DOI: 10.1002/ejoc.200901055

A New Method for the Synthesis of Multisubstituted Pyrroles of Biological Interest by Double Nucleophilic Addition to α,β-Unsaturated Imines

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Keywords: Nucleophilic addition / Nitrogen heterocycles / Synthetic methods

Double nucleophilic addition reactions of dialkoxy ketene silyl acetals proceeded with α,β-unsaturated imines to give 1,4- and 1,2-double addition products, and their subsequent transformations afforded multisubstituted pyrroles in good yields. Application of this procedure to the synthesis of an imidazole glycerol phosphate dehydratase inhibitor (IGPDI), a physiologically active 2,3,5-trisubstituted pyrrole, is also described.

Introduction

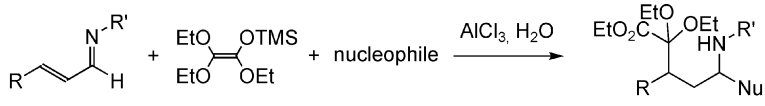
Pyrrole structures are found in many biologically important compounds[1] and are also used as monomers in the preparation of electronic materials such as electroconductive polymers.[2] Several methods for the construction of multisubstituted pyrrole rings have been published to date,[3] but they are often tedious procedures and therefore simple approaches are highly desired for their preparation.

One of the most simple and effective approaches to the construction of pyrrole rings appears to involve the cyclization of γ-amino carbonyl compounds followed by dehydrogenation. Although the most direct synthetic approach to γ-amino carbonyl compounds uses nucleophilic addition to γ-oxoimines, this method may suffer from side-reactions such as hydrolysis of the imino moiety and non-regioselective nucleophilic addition. However, to avoid these problems we have recently developed a strategy that involves a double nucleophilic addition to α,β-unsaturated imines.[4] It is expected that the use of dialkoxy ketene silyl acetals as initial nucleophiles in the 1,4- and 1,2-double nucleophilic addition[5] would make the synthesis of γ-amino carbonyl compounds much easier. Herein we describe an efficient synthesis of γ-amino carbonyl compounds and their transformation into 2,3,5-trisubstituted pyrroles with useful biological activity.

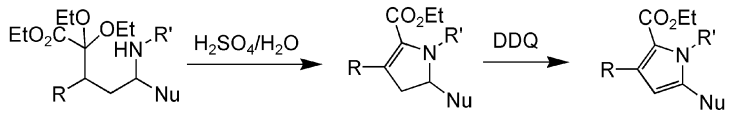
Results and Discussion

The following topics are described in this article.

1) The synthesis of γ-amino carbonyl derivatives by the double nucleophilic addition of dialkoxy ketene silyl acetals and a variety of second nucleophiles to α,β-unsaturated imines.



2) The conversion into multisubstituted pyrroles by cyclization of the 1,4- and 1,2-double addition products into dihydropyrroles followed by dehydrogenation.



3) The application of the present method to the synthesis of multisubstituted pyrroles of biological interest, namely, imidazole glycerol phosphate dehydratase inhibitors (IGPDIs).[6]

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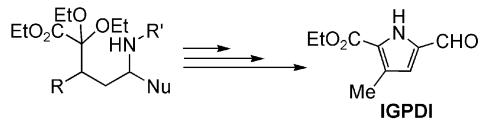
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901055.



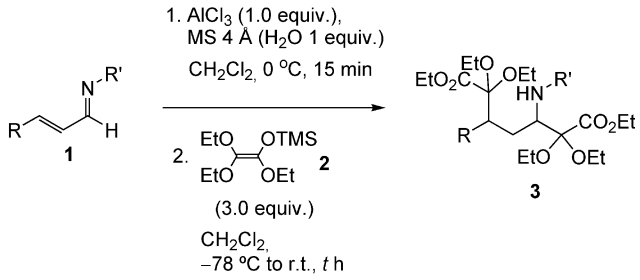
Double Nucleophilic Addition Reactions to α,β-Unsaturated Imines

Initially the use of dialkoxy ketene silyl acetal **2** as both the first and second nucleophiles was examined. The reactions of α,β-unsaturated imines **1** proceeded with dialkoxy ketene silyl acetal **2** (3.0 equiv.) in CH_2Cl_2 in the presence of aluminium chloride (1.0 equiv.) and 4 Å molecular sieves containing H_2O at –78 °C to room temperature gave the double nucleophilic addition product **3** in good yield and stereoselectivity. The results of these double nucleophilic addition reactions are summarized in Table 1.

All the 1,4- and 1,2-double addition products were obtained in moderate-to-good yields (entries 1–4). The use of the 4-(dimethylamino)phenyl derivative resulted in a decrease in the yield and stereoselectivity (entry 4). This may be due to the less selective coordination of the Lewis acid to two nitrogen atoms, the imino and 4-(dimethylamino)-phenyl groups. The best result was obtained by using *N*-(4-methoxyphenyl)crotylideneamine (entry 2; PMP = 4-methoxyphenyl).

The use of two different nucleophiles was next examined, with dialkoxy ketene silyl acetal **2** employed as the first nucleophile and the ketene silyl thioacetal **4** or trimethylsilyl cyanide (**5**) as the second. The results are collected in Table 2. Note that dialkoxy ketene silyl acetal **2** underwent 1,4-addition and the ketene silyl thioacetal **4** and trimethylsilyl cyanide (**5**) underwent 1,2-addition in a highly regioselective manner. Only a small amount of the 1,2-addition product of the dialkoxy ketene silyl acetal was obtained.

Table 1. Double nucleophilic addition reactions of dialkoxy ketene silyl acetal **2** with α,β-unsaturated imines **1**.



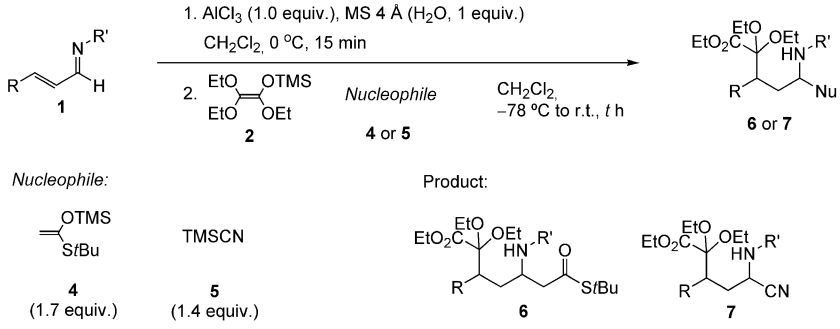
Entry	1 R	1 R′	*t* [h]	Product	% Yield[a]	*syn*/*anti*[b]
1	Ph	PMP	8.5	**3a**	85	87:13
2	Me	PMP	9.5	**3b**	77	99:1
3	Ph	$CHPh_2$	9.5	**3c**	80	75:25
4	Ph	4-$Me_2NC_6H_4$	13.5	**3d**	66	76:24

[a] Isolated yields. [b] Determined by HPLC and/or ^{1}H NMR spectroscopy.

Cyclization of the 1,4- and 1,2-Double Addition Products into Dihydropyrroles Followed by Dehydrogenation

The 1,4- and 1,2-double adducts **3**, **6** and **7** were converted into multisubstituted pyrroles by cyclization first to dihydropyrroles **8**, **9** and **10**, respectively, with acids such as H_2SO_4, TFA or methanesulfonic acid followed by dehydrogenation with DDQ.[7] Table 3 summarizes the synthesis of

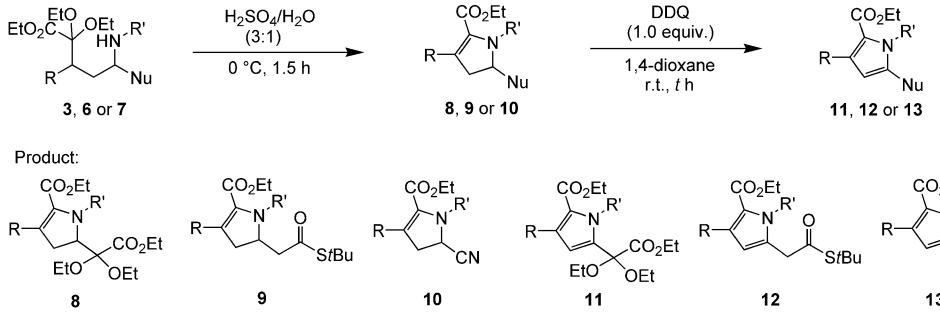
Table 2. Double nucleophilic addition reactions of α,β-unsaturated imines **1** with dialkoxy ketene silyl acetal **2** and another nucleophile **4** or **5**.



Entry	1 R	1 R′	2 [equiv.]	4 or 5	*t* [h]	6 or 7	% Yield[a]	*syn*/*anti*[b]
1	Ph	PMP	1.3	**4**	11.5	**6a**	80	90:10
2	Ph	4-$Me_2NC_6H_4$	1.3	**4**	9.5	**6b**	63	55:45
3	Ph	2,4-$(MeO)_2C_6H_3$	1.3	**4**	9.5	**6c**	62	85:15
4	Me	PMP	1.3	**4**	9.5	**6d**	70	67:33
5	Ph	PMP	1.0	**5**	9.5	**7a**	55	94:6
6	Me	PMP	1.0	**5**	16.0	**7b**	95	88:12

[a] Isolated yields. [b] Determined by HPLC and/or ^{1}H NMR spectroscopy.

Table 3. Conversion of **3**, **6** and **7** into multisubstituted dihydropyrrole and pyrrole.



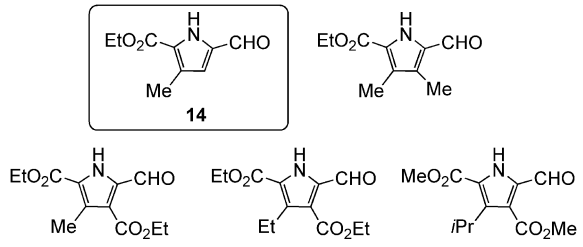
Entry	Reagent	R	R′	Dihydropyrrole	Yield [%][a]	*t* [h]	Pyrrole	% Yield[a]
1	**3a**	Ph	PMP	**8a**	88	13.0	**11a**	quant.
2	**3b**	Me	PMP	**8b**	69[b]	13.0	**11b**	95
3	**3c**	Ph	$CHPh_2$	**8c**	96	13.0	**11c**	quant.
4	**3d**	Ph	4-$Me_2NC_6H_4$	**8d**	quant.	13.0	**11d**	66
5	**6a**	Ph	PMP	**9a**	73	12.5	**12a**	62
6	**6b**	Ph	4-$Me_2NC_6H_4$	**9b**	67[c]	12.5	**12b**	93
7	**6c**	Ph	2,4-$(MeO)_2C_6H_3$	**9c**	79[c]	12.5	**12c**	97
8	**6d**	Me	PMP	**9d**	86	12.5	**12d**	69
9	**7a**	Ph	PMP	**10a**	quant.[c]	12.0	**13a**	74
10	**7b**	Me	PMP	**10b**	86[c]	12.0	**13b**	82

[a] Isolated yields. [b] H_2SO_4/H_2O = 2:1. The reaction time was 6.5 h. [c] H_2SO_4/H_2O = 1:1.

the multisubstituted pyrroles **11**, **12** and **13**. For the cyclization of some of the 1,4- and 1,2-double adducts, milder conditions were needed due to the instability of the intermediates (entries 2, 6, 7, 9 and 10). The subsequent dehydrogenation of the dihydropyrroles with DDQ gave multisubstituted pyrroles in good-to-excellent yields.

Synthesis of Monopyrrole Aldehyde

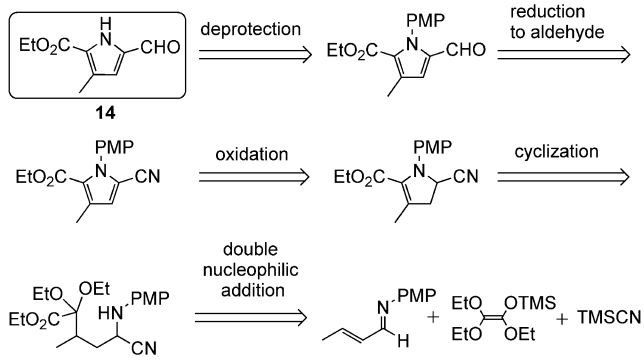
As an application of the present methodology, the synthesis of a monopyrrole aldehyde **14** with herbicidal activity (Schemes 1 and 2)[8] was next examined.



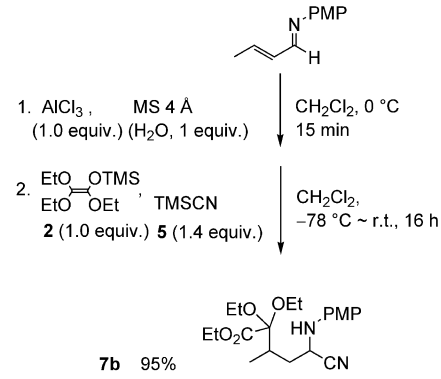
Scheme 1. Monopyrrole aldehydes with biological activity.

In the first step, the double nucleophilic addition of ketene silyl acetal **2** and trimethylsilyl cyanide (**5**) to *N*-(4-methoxyphenyl)crotylideneamine was examined. Under the best conditions, the 1,4- and 1,2-double adduct **7b** was obtained in 95% yield (Scheme 3).

In the second step, the 1,4- and 1,2-double adduct **7b** was converted into the dihydropyrrole **10b** under the influence of H_2SO_4 (Table 4). By using a mixture of conc. H_2SO_4/H_2O in a ratio of 3:1 only small amounts of the dihydropyrrole **16** were obtained (entries 1 and 2), whereas under less acidic conditions (concd. H_2SO_4/H_2O = 1:1) the product yield was much improved (entry 3).

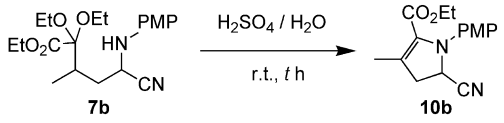


Scheme 2. Strategy for the synthesis of monopyrrole aldehyde **14**.



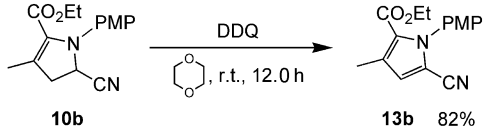
Scheme 3. Double nucleophilic addition reaction of ketene silyl acetal **2** and trimethylsilyl cyanide (**5**) with *N*-(4-methoxyphenyl)-crotylideneamine.

Table 4. Optimization of the cyclization conditions for the syntehsis of dihydropyrrole**10b**.



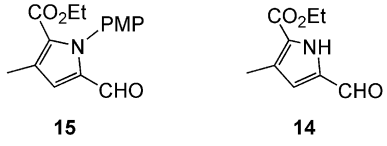
Entry	H_2SO_4/H_2O	*t* [h]	% Yield
1	3:1	0.5	14
2	3:1	1.0	16
3	1:1	1.0	86
4	1:1	1.5	58

The dihydropyrrole **10b** was readily converted into the pyrrole **13b** by dehydrogenation with DDQ (Scheme 4).

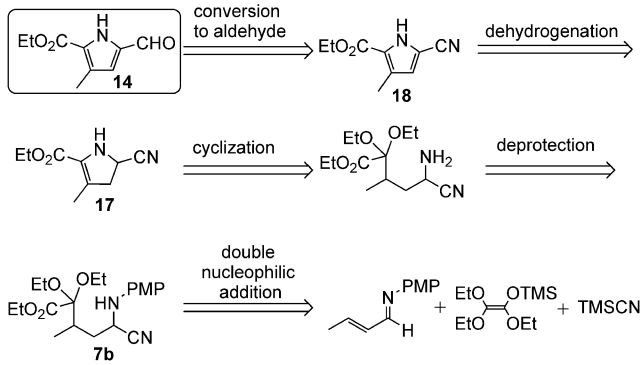


Scheme 4. Dehydrogenation of dihydropyrrole **10b**.

Although chemoselective reduction of the cyano moiety proved to be highly difficult under a variety of conditions, it could be chemoselectively reduced to aldehyde **15** with Raney Ni W4 in the presence of $NaPH_2O_2/H_2O$/acetic acid/pyridine.[9]

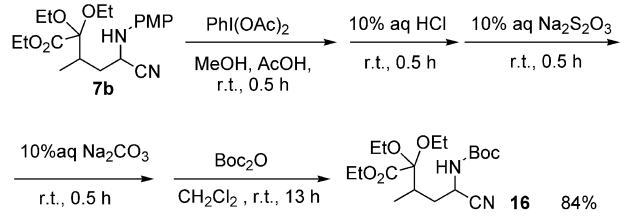


In the final step, the deprotection of the PMP group was examined under various oxidation or reduction conditions [CAN, O_3, $(NH_4)_2S_2O_8/AgNO_3$, Na/liqu. NH_3, etc]. However, the removal of the PMP group was problematic and the desired monopyrrole aldehyde **14** was not obtained. Attempted removal of the PMP group from the dihydropyrrole **10b** was also unsuccessful and therefore we modified our strategy (Scheme 5).



Scheme 5. Modified strategy for the synthesis of monopyrrole aldehyde **14**.

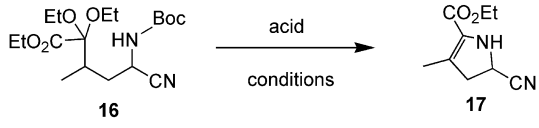
The PMP group was converted into an easily removable protecting group[10] at an earlier stage of the synthesis. We first attempted to replace the PMP group with an acetyl group, but the acetamide was obtained in only 5% yield. In the end, protection with the Boc group was found to be suitable for obtaining the desired product **16** in 84%yield (Scheme 6).



Scheme 6. Replacement of the PMP with Boc group.

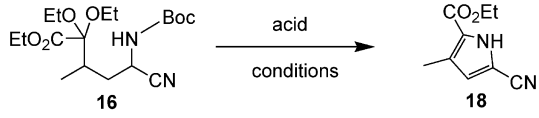
It was expected that a concomitant cyclization would take place on deprotection of the Boc group with acid. However, the desired dihydropyrrole **17** was not formed (Table 5).

Table 5. Deprotection of the Boc protecting group and cyclization.

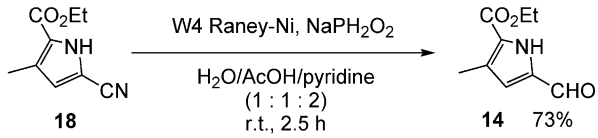


Entry	Acid	Conditions	% Yield
1	H_2SO_4/H_2O (1:1)	room temp., 0.5 h	–
2	CH_3SO_3H	0 °C, 1.5 h	–
3	TFA	0 °C, 1.5 h	–

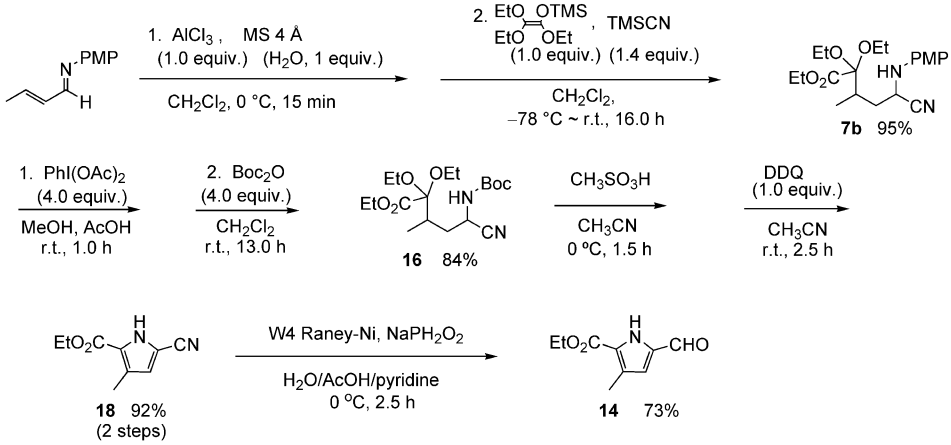
Table 6. Deprotection of the Boc-protecting group and cyclization in the presence of an oxidant.



Entry	Conditions	% Yield
1	DDQ, H_2SO_4/H_2O (3:1), 0 °C to ca. r.t., 10.5 h	–
2	DDQ, H_2SO_4/H_2O (1:1), 0 °C to ca. r.t., 10.5 h	27
3	CAN, H_2SO_4/H_2O (1:1), 0 °C to ca. r.t., 10.0 h	–
4	TFA, r.t., 2.0 h; DDQ, r.t., 3.0 h	37
5	TFA, r.t., 3.5 h; DDQ, r.t., 10.0 h	41
6	TFA, r.t., 1.0 h; DDQ, 72 °C, 2.0 h	33
7	TFA, CH_3CN, r.t., 12.0 h; DDQ, r.t., 4.0 h	39
8	TFA, CH_3CN, 72 °C, 14.0 h; DDQ, CH_3CN, r.t., 4.5 h	3
9	CH_3SO_3H, CH_3CN, 0 °C, 1.5 h; DDQ, CH_3CN, r.t., 2.5 h	92



Scheme 7. Reduction of the cyano group of the pyrrole **18**.



Scheme 8. Summary of the synthesis of IGPDI **14**.

Thus, the in situ formation of the more stable pyrrole from the dihydropyrrole was next attempted by using an oxidant (Table 6). In the presence of methanesulfonic acid and DDQ, the desired pyrrole **18** was obtained in excellent yield (entry 9).

Finally, treatment of the pyrrole **18** with Raney Ni W4 in the presence of $NaPH_2O_2/H_2O$/acetic acid/pyridine led to the desired monopyrrole aldehyde **14** in 73% yield (Schemes 7 and 8).

Conclusions

An efficient double nucleophilic addition of dialkoxy ketene silyl acetal to α,β-unsaturated imines has been developed and the subsequent conversion into multisubstituted pyrroles by cyclization to dihydropyrroles followed by deydrogenation has successfully been achieved. IGPDI, a physiologically active multisubstituted pyrrole, was synthesized by transformation of the double nucleophilic addition product. Thus, the present strategy offers a useful addition to the existing methodologies for the synthesis of pyrroles of biological interest.

Experimental Section

General: Infrared spectra were determined with a JASCO FT/ IR-460 plus spectrometer. ^1H and ^{13}C NMR spectra were recorded with a JEOL EX-270 or EX-500 spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra were recorded with a JEOL MS-700D spectrometer in EI mode at 70 eV. Dichloromethane, 1,4-dioxane and pyridine were distilled from calcium hydride and stored over molecular sieves (4 Å). THF was distilled from benzophenone ketyl immediately before use. MeOH was distilled from magnesium and stored over molecular sieves (3 Å). The products were purified by column chromatography on silica gel (Merck Silica Gel 60) and/or by preparative TLC on silica gel (Merck Kiesel Gel PF254).

Typical Procedure for the Double Nucleophilic Addition Reaction Leading to Diesters 3. Synthesis of Diethyl 3-(4-Methoxyphenylamino)-5-phenyl-2,2,6,6-tetraethoxyheptane-1,7-dioate (3a): Under argon, a suspension of $AlCl_3$ (40.0 mg, 0.30 mmol) and molecular sieves (4 Å) containing H_2O (1 equiv.) in CH_2Cl_2 (3.0 mL) were stirred at 0 °C for 15 min. A solution of *N*-(4-methoxyphenyl)-cinnamylideneamine (71.1 mg, 0.30 mmol) in CH_2Cl_2 (1.0 mL) was added to the resulting suspension at –78 °C and the mixture was stirred for 10 min. A solution of 1,2,2-triethoxy-1-(trimethylsiloxy)-ethylene (**2**; 223 mg, 0.90 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture, which was gradually warmed to room temperature over 8.5 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (15 mL × 3) and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give a crude product. Purification by TLC on silica gel (*n*-hexane/ethyl acetate = 4:1) gave the title compound **3a** (150.7 mg, 85%) as a mixture of *syn* and *anti* isomers[4a,11] (87:13, determined by HPLC).

Diethyl 3-(4-Methoxyphenylamino)-5-phenyl-2,2,6,6-tetraethoxyheptane-1,7-dioate (3a): Yellow oil. ^1H NMR ($CDCl_3$): δ = 0.96 (t, J = 6.9 Hz, 3 H, CH_3),1.09–1.34 (m, 15 H, CH_3), 1.75–1.80 (m, 1 H, CHH), 2.24–2.37 (m, 1 H, CHH), 3.28–3.34 (m, 4 H), 3.44–3.64 (m, 5 H), 3.71 (s, 3 H, OCH_3), 3.71–3.81 (br. s, 1 H, NCH), 3.95–4.19 (m, 5 H), 6.30–6.33 (m, 2 H, Ar), 6.61–6.64 (m, 2 H, Ar), 7.15–7.28 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 14.1, 14.9, 15.1, 15.2, 15.3, 31.4, 47.3, 55.7, 56.8, 58.1, 58.3, 58.7, 59.4, 60.8, 61.3, 103.1, 103.5, 114.3, 115.1, 126.9, 127.6, 130.3, 138.2, 143.4, 151.7, 168.5, 169.0 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2934, 2899, 1745, 1618, 1513, 1450, 1390, 1238, 1085, 821, 755 cm^{-1}. HRMS (EI): calcd. for $C_{32}H_{47}NO_9$ $[M]^+$ 589.3251; found 589.3253.

Diethyl 3-(4-Methoxyphenylamino)-5-methyl-2,2,6,6-tetraethoxyheptane-1,7-dioate (3b): Colourless oil (58.1 mg, 77% yield). ^1H NMR ($CDCl_3$): δ = 0.95 (d, J = 6.7 Hz, 3 H, CHCH_3), 1.10 (t, J = 7.0 Hz, 3 H, CH_3), 1.08–1.32 (m, 15 H, CH_3), 2.21 (ddd, J = 5.5, 5.5, 14.7 Hz, 1 H, CHH), 2.48 (ddd, J = 6.7, 6.7, 14.7 Hz, 1 H, CHH), 3.40–3.82 (m, 9 H), 3.72 (s, 3 H, OCH_3), 4.04 (dd, J = 4.5, 8.6 Hz, 1 H, NCH), 4.12–4.25 (m, 4 H, CH_2), 6.63–6.66 (m, 2 H, Ar), 6.71–6.73 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.2, 15.1, 15.2, 45.2, 15.4, 16.2, 33.4, 34.1, 55.8, 56.7, 57.7, 58.6, 58.7, 59.4, 61.0, 61.2, 103.4, 105.1, 114.5, 114.8, 142.9, 151.7, 168.4, 169.1 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2935, 1740, 1514, 1238, 1180, 1065, 821 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{45}NO_9$ $[M]^+$ 527.3094; found 527.3110.

Diethyl 3-(Diphenylmethylamino)-5-phenyl-2,2,6,6-tetraethoxyheptane-1,7-dioate (3c): Colourless oil (72.5 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ = 1.05 (t, J = 6.9 Hz, 3 H, CH_3), 1.12 (t, J = 7.3 Hz, 3 H, CH_3), 1.14 (t, J = 6.9 Hz, 3 H, CH_3), 1.19 (t, J = 6.9 Hz, 3 H, CH_3), 1.21 (t, J = 7.3 Hz, 3 H, CH_3), 1.23 (t, J = 6.9 Hz, 3 H, CH_3), 1.68 (br. s, 1 H, NH), 1.81 (ddd, J = 5.0, 5.3, 14.5 Hz, 1 H, CHH), 2.60–2.70 (m, 1 H, CHH), 2.79–2.90 (m, 2 H), 3.10–3.21 (m, 1 H, NCH), 3.41–3.71 (m, 8 H, CH_2), 3.94–4.08 (m, 2 H, CH_2), 4.12–4.25 (m, 2 H, CH_2), 4.17–4.22 (m, 2 H, CH_2), 4.92 (s, 1 H, Ph_2CH), 6.91–6.95 (m, 2 H, Ar), 7.06–7.33 (m, 13 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 14.2, 15.1, 15.2, 15.2, 15.2, 31.4, 48.1, 55.3, 57.6, 58.3, 58.6, 60.7, 61.0, 63.6, 104.0, 105.2, 126.4, 126.5, 127.5, 127.7, 127.8, 128.0, 128.0, 130.0, 140.1, 144.6, 144.8, 168.5, 168.8 ppm. IR (neat): $\tilde{\nu}$ = 3061, 2979, 2933, 2898, 1742, 1602, 1492, 1451, 1391, 1078, 755, 702 cm^{-1}. HRMS (EI): calcd. for $C_{38}H_{51}NO_8$ [M]$^+$ 649.3615; found 649.3589.

Diethyl 3-[4-(Dimethylamino)phenylamino]-5-phenyl-2,2,6,6-tetraethoxyheptane-1,7-dioate (3d): Yellow oil (55.7 mg, 66% yield). ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, J = 6.9 Hz, 3 H, CH_3), 1.10 (dd, J = 6.7, 7.3 Hz, 3 H, CH_3), 1.14–1.24 (m, 9 H, CH_3), 1.27 (dd, J = 6.7, 7.3 Hz, 3 H, CH_3), 1.80–1.87 (m, 1 H, CHH), 2.28–2.35 (m, 1 H, CHH), 2.79 [s, 6 H, N(CH_3)$_2$], 3.27–3.34 (m, 4 H, CH_2), 3.46–3.55 (m, 4 H, CH_2), 3.60–3.63 (m, 1 H, NCH), 3.65–3.80 (br. s, 1 H, NH), 3.96–4.00 (m, 1 H, CH), 4.10–4.18 (m, 4 H, CH_2), 6.32–6.34 (m, 2 H, Ar), 6.59–6.61 (m, 2 H, Ar), 7.19–7.27 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 14.1, 14.9, 15.1, 15.2, 15.3, 31.4, 42.4, 47.2, 56.9, 57.9, 58.4, 58.7, 59.4, 60.7, 61.2, 103.1, 103.6, 115.2, 115.6, 126.8, 127.5, 130.4, 138.3, 168.5, 169.1 ppm. IR (neat): $\tilde{\nu}$ = 2980, 2936, 2898, 1742, 1518, 1450, 1391, 1370, 1123, 1087, 911, 816, 733, 647 cm^{-1}. HRMS (EI): calcd. for $C_{33}H_{50}N_2O_8$ [M]$^+$ 602.3567; found 602.3598.

Typical Procedure for the Double Nucleophilic Addition Reactions Leading to Esters 6. Synthesis of Ethyl 6-(*tert*-Butylthiocarbonyl)-2,2-diethoxy-5-(4-methoxyphenylamino)-3-phenylhexanoate (6a): Under argon, a suspension of $AlCl_3$ (18.7 mg, 0.14 mmol) and molecular sieves (4 Å) containing H_2O (1 equiv.) in CH_2Cl_2 (1.5 mL) was stirred at 0 °C for 15 min. A solution of *N*-(4-methoxyphenyl) cinnamylideneamine (**1**, 33.2 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL) was added to the resulting solution at –78 °C and the mixture was stirred for 10 min. A solution of 1,2,2-triethoxy-1-(trimethylsiloxy)-ethylene (**2**; 44.7 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture. After stirring for 5 min, a solution of 1-*tert*-butylthio-1-(trimethylsiloxy)ethylene (**4**; 49.0 mg, 0.24 mmol) in CH_2Cl_2 (1.0 mL) was added to the resulting mixture. The mixture was gradually warmed to room temperature over 11.5 h. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give a crude product. Purification by TLC on silica gel (*n*-hexane/ethyl acetate = 5:2) gave the title compound **6a** (61.0 mg, 80%) as a mixture of *syn* and *anti* isomers (90:10, determined by HPLC).

Ethyl 6-(*tert*-Butylthiocarbonyl)-2,2-diethoxy-5-(4-methoxyphenylamino)-3-phenylhexanoate (6a): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.13–1.27 (m, 9 H, CH_3), 1.40 (s, 9 H, *t*Bu), 2.12–2.23 (m, 2 H, CH_2), 2.40–2.44 (m, 1 H, CHH), 3.58–2.61 (m, 1 H, CHH), 3.25–3.30 (br. s, 1 H, NH), 3.53–3.71 (m, 4 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.00–4.16 (m, 2 H, CH_2), 6.36–6.40 (m, 2 H, Ar), 6.66–6.70 (m, 2 H, Ar), 7.13–7.26 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 15.2, 15.3, 29.6, 35.3, 48.0, 48.1, 49.5, 51.0, 55.7, 58.8, 61.0, 103.5, 114.8, 115.6, 127.0, 127.9, 129.6, 129.8, 138.4, 141.3, 152.3, 168.8, 198.6 ppm. IR (neat): $\tilde{\nu}$ = 2976, 1742, 1676, 1512, 1239, 1080, 756 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{43}NO_6S$ [M]$^+$ 545.2811; found 545.2805.

Ethyl 6-(*tert*-Butylthiocarbonyl)-2,2-diethoxy-5-[4-(dimethylamino)-phenylamino]-3-phenylhexanoate (6b): Yellow oil (51.9 mg, 63% yield). ^{1}H NMR ($CDCl_3$): δ = 1.10–1.27 (m, 9 H, CH_3), 1.42 (s, 5 H, *t*Bu), 1.45 (s, 4 H, *t*Bu), 2.06–2.17 (m, 2 H, CH_2), 2.38–2.42 (m, 1 H, CHH), 2.57–2.62 (m, 1 H, CHH), 2.80 [s, 6 H, (NCH_3)$_2$], 3.28–3.30 (br., 1 H, NH), 3.53–3.66 (m, 4 H, CH_2), 3.97–4.17 (m, 3 H), 6.36–6.41 (m, 2 H, Ar), 6.62–6.70 (m, 2 H, Ar), 7.15–7.26 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 15.2, 15.3, 29.6, 42.2, 47.9, 48.0, 51.1, 58.7, 60.9, 103.5, 115.7, 115.8, 115.9, 126.9, 127.8, 127.9, 129.6, 129.8, 138.4, 168, 198.6 ppm. IR (neat): $\tilde{\nu}$ = 2976, 1743, 1675, 1518, 1255, 1059, 701 cm^{-1}. HRMS (EI): calcd. for $C_{31}H_{46}N_2O_5S$ [M]$^+$ 558.3127; found 558.3104.

Ethyl 6-(*tert*-Butylthiocarbonyl)-2,2-diethoxy-5-(2,4-dimethoxyphenylamino)-3-phenylhexanoate (6c): Yellow oil (49.9 mg, 62% yield). ^{1}H NMR ($CDCl_3$): δ = 1.12–1.31 (m, 11 H), 1.41 (s, 9 H, *t*Bu), 2.10–2.41 (m, 3 H, CH_3), 2.62–2.66 (m, 1 H), 3.34 (br. s, 1 H, NH), 3.50–3.68 (m, 4 H, CH_2), 3.72 (s, 3 H, OCH_3), 3.80 (s, 2 H, OCH_3), 3.87 (s, 1 H, OCH_3), 4.03–4.13 (m, 2 H, CH_2), 6.16–6.60 (m, 3 H, Ar), 7.11–7.26 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 15.4, 15.5, 29.8, 35.7, 48.0, 48.1, 50.3, 30.5, 55.7, 56.0, 58.8, 61.6, 99.4, 103.7, 103.9, 104.2, 112.1, 126.7, 127.0, 127.9, 128.6, 129.8, 130.0, 131.4, 138.6, 148.4, 152.1, 168.9, 198.5 ppm. IR (neat): $\tilde{\nu}$ = 2976, 1744, 1676, 1517, 1457, 1206, 1157, 1036, 755 cm^{-1}. HRMS (EI): calcd. for $C_{31}H_{45}NO_7$ S [M]$^+$ 575.2917; found 575.2890.

Ethyl 6-(*tert*-Butylthiocarbonyl)-2,2-diethoxy-5-(4-methoxyphenylamino)-3-methylhexanoate (6d): Colourless oil (46.0 mg, 70% yield). ^{1}H NMR ($CDCl_3$): δ = 0.98 (dd, J = 7.0, 23.5 Hz, 3 H, CH_3), 1.19–1.36 (m, 9 H, CH_3), 1.43 (s, 9 H, *t*Bu), 2.00 (ddd, J = 4.3, 7.3, 14.6 Hz, 1 H, CHH), 2.12–2.25 (m, 1 H, CHH), 2.44 (dd, J = 7.6, 14.3 Hz, 1 H, CHH), 2.62 (dd, J = 2.0, 5.5 Hz, 2 H), 2.79 (dd, J = 4.3, 14.3 Hz, 1 H), 3.42–3.60 (m, 4 H, CH_2), 3.86 (t, J = 6.3 Hz, 1 H), 4.12–4.26 (m, 2 H, CH_2), 6.56–6.61 (m, 2 H, Ar), 6.74–6.78 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 15.1, 15.2, 29.6, 35.0, 36.7, 48.0, 48.5, 51.3, 55.6, 57.2, 58.2, 61.1, 104.1, 114.7, 115.0, 141.0, 152.1, 168.2, 198.6 ppm. IR (neat): $\tilde{\nu}$ = 2975, 1740, 1676, 1512, 1239, 1120, 1063 cm^{-1}. HRMS (EI): calcd. for $C_{25}H_{41}NO_6S$ [M]$^+$ 483.2655; found 483.2635.

Typical Procedure for Double Nucleophilic Addition Reactions Leading to Esters 7. Synthesis of Ethyl 5-Cyano-2,2-diethoxy-5-(4-methoxyphenylamino)-3-methylpentanoate (7b): Under argon, a suspension of $AlCl_3$ (133.0 mg, 1.0 mmol) and molecular sieves (4 Å) containing H_2O (1 equiv.) in CH_2Cl_2 (10.0 mL) was stirred at 0 °C for 15 min. A solution of *N*-(4-methoxyphenyl)crotylideneamine (**1**, 175.0 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added to the resulting mixture at –78 °C and the mixture was stirred for 10 min. A solution of 1,2,2-triethoxy-1-(trimethylsiloxy)ethylene (**2**; 248 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added to it. After stirring for 5 min a solution of TMSCN (**5**; 138.0 mg, 1.4 mmol) in CH_2Cl_2 (3.0 mL) was added to the resulting mixture. The mixture was gradually warmed to room temperature over 16.0 h. Saturated aqueous $NaHCO_3$ (30 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL × 3) and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give a crude product. Purification by TLC on silica gel (*n*-hexane/ethyl acetate = 4:1) gave the title compound **7b** (270.0 mg, 95%) as a mixture of *syn* and *anti* isomers (88:12, determined by HPLC).

Ethyl 5-Cyano-2,2-diethoxy-5-(4-methoxyphenyl)amino-3-phenylpentanoate (7a): Yellow oil (35.1 mg, 55% yield). ^{1}H NMR ($CDCl_3$): δ = 1.15–1.22 (m, 6 H, CH_3), 1.26 (t, J = 1.8, 7.0 Hz, 3 H, CH_3), 2.37–2.52 (m, 1 H, CHH), 2.59–2.70 (m, 1 H, CHH), 3.34 (d, J = 10.7 Hz, 1 H), 3.55–3.76 (m, 5 H), 3.74 (s 3 H, OCH_3), 3.79–3.95 (m, 1 H, NCH), 4.01–4.12 (m, 2 H, CH_2), 6.49–6.54 (m,

2 H, Ar), 6.75–6.78 (m, 2 H, Ar), 7.20–7.32 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 15.3, 34.7, 46.4, 47.8, 55.6, 59.2, 59.3, 61.3, 103.1, 114.9, 115.9, 116.5, 120.1, 127.7, 128.4, 129.4, 137.3, 138.8, 154.0, 168.4 ppm. IR (neat): $\tilde{\nu}$ = 2980, 2935, 2900, 1738, 1514, 1241, 1120, 1083, 756, 702 cm^{-1}. HRMS (EI): calcd. for $C_{25}H_{32}N_2O_5$ [M]$^+$ 440.2311; found 440.2306.

Ethyl 5-Cyano-2,2-diethoxy-5-(4-methoxyphenylamino)-3-methylpentanoate (7b): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.03 (dd, J = 7.0, 22.0 Hz, 3 H, CH_3), 1.22–1.34 (m, 9 H, CH_3), 1.70 (dt, J = 6.6, 7.6 Hz, 1 H, CHH), 2,29–2.49 (m, 2 H), 3.43–3.61 (m, 4 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.21–4.30 (m, 2 H, CH_2), 4.32–4.50 (m, 1 H, NCH), 6.69–6.71 (m, 2 H, Ar), 6.82–6.84 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3, 15.1, 34.5, 46.3, 55.6, 56.9, 59.2, 61.4, 103.8, 114.9, 115.9, 120.4, 139.1, 153.7, 168.0 ppm. IR (neat): $\tilde{\nu}$ = 2979, 1739, 1389, 1241, 1181, 1120, 1062 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{30}N_2O_5$ [M]$^+$ 378.2156; found 378.2138.

Typical Procedure for the Cyclization of Esters 3, 6 and 7 to Dihydro-1*H*-pyrroles 8–10. Synthesis of Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (9a): Sulfuric acid (H_2SO_4/H_2O = 3:1, 4.0 mL) was added to ethyl 6-*tert*-butylthiocarbonyl-2,2-diethoxy-5-(4-methoxyphenylamino)-3-phenylhexanoate (**6a**; 38.4 mg, 0.07 mmol) at 0 °C and the mixture was stirred for 1.5 h. The mixture was then gradually warmed to room temperature over 1.5 h. The mixture was extracted with ethyl acetate (5 mL × 3) and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give a crude product. Purification by TLC on silica gel (*n*-hexane/ethyl acetate = 1:1) gave **9a** (23.3 mg, 73%).

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (8a): Yellow oil (8.5 mg, 88% yield). ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.11 (t, J = 7.0 Hz, 3 H, CH_3), 1.22 (t, J = 7.0 Hz, 3 H, CH_3), 1.23 (t, J = 7.0 Hz, 3 H, CH_3), 3.36–3.44 (m, 3 H), 3.48–3.55 (m, 2 H, CH_2), 3.62–3.65 (m, 1 H), 3.77 (s, 3 H, OCH_3), 3.89–3.98 (m, 2 H, CH_2), 4.02–4.06 (m, 1 H, NCH), 4.12–4.23 (m, 2 H, CH_2), 6.79–6.81 (m, 2 H, Ar), 7.19–7.22 (m, 1 H, Ar), 7.26–7.34 (m, 4 H, Ar) 7.37–7.39 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 14.1, 15.1, 36.6, 55.4, 58.2, 58.7, 60.5, 61.5, 103.1, 113.7, 124.9, 126.8, 127.3, 127.9, 134.9, 136.3, 141.6, 157.3, 163.5, 168.1 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2934, 2900, 1727, 1628, 1510, 1247, 1181, 1123, 1091, 837, 757 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{35}NO_7$ [M]$^+$ 497.2414; found 497.2390.

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(4-methoxyphenyl)-3-methyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (8b): Clear oil (12.6 mg, 69% yield). ^{1}H NMR ($CDCl_3$): δ = 0.97 (t, J = 7.1 Hz, 3 H, CH_3), 1.18 (t, J = 7.2 Hz, 3 H, CH_3), 1.12–1.26 (m, 9 H, CH_3), 2.07 (s, 3 H, CH_3), 2.94–2.97 (m, 2 H, CH_2), 3.43–3.51 (m, 4 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.80–3.89 (m, 1 H), 3.90–3.98 (m, 1 H), 4.01–4.08 (m, 1 H, NCH), 4.11–4.29 (m, 2 H, CH_2), 6.75–6.78 (m, 2 H, Ar), 7.18–7.21 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 14.0, 15.1, 15.2, 38.3, 55.4, 58.4, 59.8, 61.2, 69.4, 103.1, 113.5, 125.2, 131.8, 134.0, 144.0, 156.2, 162.6, 168.0 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2933, 1713, 1510, 1444, 1372, 1335, 1277, 1245, 1178, 1123, 1073, 836, 756 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{33}NO_7$ [M]$^+$ 435.2257; found 435.2239.

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(diphenylmethyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (8c): Yellow oil (19.6 mg, 96% yield). ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.2 Hz, 3 H, CH_3), 1.12–1.33 (m, 9 H, CH_3), 2.91 (dd, J = 4.3, 16.5 Hz, 1 H), 3.16–3.20 (m, 1 H), 3.26 (dd, J = 5.6, 16.5 Hz, 1 H), 3.44–3.70 (m, 4 H, CH_2), 3.87–3.92 (m, 2 H, CH_2), 4.14–4.30 (m, 2 H, CH_2), 5.83 (s, 1 H, Ph_2CH), 7.10–7.29 (m, 9 H, Ar), 7.32–7.43 (m, 4 H, Ar), 7.61–7.64 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3, 15.3, 15.4, 59.0, 59.2, 61.3, 62.0, 63.0, 103.1, 126.5, 126.7, 127.0, 127.2, 127.5, 128.0, 128.2, 128.4, 128.5, 133.6, 137.2, 143.4, 144.5 ppm. 168.7. IR (neat): $\tilde{\nu}$ = 2979, 2934, 2899, 1746, 1450, 1252, 1194, 1124, 1088, 758, 700 cm^{-1}. HRMS (EI): calcd. for $C_{34}H_{39}NO_6$ [M]$^+$ 557.2777; found 557.2770.

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-[4-(dimethylamino)-phenyl]-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (8d): Yellow oil (34.4 mg, 100% yield). ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.12 (t, J = 7.0 Hz, 3 H, CH_3), 1.22 (t, J = 7.0 Hz, 3 H, CH_3), 2.90 [s, 6 H, N(CH_3)$_2$], 3.37–3.43 (m, 3 H), 3.48–3.56 (m, 2 H), 3.60–3.61 (m, 1 H), 3.90–4.00 (m, 2 H, CH_2), 4.04 (dd, J = 7.9, 10.4 Hz, 1 H, NCH), 4.20–4.27 (m, 2 H, CH_2), 6.62–6.65 (m, 2 H, Ar), 7.17–7.20 (m, 1 H, Ar), 7.26–7.30 (m, 4 H, Ar), 7.37–7.38 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 14.1, 15.1, 15.1, 36.4, 41.0, 58.1, 58.6, 60.4, 61.4, 68.6, 103.2, 112.7, 123.5, 126.6, 127.1, 127.2, 127.9, 135.0, 136.8, 138.1, 148.7, 163.8, 168.1 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2932, 2896, 1727, 1616, 1518, 1267, 1154, 1123, 1090, 1056, 823, 783, 759 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{38}N_2O_6$ [M]$^+$ 510.2730; found 510.2739.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (9a): Yellow oil (23.3 mg, 73%). ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.1 Hz, 3 H, CH_3), 1.42 (s, 9 H, *t*Bu), 2.75 (dd, J = 8.8, 15.9 Hz, 1 H, CHH), 2.85 (dd, J = 9.5, 15.3 Hz, 1 H, CHH), 2.97 (dd, J = 4.3, 15.3 Hz, 1 H, CHH), 3.41 (dd, J = 9.8, 15.9 Hz, 1 H, CHH), 3.78 (s, 3 H, OCH_3), 3.95–4.10 (m, 3 H), 6.84–6.85 (m, 2 H, Ar), 7.04–7.05 (m, 2 H, Ar), 7.26–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 29.7, 40.0, 48.3, 49.2, 55.4, 60.9, 63.7, 114.5, 123.3, 125.9, 126.9, 127.2, 128.0, 134.9, 136.8, 139.3, 157.3, 163.7, 198.0 ppm. IR (neat): $\tilde{\nu}$ = 2962, 1678, 1510, 1459, 1367, 1247, 1179, 1034, 834, 758 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{31}NO_4S$ [M]$^+$ 453.1974; found 453.1990.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-[4-(dimethylamino)phenyl]-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (9b): Yellow oil (21.9 mg, 67% yield). ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.0 Hz, 3 H, CH_3), 1.42 (s, 9 H, *t*Bu), 2.75 (dd, J = 9.4, 16.5 Hz, 1 H, CHH), 2.84 (dd, J = 9.8, 15.3 Hz, 1 H, CHH), 2.92 [s, 6 H, N(CH_3)$_2$], 2.98 (dd, J = 4.3, 15.3 Hz, 1 H, CHH), 3.39 (dd, J = 9.8, 16.5 Hz, 1 H, CHH), 3.94–4.13 (m, 4 H, CH_2), 6.65–6.68 (m, 2 H, Ar), 7.18–7.20 (m, 1 H, Ar), 7.22–7.32 (m, 2 H, Ar), 7.36–7.39 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 29.7, 39.7, 40.8, 48.2, 49.1, 60.8, 63.9, 113.1, 126.1, 121.8, 126.1, 126.6, 127.0, 128.0, 135.0, 135.5, 137.6, 148.8, 163.9, 198.0 ppm. IR (neat): $\tilde{\nu}$ = 2923, 1725, 1678, 1518, 1346, 1273, 1170, 821, 756 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{34}N_2O_3S$ [M]$^+$ 466.2290; found 466.2276.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(2,4-dimethoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (9c): Yellow oil (11.4 mg, 79% yield). ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.41 (s, 9 H, *t*Bu), 2.79 (dd, J = 9.2, 16.5 Hz, 1 H, CHH), 2.83 (dd, J = 9.5, 15.3 Hz, 1 H, CHH), 2.93 (dd, J = 4.0, 14.7 Hz, 1 H, CHH), 3.35 (dd, J = 10.5, 16.5 Hz, 1 H, CHH), 3.78 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.89–4.04 (m, 2 H, CH_2), 4.11–4.17 (m, 1 H, NCH), 6.39–6.46 (m, 2 H, Ar), 7.02–7.04 (m, 1 H, Ar), 7.24–7.37 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 29.7, 39.9, 48.1, 48.9, 55.4, 55.5, 60.5, 99.4, 104.0, 126.5, 127.2, 127.9, 135.6, 156.7, 158.9, 163.5, 198.3 ppm. IR (neat): $\tilde{\nu}$ = 2926, 1724, 1678, 1610, 1509, 1459, 1258, 1209, 1159, 1034, 756 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{33}NO_5S$ [M]$^+$ 483.2079; found 483.2092.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-methyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (9d): Yellow oil

(19.8 mg, 86% yield). ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, J = 6.9 Hz, 3 H, CH_3), 1.43 (s, 9 H, *t*Bu), 2.07 (s, 3 H, CH_3), 2.30 (dd, J = 7.6, 17.4 Hz, 1 H, CHH), 2.75 (dd, J = 9.5, 15.0 Hz, 1 H, CHH), 2.96 (dd, J = 4.5, 15.0 Hz, 1 H, CHH), 2.98 (dd, J = 2.4, 3.4 Hz, 1 H, CHH), 3.77 (s, 3 H, OCH_3), 3.79–3.84 (m, 1 H), 3.94–4.00 (m, 1 H, NCH), 4.09–4.15 (m, 2 H, CH_2), 6.76–6.80 (m, 2 H, Ar), 6.81–6.94 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 14.2, 29.7, 29.7, 41.8, 48.2, 50.1, 55.4, 60.1, 64.4, 114.2, 124.2, 130.0, 134.7, 142.3, 156.5, 162.9, 198.1 ppm. IR (neat): $\tilde{\nu}$ = 2963, 1679, 1512, 1247, 1164, 1091, 1034 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{29}NO_4S$ [M]$^+$ 391.1817; found 391.1823.

Ethyl 5-Cyano-1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (10a): Yellow oil (41.8 mg, 100% yield). ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.1 Hz, 3 H, CH_3), 3.32 (dd, J = 8.3, 16.2 Hz, 1 H, CHH), 3.52 (dd, J = 10.9, 16.2 Hz, 1 H, CHH), 3.80 (s, 3 H, OCH_3), 3.98–4.07 (m, 2 H, CH_2), 4.50 (dd, J = 8.3, 10.9 Hz, 1 H, NCH), 6.88–6.91 (m, 2 H, Ar), 7.16–7.20 (m, 2 H, Ar), 7.26–7.40 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 39.1, 55.4, 55.9, 61.2, 114.8, 118.7, 122.7, 125.5, 127.4, 127.7, 128.2, 133.3, 138.1, 158.1, 162.0 ppm. IR (neat): $\tilde{\nu}$ = 2922, 2853, 2227, 1718, 1512, 1461, 1254, 1181, 804, 763 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{20}N_2O_3$ [M]$^+$ 348.1474; found 348.1477.

Ethyl 5-Cyano-1-(4-methoxyphenyl)-3-methyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (10b): Yellow oil (30.0 mg, 86% yield). ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, J = 7.1 Hz, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.87 (dd, J = 7.8, 17.0 Hz, 1 H, CHH), 3.15 (dd, J = 10.9, 17.2 Hz, 1 H, CHH), 3.78 (s, 3 H, OCH_3), 3.99–4.14 (m, 2 H, CH_2), 4.26 (dd, J = 7.7, 10.7 Hz, 1 H, NCH), 6.83–6.86 (m, 2 H, Ar), 7.05–7.02 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 40.8, 55.4, 56.0, 60.6, 114.5, 119.3, 124.3, 127.3, 134.3, 140.6, 157.4, 161.8 ppm. IR (neat): $\tilde{\nu}$ = 2981, 1716, 1509, 1374, 1247, 1178, 1141, 1033, 832 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{18}N_2O_3$ [M]$^+$ 286.1317; found 286.1321.

Typical Procedure for the Oxidation of Dihydro-1*H*-pyrroles 8–10 to -1*H*-pyrroles 11–13. Synthesis of Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (12a): Under argon, a solution of **9a** (20.4 mg, 0.045 mmol) in 1,4-dioxane (1.0 mL) was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 10.5 mg, 0.04 mmol) in 1,4-dioxane (1.0 mL) at room temperature. The mixture was stirred for 12.5 h at room temperature. Saturated aqueous 10% $NaHSO_3$ (5.0 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL × 3) and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give a crude product. Purification by TLC on silica gel (*n*-hexane/ethyl acetate = 1:1) gave **12a** (12.5 mg, 62%).

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (11a): Yellow oil (138.7 mg, 100% yield). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.16–1.26 (m, 9 H, CH_3), 3.36–3.42 (m, 2 H, CH_2), 3.46–3.52 (m, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 3.93 (q, J = 7.0 Hz, 4 H, OCH_2), 6.74 (s, 1 H, CH), 6.87–6.89 (m, 2 H, Ar), 7.12–7.14 (m, 2 H, Ar), 7.27–7.30 (m, 1 H, Ar), 7.37–7.34 (m, 2 H), 7.49–7.51 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 14.0, 14.9, 55.3, 58.2, 60.0, 61.8, 97.0, 113.0, 122.7, 126.7, 127.6, 129.3, 129.7, 130.9, 131.6, 135.7, 135.8, 159.5, 161.2, 166.7 ppm. IR (neat): $\tilde{\nu}$ = 3018, 2981, 2929, 1754, 1698, 1611, 1513, 1297, 1250, 1216, 1191, 1096, 1065, 756 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{33}NO_7$ [M]$^+$ 495.2257; found 495.2271.

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate (11b): Yellow oil (7.3 mg, 95% yield). ^{1}H NMR ($CDCl_3$): δ = 1.08 (t, J = 7.1 Hz, 3 H, CH_3), 1.13–1.25 (m, 9 H, CH_3), 2.38 (s, 3 H, CH_3), 3.30–3.48 (m, 4 H, CH_2), 3.82 (s, 3 H, OCH_3), 3.91 (q, J = 7.1 Hz, 2 H, CH_2), 4.05 (q, J = 7.1 Hz, 2 H, CH_2), 6.51 (s, 1 H, Ar), 6.82–6.85 (m, 2 H, Ar), 7.01–7.05 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3, 14.4, 14.5, 15.4, 55.8, 58.6, 60.0, 62.1, 97.5, 113.3, 114.1, 123.4, 129.1, 130.1, 131.9, 136.3, 159.7, 161.8, 167.2 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2933, 1756, 1701, 1513, 1442, 1374, 1341, 1297, 1248, 1190, 1094, 1065, 832, 755, 665 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{31}NO_7$ [M]$^+$ 433.2101; found 433.2094.

Ethyl 5-(Ethoxycarbonyldiethoxymethyl)-1-(diphenylmethyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (11c): Yellow oil (9.8 mg, 100% yield). ^{1}H NMR ($CDCl_3$): δ = 0.68 (t, J = 7.0 Hz, 3 H, CH_3), 1.07–1.13 (m, 9 H, CH_3), 3.38–3.50 (m, 6 H, CH_2), 3.66 (q, J = 7.0 Hz, 2 H, CH_2), 6.77 (s, 1 H, Ph_2CH), 7.15–7.32 (m, 14 H, Ar), 7.38–7.41 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4, 14.0, 14.6, 58.5, 60.4, 61.9, 63.8, 97.8, 111.9, 123.3, 126.3, 127.0, 127.5, 127.8, 128.4, 128.6, 128.9, 133.0, 135.5, 138.9, 162.6, 167.7 ppm. IR (neat): $\tilde{\nu}$ = 3062, 2980, 2935, 2898, 1718, 1497, 1451, 1392, 1349, 1301, 1255, 1194, 1127, 1089, 856, 828, 758, 699, 668 cm^{-1}. HRMS (EI): calcd. for $C_{34}H_{37}NO_6$ [M]$^+$ 555.2621; found 555.2628.

Ethyl 2-(Ethoxycarbonyldiethoxymethyl)-1-[4-(dimethylamino)-phenyl]-3-phenyl-1*H*-pyrrole-2-carboxylate (11d): Yellow oil (5.9 mg, 66% yield). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.17 (t, J = 7.0 Hz, 3 H, CH_3), 1.22 (t, J = 7.0 Hz, 6 H, CH_3), 2.97 [s, 6 H, N(CH_3)$_2$], 3.37–3.43 (m, 2 H, CH_2), 3.47–3.53 (m, 2 H, CH_2), 3.91–3.96 (m, 4 H, CH_2), 6.62–6.65 (m, 2 H, Ar), 6.73 (s, 1 H, Ar), 7.00–7.05 (m, 2 H, Ar), 7.26–7.30 (m, 1 H, Ar), 7.33–3.36 (m, 2 H, Ar), 7.49–7.51 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 14.0, 14.9, 40.4, 58.1, 59.9, 61.6, 97.0, 110.9, 112.6, 126.6, 127.6, 129.1, 129.3, 131.2, 135.9, 136.1, 150.2, 161.3, 166.6 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2933, 2894, 1757, 1710, 1612, 1523, 1477, 1447, 1373, 1341, 1259, 1191, 1097, 1062, 820, 764, 730 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{36}N_2O_6$ [M]$^+$ 508.2573; found 508.2580.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (12a): Yellow oil (12.5 mg, 62% yield). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.1 Hz, 3 H, CH_3), 1.40 (s, 9 H, *t*Bu), 3.53 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.94 (q, J = 7.1 Hz, 2 H, CH_2), 6.30 (s, 1 H, Ar), 6.92–6.95 (m, 2 H, Ar), 7.18–7.22 (m, 2 H, Ar), 7.31–7.38 (m, 3 H, Ar), 7.48–7.51 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 29.6, 42.2, 48.2, 55.4, 59.7, 112.4, 113.9, 121.2, 126.7, 127.5, 129.1, 129.5, 131.6, 131.9, 133.1, 136.0, 159.3, 161.0, 196.1 ppm. IR (neat): $\tilde{\nu}$ = 2962, 1701, 1607, 1511, 1467, 1250, 1178, 1036, 978, 833, 759, 699 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{29}NO_4S$ [M]$^+$ 451.1817; found 451.1822.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-[4-(dimethylamino)phenyl]-3-phenyl-1*H*-pyrrole-2-carboxylate (12b): Yellow oil (8.2 mg, 93% yield). ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H), 1.41 (s, 9 H, *t*Bu), 3.00 [s, 6 H, N(CH_3)$_2$], 3.54 (s, 2 H, CH_2), 3.95 (q, J = 7.1 Hz, 2 H, CH_2), 6.28 (s, 1 H, Ar), 6.69–6.72 (m, 2 H, Ar), 7.10–7.13 (m, 2 H, Ar), 7.30–7.50 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 29.7, 40.5, 42.4, 48.2, 59.7, 111.8, 112.0, 121.2, 126.6, 127.5, 128.6, 129.6, 132.2, 132.8, 136.4, 150.1, 161.2, 196.4 ppm. IR (neat): $\tilde{\nu}$ = 2919, 1701, 1610, 1522, 1344, 1158, 1034, 760 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{32}N_2O_3S$ [M]$^+$ 464.2134; found 464.2122.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(2,4-dimethoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (12c): Yellow oil (12.2 mg, 97% yield). ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3 H, CH_3), 1.39 (s, 9 H, *t*Bu), 3.42 (d, J = 16.5 Hz, 1 H, CHH) 3.58 (d, J = 16.5 Hz, 1 H, CHH), 3.74 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.95 (q, J = 7.1 Hz, 2 H, CH_2), 6.31 (s, 1 H, Ar), 6.53–6.55 (m, 2 H, Ar), 7.12–7.15 (m, 2 H, Ar), 7.29–7.37 (m, 3 H, Ar), 7.49–7.53 (m, 2 H,

Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 29.6, 42.2, 48, 55.5, 55.7, 59.5, 99.1, 103.9, 112.3, 121, 126.5, 127.4, 129.6, 130.1, 131.9, 133.0, 136, 157, 160.8, 196 ppm. IR (neat): $\tilde{\nu}$ = 2962, 1700, 1514, 1457, 1309, 1210, 1161, 1033, 760 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{31}NO_5S$ $[M]^+$ 481.1923; found 481.1926.

Ethyl 5-(*tert*-Butylthiocarbonylmethyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate (12d): Yellow oil (21.7 mg, 69% yield). ^{1}H NMR ($CDCl_3$): δ = 1.10 (t, J = 7.1 Hz, 3 H, CH_3), 1.40 (s, 9 H, *t*Bu), 2.39 (s, 3 H, CH_3), 3.46 (s, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 4.07 (q, J = 7.1 Hz, 4 H, CH_2), 6.08 (s, 1 H, Ar), 6.91–6.92 (m, 2 H, Ar), 7.09–7.10 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 14.1, 29.6, 42.2, 48.2, 55.4, 59.3, 113.0, 113.7, 121.9, 129.2, 129.8, 131.9, 132.0, 159.2, 161.2, 196.3 ppm. IR (neat): $\tilde{\nu}$ = 2923, 1693, 1513, 1248, 1197, 1091, 1035 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{27}NO_4S$ $[M]^+$ 389.1661; found 389.1656.

Ethyl 5-Cyano-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (13a): Yellow oil (71.8 mg, 74% yield). ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, J = 7.1 Hz, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 4.00 (q, J = 7.1 Hz, 2 H, CH_2), 6.93 (s, 1 H, Ar), 6.98–7.01 (m, 2 H, Ar), 7.29–7.45 (m, 7 H, Ar) ppm. ^{13}C NMR ($CDCl_3$) δ = 13.5, 55.5, 61.0, 110.0, 112.4, 114.2, 120.2, 125.6, 127.7, 127.9, 128.0, 129.2, 130.3, 132.0, 133.8, 160.0, 160.1 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2845, 2226, 1718, 1513, 1461, 1382, 1299, 1254, 1182, 1110, 1033, 835, 767, 699 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{18}N_2O_3$ $[M]^+$ 346.1317; found 346.1332.

Ethyl 5-Cyano-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrrole-2-carboxylate (13b): Colourless oil (65.5 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ = 1.12 (t, J = 7.3 Hz, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.13 (q, J = 7.1 Hz, 2 H, CH_2), 6.71 (s, 1 H, Ar), 6.95–6.97 (m, 2 H, Ar), 7.19–7.20 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 13.9, 55.5, 60.5, 110.0, 112.6, 114.0, 120.7, 128.1, 128.9, 130.9, 159.9 ppm. IR (neat): $\tilde{\nu}$ = 2980, 2224, 1711, 1513, 1440, 1252, 1188, 1095, 833 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{16}N_2O_3$ $[M]^+$ 284.1161; found 284.1168.

Procedure for the Synthesis of Ethyl 5-Cyano-2,2-diethoxy-5-(*tert*-butoxycarbonylamino)-3-methylpentanoate (16): Under argon, $PhI(OAc)_2$ (283.0 mg, 0.88 mmol) was completely dissolved in MeOH (2.0 mL) and AcOH (0.55 mL). A solution of ethyl 5-cyano-2,2-diethoxy-5-(4-methoxyphenylamino)-3-methylpentanoate (**7b**; 86.2 mg, 0.22 mmol) in MeOH (2.0 mL) was slowly added to the resulting solution at room temperature and the mixture was stirred for 30 min. A 1.2 N HCl solution (2.7 mL) was added to the mixture, which was stirred for 30 min. A 10% aq. $Na_2S_2O_3$ solution (2.7 mL) was added and the mixture was stirred for 30 min. The reaction mixture was then made basic by the addition of 10% aq. Na_2CO_3 (2.7 mL) upon which the solution turned dark-red. A solution of Boc_2O (192.0 mg, 0.88 mmol) in CH_2Cl_2 (1.0 mL) was added and the mixture was stirred at room temperature for 13.0 h. MeOH was distilled off under reduced pressure. The resulting solution was extracted with CH_2Cl_2 (5 mL × 3) and the combined organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure to afford a brown oil, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1). The colourless oil obtained was **16** (68.8 mg, 84%). Colourless oil. ^{1}H NMR ($CDCl_3$): δ = 0.98 (d, J = 7.0 Hz, 2.5 H, CH_3), 1.02 (d, J = 7.0 Hz, 0.5 H, CH_3), 1.25 (t, J = 7.0 Hz, 6 H, CH_3), 1.32 (t, J = 7.0 Hz, 3 H, CH_3), 1.46 (s, 9 H, *t*Bu), 1.58–1.64 (m, 1 H), 2.18–2.37 (m, 2 H), 3.41–3.50 (m, 1 H), 3.52–3.60 (m, 4 H, CH_2), 4.22–4.32 (m, 2 H, CH_2), 4.60–4.80 (m, 1 H, NC*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.3, 15.4, 15.5, 15.6, 15.8, 28.6, 35.0, 57.4, 59.7, 61.9, 81.2, 119.1, 119.9, 154.8, 168.3 ppm. IR (neat): $\tilde{\nu}$ = 2978, 1721, 1513, 1252, 1166, 1119, 758 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{32}N_2O_3$ $[M]^+$ 372.2260; found 372.2259.

Procedure for the Synthesis of Ethyl 5-Cyano-3-methyl-1*H*-pyrrole-2-carboxylate (18): Under argon, CH_3SO_3H (1.0 mL) in acetonitrile (1.2 mL) was added to **16** (41.1 mg, 0.11 mmol) at 0 °C and the mixture was stirred for 1.5 h. This mixture was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (31.4 mg, 0.11 mmol) in acetonitrile (2.4 mL) at room temperature and the mixture was stirred for 2.5 h at room temperature. The layers were separated and the organic layer was washed with a 10% aq. Na_2SO_3 (5 mL). The aqueous layer was made basic by the addition of 10% aq. Na_2CO_3 (pH = 12) and extracted with AcOEt (3 mL × 3). The combined organic layers were washed with 10% aq. Na_2CO_3 (3 mL × 3) and with brine (3 mL × 3), dried with Na_2SO_4 and concentrated. The product was purified by TLC on buffered silica gel (*n*-hexane/ethyl acetate = 2:1) to give **18** (18.1 mg, 92%). White crystals; m.p. 115–117 °C. ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, J = 7.3 Hz, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 4.42 (q, J = 7.3 Hz, 2 H, CH_2), 6.64 (s, 1 H, Ar), 10.0 (br. s, 1 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.5, 14.3, 61.5, 103.9, 113.0, 121.5, 123.8, 127.5, 161.0 ppm. IR (neat): $\tilde{\nu}$ = 3253, 2989, 2226, 1688, 1487, 1285, 819, 717 cm^{-1}. HRMS (EI): calcd. for $C_9H_{10}N_2O_2$ $[M]^+$ 178.0742; found 178.0745.

Procedure for the Synthesis of Ethyl 5-Formyl-3-methyl-1*H*-pyrrole-2-carboxylate (14):[8] A mixture of **18** (6.7 mg, 0.037 mmol) and sodium hypophosphate hydrate (23.1 mg, 0.26 mmol) in water/acetic acid/pyridine (1:1:2, 4.0 mL) was treated with Raney nickel W4 (15 mg) and the mixture was stirred at room temperature for 2.5 h. The mixture was filtered, the catalyst washed with EtOH and the extracts added to the filtrate. The remainder of the filtrate was diluted with water and extracted with Et_2O. The combined organic layers were washed with 10% aq. Na_2CO_3 (5 mL), the aqueous layer was made basic by the addition of 10% aq. Na_2CO_3 (pH = 12) and extracted with Et_2O (3 mL × 3). The combined organic layers were washed with 10% aq. Na_2CO_3 (3 mL × 3) and then with brine (3 mL × 3), dried with Na_2SO_4 and concentrated. The product was purified by TLC on silica gel (dichloromethane/ethyl acetate = 9:1) to give **14** (4.9 mg, 73%). White crystals; m.p. 104–105 °C. ^{1}H NMR ($CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 4.35 (q, J = 7.1 Hz, 2 H, CH_2), 6.76 (s, 1 H, Ar), 9.60 (s, 1 H, C*H*O) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.5, 14.3, 61.0, 121.2, 125.0, 128.3, 132.5, 160.9, 180.3 ppm. IR (neat): $\tilde{\nu}$ = 3270, 1675, 1485, 1324, 1266, 1143, 1017, 820, 724 cm^{-1}. HRMS (EI): calcd. for $C_9H_{11}NO_3$ $[M]^+$ 181.0739; found 181.0733.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR spectra of all new compounds.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (B) and Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology and the Japanese Society for the Promotion of Science.

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Received: September 15, 2009
Published Online: November 27, 2009

