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# Solid-Phase Total Synthesis of Scytalidamide A

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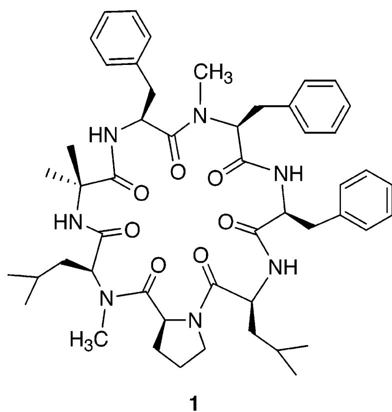
The first total synthesis of the natural cyclic heptapeptide scytalidamide A was achieved on solid phase using two different resins, a phenylalanine silane resin and a 4-methoxybenzaldehyde backbone linker resin. The synthetic product confirms the structure of the natural product reported in the preceding paper in this issue (Tan, L. T.; Cheng, X. C.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2003**, *68*, 8767).

## Introduction

Scytalidamide A (**1**), a cyclic heptapeptide that was recently isolated from a cultured marine fungus of the genus *Scytalidium*, was shown to have moderate selective anticancer activity toward CACA-2 colon carcinoma.[1]




**1**

Cyclic peptides have several advantages as potential drug candidates. Unlike linear peptides, they do not have charges at the peptide amino and carboxyl termini and lack zwitterionic character. Therefore, they are more lipophilic and membrane permeable. Oral bioavailability is increased by faster membrane absorption in the digestive tract, and cyclic peptides have much greater half-lives in vivo than linear peptides.[2,3] Because of these advantages, many laboratories have focused on the syntheses of cyclic peptides and cyclic depsipeptides, especially by solid-phase peptide synthesis (SPPS) methodologies.[4]

Since the introduction of the Merrifield method for peptide synthesis,[5] large libraries of linear biopolymers such as peptides and oligonucleotides as well as organic compounds have been generated using this approach.[6] Also, many novel linkers have been designed and employed for solid-phase peptide synthesis. Among them is the use of a resin having a linker functional group that can be excised efficiently and quantitatively at the end of the synthesis, leaving behind no trace or "memory" of its presence.[7] Recently, we designed two novel solid-phase peptide synthesis traceless linker resins: a phenylalanine silane linker resin (**2**) and 4-methoxybenzaldehyde backbone linker resin (**3**).[8−11] We have utilized the phenylalanine silane linker resin for the synthesis of the cyclic peptide analogue of the natural cyclic depsipeptide sansalvamide A.[10] The 4-methoxybenzaldehyde backbone linker resin has been shown to be compatible with a variety of acid- and base-labile protecting groups for amino acids, and it is cleaved from the peptide with refluxing trifluoroacetic acid, conditions shown to be sufficiently mild as to leave amides, esters, and sensitive amino acid side chains unscathed. This resin was used to synthesize a variety of dipeptides,[11] but its use in the synthesis of cyclic peptides has not yet been reported. In this paper, we report the application of resins **2** and **3**

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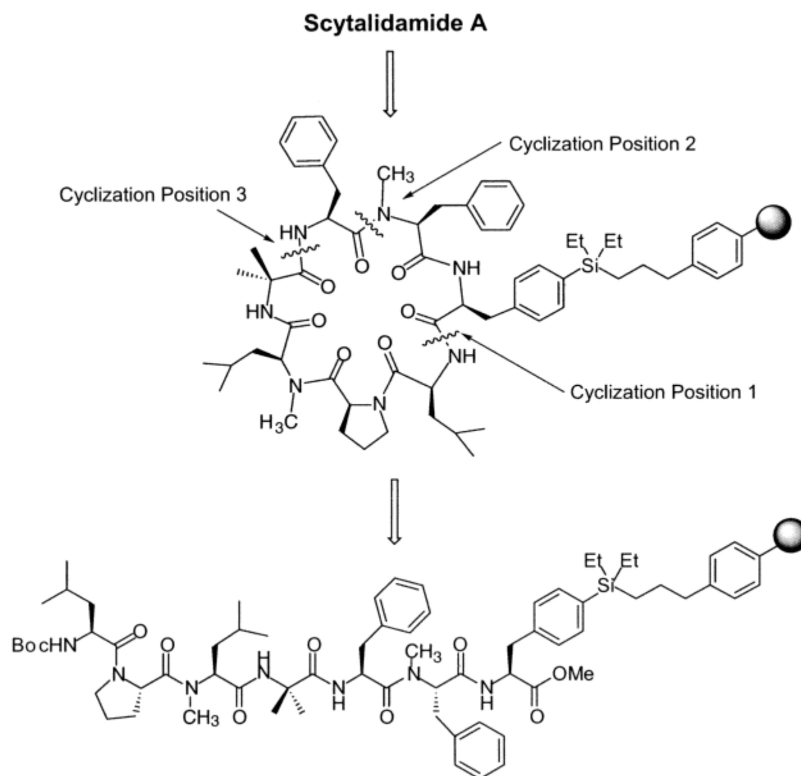
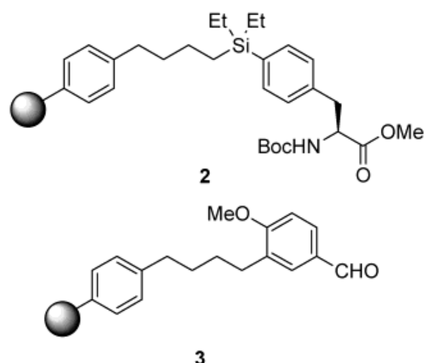



**FIGURE 1.** Retrosynthetic scheme for scytalidamide A showing three possible positions for cyclization.

for the solid-phase synthesis of the newly discovered cyclic peptide antitumor agent scytalidamide A described in the previous paper in this issue.[1]



## Results and Discussion

Scytalidamide A is a hydrophobic cyclic heptapeptide which is composed of one leucine (Leu), one *N*-methylleucine (MeLeu), two phenylalanines (Phe), one *N*-methylphenylalanine (MePhe), one proline (Pro), and one α-aminoisobutyric acid (Aib). Therefore, scytalidamide A has four hindered residue amino acids (MeLeu, MePhe, Pro, and Aib). It is well-known that efficient amide bond formation with *N*-methylamino acids can be challenging, because diketopiperazine formation is a common side reaction.[12] Bulky α,α-disubstituted residues, such as Aib, cause problems similar to those presented by the *N*-methylamino acids.[13] To avoid the side reactions mentioned above, more efficient coupling reagents are required, and the choice for the macrocyclization position is very important.

Our first approach utilized linker resin **2**. As shown in the retrosynthetic analysis in Figure 1, an initial consideration in the synthesis of **1** involved the selection of the appropriate cyclization precursor that might provide the best yield and keep the side reactions to a minimum. Because linker **2** has a phenylalanine residue, the macrocyclization will be adjacent to a phenylalanine. Therefore, there are only two cyclization positions that are reasonable, indicated in Figure 1 as cyclization positions 1 and 2. The third phenylalanine is an *N*-methylated one that cannot be considered as a candidate. Position 2, however, has a hindered *N*-methylamino acid residue, so that position is not favorable for cyclization either. Therefore, cyclization position 1 was selected as the site for macrocyclization.

As shown in Scheme 1, phenylalanine silane linker **2** was prepared from butyldiethylsilane polystyrene with Boc-4-iodophenylalanine methyl ester using a palladium catalyst as reported previously.[10] A low loading level (0.09 mmol/g) of **2** was selected to avoid problems of oligomer formation during the final cyclization step. Boc strategy was utilized for elongation of the peptide chain to reduce the possibility of diketopiperazine formation, which is known to occur during base-promoted removal of Fmoc protecting groups, even at the dipeptide stage.[14–16] Boc

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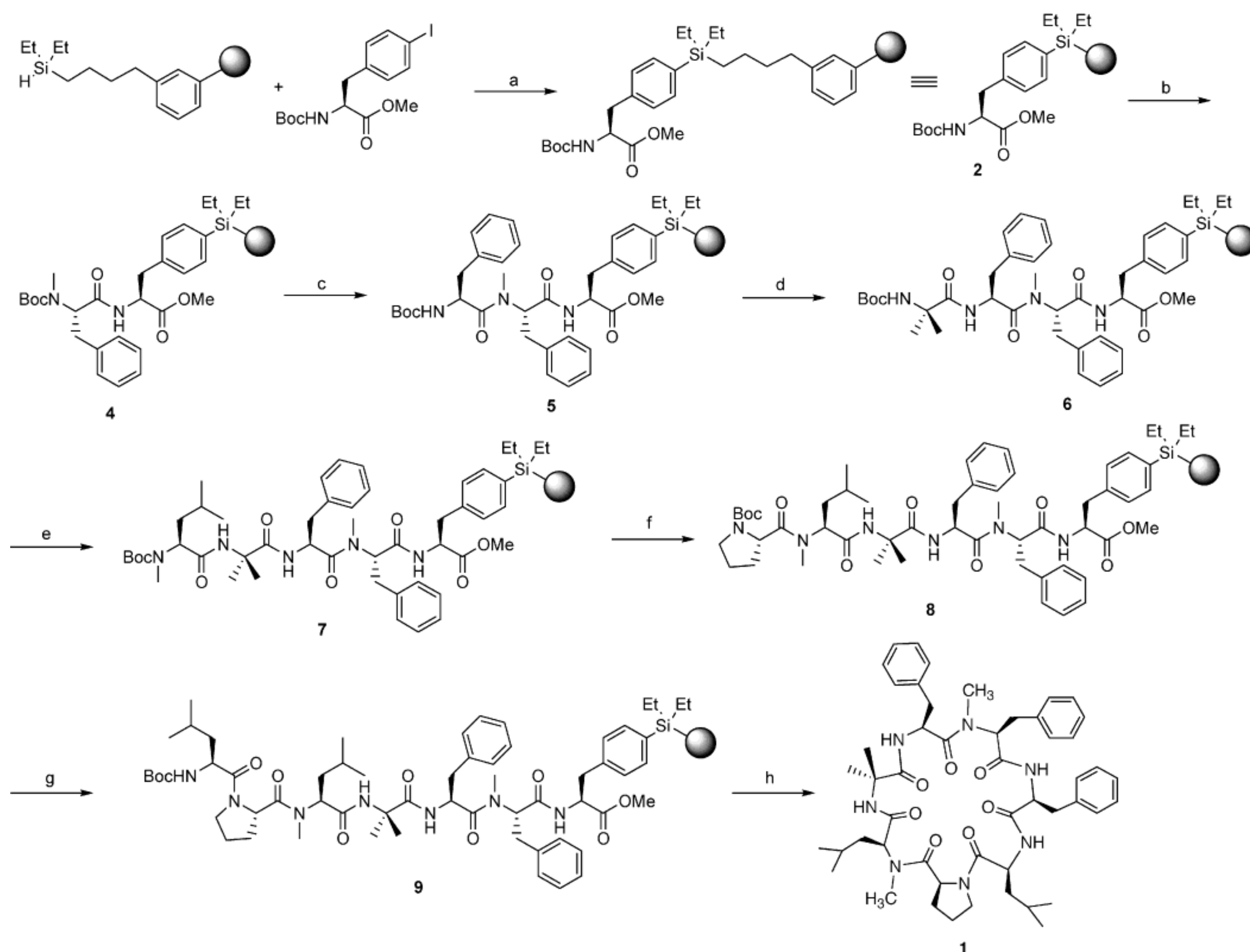
**SCHEME 1**[a]



[a] Reagents and conditions: (a) ref 10; (b) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-MePhe-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (c) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min; (ii) Boc-Phe-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), rt, 6 h; (d) (i) TFA/$CH_2Cl_2$ (1: 1), rt, 30 min, (ii) Boc-Aib-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (e) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min; (ii) Boc-MeLeu-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (f) (i) TFA/$CH_2Cl_2$, (1:1), rt, 30 min, (ii) Boc-Pro-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (g) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-Leu-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (h) (i) LiOH, $H_2O$/THF (1:7), rt, 12 h, (ii) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (iii) PyBOP (5 equiv), DIPEA (15 equiv), NMP, rt, 24 h; (iv) neat TFA, rt, 24 h.

deprotection of the amino group of **2** followed by reaction with Boc-MePhe-OH and DIPEA in the presence of a highly effective activating reagent HATU[17] in NMP as the solvent afforded polymer-bound dipeptide **4**. Elongation of the peptide chain to linear peptide **9** was accomplished by stepwise coupling of the corresponding Boc-protected amino acids under the same conditions at each step. Removal of the Boc and methyl ester groups of **9** afforded the resin-bound linear peptide. To avoid guanidine formation with the free N-terminal amino group, and prevention of cyclization, when employing an excess of the uronium salt HATU to activate the *C*-terminal carboxylic acid group of the linear heptapeptide, the phosphonium salt-based coupling reagent PyBOP was substituted for HATU in the cyclization step.[18] After macrocyclization, resin-bound scytalidamide A was released from the resin by treatment with neat TFA at room temperature for 24 h. The crude product was purified by flash chromatography to afford scytalidamide A (**1**) in an overall yield of 20% for the 16-step solid-phase synthesis. The purified product had nearly identical melting point, optical rotation, and spectral properties as those of the natural product, thus confirming the structure of the natural product.

The phenylalanine silane linker **2** is limited to peptides that have at least one phenylalanine residue, because the peptide must be linked to the polymer through the benzyl side chain of protected phenylalanine. To avoid this limitation of linker **2**, we recently developed the 4-methoxybenzaldehyde backbone linker resin **3**.[11] With backbone linker resins, amino acids can be attached to the linker at the amino group, so that any amino acid residue can be used.[19] Several hydrophilic and hydrophobic dipeptides were synthesized with the 4-methoxybenz-

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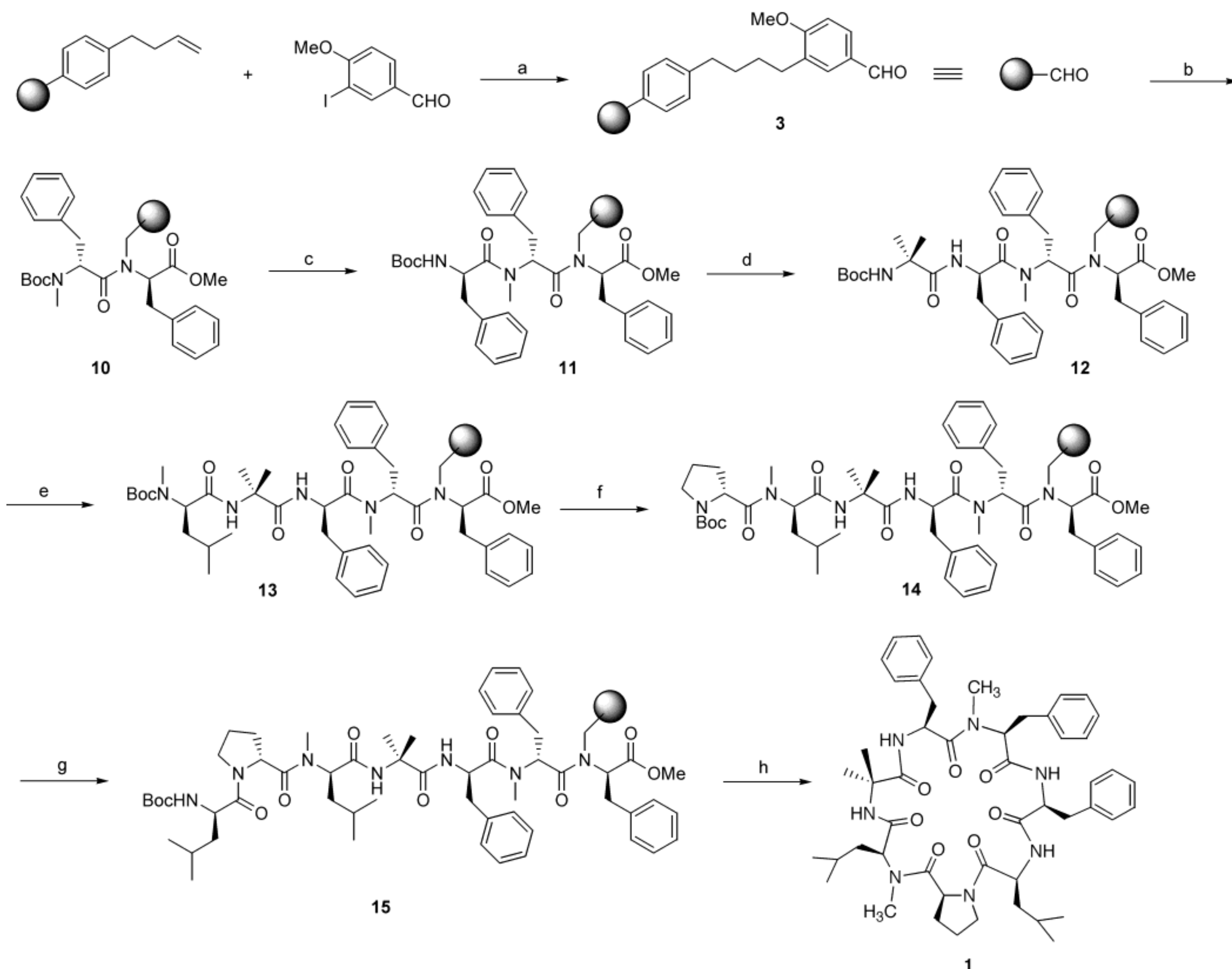
**SCHEME 2**[a]



[a] Reagents and conditions: (a) ref 11; (b) (i) 1% HOAc in DMF, $NaBH(OAc)_3$, (ii) Phe-OMe·HCl (5 equiv), rt, 6 h, (iii) Boc-MePhe-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), $CH_2Cl_2$/DMF (9:1), rt, 5 h; (c) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-Phe-OH (5 equiv), HATU (5 equiv), DIPEA (15 equiv), rt, 6 h; (d) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-Aib-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (e) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-MeLeu-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (f) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-Pro-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (g) (i) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (ii) Boc-Leu-OH, HATU (5 equiv), DIPEA (15 equiv), NMP, rt, 6 h; (h) (i) LiOH, $H_2O$/THF (1: 7), rt, 12 h, (ii) TFA/$CH_2Cl_2$ (1:1), rt, 30 min, (iii) PyBOP (5 equiv), DIPEA (15 equiv), NMP, rt, 24 h; (iv) TFA, refluxing, 3 h.

aldehyde linker resin to demonstrate its versatility.[11] Although scytalidamide A contains several phenylalanine residues, we carried out a synthesis of this natural product using our 4-methoxybenzaldehyde linker resin for comparison with the silane resin methodology.

As shown in Scheme 2, the same cyclization position as in Scheme 1 was selected. The 4-methoxybenzaldehyde linker resin was prepared according to the method developed by us recently.[10] Again a low loading level was used (0.08 mmol/g) to avoid oligomer formation during the final cyclization step. Reductive amination of **3** with H-Phe-OMe·HCl was followed, after Boc deprotection, by coupling with Boc-MePhe-OH using HATU as the coupling reagent and DIPEA as the base to afford resin-bound dipeptide **10**. After Boc deprotection, the same coupling conditions as used in Scheme 1 were employed to elongate the linear peptide chain from the N-terminus of dipeptide **10** to give resin-bound linear heptapeptide **15**. Deprotection of the methyl ester and the N-terminus of **15** gave the resin-bound linear peptide. Macrocyclization of this peptide with PyBOP as the coupling reagent afforded resin-bound scytalidamide A, which was treated with refluxing TFA for 3 h to release the crude product from the resin. Purification of the cyclic peptide by flash chromatography afforded scytalidamide A in a 46% overall yield for the 15-step synthesis. The melting point, optical rotation, and $^1H$ NMR, $^{13}C$ NMR and high-resolution mass spectra were nearly identical to those of the natural product. The crystal structure of the syn-

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thetic product (see Supporting Information) confirmed the structure of scytalidamide A reported in the previous paper.[1]

In summary, the first solid-phase total synthesis of the natural cyclic heptapeptide scytalidamide A was achieved in high overall yield using two different linker resins, a phenylalanine silane resin and a 4-methoxybenzaldehyde backbone linker resin. The latter resin gave the product in a much higher overall yield. This synthesis confirms the structure of the natural product reported in the previous paper in this issue.[1]

## Experimental Section

**General Methods.** Butyldiethylsilane polystyrene (PE-DES-SiH, 1.45 mmol/g) was bought from Argonaut Technologies, Inc. Methylene chloride was distilled under $N_2$ from calcium hydride. Flash chromatography was performed with 230−400 mesh silica gel. All $^1$H NMR spectra were recorded on either a Mercury 400 or Inova 500 spectrometer (125 MHz for $^{13}$C NMR spectra). Chemical shifts ($\delta$) are reported downfield from tetramethylsilane ($Me_4Si$) in parts per million (ppm). Compounds were visuslized with a ninhydrin spray reagent or a UV/vis lamp. Mass spectra were recorded either on a VG Instrument VG70-250SE high-resolution mass spectrometer (ESI) or on a Micromass Quattro II spectrometer (APCI).

**Phenylalanine Silane Linker Resin (2).** To a solution of *N*-Boc-4-iodophenylalanine methyl ester (800 mg, 2 mmol) in NMP (20 mL) were added butyldiethylsilane polystyrene (PE-DES-SiH, 4 g, 1.45 mmol/g) and KOAc (300 mg, 0.3 mmol). The reaction mixture was deaerated by bubbling with a slow stream of argon for 15 min. After the addition of $Pd_2(dba)_3\cdot CHCl_3$ (110 mg, 0.1 mmol), the reaction flask and reflux condenser were wrapped with aluminum foil, and the mixture was stirred at 110 °C for 24 h. After being cooled to room temperature and washed with $CH_2Cl_2$, DMF, 1 N HCl/THF (1:7, 30 min), MeOH, and $CH_2Cl_2$, an aliquot of the resin (200 mg) was treated with a solution of $Br_2$ (15 $\mu$L) in $CH_2Cl_2$ (10 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with $CH_2Cl_2$ (5 mL). Concentration of the combined filtrates gave *N*-Boc-4-bromophenylalanine methyl ester (the loading level of **2** was determined to be 0.09 mmol/g): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (s, 9 H), 3.05 (2dd, $J$ = 6.0 Hz, 13.6 Hz), 3.73 (s, 3 H), 4.57 (m, 1 H), 4.99 (d, $J$ = 7.6 Hz, NH, 1 H), 7.01 (d, $J$ = 8.0 Hz, 2 H), 7.42 (d, $J$ = 8.0 Hz, 2 H); HRMS (ESI, M + 1) calcd for $C_{15}H_{21}BrNO_4$ 358.0648 and 360.0628, found 358.0654 and 360.0635.

**4-Methoxybenzaldehyde Backbone Linker Resin (3).** A dried flask was charged with polystyrene olefin resin (5 g, prepared from Merrifield resin, 100−200 mesh, Novabiochem, 1.60 mmol/g) and 50 mL of anhydrous THF under argon. 9-BBN (0.5 M in THF, 10 mL, 5 mmol) was then added dropwise to the flask by syringe with stirring at room temperature. The reaction mixture was stirred overnight. The liquid was removed via cannula, 50 mL of anhydrous THF was added to the flask, and the mixture was stirred for 5 min. The liquid was removed via cannula again. The procedure was repeated three times to remove all of the 9-BBN from the resin. A solution of 3-iodo-4-methoxybenzaldehyde (0.42 g, 1.6 mmol) in DMF (30 mL) was added followed by an aqueous solution of $Na_2CO_3$ (2 M, 2 mL). The reaction mixture was deaerated by bubbling with a slow stream of argon for 15 min. After the addition of $Pd(PPh_3)_4$ (125 mg), the reaction flask and reflux condenser were wrapped with aluminum foil, and the mixture was stirred at 110 °C for 24 h. $Pd(PPh_3)_4$ (50 mg) was added to the reaction mixture, and stirring was continued for an additional 48 h. After being cooled to room temperature and washed with DMF (3 × 50 mL), $CH_2Cl_2$ (3 × 50 mL), 1 N HCl/THF (1:7, 50 mL, 30 min), MeOH (3 × 50 mL), and $CH_2Cl_2$ (3 × 50 mL), the product was collected on a glass funnel and suction dried for 15 min. The product was transferred to a glass tray and dried in a vacuum for 24 h to give 4-methoxybenzaldehyde linker resin **3**. IR (cm$^{-1}$): 1688 (C=O). The loading level was determined to be 0.08 mmol/g resin by reductive amination of **3** with an α-amino ester and then acetylation of the free amine followed by cleavage and subsequent determination of the mass of the product.

**Solid-Phase Synthesis of Scytalidamide A (1) Using Resin 2.** A suspension of resin **2** (1 g, 0.09 mmol/g) was treated with 50% TFA in $CH_2Cl_2$ (20 mL) for 30 min and then washed with $CH_2Cl_2$, 0.1 N HCl/THF, MeOH, and DMF. The washed resin was suspended in NMP (20 mL) and treated with Boc-MePhe-OH (5 equiv), HATU (5 equiv), and DIPEA (15 equiv) for 6 h. After being washed with DMF, 0.1 N HCl/THF, MeOH, and DMF, the resin was cycled through the same set of conditions for deprotection, washing, coupling, and washing as above using Boc-Phe-OH (5 equiv), Boc-Aib-OH (5 equiv), Boc-MeLeu-OH (5 equiv), Boc-Pro-OH (5 equiv), and Boc-Leu-OH (5 equiv) successively in the peptide elongation. After being washed with DMF, 0.1 N HCl/THF, MeOH, and DMF, the diprotected linear peptide bound to the resin was shaken with LiOH (5 equiv) in THF/$H_2O$ (7:1, 20 mL) at room temperature for 12 h. The product was washed with DMF, 0.1 N HCl/THF, MeOH, and DMF, and then the resin was treated with 50% TFA in $CH_2Cl_2$ (20 mL) for 30 min and washed with $CH_2Cl_2$, 0.1 N HCl/THF, MeOH, and DMF. Cyclization was carried out by treatment of the resin in NMP (20 mL) with PyBOP (5 equiv) and DIPEA (15 equiv) for 24 h followed by washing with DMF, 0.1 N HCl/THF, MeOH, and $CH_2Cl_2$. The resin was then treated with neat TFA for 24 h at room temperature to release the cyclic peptide. The cleavage solution was filtered, and the resin was rinsed with $CH_2Cl_2$ (20 mL). Flash chromatography of the crude product gave 16 mg of scytalidamide A (**1**) as a white solid in a 20% yield based on the loading level of **2**: mp 149−151 °C; $[\alpha]^{25}_D$ −162.8 ($c$ = 1.0, MeOH); HRMS (EI, $M^+$) calcd for $C_{50}H_{67}N_7O_7$ 877.5096, found 877.5093; $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 0.98 (d, $J$ = 6.9 Hz, 3 H), 1.00 (d, $J$ = 6.9 Hz, 3 H), 1.08 (d, $J$ = 6.0 Hz, 3 H), 1.12 (d, $J$ = 6.5 Hz, 3 H), 1.35 (s, 3 H), 1.41 (s, 3 H), 1.48 (m, 1 H), 1.64 (m, 1H), 1.74 (m, 2 H), 1.82 (m, 1 H), 1.89 (m, 1 H), 2.09 (m, 1 H), 2.25 (m, 3 H), 2.41 (s, 3 H), 2.50 (dd, $J$ = 2.5, 12.5 Hz, 1 H), 2.78 (dd, $J$ = 4.8, 12.5 Hz, 1 H), 2.93 (s, 3 H), 3.16 (m, 3 H), 3.38 (m, 1 H), 3.41 (m, 1 H), 3.76 (m, 1 H), 3.95 (m, 1 H), 4.48 (brt, $J$ = 8.0 Hz, 1 H), 4.55 (t, $J$ = 7.5 Hz, 1 H), 4.98 (t, $J$ = 9.5 Hz, 1 H), 5.09 (dt, $J$ = 12.0, 3.5, 1 H), 5.33 (t, $J$ = 7.0 Hz, 1 H), 6.39 (d, $J$ = 7.5 Hz, 2 H), 6.98 (t, 7.5 Hz, 2 H), 7.06 (t, $J$ = 7.5 Hz, 1 H), 7.17 (t, $J$ = 5.5 Hz, 1 H), 7.22 (t, $J$ = 6.5, 1 H), 7.26 (d, $J$ = 7.5 Hz, 2 H), 7.26 (d, $J$ = 7.0 Hz, 2 H), 7.32 (s, 4 H), 7.69 (d, $J$ = 9.0 Hz, 1 H), 8.36 (d, 9.5 Hz, 1 H), 8.48 (d, 9.5 Hz, 1 H), 8.56 (s, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.9, 22.6, 23.4, 23.5, 23.8, 24.7, 25.1, 26.1, 28.2, 29.0, 29.7, 33.7, 36.5, 38.0, 38.2, 38.3, 39.2, 40.7, 49.9, 50.2, 53.8, 56.3, 57.4, 58.3, 69.3, 126.7, 126.8, 127.3, 128.6, 128.8, 129.2, 129.4, 129.5, 129.9, 136.4, 136.5, 137.3, 168.0, 169.1, 170.3, 171.6, 171.7, 172.2, 173.9.

**Solid-Phase Synthesis of Scytalidamide A (1) Using Resin 3.** A 20-mL polyethylene tube was charged with 4-methoxybenzaldehyde linker resin **3** (1 g, 0.08 mmol/g) and 1% HOAc in DMF (10 mL). $NaBH(OAc)_3$ (110 mg, 0.5 mmol, 5 equiv) was added, and a white turbid suspension was generated. The suspension was agitated gently, and H-Phe-OMe·HCl (5 equiv) was added to the mixture. The resin was shaken for 6 h. The mixture was filtered and was rinsed with DMF (3 × 15 mL), $CH_2Cl_2$ (3 × 15 mL), $CH_3OH$ (3 × 15 mL), and $CH_2Cl_2$ (3 × 15 mL) to afford the resin-bound phenylalanine methyl ester. A solution of Boc-MePhe-OH (5 equiv) and DIPEA (15 equiv) in $CH_2Cl_2$−DMF (9:1, 10 mL) was added to the resin. After 30 s of shaking, solid HATU (5 equiv) was added to initiate coupling. After 5 h, the dipeptide resin was filtered and washed with DMF (3 × 15 mL), $CH_2Cl_2$ (3 × 15 mL), $CH_3OH$ (3 × 15 mL), and $CH_2Cl_2$ (3 × 15 mL) to afford the support-bound dipeptide. A suspension of the above resin was treated with 50% TFA in $CH_2Cl_2$ (20 mL) for 30 min and

then was washed with $CH_2Cl_2$, 0.1 N HCl/THF, MeOH, and DMF. The washed resin was suspended in NMP (20 mL), treated with Boc-Phe-OH (5 equiv), HATU (5 equiv), and DIPEA (15 equiv) for 6 h. After being washed with DMF, 0.1 N HCl/THF, MeOH, and DMF, the resin was cycled through the same set of conditions for deprotection, washing, coupling, and washing as above using Boc-Aib-OH (5 equiv), Boc-MeLeu-OH (5 equiv), Boc-Pro-OH (5 equiv), and Boc-Leu-OH (5 equiv) successively in the peptide elongation. After being washed with DMF, 0.1 N HCl/THF, MeOH, and DMF, the diprotected linear peptide bound to the resin was shaken with LiOH (5 equiv) in THF/$H_2O$ (7:1, 20 mL) at room temperature for 12 h followed by washing with DMF, 0.1 N HCl/THF, MeOH, and DMF. The resin was treated with 50% TFA in $CH_2Cl_2$ (20 mL) for 30 min and then washed with $CH_2Cl_2$, 0.1 N HCl/THF, MeOH, and DMF. Cyclization was carried out by treatment of the resin in NMP (20 mL) with PyBOP (5 equiv) and DIPEA (15 eq) for 24 h followed by washing with DMF, 0.1 N HCl/THF, MeOH, and $CH_2Cl_2$. The resin was then treated with refluxing TFA for 3 h to release the cyclic peptide. The cleavage solution was filtered, and the resin was rinsed with $CH_2Cl_2$ (20 mL). Concentration of the combined filtrates gave the crude product. Flash chromatography of the crude product gave 32 mg of scytalidamide A (**1**) as a white solid in a 46% yield based on the loading level of **3**: mp 148−150 °C; $[\alpha]^{25}_{D}$ −160.2 ($c$ = 1.1, MeOH). The $^{1}H$ NMR, $^{13}C$ NMR and high-resolution mass spectra were identical with the those from **2**.

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**Supporting Information Available:** ORTEP drawing of the X-ray crystal structure of synthetic scytalidamide A. This material is available free of charge via the Internet at http://pubs.acs.org.

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