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Cu/Mn Co-oxidized Cyclization for the Synthesis of Highly Substituted Pyrrole Derivatives from Amino Acid Esters: A Strategy for the Biomimetic Syntheses of Lycogarubin C and Chromopyrrolic Acid

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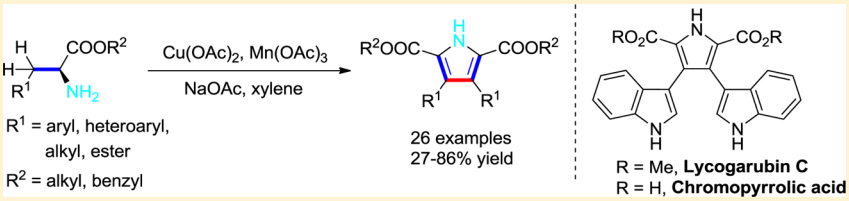
Supporting Information



ABSTRACT: An effective and concise approach to synthesis of tetrasubstituted pyrroles from readily available amino acid esters by the promotion of $Cu(OAc)_2$ in conjunction with $Mn(OAc)_3$ has been developed. This reaction proceeds through multiple dehydrogenations, deamination, and oxidative cyclization. This oxidized system tolerates substrates bearing various electron-donating or electron-withdrawing groups. With this methodology, several key intermediates of natural products have been effectively prepared, and the total syntheses of lycogarubin C and chromopyrrolic acid have been completed in high efficiency.

INTRODUCTION

The pyrrole nucleus is an essential structural subunit prevalent in numerous biologically significant natural products and plays an important role in material science and pharmaceutical chemistry.[1] Although many well-documented synthetic methods for the construction of pyrroles have been described in detail by chemists,[2] they still have some drawbacks, such as multiple reaction steps and the use of not easily available raw materials. Therefore, the development of efficient and concise approaches to the preparation of pyrroles from readily available substrates is of great significance.

In 2006, Sherman and co-workers[3] reported an interesting biosynthesis of chromopyrrolic acid (CPA, **1**).[4] This chemistry was generally believed to proceed through a stepwise mechanism that included the formation of imine intermediate **3** from L-tryptophan with the action of RebO enzyme and the transformation from **3** to CPA catalyzed by RebD enzyme via oxidative deamination and cyclization (Scheme 1A). Encouraged by their achievement, we envisioned that the commercially available amino acid esters **4** could undergo a biomimetic process mediated by transition metal via oxidation, deamination, and cyclization to prepare the highly substituted pyrroles **5** (Scheme 1B). Because of many advantages including brief reaction steps, high selectivity, and efficiency, transition-metal-promoted biomimetic synthesis has been widely used for the preparation of many natural products, pharmaceutical compounds, and key intermediates in organic synthesis and has scored rapid development.[5] However, there are few successful examples of biomimetic synthesis of pyrrole derivatives. Here, we developed an effective biomimetic method for the synthesis of highly substituted pyrroles from commercially available amino acid esters through Cu/Mn co-oxidized dehydrogenation, deamination, and cyclization.

RESULTS AND DISCUSSION

Initially, we treated the amino acid ester **4a** with 1.0 equiv of $Cu(OAc)_2$ in refluxing toluene and obtained pyrrole **5a** as a major product in 30% yield, which has been prepared by Takamura via a three-step procedure.[6] The structure of **5a** was confirmed by X-ray crystallography analysis (Scheme 1C).[7] In order to improve the yield of **5a**, different conditions were screened next. The results are summarized in Table 1. After screening the solvents, we found that xylene was more suitable for the reaction (Table 1, entries 1 and 2). Since the reaction involved oxidative cyclization and multiple deprotonations, increasing the amount of $Cu(OAc)_2$ was expected to be beneficial. When the reaction was carried out with 2.0 equiv of $Cu(OAc)_2$, the yield of **5a** was improved to 48% (entry 3). Subsequently, the yield of **5a** was increased to 62% with 3.0 equiv of $Cu(OAc)_2$ (entry 4). Other oxidative reagents were also used for deprotonation or cyclization. With $PdCl_2$ as deprotonation reagent, the yield of **5a** was slightly decreased (entry 5). When AgOAc was used as oxidative reagent, **5a** was obtained in 16% yield (entry 6). Other oxidative reagents, such as DDQ, $PhI(OAc)_2$, and TEMPO, failed to improve the yield

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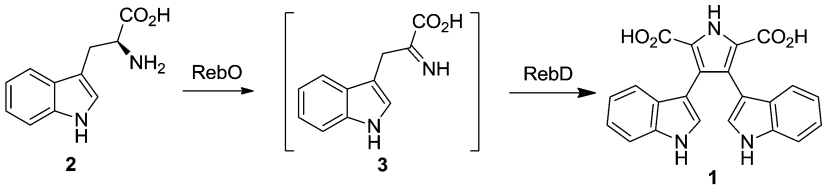
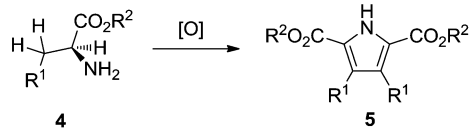
Scheme 1. Biosynthetic Route and Biomimetic Synthesis to Pyrrole Derivatives



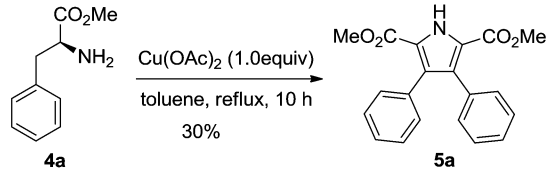
A Biosynthetic route to chromopyrrolic acid (1)



R^1 = aryl, heteroaryl, alkyl, ester

R^2 = alkyl, benzyl

B Biomimetic synthesis of pyrrole derivatives from amino acid esters



C $Cu(OAc)_2$ promoted oxidation cyclization for the synthesis to pyrrole **5a**

Table 1. Synthesis of Pyrrole 5a under Different Conditions[a]

entry	additive (equiv)	base (equiv)	yield[b] (%)
1			30[c]
2			39
3			48[d]
4			62[e]
5	$PdCl_2$ (0.05)		32
6	AgOAc (0.5)		16
7	MnO_2 (0.5)		52
8	$Mn(OAc)_3$ (0.5)		57
9	$Mn(OAc)_3$ (0.4)		66
10	$Mn(OAc)_3$ (0.3)		62
11		NaOAc (1.0)	48
12		KOAc (1.0)	11
13		pyridine (1.0)	19
14	$Mn(OAc)_3$ (0.4)	NaOAc (1.0)	79
15	$Mn(OAc)_3$ (0.4)	NaOAc (0.5)	65

[a]All reactions were carried out under the following conditions, unless otherwise noted: 0.28 mmol of **4a** and 1.0 equiv of $Cu(OAc)_2$ in 10 mL of xylene at refluxing temperature. [b]Isolated yield. [c]The solvent was toluene. [d]The reaction was carried out in 2.0 equiv of $Cu(OAc)_2$. [e]The reaction was carried out in 3.0 equiv of $Cu(OAc)_2$.

of **5a**. However, with 0.5 equiv of MnO_2 and $Mn(OAc)_3$ as oxidative additive, the yield of **5a** was improved to 52% and 57%, respectively (entries 7 and 8). Fortunately, when the amount of $Mn(OAc)_3$ decreased to 0.4 equiv, the yield of **5a** was improved to 66% (entry 9), but in the presence of 0.3 equiv of $Mn(OAc)_3$, the yield of **5a** was slightly reduced (entry 10). Since Jia[2i] had proposed that the base would neutralize the acid formed during the reaction to prepare polysubstituted pyrroles from primary amines and aldehydes, we screened the bases. We found that in the presence of 1.0 equiv of NaOAc and 1.0 equiv of $Cu(OAc)_2$, the yield of **5a** was improved to 48% (entry 11). Other bases such as KOAc and pyridine could not improve the yield (entries 12 and 13). To our delight, when 1.0 equiv of $Cu(OAc)_2$, 0.4 equiv of $Mn(OAc)_3$, and 1.0 equiv of NaOAc were merged together, the yield of **5a** was further increased to 79% (entry 14). However, when the amount of NaOAc was reduced to 0.5 equiv, the yield of **5a** decreased to 65% (entry 15). Thus, the optimum reaction conditions thus developed were as follows: 1.0 equiv of **4a**, 1.0 equiv of $Cu(OAc)_2$, 0.4 equiv of $Mn(OAc)_3$, and 1.0 equiv of NaOAc in anhydrous xylene.

With the optimal reaction conditions in hand, various α-amino acid esters were subjected to the standard reaction conditions, as shown in Table 2. For phenylalanine esters, we tested methyl, ethyl, benzyl, and *tert*-butyl for R and found that the desired products **5a–d** were generated in a high yield. For the substrates bearing either electron-withdrawing or electron-donating *para*-substituents on the benzene ring, the reaction could proceed smoothly and the desired products **5e–l** were obtained in good yields. The result that electron-withdrawing *para*-substituents on the benzene ring slightly decreased the yield of pyrroles **5g–i** might be attributed to the reduced stability of the α-imine radical cation intermediate. Notably, the product **5f**, with bromine as a *para*-substituent on the benzene ring, would allow further functionalization. Subsequently, we found that the steric hindrance effect from *ortho*- and *meta*-substituents had a negative impact on the yield of desired products **5m–p**. What should not be neglected was that the yield of pyrroles **5q–s** would drastically decrease when the steric hindrance effects and electron effects merged together. Among all of the obtained products, **5t** was obtained in the

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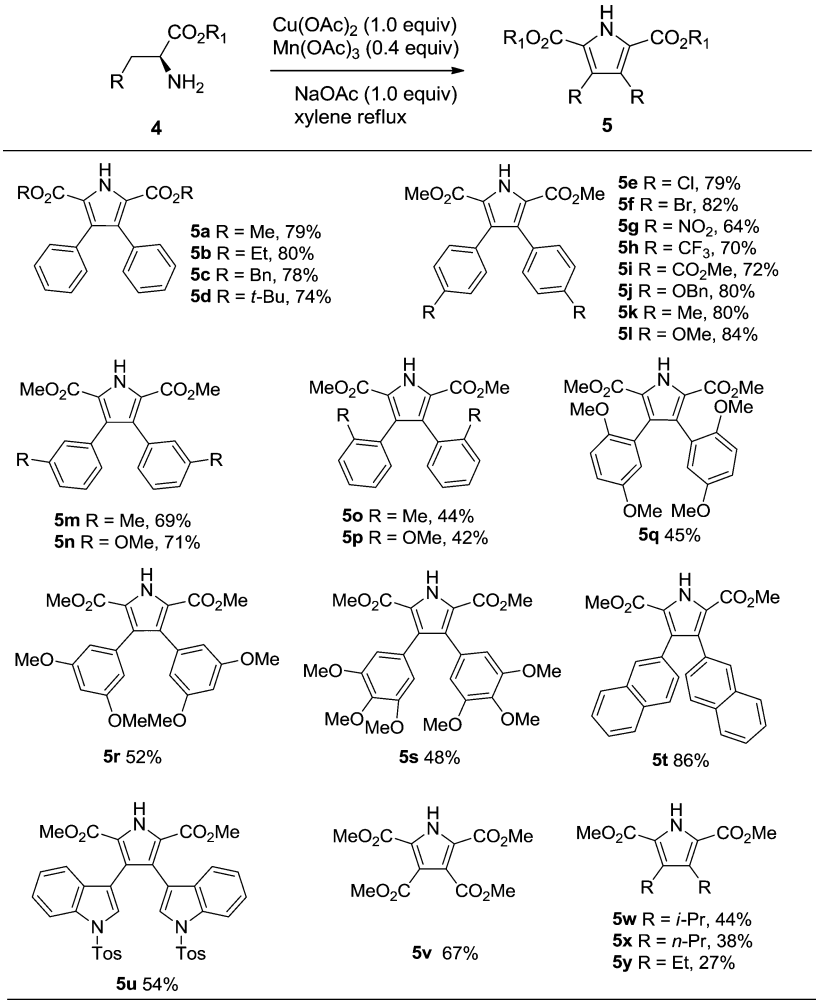
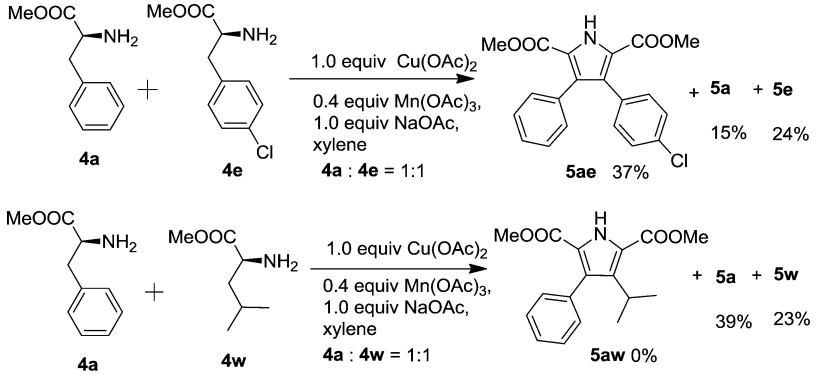
Table 2. Scope of Synthesis Pyrrole from Amino Acid Esters[a]



[a]All reactions were carried out on the scale of 0.28 mmol of amino acid esters, 1.0 equiv of $Cu(OAc)_2$, 0.4 equiv of $Mn(OAc)_3$, and 1.0 equiv of NaOAc in 10 mL of refluxing xylene.

Scheme 2. Synthesis of Unsymmetrical Pyrrole



highest yield (86%) because of the high reactivity of the naphthyl α-imine radical cation intermediate. When the Tos-tryptophan methyl ester was used as the substrate, we obtained **5u** in 54% yield, which could be directly transformed into lycogarubin C. Interestingly, the method was also suitable for aliphatic amino acid esters to prepare pyrroles **5v**–**y**. Among them, **5v** was produced in moderate yield (67%) from aspartic acid dimethyl ester, while others (**5w**–**y**) were obtained in relatively low yield, possibly because of the relatively low activity and stability of the aliphatic radical intermediate in the process. Although the yields of pyrroles prepared from aliphatic amino acid esters were relatively low, they were the first successful examples obtained by activating general sp^3 C–H bonds of alkanes to generate pyrroles.

Having successfully achieved the symmetric pyrroles, we turned to the preparation of unsymmetrical pyrroles from two different amino acid esters under the standard reaction conditions. However, there was no high selectivity observed,

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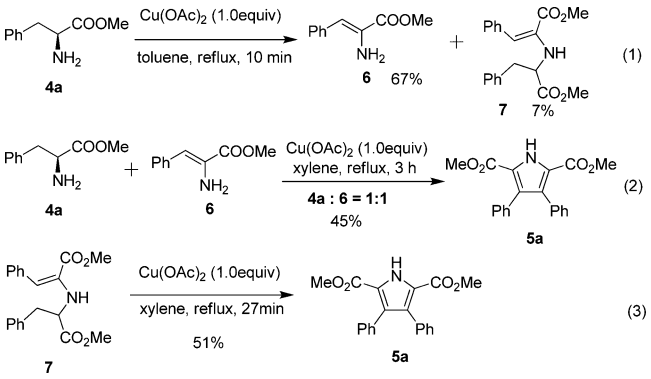
as shown in Scheme 2. The reaction of 1.0 equiv of **4a** and 1.0 equiv of **4e** gave pyrroles **5ae**, **5a**, and **5e** in yields of 37%, 15%, and 25%, respectively. However, there was no **5aw** observed in the reaction of 1.0 equiv of **4a** and 1.0 equiv of **4w**.

In order to shed light on the reaction mechanism, we further explored the reaction (Scheme 3) and obtained the

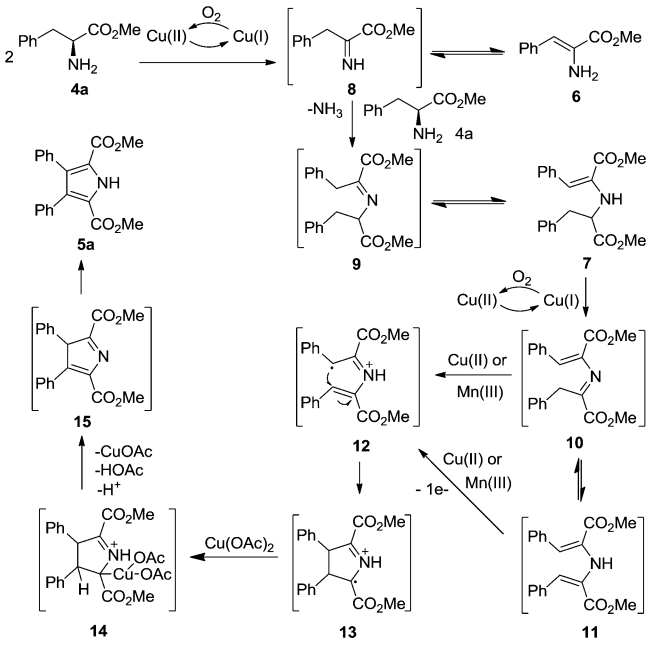
Scheme 3. Studies on the Reaction Mechanism



intermediates in the early stage of the process when the reaction slowed down in refluxing toluene. Compounds **6** and **7** were afforded when **4a** was treated with 1.0 equiv of $Cu(OAc)_2$ in refluxing toluene for 10 min (eq 1). Under the same conditions, **6** could serve as the substrate with **4a** to prepare **5a** (eq 2), and **5a** could also be obtained from **7** (eq 3). Therefore, **6** and **7** were key intermediates in the process. Moreover, the yield was better under aerobic conditions than anaerobic conditions.

On the basis of the above experimental results, a possible mechanism for the construction of **5a** had been proposed as shown in Scheme 4. First, the oxidative dehydrogenation of the amine **4a** provided imine intermediate **8** which was in equilibrium with enamine **6**. This process is very similar to formation of imine intermediate **3** from L-tryptophan with the

Scheme 4. Proposed Mechanism for the Formation of 5a



action of RebO enzyme.[3] Then, the addition of a second molecule of the primary amine of **4a** to imine **8** produced imine **9**, with the loss of NH_3.[8] Further, **7**, in equilibrium with imine **9**, was converted to **10** by oxidative dehydrogenation, and a single-eletron oxidation produced α-imine radical cation **12** from **10** or **11**,[9] which underwent intramolecular radical addition on alkene to give γ-imine cation species **13**. Next, oxidation of the intermediate **13** proceeded through the Cu(III) complex **14** to give **15** along with loss of CuOAc and HOAc.[10] Finally, **15** was configured to aromatize to the pyrrole **5a**. The mechanism studies would be helpful to unravel the biosynthesis of pyrrole alkaloid from amino acid.[3]

It is noteowothy that the effectiveness and utility of the methodology are adequately demonstrated by the total syntheses of lycogarubin C and CPA (Scheme 5). CPA is a key intermediate in the biosynthesis of the indolo[2,3-*a*]carbazole alkaloids rebeccamycin and staurosporine, which exhibit broad spectrum activity as inhibitors of protein kinases as well as topoisomerase I,[11] and has been synthesized by Steglich, Thiel, Gribble, and Boger.[4a,12] Now, we have efficiently achieved the two natural products from Tos-tryptophan methyl ester **4u**. Under the optimized conditions, the desired pyrrole **5u** was acquired in 54% yield, and then, after being subjected to Mg in MeOH, **5u** was transformed to lycogarubin C in 93% yield.[12c] Finally, CPA was obtained in 95% yield by the reaction of lycogarubin C with KOH.[12d] This new biomimetic strategy has made a valuable contribution to the total synthesis of lycogarubin C (in 50% overall yield over two steps) and CPA (in 48% overall yield over three steps) from Tos-tryptophan methyl ester. The utility of the methodology would be further demonstrated by the syntheses of pyrrole-derived alkaloids which were isolated from marine organisms.[1a]

CONCLUSION

In summary, we have found an efficient biomimetic strategy for the synthesis of pyrrole derivatives from commercial amino acid esters through multiple dehydrogenations, deamination, and oxidative cyclization promoted by $Cu(OAc)_2$ and $Mn(OAc)_3$. This protocol exhibits a wide range of applications for various α-amino acid ester derivatives having an aryl, heteroaryl, alkyl, or ester group on the β-position to give the corresponding products in moderate to good yields. The mechanism is useful for further unravelling the biosynthesis of natural pyrrole-derived alkaloids from amino acid derivatives. In addition, the effectiveness and utility of this method are fully demonstrated by the total synthesis of lycogarubin C and CPA, and further research on the oxidation cyclization of amino acid esters for the synthesis of the nitrogen-bearing heterocyclic compounds is underway in our group.

EXPERIMENTAL SECTION

General Experimental Methods. All manipulations were conducted with a round-bottom flask in dry air. Xylene was freshly distilled from sodium. ^1H NMR spectra were recorded on 400 MHz spectrometers, and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.00 ppm). High-resolution mass spectra (HRMS) were obtained on a 4G mass spectrometer by using electrospray ionization (ESI) analyzed by quadrupole time-of-flight (QTof). IR spectra were recorded on a FT-IR spectrometer, and only major peaks were reported in cm^{-1}. Melting points were

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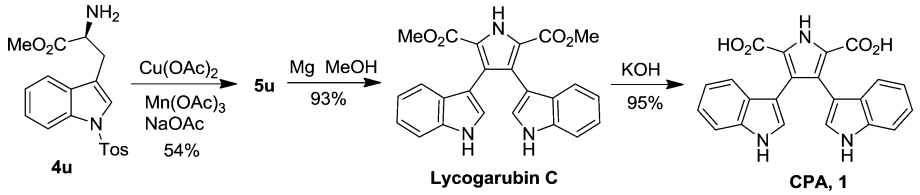
Scheme 5. Biomimetic Synthesis of Lycogarubin C and CPA



determined on an X-4 microscopic apparatus and were uncorrected. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, brs, broad singlet for proton spectra. Coupling constants (J) are reported in hertz (Hz). Flash column chromatography was performed using silica gel (200−300 mesh) with solvents distilled prior to use.

Typical Procedure for Syntheses of Pyrroles. To a solution of the amino acid ester (0.28 mmol) in anhydrous xylene (10 mL) were added the $Cu(OAc)_2$ (0.28 mmol, 1.0 equive), NaOAc (0.28 mmol, 1.0 equive), and $Mn(OAc)_3$ (0.11 mmol, 0.4 equive) in dry air. After being stirred in refluxing xylene, the mixture was cooled to room temperature and evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography to give the pure pyrroles.

*Dimethyl 3,4-diphenyl-1H-pyrrole-2,5-dicarboxylate (**5a**):* 37 mg; isolated yield 79%; yellow solid; mp 187−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (brs, 1H), 7.21−7.19 (m, 6H), 7.12−7.10 (m, 4H), 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 132.9, 131.6, 130.8, 127.4, 127.0, 121.3, 51.8; HRMS (ESI) m/z calcd for $C_{20}H_{18}NO_4$ $(M + H)^+$ 336.1230, found 336.1238; IR (neat) 3305, 1706, 1434, 1299, 1245, 1034, 1014, 947, 766, 700, 538 cm^{-1}.

*Diethyl 3,4-diphenyl-1H-pyrrole-2,5-dicarboxylate (**5b**):* 41 mg; isolated yield 80%; yellow solid; mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.87 (brs, 1H), 7.19 (d, J = 3.2 Hz, 6H), 7.13−7.11 (m, 4H), 4.22 (q, J = 7.2 Hz, 4H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.4, 133.1, 131.4, 130.8, 127.2, 126.9, 121.5, 60.8, 14.0; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1543, found 364.1558; IR (neat) 3283, 3065, 2983, 1703, 1461, 1369, 1300, 1247, 1167, 1026, 760, 700, 543, 487 cm^{-1}.

*Dibenzyl 3,4-diphenyl-1H-pyrrole-2,5-dicarboxylate (**5c**):* 53 mg; isolated yield 78%; yellow solid; mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.90 (brs, 1H), 7.27−7.25 (m, 6H), 7.20−7.12 (m, 6H), 7.10−7.07 (m, 8H), 5.20 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.3, 135.2, 133.0, 131.8, 130.8, 128.4, 128.1, 128.0, 127.4, 127.0, 121.6, 66.5; HRMS (ESI) m/z calcd for $C_{32}H_{26}NO_4$ $(M + H)^+$ 488.1856, found 488.1861; IR (neat) 3396, 3339, 1714, 1601, 1450, 1382, 1294, 1245, 1158, 1071, 1032, 919, 844, 741, 698, 630, 513, 470, 412 cm^{-1}.

*Di-tert-butyl 3,4-diphenyl-1H-pyrrole-2,5-dicarboxylate (**5d**):* 43 mg; isolated yield 74%; yellow solid; mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.71 (brs, 1H), 7.16 (s, 6H), 7.09 (d, J = 7.2 Hz, 4H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.0, 133.7, 130.8, 130.7, 127.2, 126.6, 122.5, 81.8, 28.0; HRMS (ESI) m/z calcd for $C_{26}H_{29}NO_4K(M + K)^+$ 458.1728, found 458.1742; IR (neat) 3446, 3294, 2977, 2929, 1704, 1458, 1369, 1309, 1252, 1156, 844, 787, 756, 697, 498, 439 cm^{-1}.

*Dimethyl 3,4-bis(4-chlorophenyl)-1H-pyrrole-2,5-dicarboxylate (**5e**):* 45 mg; isolated yield 79%; yellow solid; mp 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.94 (brs, 1H), 7.21−7.18 (m, 4H), 7.05−7.01 (m, 4H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.4, 133.2, 132.0, 131.0, 130.0, 127.8, 121.4, 51.92, 51.88; HRMS (ESI) m/z calcd for $C_{20}H_{16}Cl_2NO_4$ $(M + H)^+$ 404.0451, found 404.0460; IR (neat) 3412, 3281, 2954, 2362, 1711, 1467, 1441, 1300, 1245, 1091, 1016, 824, 753, 664, 610, 506 cm^{-1}.

*Dimethyl 3,4-bis(4-bromophenyl)-1H-pyrrole-2,5-dicarboxylate (**5f**):* 56 mg; isolated yield 82%; yellow solid; mp 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.91 (brs, 1H), 7.35 (d, J = 8.4 Hz, 4H), 6.96 (d, J = 8.4 Hz, 4H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.4, 132.4, 131.5, 130.8, 130.0, 121.6, 121.4, 51.9; HRMS (ESI) m/z calcd for $C_{20}H_{15}Br_2NO_4Na$ $(M + Na)^+$ 513.9260, found 513.9264; IR (neat) 3301, 2923, 1715, 1461, 1430, 1301, 1248, 1158, 1070, 1016, 949, 856, 821, 786, 730, 553, 407 cm^{-1}.

*Dimethyl 3,4-bis(4-nitrophenyl)-1H-pyrrole-2,5-dicarboxylate (**5g**):* 38 mg; isolated yield 64%; yellow solid; mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.08 (brs, 1H), 8.12−8.09 (m, 4H), 7.30−7.26 (m, 4H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.9, 147.1, 139.2, 131.6, 128.8, 123.0, 121.9, 52.3, 52.2; HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O_8Na$ $(M + Na)^+$ 448.0751, found 448.0754; IR (neat) 3412, 3326, 2923, 2840, 1715, 1600, 1518, 1345, 1244, 1111, 1019, 856, 754, 630, 513, 489, 412 cm^{-1}.

*Dimethyl 3,4-bis(4-(trifluoromethyl)phenyl)-1H-pyrrole-2,5-dicarboxylate (**5h**):* 46 mg; isolated yield 70%; yellow solid; mp 167−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.99 (brs, 1H), 7.48 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 8.0 Hz, 4H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.3, 136.2, 131.1, 129.9, 129.6, 129.3, 125.5, 124.6, 122.8, 121.7, 52.0; HRMS (ESI) m/z calcd. for $C_{22}H_{15}F_6NO_4K$ $(M + K)^+$ 510.0537, found 510.0540; IR (neat) 3291, 2925, 2362, 1718, 1619, 1443, 1324, 1250, 1163, 1119, 1067, 1025, 854, 415 cm^{-1}.

*Dimethyl 3,4-bis(4-(methoxycarbonyl)phenyl)-1H-pyrrole-2,5-dicarboxylate (**5i**):* 45 mg; isolated yield 72%; yellow solid; mp 215−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.95 (brs, 1H), 7.88 (d, J = 8.0 Hz, 4H), 7.16 (d, J = 8.0 Hz, 4H), 3.89 (s, 6H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.9, 160.4, 137.5, 130.8, 130.3, 128.9, 128.8, 121.6, 52.04, 51.98; HRMS (ESI) m/z calcd for $C_{24}H_{21}NO_8Na$ $(M + Na)^+$ 474.1159, found 474.1159; IR (neat) 3395, 2923, 2854, 1719, 1438, 1280, 1105, 1018, 856, 754, 702, 611, 546, 513, 412 cm^{-1}.

*Dimethyl 3,4-bis(4-(benzyloxy)phenyl)-1H-pyrrole-2,5-dicarboxylate (**5j**):* 61 mg; isolated yield 80%; yellow solid; mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.77 (brs, 1H), 7.44−7.36 (m, 8H), 7.34−7.30 (m, 2H), 7.05 (d, J = 8.8 Hz, 4H), 6.84 (d, J = 8.8 Hz, 4H), 5.02 (s, 4H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 157.9, 137.1, 132.0, 131.3, 128.5, 127.9, 127.6, 125.4, 121.1, 113.9, 69.9, 51.7; HRMS (ESI) m/z calcd for $C_{34}H_{29}NO_6K$ $(M + K)^+$ 586.1626, found 586.1628; IR (neat) 3367, 3338, 3034, 2925, 1713, 1605, 1506, 1461, 1380, 1299, 1243, 1173, 1114, 1027, 837, 745, 697, 416 cm^{-1}.

*Dimethyl 3,4-di-p-tolyl-1H-pyrrole-2,5-dicarboxylate (**5k**):* 41 mg; isolated yield 80%; yellow solid; mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 7.01 (s, 8H), 3.77 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.7, 136.5, 131.6, 130.6, 129.8, 128.1, 121.2, 51.7, 21.2; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1543, found 364.1550; IR (neat) 3440, 3280, 2923, 1709, 1467, 1441, 1300, 1245, 1016, 813, 756, 691, 552, 462, 430, 420, 405 cm^{-1}

*Dimethyl 3,4-bis(4-methoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**5l**):* 46 mg; isolated yield 84%; yellow solid; mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.80 (brs, 1H), 7.04 (d, J = 8.8 Hz, 4H), 6.76 (d, J = 8.8 Hz, 4H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 158.5, 131.9, 131.3, 125.1, 121.1, 112.9, 55.1, 51.7; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_6$ $(M + H)^+$ 396.1442, found 396.1452; IR (neat) 3286, 2951, 1710, 1609, 1468, 1298, 1245, 1179, 1114, 1032, 839, 754, 630, 513, 416 cm^{-1}.

*Dimethyl 3,4-di-m-tolyl-1H-pyrrole-2,5-dicarboxylate (**5m**):* 35 mg; isolated yield 69%; yellow solid; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.82 (brs, 1H), 7.10−7.07 (m, 2H), 7.00 (d, J = 3.2 Hz, 2H), 6.93−6.89 (m, 4H), 3.77 (s, 6 H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 136.6, 132.7, 131.7, 131.5,

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127.8, 127.7, 127.1, 121.2, 51.7, 21.3; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1543, found 364.1550; IR (neat) 3445, 3294, 2952, 1710, 1464, 1438, 1305, 1252, 1037, 782, 494, 458, 421 cm^{-1}.

*Dimethyl 3,4-bis(3-methoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**5n**):* 39 mg; isolated yield 71%; yellow solid; mp 156−158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (brs, 1H), 7.13 (t, J = 3.6 Hz, 2H), 6.77−6.74 (m, 4H), 6.64 (s, 2H), 3.78 (s, 6H), 3.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.7, 158.7, 134.1, 131.3, 128.3, 123.4, 121.2, 116.1, 113.1, 55.1, 51.8; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_6$ $(M + H)^+$ 396.1442, found 396.1441; IR (neat) 3294, 2922, 2852, 2363, 1711, 1607, 1584, 1466, 1435, 1304, 1254, 1218, 1049, 1023, 783, 716, 627 cm^{-1}.

*Dimethyl 3,4-di-o-tolyl-1H-pyrrole-2,5-dicarboxylate (**5o**):* 22 mg; isolated yield 44%; yellow solid; mp 182−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.88 (brs, 1H), 7.11−7.05 (m, 4H), 7.02 (d, J = 3.6 Hz, 2H), 7.97−6.94 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 3.724 (s, 3H), 3.720 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.71, 160.70, 137.1, 136.7, 133.1, 132.6, 131.2, 131.2, 131.1, 129.8, 129.4, 129.2, 127.34, 127.31, 124.9, 124.6, 122.0, 121.9, 51.8, 20.2, 19.8; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1543, found 364.1544; IR (neat) 3290, 2923, 1711, 1463, 1296, 1243, 1011, 764, 732, 555, 468, 408 cm^{-1}.

*Dimethyl 3,4-bis(2-methoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**5p**):* 23 mg; isolated yield 42%; yellow solid; mp 169−171 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.85 (brs, 1H), 7.20−7.15 (m, 2H), 7.00−6.98 (m, 2H), 6.81−6.76 (m, 4H), 3.73 (s, 6H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 157.1, 131.7, 128.5, 127.9, 122.7, 122.1, 119.6, 110.2, 55.2, 51.6; HRMS (ESI) m/z calcd for $C_{22}H_{22}NO_6$ $(M + H)^+$ 396.1442, found 396.1440; IR (neat) 3428, 3288, 2923, 1714, 1464, 1246, 1028, 756, 447 cm^{-1}.

*Dimethyl 3,4-bis(2,5-dimethoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**5q**):* 28 mg, Isolated yield 45%; yellow solid; mp 149−150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.84 (brs, 1H), 6.72 (d, J = 2.4 Hz, 4H), 6.58 (s, 2H), 3.74 (s, 6H), 3.60 (s, 6H), 3.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160. 8, 152.7, 127.5, 123.4, 120.2, 117.2, 113.8, 111.3, 55.8, 55.7, 51.7; HRMS (ESI) m/z calcd for $C_{24}H_{26}NO_8$ $(M + H)^+$ 456.1653, found 456.1658; IR (neat) 3368, 2950, 2846, 1711, 1599, 1460, 1205, 1155, 1065, 1029, 984, 847, 776, 643, 550, 407 cm^{-1}.

*Dimethyl 3-(3,5-dimethoxyphenyl)-4-(3-hydroxy-5-methoxyphenyl)-1H-pyrrole-25-dicarboxylate (**5r**):* 33 mg; isolated yield 52%; yellow solid; mp 150−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (brs, 1H), 6.34−6.31 (m, 6H), 3.79 (s, 6H), 3.64 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.7, 159.8, 134.7, 131.2, 121.2, 108.9, 99.8, 55.3, 51.9; HRMS (ESI) m/z calcd for $C_{24}H_{26}NO_8$ $(M + H)^+$ 456.1653, found 456.1658; IR (neat) 3284, 2997, 2948, 2837, 1714, 1495, 1461, 1439, 1262, 1223, 1151, 1044, 878, 806, 742, 653, 631, 489, 471, 450, 434, 410 cm^{-1}.

*Dimethyl 3,4-bis(3,4,5-trimethoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**5s**):* 34 mg; isolated yield 48%; yellow solid; mp 124−126 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.84 (brs, 1H), 6.38 (s, 4H), 3.83 (s, 12H), 3.65 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.6, 152.4, 137.4, 131.2, 128.1, 121.0, 108.5, 60.9, 56.1, 51.9; HRMS (ESI) m/z calcd for $C_{26}H_{30}NO_{10}$ $(M + H)^+$ 516.1864, found 516.1866; IR (neat) 3457, 3292, 3008, 2924, 2854, 1714, 1586, 1460, 1341, 1238, 1123, 1008, 83, 832, 768, 689, 659, 553, 407 cm^{-1}.

*Dimethyl 3,4-di(naphthalen-2-yl)-1H-pyrrole-2,5-dicarboxylate (**5t**):* 52 mg; isolated yield 86%; yellow solid; mp 212−214 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.99 (brs, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.66−7.60 (m, 6H), 7.40−7.33 (m, 4H), 7.23 (d, J = 7.6 Hz, 2H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 132.8, 132.4, 131.5, 130.3, 129.9, 128.8, 128.0, 127.5, 126.8, 125.8, 125.6, 121.6, 51.8; HRMS (ESI) m/z calcd for $C_{28}H_{21}NO_4K$ $(M + K)^+$ 474.1102, found 474.1104; IR (neat) 3423, 2360, 2342, 1736, 1701, 1295, 1252, 1224, 751, 479, 459, 420 cm^{-1}.

*Dimethyl 3,4-bis(1-tosyl-1H-indol-3-yl)-1H-pyrrole-2,5-dicarboxylate (**5u**):* 54 mg; isolated yield 54%; yellow solid; mp 198−199 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.16 (brs, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 6H), 7.17 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 8.0 Hz, 6H), 7.01 (d, J = 7.6 Hz, 2H), 3.58 (s, 6H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.4, 144.7, 135.0, 134.3, 129.8, 126.4, 125.8, 124.4, 123.4, 123.1, 122.1, 120.4, 114.7, 113.3, 51.8, 21.5; HRMS (ESI) m/z calcd for $C_{38}H_{31}N_3O_8S_2K$ $(M + K)^+$ 760.1184, found 760.1193; IR (neat) 3408, 2924, 2854, 2361, 2324, 1715, 1407, 1374, 1261, 1166, 1076, 1025, 803, 751, 703, 664, 403 cm^{-1}.

*Tetramethyl 1H-pyrrole-2,3,4,5-tetracarboxylate (**5v**):* 28 mg; isolated yield 67%; yellow solid; mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.23 (brs, 1H), 3.92 (s, 6H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.2, 159.1, 123.3, 121.7, 52.7, 52.5; HRMS (ESI) m/z calcd for $C_{12}H_{14}NO_8$ $(M + H)^+$300.0714, found 300.0721; IR (neat) 3242, 2956, 1725, 1571, 1450, 1262, 1058, 991, 792, 631, 545, 514, 470, 412 cm^{-1}.

*Dimethyl 3,4-diisopropyl-1H-pyrrole-2,5-dicarboxylate (**5w**):* 16 mg; isolated yield 44%; yellow solid; mp 104−106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.45 (brs, 1H), 3.87 (s, 6H), 3.63−3.59 (m, 2H), 1.33 (d, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.6, 137.5, 120.3, 51.5, 25.2, 21.5; HRMS (ESI) m/z calcd for $C_{14}H_{22}NO_4$ $(M + H)^+$ 268.1543, found 268.1555; IR (neat) 3389, 3353, 2958, 2941, 2868, 1715, 1467, 1442, 1372, 1248, 1029, 754, 663, 630, 514, 470, 410 $cm^{-1.}$

*Dimethyl 3,4-dipropyl-1H-pyrrole-2,5-dicarboxylate (**5x**):* 14 mg; isolated yield 38%; yellow solid; mp 53−55 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.39 (brs, 1H), 3.87 (s, 6H), 2.68 (q, J = 6.0 Hz, 4H), 1.57−1.47 (m, 4H), 0.95 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.1, 132.1, 121.3, 51.5, 26.5, 24.5, 14.2; HRMS (ESI) m/z calcd for $C_{14}H_{22}NO_4$ $(M + H)^+$ 268.1543, found 268.1541; IR (neat) 3457, 3319, 2958, 2869, 1711, 1559, 1464, 1438, 1349, 1261, 1201, 1144, 1097, 1030, 981, 789, 630, 514, 485, 413 cm^{-1}.

*Dimethyl 3,4-diethyl-1H-pyrrole-2,5-dicarboxylate (**5y**):* 9 mg; isolated yield 27%; yellow solid; mp 80−81 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.40 (brs, 1H), 3.91 (s, 6H), 2.76 (q, J = 7.6 Hz, 4H), 1.16 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.1, 133.4, 121.0, 51.5, 17.7, 15.8; HRMS (ESI) m/z calcd for $C_{12}H_{18}NO_4$ $(M + H)^+$ 240.1230, found 240.1228; IR (neat) 3288, 2969, 2923, 2852, 1716, 1463, 1422, 1264, 1201, 1139, 1088, 983, 787, 414 cm^{-1}.

*Dimethyl 3-(4-chlorophenyl)-4-phenyl-1H-pyrrole-2,5-dicarboxylate (**5ae**):* 19 mg; isolated yield 37%; yellow solid; mp 167−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (brs, 1H), 7.26−7.16 (m, 5H), 7.10−7.09 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.6, 160.5, 133.1, 132.5, 132.1, 131.4, 131.3, 130.7, 130.2, 127.7, 127.5, 127.3, 127.2, 121.4, 121.2, 51.9, 51.8; HRMS (ESI) m/z calcd for $C_{20}H_{17}ClNO_4$ $(M + H)^+$ 370.0841, found 370.0848; IR (neat) 3432, 3283, 2954, 1712, 1469, 1438, 1300, 1247, 1092, 1008, 911, 779, 733, 702, 647, 612, 539, 503, 451 cm^{-1}.

General Procedure for the Synthesis of the Intermediate 6 and 7. To a solution of the phenylalanine methyl ester **4a** (370 mg, 2.067 mmol) in anhydrous toluene (15 mL) was added $Cu(OAc)_2$ (380 mg, 2.093 mmol) in dry air. After being stirred in refluxing toluene for 20 min, the mixture was cooled to room temperature and evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (FCC) (SiO_2, EtOAc/PE = 1:16, EA) to give colorless oil **6** 100 mg (67%), colorless oil **7** 21 mg (7%), and **4a** 219 mg with 59% in recovery.

*(Z)-Methyl 2-amino-3-phenylacrylate (**6**):* ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.25−7.20 (m, 1H), 6.48 (s, 1H), 4.22 (brs, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.3, 136.2, 132.2, 128.8 (2C), 128.3 (2C), 126.8, 109.2, 52.6; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO_2$ $(M + H)^+$ 178.0863, found 178.0865; IR (neat) 3447, 3368, 3024, 2952, 2711, 1633, 1593, 1441, 1398, 1276, 1228, 1076, 988, 856, 769, 694, 592, 531, 498, 454, 415 cm^{-1}

*(Z)-Methyl 2-((1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-phenylacrylate (**7**):* ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.29−7.18 (m, 8H), 7.07 (m, 2H), 6.66 (s, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.20−4.18 (m, 1H), 3.82 (s, 3H), 3.57 (s, 3H), 3.98−2.87 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.3, 166.6, 136.4, 135.3, 133.3, 129.3 (3C), 129.0 (2C), 128.3 (3C), 127.3, 126.9, 114.8, 58.5, 52.6, 51.8, 39.2; HRMS (ESI) m/z calcd for $C_{20}H_{22}NO_4$ $(M + H)^+$

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340.1543, found 340.1550; IR (neat) 3391, 3022, 2925, 2854, 2406, 1742, 1554, 1494, 1444, 1400, 1371, 1249, 1164, 1076, 1027, 992, 764, 700, 665, 470, 412 cm^{-1}

General Procedure for the Synthesis of Lycogarubin C. To a solution of compound **5u** (20 mg, 0.02773 mmol) in strictly anhydrous methanol (5 mL) were added magnesium turnings (102 mg, 4.2500 mmol) and the solution sonicated for 2 h at rt. The reaction mixture was then quenched with aq NH_4Cl solution (10 mL) and water (5 mL) and extracted with EtOAc (4 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by FCC (SiO_2, 30% EtOAc/PE) to give compound lycogarubin C as a yellow solid (11 mg, 93%): mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.92 (s, 2H), 7.26−7.23 (m, 3H), 7.14−7.06 (m, 3H), 7.00−6.93 (m, 3H), 6.86 (s, 2H), 3.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.0, 135.5, 127.6, 125.0, 124.4, 122.6, 121.5, 120.1, 119.4, 110.9, 108.8, 51.7; HRMS (ESI) m/z calcd for $C_{24}H_{19}N_3O_4K$ $(M + K)^+$ 452.1007, found 452.1004; IR (neat) 3409, 2925, 1702, 1514, 1457, 1267, 1239, 1121, 1097, 1063, 925, 794, 741, 668, 581, 501, 436 cm^{-1}

General Procedure for the Synthesis of Chromopyrrolic Acid (CPA, 1). A sample of lycogarubin C (18 mg, 0.04354 mmol) was dissolved in a 2 mL solution of 1:1 (v/v) THF/H_2O and treated with KOH (17.7 mg, 0.3154 mmol). The reaction mixture concentrated under reduced pressure, dissolved in H_2O, and extracted with EtOAc. The aqueous layer was acidified (pH 2−3) and extracted with EtOAc (4 × 10 mL). The resulting organic layer was concentrated under reduced pressure and purified by flash column chromatography (SiO_2, toluene/EtOAc/HCOOH = 35:10:1) to yield chromopyrrolic acid as a tan power (16 mg, 95%): mp 186−188 °C; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.37−7.29 (m, 2H), 7.22 (dd, J = 3.6 Hz, 8.0 Hz, 2H),7.12 (d, J = 8.0 Hz, 2H), 6.96 (q, J = 8.0 Hz, 2H), 6.82−6.76 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ ppm 163.1, 137.4, 129.9, 129.2, 128.0, 125.9, 121.7, 120.7, 119.5, 111.8, 109.6; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_4O_4$ $(M + NH_4)^+$ 403.1401, found 403.1410; IR (KBr) 3412, 2950, 1688, 1543, 1509, 1437, 1382, 1241, 1094, 1056, 1102, 967, 831, 788, 752, 581, 543, 497, 427 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data (^1H and ^{13}C) and data for the X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Fan, H.; Peng, J. N.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264−287. (b) Young, I. S.; Thorntonb, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801−1839. (c) Al-Mourabit, A.; Zancanella, M. A.; Tilvic, S.; Romo, D. *Nat. Prod. Rep.* **2011**, *28*, 1229−1260. (d) Heugebaert, T. S. A.; Roman, B. L.; Stevens, C. V. *Chem. Soc. Rev.* **2012**, *41*, 5626−5640. (e) Kathirav, M. K.; Salake, A. B.; Chothe, A. S.; Dudhe, P. B.; Watode, R. P.; Mukta, M. S.; Gadhwe, S. *Bioorg. Med. Chem.* **2012**, *20*, 5678−5698. (f) Su, T.-L.; Lee, T.-C.; Kakadiya, R. *Eur. J. Med. Chem.* **2013**, *69*, 609−621.

(2) For selected recent examples on pyrrole synthesis, see: (a) Black, D. S. *Sci. Synth.* **2001**, *9* (13), 441−535. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. (c) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260−9266. (d) Bergman, J.; Janosik, T. 3.03 − Pyrroles and their Benzo Derivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: New York, 2008; Vol. 3, p 269−351. (e) Yasui, E.; Wada, M.; Takamura, N. *Tetrahedron Lett.* **2009**, *50*, 4762−4765. (f) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318−8320. (g) Ciez, D. *Org. Lett.* **2009**, *11*, 4282−4285. (h) Lourdusamy, E.; Yao, L.; Park, C.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7963−7967. (i) Li, Q. J.; Fan, A. L.; Z. Lu, Y.; Cui, Y. X.; Lin, W. H.; Jia, Y. X. *Org. Lett.* **2010**, *12*, 4066−4069. (j) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693−1697. (k) Jiang, Y.; Chan, W. C.; Park, C.-M. *J. Am. Chem. Soc.* **2012**, *134*, 4104−4107. (l) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088−11091. (m) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696−4699. (n) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716−4718. (o) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384−11388. (p) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712−11715. (q) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140−144. (r) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629−633. (s) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015.

(3) Nishizawa, T.; Gruschow, S.; Jayamaha, D.-H. E.; Nishizawa-Haraha, C.; Sherman, D. H. *J. Am. Chem. Soc.* **2006**, *128*, 724−725.

(4) (a) Frode, R.; Hinze, C.; Josten, I.; Schmidt, B.; Steffan, B.; Steglich, W. *Tetrahedron Lett.* **1994**, *35*, 1689−1690. (b) Hashimoto, T.; Yasuda, A.; Akazawa, K.; Takaoka, S.; Tori, M.; Akazawa, Y. *Tetrahedron Lett.* **1994**, *35*, 2559−2560.

(5) For recent reviews of biomimetic synthesis of natural products, see: (a) Razzak, M.; Brabander, J. D. *Nat. Chem. Biol.* **2011**, *7*, 865−875. (b) Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32−56. (c) Lautu, S.; Song, L.; Demange, L.; Lombes, T.; Galons, H.; Challis, G. L.; Pemodet, J.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 7454−7458. (d) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254−297. (e) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757−4778.

(6) Yasui, E.; Wada, M.; Takamura, N. *Tetrahedron Lett.* **2009**, *50*, 4762−4765.

(7) CCDC 969628 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) (a) Al-Hmoud, L.; Jones, C. W. *J. Catal.* **2013**, *301*, 116−124. (b) Zhu, B. L.; Lazar, M.; Trewyn, B. G.; Angelici, R. J. *J. Catal.* **2008**, *260*, 1−6.

(9) (a) Koch, D.; Schäfer, H. *Angew. Chem., Int. Ed.* **1973**, *12*, 245−246. (b) Khetan, S. K. *Chem. Commun.* **1972**, 917−917. (c) Herten, B. W.; Poulton, G. A. *Chem. Commun.* **1975**, 456−457. (d) Carr, R. M.; Norman, R. O. C.; Vernon, J. M. *Chem. Commun.* **1977**, 854−855. (e) Carr, R. M.; Norman, R. O. C.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 156−162. (f) Sukari, M. A.; Vernon, J. M. *Tetrahedron* **1983**, *39*, 793−796. (g) Tsai, A.; Chuang, C.-P. *Tetrahedron* **2006**, *62*, 2235−2239. (h) Wang, J.-Y.; Liu, S.-P.; Yu, W. *Synlett* **2009**, 2529−2533.

(10) For selected radicals by copper(II), see: (a) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 1965−1968. (b) Yin, J.; Wang, C.; Kong, L. L.; Cai, S. J.; Gao, S. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 7786−7789.

(11) Knolker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4428.

(12) (a) Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373−6380. (b) Hinze, C.; Kreipl, A.; Terpin, A.; Steglich, W. *Synthesis* **2007**, *4*, 608−612. (c) Fu, L. F.; Gribble, G. W. *Tetrahedron Lett.* **2010**, *51*, 537−539. (d) Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132−1134.