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Total Synthesis of Dendroamide A: Oxazole and Thiazole Construction Using an Oxodiphosphonium Salt

Shu-Li You and Jeffery W. Kelly*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California 92037

jkelly@scripps.edu

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Abstract: The total synthesis of dendroamide A (**1**), a multidrug-resistance reversing bistratamide-type peptide-derived macrocycle, has been accomplished in 19% yield. Fmoc-protected amino acids were condensed into appropriately protected dipeptides which were treated with bis-(triphenyl)oxodiphosphonium trifluoromethanesulfonate to afford oxazoles and thiazolines (oxidized to thiazoles) with high chemo- and stereoselectivity. The convergent condensation of three heterocyclic amino acids followed by macrocyclization afforded the natural product.

Dendroamide A (**1**) was first isolated from the terrestrial blue-green alga (cyanobacterium) *Stigonema dendroideum fremy* in 1996.[1] This natural product reverses multiple drug resistance (MDR)[2] by acting as a P-glycoprotein and MRP1 antagonist at noncytotoxic doses. Dendroamide A could be useful against cancers exhibiting MDR and therefore has attracted the attention of synthetic and natural product chemists. Its total synthesis has been reported by two groups.[3] The thiazole substructure was prepared either by Hantzsch's procedure using a thioamide as an intermediate[4] or by employing a condensation reaction between cysteine esters and *N*-protected imino esters, followed by the oxidation of the resulting thiazolines.[5] Synthesis of the oxazole substucture was achieved by oxidation of the oxazoline, made from a β-hydroxy amide utilizing the Burgess reagent.[6]

In this paper, we report the synthesis of dendroamide A in 19% overall yield. Highlights include the preparation of the oxazole substructure from a β-ketodipeptide and the thiazolines from fully protected cysteine-containing dipeptides, in all cases utilizing bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate.[7]

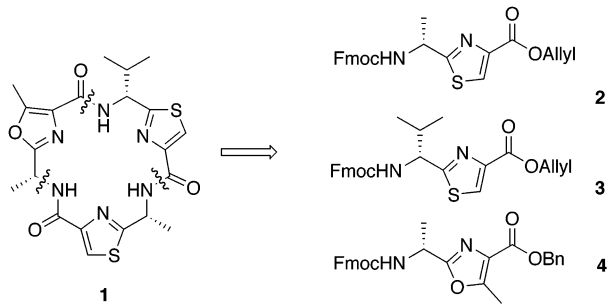

FIGURE 1. Retrosynthetic analysis of dendroamide A (**1**).

Our retrosynthetic analysis of dendroamide A (**1**), outlined in Figure 1, features disconnection at three amide bonds. The resulting appropriately protected heterocyclic amino acid fragments **2**−**4** are derived from dipeptides, which were synthesized from ordinary Fmoc-protected amino acids. The ketone side chain used to produce **4** results from the Dess−Martin oxidation of a threonine-containing dipeptide.

As shown in Scheme 1, compound **5** was synthesized by coupling *N*-Fmoc-L-*S*-tritylcysteine with allyl alcohol utilizing HBTU (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and HOBt (*N*-hydroxybenzotriazole) in the presence of DIEA (*N*, *N*-diisopropylethylamine). Diethylamine removal of the Fmoc protecting group afforded an amine that was coupled with *N*-Fmoc-D-alanine or *N*-Fmoc-D-valine employing HBTU and HOBt in the presence of DIEA, yielding dipeptides **6** and **7**, respectively. Transformation of the fully protected cysteine-containing dipeptides to thiazolines **8** and **9** was accomplished in high yield utilizing bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate,[7,8] generated from triphenyl phosphine oxide and triflic anhydride. The thiazolines in **8** and **9** were oxidized to thiazoles using activated manganese oxide. The stereochemical purity of **2** and **3** exceeded 96% ee as ascertained by chiral HPLC.

The synthesis of oxazole fragment **4** is outlined in Scheme 2. Dipeptide **10** was synthesized by coupling Fmoc-D-alanine and L-threonine benzyl ester. A Dess−Martin oxidization of the hydroxy group in dipeptide **10** led to ketone **11** in 80% yield.[9] Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate was utilized to convert the β-ketodipeptide **11** to the protected oxazole amino acid **4** in 84% yield without compromising the Ala-derived stereocenter (98% ee). Unlike the oxobisphosphonium salt utilized here, the PPh_3/I_2 reagent utilized

* To whom correspondence should be addressed. Fax: 858-784-9899.

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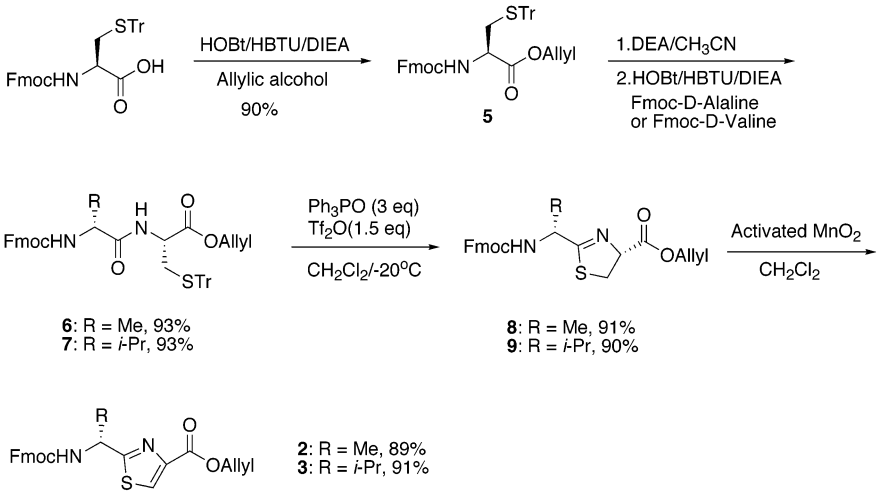
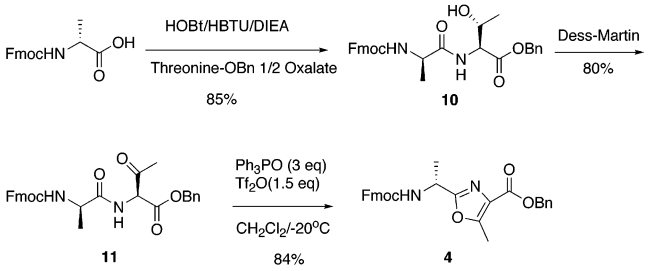
SCHEME 1. Synthesis of Thiazole-Containing Amino Acids 2 and 3



SCHEME 2. Synthesis of Oxazole-Containing Amino Acid 4 from a Thr-Based Dipeptide



previously for this transformation requires the use of a base increasing the risk of racemization.[10]

The allyl group in compound **3** was removed utilizing a palladium catalyst, generated from $Pd(OAc)_2$ and polymer-supported triphenylphosphine, in the presence of phenylsilane.[11] The use of this solid-phase catalyst greatly simplified workup of the reaction, as the carboxylic acid could be separated from the catalyst by filtration through a short silica gel column. The Fmoc group in compound **2** was removed by diethylamine, allowing its amino terminus to be coupled with the carboxylic acid derived from **3**, utilizing HBTU and HOBt in the presence of DIEA, affording the peptidic bis-heterocycle **12** (92%). The benzyl group in **4** was removed by a Pd/C-mediated hydrogenation. The resulting carboxylic acid was coupled with the free amine resulting from the diethylamine deprotection of compound **12**, yielding compound **13** in 94% yield. The macrolide precursor **14** can be obtained from peptide **13** by removing the Fmoc and allyl groups as described above. The final cyclization promoted by PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and DMAP can be achieved by slowly adding **14** to a solution of PyBOP and DMAP in CH_2Cl_2/DMF (2/1) with a syringe pump affording **1** in 81% yield as a white solid (Scheme 3). The ^1H and ^{13}C NMR spectra of **1** are identical to those reported in the literature.[1, 3]

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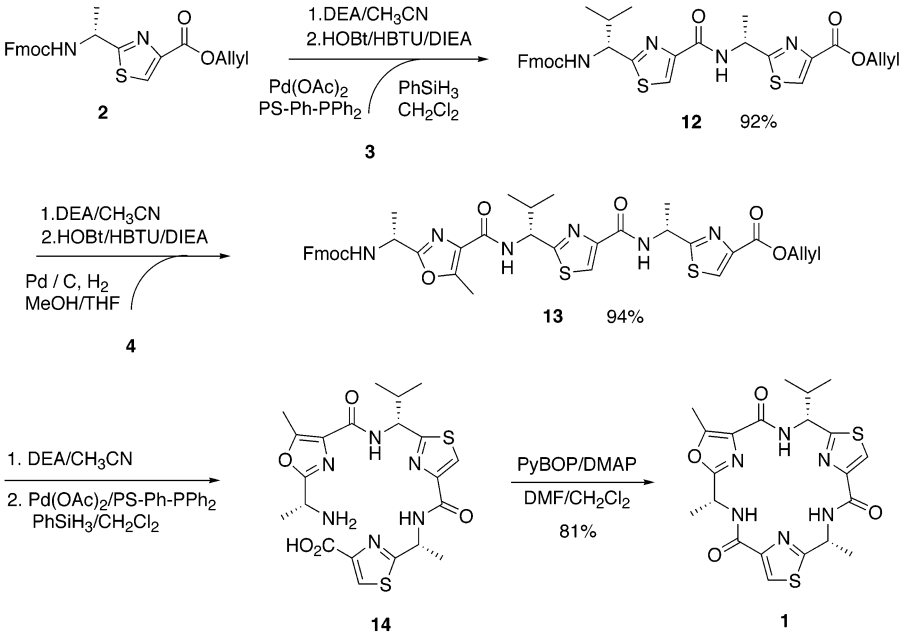
In summary, dendroamide A (**1**) has been synthesized in a highly convergent fashion from three appropriately protected heterocyclic amino acids. The oxazole amino acid results from cyclodehydration of a β-ketodipeptide. The thiazole amino acids are obtained from oxidation of their corresponding thiazoline amino acids, which are synthesized by the cyclodehydration of fully protected cysteine-based dipeptides. In each case bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate was employed to make the heterocyclic amino acids from the dipeptide by amide carbonyl activation/dehydration. The oxophosphonium salt accomplished these reactions with notable chemo- and stereoselectivity. The final macrocyclization proceeds in high yield (81%) affording **1** in an overall yield of 19%.

Experimental Section

Compound 5. A solution of N^{α}-Fmoc-L-Cys(S-trityl)-OH (5.86 g, 10 mmol) in DMF (50 mL) was treated with HOBt·H_2O (1.68 g, 11 mmol) and HBTU (4.17 g, 11 mmol) at 25 °C. After 10 min, allyl alcohol (1.36 mL, 20 mmol) and DIEA (3.65 mL, 21 mmol) were added separately, and the resulting mixture was stirred at 25 °C overnight. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/3) to afford compound **5** (5.63 g, 90%) as a white foam: $[\alpha]^{24}_D = +18.1$ (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.63−2.70 (m, 2H), 4.22 (dd, J = 7.0, 6.6 Hz, 1H), 4.33−4.39 (m, 3H), 4.58 (m, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.28−5.30 (m, 2H), 5.86 (m, 1H), 7.18−7.29 (m, 11H), 7.37−7.40 (m, 8H), 7.60 (dd, J = 6.1, 5.7 Hz, 2H), 7.75 (dd, J = 6.6, 6.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 34.0, 47.0, 52.9, 66.2, 67.0, 67.1, 118.7, 119.9, 125.1 (2 C), 126.8, 126.9, 127.0, 127.7, 127.9, 128.0 (3 C), 129.4 (3 C), 129.5, 131.3, 141.2 (2 C), 143.7, 143.8, 144.2, 155.5, 170.2; HRMS (MALDI-FTMS) calcd for $C_{40}H_{35}NO_4S$ ($M + Na^+$) 648.2179, found 648.2176.

Compound 6 (General Procedure for Diethylamine-Mediated Deprotection of Fmoc Group and HOBt, HBTU-Mediated Peptide Coupling). Diethylamine (30 mL) was added to a solution of **5** (5.63 g, 9 mmol) in CH_3CN (30 mL), and the resulting mixture was stirred at 25 °C for 30 min to ensure complete removal of the Fmoc protecting group. After concentration in vacuo, the reaction mixture was azeotroped to dryness with CH_3CN (2 × 30 mL), and the residue was dissolved in DMF (40 mL). In another flask, a solution of N^{α}-Fmoc-D-alanine (3.11 g, 10 mmol) in DMF (40 mL) was treated with HOBt·H_2O (1.53 g, 10 mmol) and HBTU (3.79 g, 10 mmol). After 10 min, this mixture and DIEA (3.65 mL, 21 mmol) were sequentially added to the above free amino ester. The reaction

SCHEME 3. Synthesis of Dendroamide A (1) from 3 Heterocyclic Amino Acids Derived from Dipeptides



was stirred at 25 °C for 8 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/3) to afford compound **6** (5.83 g, 93%) as a pale oil: $[\alpha]^{24}_D = +42.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.40 (d, J = 6.6 Hz, 3H), 2.61−2.63 (m, 2H), 4.18 (t, J = 7.0 Hz, 1H), 4.30−4.38 (m, 3H), 4.52 (m, 1H), 4.56 (d, J = 5.7 Hz, 2H), 5.20 (d, J = 10.5 Hz, 1H), 5.25 (dd, J = 17.1, 1.3 Hz, 1H), 5.48 (d, J = 7.0 Hz, 1H), 5.85−5.79 (m, 1H), 6.67 (d, J = 6.6 Hz, 1H), 7.18−7.29 (m, 11H), 7.35−7.39 (m, 8H), 7.54 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.74 (d, J = 7.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.8, 33.7, 47.0, 50.3, 51.2, 66.2, 66.7, 67.1, 118.8, 119.9, 125.0, 125.1, 126.8, 127.0 (2 C), 127.6, 127.8, 128.0, 129.4, 131.3, 141.2, 143.6, 143.9, 144.1, 155.8, 169.8, 171.9; HRMS (MALDI-FTMS) calcd for $C_{43}H_{40}N_2O_5S$ ($M + Na^+$) 719.2550, found 719.2551.

Compound 7. Compound **7** was synthesized from **5** and N^{α}-Fmoc-D-valine in 93% yield as a white foam by following the procedure used for the synthesis of **6**: $[\alpha]^{24}_D = +33.5$ (*c* 0.68, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.93 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 5.7 Hz, 3H), 2.14 (m, 1H), 2.61 (m, 2H), 4.07 (m, 1H), 4.19 (m, 1H), 4.36 (m, 2H), 4.56 (m, 1H), 4.60 (m, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.37 (d, J = 8.8 Hz, 1H), 5.85 (m, 1H), 6.42 (d, J = 7.9 Hz, 1H), 7.19−7.30 (m, 11H), 7.36−7.39 (m, 8H), 7.57 (m, 2H), 7.76 (d, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 19.2, 31.2, 33.8, 47.1, 51.2, 59.9, 66.3, 66.7, 67.0, 118.8, 119.9, 125.1, 126.8, 126.9, 127.0, 127.6, 127.9, 128.0, 129.3, 129.4, 131.3, 141.2, 143.6, 143.9, 144.1, 156.3, 169.8, 170.8; HRMS (MALDI-FTMS) calcd for $C_{45}H_{44}N_2O_5S$ ($M + Na^+$) 747.2863, found 747.2854.

Compound 8. To a solution of triphenylphosphine oxide (8.35 g, 30 mmol) in dry CH_2Cl_2 (100 mL) was added trifluoromethanesulfonic anhydride (2.35 mL, 15 mmol) slowly at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then adjusted to −20 °C using a brine−ice bath. Then, a solution of **6** (6.97 g, 10 mmol) in 10 mL CH_2Cl_2 was added. The reaction progress was monitored by TLC and was completed in 2 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/3) to afford compound **8** (3.97 g, 91%) as an oil: $[\alpha]^{24}_D = +37.8$ (*c* 2.67, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.46 (d, J = 7.0 Hz, 3H), 3.51 (t, J = 11.0 Hz, 1H), 3.59 (dd, J = 11.0, 8.0 Hz, 1H), 4.21 (t, J = 7.0 Hz, 1H), 4.34 (dd, J = 10.1, 7.5 Hz, 1H), 4.42 (dd, J = 10.5, 7.0 Hz, 1H), 4.67−4.69 (m, 3H), 5.12 (dd, J = 9.2, 8.8 Hz, 1H), 5.23 (d, J = 10.5 Hz, 1H), 5.33 (d, J = 17.1 Hz, 1H), 5.66 (d, J = 7.5 Hz, 1H), 5.91 (m, 1H), 7.26−7.30 (m, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.2, 35.3, 47.0, 49.7, 66.1, 66.7, 77.7, 118.8, 119.8, 124.9, 125.0, 126.9, 127.0, 127.6, 127.7, 127.8, 131.3, 141.1 (2 C), 143.6, 143.8, 146.8, 155.4, 170.0, 176.9; HRMS (MALDI-FTMS) calcd for $C_{24}H_{24}N_2O_4S$ ($M + H^+$) 437.1529, found 437.1525.

Compound 9. Compound **9** was synthesized from **7** in 90% yield as a white solid by following the procedure used for the synthesis of **8**: mp 73−75 °C; $[\alpha]^{24}_D = +47.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.94 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 2.19 (m, 1H), 3.54 (dd, J = 10.0, 9.6 Hz, 1H), 3.62 (m, 1H), 4.25 (dd, J = 7.5, 7.0 Hz, 1H), 4.38 (m, 1H), 4.44 (m, 1H), 4.56 (dd, J = 8.8, 5.3 Hz, 1H), 4.68 (d, J = 6.1 Hz, 2H), 5.17 (dd, J = 9.2, 8.3 Hz, 1H), 5.24 (d, J = 9.2 Hz, 1H), 5.32−5.35 (m, 1H), 5.42 (d, J = 8.8 Hz, 1H), 5.91 (m, 1H), 7.27−7.33 (m, 2H), 7.40 (dd, J = 7.5, 7.0 Hz, 2H), 7.60 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.0, 19.3, 32.2, 35.3, 47.1, 58.8, 66.2, 66.9, 77.8, 118.9, 119.9, 125.0, 125.1, 127.0, 127.1, 127.6, 127.8, 127.9, 131.4, 141.2, 143.7, 143.9, 146.8, 156.1, 170.1, 175.9; HRMS (MALDI-FTMS) calcd for $C_{26}H_{28}N_2O_4S$ ($M + H^+$) 465.1842, found 465.1846.

Compound 2. To a solution of **8** (436 mg, 1 mmol) in CH_2Cl_2 (5 mL), activated MnO_2 (<5 μm, 85%, 1.02 g, 10 mmol) was added. The reaction mixture was stirred overnight at 25 °C, then filtered through a short silica gel and Celite column and washed with EtOAc. The organic solution was concentrated. The resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/3) to afford compound **2** (387 mg, 89%) as a white solid: mp 154−157 °C; $[\alpha]^{24}_D = +19.8$ (*c* 0.61, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.63 (d, J = 5.7 Hz, 3H), 4.20 (m, 1H), 4.40 (m, 1H), 4.47 (dd, J = 10.5, 6.6 Hz, 1H), 4.84 (d, J = 4.8 Hz, 2H), 5.17 (m, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.67 (br, 1H), 6.02 (m, 1H), 7.25−7.27 (m, 4H), 7.56 (br, 2H), 7.74 (br, 2H), 8.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 47.0, 49.2, 65.9, 66.8, 118.9, 119.9, 124.9, 125.0, 127.0, 127.5, 127.6, 131.7, 141.2, 143.6, 146.7, 155.5, 160.8, 173.9; HRMS (MALDI-FTMS) calcd for $C_{24}H_{22}N_2O_4S$ ($M + H^+$) 435.1373, found 435.1371; HPLC (Chiralcel OD-H column, 254 nm, 90/10 hexane/2-propanol to 70/30 hexane/2-propanol gradient over 60 min, flow = 1.0 mL/min) t_R = 50.8 (*S*), 57.6 (*R*) min.

Compound 3. Compound **3** was synthesized from **9** in 91% yield as a white solid by following the procedure used for the

synthesis of **2**: mp 104−106 °C; $[\alpha]^{24}_D = +42.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.94 (d, $J = 7.0$ Hz, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 2.43 (m, 1H), 4.22 (dd, $J = 6.6$, 6.1 Hz, 1H), 4.44 (m, 2H), 4.85 (d, $J = 5.7$ Hz, 2H), 4.94 (dd, $J = 8.8$, 6.6 Hz, 1H), 5.30 (d, $J = 10.5$ Hz, 1H), 5.41 (d, $J = 15.1$ Hz, 1H), 5.59 (d, $J = 8.3$ Hz, 1H), 6.04 (m, 1H), 7.31 (m, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.60 (dd, $J = 6.1$, 5.3 Hz, 2H), 7.76 (d, $J = 7.5$ Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.5, 19.4, 33.3, 47.1, 58.5, 65.9, 66.8, 118.8, 119.9, 124.9, 125.0, 127.0, 127.2, 127.6, 131.8, 141.2, 143.6, 143.7, 146.9, 156.0, 160.8, 172.2; HRMS (MALDIFTMS) calcd for $C_{26}H_{26}N_2O_4S$ ($M + H^+$) 463.1686, found 463.1684; HPLC (Chiralcel OD-H column, 254 nm, 90/10 hexane/2-propanol to 70/30 hexane/2-propanol gradient over 60 min, flow = 1.0 mL/min) $t_R = 26.5$ (*S*), 30.9 (*R*) min.

Compound 10. Compound **10** was synthesized from N^{α}-Fmoc-D-valine and L-threonine benzyl ester oxalate in 85% yield as a white foam by following the procedure used for the synthesis of **6**: $[\alpha]^{24}_D = -25.7$ (*c* 0.77, DMSO); ^1H NMR (600 MHz, DMSO-d_6, 25 °C) δ 1.04 (d, $J = 6.1$ Hz, 3H), 1.26 (d, $J = 7.0$ Hz, 3H), 4.18−4.27 (m, 5H), 4.37 (d, $J = 8.8$ Hz, 1H), 5.08−5.11 (m, 1H), 5.13−5.16 (m, 2H), 7.30−7.37 (m, 7H), 7.41 (t, $J = 7.5$ Hz, 2H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.73 (m, 2H), 7.89−7.91 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 18.5, 20.1, 46.6, 57.6, 65.7, 65.9, 66.4, 120.1, 125.3 (2 C), 127.1, 127.6, 127.9, 128.3, 135.9, 140.7, 143.8, 143.9, 155.7, 170.4, 173.2; HRMS (MALDI-FTMS) calcd for $C_{29}H_{30}N_2O_6$ ($M + Na^+$) 525.1996, found 525.1996.

Compound 11. Dess−Martin periodinane (306 mg, 97% purity, 0.7 mmol) was added to a flask containing **10** (251 mg, 0.5 mmol) in 30 mL of CH_2Cl_2. The resulting reaction mixture was stirred at 25 °C for 1 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/2) to afford compound **11** (200 mg, 80%) as a gel: $[\alpha]^{24}_D = +28.7$ (*c* 0.90, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.38 (m, 3H), 2.27 (s, 3H), 4.19 (t, $J = 5.7$ Hz, 1H), 4.36−4.42 (m, 3H), 5.13 (m, 1H), 5.22 (dd, $J = 12.3$, 7.9 Hz, 1H), 5.28 (d, $J = 5.7$ Hz, 1H), 5.59 (dd, $J = 17.7$, 7.5 Hz, 1H), 7.26−7.30 (m, 8H), 7.36 (t, $J = 7.0$ Hz, 2H), 7.56 (m, 2H), 7.73 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.6, 27.9, 47.0, 50.1, 63.1, 67.0, 68.2, 119.9, 125.0, 127.0, 127.6, 128.3, 128.4 (2 C), 128.6 (2 C), 128.7, 128.8, 134.4, 141.2, 143.6, 143.8, 155.9, 165.6, 172.3, 197.9; HRMS (MALDI-FTMS) calcd for $C_{29}H_{28}N_2O_6$ ($M + Na^+$) 523.1839, found 523.1836.

Compound 4. Compound **4** was synthesized from **11** in 84% yield as a colorless gel following the procedure used for the synthesis of **8**: $[\alpha]^{24}_D = +26.2$ (*c* 0.81, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.54 (d, $J = 6.6$ Hz, 3H), 2.53 (s, 3H), 4.20 (t, $J = 7.0$ Hz, 1H), 4.40 (d, $J = 6.6$ Hz, 2H), 5.00 (m, 1H), 5.35 (s, 2H), 5.59 (d, $J = 7.4$ Hz, 1H), 7.28−7.39 (m, 7H), 7.42 (d, $J = 7.0$ Hz, 2H), 7.58 (t, $J = 7.9$ Hz, 2H), 7.75 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.1, 20.2, 45.1, 47.1, 66.6, 67.0, 119.9, 125.0, 127.0, 127.4, 127.6, 128.3, 128.4, 128.5, 135.6, 141.2, 143.7, 143.8, 155.5, 156.6, 162.5, 168.9; HRMS (MALDI-FTMS) calcd for $C_{29}H_{26}N_2O_5$ ($M + Na^+$) 483.1914, found 483.1916; HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/2-propanol to 70/30 hexane/2-propanol gradient over 60 min, flow = 1.0 mL/min) $t_R = 30.9$ (*R*), 39.8 (*S*) min.

Compound 12. $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and styrene polymer-bound triphenylphosphine (101 mg, 1.59 mol/g, 0.16 mmol) were added to a flask containing CH_2Cl_2 (10 mL). After the mixture was stirred for 10 min, **3** (462 mg, 1 mmol) and $PhSiH_3$ (0.24 mL, 2 mmol) were added separately. The reaction progress was monitored by TLC, and the reaction was complete in 15 min. After removal of the solvent, the residue was passed through a short silica gel column eluted with $CHCl_3$/EtOH (1/1). The carboxylic acid was used in the next step without further purification. Coupling with **2** (391 mg, 0.9 mmol) following the procedure used for the synthesis of **6** gave **12** as a white foam (511 mg, 92%): $[\alpha]^{24}_D = +23.6$ (*c* 0.74, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.93 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.79 (d, $J = 6.5$ Hz, 3H), 2.28 (m, 1H), 4.22 (m, 1H), 4.47 (d, $J = 6.6$ Hz, 2H), 4.81 (d, $J = 5.7$ Hz, 2H), 4.87 (dd, $J = 8.3$, 6.6 Hz, 1H), 5.27 (d, $J = 10.5$ Hz, 1H), 5.38 (d, $J = 17.1$ Hz, 1H), 5.60 (m, 1H), 5.73 (d, $J = 8.8$ Hz, 1H), 6.01 (m, 1H), 7.25−7.29 (m, 2H), 7.38 (dd, $J = 7.5$, 7.0 Hz, 2H), 7.59 (t, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 7.5$ Hz, 2H), 8.02 (s, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 19.4, 20.9, 33.0, 47.1 (2 C), 58.4, 65.8, 66.7, 118.8, 119.9, 123.6, 124.9, 126.9, 127.6 (2 C), 131.7, 141.2, 143.6, 146.6, 149.2, 156.0, 160.4, 160.7, 171.9, 173.0; HRMS (MALDI-FTMS) calcd for $C_{32}H_{32}N_4O_5S_2$ ($M + H^+$) 617.1887, found 617.1902.

Compound 13. Pd on activated carbon (15 mg) was added to a flask containing **4** (154 mg, 0.32 mmol) in MeOH (3 mL) and THF (3 mL). The reaction flask was filled with a H_2 balloon, evacuated, and purged with H_2 three times. The reaction progress was monitored by TLC and was complete in 1 h. After removal of the solvent, the residue was passed through a short silica gel column eluted with MeOH. The carboxylic acid was used in the next step without further purification. By following the procedure for the synthesis of **6**, the carboxylic acid was coupled with **12** (185 mg, 0.3 mmol) affording **13** as a white foam (217 mg, 94%): $[\alpha]^{24}_D = +30.7$ (*c* 1.46, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.01 (d, $J = 6.1$ Hz, 3H), 1.02 (d, $J = 6.1$ Hz, 3H), 1.59 (d, $J = 6.6$ Hz, 3H), 1.79 (d, $J = 7.0$ Hz, 3H), 2.45 (m, 1H), 2.61 (s, 3H), 4.22 (dd, $J = 7.0$, 6.6 Hz, 1H), 4.42−4.44 (m, 2H), 4.82 (d, $J = 5.7$ Hz, 2H), 5.02 (m, 1H), 5.25−5.85 (m, 2H), 5.38 (d, $J = 17.1$ Hz, 1H), 5.56−5.61 (m, 2H), 6.00 (m, 1H), 7.27−7.29 (m, 2H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 9.2$ Hz, 1H), 7.58 (dd, $J = 8.7$, 8.3 Hz, 2H), 7.75 (d, $J = 7.5$ Hz, 2H), 7.91 (d, $J = 7.9$ Hz, 1H), 8.01 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.7, 17.9, 19.5, 19.6, 20.9, 33.0, 45.0, 47.0 (2 C), 55.9, 65.9, 66.9, 118.8, 119.9, 123.6, 124.9, 126.9, 127.7, 128.4, 131.7, 141.2, 143.5, 143.7, 146.6, 149.1, 154.0, 155.5, 160.4, 160.8, 161.3, 161.5, 171.8, 173.1; HRMS (MALDI-FTMS) calcd for $C_{39}H_{40}N_6O_7S_2$ ($M + H^+$) 769.2473, found 769.2479.

Dendramide A (**1**). Deprotecting the Fmoc group in **13** (76.9 mg, 0.1 mmol) used the procedure described for the synthesis of **6**. The allyl group was removed by a palladium catalyst as described in the synthesis of **12**. The resulting amino acid **14** was dissovled in CH_2Cl_2/DMF (10 mL, v/v: 2/1) as a 0.01 M solution. This solution was added to a flask containing PyBOP (104 mg, 0.2 mmol) and DMAP (24.4 mg, 0.2 mmol) in CH_2Cl_2/DMF (20 mL, v/v 2/1) over 8 h using a syringe pump. After the addition was complete, the mixture was stirred for 2 h. Regular workup and purification by flash chromatography gave **1** as a colorless semisolid (39.6 mg, 81%): $[\alpha]^{25}_D = +83.8$ (*c* 0.76, $CHCl_3$) [lit.[3b] $[\alpha]_D = +53.9$ (*c* 0.2, $CHCl_3$)]; ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.98 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.71 (d, $J = 7.0$ Hz, 3H), 1.73 (d, $J = 7.0$ Hz, 3H), 2.33 (m, 1H), 2.68 (s, 3H), 5.21 (q, $J = 6.6$ Hz, 1H), 5.31 (dd, $J = 7.9$, 4.8 Hz, 1H), 5.72 (dq, $J = 8.3$, 6.6 Hz, 1H), 8.14 (s, 1H), 8.15 (s, 1H), 8.49 (d, $J = 8.3$ Hz, 1H), 8.55 (d, $J = 8.3$ Hz, 1H), 8.65 (d, $J = 6.1$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.6, 18.3, 18.4, 20.9, 24.9, 35.1, 44.3, 47.0, 55.9, 123.7,123.8, 128.4, 148.8 (2 C), 153.8, 159.6, 159.8, 160.5, 161.7, 168.2, 171.1; HRMS (MALDI-FTMS) calcd for $C_{21}H_{24}N_6O_4S_2$ ($M + H^+$) 489.1373, found 489.1373.

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Supporting Information Available: General procedures and NMR spectra for **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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