Total Synthesis and Revision of Stereochemistry of the Marine Metabolite Trunkamide A

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Received September 14, 1999

The isolation of the cytotoxic *Lissoclinum* sp. metabolite trunkamide A was reported in 1996. After completion of a total synthesis in 1999, it became clear that the structure of this marine natural product had to be revised. We now report the first preparation of actual trunkamide A in a total synthesis that serves as an unambiguous structural and stereochemical proof. Highlights of our synthetic strategy are a Lewis acid assisted aziridine opening that was used for the preparation of the novel reverse-prenylated serine and threonine side chains as well as an efficient oxazoline−thiazoline interconversion on the macrocyclic skeleton. In addition, several stereoisomers prepared by complementary synthetic protocols serve to illustrate the general scope of our methodology and confirm the configurational assignment.

Among the azole-containing cyclopeptide alkaloids found in marine organisms,[1] in particular ascidians from the genus *Lissoclinum*,[2] patellin 1 (**1**),[3] patellin 2 (**2**),[3,4] patellin 3 (**3**),[3] patellin 4 (**4**),[3] patellin 5 (**5**),[3] patellin 6 (**6**),[3] and mollamide (**7**),[5] as well as comoramides A (**8**)[6] and B (**9**),[6] are structurally uniquely characterized by the presence of a single thiazoline heterocycle in the peptide backbone as well as threonine and serine residues whose side chains have been modified as dimethylallyl (reverse prenylated) ethers (Figure 1).[7] While all of these moderately cytotoxic natural products have been isolated from ascidians, albeit from many different geographic locations, it is quite likely that they are actually produced by symbiotic prochlorophytes, prokaryotic algal symbionts such as *Prochloron* sp., that are associated with most *Lissoclinum* and *Didemnum* ascidians.[6,8] In support of this hypothesis, the structurally closely related keenamide A (**10**) has been isolated from the marine mollusk *Pleurobranchus forskalii*.[9]

The cycloheptapeptide alkaloid trunkamide A (**11**)[3] was isolated in 1996 from a small green and colorless colonial ascidian, *Lissoclinum* sp., collected at the Great Barrier Reef, Australia, and its structure was reported as shown in Figure 2. While details of trunkamide A's biological effects are not available, this compound appears to have quite promising antitumor activity.[10]

Recent synthetic activity toward other azole-containing cyclopeptide alkaloids has been intense,,[2,11,12] but no synthesis of a reverse-prenylated member of this class has yet been reported.[13] As part of our program toward the total synthesis,[14] stereochemical and conformational analysis,[15] and bioinorganic chemistry[16] of these structurally unique marine metabolites, we were interested in a synthetic approach toward trunkamide A. Total synthesis of trunkamide A represents the only realistic supply of natural product necessary for further biological evaluation,[17] and allows the preparation of analogues for SAR studies.[15]

Our retrosynthetic analysis of trunkamide A is shown in Scheme 1. A key feature of our approach was the use of oxazoline **12** as a precursor to the thiazoline ring in trunkamide A.[18] We have previously demonstrated the advantages of using oxazolines as masked thiazolines,[14a] i.e., a much lower risk of racemization at chiral centers attached to the heterocycle as well as a simplified protective group scheme since thiol-containing building blocks are avoided.[19] Disconnection of the macrocycle at the L-alanine/L-isoleucine amide bond leads to the *N*-Fmoc-protected heptapeptide derivative **13**. While other disconnections (e.g., at the proline/phenylalanine amide

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.
(2) (a) Wipf, P. In *Alkaloids: Chemical and biological perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1998; pp 187−228. (b) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771.
(3) Carroll, A. R.; Coll, J. C.; Bourne, D. J.; MacLeod, J. K.; Zabriskie, T. M.; Ireland, C. M.; Bowden, B. F. *Aust. J. Chem.* **1996**, *49*, 659.
(4) Zabriskie, T. M.; Foster, M. P.; Stout, T. J.; Clardy, J.; Ireland, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 8080.
(5) . Carroll, A. R.; Bowden, B. F.; Coll, J. C.; Hockless, D. C. R.; Skelton, B. W.; Colorless, A. H. *Aust. J. Chem.* **1994**, *47*, 61.
(6) Rudi, A.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *Tetrahedron* **1998**, *54*, 13203.
(7) For other reverse-prenylated peptide derivatives from the marine environment, see: (a) Nagatsu, A.; Kajitani, H.; Sakakibara, J. *Tetrahedron Lett.* **1995**, *36*, 4097. (b) Carroll, A. R.; Feng, Y.; Bowden, B. F.; Coll, J. C. *J. Org. Chem.* **1996**, *61*, 4059.
(8) Prinsep, M. R.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L. *J. Nat. Prod.* **1992**, *55*, 140.
(9) Wesson, K. J.; Hamann, M. T. *J. Nat. Prod.* **1996**, *59*, 629.
(10) Bowden, B. F.; Garcia, G. D. WO9739025A1, Oct. 23, 1997; *Chem. Abstr.* **1997**, *127*, 290919m.
(11) For recent total syntheses, see: (a) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826. (b) Freeman, D. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3251. (c) Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3087. (d) Moody, C. J.; Bagley, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 601. (e) Kigoshi, H.; Yamada, S. *Tetrahedron* **1999**, *55*, 12301.
(12) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
(13) For a preliminary account of our work, see: Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165. Note added in proof: For a synthesis of mollamide, see: McKeever, B.; Pattenden, G. *Tetrahedron Lett.* **1999**, *40*, 9317.
(14) (a) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (b) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975.
(15) Wipf, P.; Fritch, P. C.; Geib, S. J.; Sefler, A. M. *J. Am. Chem. Soc.* **1998**, *120*, 4105.
(16) Wipf, P.; Venkatraman, S.; Miller, C. P.; Geib, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1516.
(17) The yield of isolated trunkamide A from freeze-dried ascidian is 0.016%, and samples of *Lissoclinum* sp. have to be collected using SCUBA.[3]
(18) Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395.
(19) (a) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397. (b) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1.

10.1021/jo9914566 CCC: $19.00
Published on Web 12/31/1999

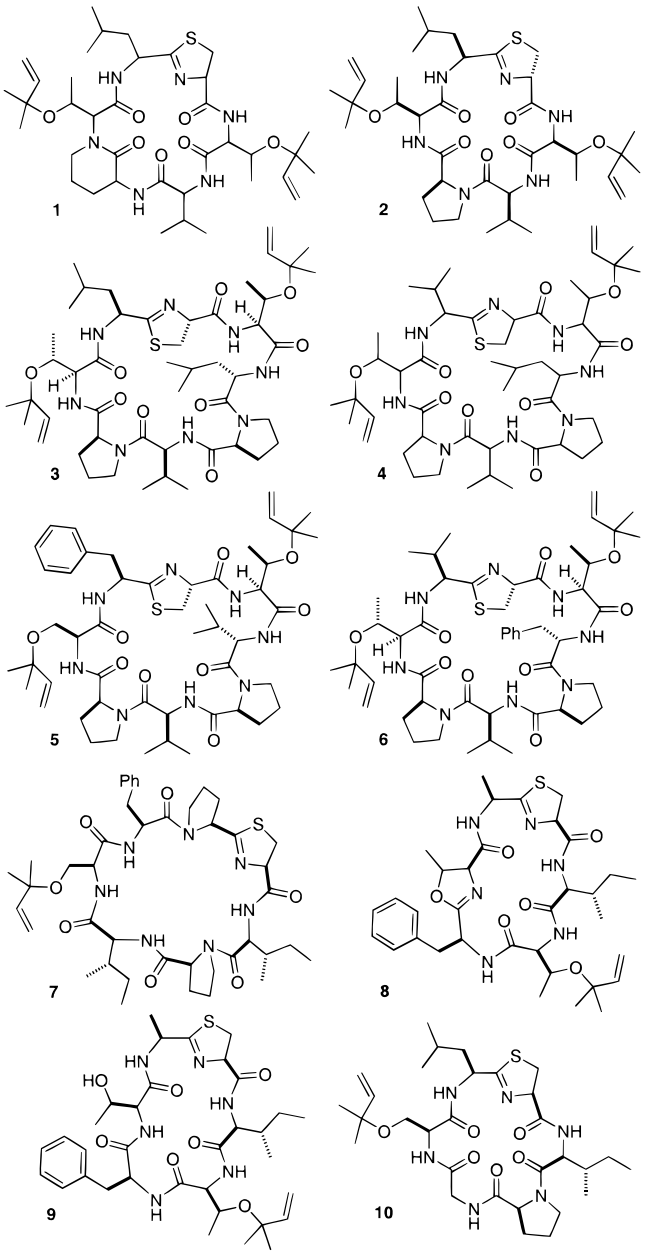


Figure 1. Structures of reverse-prenylated cyclopeptide alkaloids.

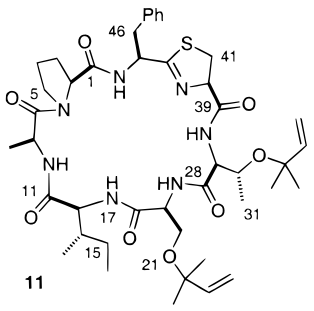
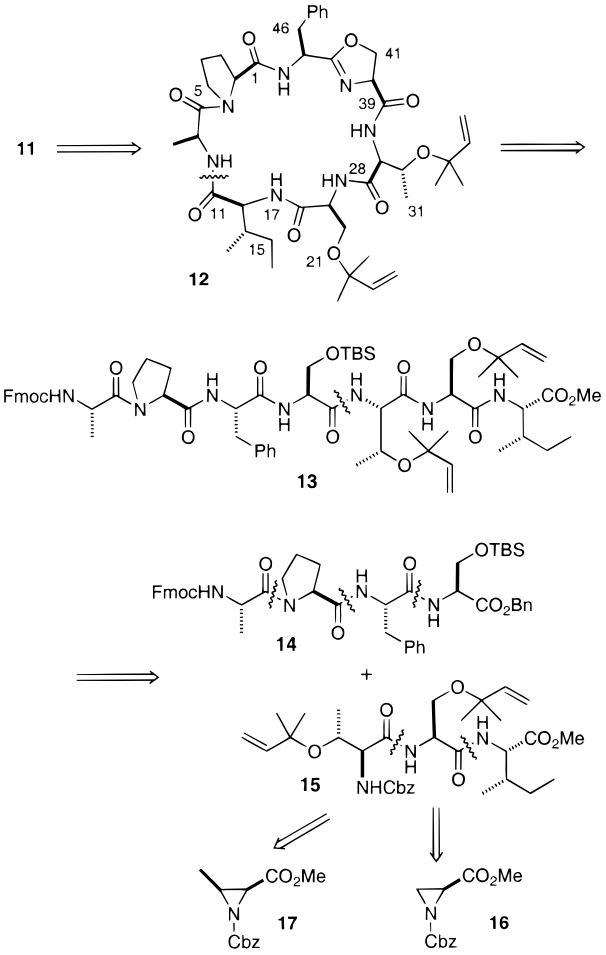


Figure 2. Structure originally assigned to the reverse-prenylated cyclopeptide alkaloid trunkamide A.

bond) and protective group strategies were explored as well, we were unable to identify a viable alternative. To ensure a highly convergent approach to the natural product target, a tetrapeptide sequence **14** of all standard amino acid residues was to be combined with a tripeptide

Scheme 1



15 containing the novel reverse-prenylated threonine and serine side chains. Simple *O*-allylation of serine and threonine is straightforward;[20] however, a direct installment of the reverse prenyl ether moiety onto these amino acids was low-yielding under basic and acidic protocols due to the ease of β-elimination to the dehydroamino acids and regioisomeric ether formation. Therefore, we employed a Lewis-acid assisted ring-opening of activated aziridine derivatives **16** and **17**,[21] which were obtained in 52−61% overall yield according to literature protocols.[22] The modular approach of this retrosynthetic strategy, as well as the use of the oxazoline intermediate, allowed a ready access to stereoisomers and analogues of trunkamide A. In particular, the ability to prepare a series of stereoisomeric sequences would become a crucial advantage at a later stage in this work.

Results and Discussion

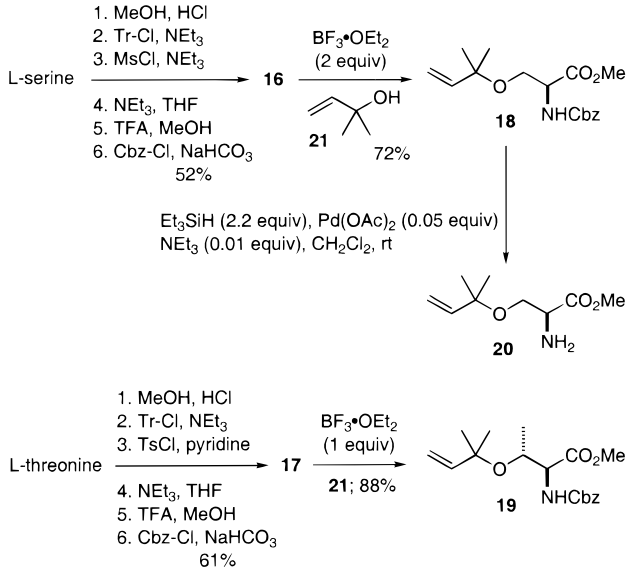
Esterification of L-serine, *N*-tritylation, mesylation of the side chain hydroxy group, intramolecular displacement of the mesylate to give the aziridine, and *N*-deprotection followed by carbamoylation with Cbz-Cl provided a convenient route for the synthesis of aziridine

(20) Stanley, M. S. *J. Org. Chem.* **1992**, *57*, 6421.

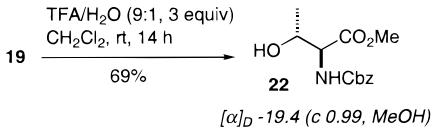
(21) (a) Nakajima, K.; Neya, M.; Yamada, S.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3049. (b) Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett.* **1995**, *36*, 3639.

(22) (a) Tanaka, T.; Nakajima, K.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1352. (b) Larsson, U.; Carlson, R. *Acta Chem. Scand.* **1994**, *48*, 511.

Scheme 2



Scheme 3



[α]D -19.4 (c 0.99, MeOH)

16 (Scheme 2).[22] In analogous sequence, L-threonine was converted to the corresponding aziridine **17** in 61% yield. Treatment of **16** and **17** with an excess of 1,1-dimethylallyl alcohol (**21**) in the presence of 2 equiv of $BF_3{\cdot}OEt_2$ opened the aziridine ring selectively to give the desired ethers **18** and **19** in 72% and 88% yield, respectively. Chemoselective deprotection of the Cbz group in the presence of the alkene was readily accomplished by exposure of **18** to Et_3SiH and catalytic $Pd(OAc)_2$ in 97% yield.[23]

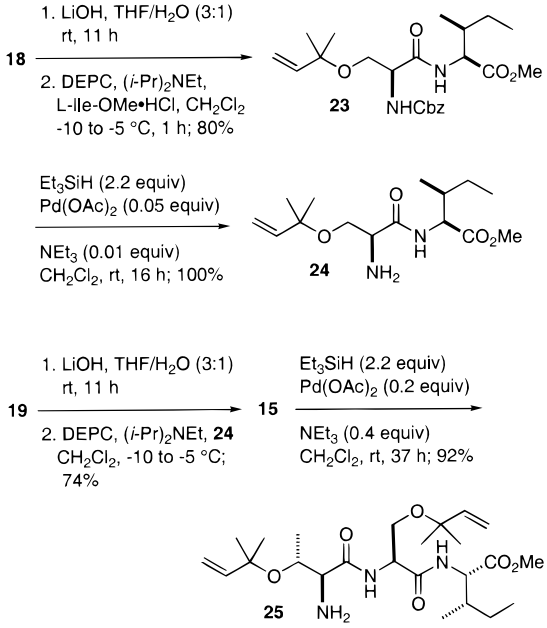
The diastereomeric purity of **19** was ascertained by cleavage of the reverse prenyl group with TFA and comparison with authentic Cbz-protected amino acid (Scheme 3). Diprotected threonine derivative **22** was identical in all regards to a literature sample.[24]

After saponification of **18** and coupling of the resulting acid with L-isoleucine methyl ester in the presence of diethyl phosphorcyanidate (DEPC),[25] the *N*-terminus of dipeptide **23** was deprotected selectively under catalytic hydrogen transfer conditions and acylated with the acid derived from reverse-prenylated threonine **19** (Scheme 4). The tripeptide segment **15** was thus obtained in an overall yield of 59% based on **18**. Increased palladium catalyst loadings were necessary for the subsequent Cbz-group deprotection to amine **25**, which was used in the segment condensation with tetrapeptide **14**.

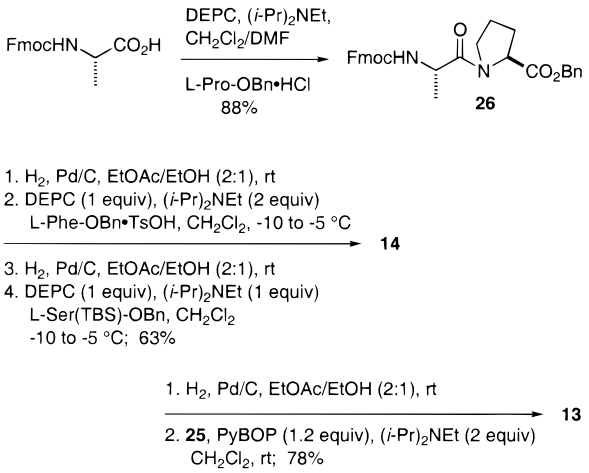
The assembly of **14** employed iterative DEPC-mediated couplings of Fmoc-L-alanine, L-proline, L-phenylalanine, and *O*-TBS-protected L-serine (Scheme 5).[26] Fmoc-protection of the *N*-terminus of **14** was crucial since in our preliminary studies we were unable to cleave an *N*-terminal Cbz-group in extended chains without partial hydrogenation of prenyl groups. Boc-technology was also incompatible with the acid-sensitive reverse prenyl functions. The use of *C*-terminal benzyl esters was superior to methyl esters because considerable cleavage of the Fmoc-group was observed during slow saponification processes. With both peptide strands **14** and **25** in hand, segment condensation was initiated by catalytic hydrogenation of the benzyl ester and addition of PyBOP[27] to a solution of acid and amine **25** in CH_2Cl_2. While successful use of this coupling method was somewhat sequence-dependent and not without potential stereochemical pitfalls (vide infra), PyBOP-mediated condensation provided heptapeptide **13** in 78% yield.

After successful segment coupling, the Fmoc group in **13** was removed by tris(2-aminoethyl)amine (TAEA)[28]

Scheme 4



Scheme 5



(23) (a) Sakatani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753. (b) Coleman, R. S.; Shah, J. A. *Synthesis* **1999**, 1399.

(24) Lit. $[\alpha]_D$ −18.7 (*c* 1.0, MeOH); Yamada, T.; Isono, N.; Inui, A.; Miyazawa, T.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1897.

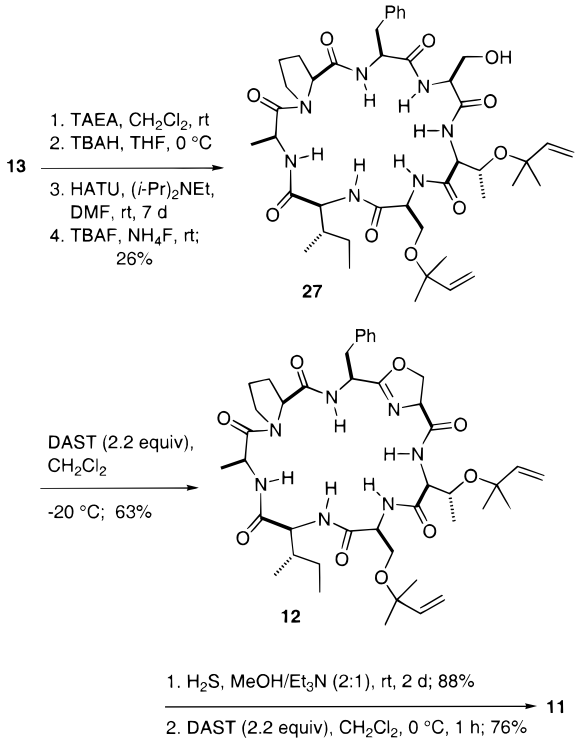
(25) Hamada, Y.; Rishi, S.; Shioiri, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 224.

(26) An *N*- to *C*-terminal chain extension sequence was chosen for the preparation of segment **14** rather than the commonly used *C*- to *N*-terminus strategy, since removal of the *N*-Fmoc protective group from dipeptide Fmoc-Phe-Ser(OTBS)-OBn led to diketopiperazine formation.

(27) . Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259.

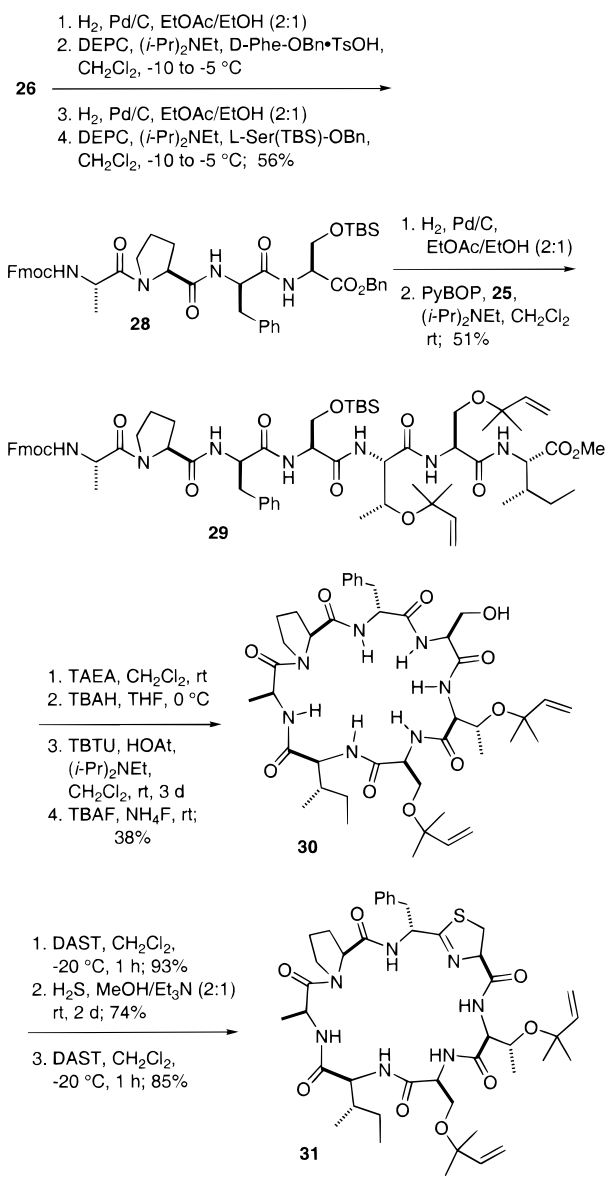
(28) Carpino, L. A.; Sadat-Aalaee, D.; Beyermann, M. *J. Org. Chem.* **1990**, *55*, 1673.

Scheme 6



treatment, and the methyl ester was cleaved with tetrabutylammonium hydroxide (TBAH)[29] in preparation for the macrocyclization step (Scheme 6). The 21-membered ring was closed with HATU,[30] and after desilylation of the serine residue with TBAF, cycloheptapeptide **27** was isolated in 26% yield. HPLC analysis of the constituent amino acids after hydrolysis of **27** and derivatization according to Marfey's procedure[31] confirmed the presence of L-Ile and the absence of any detectable amounts of epimeric D-*allo*-Ile. Accordingly, macrolactamization proceeded without racemization at the peptide *C*-terminus. After cyclodehydration of the serine residue in **27** with DAST to the oxazoline **12**,[32] we applied our oxazoline → thiazoline interconversion protocol for the conversion of **12** to the target heterocycle **11**.[14a,18] Thiolysis of the oxazoline with hydrogen sulfide in a solution of methanol/triethylamine (2:1) provided the thioamide intermediate in 88% yield. Finally, a second cyclodehydration with 2 equiv of DAST[33] proceeded to the desired thiazoline-containing **11**. To our considerable surprise, while all spectroscopic data for synthetic **11** were consistent with our structural assignment, there were significant differences in ^{1}H and ^{13}C NMR spectra and a major difference in the $[\alpha]_D$ measured for **11** and the corresponding data reported for the natural product.[34]

Scheme 7



A thorough analysis of the absolute configuration of all amino acid building blocks in synthetic **11** was complicated by thiazoline-related side reactions during the acid hydrolysis step of the Marfey analysis. Since the assignment of the configuration of the natural product had originally also been based on HPLC assays of Marfey fragments,[3] we immediately suspected that natural trunkamide A was in fact a stereoisomer of **11**, most likely at the readily epimerizable C(40) or C(45) centers.[13] Another potential source of errors was the assignment of the configuration at the reverse-prenylated threonine C(30), since it was highly questionable that L-threonine and L-*allo*-threonine were clearly distinguishable after Marfey derivatization. Since natural product was unavailable for further examination or derivatization,[35] only total synthesis of trunkamide A stereoisomers was able to solve the structural puzzle.

Among the new synthetic targets that we considered essential as reference materials for an unambiguous structural correlation were the (40*R*,45*R*)-, (40*S*,45*S*)-,

(29) Abdel-Magid, A.; Cohen, J. H.; Maryanoff, C. A.; Shah, R. D.; Villani, F. J.; Zhang, F. *Tetrahedron Lett.* **1998**, *39*, 3391.

(30) Ehrlich, A.; Heyne, H.-U.; Winter, R.; Beryermann, M.; Haber, H.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1996**, *61*, 8831.

(31) Adamson, J. G.; Hong, T.; Crivici, A.; Lajoie, G. *Anal. Biochem.* **1992**, *202*, 210.

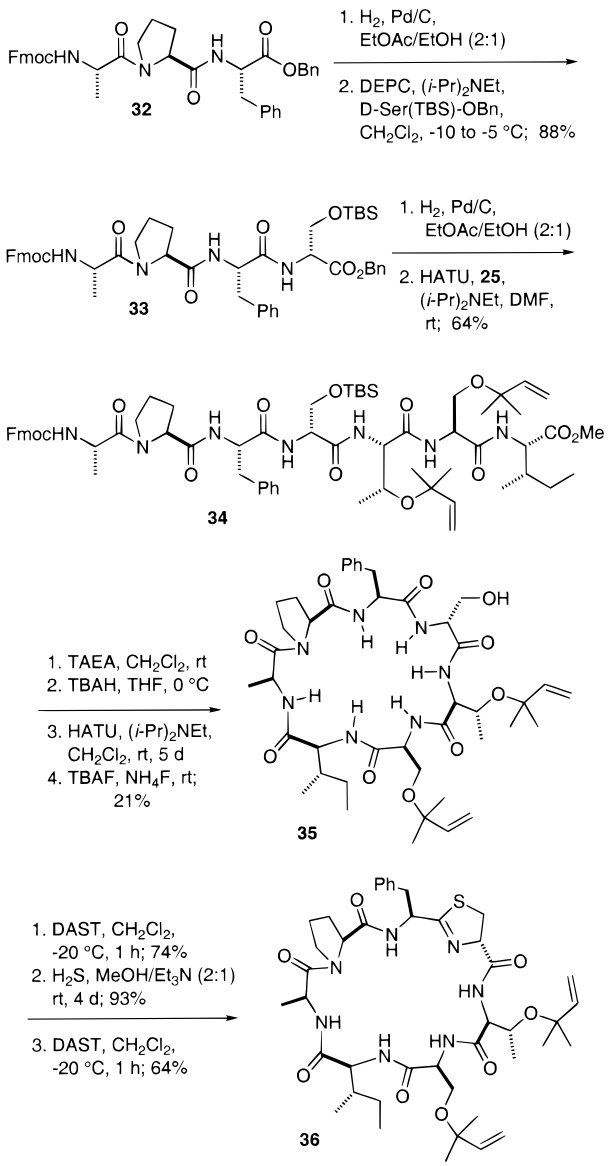
(32) (a) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947. (b) Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677. (c) Muir, J. C.; Pattenden, G.; Thomas, R. M. *Synthesis* **1998**, 613.

(33) . Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Synlett* **1995**, 171.

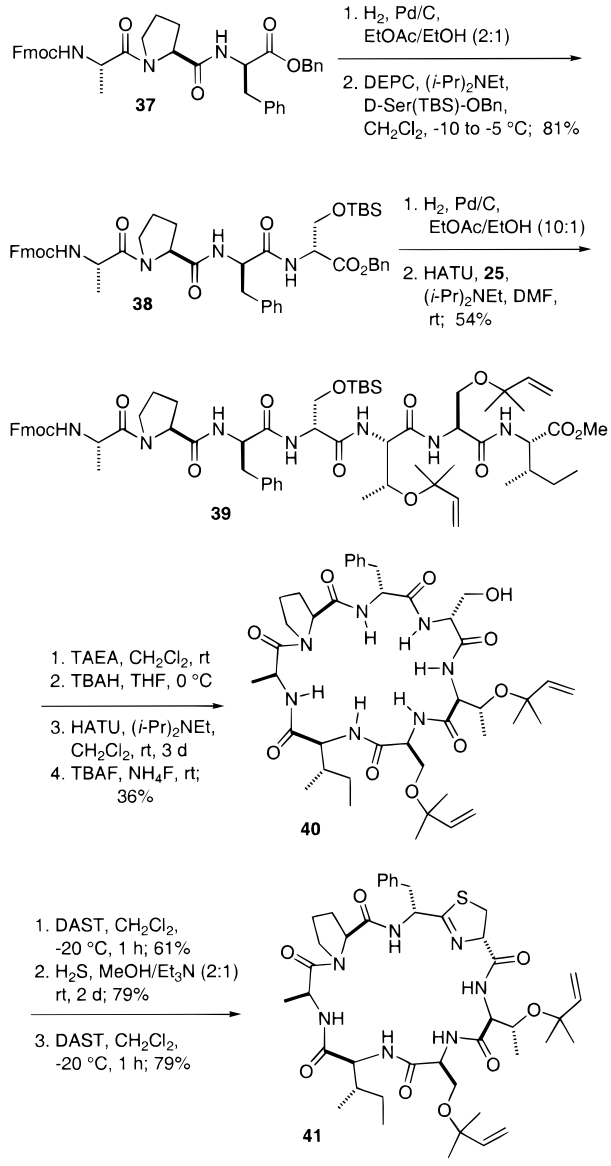
(34) The $[\alpha]_D$ originally reported[3] for natural trunkamide A needs to be corrected to −23.1 (*c* 0.06, $CHCl_3$); there were also minor adjustments necessary for NMR spectral data (see Table 1). Prof. B. F. Bowden, personal communication.

(35) Prof. B. F. Bowden, James Cook Unversity, Australia, personal communication.

Scheme 8



Scheme 9



and (40*S*,45*R*)-stereoisomers of **11**. The total synthesis of the (40*R*,45*R*)-isomer **31** is summarized in Scheme 7. D-Phenylalanine benzyl ester was now used for the chain extension of dipeptide **26**, but tripeptide **25** could be used unchanged in the segment condensation reaction. The macrolactamization of the amino acid derived from heptapeptide **29** gave only poor yields using the standard (HATU) conditions. A significantly improved result was achieved with 3 equiv of TBTU[36] in the presence of HOAt.[37] Further cyclodehydration and oxazoline → thiazoline conversion proceeded uneventfully to the desired (40*R*,45*R*)-macrocycle **31**. In a similar fashion, the (40*S*,45*S*)- and (40*S*,45*R*)-stereoisomers **36** and **41**, respectively, were prepared from intermediates of the previous syntheses (Schemes 8 and 9). Ester **32** had been obtained in the conversion of **26** to **14** (Scheme 5), and ester **37** was formed in the *C*-terminal chain extension from **26** to **28** (Scheme 7). A major experimental modification, however, was necessary for the segment coupling with **25**. The use of PyBOP, which had been successful for preparations of the L-serine containing **13** and **29**, led to a significant amount of epimerization at the D-serine α-carbon in **34** and **39**. With HATU as the coupling agent, we were able to overcome this problem and prepare the desired heptapeptide intermediates in high diastereomeric purity.

In summary, we were able to extend our original approach[13] toward the cyclopeptide alkaloid **11** with some tactical modifications toward the total synthesis of three stereoisomers, **31**, **36**, and **41**, in overall yields of 3−5% based on Fmoc-L-alanine. A careful comparison of ^{1}H and ^{13}C NMR resonances for all synthetic trunkamide A analogues with the data available for the natural product revealed that the (40*R*,45*R*)-isomer **31** provided an excellent spectroscopic match (Table 1). Major differences between the natural compound and isomers **11**, **36**, and **41** were reflected by a large number of shift disagreements $\Delta\delta > 0.05/0.5$ ppm ($^{1}H/^{13}C$) for methyl groups, amide bond hydrogens, and even carbonyl groups. Most significantly, there were no differences $\Delta\delta > 0.5$ ppm in the ^{13}C NMR spectra of natural product and synthetic

(36) (a) Zimmer, S.; Hoffmann, E.; Jung, G.; Kessler, H. *Liebigs Ann. Chem.* **1993**, 497. (b) Trzeciak, A.; Bannwarth, W. *Tetrahedron Lett.* **1992**, *33*, 4557. (c) Ehrlich, A.; Rothemund, S.; Brudel, M.; Beyermann, M.; Carpino, L. A.; Bienert, M. *Tetrahedron Lett.* **1993**, *34*, 4781.

(37) Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1995**, *60*, 3561.

Table 1. Comparison of ^{1}H and ^{13}C NMR Chemical Shifts of Natural Trunkamide A[3,34] with Synthetic 11, 31, 36, and 41. Differences $\Delta\delta$ > 0.05/0.5 ppm (^{1}H/^{13}C) Are Marked in Bold. Assignments Are Supported by 500 MHz H/C-COSY

	trunkamide A		**11**		**31**		**36**		**41**	
Position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
C(1)	-	171.1	–	170.8	–	171.0	–	**170.5**	–	170.9
C(2)H	4.38	59.8	**4.78**	59.8	4.40	60.0	**4.82**	**60.5**	**4.69**	59.6
C(3)H$_2$	1.80	28.5	**1.87**, **1.54**	**29.9**	**1.89**	28.7	**1.95**, 1.83	**27.9**	**2.01**	**26.9**
C(4)H$_2$	2.30, 1.80	25.5	**2.49**, **1.87**	25.3	**2.22**, **1.89**	25.7	**2.66**, **2.06**	25.2	**2.36**, **1.70**	25.8
C(5)H$_2$	3.52, 3.50	47.1	**3.33**	47.4	3.51	47.2	**3.34**, 3.52	46.9	3.54	47.3
C(7)	-	170.0	–	169.9	–	170.1	–	170.3	–	170.0
C(8)H	4.49	47.7	4.53	47.9	4.50	47.8	**4.75**	47.4	**4.90**	**46.6**
C(9)H$_3$	1.20	17.8	1.18	**18.5**	1.21	18.1	**0.96**	**18.4**	1.24	**20.1**
N(10)H	7.20	–	7.22	–	7.22	–	**7.52**	–	**7.57**	–
C(11)	–	170.5	–	170.5	–	170.6	–	170.5	–	170.2
C(12)H	4.55	57.9	4.59	57.7	4.59	58.0	**4.66**	57.4	**4.69**	57.8
C(13)H	2.50	36.5	**2.36**	36.6	**2.35**	36.6	2.45	**35.8**	2.45	**35.9**
C(14)H$_3$	0.95	16.1	**0.88**	16.3	0.94	16.2	0.96	16.4	0.91	16.4
C(15)H$_2$	1.35	23.6	1.34	24.0	**1.26**	23.8	**1.21**	**24.4**	**0.91**	**24.4**
C(16)H$_3$	0.95	11.9	**0.88**	12.3	0.94	12.1	0.96	**12.5**	0.91	**12.5**
N(17)H	6.32	–	**6.19**	–	6.32	–	**6.11**	–	**6.05**	–
C(18)	–	170.9	–	**171.9**	-	171.0	–	170.5	–	170.5
C(19)H	4.55	56.5	**4.39**	56.5	4.59	56.6	4.56	**57.2**	**4.44**	**57.3**
C(20)H$_2$	3.89, 3.44	62.2	3.83, 3.43	62.1	3.89, 3.45	62.3	3.85, **3.58**	61.7	3.88, **3.54**	61.7
C(22)	–	77.8	–	77.9	-	78.0	–	**78.4**	–	**78.4**
C(23)H$_3$	1.50	25.6	**1.43**	25.6	1.48	25.8	1.52	25.8	1.53	25.8
C(24)H$_3$	1.35	27.3	1.34	27.5	1.38	27.5	**1.41**	**26.4**	**1.42**	**27.9**
C(25)H	5.91	142.0	5.88	142.4	5.91	142.2	5.95	142.4	5.95	142.4
C(26)H$_2$	5.27, 5.23	115.7	5.25, 5.22	115.9	5.27, 5.24	116.0	5.30, 5.26	115.9	5.31, 5.25	115.9
N(27)H	7.55	–	**7.49**	–	7.56	–	**8.03**	–	**8.26**	–
C(28)	–	168.6	–	**169.3**	-	168.7	–	**170.3**	–	**170.0**
C(29)H	4.55	55.2	4.53	**56.2**	4.59	55.4	**4.35**	**57.0**	**4.36**	**57.3**
C(30)H	4.02	67.2	**3.91**	67.4	4.02	67.4	**4.26**	**66.4**	**4.55**	**65.5**
C(31)H$_3$	1.10	18.5	1.11	**19.1**	1.06	18.7	1.08	**19.5**	1.07	18.4
C(33)	–	75.9	–	76.2	-	76.1	–	76.0	–	76.0
C(34)H$_3$	1.25	25.6	1.21	26.0	1.24	25.8	1.28	25.6	1.30	25.8
C(35)H$_3$	1.25	25.6	**1.18**	25.9	1.27	25.9	1.26	25.5	1.28	25.8
C(36)H	5.73	142.6	**5.68**	142.4	5.73	142.7	5.75	142.8	5.78	142.9
C(37)H$_2$	5.15, 5.11	114.9	**5.09**, 5.06	115.2	5.15, 5.12	115.1	5.15, 5.14	115.1	5.17, 5.16	115.2
N(38)H	7.93	–	**8.10**	–	7.95	–	7.98	–	**8.13**	–
C(39)	–	170.1	–	169.9	-	170.3	–	**172.9**	–	**172.5**
C(40)H	4.92	78.1	4.94	77.9	4.92	78.3	**4.66**	**79.2**	**4.81**	**78.8**
C(41)H$_2$	3.71, 3.62	36.4	**3.59**, 3.54	36.6	3.72, 3.62	36.6	3.71, **3.34**	36.5	**3.54**	**35.5**
C(43)	–	173.3	–	172.8	-	173.5	–	173.8	–	173.3
C(45)H	5.25	52.6	**4.94**	**53.7**	5.20	52.8	**5.03**	**53.8**	**5.08**	**53.4**
C(46)H$_2$	3.20, 2.90	40.0	3.15, 2.87	**40.7**	3.15, 2.93	40.2	**3.34**, **2.96**	**39.0**	3.15, **2.96**	**41.5**
N(53)H	7.30	–	**8.38**	–	7.25	–	**7.98**	–	**8.26**	–

31, and the small differences for methylene protons at positions C(3), C(4), and C(15) could well be due to the broad character of the multiplets at these positions, which, in addition, are partially covered by other peaks even at 500 MHz. Accordingly, we conclude that the stereochemistry of trunkamide A has to be revised as shown for synthetic **31**, e.g., the D-configuration at the phenylalanine-derived C(45)-stereocenter. Despite the differences in $[\alpha]_D$ values between synthetic and natural product, the NMR analysis provides overwhelming support for this structural assignment.

Conclusions

The total synthesis of marine natural products poses considerable challenges for synthetic methodology due to the frequent combinations of unusual new functionalities, incomplete structural assignment, and the high degree of diversity among these targets. While many successful approaches to cyclopeptides have been realized, every sequence defines new and unexpected limitations for protective group manipulations and, in particular, macrocyclization steps. This is especially true for the preparation of heavily backbone- and side chain-modified cyclopeptide alkaloids. As an extension of our prior work in the field of *Lissoclinum* peptides, we have now been able to realize a general and efficient synthetic strategy that provides trunkamide A and a series of unnatural analogues in sufficient quantities (>10 mg) for further evaluation of their biological profile. In addition, on the basis of the total synthesis of the structure originally proposed for trunkamide A as well as three specific stereoisomers, we were able to revise the assignment of the stereochemistry of the natural product to **31**. As observed for many other thiazoline-containing metabolites, the stereocenter exocyclic to the heterocyclic ring assumes a D-amino acid configuration. This trend is likely due to conformational preferences in the macrocycle.[15] Further analysis of the three-dimensional structure of trunkamide A and its congeners as well as the results of structure−activity studies will be reported in due course.

Experimental Section

General Methods. NMR spectra are reported at 300 MHz in $CDCl_3$ unless otherwise noted. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. Flash chromatography was used to separate and purify the crude reaction mixtures.

General Procedure A for Deprotection and Reprotection of Aziridines. (2*S*)-Aziridine-1,2-dicarboxylic acid 1-Benzylester 2-Methyl Ester (16). A solution of 0.755 g

(2.20 mmol) of (*S*)-1-trityl-aziridine-2-carboxylic acid methyl ester[22] in 3 mL of $CHCl_3$ and 3 mL of MeOH was cooled to 0 °C, treated with 3 mL of TFA, and allowed to stir for 2.5 h at 0 °C. Evaporation of the solvent in vacuo gave a solid residue which was dissolved in ether. The solvent was evaporated, and the ether treatment was repeated two additional times to ensure complete removal of TFA. The resulting residue was dissolved in ether and extracted with water. The combined aqueous extracts were treated portionwise with 0.93 g (11 mmol) of $NaHCO_3$. After addition of EtOAc, the mixture was cooled to 0 °C and a solution of benzyl chloroformate (0.35 mL, 2.5 mmol) in 2 mL of EtOAc was added dropwise over 10 min under vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirred overnight (13 h). After addition of water and EtOAc, the organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 8:1) yielded 0.375 g (73%) of **16** as a colorless oil: ^{1}H NMR δ 7.34 (s, 5 H), 5.15 (s, 2 H), 3.71 (s, 3 H), 3.12 (dd, 1 H, J = 3.2, 5.4 Hz), 2.60 (dd, 1 H, J = 3.2, 1.4 Hz), 2.49 (dd, 1 H, J = 1.4, 5.4 Hz); ^{13}C NMR δ 168.8, 160.9, 135.4, 128.7, 128.6, 127.8, 68.8, 52.9, 35.0, 31.6; MS(EI) m/z (rel intensity) 235 (M^+, 0.3), 129 (23), 107 (52), 91 (100); HRMS m/z calcd for $C_{12}H_{13}NO_4$ 235.0845, found 235.0836.

General Procedure B for Aziridine Opening by 2-Methyl-3-buten-2-ol. (2*S*)-2-(Benzyloxycarbonylamino)-3-(1,1-dimethylallyloxy)propionic Acid Methyl Ester (18). To a solution of **16** (2.47 g, 10.5 mmol) in 2-methyl-3-buten-2-ol (330 mL) was added dropwise at 0 °C $BF_3{\cdot}Et_2O$ (2.7 mL, 21 mmol). The reaction mixture was allowed to stir overnight (16 h) at room temperature and then washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 6:1) yielded 2.43 g (72%) of **18** as a colorless solid: mp 46.0−47.7 °C; $[\alpha]_D$ +9.9 (*c* 0.95, $CHCl_3$, 23 °C); IR (film) 3440, 3089, 3069, 1724, 1509 cm^{-1}; ^{1}H NMR δ 7.38−7.26 (m, 5 H), 5.70 (dd, 1 H, J = 10.5, 17.8 Hz), 5.62 (d, 1 H, J = 8.7 Hz), 5.13, 5.12 (AB, 2 H, J = 12.1 Hz), 5.12−5.06 (m, 2 H), 4.45 (ddd, 1 H, J = 3.0, 3.0, 8.7 Hz), 3.75 (s, 3 H), 3.74 (dd, 1 H, J = 3.0, 9.2 Hz), 3.53 (dd, 1 H, J = 3.0, 9.2 Hz), 1.21 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR δ 171.2, 156.2, 143.1, 136.4, 128.7, 128.3, 114.5, 75.6, 67.2, 62.9, 54.7, 52.5, 25.7, 25.6; MS (FAB) m/z (rel intensity) 344 ([M + Na]$^+$, 40), 322 ([M + H]$^+$, 26), 91 (100); HRMS m/z calcd for $C_{17}H_{24}NO_5$ (M + H) 322.1654, found 322.1663.

(2*S*,3*S*)-3-Methylaziridine-1,2-dicarboxylic acid 1-Benzyl Ester 2-Methyl Ester (17). According to general procedure A, 5.14 g (14.4 mmol) of (2*S*,3*S*)-1-trityl-3-methylaziridine-2-carboxylic acid methyl ester[22] provided 3.46 g (96%) of **17** as a colorless oil: ^{1}H NMR δ 7.36−7.27 (m, 5 H), 5.14, 5.12 (AB, 2 H, J = 12.1 Hz), 3.78 (s, 3 H), 3.19 (d, 1 H, J = 6.7 Hz), 2.81 (dq, 1 H, J = 6.7, 5.7 Hz), 1.35 (d, 3 H, J = 5.7 Hz); ^{13}C NMR δ 167.8, 161.7, 135.4, 128.7, 128.6, 128.5, 68.7, 52.6, 39.9, 39.0, 13.0; MS(EI) m/z (rel intensity) 249 (M^+, 0.6), 232 (1), 207 (2), 190 (1), 114 (52), 91 (100); HRMS m/z calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1008.

(2*S*)-(Benzyloxycarbonylamino)-(3*S*)-(1,1-dimethylallyloxy)butyric Acid Methyl Ester (19). According to general procedure B, aziridine **17** (3.46 g, 13.9 mmol) and $BF_3{\cdot}Et_2O$ (1.8 mL, 14 mmol) in 2-methyl-3-buten-2-ol (290 mL) provided 4.09 g (88%) of **19** as a pale yellow oil: $[\alpha]_D$ +17.2 (*c* 1.1, $CHCl_3$, 23 °C); IR (film) 3444, 3033, 1754, 1728, 1506 cm^{-1}; ^{1}H NMR δ 7.41−7.31 (m, 5 H), 5.69 (dd, 1 H, J = 10.7, 17.7 Hz), 5.58 (d, 1 H, J = 9.6 Hz), 5.13 (s, 2 H), 5.10 (dd, 1 H, J = 17.8, 0.8 Hz), 5.08 (dd, 1 H, J = 10.8, 0.8 Hz), 4.21 (dd, 1 H, J = 9.6, 1.7 Hz), 4.11 (dq, 1 H, J = 1.7, 6.9 Hz), 3.73 (s, 3 H), 1.21 (s, 6 H), 1.17 (d, 1 H, J = 6.9 Hz); ^{13}C NMR δ 171.7, 156.9, 143.7, 136.5, 128.7, 128.3, 128.0, 114.1, 76.0, 68.3, 67.2, 59.9, 52.3, 26.4, 26.2, 21.1; MS (FAB) m/z (rel intensity) 358 ([M + Na]$^+$, 56), 336 ([M + H]$^+$, 10), 91 (100); HRMS (FAB) m/z calcd for $C_{18}H_{26}NO_5$ (M + H) 336.1811, found 336.1819.

Cbz-Thr-OMe (22). A solution of **19** (48.4 mg, 0.144 mmol) in CH_2Cl_2 (1.0 mL) was treated with 40 μL of TFA/H_2O (9:1) for 14 h. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to yield 26.4 mg (69%) of **22** as a colorless solid: $[\alpha]_D$ −19.4 (*c* 0.99, MeOH, 23 °C), lit $[\alpha]_D$ −18.7 (*c* 1.0, MeOH, 20 °C);[24] ^{1}H NMR δ 7.36−7.26 (m, 5 H), 5.62 (d, 1 H, J = 8.3 Hz), 5.13 (s, 2 H), 4.34 (d, 2 H, J = 7.5 Hz), 3.77 (s, 3 H), 2.02 (s, 1 H), 1.25 (d, 3 H, J = 6.8 Hz).

Cbz-Ser(rprenyl)-Ile-OMe (23). A solution of Cbz-Ser(rprenyl)-OMe **18** (2.15 g, 6.96 mmol) in THF/H_2O (3:1, 120 mL) was treated with $LiOH{\cdot}H_2O$ (0.306 g, 7.29 mmol). The reaction mixture was stirred at room temperature for 11 h, H_2O (30 mL) was added, and THF was removed in vacuo. The solution was acidified with 1 M KH_2PO_4 and extracted with EtOAc, dried (Na_2SO_4), and concentrated to afford 2.1 g (100%) of acid intermediate as a colorless solid. A solution of this acid (2.06 g, 6.69 mmol) in CH_2Cl_2 (22 mL) was cooled to −10 °C, and DEPC (93%, 1.1 mL, 6.7 mmol) was added dropwise.[38] After the mixture had been stirred for 15 min and warmed to −5 °C, a solution of L-Ile-OMe·HCl (1.22 g, 6.69 mmol) and $(i\text{-Pr})_2$NEt (2.3 mL, 13 mmol) in CH_2Cl_2 (14 mL) was added slowly. The reaction mixture was stirred at −5 °C for 1 h, quenched with water (100 mL), extracted with chloroform, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 4:1) yielded 2.33 g (80%) of **23** as a colorless solid: mp 55.5−57.5 °C; $[\alpha]_D$ +30.8 (*c* 0.39, $CHCl_3$, 22 °C), IR (film) 3331, 1738, 1667, 1501 cm^{-1}; ^{1}H NMR δ 7.37−7.20 (m, 6 H), 5.83 (dd, 1 H, J = 17.7, 10.6 Hz), 5.71 (d, 1 H, J = 4.7 Hz), 5.18−5.02 (m, 4 H), 4.58 (dd, 1 H, J = 4.9, 8.7 Hz), 4.35−4.25 (m, 1 H), 3.80−3.65 (m, 4 H), 3.35 (t, 1 H, J = 8.4 Hz), 1.93−1.83 (m, 1 H), 1.50−1.30 (m, 1 H), 1.30 (s, 6 H), 1.25−1.10 (m, 1 H), 0.95−0.85 (m, 6 H); ^{13}C NMR δ 172.2, 170.3, 156.2, 142.9, 136.3, 128.8, 128.4, 115.0, 67.3, 62.7, 56.8, 54.4, 52.3, 38.2, 25.7, 25.3, 15.7, 11.8; MS (EI) m/z (rel intensity), 434 (M^+, 0.7), 336 (40), 291 (30), 253 (39), 91 (100); HRMS m/z calcd for $C_{23}H_{34}N_2O_6$ 434.2417, found 434.2399.

Cbz-Thr(rprenyl)-Ser(rprenyl)-Ile-OMe (15). A suspension of Et_3SiH (0.81 mL, 5.1 mmol), $Pd(OAc)_2$ (51.4 mg, 0.229 mmol), and Et_3N (64 μL, 0.46 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 15 min under a nitrogen atmosphere. To this mixture was added a solution of Cbz-Ser(rprenyl)-Ile-OMe **23** (995 mg, 2.29 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 16 h and quenched with saturated aqueous $NaHCO_3$ solution. The product was extracted with $CHCl_3$, dried (Na_2SO_4), and then concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 4:1, then 1:1, followed by $CHCl_3$/MeOH, 10:1) yielded 780 mg of **24** as a dark oil. A solution of Cbz-Thr(rprenyl)-OMe (**19**, 2.53 g, 7.55 mmol) in THF/H_2O (3:1, 120 mL) was treated with $LiOH{\cdot}H_2O$ (0.352 g, 8.39 mmol). The reaction mixture was stirred at room temperature for 14.5 h, H_2O was added, and THF was removed in vacuo. The solution was acidified with 1 M KH_2PO_4, extracted with EtOAc, dried (Na_2SO_4), and concentrated to afford 2.41 g (100%) of acid intermediate as a colorless solid. A solution of this acid (739 mg, 2.29 mmol) in CH_2Cl_2 (8 mL) was cooled to −10 °C, and DEPC (93%, 376 μL, 2.29 mmol) was added dropwise.[38] After the mixture had been stirred for 15 min and warmed to −5 °C, a solution of the amine **24** prepared above (780 mg) and $(i\text{-Pr})_2$NEt (0.40 mL, 2.3 mmol) in CH_2Cl_2 (5 mL) was added slowly. The reaction mixture was stirred at −5 °C for 3 h, diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 2:1) yielded 2.33 g (74%) of **15** as a colorless solid: mp 86.0−88.0 °C; $[\alpha]_D$ +40.6 (*c* 0.83, $CHCl_3$, 23 °C); IR (film) 3325, 3086, 1747, 1741, 1666 cm^{-1}; ^{1}H NMR δ 7.45 (d, 1 H, J = 7.6 Hz), 7.39−7.26 (m, 5 H), 7.06 (d, 1 H, J = 8.9 Hz), 5.96−5.89 (m, 2 H), 5.80 (dd, 1 H, J = 10.5, 17.9 Hz), 5.30−5.05 (m, 6 H), 4.62−4.56 (m, 2 H), 4.25−4.20 (m, 1 H), 4.10−4.00 (m, 1 H), 3.84 (dd, 1 H, J = 2.7, 8.6 Hz), 3.71 (s, 3 H), 3.33 (dd, 1 H, J = 6.1, 8.5 Hz), 1.95−1.85

(38) According to Shioiri's original DEPC protocol, a solution of acid and amine in DMF should be treated with DEPC and then triethylamine.[25] We used an alternative sequence of additions following a protocol by Pettit, G. R.; Taylor, S. R. *J. Org. Chem.* **1996**, *61*, 2322.

(m, 1 H), 1.50−1.40 (m, 2 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.28 (s, 6 H), 1.09 (d, 3 H, J = 6.4 Hz), 0.98−0.84 (m, 6 H); ^{13}C NMR δ 172.1, 170.0, 169.2, 156.1, 142.9, 136.4, 128.7, 128.4, 128.2, 115.2, 114.9, 76.1, 68.0, 67.1, 62.6, 59.0, 56.8, 53.5, 52.1, 37.9, 27.5, 25.9, 25.7, 25.5, 25.1, 17.3, 15.7, 11.7; MS(FAB) *m/z* (rel intensity) 626 ([M + Na]$^+$, 42), 604 ([M + H]$^+$, 100); MS (EI) *m/z* (rel intensity) 603 (M$^+$, 0.3), 423 (23), 358 (30), 315 (57), 146 (35), 91 (76); HRMS (EI) *m/z* calcd for $C_{32}H_{49}N_3O_8$ 603.3520, found 603.3514.

Fmoc-Ala-Pro-OBn (26). A solution of Fmoc-Ala-OH (3.45 g, 11.1 mmol) in DMF (18 mL) was cooled to −14 °C and DEPC (93%, 1.8 mL, 11 mmol) was added dropwise. After the reaction mixture had been stirred for 25 min at −10 °C, a solution of L-Pro-OBn·HCl (2.68 g, 12.1 mmol) and (*i*-Pr)$_2$NEt (3.8 mL, 21 mmol) in CH_2Cl_2 (18 mL) was added via syringe pump over a period of 30 min. The reaction mixture was stirred for 11 h, diluted with $CHCl_3$, washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 2:1) yielded 4.85 g (88%) of **26** as a colorless foam: $[\alpha]_D$ −62.2 (*c* 0.94, $CHCl_3$, 23 °C); IR (film) 3415, 3292, 3066, 3015, 1716, 1647 cm^{-1}; ^{1}H NMR δ 7.76 (d, 2 H, J = 4.7 Hz), 7.59 (d, 2 H, J = 7.2 Hz), 7.42−7.25 (m, 9 H), 5.75 (d, 1 H, J = 7.9 Hz), 5.22, 5.12 (AB, 2 H, J = 12.3 Hz), 4.63−4.59 (m, 1 H), 4.53 (p, 1 H, J = 7.2 Hz), 4.36−4.30 (m, 2 H), 4.23−4.18 (m, 1 H), 3.7−3.55 (m, 2 H), 2.23−2.20 (m, 1 H), 2.10−1.90 (m, 3 H), 1.36 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 171.8, 171.5, 155.8, 144.0, 143.9, 141.4, 135.6, 128.7, 128.5, 128.3, 127.8, 127.2, 125.3, 120.1, 67.1, 59.1, 48.4, 47.2, 47.0, 46.6, 29.0, 25.1,18.4; MS (EI) *m/z* (rel intensity) 498 (M$^+$, 0.2), 302 (39), 258 (36), 178 (100), 167 (36); HRMS *m/z* calcd for $C_{30}H_{30}N_2O_5$ 498.2155, found 498.2179.

General Procedure C for the Synthesis of Stereoisomers of Fmoc-Ala-Pro-Phe-OBn (32). A solution of Fmoc-Ala-Pro-OBn (**26**, 3.83 g, 7.68 mmol) in EtOAc/EtOH (2:1, 60 mL) was treated with Pd/C (10% Pd, 0.419 g) and H_2 gas for 17 h. The reaction mixture was filtered through a plug of Celite and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:1, then $CHCl_3$/MeOH, 5:1) yielded 3.11 g (99%) of the acid as a colorless solid. A solution of this acid (3.11 g, 7.61 mmol) in CH_2Cl_2 (25 mL) was cooled to −10 °C, and DEPC (93%, 1.2 mL, 7.4 mmol) was added dropwise. After the mixture had been stirred for 30 min and warmed to −5 °C, a solution of L-Phe-OBn·TsOH (3.25 g, 7.61 mmol) and (*i*-Pr)$_2$NEt (2.6 mL, 15 mmol) in CH_2Cl_2 (15 mL) was added via cannula. The reaction mixture was stirred at −5 °C for 11 h, diluted with chloroform, washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:1, then 1:2) yielded 3.88 g (79%) of **32** as a colorless wax: $[\alpha]_D$ −62.2 (*c* 0.94, $CHCl_3$, 23 °C); IR (film) 3300, 3064, 1739, 1643 cm^{-1}; ^{1}H NMR (methanol-d_4) δ 7.83−7.75 (m, 2 H), 7.70−7.62 (m, 2 H), 7.42−7.10 (m, 14 H), 5.13−5.05 (m, 2 H), 4.70−4.60 (m, 1 H), 4.50−4.35 (m, 4 H), 4.35−4.28 (m, 1 H), 3.78−3.68 (m, 1 H), 3.68−3.45 (m, 1 H), 3.15−3.05 (m, 2 H), 2.22−2.00 (m, 2 H), 2.00−1.80 (m, 2 H), 1.40−1.22 (m, 3 H); ^{13}C NMR δ 172.7, 171.3, 170.7, 155.8, 144.0, 141.4, 137.2, 135.9, 135.2, 129.5, 128.8, 127.9, 127.2, 125.3, 120.1, 67.4, 67.1, 60.1, 53.5, 48.3, 47.3, 37.9, 27.6, 25.1, 18.6, 16.6; MS (EI) *m/z* (rel intensity) 645 (M$^+$, 0.1), 380 (31), 352 (10), 178 (95); HRMS (FAB) *m/z* calcd for $C_{39}H_{40}N_3O_6$ (M + H) 646.2917, found 646.2930.

General Procedure D for the Synthesis of Stereoisomers of Fmoc-Ala-Pro-Phe-Ser(TBS)-OBn (14). A solution of Fmoc-Ala-Pro-Phe-OBn (**32**, 3.82 g, 5.92 mmol) in EtOAc/EtOH (2:1, 60 mL) was treated with Pd/C (10% Pd, 0.32 g) and H_2 gas for 17 h. The reaction mixture was filtered through a plug of Celite and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:1, then $CHCl_3$/MeOH, 5:1) yielded 3.19 g (96%) of Fmoc-Ala-Pro-Phe-OH as a colorless solid.

To a solution of L-Ser-OBn·TsOH (10.0 g, 27.2 mmol) and imidazole (6.48 g, 95.2 mmol) in DMF (20 mL) was added TBS−Cl (4.64 g, 30.8 mmol) at room temperature. The reaction mixture was stirred for 24 h and diluted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave 5.40 g (64%) of L-Ser(TBS)-OBn.

A solution of Fmoc-Ala-Pro-Phe-OH (3.01 g, 5.42 mmol) in CH_2Cl_2 (18 mL) was cooled to −10 °C, and DEPC (0.89 mL, 5.5 mmol) was added dropwise. After the reaction mixture had been stirred for 30 min and warmed to −5 °C, a solution of L-Ser(TBS)-OBn (1.68 g, 5.42 mmol) and (*i*-Pr)$_2$NEt (0.94 mL, 5.3 mmol) in CH_2Cl_2 (12 mL) was added via cannula. The mixture was stirred at −5 °C for 11 h, diluted with $CHCl_3$ (70 mL), washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:1, then 1:2) yielded 3.88 g (80% over two steps) of **14** as a colorless amorphous solid: $[\alpha]_D$ −39.0 (*c* 0.97, $CHCl_3$, 23 °C); IR (film) 3304, 3065, 1716, 1639 cm^{-1}; ^{1}H NMR (benzene-d_6, 343 K) δ 7.58 (d, 2 H, J = 7.6 Hz), 7.55−7.45 (m, 2 H), 7.35−6.95 (m, 15 H), 6.72 (bs, 1 H), 5.42 (bs, 1 H), 5.05, 5.00 (AB, 2 H, J = 12.4 Hz), 4.86−4.68 (m, 2 H), 4.48−4.30 (m, 4 H), 4.10 (t, 1 H, J = 6.6 Hz), 3.95 (dd, 1 H, J = 3.3, 10.0 Hz), 3.79 (dd, 1 H, J = 3.9, 10.0 Hz), 3.20−2.80 (m, 4 H), 2.13−2.04 (m, 1 H), 1.64−1.48 (m, 1 H), 1.47−1.23 (m, 2 H), 1.09 (d, 3 H, J = 6.6 Hz), 0.88 (s, 9 H), −0.01 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR δ 172.8, 170.8, 170.5, 169.9, 155.8, 144.0, 143.9, 141.4, 136.5, 135.4, 129.5, 129.2, 128.8, 128.7, 128.5, 127.9, 127.2, 125.3, 120.2, 67.4, 67.1, 63.4, 60.2, 54.6, 54.3, 48.4, 47.3, 47.2, 38.4, 27.7, 25.9, 25.1, 18.7, 18.3, −5.4, −5.5; MS (FAB) *m/z* (rel intensity) 848 ([M + H]$^+$, 10), 391 (8), 310 (11), 179 (100).

General Procedure E for Segment Condensation with PyBOP. Fmoc-Ala-Pro-Phe-Ser(TBS)-Thr(rprenyl)-Ser-(rprenyl)-Ile-OMe (13). A suspension of Et_3SiH (228 μL, 1.43 mmol), Pd(OAc)$_2$ (29.2 mg, 0.130 mmol), and Et_3N (36 μL, 0.260 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 15 min under a nitrogen atmosphere. To this mixture was added a solution of Cbz-Thr(rprenyl)-Ser(rprenyl)-Ile-OMe (**15**, 391 mg, 0.648 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 37 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1, then 1:1, followed by $CHCl_3$/MeOH, 10:1) to yield 280 mg (92%) of **25** as a dark oil.

A solution of Fmoc-Ala-Pro-Phe-Ser(TBS)-OBn (**14**, 1.00 g, 1.18 mmol) in EtOAc/EtOH (2:1, 15 mL) was treated with Pd/C (10% Pd, 64 mg) and H_2 gas for 20 h. The reaction mixture was filtered through a plug of Celite and concentrated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:1, then $CHCl_3$/MeOH, 5:1) yielded 0.805 g (90%) of the acid as a colorless solid. This acid (79.0 mg, 0.104 mmol) and the amine **25** (48.9 mg, 0.104 mmol) prepared above and PyBOP (65.4 mg, 0.125 mmol) were dissolved in CH_2Cl_2 (2.0 mL), and the coupling reaction was initiated by addition of (*i*-Pr)$_2$NEt (37 μL, 0.208 mmol). The reaction mixture was stirred at room temperature for 16 h and diluted with $CHCl_3$, and the organic layer was washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:2) yielded 102 mg (78% over two steps) of **13** as a colorless foam: $[\alpha]_D$ −6.5 (*c* 0.95, $CHCl_3$, 23 °C); IR (film) 3303, 1721, 1690 cm^{-1}; ^{1}H NMR (benzene-d_6, 343 K), δ 7.78 (d, 1 H, J = 6.7 Hz), 7.67 (d, 3 H, J = 6.9 Hz), 7.61 (d, 2 H, J = 6.8 Hz), 7.35−7.05 (11 H, m), 7.00 (bs, 1 H), 6.12 (dd, 1 H, J = 10.9, 17.6 Hz), 5.94 (dd, 1 H, J = 10.9, 17.6 Hz), 5.67 (bs, 1 H), 5.29−5.06 (m, 4 H), 4.93−4.82 (m, 2 H), 4.76−4.66 (m, 2 H), 4.53−4.39 (m, 5 H), 4.25−4.20 (m, 2 H), 4.06−4.00 (m, 2 H), 3.82 (dd, 1 H, J = 6.8, 9.7 Hz), 3.48−3.40 (m, 1 H), 3.44 (s, 3 H), 3.32−3.25 (m, 2 H), 3.20−3.05 (m, 2 H), 2.25−2.10 (m, 1 H), 2.05−1.90 (m, 1 H), 1.60−1.40 (m, 3 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.40−1.15 (m, 14 H), 1.06 (s, 9 H), 1.05−0.90 (m, 6 H), 0.21 (s, 6 H); ^{13}C NMR (benzene-d_6, 343 K) δ 172.9, 172.5, 171.6, 170.4, 169.9, 156.4, 145.1, 144.6, 144.1, 142.3, 138.3, 130.2, 129.1, 127.8, 127.3, 125.8, 120.6, 114.5, 114.4, 77.8, 76.6, 68.3, 67.6, 64.2, 63.5, 61.0, 59.3, 57.5, 56.2, 55.8, 54.6, 51.6, 49.3, 48.5, 47.4, 38.9, 28.1, 26.6, 26.4, 26.3, 26.2, 25.2, 19.0, 18.8, 18.1, 16.4, 16.1, 11.9, −4.8; MS (FAB) *m/z* (rel intensity) 1230 ([M + Na]$^+$, 9), 179 (100).

General Procedure F for Macrolactamization with HATU. Cyclo[Ala-Pro-Phe-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (27). A solution of **13** (90.2 mg, 74.7 μmol) in CH_2Cl_2 (3.0 mL) was treated with tris(2-aminoethyl)amine (TAEA, 185 μL, 1.24 mmol) under a nitrogen atmosphere at room temperature for 30 min. The reaction mixture was diluted with $CHCl_3$ and washed with brine and phosphate buffer (pH 5.5). Additional $CHCl_3$ was used for back extractions. The organic layer was dried (Na_2SO_4) and concentrated. The purification of the residue by chromatography on a short plug of SiO_2 (EtOAc, then $CHCl_3$/MeOH, 5:1) yielded 73.6 mg of amine as a colorless solid.

A suspension of this amine in THF (3.0 mL) was treated with tetrabutylammonium hydroxide (TBAH, 40 wt %, 98 μL, 0.15 mmol) at 0 °C for 4 h. The reaction mixture was diluted with $CHCl_3$, washed with phosphate buffer (pH 5.5), dried (Na_2SO_4), and concentrated to yield 60.1 mg (83% over two steps) of amino acid that was used without further purification.

This amino acid (18.9 mg, 0.0195 mmol) and HATU (8.8 mg, 0.023 mmol) were dissolved in DMF (20 mL), and the coupling reaction was initiated by addition of $(i\text{-Pr})_2NEt$ (10.5 μL, 0.0585 mmol) at room temperature. The reaction mixture was stirred for 7 d and treated with $NaHCO_3$, and the solvents were removed at reduced pressure. The residue was dissolved in $CHCl_3$ and washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), concentrated, and purified by preparative TLC ($CHCl_3$/MeOH, 15:1) to give 7.1 mg of colorless solid that was dissolved in THF (1.0 mL) and treated with NH_4F (1.5 mg, 0.040 mmol) and 1 M TBAF in THF (20 μL, 0.020 mmol). After 30 min, the reaction mixture was dissolved in $CHCl_3$, washed with 10% citric acid and brine, dried (Na_2SO_4), and concentrated. The purification of the residue by preparative TLC ($CHCl_3$/MeOH, 15:1) yielded 5.2 mg (26% over four steps) of **27** as a colorless solid: mp 167−169 °C; $[\alpha]_D$ −94.0 (*c* 0.60, $CHCl_3$, 23 °C); IR (film) 3311, 1637, 1517, cm^{-1}; ^1H NMR δ 7.87 (d, 2 H, *J* = 6.5 Hz), 7.34−7.16 (m, 5 H), 7.10 (d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 8.6 Hz), 6.65 (d, 1 H, *J* = 6.4 Hz), 6.47 (d, 1 H, *J* = 4.9 Hz), 5.75 (dd, 1 H, *J* = 10.6, 17.2 Hz), 5.73 (dd, 1 H, *J* = 10.8 Hz, 17.5 Hz), 5.25−5.10 (m, 4 H), 4.79−4.64 (m, 3 H), 4.47−4.42 (m, 2 H), 4.34 (d, 1 H, *J* = 7.7 Hz), 4.23−4.04 (m, 3 H), 3.98−3.88 (m, 1 H), 3.80−3.70 (m, 1 H), 3.65−3.55 (m, 1 H), 3.43−3.32 (m, 3 H), 3.10−2.98 (m, 1 H), 2.33−2.27 (m, 1 H), 1.92−1.47 (m, 4 H), 1.40−1.10 (m, 20 H), 1.00−0.87 (m, 6 H); ^{13}C NMR δ 172.2, 171.8, 171.0, 170.8, 170.4, 170.1, 169.6, 143.3, 142.9, 136.7, 129.8, 129.2, 129.0, 128.3, 127.5, 115.2, 114.6, 76.2, 75.9, 66.9, 64.2, 62.5, 61.2, 60.9, 57.9, 55.9, 54.4, 53.9, 48.8, 46.9, 38.3, 36.6, 31.7, 29.9, 27.0, 25.9, 25.8, 25.0, 24.8, 21.9, 21.4, 16.4, 15.4, 11.5; MS (EI) *m*/*z* (rel intensity) 839 (M^+, 0.2), 822 (1), 753 (1), 727 (2); HRMS *m*/*z* calcd for $C_{38}H_{55}N_7O_9$ ($M-C_5H_{10}O$) 753.4061, found 753.4026.

General Procedure G for Cyclodehydration with DAST. Cyclo[Ala-Pro-Phe-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (12). A solution of **27** (21.5 mg, 25.6 μmol) in CH_2Cl_2 (0.2 mL) was cooled to −20 °C under a N_2 atmosphere, and a 0.28 M solution of DAST in CH_2Cl_2 (100 μL) was slowly added. After 30 min, additional DAST solution (100 μL) was added slowly. After stirring for an additional 30 min, the reaction mixture was quenched at −20 °C with saturated aqueous $NaHCO_3$, warmed to room temperature, and treated with additional saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The purification of the residue by chromatography on SiO_2 ($CHCl_3$/MeOH, 30:1) gave 13.2 mg (63%) of **12** as a colorless solid: mp 148−150 °C; $[\alpha]_D$ +9.8 (*c* 0.66, $CHCl_3$, 22 °C); IR (film) 3371, 1666 cm^{-1}; ^1H NMR δ 8.21 (d, 1 H, *J* = 6.7 Hz), 8.06, (d, 1 H, *J* = 6.5 Hz), 7.47 (d, 1 H, *J* = 6.8 Hz), 7.29−6.98 (m, 6 H), 6.22 (d, 1 H, *J* = 9.7 Hz), 5.91 (dd, 1 H, *J* = 10.7, 17.6 Hz), 5.73 (dd, 1 H, *J* = 10.9, 17.6 Hz), 5.31 (d, 1 H, *J* = 17.5 Hz), 5.29 (d, 1 H, *J* = 10.6 Hz), 5.15 (d, 1 H, *J* = 10.7 Hz), 5.11 (d, 1 H, *J* = 17.6 Hz), 4.98−4.86 (m, 2 H), 4.76−4.54 (m, 5 H), 4.51−4.44 (m, 2 H), 3.98−3.86 (m, 2 H), 3.54−3.41 (m, 3 H), 3.17 (dd, 1 H, *J* = 5.0, 13.9 Hz), 2.95 (dd, 1 H, *J* = 5.2 Hz, 13.9 Hz), 2.61−2.54 (m, 1 H), 2.45−2.39 (m, 1 H), 2.06−1.86 (m, 2 H), 1.76−1.56 (m, 1 H), 1.48 (s, 3 H), 1.39 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 1.15 (d, 3 H, *J* = 6.7 Hz), 1.20−1.05 (m, 2 H), 1.00−0.85 (m, 6 H), 0.81−0.74 (m, 3 H); ^{13}C NMR δ 172.8, 170.8, 170.4, 170.2, 169.1, 167.7, 142.7, 142.3, 136.6, 129.7, 128.4, 126.9, 115.9, 115.2, 77.9, 76.1, 70.9, 68.0, 67.1, 62.1, 59.9, 57.7, 56.3, 56.1, 49.4, 47.9, 47.4, 38.0, 36.7, 29.9, 27.5, 25.9, 25.8, 25.6, 25.3, 23.8, 19.1, 18.4, 16.2, 12.3; MS (FAB) *m*/*z* (rel intensity) 844 ($[M + Na]^+$, 80), 822 ($[M + H]^+$, 100); HRMS (FAB) *m*/*z* calcd for (M + Na) $C_{43}H_{63}N_7O_9Na$ 844.4585, found 844.4605.

General Procedure H for Thiolysis of Oxazolines. Cyclo[Ala-Pro-PheΨ{(C═S)NH}-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile]. A solution of **12** (13 mg, 16 μmol) in MeOH/Et_3N (2:1, 1.0 mL) was saturated with H_2S gas at room temperature. The reaction mixture was stirred for 2 d and then concentrated. Purification of the residue by preparative TLC gave 11.7 mg (88%) of cyclo[Ala-Pro-PheΨ{(C═S)NH}-Ser-Thr-(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 181−183 °C; $[\alpha]_D$ −68.6 (*c* 0.64, $CHCl_3$, 22 °C); IR (film) 3296, 1641, 1519 cm^{-1}; ^1H NMR δ 9.47 (d, 1 H, *J* = 6.7 Hz), 7.40−7.05 (m, 7 H), 6.98 (d, 1 H, *J* = 8.5 Hz), 6.72 (d, 1 H, *J* = 6.5 Hz), 6.62 (d, 1 H, *J* = 5.4 Hz), 5.75 (dd, 1 H, *J* = 17.7, 10.7 Hz), 5.73 (dd, 1 H, *J* = 17.5, 10.7 Hz), 5.35−5.25 (m, 1 H), 5.17 (d, 1 H, *J* = 17.5 Hz), 5.18 (d, 1 H, *J* = 11.2 Hz), 5.14 (d, 1 H, *J* = 17.5 Hz), 5.11 (d, 1 H, *J* = 10.6 Hz), 5.05−4.90 (m, 1 H), 4.74 (dd, 1 H, *J* = 1.2, 9.6 Hz), 4.59 (p, 1 H, *J* = 6.6 Hz), 4.30−4.20 (m, 2 H), 4.20−4.10 (m, 2 H), 4.05−3.90 (m, 2 H), 3.75 (d, 1 H, *J* = 9.1 Hz), 3.68 (dd, 1 H, *J* = 3.9, 13.7 Hz), 3.38−3.10 (m, 2 H), 3.00−2.75 (m, 2 H), 2.30−2.20 (m, 1 H), 1.85−1.68 (m, 2 H), 1.65−1.45 (m, 3 H), 1.33 (d, 3 H, *J* = 7.0 Hz), 1.29 (s, 6 H), 1.23 (s, 3 H), 1.20 (s, 3 H), 1.18−1.02 (m, 2 H), 1.00 (d, 3 H, *J* = 6.5 Hz), 0.95−0.75 (m, 6 H); ^{13}C NMR δ 201.5, 172.3, 171.6, 170.8, 170.4, 169.7, 168.9, 143.1, 142.8, 137.1, 129.3, 129.0, 127.6, 115.4, 114.8, 76.3, 75.0, 73.1, 66.9, 64.1, 63.0, 62.5, 60.9, 59.1, 57.9, 53.8, 48.9, 46.8, 41.6, 36.1, 31.7, 27.1, 25.9, 25.0, 22.1, 21.5, 16.6, 15.5, 11.4; MS (FAB) *m*/*z* (rel intensity) 878 ($[M + Na]^+$, 100); HRMS (FAB) *m*/*z* calcd for $C_{43}H_{65}N_7O_9NaS$ (M + Na) 878.4462, found 878.4478.

Cyclo[Ala-Pro-Phe-Ser(thiaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (11). According to general procedure G, cyclo[Ala-Pro-PheΨ{(C═S)NH}-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (5.4 mg, 6.3 μmol) provided 4.0 mg (76%) of **11** as a colorless amorphous solid: $[\alpha]_D$ −10.4° (*c* 0.5, $CHCl_3$, 22 °C); IR (neat) 3375, 1671, 1634 cm^{-1}; ^1H NMR (500 MHz) δ 8.38 (d, 1 H, *J* = 6.9 Hz), 8.10 (d, 1 H, *J* = 7.0 Hz), 7.49 (d, 1 H, *J* = 7.0 Hz), 7.22 (d, 1 H, *J* = 5.6 Hz), 7.12−7.08 (m, 3 H), 7.02−6.98 (m, 2 H), 6.19 (d, 1 H, *J* = 10.0 Hz), 5.88 (dd, 1 H, *J* = 10.8, 17.5 Hz), 5.68 (dd, 1 H, *J* = 10.9, 17.5 Hz), 5.25 (d, 1 H, *J* = 17.5 Hz), 5.22 (d, 1 H, *J* = 10.6 Hz), 5.09 (d, 1 H, *J* = 11.0 Hz), 5.06 (d, 1 H, *J* = 18.4 Hz), 4.97−4.90 (m, 2 H), 4.78 (d, 1 H, *J* = 7.8 Hz), 4.59 (dd, 1 H, *J* = 2.9, 10.0 Hz), 4.56−4.51 (m, 2 H), 4.40−4.38 (m, 1 H), 3.91 (p, 1 H, *J* = 5.9 Hz), 3.83 (dd, 1 H, *J* = 1.5, 9.0 Hz), 3.59 (t, 1 H, *J* = 11.2 Hz), 3.54 (t, 1 H, *J* = 11.1 Hz), 3.43 (dd, 1 H, *J* = 3.2, 9.2 Hz), 3.41−3.24 (m, 2 H), 3.15 (dd, 1 H, *J* = 5.5, 14.0 Hz), 2.87 (dd, 1 H, *J* = 5.7, 14.1 Hz), 2.51−2.47 (m, 1 H), 2.37−2.34 (m, 1 H), 1.93−1.80 (m, 2 H), 1.58−1.50 (m, 1 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 1.24−1.17 (m, 2 H), 1.21 (s, 3 H), 1.18 (s, 6 H), 1.11 (d, 3 H, *J* = 6.6 Hz), 0.92−0.84 (m, 6 H); ^{13}C NMR δ 172.8, 171.9, 170.8, 170.5, 169.9, 169.3, 142.8, 142.4, 136.5, 129.7, 128.3, 127.0, 115.9, 115.2, 77.9, 76.2, 67.4, 62.1, 59.8, 57.7, 56.5, 56.2, 53.7, 47.9, 47.4, 40.7, 36.6, 35.9, 29.9, 27.5, 26.0, 25.9, 25.6, 25.3, 24.0, 19.1, 18.5, 16.3, 12.3; MS (FAB) *m*/*z* (rel intensity), 838 ($[M + H]^+$, 100), 860 ($[M + Na]^+$, 24); HRMS (FAB) *m*/*z* calcd for $C_{43}H_{63}N_7O_8NaS$ (M + Na) 860.4357, found 860.4314.

Fmoc-Ala-Pro-D-Phe-OBn (37). According to general procedure C, Fmoc-Ala-Pro-OH (1.36 g, 3.33 mmol) and D-Phe-OBn·TsOH (1.43 g, 3.33 mmol) provided 1.78 g (83%) of **37** as a colorless amorphous wax: $[\alpha]_D$ −53.0 (*c* 0.27, $CHCl_3$, 22 °C); IR (film) 3399, 3307, 3059, 3032, 1716, 1680 cm^{-1}; ^1H NMR (methanol-d_4) δ 7.73 (d, 2 H, *J* = 7.3 Hz), 7.65−7.50 (m, 2 H), 7.38−7.00 (m, 14 H), 5.08 (s, 2 H), 4.72−4.58 (m, 1 H), 4.40−4.20 (m, 3 H), 4.14 (t, 1 H, *J* = 6.4 Hz), 4.10−3.90 (m, 1 H), 3.70−3.53 (m, 1 H), 3.50−3.40 (m, 1 H), 3.17 (dd, 1 H, *J* = 5.4, 13.7 Hz), 2.95 (dd, 1 H, *J* = 9.0, 13.7 Hz), 2.05−1.83 (m, 1 H), 1.80−1.65 (m, 2 H), 1.63−1.50 (m, 1 H), 1.23 (d, 3 H, *J*

= 6.9 Hz); ^{13}C NMR (methanol-d_4) δ 174.2, 174.0, 172.5, 158.4, 145.4, 145.3, 142.7, 138.1, 137.2, 130.6, 129.7, 129.5, 128.9, 128.3, 128.0, 126.3, 121.1, 68.2, 68.0, 61.4, 55.2, 38.8, 30.4, 25.9, 17.2; MS (EI) *m/z* (rel intensity) 645 (M^+, 0.4), 449 (3), 167 (68); HRMS *m/z* calcd for $C_{39}H_{39}N_3O_6$ 645.2839, found 645.2856.

Fmoc-Ala-Pro-D-Phe-Ser(TBS)-OBn (28). According to general procedure D, Fmoc-Ala-Pro-D-Phe-OBn (**37**, 1.78 g, 2.75 mmol) and L-Ser-(TBS)-OBn (0.836 g, 2.70 mmol) provided 1.59 g (68% over two steps) of **28** as a colorless foam: $[\alpha]_D$ −37.1 (*c* 0.35, $CHCl_3$, 22 °C); IR (film) 3329, 3030, 1743, 1704, 1650 cm^{-1}; ^{1}H NMR (methanol-d_4) δ 7.79 (d, 2 H, *J* = 7.5 Hz), 7.64 (t, 2 H, *J* = 6.3 Hz), 7.42−7.17 (m, 14 H), 5.16 (s, 2 H), 4.73 (dd, 1 H, *J* = 4.9, 9.7 Hz), 4.56 (t, 1 H, *J* = 4.8 Hz), 4.42−4.30 (m, 4 H), 4.23−4.13 (m, 1 H), 3.98−3.82 (m, 2 H), 3.72−3.62 (m, 1 H), 3.56−3.48 (m, 1 H), 3.25 (dd, 1 H, *J* = 5.1, 14.0 Hz), 2.82 (dd, 1 H, *J* = 13.9, 10.0 Hz), 2.01−1.90 (m, 1 H), 1.90−1.78 (m, 2 H), 1.61−1.48 (m, 1 H), 1.28 (d, 3 H, *J* = 6.9 Hz), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (methanol-d_4) δ 174.3, 173.7, 173.2, 171.5, 158.1, 145.4, 145.3, 142.7, 138.7, 137.1, 130.5, 129.7, 129.5, 128.9, 128.3, 127.9, 126.3, 121.1, 68.2, 68.0, 64.1, 61.7, 56.4, 55.5, 48.5, 38.9, 30.3, 26.5, 26.0, 19.2, 17.5, −5.1, −5.2; MS (EI) *m/z* (rel intensity) 790 ([M − C_4H_8]$^+$, 2), 567 (100), 310 (55), 178 (55); HRMS *m/z* calcd for $C_{44}H_{50}N_4O_8Si$ (M − C_4H_8) 790.3398, found 790.3404.

Fmoc-Ala-Pro-D-Phe-Ser(TBS)-Thr(rprenyl)-Ser(rprenyl)-Ile-OMe (29). According to general procedure E, Fmoc-Ala-Pro-D-Phe-Ser(TBDMS)-OBn (**28**, 0.964 g, 1.14 mmol) and amine **25** (0.490 g, 1.04 mmol) provided 0.702 g (51% over two steps) of **29** as a colorless foam: $[\alpha]_D$ +8.8 (*c* 0.43, $CHCl_3$, 22 °C); IR (film) 3301, 1642 cm^{-1}; ^{1}H NMR (methanol-d_4) δ 7.78 (d, 2 H, *J* = 6.8 Hz), 7.70−7.52 (m, 2 H), 7.40−7.10 (m, 9 H), 5.92 (dd, 1 H, *J* = 10.9, 17.4 Hz), 5.77 (dd, 1 H, *J* = 10.6, 17.6 Hz), 5.25−5.05 (m, 4 H), 4.70−4.60 (m, 1 H), 4.54−4.48 (m, 1 H), 4.47−4.36 (m, 4 H), 4.35−4.23 (m, 3 H), 4.42−4.12 (m, 1 H), 4.05−3.97 (m, 1 H), 3.92−3.78 (m, 2 H), 3.67 (s, 3 H), 3.72−3.60 (m, 2 H), 3.58−3.45 (m, 1 H), 3.43−3.33 (m, 1 H), 3.33−3.23 (m, 1 H), 2.86 (t, 1 H, *J* = 12 Hz), 2.00−1.77 (m, 3 H), 1.60−1.00 (m, 22 H), 0.92−0.75 (m, 6 H), 0.87 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (benzene-d_6) δ 172.9, 172.4, 172.1, 171.4, 171.0, 170.4, 169.7, 156.4, 145.0, 144.8, 143.9, 143.6, 142.1, 138.3, 130.2, 129.0, 127.2, 126.0, 125.9, 123.3, 120.6, 115.1, 114.9, 77.8, 76.5, 68.3, 67.4, 64.0, 63.3, 60.6, 58.7, 57.2, 55.1, 54.0, 51.8, 49.2, 48.0, 47.0, 38.5, 28.4, 26.6, 26.2, 26.0, 25.8, 25.6, 25.4, 18.8, 17.9, 16.0, 12.0, −4.8; MS (FAB) *m/z* (rel intensity) 1247 ([M + K], 100).

Cyclo[Ala-Pro-D-Phe-Ser-Thr(rev)-Ser(rev)-Ile] (30). A solution of Fmoc-Ala-Pro-D-Phe-Ser(TBS)-Thr(rprenyl)-Ser-(rprenyl)-Ile-OMe (**29**, 218 mg, 0.180 mmol) in CH_2Cl_2 (5.0 mL) was treated with tris(2-aminoethyl)amine (TAEA, 0.45 mL, 3.0 mmol) at room temperature for 30 min. The reaction mixture was diluted with $CHCl_3$ and washed with brine and phosphate buffer (pH 5.5). Additional $CHCl_3$ was used for back extraction. The combined organic layers were dried (Na_2SO_4) and concentrated. The purification of the residue by chromatography on a short plug of SiO_2 (EtOAc, then $CHCl_3$/MeOH, 5:1) yielded 210 mg of amine as a colorless solid.

A solution of TBAH (40 wt %) in THF (0.072 M, 5.0 mL) was added slowly at 0 °C to this amine. The reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was diluted with $CHCl_3$, washed with phosphate buffer (pH 5.5), dried (Na_2SO_4), and then concentrated to yield 142.3 mg (82% over two steps) of amino acid that was used without further purification.

To a solution of this amino acid in CH_2Cl_2 (98 mL) was added at 0 °C a solution of TBTU (144 mg, 0.447 mmol) in acetonitrile (3.0 mL), followed by HOAt (59.7 mg, 0.441 mmol). After addition of (*i*-Pr)$_2$NEt (0.98 mL, 1% v/v) over a period of 15 min at 0 °C, the reaction mixture was stirred for 2 h at 0 °C and then for 3 d at room temperature. The solution was washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Chromatography on a short plug of SiO_2 ($CHCl_3$/MeOH, 20:1) yielded 102.1 mg of a colorless solid, which was mixed with NH_4F (11.7 mg, 0.316 mmol), dissolved in THF (15 mL), and treated with 1 M TBAF in THF (150 μL, 0.150 mmol) for 30 min. The reaction mixture was diluted with $CHCl_3$, washed with 10% citric acid and brine, and dried (Na_2SO_4). Chromatography on SiO_2 ($CHCl_3$/MeOH, 40:1) yielded 57.6 mg (38% over four steps) of **30** as a colorless solid: mp 162−164 °C; $[\alpha]_D$ −12.4 (*c* 0.33, $CHCl_3$, 22 °C); IR (film) 3319, 1643 cm^{-1}; ^{1}H NMR δ 8.13 (d, 1 H, *J* = 8.1 Hz), 7.77 (d, 1 H, *J* = 7.5 Hz), 7.32−7.15 (m, 8 H), 6.80 (d, 1 H, *J* = 5.4 Hz), 5.82 (dd, 1 H, *J* = 10.8 Hz, 17.5 Hz), 5.80 (dd, 1 H, *J* = 10.8, 17.8 Hz), 5.21−5.09 (m, 4 H), 4.96 (d, 1 H, *J* = 7.4 Hz), 4.80−4.65 (m, 3 H), 4.48−4.44 (m, 1 H), 4.34 (d, 1 H, *J* = 7.6 Hz), 4.22−4.15 (m, 2 H), 4.02−3.88 (m, 2 H), 3.72 (d, 1 H, *J* = 11.0 Hz), 3.61−3.52 (m, 2 H), 3.48−3.43 (m, 1 H), 3.31 (dd, 1 H, *J* = 5.0, 14.4 Hz), 3.04 (dd, 1 H, *J* = 9.3, 14.3 Hz), 2.22−2.10 (m, 1 H), 2.10−1.80 (m, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 6 H), 1.15 (d, 3 H, *J* = 6.3 Hz),1.20−1.00 (m, 6 H), 0.98−0.85 (m, 6 H); ^{13}C NMR δ 172.3, 171.7, 171.4, 171.2, 171.1, 170.0, 169.7, 143.6, 142.4, 137.1, 129.2, 128.8, 127.1, 115.5, 114.4, 77.0, 76.6, 66.9, 65.0, 62.6, 61.5, 59.5, 59.1, 54.7, 54.5, 53.2, 48.0, 46.7, 37.5, 35.9, 29.3, 27.6, 26.0, 25.9, 25.8, 25.5, 24.6, 20.7, 17.0, 16.4, 12.0; HRMS (FAB) *m/z* calcd for $C_{43}H_{65}N_7O_{10}Na$ (M + Na) 862. 4691, found 862.4763.

Cyclo[Ala-Pro-D-Phe-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile]. According to general procedure G, **30** (44.8 mg, 53.4 μmol) provided 40.7 mg (93%) of cyclo[Ala-Pro-D-Phe-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 147−149 °C; $[\alpha]_D$ +14.6 (*c* 0.35, $CHCl_3$, 22 °C); IR (film) 3380, 1664 cm^{-1}; ^{1}H NMR δ 7.87 (d, 1 H, *J* = 6.5 Hz), 7.48 (d, 1 H, *J* = 7.9 Hz), 7.30−7.22 (m, 4 H), 7.10−7.07 (m, 2 H), 6.92 (d, 1 H, *J* = 7.5 Hz), 6.32 (d, 1 H, *J* = 9.8 Hz), 5.90 (dd, 1 H, *J* = 10.7, 17.6 Hz), 5.73 (dd, 1 H, *J* = 10.9, 17.6 Hz), 5.27 (d, 1 H, *J* = 17.5 Hz), 5.24 (d, 1 H, *J* = 10.7 Hz), 5.15 (d, 1 H, *J* = 10.8 Hz), 5.11 (d, 1 H, *J* = 17.6 Hz), 4.99 (dd, 1 H, *J* = 6.9, 12.6 Hz), 4.64−4.55 (m, 5 H), 4.53−4.48 (m, 2 H), 4.42−4.37 (m, 1 H), 4.01 (p, 1 H, *J* = 5.7 Hz), 3.90 (dd, 1 H, *J* = 1.8, 9.0 Hz), 3.55−3.47 (m, 2 H), 3.43 (dd, 1 H, *J* = 3.2, 9.0 Hz), 3.20 (dd, 1 H, *J* = 5.0, 13.7 Hz), 2.93 (dd, 1 H, *J* = 6.8, 13.7 Hz), 2.42−2.35 (m, 1 H), 2.22−2.13 (m, 1 H), 2.00−1.78 (m, 3 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.40−1.30 (m, 2 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 1.21 (d, 3 H, *J* = 6.6 Hz), 1.03 (d, 3 H, *J* = 6.5 Hz), 0.96−0.80 (m, 6 H); ^{13}C NMR δ 171.6, 171.0, 170.8, 170.5, 170.2, 169.0, 168.7, 142.8, 142.2, 136.0, 129.6, 128.6, 127.3, 115.9, 115.2, 78.0, 76.1, 71.5, 68.1, 67.3, 62.4, 60.1, 58.0, 56.5, 55.4, 48.2, 48.0, 47.3, 39.1, 36.6, 28.9, 27.4, 26.0, 25.9, 25.8, 25.7, 23.7, 18.6, 18.1, 16.2, 12.2; MS (FAB) *m/z* (rel intensity) 844 ([M + Na]$^+$, 100), 822([M + H]$^+$, 30); HRMS (FAB) *m/z* calcd for $C_{43}H_{64}N_7O_9$ (M + H) 822.4766, found 822.4811.

Cyclo[Ala-Pro-D-PheΨ{(C=S)NH}-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile]. According to general procedure H, cyclo-[Ala-Pro-D-Phe-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (36 mg, 44 μmol) provided 28 mg (74%) of cyclo[Ala-Pro-D-PheΨ{(C=S)NH}-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 150−152 °C; $[\alpha]_D$ +0.5 (*c* 0.40, $CHCl_3$, 22 °C); IR (film) 3304, 1675 cm^{-1}; ^{1}H NMR δ 9.03 (bs, 1 H), 8.12 (d, 1 H, *J* = 7.4 Hz), 7.32−7.21 (m, 6 H), 7.08 (bs, 1 H), 6.83 (bs, 1 H), 6.76 (bs, 1 H), 5.81 (dd, 1 H, *J* = 10.8, 17.5 Hz), 5.80 (dd, 1 H, *J* = 10.4, 17.8 Hz), 5.70 (d, 1 H, *J* = 6.7 Hz), 5.19 (d, 1 H, *J* = 11.4 Hz), 5.18 (d, 1 H, *J* = 16.9 Hz), 5.14 (d, 1 H, *J* = 17.3 Hz), 5.11 (d, 1 H, *J* = 10.8 Hz), 5.12−5.08 (m, 1 H), 4.78−4.60 (m, 2 H), 4.43 (d, 1 H, *J* = 6.2 Hz), 4.35 (d, 1 H, *J* = 6.9 Hz), 4.19 (d, 2 H, *J* = 6.2 Hz), 4.05−3.95 (m, 1 H), 3.90−3.80 (m, 1 H), 3.77−3.65 (m, 1 H), 3.60−3.44 (m, 4 H), 3.03 (dd, 1 H, *J* = 9.6, 14.1 Hz), 2.20−1.70 (m, 6 H), 1.52−1.40 (m, 1 H), 1.32 (s, 6 H), 1.26 (s, 6 H), 1.30−1.10 (m, 4 H), 1.15 (d, 3 H, *J* = 6.3 Hz), 0.97−0.85 (m, 6 H); ^{13}C NMR δ 202.8, 172.4, 171.4, 171.2, 169.7, 169.3, 168.5, 143.6, 142.3, 137.0, 129.2, 128.9, 127.2, 115.6, 114.4, 79.2, 67.0, 62.8, 62.0, 61.2, 59.9, 59.1, 52.7, 47.9, 46.7, 35.9, 29.2, 27.6, 26.1, 25.9, 25.6, 24.6, 21.0, 16.9, 16.4, 12.0; MS (FAB) *m/z* (rel intensity) 878 ([M + Na]$^+$, 100).

Cyclo[Ala-Pro-D-Phe-Ser(thiaz)-Thr(rprenyl)-Ser-(rprenyl)-Ile] (31). According to general procedure G, cyclo-[Ala-Pro-D-PheΨ{(C=S)NH}-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (27.6 mg, 32.6 μmol) provided 23.1 mg (85%) of **31** as a colorless amorphous solid: $[\alpha]_D$ −4.1 (*c* 0.32 $CHCl_3$, 22 °C); IR (film) 3375, 3054, 1669 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.95 (d, 1 H, *J* = 6.7 Hz), 7.56 (d, 1 H, *J* = 7.9 Hz), 7.27−7.22 (m, 4 H), 7.22 (d, 1 H, *J* = 7.6 Hz), 7.14−7.10 (m, 2 H), 6.32 (d, 1 H, *J*

= 9.7 Hz), 5.91 (dd, 1 H, *J* = 10.7, 17.5 Hz), 5.73 (dd, 1 H, *J* = 10.9, 17.4 Hz), 5.27 (d, 1 H, *J* = 19.4 Hz), 5.24 (d, 1 H, *J* = 10.9 Hz), 5.30−5.10 (m, 1 H), 5.15 (d, 1 H, *J* = 10.9 Hz), 5.12 (d, 1 H, *J* = 17.7 Hz), 4.92 (t, 1 H, *J* = 9.6 Hz), 4.62−4.55 (m, 3 H), 4.52−4.47 (m, 1 H), 4.41−4.38 (m, 1 H), 4.02 (p, 1 H, *J* = 6.0 Hz), 3.89 (dd, 1 H, *J* = 1.5, 9.5 Hz), 3.72 (t, 1 H, *J* = 10.5 Hz), 3.62 (t, 1 H, *J* = 10.5 Hz), 3.55−3.47 (m, 2 H), 3.45 (dd, 1 H, *J* = 3.1, 9.2 Hz), 3.15 (dd, 1 H, *J* = 5.5, 14.0 Hz), 2.93 (dd, 1 H, *J* = 6.0, 13.9 Hz), 2.39−2.31 (m, 1 H), 2.26−2.18 (m, 1 H), 1.97−1.81 (m, 3 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 1.33−1.20 (m, 2 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 1.21 (d, 3 H, *J* = 6.6 Hz), 1.06 (d, 3 H, *J* = 6.6 Hz), 0.98−0.90 (m, 6 H); ^{13}C NMR *δ* 173.5, 171.3, 171.0, 170.6, 170.3, 170.1, 168.7, 142.7, 142.2, 135.8, 129.8, 128.5, 127.3, 116.0, 115.1, 78.3, 78.0, 76.1, 67.4, 62.3, 60.0, 58.0, 56.6, 55.4, 52.8, 47.8, 47.2, 40.2, 36.6, 36.4, 28.7, 27.5, 25.9, 25.8, 25.7, 23.8, 18.7, 18.1, 16.2, 12.1; MS (FAB) *m*/*z* (rel intensity) 860 ([M + Na]$^+$, 100), 838 ([M + H]$^+$, 34); HRMS (FAB) *m*/*z* calcd for $C_{43}H_{64}N_7O_8S$ (M + H) 838.4537, found 838.4588.

Fmoc-Ala-Pro-Phe-D-Ser(TBS)-OBn (33). According to general procedure D, **32** (1.87 g, 3.36 mmol) and D-Ser(TBS)-OBn (1.04 g, 3.36 mmol) provided 2.61 g (88% over two steps) of **33** as a colorless amorphous solid: [α]$_D$ −52.6 (*c* 0.43, $CHCl_3$, 22 °C); IR (film) 3411, 3301, 3059, 1739, 1719 cm^{-1}; ^{1}H NMR (methanol-d_4, major rotamer) *δ* 7.80 (d, 2 H, *J* = 7.4 Hz), 7.65 (d, 2 H, *J* = 7.5 Hz), 7.45−7.15 (m, 14 H), 5.16 (s, 2 H), 4.72 (t, 1 H, *J* = 7 Hz), 4.55−4.44 (m, 1 H), 4.43−4.25 (m, 4 H), 4.25−4.18 (m, 1 H), 3.90 (dd, 1 H, *J* = 4.4, 10.3 Hz), 3.75−3.62 (m, 2 H), 3.60−3.47 (m, 1 H), 3.14 (dd, 1 H, *J* = 7, 13.7 Hz), 2.97 (dd, 1 H, *J* = 7.5, 13.8 Hz), 2.25−2.00 (m, 1 H), 2.00−1.75 (m, 3 H), 1.30 (d, 3 H, *J* = 6.8 Hz), 0.84 (s, 9 H), −0.00 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (benzene-d_6) *δ* 173.1, 171.8, 171.4, 170.9, 156.5, 144.9, 142.1, 138.0, 136.4, 130.3, 130.0, 129.0, 127.8, 127.3, 126.0, 120.6, 67.4, 64.0, 60.9, 55.3, 54.4, 49.1, 48.0, 47.3, 38.0, 28.6, 26.3, 25.3, 18.7, 18.6, −5.1, −5.3; MS (FAB) *m*/*z* (rel intensity) 885 ([M + K]$^+$, 74), 869 ([M + Na]$^+$, 39), 847 ([M + H]$^+$, 100); HRMS (FAB) *m*/*z* calcd for $C_{48}H_{58}N_4O_8NaSi$ (M + Na) 869.3922, found 869.3948.

General Procedure I for Segment Condensation with HATU. Fmoc-Ala-Pro-Phe-D-Ser(TBS)-Thr(rprenyl)-Ser(rprenyl)-Ile-OMe (34). A solution of **33** (2.28 g, 2.69 mmol) in EtOAc/EtOH (2:1, 50 mL) was treated with Pd/C (10% Pd, 146 mg) and H_2 gas for 12 h. The reaction mixture was filtered through a plug of Celite and concentrated. Chromatography on SiO_2 ($CHCl_3$/MeOH, 1:0, 20:1, and 5:1) yielded 1.55 g (76%) of the acid as a colorless solid. This acid (41.3 mg, 54.5 μmol), amine **25** (25.5 mg, 54.5 μmol), and HATU (20.7 mg, 54.5 μmol) were dissolved in DMF (0.5 mL), and the coupling reaction was initiated by addition of (*i*-Pr)$_2$NEt (19 μL, 0.11 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with $CHCl_3$, and the organic layer was washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Chromatography on SiO_2 (hexanes/EtOAc, 1:2, then 1:4) yielded 55.1 mg (64% over two steps) of **34** as a colorless foam: [α]$_D$ −14.4 (*c* 0.50, $CHCl_3$, 22 °C); IR (film) 3310, 1650 cm^{-1}; ^{1}H NMR (methanol-d_4) *δ* 7.80 (d, 2 H, *J* = 7.5 Hz), 7.70−7.60 (m, 2 H), 7.45−7.10 (m, 9 H), 5.94 (dd, 1 H, *J* = 10.7, 17.6 Hz), 5.83 (dd, 1 H, *J* = 10.9, 17.7 Hz), 5.25−5.05 (m, 4 H), 4.65−4.50 (m, 2 H), 4.45−4.30 (m, 7 H), 4.21 (t, 2 H, *J* = 6.5 Hz), 4.05−3.97 (m, 1 H), 3.85−3.60 (m, 3 H), 3.67 (s, 3 H), 3.57−3.48 (m, 2 H), 3.20−3.10 (m, 1 H), 3.04−2.95 (m, 1 H), 2.15−2.00 (m, 1 H), 1.97−1.65 (m, 4 H), 1.55−1.46 (m, 1 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 6 H), 1.30−1.22 (m, 3 H), 1.10 (d, 3 H, *J* = 6.4 Hz), 1.08−0.99 (m, 1 H), 0.98−0.87 (m, 6 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR *δ* 172.7, 172.2, 171.1, 170.8, 170.1, 169.6, 168.8, 155.9, 144.1, 142.9, 141.4, 136.8, 129.4, 128.7, 127.9, 127.2, 125.3, 120.1, 115.1, 114.8, 76.0, 67.3, 67.2, 63.0, 62.8, 60.4, 57.8, 56.8, 55.0, 54.4, 53.4, 52.1, 48.5, 47.5, 47.3, 37.9, 28.1, 27.5, 26.0, 25.7, 25.4, 25.2, 25.0, 18.4, 17.3, 15.6, 11.6, −5.3; MS (FAB) *m*/*z* (rel intensity) 1246 ([M + K]$^+$, 27), 1230 ([M + Na]$^+$, 100), 1208 ([M + H]$^+$, 39).

Cyclo[Ala-Pro-Phe-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (35). According to general procedure F, **34** (38.8 mg, 32.1 μmol) provided 5.7 mg (21% over four steps) of **35** as a colorless solid: mp 143−145 °C; [α]$_D$ −59.4 (*c* 0.48, $CHCl_3$, 22 °C); IR (film) 3319, 1642 cm^{-1}; ^{1}H NMR (methanol-d_4) *δ* 7.40−7.10 (m, 5 H), 5.86 (dd, 2 H, *J* = 10.8, 17.6 Hz), 5.22−5.03 (m, 4 H), 4.63−4.52 (m, 2 H), 4.52−4.47 (m, 2 H), 4.45−4.35 (m, 1 H), 4.29 (d, 1 H, *J* = 7.2 Hz), 4.14 (dd, 1 H, *J* = 2.6, 6.4 Hz), 3.98 (d, 1 H, *J* = 2.4 Hz), 3.87 (dd, 1 H, *J* = 4.2, 10.9 Hz), 3.75 (dd, 1 H, *J* = 4.7, 9.3 Hz), 3.70 (dd, 1 H, *J* = 6.3, 10.7 Hz), 3.61 (dd, 1 H, *J* = 4.6, 9.5 Hz), 3.38−3.25 (m, 2 H), 3.09 (t, 1 H, *J* = 13 Hz), 2.78 (t, 1 H, *J* = 10.3 Hz), 2.39−2.32 (m, 1 H), 2.12−2.00 (m, 1 H), 1.90−1.77 (m, 1 H), 1.67−1.50 (m, 2 H), 1.30 (s, 6 H), 1.28 (s, 3 H), 1.25 (s, 3 H), 1.25 (d, 3 H, *J* = 5.9 Hz), 1.20−1.10 (m, 2 H), 1.06 (d, 3 H, *J* = 6.7 Hz), 1.0−0.80 (m, 6 H); ^{13}C NMR *δ* 173.0, 171.8, 170.7, 170.2, 142.5, 142.1, 137.5, 128.8, 128.5, 126.8, 115.8, 115.1, 78.1, 76.7, 66.9, 62.3, 60.8, 57.6, 56.9, 56.2, 47.7, 28.6, 27.2, 25.6, 24.2, 17.9, 16.4; HRMS (FAB) *m*/*z* calcd for $C_{43}H_{66}N_7O_{10}$ (M + H) 840.4871, found 840.4898.

Cyclo[Ala-Pro-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile]. According to general procedure G, **35** (65.7 mg, 78.3 μmol) provided 47.8 mg (74%) of cyclo[Ala-Pro-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 193−195 °C; [α]$_D$ −37.8 (*c* 0.55, $CHCl_3$, 22 °C); IR (film) 3349, 1651 cm^{-1}; ^{1}H NMR *δ* 8.00 (d, 1 H, *J* = 4.2 Hz), 7.80 (d, 1 H, *J* = 7.8 Hz), 7.72 (d, 1 H, *J* = 4.4 Hz), 7.25−7.18 (m, 3 H), 6.98−6.92 (m, 3 H), 5.97 (d, 1 H, *J* = 10.2 Hz), 5.92 (dd, 1 H, *J* = 10.8, 17.6 Hz), 5.74 (dd, 1 H, *J* = 10.6, 17.8 Hz), 5.27 (d, 1 H, *J* = 16.2 Hz), 5.22 (d, 1 H, *J* = 10.7 Hz), 5.14 (d, 1 H, *J* = 10.7 Hz), 5.13 (d, 1 H, *J* = 17.5 Hz), 4.89−4.76 (m, 3 H), 4.70−4.60 (m, 2 H), 4.51 (t, 1 H, *J* = 10.6 Hz), 4.40−4.23 (m, 4 H), 3.83 (dd, 1 H, *J* = 2.8, 9.4 Hz), 3.57 (dd, 1 H, *J* = 3.4, 9.4 Hz), 3.54−3.50 (m, 1 H), 3.40−3.30 (m, 2 H), 3.04 (dd, 1 H, *J* = 3.1, 13.7 Hz), 2.48−2.41 (m, 2 H), 2.08−1.90 (m, 3 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 1.22−1.18 (m, 2 H), 1.10 (d, 3 H, *J* = 6.9 Hz), 1.02 (d, 3 H, *J* = 6.4 Hz), 0.98−0.8 (m, 6 H); ^{13}C NMR 172.3, 170.8, 170.7, 170.4, 170.1, 169.8, 168.6, 142.8, 142.3, 136.0, 129.7, 128,1, 127.1, 115.9, 115.1, 78.4, 75.9, 70.4, 69.0, 66.0, 61.6, 60.7, 57.6, 57.3, 57.1, 49.3, 47.3, 46.7, 37.4, 35.5, 28.0, 25.8, 25.6, 25.3, 25.1, 24.5, 20.1, 17.9, 16.5, 12.5; MS (FAB) *m*/*z* (rel intensity) 860 ([M + K]$^+$, 13), 844 ([M + Na]$^+$, 39), 822 ([M + H]$^+$, 62), 686 (100); HRMS (FAB) *m*/*z* calcd for $C_{43}H_{63}N_7O_9Na$ (M + Na) 844.4585, found 844.4612.

Cyclo[Ala-Pro-PheΨ{(C═S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile]. According to general procedure H, cyclo[Ala-Pro-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (32.7 mg, 39.8 μmol) provided 31.5 mg (93%) of cyclo[Ala-Pro-PheΨ{(C═S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 145−147 °C; [α]$_D$ +22.9 (*c* 0.58, $CHCl_3$, 22 °C); IR (film) 3388, 1644 cm^{-1}; ^{1}H NMR (methanol-d_4) *δ* 9.35−9.25 (bs, 1 H), 8.78−8.68 (bs, 1 H), 8.58−8.48 (bs, 1 H), 8.45−8.35 (bs, 1 H), 7.49 (d, 1 H, *J* = 7.5 Hz), 7.32−7.15 (m, 5 H), 6.95−6.85 (bs, 1 H), 5.81 (dd, 2 H, *J* = 11.5, 17.1 Hz), 5.25−5.03 (m, 6 H), 4.59−4.44 (m, 2 H), 4.43−4.30 (m, 2 H), 4.15−4.05 (m, 2 H), 3.97−3.85 (m, 3 H), 3.70 (dd, 1 H, *J* = 4.7, 9.4 Hz), 3.63−3.50 (m, 2 H), 3.24−3.05 (m, 1 H), 2.85−2.75 (m, 1 H), 2.33−2.21 (m, 1 H), 2.18−2.05 (m, 1 H), 1.92−1.78 (m, 1 H), 1.65−1.45 (m, 2 H), 1.43−1.35 (m, 1 H), 1.27 (s, 6 H), 1.30−1.00 (m, 7 H), 1.20 (s, 3 H), 1.00 (d, 3 H, *J* = 6.7 Hz), 0.95−0.83 (m, 6 H); ^{13}C NMR (methanol-d_4) *δ* 203.4, 174.2, 173.7, 173.3, 173.1, 172.4, 145.1, 144.2, 139.3, 130.3, 129.9, 129.6, 128.1, 115.7, 115.0, 77.5, 68.6, 64.1, 63.4, 63.1, 62.4, 61.8, 59.5, 56.9, 47.6, 40.9, 31.5, 27.3, 26.6, 26.4, 26.1, 22.5, 21.4, 16.9, 16.5, 15.8, 12.2; MS (FAB) *m*/*z* (rel intensity) 894 ([M + K]$^+$, 19), 878 ([M + Na]$^+$, 100); HRMS (FAB) *m*/*z* calcd for $C_{43}H_{65}N_7O_9NaS$ (M + Na) 878.4462, found 878.4479.

Cyclo[Ala-Pro-Phe-D-Ser(thiaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (36). According to general procedure G, cyclo[Ala-Pro-PheΨ{(C═S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (19.5 mg, 22.8 μmol) provided 12.1 mg (64%) of **36** as a colorless amorphous solid: [α]$_D$ −36.6 (*c* 0.50, $CHCl_3$, 22 °C); IR (film) 3354, 1666 cm^{-1}; ^{1}H NMR *δ* 8.03 (d, 1 H, *J* = 5.4 Hz), 7.98 (d, 2 H, *J* = 4.8 Hz), 7.51 (d, 1 H, *J* = 7.0 Hz), 7.20−7.08 (m, 3 H), 7.02−6.90 (m, 2 H), 6.10 (d, 1 H, *J* = 10.1 Hz), 5.94 (dd, 1 H, *J* = 10.7, 17.5 Hz), 5.75 (dd, 1 H, *J* = 11.3, 17.1 Hz), 5.29 (d, 1 H, *J* = 16.8 Hz), 5.25 (d, 1 H, *J* = 10.2 Hz), 5.15

(d, 1 H, J = 10.5 Hz), 5.14 (d, 1 H, J = 17.8 Hz), 5.05−4.95 (m, 1 H), 4.81 (d, 1 H, J = 7.4 Hz), 4.77−4.67 (m, 1 H), 4.65−4.58 (m, 2 H), 4.56 (t, 1 H, J = 5.0 Hz), 4.38−4.30 (m, 1 H), 4.30−4.20 (m, 1 H), 3.84 (dd, 1 H, J = 2.2, 9.3 Hz), 3.70 (dd, 1 H, J = 8.7, 11.0 Hz), 3.53−3.43 (m, 2 H), 3.40−3.20 (m, 3 H), 2.96 (dd, 1 H, J = 3.3, 13.7 Hz), 2.68−2.55 (m, 1 H), 2.48−2.38 (m, 1 H), 2.13−1.97 (m, 1 H), 1.97−1.75 (m, 2 H), 1.52 (s, 3 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.25 (s, 3 H), 1.21−1.10 (m, 2 H), 1.07 (d, 3 H, J = 6.5 Hz), 1.00−0.82 (m, 9 H); ^{1}H NMR (500 MHz) δ 8.03 (d, 1 H, J = 5.4 Hz), 7.98 (t, 2 H, J = 4.6 Hz), 7.52 (d, 1 H, J = 7.1 Hz), 7.22−7.15 (m, 3 H), 7.03−6.98 (m, 2 H), 6.11 (d, 1 H, J = 10.1 Hz), 5.95 (dd, 1 H, J = 10.8, 17.6 Hz), 5.75 (dd, 1 H, J = 11.0, 17.4 Hz), 5.30 (d, 1 H, J = 17.6 Hz), 5.26 (d, 1 H, J = 10.8 Hz), 5.15 (d, 1 H, J = 10.7 Hz), 5.14 (d, 1 H, J = 17.7 Hz), 5.06−5.00 (m, 1 H), 4.82 (d, 1 H, J = 7.8 Hz), 4.75 (t, 1 H, J = 6.8 Hz), 4.72−4.60 (m, 2 H), 4.56 (t, 1 H, J = 5.0 Hz), 4.40−4.30 (m, 1 H), 4.30−4.22 (m, 1 H), 3.85 (dd, 1 H, J = 2.4, 9.4 Hz), 3.71 (dd, 1 H, J = 8.7, 11.1 Hz), 3.58 (dd, 1 H, J = 3.3, 9.4 Hz), 3.52 (dd, 1 H, J = 9.9, 17.1 Hz), 3.43−3.25 (m, 3 H), 2.96 (dd, 1 H, J = 3.3, 13.7 Hz), 2.70−2.62 (m, 1 H), 2.50−2.40 (m, 1 H), 2.10−2.02 (m, 1 H), 2.00−1.90 (m, 1 H), 1.88−1.78 (m, 1 H), 1.52 (s, 3 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.26−1.16 (m, 2 H), 1.08 (d, 3 H, J = 6.4 Hz), 1.02−0.90 (m, 9 H); ^{13}C NMR δ 173.8, 172.9, 170.5, 170.3, 142.8, 142.4, 136.0, 129.9, 128.0, 127.0, 115.9, 115.1, 79.2, 78.4, 76.0, 66.4, 61.7, 60.5, 57.4, 57.2, 57.0, 53.8, 47.4, 46.9, 39.0, 36.5, 35.8, 27.9, 26.4, 25.8, 25.6, 25.5, 25.2, 24.4, 19.5, 18.4, 16.4, 12.5; MS (FAB) m/z (rel intensity) 860 ([M + Na]$^+$, 48), 838 ([M + H]$^+$, 55), 770 (35), 702 (100); HRMS (FAB) m/z calcd for $C_{43}H_{63}N_7O_8NaS$ (M + Na), 860.4357, found 860.4412.

Fmoc-Ala-Pro-D-Phe-D-Ser(TBS)-OBn (38). According to general procedure D, **37** (2.15 g, 3.88 mmol) and D-Ser(TBS)-OBn (1.20 g, 3.88 mmol) provided 1.59 g (81%) of **38** as a colorless foam: $[\alpha]_D$ −43.8 (c 0.26, $CHCl_3$, 22 °C); IR (film) 3418, 3300, 1724, 1658 cm^{-1}; ^{1}H NMR (benzene-d_6) δ 7.60−7.35 (m, 5 H), 7.28−6.95 (m, 15 H), 5.95 (d, 1 H, J = 8.0 Hz), 5.05−4.78 (m, 4 H), 4.53−4.36 (m, 3 H), 4.30−4.22 (m, 1 H), 4.15−4.10 (m, 1 H), 3.92 (dd, 1 H, J = 3.2, 10.0 Hz), 3.80 (dd, 1 H, J = 3.8, 10.0 Hz), 3.23 (dd, 1 H, J = 5.3, 14.0 Hz), 3.11 (dd, 1 H, J = 8.1, 13.9 Hz), 3.05−2.92 (m, 1 H), 2.90−2.80 (m, 1 H), 2.05−1.95 (m, 1 H), 1.72−1.55 (m, 1 H), 1.33 (d, 3 H, J = 6.8 Hz), 1.25−1.10 (m, 2 H), 0.87 (s, 9 H), −0.03 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (benzene-d_6) δ 173.2, 171.5, 171.4, 170.8, 156.3, 144.9, 144.8, 142.1, 138.0, 136.3, 130.2, 129.5, 128.9, 127.7, 127.3, 125.9, 120.6, 67.4, 64.1, 60.5, 55.7, 55.5, 49.1, 48.0, 47.2, 38.7, 27.5, 26.4, 25.3, 18.9, −5.0, −5.1; HRMS (FAB) m/z calcd for $C_{48}H_{59}N_4O_8Si$ (M + H) 847.4102, found 847.4132.

Fmoc-Ala-Pro-D-Phe-D-Ser(TBS)-Thr(rprenyl)-Ser(rprenyl)-Ile-OMe (39). According to general procedure I, benzyl ester deprotection of **38** (0.768 g, 0.917 mmol) in EtOAc/EtOH (10:1, 8 mL) and the condensation with the amine **25** (30.8 mg, 65.8 μmol) provided 55.1 mg (54% over two steps) of **39** as a colorless foam: $[\alpha]_D$ −4.4 (c 0.18, $CHCl_3$, 22 °C); IR (film) 3315, 1719, 1644 cm^{-1}; ^{1}H NMR δ 7.77 (d, 2 H, J = 7.4 Hz), 7.65−7.55 (m, 2 H), 7.41 (t, 4 H, J = 7.2 Hz), 7.34−7.20 (m, 9 H), 7.06 (d, 2 H, J = 8.5 Hz), 6.90 (d, 1 H, J = 6.9 Hz), 5.94 (dd, 1 H, J = 10.7, 17.6 Hz), 5.87−5.75 (m, 2 H), 5.32−5.04 (m, 4 H), 4.70−4.45 (m, 4 H), 4.36 (d, 3 H, J = 7.4 Hz), 4.25−4.18 (m, 1 H), 4.05−3.95 (m, 1 H), 3.90−3.80 (m, 2 H), 3.75−3.55 (m, 2 H), 3.70 (s, 3 H), 3.34 (t, 1 H, J = 7.4 Hz), 3.20−3.00 (m, 3 H), 2.25−2.18 (m, 1 H), 2.20−1.75 (m, 4 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 1.35−1.10 (m, 5 H), 1.29 (s, 6 H), 1.03 (d, 3 H, J = 6.4 Hz), 0.98−0.83 (m, 6 H), 0.87 (s, 9 H), 0.06 (2s, 6 H); ^{13}C NMR δ 172.8, 172.1, 171.4, 171.0, 170.3, 169.8, 168.8, 155.9, 144.0, 142.8, 141.4, 136.8, 136.5, 129.5, 128.8, 128.5, 127.9, 127.2, 125.3, 120.1, 115.1, 114.9, 76.2, 67.2, 63.0, 62.5, 60.4, 58.0, 56.9, 55.3, 54.6, 53.4, 52.1, 48.7, 47.3, 37.8, 27.6, 26.0, 25.7, 25.3, 25.2, 18.4, 18.2, 17.5, 15.7, 11.6, −5.2; MS (FAB) m/z (rel intensity) 1247 ([M + K]$^+$, 100), 1231 ([M + Na]$^+$, 75).

Cyclo[Ala-Pro-D-Phe-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (40). According to general procedure F, **39** (119 mg, 92.7 μmol) provided 27.9 mg (36% over four steps) of **40** as a colorless solid: mp 154−156 °C; $[\alpha]_D$ −8.0 (c 0.50, $CHCl_3$, 22 °C); IR (film) 3378, 3315, 1668 cm^{-1}; ^{1}H NMR δ 8.57 (d, 1 H, J = 9.0 Hz), 7.75 (d, 1 H, J = 7.6 Hz), 7.38 (d, 1 H, J = 5.7 Hz), 7.30−7.20 (m, 5 H), 7.06 (d, 1 H, J = 8.8 Hz), 6.95 (d, 1 H, J = 8.6 Hz), 6.57 (d, 1 H, J = 9.3 Hz), 5.85 (dd, 1 H, J = 10.8, 17.4 Hz), 5.75 (dd, 1 H, J = 10.9, 17.5 Hz), 5.26 (d, 1 H, J = 10.7 Hz), 5.24 (d, 1 H, J = 17.4 Hz), 5.18 (d, 1 H, J = 10.8 Hz), 5.15 (d, 1 H, J = 17.6 Hz), 5.02−4.90 (m, 1 H), 4.87−4.78 (m, 1 H), 4.68 (dd, 1 H, J = 5.5, 8.5 Hz), 4.55−4.40 (m, 3 H), 4.17−4.05 (m, 2 H), 3.90−3.75 (m, 2 H), 3.70−3.50 (m, 2 H), 3.48−3.37 (m, 3 H), 2.93 (dd, 1 H, J = 10.3, 14.0 Hz), 2.45−2.10 (m, 2 H), 1.90−1.78 (m, 2 H), 1.75−1.60 (m, 1 H), 1.60−1.42 (m, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.27 (s, 3 H), 1.26 (d, 3 H, J = 5.5 Hz), 1.06 (d, 3 H, J = 6.3 Hz), 1.00−0.93 (m, 6 H), 0.90−0.80 (m, 2 H); ^{13}C NMR δ 172.3, 171.8, 171.3, 170.7, 170.1, 142.4, 142.2, 137.3, 129.4, 128.7, 127.1, 116.2, 115.5, 67.5, 63.8, 62.0, 60.8, 58.1, 57.1, 55.9, 55.6, 54.4, 47.9, 47.7, 38.4, 36.3, 29.3, 26.9, 26.5, 26.1, 25.7, 25.5, 23.9, 19.7, 17.3, 16.5, 12.1; HRMS (FAB) m/z calcd for $C_{43}H_{66}N_7O_{10}$ (M + H) 840.4871, found 840.4911.

Cyclo[Ala-Pro-D-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser-(rprenyl)-Ile]. According to general procedure G, **40** (34.6 mg, 41.2 μmol) provided 20.8 mg (61%) of cyclo[Ala-Pro-D-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless glass: $[\alpha]_D$ −27.1 (c 0.93, $CHCl_3$, 22 °C); IR (film) 3338, 1666 cm^{-1}; ^{1}H NMR δ 8.18 (d, 1 H, J = 6.1 Hz), 8.03 (d, 1 H, J = 4.3 Hz), 7.87 (d, 1 H, J = 3.9 Hz), 7.68 (d, 1 H, J = 8.1 Hz), 7.20−7.05 (m, 5 H), 6.00 (d, 1 H, J = 10.6 Hz), 5.93 (dd, 1 H, J = 17.6, 10.8 Hz), 5.78 (dd,1 H, J = 17.7, 10.7 Hz), 5.28 (d, 1 H, J = 17.7 Hz), 5.24 (1 H, J = 10.8 Hz), 5.16 (d, 1 H, J = 17.0 Hz), 5.16 (d, 1 H, J = 11.5 Hz), 5.07−4.97 (m, 1 H), 4.95−4.85 (m, 1 H), 4.75−4.60 (m, 2 H), 4.55−4.30 (m, 5 H), 4.25−4.15 (m, 1 H), 3.87 (dd, 1 H, J = 2.8, 9.4 Hz), 3.62 (dd, 1 H, J = 3.3, 9.3 Hz), 3.55−3.35 (m, 2 H), 3.12 (dd, 1 H, J = 4.6, 14.0 Hz), 2.91 (dd, 1 H, J = 7.6, 13.9 Hz), 2.50−2.35 (m, 2 H), 2.10−1.85 (m, 2 H), 1.77−1.60 (m, 1 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.35−1.10 (m, 11 H), 1.03 (d, 3 H, J = 6.4 Hz), 0.98−0.82 (m, 6 H); ^{13}C NMR δ 172.4, 171.5, 170.5, 170.2, 170.1, 169.8, 168.8, 142.9, 142.4, 136.6, 129.4, 128.6, 126.7, 115.9, 115.1, 79.1, 78.3, 76.0, 70.4, 68.5, 65.6, 61.7, 59.4, 57.5, 57.3, 48.6, 47.2, 46.7, 39.3, 35.8, 27.9, 25.7, 25.5, 24.3, 20.0, 18.0, 16.4, 12.5; HRMS (FAB) m/z calcd for $C_{43}H_{63}N_7O_9Na$ (M + Na) 844.4585, found 844.4594.

Cyclo[Ala-Pro-D-PheΨ{(C=S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile]. According to general procedure H, cyclo-[Ala-Pro-D-Phe-D-Ser(oxaz)-Thr(rprenyl)-Ser(rprenyl)-Ile] (19.5 mg, 23.8 μmol) provided 16 mg (79%) of cyclo[Ala-Pro-D-PheΨ-{(C=S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] as a colorless solid: mp 140−142 °C; $[\alpha]_D$ +25.7 (c 0.23, $CHCl_3$, 22 °C); IR (film) 3314, 1670 cm^{-1}; ^{1}H NMR δ 9.79 (d, 1 H, J = 7.8 Hz), 7.83 (d, 1 H, J = 7.6 Hz), 7.38 (d, 2 H, J = 5.9 Hz), 7.35−7.20 (m, 5 H), 6.65 (d, 1 H, J = 8.9 Hz), 6.52 (d, 1 H, J = 9.4 Hz), 5.85 (dd, 1 H, J = 10.9, 17.3 Hz), 5.75 (dd, 1 H, J = 10.9, 17.5 Hz), 5.45−5.40 (m, 1 H), 5.25 (d, 1 H, J = 10.6 Hz), 5.23 (d, 1 H, J = 17.5 Hz), 5.19 (d, 1 H, J = 10.5 Hz), 5.15 (d, 1 H, J = 17.6 Hz), 4.74 (dd, 1 H, J = 5.4, 8.6 Hz), 4.65−4.32 (m, 4 H), 4.22−4.10 (m, 2 H), 3.93−3.68 (m, 4 H), 3.59 (dd, 1 H, J = 4.7, 9.3 Hz), 3.40−3.25 (m, 2 H), 2.90 (dd, 1 H, J = 10.8, 13.9 Hz), 2.47−2.30 (m, 1 H), 1.85−1.70 (m, 2 H), 1.70−1.48 (m, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, 3 H, J = 6.7 Hz), 1.25−1.00 (m, 3 H), 1.03 (d, 3 H, J = 6.3 Hz), 1.00−0.83 (m, 6 H); ^{13}C NMR δ 205.2, 171.8, 171.3, 171.0, 170.4, 170.1, 170.0, 142.3, 142.1, 137.5, 129.3, 128.7, 127.1, 116.3, 115.6, 76.5, 67.5, 63.0, 61.9, 60.5, 58.0, 57.2, 55.7, 47.9, 47.7, 41.9, 36.4, 29.1, 26.8, 26.5, 26.0, 25.7, 25.4, 23.7, 19.8, 17.2, 16.5, 12.1; HRMS (FAB) m/z calcd for $C_{43}H_{66}N_7O_9S$ (M + H) 856.4643, found 856.4669.

Cyclo[Ala-Pro-D-Phe-D-Ser(thiaz)-Thr(rprenyl)-Ser-(rprenyl)-Ile] (41). According to general procedure G, cyclo-[Ala-Pro-D-PheΨ{(C=S)NH}-D-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (6.4 mg, 8.1 μmol) provided 4.9 mg (79%) of **41** as a colorless amorphous solid: $[\alpha]_D$ −28.0 (c 0.49, $CHCl_3$, 22 °C); IR (film) 3345, 1667 cm^{-1}; ^{1}H NMR δ 8.30−8.20 (m, 2 H), 8.13 (d, 1 H, J = 4.8 Hz), 7.58 (d, 1 H, J = 7.8 Hz), 7.27−7.10 (m, 5 H), 6.05 (d, 1 H, J = 10.4 Hz), 5.95 (dd, 1 H, J = 10.8, 17.6

Hz), 5.78 (dd, 1 H, J = 10.6, 17.8 Hz), 5.31 (d, 1 H, J = 17.7 Hz), 5.25 (d, 1 H, J = 10.9 Hz), 5.19−5.13 (m, 2 H), 5.17−5.01 (m, 1 H), 4.92 (t, 1 H, J = 7.0 Hz), 4.81 (t, 1 H, J = 11 Hz), 4.69 (d, 2 H, J = 9.5 Hz), 4.60−4.50 (m, 1 H), 4.48−4.38 (m, 1 H), 4.37−4.33 (m, 1 H), 3.88 (dd, 1 H, J = 9.3, 2.3 Hz), 3.65−3.40 (m, 5 H), 3.16 (dd, 1 H, J = 5.4, 14.0 Hz), 2.96 (dd, 1 H, J = 7.6, 13.9 Hz), 2.50−2.30 (m, 2 H), 2.10−1.95 (m, 2 H), 1.80−1.65 (m, 1 H), 1.53 (s, 3 H), 1.42 (s, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.23 (d, 3 H, J = 6.8 Hz), 1.07 (d, 3 H, J = 6.4 Hz), 1.00−0.85 (m, 8 H); ^{1}H NMR (500 MHz) δ 8.30−8.22 (m, 2 H), 8.13 (d, 1 H, J = 4.4 Hz), 7.57 (d, 1 H, J = 7.7 Hz), 7.30−7.22 (m, 3 H), 7.20−7.13 (m, 2 H), 6.05 (d, 1 H, J = 10.4 Hz), 5.95 (dd, 1 H, J = 10.8, 17.5 Hz), 5.78 (dd, 1 H, J = 10.8, 17.7 Hz), 5.31 (d, 1 H, J = 17.5 Hz), 5.25 (d, 1 H, J = 10.8 Hz), 5.17 (d, 1 H, J = 11.6 Hz), 5.16 (d, 1 H, J = 16.3 Hz), 5.12−5.04 (m, 1 H), 4.90 (t, 1 H, J = 7.1 Hz), 4.81 (t, 1 H, J = 10 Hz), 4.69 (d, 2 H, J = 8.1 Hz), 4.55 (t, 1 H, J = 5.5 Hz), 4.47−4.40 (m, 1 H), 4.36 (s, 1 H), 3.88 (d, 1 H, J = 9.2 Hz), 3.68−3.40 (m, 5 H), 3.15 (dd, 1 H, J = 5.4, 13.9 Hz), 2.96 (dd, 1 H, J = 7.7, 13.9 Hz), 2.50−2.40 (m, 1 H), 2.42−2.32 (m, 1 H), 2.10−1.92 (m, 2 H), 1.78−1.62 (m, 1 H), 1.53 (s, 3 H), 1.42 (s, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.28−1.20 (m, 3 H), 1.07 (d, 3 H, J = 6.3 Hz), 1.00−0.82 (m, 8 H); ^{13}C NMR δ 173.3, 172.5, 170.9, 170.5, 170.2, 170.0, 142.9, 142.4, 136.7, 129.6, 128.5, 126.9, 115.9, 115.2, 78.8, 78.4, 76.0, 65.5, 61.7, 59.6, 57.8, 57.3, 53.4, 47.3, 46.6, 41.5, 35.9, 35.5, 27.9, 26.0, 25.8, 25.5, 24.4, 20.1, 18.4, 16.4, 12.5; HRMS (FAB) m/z calcd for $C_{43}H_{64}N_7O_8S$ (M + H) 838.4537, found 838.4566.

Degradation of Cyclo[Ala-Pro-Phe-Ser-Thr(rprenyl)-Ser(rprenyl)-Ile] (27). A solution of **27** (0.4 mg) in 6 N HCl (5 mL) was heated in a sealed tube at 105 °C for 22 h. The resulting mixture was concentrated, dried in vacuo, dissolved in distilled water (40 μL), and derivatized with 5-fluoro-2,4-dinitrophenyl-L-alanine amide (FDAA, 0.5 mg) in acetone (60 μL) and 1 N sodium bicarbonate (20 μL) at 40 °C for 1 h. The reaction mixture was acidified with 2 N HCl (10 μL) and stored in the dark until HPLC analysis (Varian C18 MICROSORB-MV 100 Å; linear gradient elution, aqueous TFA/acetonitrile (0.1%), from 95:5 to 60:40 in 100 min; 1.2 mL/min; UV detection at 340 nm). No D-amino acid residues were detected in comparison to a standard mixture containing the following: D/L mixture of serine, threonine, proline, alanine, isoleucine, and phenylalanine.

Acknowledgment. This work was supported by the National Institutes of Health (GM55433). We thank Prof. Bruce Bowden (James Cook University, Townsville, Australia) for copies of NMR spectra of natural trunkamide A.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all synthetic intermediates and trunkamide A stereoisomers. ^{1}H and ^{13}C NMR spectra for natural trunkamide A. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9914566