Studies on *N*-Deprotection of ψ(CH_2NH) Pseudodipeptide Methyl Esters. Cyclization to 2-Ketopiperazines

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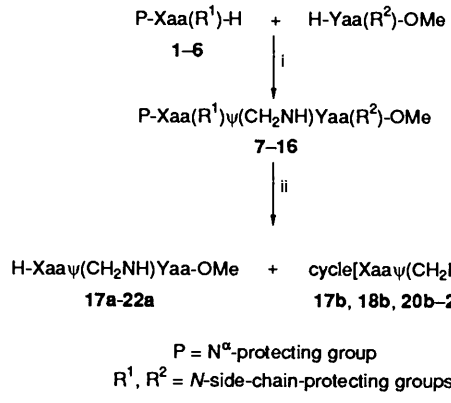
N-Deprotection of Z- and Boc-aminomethylene pseudodipeptide methyl esters yielded not only the expected linear deprotected compounds but also the 2-ketopiperazine cyclic analogues. The extent of lactamization was found to be dependent on the nature of the amino acid, the sequence order, and the deprotection conditions. Hydrogenation of Z-pseudodipeptides containing *N*-terminal basic amino acids in acidic media afforded linear compounds, while replacement of these basic residues by Leu gave mixtures of linear and cyclic pseudodipeptides. The reverse-sequence analogues, with Lys or Arg at the *C*-terminus, yielded the corresponding 2-ketopiperazines as the only reaction products. Opposite results were obtained for *C*-terminal Leu derivatives in which almost no cyclization occurred. Hydrogenation under neutral conditions gave mainly cyclic derivatives, while linear analogues were predominant after treatment of Boc-protected pseudodipeptides with trifluoroacetic acid or HCl.

Replacement of the scissile peptide amide bond –CONH– by the non-hydrolysable ψ(CH_2NH) isostere has been widely used for the preparation of biologically active peptide analogues with greater stability towards enzymatic degradation.[1–4] The usual method for the formation of this peptide bond surrogate is the reductive alkylation of an α-amino group by a protected amino acid aldehyde.[5–7] Studies on racemization during the generation, storage and condensation of the aldehyde have been reported.[8 11] Cyclization to 2-ketopiperazines have been described[11] as occurring in the derivatization of Boc-protected aminomethylene pseudodipeptide methyl esters with trifluoroacetic anhydride (TFAA) at 100–120 °C and in attempts to couple H–Leuψ(CH_2NH)Gly–NH_2 using the DCC–HOBt method.[12]

In the course of our search for pseudodipeptide analogues of the analgesic compound Trp(NPS)–Lys–OMe,[13] we have found that catalytic hydrogenation of Z–Trpψ(CH_2NH)Lys(Z)–OMe in (1:20) HCl–MeOH does not lead to the Z-deprotected linear derivative, but to the corresponding 2-ketopiperazine. On the other hand, similar deprotection of the reverse-sequence pseudodipeptide Z–Lys(Z)ψ(CH_2NH)Trp–OMe yields the linear analogue as the only reaction product.[14] These results, and the fact that neither *N*-deprotection of ψ(CH_2NH) pseudodipeptides nor methods of lactamization to the corresponding 2-ketopiperazines have been thoroughly investigated, prompted us to study the formation of these cyclic aminomethylene pseudodipeptides from linear *N*-protected analogues, under conditions normally used for the removal of Z- and Boc-protecting groups. Owing to our interest in peptide derivatives having aromatic and basic amino acids,[13–16] Phe-, Trp-, Lys- and Arg-containing pseudodipeptides were chosen for the initial study. Leu-containing analogues were also included for comparative purposes.

Results and Discussion

Protected pseudodipeptides P–Xaa(R^1)ψ(CH_2NH)Yaa(R^2)–OMe (**7–16**) were synthesized according to Scheme 1. The –CH_2NH– bond was formed by condensation of the corresponding amino acid aldehyde, prepared by the Fehrentz and Castro method,[17] with the appropriate amino acid methyl ester, followed by reduction with $NaBH_3CN$–$ZnCl_2$ in MeOH.[18] In our case, the use of this Zn-modified cyanoborohydride reducing agent, instead of $NaBH_3CN$–AcOH,[19] resulted in better yields and shorter reaction times. As shown by ^1H NMR spectroscopy, compound **11** was obtained as a mixture of two diastereoisomers, due to almost total racemization at the *N*-terminal Phe residue. In this sense, it is known that phenylalaninal derivatives racemize easily and that racemization can also occur during the reductive amination.[8–10]



Scheme 1 *Reagents and conditions:* i, $NaBH_3CN$, $ZnCl_2$; ii, *N*-deprotection

The extent of cyclization found for both Z- and Boc-group elimination, under a variety of deprotection methods, is shown in Table 1. In general, the cyclization ratio was dependent on three factors: (i) nature of the amino acid, (ii) sequence order, and (iii) deprotection conditions. Hence, catalytic hydrogenation of Z–Leuψ(CH_2NH)Xaa–OMe [Xaa = Phe (**7**), Trp (**8**)] in (1:20) HCl–MeOH for 3 h at room temperature and under 30 psi pressure, using 10% Pd/C as catalyst, gave a mixture of linear and cyclic pseudodipeptides **17a** and **17b**, and **18a** and **18b**, in different ratios while only the linear compound **19a** or **20a** was obtained when Leu was replaced by Lys or Arg. In contrast, similar hydrogenolysis of the analogues **13** and **14**, containing these basic amino acids at the *C*-terminus, exclusively led to the cyclic derivatives **23b** and **24b** while almost no cyclization occurred (<10%) from the Leu derivatives Z–Xaaψ(CH_2NH)Leu–OMe [Xaa = Phe (**11**), Trp (**12**)]. Total cyclization of these Leu derivatives took place when hydrogenolysis was achieved in the absence of the protonating

Table 1 Results of *N*-deprotection of the aminomethylene pseudodipeptide derivatives P–Xaa(R^1)ψ(CH_2NH)Yaa(R^2)–OMe **7–16**

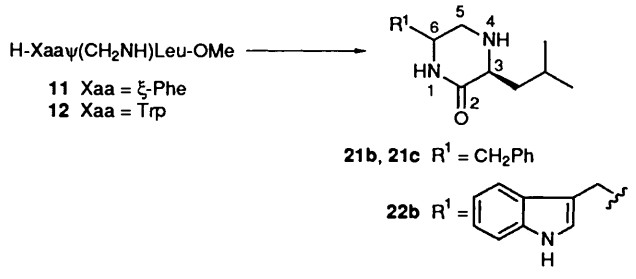
Starting compound	P	Xaa(R^1)	Yaa(R^2)	Deprotection conditions	Final compounds	Linear:cyclic ratio[a]
7	Z	Leu	Phe	H_2, Pd/C, MeOH–HCl	**17a**, **17b**	2:1
8	Z	Leu	Trp	H_2, Pd/C, MeOH–HCl	**18a**, **18b**	1:6
9	Z	Lys(Z)	Trp	H_2, Pd/C, MeOH–HCl	**19a**	1:0
10	Z	Arg(Z_2)	Trp	H_2, Pd/C, MeOH–HCl	**20a**	1:0
11[b]	Z	Phe	Leu	H_2, Pd/C, MeOH–HCl	**21a**,[b] **21b**, **21c**	1:0[c]
12	Z	Trp	Leu	H_2, Pd/C, MeOH–HCl	**22a**, **22b**	1:0[c]
13	Z	Trp	Lys(Z)	H_2, Pd/C, MeOH–HCl	**23b**	0:1
14	Z	Trp	Arg(Z_2)	H_2, Pd/C, MeOH–HCl	**24b**	0:1
11[b]	Z	Phe	Leu	H_2, Pd/C, MeOH	**21a**,[b] **21b**, **21c**	0[c]:1
12	Z	Trp	Leu	H_2, Pd/C, MeOH	**22a**, **22b**	0[c]:1
15	Boc	Leu	Phe	aq. TFA	**17a**	1:0
16	Boc	Leu	Trp	aq. TFA	**18a**, **18b**	1:10
16	Boc	Leu	Trp	HCl–MeOH	**18a**	1:0

[a] From the ^{1}H NMR spectrum of the reaction mixture. [b] Racemic mixture at Phe residue. [c] Traces (< 10%) of these compounds were observed.

Table 2 ^{1}H NMR data of protected pseudodipeptides **7–16** in $CDCl_3$ solution at 300 MHz (δ)

Compound	CH^aXaa	OMe	CH^aYaa	$CH_2\beta^a$ Aromatic	CH_2NH
7	3.61 (m)	3.56 (s)	3.38 (br t)	2.76 (dd), 2.87 (dd)	2.35 (dd), 2.61 (dd)
8	3.70 (m)	3.64 (s)	3.55 (dd)	3.03 (dd), 3.17 (dd)	2.44 (dd), 2.70 (dd)
9	3.55 (m)	3.63 (s)	3.52 (dd)	2.94 3.24 (m)	2.42 (dd), 2.66 (dd)
10	3.77 (m)	3.68 (s)	3.44 (m)	2.89 (dd), 3.16 (dd)	2.40 (dd), 2.58 (dd)
11	3.90 (m)	3.67 (s) 3.66(s)	3.20 (m)	2.72 (m), 2.85 (m)	2.41 (m), 2.63 (dd)
12	4.01 (m)	3.65 (s)	3.23 (t)	3.01 (m)	2.46 (dd), 2.74 (dd)
13	4.10 (m)	3.64 (s)	3.33 (m)	3.00 (m)	2.57 (m), 2.74 (dd)
14	3.92 (m)	3.53 (s)	3.11 (dd)	2.82 (dd), 2.96 (dd)	2.36 (dd), 2.64 (dd)
15	3.63 (m)	3.66 (s)	3.48 (br t)	2.88 (dd), 2.97 (dd),	2.43 (dd), 2.66 (dd)
16	3.60 (m)	3.64 (s)	3.60 (m)	3.07 (dd), 3.18 (dd)	2.46 (m), 2.66 (dd)

[a] β-CH_2 Aromatic amino acid.



Scheme 2 *Reagents and conditions:* 0.1 mol dm^{-3} AcOH, BuOH, reflux

agent (HCl). The 2-ketopiperazines **21b** and **21c**, obtained from the diastereoisomeric compound **11** (Scheme 2), were separated chromatographically.

The influence of the amino acid residues on the extent of lactamization in the *N*-deprotection reactions under study was also evident from treatment of the Boc-protected compounds **15** and **16** with (1:1) trifluoroacetic acid (TFA)–water for 2 h. Thus, the linear pseudodipeptide **17a** was obtained from the Phe-containing derivative **15** as the only reaction product. On the other hand, the 2-ketopiperazine **18b** was formed as the major compound when the Trp analogue **16** was treated under identical conditions. However, deprotection of compound **16** using (1:20) HCl–MeOH exclusively gave the linear pseudodipeptide **18a**.

^{1}H NMR spectra of all linear and cyclic aminomethylene pseudodipeptides were in accord with the proposed structures (Tables 2 and 3). The absence of the methyl ester signal and the appearance of one NH amide-type bond in compounds **17b**, **18b**, **21b**, **21c** and **22b** demonstrated that lactamization had taken place (Table 3). In the case of the diastereoisomeric 2-ketopiperazines **21b** and **21c**, $J_{5,6}$- and $J_{5',6}$-values for compound **21b** were determined to be 4.4 and 4.7 Hz, while those for compound **21c** were found to be 4.2 and 9.6 Hz. These values, consistent with pseudoequatorial and pseudoaxial dispositions for 6-H in compounds **21b** and **21c**, respectively, indicated that racemization of the parent pseudodipeptide **11** occurred at the Phe residue. At the same time, comparison of these coupling-constant values with those of compounds **17b**, **18b**, **23b** and *cis*-2,6-dialkyl-2,5-diketopiperazines described in the literature[20] allowed us to assign the L–L configuration for **21b** and D–L for **21c**.

With the aim of comparing the facility of lactamization of aminomethylene pseudodipeptides with that of the peptide analogues, compounds **21a** and **22a** were refluxed in 0.1 mol dm^{-3} AcOH–BuOH. Under these conditions, generally used for the cyclization of dipeptide methyl esters,[21] these pseudodipeptides cyclized 3-times more rapidly than did the corresponding dipeptides. At this point it is interesting to note that cyclization of compounds **17a**, **18a**, **21a** and **22a**, as HCl or TFA salts, was detected, to a greater or lesser extent, when these linear compounds were kept in solution at room temperature.

In conclusion, this preliminary study indicates that lactamization of ψ(CH_2NH) pseudodipeptide methyl esters occurs easily. Likewise, the resulting conformationally restricted cyclic analogues, obtained with defined stereochemistry at C-3 and C-6, could be of interest as building blocks in the peptide-mimics field. Introduction of these 2,5-disubstituted-2-ketopiperazines into higher peptides by extension at N-4 is in progress.

Experimental

^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer operating at 300 MHz with $SiMe_4$ as internal standard. Elemental analyses were obtained on a CHN-O-RAPID instrument. Column chromatography was performed on silica gel (60, 230–240 mesh, Merck) using the indicated solvent systems. Compounds were detected with UV light (254 nm) and ninhydrin spray.

Protected amino acids were from Bachem. Aldehydes, Z–

Table 3 ^{1}H NMR data of deprotected linear and cyclic pseudodipeptides (300 MHz)

Compound	Solvent	δ (J/Hz) NH[a]	CH[a]Xaa	CO_2Me	CH[a]Yaa	$CH_2\beta$[b]	CH_2NH
H Leuψ(CH_2NH)Phe–OMe **17a**	$CDCl_3$	4.29 (br s)	3.02 (m)	3.51 (s)	3.45 (br t)	2.82 (m)	2.31 (dd) (8.8, 13.4), 2.70 (dd) (4.2, 13.4)
Cycle[Leuψ(CH_2NH)Phe] **17b**	$CDCl_3$	6.40 (s)	3.42 (m)		3.65 (dd) (9.0, 3.9)	3.03 (dd) (9.0, 13.7), 3.24 (dd) (3.8, 13.7)	2.76 (dd) (4.5, 12.7), 2.98 (dd) (4.2, 12.7)
H Leuψ(CH_2NH)Trp–OMe **18a**	CD_3OD		3.52 (m)	3.62 (s)	3.50 (m)	3.31 (m)	2.85 (m)
Cycle[Leuψ(CH_2NH)Trp] **18b**	$CDCl_3$	6.31 (s)	3.38 (m)		3.74 (dd) (8.7, 3.8)	3.21 (dd) (8.7, 14.5), 3.41 (dd (3.7, 14.5)	2.75 (dd) (4.3, 12.7), 2.94 (dd) (4.2, 12.7)
H Lysψ(CH_2NH)Trp–OMe **19a**	D_2O		3.61 (m)	3.68 (s)	3.74 (t)	3.15–3.24 (m)	2.59 (dd), 2.88 (m)
H Argψ(CH_2NH)Trp–OMe **20a**	D_2O		3.42 (m)	3.59 (s)	4.35 (br t)	3.37 (m)	3.19 (m)
H ζ-Pheψ(CH_2NH)Leu–OMe **21a**	$CDCl_3$	4.70 (br s)	3.21 (m)	3.66 (s) 3.63 (s)	3.18 (m)	2.70 (m)	2.50 (dd) (8.9, 12.1), 2.70 (dd) (5.0, 12.1)
Cycle[Pheψ(CH_2NH)Leu] **21b**	$CDCl_3$	5.76 (s)	3.62 (m)		3.41 (dd) (10.3, 3.4)	2.74 (dd) (8.7, 13.4), 2.89 (dd) (5.4, 13.4)	2.92 (dd) (5.5, 13.1), 3.06 (dd) (4.4, 13.1)
Cycle[D Pheψ(CH_2NH)Leu] **21c**	$CDCl_3$	5.66 (s)	3.73 (m)		3.40 (dd) (10.2, 3.3)	2.57 (dd) (9.1, 13.6), 2.86 (dd) (5.0, 13.6)	2.71 (dd) (9.6, 12.7) 3.24 (ddd) (4.2, 12.7)[c]
H Trpψ(CH_2NH)Leu–OMe **22a**	$CDCl_3$	4.37 (br s)	3.26 (m)	3.63 (s)	3.22 (t) (7.1)	3.01 (m)	2.54 (dd) (9.0, 12.6), 2.88 (dd) (4.0, 12.6)
Cycle[Trpψ(CH_2NH)Leu] **22b**	$CDCl_3$	5.81 (s)	3.72 (m)		3.42 (dd) (10.2, 3.4)	2.86 (dd) (8.9, 14.1), 3.04 (dd) (4.3, 14.1)	2.96 (dd) (5.9, 13.2) 3.11 (dd) (4.4, 13.2)
Cycle [Trpψ(CH_2NH)Lys] **23b**	D_2O		3.93 (m)		3.41 (dd) (7.4, 4.8)	2.93–3.18 (m)	
Cycle[Trpψ(CH_2NH)Arg] **24b**	D_2O		3.80 (m)		3.20 (dd) (7.4, 4.7)	2.92–3.15 (m)	

[a] α-NH of *N*-terminal amino acid (NH_3^+ for linear analogues). [b] β-CH_2 aromatic amino acid. [c] $J_{1,6}$ 1.4 Hz.

Table 4 Analytical data for compounds **7**–**16**

Compound	Yield (%)	Chromatographic purification	Mol. formula	Found % (Required) C	H	N
Z–Leuψ(CH_2NH)Phe–OMe **7**	90	Hexane–EtOAc (6:1)	$C_{24}H_{32}N_2O_4$	69.7 (69.88)	7.9 (7.82)	6.75 (6.79)
Z–Leuψ(CH_2NH)Trp–OMe **8**	79	$CHCl_3$–MeOH (80:1)	$C_{26}H_{33}N_3O_4$	69.0 (69.16)	7.4 (7.37)	9.2 (9.30)
Z–Lys(Z)ψ(CH_2NH)Trp–OMe **9**	55	Hexane–EtOAc (1:2)	$C_{34}H_{40}N_4O_6$	68.0 (67.98)	6.7 (6.71)	9.3 (9.33)
Z–Arg(Z_2)ψ(CH_2NH)Trp–OMe **10**	40	Hexane–EtOAc (2:1)	$C_{42}H_{46}N_6O_8$	66.0 (66.13)	6.1 (6.08)	10.9 (11.02)
Z–Pheψ(CH_2NH)Leu–OMe **11**	57	Hexane–EtOAc (12:1)	$C_{24}H_{32}N_2O_4$	69.8 (69.88)	7.6 (7.82)	6.7 (6.79)
Z–Trpψ(CH_2NH)Leu–OMe **12**	65	Hexane–Acetone (5:1)	$C_{26}H_{33}N_3O_4$	69.0 (69.16)	7.5 (7.37)	9.25 (9.30)
Z–Trpψ(CH_2NH)Lys(Z)–OMe **13**	69	Hexane–EtOAc (3:1)	$C_{34}H_{40}N_4O_6$	68.1 (67.98)	6.55 (6.71)	9.2 (9.33)
Z–Trpψ(CH_2NH)Arg(Z_2)–OMe **14**	48	$CHCl_3$–MeOH (50:1)	$C_{42}H_{46}N_6O_8$	66.1 (66.13)	6.15 (6.08)	10.85 (11.02)
Boc–Leuψ(CH_2NH)Phe–OMe **15**	81	Hexane–EtOAc (6:1)	$C_{21}H_{34}N_2O_4$	66.5 (66.64)	9.2 (9.05)	7.3 (7.40)
Boc–Leuψ(CH_2NH)Trp–OMe **16**	70	Cyclohexane–EtOAc (4:1)	$C_{23}H_{35}N_3O_4$	65.9 (66.16)	8.6 (8.45)	9.8 (10.06)

Leu–H **1**,[22] Z–Lys–(Z)–H **2**,[22] Z–Arg(Z_2)–H **3**, Z–Phe–H **4**,[23] Z–Trp–H **5**[22] and Boc–Leu–H **6**[17] were prepared according to the Fehrentz and Castro method.[17]

General Procedure for the Synthesis of P–Xaa(R^1)ψ(CH_2NH)–Yaa(R^2)–OMe **7**–**16**.—A solution of the aldehyde (5 mmol) and the corresponding amino acid methyl ester (20 mmol) in MeOH (15 cm^3) was stirred at room temperature for 10 min in the presence of molecular sieves (4 Å). Then, a solution of $NaBH_3CN$ (5 mmol) and $ZnCl_2$ (2.5 mmol) in MeOH (10 cm^3) was added. After being stirred for 1–2 h at room temperature the reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was extracted with EtOAc. The extracts were washed successively with water, 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated. The products obtained by this method were purified on silica gel column, using the solvent systems indicated in Table 4. Analytical data and ^{1}H NMR chemical shifts of compounds **7**–**16** are recorded in Tables 2 and 4.

Studies on N-*Deprotection of Pseudodipeptide Derivatives* **7**–**16**.—1. *Elimination of benzyloxycarbonyl group. Method A:* Z-protected pseudodipeptides **7**–**14** (2 mmol) in (1:20) HCl–MeOH (100 cm^3) were hydrogenated for 3 h at room temperature under 30 psi pressure, using Pd/C (10%) as catalyst. After filtration of the catalyst and evaporation to dryness, the obtained residues were purified on a silica gel column as indicated in Table 5.

Method B: Compounds **11** and **12** (1 mmol) in MeOH (50 cm^3) were hydrogenated as described in method A to give the cyclic compounds **21b**, **21c** (from **11**) and **22b** (from **12**).

2. *Elimination of* t-*butyloxycarbonyl group. Method A:* A solution of a Boc-protected compound **15** or **16** (1 mmol) in (1:1) TFA–water solution (5 cm^3) was stirred at 0 °C for 30 min and then at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography (Table 5).

Method B: A solution of compound **16** (1 mmol) in (20:1) MeOH–HCl (10 cm^3) was stirred at room temperature overnight to yield, after evaporation and column chromatographic purification, compound **18a** (Table 5).

Analytical and ^{1}H NMR data of linear and cyclic analogues obtained by all these methods are recorded in Tables 3 and 5.

Cyclization of H–Xaaψ(CH_2NH)Leu–OMe (Xaa = Phe, Trp) **11** *and* **12**.—A solution of linear pseudodipeptide **11** or **12**

Table 5 Analytical data for compounds **17a–22a**, **17b**, **18b**, **21b–24b** and **21c**

Compound	Yield (%) (starting compound)	Chromatographic purification	Mol. formula	Elemental analyses					
				Calc.			Found		
				C	H	N	C	H	N
H–Leuψ(CH_2NH)Phe–OMe **17a**	98[a] (**15**) 25[b] (**7**)	$CHCl_3$–MeOH (15:1)	*f*						
Cycle[Leuψ(CH_2NH)Phe] **17b**	54[b] (**7**) 6[a] (**16**)	$CHCl_3$–MeOH (10:1)	$C_{15}H_{22}N_2O$	73.13	9.00	11.37	73.0	9.2	11.25
H–Leuψ(CH_2NH)Trp–OMe **18a**	10[b] (**8**) 85[c] (**16**)	$CHCl_3$–MeOH (10:1)	*f*						
Cycle[Leuψ(CH_2NH)Trp] **18b**	80[a] (**16**) 66[b] (**8**)	$CHCl_3$–MeOH (10:1)	$C_{17}H_{23}N_3O$	71.55	8.12	14.72	71.4	8.2	14.6
H–Lysψ(CH_2NH)Trp–OMe **19a**	87[b] (**9**)	$CHCl_3$–MeOH (4:1)	*g*						
H–Argψ(CH_2NH)Trp–OMe **20a**	90[b] (**10**)	$CHCl_3$–MeOH (3:1)	*g*						
H–ζ-Pheψ(CH_2NH)Leu–OMe **21a**	74[b] (**11**)	$CHCl_3$–MeOH (10:1)	*g*						
Cycle[Pheψ(CH_2NH)Leu] **21b**	85[a] (**11**)	$CHCl_3$–MeOH (10:1)	$C_{15}H_{22}N_2O$	73.13	9.00	11.37	73.1	9.15	11.2
Cycle[D-Pheψ(CH_2NH)Leu] **21c**	96[e] (**21a**)	$CHCl_3$–MeOH (10:1)	$C_{15}H_{22}N_2O$	73.13	9.00	11.37	73.0	9.2	11.2
H–Trpψ(CH_2NH)Leu–OMe **22a**	68[b] (**12**)	$CHCl_3$–MeOH (10:1)	*f*						
Cycle[Trpψ(CH_2NH)Leu] **22b**	60[a] (**12**) 92[e] (**22a**)	$CHCl_3$–MeOH (10:1)	$C_{17}H_{23}N_3O$	71.55	8.12	14.72	71.4	8.0	14.6
Cycle[Trpψ(CH_2NH)Lys] **23b**	94[b] (**13**)	$CHCl_3$–MeOH–water (5:5:1)	$C_{17}H_{25}ClN_4O$	60.61	7.48	16.63	60.35	7.6	16.5
Cycle[Trpψ(CH_2NH)Arg] **24b**	89[b] (**14**)	$CHCl_3$–MeOH–water (40:5:0.2)	$C_{17}H_{25}ClN_6O$	55.96	6.91	23.03	55.7	7.1	22.8

[a] Treatment of N^{α}-Boc-protected derivatives with (1:1) TFA–water. [b] Hydrogenation of Z-protected analogues in (1:20) HCl–MeOH. [c] Treatment of N^{α}-Boc derivative with (1:20) HCl–MeOH. [d] Hydrogenation of Z-analogues in MeOH. [e] From cyclization reaction of the linear analogue. [f] Pure samples were not obtained due to spontaneous cyclization. [g] Highly hygroscopic.

(0.4 mmol) in 0.1 mol dm^{-3} AcOH–BuOH (6 cm^3) containing *N*-methylmorpholine (0.4 mmol) was refluxed for 1 h. After evaporation of the solvent, the corresponding cyclic analogues were purified on silica gel column (Table 5).

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