Pergamon

*Tetrahedron*, Vol. 53, No. 23, pp. 7731-7752, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00469-5

# A New Approach to Porphobilinogen and its Analogs

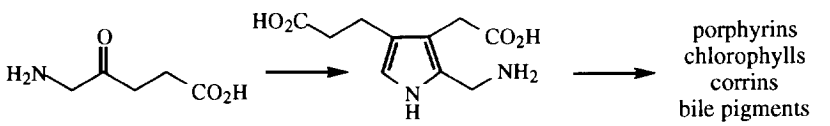
Christine Y. de Leon and Bruce Ganem*

Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, New York 14853-1301 USA

**Abstract:** *The van Leusen pyrrole synthesis was used to assemble three potential precursors of porphobilinogen, one of which was converted to the natural product using a new method for the direct alkylation of β-hydroxymethylpyrroles.* © 1997 Elsevier Science Ltd.

## INTRODUCTION AND BACKGROUND

Porphobilinogen (PBG, **1**) is the central building block for all naturally-occurring porphyrins, including heme, chlorophyll, phycobilin, and cobalamine. Since its isolation[1] and structure determination[2] in the early 1950s, PBG has been the subject of several synthetic and biosynthetic studies. Nevertheless, PBG remains difficult to synthesize in preparatively useful amounts. Past approaches to PBG include syntheses from unsubstituted pyrroles,[3] from tri-[4] and tetra-substituted pyrroles,[5] and from azaindoles.[6] Commerically, PBG is most efficiently produced in a chemoenzymatic process involving PBG synthase, and can cost as much as $10,000 per gram.




ALA PBG

**1**

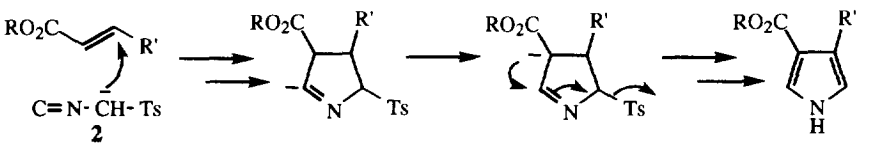
Interest in a practical, low-cost synthesis has been rekindled by the potential uses of PBG and its analogs in medicine. Natural porphyrins sensitize cells to light, and are finding use in the emerging technique of photodynamic therapy (PDT), wherein photosensitizers that accumulate in tumorous growths can be used to eradicate cancer cells. For example, synthetic porphyrin-based pigments have been used as sensitizers in conjunction with laser therapy to eradicate systemic cancer, superficial malignancies and small localized tumors.[7] Photofrin II, a mixture of modified hematoporphyrins, chemically eradicates tumor cells by generating singlet oxygen.[8] However, Phorofrin II lingers in the tissue for weeks, sensitizing patients to sunlight for prolonged periods. A recent study found that the biosynthetic precursor of PBG, aminolevulinic acid (ALA), is readily taken up by cancer cells to form the photoactive pigment protoporphyrin IX, whose production peaks at 4-6 hours and returns to normal levels after 24 hours.[9] This finding opens up the possibility that other porphyrin biosynthetic intermediates, such as PBG, may result in superior PDT agents.

In an unrelated application, an improved synthesis of PBG could help in treating lead poisoning, which represents a serious health problem in children who inhabit environmentally contaminated areas. Lead and other heavy metals can inactivate PBG synthase and retard the dimerization of ALA to PBG, thus altering cellular heme synthesis and disrupting normal brain and central nervous system development. With ready access to PBG and its analogs as haptens, anti-PBG antibodies might be produced for the development of immunoreagents in lead determination assays.[4,10]

## RESULTS AND DISCUSSION

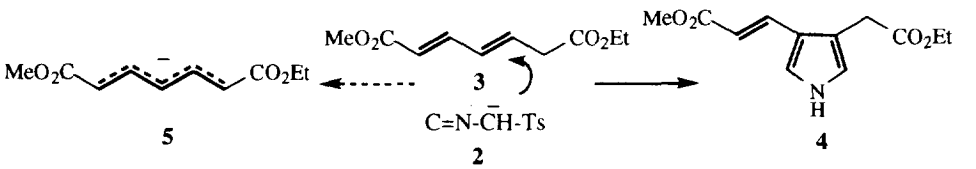
A convergent approach to the synthesis of PBG can be envisioned by assembling the pyrrole nucleus containing the acetic and propionic acid side chains at the β and β' positions. Once the appropriately disubstituted pyrrole nucleus is assembled, selective aminomethylation at the requisite α-position would give the 2,3,4-trisubstituted pattern of PBG.

One well-documented method of 3,4-disubstituted pyrrole construction is the base-induced cyclization of tosylmethyl isocyanide (TosMIC, **2**) with α,β-unsaturated esters, ketone or nitriles developed by van Leusen.[11] The mechanism of the reaction involves conjugate addition of the TosMIC anion with the α,β-unsaturated compound, followed by ring closure and elimination of the *p*-toluenesulfinic acid (Scheme 1). The ease of use of TosMIC, its ready availability, and the access it provides to 3,4-disubstituted pyrroles make it an attractive starting point for the synthesis of PBG and its analogs.



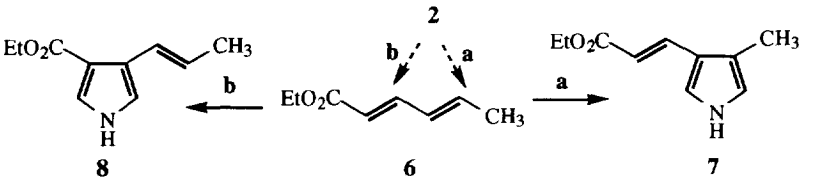

**Scheme 1**

For a convergent synthesis of PBG, the van Leusen reaction should introduce the acetic and/or propionic acid side chain at the β and β' positions of the pyrrole directly or in a latent form. In principle, both acid side chains of PBG might be introduced by the direct condensation of TosMIC with dienediester **3** as shown in Scheme 2, although such a reaction posed two formidable experimental challenges. In the first place, it was not obvious what factors might control the regiochemistry of addition (i.e. 1,4 versus 1,6-attack) to the dienoate system of **3**. Secondly, a diffusion-controlled acid/base reaction between anion **2** and the acidic methylene group of diester **3** might take place (dashed arrow, Scheme 2), thus subverting the desired nucleophilic addition. Here we report on our efforts to address these issues individually, with studies on the adaptation of the van Leusen pyrrole construction to the synthesis of PBG.




**Scheme 2**

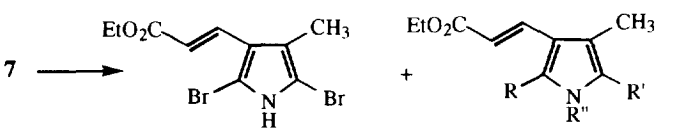
A promising precedent was reported by Magnus *et al.* who noted the effect of cation structure on the conjugate addition of TosMIC anions to ethyl sorbate **6**.[12] The sodium salt of TosMIC in DMSO:ether reacted with **6** to afford pyrrole **7** (pathway **a**, Scheme 3) in 80% yield, whereas the lithium salt of **2** in THF afforded the 1,4 addition adduct **8** in 61% yield (pathway **b**, Scheme 3). The combination of more polar solvent and more highly dissociated anion favored reaction at the terminally polarized δ-position of dienoate **6**, leading to the desired 1,6-addition product.[13]




**Scheme 3**

Pyrrole **7** was itself a potential precursor of PBG, requiring only hydrogenation of the acrylate substituent and a one-carbon elongation of the methyl group to install the propionate and acetate side chains. To investigate various homologation strategies on **7**, bromination of the methyl substituent was attempted using N-bromosuccinimide (NBS).

Under standard conditions (1.2 equiv NBS, $CCl_4$, reflux, 2 h, sunlamp illumination), a complex mixture of polybrominated products was obtained. Further investigation revealed that a rapid dark reaction at room temperature ($CCl_4$, 30 min) furnished dibrominated pyrrole **9** in 11% yield, along with a 5:1 inseparable mixture of monobrominated pyrroles **10** and **11** in 44% yield. Compounds **9**-**11** were isolated as yellow solids, but rapidly decomposed upon exposure to light and air. Further bromination of **11** with excess NBS afforded only tribromide **12** and none of the desired bromomethyl compound.

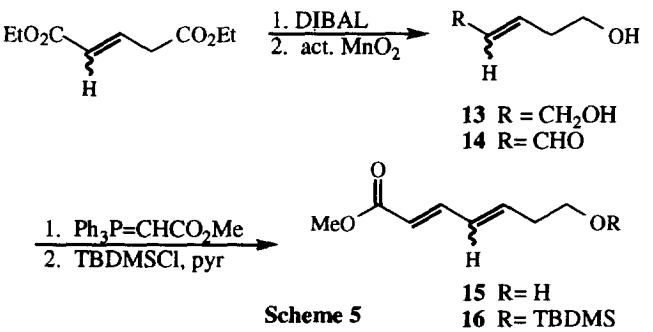



**9**

**10** R, R" = H, R'= Br
**11** R= Br, R', R"= H
**12** R, R', R" = Br

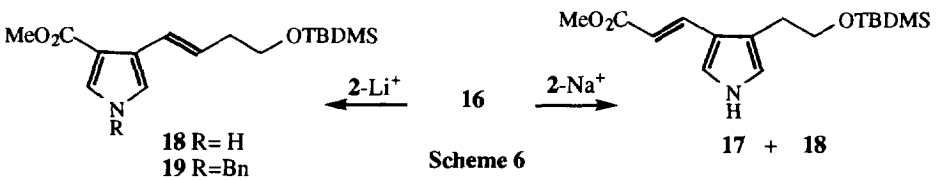
**Scheme 4**

Satisfied that 1,6-addition of TosMIC to dienoates was achievable, but that ring bromination of pyrrole **7**, even in the presence of protecting groups, seemed unavoidable,[14] we turned our attention to reactions of TosMIC with methyl 7-(*t*-butyldimethylsilyloxy)-2,4-heptadienoate **16** (Scheme 5). This dienoate, which contains all the requisite carbons for the acetate and propionate side chains of PBG, was prepared from commercially available diethylglutaconate. Reduction of diethylglutaconate with excess DIBAL gave unsaturated diol **13** in 80% yield. Oxidation of **13** with activated $MnO_2$ gave aldehyde **14**. Wittig reaction of **14** with methyl(triphosphoranylidene)acetate gave alcohol **15**, which was protected using TBDMSCl to afford the desired conjugate dienoate **16** in 41% overall yield.



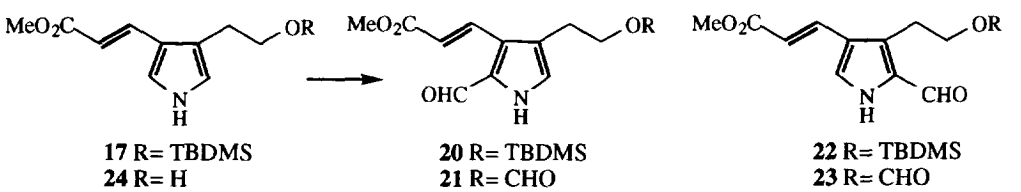

**Scheme 5**

Condensation of **16** with the sodium anion of TosMIC in DMSO:ether gave a 7:1 mixture of regioisomers **17** and **18** in 55% yield (Scheme 6). Under classic kinetic conditions using $LiN(TMS)_2$ in THF at -78 °C, pyrrole **18** was obtained as the only detectable product. Since **18** could not be separated from unreacted TosMIC, the reaction mixture was subsequently benzylated (BnBr, NaH, DMF) to afford the corresponding N-benzyl derivative **19**, which was fully characterized. Thus, the regioselectivity of addition observed with **16** closely paralleled that noted with ethyl sorbate **6**.



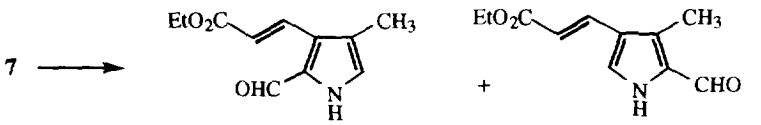

**Scheme 6**

With the two- and three-carbon β–substituents in place, pyrrole **17** was an attractive intermediate for the synthesis of PBG. A variety of methods based on α–methylations, cyanations, and formylations have been used in past PBG syntheses for regioselective aminomethylations. Using the Vilsmeier-Haack formylation, reaction of **17** with $POCl_3$-DMF at -78 °C led to a mixture of silyl ether (5:1 **20:22**, 9%) and formate ester products (3:1 **21:23**, 34%) favoring the undesired regioisomer, as shown in Scheme 7. It was unclear whether loss of the silyl ether preceded formylation of the pyrrole nucleus. To ascertain whether the regioselectivity might be influenced by a proximal hydroxyl group, the TBDMS protecting group in **17** was removed ($Bu_4NF$, THF) to afford alcohol **24** in 90% yield. Slow addition of **24** to the Vilsmeier reagent (1.3 equiv) at -78 °C afforded esters **21** and **23** in a 9:1 ratio (34%).




**Scheme 7**

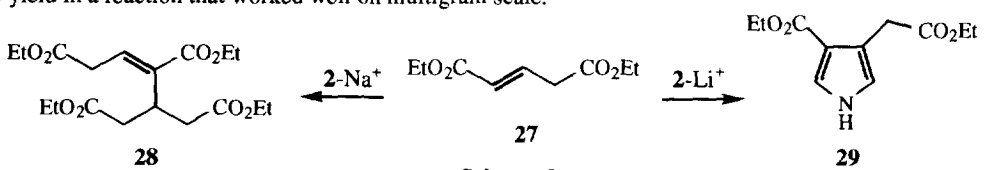
The selective formation of **21** was surprising at first, since the electron-withdrawing inductive effect of the acrylate group was expected to retard formylation at the adjacent position. Consistent with that rationale, formylation of **7** under identical conditions led to a 2:3 ratio of **25** and **26** in 43% yield (Scheme 8). However, reaction of the primary alcohol in **24** with the Vilsmeier reagent likely formed an initial formiminium ion (not shown), which exerted a strong inductive effect to divert electron density from the pyrrole ring, thus favoring formylation at the distal α-position.




**Scheme 8**

While the proposed 1,6-addition reaction of **2** with **3** to furnish **4** (Scheme 2) gained support from studies with dienoates **6** and **16**, the regiochemical problems in formylating **7**, **17**, and **24** clearly indicated that the subsequent aminomethylation of **4** leading to PBG was not likely to be successful. We therefore turned our attention to β, β'-disubstituted pyrroles in which regioselective aminomethylation might be possible.

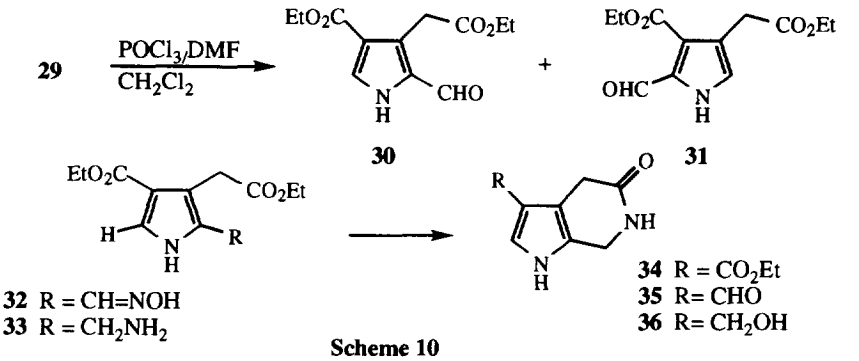
Michael addition of **2** with diethylglutaconate **27** would be expected to form pyrrole **29** (Scheme 9), formylation of which ought to occur with the desired regioselectivity. Unlike previous electrophiles in this study, **27** was a vinylogous malonic ester, whose deprotonation could subvert the desired cycloaddition. When the sodium salt of **2** reacted with **27** in DMSO:ether, the major product was diethylglutaconate dimer **28** and the desired pyrrole **29** was formed in only 10% yield. To minimize proton transfer and retard dimerization, diethylglutaconate was added to the preformed lithium salt of TosMIC [$LiN(TMS)_2$, THF, -78 °C], and the reaction was allowed to warm slowly to rt. Gratifyingly, the desired pyrrole **29** was obtained in 72% yield in a reaction that worked well on multigram scale.




**Scheme 9**

Slow addition of pyrrole **29** to a solution of the Vilsmeier reagent at -78 °C, followed by gradual warming to rt over 4 h gave an 8:1 regioisomeric mixture of **30** and **31** in 96% yield (Scheme 10). Since the two aldehydes were separated only with difficulty, the mixture was used directly in the next step.

Reductive amination of **30/31** (Scheme 10) with $NaBH_3CN$-$NH_4OAc$ using the method of Borch[15] gave a complex mixture of products. Faber *et al.* was unsuccessful in reductive aminations of the closely related system, ethyl 2-formylpyrrole-3-acetic acid.[16] Therefore, the aminomethyl side chain was installed by oximation ($NH_2OH$, EtOH) and subsequent catalytic hydrogenation with $Pd(OH)_2$ to afford amine **33**.




**Scheme 10**

Treatment of **33** with base (NaOEt, EtOH) led to the formation of bicyclic lactam **34** in 86% yield from **32**. Lactam **34** precipitated as a fine powder, thus facilitating its purification.

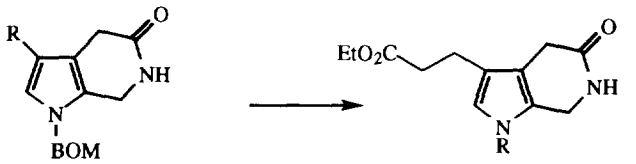
With the acetic acid side chain protected as a lactam, attention was focused on transforming the carboethoxy group of **34** into a propionic acid chain. A standard protocol involved Knoevenagel condensation on the corresponding aldehyde **35**. However, lactam **34** had poor solubility properties in all solvents commonly used for diisobutylaluminum hydride (DIBAL) reductions, so that attempts to prepare **35** by partial reduction of **34** were unsuccessful. Hydroxymethylpyrrole **36** could be obtained in 86% yield using excess DIBAL at room temperature. Alcohol **36** was also poorly soluble, thus hampering attempted oxidations to **35**.

To improve the solubility properties of these bicyclic lactams, substitution of one or both nitrogens with benzyl or benzyloxymethyl (BOM) groups was explored. Monobenzyllactam **37** was prepared by reductive amination of **30** using benzylamine in 80% overall yield. Further benzylation of **37** (NaH, BnBr, DMF) afforded dibenzyllactam **38** in 85-89% yield. BOM-protected lactam **39** was synthesized in 83% yield from the monosodium salt of **34** (NaH, THF, BOM-Cl). The solubility of **37** was not much improved, and reduction with DIBAL under heterogeneous conditions afforded amine **40** in 46% yield. Pyrrole **38** was readily soluble in THF, so that low-temperature DIBAL reduction could be conducted under homogeneous conditions. Nevertheless, reduction of **38** at -60 °C afforded amine **41** along with recovered **38**.


**Scheme 11**

Controlled reduction of the soluble BOM-protected lactam **39** gave none of the desired aldehyde **43** and only the corresponding primary alcohol **42** (Scheme 12), which, when optimized, could be obtained in 66% yield. Oxidation of **42** with several common oxidants ($MnO_2$, PCC, Jones reagent, DMSO-oxalyl chloride) gave variable results, but aldehyde **43** was obtained using the Dess-Martin periodinane (rt, 15 h) in 70% yield. Knoevenagel condensation of **43** with ethyl hydrogen malonate generated **44** (92% yield), which underwent

slow hydrogenolysis with $Pd(OH)_2$ to the debenzylated product **45**. Removal of the residual hydroxymethyl group utilizing Triton B[17] failed in this case, but could be achieved using 1,3-diaminopropane to afford **46** in 72% yield from **44**. Compound **46**, the ethyl ester of PBG lactam, has previously been converted to PBG.[6]

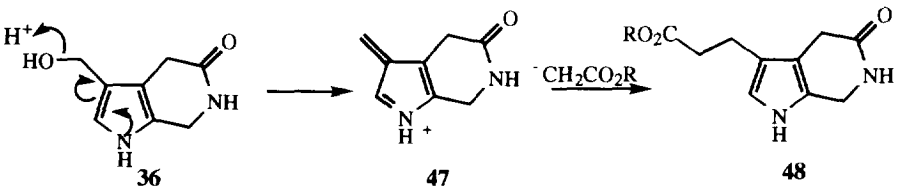


**42** R= $CH_2OH$
**43** R= CHO
**44** R= CH=CH-$CO_2Et$

**45** R= $CH_2OH$
**46** R= H

**Scheme 12**

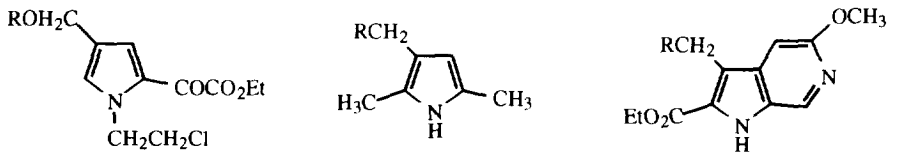
To circumvent the use of protecting groups and thus streamline the synthesis, attention was focused on β-(hydroxymethyl)pyrrole **36**. Interestingly, α-(hydroxymethyl)pyrroles are known to polymerize in acid, presumably via reactive exocyclic methylene intermediates that are susceptible to nucleophilic attack.[18] We envisioned that an appropriate carbon nucleophile might be used to substitute the OH group in **36** with a carboxymethyl group by a process of elimination-addition involving a β-alkylidenepyrrolenine cation **47** (Scheme 13).



**36** **47** **48**

**Scheme 13**

Such a transformation finds precedent in other studies. The sodium borohydride reduction of β-acylpyrroles to β-alkylpyrroles involves β-(hydroxymethyl)pyrroles as intermediates.[19] Moreover, Carpio *et al.* have converted **49** into the corresponding methyl ether **50** by heating with methanol and acid (Scheme 14).[20] The alkylation of β-(dimethylaminomethyl)pyrroles with stabilized nucleophiles has also been achieved. In an early report, pyrrole **51** reacted with diethyl acetamidomalonate and a catalytic amount of NaOH to give **52**.[21] Likewise, the condensation of **53** with sodium diethylmalonate also furnished **54**.[6a] No prior examples of the direct alkylation of β-(hydroxymethyl)pyrroles were found in the literature.



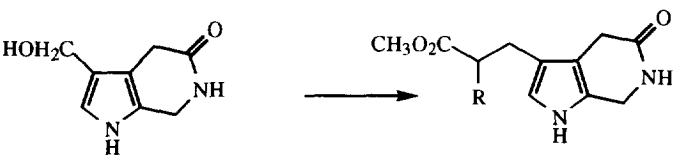
**49** R= H
**50** R= $CH_3$

**51** R= $N(CH_3)_2$
**52** R= $C(NHAc)(CO_2Et)_2$

**53** R= $N(CH_3)_2$
**54** R= $CH(CO_2Et)_2$

**Scheme 14**

In the absence of an external nucleophile, **36** proved to be unstable in DMF at 130 °C, forming a dark insoluble material. When **36** was heated with the sodium salt of dimethyl malonate in DMF at 130 °C, diester **55** was obtained in 68% yield (Scheme 15). Nucleophilic deesterification and decarboxylation with NaCN in DMF afforded the methyl ester of PBG lactam **56**, a known intermediate to PBG, in 59-73% yield.[2,5i]




**36** **55** R= $CO_2CH_3$
**56** R= H

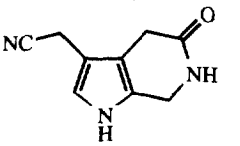
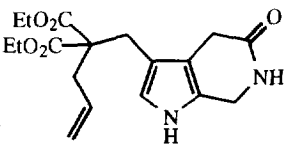
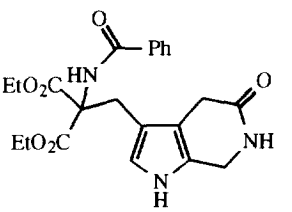
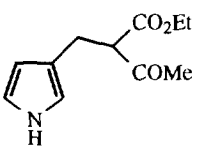
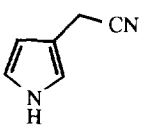
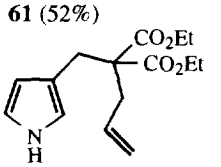
**Scheme 15**

The direct alkylation of β-hydroxymethylpyrroles is a reaction with broad scope and generality, judging from condensations using a variety of carbon nucleophiles with **36** and with 3-hydroxymethylpyrrole as reported in Table 1. Reactions were normally carried out in DMF with 5 equiv of nucleophile at 130-140 °C for 1-4 hours. Direct alkylation of **36** with NaCN gave **57** in 38% yield, representing a one carbon homologation of the β-side chain. With potassium diethylallylmalonate, the corresponding alkylated pyrrole **58** was isolated in 66% yield. The reaction of **36** with sodium diethylbenzamidomalonate gave the desired pyrrole **59** in 44% yield. Products **58** and **59** illustrate the introduction of quaternary centers and other latent functionalities at the β-position of the pyrrole ring. Alkylation of the parent 3-hydroxymethylpyrrole with ethyl acetoacetate gave the expected 1,3-dicarbonyl compound **60** in 66% yield. Besides undergoing two carbon extension, 3-hydroxymethylpyrrole also reacted with NaCN to afford **61** in 52% yield, and with sodium diethylallylmalonate to form **62** in 70% yield.

In summary, three functionalized pyrroles (i.e. **7**, **17**, and **29**) were prepared as potential intermediates for the synthesis of PBG using a novel adaptation of the van Leusen pyrrole construction. Two formal syntheses of PBG have been achieved, one of which comprises a short and efficient route to the methyl ester of PBG lactam **56** from **29** in 7 steps in 24-30% yield. A new method for the direct alkylation of β-(hydroxymethyl)pyrroles has been developed that accommodates a variety of simple carbon nucleophiles such as malonates, substituted malonates, acetoacetates, and cyanide.

The synthesis of pyrrole-containing α-aminoacids derived from intermediates like **59** may be of therapeutic interest in PDT. Active transport mechanisms for α-aminoacids have evolved in eucaryotic cells,[22] suggesting that α-aminoacid congeners of PBG might serve as precursors for highly tissue-selective PDT sensitizers. Properties of such agents may include lower toxicity and reduced skin photosensitization.

**Table 1**
Nucleophilic Alkylation of β-(Hydroxymethyl)pyrroles

| Reactant | Nucleophile | Product (Yield) |
|---|---|---|
| **36** | NaCN |  **57** (38%) |
| **36** | $KC(CH_2CH{=}CH_2)(CO_2Et)_2$ |  **58** (66%) |
| **36** | $PhCONHC(Na)(CO_2Et)_2$ |  **59** (44%) |
| 3-hydroxymethyl pyrrole | $CH_3COCH(Na)CO_2Et$ |  **60** (66%) |
| 3-hydroxymethyl pyrrole | NaCN |  **61** (52%) |
| 3-hydroxymethyl pyrrole | $NaC(CH_2CH{=}CH_2)(CO_2Et)_2$ |  **62** (70%) |

## EXPERIMENTAL SECTION

Proton-NMR spectra were taken on a Bruker AF-300 or Varian VXR-400S spectrometer. All chemical shifts were reported on the δ scale in parts per million downfield from $Me_4Si$ (0.00 ppm). Carbon-13-NMR spectra were taken on a Varian VXR-400S or Bruker AF-300 (75 MHz) spectrometer. Infrared spectra were taken on a Mattson Galaxy Model infrared spectrometer. Mass spectra were acquired using a Finnigan 3300 mass spectrometer at Cornell or at the University of Illinois Mass Spectrometry Laboratory using a VG ZAB-SE or VG 70-VSE instrument. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

Synthesis of pyrrole **7**: To a solution of NaH (67 mg, 1.69 mmol) in ether (2.11 mL) at 0 °C under Ar was added a solution of tosylmethyl isocyanide (280 mg, 1.43 mmol) and ethyl sorbate **6** (0.2 mL, 191 mg, 1.36 mmol) in DMSO:ether (1:2, 3 mL) dropwise over 15 min. The reaction was slowly warmed to rt over 3 h, then quenched with aqueous saturated $NH_4Cl$ (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting yellow solid was chromatographed (3:1 hexane:EtOAc) to afford pyrrole **7** (127 mg, 52%) as a yellow solid: $R_f$ 0.26 (3:1 hexane:EtOAc); mp 84-85 °C; $^1$H-NMR ($CDCl_3$) 8.25 (bs, 1H), 7.69 (d, 1 H, J = 16.0 Hz), 7.03 (t, 1 H, J = 2.4 Hz), 6.56 (bs, 1 H), 6.12 (d, 1 H, J = 16.0 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 2.21 (s, 3 H), 1.32 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 168.6, 139.2, 121.3, 119.1, 118.7, 118.0, 60.0, 14.3, 11.5; IR (film) 3350, 2910, 2890, 1690, 1610, 1550, 1500, 1450, 1380, 1350, 1320, 1300, 1260, 1200, 1150, 1160, 1140, 980, 850, 800 cm$^{-1}$; FABMS (m/z) 180.1 (M+1, 100%).

Synthesis of pyrrole **8**: To a solution of 1 M lithium hexamethyldisilazide in THF (1.0 mL, 1.0 mmol) at -78 °C under Ar was added a solution of tosylmethyl isocyanide (200 mg, 1.02 mmol) in THF (5 mL) dropwise over 10 min. After 40 min at -78 °C, a solution of ethyl sorbate **6** (158 mg, 1.13 mmol) in THF (1.25 mL) was added over 20 min. When the addition was complete, the bath was removed and the reaction allowed to warm to rt over 4 h. The dark red suspension was concentrated *in vacuo*, and the residue partitioned between $H_2O$ (5 mL) and $CH_2Cl_2$ (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The oil was chromatographed (3:1 hexane:EtOAc) to afford **8** (104 mg, 57%) as a yellow solid: $R_f$ 0.33 (2:1 hexane:EtOAc); mp 85-86 °C; $^1$H-NMR ($CDCl_3$) 9.69 (bs, 1 H), 7.33 (t, 1 H, J = 2.3 Hz), 6.86 (d, 1 H, J = 12.8 Hz), 6.82 (bs, 1 H), 5.97 (dq, 1 H, J = 12.8, 6.8 Hz), 4.27 (q, 2 H, J = 6.9 Hz), 1.82 (d, 3 H, J = 6.8 Hz), 1.33 (t, 3 H, J = 6.9 Hz); $^{13}$C-NMR ($CDCl_3$) 165.7, 124.5, 124.2, 123.8, 123.1, 115.3, 112.9, 59.6, 18.4, 14.3; IR (film) 3200, 2975, 2900, 1675, 1550, 1525, 1425, 1400, 1375, 1325, 1250, 1200, 1150, 1100, 1075, 1025, 975, 900, 750 cm$^{-1}$; FABMS (m/z) 180.1 (M+1, 100%).

Synthesis of bromopyrroles **9**, **10**, and **11**: To a solution of pyrrole **7** (76 mg, 0.42 mmol) in $CCl_4$ (3 mL) under Ar was added N-bromosuccinimide (83 mg, 0.47 mmol). The solution became red and a precipitate formed. After 30 min, the precipitate was filtered through Celite and washed with $CCl_4$ (7 mL). The filtrate was washed with $H_2O$ (3 x 10 mL), dried with MgSO4, filtered, and concentrated *in vacuo*. The resulting brown oil was chromatographed (3:1 hexane:EtOAc) to afford **9** (16 mg, 11%) and a 1:5 mixture of **10** and **11** (48 mg, 44%) as yellow solids that slowly turned dark on standing.

**9**: $R_f$ 0.42 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.37 (bs, 1 H), 7.55 (d, 1 H, J = 16.2 Hz), 6.29 (d, 1 H, J = 16.2 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 2.15 (s, 1 H), 1.33 (t, 3 H, J = 7.1 Hz).
**10** (minor): $R_f$ 0.23 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.70 (bs, 1 H), 7.55 (d, 1 H, J = 16.2 Hz), 7.37 (d, 1 H, J = 3.2 Hz), 6.28 (d, 1 H, J = 16.2 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 2.15 (s, 3 H), 1.33 (t, 3 H, J = 7.1 Hz).
**11** (major): $R_f$ 0.31 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.46 (bs, 1 H); 7.59 (d, 1 H, J = 16.0 Hz), 7.02 (d, 1 H, J = 2.9 Hz), 6.11 (d, 1 H, J = 16.0 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 2.14 (s, 3 Hz), 1.32 (t, 3 H, J = 7.1 Hz).
Synthesis of tribromopyrrole **12**: To a solution of pyrrole **7** (44 mg, 0.17 mmol) in $CCl_4$ (3 mL) under Ar was added N-bromosuccinimide (92 mg, 0.51 mmol). The solution turned red and a precipitate formed. After 1.5 h, the reaction mixture was filtered through Celite and washed with $CCl_4$ (15 mL). The filtrate was concentrated *in vacuo*, and the resulting brown oil was chromatographed (15:1 hexane:EtOAc) to afford **12** (20 mg, 27%) as a yellow solid that darkened on standing: $R_f$ 0.13 (9:1 hexane:EtOAc), $^1$H-NMR ($CDCl_3$) 7.46 (d, 1 H, J = 16.2 Hz), 6.68 (d, 1 H, J = 16.2 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 2.16 (s, 3 H), 1.37 (t, 3 H, J = 7.1 Hz).
Synthesis of pent-2-en-1,5-diol **13**: To a 1 M DIBAL solution in toluene (11.6 mL, 11 mmol) at 0 °C under Ar was added a solution of diethylglutaconate (0.5 mL, 526 mg, 2.82 mmol) in $CH_2Cl_2$ (2 mL) dropwise over 15 min. The reaction was slowly warmed to rt over 3 h, then quenched with MeOH (12 mL) at 0 °C. The resulting precipitate was filtered and washed with hot MeOH (12 mL). The filtrate was concentrated *in vacuo* to give a semi-solid product that was purified by flash chromatography (9:1 $CH_2Cl_2$:MeOH) to afford **13** (230 mg, 80%) as a clear oil: $R_f$ 0.14 (9:1 $CH_2Cl_2$:MeOH); $^1$H-NMR ($CDCl_3$) 5.63 (m, 2 H), 4.30 (bs, 1 H), 4.16 (bs, 1 H), 3.99 (bs, 2 H), 3.57 (bs, 2 H), 2.23 (t, 2 H, J = 5.8 Hz); $^{13}$C-NMR ($CDCl_3$) 131.2, 128.7, 62.6, 61.1, 35.1; IR (neat) 3300, 2950, 2900, 1700, 1450, 1250, 1200, 1100, 1050, 1000, 975, 900 $cm^{-1}$.
Synthesis of Dienoate **16**: A solution of **13** (167 mg, 1.64 mmol) in acetonitrile (6 mL) under Ar was stirred with activated manganese dioxide (3.3 g, 20 wt. equiv) at rt for 4 h. The suspension was filtered through Celite and washed with acetonitrile (14 mL). Because **14** was volatile, the acetonitrile solution was typically used in the next step without purification. A portion of the filtrate was concentrated *in vacuo* to give an analytical sample of **14** as a clear oil: $R_f$ 0.51 (9:1 $CH_2Cl_2$:MeOH); $^1$H-NMR ($CDCl_3$) 9.53 (d, 1 H, J = 7.0 Hz), 6.91 (dt, 1 H, J = 15.7, 6.8 Hz), 6.21 (ddt, 1 H, J = 15.7, 6.8, 1.4 Hz), 4.43 (t, 1 H, J = 6.8 Hz), 3.85 (m, 2 H), 2.61 (ddt, 2 H, J = 6.8, 6.8, 1.4 Hz); $^{13}$C-NMR ($CDCl_3$) 193.9, 154.9, 134.4, 60.6, 35.7.
To the abovementioned acetonitrile solution of **14** under Ar was added methyl(triphenylphosphoranylidene)acetate (1.32 g, 3.93 mmol) at rt and the solution heated at reflux for 12 h. Solvent was distilled to leave an oil containing the conjugated dienol **15**, which was typically used in the next step without purification: $R_f$ 0.47 (1:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 7.26 (dd, 1 H, J = 15.4, 10.6 Hz), 6.27 (dd, 1 H, J = 15.2, 10.7 Hz), 6.13 (dt, 1 H, J = 15.2, 6.7 Hz), 5.82 (d, 1 H, J = 15.4 Hz), 3.74 (s, 3 H), 3.72 (t, 2 H, J = 6.0 Hz), 2.44 (dt, 2 H, J = 6.7, 6.0 Hz), 2.2 (bs, 1 H); $^{13}$C-NMR ($CDCl_3$) 167.6, 144.7, 140.2, 130.4, 119.5, 61.3, 51.4, 36.1.

Dienol **15** was diluted with pyridine (5 mL) and treated with *t*-butyldimethylsilyl chloride (320 mg, 2.12 mmol) under Ar at rt for 5 h. The reaction was cooled to 0 °C, diluted with cold ether (10 mL), and poured into cold 2 N HCl (10 mL). The aqueous layer was extracted with ether (4 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting red oil was chromatographed (20:1 petroleum ether:ether) to afford **16** (181 mg, 41%) as a mixture of isomers:

**16** (*trans, trans* isomer; major): clear oil; $R_f$ 0.15 (20:1 petroleum ether:ether); $^1$H-NMR ($CDCl_3$) 7.27 (dd, 1 H, J = 15.4, 10.0 Hz); 6.23 (dd, 1 H, J = 15.4, 10.0 Hz), 6.13 (dt, 1 H, J = 15.2, 6.6 Hz), 5.80 (d, 1 H, J = 15.4 Hz), 3.73 (s, 3 H), 3.69 (t, 2 H, J = 6.4 Hz), 2.38 (dt, 2 H, J = 6.6, 6.4 Hz), 0.88 (s, 9 H), 0.04 (s, 6 H); $^{13}$C-NMR ($CDCl_3$) 167.5, 144.9, 140.9, 129.9, 119.1, 62.0, 51.4, 36.4, 25.8, -5.4; IR (film) 2950, 2925, 2900, 2850, 1725, 1650, 1625, 1475, 1450, 1425, 1375, 1325, 1300, 1250, 1200, 1150, 1125, 1100, 1050, 1000, 925, 850, 775 $cm^{-1}$; CIMS (m/z) 271.2 (M+1, 100%).

**16** (*trans, cis* isomer; minor): clear oil; $R_f$ 0.22 (20:1 petroleum ether:ether); $^1$H-NMR ($CDCl_3$) 7.39 (ddt, 1 H, J = 15.3, 11.3, 1.3 Hz), 6.55 (dd, 1 H, J = 11 .3, 11.3 Hz), 6.09 (dt, 1 H, J = 15.3, 7.2 Hz), 5.59 (d, 1 H, J = 11.3 Hz), 3.72 (s, 3 H), 3.70 (t, 2 H, J = 6.6 Hz), 2.42 (ddt, 2 H, J = 7.2, 6.6, 1.3 Hz), 0.88 (s, 9 H), 0.05 (s, 6 H); $^{13}$C-NMR ($CDCl_3$) 166.9, 145.2, 141.9, 128.4, 115.5, 62.3, 51.1, 36.5, 25.9, 18.3, -5.3; IR (film) 2975, 2960, 2950, 1725, 1650, 1625, 1475, 1460, 1450, 1400, 1375, 1350, 1250, 1200, 1175, 1100, 1025, 975, 950, 850, 775, 750, 675 $cm^{-1}$; CIMS (m/z) 271.22 ($M^+$, 4%), 139.4 ($M^+$ - OTBDMS, 100%).

Synthesis of pyrroles **17** and **18**: To a solution of NaH (32 mg, 0.81 mmol) in ether (1 mL) under Ar was added a solution of tosylmethyl isocyanide (158 mg, 0.81 mmol) and **16** (0.2 mL, 199 mg, 0.73 mmol) in DMSO:ether (1:2, 2 mL) dropwise over 15 min. Gas evolution was observed, and the reaction was stirred at rt for 1 h. The resulting two-phase mixture was partitioned between $H_2O$ (3 mL) and ether (3 mL). The aqueous layer was extracted with ether (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a dark oil. Chromatography of the product [6:1 hexane:EtOAc (40 mL) and 3:1 hexane:EtOAc (40 mL)] afforded a 7:1 mixure of regioisomers **17** and **18** as an oil (125 mg, 55%; 70% based on recovered **16**).

**17** (major): $R_f$ 0.38 (2:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.02 (bs, 1 H), 7.69 (d, 1 H, J = 16.0 Hz), 7.05 (t, 1 H, J = 2.4 Hz), 6.62 (s, 1 H), 6.11 (d, 1 H, J = 16.0 Hz), 3.77 (t, 2 H, J = 7.0 Hz), 3.76 (s, 3 H), 2.80 (t, 2 H, J = 7.0 Hz), 0.88 (s, 9 H), 0.02 (s, 6 H); $^{13}$C-NMR ($CDCl_3$) 168.7, 138.8, 120.5, 120.1, 119.0, 118.0, 112.3, 63.7, 51.3, 29.3, 25.9, 18.3, -5.4; IR (film) 3350, 2975, 2960, 2850, 1700, 1625, 1550, 1525, 1475, 1450, 1400, 1350, 1275, 1175, 1100, 1000, 850, 825, 775 $cm^{-1}$; CIMS (m/z) 310.2 (M+1, 19%), 178.1 ($M^+$ - OTBDMS, 100%).

**18** (minor): $R_f$ 0.38 (2:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) [partial data] 7.36 (m, 1 H), 6.41 (d, 1 H, J = 16.0 Hz), 6.35 (m, 1 H), 5.88 (dt, 1 H, J = 16.0, 7.0 Hz), 3.72 (t, 2 H, J = 7.0 Hz), 2.81 (s, 3 H), 2.41 (ddt, 1 H, J = 7.0, 7.0, 1.4 Hz), 0.91 (s, 9 H), 0.03 (s, 6 H); $^{13}$C-NMR ($CDCl_3$) [partial data] 165.7, 125.4, 124.5, 123.8, 115.3, 113.1, 63.3, 50.8, 36.7, 18.3, -5.2.

Synthesis of N-benzylpyrrole ester **19**: To a solution of 1 M lithium hexamethyldisilazide in THF (0.28 mL, 0.28 mmol) at -78 °C under Ar was added a solution of tosylmethyl isocyanide (55 mg, 0.28 mmol) in THF (2 mL) dropwise over 10 min. After 40 min at -78 °C, a solution of **16** (70 mg, 0.26 mmol) in THF (1 mL) was added over 20 min, and the reaction allowed to warm to rt over 4 h. The dark suspension was concentrated *in vacuo*, and the residue partitioned between $H_2O$ (5 mL) and $CH_2Cl_2$ (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an oil.

The product was dissolved in DMF (2 mL) under Ar and treated with NaH (11 mg, 0.27 mmol). The reaction was stirred at rt for 30 min, then treated with benzyl bromide (0.03 mL, 39 mg, 2.33 mmol). After 15 min, the reaction was concentrated *in vacuo*. The oily product was chromatographed (6:1 hexane:EtOAc) to

afford **19** (24 mg, 23%) as an oil: $R_f$ 0.48 (6:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 7.36 - 7.28 (m, 2 H), 7.25 - 7.24 (m, 1 H), 7.16 - 7.12 (m, 2 H), 6.89 (d, 1 H, J = 16.0 Hz), 6.74 (d, 1 H, J = 2.3 Hz), 5.92 (dt, 1 H, J = 16.0, 7.0 Hz), 4.99 (s, 2 H), 3.77 (s, 3 H), 3.68 (t, 2 H, J = 7.0 Hz), 2.39 (ddt, 2 h, J = 7.0, 7.0, 1.4 Hz), 0.88 (s, 9 H), 0.12 (s, 6 H); $^{13}$C-NMR ($CDCl_3$) 165.3, 136.4, 128.9, 128.2, 127.3, 127.2, 125.4, 124.6, 123.7, 118.6, 113.0, 63.3, 53.9, 50.8, 36.8, 26.0, 18.4, -5.2; IR (film) 2950, 2925, 2850, 1700, 1525, 1450, 1400, 1250, 1200, 1150, 11000, 975, 850, 775, 700 $cm^{-1}$; CIMS (m/z) 400.3 (M+1, 29%), 212.1 ($M^+$ - $CHCH_2CH_2OTBDMS$ - $CH_3$, 100%).

Synthesis of formylpyrroles **20** and **22**: To a solution of DMF (0.04 mL, 40 mg, 0.53 mmol) in $CH_2Cl_2$ (0.3 mL) at 0 °C under Ar was added $POCl_3$ (0.03 mL, 0.45 mg, 0.29 mmol) dropwise. The ice bath was removed and the clear solution was allowed to warm to rt for 30 min, then recooled to -78 °C. A solution of **17** (43 mg, 0.22 mmol) in $CH_2Cl_2$ (1.3 mL) was added dropwise over 20 min. The bath gradually warmed to rt over 4 h, and the reaction was quenched with a solution of NaOAc (49 mg, 0.5 mmol) in $H_2O$ (2 mL). The two layers were stirred for 30 min, then separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting yellow solid was chromatographed [19:1 $CH_2Cl_2$:$CH_3CN$ (25 mL) and 19:1 $CH_3CN$:MeOH (25 mL)] to afford a 5:1 mixture of **20** and **22** (7 mg, 9%) and a 3:1 mixture of **21** and **23** (21 mg, 38%):

**20** (major): oil; $R_f$ 0.23 (19:1 $CH_2Cl_2$:$CH_3CN$); $^1$H-NMR ($CDCl_3$) 9.85 (s, 1 H), 9.62 (bs, 1 H), 7.99 (d, 1 H, J = 16.1 Hz), 7.06 (d, 1 H, J = 2.8 Hz), 6.36 (d, 1 H, J = 16.1 Hz), 3.88 (s, 3 H), 3.86 (t, 2 H, J = 6.5 Hz), 2.87 (t, 2 H, J = 6.5 Hz), 0.93 (s, 9 H), 0.07 (s, 6 H).

**22** (minor): oil; $R_f$ 0.15 (19:1 $CH_2Cl_2$:$CH_3CN$), $^1$H-NMR ($CDCl_3$) [partial data] 9.72 (s, 1 H), 9.70 (s, 1 H), 7.55 (d, 1 H, J = 16.0 Hz), 7.44 (d, 1 H, J = 3.0 Hz), 6.25 (d, 1 H, J = 16.0 Hz), 3.13 (t, 2 H, J = 6.2 Hz), 0.96 (s, 9 H), 0.06 (s, 6 H).

Synthesis of hydroxypyrrole **24**: To a solution of **17** (76 mg, 0.24 mmol) in THF (2.5 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (0.49 mL, 0.49 mmol). The resulting dark solution was stirred at rt for 3 h, then concentrated *in vacuo* to a dark oil. The product was chromatographed [2:1 hexane:EtOAc (50 mL) and 1:1 hexane: EtOAc (50 mL)] to afford **24** (43 mg, 90%) as an oil: $R_f$ 0.1 (1:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 7.68 (d, 1 H, J = 16.0 Hz), 7.13 (d, 1 H, J = 2.0 Hz), 6.61 (d, 1 H, J = 2.0 Hz), 6.07 (d, 1 H, J = 16.0 Hz), 3.72 (s, 3 H), 3.67 (t, 2 H, J = 7.0 Hz), 2.78 (t, 2 H, J = 7.0 Hz); $^{13}$C-NMR ($CDCl_3$) 170.8, 141.2, 125.7, 122.6, 120.7, 119.4, 111.5, 63.7, 51.7, 30.3.

Synthesis of formylpyrroles **21** and **23**: To a solution of DMF (0.04 mL, 38 mg, 0.53 mmol) in $CH_2Cl_2$ (0.25 mL) at 0 °C under Ar was added $POCl_3$ (0.03 mL, 0.45 mg, 0.29 mmol) dropwise. The ice bath was removed and the clear solution was allowed to warm to rt for 30 min, then recooled to -78 °C. A solution of **24** (43 mg, 0.22 mmol) in $CH_2Cl_2$ (1.2 mL) was added dropwise over 20 min. The bath warmed to rt over 4 h, and the reaction was quenched with a solution of NaOAc·3$H_2O$ (49 mg, 0.36 mmol) in $H_2O$ (2 mL). The two layers were stirred for 30 min, then separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow solid. Chromatography of the solid (19:1 $CH_2Cl_2$:$CH_3CN$) afforded a 9:1 mixture of regioisomers **21** and **23** (16 mg, 34%):

**21** (major): oil; $R_f$ 0.19 (19:1 $CH_2Cl_2$:$CH_3CN$); $^1$H-NMR ($CDCl_3$) 9.86 (bs, 1 H), 9.80 (s, 1 H), 8.06 (s, 1 H), 7.93 (d, 1 H, J = 16.1 Hz), 7.01 (d, 1 H, J = 2.6 Hz), 6.30 (1 H, J = 16.1 Hz), 4.37 (t, 2 H, J = 6.8 Hz), 3.88 (s,

3 H), 2.99 (t, 2 H, J = 6.8 Hz); $^{13}$C-NMR ($CDCl_3$) 178.1, 160.9, 134.4, 131.1, 127.0, 124.9, 121.8, 121.3, 63.0, 51.9, 25.2; IR (film) 3550, 3250, 2950, 1725, 1625, 1550, 1500, 1450, 1425, 1400, 1350, 1300, 1175, 975, 775 $cm^{-1}$; CIMS (m/z) 252.1 (M+1, 16%), 220.1 ($M^+$ - CHO - 2 H, 100%).

**23** (minor): oil; $R_f$ 0.1 (19:1 $CH_2Cl_2$:$CH_3CN$); $^1$H-NMR ($CDCl_3$) 9.98 (bs, 1 H), 9.69 (s, 1 H), 8.03 (s, 1 H), 7.63 (d, 1 H, J = 16.0 Hz), 7.41 (d, 1 H, J = 3.3 Hz), 6.22 (d, 1 H, J = 16.0 Hz), 4.33 (t, 2 H, J = 6.7 Hz), 3.80 (s, 3 H), 3.25 (t, 2 H, J = 6.7 Hz); $^{13}$C-NMR ($CDCl_3$) 178.2, 160.7, 135.3, 131.2, 130.0, 125.5, 121.3, 116.0, 63.6, 51.7, 23.0.

Synthesis of formylpyrroles **25** and **26**: To a solution of DMF (0.4 mL, 37 mg, 0.51 mmol) in $CH_2Cl_2$ (0.25 mL) at 0 °C under Ar was added $POCl_3$ (0.026 mL, 43 mg, 0.28 mmol) dropwise. The cooling bath was removed and the clear solution allowed to warm to rt for 30 min, then recooled to -78 °C. A solution of pyrrole **7** (42 mg, 0.23 mmol) in $CH_2Cl_2$ (1.5 mL) was added dropwise over 20 min. The reaction was gradually warmed to rt over 4 h, and the reaction was quenched with a solution of NaOAc (38 mg, 0.28 mmol) in $H_2O$ (1.4 mL). The two layers were stirred for 30 min, then separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow solid. The solid was purified by flash chromatography (3:1 hexane:EtOAc) to afford **25** and **26** (21 mg, 43%) as a 2:3 mixture of regioisomers:

**25** (minor): yellow solid; $R_f$ 0.26 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 10.08 (bs, 1 H), 9.80 (s, 1 H), 7.98 (d, 1 H, J = 16.1 Hz), 6.93 (d, 1 H, J = 2.6 Hz), 6.31 (d, 1 H, J = 16.1 Hz), 4.27 (q, 2 H, J = 7.1 Hz), 2.23 (s, 3 H), 1.34 (t, 3 H, J = 7.1 Hz).

**26** (major): yellow solid; $R_f$ 0.18 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 10.30 (bs, 1 H), 9.79 (s, 1 H), 7.63 (d, 1 H, J = 16.1 Hz), 7.37 (d, 1 H, J = 3.2 Hz), 6.17 (d, 1 H, J = 16.1 Hz), 4.24 (q, 2 H, J = 7.1 Hz), 2.46 (s, 3 H), 1.32 (t, 3 H, J = 7.1 Hz).

Synthesis of glutaconate dimer **28**: To a solution of sodium hydride (80% in mineral oil, 20 mg, 0.64 mmol) in ether (1 mL) under Ar was added a solution of tosylmethyl isocyanide (105 mg, 0.54 mmol) and diethylglutaconate **27** (100 mg, 0.54 mmol) in DMSO:ether (1:2, 2.5 mL) dropwise over 15 min. Gas evolution was observed, and the reaction was stirred at rt for 4 h. The resulting two-phase mixture was partitioned between $H_2O$ (3 mL) and ether (3 mL). The aqueous layer was extracted with ether (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Chromatography of the product (2:1 hexane:EtOAc) afforded **28** (88 mg, 88%) as a yellow oil: $R_f$ 0.13 (7:3 petroleum ether:ether); $^1$H-NMR ($CDCl_3$) 7.05 (t, 1 H, J = 7.0 Hz), 4.24 - 4.0 (m, 8 H), 3.53 (d, 2 H, J =2.7 Hz), 2.77 (dd, 2 H, J = 16.0, 9.0 Hz), 2.57 (dd, 2 H, J = 16.0, 6.0 Hz), 2.52 - 2.33 (m, 1 H), 1.60 - 1.16 (m, 12 H); IR (film) 3000, 2950,1740, 1490, 1450, 1390, 1275, 1125, 1050 $cm^{-1}$.

Synthesis of pyrrole diester **29**: To a 1 M solution of lithium hexamethyldisilazide in THF (25 mL, 25 mmol) cooled to -78 °C under Ar was added a solution of tosylmethyl isocyanide (5 g, 25 mmol) in THF (120 mL) dropwise over 40 min via syringe pump. After 40 min at -78 °C, a solution of **27** (4.95 mL, 5.24 g, 28 mmol) in THF (30 mL) was added over 40 min via syringe pump at -78 °C, the cold bath was removed, and the reaction allowed to warm to rt over 4 h. The dark red suspension was concentrated *in vacuo*, and the residue partitioned between $H_2O$ (150 mL) and $CH_2Cl_2$ (150 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 150 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a red oil. The oil was chromatographed (2:1 hexane:EtOAc) to afford **29** (4.02 g, 72%) as a yellow oil:

$R_f$ 0.17 (2:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 9.62 (br. s, 1 H), 7.39 (t, 1 H, J = 2.8 Hz), 6.67 (t, 1 H, J = 2.0 Hz), 4.32 (q, 2 H, J = 7.1 Hz), 4.25 (q, 2 H, J = 7.0 Hz), 3.84 (s, 2 H), 1.39 (t, 3 H, J = 7.1 Hz), 1.35 (t, 3 H, J = 7.0 Hz); $^{13}$C-NMR ($CDCl_3$) 172.6, 165.1, 124.6, 118.8, 117.3, 114.6, 60.6, 59.5, 31.9, 29.7, 14.4, 14.2; IR (film) 3350, 3000, 2900, 2850, 1740, 1700, 1550, 1525, 1450, 1400, 1360, 1325, 1250, 1150, 1060, 1030, 750 $cm^{-1}$; CIMS (m/z) 226.1 (M+1, 90%), 180.1 ($M^+$ - EtOH, 100%).

Synthesis of formylpyrroles **30** and **31**: To a solution of DMF (1.85 mL, 1.76 g, 24 mmol) in $CH_2Cl_2$ (12 mL) at 0 °C under Ar was added $POCl_3$ (1.23 mL, 2.02 g, 13 mmol) dropwise. The ice bath was removed and the clear solution was allowed to warm to rt for 30 min, then recooled to -78 °C. A solution of pyrrole **29** (2.49 g, 11 mmol) in $CH_2Cl_2$ (55 mL) was added dropwise over 20 min. The bath warmed to rt over 4 h, and the reaction was quenched with a solution of NaOAc (1.8 g, 13 mmol) in $H_2O$ (40 mL). The two layers were stirred for 30 min, then separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow solid. The product was purified by flash chromatography (2:1 hexane:EtOAc) to afford an 8:1 mixture of regioisomers **30** and **31** (2.7 g, 96%) as a yellow solid:

**30** (major; an analytical sample was obtained after 1 more flash column on the mixture): $R_f$ 0.26 (1:1 hexane:EtOAc); mp 121-122 °C; $^1$H-NMR ($CDCl_3$) 10.52 (br. s, 1 H), 9.62 (s, 1 H), 7.62 (d, 1 H, J = 3.5 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 4.15 (q, 2 H, J = 7.1 Hz), 4.1 (s, 2 H), 1.30 (t, 3 H, J = 7.1 Hz), 1.24 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 178.8, 170.8, 163.8, 131.0, 130.3, 128.7, 117.3, 61.3, 60.2, 30.0, 14.3, 14.2; IR (film) 3330, 3200, 300, 2950, 2900, 1730, 1660, 1575, 1525, 1440, 1410, 1375, 1350, 1280, 1225, 1190, 1100, 1040, 810, 760 $cm^{-1}$; FABMS (m/z) 254.1 (M+1, 100%); CIMS (m/z) 254.1 (M+1, 18%), 208.1 ($M^+$ - EtOH, 98%).

**31** (minor; an analytical sample was obtained after 2 more flash columns on the mixture): $R_f$ 0.33 (1:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 10.19 (s, 1H), 9.61 (br. s, 1 H), 7.02 (d, 1 H, J = 2.4 Hz), 4.36 (q, 2 H, J = 7.1 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.79 (s, 2 H), 1.38 (t, 3 H, J = 7.1 Hz), 1.28 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 182.0, 171.5, 163.6, 133.2, 124.7, 121.0, 120.4, 60.7, 60.6, 31.9, 14.1, 14.1; IR (film) 3250, 2975, 2900, 1700, 1650, 1575, 1500, 1450, 1600, 1350, 1325, 1275, 1250, 1125, 1075, 1025, 775 $cm^{-1}$; CIMS (m/z) 254.1 (M+1, 44%), 208.1 ($M^+$ -EtOH, 100%).

Synthesis of oxime **32**: A suspension of $NH_2OH$ •HCl (1.45 g, 20 mmol) in EtOH (25 mL) was titrated with 10 M NaOH (1-2 mL) from pH 1 to 6. The NaCl was filtered and the solution was kept under Ar for use. A solution of **30** and **31** (726 mg, 2.86 mmol) in EtOH (33 mL) was treated with four 5 mL (4.3 mmol) portions of the above solution of $NH_2OH$ in EtOH after 0, 2, 4, and 6 h (adding a total of 20 mL, 17.2 mmol). After 16 h, the reaction was concentrated and the residue partitioned between $H_2O$ (20 mL) and $CH_2Cl_2$ (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The yellow product was chromatographed (2:1 hexane:EtOAc) to yield a mixture of oxime **32** and its regioisomer (769 mg, quant.):

**32** (major; an analytical sample was obtained after 1 more flash column on the mixture): $R_f$ 0.37 (1:1 hexane:EtOAc); mp 93-97 °C; $^1$H-NMR ($CDCl_3$) *anti* (major) 10.51 (s, 1 H), 7.99 (s, 1 H), 7.44 (d, 1 H, J = 3.4 Hz), 7.31 (bs, 1 H), 4.23 (q, 2 H, J = 7.2 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 1.29 (t, 3 H, J = 7.2 Hz), 1.23 (t, 3 H, J = 7.2 Hz); $^1$H-NMR ($CDCl_3$) *syn* (minor) 10.20 (s, 1 H), 7.99 (s, 1 H), 7.38 (d, 1 H, J = 3.2 Hz), 7.31 (bs, 1 H), 4.23 (q, 2 H, J = 7.2 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 3.81 (s, 2 H), 1.29 (t, 3 H, J = 7.2 Hz), 1.23 (t, 3 H, J = 7.2 Hz); $^{13}$C-NMR ($CDCl_3$) *anti* (major) 171.6, 164.7, 135.8, 126.4, 123.9, 121.4, 115.2, 61.1, 59.9, 30.4,

14.2; $^{13}$C-NMR ($CDCl_3$) *syn* (minor) 171.9, 164.7, 140.1, 127.0, 124.1, 119.9, 115.8, 61.0, 59.8, 30.2, 14.1; IR (film) 3400, 2990, 2880, 1700, 1550, 1500, 1400, 1350, 1300, 1250, 1160, 1140, 1075, 950, 900, 825, 760, 740, 700 cm$^{-1}$; EIMS (m/z) 268.1 ($M^+$, 64%), 223.1 ($M^+$ - EtO, 100%); CIMS (m/z) 269.1 (M+1, 100%), 223.0 ($M^+$ - EtOH, 82%).

Regioisomer (minor; an analytical sample was obtained after 2 more columns on the mixture): $R_f$ 0.20 (2:1 hexane:EtOAc); mp 150-153 °C; $^1$H-NMR ($CDCl_3$) *anti* (major) 10.59 (bs, 1 H), 8.30 (s, 1 H), 6.83 (d, 1 H, J = 2.7 Hz), 4.29 (q, 2 H, J = 7.1 Hz); 4.18 (q, 2 H, J = 7.1 Hz), 3.73 (s, 2 H), 1.37 (t, 3 H, J = 7.1 Hz), 1.28 (t, 3 H, J = 7.1 Hz); $^1$H-NMR ($CDCl_3$) *syn* (minor) 9.73 (s, 1 H), 8.66 (s, 1 H), 6.71 (d, 1 H, J = 2.4 Hz), 4.25 (q, 2 H, J = 7.0 Hz), 4.17 (q, 2 H, J = 7.2 Hz), 3.73 (s, 2 H), 1.33 (t, 3 H, J = 7.0 Hz), 1.25 (t, 3 H, J = 7.2 Hz), $^{13}$C-NMR ($CDCl_3$) *anti* (major) 172.6, 164.5, 142.5, 137.1, 120.9, 118.8, 115.5, 60.9, 60.2, 32.6, 14.2, 14.2; $^{13}$C-NMR ($CDCl_3$) *syn* (minor) 172.7, 164.6, 129.1, 127.6, 120.5, 119.0, 115.5, 60.8, 60.1, 32.4, 14.3, 14.2; IR (film) 3300, 2900, 1725, 1700, 1425, 1400, 1375, 1350, 1250, 1200, 1075, 1025, 925, 775 cm$^{-1}$; EIMS (m/z) 268.1 ($M^+$, 28%), 148 ($M^+$ - 2 EtO - NO, 100%).

Synthesis of bicyclic lactam **34**: To a solution of oximes **32** and its regioisomer (769 mg, 2.86 mmol) in EtOH (47 ml) was added $Pd(OH)_2$ on carbon (Pearlman's catalyst, 160 mg) and 2 N HCl (1.45 mL, 2.9 mmol). The suspension was flushed with $H_2$ three times and maintained under a balloon for 2 h at rt. The reaction was filtered through Celite and concentrated to give amine **33** as a yellow solid.

Amine **33** was redissolved in EtOH (40 mL) and treated with a 0.35 M solution of NaOEt (8.3 mL, 2.9 mmol). The reaction was heated to 40 °C for 5 h. The suspension was then cooled to rt and concentrated *in vacuo*, suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (100 mg), and concentrated *in vacuo*. The resulting powder was added to a pre-packed column and chromatographed [9:1 $CH_2Cl_2$:MeOH (100 mL) and 4:1 $CH_2Cl_2$:MeOH (100 mL)] to afford bicyclic lactam **34** (474 mg, 86%) as a yellow solid: $R_f$ 0.25 (9:1 $CH_2Cl_2$:MeOH); mp 260 °C; $^1$H-NMR (DMSO-$d_6$) 11.33 (bs, 1 H), 7.80 (s, 1H), 7.39 (d, 1 H, J = 3.0 Hz), 4.27 (s, 2 H), 4.13 (q, 2 H, J = 7.1 Hz), 1.23 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR (DMSO-$d_6$) 169.0, 164.2, 124.6, 122.1, 112.9, 111.7, 58.8, 40.4, 30.4, 14.1; IR (KBr) 3290, 3190, 3100, 3010, 2910, 2850, 2700, 1700, 1640, 1600, 1550, 1490, 1350, 1300, 1250, 1200, 1160, 1100, 1090, 1050, 1010, 860, 750 cm$^{-1}$; EIMS (m/z) 208.1 ($M^+$, 100%).

Synthesis of hydroxymethylpyrrole **36**: To a suspension of **34** (111 mg, 0.533 mmol) in THF (10 mL) under Ar was added 1 M DIBAL in toluene (2.60 mL, 2.60 mmol). A mild exotherm was noted and the reaction was stirred at rt for 30 min. The solution was cooled to 0 °C and quenched slowly with MeOH (10 mL). The resulting precipitate was filtered, then washed with hot MeOH (10 mL), and the filtrate concentrated *in vacuo* to give a yellow solid. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (100 mg), and concentrated *in vacuo*. The resulting powder was added to a pre-packed column and chromatographed [4:1 $CH_2Cl_2$:MeOH (150 mL) and 7:3 $CH_2Cl_2$:MeOH (150 mL)] to afford **36** (760 mg, 86%) as a solid: $R_f$ 0.25 (4:1 $CH_2Cl_2$:MeOH); mp 250 °C (dec.); $^1$H-NMR (DMSO-$d_6$) 10.35 (s, 1 H), 7.69 (s, 1 H), 6.57 (s, 1 H), 4.42 (t, 1 H, J = 5.1 Hz), 4.24 (bs, 2 H), 4.22 (d, 2 H, J = 5.1 Hz), 3.18 (t, 2 H, J = 2.9 Hz); $^{13}$C-NMR (DMSO-$d_6$) 169.6, 120.4, 120.0, 116.2, 110.8, 55.3, 40.4, 29.1; IR (KBr) 3400, 3350, 3200, 2850, 2800, 1650, 1620, 1520, 1490, 1410, 1350, 1260, 1250, 1200, 1180, 1090, 1060, 1030, 980, 960, 850, 760, 740 cm$^{-1}$.

Synthesis of monobenzyllactam **37**: To a solution of aldehyde **30** (582 mg, 2.3 mmol) in benzene (23 mL) under Ar was added benzylamine (246 mg, 0.25 mL, 2.3 mmol). After 5 h at reflux, the solution was

concentrated *in vacuo* to give the corresponding imine as a pale yellow solid: $^1$H-NMR ($CDCl_3$) 8.25 (s, 1 H), 7.31 (m, 4 H), 4.73 (s, 2 H), 4.25 (q, 2 H, J = 7.1 Hz), 4.17 (q, 2 H, J = 7.1 Hz), 3.94 (s, 2 H), 1.32 (t, 3 H, J = 7.1 Hz), 1.26 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 171.3, 164.4, 150.1, 139.0, 128.7, 128.5, 127.9, 127.2, 126.9, 121.3, 116.2, 64.6, 60.9, 59.7, 30.1, 14.4, 14.2; IR (film) 3200, 2920, 2820, 1730, 1700, 1630, 1510, 1480, 1410, 1390, 1350, 1330, 1275, 1250, 1210, 1190, 1100, 1050, 1020, 760, 750, 740, 700 cm$^{-1}$.

The imine was dissolved in MeOH (20 mL) and cooled to 0 °C under Ar. To this solution was added $NaBH_4$ (87 mg, 2.3 mmol). Gas evolution was observed. After stirring at 0 °C for 30 min, the solution was quenched with 2 N HCl dropwise until gas evolution ceased. The solution was concentrated *in vacuo* and the residue partitioned between $H_2O$ (10 mL) and $CH_2Cl_2$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the corresponding amine as a yellow solid, which was used without purification in the next step: $R_f$ 0.25 (9:1 $CH_2Cl_2$:MeOH); mp 153-159 °C; $^1$H-NMR ($CDCl_3$) 10.61 (br. s, 1 H), 7.32 (m, 5 H), 6.89 (br. s, 1 H), 4.22 (q, 2 H, J = 7.1 Hz), 4.13 (q, 2 H, J = 7.1 Hz), 3.82 (s, 2 H), 3.80 (s, 2 H), 3.71 (s, 2 H), 1.30 (t, 3 H, J = 7.1 Hz), 1.26 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 172.5, 165.0, 138.8, 128.9, 128.5, 128.2, 127.4, 123.5, 114.8, 114.1, 60.7, 59.4, 53.0, 43.2, 30.3, 14.4, 14.2; IR (film) 3400, 3320, 3190, 3090, 3000, 2990, 2900, 1700, 1600, 1525, 1450, 1425, 1375, 1340, 1260, 1240, 1180, 1150, 1100, 1025, 940, 750, 700 cm$^{-1}$.

To a suspension of amine in absolute EtOH (30 mL) under Ar was added 1 M NaOEt (5 mL). The suspension became homogeneous at reflux, then a precipitate formed. After 6 h, the reaction mixture was concentrated *in vacuo* to give a yellow solid. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (200 mg), and concentrated *in vacuo*. The resulting powder was added to a pre-packed flash column and chromatographed (9:1 $CH_2Cl_2$:MeOH) to afford **37** (616 mg, 90%) as a white solid: $R_f$ 0.55 (9:1 $CH_2Cl_2$:MeOH); mp 248 °C; $^1$H-NMR (DMSO-$d_6$) 11.29 (br. s, 1 H), 7.31 (m, 5 H), 4.66 (s, 2H), 4.30 (s, 2 H), 4.14 (q, 2 H, J = 7.1 Hz), 3.56 (s, 2 H), 1.24 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR (DMSO-$d_6$) 167.2, 164.0, 137.2, 128.6, 127.6, 127.2, 124.5, 121.3, 112.7, 111.6, 58.8, 49.2, 44.6, 30.9, 14.4; IR (KBr) 3450, 3150, 3050, 2900, 1700, 1625, 1525, 1475, 1375, 1350, 1325, 1250, 1225, 1175, 1150, 1050, 750, 700 cm$^{-1}$; CIMS (m/z) 299.2 (M+1, 100%).

Synthesis of dibenzyllactam **38**: To a solution of **37** (200 mg, 0.67 mmol) in DMF (20 mL) under Ar was added NaH (35 mg, 0.87 mmol). The yellow solution was stirred for 2 h at rt. The pyrrolyl anion was then treated with benzyl bromide (0.088 mL, 126 mg, 0.73 mmol) and stirred for 7 h at rt, then concentrated *in vacuo* to give a yellow solid. The product was purified by column chromatography (1:1 hexane:EtOAc) to afford **38** (233 mg, 89%) as a white solid: $R_f$ 0.19 (1:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 7.32 - 7.19 (m, 9 H), 7.00 - 6.97 (m, 2 H), 4.88 (s, 2 H), 4.68 (s, 2 H), 4.26 (q, 2 H, J = 7.1 Hz), 4.12 (t, 2 H, J = 3.4 Hz), 3.82 (t, 2 H, J = 3.4 Hz), 1.33 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 168.4, 164.6, 136.5, 135.5, 129.1, 128.7, 128.3, 128.0, 127.7, 127.6, 126.7, 121.6, 115.1, 112.7, 59.8, 51.4, 50.5, 44.5, 31.3, 14.5; IR (film) 3000, 2950, 2900, 1700, 1640, 1530, 1500, 1450, 1400, 1390, 1350, 1300, 1250, 1220, 1160, 1140, 1090, 1080, 1030, 950, 810, 750, 700, 680 cm$^{-1}$.

Synthesis of BOM-protected lactam **39**: To a solution of **34** (218 mg, 1.04 mmol) in DMF (17 mL) under Ar was added NaH (38 mg, 1.57 mmol). The suspension was stirred for 40 min at rt. The reaction was then treated with BOMCl (0.219 mL, 246 mg, 1.57 mmol) and stirred for 5 h. The reaction was quenched with MeOH (2 mL) and concentrated *in vacuo*. The residue was suspended in $CH_2Cl_2$ (2 mL), mixed with silica

gel (100 mg), and concentrated. The resulting powder was added to a pre-packed column and purified by column chromatography (19:1 $CH_2Cl_2$:MeOH) to afford **39** (286 mg, 83%) as a white solid: $R_f$ 0.39 (9:1 $CH_2Cl_2$:MeOH); mp 167 °C; $^1$H-NMR ($CDCl_3$) 7.39 - 7.25 (m, 6 H), 6.75 (s, 1 H), 5.17 (s, 2 H), 4.52 (m, 2 H), 4.42 (s, 2 H), 4.28 (q, 2 H, J = 7.1 Hz), 1.34 (t, 3 H, J = 7.1 Hz) $^{13}$C-NMR ($CDCl_3$) 171.2, 164.5, 135.9, 128.6, 128.3, 128.0, 127.9, 121.9, 115.6, 113.2, 76.2, 69.9, 59.8, 39.8, 30.3, 14.4; IR (film) 3500, 3200, 3050, 2950, 2900, 2800, 1700, 1650, 1610, 1530, 1500, 1450, 1360, 1290, 1250, 1230, 1190, 1150, 1100, 1050, 1000, 750 cm$^{-1}$.

Synthesis of amine **40**: To a dilute solution of **37** (6 mg, 0.02 mmol) in THF (3 mL) under Ar was added a 1 M solution of DIBAL in toluene (0.061 mL, 0.06 mmol) causing the solution to turned yellow. The reaction was stirred for 5 h at rt before it was quenched with MeOH (1 mL) and a few drops of $H_2O$. The solution was concentrated *in vacuo* to obtain a white solid. The product was chromatographed (19:1 $CH_2Cl_2$:MeOH) to afford **40** (2.5 mg, 46%) as a white solid: $R_f$ 0.13 (19:1 $CH_2Cl_2$:MeOH); $^1$H-NMR ($CDCl_3$) 8.20 (s, 1 H), 7.39 - 7.26 (m, 5 H), 4.25 (q, 2 H, J = 7.1 Hz), 3.71 (s, 2 H), 3.46 (s, 2 H), 2.79 (m, 2 H), 1.31 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 165.3, 138.3, 129.1, 128.3, 127.2, 126.2, 122.5, 116.1, 114.2, 62.1, 59.3, 51.1, 49.8, 23.1, 14.5; IR (film) 3490, 3310, 3090, 3000, 2940, 2800, 1700, 1540, 1440, 1370, 1340, 1300, 1260, 1200, 1150, 1140, 1100, 900, 750, 700 cm$^{-1}$.

Synthesis of N-BOM-protected hydroxymethylpyrrole **42**: To a solution of 1 M DIBAL in toluene (4.2 mL, 4.2 mmol) in a constant rt water bath under Ar was added a solution of **39** (276 mg , 0.84 mmol) in $CH_2Cl_2$ (10 mL). The exothermic reaction was stirred for 30 min, cooled to 0 °C, then quenched slowly with MeOH (10 mL). The precipitate was filtered and washed with hot MeOH (10 mL). The filtrate was concentrated *in vacuo* to give a yellow solid. Chromatography of the product (9:1 $CH_2Cl_2$:MeOH) afforded **42** (156 mg, 65%) as a white solid: $R_f$ 0.25 (9:1 $CH_2Cl_2$:MeOH); mp 148 °C; $^1$H-NMR ($CDCl_3$) 7.37 - 7.25 (m, 5 H), 6.70 (s, 1 H), 6.47 (bs, 1 H), 5.11 (s, 2 H), 4.50 (bs, 2 H), 4.42 (s, 2 H), 3.50 (t, 2 H, J = 3.4 Hz); $^{13}$C-NMR ($CDCl_3$) 171.1, 136.5, 128.6, 128.2, 127.9, 121.3, 121.2, 120.4, 113.7, 75.7, 69.7, 59.8, 40.2, 28.9; IR (film) 3400, 3150, 3000, 2900, 2850, 2800, 1700, 1550, 1500, 1450, 1410, 1390, 1300, 1250, 1150, 1060, 1000, 900, 850, 740 cm$^{-1}$; FABMS (m/z) 287.1 (M+1, 100%), 269.1 (M$^+$ - $H_2O$, 34%).

Synthesis of N-BOM-protected pyrrole aldehyde **43**: To a solution of **42** (156 mg, 0.54 mmol) in $CH_2Cl_2$ (26 mL) under Ar was added Dess Martin periodinane (347 mg, 0.81 mmol) at rt causing precipitate formation. The reaction was stirred at rt for 1 h, then quenched with sodium thiosulfate (1.52 g, 6.12 mmol) in a saturated aqueous solution of $NaHCO_3$ (25 mL). The two-phase mixture was stirred for 30 min, then separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 x 20 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (1 x 80 mL) and with water (1 x 80 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow solid. The product was purified by flash chromatography (19:1 $CH_2Cl_2$:MeOH) to afford **43** (108 mg, 70%) as a solid: $R_f$ 0.18 (19:1 $CH_2Cl_2$:MeOH); mp 186 °C; $^1$H-NMR ($CDCl_3$) 9.78 (s, 1 H), 7.91 - 7.20 (m, 6 H), 5.2 (s, 2 H), 4.53 (bs, 2 H), 4.46 (s, 2 H), 3.73 (t, 2 H, J = 3.3 Hz); $^{13}$C-NMR ($CDCl_3$) 184.9, 170.6, 135.7, 131.3, 128.7, 128.5, 127.9, 123.5, 123.0, 114.9, 76.3, 70.2, 39.7, 29.8; IR (film) 3150, 2990, 2800, 1660, 1610, 1520, 1500, 1450, 1380, 1300, 1290, 1150, 1180, 1000, 950, 850, 750, 740 cm$^{-1}$; EIMS (m/z) 284.2 (M$^+$, 16%), 178.1 (M$^+$ - CHO - Ph, 33%), 91.1 (Bn$^+$, 100%); CIMS (m/z) 285.2 (M+1, 100%).

Synthesis of α,β-unsaturated ester **44**: To a solution of **43** (62 mg, 0.22 mmol) in pyridine (4.5 mL) under Ar was added ethyl hydrogen malonate (0.10 mL, 124 mg, 0.94 mmol) and a catalytic amount of piperidine. The solution was heated to 80 °C for 16 h, then at reflux for 6 h. The dark solution was poured over ice (5 mL), acidified with conc. HCl to pH 2 (2-3 mL), and $CH_2Cl_2$ (5 mL) added. The aqueous layer was extracted with $CH_2Cl_2$ (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow solid, which was chromatographed (19:1 $CH_2Cl_2$:MeOH) to afford **44** (71 mg, 92%) as a solid: $R_f$ 0.5 (9:1 $CH_2Cl_2$:MeOH); mp 198-200 °C; $^1$H-NMR ($CDCl_3$) 7.56 (d, 1 H, J = 16.1 Hz), 7.37 - 7.25 (m, 5 H), 6.94 (s, 1 H), 6.82 (s, 1 H), 6.04 (d, 1 H, J = 16.1 Hz), 5.14 (s, 2 H), 4.53 (bs, 2 H), 4.42 (s, 2 H), 4.23 (q, 2 H, J = 7.1 Hz), 3.60 (t, 2 H, J = 3.5 Hz), 1.32 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 170.2, 167.8, 137.3, 136.1, 128.7, 128.4, 127.9, 125.8, 122.9, 117.5, 114.6, 113.9, 69.9, 60.2, 40.0, 30.4, 14.4; IR (film) 3150, 3050, 3000, 2900, 2850, 1700, 1680, 1610, 1490, 1440, 1360, 1350, 1330, 1290, 1250, 1200, 1150, 1060, 1050, 960, 840, 750 cm$^{-1}$; EIMS (m/z) 354.1 (M+, 2.3%), 73 ($EtOCO^+$, 100%).

Synthesis of PBG lactam ethyl ester **46**: To a solution of pyrrole **44** (54 mg, 0.15 mmol) in EtOH (25 mL) was added a catalytic amount of $Pd(OH)_2$ on charcoal (20 mg). The reaction was flushed with $H_2$ three times and maintained under a balloon at rt. After 4 d, more catalyst (10 mg) was added. After a total of 6 d, the catalyst was filtered through Celite to give **45** as a white solid, which was used without further purification in the next step: $R_f$ 0.24 (9:1 $CH_2Cl_2$:MeOH); $^1$H-NMR ($CD_3OD$) 6.56 (s, 1 H), 5.10 (s, 2 H), 4.48 (t, 2 H, J = 3.7 Hz), 4.08 (q, 2 H, J = 7.1 Hz), 3.32 (t, 2 H, J = 3.7 Hz), 2.65 (t, 2 H, J = 7.3 Hz), 2.51 (t, 2 H, J = 7.3 Hz), 1.20 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CD_3OD$) 175.0, 174.0, 121.3, 120.3, 119.9, 113.2, 70.5, 61.5, 40.7, 36.1, 29.7, 21.5, 14.5; IR (film) 3200, 2900, 1725, 1650, 1500, 1450, 1350, 1275, 1250, 1175, 1150, 1025, 1000 cm$^{-1}$; FABMS (m/z) 265.1 (M + 1, 100%).

Pyrrole **45** was taken up in EtOH (9 mL) and heated at reflux with 1,3-diaminopropane (0.063 mL, 55 mg, 0.75 mmol). After 24 h, the reaction was cooled and concentrated *in vacuo*. The product was purified by column chromatography (9:1 $CH_2Cl_2$:MeOH) to afford **46** (26 mg, 72%) as a white solid: $R_f$ 0.25 (9:1 $CH_2Cl_2$:MeOH); mp 235-239 °C; $^1$H-NMR (1:1 $CD_3OD$:$CDCl_3$) 9.80 (bs, 1 H), 6.53 (s, 1 H), 4.44 (t, 2 H, J = 3.0 Hz), 4.13 (q, 2 H, J = 6.6 Hz), 3.39 (t, 2 H, J = 3.0 Hz), 7.72 (t, 2 H, J = 7.4 Hz), 2.55 (t, 2 H, J = 7.4 Hz), 1.26 (t, 3 H, J = 6.6 Hz); $^{13}$C-NMR (1:1 $CD_3OD$:$CDCl_3$) 173.5, 172.5, 118.8, 118.1, 115.4, 109.8, 60.0, 40.2, 34.7, 28.5, 20.1, 13.3; IR (KBr) 3250, 3200, 2900, 2850, 1730, 1660, 1650, 1600, 1380, 1300, 1250, 1160, 1050, 850, 750 cm$^{-1}$; EIMS (m/z) 236.2 ($M^+$, 83%).

Synthesis of malonic ester **55**: To a solution of dimethylmalonate (0.57 mL, 66 mg, 0.51 mmol) under Ar was added NaH (20 mg, 0.51 mmol) in DMF (2 mL). Gas evolution was observed, and the reaction stirred at rt for 30 min. The solution of sodium dimethylmalonate was then added to **36** (17 mg, 0.10 mmol) under Ar, heated to 130-140 °C for 4 h, then cooled and concentrated *in vacuo* to give a dark solid. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated *in vacuo*. The resulting powder was added to a pre-packed column and chromatographed [19:1 $CH_2Cl_2$:MeOH (20 mL) and 9:1 $CH_2Cl_2$:MeOH (30 mL)] to yield malonate **55** (19 mg, 68%) as a yellow solid: $R_f$ 0.28 (9:1 $CH_2Cl_2$:MeOH); mp 208 °C; $^1$H-NMR (1:1 $CD_3OD$:$CDCl_3$) 6.51 (s, 1 H), 4.41 (t, 2 H, J = 3.4 Hz), 3.71 (s, 6 H), 3.58 (t, 1 H, J = 7.8 Hz), 3.37 (t, 2 H, J = 3.4 Hz), 2.97 (d, 2 H, J = 7.8 Hz); $^{13}$C-NMR (DMSO-$d_6$) 173.3, 170.3, 119.8, 117.2, 116.0, 110.8, 53.5, 52.8, 41.0, 29.3, 25.0; IR (KBr) 3200, 2950, 2850, 1750, 1650, 1625, 1500, 1425, 1375, 1325, 1275,

1225, 1200, 1175, 1150, 1100, 1075, 1040, 1025, 950, 850 $cm^{-1}$; FABMS (m/z) 281.15 (M+1, 50%), 119.0 ($M^+$ - $CH_2C(CO_2Me)_2$ - $NH_2$, 100%).

Synthesis of PBG lactam methyl ester **56**: Sodium cyanide (10 mg, 0.21 mmol) was added to a solution of **55** (40 mg, 0.14 mmol) in wet DMF (1 mL) under Ar, and the reaction heated to 140 °C for 24 h, cooled and concentrated *in vacuo* to give a dark solid. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated *in vacuo*. The resulting powder was added to a pre-packed column and purified by flash chromatography (9:1 $CH_2Cl_2$:MeOH) to afford **56** (23 mg, 73%) as a white solid: $R_f$ 0.22 (9:1 $CH_2Cl_2$:MeOH); mp 256 °C (lit.,[5i] 245-246°; lit.,[2] 248-250°); $^1$H-NMR (DMSO-$d_6$) 10.22 (bs, 1 H), 7.62 (bs, 1 H), 6.37 (d, 1 H, J = 2.1 Hz), 4.16 (bs, 2 H), 3.49 (s, 3 H), 3.05 (t, 2 H, J = 3.1 Hz), 2.48 - 2.36 (m, 4 H); $^{13}$C-NMR (DMSO-$d_6$) 173.1, 169.5, 119.9, 117.7, 115.2, 110.6, 51.2, 38.9, 34.5, 29.0, 20.3; IR (KBr) 3250, 3150, 2950, 2900, 2850, 1740, 1650, 1625, 1500, 1450, 1425, 1375, 1275, 1275, 1200, 1175, 1050, 825 $cm^{-1}$; FABMS (m/z) 223.16 ($M^+$, 13%), 118.98 ($M^+$ - $CH_2CH_2CO_2Me$ - $CH_2NH_2$, 100%).

Synthesis of nitrile **57**: Sodium cyanide (200 mg, 4.11 mmol) was added to a suspension of **36** (68 mg, 0.41 mmol) in DMF (6 mL), and heated to 130-140 °C for 3.5 h. The reaction was then cooled to rt and concentrated to a dark solid. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated. The resulting powder was added to a pre-packed column and purified by flash chromatography [9:1 $CH_2Cl_2$:MeOH (15 mL) and 4:1 $CH_2Cl_2$:MeOH (15 mL)] to afford **57** (28 mg, 38%) as a solid: $R_f$ 0.25 (9:1 $CH_2Cl_2$:MeOH); $^1$H-NMR (DMSO-$d_6$) 10.61 (bs, 1 H), 7.75 (bs, 1 H), 6.66 (d, 1 H, J = 2.5 Hz), 4.25 (bs, 2 H), 3.64 (s, 2 H), 3.17 (t, 2 H, J = 3.2 Hz); $^{13}$C-NMR (DMSO-$d_6$) 168.9, 121.0, 119.4, 116.6, 110.6, 108.2, 39.9, 28.6, 13.2; IR (KBr) 3150, 3050, 2890, 2800, 1650, 1625, 1500, 1425, 1400, 1350, 1250, 1225, 1150, 1075, 1050, 850, 750, 650, 600, 550 $cm^{-1}$; CIMS (m/z) 176.1 (M+1, 100%).

Synthesis of pyrrole **58**: To a solution of diethylallylmalonate (0.148 mL, 151 mg, 0.75 mmol) in DMF (2 mL) under Ar was added KH (35% in mineral oil, 87 mg, 0.75 mmol). After stirring at rt for 30 min, the solution of potassium diethylallylmalonate was added to **36** (19 mg, 0.11 mmol) under Ar, heated to 130-140 °C for 2 h, then cooled and concentrated to a dark solid, which was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated. The resulting powder was added to a pre-packed column and chromatographed [19:1 $CH_2Cl_2$:MeOH (20 mL) and 9:1 $CH_2Cl_2$:MeOH (20 mL)] to afford **58** (26 mg, 66%) as a yellow solid: $R_f$ 0.26 (9:1 $CH_2Cl_2$:MeOH); mp 165-167 °C; $^1$H-NMR ($CDCl_3$) 8.19 (s, 1 H), 6.70 (s, 1 H), 6.50 (d, 1 H, J = 2.3 Hz), 5.80 - 5.69 (m, 1 H), 5.12 (m, 1 H), 5.08 (m, 1 H), 4.42 (bs, 2 H), 4.27 - 4.11 (m, 4 H), 3.34 (t, 2 H, J = 3.2 Hz), 3.02 (s, 2 H), 2.61 (d, 2 H, J = 7.2 Hz), 1.24 (t, 6 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 171.6, 171.1, 132.7, 119.0, 118.9, 117.6, 114.5, 112.7, 61.2, 58.6, 40.8, 36.9, 29.3, 27.9, 14.1; IR (film) 3100, 2900, 1725, 1650, 1625, 1500, 1450, 1350, 1250, 1200, 900, 740, 850, 600 $cm^{-1}$; EIMS (m/z) 348.1 ($M^+$, 7%), 69.0 ($CH_4^+$ + $CH_2CHCH_2^+$, 100%).

Synthesis of pyrrole **59**: To a solution of diethylbenzamidomalonate (219 mg, 0.78 mmol) in DMF (2 mL) under Ar was added NaH (32 mg, 0.78 mmol). After stirring at rt for 30 min, the solution of sodium diethylbenzamidomalonate was added to **36** (26 mg, 0.16 mmol) under Ar, heated to 130-140 °C for 1.5 h, then cooled and concentrated. The solid product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated. The resulting powder was added to a pre-packed column and purified by flash chromatography [19:1 $CH_2Cl_2$:MeOH (20 mL) and 9:1 $CH_2Cl_2$:MeOH (20 mL)] to afford **59** (29 mg, 44%) as a yellow solid: $R_f$ 0.29 (9:1 $CH_2Cl_2$:MeOH); $^1$H-NMR ($CDCl_3$) 8.48 (bs, 1 H), 7.76 (d, 2 H, J = 7.0 Hz),

7.52 - 7.38 (m, 3 H), 6.80 (bs, 1 H), 6.41 (d, 1 H, J = 2.2 Hz), 4.37 (m, 2 H), 4.35 - 4.17 (m, 4 H), 3.56 (s, 2 H), 3.20 (t, 2 H, J = 2.8 Hz), 1.26 (t, 6 H, J = 7.0 Hz); $^{13}$C-NMR ($CDCl_3$) 171.6, 168.0, 166.1, 133.5, 132.0, 128.8, 127.1, 119.3, 118.0, 113.3, 112.4, 67.3, 62.7, 40.8, 29.0, 28.1, 17.5, 14.0; IR (film) 3400-3200, 2950, 1750, 1650, 1500, 1475, 1350, 1300, 1275, 1250, 1200, 1100, 1050, 1000, 850, 700 $cm^{-1}$.

Synthesis of pyrrole **60**: To a solution of ethyl acetoacetate (0.18 mL, 187 mg, 1.44 mmol) in DMF (4 mL) under Ar was added NaH (57 mg, 1.44 mmol). After stirring at rt for 30 min, the solution of sodium ethyl acetoacetate was added to 3-hydroxymethylpyrrole (28 mg, 0.28 mmol) under Ar, heated to 130-140 °C for 4 h, then cooled and concentrated to a dark oil. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated. The resulting powder was added to a pre-packed column and chromatographed (3:1 hexane:EtOAc) to afford **60** (39 mg, 66%) as a clear oil: $R_f$ 0.47 (1:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.25 (bs, 1 H), 6.69 - 6.66 (m, 1 H), 6.56 - 6.54 (m, 1 H), 6.04 - 6.02 (m, 1 H), 4.16 (q, 2 H, J = 7.1 Hz), 3.72 (t, 1 H, J = 7.6 Hz), 3.05 (d, 2 H, J = 7.6 Hz), 2.19 (s, 3 H), 1.23 (t, 3 H, J = 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) 203.5, 169.5, 119.4, 117.9, 115.8, 108.3, 61.4, 61.2, 29.4, 25.7, 13.9; IR (film) 3400, 2990, 2900, 1740, 1710, 1450, 1360, 1225, 1150, 1075, 1025, 850, 800, 725, 650, 600 $cm^{-1}$; FABMS (m/z) 210.1 (M+1, 100%).

Synthesis of nitrile **61**: To a solution of 3-hydroxymethylpyrrole (30 mg, 0.31 mmol) in DMF (5 mL) under Ar was added NaCN (77 mg, 1.56 mmol). The resulting suspension was heated to 140 °C for 27 h. The dark reaction mixture was cooled and concentrated. Chromatography [6:1 hexane:EtOAc (20 mL) and 3:1 hexane:EtOAc (20 mL)] afforded **61** (17 mg, 52%) as a solid: $R_f$ 0.47 (1:1 hexane:EtOAc); mp 270 °C; $^1$H-NMR ($CDCl_3$) 8.33 (bs, 1 H), 6.84 - 6.75 (m, 2 H), 6.16 (m, 1 H), 3.59 (s, 2 H); $^{13}$C-NMR ($CDCl_3$) 119.0, 118.9, 116.3, 111.9, 108.2, 15.9; IR (neat) 3400, 3100, 2900, 2200, 1550, 1500, 1425, 1175, 1170, 975, 925, 800, 725, 575 $cm^{-1}$; EIMS (m/z) 105.1 ($M^+$ - 1, 100%).

Synthesis of pyrrole **62**: To a solution of diethylallylmalonate (0.228 mL, 232 mg, 1.16 mmol) in DMF (2 mL) under Ar was added NaH (46 mg, 1.16 mmol). After stirring at rt for 30 min, the solution of sodium diethylallylmalonate was added to 3-hydroxymethylpyrrole (22 mg, 0.23 mmol) under Ar, heated to 130-140 °C for 4 h, then cooled and concentrated. The product was suspended in $CH_2Cl_2$ (2 mL), mixed with silica gel (50 mg), and concentrated. The resulting powder was chromatographed (3:1 hexane:EtOAc) to afford **62** (45 mg, 70%) as a clear oil: $R_f$ 0.40 (3:1 hexane:EtOAc); $^1$H-NMR ($CDCl_3$) 8.10 (bs, 1 H), 6.67 (dd, 1 H, J = 5.0, 2.6 Hz), 6.54 (dd, 1 H, J = 4.1, 1.9 Hz), 5.97 (dd, 1 H, J = 4.1, 2.6 Hz), 5.82 - 5.69 (m, 1 H), 5.15 - 5.12 (m, 1 H), 5.09 (s, 1 H), 4.23 - 4.10 (m, 4 H), 3.12 (s, 2 H), 2.59 (d, 2 H, J = 7.0 Hz), 1.25 (t, 6 H, J = 7.0 Hz); $^{13}$C-NMR ($CDCl_3$) 171.3, 133.1, 118.8, 117.7, 117.1, 117.0, 109.7, 61.1, 58.7, 36.4, 29.7, 14.1; IR (film) 3400, 2950, 1725, 1625, 1350, 1300, 1250, 1225, 1175, 1050, 900, 850, 750, 700 $cm^{-1}$; CIMS (m/z) 280.2 (M+1, 66%), 234.1 ($M^+$ - OEt, 100%).

**ACKNOWLEDGMENT:** We thank the National Institutes of Health for financial assistance in the form of a Program Project Grant, NIH GM 44874, in support of structure-based drug design. Support of the Cornell NMR Facility by the NSF (CHE 7904825; PGM 8018643) and NIH (RR02002) is gratefully acknowledged.

## REFERENCES


1. Westfall, R. G. *Nature* **1952,** *170,* 614.
2. Cookson, G. H.; Rimington, C. *Biochem. J.* **1954,** *57,* 476.
3. (a) Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1983,** *61,* 2415; (b) Faber, K.; Anderson, H. J.; Loader, C. E.; Daley, C. S. *Can. J. Chem.* **1984,** *62,* 1046.
4. (a) Adamczyk, M.; Reddy, R. E. *Tetrahedron Lett.* **1995,** *36,* 9121; (b) Adamczyk, M., Reddy, R. *Tetrahedron Lett.* **1996,** *37,* 2335.
5. a); Jackson, A. H.; McDonald, D. M.; McDonald, S. F. *J. Am. Chem. Soc.* **1956,** *78,* 505; (b) Jackson, A. H.; MacDonald, S. F. *Can. J. Chem.* **1957,** *35,* 715; (c) Arsenault, G. P.; MacDonald, S. F. *Can J. Chem.* **1961,** *39,* 2043; (d) Plieninger, H.; Hess, P.; Ruppert, J. *Chem. Ber.* **1968,** *101,* 240; (e) Battersby, A. R.; Moron, J.; McDonald, E.; Feeney, J. *J. Chem. Soc. Chem. Commun.* **1972,** 920; (f) Kenner, G. W.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc. Chem. Commun.* **1973,** 43; (g) Battersby, A. R.; Hunt, E.; McDonald, E.; Moron, J. *J. Chem. Soc. Perkin Trans. I* **1973,** 2973; (h) Jones, M.; Froussions, C.; Evans, D. A. *J. Chem. Soc. Chem. Commun.* **1976,** 472; (i) Kenner, G. W.; Rimmer, J.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc. Perkin Trans. I* **1977,** 332; (j) Ufer, G.; Tjoa, S. S.; MacDonald, S. F. *Can. J. Chem.* **1978,** *56,* 2437.
6. (a) Frydman, B.; Reil, S.; Despuy, M. E.; Rapoport, H. *J. Am. Chem. Soc.* **1969,** *91,* 2338; (b) Frydman, B.; Buldain, G.; Repetto, J. C.; *J. Org. Chem.* **1973,** *38,* 1824; (c) Valasinas, A.; Levy, E. S.; Frydman, B. *J. Org. Chem.* **1974,** *39,* 2874; (d) Battersby, A. R.; McDonald, E.; Wurziger, H. K. W.; James, K. J. *J. Chem. Soc. Chem. Commun.* **1975,** 493.
7. Bonnet, R. *Chem. Soc. Rev.* **1995,** *24,* 19.
8 Dougherty, T. J. *Photochem. Photobiol.* **1987,** *46,* 569.
9. Grant, W. E.; Hopper, C.; MacRobert, A. J.; Speight, P. M.; Bown, S. G. *Lancet* **1993,** *342,* 147.
10. Gibbs, P. N. B.; Chaudhry, a. G.; Jordan, P. M. *Biochem. J.* **1985,** *230,* 25.
11. van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972,** 5337.
12. (a) Magnus, P.; Or, Y.-S. *J. Chem. Soc. Chem. Commun.* **1983,** 26; (b) Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y.-S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987,** *109,* 2706.
13. Ralls, J. W. *Chem. Rev.* **1959,** *59,* 329.
14. De Kimpe, N.; Tehrani, K. A.; Stevens, C.; De Cooman, P. *Tetrahedron* **1997,** *53,* 3693.
15. Borch, R. F.; Bernstein, M. K.; Durst, H. D. *J. Am. Chem. Soc.* **1971,** *93,* 2897.
16. Faber, K.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1984,** *62,* 1046.
17. Anderson, H. J.; Groves, J. K. *Tetrahedron Lett.* **1971,** *34,* 3165.
18. Jones, R. A.; Beans, B. P. *The Chemistry of Pyrroles*; Academic Press: New York, **1977,** 115.
19. Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985,** *50,* 2961.
20. Carpio, H.; Galeazzi, E.; Greenhouse, R.; Guzman, A.; Velarde, E.; Antonio, Y.; Franco, F.; Leon, A.; Perez, V.; Salas, R.; Valdes, D.; Ackrell, J.; Cho, D.; Gallegra, P.; Halpern, H.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; Van Horn, A. R.; Wren, D. *Can J. Chem.* **1982,** *60,* 2295.
21. Herz, W.; Settine, R. L. *J. Org. Chem.* **1959,** *24,* 201.
22. (a) Meister, A.; Anderson, M. E. *Annu. Rev. Biochem.* **1983,** *52,* 711; (b) Christensen, H. N. "Biological Transport," Second Edition, Benjamin, **1975**.


(*Received in USA* 26 *March* 1997; *accepted* 22 *April* 1997)