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Pyrrole-Assisted and Easy Oxidation of Cyclic α-Amino Acid-Derived Diketopiperazines under Mild Conditions

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Abstract: A new procedure for the aerobic oxidation of α-amino acids acylated by pyrrole-carboxylic acid with triplet dioxygen is introduced. The reaction is general for a variety of pyrrole-amino acid derivatives and represents a very practical and controllable method for the selective preparation of α-hydroperoxy- or α-hydroxy-α-amino acid diketopiperazines with molecular dioxygen. Furthermore, the non-catalyzed direct oxidation of amino acid derivatives at the α-position with molecular dioxygen represents a fundamental question.

Keywords: amino acids; diketopiperazines; dioxygen; peroxidation; pyrroles

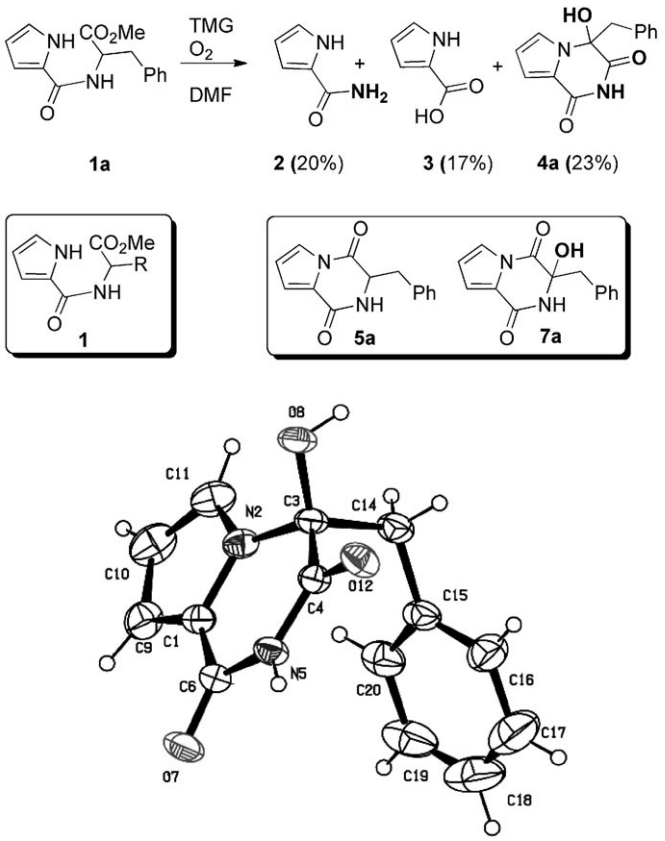
Introduction

The oxygenization reaction directly involving triplet O_2 represents a fundamental question in organic and biological chemistry.[1] There are limited reports on reactions involving triplet dioxygen without activation.[2] Triplet dioxygen is inert to most ground-state organic molecules. The usually observed peroxidation requires the presence of photo-excitable sensitizers or metal catalysis. The production of toxic reactive dioxygen species (ROS) as well as dioxygen-mediated oxidation is well known in many metabolic processes.[3] In Nature, dioxygen is largely used by activating enzymes involved in metabolically important oxidative transformations as a primary oxidant.[4] From a synthetic point of view, dioxygen-consuming reactions proceed more readily with electron-rich aromatic structures, such as flavins,[5] pterins,[6] and quinones.[7] Reactions incorporating O_2 to form hydroperoxide intermediates in the dark and without any photo-activation are rare. Herein, we would like to report a new and easy aerobic oxidation of α-amino acids acylated by pyrrole-2-carboxylic acid. The α-hydroxy[8] and α,β-dehydro[9] amino acid derivatives as a higher oxidized level of amino acids have been widely discovered in fungal metabolites.[10] Easton very recently reported the peculiar resistance of free amino acids and peptides to α-hydrogen atom transfer.[11]

Previously, during our investigation of biomimetic syntheses of marine metabolites, we reported the unexpected oxidation of the pseudo-peptide pyrrole-proline as a key step in the formation of the natural product dispacamide skeleton.[12] We then decided to study the mechanism of the oxidation step of this reaction. We have used α-amino acid derivatives to test their reactivity towards molecular dioxygen without any activation. The mechanism of this interesting reaction with various amino acids and the conditions controlling its progression will be described.

Results and Discussion

Preliminary trials conducted with the phenylalanine derivative **1a** (Scheme 1) in the presence of tetramethylguanidine as a base showed the formation of several compounds. The rearrangement compound **4a**, as well as pyrrole-carboxamide (**2**) and acid (**3**) were isolated from the reaction mixture. Since we had occasionally isolated the minor compounds **5a** and **7a** in our earlier preliminary trials,[13] the identification of the isomers **4a** and **7a** by their NMR spectra was not obvious. The structure of **4a** was determined by X-ray diffraction analysis (Scheme 1). While the simple hydrolysis can explain the formation of **3**, the mechanism leading to the unexpected amide **2** and the pyrrolopyrazinedione **4a** was not intuitive. Thus, the in-

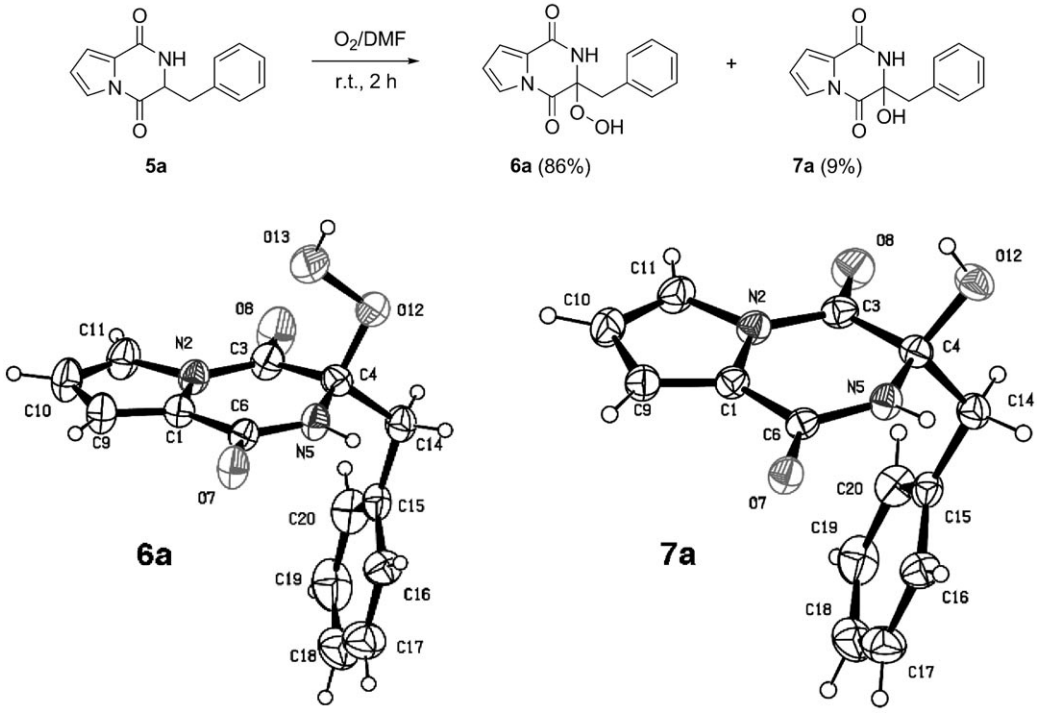


Scheme 1. Oxidative transformation of **1a** in the presence of O_2 and tetramethylguanidine. X-ray analysis of **4a**.

vestigation of the mechanism of the reaction became essential.

Since we had assumed the key role of the diketopiperazine intermediate **5a**,[12] we decided to prepare a series of amino acid derivatives for reactivity and mechanistic studies. Oxidation of cyclic dipeptides in the presence of light and initiators was reported by Schmidt in 1976.[14] Pyrrolopyrazines of type **5a** are deemed to be susceptible to hydrolysis.[15] The initial phenylalanine-derived substrate **5a** was synthesized in 98% yield from the pseudo-peptide **1a** in the presence of sodium hydride followed by treatment with acetate buffer at pH 3.8.[16] We next investigated its oxidation in various conditions. Preliminary trials revealed that the reaction was strongly related to the solvent and the presence or absence of a base. While in the absence of a base in THF solution, **5a** was relatively stable, a slow conversion into oxidized compounds was observed in acetonitrile. About one-half of the starting material was consumed after two days. Remarkably, compound **5a** was totally consumed in only 2 h in DMF. Hydroperoxide **6a** and the corresponding reduced derivative **7a** were isolated in 86% and 9% yields, respectively (Scheme 2). The structures of **6a** and **7a** were elucidated on the basis of their spectroscopic characteristics and unambiguously confirmed by X-ray diffraction analysis.

Importantly, the use of air dioxygen instead of pure O_2 slightly affects the rate and the yield of the oxidation.

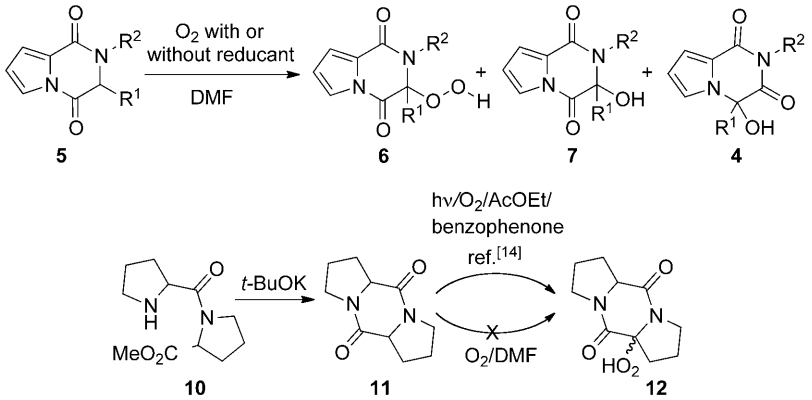


Scheme 2. DKP oxidation with molecular dioxygen in neutral conditions and ORTEP diagrams of **6a** and **7a**.

It is clear that the reaction dramatically depends on the solvent and the pH of the reaction mixture. Our first concern was to selectively prepare hydroperoxide derivatives of type **6a** in good yield. The general procedure was successfully applied to various amino acids. The cyclic compounds **5b–g** were prepared from **1b–g** by the route used for the synthesis of **5a**. Treatment of the proline derivative **5b** with O_2 in the same conditions gave quantitatively hydroperoxide **6b** in 30 min (entry 3). The structure of **6b** was also confirmed by X-ray analyses. The slight reactivity difference between **5a** and **5b** could be explained by conformational consideration as shown by X-ray analyses of the corresponding products **6a** and **6b.** The dihedral angles of C-6–N-5–C-4–C-3 (**6b**/**6a**, −21.2°/−9.7°), and N-2–C-3–C-4–N-5 (**6b**/**6a**, 19.1°/7.4°) (Scheme 2)[17] indicated that diketopiperazine ring adopted the twist form in **6b** while it was nearly flat in **6a**. Henceforth, one may assume that substrates **5a** and **5** possibly have similar conformations, respectively. This tension difference is believed to account for the observed reaction rate difference.

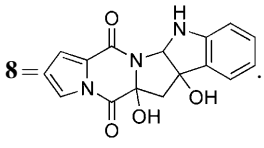
We next wanted to test the oxidation of a non-pyrrolic cyclic amino acid derivatives in the same conditions. Cyclo(Pro,Pro) (**11**) was prepared from the commercial HCl salt of L-proline in the presence of $NaHCO_3$ in 50% yield.[18] As expected, we found that cyclo(Pro,Pro) (**11**) when in contact with triplet oxygen in DMF did not give rise to the corresponding peroxide **12** (Table 1). The peroxidation of such deriv-

Table 1. The oxidation of diketopiperazines with O_2 in DMF.[a]



	Diketopiperazine	R^1	R^2	Reducant	Products [%][b]
1	**5a**	CH_2Ph	H	–	**6a** (86), **7a** (9)
2	**5a**	CH_2Ph	H	$(n\text{-Bu})_2S$	**7a** (95), **4a** (trace)
3	**5b**	-$CH_2CH_2CH_2$-		–	**6b** (100)
4	**5b**	-$CH_2CH_2CH_2$-		$(n\text{-Bu})_2S$	**7b** (93)
5	**5c**	2-methylpropyl	H	–	**6c** (93), **7c** (5)
6	**5c**	2-methylpropyl	H	$(n\text{-Bu})_2S$	**7c** (96)
7	**5d**	4-methoxybenzyl	H	–	**6d** (88), **7d** (10)
8	**5d**	4-methoxybenzyl	H	$(n\text{-Bu})_2S$	**7d** (94)
9	**5e**	indol-3-ylmethyl	H	–	**7e** (33), **8**[e] (5)
10	**5e**	indol-3-ylmethyl	H	PPh_3	**7e** (93)
11	**5f**	$CH_2CH_2SCH_3$	H	–	**7f** (6), **7h**[c] (88)[d]
12	**5f**	$CH_2CH_2SCH_3$	H	PPh_3	**7f** (50)
13	**5f**	$CH_2CH_2SCH_3$	H	$(n\text{-Bu})_2S$	**7f** (75), **7h** (15)
14	**5g**	CH_2Ph	Me	–	**6g** (53), **7g** (31), **4g** (4)
15	**5g**	Bn	Me	$(n\text{-Bu})_2S$	**7g** (75), **4g** (20)
16	**11** = cyclo(Pro-Pro)	–	–	–	No reaction

[a] The reaction was performed at room temperature in 0.04 M DMF solution.
[b] isolated yield.
[c] R^1 for **7h** = $CH_2CH_2SOCH_3$.
[d] *dr* = 3.5:1, determined by ^1H NMR.
[e] **8** =



atives is only possible in the presence of light and an initiator.[14] The contrast is disconcerting since the pyrrolic cyclic amino acid derivative reacts rapidly with $^3O_2$. The result is unchanged when the reaction was carried out in the dark.

The oxidation of pyrrolic derivatives was further extended to cyclic pseudo-peptides derived from leucine and *O*-methyltyrosine in excellent yields (Table 1, entries 5 and 7). Treatment of indole and sulfur-containing amino acid derivatives **5e** and **5f** (Table 1, entries 9 and 11) under similar conditions gave only moderate to low yields. The propensity of these amino acid chains to over-oxidation is not compatible with the hydroperoxide, which is the product of the reaction. The strong oxidizing properties of the hydroperoxide, especially when adjacent to a carbonyl group,[19] explain the formation of the corresponding hydroxy derivatives. In the case of the indole **5e** (entry 9), we have identified the hydroxy derivative **7e** and the over-oxidation compound **8**. The latter compound is the result of an epoxidation of **7e** followed by its intramolecular cyclization. We therefore decided to add a reducing agent to the reaction mixture, which could immediately convert the formed hydroperoxide compound into its non-reactive hydroxy derivative. Several experiments with NEt_3 and *tert*-butylmercaptan[20] showed occasionally either over-oxidation compounds or complete inhibition of the O_2 oxidation reaction. After extensive experimentation, we found that dibutyl sulfide or triphenylphosphine[21] can efficiently prevent over-oxidation through peroxide reduction without hampering the desired reaction. The reaction conditions in the presence or absence of a reducant were tested for the entire selected series of amino acid derivatives (Table 1). Thus, treatment of **5a** in the presence of dibutyl sulfide during 3 h gave **7a** in 95% yield (entry 2). The presence of the reducing agent proved essential to avoid non-desired over-oxidation compounds and to obtain the hydroxylated product in good yield. The procedure was found to be general for the selective preparation of compounds of type **6** or **7** (Table 1).

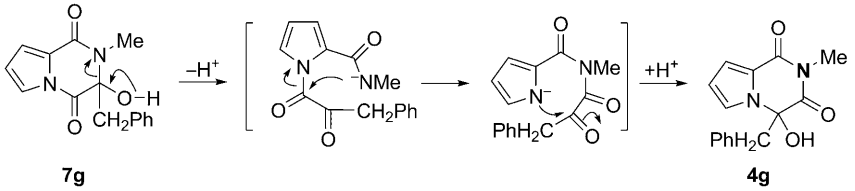
The result of the reaction depends upon the presence or absence of the reducant. In the particular case of tryptophan derivative **5e**, the reaction in the presence of the reducant PPh_3 gave **7e** in 93% (entry 10). ^{31}P NMR analysis[22] revealed that triphenylphosphine oxide was co-generated in the NMR tube when triphenylphosphine was added to the reaction with **5e**. A similar result was observed for the methionine derivative **5f**. The oxidation of **5f** in the presence of four equivalents of dibutyl sulfide could decrease the amount of sulfide oxide **7h** from 88% to 15% (entries 11 and 13) while the yield of **7f** was increased to 75%. Interestingly, the intramolecular sulfide oxidation into **7h** could be minimized by the addition of 4 equivalents of dibutyl sulfide.

It is worthy of note that the *N*-methylated derivative **5g** needed two days for full conversion. In the presence of dibutyl sulfide, 20% of **7g** was rearranged into **4g** through ring opening followed by amide exchange and hemiacetalization (Scheme 3).

The same mechanism is probably contributing to the formation of **4a** obtained from **1a** in the presence of tetramethylguanidine (Scheme 1). The formation of the amide **2** becomes conceivable from **1a** through the diketopiperazine intermediate and the rearrangement process presented in Scheme 3.

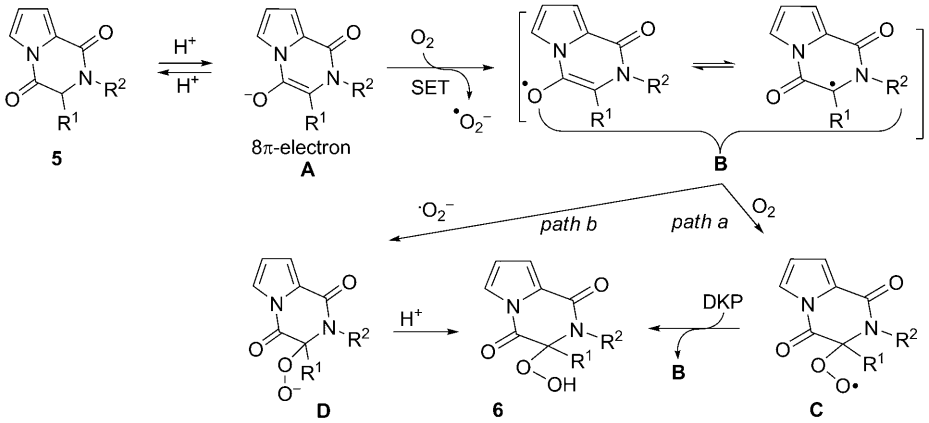
The above work provides an example of an interesting oxidation without any metal or light catalysis. Neither weak acid such as AcOH nor radical scavenger such as 2,6-di-*tert*-butyl-4-methylphenol could inhibit the oxidation. In contrast, a strong acid such as TFA and a radical scavenger such as *tert*-butylmercaptan completely inhibit the peroxidation. Based on the above observations, a possible mechanism was proposed. The first step would be the enolization of diketopiperazines of type **5** into **A** (Scheme 4). The 8π-electron anti-aromatic conjugation system in **A** is probably generated from the electron-deficient diketopiperazine cycle. Then, a single-electron transfer (SET) process can occur between the enolate anion **A** and the O_2 triplet affording the anion radical superoxide and the radical (**B**) which reacts with molecular dioxygen to give the radical hydroperoxide **C** (*path a*). Another possible pathway is the reaction of **B** with the residual anion radical superoxide affording the anion **D** (*path b*). Final hydroperoxide product **6** could be either formed from **C** in a chain reaction with **5** generating a new radical **B** or from **D** by a simple protonation.

This oxidation reaction by triplet dioxygen can be an interesting method to generate α,β-dehydro amino acid derivatives as a useful synthetic block.[23] Dehydrated compounds **9a** and **9b** were prepared from the alcohols **7a** and **7b** by simple treatment with a catalyt-



7g 4g

Scheme 3. Mechanism of the rearrangement of **7g** into **4g**.



Scheme 4. The proposed mechanism for the O_2 oxidation.

Scheme 5. Example of dehydration of alcohols of type **7** into alkenes of type **9**.

ic amount of HCl in acetonitrile in quantitative yield (Scheme 5).

In conclusion, we have demonstrated that the aerobic peroxidation at the α-position of α-amino acids acylated by pyrrolecarboxylic acid proceeds easily with triplet dioxygen in DMF under neutral conditions in good yields. This oxidation in the presence of a reducing reagent such as dibutyl sulfide or triphenylphosphine afforded the corresponding α-hydroxide derivatives in excellent yields. This reaction is general for a variety of pyrrole-amino acid derivatives and represents a very practical method for the selective preparation of α-hydroperoxy- or α-hydroxy-α-amino acid derivatives with molecular dioxygen. The study of this oxidation could clarify the mechanism of similar bioorganic reactions involving ground state O_2 such as the oxidation of the chemiluminescent luciferins,[24] flavins[19] or uric acid.[25] Furthermore, the easily available peroxides could be highly interesting for selective oxidative reactions such as with flavins.[19] Further studies on the oxidation mechanism and its application in synthesis are ongoing.

Experimental Section

General Remarks

Commercially available reagents and solvents were purchased from Aldrich and used without further purification. Chromatographic purifications were performed by the flash technique using silica gel P60 (230–400 mesh). THF was distilled from sodium/benzophenone and freshly used. Spectroscopic data and HR-MS analyses are reported for all new compounds. NMR spectra were recorded on Brucker Avance 300 MHz and 500 MHz spectrometers for ^{1}H and ^{13}C NMR and 2D NMR experiments. Chemical shifts (expressed in ppm) of ^{1}H and ^{13}C NMR spectra were referenced to the solvent peaks $\delta_H = 2.05$ and $\delta_C = 29.9$, 206.7 for acetone-d_6, $\delta_H = 2.50$ and $\delta_C = 39.5$ for DMSO-d_6, $\delta_H = 7.26$ and $\delta_C = 77.2$ for $CDCl_3$, $\delta_H = 3.58$, 1.73 and $\delta_C = 64.7$, 25.2 for THF, $\delta_H = 8.04$, 2.93, 2.72 and $\delta_C = 162.4$, 34.9, 29.8 for DMF-d_7. ^{31}P NMR spectrum was recorded with 120-sec pulse ($>5T_1$) cycle and 12 accumulations before Fourier transformation, while the relaxation time (T_1) of triphenylphosphine and its oxide were 1.9 and 13.8 sec at 30 °C, respectively, as indicated in *J. Magnetic Resonance*, **1979**, *33*, 127–134. HR-MS were obtained with using an electrospray source (Lockspray) coupled with a time of flight analyser (LCT, Micromass). Samples were prepared in acetonitrile and injected in the MS system using a Waters 2795 system. IR spectra were acquired (neat) using a Perkin–Elmer Spectrometer BX FT-IR system.

General Procedure for the Synthesis of Pyrrole-amino Acid Methyl Esters 1

To a mixture of 2-(trichloroacetyl)pyrrole (10.0 mmol, 1 equiv.) and the HCl salt of an amino acid methyl ester (15.0 mmol, 1.5 equiv.) in dry acetonitrile (150 mL) was added Et_3N (20 mmol, 2 equiv.). The reaction mixture was stirred at room temperature during 48 h, then filtered and concentrated. The residue was dissolved in EtOAc and washed successively with 1N HCl, H_2O and brine, dried, concentrated and purified by flash chromatography using heptane/EtOAc.

Pyrrole-Phe-OMe ester (1a): Prepared from phenylalanine methyl ester using the general procedure described above as a white solid; yield: 82% yield. IR (neat): $\nu_{max} =$ 1735, 1633 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.77$ (s, 1H), 7.31–7.20 (m, 3H), 7.16–7.12 (m, 2H), 6.93 (m, 1H), 6.54 (m, 1H), 6.35 (d, $J = 7.8$ Hz, 1H), 6.17 (m, 1H), 5.05 (td, $J = 7.8$ and 5.7 Hz, 1H), 3.73 (s, 3H), 3.21 (d, $J = 5.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.3$, 160.8, 136.0,

129.4, 128.7, 127.2, 125.3, 122.3, 110.0, 109.9, 53.2, 52.4, 38.3; MS (ESI$^+$): $m/z = 273.0$ $[M+H]^+$.

Pyrrole-Pro-OMe ester (1b): Prepared from proline methyl ester by the procedure described above; yield: 95% (see ref.[12]).

Pyrrole-Leu-OMe ester (1c): Prepared from leucine methyl ester using the general procedure described above as a pale yellow solid; yield: 87%. IR (neat): $\nu_{max} = 1731$, 1631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.93$ (s, 1H), 6.90 (m, 1H), 6.67 (m, 1H), 6.43 (d, $J = 8.4$ Hz, 1H), 6.21 (m, 1H), 4.83 (m, 1H), 3.76 (s, 3H), 1.81–1.76 (m, 3H), 1.00 (dd, $J = 5.0$ Hz and 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 173.9, 161.0, 125.3, 122.1, 109.7, 109.7, 52.3, 50.5, 41.8, 24.9, 22.8, 21.9; MS (ESI$^+$): $m/z = 239.0$ $[M+H]^+$.

Pyrrole-Tyr-(OMe)-OMe ester (1d): Prepared from *para*-methoxytyrosine methyl ester using the general procedure described above as a pale yellow solid; yield: 74%. IR (neat): $\nu_{max} = 1735$, 1664, 1598, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.94$ (brs, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.85–6.81 (m, 1H), 6.74 (d, $J = 8.3$ Hz, 1H), 6.50–6.46 (m, 1H), 6.36 (d, $J = 7.8$ Hz, 1H), 6.16–6.09 (m, 1H), 4.98–4.88 (m, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.07 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.2$, 160.6, 158.7, 130.3, 127.7, 125.3, 122.1, 114.0, 109.8, 55.2, 53.1, 52.3, 37.3; MS (ESI$^+$): $m/z = 239.0$ $[M+H]^+$.

Pyrrole-Try-OMe ester (1e): Prepared from tryptophane methyl ester using the general procedure described above as a pale yellow solid; yield: 63%. IR (neat): $\nu_{max} = 1732$, 1634, 1557, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.03$ (s, 1H), 8.29 (s, 1H), 7.59 (d, $J = 7.9$ Hz, 1H), 7.36 (d, $J =$ 8.1 Hz, 1H), 7.35 (m, 2H), 6.98 (d, $J = 2.3$ Hz, 1H), 6.88 (m, 1H), 6.47–6.38 (m, 2H), 6.18 (m, 1H), 6.21 (m, 1H), 5.11 (td, $J = 8.1$ and 5.3 Hz, 1H), 3.70 (s, 3H), 3.41 (d, $J = 5.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.6$, 161.2, 136.5, 125.3, 122.9, 122.3, 120.1, 120.0, 118.5, 112.6, 110.3, 110.0, 53.5, 52.6, 27.9; MS (ESI$^+$): $m/z = 312.0$ $[M+H]^+$.

Pyrrole-Met-OMe ester (1f): Prepared from methionine methyl ester using the general procedure described above as a white solid; yield: 70%. IR (neat): $\nu_{max} = 3271$, 1734, 1632, 1558, 1521 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.84$ (br s, 1H), 6.94 (m, 1H), 6,78 (d, $J = 7.8$ Hz, 1H), 6.67 (m, 1H), 6.22 (m, 1H), 4.89 (td, $J = 7.8$ and 5.1 Hz, 1H), 3.76 (s, 3H), 2.25 (m, 2H), 2.06 (s, 3H), 2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.8$, 161.1, 125.1, 122.4, 110.1, 109.8, 52.6, 51.5, 31.7, 30.1, 15.4; MS (ESI$^+$): $m/z = 239.0$ $[M+H]^+$.

Pyrrole-(N-Me-Phe)-OMe ester (1g): Prepared from pyrrole 2-carboxylic acid and *N*-methylphenylalanine methyl ester using the procedure described above for 3 h as a white solid; yield: 72%. IR (neat): $\nu_{max} = 3260$, 2949, 1735, 1587, 1402, 1112, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 9.99 (br s, 1H), 7.31–7.16 (m, 5H), 6.94 (m, 1H), 6.51 (m, 1H), 6.23 (dd, $J = 3.8$, 2.7 Hz, 1H), 5.24 (br s, 1H), 3.75 (s, 3H), 3.44 (dd, $J = 14.3$, 5.2 Hz, 1H), 3.18 (dd, $J = 14.3$, 10.2 Hz, 1H), 3.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 171.4, 162.7, 137.2, 128.8, 128.5, 126.7, 124.4, 121.6, 113.2, 113.0, 109.7, 60.7, 52.3, 35.0; MS (HR-MS-ESI): $m/z =$ 309.1216, calcd. for $C_{16}H_{18}N_2O_3$ $[M+Na^+]$: 309.1215.

General Procedure for the Synthesis of Diketopiperazine Pyrrole-AA 5

Methyl ester (pyrrole-AA) **1** (10 mmol, 1 equiv.) was dissolved in degassed anhydrous THF (200 mL) and was cooled to 0 °C. Sodium hydride (335 mg, 14 mmol, 1.4 equiv.) was added and the mixture was stirred at 0 °C for five minutes and then at room temperature for the time indicated in each case. After the completion of the reaction, the mixture was poured into acetate buffer pH 3.8 (300 mL) and quickly extracted with AcOEt. The organic layer was dried on $MgSO_4$, the solvent was evaporated and the residue was then dried under vacuum during 12 h to give the corresponding diketopiperazine **5**. The compound was stored and used without further purification.

Pyrrole-Phe diketopiperazine (5a): Prepared from the corresponding methyl ester **1a** by the general procedure as a white solid; yield: 98%. IR: $\nu_{max} = 1722$, 1671, 1626, 1421 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$ (dd, $J = 1.5$, 3.4 Hz, 1H), 7.22–7.10 (m, 5H), 6.93 (dd, $J = 1.5$, 3.4 Hz, 1H), 6.39 (t, $J = 3.4$ Hz, 1H), 4.59 (ddd, $J = 2.1$, 4.1, 7.8 Hz, 1H), 3.39 (dd, $J = 4.1$, 13.7 Hz, 1H), 3.09 (dd, $J = 7.8$, 13.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.0$, 157.2, 134.3, 129.4, 128.9, 127.7, 125.1, 119.5, 118.5, 115.5, 58.6, 41.0; MS (ESI$^+$): $m/z = 241.1$ $[M+H]^+$; HR-MS (ESI): $m/z =$ 241.0967, calcd. for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: 241.0977.

Pyrrole-Pro diketopiperazine (5b): Prepared from the corresponding methyl ester **1b** by the general procedure for 2 h 30 min as a white solid; yield: 93%. IR (neat): $\nu_{max} = 1727$, 1641, 1435,1409 cm^1; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$ (dd, $J = 1.5$, 3.2 Hz, 1H), 7.06 (dd, $J = 1.5$, 3.4 Hz, 1H), 6.47 (dd, $J = 3.2$, 3.4 Hz, 1H), 4.48 (dd, $J = 6.4$, 10.8 Hz, 1H), 3.83 (m, 1H), 3.63 (m, 1H), 2.56 (m, 1H), 2.21–1.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.5$, 155.2, 127.3, 118.8, 117.8, 115.5, 61.4, 44.7, 29.0, 22.2; MS (ESI$^+$): $m/z = 191.1$ $[M+H]^+$, 213.1 $[M+Na]^+$; HR-MS (ESI): $m/z = 213.0642$, calcd. for $C_{10}H_{10}N_2O_2Na$ $[M+Na]^+$: 213.0640.

Pyrrole-Leu diketopiperazine (5c): Prepared from the corresponding methyl ester **1c** by the general procedure for 40 min as a white powder; yield: 85%. IR (neat): $\nu_{max} =$ 1720, 1644, 1430, 1327 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.40$ (brs, 1H), 7.57 (dd, $J = 1.6$, 3.1 Hz, 1H), 6.95 (dd, $J = 1.6$, 3.4 Hz, 1H), 6.58 (dd, $J = 3.1$, 3.4 Hz, 1H), 4.51 (dt, $J = 2.4$, 6.0 Hz, 1H), 1.88–1.79 (m, 1H), 1.77–1.71 (m, 2H), 0.88 (d, $J = 6.0$ Hz, 1H), 0.79 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6): $\delta = 165.7$, 155.8, 126.0, 118.9 (CH), 116.6 (CH), 115.0 (CH), 55.2 (CH), 43.1 (CH_2), 23.6 (CH), 22.4 (CH_3), 22.2 (CH_3); MS (ESI$^-$): $m/z = 205.0$ $[M-H]^-$; HR-MS (ESI): $m/z = 205.0976$, calcd. for $C_{11}H_{13}N_2O_2$ $[M-H]^-$: 205.0977.

Pyrrole-Tyr(OMe) diketopiperazine (5d): Prepared from the corresponding methyl ester **1d** by the general procedure for 30 min as a pale yellow solid; yield: 93%. IR (neat) $\nu_{max} = 1718$, 1654, 1508, 1419 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$ (dd, $J = 1.2$, 3.4 Hz, 1H), 7.20 (br. s, 1H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.91 (dd, $J = 1.2$, 3.4 Hz, 1H), 6.69 (d, $J = 8.5$ Hz, 2H), 6.38 (t, $J = 3.4$ Hz, 1H), 4.55 (ddd, $J =$ 2.1, 4.0, 7.3 Hz, 1H), 3.65 (s, 3H), 3.29 (dd, $J = 4.0$, 13.7 Hz, 1H), 3.07 (dd, $J = 7.3$, 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta =$ 164.1, 159.0, 157.3, 130.5, 126.1, 125.1, 119.4, 118.3, 115.4, 114.2, 58.7, 55.2, 40.2; MS (ESI$^+$): $m/z = 293.1$ $[M+Na]^+$;

HR-MS (ESI): $m/z = 293.0899$, calcd. for $C_{15}H_{14}N_2O_3Na$ $[M+Na]^+$: 293.0902.

Pyrrole-Try diketopiperazine (5e): Prepared from the corresponding methyl ester **1e** by the general procedure for 2 h and purified by flush chromatography (CH_2Cl_2/EtOAc: 1/1) as an orange froth; yield: 83%. IR (neat): $\nu_{max} = 1727$, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (br. s, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.37 (dd, $J = 1.5$, 3.2 Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 7.07 (ddd, $J = 1.1$, 7.0, 7.9 Hz, 1H), 7.00 (ddd, $J = 1.1$, 7.0, 7.9 Hz, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 6.90 (dd, $J = 1.5$, 3.4 Hz, 1H), 6.64 (br. s, 1H), 6.32 (dd, $J = 3.2$, 3.4 Hz, 1H), 4.54 (ddd, $J = 1.9$, 3.7, 8.3 Hz, 1H), 3.52 (dd, $J = 3.7$, 14.4 Hz, 1H), 3.19 (dd, $J = 8.3$, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.4$, 157.1, 136.3, 126.7, 125.2, 124.0, 122.4, 119.8, 119.6, 118.4, 118.4, 115.3, 111.4, 108.4, 57.7, 31.3; MS (ESI^+): $m/z = 302.1$ $[M+Na]^+$; HR-MS (ESI): $m/z = 302.0903$, calcd. for $C_{16}H_{13}N_3O_2Na$ $[M+Na]^+$: 302.0905.

Pyrrole-Met diketopiperazine (5f): Prepared from the corresponding methyl ester **1f** by the general procedure for 2 h 30 min as a white solid; yield: 95%. IR (neat): $\nu_{max} = 1719$, 1644, 1426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.26$ (br. s, 1H), 7.53 (dd, $J = 1.5$, 3.2 Hz, 1H), 7.11 (dd, $J = 1.5$, 3.4 Hz, 1H), 6.52 (dd, $J = 3.2$, 3.4 Hz, 1H), 4.63 (td, $J = 1.5$, 5.5 Hz, 1H), 2.70 (m, 2H), 2.40–2.31 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.5$, 157.9, 125.1, 119.7, 118.5, 115.3, 56.0, 33.1, 29.2, 15.1; MS (ESI^+): $m/z = 225.1$ $[M+H]^+$; HR-MS (ESI): $m/z = 247.0519$, calcd. for $C_{10}H_{12}N_2O_2SNa$ $[M+Na]^+$: 247.0517.

Pyrrole-(N-Me-Phe) diketopiperazine (5g): Prepared from the corresponding methyl ester **1g** by the general procedure for 1 h as a white solid; yield: 90%. IR (neat): $\nu_{max} =$ 1717, 1656, 1650, 1373, 1326, 758, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$ (dd, $J = 3.5$,1.5 Hz, 1H), 7.15–7.08 (m, 3H), 6.98–6.90 (m, 2H), 6.72 (dd, $J = 3.5$,1.5 Hz, 1H), 6.27 (t, $J = 3.5$ Hz, 1H), 4.52 (t, $J = 4.4$ Hz, 1H), 3.33 (d, $J = 4.1$ Hz, 1H), 3.32 (d, $J = 4.1$ Hz, 1H), 3.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.2$, 156.2, 133.2, 128.9, 128.5, 127.6, 125.5, 117.9, 117.6, 115.4, 65.2, 38.7, 32.2; HR-MS (ESI): $m/z = 255.1131$, calcd. for $C_{15}H_{15}N_2O_2$ $[M+H]^+$: 255.1134.

General Procedure for the Oxidation of Diketopiperazines Pyrrole-AA 5 into Hydroperoxides 6

Diketopiperazine **5** (1 mmol) was dissolved in dry DMF (25 mL) and then dioxygen was bubbled into the stirred solution for the time indicated in each case at room temperature. Upon completion of the reaction, the solvent was evaporated and the hydroperoxide **6** was purified as indicated for each compound.

Pyrrole-Phe-OOH (6a): Prepared from **5a** by the general procedure for 2 h as a white solid; yield: 86%. The hydroperoxide was purified by column flash chromatography with heptane/EtOAc: 1/1. IR (neat): $\nu_{max} = 3143$, 1745, 1668, 1496, 1455, 1639, 1582,1466 cm^{-1}; ^1H NMR (500 MHz, DMF-d_7): $\delta = 12.94$ (br s, 1H), 9.08 (br s, 1H), 7.63 (dd, $J =$ 3.3,1.4 Hz, 1H), 7.39–7.22 (m, 5H), 6.92 (dd, $J = 3.0$, 1.4 Hz, 1H), 6.54 (t, $J = 3.3$, 3.0 Hz, 1H), 3.56 (d, $J = 13.0$ Hz, 1H), 3.56 (d, $J = 13.0$ Hz, 1H); ^{13}C NMR (75 MHz, dioxane-d_8): $\delta = 162.4$, 157.3, 133.4, 131.2, 129.1, 128.2, 126.4, 120.2, 118.7, 115.8, 94.5, 41.5; HR-MS (ESI): $m/z = 271.0709$,: calcd. for $C_{14}H_{11}N_2O_4$ $[M-H]^-$: 271.0719. The single crystal was cultured by solvent diffusion of THF and heptane mixed solution.

Pyrrole-Pro-OOH (6b): Prepared from **5b** by the general procedure for 0.5 h as a white solid; yield: quantitative. IR (neat): $\nu_{max} = 3114$, 1738, 1629, 1428, 1335 cm^{-1}; ^1H NMR (500 MHz, DMF-d_7): $\delta = 12.6$ (s, 1H); 7.61 (dd, $J = 3.2$, 1.6 Hz, 1H), 6.99 (dd, $J = 3.4$, 1.6 Hz, 1H), 6.58 (t, $J =$ 3.3 Hz, 1H), 3.9 (td, $J = 11.1$, 8.0 Hz, 1H), 3.63 (ddd, $J =$ 11.3, 8.7, 5.1 Hz, 1H), 2.53 (td, $J = 13.8$, 10.0 Hz, 1H), 2.53 (td, $J = 13.8$, 10.0 Hz, 1H), 2.10–2.03 (m, 2H); ^{13}C NMR (DMF-d_7, 75 MHz): $\delta = 162.2$, 155.6, 127.8, 119.3, 117.0, 115.1, 97.3, 44.3, 32.7, 19.8; HR-MS (ESI): $m/z = 223.0714$, calcd. for $C_{10}H_{11}N_2O_4$ $[M+H]^+$: 223.0719. The single crystal was cultured by solvent diffusion of THF and heptane mixed solution.

Pyrrole-Leu-OOH (6c): Prepared from **5c** by the general procedure for 10 h as a pale yellow oil; yield: 93%. The hydroperoxide was purified by column flash chromatography with heptane/EtOAc: 6/4. IR (neat): $\nu_{max} = 3164$, 2948, 1720, 1649, 1433 cm^{-1}; ^1H NMR (300 MHz, DMF-d_7): $\delta = 12.71$ (s, 1H), 8.90 (br s, 1H), 7.70 (dd, $J = 3.2$, 1.5 Hz, 1H), 7.07 (dd, $J = 3.5$,1.6 Hz, 1H), 6.63 (t, $J = 3.3$ Hz, 1H), 2.12 (dd, $J =$ 15.0, 9.9 Hz, 1H), 1.85 (m, 2H), 0.94 (d, $J = 6.5$ Hz, 1H), 0.76 (d, $J = 6.48$ Hz, 1H); ^{13}C NMR (75 MHz, DMF-d_7): $\delta =$ 162.9, 157.0, 126.2, 119.8, 117.7, 115.4, 93.2, 41.8, 24.4, 23.0, 22.0; HR-MS (ESI): $m/z = 261.0853$, calcd. for $C_{11}H_{14}N_2O_4Na$ $[M+Na]^+$: 261.0851.

Pyrrole-Tyr(OMe)-OOH (6d): Prepared from **5d** by the general procedure for 6 h as a yellow oil; yield: 88%. The hydroperoxide was purified by column flash chromatography with heptane/EtOAc: 4/6. IR (neat): $\nu_{max} = 3190$, 1741, 1650, 1513, 1467, 1644, 1582, 1454 cm^{-1}; ^1H NMR (THF-d_8, 300 MHz): $\delta = 11.69$ (s, 1H), 8.03 (br s, 1H), 7.42 (dd, $J =$ 3.3, 1.5 Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 2H), 6.82 (dd, $J = 3.3$, 1.5 Hz, 1H), 6.72 (d, $J = 8.8$ Hz, 2H), 6.35 (t, $J = 3.3$ Hz, 1H), 3.66 (s, 3H), 3.43 (d, $J = 13.4$ Hz, 1H), 2.93 (d, $J =$ 13.4 Hz, 1H); ^{13}C NMR (THF-d_8, 75 MHz): $\delta = 162.7$, 160.1, 157.6, 132.4, 127.1, 125.5, 119.9, 118.0, 115.4, 114.5, 94.8, 55.2, 40.4; HR-MS (ESI): $m/z = 303.2889$, calcd. for $C_{15}H_{15}N_2O_5$ $[M+H^+]$: 303.2895.

Pyrrole-Phe(NMe)-OOH (6g): Prepared from **5g** by the general procedure for 48 h; yield: 53%. Purification was made by column flash chromatography with heptane/EtOAc: 6/4. IR (neat): $\nu_{max} = 3103$, 1716, 1650, 1415, 1326, 1261, 750, 614 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): $\delta =$ 11.91 (br s, 1H), 7.44 (dd, $J = 3.3$, 1.5 Hz, 1H), 7.20–7.12 (m, 3H), 7.10–7.04 (m, 2H), 6.75 (dd, $J = 3.5$, 1.5 Hz, 1H), 6.41 (dd, $J = 3.5$, 3.3 Hz, 1H), 3.42 (d, $J = 13.5$ Hz, 1H), 3.36 (d, $J = 13.5$ Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 161.8$, 155.8, 132.1, 129.6, 128.5, 127.6, 125.4, 118.5, 117.5, 115.5, 97.8, 38.9, 26.38; HR-MS (ESI): $m/z = 287.1027$, calcd. for $C_{15}H_{15}N_2O_4$ $[M+H]^+$: 287.1032.

General Procedure for the Oxidation of Diketopiperazine Pyrrole-AA 5 into Alcohol 7 in the Presence of Reductant

Diketopiperazine pyrrole-AA **5** (1.0 mmol) was added to a solution of the corresponding reductant (4.0 mmol of Bu_2S or 3.0 mmol of Ph_3P) in dry DMF (24 mL) and stirred for

the time indicated in each case in the presence of an O_2 flow. Upon completion of the reaction, the solvent was evaporated and the alcohol **7** was purified.

Pyrrole-Phe-OH (7a): Prepared from **5a** in the presence of Bu_2S for 3 h; yield: 95%. Purification was made by column flash chromatography in heptane/EtOAc: 6/4 and furnished alcohols **7a** and **4a** (trace).

7a: IR (neat): ν_{max} = 3217, 3117, 1728, 1668, 1496, 1455, 1646, 1580, 1464 cm^{-1}; ^1H NMR (300 MHz, dioxane-d_8): δ = 7.57 (br s, 1H), 7.46 (dd, J = 3.2, 1.5 Hz, 1H), 7.21–7.15 (m, 5H), 6.83 (dd, J = 3.4, 1.5 Hz, 1H), 6.83 (dd, J = 3.4, 3.2 Hz, 1H), 5.73 (br s, 1H), 3.4 (d, J = 13.3 Hz, 1H), 3.08 (d, J = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, dioxane-d_8): δ = 166.0, 156.2, 134.3, 131.1, 128.8, 127.9, 126.7, 119.9, 118.2, 115.9, 85.5, 47.1; HR-MS (ESI): m/z = 255.0759, calcd. for $C_{14}H_{11}N_2O_3$ $[M-H]^-$: 255.0770. The single crystal was cultured by solvent diffusion of THF and toluene mixed solution.

4a: IR (neat): ν_{max} = 3358, 3179, 3062, 1657, 1493, 1454, 1693, 1681, 1545,1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br s, 1H), 7.19–7.04 (m, 4H), 6.94 (dd, J = 3.9, 1.4 Hz, 1H), 6.66 (m, 2H), 6.38 (dd, J = 3.9, 2.8 Hz, 1H), 4.75 (s, 1H), 3.32 (d, J = 13.3 Hz, 1H), 3.24 (d, J = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 155.5, 131.4, 129.4, 128.5, 128.2, 124.8, 120.9, 116.6, 112.8, 85.8, 50.4; HR-MS (ESI): m/z = 279.0742, calcd. for $C_{14}H_{12}N_2O_3Na$ $[M+Na]^+$: 279.0746. The single crystal was cultured by solvent diffusion of acetone and heptane mixed solution.

Pyrrole-Pro-OH (7b): Prepared from **5b** in the presence of Bu_2S for 3 h and purified by recrystallization from CH_2Cl_2 and heptane. The mother liquid was concentrated and purified by silica column chromatography in heptane/EtOAc: 1/1; total yield: 93%. IR (neat): ν_{max} = 3214, 3124, 1740, 1616, 1428, 1326, 1133, 1025, 956, 742 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 7.57 (dd, J = 3.4, 1.5 Hz, 1H), 7.23 (s, 1H), 6.95 (dd, J = 3.3, 1.5 Hz, 1H), 6.54 (dd, J = 3.4, 3.3 Hz, 1H), 3.65–3.48 (m, 2H), 2.27–2.16 (m, 2H), 2.16–1.91 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.9, 154.6, 127.0, 119.7, 116.8, 115.1, 88.1, 44.2, 34.9, 19.5; HR-MS (ESI): m/z = 205.0611, calcd. for $C_{10}H_9N_2O_3$ $[M-H]^-$: 205.0613. The single crystal was cultured by solvent diffusion of THF and heptane mixed solution.

Pyrrole-Leu-OH (7c): Prepared from **5c** in the presence of Bu_2S for 20 h as a pale yellow solid; yield: 96%. The alcohol was purified by recrystallization from CH_2Cl_2 and heptane. IR (neat): ν_{max} = 3235, 1962, 1727, 1642, 1417 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 7.88 (br s, 1H), 7.56 (dd, J = 3.3,1.5 Hz, 1H), 6.99 (dd, J = 3.5, 1.5 Hz, 1H), 6.57 (t, J = 3.3 Hz, 1H), 6.16 (br s, 1H), 2.28 (dd, J = 14.0, 7.5 Hz, 1H), 1.95 (dd, J = 14.0, 5.6 Hz, 1H), 1.77 (sept dd, J = 7.5, 6.7, 5.6 Hz, 1H), 0.96 (d, J = 6.7 Hz, 1H), 0.8 (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.7, 157.0, 126.8, 120.6, 118.3, 116.1, 85.1, 47.6, 25.1, 24.1, 23.2; HR-MS (ESI): m/z = 223.2481, calcd. for $C_{11}H_{15}N_2O_3$ $[M+H]^+$: 223.2479.

Pyrrole-Tyr(OMe)-OH (7d): Prepared from **5d** in the presence of Bu_2S for 15 h as a pale yellow solid; yield: 94%. The alcohol was purified by recrystallization from CH_2Cl_2 and heptane. IR (neat): ν_{max} = 3220, 3120, 1730, 1664, 1512, 1650, 1580,1466 cm^{-1}; ^1H NMR (500 MHz, THF-d_8): δ = 7.86 (br s, 1H), 7.39 (dd, J = 3.2, 1.4 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 6.76 (dd, J = 3.2, 1.4 Hz, 1H), 6.69 (d, J = 8.7 Hz, 2H), 6.37 (s, 1H), 6.35 (t, J = 3.2 Hz, 1H), 3.69 (s, 3H), 3.42 (d, J = 13.3 Hz, 1H), 3.00 (d, J = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, THF-d_8): δ = 165.8, 159.9, 156.4, 132.3, 127.2, 126.8, 119.7, 117.6, 115. 5, 114.3, 85.2, 55.2, 45.5; HR-MS (ESI): m/z = 287.2909, calcd. for $C_{15}H_{15}N_2O_4$ $[M+H^+]$: 287.2901.

Pyrrole-Try-OH (7e): Prepared from **5e** in the presence of Ph_3P for 3 h as a yellow solid; yield: 93%. The alcohol was purified by silica column chromatography with heptane/EtOAc: 6/4. IR (neat): ν_{max} = 3314, 3220, 3140, 1732, 1660, 1580, 1467 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ = 10.10 (br s, 1H), 7.80 (br s, 1H), 7.72 (dd, J = 7.5, 2.0 Hz, 1H), 7.37 (dd, J = 3.2, 1.6, Hz, 1H), 7.3 (d, J = 7.8 Hz, 1H), 7.3 (d, J = 7.8 Hz, 1H), 7.08–6.96 (m, 2H), 6.75 (dd, J = 3.4, 1.6 Hz, 1H), 6.36 (dd, J = 3.4, 3.1 Hz, 1H), 6.32 (br s, 1H), 3.8 (d, J = 14.2 Hz, 1H), 3.44 (d, J = 14.2 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ = 166.4, 156.6, 137.2, 126.9, 128.7, 125.9, 122.2, 120.1, 119.8, 117.8, 115.8, 112.0, 108.0, 86.1, 36.3; HR-MS (ESI): m/z = 294.0876, calcd. for $C_{16}H_{12}N_3O_3$ $[M-H^-]$: 294.0879.

Pyrrole-Met-OH (7f): Prepared from **5f** in the presence of Bu_2S for 2 h as a yellow solid; yieled: 75%. The alcohol was purified by silica column chromatography in EtOAc. 15% of **7h** was isolated as a yellow solid in addition.

7f: IR (neat): ν_{max} = 3244, 3100, 1735, 1632, 1580, 1469 cm^{-1}; ^1H NMR (300 MHz, THF-d_8): δ = 8.06 (br s, 1H), 7.5 (dd, J = 3.1, 1.9 Hz, 1H), 6.96 (dd, J = 3.3, 1.9 Hz, 1H), 6.48 (dd, J = 3.3, 3.1 Hz, 1H), 6.31 (br s, 1H), 2.58–2.43 (m, 3H), 2.13–2.07 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, THF-d_8): δ = 165.1, 127.0, 120.2, 117.9, 115.5, 84.3, 39.1, 28.7, 15.1; HR-MS (ESI): m/z = 239.0500, calcd. for $C_{10}H_{11}N_2O_3S$ $[M-H]^-$: 239.0490.

7h: $dr.$ = 3.5; IR (neat): ν_{max} = 3217, 3114, 1737, 1660, 1579,1462 cm^{-1}; ^1H NMR (300 MHz, DMF-d_7): δ = 9.08 (br s, 0.72H), 9.02 (br s, 0.21H), 7.83 (dd, J = 3.2, 1.5 Hz, 1H), 7.76 (br s, 1H), 7.21 (dd, J = 3.4, 1.5 Hz, 1H), 6.82 (dt, J = 3.5, 1.5 Hz, 1H), 3.25–3.15 (m, 1H), 3.1–2.98), 2.87–2.75(m, 1H), 2.82 (s, 3H), 2.73–2.58 (m, 1H); ^{13}C NMR (75 MHz, DMF-d_7): δ = 164.8, 156.8, 126.6, 120.3, 117.6, 115.6, 83.8, 48.5 (minor), 48.1 (major), 38.4 (minor), 38.1 (major), 31.7 (minor), 31.3 (major); HR-MS (ESI): m/z = 255.0443, calcd. for $C_{10}H_{11}N_2O_4S$ $[M-H]^-$: 255.0440.

Pyrrole-Phe(NMe)-OH (7g): Prepared from **5g** in the presence of Bu_2S for 48 h as a white solid; yield: 75%. **7g** and **4g** were purified by column chromatography in heptane/EtOAc: 6/4.

7g: IR: ν_{max} = 3125, 1737, 1614, 1444, 1369, 1337, 771, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (dd, J = 3.3, 1.5 Hz, 1H), 7.08–7.02 (m, 3H), 6.89–6.83 (m, 2H), 6.56 (dd, J = 3.5, 1.5 Hz, 1H), 6.19 (dd, J = 3.5, 3.3 Hz, 1H), 5.42 (br s, 1H), 3.27 (s, 2H), 3.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 155.6, 132.1, 129.1, 128.4, 127.7, 125.0, 118.5, 118.1, 115.8, 88.6, 44.9, 26.9; HR-MS (ESI): m/z = 271.1075, calcd. for $C_{15}H_{15}N_2O_3$ $[M+H]^+$: 271.1083.

4g: white solid; IR (neat): ν_{max} = 3356, 1708, 1660, 1545, 1319, 1067, 1088, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.2–7.03 (m, 3H), 6.89 (dd, J = 3.9, 1.7 Hz, 1H), 6.5 (dd, J = 3.0, 1.7 Hz, 1H), 6.37 (dd, J = 4.0, 3.0 Hz, 1H), 4.54, (br s, 1H), 3.29 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 13.2 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 155.9, 131.7, 129.0, 128.4, 128.2, 123.5, 121.2, 115.9, 112.6, 85.6, 51.4, 26.1; HR-MS (ESI): m/z = 269.0913, calcd. for $C_{15}H_{13}N_2O_3$ $(M-H)^-$: 269.0926.

Compound 8: Yellow oil; IR (neat): $\nu_{max}=3332$ (NH indole), 1737 (C=O amide), 1643 (C=O amide), 1616, 1464 cm^{-1} (C=C); ^1H NMR (300 MHz, acetone-d_6): $\delta=7.50$ (dd, $J=3.1$, 1.6 Hz, 1H), 7.30 (d, $J=7.7$ Hz, 1H), 7.08 (t, $J=7.7$ Hz, 1H), 7.02 (dd, $J=3.5$, 1.6 Hz, 1H), 6.71 (t, $J=7.7$ Hz, 1H), 6.60 (d, $J=7.7$ Hz, 1H), 6.52 (dd, $J=3.5$, 3.1 Hz, 1H), 6.05 (br s, 1H), 5.77 (d, $J=2.4$ Hz, 1H), 5.17 (br s, 1H), 2.92 (d, $J=14.0$ Hz, 1H), 2.71 (d, $J=14.0$ Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6): $\delta=164.2$, 157.6, 150.3, 132.4, 130.9, 128.5, 124.6, 121.6, 119.8, 119.2, 116.3, 111.2, 91.3, 87.4, 85.6, 49.8; HR-MS (ESI): $m/z=312.3006$, calcd. for $C_{16}H_{14}N_3O_4$ $[M+H^+]$: 312.2995.

General Procedure for Dehydration of Alcohols 7 into 9

Diketopiperazine pyrrole-AA-OH **7** (1 mmol) was dissolved in CH_3CN (15 mL), and then HCl solution in dioxane (4 μL, 0.05 mmol) was added. The mixture was stirred for 10 min at room temperature, then 10 min at 50°. The solvent was removed to afford the pure light yellow solid; yield: quantitative.

9a: IR (neat): $\nu_{max}=3222$ (NH); 1677 (amide); 1613, 1494, 1458 (C=C); 1570 cm^{-1} (pyrrole); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.99$ (br s, 1H), 7.74 (dd, $J=1.5$, 3.2 Hz, 1H), 7.54–7.46 (m, 5H), 7.35 (s, 1H), 7.23 (dd, $J=1.5$, 3.6 Hz, 1H), 6.60 (dd, $J=3.2$, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=154.8$, 153.9, 132.6, 129.7, 129.6, 128.8, 126.3, 124.2, 121.5, 120.9, 119.3, 115.5; HR-MS (ESI): $m/z=$ 261.0638, calcd. for $C_{14}H_{10}N_2O_2Na$ $[M+Na]^+$: 261.0640.

9b: IR (neat): $\nu_{max}=1726$, 1621, 1415, 1321, 736 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta=7.68$ (dd, $J=3.2$, 1.5 Hz, 1H), 6.99 (dd, $J=3.5$, 1.5 Hz, 1H), 6.74 (t, $J=3.5$ Hz, 1H), 6.60 (t, $J=3.3$ Hz, 1H), 4.03 (t, $J=8.9$ Hz, 1H), 2.89 (dt, $J=$ 8.9, 3.5 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6): $\delta=152.1$, 151.7, 133.6, 127.6, 127.0, 119.8, 116.1, 115.4, 44.8, 28.9; HR-MS (ESI): $m/z=211.0482$, calcd. for $C_{10}H_8N_2O_2Na$ $[M+$ $Na]^+$: 211.0483.

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