 (3H, s, ArCH_3), 2.56 (2H, br t, *J* 5.6, CH_2CH$_2$N), 3.48 (2H, br q, *J* 5.6, CH$_2$CH_2N), 4.53 (2H, s, ArCH_2N), 5.08 (2H, s, PhCH_2), 5.43 (1H, br s, NH), 5.57 (1H, br s, NH), 6.76 (1H, t, *J* 9.7, ArH), 7.32 (6H, m, ArH); δ_F ($CDCl_3$) −114.6 (m), −119.4 (m); *m*/*z* (EI) 503 (M^+); HRMS Found: M^+, 503.2596. $C_{26}H_{35}F_2N_3O_4$ requires *M*, 503.2596.

***N*-(*tert*-Butoxycarbonyl-β-alanyl)-*N*-(4-fluorobenzyl)-glycine *N*-*tert*-butylamide 5a [Boc-βAla-Gly(*N*-4-fluorobenzyl)-NBu^t].** Condensation of **9a** (200 mg, 1.59 mmol), paraformaldehyde (572 mg, 3.18 mmol), **10b** (601 mg, 3.18 mmol) and **8a** (264 mg, 3.18 mmol) yielded **5a** (299 mg, 45%) as a white solid mixture of rotamers; mp 103–104 °C (Found C, 61.52; N 10.25; H, 7.83. Calc. for $C_{21}H_{32}FN_3O_4$: C, 61.59; N, 10.26; H, 7.88%); ν_{max} (neat)/cm^{-1} 3451, 3333, 3006, 2977, 1695, 1510, 757; δ_H ($CDCl_3$) 1.23, 1.31 (total 9H, each s, Bu^{t}N), 1.39, 1.42 (total 9H, each s, Bu^{t}O), 2.52, 2.64 (total 2H, each br t, *J* 5.4, NCH$_2$CH_2CO), 3.44 (2H, br q, *J* 5.9, NHCH_2CH$_2$), 3.78, 3.84 (total 2H, each s, NCH$_2$CO), 4.59 (2H, s, ArCH_2), 5.21, 5.33 (total 1H, each br s, NH), 5.92 (1H, br s, NH), 7.03 (2H, m, ArH), 7.14 (2H, m, ArH); δ_F ($CDCl_3$) −114.5 (m); δ_C (125.76 MHz; $CDCl_3$) 28.52, 28.54 [each s, NC(CH_3)$_3$], 28.66, 28.81 [each s, OC(CH_3)$_3$], 33.44, 33.86 (each s, CH_2), 36.52, 49.97 (each s, CH_2), 50.89, 51.56 (each s, CH_2), 51.45, 51.80 [each s, N*C*(CH_3)$_3$], 51.86 (CH_2), 79.40 [O*C*(CH_3)$_3$], 115.87 (m, F–Ar–CH), 128.68, 130.47 (each d, $^3J_{C,F}$ 8.3, F–Ar–CH), 131.50, 131.70 (each d, $^4J_{C,F}$ 4.4, F–Ar–C), 156.11 (C=O), 163.52 (d, $^1J_{C,F}$ 245.0, Ar–C–F), 166.77, 167.89 (each s, C=O), 172.71, 172.94 (each s, C=O); *m*/*z* (EI) 410 (M^+ + 1), 409 (M^+), 353 [(M^+ + 1) − Bu^t]; HRMS Found: M^+, 409.2383. $C_{21}H_{32}FN_3O_4$ requires *M*, 409.2377.

***N*-(*tert*-Butoxycarbonyl-β-alanyl)-*N*-(2,4-difluoro-5-methylbenzyl)-glycine (*N*-cyclohex-1-enyl)amide 5b [Boc-βAla-Gly(*N*-2,4-difluoro-5-methylbenzyl)-*N*-(cyclohex-1-enyl)].** Condensation of **9d** (200 mg, 1.27 mmol), paraformaldehyde (457 mg, 2.54 mmol), **10b** (513 mg, 2.54 mmol), and **8c** (211 mg, 2.54 mmol) gave **5b** (240 mg, 45%) as a yellow oily mixture of rotamers; ν_{max} (neat)/cm^{-1} 3453, 3333, 3007, 1706, 1615, 1507, 891; δ_H ($CDCl_3$) 1.43 (9H, s, Bu^{t}O), 1.57–2.09 (8H, m, CH_2 × 4), 2.23 (3H, s, ArCH_3), 2.43, 2.52 (total 2H, br s and t, *J* 6.0, NCH$_2$CH_2CO), 3.38 (2H, m, NHCH_2CH$_2$), 3.73 (2H, s, NCH$_2$CO), 4.26 (2H, s, ArCH_2), 5.02 (2H, br), 5.39 (1H, br s), 6.76 (1H, t,*J* 9.5, ArH), 7.19 (1H, t, *J* 8.3, ArH); δ_F ($CDCl_3$) −114.4 (q, *J* 7.4), −119 (q, *J* 8.3); *m*/*z* (EI) 465 (M^+); HRMS Found: M^+, 465.2427. $C_{24}H_{33}F_2N_3O_4$ requires *M*, 465.2507.

***N*-β-Alanyl-*N*-(2,4-difluorobenzyl)-2-methylalanine 4g [βAla-Aib(*N*-2,4-difluorobenzyl)].** Compound **4g** (12.0 mg, 96%) was prepared from **4d** (20 mg, 0.04 mmol), THF (2 ml) and 3 M HCl (1 ml), according to the procedure analogous to the prepration of **2h**, as a yellow oily mixture of rotamers; δ_H (D_2O) 1.29, 1.44 (total 6H, each s, Me_2C<), 2.56, 2.73 (total 2H, each br t, *J* 5.9, CH_2CH$_2$N), 3.08 (2H, br t, *J* 5.9, CH$_2$CH_2N), 6.93 (2H, m, ArH), 7.47 (1H, m, ArH); other peaks may be hidden beneath the D_2O signal; δ_F (D_2O) −122.2 (m), −124.6 (m); *m*/*z* (EI) 300.13 (M^+).

***N*-β-Alanyl-*N*-(2,4-difluoro-5-methylbenzyl)glycine 5c [βAla-Gly(*N*-2,4-difluoro-5-methylbenzyl)].** To a solution of **5b** (25.0 mg, 0.05 mmol) in THF (4 ml) was added 3 M HCl (3 ml) and the mixture was stirred overnight at room temperature. A similar work-up as that for **4g** gave **5c** (14.0 mg, 92%) as a yellow oily mixture of rotamers; δ_H (D_2O) 2.10, 2.13 (total 3H, each s, ArCH_3), 2.66 (2H, br t, *J* 6.1, NHCH_2CH$_2$), 3.14 (2H, br t, *J* 6.1, CH$_2$CH_2CO), 3.89, 4.46 (total 2H, each s, >NCH$_2$CO), 6.92 (1H, t, *J* 9.7, ArH), 7.32 (1H, t, *J* 8.2, ArH), other peaks may be hidden beneath the D_2O signal; δ_F (D_2O) −113.8 (q, *J* 8.3), −120.9 (q, *J* 9.2); *m*/*z* (EI) 286 (M^+), 284 (M^+ − 2); HRMS Found: (M^+ − 2), 284.0596. $C_{13}H_{14}F_2N_2O_3$ requires *m*/*z*, 284.0596.

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