Total Synthesis of the Cyclic Depsipeptide Leualacin

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The fungal metabolite leualacin (**1**), a potent calcium channel antagonist, was synthesized in 15 steps from commercially available amino acids in 25% overall yield using standard solution methods. The synthesis is general and thus would accommodate the incorporation of amino acid replacements as well as the inclusion of peptide mimics and isosteres.

Introduction

Leualacin (**1**), a metabolite from the fungus *Hapsidospora irregularis*, was found in a soil sample from Nepal.[2,3] This cyclic depsipeptide (Figure 1) has displayed potent calcium channel activity at levels comparable to the known calcium channel antagonists nitrendipine and diltiazem. While the microbial preparation of this compound has been disclosed,[4] a high-yielding organic synthesis would allow for amino acid substitutions and the incorporation of peptidomimetics to further refine the activity of **1** through analog synthesis.

Macrolactamization to form **1** was chosen to proceed between the β-alanyl and phenylalanyl residues, thus requiring depsipentapeptide **2**. The rate of cyclization should be facilitated by using the least sterically demanding residue, the β-alanyl nitrogen, as the nucleophile (Scheme 1).[5] A convergent approach to **2** suggests initial preparation of depsipeptide esters **3** and **4**, both of which may be prepared from commercially available amino acids, β-alanine, D-leucine, and L-leucine.

Results and Discussion

(*R*)-Leucic acid (**8**) and (*S*)-leucic acid (**13**) were each prepared by diazotization with retention from the corresponding α-amino acids, D-leucine and L-leucine respectively, using standard methods.[6] Selective esterification without hydroxyl protection was accomplished with diphenyldiazomethane, generated *in situ* to afford benzhydryl esters **7** and **12** (Scheme 2).[7] Commercially available Boc-β-Ala-OH (**6**, Boc = *N*-(1,1-dimethylethoxycarbonyl)) was coupled with hydroxy acid **7** to form depsidipeptide **9** using isopropenyl chloroformate.[8] Similarly, ester formation between commercially available Boc-L-Leu-OH (**11**) and alcohol **12** gave dipeptide analog **14**. Catalytic hydrogenolysis of the benzhydryl esters of **9** and **14** gave the desired dipeptide analogs **10** and **15**, respectively.

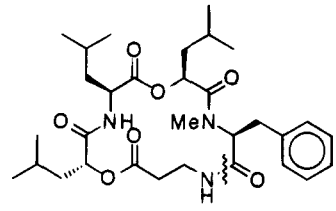
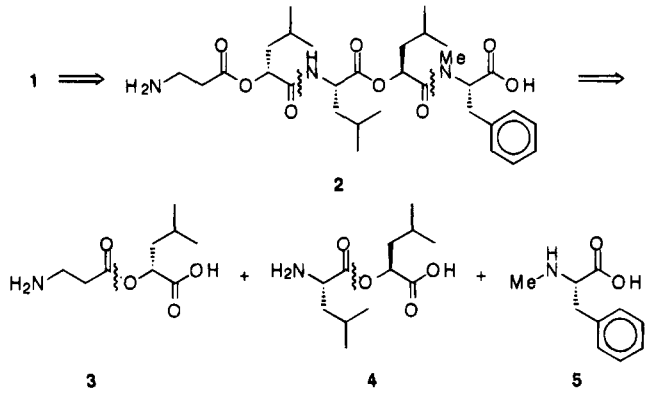


Figure 1. Leualacin (**1**).

Scheme 1. Retrosynthetic Analysis of 1



Finally, commercially available Boc-L-*N*(Me)Phe-OH (**16**) was protected as the corresponding benzyl ester **17** upon treatment with benzyl chloroformate.[9] Acid-catalyzed removal of the Boc protection group gave the desired amine H-L-*N*(Me)Phe-OBn (**18**) in 67% overall yield.[10]

Convergent preparation of the protected pentapeptide analog **21** was completed by coupling sequentially the three fragments. Phenylalanine derivative **18** was coupled to depsidipeptide **15** using BOP-Cl to give the protected depsitripeptide **19** (Scheme 3).[6] Acid-catalyzed deprotection of the amine afforded tripeptide analog **20**, which was coupled to ester **10** under identical conditions to afford depsipentapeptide **21**.

The deprotection of pentapeptide analog **21** was accomplished in a similar manner to those conditions used in the preparation of the fragments. Macrolactamization of **2** was accomplished according to the method of

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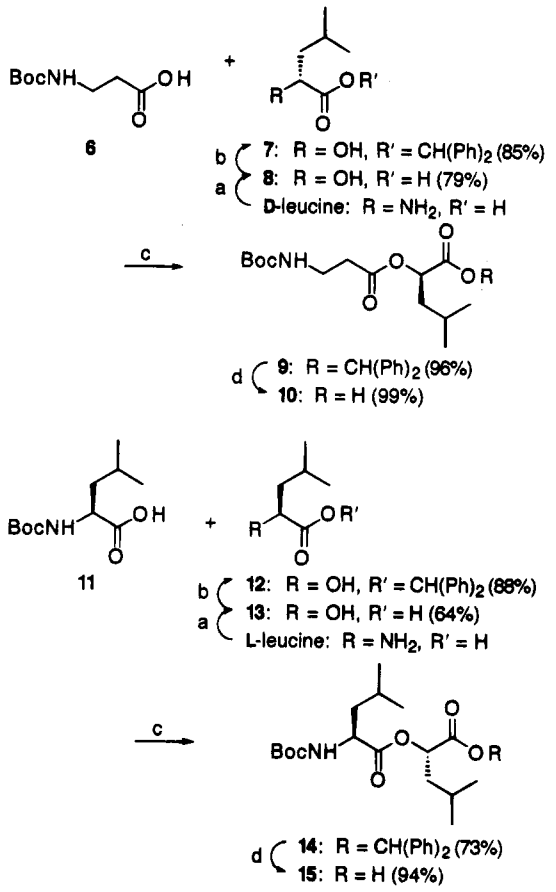
Scheme 2. Synthesis of Protected Versions of Depsipeptide Fragments 3 and 4[a]



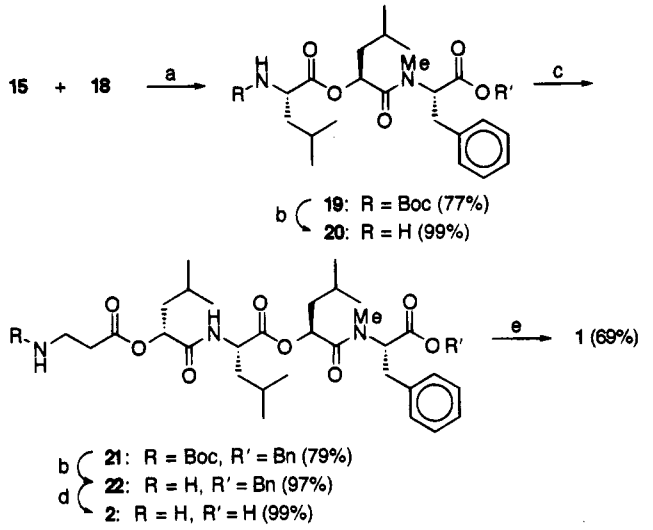
[a] (a) $NaNO_2$, H_2SO_4, H_2O, 0 °C; (b) $Ph_2C{=}NNH_2$, $PhI(OAc)_2$, I_2, CH_2Cl_2, −10 °C; (c) $H_2C{=}C(Me)OCOCl$, Et_3N, DMAP, CH_2Cl_2, 0 °C; (d) H_2, Pd/C, EtOAc, MeOH.

Williams *et. al.*[11] with DPPA to afford leualacin (**1**) in 25% overall yield from commercially available starting materials. The identity of leualacin was confirmed by displaying ^1H and ^{13}C NMR spectra, as well as a consistent melting point and specific rotation, identical to the reported values.[3]

Experimental Section

General. All reagents and solvents were used directly as purchased from commercial suppliers, and all reactions were conducted with constant magnetic stirring at ambient temperature (20−22 °C), unless otherwise noted. All reactions involving organometallic, moisture sensitive, or metal hydride reagents were conducted in commercially available dry solvents under a dry N_2 atmosphere. Partitions, extractions, or washes with NaCl, $NaHCO_3$, NH_4Cl, NaH_2PO_4, or $NaHSO_3$/$Na_2S_2O_5$ refer to saturated aqueous solutions of these salts. Reactions were typically "worked up" by extraction of an organic solution of the product(s) with NaCl; the organic layer was dried with Na_2SO_4, filtered, and evaporated *in vacuo*. Purifications were accomplished via MPLC using the eluting solvent(s) indicated with silica gel 60 (230−400 mesh ASTM) packed columns. Melting points (Pyrex capillary) were uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ as solvent, unless otherwise noted. *J* values are in hertz. Amide bonds in the peptides elicit various rotameric forms in the ^1H NMR spectra; therefore, for simplicity only signals for the major isomer were reported. Elemental analyses and mass spectra (EI and CI) were furnished by R. K. Hallberg at the Indianapolis Research Facility of DowElanco.

Scheme 3. Synthesis of Depsipentapeptide 2 and Cyclization to Leualacin (1)[a]



[a] (a) BOP-Cl, NMM, CH_2Cl_2, −10 °C; (b) TFA, CH_2Cl_2, 0 °C; (c) compound **10**, BOP-Cl, NMM, CH_2Cl_2, −10 °C; (d) H_2, Pd, C, EtOAc, MeOH; (e) DPPA, $NaHCO_3$, DMF, 0 °C.

***cyclo*(β-Ala-*O*-D-Leu-Leu-*O*-Leu-*N*(Me)Phe) (Leualacin (1)).**[11] A 0 °C slurry of depsipentapeptide **2** (0.10 g, 0.17 mmol) in dry DMF (60 mL) was treated sequentially with DPPA (80 μL, 100 mg, 0.37 mmol) and $NaHCO_3$ (0.15 g, 1.8 mmol). Stirring at 0 °C was continued for 3 d. The mixture was evaporated (30−40 °C/0.3 mmHg), and the residue was dissolved into EtOAc and worked up. Purification by MPLC (1:1 EtOAc/hexane) gave 67 mg (69%) of **1** as a white powder, mp 138−139 °C, $[\alpha]^{25}_D$ −99.0° {*lit.*[3] mp 139−141 °C, $[\alpha]^{25}_D$ −102°}.

H-β-Ala-*O*-D-Leu-L-Leu-*O*-L-Leu-*N*(Me)-L-Phe-OH (2). General Hydrogenation Procedure. The atmosphere above a slurry of benzyl ester **25** (0.21 g, 0.31 mmol) and Pd (5% on carbon, 31 mg, 100 mg/mmol) in 1:1 EtOAc/MeOH (4 mL) was replaced initially with N_2 and subsequently exchanged with H_2. The H_2 atmosphere was maintained for 2 h, evacuated, and replaced with N_2. The mixture was filtered through Celite, and the filtrate was evaporated to afford 0.15 g (83%) of **2** as a white powder. This material was used without further purification.

Diphenylmethyl (2*R*)-2-Hydroxy-4-methylpentanoate (7). General Diphenylmethyl Ester Formation Procedure. A 1:99 w/v solution of I_2/CH_2Cl_2 (1.0 mL) was added to a −10 °C slurry of (*R*)-leucic acid (**8**) (1.01 g, 7.64 mmol) and Ph_2CNNH_2 (2.28 g, 11.6 mmol) in CH_2Cl_2 (25 mL). After 5 min $PhI(OAc)_2$ (3.69 g, 11.5 mmol) was added over 1 h via a powder addition funnel, causing a deep red color and vigorous gas evolution. After 2 h the mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. The mixture was evaporated, and the residue was resuspended in CH_2Cl_2 (20 mL), slurried with SiO_2 (10 g), and evaporated. The residue was loaded into a precolumn. Purification by MPLC (1:1 CH_2Cl_2/hexane) gave 1.93 g (85%) of **7** as a colorless oil, which solidified on standing, mp 57−8 °C: ^1H NMR δ 0.92 (d, 3H, J = 6.7), 0.94 (d, 3H, J = 6.6), 1.56 (ddd, 1H, J = 5.3, 9.1, 13.8), 1.63 (ddd, 1H, J = 4.2, 8.6, 13.8), 1.9 (m, 1H), 2.4−2.5 (br s, OH), 4.29 (dd, 1H, J = 4.2, 9.1), 6.93 (s, 1H), 7.3−7.4 (m, 10H). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.28; H, 7.39.

***N*-((1,1-Dimethylethoxy)carbonyl)-β-Ala-*O*-D-Leu Diphenylmethyl Ester (9). General Depsipeptide Formation Procedure.** Boc-β-Ala-OH (**6**) (0.35 g, 1.8 mmol) was added to a 0 °C solution of alcohol **7** (0.48 g, 1.6 mmol) in CH_2Cl_2 (8 mL). This mixture was treated sequentially with Et_3N (0.55 mL, 0.40 g, 3.9 mmol), DMAP (0.04 g, 0.3 mmol), and isopropenyl chloroformate (0.21 mL, 0.23 g, 1.9 mmol), which caused a precipitate and gas evolution. After 2 h the mixture

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was partitioned between Et_2O and 1 M HCl. The organic layer was washed with $NaHCO_3$ and worked up. Purification by MPLC (1:9 EtOAc/hexane) gave 0.73 g (96%) of **9** as a colorless oil: ^1H NMR δ 0.89 (d, 3H, J = 6.2), 0.90 (d, 3H, J = 6.3), 1.41 (s, 9H), 1.6–1.8 (m, 3H), 2.56 (t, 2H, J = 6.0), 3.37 (dt, 2H, J = 5.9, 5.7), 5.1 (br t, NH, J = 5.6), 5.16 (dd, 1H, J = 3.9, 9.4), 6.89 (s, 1H), 7.3–7.4 (m, 10H). Anal. Calcd for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98. Found: C, 68.83; H, 7.46; N, 3.01.

***N*-((1,1-Dimethylethoxy)carbonyl)-β-Ala-*O*-D-Leu-OH (10).** This compound was prepared according to the method for **2** from diphenylmethyl ester **9** (3.32 g, 7.07 mmol), Pd (5% on carbon, 0.74 g), and 1:1 EtOAc/MeOH (50 mL). Purification by MPLC (CH_2Cl_2 → 1:9 MeOH/CH_2Cl_2) gave 2.24 g (99%) of **10** as a pale oil: ^1H NMR δ 0.93 (d, 3H, J = 6.3), 0.95 (d, 3H, J = 6.2), 1.42 (s, 9H), 1.7–1.9 (m, 3H), 2.6 (br m, 2H), 3.4–3.5 (br m, 2H), 5.09 (dd, 1H, J = 3.8, 9.6), 5.2 (br m, NH), 7.8–8.0 (br s, OH). Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62. Found: C, 53.08; H, 7.88; N, 4.56.

Diphenylmethyl (2*S*)-2-Hydroxy-4-methylpentanoate (12).[7] This compound was prepared according to the method for **7** from (*S*)-leucic acid (**13**) (5.04 g, 38.1 mmol), Ph_2CNNH_2 (11.2 g, 57.1 mmol), a 1:99 w/v solution of I_2/CH_2Cl_2 (5 mL), $PhI(OAc)_2$ (18.4 g, 57.1 mmol), and CH_2Cl_2 (120 mL). Purification by MPLC (1:9 EtOAc/hexane) gave 9.26 g (81%) of **12** as a pale powder, mp 57–8 °C: ^1H NMR δ 0.92 (d, 3H, J = 6.7), 0.95 (d, 3H, J = 6.6), 1.56 (ddd, 1H, J = 5.4, 9.1, 13.8), 1.63 (dd, 1H, J = 4.2, 8.6, 13.8), 1.9 (m, 1H), 2.5–2.8 (br s, OH), 4.29 (dd, 1H, J = 4.2, 9.1), 6.93 (s, 1H), 7.3–7.4 (m, 10H). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.40; H, 7.70.

***N*-((1,1-Dimethylethoxy)carbonyl)-L-Leu-*O*-L-Leu Diphenylmethyl Ester (14).**[6,8] This compound was prepared according to the method for **9** from Boc-Leu-OH (**11**) (0.68 g, 2.9 mmol), alcohol **12** (0.87 g, 2.9 mmol), Et_3N (0.90 mL, 0.65 g, 6.5 mmol), DMAP (0.07 g, 0.6 mmol), and isopropenyl chloroformate (0.35 mL, 0.39 g, 3.2 mmol) in CH_2Cl_2 (15 mL). Purification by MPLC (1:9 EtOAc/hexane) gave 0.94 g (63%) of **14** as a colorless glass: ^1H NMR δ 0.90 (m, 12H), 1.3–1.5 (m, 1H), 1.41 (s, 9H), 1.6–1.8 (m, 5H), 4.34 (ddd, 1H, J = 4.3, 9.1, 9.4), 4.81 (br d, NH, J = 8.8), 5.17 (dd, 1H, J = 3.9, 9.4), 6.88 (s, 1H), 7.3–7.4 (m, 10H). Anal. Calcd for $C_{30}H_{41}NO_6$: C, 70.42; H, 8.08; N, 2.74. Found: C, 70.30; H, 8.02; N, 2.70.

***N*-((1,1-Dimethylethoxy)carbonyl)-L-Leu-*O*-L-Leu-OH (15).** This compound was prepared according to the method for **2** from diphenylmethyl ester **14** (1.43 g, 2.79 mmol), Pd (5% on carbon, 0.55 g), and 1:1 EtOAc/MeOH (16 mL). The resulting waxy solid was triturated with hexanes and filtered repeatedly to yield 0.91 g (94%) of **15** as a white powder: ^1H NMR δ 0.9–1.0 (m, 12H), 1.42 (s, 9H), 1.5 (m, 1H), 1.7–1.9 (m, 5H), 3.3–3.7 (br s, OH), 4.3 (m, 1H), 4.87 (br d, NH, J = 7.8), 5.1 (m, 1H). Anal. Calcd for $C_{17}H_{31}NO_6$: C, 59.11; H, 9.05; N, 4.05. Found: C, 59.24; H, 9.17; N, 4.01.

***N*-((1,1-Dimethylethoxy)carbonyl)-*N*-methyl-L-phenylalanine Phenylmethyl Ester (17).**[10] A 0 °C solution of Boc-*N*(Me)Phe-OH (**16**) (2.03 g, 7.27 mmol) in CH_2Cl_2 (25 mL) was treated sequentially with Et_3N (1.2 mL, 0.87 g, 8.6 mmol), benzyl chloroformate (1.2 mL, 1.4 g, 8.4 mmol), DMAP (0.09 g, 0.7 mmol), and DMAP·HCl (0.01 g, 0.06 mmol), resulting in gas evolution. After 3 h the mixture was partitioned between Et_2O and $NaHCO_3$. The organic layer was washed with 0.1 M HCl and worked up. Purification by MPLC (1:9 EtOAc/hexane) gave 1.89 g (71%) of **17** as a colorless oil: ^1H NMR δ 1.30 and 1.36 (2s, Σ = 9H), 2.67 and 2.72 (2s, Σ = 3H), 3.0–3.1 and 3.3–3.4 (2m, Σ = 2H), 4.62 and 4.94 (2dd, Σ = 1H, J = 4.4, 10.6 and J = 5.3, 10.5), 5.2 (m, 2H), 7.2–7.3 (m, 10H). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.52; H, 7.41; N, 4.08.

***N*-Methyl-L-phenylalanine Phenylmethyl Ester (18).**[9] **General Boc Removal Procedure.** TFA (2.5 mL, 3.7 g, 32 mmol) was added dropwise to a 0 °C solution of Boc amino ester **17** (1.73 g, 4.68 mmol) in CH_2Cl_2 (10 mL), resulting in gas evolution. After 2 h the mixture was evaporated and the residue was partitioned between EtOAc and $NaHCO_3$. The organic layer was worked up to afford 1.19 g (94%) of **18** as a colorless glass: ^1H NMR δ 1.6 (br s, NH), 2.35 (s, 3H), 2.92 (dd, 1H, J = 7.1, 13.6), 2.97 (dd, 1H, J = 6.6, 13.6), 3.48 (dd, 1H, J = 6.9, 6.9), 5.07 (s, 2H), 7.11 (dd, 2H, J = 1.7, 7.9), 7.2–7.3 (m, 5H), 7.3 (m, 3H). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 74.13; H, 8.01; N, 5.20.

***N*-((1,1-Dimethylethoxy)carbonyl)-L-Leu-*O*-L-Leu-*N*-(Me)-L-Phe Phenylmethyl ester (19).**[6] **General Peptide Coupling Procedure.** A −10 °C solution of depsidipeptide acid **15** (0.74 g, 2.1 mmol) in CH_2Cl_2 (20 mL) was treated sequentially with BOP-Cl (0.66 g, 2.6 mmol) and 4-methylmorpholine (NMM) (0.30 mL, 0.28 g, 2.7 mmol). After 2 h amine **18** (0.60 g, 2.2 mmol) and NMM (0.30 mL, 0.28 g, 2.7 mmol) were added. After 8 h the mixture was partitioned between Et_2O and 1 M HCl. The organic layer was washed with $NaHCO_3$ and worked up. Purification by MPLC (15:85 EtOAc/hexane) gave 1.05 g (82%) of **19** as a colorless glass: ^1H NMR δ 0.83 (d, 3H, J = 6.4), 0.87 (d, 3H, J = 6.4), 0.92 (d, 6H, J = 6.4), 1.3–1.4 (m, 2H), 1.41 (s, 9H), 1.6–1.8 (m, 4H), 2.82 (s, 3H), 3.02 (dd, 1H, J = 9.7, 14.6), 3.34 (dd, 1H, J = 6.0, 14.6), 4.27 (ddd, 1H, J = 4.4, 9.4, 9.4), 4.75 (br d, NH, J = 9.0), 5.07 (d, 1H, J = 12.2), 5.1–5.2 (m, 1H), 5.13 (d, 1H, J = 12.3), 5.27 (dd, 1H, J = 6.0, 9.6), 7.1–7.4 (m, 10H); ^1H NMR (DMSO-d_6, 380 K) δ 0.83 (br d, 6H, J = 6.9), 0.86 (d, 3H, J = 6.6), 0.90 (d, 3H, J = 6.6), 1.39 (s, 9H), 1.4–1.5 (m, 2H), 1.49 (ddd, 1H, J = 4.6, 6.1, 13.8), 1.54 (ddd, 1H, J = 3.7, 6.0, 13.7), 1.7 (m, 2H), 2.89 (s, 3H), 3.07 (dd, 1H, J = 9.2, 14.6), 3.29 (dd, 1H, J = 6.0, 14.6), 4.02 (ddd, 1H, J = 5.9, 8.4, 8.5), 5.1 (m, 1H), 5.14 (s, 2H), 5.24 (dd, 1H, J = 4.0, 9.1), 6.5 (br s, NH), 7.2–7.4 (m, 10H); ^{13}C NMR δ 21.46, 21.63, 22.93, 23.12, 24.36, 24.66, 28.27, 32.43, 34.32, 39.27, 41.36, 51.64, 58.62, 66.97, 69.64, 79.60, 126.59, 128.26, 128.33, 128.41, 128.52, 128.93, 135.40, 136.71, 155.30, 170.25, 170.39, 172.83. Anal. Calcd for $C_{34}H_{48}N_2O_7$: C, 68.43; H, 8.11; N, 4.69. Found: C, 68.57; H, 7.95; N, 4.66.

H-L-Leu-*O*-L-Leu-*N*(Me)-L-Phe Phenylmethyl ester (20). This compound was prepared according to the method of **18** from Boc depsitripeptide **19** (0.51 g, 0.85 mmol), TFA (1.0 mL), and CH_2Cl_2 (4.0 mL) to afford 0.38 g (90%) of **20** as a colorless oil. This material was used without further purification.

***N*-((1,1-Dimethylethoxy)carbonyl)-β-Ala-*O*-D-Leu-L-Leu-*O*-L-Leu-*N*(Me)-L-Phe Phenylmethyl ester (21).** This compound was prepared according to the method of **19** from depsidipeptide acid **10** (0.25 g 0.82 mmol), BOP-Cl (0.26 g, 1.0 mmol), NMM (2 × 0.12 mL, 2 × 0.11 g, 2 x 1.1 mmol), depsitripeptide amine **20** (0.38 g, 0.77 mmol), and CH_2Cl_2 (8.0 mL). Purification by MPLC (30:70 EtOAc/hexane) gave 0.48 g (75%) of **21** as a colorless glass: ^1H NMR δ 0.84 (d, 3H, J = 6.4), 0.88 (d, 3H, J = 6.4), 0.9 (m, 12H), 1.40 (s, 9H), 1.5 (m, 1H), 1.6–1.8 (m, 8H), 2.6 (m, 2H), 2.82 (s, 3H), 3.02 (dd, 1H, J = 9.5, 14.6), 3.34 (dd, 1H, J = 6.1, 14.7), 3.4 (m, 2H), 4.56 (ddd, 1H, J = 4.7, 8.7, 9.1), 5.08 (d, 1H, J = 12.2), 5.13 (d, 1H, J = 12.2), 5.1–5.2 (m, 3H), 5.28 (dd, 1H, J = 6.2, 9.4), 6.32 (br d, NH, J = 8.3), 7.2–7.3 (m, 10H). Anal. Calcd for $C_{43}H_{63}N_3O_{10}$: C, 66.05; H, 8.12; N, 5.37. Found: C, 66.14; H, 8.37; N, 5.37.

H-β-Ala-*O*-D-Leu-L-Leu-*O*-L-Leu-*N*(Me)-L-Phe Phenylmethyl Ester (22). This compound was prepared according to the method of **18** from Boc depsipentapeptide **21** (0.45 g, 0.58 mmol), TFA (1.5 mL), and CH_2Cl_2 (6 mL) to afford 0.38 g (97%) of **22** as a colorless glass. This material was used without further purification.

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