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A facile synthesis of 5-alkoxypyrrol-2(5*H*)-ones using a modified aza-Achmatowicz oxidation

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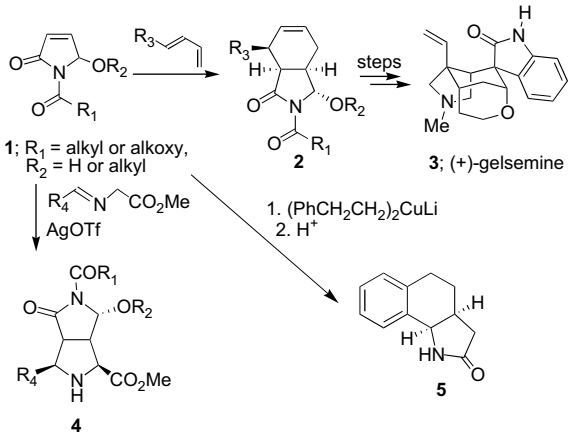
ABSTRACT

An efficient approach to 2,4-disubstituted pyrroles has been uncovered and is based on an oxidative rearrangement of a furanyl carbamate followed by sequential reaction of the resulting 5-methoxypyrrol-2(5*H*)-one with various alkyl lithiates. The final step of the procedure involves heating the ring opened 1-methoxy-5-oxopentylcarbamate with a primary amine. The overall process can be carried out under mild conditions and complements existing methods to prepare 2,4-disubstituted pyrroles.

1. Introduction

5-Hydroxy and the related 5-alkoxypyrrol-2(5*H*)-one (**1**) systems exhibit a wide range of interesting pharmacological properties,[1] and have been used on occasion as intermediates in the synthesis of several alkaloids[2] and are also suitable precursors for the preparation of unusual γ-amino acids such as statine and its analogues.[3] The chemistry of this unique pyrrolidinone ring has been explored by a number of research groups.[4] Because of its multifunctional core, this heterocyclic system can take part in several stereoselective transformations such as conjugate addition,[5] cycloadditions,[6] acyliminium ion chemistry,[7] and allylic substitutions[8] (Scheme 1). A noteworthy example from the Hiemstra/Speckamp laboratory involves the use of 5-isopropoxypyrrolinone **1** (R_1=Me; R_2=$(CH_3)_2CH$) as an effective starting material for the synthesis of gelsemine (**3**).[6]

5-Hydroxypyrrol-2(5*H*)-ones derivatives have been prepared by the oxidative bromination reaction of nicotine,[9] amination of the corresponding lactones,[10] metal-catalyzed condensation–cyclization reaction of acyl cyanides with 3-oxoamides,[11] and the Ni-catalyzed cyanation of α-keto-alkynes in H_2O.[12] The majority of synthetic approaches used for the preparation of the related 5-alkoxypyrrol-2(5*H*)-one system are based on the cyclization of α,β-unsaturated keto amides,[13] amination reactions of the corresponding γ-lactones,[10,14] Grignard addition to maleimide derivatives,[15] and the photosensitized oxygenation of pyrroles,[16] diazepines,[17] and 2-furyl carbamates.[18] In spite of the availability of these methods, the development of a highly efficient protocol for the synthesis of various 5-alkoxypyrrol-2(5*H*)-ones is still of high interest, especially since the known routes to these α,β-unsaturated lactams generally suffer from either low yields or long reaction times.



Scheme 1.

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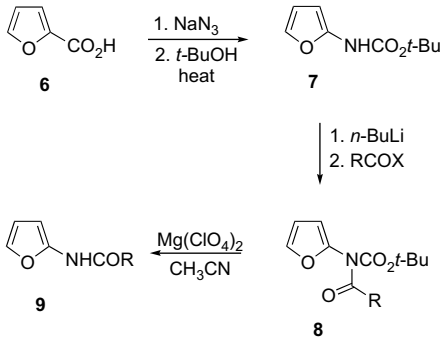
Some years ago, we reported on a useful approach for the preparation of hydroxylated piperidine alkaloids[19] by making use of the aza-Achmatowicz oxidation.[20] This earlier work prompted us to explore the related oxidative rearrangement of furanyl amides and carbamates into 5-alkoxypyrrol-2(5*H*)-ones. This paper describes in detail our studies dealing with the iodine-promoted oxidation of 2-amidofurans and 2-furanyl carbamates as well as a subsequent adaptation of the reaction, which allows for the synthesis of a wide range of 2,4-disubstituted pyrroles.

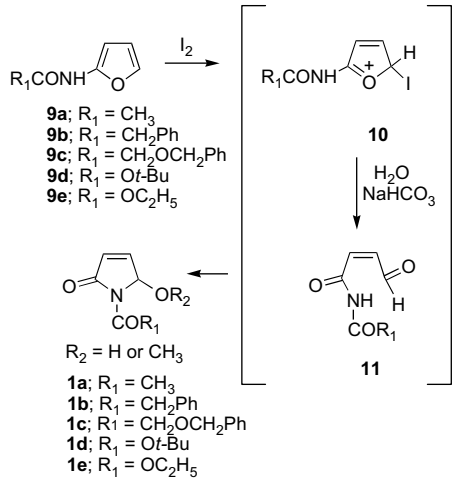
2. Results and discussion

As part of an ongoing research program dealing with the synthesis of novel azapolycyclic compounds, we have been investigating the intramolecular [4+2]-cycloaddition/rearrangement cascade of 2-amidofurans as a strategy for the preparation of hexahydroindolinone alkaloids.[21] During the course of this work we developed an efficient, scalable method for the synthesis of various 2-furanyl amides of type **9** by an acyl azide formation/Curtius rearrangement sequence (Scheme 2) starting from furoic acid **6**.[22] Treatment of the resulting carbamate **7** with *n*-BuLi provides the corresponding anion, which undergoes ready acylation with a number of acid chlorides or mixed anhydrides.[23] The Boc protecting group of the acylated imidofuran **8** can be easily removed by treatment with $Mg(ClO_4)_2$ in CH_3CN to provide a variety of amidofurans **9**.[24] The compounds synthesized include products which contain alkyl, aryl, or heteroaryl R-substituents. The reaction of the resulting furanyl amide **9** with 3.0 equiv of I_2 and 6.0 equiv of $NaHCO_3$ in aqueous acetone at 25 °C occurred smoothly and furnished a variety of 5-hydroxypyrrol-2(5*H*)-ones (**1**). More than likely the reaction proceeds via intermediates **10** and **11** as indicated in Scheme 3. The initially formed 2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole (**1**) could be readily converted into the corresponding methoxy derivative by treatment with methyl iodide and silver(I) oxide in CH_2Cl_2 at 25 °C (vide infra). The yield of the resulting 5-hydroxypyrrol-2(5*H*)-one from the amido furan is quite good (ca. 85%) and the final product is easily isolated by column chromatography on silica gel.

Having ascertained the reaction conditions necessary for *N*-hydroxypyrrolinone formation, we became interested in exploring the use of these intermediates for alkaloid synthesis. Because of our interest in using *N*-acyliminium ion chemistry for total synthesis,[25] we decided to explore the possibility of using a cyclization reaction of 5-hydroxypyrrolinone **12** to generate the core structure **13** whose skeleton is found in a number of natural products such as crispine A (**14**).[26] This potential synthetic route would allow us to readily convert furanyl carbamate **9d** into a crispine A precursor (i.e., **13**) in only four steps (Scheme 4). Unfortunately, all of our attempts to induce the cyclization of **12**

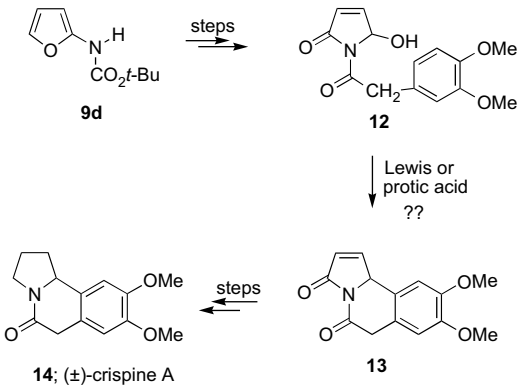


Scheme 2.



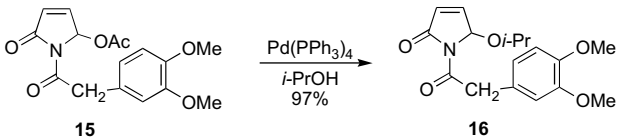
Scheme 3.

into **13** using a wide variety of Lewis acids (i.e., $SnCl_4$, $TiCl_4$, MgI_2, $BF_3{\cdot}OEt_2$, etc.) failed and only recovered starting material was obtained, even under prolonged reaction conditions. We also attempted to induce this cyclization using a variety of acids (i.e., *p*-TsOH, HCl, TFA, TfOH, PPA, etc.) at high temperatures but this also resulted in complete failure. While the cyclization of *N*-acylamines has been well explored,[27] it would seem that the cyclization behavior of a *N*-diacylamine such as **12** is dramatically different. More than likely, the inability of this system to cyclize is due to the lack of interaction of the nitrogen lone pair of electrons of the diacylated amine with the adjacent hydroxyl group thereby retarding formation of the required cationic intermediate.



Scheme 4.

Realizing that simple iminium ion generation and cyclization of **12** is unlikely to produce the desired product **13**, we then became interested in determining whether a π-allyl palladium mediated cyclization might occur.[28] With this in mind, we prepared the necessary allylic acetate intermediate **15** in 73% yield by treating **12** with acetic acid and pyridine. As before, all of our attempts to induce the desired cyclization reaction failed. A variety of palladium-catalyzed conditions were examined but all failed to give any characterizable products. Only in the case when $Pd(Ph_3)_4$ and *i*-propanol was used were we able to isolate a product (97%) whose structure was subsequently identified as 5-isopropoxypyrrolin-2(5*H*)-one **16**. It would appear that a large excess of a nucleophilic solvent (i.e., *i*-PrOH) is necessary before addition to the π-allyl complexed pyrrolinone core can occur (Scheme 5).



15 16

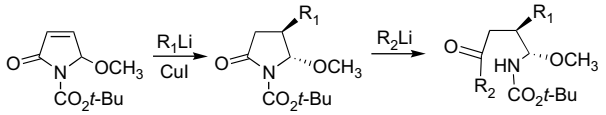
Scheme 5.

Even though our attempted iminium ion cyclization studies did not proceed as we had hoped, we did see some other synthetic utility for these substituted hydroxypyrrolinones. In particular, we became interested in using these compounds for the synthesis of various 2,4-disubstituted pyrroles. The biological activity of substituted pyrroles has made them a focus of medicinal chemistry over the years.[29] Pyrroles occur in numerous pharmacologically active natural and unnatural products.[30] Additionally, functionalized pyrroles represent building blocks of natural tetrapyrrole pigments, such as porphyrobilinogen or bilirubin, and of various other natural products and their analogues.[31] For more than a century, many diverse methods have been developed to prepare pyrroles with various ring substitution patterns,[32] including the classical Hantzsch, Knorr, and Paal–Knorr procedures.[33] With this in mind, we have developed a four-step approach to a variety of 2,4-disubstituted pyrroles using 5-methoxypyrrol-2(5*H*)-one (**17**). This compound was readily obtained from the corresponding hydroxy derivative **1d** by treatment with methyl iodide and silver(I) oxide in CH_2Cl_2 at 25 °C. The yield of the resulting 5-methoxypyrrol-2(5*H*)one **17** from the starting furanyl carbamate **9d** is quite good (ca. 85%) and the final product is easily isolated by column chromatography on silica gel.

The conjugate addition of various cuprates to the α,β-unsaturated lactam system of **17** proceeded in 60–92% yield with high stereoselectivity. The ^{1}H NMR spectra of the crude product only showed the presence of a single trans-addition product in all cases. The assignment was based on the ^{1}H NMR vicinal coupling constant of H_5. In a *trans*-lactam this coupling is 0–1 Hz, whereas a *cis*-lactam has a coupling of 5–6 Hz.[34] The products obtained from the cuprate additions were then used in the next step, which consisted of treating the 2-methoxy-3-alkyl substituted oxypyrrolidinone **18** with an alkyl lithium reagent to give the ring opened 1-methoxy-5-oxopentylcarbamate **19**. The results for the conjugate addition–alkyl lithiation reaction of differently substituted systems in THF at −78 °C are summarized in Table 1. From the table it can be seen that the reaction is quite general: R_2=various alkyl, phenyl or 2-thienyl groups with yields ranging from 65% to 94%.

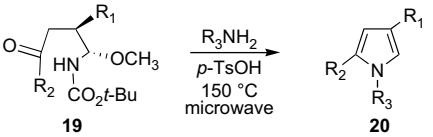
The 2,4-disubstituted pyrrole (**20**) system was then prepared by heating a mixture of the 1-methoxy-5-oxopentylcarbamate **19** and an appropriate amine in the presence of a trace amount of *p*-TsOH in a microwave reactor at 150 °C (Scheme 6). In all cases, the desired 2,4-disubstituted pyrrole was obtained in good yield with no evidence of any products arising from simple hydrolysis or alternatively by furan formation. On the other hand, heating an aqueous DMF solution of **19a** (R_1=Ph; R_2=*n*-C_4H_9) in a microwave reactor afforded an almost quantitative yield of the NH-pyrrole **20j**. However, when **19a** is heated in toluene in the presence of a CSA/quinoline catalyst, only the Boc-pyrrole **20k** was formed in 76% yield.

Table 1
Conjugate addition–alkyl lithiation reaction of 5-methoxypyrrol-2(5*H*)-one (**17**)

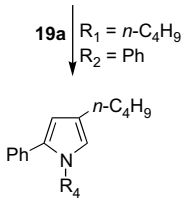


17 18 19

Entry	R_1	Yield of **18**	R_2	Yield of **19**
a	*t*-Bu	80%	Allyl	72%
b	Ph	75%	CH_3	70%
c	*n*-C_4H_9	92%	Ph	94%
d	*n*-C_4H_9	—	CH_3	85%
e	CH_3	80%	2-Thienyl	86%
f	CH_3	—	*n*-C_4H_9	80%
g	*n*-C_6H_{13}	60%	C_2H_5	65%



19 20

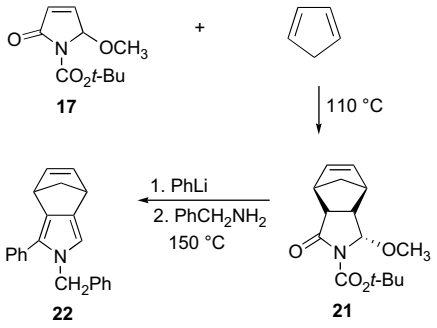


20a; R_1 = *n*-C_4H_9; R_2 = Ph; R_3 = CH_2Ph (90%)
20b; R_1 = *n*-C_4H_9; R_2 = R_3 = Ph (97%)
20c; R_1 = *n*-C_4H_9; R_2 = Ph; R_3 = 2-CH_2(furanyl) (65%)
20d; R_1 = *n*-C_4H_9; R_2 = Ph; R_3 = cyclohexyl (90%)
20e; R_1 = Ph; R_2 = CH_3; R_3 = CH_2Ph (70%)
20f; R_1 = *n*-C_4H_9; R_2 = CH_3; R_3 = CH_2Ph (81%)
20g; R_1 = CH_3; R_2 = 2-thienyl; R_3 = CH_2Ph (86%)
20h; R_1 = *n*-C_6H_{13}; R_2 = C_2H_5; R_3 = CH_2Ph (42%)
20i; R_1 = CH_3; R_2 = *n*-C_4H_9; R_3 = CH_2Ph (54%)

20j; R_4 = H (98%)
20k; R_4 = CO_2t-Bu (76%)

Scheme 6.

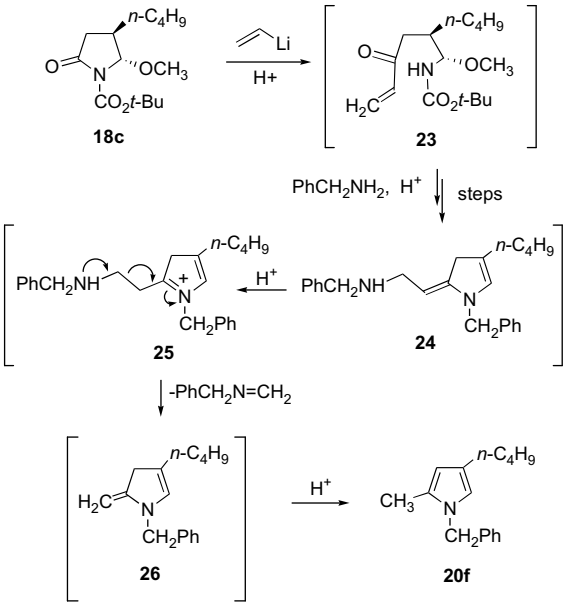
We have also examined the Diels–Alder cycloaddition reaction of 5-methoxypyrrol-2(5*H*)-one (**17**) with cyclopentadiene (Scheme 7). The reaction works well and the expected cycloadduct **21** was obtained in almost quantitative yield. Further treatment of adduct **21** with phenyllithium followed by heating with benzylamine afforded the novel bridged pyrrole **22** in 43% yield.



17 22 21

Scheme 7.

Interestingly, when the reaction sequence was carried out in a one-pot fashion using 5-oxopyrrolidinone **18c** and vinyl lithium followed by heating with benzylamine, the only product that could be isolated corresponded to *N*-benzyl-4-*n*-butyl-2-methyl-1*H*-pyrrole (**20f**). This somewhat surprising result can be explained by the series of reactions outlined in Scheme 8. More than likely, the transient vinyl oxypentylcarbamate **23** that is first formed reacts with excess benzylamine to eventually give enamine **24**. Protonation of **24** to iminium ion **25** followed by loss of $PhCH_2N{=}CH_2$ under the reaction conditions furnishes **26**, which is readily isomerized to pyrrole **20f**.



Scheme 8.

3. Conclusion

In summary, the new oxidative rearrangement chemistry of furanyl carbamates described herein gives rapid access to a variety of 5-alkoxypyrrol-2(5*H*)-ones. Treatment of these heterocycles with various cuprate reagents followed by a subsequent reaction with an alkyl lithiate and then a primary amine furnishes 2,4-disubstituted pyrroles in good yield.

4. Experimental

4.1. General

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. A representative procedure for the oxidative rearrangement of the furanyl carbamate involved stirring a sample of the furan in acetone/H_2O at 0 °C. Sodium bicarbonate was added followed by iodine crystals in 3 portions. After stirring for 3 h at 0 °C, the mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise.

*4.1.1. 1-Acetyl-5-hydroxy-1H-pyrrol-2(5H)-one (**1a**)*

To a stirred solution of *N*-(furan-2-yl)acetamide (**9a**) (0.08 g, 0.65 mmol) in acetone/H_2O (20:1, 50 mL) at 0 °C was added $NaHCO_3$ (0.33 g, 3.9 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (0.49 g, 1.9 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.05 g (57%) of 1-acetyl-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (**1a**) as a white solid, mp 86–87 °C.[35] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 4.38 (d, 1H, J=4.0 Hz), 6.14–6.15 (m, 1H), 6.21 (dd, 1H, J=6.0 and 1.2 Hz), and 7.16 (dd, 1H, J=6.0 and 1.6 Hz).

*4.1.2. 5-Hydroxy-1-(2-phenylacetyl)-1H-pyrrol-2(5H)-one (**1b**)*

To a stirred solution of *tert*-butyl furan-2-ylcarbamate (**9d**) (0.2 g, 1.1 mmol) in THF (8 mL) at 0 °C was added *n*-BuLi (0.5 mL, 1.3 mmol, 2.5 M in hexane) dropwise and the mixture was stirred at 0 °C for 30 min. In a separate flask, phenylacetic acid (0.15 g, 1.1 mmol) was dissolved in THF (8 mL) and the mixture was cooled to 0 °C. 4-Methylmorpholine (0.12 mL, 1.1 mmol) and isobutyl chloroformate (0.14 mL, 1.1 mmol) were added dropwise and the solution was stirred for 5 min. The mixture was filtered over Celite with THF (4 mL) and the filtrate was cooled to 0 °C. The preformed furanyl lithiate from above was added dropwise by cannula. The resulting reaction mixture was stirred for 2 h at 0 °C and was then quenched with H_2O and extracted with EtOAc. The organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered over a pad of silica gel, and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and was added to a stirred solution of $Mg(ClO_4)_2$ (0.23 g, 1.0 mmol) in CH_3CN (5 mL) at 40 °C and the mixture was heated at 40 °C for 25 min. The solution was cooled to 0 °C and quenched with H_2O and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.03 g (12%) of *N*-(furan-2-yl)-2-phenylacetamide (**9b**) as pale yellow oil. IR (thin film) 3242, 3064, 2918, 1666, 1562, 1379, 1248, 1196, 1147, 791, and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.73 (s, 2H), 6.31–6.35 (m, 2H), 7.00 (dd, 1H, J=2.0 and 0.8 Hz), 7.30–7.41 (m, 5H), and 7.65 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.0, 95.6, 111.7, 128.0, 129.5, 129.7, 134.1, 135.6, 145.2, and 167.6.

To a stirred solution of the above furanyl amide **9b** (0.02 g, 0.12 mmol) in acetone/H_2O (18:1, 9.5 mL) at 0 °C was added $NaHCO_3$ (0.06 g, 0.7 mmol). The solution was then stirred at this temperature for 10 min. A sample of iodine (0.09 g, 0.36 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 40 min, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.02 mg (67%) of the titled compound **1b** as a white solid, mp 109–110 °C. IR (thin film) 3450, 3102, 2924, 1738, 1686, 1348, 1242, 1197, and 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28 (s, 1H), 4.29 (s, 2H), 6.15–6.16 (m, 1H), 6.22 (d, 1H, J=6.0 Hz), 7.17 (dd, 1H, J=6.0 and 1.6 Hz) and 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7, 82.4, 127.5, 128.8, 130.0, 133.5, 147.7, 167.8, and 172.6.

*4.1.3. 1-(2-(Benzyloxy)acetyl)-5-hydroxy-1H-pyrrol-2-(5H)-one (**1c**)*

To a stirred solution of 2-(benzyloxy)acetic acid (1.0 g, 6.0 mmol) in CH_2Cl_2 (15 mL) was added oxalyl chloride (1.6 mL, 18.0 mmol) followed by 2 drops of DMF. The reaction mixture was stirred at rt for 1 h and was then concentrated under reduced pressure, taken up in THF (15 mL), and cooled to −78 °C. In a separate flask, *tert*-butyl furan-2-ylcarbamate (**9d**) (1.3 g, 7.2 mmol) was dissolved in THF (10 mL) at 0 °C. To this mixture was added *n*-BuLi (2.6 mL, 6.6 mmol, 2.5 M in hexane) dropwise and the mixture was stirred at 0 °C for 0.5 h. The resulting solution was transferred dropwise by cannula into a solution of the above acid chloride at −78 °C. The solution was stirred for 1 h while slowly warming from −78 °C to 0 °C. The mixture was then quenched with H_2O, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 1.5 g (77%) of *tert*-butyl-2-(benzyloxy)-acetyl(furan-2-yl)carbamate as a white solid, mp 64–66 °C. IR (thin film) 3127, 2981, 2934, 1790, 1745, 1611, 1500, 1371, 1306, 1271, 1153, 1092, 1013, 955, 847, 772, 738, and 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 4.65 (s, 2H), 4.66 (s, 2H), 6.17–6.18 (m, 1H), 6.43 (dd, 1H, J=3.6 and 2.0 Hz), and 7.27–7.41 (m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 27.9, 71.2, 73.5, 84.6, 106.4, 111.5, 128.1, 128.3, 128.6, 137.7, 140.9, 142.8, 151.6, and 172.8; HRMS calcd for $[(C_{13}H_{13}NO_4)+K^+]$: 286.0482, found: 286.0459.

The above Boc furanyl carbamate (1.1 g, 3.0 mmol) was dissolved in CH_3CN (5 mL) and was added to a stirred solution of $Mg(ClO_4)_2$ (0.84 g, 3.8 mmol) in CH_3CN (50 mL) at 40 °C. The reaction mixture was heated at 40 °C for 10 min, cooled to rt, and diluted with H_2O. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 0.63 g (90%) of 2-(benzyloxy)-*N*-(furan-2-yl)acetamide (**9c**) as a pale yellow oil. IR (neat) 3375, 3281, 3155, 3064, 2914, 2867, 1694, 1608, 1531, 1455, 1376, 1344, 1239, 1208, 1108, and 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 2H), 4.64 (s, 2H), 6.35–6.39 (m, 2H), 7.07 (dd, 1H, *J*=2.0 and 0.8 Hz), 7.32–7.42 (m, 5H), and 8.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.3, 74.0, 95.6, 111.8, 128.3, 128.7, 129.0, 135.8, 136.5, 144.7, and 166.1.

To a stirred solution of the above furanyl amide **9c** (0.35 g, 1.5 mmol) in acetone/H_2O (18:1, 51 mL) at 0 °C was added $NaHCO_3$ (0.77 g, 9.1 mmol) and the mixture was stirred for 10 min. A sample of iodine (1.2 g, 4.6 mmol) was added in 3 portions. The reaction mixture was stirred at 0 °C for 40 min, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.26 g (70%) of the titled compound **1c** as a white solid, mp 105–106 °C. IR (thin film) 3403, 3056, 2925, 2855, 1742, 1707, 1265, 1132, 1092, and 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 2H), 4.64 (s, 2H), 4.99 (s, 1H), 6.04 (d, 1H, *J*=6.4 Hz), 6.09 (s, 1H), 7.01 (dd, 1H, *J*=6.4 and 2.0 Hz), and 7.25–7.36 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 73.1, 81.1, 127.2, 127.7, 127.8, 128.2, 136.9, 148.6, 168.0, and 170.8. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.08; H, 5.21; N, 5.73.

4.1.4. 1-(2-(3,4-Dimethoxyphenyl)acetyl)-5-hydroxy-1H-pyrrol-2(5H)-one (**12**)

To a stirred solution of *tert*-butyl furan-2-ylcarbamate (**9d**) (2.1 g, 11.7 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (4.9 mL, 12.3 mmol, 2.5 M in hexane) dropwise and the reaction mixture was stirred at 0 °C for 30 min. In a separate flask, 3,4-dimethoxybenzoic acid (2.75 g, 14.0 mmol) was dissolved in THF (20 mL) and the mixture was cooled to 0 °C. 4-Methylmorpholine (1.5 mL, 14.0 mmol) was first added and then isobutyl chloroformate (1.8 mL, 14.0 mmol) was subsequently added dropwise and the solution was stirred for 5 min. The mixture was filtered over Celite with THF and the filtrate was cooled to 0 °C and the preformed furanyl lithiate was added dropwise by cannula. The resulting mixture was stirred for 30 min, quenched with H_2O, and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 3.1 g (76%) of *tert*-butyl 2-(3,4-dimethoxyphenyl)acetyl(furan-2-yl)carbamate as a yellow oil. IR (thin film) 2980, 2936, 2836, 1783, 1746, 1609, 1516, 1265, 1154, 1093, and 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 3.85 (s, 6H), 4.04 (s, 2H), 6.11–6.12 (m, 1H), 6.39–6.41 (m, 1H), 6.77–6.81 (m, 3H), and 7.32 (dd, 1H, *J*=2.0 and 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 43.3, 56.00, 56.03, 84.1, 106.2, 111.2, 111.4, 112.9, 121.9, 126.5, 140.7, 144.0, 148.2, 148.9, 151.5, and 173.3.

To a stirred solution of $Mg(ClO_4)_2$ (0.24 g, 1.1 mmol) in CH_3CN (9 mL) at 45 °C was added a solution of the above Boc carbamate (0.3 g, 0.84 mmol) in CH_3CN (2 mL). The mixture was stirred at 45 °C for 15 min and was then diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.2 g (93%) of 2-(3,4-dimethoxyphenyl)-*N*-(furan-2-yl)acetamide as a yellow oil. IR (thin film) 3268, 3151, 3061, 2943, 2836, 1666, 1608, 1552, 1515, 1464, 1263, 1235, 1143, and 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 6.33–6.35 (m, 1H), 6.31–6.32 (m, 1H), 6.80–6.89 (m, 3H), 6.99 (dd, 1H, *J*=2.0 and 0.8 Hz), and 7.59 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.6, 56.1, 95.5, 111.7, 111.9, 112.6, 122.0, 126.4, 135.6, 145.2, 148.9, 150.7, and 167.8.

To a stirred solution of the above furanyl amide (1.66 g, 6.4 mmol) in acetone/H_2O (20:1, 50 mL) at 0 °C was added $NaHCO_3$ (3.2 g, 38.1 mmol) and the mixture was stirred at 0 °C for 5 min. A sample of iodine (4.8 g, 19.1 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 1.76 g (77%) of **12** as a white solid, mp 109–110 °C. IR (thin film) 3454, 3101, 3002, 2938, 2837, 1736, 1686, 1517, 1349, 1264, 1228, and 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.87 (s, 3H), 4.23 (s, 2H), 4.30 (d, 1H, *J*=3.6 Hz), 6.15–6.16 (m, 1H), 6.22 (dd, 1H, *J*=6.0 and 0.4 Hz), 6.82–6.88 (m, 3H), and 7.17 (dd, 1H, *J*=6.4 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1, 56.0, 56.1, 82.4, 111.3, 113.0, 122.1, 125.8, 128.7, 147.7, 148.4, 149.0, 167.8, and 172.8. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65, H, 5.45; N, 5.05. Found: C, 60.43; H, 5.41; N, 5.14.

4.1.5. Acetic acid 1-[2-(3,4-dimethoxyphenyl)acetyl]-5-oxo-2,5-dihydro-1H-pyrrol-2-yl ester (**15**)

To a stirred solution of 5-hydroxypyrrol-2(5*H*)-one **12** (0.5 g, 2.0 mmol) in pyridine (10 mL) was added acetic anhydride (0.2 mL, 2.4 mmol). The reaction mixture was stirred at rt for 16 h, quenched with H_2O, and extracted with EtOAc. The organic layer was washed with 1 N HCl followed by H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.6 g (95%) of **15** as a colorless oil. IR (thin film) 3098, 2938, 2837, 1742, 1704, 1516, 1351, 1265, 1237, and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.17 (d, 1H, *J*=16.0 Hz), 4.23 (d, 1H, *J*=16.0 Hz), 6.23 (d, 1H, *J*=6.0 Hz), 6.79–6.86 (m, 3H), and 7.12–7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 42.1, 55.8, 80.4, 111.0, 112.7, 121.9, 125.5, 128.7, 145.1, 148.1, 148.7, 167.9, 169.3, and 169.9.

4.1.6. 1-[2-(3,4-Dimethoxyphenyl)acetyl]-5-isopropoxy-1,5-dihydropyrrol-2-one (**16**)

To a stirred solution of 5-acetoxypyrrol-2(5*H*)-one **15** (0.42 g, 1.45 mmol) in *i*-PrOH (20 mL) was added $Pd(PPh_3)_4$ (0.08 g, 0.073 mmol) and the reaction mixture was stirred at rt for 5 h. The mixture was then concentrated under reduced pressure and purified by silica gel chromatography to give 0.41 g (97%) of **16** as a colorless oil. IR (thin film) 2971, 2934, 2836, 1737, 1699, 1516, 1465, 1342, 1263, 1222, and 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3H, *J*=6.4 Hz), 1.19 (d, 3H, *J*=6.0 Hz), 3.86 (s, 3H), 3.87 (s, 3H), 4.22 (s, 2H), 4.27 (p, 1H, *J*=12.4, 6.4, and 6.0 Hz), 5.98 (d, 1H, *J*=2.0 Hz), 6.10 (d, 1H, *J*=6.0 Hz), 6.81–6.87 (m, 3H), and 7.01 (dd, 1H, *J*=6.0 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 42.7, 55.99, 56.0, 73.6, 87.0, 111.3, 112.9, 122.1, 126.5, 127.1, 148.1, 148.2, 149.0, 168.7, and 171.4.

4.1.7. 2-Methoxy-5-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester (**17**)

To a stirred solution of *tert*-butyl furan-2-ylcarbamate (**9d**) (0.37 g, 2.0 mmol) in 35 mL of an 18:1-mixture of acetone/H_2O at 0 °C was added $NaHCO_3$ (1.0 g, 12.0 mmol) and the solution was stirred at 0 °C for 10 min. A sample of iodine (1.5 g, 6.0 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then

quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide 0.35 g (87%) of *tert*-butyl 2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**1d**) as a pale yellow solid, mp 80–81 °C. IR (thin film) 1766, 1368, 1314, 1258, 1160, 1106, and 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 4.26–4.27 (m, 1H), 5.93 (d, 1H, J=2.4 Hz), 6.09 (d, 1H, J=4.4 Hz), and 7.00 (dd, 1H, J=4.4 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 82.1, 83.9, 128.4, 146.3, 149.9, and 166.4. Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.13; H, 6.41; N, 7.28.

To a stirred solution containing the above 5-hydroxypyrrol-2(5*H*)-one **1d** (0.24 g, 1.2 mmol) in CH_2Cl_2 (10 mL) were added silver(I) oxide (1.4 g, 6.0 mmol) and iodomethane (3 mL, 48 mmol). The resulting solution was stirred for 14 h at rt and then filtered over Celite. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography to yield 0.25 g (99%) of the titled compound **17** as a colorless oil. IR (thin film) 1783, 1723, 1612, 1356, 1285, 1163, and 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 3.33 (s, 3H), 5.86–5.87 (m, 1H), 6.18–6.20 (m, 1H), and 6.96 (dd, 1H, J=6.4 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 53.1, 82.9, 87.8, 128.4, 145.3, 148.7, 167.1; HRMS calcd for $[(C_{10}H_{15}NO_4)+H]^+$: 214.1079, found: 214.1074.

4.1.8. 2-Methoxy-5-oxo-2,5-dihydropyrrole-1-carboxylic acid ethyl ester

To a stirred solution of ethyl furan-2-ylcarbamate (**9e**) (6.1 g, 39 mmol) in 667 mL of an 18:1-mixture of acetone/H_2O at 0 °C was added $NaHCO_3$ (19.8 g, 236 mmol) and the resulting mixture was stirred for 5 min at 0 °C. A sample of iodine (30 g, 118 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide 5.2 g (83%) of ethyl 2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**1e**) as a pale yellow oil. IR (thin film) 1775, 1726, 1532, 1374, 1207, 1098, and 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, 3H, J=7.2 Hz), 4.11 (br s, 1H), 4.40 (q, 2H, J=14.0 and 7.2 Hz), 6.05 (s, 1H), 6.19–6.21 (m, 1H), and 7.10 (dd, 1H, J=6.0 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 63.5, 82.4, 128.9, 146.7, 151.9, and 166.3.

To a stirred solution of the above compound (4.2 g, 25 mmol) in CH_2Cl_2 (200 mL) were added silver(I) oxide (28.7 g, 124 mmol) and iodomethane (62 mL, 992 mmol). The mixture was stirred for 14 h at rt and then filtered over Celite. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography to furnish 4.48 g (98%) of the titled compound as a colorless oil. IR (thin film) 1788, 1753, 1466, 1373, 1299, 1272, and 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 3H, J=7.2 Hz), 3.34 (s, 3H), 4.34 (q, 2H, J=7.2 Hz), 5.90 (dd, 1H, J=2.0 and 0.8 Hz), 6.18 (dd, 1H, J=6.4 and 0.8 Hz), and 7.00 (d, 1H, J=6.4 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 53.6, 62.9, 88.1, 128.6, 145.9, 150.6, and 166.9.

4.1.9. tert-Butyl 3-tert-butyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (**18a**)

To a stirred suspension of CuI (0.3 g, 1.6 mmol) in THF (5 mL) at 0 °C was added *t*-BuLi (1.4 mL, 2.2 mmol, 1.6 M in pentane) dropwise. The mixture was stirred at 0 °C for 1.5 h, then cooled to −78 °C and TMSCl (5.8 mL) was added. The mixture was stirred for an additional 5 min and then a solution of compound **17** (0.06 g, 0.28 mmol) in THF (1 mL) was slowly added. The solution was stirred at −78 °C for 5 min and then warmed to rt and stirred for an additional 2 h. The mixture was quenched by the slow addition of a saturated aqueous NH_4Cl solution and was then extracted with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to afford 0.06 g (80%) of compound **18a** as a colorless oil. IR (thin film) 1792, 1760, 1476, 1370, 1304, 1158, and 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (s, 9H), 1.54 (s, 9H), 1.92 (dd, 1H, J=9.2 and 1.2 Hz), 2.33 (d, 1H, J=18.4 and 1.6 Hz), 2.76 (dd, 1H, J=18.4 and 9.2 Hz), 3.39 (s, 3H), and 5.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 28.2, 31.9, 33.4, 47.6, 56.1, 83.5, 91.3, 150.1, and 174.2; HRMS calcd for $[(C_{14}H_{25}NO_4)+H]^+$: 271.1783, found: 271.1781.

4.1.10. tert-Butyl 2-methoxy-5-oxo-3-phenylpyrrolidine-1-carboxylate (**18b**)

To a 0 °C stirred suspension of $CuBr\cdot Me_2S$ (1.0 g, 4.9 mmol) in THF (10 mL) was added phenyllithium (6.2 mL, 11.0 mmol, 1.8 M in cyclohexane) dropwise. The resulting mixture was stirred at 0 °C for 1.5 h, cooled to −78 °C, and TMSCl (3.6 mL) was added. The mixture was stirred for an additional 10 min and then a solution of compound **17** (0.3 g, 1.4 mmol) in THF (3 mL) was slowly added. The mixture was stirred at −78 °C for 5 min, warmed to rt, and stirred for an additional 3 h. The reaction mixture was quenched by the slow addition of a saturated aqueous NH_4Cl solution and then extracted with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.41 g (75%) of **18b** as a colorless oil. IR (thin film) 1792, 1723, 1455, 1369, 1154, 1085, and 943 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 2.54 (dd, 1H, J=17.6 and 0.8 Hz), 3.17 (dd, 1H, J=17.6 and 8.8 Hz), 3.38 (d, 1H, J=8.8 Hz), 3.47 (s, 3H), 5.17 (s, 1H), 7.14–7.16 (m, 2H), and 7.24–7.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 37.7, 42.9, 56.6, 83.5, 95.2, 126.6, 127.5, 129.1, 140.6, 149.7, and 173.5; HRMS calcd for $[(C_{16}H_{21}NO_4)+K^+]$: 330.1108, found: 330.1101.

4.1.11. tert-Butyl 3-butyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (**18c**)

To a stirred suspension of CuI (4.9 g, 26 mmol) in THF (80 mL) 0 °C was added *n*-BuLi (14.7 mL, 37 mmol, 2.5 M in hexane) dropwise. The mixture was stirred at 0 °C for 1.5 h, cooled to −78 °C, and TMSCl (12 mL) was added. The mixture was stirred for an additional 5 min and compound **17** (1.0 g, 4.7 mmol) in THF (3 mL) was slowly added. The solution was stirred at −78 °C for 10 min, then warmed to rt and stirred for an additional 1 h. The mixture was quenched by the slow addition of a saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 1.17 g (92%) of **18c** as a colorless oil. IR (thin film) 1793, 1760, 1458, 1368, 1305, 1158, and 843 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, J=7.2 Hz), 1.21–1.43 (m, 6H), 1.52 (s, 9H), 2.08–2.12 (m, 2H), 2.82 (dd, 1H, J=17.6 and 7.6 Hz), 3.37 (s, 3H), and 5.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 22.5, 27.9, 29.0, 32.2, 36.9, 37.4, 56.2, 83.2, 93.8, 150.2, and 173.7; HRMS calcd for $[(C_{14}H_{25}NO_4)+H]^+$: 272.1862, found: 272.1864.

4.1.12. tert-Butyl 2-methoxy-3-methyl-5-oxopyrrolidine-1-carboxylate (**18e**)

To a 0 °C stirred suspension of CuI (0.98 g, 5.1 mmol) in THF (20 mL) was added MeLi (4.6 mL, 7.2 mmol, 1.6 M in ether) dropwise. The resulting solution was stirred at 0 °C for 1.5 h, cooled to −78 °C, and TMSCl (2.4 mL) was added. The mixture was stirred for 5 min and a solution of compound **17** (0.2 g, 0.94 mmol) in THF (3 mL) was slowly added. The mixture was stirred at −78 °C for 5 min, warmed to rt, and stirred for an additional 45 min. The

mixture was quenched by the slow addition of an aqueous NH_4Cl solution and then extracted with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.06 g (80%) of **18e** as a colorless oil. IR (thin film) 1790, 1760, 1721, 1368, 1310, 1093, and 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (d, 3H, J=7.2 Hz), 1.55 (s, 9H), 2.03 (d, 1H, J=17.2 Hz), 2.30 (p, 1H, J=14.8 and 7.6 Hz), 2.90 (dd, 1H, J=25.2 and 8.0 Hz), 3.42 (s, 3H), and 4.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 28.2, 32.4, 38.8, 56.7, 83.5, 95.3, 150.5, and 173.9.

4.1.13. *tert-Butyl 3-hexyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (**18g**)*

To a stirred suspension of CuI (0.98 g, 5.1 mmol) in THF (20 mL) at 0 °C was added hexyllithium (3.2 mL, 7.2 mmol, 2.3 M in hexane) dropwise. The mixture was stirred at 0 °C for 1.5 h, cooled to −78 °C, and TMSCl (2.4 mL) was added. The solution was stirred for 5 min and compound **17** (0.2 g, 0.94 mmol) in THF (3 mL) was slowly added. The mixture was stirred at −78 °C for 5 min, warmed to rt, and stirred for an additional 2 h. The reaction mixture was quenched by the slow addition of a saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.17 g (60%) of **18g** as a colorless oil. IR (thin film) 1794, 1760, 1459, 1368, 1304, 1157, and 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J=6.8 Hz), 1.25–1.55 (m, 10H), 1.55 (s, 9H), 2.10–2.15 (m, 2H), 2.85 (dd, 1H, J=17.6 and 7.6 Hz), 3.40 (s, 3H), and 5.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 22.8, 27.0, 28.2, 29.3, 31.8, 32.7, 37.1, 37.7, 56.5, 83.5, 94.1, 150.5, and 174.0; HRMS calcd for $[(C_{16}H_{29}NO_4)+K^+]$: 338.1734, found: 338.1728.

4.1.14. *tert-Butyl 1-methoxy-2-(2-oxo-2-phenylethyl)-hexylcarbamate (**19c**)*

To a stirred solution containing 0.21 g (0.76 mmol) of **18c** in 4 mL of THF at −78 °C was added phenyllithium (0.84 mL, 1.5 mmol, 1.8 M in di-*n*-butylether) slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and was then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide 0.25 g (94%) of **19c** as a colorless oil. IR (thin film) 3351, 3360, 2957, 2931, 1716, 1689, 1596, 1503, and 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=7.2 Hz), 1.25–1.53 (m, 15H), 245–2.51 (m, 1H), 2.82 (dd, 1H, J=16.8 and 5.6 Hz), 3.09 (dd, 1H, J=16.8 and 6.8 Hz), 3.30 (s, 3H), 4.77 (dd, 1H, J=10.8 and 6.4 Hz), 5.02 (d, 1H, J=10.8 Hz), 7.45–7.47 (m, 2H), 7.53–7.57 (m, 1H), and 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.1, 28.3, 29.2, 30.7, 39.0, 39.1, 55.5, 79.8, 85.3, 128.3, 128.7, 133.2, 137.3, 156.0, and 200.4; HRMS calcd for $[(C_{20}H_{31}NO_4)+K]$: 388.1890, found: 388.1886.

4.1.15. *1-Benzyl-4-butyl-2-phenyl-1H-pyrrole (**20a**)*

To a sample containing 0.07 g (0.2 mmol) of **19c** in benzylamine (0.5 mL) was added a catalytic amount of *p*-TsOH in a sealed tube. The mixture was subjected to microwave irradiation at 150 °C (200 W) and a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.05 g (90%) of pyrrole **20a** as a colorless oil. IR (thin film) 3064, 3029, 2955, 2925, 1603, 1453, and 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=7.6 Hz), 1.31–1.37 (m, 2H), 1.51–1.57 (m, 2H), 2.43 (t, 2H, J=7.6 Hz), 5.03 (s, 2H), 6.08 (d, 1H, J=1.6 Hz), 6.45 (d, 1H, J=1.6 Hz), 6.96–6.98 (m, 2H), and 7.16–7.26 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 26.9, 33.4, 50.6, 109.3, 120.5, 125.2, 126.6, 126.9, 127.4, 128.5, 128.8, 133.6, 134.9, and 139.3; HRMS calcd for $[(C_{21}H_{23}N)+H]^+$: 290.1909, found: 290.1907.

4.1.16. *4-Butyl-1,2-diphenyl-1H-pyrrole (**20b**)*

A sample of **19c** (0.03 g, 0.79 mmol) was mixed with aniline (0.5 mL) and a catalytic amount of *p*-TsOH in a sealed tube. The mixture was subjected to microwave irradiation at 150 °C (200 W) and a maximum internal pressure of 120 psi for 30 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.02 g (97%) of pyrrole **20b** as a yellow oil. IR (thin film) 3064, 2955, 2926, 1599, 1500, 1407, and 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.6 Hz), 1.40–1.50 (m, 2H), 1.61–1.69 (m, 2H), 2.55 (t, 2H, J=7.6 Hz), 6.33 (d, 1H, J=2.0 Hz), 6.75 (d, 1H, J=2.0 Hz), and 7.12–7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 26.8, 33.3, 111.6, 121.9, 125.7, 125.8, 126.2, 126.4, 128.2, 128.3, 129.1, 133.3, 133.5, and 140.8; HRMS calcd for $[(C_{20}H_{21}N)+H^+]$: 276.1747, found: 276.1749.

4.1.17. *4-Butyl-1-(furan-2-ylmethyl)-2-phenyl-1H-pyrrole (**20c**)*

A sample of **19c** (0.03 g, 0.8 mmol) was mixed with furfurylamine (0.5 mL) and a catalytic amount of *p*-TsOH in a sealed tube. The mixture was subjected to microwave irradiation at 150 °C (200 W) and a maximum internal pressure of 120 psi for 30 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.015 g (65%) of pyrrole **20c** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J=7.6 Hz), 1.38–1.44 (m, 2H), 1.54–1.62 (m, 2H), 2.47 (t, 2H, J=7.6 Hz), 6.08 (d, 1H, J=2.0 Hz), 6.13 (dd, 1H, J=3.2 and 2.0 Hz), 6.31 (dd, 1H, J=3.2 and 2.0 Hz), 7.27–7.31 (m, 1H), and 7.36–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 26.9, 33.3, 43.8, 108.0, 109.3, 110.5, 119.9, 125.2, 127.0, 128.5, 129.1, 133.4, 134.6, 142.6, and 151.7.

4.1.18. *4-Butyl-1-cyclohexyl-2-phenyl-1H-pyrrole (**20d**)*

A sample of **19c** (0.02 g, 0.63 mmol) was mixed with cyclohexylamine (0.5 mL) and a catalytic amount of *p*-TsOH in a sealed tube. The mixture was subjected to microwave irradiation at 150 °C (200 W) and a maximum internal pressure of 120 psi for 30 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.013 g (90%) of pyrrole **20d** as a colorless oil. IR (thin film) 3064, 2928, 2855, 1603, 1510, 1466, 1450, and 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J=7.6 Hz), 1.15–1.30 (m, 3H), 1.36–1.45 (m, 2H), 1.57–1.68 (m, 5H), 1.77–1.90 (m, 2H), 1.95–2.01 (m, 2H), 3.97 (1H, dt, J=12.0 and 4.0 Hz), 5.99 (d, 1H, J=2.0 Hz), 6.64 (d, 1H, J=2.0 Hz), and 7.25–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.9, 25.6, 26.1, 27.1, 33.3, 35.1, 55.2, 108.6, 115.7, 124.4, 126.7, 128.5, 129.1, 133.7, and 134.2.

4.1.19. *1-Benzyl-2-methyl-4-phenyl-1H-pyrrole (**20e**)*

To a stirred solution containing 0.09 g (0.3 mmol) of **18b** in 1.5 mL of THF at −78 °C was added MeLi (0.25 mL, 0.39 mmol, 1.6 M in diethyl ether) slowly. After stirring for 30 min at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel. The residue was then mixed with benzylamine (0.5 mL) and

catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.06 g (70%, over 2 steps) of pyrrole **20e** as a colorless oil. IR (thin film) 3060, 3031, 2922, 1603, 1528, 1452, and 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 5.05 (s, 2H), 6.30 (s, 1H), 6.96 (d, 1H, J=2.4 Hz), 7.07–7.09 (m, 2H), 7.13–7.17 (m, 1H), 7.30–7.36 (m, 5H), and 7.49–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 50.7, 105.6, 117.8, 123.8, 125.0, 125.3, 126.6, 127.6, 128.7, 129.0, 130.2, 136.1, and 138.3; HRMS calcd for $[(C_{18}H_{17}N)+H^+]$: 248.1434, found: 248.1435.

4.1.20. 1-Benzyl-4-butyl-2-methyl-1H-pyrrole (**20f**)

To a stirred solution containing 0.02 g (0.074 mmol) of **18c** in 0.8 mL of THF at −78 °C was added methyllithium (0.09 mL, 0.15 mmol, 1.6 M in diethyl ether) slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and was then mixed with benzylamine (0.5 mL) and catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.014 g (81%, over 2 steps) of pyrrole **20f** as a colorless oil. IR (thin film) 3064, 3030, 2955, 2925, 2855, 1606, 1514, 1454, 1416, 1353, and 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=3.6 Hz), 1.32–1.41 (m, 2H), 1.50–1.53 (m, 2H), 2.10 (s, 3H), 2.42 (t, 2H, J=3.6 Hz), 4.95 (s, 2H), 5.79 (s, 1H), 6.39 (s, 1H), 7.00 (m, 2H), and 7.22–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.2, 22.8, 26.9, 33.6, 50.3, 107.6, 118.0, 123.8, 126.5, 127.3, 128.7, 128.8, and 138.9; HRMS calcd for $[(C_{16}H_{21}N)+H]^+$: 228.1752, found: 228.1746.

4.1.21. One-pot reaction of tert-butyl 3-butyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (**18c**) with vinyl lithium followed by benzylamine

To a stirred solution containing 0.05 g (0.17 mmol) of **18c** in 1.0 mL of THF at −78 °C was added a freshly prepared vinyl lithium solution (0.84 mL, 0.25 mmol, 0.3 M in THF) slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and was then mixed with benzylamine (0.5 mL) and catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.03 g (42%, over 2 steps) of pyrrole **20f** as a colorless oil.

4.1.22. 1-Benzyl-4-methyl-2-(thiophenyl-2-yl)-1H-pyrrole (**20g**)

To a stirred solution containing 0.02 g (0.1 mmol) of **18e** in 0.8 mL of THF at −78 °C was added 0.2 mL (0.21 mmol, 1.0 M in THF) of 2-thienyllithium slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and was then mixed with benzylamine (0.5 mL) and catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The residue was purified by silica gel chromatography to furnish 0.023 g (86%, over 2 steps) of pyrrole **20g** as a colorless oil. IR (thin film) 3029, 2923, 2854, 1539, 1495, 1453, 1422, and 1352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 5.15 (s, 2H), 6.21 (d, 1H, J=1.6 Hz), 6.50 (s, 1H), 6.81 (dd, 1H, J=3.2 and 1.2 Hz), 6.94–6.97 (m, 1H), 7.02–7.05 (m, 2H), 7.19 (dd, 1H, J=5.2 and 1.2 Hz), and 7.20–7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 50.7, 111.8, 119.3, 121.7, 124.8, 125.2, 126.6, 127.0, 127.4, 127.5, 128.9, 135.0, and 139.0.

4.1.23. 1-Benzyl-2-ethyl-4-hexyl-1H-pyrrole (**20h**)

To a stirred solution containing 0.08 g (0.38 mmol) of **18g** in 2.0 mL of THF at −78 °C was added ethyllithium (0.9 mL, 0.46 mmol 0.5 M in benzene/cyclohexane) slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and was then mixed with benzylamine (0.5 mL) and catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.044 g (42%, over 2 steps) of pyrrole **20h** as a colorless oil. IR (thin film) 3064, 2958, 2925, 1496, 1454, 1426, 1376, and 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.91 (m, 3H), 1.18 (d, 3H, J=7.2 Hz), 1.30–1.40 (m, 6H), 1.53–1.59 (m, 2H), 2.42–2.46 (m, 4H), 4.97 (s, 2H), 5.83 (s, 1H), 6.40 (s, 1H), 6.71–6.99 (m, 2H), and 7.22–7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.3, 19.6, 22.9, 27.3, 29.5, 31.4, 32.0, 50.1, 105.5, 118.1, 123.8, 126.5, 127.3, 128.8, 135.0, and 139.0; HRMS calcd for $[(C_{14}H_{17}N)+H^+]$: 200.1434, found: 200.1433.

4.1.24. 1-Benzyl-2-butyl-4-methyl-1H-pyrrole (**20i**)

To a stirred solution containing 0.08 g (0.34 mmol) of **18e** in 2.0 mL of THF at −78 °C was added *n*-butyllithium (0.26 mL, 0.41 mmol, 1.6 M in hexane) slowly. After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and was then mixed with benzylamine (0.5 mL) and catalytic amount of *p*-TsOH in a sealed tube and subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.04 g (54%, over 2 steps) of pyrrole **20i** as a colorless oil. IR (thin film) 3064, 3029, 2956, 2928, 1605, 1496, 1454, 1420, 1384, and 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=3.2 Hz), 1.35 (m, 1H, J=3.2 Hz), 1.50–1.57 (m, 2H), 2.07 (s, 3H), 2.42 (t, 2H, J=3.2 Hz), 4.96 (s, 2H), 5.80 (d, 1H, J=1.2 Hz), 6.37 (d, 1H, J=1.2 Hz), 7.00–7.02 (m, 2H), and 7.25–7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 14.1, 22.7, 26.1, 31.2, 50.1, 107.4, 117.8, 118.7, 126.6, 127.4, 128.8, 133.8, and 139.0.

*4.1.25. 4-Butyl-2-phenyl-1H-pyrrole (**20j**)*

To a 0.03 g (0.084 mmol) sample of **19c** dissolved in 0.5 mL of DMF and H_2O (1:1) was added a small amount of *p*-TsOH. The mixture was subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.016 g (98%) of pyrrole **20j** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J=7.2 Hz), 1.43 (m, 2H), 1.60 (m, 2H), 2.51 (t, 2H, J=3.6 Hz), 6.38–6.40 (m, 1H), 6.64 (m, 1H), 7.16–7.20 (m, 1H), 7.32–7.36 (m, 2H), 7.46 (m, 2H), and 8.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 26.9, 33.4, 106.6, 116.2, 123.8, 126.1, 126.7, 129.0, 132.0, and 133.1.

*4.1.26. tert-Butyl 4-butyl-2-phenyl-1H-pyrrole-1-carboxylate (**20k**)*

To a 0.03 g (0.077 mmol) sample of **19c** dissolved in 0.5 mL of toluene and was added a small amount of CSA/quinoline catalyst. The mixture was subjected to microwave irradiation at 100 °C (150 W) with a maximum internal pressure of 100 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.018 g (76%) of pyrrole **20k** as a yellow oil. IR (thin film) 3062, 3026, 2957, 2929, 2857, 1734, 1600, 1524, 1476, 1343, and 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, J=7.2 Hz), 1.26–1.39 (m, 11H), 1.45–1.53 (m, 2H), 2.35 (t, 3H, J=7.2 Hz), 5.99 (d, 1H, J=2.0 Hz), 7.02 (m, 1H), and 7.20–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.6, 27.8, 32.5, 83.3, 115.9, 119.2, 126.7, 127.2, 127.7, 129.2, 134.8, 135.1, and 149.6.

*4.1.27. 3-Methoxy-5-oxo-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylic acid tert-butyl ester (**21**)*

To a solution of 0.45 g (2.1 mmol) of 2-methoxy-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (**9d**) in 5 mL of toluene was added 1 mL of fresh distilled cyclopentadiene and the mixture was heated at 110 °C in a sealed pressure tube for 6 h. The solution was cooled to rt, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.57 g (97%) of the titled compound **21** as a colorless oil. IR (neat) 3061, 2979, 2937, 2874, 2833, 1784, 1747, 1458, 1354, 1301, and 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, 1H, J=6.0 Hz), 1.48 (s, 9H), 1.54 (d, 1H, J=6.0 Hz), 2.60 (dd, 1H, J=5.6 and 3.0 Hz), 3.13 (s, 1H), 3.22 (dd, 1H, J=5.6 and 3.2 Hz), 3.30 (s, 1H), 3.34 (s, 3H), 4.76 (s, 1H), 6.08 (dd, 1H, J=4.0 and 2.0 Hz), 6.14 (dd, 1H, J=4.0 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 41.9, 45.2, 46.0, 49.5, 50.8, 54.6, 82.6, 90.2, 132.7, 135.7, 149.2, and 174.6; HRMS calcd for $[(C_{15}H_{21}NO_4)+H]^+$: 280.1549, found: 280.1543.

*4.1.28. Formation of pyrrole **22***

To a stirred solution containing 0.05 g (0.17 mmol) of **21** in 1.0 mL of THF at −78 °C was slowly added phenyllithium (0.2 mL, 0.34 mmol, 1.8 M in di-*n*-butylether). After stirring for 1 h at −78 °C, the reaction mixture was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and mixed with benzylamine (0.5 mL) together with a catalytic amount of *p*-TsOH in a sealed tube. The mixture was subjected to microwave irradiation at 150 °C (200 W) with a maximum internal pressure of 120 psi for 10 min. After cooling to rt, the mixture was diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.03 g (43%, over 2 steps) of pyrrole **22** as a colorless oil. IR (thin film) 3060, 1604, 1561, 1531, 1494, 1452, 1400, 1301, and 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36–2.45 (m, 2H), 3.80 (s, 1H), 3.84 (s, 1H), 4.96 (d, 1H, J=16.4 Hz), 5.04 (d, 1H, J=16.4 Hz), 6.40 (s, 1H), 6.75 (s, 2H), 7.02–7.04 (m, 2H), and 7.22–7.36 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.8, 44.9, 50.6, 69.5, 114.3, 126.5, 126.6, 126.9, 127.2, 128.6, 128.7, 129.1, 133.2, 136.3, 136.4, 140.0, 142.8, and 142.9; HRMS calcd for $[(C_{22}H_{19}N)+H^+]$: 298.1590, found: 298.1591.

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