Total Syntheses of Conformationally Constrained Didemnin B Analogues. Replacements of *N*,*O*-Dimethyltyrosine with L-1,2,3,4-Tetrahydroisoquinoline and L-1,2,3,4-Tetrahydro-7-methoxyisoquinoline

James E. Tarver Jr., Amy J. Pfizenmayer, and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

mjoullie@sas.upenn.edu

Received June 13, 2001

The design and synthesis of two conformationally constrained analogues of didemnin B are described. The [*N*,*O*-Me_2Tyr^5]residue of didemnin B was replaced with L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) and L-1,2,3,4-tetrahydro-7-methoxyisoquinoline-3-carboxylic acid (MeO-Tic), which mimic the *N*,*O*-dimethylated tyrosine while constraining the conformation of the molecule. Preliminary results indicate that the conformation of the [*N*,*O*-Me_2Tyr^5]residue closely matches the conformation imposed by the Tic replacement.

Introduction

Didemnin B (**1**, Figure 1), a cyclic depsipeptide, is the lead member of a class of marine natural products isolated from tunicates.[1] This family of natural products exhibits potent antitumor, antiviral, and immunosuppressive activities.[2] Didemnin B has the ability to inhibit protein biosynthesis in vitro,[3,4] to induce rapid apoptosis,[5−10] and to interfere with phosphoinositol uptake.[11] The mechanisms by which didemnin B effects these biological activities are still under investigation, but some progress has been reported in this area.[12]

Peptides can exist in a large number of conformations, making their structural investigations a challenging goal. One approach to analogue design is to restrict rotation around certain bonds in order to minimize the number of low energy conformations that can be observed. This strategy aids in the determination of conformations important for receptor binding, since the introduction of the proper constraints in the ligand should reduce the entropy cost of the receptor−ligand complex and result in greater stability.

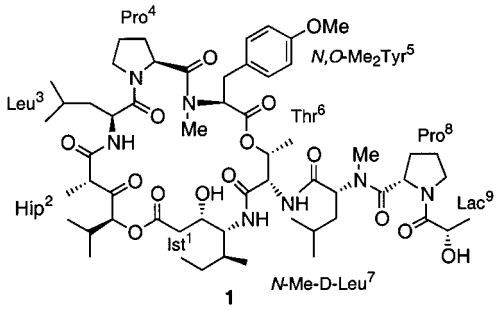


Figure 1. Didemnin B (**1**).

Conformational analyses for individual amino acids in a peptide have many aspects. Torsion angles within the backbone of a peptide (characterized by the dihedral angles ϕ and ψ) and within the side chains of amino acids (characterized by the dihedral angles χ_1 and χ_2 about C^{α}−C^{β} and C^{β}−C^{γ}, respectively) may be constrained. The strategy of constraining the χ_1 and χ_2 bonds of tyrosine (Tyr) or phenylalanine (Phe) is accomplished by replacing these groups with moieties such as L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), and L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (HO-Tic). The manner in which χ_1 and χ_2 may be restricted is shown in Figure 2 using L-MeO-Tic (L-1,2,3,4-tetrahydro-7-methoxyisoquinoline-3-carboxylic acid) as an example. The Newman projections show the three staggered conformations possible when looking down the α−β bond (χ_1) of an L-amino acid. Note that an unconstrained amino acid can reach all three conformers, but due to its tether, MeO-Tic cannot reach conformer II.

The strategy of constraining the χ_1 and χ_2 bond angles of tyrosine or phenylalanine by replacing them with a Tic moiety has been used extensively by Hruby et al. to prepare analogues of somatostatin which have significantly enhanced opioid receptor activity in comparison to somatostatin itself.[13,14] Tic analogues of *N*-methylated amino acids constrain the side chain yet do not affect the degree of substitution at the amino group, making Tic-based analogues ideal to use as mimics of *N*-methylated amino acids.

(1) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857−1859.
(2) Sakai, R.; Rinehart, K. L.; Kishore, V.; Kundu, B.; Faircloth, G.; Gloer, J. B.; Carney, J. R.; Namikoshi, M.; Sun, F.; Hughes, J., R. G.; Gravalos, G.; de Quesada, T. G.; Wilson, G. R.; Heid, R. M. *J. Med. Chem.* **1996**, *39*, 2819−2834.
(3) Ahuja, D.; Vera, M. D.; SirDeshpande, B. V.; Morimoto, H.; Williams, P. G.; Joullié, M. M.; Toogood, P. L. *Biochemistry* **2000**, *39*, 4339−4346.
(4) Ahuja, D.; Geiger, A.; Ramanjulu, J. M.; Vera, M. D.; SirDeshpande, B. V.; Pfizenmayer, A.; Abazecd, M.; Krosky, D. J.; Beidler, D.; Joullié, M. M.; Toogood, P. L. *J. Med. Chem.* **2000**, *43*, 4212−4218.
(5) Grubb, D. R.; Wolvetang, E. J.; Lawen, A. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 1130−1136.
(6) Beidler, D. R.; Ahuja, D.; Wicha, M. S.; Toogood, P. L. *Biochem. Pharmacol.* **1999**, *58*, 1067−1074.
(7) Johnson, K. L.; Vaillant, F.; Lawen, A. *FEBS Lett.* **1996**, *383*, 1−5.
(8) Johnson, K. L.; Grubb, D. R.; Lawen, A. *J. Cellular Biochem.* **1999**, *72*, 269−278.
(9) Johnson, K. L.; Lawen, A. *Immunol. Cell Biol.* **1999**, *77*, 242−248.
(10) Grubb, D. R.; Ly, J. D.; Vaillant, F.; Johnson, K. L.; Lawen, A. *Oncogene* **2001**, *20*, 4085−4094.
(11) Dominice, C.; Dufour, M.-N.; Patino, N.; Maanzoni, O.; Grazzini, E.; Jouin, P.; Guillon, G. *J. Pharm. Exp. Ther.* **1994**, *271*, 107−117.
(12) Vera, M. D. Ph.D. Dissertation, University of Pennsylvania, 2000 and references therein.

10.1021/jo0105991 CCC: $20.00
Published on Web 10/20/2001

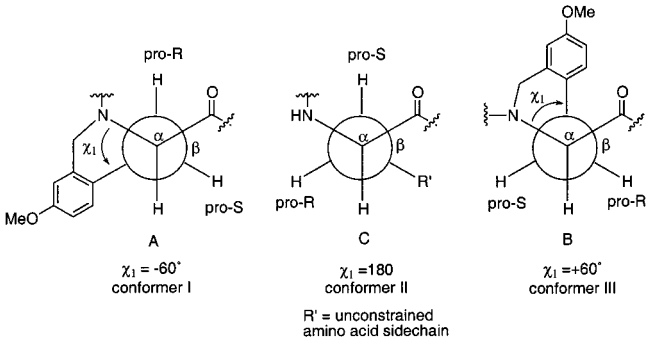


Figure 2. Newman projections of the torsional angle (χ_1) of the C^{α}-C^{β} bond of MeO-Tic.

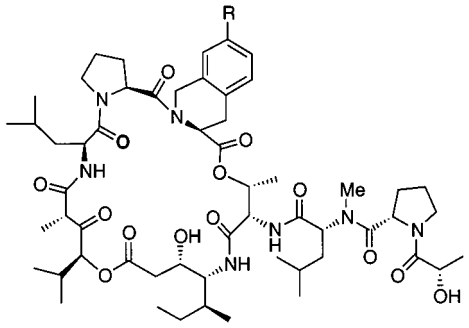


Figure 3. Constrained analogues (**2** and **3**) of didemnin B.

Structural studies and chemical modifications[2] at the [*N*,*O*-Me_2Tyr^5]residue of the didemnins have shown that changes in this position are tolerated. The tyrosine side chain in didemnin B is thought to be involved in binding to the receptor because it protrudes outward from the center of the interior of the molecule both in solid state and in solution phase.[15,16] We prepared two didemnin B analogues in which the tyrosine moiety was replaced with *N*-Me-leucine (*N*-MeLeu) and *N*-Me-phenylalanine (*N*-MePhe).[17,18] These analogues exhibited biological activity comparable to that of didemnin B analogues. This similarity led us to synthesize other analogues in which the tyrosine moiety was replaced with Tic and MeO-Tic. According to the numbering shown in Figure 1 these two analogues are designated as [Tic^5]didemnin B and [MeO-Tic^5]didemnin B (**2** and **3**, Figure 3) and will be referred to as the Tic and MeO-Tic analogues, respectively.

Before beginning the synthetic process, molecular modeling studies were conducted.[19] The X-ray coordinates of didemnin B were used as the basis for the minimization. The minimizations were generated using PRCG (Conjugate gradient minimization using the Polak−Ribiere first derivative method) followed by FMNR (Full matrix Newton Raphson minimization) with the MM2 force field. This lowest energy conformation was manipulated so that the [*N*,*O*-Me_2Tyr^5]residue was replaced with Tic and was minimized again with the same procedure.

The overlay of didemnin B and [Tic^5]didemnin B (**2**) showed that the torsional angle (χ_1) of Tic was very similar to that in the tyrosine moiety of didemnin B. Therefore, the torsional angles of both compounds were close to that of conformer I, the lowest energy conformer. Note that conformer II cannot be reached by Tic analogues and conformer III is much higher in energy. Although the torsional angles (χ_1) of Tic and Tyr (in **2** and **1**, respectively) were very similar, the torsional angles (χ_2) for the same moieties were different. The aromatic ring in the Tyr side chain of **1** was perpendicular to that of the aromatic ring in the Tic side chain of **2**.

Analogues **2** and **3** were designed to investigate the effects of constraining the tyrosine side chain in didemnin B. Although **3** closely mimics the natural product's [*N*,*O*-Me_2Tyr^5] moiety, we also prepared analogue **2** (with no methoxy group) since its biological activity would be directly comparable to that of the *N*-MePhe analogue.[18] In addition, the synthesis of **2** was expected to be more facile than that of **3** which would allow us to obtain biological activity results more rapidly.

Our synthesis of **1** affords stereocontrol and convergence allowing modification at any point in construction.[20] This approach has permitted the synthesis of several analogues of didemnin B, which contain modifications in the side chain peptide,[21−23] the macrocyclic peptide,[24,25] or the nonpeptidic HIP-isostatine fragment.[26] Thus, tyrosine was replaced with Tic and MeO-Tic to probe the importance of free rotation of the side chain moiety. Additionally, these analogues provide constraint without loss of α-nitrogen substitution.

Results and Discussion

The retrosyntheses of the Tic and MeO-Tic analogues (Figure 4**)** paralleled that of the natural product.[20] After the initial side chain removal, the molecule was divided into a tetrapeptide and a nonpeptidic HIP-isostatine portion. The HIP-isostatine fragment construction has previously been described.[20,21] The tetrapeptide was formed by a series of classical peptide couplings of protected natural amino acids and the constrained tyrosine analogues Tic and MeO-Tic.

Syntheses of Linear Precursors. The synthesis of the tetrapeptide of **2** began with a Pictet−Spengler condensation[27] performed on L-phenylalanine to yield the

(13) Hruby, V. J. In *Conformationally Directed Drug Design*: *Peptides and Nucleotides as Templates or Targets*; Vida, J. A., Gordon, M., Eds.; American Chemical Society: Washington, D. C., 1983; pp 9−28.
(14) Hruby, V. J.; Cody, W. L.; Castrucci De Lauro, A. M.; Hadley, M. E. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2549−2573.
(15) Hossain, M. B.; Van der Helm, D.; Antel, J.; Sheldrick, G. M.; Weinheimer, A. J.; Sanduka, S. K. *Int. J. Pept. Protein Res.* **1996**, *47*, 20−27.
(16) Kessler, H.; Will, M.; Antel, J.; Beck, H.; Sheldrick, G. M. *Helv. Chim. Acta* **1989**, *72*, 530−555.
(17) Pfizenmayer, A. J.; Ramanjulu, J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Joullié, M. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2713−2716.
(18) Pfizenmayer, A. J.; Ramanjulu, J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Joullié, M. M. *Tetrahedron* **1999**, *55*, 313−334.
(19) Mayer, S. C. Ph.D. Dissertation, University of Pennsylvania, 1995.
(20) Li, W.-R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659−7672.
(21) Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A.; Joullié, M. M. *J. Org. Chem.* **1994**, *59*, 5192−5205.
(22) Ding, X.; Vera, M. D.; Liang, B.; Zhao, Y.; Leonard, M. S.; Joullié, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 231−234.
(23) Vera, M. D.; Pfizenmayer, A. J.; Ding, X.; Ahuja, D.; Toogood, P. L.; Joullié, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1871−1874.
(24) Ramanjulu, J.; Ding, X.; Li, W.-R.; Joullié, M. M. *J. Org. Chem.* **1997**, *62*, 4961−4969.
(25) Vera, M. D.; Pfizenmayer, A. J.; Ding, X.; Xiao, D.; Joullie, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 13−16.
(26) Xiao, D.; Vera, M. D.; Liang, B.; Joullié, M. M. *J. Org. Chem.* **2001**, *66*, 2734−2742.
(27) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.

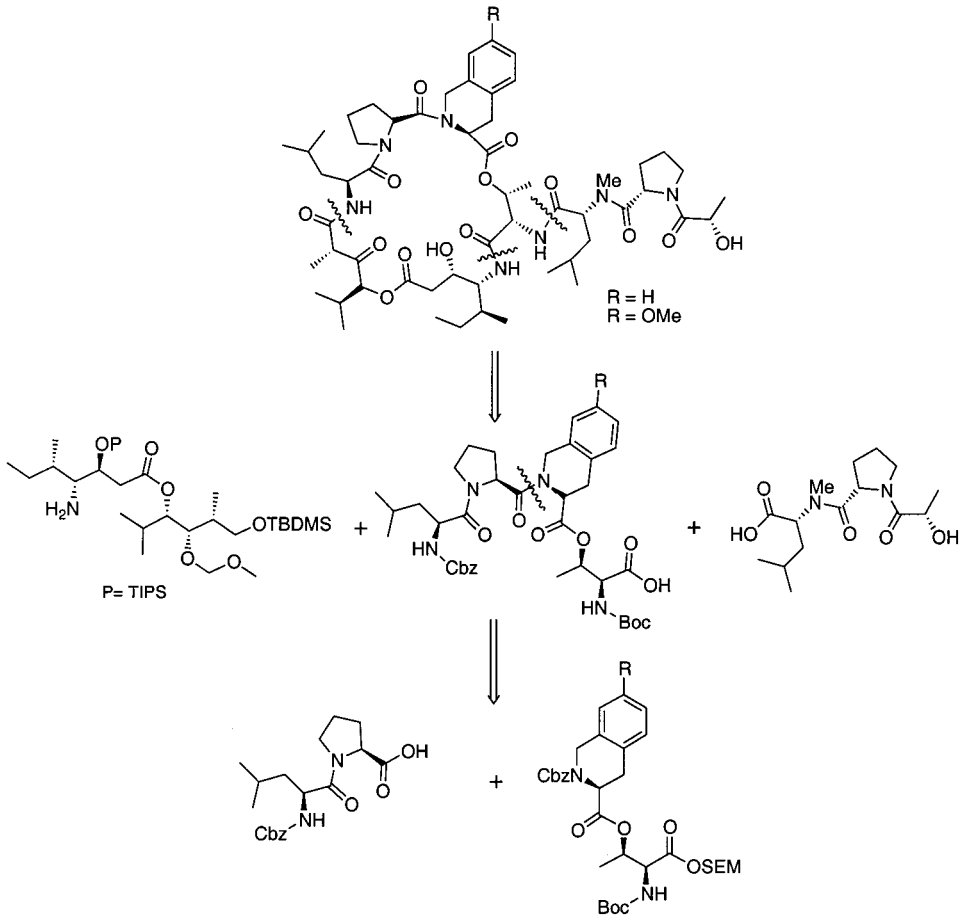
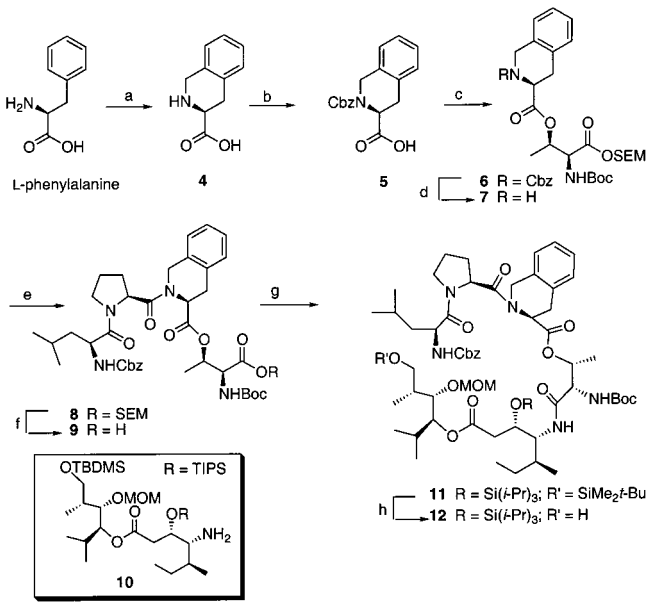


Figure 4. Retrosynthetic analysis of the constrained analogues (**2** and **3**).

salt of Tic, which was neutralized to form L-Tic in 38% yield (**4**, Scheme 1). The nitrogen of L-Tic was protected with a benzyloxycarbonyl group (Cbz) under standard conditions (97% yield). Coupling of the Cbz-Tic (**5**) to the alcohol of Boc-Thr-OSEM using isopropenyl chloroformate afforded dipeptide **6** in 89% yield. Removal of the Cbz group under hydrogenolysis afforded a secondary amine (**7**) in 86% yield, which was coupled directly to the dipeptide acid Cbz-Leu-Pro-OH using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) to form the fully protected tetrapeptide (**8**) in 60% yield. Removal of the 2-(trimethylsilyl)ethoxymethyl (SEM) group with magnesium bromide etherate provided **9** in quantitative yield. Reaction of **9** with the protected non-peptide portion, Hip-isostatine (**10**), was achieved using isopropenyl chloroformate and *N*-methylmorpholine to provide the protected linear precursor (**11**) in 47% yield. The Hip-isostatine unit (**10**) was derived from protected Hip-acetate and Cbz-D-alloisoleucine.[20,21] The *tert*-butyldimethylsilyl (TBDMS) group of the Hip-isostatine moiety was removed with a mixture of acetic acid, THF, and water to give the primary alcohol (**12**) in 73% yield.

The synthesis of MeO-Tic tetrapeptide began from the commercially available 3′,5′-diiodo-L-tyrosine dihydrate (Scheme 2). This substrate was chosen to avoid polymerization, which is known to occur when the Pictet–Spengler reaction is carried out on tyrosine unprotected at the *ortho*-positions.[28] Although the iodo groups could be removed immediately before the carbamate protection, this reaction did not proceed well on the free amine. Therefore the iodo groups were carried through the next

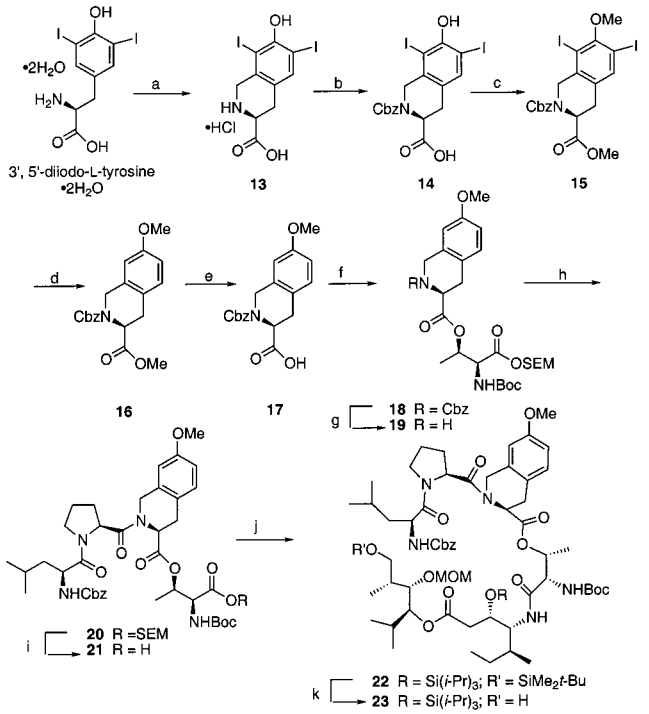
Scheme 1[a]



[a] Reagents and conditions: (a) 1. 37% aq CH_2O, concentrated HCl, 60 °C; 2. aq EtOH, $NH_4^+OH^-$, 38%; (b) $NaHCO_3$, H_2O, CbzCl, 97%; (c) isopropenyl chloroformate, Boc-Thr-OSEM, Et_3N, DMAP, CH_2Cl_2, 89%; (d) H_2, Pd/C, EtOAc, MeOH, 86%; (e) 1. Cbz-Leu-Pro-OH, BOP-Cl, NMM, CH_2Cl_2, −15 °C; 2. amine (**7**), NMM, 0 °C, 60%; (f) $MgBr_2 \cdot Et_2O$, CH_2Cl_2, −20 °C, quant. (g) NMM, isopropenyl chloroformate, **10**, 47%; (h) AcOH, THF, H_2O, 16 h, 73%.

(28) Vert, M. *Eur. Polym. J.* **1972**, *8*, 513–524.

Scheme 2[a]

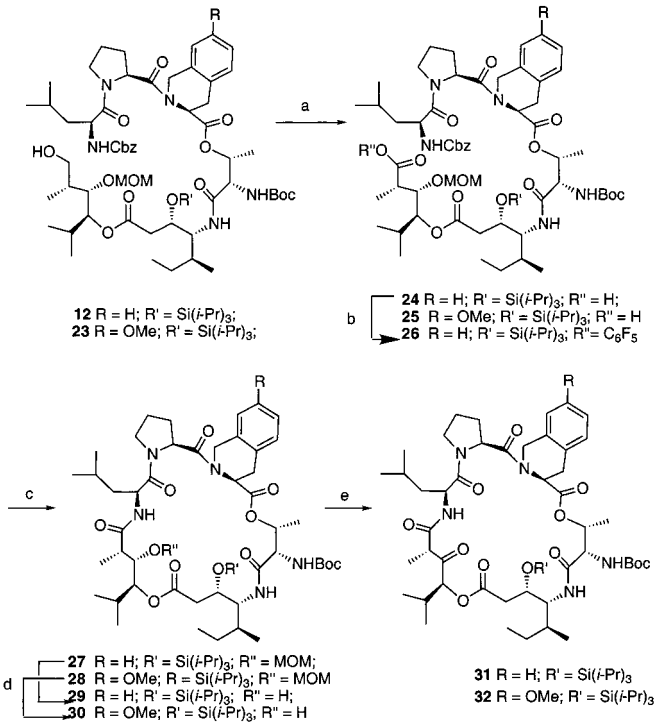


[a] Reagents and conditions: (a) aq CH_2O, concentrated HCl, 1,2-dimethoxyethane, 72 °C, 54%; (b) CH_2Cl_2, Et_3N, Cbz- succinimide, 79%; (c) THF, KOH, dimethyl sulfate, nBu$_4$N$^+$HSO$_4^-$, 91%; (d) MeOH, Cu_2Cl_2, $NaBH_4$, 0 °C, 87%; (e) LiOH·H_2O, THF, H_2O, MeOH, 97%; (f) isopropenyl chloroformate, Boc-Thr-OSEM, Et_3N, DMAP, CH_2Cl_2, 78%; (g) H_2, Pd/C, EtOAc, MeOH, 87%; (h) 1. Cbz-Leu-Pro-OH, BOP−Cl, NMM, CH_2Cl_2, −15 °C; 2. amine **19**, NMM, 0 °C, 64%; (i) $MgBr_2$, CH_2Cl_2, 98%; (j) HATU, DIEA, CH_2Cl_2, **10**, 63%; (k) AcOH, THF, H_2O, 24 h, 75%.

few steps until their removal was convenient. 3′,5′-Diiodo-L-tyrosine hydrate was treated with formaldehyde and hydrochloric acid to form the trisubstituted tetrahydroisoquinoline hydrochloride salt (**13**) in 54% yield. Protection of nitrogen as a carbamate using triethylamine and Cbz-succinimide afforded **14** in 79% yield. Concomitant methylation of the free hydroxyl group and the carboxylic acid was achieved using dimethyl sulfate and potassium hydroxide to provide **15** in 91% yield. A simple procedure using cuprous chloride and sodium borohydride cleanly reduced the diiodide in 87% yield by a mechanism, which is believed to proceed through the copper hydride intermediate.[29] The resulting ester (**16**) was saponified to carboxylic acid **17** using lithium hydroxide (97% yield). The depsipeptide linkage of *N*-Boc-Thr-OSEM ester and Cbz-MeOTic was achieved by preactivation of the acid via the mixed anhydride generated with isopropenyl chloroformate (78% yield). Catalytic hydrogenation of **18** removed the Cbz group to form **19** in 87% yield. The ensuing coupling with Cbz-Leu-Pro-OH was mediated by BOP-Cl to give **20** in 64% yield. Removal of the SEM group with magnesium bromide provided **21** in 98% yield. Reaction of **21** with the protected non-peptide portion, Hip-isostatine (**10**) was achieved using *O*-(7-azabenzotriazol-1-yl)*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) to afford the linear precursor (**22**) in 63% yield. The TBDMS group of the Hip-isostatine moiety was removed with a mixture

(29) Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* **1989**, *54*, 5308−5313.

Scheme 3[a]



[a] Reagents and conditions: (a) 1. Dess−Martin periodinane, CH_2Cl_2; 2. $NaClO_2$, aq NaH_2PO_4, in H_2O/DMSO/CH_3CN or in *t*-BuOH/2-methyl-2-butene, 84%; (b) EDC·HCl, DMAP, CH_2Cl_2, pentafluorophenol, 67%; (c) EtOAc, EtOH, Pd/C, 4-pyrrolidinopyridine, H_2, 58% for **26**; 1. H_2, Pd/C, EtOH; 2. HATU, DIEA, CH_2Cl_2, 61% for **28**; (d) Me_2BBr, CH_2Cl_2, 82% for 28; 87% for **30**; (e) Dess−Martin periodinane, CH_2Cl_2, 68−94%.

of acetic acid, THF, and water to give the primary alcohol (**23**) in 75% yield.

Cyclization. With linear precursor **12** in hand (Scheme 1), the next step was the oxidation of the primary alcohol to an acid (Scheme 3) using the two-step oxidation we had devised for the synthesis of other didemnins.[30] This protocol involved oxidation to the aldehyde with the Dess−Martin periodinane reagent,[31,32] followed by oxidation to the acid with buffered potassium permanganate.[33] An intense spot appearing on the TLC plate when visualized under a UV lamp indicated the presence of aromatized product. It was known that several oxidation reagents are too strong to be used in the presence of a 1,2,3,4-tetrahydroisoquinoline. Reagents such as potassium permanganate,[34,35] molecular oxygen with lead tetraacetate,[36] copper chloride,[37] nitric acid, mercuric acetate, sulfur, selenium, thionyl chloride, Fremy's salt, sodium hypochlorite, NBS, and manganese dioxide[35,38] are known to oxidize tetrahydroisoquinolines to 3, 4-di-

(30) Pfizenmayer, A. J.; Ramanjulu, J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Joullié, M. M.; Tandon, D.; Toogood, P. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3653−3656.

(31) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(32) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(33) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537−4540.

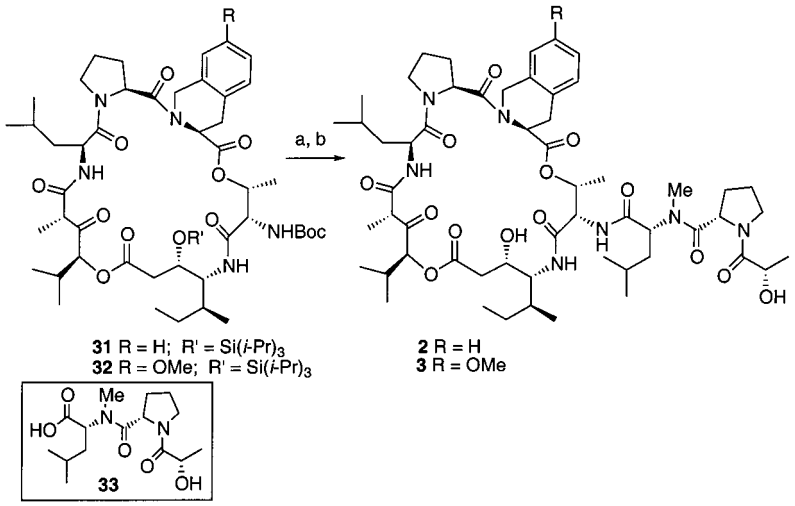
(34) Venkov, A. P.; Statkova-Abeghe, S. M. *Tetrahedron* **1996**, *52*, 1451−1460.

(35) Dyke, S. F.; Kinsman, R. G. *Properties and Reactions of Isoquinolines and their Hydrogenated Derivatives*; John Wiley & Sons: New York, 1981; Vol. 38.

(36) Umezawa, B.; Hoshino, O. *Heterocycles* **1975**, *3*, 1005−1033.

(37) Shimizu, M.; Orita, H.; Hayakawa, T.; Suzuki, K.; Takehira, K. *Heterocycles* **1995**, *41*, 773−779.

Scheme 4[a]



[a] Reagents and conditions: (a) HCl, EtOAc, −30 °C to 0 °C, 100%. (b) BOP, NMM, CH_2Cl_2, **33**, 0 °C to room temperature, 63% for 2; HATU, DIEA, CH_2Cl_2, 33; 0 °C to room temperature, 74% for **3**.

hydroisoquinolines, fully aromatized isoquinolines, or other degradation or ring-opened products. After model studies of the oxidation of tetrahydroisoquinolines with a variety of oxidizing reagents at various stages of the synthesis,[39] we achieved the desired oxidation using sodium chlorite in the presence of a chlorine scavenger, either DMSO or 2-methyl-2-butene. Other chlorine scavengers are also available, and their advantages and disadvantages have been discussed by Dalcanale and Montanari.[40]

The linear precursor **12** was oxidized with Dess−Martin reagent to the corresponding unstable aldehyde, which was directly oxidized to the acid (**24**) in 84% yield using sodium chlorite and DMSO[40,41] as both solvent and chlorine scavenger (Scheme 3). Due to difficulties in removing DMSO, 2-methyl-2-butene[42] was employed as an alternate scavenger.

Cyclization attempts began after removal of the Cbz group of **24** by hydrogenolysis. Coupling reagents such as *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate[43] (TBTU) in methylene chloride and pentafluorophenyl diphenyl phosphinate[21] (FDPP) in dimethylformamide were utilized and produced the desired cyclized product only in low yield. As we had previously employed a modification[44] of the Schmidt cyclization for a leucine analogue of didemnin B,[17] we opted for a similar approach. Acid **24** was converted to the corresponding pentafluorophenyl ester (**26**) by treatment with pentafluorophenol and EDC hydrochloride with a catalytic amount of DMAP. A dilute solution of the pentafluorophenyl ester (**26**) in ethyl acetate with a small amount of ethanol was used for the cyclization at room temperature, instead of at 95 °C as in the Schmidt protocol. An external source of hydrogen was used to deprotect the amino group, and 4-pyrrolidinopyridine was used as base. This protocol afforded a 58% yield of cyclized product (**27**). The MOM ether was removed with dimethylboron bromide, and the resulting secondary alcohol (**29**) was oxidized to a ketone (**31**) with Dess−Martin periodinane (Scheme 3). Removal of the TIPS ether and Boc groups with hydrogen chloride provided the macrocycle salt. The side chain of didemnin B was attached to the macrocycle salt to give **2** in 63% yield using the BOP reagent (Scheme 4).

Cyclization of linear precursor **23** (Scheme 2) proceeded in a similar manner (Scheme 3). Deprotection of the primary TBDMS afforded a free hydroxyl group, which could be oxidized with Dess−Martin reagent to the corresponding aldehyde. Further oxidation to the acid was accomplished using sodium chlorite and DMSO as the chlorine scavenger and solvent in 84% yield for both steps. Chromatographic purification of the acid (**25**) was necessary to effect the subsequent hydrogenation. Several conditions, including transfer hydrogenation with palladium hydroxide, palladium, and ammonium formate and direct hydrogenolysis in various solvents, were attempted. Only hydrogenation with 10% palladium on carbon in absolute ethanol and a heavy catalyst loading was successful. Ethanol/EtOAc mixtures proceeded more slowly, but methanol could not replace ethanol. The unstable intermediate was successfully cyclized (**28**) with HATU and 3-(diethoxyphosphoryloxy)-1, 2, 3-benzotriazin-4(3*H*)-one[45] (DEPBT) reagents in dichloromethane, but HATU proved superior as cyclization with DEPBT produced complex reaction mixtures and difficulties in purification. The postcyclization modifications proved similar to those outlined for Tic. The MOM deprotection afforded the free hydroxyl (**30**) in 87% yield. This compound was oxidized to the corresponding ketone (**32**) in 94% yield. The final sequence involved the simultaneous removal of the TIPS ether and Boc protecting groups with hydrogen chloride to afford the macrocycle amine hydrochloride salt, which was coupled to the didemnin B side chain (**33**) to give **3** in 74% yield using HATU (Scheme 4).

(38) Sotomayor, N.; Dominguez, E.; Lete, E. *Tetrahedron* **1995**, *51*, 12721−12730.
(39) Pfizenmayer, A. J. Ph.D. Dissertation, University of Pennsylvania, 1998.
(40) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.
(41) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.
(42) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825−4830.
(43) Pettit, G. R.; Taylor, S. R. *J. Org. Chem.* **1996**, *61*, 2322−2325.
(44) Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181−10189.
(45) Haitao, L.; Xiaohui, J.; Yun-hua, Y.; Chongxu, F.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91−93.

Biological Activity and Conclusions

Analogue **2** was tested at the National Cancer Institute against various cell lines in vitro.[46] The NCI-60 mean data from the NCI-60 tumor cell screen[46] for **2** and **1** gave the following values: GI_{50} 0.40 μM; TGI 7.8 μM; LC_{50} 81 μM (**2**); GI_{50} 0.013 μM; TGI 0.066 μM; LC_{50} 3.8 μM (**1**). This result shows that **2** is less active but also less toxic than didemnin B (**1**), which may result in a better therapeutic window as a growth inhibitor. In a protein synthesis inhibition assay, the IC_{50} value for rabbit reticulocyte lysates was 2.68 μM $\pm$ 0.17 μM whereas the IC_{50} value for **1** was 4.4 μM $\pm$ 0.1 μM.[47] X-ray and modeling suggest similar conformations. The biological data supports the hypothesis that this residue exists in a hydrophobic pocket in the target protein that must be filled in the protein ligand complex for optimal binding.[4]

Experimental Section

General Methods. Reactions requiring air-sensitive manipulations were conducted under an argon atmosphere. Methylene chloride was distilled from calcium hydride, and tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl. Petroleum ether refers to the fraction boiling in the range 40−60 °C. Analytical TLC was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. Proton and carbon magnetic resonance spectra (^{1}H, ^{13}C NMR) were recorded on a Bruker AM-500 [500 MHz (125 MHz for ^{13}C NMR)] Fourier transform spectrometer. Chemical shifts (δ) were measured in parts per million, and coupling constants (J values) are in hertz (Hz). A range of pseudorotations are often present in cyclic peptides[48] and their chemical shifts are indicated by RI (rotational isomers). Infrared spectra (IR) were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Unless otherwise indicated, high-resolution mass spectra (HRMS) were recorded on a Micromass AutoSpec spectrometer using electron impact (EI). Optical rotations were recorded on a Perkin-Elmer Model 341 polarimeter at the sodium D line.

L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (4).[49] A mixture of L-Phe (5 g, 30.3 mmol), 37 wt % aqueous formaldehyde (12.1 mL), and concentrated aqueous HCl (36.4 mL) was stirred at 60 °C for 1 h. An additional 4.9 mL of formaldehyde and 9.7 mL of HCl were added, and the reaction was stirred (still at 60 °C) for 3 h. After cooling to room temperature, the mixture was left to stand overnight at 5 °C. (Note: the combination of concentrated HCl and aqueous formaldehyde forms a potent carcinogen, so the compound should be cooled in the hood instead of the refrigerator before filtration). The precipitated salt was collected by filtration, washed with a small amount of ice cold water and dried in vacuo over solid KOH. The crude salt was dissolved in 181 mL of refluxing aqueous EtOH (60%). While hot, the solution was neutralized to pH 6−7 with aqueous ammonia. After this solution was cooled, it was left standing at 5 °C for 5 h. The precipitate was collected by filtration, washed with cold aqueous EtOH, and dried in a desiccator. Acid **4** (2.02 g, 38%) was obtained as a solid. The product was normally used without purification but was recrystallized from aqueous EtOH (60%) in order to obtain the following data. **4**: R_f 0.49 (4:1:1 CH_3CN:MeOH:H_2O); HRMS (CI) m/z calcd for $C_{10}H_{12}NO_2$ $(M + H)^+$ 178.0868, found 178.0871; $[\alpha]_D^{25}$ −169.4 (*c* 0.55, 1 M NaOH). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.92; H, 6.30; N, 7.87. lit.[49] $[\alpha]_D^{25}$ −160 to −162 (*c* 1, 1M NaOH; before recrystallization) or $[\alpha]_D^{25}$ −172 (after recrystallization from EtOH).

***N*-Cbz-L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (5).** To a 2 M aqueous solution of $NaHCO_3$ (8.31 g, 99.0 mmol in 49.5 mL of H_2O) were added **4** (7.01 g, 39.6 mmol) and benzyl chloroformate (6.2 mL, 43.5 mmol) in portions over a period of 30 min. The reaction was stirred at room temperature for 1.5 h before diluting and washing with Et_2O. The aqueous layer was cooled to 0 °C and acidified to pH 2 with 2 N $KHSO_4$. This solution was extracted into EtOAc. The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. Acid **5** (11.92 g, 97%) was obtained as a white foam and used directly in the next step without purification. However, column chromatography was performed with acetone/hexanes (10:90 to 15:85) to obtain the characterization data listed below; **5**: R_f 0.50 (40:60 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16−3.28 (m, 2H), 4.58 (d, J = 17.1 Hz, 1H), 4.77 (d, J = 16.3 Hz, 1H), 4.97 (t, J = 5.0 Hz) and 5.17−5.24 (m, 3H, RI), 7.06−7.40 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.8 and 31.2 (RI), 44.3 and 44.4 (RI), 53.0, 67.6 and 67.8 (RI), 126.2 and 126.4 (RI), 126.9, 127.0, 127.9, 127.98, 128.09, 128.2, 128.46, 128.54, 131.3, 132.2 and 132.9 (RI), 136.2, 155.4, 176.7 (RI); IR (neat) 3033, 1702, 1684, 1420, 1319, 1122, 747 cm^{-1}; HRMS (CI) m/z calcd for $C_{17}H_{17}N_2O_6$ $(M + H)^+$ 312.1236, found 312.1235; $[\alpha]_D^{25}$ +8.47 (*c* 1.21, $CHCl_3$).

***N*-Cbz-L-3-Carboxy-1,2,3,4-tetrahydroisoquinoline-*O*-Boc-threonine-*O*SEM (6).** To acid **5** (2.07 g, 6.64 mmol) in CH_2Cl_2 (25 mL) was added Boc-threonine[(2-trimethylsilyl)-ethoxy]methyl ester (2.21 g, 6.32 mmol) at 0 °C. To the resulting solution were added triethylamine (2.03 mL. 14.5 mmol), DMAP (0.16 g, 1.3 mmol), and isopropenyl chloroformate (0.80 mL, 7.3 mmol). The reaction was stirred at 0 °C for 1 h and diluted with Et_2O. The organic layer was washed sequentially with 10% HCl, 5% $NaHCO_3$ and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (16:84 to 20:80). The dipeptide (3.62 g, 89%) was obtained as a thick yellow oil. **6**: R_f 0.81 (30:70 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 9H), 0.88 (t, J = 8.4 Hz, 2H), 1.03 (d, J = 6.4 Hz) and 1.13 (d, J = 6.4 Hz, 3H, RI), 1.46 and 1.47 (s, 9H, RI), 3.10−3.21 (m, 2H), 3.50−3.69 (m, 2H), 4.33−4.39 (m, 1H), 4.53 and 4.73 (AB, J = 16.4 Hz, 2H), 4.85−4.88 (m) and 4.95 (t, J = 4.8 Hz, 1H, RI), 4.97−5.15 (m, 2H), 5.17−5.38 (m, 4H), 7.08−7.23 and 7.27−7.42 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.4, 16.6, 17.8, 28.3, 30.9 and 31.4 (RI), 44.4 and 44.6 (RI), 53.3 and 53.8 (RI), 56.7 and 57.0 (RI), 67.5 and 67.7 (RI), 68.1, 71.6 and 71.7 (RI), 80.2, 90.3 and 90.4 (RI), 126.3, 126.8, 126.9, 127.1, 127.95, 128.01, 128.1 and 128.2, 128.4, 128.5, 131.5, 132.2, 136.3, 155.8, 156.0, 169.3, 169.8 and 170.0 (RI); IR (neat) 3449, 2952, 1719, 1714, 1575, 1497, 1408, 1322, 1249, 1169, 1118, 914, 837 cm^{-1}; HRMS (FAB) m/z calcd for $C_{33}H_{46}N_2O_9SiNa$ $(M + Na)^+$ 665.2871, found 665.2900; $[\alpha]_D^{25}$ +28.66 (*c* 0.71, $CHCl_3$).

L-3-Carboxy-1,2,3,4-tetrahydroisoquinoline-*O*-Boc-threonine-*O*SEM (7). To a MeOH/EtOAc solution (1:1, 22 mL) under N_2 in a thick-walled Parr test tube was added 10% Pd/C (1.1 g). To the resulting suspension was added **6** (3.49 g, 5.4 mmol) in MeOH (6 mL). The solution was shaken for 3 h in a Parr hydrogenator under 40 psi of H_2. The mixture was filtered through Celite, and the Celite was washed with CH_3OH. After the filtrate was concentrated, the resulting amine **7** (0.125 g, 86%) was obtained as a yellow oil and was used directly in the next step without purification. **7**: R_f 0.67 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.89−0.93 (m, 2H), 1.11 (d, J = 6.3 Hz) and 1.32 (d, J = 6.4 Hz, 3H, RI), 1.45 (s, 9H), 2.48 (brs, 1H), 2.85−3.13 (m, 2H), 3.59−3.76 (m, 2H), 3.86−4.08 (m, 2H), 4.33 (d, J = 9.6 Hz) and 4.47 (d, J = 9.7 Hz, 1H, RI), 5.13−5.47 (m, 4H), 6.99−7.13 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.6 and −1.4 (RI), 16.9, 18.0, 28.3, 31.5, 47.0, 55.8, 57.1, 68.2 and 68.3 (RI), 71.2, 80.3, 90.2 and 90.4 (RI), 126.1, 126.2, 126.3, 128.4 and 129.0 (RI), 132.8, 134.1 and 134.7 (RI), 155.8, 169.7, 171.9; IR (neat) 2954, 1730,

(46) Boyd, M. R.; Paull, K. D. *Drug Dev. Res.* **1995**, *34*, 91−109.
(47) SirDeshpande, B. V.; Toogood, P. L. *Biochemistry* **1995**, *34*, 9177−9184.
(48) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−523.
(49) Majer, P.; Slaninová, I.; Lebl, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 62−68.

1720, 1503, 1454, 1367, 1249 1167, 1082, 1062, 937, 860, 837, 749 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{25}H_{41}N_2O_7Si$ $(M + H)^+$ 509.2683, found 509.2672; $[\alpha]_D^{25}$ +7.72 (*c* 0.745, $CHCl_3$).

Cbz-Leucylprolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline)-*O*-Boc-threonine-*O*SEM (8). Cbz-Leu-Pro-OH (1.91 g, 5.26 mmol) was dissolved in CH_2Cl_2 (58 mL), and the solution was cooled to −15 °C. To this solution was added BOP-Cl (1.48 g, 5.79 mmol), followed by the dropwise addition of NMM (0.64 mL, 5.79 mmol). After stirring for 0.5 h at −15 °C, the reaction mixture was concentrated to half of its volume (using a rotary evaporator with a water bath at 0 °C), and amine **7** (2.23 g, 4.39 mmol) was added followed by NMM (0.64 mL, 5.79 mmol). The solution was kept at 0 °C for 6 h and then diluted with Et_2O. The organic layer was washed sequentially with 10% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by column chromatography eluting with acetone/CH_2Cl_2 (7:93 to 10:90). The fully protected tetrapeptide **8** (2.22 g, 60%) was obtained as a white solid. **8**: mp 75 °C; R_f 0.45 (5:95 acetone:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ −0.03 (s, 9H), 0.76−0.84 (m, 2H), 0.91 (d, J = 6.7 Hz) and 0.95 (d, J = 6.7 Hz) and 0.98 (d, J = 6.4 Hz) and 1.03 (d, J = 6.4 Hz, 6H, RI), 1.09 (d, J = 6.4 Hz) and 1.21−1.29 (m, 3H, RI), 1.44 (s, 9H), 1.73−1.91 (m, 3H), 2.02−2.32 (m, 4H), 3.06−3.2 (m, 2H), 3.44−3.59 (m, 2H), 3.67−3.82 (m, 2H), 4.27−4.30 (m, 1H), 4.53−4.86 (m, 3H), 4.87−5.08 (m, 4H), 5.05 and 5.18 (AB, J = 6.0 Hz, 2H), 5.20−5.22 (m, 1H), 5.33−5.40 (m, 2H), 7.07−7.30 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.5, 15.6, 16.8, 20.5, 22.3, 23.5, 23.8, 27.2, 29.5, 30.1, 40.5, 44.3, 45.6 and 45.9 (RI), 49.9 and 50.6 (RI), 53.4, 55.8 and 56.0 (RI), 56.6, 65.6 and 65.7 (RI), 67.0, 70.8, 79.2, 88.9 and 89.4 (RI), 125.2, 125.8 and 125.9 (RI), 126.2, 126.8, 126.9, 127.0, 127.28 and 127.30 (RI), 127.37, 127.40, 130.3, 130.8 and 131.2 (RI), 135.3, 154.6, 155.2 and 155.5 (RI), 168.1, 168.4, 168.6, 170.2; IR (neat) 3302, 2956, 1720, 1715, 1656, 1642, 1528, 1501, 1451, 1366, 1249, 1168, 860, 837, 753 cm^{-1}; HRMS *m/z* calcd for $C_{44}H_{64}O_{11}N_4Si$ $(M + Na)^+$ 875.4239, found 875.4220; $[\alpha]_D^{25}$ −11.64 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{44}H_{64}O_{11}N_4Si$: C, 61.95; H, 7.56; N, 6.57; Found: C, 61.67; H, 7.82; N, 6.63.

Cbz-Leucylprolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline)-*O*-Boc-threonine (9).[50] The fully protected tetrapeptide **8** (1.77 g, 2.08 mmol) was dissolved in CH_2Cl_2 (117 mL) and cooled to −20 °C. Magnesium bromide etherate (1.61 g, 6.24 mmol) was added, and the reaction was stirred at −20 °C for 1 h and then at 0 °C for 3.5 h. The reaction was diluted with EtOAc and washed sequentially with 5% HCl and saturated NaCl solutions. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude foam was used without purification in the next step (1.5 g, 100%).

***N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-[(Triisopropylsilyl)oxy]-4-[(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutyramido]-5-methylheptanoic Acid, (1S,2S,3R)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (11).** To the tetrapeptide acid **9** (161 mg, 0.222 mmol) in THF (1.8 mL) at −15 °C was added dropwise NMM (24.5 μL, 0.222 mmol) followed by isopropenyl chloroformate (24.3 μL, 0.222 mmol). After the mixture was stirred for 3 min, protected amine **10** (128 mg, 0.202 mmol) was added. The reaction was warmed to 0 °C and stirred for 1 h. After 3 h at room temperature, the reaction was concentrated in vacuo. The resulting oil was diluted with Et_2O and washed sequentially with 5% citric acid, 5% $NaHCO_3$, and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (30:70 to 35:65). Compound **11** (0.138 g, 47%) was obtained as a white solid. **10**: mp 77−79 °C; R_f 0.46 (30:70 EtOAc:petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.81−0.99 (m, 30H), 1.04−1.09 (m, 21H), 1.11−1.17 and 1.28−1.35 (m, 2H), 1.23−1.25 (m, 3H), 1.41 (s, 9H), 1.47−1.57 (m, 1H), 1.71−2.23 (m, 8H), 2.24−2.28 (m, 1H), 2.61−2.68 (m, 2H), 3.07−3.11 (m, 1H), 3.19−3.24 (m, 1H), 3.28 (s, 3H), 3.41−3.48 (m, 2H), 3.66−3.67 (m, 1H), 3.76−3.79 (m, 2H), 4.08−4.11 (m, 1H), 4.34−4.38 (m, 1H), 4.51−4.59 (m, 5H), 4.67 and 4.89 (AX, J = 15.1 Hz, 2H), 4.99−5.12 (m, 5H), 5.34−5.43 (m, 2H), 6.30 (d, J = 10.0 Hz, 1H), 7.06−7.18 and 7.27−7.31 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 10.3, 11.8, 12.7, 14.5, 15.8, 16.1 (cont.), 17.9, 18.2, 20.0, 21.6, 23.4, 24.6, 24.7, 25.8, 27.6, 28.1, 28.3, 28.7, 30.7, 34.8, 37.5, 40.7, 41.7, 45.5, 47.0, 50.9, 51.9, 56.0, 56.3, 57.1, 57.6, 65.0, 66.8, 70.1, 71.2, 78.7, 78.8, 79.9, 98.6, 155.3, 156.3, 168.3, 169.7, 171.0, 171.1 (overlap); IR (neat) 3333, 2958, 2867, 1721, 1681, 1640, 1498, 1453, 1367, 1250, 1173, 1040, 919, 734 cm^{-1}; HRMS *m/z* calcd for $C_{71}H_{119}O_{15}N_5Si_2Na$ $(M + Na)^+$ 1360.8139, found 1360.8162; $[\alpha]_D^{25}$ −25.78 (*c* 0.64, $CHCl_3$). Anal. Calcd for $C_{71}H_{119}O_{15}N_5Si_2$: C, 63.69; H, 8.96; N, 5.23; Found: C, 63.65; H, 8.89; N, 4.96.

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-[(Triisopropylsilyl)oxy]-4-[(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutyramido]-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-4-Hydroxy-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (12).** To TBDMS ether **11** (328 mg, 0.245 mmol) in THF (0.69 mL) was added HOAc/H_2O (3:1, 2.76 mL). After stirring 16 h, the reaction was diluted with toluene (14 mL) and concentrated. The resulting oil was again diluted with toluene and concentrated. This operation was repeated until no HOAc remained. The crude oil was purified by column chromatography, eluting with acetone/hexanes (35:65 to 40:60). Compound **12** (250.4 mg, 83%) was obtained as a white solid. **12**: mp 86−88 °C; R_f 0.375 (30:70 acetone:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.84−0.99 (m, 21H), 1.04−1.06 (m, 21H), 1.12−1.28 (m, 3H), 1.41 (s, 9H), 1.42−1.54 (m, 3H), 1.74−1.93 (m, 4H), 2.01−2.14 (m, 5H), 2.65−2.67 (m, 2H), 3.13−3.23 (m, 2H), 3.36 (s, 3H), 3.46−3.49 (m, 2H), 3.64−3.67 and 3.76−3.79 (m, 2H), 4.09−4.11 (m, 2H), 4.31−4.32 (m, 1H), 4.52−4.62 (m, 6H), 4.67−4.69 and 4.98−5.00 (m, 9H), 5.02−5.13 (m, 4H), 5.33−5.51 (m, 2H), 6.55−6.60 (m, 1H), 7.06−7.31 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8, 11.8, 12.8, 14.5, 18.1 (overlap), 20.0, 20.5, 21.47 and 21.53 (RI), 23.4, 24.6, 24.7, 27.6, 28.2, 28.3, 28.5, 30.9, 34.9 and 35.1 (RI), 36.8, 40.6, 41.7, 45.6, 47.0, 50.9, 51.9, 56.3 (overlap), 57.1, 64.2, 65.9, 66.8, 69.4, 70.8, 78.4 (overlap), 79.3, 98.5, 126.3, 127.03, 127.1, 127.9, 128.0, 128.2, 128.5, 131.8, 132.2, 136.4, 155.2, 156.3, 168.4, 169.5 (overlap), 171.2, 171.8; IR (neat) 3334, 2961, 2868, 1720, 1680, 1639, 1498, 1453, 1367, 1248, 1171, 1111, 1042, 918 cm^{-1}; HRMS *m/z* calcd for $C_{65}H_{105}O_{15}N_5SiNa$ $(M + Na)^+$ 1246.7274, found 1246.7270; $[\alpha]_D^{25}$ −23.08 (*c* 6.15 $CHCl_3$). Anal. Calcd for $C_{65}H_{105}O_{15}N_5Si$: C, 63.75; H, 8.64; N, 5.72; Found: C, 63.60; H, 8.60; N, 5.71.

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-[(Triisopropylsilyl)oxy]-4-[(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutyramido]-5-methylheptanoic Acid, (1*S*,2*S*,3*S*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoic Acid Ester (24).** To a solution of the linear precursor alcohol **12** (339.2 mg, 0.277 mmol) in CH_2Cl_2 (15 mL) was added the Dess−Martin periodinane reagent (294 mg, 0.693 mmol). After 2 h the reaction was diluted with Et_2O and poured onto a solution of $Na_2S_2O_3 \cdot 5H_2O$ in saturated aqueous $NaHCO_3$ solution (1.2 g in 10 mL). This mixture was stirred for about 10 min, and when the upper Et_2O layer became clear, the layers were separated. The Et_2O layer was washed sequentially with saturated aqueous $NaHCO_3$, H_2O, and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The resulting unstable aldehyde could then be treated in one of two manners.

Method A.[40,51,52] To the aldehyde (339 mg, 0.277 mmol) dissolved in DMSO:H_2O:CH_3CN (1:1:1, 13 mL) at room temperature was added $NaH_2PO_4 \cdot 2H_2O$ (8.64 mg, 55.2 μmol)

(50) Chen, W.-C.; Vera, M. D.; Joullié, M. M. *Tetrahedron Lett.* **1997**, *38*, 4025−4028.

(51) Rich, R. H.; Bartlett, P. A. *J. Org. Chem.* **1996**, *61*, 3916−3919.

(52) Wood, J. L.; Porco, J. A.; Tuanton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898−5900.

followed by $NaClO_2$ (43.8 mg (80%), 0.387 mmol). After being stirred overnight at room temperature, the mixture was diluted with Et_2O and cooled to 0 °C. It was then acidified with 5% HCl until the pH of the aqueous layer was 3. The layers were separated, and the aqueous layer was washed with EtOAc. The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. Most residual DMSO could be removed by lyophilizing with H_2O/CH_3CN or by dissolving the compound in ether and washing the solution with water. The acid (**24**) was obtained (326 mg, 95%) as a white powder and was used without purification in the next step.

Method B.[42] To the aldehyde (109 mg, 89.1 μmol) dissolved in *tert*-butyl alcohol (2.2 mL) was added 2-methyl-2-butene (1.9 mL, 17.8 mmol) followed by 5% NaH_2PO_4 (0.733 mL) and $NaClO_2$ (12.1 mg (80%), 0.107 mmol). After stirring overnight at room temperature, the reaction was diluted with Et_2O (15 mL) and cooled to 0 °C before adding a few drops of $Na_2S_2O_3 \cdot 5H_2O$ to quench excess oxidant. The mixture was acidified with 5% HCl until the aqueous layer reached pH 2. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. Acid **24** was obtained (0.11 g, 100%) as a white powder and used without purification in the next step. Although a large excess of 2-methyl-2-butene has to be used, this scavenger's boiling point is much lower than that of DMSO and it is easier to remove it. **24**: mp 77−80 °C; R_f 0.34 (30:70 acetone:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84−1.00 (m, 8H), 1.03−1.09 (m, 21H), 1.12−1.15 (m, 3H), 1.20−1.26 (m, 3H), 1.25 and 1.40 (s, 9H), 1.44−1.74 (m, 3H), 1.75−1.82 (m, 2H), 2.04−2.15 (m, 5H), 2.24−2.27 (m, 1H), 2.51−2.73 (m, 3H), 3.11−3.18 (m, 2H), 3.40 (s, 3H), 3.69−3.83 (m, 3H), 4.01−4.08 (m, 2H), 4.38−4.40 (m, 2H), 4.53−4.77 (m, 4H), 4.77−4.79 and 4.89−4.92 (m, 2H), 5.00−5.13 (m, 4H), 5.33−5.50 (m, 2H), 6.76 (d, J = 10.3 Hz, 1H), 7.02−7.44 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 12.7, 14.7, 15.8, 17.7, 18.06 and 18.13 (RI), 19.0 and 19.2 (RI), 21.6, 23.4, 24.6, 24.8, 27.3, 28.1, 28.3 and 28.4 (RI), 29.7, 30.7, 35.6, 39.5, 41.1, 41.5, 45.7, 47.0, 51.0, 52.3, 56.4, 56.9, 57.2, 58.3, 66.8, 68.7, 70.6, 78.3, 78.9, 80.2, 97.9, 126.2, 127.1, 127.3, 127.7, 127.95, 128.04, 128.3, 128.5, 131.6, 132.2, 136.4, 155.5, 156.3, 168.7, 169.4, 171.4, 171.9 (overlap), 175.9; IR (neat) 3322, 2960, 1722, 1678, 1640, 1529, 1453, 1367, 1171, 1041 cm^{-1}; HRMS *m/z* calcd for $C_{65}H_{104}O_{16}N_5Si$ $(M + H)^+$ 1260.7247, found 1260.7294; $[\alpha]_D^{25}$ −16.95 (*c* 0.64, $CHCl_3$).

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydroisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-[(Triisopropylsilyl)oxy]-4-[(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutyramido]-5-methylheptanoic Acid, Pentafluorophenyl (1*S*,2*S*,3*S*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoate Ester (26).** Acid **24** (157.7 mg, 0.127 mmol) and pentafluorophenol (25.7 mg, 0.14 mmol) were dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. To this solution were added EDC·HCl (26.8 mg, 0.14 mmol) and catalytic DMAP. After being stirred at 0 °C for 1 h, the reaction was stirred at room temperature for 12 h. The solution was concentrated, and the residue was diluted with EtOAc and washed sequentially with 10% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The EtOAc layer was dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by column chromatography eluting with acetone/hexanes (18:82). Compound **26** (119 mg, 67%) was obtained as a white solid. **26**: mp 73−75 °C; R_f 0.55 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83−0.98 (m, 18H), 1.04−1.07 (m, 21H), 1.12−1.26 (m, 3H), 1.35 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H), 1.41−1.56 (m, 2H), 1.68−1.82 (m, 3H), 1.95−2.29 (m, 6H), 2.61−2.70 (m, 2H), 2.95−2.99 (m, 1H), 3.10 (dd of ABX, J = 15.7, 5.1 Hz, 1H), 3.21 (dd of ABX, J = 15.7, 3.3 Hz, 1H), 3.29 (s, 3H), 3.65−3.67 and 3.76−3.80 (m, 2H), 4.08−4.10 (m, 2H), 4.14−4.16 (m, 1H), 4.33−4.36 (m, 1H), 4.53−4.55 (m, 1H), 4.56−4.64 (m, 2H), 4.66−4.68 (m, 1H), 4.90 (d, J = 15.1 Hz, 1H), 4.92−5.02 (m, 2H), 5.04−5.08 (m, 3H), 5.28−5.30 (m, 1H), 5.35 (d, J = 9.0 Hz, 1H), 5.42−5.44 (m, 1H), 6.38 (d, J = 10.0 Hz, 1H), 7.06−7.08 and 7.13−7.18 and 7.27−7.32 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 12.7, 14.5, 16.0, 17.0, 18.1, 19.6, 21.5, 23.4, 24.6, 24.7, 27.6, 28.1, 28.2, 28.8, 30.7, 34.9, 37.0, 40.0, 41.3, 41.7, 45.5, 47.0, 50.9, 51.8, 56.2, 56.4, 57.1, 66.3, 66.8, 69.9, 71.3, 78.3, 78.5, 79.9, 98.2, 126.2, 126.9, 127.1, 127.8, 127.9 (overlap), 128.0, 128.3, 128.5 (overlap), 131.5, 132.2, 136.1, 136.4, 138.8, 140.2, 142.2, 142.7, 156.1, 156.3, 168.3, 169.7, 169.8, 170.1, 171.1, 171.2; IR (neat) 3328, 2961, 1785, 1719, 1681, 1639, 1251, 1456, 1367, 1247, 1169, 1033, 861 cm^{-1}; HRMS *m/z* calcd for $C_{71}H_{102}O_{16}N_5SiF_5Na$ $(M + Na)^+$ 1426.6909, found 1426.6943; $[\alpha]_D^{25}$ −18.25 (*c* 0.92, $CHCl_3$).

Cyclo[*N*-(*tert*-butyloxycarbonyl)-*O*-[[*N*-[(2*S*,3*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]-oxy-3-(methoxymethoxy)-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinolyl)]-L-threonyl] (27).[17,44,53,54] To a solution of activated ester **26** (100 mg, 71.1 μmol) in EtOAc and EtOH (98:2, 71.1 mL) at 0 °C were added 10% Pd/C (0.242 g) and 4-pyrrolidinopyridine (31.65 mg, 0.21 mmol). The flask was evacuated and then placed under a H_2 atmosphere. The reaction was allowed to warm to room temperature and was stirred under H_2 for 6 h before filtering through Celite. The filtrate was washed sequentially with 10% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography eluting with acetone/hexanes (15:85). Compound **27** (44.5 mg, 58%) was obtained as a white foam. **27**: R_f 0.57 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79−1.04 (m, 18H), 1.05−1.07 (m, 21H), 1.26 (d, J = 6.3 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 1.39 and 1.42 (s, 9H, RI), 1.43−1.56 (m, 2H), 1.64−1.66 (m, 3H), 1.85−2.20 (m, 6H), 2.50−2.60 (m, 2H), 2.76 (q, J = 8.5 Hz, 1H), 2.92 (dd of ABX, J = 18.6, 2.0 Hz, 1H), 3.00 (dd of ABX, J = 17.0, 4.1 Hz, 1H), 3.37 and 3.39 (s, 3H, RI), 3.63−3.70 (m, 2H), 3.73 (dd, J = 12.4, 4.2 Hz, 1H), 3.88−3.92 (m, 1H), 4.09−4.19 (m, 1H), 4.31−4.33 (m, 1H), 4.43−4.58 (m, 3H), 4.61−4.69 (m, 2H), 4.70−4.87 (m, 2H), 4.90−4.95 (m, 1H), 5.02 (d, J = 10.5 Hz, 1H), 5.18−5.20 (m, 1H), 7.01−7.21 (m, 4H), 7.47 (d, J = 9.6 Hz, 1H, cont.), 7.86 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 13.0, 13.55 and 13.62, 14.6, 17.7 and 18.3 (RI), 18.4 and 18.5 (RI), 19.0, 19.1, 20.8, 23.6 and 24.7 (RI), 25.0 and 25.1 (RI), 27.9, 28.1 and 28.2 (RI), 28.3, 28.8 and 28.9 (RI), 29.2, 31.7, 34.4, 39.8, 40.6 and 40.9 (RI), 42.8 and 43.3 (RI), 44.6, 47.1, 48.4 and 48.7 (RI), 53.7 and 54.1, 55.1 and 55.2 (RI), 56.2, 56.3 and 56.4 (RI), 57.1 and 57.8 (RI), 68.8, 71.1, 78.7, 79.2, 80.2 and 80.4 (RI), 98.7, 125.3 and 126.5 (RI), 126.8 and 127.2 (RI), 127.7 and 127.8 (RI), 130.1, 132.3 and 132.7 (RI), 133.5, 155.3 and 156.0 (RI), 167.9, 169.0 and 169.7 (RI), 170.7, 171.5, 172.2, 174.3; IR (neat) 3346, 2961, 1742, 1668, 1642, 1534, 1515, 1450, 1380, 1367, 1247, 1166, 1016, 821, 754 cm^{-1}; HRMS *m/z* calcd for $C_{57}H_{95}O_{13}N_5Si$ $(M + Na)^+$ 1108.6593, found 1108.6575; $[\alpha]_D^{25}$ −20.58 (*c* 1.82, $CHCl_3$). Anal. Calcd for $C_{57}H_{95}O_{13}N_5Si$: C, 63.01; H, 8.81; N, 6.45; Found: C, 62.66; H, 8.87; N, 6.09.

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[*N*-[(2*S*,3*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]oxy-3-hydroxy-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinolyl)]-L-threonyl] (29). To a cold (−78 °C) stirred solution of the MOM ether **27** (45 mg, 41.4 μmol) in dry CH_2Cl_2 (1 mL) was added dropwise a solution of dimethylboron bromide (1.5 M, 0.138 mL) in CH_2Cl_2. After 2 h, the reaction was not complete so the same amount of dimethylboron bromide was added again. After 2 additional h at −78 °C, a solution of THF (2 mL) and saturated aqueous $NaHCO_3$ was added with vigorous stirring. After 5 min, the mixture was diluted with ether and the reaction warmed to room temperature. The organic layer was separated and washed sequentially with water, 10% $KHSO_4$, and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified

(53) Schmidt, U.; Lieberknecht, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 281−282.
(54) Schmidt, U.; Griesser, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280−281.

by column chromatography eluting with acetone/hexanes (22:78) to give alcohol **29** (35.3 mg, 82%) as a white foam. **29**: R_f 0.48 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80−0.97 (m, 18H), 1.02−1.14 (m, 21H), 1.28 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.41 and 1.44 (s, 9H), 1.46−1.64 (m, 6H), 1.88−2.20 (m, 4H), 2.32−2.35 (m, 1H), 2.47−2.57 (m, 1H), 2.63−2.77 (m, 1H), 2.93−3.05 (m, 1H), 3.18−3.39 (m, 1H), 3.39−3.50 (m, 1H), 3.63−3.78 (m, 2H), 3.84−3.93 (m, 1H), 4.03−4.17 (m, 2H), 4.27−4.37 (m, 1H), 4.48−4.64 (m, 3H), 4.67−4.90 (m, 3H), 4.93−4.97 (m, 1H), 5.00−5.04 (m, 1H), 5.73−5.74 (m, 1H), 7.01−7.25 (m, 4H), 7.38−7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 12.9, 13.5 and 13.6 and 13.8 (RI), 14.7, 17.6, 18.2 and 18.4 (RI), 18.5, 19.2, 20.9, 23.4 and 23.6 (RI), 24.7 and 24.8 (RI), 25.0 and 25.1 (RI), 27.9 and 28.0 (RI), 28.1 and 28.2 (RI), 28.7 and 28.9 (RI), 29.6, 34.3, 34.8, 39.8, 40.5 and 40.9 (RI), 45.1, 47.1, 48.2, 49.7, 55.2, 56.0, 57.1 and 57.8 (RI), 69.0, 71.0, 72.0, 73.0, 79.1, 80.2, 125.3, 126.5 and 126.8 (RI), 127.2 and 127.7 (RI), 130.1, 132.2, 132.7 and 133.5, 156.1, 167.8, 169.0 and 169.5 (RI), 170.7, 171.5, 172.1 and 172.2 (RI), 173.7; IR (neat) 3355, 2960, 2869, 1740, 1702, 1670, 1642, 1540, 1450, 1387, 1301, 1227, 1168, 918, 883, 732 cm^{-1}; HRMS m/z calcd for $C_{55}H_{91}O_{12}N_5SiNa$ $(M + Na)^+$ 1064.6331, found 1064.6355; $[\alpha]_D^{25}$ −24.5 (c 0.96, $CHCl_3$).

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinolyl)]-L-threonyl] (31). To a solution of the alcohol **29** (10 mg, 9.59 μmol) in CH_2Cl_2 (1 mL) was added the Dess−Martin periodinane reagent (6 mg, 14.1 μmol). After 2 h, the reaction was not complete so more reagent (5 mg, 11.8 μmol) was added. After an additional 2 h, the solution was diluted with Et_2O and poured onto a solution of $Na_2S_2O_3$·$5H_2O$ in saturated aqueous $NaHCO_3$ solution (48.3 mg in 4 mL). This mixture was stirred for about 10 min, and when the upper Et_2O layer became clear, the layers were separated. The Et_2O layer was washed sequentially with saturated aqueous $NaHCO_3$, H_2O, and saturated NaCl solutions. The Et_2O layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography eluting with acetone/hexanes (15:85 to 18:82) to give the desired ketone **31** (6.8 mg, 68%) as a white foam. **31**: R_f 0.55 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−0.98 (m, 18H), 1.01−1.08 (m, 21H), 1.16−1.25 (m, 5H), 1.26−1.36 (m, 4H), 1.38 and 1.44 (s, 9H), 1.48−1.71 (m, 2H), 1.82−2.24 (m, 5H), 2.55−2.76 (m, 2H), 3.00 (dd of ABX, J = 17.1, 4.1 Hz) and 3.15 (dd of ABX, J = 17.6, 2.2 Hz, 1H, RI), 3.18−3.29 (m, 1H), 3.37−3.47 (m, 1H), 3.53−3.57 (m, 1H) and 3.63−3.69 (m, 1H), 3.73 (dd, J = 12.4, 4.2 Hz) and 3.70−3.82 (m, 1H), 3.89−3.94 (m) and 4.10−4.15 (m, 1H), 4.24−4.37 (m, 1H), 4.38−4.46 (m, 1H), 4.49−4.63 (m, 2H), 4.70−4.83 (m, 2H), 90−5.01 (m, 2H), 5.09 (d, J = 10.3 Hz) and 5.18 (d, J = 7.6 Hz, 1H), 5.65−5.68 (m, 1H), 6.95−7.22 (m, 4H), 7.43 (d, J = 10.5 Hz) and 7.70 (d, J = 9.1 Hz, 1H), 8.46 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0 and 12.1 (RI), 12.8 and 13.3 and 13.8 (RI), 14.4 and 14.7 (RI), 15.3 and 15.9 (RI), 17.1, 18.1 and 18.2 and 18.4 and 18.5 (RI), 20.3, 20.8 and 21.1 (RI), 23.3 and 23.6 (RI), 24.8 and 24.9 (RI), 25.2, 27.4, 27.8 and 27.9 (RI), 28.11 and 28.14 (RI), 28.3 and 28.5 (RI), 28.9 and 30.0 and 30.4 (RI), 32.8, 33.4 and 33.7 (RI), 39.5 and 39.8 and 40.3 (RI), 41.8, 46.4, 47.1 and 48.3 (RI), 49.6 and 49.9 (RI), 52.6 and 54.1 (RI), 55.3 and 55.5 (RI), 56.1 and 56.3 (RI), 57.2 and 57.4 and 57.9 (RI), 69.2 and 69.4 (RI), 80.1 and 80.3 and 80.4 (RI), 81.7, 125.5, 126.6 and 126.8 (RI), 127.4 and 127.6 and 127.7 (RI), 129.7 and 130.1 (RI), 132.2 and 132.7 (RI), 133.4, 155.6 and 156.3 (RI), 167.8, 168.5 and 169.2 (RI), 169.3 and 169.6 (RI), 170.9 and 171.6 (RI), 171.3 and 171.6 (RI), 172.0 and 172.6 (RI), 202.5 and 204.5 (RI); IR (neat) 3331, 2960, 2868, 1735, 1670, 1642, 1534, 1497, 1449, 1387, 1367, 1314, 1247, 1166, 1103, 1048, 1016, 916, 883, 732 cm^{-1}; HRMS m/z calcd for $C_{55}H_{89}O_{12}N_5SiNa$ $(M + Na)^+$ 1062.6175, found 1062.6143; $[\alpha]_D^{25}$ −36.34 (c 1.1, $CHCl_3$).

Cyclo[*O*-[[*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinolyl)]-L-threonyl] Hydrochloride. A solution of ketone **31** (10 mg, 9.6 μmol) in EtOAc (0.6 mL) was cooled to −30 °C. Gaseous HCl was introduced (via a glass pipet through a septum in one neck of the flask) at such a rate that the temperature of the reaction mixture was maintained between −10 °C and −20 °C for 30 min. During this time, the second neck of the flask was attached first to an oil bubbler and then to a water bubbler. After stopping the flow of HCl (g) and placing the flask under a N_2 atmosphere, the solution was stirred for 2 h at this temperature and then stirred at 0 °C for 4 h. The solution was then purged with N_2 for about 30 min, maintaining the temperature at 0 °C. After the solution was concentrated, the residue was triturated and washed by decantation with three 1.7 mL portions of *tert*-butyl methyl ether/hexanes (1:4). The product was dried in vacuo. The salt (8.2 mg, 100%) was obtained as a white solid: R_f 0.55 (10:90 MeOH: CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD) δ 0.85−1.10 (m, 18H), 1.16−1.22 (m, 1H), 1.24−1.25 (m, 3H), 1.27−1.30 (m, 1H), 1.32 (d, J = 6.3 Hz, 3H), 1.36−1.44 (m, 1H), 1.49−1.57 (m, 1H), 1.73−1.81 (m, 3H), 1.86−1.94 (m, 1H), 2.06−2.17 (m, 2H), 2.29−2.37 (m, 1H), 2.47 (dd, J = 17.9, 10.5 Hz, 1H), 3.03 (dd of ABX, J = 16.8, 4.0 Hz, 1H), 3.27−3.34 (m, 2H), 3.41−3.46 (m, 1H), 3.64−3.67 (m, 1H) and 3.75−3.79 (m, 1H), 4.03−4.09 (m, 2H), 4.11−4.17 (m, 2H), 4.28−4.30 (m, 1H), 4.56−4.60 (m, 1H) and 4.73−4.78 (m, 1H), 4.86−4.88 (m, 2H), 4.98−5.01 (m, 2H), 5.09−5.11 (m, 1H), 5.27−5.29 (m, 2H), 7.20−7.22 (m, 4H), 7.43−7.45 (m, 1H), 8.91−8.93 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.4, 13.8, 14.8, 15.4, 17.2, 19.3, 21.1, 23.8, 25.8, 26.1, 28.8, 29.0, 29.8, 31.5, 35.7, 40.8, 41.4, 49.8, 51.2, 55.8, 57.3, 58.4, 59.4, 67.6, 69.0, 82.3, 126.8, 127.8, 128.5, 130.9, 134.5 (overlap), 169.2, 172.4, 172.6, 172.7, 173.2, 173.5, 207.0; IR (neat) 2960, 2878, 2358, 2340, 1730, 1639, 1454, 1389, 1312, 1247, 1225, 1166, 1087 cm^{-1}; HRMS m/z calcd for $C_{41}H_{61}O_{10}N_5$·HClNa $(M + Na - HCl)^+$ 806.4316, found 806.4330; $[\alpha]_D^{25}$ −127.1 (c 1.26, MeOH).

Cyclo-*N*-L-lactyl-L-prolyl-*N*-methyl-D-leucine[*O*-[[*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydroisoquinolyl)]-L-threonyl] (2). To a solution of amine salt (10 mg, 12.1 μmol) and L-lactyl-L-prolyl-*N*-methyl-D-leucine (5.75 mg, 18.29 μmol), in CH_2Cl_2 (0.5 mL) at 0 °C, were added BOP (8.1 mg, 18.29 μmol) and NMM (5.36 μL, 48.4 μmol). After 30 min, the solution was brought to room temperature and stirred for 3 h. The reaction mixture was treated with 1.5 mL of saturated NaCl solution and then extracted with EtOAc. The combined organic layers were washed successively with 5% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The resulting organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by column chromatography, eluting with MeOH/CH_2Cl_2 (5:95) to afford **2** (8.3 mg, 63%) as a white solid. **2**: R_f 0.59 (10:90 MeOH:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84−0.95 (m, 24H), 1.16−1.25 (m, 3H), 1.31 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.40 (d, J = 6.3 Hz, 3H), 1.42−1.44 (m, 1H), 1.52−1.57 (m, 1H), 1.58−1.67 (m, 1H), 1.69−1.72 (m, 1H), 1.81−1.91 (m, 2H), 1.95−2.04 (m, 6H), 2.15−2.21 (m, 2H), 2.31−2.37 (m, 1H), 2.56 (dd, J = 18.0, 9.9 Hz, 1H), 2.9 (brs, 1H), 3.04 (dd, J = 17.0, 4.1 Hz, 1H), 3.15 (s, 3H), 3.36 (d, J = 12.5 Hz, 1H), 3.38−3.43 (m, 1H), 3.52 (d, J = 18 Hz, 1H), 3.55−3.58 and 3.62−3.65 (m, 4H), 3.79 (dd, J = 12.3, 4.0 Hz, 1H), 4.06−4.13 (m, 2H), 4.21 (q, J = 6.8 Hz, 1H), 4.34−4.38 (m, 2H), 4.54 and 4.66, (AB, J = 16.9 Hz, 2H), 4.69−4.79 (m, 3H), 5.22 (d, J = 3.4 Hz, 1H), 5.34−5.37 (m, 2H), 7.08 (d, 6.3H), 7.10−7.23 (m, 4H), 7.51 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 9.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 13.2, 15.3, 16.0, 16.7, 18.8, 20.2, 20.9, 21.4, 23.4, 23.8, 24.9, 25.2, 26.0, 27.5, 28.0, 28.2, 28.4, 29.7, 31.3, 33.6, 36.3, 39.1, 41.1, 47.0, 49.3, 49.7, 49.8 (overlap), 54.6, 54.9,56.7, 57.5, 57.7, 57.9, 65.9 (overlap), 67.4, 69.7, 81.1, 125.4, 126.8, 127.7, 130.1, 132.2, 133.5, 167.3, 168.0, 169.4, 171.2, 171.5, 171.7, 172.8 (overlap), 173.8, 205.0; IR (neat) 3346, 2958, 1732, 1641, 1535, 1449, 1217, 1166, 1089, 753 cm^{-1}; HRMS m/z calcd for $C_{56}H_{85}N_7O_{14}$-Na $(M + Na)^+$ 1102.6052, found 1102.6046; $[\alpha]_D^{25}$ −71.81 (c 0.415, $CHCl_3$).

L-1,2,3,4-Tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic Acid Hydrochloride (13).[55] Concentrated HCl (248.6 mL), 1, 2-dimethoxyethane (16.6 mL), and formaldehyde (37 wt %, 18.2 mL) were added under nitrogen to 3′,5′-diiodo-L-tyrosine·$2H_2O$ (25 g, 53.3 mmol) with stirring with a mechanical stirrer. CAUTION: the combination of concentrated HCl and aqueous formaldehyde forms a potent carcinogen. The resulting suspension was heated slowly to 72 °C for 30 min. After 30 min at this temperature, additional concentrated HCl (110 mL), 1,2-dimethoxyethane (8.3 mL), and formaldehyde (37 wt %, 9.1 mL) were added. Stirring was continued for 18 h at 72−75 °C. The suspension was cooled in an ice bath, and the solids were collected by filtration. The filter cake was washed thoroughly with cold 1,2-dimethoxyethane until the color lightened, and the solid was dried in vacuo overnight. The resulting salt **13** (13.8 g, 54%) was obtained as a tan solid. Although this product could be recrystallized from MeOH/H_2O, it was normally used without purification; $[\alpha]_D^{25}$ −79.44 (*c* 0.27, glacial HOAc); lit.[55] $[\alpha]_D^{25}$ −88.83 (*c* 0.20, glacial HOAc).

Cbz-L-1,2,3,4-Tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic Acid (14). The hydrochloride salt (**13**, 6.00 g, 12.44 mmol) was dissolved in anhydrous CH_2Cl_2 (150 mL) and the solution cooled to 0 °C while stirring. Triethylamine (3.78 g, 37.44 mmol) was added dropwise, and after 5 min Cbz-succinimide (3.41 g, 13.68 mmol) was added. The reaction was monitored by TLC. At the end of the reaction, the mixture was concentrated and washed first with $NaHCO_3$ solution and then with EtOAc. The solution was extracted three times into EtOAc. TLC comparison of aqueous vs organic layers showed that the product remained at the baseline while the undesired product had an R_f 0.60 (30%EtOAc/petroleum ether). The aqueous layer was acidified to pH 2 using 2 N $KHSO_4$. The carboxylic acid was extracted into ethyl acetate three times, and the solution was dried over $MgSO_4$ and filtered. The filtrate was concentrated to provide 5.67 g of **14** as a white/gray solid, 79%. yield. mp 94−96 °C; R_f 0.50 (10:90 MeOH:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08−3.19 (m, 2H), 4.32 (d, J = 17.6 Hz) and 4.38 (d, J = 17.3 Hz) and 4.69 (d, J = 11.8 Hz) and 4.73 (d, J = 13.1 Hz, 2H, RI), 5.06−5.32 (m, 3H), 5.82 (br, 1H), 7.32−7.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7 and 30.1 (RI), 50.7, 52.3 and 52.6 (RI), 68.0, 80.2 (overlap), 126.8, 127.2, 127.7, 128.1, 128.2, 128.3, 128.6,136.1, 138.5 and 138.7 (RI), 152.5, 156.1,175.0; IR (KBr) 3424, 1682, 1424, 1324 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{18}H_{15}I_2NO_5Na$-$(M + Na)^+$ 601.8938, found 601.8953; $[\alpha]_D^{25}$ +44.08 (*c* 0.52, $CHCl_3$).

Methyl *N*-Cbz-L-1,2,3,4-Tetrahydro-7-hydroxy-6,8-diiodo-isoquinoline-3-carboxylate (15). Acid **14** (5.00 g, 8.63 mmol) was dissolved in anhydrous THF under N_2. Potassium hydroxide (3.19 g, 56.9 mmol) was added in portions to the stirring solution, and then tetrabutylammonium hydrogen sulfate (0.500 g, 1.48 mmol) was added. After initiating vigorous stirring, dimethyl sulfate was added dropwise. Once the reaction was judged complete by TLC, the KOH was collected and the filtrate was stirred with 50% ammonium hydroxide solution at 0 °C to quench any excess dimethyl sulfate (CAUTION: toxic and potent carcinogen). The mixture was concentrated and extracted with ethyl acetate twice. The organic layer was washed with 10% HCl, 5% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. The crude oil was purified by flash column chromatography, eluting with EtOAc:petroleum ether (18:82) to afford the ester (**15**) as a white solid (4.77 g, 91%) Recrystallization of the solid from ether/petroleum ether was done prior to elemental analysis. **15**: mp 47−49 °C; R_f 0.32 (30:70 acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13−3.21 (m, 2H), 3.60 and 3.66 (s, 3H, RI), 3.84 (s, 3H), 4.29−4.39 (m) and 4.75−4.81 (m, 2H), 5.03 and 5.20−5.31 (m, 3H), 7.35−7.58 and 7.56−7.57 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0 and 30.4 (RI), 50.9, 52.3 and 52.6 (RI), 52.8, 60.6, 67.8, 87.7, 95.1, 127.7, 128.0, 128.1, 128.2, 128.5, 131.2, 136.7, 139.1, 139.5, 155.9, 157.7, 170.9; IR (neat) 2952, 1741, 1703, 1412, 1324, 1210 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{20}H_{20}I_2NO_5$ $(M + H)^+$ 607.9434, found 607.9425; $[\alpha]_D^{25}$ +35.19 (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{20}H_{19}I_2NO_5$: C, 39.56; H, 3.15; N, 2.31; Found: C, 39.73; H, 3.22; N, 2.00.

Methyl *N*-Cbz-*N*-L-1,2,3,4-Tetrahydro-7-methoxyisoquinoline-3-carboxylate (16). Methyl ester **15** (4.32 g, 7.12 mmol) was slowly dissolved in HPLC grade methanol (230 mL). The solution was cooled to 0 °C, and CuCl (1.04 g, 5.26 mmol) was added with stirring, turning the solution green. Sodium borohydride (2.70 g, 71.2 mmol) was added in portions over a period of 15 min, and the solution turned brown, then black. After no starting material remained, the reaction mixture was filtered through a Celite/MeOH slurry to obtain a clear yellow solution. The solution was concentrated to afford an orange residue that was dissolved in ethyl acetate. The organic layer was washed with 10% HCl, 5% $NaHCO_3$, and brine and then dried over $MgSO_4$. After removal of the drying agent, the solution was concentrated and the crude oil was purified by flash column chromatography, eluting with EtOAc/petroleum ether (22:78) to afford **16** as a yellow oil (2.20 g, 87%). **16**: R_f 0.63 (25:75 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08−3.22 (m, 2H), 3.54 and 3.62 (s, 3H, RI), 3.76 and 3.77 (s, 3H, RI), 4.54 (d, J = 16.3 Hz) and 4.59 (d, J = 16.4 Hz) and 4.77 (d, J = 16.4 Hz) and 4.77 (d, J = 16.4 Hz, 2H, RI), 4.94 (t, J = 5.0 Hz) and 5.14−5.26 (m, 3H, RI), 6.61 and 6.69 (s, 1H, RI) and 6.72 (d, 8.3 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.26−7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3 and 30.7 (RI), 44.6 and 44.8 (RI), 52.2 and 52.3 (RI), 53.4 and 54.0 (RI), 55.3, 67.5 and 67.6 (RI), 111.0 and 111.2 (RI), 113.2, 123.6, 123.7, 127.9, 128.0, 128.1, 128.5 and128.6 (RI), 129.0, 129.5, 133.5, 155.9, 158.5, 171.7 and 171.92 (RI); IR (neat) 1742, 1702, 1613, 1505, 1410, 1321 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{20}H_{25}N_2O$ $(M + NH_4)^+$ 373.1763, found 373.1758; $[\alpha]_D^{25}$ +13.95 (*c* 1.14, $CHCl_3$).

***N*-Cbz-L-1,2,3,4-Tetrahydro-7-methoxyisoquinoline-3-carboxylic Acid (17).** Methyl ester **16** (1.822 g, 5.13 mmol) was dissolved in a 1:1:1 THF−water−MeOH mixture and cooled to 0 °C. While stirring, lithium hydroxide hydrate (0.538 g, 12.82 mmol) was added. The reaction was allowed to stir and was warmed to room temperature after 4 h. After stirring for another 14 h, the reaction mixture was concentrated and treated with $NaHCO_3$. The solution was extracted twice with EtOAc. The aqueous layer was acidified to pH 3 using 2 N $KHSO_4$ solution. The resulting acid was extracted into EtOAc three times and washed with brine. After drying over $MgSO_4$, the solution was filtered and concentrated to afford the acid (**17**) as a white foam (1.70 g, 97%). The acid was usually used directly in the next step without purification. However, a small amount was purified by column chromatography eluting with MeOH/CH_2Cl_2 (7:93) to obtain a sample for characterization. **17**: mp 52−54 °C; R_f 0.46 (25:75 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.09 (d, J = 6.0 Hz) and 3.13 (d, J = 6.0 Hz) and 3.20−3.23 (m, 2H, RI), 3.76 and 3.77 (s, 3H, RI), 4.52−4.57 and 4.72−4.76 (m, 2H), 4.97−4.99 and 5.18−5.23 (m, 3H, RI), 6.62−6.74 (m, 2H), 7.04−7.07 (m, 1H), 7.31−7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0 and 30.5 (RI), 44.5 and 44.7 (RI), 53.3 and 53.7 (RI), 55.2, 67.6 and 67.8 (RI), 111.0 and 111.2 (RI), 113.3, 123.4, 127.9, 128.0, 128.1 and 128.2, 128.5, 129.1 and 129.5 (RI), 133.3, 134.0, 136.3, 156.3, 158.5, 176.5; IR (neat) 2954, 1700, 1680, 1613, 1505, 1263, 1428, 1321 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{19}H_{23}N_2O_5$ $(M + NH_4)^+$ 359.1607, found 359.1601; $[\alpha]_D^{25}$ +16.42 (*c* 0.14, $CHCl_3$).

***N*-Cbz-L-3-Carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline-*O*-Boc-threonine-*O*SEM (18).** Acid **18** (3.34 g, 9.65 mmol) and Boc-Thr-*O*SEM (2.34 g, 8.98 mmol) were dissolved in CH_2Cl_2 (1.85 mL, *Note*: Solution should be no more concentrated than 0.25 M). The solution was cooled to 0 °C, and then triethylamine (2.9 mL, 20.65 mmol), DMAP (0.274 g, 2.25 mmol), and isopropenyl chloroformate (1.1 mL, 9.88 mmol) were added, in that order. After stirring at 0 °C for 1.5 h, the reaction was diluted with ether (20 mL) and washed with 10% HCl, 5% $NaHCO_3$, and brine and then dried over $MgSO_4$. After removal of the drying agent, the solution was concentrated under reduced pressure to afford **18** as a

(55) Verschueren, K.; Toth, G.; Tourwé, D.; Lebl, M.; Van Binst, G.; Hruby, V. J. *Synthesis* **1992**, 458−460.

yellow oil (4.75 g, 78%). Compound **18** was purified by column chromatography, eluting with 5%−10% acetone/hexanes gradient. **18**: R_f 0.71 (20:80 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 9H), 0.86 (t, J = 8.2 Hz, 2H), 1.04 (d, J = 6.3 Hz) and 1.12 (d, J = 6.3 Hz, 3H, RI), 1.44 and 1.45 (s, 9H, RI), 3.01−3.14 (m, 2H), 3.51−3.63 (m, 2H), 3.73 and 3.75 (s, 3H, RI), 4.34−4.39 (m, 1H), 4.48 and 4.69 (AB quartet, J = 16.4 Hz, 2H), 4.85 (d, J = 5.7 Hz) and 4.91 (t, J = 4.7 Hz, 1H, RI), 5.00 (d, J = 8.5 Hz, 1H), 5.05−5.14 (m, 1H), 5.17 and 5.20 (s, 2H, RI), 5.24−5.28 (m, 2H), 6.60 and 6.68−6.71 (m, 2H), 7.01 (d, J = 8.5 Hz, 1H), 7.28−7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.6 and −1.4 (RI), 16.6, 17.9, 28.3, 30.2 and 30.7 (RI), 44.6 and 44.9 (RI), 53.5 and 54.0 (RI), 55.2, 56.9 and 57.0 (RI), 67.5 and 67.7 (RI), 68.1, 71.6 and 71.7 (RI), 80.3, 90.3, and 90.4 (RI), 111.1 and 111.3 (RI), 113.2, 123.3 and 123.5 (RI), 128.0, 128.1, 128.5, 129.0, 129.3, 133.4, 134.0, 136.3 and 136.4 (RI), 155.8, 156.0, 158.5, 169.5, 170.0; IR (neat) 1730, 1713, 1504, 1413, 1163 cm^{-1}; HRMS (FAB) m/z calcd for $C_{34}H_{48}N_2O_{10}SiNa$ $(M + Na)^+$ 695.3076, found 695.3071; $[\alpha]_D^{25}$ +29.85 (c 1.37, $CHCl_3$).

Cbz-Leucylprolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxy-isoquinoline)-*O*-Boc-threonine-*O*SEM (20). A solution of carbamate **18** (3.45 g, 5.13 mmol) and 10% Pd on carbon (0.080 g) in 1:1 MeOH/EtOAc solvent (25 mL) was placed in a Parr hydrogenator vessel under 50 psi for 8 h. After all the starting material had been consumed, the reaction was filtered through a Celite/MeOH slurry and concentrated under reduced pressure. The resulting yellow oil (**19**) was used without purification in the next step. Crude yield 87%. To a solution of Cbz-Leu-Pro-OH (2.13 g, 5.89 mmol) in CH_2Cl_2 (12 mL) cooled to −15 °C were added BOP-Cl (1.66 g, 6.52 mmol) and *N*-methylmorpholine (0.7 mL, 6.52 mmol). The reaction was stirred for 40 min and then warmed to 0 °C for 5 min before adding a stirred, cooled solution of amine **19** (2.76 g, 5.13 mmol) in CH_2Cl_2 (12 mL) and NMM (0.7 mL, 6.52 mmol). The reaction was stirred at 0 °C for 6 h, diluted with ether (50 mL), washed with 10% HCl, saturated $NaHCO_3$, and brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure to provide **20** as a white foam. Compound **20** was purified by column chromatography, eluting with acetone/hexanes gradient, to afford 2.90 g of a solid, 64% yield. **20**: mp 66−68 °C; R_f 0.45 (30:70 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.02 (s, 9H), 0.80−0.89 (m, 2H), 0.92 (d, J = 6.6 Hz) and 0.95 (d, J = 6.7 Hz, 3H, RI) and 0.99 (d, J = 6.4 Hz) and 1.03 (d, J = 6.5 Hz, 6H, RI), 1.10 (d, J = 6.3 Hz) and 1.23 (d, J = 6.1 Hz, 3H, RI), 1.38−1.40 (m, 2H), 1.42 and 1.44 (s, 9H, RI), 1.48−1.60 (m, 1H), 1.83−1.86 and 2.01−2.32 (m, 4H), 3.00−3.14 (m, 2H), 3.47−3.59 (m, 2H), 3.60−3.68 and 3.80−3.82 (m, 2H), 3.74 and 3.75 (s, 3H, RI), 4.33−4.38 (m, 1H), 4.50−4.69 (m, 2H), 4.75−5.03 (m, 4H), 5.05−5.17 (m, 2H), 5.20−5.22 (m, 2H), 5.29−5.40 (m, 2H), 6.60−6.63 and 6.69−6.73 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 7.27−7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.3, 16.7, 17.9, 21.5, 23.4, 24.6, 24.9, 28.3 and 28.5 (RI), 29.9, 30.4 and 30.5 (RI), 41.7, 45.6, 47.0, 51.9, 55.2, 55.3, 57.3, 57.7, 66.8, 68.1, 71.9, 80.3, 90.4, 111.2, 113.4, 124.2, 127.9, 128.0, 128.2, 128.4, 128.5, 129.3, 129.4, 132.4, 155.6, 156.3, 158.6, 169.4, 169.8, 170.8, 171.2; IR (neat) 3287, 2955, 2360, 1715, 1644 cm^{-1}; HRMS m/z calcd for $C_{45}H_{66}N_4O_{12}SiNa$ $(M + Na)^+$ 905.4344, found 905.4368; $[\alpha]_D^{25}$ −9.36 (c 0.55, $CHCl_3$). Anal. Calcd for $C_{45}H_{66}N_4O_{12}Si$: C, 61.20; H, 7.53; N, 6.34; Found: C, 60.82; H, 7.45; N, 5.94.

Cbz-Leucylprolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline)-*O*-Boc-threonine (21). To a solution of SEM ester **20** (1.21 g, 1.37 mmol) in CH_2Cl_2 (14 mL) cooled to 0 °C was added $MgBr_2$ (0.757 g, 4.11 mmol) in one portion. After stirring at 0 °C for 3 h, no starting material remained. The reaction was diluted with ethyl acetate (25 mL) and washed with 10%HCl. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure, affording **21** as a yellow foam which was used without purification in the next step. (1.01 g, crude yield 98%).

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-Hydroxybutyramido]-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (22).** To a solution of tetrapeptide acid **21** (1.01 g, 1.34 mmol) and protected HIP-isostatine (0.663 g, 1.04 mmol) in CH_2Cl_2 (2 mL, 0.6M) was added HATU (0.566 g, 1.49 mmol). The reaction was cooled to 0 °C, DIEA (0.65 mL, 3.72 mmol) was added, and the reaction was allowed to warm slowly to room temperature. After 14 h, the reaction color changed from yellow to dark reddish brown. The reaction was diluted with ether, washed with 10% HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to leave an orange foam. The residue was purified by column chromatography, eluting with acetone/hexanes gradient, to afford 1.84 g of **22** as a white solid (63% yield). **22**: mp 77−80 °C; R_f 0.71 (30:70 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.83−0.99 (m, 30H), 1.04−1.06 (m, 21H), 1.07−1.34 (m, 3H), 1.40 (s, 9H), 1.44−1.56 (m, 3H), 1.71−1.88 (m, 3H), 1.90−2.16 (m, 5H), 2.21−2.27 (m, 1H), 2.65−2.66 (m, 2H), 3.02 (dd, J = 15.5, 5.6 Hz, 1H), 3.14 (dd, J = 15.5, 3.2 Hz, 1H), 3.28 (s, 3H), 3.39−3.47 (m, 2H), 3.65−3.72 (m, 1H), 3.74 (s, 3H), 3.75−3.77 (m, 2H), 4.08−4.11 (m, 2H), 4.34−4.37 (m, 1H), 4.50−4.67 (m, 2H), 4.84−4.87 (m, 1H), 4.92−5.13 (m, 6H), 5.36−5.40 (m, 2H), 6.34 (d, J = 10.1 Hz, 1H), 6.59−6.70 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 7.23−7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 0.3, 17.7, 17.9, 18.1, 20.0, 21.5, 23.4, 24.5, 24.7, 25.8, 27.6, 28.1, 28.2, 28.6, 29.9, 34.8, 37.5, 40.6, 41.7, 45.6, 47.0, 50.9, 52.1, 55.2, 55.9, 56.3, 57.1, 57.5, 65.0, 66.7, 70.1, 71.1, 78.6, 78.8, 79.8, 98.6, 111.0, 113.3, 124.3, 127.9, 128.0, 128.4, 129.2, 132.8, 136.4, 155.3, 156.3, 158.5, 168.3, 169.8, 171.0, 171.1, 171.4; IR (neat) 3330, 2958, 1719, 1680, 1640 cm^{-1}; HRMS m/z calcd for $C_{72}H_{121}N_5O_{16}Si_2Na$ $(M + Na)^+$ 1390.8245, found 1390.8284; $[\alpha]_D^{25}$ −19.95 (c 2.9, $CHCl_3$). Anal. Calcd for $C_{72}H_{121}N_5O_{16}Si_2$: C, 63.17; H, 8.91; N, 5.12; Found: C, 63.06; H, 8.93; N, 5.28.

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-Hydroxybutyramido]-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-4-Hydroxy-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (23).** To a stirred solution of TBDMS ether **22** (0.900 g, 0.660 mmol) in "wet" THF (1.6 mL, distilled but not anhydrous) at ambient temperature was added a 3:1 HOAc:water solution (6.4 mL) in a steady stream. The reaction was allowed to stir 24 h then worked up by removing solvent as an azeotrope with toluene until no acetic acid remained. The compound was purified by column chromatography, eluting with acetone/hexanes gradient, affording **23** as a white solid (0.619 g, 75%); **23**: mp 86−87 °C; R_f 0.33 (50:50 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86−0.94 (m, 21H), 0.97−1.07 (m, 21H), 1.13 (m, 3H), 1.42 (s, 9H), 1.45−1.56 (m, 3H), 1.77−1.83 (m, 3H), 1.91−1.96 (m, 4H),2.04−2.26 (m, 3H), 2.66−2.68 (m, 2H), 3.06−3.18 (m, 2H), 3.38 (s, 3H), 3.43−3.49 (m, 2H), 3.68−3.80 (m, 3H), 3.76 (s, 3H), 4.09−4.14 (m, 2H), 4.32−4.34 (m, 1H), 4.55−4.56 (m, 2H), 4.66−4.68 (m, 2H), 4.90 (d, J = 4.90, 15.0 Hz, 1H), 4.99−5.16 (m, 5H), 5.36−5.52 (m, 3H), 6.62−6.73 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 7.26−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 12.7, 12.9, 14.5, 15.8, 18.1, 19.8, 21.5, 23.4, 24.6, 24.7, 27.5, 27.6, 28.1, 28.3, 28.5, 30.0, 35.2, 36.8, 40.6, 41.6, 45.8, 47.0, 50.9, 52.0, 55.3, 56.3, 57.1, 64.1, 64.2, 66.8, 69.3, 70.5, 70.7, 77.5, 78.3, 79.4, 98.5, 111.1, 113.3, 124.1, 127.9, 128.0, 128.4, 129.2, 132.8, 136.4, 155.0, 156.3, 158.6, 167.9, 168.2, 169.6, 171.2, 171.8; IR (neat) 3334, 2961, 2868, 1718, 1682, 1638, 1506, 1455, 1367, 1253, 1174, 1040, 919 cm^{-1}; HRMS m/z calcd for $C_{66}H_{107}N_5O_{16}SiNa$ $(M + Na)^+$ 1276.7380, found 1276.7361; $[\alpha]_D^{25}$ −27.55 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{66}H_{107}N_5O_{16}Si$: C, 63.18; H, 8.60; N, 5.58; Found: C, 62.83; H, 8.58; N, 5.46.

***N*-[*N*-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-L-(3-carboxy-1,2,3,4-tetra-hydro-7-methoxyisoquinoline), Ester with (3*S*,4*R*,5*S*)-3-Hydroxybutyramido]-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-1-Isopropyl-2-(methoxymethoxy)-**

3-methyl-butanoic Acid Ester (25). To a solution of alcohol **23** (0.595 g, 0.474 mmol) in CH_2Cl_2 (9 mL) was added the Dess−Martin periodinane reagent. After the starting material had been consumed (TLC, 30%acetone/hexanes), the reaction was diluted with ether (60 mL) and 1:1 saturated $Na_2S_2O_3$/saturated $NaHCO_3$ solution or, alternatively, $Na_2S_2O_3$ (898 mg, 5.68 mmol) dissolved in saturated $NaHCO_3$ solution (20 mL) was added. The mixture was stirred until the ether layer became clear (10 min), and then the layers were separated. The organic phase was washed with saturated $NaHCO_3$, water, and brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure to leave an odorous tan foam. The aldehyde was dissolved in DMSO (5 mL). To the solution was added acetonitrile (5 mL) and water (5 mL). The stirring solution became cloudy, and then sodium chlorite (60 mg, 0.664 mmol) and sodium monobasic phosphate hydrate (13 mg, 0.095 mmol) were added. The reaction was stirred for 16 h then diluted with ethyl acetate and cooled to 0 °C. The cooled solution was acidified carefully to pH 3 using 10% HCl. The acid was extracted thrice into ethyl acetate, and the organic phase was concentrated. The oily residue was dissolved in ether and washed with water to remove residual DMSO. The organic phase was dried over Na_2SO_4, and solvent was removed under reduced pressure. Compound **25** was purified by column chromatography, eluting with acetone/hexanes gradient (10%−40%), to yield a white/tan solid (0.504 g, 84%). **25**: mp 76−79 °C; R_f 0.38 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84−0.99 (m, 18H), 1.02−1.04 (m, 21H), 1.13−1.31 (m, 5H), 1.40 (s, 9H), 1.41−1.57 (m, 2H), 1.72−1.78 (m, 2H), 2.04−2.45 (m, 5H), 2.51−2.73 (m, 3H), 3.06 (dd, J = 15.4, 5.2 Hz, 1H), 3.12−3.15 (m, 1H), 3.39 (s, 3H), 3.75 (s, 3H), 3.77−3.83 (m, 3H), 4.06−4.08 (m, 1H), 4.37−4.39 (m, 2H), 4.55−4.70 (m, 4H), 4.78 (d, J = 9.9 Hz, 1H), 4.87 (d, J = 15.1 Hz, 1H), 4.92−5.14 (m, 4H), 5.39−5.50 (m, 3H), 6.61 (m, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.24−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 12.6, 14.5 and 14.7 (RI), 15.8, 17.7, 18.1, 19.0, 21.5, 23.3, 24.5, 24.6, 24.7, 27.3, 28.2, 28.4, 29.7, 29.9, 35.6, 39.5, 40.5, 41.1 and 41.3 (RI), 42.6, 45.8, 47.1, 51.0, 55.3, 56.4, 56.9, 57.3, 58.3, 66.8, 68.7, 70.6, 78.4, 78.9, 80.2, 97.8, 111.2, 113.4, 124.1, 127.7, 127.9, 128.0, 128.2, 128.4, 129.1, 132.6, 136.4, 155.5, 156.3, 158.6, 168.7, 169.5, 171.6, 171.8, 171.9, 175.6; IR (neat) 3325, 2961, 1714, 1650, 1506, 1452, 1170, 1040, 750 cm^{-1}; HRMS m/z calcd for $C_{66}H_{106}N_5O_{17}Si$ $(M + H)^+$ 1268.7352, found 1268.7302; $[\alpha]_D^{25}$ −16.89 (c 0.305, $CHCl_3$).

Cyclo[*N*-*tert*-butyloxycarbonyl)-*O*-[[*N*-[(2S,3S,4S)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]-oxy-3-(methoxymethoxy)-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinolyl)]-L-threonyl] (28). A stirred solution of carbamate **25** (12.3 mg, 9.7 μmol) and 10% Pd/C (200 mg) in absolute ethanol (0.7 mL) was evacuated thrice and placed under a hydrogen atmosphere. The reaction was left under hydrogen atmosphere for 24 h.The catalyst was then filtered and washed with ethanol. The solvent was removed under reduced pressure to provide a tan foam. The amine was used without purification in the next step.

To a solution of amino acid in CH_2Cl_2 (1.5 mL, 0.005 M) was added *O*-(7-azabenzotriazol-1-yl-*N*, *N*, *N*′,*N*′-tetramethyluronium PF_6^- salt (HATU) (4 mg, 0.353 mmol), and the solution was cooled to 0 °C. DIEA (0.061 mL, 0.353 mmol) was added dropwise, and then the reaction was allowed to warm to room temperature. After 18 h, the reaction was diluted with ether, washed with 10% HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting compound was purified by column chromatography, eluting with acetone/hexanes gradient, to afford **28** as an orange/tan foam (6 mg, 61%); **28**: R_f 0.45 (30:70 acetone:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 5H), 0.89−1.04 (m,13H),1.06 (m, 21H), 1.12−1.35 (m, 9H), 1.39 and 1.42 (s, 9H), 1.90−2.09 (m, 5H), 2.15−2.20 (m, 1H), 2.40 (broad, 0.5H), 2.51 (d, J = 6.6, 0.5H), 2.54−2.60 (m, 1H), 2.63 (broad, 0.5H), 2.74−2.80 (m, 0.5H), 2.93 (dd, J = 18.7, 2.3, 1H), 3.13 (m, 1H), 3.32 (dd, J = 16.4, 12.5), 3.37 (s) and 3.39 (s, 3H, RI), 3.46 (q, 1H), 3.69 (dd, J = 12.4, 4.3, 1H), 3.74(s) and 3.78 (s, 3H, RI), 3.88(m) and 3.91 (dd, J = 9.0, 1.6, 1H), 4.11 (t) and 4.20 (m, 1H), 4.35 (q, J = 7.2, 1H), 4.45 (dd, J = 16.4, 2.1) and 4.67 (d, J = 17.1, 1H), 4.53−4.57 (m, 1H), 4.66 (m) and 4.69 (d, J = 6.4, 2H), 4.78 (m,), 4.84 (m, sextet, 1H), 5.03 (d, J = 10.6) and 5.15 (d, J = 6.7, 1H), 5.70 (m, 1H), 6.60 (d, J = 2.4) and 6.63 (d, J = 2.2, 1H), 6.68 (dd, J = 8.3, 2.4) and 6.78 (dd, J = 8.4, 2.5, 1H), 6.93 (d, J = 8.4) and 7.09 (d, J = 8.5, 1H), 7.39 (d, J = 9.5) and 7.52 (d, J = 10.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 13.0, 13.6, 13.6,14.1, 14.6, 17.4, 17.7,18.3, 18.4 18.5, 19.1, 19.1, 19.3, 20.9, 21.2, 22.7, 23.4, 23.6, 24.7, 24.8, 25.1, 25.2, 27.2, 27.4, 27.7, 27.8, 27.9, 28.2, 28.3, 28.8, 28.9, 29.2, 29.7, 31.9, 34.4, 34.7, 39.8, 40.6, 40.9, 42.8 and 43.3 (RI), 44.9, 46.5, 47.1, 48.4, 48.7, 49.9, 54.0, 55.0, 55.2, 55.4, 56.2, 56.3, 57.4, 57.8, 61.6, 68.9, 71.1, 78.7, 79.2, 79.6, 80.1, 80.4, 98.6, 110.3, 111.1, 113.2, 113.6, 122.1, 125.4, 128.9, 130.9, 131.0, 133.3, 133.9, 155.3, 156.0, 158.3, 158.8, 167.9, 168.8, 169.0, 169.4, 170.8, 171.4, 172.2, 174.1, 174.2; HRMS m/z calcd for $C_{58}H_{97}N_5O_{14}SiNa$ $(M + Na)^+$ 1138.6699, found 1138.6705.

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[*N*-[(2*S*,3*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]oxy-3-hydroxy-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinolyl)]-L-threonyl] (30). To a solution of MOM ether **28** (70 mg, 62.7 μmol) in CH_2Cl_2 (0.6 mL) cooled to −78 °C was added 3.0 M Me_2BBr solution in CH_2Cl_2 (0.06 mL, 0.188 mmol) dropwise. After 1 h, the reaction was treated with a 3:1 THF:saturated $NaHCO_3$ solution (0.06 mL) at −78 °C, stirred 5 min, and then warmed to RT and diluted with ether. The aqueous layer was separated, and the organic phase was washed successively with water, 10% $NaHSO_4$, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by column chromatography, eluting with 20% acetone/hexanes, affording **30** as a white powder (59.6 mg, 87%). **30**: R_f 0.43 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84−0.95 (m, 18H), 1.00−1.13 (m, 21H), 1.14−1.35 (m, 6H), 1.39 (s) and 1.42 (s, 9H, RI), 1.44−1.60 (m, 4H), 1.90 (m, 2H), 1.97−2.28 (m, 4H), 2.29−2.35 (m, 1H), 2.47 (dd, J = 18.4, 6.8) and 2.53 (d, J = 17.1, 1H), 2.65 (m) and 2.73 (dd, J = 15.4, 7.8, 1H), 2.93 (m), 3.10 (dd, J = 16.5, 5.2) and 3.20 (d, J = 14.8, 2H) 3.31 (dd, J = 16.5, 12.6) and 3.46 (q, 1H), 3.62−3.76 (m, 2H), 3.73 (s) and 3.78 (s, 3H, RI), 3.86 (d, J = 8.0) and 3.91 (d, J = 9.1, 1H), 3.99 (m) and 4.12 (t, 1H), 4.23 (t) and 4.33 (t,1H), 4.48−4.65 (m, 3H), 4.69 (d, J = 3.7) and 4.72 (d, J = 7.8) and 4.76 (t, 2H), 4.85 (m, 1H), 4.92 (m, 1H), 4.97 (d, J = 10.6) and 5.18 (d, J = 7.3), 5.03 (br) and 5.41 (br) and 5.69 (m,1H), 6.50 (br), 6.59 (d, J = 2.2) and 6.63 (d=2.4, 1H), 6.67 (dd, J = 7.2, 2.4) and 6.78 (dd, J = 8.5, 2.5, 1H), 6.91 (d, J = 8.4) and 7.09 (d, J = 8.6, 1H), 7.37 (d, J = 7.6) and 7.43 (dd, J = 10.2, 3.0, 2H); ^{13}C NMR**:** (125 MHz, $CDCl_3$) δ 12.1, 12.9, 13.5, 13.6, 14.7, 17.6, 18.2, 18.4, 18.5, 18.5, 19.2, 20.9, 21.1, 23.4, 23.6, 24.7, 24.8, 25.1, 25.1, 27.2, 27.7, 28.0, 28.2, 28.3, 28.7, 29.0, 29.6, 31.8, 34.4, 34.7, 34.8, 39.8, 40.1, 41.0, 43.4, 45.0, 45.2, 46.5, 47.1, 48.2, 49.8, 54.2, 55.2, 55.2, 55.4, 56.0, 57.4, 57.8, 69.0, 71.0, 72.0, 73.1, 79.1, 80.2, 80.4, 110.4, 111.1, 113.2, 113.6, 122.1, 125.4, 128.8, 131.0, 133.3, 133.9, 155.3, 156.1, 158.3, 158.8, 167.9, 169.1, 169.5, 170.8, 171.5, 172.1, 172.2, 173.7; IR (neat) 3326, 2924, 2852, 2364, 1734, 1636 cm^{-1}; HRMS m/z calcd for $C_{56}H_{93}N_5O_{13}SiNa$ $(M + Na)^+$ 1094.6436, found 1094.6460; $[\alpha]_D^{25}$ −15.17 (c 0.15, $CHCl_3$).

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-[(triisopropylsilyl)oxy]-5-methylheptanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinolyl)]-L-threonyl] (32). To a solution of alcohol **30** (27.3 mg, 25.5 μmol) in CH_2Cl_2 (1.8 mL) was added Dess−Martin periodinane (DMP) (24 mg, 57 μmol). After 2 h, starting material still remained so another 3 equiv of DMP was added, and the reaction allowed to stir another 2 h. The reaction was diluted with ether (7 mL) and treated with 2 mL of 1:1 saturated $Na_2S_2O_3$/saturated $NaHCO_3$ solution and added $Na_2S_2O_3$ (24 mg). The mixture was stirred until the ether layer

became clear (10 min), and then the layers were separated. The organic phase was washed with sat. $NaHCO_3$, water, and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a white foam. The product was purified by column chromatography, eluting with 20% acetone/hexanes, affording **32** as a white foam (25.7 mg, 94%). R_f 0.49 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83−0.98 (m, 18H), 1.02−1.12 (m, 21H), 1.14−1.30 (m, 9H), 1.39 and 1.44 (s, 9H), 1.52−1.71 (m, 2H), 1.78−1.90 (m, 1H), 1.98−2.25 (m, 2H), 2.55−2.63 (m, 1H), 2.67 (dd of ABX, J = 14.8, 3.2) and 2.72 (m, 1H), 2.93 (dd, of ABX, J = 16.7, 4.1) and 3.17 (m, 2H), 3.33 (dd, J = 16.3, 12.5) and 3.45 (q, 1H), 3.56 (q, 1H) and 3.68 (m, 1H), 3.74 and 3.78 (s, 3H), 3.80−3.95 (m) and 3.92 (q, 1H), 4.13 and 4.27 (t, 1H), 4.36−4.63 (m, 4H), 4.72−4.84 (m, 2H), 4.90 (m, 1H), 4.95 (d, J = 4.0) and 5.01 (m, 1H), 5.09 (d, J = 10.3) and 5.17 (d, J = 7.7, 1H), 5.66 (m, 1H), 6.60−6.68 (m, 1H) and 6.78 (dd, J = 7.4, 2.1) and 6.86 (d, J = 8.3), 7.05 (d, J = 6.8) and 7.09 (d, J = 8.5, 1H), 7.38 (m) and 7.43 (d, J = 10.6, 1H), 7.70 (d, J = 9.0) and 8.45 (d, J = 8.3, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 11.9, 12.0, 12.9, 13.3, 13.8,14.1, 14.4, 14.7, 15.3, 15.9, 17.2, 17.5 18.1,18.1, 18.2, 18.3,18.4, 18.4, 18.4, 18.5, 18.5, 18.7, 20.3, 20.8, 21.1, 23.3, 23.6, 24.8, 24.9, 25.2, 26.8, 27.2, 27.4, 28.1, 28.2, 28.3, 28.3, 28.4, 28.5, 28.9, 29.3, 29.4, 29.6, 29.7, 30.3, 30.4 31.9, 32.0, 33.4, 33.7, 39.5, 39.8, 40.3, 41.8, 45.2, 46.4, 47.1, 48.3, 49.6, 49.9, 50.0, 52.5, 54.1, 55.2, 55.4, 55.6, 56.1, 56.3, 57.4, 57.5, 58.0, 69.3, 69.4, 69.9, 71.0, 80.1, 80.3, 80.4, 81.8, 110.2, 111.2, 113.2, 113.8, 114.1, 121.8, 125.3, 126.9, 127.2, 127.8, 127.9, 127.9, 127.9, 128.0, 128.2, 128.7, 129.7, 131.0, 131.8, 133.2, 133.4, 133.8, 155.6, 156.4, 158.3 and 158.9 (RI), 167.8, 168.6, 169.3, 169.4, 169.7, 170.9, 171.1, 171.4, 171.4, 171.6, 172.0, 172.6, 202.5 and 204.5 (RI); IR (neat) 3341, 2961, 2868, 2361, 1733, 1716, 1700, 1683, 1670, 1652, 1646 cm^{-1}; HRMS *m/z* calcd for $C_{56}H_{91}N_5O_{13}SiNa$ $(M + Na)^+$ 1092.6280, found 1092.6233.

Cyclo-*N*-L-lactyl-L-prolyl-*N*-methyl-D-leucine[*O*-[[*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-L-(3-carboxy-1,2,3,4-tetrahydro-7-methoxyisoquinolyl)]-L-threonyl] (3). A solution of Boc-ketone **32** (5.9 mg) in HPLC grade EtOAc was cooled to −30 °C and purged with argon. HCl gas was bubbled through the solution via a submerged pipet. The reaction was equipped with an oil bubbler and then a water scrubber. As the gas bubbled the reaction was maintained at −15 °C for 40 min, and then the flow was stopped. A stir bar was added, and the reaction was warmed to 0 °C and left stirring for 3.5 h. The flask was purged with argon and the reaction mixture concentrated. The residue was carefully triturated three times using 4:1 hexane:methyl *tert*-butyl ether solution, and the reaction was concentrated to afford a tan powder. The salt (4.6 mg, 5.61 μmol) was dissolved in CH_2Cl_2, and the didemnin B side chain (2 mg, 6.17 μmol) was added. At room temperature, HATU (2.5 mg, 6.73 μmol) and DIEA (4 μL, 20.4 μmol) were added to the solution. After stirring 14 h, the reaction was diluted with ether and washed with 10% HCl, saturated $NaHCO_3$, and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography, eluting with 30%−50% acetone/hexanes gradient, to afford **3** a white powder (4.6 mg, 74%); R_f 0.59 (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82−0.95 (m, 12H), 0.98−1.05 (m, 6H), 1.08−1.49 (m, 6H), 1.53−1.68 (m, 3H), 1.71−1.92 (m, 3H), 1.96−2.05 (m, 8H), 2.21 (m, 2H), 2.26−2.38 (m, 3H), 2.54−2.59 (m, 2H), 2.87−3.17 (m, 3H), 3.13 (s) and 3.15 (s, 3H), 3.18−3.32 (m, 1H), 3.41−3.48 (m, 1H), 3.51−3.71 (m, 4H), 3.73−3.80 (m, 2H), 3.79 (s, 3H), 4.01−4.16 (m, 4H), 4.17−4.23 (m, 1H), 4.32−4.39 (m, 2H), 4.49−4.65 (m, 2H), 4.70−4.90 (m,-3H), 5.18−5.25 (m, 1H), 5.32−5.39 (m, 2H), 6.61 (m) and 6.70 (d, J = 2.6, 1H), 6.79 (m, 2H), 7.07−7.13 (m, 3H), 7.25−7.34 (m, 1H), 7.47−7.53 (m, 1H), 7.68−7.77 (m, 1H), 7.90 (d, J = 9.2, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 11.8, 12.0, 13.2, 14.1, 14.1, 14.9, 15.4, 15.5, 16.1, 16.3, 16.7, 18.8, 18.8, 20.2, 20.8, 21.1, 21.2, 21.4, 22.7, 23.0, 23.4, 23.7, 23.8, 24.8, 24.8, 25.2, 26.0, 26.7, 27.1, 27.2, 27.4, 28.1, 28.2, 28.4, 28.9, 29.0, 29.1, 29.1, 29.2, 29.4, 29.5, 29.7, 30.0, 30.2, 30.3, 30.4, 31.0, 31.1, 31.3, 31.3, 31.4, 31.9, 33.6, 33.7, 33.7, 36.0, 36.2, 38.7, 41.1, 41.7, 47.1, 47.2, 49.0, 49.3, 49.8, 50.0, 54.5, 54.6, 54.8, 54.9, 55.3, 55.4, 55.4, 56.0, 56.7, 57.7, 57.8, 65.9, 66.0, 67.8, 68.6, 68.8, 71.3, 77.6, 77.8, 78.1, 78.4, 78.5, 78.7, 78.8, 79.0, 79.2, 79.3, 79.4, 79.5, 79.6, 81.0, 81.2, 110.2, 111.6, 113.1, 113.7, 113.9, 127.8, 128.8, 128.8, 130.9, 131.0,143.6, 156.2, 158.8, 167.5, 169.4, 169.9, 170.2, 170.8, 171.4, 171.6, 172.8, 173.0,-174.0, 205.1; IR (neat) 3316, 2963, 2922, 1726, 1641 cm^{-1}; HRMS *m/z* calcd for $C_{57}H_{87}N_7O_{15}Na$ $(M + Na)^+$ 1132.6157, found 1132.6155; $[\alpha]_D^{25}$ −20.85 (*c* 0.24, $CHCl_3$).

Acknowledgment. We gratefully acknowledge the National Institutes of Health (CA-40081), the NSF (CHE 99-01449), UNCF·Merck Science Initiative, and the University of Pennsylvania for financial support. We also thank Dr. Peter Toogood and Dr. Deepika Ahuja at the University of Michigan for the biological testing.

JO0105991