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Total Synthesis of Amamistatin A, an Antiproliferative Linear Peptide from an Actinomycete

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Abstract—Amamistatin A, a linear lipopeptide and a growth inhibitor of human tumor cell lines from an actinomycete, was efficiently synthesized by a convergent approach. The asymmetric synthesis of β-hydroxy acid fragment was achieved by using chiral oxazaborolidinone mediated aldol reaction. The oxazole ring was constructed from *N*-acylthreonine via side-chain oxidation and cyclodehydration. The synthesis of the linear peptide was carried out in a stepwise manner from the cyclic hydroxamic acid fragment, and the final deprotection provided amamistatin A.

Amamistatin A (**1a**) was isolated, together with Amamistatin B (**1b**), by Uemura and co-workers from an actinomycete collected on Amami Island in Kagoshima prefecture, Japan, and its absolute stereostructure was determined by spectroscopic and chemical analysis as shown in Fig. 1.[1] The structures of Amamistatins are closely related to those of formobactin,[2] nocobactin,[3] and mycobactins,[4] bacterial siderophores. These compounds are linear lipopeptides and consist of hydroxamic acids, oxazoles or oxazolines, and β-hydroxy acids. Amamistatin A does not show a cell-killing effect but shows an antiproliferative effect against several kinds of human tumor cell lines. The IC_{50} values of Amamistatin A are 0.48, 0.56, and 0.24 μM against MCF-7 breast, A-549 lung, and MKN 45 stomach cancer cell lines, respectively. Amamistatin A is a structurally and biologically attractive natural product. As a part of our program toward the synthesis and study of biologically active peptides,[5] we have recently investigated the total synthesis of Amamistatin A. In this paper, we wish to describe the details of our synthetic efforts toward Amamistatin A.

Our retrosynthetic analysis of Amamistatin A is shown in Fig. 2. Disconnection of the ester bond and two amide bonds gives four fragments, cyclic hydroxamic acid **2**, β-hydroxy acid **3**, acyclic hydroxamic acid **6**, and oxazole fragment **7**. Cyclic hydroxamic acid **2** has been already synthesized from L-lysine by Miller and co-workers.[6] The β-hydroxy

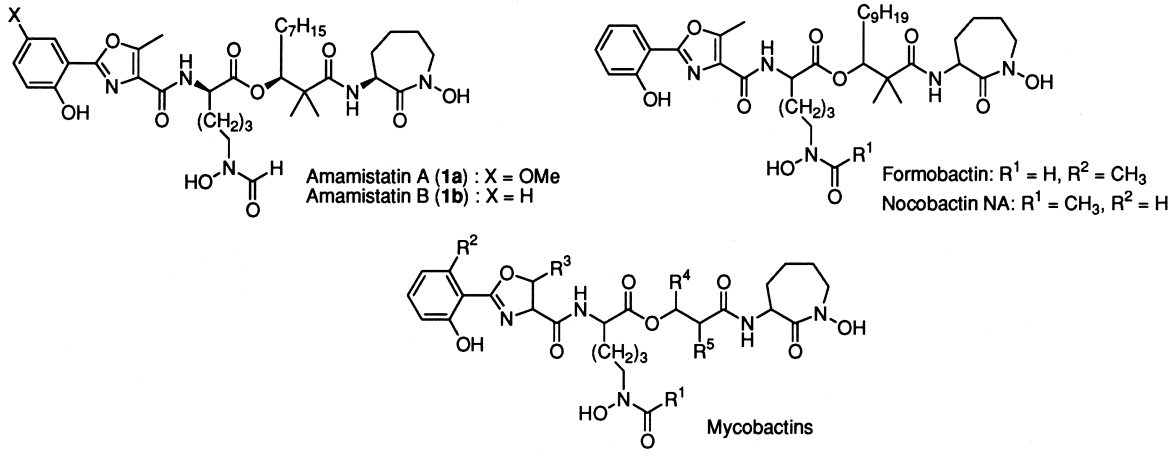

Figure 1. Amamistatin A and its related compounds.

Keywords: Amamistatin; linear peptide; total synthesis; oxazole; aldol reaction.

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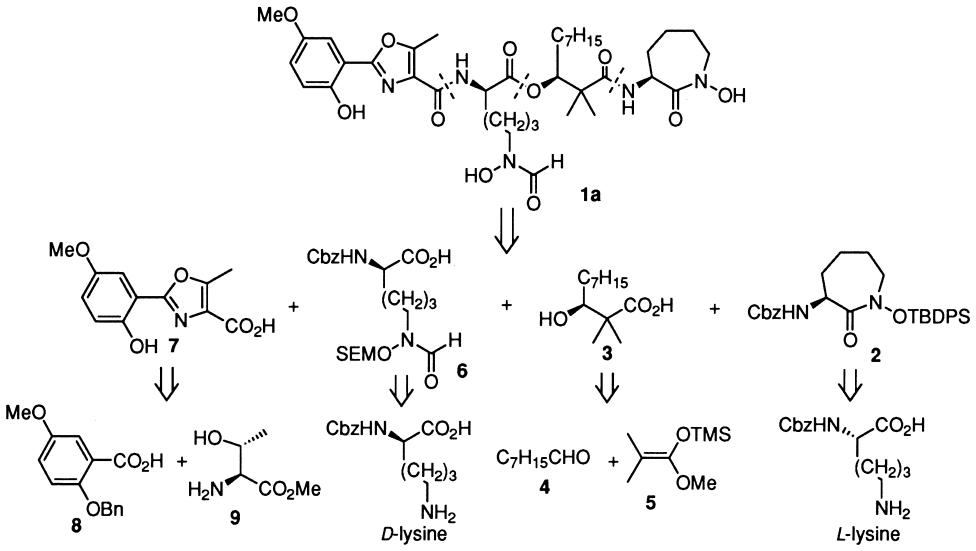
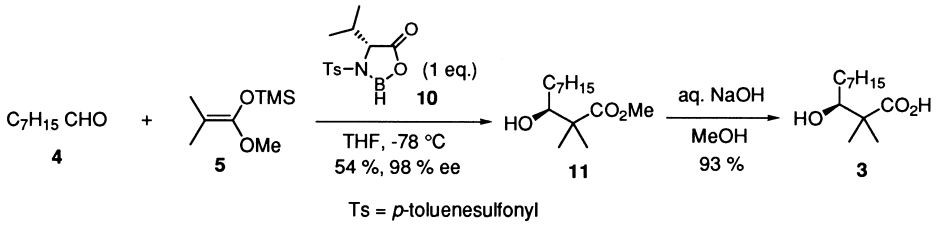


Figure 2. Retrosynthetic analysis.



Scheme 1.

acid **3** can be prepared by asymmetric aldol reaction of octanal (**4**) with silyl ketene acetal (**5**). The acyclic hydroxamic acid **6** can be also synthesized from D-lysine using Miller's methodology.[6] The oxazole fragment **7** can be synthesized from the salicylic acid derivative **8** and threonine methyl ester (**9**).

Results and Discussion

The stereoselective synthesis of the β-hydroxy acid fragment was achieved by the enantioselective aldol reaction developed by Kiyooka (Scheme 1).[7] The aldol reaction of octanal (**4**) with commercially available methyl trimethylsilyl dimethylketene acetal (**5**) by the use of a stoichiometric amount of the chiral oxazaborolidinone **10** derived from D-valine in dichloromethane proceeded to give the (*S*)-β-hydroxy ester **11** with 91% ee in 62% yield. We also found that the use of tetrahydrofuran (THF) as a solvent allowed this aldol reaction to proceed without loss of both enantioselectivity and chemical yield (98% ee, 54% yield), and the use of toxic dichloromethane could be avoided.

The enantiomeric purity was determined by ^{1}H NMR analysis in the presence of chiral shift reagent Eu(hfc)$_3$. The absolute configuration of **11** was ascertained by transformation into the corresponding (*S*)- and (*R*)-MTPA esters **12**, and comparison of ^{1}H NMR spectra as shown in Fig. 3.[8] Due to the diamagnetic effect of the benzene ring, $\Delta\delta$ values ($\delta_S-\delta_R$ ppm) on the right side of the MTPA plane must have positive values ($\Delta\delta>0$) and Δ values on the left side of the plane must have negative values ($\Delta\delta<0$). These results established that the absolute stereochemistry of **11** was *S*. Saponification of the β-hydroxy ester **11** provided the β-hydroxy acid **3** in 93% yield, which was one partner for the upcoming fragment condensation.

The synthesis of the acyclic hydroxamic acid fragment commenced with the nitrone **13**, which was derived from D-lysine by Miller's methodology (Scheme 2).[6] After treatment of the nitrone **13** with hydroxylamine hydrochloride, the product hydroxylamine was reacted with an excess of formic acid by the use of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) to give the *N*- and *O*-formate moiety. Subsequent removal of the *O*-formate group afforded the hydroxamate **14** in 71% yield. Reaction of **14** with [2-(trimethylsilyl)ethoxy]methyl chloride (SEMCl) in the presence of *N*,*N*-diisopropylethylamine and 4-(dimethylamino)pyridine (DMAP) in dichloromethane provided the SEM protected ester **15** in 92% yield.

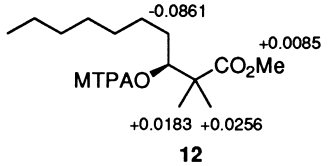
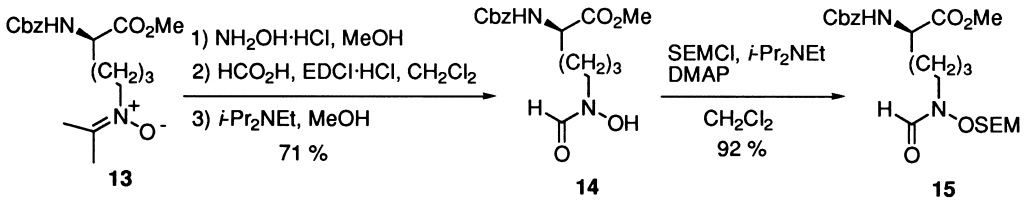


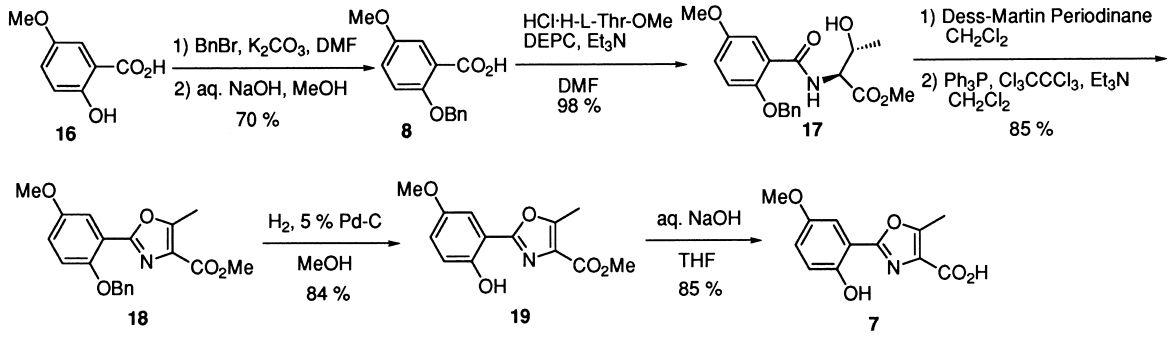
Figure 3. Determination of the absolute configuration; $\Delta\delta$ ($\delta_S-\delta_R$) values (ppm) obtained from ^{1}H NMR spectral data in $CDCl_3$.

The oxazole fragment was synthesized by the use of Wipf's developed variant of the Robinson–Gabriel oxazole synthesis (Scheme 3).[9] Commercially available 5-methoxysalicylic acid (**16**) was reacted with an excess of benzyl bromide in the presence of potassium carbonate, followed by hydrolysis of the benzyl ester to afford the benzoic acid derivative **8**[10] in 70% yield. Coupling of the acid **8** with L-threonine methyl ester was carried out using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[11] to give the amide **17** in 98% yield. Oxidative cyclocondensation of the threonine residue by side-chain oxidation with Dess–Martin periodinane[12] followed by exposure to triphenylphosphine (Ph_3P) and hexachloroethane (Cl_3CCCl_3) provided the oxazole **18** in 85% yield. Hydrogenolytic removal of the benzyl ether from **18** gave the phenol **19** in 84% yield. Subsequent saponification of **19** with NaOH in aqueous THF afforded the oxazole fragment **7** in 85% yield.

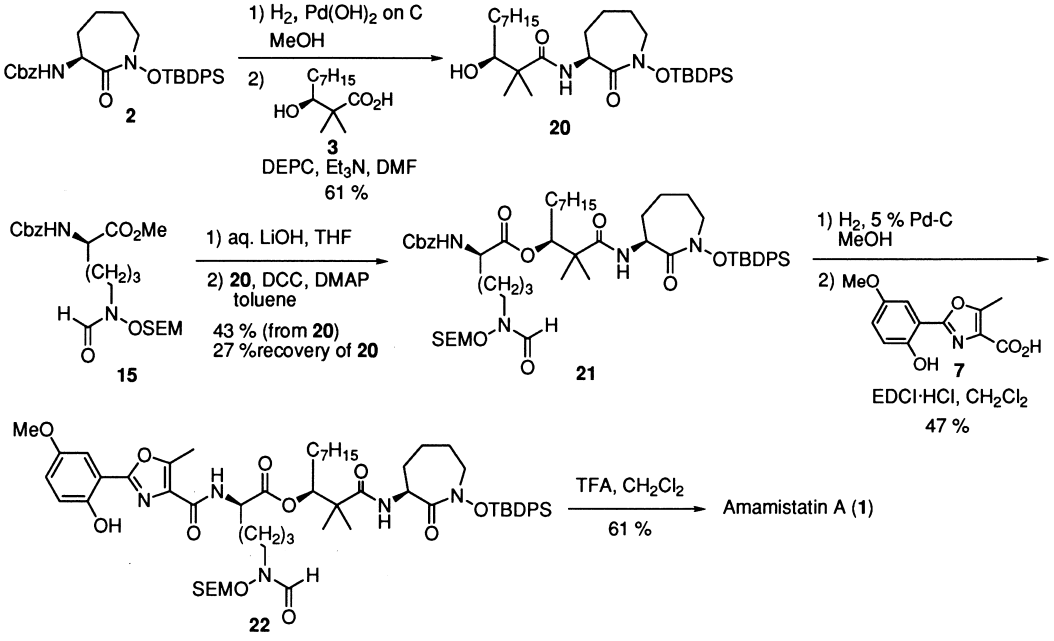
The construction of whole carbon skeleton for Amamistatin A was carried out by stepwise elongation from the cyclic hydroxamate (Scheme 4). After removal of the Cbz group from **2**[6] hydrogenolytically, the corresponding amine was condensed with the β-hydroxy acid **3** using the DEPC methodology to give the dipeptide **20** in 61% yield. After saponification of **15**, coupling of the resulting acid with the



Scheme 2.



Scheme 3.



Scheme 4.

sterically hindered secondary alcohol of the dipeptide **20** required considerable optimization of yields and was accomplished in the presence of 1.5 equiv. of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 1.5 equiv. of DMAP in toluene. The desired coupling product **21** was purified in 43% yield by chromatography on silica gel, and unreacted **20** was recovered in 27% yield. Yamaguchi conditions,[13] Mitsunobu conditions,[14] and the use of *O*,*O*-di(2-pyridyl)-thiocarbonate[15] as a coupling reagent did not lead to the effective condensation. Subsequent hydrogenolytic removal of the Cbz group from the ester **21** gave the corresponding amine, which was then coupled with the oxazole fragment **7** using EDCI·HCl to give the protected Amamistatin A **22** in 47% yield. Final deprotection of the SEM and TBDPS (*tert*-butyldiphenylsilyl) groups using trifluoroacetic acid (TFA) in dichloromethane provided Amamistatin A (**1**) in 61% yield. Our synthetic Amamistatin A was identified with the natural product by ^{1}H NMR, ^{13}C NMR, high-resolution FAB mass spectra, and TLC.

In summary, we have developed a straightforward convergent strategy for the preparation of the structurally and biologically attractive liner lipopeptide Amamistatin A. Our synthesis of Amamistatin A has not only proved the proposed structure, but also promised availability of this compound in quantities. We are currently evaluating the spectra of biological activities and iron-chelating properties of Amamistatin A.

Experimental

General information

Melting points were measured with YANACO melting point apparatus (hot plate) or Yamato melting point apparatus Model MP-21 and are uncorrected. Infrared spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a DIP-1000 digital polarimeter with a sodium lamp (λ=589 nm, D line) and are reported as follows: $[\alpha]_D^T$(c g/100 ml, solvent).

^{1}H NMR spectra were recorded on a JEOL EX-270 (270 MHz), ALPHA 500 (500 MHz), or LAMBDA (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. Amamistatin A numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz), ALPHA 500 (125.7 MHz), or LAMBDA 500 (125.4 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm).

Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Preparative thin layer chromatography was performed on Merck Art. 5744, Kiselgel 60F_{254}/0.5 mm thickness plates. Elementary analysis (Anal) and high resolution mass spectra (HRMS) were done at the Analytical Facility at Nagoya City University.

Solvents for extraction and chromatography were reagent grade. Liquid chromatography was performed with forced flow (flash chromatography of the indicated solvent mixture on silica gel BW-820MH or BW-200 (Fuji Davison Co.)). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Toluene and *N*,*N*-dimethylformamide (DMF) were dried over 4-Å molecular sieves. Triethylamine and *N*,*N*-diisopropylethylamine were dried over potassium hydroxide. All other commercially obtained reagents were used as received.

Methyl (3*S*)-3-hydroxy-2,2-dimethyldecanoate (11). To a solution of *N*-tosyl-D-Val-OH (694.8 mg, 2.56 mmol) in THF (25.6 ml) at room temperature under Ar, BH_3–THF (1 M in THF, 2.56 ml, 2.56 mmol) was added. The solution was stirred at room temperature for 0.5 h. To the resulting solution was successively added octanal (**4**) (0.4 ml, 2.56 mmol) and 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene (**5**) (0.572 ml, 2.82 mmol) at −78°C. After being stirred at −78°C for 1 h, the reaction mixture was quenched by the addition of pH 7 buffer solution. The mixture was extracted with ether (×1), and the organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel BW-820MH, hexane–EtOAc=10:1) to afford the desired product **11** as a colorless oil (320 mg, 54%, 98% ee). The enantiomeric excess of **11** (11.6 mg) was determined by ^{1}H NMR analysis in the presence of chiral shift reagent Eu(hfc)$_3$ (6.0 mg). **11**: $[\alpha]_D^{25}$=−21.6 (c 1.0 $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3496, 2928, 1732, 1271; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, J=6.8 Hz, CH_3CH$_2$), 1.16 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.28–1.62 (12H, m, CH$_3$(CH_2)$_6$CH), 2.35 (1H, d, J=16.9 Hz, OH), 3.59 (1H, m, CH), 3.70 (3H, s, CO$_2$CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.3, 20.7, 22.4, 22.9, 27.0, 29.5, 29.8, 32.0, 32.1, 47.5, 52.1, 76.9, 178.5. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.55; H, 11.50.

(3*S*)-3-Hydroxy-2,2-dimethyldecanoic acid (3). To a solution of the ester **11** (53 mg, 0.23 mmol) in methanol (2.3 ml) at 0°C, 4N aqueous NaOH (0.173 ml, 0.69 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 1 h, and then an additional 4N aqueous NaOH (0.345 ml, 1.38 mmol) was added. After the mixture was stirred at room temperature for 1.5 h, an additional 4N aqueous NaOH (0.173 ml, 0.69 mmol) was added. After being stirred at room temperature for 1 h, the mixture was quenched by the addition of 1N HCl and the mixture was extracted with ether. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel BW-820MH hexane–EtOAc=5:1) to afford the desired product **3** as a pale yellow oil (46 mg, 93%): $[\alpha]_D^{26}$=−23.0 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3500–2500, 3450, 1700, 1279; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (1H, t, J=6.93 Hz, CH_3CH$_2$), 1.19 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.28–1.56 (14H, m, CH$_3$(CH_2)$_6$), 3.61 (1H, m, CHOH), 6.75 (1H, br,

CO_2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 20.1, 22.4, 22.6, 26.6, 29.2, 29.5, 31.5, 31.8, 47.0, 76.5, 183.2. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.65; H, 11.41.

(*R*)-MTPA ester ((*R*)-12). (*R*)-MTPA (216 mg, 0.92 mmol) and oxalyl chloride (2 ml) were refluxed together at 80°C for 6 h. After the excess oxalyl chloride was removed by vacuum evaporation, the residue was distilled to give the (*R*)-MTPA anhydride, bp 130–155°C (1 mmHg). To a solution of (*R*)-MTPA anhydride (55 mg, 0.122 mmol) in CH_2Cl_2 (0.2 ml) at 0°C was added the aldol **11** (7 mg, 0.030 mmol), DMAP (1.9 mg, 0.016 mmol) and triethylamine (0.017 ml, 0.122 mmol). The mixture was stirred at room temperature for 1 h and purified by flash chromatography (silica gel BW-200 hexane–EtOAc=20:1) to afford the desired product (*R*)-**12** as a colorless oil (17 mg, quant.); $[\alpha]_D^{25}=+7.77$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 2857, 1744, 1497, 1468, 1393, 1256, 1188, 1169, 1123, 1082, 1019, 766; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=6.8 Hz, C*H*$_3$CH$_2$), 1.14 (3H, s, (C*H*$_3$)$_2$C), 1.15 (3H, s, (C*H*$_3$)$_2$C), 1.57 (12H, m, CH$_3$(C*H*$_2$)$_6$), 3.54 (3H, d, *J*=1.3 Hz, OC*H*$_3$), 3.63 (3H, s, CO$_2$C*H*$_3$), 5.46 (1H, dd, *J*=9.4 Hz, C*H*-OMTPA), 7.38–7.59 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 175.8, 165.9, 132.0, 129.5, 128.3, 127.5, 121.3, 80.3, 55.3, 52.0, 46.7, 31.7, 30.7, 29.3, 29.0, 26.2, 22.6, 21.5, 20.3, 14.0. Anal. Calcd for $C_{23}H_{33}F_3O_5$: C, 61.87; H, 7.45. Found: C, 61.97; H, 7.56.

(*S*)-MTPA ester ((*S*)-12). (*S*)-MTPA (201 mg, 0.86 mmol) and oxalyl chloride (2 ml) were refluxed together at 80°C for 2 days. After the excess oxalyl chloride was removed by vacuum evaporation, the residue was distilled to give the (*S*)-MTPA chloride. To a solution of (*S*)-MTPA chloride (0.030 ml, 0.160 mmol) in CH_2Cl_2 (2.5 ml) at 0°C was added aldol **11** (9.5 mg, 0.041 mmol), DMAP (2.0 mg, 0.016 mmol) and triethylamine (0.023 ml, 0.165 mmol). The mixture was stirred at room temperature for 2 days and purified by flash chromatography (silica gel BW-200 hexane–EtOAc=20:1) to afford the desired product (*S*)-**12** as a colorless oil (15 mg, 81%); $[\alpha]_D^{25}=-32.1$ (*c* 0.8, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 2857, 1744, 1499, 1468, 1393, 1258, 1186, 1169, 1123, 1082, 1017, 766; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=6.8 Hz, C*H*$_3$CH$_2$), 1.16 (3H, s, (C*H*$_3$)$_2$C), 1.18 (3H, s, (C*H*$_3$)$_2$C), 1.48 (12H, m, CH$_3$(C*H*$_2$)$_6$), 3.54 (3H, d, *J*=1.3 Hz, OC*H*$_3$), 3.64 (3H, s, CO$_2$C*H*$_3$), 5.44 (1H, dd, *J*=9.4 Hz, C*H*-OMTPA), 7.37–7.59 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 175.9, 166.0, 131.9, 129.6, 128.3, 127.6, 121.2, 80.3, 55.3, 52.0, 46.6, 31.7, 30.3, 29.2, 29.0, 25.9, 22.6, 21.3, 20.9, 14.0. Anal. Calcd for $C_{23}H_{33}F_3O_5$: C, 61.87; H, 7.45. Found: C, 62.09; H, 7.68.

N^{α}-Cbz-N^{ϵ}-Hydroxy-N^{ϵ}-formyl-D-lysine methyl ester (14). To a solution of the nitrone **13**[6] (217 mg, 0.619 mmol) in MeOH (3 ml) at 40°C was added hydroxylamine hydrochloride (60 mg, 0.930 mmol). After the solution was stirred at 40°C for 12 min, the solvent was removed. The residue was dissolved in saturated aqueous $NaHCO_3$ (20 ml) and then extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the corresponding hydroxylamine.

To a solution of HCO_2H (0.095 ml, 2.50 mmol) in CH_2Cl_2 (2 ml) was added EDCI·HCl (475 mg, 2.48 mmol) at 0°C. After the solution was stirred at 0°C for 15 min, to the resulting solution was added a solution of the hydroxylamine in CH_2Cl_2 (4 ml). After the mixture was stirred at 0°C for 50 min and then at room temperature for 1 h, an additional HCO_2H (0.095 ml, 2.50 mmol) and EDCI·HCl (475 mg, 2.48 mmol) were added to the reaction mixture at 0°C. After stirring at 0°C for 40 min, the bulk of solvent was removed. The residue was diluted with EtOAc, then washed with H_2O (×2) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated.

The residue was treated with *i*-Pr$_2$NEt (0.24 ml) in MeOH (4 ml) at room temperature for 62 h. The resulting mixture was concentrated and purified by flash chromatography (BW-820MH, hexane–EtOAc=1:2–0:1) to afford the desired product **14** as a colorless oil (149 mg, 71% in 3 steps): $[\alpha]_D^{26}=-8.2$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3325, 1738, 1717, 1669, 1532, 1456, 1439, 1383, 1352, 1217; ^1H NMR (270 MHz, $CDCl_3$) δ 1.30–1.38 (2H, m, C*H*$_2$), 1.63–1.88 (4H, m, C*H*$_2$×2), 3.37 (2H, t, *J*=6.3 Hz, NC*H*$_2$), 3.75 (3H, s, C*H*$_3$ ester), 4.31–4.41 (1H, m, C*H*), 5.10 (2H, s, C*H*$_2$Ph), 5.71 (1H, d, *J*=7.9 Hz, N*H*), 7.35 (5H, s, Ar*H*), 7.76 (1H, s, NC*H*O), 9.11 (1H, br, NO*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.4, 25.9, 31.6, 49.5, 52.3, 53.5, 66.9, 127.8, 128.1, 128.4, 136.1, 156.0, 157.0, 172.7. HRMS (EI) *m/z* Calcd for $C_{16}H_{22}N_2O_6$: 338.1477. Found: 338.1489.

N^{α}-Cbz-N^{ϵ}-Formyl-N^{ϵ}-[[2-(trimethylsilyl)ethoxy]-methoxy]-D-lysine methyl ester (15). To a solution of the formate **14** (119 mg, 0.352 mmol) in CH_2Cl_2 (2 ml) were added *i*-Pr$_2$NEt (0.31 ml, 1.78 mmol), DMAP (2 mg, 0.016 mmol) and SEMCl (0.16 ml, 0.904 mmol) at 0°C. After being stirred at 0°C for 30 min and then at room temperature for 17 h, the mixture was diluted with ether. The mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel BW-820MH, hexane–EtOAc=5:1–2:1–1:1) to afford the desired product **15** as a colorless oil (151 mg, 92%): $[\alpha]_D^{25}=-7.3$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3333, 1725, 1678, 1530, 1456, 1437, 1354, 1250; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, (C*H*$_3$)$_3$Si), 0.96 (2H, dd, *J*=8.3, 6.9 Hz, TMSC*H*$_2$CH$_2$), 1.34–1.36 (2H, m, C*H*$_2$), 1.67–1.85 (4H, m, C*H*$_2$×2), 3.58 (2H, m, NC*H*$_2$), 3.73 (5H, s and br C*H*$_3$ ester and TMSCH$_2$C*H*$_2$), 4.37 (1H, m, C*H*), 3.73 (2H, s, OC*H*$_2$O), 5.10 (2H, s, C*H*$_2$Ph), 5.33 (1H, d, *J*=7.9 Hz, N*H*), 7.30–7.36 (5H, m, Ar*H*), 8.30 (1H, s, NC*H*O); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −0.38, 19.1, 23.3, 27.3, 33.0, 45.8, 53.4, 54.8, 68.0, 68.2, 99.3, 129.1, 129.2, 129.6, 137.4, 157.0, 164.6, 173.9. Anal. Calcd for $C_{22}H_{36}N_2O_7Si$: C, 56.39; H, 7.74; N, 5.98. Found: C, 56.14; H, 7.77; N, 5.83.

2-Benzyloxy-5-methoxybenzoic acid (8). 5-Methoxysalicylic acid (**16**) (2 g, 11.89 mmol) was dissolved in DMF (40 ml). K_2CO_3 (8.22 g, 59.45 mmol) and BnBr (4.24 ml, 35.67 mmol) were added at 0°C. The solution was stirred at 0°C for 30 min and then at room temperature for 21 h. After dilution with EtOAc, the mixture was washed

with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in MeOH (38 ml) and 40% aqueous NaOH (7 ml). The resulting mixture was stirred at room temperature for 1 h. After dilution with water, the mixture was washed with ether. The aqueous layer was acidified by the addition of 1N aqueous HCl and salted out. The mixture was extracted with ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the desired product **8** as yellow crystals (2.15 g, 70%): mp 85–87°C (hexane–EtOAc) (Ref. 8 mp 93–94.5°C); IR ν_{max}^{KBr} cm^{-1} 3034, 1728, 1620, 1589, 1502, 1406, 1290, 1197, 1151; ^1H NMR (270 MHz, $CDCl_3$) δ 3.82 (3H, s, OC*H*$_3$), 4.70 (1H, s, CO_2*H*), 5.25 (2H, s, PhC*H*$_2$), 7.08 (2H, dd, *J*=1.64, 2.97 Hz C_{33} and C34-*H*), 7.42 (5H, m, Ar*H*), 7.70 (1H, s, C_{36}-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.0, 72.7, 114.9, 116.2, 118.5, 121.6, 127.7, 128.9, 134.5, 151.4, 154.3, 165.3. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.68; H, 5.64.

***N*-(2-Benzyloxy-5-methoxy)benzoyl-L-threonine methyl ester (17).** To a solution of **8** (6.47 g, 25.1 mmol) and L-Thr-OMe·HCl (4.25 g, 25.1 mmol) in DMF (84 ml) was successively added dropwise DEPC (3.8 ml, 25.1 mmol) and triethylamine (10.4 ml, 75.3 mmol). After being stirred at 0°C and then at room temperature for 12 h, the reaction mixture was diluted with EtOAc and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel BW-820MH, hexane–EtOAc=1:1) to afford the desired product **17** as yellow crystals (9.18 g, 98%): mp 75–77°C (hexane–EtOAc); $[\alpha]_D^{24}$=+3.86 (*c* 1.17, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 3383, 3076, 2949, 2843, 1740, 1610, 1579, 1433, 1385, 1371, 1207, 1167; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (3H, d, *J*=6.3 Hz, Thr-C*H*$_3$), 3.71 (3H, s, CO_2*Me*), 3.84 (3H, s, C*H*$_3$O), 4.26 (1H, m, N-C*H*-CO_2Me), 4.76 (1H, d, *J*=5.6 Hz, C*H*OH), 5.18 (2H, m, PhC*H*$_2$), 7.02 (2H, s, C_{33} and C_{34}-*H*), 7.35–7.51 (5H, m, Ar*H*), 7.77 (1H, s, C_{36}-*H*), 8.65 (1H, d, *J*=8.6 Hz, N*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.7, 52.1, 55.6, 57.8, 67.7, 71.7, 114.3, 115.5, 119.5, 121.7, 128.2, 128.4, 128.6, 135.6, 151.1, 153.8, 165.3, 171.2. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.22; H, 6.23; N, 3.74.

Methyl 2-[(2-benzyloxy-5-methoxy)phenyl]-5-methyloxazole-4-carboxylate (18). To a solution of **17** (208 mg, 0.56 mmol) in CH_2Cl_2 (2 ml) was added Dess–Martin periodinane (354 mg, 0.84 mmol) in one portion. The mixture was stirred at room temperature for 1 h, and concentrated. The residue was purified by flash chromatography (silica gel BW-820MH, hexane–EtOAc=3:1) to afford the corresponding ketone (180 mg), which was used for the next step without further purification. To a solution of the ketone (180 mg, 0.49 mmol) in CH_2Cl_2 (1.6 ml) was added Ph_3P (191 mg, 0.73 mmol) and triethylamine (0.30 ml, 2.18 mmol) under Ar at −10°C. After addition of hexachloroethane (172 mg, 0.73 mmol), the mixture was stirred at −10°C for 30 min. The mixture was concentrated, and purified by flash chromatography (silica gel BW-820MH, hexane–EtOAc=3:1) to afford the desired product **18** as white crystals (146 mg, 0.41 mmol, 85%): mp 98–100°C (hexane–EtOAc); IR ν_{max}^{KBr} cm^{-1} 2361, 2341, 1713, 1616, 1541, 1491, 1468, 1448; ^1H NMR (270 MHz, $CDCl_3$) δ 2.68 (3H, s, C_{29}-C*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.95 (3H, s, CO_2*Me*), 5.14 (2H, s, PhC*H*$_2$), 6.99 (2H, m, C_{33} and C_{34}-*H*), 7.35 (6H, m, C_{34}-*H* and Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.9, 51.7, 55.7, 71.5, 114.2, 115.8, 116.9, 118.4, 126.8, 127.6, 128.0, 136.9, 150.9, 153.7, 156.1, 158.3, 162.8. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.94; H, 5.45; N, 3.89.

Methyl 2-[(2-hydroxy-5-methoxy)phenyl]-5-methyloxazole-4-carboxylate (19). To a solution of **18** (70 mg, 0.20 mmol) in MeOH (1 ml) was added Pd/C (5%, 40 mg). The mixture was stirred under H_2 (1 atm) at room temperature for 2.5 h. The mixture was filtered and concentrated to afford the desired product **19** as yellow crystals (44 mg, 0.17 mmol, 84%): mp 139–142°C (hexane–EtOAc); IR ν_{max}^{KBr} cm^{-1} 3856, 3676, 2361, 1719, 1620, 1560, 1500, 1443, 1352, 1285, 1100, 1051; ^1H NMR (270 MHz, $CDCl_3$) δ 2.73 (3H, s, C_{29}-C*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.93 (3H, s, CO_2*Me*), 7.00 (3H, m, C_{33} and C_{34} and C_{36}-*H*), 10.38 (1H, s, O*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.9, 51.9, 55.9, 109.0, 109.8, 118.3, 120.2, 127.0, 151.6, 152.4, 155.0, 159.2, 162.0. HRMS (EI) *m*/*z* Calcd for $C_{13}H_{13}NO_5$: 263.0794. Found: 263.0794.

2-[(2-Hydroxy-5-methoxy)phenyl]-5-methyloxazole-4-carboxylic acid (7). To a solution of the methyl ester **19** (51 mg, 0.184 mmol) in THF (1.8 ml) was added 4N aqueous NaOH (0.2 ml, 0.8 mmol) at 0°C. After the mixture was stirred at room temperature for 40 min, the additional 4N aqueous NaOH (0.2 ml, 0.8 mmol) and THF (1 ml) were added to the reaction mixture. After being stirred at room temperature for 30 min, the reaction mixture was quenched by the addition of 1N HCl. The mixture was extracted with EtOAc (×1). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was recrystallized from EtOAc–hexane to afford the desired product **7** as white crystals (39 mg, 85%): mp 190–191°C; IR ν_{max}^{KBr} cm^{-1} 3475, 3500–2000, 1701, 1613, 1561, 1493, 1331, 1287, 1233, 1202; ^1H NMR (270 MHz, DMSO-d_6) δ 2.67 (3H, s, C_{29}-C*H*$_3$), 3.76 (3H, s, C*H*$_3$O), 6.97–7.06 (2H, m, C_{33} and C_{34}-C*H*), 7.22 (1H, d, *J*=2.6 Hz, C_{36}-C*H*), 10.03 (1H, s, O*H*), 12.8–13.4 (1H, br, CO_2*H*); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 12.1, 55.9, 109.6, 110.4, 118.4, 120.4, 127.5, 150.8, 152.5, 155.5, 158.4, 162.6. HRMS (EI) *m*/*z* Calcd for $C_{12}H_{11}NO_5$: 249.0637. Found: 249.0612.

Lactam Derivative (20). To a solution of the lactam **2**[6] (47 mg, 0.091 mmol) in MeOH (0.9 ml) was added $Pd(OH)_2$ on carbon (20 mg). After being stirred at room temperature for 1.5 h under H_2 (1 atm), the reaction mixture was filtered and concentrated to afford the corresponding amine. To the mixture of amine and carboxylic acid **3** (20 mg, 0.092 mmol) in DMF (0.3 ml) were successively added DEPC (0.015 ml, 0.099 mmol) and *i*-Pr_2NEt (0.018 ml, 0.103 mmol) at 0°C. After being stirred at 0°C for 1 h and then at room temperature for 3.5 h, the reaction mixture was diluted with EtOAc and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water

and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (0.5 mm thickness, hexane–EtOAc=2:1) to afford the desired product **20** as a colorless oil (32 mg, 61% in 2 steps): $[\alpha]_D^{24}=+14.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3407, 1674, 1640, 1510, 1462, 1429, 1115; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.3 Hz, $CH_3(CH_2)_6$), 1.11 (3H, s, CH_3), 1.15 (9H, s, $SiC(CH_3)_3$), 1.19 (3H, s, CH_3), 1.21–1.28 (12H, m, $CH_3(CH_2)_6$), 1.55–1.59 (4H, m, C_4 and C_5-CH_2), 1.77–1.81 (2H, m, C_3-CH_2), 3.38–3.48 (3H, m, C_6-CH_2, C_9-CH), 4.13–4.19 (1H, m, C_2-CH), 7.09 (1H, d, *J*=5.9 Hz, NH), 7.33–7.48 (6H, m, ArH), 7.71–7.77 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 19.5, 20.7, 22.6, 23.6, 25.4, 26.7, 26.9, 27.3, 29.3, 29.6, 30.6, 31.7, 31.8, 45.7, 51.5, 54.2, 127.5, 127.6, 130.2, 131.6, 132.1, 136.1, 136.2, 170.1, 177.5. HRMS (EI) *m/z* Calcd for $C_{30}H_{43}N_2O_4Si$ (M^+-t-Bu): 523.2992. Found: 523.2993.

Ester (21). To a solution of the methyl ester **15** (44 mg, 0.939 mmol) in THF (0.44 ml) was added 0.5N aqueous LiOH (0.28 ml, 0.14 mmol) at 0°C. After being stirred at 0°C for 30 min and then at room temperature for 1 h, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated to afford the corresponding carboxylic acid, which was used for the next step without further purification.

To a solution of the carboxylic acid, lactam derivative **20** (45 mg, 0.077 mmol), and DMAP (19 mg, 0.156 mmol) in toluene (0.5 ml) was added DCC (31 mg, 0.150 mmol). After being stirred at room temperature for 39 h, the mixture was concentrated. The residue was purified by preparative thin layer chromatography (0.5 mm thickness, hexane–EtOAc=2:1) to afford the desired product **21** as a colorless oil (34 mg, 43%) followed by the recovered **20** (12 mg, 27%). **21**: $[\alpha]_D^{28}=+14.6$ (*c* 0.81, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3405, 3345, 1727, 1680, 1653, 1514, 1456, 1429, 1364, 1250; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $(CH_3)_3Si$), 0.85 (3H, t, *J*=6.9 Hz, C_{16}-CH_3), 0.96 (2H, t, *J*=8.6 Hz, $TMSCH_2CH_2$), 1.02 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.12 (9H, s, $SiC(CH_3)_3$), 1.21–1.25 (14H, m, C_4 and C_{22}-CH_2, $CH_3(CH_2)_5CH_2$), 1.37–1.40 (4H, m, C_5 and C_{23}-CH_2), 1.51–1.60 (2H, m, C_{10}-CH_2), 1.67–1.73 (2H, m, C_3-CH_2), 1.79–1.84 (2H, m, C_{21}-CH_2), 3.38–3.44 (4H, m, C_6 and C_{24}-CH_2), 3.56–3.73 (2H, m, $TMSCH_2CH_2$), 4.03–4.09 (1H, m, C_{20}-CH), 4.32–4.34 (1H, m, C_2-CH), 4.85 (2H, s, OCH_2O), 4.94–4.97 (1H, m, C_9-CH), 5.11 (2H, d, *J*=6.3 Hz, CH_2Ph), 6.31 (1H, d, *J*=9.2 Hz, CbzNH), 7.29–7.41 (12H, m, ArH, NH), 7.67 (2H, d, *J*=6.6 Hz, ArH), 7.73 (2H, d, *J*=6.6 Hz, ArH), 8.31 (1H, s, NCHO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.5, 14.0, 18.0, 19.6, 22.3, 22.6, 22.8, 23.7, 25.3, 25.6, 26.1, 27.2, 29.0, 29.2, 30.2, 30.6, 31.5, 31.7, 44.7, 45.8, 51.6, 54.1, 54.6, 66.5, 67.1, 79.4, 98.1, 127.4, 127.5, 127.7, 127.9, 128.4, 130.1, 130.2, 131.7, 131.9, 135.9, 136.0, 156.3, 163.5, 169.5, 171.5, 173.8. Anal. Calcd for $C_{55}H_{84}N_4O_{10}Si_2$: C, 64.93; H, 8.32; N, 5.51. Found: C, 64.89; H, 8.48; N, 5.30.

Protected Amamistatin A (22). To a solution of the ester **21** (31 mg, 0.031 mmol) in MeOH (0.4 ml) was added Pd/C (5%, 31 mg). After being stirred at room temperature for 2 h under H_2 (1 atm), the reaction mixture was filtered and concentrated to afford the corresponding amine. To a mixture of the amine and carboxylic acid **7** (7.6 mg, 0.030 mmol) in CH_2Cl_2 (0.3 ml) was added EDCI·HCl (7 mg, 0.037 mmol) at 0°C. After being stirred at room temperature for 2 h, the reaction mixture was purified by preparative thin layer chromatography (0.5 mm thickness, hexane–EtOAc=3:2) to afford the desired product **22** as a colorless oil (16 mg, 47% in 2 steps): $[\alpha]_D^{25}=+3.7$ (*c* 0.70, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368, 1744, 1663, 1501, 1456, 1429, 1364, 1248; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (9H, s, $(CH_3)_3Si$), 0.82 (3H, t, *J*=6.7 Hz, C_{16}-CH_3), 0.95 (2H, t, *J*=8.5 Hz, $TMSCH_2CH_2$), 1.10 (9H, s, $SiC(CH_3)_3$), 1.11 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.16–1.29 (12H, m, C_4 and C_{22}-CH_2, $CH_3CH_2(CH_2)_4$), 1.42–1.58 (4H, m, and C_5 and C_{15}-CH_2), 1.60–1.81 (6H, m, C_3 and C_{10} and C_{23}-CH_2), 1.97–1.98 (2H, m, C_{21}-CH_2), 2.76 (3H, s, C_{29}-CH_3), 3.48 (2H, m, $TMSCH_2CH_2$), 3.56 (1H, m, C_{24}-CH_2), 3.64 (1H, m, C_{24}-CH_2), 3.73 (2H, m, C_6-CH_2), 3.83 (3H, s, C_{37}-OCH_3), 4.17 (1H, dd, *J*=10.0, 6.1 Hz, C_{20}-CH), 4.75 (1H, br, C_2-CH), 4.85 (2H, s, OCH_2O), 5.07 (1H, dd, *J*=9.8, 3.1 Hz, C_9-CH), 6.97 (1H, s, C_{33}-CH), 6.98 (1H, s, C_{34}-CH), 7.28–7.35 (5H, m, ArH, C_{36}-CH), 7.38–7.43 (2H, m, ArH), 7.67 (2H, d, *J*=6.7 Hz, ArH), 7.74 (2H, dd, *J*=7.9, 1.2 Hz, ArH), 7.84 (2H, br, NH×2), 8.33 (1H, s, NCHO), 9.93 (1H, s, OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −1.5, 11.6, 14.0, 18.0, 19.5, 22.0, 22.5, 22.6, 22.8, 25.1, 25.9, 26.3, 26.8, 27.3, 29.0, 29.3, 30.0, 30.5, 31.0, 31.7, 44.7, 46.1, 51.9, 52.3, 54.3, 56.0, 67.1, 79.2, 98.1, 109.3, 118.3, 120.2, 127.5, 128.8, 130.1, 130.2, 131.7, 132.0, 136.0, 136.2, 151.3, 152.5, 152.6, 158.2, 161.2, 163.7, 169.9, 174.3. Anal. Calcd for $C_{59}H_{87}N_5O_{12}Si_2$: C, 63.58; H, 7.87; N, 6.28. Found: C, 63.62; H, 8.25; N, 5.96.

Amamistatin A (1a). The protected Amamistatin A **22** (17 mg, 0.015 mmol) was stirred in TFA/CH_2Cl_2 (0.3 ml, 1:1) at room temperature for 1 h. The mixture was concentrated and then purified by flash chromatography (silica gel BW-820MH, hexane–acetone=1:1) to afford the desired product (**1**) as a purple oil (7 mg, 61%): $[\alpha]_D^{26}=-6.8$ (*c* 0.19, MeOH); IR ν_{max}^{neat} cm^{-1} 3240, 1740, 1667, 1661, 1651, 1646, 1559, 1501, 1456, 1385, 1285, 1260, 1235, 1184; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.0 Hz, C_{16}-CH_3), 1.22 (6H, s, C_{17} and C_{18}-CH_3), 1.25 (4H, m, C_{12} and C_{14}-CH_2), 1.29 (3H, m, C_{11} and C_{15}-CH_2), 1.33 (3H, m, C_{11} and C_{13}-CH_2), 1.45 (2H, m, C_{10} and C_{22}-CH_2), 1.55–1.60 (4H, m, C_3, C_5, C_{10} and C_{22}-CH_2), 1.81 (3H, m, C_5 and C_{23}-CH_2), 1.91–1.97 (2H, m, C_3 and C_4-CH_2), 1.99–2.05 (2H, m, C_{21}-CH_2), 2.76 (3H, s, C_{29}-CH_3), 3.57 (2H, m, C_{24}-CH_2), 3.68–3.71 (1H, m, C_6-CH_2), 3.86 (3H, s, C_{37}-CH_3), 3.96 (1H, dd, *J*=15.1, 12.4 Hz, C_6-CH_2), 4.56 (1H, m, C_2-CH), 4.70 (1H, m, C_{20}-CH), 5.21 (1H, d, *J*=10.4 Hz, C_9-CH), 7.01 (1H, d, *J*=8.9 Hz, C_{33}-CH), 7.07 (1H, d, *J*=8.9 Hz, C_{34}-CH), 7.39 (1H, s, C_{36}-CH), 8.31 (1H, s, C_{25}-CHO); ^{13}C NMR (125.4 MHz, CD_3OD) δ 11.8, 14.4, 21.4, 22.8, 23.1, 24.0, 24.2, 27.1, 27.7, 28.7, 30.2, 30.3, 31.0, 31.5, 31.6, 31.7, 31.8, 32.9, 47.1, 47.5, 51.0, 52.9, 53.9, 54.0, 54.1, 56.4, 80.2, 80.3, 110.7, 111.5, 119.3, 121.2, 129.9, 152.1, 154.3, 154.4, 159.7, 163.5, 164.0, 170.6, 172.6, 172.8, 176.8. The ^1H NMR and ^{13}C NMR spectra were identical with the spectra of the natural Amamistatin A provided by Professor

Daisuke Uemura. HRMS (FAB) *m/z* Calcd for $C_{37}H_{56}N_5O_{11}$ $(M+H)^+$: 746.3981. Found: 746.4000.

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