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A General Route to 1,3′-Bipyrroles

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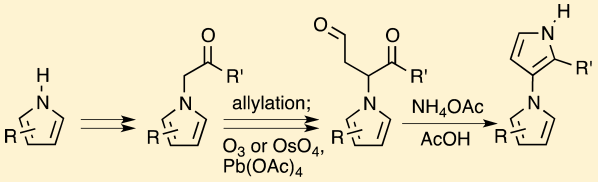
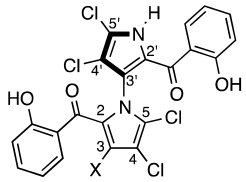
Supporting Information

ABSTRACT: A general method is described for the synthesis of 1,3′-bipyrroles. The route involves constructing a pyrrole ring on the nitrogen of a substituted 1*H*-pyrrole, so as to generate the 1,3′-bipyrrole. In this approach the nitrogen of the starting pyrrole was alkylated with a special Michael acceptor having an allylic leaving group, and the product was then modified in such a way that the second pyrrole ring could be formed by a Paal–Knorr reaction. Two variants of this sequence were examined, one of which led to formation of a 3-hydroxypyridine instead of the second pyrrole ring; the other variant used phenacyl bromide instead of the special Michael acceptor.



INTRODUCTION

The discovery of marinopyrroles A (**1**) and B (**2**)[1] and the observation that they show strong activity against methicillin-resistant bacteria[1−3] have served to identify the 1,3′-bipyrrole system as a potentially important structural type in medicinal chemistry. Prior to the isolation of these compounds and the recognition of their antibacterial properties, few methods had been reported for the synthesis of 1,3′-bipyrroles, and the methods available proved to be inappropriate[4] for the synthesis of marinopyrrole B, although they were adequate for the less highly halogenated marinopyrrole A.[2,4,5]



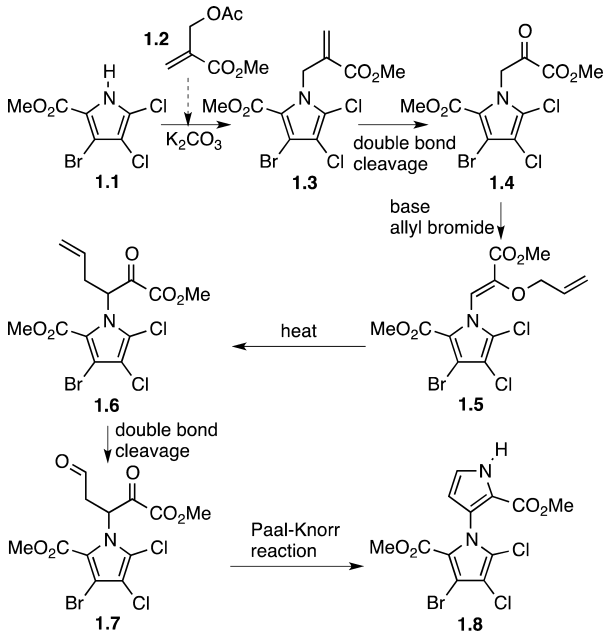
X = H, (-)-marinopyrrole A (**1**)
X = Br, (-)-marinopyrrole B (**2**)

One of the established routes to 1,3′-bipyrroles is based on the standard Clauson–Kaas reaction with a 3-aminopyrrole[4c,6] This procedure appears to have been used only where the newly generated pyrrole is unsubstituted. A variant of the Paal–Knorr reaction that uses a keto-ketal instead of a diketone has likewise been applied to 3-aminopyrroles.[4a,b] Again, the pyrrole unit that is formed has been unsubstituted. The classical Paal–Knorr reaction[7] itself has been used with 3-aminopyrroles[1b,8,9] and a number of 1,4-diketones.

Copper-mediated *N*-arylation of a pyrrole (Ullmann coupling) with a 3-bromopyrrole was the key step in a synthesis of marinopyrrole A.[5] While the method was suitable for making this particular natural product, there are intrinsic limitations[1b,5] on the types of substitution allowed in the starting pyrroles. In general, metal-mediated coupling processes would be expected to be incompatible with halogen substitution in the starting materials beyond the single halogen required for the metal-mediated reaction; unfortunately, such polyhalo substitution is *the* conspicuous feature of the marinopyrroles. A number of 1,3′-bipyrroles, lightly substituted in both pyrrole rings (3-OR, 4-CN, 4′-CN or 3-OR, 4-CO_2R, 4′-CO_2R), have been made[10] by reaction of *p*-toluenesulfonylmethyl isocyanide (TOSMIC) with α,β-unsubstituted ketones and esters.

Recently, a synthesis of marinopyrrole B was developed in this laboratory (Scheme 1),[11] which was based on the use of a

Scheme 1. Principle of the Method Used for Synthesis of Marinopyrrole B



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preformed bromodichloropyrrole (**1.1**). This substance was alkylated on nitrogen (Scheme 1) by taking advantage of the high reactivity of the Michael acceptor **1.2**,[12] which has a leaving group in the allylic position. The resulting *N*-alkylpyrrole **1.3** was then modified to generate keto aldehyde **1.7**, a substance that is correctly constituted to undergo a Paal–Knorr reaction that generates the second pyrrole ring (**1.7** → **1.8**). In principle, compounds of type **1.4** should be available by *N*-alkylation of **1.1** with an *α*-bromopyruvate, but experiments directed to that end in model studies were unsuccessful and eventually led to the use of **1.2**.[11] The approach shown in Scheme 1 avoids the difficulties of introducing bromine at the 1,3′-bipyrrole stage; the available evidence suggests that tetrachloro- and tetrabromo-1,3′-bipyrroles, at least those that also carry carbonyl substituents at the C2- and C2′-positions,[4a,c] resist further halogenation, and attempts to perform such late-stage brominations have been unsuccessful.[4a,c] As the biological evaluation of other 1,3′-bipyrroles is worthwhile because of the very high antibiotic activity of **1** and **2** and some of their analogues,[2] we have examined the generality of the method that was used to make marinopyrrole B and find that it is indeed a general approach not only to halogenated 1,3′-bipyrroles but also to 1,3′-bipyrroles carrying substituents other than halogens.

RESULTS AND DISCUSSION

Our starting monopyrroles are compounds **3**–**10** (Figure 1); these are all known compounds, except for **9**, which was made

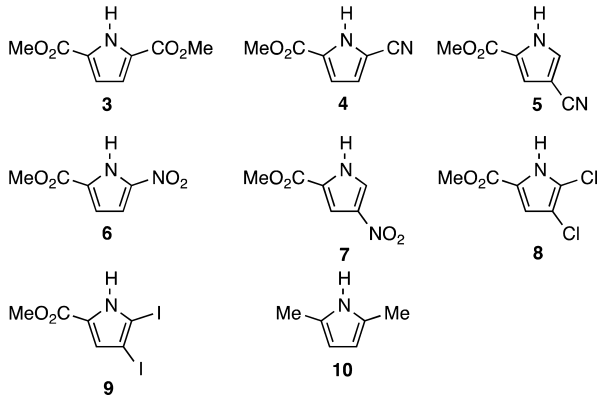
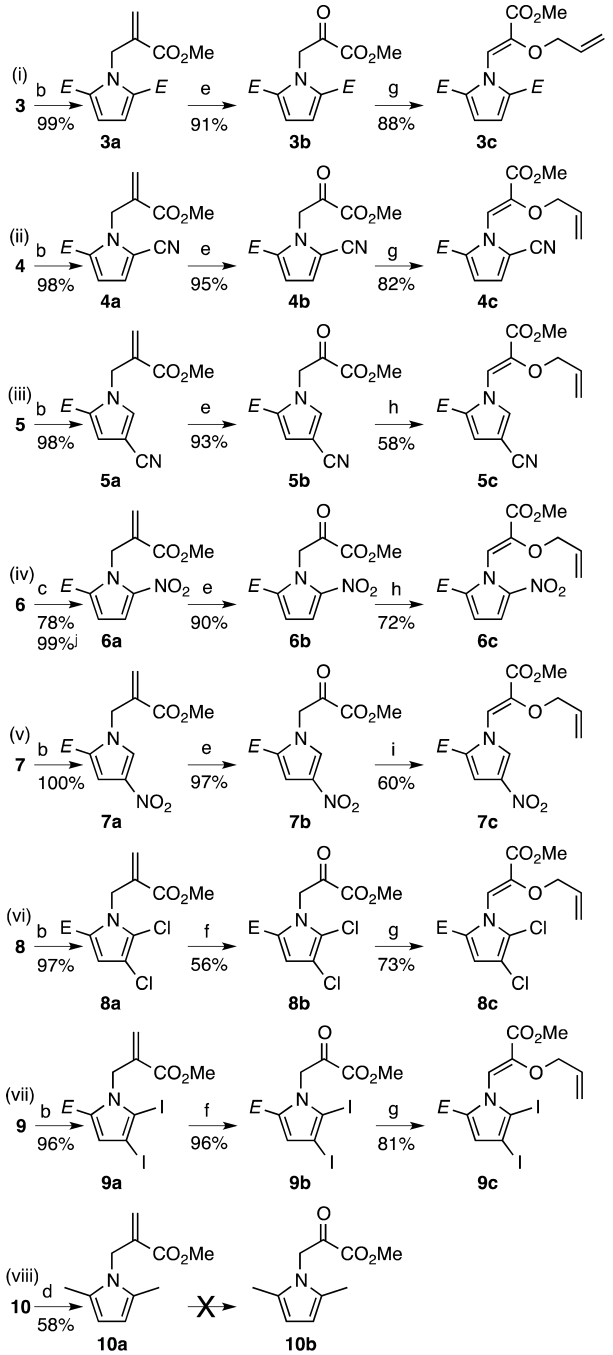


Figure 1. Starting monopyrroles.

from the known and readily accessible 2,2,2-trichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethanone[13] by treatment with MeONa in MeOH, following a procedure described[11] for the dichloro analogue **8**. Each monopyrrole was found to react with the Michael acceptor **1.2** to give the products listed in Table 1, and with one exception, the adducts were formed in yields of 78–100%. Usually, the pyrroles were treated with **1.2** in the presence of K_2CO_3 in refluxing MeCN for up to 24 h. The sensitive 2,5-dimethylpyrrole **10** gave a significantly lower yield (58%) and also required different conditions (the reaction worked with NaH/DMF but not with the usual K_2CO_3/MeCN). The poor yield was due in part to the fact that the starting 2,5-dimethylpyrrole undergoes Michael addition to the initial adduct **10a**. In the case of the 5-nitro compound **6**, Na_2CO_3 and 18-crown-6 (1 equiv) were required to give an acceptable yield; in the absence of the crown ether, the starting material was largely recovered, and with K_2CO_3, starting

Table 1. Preparation of the *O*-Allyl Ethers[a]



[a]*E* = CO_2Me. [b]K_2CO_3, MeCN. [c]Na_2CO_3, 18-crown-6, MeCN. [d]NaH, DMF. [e]O_3; Me_2S. [f]OsO_4, NMO; $Pb(OAc)_4$. [g]NaH, DMF, allyl bromide, ca. −40 °C to room temp. [h]K_2CO_3, DMF, allyl bromide, room temp. [i]K_2CO_3, 18-crown-6, DMF, allyl bromide, room temp. [j]Corrected for recovered **6**.

material was also largely recovered irrespective of whether the crown ether was present or absent.

Cleavage of the initial double bond (cf. **3a** → **3b**, Table 1) was usually done by ozonolysis in CH_2Cl_2 at −78 °C, using Sudan Red 7B as an indicator,[15] and Me_2S as the reductant. In the case of the dihalo compounds **8a** and **9a**, much better results were obtained by a two-step process: dihydroxylation with OsO_4/NMO and diol cleavage with $Pb(OAc)_4$. Our attempts to cleave the double bond of **10a** by ozonolysis

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without degrading the pyrrole nucleus were unsuccessful, even when only 1 equiv of O_3 was added, using a special apparatus[16] to deliver a measured aliquot of CH_2Cl_2 saturated with O_3. Likewise, experiments based on dihydroxylation (OsO_4/NMO or $RuCl_3$/$NaIO_4$) also failed to generate the desired product, and we conclude that our approach is unsuitable for pyrroles having electron-donating substituents, even though double bond cleavage in a system carrying a 2,5-dimethylpyrrole subunit has indeed been reported.[17]

Alkylation with allyl bromide, using either NaH or K_2CO_3 (depending on the case) in DMF, gave the *O*-allyl products (see Table 1) and, in two examples (**1.5** from the marinopyrrole B synthesis itself[11] and **3c** from the present work), the double bond geometry was established by single crystal X-ray analysis. The depicted *Z* geometry of the other *O*-allylated products is an arbitrary assignment. The nitro compound **7b** required the addition of 18-crown-6 to facilitate the *O*-alkylation.

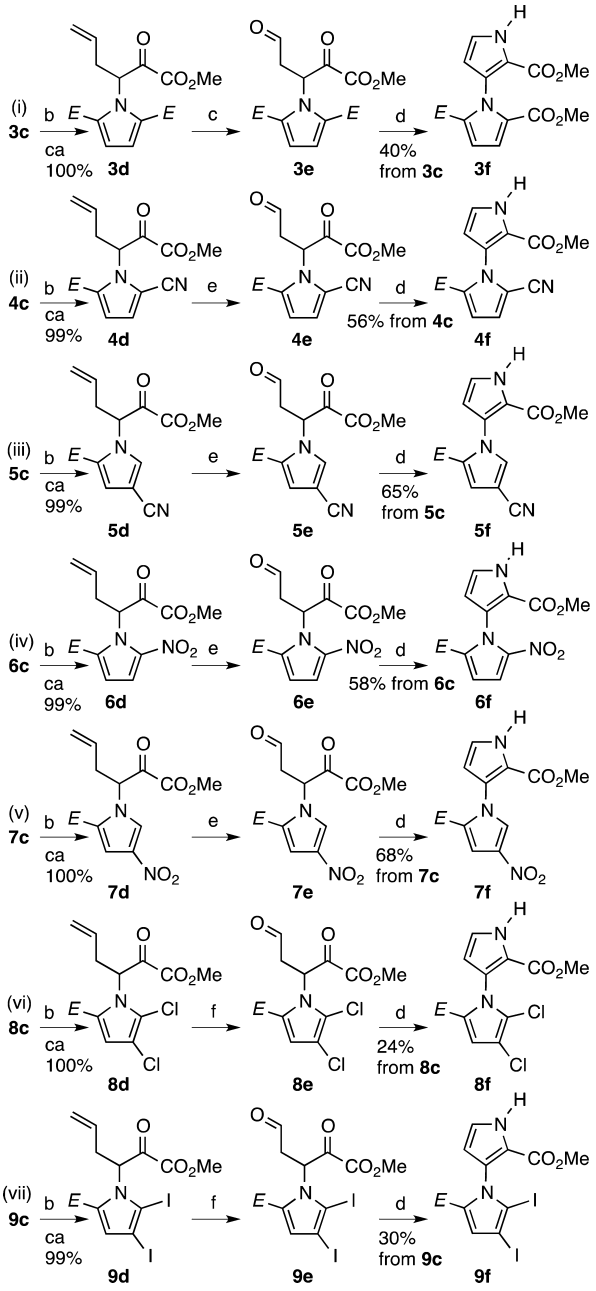
Each of the *O*-allyl ethers underwent smooth Claisen rearrangement (Table 2) on heating in refluxing PhMe to give very clean products that usually did not require chromatography before the next step. We noticed that **5c** and **7c**, which are the only examples that do not have *two* substituents that flank the nitrogen, showed some tendency to isomerize to the Claisen products at room temperature during handling. Formation of the diiodide **9d** was slow, but the reflux period should not be extended beyond 42 h for best results.

The second double bond cleavage (cf. **3d** → **3e**, Table 2) was again usually best done by ozonolysis, using Sudan Red 7B as an indicator. The intermediate keto aldehydes **3e**–**9e** were sensitive compounds and tended to decompose by loss of the pyrrole unit; fortunately, this pathway could be adequately suppressed by proper temperature control: specifically, during isolation of the keto aldehydes, solvent evaporation must be done below room temperature, and the product used promptly without purification. For example, the conversion of **4d** to **4f** was improved from 43 to 56% by evaporating solutions of the intermediate **4e** at no higher than 15 °C. Our conditions for the final (Paal–Knorr) step called for treatment of the keto aldehyde in AcOH with NH_4OAc.[18]

Double bond cleavage in the case of the two halogenated examples (**8d** and **9d**) had to be done in two steps [dihydroxylation at room temperature (OsO_4/NMO) and diol cleavage with $Pb(OAc)_4$], rather than by ozonolysis, as attempted cleavage with O_3 was unsuccessful. In both cases (**8e** and **9e**) the excess of $Pb(OAc)_4$ must be removed by quenching with pinacol[19] before the Paal–Knorr cyclization.[20] The diiodo keto aldehyde **9e** is light-sensitive, and as a precaution, we protected all compounds in the diiodo series from light.

Although the overall yields for the three steps from the *O*-allyl compounds **3c**–**9c** to the 1,3′-bipyrroles **3f**–**9f** were modest (see Table 2), the products would be difficult to make, if indeed possible in all cases, by existing methods. We did not establish the individual yields for the last two steps of the sequence (the double bond cleavage and the Paal–Knorr pyrrole formation), except for observing that the yields for the crude intermediate diols generated from **8d** and **9d** were no greater than 50 and 61%, respectively. The 1,3′-bipyrroles we made are all crystalline; their structures are clear from spectral data, but in one case (**3f**) the assignment was also supported by single crystal X-ray analysis.

Table 2. 1,3′-Bipyrrole Formation[a]



[a]*E* = CO_2Me. [b]PhMe, reflux. The products of the thermal rearrangement were not purified; the reactions were very clean, and the crude products were suitable for direct use in the next step. [c]O_3, MeOH–CH_2Cl_2, −78 °C; Ph_3P. [d]NH_4OAc, AcOH. [e]O_3, CH_2Cl_2, Sudan Red 7B, CH_2Cl_2, −78 °C; Me_2S. [f]OsO_4, NMO; $Pb(OAc)_4$.

All the examples of Table 2 have an ester substituent (−CO_2Me) at C2′ in the newly generated pyrrole ring, and during the synthesis of marinopyrrole B, the possibility of using a keto group, instead of an ester, was examined. As reported previously,[11] but without experimental details, the α-diketone **4.3** (see Scheme 4) had been prepared for this purpose. One of the required subunits for synthesis of this compound was the keto acetate **2.7**, which was made from the known[21] Baylis–Hillman adduct **2.1** by the reactions summarized in Scheme 2. The only complication met in this sequence was the acetyl migration leading to **2.6**, but fortunately, this minor byproduct

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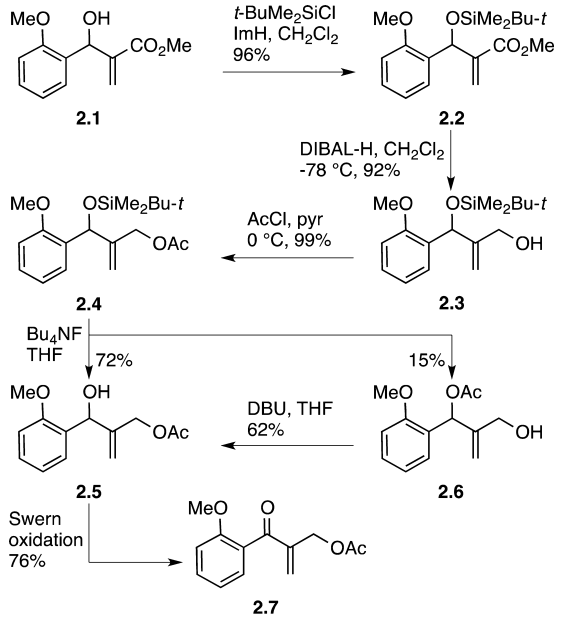
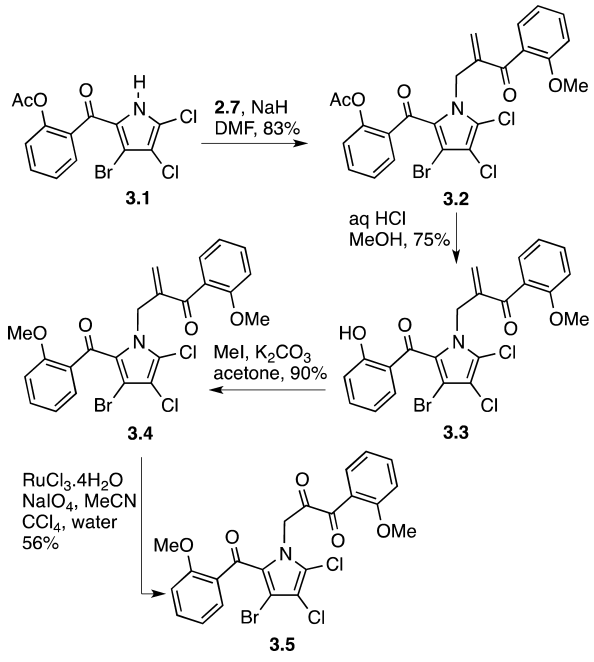
Scheme 2. Preparation of Keto Acetate 2.7



could be converted, by the action of DBU, into the desired primary acetate **2.5**, which was then oxidized (**2.5** → **2.7**).

The other component needed was the known and easily prepared bromodichloropyrrole **3.1**.[1b] This reacted with **2.7** (Scheme 3) after deprotonation with NaH. Hydrolysis under

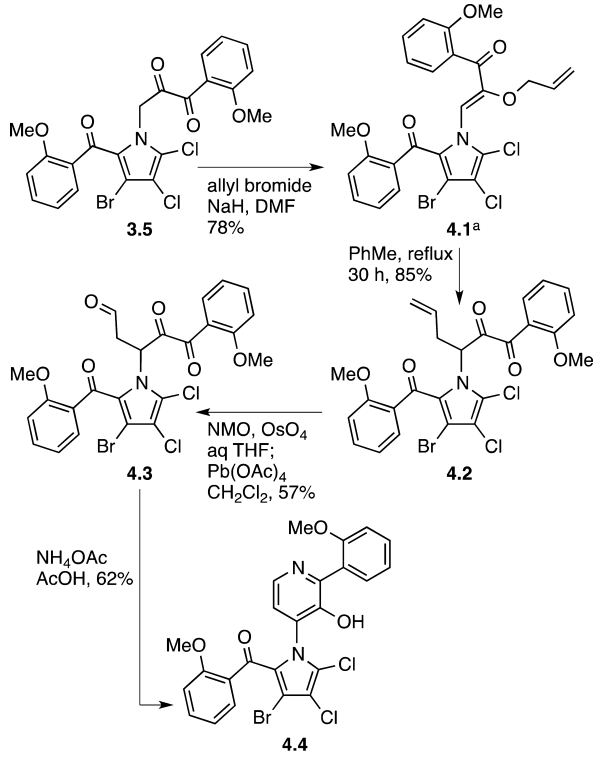
Scheme 3. Linking 2.7 and 3.1



acidic conditions[1b] then served to release phenol **3.3** (75%). Methylation of the phenolic hydroxyl of **3.3** under classical conditions and double bond cleavage[22] gave diketone **3.5**, the desired substrate for allylation. In the case of **3.4** the double bond cleavage was best done with $RuCl_3$, $NaIO_4$;[22] other methods [dihydroxylation with OsO_4/NMO, followed by diol cleavage with $Pb(OAc)_4$ or $NaIO_4$–SiO_2] were less satisfactory and ozonolysis failed.

Allylation of **3.5** (NaH, allyl bromide) afforded the *O*-allyl derivative **4.1**, and this rearranged on heating in PhMe. Lemieux–Johnson oxidation and ozonolysis were then examined for the purpose of cleaving the terminal double bond, but neither of these procedures was successful. Fortunately, the two-stage process involving dihydroxylation with OsO_4/NMO and cleavage with $Pb(OAc)_4$ afforded the required aldehyde **4.3** in 57% yield. However, exposure of this compound to NH_4OAc in AcOH did not furnish a 1,3′-bipyrrole, but gave instead the hydroxypyridine **4.4** (62%) (Scheme 4). The 3-hydroxypyridine unit is of pharmaceutical

Scheme 4. Formation of the 3-Hydroxypyridine 4.4



[a]*Z*-Geometry is an arbitrary assignment.

interest and, as far as we can determine, has not been generated this way before.[23,24] This sequence leading to **4.4** had actually been the first approach for implementing the principle summarized in Scheme 1, and the unexpected outcome suggested the use of an ester group in the route to marinopyrrole B that was ultimately successful.

We have also examined the substrate **5.2** (see Scheme 5), in which a phenyl group is present instead of the CO_2Me group at C2′ of the examples listed in Tables 2. The compound was readily made by *N*-alkylation of pyrrole **4**, using phenacyl bromide (**5.1**). The subsequent allylation afforded the products of *O*-allylation (**5.3**) and *C*-allylation (**5.4**),[25] in a ratio of ca. 2:1, but the former was easily converted into the latter by heating the mixture of **5.3** and **5.4** in PhMe, the overall yield of **5.4** from **5.2**, then being 36% (53% corrected for recovered **5.2**).[26] The double bond of **5.4** was easily cleaved by ozonolysis under our standard conditions, and the resulting keto aldehyde **5.5** underwent a smooth Paal–Knorr reaction to give **5.6** in 71% yield (from **5.4**). We formed the impression that keto aldehyde **5.5** was more stable than the other keto aldehydes we had generated; the presence of a phenyl group instead of an

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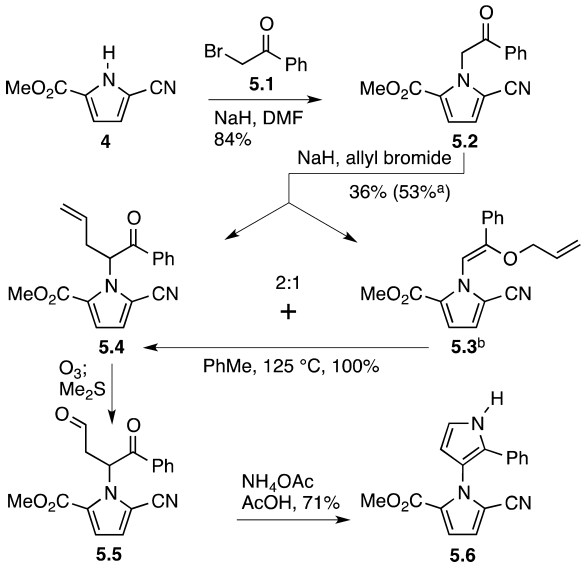
Scheme 5. Formation of 5.6

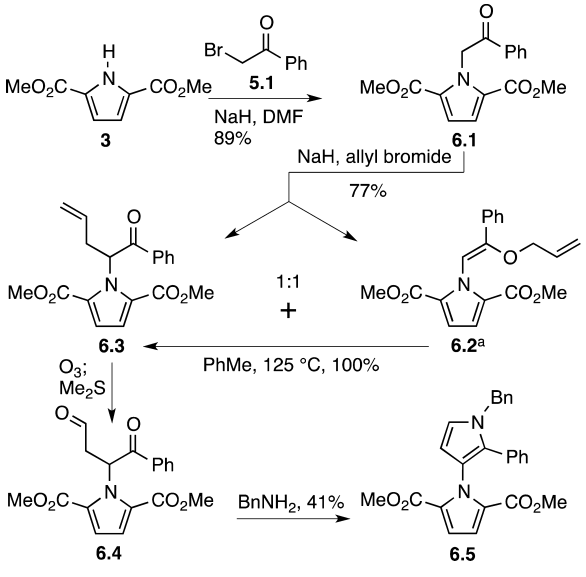


[a]Combined yield corrected for recovered **5.2**. [b]*Z*-Geometry is an arbitrary assignment.

ester must lower the tendency for elimination of the pyrrole subunit.

Finally, we have prepared the *N*-protected 1,3′-bipyrrole **6.5** by the analogous route shown in Scheme 6. Again, both *O*- and

Scheme 6. Formation of 6.5



[a]*Z*-Geometry is an arbitrary assignment.

C-allylation products were generated, and the intermediate keto aldehyde **6.4** proved to be decidedly more stable than the keto aldehydes in Table 2. The final step was done using $BnNH_2$ and catalysis by I_2[27] with THF as solvent instead of NH_4OAc/AcOH.

CONCLUSION

Our experiments establish that the approach to 1,3′-bipyrroles summarized in Scheme 1 represents a general route that accommodates a range of electron-withdrawing substituents on the initial pyrrole subunit. The method is not applicable when the initial pyrrole carries electron-donating groups (e.g., methyl), as the double bond in the allyl substituent could not then be cleaved without degradation of the pyrrole ring.

The variation described in Schemes 5 and 6 shows that the second pyrrole ring need not be substituted by an ester group but can have an aromatic ring. The sequence of Scheme 4 is a new route to the hydroxypyridine system. The antibacterial properties of the marinopyrroles suggest that extensive SAR studies with 1,3′-bipyrroles is warranted, and the present method should provide opportunities for far more extensive structure−activity studies than have hitherto been practicable.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230−400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t, and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under a water pump vacuum and the residue was then kept under an oil pump vacuum. High resolution electrospray mass spectrometry analyses were done on an orthogonal time-of-flight analyzer.

2,5-Dimethyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2,5-dicarboxylate (3a). A solution of **1.2**[12] (529.2 mg, 3.348 mmol) in MeCN (5 mL) was added to a stirred suspension of K_2CO_3 (1.25 g, 8.95 mmol) in a solution of **3**[28] (408.6 mg, 2.231 mmol) in MeCN (25 mL). The mixture was refluxed for 12 h, cooled, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 1:10 EtOAc−hexanes, gave **3a** (621.1 mg, 99%) as a white solid: mp 77−81 °C; FTIR ($CDCl_3$, cast) 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 3.79 (s, 6 H), 4.69 (apparent t, J = 1.5 Hz, 1 H), 5.73 (apparent t, J = 1.5 Hz, 2 H), 6.11 (apparent t, 1 H), 6.93 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.8 (t), 51.6 (q), 51.9 (q), 116.9 (d), 122.9 (t), 127.4 (s), 138.2 (s), 160.6 (s), 165.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{15}NNaO_6$ $(M + Na)^+$ 304.0792, found 304.0788.

2,5-Dimethyl 1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2,5-dicarboxylate (3b). A stream of ozonized oxygen was bubbled through a stirred and cooled (−78 °C) solution of **3a** (1.17 g, 3.15 mmol) in CH_2Cl_2 (20 mL). After 18 min, the solution became blue, and O_2 was then bubbled through the solution for 20 min to remove the excess of O_3. Me_2S (1.80 mL, 24.2 mmol) was then added, the cold bath was removed, and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.8 × 25 cm), using 1:5 to 3:10 EtOAc−hexanes, gave **3b** (625.5 mg, 91%) as a white solid: mp 84−87 °C; FTIR ($CDCl_3$, cast) 1761, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 6 H), 3.94 (s, 3 H), 6.23 (s, 2 H), 6.96 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 53.2 (q), 53.5 (t), 117.0 (d), 127.2 (s), 159.9 (s), 161.2 (s), 186.9 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{13}NNaO_7$ $(M + Na)^+$ 306.0584, found 306.0584.

2,5-Dimethyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2,5-dicarboxylate (3c). NaH (60% w/w in oil, 16.0 mg, 0.400 mmol) was added to a stirred and cooled (−42 °C) solution of **3b** (87.0 mg, 0.307 mmol) in DMF (5 mL). After 20 min, allyl bromide (0.033 mL, 0.38 mmol) was added. The reaction flask was transferred to a single-walled cold bath at −42 °C, and stirring was continued for 2 h, during which time the reaction mixture reached room temperature. Stirring was continued for a further 8 h, saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O and then with EtOAc. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 20 cm),

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using 3:50 to 3:20 EtOAc–hexanes, gave **3c** (87.9 mg, 88%) as a white solid: mp 81–84 °C; FTIR ($CDCl_3$, cast) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 6 H), 3.83 (s, 3 H), 4.17 (apparent dt, J = 7.0, 1.0 Hz, 2 H), 4.98–5.04 (m, 2 H), 5.45–5.55 (m, 1 H), 6.90 (s, 2 H), 7.89 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 52.3 (q), 72.9 (t), 117.0 (d), 118.2 (t), 123.2 (d), 128.8 (s), 132.6 (d), 141.0 (s), 160.5 (s), 163.5 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{17}NNaO_7$ $(M + Na)^+$ 346.0897, found 346.0895. A sample was crystallized from i-Pr_2O for X-ray analysis.

2,5-Dimethyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (3d). A solution of **3c** (427.8 mg, 1.323 mmol) in PhMe (10 mL) was stirred and refluxed for 21.5 h and then cooled to room temperature. Evaporation of the solution gave **3d** as a white solid (427.6 mg, 100%), which was used directly in the next step: mp 100–102 °C; FTIR ($CDCl_3$, cast) 1759, 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.59–2.66 (m, 1 H), 3.19–3.24 (m, 1 H), 3.69 (s, 3 H), 3.83 (s, 6 H), 4.83 (dm, J = 7.0 Hz, 1 H), 4.86 (apparent t, J = 1.0 Hz, 1 H), 5.54–5.63 (m, 1 H), 6.95 (s, 2 H), 7.09 (dd, J = 10.0, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.4 (t), 52.0 (q), 52.7 (q), 62.3 (d), 117.6 (d), 118.5 (t), 127.2 (s), 132.6 (d), 161.5 (s), 161.6 (s), 188.1 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{17}NNaO_7$ $(M + Na)^+$ 346.0897, found 346.089.

2,5-Dimethyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (3e) and 2,5-Dimethyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2,5-dicarboxylate (3f). A stream of ozonized oxygen was bubbled through a stirred and cooled (−78 °C) solution of the above crude keto ester (**3d**) (427.6 mg, 1.323 mmol) in a mixture of MeOH (7 mL) and CH_2Cl_2 (7 mL). After 22 min, the solution became blue and O_2 was then bubbled through the solution for 20 min to remove the excess of O_3. Ph_3P (702 mg, 2.65 mmol) was added, the cooling bath was left in place but not recharged, and stirring was continued for 15 h. Evaporation of the solution gave **3e** as a yellow residue, which was used directly in the next step.

NH_4OAc (1.62 g, 21.0 mmol) was added to a stirred solution of the above crude keto aldehyde **3e** in AcOH (9 mL), and stirring was continued for 30 min. Water was then added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.2 × 25 cm), using 1:5 to 1:2 EtOAc–hexanes, gave **3f** (161.6 mg, 40% over three steps) as a white solid: mp 143–149 °C; FTIR ($CDCl_3$, cast) 3327, 3139, 1736, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.60 (s, 3 H), 3.72 (s, 6 H), 6.29 (apparent t, J = 3.0 Hz, 1 H), 6.92 (apparent t, J = 3.0 Hz, 1 H), 7.02 (s, 2 H), 9.26 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.3 (q), 51.5 (q), 110.6 (d), 116.7 (d), 117.6 (s), 120.5 (d), 128.1 (s), 129.1 (s), 159.8 (s), 160.3 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{14}N_2NaO_6$ $(M + Na)^+$ 329.0744, found 329.0738. A sample was crystallized from $CHCl_3$ for X-ray analysis.

Methyl 5-cyano-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (4a). K_2CO_3 (1.98 g, 14.3 mmol) was added to a stirred solution of **4**[29] (537 mg, 3.58 mmol) and ester **1.2**[12] (647 mg, 4.09 mmol) in MeCN (30 mL). The resulting mixture was stirred and refluxed for 10 h, cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:6 EtOAc–hexane, gave **4a** (870 mg, 98%) as a white solid: mp 77–80 °C; FTIR ($CDCl_3$, cast) 2227, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.83 (s, 3 H), 4.93 (apparent t, J = 2.0 Hz, 1 H), 5.38 (apparent t, J = 2.0 Hz, 2 H), 6.27 (apparent t, J = 2.0 Hz, 1 H), 6.82 (d, J = 4.0 Hz, 1 H), 6.96 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.9 (t), 51.9 (q), 52.2 (q), 110.8 (s), 112.0 (s), 117.5 (d), 118.7 (d), 125.1 (t), 126.7 (s), 136.3 (s), 159.8 (s), 165.1 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{12}N_2NaO_4$ $(M + Na)^+$ 271.0689, found 271.0684.

Methyl 5-cyano-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (4b). A slow stream of ozonized oxygen was bubbled via a Pasteur pipet through a stirred and cooled (−78 °C) solution of **4a** (301 mg, 1.21 mmol) and Sudan Red 7B (1.6 mg) in CH_2Cl_2 (24 mL). When the color changed from red to light yellow, the O_3 flow was stopped and O_2 was bubbled through the solution for 15 min at −78 °C. Me_2S (0.45 mL, 6.1 mmol) was then added. The cold bath was left in place, but not recharged, and stirring was continued for 5 h, during which time the reaction mixture reached room temperature. The mixture was washed with water and brine, and the organic extract was dried ($MgSO_4$) and evaporated to give **4b** (289 mg, 95%) as an almost white solid that was used directly in the next step: mp 100–105 °C; FTIR ($CDCl_3$, cast) 2229, 1761, 1739, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.97 (s, 3 H), 5.70 (s, 2 H), 6.85 (d, J = 4.5 Hz, 1 H), 6.98 (d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (q), 53.5 (q), 54.2 (s), 111.0 (s), 111.8 (s), 117.4 (d), 119.0 (d), 126.5 (s), 159.4 (s), 160.4 (s), 185.1 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{11}N_2O_5$ $(M + H)^+$ 251.0662, found 251.0657.

Methyl 5-cyano-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (4c). A solution of **4b** (780 mg, 3.12 mmol) in DMF (20 mL) was added over 10 min to a stirred and cooled (−40 °C) mixture of NaH (60% w/w in mineral oil, 150 mg, 3.76 mmol) and DMF (16 mL). Stirring at −40 °C was continued for 30 min, and allyl bromide (0.35 mL, 4.13 mmol) was added dropwise over ca. 5 min. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:10 EtOAc–hexane to 1:4 EtOAc–hexane, gave **4c** (740 mg, 82%) as a white solid: mp 72–75 °C; FTIR ($CDCl_3$, cast) 3136, 2231, 1776, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.84 (s, 3 H), 3.87 (s, 3 H), 4.48 (ddd, J = 6.0, 1.0, 1.0 Hz, 2 H), 5.12 (ddd, J = 10.0, 2.5, 1.0 Hz, 1 H), 5.17 (ddd, J = 17.0, 3.0, 1.5 Hz, 1 H), 5.73 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.87 (d, J = 4.0 Hz, 1 H), 6.96 (d, J = 4.0 Hz, 1 H), 7.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (s), 52.6 (s), 110.8 (s), 112.1 (s), 117.3 (d), 118.7 (t), 119.5 (d), 120.0 (d), 127.5 (s), 132.5 (d), 142.9 (s), 159.7 (s), 162.8 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{15}N_2O_5$ $(M + H)^+$ 291.0975, found 291.0976.

Methyl (±)-5-cyano-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (4d). A solution of **4c** (494 mg, 1.70 mmol) in PhMe (17 mL) was refluxed for 18 h, cooled and evaporated to afford **4d** (491 mg, ca. 99%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 2227, 1736, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.72–2.84 (m, 1 H), 3.19–3.25 (m, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 4.97–5.02 (m, 2 H), 5.59–5.67 (m, 1 H), 5.97 (br, 1 H), 6.82 (d, J = 4.5 Hz, 1 H), 6.97 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.6 (t), 52.3 (q), 53.2 (q), 64.4 (d), 111.9 (s), 112.4 (s), 118.3 (d), 119.3 (d), 120.0 (t), 125.9 (s), 131.3 (d), 160.6 (s), 160.8 (s), 186.5 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0788.

Methyl (±)-5-cyano-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (4e) and Methyl 5-cyano-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (4f). A slow stream of ozonized oxygen was bubbled via a Pasteur pipet through a stirred and cooled (−78 °C) solution of **4d** (159 mg, 0.548 mmol) and Sudan Red 7B (1 mg) in CH_2Cl_2 (12 mL). When the color changed from red to light yellow, the O_3 flow was stopped and O_2 was bubbled through the solution for 15 min at −78 °C. Me_2S (0.12 mL, 1.6 mmol) was then added. The cold bath was left in place, but not recharged, and stirring was continued for 14 h, during which time the reaction mixture reached room temperature. The mixture was evaporated directly at ca. 15 °C to give **4e** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (630 mg, 8.18 mmol), the above crude keto aldehyde **4e** in AcOH (6 mL) and a reaction time of 45 min. In this case extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 × 20 cm), using 1:4 to 1:2 EtOAc–hexane, gave **4f** (83.7 mg, 56% over three steps) as a white solid: mp 149–154 °C; FTIR ($CDCl_3$, cast) 3321, 2229, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 3 H),

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3.75 (s, 3 H), 6.36 (dd, J = 3.0, 3.0 Hz, 1 H), 6.88 (d, J = 4.5 Hz, 1 H), 6.92 (dd, J = 3.0, 3.0 Hz, 1 H), 7.01 (d, J = 4.5 Hz, 1 H), 9.55 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.8 (q), 110.2 (d), 112.3 (s), 112.4 (s), 116.9 (d), 117.7 (s), 119.0 (d), 121.2 (d), 125.7 (s), 128.5 (s), 159.5 (s), 159.7 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{11}N_3O_4$ $(M + H)^+$ 274.0822, found 274.0823.

Methyl 4-cyano-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (5a). The method for **4a** was followed, using K_2CO_3 (2.42 g, 17.5 mmol), **5**[29] (659 mg, 4.39 mmol) and **1.2**[12] (763 mg, 4.83 mmol) in MeCN (40 mL). Flash chromatography of the crude product over silica gel (3 × 20 cm), using 1:6 EtOAc–hexane, gave **5a** (1.06 g, 98%) as a white solid: mp 92–95 °C; FTIR ($CDCl_3$, cast) 3129, 2232, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.79 (s, 3 H), 5.20 (apparent t, J = 1.5 Hz, 1 H), 5.43 (apparent t, J = 1.5 Hz, 1 H), 6.29 (s, 2 H), 7.16 (d, J = 2.0 Hz, 1 H), 7.37 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.4 (t), 51.7 (q), 52.2 (q), 93.3 (s), 115.0 (s), 120.8 (d), 123.2 (t), 127.7 (s), 134.3 (d), 136.1 (s), 160.0 (s), 165.5 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{13}N_2O_4$ $(M + H)^+$ 249.0870, found 249.0872.

Methyl 4-cyano-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (5b). The method for **4b** was followed, using **5a** (750 mg, 3.02 mmol), Sudan Red 7B (2 mg) in CH_2Cl_2 (30 mL) and Me_2S (1.33 mL, 18.1 mmol), with a reduction period of 4 h. Evaporation of the organic extract gave **5b** (701 mg, 93%) as an almost white solid that was used directly in the next step: mp 114–115 °C; FTIR ($CDCl_3$, cast) 3133, 2233, 1759, 1738, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 3 H), 3.97 (s, 3 H), 5.53 (s, 2 H), 7.23 (AB q, J = 1.74 Hz, $\Delta\nu_{AB}$ = 1.73 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.0 (q), 53.6 (q), 56.0 (t), 94.2 (s), 114.6 (s), 120.6 (d), 123.1 (s), 134.1 (d), 159.7 (s), 160.6 (s), 185.2 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{10}N_2NaO_5$ $(M + Na)^+$ 273.0482, found 273.0483.

Methyl 4-cyano-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (5c). A solution of **5b** (137 mg, 0.55 mmol) in DMF (5 mL) was added over 10 min to a stirred mixture of K_2CO_3 (77 mg, 0.55 mmol), allyl bromide (0.19 mL, 2.2 mmol) and DMF (10 mL), and stirring was continued for 5 h. The reaction mixture was diluted with water and extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:10 EtOAc–hexane to 1:5 EtOAc–hexane, gave **5c** (98.1 mg, 58%) as a white solid: mp 107–110 °C; FTIR ($CDCl_3$, cast) 3137, 2235, 1724 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 3.27 (s, 3 H), 3.28 (s, 3 H), 4.22 (ddd, J = 6.0, 1.5, 1.0 Hz, 2 H), 4.86 (ddd, J = 10.5, 2.5, 1.0 Hz, 1 H), 4.96 (ddd, J = 17.0, 2.5, 1.5 Hz, 1 H), 5.54 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.73 (d, J = 1.5 Hz, 1 H), 8.04 (d, J = 1.5 Hz, 1 H), 8.56 (s, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 50.9 (q), 51.4 (q), 72.7 (t), 95.8 (s), 114.1 (s), 119.1 (t), 119.7 (d), 120.5 (d), 123.5 (s), 132.3 (d), 133.1 (d), 136.2 (s), 163.0 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0792.

Methyl (±)-4-cyano-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (5d). A solution of **5c** (370 mg, 1.28 mmol) in PhMe (12 mL) was refluxed for 20 h, cooled and evaporated to afford **5d** (367 mg, ca. 99%) as a thick, light yellow oil that was pure enough for use directly in the next step: FTIR ($CDCl_3$, cast) 2233, 1739, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.70–2.77 (m, 1 H), 3.01–3.07 (m, 1 H), 3.81 (s, 1 H), 3.92 (s, 3 H), 5.15 (ddd, J = 7.0, 2.5, 1.0 Hz, 1 H), 5.17 (apparent t, J = 2.0 Hz, 1 H), 5.67–5.75 (m, 1 H), 6.47 (dd, J = 10.0, 4.5 Hz, 1 H), 7.20 (d, J = 2.0 Hz, 1 H), 7.46 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.2 (t), 52.1 (q), 53.5 (q), 62.4 (d), 94.1 (s), 114.8 (s), 120.2 (t), 120.9 (d), 123.1 (s), 130.8 (d), 132.2 (d), 160.0 (s), 160.7 (s), 187.8 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0794.

Methyl (±)-4-cyano-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (5e) and Methyl 4-cyano-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (5f). The procedure for **4e** was followed, using, **5d** (117 mg, 0.403 mmol), Sudan Red 7B (0.5 mg) in CH_2Cl_2 (20 mL), Me_2S (0.18 mL, 2.5 mmol) and an overnight reduction period. The mixture was evaporated directly at ca. 15 °C to give **5e** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (500 mg, 6.49 mmol), the above crude keto aldehyde **5e** in AcOH (8 mL) and a reaction time of 3.5 h. In this case extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 × 20 cm), using 1:1 EtOAc–hexane, gave **5f** (72.3 mg, 65% over three steps) as a white solid: mp 159–165 °C; FTIR ($CDCl_3$, cast) 3320, 3133, 2234, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.73 (s, 3 H), 6.31 (apparent t, J = 3.0 Hz, 1 H), 6.95 (apparent t, J = 3.0 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H), 9.25 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.7 (q), 93.8 (s), 109.8 (d), 115.1 (s), 117.3 (s), 119.8 (d), 120.9 (d), 125.5 (s), 127.5 (s), 135.1 (d), 159.6 (s), 159.7 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{11}N_3NaO_4$ $(M + Na)^+$ 296.0642, found 296.0638.

Methyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-5-nitro-1*H*-pyrrole-2-carboxylate (6a). Na_2CO_3 (242 mg, 2.28 mmol) was added to a stirred solution of **6**[30] (195 mg, 1.14 mmol), 18-crown-6 (300 mg, 1.14 mmol) and ester **1.2**[12] (202 mg, 1.28 mmol) in MeCN (12 mL). The resulting mixture was stirred and refluxed for 36 h, cooled to room temperature, diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:6 EtOAc–hexane, gave **6a** (240 mg, 78 or 99% corrected for recovered **6**) as a colorless oil: FTIR ($CDCl_3$, cast) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.86 (s, 3 H), 4.98 (apparent t, J = 1.5 Hz, 1 H), 5.78 (apparent t, J = 1.5 Hz, 2 H), 6.21 (apparent t, J = 1.5 Hz, 1 H), 6.96 (d, J = 4.5 Hz, 1 H), 7.19 (d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3 (t), 52.1 (q), 52.2 (q), 112.7 (d), 116.2 (d), 124.5 (t), 126.8 (s), 136.5 (s), 140.7 (s), 160.1 (s), 165.2 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{12}N_2NaO_6$ $(M + Na)^+$ 291.0588, found 291.0581.

The aqueous layer was acidified with 1.0 M hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **6** (41.9 mg).

Methyl 1-(3-methoxy-2,3-dioxopropyl)-5-nitro-1*H*-pyrrole-2-carboxylate (6b). The method for **4b** was followed, using **6a** (309 mg, 1.15 mmol), Sudan Red 7B (1 mg) in CH_2Cl_2 (20 mL) and Me_2S (0.5 mL, 7 mmol) and a reduction period of 6 h. In this case, flash chromatography of the crude product over silica gel (2 × 20 cm), using 1:3 EtOAc–hexane, gave **6b** (280 mg, 90%) as a white solid: mp 121–123 °C; FTIR ($CDCl_3$, cast) 1761, 1738, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.86 (s, 3 H), 3.98 (s, 3 H), 6.29 (s, 2 H), 7.00 (d, J = 4.5 Hz, 1 H), 7.25 (d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.4 (q), 53.5 (q), 54.0 (t), 113.0 (d), 116.4 (d), 126.4 (s), 140.5 (s), 159.4 (s), 160.2 (s), 185.6 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{10}N_2NaO_7$ $(M + Na)^+$ 293.0380, found 93.0377.

Methyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-5-nitro-1*H*-pyrrole-2-carboxylate (6c). The method for **5c** was followed, using **6b** (249 mg, 0.922 mmol) in DMF (2 mL), and an addition time of ca. 2 min, allyl bromide (0.16 mL, 1.9 mmol), K_2CO_3 (150 mg, 1.09 mmol) and DMF (10 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (2 × 15 cm), using 1:2 EtOAc–hexane, gave **6c** (206 mg, 72%) as a white solid: mp 52–55 °C; FTIR ($CDCl_3$, cast) 3140, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.847 (s, 3 H), 3.863 (s, 3 H), 4.27 (ddd, J = 6.0, 1.0, 1.0 Hz, 2 H), 5.01–5.03 (m, 1 H), 5.04–5.06 (m, 1 H), 5.50 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.93 (d, J = 4.5 Hz, 1 H), 7.12 (d, J = 4.5 Hz, 1 H), 7.73 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.3 (q), 52.5 (q), 73.0 (t), 112.3 (d), 116.0 (d), 119.0 (t), 127.8 (s), 132.1 (d), 141.2 (s), 142.3 (s), 159.7 (s), 162.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0686.

Methyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-5-nitro-1*H*-pyrrole-2-carboxylate (6d). A solution of **6c** (320 mg, 1.03 mmol) in PhMe (10.3 mL) was refluxed for 36 h, cooled and evaporated to afford **6d** (317 mg, ca. 99%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.59–2.66 (m, 1 H), 3.25–3.30 (m, 1 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 4.86–4.92 (m, 2 H), 5.57–5.65 (m, 1 H), 6.99 (d, J = 5.0 Hz, 1 H), 7.11 (dd, J = 10.0, 4.5 Hz, 1 H), 7.21 (d, J = 4.5 Hz, 1 H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 35.1 (t), 52.6 (q), 53.1 (q), 62.9 (d), 113.8 (d), 116.9 (d), 119.6 (t), 126.8 (s), 131.6 (d), 140.3 (s), 161.0 (s), 161.1 (s), 186.2 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0686.

Methyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-5-nitro-1*H*-pyrrole-2-carboxylate (6e) and Methyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-5-nitro-1*H*-pyrrole-2-carboxylate (6f). The method for **4e** was followed, using **6d** (95.6 mg, 0.308 mmol), Sudan Red 7B (0.2 mg) in CH_2Cl_2 (10 mL), Me_2S (0.10 mL, 1.4 mmol) and a reduction period of 6 h. The mixture was evaporated directly at ca. 15 °C to give **6e** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (360 mg, 4.68 mmol), the above crude keto aldehyde **6e** in AcOH (6 mL) and a reaction time of 3.5 h. (The addition of NH_4OAc was made within ca. 2 min of dissolving the keto aldehyde in AcOH.) In this case extraction was done with EtOAc. Flash chromatography of the crude reaction product over silica gel (1 × 15 cm), using 1:3 EtOAc–hexane to 1:2 EtOAc–hexane, gave **6f** (52.2 mg, 58% over three steps) as a white solid: mp 127–132 °C; FTIR ($CDCl_3$, cast) 3332, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 125 MHz) δ 3.63 (s, 3 H), 3.75 (s, 3 H), 6.35 (apparent t, J = 3.0 Hz, 1 H), 6.98 (apparent t, J = 3.0 Hz, 1 H), 7.02 (d, J = 4.5 Hz, 1 H), 7.24 (d, J = 4.5 Hz, 1 H), 9.32 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 52.0 (q), 110.6 (d), 112.1 (d), 116.0 (d), 117.6 (s), 121.0 (d), 125.7 (s), 128.1 (s), 141.4 (s), 159.5 (s), 159.6 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{11}N_3NaO_6$ $(M + Na)^+$ 316.0540, found 316.0533.

Methyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-4-nitro-1*H*-pyrrole-2-carboxylate (7a). The method for **4a** was followed, using K_2CO_3 (1.98 g, 14.3 mmol), **7**[31] (610 mg, 3.59 mmol) and ester **1.2**[12] (630 mg, 3.99 mmol) in MeCN (36 mL), and a reflux period of 22 h. Flash chromatography of the crude product over silica gel (3 × 20 cm), using 1:6 EtOAc–hexane, gave **7a** (960 mg, 100%) as a white solid: mp 100–103 °C; FTIR ($CDCl_3$, cast) 3137, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3 H), 3.84 (s, 3 H), 5.25 (s, 2 H), 5.58 (s, 1 H), 6.37 (s, 1 H), 7.44 (d, J = 2.0 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.7 (t), 51.9 (q), 52.3 (q), 113.2 (d), 122.2 (t), 127.7 (d), 128.3 (s), 135.7 (s), 135.8 (s), 160.2 (s), 165.4 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{12}N_2NaO_6$ $(M + Na)^+$ 291.0588, found 291.0584.

Methyl 1-(3-methoxy-2,3-dioxopropyl)-4-nitro-1*H*-pyrrole-2-carboxylate (7b). The method for **4b** was followed, using **7a** (960 mg, 3.58 mmol), Sudan Red 7B (1 mg) in CH_2Cl_2 (48 mL) and Me_2S (0.7 mL, 10 mmol), with a reduction period of 6 h. In this case, flash chromatography of the crude product over silica gel (3 × 15 cm), using 1:2 EtOAc–hexane, gave **7b** (940 mg, 97%) as a white solid: mp 118–121 °C; FTIR ($CDCl_3$, cast) 3140, 1759, 1738, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.97 (s, 3 H), 5.56 (s, 2 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.61 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.2 (q), 53.6 (q), 56.3 (t), 113.0 (d), 122.2 (s), 127.7 (d), 136.2 (s), 159.6 (s), 160.7 (s), 185.0 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{10}N_2NaO_7$ $(M + Na)^+$ 293.0830, found 293.0830.

Methyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-4-nitro-1*H*-pyrrole-2-carboxylate (7c). A solution of **7b** (199 mg, 0.737 mmol) in DMF (5 mL) was added over 10 min to a stirred mixture of K_2CO_3 (102 mg, 0.739 mmol), allyl bromide (0.60 mL, 7.1 mmol), 18-crown-6 (195 mg, 0.739 mmol) and DMF (10 mL). Stirring was continued, and the progress of the reaction was monitored by TLC every 10 min. When all of **7b** had been consumed (ca. 45 min), the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Crystallization of the residue from Et_2O gave **7c** (137 mg, 60%) as a white solid: mp 107–110 °C; FTIR ($CDCl_3$, cast) 3142, 1724 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.25 (s, 3 H), 3.27 (s, 3 H), 4.26 (ddd, J = 6.0, 1.5, 1.0 Hz, 2 H), 4.92 (ddd, J = 10.5, 2.5, 1.0 Hz, 1 H), 5.04 (ddd, J = 17.0, 2.5, 1.5 Hz, 1 H), 5.63 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 7.28 (d, J = 2.0 Hz, 1 H), 8.51 (dd, J = 2.0, 0.5 Hz, 1 H), 8.60 (d, J = 0.5 Hz, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 51.0 (q), 51.4 (q), 72.8 (t), 113.2 (d), 119.2 (d), 119.3 (t), 122.4 (s), 126.4 (d), 132.2 (d), 136.7 (s), 137.2 (s), 159.7 (s), 162.8 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{15}N_2O_7$ $(M + H)^+$ 311.0874, found 311.0871.

Compound **7c** is sensitive to silica gel and acidic solvents ($CDCl_3$), and it rearranges to a significant extent within several h in solution ($CDCl_3$) at room temperature.

Methyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-4-nitro-1*H*-pyrrole-2-carboxylate (7d). A solution of **7c** (110 mg, 0.355 mmol) in PhMe (3.6 mL) was refluxed for an arbitrary period of 24 h, cooled and evaporated to afford **7d** (110.1 mg, ca. 100%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 3148, 1739, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.74–2.81 (m, 1 H), 3.05–3.11 (m, 1 H), 3.83 (s, 3 H), 3.94 (s, 3 H), 5.19 (apparent t, J = 1.5 Hz, 1 H), 5.22 (ddd, J = 7.0, 2.5, 1.0 Hz, 1 H), 5.72–5.80 (m, 1 H), 6.50 (dd, J = 10.0, 4.5 Hz, 1 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.83 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.1 (t), 52.2 (q), 53.6 (q), 62.5 (d), 113.4 (d), 120.5 (t), 122.2 (s), 125.7 (d), 130.6 (d), 136.3 (s), 159.9 (s), 160.9 (s), 187.5 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0685.

Methyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-4-nitro-1*H*-pyrrole-2-carboxylate (7e) and Methyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxylate (7f). The method for **4e** was followed, using **7d** (73.3 mg, 0.236 mmol), Sudan Red 7B (0.2 mg) in CH_2Cl_2 (6 mL), Me_2S (0.10 mL, 1.4 mmol) and a reduction period of 12 h. The mixture was evaporated directly at ca. 15 °C to give **7e** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (180 mg, 2.34 mmol), the above crude keto aldehyde **7e** in AcOH (2 mL) and a reaction time of 3 h. In this case the extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 × 15 cm), using 1:1 EtOAc–hexane, gave **7f** (46.9 mg, 68% over three steps) as a white solid: mp 168–170 °C; FTIR ($CDCl_3$, cast) 3327, 3142, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.76 (s, 3 H), 6.33 (apparent t, J = 3.0 Hz, 1 H), 6.94 (apparent t, J = 3.0 Hz, 1 H), 7.51 (d, J = 2.0 Hz, 1 H), 7.69 (d, J = 2.0 Hz, 1 H), 9.54 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 51.9 (q), 109.5 (d), 112.3 (d), 117.3 (s), 121.2 (d), 124.6 (s), 127.2 (s), 128.6 (d), 136.3 (s), 159.7 (s), 159.8 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{11}N_3NaO_6$ $(M + Na)^+$ 316.0540, found 316.0533.

Methyl 4,5-dichloro-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (8a). The method for **3a** was followed, using **1.2**[12] (515.9 mg, 3.264 mmol) in MeCN (5 mL), K_2CO_3 (1.22 g, 8.74 mmol) and **8**[11,32] (422 mg, 2.18 mmol) in MeCN (15 mL), and a reflux period of 38 h. Flash chromatography of the crude product over silica gel (2.8 × 20 cm), using first hexane and then 2:25 EtOAc–hexane, gave **8a** (618.7 mg, 97%) as a white solid: mp 76–79 °C; FTIR ($CDCl_3$, cast) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3 H), 3.80 (s, 3 H), 4.82 (apparent t, J = 2.0 Hz, 1 H), 5.28 (apparent t, J = 2.0 Hz, 2 H), 6.20 (apparent t, J = 2.0 Hz, 1 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.3 (t), 51.5 (q), 52.1 (q), 110.5 (s), 116.8 (d), 120.5 (s), 121.8 (s), 124.2 (t), 136.0 (s), 159.6 (s), 165.3 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{11}Cl_2NNaO_4$ $(M + Na)^+$ 313.9957, found 313.9951.

Methyl 4,5-dichloro-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (8b). NMO (921 mg, 7.63 mmol) and OsO_4 (0.1 M in PhMe, 4.24 mL, 0.42 mmol) were added successively to a stirred solution of **8a** (619 mg, 2.12 mmol) in a mixture of THF (11 mL) and water (11 mL) (protected from light). After 19 h, the reaction mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$) and evaporated to give a yellow residue. A solution of $Pb(OAc)_4$ (1.22 g, 2.61 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of the yellow residue in CH_2Cl_2 (15 mL), and stirring was continued for 20 min in subdued light. The mixture was then filtered through a pad of silica gel, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.8 × 25 cm), using 1:10 to 1:5 EtOAc–hexanes, gave **8b** (538.2 mg, 86%) as a white solid: mp 63–67 °C; FTIR ($CDCl_3$, cast) 3137, 1762, 1738, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.94 (s, 3 H), 5.63 (s, 2 H), 6.96 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

51.7 (q), 52.7 (t), 53.4 (q), 110.9 (s), 116.9 (d), 120.5 (s), 121.9 (s), 159.7 (s), 160.3 (s), 185.5 (s); exact mass (electrospray) m/z calcd for $C_{10}H_9Cl_2NNaO_5$ $(M + Na)^+$ 315.9750, found 315.9745.

Methyl 4,5-dichloro-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (8c). NaH (12.7 mg, 60% w/w in oil, 0.322 mmol) was added to a stirred and cooled (−42 °C) solution of **8b** (71.8 mg, 0.244 mmol) in DMF (5 mL). After 20 min, allyl bromide (0.026 mL, 0.30 mmol) was added. The cold bath was left in place but not recharged, and stirring was continued for 1.5 h, during which time the reaction mixture reached room temperature. Stirring was continued for a further 6.5 h, water was then added, and the mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 × 15 cm), using 1:25 to 1:10 EtOAc−hexanes, gave **8c** (59.5 mg, 73%) as a colorless oil: FTIR ($CDCl_3$, cast) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.86 (s, 3 H), 4.31 (ddd, J = 6.0, 1.5, 1.5 Hz, 2 H), 5.08−5.15 (m, 2 H), 5.68 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.95 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7 (q), 52.6 (q), 72.9 (t), 111.8 (s), 117.0 (d), 118.6 (t), 119.2 (d), 121.8 (s), 122.0 (s), 132.4 (d), 143.5 (s), 159.6 (s), 163.0 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{13}Cl_2NNaO_5$ $(M + Na)^+$ 356.0063, found 356.0057.

Methyl (±)-4,5-dichloro-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (8d). A solution of **8c** (257.6 mg, 0.7709 mmol) in PhMe (8 mL) was stirred and refluxed for 20 h and then cooled to room temperature. Evaporation of the solution gave **8d** as a light yellow solid (257.6 mg, 100%), which was used directly in the next step: mp 92−96 °C; (crude) FTIR ($CDCl_3$, cast) 3136, 1735, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.66−2.73 (m, 1 H), 3.11−3.16 (m, 1 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.94−4.98 (m, 2 H), 5.23−5.61 (m, 1 H), 5.94 (br, 1 H), 6.96 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.4 (t), 51.9 (q), 53.0 (q), 62.9 (d), 111.3 (s), 117.9 (d), 119.5 (t), 120.2 (s), 131.7 (d), 160.4 (s), 161.3 (s), 187.4 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{13}Cl_2NNaO_5$ $(M + Na)^+$ 356.0063, found 356.0058.

Methyl (±)-4,5-dichloro-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (8e) and Methyl 4,5-dichloro-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (8f). NMO (580 mg, 4.96 mmol) and OsO_4 (0.05 M in PhMe, 2.8 mL, 0.14 mmol) were added to a stirred solution of **8d** (471 mg, 1.41 mmol) in 1:1 THF−water (16 mL) (protected from light). The yellow mixture was stirred for 6 h, quenched with aqueous $NaHSO_3$ (10% w/v) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford a pale yellow residue (260 mg, 50%). $Pb(OAc)_4$ (320 mg, 0.722 mmol) was added to a stirred and cooled (0 °C) solution of the residue in MeCN (10 mL) and stirring at 0 °C was continued. When all the starting material had reacted (ca. 5 min, TLC control, silica, 1:1 EtOAc−hexane), pinacol solution (0.05 M in MeCN, several drops) was added dropwise. When the excess of $Pb(OAc)_4$ had reacted (ca. 2 min, TLC control, silica, 1:1 EtOAc−hexane), the mixture was diluted with EtOAc and filtered while still cold through a sintered disc. The organic layer was evaporated at 10 °C to give **8e** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (540 mg, 7.01 mmol), the above crude keto aldehyde **8e** in AcOH (8 mL) and a reaction time of 3.5 h. In this case the extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (2 × 15 cm), using 1:3 EtOAc−hexane, gave **8f** (107 mg, 24% over three steps) as a white solid: mp 161−165 °C; FTIR ($CDCl_3$, cast) 3308, 3137, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.71 (s, 3 H), 6.29 (apparent t, J = 3.5 Hz, 1 H), 6.98 (apparent t, J = 3.5 Hz, 1 H), 7.01 (s, 1 H), 9.26 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4 (q), 51.7 (q), 110.7 (s), 110.9 (d), 116.6 (d), 118.3 (s), 120.9 (d), 122.6 (s), 123.0 (s), 125.6 (s), 159.4 (s), 159.7 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{10}Cl_2N_2NaO_4$ $(M + Na)^+$ 338.9910, found 338.9908.

Methyl 4,5-diiodo-1*H*-pyrrole-2-carboxylate (9). MeONa (167 mg, 3.09 mmol) was added to a stirred and cooled (0 °C) solution of 2,2,2-trichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethan-1-one[13,14] (1.20 g, 2.58 mmol) in MeOH (26 mL). The cold bath was left in place but not recharged, and stirring was continued for 2 h, during which time the reaction mixture reached room temperature. The mixture was evaporated directly, and the residue was acidified with dilute hydrochloric acid (1.0 M) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm), using 1:5 EtOAc−hexane, gave **9** (943 mg, 96%) as a white solid: mp 200−204 °C; FTIR ($CDCl_3$, cast) 3235, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.89 (s, 3 H), 6.93 (d, J = 3.0 Hz, 1 H), 9.83 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (q), 77.0 (s), 83.3 (s), 123.1 (d), 128.7 (s), 159.7 (s); exact mass (electrospray) m/z calcd for $C_6H_5I_2NNaO_2$ $(M + Na)^+$ 399.8302, found 399.8301.

Methyl 4,5-diiodo-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (9a). The procedure for **4a** was followed, using K_2CO_3 (790 mg, 5.72 mmol), **9** (1.08 g, 2.87 mmol) and ester **1.2**[12] (480 mg, 3.04 mmol) in MeCN (29 mL). At the end of the reaction the extraction was done with Et_2O. Flash chromatography of the crude product over silica gel (3 × 20 cm), using 1:5 EtOAc−hexane, gave **9a** (1.30 g, 96%) as a white solid: mp 101−104 °C; FTIR ($CDCl_3$, cast) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 3.82 (s, 3 H), 4.73 (apparent t, J = 2.0 Hz, 1 H), 5.39 (apparent t, 2 H), 6.22 (apparent t, J = 2.0 Hz, 1 H), 7.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 52.1 (t), 52.2 (q), 76.4 (s), 94.5 (s), 124.5 (t), 126.0 (d), 127.5 (s), 136.2 (s), 159.1 (s), 165.4 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{11}I_2NNaO_4$ $(M + Na)^+$ 497.8670, found 497.8661.

Methyl 4,5-diiodo-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (9b). NMO (260 mg, 2.22 mmol) and OsO_4 (0.05 M in PhMe, 1.2 mL, 0.06 mmol) were added to a stirred solution of **9a** (300 mg, 0.632 mmol) in 1:1 THF−water (7 mL) (protected from light). The yellow mixture was stirred for 36 h and then quenched with aqueous $NaHSO_3$ (10% w/v). The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. $Pb(OAc)_4$ (310 mg, 0.699 mmol) was added to a stirred and cooled (0 °C) solution of the residue in MeCN (7 mL) and stirring at 0 °C was continued. The reaction was monitored by TLC (silica, 1:1 EtOAc−hexane) and, when all **9a** had been consumed (ca. 5 min), pinacol (8.3 mg, 0.070 mmol) was added. Stirring was continued for ca. 2 min, and the mixture was diluted with EtOAc and filtered through a sintered disc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc−hexane, gave **9b** (290 mg, 96%) as a white solid: mp 95−98 °C; FTIR ($CDCl_3$, cast) 1758, 1736, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.97 (s, 3 H), 5.76 (s, 2 H), 7.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 53.4 (q), 58.7 (t), 76.6 (s), 95.2 (s), 125.9 (d), 127.4 (s), 159.7 (s), 159.8 (s), 185.8 (s); exact mass (electrospray) m/z calcd for $C_{10}H_9I_2NNaO_5$ $(M + Na)^+$ 499.8462, found 499.8461.

Methyl 4,5-diiodo-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (9c). The method for **8c** was followed, using NaH (60% w/w in mineral oil, 26.2 mg, 0.655 mmol), a reaction temperature of −40 °C, **9b** (260 mg, 0.545 mmol), DMF (10 mL), a stirring period of 30 min, allyl bromide (0.06 mL, 0.7 mmol), and a final stirring period of 12 h. In this case the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. Flash chromatography of the crude product over silica gel (2 × 15 cm), using 1:6 EtOAc−hexane), gave **9c** (227 mg, 81%) as a thick, colorless oil: FTIR ($CDCl_3$, cast) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.88 (s, 3 H), 4.26 (ddd, J = 6.0, 1.5, 1.5 Hz, 2 H), 5.09 (ddd, J = 4.5, 3.0, 1.5 Hz, 1 H), 5.12 (ddd, J = 6.0, 3.0, 1.5 Hz, 1 H), 5.65 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 7.14 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7 (q), 52.6 (q), 72.9 (t), 77.6 (s), 92.8 (s), 118.6 (t), 123.2 (d), 125.6 (d), 129.5 (s), 132.5 (d), 143.5 (s), 158.9 (s), 163.1 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{13}I_2NNaO_5$ $(M + Na)^+$ 539.8775, found 539.8776.

Methyl (±)-4,5-diiodo-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (9d). A solution of **9c** (210 mg, 0.406 mmol) in PhMe (4.1 mL) was refluxed for 42 h in the dark, cooled and evaporated to afford **9d** (208.2 mg, ca. 99%) as a brown solid: FTIR ($CDCl_3$, cast) 1732, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.69−2.76 (m, 1 H), 3.14−3.19 (m, 1 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 4.95−4.99 (m, 2 H), 5.58−5.67 (m, 1 H), 5.72 (br, 1 H), 7.23 (s, 1 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 35.0 (t), 52.0 (q), 53.0 (q), 118.6 (s), 119.4 (t), 127.1 (d), 131.9 (d), 132.5 (d), 159.8 (s), 161.5 (s), 187.6 (s), other expected signals were not observed; exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{13}I_2NNaO_5$ $(M + Na)^+$ 539.8775, found 539.8776. Compound **9d** is sensitive to light.

Methyl (±)-4,5-diiodo-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (9e) and Methyl 4,5-diiodo-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (9f). The method for **8f** was followed, using NMO (160 mg, 1.37 mmol) and OsO_4 (0.05 M in PhMe, 0.8 mL, 0.04 mmol), **9d** (210 mg, 0.406 mmol) in 1:1 THF−water (4 mL) (protected from light). The yellow mixture was stirred for 6 h and then quenched with aqueous $NaHSO_3$ (10% w/v). $Pb(OAc)_4$ (180 mg, 0.406 mmol) was added to a stirred and cooled (0 °C) solution of the crude product, which is sensitive to light, in MeCN (5 mL). The reaction was monitored by TLC (silica, 1:1 EtOAc−hexane) and when all of the diol had been consumed (ca. 5 min), pinacol solution (0.05 M in MeCN, 5 drops) was added dropwise. When the excess of $Pb(OAc)_4$ had reacted (ca. 2 min), the mixture was diluted with EtOAc, and the cold reaction mixture was filtered through a sintered disc. The organic layer was quickly washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated at 15 °C to give **9e** as a thick, yellow oil, which is sensitive to light and was used immediately, as follows.

With the exception that the reaction flask was protected from light, the method for **3f** was followed, using NH_4OAc (460 mg, 5.98 mmol), the above crude keto aldehyde **9e** in AcOH (4 mL) and a reaction time of 5 h (protected from light). In this case the extraction was done with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the crude product over silica gel (1 × 20 cm), using 1:3 EtOAc−hexane, gave **9f** (60.7 mg, 30% over three steps) as a white solid: mp 177−182 °C; FTIR ($CDCl_3$, cast) 3308, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 3 H), 3.69 (s, 3 H), 6.24 (apparent t, *J* = 3.0 Hz, 1 H), 6.98 (apparent t, *J* = 3.0 Hz, 1 H), 7.22 (s, 1 H), 9.25 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4 (q), 51.7 (q), 76.0 (s), 96.6 (s), 111.0 (d), 118.3 (s), 120.8 (d), 125.4 (d), 129.5 (s), 130.1 (s), 158.8 (s), 159.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{10}I_2N_2NaO_4$ $(M + Na)^+$ 522.8622, found 522.8622.

Methyl 2-[(2,5-dimethyl-1*H*-pyrrol-1-yl)methyl]prop-2-enoate (10a). NaH (60% w/w in mineral oil 34.0 mg, 0.850 mmol) was added to a cold (0 °C) and stirred solution of **10**[33] (freshly distilled, 74 mg, 0.78 mmol) in DMF (2 mL) (N_2 atmosphere, exclusion of oxygen is important). The cold bath was left in place but not recharged, and stirring was continued for 1 h. Ester **1.2**[12] (123 mg, 0.778 mmol) in DMF (2 mL) was added at a fast dropwise rate, and stirring was continued for 24 h. The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 12 cm), using 1:10 EtOAc−hexane, gave **10a** (87.0 mg, 58%) as a colorless oil: FTIR ($CDCl_3$, cast) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.16 (s, 6 H), 3.86 (s, 3 H), 4.63 (apparent t, *J* = 2.0 Hz, 2 H), 4.79 (apparent td, *J* = 2.0, 1.0 Hz, 1 H), 5.85 (s, 2 H), 6.23 (apparent td, *J* = 2.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (q), 43.7 (t), 52.0 (q), 105.6 (d), 125.0 (t), 127.6 (s), 137.2 (s), 166.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.1176, found 194.1176.

Methyl (±)-2-{[(*tert*-butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}prop-2-enoate (2.2). Imidazole (1.55 g, 22.5 mmol) and *t*-$BuMe_2SiCl$ (2.08 g, 13.5 mmol) were added successively to a stirred solution of **2.1**[21] (2.00 g, 9.01 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 5 h, and the mixture was then quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 × 20 cm), using 3:50 EtOAc−hexanes, gave **2.2** (2.92 g, 96%) as a colorless oil: FTIR ($CDCl_3$, cast) 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.07 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 3.72 (s, 3 H), 3.85 (s, 3 H), 5.85 (t, *J* = 2.0 Hz, 1 H), 6.09 (s, 1 H), 6.25−6.26 (m, 1 H), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.95 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.23−7.27 (m, 1 H), 7.39 (dd, *J* = 7.5, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.1 (q), −5.0 (q), 18.2 (s), 25.8 (q), 51.6 (q), 55.4 (q), 66.1 (d), 110.4 (d), 120.4 (d), 124.5 (t), 127.9 (d), 128.4 (d), 131.0 (s), 143.9 (s), 156.2 (s), 166.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{28}NaO_4Si$ $(M + Na)^+$ 359.1649, found 359.1650.

(±)-2-{[(*tert*-Butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}prop-2-en-1-ol (2.3). DIBAL-H (1.0 M in PhMe, 22 mL, 22 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **2.2** (2.92 g, 8.69 mmol) in CH_2Cl_2 (40 mL). Stirring at −78 °C was continued for 2.5 h and then MeOH (2.0 mL) was added. The cooling bath was removed and a saturated aqueous solution of Rochelle's salt (ca. 100 mL) was added. Stirring was continued for 4 h, and the mixture was then extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 × 20 cm), using 1:10 to 3:25 EtOAc−hexanes, gave **2.3** (2.46 g, 92%) as a colorless oil: FTIR ($CDCl_3$, cast) 3374 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.06 (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 2.34 (br, 1 H), 3.85 (s, 3 H), 3.98−4.02 (m, 1 H), 4.13 (d, *J* = 13.5 Hz, 1 H), 5.09−5.11 (m, 1 H), 5.21−5.22 (m, 1 H), 5.78 (s, 1 H), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.98−7.02 (m, 1 H), 7.23−7.27 (m, 1 H), 7.52 (dd, *J* = 8.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.2 (q), −5.0 (q), 18.2 (s), 25.8 (q), 55.4 (q), 63.8 (t), 70.2 (d), 110.3 (d), 111.6 (t), 120.8 (d), 127.5 (d), 128.3 (d), 131.1 (s), 149.6 (s), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{28}NaO_3Si$ $(M + Na)^+$ 331.1700, found 331.1696.

(±)-2-{[(*tert*-Butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}prop-2-en-1-yl acetate (2.4). Pyridine (1.30 mL, 16.1 mmol) and AcCl (0.93 mL, 12.8 mmol) were added successively to a stirred and cooled (0 °C) solution of **2.3** (2.00 g, 9.01 mmol) in CH_2Cl_2 (40 mL). After 40 min, the mixture was quenched with saturated aqueous $NaHCO_3$ and washed with saturated aqueous $CuSO_4$, water and brine. The organic solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 × 20 cm), using 3:50 EtOAc−hexanes, gave **2.4** (2.76 g, 99%) as a colorless oil: FTIR ($CDCl_3$, cast) 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.10 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.98 (s, 3 H), 3.80 (s, 3 H), 4.49 (AB q, *J* = 13.5 Hz, $\Delta\nu_{AB}$ = 9.6 Hz, 2 H), 5.11−5.12 (m, 1 H), 5.31−5.32 (m, 1 H), 5.69 (s, 1 H), 6.82 (dd, *J* = 8.5, 1.0 Hz, 1 H), 6.94 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.21 (ddd, *J* = 8.3, 7.3, 2.0 Hz, 1 H), 7.44 (dd, *J* = 7.5, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.2 (q), −5.1 (q), 18.2 (s), 20.8 (q), 25.8 (q), 55.3 (q), 63.9 (t), 68.6 (d), 110.2 (d), 112.3 (t), 120.6 (d), 127.6 (d), 128.2 (d), 131.0 (s), 145.9 (s), 155.9 (s), 170.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{30}NaO_4Si$ $(M + Na)^+$ 373.1806, found 373.1806.

(±)-3-Hydroxy-3-(2-methoxyphenyl)-2-methylidenepropyl acetate (2.5) and (±)-3-Hydroxy-1-(2-methoxyphenyl)-2-methylidenepropyl acetate (2.6). Bu_4NF (1.0 M in THF, 3.8 mL, 3.8 mmol) was added dropwise to a stirred solution of **2.4** (1.33 g, 3.79 mmol) in THF (40 mL). Stirring was continued for 3.5 h, and the mixture was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 3:20 to 3:10 EtOAc−hexanes, gave **2.5** (646.2 mg, 72%) as a colorless oil. Further development of the column, using 2:5 to 3:5 EtOAc−hexanes, gave **2.6** (135.0 mg, 15%) as a colorless oil. Compound **2.5**: FTIR ($CDCl_3$, cast) 3464, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (s, 3 H), 2.98 (s, 1 H), 3.84 (s, 3 H), 4.57 (AB q, *J* = 13.5 Hz, $\Delta\nu_{AB}$ = 37.7 Hz, 2 H), 5.25−5.26 (m, 1 H), 5.29−5.31 (m, 1 H), 5.52 (s, 1 H), 6.90 (dd, *J* = 8.5, 1.0 Hz, 1 H), 6.98 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.28 (ddd, *J* = 8.3, 7.5, 2.0 Hz, 1 H), 7.33 (dd, *J* = 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 55.4 (q), 64.7 (t), 70.5 (d), 110.8 (d), 113.5 (t), 120.9 (d),

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127.8 (d), 129.0 (d), 129.5 (s), 145.1 (s), 156.9 (s), 170.7 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{16}NaO_4$ $(M + Na)^+$ 259.0941, found 259.0937.

Compound **2.6**: FTIR ($CDCl_3$, cast) 3444, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 3 H), 2.20 (br, 1 H), 3.86 (s, 3 H), 4.11 (s, 2 H), 5.17 (t, J = 1.0 Hz, 1 H), 5.28 (t, J = 1.0 Hz, 1 H), 6.74 (s, 1 H), 6.91 (dd, J = 8.5, 1.0 Hz, 1 H), 6.99 (td, J = 7.5, 1.0 Hz, 1 H), 7.31 (m, 1 H), 7.38 (dd, J = 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (q), 55.7 (q), 63.6 (t), 69.6 (d), 110.8 (d), 112.3 (t), 120.7 (d), 126.7 (s), 127.4 (d), 129.4 (d), 147.1 (s), 156.6 (s), 170.0 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{16}NaO_4$ $(M + Na)^+$ 259.0941, found 259.0937.

(±)-3-Hydroxy-3-(2-methoxyphenyl)-2-methylidenepropyl acetate (2.5) from 2.6. DBU (0.1 mL, 0.7 mmol) was added to a stirred solution of **2.6** (74.1 mg, 0.314 mmol) in THF (4 mL). After 3 days, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 × 20 cm), using 1:10 to 1:5 EtOAc–hexanes, gave **2.5** (46.0 mg, 62%) as a colorless oil.

3-(2-Methoxyphenyl)-2-methylidene-3-oxopropyl acetate (2.7). DMSO (0.77 mL, 11 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.47 mL, 5.4 mmol) in CH_2Cl_2 (10 mL). After 15 min, a solution of **2.5** (629 mg, 2.67 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 20 min and stirring at −78 °C was continued for 45 min. Then Et_3N (1.20 mL) was added dropwise (ca. 1–2 drop per sec), and stirring was continued at −78 °C for 5 min. The cooling bath was removed, stirring was continued for 50 min, and water (10 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 2:25 to 1:5 EtOAc–hexanes, gave **2.7** (473.8 mg, 76%) as a colorless oil: FTIR ($CDCl_3$, cast) 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 3 H), 3.83 (s, 3 H), 4.99 (t, J = 1.5 Hz, 2 H), 5.84 (d, J = 1.0 Hz, 1 H), 6.07 (td, J = 1.5, 0.5 Hz, 1 H), 6.97 (d, J = 8.5 Hz, 1 H), 7.01 (td, J = 7.5, 1.0 Hz, 1 H), 7.30 (dd, J = 7.5, 1.5 Hz, 1 H), 7.44 (ddd, J = 8.5, 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 55.7 (q), 62.3 (t), 111.5 (d), 120.4 (d), 128.3 (s), 128.8 (t), 129.3 (d), 131.9 (d), 143.9 (s), 157.2 (s), 170.5 (s), 196.3 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{14}NaO_4$ $(M + Na)^+$ 257.0784, found 257.0782.

Preparation of (3.1). The preparation of this compound is reported in the literature[1b] but without experimental details for the following two intermediates:

a. 2-[(1H-Pyrrol-2-yl)carbonyl]phenyl acetate (ii). DMAP (45 mg, 0.37 mmol), pyridine (1.80 mL, 22.3 mmol) and AcCl (1.60 mL, 22.1 mmol) were added successively to a stirred and cooled (0 °C) solution of 2-[(1*H*-pyrrol-2-yl)carbonyl]phenol (**i**)[34] (3.13 g, 16.7 mmol) in CH_2Cl_2 (60 mL). Stirring was continued for 1 h, and the mixture was then quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 × 20 cm), using 3:10 to 2:5 EtOAc–hexanes, gave 2-[(1*H*-pyrrol-2-yl)carbonyl]phenyl acetate (**ii**) (3.79 g, 99%) as a colorless oil: FTIR ($CDCl_3$, cast) 3293, 1767 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3 H), 6.32 (dt, J = 4.0, 2.5 Hz, 1 H), 6.75–6.78 (m, 1 H), 7.18–7.21 (m, 1 H), 7.23 (dd, J = 8.0, 1.0 Hz, 1 H), 7.35 (td, J = 7.5, 1.0 Hz, 1 H), 7.55 (ddd, J = 8.0, 7.5, 2.0 Hz, 1 H), 7.71 (dd, J = 8.0, 2.0 Hz, 1 H), 10.63 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 111.1 (d), 120.6 (d), 123.6 (d), 125.6 (d), 126.7 (d), 130.2 (d), 131.62 (s), 131.64 (s), 131.7 (d), 148.6 (s), 169.5 (s), 182.9 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{11}NNaO_3$ $(M + Na)^+$ 252.0631, found 252.0630.

b. 2-[(4,5-Dichloro-1H-pyrrol-2-yl)carbonyl]phenyl acetate (iii). SO_2Cl_2 (1.45 mL, 17.5 mmol) was added dropwise to a stirred solution of 2-[(1*H*-pyrrol-2-yl)carbonyl]phenyl acetate (**ii**)[1b] (1.87 g, 8.15 mmol) in CH_2Cl_2 (40 mL). After 7 h, the solvent was evaporated, and flash chromatography of the residue over silica gel (3.8 × 20 cm), using 2:25 to 3:20 EtOAc–hexanes, gave 2-[(4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]phenyl acetate (**iii**) (2.20 g, 90%) as a white solid: mp 164–167 °C; FTIR ($CDCl_3$, cast) 3221, 1768, 1746 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3 H), 6.66 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.5, 1.0 Hz, 1 H), 7.33 (td, J = 7.5, 1.0 Hz, 1 H), 7.55 (ddd, J = 8.0, 7.5, 1.5 Hz, 1 H), 7.62 (dd, J = 8.0, 1.5 Hz, 1 H), 10.15 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 112.3 (s), 119.0 (d), 122.0 (s), 123.6 (d), 125.7 (d), 128.5 (s), 129.9 (d), 130.1 (s), 132.4 (d), 148.6 (s), 169.3 (s), 181.4 (s); exact mass (electrospray) m/z calcd for $C_{13}H_9{}^{35}Cl_2NNaO_3$ $(M + Na)^+$ 319.9852, found 319.9850.

2-({3-Bromo-4,5-dichloro-1-[3-(2-methoxyphenyl)-2-methylidene-3-oxopropyl]-1*H*-pyrrol-2-yl}carbonyl)phenyl acetate (3.2). NaH (60% w/w in oil, 30.5 mg, 0.763 mmol) was added to a stirred solution of **3.1** (222 mg, 0.592 mmol) in DMF (5 mL). After 20 min, a solution of **2.7** (165 mg, 0.704 mmol) in DMF (6 mL) was added, and stirring was continued for 84 h. The mixture was quenched with water and extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 2:25 to 3:20 EtOAc–hexanes, gave **3.2** (267.1 mg, 83%) as a white foam: FTIR ($CDCl_3$, cast) 1768 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3 H), 3.72 (s, 3 H), 5.40–5.42 (m, 2 H), 5.45 (apparent t, J = 1.5 Hz, 1 H), 5.75 (apparent t, J = 1.5 Hz, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 6.99 (td, J = 7.5, 1.0 Hz, 1 H), 7.23 (dd, J = 8.0, 1.0 Hz, 1 H), 7.29–7.33 (m, 2 H), 7.43 (ddd, J = 8.3, 7.5, 1.5 Hz, 1 H), 7.53–7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 47.0 (t), 55.5 (q), 106.2 (s), 111.4 (d), 113.4 (s), 120.3 (d), 123.5 (d), 123.6 (s), 125.9 (d), 127.4 (t), 128.0 (s), 128.1 (s), 129.4 (d), 130.9 (d), 131.2 (s), 132.1 (d), 132.8 (d), 144.4 (s), 149.0 (s), 157.3 (s), 169.1 (s), 182.9 (s), 196.0 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{18}{}^{79}Br^{35}Cl_2NNaO_5$ $(M + Na)^+$ 571.9638, found 571.9631.

2-({3-Bromo-4,5-dichloro-2-[(2-hydroxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}methyl)-1-(2-methoxyphenyl)prop-2-en-1-one (3.3). Concentrated hydrochloric acid (36.5–38%, 0.6 mL) was added dropwise to a stirred solution of **3.2** (552.8 mg, 1.003 mmol) in MeOH (11 mL). Stirring was continued for 6.5 h, and the solvent was then evaporated. The residue was dissolved in Et_2O, and the solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 1:50 to 1:20 EtOAc–hexanes, gave **3.3** (385.6 mg, 75%) as a yellow oil: FTIR ($CDCl_3$, cast) 3500–3000, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.68 (s, 3 H), 5.21 (br, 2 H), 5.51 (apparent t, J = 1.5 Hz, 1 H), 5.74 (apparent t, J = 1.5 Hz, 1 H), 6.90–6.98 (m, 3 H), 7.05–7.08 (m, 1 H), 7.21 (dd, J = 7.5, 1.5 Hz, 1 H), 7.42 (ddd, J = 8.5, 7.5, 2.0 Hz, 1 H), 7.52–7.56 (m, 1 H), 7.66–7.69 (m, 1 H), 11.5 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.6 (t), 55.4 (q), 102.9 (s), 111.4 (d), 112.8 (s), 118.2 (d), 119.2 (d), 119.3 (s), 120.4 (d), 121.5 (s), 127.71 (s), 127.73 (s), 128.3 (t), 129.3 (d), 132.2 (d), 134.3 (d), 137.1 (d), 144.0 (s), 157.2 (s), 162.8 (s), 189.8 (s), 195.9 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{16}{}^{79}Br^{35}Cl_2NNaO_4$ $(M + Na)^+$ 529.9532, found 529.9536.

2-({3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}methyl)-1-(2-methoxyphenyl)prop-2-en-1-one (3.4). K_2CO_3 (131.8 mg, 0.954 mmol), followed by MeI (0.06 mL, 1 mmol), were added to a stirred solution of **3.3** (97 mg, 0.19 mmol) in dry acetone (3 mL). Stirring was continued for 22 h, and the mixture was then filtered through a pad of Celite, using Et_2O as a rinse. The filtrate was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 × 20 cm), using 3:50 to 3:20 EtOAc–hexanes, gave **3.4** (90.1 mg, 90%) as a white solid: mp 142–145 °C; FTIR ($CDCl_3$, cast) 1661, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.77 (s, 3 H), 5.46 (apparent t, J = 1.5 Hz, 1 H), 5.51–5.54 (m, 2 H), 5.77 (apparent t, J = 1.5 Hz, 1 H), 6.94 (d, J = 3.5 Hz, 1 H), 6.96 (d, J = 4.5 Hz, 1 H), 6.99 (td, J = 7.5, 1.0 Hz, 1 H), 7.06 (td, J = 7.5, 1.0 Hz, 1 H), 7.33 (dd, J = 7.5, 2.0 Hz, 1 H), 7.40 (dd, J = 7.5, 2.0 Hz, 1 H), 7.43 (ddd, J = 8.3, 7.5, 1.5 Hz, 1 H), 7.50 (ddd, J = 8.3, 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.7 (t), 55.6 (q), 55.7 (q), 105.7 (s), 111.3 (d), 111.4 (d), 113.1 (s), 120.3 (d), 120.9 (d), 123.0 (s), 127.3 (t), 128.1 (s), 129.0 (s), 129.5 (d), 130.1 (d), 132.0 (d), 132.9 (d), 144.4 (s), 157.3 (s), 157.9 (s), 184.4 (s), 196.1 (s); exact mass (electrospray) m/z calcd for $C_{23}H_{18}{}^{79}Br^{35}Cl_2NNaO_4$ $(M + Na)^+$ 543.9688, found 543.9686.

3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-1-(2-methoxyphenyl)propane-1,2-dione (3.5). $NaIO_4$ (156 mg, 0.729 mmol) and $RuCl_3·4H_2O$ (7.5 mg, 0.027 mmol) were added successively to a stirred solution of **3.4** (126.8 mg, 0.24 mmol) in a mixture of MeCN (0.9 mL), CCl_4 (0.9 mL) and water (1.4 mL). After 1.5 h, the mixture changed to dark green-brown. At that time an additional quantity of $NaIO_4$ (60 mg, 0.28 mmol) was added, stirring was continued for 1 h, and CH_2Cl_2 (ca. 6 mL) and water (ca. 5 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 × 20 cm), using 3:50 to 3:25 EtOAc–hexanes, gave **3.5** (71.5 mg, 56%) as a light yellow solid: mp 110–113 °C; FTIR ($CDCl_3$, cast) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3 H), 3.79 (s, 3 H), 5.96 (br, 2 H), 6.96 (d, J = 6.0 Hz, 1 H), 6.97 (d, J = 6.0 Hz, 1 H), 7.04 (td, J = 7.5, 1.0 Hz, 1 H), 7.10 (td, J = 7.5, 1.0 Hz, 1 H), 7.40 (dd, J = 7.5, 2.0 Hz, 1 H), 7.49 (ddd, J = 8.5, 7.5, 2.0 Hz, 1 H), 7.59 (ddd, J = 8.5, 7.5, 2.0 Hz, 1 H), 7.80 (dd, J = 8.0, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (t), 55.8 (q), 55.9 (q), 107.0 (s), 111.4 (d), 111.9 (d), 113.7 (s), 120.8 (d), 121.3 (d), 123.0 (s), 123.6 (s), 128.8 (s), 129.1 (s), 129.9 (d), 130.8 (d), 132.8 (d), 136.2 (d), 157.9 (s), 160.2 (s), 185.1 (s), 192.8 (s), 193.0 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{16}{}^{79}Br^{35}Cl_2NNaO_5$ $(M + Na)^+$ 545.9481, found 545.9479.

(2*Z*)-3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)-carbonyl]-1*H*-pyrrol-1-yl}-1-(2-methoxyphenyl)-2-(prop-2-en-1-yloxy)prop-2-en-1-one (4.1). The method for **8c** was followed, using NaH (60% w/w in oil, 11.8 mg, 0.295 mmol), **3.5** (107 mg, 0.204 mmol) in DMF (4 mL) and allyl bromide (0.025 mL, 0.29 mmol) was added. In this case, the cold bath was removed, and stirring was continued overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl extracted with Et_2O. Flash chromatography of the crude product over silica gel (1.4 × 20 cm), using 3:50 to 1:10 EtOAc–hexanes, gave **4.1** (90.1 mg, 78%) as a light yellow oil: FTIR ($CDCl_3$, cast) 3078, 1670, 1640, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.82 (s, 3 H), 4.43 (ddd, J = 6.0, 1.1.5, 1.5 Hz, 2 H), 5.11–5.15 (m, 2 H), 5.79 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.77 (s, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 6.95 (d, J = 8.5 Hz, 1 H), 7.01 (td, J = 7.5, 1.0 Hz, 2 H), 7.38 (dd, J = 7.5, 1.5 Hz, 1 H), 7.44–7.49 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.6 (q), 55.8 (q), 72.0 (t), 105.9 (s), 111.3 (d), 111.4 (d), 114.1 (s), 118.4 (t), 120.1 (d), 120.4 (d), 120.8 (d), 122.0 (s), 127.2 (s), 128.1 (s), 129.8 (s), 130.20 (d), 130.25 (d), 130.3 (d), 133.0 (d), 133.1 (d), 151.0 (s), 158.02 (s), 158.03 (s), 183.3 (s), 191.2 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{20}{}^{79}Br^{35}Cl_2NNaO_5$ $(M + Na)^+$ 585.9794, found 585.9791.

(±)-3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)-carbonyl]-1*H*-pyrrol-1-yl}-1-(2-methoxyphenyl)hex-5-ene-1,2-dione (4.2). A solution of **4.1** (90.4 mg, 0.159 mmol) in PhMe (3 mL) was stirred and refluxed for 30 h, cooled to room temperature and evaporated. Flash chromatography of the yellow residue over silica gel (1.4 × 20 cm), using 3:50 to 1:10 EtOAc–hexanes, gave **4.2** (76.4 mg, 85%) as a light yellow oil: FTIR ($CDCl_3$, cast) 1722, 1662, 1628, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.98 (br, 1 H), 3.17 (br, 1 H), 3.67 (s, 3 H), 3.73–3.86 (m, 4 H), 5.04–5.16 (m, 2 H), 5.75 (br, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 6.94–7.00 (m, 2 H), 7.06 (t, J = 7.5 Hz, 1 H), 7.18 (br d, J = 6.3 Hz, 1 H), 7.42–7.46 (m, 1 H), 7.53–7.57 (m, 1 H), 7.96 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) we were unable to obtain a satisfactory spectrum as several expected signals were not observed; exact mass (electrospray) m/z calcd for $C_{25}H_{20}{}^{79}Br^{35}Cl_2NNaO_5$ $(M + Na)^+$ 585.9794, found 585.9783.

(±)-3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)-carbonyl]-1*H*-pyrrol-1-yl}-5-(2-methoxyphenyl)-4,5-dioxopentanal (4.3). NMO (41.2 mg, 0.352 mmol) and OsO_4 (0.1 M in PhMe, 0.1 mL, 0.01 mmol) were added successively to a stirred solution of **4.2** (53.6 mg, 0.095 mmol) in a mixture of THF (1 mL) and water (1 mL) (protected from light). After 2 h, the reaction mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$) and evaporated to give a yellow residue. A solution of $Pb(OAc)_4$ (54.8 mg, 0.124 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of the yellow residue in CH_2Cl_2 (1.5 mL), and stirring was continued for 15 min. The mixture was then filtered through a pad of silica gel, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.2 × 15 cm), using 1:5 to 2:5 EtOAc–hexanes, gave **4.3** (30.7 mg, 57%) as a yellow oil: FTIR ($CDCl_3$, cast) 2840, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.11 (d, J = 16.3 Hz, 1 H), 3.60–4.00 (m, 8 H), 6.90 (d, J = 8.5 Hz, 1 H), 6.94–7.04 (m, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.23 (d, J = 7.0 Hz, 1 H), 7.45–7.50 (m, 1 H), 7.56–7.60 (m, 1 H), 7.88 (br, 1 H), 9.88 (s, 1 H); we were unable to obtain a satisfactory ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum as many signals were not detected; exact mass (electrospray) m/z calcd for $C_{24}H_{18}{}^{79}Br^{35}Cl_2NNaO_6$ $(M + Na)^+$ 587.9587, found 587.9587.

4-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-2-(2-methoxyphenyl)pyridin-3-ol (4.4). The method for **3f** was followed, using NH_4OAc (119 mg, 1.54 mmol), **4.3** (54.9 mg, 0.0968 mmol) in AcOH (1 mL) and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1.2 × 15 cm), using 2:5 to 1:2 EtOAc–hexanes, gave **4.4** (33.0 mg, 62%) as a yellow oil: FTIR ($CDCl_3$, cast) 3246, 1646, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.86 (s, 3 H), 6.87 (d, J = 8.5 Hz, 1 H), 6.93 (td, J = 7.5, 1.0 Hz, 1 H), 7.05 (dd, J = 8.5, 1.0 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.37–7.48 (m, 3 H), 7.57 (br, 1 H), 7.75 (dd, J = 8.0, 2.0 Hz, 1 H), 8.38 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.9 (q), 57.0 (q), 105.4 (s), 111.3 (d), 112.4 (d), 114.1 (s), 120.5 (d), 121.7 (s), 122.6 (d), 123.0 (d), 126.8 (s), 127.88 (s), 127.89 (s), 130.5 (d), 130.7 (d), 130.8 (s), 133.0 (d), 133.3 (d), 133.7 (s), 142.2 (d), 146.7 (s), 147.0 (s), 155.0 (s), 158.1 (s), 183.3 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{17}{}^{79}Br^{35}Cl_2N_2NaO_4$ $(M + Na)^+$ 568.9641, found 568.9637.

Methyl 5-cyano-1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (5.2). NaH (60% w/w in mineral oil, 102 mg, 2.55 mmol) was added to a stirred and cooled (0 °C) solution of **4** (318 mg, 2.12 mmol) in DMF (21 mL). Stirring at 0 °C was continued for 30 min, and bromoacetophenone (**5.1**) (548 mg, 2.75 mmol) was added in one portion. The cold bath was left in place, but not recharged, and stirring was continued for 3.5 h, during which time the reaction mixture reached room temperature. The mixture was diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:9 EtOAc–hexane to 1:3 EtOAc–hexane, gave **5.2** (477 mg, 84%) as a white solid: mp 110–115 °C; FTIR ($CDCl_3$, cast) 3138, 2226, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 5.95 (s, 2 H), 6.87 (d, J = 4.0 Hz, 1 H), 7.02 (d, J = 4.0 Hz, 1 H), 7.52–7.55 (m, 2 H), 7.64–7.67 (m, 1 H), 8.00–8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 53.7 (t), 111.3 (s), 112.3 (s), 117.3 (d), 118.7 (d), 127.0 (s), 128.1 (d), 129.0 (d), 134.2 (d), 134.3 (s), 160.5 (s), 191.4 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{12}N_2NaO_3$ $(M + Na)^+$ 291.0740, found 291.0741.

(±)-Methyl 5-cyano-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2-carboxylate (5.4) and Methyl 5-cyano-1-[(*Z*)-2-phenyl-2-(prop-2-en-1-yloxy)ethenyl]-1*H*-pyrrole-2-carboxylate (5.3). A solution of **5.2** (155 mg, 0.578 mmol) in DMF (4 mL) was added to a stirred and cooled (0 °C) mixture of NaH (60% w/w in mineral oil, 23.3 mg, 0.582 mmol) and DMF (1 mL). Stirring at 0 °C was continued for 30 min and allyl bromide (0.05 mL, 0.6 mmol) in DMF (1 mL) was added over 10 min. The cold bath was left in place, but not recharged, and stirring was continued for 7 h, during which time the reaction mixture reached room temperature. The mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:20 EtOAc–hexane to 1:5 EtOAc–hexane, gave **5.3** (21.6 mg, 12%) and **5.4** (42.7 mg, 24%) as colorless oils. The starting ketone **5.2** (49.4 mg) was recovered.

Compound **5.4**: FTIR ($CDCl_3$, cast) 2225, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.02–3.16 (m, 2 H), 3.86 (s, 3 H), 5.01 (ddd, J = 10.0, 2.0, 1.0 Hz, 1 H), 5.06 (ddd, J = 17.0, 3.0, 2.0 Hz, 1 H), 5.66–5.72 (m, 1 H), 6.79 (d, J = 4.5 Hz, 1 H), 6.93 (d, J = 4.5 Hz, 1 H), 7.12 (br, 1 H), 7.41–7.45 (m, 2 H), 7.54 (tt, J = 7.5, 1.5 Hz, 1 H), 7.83 (d, J

= 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 52.1 (q), 62.8 (d), 110.5 (s), 113.2 (s), 117.8 (d), 119.4 (t), 120.2 (d), 126.2 (s), 128.3 (d), 128.8 (d), 132.1 (d), 133.3 (d), 135.3 (s), 161.0 (s), 194.9 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{17}N_2O_3$ $(M + H)^+$ 309.1234, found 309.1234.

Compound **5.3**: FTIR ($CDCl_3$, cast) 3135, 2229, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3 H), 4.16 (ddd, J = 6.0, 1.5, 1.5 Hz, 2 H), 5.07−5.13 (m, 2 H), 5.71 (ddt, J = 17.5, 10.5, 5.5 Hz, 1 H), 6.61 (s, 1 H), 6.84 (d, J = 4.5 Hz, 1 H), 6.96 (d, J = 4.5 Hz, 1 H), 7.42−7.43 (m, 3 H), 7.58−7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 71.0 (t), 108.1 (d), 111.7 (s), 112.8 (s), 116.6 (d), 117.7 (t), 118.7 (d), 127.4 (s), 127.7 (d), 128.6 (d), 129.8 (d), 132.7 (s), 132.8 (d), 155.0 (s), 160.0 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{17}N_2O_3$ $(M + H)^+$ 309.1234, found 309.1234.

(±)-Methyl 5-cyano-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2-carboxylate (5.4). A solution of **5.3** and **5.4** (45.9 mg, 0.149 mmol) in PhMe (1.5 mL) was refluxed for 18 h, cooled and evaporated to afford **5.4** (45.7 mg, ca. 99%) as a thick, light yellow oil.

Methyl (±)-5-cyano-1-(1,4-dioxo-1-phenylbutan-2-yl)-1*H*-pyrrole-2-carboxylate (5.5) and Methyl 5-cyano-1-(2-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-2-carboxylate (5.6). The method for **4b** was followed, using **5.4** (45.7 mg, 0.147 mmol), Sudan Red 7B (ca. 0.5 mg) in CH_2Cl_2 (5 mL), Me_2S (0.03 mL, 0.4 mmol) and a reduction period of 8 h. The mixture was evaporated directly at ca. 10 °C to give **5.5** as a thick, yellow oil, which was used immediately, as follows.

The method for **3f** was followed, using NH_4OAc (110 mg, 1.43 mmol), the above crude keto aldehyde **5.5** in AcOH (3 mL) and a reaction time of 3.5 h. Flash chromatography of the crude product over silica gel (1 × 20 cm), using 1:4 EtOAc−hexane, gave **5.6** (30.6 mg, 71% over three steps) as a white solid: mp 152−156 °C; FTIR ($CDCl_3$, cast) 3369, 3138, 2230, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.70 (s, 3 H), 6.31 (apparent t, J = 3.0 Hz, 1 H), 6.79 (apparent t, J = 3.0 Hz, 1 H), 6.85 (d, J = 4.5 Hz, 1 H), 6.92 (dt, J = 6.5, 1.5 Hz, 2 H), 7.02 (d, J = 4.0 Hz, 1 H), 7.17−7.24 (m, 3 H), 8.62 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 109.1 (d), 112.4 (s), 112.7 (s), 117.3 (d), 117.4 (d), 118.0 (s), 118.9 (d), 125.1 (d), 127.2 (d), 127.5 (s), 128.3 (s), 129.0 (d), 130.3 (s), 159.4 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{13}N_3NaO_2$ $(M + Na)^+$ 314.0900, found 314.0898.

2,5-Dimethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2,5-dicarboxylate (6.1). The method for **5.2** was followed, using NaH (60% w/w in mineral oil, 80.0 mg, 2.00 mmol), **3** (332 mg, 1.82 mmol) in DMF (19 mL), bromoacetophenone (**5.1**) (435 mg, 2.18 mmol) and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (2 × 15 cm), using 1:9 EtOAc−hexane, gave **6.1** (493 mg, 90%) as a white solid: mp 116−121 °C; FTIR ($CDCl_3$, cast) 1723, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 6 H), 6.49 (s, 2 H), 7.01 (s, 2 H), 7.49−7.53 (m, 2 H), 7.61 (tt, J = 7.5, 1.5 Hz, 1 H), 8.02−8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 53.1 (t), 116.8 (d), 127.6 (s), 128.0 (d), 128.8 (d), 133.6 (d), 135.0 (s), 161.4 (s), 193.5 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{16}NO_5$ $(M + H)^+$ 302.1023, found 302.1023.

2,5-Dimethyl (±)-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (6.3) and 2,5-Dimethyl 1-[(*Z*)-2-phenyl-2-(prop-2-en-1-yloxy)ethenyl]-1*H*-pyrrole-2,5-dicarboxylate (6.2). The method for **5.3** was followed, using **6.1** (320 mg, 1.06 mmol) in DMF (11 mL), NaH (60% w/w in mineral oil, 42.5 mg, 1.06 mmol) and DMF (5 mL), allyl bromide (0.09 mL, 1 mmol) in DMF (10 mL), an addition period of 20 min, and an overnight reaction time. Flash chromatography of the crude product over silica gel (2 × 20 cm), using 1:25 EtOAc−hexane, gave **6.3** (140 mg, 39%) and **6.2** (138 mg, 38%) as colorless oils. Compound **6.3** contained an impurity.

Compound **6.2**: FTIR ($CDCl_3$, cast) 1734, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.83 (s, 6 H), 3.94 (ddd, J = 6.0, 1.5, 1.5 Hz, 2 H), 4.99 (ddd, J = 8.0, 3.0, 1.5 Hz, 1 H), 5.02 (apparent t, J = 1.5 Hz, 1 H), 5.53−5.61 (m, 1 H), 6.92 (s, 1 H), 6.94 (s, 2 H), 7.37−7.42 (m, 3 H), 7.59−7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 70.9 (t), 110.8 (d), 116.3 (d), 117.3 (t), 127.1 (d), 128.6 (d), 128.9 (s), 129.1 (d), 133.2 (d), 133.8 (s), 151.9 (s), 160.8 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{19}NNaO_5$ $(M + Na)^+$ 364.1155, found 364.1155.

Compound **6.3**: FTIR ($CDCl_3$, cast) 1725, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.70−2.80 (m, 1 H), 3.37−3.40 (m, 1 H), 3.82 (s, 6 H), 4.84−4.88 (m, 2 H), 5.59−5.69 (m, 1 H), 6.89 (s, 2 H), 7.20 (dd, J = 10.0, 4.5 Hz, 1 H), 7.23−7.28 (m, 2 H), 7.37 (tt, J = 7.5, 1.5 Hz, 1 H), 7.53−7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.2 (t), 51.8 (q), 63.3 (d), 117.7 (d), 118.1 (t), 127.5 (s), 127.6 (d), 128.0 (d), 131.6 (d), 133.7 (d), 137.4 (s), 161.4 (s), 197.0 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{19}NNaO_5$ $(M + Na)^+$ 364.1155, found 364.1154.

2,5-Dimethyl (±)-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (6.3). A solution of a mixture of **6.3** and **6.2** (179 mg, 0.525 mmol) in PhMe (6 mL) was refluxed for 13 h, cooled to room temperature and evaporated to give **6.3** as a thick, colorless oil (178 mg, 99%), which was used directly in the next step. Compound **6.3** had same spectral data as above.

2,5-Dimethyl (±)-1-(1,4-dioxo-1-phenylbutan-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (6.4) and 2,5-Dimethyl 1-(1-benzyl-2-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (6.5). With the exception that THF was used instead of CH_2Cl_2, the method for **4b** was followed, using **6.3** (75.6 mg, 0.221 mmol), Sudan Red 7B (ca. 0.1 mg) in THF (5 mL) and Me_2S (0.03 mL, 0.4 mmol). During the reduction the cold bath was left in place, but not recharged, and stirring was continued for 3 h, during which time the reaction mixture reached 0 °C. Iodine (5.6 mg, 0.022 mmol) and $BnNH_2$ (0.03 mL, 0.3 mmol) were added. The cold bath was left in place but not recharged, and stirring was continued for 4 h. The mixture was diluted with aqueous $NaHSO_3$ (10% w/v) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated at <12 °C (cold water bath with some ice). The residue was dissolved in MeOH (2 mL) and cooled in an ice bath. $NaBH_4$ (4.2 mg, 0.11 mmol) was added, and the cold bath was left in place, but not recharged, and stirring was continued for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc−hexane, gave **6.5** (37.4 mg, 41% over four steps) as a colorless oil. Compound **6.5**: FTIR ($CDCl_3$, cast) 1737, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.71 (s, 6 H), 5.07 (s, 2 H), 6.28 (d, J = 3.5 Hz, 1 H), 6.75 (d, J = 3.5 Hz, 1 H), 6.85 (s, 2 H), 7.03−7.08 (m, 4 H), 7.14−7.17 (m, 3 H), 7.22−7.25 (m, 1 H), 7.30−7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.9 (q), 51.3 (t), 107.8 (d), 116.4 (d), 119.9 (d), 120.8 (s), 126.2 (d), 127.2 (d), 127.6 (d), 128.1 (d), 128.6 (d), 129.6 (d), 130.2 (s), 130.3 (s), 138.7 (s), 160.2 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{22}N_2NaO_4$ $(M + Na)^+$ 437.1472, found 437.1469.

Compound **6.4**: FTIR ($CDCl_3$, cast) 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.98 (ddd, J = 17.5, 6.0, 1.0 Hz, 1 H); 3.87 (br, 6 H), 3.94 (ddd, J = 17.5, 6.0, 1.0 Hz, 1 H), 6.92 (s, 2 H), 7.27−7.31 (m, 2 H), 7.39−7.44 (m, 2 H), 7.50−7.52 (m, 2 H), 9.89 (t, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.2 (t), 52.0 (q), 59.0 (d), 118.0 (d), 127.5 (d), 127.6 (s), 128.2 (d), 132.1 (d), 136.2 (s), 195.8 (s), 198.4 (d); exact mass (electrospray) m/z calcd for $C_{18}H_{17}NNaO_6$ $(M + Na)^+$ 366.0948, found 366.0944.

■ ASSOCIATED CONTENT

Supporting Information

ORTEP diagram of **3f**. Copies of NMR spectra and, for compounds **3c** and **3f**, X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629−631. (b) Hughes, C. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2010**, *75*, 3240−3250.

(2) Review of chemistry and biological properties of the marinopyrroles: Clive, D. L. J.; Cheng, P. *Tetrahedron* **2013**, *69*, 5067−5078.

(3) Haste, N. M.; Hughes, C. C.; Tran, D. N.; Fenical, W.; Jensen, P. R.; Nizet, V.; Hensler, M. E. *Antimicrob. Agents Chemother.* **2011**, *55*, 3305−3312.

(4) (a) Cheng, C.; Pan, L.; Chen, Y.; Song, H.; Qin, Y.; Li, R. *J. Comb. Chem.* **2010**, *12*, 541−547. (b) Qin, Y.; Song, H.; Cheng, C.; Deng, X.; Wang, X. Chinese Patent 2010, 101786979 A (*Chem. Abstr.* **2010**, *153*, 952585). (c) Nicolaou, K. C.; Simmons, N. L.; Chen, J. S.; Haste, N. M.; Nizet, V. *Tetrahedron Lett.* **2011**, *52*, 2041−2043.

(5) Kanakis, A. A.; Sarli, V. *Org. Lett.* **2010**, *12*, 4872−4875.

(6) (a) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Santos, J. S.-d. O.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448−1464. (b) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2004**, *45*, 6353−6355. (c) Bu, X.; Li, Y.; Liu, J.; Zeng, D.; Zhao, W. *Chem. Nat. Prod.* **2012**, *48*, 194−197. (d) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162−8175. (e) Rochais, C.; Vu Duc, N.; Lescot, E.; Santos, J. S.-d. O.; Bureau, R.; Meijer, L.; Dallemagne, P.; Rault, S. *Eur. J. Med. Chem.* **2009**, *44*, 708−716. (f) Liu, Y.; Haste, N. M.; Thienphrapa, W.; Nizet, V.; Hensler, M.; Li, R. *Mar. Drugs* **2012**, *10*, 953−962.

(7) Review of Paal−Knorr and Knorr pyrrole syntheses: Gribble, G. W. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2005, pp 79−88.

(8) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 3545−3548.

(9) (a) Treibs, A.; Hitzler, O. *Chem. Ber.* **1957**, *90*, 787−788. (b) Mingoia, F. *Tetrahedron* **2001**, *51*, 10147−10154.

(10) (a) Santo, R.; Di Massa, S.; Costi, R.; Simonetti, G.; Retico, A.; Apuzzo, G.; Troccoli, F. *Farmaco* **1994**, *49*, 229−236. (b) Qiu, F.; Wu, J.; Zhang, Y.; Hu, M.; Yu, Y. *Tetrahedron Lett.* **2012**, *53*, 446−448.

(11) Cheng, P.; Clive, D. L. J.; Fernandopulle, S.; Chen, Z. *Chem. Commun.* **2013**, *48*, 558−560.

(12) (a) Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 3701−3712. (b) Vloon, W. J.; van den Bos, J. C.; Koomen, G.-J.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8317−8328.

(13) The diiodo ester **9** is a new compound, although the parent acid is known. For iodination of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethan-1-one, see ref 14 and Essa, A. H.; Lerrick, R. I.; Tuna, F.; Harrington, R. W.; Clegg, W.; Hall, M. J. *Chem. Commun.* **2013**, *49*, 2756−2758.

(14) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300−1302.

(15) (a) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807−810. (b) Boer, H.; Kooyman, E. C. *Anal. Chim. Acta* **1951**, *5*, 550−562.

(16) Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

(17) Sakamuri, S.; Kozikowski, A. P. *Chem. Commun.* **2001**, 475−476.

(18) Laatsch, H.; Pudleiner, H. *Liebigs Ann. Chem.* **1989**, 863−881.

(19) Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095−3097.

(20) Filtration through Florisil was tried with the dichloro compound, but the pinacol method is better.

(21) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301−1305.

(22) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. (b) Krohn, K.; Frese, P.; Flörke, U. *Chem.—Eur. J.* **2000**, *6*, 3887−3896.

(23) Leading reference to 3-hydroxypyridines: Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 515−518. Schmidt, A. *Curr. Org. Chem.* **2004**, *8*, 653−670.

(24) Qi, X.; Dai, L.; Park, C.-M. *Chem. Commun.* **2012**, *48*, 11244−11246.

(25) For the closest analogy we could find (by a search of the Reaxys database) of an example of simultaneous *O*- and *C*-alkylation in the presence of a nitrogen atom α to a ketone, see: Yasuda, S.; Yamamoto, Y.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull.* **1988**, *36*, 4229−4231.

(26) A byproduct of the allylation appeared to be (^{1}H NMR) the result of double allylation α to the ketone carbonyl.

(27) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213−216.

(28) Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373−6380. (b) Hasse, K.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem.* **2011**, 88−99.

(29) Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1981**, *59*, 2673−2976.

(30) Schmuck, C.; Dudaczek, J. *Tetrahedron Lett.* **2005**, *46*, 7101−7105.

(31) Kumar, R.; Lown, J. W. *Org. Biomol. Chem.* **2003**, *1*, 3327−3342.

(32) (a) Smith, J. A.; Ng, S.; White, J. *Org. Biomol. Chem.* **2006**, *4*, 2477−2482. (b) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. In *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. *6*, p 618.

(33) Yang, H.; Baralt, E. J. US Patent 2010256391 A1, 2010 (*Chem. Abstr.* **2010**, *153*, 1256790).

(34) Petruso, S.; Bonanno, S.; Caronna, S.; Ciofalo, M.; Maggio, B.; Schillaci, M. *J. Heterocycl. Chem.* **1994**, *31*, 941−945.