5-Methyl-1,3-benzodithiole-2-thione (26): yield 1.12 g (5.7 mmol, 61%), from ethanol; mp 85 °C (lit.[22] mp 84 °C); ^{13}C NMR ($CDCl_3$) δ 141.0, 137.9, 137.6, 128.4, 121.7, 121.3, 21.1; mass spectrum (70 eV), m/z (relative intensity) 194 (100, M^+), 154 (57), 153 (22), 121 (40), 69 (21); IR (KBr disc), ν_{max} 1460, 1120, 1070, 900, 810 cm^{-1}.

(22) Soder, L.; Wizinger, R. *Helv. Chim. Acta* **1959**, *42*, 1733–1737.
(23) This dianion has previously been generated in low yield (ca. 14%) in ether solution: Kirchlechner, R. *Chem. Ber.* **1982**, *115*, 2461–2466.

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Registry No. 1, 108-98-5; **3**, 119-80-2; **4**, 106-45-6; **6**, 13616-79-0; **7**, 38360-81-5; **9**, 117371-40-1; **10**, 696-63-9; **12**, 71993-03-8; **13**, 15570-12-4; **15**, 19532-68-4; **16**, 117371-41-2; **17**, 117371-42-3; **18**, 14092-00-3; **19**, 34678-67-6; **20**, 33356-45-5; **21**, 117371-43-4; **22**, 117371-44-5; **23**, 117371-45-6; **24**, 117371-46-7; **25**, 934-36-1; **26**, 54199-61-0.

Efficient Total Synthesis of Didemnins A and B†,1

Yasumasa Hamada, Yutaka Kondo, Makoto Shibata, and Takayuki Shioiri*

Contribution from the Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan. *Received June 1, 1988. Revised Manuscript Received September 6, 1988*

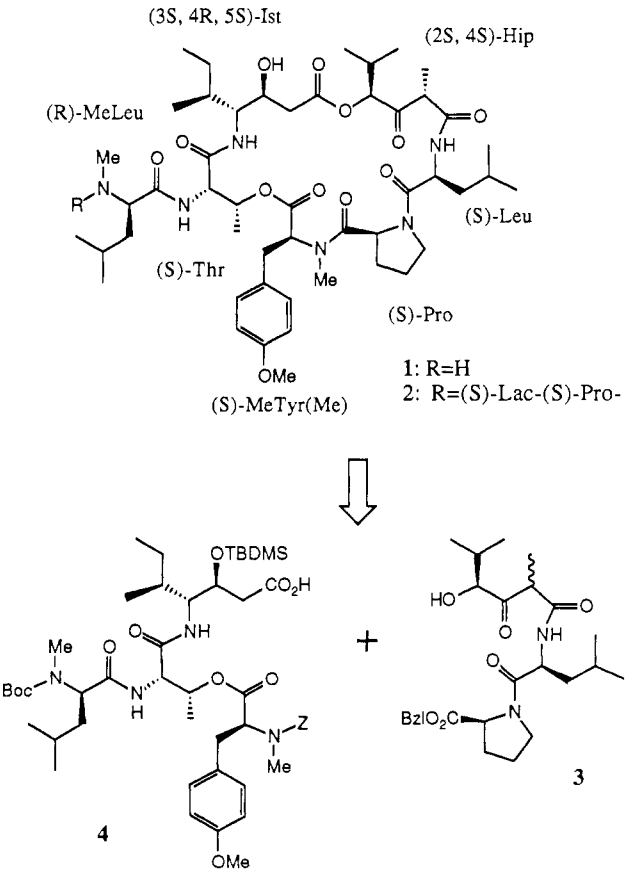
Abstract: Didemnins A and B (**1** and **2**), cytotoxic cyclic peptides from a Caribbean tunicate *Tridemnum solidum*, have been efficiently prepared by a convergent scheme from two key eastern and western fragments. Efficient routes to derivatives of the constituents of didemnins were explored. Benzyl (2*RS*,4*S*)-[*O*-(*tert*-butyldimethylsilyl)hydroxyisovaleryl]propionate (Hip derivative) was prepared from 2-hydroxyisovaleric acid by use of C-acylation of Meldrum's acid with diethyl phosphorocyanidate as a key step. Derivatives of (3*S*,4*R*,5*S*)-isostatine (Ist) were prepared from Boc-(*R*)-alloisoleucine. Methylation of Boc-(*R*)-Leu-OH and Z-(*S*)-Tyr-OH respectively afforded the corresponding *N*-methyl and *N*,*O*-dimethyl derivatives. The key eastern fragment, (2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl (**3**), was prepared stepwise from (*S*)-Pro-OBzl, while Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OH (**4**), the key western fragment for didemnin A (**1**), was prepared from Ist derivatives. Coupling of **3** with **4** and cyclization, followed by deprotection, afforded didemnin A (**1**), which was converted to didemnin B (**2**).

Didemnins were isolated by Rinehart and co-workers[2] from a Caribbean tunicate *Tridemnum solidum*. These structurally unique cyclic depsipeptides have quite interesting cytotoxic, antiviral, and immunosuppressive activities.[2,3] The structures of didemnins A and B have been firmly established as **1** and **2**, respectively, through their total synthesis.[2c] We have already reported[1a] a preparation of [(3*S*,4*R*)-Sta]didemnin A (the second proposed structure of didemnin A)[2b] in which the isostatine part of **1** is replaced with (3*S*,4*R*)-statine. We now describe a total synthesis of didemnins A and B, which will promise an efficient route to prepare these medicinally interesting compounds on a large scale.[4] Our synthetic strategy leading to **1** was based upon a convergent scheme involving the key eastern and western fragments **3** and **4**, which contained the (hydroxyisovaleryl)-propionyl (Hip) and isostatine (Ist) units, respectively, as shown in Scheme I.

Preparation of the Hip derivative **7b** originated with (*S*)-2-hydroxyisovaleric acid (**5a**)[5] (Scheme II). Treatment of **5a** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) followed by alkaline treatment afforded **5b**, which was condensed with Meldrum's acid by use of diethyl phosphorocyanidate (DEPC).[6] Without purification, the product **6** was refluxed with benzyl alcohol in benzene to give the β-keto ester **7a** ($[\alpha]^{23}_D$ −19.8° (*c* 0.53, MeOH)), which was methylated to produce **7b** as a mixture of diastereomers.[7] Our method is much superior to the reported ones[2c,8] in both overall yield and simplicity of the reaction workups.

The required Ist derivative **9d** was prepared from Boc-(*R*)-alloisoleucine (**8**)[9] (Scheme III). After activation of its carboxyl group as the imidazolide by use of carbonyldiimidazole, treatment with ethyl lithioacetate according to the method of Joullie[10] afforded the β-keto ester **9a** ($[\alpha]^{23}_D$ −31.1° (*c* 0.33, $CHCl_3$)) in 78% yield. Alternatively, **8** was transformed to Boc-(*R*)-alloisoleucinal via Boc-(*R*)-alloisoleucinol (mp 42–45 °C, $[\alpha]^{23}_D$ −1.2° (*c* 1, MeOH)) by our own method.[11] Condensation of Boc-(*R*)-alloisoleucinal with ethyl lithioacetate gave Boc-(3*RS*,4*R*,5*S*)-Ist-OEt

Scheme I

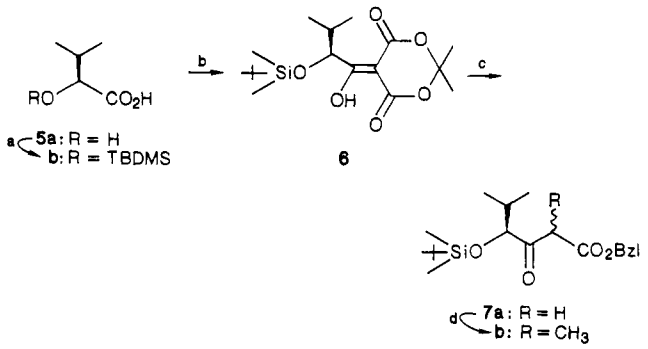


(**9b** and **9c**, 51% yield from Boc-(*R*)-alloisoleucinol), which was oxidized with pyridinium dichromate (PDC)[12] to give the β-keto

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

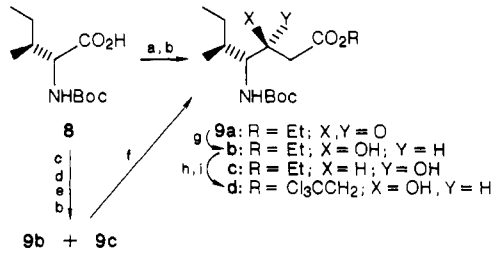
0002-7863/89/1511-0669$01.50/0

Scheme II[a]



[a](a) TBDMS-Cl, imidazole, DMF, room temperature, 22 h and then K_2CO_3 (aqueous), room temperature, 4 h, 82% yield; (b) Meldrum's acid, DEPC, Et_3N, THF, 0 °C, 2 h and then room temperature, 20 h; (c) $PhCH_2OH$, benzene, reflux, 3 h, 69% yield; (d) MeI, NaH, room temperature, 20 h, 77% yield.

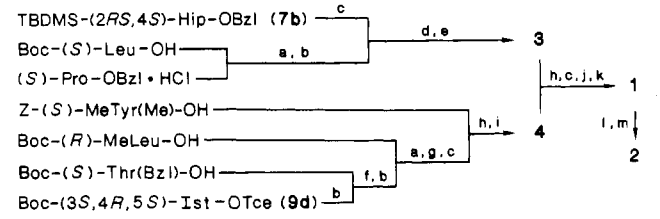
Scheme III[a]



[a](a) Carbonyldiimidazole, THF, 0 °C, 0.5 h and then room temperature, 2 h; (b) $LiCH_2CO_2Et$, THF, −70 °C, 1.25 h; (c) MeI, $KHCO_3$, DMF, room temperature, 5 h; (d) $NaBH_4$, LiCl, THF/EtOH, room temperature, overnight; (e) DMSO, pyridine SO_3, Et_3N, 10 °C, 10 min; (f) PDC, powdered 3A molecular sieves, AcOH, CH_2Cl_2, room temperature, 3 h, 80% yield; (g) $NaBH_4$, EtOH, −70 °C, 2.5 h, 65% yield; (h) 1 N NaOH (aqueous), EtOH, 0 °C, 0.5 h, room temperature, 1.5 h, 97% yield; (i) TceOH, DCC, DMAP, CH_2Cl_2, 0 °C, 3 h, room temperature, 21 h, 99% yield.

ester **9a**. Remarkably, the addition of the hydride from $NaBH_4$ to the carbonyl group of the β-keto ester **9a** was effectively ste-

Scheme IV[a]



[a](a) DEPC, Et_3N, DMF, 0 °C, 4 h, and then room temperature, 20 h; (b) 4 N HCl/dioxane, room temperature, 1 h; (c) H_2, 5% Pd–C, THF, room temperature, 2–3 h; (d) DCC, 1-hydroxybenzotriazole, *N*-methylmorpholine, THF/DMF (2:1), 0 °C, 3 h and then room temperature, 26 h, 79% yield; (e) $Bu_4N^+F^-$, THF, room temperature, 1 h, 90% yield; (f) DEPC, *i*-Pr_2EtN, DMF, 0 °C, 4 h and then room temperature, 20 h, 31% yield; (g) TBDMS-Cl, imidazole, DMF, room temperature, 37 h, 72% yield; (h) DCC, DMAP, CH_2Cl_2, 0 °C, 3 h, then room temperature, 16–22 h; (i) Zn, 1 M NH_4OAc (aqueous), THF, room temperature, 30 h, 89% yield; (j) Bop-Cl, Et_3N, CH_2Cl_2, 2 °C, 3 days, 68% yield; (k) TMSOTf, CH_2Cl_2, 0 °C, 3 h, 98% yield; (l) Bzl-(*S*)-Lac-(*S*)-Pro-OH, Bop-Cl, Et_3N, 2 °C, 23 h; (m) Pd, HCO_2H, MeOH, 49% yield.

reospecific, generating the desired (3*S*,4*R*,5*S*)-**9b** ($[\alpha]^{23}_D$ −6.4° (*c* 0.5, MeOH)) as the major product (**9b**:**9c** = >10:1) after chromatographic separation. Saponification followed by reesterification with trichloroethanol (TceOH) gave **9d** ($[\alpha]^{23}_D$ −4.8° (*c* 0.49, MeOH)).

The required *N*-methylamino acids, Boc-(*R*)-MeLeu-OH (mp 60.5–61.5 °C, $[\alpha]^{26}_D$ +30.7° (*c* 0.5, EtOH)) and Z-(*S*)-MeTyr(Me)-OH (dicyclohexylamine salt: mp 117–118 °C, $[\alpha]^{26}_D$ −15.2° (*c* 1, EtOH)), were easily prepared in 80–90% yields by treatment of Boc-(*R*)-Leu-OH and Z-(*S*)-Tyr-OH, respectively, with 3–5 equiv of NaH and 8–10 equiv of MeI in THF according to the method of Benoiton.[13]

Construction of the eastern fragment **3** was initiated from the condensation of Boc-(*S*)-Leu-OH with (*S*)-Pro-OBzl·HCl by the DEPC method, giving Boc-(*S*)-Leu-(*S*)-Pro-OBzl in 93% yield, which was deprotected at the N-terminal with acid to give HCl·H-(*S*)-Leu-(*S*)-Pro-OBzl (Scheme IV). Coupling of the deprotected dipeptide with TBDMS-(2*RS*,4*S*)-Hip-OH, obtained by the catalytic hydrogenolysis of **7b**, turned out to be unexpectedly challenging, owing to the ready decarboxylation of the β-keto acid. However, success was achieved by the direct use of the reaction mixture of the hydrogenolysis after removal of the catalyst. Combination of DCC, 1-hydroxybenzotriazole, and *N*-methylmorpholine proved to give the best result. TBDMS-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl thus obtained afforded the eastern fragment **3** after treatment with fluoride anion.

The western fragment **4** was obtained from the Ist derivative **9d**, which, after deprotection with acid, was coupled with Boc-(*S*)-Thr(Bzl)-OH by the DEPC method to produce the dipeptide (mp 114–115 °C, $[\alpha]^{25}_D$ +7.7° (*c* 1.1, MeOH)). After removal of its Boc function, Boc-(*R*)-MeLeu-OH was introduced by the DEPC method to give the tripeptide (mp 101–102 °C, $[\alpha]^{24}_D$ +24.9° (*c* 0.5, MeOH)) in 71% yield. The hydroxyl function of the Ist part was protected with TBDMS-Cl. Catalytic removal of the benzyl function at the Thr part afforded Boc-(*R*)-MeLeu-(*S*)-Thr-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce, which was condensed with Z-(*S*)-MeTyr(Me)-OH by use of DCC. The depsipeptide obtained quantitatively was treated with zinc powder to give the western fragment **4**.

Coupling of the eastern and western fragments **3** and **4** was accomplished by the DCC method in 78% yield. After simultaneous catalytic removal of both the benzyloxycarbonyl function

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(4) Schmidt, Kroner, and Griesser (Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *29*, 3057) reported the preparation of the ring structure of didemnins.

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(7) We proceeded to the synthesis using a mixture of diastereomers since the chiral center at C-2 of the Hip part was thought to be very easily epimerized. Furthermore, we expected that natural didemnins would have the stable configuration and that an epimeric mixture of didemnins synthesized would be transformed to the more stable natural stereoisomers. In fact, this was the case, and Rinehart and co-workers[2c] also confirmed this in their total synthesis.

(8) (a) Ewing, W. R.; Bhat, K. L.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 5863. (b) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531.

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(10) Harris, B. D.; Bhat, K. L.; Joullie, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837 and references therein.

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(12) Czerneki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699; *Synth. Commun.* **1986**, *16*, 11.

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from the Tyr part and the benzyl function from the Pro part, final cyclization was performed by use of bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (Bop-Cl).[14] Deprotection of the product with TMSOTf followed by recrystallization from ethyl acetate/hexane afforded didemnin A (**1**) (mp 146–148 °C, $[\alpha]^{24}_D$ −149° (*c* 0.4, $CHCl_3$)) in 52% overall yield from **4**. Our synthetic sample was completely identical with the natural one in every respect.

Finally, didemnin B (**2**) was synthesized from didemnin A (**1**). Treatment of ethyl (*S*)-lactate ((*S*)-Lac-OEt) with benzyl bromide and silver oxide in DMF (room temperature, 20 h),[2c] followed by saponification (1 N aqueous NaOH in ethanol; 0 °C, 30 min; room temperature, 1 h), gave Bzl-(*S*)-Lac-OH in 76% yield. Condensation with (*S*)-Pro-OMe·HCl by the DEPC method furnished Bzl-(*S*)-Lac-(*S*)-Pro-OMe in 82% yield, which was quantitatively hydrolyzed with 1 N aqueous NaOH in methanol (0 °C, 1 h; room temperature, 2 h). Coupling of the product with didemnin A (**1**) by use of Bop-Cl followed by the transfer hydrogenation afforded didemnin B (**2**) ($[\alpha]^{22}_D$ −82.6° (*c* 0.2, $CHCl_3$)), which was identical with natural didemnin B.

The above synthesis of didemnins will be useful for the supply of medicinally important didemnin B and may provide an efficient entry into new anticancer drugs of the didemnin type.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on JASCO IRA-2 or IRA-180 spectrometers. NMR spectra were recorded on JEOL PMX-60, FX-100, or GSX-400 spectrometers in $CDCl_3$ using TMS as an internal standard. FABMS spectra were obtained with a JEOL DX-300 spectrometer using *m*-nitrobenzyl alcohol as a liquid matrix. Optical rotations were determined on a JASCO DIP-140 automatic polarimeter. Analytical TLC was performed on a silica gel plate (E. Merck Art. 5715). Column chromatography was carried out with silica gel BW-820MH or BW-200 (purchased from Fuji Davison Co.) by using a low-pressure technique.

Preparation of the Hip Derivative 7b. (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutanoic Acid (5b). (*S*)-2-Hydroxy-3-methylbutanoic acid (**5a**)[5] (2.36 g, 20 mmol) was dissolved in DMF (10 mL), and TBDMS-Cl (7.24 g, 48 mmol) and imidazole (6.54 g, 96 mmol) were added at room temperature. After being stirred for 22 h, the reaction mixture was diluted with benzene/EtOAc (1/1, 500 mL), washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, and dried over Na_2SO_4. The organic layer was removed in vacuo. The residue was dissolved in MeOH (200 mL) and cooled in an ice bath, and potassium carbonate (6.9 g, 50 mmol) in water (60 mL) was added. After the reaction mixture was stirred at ambient temperature for 4 h, the solvent was removed and the residue was diluted with water (100 mL). The whole was cooled in an ice bath, acidified to pH 4 with 10% aqueous citric acid, and extracted three times with EtOAc (each 200 mL). The EtOAc layer was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification (BW 820MH, 120 g, hexane/EtOAc = 4/1) of the residue gave 3.79 g (82%) of **5b** as a colorless oil: IR (neat) ν_{max} 1720, 1250, 1150, 1070 cm^{-1}; ^1H NMR δ 0.1 (s, 6 H), 0.9 (s, 9 H), 0.91 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 2.0 (m, 1 H), 4.07 (d, J = 4 Hz, 1 H), 8.6 (br, 1 H).

Benzyl (*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-3-oxohexanoate (7a). To a cooled (0 °C), stirred solution of **5b** (3.76 g, 16.2 mmol) and Meldrum's acid (1.95 g, 13.5 mmol) in THF (20 mL) was added dropwise DEPC (2.87 g, 17.4 mmol) in THF (4 mL), followed by Et_3N (4.37 g, 43.2 mmol) in THF (4 mL). The mixture was stirred at 0 °C for 2 h and then at ambient temperature for 20 h. Volatiles were removed in vacuo, and the residue was taken up with EtOAc (300 mL). The whole was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (BW 820MH, 120 g, hexane/EtOAc = 4/1) to give 4.02 g of the acyl Meldrum's acid **6**, which was directly treated with benzyl alcohol (3.62 g, 33.6 mmol) in refluxing benzene (35 mL) for 3 h. After removal of the solvent, purification of the residue by chromatography (BW 820MH, 100 g, ether/benzene = 1/30) gave 4.08 g (69%) of **7a** as a light orange oil: $[\alpha]^{23}_D$ −19.8° (*c* 0.53, MeOH); IR (neat) ν_{max} 1750, 1720, 1480, 1270 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.06 (s, 3 H), 1.0 (s, 9 H), 0.7–1.1 (m, 6 H), 2.0 (m, 1 H), 3.63 (s, 2 H), 3.76 (d, J = 5 Hz, 1 H), 5.16 (s, 2 H), 7.33 (s, 5 H). Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.88; H, 8.86. Found: C, 65.62; H, 9.02.

(14) Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342.

Benzyl (2*RS*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,5-dimethyl-3-oxohexanoate [(2*RS*,4*S*)-TBDMS-Hip-OBzl] (7b). To a cooled (0 °C), stirred solution of **7a** (3.28 g, 9 mmol) in THF (18 mL) was added in one portion sodium hydride (60%, 378 mg, 9.45 mmol) in THF (14 mL). After 5 min, methyl iodide (6.75 mL, 108 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 20 h. Then the mixture was recooled in an ice bath, quenched with saturated aqueous NH_4Cl (20 mL) and water (40 mL), and extracted twice with benzene/EtOAc (1/1, each 240 mL). The combined organic layer was washed with water and saturated brine and was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel (BW 200, 140 g, ether/benzene/hexane = 1/4/15) to give 2.61 g (77%) of **7b** as a colorless oil: IR (neat) ν_{max} 1750, 1720, 1640, 1460, 1310, 1260, 1220 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.07 (s, 3 H), 0.94 (s, 9 H), 0.7–1.1 (m, 6 H), 1.36 (d, J = 7 Hz, 3 H), 1.9 (m, 1 H), 4.0 (m, 2 H), 5.13 (s, 2 H), 7.31 (s, 5 H). Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.61; H, 9.60. Found: C, 66.88; H, 9.30.

Preparation of the Ist Derivative 9d. Ethyl (4*R*,5*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-methyl-3-oxoheptanoate (9a). To a cooled (0 °C), stirred solution of **8**[9] (4.65 g, 20 mmol) in THF (20 mL) was added in one portion carbonyldiimidazole (3.57 g, 22 mmol), and the solution was stirred at 0 °C for 30 min and at ambient temperature for 2 h. This solution was added dropwise to a precooled (−72 °C) solution of ethyl lithioacetate, obtained from EtOAc (6.3 mL, 64 mmol) and LDA (64 mmol) at −72 °C, in THF (10 mL) over 1 h under an atmosphere of argon. After the reaction mixture was kept at this temperature for 15 min, it was quenched with 1 N hydrochloric acid (64 mL), allowed to warm to 0 °C, acidified to pH 3, and extracted three times with EtOAc (each 150 mL). The combined EtOAc layer was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatographic purification (BW 200, 150 g, hexane/EtOAc = 7/1) of the residue provided 4.67 g (78%) of **9a** as a pale yellow oil: $[\alpha]^{23}_D$ −31.1° (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 3350, 1750, 1700 cm^{-1}; ^1H NMR δ 0.78 (d, J = 7 Hz, 3 H), 1.26 (t, J = 7 Hz, 3 H), 1.43 (s, 9 H), 0.7–2.3 (m, 6 H), 3.47 (s, 2 H), 4.15 (q, J = 7 Hz, 2 H), 3.9–4.6 (m, 1 H), 4.99 (d, J = 9 Hz, 1 H); FABMS, m/z 302 (M + 1).

Boc-(3*S*,4*R*,5*S*)-Ist-OEt (9b). The β-keto ester **9a** (3.62 g, 12 mmol) was dissolved in EtOH (36 mL) under an atmosphere of argon and was cooled in a dry ice–acetone bath. Then sodium borohydride (545 mg, 14.4 mmol) was added portionwise at below −67 °C and the reaction mixture was kept for 2.5 h under this condition. After quenching of the reaction mixture with 10% aqueous citric acid (50 mL), the mixture was allowed to warm to ambient temperature, concentrated, and diluted with water (50 mL). The whole was extracted three times with EtOAc (each 120 mL). The EtOAc solution was dried over Na_2SO_4 and removed in vacuo. The residue was chromatographed on silica gel (BW 200, 180 g, hexane/EtOAc = 4/1) to give 2.36 g (68.5%) of the desired isomer **9b** together with 173 mg (4.5%) of the minor isomer **9c**. **9b**: R_f 0.19 (hexane/EtOAc = 3/1); $[\alpha]^{23}_D$ −6.4° (*c* 0.5, MeOH); IR (neat) ν_{max} 3350, 1740, 1700 cm^{-1}; ^1H NMR δ 0.86 (d, J = 6 Hz, 3 H), 0.91 (t, J = 6 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.45 (s, 9 H), 0.7–1.6 (m, 2 H), 1.7–2.1 (m, 1 H), 2.5 (m, 2 H), 2.75 (br, 1 H), 4.21 (q, J = 7 Hz, 2 H), 4.42 (d, J = 9 Hz, 1 H), 3.4–4.6 (m, 2 H). **9c**: R_f 0.21 (hexane/EtOAc = 3/1); $[\alpha]^{23}_D$ +26.4° (*c* 0.5, MeOH); IR (neat) ν_{max} 3400, 1740, 1710 cm^{-1}; ^1H NMR δ 0.87 (t, J = 7 Hz, 3 H), 0.93 (d, J = 6 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.43 (s, 9 H), 0.7–1.9 (m, 3 H), 2.55 (m, 2 H), 2.7 (br, 1 H), 3.3 (m, 1 H), 4.21 (q, J = 7 Hz, 2 H), 3.9–4.4 (m, 1 H), 4.81 (d, J = 9 Hz).

Boc-(3*S*,4*R*,5*S*)-Ist-OTce (9d). To a cooled (0 °C), stirred solution of **9b** (2.13 g, 7 mmol) in EtOH (21 mL) was added 1 N aqueous NaOH (7.4 mL) and the solution was kept at 0 °C for 30 min and stirred at ambient temperature for 1.5 h. After dilution with benzene/EtOAc (1/1, 150 mL), the whole was washed with 10% aqueous citric acid, water, and saturated brine, dried over Na_2SO_4, and concentrated to give 1.87 g (97%) of the corresponding carboxylic acid as a yellow caramel, which was directly used in the next step without further purification. The above material (1.82 g, 6.6 mmol), 2,2,2-trichloroethanol (0.76 mL, 7.9 mmol), and DMAP (403 mg, 3.3 mmol) were dissolved in CH_2Cl_2 (33 mL) and cooled to 0 °C. To this solution was added DCC (1.63 g, 7.9 mmol), and the reaction mixture was kept at 0 °C for 3 h and was stirred at ambient temperature for 21 h. The precipitates were filtered, and the filtrate was diluted with EtOAc (500 mL). The whole was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine and was concentrated in vacuo. Purification of the residue by flash chromatography (BW 200, 200 g, hexane/EtOAc = 4/1) provided 2.67 g (99%) of **9d** as a pale yellow oil: $[\alpha]^{23}_D$ −4.8° (*c* 0.49, MeOH); IR (neat) ν_{max} 3400, 1750, 1690 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (d, J = 6.7 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H), 1.44 (s, 9 H), 1.2–1.5 (m, 2 H), 1.44 (s, 9 H), 1.9 (m, 1 H), 2.66 (dd, J = 8.6 Hz, 16.7 Hz, 1 H), 2.78

(dd, J = 2.8 Hz, 16.7 Hz, 1 H), 2.96 (br, 1 H), 3.68 (m, 1 H), 3.99 (m, 1 H), 4.44 (d, J = 9.7 Hz, 1 H), 4.75 (d, J = 11 Hz, 1 H), 4.81 (d, J = 11 Hz, 1 H); FABMS, m/z 407 (M + 1).

General Procedure for Peptide Bond Formation Using the DEPC Method. The carboxylic acid and amine components were dissolved in DMF and cooled to 0 °C. To this solution was added DEPC followed by base (tertiary amine). After being stirred at 0 °C for 4 h and at ambient temperature for 19 h, the reaction mixture was diluted with benzene/EtOAc (1/2), washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over Na_2SO_4, and concentrated to give the crude product.

General Procedure for Removal of Boc Function with HCl/Dioxane. The *N*-Boc amino acid or peptide was treated with 4 N HCl/dioxane (100 equiv) at ambient temperature for 1.5 h. Volatiles were removed in vacuo. The residue was triturated with dry ether, washed with dry ether by decantation, dried under reduced pressure, and used in the next step without further purification.

Preparation of the Eastern Fragment 3. Boc-(*S*)-Leu-(*S*)-Pro-OBzl: prepared by the DEPC method as described above with Boc-(*S*)-Leu-OH·H_2O (5 g, 20 mmol), HCl·H-(*S*)-Pro-OBzl (5.8 g, 24 mmol), DEPC (3.87 g, 24 mmol), Et_3N (4.86 g, 48 mmol), and DMF (30 mL). After the usual workup, chromatographic purification (BW 820MH, 70 g, hexane/EtOAc = 2/1) gave 7.82 g (93%) of the title dipeptide as a colorless oil: IR (neat) ν_{max} 3300, 1740, 1705 cm^{-1}; ^1H NMR δ 0.9 (d, J = 6 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.42 (s, 9 H), 0.8–2.4 (m, 7 H), 3.3–4.0 (m, 2 H), 4.2–4.7 (m, 2 H), 5.09 (s, 2 H), 4.9–5.3 (m, 1 H), 7.25 (s, 5 H); FABMS, m/z 419 (M + 1).

TBDMS-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl. The benzyl ester **7b** (1.89 g, 5 mmol) was dissolved in THF (5 mL) and stirred under a hydrogen atmosphere in the presence of 5% Pd–C (189 mg) at room temperature for 2 h. The catalyst was filtered and washed with THF (10 mL). To the combined filtrate was added HCl·H-(*S*)-Leu-(*S*)-Pro-OBzl (2.13 g, 6 mmol), obtained from the above Boc derivative by general procedure in 94% yield, and the solution was cooled to 0 °C. Then *N*-methylmorpholine (0.66 mL) and 1-hydroxybenzotriazole (1.15 g, 7.5 mmol) in DMF (5 mL), followed by DCC (1.24 g, 6 mmol), were added, and the reaction mixture was kept at 0 °C for 3 h and at room temperature for 26 h with stirring. After removal of the solvent, EtOAc (50 mL) was added and the whole was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine. Concentration followed by flash chromatography (BW 200, 100 g, hexane/EtOAc = 3/1–2/1) gave 2.32 g (79%) of the title compound as a slightly yellow caramel: IR (neat) ν_{max} 3300, 1740, 1720, 1630 cm^{-1}; ^1H NMR δ 0.06 (s, 6 H), 0.92 (s, 9 H), 0.6–1.1 (m, 12 H), 1.32 (d, J = 7 Hz, 3 H), 2.0 (m, 4 H), 3.4–4 (m, 3 H), 4.1–4.9 (m, 3 H), 5.03 (d, J = 12 Hz, 1 H), 5.20 (d, J = 12 Hz, 1 H), 6.66 (d, J = 9 Hz, 1 H), 7.31 (s, 5 H); FABMS, m/z 589 (M + 1).

H-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl (3). To a stirred solution of TBDMS-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl (2.06 g, 3.5 mmol) in THF (20 mL) at room temperature was added in one portion *n*-Bu_4NF (1.83 g, 7 mmol) and the solution was stirred for 1 h. The reaction mixture was diluted with water (150 mL) and extracted three times with EtOAc (each 200 mL). The combined organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatographic purification (BW 200, 100 g, hexane/EtOAc = 2/1) of the residue provided 1.28 g (90%) of the key eastern fragment **3** as a slightly yellow caramel. Recrystallization from hexane/EtOAc gave the configurationally pure material (judged from 400-MHz ^1H NMR) as colorless crystals: mp 128–130 °C; $[\alpha]^{25}_D$ −28.4° (*c* 0.5, MeOH); IR (KBr disk) ν_{max} 3450, 3350, 1730, 1710, 1670, 1640, 1530, 1430, 1280, 1240, 1160, 1100 cm^{-1}; ^1H NMR (400 MHz) δ 0.74 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.38 (d, J = 6.8 Hz, 3 H), 1.5 (m, 2 H), 1.65 (m, 1 H), 2.0–2.2 (m, 5 H), 3.4–4.8 (m, 4 H), 4.24 (s, 1 H), 4.57 (dd, J = 4.2 Hz, 8.8 Hz, 1 H), 4.73 (dt, J = 5 Hz, 8.8 Hz, 1 H), 5.09 (d, J = 12.3 Hz, 1 H), 5.19 (d, J = 12.3 Hz, 1 H), 6.69 (d, J = 8.4 Hz, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{26}H_{38}N_2O_6$: C, 65.79; H, 8.09; N, 5.90. Found: C, 65.50; H, 7.98; N, 5.81.

Preparation of the Western Fragment 4. Boc-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist-OTce: prepared by the DEPC method as described above with Boc-(*S*)-Thr(Bzl)-OH (743 mg, 2.4 mmol), HCl·H-(3*S*,4*R*,5*S*)-Ist-OTce (quantitatively obtained from **9d** (813 mg, 2 mmol) by the general procedure), DEPC (0.38 mL, 2.5 mmol), *i*-Pr_2NEt (0.87 mL, 5 mmol), and DMF (3 mL). After the usual workup, chromatographic purification provided 370 mg (31%) of the title compound as a pale yellow caramel: IR (neat) ν_{max} 3350, 1750, 1700, 1660 cm^{-1}; ^1H NMR δ 0.73 (d, J = 7 Hz, 3 H), 0.89 (t, J = 6 Hz, 3 H), 1.21 (d, J = 6 Hz, 3 H), 1.47 (s, 9 H), ~2.2 (m, 3 H), 2.3 (br, 1 H), 2.6 (d, J = 5 Hz, 2 H), 3.6–4.8 (m, 4 H), 4.59 (s, 2 H), 4.74 (s, 2 H), 5.49 (br, 1 H), 6.48 (d, J = 8.6 Hz, 1 H), 7.33 (s, 5 H); FABMS, m/z 599 (M + 1).

Boc-(*R*)-MeLeu-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist-OTce: prepared by the DEPC method as described above with Boc-(*R*)-MeLeu-OH (210 mg, 0.86 mmol), HCl·H-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist-OTce (prepared from Boc-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist-OTce (568 mg, 0.95 mmol) by the general procedure in 85% yield), DEPC (0.14 mL, 0.92 mmol), Et_3N (0.23 mL, 1.64 mmol), and DMF (2.5 mL). After the usual workup, chromatographic purification followed by recrystallization from EtOAc/hexane gave 432 mg (83%) of the title tripeptide as colorless crystals: mp 101–102 °C; $[\alpha]^{24}_D$ +24.85° (*c* 0.5, MeOH); IR (KBr disk) ν_{max} 3450, 3375, 3275, 1740, 1670, 1650, 1530, 1450, 1370, 1160 cm^{-1}; ^1H NMR δ 0.73 (d, J = 6 Hz, 3 H), 0.8–1.0 (m, 9 H), 1.15 (d, 3 H), 1.43 (s, 9 H), 2.55 (d, 2 H), 2.83 (s, 3 H), 3.1 (br, 1 H), 4.61 (br, 2 H), 4.74 (s, 2 H), 3.8–4.8 (m, 5 H), 6.5 (br, 1 H), 7.0 (br, 1 H), 7.31 (s, 5 H). Anal. Calcd for $C_{33}H_{52}Cl_3N_3O_8$: C, 54.66; H, 7.24; N, 5.80. Found: C, 54.47; H, 7.10; N, 5.74.

Boc-(*R*)-MeLeu-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce. A mixture of Boc-(*R*)-MeLeu-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist-OTce (413 mg, 0.57 mmol), TBDMS-Cl (172 mg, 1.14 mmol), and imidazole (120 mg, 1.7 mmol) in DMF (0.3 mL) was stirred at room temperature for 16 h. After dilution with benzene/EtOAc (1/1, 150 mL), the mixture was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatographic purification (BW 820MH, hexane/EtOAc = 5/1) gave, along with 76 mg (18%) of the starting material, 346 mg (72%) of the title compound as a colorless caramel: IR (neat) ν_{max} 3350, 1750, 1680, 1500, 1390, 1160 cm^{-1}; ^1H NMR δ 0.01 (s, 6 H), 0.63 (d, J = 6 Hz, 3 H), 0.82 (s, 9 H), 0.8–1.0 (m, 9 H), 1.13 (d, J = 6 Hz, 3 H), 1.46 (s, 9 H), 2.54 (br, 2 H), 2.78 (s, 3 H), 3.9–4.1 (m, 3 H), 4.57 (d, J = 11 Hz, 1 H), 4.59 (s, 2 H), 4.72 (d, J = 11 Hz, 1 H), 4.1–4.9 (m, 2 H), 6.34 (d, J = 8 Hz, 1 H), 7.0 (br, 1 H), 7.31 (s, 5 H); FABMS, m/z 840 (M + 1).

Boc-(*R*)-MeLeu-(*S*)-Thr-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce. Boc-(*R*)-MeLeu-(*S*)-Thr(Bzl)-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce (332 mg, 0.4 mmol) was dissolved in THF (4 mL) and stirred under a hydrogen atmosphere in the presence of 5% Pd–C (40 mg) at room temperature for 3 h. The catalyst was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (BW 200, hexane/EtOAc = 2/1) to give 297 mg (99%) of the title compound as a colorless caramel: IR (neat) ν_{max} 3350, 1750, 1680, 1450, 1390, 1370, 1160 cm^{-1}; ^1H NMR δ 0.06 (s, 3 H), 0.1 (s, 3 H), 0.87 (s, 9 H), 0.8–1.0 (m, 3 H), 1.16 (d, J = 6 Hz, 3 H), 1.5 (s, 9 H), 2.63 (br, 2 H), 2.82 (s, 3 H), 4.66 (d, J = 11 Hz, 1 H), 4.81 (d, J = 11 Hz, 1 H), 3.9–4.9 (m, 9 H), 6.55 (d, J = 9 Hz, 1 H), 6.96 (br, 1 H).

Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist-(TBDMS)-OTce. To a cooled (0 °C), stirred solution of Boc-(*R*)-MeLeu-(*S*)-Thr-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce (285 mg, 0.38 mmol), Z-(*S*)-MeTyr(Me)-OH (196 mg, 0.57 mmol), and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (1.9 mL) was added in one portion DCC (118 mg, 0.57 mmol). The reaction mixture was stirred at 0 °C for 3 h and at ambient temperature for 22 h. The precipitates were filtered, and the filtrate was diluted with EtOAc (50 mL). The whole was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (BW 200, benzene/EtOAc = 9/1) to give 408 mg (quantitative) of the title depsipeptide as a colorless amorphous solid: IR (neat) ν_{max} 3300, 1740, 1680, 1510, 1450, 1390, 1320, 1250, 1150 cm^{-1}; ^1H NMR δ 0.04 (s, 3 H), 0.09 (s, 3 H), 0.84 (s, 9 H), 0.8–1.0 (m, 3 H), 1.47 (s, 9 H), 2.75 (s, 3 H), 2.96 (s, 3 H), 2.6–3.4 (m, 4 H), 3.78 (s, 3 H), 4.69 (br, 2 H), 3.9–5.4 (m, 6 H), 5.12 (br, 2 H), 6.48 (br, 1 H), 6.79 (d, J = 9 Hz, 2 H), 7.07 (d, J = 9 Hz, 2 H), 7.3 (s, 5 H), 6.6–7.4 (m, 1 H).

Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist-(TBDMS)-OH (4). To a stirred solution of Boc-(*R*)-MeLeu-(*S*)-Thr-[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OTce (397 mg, 0.37 mmol) in THF (4 mL) at room temperature was added Zn dust (800 mg) followed by 1 M aqueous ammonium acetate (0.8 mL), and the reaction mixture was stirred for 18 h. After dilution with EtOAc, the insoluble materials were filtered, and the filtrate was washed with 10% aqueous citric acid, water, and saturated brine and was dried over Na_2SO_4. Concentration followed by chromatographic purification (BW 820MH, CH_2Cl_2/EtOH = 40/1) gave 311 mg (89%) of the western fragment **4** as a colorless amorphous solid: IR (neat) ν_{max} 3300, 1740, 1700, 1650, 1510, 1450, 1390, 1320, 1250, 1150 cm^{-1}; ^1H NMR δ 0.07 (s, 6 H), 0.87 (s, 9 H), 0.75–1.0 (m, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.47 (s, 9 H), 2.51 (br 2 H), 2.86 (s, 3 H), 2.88 (s, 3 H), ~3.4 (m, 2 H), 3.78 (s, 3 H), 4.1 (br, 2 H), 4.4–5.6 (m, 4 H), 5.06 (br, 2 H), 6.14 (br, 1 H), 7.26 (s, 5 H), 6.6–7.6 (m, 5 H).

Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist-(TBDMS)-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl. To a cooled (0 °C), stirred solution of **3** (227 mg, 0.48 mmol), **4** (302 mg, 0.32 mmol), and

DMAP (19 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) was added DCC (75 mg, 0.38 mmol), and the reaction mixture was stirred at 0 °C for 3 h and at ambient temperature for 16 h. The precipitates were filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (BW 820MH, hexane/EtOAc = 3/1) to provide 350 mg (78%) of the title depsipeptide as a colorless caramel: IR (neat) ν_{max} 3300, 1740, 1690, 1650, 1510, 1450, 1380, 1360, 1320, 1270, 1250, 1160 cm^{-1}; ^1H NMR δ −0.03 (s, 3 H), 0.09 (s, 3 H), 0.83 (s, 9 H), 0.75–1.0 (m, 3 H), 1.32 (d, J = 6 Hz, 3 H), 1.45 (s, 9 H), 2.79 (s, 3 H), 3.77 (s, 3 H), 6.79 (d, J = 9 Hz, 2 H), 7.09 (d, J = 9 Hz, 2 H), 7.26 (s, 5 H), 7.34 (s, 5 H), 8.19 (d, J = 9 Hz, 1 H); FABMS, m/z 1401 (M + 1).

Didemnin A. Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist(TBDMS)-(2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl (322 mg, 0.23 mmol) was dissolved in THF (10 mL) and stirred under a hydrogen atmosphere in the presence of 5% Pd–C (70 mg) at room temperature for 3.5 h. The catalyst was filtered, and the filtrate was concentrated in vacuo to give the N,O-deprotected depsipeptide. This crude material was dissolved in CH_2Cl_2 (230 mL) and cooled in an ice bath. To the solution was added Et_3N (70 μl, 0.5 mmol) followed by Bop-Cl (70 mg, 0.27 mmol), and the mixture was kept at 2 °C for 3 days with stirring. After removal of the solvent, the residue was taken up with EtOAc (150 mL), washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, and dried over Na_2SO_4. Concentration followed by chromatographic purification (BW 820MH, 21 g, CH_2Cl_2/EtOAc = 8/1) gave 180 mg (68%) of the cyclized material as colorless crystals, which was directly used in the next deprotection. The above cyclic depsipeptide (174 mg, 0.15 mmol) was treated with a 2 M solution of TMSOTf in CH_2Cl_2 (1.5 mL, 3 mmol) at 0 °C for 3 h. Volatiles were removed in vacuo, and the residue was diluted with CH_2Cl_2 (50 mL). The whole was washed with chilled saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 (each 50 mL). The combined CH_2Cl_2 solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (BW 200, 9 g, $CHCl_3$/MeOH = 30/1) to give 144 mg (98%) of didemnin A (**1**) as colorless crystals. Recrystallization from hexane/EtOAc afforded the pure material: mp 146–148 °C; $[\alpha]^{25}_D$ −148.7° (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 3325, 1730, 1650, 1630, 1540, 1510, 1450, 1380, 1320, 1300, 1270, 1240, 1220, 1160 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (d, J = 6.8 Hz), 0.87 (d, J = 7 Hz), 0.9, 1.18, 1.32 (d, J = 6.6 Hz), 1.33 (d, J = 6 Hz), 1.42, 1.70, 1.78, 2.05, 2.15, 2.34, 2.49 (s), 2.52, 2.55 (s), 2.96, 3.14, 3.19 (dd, J = 10.6 Hz, 14.1 Hz), 3.38 (dd, J = 4.2 Hz, 14.1 Hz), 3.57 (dd, J = 4.4 Hz, 10.6 Hz), 3.62, 3.73, 3.80 (s), 4.01, 4.10 (dt, J = 5.1 Hz, 8.1 Hz), 4.23, 4.58 (dd, J = 6 Hz, 8.1 Hz), 4.80 (t, J = 9.9 Hz), 4.88 (dd, J = 3.1 Hz, 8.6 Hz), 5.06 (dd, J = 3.3 Hz, 6.4 Hz), 5.17 (d, J = 3.5 Hz), 6.85 (d, J = 8.6 Hz), 7.09 (d, J = 8.6 Hz), 7.48 (br), 8.08 (br); FABMS, m/z 943 (M + 1).

Didemnin B from Didemnin A. Didemnin A (28 mg, 0.03 mmol) and Bzl-(*S*)-Lac-(*S*)-Pro-OH (13 mg, 0.045 mmol) were dissolved in CH_2Cl_2 (0.1 mL) and cooled to 0 °C. Triethylamine (14 μl, 0.1 mmol) and Bop-Cl (12 mg, 0.045 mmol) were added, and the reaction mixture was kept at 2 °C for 23 h with stirring. After dilution with EtOAc (30 mL), the mixture was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over Na_2SO_4, and concentrated to give 39 mg of *O*-benzyldidemnin B as pale yellow crystals, which was directly used in the next step. Palladium black (50 mg) in MeOH (1 mL) was activated with 3% HCO_2H/MeOH (1 mL) for 15 min and the above *O*-benzyldidemnin B (36 mg) in MeOH (2 mL) was added. After 2 h, 4 h, and 5 h, an additional 1 mL of 3% HCO_2H/MeOH was added. After 6 h the catalyst was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography ($CHCl_3$/MeOH = 20/1) to produce, together with recovery (14 mg, 42%) of *O*-benzyldidemnin B, 15 mg (49%) of didemnin B as colorless crystals: $[\alpha]^{22}_D$ −82.6° (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3325, 1730, 1635, 1540, 1510 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (d, J = 6.4 Hz), 0.88 (d, J = 7 Hz), 0.9, 1.32 (d, J = 6.8 Hz), 1.38 (d, J = 6 Hz), 1.39 (d, J = 6.8 Hz), 1.6, 1.83, 2.0, 2.13, 2.22, 2.36, 2.56 (s), 2.63 (dd, J = 10.3 Hz, 16.9 Hz), 3.15 (s), 3.25, 3.38 (dd, J = 4 Hz, 14.3 Hz), 3.58 (dd, J = 4.2 Hz, 11 Hz), 3.68, 3.79 (s), 4.09, 4.24 (q, J = 7 Hz), 4.39 (q, J = 6.6 Hz), 4.55 (dd, J = 2 Hz, 5.1 Hz), 4.64 (dd, J = 5 Hz, 7.7 Hz), 4.74 (t, J = 7.7 Hz), 4.81, 5.19 (d, J = 3.5 Hz), 5.37 (dd, J = 3.8 Hz, 11.3 Hz), 5.41 (dd, J = 2.4 Hz, 6.4 Hz), 6.84 (d, J = 8.6 Hz), 7.07 (d, J = 8.6 Hz), 7.20 (d, J = 9.7 Hz), 7.66 (d, J = 5.1 Hz), 7.80 (d, J = 9.2 Hz).

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Supplementary Material Available: Spectral charts are available for key compounds **1–4**, **7b**, **9d**, and Bzl-(*S*)-Lac-(*S*)-Pro-OMe (14 pages). Ordering information is given on any current masthead page.