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Mild Method for Cleavage of Dehydroalanine Units: Highly Efficient Conversion of Nocathiacin I to Nocathiacin IV

Alicia Regueiro-Ren* and Yasutsugu Ueda

The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492

alicia.regueiroren@bms.com

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Abstract: Thiazolyl peptide antibacterial nocathiacin I (**1**) was converted to nocathiacin IV (**4**) in high yield using iodomethane and hydriodic acid in THF at 45 °C. Several simplified dehydroalanine-containing systems undergo dehydroalanine cleavage under the same conditions, although in these cases iodomethane is not needed for efficient conversion. The mild reaction conditions are in contrast with other methods described in the literature.

Resistance developed by pathogenic bacteria against antimicrobial agents has increased worldwide at an alarming rate, threatening the clinical usefulness of a number of existing antibacterial agents.[1] Reports describing methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) highlight the need for alternative antibacterial agents that retain activity against resistant strains.[2]

Nocathiacins[3,4] are a new group of thiazolyl peptide antibiotics isolated from fermentation of *Nocardia* spp.[3] or a fungus *Amicolaptosis sp.*[4] (Figure 1). Nocathiacin I[5] (**1**) has shown high in vitro potency against a variety of Gram-positive bacteria, including multiple resistant strains such as MRSA, VRE, and PRSP. More importantly, nocathiacin I shows in vivo efficacy in a systemic *Staphylococcus aureus* infection model in mice.[3a] In addition, it appears to be more soluble at low pH than other thiazolyl peptides such as thiostrepton and nosiheptide.[6] However, its aqueous solubility is not sufficient for development as an intravenous agent. As a part of our efforts to develop new antibacterial agents, we set out to investigate modifications of this class of compounds which would maintain the biological activity of nocathiacins while increasing their water solubility. One of our approaches is the introduction of water-solubilizing groups in amide **4**,[7] which lacks the dehydroalanine unit of the side chain present in **1**. Although nocathiacin IV was originally obtained from nocathiacin I enzymatically,[8] an alternative and complementary chemical method which could supply large amounts of **4** more efficiently would be preferable. In this paper, we described a novel and highly efficient chemical method for converting nocathiacin I (**1**) to nocathiathin IV (**4**) by selective cleavage of the dehydroalanine unit.

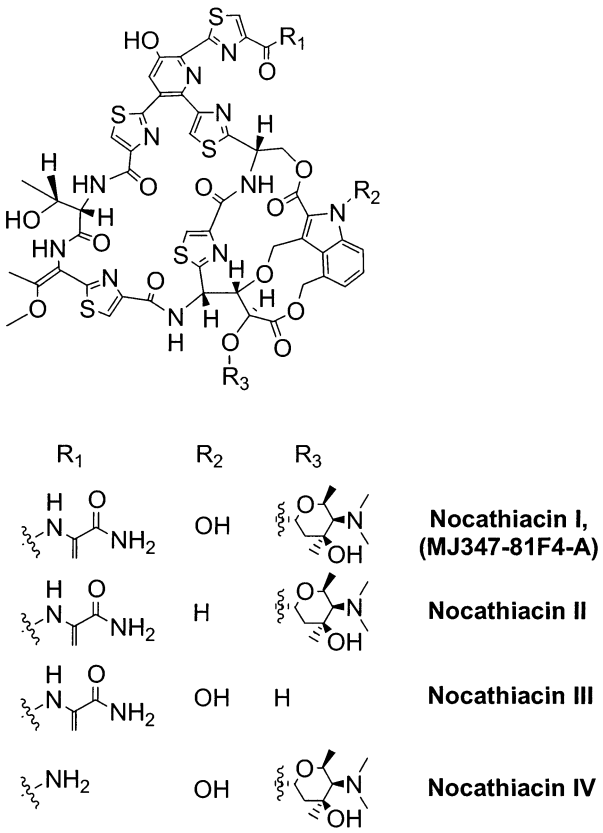

FIGURE 1. Structures of nocathiacins.

α,β-Dehydroamino acids, and specifically α,β-dehydroalanine, are constituents of a variety of naturally occurring antibiotic and phytotoxic peptides including the lantibiotics nisin, subtilin, and epidermin and other highly modified peptides such as thiostrepton, nosiheptide, and berninamycin.[9] Several methods have been reported for the degradation of peptides and other molecules containing dehydroalanine moieties.[10] All of

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(5) For stereochemical assignment, see: Konstantine, K. L.; Mueller, L.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 7284.

(6) The presence of an amino sugar moiety in nocathiacins may contribute to the improved solubility when compared with other thiazolyl peptides.

(7) Hrnciar, P.; Ueda, Y.; Huang, S.; Leet, J. E.; Bronson, J. J. Submitted for publication.

(8) (a) Li, W.; Leet, J.; Huang, X.; Lam, K. S.; Regueiro-Ren, A. PCT Int. Appl. WO0213834, 2002. (b) Li, W.; Leet, J. E.; Ax, H. A.; Gustavson, D. R.; Brown, D. M.; Turner, L.; Brown, K.; Clark, J.; Yang H.; Lam, K. S. Manuscript in preparation.

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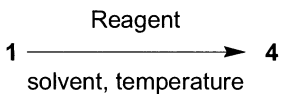
TABLE 1. Conversion of Nocathiacin I (1) to Nocathiacin IV (4)[a]



entry	reagent	solvent	T (°C)	t (h)	**4** (%)	**1** (%)
1	I_2[b]	DMF	0−25	24		
2	I_2[b]	THF/H_2O	0−25	24	20[g]	55[g]
3	HI[c]	DMF	25	3	20−40[h]	
4	HI/MeI[d]	DMF	45	5	60[g]	30[g]
5	HI /MeI[d]	THF	45	3	86−90[h]	
6	MeI[e]	THF	75	24		99[h]
7	HI[f]	THF	25	24	40[h]	

[a] Reaction conditions: In a sealed tube, 1 mmol of **1** in 4 mL of THF was treated with the corresponding reagents and heated at the temperature and for the period of time indicated. [b] 6 mmol. [c] 2−5 mmol. [d] 2 mmol of HI/ 10 mmol of MeI. [e] 10 mmol. [f] 2 mmol. [g] HPLC ratios. [h] Isolated yields.

them involved relatively harsh conditions such as elevated temperatures and strongly acidic, basic, or oxidative reaction media (e.g., aq HCl, 100 °C; H_2O, 100 °C; I_2, NaOH; aq Br_2; HCHO, H_2O_2).[11] When applied to nocathiacin I, none of these methods afforded **4** in a practical manner; instead total destruction of the natural product occurred. Nocathiacin I (**1**) contains, among other features, a tricyclic skeleton attached by two labile lactone moieties, a vinyl ether, and a dimethylamino sugar, all of which may not survive under severe reaction conditions.[12] Therefore, it was clear that new reaction conditions needed to be developed in order to achieve the desired transformation from **1** to **4** in a useful manner.

We initially observed the conversion of **1** to **4**[13] in 56% yield upon treating **1** with iodomethane in DMF at 75 °C for 12 h in a sealed tube. However, there were still a few problems with the reproducibility of these reaction conditions. Prolonged reaction times and exposure to open air produced many other degradation products. Large amounts of iodomethane (40 equiv) were also needed for completion, and the use of different batches of reagent led to variable yield.

We contemplated the idea that the active reagent responsible for the transformation from **1** to **4** may not be iodomethane but rather some impurities present in this reagent or other entities generated in the process. Iodomethane is often an unstable chemical entity and needs to be stabilized using, for example, copper wire.[14] We decided to explore this hypothesis further and treat **1** with iodine or hydriodic acid.[15] The results are summarized in Table 1.

Iodine in DMF produced only decomposition of the starting material (entry 1) while with iodine in THF no reaction was observed until H_2O was added. Thus, **4** was formed in 20% yield and an equal amount of an iodohydrin (detected by LC/MS $[M + 1]^+ = 1581$)[16] was also produced, although most of the starting material remained unreacted (entry 2). Higher reaction temperatures or addition of more iodine yielded a complex mixture.

Hydriodic acid (57% in water) in DMF afforded 20−40% of **4** and 5−40% of a hydrolysis product resulting from opening of one of the lactones (detected by LC/MS $[M + 1]^+ = 1455$) (entry 3). When iodomethane was used in combination with HI at 45 °C (entry 4), **4** was obtained in 60% yield but the reaction could not be driven to completion without increasing the amount of open lactone side products. Acetonitrile, MeOH, or dioxane as the reaction solvent produced similar results. However, the use of THF as the solvent afforded a dramatic improvement in product yields. Complete conversion to **4** was achieved (entry 5) while no undesired hydrolysis product was detected. Also, the transformation occurred smoothly at a lower reaction temperature and much more rapidly.[17] Iodomethane alone in THF was not effective (entry 6). HI in THF afforded **4** in 40% yield with 50−60% of the hydrolysis product (entry 7). Several other acids, i.e., HCl, HBr, and HOAc, were screened using similar experimental conditions described above and were found to produce only trace amounts of **4**. In most cases, complex mixtures of many products were detected.

The optimal results were obtained when **1** was suspended in THF and treated with 7−10 equiv of MeI and 1.8−3 equiv of HI at 45 °C for 1−5 h.

To study the scope and limitations of this reaction, we applied the conditions to a few model compounds containing terminal dehydroalanine units, **5**−**7** (Table 2). In a typical experiment, 1 mmol of starting material was dissolved in 4 mL of THF and heated at 45 °C in a sealed tube with 2 mmol of HI and 10 mmol of MeI for 1 h. In all cases, the dehydroalanine moiety was cleaved readily and the desired products were isolated in good yields (entries 2, 5, and 8). When iodomethane (10 mmol) was used in the absence of HI, no reaction was observed, even after 24 h at 75 °C (entries 1, 4, and 7). In contrast, for these simple substrates hydriodic acid (2 mmol) alone produced results similar to those when the mixture of MeI/HI was used (entries 3, 6, and 9). Hydriodic acid in THF at 45 °C may be an alternative to the use of excess aqueous HCl solution at 100 °C in thoses cases where the compounds are insoluble in aqueous solution or unstable under these conditions.

A terminal tyramine amide was incorporated in one of the substrates **7** with the purpose of visualizing both cleaved moieties resulting from the reaction (entries 8 and 9). Along with the expected des-dehydroalanine amide, tyramine pyruvate **8** was isolated in both cases, suggesting a hydrolysis mechanism for this reaction where the MeI may not be involved (Scheme 1). In the presence of acid, the enamide can equilibrate to the iminium form, which is then attacked by water to produce

(10) (a) Bergman, M.; Grafe, K. *Z. Physiol. Chem.* **1930**, 187. (b) Patchornik, A.; Sokolowsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1206.

(11) The peptides where these conditions were successfully used were simple synthetic dipeptides (see ref 10). To the best of our knowledge, there is no report about their use in natural or structurally more complex peptides.

(12) Oxidation of the dimethylamino sugar, cleavage of the sugar moiety, and lactone opening are among the side reactions observed.

(13) The synthetic product was found to be identical to a sample of nocathiacin IV obtained by enzymatic cleavage of **1**.

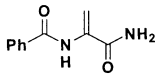
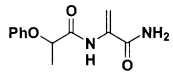
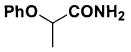
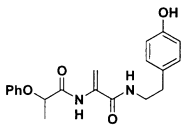
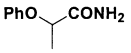
(14) Sulikowski, G. A.; Sulikowski, M. M. In *Encyclopedia of the Reagents*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 4, p 2828.

(15) HI may be present by reaction of MeI with H_2O.

(16) Iodohydrin can be formed by H_2O attack to an iodonium intermediate from reaction between iodine and the olefin of the dehydroalanine moiety.

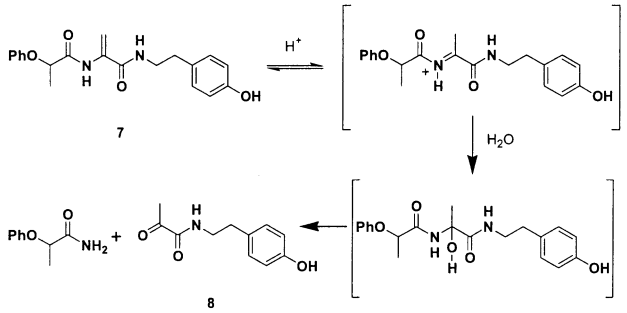
(17) Reaction time was reduced from >12 h to 1 h in small scale (<1.0 g) and 3−5 h for larger scale (1−10 g).

TABLE 2. Dehydroalanine Cleavage of Simplified Systems[a]

entry	reagents	compound	T (°C)	time (h)	product	yields[e]
1	MeI[b]		75	24		-
2	MeI/HI[c]		45	1	$PhCONH_2$	82
3	HI[d]	**5**	45	1		84
4	MeI[b]		75	24		-
5	MeI/HI[c]		45	1		85
6	HI[d]	**6**	45	1		80
7	MeI[b]		75	24		-
8	MeI/HI[c]		45	1		80
9	HI[d]	**7**	45	1		83

[a] Reaction conditions: In a sealed tube, 1 mmol of compound in 4 mL of THF was treated with the corresponding reagents and heated at the temperature and for the period of time indicated. [b] 10 mmol. [c] 10 mmol of MeI/2 mmol of HI. [d] 2 mmol. [e] Isolated yields.

SCHEME 1. Proposed Mechanism for Dehydroalanine Cleavage



the corresponding truncated amide and tyramine pyruvate **8**.

In summary, a practical and efficient conversion of antibacterial nocathiacin I (**1**) to nocathiacin IV (**4**) has been developed. Cleavage of the dehydroalanine unit present in **1** is achieved by using a mixture of iodomethane and hydriodic acid in THF at 45 °C. The conditions are useful also for the cleavage of dehydroalanine units in simple substrates although in these cases iodomethane is not required. This mild method represent a convenient alternative to other processes published in the literature which usually employ harsh conditions which are incompatible with other labile functional groups.

Experimental Section

General Methods. Solvents and other reagents were used as purchased without further purification. Reactions were monitored by LC/MS. Detection (UV) was at 220 nm. Compounds were purified by reversed-phase HPLC chromatography using MeOH/H_2O/0.1%TFA (gradient elution 30−100%) as mobile phase, unless otherwise specified.

Preparation of Nocathiacin IV (4). A suspension of nocathiacin I (**1**) (3.1 g, 2.1 mmol) in THF (10 mL) was treated with hydriodic acid (57% in water, 0.8 mL, 3.8 mmol) and iodomethane (1.0 mL, 16 mmol). The reaction mixture was heated in a sealed tube at 45 °C for 5 h before it was allowed to cool to room temperature. Diethyl ether (25 mL) was added, and the resulting yellow precipitate was collected by filtration, washed with diethyl ether (3 × 25 mL), and dried under reduced pressure to afford the HI salt of nocathiacin IV (**4**) (3.4 g, 88% yield) as a bright yellow solid. For characterization, this material was further purified as the TFA salt using reversed-phase chromatography (preparative C-18 column using CH_3CN/H_2O/1%TFA as mobile phase, gradient elution 10−50%). Analytical data for **4**: yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (1 H, s), 10.78 (1 H, s), 9.11 (1 H, s), 8.65 (1 H, s), 8.59 (1 H, br), 8.57 (1 H, br), 8.54 (1 H, s), 8.46 (1 H, s), 8.22 (1 H, s), 7.99 (1 H, s), 7.89 (1 H, s), 7.86 (1 H, d, J = 11.0 Hz), 7.75 (1 H, d, J = 8.5 Hz), 7.71 (1 H, s), 7.37 (2 H, m), 7.19 (1 H, d, J = 7.0 Hz), 6.02 (1 H, d, J = 12.0 Hz), 5.76 (1 H, dd, J = 11.2, 4.2 Hz), 5.72 (1 H, d, J = 10.0 Hz), 5.23 (1 H, m), 5.05 (3 H, m), 4.79 (1 H, d, J = 10.5 Hz), 4.53 (1 H, d, J = 11.0 Hz), 4.30 (1 H, d, J = 9.5 Hz), 4.25 (1 H, m), 4.16 (3 H, d, J = 0.5 Hz), 4.05 (1 H, dd, J = 9.5, 1.5 Hz), 3.91 (1 H, s), 3.87 (1 H, s), 3.13 (1 H, br), 2.88 (6 H, m), 2.50 (1 H, br), 2.12 (1 H, m), 2.0 (3 H, s), 1.94 (1 H, d, J = 14.5 Hz), 1.60 (3 H, s), 1.52 (1 H, d, J = 7.0 Hz), 1.17 (3 H, br), 0.8 (3 H, d, J = 7.0 Hz); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 171.3, 168.0, 167.8, 167.6, 166.8, 163.6, 163.1, 161.4, 160.9, 160.4, 160.2, 158.7, 154.1, 150.9, 150.6, 149.5, 148.6, 145.39, 143.1, 134.8, 134.2, 130.1, 127.8, 127.4, 126.7, 126.3, 126.1, 125.6, 125.5, 123.8, 123.0, 119.8, 119.3, 112.7, 111.0, 109.4, 94.5, 78.9, 72.2, 70.9, 68.8, 67.5, 66.3, 65.1, 64.4, 63.0, 62.7, 56.0, 49.9, 49.7, 46.5, 42.1, 38.1, 30.0, 17.7, 17.3, 12.9; HR-ESI MS $[M + H]^+$ m/z calcd for $C_{58}H_{57}N_{13}O_{17}S_5$ 1368.267, found 1368.267; ESI-MS/MS fragmentation ions m/z 1197, 1179, 1153, 1135, 1117, 719; major IR bands (cm^{-1}) 3438, 1676, 1536, 1475, 1204, 1132, 596; UV λ_{max} (MeOH) nm 219, 294, 359; CD λ nm ($\Delta\epsilon$) (MeOH) 305.2 (−5.7), 265.2 (+15.8), 236.6 (−44.1), 209.6 (+29.6).

Preparation of *N*-(1-Carbamoylvinyl)benzamide (5). Compound **5** was prepared in three steps from commercially available DL-serine methyl ester and benzoyl chloride as follows: Benzoyl chloride (5.38 mL, 46.6 mmol) was added dropwise to a stirred solution of serine methyl ester hydrochloride (7.26 g, 46.6 mmol) and triethylamine (16.0 mL, 116 mmol) in anhydrous CH_2Cl_2 (100 mL), and the mixture was stirred at rt for 4 h. A saturated aqueous solution of $NaHCO_3$ was added, and the organic phase was extracted with CH_2Cl_2. The combined organic layers were dried over $NaSO_4$, filtered, and concentrated. The crude residue was taken to the next step without further

purification. Mesylation of the alcohol followed by elimination was accomplished in one pot by treatment of the crude from above with triethylamine (16.0 mL, 46.6 mmol) and mesyl chloride (5.4 mL, 70.0 mmol) in CH_2Cl_2 (100 mL) at rt overnight. Methanol (5 mL) was added, and the stirring was continued for 15 min. Water was added, and the organic phase was extracted with CH_2Cl_2, dried over $NaSO_4$, filtered, concentrated, and chromatographed in silica gel using 20%AcOEt/hexanes to afford 2-benzoylaminoacrylic acid methyl ester (7.73 g, 81% in two steps): white solid; mp 205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (1 H, bs), 7.85 (2 H, m), 7.49 (3 H, m), 6.80 (1 H, s), 5.59 (1 H, s), 3.91 (3 H, s); MS (ESI) $(M + H)^+$ 206.1, $(M - H)^-$ 204.1.

The 2-benzoylaminoacrylic acid methyl ester was treated with a 6 N solution of ammonia in MeOH (25 mL) at rt for 6 h. After the solvent was removed in vacuo, the residue was purified to afford compound **5** (3.22, 45%): white solid; mp 85−87 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (1 H, bs), 7.84 (2 H, m), 7.47 (3 H, m), 6.75 (1 H, s), 5.38 (1 H, s); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.0, 134.4, 133.5, 132.2, 128.9, 127.1, 102.7; MS (ESI) $(M + H)^+$ 191.4, $(M - H)^-$ 189.2.

Preparation of 2-(2-Phenoxypropionylamino)acrylamide (6). Compound **6** was prepared in three steps from commercially available 2-phenoxypropionyl chloride and DL-serine methyl ester as follows: 2-Phenoxypropionyl chloride (16.7 mL, 0.1 mol) was added dropwise to a stirred solution of serine methyl ester hydrochloride (16.6 g, 0.1 mol) and triethylamine (46 mL, 0.3 mol) in anhydrous CH_2Cl_2 (250 mL), and the mixture was stirred at rt for 2 h. A saturated aqueous solution of $NaHCO_3$ was added, and the organic phase was extracted with CH_2Cl_2. The combined organic layers were dried over $NaSO_4$, filtered, and concentrated. The crude residue was dissolved in CH_2Cl_2 (250 mL) and treated with triethylamine (46 mL, 0.3 mol) and mesyl chloride (12.5 mL, 0.16 mol), and the reaction mixture was stirred at rt overnight. Methanol (25 mL) was added, and the stirring was continued for 15 min. Water was added, and the organic phase was extracted with CH_2Cl_2, dried over $NaSO_4$, filtered, concentrated, and chromatographed in silica gel using AcOEt/hexanes (gradient elution: 0−30%) to afford 2-(2-phenoxypropionylamino)acrylic acid methyl ester (18.9 g, 76%): white solid; mp 272−273 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (1 H, bs), 7.29 (2 H, m), 7.02 (1 H, m), 6.96 (2 H, m), 6.66 (1 H, s), 5.92 (1 H, s), 4.74 (1 H, q, J = 7 Hz), 3.82 (3 H, s), 1.61 (3 H, d, J = 7 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.1, 164.2, 156.8, 130.7, 129.9, 122.4, 115.8, 109.4, 75.3, 53.0, 18.6; GC (MS) 249.

2-(2-Phenoxypropionylamino)acrylic acid methyl ester (18.9 g, 75.9 mmol) was dissolved in a mixture of THF (100 mL) and water (10 mL) and treated with lithium hydroxide (15.5 g, 0.37 mol). The reaction was heated at 40 °C for 15 min, and then a solution of 1 N HCl was added until pH = 1. EtOAc was used to extract the organic phase. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude was purified to afford 2-(2-phenoxypropionylamino)acrylic acid (18.2 g, 99 %): white solid; mp 135−137 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (1 H, bs), 7.30 (2 H, m), 7.02 (1 H, m), 6.96 (2 H, m), 6.75 (1 H, s), 6.08 (1 H, d, J = 1 Hz), 4.77 (1 H, q, J = 7 Hz), 1.61 (3 H, d, J = 7 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.5, 167.7, 156.7, 130.1, 129.9, 122.5, 115.9, 111.9, 75.2, 18.6; MS (ESI) $(M - 1)^-$ 334.2.

A mixture of 2-(2-phenoxypropionylamino)acrylic acid (6.1 g, 26 mmol) and ammonium chloride (2.78 g, 52 mmol) in THF (250 mL) was treated with 4-methylmorpholine (17 mL, 154 mmol), 1-hydroxybenzotriazole (HOBt) (7.1 g, 52 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (9.9 g, 52 mmol) and stirred at rt for 12 h. Water was added, and the organic phase was extracted with AcOEt and $CHCl_3$. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified to afford compound **6** (3.1 g, 50%): white solid; mp 165−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (1 H, bs), 7.27 (2 H, m), 6.93 (3 H, m), 6.57 (1 H, s), 5.33 (1 H, s), 4.73 (2 H, d, J = 7.0 Hz), 1.60 (3 H, d, J = 7.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.4, 165.6, 156.9, 133.2, 129.9, 122.4, 115.9, 103.4, 75.4, 18.7; MS (ESI) $(M + 1)^-$ 233.

Preparation of *N*-[2-(4-Hydroxyphenyl)ethyl]-2-(2-phenoxypropionylamino)acrylamide (7). A mixture of 2-(2-phenoxypropionylamino)acrylic acid (6.1 g, 26 mmol) from above and tyramine (7.1 g, 52 mmol) in THF (250 mL) was treated with 4-methylmorpholine (17 mL, 154 mmol), HOBt (7.1 g, 52 mmol), and EDC (9.9 g, 52 mmol) and stirred at rt for 1 h. Water was added, and the organic phase was extracted with AcOEt and $CHCl_3$. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified to afford compound **7** (3.12 g, 34%): white solid; mp 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (1 H, bs), 7.27 (2 H, m), 6.96 (6 H, m), 6.78 (2 H, m), 6.43 (1 H, d, J = 1.8 Hz), 6.24 (1 H, bs), 5.12 (1 H, s), 4.73 (1 H, q, J = 6.8 Hz), 3.50 (2 H, m), 2.75 (2 H, m), 1.60 (3 H, d, J = 6.8 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.6, 163.7, 156.8, 154.9, 134.0, 130.1, 129.9, 122.3, 116.1, 115.8, 115.5, 102.0, 75.2, 41.5, 34.5, 18.6; MS (ESI) $(M + H)^+$ 355.4, $(M - H)^-$ 353.2; HR-ESI MS $[M - H]^-$ *m/z* calcd for $C_{20}H_{21}N_2O_4$ 353.150, found 353.149.

Hydrolysis of Compound 7. To a solution of **7** (354 mg, 1.0 mmol) in THF (3 mL) in a sealed tube was added hydriodic acid (57% in H_2O, 0.45 mL, 2.0 mmol), and the mixture was heated at 45 °C for 1 h. The volatiles were removed in vacuo, and the residue was purified to afford tyramine pyruvate (*N*-[2-(4-hydroxyphenyl)ethyl]-2-oxopropionamide) **8** (80 mg, 79%) [white solid; mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.02 (2 H, d, J = 8.4 Hz), 6.77 (2 H, d, J = 8.4 Hz), 3.50 (2 H, q, J = 7.0 Hz), 2.76 (2 H, d, J = 7.0 Hz), 2.45 (3 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.0, 160.3, 154.8, 129.8, 115.7, 40.9, 34.5, 24.5; MS (ESI) $(M - H)^-$ 206.2] and 2-phenoxypropionamide (68 mg, 83%): white solid; mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.29 (2 H, m), 7.01 (1 H, m), 6.91 (2 H, m), 6.42 (1 H, bs), 6.15 (1 H, bs), 4.65 (2 H, q, J = 6.5 Hz), 1.58 (3 H, d, J = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.4, 157.0, 129.9, 122.2, 115.5, 74.8, 18.7; MS (ESI) $(M - H)^-$ 164.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, and MS spectra for compounds **4**−**8** as well as for 2-phenoxypropionamide and intermediates involved in the syntheses of **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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