JOC*Note*

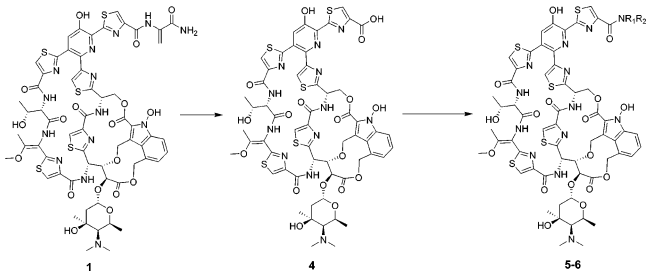
Conversion of Nocathiacin I to Nocathiacin Acid by a Mild and Selective Cleavage of Dehydroalanine

Libo Xu,* Amy K. Farthing, Yao-Jun Shi, Peter T. Meinke, and Kun Liu

Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

libo_xu@merck.com

Received May 25, 2007



Thiazolyl peptide antibiotic nocathiacin I (**1**) was converted to nocathiacin acid (**4**) in high yield by treatment with trifluoroacetic anhydride and pyridine in THF at room temperature. Two equipotent water-soluble amide analogues of nocathiacin I were readily prepared from this important and versatile carboxylic acid intermediate under mild peptide coupling conditions. The present method is useful for chemical derivatization of complex natural products that contain C-terminal dehydroalanine.

Nocathiacins are a group of thiazolyl peptide antibiotics recently discovered and isolated from the fermentation broth of *Norcadia* sp.[1−2] and fungus *Amicolaptosis* sp.[3] Nocathiacin I (**1**), the most abundant member of the family, displays potent in vitro antibacterial activity[4] against a variety of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Enterococcus faecium* (MREF), vancomycin-resistant *Enterococci* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Similar to other thiazolyl peptide antibiotics, nocathiacins function through inhibition of bacterial protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit at the L11 binding domain. Though nocathiacin I exhibits desirable bactericidal activity against *S. aureus* and shows in vivo efficacy in a systemic *S. aureus* infection mouse model,[5] its poor aqueous solubility precludes its development as a hospital *i.v.* drug for serious infections. However, with its novel structure and high intrinsic activity, nocathiacin I provides a promising lead for the development of new antibacterial agents with broad spectrum efficacy against resistant pathogens with minimal risk of cross-resistance to currently marketed agents.

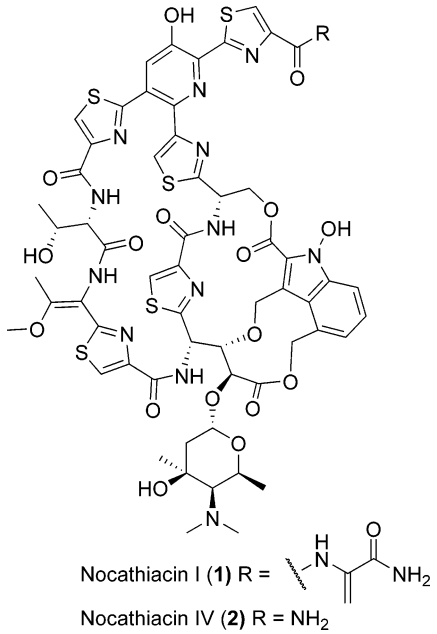


FIGURE 1. Structures of nocathiacins I and IV.

Several approaches have been applied to **1** and its analogues to obtain compounds with increased aqueous solubility.[6−10] As part of our effort to generate water-soluble analogues while maintaining antibacterial activity, we intended to substitute the dehydroalanine side chain with polar, water-solubilizing amides. Although a similar approach has been described in the literature,[8] which involved condensation of nocathiacin IV (**2**) with glycoaldehyde and reductive amination of the Amadori rearranged intermediate, products from this sequence of transforma-

(1) Li, W.; Leet, J. E.; Ax, H. A.; Gustavson, D. R.; Brown, D. M.; Turner, L.; Brown, K.; Clark, J.; Yang, H.; Fung-Tomc, J.; Lam, K. S. *J. Antibiot*. **2003**, *56*, 226−231.

(2) Leet, J. E.; Li, W.; Ax, H. A.; Matson, J. A.; Huang, S.; Huang, R.; Cantone, J. L.; Drexler, D.; Dalterio, R.; Lam, K. S. *J. Antibiot*. **2003**, *56*, 232−242.

(3) Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. *J. Antibiot.* **1998**, *51*, 715−721.

(4) Pucci, M. J.; Bronson, J. J.; Barrett, J. F.; DenBleyker, K. L.; Discotto, L. F.; Fung-Tomc, J. C.; Ueda, Y. *Antimicrob. Agents Chemother*. **2004**, *48*, 3697−3701.

(5) Yang, H.; Chaniewski, S.; Clark, J.; Ferraro, C.; Gali, V.; Lamb, L.; Medina, I. *Abstracts of Papers*, 43rd Annual ICAAC Meeting, Chicago, IL, Sept 14−17; American Society for Microbiology: Washington, DC, 2003; B-319.

(6) Regueiro-Ren, A.; Naidu, B. N.; Zheng, X.; Hudyma, T. W.; Connolly, T. P.; Matiskella, J. D.; Zhang, Y.; Kim, O. K.; Sorenson, M. E.; Pucci, M.; Clark, J.; Bronson, J. J.; Ueda, Y. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 171−175.

(7) Naidu, B. N.; Sorenson, M. E.; Zhang, Y.; Kim, O. K.; Matiskella, J. D.; Wichtowski, J. A.; Connolly, T. P.; Li, W.; Lam, K. S.; Bronson, J. J.; Pucci, M. J.; Clark, J. M.; Ueda, Y. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 5573−5577.

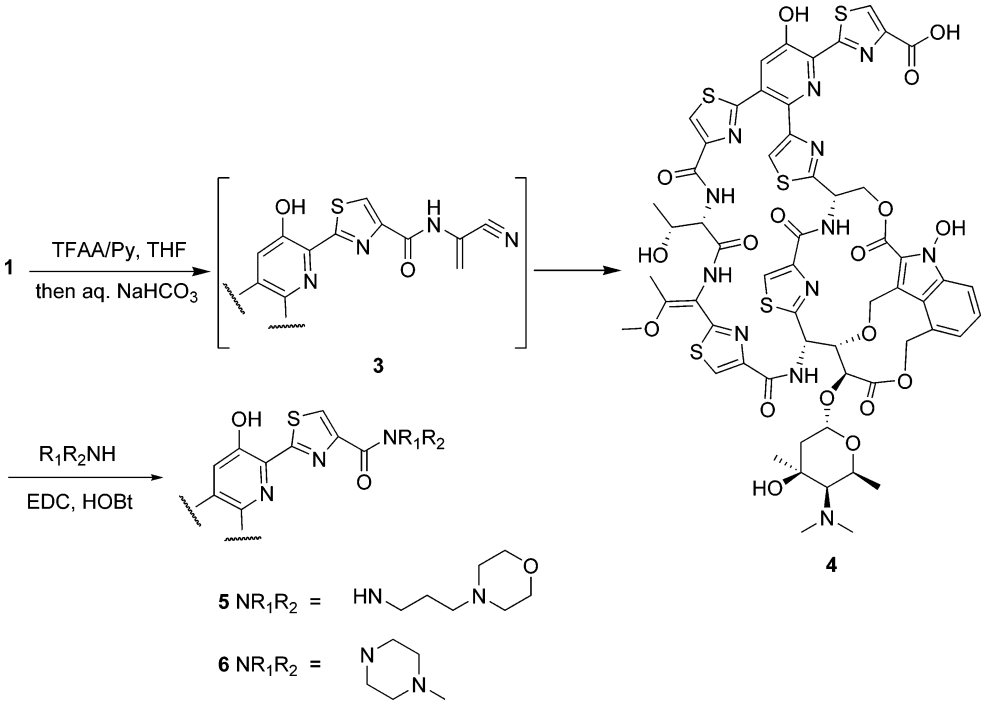
(8) Hrnciar, P.; Ueda, Y.; Huang, S.; Leet, J. E.; Bronson, J. J. *J. Org. Chem*. **2002**, *67*, 8789−8793.

(9) Naidu, B. N.; Sorenson, M. E.; Matiskella, J. D.; Wichtowski, J. A.; Li, W.; Sauaker, J. B.; Zhang, Y.; Connolly, T. P.; Lam, K. S.; Bronson, J. J.; Pucci, M. J.; Yang, H.; Ueda, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3545−3549.

(10) Naidu, B. N.; Li, W.; Sorenson, M. E.; Connolly, T. P.; Wichtowski, J. A.; Zhang, Y.; Kim, O. K.; Matiskella, J. D.; Lam, K. S.; Bronson, J. J.; Ueda, Y. *Tetrahedron Lett.* **2004**, *45*, 1059−1063.

10.1021/jo071115p CCC: $37.00
Published on Web 08/18/2007

SCHEME 1. Conversion of 1 to 4 and Synthesis of Water-Soluble Amides 5 and 6



tions are limited to only aminoethyl amides. Other literature precedents on chemical modifications of the dehydroalanine unit of **1** also suffer from lengthy sequence or limited scope of structural features that can be installed.[9,10] We envisioned a more straightforward strategy that involves the formation of carboxylic acid **4**, which can serve as a versatile intermediate to be transformed to a variety of amide analogues under mild and selective peptide coupling conditions.

The complex structure and chemical instability of nocathiacins present a formidable challenge for their synthetic modifications. Similar to the disappointing results reported in the literature,[8] our initial attempts to cleave the dehydroalanine moiety directly from **1** or hydrolyze the primary amide bond in **2** failed. Instead of the desired carboxylic acid **4**, complete decomposition of nocathiacin I or IV was observed under a variety of mild amide bond cleavage conditions, including acidic, basic, and oxidative conditions.[11−17] It became clear that a novel and mild method would need to be developed to achieve the desired transformation from **1** to **4**.

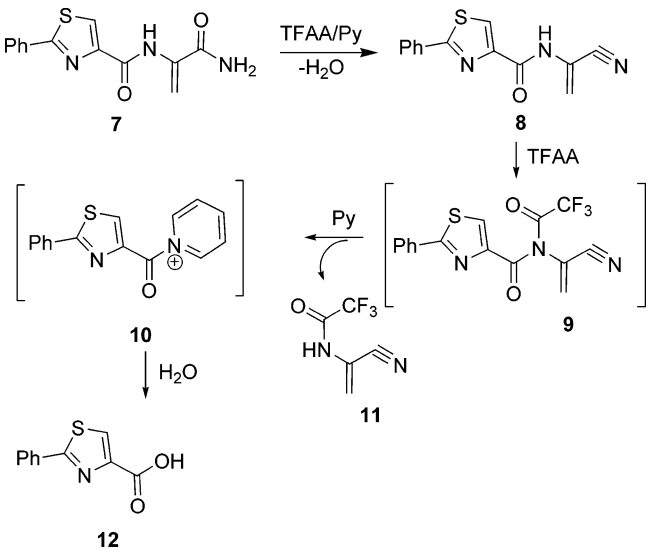
We first observed the formation of nocathiacin acid **4** in trace amount during the synthesis of nitrile **3** by treatment of **1** with trifluoroacetic anhydride (TFAA) in pyridine. After carefully monitoring the reaction process and surveying different reaction conditions, we discovered that **4** can be formed as the major product by reacting **1** with excess TFAA and pyridine in THF or acetonitrile at room temperature, followed by quenching with water (Scheme 1). LC-MS analyses of the reaction mixture revealed that under these conditions, **1** is first converted to **3**, which is then gradually transformed to **4.** The reaction can be stopped at the nitrile stage by using less TFAA or running the reaction at 0 °C. When isolated **3** was subjected to the same reaction conditions (TFAA and pyridine in THF), it was smoothly transformed to **4**. Under optimal conditions (5 equiv of TFAA, 10 equiv of pyridine, 0.01−0.1 M concentration), **4** was formed almost quantitatively by LC-MS and isolated in 50−80% yield by preparative HPLC.

It should be noted that acid **4** formed in the reaction was mono-trifluoroacetylated based on LC-MS analysis. However, the trifluoroacetyl group can be easily removed with aqueous sodium bicarbonate or under other mild hydrolytic conditions. The precise point of acylation was not established, but preliminary studies exclude the indole N-OH, pyridyl OH, or sugar OH as the acylation site because both dimethyl nocathiacin I,[6] which lacks indole N-OH and pyridyl OH, and thiazomycin,[18] which lacks the sugar OH, form mono-trifluoroacetylated acid upon treatment with TFAA/pyridine.

Mechanistic studies of the newly discovered transformation using **1** were complicated by its complex structure and limited supply, therefore a model compound (**7**) bearing the dehydroalanine unit was synthesized. Compound **7** was prepared in three steps from known *N*-(*tert*-butoxycarbonyl)-L-(Se)-phenylselenocysteine[19] by the method developed by van der Donk in which the dehydroalanine unit was formed by oxidative elimination of phenylselenocysteine. When compound **7** was

(11) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.
(12) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1569−1572.
(13) Gassman, P. G.; Hodgwon, P. K. G.; Balcunis, R. J. *J. Am. Chem. Soc*. **1976**, *98*, 1275−1276.
(14) Pascal, R.; Sola, R. *Tetrahedron Lett.* **1998**, *39*, 5031−5034.
(15) Tsunoda, T.; Sasaki, O.; Itô, S. *Tetrahedron Lett.* **1990**, *31*, 731−734.
(16) Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263−4266.
(17) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535−4538.
(18) Jayasuriya, H.; Herath, K.; Ondeyka, J. G.; Zhang, C.; Zink, D. L.; Brower, M.; Gailliot, F. P.; Greene, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Russotti, G.; Walker, A.; Hesse, M.; Seeley, A.; Junker, B.; Connors, N.; Salazar, O.; Genilloud, O.; Liu, K.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Antibiot*. Submitted for publication.
(19) Okeley, N. M.; Zhu, Y.; van der Donk, W. A. *Org. Lett*. **2000**, *2*, 3603−3606.

SCHEME 2. Proposed Mechanism for Dehydroalanine Cleavage



treated with excess TFAA/pyridine in THF, immediate formation of nitrile **8** was observed, and the corresponding acid **12** was formed quantitatively within 2 h upon quenching with water. In the absence of pyridine, nitrile **8** was still formed after the addition of TFAA, but no acid formation was detected even after 24 h. Substituting pyridine with *N*,*N*-diisopropylethylamine also resulted in complete conversion of **7** to **8**, but again no acid formation was observed. Thus it seems that pyridine is mechanistically involved in the transformation. We postulate that the reaction proceeds through *N*-acylation of **8** to form the reactive intermediate **9**, followed by nucleophilic attack by pyridine to generate the acyl pyridinium species **10** (Scheme 2), which yields acid **12** upon quenching with water. If the reaction mixture is quenched with methanol instead, the corresponding methyl ester is formed, presumably through the same reactive intermediate **10**. To further support the above mechanistic hypothesis, acrylonitrile **11** was isolated from the reaction mixture and its structure was confirmed by spectroscopic analyses. A brief survey of the same reaction on structurally related substrates suggests that this reaction is specific for the degradative cleavage of dehydroalanine amides or esters. The corresponding saturated compound containing alanine did not yield any 2-phenyl-1,3-thiazo-4-carboxylic acid (**12**) under the same conditions.

To demonstrate the synthetic utility of this important intermediate, carboxylic acid **4** was converted under mild and selective conditions to a variety of amide and ester derivatives containing various water-solubilizing groups, as exemplified by **5** and **6** (Scheme 1). Standard peptide coupling reactions (PyBop or EDC/HOBt in DMF) between **4** and *N*-(3-aminopropyl)-morpholine or 1-methylpiperazine afforded amides **5** and **6**, respectively, in good isolated yield.[20] Both **5** and **6** retained potent antibacterial activity and showed much improved solubility relative to nocathiacin I at acidic pH. The solubility of these two compounds as their TFA salts is greater than 10 mg/mL in water containing 5% dextrose with a pH of 4.0. The in vitro antibacterial activity of **5** and **6** is comparable to that of **1**, with the minimum inhibitory concentrations (MICs) against *S. aureus* of 0.0075 and 0.06 μg/mL, respectively. In comparison, **1** shows solubility of 0.34 mg/mL at pH 4.0 and MIC against *S. aureus* of 0.007 μg/mL.[8]

In summary, we have developed a mild and efficient method to convert thiazolyl peptide antibiotic **1** to nocathiacin acid (**4**) through a facile cleavage of dehydroalanine using trifluoroacetic anhydride and pyridine in THF. We also demonstrated the synthetic utility of this highly desirable intermediate by the convenient synthesis of two novel water-soluble amide analogues (**5** and **6**) of nocathiacin I in good yields. More synthetic applications of **4** in the preparation of water-soluble amides, esters, thioesters, and their biological activities will be the subject of a separate publication. The C-terminal dehydroalanine motif is found in a number of natural products, such as nosiheptide, glycothiohexide, siomycins, sulfomycins, promothiocin,[21−24] and thiazomycin.[18] The method described herein was already successfully applied to thiazomycin, a new member of the nocathiacin family, and generated many useful analogues (data not shown). It can potentially be applied to other antibiotics mentioned above and facilitate their derivitization under mild conditions compatible with their structural complexity and chemical sensitivity.

Experimental Section

Nocathiacin Acid (4). To a solution of nocathiacin I (**1**, 100 mg, 0.07 mmol) in tetrahydrofuran (4 mL) at 0 °C was added pyridine (0.11 mL, 1.4 mmol) and trifluoroacetic anhydride (0.1 mL, 0.7 mmol) slowly. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 6 h. A second portion of pyridine (0.05 mL) and TFAA (0.05 mL) were added, and after 4 h the reaction was quenched by addition of a small amount of water while being kept in an ice bath and stirred for 30 min at room temperature. It was then concentrated until solid started to precipitate out. More water was added and the solid was collected by filtration. After being washed with water, the solid was dissolved in methanol/chloroform and evaporated repeatedly until dry. The crude acid product was obtained as an orange crystalline solid (100 mg). LC-MS analysis indicated that this material consisted of approximately 80% of 1:1 mixture of **4** and trifluoroacetylated **4**, and can be used satisfactorily in the subsequent coupling reactions without further purification. For characterization, this material was treated with saturated sodium bicarbonate solution and purified by reversed-phase HPLC with a 10−50% B gradient. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s. 1H), 10.77 (s, 1H), 9.10 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.57 (m, 2H), 8.54 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H) (d, 1H, J = 9.5 Hz), 7.90 (s, 1H), 7.86 (d, 1H, J = 11.5 Hz), 7.75 (d, 1H, J = 8.5 Hz), 7.38 (m, 2H), 7.20 (d, 1H, J = 7 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.76 (dd, 1H, J = 11.0 and 4.5 Hz), 5.72 (d, 1H, J = 9.5 Hz), 5.24 (dd, 1H, J = 11.0 and 4.5 Hz), 5.06 (m, 2H), 5.00 (d, 1H, J = 8.0 Hz), 4.80 (d, 1H, J = 10.5 Hz), 4.54 (d, 1H, J = 11.0 Hz), 4.30 (d, 1H, J = 9.5 Hz), 4.26 (m, 1H), 4.16 (d, 1H, J = 10.5 Hz), 4.05 (d, 1H, J = 8.0 Hz), 3.92 (s, 3H), 3.13 (s, br, 1H), 2.89 (s, 3H), 2.87 (s, 3H), 2.13 (m, 1H), 2.01 (s, 3H), 1.95 (d, 1H, J = 14.5 Hz), 1.61 (s, 3H), 1.57 (s, br, 3H), 0.81 (d, 3H, J = 6.5 Hz).

(20) The coupling reactions with EDC/HOBt or PyBop converted nocathiacin acid **4** to amide analogues quantitatively as analyzed by LC-MS, but isolated yields after reversed-phase HPLC purification typically fell between 50% and 80%.

(21) Pascard, C.; Ducruix, A.; Lunel, J.; Prangé, T. *J. Am. Chem. Soc.* **1977**, *99*, 6418−6423.
(22) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685−714.
(23) Northcote, P. T.; Siegel, M.; Borders, D. B.; Lee, M. D. *J. Antibiot.* **1994**, *47*, 901−908.
(24) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301−3313.

^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 168.8, 168.4, 167.6, 164.3, 163.9, 162.3, 161.9, 161.7, 161.2, 160.9, 159.6, 159.9 (q, J = 96.5 Hz, TFA), 154.9, 152.2, 150.2, 149.4, 147.4, 146.2, 143.9, 135.6, 134.9, 131.1, 130.9, 128.6, 127.6, 127.1, 126.9, 126.4, 126.3, 124.6, 123.8, 120.6, 120.0, 113.4, 111.8, 110.2, 95.3, 79.8, 71.7, 69.7, 68.3, 67.1, 65.8, 65.2, 63.9, 63.5, 56.8, 56.1, 50.6, 50.5, 47.1, 43.0, 38.9, 30.8, 23.2, 18.6, 18.0, 13.7. HRMS-TOF (*m/z*) [M + H]$^+$ calcd for $C_{58}H_{56}N_{12}O_{18}S_5$ 1369.252, found 1369.258.

***N*-(3-Morpholin-4-yl-propyl)amide 5.** Compound **4** (30 mg, 0.016 mmol) was mixed with *N*-(3-aminopropyl)morpholine (3.5 mg, 0.024 mmol), 1-hydroxybenzotriazole (3.1 mg, 0.020 mmol), and EDC (5.8 mg, 0.03 mmol) in anhydrous DMF (0.4 mL). After 1 h, the reaction mixture was directly purified by reversed-phase HPLC with a gradient of 5−45% B. Compound **5** was obtained as a light yellow solid after lyophilization (TFA salt, 12.5 mg, 49% yield). ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.62 (d, 1H, J = 9.5 Hz), 8.56 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 8.14 (d, 1H, J = 11.0 Hz), 7.88 (s, 1H), 7.86 (d, 1H, J = 7.0 Hz), 7.84 (m, 2H), 7.43 (t, 1H, J = 8.0 Hz), 7.22 (d, 1H, J = 7.0 Hz), 6.13 (d, 1H, J = 13.0 Hz), 5.91 (dd, 1H, J = 9.5 and 2.0 Hz), 5.78 (dd, 1H, J = 11.0 and 5.0 Hz), 5.39 (dd, 1H, J = 11.3 and 5.3 Hz), 5.21 (m, 1H), 5.06 (d, 1H, J = 12.5 Hz), 4.96 (d, 1H, J = 10.5 Hz), 4.59 (d, 1H, J = 11.5 Hz), 4.42 (d, 1H, J = 10.0 Hz), 4.37 (m, 1H), 4.29 (d, 1H, J = 10.5 Hz), 4.05−4.18 (m, 4H), 3.96 (s, 3H), 3.80 (m, 2H), 3.53−3.60 (m, 4H), 3.29 (t, 2H, J = 7.8 Hz), 3.12−3.22 (m, 3H), 3.03 (s, 6H), 2.80 (m, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.75 (s, 3H), 1.42 (d, 3H, J = 6.0 Hz), 1.00 (d, 3H, J = 7.0 Hz). HRMS-TOF (*m/z*) ([M + 2H]/2)$^+$ calcd for $C_{65}H_{70}N_{14}O_{18}S_5$ 748.187, found 748.189.

4-Methylpiperazin-1-ylamide 6. Compound **4** (30 mg, 0.016 mmol) was mixed with 1-methylpiperazine (2.4 mg, 0.024 mmol), 1-hydroxybenzotriazole (3.1 mg, 0.020 mmol), and EDC (5.8 mg, 0.03 mmol) in anhydrous DMF (0.4 mL) and the mixture was stirred at room temperature for 1 h. Purification by reversed-phase HPLC with a gradient of 10−30% B afforded compound **6** as a light yellow solid after lyophilization (TFA salt, 12 mg, 50% yield). ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.64 (d, J = 9.3 Hz, 1 H), 8.59 (s, 1 H), 8.44 (s, 1 H), 8.29 (s, 1 H), 8.20 (s, 1 H), 8.16 (d, J = 11.0 Hz, 1 H), 7.91−7.83 (m, 4 H), 7.45 (t, J = 7.7 Hz, 1 H), 7.25 (d, J = 7.0 Hz, 1 H), 6.16 (d, J = 12.5 Hz, 1 H), 5.92 (d, J = 9.4 Hz, 1 H), 5.79 (dd, J = 4.8, 10.9 Hz, 1 H), 5.40 (dd, J = 5.1, 11.4 Hz, 1 H), 5.23 (s, 1 H), 5.08 (d, J = 12.6 Hz, 1 H), 4.98 (d, J = 10.5 Hz, 1 H), 4.61 (d, J = 11.3 Hz, 1 H), 4.43 (d, J = 9.7 Hz, 1 H), 4.38 (dd, J = 4.4, 6.7 Hz, 1 H), 4.32 (d, J = 10.6 Hz, 1 H), 4.16 (q, J = 7.0 Hz, 1 H), 4.08 (d, J = 9.6 Hz, 1 H), 3.97 (s, 3 H), 3.35 (m, 2 H), 3.22 (s, 1 H), 3.04 (s, 6 H), 2.96 (s, 3 H), 2.82 (m, 1 H), 2.18 (s, 2 H), 2.07 (s, 3 H), 1.77 (s, 3 H), 1.43 (d, J = 6.1 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H). HRMS-TOF (*m/z*) ([M + 2H]/2)$^+$ calcd for $C_{63}H_{66}N_{14}O_{17}S_5$ 726.174, found 726.177.

***N*-(2-Phenyl-1,3-thiazo-2-lyl)carbonyl aminoacrylamide (7).** To a solution of *N*-(*tert*-butoxycarbonyl)-L-(Se)-phenylselenocysteine[19] (5.6 g, 16.2 mmol) in THF (125 mL) at −15 °C was added *N*-methylmorpholine (1.8 mL, 16 mmol) and ethylchloroformate (1.55 mL, 16.2 mmol). After 20 min aqueous NH_4OH (3.4 mL, 48 mmol) was added to solution, and the mixture was allowed to warm up to room temperature. The residue was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. Recrystallization from ethyl acetate/hexanes afforded *N*-(*tert*-butoxycarbonyl)-L-(Se)-phenylselenocysteine amide as a white solid (4.11 g, 74% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ) 7.60 (dd, J = 3.6, 7.1 Hz, 2 H), 7.32 (m, 3 H), 6.26 (s, 1 H), 5.48 (s, 1 H), 5.28 (s, 1 H), 4.40 (s, 1 H), 3.35 (s, 1 H), 3.26 (dd, J = 5.8, 12.2 Hz, 1 H), 1.47 (s, 12 H). LC-MS (ESI) *m/z* 344.9 (M + 1).

The TFA salt of L-(Se)-phenylselenocysteine amide (3 g, 12.3 mmol) obtained after deprotection with 1:1 TFA/CH_2Cl_2 was coupled to 2-phenyl-1,3-thiazo-4-carboxylic acid (2.4 g, 11.7 mmol) in DMF (50 mL) under peptide coupling conditions with EDC (4.49 g, 23.4 mmol) and HOBt (158 mg, 1.17 mmol). After being stirred at room temperature for 3 h, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (15−80% EtOAc/hexanes) yielded the *N*-(2-phenyl-1,3-thiazo-2-lyl)carbonyl-Se-phenylselenocysteine amide (4.64 g, 92% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (d, J = 8.3 Hz, 1 H), 8.32 (s, 1 H), 8.03−8.01 (m, 2 H), 7.66 (s, 1 H), 7.57−7.54 (m, 3 H), 7.50 (t, J = 4.2 Hz, 2 H), 7.33 (s, 1 H), 7.23−7.15 (m, 3 H), 4.74−4.70 (m, 1 H), 3.47 (dd, J = 4.9, 12.4 Hz, 1 H), 3.38 (dd, J = 8.0, 12.5 Hz, 1 H). LC-MS (ESI) *m/z* 431.8 (M + 1).

Finally, oxidative elimination was carried out by adding an aqueous solution of sodium periodate (9.05 g, 42.3 mmol) to a THF (100 mL) solution of *N*-(2-phenyl-1,3-thiazo-2-lyl)carbonyl-Se-phenylselenocysteine amide (4.55 g, 10.6 mmol) at room temperature. After the mixture was stirred for 3 h, precipitate was collected by filtration and washed with 1:1 THF/water and dried in vacuo to give *N*-(2-phenyl-1,3-thiazo-2-lyl)carbonylaminoacrylamide (**7**) as a white solid (3.0 g, 73% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1 H), 8.48 (s, 1 H), 8.15 (s, 1 H), 8.00 (dd, J = 7.2 Hz, 2 H), 7.66 (s, 1 H), 7.57 (m, 3 H), 6.50 (s, 1 H), 5.77 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.4, 165.6, 159.3, 134.5, 132.7, 131.7, 127.0, 126.2, 103.0. HRMS-TOF (*m/z*) [M + H]$^+$ calcd for $C_{13}H_{11}N_3O_2S$ 274.065, found 274.067.

Acknowledgment. We thank Dr. Bernard C. Choi for performing HRMS analyses, and Fermentation Development & Operations and Biopurification Development for the supply of nocathiacin I and thiazomycin.

Supporting Information Available: Experimental conditions for the synthesis and isolation of compounds **8**, **11**, and **12**, copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra for compounds **4**, **7**, **8**, and **11**, and ^{1}H NMR and HRMS spectra for compounds **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071115P