Synthesis and Anti-Cancer Activity of C-Ring-Functionalized Prodigiosin Analogues

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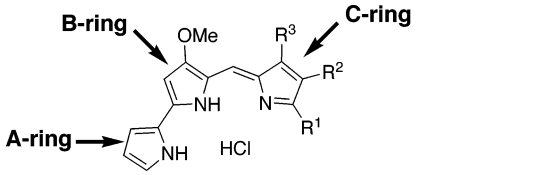
Prodigiosin is the parent member of the 4-methoxypyrrolyldipyrromethene family of natural products and is known for its anti-cancer activity. A new series of analogues was synthesized, incorporating pendent functional esters and β-carbonyl substituents on the C-ring. The β-carbonyl group allowed for the facile isolation of the prodigiosenes, and the pendent esters allow for further derivatization. The novel prodigiosenes generally retain the anti-cancer activity of prodigiosin in 60 human cell lines derived from nine cancer cell types, with neither the conjugated β-carbonyl group, as either ketone or ester, nor the pendent ester significantly reducing the anti-cancer activity of the core skeleton.

Introduction

Prodigiosin (**1**) is the parent member of the 4-methoxypyrrolyldipyrromethene family of natural products isolated from certain *Serratia*, *Streptomyces*, and *Bacillus* bacterial strains, and it possesses potent immunosuppressive, antimicrobial, antimalarial, and cytotoxic properties that have sparked intensive study.[1−3] Regarding its anti-cancer activity, prodigiosin has been reported to be an efficient H^+/Cl^- symporter[3,4] that induces apoptosis in a variety of cell lines.[5−8] However, a recent report describes prodigiosin as able to transport chloride across lipid vesicles via an antiport mechanism.[9] Furthermore, in an attempt to understand the mechanism by which apoptosis is induced, the DNA interaction and dual topoisomerase inhibition properties of prodigiosin have been studied.[10] An alternative mode of action thought to be partly responsible for the cytotoxicity of prodigiosin lies in its ability to induce copper-mediated double-strand DNA cleavage.[11−17] For derivatives with the general pyrrolyldipyrromethene general skeleton, Hearn et al. suggested the term "prodigosenes",[18] thus avoiding confusion between derivatives, both synthetic and natural, and the parent compound. Since we recently began our work in this area, a number of articles have appeared that describe the synthesis and evaluation of prodigiosenes as potential anti-cancer agents,[19−21] including research at three commercial ventures. For example, SAR studies of prodigiosenes modified at the A-ring were reported (see Figure 1 for ring nomenclature) as structures for antineoplastic scaffolds for potential use as pharmaceuticals for cervical carcinoma.[22] As part of this project, a prodigiosene with an 2-indolic A-ring was characterized as an inhibitor of Bcl-2 family anti-apoptotic proteins, thereby offering the opportunity to therapeutically restore the natural apoptotic cascade in malignant cells.[22] This work was facilitated by the development of new synthetic methodology by which to prepare A-ring modified prodigiosenes.[23] Furthermore, a novel series of 3-indolic A-ring prodigiosenes has recently been reported, and some of these compounds maintain the anti-proliferative behavior of prodigiosin.[24] Studies regarding the preparation of bipyrroles via pyrrole-singlet oxygen reactions have facilitated the synthesis of A-ring prodigiosenes,[25,26] as have advances in Pd-catalyzed coupling reactions that allow a variety of A-ring precursors to be appended. Amidopyrroles, designed as biologically active mimics of prodigiosin, are efficient anion receptors and membrane transport agents for HCl, and also show anti-cancer activity.[27−29]



1, R^1 = Me, R^2 = $(CH_2)_4CH_3$, R^3 = H, prodigiosin
2HCl, R^1 = R^3 = Me, R^2 = $CH_2CH_2CO_2Et$
3HCl, R^1 = R^3 = Me, R^2 = CH_2CO_2Et
4HCl, R^1 = R^3 = Me, R^2 = CO_2Et
5HCl, R^1 = R^3 = Me, R^2 = C(O)Me

Figure 1. Prodigiosin (**1**) and prodigiosenes (**2**−**5**).

With a few exceptions,[30−32] the synthesis of prodigiosenes bearing groups that may be further functionalized has not been reported, and C-ring derivatives of prodigiosenes have not been investigated. Certainly, there have been no reports of a comprehensive series of functionalized prodigiosenes being prepared and evaluated. With the goal of synthesizing prodigiosenes with enhanced cytotoxity and improved toxicological profiles, derivatives with pendent functional groups became desirable with the ultimate goal of using the functional groups to append targeting moieties.[33]

Results and Discussion

Synthesis. With the goal of synthesizing prodigiosenes that bear functional groups for further derivatization, **2** and **3** became target compounds. These prodigiosenes both feature pendent esters and would serve as models for investigating the robustness of existing synthetic routes when applied to the preparation of functionalized derivatives. By modification of D'Alessio's methodology,[31,34] 2-formyl-4-[methoxycarbonyl)ethyl]-3,5-dimethylpyrrole (**6**)[35] was reacted with 4-methoxy-3-pyrrolin-2-one[36−38] under basic conditions (Scheme 1). The condensation was accompanied by saponification of the ester giving the carboxylic acid **11** in excellent yield, and re-esterification using acidic methanol gave the corresponding dipyrrinone **12**. The chain-reduced analogue **14** was similarly prepared by condensation of 2-formyl-4-[(methoxycarbonyl)methyl]-3,5-dimethylpyrrole (**7**)[39] with 4-methoxy-3-pyrrolin-2-one, followed by conversion of the resulting acid to the methyl ester. Treatment of dipyrrinones **12** and **14** with Tf_2O gave the triflates **17** and **18**, respectively, as liquids that were used promptly in the next step as they proved prone to decomposition. Cross coupling of **17**

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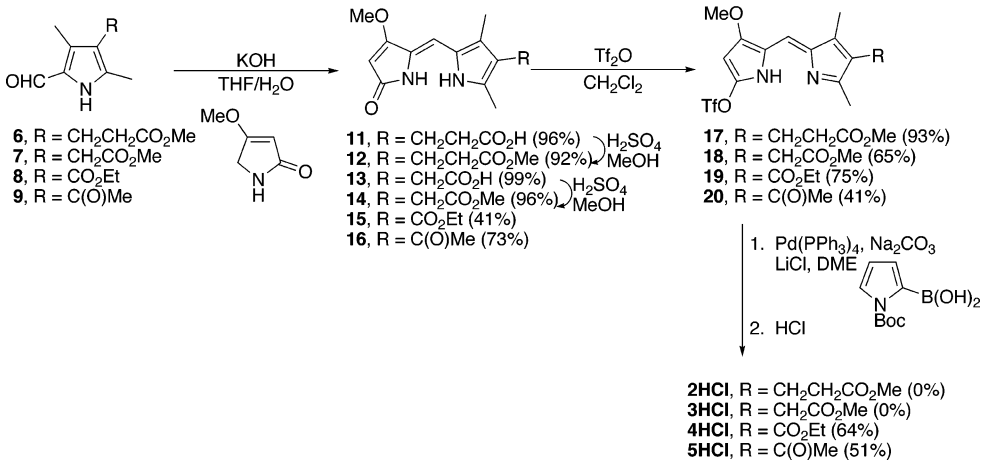
Scheme 1. Synthesis of 3-Substituted Prodigiosenes



and **18** with 1-*N*-Boc-pyrrole-2-boronic acid was repeatedly attempted under a variety of conditions, but the corresponding prodigiosenes could not be isolated. Although TLC and crude ^{1}H NMR spectroscopic analyses both repeatedly indicated the presence of the required product, purification of the free base by chromatography was unsuccessful, as was precipitation/crystallization of the HCl salts.

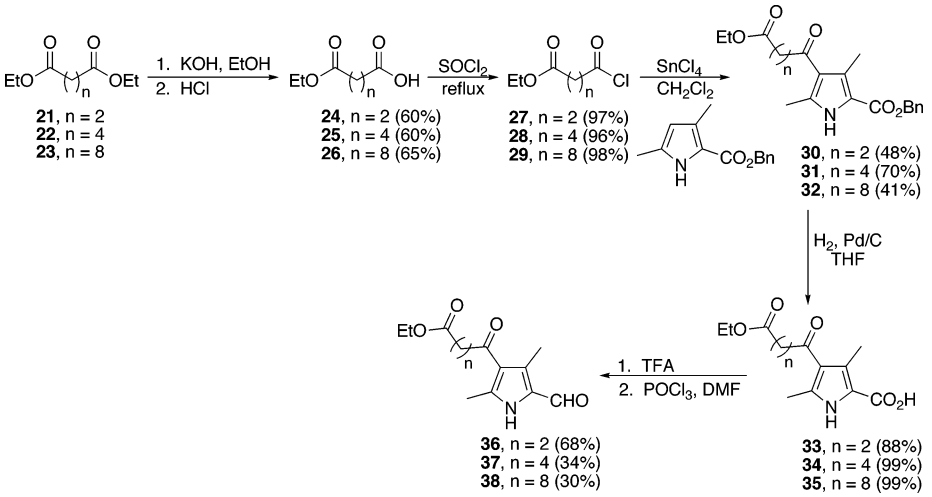
Given that the presence of conjugated carbonyl functionality directly adjacent to a pyrrole ring results in more stable and more crystalline heterocycles,[40] the synthesis of prodigiosene **4** was attempted. Thus, ethyl 5-formyl-2,4-dimethylpyrrole-3-carboxylate (**8**)[41] was condensed with 4-methoxy-3-pyrrolin-2-one to give **15**, with no need for re-esterification (Scheme 1). Triflation of **15** gave the stable solid triflate **19**, and coupling with 1-*N*-Boc-pyrrole-2-boronic acid gave the free-base **4**, which was purified by chromatography over neutral aluminum oxide. Concentration of the combined fractions followed by the addition of HCl in ether resulted in the precipitation of the prodigiosene salt **4HCl**. The effect of the carbonyl group in stabilizing the prodigiosene skeleton was further verified by the preparation of the methyl ketone analogue **5HCl**. The isolation of the prodigiosene salt was optimized by totally removing the solvent from the combined chromatographic fractions, dissolving the residue in minimal acetone, and then adding HCl in ether to the solution to effect precipitation. Applying the improved isolation procedure to reaction mixtures containing **2** and **3** did not result in precipitation. Evidently, the placement of the carbonyl group directly adjacent to the heterocyclic skeleton provides increased stability and allows for easier isolation of the corresponding functionalized prodigiosene.

With the success in isolating **4HCl** and **5HCl**, the β-keto group was retained in the design of a series of prodigiosenes bearing pendent esters that would be facile to derivatize. Thus, formyl pyrroles **36**−**38** were synthesized according to Scheme 2. Diesters **21**−**23** were mono-saponified, and the resultant mono-acids were chlorinated[42] to give the chlorocarbonyl esters **27**−**29**. Subsequent Friedel−Crafts acylation of benzyl 3,5-dimethyl-pyrrole-2-carboxylate[43] gave the pyrroles **30**−**32**, which were hydrogenolyzed, and the resultant carboxylic acids (**33**−**35**) were decarboxylated by treatment with TFA.[44] Finally, in-situ Vilsmeier−Haack formylation[40] gave the formyl pyrroles **36**−**38**.

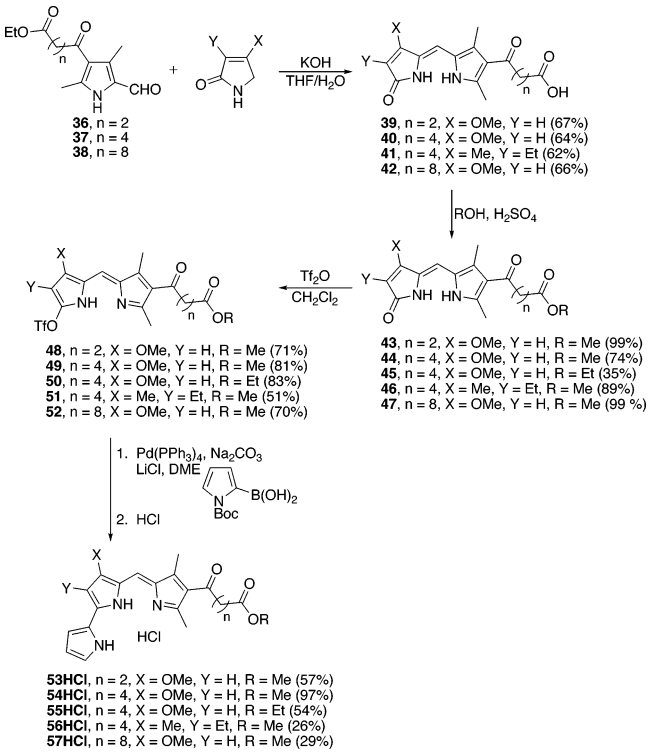
Following the strategy used for the synthesis of **4HCl** and **5HCl**, **36**−**38** were condensed with 4-methoxy-3-pyrrolin-2-one (Scheme 3). The adipate **37** was also condensed with 4-methyl-3-ethyl-3-pyrrolin-2-one.[45] Re-esterification of **39**−**42** with either methanol or ethanol gave the dipyrrinones **43**−**47**. Triflation and Pd-catalyzed coupling of the resultant triflates with 1-*N*-Boc-pyrrole-2-boronic acid gave the target prodigiosenes **53**−**57** as their HCl salts. The adipate analogue **54** was also isolated in its stable free-base form.

Complexation. Having isolated seven novel prodigiosenes bearing functionalization patterns that had not previously been appended to the prodigiosene skeleton, attention turned to verifying that the coordination abilities and biological activities were not seriously compromised by the presence of the β-keto

Scheme 2. Synthesis of 3-Carbonyl-2-formylpyrroles



Scheme 3. Synthesis of 3-Carbonyl Prodigiosenes



36, n = 2
37, n = 4
38, n = 8

39, n = 2, X = OMe, Y = H (67%)
40, n = 4, X = OMe, Y = H (64%)
41, n = 4, X = Me, Y = Et (62%)
42, n = 8, X = OMe, Y = H (66%)

43, n = 2, X = OMe, Y = H, R = Me (99%)
44, n = 4, X = OMe, Y = H, R = Me (74%)
45, n = 4, X = OMe, Y = H, R = Et (35%)
46, n = 4, X = Me, Y = Et, R = Me (89%)
47, n = 8, X = OMe, Y = H, R = Me (99 %)

48, n = 2, X = OMe, Y = H, R = Me (71%)
49, n = 4, X = OMe, Y = H, R = Me (81%)
50, n = 4, X = OMe, Y = H, R = Et (83%)
51, n = 4, X = Me, Y = Et, R = Me (51%)
52, n = 8, X = OMe, Y = H, R = Me (70%)

53HCl, n = 2, X = OMe, Y = H, R = Me (57%)
54HCl, n = 4, X = OMe, Y = H, R = Me (97%)
55HCl, n = 4, X = OMe, Y = H, R = Et (54%)
56HCl, n = 4, X = Me, Y = Et, R = Me (26%)
57HCl, n = 8, X = OMe, Y = H, R = Me (29%)

and pendent ester moieties. The Zn(II) complex of **54** was prepared in excellent yield using standard conditions[46] for the complexation of dipyrromethenes. Titration of $Zn(OAc)_2$ (Figure 2a) revealed a 1:2 stoichiometry for Zn:**54**, and the mononuclearity of dimeric Zn(**54**)$_2$ was confirmed by mass spectrometry. Thus, the Zn(II) complexation of functionalized **54** was similar to that of prodigiosin itself.[17]

Manderville at al. have reported that prodigiosin reacts with Cu(II) in the presence of oxygen to give an oxidized 1:1 square-planar Cu(II):prodigiosene complex[17] that has been characterized by X-ray crystallography and inferred in copper-mediated double-strand DNA cleavage induced by prodigiosin.[15] Although absorption spectroscopy (Figure S1) and ESI mass spectrometry (Figure S2) both clearly showed that the prodigiosene interacts with the metal ion, the reaction of **54** with $Cu(OAc)_2$ did not result in the isolation of a complex. Titration of $Cu(OAc)_2$ into a solution of **54** (λ_{max} 454 nm) initially resulted in the formation of a dimeric Cu(**54**)$_2$ complex, according to mass spectrometry. Addition of >0.6 equiv of Cu(II) resulted in the decomposition of the dimer, and the formation of a new monomeric complex. Despite the fact that a copper complex of **54** was never isolated, the absorption spectroscopy and mass spectrometry results support the presence of a prodigiosene−copper interaction, and thus copper-mediated double-strand DNA cleavage by **54**, and the other novel functionalized prodigiosenes, is being investigated.

Biological Activity. The anti-cancer abilities of prodigiosin and simple prodigiosenes are well documented, as are their toxicological effects.[1−3] With the long-term goal being to introduce targeting moieties onto the prodigiosene skeleton through derivatization of the pendent esters, establishing that biological activity was not lost with the introduction of such functionality was an essential component of the project. Furthermore, with the discovery that β-keto prodigiosenes are much more stable than their alkyl analogues, determining the biological consequences of the conjugated keto group was also important. The prodigiosenes **4HCl**, **5HCl**, **53HCl**, **54HCl**, **56HCl**, and **57HCl** were selected by the U.S. National Cancer Institute (NCI) for evaluation against 60 human cell lines derived from nine cancer cell types: mean GI_{50}, TGI, and LC_{50} values (average of two identical screens) are presented in Table 1, along with those of prodigiosin. Importantly, **4HCl** completely retains the anti-cancer activity of prodigiosin (compare entries 1 and 2), and **53HCl** and **54HCl** (compare entries 4 and 5 with entry 1) both exhibit sufficient activity to indicate potential broad-spectrum growth inhibition of a variety of tumors. The methyl ketone **5HCl** exhibited no relevant anti-cancer activity, and the long-chain analogue **57HCl** was equally inactive. The methoxy group on the B-ring is essential for anti-cancer activity (entry 6), as noted by others.[31,47] Collectively, these results indicate that neither the conjugated β-carbonyl group, as either ketone or ester, nor the pendent ester significantly reduce the anti-cancer activity of the prodigiosenes because derivatives bearing these two structural motifs exhibit anti-cancer activity similar to that of prodigiosin.

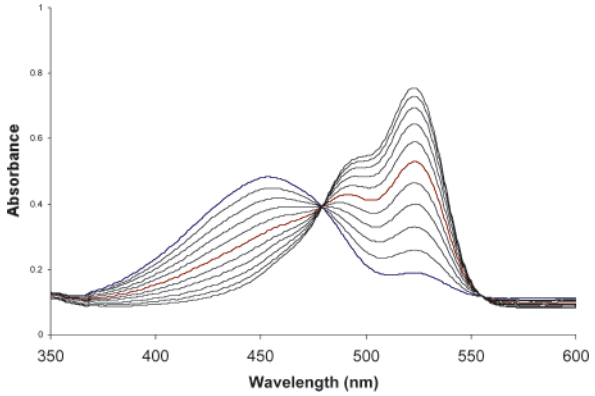


Figure 2. UV−vis titration of **54** with 0.05 equiv aliquots of $Zn(OAc)_2$.

Table 1. Mean in-Vitro Activity[a] of Prodigiosenes over 60 Cancer Cell Lines

entry	compound	Log_{10} mean GI_{50}	Log_{10} mean TGI	Log_{10} mean LC_{50}
1	**prodigiosin**	−7.85	−5.68	−6.65
2	**4HCl**	−7.33	−5.96	−4.91
3	**5HCl**	−6.15	−4.39	−4.05
4	**53HCl**	−6.10	−5.49	−4.91
5	**54HCl**	−6.19	−5.65	−5.19
6	**56HCl**	−5.03	−4.47	−4.08
7	**57HCl**	−4.79	−4.17	−4.02

[a] http://dtp.nci.nih.gov/branches/btb/ivclsp.html; average of two repeat screens.

Conclusions

Seven novel functionalized prodigiosenes have been synthesized, and their anti-cancer activity has been evaluated. The discovery that a β-carbonyl functionality stabilizes the prodigiosene skeleton led to the facile isolation of derivatives bearing pendent esters. The general complexation behavior and biological activity of prodigiosin was retained by prodigiosenes bearing a β-carbonyl group and a pendent ester. The factors determining why the methyl ketone (**5HCl**) exhibited no relevant anti-cancer activity while other ketones were active, and why the β-ester (**4HCl**) was the most active, are currently under investigation. Targeted derivatives of the most active compounds are being synthesized and evaluated, as are those incorporating different functional groups.

Experimental Section

(5*Z*)-Ethyl-5-((3-methoxy-5-(1*H*-pyrrol-2-yl)-1*H*-pyrrol-2-yl)-methylene)-2,4-dimethyl-5*H*-pyrrole-3-carboxylate Hydrochlo-

ric Salt (4HCl). LiCl (0.12 g, 2.73 mmol), **19** (0.38 g, 0.91 mmol), 1-*N*-Boc-pyrrole-2-boronic acid (0.38 g, 1.82 mmol), and $Pd(PPh_3)_4$ (52.0 mg, 0.045 mmol) were dissolved in dimethoxyethane (15 mL), and the solution was purged by bubbling with argon for 10 min. A solution of Na_2CO_3 (2 M, 1.82 mL, 3.64 mmol) was added, and the reaction mixture was stirred at 85 °C for 19 h and then poured into water. Extraction with ethyl acetate (3 × 15 mL), followed by washing of the combined organics with brine (15 mL), drying with anhydrous Na_2SO_4, filtering, and removal of the solvent under reduced pressure gave the crude product. Purification by flash chromatography on neutral aluminum oxide (grade I) using a gradient of ethyl acetate:hexane (0:100−40:60) as eluent furnished, after the addition of HCl in ether (1 M, 1 mL) to the concentrated fractions, the title compound as a fuchsia solid (0.22 g, 64%); mp = 224 °C; R_f (free base) 0.52 (50:50 ethyl acetate:hexane); λ_{max}-$CHCl_3$ 528 (ϵ 108 057), 499 (ϵ 52 048); δ_H (500 MHz, $CDCl_3$) 13.00 (1H, bs), 12.76 (1H, bs), 12.69 (1H, bs), 7.30 (1H, s), 7.13 (1H, s), 7.02−7.00 (1H, m), 6.42−6.38 (1H, m), 6.11 (1H, d, *J* 1.6), 4.32 (2H, d, *J* 7.1), 4.06 (3H, s), 2.82 (3H, s), 2.52 (3H, s), 1.38 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 166.7, 164.6, 150.4, 150.0, 140.5, 128.5, 123.5, 122.5, 122.1, 119.0, 115.9, 112.9, 112.4, 93.3, 59.9, 59.0, 14.8, 14.4, 11.8; *m*/*z* EI$^+$ 339.1 [(M − HCl)$^+$, 100%)] [found 339.1588 $C_{19}H_{21}N_3O_3$ expected 339.1583]. Anal. Calcd for $C_{19}H_{22}ClN_3O_3$: C, 60.72; H, 5.90; N, 11.18. Found: C, 60.87; H, 5.88; N, 10.78.

1-[5-((3-Methoxy-5-(1*H*-pyrrol-2-yl)-1*H*-pyrrol-2-yl)methylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]ethanone Hydrochloride (5HCl). Following the procedure as for the synthesis of **4HCl**, the title compound was obtained as a dark solid after purification by flash chromatography on neutral aluminum oxide (grade I) using a gradient of ethyl acetate:hexane (0:100−50:50) as eluent. After removal of the solvent under reduced pressure, the crude free base was dissolved in acetone (1 mL) and then treated with HCl in ether (1 M, 2 mL). The resulting precipitate was filtered and dried under vacuum to give the title compound as a dark pink solid (51%); mp = (dec) 260 °C; R_f (free base) 0.53 (50:50 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 529 (ϵ 107 321), 501 (ϵ 53 037); δ_H (500 MHz, $CDCl_3$) 12.99 (1H, bs), 12.70 (2H, bs), 7.31 (1H, s), 7.13 (1H, s), 7.03−7.01 (1H, m), 6.42−6.40 (1H, m), 6.12−6.10 (1H, m), 4.06 (3H, s), 2.85 (3H, s), 2.51 (3H, s), 2.48 (3H, s); δ_C (125 MHz, $CDCl_3$) 194.6, 166.8, 150.5, 148.9, 138.8, 128.8, 125.1, 123.4, 123.0, 122.0, 119.4, 112.7, 112.6, 93.5, 59.1, 31.4, 15.6, 12.5; δ_N (50 MHz, $CDCl_3$) −241.27, −218.71, −213.53; *m*/*z* EI$^+$ 309.0 [(M − HCl)$^+$, 100%] [found 309.1477 $C_{18}H_{19}N_3O_2$ expected 309.1477].

5-[(4-Propanoic acid-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene]-4-methoxy-1*H*-2(5*H*)-one (11). Purged KOH (aq) (4 M, 5.4 mL, 21.5 mmol) was added dropwise to a purged solution of 4-methoxy-3-pyrrolin-2-one (2.1 g, 18.57 mmol) in THF (100 mL). The reaction mixture was stirred under argon at 60 °C for 1 h, and **6**[35] (2.5 g, 11.94 mmol) was added. After 48 h, the solvent was removed under reduced pressure, and the resulting yellow solid was crystallized from hot methanol, filtered, and dried in a vacuum oven, affording the title compound as a green-yellow solid (3.37 g, 96%); mp = 250 °C (dec); R_f 0.55 (10:90 methanol:dichloromethane); δ_H (500 MHz, DMSO-d_6) 10.95 (1H, bs), 10.24 (1H, bs), 5.98 (1H, s), 5.10 (1H, s), 3.82 (3H, s), 2.44−2.41 (2H, m), 2.09 (3H, s), 1.93 (3H, s), 1.89−1.91 (2H, m); δ_C (125 MHz, DMSO-d_6) 176.0, 171.0, 167.3, 130.3, 123.2, 122.1, 121.8, 121.2, 96.9, 90.7, 58.5, 40.6, 22.1, 11.5, 9.7; *m*/*z* ESI$^-$ 289.0 [(M − H)$^+$, 100%)].

5-[(4-[(Methoxycarbonyl)ethyl]-3,5-dimethyl-1*H*-pyrrol-2-yl)-methylene]-4-methoxy-1*H*-2(5*H*)-one (12). A solution of **11** (2.1 g, 7.23 mmol) in MeOH (700 mL) and H_2SO_4 (conc., 5 mL) was heated to reflux for 3 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The solid was washed with water, filtered, and dried to give the title compound as a white solid (2.03 g, 92%); mp = 200 °C; R_f 0.50 (ethyl acetate); δ_H (500 MHz, DMSO-d_6) 10.27 (1H, bs), 10.50 (1H, bs), 6.00 (1H, s), 5.18 (1H, s), 3.83 (3H, s), 3.57 (3H, s), 2.58 (2H, t, *J* 7.6), 2.37 (2H, t, *J* 7.6), 2.17 (3H, s), 1.98 (3H, s); δ_C (125 MHz, $CDCl_3$) 173.7, 173.1, 167.9, 132.4, 125.6, 121.8, 121.7, 119.2, 100.6, 89.6, 58.1, 51.6, 35.1, 19.9, 11.4, 9.5; *m*/*z* EI$^+$ 304.1 (M$^+$, 100%) [found 304.1420 $C_{16}H_{20}N_2O_4$ expected 304.1423].

5-[(4-Ethanoic acid-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene]-4-methoxy-1*H*-2(5*H*)-one (13). Following the procedure as for **11**, using **7**,[39] the title compound was obtained as a yellow solid (99%); mp = 260 °C (dec); R_f 0.71 (10:90 methanol:dichloromethane); δ_H (250 MHz, DMSO-d_6) 10.64 (1H, bs), 9.95 (1H, bs), 6.00 (1H, s), 5.10 (1H, s), 3.82 (3H, s), 2.87 (2H, s), 2.01 (3H, s), 1.94 (3H, s); δ_C (125 MHz, DMSO-d_6) 174.3, 170.9, 167.3, 131.2, 124.6, 121.6, 120.9, 119.9, 97.3, 90.5, 58.5, 35.6, 11.8, 10.1; *m*/*z* EI$^+$ 276.1 (M$^+$, 1%) [found 276.1244 $C_{14}H_{16}N_2O_4$ expected 276.1110].

5-[(4-[Methoxycarbonyl)methyl]-3,5-dimethyl-1*H*-pyrrol-2-yl-)methylene]-4 -methoxy-1*H*-2(5*H*)-one (14). Following the procedure as for **12**, the title compound was obtained as a yellow solid (96%); mp = 200 °C; R_f 0.74 (10:90 methanol:dichloromethane); δ_H (500 MHz, $CDCl_3$) 10.88 (1H, bs), 10.31 (1H, bs), 6.40 (1H, s), 5.13 (1H, s), 3.93 (3H, s), 3.70 (3H, s), 3.44 (2H, s), 2.42 (3H, s), 2.17 (3H, s); δ_C (125 MHz, $CDCl_3$) 173.1, 172.4, 168.0, 133.2, 126.0, 122.1, 121.9, 113.5, 100.6, 89.8, 58.1, 51.9, 30.3, 11.5, 9.6; *m*/*z* EI$^+$ 289.9 (M$^+$, 100%) [found 290.1265 $C_{15}H_{18}N_2O_4$ expected 290.126].

Ethyl 5-[(12*Z*)-(3-Methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (15). Following the procedure as for **11**, using **8**,[41] the title compound was obtained as a bright yellow solid (41%); mp = 157 °C; R_f 0.82 (10:90 methanol:dichloromethane); δ_H (500 MHz, DMSO-d_6) 10.40−9.50 (2H, bs), 6.03 (1H, s), 5.27 (1H, s), 4.18 (2H, q, *J* 7.1), 3.87 (3H, s), 2.47 (3H, s), 2.23 (3H, s), 1.28 (3H, t, *J* 7.1); δ_C (125 MHz, DMSO-d_6) 171.3, 163.4, 165.2, 139.6, 125.7, 124.4, 122.6, 112.0, 95.0, 91.8, 59.2, 58.9, 14.8, 14.1, 11.4; *m*/*z* EI$^+$ 290.0 (M$^+$, 44%) [found 290.1264 $C_{15}H_{18}N_2O_4$ expected 290.1266].

5-[(4-Acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene]-4-methoxy-1*H*-2(5*H*)-one (16). Following the procedure as for the synthesis of **11**, using **9**,[41] the title compound was obtained as a yellow solid (73%); mp > 300 °C; R_f 0.41 (50:50 ethyl acetate: hexanes); δ_H (500 MHz, DMSO-d_6) 10.50−9.50 (2H, bs), 6.03 (1H, s), 5.26 (1H, s), 3.86 (3H, s), 2.49 (3H, s), 2.35 (3H, s), 2.23 (3H, s); δ_C (125 MHz, DMSO-d_6) 194.4, 171.3, 167.3, 139.2, 126.0, 123.9, 122.7, 122.3, 95.0, 91.9, 58.9, 31.5, 15.2, 12.1; *m*/*z* EI$^+$ 260.0 (M$^+$, 100%) [found 260.1162 $C_{14}H_{16}N_2O_3$ expected 260.1161].

5-((1*Z*)-(4-[(Methoxycarbonyl)ethyl)]-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-4-methoxy-1*H*-pyrrol-2-yl Trifluoromethanesulfonate (17). Tf_2O (0.17 mL, 1.86 mmol) was slowly added to a solution of **12** (0.20 g, 0.66 mmol) in dichloromethane (30 mL) cooled to 0 °C. The reaction mixture was stirred for 1 h and then poured into a 2% solution of sodium bicarbonate (30 mL). The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organics were washed with brine (50 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica using dichloromethane as eluent, followed by removal of the solvents under reduced pressure, gave the title compound as a yellow solid (0.22 g, 93%), which was prone to decomposition and so was used immediately in the attempted syntheses of **2HCl**; mp = 55 °C; R_f 0.95 (ethyl acetate); δ_H (500 MHz, $CDCl_3$) 10.76 (1H, bs), 7.04 (1H, s), 5.41 (1H, s), 3.86 (3H, s), 3.66 (3H, s), 2.72 (2H, t, *J* 7.5), 2.43 (2H, t, J 7.5), 2.30 (3H, s), 2.15 (3H, s); δ_C (125 MHz, $CDCl_3$) 173.2, 167.1, 159.7, 138.7, 132.7, 130.4, 126.1, 121.9, 119.2, 118.7 (q, *J* 319, *C*F_3), 86.4, 58.6, 51.6, 34.5, 19.5, 12.1, 9.4.

5-((1*Z*)-(4-[(Methoxycarbonyl)methyl)]-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-4-methoxy-1*H*-pyrrol-2-yl Trifluoromethanesulfonate (18). Following the procedure as for **17**, with purification using flash chromatography on silica and a gradient of ethyl acetate:hexane (0:100−20:80) as eluent, gave the title compound as a yellow oil (65%), which was prone to decomposition and so was used immediately in the attempted syntheses of **3HCl**; R_f 0.81 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 10.75 (1H, bs), 7.06 (1H, s), 5.40 (1H, s), 3.87 (3H, s), 3.67 (3H, s), 3.38 (2H, s), 2.31 (3H, s), 2.17 (3H, s); δ_C (125 MHz, $CDCl_3$) 171.8, 167.4, 160.2, 138.9, 133.0, 131.2, 126.0, 119.4, 118.7 (q, *J* 319, *C*F_3), 116.0, 86.7, 58.6, 52.0, 30.0, 12.3, 9.6.

5-((1*Z*)-(4-(Ethoxycarbonyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-4-methoxy-1*H*-pyrrol-2-yl Trifluoromethanesulfonate (19). Following the procedure as for **11**, with purification using flash chromatography on silica and a gradient of ethyl acetate:hexane (0:100−15:85) as eluent, followed by removal of the solvents under reduced pressure, gave the title compound as a yellow solid (0.39 g, 75%); mp = 106 °C; R_f 0.66 (30:70 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 10.98 (1H, bs), 7.12 (1H, s), 5.43 (1H, s), 4.30 (2H, q, *J* 7.1), 3.90 (3H, s), 2.57 (3H, s), 2.42 (3H, s), 1.37 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 168.1, 165.1, 161.7, 144.6, 135.3, 133.2, 126.0, 119.0, 118.7 (q, *J* 321.0, *C*F_3), 114.2, 87.5, 59.6, 58.8, 14.9, 14.4, 11.4; δ_F (235 MHz, $CDCl_3$) −73.78; *m*/*z* EI$^+$ 422.0 (M^+, 7%) [found 422.0756 $C_{16}H_{17}F_3N_2O_6S$ expected 422.0759].

5-[(4-Acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene]-4-methoxy-1*H*-2-yl Trifluoromethanesulfonate (20). Following the procedure as for the synthesis of **19**, the title compound was obtained as a yellow film (41%) after purification by flash chromatography on silica using a gradient of ethyl acetate:hexane (0:100−50:50) as eluent; mp = 160 °C (dec); R_f 0.59 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.05 (1H, bs), 7.12 (1H, s), 5.43 (1H, s), 3.90 (3H, s), 2.58 (3H, s), 2.45 (3H, s), 2.43 (3H, s); δ_C (125 MHz, $CDCl_3$) 194.7, 168.2, 162.1, 143.8, 133.8, 133.4, 126.0, 123.8, 118.8, 118.7 (q, *J* 321.1, *C*F_3), 87.6, 58.9, 31.2, 15.9, 12.3; δ_F (235 MHz, $CDCl_3$) δ −73.64; *m*/*z* EI$^+$ 392.0 (M^+, 55%) [found 392.0644 $C_{15}H_{15}F_3N_2O_5S$ expected 392.0653].

Butanedioic Acid Monoethyl Ester (24). Following methods for the preparation of the malonate analogue,[48,49] KOH (32.5 g, 0.58 mol) in ethanol (300 mL) was slowly added to a solution of diethyl succinate (100 mL, 0.58 mol) in ethanol (300 mL) at 0 °C. The reaction mixture was stirred for 16 h and then heated to a boil (to dissolve the mono-potassium salt) and then hot-filtered (to recover the corresponding insoluble dipotassium salt). The solvent was removed under reduced pressure, and the resulting white solid was dissolved in water (90 mL), extracted with diethyl ether (2 × 100 mL, to recover the unreacted starting material), and treated with hydrochloric acid (12 M, 50 mL) at 0 °C. After being stirred for 1.5 h, the reaction mixture was extracted with dichloromethane (3 × 100 mL), and the combined organics were dried with anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave the title compound as a colorless oil (51.1 g, 60%); R_f 0.47 (30:70 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.27 (1H, bs), 4.16 (2H, dq, *J* 1.6, 7.1), 2.68 (2H, dt, *J* 1.6, 6.0), 2.68 (2H, dt, *J* 1.6 6.0), 1.26 (3H, dt, *J* 1.6 7.1); δ_C (125 MHz, $CDCl_3$) 178.3, 172.2, 60.8, 28.9, 28.8, 14.0; *m*/*z* ESI$^-$ 144.9 [($M - H)^+$, 100%)].

Hexanedioic Acid Monoethyl Ester (25). Following the procedure as for the synthesis of **24**, the title compound was obtained as a colorless oil (60%); R_f 0.49 (30:70 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1), 2.38 (2H, t, *J* 7.0), 2.33 (2H, t, *J* 7.0), 1.70−1.65 (4H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 179.4, 173.4, 60.4, 33.9, 33.6, 24.3, 24.1, 14.2; *m*/*z* EI$^+$ 174.1 (M^+, 0.4%) [found 174.0890 $C_8H_{14}O_4$ expected 174.0892].

Octanedioic Acid Monoethyl Ester (26). Following the procedure as for the synthesis of **24**, the title compound was obtained as a white solid (65%); mp = 33 °C; R_f 0.76 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.1), 2.35 (2H, t, *J* 7.5), 2.29 (2H, t, *J* 7.5), 1.63 (2H, t, *J* 7.5), 1.61 (2H, t, *J* 7.5), 1.35−1.29 (8H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 180.0, 174.0, 60.2, 34.3, 34.0, 29.1 (3C), 29.0, 24.9, 24.6, 14.3; *m*/*z* ESI$^-$ 229.1 [($M - H)^+$, 100%)].

3-Chlorocarbonyl-propanoic Acid Ethyl Ester (27). Following the method used by Schirlin et al.[42] for the preparation of the malonate analogue, **24** (6.5 g, 44.47 mmol) was reacted with $SOCl_2$ (4.05 mL, 55.59 mmol) at reflux for 1.5 h. Excess $SOCl_2$ was removed under reduced pressure to give the title product as a yellow oil (7.10 g, 97%); δ_H (500 MHz, $CDCl_3$) 4.17 (2H, q, *J* 7.1), 3.22 (2H, t, *J* 6.6), 2.68 (2H, t, *J* 6.6), 1.27 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 173.0, 170.8, 61.1, 41.8, 29.4, 14.0.

3-Chlorocarbonyl-pentanoic Acid Ethyl Ester (28). Following the procedure as for the synthesis of **27**, the title compound was obtained as a light yellow oil (96%); δ_H (500 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.1), 2.92 (2H, t, *J* 7.0), 2.33 (2H, t, *J* 7.0), 1.77−1.67 (4H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 173.5, 172.9, 60.5, 46.7, 33.7, 24.5, 23.7, 14.2.

9-Chlorocarbonyl-nonanoic Acid Ethyl Ester (29). Following the procedure as for the synthesis of **27**, the title compound was obtained as a yellow oil (98%); δ_H (500 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1), 2.88 (2H, t, *J* 7.2), 2.29 (2H, t, *J* 7.3), 1.71 (2H, quintet, *J* 7.2), 1.62 (2H, t, *J* 7.3), 1.36−1.31 (8H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 173.9 (2C), 60.2, 47.1, 34.3, 29.0 (2C), 28.9, 28.4, 25.0, 24.9, 14.3.

4-(3-Ethoxycarbonyl-propanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (30). Benzyl 3,5-dimethyl-pyrrole-2-carboxylate[43] (9.98 g, 43.62 mmol) was dissolved in degassed CH_2Cl_2 (75 mL) and stirred for 15 min at 0 °C under N_2. $SnCl_4$ (6.1 mL, 52.12 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for a further 10 min, after which **27** (7.10 g, 43.62 mol) in anhydrous dichloromethane (20 mL) was slowly added. After 2 h, the reaction mixture was poured into 2% aq HCl and then stirred for 5 min. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting dark solid was crystallized from hot methanol, chilled, filtered, and dried in a vacuum oven to give the title compound as a white solid (7.41 g, 48%); mp = 116 °C; R_f 0.29 (30:70 ethyl acetate:dichloromethane); δ_H (500 MHz, $CDCl_3$) 9.10 (1H, bs), 7.42−7.34 (5H, m), 5.32 (2H, s), 4.15 (2H, q, *J* 7.1), 3.04 (2H, t, *J* 6.5), 2.69 (2H, t, *J* 6.5), 2.62 (3H, s), 2.50 (3H, s), 1.27 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 195.4, 173.3, 161.2, 138.4, 136.0, 129.9, 128.7, 128.4, 128.3, 123.1, 117.7, 66.1, 60.6, 37.5, 28.3, 15.3, 14.2, 12.9; *m*/*z* EI$^+$ 357.1 (M^+, 16%) [found 357.1574 $C_{20}H_{23}NO_5$ expected 357.1576].

4-(5-Ethoxycarbonyl-pentanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (31). Following the procedure as for the synthesis of **30**, the title compound was obtained as a white solid (70%); mp = 113 °C; R_f 0.67 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 8.99 (1H, bs), 7.42−7.33 (5H, m), 5.32 (2H, s), 4.12 (2H, q, *J* 7.1), 2.74 (2H, t, *J* 6.9), 2.60 (3H, s), 2.49 (3H, s), 2.34 (2H, t, *J* 7.2), 1.74−1.67 (4H, m), 1.25 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 197.6, 173.6, 161.2, 138.0, 136.0, 129.6, 128.7, 128.4, 128.3, 123.6, 117.6, 66.1, 60.3, 42.5, 34.3, 24.7, 23.6, 15.3, 14.3, 12.8; *m*/*z* EI$^+$ 385.2 (M^+, 100%) [found 385.1891 $C_{22}H_{27}NO_5$ expected 385.1889].

4-(5-Ethoxycarbonyl-nonoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (32). Following the procedure as for the synthesis of **30**, the title compound was obtained as a white solid (41%); mp = 83 °C; R_f 0.43 (30:70 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 8.95 (1H, bs), 7.42−7.34 (5H, m), 5.31 (2H, s), 4.12 (2H, q, *J* 7.1), 2.71 (2H, t, *J* 7.3), 2.60 (3H, s), 2.49 (3H, s), 2.28 (2H, t, *J* 7.5), 1.68−1.61 (4H, m), 1.35−1.29 (8H, m), 1.25 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 198.4, 173.9, 161.1, 137.9, 136.0, 129.6, 128.7, 128.4, 128.3, 123.7, 117.5, 66.1, 60.2, 42.9, 34.4, 29.4 (2C), 29.2, 29.1, 25.0, 24.2, 15.2, 14.3, 12.8; *m*/*z* EI$^+$ 441.2 (M^+, 7%) [found 441.2502 $C_{26}H_{35}NO_5$ expected 441.2515].

4-(5-Ethoxycarbonyl-propanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (33). A solution of pyrrole **30** (11.3 g, 31.62 mmol) and 10% Pd/C (1.0 g) in THF (100 mL) was stirred under H_2 at 1.0 atm for 16 h. The reaction mixture was filtered through celite, which was then rinsed with hot methanol (50 mL). The solvent was removed under reduced pressure from the combined filtrates to give the title compound as a white solid (7.33 g, 88%); mp = 165 °C; R_f 0.48 (50:50 ethyl acetate:hexane); δ_H (500 MHz, DMSO-d_6) 11.74 (1H, bs), 4.05 (2H, q, *J* 7.1), 2.98 (2H, t, *J* 6.3), 2.56 (2H, t, *J* 6.3), 2.50 (3H, s), 2.45 (3H, s), 1.18 (3H, t, *J* 7.1); δ_C (125 MHz, DMSO-d_6) 195.2, 173.0, 162.9, 138.5, 128.6, 122.3, 118.7, 60.1, 37.2, 28.3, 14.9, 14.5, 12.8; *m*/*z* EI$^+$ 267.1 (M^+, 10%) [found 267.1090 $C_{13}H_{17}NO_5$ expected 267.1106].

4-(5-Ethoxycarbonyl-pentanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (34). Following the procedure as for the synthesis of **33**, the title compound was obtained as a white solid (99%); mp = 173 °C; R_f 0.33 (50:50 ethyl acetate:hexane); δ_H (500 MHz, CD_3OD) 4.10 (2H, q, *J* 7.1), 2.79 (2H, t, *J* 7.0), 2.56 (3H, s), 2.47 (3H,

s), 2.35 (2H, t, *J* 7.0), 1.73−1.66 (4H, m), 1.23 (3H, t, *J* 7.1); δ_C (125 MHz, CD_3OD) 199.0, 174.0, 163.0, 138.6, 129.4, 122.6, 118.3, 60.0, 41.8, 33.6, 24.3, 23.7, 13.3, 13.1, 11.5; *m/z* ESI$^-$ 294.1 [$(M - H)^+$, 100%)].

4-(9-Ethoxycarbonyl-nonanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (35). Following the procedure as for the synthesis of **33**, the title compound was obtained as a white solid (99%); mp = 96 °C; R_f 0.24 (30:70 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 9.23 (1H, bs), 4.13 (2H, q, *J* 7.1), 2.73 (2H, t, *J* 7.3), 2.62 (3H, s), 2.53 (3H, s), 2.29 (2H, t, *J* 7.5), 1.70−1.60 (4H, m), 1.35−1.28 (8H, m), 1.27 (3H, t, *J* 7.1); δ_H (500 MHz, $CDCl_3$) 198.5, 174.0, 166.2, 139.1, 131.5, 124.1, 117.0, 60.2, 42.9, 34.4, 29.4 (2C), 29.2, 29.1, 25.0, 24.3, 15.3, 14.3, 12.8; *m/z* ESI$^+$ 352.0 [$(M + H)^+$, 31%)], 374.2 [$(M + Na)^+$, 33%)].

Ethyl 6-(5-Formyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-6-oxohexanoate (36). A mixture of TFA (13.9 mL, 175.90 mmol) and **33** (4.7 g, 17.58 mmol) was stirred at room temperature for 1.5 h, after which dichloromethane (100 mL) and water (100 mL) were added.[44] The organic phase was separated and washed with sat. $NaHCO_3$ (100 mL) and water (2 × 100 mL), and then dried over anhydrous $MgSO_4$. Filtration, followed by removal of the solvent under reduced pressure, gave the α-free pyrrole as an off-white solid. A solution containing CH_2Cl_2 (20 mL), $POCl_3$ (15 mL), and DMF (15 mL) was cooled in an ice bath and then added dropwise to the α-unsubstituted pyrrole (3.8 g, 17.02 mmol) in dichloromethane (30 mL). The mixture was heated under reflux for 1 h, cooled to room temperature, and then added dropwise to 30% aq $NaHCO_3$ (1 L). The mixture was then heated under reflux for 1 h and stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate (3 × 300 mL), and the combined organics were washed with brine (100 mL) and water (100 mL). Drying over anhydrous $MgSO_4$, followed by filtration, removal of the solvent under reduced pressure, and purification using flash chromatography on silica with a gradient of ethyl acetate:hexane (0:100−30:70) as eluent, gave the title compound as a white solid (2.9 g, 68%); mp = 115 °C; R_f 0.39 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 10.29 (1H, bs), 9.64 (1H, s), 4.17 (2H, q, *J* 7.1), 3.07 (2H, t, *J* 6.5), 2.72 (2H, t, *J* 6.5), 2.61 (3H, s), 2.60 (3H, s), 1.27 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 195.0, 177.6, 173.2, 142.8, 134.2, 128.3, 123.1, 60.6, 37.4, 28.2, 15.4, 14.2, 11.5; *m/z* EI$^+$ 251.1 (M^+, 56%) [found 251.1151 $C_{13}H_{17}NO_4$ expected 251.1157].

Ethyl 6-(5-Formyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-6-oxohexanoate (37). Following the procedure as for the synthesis of **36**, the title compound was obtained as a white solid (34%); mp = 83 °C; R_f 0.55 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 9.84 (1H, bs), 9.65 (1H, s), 4.13 (2H, q, *J* 7.1), 2.76 (2H, t, *J* 6.8), 2.58 (3H, s), 2.57 (3H, s), 2.36 (2H, t, *J* 7.0), 1.76−1.69 (4H, m), 1.25 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 197.0, 177.5, 173.5, 142.1, 133.6, 128.2, 123.6, 60.3, 42.5, 34.3, 24.7, 23.5, 15.4, 14.3, 11.5; *m/z* EI$^+$ 279.1 (M^+, 12%) [found 279.1467 $C_{15}H_{21}NO_4$ expected 279.1470].

Ethyl 10-(5-Formyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-10-oxodecanoate (38). Following the procedure as for the synthesis of **36**, the title compound was obtained as a white solid (30%); mp = 69 °C; R_f 0.56 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 9.80 (1H, bs), 9.68 (1H, s), 4.16 (2H, q, *J* 7.1), 2.76 (2H, t, *J* 7.3), 2.61 (3H, s), 2.60 (3H, s), 2.32 (2H, t, *J* 7.5), 1.74−1.64 (4H, m), 1.39−1.31 (8H, m), 1.29 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 197.8, 177.5, 173.9, 142.0, 133.6, 128.2, 123.7, 60.2, 42.9, 34.4, 29.4 (2C), 29.2, 29.1, 25.0, 24.1, 15.4, 14.3, 11.4; *m/z* EI$^+$ 335.2 (M^+, 71%) [found 335.2088 $C_{19}H_{29}NO_4$ expected 335.2096].

Methyl 4-[5-(3-Methoxy-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-4-oxobutanoate (43). Purged KOH (4 M, 4 mL, 16.00 mmol) was added dropwise to a purged solution of 4-methoxy-3-pyrrolin-2-one (1.36 g, 12.00 mmol) in THF (80 mL), and the reaction mixture was stirred at 60 °C for 1 h under N_2, after which **36** (2.01 g, 8.00 mmol) was added. After being stirred for 48 h at 60 °C, the solvent was removed under reduced pressure, and the resulting yellow solid was crystallized from hot methanol, filtered, and dried in a vacuum oven to give **39** as a bright yellow solid (1.70 g, 67%); mp = 220 °C (dec); R_f 0.50 (10:90 methanol:dichloromethane). A solution of **39** (1.0 g, 3.14 mmol) and H_2SO_4 (conc, 32 drops) in MeOH (250 mL) was heated under reflux for 3 h, and the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The resulting precipitate was filtered and dried under vacuum to give the title compound as a yellow solid (1.03 g, 99%); mp = 235 °C (dec); R_f 0.74 (10:90 methanol:dichoromethane); δ_H (500 MHz, DMSO-d_6) 10.87 (1H, bs), 9.65 (1H, bs), 6.04 (1H, s), 5.27 (1H, s), 3.87 (3H, s), 3.60 (3H, s), 2.99 (2H, t, *J* 6.3), 2.58 (2H, t, *J* 6.3), 2.51 (3H, s), 2.25 (3H, s); δ_H (125 MHz, DMSO-d_6) 194.8, 173.6, 171.3, 167.4, 138.9, 126.2, 123.7, 122.6, 121.6, 94.8, 91.9, 58.9, 51.7, 37.1, 28.2, 15.2, 12.2; *m/z* EI$^+$ 330.7 (M^+, 1%) [found 332.1347 $C_{17}H_{20}N_2O_5$ expected 332.1372].

Methyl 6-[5-(3-Methoxy-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-6-oxohexanoate (44). Following the procedure as for the synthesis of **39**, **40** was obtained as a bright yellow solid (64%); mp = 221−224 °C; R_f 0.54 (10:90 methanol:dichloromethane). Following the procedure as for the synthesis of **43**, the title compound was obtained as a dark yellow solid (0.62 g, 74%); mp = 206 °C; R_f 0.75 (10:90 methanol:dichloromethane); δ_H (500 MHz, $CDCl_3$) 10.98 (1H, bs), 10.53 (1H, bs), 6.39 (1H, s), 5.11 (1H, s), 3.91 (3H, s), 3.67 (3H, s), 2.75 (2H, t, *J* 6.6), 2.66 (3H, s), 2.38−2.36 (5H, m), 1.74−1.72 (4H, m); δ_C (125 MHz, $CDCl_3$) 197.1, 174.0, 173.5, 168.1, 140.4, 126.7, 123.9, 122.5, 122.4, 99.4, 90.2, 58.3, 51.5, 42.2, 34.0, 24.7, 23.7, 15.1, 12.2; *m/z* ESI$^+$ 359.1 [$(M - H)^+$, 100%)].

Ethyl 6-[5-(3-Methoxy-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-6-oxohexanoate (45). Following the procedure as for the synthesis of **43**, using EtOH instead of MeOH, the title compound was obtained as a yellow solid (35%); mp = 166 °C; R_f 0.69 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 10.95 (1H, bs), 10.49 (1H, bs), 6.40 (1H, s), 5.12 (1H, s), 4.11 (2H, q, *J* 7.1), 3.91 (3H, s), 2.75 (2H, t, *J* 6.5), 2.66 (3H, s), 2.38 (3H, s), 2.36 (2H, t, *J* 6.7), 1.74−1.72 (4H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 197.1, 173.6, 173.5, 168.2, 140.4, 126.7, 123.9, 122.5 (2C), 99.5, 90.2, 60.2, 58.3, 42.2, 34.3, 24.8, 23.7, 15.1, 14.2, 12.1; *m/z* ESI$^+$ 373.1 (M^+, 100%).

Methyl 6-[5-(3-Methyl-4-ethyl-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-6-oxohexanoate (46). Following the procedure as for the synthesis of **39** and using 4-methyl-3-ethyl-3-pyrrolin-2-one, **41** was obtained as a bright yellow solid (62%); mp = 240 °C (dec); R_f 0.56 (10:90 methanol:dichloromethane). Following the procedure as for the synthesis of **43**, the title compound was obtained as a dark yellow solid (89%); mp = 188 °C; R_f 0.72 (10:90 methanol:dichloromethane); δ_H (500 MHz, $CDCl_3$) 11.28 (1H, bs), 10.65 (1H, bs), 6.19 (1H, s), 3.71 (3H, s), 2.80 (2H, t, *J* 6.7), 2.75 (3H, s), 2.43 (3H, s), 2.44−2.40 (4H, m), 2.19 (3H, s), 1.77−1.72 (4H, m), 1.14 (3H, t, *J* 7.5); δ_C (125 MHz, $CDCl_3$) 197.1, 174.2, 174.1, 142.5, 139.8, 130.5, 130.3, 126.0, 123.1, 122.5, 100.3, 51.5, 42.3, 34.1, 24.8, 23.8, 16.9, 15.1, 13.7, 12.2, 9.7; *m/z* EI$^+$ 372.1 (M^+, 25%) [found 372.2056 $C_{21}H_{28}N_2O_4$ expected 372.2049].

Methyl 10-[5-(3-Methoxy-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-10-oxodecanoate (47). Following the procedure as for the synthesis of **39**, **42** was obtained as a yellow solid (66%); mp = 226 °C; R_f 0.79 (10:90 methanol:dichoromethane). Following the procedure as for the synthesis of **43**, the title compound was obtained as a yellow solid (99%); mp = 168 °C; R_f 0.79 (10:90 methanol:dichoromethane); δ_H (500 MHz, $CDCl_3$) 10.99 (1H, bs), 10.52 (1H, bs), 6.41 (1H, s), 5.13 (1H, s), 3.92 (3H, s), 3.66 (3H, s), 2.72 (2H, t, *J* 7.3), 2.67 (3H, s), 2.39 (3H, s), 2.30 (2H, t, *J* 7.5), 1.71−1.61 (4H, m), 1.34−1.29 (8H, m); δ_C (125 MHz, $CDCl_3$) 198.0, 174.3, 173.5, 168.2, 140.9, 126.8, 123.8, 122.6, 122.5, 99.7, 90.2, 58.4, 51.4, 42.7, 34.1, 29.5, 29.4, 29.2, 29.1, 25.0, 24.3, 15.1, 12.2; *m/z* ESI$^+$ 415.3 [$(M - H)^+$, 100%)].

Methyl 4-[5-(3-Methoxy-5-trifluoromethanesulfonyloxy-1*H*-pyrrol-2-ylidenemethyl)-2,4-dimethyl-5*H*-pyrrol-3-yl]-4-oxobutanoate (48). Following the procedure as for the synthesis of **11** followed by purification using chromatography on silica and a

gradient of ethyl acetate:hexane (0:100−30:70) as eluent, the title compound was obtained as a yellow film (71%); R_f 0.65 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.08 (1H, bs), 7.12 (1H, s), 5.43 (1H, s), 3.90 (3H, s), 3.71 (3H, s), 3.07 (2H, t, *J* 6.5), 2.72 (2H, t, *J* 6.5), 2.60 (3H, s), 2.45 (3H, s); δ_C (125 MHz, $CDCl_3$) 194.6, 173.6, 168.2, 162.0, 143.8, 133.7, 133.2, 126.0, 123.1, 118.7, 118.6 (q, *J* 321.1, *C*F_3), 87.6, 58.9, 51.8, 37.4, 28.0, 16.0, 12.4; δ_F (235 MHz, $CDCl_3$) −73.83; *m*/*z* ESI$^+$ 464.9 [$(M + H)^+$, 15%)], 486.9 [$(M + Na)^+$, 100%)].

Methyl 6-[5-(3-Methoxy-5-trifluoromethanesulfonyloxy-1*H*-pyrrol-2-ylidenemethyl)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate (49). Following the procedure as for the synthesis of **11**, the title compound was obtained as a yellow solid (81%); mp = 58 °C; R_f 0.71 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.05 (1H, bs), 7.12 (1H, s), 5.43 (1H, s), 3.90 (3H, s), 3.67 (3H, s), 2.75 (2H, t, *J* 6.7), 2.58 (3H, s), 2.43 (3H, s), 2.37 (2H, t, *J* 6.8), 1.73−1.70 (4H, m); δ_C (125 MHz, $CDCl_3$) 196.7, 173.9, 168.1, 162.0, 143.5, 133.7, 133.0, 126.0, 123.5, 118.7, 118.6 (q, *J* 321.1, *C*F_3), 87.6, 58.9, 51.5, 42.3, 34.0, 24.6, 23.5, 15.9, 12.3; δ_F (235 MHz, $CDCl_3$) −73.89; *m*/*z* ESI$^+$ 515.0 [$(M + Na)^+$, 100%)].

Ethyl 6-[5-(3-Methoxy-5-trifluoromethanesulfonyloxy-1*H*-pyrrol-2-ylidenemethyl)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate (50). Following the procedure as for the synthesis of **11** followed by purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−50:70) as eluent, the title compound was obtained as a yellow film (83%); R_f 0.72 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.06 (1H, bs), 7.13 (1H, s), 5.43 (1H, s), 4.12 (2H, q, *J* 7.1), 3.90 (3H, s), 2.75 (2H, t, *J* 6.5), 2.58 (3H, s), 2.43 (3H, s), 2.35 (2H, t, *J* 6.8), 1.75−1.71 (4H, m), 1.25 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 196.8, 173.9, 173.5, 168.1, 162.0, 143.5, 133.7, 126.0, 123.6, 118.7, 118.4 (q, *J* 320.1, *C*F_3), 87.6, 60.3, 58.9, 42.3, 34.2, 24.7, 23.5, 15.9, 14.2, 12.3; δ_F (235 MHz, $CDCl_3$) −73.76; *m*/*z* ESI$^+$ 504.9 [$(M - H)^+$, 52%)].

Methyl 6-[5-(3-Methyl-4-ethyl-5-trifluoromethanesulfonyloxy-1*H*-pyrrol-2-ylidenemethyl)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate (51). Following the procedure as for the synthesis of **11**, the title compound was obtained as a yellow film (51%); R_f 0.84 (50:50 ethyl acetate:hexane); δ_H (500 MHz, $CDCl_3$) 11.36 (1H, bs), 6.96 (1H, s), 3.70 (3H, s), 2.78 (2H, t, *J* 6.7), 2.60 (3H, s), 2.47 (3H, s), 2.40 (2H, t, *J* 6.8), 2.40 (2H, q, *J* 7.6), 2.21 (3H, s), 1.75 (4H, m), 1.14 (3H, t, *J* 7.6); δ_C (125 MHz, $CDCl_3$) 196.7, 174.0, 163.3, 143.4, 142.8, 141.3, 132.6, 126.6, 126.4, 123.4, 119.8 , 118.7 (q, *J* 321.2, *C*F_3), 51.5, 42.3, 31.0, 24.7, 23.6, 16.6, 15.9, 13.7, 12.4, 9.9; δ_F (235 MHz, $CDCl_3$) −73.60; *m*/*z* ESI$^+$ 505.1 [$(M + H)^+$, 10%], 527.0 [$(M + Na)^+$, 98%)].

Methyl 10-[5-(3-Methoxy-5-trifluoromethanesulfonyloxy-1*H*-pyrrol-2-ylidenemethyl)-2,4-dimethyl-5*H*-pyrrol-3-yl]-10-oxodecanoate (52). Following the procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−20:80) as eluent, the title compound was obtained as a yellow film (70%); R_f 0.76 (50:50 ethyl acetate: hexane); δ_H (500 MHz, $CDCl_3$) 11.04 (1H, bs), 7.12 (1H, s), 5.43 (1H, s), 3.90 (3H, s), 3.66 (3H, s), 2.71 (2H, t, *J* 7.3), 2.58 (3H, s), 2.43 (3H, s), 2.30 (2H, t, *J* 7.5), 1.70−1.60 (4H, m), 1.35−1.30 (8H, m); δ_C (125 MHz, $CDCl_3$) 197.5, 174.3, 168.1, 162.0, 143.5, 133.6, 133.2, 126.0, 123.7, 118.8, 118.7 (q, *J* 321.1, *C*F_3), 87.5, 58.9, 51.4, 42.8, 34.1, 29.4 (2C), 29.2, 29.1, 24.9, 24.1, 15.9, 12.3; δ_F (235 MHz, $CDCl_3$) −73.64; *m*/*z* ESI$^+$ 549.0 [$(M + H)^+$, 20%)], 571.0 [$(M + Na)^+$, 100%)].

Methyl 4-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-4-oxobutanoate Hydrochloric Salt (53HCl). Following the procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−25:75) as eluent, the title compound was obtained as a dark crimson solid (57%); mp = 194 °C; R_f (free base) 0.43 (50:50 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 529 (ϵ 96 425), 501 (ϵ 54 072); δ_H (500 MHz, $CDCl_3$) 12.98 (1H, bs), 12.72 (1H, bs), 12.68 (1H, bs), 7.30 (1H, s), 7.11 (1H, s), 7.02 (1H, s), 6.40 (1H, s), 6.11 (1H, s), 4.05 (3H, s), 3.72 (3H, s), 3.07 (2H, t, *J* 6.4), 2.86 (3H, s), 2.72 (2H, t, *J* 6.4), 2.52 (3H, s); δ_C (125 MHz, $CDCl_3$) 194.5, 173.5, 166.8, 150.4, 148.8, 138.5, 128.8, 124.4, 123.4, 123.0, 122.0, 119.4, 112.6 (2C), 93.4, 59.0, 51.8, 37.6, 27.9, 15.7, 12.6; *m*/*z* EI$^+$ 380.6 [$(M - HCl)^+$, 6%] [found 381.1677 $C_{21}H_{23}N_3O_4$ expected 381.1688].

Methyl 6-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate Hydrochloric Salt (54HCl). The procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−40:60) as eluent gave the brick-red free-base **54** after addition of acetone to the concentrated chromatography fractions and filtration (82%); mp = 165 °C; R_f 0.48 (50:50 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 460 (ϵ 35 340), 528 (ϵ 21 631); δ_H (500 MHz, $CDCl_3$) 6.92 (1H, s), 6.77 (1H, s), 6.73 (1H, s), 6.22 (1H, s), 6.05 (1H, s), 3.98 (3H, s), 3.64 (3H, s), 2.68 (2H, t, *J* 6.3), 2.40 (3H, s), 2.33 (2H, t, *J* 6.3), 2.21 (3H, s), 1.69−1.66 (4H, m); δ_C (125 MHz, $CDCl_3$) 197.2, 174.0 (2C), 168.9, 160.7, 141.9, 129.5, 128.2, 126.3, 123.4, 123.1, 113.7, 112.0, 110.7, 95.9, 58.6, 51.5, 42.3, 34.0, 24.7, 23.6, 14.3, 12.3; *m*/*z* EI$^+$ 409.2 (M^+, 5%) [found 409.2007 $C_{23}H_{27}N_3O_4$ expected 409.2001]. Addition of HCl in ether to the filtrate, followed by filtration, gave the title compound as a crimson solid (15%, total yield 97%); mp = 189 °C; $\lambda_{max}CHCl_3$ 529 (ϵ 92 087), 499 (ϵ 45 765); δ_H (500 MHz, $CDCl_3$) 13.01 (1H, bs), 12.72 (1H, s), 12.69 (1H, s), 7.31 (1H, s), 7.13 (1H, s), 7.02 (1H, s), 6.40 (1H, s), 6.12 (1H, s), 4.07 (3H, s), 3.67 (3H, s), 2.85 (3H, s), 2.77 (2H, t, *J* 6.6), 2.51 (3H, s), 2.37 (2H, t, *J* 6.6), 1.73−1.70 (4H, m); δ_C (125 MHz, $CDCl_3$) 196.6, 173.9, 166.7, 150.4, 148.6, 138.5, 128.7, 125.0, 123.4, 122.9, 122.0, 119.3, 112.7, 112.6, 93.4, 59.0, 51.5, 42.6, 34.0, 24.6, 23.5, 15.6, 12.5; δ_N (50 MHz, $CDCl_3$) −213.40, −218.67, −241.13; *m*/*z* EI$^+$ 409.0 [$(M - HCl)^+$, 0.2%] [found 409.2008 $C_{23}H_{27}N_3O_4$ expected 409.2001].

Ethyl 6-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate Hydrochloric Salt (55HCl). The procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate: hexane (0:100−40:60) gave the title compound dark crimson solid (54%); mp = 146 °C; R_f (free base) 0.48 (50:50 ethyl acetate: hexane); $\lambda_{max}CHCl_3$ 529 (ϵ 110 605), 503 (ϵ 54 168); δ_H (500 MHz, $CDCl_3$) 12.94 (1H, bs), 12.68 (2H, bs), 7.29 (1H, s), 7.02 (1H, s), 7.00 (1H, s), 6.39 (1H, s), 6.10 (1H, s), 4.13 (2H, q, *J* 7.1), 4.05 (3H, s), 2.83 (3H, s), 2.75 (2H, t, *J* 7.2), 2.49 (3H, s), 2.35 (2H, t, *J* 6.7), 1.76−1.71 (4H, m), 1.26 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 196.6, 173.5, 166.7, 150.3, 148.6, 138.4, 128.6, 124.9, 123.3, 122.9, 122.0, 119.3, 112.6, 112.5, 93.5, 60.3, 59.2, 42.6, 34.2, 24.6, 23.5, 15.6, 14.2, 12.6; *m*/*z* EI$^+$ 423.1 [$(M - HCl)^+$, 3%)] [found 423.2156 $C_{24}H_{29}N_3O_4$ expected 423.2158].

Methyl 6-[5-(3-Ethyl-4-methyl-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoate Hydrochloric Salt (56HCl). The procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−30:70) gave the title compound as a dark purple solid (26%); mp = 208 °C; R_f (free base) 0.70 (50:50 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 562 (ϵ 104 039), 532 (ϵ 55 377); δ_H (500 MHz, $CDCl_3$) 13.16 (1H, bs), 13.06 (1H, bs), 12.65 (1H, bs), 7.36 (1H, s), 7.16 (1H, s), 7.05 (1H, s), 6.47 (1H, s), 3.71 (3H, s), 2.87 (3H, s), 2.79−2.71 (4H, m), 2.52 (3H, s), 2.40 (2H, t, *J* 6.5), 2.35 (3H, s), 1.75 (4H, m), 1.23 (3H, t, *J* 7.4); δ_C (125 MHz, $CDCl_3$) 196.6, 173.9, 149.8, 148.5, 145.3, 139.7, 132.3, 130.2, 128.2, 125.4, 124.4, 121.5, 119.2, 115.3, 112.9, 51.6, 42.7, 34.0, 24.6, 23.5, 18.7, 15.6, 13.3, 12.7, 10.1; *m*/*z* ESI$^+$ 422.3 [$(M - HCl)^+$, 100%)].

Methyl 10-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-10-oxodecanoate Hydrochloric Salt (57HCl). The procedure as for the synthesis of **11** and purification using chromatography on silica and a gradient of ethyl acetate:hexane (0:100−30:70) gave the title compound as a dark crimson solid (29%); mp = 167 °C; R_f (free base) 0.37 (50: 50 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 530 (ϵ 108 531), 500 (ϵ 55 742); δ_H (500 MHz, $CDCl_3$) 13.01 (1H, bs), 12.73 (2H, bs), 7.34 (1H, s), 7.16 (1H, s), 7.05 (1H, s), 6.43 (1H, s), 6.14 (1H, s), 4.10 (3H, s), 3.70 (3H, s), 2.88 (3H, s), 2.76 (2H, t, *J* 7.3), 2.53

(3H, s), 2.34 (2H, t, *J* 7.5), 1.73−1.64 (4H, m), 1.37−1.33 (8H, m); δ_C (125 MHz, $CDCl_3$) 197.5, 174.3, 166.7, 150.3, 148.6, 138.7, 128.7, 125.2, 123.4, 122.8, 122.1, 119.3, 112.8, 112.6, 93.6, 59.2, 51.5, 43.1, 34.1, 29.4, 29.3, 29.1 (2C), 25.0, 24.1, 15.6, 12.5; *m*/*z* ESI^+ 466.3, 467.3 [$(M - Cl)^+$, 100%, 30%)]. Anal. Calcd for $C_{27}H_{36}ClN_3O_4$: C, 64.59; H, 7.23; N, 8.37. Found: C, 64.22; H, 7.25; N, 8.08.

Zn(54)$_2$. To a solution of **54** (10 mg, 0.024 mmol) in $CHCl_3$ (5 mL) was added a solution of $Zn(OAc)_2{\cdot}2H_2O$ (13 mg, 0.058 mmol) and $NaOAc{\cdot}3H_2O$ (8 mg, 0.058 mmol) in MeOH (3 mL). The reaction mixture was stirred at room temperature for 90 min, and then more $CHCl_3$ (10 mL) was added. Washing with H_2O (2 × 20 mL), filtration, and removal of the solvent under reduced pressure gave the product as a red/green iridescent film (10 mg, 92%); mp > 250 (dec); R_f 0.84 (30:70 ethyl acetate:hexane); $\lambda_{max}CHCl_3$ 529 (ϵ 157 364), 500 (ϵ 97 101); δ_H (500 MHz, $CDCl_3$) 9.22 (1H, bs), 7.35 (1H, s), 6.62−6.60 (1H, m), 6.51−49 (1H, m), 6.12−6.10 (1H, m), 6.05 (1H, s), 3.99 (3H, s), 3.63 (3H, s), 2.69 (2H, t, *J* 6.3), 2.54 (3H, s), 2.32 (2H, t, *J* 6.7), 2.16 (3H, s), 1.67−1.64 (4H, m); δ_C (125 MHz, $CDCl_3$) 197.2, 174.1, 167.0, 155.7, 155.5, 138.6, 133.0, 131.9, 126.9, 126.4, 123.0, 117.8, 114.3, 110.6, 96.0, 58.4, 51.5, 42.2, 34.1, 24.8, 23.8, 18.0, 13.0; δ_N (50 MHz, $CDCl_3$) −174.21, −203.13, 234.77; *m*/*z* ESI^+ 880 (M^+, 34%).

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Supporting Information Available: General synthetic methods; absorption and mass spectra for copper complexes; NMR spectra for all novel compounds; and HPLC traces for all prodigiosenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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