Stereoselective Modification of a Cyclopentapeptide via an α-(Ethylthio)glycine Residue†

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The solid-phase synthesis of cyclo[Val-D-Gly(SEt)-Pro-Phe-D-Ala] (**5**) on Kaiser's oxime resin is described. Conversion of **5** to the reactive α-chloroglycine derivative **9** allowed the stereoselective addition of thiols, alcohols, amines and other nucleophiles with formation of the modified cyclopeptides **11a**−**n**.

Introduction

Several naturally occurring[1−3] and synthetic[4−11] cyclopeptides exhibit important biological activities. To optimize these properties, e.g. their binding to a receptor,[12,13] methods for the modification of cyclopeptides without *de novo* peptide syntheses are of interest. Seebach et al.[14,15] used this approach for the synthesis of cyclosporine A analogues by means of enolate alkylation. We now describe the structural variation of a cyclopeptide by use of α-(ethylthio)glycine as a stable electrophilic glycine equivalent.[16−20]

Results and Discussion

Synthesis of Cyclopeptide 5. cyclo[Val-D-Gly(SEt)-Pro-Phe-D-Ala][21] (**5**) was chosen as a model compound. This peptide sequence should facilitate NMR spectroscopic characterization and was expected to form only one stable conformation in solution.[4] Synthesis was performed on Kaiser's 4-nitrobenzophenone oxime resin[22−24] starting from the D-alanine derivative **1** by application of standard Boc methodology (Scheme 1). Due to the known instability of *N*-deprotected α-heterosubstituted glycine derivatives,[25] the α-(ethylthio)glycyl residue was introduced by coupling of resin bound H-Pro-Phe-D-Ala-OH (**2**) with Boc-Val-DL-Gly(SEt)-OH (**3**) (vide supra) using TBTU [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate] as coupling reagent.[26,27] During the fragment coupling the reaction time for complete acylation had to be increased to 24 h. After removal of the Boc protecting group from the resin bound pentapeptide **4** only the cyclopentapeptide **5** with the D-(α-ethylthio)glycyl residue was released[28,29] whereas the L-epimer remained fixed to the resin. This points to a remarkable difference in the cyclization tendency of both epimers.

The dipeptide **3** was obtained from Boc-Val-Ser-OMe (**6**) in 79% overall yield. Oxidative degradation of the serine residue in **6** with lead(IV)acetate followed by treatment of the resulting acetoxy derivative **7** with ethanethiol/triethylamine[16−18] afforded the ester **8** which was hydrolyzed to **3** with lithium hydroxide (Scheme 2).

Structure of Cyclopeptide 5. NMR spectroscopic evidence indicated a single preferred conformation of cyclopeptide **5** in DMSO-d_6 and $CDCl_3$ solution at 25 °C. The temperature gradients ($-\Delta\delta/T$) for the N*H*-protons of **5** in DMSO-d_6 (300 MHz) were 0.3×10^{-3} for D-Ala

† This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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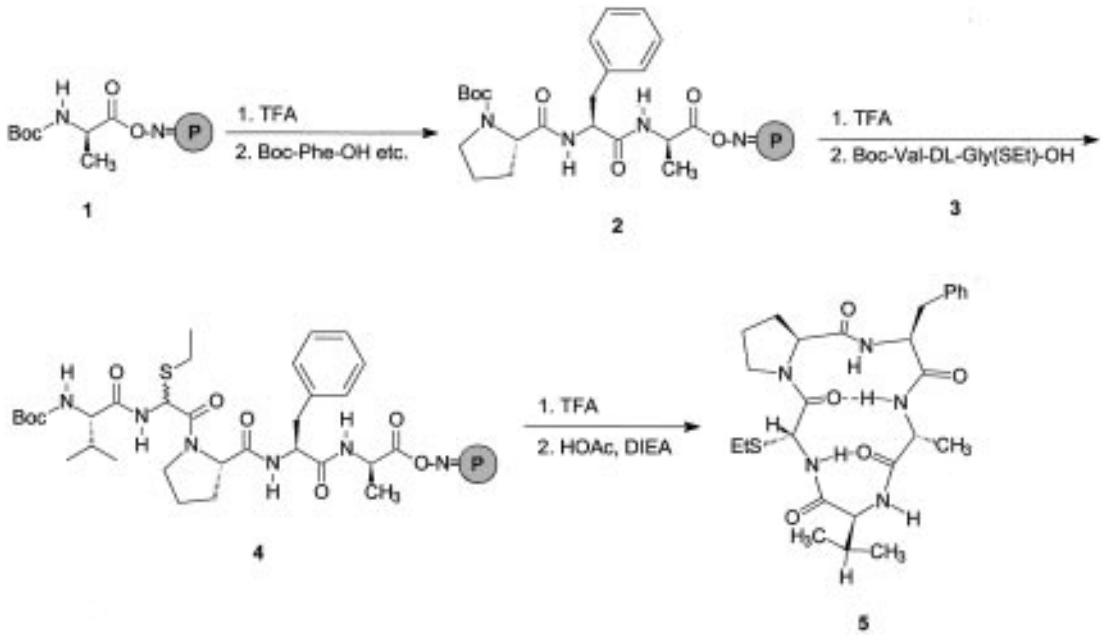
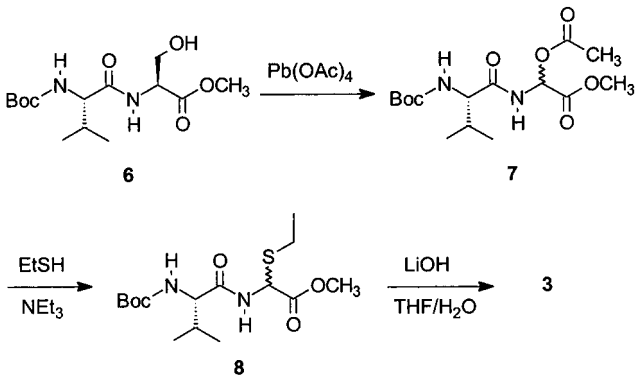
Scheme 1



Scheme 2



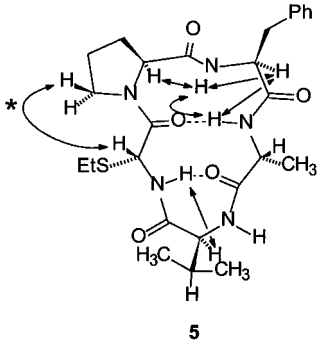


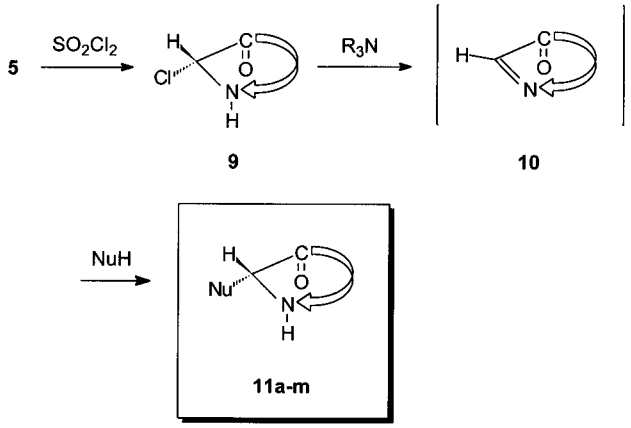
Figure 1. Important NOESY correlations in cyclopeptide **5**.

and 2.0×10^{-3} for Gly(SEt) in accord with two intramolecular hydrogen bonds, forming a γ-turn around Val and another turn (γ or β) on the opposite side of the cyclopeptide. The gradients for Phe (5.3×10^{-3}) and for Val (7.0×10^{-3}) indicated exposure to the solvent.[4] H,H-COSY and NOESY spectra recorded at 600 MHz in a mixture of pyridine-d_5/DMSO-d_6 5/2 allowed peak assignment for every single proton. Especially the diastereotopic Pro δ-protons could be distinguished by determining the NOE connectivity of the protons on both sides of the ring. Consequently, the D-configuration of the α-(ethylthio)glycyl residue was deduced from the NOE correlation marked with an asterisk in Figure 1, showing the possible β/γ-turn structure of **5** together with important NOESY correlations.

Reaction of the α-Chloroglycyl derivative 9 with Nucleophiles. On reaction with sulfuryl chloride, cyclopeptide **5** was smoothly converted to the α-chloroglycyl derivative **9** (Scheme 3). Treatment of chloride **9** at −78 °C with tertiary amines generated the reactive dehydroglycine intermediate **10** which added nucleophiles in situ to form the cyclopeptide derivatives **11a**−**m** (Table 1).[16−18]

In contrast to linear α-chloroglycyl peptides[16−18] cyclopeptide **9** adds simple nucleophiles such as thiols, amines, and alcohols highly stereoselective with retention of the configuration.[31] This observation can be explained by steric shielding of the "upper" side of the conformationally

Scheme 3



rigid structure of **10**. The stereochemistry of the major diastereomers of **11k**−**m** was determined as "D"[21] by means of 2D NOESY experiments as described for cyclopeptide **5**. The ^{1}H NMR data of all other adducts were in such close agreement that the D-configuration can also be assumed for these compounds.

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Table 1. Products 11a−n Obtained by the Addition of Nucleophiles NuH to α-Chloroglycyl Cyclopeptide 9

Nucleophile	No.	R	yield (%)	d.e. (%)
Propane-2-thiol	**11a**	-S-CH(CH_3)$_2$	64	83[a]
Hexane-1,6-dithiol	**11b**	-S-(CH_2)$_6$-S-	45	[b]
Methyl *N*-*tert*-butyloxycarbonyl-L-cysteinate	**11c**	Boc-Cys-OMe	38	87[a]
Methyl L-alaninate hydrochloride	**11d**	-L-Ala-OMe	57	89[a]
Methyl D-alaninate hydrochloride	**11e**	-D-Ala-OMe	91	>97[c]
Benzylamine	**11f**	-NH-CH_2-Ph	81	75[a]
1-Morpholinocyclohexene	**11g**		63	83[a, d]
Trimethyl phosphite	**11h**	-PO(OMe)$_2$	82	>97[c]
Trimethylsilyl cyanide	**11i**	-C≡N	87	89[a]
Water	**11j**	-OH	76	>97[c]
3,5-Dinitrobenzyl alcohol	**11k**	-O$CH_2C_6H_3(NO_2)_2$-3,5	46	94[a]
Methanol	**11l**	-OMe	40	>97[c]
Tri-*n*-butyltin deuteride[e]	**11m**	-D	77	63[a]

[a] The diastereomeric ratio was determined by NMR and HPLC analyses.

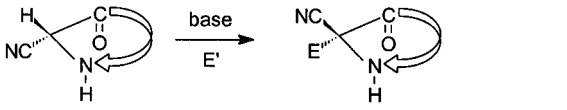
[b] According to NMR and HPLC analyses three diastereomers were formed in a ratio of 10:1.45:1.

[c] Only one diastereomer could be detected by NMR and HPLC analyses.

[d] Only the *anti*-adducts are obtained on reacting enamines with acyliminoesters.[17,30]

[e] Radical reaction.

Scheme 4



11i **12** (E = CH_2-Ph)
13 (E = CH_2-CH_2-CO_2Me)

In its reactions with nucleophiles the cyclic α-chloroglycyl peptide **9** not only excels its linear analogues in respect to stereoselectivity but offers also new synthetic possibilities.

Thus, treatment of chloride **9** with trimethylsilyl cyanide afforded the cyanide **11i** whereas linear analogues form dimeric products. They arise from addition of a second molecule of acylimine to the acidic α-CH group of the cyano compound.[32] The α-cyanoglycyl peptide **11i** can be further modified by alkylation in the presence of a strong base (Scheme 4).[33] Reaction of nitrile **11i** with benzyl bromide and sodium hydride yielded the α-(cyano)-phenylalanyl derivative **12**, and with methyl acrylate in the presence of Schwesinger's phosphazene base P_1-*tert*-butyl[34] the optically pure α-(cyano)glutamyl derivative **13** was obtained. The (*S*)-configuration at the newly formed stereogenic center was established by 2D NOESY experiments. In the case of benzyl derivative **12** the formation of small amounts of inseparable *N*-alkylation products prohibited the determination of its stereochemistry.

In contrast to chloride **9**, which formed with water the α-hydroxyglycyl derivative **11j**, linear chloroglycyl peptides yield mainly the corresponding ethers.[35,36] Reaction of **9** with trimethyl phosphite afforded the optically pure phosphonate **11h**, which failed to react with aromatic aldehydes even under drastic Horner−Wittig reaction conditions.[16]

Treatment with ^{n}Bu$_3$SnD/AIBN converts cyclopeptide **5** directly to a 4.4:1 mixture of the corresponding monodeutero compounds **11m** in which the *R*-epimer is the major product (de 63%).[17,37−39]

In summary, these results demonstrate the easy introduction of an α-(ethylthio)glycyl residue in a cyclopeptide by standard solid-phase methods. The exchange of the ethylthio group against other residues allows the synthesis of numerous peptide analogues from a single starting material. Experiments to determine the degree of stereoselectivity for these transformations with less constrained cyclopeptides are in progress. The use of this technique for combinatorial approaches, e.g. the synthesis of libraries from libraries,[40] and the optimization of biologically active peptide ligands is under investigation.

Experimental Section

General Methods. Satisfactory elementary analysis and/or high-resolution FAB mass spectra have been obtained for all new compounds. CH_2Cl_2 was distilled from Sicapent and THF from potassium. Phosphazene base P_1-*tert*-butyl was purchased from Fluka and sulfuryl chloride as a 1 M solution in CH_2Cl_2 from Aldrich. All reactions were carried out under an argon atmosphere. Kaiser's 4-nitrobenzophenone oxime resin was prepared according to ref 22. Standard procedures[26,41] were used for the synthesis of the resin-bound tripeptide **2** in a manual solid-phase reactor.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-L-serine Methyl Ester (6).** To a solution of Boc-Val-OH (21.7 g, 100 mmol) and triethylamine (15.3 mL, 110 mmol) in THF (350 mL) was added dropwise ethyl chloroformate (10.5 mL, 110 mmol) at −15 °C. After the mixture was stirred for 15 min at −15 °C, a solution of L-serine methyl ester hydrochloride (15.9 g, 102 mmol) and triethylamine (15.3 mL, 110 mmol) in THF (350 mL) was added dropwise. During preparation of the ester solution a solid was formed which was redissolved by adding some drops of water. The reaction mixture was allowed to warm to 25 °C over a 2 h interval, and stirring was maintained for 3 h. The solvent was removed under reduced pressure and the resulting oil suspended in EtOAc. The solution was washed successively with 10% aqueous citric acid (3×), saturated aqueous $NaHCO_3$ (3×), water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 6.13 g (81%) of pure **6** as a colorless solid: mp 77.5−79.5 °C; $[\alpha]^{20}_D = -21.1$ (c = 1.03, MeOH); IR (KBr) 3336 (br), 2965, 1748, 1658, 1524, 1393, 1367, 1247, 1169 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 8.8 Hz), 5.00 (t, 1H, J = 5.6 Hz), 4.34 (ddd, 1H, J = 4.8 Hz, J = 4.8 Hz, J = 7.6 Hz), 3.88 (dd, 1H, J = 6.8 Hz, J = 8.8 Hz), 3.63−3.70 (m, 1H), 3.58−3.62 (m, 4H), 1.90−1.98 (m, 1H), 1.37 (s, 9H), 0.85 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 6.8 Hz); MS (FAB, mNBA) m/z (%) 341 ([M + Na]$^+$,

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15), 319 ([M + H]$^+$, 16). Anal. Calcd for $C_{14}H_{26}N_2O_6$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.95; H, 8.03; N, 8.63.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-DL-α-acetoxyglycine Methyl Ester (7).** To a solution of the seryl peptide **6** (5.02 g, 15.8 mmol) in EtOAc (60 mL, dried over molecular sieve 4 Å) were added $Pb(OAc)_4$ (10.78 g) and molecular sieve 4 Å (1.5 g). The mixture was heated to reflux for 2 h with vigorous stirring, cooled to rt, and filtered through a pad of Celite. After the addition of 10% aqueous citric acid (60 mL), the mixture was stirred for 10 min. The organic layer was separated, washed with water (3×), and dried over $MgSO_4$. Evaporation of the solvent afforded 5.42 g of **7** (99%) as a colorless oil which was used for the next step without further purification.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-DL-α-(ethylthio)glycine Methyl Ester (8).** To a solution of α-acetoxyglycine peptide **7** (5.42 g, 15.6 mmol) in CH_2Cl_2 (150 mL) were added at 25 °C ethanethiol (1.23 mL, 16.6 mmol) and triethylamine (4.84 mL, 34.7 mmol). After 12 h of stirring the mixture was diluted with *tert*-butyl methyl ether (150 mL) and washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromtography on silica gel. Elution with petroleum ether/EtOAc 3:1 gave **8** (4.35 g, 79%) as a colorless solid: mp 104−105 °C; IR (KBr) 3324, 2976, 2933, 2873, 1750, 1685, 1653, 1529, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, 1H, J = 8.5 Hz), 5.55/5.56 (each d, 1H, J = 8.5 Hz), 4.97 (br, 1H), 3.90−4.04 (m, 1H), 3.80 (s, 3H), 2.61−2.77 (m, 2H), 2.11−2.23 (m, 1H), 1.44 (s, 9H), 1.28/1.28 (each t, 3H, J = 7.4 Hz), 0.90−1.00 (m, 1H); MS (FAB, mNBA) m/z (%) 371 ([M + Na]$^+$, 13), 349 ([M + H]$^+$, 17). Anal. Calcd for $C_{15}H_{28}N_2O_5S$: C, 51.70; H, 8.10; N, 8.04; S, 9.20. Found: C, 51.81; H, 7.95; N, 8.12; S, 8.83.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-DL-α-(ethylthio)glycine (3).** To a solution of ester **8** (4.35 g, 12.5 mmol) in THF (80 mL) were added water (27 mL) and LiOH (0.68 g, 28.3 mmol) at 0 °C. After 1 h of stirring at rt, the solution was adjusted to pH 2 with 1.1 M $KHSO_4$ and extracted with EtOAc (3×). The combined organic layers were washed with water (2×) and dried over $MgSO_4$. Evaporation of the solvent yielded 4.18 g of **3** (quant) as a colorless foam: IR (KBr) 3335 (br), 2974, 2934, 2876, 1722, 1695, 1660, 1524, 1393, 1368, 1248, 1168 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.0 (br, 1H), 8.44/8.53 (each d, 1H, J = 8.8 Hz), 6.60/6.82 (each d, 1H, J = 8.8 Hz), 5.33/5.35 (each d, 1H, J = 8.8 Hz, J = 10.4 Hz), 3.81−3.92 (m, 1H), 2.54−2.68 (m, 2H), 1.86−1.94 (m, 1H), 1.36 (s, 9H), 1.15/1.16 (each t, 3H, J = 7.4 Hz), 0.80−0.84 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.53/172.61, 171.00/171.07, 156.66/156.71, 79.32/79.36, 60.69/61.02, 54.00/54.07, 31.47/31.80, 29.43, 24.94/25.07, 20.30/20.36, 19.29/19.57, 15.67/15.72; MS (FAB, mNBA) m/z (%) 357 ([M + Na]$^+$, 32), 335 ([M + H]$^+$, 5); HRMS (FAB, mNBA) calcd for $C_{14}H_{27}N_2O_5S$ ([M + H]$^+$) 335.1641, found 335.1638.

Cyclopeptide 5. A. Synthesis of Peptide 4 by Fragment Condensation: Boc-Pro-Phe-D-Ala-polymer (**2**) (4.9 g, 0.41 mmol/g, 2.01 mmol) was deprotected with 25% TFA in CH_2Cl_2 (1 × 1 min, 1 × 30 min), washed with CH_2Cl_2 (2×), *i*-PrOH, CH_2Cl_2 (2×), *i*-PrOH, CH_2Cl_2 (3×), and DMF. A solution of dipeptide **3** (1.01 g, 3.01 mmol), TBTU (1.45 g, 4.52 mmol), and *N*-hydroxybenzotriazole (HOBt, 0.46 g, 3.01 mmol) in DMF (25 mL) was added to the resin. After 1 min of shaking, diisopropylethylamine (DIEA, 1.38 mL, 8.04 mmol) was added, and the shaking was maintained for 24 h. After this period the resin was washed with DMF (1×), CH_2Cl_2 (3×), CH_2Cl_2/EtOH = 1/1 (2×), and CH_2Cl_2 (2×).

B. Cyclization: Boc-Val-DL-Gly(SEt)-Pro-Phe-D-Ala-polymer **4** was deprotected with 25% TFA in CH_2Cl_2 (1 × 1 min, 1 × 30 min), washed with CH_2Cl_2 (2×), *i*-PrOH, CH_2Cl_2 (2×), *i*-PrOH, CH_2Cl_2 (3×), and DMF. A solution of DIEA (0.69 mL, 4.02 mmol) and glacial acetic acid (0.23 mL, 4.02 mmol) in DMF (75 mL) was added to the resin. After 24 h of shaking, the resin was filtered off and washed with DMF (3×). Evaporation of the combined filtrates in vacuo yielded a yellowish solid which was washed with water (50 mL) and a few milliliters of cold MeOH. Lyophylization yielded 0.53 g of cyclopeptide **5** (49%) as a colorless solid: mp 255 °C (sublimation); $[\alpha]^{20}_D$ = +28.0 (c 0.28, DMSO); CD (c = 1.65 × 10^{-4} mol × L^{-1}, MeOH) λ_{max} nm ($\Delta\epsilon$) = 206 (−1.9), λ_{min}= 219 (−5.3), 226 (−5.1); IR (KBr) 3420 (br), 3380, 2960, 2920, 2860, 1645, 1540, 1460, 1375, 1260, 745, 700 cm^{-1}; ^{1}H NMR (600 MHz, pyridine-d_5/DMSO-d_6 = 5/2) δ 9.03 (d, 1H, J = 7.8 Hz, Gly(SEt)-NH), 8.67 (d, 1H, J = 9.0 Hz, Val-NH), 8.22 (d, 1H, J = 7.2 Hz, Ala-NH), 7.94 (d, 1H, J = 8.4 Hz, Phe-NH), 7.21−7.43 (m, 5H, aromat H), 5.87 (d, 1H, J = 7.8 Hz, Gly(SEt)-α-H), 5.01−5.87 (m, 1H, Phe-α-H), 4.82 (dq, 1H, J = 7.2 Hz, J = 6.5 Hz, Ala-α-H), 4.61 (dd, 1H, J = 9.0 Hz (both), Val-α-H), 4.39−4.43 (m, 1H, Pro-α-H), 3.90−3.96 (m, 1H, Pro-δ'−H), 3.74−3.78 (m, 1H, Pro-δ-H), 3.58−3.63 (m, 1H, Phe-CH_2), 3.04−3.10 (m, 1H, Phe-CH_2), 2.74−2.88 (m, 2H, SCH_2), 2.27−2.35 (m, 1H, Val-CH(CH$_3$)$_2$), 2.01−2.10 (m, 1H, Pro-β-H), 1.87−1.96 (m, 1H, Pro-γ'−H), 1.77−1.85 (m, 1H, Pro-γ-H), 1.66−1.74 (m, 1H, Pro-β'−H), 1.37 (d, 3H, J = 6.5 Hz, Ala-CH_3), 1.26−1.29 (m, 3H, SCH_2CH_3), 1.09 (d, 3H, J = 6.5 Hz, Val-CH_3), 1.07 (d, 3H, J = 6.5 Hz, Val-CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.62, 171.52, 171.42, 170.91, 167.25, 138.88, 129.94, 128.79, 126.97, 62.48, 58.32, 53.86, 53.63, 49.15, 47.77, 37.50, 29.55, 28.10, 25.12, 24.58, 20.55, 19.42, 16.87, 15.64; MS (FAB, mNBA) m/z (%) 554 ([M + Na]$^+$, 10), 532 ([M + H]$^+$, 45). Anal. Calcd for $C_{26}H_{37}N_5O_5S$: C, 58.74; H, 7.01; N, 13.17; S, 6.03. Found: C, 58.53; H, 7.00; N, 13.08; S, 6.14.

General Procedure for the Synthesis of Cyclopeptides 11. A 0.22 mL (0.22 mmol) volume of 1 M SO_2Cl_2 in CH_2Cl_2 was added at 0 °C to a solution of **5** (106 mg, 0.2 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 1 h at 0 °C whereby the chloropeptide **9** precipitated. The solvent and all volatile byproducts were evaporated (cool trap), and the resulting residue was suspended in the appropriate solvent (THF or CH_2Cl_2, 20 mL). After cooling the mixture to −78 °C, the appropriate base (DIEA or DABCO, 0.42 mmol) was added and the solution stirred for 5 min.

The nucleophile (0.21 mmol, cf. Table 1) was added, and stirring was maintained for 12 h, allowing the solution to warm to rt. If THF was used, the solvent was removed and the resulting residue dissolved in EtOAc or CH_2Cl_2 (20 mL). The organic layer was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude cyclopeptide **11** which was purified by column chromatography, recrystallization, or HPLC.

α-Cyanoglycyl Cyclopeptide 11i. As an example, the chloro peptide **9** was suspended in THF, DIEA (72 μL, 0.42 mmol) and, after stirring for 5 min, trimethylsilyl cyanide (27 μL, 0.21 mmol) were added. Stirring was continued for 12 h, allowing the reaction mixture to warm to rt. The solvent was removed and the resulting residue suspended in EtOAc (20 mL). The organic layer was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo until a crystalline solid precipitated. The precipitate was filtered off and dried in vacuo to yield **11i** (87 mg, 88%) as a colorless solid: mp 312 °C (sublimation); IR (KBr) 3420 (br), 2950, 2910, 2840, 1650, 1515, 1450, 1370, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (d, 1H, J = 6.0 Hz), 7.98 (d, 1H, J = 9.1 Hz), 7.91 (d, 1H, J = 7.4 Hz), 7.14−7.28 (m, 6H), 5.71 (d, 1H, J = 6.0 Hz), 4.45−4.54 (m, 1H), 4.28−4.41 (m, 1H), 4.14−4.26 (m, 2H), 3.85−3.96 (m, 1H), 3.55−3.67 (m, 1H), 3.13 (dd, 1H, J = 7.4, 13.3 Hz), 2.73 (dd, 1H, J = 7.4, 13.3 Hz), 1.72−2.20 (m, 4H), 1.51−1.65 (m, 1H), 1.06 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 171.56, 171.51, 170.02, 169.75, 161.43, 137.64, 128.96, 127.93, 126.11, 114.90, 61.80, 57.05, 53.55, 47.75, 47.11, 42.76, 36.69, 28.89, 28.62, 23.96, 19.30, 18.22, 15.27; MS (FAB, mNBA) m/z (%) 470 ([M-CN]$^+$, 25). Anal. Calcd for $C_{25}H_{32}N_6O_5$: C, 60.47; H, 6.50; N, 16.92. Found: C, 60.15; H, 6.41; N, 16.80.

α-Cyanoglutamyl Cyclopeptide 13. In a pressure tube **11i** (51 mg, 0.10 mmol) was dissolved in THF (10 mL). To the solution were added methyl acrylate (0.10 mL, 1.11 mmol) and P_1-*tert*-butyl base[34] (53 μL, 0.21 mmol). The reaction mixture was heated to 100 °C for 2 h and cooled to rt. After addition of saturated aqueous NH_4Cl, the mixture was ex-

tracted with $CHCl_3$ (3×), and the organic layer was washed with water and brine. The solution was dried over $MgSO_4$, filtered, and concentrated in vacuo and the resulting residue purified by column chromatography on silica gel. Elution with CH_2Cl_2/EtOAc/MeOH 12:2:1 afforded 32 mg of **13** (53%) as a colorless oil: $[\alpha]^{20}_D = 63.8$ (*c* 1.3, $CHCl_3$); IR (KBr) ν 3340 (br), 2920, 1735, 1652, 1520, 1450, 1380 cm^{-1}; ^1H NMR (300 MHz, pyridine-d_5/DMSO-d_6 = 5:2) δ 10.45 (s, 1H), 9.03 (d, 1H, J = 7.7 Hz), 8.08 (d, 1H, J = 9.6 Hz), 7.21−7.45 (m, 6H), 4.93−5.08 (m, 1H), 4.58−4.85 (m, 3H), 4.40−4.55 (m, 1H), 4.05−4.18 (m, 1H), 3.67 (s, 3H), 3.38−3.53 (m, 1H), 3.13−3.25 (m, 1H), 2.60−3.06 (m, 4H), 2.06−2.24 (m, 2H), 1.78−2.01 (m, 3H), 1.25 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.7 Hz), 1.03 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, pyridine-d_5/DMSO-d_6 = 5:2): δ 174.11, 172.66, 171.99, 170.91, 170.73, 165.35, 138.24, 129.67, 128.54, 126.68, 118.61, 64.44, 57.76, 56.03, 55.13, 51.85, 49.30, 48.05, 37.90, 31.61, 31.21, 29.31, 29.05, 25.35, 19.26, 18.60, 14.52; MS (FAB, mNBA) *m*/*z* (%) 605 ($[M + Na]^+$, 3), 583 ($[M + H]^+$, 86); HRMS (FAB, mNBA) calcd for $C_{29}H_{39}N_6O_7$ ($[M + H]^+$) 583.2880, found 583.2890.

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Supporting Information Available: Experimental details for the cyclopeptides **11a**−**h** and **11j**−**m**, and spectral and analytical data for these compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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