Solid-Phase S_NAr Macrocyclizations To Give Turn – Extended-Turn Peptidomimetics

Yangbo Feng and Kevin Burgess*[a]

Abstract: Solid-phase supported S_NAr macrocyclization reactions were investigated to test the viability of preparing libraries of β-turn mimics. An optimized set of conditions for this type of transformation was developed for various amino acid derived nucleophiles and ring sizes. The reaction conditions were optimized for the ideal resin types, resin loadings, bases, and cyclization time for the macrocyclization reactions. Finally, these conditions were applied in a series of model syntheses in which the products were isolated and purified. Access to this type of peptidomimetic on the solid phase lays foundations for the syntheses of libraries designed for targets involving protein – protein interactions.

Keywords: β-turn · macrocyclizations · nucleophilic aromatic substitutions · peptidomimetics · solid-phase synthesis

Introduction

Historically, therapeutic strategies based on enzyme – substrate interactions are more common than those based on protein – protein contacts. At least two factors have contributed to this situation. The first is that enzyme – substrate interactions are far easier to mimic, for example with small organic compounds, than protein – protein contacts which are harder to identify and are usually not localized. The second is that the biological role of extracellular receptors in cell signaling is complex and is yet to be fully understood. Despite these intrinsic difficulties, there are strong indications that treatments based on interfering with protein – protein interactions will become increasingly important. This is especially true since the "Human Genome Project" is exposing many new protein – protein interactions that could be exploited in medicinal chemistry.

Libraries of β-turn mimics are likely to play a pivotal role in the development of therapeutic approaches based on protein – protein interactions. Figure 1 illustrates a typical approach to identify relatively small molecules that will mimic protein – protein contact sites, and the role that libraries of β-turn mimics play in such efforts. "Hot spots",[1–4] that is key molecular recognition regions wherein the protein – ligand interacts with its receptor, are first identified from structural data and from activities of protein mutants and/or chimeras. These hot spots often feature turn or loop protein regions.[5] Simple mimics of the putative protein – ligand hot spots, typically disulfide-linked cyclic peptides encapsulating the sequence of interest,[6–13] are then prepared to test for binding and activity. The next logical step is to prepare peptidomimetics with increased rigidity and reduced size. Libraries of

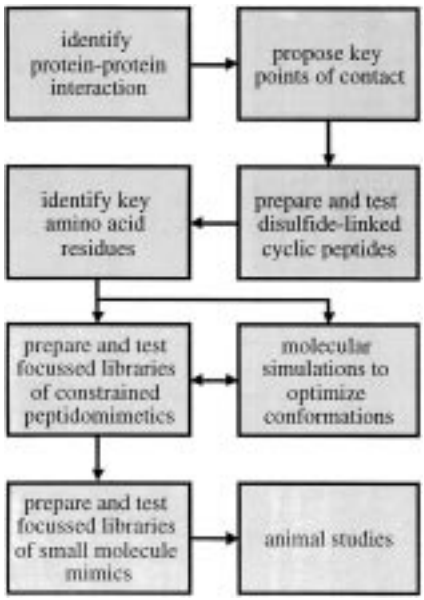

Figure 1. A possible initial strategy for exploring protein – protein interactions for pharmaceutical applications.

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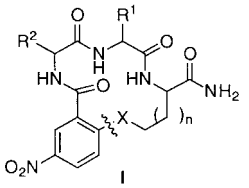
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. This file contains DQF-COSY spectra and analytical HPLC traces for selected compounds.

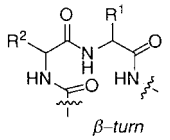
  0947-6539/99/0511-3261 $ 17.50+.50/0

turn or loop peptidomimetics in which amino acid sequences are displayed in various relatively rigid conformations will therefore be extremely useful. These could be focussed libraries wherein the amino acid residues correspond to one component of the protein–ligand interaction, or larger libraries designed to test a diverse set of pharmacophores arranged in different ways. Often, both focussed and more diverse libraries will be used.

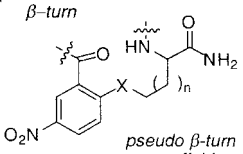
The work described herein was undertaken to develop a methodology that would enable preparation of β-turn analogues conforming to the criteria described above. The target molecular type **I** was selected,[14] because the scaffold can be varied to display different amino acid sequences in different conformations. These scaffolds might also be varied to impart favorable pharmacokinetic properties.



I
target molecules

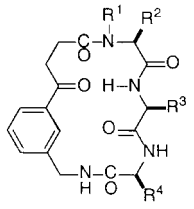


β–turn

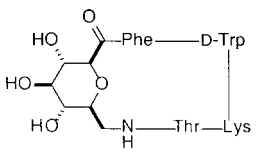


pseudo β-turn scaffold

Syntheses of β-turn mimics incorporating amino acids have been studied intensively, but many solid-phase syntheses of rigid β-turn mimetics containing amino acid pharmacophores must be developed to match the anticipated need for this type of library. DuPont–Merck's macrocyclic turn mimics **A**[15, 16] and Kessler's carbohydrate derivatives **B**[17, 18] are excellent illustrations of pharmacologically active molecules featuring key amino acids held in favorable conformations by non-peptidic scaffolds. However, it has yet to be demonstrated that



A

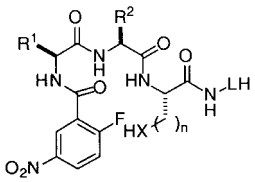


B

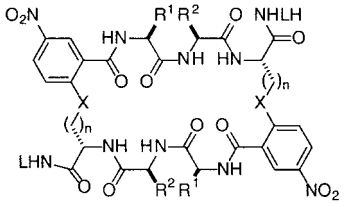
these systems are amenable to construction on a solid-phase and hence high-throughput parallel syntheses. Consequently, the value of the work described herein should be gauged against its suitability for: i) forming relatively small focussed libraries of products containing key amino acid sequences; and, ii) accessing larger libraries through high-throughput parallel syntheses.

Results and Discussion

Table 1 shows the compounds that were prepared and isolated in this study, and illustrates the numbering system that will be used throughout this paper. An "**m**" suffix is used to indicate the desired cyclic monomer (compare target molecule **I** above). Two unwanted by-products frequently observed in this study were uncyclized linear peptide, and the cyclized dimer. These are given the same number as the parent cyclized monomer (thus defining R^1, R^2, X, and L), while "**l**" and "**d**" suffixes denote the linear peptide and dimer, respectively.



undesired uncyclized peptide
L = linker



undesired cyclized dimer

The compounds shown in Table 1 were prepared after extensive optimization of the reaction conditions and other reaction parameters. Most of this paper is devoted to explaining how these optimized conditions and parameters were identified. An outline of the optimization approach is as follows. First, a protocol was developed to determine the product purity, which was then applied to probe experiments to access the effects of the S_NAr nucleophile, product ring size, resin type and loading, spacers, different bases, and reaction times. These experiments enabled us to access workable conditions for the critical S_NAr macrocyclization.[19] Products were not fully characterized in these optimization experiments, instead they were only tentatively identified with HPLC and MS. However, in the final part of this work the idealized conditions were applied to a series of illustrative syntheses in which the yield of isolated material was obtained (Table 1) and spectroscopic data was collected. Details of each step of the optimization process are presented in the following sections.

Coupling and protecting group strategies: Cyclization precursors were prepared on the solid phase with the conventional Fmoc approach[20] with diisopropylcarbodiimide/*N*-hydroxybenzotriazole (DIC/HOBt) for activation. Standard acid-labile side chain protecting groups were used for most of the amino acids.[21] However, careful consideration and some time-consuming experimentation were required in selecting the appropriate protecting groups for the amino acid side chain that would serve as the nucleophile in the S_NAr macrocyclization. The difficulty was that those nucleophilic side chains had to be protected during the syntheses of the linear peptidomimetic sequence, then unmasked without cleaving the cyclization precursor from the resin. This was not a routine exercise, and the approach taken proved to be critical for success in this work.

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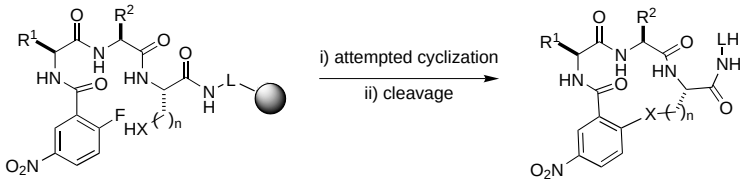
Table 1. Compounds prepared and isolated.

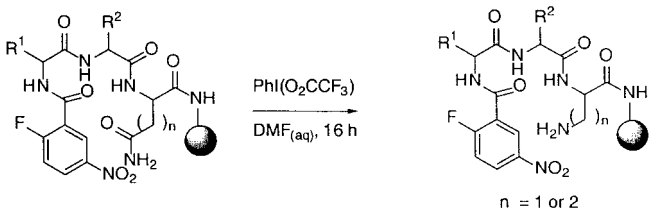


Compound[a]	Ring size	R^1	R^2	X	L	Purity [%]	Isolated yield [%]
1m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	S	–	75	33
2m	13	$(CH_2)_4NH_2$	$(CH_2)_2CONH_2$	S	–	55	24
3m	13	MeEtCH	$(CH_2)_4NH_2$	S	–	67	23
4m	13	$(CH_2)_4NH_2$	H	S	–	85	38
5m	13	CH_3	H	S	-	93	39
6m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	S	CH_2CONH	70	31
7m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	S	$(CH_2)_2CONH$	66	32
8m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	S	$(CH_2)_5CONH$	63	32
9m	13	$(CH_2)_4NH_2$	H	S	CH_2CONH	87	27
10m	13[b]	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	S	CH_2CO_2	40	23
11m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	O	–	30	14
12m	14	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	O	–	89	43
13m	14	D-$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	O	–	60	48
14m	14	$(CH_2)_2CO_2H$	D-$(CH_2)_4NH_2$	O	–	59	38
15m	14	MeEtCH	CH_2CONH_2	O	–	61	23
16m	14	CH_2CONH_2	$(CH_2)_3$ (from Pro)	O	–	51	18
17m	14	MeEtCH	$(CH_2)_4NH_2$	O	–	80	37
18m	14	CH_2CONH_2	CH_2OH	O	–	49	11
19m	14	CH_2OH	CH_2*i*Pr	O	–	94	65
20m	14	*i*Pr	$(CH_2)_2CO_2H$	O	–	77	43
21m	14	CH_2CO_2H	MeEtCH	O	–	70	25
22m	14	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	O	CH_2CONH	63	32
23m	13[b]	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	O	CH_2CO_2	71	33
24m	13	MeEtCH	CH_2CONH_2	O	CH_2CONH	56	20
25m	13	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	–	30	9
26m	14	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	–	90	30
27m	14	EtMeCH	$(CH_2)_4NH_2$	NH	–	86	48
28m	14	$(CH_2)_3$ (from Pro)	$CH(CH_3)_2$	NH	–	78	43
29m	14	CH_2OH	$(CH_2)_4NH_2$	NH	–	82	40
30m	14	CH_2Ph	$CH_2CH_2SCH_3$	NH	–	93	37
31m	15	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	–	93	56
32m	15	*i*Pr	$(CH_2)_2CO_2H$	NH	–	91	74
33m	15	CH_2*i*Pr	$CH_2(CH_3)OH$	NH	–	90	89
34m	15	CH_2Ph	$CH_2C_3H_3N_2$	NH	–	96	73
35m	15	$(CH_2)_3$ (from Pro)	CH_2SCH_2NH-$COCH_3$	NH	–	91	67
36m	16	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	–	83	52
37m	16	EtMeCH	$(CH_2)_4NH_2$	NH	–	89	52
38m	14[b]	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	CH_2CO_2	60	23
39m	15[b]	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	NH	CH_2CO_2	96	59

[a] Desired cyclized monomer denoted with "**m**" suffix in compound number. [b] Compounds with a carboxylate C-terminus were prepared on resins equipped with Wang linkers.

Three protecting group strategies were investigated when cysteine was used as the nucleophilic component in the cyclization. Use of the S*t*Bu disulfide (deprotection PBu_3 in DMF/*i*PrOH)[22] gave variable results. Trityl protection (deprotection 3% TFA, 4% HSi*i*Pr_3 in CH_2Cl_2) or, better, Mmt (Mmt = 4-methoxytrityl; deprotection 1% TFA, 4% HSi*i*Pr_3 in CH_2Cl_2) was superior. Trityl protection was also used for serine, homoserine, and threonine residues (deprotection 1% TFA, 4% HSi*i*Pr_3 in CH_2Cl_2).

Lysine and ornithine side chains were protected with Mtt (Mtt = 4-methyltrityl; deprotection 1% TFA, 4% HSi*i*Pr_3 in CH_2Cl_2). Shorter amine-containing side chains presented a problem because these amino acid precursors are comparatively expensive or not available commercially. Consequently, the side chains were generated by on-resin Hofmann degradation reactions[23–25] of asparagine or glutamine side chains immediately prior to the attempted macrocyclization as illustrated below.



Scheme 1. On-resin Hofmann degradation.

Assays of purity: A convenient HPLC assay of product purity was required for the optimization studies reported here. Selection of a UV wavelength for HPLC detection in the absence of authentic product and by-product samples is a perennial problem in solid-phase syntheses, and the way in which this problem is approached directly influences the data obtained.[26, 27] For instance, studies have been performed in which 4-nitrophenylalanine was used as a spacer so that the products could be assayed at the 4-nitrophenyl absorption maximum.[28–30] This approach overrepresents the product purity with respect to impurities that do not absorb strongly at λ_{max} for the 4-nitrophenyl group. While that type of bias is not a concern for evaluations within a series of data recorded under identical conditions, it does not allow broader comparisons because the purity data obtained in such experiments are the maximum possible values that could conceivably be measured.

The following experiments were performed to develop relatively stringent tests of product purity and product ratios. Syntheses of two turn mimics, the same sequence with and without a UV silent spacer, were examined (Table 2). The

Table 2. Selection of UV wavelengths for purity determination based on formation of a model macrocyclic sulfide.

Detection method	Product	Cyclic monomer (**1m** or **6m**) [%]	Cyclic dimer (**1d** or **6d**) [%]
UV at 280 nm	**1**[a]	75	22
UV at 254 nm	**1**	63	33
UV at 215 nm	**1**	49	46
254/215 nm average	**1**	56	40
product ratios [%]	**1**	56	39
UV at 280 nm	**6**[b]	66	34
UV at 254 nm	**6**	47	53
UV at 215 nm	**6**	30	70
254/215 nm average	**6**	39	62
product ratios [%]	**6**	42	58

[a] Rink amide AM resin at 0.66 mmol g^{-1} for **1**. [b] HMPB-BHA resin[33, 34] at 0.69 mmol g^{-1} for **6**.

desired cyclized materials **1m** and **6m** were formed along with undesired cyclic dimer (**1d** and **6d**) and some minor uncharacterized products; an illustrative HPLC trace is shown in Figure 2. Ratios of the cyclic monomer and dimers were measured by UV detection at three wavelengths. These

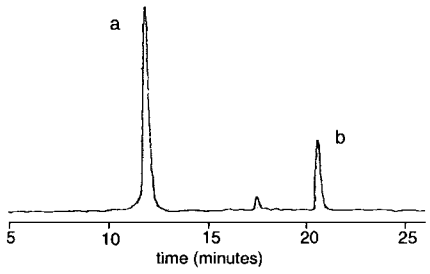


Figure 2. HPLC profile corresponding to entry 1 in Table 2 at 254 nm detection, no spacer. Peak **a** is the desired cyclic monomer, peak **b** the undesired cyclic dimer. The small peak in the middle gave three times the molecular weight of that of peak **a**, but was not characterized further.

data were then compared with the ratios of the products isolated from these same experiments (for instance, material corresponding to all three major peaks in Figure 2 was collected, and the ratio of monomer-to-dimer was based on the total mass of these three peaks). None of the purities indicated by UV detection at any of the three wavelengths used perfectly matched the ratios of isolated products, but only the average of data collected at 254 and 215 nm gave a reasonable fit. Consequently, 254/215 nm averages were used to compare purities for all the optimization work presented in this paper.

Effects of nucleophile and product ring size: The data for testing the macrocyclization reactions involving readily available amino acids with nucleophilic side chains are shown in Table 3. Residues used for the nucleophilic components of the S_NAr reaction included cysteine, serine, threonine, homoser-

Table 3. Influence of nucleophile and ring size on macrocyclization efficiency.

Entry	Ring size	X[a]	Compound/Purity [%][b]		
			Linear monomer	Cyclic monomer	Cyclic dimer
1	13	S	**1l**/0	**1m**/56	**1d**/40
2	13	NH	**25l**/0	**25m**/30[c]	**25d**/0
3	13	O	**11l**/55	**11m**/2[d]	**11d**/38
4	14	NH	**26l**/0	**26m**/90	**26d**/0
5	14	O	**12l**/0	**12m**/61	**12d**/0
6	15	NH	**31l**/0	**31m**/93	**31d**/0
7	16	NH	**36l**/0	**36m**/82	**36d**/0

[a] See Table 1 for definition of X. [b] Based on HPLC/UV detection for average values monitored at 215 and 254 nm for macrocyclization conditions: i) 5.0 equiv K_2CO_3, DMF, 25 °C, 35 h; ii) TFA cleavage, on Rink amide AM resin at 0.66 mmol g^{-1}. [b] Other unidentified products also formed. [c] The desired monocyclic compounds were obtained with different cyclization conditions.

ine, ornithine, lysine, and the Hofmann degradation products from asparagine and glutamine. Homocysteine was not included since this amino acid is relatively expensive, especially in the protected form.

Entries 1–3 of Table 3 reveal that the desired 13-membered ring cyclic monomer formed with the S-nucleophile (Cys) and the N-nucleophile, but not with the O-nucleophile (Ser; Thr was also tested, data not shown). Overall, the data in Table 3 shows that the formation of the 13-membered ring system was the most demanding of the four ring sizes examined. For N-nucleophiles, the desired product 13-membered ring was formed in significantly lower yield (entry 2) than the others (entries 4, 6, and 7). This could be a result of the ring strain and/or an anomalous Hofmann degradation for asparagine compared with glutamine. However, the data for the O-nucleophiles follows the same trend; no product was obtained for the 13-membered ring cases (entry 3) whereas a reasonable yield of the cyclic monomer was obtained for the 14-membered ring case (entry 5). These observations indicate that ring strain is a major factor in determining the efficiency of the macrocyclization, and that 13-membered rings are unfavorable. Incidentally, it was shown later that the amount of the cyclic monomer formed could be enhanced significantly by changing the resin type or the loading.

0947-6539/99/0511-3264 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 11

A similar macrocyclization was also attempted with (2*S*,4*R*)-4-hydroxyproline as the nucleophile to yield the desired product as a 13/14-membered ring. However, no cyclic monomer was detected when potassium carbonate was used as a base. Low yields of cyclic monomer were detected when TBAF was used. This is another example of how difficult it is to achieve S_NAr cyclizations to 13-membered rings with O-nucleophiles.

Effects of resin type and resin loading: The work outlined in Table 4 indicate that cyclic dimers could be significant by-products, especially when the intended product was a strained 13-membered ring system. It was anticipated that resin type and resin loading might have significant effects on the ratio of the desired cyclized monomer to undesired cyclized dimer (**m**/**d**), so studies were initiated to probe this issue. Two resin types were compared: polyethylene glycol/polystyrene graft resin, also called TentaGel S RAM, and conventional polystyrene resin as the Rink Amide AM resin. Both were functionalized with Rink's amide handle.[31] The commercially available polystyrene resin has a higher loading than the TentaGel resin, but a batch of the former was "capped-down" to a loading approximately the same as the latter.

The data presented for the TentaGel S RAM and Rink AM resins in Table 4 at similar loadings indicate the latter gives a slightly higher monomer-to-dimer (**m**/**d**) ratio for each of the three examples tested. However, when the loading was increased by a factor of 2.5 (i.e., 0.66/0.26) the corresponding **m**/**d** ratios decreased by approximately the same factor. Resin loading was therefore critical in determining the ratio of desired product to cyclized dimer.

Experiments performed to accumulate data for Table 4 also revealed that the purity of the desired product depends on the resin loading. More by-products were observed when higher loadings were involved. Figure 3 compares crude HPLC traces for synthesis of a 14-membered ring system made on a support at two different loadings.

Effects of spacer: Incorporation of a spacer between the resin handle and the first amino acid in the sequence might be envisaged to project the cyclization precursor more effectively into solution, thereby increasing the cyclization efficiency. In fact, it was found that linker groups (L in Table 1) such as glycine, β-alanine, and 6-aminohexanoic acid (6-Aha) caused slight increases of cyclic dimers (Table 5). One possible

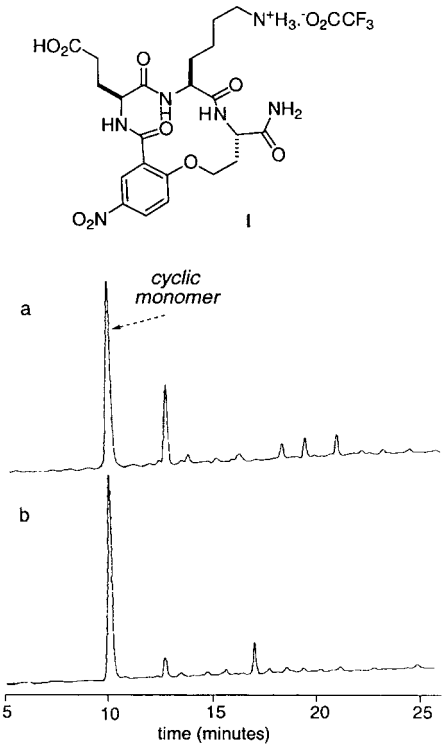
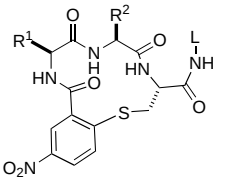


Figure 3. HPLC profiles corresponding to synthesis of compound **I** on **a** Rink amide AM resin (0.66 mmol g^{-1}), and **b** TentaGel S RAM resin (0.30 mmol g^{-1}). Conditions: K_2CO_3, DMF, 25 °C, 24 h then TFA cleavage.

Table 5. Effect of spacer on cyclization to a 13-membered ring.[a]



macrocyclization conditions:
i) 5.0 equiv. K_2CO_3, DMF, 25 °C, 35 h
ii) TFA cleavage

Compound **m**/**d**	R^1	R^2	L	**m** [%]	**d** [%]	
1	$(CH_2)_2CO_2H$	$(CH_2)_4NH_2$	H	75	25	3.0
6			Gly	70	26	2.7
7			β-Ala	66	33	2.0
8			6-Aha	63	30	2.1
4	$(CH_2)_4NH_2$	H	H	85	12	7.1
9			Gly	87	9	9.6

[a] Based on the averaged values monitored at 215 nm and 254 nm. TentaGel S RAM resin at 0.30 mmol g^{-1} loading was used throughout.

Table 4. Effect of resin loading on cyclization to the 13-membered ring systems **2m**, **3m**, and **7m**.[a]

Compound	TentaGel S RAM (0.30 mmol g^{-1})			Rink amide AM[b] (0.26 mmol g^{-1})			Rink amide AM (0.66 mmol g^{-1})		
	m[c] [%]	**d**[d] [%]	**m**/**d**	**m**[c] [%]	**d**[d] [%]	**m**/**d**	**m**[c] [%]	**d**[d] [%]	**m**/**d**
1	70	26	2.7	73	22	3.3	55	42	1.3
3	75	25	3.0	70	17	4.0	56	40	1.4
4	85	12	7.1	67	7	9.0	73	25	2.9

[a] HPLC purities based on the averaged values monitored at 215 nm and 254 nm on analytical RP-HPLC traces for macrocyclization conditions: i) 5.0 K_2CO_3, DMF, 25 °C, 35 h; ii) TFA cleavage. [b] Resin obtained by capping (acetic anhydride) Rink amide AM resin (0.66 mmol g^{-1}). [c] Cyclic monomer. [d] Cyclic dimer.

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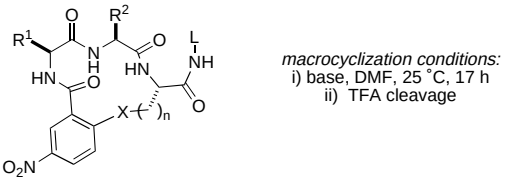
explanation is that unfavorable intermolecular reactions are facilitated by the increased mobility of the substrate when a linker is included; this counteracts the other effects. The loss of selectivity for the cyclic monomer was, however, relatively small. Spacers are incorporated into the product to provide additional sites for diversification, hence this consideration may, for some applications, compensate for the slight loss of purity of the product.

Scheme 2. Epimerization with TBAF and O-nucleophiles.

Effects of bases: The bases examined in this project were TBAF, CsF, K_2CO_3, and TMG (tetramethylguanidine). A few reactions were also attempted with Cs_2CO_3. The data obtained is shown in Table 6. Throughout, the reaction time was 17 h. It is possible that in some cases a even longer reaction time would have given a higher conversion to the cyclic monomer, but at the same time this might also have increased the degree of epimerization.

Entry 1 of Table 6 shows that a good conversion to the cyclic monomer was obtained for all the bases when an N-nucleophile was cyclized to form a 16-membered ring. The best yield of cyclic monomer for O-nucleophiles was obtained when TBAF or CsF was used. However, when the O-nucleophile was serine or threonine these reactions were accompanied by significant epimerization (see below). TBAF was not a good base for S-nucleophiles (entries 4 and 5).

Table 6. Effects of base on the macrocyclizations.



Entry	Compound	X	n	Bases and corresponding purities [%][a]				
				TBAF	CsF	Cs_2CO_3	K_2CO_3	TMG
1[b]	**37m**	NH	4	90	85	89	89	89
2[c]	**17m**	O	2	90	83	80	67	62
3[c]	**22m**	O	2	62	63		57	29[e]
4[b]	**4m**	S	1	1.6[f]	61[g]	65[f]	67[i]	67[j]
5[c]	**2m**	S	1	29[k]	68[l]	48[l]	56[f]	57[m]

[a] Based on the averaged values monitored at 215 nm and 254 nm. [b] On Rink amide AM resin at 0.66 mmol g^{-1}. [c] On TentaGel S RAM resin at 0.30 mmol g^{-1}. [d] 9% uncyclized monomer detected. [e] 21% uncyclized monomer detected. [f] 15% cyclized dimer detected. [h] 8% cyclized dimer detected. [i] 7% cyclized dimer detected. [j] 4% cyclized dimer detected. [k] 20% cyclized dimer detected. [l] 7% cyclized dimer detected. [m] 16% cyclized dimer detected.

Extensive epimerization was observed with TBAF as the base and serine or threonine as the O-nucleophile, but not with homoserine (as in Table 6, entries 2 and 3). The reaction shown below is illustrative of this effect. Serine and threonine residues are known to be particularly sensitive to basic conditions,[32] hence the loss of stereochemistry observed appears to be a result to this factor. It is also possible that epimerization was less of a problem in reactions run with K_2CO_3 because this salt forms heterogeneous mixtures in DMF thereby keeping the absolute concentration of base low.

Effects of cyclization time: A relatively long cyclization time was selected for most of the reactions studied in this work to avoid skewing the data by terminating transformations prematurely. However, investigations of the actual cyclization times required revealed significant variations for different linear precursors. Kinetically unfavorable cyclizations wherein a hindered amino acid residue was involved (e.g. Val) were slower but still tended to completion within a matter of hours.

Illustrative optimized syntheses: The following conclusions can be drawn from the data presented above:

- N-nucleophiles cyclize comparatively clean to give 14- to 16-membered ring products; 13-membered ring products are harder to form,
- for S-nucleophiles, the desired cyclic monomer products were contaminated in some cases with significant formation of cyclic dimer products (the only ring size examined was 13-membered and this probably made the cyclization even harder to achieve),
- cyclizations with O-nucleophiles worked well for the 14-membered rings, but not for 13-membered rings,
- low resin loads are desirable, specifically with TentaGel S RAM resin for 13-membered ring products and for all reactions involving O-nucleophiles,
- Rink amide AM resin can be used for N-nucleophiles and all the ring sizes studied (i.e., 13–16-membered rings),
- K_2CO_3/DMF is the appropriate base for most of the cyclization reactions,
- TBAF/DMF gives higher conversion than K_2CO_3/DMF when O-nucleophiles are involved, although considerable epimerization occurs, and,
- a 24 h reaction time is generally sufficient even when sterically hindered amino acids are involved.

These conclusions were applied to approximately 38 syntheses of S_NAr products that were isolated by preparative HPLC (see Table 1). At the moment further studies are in progress to apply these findings to high-throughput parallel syntheses of a larger library of products. These results indicate that large libraries of β-turn analogues with N-nucleophiles cyclizing to 14, 15, and 16-membered rings should be accessible by parallel syntheses.

0947-6539/99/0511-3266 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 11

Experimental Section

General methods: All α-amino acids had the L-configuration, except where otherwise indicated. All chemicals were obtained from commercial suppliers and used without further purification. Diisopropylcarbodiimide (DIC), *N*-hydroxybenzotriazole (HOBt), diisopropylethylamine (DIEA), *N*-methylmorpholine (NMM), trifluoroacetic acid (TFA), CH_2Cl_2, DMF, thionyl chloride, tin chloride dihydrate ($SnCl_2 \cdot 2H_2O$), bis(trifluoroacetoxy)iodobenzene (IBTFA), piperidine, tetrabutylammonium fluoride (TBAF), and triisopropylsilane (TIS) were purchased from Aldrich. 2-Fluoro-5-nitrobenzoyl chloride was obtained by refluxing 2-fluoro-5-nitrobenzoic acid (from Aldrich) in thionyl chloride for 4 h. Rink amide AM resin was obtained from NovaBiochem. TentaGel S RAM Fmoc resin was purchased from Advanced ChemTech. All α-amino acids were obtained either from Advanced ChemTech or from Chem–Impex, except for Fmoc-Cys(Mmt)-OH and Fmoc-Orn(Mtt)-OH which were purchased from NovaBiochem.

Reverse-phase high-performance liquid chromatography (HPLC) was carried out on Vydac C-18 columns of the following dimensions: 25 × 0.46 cm for analysis, and 25 × 2.2 cm for preparative work. All HPLC experiments were performed with gradient conditions. Eluents used were solvent A (H_2O with 0.1% TFA) and solvent B (CH_3CN with 0.1% TFA). Flow rates used were 1.0 mL min^{-1} for analytical, and 6 mL min^{-1} for preparative HPLC.

All NMR spectra were recorded on a Varian instruments at 500 MHz or 300 MHz (^{1}H), and 75 MHz (^{13}C). NMR chemical shifts δ are expressed in ppm relative to internal solvent peaks; the coupling constants J were measured in Hz.

Peptidomimetics in the following experimental section are given as shortened abbreviations according to their constituent amino acids. One letter coding is used for the amino acids in the dipeptide fragment, and three letter abbreviations are used for the amino acids that constitute part of the template. Less common abbreviations used include: Orn = ornithine; Hse = homoserine; Dbu = 2,4-diaminobutyric acid; Dpr = 2,3-diaminopropionic acid; and, Acm = acetamidomethyl.

General experimental procedure for the preparation of the peptidomimetics: **Synthesis of compound 1m**: TentaGel S RAM resin (0.1 mmol, 0.30 mmol g^{-1}) was allowed to swell in DMF (10 mL g^{-1}) in a manual solid-phase synthesis shaker for 30 min, then rinsed with DMF (2 × ca. 10 mL g^{-1}, for each washing cycle throughout). The Fmoc protecting group on the Rink handle was removed by treating the resin with 20% piperidine in DMF (2 × 10 min). The resin was rinsed with DMF (3 ×), MeOH (3 ×), and CH_2Cl_2 (3 ×), and then Fmoc-Cys(Mmt)-OH (3 equiv), DIC (4 equiv), HOBt (4 equiv), and NMM (5 equiv) were added in CH_2Cl_2/DMF (*v*/*v* 4:1). After a reaction time of usually 1 h with gentle shaking, a ninhydrin test on a small sample of beads gave a negative result. The reaction mixture was drained and the resin was rinsed with DMF (4 ×). The above deprotection/coupling cycles were repeated to introduce Fmoc-Lys(Boc)-OH and Fmoc-Glu(O*t*Bu)-OH consecutively. The 2-fluoro-5-nitrobenzoic acid moiety was introduced to the N-terminus of the tripeptide resin by treatment with 2-fluoro-5-nitrobenzoyl chloride (2 equiv) and DIEA (4 equiv) in CH_2Cl_2 for 1 h. The side chain protecting group (Mmt, 4-methoxytrityl) of Cys was removed by treatment with 1% TFA and 5% TIS in CH_2Cl_2 (6 × 5 min). After the resin was rinsed with CH_2Cl_2 (3 ×), MeOH (2 ×), and DMF (3×), the macrocyclization step was carried out by treating the on-resin peptide with K_2CO_3 (5 equiv) in DMF at 25 °C. After gentle shaking for 30 h, the peptide resin was washed with DMF (2 ×), H_2O (2 ×), DMF (2 ×), H_2O (2 ×), MeOH (2 ×), CH_2Cl_2 (2 ×), and MeOH (2 ×), and then dried in vacuo for 4 h. The peptide was cleaved from the resin by treatment with a mixture of 90% TFA, 5% TIS, and 5% H_2O for 3 h. The cleavage solution was separated from the resin by filtration. Most of the cleavage cocktail (about 90%) was evaporated by passing N_2 over the solution. The crude peptide was precipitated with anhydrous diethyl ether, dissolved in H_2O, and then lyophilized to give the crude product. Preparative HPLC (Rainin System, 15–35% B in 30 min) was carried out to provide a white powder (17 mg, 27%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.2 (br, 1H), 8.62 (d, J = 8.7 Hz, 1H), 8.28–8.22 (m, 2H), 7.87 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.67 (br, 3H), 7.64 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.33 (s, 1H), 4.40–4.24 (m, 3H), 3.56 (dd, J = 4.2, 12.6 Hz, 1H), 3.29 (dd, J = 8.7, 12.6 Hz, 1H), 2.80–2.70 (m, 2H), 2.47–2.30 (m, 2H), 1.96–1.86 (m, 2H), 1.76–1.62 (m, 1H), 1.60–1.40 (m, 3H), 1.34–1.17 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 173.9, 171.7, 171.3, 171.2, 167.0, 145.5, 143.3, 140.1, 132.3, 124.5, 121.1, 55.5, 52.4, 50.8, 36.7, 30.5, 30.3, 26.9, 26.2, 22.4; analytical HPLC: homogeneous single peak, t_R = 10.6 min (5–40% B in 30 min); MALDI MS: calcd for $C_{21}H_{28}N_6O_8S$ [*M*H]$^+$ 525.2, found 525.2.

Compound 2m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (25 mg, 20%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.65 (d, J = 8.7 Hz, 1H), 8.27 (dd, J = 2.7, 8.7 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.71 (br, 3H), 7.57 (d, J = 9.0 Hz, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 6.76 (s, 1H), 4.38–4.25 (m, 3H), 3.60 (dd, J = 4.5, 13.2 Hz, 1H), 3.28 (dd, J = 8.7, 13.2 Hz, 1H), 2.88–2.78 (m, 2H), 2.10–2.00 (m, 2H), 1.95–1.80 (m, 1H), 1.80–1.65 (m, 3H), 1.64–1.56 (m, 2H), 1.55–1.40 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 173.8, 172.0, 171.3 (two carbons), 167.0, 145.4, 143.5, 139.9, 131.9, 124.6, 120.8, 55.9, 52.7, 50.8, 36.4, 31.7, 30.2, 26.9, 26.7, 22.8; analytical HPLC: homogeneous single peak, t_R = 7.8 min (5–40% B in 30 min); MALDI MS: calcd for $C_{21}H_{29}N_7O_7S$ [*M*H]$^+$ 523.2, found 523.4.

Compound 3m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (28 mg, 23%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 0.80–1.00 (m, 6H), 1.20–1.35 (m, 3H), 1.42–1.90 (m, 6H), 2.70–2.85 (m, 2H), 3.30 (dd, J = 8.4, 12.9 Hz, 1H), 3.60 (dd, J = 4.2, 17.1 Hz, 1H), 4.15 (t, J = 9.6 Hz, 1H), 4.25–4.40 (m, 2H), 7.35 (s, 1H), 7.53 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.70 (br, 3H), 7.80 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.96 (s, 1H), 8.14 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.4, 8.4 Hz, 1H), 8.60 (d, J = 9.6 Hz, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 171.4, 171.3, 167.0, 162.5, 145.5, 143.1, 140.4, 132.0, 124.5, 120.7, 60.7, 52.5, 50.8, 36.4, 35.0, 30.1, 26.9, 25.5, 22.6, 15.7, 10.7; analytical HPLC: homogeneous single peak, t_R = 14.0 min (8–70% B in 30 min); MALDI MS: calcd for $C_{22}H_{32}N_6O_6S$ [*M*H]$^+$ 509.2, found 509.3.

Compound 4m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (43 mg, 38%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 9.30 (d, J = 7.2 Hz, 1H), 9.01 (t, J = 5.7 Hz, 1H), 8.25 (dd, J = 2.4, 8.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 1.2, 7.4 Hz, 1H), 7.70 (br, 3H), 7.62 (d, J = 7.2 Hz, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 4.43–4.33 (m, 1H), 4.16–4.07 (m, 1H), 3.91 (dd, J = 7.2, 16.5 Hz, 1H), 3.60–3.40 (m, 3H, covered under the signal of water), 2.88–2.76 (m, 2H), 1.78–1.66 (m, 2H), 1.64–1.53 (m, 2H), 1.48–1.24 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 171.6, 171.5, 169.4, 168.6, 147.5, 144.4, 139.4, 138.5, 124.6, 121.8, 54.5, 51.8, 43.3, 36.0, 31.0, 29.2, 27.0, 22.5; analytical HPLC: homogeneous single peak, t_R = 8.1 min (5–40% B in 30 min); MALDI MS: calcd for $C_{18}H_{24}N_6O_6S$ [*M*H]$^+$ 453.2, found 453.3.

Compound 5m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (12 mg, 39%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 9.36 (d, J = 6.9 Hz, 1H), 8.89 (dd, J = 4.5, 7.5 Hz, 1H), 8.28 (dd, J = 2.7, 8.4 Hz, 1H), 8.23 (d, J = 2.7 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.51 (s, 1H), 7.21 (s, 1H), 4.58–4.47 (m, 1H), 4.17–4.07 (m, 1H), 3.93 (dd, J = 7.2, 13.5 Hz, 1H), 3.64–3.50 (m, 2H), 3.28 (t, J = 11.7 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.1, 171.5, 169.5, 168.4, 147.5, 144.4, 139.4, 138.5, 124.4, 121.9, 51.9, 50.0, 43.3, 15.6; analytical HPLC: homogeneous single peak, t_R = 9.3 min (5–40% B in 30 min); MALDI MS: calcd for $C_{15}H_{17}N_5O_6S$ [*M* − O]$^+$ 379.2, found 378.9.

Compound 6m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (15 mg, 27%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.2 (br, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.30–8.22 (m, 3H), 8.02 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.68 (br, 3H), 7.65 (s, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 4.42–4.28 (m, 3H), 3.80–3.58 (m, 3H), 3.25 (dd, J = 8.7, 13.5 Hz, 1H), 2.83–2.72 (m, 2H), 2.46–2.32 (m, 2H), 1.98–1.88 (m, 2H), 1.78–1.62 (m, 1H), 1.62–1.44 (m, 3H), 1.34–1.20 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 173.9, 171.7,

170.6, 169.5, 167.1, 145.5, 143.1, 140.0, 132.1, 124.5, 121.2, 55.6, 52.6, 51.0, 42.1, 36.3, 30.5, 30.4, 26.9, 26.1, 22.5; analytical HPLC: homogeneous single peak, $t_R = 10.9$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{23}H_{31}N_7O_9S$ $[M\mathrm{H}]^+$ 582.2, found 581.9.

Compound 7m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (15 mg, 26%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.3$ (br, 1H), 8.67 (d, $J = 8.7$ Hz, 1H), 8.28 (s, 1H), 8.26 (dd, $J = 2.7$, 9.9 Hz, 1H), 8.13 (t, $J = 5.7$ Hz, 1H), 7.90 (dd, $J = 9.0$, 9.9 Hz, 1H), 7.69 (br, 3H), 7.67 (s, 1H), 7.38 (s, 1H), 6.87 (s, 1H), 4.42–4.27 (m, 3H), 3.58 (dd, $J = 4.2$, 12.9 Hz, 1H), 3.34–3.21 (m, 3H), 2.84–2.72 (m, 2H), 2.48–2.38 (m, 2H), 2.30–2.22 (m, 2H), 2.00–1.88 (m, 2H), 1.76–1.64 (m, 1H), 1.63–1.43 (m, 3H), 1.36–1.18 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.9$, 172.6, 171.7, 171.5, 169.2, 167.1, 145.5, 143.2, 140.1, 132.3, 124.5, 121.2, 55.6, 52.5, 52.4, 51.0, 45.4, 35.5, 34.8, 30.5, 30.3, 26.9, 26.1, 22.5; analytical HPLC: homogeneous single peak, $t_R =$ 11.4 min (5–40% B in 30 min); MALDI MS: calcd for $C_{25}H_{34}N_6O_{10}S$ $[M\mathrm{H} - \mathrm{O}]^+$ 595.2, found 595.8.

Compound 8m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (16 mg, 27%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.3$ (br, 1H), 8.68 (d, $J = 8.7$ Hz, 1H), 8.28 (s, 1H), 8.26 (dd, $J = 2.7$, 9.3 Hz, 1H), 8.09 (t, $J = 5.7$ Hz, 1H), 7.90 (d, $J = 9.0$ Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 7.71 (s, 1H), 7.68 (br, 3H), 7.25 (s, 1H), 6.71 (s, 1H), 4.42–4.30 (m, 3H), 3.55 (dd, $J = 4.2$, 12.6 Hz, 1H), 3.30 (dd, $J = 8.7$, 12.6 Hz, 1H), 3.08 (dd, $J = 6.3$, 12.9 Hz, 2H), 2.84–2.73 (m, 2H), 2.48–2.32 (m, 2H), 2.05 (t, $J = 7.5$ Hz, 2H), 2.00–1.90 (m, 2H), 1.78–1.64 (m, 1H), 1.63–1.36 (m, 7H), 1.35–1.18 (m, 4H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.4$, 173.9, 171.7, 171.4, 169.0, 167.1, 145.6, 143.3, 140.2, 132.5, 124.5, 121.1, 56.4, 55.5, 52.4, 51.0, 37.1, 35.2, 30.5, 30.2, 28.9, 26.9, 26.2, 26.1, 24.9, 22.5; analytical HPLC: homogeneous single peak, $t_R = 14.6$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{27}H_{38}N_6O_{10}S$ $[M\mathrm{H}]^+$ 538.2, found 538.0.

Compound 9m: TentaGel S RAM resin (0.10 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (25 mg, 40%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 9.37$ (d, $J = 6.9$ Hz, 1H), 9.07 (t, $J =$ 6.3 Hz, 1H), 8.31 (d, $J = 6.0$ Hz, 1H), 8.26 (dd, $J = 2.7$, 8.4 Hz, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 7.76 (d, $J = 6.6$ Hz, 1H), 7.72 (br, 3H), 7.22 (s, 1H), 7.09 (s, 1H), 4.39 (dd, $J = 7.5$, 14.4 Hz, 1H), 4.27–4.18 (m, 1H), 3.96 (dd, $J = 7.2$, 16.5 Hz, 1H), 3.72–3.50 (m, 4H), 3.26 (t, $J = 12.0$ Hz, 1H), 2.84 (dd, $J = 6.6$, 13.5 Hz, 2H), 1.80–1.67 (m, 2H), 1.66–1.54 (m, 2H), 1.52–1.30 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 167.4$, 166.4, 165.6, 165.5, 164.4, 143.3, 140.2, 135.2, 134.5, 120.3, 117.6, 56.6, 50.4, 47.9, 39.1, 37.9, 24.9, 22.8, 18.3; analytical HPLC: homogeneous single peak, $t_R = 7.1$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{20}H_{27}N_7O_7S$ $[M\mathrm{H}]^+$ 510.0, found 509.8.

Compound 10m: HMPB-BHA resin[33, 34] (0.075 mmol, 0.69 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (18 mg, 35%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.5$ (br, 2H), 8.69 (d, $J = 8.4$ Hz, 1H), 8.42 (t, $J = 5.4$ Hz, 1H), 8.28 (d, $J = 2.4$ Hz, 1H), 8.25 (dd, $J = 2.4$, 8.4 Hz, 1H), 7.96 (d, $J = 7.8$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.69 (s, 1H), 7.66 (br, 3H), 4.40–4.28 (m, 3H), 3.78 (d, $J = 6.6$ Hz, 2H), 3.62 (dd, $J = 4.2$, 13.2 Hz, 1H), 3.23 (dd, $J = 9.3$, 12.9 Hz, 1H), 2.82–2.71 (m, 2H), 2.46–2.34(m, 2H), 1.98–1.88 (m, 2H), 1.78–1.64 (m, 1H), 1.60–1.44 (m, 3H), 1.33–1.18 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.9$, 171.8, 171.6, 171.0, 170.7, 169.8, 167.2, 146.6, 143.0, 140.1, 132.4, 124.6, 121.3, 55.6, 52.5, 50.8, 40.9, 36.7, 30.5, 30.4, 30.3, 26.9, 26.0, 22.5; analytical HPLC: homogeneous single peak, $t_R = 12.5$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{23}H_{30}N_6O_{10}S$ $[M\mathrm{H}]^+$ 583.2, found 583.4.

Compound 11m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (17 mg, 14%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 13.5$ (br, 1H), 9.37 (d, $J = 5.4$ Hz, 1H), 9.04 (s, 1H), 8.98 (s, 1H), 8.35 (s, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.68 (br, 3H, TFA salt), 7.49 (s, 1H), 7.18 (d, $J = 9.0$ Hz, 1H), 4.53 (br, 1H), 4.38–4.26 (m, 2H), 4.20–3.70 (m, 3H, covered under the signal of water), 2.86–2.72 (m, 2H), 2.42–2.16 (m, 3H), 2.10–1.94 (m, 1H), 1.80–1.67 (m, 1H), 1.62–1.46 (m, 3H), 1.44–1.26 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 171.6, 171.2, 171.1, 171.0, 166.3, 161.1, 140.0, 136.7, 127.5, 125.9, 124.3, 113.1, 67.7, 55.8, 53.1, 51.7, 40.8, 31.1, 30.5, 30.0, 26.6, 25.7, 22.6; analytical HPLC: homogeneous single peak, $t_R = 13.1$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{21}H_{28}N_6O_9$ $[M\mathrm{H}]^+$ 509.2, found 509.1.

Compound 12m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (50 mg, 39%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.18–1.32$ (m, 2H), 1.44–1.60 (m, 3H), 1.82–2.10 (m, 4H), 2.14–2.28 (m, 1H), 2.43 (t, $J = 7.5$ Hz, 2H), 2.68–2.80 (m, 2H), 4.08–4.18 (m, 2H), 4.25–4.37 (m, 1H), 4.37–4.46 (m, 2H), 7.17 (s, 1H), 7.23 (d, 7.8, 1H), 7.30 (s, 1H), 7.35 (d, $J = 9.3$ Hz, 1H), 7.67 (br, 3H), 8.26 (d, $J = 9.0$ Hz, 1H), 8.32 (d, $J = 2.7$ Hz, 1H), 8.36 (dd, $J = 2.7$ Hz, 9.0, 1H), 8.99 (d, $J = 5.1$ Hz, 1H), 12.24 (br, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 172.6, 171.7, 171.2, 166.2, 160.9, 140.2, 127.6, 126.1, 1 24.3, 113.2, 68.0, 56.1, 53.1, 51.6, 47.9, 30.9, 30.5, 30.2, 26.6, 25.8, 22.6; analytical HPLC: homogeneous single peak, $t_R = 9.9$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{22}H_{30}N_6O_9$ $[M\mathrm{H}]^+$ 523.2, found 523.3.

Compound 13m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (50 mg, 39%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.2$ (br, 1H), 9.22 (d, $J = 7.5$ Hz, 1H), 8.52 (d, $J = 7.2$ Hz, 1H), 8.35 (dd, $J = 3.0$, 9.3 Hz, 1H), 8.25 (d, $J = 3.0$ Hz, 1H), 7.73 (br, 3H, TFA salt), 7.36 (d, $J = 9.3$ Hz, 1H), 7.21 (s, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 7.10 (s, 1H), 4.55–4.40 (m, 2H), 4.40–4.31 (m, 1H), 4.26–4.17 (m, 1H), 4.16–4.06 (m, 1H), 2.80 (dd, $J = 6.2$, 12.3 Hz, 2H), 2.43–2.28 (m, 3H), 2.14–1.94 (m, 3H), 1.93–1.77 (m, 1H), 1.72–1.50 (m, 3H), 1.47–1.32 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 172.2, 171.6, 171.2, 165.5, 160.8, 140.2, 127.4, 126.1, 124.1, 113.1, 67.5, 53.1, 52.6, 51.7, 50.7, 30.3, 30.2, 30.0, 26.8, 24.6, 22.5; analytical HPLC: homogeneous single peak, $t_R = 8.2$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{22}H_{30}N_6O_9$ $[M\mathrm{H}]^+$ 523.2, found 523.2.

Compound 14m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (40 mg, 31%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.2$ (br, 1H), 9.02 (d, $J = 8.1$ Hz, 1H), 8.36 (d, $J = 6.7$ Hz, 1H), 8.35 (dd, $J = 3.0$, 9.3 Hz, 1H), 8.20 (d, $J = 9.0$ Hz, 1H), 7.70 (br, 3H, TFA salt), 7.43 (s, 1H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.23 (s, 1H), 4.64–4.52 (m, 2H), 4.40–4.20 (m, 2H), 4.15 (t, $J = 10.5$ Hz, 1H), 2.80 (dd, $J = 6.9$, 12.9 Hz, 2H), 2.37–2.25 (m, 3H), 2.14–2.00 (m, 2H), 2.00–1.80 (m, 2H), 1.70–1.50 (m, 3H), 1.50–1.30 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 172.0, 171.2, 170.9, 165.3, 160.8, 140.4, 127.6, 125.5, 124.8, 113.2, 67.7, 52.9, 52.2, 51.5, 30.6, 30.3, 30.2, 26.7, 24.4, 22.6; analytical HPLC: homogeneous single peak, $t_R =$ 7.9 min (5–40% B in 30 min); MALDI MS: calcd for $C_{22}H_{30}N_6O_9$ $[M\mathrm{H}]^+$ 523.2, found 523.2.

Compound 15m: TentaGel S RAM resin (0.15 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (17 mg, 23%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.94$ (d, $J = 6.0$ Hz, 1H), 8.34 (dd, $J = 2.7$, 9.3 Hz, 1H), 8.23 (d, $J = 3.0$ Hz, 1H), 8.03 (d, $J = 8.7$ Hz, 1H), 7.35 (d, $J =$ 9.0 Hz, 1H), 7.33 (s, 1H), 7.31 (s, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.18 (s, 1H), 6.84 (s, 1H), 4.62–4.54 (m, 1H), 4.51–4.43 (m, 1H), 4.42–4.32 (m, 1H), 4.22–4.12 (m, 1H), 4.05 (t, $J = 6.6$ Hz, 1H), 2.62–2.56 (m, 2H), 2.24–2.12 (m, 1H), 2.10–1.97 (m, 1H), 1.92–1.78 (m, 1H), 1.62–1.48 (m, 1H), 1.32–1.18 (m, 1H), 0.95–0.80 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 172.3$, 172.2, 170.5, 170.2, 166.1, 160.9, 140.2, 127.4, 126.3, 124.3, 113.2, 68.1, 60.1, 52.5, 49.5, 36.4, 34.9, 31.0, 25.5, 15.4, 11.3; analytical HPLC: homogeneous single peak, $t_R = 14.1$ min (8–50% B in 30 min); MALDI MS: calcd for $C_{21}H_{28}N_6O_8$ $[M+\mathrm{Na}]^+$ 515.2, found 515.6.

Compound 16m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation

0947-6539/99/0511-3268 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 11

and lyophilization to give a white powder (7.0 mg, 18%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.68 (d, J = 8.1 Hz, 1H), 8.43 (d, J = 3.0 Hz, 1H), 8.33 (dd, J = 3.0, 9.0 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.45 (s, 1H), 7.31 (d, J = 9.3 Hz, 1H), 7.28 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 4.96 (dd, J = 7.5, 15.0 Hz, 1H), 4.61 (dd, J = 2.4, 8.1 Hz, 1H), 4.50–4.30 (m, 3H), 3.56–3.46 (m, 2H), 3.40–3.30 (m, 1H), 2.82 (dd, J = 15.3, 6.9 Hz, 1H), 2.32–2.12 (m, 2H), 2.11–1.92 (m, 2H), 1.78–1.60 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 168.9, 167.9, 166.8, 164.4, 159.3, 157.2, 136.1, 123.5, 121.7, 120.0, 109.3, 64.6, 55.5, 47.8, 45.9, 43.4, 33.5, 28.5, 26.3, 17.1; analytical HPLC: homogeneous single peak, t_R = 6.6 min (5–40% B in 30 min); MALDI MS: calcd for $C_{20}H_{24}N_6O_8$ [MH]$^+$ 477.2, found 477.1.

Compound 17m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (47 mg, 37%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.86 (d, J = 9.3 Hz, 1H), 8.35 (dd, J = 2.7, 9.0 Hz, 1H), 8.26 (d, J = 2.7 Hz, 1H), 8.24 (d, J = 9.6 Hz, 1H), 7.69 (br, 3H), 7.37 (d, J = 9.3 Hz, 1H), 7.33 (s, 1H), 7.25 (d, J = 9.1 Hz, 1H), 7.19 (s, 1H), 4.50–4.40 (m, 2H), 4.32–4.21 (m, 1H), 4.18–4.04 (m, 2H), 2.80–2.68 (m, 2H), 2.30–2.16 (m, 1H), 2.12–1.88 (m, 1H), 1.96–1.82 (m, 2H), 1.66–1.42 (m, 4H), 1.36–1.22 (m, 3H), 0.98–0.88 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.5, 171.1, 170.8, 160.9, 140.2, 126.4, 124.5, 113.2, 67.9, 60.6, 52.7, 52.1, 35.0, 30.9, 30.0, 26.6, 25.7, 22.8, 15.8, 11.4; analytical HPLC: homogeneous single peak, t_R = 13.9 min (8–50% B in 30 min); MALDI MS: calcd for $C_{23}H_{34}N_6O_7$ [MH]$^+$ 507.2, found 507.4

Compound 18m: TentaGel S RAM resin (0.10 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (5 mg, 11%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 9.15 (d, J = 6.6 Hz, 1H), 8.39 (dd, J = 3.0, 9.3 Hz, 1H), 8.22 (d, J = 2.7 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.33 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.20 (s, 1H), 7.09 (s, 1H), 4.57 (dd, J = 6.3, 12.3 Hz, 1H), 4.50–4.38 (m, 2H), 4.34–4.24 (m, 1H), 4.24–4.16 (m, 1H), 3.77 (dd, J = 6.0, 9.6 Hz, 1H), 3.67 (dd, J = 4.2, 8.1 Hz, 1H), 2.66–2.58 (m, 2H), 2.30–2.18 (m, 1H), 2.17–2.40 (m, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.4, 171.4, 171.3, 169.7, 165.7, 160.9, 140.2, 127.6, 126.1, 124.0, 113.3, 68.1, 61.6, 55.2, 52.6, 35.5, 30.8, 19.2; analytical HPLC: homogeneous single peak, t_R = 5.0 min (5–40% B in 30 min); MALDI MS: calcd for $C_{18}H_{22}N_6O_9$ [MH]$^+$ 467.1, found 467.2.

Compound 19m: TentaGel S RAM resin (0.10 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (30 mg, 65%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.92 (d, J = 5.7 Hz, 1H), 8.38 (dd, J = 2.7, 9.0 Hz, 1H), 8.29 (d, J = 3.0 Hz, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.28 (s, 1H), 7.26 (d, J = 9.1 Hz, 1H), 7.15 (s, 1H), 4.50–4.40 (m, 1H), 4.40–4.31 (m, 2H), 4.20–4.08 (m, 2H), 3.82–3.60 (m, 2H), 2.24–2.12 (m, 1H), 2.10–1.98 (m, 1H), 1.62–1.44 (m, 3H), 0.83 (d, J = 6.0 Hz, 3H), 0.81 (d, J = 6.0 Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.6, 171.8, 170.3, 166.3, 161.0, 140.1, 127.5, 126.4, 124.0, 113.1, 67.8, 60.6, 59.6, 53.1, 50.6, 30.8, 24.1, 23.5, 21.1; analytical HPLC: homogeneous single peak, t_R = 9.4 min (8–70% B in 30 min); MALDI MS: calcd for $C_{20}H_{27}N_5O_8$ [M+Na]$^+$ 488.2, found 488.8.

Compound 20m: TentaGel S RAM resin (0.07 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (15 mg, 43%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.1 (br, 1H), 8.77 (d, J = 6.0 Hz, 1H), 8.36 (dd, J = 3.0, 9.3 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.18 (s, 1H), 4.50–4.39 (m, 2H), 4.36–4.26 (m, 1H), 4.22–4.12 (m, 1H), 4.01 (t, J = 6.6 Hz, 1H), 2.30–2.22 (m, 6H), 1.84–1.70 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 174.1, 172.5, 170.8, 170.7, 166.2, 160.9, 140.2, 127.4, 126.4, 124.4, 113.2, 68.0, 62.0, 52.7, 51.9, 30.9, 30.5, 28.7, 26.0, 19.4, 19.2; analytical HPLC: homogeneous single peak, t_R = 11.3 min (8–70% B in 30 min); MALDI MS: calcd for $C_{21}H_{27}N_5O_9$ [M+Na]$^+$ 516.2, found 516.6.

Compound 21m: TentaGel S RAM resin (0.08 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (10 mg, 25%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.7 (br, 1H), 9.13 (d, J = 6.0 Hz, 1H), 8.38 (dd, J = 2.7, 9.0 Hz, 1H), 8.21 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 9.6 Hz, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.31 (s, 1H), 7.15 (s, 1H), 4.54–4.36 (m, 3H), 4.25 (dd, J = 5.4, 9.3 Hz, 1H), 4.20–4.10 (m, 1H), 2.78 (d, J = 6.9 Hz, 2H), 2.28–2.16 (m, 1H), 2.14–2.00 (m, 2H), 1.38–1.24 (m, 1H), 1.18–1.02 (m, 1H), 0.90–0.78 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.5, 171.6, 171.0, 170.3, 166.0, 160.9, 140.1, 127.6, 126.3, 124.0, 113.4, 67.9, 57.1, 53.2, 52.8, 35.7, 35.2, 30.8, 24.3, 16.1, 11.5; analytical HPLC: homogeneous single peak, t_R = 15.5 min (5–40% B in 30 min); MALDI MS: calcd for $C_{21}H_{27}N_5O_9$ [M+Na]$^+$ 516.2, found 516.4.

Compound 22m: TentaGel S RAM resin (0.16 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (35 mg, 32%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.2 (br, 1H), 8.95 (d, J = 5.4 Hz, 1H), 8.38 (dd, J = 2.7, 9.0 Hz, 1H), 8.33 (d, J = 2.7 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.70 (br, 3H, TFA salt), 7.34 (d, J = 9.3 Hz, 1H), 7.28 (d, J = 6.3 Hz, 1H), 7.15 (s, 1H), 7.01 (s, 1H), 4.46–4.32 (m, 3H), 4.18 (dd, J = 6.9, 12.3 Hz, 1H), 3.69 (dd, J = 6.3, 16.8 Hz, 1H), 3.53 (dd, J = 5.7, 16.8 Hz, 1H), 2.83–2.70 (m, 2H), 2.52–2.43 (m, 2H), 2.26–2.08 (m, 2H), 2.07–1.87 (m, 3H), 1.62–1.44 (m, 3H), 1.33–1.21 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 174.1, 171.8, 171.7, 171.0, 170.9, 166.1, 161.1, 140.0, 127.5, 125.9, 124.2, 113.1, 68.3, 55.8, 54.0, 51.4, 42.1, 30.9, 30.6, 30.2, 26.7, 25.9, 22.5; analytical HPLC: homogeneous single peak, t_R = 9.2 min (5–40% B in 30 min); MALDI MS: calcd for $C_{24}H_{33}N_7O_{10}$ [MH]$^+$ 580.2, found 580.5.

Compound 23m: Wang resin (0.20 mmol, 1.00 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (45 mg, 32%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.4 (br, 2H), 9.0 (d, J = 4.8 Hz, 1H), 8.37 (dd, J = 2.7, 9.0 Hz, 1H), 8.32 (d, J = 3.0 Hz, 1H), 8.29 (d, J = 4.8 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 7.69 (br, 3H, TFA salt), 7.34 (d, J = 9.3 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 4.54–4.47 (m, 1H), 4.46–4.36 (m, 2H), 4.36–4.27 (m, 1H), 4.18 (dd, J = 7.5, 12.6 Hz, 1H), 3.83 (dd, J = 6.3, 17.4 Hz, 1H), 3.64 (dd, J = 5.4, 17.7 Hz, 1H), 2.84–2.71 (m, 2H), 2.45 (t, J = 7.8 Hz, 2H), 2.32–2.18 (m, 1H), 2.17–2.07 (m, 1H), 2.06–1.84 (m, 3H), 1.64–1.46 (m, 3H), 1.40–1.22 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 174.1, 171.6, 171.2, 171.1, 171.0, 166.3, 161.1, 140.0, 136.7, 127.5, 125.9, 124.3, 113.1, 67.7, 55.8, 53.1, 51.7, 40.8, 31.1, 30.5, 30.0, 26.6, 25.7, 22.6; analytical HPLC: homogeneous single peak, t_R = 11.5 min (4–30% B in 30 min); MALDI MS: calcd for $C_{24}H_{32}N_6O_{11}$ [MH]$^+$ 581.2, found 581.8.

Compound 24m: TentaGel S RAM resin (0.20 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (22 mg, 20%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.94 (d, J = 6.3 Hz, 1H), 8.35 (dd, J = 2.7, 9.0 Hz, 1H), 8.23 (d, J = 6.6 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.37 (s, 1H), 7.33 (d, J = 9.3 Hz, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.16 (s, 1H), 6.98 (s, 1H), 6.86 (s, 1H), 4.68–4.58 (m, 1H), 4.54–4.47 (m, 1H), 4.45–4.28 (m, 2H), 4.09 (t, J = 6.9 Hz, 1H), 3.67 (dd, J = 6.6, 16.5 Hz, 1H), 3.54 (dd, J = 5.7, 16.8 Hz, 1H), 2.68–2.55 (m, 2H), 2.27–2.04 (m, 2H), 1.94–1.79 (m, 1H), 1.63–1.48 (m, 1H), 1.34–1.17 (m, 1H), 0.98–0.85 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 172.4, 171.0, 170.7, 170.3, 167.0, 166.1, 161.0, 140.1, 127.4, 126.1, 124.3, 113.2, 68.4, 59.9, 53.2, 49.4, 42.1, 36.3, 34.9, 31.0, 25.4, 15.5, 11.3; analytical HPLC: homogeneous single peak, t_R = 11.7 min (8–70% B in 30 min); MALDI MS: calcd for $C_{23}H_{31}N_7O_9$ [M+Na]$^+$ 572.2, found 572.4.

Compound 25m: Rink amide AM resin (0.16 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (14 mg, 11.2%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.2 (br, 1H), 8.45 (d, J = 7.8 Hz, 1H), 8.34 (d, J = 2.7 Hz, 1H), 8.32 (d, J = 7.2 Hz, 1H), 8.16 (dd, J = 2.4, 9.3 Hz, 1H), 7.77 (dd, J = 3.6, 8.7 Hz, 1H), 7.69 (br, 3H), 7.52 (s, 1H), 7.25 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 9.6 Hz, 1H), 4.40–4.28 (m, 1H), 4.22–4.15 (m, 1H), 4.14–4.06 (m, 1H), 4.05–3.95 (m, 1H), 3.36–3.22 (m, 1H), 2.80–2.68 (m, 2H), 2.48–2.32 (m, 2H), 2.02–1.84 (m, 2H), 1.62–1.46 (m, 3H), 1.44–1.30 (m, 1H), 1.28–1.15 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 174.0, 172.8, 172.0, 171.3, 169.5, 151.7, 135.8, 127.8,

124.4, 118.3, 111.9, 57.6, 53.0, 51.0, 43.0, 40.8, 31.6, 30.7, 27.1, 25.2, 22.4; analytical HPLC: homogeneous single peak, $t_R = 14.7$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{21}H_{29}N_7O_8$ $[M\mathrm{H}]^+$ 508.2, found 508.0.

Compound 26m: Rink amide AM resin (0.20 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin (50 mg crude material was obtained), the crude material (40 mg) was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (30 mg, 36%). The 1,3-diaminobutyric acid was generated through a Hofmann rearrangement reaction on the resin just before the cyclization with IBTFA (10 equiv), CH_3CN/H_2O (v/v 4:1) at 16 h at 25 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.12-1.26$ (m, 2H), 1.32–1.44 (m, 1H), 1.45–1.58 (m, 2H), 1.65–1.78 (m, 1H), 1.85–2.04 (m, 4H), 2.36–2.55 (m, 2H), 2.66–2.78 (m, 2H), 3.22–3.34 (m, 1H), 3.44–3.56 (m, 1H), 4.00–4.08 (m, 1H), 4.20–4.28 (m, 1H), 4.28–4.33 (m, 1H), 6.82 (d, $J = 10.0$ Hz, 1H), 7.14 (s, 1H), 7.39 (s, 1H), 7.62 (br, 2H), 7.67 (d, $J =$ 8.0 Hz, 1H), 7,60–7.73 (m, 1H) 7.78 (d, $J = 9.5$ Hz, 1H), 8.13 (dd, $J = 2.0$, 9.0 Hz, 1H), 8.37 (d, $J = 3$ Hz, 1H), 8.68 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 173.0, 171.8, 170.8, 168.9, 152.2, 134.8, 128.0, 125.1, 117.0, 110.6, 56.4, 53.1, 51.8, 31.2, 31.0, 30.8, 26.8, 25.8, 22.4; analytical HPLC: homogeneous single peak, $t_R = 15.0$ min (5–40% B in 30 min); FAB MS: calcd for $C_{22}H_{31}N_7O_8$ $[M\mathrm{H}]^+$ 522.2, found 522.0.

Compound 27m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (30 mg, 48%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.58$ (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J =$ 2.7 Hz, 1H), 8.15 (dd, $J = 2.7$, 9.3 Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.70 (br, 4H), 7.57–7.50 (m, 1H), 7.41 (s, 1H), 7.16 (s, 1H), 6.82 (d, $J = 9.3$ Hz, 1H), 4.36–4.23 (m, 2H), 3.96 (t, $J = 6.9$ Hz, 1H), 3.55–3.40 (m, 2H, covered under the signal of water), 2.82–2.68 (m, 2H), 2.05–1.94 (m, 2H), 1.92–1.80 (m, 1H), 1.79–1.70 (m, 1H), 1.69–1.48 (m, 2H), 1.46–1.20 (m, 4H), 0.94 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.1$, 171.0, 170.8, 168.9, 151.9, 134.8, 127.8, 125.0, 117.8, 110.8, 60.9, 53.0, 52.1, 41.4, 34.9, 31.0, 26.9, 26.0, 22.6, 15.8, 11.2; analytical HPLC: homogeneous single peak, $t_R = 13.8$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{23}H_{35}N_7O_6$ $[M\mathrm{H}]^+$ 506.3, found 506.6.

Compound 28m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (20 mg, 43%). Two sets of signals were obtained in both the proton and the carbon NMR spectra of this compound, but the analytical HPLC profile shows only one peak. This is attributed to two conformers that do not interchange rapidly on the NMR time scale. Data for the minor conformer are shown in square brackets. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.22$ [8.16] (d, $J =$ 2.4 Hz, 1H), 8.13 [8.07] (dd, $J = 2.7$, 6.6 Hz, 1H), 7.87 [7.84] (s, 1H), 7.50 (d, $J = 6.9$ Hz, 1H), 7.32 [7.29] (s, 1H), 7.15 [7.12] (s, 1H), 7.05 [6.96] (t, $J =$ 5.7 Hz, 1H), 6.81 [7.73] (d, $J = 9.3$ Hz, 1H), 4.50–4.44 [4.38] (m, 1H), 4.30–4.22 (m, 1H), 4.18–4.07 (m, 1H), 3.80–3.66 (m, 2H), 3.65–3.52 (m, 1H), 3.50–3.24 (m, 2H), 2.48–1.75 (m, 6H), 0.90–0.76 (m, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 169.6$, 168.9, 167.3, 167.1, 166.2, 165.3, 162.4, 161.8, 148.0, 146.5, 130.8, 130.2, 123.2, 122.8, 120.2, 119.5, 116.3, 113.0, 106.1, 59.3, 53.2, 52.1, 50.9, 49.6, 45.6, 42.2, 38.3, 37.8, 27.2, 26.5, 25.6, 25.0, 24.8, 20.6, 18.2, 16.1, 14.4, 13.8; analytical HPLC: single peak, $t_R = 13.1$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{21}H_{28}N_6O_6$ $[M\mathrm{H}]^+$ 461.2, found 461.4.

Compound 29m: Rink amide AM resin (0.08 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (23 mg, 39%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.59$ (d, $J = 6.6$ Hz, 1H), 8.38 (d, $J =$ 2.7 Hz, 1H), 8.17 (dd, $J = 2.7$, 9.6 Hz, 1H), 7.83 (d, $J = 5.4$ Hz, 1H), 7.77 (d, $J = 9.0$ Hz, 1H), 7.68 (br, 3H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.44 (s, 1H), 7.19 (s, 1H), 6.88 (d, $J = 9.0$ Hz, 1H), 5.10 (br, 1H), 4.38–4.28 (m, 2H), 4.20–4.13 (m, 1H), 3.70–3.50 (m, 2H, covered under the signal of water), 3.65–3.50 (m, 1H), 3.38–3.24 (m, 1H), 2.80–2.70 (m, 2H), 2.08–1.84 (m, 2H), 1.80–1.66 (m, 1H), 1.60–1.46 (m, 1H), 1.44–1.32 (m, 1H), 1.30–1.16 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 172.9$, 170.9, 170.2, 168.9, 152.2, 134.8, 128.0, 124.8, 117.4, 110.6, 60.5, 59.8, 52.9, 51.9, 40.9, 37.5, 31.1, 30.9, 26.8, 22.2; analytical HPLC: homogeneous single peak, $t_R = 12.2$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{20}H_{29}N_7O_7$ $[M\mathrm{H}]^+$ 480.21, found 480.23.

Compound 30m: Rink amide AM resin (0.06 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (12 mg, 37%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.79$ (d, $J = 6.9$ Hz, 1H), 8.12 (dd, $J =$ 2.4, 9.3 Hz, 1H), 8.07 (d, $J = 2.7$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 7.2$ Hz, 1H), 7.60–7.50 (m, 1H), 7.43–7.25 (m, 6H), 7.14 (s, 1H), 6.80 (d, $J = 9.6$ Hz, 1H), 4.40–4.18 (m, 3H), 3.60–3.40 (m, 2H, covered under the signal of water), 3.16–2.98 (m, 2H), 2.38–2.18 (m, 2H), 2.12–1.90 (m, 6H), 1.80–1.66 (m, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.2$, 171.4, 170.4, 168.7, 151.8, 137.6, 134.7, 129.2, 128.5, 127.6, 126.8, 125.1, 117.5, 112.1, 57.7, 52.8, 52.0, 41.6, 36.3, 31.0, 30.6, 30.0, 14.7; analytical HPLC: single peak, $t_R = 19.1$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{25}H_{30}N_6O_6S$ $[M\mathrm{H}]^+$ 543.2, found 543.4.

Compound 31m: Rink amide AM resin (0.1 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. The peptidomimetic was cleaved from the resin, dissolved in H_2O, and then lyophilized to give the crude product (50 mg, 93%). The purity of this crude material was determined by analytical HPLC (SSI system, 5–40% B in 30 min) to be 93% based on absorption at 215 nm. Preparative HPLC (Rainin System, 17–35% B in 30 min) was carried out to provide a yellow powder (36.5 mg, 56%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.90$ (d, $J = 6.3$ Hz, 1H), 8.42 (d, $J =$ 2.7 Hz, 1H), 8.17 (dd, $J = 9.3$, 2.7 Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 6.0$ Hz, 1H), 7.70 (br, 3H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.43 (s, 1H), 7.14 (s, 1H), 6.85 (d, $J = 9.6$ Hz, 1H), 4.34 (dd, $J = 13.5$, 8.1 Hz, 1H), 4.28–4.18 (m, 1H), 4.08 (dd, $J = 13.8$, 7.8 Hz, 1H), 3.40–3.20 (m, 2H), 2.82–2.70 (m, 2H), 2.50–2.40 (m, 2H), 2.08–1.94 (m, 2H), 1.82–1.70 (m, 1H), 1.70–1.40 (m, 7H), 1.38–1.16 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 172.8, 172.0, 171.4, 168.8, 153.7, 134.7, 128.3, 125.5, 115.8, 111.2, 56.2, 52.3, 51.4, 41.5, 31.4, 30.7, 29.4, 26.8, 25.9, 24.9, 22.4; analytical HPLC: homogeneous single peak, $t_R = 16.9$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{23}H_{33}N_7O_8$ $[M\mathrm{H}]^+$ 536.2, found 536.9.

Compound 32m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (75 mg, 74%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.2$ (br, 1H), 8.74 (d, $J = 5.1$ Hz, 1H), 8.27 (d, $J = 2.7$ Hz, 1H), 8.17 (dd, $J = 2.4$, 9.3 Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.39 (s, 1H), 7.20 (br, 1H), 7.11 (s, 1H), 6.84 (d, $J = 9.6$ Hz, 1H), 4.35–4.20 (m, 2H), 3.91 (t, $J = 7.5$ Hz, 1H), 3.32–3.18 (m, 2H), 2.23 (br, 2H), 2.20–2.04 (m, 1H), 2.03–1.88 (m, 1H), 1.83–1.46 (m, 5H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 172.9$, 171.4, 171.0, 168.5, 156.0, 153.3, 134.7, 128.1, 125.4, 117.0, 111.0, 62.2, 52.2, 51.4, 41.6, 30.4, 29.2, 27.1, 26.1, 24.8, 19.9, 19.4; analytical HPLC: homogeneous single peak, $t_R = 14.7$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{22}H_{30}N_6O_8$ $[M+\mathrm{Na}]^+$ 529.2, found 529.4.

Compound 33m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (44 mg, 89%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 9.12$ (d, $J = 9.3$v, 1H), 8.33 (d, $J = 2.7$ Hz, 1H), 8.15 (dd, $J = 2.7$, 9.3 Hz, 1H), 7.86 (d, $J = 5.7$ Hz, 1H), 7.62 (d, $J =$ 7.8 Hz, 1H), 7.31 (s, 1H), 7.14 (s, 1H), 7.06 (d, $J = 7.8$ Hz, 1H), 6.85 (d, $J =$ 9.3 Hz, 1H), 4.83 (d, $J = 4.5$ Hz, 1H), 4.26–4.14 (m, 2H), 4.12–4.04 (m, 1H), 4.02–3.92 (m, 1H), 3.30–3.18 (m, 2H), 1.91–1.70 (m, 3H), 1.64–1.45 (m, 4H), 0.99 (d, $J = 2.7$ Hz, 3H), 0.97 (d, $J = 3.0$ Hz, 3H), 0.92 (d, $J =$ 6.0 Hz, 1H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.2$, 172.9, 170.1, 169.0, 153.8, 134.6, 128.4, 125.6, 115.4, 111.4, 66.3, 57.8, 55.5, 51.5, 41.4, 28.8, 24.9, 22.9, 21.9, 19.6; analytical HPLC: homogeneous single peak, $t_R =$ 17.4 min (8–70% B in 30 min); MALDI MS: calcd for $C_{22}H_{32}N_6O_7$ $[M+\mathrm{Na}]^+$ 515.2, found 515.5.

Compound 34m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (45 mg, 67%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 14.2$ (s, 2H), 8.98 (s, 1H), 8.92 (d, $J =$ 6.9 Hz, 1H), 8.16 (dd, $J = 2.7$, 9.3 Hz, 1H), 8.06 (d, $J = 3.0$ Hz, 1H), 8.04 (d,

0947-6539/99/0511-3270 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 11

$J = 6.9$ Hz, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.47 (s, 1H), 7.44–7.24 (m, 7H), 7.14 (s, 1H), 6.84 (d, $J = 9.3$ Hz, 1H), 4.62 (m, 1H), 4.70–4.55 (m, 1H), 4.40–4.20 (m, 1H), 3.25–3.10 (m, 3H), 3.00–2.85 (m, 3H), 1.80–1.55 (m, 4H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 172.8$, 171.7, 169.8, 168.3, 153.3, 137.8, 134.8, 133.9, 130.1, 129.1, 128.5, 128.1, 126.8, 125.0, 117.0, 111.3, 60.8, 57.4, 51.7, 41.8, 36.5, 29.5, 26.6, 25.1; analytical HPLC: homogeneous single peak, $t_R = 15.7$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{27}H_{30}N_8O_6$ [MH]$^+$ 563.2, found 563.5.

Compound 35m: Rink amide AM resin (0.10 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (40 mg, 73%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.80$ (d, $J = 6.6$ Hz, 1H), 8.53 (t, $J = 6.3$ Hz, 1H), 8.13 (dd, $J = 2.7$, 9.0 Hz, 1H), 8.06 (d, $J = 2.7$ Hz, 1H), 7.45 (s, 1H), 7.13 (s, 1H), 7.10 (d, $J = 9.6$ Hz, 1H), 6.70 (d, $J = 9.3$ Hz, 1H), 6.39 (s, 1H), 4.61 (dd, $J = 2.4$, 8.1 Hz, 1H), 4.45–4.26 (m, 3H), 4.18 (dd, $J = 6.3$, 13.5 Hz, 1H), 3.53 (dd, $J = 8.7$, 18.1 Hz, 1H), 3.42–3.32 (m, 1H), 3.28–3.20 (m, 1H), 3.15 (dd, $J = 4.8$, 13.5 Hz, 1H), 3.15–3.02 (m, 1H), 2.91 (dd, $J = 10.8$, 13.5 Hz, 1H), 2.32–2.16 (m, 1H), 2.12–2.00 (m, 1H), 1.98–1.77 (m, 6H), 1.58–1.41 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 172.8$, 172.7, 170.2, 169.5, 166.6, 151.6, 135.2, 127.3, 122.8, 121.1, 110.2, 60.5, 53.7, 51.7, 48.7, 42.8, 38.6, 30.7, 30.0, 29.5, 24.3, 24.1, 22.7; analytical HPLC: homogeneous single peak, $t_R = 14.3$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{23}H_{30}N_7O_7S$ [M+Na]$^+$ 572.2, found 572.6.

Compound 36m: Rink amide AM resin (0.20 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin (105 mg crude material was obtained), the crude (98 mg) was subjected to preparative HPLC and lyophilization to give a yellowish powder (65 mg, 52%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.3$ (br, 1H), 8.88 (d, $J = 6.3$ Hz, 1H), 8.68–8.60 (m, 1H), 8.58 (d, $J = 2.1$ Hz, 1H), 8.17 (dd, $J = 2.7$, 9.3 Hz, 1H), 7.72 (s, 1H), 7.69 (br, 3H, TFA salt of Lys side chain), 7.61 (d, $J = 8.4$ Hz, 1H), 7.35 (s, 1H), 7.09 (s, 1H), 6.90 (d, $J = 9.6$ Hz, 1H), 4.39 (dd, $J = 8.4$, 14.1 Hz, 1H), 4.25–4.08 (m, 2H), 3.55–3.40 (m, 1H), 3.34–3.20 (m, 1H), 2.82–2.70 (m, 2H), 2.50–2.43 (m, 2H), 2.10–1.98 (m, 2H), 1.80–1.17 (m, 12H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.1$, 173.5, 171.8, 171.2, 168.8, 153.8, 134.6, 128.4, 126.1, 114.3, 111.1, 55.6, 52.1, 51.8, 31.8, 31.3, 30.9, 26.9, 26.7, 26.4, 22.3, 22.2; analytical HPLC: homogeneous single peak, $t_R = 19.3$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{24}H_{35}N_7O_8$ [MH]$^+$ 550.2, found 550.3.

Synthesis of 37m: Rink amide AM resin (0.25 mmol, 0.66 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin (125 mg crude material was obtained), the crude (60 mg) was subjected to preparative HPLC and lyophilization to give a yellowish powder (40 mg, 52%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.70$ (d, $J = 7.8$ Hz, 1H), 8.38 (d, $J = 2.4$ Hz, 1H), 8.30–8.23 (m, 1H), 8.17 (dd, $J = 2.7$, 9.3 Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.69 (br, 3H, TFA salt of Lys side chain), 7.53 (d, $J = 8.4$ Hz, 1H), 7.35 (s, 1H), 7.08 (s, 1H), 6.89 (d, $J = 9.3$ Hz, 1H), 4.41 (dd, $J = 7.8$, 14.1 Hz, 1H), 4.24–4.14 (m, 1H), 4.02 (t, $J = 7.5$ Hz, 1H), 3.55–3.42 (m, 1H), 3.32–3.18 (m, 1H), 2.81–2.68 (m, 2H), 2.04–1.90 (m, 1H), 1.80–1.17 (m, 14H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 173.5$, 171.1, 170.9, 168.6, 153.3, 134.5, 128.3, 125.7, 115.4, 111.0, 60.3, 51.9, 44.7, 41.3, 35.5, 32.0, 31.6, 27.1, 26.8, 25.8, 22.4, 22.2, 15.9, 11.1; analytical HPLC: homogeneous single peak, $t_R = 15.9$ min (8–70% B in 30 min); MALDI MS: calcd for $C_{25}H_{39}N_7O_6$ [MH]$^+$ 534.2, found 534.3.

Compound 38m: TentaGel S PHB resin (0.10 mmol, 0.18 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (16 mg, 23%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.4$ (br, 2H), 8.72 (br, 1H), 8.41 (br, 1H), 8.18 (s, 1H), 8.15 (s, 1H), 7.83 (br, 5H), 6.88 (d, $J = 9.0$ Hz, 1H), 6.58 (br, 1H), 4.44 (br, 1H), 4.34 (br, 1H), 4.06 (br, 1H), 3.70–3.40 (br, 2H, covered under the signal of water), 2.75 (br, 2H), 2.01 (br, 5H), 1.78 (br, 2H), 1.55 (br, 3H), 1.43 (br, 1H), 1.26 (br, 3H); analytical HPLC: single peak, $t_R = 15.3$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{24}H_{33}N_7O_{10}$ [MH]$^+$ 581.2, found 581.1.

Compound 39m: TentaGel S PHB resin (0.10 mmol, 0.30 mmol g^{-1}) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a yellowish powder (35 mg, 59%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 12.4$ (br, 2H), 8.80 (d, $J = 6.3$ Hz, 1H), 8.41 (d, $J = 2.4$ Hz, 1H), 8.34 (t, $J = 5.7$ Hz, 1H), 8.17 (dd, $J = 2.7$, 9.6 Hz, 1H), 7.94 (d, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.69 (br, 3H), 7.51 (d, $J = 8.1$ Hz, 1H), 6.85 (d, $J = 9.3$ Hz, 1H), 4.40–4.29 (m, 2H), 4.10 (dd, $J = 6.9$, 13.5 Hz, 1H), 3.90–3.67 (m, 2H), 2.83–2.70 (m, 2H), 2.50–2.40 (m, 2H), 2.00 (dd, $J = 6.9$, 14.7 Hz, 1H), 1.82–1.62 (m, 4H), 1.62–1.40 (m, 4H), 1.36–1.18 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): $\delta = 174.0$, 171.9, 171.4, 171.2, 168.7, 153.6, 134.6, 128.2, 125.4, 115.9, 111.1, 56.0, 52.1, 51.2, 31.3, 30.8, 30.7, 29.7, 29.5, 26.8, 25.9, 24.7, 23.7, 22.3; analytical HPLC: single peak, $t_R = 17.1$ min (5–40% B in 30 min); MALDI MS: calcd for $C_{25}H_{35}N_7O_{10}$ [MH]$^+$ 595.2, found 595.5.

Acknowledgments

We thank Zhicheng Wang for 2D NMR analyses, and Alex J. Zhang for MALDI MS analyses. This research was supported by Boehringer–Ingelheim Pharmaceuticals Inc., The Texas Advanced Research Program, The National Institutes of Health (CA 82642 and DA 09358-01) and The Robert A. Welch Foundation. K.B. thanks the NIH for a Research Career Development Award and the Alfred P. Sloan Foundation for a fellowship.

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Received: March 8, 1999 [F1659]

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