A Total Synthesis of Nannochelin A. A Short Route to Optically Active N^{ω}-Hydroxy-α-amino Acid Derivatives

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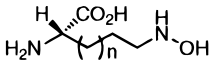
The total synthesis of nannochelin A, a lysine-basd cinnamoyl hydroxamate produced by *Nannocystis exedens*, is described. The key transformation involves construction of the N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester fragment by partial reduction of the lactam carbonyl of **6** derived from L-lysine, oximation of this aldehyde equivalent compound **8** with *O*-[2-(trimethylsilyl)ethyl]hydroxylamine, and reduction of the oxime **10**, followed by N-acylation prior to coupling with the external carbonyls of citric acid. This methodology will be applicable to synthesis of other hydroxamate-containing siderophores bearing hydrogenolyzable groups in the molecule.

Siderophores are low molecular weight iron-sequestering agents produced by most microorganisms.[1] The most common iron-binding functional groups incorporated into hydroxamate-containing siderophores are derived from derivatives of N^{δ}-hydroxy-L-ornithine (**1**) and N^{ϵ}-hydroxy-L-lysine (**2**). Although several syntheses of these modified amino acids have been reported,[2] the methods are either multistep or low yielding and sometimes do not yield derivatives having suitable protecting groups for further reactions.



1: n=1
2: n=2

We now report simple alternate approaches to the syntheses of the protected **1** and **2** from readily available and inexpensive starting materials. L-Pyroglutamic acid and L-lysine were chosen as the starting materials, since they are commercially available chiral compounds and contain the appropriate carbon framework. L-Pyroglutamic acid was converted to benzyl 1-Boc-L-pyroglutamate (**5**) by esterification and N-acylation using literature procedures.[3] L-Lysine was also readily converted to methyl ester of N^{α}-Boc-N^{δ}-Boc-amide of L-2-aminoadipic acid (**13**) and small amounts of 1-Boc-6-Boc-aminopiperidine-2-carboxylic acid methyl ester (**14**) by N-protection, esterification, and oxidation of the ω-amino function with ruthenium dioxide/sodium periodate using a literature procedure.[4] Cyclization of the adipamide in refluxing trifluoroacetic acid (TFA) and N-*tert*-butoxycarbonylation gave methyl 1-Boc-L-6-oxopipecolate (**6**).[5] These N-acylated esters (**5** and **6**) are the key intermediates for the synthesis. The key transformation involves partial reduction of the lactam carbonyl with DIBAL[6] or $LiBEt_3H$[7] to produce the aldehyde equivalent derivatives (**7** and **8**) which reacted readily with *O*-[2-(trimethylsilyl)-ethyl]hydroxylamine[8] to give the oximes (**9** and **10**). This transformation is novel and useful to introduce a nitrogen source into the molecules. Compound **14** also reacted with the hydroxylamine to give **10**. Reduction of the oximes with pyridine−borane[2l,9] or $NaBH_3CN$[10] and subsequent N-acylation produced **11** and **12** in high yield.

Nannochelin A[11] which contains two cinnamoyl moieties in the molecule, is an interesting target for the synthesis because previous strategies utilizing *O*-benzyl protected hydroxamates are not applicable. Mulqueen and co-workers overcame this problem by use of a $BF_3 \cdot Et_2O$−ethanethiol reagent for the debenzylation without affecting the cinnamoyl double bonds[12] and Bergeron and Phanstiel IV used *O*-benzoyl protection and O-deprotection with 10% NH_3/MeOH.[13]

We report an alternate approach to the synthesis of this siderophore utilizing two key transformations which involve construction of the N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester fragment by use of the above mentioned strategy and use of the 2-(trimethylsilyl)ethyl group, which is readily removed by boron trifluoride

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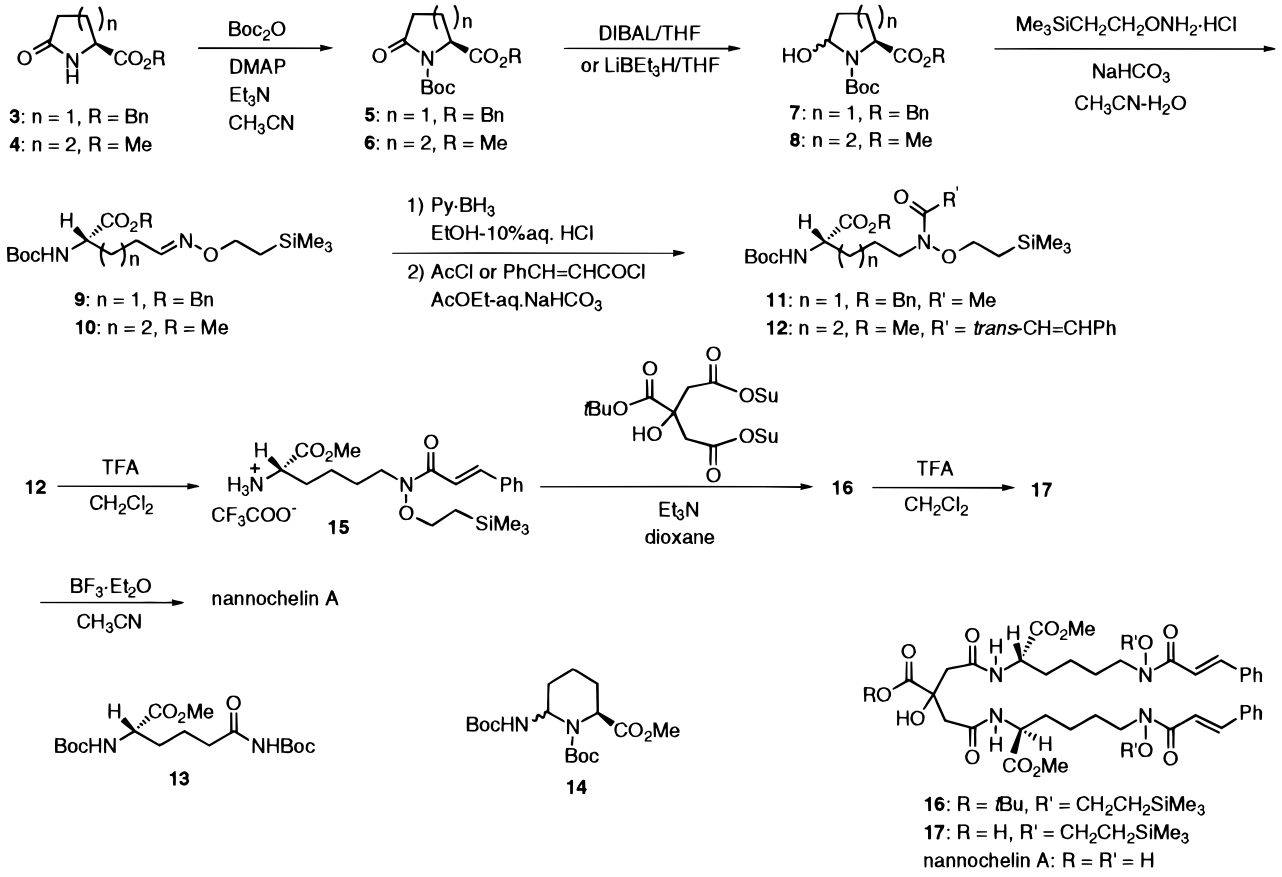
Scheme 1



etherate or fluoride ion, as a protection of the hydroxamic acid group.[2l,8] Thus, methyl 1-Boc-L-6-oxopipecolate (**6**) was prepared from L-lysine following the literature procedures described above. Partial reduction of **6** with $LiEt_3BH$ in THF at −78 °C for 30 min and subsequent treatment of the crude hemiaminal **8** with *O*-[2-(trimethylsilyl)ethyl]hydroxylamine in CH_3CN-H_2O (1:1) refluxing for 1.5 h gave the oxime **10** (73%). Pyridine−borane reduction of **10** in EtOH−10% HCl (1:1) at 0 °C for 15 min followed by N-acylation with *trans*-cinnamoyl chloride under Schotten−Baumann conditions gave **12** (76%). To determine the optical purity of **12**, the enantiomer of **12** was prepared from D-lysine using the same procedures, and the HPLC analyses of **12** and its enantiomer on a chiral column showed that the optical purity of **12** was fully retained.

Treatment of **12** with TFA−CH_2Cl_2 (1:1) at room temperature for 30 min gave N^{ϵ}-cinnamoyl-N^{ϵ}-[2-(trimethylsilyl)ethoxy]-L-lysine methyl ester TFA salt (**15**). Coupling of the crude **15** with 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate[14] in dioxane in the presence of triethylamine afforded the fully protected *O*-[2-(trimethylsilyl)-ethyl]nannochelin A *tert*-butyl ester **16** in 72% yield. An initial attempt to generate nannochelin A by deprotection of the *O*-[2-(trimethylsilyl)ethyl] group with $BF_3{\cdot}Et_2O$ in CH_3CN and subsequent treatment with TFA−CH_2Cl_2 (1:1) to remove the Boc group gave ambiguous results, probably because the Boc group was partially removed with $BF_3{\cdot}Et_2O$ and undesirable side reactions occurred. On the other hand, stepwise removal of Boc with TFA−CH_2Cl_2 (1:1) and *O*-[2-(trimethylsilyl)ethyl] groups with $BF_3{\cdot}Et_2O$ afforded the "free" nannochelin A in 70% yield, and the total yield is 11% from L-lysine.

^1H and ^{13}C NMR, UV, and MS spectra of the synthetic nannochelin A were in agreement with those reported for the natural product,[11] and the optical rotation was almost the same as the literature values (see Experimental Section).

This methodology will be applicable to syntheses of other hydroxamate-containing siderophores, especially to siderophores bearing hydrogenolyzable groups in the molecule.

Experimental Section

General. All melting points are uncorrected. The ^1H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were measured in $CDCl_3$ as solvent, unless otherwise noted. Chemical shifts for ^1H NMR spectra and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). Elemental analyses were performed in the Microanalytical Laboratory of this University.

Reagents and Materials. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. CH_3CN and CH_2Cl_2 were distilled from CaH_2. Compound **5**,[3] *O*-[2-(trimethylsilyl)ethyl]hydroxylamine hydrochloride[8] and pyridine−borane[15] were prepared according to the published procedures. Compound **13** and **14** were prepared by the procedure of Yoshifuji.[4] 2-*tert*-Butyl 1,3-di-*N*-succinimidyl citrate was prepared by the literature procedure[14] using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride instead of dicyclohexylcarbodiimide (48%): pale yellow crystals; mp 185−187 °C (CH_3CN) (lit.[13] 188−189 °C).

Methyl L-2-Oxopipecolate (4). A solution of L-**13** (5.00 g, 13.4 mmol), TFA (25 mL), and CH_2Cl_2 (25 mL) was refluxed

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for 45 min. The solvent was concentrated under reduced pressure, and the residue was chromatographed on a column of silica gel with AcOEt−EtOH (100:0−10:1) as the eluent to give L-**4** (1.87 g, 89%): colorless oil; $[\alpha]^{22}_D$ −11.0° (*c* 3.2, CH_2Cl_2); IR (film) 3340, 1745, 1660 cm^{-1}; ^1H NMR δ 1.72−1.98 (m, 3H), 2.17−2.29 (m, 1H), 2.39 (q, J = 7.2 Hz, 2H), 3.79 (s. 3H), 4.12 (t, J = 5.8 Hz, 1H), 6.41 (br s, 1H); ^{13}C NMR δ 19.3, 25.3, 31.0, 52.7, 54.6, 171.8, 172.0; HRMS *m*/*z* calcd for $C_7H_{11}NO_3$ 157.0739, found 157.0754.

Compound D-**4** (2.90 g, 82%) was prepared similarly using the methyl ester of N^{α}-Boc-N^{δ}-Boc-amide of D-2-aminoadipic acid (D-**13**) (8.38 g, 22.4 mmol) which was prepared from D-lysine.

D-**4**: $[\alpha]^{22}_D$ +11.1° (*c* 3.6, CH_2Cl_2).

Methyl 1-Boc-L-6-oxopipecolate (6). To a mixture of L-**4** (2.00 g, 12.7 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.31 g, 2.54 mmol) in CH_3CN (40 mL) was added di-*tert*-butyl dicarbonate (3.5 mL, 15.2 mmol) at room temperature, and the mixture was stirred for 7.5 h. After the solvent was concentrated under reduced pressure, the residue was diluted with AcOEt (50 mL). The solution was washed with 10% HCl (2 × 25 mL) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt−hexanes (1:2−1:1) as the eluent to give L-**6** (2.91 g, 89%): colorless oil; $[\alpha]^{22}_D$ +3.5° (*c* 3.1, CH_2Cl_2); mp 52−53 °C (cyclohexane); IR (film) 1780, 1750, 1735 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 1.66−1.83 (m, 2H), 1.89−2.22 (m, 2H), 2.41−2.63 (m, 2H), 3.77 (s, 3H), 4.71 (dd, J = 6.0, 3.8 Hz, 1H); ^{13}C NMR δ 18.3, 25.9, 27.9, 34.6, 52.5, 58.6, 83.5, 152.2, 170.1, 172.1; MS (CI, isobutane) *m*/*z* 258 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.85; H, 7.55; N, 5.29.

Compound D-**6** (3.22 g, 68%) was prepared similarly using D-**4** (2.90 g, 18.5 mmol).

D-**6**: mp 52−53 °C (cyclohexane); $[\alpha]^{22}_D$ −3.4° (*c* 3.5, CH_2Cl_2).

Benzyl Ester of N^{α}-Boc-O^{γ}-[2-(trimethylsilyl)ethyl]-oxime of L-Glutamic Acid Semialdehyde (9). A solution of DIBAL in toluene (1.5 M, 0.78 mL, 1.11 mmol) was added to a solution of L-**5** (1.01 g, 3.15 mmol) in THF (15 mL) at −78 °C under argon. After being stirred for 20 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) and warmed to room temperature. The mixture was extracted with AcOEt (2 × 20 mL), and the combined organic layers were washed with brine (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was dissolved in CH_3CN−H_2O (1:1, 14 mL). To the solution were added $Me_3SiCH_2CH_2ONH_2$·HCl (587 mg, 3.46 mmol) and $NaHCO_3$ (132 mg, 1.57 mmol), and then the reaction mixture was refluxed for 1 h. The solution was extracted with AcOEt (2 × 25 mL). The combined organic layers were washed with brine (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with benzene−AcOEt (15:1) as the eluent to give L-**9** (937 mg, 71%) as a mixture of *E* and *Z* isomers (2:3): colorless oil; $[\alpha]^{22}_D$ −12.5° (*c* 3.8, MeOH); IR (film) 3370, 1750, 1725, 1505, 1370, 1250, 1175 cm^{-1}; ^1H NMR δ 0.03 (s, 9H), 0.94 −1.06 (m, 2H), 1.44 (s, 9H), 1.74−2.45 (m, 4H), 4.03−4.21 (m, 2H), 4.31−4.46 (m, 1H), 5.05−5.17 (m, 3H), 6.61 (t, J = 5.2 Hz, 0.4H), 7.25−7.45 (m, 5.6H); ^{13}C NMR δ -1.4, 17.4, 21.8, 28.8, 28.3, 29.0, 29.5, 53.1, 67.1, 71.0, 71.4, 79.9, 128.2, 128.4, 128.6, 135.2, 148.5, 149.1, 155.3, 172.1; HRMS (FAB) calcd for $C_{22}H_{37}N_2O_5Si$ 437.2472, found 437.2443.

Methyl Ester of N^{α}-Boc-O^{δ}-[2-(trimethylsilyl)ethyl]-oxime of L-2-Aminoadipic Acid Semialdehyde (10) from 6. A solution of lithium triethylborohydride in THF (1 M, 6.3 mL, 6.31 mmol) was added to a solution of L-**6** (1.48 g, 5.73 mmol) in THF (30 mL) at −78 °C under argon. After being stirred for 20 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and warmed to 0 °C. H_2O_2 (30%) (1 mL) was added, and the mixture was stirred at 0 °C for 20 min. The organic solvent was removed under reduced pressure, and the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product containing hemiaminal (**8**) was dissolved in CH_3CN−H_2O (1:1, 30 mL). To the solution were added $Me_3SiCH_2CH_2ONH_2$·HCl (1.02 g, 6.02 mmol) and $NaHCO_3$ (241 mg, 2.87 mmol), and then the reaction mixture was refluxed for 1 h. The solution was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with benzene−AcOEt (8:1−5:1) as the eluent to give L-**10** (1.56 g, 73%) as a mixture of *E* and *Z* isomers (1:1): colorless oil; $[\alpha]^{22}_D$ +9.9° (*c* 4.9, CH_2Cl_2); IR (film) 3375, 1750, 1720, 1250, 1170 cm^{-1}; ^1H NMR δ 0.03 (s, 9H), 0.91−1.12 (m, 2H), 1.32−1.90 (m, 4H), 1.45 (s, 9H), 2.18 (dd, J = 14.0, 6.4 Hz, 1H), 2.32 (dd, J = 14.0, 6.4 Hz, 1H), 3.74 (s, 3H), 4.01−4.15 (m, 2H), 4.28 (dd, J = 14.0, 6.4 Hz, 1H), 5.02 (br s, 1H), 6.59 (t, J = 7.4 Hz, 0.5 H), 7.34 (t, J = 7.4 Hz, 0.5 H); ^{13}C NMR δ −1.4, 17.5, 17.6, 22.2, 22.6, 25.4, 28.3, 29.2, 32.2, 32.5, 52.3, 53.2, 71.0, 71.4, 79.9, 149.3, 150.1, 155.4, 183.2; HRMS (FAB, added KI) calcd for $C_{17}H_{34}N_2O_5SiK$ 413.1874, found 413.1873.

Compound D-**10** (901 mg, 69%) was prepared similarly as a mixture of *E* and *Z* isomers (1:1) using D-**6** (897 mg, 3.49 mmol).

D-**10**: colorless oil; $[\alpha]^{22}_D$ −10.0° (*c* 5.0, CH_2Cl_2).

Compound 10 from 14. A mixture of L-**14** (1.41 g, 3.93 mmol), $Me_3SiCH_2CH_2ONH_2$·HCl (733 mg, 4.31 mmol), and $NaHCO_3$ (165 mg, 1.97 mmol) in CH_3CN−H_2O (1:1, 24 mL) was refluxed for 1.5 h. The reaction mixture was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with benzene−AcOEt (8:1−5:1) as the eluent to give L-**10** (1.57 g, 82%) as a mixture of *E* and *Z* isomers (1:1): colorless oil; $[\alpha]^{22}_D$ +9.9° (*c* 5.0, CH_2Cl_2).

Compound D-**10** (544 mg, 77%) was prepared similarly as a mixture of *E* and *Z* isomers (1:1) using D-**14** (676 mg, 1.89 mmol).

D-**10**: colorless oil; $[\alpha]^{22}_D$ −9.9° (*c* 5.0, CH_2Cl_2).

N^{δ}-Acetyl-N^{δ}-[2-(trimethylsilyl)ethoxy]-L-ornithine Benzyl Ester (11). This compound (388 mg, 73%) was prepared from the oxime (L-**9**) (489 mg, 1.12 mmol), analogous to **12** described below: colorless oil; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 9/1, flow rate = 0.4 mL/min) t_R = 39.6 min; $[\alpha]^{22}_D$ −16.6° (*c* 5.9, CH_2Cl_2); IR (film) 3325, 1750, 1720, 1660, 1250, 1170 cm^{-1}; ^1H NMR δ 0.01 (s, 9H), 0.95 (t, J = 9.0 Hz, 2H), 1.43 (s, 9H), 1.59−1.92 (m, 4H), 2.09 (s, 3H), 3.60 (t, J = 7.0 Hz, 2H), 3.82 (t, J = 9.0 Hz, 2H), 4.23−4.41 (m, 1H), 5.08 (br s, 1H, NH), 5.16 (d, J = 2.0 Hz, 2H), 7.31−7.39 (m, 5H); ^{13}C NMR δ −1.4, 16.8, 20.3, 23.1, 28.3, 29.8, 44.3, 53.4, 67.0, 71.7, 79.8, 128.2, 128.3, 128.6, 155.4, 171.8, 172.2; HRMS (FAB) calcd for $C_{24}H_{41}N_2O_6Si$ 481.2734, found 481.2695.

Compound DL-**11** (79 mg, 72%) was prepared similarly using DL-**9** (100 mg, 0.229 mmol).

DL-**11**: colorless oil; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 9/1, flow rate = 0.4 mL/min) t_R = 32.4, 39.6 min.

N^{ϵ}-Cinnamoyl-N^{ϵ}-[2-(trimethylsilyl)ethoxy]-L-lysine Methyl Ester (12). Pyridine−borane (950 mg, 10.2 mmol) was added to a solution of L-**10** (1.28 g, 3.41 mmol) in EtOH−10% aqueous HCl (6:1, 22 mL) with ice cooling. After being stirred for 15 min, the reaction mixture was concentrated under reduced pressure, and the residue was diluted with AcOEt (50 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated. A solution of *trans*-cinnamoyl chloride (795 mg, 4.77 mmol) in AcOEt (6 mL) was added dropwise to the mixture of the crude reduction product of L-**10**, AcOEt (24 mL), and 5% aqueous $NaHCO_3$ (11.5 mL) at 0 °C. After being stirred for 5 h, the mixture was extracted with AcOEt (2 × 25 mL), and the combined organic layers were washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with benzene−AcOEt (1:8) as the eluent to give L-**12** (1.32 g, 76%): colorless oil; HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 5/5, flow rate = 0.5 mL/min) t_R = 36 min; $[\alpha]^{21}_D$ +3.8° (*c* 3.7, CH_2Cl_2);

IR (film) 3325, 1750, 1710, 1650, 1620, 1365, 1250, 1170, 1060, 1040 cm^{-1}; ^1H NMR δ 0.07 (s, 9H), 1.05 (dd, J = 10.0, 8.0 Hz, 2H), 1.32−1.52 (m, 2H), 1.43 (s, 9H), 1.60−1.93 (m, 4H), 3.63−3.79 (m, 2H), 3.73 (s, 3H), 3.93 (dd, J = 10.0, 8.0 Hz, 2H), 4.22−4.34 (m, 1H), 5.09 (br s, 1H), 7.01 (d, J = 15.5 Hz, 1H), 7.32−7.44 (m, 3H), 7.50−7.59 (m, 2H), 7.33 (d, J = 15.5 Hz, 1H); ^{13}C NMR δ −1.4, 16.8, 22.5, 26.7, 28.3, 32.1, 45.0, 52.2, 53.4, 72.7, 79.7, 116.3, 128.0, 128.8, 129.8, 135.3, 143.3, 155.5, 166.9, 173.3; HRMS (FAB, added KI) calcd for $C_{26}H_{42}N_2O_6SiK$ 545.2449, found 545.2473.

Compound D-**12** (296 mg, 73%) was prepared similarly using D-**10** (300 mg, 0.801 mmol).

D-**12**: colorless oil; HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 5/5, flow rate = 0.5 mL/min) t_R = 43 min; $[\alpha]^{22}_D$ −3.7° (*c* 4.0, CH_2Cl_2).

***N*$^\epsilon$-Cinnamoyl-*N*$^\epsilon$-[2-(trimethylsilyl)ethoxy]-L-lysine Methyl Ester TFA Salt (15).** A solution of **12** (1.14 g, 2.24 mmol), TFA (12 mL), and CH_2Cl_2 (12 mL) was stirred for 0.5 h at room temperature. The volatiles were removed under high vacuum to give the crude **13** (1.17 g, 100%), which was subjected to condensation with 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate.

***N*$^\alpha$,*N*$^{\alpha'}$-[3-Boc-3-hydroxy-1,5-dioxo-1,5-pentanediyl]bis{*N*$^\epsilon$-cinnamoyl-*N*$^\epsilon$-[2-(trimethylsilyl)ethoxy]-L-lysine Methyl Ester} (16).** Triethylamine (1.6 mL, 11.2 mmol) was added dropwise to a mixture of **15** (1.17 g, 2.24 mmol), 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate (496 mg, 1.12 mmol), and dioxane (20 mL) at room temperature. After being stirred for 20 h, the solvent was removed under reduced pressure, and the residue was diluted with AcOEt (50 mL). The solution was washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt−hexanes (3:1) as the eluent to give **16** (827 mg, 72%): colorless oil; $[\alpha]^{21}_D$ +1.8° (*c* 3.6, CH_2Cl_2); IR (film) 3475, 3350, 1750, 1680, 1655, 1620, 1250, 1210, 1175, 1160, 860, 840 cm^{-1}; ^1H NMR δ 0.06 (s, 18H), 1.01 (dd, J = 9.4, 7.8 Hz, 4H), 1.30−1.93 (m, 13H), 1.48 (s, 9H), 2.62 (d, J = 14.0 Hz, 1H), 2.79 (d, J = 14.0 Hz, 1H), 2.72 (s, 2H), 3.60−3.81 (m, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 3.93 (dd, J = 9.4, 7.8 Hz, 4H), 4.43−4.59 (m, 1H), 7.03 (d, J = 15.5 Hz, 2H), 7.34−7.59 (m, 10H), 7.72 (d, J = 15.5 Hz, 2H); ^{13}C NMR δ −1.4, 16.9, 22.7, 22.8, 26.6, 27.8, 31.0, 31.2, 41.0, 44.9, 45.0, 52.1, 52.3, 52.45, 52.52, 72.6, 72.7, 72.8, 82.5, 116.2, 116.3, 128.0, 128.1, 128.8, 129.8, 129.9, 135.2, 135.3, 143.3, 143.5, 166.9, 167.0, 169.6, 171.2, 171.5, 173.5, 179.9; HRMS (FAB, added NaI) calcd for $C_{52}H_{80}N_4O_{13}Si_2Na$ 1047.5160, found 1047.5136.

***N*$^\alpha$,*N*$^{\alpha'}$-[3-Carboxy-3-hydroxy-1,5-dioxo-1,5-pentanediyl]bis{*N*$^\epsilon$-cinnamoyl-*N*$^\epsilon$-[2-(trimethylsilyl)ethoxy]-L-lysine Methyl Ester} (17).** A solution of **16** (214 mg, 0.209 mmol), CH_2Cl_2 (2 mL), and TFA (2 mL) was stirred for 5 h at 0 °C. The solution was warmed to room temperature and stirred for an additional 2 h. After the solvents were removed under reduced pressure, the residue was diluted with AcOEt (40 mL). The solution was washed with brine (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt−EtOH (100:1−10:1) as the eluent to give **17** (182 mg, 90%): white form; $[\alpha]^{22}_D$ −2.3° (*c* 4.4, MeOH); IR (film) 3424, 2920, 2880, 1740, 1692, 1655, 1610, 1420, 1210, 1123 cm^{-1}; ^1H NMR δ 0.03 (s, 18H), 1.01 (t, J = 8.3 Hz, 4H), 1.20−1.43 (m, 4H), 1.52−1.90 (m, 8H), 2.61−2.92 (m, 4H), 2.82−3.44 (m, 9H), 3.52−3.32 (m, 4H), 3.66 (s, 6H), 3.89 (t, J = 8.3, 4H), 4.28−4.61 (m, 2H), 6.96 (d, J = 15.3 Hz, 2H), 7.25−7.42 (m, 6H), 7.43−7.59 (m, 4H), 7.73 (d, J = 15.3 Hz, 2H); ^{13}C NMR (CD_3OD) δ −1.3, 17.6, 23.7, 27.5, 32.1, 44.0, 44.3, 45.9, 52.9, 53.2, 53.4, 73.9, 76.7, 116.8, 116.9, 129.3, 130.1, 131.4, 136.2, 145.2, 145.4, 168.4, 168.5, 173.2, 173.5, 173.7, 173.9, 181.8; MS (FAB, added NaI) 1013 (M^+ + 2Na).

Nannochelin A. To a solution of **17** (243 mg, 0.251 mmol) in CH_3CN (10 mL) was added boron trifluoride etherate (0.15 mL, 1.26 mmol) at 0 °C. After being stirred for 0.5 h, the reaction mixture was concentrated under reduced pressure, and deionized water (10 mL) was added to the residue. The mixture was extracted with AcOEt (2 × 25 mL), and the combined organic layers were washed with deionized water (2 × 15 mL). The organic solvent was removed under reduced pressure and the residue was eluted on Sephadex G-15 (20 g) with 30% MeOH−H_2O to give nannochelin A (135 mg, 70%): colorless glass; $[\alpha]^{21}_D$ −13° (*c* 1.1, MeOH) (lit.[11] $[\alpha]^{25}_D$ −13.0° (*c* 0.9, MeOH); lit.[13] $[\alpha]^{26}_D$ −12° (*c* 0.65, MeOH)); IR (film) 3400, 1740, 1650, 1580, 1455, 1440, 1220, 980 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ (1:1)) δ 1.27−1.46 (m, 4H), 1.52−1.86 (m, 8H) 2.58−2.71 (m, 4H), 3.52−3.80 (m, 4H), 3.65 (s, 6H), 4.22−4.38 (m, 2H), 7.19 (d, J = 15.9 Hz, 2H), 7.31−7.45 (m, 6H), 7.53 (d, J = 15.9 Hz, 2H), 7.52−7.63 (m, 4H), 8.18 (d, 1H), 8.25 (d, 1H), 9.86 (br s, 1H); ^{13}C NMR (CD_3OD) δ 23.8, 27.2, 32.1, 44.5, 44.8, 52.8, 53.5, 53.6, 75.2, 117.6, 129.1, 130.0, 131.1, 136.6, 143.81, 143.84, 172.0, 172.1, 174.1, 176.6; HRMS (FAB, added NaI) calcd for $C_{38}H_{47}N_4O_{13}Na_2$ 813.2935 (M^+ + 2Na), found 813.2966.

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