μL) as an internal reference for chemical shift and quantification. Proton-decoupled ^2H NMR spectra (61.4 MHz) were obtained with sweep width 1433 Hz, 4K data points zero-filled to 16K, 1.43 s acquisition time, 90° pulse width, and 1- or 3-Hz line broadening: **8a** (20 mg, *t*-BuOH reference, 20 μL of pyridine to improve the solubility) 35 837 scans, 3.0-Hz line broadening; **10a,b** (40 mg, 1,4-dioxane reference) 99226 scans, 3.0 Hz line broadening; **20a,b** (5 mg, 1,4-dioxane reference) 43 367 scans, 3.0-Hz line broadening; **20c** (5 mg, *t*-BuOH reference) 2774 scans, 1.0-Hz line broadening.

Deuteration of 20. Pentopyranone (5 mg, 0.02 mmol) was dissolved in D_2O (400 μL) in an NMR tube, and the ^1H NMR spectrum was acquired. The sample was then treated with ND_4OD (15 μL of a 28% solution, giving a final pD 9.3), and the ^1H NMR spectrum was immediately recorded. After 45 min at room temperature, the spectrum was again recorded, and the sample was then lyophilized. It was next triturated with H_2O and then lyophilized, and this procedure was repeated once again to yield **20c**. The H-3′ resonances were no longer detected in the ^1H NMR spectrum, and the H-5′ resonances were reduced in intensity; ^2H NMR (deuterium-depleted water) δ 1.23 (*t*-BuOH, added for chemical shift reference and deuterium quantitation), 1.98 (1 H, H-3′$_{ax}$), 2.48 (1 H, H-3′$_{eq}$), 3.72 (0.18 H, H-5′$_{ax}$), 3.81 (0.18 H, H-5′$_{eq}$); FAB-MS (glycerol) *m/z* (rel intensity) 246 ([M + H]$^+$, 45%), 228 (25%), 207 (50%), 204 (100%), 195 (35%); HR FAB-MS (glycerol) exact mass calculated for $C_9H_{12}D_2N_3O_5$ 246.10590 ([M + H]$^+$), found 246.10588.

Acknowledgment. Dr. Y. Miyazaki, Kaken Chemical Co., Ltd., Japan, is thanked for providing a culture of *S. griseochromogenes* and the recipe for the standard seed growth medium. Professor H. Seto is thanked for an authentic sample of pentopyranine C. Dr.V. A. Palaniswamy is thanked for preparing the [3-^2H]-D-glucose used in this study. This work was supported by Public Health Service Research Grant GM 32110 to S.J.G. The Bruker AM 400 NMR spectrometer was purchased in part through grants from the National Science Foundation (CHE-8216190) and from the M. J. Murdock Charitable Trust to Oregon State University, and the Bruker AC 300 spectrometer was purchased in part though grants from the Public Health Service Division of Research Resources (RR04039-01) and the National Science Foundation (CHE-8712343) to Oregon State University.

Total Synthesis of (−)-Nummularine F

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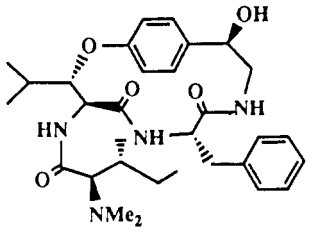
Abstract: The first total synthesis of the 14-membered para ansa cyclopeptide alkaloid (−)-nummularine F is reported. The pivotal transformations of the synthetic strategy are (1) a stereocontrolled approach for introducing the absolute stereochemistry at the α- and β-carbons of the parent β-hydroxyproline utilizing D-serine as a source of chirality; (2) cyclization to a rigid 14-membered ring; and (3) introduction of the enamide double bond. The synthesis began with the conversion of D-serine to (2*S*,3*S*)-3-(4-cyanophenoxy)-1-[(1,1-dimethylethoxy)carbonyl]proline. After conversion of the cyano function to a formyl group, a Henry reaction between the 4-formylphenoxy group and the anion of nitromethane gave a mixture of epimeric benzyl alcohols containing a terminal nitro group. The nitro group was reduced to an amine and coupled to Z-protected L-isoleucine to afford the desired acyclic precursor. Cyclization was achieved by the coupling of the proline pentafluorophenyl ester and the amino group of the L-isoleucine. The enamide bond was introduced after cyclization, via thermal selenoxide elimination.

Introduction

Cyclopeptide alkaloids are a group of closely related polyamide bases of plant origin.[1-7] Although cyclopeptide alkaloids were mentioned in the literature as early as 1884,[8] the isolation and structural elucidation of pandamine (**1**) in 1966 marks the beginning of a widespread interest in these natural products.[9] Cyclopeptide alkaloids are particularly common in plants of the Rhamnacea family and also in more than 25 other species. Their widespread occurrence makes them an important class of natural products.



Pandamine (1)

Except for the 15-membered macrocycles, all cyclopeptide alkaloids contain one β-hydroxy-α-amino acid whose oxygen is contained in the macrocycle. This unit determines the family to which they belong, and the amino acids may be β-hydroxyproline, β-hydroxyleucine, or β-hydroxyphenylalanine. Cyclopeptide alkaloids may also be classified according to size: 13-, 14-, or 15-membered rings. In addition, cyclopeptide alkaloids contain another ring-bound amino acid which forms an enamide bond with another fragment, a phenethylamine. This moiety may be a hydroxyphenethylamine, its oxidation product, or, most commonly, its dehydration product. Finally, attached to the amino group of the β-hydroxy-α-amino acid is an acyl unit derived from another amino acid or from a di- or tripeptide which contains the basic monomethylated or dimethylated amino group. The main structural features and the numbering of a 14-membered macrocycle are shown in Figure 1.

Cyclopeptide alkaloids are usually present as complex mixtures isolated from various parts of the plant. Yields from dried plants vary from 0.01 to 1% depending on the plant source, location, method of isolation, and the plant maturity. Therefore, the biological profile of this class of natural products is not well defined.

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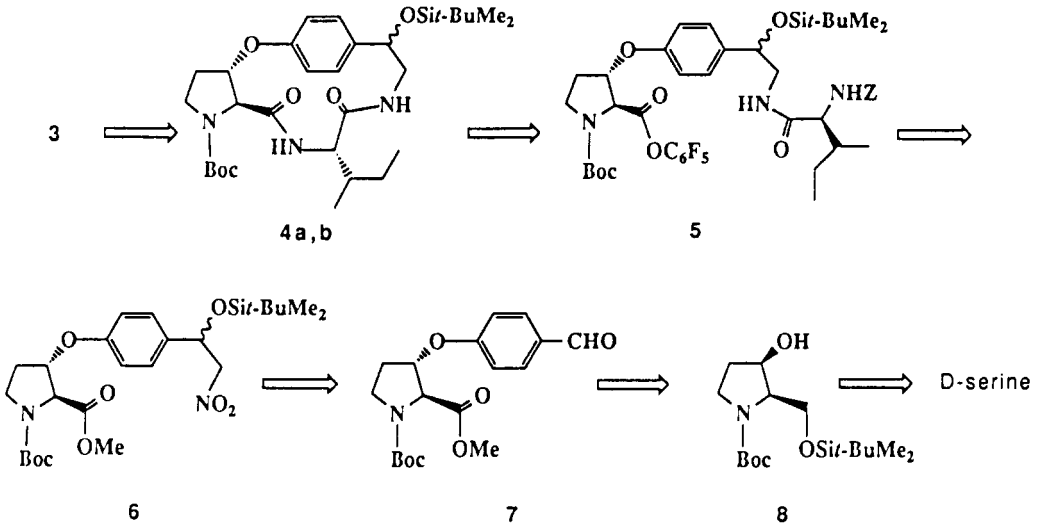
Scheme I



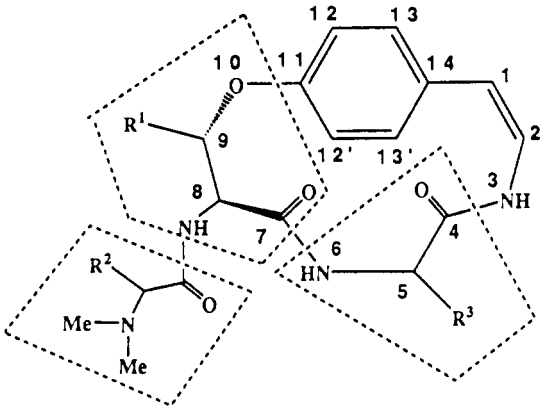
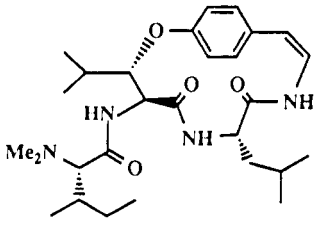


Figure 1. Structural features and numbering of a 14-membered cyclopeptide alkaloid.

Some cyclopeptides have been reported to show activity against Gram-positive bacteria and some fungi.[3] Others have been found to inhibit energy transfer in plants by interrupting photophosphorylation in isolated spinach chloroplasts.[10] Frangulanine (**2**), a 14-membered para ansa cyclopeptide, has exhibited selective



Frangulanine (2)

ionophoric properties by inducing mitochondrial swelling in KCl and RbCl solutions but not in solutions of NaCl or LiCl.[11] Recent studies report sedative or hypnotic properties for sanjoin, a cyclopeptide isolated from the seeds of the plant *Ziziphus vulgaris*, which has been used in Chinese medicine for the treatment of insomnia.[12,13] The limited supplies of cyclopeptide alkaloids obtained from dried plants have not been sufficient for extensive pharmacological investigations of this class of compounds. Therefore, efficient synthetic strategies are needed to produce larger amounts of these natural products.

Cyclopeptide alkaloids are deceptively simple molecules. Successful syntheses must provide a stereoselective route to the β-hydroxy-α-amino acid, an effective cyclization protocol, and the efficient introduction of the enamide unit. Since the initial synthetic approaches by French investigators,[14] numerous studies have been carried out in many laboratories. While many of these investigations did not produce a natural product, the strategies developed have been invaluable for the understanding of this challenging class of compounds. Although many aspects of the synthetic routes to cyclopeptide alkaloids have been examined, cyclization to a 14-membered ring has received the most attention. Rapoport et al. investigated the effect that substituted amides would have on the cyclization in model compounds.[15-17] In 1981, we completed the synthesis of a 14-membered dihydrocyclopeptide alkaloid (dihydromauritine A).[18] Lipshutz et al. designed a totally novel approach to cyclization utilizing [3.3]oxazolophanes as precursors.[19-21] In all of these investigations, the introduction of the styrylamide function had not been examined. Major contributions to the field were made by Schmidt et al., who completed the total syntheses of a 14-membered dihydrocyclopeptide alkaloid (dihydroziziphine G),[22] a 13-membered cyclopeptide alkaloid (ziziphine A),[22,23] and a 15-membered cyclopeptide alkaloid (mucronine B).[24,25] More recently, the same authors reported the total synthesis of the 14-membered natural product frangulanine (**2**).[26]

Nummularine F (**3**) was isolated in 1975 by Tschesche and

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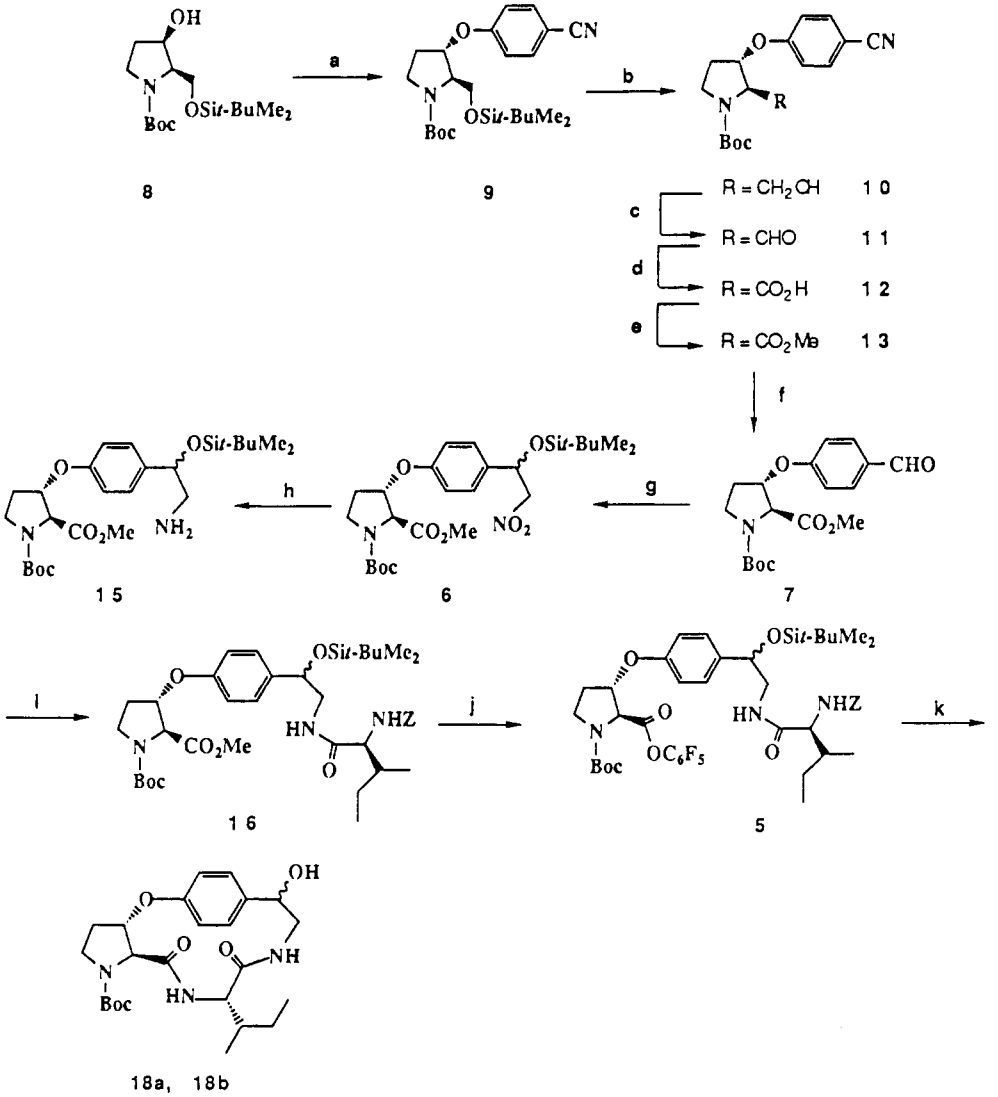
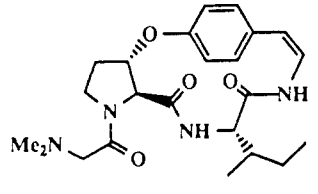
Scheme II[a]



[a] (a) *p*-Cyanophenol, Ph_3P, DEAD, THF, 10–25 °C, 78%. (b) HOAc:H_2O:THF (3:1:1), 45 °C, 91%. (c) TFAA, DMSO, CH_2Cl_2, Et_3N, −78 °C, 85%. (d) $KMnO_4$, NaH_2PO_4, *t*-BuOH, 5 °C, 93.5%. (e) DCC, DMAP, MeOH, CH_2Cl_2, 81%. (f) Raney Ni, $NaH_2PO_2{\cdot}H_2O$, pyridine:HOAc:H_2O (2:1:1), 40 °C, 78%. (g) (1) $MeNO_2$, NaOMe, 0–25 °C, 93%; (2) *t*-$BuMe_2SiCl$, DMF, imidazole, 25 °C, 72%. (h) HCO_2NH_4, MeOH, 10% Pd/C, 25 °C, 91%. (i) Z-L-Isoleucine, DCC, THF, HOBT, 91%. (j) (1) $LiOH{\cdot}H_2O$, H_2O, MeOH, 5 °C; (2) pentafluorophenol, DCC, CH_2Cl_2, 87% (2 steps). (k) (1) 10% Pd/C, cyclohexene, dioxane, 4-pyrrolidinopyridine, 95 °C, 1.5 h, 60–75%; (2) TBAF, THF, 25 °C, 90%.

co-workers from the benzene extract of the root bark of *Ziziphus nummularia*. Its structure was established from chemical and



Nummularine F (3)

spectral data.[27] No biological data were available for this natural product. As a continuation of our investigations of the total syntheses of 14-membered cyclopeptide alkaloids,[18,28,29] we chose to synthesize **3** and completed its total synthesis in 1990.[30]

Results and Discussion

Our first approach toward **3** utilized a Ugi four-component condensation.[31,32] Elaboration of the Ugi products afforded linear precursors for cyclization either at N-3,C-4 or at C-9,O-10. Both courses were unsuccessful, possibly because of the chosen cyclization sites. Therefore, we had to devise a new approach that would permit reaction at N-6,C-7, a position at which both we and the Schmidt group had previously cyclized successfully.

Our strategy for the synthesis of **3** is summarized in the retrosynthetic analysis presented in Scheme I. We envisioned introduction of the enamide unit in **3** after cyclization. This transformation was to be implemented by converting the benzylic hydroxyl group of a cyclic diastereomeric mixture (**4a**, **4b**) into an appropriate leaving group, which would favor elimination. The site of coupling was chosen to be the peptide linkage between the carboxyl function of the β-hydroxyproline unit and the amine of the isoleucine residue (N-6,C-7). Cyclization of the linear pentafluorophenyl ester **5** to the desired 14-membered ring required removal of the Z-protecting group from the amine of the isoleucine residue under catalytic transfer hydrogenolysis conditions. The needed acyclic precursor was to be derived from a reaction between

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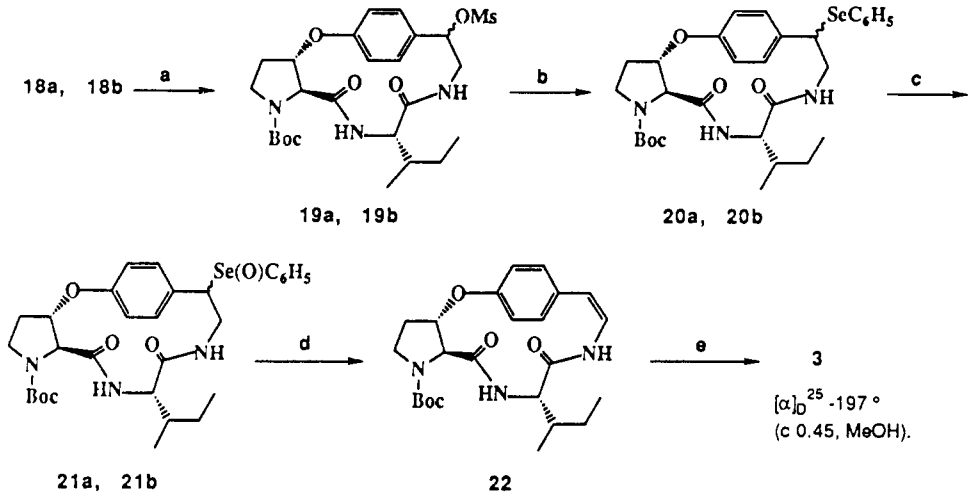
Scheme III[a]



[a] (a) MsCl, NEt_3, CH_2Cl_2, −5 °C. (b) Diphenyl diselenide, $NaBH_4$, ethanol, 5 °C–80 °C, 67% (2 steps). (c) H_2O_2, pyridine, CH_2Cl_2, 25 °C, 80%. (d) Benzene, 60 °C, 53%. (e) (1) TFA, CH_2Cl_2, 5 °C; (2) *N,N*-Dimethylglycine, DCC, 25 °C, 17% (2 steps).

the Z-protected L-isoleucine residue and the product resulting from the reduction of the nitro group. Intermediate **6** was obtained via a Henry reaction between the aromatic aldehyde **7** and the anion of nitromethane, followed by protection of the hydroxyl group as its silyl ether. Installation of the *trans*-aryloxy ether linkage hinged on a successful inversion of configuration at the C-3 hydroxyl center of the protected *cis*-2-(hydroxymethyl)-3-pyrrolidinol **8**, using Mitsunobu reaction conditions. The protected 1,3-diol **8** was a key intermediate and was prepared by a route developed in our laboratory[33] which utilized D-serine as the source of chirality.

The steps from D-serine to **8** have already been described.[33,34] Continuation of the synthesis is shown in Scheme II. The stereochemistry at the 3-hydroxyl center was inverted using *p*-cyanophenol, triphenylphosphine, and diethyl azodicarboxylate at 10–25 °C to afford **9** in 78% yield. The trans stereochemistry of **9** was confirmed by an X-ray analysis and ^1H NMR decoupling experiments. The silyl ether was cleaved in a 3:1:1 mixture of acetic acid, water, and tetrahydrofuran to give the alcohol **10**, which was oxidized to the carboxylic acid, in a sequential manner. Treatment of the alcohol under Swern conditions furnished the aldehyde **11**, which was oxidized to the acid **12** employing the protocol described by Masamune.[35] Esterification of the acid was carried out using 1,3-dicyclohexylcarbodiimide (DCC) and methanol[36] to afford **13**.

The cyano group of the *p*-cyanoaryl ether was converted to the corresponding aldehyde **7** using Raney nickel and sodium hypophosphite hydrate (which serves as a hydrogen source) in a buffered pyridine, acetic acid, and water medium.[29,37] Addition of the sodium anion of nitromethane to the aldehyde at low temperature,[38] gave an inseparable mixture of epimeric benzyl alcohols containing a terminal nitro group (**14**) that served as the latent amino function. The diastereomers could not be separated at this stage and were used as a mixture in the next steps until separation could be effected. The existence of diastereomers, epimeric at the benzylic position, was not a problem since they had to be converted to the same enamide moiety. The hydroxyl function was protected as the *tert*-butyldimethylsilyl ether under standard conditions to give a mixture of diastereomers (**6**).

Reduction of the nitro group to an amino group (**15**) was accomplished with ammonium formate over 10% palladium on carbon in methanol.[29] The diastereomeric mixture of amines was coupled with Z-L-isoleucine to give **16** using 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole hydrate (HOBT). The methyl ester of **16** was then saponified with lithium hydroxide in aqueous methanol to give **17**, followed by formation of the pentafluorophenyl ester **5** employing pentafluorophenol and 1,3-dicyclohexylcarbodiimide in methylene chloride.

Cyclization of the active ester to the desired macrocycle was effected by utilizing a modification of Schmidt's method[39,40] which removed the Z-protecting group by catalytic transfer hydrogenolysis over 10% palladium on carbon, under high dilution conditions in dioxane at 95 °C. We devised a more convenient protocol using cyclohexene or cyclohexadiene as the hydrogen source to produce a slow evolution of hydrogen in the presence of the catalyst. Cyclization gave a 60–75% yield of diastereomers (**4a**, **4b**) in a 1:1 ratio. Tetrabutylammonium fluoride removed the silyl groups to provide the corresponding alcohols (**18a**, **18b**).

For the last crucial step in the synthesis (Scheme III), the introduction of the enamide, each epimeric alcohol was used independently. Elimination to the olefin could not be accomplished directly using Martin's sulfurane or via the standard two-step selenium route, which utilizes tributylphosphine and *o*-nitrophenyl selenocyanate followed by oxidation to the selenoxides.[41] This resistance to dehydration may be due to the fact that the incipient double bond is not conjugated to the aromatic ring and, therefore, does not benefit from the driving force resulting from conjugation. However, the alcohols afforded the corresponding mesylates when treated with methanesulfonyl chloride and triethylamine in methylene chloride at −5 °C. The mesylates (**19a**, **19b**) were unstable and were converted directly to the corresponding phenyl selenides (**20a**, **20b**) by treatment with sodium phenyl selenide in refluxing ethanol in 67% and 72% isolated yields, respectively, from the corresponding alcohols. Both selenides were oxidized to their corresponding selenoxides (**21a**, **21b**). One selenoxide was unstable and underwent rapid elimination to the desired macrocycle **22** in 53% isolated yield. The other selenoxide was stable to elimination at 25 °C and was shown to be a mixture of diastereomers differing in their configurations at selenium. The best conditions for the elimination were heating in benzene at 60 °C. An interesting observation in these investigations was that of the differences in ^1H NMR and ^{13}C NMR spectra of the acyclic and cyclic intermediates as compared to the unsaturated products. Introduction of the double bond removes the degrees of freedom

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Table I. ^{1}H NMR[a] and ^{13}C NMR[b] of (-)-Nummularine F

amino acid residue	^{1}H NMR			^{13}C NMR
N,N-dimethylglycine	N-CH_3	C-H_2		C=O[c] 170.7
δ	s, 2.28	AB q, 3.04, 3.15		C-α 61.6
J		14.2		N-Me 45.2
3-hydroxyproline	α, C-H	β, C-H	γ, C-H_{proR}	C=O[c] 170.7
δ	d, 4.29	m, 5.56-5.61	m, 2.11-2.16	C-α 63.8
J	5.4 (α,β)	7.1 (β,γ_{proR})	5.4 (γ_{proR},δ_{proS})	C-β 83.7
		9.8 (β,γ_{proS})	10.6(γ_{proR},γ_{proS})	C-γ 32.1
				C-δ 46.4
δ	γ, C-H_{proS}	δ, C-H_{proR}	δ, C-H_{proR}	
	m, 2.55-2.60	m, 3.42-3.48	dd, 4.08	
J	12.9 (γ_{proS},δ_{proS})		8.3 (γ_{proR},δ_{proR})	
			11.5 (δ_{proS},δ_{proR})	
isoleucine	N-H	α, C-H	β, C-H	C=O[c] 169.1
δ	d, 6.62	dd, 4.18	m, 2.17-2.25	C-α 58.9
J		8.7 (N,α), 3.1 (α,β)		C-β 35.2
δ	γ, C-CH_3	γ, C-H_2	δ, C-H_3	C-γ, Me 15.9
	d, 0.75	m, 1.08-1.24	t, 0.85	C-γ 23.7
J	6.9 (Me,β)		7.3 (γ,δ)	C-δ 12.2
styrylamide[d]	N-H	α, C-H	β, C-H	C-α 125.5
δ	d, 6.52	dd, 6.76	d, 6.30	C-β 114.3
J		7.8 (α,β)		C-γ 157.4
		10.6 (N,α)		C-δ 122.8
δ	aromatic			C'-δ 130.3
	m, 7.10-7.30			C-ϵ 122.9
				C'-ϵ 132.5
				C-ζ 167.0

[a] Spectra recorded in $CDCl_3$ at 500 MHz. J is given in hertz and δ values in ppm. Assignments were obtained by correlation analysis (COSY). [b] Spectra recorded in $CDCl_3$ at 125 MHz. J is given in hertz and δ values in ppm. Assignments were obtained by correlation analysis (Hetcorr). [c] Peaks could not be unambiguously assigned by Hetcorr. [d] The carbons of styrylamide are named in analogy to phenylalanine.

that allow for conformational equilibria in the preceding intermediates. After cyclization, both ^{1}H NMR and ^{13}C NMR spectra are well resolved and show no evidence of conformational isomers.

Treatment of the unsaturated macrocycle **22** with trifluoroacetic acid in methylene chloride at 5 °C removed the Boc group to afford the deprotected intermediate **23** in a disappointing 28% yield. The difficulty in removing this group probably indicates steric hindrance or hydrogen bonding at this position. Support for hydrogen bonding is found in the ^{1}H NMR of **3**, which exhibits an AB quartet for the methylene group of *N,N*-dimethylglycine. Coupling of the macrocycle with *N,N*-dimethylglycine in the presence of 1,3-dicyclohexylcarbodiimide provided nummularine F in 59% isolated yield.

The pivotal transformations of this approach were (1) a stereoselective synthesis of the *cis*-2-(hydroxymethyl)-3-pyrrolidinol derivative, (2) the inversion of the *cis*-3-hydroxyl function, under Mitsunobu conditions, to the desired β-aryl ether, (3) cyclization to a pair of rigid para ansa 14-membered cyclopeptides, and (4) installation of the double bond of the enamide unit. The synthesis of the 14-membered para ansa cyclopeptide alkaloid nummularine F (**3**) from D-serine was accomplished in 25 steps and an overall yield of 0.48%.

A sample of the natural product was not available, and the only physical data on this compound were those of its rotation and mass spectrum. Therefore, we carried out extensive NMR studies in addition to the usual characterization protocol. We have obtained the first COSY of a cyclopeptide alkaloid to identify all four amino acid residues. We used a DEPT experiment to assign the individual signals due to methyl, methylene, methine, or quaternary carbons and a 2D ^{1}H-^{13}C NMR chemical shift correlation (Hetcorr) to further confirm the ^{1}H assignments, especially those for geminal protons. The carbon peaks of C-1,C-2, and C-12,C-12′,C-13,C-13′ could only be assigned from the Hetcorr spectrum since these peaks were all in the 114-134 ppm range. The Hetcorr experiment allowed for the correct assignment of these aromatic and double bond carbons. The ^{1}H NMR and ^{13}C NMR assignments are summarized in Table I.

Experimental Section

General Procedures. All solvents were reagent grade and were distilled before use. Ethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Benzene, methylene chloride, toluene, and triethylamine were distilled from calcium hydride. *N,N*-Dimethylformamide (DMF) was distilled from phosphorus pentoxide. Nitromethane was dried over calcium chloride and then distilled. Organic acids and bases were reagent grade. Melting points were determined with a Thomas-Hoover melting point apparatus. They are expressed in degrees centigrade (°C) and are uncorrected. Optical rotations (in degrees) were measured with a Perkin-Elmer Model 241 polarimeter at the sodium D line. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker/IBM AC-250 (250 MHz) or a Bruker AMX-500 (500 MHz) spectrometer. Chemical shifts are measured in parts per million (ppm) relative to tetramethylsilane (TMS) or chloroform as the internal standard. Coupling constants (J values) are in hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), AB quartet (AB q), or multiplet (m). The multiplicities in the nummularine F carbon spectrum were obtained from ^{1}H-^{13}C correlations (Hetcorr and DEPT). The presence of conformational isomers is noted with the abbreviation C.I. Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrometer. Solid samples were analyzed as potassium bromide (KBr) disks or as chloroform ($CHCl_3$) solutions in sodium chloride cells. Absorptions are reported in wavenumbers (cm^{-1}), and intensities are designated as broad (b), strong (s), medium (m), or weak (w). The spectra taken were referenced to the 1601 cm^{-1} band of polystyrene. High-resolution mass spectra (HRMS) were obtained on either a VG 70-70HS or a VG ZAB-E, both high-resolution, double focusing mass spectrometers, using either chemical ionization (CI) or fast atom bombardment (FAB) using a cesium (Cs) ion gun. The mass spectrometers were interfaced with a VG/DEC 11-73 data system. The mass spectra were obtained at the University of Pennsylvania Analytical Facilities. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60F-254) plates (0.25 mm), percoated with a fluorescent indicator. Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in absolute ethanol containing 2% acetic acid, phosphomolybdic acid reagent (7% w/v) in 95% ethanol, or (2,4-dinitrophenyl)hydrazine reagent (2.6% w/v) in 95% ethanol:water:concentrated sulfuric acid (25:7:5). Flash column chromatography was carried out on E. Merck silica gel 60 (240-400 mesh) using the solvent systems listed under the individual experiments.

(2*R*,3*S*)-3-(4-Cyanophenoxy)-2-[[((1,1-dimethylethyl)dimethylsilyl)oxy]methyl]-1-[(1,1-dimethylethoxy)carbonyl]pyrrolidine (9). To a solution of compound **8** (7.45 g, 22.5 mmol), triphenylphosphine (7.70 g, 29.2 mmol), and *p*-cyanophenol (3.66 g, 29.2 mmol) in THF (75 mL) at -10 °C was added a solution of diethyl azodicarboxylate (DEAD) (5.78 g,

31.5 mmol) in THF (75 mL) over a 2-h period. After the addition was completed, the reaction was allowed to warm to 25 °C and stirred for 18 h. The reaction mixture was concentrated under reduced pressure to give a crude residue which was purified by column chromatography, eluting with petroleum ether:EtOAc (95:5 to 90:10). Pure **9** (7.52 g, 78% yield) was obtained as a colorless oil which crystallized upon cooling: mp 95–97 °C; R_f 0.25 (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ −40.6° (*c* 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 and 0.10 (6 H, 2 s, C.I.), 0.93 and 0.94 (9 H, 2 s, C.I.), 1.45 and 1.46 (9 H, 2 s, C.I.), 2.12–2.19 (1 H, m), 2.21–2.28 (1 H, m), 3.38–3.56 (2 H, m), 3.56–3.63 (1 H, m), 3.85–4.04 (2 H, m), 4.90–4.95 (1 H, m), 7.06–7.09 (2 H, m), 7.54–7.57 (2 H, m); ^{13}C NMR (125 MHz, C_6D_6) δ −5.3, 5.4, 18.3, 25.9, 28.4, 29.9, 45.3, 62.7 and 63.3 (C.I.), 64.2, and 65.5 (C.I.), 79.1 and 79.7 (C.I.), 79.4 and 79.5 (C.I.), 105.0 and 105.1 (C.I.), 116.1, 119.0, 133.9, 154.0 and 154.4 (C.I.), 160.5; IR ($CHCl_3$) 2960 (m), 2900 (w), 2870 (m), 2230 (m), 1690 (s), 1605 (s), 1500 (w), 1470 (w), 1400 (s), 1365 (m), 1250 (s), 1170 (m), 1120 (m), 1090 (m), 1000 (w), 980 (w), 905 (w), 870 (w), 835 (s) cm^{-1}; HRMS calcd for $C_{23}H_{37}N_2O_4Si$ (M + H) 433.251, found 433.252.

(2*R*,3*S*)-3-(4-Cyanophenoxy)-2-(hydroxymethyl)-1-[(1,1-dimethylethoxy)carbonyl]pyrrolidine (10). To a solution of compound **9** (9.50 g, 21.9 mmol) in THF (47.5 mL) at 20 °C were added glacial acetic acid (143 mL) and water (37.5 mL). The reaction mixture was heated at 45 °C for 18 h. After this time, the reaction mixture was concentrated under reduced pressure, and the excess water and acetic acid were removed by azeotropic distillation with toluene. The resulting crude oil was purified by column chromatography, eluting with petroleum ether:EtOAc (70:30 to 60:40). Pure **10** (6.34 g, 91% yield) was obtained as an oil which crystallized upon cooling: mp 128–130 °C; R_f 0.44 (petroleum ether:EtOAc 50:50); $[\alpha]^{20}_D$ −34.7° (*c* 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (9 H, s), 2.11–2.16 (1 H, m), 2.18–2.23 (1 H, m), 3.18 (1 H, bs), 3.54–4.08 (5 H, m), 4.77 and 4.95 (1 H, 2 bs, C.I.), 7.00–7.05 (2 H, m), 7.57–7.59 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 29.4, 44.9, 62.8, 64.4, 78.8, 80.3, 104.1, 116.0, 119.0, 133.9, 155.3, 160.5; ^{13}C NMR (125 MHz, C_6D_6) δ 28.4 and 28.8 (C.I.), 29.5, 45.2, 62.9, 64.7 and 65.1 (C.I.), 78.7, 79.8 and 80.0 (C.I.), 104.9, 116.1, 119.1, 133.9, 155.5, 160.4; IR ($CHCl_3$) 3610 (w), 3430 (m), 2995 (m), 2910 (w), 2215 (m), 1680 (s), 1610 (s), 1575 (w), 1505 (m), 1480 (w), 1410 (s), 1370 (s), 1285 (m), 1255 (s), 1170 (s), 1125 (m), 1095 (w), 1065 (w), 1035 (w), 980 (m), 905 (w), 835 (m) cm^{-1}; HRMS calcd for $C_{17}H_{23}N_2O_4$ (M + H) 319.166, found 319.163. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.12; H, 6.97. Found: C, 64.19; H, 6.95.

(2*S*,3*S*)-3-(4-Cyanophenoxy)-1-[(1,1-dimethylethoxy)carbonyl]prolinal (11). To a precooled solution of methylene chloride (3 mL) and dimethyl sulfoxide (0.21 mL, 3.1 mmol) at −78 °C was added trifluoroacetic anhydride (0.33 mL, 2.3 mmol). After 1 h, compound **10** (0.50 g, 1.6 mmol) in methylene chloride (3 mL) was added over a period of 5 min. The reaction mixture was stirred at −78 °C for 1 h, at which time triethylamine (0.65 mL, 4.7 mmol) was added. The resulting solution was warmed to 25 °C, quenched with saturated aqueous NaCl solution (3 mL), and extracted twice with ethyl ether (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude oil. The oil was purified by column chromatography, eluting with methylene chloride:acetone (98:2). Pure aldehyde **11** (0.42 g, 85% yield) was obtained as an oil which crystallized upon cooling: mp 139–141 °C; R_f 0.38 (methylene chloride:acetone (95:5); $[\alpha]^{20}_D$ −73.6 (*c* 1.09, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 and 1.50 (9 H, 2 s, C.I.), 2.05–2.07 (1 H, m), 2.23–2.26 (1 H, m), 3.60–3.82 (2 H, m), 4.26 and 4.46 (1 H, 2 s, C.I.), 4.98–5.29 (1 H, m), 7.02–7.05 (2 H, m), 7.60–7.64 (2 H, m), 9.65–9.69 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 and 28.3 (C.I.), 30.3 and 31.0 (C.I.), 44.8 and 45.0 (C.I.), 70.3 and 70.5 (C.I.), 78.7, 81.3, 105.1 and 105.2 (C.I.), 115.9, 118.8, 134.2 and 134.3 (C.I.), 153.7 and 154.9 (C.I.), 159.9, 199.7 and 199.9 (C.I.); IR ($CHCl_3$) 2995 (m), 2945 (w), 2905 (w), 2830 (w), 2245 (m), 1730 (m), 1690 (s), 1605 (m), 1575 (w), 1500 (m), 1475 (w), 1390 (s), 1370 (s), 1320 (w), 1295 (w), 1280 (w), 1245 (s), 1175 (s), 1125 (s), 1095 (m), 1060 (w), 980 (m), 825 (m) cm^{-1}; HRMS calcd for $C_{17}H_{24}N_3O_4$ (M + NH_4) 334.172, found 334.169.

(2*S*,3*S*)-3-(4-Cyanophenoxy)-1-[(1,1-dimethylethoxy)carbonyl]proline (12). To a solution of compound **11** (4.74 g, 14.9 mmol) in *tert*-butyl alcohol (89 mL), methylene chloride (10 mL), and 1.25 M $NaH_2PO_4 \cdot H_2O$ buffer (59.6 mL) at a pH of 4.0–4.5 was added an aqueous solution of 1 M $KMnO_4$ (89 mL) at 25–30 °C. The reaction was allowed to proceed for 15 min, at which time it was cooled to 5 °C and excess $KMnO_4$ was added. The reaction was quenched with the addition of a saturated solution of Na_2SO_3 (40 mL). Acidification to pH 3.0–3.5 with 2 N HCl solution (75 mL) at 5 °C dissolved all of the solid MnO_2 formed. The resulting solution was extracted three times with ethyl ether (150 mL) at 5 °C. The organic layers were combined and extracted with a 0.3 M $NaHCO_3$ solution (200 mL and 100 mL, respectively). The aqueous layers were combined, acidified with 2 N HCl at 5 °C to pH 3.0–3.5, and extracted with ethyl ether (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide compound **12** as a crude solid (4.63 g, 94% yield). The solid was purified by dissolving it in a minimum amount of ethyl ether at 25 °C and then precipitating it with excess hexane: mp 143–144.5 °C; R_f 0.45 (methylene chloride:methanol:concentrated NH_4OH 80:20:1); $[\alpha]^{20}_D$ −43.0° (*c* 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 and 1.51 (9 H, 2 s, C.I.), 2.21–2.30 (2 H, m), 3.61–3.81 (2 H, m), 4.42 and 4.51 (1 H, 2 s, C.I.), 5.01 and 5.30 (1 H, 2 s, C.I.), 7.00–7.05 (2 H, m), 7.61–7.63 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 and 28.3 (C.I.), 29.3 and 30.3 (C.I.), 44.5 and 45.1 (C.I.), 65.3, 79.0 and 80.2 (C.I.), 80.8 and 81.5 (C.I.), 104.7 and 104.8 (C.I.), 115.9, 118.8, 134.1, 153.9 and 155.7 (C.I.), 159.9, 173.2 and 173.9; IR ($CHCl_3$) 2980 (s), 2238 (m), 1744 (s), 1728 (s), 1693 (s), 1608 (s), 1500 (m), 1476 (m), 1399 (s), 1368 (s), 1323 (w), 1282 (m), 1248 (s), 1170 (s), 1133 (s), 1092 (m), 1048 (w), 988 (m), 890 (w), 832 (m) cm^{-1}; HRMS calcd for $C_{17}H_{21}N_2O_5$ (M + H) 333.145, found 333.146.

Methyl (2*S*,3*S*)-3-(4-Cyanophenoxy)-1-[(1,1-dimethylethoxy)carbonyl]prolinate (13). To a solution of compound **12** (4.63 g, 13.9 mmol), 4-(*N*,*N*-dimethylamino)pyridine (0.169 g, 1.39 mmol), and methanol (0.620 g, 15.3 mmol) in methylene chloride (69.5 mL) at 24 °C was added dicyclohexylcarbodiimide (DCC) (3.16 g, 15.3 mmol). During the addition, the temperature initially rose to 32 °C but dropped again to 24 °C within 20 min. After 3 h, ethyl ether was added to precipitate dicyclohexylurea, which was then collected by filtration. The filtrate was concentrated under reduced pressure to afford a crude residue which was purified by column chromatography, eluting with petroleum ether:EtOAc (80:20 to 70:30). Pure compound **12** (3.90 g, 81% yield) was obtained as a colorless oil: R_f 0.26 (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ +20.6° (*c* 1.15, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 and 1.40 (9 H, 2 s, C.I.), 2.06–2.21 (2 H, m), 3.39–3.48 (1 H, m), 3.56–3.64 (1 H, m), 3.73 and 3.75 (3 H, 2 s, C.I.), 4.23 and 4.28 (1 H, 2 s, C.I.), 5.23–5.24 and 5.28–5.29 (1 H, 2 m, C.I.), 7.16–7.18 (2 H, m), 7.81–7.84 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0 and 28.2 (C.I.), 29.5 and 30.3 (C.I.), 44.3 and 44.5 (C.I.), 52.4 and 52.6 (C.I.), 64.3 and 64.7 (C.I.), 78.9, 79.9 and 80.3 (C.I.), 104.7 and 104.8 (C.I.), 115.9, 118.7, 133.9 and 134.0 (C.I.), 153.3 and 154.2 (C.I.), 159.2 and 159.8 (C.I.), 170.1 and 170.4 (C.I.); IR ($CHCl_3$) 3026 (w), 3001 (w), 2990 (m), 2966 (m), 2886 (w), 2236 (m), 1756 (s), 1706 (s), 1686 (s), 1606 (m), 1573 (w), 1499 (w), 1476 (w), 1451 (w), 1436 (w), 1397 (s), 1366 (s), 1336 (w), 1286 (w), 1245 (s), 1166 (s), 1126 (m), 1092 (w), 1047 (w), 986 (m), 921 (w), 901 (w), 882 (w), 831 (m) cm^{-1}; HRMS calcd for $C_{18}H_{23}N_2O_5$ (M + H) 347.161, found 347.160.

Methyl (2*S*,3*S*)-3-(4-Formylphenoxy)-1-[(1,1-dimethylethoxy)carbonyl]prolinate (7). To a solution of compound **13** (3.80 g, 10.9 mmol), $NaH_2PO_2 \cdot H_2O$ (7.60 g, 86.3 mmol) in water (38 mL), pyridine (71 mL), and acetic acid (38 mL) at 5 °C was added Raney nickel (2.50 g). This mixture was heated at 40 °C for 2 h, at which time it was cooled to 25 °C and filtered through a bed of Celite. The solids were collected and rinsed with methanol. The resulting filtrate was concentrated under reduced pressure, and the residue was diluted with ethyl ether (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl ether (50 mL). The organic layers were combined and concentrated under reduced pressure to provide a crude residue which was azeotroped with toluene to remove excess pyridine and acetic acid. The residue was purified by column chromatography, eluting with petroleum ether:acetone (80:20). Pure compound **7** (2.98 g, 78% yield) was obtained as a colorless oil: R_f 0.31 (petroleum ether:acetone 80:20); $[\alpha]^{20}_D$ +27.5° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 and 1.47 (9 H, 2 s, C.I.), 2.20–2.24 (2 H, m), 3.61–3.80 (2 H, m), 3.83 and 3.84 (3 H, 2 s, C.I.), 4.42 and 4.59 (1 H, 2 s, C.I.), 4.96–4.97 (1 H, m), 7.07–7.09 (2 H, m), 7.85–7.87 (2 H, m), 9.91–9.92 (1 H, m, C.I.); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9 and 28.1 (C.I.), 29.5 and 30.2 (C.I.), 44.2 and 44.5 (C.I.), 52.3 and 52.5 (C.I.), 64.4 and 64.8 (C.I.), 78.8, 79.9 and 80.1 (C.I.), 115.4, 130.3, 131.8, 153.3 and 154.1 (C.I.), 161.3 and 161.4 (C.I.), 170.2 and 170.4 (C.I.), 190.4; IR ($CHCl_3$) 3036 (w), 3016 (w), 2991 (m), 2966 (w), 2941 (w), 2911 (w), 2846 (w), 1751 (s), 1686 (s), 1601 (s), 1576 (m), 1501 (w), 1476 (w), 1446 (w), 1434 (w), 1405 (s), 1366 (m), 1336 (w), 1300 (w), 1282 (w), 1244 (s), 1161 (s), 1126 (m), 1091 (w), 1046 (w), 986 (m), 886 (w), 851 (m), 826 (m) cm^{-1}; HRMS calcd for $C_{18}H_{24}NO_6$ (M + H) 350.161, found 350.160.

Methyl (2*S*,3*S*)-3-[4-(2-Nitro-1-hydroxyethyl)phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]prolinate (14). A solution of sodium methoxide was generated by the addition of sodium metal (0.600 g, 25.6 mmol) to anhydrous methanol (7.00 mL, 0.173 mol) and heated at reflux for 30 min. To this solution at 5 °C was added nitromethane (17.0 mL, 0.310 mol), followed by the addition of compound **7** (2.98 g, 8.53 mmol). The resulting mixture was allowed to warm to 25 °C. After being stirred for 7 h, the reaction mixture was cooled to 5 °C and quenched with saturated

NH_4Cl solution (50 mL), followed by extraction with ethyl ether (50 mL, 3 times). The organic layers were combined, washed with saturated Na_2SO_4, filtered, and concentrated under reduced pressure to afford a mixture of diastereomers **14** as a crude oil (3.20 g, 93% yield) which was purified by column chromatography, eluting with petroleum ether:EtOAc (80:20): R_f 0.13 (petroleum ether:EtOAc 80:20); $[\alpha]^{20}_D$ +15.2° (*c* 0.71, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 and 1.46 (9 H, 2 s, C.I.), 2.16–2.23 (2 H, m), 2.93–2.97 (1 H, m), 3.59–3.78 (2 H, m), 3.80 (3 H, s), 4.39 and 4.45 (1 H, 2 s, C.I.), 4.47–4.51 (1 H, m), 4.58–4.64 (1 H, m), 4.85 (1 H, s), 5.42–5.43 (1 H, m), 6.98–6.99 (2 H, m), 7.34–7.37 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 and 28.3 (C.I.), 29.6 and 30.3 (C.I.), 44.4 and 44.7 (C.I.), 52.6 and 53.4 (C.I.), 64.4, and 64.9 (C.I.), 70.4, 78.7 and 79.7 (C.I.), 80.3 and 80.4 (C.I.), 81.2 and 81.3 (C.I.), 115.7, 127.5, 131.6, 153.7 and 154.4 (C.I.), 156.8, 170.7 and 170.9 (C.I.); IR ($CHCl_3$) 3610 (w), 2990 (m), 1750 (s), 1690 (s), 1610 (w), 1585 (w), 1555 (s), 1510 (m), 1480 (w), 1450 (w), 1440 (w), 1400 (s), 1370 (m), 1335 (w), 1240 (s), 1170 (s), 1130 (m), 1090 (w), 990 (m), 890 (w), 830 (m) cm^{-1}; HRMS calcd for $C_{19}H_{30}N_3O_8$ (M + NH_4) 428.203, found 428.201.

Methyl (2*S*,3*S*)-3-[4-[2-Nitro-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]prolinate (6). To a solution of compound **14** (3.50 g, 8.53 mmol) in *N*,*N*-dimethylformamide (DMF) (28 mL) at 5 °C were added *tert*-butyldimethylsilyl chloride (3.34 g, 22.2 mmol) and imidazole (2.90 g, 42.6 mmol). This solution was allowed to warm to 25 °C and stirred for 24 h. After this time, the reaction mixture was diluted with water (50 mL) and extracted twice with EtOAc (150 and 50 mL, respectively). The organic layers were combined, washed with 1 N $KHSO_4$ solution (100 mL) followed by a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide a crude oil. The oil was purified by column chromatography, eluting with petroleum ether:EtOAc (90:10 to 80:20) to afford a pure mixture of diastereomers (**6**, 3.20 g, 72% yield) as a colorless oil: R_f 0.27 (petroleum ether:EtOAc 80:20); $[\alpha]^{20}_D$ +14.4 (*c* 1.78, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.14 and 0.03 (6 H, 2 s, C.I.), 0.84 (9 H, s), 1.39 and 1.47 (9 H, 2 s, C.I.), 2.17–2.23 (2 H, m), 3.59–3.78 (2 H, m), 3.80–3.82 (3 H, m), 4.33–4.37 (1 H, m), 4.41 and 4.44–4.47 (1 H, s and m, C.I.), 4.49–4.55 (1 H, m), 4.83–4.85 (1 H, m), 5.36–5.39 (1 H, m), 6.94–6.97 (2 H, m), 7.31–7.33 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.6, −4.8 and −4.7 (C.I.), 17.9, 25.5, 28.2 and 28.4 (C.I.), 29.7 and 30.5 (C.I.), 44.5 and 44.8 (C.I.), 52.4 and 52.6 (C.I.), 64.5 and 65.1 (C.I.), 72.2, 78.7 and 79.9 (C.I.), 80.7, 82.8, 115.5 and 115.6 (C.I.), 127.5 and 127.6 (C.I.), 132.4, 154.4, 156.8 and 156.9 (C.I.), 170.7 and 170.9 (C.I.); IR ($CHCl_3$) 2970 (m), 2950 (m), 2910 (m), 2880 (m), 1755 (s), 1695 (s), 1615 (m), 1590 (w), 1560 (s), 1510 (m), 1475 (w), 1455 (w), 1440 (w), 1410 (s), 1370 (s), 1340 (w), 1290 (w), 1240 (s), 1170 (s), 1120 (m), 1100 (s), 990 (m), 965 (m), 835 (s) cm^{-1}; HRMS calcd for $C_{25}H_{44}N_3O_8Si$ (M + NH_4) 542.289, found 542.282.

Methyl (2*S*,3*S*)-3-[4-[2-Amino-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]prolinate (15). To a solution of compound **6** (3.10 g, 5.91 mmol) in methanol (35 mL) at 5 °C were added ammonium formate (1.86 g, 29.5 mmol) and 10% palladium on carbon (0.930 g). The reaction was allowed to warm to 25 °C, where it was stirred for 4 h. After this time, the reaction mixture was filtered through a bed of Celite, and then the solids were collected and washed with methanol. The filtrate was concentrated under reduced pressure to afford a crude residue which was diluted with saturated NaCl solution (100 mL) and extracted twice with EtOAc (50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude oil. This oil was purified by column chromatography, eluting with methylene chloride:methanol (98:2 to 95:5 to 90:10) to give an inseparable diastereomeric mixture (**15**, 2.65 g, 91% yield) as a colorless oil: R_f 0.26 (methylene chloride:methanol:concentrated NH_4OH 95:5:0.1); $[\alpha]^{20}_D$ +15.7° (*c* 1.63, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.15 and 0.13 (6 H, 2 s, C.I.), 0.88 (9 H, s), 1.39 and 1.46 (9 H, 2 s, C.I.), 2.03–2.18 (2 H, m), 2.94–3.00 (2 H, m), 3.59–3.77 (2 H, m), 3.79–3.80 (3 H, m), 4.41 and 4.56 (1 H, 2 s, C.I.), 4.82–4.87 (2 H, m), 5.80–6.30 (2 H, bs), 6.90–6.92 (2 H, m), 7.27–7.28 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.8, 17.9, 25.8, 28.1 and 28.2, 29.6 and 30.4, 44.4 and 44.7, 49.0, 52.3 and 52.5 (C.I.), 64.5 and 64.9 (C.I.), 73.5, 78.7 and 79.8 (C.I.), 80.1, 115.2, 127.5, 134.7, 153.6 and 154.3 (C.I.), 156.2, 170.7 and 170.9 (C.I.); IR ($CHCl_3$) 3600–3100 (b), 2970 (m), 2950 (m), 2910 (m), 2880 (m), 1750 (s), 1695 (s), 1610 (m), 1590 (w), 1510 (m), 1475 (m), 1465 (m), 1440 (m), 1410 (s), 1370 (s), 1350 (w), 1240 (s), 1170 (s), 1130 (m), 1090 (s), 990 (m), 960 (m), 940 (w), 915 (w), 890 (w), 870 (w), 835 (m) cm^{-1}; HRMS calcd for $C_{25}H_{43}N_2O_6Si$ (M + H) 495.289, found 495.293.

Methyl (2*S*,3*S*)-3-[4-[2-(*N*-(*N*-Carbobenzoxy-(*S*)-isoleucyl)-amino)-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]prolinate (16). To a solution of compound **15** (1.07 g, 2.16 mmol) and L-*N*-Z-isoleucine (0.630 g, 2.37 mmol) in methylene chloride (39 mL) at 25 °C were added 1,3-dicyclohexylcarbodiimide (DCC) (0.490 g, 2.37 mmol) and 1-hydroxybenzotriazole hydrate (HOBT) (0.390 g, 2.87 mmol). This solution was cooled to 5 °C, followed by the addition of *N*-methylmorpholine (NMM) (0.260 mL, 2.37 mmol), after which time the reaction was allowed to warm to 25 °C. After 3 h, the reaction mixture was filtered through a bed of Celite, and then the solids were collected and washed with methylene chloride. The filtrate was concentrated under reduced pressure to provide a crude residue which was purified by column chromatography, eluting with petroleum ether:EtOAc (80:20 to 75:25 to 70:30) to afford pure **16** (1.46 g, 91% yield) as a colorless oil: R_f 0.75 (methylene chloride:methanol 90:10); $[\alpha]^{20}_D$ −47.0 (*c* 2.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.16–(−0.14) and 0.00–0.01 (6 H, 2 m, C.I.), 0.80–1.04 (16 H, m), 1.37–1.44 (10 H, m), 1.85–1.87 (1 H, m), 2.12–2.18 (2 H, m), 3.25–3.73 (4 H, m), 3.76 and 3.77 (3 H, 2 s, C.I.), 3.93–3.96 (1 H, m), 4.39 and 4.54 (1 H, 2 s, C.I.), 4.71 (1 H, bs), 4.78–4.80 (1 H, m), 5.03–5.10 (2 H, m), 5.27–5.32 (1 H, m), 6.02–6.09 (1 H, m), 6.86–6.88 (2 H, m), 7.21–7.22 (2 H, m), 7.26–7.34 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1, −4.7, 11.3 and 11.4 (C.I.), 15.3 and 15.5 (C.I.), 18.1, 24.5 and 24.6 (C.I.), 25.7, 28.2 and 28.4 (C.I.), 29.7 and 30.5 (C.I.), 37.2 and 37.5 (C.I.), 44.5 and 44.8 (C.I.), 47.5, 52.3 and 52.5 (C.I.), 59.8 and 59.9 (C.I.), 64.6 and 65.1 (C.I.), 66.9 and 67.0 (C.I.), 72.8 and 72.9 (C.I.), 78.7 and 79.9 (C.I.), 80.2, 115.1 and 115.2 (C.I.), 127.4 and 127.9 (C.I.), 128.1–128.5, 134.9 and 135.1 (C.I.), 136.2, 153.6 and 154.4 (C.I.), 156.1 and 156.2 (C.I.), 170.8 and 171.1 (C.I.); IR ($CHCl_3$) 3630–3300 (b), 2970 (m), 2950 (m), 2910 (m), 2870 (m), 1680 (s), 1470 (m), 1400 (s), 1370 (m), 1255 (m), 1170 (m), 1120 (m), 1080 (s), 1020 (w), 1000 (w), 970 (w), 940 (w), 890 (w), 835 (s) cm^{-1}; HRMS calcd for $C_{39}H_{60}N_3O_9Si$ (M + H) 742.410, found 742.407.

(2*S*,3*S*)-3-[4-[2-(*N*-(*N*-Carbobenzoxy-(*S*)-isoleucyl)amino)-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)-carbonyl]proline (17). To a solution of compound **16** (0.50 g, 0.67 mmol) in tetrahydrofuran (9.6 mL), methanol (3.2 mL), and water (0.80 mL) at 5 °C was added $LiOH{\cdot}H_2O$ (0.14 g, 3.4 mmol). After being stirred for 3 h at 5 °C, the reaction mixture was acidified to pH 3.0–3.5 with 1 N $KHSO_4$ solution (4.5 mL), and the aqueous layer was extracted twice with EtOAc (20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide a solid residue. This solid was purified by column chromatography, eluting with methylene chloride:ethanol (90:10) to provide pure **17** (0.44 g, 90% yield): R_f 0.18 (methylene chloride:ethanol 90:10); $[\alpha]^{20}_D$ = −16.6° (*c* 3.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.12–(−0.11) and 0.04 (6 H, m and s, C.I.), 0.82–0.89 (16 H, m), 1.38–1.49 (10 H, m), 1.81–1.87 (1 H, m), 2.10–2.18 (2 H, m), 3.32–3.62 (4 H, m), 3.95–3.97 (1 H, m), 4.40 and 4.50 (1 H, m and s, C.I.), 4.74 (1 H, bs), 4.80–4.85 (1 H, m), 5.10 (2 H, s), 5.57–5.90 (1 H, m), 6.12–6.39 (1 H, m), 6.87–6.94 (2 H, m), 7.21–7.23 (2 H, m), 7.30–7.35 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1, −4.6, 11.2, 15.3 and 15.5, 18.1, 24.6, 25.7, 28.2 and 28.3 (C.I.), 30.3, 37.2, 45.2, 47.7, 60.0, 64.8, 66.9, 72.9, 78.4, 80.3, 115.2, 127.4, 127.9–128.4, 134.9, 136.2, 154.0, 156.3, 172.1; IR ($CHCl_3$) 3450 (m), 3340 (w), 2990 (m), 2950 (m), 2910 (m), 2880 (m), 1680 (s), 1610 (w), 1505 (s), 1405 (s), 1370 (m), 1240 (s), 1170 (m), 1130 (m), 1090 (m), 990 (w), 895 (w), 860 (w), 835 (m) cm^{-1}; HRMS calcd for $C_{38}H_{58}N_3O_9Si$ (M + H) 728.394, found 728.399.

Pentafluorophenyl (2*S*,3*S*)-3-[4-[2-(*N*-(*N*-Carbobenzoxy-(*S*)-isoleucyl)amino)-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]prolinate (5). To a solution of compound **17** (0.440 g, 0.605 mmol) and pentafluorophenol (0.131 g, 0.712 mmol) in methylene chloride (3 mL) at 5 °C was added DCC (0.147 g, 0.713 mmol). After 1 h, the reaction mixture was filtered through a bed of Celite, and then the solids were collected and rinsed with methylene chloride. The filtrate was washed sequentially with 1% aqueous $KHCO_3$ solution (3 mL), 0.1 N HCl solution (3 mL), and water (3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide a crude oil. The oil was purified by column chromatography, eluting with petroleum ether:ethyl ether (60:40 to 50:50) to afford pure **5** (0.524 g, 97% yield): R_f 0.23 (petroleum ether:ethyl ether 60:40); $[\alpha]^{20}_D$ +14.1° (*c* 1.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.15–(−0.14) (3 H, m), 0.02–0.05 (3 H, m), 0.81–0.89 (15 H, m), 1.39–1.47 (10 H, m), 1.74–1.94 (1 H, m), 2.24–2.27 (2 H, m), 3.25–3.48 (2 H, m), 3.50–3.61 (2 H, m), 3.67–3.81 (2 H, m), 3.93–3.96 (1 H, m), 4.70–4.71 and 4.83 (1 H, m and s, C.I.), 4.70–4.71 (1 H, m), 5.01–5.03 (1 H, m), 5.07–5.11 (2 H, m), 5.22–5.27 (1 H, m), 6.01–6.10 (1 H, m), 6.90–6.91 (2 H, m), 7.24–7.27 (2 H, m), 7.29–7.34 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1, −4.8, 11.3, 15.3 and 15.4 (C.I.), 18.0, 24.5 and 24.6 (C.I.), 25.7, 28.0 and 28.2 (C.I.), 29.8 and 30.8 (C.I.), 37.1 and 37.4 (C.I.), 44.6 and 44.8 (C.I.), 47.4, 59.8 and 59.9 (C.I.), 64.5 and 64.7 (C.I.), 66.9, 72.7 and 72.9 (C.I.), 78.8 and 80.1 (C.I.), 80.7 and 81.1 (C.I.), 115.2, 124.6, 127.5, 127.6–128.4, 135.5 and 135.6 (C.I.), 136.1 and 136.2 (C.I.),

136.8–142.0, 153.3 and 154.1 (C.I.), 155.8 and 156.2 (C.I.), 166.7 and 166.9 (C.I.), 170.9; IR ($CHCl_3$) 3460 (m), 2980 (m), 2950 (m), 2920 (m), 2900 (m), 2880 (m), 1800 (m), 1710 (s), 1610 (m), 1590 (w), 1510 (s), 1400 (s), 1370 (m), 1235 (s), 1170 (s), 1092 (s), 1000 (s), 940 (w), 910 (w), 890 (w), 860 (w), 835 (m) cm^{-1}; HRMS calcd for $C_{44}H_{57}N_3O_9F_5Si$ (M + H) 894.378, found 894.376.

Cyclo[*N*-[3-[4-[2-amino-1-[((1,1-dimethylethyl)dimethylsilyl)oxy]ethyl]phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]-(2*S*,3*S*)-prolyl]-(*S*)-isoleucyl] (4a and 4b). To a mixture of dioxane (560 mL) containing 10% palladium on carbon (1.90 g), ethanol (11.0 mL), and 4-pyrrolidinopyridine (0.248 g, 1.67 mmol) at 95 °C was added a solution of compound **5** (0.500 g, 0.559 mmol), containing cyclohexene (51.0 mL) in dioxane (100 mL) over a period of 1.5 h. After the addition, the reaction was allowed to stir for an additional 1.5 h, at which time it was cooled to 25 °C and filtered through a bed of Celite, and the filtrate was concentrated under reduced pressure to afford a crude oil. This oil was purified by column chromatography, eluting with petroleum ether:EtOAc (80:20 to 75:25 to 70:30) to provide pure diastereomers **4a** (0.124 g, 39% yield) and **4b** (0.120 g, 37% yield). **4a**: R_f 0.37 (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ −37.3° (*c* 1.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 and 0.11 (6 H, 2 s, C.I.), 0.76 and 0.77 (6 H, 2 s, C.I.), 0.81–0.85 (1 H, m), 0.95 (9 H, s), 1.26–1.30 (1 H, m), 1.41 (9 H, s), 1.53–1.57 (1 H, m), 2.04–2.17 (1 H, m, C.I.), 2.36–2.41 (1 H, m), 3.00 (1 H, d, *J* = 13.3), 3.42–3.45 (1 H, m), 3.47–3.51 (1 H, m), 3.60–3.67 and 3.96 (2 H, m and s, C.I.), 4.28–4.30 (1 H, m), 5.05–5.09 (1 H, m), 5.25–5.31 (1 H, m), 5.35–5.45 (1 H, m), 5.67 and 5.84–5.86 (1 H, s and m, C.I.), 6.84 and 6.88 (1 H, m), 6.95–6.97 (1 H, m), 7.11 (1 H, d, *J* = 8.4), 7.39 (1 H, dd, J_1 = 1.8, J_2 = 8.4); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2, −4.9, 10.7, 14.9, 18.1, 24.1, 25.0, 28.1, 30.6 and 30.8 (C.I.), 37.9 and 38.4 (C.I.), 44.7, 48.1 and 48.6 (C.I.), 59.2 and 60.2 (C.I.), 65.9, 72.3, 79.8 and 80.6 (C.I.), 82.2 and 83.5 (C.I.), 116.7 and 117.8 (C.I.), 119.4 and 119.8 (C.I.), 126.3 and 126.5 (C.I.), 127.3 and 127.5 (C.I.), 135.4 and 135.6 (C.I.), 153.8, 156.8, 170.0, 171.0 and 171.2 (C.I.); IR ($CHCl_3$) 3450 (m), 2980 (m), 2950 (m), 2910 (m), 2870 (m), 1690 (s), 1670 (s), 1610 (w), 1510 (m), 1465 (w), 1405 (s), 1370 (m), 1330 (w), 1320 (w), 1290 (w), 1260 (m), 1235 (m), 1170 (m), 1135 (m), 1115 (m), 1090 (m), 1055 (m), 1010 (w), 935 (w), 910 (w), 835 (m) cm^{-1}; HRMS calcd for $C_{30}H_{50}N_3O_6Si$ (M + H) 576.347, found 576.342. **4b**: R_f 0.19 (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ −40.0° (*c* 1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.05 and 0.06 (6 H, 2 s), 0.73–0.75 (6 H, m), 0.76–0.85 (1 H, m), 0.89 (9 H, s), 1.23–1.28 and 1.38–1.43 (9 H, 2 m, C.I.), 1.95–2.15, (2 H, m), 2.35–2.42 (1 H, m), 3.05–4.04 (6 H, m), 4.54–4.62 (1 H, m), 5.07–5.12 (1 H, m), 5.35–5.42 (1 H, m), 5.60–5.68 and 5.93–6.00 (1 H, m and s, C.I.), 6.83–6.87 (1 H, m), 6.92–7.05 (2 H, m), 7.40–7.47 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −4.7, 10.9, 14.9 and 15.1 (C.I.), 18.0, 24.2, 25.6, 28.2, 30.7 and 30.9 (C.I.), 37.9 and 38.5 (C.I.), 44.7 and 44.9 (C.I.), 46.1 and 46.3 (C.I.), 59.5 and 59.9 (C.I.), 65.7 and 66.1 (C.I.), 73.7, 80.0 and 80.7 (C.I.), 82.3 and 83.6 (C.I.), 115.7 and 117.3 (C.I.), 120.4 and 121.2 (C.I.), 127.5 and 127.9 (C.I.), 128.9, 136.4, 153.7 and 154.1 (C.I.), 157.3, 170.6 and 170.7 (C.I.); IR ($CHCl_3$) 3460 (m), 3430 (m), 3350 (m), 2980 (s), 2950 (s), 2900 (m), 2875 (m), 1795 (s), 1765 (s), 1610 (w), 1510 (m), 1465 (m), 1400 (s), 1370 (m), 1315 (w), 1290 (w), 1255 (m), 1165 (s), 1135 (s), 1090 (s), 1005 (w), 990 (w), 910 (w), 865 (s), 835 (m) cm^{-1}; HRMS calcd for $C_{30}H_{50}N_3O_6Si$ (M + H) 576.347, found 576.353.

Cyclo[*N*-[3-[4-(2-amino-1-hydroxyethyl)phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]-(2*S*,3*S*)-prolyl]-(*S*)-isoleucyl] (18a and 18b). To a solution of compound **4a** (0.231 g, 0.401 mmol) in tetrahydrofuran (6 mL) at 5 °C was added a 1.1 M solution of tetrabutylammonium fluoride (TBAF) (0.730 mL, 0.800 mmol) in tetrahydrofuran. The reaction was allowed to warm to 25 °C, where it was stirred for 2 h. After this time, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography eluting with petroleum ether:EtOAc (50:50) followed by EtOAc to provide pure alcohol **18a** as a solid (0.166 g, 90% yield): R_f 0.49 (EtOAc); $[\alpha]^{20}_D$ −44.2° (*c* 2.53, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.73–0.74 (3 H, m), 0.78–0.80 (3 H, m), 0.87–1.00 (1 H, m), 1.38–1.45 (9 H, m), 1.48–1.52 (1 H, m), 1.60–1.68 (1 H, m), 1.91–2.04 (3 H, m), 3.07–3.09 (2 H, m), 3.15–3.40 (1 H, m), 3.50–3.85 (3 H, m), 4.35–4.37 (1 H, m), 5.04–5.13 (1 H, m), 5.23 (1 H, s), 5.80 (1 H, bs), 6.06 (1 H, d, *J* = 8.7 Hz), 6.82–6.90 (1 H, m), 7.00–7.12 (2 H, m), 7.72–7.79 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 14.4 and 14.6 (C.I.), 24.2 and 24.9 (C.I.), 28.1, 30.2 and 30.4 (C.I.), 38.3 and 38.5 (C.I.), 44.7, 46.3 and 46.6 (C.I.), 59.1 and 59.5 (C.I.), 66.1, 71.9, 79.9, 80.7 and 82.5 (C.I.), 115.9 and 116.7 (C.I.), 119.4 and 119.6 (C.I.), 127.0 and 127.4 (C.I.), 136.1, 153.8, 157.1, 170.3, 170.9; IR ($CHCl_3$) 3430 (m), 3320 (m), 2990 (m), 2950 (m), 2890 (w), 1690 (s), 1660 (s), 1605 (w), 1510 (m), 1475 (w), 1450 (w), 1400 (s), 1365 (m), 1330 (w), 1285 (w), 1230 (m), 1165 (m), 1135 (m), 1110 (s), 1085 (m), 1050 (m), 995 (w), 905 (w), 855 (w) cm^{-1}; HRMS calcd for $C_{24}H_{36}N_3O_6$ (M + H) 462.260, found 462.263. Compound **18b** can be obtained from **4b** by using the same procedure (0.115 g, 90% yield): R_f 0.35 (EtOAc); $[\alpha]^{20}_D$ −42.7° (*c* 1.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.74–0.76 (6 H, m), 0.80–0.83 (1 H, m), 0.87–0.98 (1 H, m), 1.41 (9 H, s), 1.54–1.69 (1 H, m), 2.09–2.18 (1 H, m), 2.40–2.45 (1 H, m), 3.34–3.40 (1 H, m), 3.42–3.46 (1 H, m), 3.62–3.66 (1 H, m), 3.73–3.77 (1 H, m), 3.83 (1 H, d, *J* = 6.3), 3.88–3.93 (1 H, m), 4.30 (1 H, d, *J* = 7.5), 4.89 (1 H, d, *J* = 6.2), 5.22–5.27 (1 H, m), 5.80–5.86 (1 H, m), 6.01–6.03 (1 H, m), 6.93–7.02 (1 H, m), 7.02–7.05 (1 H, m), 7.07–7.09 (1 H, m), 7.52–7.54 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.6, 15.3, 23.9, 28.3, 31.3, 36.5, 45.1, 47.4, 58.7, 65.4, 72.5, 80.4, 84.4, 119.6, 121.8, 126.9, 128.6, 137.0, 154.4, 157.3, 170.5, 171.9; IR ($CHCl_3$) 3430 (m), 3360 (m), 2980 (m), 2950 (m), 2890 (m), 1680 (s), 1610 (w), 1510 (s), 1475 (w), 1400 (s), 1370 (m), 1220 (m), 1165 (m), 1130 (m), 1050 (m), 990 (w), 905 (w), 840 (m) cm^{-1}; HRMS calcd for $C_{24}H_{36}N_3O_6$ (M + H) 462.260, found 462.256.

Cyclo[*N*-[3-[4-(2-amino-1-(phenylselenenyl)ethyl)phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]-(2*S*,3*S*)-prolyl]-(*S*)-isoleucyl] (20a and 20b). To a solution of compound **18a** (0.180 g, 0.390 mmol) in methylene chloride (3 mL) at −10 °C was added triethylamine (0.330 mL, 2.34 mmol), followed by the addition of methanesulfonyl chloride (0.120 mL, 1.56 mmol). After 30 min, the solution was concentrated under reduced pressure to a crude residue. Due to the instability of the mesylate **19a** on silica gel, the material was not purified but was taken directly on to the next step. To a solution of crude **19a** in ethanol (3 mL) was added a solution of sodium phenyl selenide (0.420 g, 2.34 mmol) in ethanol (5 mL). The sodium phenyl selenide was generated by addition of $NaBH_4$ (0.144 g, 3.80 mmol) to a mixture of diphenyldiselenide (0.365 g, 1.17 mmol) in ethanol (5 mL) at 5 °C. The resulting mixture was heated at 80 °C for 30 min, cooled to 25 °C, and concentrated under reduced pressure to provide a crude residue. The residue was purified by column chromatography, eluting with petroleum ether:EtOAc (70:30) to afford pure selenide **20a** (0.156 g, 67% yield, over 2 steps): R_f 0.24 (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ −147.6° (*c* 2.72, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.74–0.78 (6 H, m), 0.90–0.96 (1 H, m), 1.35–1.47 (10 H, m), 1.50–1.62 (1 H, m), 2.08–2.16 (1 H, m), 2.41–2.45 (1 H, m), 3.19–3.24 (1 H, m), 3.37–3.43 (1 H, m), 3.65–3.69 (1 H, m), 3.73–3.77 and 3.95–4.02 (2 H, 2 m, C.I.), 4.13–4.19 (1 H, m), 4.84–4.86 (1 H, m), 5.26–5.39 (1 H, m), 5.87 (1 H, d, *J* = 9.1), 5.94 and 6.00 (1 H, 2 s, C.I.), 6.87 (1 H, d, *J* = 7.9), 7.04 (1 H, d, *J* = 7.7), 7.12 (1 H, d, *J* = 7.5), 7.22 (1 H, d, *J* = 8.3), 7.27–7.29 (3 H, m), 7.56 (2 H, d, *J* = 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7 and 11.1 (C.I.), 14.9 and 15.2 (C.I.), 23.9, 28.2, 30.8 and 31.2 (C.I.), 36.6 and 38.3 (C.I.), 44.4, 45.2, 45.5, 58.6 and 59.7 (C.I.), 65.3 and 65.9 (C.I.), 80.2 and 80.8 (C.I.), 83.9, 119.8, 121.1, 128.0, 128.4, 129.1, 129.8, 130.9, 134.4, 134.9, 154.1, 156.9 and 157.7 (C.I.), 170.4 and 170.6 (C.I.); IR ($CHCl_3$) 3470 (m), 2990 (m), 2950 (m), 2890 (w), 1690 (s), 1675 (s), 1605 (w), 1505 (m), 1475 (w), 1455 (w), 1400 (s), 1370 (m), 1315 (w), 1290 (w), 1235 (m), 1165 (m), 1135 (m), 1045 (m), 970 (w), 905 (w), 850 (w) cm^{-1}; HRMS calcd for $C_{30}H_{40}N_3O_5Se$ (M + H) 602.213, found 602.207. Compound **20b** could be obtained from **18b** by using same procedure (0.087 g, 72% yield, over two steps): R_f 0.40 (petroleum ether:EtOAc 50:50); $[\alpha]^{20}_D$ +19.2° (*c* 2.15, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (3 H, d, *J* = 6.7), 0.75–0.76 (3 H, m), 0.80–0.85 (1 H, m), 0.87–0.94 (1 H, m), 1.40 (9 H, s), 1.48–1.59 (1 H, m), 2.09–2.13 (1 H, m), 2.37–2.42 (1 H, m), 3.23–3.27 (1 H, m), 3.37–3.41 (1 H, m), 3.46–3.49 (1 H, m), 3.65–3.70 (2 H, m), 4.09–4.11 (1 H, m), 4.37–4.44 (1 H, m), 5.21–5.27 (2 H, m), 6.02 (1 H, d, *J* = 8.6), 6.92–6.99 (3 H, m), 7.23–7.31 (3 H, m), 7.35–7.36 (1 H, m), 7.55–7.57 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 15.1, 24.2, 28.2, 31.0, 37.7, 44.7, 45.0, 45.9, 59.4, 65.9, 80.2, 83.9, 118.9, 122.0, 128.2, 128.5, 129.0, 129.2, 131.4, 134.6, 135.1, 154.2, 157.4, 169.9, 170.7; IR ($CHCl_3$) 3470 (m), 2990 (m), 2950 (m), 2890 (w), 1690 (s), 1675 (s), 1605 (w), 1505 (m), 1475 (w), 1455 (w), 1400 (s), 1370 (m), 1315 (w), 1290 (w), 1235 (m), 1165 (m), 1135 (m), 1045 (m), 970 (w), 905 (w), 850 (w) cm^{-1}; HRMS calcd for $C_{30}H_{40}N_3O_5Se$ (M + H) 602.213, found 602.207.

Cyclo[*N*-[3-[4-(2-(*Z*)-aminovinyl)phenoxy]-1-[(1,1-dimethylethoxy)carbonyl]-(2*S*,3*S*)-prolyl]-(*S*)-isoleucyl] (22) from 20a. To a solution of compound **20a** (0.068 g, 0.11 mmol) and pyridine (0.10 mL) in methylene chloride (4 mL) at 5 °C was added 30% hydrogen peroxide (0.15 mL). The reaction was allowed to warm to 25 °C, and after 1 h it was diluted with dimethyl sulfide to quench the excess peroxide. The reaction was stirred for an additional 5 h, at which time it was concentrated under reduced pressure and the residue was distilled azeotropically with benzene to remove any traces of H_2O. The crude residue was purified by column chromatography, eluting with petroleum ether:EtOAc (80:20) to provide pure **22** (0.025 g, 53% yield): R_f (petroleum ether:EtOAc 70:30); $[\alpha]^{20}_D$ −315° (*c* 0.81, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (3 H, d, *J* = 6.9), 0.81–0.89 (3 H, m), 1.05–1.12 (1 H, m), 1.21–1.33 (1 H, m), 1.43 (9 H, s), 2.10–2.17 (1 H, m), 2.23–2.28 (1 H, m), 2.46–2.51 (1 H, m), 3.22–3.28 (1 H, m), 3.86–3.89 (1 H, m),

4.05 (1 H, d, J = 5.3), 4.19 (1 H, dd, J_1 = 2.8, J_2 = 8.7), 5.51-5.61 (1 H, m), 6.27 (1 H, d, J = 7.8), 6.52-6.60 (2 H, m), 6.76 (1 H, dd, J_1 = 7.8, J_2 = 10.7), 7.05-7.12 (2 H, m), 7.13-7.15 (1 H, m), 7.29-7.31 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 15.8, 23.4, 28.3, 31.7, 34.8, 45.7, 58.9, 63.6, 81.1, 84.1, 113.8, 123.1, 125.5, 130.2, 132.5, 155.2, 157.5, 167.0, 171.2; IR ($CHCl_3$) 3410 (m), 2990 (m), 2950 (m), 1730 (m), 1690 (s), 1625 (m), 1600 (w), 1500 (s), 1485 (s), 1400 (s), 1370 (m), 1315 (w), 1250 (s), 1160 (s), 1135 (m), 1095 (w), 1075 (w), 1030 (m), 980 (w), 905 (w), 860 (w), 830 (w) cm^{-1}; HRMS calcd for $C_{24}H_{34}N_3O_5$ (M + H) 444.251, found 444.247. Compound **22** can be obtained from **20b** by using same procedure, and all the physical and spectral data are identical.

Cyclo[*N*-[3-[4-(2-(*Z*)-aminovinyl)phenoxy]-(2*S*,3*S*)-prolyl]-(*S*)-isoleucyl] (23). To a solution of compound **22** (0.0580 g, 0.139 mmol) and thioanisole (0.173 g, 1.39 mmol) in methylene chloride (3 mL) at 5 °C was added trifluoroacetic acid (TFA) (0.316 g, 2.78 mmol). After 5 h, the reaction was diluted with methylene chloride (10 mL) and made basic with a saturated sodium bicarbonate solution (20 mL). The organic layer was separated and extracted with a 5% citric acid solution (2 mL, twice), and the aqueous layers were combined. The aqueous layer was made basic with a saturated $NaHCO_3$ solution, extracted with methylene chloride (20 mL, five times), dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure to provide pure **23** (0.0130 g, 28% yield): R_f 0.52 (methylene chloride:ethanol 90:10); $[\alpha]^{20}_D$ -145.9° (c 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3 H, d, J = 6.9), 0.84-0.90 (3 H, m), 0.91-0.98 (1 H, m), 1.21-1.33 (1 H, m), 2.07-2.13 (1 H, m), 2.17-2.18 (2 H, m), 2.35-2.43 (1 H, m), 3.04-3.09 (1 H, m), 3.23-3.24 (2 H, m), 4.22-4.25 (1 H, m), 5.18-5.22 (1 H, m), 5.55 (1 H, d, J = 9.2), 6.42 (1 H, d, J = 7.6), 6.48 (1 H, d, J = 8.7), 6.59-6.63 (1 H, m), 7.09-7.10 (3 H, m), 7.23-7.25 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 15.7, 24.1, 33.8, 36.6, 46.7, 58.5, 69.6, 85.6, 118.2, 121.3, 122.2, 125.1, 130.0, 131.7, 132.1, 157.5, 167.0, 172.6; IR ($CHCl_3$) 3410 (s), 2970 (m), 2940 (m), 1690 (s), 1625 (m), 1600 (w), 1500 (m), 1475 (s), 1455 (w), 1260 (w), 1230 (w), 1165 (w), 1070 (w), 860 (w) cm^{-1}; HRMS calcd for $C_{19}H_{26}N_3O_3$ (M + H) 344.197, found 344.193.

(-)-Nummularine F (3). To a solution of compound **22** (0.013 g, 0.039 mmol) and *N*,*N*-dimethylglycine (0.082 g, 0.079 mmol) in methylene chloride (1 mL) at 5 °C was added 1,3-dicyclohexylcarbodiimide (DCC) (0.016 g, 0.079 mmol). After 1 h, the reaction was extracted with a 5% citric acid solution (1 mL). The aqueous layer was made basic to pH 8 with a 5% $NaHCO_3$ solution and extracted with EtOAc (1 mL, six times). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure to afford a crude residue. This material was purified by preparative thin-layer chromatography, eluting with methylene chloride:ethanol (90:10) to provide pure **3** (0.010 g, 59% yield): mp 152-154 °C (lit.[27] mp 120 °C); R_f 0.29 (methylene chloride:ethanol 90:10); $[\alpha]^{20}_D$ -197° (c 0.45, MeOH) (lit[27] $[\alpha]^{20}_D$ -204° (c 0.2, MeOH); ^{1}H NMR (500 MH, $CDCl_3$) δ 0.75 (3 H, d, J = 6.9), 0.85 (3 H, t, J = 7.3), 1.08-1.14 (1 H, m), 1.22-1.24 (1 H, m), 2.11-2.16 (1 H, m, J = 5.4, 7.1, 8.3, 10.6), 2.17-2.25 (1 H, m), 2.28 (6 H, s), 2.55-2.60 (1 H, m, J = 9.8, 10.6, 12.9), 3.04, 3.15 (2 H, AB q, δ_1 = 3.04, δ_2 = 3.15, J = 14.2), 3.42-3.48 (1 H, m, J = 5.4, 11.5, 12.9), 4.08 (1 H, dd, J_1 = 8.3, J_2 = 11.4), 4.18 (1 H, dd, J_1 = 3.1, J_2 = 8.7), 4.29 (1 H, d, J = 5.4), 5.56-5.61 (1 H, m, J = 5.4, 7.1, 9.8), 6.30 (1 H, d, J = 7.8), 6.52 (1 H, d, J = 10.6), 6.62 (1 H, d, J = 8.7), 6.76 (1 H, dd, J_1 = 7.8, J_2 = 10.6), 7.10 (1 H, d, J = 8.8), 7.14 (2 H, s), 7.30 (1 H, d, J = 8.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.2 (q), 15.9 (q), 23.7 (t), 32.1 (t), 35.2 (d), 45.2 (q), 46.5 (t), 59.0 (d, C_5), 62.0 (t), 63.7 (d, C_8), 83.7 (d, C_9), 114.1 (d, C_1), 122.9 (d, C_{12}), 130.0 (d, C_{13}), 125.5 (d, C_2), 130.3 (d, C_{12}'), 132.6 (d, C_{13}'), 157.5 (s), 167.0 (s), 169.1 (s), 170.7 (s); IR ($CHCl_3$) 3410 (s), 2980 (m), 2950 (m), 2890 (m), 2870 (w), 2840 (w), 2790 (m), 1690 (s), 1625 (s), 1500 (s), 1480 (m), 1455 (w), 1360 (w), 1310 (w), 1255 (w), 1170 (w), 1115 (w), 1095 (w), 1080 (w), 1020 (w), 860 (w) cm^{-1}; HRMS calcd for $C_{23}H_{33}N_4O_4$ (M + H) 429.250, found 429.255.

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Supplementary Material Available: 500-MHz 1D NMR (^{1}H, ^{13}C, DEPT), 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C XHCORR) spectra and full-range EI mass spectra for **3**; ^{13}C NMR for all compounds; HRMS for **16** (30 pages). Ordering information is given on any current masthead page.

Approaches to Quantitative Supramolecular Chemistry. Hydrogen-Bond-Based Molecular Recognition Phenomena and Sigmoidal Behavior in Multicomponent Mixtures[1]

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Abstract: In this paper we present NMR data from continuous titration competition experiments and describe a method for quantitative analysis of these data. Host **1** is evaluated and shown to have an extremely high affinity for adenine derivative **4** (K_a = 505 000 ± 100 000 M^{-1}). Two different experiments showing sigmoidal solute response are presented and analyzed. The methods discussed here promise greater accuracy than the formulae previously used for competition experiments because exact terms for all equilibria are included and the methods can be extended to analyses of more complex supramolecular ensembles. For example, a competition experiment here required adding host **1** to a 1.0 mM solution of 9-ethyladenine (**4**) in the presence of 20 mM dimethyleneurea (**3**). Before any host is added, 10% of the 9-ethyladenine is bound to dimethyleneurea and 12% of the dimethyleneurea is present as the dimer. These equilibria will obviously contribute to the observed chemical shifts for the solutes during the titration, and failure to consider these equilibria in calculations will lead to inaccurate results. These unnecessary inaccuracies can be avoided by using the methods detailed here.

By observation of natural phenomena and studies of artificial systems, it has been shown that orderly groups of hydrogen-bonding functional groups, arranged according to a reasoned plan, can effectively control and enhance solute–solute interactions.[3-7,11-15,21] This ability to control solute–solute interactions and to predict the stereochemical features of such interactions

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