alkene: ^{13}C NMR (90 MHz) δ 170.0 (s, C15), 168.1 (s, C9), 139.2 (d, C1), 134.5 (s, C11), 129.0 (d, C14), 128.6 (d, C13), 127.7 (d, C12), 125.8 (d, C2), 76.4 (d, C3), 74.8 (d, C10), 42.8 (d, C1'), 34.4 (t, C4), 32.8 (t, C2'), 31,4 (t, C6), 25.1 (t, C3'), 24.4 (t, C5), 22.4 (t, C7), 20.7 (q, C16), 13.8 (q, C8); ^{1}H NMR (361 MHz, acetone-d_6) δ 7.46 (m, 5 H), (s, 1 H), 5.68 (dd, J = 7.6, 15.5 Hz, 1 H), 5.41 (ddd, J = 1.4, 6.1, 15.5 Hz, 1 H), 5.20 (q, J = 6.1 Hz, 1 H), 2.42 (hx, J = 7.6 Hz, 1 H), 2.12 (s, 3 H), 2.08–0.94 (m, 16 H), 0.78 (t, J = 6.8 Hz, 3 H); IR, 2925, 2850, 1738, 1660, 1208, 1050 cm^{-1}.

The O-acetylmandelic acid esters were also prepared from racemic **23**, providing both the above as well as a second diastereomer: ^{13}C NMR (90 MHz) δ 170.0 (s, C15), 168.2 (s, C9), 139.0 (d, C1), 134.3 (s, C11), 129.0 (d, C14), 128.7 (d, C13), 127.8 (d, C12), 125.6 (d, C2), 76.3 (d, C3), 74.8 (d, C10), 42.6 (d, C1'), 34.5 (t, C4), 32.8 (t, C2'), 31.6 (t, C6), 25.1 (t, C3'), 24.8 (t, C5), 22.5 (t, C7), 20.7 (q, C16), 13.9 (q, C8); ^{1}H NMR (361 MHz, acetone-d_6) δ 7.46 (m, 5 H), 5.86 (s, 1 H), 5.68 (dd, J = 7.6, 15.5 Hz, 1 H), 5.37 (dd, J = 6.1, 15.5 Hz, 1 H), 5.25 (m, 1 H), 2.30 (hx, J = 7.6 Hz, 1 H), 2.12 (s, 3 H), 2.08–0.94 (m, 16 H), 0.78 (t, J = 6.8 Hz, 3 H).

***exo-cis*-Bicyclo[3.3.0]oct-3-en-2-ol (26).** To 1.41 g (3.78 mmol) of sulfinamide (*S*)-**12** in 30 mL of CH_2Cl_2 in a −10 °C bath were added 0.99 mL (5.7 mmol) of Huenig's base and then 1.44 g (7.56 mmol) of triethyloxonium tetrafluoroborate. After the solution was stirred for 30 min, the solvent was removed and the mixture was partitioned between 0.1 N HCl and EtOAc. The organic layer was washed with 0.1 N NaOH and then a saturated NaCl solution. After the solution was filtered through cotton, the solvent was removed, yielding a light yellow oil. This N-ethylsulfinamide was reacted in 30 mL of ether at −78 °C with a 3.8-mL solution of 3.0 N (11 mmol) phenylmagnesium bromide, stirring for 40 min. Then the reaction was quenched with a solution of 0.60 g (11 mmol) of NH_4Cl in 30 mL of MeOH followed immediately by 5.2 mL (20 mmol) of piperidine. This mixture was allowed to warm to room temperature and was then heated at reflux for 40 h. The solvent was removed, and the resulting oil was filtered through a chromatography-grade silica gel, eluting with a 2:1 mixture of Skelly B–EtOAc. Preparative chromatography yielded 0.28 g (62%) of the exo alcohol as well as 0.67 g (71%) of *trans*-2-phenylcyclohexyl N-ethylcarbamate (**28**).

For N-ethyl-N-[[*trans*-(2-phenylcyclohexyl)oxy]carbonyl]bicyclo-[3.3.0]-3-oct-2-enesulfinamide: ^{13} NMR (90 MHz) δ 153.8, 143.3, 143.2 (C4), 128.5, 127.2, 126.4 123.8 (C3), 78.4 (C2), 78.1, 50.7 (C5), 49.8, 40.6 (C1), 35.3 (C1'), 34.4, 33.7 (C8), 32.5, 31.1 (C6), 25.9, 24.8, 24.8 (C7), 15.3 (C2').

For exo alcohol: $[\alpha]^{25}_D$ +171.4° (c = 1.4, EtOH) derived from (*S*)-**1**; ^{13}C NMR (90 MHz) δ 139.8 (C4), 132.2 (C3), 85.5 (C2), 51.8 (C5), 49.4 (C1), 32.4 (C6), 30.7 (C8), 24.8 (C7); ^{1}H NMR (361 MHz) δ 5.80 (dd, J = 2.7, 6.8 Hz), 5.74 (ddd, J = 2.2, 2.2, 6.8 Hz, 1 H), 4.45 (d, J = 2.2 Hz, 1 H), 3.34 (m, 1 H), 2.44 (m, 1 H), 0.75–1.80 (m, 7 H); IR, 3590, 2940, 2830, 1250, 895, 730 cm^{-1}; MS, m/e 123, 96, 95, 91.

For the N-ethylcarbamate **28**: ^{13}C (90 MHz) δ 156.1 (s), 143.6 (s), 128.2 (d), 127.6 (d), 126.2 (d), 76.1 (d), 50.2 (d), 35.7 (t, C1), 34.4 (t), 32.9 (t), 26.0 (t), 24.8 (t), 15.1 (q, C2); ^{1}H NMR (361 MHz) δ 7.07–7.42 (m, 5 H), 4.86 (dt, J = 4.2, 10.8 Hz, 1 H), 4.36 (brs, 1 H), 2.98 (brs, 2 H), 2.62 (m, 1 H), 2.22 (brd, J = 10.8 Hz, 1 H), 1.95–1.65 (m, 3 H), 1.10–1.60 (m, 4 H), 1.00–0.70 (brs, 3 H); IR, 3445, 3043, 2980, 2935, 1714, 1422, 1265, 897 cm^{-1}; MS, m/e 176, 159, 158, 157, 143, 132, 131, 130, 129, 128, 117, 116, 115, 105, 104, 103, 98, 92, 91.

Recovery of Chiral Auxiliary *trans*-2-phenylcyclohexanol [(*R*)-1]. To 435 mg (1.76 mmol) of *trans*-2-phenylcyclohexyl N-ethylcarbamate (**28**) in 14 mL of THF at 0 °C was added 201 mg (5.28 mmol) of $LiAlH_4$. The mixture was stirred for 15 min, allowed to warm to room temperature, and then heated at reflux for 14 h. Saturated aqueous Na_2SO_4 was added until no more H_2 gas evolution could be detected, and then excess Na_2SO_4 was added to adsorb the water. The salts were removed by vacuum filtration and washed with EtOAc. Concentration of the filtrate afforded 288 mg (93%) of a crystalline material (mp 62–63 °C) that was clean alcohol (*R*)-**1** by ^{13}C NMR analysis [$[\alpha]^{25}_D$ −58.3° (c = 23.5, MeOH)].

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Supplementary Material Available: Full experimental details for the synthesis of all compounds listed in Tables I–IV not otherwise provided (19 pages). Ordering information is given on any current masthead page.

Total Synthesis and Structural Investigations of Didemnins A, B, and C

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Contribution from the Department of Chemistry of the University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323. *Received April 19, 1990*

Abstract: Didemnins A, B, and C, cyclodepsipeptides isolated from a marine tunicate of the family *Didemnidae*, were efficiently prepared in a stereocontrolled manner, producing the common macrocycle and, in a separate step, introducing the substituents on the amino group of L-threonine as optically pure units. We envisaged that disconnections between L-leucine and the HIP group (2*S*,4*S*) and between L-threonine and isostatine (3*S*,4*R*,5*S*) would afford two units: a HIP-isostatine unit (I) and a tetrapeptide unit (II). The HIP-isostatine unit was synthesized stereoselectively, and a convergent strategy was used to construct the tetrapeptide. The two units were coupled to afford a linear precursor which was cyclized after appropriate functionalization. Macrocyclization was accomplished at the carboxylic acid of the HIP unit and the free amino group of leucine by using diphenylphosphoryl azide (DPPA). After selective deprotection of the hydroxyl and amino groups of the macrocycle, the substituents attached to the amino group of L-threonine were introduced by using benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP).

Introduction

In 1981, a new class of cyclodepsipeptides, the didemnins (**1**), were isolated from a Caribbean tunicate of the family *Didemnidae* (*Tridemnum genus*).[1] These marine invertebrates have been found in waters off the coasts of Colombia, Honduras, Mexico, Belize, and Panama. *Tridemnum solidum* and *Tridemnum cyanophorum* both have been reported to contain didemnins.[2,3] Originally, five active components were isolated, didemnins A–E. Lower homologs, the nordidemnins, were also found. More re-

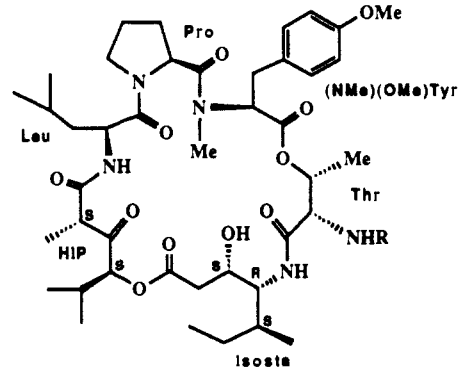
(1) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857.

(2) Banaigs, B.; Jeanty, G.; Francisco, C.; Jouin, P.; Poncet, J.; Heitz, A.; Cave, A.; Prome, J. C.; Wahl, M.; Lafargue, F. *Tetrahedron* **1989**, *45*, 181.

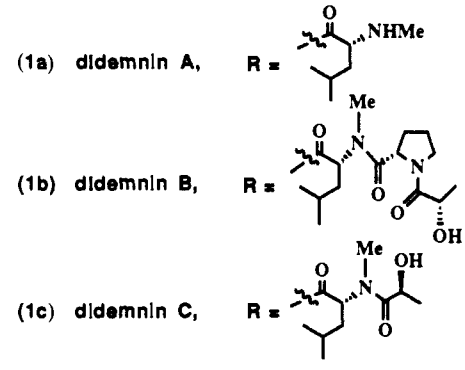
(3) Guyot, M.; Davoust, D.; Morel, E. *C. R. Acad. Sci. Ser.* **1987**, *305*, 681.

0002-7863/90/1512-7659$02.50/0

cently, additional cyclic depsipeptides, didemnins X and Y, have been isolated from *Tridemnum solidum*.[4] All didemnins contain a common macrocycle, and differ only in the side chains attached to the backbone through the amino group of threonine. Didemnin A (**1a**) has D-*N*-methylleucine in its side chain. The other didemnins are derivatives of didemnin A and have different residues attached to the *N*-methylamino group of D-*N*-methylleucine (**1b** and **1c**). In our discussion, we will refer to the appendages attached to the macrocycle via the amino group of threonine as "side chains".

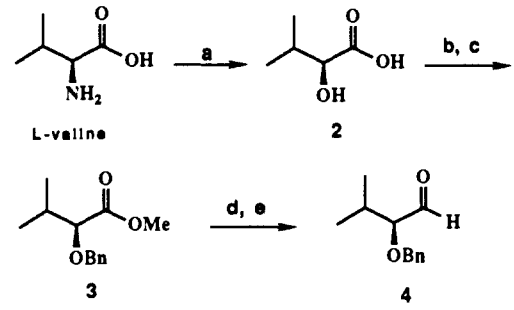


(1)



Didemnin A is the most abundant component of the tunicate extracts. Most of the other didemnins and nordidemnins have been isolated in amounts too small for biological testing. Though less abundant than didemnin A (**1a**), didemnin B (**1b**) is the most active congener tested so far. Didemnin B has shown high cytotoxicity, specific antiviral activity against some previously uncontrollable lethal viruses, and potent immunosuppressive activity both in vivo and in vitro. A remarkable characteristic of the didemnins is the relationship between the side chains attached to **1d** and the biological activities.[5-7] The unique structural features of the didemnins, their potent and diverse biological activities, and their present scarcity have stimulated many structural[3,8-11] and synthetic investigations.[12-17]

Scheme I[a]



[a] (a) 1 N H_2SO_4, $NaNO_2$, 57%; (b) MeOH, H_2SO_4 (catalyst), 87%; (c) benzyl 2,2,2-trichloroacetimidate, CF_3SO_3H (catalyst), C_6H_{12}/CH_2Cl_2 (2:1), 80%; (d) $LiAlH_4$, Et_2O, 89%; (e) SO_3·pyr, DMSO/CH_2Cl_2 (1:10), Et_3N, 68%.

Results and Discussion

Structural Investigations. Originally, the didemnins were structurally characterized by spectroscopic and degradative studies.[18] The most difficult assignments were those involving the stereochemistry of the α-(α-hydroxyisovaleryl)propionyl (HIP) unit and the structure of the nonproteinogenic β-hydroxy-γ-amino acid in the macrocycle. In the early investigations, the stereochemistry of the HIP unit was established by degradative studies of didemnin A. Because of the possible ambiguities in the method used to assign the absolute configuration and because of the uncertainties associated with the use of coupling constants to determine the stereochemistry of substituted γ-lactones,[19] we decided to confirm the validity of the reported assignments by using synthetic methods[8] to prepare all possible stereoisomers corresponding to the γ-butyrolactone isolated from the degradation of **1a**. To this end, we envisaged an aldol condensation on an appropriately protected aldehyde. The amino acid valine was chosen as the source of chirality, since it could be obtained in both D- and L-forms. For the synthesis of the reported 2*R**,3*R**,4*R** reduced cyclo-HIP, the desired aldehyde (**11**) was obtained from D-valine by the same procedure used to prepare its epimer from L-valine, as shown in Scheme I. Conversion of L-valine to the corresponding α-hydroxy acid **2** was accomplished by using a well-known procedure[20] that affords overall retention of configuration via a double inversion. We improved the yield of this reaction and obtained a crystalline product by the slow simultaneous addition of 2 N sulfuric acid and sodium nitrite. Esterification was carried out by using standard acid catalysis, and the corresponding α-hydroxy methyl ester was protected as its benzyloxy derivative (**3**). Initial attempts at benzylation with benzyl bromide, in the presence of sodium hydride or silver oxide, gave low yields of **3**. However, the use of benzyl 2,2,2-trichloroacetimidate and a catalytic amount of triflic acid afforded the desired compound in high yield and shorter reaction time.[21] Conversion of the ester function (**3**) to an aldehyde (**4**) was accomplished in a sequential manner, by first reducing the ester to the corresponding alcohol and then oxidizing the alcohol with SO_3·pyridine

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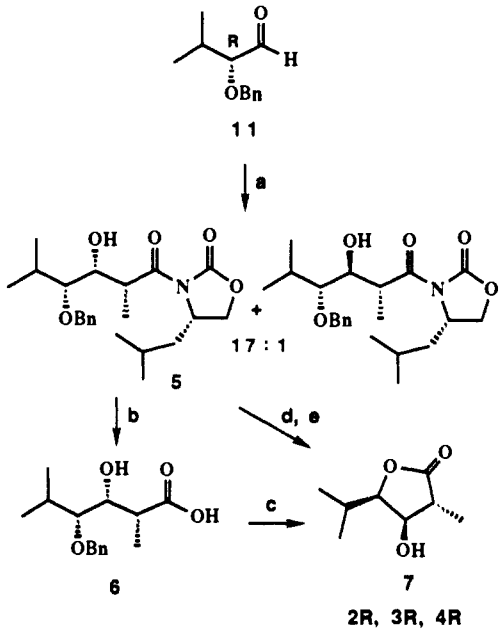
Scheme II[a]



[a](a) , Bu_2BOTf, iPr_2NEt, CH_2Cl_2, 89%; (b) 2 N KOH 78%; (c) H_2, Pd/C, MeOH/EtOAc (4:1), 68%; (d) H_2, Pd/C, dioxane/EtOAc (4:1), 65%; (e) imidazole, CH_2Cl_2, 81%.

complex in the presence of DMSO and triethylamine. The epimeric *R*-aldehyde was obtained by a similar reaction sequence. We then set the stereochemistry at C-2 and C-3 via an Evans aldol condensation, with the stereochemistry of the 4-position derived from the stereogenic centers of the *R*- and *S*-forms of the aldehyde. Assignment of the stereocenters was based on the determined configurations of the corresponding dihydrotetronic acid derivatives. Conversion of the aldol products to the corresponding tetronic acids could be accomplished either by (1) treatment with aqueous potassium hydroxide followed by debenzylation under reductive catalytic conditions to give a γ-hydroxy acid that cyclized spontaneously or (2) by debenzylation followed by treatment with imidazole,

The product, which corresponded to the reported reduced cyclo-HIP obtained from didemnin A, was synthesized as shown in Scheme II. The *N*-propionyloxazolidinone derived from L-leucine was treated with di-*n*-butylboryl triflate and diisopropylethylamine in CH_2Cl_2, at 0 °C, followed by addition of the *R*-aldehyde derived from D-valine, at −78 °C. Diastereomer **5** (syn) was converted to the corresponding lactone **7**. The correct stereochemistry (2*R*,3*R*,4*R*) of the reduced cyclo-HIP was confirmed by a single-crystal X-ray analysis. The ^{1}H-NMR spectra of this compound was identical with that reported in the literature.[18] Comparison of the optical rotation of this product to the rotation of the compound isolated from didemnin A revealed that these rotations were of the same magnitude but of opposite signs. Although we had also obtained the 2*S*,3*S*,4*S* enantiomer by using the aldol approach, in order to further support our assignment we synthesized the corresponding cyclo-HIP **10** by a different route (Scheme III). By using a similar protocol to that reported by Kelly,[22] methyl (*S*)-2-hydroxy-3-methylbutanoate (prepared from L-valine) was condensed with 2-bromopropionyl bromide. The resulting bromo diester **9** was then subjected to an intramolecular Grignard reaction, by using magnesium in ether with sonication. The resulting product had an optical rotation that agreed both in sign and magnitude with that reported for the cyclo-HIP obtained from the didemnins.[18] On the basis of these results, we reassigned the stereochemistry of the HIP unit as 2*S*,4*S*.[8] The

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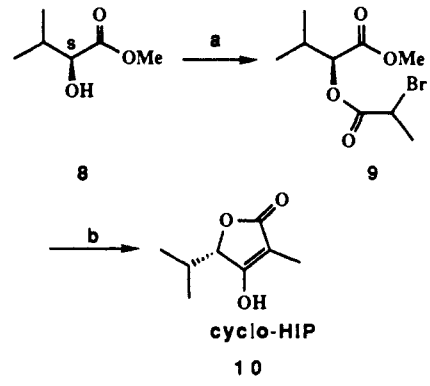
Scheme III[a]



[a](a) 2-Bromopropionyl bromide, 65%; (b) Mg, Et_2O, sonication, 42%.

absolute configuration of this unit was also reexamined by Rinehart and co-workers,[23] Finally, in 1988 a crystal structure analysis of didemnin B confirmed the stereochemistry of the HIP unit.

Another ambiguity in the earlier structural determination, the structure of the β-hydroxy-γ-amino acid in the macrocycle, was also resolved. This unit was shown to be 3*S*,4*R*,5*S*-isostatine rather than 4*R*,5*S*-statine, thereby confirming the results of French investigators.[3] The structure of this nonproteinogenic amino acid had been uncertain, due to the difficulties involved in assigning the position of the methyl group on the chain by using ^{1}H NMR studies on didemnin B. In our laboratory, we had devised practical syntheses for all the stereoisomers of both statine and isostatine,[24,25] The synthesis of 3*S*,4*R*,5*S*-isostatine used Boc-D-alloleucine as the precursor. This compound was treated with 1,1'-carbonyldiimidazole (CDI) in THF to produce the corresponding imidazolide, which was not isolated but treated directly with *tert*-butyl lithioacetate at −78 °C to afford the corresponding β-keto ester in 79% overall yield. Reduction of this compound with potassium borohydride produced a mixture (10.5:1) of chromatographically separable diastereoisomers, the desired isomer being formed in excess. The stereochemistry of this product was verified by converting this compound to an oxazolidine that was subjected to decoupling experiments. The coupling constant between the ring protons was 5,2 Hz, indicative of a cis relationship and therefore confirming the 3*S*,4*R*,5*S* assignment.[25]

Synthetic Strategy. Although there have been several syntheses of the didemnins, our approach to the total syntheses of didemnins A, B, and C is unique, in that we chose to focus on stereocontrolled routes to the macrocycle and envisioned the introduction of the side chains on the amino group of L-threonine as a separate step so that these could be introduced as optically pure units.

In previous syntheses, cyclization was accomplished between the following residues: Pro-Leu,[14] Ile-Thr,[12] *N*,*O*-Me_2Tyr-Pro.[13] In all but one of these investigations, D-*N*-MeLeu side chain was incorporated before cyclization.[14] Only Schmidt and co-workers[14] protected the threonine as its Cbz derivative. In all previous syntheses, the linear precursor leading to the macrocycle was prepared in a nonstereoselective manner. Specifically, the stereochemistry of the 2-methyl group found in the HIP unit was not controlled. In the macrocycle, the 3-keto group and the amide cannot lie in the same plane, and therefore racemization at the 2-position cannot occur readily. We sought to preserve the stereochemistry of the HIP unit by introducing the keto group after cyclization had been accomplished. To this end, we kept the 3-keto function masked as a methoxymethyl-(MOM) protected

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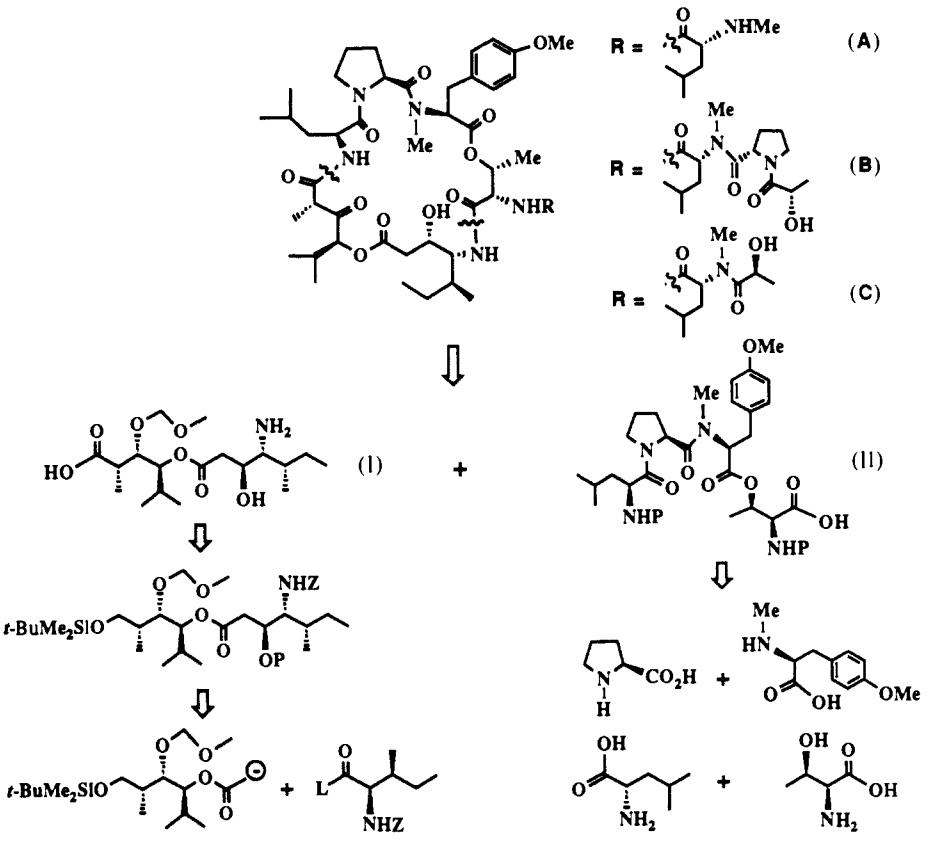
Scheme IV. Retrosynthetic Analysis



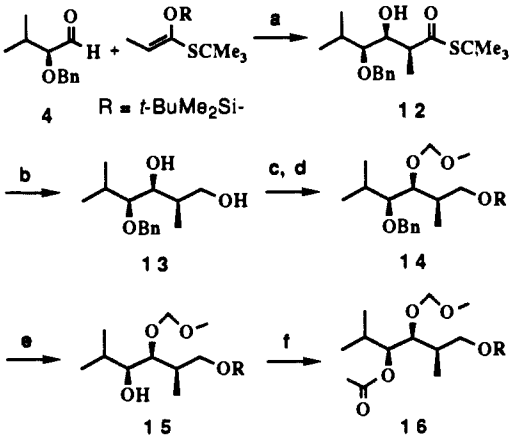
alcohol. Furthermore, we sought to prepare the macrocycle itself,[17] in order to further investigate the effects of the side chains on the ring conformation, and to facilitate the syntheses of other analogues.

For the retrosynthetic analysis of the didemnins (Scheme IV), we envisaged disconnection of the amide function between L-leucine and the HIP unit (2*S*,4*S*) and between L-threonine and isostatine (3*S*,4*R*,5*S*) to afford two units: a HIP-isostatine unit (I) and a tetrapeptide unit (II). The synthesis of the HIP-isostatine unit was accomplished using methodology previously developed in our laboratories.[24,25] To carry out this strategy, a suitably activated and protected D-alloisoleucine was condensed with the enolate of HIP-acetate.

Synthesis of the HIP-Isostatine Unit (I). Preparation of the HIP-acetate is shown in Scheme V. Our approach began with (*S*)-2-(benzyloxy)-3-methylbutanal (**4**). As previously noted, the keto group was masked as a suitably protected alcohol. A chelation-controlled aldol condensation reported by Gennari was employed.[26] By using tin tetrachloride as the chelation-controlling reagent, the (*E*)-silylketene thioacetal was condensed with the aldehyde (**4**) to afford the syn diastereomer (**12**) as the only observable product. Reduction to the diol **13** with lithium aluminum hydride (LAH) occurred in 92% yield. In contrast with this protocol, Evans' methodology, with use of the oxazolidinone, afforded low yields for the reduction to the diol. The thioester **12** reduced cleanly and rapidly to give a crystalline diol **13**. The primary hydroxyl group was protected selectively with *tert*-butyldimethylsilyl chloride in the presence of triethylamine and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), in 94% yield. The secondary alcohol was then converted to its MOM derivative (**14**). After various attempts to remove the benzyl group catalytically, sodium in liquid ammonia afforded a high yield of alcohol **15**. Examination of its Mosher's ester, by using ^{19}F NMR, revealed a 94% ee. Treatment of this alcohol **15** with acetic anhydride in the presence of DMAP gave the desired HIP-acetate **16**.

(26) Gennari, C.; Beratta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

Scheme V[a]

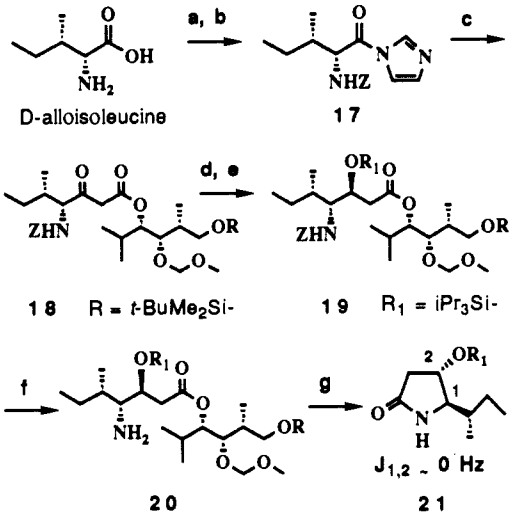


[a] (a) 1. LDA, THF/HMPA, *t*-BuMe$_2$SiCl, 2. SnCl$_4$, CH$_2$Cl$_2$, 74%; (b) LiAlH$_4$, ether, 92%; (c) *t*-BuMe$_2$SiCl, DMAP, Et$_3$N, 99.8%; (d) CH$_3$OCH$_2$Cl, iPr$_2$NEt, CH$_2$Cl$_2$, 96%; (e) Na, NH$_3$, THF, −78 °C, 82%; (f) (MeCO)$_2$O, DMAP, CH$_2$Cl$_2$, 90%.

The formation of the HIP-isostatine unit is shown in Scheme VI. Treatment of D-alloisoleucine with *N*-[[(benzyloxy)-carbonyl]oxy]-5-norbornene-2,3-dicarboximide followed by conversion of the carboxylic acid to the imidazolide, with use of CDI, gave compound **17**. The imidazolide (**17**) was directly condensed with the lithium enolate of the HIP-acetate (**16**) to afford β-keto ester **18** in 76% overall yield from D-alloisoleucine.

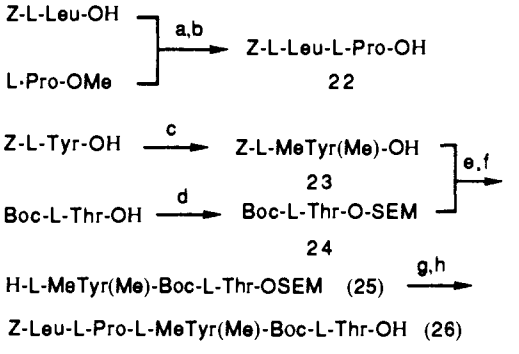
For the reduction of β-keto esters of this type, we had found that potassium borohydride in ethanol gave the highest selectivity for the anti diastereomer.[25] Treatment of compound **18** with potassium borohydride in ethanol, followed by treatment of the resulting diastereomeric mixture with triisopropylsilyl triflate, gave a chromatographically separable mixture of two silyl ethers. The ratio of these two diastereomers was found to be 12.6:1 by HPLC analysis. The carbobenzyloxy group of the major anti diastereomer **19** was removed by catalytic hydrogenation. Confirmation of the

Scheme VI[a]



[a](a) *N*-[[(benzyloxy)carbonyl]oxy]-5-norbornene-2,3-dicarboximide, Et_3N, THF, H_2O; (b) CDI; (c) LDA, THF, **16**, a–c = 76%; (d) KBH_4, EtOH, 83%; (e) iPr_3SiOTf, 2,6-lutidine, 93%; (f) H_2, Pd/C, 100%; (g) imidazole, MeOH, 100%.

Scheme VII[a]



[a](a) DCC, HOBT, *N*-methylmorpholine, CH_2Cl_2, 96%; (b) LiOH, 0 °C, 94%; (c) 1. Me_2SO_4, KOH, $Bu_4N^+HSO_4^-$, THF, 2. H_2O, 82%; (d) $ClCH_2OCH_2CH_2SiMe_3$ (SEM-Cl), Li_2CO_3, DMF, 52%; (e) 1. 2,4,6-trichlorobenzoyl chloride THF, 2. DMAP, benzene, 81%, or isopropenyl chloroformate, Et_3N, DMAP, 87%; (f) H_2, Pd/C; (g) 1. **22**, BOP-Cl, Et_3N, CH_2Cl_2, −15 °C, 2. amine (**25**), Et_3N, 0 °C, 85%; (h) HF, MeCN, 88%.

assigned stereochemistry (Scheme VI) was accomplished by converting the amino derivative **20** to a protected pyrrolidinone (**21**), which was then subjected to ^1H NMR decoupling experiments and showed a trans relationship for protons 1 and 2 ($J_{1,2} \sim 0$ Hz).

Synthesis of Tetrapeptide (II). Sequential coupling procedures were examined first. Attempts to couple the Z-leucylprolyltyrosine tripeptide with the hydroxyl group of protected threonine, with use of different activation methods, gave uniformly low yields of tetrapeptide. Coupling of leucylproline with the threonyl-*N,O*-dimethyltyrosine dipeptide was found to be the best approach. The synthesis of tetrapeptide II is shown in Scheme VII. Coupling of the L-proline methyl ester to Z-leucine was accomplished with dicyclohexylcarbodiimide (DCC) and the racemization suppressor 1-hydroxybenzotriazole (HOBT). Ester hydrolysis with lithium hydroxide afforded the desired Z-leucylproline (**22**). For the synthesis of *N,O*-dimethyl-L-tyrosine, a one-pot, solid–liquid phase-transfer reaction was developed. Treatment of Z-L-tyrosine in THF with dimethyl sulfate and powdered potassium hydroxide, with tetrabutylammonium hydrogen sulfate as the catalyst, gave a permethylated product. Addition of water to the reaction mixture gave the desired product (**23**). The carboxyl group of Boc-L-threonine was then protected as its SEM derivative (**24**), by using 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in the presence of lithium carbonate.

Coupling of Z-L-*N,O*-dimethyltyrosine with the protected threonine with carbodiimides gave poor yields after long reaction times (48 h). The esterification was greatly improved by using a two-step coupling procedure devised by Yamaguchi.[27] Treatment of acid **23** with 2,4,6-trichlorobenzoyl chloride gave a mixed anhydride that was not purified but dissolved in benzene and treated with DMAP and alcohol **24** to afford the coupled product in 81% yield. It was subsequently found that a one-pot esterification procedure reported by Castro[28] proved to be more efficient, due to its shorter reaction time. Treatment of acid **23** with isopropenyl chloroformate in the presence of protected threonine (**24**) and DMAP gave the ester in 87% yield. The carbobenzyloxy protecting group was then removed by catalytic hydrogenation to afford the secondary amine **25**. Coupling of the amine with the Z-leucylproline (**22**) was accomplished by using *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl).[29] A preactivation protocol developed by Anteunis greatly improved the yields.[30] The acid (**22**) was treated with BOP-Cl at −15 °C, and, after 15 min, the corresponding amine (**25**) was added to afford the coupled product in 85% yield. At this point, removal of the SEM-protecting group of the fully protected tetrapeptide had to be carried out. Initial attempts to use tetrabutylammonium fluoride in DMF not only removed the SEM group but also caused decarboxylation followed by β-elimination to give [Z-Leu-Pro-*N,O*-$(Me)_2$Tyr]-OH. Aqueous hydrofluoric acid in acetonitrile at −10 °C gave the deprotected compound (**26**) cleanly.

Synthesis of the Macrocycle. The formation of the linear precursor to the macrocycle found in the didemnins is shown in Scheme VIII. Construction of the linear precursor was accomplished from the condensation of tetrapeptide with the HIP-isostatine unit by using isopropenyl chloroformate. This compound was found to be superior to other coupling reagents such as BOP-Cl, benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP), or 1,1′-bis[6-(trifluoromethyl)-benzotriazolyl]oxalate (BTOB). A protocol reported by Benoiton for couplings employing chloroformates gave the best results.[31] The tetrapeptide **26** was treated with isopropenyl chloroformate at −15 °C for 3 min and then with the amine (**20**), at 0 °C, to afford the linear precursor **27** in 60% yield.

To effect cyclization, the protected primary hydroxyl group in the HIP-unit had to be oxidized to a carboxylic acid. This operation was accomplished by first removing the *tert*-butyldimethylsilyl group, with use of HOAc/THF/H_2O (3:1:1), to give alcohol **28** in 86% yield. The primary alcohol function (**28**) was then oxidized to its corresponding carboxylic acid **29**. Initially, direct conversion to the carboxylic acid **29** was accomplished by using the Sharpless oxidation protocol employing ruthenium(IV) oxide as a catalyst.[32] However, the yield varied according to the scale used, and removal of the ruthenium salts was difficult. Therefore, a stepwise oxidation was chosen. Conversion of the alcohol **28** to the aldehyde was accomplished by a Swern oxidation with trifluoroacetic anhydride as the DMSO activator. The unstable aldehyde was immediately oxidized to the carboxylic acid **29**, by using a procedure developed by Masamune for oxygen-rich molecules containing acid-sensitive groups.[33] Treatment of the aldehyde with potassium permanganate in *tert*-butyl alcohol, with use of 5% sodium hydrogen phosphate, gave, after 30 min, the carboxylic acid **29** in 90% yield. Although this material could be purified, it was used directly in the subsequent cyclization. For cyclization of hexapeptides, it has been found that diphenyl-

(27) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(28) Jouin, P.; Castro, B.; Zeggaf, C.; Pantaloni, A.; Senet, J. P.; Lecolier, S.; Sennyey, G. *Tetrahedron Lett.* **1987**, *28*, 1661.
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(30) van der Auwera, C.; van Damme, S.; Anteunis, M. J. O. *Int J. Peptide Res.* **1987**, *29*, 464.
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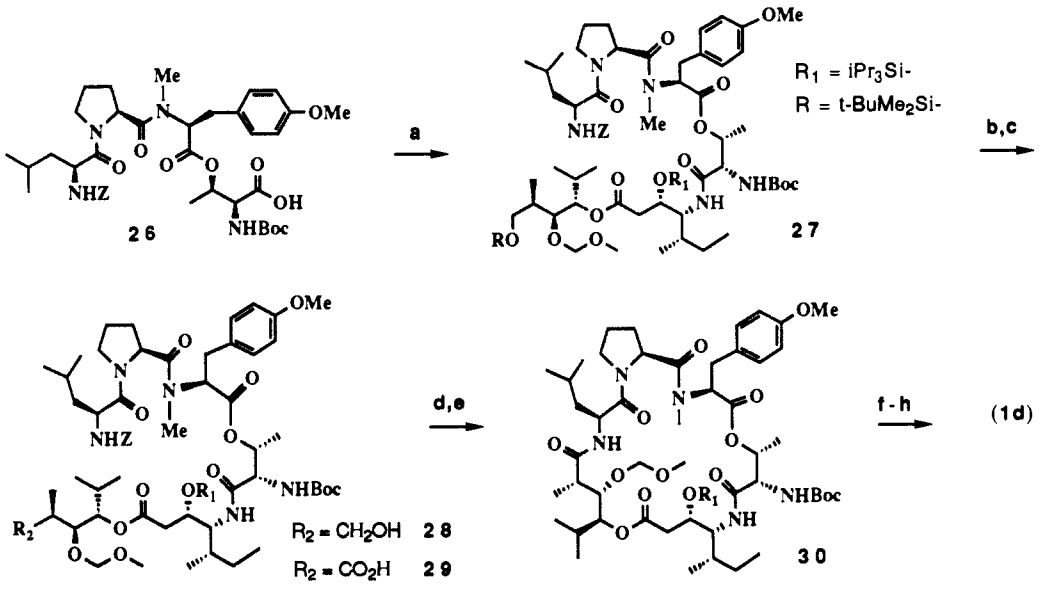
(33) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

Scheme VIII[a]



[a] (a) **20**, isopropenyl chloroformate, *N*-methylmorpholine, THF, −15 °C to 0 °C, 60%; (b) AcOH, THF, H_2O, 12 h, 83%; (c) 1. TFAA, DMSO, CH_2Cl_2, Et_3N, 2. $KMnO_4$, 5% NaH_2PO_4, *t*-BuOH; (d) H_2, Pd/C; (e) diphenyl phosphoryl azide, DMF, $NaHCO_3$, 0 °C, 3 days, c–e = 40%; (f) Me_2BBr, CH_2Cl_2, 93%; (g) TFAA, DMSO, Et_3N, 92%; (h) HCl, EtOAc, −30 °C to 0 °C, 90%.

phosphoryl azide (DPPA) generally gives the highest yields. Furthermore, a modification developed at Merck, employing sodium bicarbonate as the base, allowed the use of more concentrated solutions and produced fewer side products,[34] After removal of the Z protecting group by catalytic hydrogenation, treatment of the amine for 3 days with DPPA, at a concentration of 0.01 M, gave the protected macrolide **30** in 40% yield for four steps from alcohol **28**.

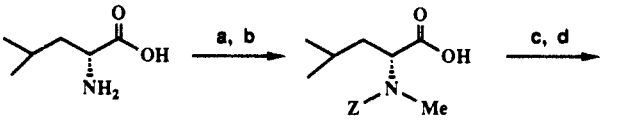
The next task was the deprotection of the various protecting groups in a selective manner. This operation proved far from trivial. Many deprotection protocols were attempted. Finally, the selective deprotection of the HIP-alcohol was accomplished with dimethylboron bromide in 93% yield. Swern oxidation afforded the ketone (**31**) in 92% yield. Epimerization of the 2-methyl center was not observed. Unexpectedly, the Boc group proved very stable to acidic conditions, such as trifluoroacetic acid, formic acid, or tosic acid, possibly because of its crowded steric environment or because it is hydrogen-bonded to the macrocycle. Both the triisopropylsilyl group and the Boc group were removed with hydrogen chloride in ethyl acetate (EtOAc), at −30 °C to 0 °C, to afford the corresponding hydrochloride salt of the macrocycle (**1d**).

Syntheses of Didemnins A, B, and C (Schemes IX–XI). Didemnin A was synthesized as shown in Scheme IX. D-Leucine was protected with *N*-[[(benzyloxy)carbonyl]oxy]-5-norbornene-2,3-dicarboximide, in the presence of triethylamine and aqueous THF. Methylation was accomplished by phase-transfer catalysis, as previously described. The BOP-promoted coupling[35] between side-chain A and the macrocycle, followed by deprotection of the Z group, afforded didemnin A. The NMR, MS, and IR of this sample all agreed with the spectral data reported for natural didemnin A.

Didemnin B was synthesized as shown in Scheme X. The hydroxyl group of ethyl lactate was protected with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide. Hydrolysis of the ester (**32**) with lithium hydroxide gave the corresponding acid. Coupling of L-proline methyl ester and the protected lactic acid, with use of DCC and HOBT in the presence of *N*-methylmorpholine, gave the lactyl proline segment **34**, after hydrolysis of the ester (**33**) in the usual manner. Side-chain B was then obtained by protecting the acid group of Z-D-*N*-methylleucine as its 2-(trimethylsilyl)ethyl ester with trimethylsilylethanol, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), DMAP, and triethylamine. After removal of the Z group, coupling of the D-*N*-methylleucine trimethylsilylethyl ester and the protected lactyl proline unit was effected by premixing BOP-Cl and triethylamine with the acid **34**, at −15 °C, and adding the secondary amine **35** and triethylamine at 0 °C. Removal of the silyl groups was effected with tetrabutylammonium fluoride in DMF. The side chain was then attached to the macrocycle by using the BOP reagent to provide didemnin B in pure form with no observable epimerization in the purified compound.

As shown in Scheme XI, coupling of the trimethylsilylethyl ester of D-*N*-methylleucine (**35**) with the protected lactic acid **37** was carried out with BOP-Cl and triethylamine. Deprotection of the two silyl groups resulted in an undesired cyclization. Therefore, D-leucine was converted into its Boc derivative with di-*tert*-butyl dicarbonate in basic medium, followed by methylation with methyl iodide and sodium hydride to afford **39**. Esterification of the carboxylic acid group with benzyl bromide, in the presence of lithium carbonate in DMF, afforded the corresponding benzyl ester **40** in 91% yield. Removal of the Boc group with trifluoroacetic acid gave the corresponding salt. The salt was then coupled with protected lactic acid **37**, by using BOP-Cl under the previously mentioned conditions to afford compound **41**. Removal of the benzyl group by catalytic hydrogenation was followed by coupling to the macrocycle, by using the BOP reagent in the presence of *N*-methylmorpholine. Removal of the *tert*-butyldimethylsilyl group with hydrogen fluoride in acetonitrile afforded didemnin C.

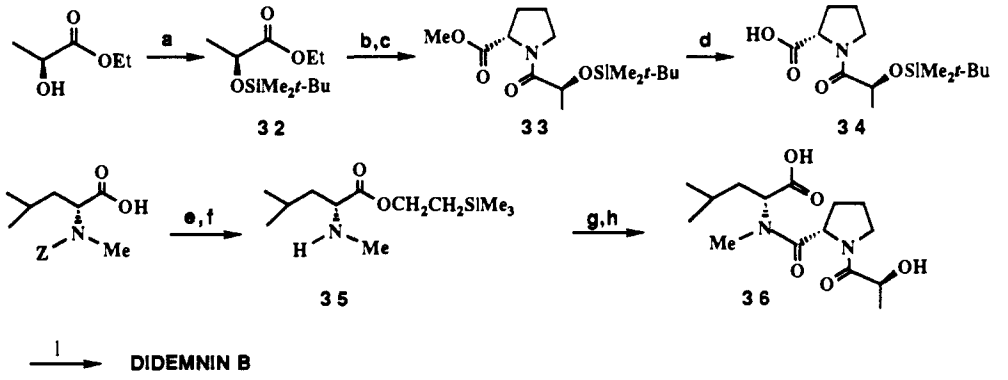
Scheme IX[a]



[a] (a) *N*-[[(benzyloxy)carbonyl]oxy]-5-norbornene-2,3-dicarboximide, Et_3N, THF, H_2O; (b) 1. KOH(s), $Bu_4N^+HSO_4^-$, Me_2SO_4, 2. H_2O, 77%; (c) **1d**, BOP, *N*-methylmorpholine, CH_2Cl_2, 75%; (d) H_2, Pd/C, 85%.

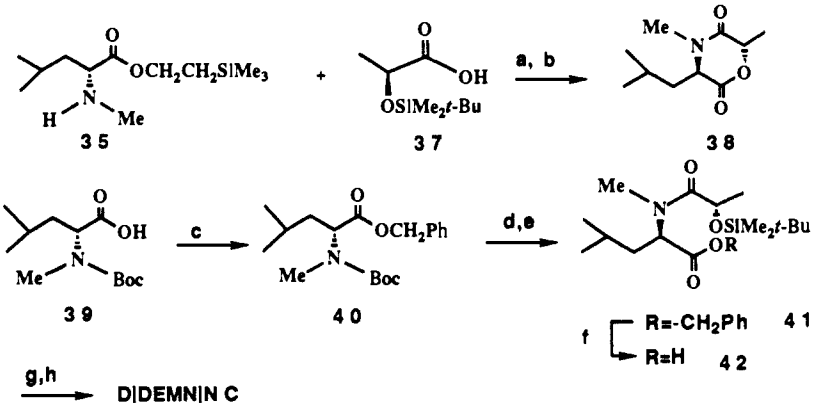
(34) Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Cotton, C. D.; Homnick, C. F.; Whittier, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764.
(35) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219.
(36) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915.

Scheme X[a]



[a](a) *t*-BuMe$_2$SiCl, imidazole, DMF, 92%; (b) LiOH, THF, H_2O; (c) L-proline methyl ester, DCC, HOBT, *N*-methylmorpholine, 60%; (d) LiOH, THF, H_2O, 89%; (e) $Me_3SiCH_2CH_2OH$, EDCI, DMAP, Et_3N, 86%; (f) H_2, Pd/C, 97%; (g) 1. **34**, BOP-Cl, Et_3N, CH_2Cl_2, −15 °C, 2. amine (**35**), Et_3N, 0 °C, 69%; (h) $Bu_4N^+F^-$, DMF, 78%; (i) **1d**, BOP, CH_2Cl_2, *N*-methylmorpholine, 59%.

Scheme XI[a]



[a](a) BOP-Cl, Et_3N, CH_2Cl_2, 57%; (b) 5% HF/CH_3CN, 74%; (c) $PhCH_2Br$, Li_2CO_3, DMF, 91%; (d) TFA, CH_2Cl_2, 98%; (e) 1. **37**, BOP-Cl, Et_3N, CH_2Cl_2, −15 °C, 2. amine from (**40**), Et_3N, 0 °C, 82%; (f) H_2, Pd/C, 99%; (g) **1d**, BOP, CH_2Cl_2, *N*-methylmorpholine, 75%; (h) HF, CH_3CN, 89%.

It should be noted that although several syntheses of didemnins A and B have been reported, there are some discrepancies in physical properties that are unexplained. While there are several extensive studies of the ^1H NMR and ^{13}C NMR spectra of these compounds, the data on optical rotations and melting points are scarce. Only two melting points have been reported for natural didemnin B, one in the original work of Rinehart[1] and the other in the report of Guyot[3] (152–154 °C and 163–165 °C, respectively). The optical rotations for natural didemnin B have been reported as $[\alpha]_D^{25}$ −77.5° (*c* 6,91, CH_2Cl_2),[18] $[\alpha]_D^{22}$ −70° (*c* 0.06, $CHCl_3$),[2] and $[\alpha]_D$ 93° ($CHCl_3$).[3] The only optical rotation of a synthetic sample was reported as $[\alpha]_D^{22}$ −82.6° (*c* 0.2, $CHCl_3$).[13] The physical constants of our synthetic sample of didemnin B are mp 158–160 °C, $[\alpha]_D^{24}$ −91.9° (*c* 0.48, $CHCl_3$). The NMR, MS, and IR of this sample all agreed with the spectral data reported for natural didemnin B.

Experimental Section

All solvents were reagent grade. Anhydrous ether, tetrahydrofuran (THF), benzene, and toluene were distilled from sodium/benzophenone. Acetonitrile and *N*,*N*-dimethylformamide (DMF) were distilled from phosphorus pentoxide. Nitromethane was dried over calcium chloride and then distilled. Organic bases and acids were reagent grade. Triethylamine and diisopropylamine were distilled from calcium hydride. Trifluoroacetic acid was distilled from phosphorus pentoxide. Melting points were determined with a Thomas-Hoover melting point apparatus. They are expressed in degrees centigrade (°C) and are uncorrected. Optical rotations (in deg, °) were measured with a Perkin-Elmer Model 241 polarimeter at the sodium D line. Proton magnetic resonance spectra (^1H NMR) were recorded on a Bruker WM 250 (250 MHz) or 500 (500 MHz) Fourier transform spectrometer. Chemical shifts are measured in parts per million (δ) relative to tetramethylsilane (TMS) or deuterated chloroform as an internal standard. For deuterium oxide (D_2O), 3-(trimethylsilyl)propionic acid was used as the internal standard. Coupling constants (*J* values) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281 B spectrometer. Solid samples were analyzed as potassium bromide (KBr) disks or as chloroform ($CHCl_3$) solutions in sodium chloride cells. Liquids or oils were analyzed as neat films between sodium chloride plates or as $CHCl_3$ solutions in sodium chloride cells. Absorptions are reported in wave numbers (cm^{-1}), and their intensities are designated as broad (br) strong (s), medium (m), or weak (w). The spectra taken was referenced to the 1601-cm^{-1} band of polystyrene, and only the most prominent or characteristic absorptions are noted. High-resolution mass spectra (HRMS) were obtained on a Hitachi-Perkin-Elmer RMH-2 high resolution, double focusing, electron impact spectrometer or on a Vacuum Generator's 7070H spectrometer interfaced with a Kratos DS-50-S data system. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 cm), precoated with a fluorescent indicator. Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in absolute ethanol containing 2% acetic acid, and phosphomolybdic acid reagent (7% w/v) in absolute ethanol. Chromatography was performed on Merck silica gel 60 (230–400 mesh).

(*S*)-2-Hydroxy-3-methylbutanoic acid (2). L-Valine (160 g, 1.366 mol) was placed into a 4-L, three-necked flask, and water (1000 mL) was added. The flask was fitted with two addition funnels and a mechanical stirrer. In one addition funnel, was placed 2 N H_2SO_4 (750 mL). To the other addition funnel was added 2 N $NaNO_2$ (750 mL). The reaction vessel was cooled to 0 °C, and the acid was added dropwise with stirring. After the L-valine dissolved, the sodium nitrite solution was added dropwise, and the rate of addition of the acid was adjusted similarly. After the addition was complete, the reaction was stirred at 0 °C for 3 h and then allowed to stir at room temperature for 12 h. After this time, the reaction mixture was extracted with EtOAc (5 × 600 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated. The resulting crude solid was recrystallized twice from ether/petroleum ether to afford compound **2** (92 g, 57% yield) as a white, crystalline solid: mp 65–66 °C; $[\alpha]_D^{22}$ +19° (*c* 2.08, $CHCl_3$), lit.[20] $[\alpha]_D^{20}$ +19° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 3580 (m), 3400–2500 (br), 1725 (s), 1480 (w), 1380 (w), 1190 (w), 1150 (m), 1080 (w), 1040 (s), 900 (w)

cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 6.9), 1.05 (3 H, d, J = 6.9), 2.09–2.19 (1 H, m), 4.16 (1 H, d, J = 3.6), 7.30 (2 H, br s).

Methyl (*S*)-2-(Benzyloxy)-3-methylbutanoate (3). Compound **2** was esterified in the usual manner by refluxing a solution of (*S*)-2-hydroxy-3-methylbutanoic acid (10.0 g, 84.7 mmol) in CH_3OH (100 mL) with a catalytic amount of concentrated H_2SO_4 (2 mL) for 3 h. The reaction was concentrated in vacuo, diluted with ether (1000 mL), and washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL) solutions. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude oil was then distilled in vacuo (bp 78–80 °C, 10 Torr) to afford methyl (*S*)-2-hydroxy-3-methylbutanoate (9.7 g, 87% yield) as a colorless liquid: R_f 0.57 EtOAc/petroleum ether (40:60); $[\alpha]_D^{24}$ +18.4° (*c* 1.2, $CHCl_3$), lit.[23c] $[\alpha]_D^{20}$ +17.5° (*c* 2.82, $CHCl_3$); IR (neat) 3500 (s), 2990 (s), 1745 (s), 1450 (m), 1270 (m), 1225 (m), 1150 (m), 1040 (m), 770 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.87 (3 H, m), 1.03 (3 H, d, J = 6.9), 2.01–2.12 (1 H, m), 2.70 (1 H, d, J = 6.2), 3.80 (3 H, s), 4.06 (1 H, dd, J^1 = 3.5, J^2 = 6.2). Methyl (*S*)-2-hydroxy-3-methylbutanoate (7.5 g, 56.8 mmol) was dissolved in a solution of cyclohexane/CH_2Cl_2 (2:1, 100 mL). The reaction flask was cooled to 0 °C, and benzyl 2,2,2-trichloroacetimidate (10.6 mL, 56.8 mmol) was added with stirring. To the resulting solution was added a catalytic amount of trifluoromethanesulfonic acid (0.75 mL, 8.5 mmol). After addition was completed, the reaction was filtered, and the collected solid was rinsed with cyclohexane. The filtrate was washed with saturated $NaHCO_3$ (3 × 150 mL) and saturated NaCl (100 mL) solutions. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude oil was then distilled in vacuo (bp 160–165 °C, 20 Torr). Pure methyl (*S*)-2-(benzyloxy)-3-methylbutanoate (10.3 g, 80% yield) was obtained as a colorless oil: R_f 0.33 EtOAc/petroleum ether (5:95); $[\alpha]_D^{22}$ +53° (*c* 2.68, CH_2Cl_2), lit.[23c] $[\alpha]_D^{20}$ +48° (*c* 1.76, CH_2Cl_2); IR (neat) 3100 (w), 3040 (w), 3000 (s), 1750 (s), 1465 (m), 1440 (m), 1280 (s), 1210 (s) 1050 (m), 1030 (m), 770 (s), 700 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 6.2), 0.98 (3 H, d, J = 6.2), 2.02–2.15 (1 H, m), 3.70 (1 H, d, J = 5.6), 3.75 (3 H, s), 4.53 (2 H, AB, J = 11.8), 7.46–7.25 (5 H, m).

(*S*)-2-(Benzyloxy)-3-methylbutanal (4). A solution of methyl (*S*)-2-(benzyloxy)-3-methylbutanoate (6.2 g, 28.0 mmol) in anhydrous ether (10 mL) was added to a slurry of LAH (3.5 g, 92.5 mmol) in anhydrous ether (100 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and worked up in the usual manner. The organic layers were combined, dried (Na_2SO_4), and concentrated. The resulting oil was purified by distillation (bp 132–135 °C, 0.5 Torr) to give 4.8 g (89% yield) of (*S*)-2-(benzyloxy)-3-methylbutanol as a colorless oil: R_f 0.49 EtOAc/petroleum ether (30:70), $[\alpha]_D^{22}$ +10.8° (*c* 2.30, $CHCl_3$), lit.[20] $[\alpha]_D^{20}$ +9° (*c* 5.8, $CHCl_3$); IR (neat) 3400 (s), 3100 (w), 3050 (w), 3000 (s), 2900 (s), 1500 (m), 1470 (s), 1400 (m), 1380 (m), 1210 (m), 1100 (m), 880 (w), 740 (s), 700 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.9), 0.99 (3 H, d, J = 7.1), 1.94–2.02 (2 H, m), 3.21–3.28 (1 H, m), 3.55–3.75 (2 H, m), 4.59 (2 H, AB, J = 11.3), 7.27–7.37 (5 H, m). Triethylamine (92 mL, 660 mmol) was added to a solution of (*S*)-2-(benzyloxy)-3-methylbutanol (15.87 g, 82.56 mmol) in CH_2Cl_2 (360 mL) and DMSO (40 mL). To the resulting solution was added, in portions, sulfur trioxide–pyridine complex (53 g, 333 mmol). After 4 h at ambient temperature, the reaction mixture was diluted with ether, and the organic layer was washed with 5% HCl (50 mL) until the aqueous extract was acidic to litmus, followed by washes with 5% $NaHCO_3$ (50 mL) and saturated NaCl (50 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by distillation under reduced pressure (bp 85–88 °C, 0.5 Torr). (*S*)-2-(Benzyloxy)-3-methylbutanal (10.74 g, 68% yield) was obtained as a colorless oil: R_f 0.28 EtOAc/petroleum ether (5:95); IR (neat) 3110 (w), 3090 (w), 3050 (m), 3000 (s), 2900 (s), 1740 (s), 1505 (m), 1480 (s), 1460 (s), 1400 (m), 1380 (m), 1210 (w), 1090 (s), 1030 (m), 750 (s), 700 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 4.8), 1.01 (3 H, d, J = 4.6), 2.03–2.17 (1 H, m), 3.48 (1 H, dd, J^1 = 2.7, J^2 = 5.8), 4.59 (2 H, AB, J = 11.8), 7.28–7.54 (5 H, m), 9.66 (1 H, d, J = 2.7).

The syntheses of compounds **5–10** in Schemes II and III are described in ref 8.

Synthesis of the H|P-Isostatine Unit (1). 2,2-Dimethylethyl-(2*S*,3*S*,4*S*)-4-(Benzyloxy)-2,5-dimethyl-3-hydroxythiohexanoate (12). *tert*-Butyl thiopropionate was prepared according to the procedure of Gennari[26] and trapped with *tert*-butyldimethylsilyl chloride to give the (*E*)-silylketene thioacetal. Aldehyde **11** (3.58 g, 18.80 mmol) was dissolved in CH_2Cl_2 (40 mL) and treated with a solution of stannic chloride (1 M in CH_2Cl_2, 18.8 mL, 18.8 mmol), added dropwise, at −78 °C. After 5 min, the (*E*)-silylketene thioacetal (18.8 mmol), in CH_2Cl_2 (5 mL), was added. After stirring for 0.5 h at −78 °C, the reaction mixture was diluted with ether (150 mL), and 1 M KOH (20 mL) was added. The organic layer was collected and washed with 10% HCl (25 mL), 5% $NaHCO_3$, and saturated NaCl (25 mL) solutions. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with ether/petroleum ether (4:96). Pure **12** (4.70 g, 74% yield) was obtained as an oil: R_f 0.40 EtOAc/petroleum ether (5:95); $[\alpha]_D^{21}$ +69.4° (*c* 1.03, $CHCl_3$); IR (neat) 3550 (s), 3100 (w), 3050 (s), 2975 (s), 1750 (m), 1685 (s), 1460 (s), 1370 (s), 1150 (w), 1100 (w), 1170 (w), 960 (s), 885 (w), 840 (w), 770 (m), 700 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (6 H, AB), 1.28 (3 H, d, J = 6.9), 1.47 (9 H, s), 1.94–2.07 (1 H, m), 2.33 (1 H, br s), 2.68–2.80 (1 H, m), 3.19 (1 H, dd, J^1 = 1.8, J^2 = 7.8), 3.80 (1 H, dd, J^1 = 1.8, J^2 = 7.8), 4.68 (2 H, s), 7.27–7.40 (5 H, m); HRMS calcd for $C_{19}H_{31}SO_3$ (M + 2 H) 339.1837, found 339.1994.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2,5-dimethylhexane-1,3-diol (13). A slurry of LAH (1.40 g, 38 mmol) in ether (60 mL) was cooled to 0 °C, and compound **12** (4.25 g, 12.3 mmol) in ether (10 mL) was added to it. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. The reaction mixture was diluted with ether (100 mL) and treated with a saturated sodium potassium tartrate solution (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered through Celite, and concentrated. The resulting oil was purified by column chromatography eluting with EtOAc/petroleum ether (20:80) to give a white solid, which was recrystallized from ether/petroleum ether to afford **13** (2.85 g, 92% yield) as a white solid: mp 45–46 °C; R_f 0.35 EtOAc/petroleum ether (40:60); $[\alpha]_D^{21}$ +19.0° (*c* 2.15, $CHCl_3$); IR ($CHCl_3$) 3500 (s), 3050 (w), 3000 (s), 1480 (m), 1470 (m), 1400 (w), 1350 (w), 1080 (s), 1040 (m), 980 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (6 H, AB), 1.07 (3 H, d, J = 6.9), 1.70–1.77 (1 H, m), 1.89–1.96 (1 H, m), 2.50 (2 H, s), 3.30 (1 H, dd, J^1 = 3.2, J^2 = 6.6), 3.60–3.73 (2 H, m), 3.80 (1 H, dd, J^1 = 3.1, J^2 = 6.6), 4.58 (1 H, d, J = 11.2), 4.75 (1 H, d, J = 11.2), 7.27–7.37 (5 H, m); HRMS calcd for $C_{15}H_{25}O_3$ (M + H) 253.1725, found 253.1774. Anal. Calcd for $C_{15}H_{25}O_3$: C, 71.39; H, 9.59. Found: C, 71.64; H, 9.76.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,5-dimethyl-3-hexanol. Compound **13** (1.55 g, 6.12 mmol) was dissolved in CH_2Cl_2 (30 mL) and treated sequentially with triethylamine (1.0 mL, 7.3 mmol), *tert*-butyldimethylsilyl chloride (0.97 g, 6.43 mmol), and DMAP (0.15 g, 1.2 mmol). The reaction mixture was stirred for 6 h. The reaction was then diluted with ether (100 mL) and washed with 10% HCl (20 mL), 5% $NaHCO_3$ (20 mL), and saturated NaCl (20 mL) solutions. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (10:90) to give an oil (2.24 g, 99.8%): R_f 0.75 EtOAc/petroleum ether (10:90); IR (neat) 3550 (s), 3050 (w), 2950 (s), 1489 (w), 1270 (m), 1100 (s) 1070 (s), 840 (m), 780 (m), 700 (w), 680 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.89 (9 H, s), 0.93 (6 H, AB), 1.02 (3 H, d, J = 3.7), 1.71–1.75 (2 H, m), 3.30 (1 H, m), 3.58 (2 H, ddd, J^1 = 5.3, J^2 = 6.7, J^3 = 9.8), 3.80 (1 H, dd, J^1 = 3.5, J^2 = 6.2), 4.66 (2 H, AB), 7.28–7.38 (5 H, m); HRMS calcd for $C_{21}H_{39}O_3Si$ (M + H) 367.2590, found 367.2668.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxymethoxy)-2,5-dimethylhexane (14). To a solution of (2*R*,3*S*,4*S*)-4-(benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,5-dimethyl-3-hexanol (2.24 g, 6.11 mmol) in CH_2Cl_2 (20 mL) was added diisopropylethylamine (3.2 mL, 18 mmol). The solution was cooled to 0 °C, and chloromethyl methyl ether (0.93 mL, 12 mmol) was added dropwise. The solution was stirred for 24 h. After this time, the reaction was diluted with ether (60 mL) and washed with 10% HCl (20 mL), 5% $NaHCO_3$ (20 mL), and saturated NaCl (20 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with ether/petroleum ether (5:95). Compound **14** (2.41 g, 96% yield) was obtained as a colorless oil: R_f 0.65 EtOAc/petroleum ether (5:95); IR (neat) 3050 (w), 3000 (s), 2900 (s), 1480 (w), 1270 (m), 1150 (m), 1100 (s), 1080 (s), 1045 (s), 850 (s), 780 (m), 700 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.89 (9 H, s), 0.90–0.92 (6 H, AB), 1.01 (3 H, d, J = 6.8), 1.75–1.81 (2 H, m), 3.32–3.38 (1 H, m), 3.37 (3 H, s), 3.53 (2 H, ddd, J^1 = 6.3, J^2 = 7.8, J^3 = 9.6), 3.77 (1 H, dd, J^1 = 2.0, J^2 = 8.6), 4.60 (2 H, d, AB), 4.78 (2 H, AB), 7.27–7.35 (5 H, m); HRMS calcd for $C_{22}H_{39}O_3Si$ (M − OCH_3) 379.2668, found 379.2669.

(3*S*,4*S*,5*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-2,5-dimethyl-3-hexanol (15). Sodium (0.75 g atom, 33 mmol) was dissolved in freshly distilled liquid ammonia (30 mL), at −78 °C, and treated with a solution of compound **14** (4.45 g, 10.8 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 0.5 h. The reaction was then quenched with ammonium chloride (5.8 g, 110 mmol). The reaction was concentrated in vacuo, and the residue was dissolved in ether (150 mL) and washed with 5% HCl (25 mL), 5% $NaHCO_3$ (25 mL), and saturated NaCl (25 mL) solutions. The organic layer was dried (Na_2-

SO_4), filtered, and concentrated. The resulting oil was purified by column chromatography eluting with ether/petroleum ether (10:90). Compound **15** (2.85 g, 82% yield) was obtained as a colorless oil: R_f 0.62 EtOAc/petroleum ether (10:90); IR (neat) 3500 (s), 2950 (m), 1270 (m), 1165 (s), 1110 (s), 1050 (s), 840 (s), 780 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.89 (9 H, s), 0.90 (6 H, AB), 1.02 (3 H, d, J = 6.8), 1.73–1.85 (2 H, m), 3.40–3.52 (2 H, m), 3.43 (3 H, s), 3.66 (1 H, dd, J^1 = 2.7, J^2 = 6.9), 4.70 (2 H, AB); HRMS calcd for $C_{16}H_{37}O_4Si$ (M + H) 321.2383, found 321.2427.

(3*S*,4*S*,5*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-2,5-dimethyl-3-hexanol Acetate (16). To compound **15** (2.7 g, 8.58 mmol), in CH_2Cl_2 (42 mL) at ambient temperature, was added triethylamine (1.5 mL, 11 mmol), acetic anhydride (1.0 mL, 11 mmol), and DMAP (1.6 g, 13 mmol). After the reaction was completed (12 h), it was diluted with ether (150 mL) and washed with 10% HCl (25 mL), 5% $NaHCO_3$ (25 mL), and saturated NaCl (25 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with ether/petroleum ether (5:95). Acetate **16** (2.8 g, 90% yield) was obtained as an oil: R_f 0.57 EtOAc/petroleum ether (10:90); $[\alpha]_D^{21}$ −30.1° (*c* 2.09, $CHCl_3$); IR (neat) 2950 (s), 2900 (m), 1745 (s), 1250 (s), 1100 (m), 1050 (s), 840 (s), 780 (w) cm^{-1}; ^1H NMR (250 MHz, $CHCl_3$) δ 0.05 (6 H, s), 0.88–0.94 (18 H, m), 1.73–1.91 (2 H, m), 2.10 (3 H, s), 3.36 (3 H, s), 3.48 (2 H, ddd, J^1 = 5.7, J^2 = 7.9, J^3 = 9.8), 3.83 (1 H, dd, J^1 = 2.8, J^2 = 7.6), 4.65 (2 H, AB), 5.00 (1 H, dd, J^1 = 4.3, J^2 = 7.5); HRMS calcd for $C_{18}H_{39}O_5Si$ (M + H) 363.2568, found 363.2583.

(4*R*,5*S*)-4-[[(Benzyloxy)carbonyl]amino]-5-methyl-3-oxoheptanoic Acid, (1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (18). Triethylamine (2.0 mL, 14.3 mmol) was added dropwise to a solution of D-alloisoleucine (0.86 g, 6.57 mmol), in THF/H_2O (1:1, 70 mL), at 0 °C, and *N*-[(benzyloxy)-carbonyl]-5-norbornene-2,3-dicarboximide (2.16 g, 6.89 mmol). The solution was then stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure to one-half its volume and then washed with ether (2 × 10 mL). The ether layers were collected and extracted with 5% $NaHCO_3$ solution (2 × 5 mL). The combined aqueous layers were acidified carefully to pH 3–3.5 wtih 2 N $KHSO_4$. The aqueous layer was then extracted with ether (2 × 25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was then dissolved in anhydrous THF (65 mL), cooled to 0 °C, and treated with CDI (1.17 g, 7.22 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then cooled to −78 °C. The enolate of compound **16** was prepared by dissolving compound **16** (7.83 g, 29.5 mmol) in dry THF (75 mL). To this solution was added LDA (75 mL of a 0.4 M solution in THF, 31.0 mmol). The solution was stirred at −78 °C for 1 h. The solution containing the enolate of compound **16** was then added dropwise, with vigorous stirring, to the solution containing the imidazolide of Z-D-alloisoleucine (at −78 °C). Saturated ammonium chloride (100 mL) and ether (400 mL) were added to the reaction mixture. The aqueous layer was separated and extracted with ether (2 × 100 mL), and the ether layer washed with saturated NaCl (50 mL) solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (10:90) to remove unreacted compound **16**, and then eluting first with EtOAc/petroleum ether (20:80) to obtain compound **18**. Compound **18** (3.04 g, 76% yield) was obtained as a colorless oil: R_f 0.85 EtOAc/petroleum ether (20:80); $[\alpha]_D^{21}$ −29° (*c* 0.303, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 1755 (s), 1735 (s), 1725 (s), 1510 (m), 1475 (m), 1400 (w), 1360 (m), 1100 (m), 1040 (s), 920 (w), 850 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.78 (3 H, d, J = 6.9), 0.85–1.00 (21 H, m), 1.24–1.31 (1 H, m), 1.47–1.51 (1 H, m), 1.76–1.79 (1 H, m), 1.89–1.93 (1 H, m), 2.03–2.05 (1 H, m), 3.33 (3 H, s), 3.43–3.52 (2 H, m), 3.60 (2 H, AB), 3.80 (1 H, dd, J^1 = 2.6, J^2 = 7.9), 4.61 (2 H, AB), 5.05 (1 H, dd, J^1 = 3.7, J^2 = 7.9), 5.10 (2 H, s), 5.40 (1 H, d, J = 8.8), 7.28–7.37 (5 H, m); HRMS calcd for $C_{32}H_{59}O_8N_2Si$ (M + NH_3) 627.405, found 627.404.

(4*R*,5*S*)-4-[[(Benzyloxy)carbonyl]amino]-3-hydroxy-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester. To β-keto ester **18** (2.36 g, 3.86 mmol), in absolute ethanol (16 mL) and at 0 °C, was added, in portions, potassium borohydride (0.84 g, 15.5 mmol). The reaction mixture was stirred at 0 °C, for 1 h and then at room temperature for 24 h. The solution was diluted with ether (200 mL). A 1 N HOAc solution was added dropwise until the aqueous layer was neutral to litmus. The resulting solution was concentrated in vacuo, dissolved in ether, and washed with 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and saturated NaCl (25 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (10:90 to 15:85). The reduction product (1.96 g, 83% yield) was obtained as an oil: R_f 0.67 EtOAc/petroleum ether (20:80); IR ($CHCl_3$) 3475 (s), 1735 (s), 1715 (s), 1520 (s), 1465 (m), 1270 (m), 1195 (w), 1105 (s), 1050 (s), 1030 (s), 925 (w), 850 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.86–0.98 (15 H, m), 1.19–1.37 (2 H, m), 1.56 (1 H, br), 1.77–1.79 (1 H, m), 1.90–1.93 (1 H, m), 1.95–1.98 (1 H, m), 2.54 (1 H, dd, J^1 = 9.8, J^2 = 16.9), 2.67 (1 H, dd, J^1 = 2.5, J^2 = 16.9), 3.32 (1 H, s), 3.43–3.49 (2 H, m), 3.71–3.75 (1 H, m), 3.84 (1 H, dd, J^1 = 2.5, J^2 = 7.7), 3.93–3.96 (1 H, m), 4.56 (2 H, AB), 4.69–4.70 (1 H, m), 5.06 (1 H, dd, J^1 = 3.9, J^2 = 9.2), 5.11 (2 H, AB), 7.26–7.36 (5 H, m); HRMS calcd for $C_{32}H_{62}O_8N_2Si$ (M + NH_3) 629.4197, found 629.4160.

(3*S*,4*R*,5*S*)- and (3*R*,4*R*,5*S*)-4-[[(Benzyloxy)carbonyl]amino]-3-[(triisopropylsilyl)oxy]-5-methylheptanoic Acid, (1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (19a) and (19b). To the alcohol prepared from **18** (1.96 g, 3.2 mmol), in CH_2Cl_2 (30 mL) and at 0 °C, was added 2,6-lutidine (0.8 mL, 6.9 mmol). To the resulting solution was added dropwise triisopropylsilyl triflate (1.1 mL, 3.5 mmol). The reaction mixture was stirred at 0 °C for 3 h and then diluted with ether (150 mL). The organic layer was washed with 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and saturated NaCl (25 mL) solutions. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (2:98 to 5:95). Compound **19a** (2.29 g, 93% yield) and compound **19b** (0.17 g, 7% yield) were obtained as oils. Major isomer **19a**: (3*S*,4*R*,5*S*) R_f 0.73 EtOAc/petroleum ether (10:90); $[\alpha]_D^{21}$ −7° (*c* 0.240, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 1725 (s), 1510 (m), 1470 (m), 1100 (s), 1050 (s), 915 (w), 890 (w), 855 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (6 H, s), 0.74–0.95 (15 H, m), 0.99–1.08 (18 H, m), 1.17–1.20 (1 H, m), 1.34–1.39 (1 H, m), 1.71–1.74 (1 H, m), 1.82–1.89 (1 H, m), 1.91–1.98 (1 H, m), 2.66–2.71 (2 H, m), 3.29 (3 H, s), 3.40–3.48 (2 H, m), 3.77 (1 H, dd, J^1 = 2.8, J^2 = 7.5), 3.80–3.82 (1 H, m), 4.39 (1 H, m), 4.57 (2 H, AB), 4.95–4.99 (1 H, m), 5.06 (2 H, AB), 5.12 (1 H, br s), 7.25–7.32 (5 H, m); HRMS calcd for $C_{41}H_{78}O_8NSi_2$ (M + H) 768.5266, found 768.528. Minor isomer **19b**: (3*R*,4*R*,5*S*) R_f 0.77 EtOAc/petroleum ether (10:90); $[\alpha]_D^{21}$ −16° (*c* 0.247, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 1740 (s), 1510 (m), 1475 (m), 1380 (m), 1260 (m), 1105 (s), 920 (w), 890 (m), 850 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.75–0.98 (15 H, m), 1.05–1.11 (18 H, m), 1.13–1.25 (2 H, m), 1.59–1.66 (1 H, m), 1.75–1.78 (1 H, m), 1.87–1.91 (1 H, m), 2.50 (1 H, dd, J^1 = 2.8, J^2 = 16.8), 2.71 (1 H, dd, J^1 = 10.7, J^2 = 16.8), 3.33 (3 H, s), 3.41–3.53 (3 H, m), 3.81 (1 H, dd, J^1 = 2.6, J^2 = 7.7), 4.54–4.65 (3 H, m), 5.02 (1 H, dd, J^1 = 4.0, J^2 = 7.7), 5.09 (1 H, br s), 5.11 (2 H, AB), 7.27–7.34 (5 H, m).

Synthesis of Tetrapeptide (11). Z-Leucylproline Methyl Ester. L-Proline methyl ester hydrochloride (2.00 g, 12.1 mmol) was dissolved in CH_2Cl_2 (40 mL). To this solution was added *N*-methylmorpholine (4.4 mL, 40.0 mmol) at 0 °C. The reaction was stirred for 15 min, and Z-leucine (3.20 g, 12.1 mmol) in CH_2Cl_2 (20 mL) was added via a cannula needle. DCC (3.35 g, 16.2 mmol) and HOBT (1.93 g, 14.3 mmol) were added with stirring. After 24 h, the reaction mixture was filtered, and the collected solid was rinsed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and diluted with ether (250 mL). The ether layer was washed with 10% HCl (40 mL), 5% $NaHCO_3$ (40 mL), and saturated NaCl (40 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (40:60). Z-Leucylproline methyl ester (4.38 g, 96%) was obtained as a white foam: R_f 0.36 EtOAc/petroleum ether (40:60); $[\alpha]_D^{21}$ −61° (*c* 0.585, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3100 (w), 3050 (w), 3000 (s), 2900 (s), 1770 (s), 1740 (s), 1670 (s), 1650 (s), 1520 (s), 1450 (s), 1380 (m), 1360 (m), 1340 (m), 1300 (m), 1250 (s), 1190 (s), 1050 (s), 1030 (m), 920 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (3 H, d, J = 6.6), 1.01 (3 H, d, J = 6.5), 1.50–2.08 (6 H, m), 2.16–2.25 (1 H, m), 3.57–3.68 (2 H, m), 3.88 (3 H, s), 4.50–4.57 (2 H, m), 5.1 (2 H, s), 5.44 (1 H, d, J = 8.7), 7.29–7.34 (5 H, m); HRMS calcd for $C_{20}H_{29}O_5N_2$ (M + H) 377.2076, found 377.2076.

Z-Leucylproline (22). To Z-leucylproline methyl ester (2.80 g, 7.44 mmol) was added a solution of THF, H_2O, and MeOH (1:1:1, 30 mL). The reaction was cooled to 0 °C, and lithium hydroxide monohydrate (1.56 g, 37.1 mmol) was added. The reaction was stirred at 0 °C for 6 h, concentrated to 10 mL, and washed with ether (2 × 15 mL). The combined ether layers were extracted with saturated $NaHCO_3$ solution (10 mL). The aqueous layers were combined and acidified to pH 1 with 1 N potassium hydrogen sulfate solution. The acidified aqueous layer was extracted with ether (3 × 50 mL). The ether extracts were dried (Na_2SO_4), filtered, and concentrated. Compound **22** (2.54 g, 94%) was obtained as a white hygroscopic foam: R_f 0.35 acetone/CH_2Cl_2 (5:95); $[\alpha]_D^{21}$ −66° (*c* 3.25, $CHCl_3$); IR ($CHCl_3$) 3475 (s), 3500–2500 (br), 1730 (s), 1650 (s), 1520 (m), 1470 (s), 1250 (m), 1130 (w) 1060 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (6 H, AB), 1.46–2.19 (7 H,

m), 3.60–3.79 (2 H, m), 4.56–4.71 (2 H, m), 5.09 (2 H, s) 5.67 (1 H, d, J = 8.9), 6.8 (1 H, br s), 7.31–7.37 (5 H, m); HRMS calcd for $C_{19}H_{27}O_5N_2$ (M + H) 363.1920, found 363.1920.

Z-*N*,*O*-Dimethyltyrosine (23). To Z-tyrosine (3.48 g, 11.0 mmol), at ambient temperature, was added THF (60 mL). Finely powdered KOH (6.20 g, 110 mmol) was then added in portions, followed by the addition of tetrabutylammonium hydrogen sulfate (0.35 g, 10% by weight). Rapid stirring was initiated, and dimethyl sulfate (6.3 mL, 67 mmol) was added dropwise over 15 min. The reaction was stirred for an additional 0.5 h and then cooled to 0 °C and H_2O (60 mL) was added. The reaction was diluted with ether (100 mL), the aqueous layer was separated, and the organic layer was extracted with saturated $NaHCO_3$ solution (2 × 50 mL). The aqueous layers were combined, acidified to pH 1 with potassium hydrogen sulfate (1 M), and extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with $CHCl_3$/EtOAc/CH_3OH (38:8:4). Compound **23** (3.12 g, 82% yield) was obtained as a foam: R_f 0.78 $CHCl_3/CH_3OH/H_2O$ (70:30:5); $[\alpha]_D^{21}$ −48° (c 2.23, $CHCl_3$); IR ($CHCl_3$) 3500–2500 (br), 1740 (s), 1700 (s), 1620 (w) 1600 (w), 1520 (m), 1460 (m), 1410 (m), 1340 (s), 1330 (s), 1260 (m), 1190 (s), 1150 (w), 1050 (m), 830 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.79 and 2.86 (3 H, s, rotational isomers), 2.90–3.10 (1 H, m), 3.23–3.35 (1 H, m), 3.87 (3 H, s), 4.82–4.93 (1 H, m), 5.03–5.12 (2 H, AB), 6.78 (1 H, d, J = 8.3), 6.80 (1 H, d, J = 8.2), 7.03 (1 H, d, J = 8.3), 7.10 (1 H, d, J = 8.2), 7.18–7.34 (5 H, m); HRMS calcd for $C_{19}H_{22}O_5N$ (M + H) 344.149, found 344.146.

Boc-threonine [2-(Trimethylsilyl)ethoxy]methyl Ester. (24). To Boc-threonine (3.57 g, 16.30 mmol), at ambient temperature in DMF (50 mL), was added lithium carbonate (1.33 g, 17.93 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (3.2 mL, 18 mmol). After 16 h, the reaction mixture was diluted with H_2O (200 mL) and extracted with ether (3 × 50 mL). The ether layers were combined and washed with saturated NaCl solution (2 × 10 mL). The ether layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (10:90). Compound **24** (2.94 g, 52% yield) was obtained as an oil: R_f 0.44 EtOAc/petroleum ether (20:80); $[\alpha]_D^{21}$ −6.8° (c 2.09, $CHCl_3$); IR (neat) 3450 (s), 3000 (s), 2990 (s), 1760 (s), 1750 (s), 1730 (s), 1510 (s), 1380 (m), 1260 (s), 1170 (s), 1120 (m), 1080 (m), 950 (m), 870 (s), 850 (s), 770 (w), 700 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0 .02 (9 H, s), 0.93–1.00 (2 H, m), 1.27 (3 H, d, J = 6.6), 1.46 (9 H, s), 2.05 (1 H, br s), 3.69–3.76 (2 H, m), 4.26–4.35 (2 H, m), 5.34–5.40 (3 H, m); HRMS calcd for $C_{15}H_{32}O_6NSi$ (M + H) 350.1991, found 350.1999.

Z-*N*,*O*-Dimethyltyrosine-*O*-Boc-threonine-OSEM. Method A. Compound **23** (2.04 g, 5.94 mmol) was dissolved in THF (15 mL), and treated with triethylamine (0.87 mL, 6.24 mmol). To this solution was added, via a cannula, 2,4,6-trichlorobenzoyl chloride (1.52 g, 6.23 mmol) in THF (15 mL). The reaction mixture was stirred for 1 h, then filtered, and concentrated. The resulting oil was dissolved in benzene (15 mL) and treated with Boc-threonine-OSEM (**24**) (2.07 g, 5.92 mmol), in benzene (5 mL), followed by addition of DMAP (1.8 g, 15 mmol). After 4 h, the reaction mixture was diluted with ether (100 mL) and washed with 10% HCl (20 mL), 5% $NaHCO_3$ (20 mL), and saturated NaCl (20 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (15:85). The dipeptide (3.23 g, 81% yield) was obtained as an oil.

Method B. To Z-*N*,*O*-dimethyltyrosine (2.10 g, 6.11 mmol), in CH_2Cl_2 (25 mL) and at 0 °C, was added compound **24** (2.14 g, 6.11 mmol). To the resulting solution was added triethylamine (1.9 mL, 13.5 mmol), DMAP (0.15 g, 1.23 mmol), and isopropenyl chloroformate (0.81 g, 6.72 mmol). The reaction was stirred at 0 °C for 1 h and diluted with ether (150 mL). The organic layer was washed with 10% HCl (30 mL), 5% $NaHCO_3$ (30 mL), and saturated NaCl (30 mL) solutions. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (15:85). The dipeptide (3.58 g, 87% yield) was obtained as an oil: R_f 0.46 EtOAc/petroleum ether (25:75); $[\alpha]_D^{21}$ −15.2° (c 1.14, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3100 (w), 3050 (w), 3000 (s), 1770 (s), 1760 (s), 1720 (s), 1700 (s), 1620 (w), 1510 (s), 1470 (m), 1410 (m), 1380 (m), 1330 (s) 1280 (s), 1100 (s), 1070 (s), 1040 (w), 1000 (w), 950 (w), 910 (w), 870 (s), 850 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (9 H, s), 0.89–0.93 (2 H, m), 1.28 (3 H, d, J = 6.7), 1.45 (9 H, s), 2.74 and 2.86 (3 H, s, rotational isomers), 2.86–3.00 (1 H, m), 3.14–3.23 (1 H, m), 3.68–3.74 (2 H, m), 3.77 (3 H, s), 4.73–4.76 (1 H, m), 5.05–5.13 (2 H, m), 5.27–5.35 (2 H, m), 5.46–5.47 (1 H, m), 6.76–6.80 (2 H, m), 6.99–7.08 (2 H, m), 7.22–7.36 (5 H, m); HRMS calcd for $C_{34}H_{51}O_{12}N_2Si$ (M + H) 675.330, found 675.330.

***N*,*O*-Dimethyltyrosine-*O*-Boc-threonine-OSEM (25).** To a CH_3OH/EtOAc solution (1:1, 20 mL) was added 10% Pd/C (0.96 g). To the resulting suspension was added Z-*N*,*O*-dimethyltyrosine-*O*-Boc-threonine-OSEM (3.23 g, 4.76 mmol) in CH_3OH (5 mL). The solution was subjected to an atmosphere of hydrogen (40 psi) and stirred for 3 h. The reaction mixture was filtered through Celite. The Celite was washed with CH_3OH, and the filtrate was concentrated. The resulting amine was used directly in the next step: R_f 0.24 acetone/CH_2Cl_2 (25:75); $[\alpha]_D^{21}$ +22.2° (c 0.930, $CHCl_3$); IR (neat) 3400 (m), 3100 (w), 3000 (s), 2950 (m), 1750 (s), 1520 (m), 1270 (m), 1180 (s), 870 (m), 770 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (9 H, s), 0.91–0.98 (2 H, m), 1.12 (3 H, d, J = 6.4), 1.47 (9 H, s), 2.31 (3 H, s), 2.80 (1 H, dd, J^1 = 7.6, J^2 = 13.7), 2.92 (1 H, dd, J^1 = 6.6, J^2 = 13.7), 3.34–3.40 (1 H, m), 3.67–3.75 (2 H, m), 3.77 (3 H, s), 4.42 (2 H, m), 5.23 (1 H, d, J = 6.0), 5.33 (1 H, d, J = 6.0), 5.36–5.43 (1 H, m), 6.80–6.84 (2 H, m), 7.07–7.10 (2 H, m); HRMS calcd for $C_{26}H_{45}O_8N_2Si$ (M + H) 541.2937, found 541.2916.

Z-Leucylprolyl-*N*,*O*-dimethyltyrosine-*O*-Boc-threonine-OSEM. Acid **22** (0.81 g, 2.24 mmol) was dissolved in CH_2Cl_2 (25 mL), and the solution was cooled to −15 °C. BOP-Cl (0.68 g, 2.68 mmol) was added, followed by the dropwise addition of *N*-methylmorpholine (0.30 mL, 2.7 mmol). The reaction mixture was stirred at −15 °C for 0.5 h. The solution was then concentrated to 10 mL, and amine **25** (1.45 g, 2.68 mmol) and *N*-methylmorpholine (0.30 mL, 2.7 mmol) were added. The solution was kept at 0 °C for 6 h and then diluted with ether (50 mL). The organic layer was washed with 10% HCl (20 mL), 5% $NaHCO_3$ (20 mL), and saturated NaCl (20 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (25:75 to 30:70). The fully protected tetrapeptide (1.59 g, 85% yield) was obtained as a white solid that was recrystallized from ether/petroleum ether: mp 132–133 °C; R_f 0.37 acetone/CH_2Cl_2 (10:90); $[\alpha]_D^{21}$ −44.1° (c 1.50, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3300 (m), 3050 (w), 3000 (s), 2900 (s), 1750 (s), 1720 (s), 1650 (s), 1520 (m), 1470 (m), 1380 (w), 1270 (s), 1120 (m), 1070 (m), 870 (w), 850 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 (9 H, s), 0.81–0.87 (2 H, m), 0.90–1.00 (9 H, m), 1.44 (9 H, s), 1.29–1.82 (4 H, m), 1.96–2.03 (3 H, m), 2.94 and 3.04 (3 H, s, rotational isomers), 2.78–2.94 (1 H, m), 3.09–3.19 (1 H, m), 3.51–3.87 (4 H, m), 3.77 (3 H, s), 4.28–4.69 (3 H, m), 4.91 (1 H, dd, J^1 = 3.4 , J^2 = 11.5), 5.02–5.15 (3 H, m), 5.46–5.61 (3 H, m), 6.79–6.83 (2 H, m), 7.01–7.14 (2 H, m), 7.28–7.38 (5 H, m), 7.99 and 7.69 (1 H, d, J = 9.1, rotational isomers). Anal. Calcd for $C_{45}H_{68}O_{12}N_4Si$: C, 61.06; H, 7.74; N, 6.33. Found: C, 60.99; H, 7.70; N, 6.42.

Z-Leucylprolyl-*N*,*O*-dimethyltyrosine-*O*-Boc-threonine (26). A solution of the fully protected tetrapeptide (1.00 g, 1.15 mmol) in acetonitrile (6 mL) was cooled to −20 °C. A 15% solution of HF (48%) in acetonitrile was cooled to −20 °C, and 3 mL of this solution was added to the reaction mixture dropwise. The reaction was kept at −10 °C for 5 h. The reaction was then poured into 25 mL of 1 N potassium hydrogen sulfate and extracted with ether (3 × 20 mL). The combined ether layers were dried (Na_2SO_4), filtered through Celite, and concentrated. The resulting crude solid was purified by column chromatography eluting with CH_3OH/CH_2Cl_2 (7:93). The resulting solid was recrystallized from EtOAc/petroleum ether to afford compound **26** (0.74 g, 88% yield) as a white solid: mp 120 °C (dec); R_f 0.45 acetone/CH_2Cl_2 (7:93); $[\alpha]_D^{21}$ −55° (c 0.585, benzene); IR (KBr) 3600–3150 (br), 3075 (w), 3000 (s), 1740 (s), 1710 (s), 1650 (s), 1520 (m), 1450 (m), 1380 (s), 1260 (m), 1180 (m), 1060 (m), 1050 (m), 870 (w), 830 (w), 750 (w), 700 (w) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.86–0.90 (6 H, m), 1.13 (3 H, d, J = 5.7), 1.40 (9 H, s), 1.43–1.49 (2 H, m), 1.68–1.95 (4 H, m), 2.12–2.19 (1 H, m), 2.74–2.92 (1 H, m), 2.88 (3 H, s), 3.15 (1 H, dd, J^1 = 5.2, J^2 = 15.2), 3.38–3.62 (2 H, m), 3.72 (3 H, s), 3.86–3.88 (1 H, m), 4.27–4.30 (2 H, m), 4.76–4.77 (1 H, m), 5.02 (2 H, AB), 5.12–5.13 (1 H, m), 5.19–5.20 (1 H, m), 5.96 (1 H, br s), 6.80–6.83 (2 H, m), 7.10–7.18 (2 H, m), 7.32–7.38 (5 H, m), 7.44 (1 H, d, J = 8.0); HRMS calcd for $C_{39}H_{54}O_{11}N_4Na$ (M + Na) 777.3687, found 777.3696.

Synthesis of the Macrocycle of the Didemnins. *N*-[1-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, 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-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (27). To acid **26** (0.43 g, 0.57 mmol), in THF (6 mL) and at −15 °C, was added dropwise *N*-methylmorpholine (0.57 mL of a 1 M solution in THF, 0.57 mmol). To this solution was added isopropenyl chloroformate (0.57 mL of a 1 M solution in THF, 0.57 mmol). After the mixture was stirred for 3 min, amine **20** (0.57 mmol) was added. This amine was prepared from treatment of compound **19a** (0.44 g, 0.57 mmol), in CH_3OH/EtOAc (1:1, 6 mL), with 10% Pd/C (88 mg) under an atmosphere of hydrogen (40 psi) for 24 h. The solution 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 ether (50 mL) and washed with 5% citric acid (10 mL), 5% $NaHCO_3$ (10 mL), and saturated sodium chloride (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (25:75 to 30:70). Compound **27** (0.47 g, 60% yield) was obtained as a white foam: R_f 0.43 EtOAc/petroleum ether (40:60); $[\alpha]_D^{25}$ −51° (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3425 (w), 3400 (w), 1750–1715 (s), 1680–1650 (s), 1510 (m), 1470 (m), 1400 (w), 1380 (w), 1310 (w), 1255 (s), 1170 (m), 1100 (m), 1050 (s), 920 (w), 890 (w), 840 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.83–0.99 (21 H, m), 1.04–1.08 (18 H, m), 1.24 (3 H, d, J = 6.3), 1.40 (9 H, s), 1.51–2.17 (12 H, m), 2.66–2.68 (2 H, m), 2.82 (3 H, s), 2.89–2.99 (1 H, m), 3.02–3.10 (1 H, m), 3.29 (3 H, s), 3.24–3.34 (2 H, m), 3.43–3.49 (2 H, m), 3.65–3.68 (1 H, m), 3.76 (3 H, s), 4.12 (1 H, dd, J^1 = 5.0, J^2 = 10.3), 4.55 (2 H, AB), 4.45–4.78 (5 H, m), 5.00 (1 H, dd, J^1 = 3.5, J^2 = 8.0), 5.05 (2 H, AB), 5.12–5.18 (1 H, m), 5.37–5.39 (1 H, m), 5.80 (1 H, br), 6.71 (1 H, br), 6.80 (2 H, d, J = 8.6), 7.09 (2 H, d, J = 8.6), 7.29–7.32 (5 H, m); HRMS calcd for $C_{72}H_{125}O_{16}N_5Si_2$ (M + 2 H) 1371.866, found 1371.879.

***N*-[1-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, 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 (28).** To compound **27** (483 mg, 0.355 mmol), in THF (1 mL), was added HOAc/H_2O (3:1, 4 mL). After 12 h, the reaction was diluted with toluene (20 mL) and concentrated. The resulting oil was again diluted with toluene (20 mL) and concentrated until no HOAc remained. The crude oil was then purified by column chromatography eluting with EtOAc/petroleum ether (1:1). Pure **28** (370 mg, 83% yield) was obtained as a white foam: R_f 0.18 EtOAc/petroleum ether (1:1); $[\alpha]_D^{26}$ −63° (*c* 0.26, $CHCl_3$); IR (KBr) 3600–3400 (br), 1750–1700 (s), 1680–1650 (s), 1520 (m), 1465 (m) 1380 (w), 1310 (w), 1255 (s), 1170 (s), 1115 (w), 1040 (s), 920 (w), 890 (w), 680 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0,98 (21 H, m), 1.04–1.08 (18 H, m), 1.24 (3 H, d, J = 6.1), 1.41 (9 H, s), 1.50–2.13 (12 H, m), 2.61–2.69 (2 H, m), 2.85 (3 H, s), 2.82–2.90 (1 H, br), 2.99–3.04 (1 H, m), 3.25–3.29 (1 H, dd, J^1 = 5.5, J^2 = 14.5), 3.39 (3 H, s), 3.46–3.51 (2 H, m), 3.62–3.65 (1 H, m), 3.72–3.78 (1 H, m), 3.77 (3 H, s), 4.08–4.11 (1 H, m), 4.36–4.38 (2 H, AB), 4.65 (2 H, AB), 4.51–4.89 (5 H, m), 5.02 (2 H, AB), 5.05–5.16 (2 H, m), 5.41 (1 H, br), 5.72 (1 H, br), 6.80 (2 H, d, J = 8.5), 7.02 (1 H, br), 7.10 (2 H, d, J = 8.5), 7.29–7.32 (5 H, m); HRMS calcd for $C_{66}H_{109}O_{16}N_5Si$ (M) 1255.764, found 1255.764.

***N*-[1-[*N*-[(Benzyloxy)carbonyl]-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, 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 (29).** To a solution of DMSO (0.07 mL, 0,99 mmol) in CH_2Cl_2 (2 mL), at −78 °C, was added, dropwise, trifluoroacetic anhydride (0.1 mL, 0.71 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at −78 °C for 20 min, and alcohol **28** (253 mg, 0.201 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 1.5 h, triethylamine (0.14 mL, 1.0 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. After 1 h at ambient temperature, the reaction was diluted with ether (25 mL). The organic solution was washed with 5% HCl (5 mL), 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting unstable aldehyde was then dissolved in *tert*-butyl alcohol (0.9 mL) and treated with 5% NaH_2PO_4 (0.6 mL) and 1 M $KMnO_4$ (0.9 mL) solutions. After 0.5 h, the solution was diluted with ether (10 mL) and cooled to 0 °C. A saturated solution of Na_2SO_3 was added dropwise (2 mL). To the resulting solution was added 10% HCl until the aqueous layer was pH 3. The aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. It was found that the resulting crude foam could be purified by column chromatography eluting with $CH_3OH/CHCl_3$ (1:9); however, the recovery varied. The crude material from this oxidation sequence was usually used directly in the next step without purification: R_f 0.46 $CHCl_3/CH_3OH$ (90:10), $[\alpha]_D^{25}$ −15° (*c* 0.27, $CHCl_3$); IR (KBr) 3600–3300 (br), 1745–1710 (s), 1670–1650 (s), 1525 (m), 1465 (m), 1400 (w), 1380 (w), 1260 (s), 1230 (w), 1185 (s), 930 (w), 890 (w), 680 (w) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.83–1.02 (15 H, m), 1.04–1.09 (18 H, m), 1.29 (3 H, d, J = 6.1), 1.32 (3 H, d, J = 5.5), 1.41 (9 H, s), 1.41–1.43 (3 H, m), 1.36–2.31 (12 H, m), 2.53–2.61 (1 H, m), 2.63–2.77 (2 H, m), 2.88 (3 H, s), 3.02–3.10 (1 H, m), 3.24 (1 H, J^1 = 4.9, J^2 = 13.6), 3.32 (3 H, s), 3.60–3.68 (2 H, m), 3.74 (3 H, s), 3.78–3.83 (1 H, m), 4.03–4.12 (2 H, m), 4.48–4.53 (3 H, m), 4.61 (2 H, AB), 4.86–4.89 (1 H, m), 5.03–5.10 (1 H, m), 5.08 (2 H, AB), 6.84 (2 H, d, J = 8.4), 7.16 (2 H, d, J = 8.4), 7.32–7.39 (5 H, m); HRMS calcd for $C_{66}H_{107}O_{17}N_5SiNa$ (M + Na) 1292.733, found 1292.740.

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-(methoxymethoxy)-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (30). Crude acid **29** (0.201 mmol), obtained from the previous reaction sequence, was dissolved in CH_3OH/EtOAc (1:1, 2 mL). To the resulting solution was added 10% Pd/C (50 mg). The reaction mixture was stirred under an atmosphere of hydrogen (40 psi). After 24 h, the solution was filtered through Celite, dried (Na_2SO_4), dissolved in toluene, and concentrated several times. The crude product was then dissolved in degassed DMF (20 mL) and cooled to 0 °C. To this solution was added diphenylphosphoryl azide (0.45 mL of a 0.5 M solution in DMF, 0.23 mmol) and solid $NaHCO_3$ (170 mg, 2.0 mmol). After 3 days at 0 °C, the DMF was removed by distillation in vacuo. The remaining crude oil was dissolved in EtOAc (25 mL) and washed with 10% citric acid (5 mL), 5% $NaHCO_3$ (5 mL), and saturated sodium chloride (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude material was purified by column chromatography eluting with acetone/$CHCl_3$ (10:90 to 20:80). Compound **30** (90 mg, 40% yield from compound **28**) was obtained as a white foam: R_f 0,68 $CHCl_3$/acetone (80:20); $[\alpha]_D^{25}$ −84.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3400 (m), 1755–1715 (s), 1670–1650 (s), 1510 (m), 1470 (m), 1380 (w), 1260 (w), 1170 (s), 1120 (w), 1050 (m), 930 (w), 890 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0,84–1.09 (36 H, m), 1.23–1.32 (9 H, m), 1,44 (9 H, s), 1.56–1.60 (2 H, m), 1.74–1.77 (4 H, m), 1.99–2.18 (5 H, m), 2.51 (3 H, s), 2.55–2.63 (3 H, m), 2.87–2.94 (1 H, m), 3.19–3.21 (1 H, m), 3.36 (1 H, dd, J^1 = 4.5, J^2 = 14.2), 3.40 (3 H, m), 3.53 (1 H, J^1 = 4.5, J^2 = 10.5), 3.60–3.72 (3 H, m), 3.80 (3 H, s), 3,91–3.93 (1 H, m), 4.09–4.11 (1 H, m), 4.31–4.37 (4 H, m), 4.58–4.60 (1 H, m), 4.67–4.77 (4 H, m), 4.86–4.89 (1 H, m), 5.00 (1 H, d, J = 10.5), 6.79–6.86 (2 H, m), 7.08–7.10 (2 H, m), 7.30–7.44 (1 H, m); HRMS calcd for $C_{58}H_{100}O_{14}N_5Si$ (M + H) 1118.704, found 1118.700.

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-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl]. To a cold (−78 °C), stirred solution of the MOM ether **30** (161 mg, 0.143 mmol) in 0.95 mL of dry CH_2Cl_2 was added dropwise a solution of dimethylboron bromide (1.79 M, 0.240 mL) in CH_2Cl_2. After 1 h at −78 °C, the reaction mixture was cannulated into a vigorously stirred mixture of THF (2 mL) and saturated aqueous $NaHCO_3$ (1 mL). After 5 min, the mixture was diluted with ether, and the organic layer was separated and washed successively with water, 10% aqueous sodium bisulfate, and saturated NaCl. The aqueous layers were extracted with ether, and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography, eluting with acetone/$CHCl_3$ (3:97) to give the desired alcohol (142 mg, 93% yield) as a foam: R_f 0.44 $CHCl_3$/acetone (90:10); $[\alpha]_D^{24}$ −73.5° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3370 (w), 3000 (s), 2895 (s), 1750 (m), 1720 (m), 1670 (m), 1660 (s), 1520 (m), 1455 (m), 1395 (m), 1250 (m), 1170 (m), 1120 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87–0.95 (18 H, m), 1.0–1.1 (21 H, m), 1,15 (1 H, m), 1.25 (3 H, d, J = 5.74), 1.34 (3 H, d, J = 6.68), 1.43 (9 H, s), 1.53 (3 H, m), 1.77 (2 H, m), 2.02 (1 H, m), 2.16 (4 H, m), 2.32 (1 H, m), 2,49 (1 H, m), 2,52 (3 H, s), 2,90 (1 H, d, J = 19,1), 3.18 (1 H, m), 3.34 (1 H, m), 3.52 (1 H, m), 3.62 (1 H, m), 3.73 (1 H, m), 3.79 (3 H, s), 3.88 (1 H, m), 4.11 (1 H, m), 4.35 (1 H, m), 4.59 (1 H, m), 4.68 (2 H, m), 4.85–4,92 (2 H, m), 4,96 (1 H, d, J = 10.43), 6.84–6.86 (2 H, m), 7.08–7.10 (2 H, m), 7.45–7.47 (1 H, d); HRMS calcd for $C_{56}H_{96}O_{13}N_5Si$ (M + H) 1074.677, found 1074.683.

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-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (31). To a solution containing DMSO (0.18 mL, 2.54 mmol) and CH_2Cl_2 (1.44 mL), at −78 °C, was added, dropwise, trifluoracetic anhydride (0.18 mL, 1.27 mmol) in CH_2Cl_2 (0.72 mL). The resulting mixture was stirred at −78 °C for 30 min, and the alcohol obtained from **30** (128 mg, 0.119 mmol), in CH_2Cl_2 (4.2 mL), was added dropwise. Stirring at −78 °C was continued for 1.5 h, and triethylamine (0.05 mL, 0.358 mmol) in CH_2Cl_2 (0.1 mL) was added dropwise to the reaction mixture. After 5 min at room temperature, the reaction was diluted with ether (25 mL). The organic solution was extracted with 5% HCl (5 mL), 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was then purified by column chromatography, eluting with acetone/$CHCl_3$ (3:97) to afford ketone **31** (118 mg, 92%) as a white foam: R_f 0.54 chloroform/acetone (90:10); $[\alpha]_D^{25}$ −140° (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3370 (w), 3000 (m), 2900 (m), 1750 (s), 1720 (s), 1650-1700 (s), 1590 (w), 1520 (m), 1460 (m), 1310 (w), 1260 (m), 1180 (s), 890 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85–0.98 (18 H, m),

1.01–1.09 (21 H, m), 1.15–1.19 (1 H, m), 1.25 (3 H, d, J = 5.80), 1.35 (3 H, d, J = 7.20), 1.44 (9 H, s), 1.51–1.55 (1 H, m), 1.60–1.64 (2 H, m), 1.72–1.81 (2 H, m), 2.0 (1 H, m), 2.11–2.21 (4 H, m), 2.51 (3 H, s), 2.52–2.58 (1 H, m), 3.10–3.14 (1 H, m), 3.15–3.20 (1 H, m), 3.35 (1 H, m), 3.51–3.54 (1 H, m), 3.62–3.64 (1 H, m), 3.72–3.75 (1 H, m), 3.81 (3 H, s), 4.11–4.18 (1 H, t), 4.32–4.38 (1 H, t), 4.55 (1 H, m), 4.61–4.67 (1 H, m), 4.80–4.88 (1 H, m), 4.91–4.97 (1 H, m), 4.98 (1 H, m), 5.07–5.14 (1 H, d, J = 10.21), 6.84–6.87 (2 H, m), 7.08–7.11 (2 H, m), 7.21–7.26 (1 H, m), 7.72–7.76 (1 H, m); HRMS calcd for $C_{56}H_{94}O_{13}N_5Si$ (M + H) 1072.662, found 1072.659.

Cyclo-[*O*-[[*N*-[(2*S*,3*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-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] Hydrochloride. A solution of ketone **31** (114 mg, 0.106 mmol) in 2.0 mL of EtOAc was cooled to −30 °C. Gaseous HCl was then introduced at such a rate that the temperature of the reaction mixture was maintained between −10 °C and −20 °C at saturation. The solution was kept for 2 h at this temperature and then kept 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 concentrating the solution, the residue was triturated and washed by decantation with three 2-mL portions of *tert*-butyl methyl ether/hexane (1:4). The product was collected by filtration and dried in vacuo. Compound **1d** (81 mg, 90%) was obtained as a white solid salt: R_f 0.54 methanol/chloroform (10:90); $[\alpha]_D^{25}$ −164.7° (c 1.28, $CHCl_3$); IR ($CHCl_3$) 3260–3360 (m), 3000 (m), 2980 (m), 1740 (s), 1700 (m), 1670 (s), 1650 (s), 1520 (m), 1470 (m), 1315 (w), 1260 (m), 1180 (m), 1130 (m), 970 (w), 830 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80–1.17 (18 H, m), 1.21–1.26 (1 H, m), 1.31–1.36 (3 H, d), 1.38–1.42 (3 H, d), 1.51–1.58 (1 H, m), 1.71–1.78 (2 H, m), 1.81–1.88 (2 H, m), 2.11–2.19 (3 H, m), 2.2–2.3 (2 H, m), 2.55 (3 H, s), 2.65–2.73 (1 H, m), 2.8–3.0 (1 H), 3,05–3.14 (1 H, m), 3.31–3.39 (1 H, m), 3.57–3.64 (1 H, m), 3.66–3.72 (1 H, m), 3.81 (3 H, s), 3.83–3.90 (2 H, m), 4.07–4.16 (2 H, m), 4.31–4.39 (2 H, m), 4.6–4.7 (2 H, m), 5.01–5.08 (1 H, m), 5.45–5.48 (1 H, m), 6.81–6.89 (2 H, m), 7.11–7.18 (2 H, m), 7.43–7.52 (1 H, m), 8.13–8.31 (2 H, m), 8.46–8.52 (1 H, m); HRMS calcd for $C_{42}H_{66}O_{11}N_5$ (M − Cl) 816.4759, found 816.4702.

Didemnin A (1a). BOP (18.2 mg, 41.2 μmol) and N-methylmorpholine (7.6 μL) were added to a solution of amine salt **1d** (23.4 mg, 27.5 μmol) and N-Z-methyl-D-leucine (15 mg, 41.2 μmol), in CH_2Cl_2 (0.15 mL) at 0 °C. After 30 min, the solution was brought to room temperature and stirred for 3 h. After this time, the reaction mixture was treated with 2 mL of saturated NaCl solution, and the solution was extracted with 5 mL of EtOAc. The organic layers were combined and washed with 5% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with methanol/chloroform (3:97) to give a white solid (22 mg, 75% yield), which was directly used in the next deprotection. To a suspension of 10% Pd/C (4.4 mg) in CH_3OH/EtOAc solution (1:1, 0.3 mL) was added the cyclic depsipeptide (22 mg, 20.6 μmol) in CH_3OH (0.1 mL). The solution was subjected to an atmosphere of hydrogen (40 psi) and stirred for 18 h. After this time, the reaction mixture was filtered through Celite. The Celite was washed with methanol and the filtrate was concentrated. The residue was purified by chromatography, eluting with MeOH/$CHCl_3$ (3:97) to give 16.5 mg (85% yield) of didemnin A (**1a**) as white crystals. Recrystallization from chloroform/hexane afforded the pure material: mp 140–142 °C; R_f 0.5 chloroform/methanol (90:10); $[\alpha]_D^{25}$ −149.1° (c 0.40, $CHCl_3$); IR ($CHCl_3$) 3325 (m), 3000 (s), 1730 (s), 1650 (s), 1630 (s), 1540 (m), 1510 (m), 1450 (m), 1380 (w), 1320 (w), 1300 (w), 1270 (m), 1170 (m), 1080 (w), 830 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.97 (24 H, m), 1.15–1.19 (1 H, m), 1.22–1.25 (1 H, m), 1.31 (3 H, d, J = 5.7), 1.33 (3 H, d, J = 6.4), 1.37–1.42 (2 H, m), 1.59–1.63 (2 H, m), 1.63–1.72 (1 H, m), 1.74–1.78 (1 H, m), 1.80–1.84 (1 H, m), 2.02–2.09 (2 H, m), 2.11–2.16 (2 H, m), 2.35–2.39 (1 H, m), 2.43 (3 H, s), 2.47–2.53 (1 H, m), 2.56 (3 H, s), 2.96–2.98 (1 H, m), 3.04–3.2 (2 H, m), 3.38 (1 H, dd, J = 3.7 Hz, 14 Hz), 3.52–3.61 (2 H, m), 3.71–3.76 (1 H, m), 3.8 (3 H, s), 4.0–4.05 (1 H, m), 4.05–4.14 (1 H, m), 4.16–4.19 (1 H, m), 4.58–4.62 (1 H, m), 4.77–4.81 (1 H, m), 4.82–4.86 (1 H, m), 5.03–5.07 (1 H, m), 5.19 (1 H, d, J = 4.3 Hz), 6.85 (2 H, d, J = 8.54 Hz), 7.09 (d, J = 8.5 Hz), 7.48 (1 H, m), 7.91 (1 H, br s), 8.12 (1 H, br); HRMS calcd for $C_{49}H_{79}N_6O_{12}$ (M + H) 943.575, found 943.579.

(*S*)-Ethyl 2-[(*tert*-Butyldimethylsilyl)oxy]lactate (32). (*S*)-Ethyl lactate (2.50 g, 21.2 mmol) was dissolved in DMF (71.6 mL). To this solution was added *tert*-butyldimethylsilyl chloride (4.79 g, 31.8 mmol) and imidazole (5.05 g, 74.2 mmol). The reaction mixture was stirred for 3 h. After this time, the reaction mixture was diluted with saturated NaCl solution (100 mL) and extracted with ether (3 × 50 mL). The combined ether layers were washed with ice cold 5% HCl and saturated NaCl solutions. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (3:97). Compound **32** (4.52 g, 92%) was obtained as an oil: R_f 0.56 EtOAc/petroleum ether (5:95); $[\alpha]_D^{23}$ −28.9° (c 1.26, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2980 (s), 2960 (s), 2860 (s), 1750 (s), 1470 (m), 1380 (m), 1260 (s), 1150 (s), 840 (s); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.88 (9 H, s), 1.2 (3 H, t), 1.35 (3 H, d, J = 6.7), 4.2 (2 H, m), 4.3 (1 H, q); HRMS calcd for $C_{11}H_{28}O_3NSi$ (M + NH_4) 250.1838, found 250.1821

2-[(*tert*-Butyldimethylsilyl)oxy]-L-lactyl-L-proline Methyl Ester (33). To a cold solution of compound **32** (2.87 g, 12.35 mmol) in THF (123.5 mL) was added, dropwise, a cold 0.2 M lithium hydroxide solution (123.5 mL) over a 10-min period. Stirring was continued for 3 h at ambient temperature. After this time, the solution was concentrated to half its volume and washed with ether (2 × 15 mL). The combined ether layers were extracted with saturated $NaHCO_3$ (10 mL), and the aqueous layers were combined. The aqueous layers were acidified to pH 4 with 1 N potassium hydrogen sulfate. The acidified aqueous layer was extracted with ether (3 × 50 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, providing the corresponding acid as an oil, which was used directly in the next step. L-Proline methyl ester hydrochloride (1.00 g, 6.03 mmol) was dissolved in CH_2Cl_2 (16 mL). To this solution was added N-methylmorpholine (1.99 mL, 18.09 mmol) at 0 °C. The reaction was stirred for 10 min, and the acid (1.35 g, 6.64 mmol) in CH_2Cl_2 (18 mL) was added via a cannula needle. DCC (1.37 g, 6.64 mmol) and HOBT (0.978 g, 7.24 mmol) were then added. After 24 h, the solid formed was collected by filtration and washed with EtOAc. The filtrate was concentrated under reduced pressure and diluted with ether (200 mL). The reaction mixture was filtered again, and the collected solid was washed with ether. The ether layer was washed with 5% HCl (25 mL), 5% $NaHCO_3$ (25 mL), and saturated NaCl (25 mL) solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (20:80). Compound **33** (1.14 g, 60%) was obtained as an oil: R_f 0.64 acetone/methylene chloride (10:90); $[\alpha]_D^{25}$ −77.1° (c 2.30, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2980 (s), 2950 (s), 1750 (s), 1670–1630 (s), 1470–1430 (s), 1370 (m), 1270 (m), 1180 (m), 1140 (m), 1100 (m), 840 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05–0.07 (6 H, s), 0.86 (9 H, s), 1.34 (3 H, d, J = 6.74), 1.84–2.14 (4 H, m), 3.67 (3 H, s), 3.67–3.73 (2 H, m), 4.42–4.45 (1 H, m), 4.46–4.47 (1 H, m); HRMS calcd for $C_{15}H_{30}O_4NSi$ (M + H) 316.1946, found 316.1945.

2-[(*tert*-Butyldimethylsilyl)oxy]-L-lactyl-L-proline (34). To a cold solution of compound **33** (0.45 g, 1.43 mmol) in THF (38 mL) was added, dropwise, a cold 0.1 M LiOH solution (38 mL) over a 10-min period. Stirring was continued for 5 h at room temperature. The solution was then concentrated to half its volume and washed with ether (2 × 10 mL). The combined ether layers were extracted with saturated $NaHCO_3$ (10 mL), and the aqueous layers were combined. The aqueous layers were acidified to pH 4 with 1 N potassium hydrogen sulfate. The acidified aqueous layer was extracted with ether (3 × 30 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated. Recrystallization of the residue from ether/petroleum ether afforded acid **34** (0.38 g, 89%) as a white solid: mp 72–73 °C; R_f 0.36 $CHCl_3$/MeOH (80:20); $[\alpha]_D^{26}$ −131.7° (c 1.16, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2990 (s), 2960 (s), 1775 (s), 1735 (s), 1640 (s), 1475 (m), 1455 (m), 1445 (m), 1265 (m), 1145 (m), 950 (w), 845 (s); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08 (6 H, s), 0.89 (9 H, s), 1.41 (3 H, d, J = 6.65), 1.9–2.4 (4 H, m), 3.68–3.73 (2 H, m), 4.48–4.56 (1 H, m), 4.59–4.63 (1 H, m); HRMS calcd for $C_{14}H_{28}O_5NSi$ (M + H) 302.1789, found 302.1790.

***N*-[(Benzyloxy)carbonyl]-*N*-methyl-D-leucine 2-(Trimethylsilyl)ethyl Ester.** Z-D-Me-Leu was prepared on a 10-mmol scale by phase-transfer catalysis, as previously described [77% from D-leucine; $[\alpha]_D^{24}$ + 23° (c 1 ethanol) (lit.[36] $[\alpha]_D^{25}$ −23° for the L-isomer)]. To Z-D-Me-Leu (2.15 g, 7.69 mmol), at 0 °C in DMF (38 mL), were added sequentially triethylamine (1.34 mL, 9.61 mmol), 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (3.69 g, 19.2 mmol), DMAP (5.17 g, 42.3 mmol), and 2-(trimethylsilyl)ethanol (1.65 mL, 11.5 mmol). After 30 min, the reaction was brought to ambient temperature and was stirred for 24 h. After this time, the reaction was diluted with ether (150 mL) and washed successively with 10% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (4:96). The pure ester (2.51 g, 86%) was obtained as an oil: R_f 0.28 EtOAc/petroleum ether (5:95); $[\alpha]_D^{23}$ +29.2° (c 1.87, $CHCl_3$); IR ($CHCl_3$) 2990 (s), 1745 (s), 1710 (s), 1470 (w), 1415 (w), 1330 (m), 1260 (m), 1165 (m), 870 (w), 850 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (9 H, s), 0.8–0.9 (8 H, m), 1.45–1.70 (3 H, m), 2.85 (3 H, s), 4.15 (2 H, m), 4.62–4.9 (1 H, m), 5.15 (2 H, s), 7.3 (5 H, m); HRMS calcd for $C_{20}H_{34}NO_4Si$ (M + H) 380.2259, found 380.2246.

***N*-Methyl-D-leucine 2-(Trimethylsilyl)ethyl Ester (35).** The previously prepared ester (4.24 g, 11.14 mmol) was dissolved in CH_3OH/EtOAc (1:1, 55.6 mL). To the resulting solution was added 10% Pd/C (0.848 g). The reaction mixture was stirred under an atmosphere of hydrogen (35 psi). After 15 h, the solution was filtered through Celite, dried (Na_2SO_4), and concentrated. The resulting amine (**35**) was used directly in the next step: R_f 0.28 EtOAc/petroleum ether (20:80); $[\alpha]_D^{23}$ +5.9° (*c* 1.75, $CHCl_3$); IR ($CHCl_3$) 3520 (s), 3015 (s), 2970 (m), 1750 (s), 1470 (w), 1410 (m), 1300 (m), 890 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (9 H, s), 0.9–1.05 (8 H, m), 1.45 (2 H, m), 1.7 (1 H, m), 2.35 (3 H, s), 3.15 (1 H, m), 4.2 (2 H, m); HRMS calcd for $C_{12}H_{28}NO_2Si$ (M + H) 246.1891, found 246.1860.

L-Lactyl-L-propyl-*N*-methyl-D-leucine (36). Acid **34** (0.43 g, 1.44 mmol) was dissolved in CH_2Cl_2 (15 mL), and the solution was cooled to −15 °C. To this solution was added BOP-Cl (0.404 g, 1.58 mmol), followed by the dropwise addition of triethylamine (0.22 mL, 1.58 mmol). The mixture was stirred at −15 °C for 30 min and then was concentrated to 6 mL. Amine **35** (0.42 g, 1.58 mmol) and triethylamine (0.20 mL, 1.44 mmol) were added, and, after this addition, the reaction was brought to 0 °C and kept at this temperature until no acid component could be detected by TLC. The reaction mixture was then diluted with ether (40 mL), and the organic layer was washed with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (20:80 to 25:75). The fully protected dipeptide (0.53 g, 69%) was obtained as an oil. The above dipeptide (0.30 g, 0.567 mmol) was dissolved in DMF (2.12 mL) at 0 °C and treated with tetrabutylammonium fluoride (1.1 M, 1.69 mL) in THF. The reaction was stirred and followed by TLC to completion. The reaction was then diluted with saturated NaCl solution (2 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were combined and washed with 5% HCl and saturated NaCl solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Recrystallization from 2-propanol/hexane afforded the pure material (0.14 g, 78%): mp 225–230 °C; R_f 0.8 chloroform/methanol/water (6:4:1); $[\alpha]_D^{25}$ −23.9° (*c* 0.85, ethanol); IR (KBr) 3400 (m), 3000 (m), 1715 (s), 1665 (s), 1610 (s), 1455 (m), 1415 (w), 1275 (w), 1135 (m), 1040 (m), 920 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87–0.92 (6 H, m), 1.41 (3 H, d, *J* = 6.74), 1.63–1.69 (1 H, m), 1.81–1.87 (2 H, m), 1.97–2.23 (4 H, m), 2.99 (3 H, s), 3.6 (2 H, m), 4.4 (1 H, q), 4.8 (1 H, m), 5.3 (1 H); HRMS calcd for $C_{15}H_{27}O_5N_2$ (M + H) 315.1922, found 315.1924.

Didemnin B. To a solution of amine salt (**1d**) (21.1 mg, 24.8 μmol) and L-lactyl-L-prolyl-*N*-methyl-D-leucine (**36**) (11.7 mg, 37.2 μmol), in CH_2Cl_2 (0.16 mL) and at 0 °C, were added BOP (16.5 mg, 37.2 μmol) and *N*-methylmorpholine (6.82 μL). After 30 min, the solution was brought to room temperature and stirred for 3 h. After this time, the reaction mixture was treated with 2 mL of saturated NaCl solution and then extracted with 5 mL of EtOAc. The organic layers were combined and washed successively with 5% HCl, saturated NaCl, 5% $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with $CH_3OH/CHCl_3$ (3:97) to afford 16 mg (59%) of didemnin B as white crystals. Recrystallization from chloroform/hexane afforded the pure material: mp 158–160 °C; R_f 0.63 chloroform/methanol (90:10); $[\alpha]_D^{24}$ −91.9° (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 3325 (m), 3000 (s), 1730 (s), 1645 (s), 1635 (s), 1540 (w), 1510 (m), 1460 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86–0.97 (24 H, m), 1.17–1.25 (3 H, m), 1.32 (3 H, d, *J* = 6.8 Hz), 1.38 (3 H, d, *J* = 5.2), 1.39 (3 H, d, *J* = 6.7 Hz), 1.43–1.48 (1 H, m), 1.61–1.62 (1 H, m), 1.63–1.71 (1 H, m), 1.72–1.78 (1 H, m), 1.81–1.86 (2 H, m), 1.98–2.02 (2 H, m), 2.02–2.04 (2 H, m), 2.12–2.14 (2 H, m), 2.22–2.23 (2 H, m), 2.35–2.36 (1 H, m), 2.56 (3 H, s), 2.60–2.63 (1 H, dd, *J* = 10.6 Hz, 16.8 Hz), 3.16 (3 H, s), 3.17–3.18 (1 H, m), 3.25–3.26 (1 H, m), 3.37–3.38 (1 H, dd, *J* = 3.9 Hz, 14.2 Hz), 3.56–3.59 (2 H, dd, *J* = 4.2 Hz, 11 Hz), 3.61–3.62 (1 H, m), 3.67–3.69 (2 H, m), 3.79 (3 H, s), 4.05–4.11 (2 H, m), 4.24–4.25 (1 H, m), 4.38–4.39 (1 H, m), 4.55 (1 H, m), 4.64 (1 H, m), 4.74 (1 H, t, *J* = 7.7 Hz), 4.81 (1 H, m), 5.18–5.19 (1 H, d, *J* = 3.5 Hz), 5.36–5.42 (2 H, m), 6.83–6.85 (2 H, d, *J* = 8.6 Hz), 7.06–7.08 (2 H, d, *J* = 8.5 Hz), 7.18–7.20 (1 H, m), 7.65–7.66 (1 H, m), 7.79–7.81 (1 H, m); HRMS calcd for $C_{57}H_{90}N_7O_{15}$ (M + H) 1112.650, found 1112.658.

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-D-leucine Benzyl Ester (40).** To a solution of Boc-D-MeLeu (5.50 g, 22.4 mmol), at 0 °C in DMF (90 mL), were added lithium carbonate (1.74 g, 23.5 mmol) and benzyl bromide (3.99 g, 33.6 mmol). The reaction was brought to ambient temperature and stirred for 6 h. After this time, the reaction was diluted with H_2O (200 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with saturated NaCl solution (2 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/petroleum ether (5:95). Compound **40** (6.83 g, 91%) was obtained as a solid: R_f 0.4 EtOAc/petroleum ether (10:90); $[\alpha]_D^{25}$ +32.9° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3040 (m), 2990 (s), 1750 (s), 1680–1710 (s), 1465 (m), 1405 (s), 1380 (s), 1340 (s), 1260 (m), 1160 (s), 980 (w), 920 (w), 870 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (6 H, m), 1.45 (9 H, d), 1.5–1.8 (3 H, m), 2.75–2.8 (3 H, d, *J* = 12.1), 4.6–4.9 (1 H, m), 5.2 (2 H, s), 7.4 (5 H, s); HRMS calcd for $C_{19}H_{30}O_4N$ (M + H) 336.2175, found 336.2227.

2-[(*tert*-Butyldimethylsilyl)oxy]-L-lactyl-*N*-methyl-D-leucine Benzyl Ester (41). To a stirred solution of *N*-Boc-*N*-methyl-D-leucine benzyl ester (4.94 g, 14.7 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C, and under a nitrogen atmosphere, was added anhydrous trifluoracetic acid (22.6 mL, 294 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at 0 °C for 1.5 h, after which the solvent was removed under reduced pressure. The residual TFA and water were removed with dry toluene (4 × 20 mL) and hexane (2 × 50 mL). The crude material was used in the next step. TBDMS-lactic acid (0.21 g, 1.03 mmol) was dissolved in methylene chloride (10.3 mL). The solution was then cooled to −15 °C and treated with BOP-Cl (0.26 g, 1.12 mmol), followed by the dropwise addition of triethylamine (0.16 mL, 1.12 mmol). After stirring for 0.5 h, the reaction mixture was concentrated to 4 mL and treated with the previously prepared amine TFA salt (0.30 g, 0.86 mmol) and triethylamine (0.24 mL, 1.76 mmol). After the addition, the reaction was brought to 0 °C and kept there until the secondary amine had been consumed (TLC). The reaction was diluted with ether (30 mL) and washed with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (10:90 to 15:85). Compound **41** (0.30 g, 82%) was obtained as an oil: R_f 0.38 EtOAc/petroleum ether (15:85); $[\alpha]_D^{24}$ +21.7° (*c* 2.33, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2960 (m), 2880 (w), 1750 (s), 1640–1670 (s), 1470 (m), 1270 (m), 1130 (s), 970 (w), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.8 (15 H, m), 1.36 (3 H, d, *J* = 6.83), 1.4 (1 H, m), 1.7 (2 H, m), 3.0 (3 H, s), 4.6 (1 H, q), 5.2 (2 H, q), 5.3 (1 H, m), 7.3 (5 H, m); HRMS calcd for $C_{23}H_{40}O_4NSi$ (M + H) 422.2726, found 422.2710.

2-[(*tert*-Butyldimethylsilyl)oxy]-L-lactyl-*N*-methyl-D-leucine (42). To benzyl ester **41** (0.21 g, 0.5 mmol) was added CH_3OH/EtOAc (1:1, 2.5 mL). To the resulting solution was added 10% Pd/C (42 mg). The reaction mixture was stirred under an atmosphere of hydrogen (35 psi). After 5 h, the solution was filtered through Celite, dried (Na_2SO_4), and concentrated. The resulting acid (**42**) (0.17 g, 0.50 mmol) was used directly in the next step: R_f 0.62 $CHCl_3$/MeOH (80:20); $[\alpha]_D^{25}$ +33.8° (*c* 1.67, $CHCl_3$); IR ($CHCl_3$) 2990 (s), 2960 (s), 2895 (m), 1730 (s), 1640 (s), 1480 (m), 1420 (m), 1270 (m), 1140 (m), 1105 (m), 970 (w), 845 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.86 (9 H, s), 1.4 (3 H, d, *J* = 6.75), 1.44–1.47 (1 H, m), 1.7 (2 H, m), 3.0 (3 H, s), 4.58 (1 H, q), 5.06 (1 H, m); HRMS calcd for $C_{23}H_{40}O_4NSi$ (M + H) 332.2258, found 332.2258.

Didemnin C. To a solution of amine salt **1d** (21.1 mg, 24.8 μmol) and TBDMS-(*S*)-lac-(*N*ME)-L-leucine (**42**) (12.3 mg, 37.2 μmol), in CH_2Cl_2 (0.16 mL) and at 0 °C, were added BOP (10.9 mg, 24.8 μmol) and *N*-methylmorpholine (6.8 μL). After 30 min at 0 °C, the reaction mixture was warmed to ambient temperature and stirred for 3 h. After addition of 2 mL of saturated sodium chloride to the reaction mixture, the solution was extracted with 5 mL of EtOAc. The organic layers were combined and washed successively with 5% HCl, 5% $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with $CH_3OH/CHCl_3$ (3:97) to give a white solid (21 mg, 75% yield), which was directly used in the next deprotection. A solution of the above cyclic depsipeptide (21.0 mg, 18.5 μmol) in acetonitrile (0.42 mL) was cooled to −15 °C. A 15% solution of HF (48%) in acetonitrile was cooled to −15 °C, and 0.21 mL of this solution was added to the reaction mixture dropwise. After 2 h, the reaction was warmed to 0 °C and stirred at this temperature for 1 h. After this time, the reaction mixture was diluted with ether (10 mL), poured in 2 mL of 2 N potassium hydrogen sulfate/saturated sodium chloride solution (1:1), and extracted again with ether. The combined ether layers were dried and concentrated. The resulting residue was purified by column chromatography, eluting with $MeOH/CHCl_3$ (3:97). The resulting solid was recrystallized from $CHCl_3$/hexane to afford didemnin C (16.8 mg, 89%) as a white solid: mp 117–120 °C; R_f 0.68 chloroform/methanol (90:10); $[\alpha]_D^{24}$ −118.9° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3325 (m), 3000 (s), 1735 (s), 1660 (s), 1640 (s), 1540 (w), 1510 (m), 1450 (m), 1370 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81–0.92 (24 H, m), 1.10–1.11 (1 H, m), 1.19 (3 H, d, *J* = 6.4 Hz), 1.34 (3 H, d, *J* = 6.9 Hz), 1.38 (3 H, d, *J* = 7.4 Hz), 1.49–1.58 (2 H, m), 1.59–1.70 (4 H, m), 1.71–1.79 (2 H, m), 2.0–2.08 (2 H, m), 2.11–2.19 (2 H, m), 2.31–2.37 (1 H, m),

2.42-2.49 (1 H, m), 2.52 (3 H, s), 2.90 (3 H, s), 2.99-3.02 (1 H, m), 3.16-3.18 (1 H, m), 3.33-3.36 (1 H, m), 3.54-3.59 (2 H, m), 3.69 (1 H, m), 3.78 (3 H, s), 3.98-4.01 (2 H, m), 4.14-4.20 (1 H, m), 4.54-4.57 (2 H, m), 4.76-4.82 (2 H, m), 5.03-5.09 (1 H, m), 5.10-5.13 (1 H, m), 5.16-5.17 (1 H, d, J = 3.6 Hz), 6.82 (2 H, d, J = 8.4 Hz), 7.0 (1 H, m), 7.05 (2 H, d, J = 8.5 Hz), 7.33 (1 H, m, J = 8.5 Hz), 7.87 (1 H, m); HRMS calcd for $C_{52}H_{83}N_6O_{14}$ (M + H) 1015.5967, found 1015.5831.

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Syntheses of Macrocyclic Enzyme Models. 7.† Octopus Cyclophanes Having L-Aspartate Residues as Novel Water-Soluble Hosts. Aggregation Behavior and Induced-Fit Molecular Recognition

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Abstract: Octopus cyclophanes (**1** and **2**), having chiral L-aspartate residues as connector units interposed between a rigid 2,11,20,29-tetraaza[3.3.3.3]paracyclophane skeleton and four double-chain hydrocarbon segments, were prepared. Aggregation behavior of the octopus cyclophanes in aqueous media was characterized by means of electron microscopy as well as by surface tension and dynamic light scattering measurements. Its consequence in guest recognition was clarified by employing ^{1}H NMR, fluorescence, and circular dichroism (CD) spectroscopy. Multiwalled bilayer vesicles were observed in an aqueous dispersion of **1** by negative-staining electron microscopy. The present cationic hosts strongly bind anionic and nonionic hydrophobic guests, such as 8-anilinonaphthalene-1-sulfonate, 6-*p*-toluidinonaphthalene-2-sulfonate, *N*-phenyl-1-naphthylamine, and *N*-phenyl-2-naphthylamine, to form inclusion complexes in 1:1 stoichiometry, regardless of aggregation status of the hosts, monomeric or vesicular. Two types of guest-binding behavior were exercised by the octopus cyclophanes, depending on the nature of media used for preparation of their stock solutions. When an aqueous stock solution of the host was injected into an aqueous buffer containing a guest, the host–guest complexation immediately reached an equilibrium state, as monitored by fluorescence spectroscopy. Concurrently, the chiral L-aspartate residues of the host molecule underwent conformational changes so as to attain effective guest incorporation. ^{1}H NMR spectroscopy applied to the host–guest complexation indicated that the guest molecule was undoubtedly incorporated into the three-dimensional cavity provided intramolecularly by the macrocyclic ring and the eight hydrocarbon chains. On the other hand, when an organic stock solution of **1** in methanol, ethanol, tetrahydrofuran, or dioxane was injected into an aqueous buffer containing a guest, time-dependent and biphasic complexation behavior was observed as reflected in various fluorescence parameters, such as fluorescence intensity, maximum, polarization, lifetime, and rotational correlation time, attributable to the incorporated guest molecule. This behavior is consistent with fast incorporation of a guest molecule into the hydrophobic host cavity followed by slow and long-range conformational changes of the host, as induced by the incorporated guest. Such biphasic complexation behavior was very sensitive to molecular architecture at the connector portions in the hosts. Dynamic aspects of the induced-fit molecular recognition by the present octopus cyclophanes are discussed.

Introduction

The hydrophobic interaction is the prevailing driving force for molecular recognition in aqueous media, and other recognition forces for distinct molecular discrimination, such as electrostatic, hydrogen-bonding, and charge-transfer interactions, become effective in the sufficiently desolvated and hydrophobic microenvironments which are well shielded from bulk aqueous phase. As artificial hosts capable of providing hydrophobic recognition sites, macrocyclic compounds bearing sizable internal cavities, such as cyclophanes[1-4] and cyclodextrins,[5,6] and molecular aggregates composed of amphiphiles,[7] such as micelles and bilayer membranes, have been widely employed. While macrocyclic hosts primarily perform the lock-and-key-type discrimination toward guest molecules due to their geometrically restricted hydrophobic cavities provided by rigid frameworks, amphiphiles provide geometrically flexible recognition sites as controlled by their aggregate morphology.

Synthetic approaches to the development of macrocyclic hosts exhibiting induced-fit functions have so far been carried out to a limited extent.[8] We have recently developed novel hosts, so-

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