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Synthesis of a Model Analogue of the Cyclic Decadepsipeptide Intercalating Agent Luzopeptin A (Antibiotic BBM 928A) Containing Proline, Valine, and Unsubstituted Quinoline Substituents

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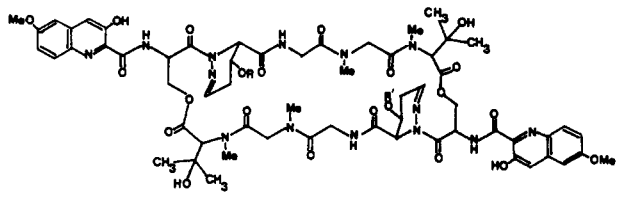
A synthetic analogue (2) of the cyclic decadepsipeptide DNA intercalation agent luzopeptin A (1) (antibiotic BBM 928A) has been prepared in which the substituted quinoline, the tetrahydropyridazinecarboxylic acid, and the *N*-methyl-β-hydroxy-L-valine units have been replaced by quinoline, L-proline, and L-valine, respectively. Analogue 2 was prepared by two routes involving the use of two different sequence related precursor pentadepsipeptides 6 and 15. The linear decadepsipeptides 9 and 18, obtained by fragment coupling of the appropriate pentadepsipeptides, each underwent cyclization, following deprotection, at high dilution with 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide and 1-hydroxybenzotriazole in tetrahydrofuran to provide cyclic product 12 in yields of 55–60%. The route to 12 from linear decadepsipeptide 18 was less satisfactory due to the modest yield (42%) obtained in the zinc-mediated removal of the *p*-chlorophenacyl ester protecting group. Analogue 2 was obtained from 12 by removal of the *N*-benzyloxycarbonyl groups at each D-serine, followed by acylation with the *p*-nitrophenyl active ester of quinoline-2-carboxylic acid.

Families of cyclic depsipeptides are known[1] that possess heteroaromatic chromophores capable of intercalation with deoxyribonucleic acids. The luzopeptin antibiotics[2,3] 1 (also



1 Luzopeptin A R = R' = Ac
Luzopeptin B R = Ac, R' = H
Luzopeptin C R = R' = H

termed BBM 928) are cyclic decadepsipeptides that have substituted quinoline-2-carbonyl units attached to the depsipeptide ring via the α-amino groups of two D-serine residues. The depsipeptides also contain two novel tetrahydropyridazine amino acid units as well as a pair of *N*-methyl-β-hydroxyl-L-valine units. Studies have established[4] luzopeptin A to be a bis-intercalating agent in binding to DNA, apparently undergoing both intra- and intermolecular binding to a single DNA molecule or to two molecules, respectively. The antibiotics are reported to possess significant antitumor activity toward several tumor systems.[5]

The luzopeptin antibiotics bear certain structural features that are related to the triostin and quinomycin depsipeptide antibiotics.[1] We previously had prepared[6] an analogue of triostin A (Figure 1) in which the *N*-methyl-L-valine and *N,N'*-dimethyl-L-cystine units were replaced with the normal amino acids lacking the *N*-methyl substituents. The preparation of such a model compound not only served to allow development of synthetic routes[6] to the triostins but also furnished an analogue that showed remarkable specificity in binding to DNA.[7] With this

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(3) Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1981**, *34*, 148.

(4) Huang, C.-H.; Mong, S.; Crooke, S. T. *Biochemistry* **1980**, *19*, 5537. Huang, C.-H.; Prestayko, A. W.; Crooke, S. T. *Ibid.* **1982**, *21*, 3704. Huang, C.-H.; Mirabelli, C. K.; Mong, S.; Crooke, S. T. *Cancer Res.* **1983**, *43*, 2718.

(5) Okhuma, H.; Sakai, F.; Nishiyama, Y.; Ohbayashi, M.; Imanishi, H.; Konishi, M.; Miyaki, T.; Koshiyama, H.; Kawaguchi, H. *J. Antibiot.* **1980**, *33*, 1087. Rose, W. C.; Schurig, J. E.; Huftalen, J. B.; Bradner, W. T. *Cancer Res.* **1983**, *43*, 1504.

(6) Ciardelli, T. L.; Chakravarty, P. K.; Olsen, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 7684. Dhaon, M. K.; Gardner, J. H.; Olsen, R. K. *Tetrahedron* **1982**, *34*, 57.

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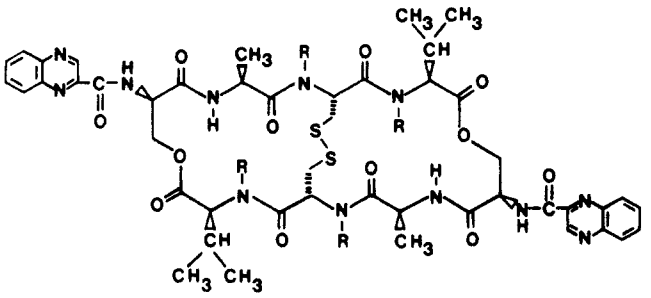
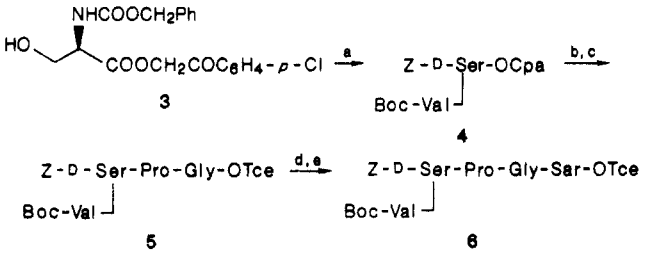


Figure 1. Structures of triostin A (R = Me) and des-*N*-tetramethyltriostin A (R = H).

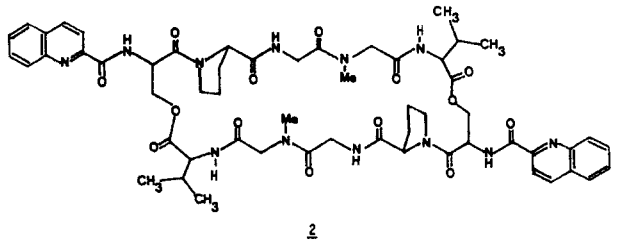
Scheme I[a]



[a] (a) DCC, HOBt, pyridine, 80–85%; (b) Zn, 90% aqueous AcOH, 90–95%; (c) H-Pro-Gly-OTce, EDC or DCC, THF or CH_2Cl_2, 53–81%; (d) Zn, 90% aqueous AcOH, 95–100%; (e) H-Sar-OTce, EDC, HOBt, THF, 65–70%.

precedence in mind, we choose to study the synthesis of an analogue (**2**) of the luzopeptins. Analogue **2** has L-proline units in place of the tetrahydropyridazinecarboxylic acids, L-valine for each *N*-methyl-β-hydroxyl-L-valine, and an unsubstituted quinoline-2-carbonyl moiety rather than the more substituted natural chromophore.

Analogue **2** possesses a 2-fold axis of symmetry. A logical approach, therefore, to its synthesis would be to prepare a pentadepsipeptide containing the five amino acids common to **2**. Fragment coupling of the appropriate pair of



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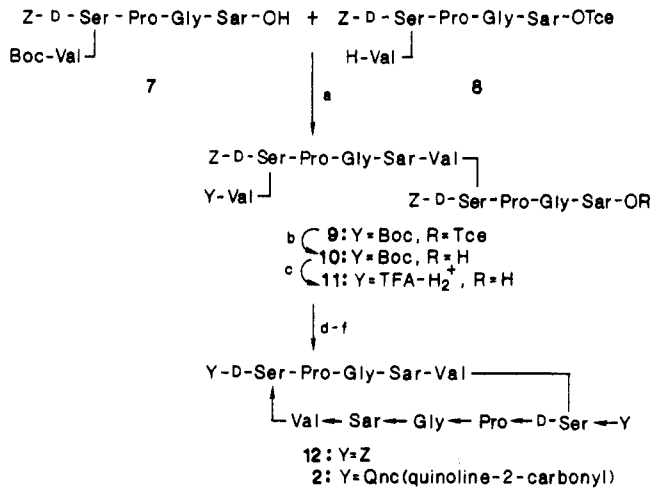
deprotected pentadepsipeptides and cyclization of the linear decadepsipeptide thus obtained would lead to the cyclic depsipeptide. In a final step, the quinoline-2-carbonyl moieties would be attached to furnish **2**.

The preparation of a requisite pentadepsipeptide is given in Scheme I. *p*-Chlorophenacyl *N*-(benzyloxycarbonyl)-D-serinate (**3**) was prepared by alkylation of the carboxylate anion of Z-D-serine with α-bromo-*p*-chloroacetophenone.[8] (Abbreviations used in this paper are listed in the Experimental Section.) Acylation of **3** with Boc-L-valine, using *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in pyridine,[6] gave didepsipeptide **4**. Treatment of **4** with zinc in 90% aqueous acetic acid[6,8] effected reductive removal of the *p*-chlorophenacyl (Cpa) ester group. Condensation of the resulting acid with the dipeptide L-prolylglycine 2,2,2-trichloroethyl ester as mediated by 1-ethyl-3-((dimethylamino)propyl)carbodiimide (EDC) or DCC, provided tetradepsipeptide **5**. Transformation of **5** to the desired pentadepsipeptide **6** was accomplished by a sequence of deprotection (Zn, 90% aqueous AcOH) and coupling (EDC, HOBt) with sarcosine 2,2,2-trichloroethyl ester. Pentadepsipeptide **6** was obtained by this route in an overall yield of 44% from Z-D-serine Cpa ester (**3**).

Scheme II[a]



[a] (a) HOBt, EDC, THF, 80%; (b) Zn, 90% aqueous AcOH, 90–95%; (c) TFA, CH_2Cl_2, 95–100%; (d) EDC, HOBt, NMM, THF, 55–60%; (e) 30% HBr in AcOH; (f) Qnc-OC_6H_4-*p*-NO_2, Et_3N, DMF, 61%.

Completion of the synthesis of analogue **2** is given in Scheme II. Treatment of pentadepsipeptide **6** with zinc in 90% AcOH freed the sarcosine carboxyl function to yield **7**, while acidic removal of the *N*-Boc group present in **6**, followed by basic workup, gave the amine **8**. Fragment coupling of **7** with **8**, as mediated by the use of EDC and HOBt, furnished the linear decadepsipeptide **9** in a yield of 80%. A series of deprotection reactions, which effected conversion of **9** to **10** to **11**, followed by neutralization and cyclization of **11** (6.7×10^{-4} M in THF) by reaction with 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide and 1-hydroxybenzotriazole[6,9] provided cyclic product **12** in a yield of 66%. Removal of the *N*-benzyloxycarbonyl groups by treatment of **12** with 30% HBr in AcOH and subsequent neutralization and acylation with the active ester *p*-nitrophenyl quinoline-2-carboxylate[10,11] resulted in the isolation (61% yield) of the target analogue, *N,N'*-bis(quinolinyl-2-carbonyl)-[Pro^2,Val^5,Pro^7,Val^{10}]luzopeptin (**2**).

The synthesis of cyclic depsipeptide **12** also was accomplished from an alternative amino acid sequence as incorporated in the requisite pentadepsipeptide Z-D-Ser-(Boc-Pro-Gly-Sar-Val)-OCpa (**15**). Depsipeptide **15** differs from the above-described pentadepsipeptide **6** in that, starting from didepsipeptide **4**, the peptide chain was extended from the amino group of valine by the stepwise attachment of the sarcosine, glycine, and proline units. The synthesis of **15** followed similar methodology as de-

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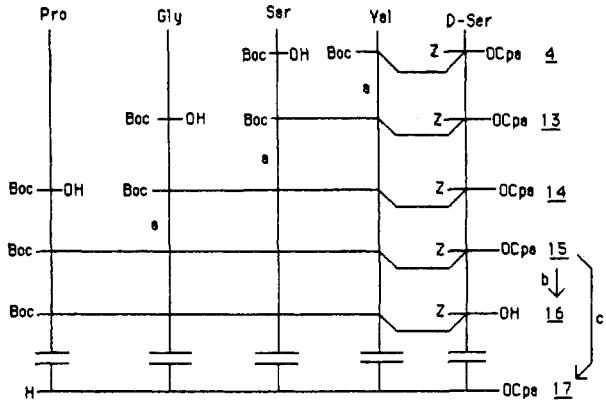
(8) For preparation and use of the *p*-bromophenacyl ester of Z-L-serine, see: Corey, E. J.; Bhattacharyya, S. *Tetrahedron Lett.* **1977**, 3919.

(9) Konig, W.; Gregier, R. *Chem. Ber.* **1970**, *103*, 788. Sheehan, J. C.; Cruickhank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.

(10) For acylation of α-amino acid esters by reaction with 2-quinolinecarboxylic acid and a carbodiimide, see: Sathi, G.; Gujrati, V. R.; Nath, C.; Agarwal, J. C.; Bhargava, K. P.; Shanker, K. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 603.

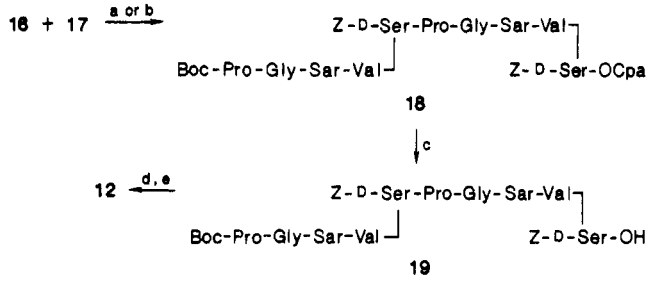
(11) Shin, M.; Inouye, K.; Otsuka, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1501. This paper reports the introduction of the 2-quinoxalinecarbonyl function into depsipeptides by use of the corresponding *p*-nitrophenyl ester.

Scheme III[a]



[a] (a) 1. TFA, CH_2Cl_2; 2. Boc-amino acid, EDC, HOBt, Et_3N; (b) **15**, Zn, 90% aqueous AcOH → **16**; (c) 1. **15**, THF, CH_2Cl_2; 2. aqueous $NaHCO_3$ → **17**.

Scheme IV[a]



[a] (a) EDC, HOBt, THF, 65%; (b) isobutyl chloroformate, NMM, THF, 45% of **21** plus Z-D-Ser(*i*-BuOCO-Pro-Gly-Sar-Val)-OCpa (37%); (c) Zn (150 mmol excess), 90% AcOH, 1 h at 0 °C, 8 h at 23 °C, 1 h at 35–40 °C, 42%; (d) TFA, CH_2Cl_2; (e) EDC, HOBt, NMM, THF, 55%.

scribed for **6** and is outlined in the format given in Scheme III.

The linear decadepsipeptide **18** was prepared in a yield of 65% by fragment coupling of the appropriate N- and C-deprotected pentadepsipeptides, **16** and **17**, derived from depsipeptide **15** (Schemes III and IV). A problem[12] was encountered upon attempting to effect the removal of the Cpa ester group in **18** by treatment with zinc in 90% aqueous acetic acid in that unreacted starting material was always recovered (≃90% recovery) under normal conditions of deprotection. Repetition of the reaction using a 3-fold increased amount of zinc, longer reaction time, and higher temperature (see Scheme IV) gave **19** in a modest yield of 42%. Deprotection of the prolyl amino function of **22** and cyclization (EDC, HOBt) gave **12** in a yield of 55%. This approach, because of the modest yield obtained in removal of the Cpa ester function, proved to be less efficient than the initial procedure described herein.

The depsipeptides prepared in this study gave 360–MHz NMR data consistent with their assigned structures. Analogue **2** was analyzed further by a 2D relayed COSY experiment, while cyclic product **12** furnished consistent ^{13}C NMR data, as analyzed by a DEPT program. Cyclic products **2** and **12**, as also linear decadepsipeptides **9** and **18**, were checked for the occurrence of any racemization during their syntheses by GC analysis of their derivatized hydrolyzates on a chiral phase capillary column.[13] No racemization of the chiral amino acids was observed.

In this study, we also prepared two other pentadepsipeptides. The first, Z-D-Ser(Boc-Sar-Val)-Pro-Gly-OTce, was prepared by condensation of Z-D-Ser(Boc-Sar-Val)-OH with H-Pro-Gly-OTce. The low yields obtained (8–14%) in this convergent 3 + 2 fragment coupling reaction, as well as unsatisfactory results obtained in preliminary studies to effect formation of the corresponding decadepsipeptide, caused us to not pursue this approach. A second pentadepsipeptide, Boc-D-Ser(Z-D-Val)-Pro-Gly-Sar-OTce, was prepared beginning with the known[14] dipeptide Boc-D-Ser(OBzl)-Pro-OH. The above pentadepsipeptide has the same sequence as **6** but differs in the location of the Boc and Z amino protecting groups. The pentadepsipeptide was converted to its corresponding linear decadepsipeptide; however, only partial removal of the Z group on valine of the decadepsipeptide by hydrogenolysis (H_2, Pd/C, AcOH or Pd/C, $NH_4OCH{=}O$, CH_3OH) was observed, thereby thwarting our attempts to obtain the corresponding cyclic product.

Experimental Section

The amino acids and coupling reagents used were obtained from commercial sources. All solvents were distilled in glass. Tetrahydrofuran was distilled from $LiAlH_4$ and stored over 3A molecular sieves. Methylene chloride was distilled from P_2O_5 and stored over molecular sieves. Dimethylformamide was distilled from CaH. Melting points were determined by capillary melting points and are uncorrected. TLC was performed on commercially prepared silica gel on 1 × 3 in. glass plates and spots were detected by ultraviolet light or iodine vapor. MPLC[15] and flash chromatography[16] were carried out on columns packed with silica gel 60 (0.040–0.064 mm). ^1H NMR spectra were recorded at 60, 90, or, as indicated in the Experimental, at 360 or 400 MHz. Optical rotations were recorded on an automatic polarimeter.

Abbreviations used in this paper are as follows: Boc, *tert*-butoxycarbonyl; Cpa, *p*-chlorophenacyl; DCC, *N,N'*-dicyclohexylcarbodiimide; DMAP, 4-(dimethylamino)pyridine; EDC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; MPLC, medium pressure liquid chromatography; NMM, *N*-methylmorpholine; Qnc, quinolinyl-2-carbonyl; Su, succinimide; Tce, 2,2,2-trichloroethyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Z, benzyloxycarbonyl.

General Procedure for Removal of the 2,2,2-Trichloroethyl (Tce) Ester Function. The depsipeptide Tce ester in a solution of 90% aqueous AcOH (35–50 mL/mmol) at 0 °C was stirred vigorously and zinc powder (50 equiv) was added in portions over a period of 20 min. The reaction mixture was stirred at 0 °C for 2–4 h and at room temperature for 3–5 h. The mixture was filtered and the solid was washed well with 90% aqueous AcOH. The filtrate was concentrated in vacuo and the solid obtained was partitioned between 1 N HCl (1 volume) and ethyl acetate (3 volumes). The organic phase was separated and the aqueous layer was saturated with NaCl and extracted with EtOAc (2 portions). The combined EtOAc extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to furnish the depsipeptide acid. Last traces of solvent were removed by the azeotropic evaporation in vacuo of three portions each of MeOH and benzene, after which the product was dried in a vacuum desiccator over KOH and P_2O_5.

General Procedure for Removal of *t*-Boc Group To Furnish the Corresponding TFA Salt. The N-Boc-protected amino acid or peptide derivative (1–20 mmol) in TFA/CH_2Cl_2 (1:1, 8–20 mL) was stirred at room temperature for 45 min. The mixture was concentrated in vacuo and last traces of TFA were removed in vacuo by evaporation of three portions each (5–20 mL) of CH_3OH, benzene, and ether, followed by vacuum desiccation for several hours over KOH and P_2O_5. The TFA salt was

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(13) Smith, G. G.; Wonnacott, D. M. *Anal. Biochem.* **1980**, *109*, 414.

(14) Ando, S.; Aoyagi, H.; Waki, M.; Kato, T.; Izumiya, N.; Okamoto, K.; Kondo, M. *Tetrahedron Lett.* **1982**, *23*, 2195.

(15) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

used as obtained for the subsequent coupling reaction.

N-(Benzyloxycarbonyl)-D-serine p-Chlorophenacyl Ester (3). A mixture of Z-D-serine (4.78 g, 20 mmol), *p*-chlorophenacyl bromide (4.66 g, 20 mmol), and potassium bicarbonate (2.2 g, 22 mmol) in acetone (300 mL) was refluxed for 7 h and cooled to room temperature. The solid salts were filtered and the filtrate was concentrated to give a white solid, which was recrystallized from hot ethyl acetate/acetone (2:1). The product was obtained as white needles: yield 6.5 g (83%); mp 158–159 °C; $[\alpha]^{24}_D$ +14.4° (*c* 1, DMF); R_f 0.12 in $CHCl_3$/acetone (95.5); ^1H NMR (Me_2SO-d_6, 90 MHz) δ 3.40 (s, 1 H, OH, exchangeable with D_2O), 3.88 (m, 2 H, Ser CH_2), 4.41 (m, 1 H, Ser α-H), 4.95 (bd, 1 H, NH, exchangeable with D_2O), 5.08 (s, 2 H, benzyl CH_2), 5.53 (s, 2 H, Cpa CH_2), 7.36 (s, 5 H, benzyl aromatic), 7.62 (d, 2 H, phenacyl aromatic), 8.0 (d, 2 H, phenacyl aromatic). Anal. Calcd for $C_{19}H_{18}ClNO_6$ (391.80): C, 58.24; H, 4.63; N, 3.57. Found: C, 58.11; H, 4.78; N, 3.63.

N-(Benzyloxycarbonyl)-O-(N-Boc-L-valyl)-D-serine p-Chlorophenacyl Ester (4). Z-D-Ser-OCpa (**3**, 1.96 g, 5.0 mmol), Boc-valine (1.19 g, 5.5 mmol), and HOBt (0.74 g, 5.5 mmol) were dissolved in 25 mL of pyridine. The solution was chilled to 0 °C followed by the addition of *N,N'*-dicyclohexylcarbodiimide (1.13 g, 5.5 mmol). The reaction mixture was stirred at 0 °C for 4 h followed by 20 h at room temperature. The separated solid was filtered and washed with pyridine (15 mL), and the combined filtrate was concentrated in vacuo to a yellow oil. This material was dissolved in EtOAc (40 mL) and washed successively with H_2O, 1 N $NaHCO_3$ aqueous 10% citric acid, water, and brine (25 mL each). The EtOAc layer was dried (anhydrous Na_2SO_4) and concentrated to give a viscous residue, which was purified by flash chromatography using 10% hexane in chloroform as eluant. The product obtained (2.4 g, 81%) slowly solidified to a white solid on standing at room temperature: mp 101–102 °C; $[\alpha]^{24}_D$ +1.6° (*c* 1, $CHCl_3$); R_f 0.32 in $CHCl_3$/acetone (95.5); ^1H NMR ($CDCl_3$, 60 MHz) δ 0.98 (pair of doublets, 6 H, valyl methyls), 1.45 (s, 9 H, Boc *t*-Bu), 2.1–2.30 (m, 1 H, valyl methine), 4.20–4.45 (m, 2 H, α-H), 4.68 (d, 2 H, seryl CH_2), 5.22 (s, 2 H, benzyl CH_2), 5.45 (s, 2 H, Cpa CH_2), 5.9–6.2 (m, 2 H, NH), 7.48 (s, 5 H, benzyl aromatic), 7.53 (d, 2 H, phenacyl aromatic), 7.90 (d, 2 H, phenacyl aromatic). Anal. Calcd for $C_{29}H_{35}N_2O_9Cl$ (591.05): C, 58.93; H, 5.97; N, 4.74. Found: C, 58.74; H, 6.17; N, 4.93.

Boc-Pro-Gly-OTce. *N*-(*tert*-Butoxycarbonyl)glycine (7.0 g, 40 mmol) and 2,2,2-trichlorethanol were stirred at 0 °C in 120 mL of CH_2Cl_2. 4-(Dimethylamino)pyridine (0.48 g, 0.1 equiv) and *N,N'*-dicyclohexylcarbodiimide (9.9 g, 48 mmol) were added, and the resulting mixture was stirred at 0 °C for 2 h and at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was taken up in 100 mL each of H_2O and EtOAc. The organic phase was washed with 50-mL portions of 10% citric acid, 5% $NaHCO_3$ (2×), H_2O, and brine and dried over anhydrous Na_2SO_4. The oil obtained was purified by MPLC, in which the product was loaded on the column in $CHCl_3$ and eluted with hexane/acetone (9:1) to give 9.14 g of Boc-Gly-OTce (75%): mp 72–73 °C from $CHCl_3$/hexane; R_f 0.4 in hexane/acetone (9:1); ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, *t*-Bu), 4.13 (d, 2 H, α-H), 4.88 (s, 2 H, Tce CH_2), 5.32 (br s, 1 H, NH).

$TFA^-H_2^+$-Gly-OTce (~20 mmol), obtained by treatment of Boc-Gly-OTce (6.12 g) with 15 mL of 1:1 TFA/CH_2Cl_2, was dissolved in EtOAc (40 mL) and cooled to 0 °C. Triethylamine (4 mL) and Boc-Pro-OSu (6.24 g, 20 mmol)[14] were added and the reaction mixture was stirred at 0 °C for 2 h and at room temperature for 20 h. The solid suspension was filtered and the filtrate was washed successively with 1 N HCl (2 × 30 mL), 1 N aqueous $NaHCO_3$ (1 × 20 mL), H_2O (1 × 20 mL), and brine (1 × 20 mL), dried (Na_2SO_4), and concentrated to give a white solid which was recrystallized from EtOAc/ether (5:95) to give 6.74 g (84%) of product: mp 141–142 °C from $CHCl_3$/hexane; R_f 0.20 in $CHCl_3$; $[\alpha]^{25}_D$ –67.7° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, *t*-Bu), 2.0 (m, 4 H, prolyl C-3, C-4 CH_2), 3.48 (m, 2 H, prolyl C-5 CH_2), 4.25 (d, 2 H, glycyl CH_2), 4.40 (m, 1 H, prolyl α-H), 4.86 (s, 2 H, Tce CH_2).

Z-D-Ser(Boc-Val)-OH. Z-D-Ser(Boc-Val)-OCpa (2.36 g, 4.0 mmol) in 90% acetic acid (140 mL) was cooled to 0 °C and treated with zinc powder (13 g, 50 equiv) as described in the general procedure. The crude oil obtained was purified by flash chromatography on a silica gel column with chloroform and 10–20% acetone in chloroform as eluants to yield product (1.66 g, 85%) as a colorless viscous oil: R_f 0.19 in $CHCl_3$/ethanol (85:15): $[\alpha]^{20}_D$ –49.8 ± 0.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 60 MHz) δ 0.86 (t, 6 H, valyl methyls), 1.45 (s, 9 H, Boc), 1.90–2.1 (m, 1 H, valyl methine), 4.20–4.90 (m, 4 H, Ser CH_2 and 2 α-H), 5.12 (s, 2 H, benzyl CH_2), 5.20–5.35 (m, 1 H, NH), 6.45 (m, 1 H, NH), 7.36 (s, 5 H, benzyl aromatic), 11.58 (s, 1 H, CO_2H).

Z-D-Ser(Boc-Val)-Pro-Gly-OTce (5). To a solution of Z-D-Ser(Boc-Val)-OH (2.60 g, 6.0 mmol) and $TFA^-H_2^+$-Pro-Gly-OTce, obtained from 2.63 g (6.5 mmol) of Boc-Pro-Gly-OTce, in 60 mL of dry THF cooled to 0 °C, were added Et_3N (1.12 mL, 8.0 mmol), HOBt (0.81 g, 6.0 mmol), and EDC (1.15 g, 6.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 20 h. The solvent was removed in vacuo and partitioned between H_2O (30 mL) and EtOAc (100 mL). The organic layer was separated, washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$, H_2O, and brine (15 mL each) and dried (Na_2SO_4). The crude material obtained (5.4 g) was purified by MPLC using acetone/chloroform (1:4) as eluant. The pure product was obtained (3.5 g, 81%) as a frothy mass: mp 61–63 °C; $[\alpha]^{22}_D$ –43.2 ± 0.3° (*c* 1.01, $CHCl_3$); R_f 0.30 in chloroform/acetone (4:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.91 (t, 6 H, valyl methyls), 1.43 (s, 9 H, Boc *t*-Bu), 1.9–2.1 (m, 5 H, valyl methine and prolyl methylenes), 3.40–3.68 (series of multiplets, 9 H, 3 α-H, and 3 CH_2), 4.72 (s, 2 H, OTce CH_2), 5.0 (s, 1 H, NH), 5.08 (s, 2 H, benzyl CH_2), 5.97 (d, 1 H, NH), 7.32 (s, 5 H, benzyl aromatic), 7.40 (m, 1 H, NH). Anal. Calcd for $C_{30}H_{41}Cl_3N_4O_{10}$: C, 49.76; H, 5.71; N, 7.74. Found: C, 49.71; H, 5.81; N, 7.72.

Z-D-Ser(Boc-Val)-Pro-Gly-OH. Z-D-Ser(Boc-Val)-Pro-Gly-OTce (**5**, 3.62 g, 5.0 mmol) was dissolved in 175 mL of 90% AcOH and cooled to 0 °C. Zinc powder (16.35 g, 50 equiv) was added in portions over a period of 20 min. The reaction mixture was then stirred at 0 °C for 3 h and at room temperature for 3 h. The reaction was worked up as described in the general procedure.

The product was obtained as a frothy mass (2.92 g, 98%), which was dried in a vacuum desiccator over KOH for $^1/_2$ h and used as such in the subsequent reaction. The product was homogeneous on TLC with an R_f 0.52 in $CHCl_3$/MeOH/AcOH (85:10:5); $[\alpha]^{25}_D$ –31.0 ± 0.2° (*c* 1, MeOH).

Z-D-Ser(Boc-Val)-Pro-Gly-Sar-OTce (6). A solution of $TFA^-H_2^+$-Sar-OTce (obtained from 1.92 g, 6.0 mmol, of Boc-Sar-OTce as described above) in 40 mL of dry THF was cooled to 0 °C and neutralized with Et_3N (1 mL, 7 mmol). To the reaction mixture was added a solution of Z-D-Ser(Boc-Val)-Pro-Gly-OH (2.9 g, 4.9 mmol) in 35 mL of dry THF, followed by addition of HOBt (0.68 g, 5 mmol) and EDC (0.96 g, 5.0 mmol). The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 20 h. The solvent was removed in vacuo and the residue was taken up in EtOAc/H_2O (75 mL:25 mL). The organic phase was separated and washed with 10 mL each of 1 N HCl, 1 N aqueous $NaHCO_3$, H_2O, and brine and dried over Na_2SO_4. The solution was concentrated to give a frothy mass, which was purified by MPLC using 20–30% acetone in $CHCl_3$. The pure product was obtained (2.5 g, 63%) as a frothy mass: mp 70–73 °C; $[\alpha]^{22}_D$ –25.7 ± 0.3° (*c* 1, $CHCl_3$); R_f 0.27 in $CHCl_3$/acetone (7:3); ^1H NMR ($CDCl_3$, 360 MHz) δ 0.87, 0.94 (two d, 6 H, valyl methyls), 1.43 (s, 9 H, Boc *t*-Bu), 1.82–2.30 (m, 5 H, prolyl methylenes and valyl methine), 3.07 (s, 3 H, N-CH_3), 3.62–4.55 (series of multiplets, 10 H, prolyl CH_2, glycyl CH_2, sarcosyl CH_2, seryl CH_2 and 2 α-H), 4.72, (s, 2 H, OTce CH_2), 4.81 (m, 1 H, α-H), 5.05 (d, 1 H, NH), 5.11 (s, 2 H, benzyl CH_2), 6.02 (d, 1 H, NH), 7.22 (m, 1 H, NH), 7.35 (s, 5 H, benzyl aromatic). Anal. Calcd for $C_{33}H_{46}Cl_3N_5O_{11}$ (795.11): C, 49.85; H, 5.83; N, 8.81. Found: C, 49.55; H, 5.86; N, 8.54.

Z-D-Ser(Boc-Val)-Pro-Gly-Sar-OH (7). Z-D-Ser(Boc-Val)-Pro-Gly-Sar-OTce (**6**, 1.19 g, 1.5 mmol) in 90% acetic acid (53 mL) was stirred with zinc powder (4.9 g, 50 equiv) at 0 °C for 4 h and at room temperature for 3 h, after which the reaction was worked up as in the general procedure. The product was obtained (1.0 g, 100%) as a frothy mass, which was found to be almost pure (R_f 0.33 in $CHCl_3$/MeOH/AcOH; 85:10:5) and was used as such in the subsequent reaction: $[\alpha]^{25}_D$ –36.8 ± 0.2° (*c* 1, MeOH).

Z-D-Ser(H-Val)-Pro-Gly-Sar-OTce (8). Z-D-Ser(Boc-Val)-Pro-Gly-Sar-OTce (**6**, 1.0 g, 1.26 mmol) was stirred in 4 mL

of TFA and 4 mL of CH_2Cl_2 at room temperature for 45 min. The solvents were removed in vacuo and the resdue was partitioned between 5% aqueous $NaHCO_3$ (30 mL) and EtOAc (60 mL). The EtOAC layer was separated and washed successively with saturated aqueous $NaHCO_3$ (1 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL). The solution was dried (Na_2SO_4) and concentrated in vacuo, and last traces of solvents were removed azetropically with dry benzene (4 × 10 mL). The product, obtained (0.87 g, 100%) as a foam, was dried overnight in a vacuum desiccator over KOH and P_2O_5 and was used as such in the subsequent reaction.

Z-D-Ser[Z-D-Ser(Boc-Val)-Pro-Gly-Sar-Val]-Pro-Gly-Sar-OTce (9). Z-D-Ser-(Boc-Val)-Pro-Gly-Sar-OH (7, 0.66 g, 1.0 mmol) and Z-D-Ser-(H-Val)-Pro (8, 0.69 g, 1.0 mmol) were dissolved in dry THF (30 mL) and cooled to 0 °C. To this were added HOBt (0.14 g, 1 mmol) and EDC (0.19 g, 1 mmol), and the reaction mixture was stirred at 0 °C for 3 h and at room temperature for 20 h. The solvent was removed in vacuo and the residue was taken up in H_2O (10 mL) and EtOAc (30 mL). The EtOAc layer was separated and washed successively with 10 mL each of 1 N HCL, 1 N aqueous $NaHCO_3$, H_2O, and brine and dried (Na_2SO_4). The product was purified by MPLC using chloroform/acetone (2:3 and 1:4) as eluants. The pure product was obtained (1.07 g, 80%) as a frothy mass: mp 120–124 °C: $[\alpha]^{2+}{}_D$ −23.6° (*c* 1, $CHCl_3$); R_f 0.5 in $CHCl_3$/EtOAc (9:1); ^1H NMR ($CDCl_3$, 360 MHz) δ 0.93 (m, 12 H, valyl methyls), 1.43 (s, 9 H, Boc *t*-Bu), 1.80–2.1 (m, 10 H, prolyl methylenes and valyl methine), 2.95–3.1 (m, 6 H, NCH_3), 3.35–4.55 (series of multiplets, 20 H, Sar CH_2, Gly CH_2, Pro CH_2, Ser CH_2, and 4 α-H), 4.70–4.87 (m, 4 H, OTce CH_2, 2 α-H), 5.16 (brs, 5 H, benzyl CH_2 and NH), 6.27 (d, 1 H, NH), 6.40 (m, 1 H, NH), 6.73 (m, 1 H, NH), 6.90 (m, 1 H, NH), 7.34 (brs, 11 H, benzyl aromatic and NH). Anal. Calcd for $C_{59}H_{81}Cl_3N_{10}O_{19}$ (1340.68): C, 52.85, H, 6.09; N, 10.45. Found: C, 52.68; H, 6.16; N, 10.46.

Z-D-Ser[Z-D-Ser(Boc-Val)-Pro-Gly-Sar-Val]-Pro-Gly-Sar-OH (10). Decadepsipeptide 9 (2.7 g, 2.0 mmol) was dissolved in 90% acetic acid (106.5 mL) and cooled to 0 °C. Zinc powder (9.8 g, 75 equiv) was added in portions over a period of 20 min. The reaction mixture was then stirred at 0 °C for 4 h and at room temperature for 5 h. Solid material was filtered and washed well with 90% AcOH (~100 mL). The combined filtrate was concentrated in vacuo to give a white solid, which was partitioned between 1 N HCl (50 mL) and EtOAc (150 mL). The EtOAc layer was separated and the aqueous layer was saturated with NaCl and extracted (2 × 50 mL) with EtOAc. The combined EtOAc extract was washed with brine (1 × 30 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography over silica gel. Elution with $CHCl_3$/acetone (2:1) gave (0.25 g, 9.3%) of unreacted starting material. Further elution with acetone and acetone/MeOH (9:1) gave 1.8 g, 75%) of pure acid 10. Last traces of solvents were removed azeotropically with dry benzene (3 × 15 mL) and the residue was dried in a vacuum desiccator over KOV and P_2O_5 for 2 h. The product was obtained as a frothy mass: mp 120–125 °C; $[\alpha]^{22}{}_D$ −40.1 ± 0.2° (*c* 1, MeOH); R_f 0.13 in $CHCl_3$/MeOH/AcOH (85:10:5). Anal. Calcd for $C_{57}H_{80}N_{10}O_{19}\cdot C_6H_6$: C, 53.18; H, 6.73; N, 10.88. Found: C, 53.39, H, 6.37, N, 10.88.

***cyclo*-[Z-D-Ser-Pro-Gly-Sar-Val-Z-D-Ser-Pro-Gly-Sar-Val] (12).** Linear decadepsipeptide acid (10), (1.2 g, 1 mmol) was stirred in 10 mL of TFA and CH_2Cl_2 (1:1) at room temperature for 1 h. The solvent was removed under reduced pressure and last traces of solvent were removed azeotropically with MeOH (3 × 10 mL), dry benzene (3 × 10 mL), and dry MeOH (1 × 10 mL). The product 11 was dried in a vacuum desiccator over P_2O_5 and KOH for 2 h and used as such in the cyclization reaction.

TFA salt 11 (≃1 mmol) was dissolved in 200 mL of dry THF, cooled to 0 °C, and neutralized with *N*-methylmorpholine (0.13 mL, 1.0 mmol). The solution was added dropwise over a period of 3.5 h to a stirred, cold solution of HOBt (0.54 g, 4.0 mmol) and EDC (0.76 g, 4.0 mmol) in 1300 mL of dry THF and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure to give a residue which was taken up in H_2O (20 mL) and EtOAc (75 mL). The EtOAc layer was separated and washed successively with 15-mL portions each of 1 N HCl, 1 N aqueous $NaHCO_3$, H_2O, and brine and dried (Na_2SO_4). Removal of the solvent gave an oil, which on trituration with dry ether gave a white solid. The solid was purified by flash chromatography using $CHCl_3$/acetone and acetone as eluants to give product 12 (0.72 g, 66%) as a white compound: mp 147–150 °C; $[\alpha]^{25.5}{}_D$ −77.6 ± 0.2 (*c* 1, $CHCl_3$); R_f 0.32 in $CHCl_3$/EtOH (85:15); ^1H NMR ($CDCl_3$, 360 MHZ) δ 0.84 (t, 12 H, valyl methyls), 1.9–2.15 (m, 10 H, Pro CH_2 and Val methine), 2.95 (s, 6 H, NCH_3), 3.37–3.87 (s, q, and m, 8 H, Sar CH_2 and Gly CH_2), 4.2–4.56 (m, 10 H, Pro CH_2, Ser CH_2 and 4 α-H), 4.93–5.09 (m, 8 H, seryl CH_2, benzyl CH_2, 2 α-H), 5.83 (brd, 2 H, NH) 7.34 (brs, 12 H, benzyl aromatic and 2 NH), 8.24 (brd, 2 H, NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 17.92 (valyl methyl), 18.58 (valyl methyl), 23.86, (prolyl C-4), 29.94 (prolyl C-3), 30.72 (valyl methine), 34.79 (*N*-CH_3), 41.40 (prolyl C-5), 47.75, 49.52 (Sar CH_2 and Gly CH_2), 50.79, 57.49, 59.59 (3 α-C), 63.20 (seryl CH_2), 66.90 (benzyl CH_2), 127.82, 128.15 (aromatic, 2 peaks for 3C), 135.83 (aromatic C_1), 155.07 (benzyloxy C=O), 166.84, 167.63, 168.36, 170.56, 171.50 (amide and ester carbonyls). Anal. Calcd for $C_{52}H_{70}N_{10}O_{16}\cdot 2H_2O$ (1127.19): C, 55.40; H, 6.62; N, 12.42. Found: C, 55.60; H, 6.59; N, 12.43.

***N*,*N*′-Bis(quinolinyl-2-carbonyl)-[Pro²,Val⁵,Pro⁷,Val¹⁰]-luzopeptin (2).** Cyclic decadepsipeptide 12 (0.35 g, 0.32 mmol) was dissolved in 10 mL of 30–32% HBr in AcOH and the solution was stirred at room temperature for 40 min. The solution was diluted with 30 mL of dry ether and the upper ether layer was carefully decanted. This process was repeated 4–5 times until much of the excess acid was removed. The remaining solvents were removed under reduced pressure and last traces of acids were removed azeotropically with dry benzene (4 × 15 mL) and dry ether (3 × 15 mL). The HBr salt thus obtained was dried in a vacuum desiccator over P_2O_5 and KOH for 2 h.

The above salt was dissolved in dry DMF (35 mL) and neutralized with triethylamine (1.4 mL, 10 mmol). To this solution was added *p*-nitrophenyl quinoline-2-carboxylate (0.21 g, 0.7 mmol), and the reaction mixture was stirred at room temperature for 48 h. The solvent was removed in vacuo by using a vacuum pump to give a solid. This solid was dissolved in CH_2Cl_2 (100 mL) and the CH_2Cl_2 solution was washed successively with water (2 × 50 mL), 1 N HCl (2 × 20 mL), 1 N aqueous $NaHCO_3$ (3 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL) and dried (Na_2SO_4). The solid obtained was purified by flash chromatography over silica gel. Elution with $CHCl_3$ gave traces of unreacted *p*-nitrophenyl quinoline-2-carboxylate along with some unidentified impurities. Further elution with 50–75% acetone in $CHCl_3$ gave (0.22 g, 61%) pure product 2 as a white powder: mp 192–195 °C; $[\alpha]^{21}{}_D$ −133.8° ± 0.4° (*c* 0.5, $CHCl_3$); R_f 0.43 in $CHCl_3$/EtOH (85:15); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0, 1.02 (two d, 12 H, valyl methyls), 2.05–2.32 (m, 10 H, Pro C_3 + C_4 methylenes, valyl methines), 3.11 (s, 6 H, NCH_3), 3.67 (d, 2 H, J = 17.23 Hz, Sar CH_2), 3.77 (q, 2 H, Pro C_5 CH_2), 3.94 (d, 2 H, J = 17.98, Gly CH_2), 4.05 (m, 2 H, Pro α-H), 4.5–4.57 (m, 4 H, Gly CH_2 and Ser CH_2), 4.62–4.7 (m, 6 H, Ser CH_2, Pro C_5 methylene, Val α-H), 5.34 (d, 2 H, J = 17.23, Sar CH_2), 5.50 (m, 2 H, Ser α-H), 7.55 (d, 2 H, NH, exchangeable with D_2O), 7.71 (t, 2 H, Qnc C_6), 7.84 (t, 2 H, Qnc C_7), 7.96 (d, 2 H, Qnc C_5), 8.15 (d, 2 H, Qnc C_8), 8.33–8.42 (d superimposed on q, 6 H, Qnc C_3 and C_4, Gly NH which are exchangeable with D_2O), 8.92 (d, 2 H, Ser NH, exchangeable with D_2O). Anal. Calcd for $C_{56}H_{68}N_{12}O_{14}\cdot H_2O$ (1151.15): C, 58.42; H, 6.13; N, 14.60. Found: C, 58.35; H, 6.19; N, 14.40.

***p*-Nitrophenyl Quinoline-2-carboxylate.** A solution of quinaldic acid (0.52 g, 3.0 mmol) in pyridine (20 mL) was cooled to 0 °C. Benzenesulfonyl chloride (0.77 mL, 6.0 mmol) was added and the mixture was stirred for 5 min. *p*-Nitrophenol (0.42 g, 3.0 mmol) was added and the mixture was stirred at 0 °C for 1.25 h. Ice water (100 mL) was added and the solid that formed was collected by filtration. Recrystallization from ethyl acetate gave the above active ester (0.68 g, 77%), mp 190–191 °C dec. This compound was only sparingly soluble in $CDCl_3$ or Me_2SO-d_6 and ^1H NMR spectra were not obtained.

Z-D-Ser(Boc-Sar-Val)-OCpa (13). Z-D-Ser-(TFA⁻H_2⁺-Val)-OCpa [obtained from 2.96 g, 5.0 mmol, of Z-D-Ser(Boc-Val-)OCpa (4), as described in general procedure] was dissolved in 100 mL of THF and cooled to 0 °C. Triethylamine (0.77 mL, 5.5 mmol), Boc-sarcosine (1.04 g, 5.5 mmol), HOBt (0.74 g, 5.5 mmol), and EDC (1.05 g, 5.5 mmol) were added sequentially and the reaction mixture was stirred at 0 °C for 4 h and at room temperature for 20 h. The solvent was distilled in vacuo and the residue was partitioned between 100 mL of ethyl acetate/H_2O (2:1). The EtOAc layer was separated and the aqueous layer was

extracted with EtOAc (1 × 25 mL). The combined EtOAc layer was washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$, water, and brine (30 mL each) and dried (anhyd Na_2SO_4). The viscous oil obtained was purified by MPLC on silica gel by elution with $CHCl_3$/acetone (95:5) to yield 2.9 g (88%) of product as a colorless viscous oil: $[\alpha]^{24}_D$ −3.36° (*c* 1.1, $CHCl_3$); R_f 0.26 in chloroform/acetone (9:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.9 (t, 6 H, valyl methyls), 1.45 (s, 9 H, Boc *t*-Bu), 2.12 (m, 1 H, valyl methyl), 2.91 (s, 3 H, NCH_3), 3.87 (s, 2 H, sarcosyl CH_2), 4.60 (m, 2 H, seryl CH_2), 4.80–4.95 (m, 2 H, two α-H), 5.11 (s, 2 H, benzyl CH_2), 5.38 (s, 2 H, Cpa CH_2), 6.29 (brs, 1 H, NH), 6.82 (brs, 1 H, NH), 7.31 (s, 5 H, benzyl aromatic), 7.42 (d, 2 H, Cpa aromatic), 7.81 (d, 2 H, Cpa aromatic). Anal. Calcd for $C_{32}H_{40}N_3O_{10}Cl$ (662.12): C, 58.04; H, 6.09; N, 6.35. Found: C, 57.86; H, 5.97; N, 6.31.

Z-D-Ser(Boc-Gly-Sar-Val)-OCpa (14). To a solution of Z-D-Ser-(TFA$^-$$H_2$$^+$-Sar-Val)-OCpa (obtained from 5.95 g, 9.0 mmol, of Z-D-Ser(Boc-Sar-Val)-OCpa as described above) in 200 mL of THF at 0 °C were added Et_3N (2.1 mL, 15 mmol), Boc-glycine (1.66 g, 9.5 mmol), HOBt (1.28 g, 9.5 mmol), and EDC (1.81 g, 9.5 mmol) in succession. The reaction mixture was stirred at 0 °C for 3 h and at room temperature overnight. The solvent was removed in vacuo and the residue was taken up in 150 mL of EtOAc/H_2O (2:1). The EtOAc layer was separated and washed successively with 1 N HCl, 1 N $NaHCO_3$, water, and brine (40 mL each) and dried (anhydrous Na_2SO_4). The crude material was purified by MPLC using acetone/$CHCl_3$ (1:4) as eluant. The product was obtained (6.2 g, 91%) as a frothy mass: mp 69–71 °C; $[\alpha]^{24}_D$ −5.23° (*c* 1.09, $CHCl_3$); R_f 0.32 in $CHCl_3$/acetone (7:3); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.91 (two d, 6 H, valyl methyls), 1.42 (s, 9 H, Boc *t*-Bu), 2.1 (m, 1 H, valyl methine), 2.99 (s, 3 H, *N*-CH_3), 4.02 (m, 4 H, methylenes of Gly and Sar), 4.45–4.9 (m, 4 H, seryl CH_2 and two α-H), 5.13 (s, 2 H, benzyl CH_2), 5.37 (s, 2 H, Cpa CH_2), 5.45 (m, 1 H, NH), 6.35 (m, 1 H, NH), 6.90 (m, 1 H, NH), 7.34 (s, 5 H, benzyl aromatic), 7.45 (d, 2 H, Cpa aromatic), 7.82 (d, 2 H, Cpa aromatic). Anal. Calcd for $C_{34}H_{43}ClN_4O_{11}\cdot H_2O$ (737.16): C, 55.39; H, 6.15; N, 7.60. Found: C, 55.62; H, 6.17; N, 7.68.

Z-D-Ser(Boc-Pro-Gly-Sar-Val)-OCpa (15). To a solution of Z-D-Ser-(TFA$^-$$H_2$$^+$-Gly-Sar-Val)-OCpa, prepared as usual from 6.47 g, 9 mmol, of Z-D-Ser(Boc-Gly-Sar-Val)-OCpa (**14**), in 100 mL of THF cooled at 0 °C were added Et_3N (1.8 mL, 12.8 mmol), Boc-proline (2.15 g, 10 mmol), HOBt (1.35 g, 10 mmol), and EDC (1.91 g, 10 mmol) sequentially. The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 20 h. The solvent was removed in vacuo and the residue was partitioned between 150 mL of EtOAc/H_2O (2:1). The organic layer was separated and washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$, H_2O, and brine (40 mL each) and dried (anhydrous Na_2SO_4). The crude material was purified by MPLC (silica gel) by elution with acetone/$CHCl_3$ (3:7) to give 5.3 g (69%) of **15** as a frothy mass: mp 72–74 °C; $[\alpha]^{24}_D$ −30.56° (*c* 1.07, $CHCl_3$); R_f 0.20 in $CHCl_3$/acetone (3:2); ^1H NMR ($CDCl_3$, 360 MHz) δ 0.91, 0.94 (two d, 6 H, valyl methyls), 1.44 (s, 9 H, Boc *t*-Bu) 1.77–2.50 (two m, 5 H, prolyl methylenes, valyl methine), 2.96, 3.02 (two s, 3 H, NCH_3), 3.32–4.88 (series of multiplets, 11 H, Sar CH_2, Gly CH_2, Pro CH_2, Ser CH_2, and 3 α-H), 5.14 (s, 2 H, benzyl CH_2), 5.40 (AB q, 2 H, Cpa CH_2), 5.47 (m, 1 H, NH), 6.15 (d, 1 H, NH), 6.73 (d, 1 H, NH), 7.35 (s, 5 H, benzyl aromatic), 7.48 (d, 2 H, Cpa aromatic), 7.83 (d, 2 H, Cpa aromatic). Anal. Calcd for $C_{39}H_{50}ClN_5O_{12}$ (816.29): C, 57.38; H, 6.17; N, 8.58. Found: C, 57.33; H, 5.99; N, 8.58.

Z-D-Ser(Boc-Pro-Gly-Sar-Val)-OH (16). Zinc powder (7.19 g, 110 mmol) was added in portions to a vigorously stirred ice cold solution of pentadepsipeptide **15** (1.88 g, 2.2 mmol) in 60 mL of 90% AcOH (aq). The mixture was stirred at 0 °C for 3 h and at room temperature for another 3 h. The reaction mixture was worked up as described in the general section to give 1.35 g (87%) of **16** as a frothy mass: mp 72–75 °C; $[\alpha]^{24}_D$ −53.96° (*c* 1.1, $CHCl_3$); TLC (R_f 0.49) homogeneous in $CHCl_3$/MeOH/AcOH (85:10:5). Anal. Calcd for $C_{31}H_{45}N_5O_{11}\cdot H_2O$ (681.72): C, 54.61; H, 6.95; N, 10.27. Found: C, 54.24; H, 6.98; N, 9.99.

Z-D-Ser(H-Pro-Gly-Sar-Val)-OCpa (17). A solution of **15** (0.816 g, 1.0 mmol) in 10 mL of TFA/CH_2Cl_2 (1:1) was stirred at room temperature for 45 min. The solution was concentrated in vacuo and the resulting oily residue was dissolved in 30 mL of EtOAc. The EtOAc solution was extracted with ice-cold saturated $NaHCO_3$ solution (2 × 20 mL) and water. After drying (anhydrous Na_2SO_4), the solution was concentrated in vacuo to give a white solid, which was dried in a desiccator over NaOH and P_2O_5 for 2 h. The free amine (0.66 g, 92%) was used as obtained in subsequent reactions.

Z-D-Ser[Z-D-Ser(Boc-Pro-Gly-Sar-Val)-Pro-Gly-Sar-Val]-OCpa (18). a. Mixed Anhydride Method. Z-D-Ser-(Boc-Pro-Gly-Sar-Val)-OH (**16**, 0.55 g, 0.83 mmol) was dissolved in dry THF (20 mL) and cooled to −20 °C in a CCl_4–dry ice bath. To this was added isobutyl chloroformate (0.12 mL, 0.83 mmol) dropwise, and the reaction mixture was stirred at −20 °C for 10 min. *N*-Methylmorpholine (0.1 mL, 0.9 mmol) was added, followed by dropwise addition of Z-D-Ser(H-Pro-Gly-Sar-Val)-OCpa (**17**, 0.59 g, 0.82 mmol) in dry THF (20 mL). The reaction mixture was stirred at −20 °C for 15 min and at room temperature overnight. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (50 mL) and H_2O (20 mL). The EtOAc layer was separated, washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$, water, and brine (15 mL each) and dried (Na_2SO_4 anhydrous). Removal of the solvent in vacuo gave a viscous residue, whose TLC showed the presence of two major products. Purification of the mixture by MPLC with elution with chloroform/acetone (9:1) gave Z-D-Ser(*N*-(isobutoxycarbonyl)-Pro-Gly-Sar-Val)-OCpa as a white solid (0.25 g, 37%), mp 74–76 °C, R_f 0.45 in $CHCl_3$/acetone. This product gave ^1H NMR (90 MHz) spectral data consistent with the assigned structure. An independent synthesis of this product by acylation of the amine depsipeptide **20** with isobutyl chloroformate confirmed the structural assignment.

Further elution with $CHCl_3$/acetone (2:1) gave the linear decadepsipeptide **18** as a white solid (0.5 g, 45%): mp 117–120 °C; $[\alpha]^{22}_D$ −32.0° (*c* 1.06, $CHCl_3$); R_f 0.11 in $CHCl_3$/acetone (1:4); ^1H NMR ($CDCl_3$, 360 MHz) δ 0.93 (m, 12 H, valyl methyls), 1.43 (s, 9 H, Boc), 1.8–2.1 (m, 10 H, Pro CH_2 and Val methines), 3.0 (m, 6 H, Sar NCH_3), 3.40–4.85 (series of multiplets, 22 H, 8 CH_2 and 6 α-H), 5.1 (d, 4 H, benzyl CH_2), 5.28–5.45 (m, 3 H, Cpa CH_2 and NH), 6.15–7.20 (series of multiplets, 5 H, NH), 7.35 (d, 10 H, benzyl aromatic), 7.45 (d, 2 H, Cpa aromatic), 7.83 (d, 2 H, Cpa aromatic). Anal. Calcd $C_{65}H_{85}ClN_{10}O_{20}\cdot 2H_2O$: C, 55.84; H, 6.42; N, 10.02. Found: C, 56.07; H, 6.40; N, 9.66.

b. HOBt–EDC Method. A mixture of Z-D-Ser(Boc-Pro-Gly-Sar-Val)-OH (**16**, 0.33 g, 0.5 mmol) and Z-D-Ser(H-Pro-Gly-Sar-Val)-OCpa (**17**, 0.36 g, 0.5 mmol) in 15 mL of dry THF was cooled to 0 °C. HOBt (0.08 g, 0.6 mmol) and EDC (0.11 g, 0.6 mmol) were added and the reaction mixture was stirred at 0 °C for 3 h and at room temperature overnight. Removal of solvent in vacuo yielded a viscous residue which was partitioned between EtOAc (40 mL) and H_2O (20 mL). The EtOAc layer was separated, washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$, H_2O, and brine (15 mL each) and dried. The crude product was purified by MPLC using $CHCl_3$/acetone (2:1) as eluant. The pure product, obtained (65%) as a frothy mass, was identical (TLC, ^1H NMR and mp) with that obtained from the mixed anhydride method.

Z-D-Ser[Z-D-Ser(Boc-Pro-Gly-Sar-Val)-Pro-Gly-Sar-Val]-OH (19). Linear decadepsipeptide **18** (0.27 g, 0.2 mmol) was dissolved in 20 mL of 90% AcOH (aq) and cooled to 0 °C. Zinc powder (2.0 g, 30.6 mmol) was added in portions and the reaction mixture was mechanically stirred at 0 °C for 1 h, at room temperature for 8 h, and at 35–40 °C for 1 h. The solvent was removed in vacuo to give a white solid, which was dissolved in 1 N HCl (10 mL) and EtOAc (30 mL). The aqueous phase was saturated with NaCl and extracted with EtOAc (2 × 10 mL). The combined bicarbonate extract was washed with EtOAc (2 × 10 mL), cooled to 0 °C, and carefully acidified to pH 3–4 with ice-cold 6 N HCl. The acidified solution was saturated with NaCl and extracted with EtOAc (5 × 20 mL). The combined EtOAc extract was washed with brine (1 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual solvents were removed azeotropically with dry methanol (3 × 10 mL) followed by dry benzene (3 × 10 mL). The product was dried overnight in a vacuum desiccator over KOH and P_2O_5 to yield acid **22** (0.10 g, 42%). This material was homogeneous on TLC and was used as such in the next reaction.

Z-D-Ser-[Z-D-Ser(TFA$^-$$H_2$$^+$-Pro-Gly-Sar-Val)-Pro-Gly-Sar-Val]-OH. The above acid (0.12 g, 0.1 mmol) was dissolved

in 4 mL of TFA and CH_2Cl_2 (1:1) and stirred at room temperature for 45 min. The reaction mixture was worked up as described in the general procedure.

***cyclo*-[Z-D-Ser-Pro-Gly-Sar-Val-Z-D-Ser-Pro-Gly-Sar-Val] (12).** A solution of the above TFA salt and *N*-methylmorpholine (0.012 mL, 0.10 mmol) in 50 mL of dry THF was added over 3.5 h to an ice-cold, stirred solution of EDC (42 mg, 0.22 mmol) and HOBt (47 mg, 0.35 mmol) in 150 mL of dry THF. After completion of the addition, the reaction mixture was stirred for 1 h at 0 °C and for 4.5 days at room temperature. The solvent was removed in vacuo and the residue was taken up in EtOAc (30 mL). The EtOAc layer was washed successively with water (1 × 15 mL), 1 N HCl (2 × 10 mL), 1 N aqueous $NaHCO_3$ (2 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL). The solution was then dried (Na_2SO_4) and concentrated in vacuo to yield an oily residue, which on trituration with diethyl ether gave the cyclized product **15** as a white solid (60 mg, 55%). This material was found to be identical (TLC, NMR, and mp) with that obtained from the cyclization of decadepsipeptide **11**.

Racemization Studies. General Procedure. Two to three milligrams of each of the cyclic depsipeptides **2** and **15**, and also the linear decadepsipeptides **12** and **18**, were hydrolyzed (3–4 mL of 6 N HCl, 100–110 °C, 12–13 h) in a sealed glass tube. The solvent was removed under a stream of air. To the residue was added 2 mL of a saturated solution of HCl in 2-propanol and the tube was resealed under nitrogen and heated at 100 °C for 2 h. The solvent was evaporated and the residue was treated at room temperature for 0.5 h with 2 mL of 30% trifluoroacetic anhydride in methylene chloride. The solvent was evaporated completely under a stream of air. The residue was redissolved in dry methylene chloride (1 mL) and a 2-μL sample solution was injected into a gas chromatograph (Hewlett-Packard Model 5880A) to analyze the enantiomeric pairs of amino acids on a chiral phase capillary column.[13] Parallel control experiments were conducted by trating each of D-serine, L-valine, and L-proline (2–3 mg each) to the same sequence of reactions, followed by analysis. No racemization of the chiral residues in the above depsipeptides was observed.

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Registry No. **2**, 103131-27-7; **3**, 103131-28-8; **4**, 103131-29-9; **5**, 103131-30-2; **6**, 103131-31-3; **7**, 103131-32-4; **8**, 103131-33-5; **9**, 103131-34-6; **10**, 103131-35-7; **11**, 103131-37-9; **12**, 103131-38-0; **12**·2HBr (deprotected), 103131-55-1; **13**, 103131-39-1; **14**, 103131-40-4; **15**, 103131-41-5; **16**, 103131-42-6; **17**, 103131-43-7; **17**·TFA, 103148-55-6; **18**, 103131-44-8; **19**, 103148-54-5; Z-D-Ser-OH, 6081-61-4; BOC-L-Val-OH, 13734-41-3; BOC-Gly-OH, 4530-20-5; BOC-Gly-OTce, 103131-45-9; Gly-OTce·TFA, 103131-46-0; BOC-L-Pro-OSu, 3392-10-7; BOC-Pro-Gly-OTce, 103131-47-1; Z-Yd-Ser(BOC-Val)-OH, 103131-48-2; Pro-Gly-OTce·TFA, 103131-50-6; Z-D-Ser(BOC-Val)-Pro-Gly-OH, 103131-51-7; BOC-Sar-OTce, 103131-52-8; Sar-OTce·TFA, 103131-54-0; Z-D-Ser(H-Val·TFA)-OCpa, 103131-58-4; BOC-Sar-OH, 13734-36-6; Z-D-Ser(H-Sar-Val·TFA)-OCpa, 103131-60-8; Z-D-Ser(H-Gly-Sar-Val·TFA)-OCpa, 103131-62-0; BOC-L-Pro-OH, 15761-39-4; Z-D-Ser(*N*-(isobutoxycarbonyl)-Pro-Glyu-Sar-Val)-OCpa, 103131-63-1; Z-D-Ser[Z-D-Ser(H-Pro-Gly-Sar-Val·TFA)-Pro-Gly-Sar-Val]-OH, 103131-65-3; *p*-chlorophenacyl bromide, 536-38-9; 2,2,2-trichloroethanol, 115-20-8; (*p*-nitrophenyl)-quinoline-2-carboxylate, 103131-56-2; quinaldic acid, 93-10-7.

Modification of Photochemistry by Cyclodextrin Complexation: Competitive Norrish Type I and Type II Reactions of Benzoin Alkyl Ethers

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The photochemical Norrish type I and type II reactions of cyclodextrin-bound benzoin methyl ether, benzoin ethyl ether, and benzoin isopropyl ether have been investigated in aqueous solution and in the solid state. Irradiation in cyclodextrin media leads to a large change in product distribution from that found in benzene and methanol. In aqueous solution type II products compete with type I, and in the solid state type II products constitute more than 90% of the product distribution. This sensitivity was interpreted as a measure of changes in the ground state distribution of reactive and nonreactive (type II) conformers brought about by cyclodextrin inclusion. Cage effects also play a significant role in altering the product distribution. ^1H NMR and X-ray powder photographic studies provide support for complexation.

The control and modification of reactivity through incorporation of molecules into organized assemblies remains an area of considerable interest. A specific subarea that has attracted recent interest concerns reactivity of molecules incorporated into "host–guest" systems.[1] These studies have paved the way to an intriguing number of possibilities by which photoreactivity can be modified. Cyclodextrins, one of the most commonly used "host" systems possess hydrophobic cavities that are able to include in aqueous solution a variety of organic compounds whose character may vary from hydrophobic to ionic.[2] Internal diameters and depths of cyclohexaamylose or α-cyclodextrin (4.2–8.8 and 7.8 Å), cycloheptaamylose or β-cyclodextrin (5.6–10.8 and 7.8 Å), and cyclooctaamylose or γ-cyclodextrin (6.8–12.0 and 7.8 Å) provide cavities for appropriately sized guest molecules. The recognized potential of cyclodextrin–guest interactions as models for enzyme active sites has prompted numerous investigations of these systems.[3] Although the potential of cyclodextrins as "reaction vessels" for thermal reactions has been widely

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