The Total Synthesis of Nannochelin: A Novel Cinnamoyl Hydroxamate-Containing Siderophore

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The total synthesis of nannochelin A, a siderophore isolated from *Nannocystis exedens*, is described. The key transformation involves the tandem oxidation–acylation of the N^{ϵ}-amino group of N^{α}-BOC-L-lysine methyl ester prior to coupling with the external carboxyls of citric acid.

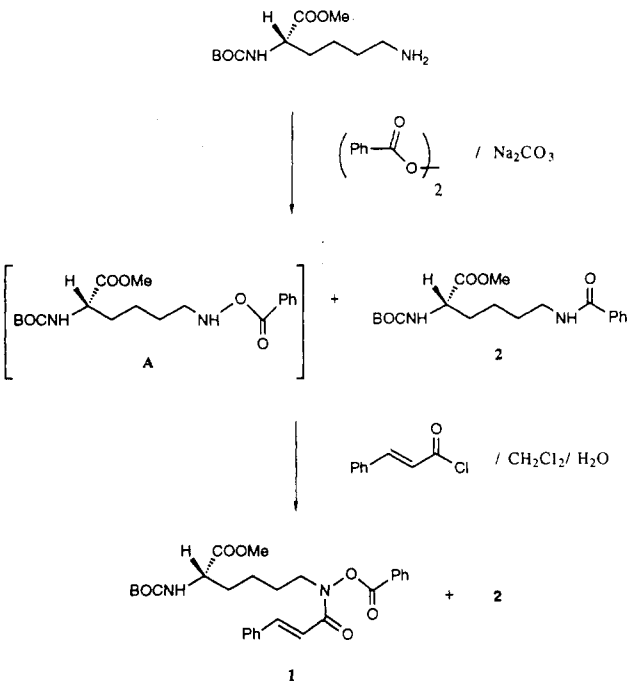
Introduction

While eukaryotes and prokaryotes have developed somewhat different machinery to exploit the redox properties of iron, the first maneuver by both systems involves accessing the metal. For example, microorganisms have evolved a group of low molecular weight, virtually ferric ion-specific chelating agents, siderophores, to solubilize and transport this essential micronutrient. Interestingly, the ability of these ligands to specifically convert ferric iron into a soluble, transportable form has found clinical use in the treatment of iron-overload diseases. In this instance, the siderophores utilized for iron internalization in microorganisms are found to promote the clearance of iron from eukaryotes. Indeed, the clinical experience with desferrioxamine, albeit not completely satisfactory in the treatment of thalassemia patients,[1-6] has promoted interest in the isolation and synthesis of potentially more effective iron chelators.

Although hydroxamate and 2,3-dihydroxybenzoyl units are the most common chelating functionalities found in siderophores, there is a wide structural dichotomy among the backbones to which these ligating groups are fixed. A relatively large number of siderophores employ the polyamines putrescine, cadaverine, or spermidine as backbones; others utilize the biological precursors to these polyamines, ornithine or lysine. A number of these polyamine precursor/polyamine–hydroxamate chelators also have a citric acid component,[7] as seen in schizokinen[8] isolated from *Bacillus megaterium*, arthrobactin[9] isolated from *Arthrobacter pascens*, and aerobactin[10] isolated from *Aerobacter* strains (Figure 1). Recently nannochelin, isolated from *Nannocystis exedens* by H. Reichenbach et al.,[11] was shown to consist of a rather unusual lysine-based cinnamoyl hydroxamate fixed to a citric acid framework (Figure 1).

Three antibiotic chelators, nannochelin A, B, and C, were isolated from *N. exedens*. The molecules differ in the number of methyl esters, that is nannochelin C has no methyl esters, while B and A have one and two, respectively (Figure 1). The nannochelins are interesting synthetic targets because of the unusual cinnamoyl hydroxamate, the chiral centers, and because previous synthetic strategies[8-10] utilizing *O*-benzyl protected hydroxamates are not applicable.[12-15] Removal of such an *O*-benzyl group from a cinnamoyl-containing nannochelin precursor via hydrogenation would compromise the nannochelin's N^{ϵ}-cinnamoyl hydroxamate functionality. We elected to first explore the synthesis of nannochelin A with the idea of developing methodologies which would allow access to nannochelin homologues.

Scheme I. Oxidation–Acylation of N^{α}-BOC-L-lysine Methyl Ester



Results and Discussion

Nannochelin A consists of two N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester fragments attached via the N^{α}-amino group to the terminal carboxyl groups of citric acid by amide bonds (Figure 1).[11] The key transformation involved in the synthesis of this siderophore was the construction of the N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl

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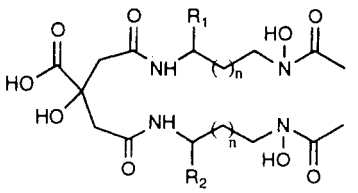
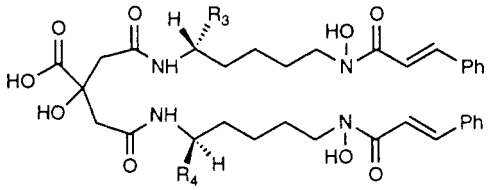


schizokinen (R_1, R_2=H, n=1)

arthrobactin (R_1, R_2=H, n=3)

aerobactin (R_1, R_2=COOH, n=3)



nannochelin

A: (R_3, R_4=COOMe)

B: (R_3=COOMe, R_4=COOH)

C: (R_3, R_4=COOH)

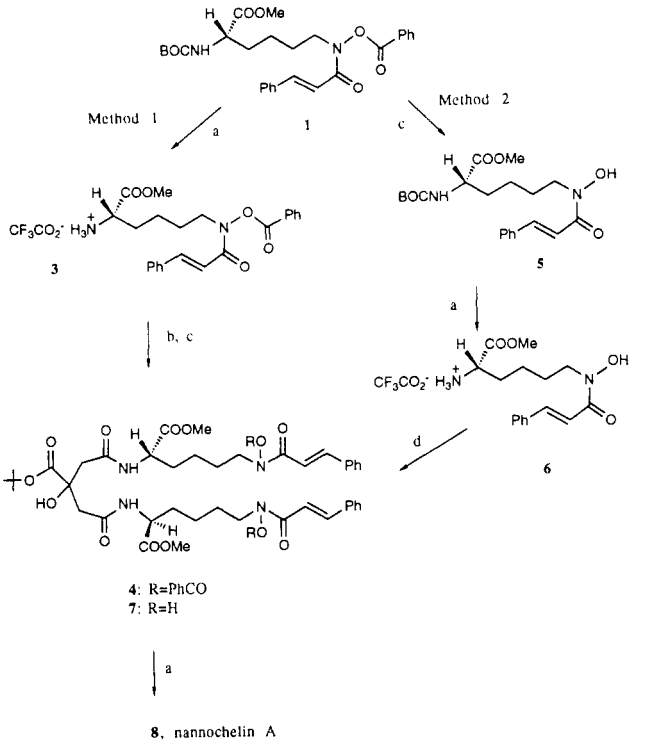
Figure 1. Hydroxamate siderophores predicted on citric acid backbones.

ester fragments via a tandem oxidation–acylation of the N^{ϵ}-amino group of N^{α}-BOC-L-lysine methyl ester prior to coupling with the external carboxyls of citric acid.

The oxidation of the free N^{γ}-amine of N^{α}-(benzyloxycarbonyl)-L-ornithine *tert*-butyl ester with benzoyl peroxide to the benzoyloxyamine, followed by N-acetylation with acetyl chloride, was recently reported by M. J. Milewska and A. Chimiak.[16] As our nannochelin strategy formally involved the N^{ϵ}-oxidation of L-lysine followed by N-acylation with *trans*-cinnamoyl chloride, this oxidation–acylation sequence seemed a worthwhile approach. However, because subsequent deprotection methods could not utilize hydrogenation, N^{α}-(benzyloxycarbonyl)-L-lysine was an unacceptable starting material. Instead, N^{α}-BOC-L-lysine methyl ester[17] was employed as the starting material. Thus, the lysine L-stereochemistry was fixed, the methyl ester of nannochelin A was in place early in the synthesis, and the N^{α}-BOC group allowed for deprotection and coupling to the selectivity-substituted citrate moiety without reduction of the cinnamoyl hydroxamate group.

As shown in Scheme I, treatment of N^{α}-BOC-L-lysine methyl ester[17] with benzoyl peroxide and Na_2CO_3 in CH_2Cl_2 generated a mixture of N^{ϵ}-benzoyl-N^{α}-BOC-L-lysine methyl ester **2** and the intermediate N^{ϵ}-(benzoyloxy)-N^{α}-BOC-L-lysine methyl ester **A** in situ. This mixture was then acylated with *trans*-cinnamoyl chloride under Schotten–Baumann conditions to give the desired N^{ϵ}-cinnamoyl-N^{ϵ}-(benzoyloxy)-N^{α}-BOC-L-lysine methyl ester **1** in 25% isolated yield. Although no attempt was made to optimize the oxidation–acylation reaction conditions, the yield was nevertheless disappointing based on the previous N^{α}-(benzyloxycarbonyl)-L-ornithine *tert*-butyl ester work.[16] However, the separation of **1** from the N^{ϵ}-benzoyl-N^{α}-BOC-L-lysine methyl ester **2** was easily accomplished by chromatography on silica gel.

Scheme II[a]



[a] (a) TFA, 0 °C; (b) 2-*tert*-butyl citrate, DPPA, NEt_3, DMF; (c) 10% NH_3 in MeOH; (d) 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate, NEt_3, dioxane.

While the selective coupling of amino substrates with the terminal carboxyls of citric acid can be achieved utilizing either 2-substituted-1,3-bis-activated esters of citric acid or anhydromethylenecitric acid,[8,9] the reported imide formation associated with the latter approach prompted us to use the activated ester methodology. The selective activation of the 1,3 carboxyls of citric acid was accomplished by either the in situ activation of 2-*tert*-butyl citrate[8] with diphenyl phosphorazidate (DPPA)[18] or by the formation of the terminally bis-activated ester, 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate.[8]

Synthesis of nannochelin A *tert*-butyl ester, **7**, was effected via two routes, each beginning with lysine derivative **1**. In both methods, coupling of the functionalized lysine fragment to the citric acid framework required the removal of the N^{α}-BOC group with trifluoroacetic acid prior to condensation. In the first method, 2-*tert*-butyl citrate was condensed with **3** before O-deprotection of the N^{ϵ}-hydroxamate (Scheme II). Treatment of **1** with TFA at 0 °C gave a quantitative yield of the N^{ϵ}-(benzoyloxy)-N^{ϵ}-cinnamoyl-L-lysine methyl ester trifluoroacetic acid salt (**3**). Condensation of **3** with 2-*tert*-butyl citrate under Yamada conditions[18] afforded a 28% yield of the fully protected *O*-benzoylnannochelin A *tert*-butyl ester, **4**. Generation of the "free" hydroxamate by reaction of **4** with 10% NH_3/MeOH solution at −23 °C provided nannochelin A *tert*-butyl ester, **7**, in 29% yield.

In the second approach, the hydroxamate **1** was deprotected prior to condensation with the activated citrate. Compound **1** was treated with 10% NH_3/MeOH solution at −23 °C to give the "free" hydroxamate, or N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-N^{α}-BOC-L-lysine methyl ester, **5** in

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93% isolated yield. Compound **5** was reacted with TFA at 0 °C to give a quantitative yield of N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester TFA salt, **6**. Because of the low yield in the condensation of **3** with 2-*tert*-butyl citrate under Yamada conditions, we elected to utilize the citrate succinimidyl ester. Condensation of **6** with 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate[8] and triethylamine (TEA) in dioxane gave nannochelin A *tert*-butyl ester, **7**, in 70% yield. Finally, treatment of nannochelin A *tert*-butyl ester, **7**, with TFA gave nannochelin A, **8**, in 80% yield. The latter route provided superior overall yields of nannochelin A. Method 1 may be less efficient because of a transacylation between the N^{ϵ}-benzoyloxy group and the free N^{α}-amine. This side reaction could not occur in method 2, as the benzoyl group was removed prior to generation of the free N^{α}-amine.

The ultraviolet and mass spectra as well as the R_f on silica gel TLC and optical rotation of synthetic nannochelin A were identical with those reported for the natural product.[11] Although we were unable to obtain either an authentic sample or a ^{1}H NMR of nannochelin A, the proton spectrum of the synthetic material was in complete agreement with the proposed structure. However, there are several noteworthy points regarding the impact of solvent on this spectrum.

The dependence of the nannochelin framework NMR spectra on solvent was first observed during characterization of nannochelin *tert*-butyl ester, **7**. In $CDCl_3$, the nannochelin *tert*-butyl ester ^{1}H NMR spectrum was poorly resolved, lines were broad, and signals overlapped. However, in 1/1 d_6-DMSO/$CDCl_3$ sample resolution improved substantially, and spectral lines were sharp and well resolved. The previously indistinguishable amide NH and cinnamoyl protons could be assigned. The amide protons appeared together at 8.12 ppm and the cinnamoyl protons as separate doublets at 7.47 and 7.18 ppm. The spectrum for nannochelin A, **8**, was also run in 1/1 d_6-DMSO/$CDCl_3$. Spectral resolution was excellent: the amide protons appeared as separate doublets at 8.19 and 8.13 ppm and the cinnamoyl protons as separate doublets at 7.46 and 7.16 ppm. All other signals were easily assignable (see Experimental Section). The relationship of these spectral changes to solvent is under further investigation in our laboratories.

In summary, the synthesis provided both proof of structure of the natural product and a method which should allow facile access to a variety of nannochelin homologues with different amino acid fragments.

Experimental Section

Materials and Methods. Lipophilic Sephadex LH-20 was obtained from the Sigma Chemical Co. Silica gel 60 (70–230) mesh was purchased from EM Science, Darmstadt, Germany. All other reagents were purchased from the Aldrich Chemical Co. and used without further purification. ^{1}H NMR spectra were recorded at 90 or 300 MHz and run in $CDCl_3$ unless otherwise indicated. N^{ϵ}-CBZ-N^{α}-BOC-L-Lysine was purchased from Sigma and converted to N^{α}-BOC-L-lysine methyl ester by a published procedure.[17]

N^{ϵ}-Cinnamoyl-N^{ϵ}-(benzoyloxy)-N^{α}-BOC-L-lysine Methyl Ester (1). A solution of N^{α}-BOC-L-lysine methyl ester (10.0 g, 0.0384 mol) in CH_2Cl_2 (75 mL) was added dropwise over 20 min to a mixture of benzoyl peroxide (9.31 g, 0.0384 mol), Na_2CO_3 (12.22 g, 0.1153 mol), and CH_2Cl_2 (150 mL). The mixture was stirred vigorously throughout the reaction. The disappearance of the lysine starting material was monitored by TLC (2% NH_3/CH_3OH). After 3 h at rt, 150 mL of H_2O and 225 mL of CH_2Cl_2 were added. Next, a solution of *trans*-cinnamoyl chloride (6.81 g, 0.0409 mol) dissolved in 75 mL of CH_2Cl_2 was added dropwise over 15 min, and the reaction was allowed to stir overnight. The layers were separated, and the organic layer was washed twice with distilled water (200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to give 18.53 g of an orange semisolid, which was subjected to flash column chromatography (500 g of SiO_2), first eluting with 60% CH_2Cl_2/hexane (3.86 g of unreacted benzoyl peroxide was obtained), followed by 40% ethyl acetate/hexane (13.2 g of an orange oil was eluted). This oil was rechromatographed (35% EtOAc/hexane) to afford N^{ϵ}-cinnamoyl-N^{ϵ}-(benzoyloxy)-N^{α}-BOC-L-lysine methyl ester **1** as a yellow solid (4.90 g, 25% yield) and N^{ϵ}-benzoyl-N^{α}-BOC-L-lysine methyl ester **2** (6.5 g, 46%). **1**: ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 2 H, aromatic), 7.71 (d, 1 H, olefinic), 7.40 (m, 8 H, aromatic), 6.61 (d, 1 H, olefinic), 5.01 (m, 1 H, NH), 4.21 (m, 1 H, CH), 3.89 (t, 2 H, CH_2N), 3.67 (s, 3 H, OCH_3), 1.65 (m, 6 H, CH_2), 1.38 (s, 9 H, *tert*-butyl); mass spectrum (FAB) M + 1 = 511, $C_{28}H_{34}N_2O_7$ (510.28). Anal. Calcd: C 65.87, H 6.71, N 5.49; found: C 65.92, H 6.74, N 5.45. **2**: ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 2 H, aromatic), 7.30 (m, 3 H, aromatic), 6.68 (t, 1 H, NH), 5.20 (broad d, 1 H, NH), 4.21 (m, 1 H, CH), 3.62 (s, 3 H, OCH_3), 3.38 (q, 2 H, CH_2N), 1.55 (m, 6 H, CH_2), 1.37 (s, 9 H, *tert*-butyl); formula weight $C_{19}H_{28}N_2O_5$ (364.44). Anal. Calcd: C 62.62, H 7.74, N 7.69; found: C 62.53, H 7.78, N 7.64.

N^{ϵ}-(Benzoyloxy)-N^{ϵ}-cinnamoyl-L-lysine Methyl Ester, Trifluoroacetic Acid Salt (3). Trifluoroacetic acid (15 mL) was added dropwise over 5 min to N^{ϵ}-(benzoyloxy)-N^{ϵ}-cinnamoyl-N^{α}-BOC-L-lysine methyl ester **1** (1.00 g, 1.96 mmol) at 0 °C. The reaction was allowed to stir for an additional 30 min. The ice bath was removed and the solution allowed to warm to rt. TLC (50% ethyl acetate/hexane) revealed that all the starting material was consumed after 30 minutes. The volatiles were removed under high vacuum to yield a clear oil of **3** (1.03 g, 100%): ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 2 H, aromatic), 7.70 (d, 1 H, olefinic), 7.30 (m, 8 H, aromatic), 6.60 (d, 1 H, olefinic), 4.10 (m, 1 H, CH), 3.93 (m, 2 H, CH_2N), 3.74 (s, 3 H, OCH_3), 2.00 (m, 2 H, CH_2), 1.68 (m, 4 H, CH_2); mass spectrum (positive FAB) M^+ = 411, $C_{23}H_{27}N_2O_5$ (411.47) expected for cation.

N^{α},$N^{\alpha'}$-[3-Hydroxy-3-(*tert*-butoxycarbonyl)glutaryl]bis-[N^{ϵ}-cinnamoyl-N^{ϵ}-(benzoyloxy)-L-lysine methyl ester] (4). Diphenyl phosphorazidate (DPPA) (0.539 g, 1.97 mmol) in 5 mL of dry DMF was added dropwise over 5 min to salt **3** (1.03 g, 1.96 mmol) and 2-*tert*-butyl citrate[8] (0.24 g, 0.967 mmol) in dry dimethylformamidate (DMF) (5 mL). The solution was stirred for 10 min at 0 °C, and triethylamine (TEA) (1.09 g, 10.7 mmol) in 5 mL of dry DMF was added over a 5 min period. The solution was stirred for an additional 3 h and slowly warmed to room temperature overnight. The solvents were removed under high vacuum, and the resulting oil was diluted with 100 mL of methylene chloride and washed with deionized water (2 × 50 mL), followed by 5% sodium bicarbonate solution (1 × 50 mL) and deionized water (1 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give a yellow crystalline solid (1.07 g). Column chromatography (70% ethyl acetate/hexane) gave 284 mg of **4** (28% yield): ^{1}H NMR ($CDCl_3$) (300 MHz) δ 8.12 (d, J^3_{H-H} = 7.3 Hz, 4 H, aromatic), 7.79 (d, J^3_{H-H} = 15.6 Hz, 2 H, olefinic), 7.70–7.30 (m, 16 H, aromatic), 6.68 (d, J^3_{H-H} = 15.6 Hz, 2 H, olefinic), 4.55 (m, 2 H, CH), 3.91 (m, 4 H, CH_2NO), 3.71 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 2.71 (m, 4 H, CH_2), 1.87 (m, 2 H, CH_2), 1.70 (m, 6 H, CH_2), 1.50 (m, 4 H, CH_2), 1.49 (s, 9 H, *tert*-butyl); formula weight $C_{56}H_{64}N_4O_{15}$ (1033.14). Anal. Calcd: C 65.10, H 6.24, N 5.42; found: C 64.96, H 6.28, N 5.40.

N^{ϵ}-Cinnamoyl-N^{ϵ}-hydroxy-N^{α}-BOC-L-lysine Methyl Ester (5). A 10% (by volume) NH_3/MeOH solution (2.0 mL) was added dropwise to N^{ϵ}-cinnamoyl-N^{ϵ}-(benzoyloxy)-N^{α}-BOC-L-lysine methyl ester (**1**) (0.544 g, 1.07 mmol) and 1.4 mL of distilled MeOH. The reaction was carried out under nitrogen at −23 °C. The reaction was monitored by TLC (6% EtOH/$CHCl_3$). After 170 min, the solvents were removed under high vacuum, and the resulting oil (0.560 g) was purified by column chromatography (38 g of LH-20 Sephadex eluted with 6% EtOH/toluene) to give the pure N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy N^{α}-BOC-L-lysine methyl ester (0.403 g, 93%); ^{1}H NMR ($CDCl_3$) (90 MHz) δ 7.61 (d, 1 H, olefinic), 7.30 (m, 6 H, aromatic and olefinic), 5.20 (broad m, 1 H, NH or OH), 4.28 (m, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.62 (m, 2 H, CH_2N), 1.70 (m, 4 H, CH_2), 1.41 (m, 2 H, CH_2), 1.40 (s, 9 H, *tert*-butyl); mass spectrum M + 1 = 407, $C_{21}H_{30}N_2O_6$ (406.48). Anal. Calcd: C 62.05, H 7.44, N 6.89; found: C 61.86, H 7.47, N 6.85.

N^{ϵ}-Cinnamoyl-N^{ϵ}-hydroxy-L-lysine Methyl Ester, Trifluoroacetic Acid Salt (6). Trifluoroacetic acid (TFA) (5.0 mL) was added dropwise over 30 s to N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-N^{α}-BOC-L-lysine methyl ester (5) (0.340 g, 0.8365 mmol) at 0 °C under nitrogen. The ice bath was removed and the solution stirred for 5 min. TLC (7% EtOH/$CHCl_3$) showed the reaction was complete after this time. The volatiles were removed under high vacuum to give the desired N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester, trifluoroacetic acid salt (0.351 g, 100%): ^{1}H NMR ($CDCl_3$) (90 MHz) δ 7.30 (broad m, 7 H, aromatic), 4.02 (broad m, 1 H, CH), 3.72 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 1.90 (m, 2 H, CH_2), 1.62 (m, 4 H, CH_2); mass spectrum (positive FAB) M^+ = 307, $C_{16}H_{23}N_2O_4$ (307.37) expected for cation.

N^{α},$N^{\alpha'}$-[Hydroxy-3-(*tert*-butoxycarbonyl)glutaryl]bis-[N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester] (7). Compound 7 was synthesized by two methods. In method 1, a 10% (by volume) NH_3/MeOH solution (0.1 mL) was added dropwise to 4 (10.1 mg, 0.0098 mmol). The reaction was carried out under nitrogen at -23 °C. The reaction was monitored by TLC (5% EtOH/$CHCl_3$). After 30 min, the solvents were removed under high vacuum, and the resulting oil was purified by column chromatography (4 g of SiO_2 eluted with 5% EtOH/$CHCl_3$) to give pure nannochelin A *tert*-butyl ester, 7 (2.3 mg, 29%).

In method 2, intermediate 6 was reacted immediately with 2-*tert*-butyl 1,3-di-N-succinimidyl citrate.[8] It should be noted that we obtained a material of identical ^{1}H NMR, but with a much higher mp than that reported for the 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate, by repeated fractionation of the partially soluble diester from boiling chloroform. 2-*tert*-Butyl 1,3-di-*N*-succinimidyl citrate: mp 188-189 °C (lit. 167 °C); formula weight $C_{18}H_{22}N_2O_{11}$ (442.38). Anal. Calcd: C 48.87, H 5.01, N 6.33; found: C 48.75, H 5.00, N 6.28. Triethylamine (0.35 g, 3.47 mmol) was added dropwise to a mixture of 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate (0.1762 g, 0.3983 mmol) and N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester, trifluoroacetic acid salt (6) (0.351 g, 0.8365 mmol) in 8.0 mL of dry dioxane at 15 °C under nitrogen. The solution was allowed to warm to room temperature and stirred overnight. TLC (8% EtOH/$CHCl_3$) showed all starting material was consumed. The solvents were removed under high vacuum, and column chromatography (6% EtOH/toluene) on LH-20 Sephadex (32 g) gave pure 7 as a colorless solid (230 mg, 70%) (with R_f = 0.42 in 9% EtOH/$CHCl_3$): ^{1}H NMR (d_6-DMSO/$CDCl_3$; 1:1 by volume) δ 8.12 (m, 2 H, NH), 7.52 (m, 4 H, aromatic), 7.47 (d, 2 H, olefinic), 7.32 (m, 6 H, aromatic), 7.18 (d, 2 H, olefinic), 4.25 (m, 2 H, CH), 3.62 (m, 10 H, CH_3 and CH_2NO), 2.60 (m, 4 H, CH_2), 1.63 (m, 8 H, CH_2), 1.35 (s, 9 H, *tert*-butyl), 1.34 (m, 4 H, CH_2); mass spectrum (FAB) M + 1 = 826, $C_{42}H_{56}N_4O_{13}$ (824.92). Anal. Calcd: C 61.15, H 6.84, N 6.79; found: C 60.89, H 6.95, N 6.60.

Nannochelin A (8). TFA (2 mL) was added dropwise to 7 (137 mg, 0.166 mmol) at 0 °C. After the addition was complete, the solution was allowed to warm to room temperature and stir for 1 h. TLC (9% EtOH/$CHCl_3$) showed no starting material remained after 1 h. The volatiles were removed under high vacuum and gave 169 mg of a crude oil. This colorless oil was eluted on LH-20 Sephadex (4.0 g) with 7% EtOH/toluene to give 102 mg (80%) of nannochelin A as a white solid (mp 88-89 °C): ^{1}H NMR (d_6-DMSO/$CDCl_3$ (1:1)) δ 9.75 (s, 1 H, COOH), 8.19 (d, 1 H, NH), 8.13 (d, 1 H, NH), 7.52 (d, 4 H, aromatic), 7.46 (d, 2 H, J^3_{H-H} = 15.9 Hz, olefinic), 7.31 (m, 6 H, aromatic), 7.18 (d, 2 H, J^3_{H-H} = 15.9 Hz, olefinic), 4.25 (m, 2 H, CH), 3.60 (m, 4 H, CH_2NO), 3.59 (s, 6 H, OCH_3), 2.62 (m, 4 H, CH_2), 1.62 (m, 8 H, CH_2), 1.30 (m, 4 H, CH_2); ^{13}C NMR (CD_3OD) δ 22.29, 25.78, 30.57, 30.66, 42.96, 43.30, 51.29, 52.05, 52.09, 73.68, 116.20, 127.59, 128.53, 129.52, 135.11, 142.33, 142.37, 170.54, 170.89, 172.63, 175.19; mass spectrum (negative FAB) M^+ = 768, $C_{38}H_{48}N_4O_{13}$ (768.82) UV spectrum λ_{max} = 280 nm (lit. 280 nm); IR (KBr pellet) 3272, 2954, 2862, 1739, 1646, 1580, 1549, 1441, 1215, 980, 764 cm^{-1}; optical rotation $[\alpha]_D$ -12° (*c* 0.65, MeOH, 26 °C) (lit. $[\alpha]_D$ -13° (*c* 0.9, MeOH, 25 °C)); TLC (SiO_2) R_f = 0.1 (10% MeOH/CH_2Cl_2) matches lit. value.[11] Anal. Calcd: C 59.37, H 6.29, N 7.29; found: C 59.13, H 6.35, N 7.21.

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C-2 Dimethyl *seco*-Mevinic Acids. Synthesis of Monocyclic HMG-CoA Reductase Inhibitors from (*R*)-(-)-Carvone

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An efficient preparation of novel monocyclic HMG-CoA reductase inhibitors from (*R*)-(-)-carvone is reported. Utilizing this chiral carbon pool, the C-2 dimethyl *seco*-mevinic acid **3a** was prepared in 17 steps and 5.2% overall yield. The key chiral intermediate aldehyde **10a** was prepared via a short and efficient synthetic sequence (six steps, 27% yield) from (*R*)-(-)-carvone. The appropriate chirality of the diol acid side chain was secured by employing the chiral acetate synthon "(*S*)-HYTRA" and by performing a stereoselective 1,3-syn reduction on the β-hydroxy ketone **19**. Structural requirements at the C-2 position are rather stringent, and deletion of or addition of an extra methyl group are both unacceptable modifications for this novel class of monocyclic HMG-CoA reductase inhibitors.

Introduction

Hypercholesterolemia is considered to be a major risk factor for coronary heart and artery disease, which is a leading cause of deaths in the United States.[1] In humans, more than half of the total body cholesterol is derived from de novo biosynthesis.[2] Thus, pharmacological intervention of this endogeneous pathway has become a popular and logical approach for reducing total plasma cholesterol levels.[3] While the cholesterol biosynthetic pathway involves more than 25 different enzymatic transformations, inhibition at key regulatory sites would be expected to produce the most profound effect. In this regard, inhib-

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