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Synthesis of Novel Nocathiacin-Class Antibiotics. Condensation of Glycolaldehyde with Primary Amides and Tandem Reductive Amination of Amadori-Rearranged 2-Oxoethyl Intermediates

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Nocathiacin I (**1**) and nocathiacin IV (**2**) are novel indole-containing thiazolyl peptide antibiotics, which exhibit potent activity against key Gram-positive bacterial pathogens, including multi drug-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *and Enterococcus faecium*. New nocathiacins **7**−**12** were prepared from **2** by a condensation with glycolaldehyde followed by tandem reductive amination of the 2-oxoethyl intermediate **4**. The latter was formed via Amadori rearrangement from initial 2-hydroxyethylideneamide **3**. This transformation readily tolerates the complex architecture of nocathiacins and allows selective incorporation of water solubilizing groups to the primary amide in **2** without protecting group manipulation.

Introduction

The emergence of multi drug-resistance of pathogenic bacteria, particularly the glycopeptide-resistant Gram-positive cocci, pose a serious challenge to academic and industrial research.[1] Thiazolyl peptide antibiotics such as thiostrepton,[2] nosiheptide,[3] or amythiamicin[4] have been reported to exhibit potent antimicrobial activity against Gram-positive bacteria in vitro. These novel antibiotics are known to inhibit the elongation cycle of bacterial protein synthesis mediated by elongation factors EF-Tu and EF-G.[5]

Nocathiacin I (**1**), a new member of the thiazolyl peptide class of antibacterial agents, was recently discovered in the fermentation broth of Nocardia sp. (strain ATCC-202099).[6] Nocathiacin I is a broad-spectrum antibiotic active in vitro against multi drug-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecium*. Unlike other thiazolyl peptides, nocathiacin I showed in vivo efficacy in a systemic *S. aureus* infection model in mice.

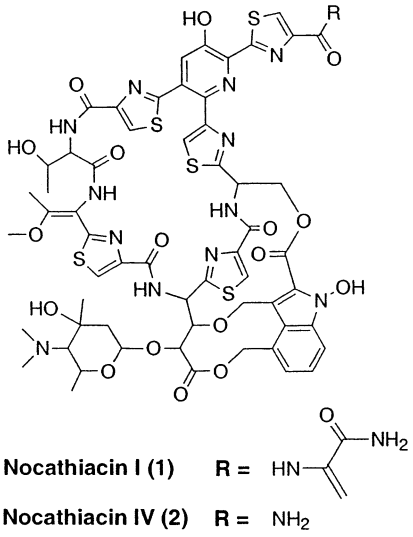

FIGURE 1. Parent nocathiacins I and IV.

The discovery of nocathiacin I (**1**) and its structural surrogate nocathiacin IV (**2**) (Figure 1),[7,8] obtained from **1** by enzymatic and chemical transformation, provided a

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SCHEME 1. Amadori Rearrangement of 2-Methylimino Ethanol to Methylamino Acetaldehyde

promising lead for the development of a parenterally administered broad-spectrum antibiotic. Central to this effort was the synthesis of analogues with improved water solubility that retained broad-spectrum antibacterial activity, compared to that of parent nocathiacins **1** and **2**. In this article, we describe a synthesis of several new nocathiacins (**7**−**12**) from **2** by a newly developed condensation of the primary amide moiety in **2** with glycolaldehyde dimer and a tandem reductive amination of the Amadori-rearranged 2-oxoethyl intermediate **4**. This convenient transformation selectively targets the primary amide in **2** and allows incorporation of solubilizing groups directly without prior protecting group manipulation.

Results and Discussion

The complex architecture and chemical instability of nocathiacins **1** and **2** hampers efforts to derive structurally modified analogues with improved pharmaceutical properties. We sought to improve the solubility profile of these natural products by substituting the dehydroalanine moiety in **1** with water-solubilizing groups. Initial efforts were focused on hydrolysis of either the primary amide bond in **2** or the corresponding secondary amide in **1** to the carboxylic acid, a pivotal intermediate. Since selective scission of these amides proved difficult, we attempted to introduce substituents directly to the primary amide **2**. In view of the inability to protect the phenol and hydroxyl moieties in **2**, modification of the primary amide would require conditions that are compatible with the unprotected moieties. Such an approach presented a considerable challenge as a result of the lack of selectivity in the deprotonation step prior to coupling of the amide with an alkylating agent.[9]

We considered a strategy of N-alkylation, without deprotonation, involving enamides (*N*-alkenylamides).[10] Enamides, from the condensation of primary amides with aldehydes, are typically converted to *N*-alkyl amides by a reductive step.[11] Similar primary amide condensation with α-hydroxyaldehydes should provide an unstable *N*-alkylidene- or *N*-alkenylamides, which tautomerize to a more stable *β*-amido-aldehyde. The intermediates conveniently provide functionality for further modification, for example, by reductive amination. The rearrangement of α-hydroxyimines, from condensation of primary amines with α-hydroxyaldehydes, to 2-oxoalkylamines is known as the Amadori rearrangement (Scheme 1).[12] Notably, the equivalent Amadori rearrangement for

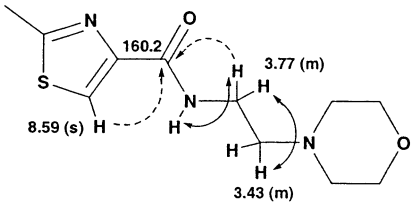

FIGURE 2. Selected H−H and H−C NMR correlations in **7**.

primary amides has not been reported. We expected that the condensation of a primary amide with an α-hydroxyaldehyde, such as glycolaldehyde, should yield a more stable 2-oxoalkylamide. Indeed, we have found that **2** readily undergoes acid-catalyzed condensation with glycolaldehyde dimer at elevated temperature. Because of the instability of the product, the structure of this intermediate was tentatively proposed based on LC−MS analysis, which revealed two major components with mass *m*/*z* 1410 ($[M + H]^+$, **4**) and *m*/*z* 1470 ($[M + H]^+$, **5**). This is consistent with equilibrium between **4** and the glycolaldehyde adduct **5**, as shown in Scheme 2. To gather further evidence to support formation of the 2-oxoethylamide **4**, the resulting mixture of **4** and **5** was treated with sodium cyanoborohydride ($NaBH_3CN$) to give the hydroxyethyl derivative **6**. The ^{1}H NMR (COSY) spectrum of **6** unambiguously revealed couplings between the amide NH (*δ* 9.08) and the methylene pair (*δ* 3.39) of the hydroxyethyl moiety in **6**. The clear disappearance of the primary amide NH_2 signals (*δ* 6.50) in **2**, as deduced by comparison with the ^{1}H NMR spectrum of the nocathiacin IV (**2**), supports the sole conversion of the primary amide in **2** during this process.

Reductive amination of **4** with morpholine [CH_3COOH, $NaBH(OAc)_3$] afforded moderate yield of **7**. The attachment of the *N*-ethylmorpholinyl group in **7** was reaffirmed by ^{1}H NMR (COSY) analysis and C−H, N−H heteronuclear coupling experiments (HMQC, HMBC). In the HMBC NMR experiment, long-range (H−C) correlations were observed between the C1′ methylene protons of the ethylene bridge (*δ* 3.77) and the amide carbonyl (*δ* 160.2), which also showed a long-range correlation with the one proton singlet (*δ* 8.59) of the exocyclic thiazole moiety of **2** (Figure 2).

In the course of these studies, we have found a noteworthy tolerance of this transformation to a broader spectrum of secondary amines. The reductive amination proceeded well with, for example, diethanolamine, 2-(ethylamino)ethanol, 2-(methylamino)ethanol, diethylamine, and *N*-ethylglycine to afford derivatives **8**−**12**, respectively (Scheme 2). Thus, the condensation-reductive amination sequence afforded a convenient means for appendage of diverse solubilizing groups to the tricyclic core of nocathiacins. The newly prepared derivatives **7**−**12** showed improved water solubility profiles compared to that of the parent nocathiacins **1** and **2** and retained good antibacterial activity.[13]

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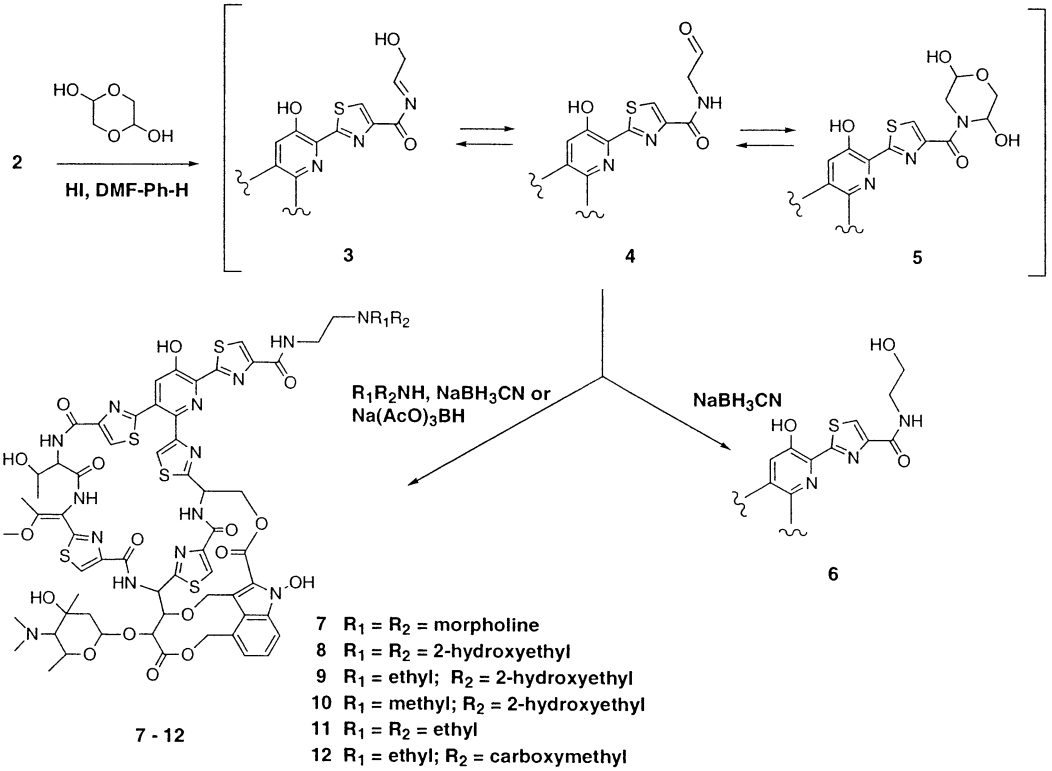
(13) From these series, amines **7**, **8**, and **9** showed solubility of greater than 9.7 mg/mL at pH 2.5−3.4 and minimum inhibitory concentrations (MICs) against *S. aureus* (A15090) of 0.015, 0.06, and 0.06 *μ*g/mL, respectively. In comparison, solubility of the parent nocathiacin IV (**2**) was 0.58 mg/mL at pH 3.6 and its MIC against *S. aureus* (A15090) was ≤0.03 *μ*g/mL. Further information concerning the solubility and MICs against selected pathogens for nocathiacins **1**, **2**, **6**−**12** are listed in Supporting Information

SCHEME 2. Tandem Condensation of Nocathiacin IV (2) with Glycolaldehyde.



Summary

Selective incorporation of solubilizing groups to the primary amide moiety of nocathiacin IV (**2**) was accomplished *via* a novel condensation with glycolaldehyde dimer and reductive amination of rearranged 2-oxoethyl intermediate **4** in tandem fashion. This novel sequence of transformations conveniently affords a new series of water-soluble nocathiacins and is noteworthy for compatibility with the structural complexity of these natural products.

Experimental Section

General Methods. Solvents and other reagents were used as purchased without further purification. Purification of the products was carried out by high performance, low-pressure liquid chromatography (HPLPLC) using an epoxy-coated chromatographic column (51 mm × 450 mm; and 40 × 350 mm) and a C-18 reverse phase gel (12 nm × 75 μm). The NMR chemical shifts are reported as δ values (in ppm) from the internal solvent standard.×′

General Procedure for Condensation of Nocathiacin IV (2) with Glycolaldehyde Dimer. Synthesis of 2-Oxoethyl Intermediate 4. To a 250-mL round-bottom, single-neck flask equipped with a magnetic stirrer-bar were added nocathiacin IV (**2**) HI salt (90% purity, 5 g, 3.00 mmol) and glycolaldehyde dimer (2.5 g, 21.0 mmol). The solids were dissolved in DMF (40 mL), and anhydrous benzene (70 mL) was added. The flask was fitted with a Dean−Stark adapter equipped with a reflux condenser and was immersed in an oil bath heated to 135 °C. The mixture was refluxed for 45 min with occasional shaking to prevent the buildup of solids on the walls of the flask. The reaction was cooled to room temperature and concentrated under reduced pressure to afford a mixture of **4** and **5** as an oily residue, which was directly used in further transformations.

2-Hydroxyethylamide 6. The 2-oxoethyl intermediate **4** was prepared according to the above procedure from nocathiacin IV (**2**) (330 mg, 0.221 mmol) and glycolaldehyde dimer (198 mg, 1.65 mmol). To the resulting mixture were added MeOH (15 mL), AcOH (1.5 mL), imidazole (150 mg), and $NaBH_3CN$ (140 mg, 2.22 mmol) in succession. The mixture was stirred for 18 h at room temperature. All volatiles were removed under reduced pressure, and the residue chromatographed (HPLPLC column i.d. 40 mm) using a gradient elution (20 mL/min) starting with (30%) methanol−water−(0.1%) TFA (400 mL) to (55%) methanol−water−(0.1%) TFA until complete elution of the product to afford 80 mg (24%) of **6** bis-TFA salt as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+25.1), 238 (−41.2), 267 (+19.4), 304 (−5.3), 355 (+4.5); ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.80 (1H, s), 10.77 (1H, s), 9.09 (1H, s), 9.08 (1H, t, J = 6 Hz), 8.65 (1H, s), 8.57 (1H, d, J = 9 Hz), 8.53 (1H, s), 8.45 (1H, s), 8.22 (1H, s), 8.00 (1H, s), 7.89 (1H, s), 7.86 (1H, d, J = 11 Hz), 7.74 (1H, d, J = 9 Hz), 7.38−7.35 (2H, m), 7.19 (1H, d, J = 7 Hz), 6.41 (1H, br s), 6.03 (1H, d, J = 12 Hz), 5.75 (1H, dd, J = 4, 11 Hz), 5.72 (1H, d, J = 9 Hz), 5.23 (1H, m), 5.07−5.04 (2H, m), 4.99 (1H, d, J = 8 Hz), 4.79 (1H, d, J = 10 Hz), 4.53 (1H, d, J = 11 Hz), 4.30 (1H, d, J = 10 Hz), 4.25 (1H, m), 4.16 (1H, d, J = 11 Hz), 4.05 (1H, d, J = 10 Hz), 3.91 (3H, s), 3.55 (2H, m), 3.39 (2H, m), 3.13 (1H, s), 2.88 (6H, s), 2.49 (1H, m), 2.12 (1H, m), 2.00 (3H, s), 1.94 (1H, d, J = 14 Hz), 1.60 (3H, s), 1.15 (2H, m), 1.10 (1H, dd, J = 6, 15 Hz), 0.81 (3H, s), 0.80 (3H, s); MS (ESI) m/z 1412.4 $[M + H]^+$; HRMS (ESI) m/z 1412.292 (calcd for $C_{60}H_{62}N_{13}O_{18}S_5$ 1412.29394)

***N*-(2-Morpholin-4-yl-ethyl)-amide 7.** The mixture obtained by condensation of **2** (5 g, 3.00 mmol) with glycolaldehyde dimer (2.5 g, 21.0 mmol) according to the aforementioned general procedure was transferred into a 500-mL round-bottom flask and dissolved in a mixture of DMF (80 mL) and THF (110 mL). The solution was cooled to −60 °C, and AcOH (12 mL) was added followed by a slow addition of $NaBH(OAc)_3$ (12 g, 56.6 mmol). The mixture was stirred for 15 min at −60 °C, and a solution of morpholine in AcOH, prepared by a careful addition of morpholine (5 mL, 57.4 mmol) to glacial AcOH (13 mL, 227 mmol), was added. The reaction mixture was stirred for 10 min at −60 °C and was allowed to gradually warm to room temperature at which time stirring was continued for 18 h. The mixture was concentrated under

reduced pressure, and the excess AcOH was removed by azeotropic distillation under reduced pressure. The resultant thick residue was dissolved in DMF (40 mL) and added to a solution of $NaHCO_3$ (20 g) and NaCl (5 g) in H_2O (500 mL). The resultant cloudy solution was centrifuged, and the solids collected and dried under reduced pressure to afford ca. 5.5 g of a yellow amorphous solid.

The solid residue was mixed with H_2O (40 mL) and TFA (1.2 mL), and to the resultant mixture was added a minimum necessary amount of MeOH to afford a homogeneous solution. The solution was transferred onto a HPLPLC chromatography column (i.d. 51 mm) and subjected to gradient elution (40 mL/min) starting with a (30%) methanol−water−(0.1%) TFA mixture (1000 mL) to a (55%) methanol−water−(0.1%) TFA mixture until complete elution of the product. The relevant fractions were concentrated under reduced pressure to remove MeOH, cooled to −60 °C, and lyophilized to afford 1.59 g (31%) of **7** as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+47.5), 238 (−70.8), 265 (+32.0), 304 (−9.5), 355 (+8.9); ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.99 (1H, s), 10.90 (1H, s), 9.31 (1H, br s), 9.17 (s, 1H), 8.72 (1H, br s), 8.70 (1H, s), 8.64 (1H, d, J = 9 Hz), 8.59 (1H, s), 8.56 (1H, s), 8.29 (1H, s), 8.07 (1H, s), 7.95 (1H, s), 9.92 (1H, m), 7.80 (1H, d, J = 8 Hz), 7.42 (2H, m), 7.25 (1H, d, J = 7 Hz), 6.08 (1H, d, J = 12 Hz), 5.79 (2H, m), 5.30 (1H, m), 5.13 (1H, s), 5.10−5.00 (2H, m), 4.85 (1H, d, J = 10 Hz), 4.58 (1H, d, J = 11 Hz), 4.36 (1H, d, J = 10 Hz), 4.32 (1H, m), 4.21 (1H, d, J = 10 Hz), 4.12 (1H, d, J = 10 Hz), 4.05 (2H, m), 3.96 (3H, s), 3.81 (2H, m), 3.77 (2H, m), 3.66 (2H, m), 3.43 (2H, m), 3.22 (2H, m), 3.18 (1H, s), 2.95 (6H, s), 2.50 (1H, m), 2.18 (1H, m), 2.06 (3H, s), 2.02−1.99 (2H, m), 1.66 (3H, s), 1.22 (3H, br s), 0.86 (3H, d, J = 7 Hz); ^{13}C NMR (125 MHz, d_6-DMSO) δ 171.3, 168.0, 167.6, 166.9, 163.4, 163.1, 161.5, 161.0, 160.5, 160.2, 160.2, 158.7, 154.2, 150.5, 149.8, 149.4, 148.6, 145.3, 143.0, 134.8, 134.1, 130.0, 127.7, 127.2, 126.9, 126.1, 125.6, 123.7, 123.7, 123.0, 119.7, 119.2, 113.0, 110.8, 109.3, 94.5, 79.1, 79.0, 70.8, 68.8, 67.5, 66.7, 65.1, 64.4, 63.0, 62.8, 67.5, 66.8, 65.1, 64.4, 63.0, 62.8, 56.0, 55.2, 51.1, 49.9, 49.7, 48.5, 45.6, 43.1, 38.2, 33.3, 30.2, 17.7, 17.4, 12.9; MS (ESI) m/z 1481.7 $[M + H]^+$, 1310.4; HRMS (ESI) m/z 1481.352 (calcd for $C_{64}H_{69}N_{14}O_{18}S_5$ 1481.35179).

The bistrifluoroacetate salt was transformed to the bishydrochloride salt by passing an aqueous solution of **7** through AG 1-X2 resin to afford a quantitative yield of the bis-HCl salt dodecahydrate. Anal. Calcd for $C_{64}H_{94}Cl_2N_{14}O_{30}S_5$: C, 43.07; H, 5.28; N, 11.16; S, 9.13; Cl, 4.04. Found: C, 43.19; H, 5.38; N, 10.97; S, 8.92; Cl, 4.11.

***N*-[Bis-(2-hydroxy-ethyl-amino)-ethyl]-amide 8.** The 2-oxoethyl intermediate **4** was prepared according to the above procedure from nocathiacin IV (**2**) (300 mg, 0.18 mmol) and glycolaldehyde dimer (198 mg, 1.65 mmol). To the resulting mixture were added MeOH (15 mL), AcOH (1.5 mL), diethanolamine (300 μL, 3.10 mmol), and $NaBH_3CN$ (140 mg, 2.22 mmol) in succession. The mixture was stirred for 18 h at room temperature. All volatiles were removed under reduced pressure, and the residue was chromatographed (HPLPLC column i.d. 40 mm) using a gradient elution (20 mL/min) starting with (30%) methanol−water−(0.1%) TFA (400 mL) to (55%) methanol−water−(0.1%) TFA until complete elution of the product to afford 93 mg (30%) of **8** bis-TFA salt as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+32.1), 239 (−51.6), 265 (+23.5), 304 (−5.8), 355 (+6.3); ^{1}H NMR(500 MHz, d_6-DMSO) δ 10.86 (1H, s), 10.77 (1H, s), 9.33 (1H, br s), 9.25 (1H, m), 9.10 (1H, s), 8.65 (1H, s), 8.58 (1H, d, J = 9 Hz), 8.53 (1H, s), 8.52 (1H, s), 8.22 (1H, s), 8.02 (1H, s), 7.89 (1H, s), 7.86 (1H, d, J = 11 Hz), 7.74 (1H, d, J = 8.5 Hz), 7.38−7.34 (2H, m), 7.19 (1H, d, J = 7 Hz), 6.42 (1H, br s), 6.02 (1H, d, J = 12 Hz), 5.75 (1H, dd, J = 4, 11 Hz), 5.71 (1H, d, J = 10 Hz), 5.36 (1H, br s), 5.23 (1H, m), 5.05 (2H, m), 5.00 (1H, d, J = 8 Hz), 4.79 (1H, d, J = 10 Hz), 4.52 (1H, d, J = 11 Hz), 4.30 (1H, d, J = 10 Hz), 4.25 (1H, m), 4.16 (1H, d, J = 10 Hz), 4.06 (1H, d, J = 10 Hz), 3.91 (3H, s), 3.81 (4H, t, J = 5 Hz), 3.72 (2H, m), 3.40 (6H, m), 2.87 (6H, s), 2.50 (1H, m), 2.13−2.11 (1H, m), 2.00 (3H, s), 1.19−1.16 (3H, m), 0.80 (3H, d, J = 7 Hz); MS (ESI) m/z 1499.9 $[M + H]^+$, 1328.5; HRMS (ESI) m/z 1499.360 (calcd for $C_{64}H_{71}N_{14}O_{19}S_5$ 1499.36235).

***N*-[2-(Ethyl-hydroxyethyl-amino)-ethyl]-amide 9.** The procedure was the same as for **8**, using nocathiacin IV (**2**) (300 mg, 0.18 mmol), glycolaldehyde dimer (198 mg, 1.65 mmol), MeOH (15 mL), AcOH (1.5 mL), 2-(ethylamino)ethanol (379 mL, 3.10 mmol), and $NaBH_3CN$ (120 mg, 1.91 mmol); 108 mg (35%) of **9** bis-TFA salt was isolated as a yellow solid: ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.86 (1H, s), 10.76 (1H, s), 9.30 (1H, br s), 9.24 (1H, m), 9.10 (1H, s), 8.66 (1H, s), 8.62−8.56 (2H, m), 8.53 (1H, s), 8.53 (1H, s), 8.22 (1H, s), 8.03 (1H, s), 7.89 (1H, s), 7.86 (1H, d. J = 11 Hz), 7.74 (1H, d, J = 8 Hz), 7.38−7.34 (1H, m), 7.19 (1H, d, J = 8 Hz), 6.41 (1H, br s), 6.03 (1H, d, J = 12 Hz), 5.75 (1H, dd, J = 4, 11 Hz), 5.71 (1H, d, J = 10 Hz), 5.23−5.22 (1H, m), 5.06−5.04 (1H, m), 5.01 (1H, d, J = 8 Hz), 4.78 (1H, d, J = 11 Hz), 4.30 (1H, d, J = 10 Hz), 4.25 (1H, m), 4.15 (1H, d, J = 11 Hz), 4.05 (1H, d, J = 9 Hz), 3.91 (3H, s), 3.86 (1H, m), 3.77 (2H, m), 3.70 (2H, m), 3.29 (6H, m), 2.88 (3H, s), 2.87 (3H, s), 2.50 (1H, m), 2.13−2.10 (1H, m), 1.99 (3H, s), 1.94 (1H, d, J = 14 HZ), 1.60 (3H, s), 1.26 (3H, t, J = 7 Hz), 1.19−1.16 (3H, m), 0.80 (3H, d, J = 7 Hz); MS (ESI) m/z 1483.5 $[M + H]^+$, 1312.7; HRMS (ESI) m/z 1483.367 (calcd for $C_{64}H_{71}N_{14}O_{18}S_5$ 1483.36744).

***N*-{2-[(2-Hydroxy-ethyl)-methyl-amino]-ethyl}-amide 10.** The procedure was the same as for **8**, using nocathiacin IV (**2**) (300 mg, 0.18 mmol), glycolaldehyde dimer (198 mg, 1.65 mmol), MeOH (15 mL), AcOH (1.5 mL), 2-(ethylamino)ethanol (379 μL, 3.10 mmol), and $NaBH_3CN$ (120 mg, 1.91 mmol); 110 mg (36%) of **10** bis-TFA salt was isolated as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+8.1), 238 (−20.2), 267 (+9.2), 305 (−1.2), 355 (+2.5); ^{1}H NMR(500 MHz, d_6-DMSO) δ 10.84 (1H, s), 10.76 (1H, s), 9.39 (1H, br s), 9.21 (1H, br s), 9.10 (1H, s), 8.65 (1H, s), 8.57 (1H, d, J = 8 Hz), 8.52 (s, 1H), 8.51 (s, 1H), 8.21 (1H, s), 8.02 (1H, s), 7.88 (1H, s), 7.85 (1H, d, J = 11 Hz), 7.73 (1H, d, J = 8 Hz), 7.34 (1H, dd, J = 7, 8 Hz), 7.18 (1H, d, J = 7 Hz), 6.37 (1H, br s), 6.01 (1H, d, J = 12 Hz), 5.74 (1H, dd, J = 4, 11 Hz), 5.70 (1H, d, J = 9 Hz), 5.22 (1H, m), 5.05−5.00 (2H, m), 4.78 (1H, d, J = 10 Hz), 4.51 (1H, d, J = 11 Hz), 4.28 (1H, d, J = 10 Hz), 4.22 (1H, m), 4.14 (1H, d, J = 10 Hz), 3.89 (3H, s), 3.75 (2H, m), 3.72 (2H, m), 3.41 (1H, m), 3.31 (1H, m), 3.28 (1H, m), 3.21 (1H, m), 3.11 (1H, s), 2.89 (6H, s), 2.85 (3H, s), 2.49 (1H, m), 2.12 (1H, m), 2.09 (1H, m), 1.98 (3H, s), 1.92 (1H, d, J = 14 Hz), 1.59 (3H, s), 1.15 (3H, br s), 0.79 (3H, d, J = 7 Hz); MS (ESI) m/z 1469.6 $[M + H]^+$, 1298.4; HRMS (ESI) m/z 1469.352 (calcd for $C_{36}H_{69}N_{14}O_{18}S_5$ 1469.35179).

***N*-(2-Diethylamino-ethyl)-amide 11.** The procedure was the same as for **8**, using nocathiacin IV (**2**) (200 mg, 0.12 mmol), glycolaldehyde dimer (100 mg, 1.65 mmol), MeOH (10 mL), AcOH (1.0 mL), Et_2NH (200 μL, 1.93 mmol), and $NaBH_3CN$ (100 mg, 1.59 mmol); 59 mg (29%) of **11** bis-TFA salt was isolated as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+23.8), 238 (−41.1), 265 (+18.5), 304 (−4.2), 355 (+4.7); ^{1}H NMR(500 MHz, d_6-DMSO) δ 10.88 (1H, s), 10.77 (1H,s), 9.30 (1H, m), 9.21 (1H, m), 9.10 (1H, s), 8.66 (1H, s), 8.58 (1H, d, J = 9 Hz), 8.53 (2H, s), 8.22 (1H, s), 8.03 (1H, s), 7.89 (1H, s), 7.86 (1H, d, J = 12 Hz), 7.74 (1H, d, J = 9 Hz), 7.38−7.34 (2H, m), 7.19 (1H, d, J = 7 Hz), 6.41 (1H, br s), 6.03 (1H, d, J = 12 Hz), 5.75 (1H, dd, J = 5, 11 Hz), 5.72 (1H, d, J = 9 Hz), 5.23 (1H, m), 5.07−5.04 (2H, m), 5.00 (1H, d, J = 8 Hz), 4.79 (1H, d, J = 11 Hz), 4.52 (1H, d, J = 11 Hz), 4.30, (1H, d, J = 10 Hz), 4.25 (1H, m), 4.16 (1H, d, J = 10 Hz), 4.06 (1H, d, J = 10 Hz), 3.91 (3H, s), 3.66 (2H, m), 3.31−3.23 (6H, m), 3.12 (1H, s), 2.88 (3H, s), 2.87 (3H, s), 2.50 (1H, m), 2.13−2.11 (1H, m), 2.00 (3H, s), 1.60 (3H, s), 1.23 (6H, t, J = 7 Hz), 1.19−1.11 (3H, m), 0.80 (3H, d, J = 7 Hz); MS (ESI) m/z 1467.5 $[M + H]^+$, 1296.3; HRMS (ESI) m/z 1467.373 (calcd for $C_{64}H_{71}N_{14}O_{17}S_5$ 1467.37253).

***N*-[2-(Carboxymethyl-ethyl-amino)-ethyl]-amide 12.** The procedure was the same as for **8**, using nocathiacin IV (**2**) (300 mg, 0.18 mmol), glycolaldehyde dimer (150 mg, 1.25 mmol),

MeOH (15 mL), AcOH (1.5 mL), *N*-ethylglycine (200 mg, 1.93 mmol), and $NaBH_3CN$ (200 mg, 3.18 mmol); 118 mg (38%) of **12** bis-TFA salt was isolated as a yellow solid: CD λ nm ($\Delta\epsilon$) (MeOH) 212 (+30.2), 238 (−44.7), 265 (+20.5), 304 (−5.2), 355 (+5.3); ^{1}H NMR(500 MHz, d_6-DMSO) δ 10.88 (1H, s), 10.85 (1H,s), 10.80 (1H, s), 9.26 (1H, m), 9.11 (1H, s), 8.65 (1H, s), 8.58 (1H, d, J = 8 Hz), 8.53 (1H, s), 8.52 (1H, s), 8.22 (1H, s), 8.02 (1H, s), 7.89 (1H, s), 7.87 (1H, d, J = 11 Hz), 7.74 (1H, d, J = 10 Hz), 7.36 (2H, m), 7.19 (1H, d, J = 7 Hz), 6.02 (1H, d, J = 12 Hz), 5.75 (1H, dd, J = 4, 11 Hz), 5.71 (1H, d, J = 9 Hz), 5.23 (1H, m), 5.06−5.04 (2H, m), 5.01 (1H, d, J = 8 Hz), 4.79 (1H, d, J = 10 Hz), 4.52 (1H, d, J = 11 Hz), 4.30 (1H, d, J = 10 Hz), 4.25 (1H, m), 4.19 (2H, s), 4.16 (1H, d, J = 10 Hz), 4.05 (1H, d, J = 9 Hz), 3.91 (3H, s), 3.86 (1H, m), 3.70 (2H, m), 3.39 (2H, m), 3.34 (2H, q, J = 7 Hz), 3.12 (1H, s), 2.88 (6H, s), 2.50 (1H, m), 2.1 (1H, m), 2.00 (3H, s), 1.94 (1H, d, J = 14 Hz), 1.60 (3H, s), 1.27 (3H, t, J = 7 Hz), 1.16−1.09 (3H, m), 0.80 (3H, d, J = 7 Hz); MS (ESI) m/z 1498.8 $[M + H]^+$, 1326.5; HRMS (ESI) m/z 1497.345 (calcd for $C_{64}H_{69}N_{14}O_{19}S_5$ 1497.3467).

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Supporting Information Available: Water solubility, minimum inhibitory concentrations (MICs),^{1}H NMR, ^{1}H COSY NMR, CD, and HRMS data of compounds **6**−**12** and additional ^{13}C NMR, HMBC, HMQC data of compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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