Total Synthesis and Assignment of Configuration of Lissoclinamide 7

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Abstract: The first total synthesis of lissoclinamide 7, a 21-membered cyclopeptide isolated from *Lissoclinum bistratum*, was accomplished in 23 steps and 4.4% overall yield. The extraordinary configurational lability of the thiazoline segments was overcome by a novel strategy combining the use of the Burgess reagent for multiple simultaneous oxazoline and thiazoline formations and an efficient oxazoline → thiazoline heterocycle interconversion. In addition to the total synthesis, this work highlights the scope of alternative strategies toward *Lissoclinum* peptides and presents the preparation of analogues for SAR studies of the cytotoxic effects of this family of marine natural products.

As part of our program toward the total synthesis of marine natural products,[1,2] we were particularly intrigued by the densely functionalized macrocyclic ring structures in a group of ascidian ("sea squirt") metabolites from the genus *Lissoclinum* (Figure 1).[3,4] Characterized by an alternating sequence of five-membered heterocycles and hydrophobic amino acid residues, these highly backbone-modified cyclopeptides assume molecular "triangle", "square", and "twisted eight" conformations in solution and the solid state.[5] Their almost symmetrical array of oxazolines, oxazoles, thiazolines, and thiazoles is reminiscent of ring-extended porphyrins[6] and aza-crown ethers[7] and nurtures speculation about ion-carrier functions.[8] Indeed, interesting metal-chelation properties have been detected for several *Lissoclinum* peptides.[9,10]

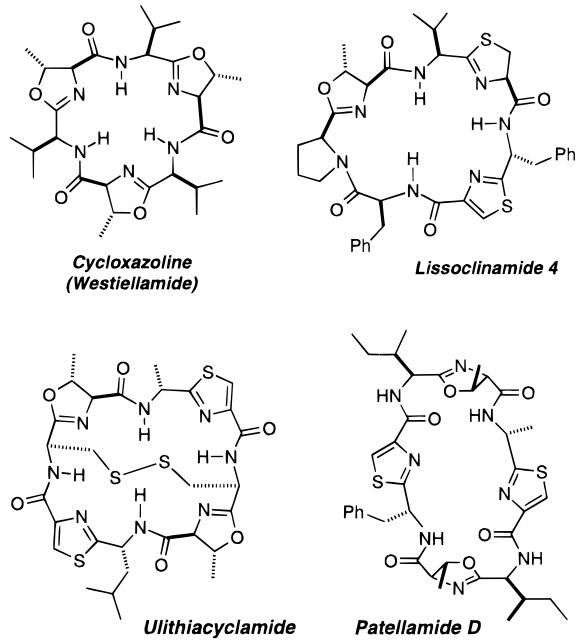

Figure 1. Cyclic peptides of the genus *Lissoclinum*.

Most *Lissoclinum* peptides display moderate to high levels of cytotoxicity that have been linked to the presence of oxazoline functions.[11,5g] Table 1 illustrates some representative structure−activity relationships for 21-membered *Lissoclinum* peptides. With IC_{50} values of 40, 60, and 80 ng/mL in MRC5CV1, T24, and lymphocytes cell assays, respectively, lissoclinamide

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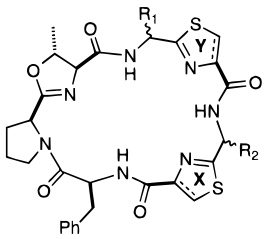
Table 1. Cytotoxic Activity of Some 21-Membered *Lissoclinum* Peptides



	R_1	R_2	X	Y	IC_{50} [μg/mL]
lissoclinamide 1	L-Val	D-Ile	thiazole	thiazole	>10[19]
lissoclinamide 6	D-Val	D-Phe	thiazole	thiazoline	7[20]
lissoclinamide 7	Val	Phe	thiazoline	thiazoline	0.06[20]
ulicyclamide	L-Ile	D-Ala	thiazole	thiazole	7[21]

7 is next to ulithiacyclamide[21] the most cytotoxic *Lissoclinum* derivative. It is also the only *L. patella* metabolite that contains two thiazoline rings in addition to the oxazoline heterocycle. Since the mechanistic link between the presence of oxazolines and cytocidal action is unclear,[11,12] we were interested in testing this hypothesis through the synthesis and biological analysis of lissoclinamide 7 and its structural variants. We expect that analogues with selective replacements of the heterocyclic moieties will provide fundamental information about the relative cytotoxic potential of oxazolines vs thiazolines.

The total synthesis of lissoclinamide 7 poses new and challenging synthetic problems. Among the large number of published syntheses of *Lissoclinum* peptides and structurally related macrocycles, thiazoline-containing target molecules are conspicuously rare.[13,14] Indeed, only very recently did Pattenden and Boden succeed in the first preparation of a thiazoline-containing *Lissoclinum* peptide, lissoclinamide 4.[15] Also in 1995, the structurally related cyclic hexapeptide dolastatin E was prepared by Yamada et al.[16] The difficulties in the formation of the sensitive thiazoline heterocycles represent the major impediments for total synthesis. In the presence of mild acid or base, thiazolines are readily epimerized exocyclic to C(2) as well as at C(4) (Figure 2).[17,18]

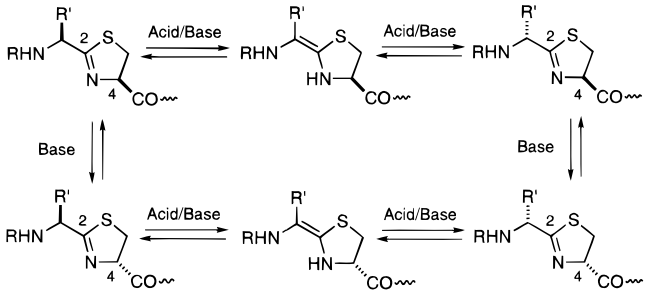


Figure 2. Thiazoline epimerization.

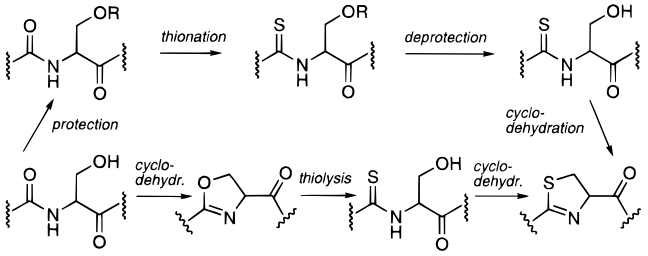


Figure 3. Conversion of serines to thiazolines.

We have recently shown that thiazolines can be prepared in high yield and diastereomeric purity by cyclodehydration of β-hydroxy thioamides.[17] In short peptide sequences, the necessary thioamides can be obtained by thionation of protected serine residues with the Lawesson reagent or by thioacylation.[18,22,23] For larger peptides, direct thionation lacks regioselectivity and the thiolysis of oxazolines becomes the method of choice (Figure 3).[24] The bisthiazoline-containing lissoclinamide 7 now represents a formidable demonstration of this new synthetic methodology.

Retrosynthetic Strategy

Due to epimerization of the amino acids adjacent to the thiazoline rings, the structure elucidation of lissoclinamide 7 by Watters and co-workers tentatively assigned the D-stereochemistry at C(21).[20a] This assignment was based on the large proportion of D-phenylalanine obtained after exhaustive hydrolysis (D/L = 0.64), and the assumption that the phenylalanine at C(11) is always of the L-configuration. In contrast, D- and L-valine were obtained in equal proportions; therefore, no specific stereochemistry was proposed for C(31). Initially, we decided arbitrarily to use D-valine for lissoclinamide 7 in our retrosynthetic approach (Figure 4). Selective thiolysis of the two serine-derived heterocycles in trisoxazoline **3** was thought to provide thioamide **2** which could subsequently be cyclodehydrated with the Burgess reagent to avoid epimerization.[17] Macrolactamization at the valine−*trans*-oxazoline peptide bond of **3** was chosen to minimize epimerization at the C-terminus and to take advantage of the turn-inducing effect of the oxazoline moiety that should facilitate ring closure.[1] The resulting secoheptapeptide **4** could be obtained by segment condensation of a tetrapeptide and a tripeptide oxazoline, with the remaining two serine-derived oxazolines being introduced either before or after the macrocyclization. In general, similar yields for ring closure of *Lissoclinum* peptides have been obtained in the presence or absence of some of the heterocyclic residues in the linear sequence.[13,15]

Results and Discussion

Preparation of the heptapeptide oxazoline **4** was initiated by coupling of the mixed anhydride of benzyloxycarbonyl(Cbz)-

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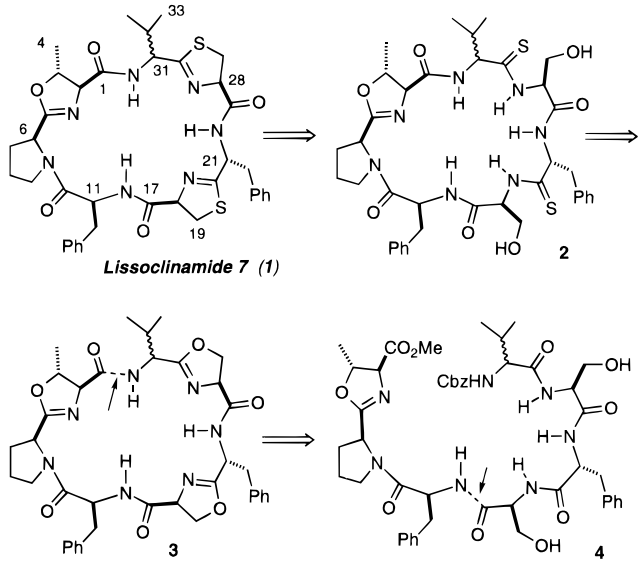
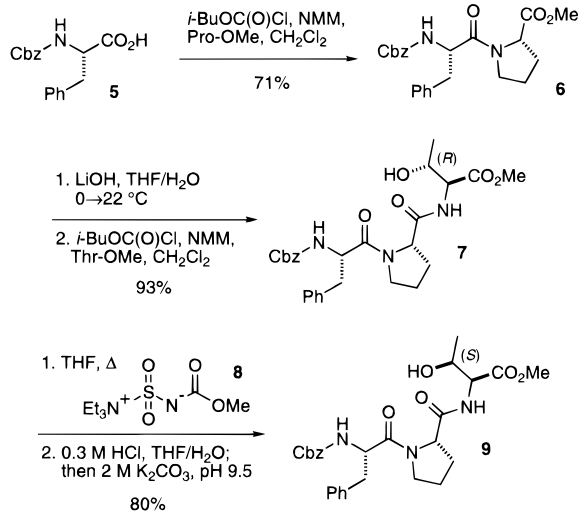


Figure 4. Retrosynthetic plan for lissoclinamide 7.

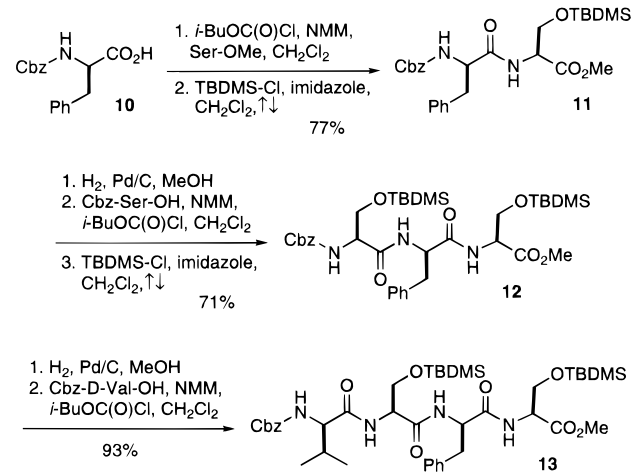
Scheme 1



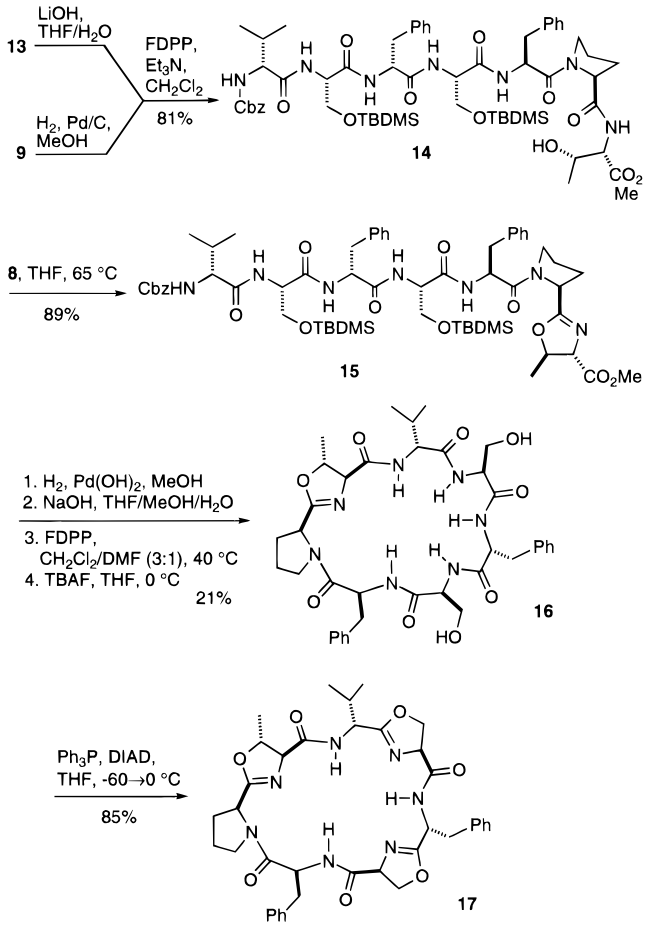
phenylalanine (**5**) with proline methyl ester using the Anderson conditions (Scheme 1).[25] The resulting dipeptide **6** was saponified and condensed with threonine methyl ester to give tripeptide **7** in 93% yield. The synthesis of this tripeptide from the C-terminus rather than the more standard N-terminal elongation strategy was chosen to allow the use of side chain-unprotected threonine and to circumvent a low yield in the coupling of Cbz-phenylalanine and prolylthreonine methyl ester. The (2*S*,3*R*)-configuration of the natural threonine residue was now selectively inverted to the (2*S*,3*S*)-configuration of nonproteinogenic *allo*-threonine by formation of the oxazoline with the Burgess reagent (**8**),[26] followed by selective hydrolysis and *in situ* $O \rightarrow N$-acyl shift.[27] This straightforward protocol was readily scaled up to multigram quantities and provided the *allo*-threonine-containing tripeptide segment **9** in 80% yield.

In an analogous series of isobutyl chloroformate-mediated condensation reactions, the D-valine-containing tetrapeptide segment **13** was obtained in an overall yield of 51% from Cbz-

Scheme 2



Scheme 3



D-phenylalanine (**10**) (Scheme 2). To avoid misacylation or peptide backbone rearrangements, the serine side chain hydroxyl functions were protected as TBDMS (*tert*-butyldimethylsilyl) ethers.

Segment condensation of the carboxylic acid derived from tetrapeptide **13** with the primary amine derived from tripeptide **9** in the presence of pentafluorophenyl diphenylphosphinate (FDPP)[28] gave the desired heptapeptide **14** in 81% yield (Scheme 3). The C-terminal *trans*-oxazoline was now introduced in 89% by cyclodehydration of the *allo*-threonine residue with the Burgess reagent.[26] In preparation for the formation of

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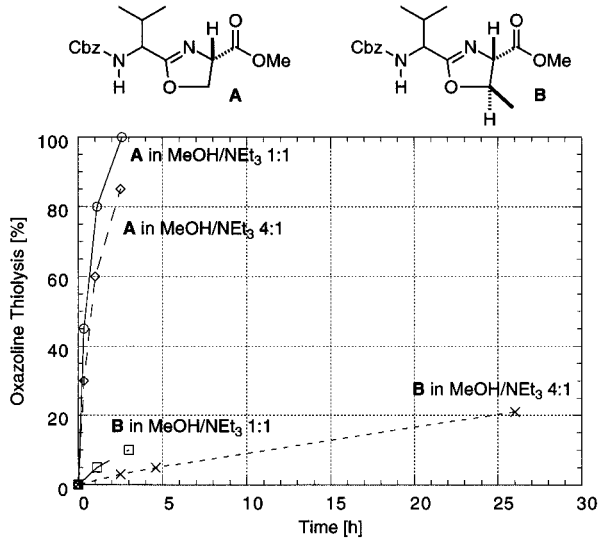

Figure 5. Rate of thiolysis of model oxazolines **A** (serine-derived) and **B** (threonine-derived).

the 21-membered macrocycle, hydrogenolysis of **15** with $Pd(OH)_2$ and saponification in aqueous base led to an intermediate amino acid that was immediately subjected to FDPP in CH_2Cl_2 and DMF. After 2.5 d at 40 °C, the silyl ethers were cleaved with TBAF (tetrabutylammonium fluoride) in THF, and the cycloheptapeptide oxazoline **16** was isolated in 21% overall yield. Closure of the two serine-derived oxazolines under Mitsunobu conditions[29] led to the trisoxazoline derivative **17**, which was of interest to us as an analog for biological testing beyond its role as a key synthetic intermediate toward lissoclinamide 7.

In earlier model studies,[24] we had noted distinctive differences in the rate of thiolysis of serine-derived vs threonine-derived oxazolines. A kinetic study confirmed that for model oxazolines **A** and **B**, thiolysis with H_2S at room temperature in MeOH/NEt_3 was considerably faster for the less-substituted serine-derived oxazoline **A** (Figure 5).

Therefore, we hoped that the selective opening of trisoxazoline **17** would provide the desired bisthioamide **2** with good selectivity and yield. However, even after considerable variation of the reaction conditions, we were unable to prevent the thiolysis of the threonine-derived oxazoline and the formation of tristhioamide **18** as the major reaction product (Scheme 4). The structure of this sensitive thiolysis product was confirmed by reaction with an excess of the Burgess reagent to give the tristhiazoline **19**. The lack of chemoselectivity in the oxazoline opening of **17** can be explained by an increased stability of the serine-derived oxazolines embedded in the macrocyclic scaffold as compared to the acyclic model oxazoline **A**. At room temperature, no thiolysis occurred, and ring opening of the heterocycles was only detected after extended exposure to H_2S in MeOH/NEt_3 1:1 at elevated temperature (36 °C). Under these conditions, both serine- and threonine-derived oxazolines converted with similar rates to the corresponding thioamides.

Accordingly, in our second-generation approach toward lissoclinamide 7, we sought to perform the selective thiolysis step on an acyclic trisoxazoline (*e.g.*, the secoderivative of **17**). On the basis of the revised structure of lissoclinamide 4, reported by Boden and Pattenden concomitant to our work,[15] we also decided to use L-valine as a precursor. Acylation of the primary amine derived from tripeptide **12** with Cbz-valine followed by segment condensation with **9** gave heptapeptide **21** in high yield

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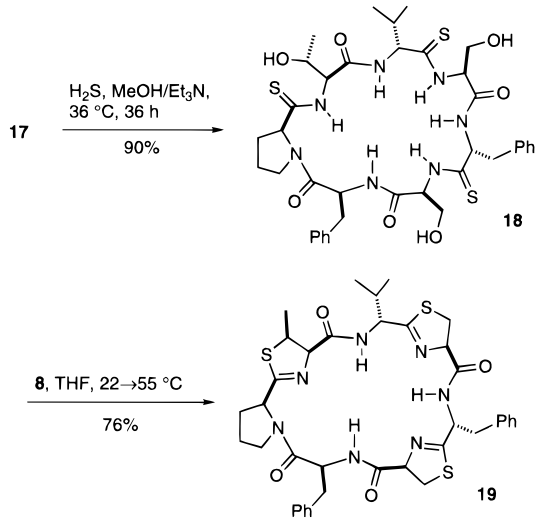
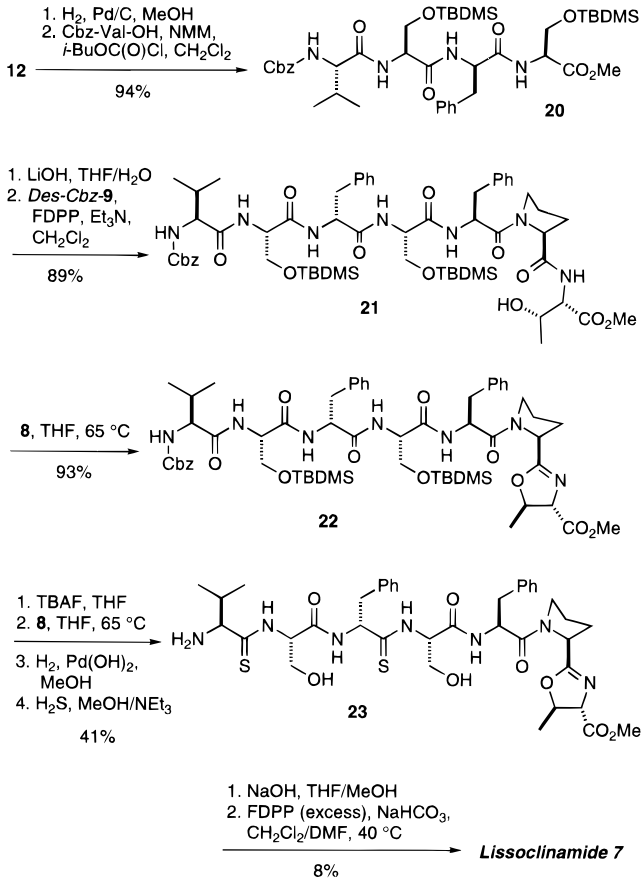
Scheme 4. First Approach toward Lissoclinamide 7



Scheme 5. Second Approach toward Lissoclinamide 7



(Scheme 5). Oxazoline formation, silyl ether deprotection, and exposure to an excess of the Burgess reagent provided a linear trisoxazoline that was highly susceptible to hydrolysis and therefore immediately subjected to hydrogenolysis of the Cbz-carbamate and thiolysis in a solution of H_2S in methanol/triethylamine at room temperature. Indeed, after 8 h, the bisthioamide **23** was isolated in 41% yield and only traces of thioamide derived from ring-opening of the trisubstituted oxazoline were detected. This confirmed our hypothesis that the lack of reactivity of the serine-derived oxazolines in **17** was due to the macrocycle conformation.

After cleavage of the methyl ester in **23**, macrocyclization with FDPP proceeded sluggishly unless a large excess of coupling agent was added to the reaction mixture. To our

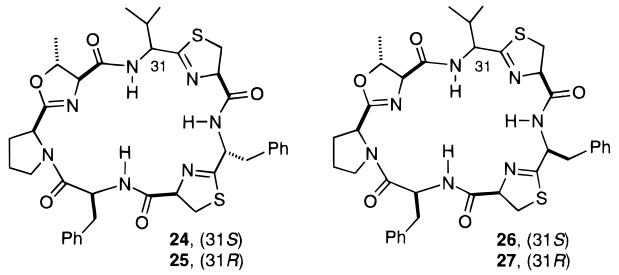


Figure 6. Lissoclinamide 7 epimers.

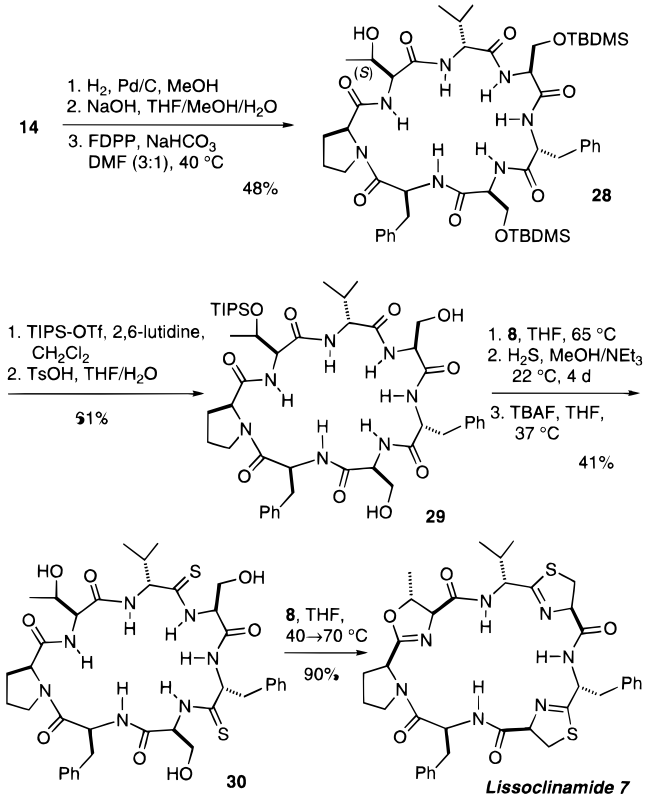
surprise, under these conditions cyclodehydration of the β-hydroxy thioamides and macrolactamization proceeded competitively, and the resulting product contained all three heterocycles. Moreover, ^{1}H and ^{13}C NMR analyses revealed the isolated material to be identical to lissoclinamide 7.[30] At this point we tentatively assigned the structure of the natural material as **24** (Figure 6). However, in light of the extraordinary ease of epimerization of thiazolines,[17,18] and since FDPP had not previously been applied for thiazoline formation, we performed a series of control experiments on model β-hydroxy thioamides[17] that indeed routinely led to considerable epimerization exocyclic to C(2) of the resulting thiazoline. Accordingly, we were unable to exclude structure **25** or even **26** and **27** for our synthetic material, and a third-generation synthesis was needed to clarify the stereochemistry.

A comparison of the ^{1}H NMR data for lissoclinamide 7 and the D-valine-containing tristhiazoline **19** revealed very similar chemical shifts at the right side, valine portion of the macrocycles. This observation cast additional doubt on the stereochemical integrity of the route shown in Scheme 5, leading, presumably, to the L-valine isomer **24**. As a control, we then used the D-valine heptapeptide **14** for the formation of the cyclopeptide **28** in 48% yield (Scheme 6). Since we had been unable to achieve chemoselectivity in the thiolysis of macrocyclic serine- and threonine-derived oxazolines, the side chain protective groups on **28** were switched from serine to threonine residues in **29** before exposure to 2.5 equiv of the Burgess reagent. The resulting bisoxazoline was thiolyzed in methanol/triethylamine, and desilylation gave bisthioamide **30**. Triple cyclodehydration of this compound with an excess of the Burgess reagent was extremely efficient, providing the two thiazolines and the oxazoline in lissoclinamide 7 in 90% yield![31]

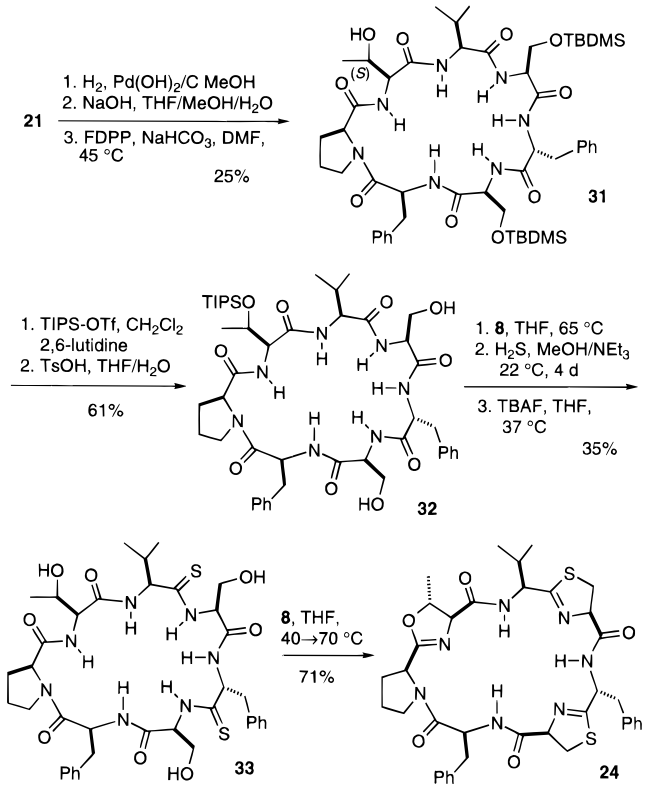
Due to the superior efficiency of this last route and since the configurationally labile thiazoline residues were only introduced in the last step of the synthesis, we were confident that the isomer shown in Scheme 6, an epimer at C(31) of **24**, was indeed representative of the structure of the natural product. On the basis of the spectral data, as well as optical rotation and $[\alpha]_D$, both routes incorporating L-valine (Scheme 5) or D-valine (Scheme 6) produced material identical to the natural product. In order to further substantiate our structure assignment of lissoclinamide 7, we embarked on an independent synthesis of **24** according to our successful third-generation strategy.

Deprotection of L-valine-containing heptapeptide **21** and macrolactamization under high dilution conditions provided cyclopeptide **31** in 25% yield (Scheme 7). The lower yield in the conversion of **21** to **31** as compared to **14** → **28** (25 vs 48%) is a consequence of the decrease in the rate of cyclization as a function of the presence of an L- vs a D-amino acid at the N-terminus of the linear peptide precursors.[32] Analogous to

Scheme 6. Third Approach toward Lissoclinamide 7



Scheme 7

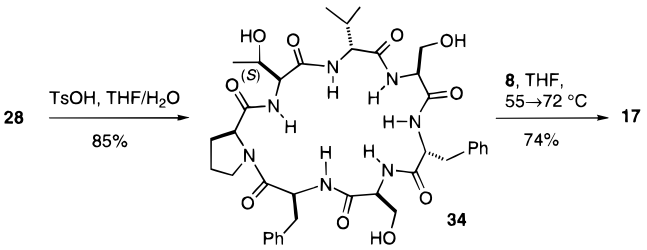


28, **31** was converted to the 21-membered heterocyclic cyclopeptide **24** in six steps and 15% overall yield.

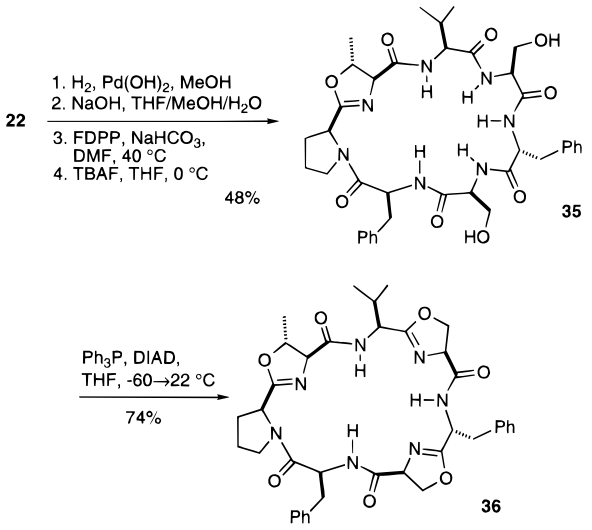
With **24** in hand, the spectral differences between lissoclinamide 7 and its L-epimer at C(31) became obvious. Indeed,

(27) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.
(28) (a) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711. (b) Dudash, J.; Jiang, J.; Mayer, S. C.; Joullié, M. M. *Synth. Commun.* **1993**, *23*, 349.
(29) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (b) Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807.

Scheme 8



Scheme 9



the FDPP-induced thiazoline formation in **23** shown in Scheme 5 had led to a selective isomerization of the C(31)-configuration from the L- to the D-series. Therefore, the caution that is necessary in the structure assignment of *Lissoclinum* peptides by hydrolysis of natural material has to be extended to the correlation of the stereochemistry of synthetic compounds with the natural product. The final structural proof for the identity of lissoclinamide 7 was provided by the X-ray structure of synthetic product.[33]

In summary, an efficient total synthesis of lissoclinamide 7 was accomplished in 18 linear steps and in 4.4% overall yield. In addition to the natural product, we have been able to prepare a series of analogs that should shed light on the structural basis of the very high levels of cytotoxicity found for *Lissoclinum* peptides in general and lissoclinamide 7 in specific. The preparation of the trisoxazoline analog **17** was further optimized by conversion of the readily available **28** to the triol **34** followed by triple cyclodehydration (Scheme 8). Analogously, the C(31)-epimeric trisoxazoline **36** was obtained in five steps and 36% yield from **22** (Scheme 9).

(30) Due to the dearth of natural product, we were unable to obtain an authentic sample of lissoclinamide 7. However, comparisons were performed with the actual ^{1}H NMR and ^{13}C NMR spectra of natural lissoclinamide 7. We thank Prof. D. Watters for providing us with copies of her data.

(31) For an example of the simultaneous formation of an oxazoline and a thiazoline using this methodology, see: Boden and Pattenden (ref 18). In the cyclopeptide area, the simultaneous formation of two oxazolines was reported by Shioiri et al. and Schmidt et al. (refs 13 and 14). For the simultaneous formation of multiple thiazolines or oxazolines in linear polyazoles, see: Parsons, R. L.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 1383. Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733. Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224.

(32) For comparison, see: Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, 3938 and references cited therein.

(33) The coordinates and a detailed discussion of the three-dimensional structure of lissoclinamide 7 will be reported elsewhere.

Conclusions

In spite of the considerable body of synthetic, structural and biological work toward *Lissoclinum* peptides,[13] major challenges in the design of stereoselective protocols for heterocycle formation and effective macrocyclization strategies have remained. In addition, a better understanding of the effects of amino acid-derived thiazoline and oxazoline heterocycles on the conformation of cyclopeptides might facilitate the *de novo* design of conformationally preorganized macrocycles. Our work toward lissoclinamide 7 highlights the potential pitfalls in the synthesis of configurationally labile natural products and the concomitant structural correlation between synthetic and isolated material. Several new strategies for *Lissoclinamide* peptide synthesis have been explored, and the successful total synthesis establishes the cyclodehydration of β-hydroxy amides and thioamides with the Burgess reagent as a versatile and stereochemically reliable method for the preparation of complex oxazolines and thiazolines. The oxazoline → thiazoline conversion via thiolysis of oxazolines offers a novel and convenient strategy for the preparation of the natural product as well as a series of analogues that will provide useful information on the structure−activity relationships of *Lissoclinum* peptides. Biological evaluation of these compounds is currently in progress.

Experimental Section

General Methods. NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise noted. IR spectra of solid samples were prepared by spreading a solution of the solid in $CHCl_3$ over a NaCl disk, slow evaporation, and measurement of the resulting dispersion. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Analytical TLC was performed with Merck silica gel 60 F-254 plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

Cbz-Phe-Pro-*allo*-Thr-OMe (9). A solution of 1.03 g (2.02 mmol) of Cbz-Phe-Pro-Thr-OMe (**7**) in 20 mL of THF was treated at room temperature with 0.58 g (2.43 mmol) of the Burgess reagent (**8**). The reaction mixture was stirred at room temperature for 10 min and then heated to 75 °C for 2.5 h, cooled to room temperature, and concentrated. Chromatography on SiO_2 (90% EtOAc/hexanes) afforded 891 mg of Cbz-Phe-Pro-Thr(oxaz)-OMe as a white foam.

A solution of 891 mg (1.805 mmol) of Cbz-Phe-Pro-Thr(oxaz)-OMe in 60 mL of THF was treated with 18 mL of 0.3 M HCl. After 10 min the pH was adjusted to 9.5 with solid K_2CO_3, and the solution was stirred for 2 h. After addition of 20 mL of H_2O, THF was removed in vacuo. The solution was acidified with 1 M HCl and extracted with EtOAc (3 × 90 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (90% EtOAc/hexanes) afforded 829 mg (80%) of **9** as a white foam: $[\alpha]_D$ −10.2° (*c* 1.1, $CHCl_3$, 22 °C); IR (neat) 3314, 1686, 1637 cm^{-1}; ^{1}H NMR (major rotamer) δ 7.39−7.18 (m, 11 H), 5.77 (d, 1 H, J = 8.5 Hz), 5.08 (d, 1 H, J = 12.4 Hz), 5.03 (d, 1 H, J = 12.4 Hz), 4.76−4.63 (m, 2 H), 4.46−4.40 (m, 1 H), 4.30−4.18 (m, 1 H), 3.79 (s, 3 H), 3.67−3.60 (m, 1 H), 3.30−3.18 (m, 1 H), 3.09−3.00 (m, 1 H), 2.97−2.88 (m, 1 H), 2.16−1.70 (m, 4 H), 1.25−1.20 (m, 3 H); ^{13}C NMR (major rotamer) δ 171.5, 171.2, 170.5, 155.8, 136.2, 135.8, 129.4, 128.3, 127.9, 127.7, 126.7, 68.2, 66.6, 60.3, 58.3, 47.4, 38.3, 28.4, 25.0, 18.9; MS (FAB) *m/e* (rel intensity) 534 ([M + Na]$^+$, 20), 512 (M + H, 35).

Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (13). A solution of 4.15 g (5.80 mmol) of Cbz-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (**12**) in 140 mL of MeOH was treated with Pd/C and H_2 gas for 2 h and then filtered through a plug of Celite and concentrated. The residue was dried by azeotropic distillation of benzene to afford the amine D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe as a white solid.

A solution of 1.60 g (6.38 mmol) of Cbz-D-valine in 125 mL of CH_2Cl_2 was treated with 0.83 mL (7.54 mmol) of *N*-methylmorpholine

and cooled to −20 °C, and 0.83 mL (6.38 mmol) of isobutyl chloroformate was added dropwise. The reaction mixture was stirred for 15 min at −15 °C. A solution of the amine prepared above in 20 mL of CH_2Cl_2 was added slowly, and the mixture was warmed to 0 °C over 1.5 h and then to room temperature over another 1 h. The solution was washed with 1 M NaH_2PO_4 (90 mL), H_2O (90 mL), and brine (90 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (30% EtOAc/hexanes) afforded 4.39 g (93%) of **13** as a colorless solid: mp 132−133 °C (EtOAc/hexanes); $[\alpha]_D$ +20.2° (*c* 1.2, CH_2Cl_2, 24 °C); IR (neat) 3269, 1672, 1632 cm^{-1}; ^1H NMR δ 7.36−7.22 (m, 11 H), 6.88 (d, 1 H, J = 6.8 Hz), 6.68 (d, 1 H, J = 8.0 Hz), 5.56 (d, 1 H, J = 8.0 Hz), 5.18 (d, 1 H, J = 12.2 Hz), 5.07 (d, 1 H, J = 12.2 Hz), 4.78 (dd, 1 H, J = 14.6, 7.3 Hz), 4.62−4.59 (m, 1 H), 4.52−4.50 (m, 1 H), 4.10−4.02 (m, 1 H), 4.00−3.92 (m, 2 H), 3.70 (s, 3 H), 3.64 (dd, 1 H, J = 9.3, 6.8 Hz), 3.56 (dd, 1 H, J = 10.0, 3.2 Hz), 3.13 (dd, 1 H, J = 13.6, 7.4 Hz), 3.04 (dd, 1 H, J = 13.6, 6.6 Hz), 2.25−2.1 (m, 1 H), 0.99 (d, 3 H, J = 6.7 Hz), 0.94−0.91 (m, 12 H), 0.85 (s, 9 H), 0.10 (s, 6 H), 0.01 (s, 6 H); ^{13}C NMR δ 171.0, 170.4, 169.8, 169.2, 156.3, 136.4, 129.2, 128.1, 127.6, 126.6, 66.5, 63.0, 59.9, 54.2, 53.9, 52.0, 38.7, 31.1, 25.6, 25.4, 19.0, 18.0, 17.8, −5.8, −6.0; MS (EI) *m/e* (rel intensity) 815 (M^+, 90), 758 (90), 91 (100); HRMS *m/e* calcd for $C_{41}H_{66}N_4O_9Si_2$ 814.4368, found 814.4376.

Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (14). A solution of 1.18 g (2.31 mmol) of Cbz-Phe-Pro-*allo*-Thr-OMe (**9**) in 125 mL of MeOH was treated with Pd/C and H_2 gas for 4 h. The reaction mixture was filtered through a plug of Celite, concentrated, and dried by azeotropic distillation with benzene to afford the amine as a white solid. A solution of 2.08 g (2.55 mmol) of Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (**13**) in 40 mL of THF/H_2O (3:1) was treated with 118 mg (2.81 mmol) of $LiOH\cdot H_2O$. The reaction mixture was stirred at room temperature for 3 h, 20 mL of H_2O was added, and THF was removed in vacuo. The solution was acidified with 1 M NaH_2PO_4 and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to afford 1.95 g (95%) of acid as a white solid. A solution of 1.95 g (2.43 mmol) of this acid, the amine prepared above, and 0.64 mL (4.62 mmol) of Et_3N in 100 mL of CH_2Cl_2 was treated at room temperature with a solution of 1.78 mg (4.62 mmol) of FDPP in 10 mL of CH_2Cl_2. The reaction mixture was stirred overnight, diluted with 150 mL of $CHCl_3$, washed with 1 M NaH_2PO_4 (90 mL), H_2O (90 mL), and brine (90 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (25% EtOAc/$CHCl_3$ followed by 4% MeOH/$CHCl_3$) and a second chromatography on SiO_2 (2.5% MeOH/$CHCl_3$) afforded 2.17 g (81%) of **14** as colorless solid: mp 106−108 °C ($CHCl_3$); $[\alpha]_D$ −34.2° (*c* 1.2, MeOH, 23 °C); IR (neat) 3289, 1659, 1525 cm^{-1}; ^1H NMR (DMSO-d_6, 368 K) δ 7.8−7.6 (b, 3 H), 7.59 (d, 1 H, J = 7.0 Hz), 7.35−7.30 (m, 3 H), 7.30−7.15 (m, 9 H), 6.73 (d, 1 H, J = 8.2 Hz), 5.09 (d, 1 H, J = 12.7 Hz), 5.02 (d, 1 H, J = 12.7 Hz), 4.80 (b, 1 H), 4.68−4.58 (m, 1 H), 4.50−4.27 (m, 4 H), 4.02 (dd, 1 H, J = 8.5, 6.3 Hz), 3.97−3.92 (m, 1 H), 3.75−3.60 (m, 6 H), 3.38 (b, 1 H), 3.07 (dd, 1 H, J = 13.9, 5.6 Hz), 2.86 (dd, 1 H, J = 13.9, 8.0 Hz), 2.09−2.00 (m, 1 H), 2.00−1.75 (m, 4 H), 1.17 (d, 3 H, J = 6.3 Hz), 0.93−0.79 (m, 24 H), 0.03 (s, 6 H), 0.02 (s, 6 H); ^{13}C NMR (DMSO-d_6, 368 K) δ 170.7, 170.1, 169.1, 168.6, 168.3, 155.5, 137.0, 136.5, 128.7, 127.7, 127.0, 125.7, 66.5, 65.2, 62.7, 62.6, 61.4, 60.0, 59.0, 58.1, 54.7, 54.2, 53.7, 51.5, 50.8, 46.2, 37.6, 37.4, 29.9, 28.0, 25.2, 23.8, 19.3, 18.5, 17.4, −3.8, −6.1; MS (FAB) *m/e* (rel intensity) 1182 ($[M + Na]^+$, 58), 1060 ($[M + H]^+$, 44).

Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-(oxaz)-OMe (15). A solution of 0.75 g (0.64 mmol) of Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (**14**) in 25 mL of THF was treated at room temperature with 253 mg (1.06 mmol) of the Burgess reagent. The solution was warmed from room temperature to 65 °C over 30 min and kept at 65 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated. Chromatography on SiO_2 (2.5% MeOH/$CHCl_3$) afforded 659 mg (89%) of **15** as a colorless solid: mp 145−146 °C (MeOH); $[\alpha]_D$ −12.0° (*c* 1.4, MeOH, 22 °C); IR (neat) 3289, 1652, 1646 cm^{-1}; ^1H NMR (MeOH-d_4, major rotamer) δ 7.28−7.00 (m, 15 H), 5.09−4.90 (m, 2 H), 4.75−4.68 (m, 1 H), 4.60−4.49 (m, 3 H), 4.27 (dd, 1 H, J = 5.3, 5.2 Hz), 4.18 (dd, 1 H, J = 7.7, 7.2 Hz), 3.92 (d, 1 H, J = 6.9 Hz), 3.85−3.32 (m, 9 H), 3.12−2.94 (m, 2 H), 2.94−2.72 (m, 2 H), 2.12−1.64 (m, 4 H), 1.28 (d, 2.1 H), J = 6.3 Hz), 0.97−0.69 (m, 24 H), 0.00 to −0.16 (m, 12 H); ^{13}C NMR (MeOH-d_4, mixture of rotamers) δ 174.5, 173.0, 172.6, 172.4, 171.7, 171.5, 171.3, 170.3, 158.7, 138.4, 138.1, 137.6, 130.7, 130.4, 129.5, 128.9, 128.3, 127.9, 81.9, 81.2, 74.9, 67.7, 64.1, 63.9, 62.5, 56.8, 56.6, 56.3, 55.9, 53.9, 53.0, 47.6, 40.9, 38.8, 38.6, 32.2, 31.8, 31.6, 30.7, 26.4, 25.4, 23.0, 20.9, 20.0, 19.1, −5.2; MS (FAB) *m/e* (rel intensity) 1165 ($[M + Na]^+$, 24), 1143 ($[M + H]^+$, 100).

Cyclo[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(oxaz)] (16). A solution of 650 mg (0.568 mmol) of Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser-(TBDMS)-Phe-Pro-*allo*-Thr(oxaz)-OMe (**15**) in 20 mL of MeOH was treated with $Pd(OH)_2$ and H_2 gas for 10 h. The reaction mixture was filtered through Celite and concentrated. The residue was dissolved in 20 mL of THF/MeOH/H_2O (10:2:1) and treated with 312 μL (0.625 mmol) of a 2.0 M NaOH solution. The reaction mixture was stirred at room temperature for 4 h, treated with 105 mg (1.25 mmol) of $NaHCO_3$ for 30 min, filtered, concentrated, and dried by azeotropic distillation with benzene. The resulting amino acid sodium salt was dissolved in 284 mL of CH_2Cl_2/DMF (3:1) and treated with 860 mg (2.25 mmol) of FDPP. The reaction mixture was stirred at 40 °C for 2.5 d and treated with 168 mg (2.0 mmol) of $NaHCO_3$, and the solvents were removed at reduced pressure. The residue was dissolved in 10% MeOH/$CHCl_3$ and adsorbed onto SiO_2. Chromatography on SiO_2 (15% EtOAc/$CHCl_3$ followed by 5% MeOH/$CHCl_3$) afforded 0.48 g of a solid, which was dissolved in 12 mL of THF and treated at 0 °C with 1.25 mL (1.25 mmol) of 1 M TBAF in THF solution for 15 min. The reaction mixture was directly chromatographed on SiO_2 (4−5% MeOH/$CHCl_3$) to afford 90 mg (21%) of **16** as a white solid: mp 229−232 °C (MeOH); $[\alpha]_D$ −5.6° (*c* 0.3, MeOH, 23 °C); IR (neat) 3302, 1670, 1657 cm^{-1}; ^1H NMR (MeOH-d_4, major rotamer) δ 7.28−7.09 (m, 10 H), 4.73−4.57 (m, 3 H), 4.47−4.38 (m, 2 H), 4.21−4.13 (m, 1 H), 4.13−4.07 (m, 2 H), 3.82−3.58 (m, 3 H), 3.58−3.50 (m, 1 H), 3.31 (dd, 1 H, J = 11.0, 3.7 Hz), 3.23−3.20 (m, 1 H), 3.10−2.80 (m, 4 H), 2.38−2.08 (m, 2 H), 1.93−1.65 (m, 3 H), 1.32 (d, 3 H, J = 6.2 Hz), 1.0−0.9 (m, 6 H); ^{13}C NMR (MeOH-d_4, major rotamer) δ 174.2, 173.6, 173.4, 172.5, 172.2, 172.0, 138.1, 137.8, 130.6, 130.3, 129.5, 127.9, 82.1, 75.1, 62.5, 62.4, 61.0, 57.6, 57.0, 56.7, 54.7, 54.5, 38.3, 37.4, 31.8, 30.5, 26.0, 21.6, 20.0, 18.7; MS (FAB) *m/e* (rel intensity) 770 ($[M + Na]^+$, 98), 748 ($[M + H]^+$, 43); HRMS *m/e* calcd for $C_{38}H_{49}N_7O_9$ 747.3592, found 747.3570.

Cyclo[D-Val-Ser(oxaz)-D-Phe-Ser(oxaz)-Phe-Pro-*allo*-Thr(oxaz)] (17). Method A. A solution of 42.7 mg (0.057 mmol) of cyclo-[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(oxaz)] (**16**) in 10 mL of THF was treated at −60 °C with a solution of 149.5 mg (0.57 mmol) of triphenylphosphine in 2 mL of THF and 118 μL (0.57 mmol) of DIAD (diisopropyl azodicarboxylate). The reaction mixture was warmed to 0 °C over 45 min, concentrated, and chromatographed on SiO_2 (EtOAc to 5% MeOH/EtOAc) to afford 34.6 mg (85%) of **17** as a colorless solid. **Method B.** A solution of 40.8 mg (0.0532 mmol) of cyclo[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr] (**34**) in 7 mL of THF was treated at room temperature with 63.4 mg (0.266 mmol) of the Burgess reagent. The reaction mixture was heated at 55 °C for 1 h and at 72 °C for 4 h, cooled to room temperature, and concentrated. Chromatography on SiO_2 (EtOAc followed by 5−10% MeOH/EtOAc) and a second chromatography on SiO_2 (3−4% MeOH/$CHCl_3$) afforded 27.9 mg (74%) of **17** as a colorless solid: mp 212−219 °C (dec, $CHCl_3$); $[\alpha]_D$ +149.8° (*c* 0.6, $CHCl_3$, 23 °C); IR (neat) 3356, 1662, 1645 cm^{-1}; ^1H NMR δ 7.35−7.02 (m, 14 H), 5.05−4.96 (m, 1 H), 4.92−4.82 (m, 2 H), 4.72−4.67 (m, 2 H), 4.55−4.39 (m, 4 H), 4.26−4.19 (m, 3 H), 3.68−3.49 (m, 1 H), 3.15−3.02 (m, 3 H), 2.87 (dd, 1 H, J = 13.4, 6.2 Hz), 2.62−2.48 (m, 2 H), 2.30−2.18 (m, 1 H), 2.04−1.87 (m, 4 H), 1.44 (d, 3 H, J = 6.3 Hz), 1.01 (d, 3 H, J = 6.9 Hz), 0.91 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 172.5, 171.4, 170.0, 169.9, 169.5, 169.3, 168.8, 135.3, 135.1, 129.7, 129.2, 128.5, 128.3, 127.2, 127.1, 81.3, 77.2, 75.8, 70.8, 70.2, 68.9, 67.8, 56.4, 51.5, 51.4, 47.2, 39.9, 38.3, 29.9, 28.9, 25.2, 21.7, 19.5, 16.4; MS (EI) *m/e* (rel intensity) 711 (M^+, 100), 620 (24); HRMS *m/e* calcd for $C_{38}H_{45}N_7O_7$ 711.3380, found 711.3390.

Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (20). A solution of 4.45 g (6.22 mmol) of Cbz-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (**12**) in 120 mL of MeOH was treated with Pd/C and H_2 gas for 2 h and then filtered through a plug of Celite and concentrated. The residue was dried by azeotropic distillation with benzene to afford the amine

as a white solid. A solution of 1.72 g (6.83 mmol) of Cbz-valine in 125 mL of CH_2Cl_2 was treated with 0.89 mL (8.07 mmol) of *N*-methylmorpholine, cooled to −20 °C, and treated with 0.89 mL (6.83 mmol) of isobutyl chloroformate. The reaction mixture was stirred for 15 min at −15 °C. A solution of the amine prepared above in 20 mL of CH_2Cl_2 was added slowly, and the reaction mixture was warmed to 10 °C over 1 h. The solution was diluted with 100 mL of CH_2Cl_2, washed with 1 M NaH_2PO_4 (90 mL), H_2O (90 mL), and brine (90 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (30% EtOAc/hexanes) afforded 4.77 g (94%) of **20** as a colorless solid: mp 118−120 °C ($CHCl_3$); $[\alpha]_D$ +19.8° (*c* 1.0, CH_2Cl_2, 22 °C); IR (neat) 3289, 1697, 1633 cm^{-1}; ^1H NMR δ 7.38−7.16 (m, 13 H), 7.12 (b, 1 H), 5.58 (b, 1 H), 5.11 (s, 2 H), 5.03 (b, 1 H), 4.62−4.57 (m, 1 H), 4.45−4.35 (m, 1 H), 4.35−4.25 (m, 1 H), 3.93 (dd, 1 H, J = 9.9, 4.2 Hz), 3.85 (dd, 1 H, J = 9.4, 2.3 Hz), 3.67 (s, 3 H), 3.58 (dd, 1 H, J = 9.9, 4.1 Hz), 3.51−3.45 (m, 1 H), 3.09 (dd, 1 H, J = 13.6, 6.8 Hz), 2.96 (dd, 1 H, J = 13.6, 7.0), 2.05−1.95 (m, 1 H), 0.93 (s, 9 H), 0.91−0.82 (m, 6 H), 0.81 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H), −0.02 (s, 6 H); ^{13}C NMR δ 171.3, 170.2, 169.0, 156.5, 136.5, 129.6, 128.1, 127.8, 127.7, 126.3, 66.5, 63.9, 63.0, 58.6, 54.1, 53.8, 53.6, 51.7, 40.1, 32.6, 25.7, 25.4, 18.9, 18.0, 17.9, 17.2, −5.6, −5.8, −5.9; MS (EI) *m/e* (rel intensity) 814 (M^+, 60), 796 (80), 755 (69), 91 (100); HRMS *m/e* calcd for $C_{41}H_{66}N_4O_9Si_2$ 814.4368, found 814.4340.

Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (21). A solution of 1.17 g (2.29 mmol) of Cbz-Phe-Pro-*allo*-Thr-OMe (**9**) in 125 mL of MeOH was treated with Pd/C and H_2 gas for 4 h. The reaction mixture was filtered through a plug of Celite, concentrated, and dried by azeotropic distillation with benzene to afford the amine as a white solid. A solution of 2.12 g (2.60 mmol) of Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-OMe (**20**) in 40 mL of THF/H_2O (3:1) was treated with 120 mg (2.86 mmol) of LiOH·H_2O. The reaction mixture was stirred at room temperature for 3 h. After addition of 20 mL of H_2O, THF was removed in vacuo. The solution was acidified with 1 M NaH_2PO_4 and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to afford 2.08 g (100%) of acid as a white solid. A solution of 1.84 g (2.29 mmol) of this acid, the amine prepared above, and 0.64 mL (4.58 mmol) of Et_3N in 90 mL of CH_2Cl_2 was treated at room temperature with a solution of 1.76 g (4.58 mmol) of FDPP in 10 mL of CH_2Cl_2. The reaction mixture was stirred overnight, diluted with 150 mL of $CHCl_3$, washed with 1 M NaH_2PO_4 (90 mL), H_2O (90 mL), and brine (90 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (25% EtOAc/$CHCl_3$ followed by 3% MeOH/$CHCl_3$) and a second chromatography on SiO_2 (2.5% MeOH/$CHCl_3$) afforded 2.37 g (89%) of **21** as colorless solid: mp 175−176 °C (MeOH); $[\alpha]_D$ −48.2° (*c* 1.1, MeOH, 21 °C); IR (neat) 3283, 1676, 1630 cm^{-1}; ^1H NMR (DMSO-d_6, 368 K) δ 7.76−7.50 (m, 5 H), 7.35−7.27 (m, 4 H), 7.24−7.16 (m, 11 H), 6.72 (d, 1 H, J = 8.2 Hz), 5.07 (d, 1 H, J = 12.7 Hz), 5.04 (d, 1 H, J = 12.7 Hz), 4.77 (b, 1 H), 4.62 (dd, 1 H, J = 8.0, 5.7 Hz), 4.55 (b, 1 H), 4.43−4.25 (m, 4 H), 3.98−3.90 (m, 2 H), 3.68−3.55 (m, 9 H), 3.4−3.3 (m, 1 H), 3.06 (dd, 2 H, J = 13.9, 5.5 Hz), 2.85 (dd, 2 H, J = 13.9, 7.9 Hz), 2.05−1.95 (m, 1 H), 1.95−1.70 (m, 4 H), 1.16 (d, 3 H, J = 6.4 Hz), 0.89−0.78 (m, 24 H), 0.02 (s, 6 H), 0.02 (s, 6 H); ^{13}C NMR (MeOH-d_4) δ 174.1, 173.9, 172.8, 172.2, 172.0, 171.9, 171.4, 158.0, 138.2, 130.5, 130.3, 129.5, 129.0, 127.8, 69.0, 68.0, 64.0, 62.4, 61.4, 59.9, 56.6, 56.3, 54.0, 52.5, 39.0, 38.7, 32.1, 30.1, 26.4, 25.7, 20.1, 19.8, 19.1, 18.6, −5.2; MS (FAB) *m/e* (rel intensity) 1182 ([M + Na]$^+$, 45), 1160 ([M + H]$^+$, 97), 1101 (100).

Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-(oxaz)-OMe (22). A solution of 138.6 mg (0.119 mmol) of Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (**21**) in 2.5 mL of THF was treated at room temperature with 44.2 mg (0.185 mmol) of the Burgess reagent and stirred for 15 min. The reaction mixture was heated to 60 °C for 2.5 h, cooled to room temperature, and concentrated. Chromatography on SiO_2 (3% MeOH/$CHCl_3$) afforded 126.8 mg (93%) of **22** as a colorless solid: $[\alpha]_D$ −23.7° (*c* 1.2, MeOH, 23 °C); IR (neat) 3287, 1693, 1678 cm^{-1}; ^1H NMR (MeOH-d_4, mixture of rotamers) δ 7.27−7.08 (m, 15 H), 5.11−4.96 (m, 2 H), 4.76−4.69 (m, 1 H), 4.60−4.48 (m, 1.6 H), 4.45−4.25 (m, 2 H), 4.24−4.16 (m, 1 H), 4.01 (d, 0.3 H, J = 6.6 Hz), 3.89 (d, 0.7 H, J = 6.5 Hz), 3.84−3.39 (m, 8.8 H), 3.39−3.29 (m, 0.6 H), 3.14−3.01 (m, 1.8 H), 2.99−2.79 (m, 2.2 H), 2.08−1.65 (m, 4.4 H), 1.62−1.44 (m, 0.6 H), 1.35 (d, 1 H, J = 6.2 Hz), 1.29 (d, 2 H, J = 6.2 Hz), 0.95−0.84 (m, 6 H), 0.84−0.73 (m, 18 H), 0.00 to −0.09 (m, 12 H); ^{13}C NMR (MeOH-d_4, mixture of rotamers) δ 174.2, 172.8, 172.6, 172.4, 171.9, 171.8, 171.7, 171.5, 171.3, 171.1, 170.3, 170.1, 158.0, 138.3, 138.2, 138.0, 137.6, 81.8, 81.1, 75.1, 68.0, 64.0, 62.6, 62.4, 56.7, 56.4, 56.3, 55.8, 53.8, 52.9, 48.0, 47.5, 41.0, 38.8, 38.7, 38.5, 32.1, 31.8, 26.4, 25.3, 23.0, 20.9, 20.8, 19.8, 19.1, 18.8, 9.2, −5.2; MS (FAB) *m/e* (rel intensity) 1142 ([M + H]$^+$, 100), 1084 (28).

Cyclo[D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr] (28). A solution of 1.05 g (0.901 mmol) of Cbz-D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (**14**) in 175 mL of MeOH was treated with Pd/C and H_2 gas for 24 h. The reaction mixture was filtered through a plug of Celite and concentrated. Chromatography on SiO_2 (5−12% MeOH/$CHCl_3$) afforded 0.85 g (92%) of amine. A solution of 265 mg (0.258 mmol) of this amine in THF/MeOH/H_2O (10:2:1) was treated with 142 μL (0.284 mmol) of a 2.0 M NaOH solution. The reaction was stirred at room temperature for 4 h and then treated with 47.7 mg (0.568 mmol) of $NaHCO_3$. After 30 min, the reaction mixture was filtered, concentrated, and dried by azeotropic distillation with benzene. A solution of the amino acid sodium salt, 86 mg (1.02 mmol) of $NaHCO_3$, and 393 mg (1.02 mmol) of FDPP in 129 mL of DMF was heated at 40 °C for 3 d. DMF was removed by distillation under reduced pressure at 45 °C. The remaining residue was dissolved in 10% MeOH/$CHCl_3$ and adsorbed onto SiO_2. Chromatography on SiO_2 (25% EtOAc/hexanes followed by 5−10% MeOH/$CHCl_3$) and a second chromatography on SiO_2 (4−7% MeOH/$CHCl_3$) afforded 123 mg (48%) of **28** as a white solid: mp 143−145 °C ($CHCl_3$); $[\alpha]_D$ −43.7° (*c* 1.0, MeOH, 22 °C); IR (neat) 3296, 1643, 1510, cm^{-1}; ^1H NMR (MeOH-d_4, major rotamer) δ 7.40 (d, 2 H, J = 7.1 Hz), 7.23−7.09 (m, 8 H), 4.71−4.55 (m, 2 H), 4.35 (d, 1 H, J = 6.4 Hz), 4.32−4.18 (m, 3 H), 4.07−3.98 (m, 2 H), 3.96−3.71 (m, 4 H), 3.56 (dd, 1 H, J = 9.4, 5.1 Hz), 3.44−3.33 (m, 1 H), 3.20−3.12 (m, 2 H), 2.96−2.88 (m, 2 H), 2.32−2.13 (m, 2 H), 2.07−1.85 (m, 3 H), 1.13 (d, 3 H, J = 6.3 Hz), 0.87−0.83 (m, 6 H), 0.78 (s, 9 H), 0.61 (s, 9 H), −0.01 to −0.11 (m, 6 H), −0.22 (s, 3 H), −0.31 (s, 3 H); ^{13}C NMR (MeOH-d_4, major rotamer) δ 174.4, 173.5, 173.0, 172.9, 172.7, 171.2, 139.0, 137.7, 130.4, 130.2, 129.6, 128.1, 127.9, 68.0, 63.9, 63.4, 63.3, 60.3, 60.0. 58.6, 55.8, 55.6, 55.1, 37.40, 31.8, 30.1, 26.4, 26.3, 26.0, 20.1, 20.0, 19.1, 18.9, 18.5, −5.2, −5.4; MS (FAB) *m/e* (rel intensity) 1016 ([M + Na]$^+$, 54), 994 ([M + H]$^+$, 100).

Cyclo[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(TIPS)] (29). A solution of 162 mg (0.163 mmol) of cyclo[D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr] (**28**) in 4 mL of CH_2Cl_2 was treated at room temperature with 25 μL (0.212 mmol) of 2,6-lutidine and 57 μL (0.212 mmol) of TIPS-OTf (triisopropylsilyl triflate). The reaction mixture was stirred for 6 h, diluted with 45 mL of EtOAc, washed with 1 M NaH_2PO_4 (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (1−3% MeOH/$CHCl_3$) afforded 156 mg (83%) of cyclo[D-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr(TIPS)] as a colorless solid. A solution of 15.4 mg (0.0134 mmol) of this silyl ether in 1 mL of THF/H_2O (20:1) was treated with 0.4 mg (0.002 mmol) of TsOH·H_2O and stirred at room temperature overnight. After addition of 0.4 mg (0.004 mmol) of $NaHCO_3$, the reaction mixture was stirred for another 15 min. The volume of the solution was reduced to about one-third of the original volume, and the remainder was directly chromatographed on SiO_2 (6−8% MeOH/$CHCl_3$). Further purification by HPLC on SiO_2 (4.5% MeOH/$CHCl_3$) afforded 9.0 mg (73%) of **29** as a colorless solid: mp 155−157 °C ($CHCl_3$); $[\alpha]_D$ −39.0° (*c* 0.8, MeOH, 22 °C); IR (neat) 3291, 1680, 1651 cm^{-1}; ^1H NMR (MeOH-d_4, mixture of rotamers) δ 7.40 (d, 0.5 H, J = 7.2 Hz), 7.34 (d, 1 H, J = 7.3 Hz), 7.30−7.10 (m, 8.5 H), 4.58−4.20 (m, 6.2 H), 4.15−4.03 (m, 0.8 H), 3.98−3.70 (m, 2 H), 3.70−3.45 (m, 3.3 H), 3.45−3.28 (m, 2 H), 3.15−2.77 (m, 2.8 H), 2.30−2.20 (m, 0.8 H), 2.17−1.85 (m, 3.2 H), 1.65−1.42 (m, 0.8 H), 1.23 (d, 1.5 H, J = 6.2 Hz), 1.20−1.10 (m, 2.6 H), 1.00 (s, 16.2 H), 0.97−0.80 (m, 5.8 H), 0.79−0.74 (m, 3.H); ^{13}C NMR (MeOH-d_4, mixture of rotamers) δ 174.62, 174.0, 173.8, 173.6, 173.4, 173.3, 173.2, 173.0, 172.6, 172.5, 172.1, 171.5, 171.3, 139.0, 138.4, 138.0, 137.4, 130.4, 129.8, 129.7, 128.8, 128.1, 69.0, 63.7, 63.5, 63.4, 62.8, 62.4, 62.2, 60.9, 60.3, 58.7, 58.1, 56.5, 55.7, 47.9, 39.1, 38.1, 37.4, 37.0, 32.6, 32.4, 32.0, 26.4, 22.8, 20.4, 20.0, 19.6, 19.1, 18.6, 18.2, 13.8,

13.6; MS (ES) *m/e* (rel intensity) 944.5 ([M + Na]$^+$, 100), 922.5 ([M + H]$^+$, 10); HRMS (ES) *m/e* calcd for $C_{47}H_{71}N_7O_{10}NaSi$ 944.4929, found 944.4969.

Cyclo[D-ValΨ{(C═S)NH}-Ser-D-PheΨ{(C═S)NH}-Ser-Phe-Pro-*allo*-Thr] (30). A solution of 40.5 mg (0.0439 mmol) of cyclo[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(TIPS)] (**29**) in 4 mL of THF was treated at room temperature with 32.0 mg (0.134 mmol) of the Burgess reagent. The mixture was stirred at 65 °C for 2.5 h, cooled to room temperature, and concentrated. The residue was dissolved in 5 mL of MeOH/Et_3N (1:1) and saturated with H_2S gas. The solution was stirred at room temperature for 4 d and then concentrated. Chromatography on SiO_2 ($CHCl_3$ to 4% MeOH/$CHCl_3$) afforded 40.6 mg of thiolysis products. The crude material was dissolved in 1 mL of THF, treated with 49 μL (0.049 mmol) of 1 M TBAF in THF, and heated at 37 °C for 3 h. The solution was cooled to room temperature and directly chromatographed on SiO_2 (6% MeOH/$CHCl_3$). Further purification by HPLC on SiO_2 (2% MeOH/EtOAc) afforded 14.4 mg (41%) of **30** as a colorless solid: mp 195−197 °C (dec, MeOH); $[\alpha]_D$ −118° (*c* 0.9, MeOH, 23 °C); IR (neat) 3292, 1657, 1649 cm^{-1}; ^{1}H NMR (MeOH-d_4, major rotamer) δ 7.39 (d, 2 H, J = 7.2 Hz), 7.35−7.05 (m, 8 H), 5.25 (dd, 1 H, J = 7.9, 5.1 Hz), 4.87−4.81 (m, 2 H), 4.70 (dd, 1 H, J = 10.7, 3.2 Hz), 4.66−4.50 (m, 2 H), 4.28−4.22 (m, 1 H), 4.10−3.94 (m, 3 H), 3.86−3.76 (m, 2 H), 3.75−3.50 (m, 5 H), 3.45−3.35 (m, 1 H), 3.35−3.26 (m, 2 H), 3.16−2.87 (m, 4 H), 2.41−2.28 (m, 1 H), 2.24−2.10 (m, 1 H), 2.00−1.85 (m, 4 H), 1.05 (d, 3 H, J = 6.3 Hz), 0.87 (d, 3 H, J = 6.7 Hz), 0.80 (d, 3 H, J = 6.7 Hz); ^{13}C NMR (MeOH-d_4, major rotamer) δ 208.2, 204.8, 174.7, 173.3, 171.9, 171.8, 171.2, 139.0, 138.1, 130.6, 130.6, 129.8, 129.6, 129.6, 128.0, 68.4, 67.8, 65.2, 64.1, 63.6, 62.1, 61.5, 61.1, 55.8, 55.4, 40.3, 37.8, 33.5, 30.3, 26.2, 23.0, 20.7, 19.9, 19.4; MS (FAB) *m/e* (rel intensity) 820 ([M + Na]$^+$, 45), 798 ([M + H]$^+$, 100).

Cyclo[D-Val-Ser(thiaz)-D-Phe-Ser(thiaz)-Phe-Pro-*allo*-Thr(oxaz)] (Lissoclinamide 7 (25)). A solution of 18.2 mg (0.0228 mmol) of cyclo[D-ValΨ{(C═S)NH}-Ser-D-PheΨ{(C═S)NH}-Ser-Phe-Pro-*allo*-Thr] (**30**) in 3 mL of THF was treated at room temperature with 27.2 mg (0.114 mmol) of the Burgess reagent. The mixture was stirred at room temperature for 10 min and then heated to 40 °C for 20 min and to 70 °C for 1.5 h. The solution was cooled, filtered, concentrated, and chromatographed on SiO_2 (3% MeOH/$CHCl_3$). Further purification with HPLC (2% MeOH/$CHCl_3$) afforded 15.3 mg (90%) of lissoclinamide 7 (**25**) as a colorless solid: mp 242−247 °C (dec, MeOH); $[\alpha]_D$ +172° (*c* 0.6, $CHCl_3$, 22 °C); IR (neat) 3379, 1674, 1651 cm^{-1}; ^{1}H NMR δ 7.74 (d, 1 H, J = 10.1 Hz), 7.36−7.11 (m, 9 H), 7.09 (d, 2 H, J = 6.7 Hz), 6.91 (d, 1 H, J = 9.2 Hz), 5.30−5.21 (m, 2 H), 5.00−4.87 (m, 3 H), 4.64 (dd, 1 H, J = 10.6, 9.9 Hz), 4.56 (dd, 1 H, J = 8.0, 7.6 Hz), 4.27 (d, 1 H, J = 4.6 Hz), 3.68−3.52 (m, 4 H), 3.21 (dd, 1 H, J = 11.3, 11.1 Hz), 3.09 (d, 2 H, J = 5.2 Hz), 3.07−2.98 (m, 1 H), 2.91 (dd, 1 H, J = 13.5, 6.2 Hz), 2.69 (dd, 1 H, J = 13.4, 8.6 Hz), 2.54−2.44 (m, 1 H), 2.30−2.22 (m, 1 H), 2.04−1.86 (m, 3 H), 1.43 (d, 3 H, J = 6.4 Hz), 0.97 (d, 3 H, J = 6.9 Hz), 0.64 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 179.9, 172.9, 172.1, 170.8, 169.6, 169.4, 135.7, 134.7, 129.7, 129.6, 128.6, 128.4, 127.4, 127.0, 81.1, 79.7, 78.2, 75.8, 56.4, 51.9, 51.6, 47.1, 39.4, 38.8, 36.2, 34.8, 30.8, 28.8, 25.4, 21.8, 19.7, 15.9; MS (FAB) *m/e* (rel intensity) 744 ([M + H]$^+$, 100); HRMS *m/e* calcd for $C_{38}H_{45}N_7O_5S_2$ 743.2924, found 743.2960; HRMS (FAB) *m/e* calcd for $C_{38}H_{46}N_7O_5S_2$ ([M + H]$^+$) 744.3027, found 744.3002.

Cyclo[Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr] (31). A solution of 1.23 g (1.060 mmol) of Cbz-Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr-OMe (**21**) in 400 mL of MeOH was treated with $Pd(OH)_2$/C and H_2 gas for 24 h. The reaction mixture was filtered through a plug of Celite and concentrated. The residue was purified by chromatography through a short plug of SiO_2 (5−10% MeOH/$CHCl_3$) to afford 0.88 g (81%) of amine as a solid. This amine was dissolved in 26 mL of THF/MeOH/H_2O (10:2:1) and treated with 0.64 mL (1.28 mmol) of a 2.0 M NaOH solution. The reaction mixture was stirred at room temperature overnight and then treated with 196 mg (2.33 mmol) of $NaHCO_3$. After 30 min, the suspension was filtered, concentrated, and dried by azeotropic distillation with benzene. A solution of the resulting amino acid sodium salt, 288 mg (3.428 mmol) of $NaHCO_3$, and 1.32 g (3.43 mmol) of FDPP in 429 mL of DMF was heated at 45 °C for 4.5 d. Volatiles were removed by distillation under reduced pressure at 45 °C. The remaining residue was dissolved in 10% MeOH/$CHCl_3$ and adsorbed onto SiO_2. Chromatography on SiO_2 (30% EtOAc/$CHCl_3$ followed by 4−7% MeOH/$CHCl_3$) and subsequent HPLC on SiO_2 (4% MeOH/$CHCl_3$) afforded 211 mg (25%) of **31** as a white solid: mp 155−160 °C (MeOH); $[\alpha]_D$ −53.4° (*c* 0.6, MeOH, 24 °C); IR (neat) 3273, 1639, 1560 cm^{-1}; ^{1}H NMR (MeOH-d_4, mixture of rotamers) δ7.28−7.02 (m, 10 H), 4.99−4.90 (m, 0.4 H), 4.52 (dd, 0.9 H, J = 9.2, 5.5 Hz), 4.49−4.30 (m, 2.6 H), 4.30−4.14 (m, 2 H), 4.14−4.02 (m, 0.8 H), 4.00−3.90 (m, 1.8 H), 3.90−3.76 (m, 1.4 H), 3.76−3.68 (m, 0.6 H), 3.67−3.58 (m, 1.1 H), 3.55−3.44 (m, 1.7 H), 3.31−3.23 (m, 1.6 H), 3.15−2.96 (m, 2 H), 2.95−2.78 (2.2 H), 2.22−2.10 (m, 0.9 H), 2.04−1.78 (m, 1.8 H), 1.65−1.51 (m, 0.6 H), 1.50−1.32 (m, 0.7 H), 1.23−1.08 (m, 3.5 H), 0.98−0.60 (m, 25 H), 0.03 to −0.03 (m, 4 H), −0.03 to −0.12 (m, 6.2 H), −0.12 to −0.20 (m, 1.8 H); ^{13}C NMR (MeOH-d_4, 318 K, major rotamer) δ 174.2, 173.9, 173.1, 172.2, 172.1, 171.8, 170.9, 138.7, 137.2, 130.6, 130.3, 129.9, 129.5, 128.5, 127.7, 67.3, 64.7, 63.7, 62.1, 61.9, 56.4, 56.2, 56.0, 55.0, 47.6, 39.4, 37.8, 31.8, 30.4, 26.5, 26.4, 23.1, 21.7, 19.7, 19.1, 18.1, −5.2, −5.4; MS (FAB) *m/e* (rel intensity) 1032 ([M+K]$^+$, 6), 1016 ([M + Na]$^+$, 100), 994 ([M + H]$^+$, 6).

Cyclo[Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(TIPS)] (32). A solution of 108 mg (0.109 mmol) of cyclo[Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr] (**31**) in 6 mL of CH_2Cl_2 was treated at room temperature with 16.5 μL (0.142 mmol) of 2,6-lutidine and 38 μL (0.142 mmol) of TIPS-OTf. The reaction mixture was stirred at room temperature for 8 h, diluted with 45 mL EtOAc, washed with 1 M NaH_2PO_4 (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (1−3% MeOH/$CHCl_3$) afforded 97.6 mg (78%) of cyclo[Val-Ser(TBDMS)-D-Phe-Ser(TBDMS)-Phe-Pro-*allo*-Thr(TIPS)] as a colorless solid. A solution of 97.6 mg (0.0848 mmol) of this silyl ether in 3 mL of THF/H_2O (20:1) was treated with 2.4 mg (0.0127 mmol) of TsOH·H_2O, stirred at room temperature overnight, and treated with 2.1 mg (0.0254 mmol) of $NaHCO_3$. The reaction mixture was stirred for another 15 min. The volume of the solution was reduced to about one-third under reduced pressure, and the reaction mixture was directly chromatographed on SiO_2 (6−8% MeOH/$CHCl_3$). Further purification by HPLC on SiO_2 (4.5% MeOH/$CHCl_3$) afforded 61 mg (78%) of **32** as a colorless solid: mp 162−165 °C (MeOH); $[\alpha]_D$ −36.4° (*c* 0.5, MeOH, 23 °C); IR (neat) 3294, 1649, 1632 cm^{-1}; ^{1}H NMR (MeOH-d_4, mixture of rotamers) δ 7.26−6.94 (m, 10 H), 4.99 (dd, 0.4 H, J = 7.4, 7.2 Hz), 4.69−4.55 (m, 0.7 H), 4.53−4.39 (m, 1 H), 4.39−4.29 (m, 1.3 H), 4.29−4.12 (m, 1.8 H), 4.12−4.00 (m, 1.4 H), 4.00−3.60 (m, 3.4 H), 3.56−3.38 (m, 3.1 H), 3.38−3.26 (m, 1.4 H), 3.10−3.00 (m, 0.9 H), 3.00−2.84 (m, 1.9 H), 2.77 (dd, 0.6 H, J = 14.3, 11.0 Hz), 2.58 (dd, 0.3 H, J = 13.7, 6.6 Hz), 2.35−1.76 (m, 3.9 H), 1.76−1.43 (m, 0.9 H), 1.38−0.69 (m, 30 H); ^{13}C NMR (MeOH-d_4, mixture of rotamers) δ 177.1, 175.1, 174.4, 173.5, 173.1, 172.9, 172.8, 172.4, 172.2, 171.6, 171.4, 170.1, 139.9, 139.2, 138.3, 138.0, 137.2, 130.6, 130.2, 130.0, 129.7, 129.4, 129.2, 128.6, 127.8, 127.6, 69.5, 69.1, 68.7, 64.4, 63.0, 62.7, 62.3, 61.5, 60.4, 58.9, 58.3, 58.0, 57.3, 56.3, 55.4, 54.8, 53.6, 47.5, 39.6, 38.2, 37.5, 32.6, 31.2, 30.9, 30.3, 26.5, 25.9, 22.9, 20.0, 19.7, 19.5, 19.2, 18.6, 18.2, 13.6; MS (FAB) *m/e* (rel intensity) 944 ([M + Na]$^+$, 17), 922 ([M + H]$^+$, 100).

Cyclo[ValΨ{(C═S)NH}-Ser-D-PheΨ{(C═S)NH}-Ser-Phe-Pro-*allo*-Thr] (33). A solution of 73.0 mg (0.079 mmol) of cyclo[Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(TIPS)] (**32**) in 8 mL of THF was treated with 56.5 mg (0.237 mmol) of the Burgess reagent. The reaction mixture was stirred at room temperature for 15 min, heated at 70 °C for 2.5 h, cooled to room temperature, and concentrated. Chromatography through two short plugs of SiO_2 (4−6% MeOH/EtOAc and 5% MeOH/$CHCl_3$) afforded 65.9 mg of crude product as a colorless solid. This solid was dissolved in 5 mL of MeOH/Et_3N (1:1) and saturated with H_2S gas. The solution was stirred at room temperature for 4 d and then concentrated. Chromatography on SiO_2 ($CHCl_3$ to 4% MeOH/$CHCl_3$) afforded 51 mg of thiolysis products. This material was dissolved in 2 mL of THF, treated with 58 μL (0.058 mmol) of TBAF (1 M in THF), and heated at 37 °C for 28 h. The mixture was cooled to room temperature and directly chromatographed on SiO_2 (6% MeOH/$CHCl_3$). Further purification by HPLC on SiO_2 (2% MeOH/EtOAc) afforded 22.0 mg (35%) of **33** as a white solid: mp 192−197 °C (dec, MeOH); $[\alpha]_D$ −131.6° (*c* 1.0, MeOH, 22 °C); IR (neat) 3250, 1670,

1657 cm^{-1}; ^1H NMR δ (MeOH-d_4, major rotamer) δ 7.26−7.02 (m, 10 H), 5.11 (dd, 1 H, J = 4.7, 4.6 Hz), 4.92 (dd, 1 H, J = 5.7, 5.6 Hz), 4.86−4.81 (m, 1 H), 4.58−4.41 (m, 2 H), 4.30−4.17 (m, 1 H), 4.13−3.92 (m, 2 H), 3.69−3.54 (m, 3 H), 3.50 (dd, 1 H, J = 11.1, 4.6 Hz), 3.34−3.20 (m, 2 H), 3.12−2.92 (m, 4 H), 2.79 (dd, 1 H, J = 12.2, 11.9 Hz), 2.69−2.55 (m, 1 H), 1.99−1.72 (m, 2 H), 1.61−1.47 (m, 1 H), 1.36−1.20 (m, 1 H), 1.07 (d, 3 H, J = 5.9 Hz), 0.93 (d, 3 H, J = 7.0 Hz), 0.71 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (MeOH-d_4, major rotamer) δ 203.7, 203.6, 173.2, 173.1, 172.0, 171.2, 170.8, 138.8, 136.7, 130.8, 130.5, 130.1, 129.3, 128.7, 127.6, 68.7, 67.2, 62.5, 62.2, 61.7, 61.2, 60.8, 60.6, 55.7, 47.6, 41.1, 38.8, 32.9, 31.0, 22.6, 22.3, 20.2, 19.7, 15.6; MS (FAB) *m/e* (rel intensity) 820 ([M + Na]$^+$, 18), 798 ([M + H]$^+$, 30), 697 (100).

Cyclo[Val-Ser(thiaz)-D-Phe-Ser(thiaz)-Phe-Pro-*allo*-Thr(oxaz)] (24). A solution of 19.8 mg (0.0248 mmol) of cyclo[ValΨ{(C═S)NH}-Ser-D-PheΨ{(C═S)NH}-Ser-Phe-Pro-*allo*-Thr] (**33**) in 3 mL of THF was treated at room temperature with 29.6 mg (0.124 mmol) of the Burgess reagent. The reaction mixture was stirred at room temperature for 10 min and heated to 40 °C for 20 min and to 70 °C for 1.5 h. The solution was cooled, filtered, concentrated, and chromatographed on SiO_2 (3% MeOH/$CHCl_3$). Further purification by HPLC on SiO_2 (2% MeOH/$CHCl_3$) afforded 13.1 mg (71%) of **24** as a colorless solid: mp 163−165 °C ($CHCl_3$); $[\alpha]_D$ +86.2° (*c* 0.6, $CHCl_3$, 22 °C); IR (neat) 3368, 1686, 1653 cm^{-1}; ^1H NMR δ 7.90−7.69 (b, 1 H), 7.62 (d, 1 H, J = 9.6 Hz), 7.49 (d, 1 H, J = 5.3 Hz), 7.38−7.11 (m, 10 H), 5.26−5.14 (m, 1 H), 5.09−4.99 (m, 1 H), 4.88−4.49 (m, 5 H), 4.24 (d, 1 H, J = 4.1 Hz), 4.02−3.88 (b, 1 H), 3.73 (dd, 1 H, J = 10.1, 9.8 Hz), 3.46 (dd, 2 H, J = 10.7, 10.5 Hz), 3.31 (dd, 2 H, J = 11.6, 11.5 Hz), 3.16−2.95 (m, 2 H), 2.77 (dd, 1 H, J = 12.6, 9.5 Hz), 2.48−2.23 (b, 2 H), 2.23−2.08 (m, 1 H), 1.99−1.70 (m, 3 H), 1.42 (d, 3 H, J = 6.2 Hz), 1.00−0.90 (m, 6 H); ^{13}C NMR δ 173.9, 171.2, 170.3, 169.5, 169.3, 169.1, 135.7, 135.4, 129.8, 129.6, 128.5, 128.2, 127.2, 127.0, 82.1, 79.6, 78.2, 75.1, 56.1, 53.9, 53.2, 47.2, 40.2, 38.4, 36.9, 33.1, 28.6, 25.1, 21.7, 19.9, 19.5; MS (EI) *m/e* (rel intensity) 743 (M$^+$, 44), 700 (28), 373 (100); HRMS *m/e* calcd for $C_{38}H_{45}N_7O_5S_2$ 743.2924, found 743.2952.

Cyclo[D-Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr] (34). A solution of 15.4 mg (0.0155 mmol) of cyclo[D-Val-Ser(TBDMS)-D-Phe-Ser-(TBDMS)-Phe-Pro-*allo*-Thr] (**28**) in 0.7 mL of THF/H_2O (20:1) was treated with 0.5 mg (0.0026 mmol) of TsOH·H_2O. The mixture was stirred overnight at room temperature, treated with 0.4 mg (0.005 mmol) of $NaHCO_3$, and stirred for another 15 min. The volume of the solution was reduced to about one-third, and the residue was directly chromatographed on SiO_2 (8% MeOH/$CHCl_3$) to afford 10.1 mg (85%) of **34** as a white solid: mp 164−168 °C (MeOH); $[\alpha]_D$ −55.1° (*c* 0.9, MeOH, 22 °C); IR (neat) 3292, 1666, 1651 cm^{-1}; ^1H NMR (MeOH-d_4, mixture of rotamers) δ 7.38 (d, 1.2 H, J = 7.1 Hz), 7.27−7.06 (m, 8.8 H), 4.69 (dd, 0.6 H, J = 11.2, 7.8 Hz), 4.60 (dd, 0.5 H, J = 9.3, 4.9 Hz), 4.53 (dd, 0.8 H, J = 7.7, 5.0 Hz), 4.40−4.36 (m, 1.3 H), 4.36−4.23 (m, 2.2 H), 4.16 (dd, 0.7 H, J = 4.1, 4.1 Hz), 4.06−3.96 (m, 1.6 H), 3.92 (d, 0.4 H, J = 5.2 Hz), 3.88−3.81 (m, 0.6 H), 3.80−3.63 (m, 2.6 H), 3.62−3.40 (m, 2.5 H), 3.39−3.23 (m, 1.7 H), 3.20−3.10 (m, 0.9 H), 3.03−2.89 (m, 2.0 H), 2.79 (dd, 0.4 H, J = 14.3, 8.8 Hz), 2.31−2.13 (m, 1.6 H), 2.04−1.88 (m, 2.2 H), 1.72−1.50 (m, 1.2 H), 1.20 (d, 1.6 H, J = 6.3 Hz), 1.15 (d, 1.8 H, J = 6.3 Hz), 0.86 (d, 3.6 H, J = 6.8 Hz), 0.78 (d, 1.2 H, J = 6.9 Hz), 0.49 (d, 1.1 H, J = 6.8 Hz); ^{13}C NMR (MeOH-d_4, mixture of rotamers) δ 174.5, 174.2, 174.0, 173.7, 173.4, 173.2, 173.0, 172.7, 171.6, 139.1, 138.6, 138.0, 137.5, 130.5, 129.7, 128.0, 68.4, 67.7, 64.0, 63.5, 63.0, 62.4, 61.8, 60.7, 60.1, 58.8, 58.1, 56.7, 56.3, 55.6, 39.2, 37.5, 37.1, 33.0, 31.7, 30.7, 30.3, 26.3, 23.1, 20.9, 20.4, 20.1, 18.6, 17.8; MS (FAB) *m/e* (rel intensity) 788 ([M + Na]$^+$, 15), 766 ([M + H]$^+$, 72).

Cyclo[Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(oxaz)] (35). A solution of 567 mg (0.496 mmol) of Cbz-Val-Ser(TBDMS)-D-Phe-Ser-(TBDMS)-Phe-Pro-*allo*-Thr(oxaz)-OMe (**22**) in 25 mL of MeOH was treated with $Pd(OH)_2$ and H_2 gas for 10 h. The reaction mixture was filtered through a plug of Celite, concentrated, and chromatographed through a short plug of SiO_2 (4 to 12% MeOH/$CHCl_3$) to afford 440 mg (88%) of amine as a solid. This amine was dissolved in 10 mL of THF/MeOH/H_2O (10:2:1), treated with 0.24 mL of a 2.0 M NaOH solution and stirred at room temperature for 2 h. After addition of 81 mg (0.96 mmol) of $NaHCO_3$, the reaction mixture was stirred for an additional 30 min, filtered, concentrated, and dried by azeotropic distillation with benzene. The amino acid sodium salt was dissolved in 218 mL of DMF and treated with 358 mg (1.86 mmol) of $NaHCO_3$ and 717 mg (1.86 mmol) of FDPP. The reaction mixture was stirred at 40 °C for 4 d, and DMF was removed under reduced pressure. The residue was dissolved in 10% MeOH/$CHCl_3$ and adsorbed onto SiO_2. Chromatography on SiO_2 (15% EtOAc/$CHCl_3$ followed by 5−7% MeOH/$CHCl_3$) afforded 264 mg of crude product, which was dissolved in 4.5 mL of THF, cooled to 0 °C, and treated for 15 min with 0.65 mL of a 1 M TBAF solution in THF. The reaction mixture was directly chromatographed on SiO_2 (4 to 10% MeOH/$CHCl_3$) to afford 176 mg (54%) of **35** as a colorless solid: mp 171−177 (dec, MeOH); $[\alpha]_D$ −2.3° (*c* 0.6, MeOH, 23 °C); IR (neat) 3300, 1647, 1630 cm^{-1}; ^1H NMR (MeOH-d_4, major rotamer) δ 7.24−7.08 (m, 10 H), 4.95 (dd, 1 H, J = 8.3, 2.3 Hz), 4.62−4.55 (m, 1 H), 4.51−4.44 (m, 1 H), 4.24−4.17 (m, 2 H), 4.14−3.94 (m, 4 H), 3.81−3.71 (m, 2 H), 3.64−3.59 (m, 1 H), 3.32−3.27 (m, 2 H), 3.07−2.81 (m, 3 H), 2.21−2.13 (m, 1 H), 1.95−1.80 (m, 4 H), 1.26 (d, 3 H, J = 6.4 Hz), 0.86 (d, 3 H, J = 6.6 Hz), 0.67 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (MeOH-d_4, major rotamer) δ 174.3, 173.2, 172.6, 172.1, 171.6, 171.5, 138.2, 138.0, 130.3, 130.1, 129.5, 127.7, 83.6, 76.0, 62.8, 62.4, 58.1, 57.4, 57.2, 56.9, 53.2, 38.1, 37.3, 34.1, 30.2, 25.9, 21.5, 19.8, 19.7; MS (FAB) *m/e* (rel intensity) 770 (M + Na, 33), 748 (M + H, 42), 154 (100).

Cyclo[Val-Ser(oxaz)-D-Phe-Ser(oxaz)-Phe-Pro-*allo*-Thr(oxaz)] (36). A solution of 26.0 mg (0.0348 mmol) of cyclo[Val-Ser-D-Phe-Ser-Phe-Pro-*allo*-Thr(oxaz)] (**35**) in 6 mL of THF at was treated at −60 °C with a solution of 91.3 mg (0.348 mmol) of triphenylphoshine in 1 mL of THF and 69 μL (0.348 mmol) of DIAD. The reaction mixture was warmed to −20 °C over 20 min, and a white precipitate appeared. The suspension was warmed to room temperature, concentrated, and purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to afford 18.2 mg (74%) of **36** as a white solid: mp 153−160 °C ($CHCl_3$); $[\alpha]_D$ +72.8° (*c* 0.4, $CHCl_3$, 22 °C); IR (neat) 3330, 2966, 1657, 1533 cm^{-1}; ^1H NMR (major rotamer) δ 7.64−7.57 (m, 2H), 7.27−7.17 (m, 9 H), 7.08−7.05 (m, 2 H), 4.87−4.60 (m, 7 H), 4.49 (dd, 1 H, J = 10.8, 9.8 Hz), 4.36−4.28 (m, 2 H), 4.26 (d, 1 H, J = 4.4 Hz), 3.37 (dd, 1 H, J = 13.7, 6.0 Hz), 3.22−3.00 (m, 3 H), 2.72 (dd, 1 H, J = 12.6, 10.1 Hz), 2.18−2.05 (m, 3 H), 1.92−1.68 (m, 1 H), 1.43 (d, 3 H, J = 6.3 Hz), 0.93 (d, 3 H, J = 6.7 Hz), 0.87 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (major rotamer) δ 171.4, 170.5, 170.4, 169.8, 169.2, 168.9, 164.0, 151.1, 135.8, 135.5, 129.6, 129.5, 128.5, 128.3, 127.2, 127.0, 82.2, 75.2, 71.4, 69.1, 68.2, 56.1, 53.4, 51.8, 49.5, 47.1, 40.3, 37.7, 34.0, 28.6, 25.1, 21.8, 19.5; MS (FAB) *m/e* (rel intensity) 734 ([M + Na]$^+$, 20), 712 ([M + H]$^+$, 100); HRMS *m/e* calcd for $C_{38}H_{45}N_7O_7$ 711.3380, found 711.3361.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of synthetic lissoclinamide 7 and intermediates and experimental details for **6**, **7**, **11**, **12**, **18**, **19**, and **23** (57 pages). See any current masthead page for ordering and Internet access instructions.

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