An Efficient Route to Dipyrrinones: Synthesis of Xanthobilirubic Acid Methyl Ester

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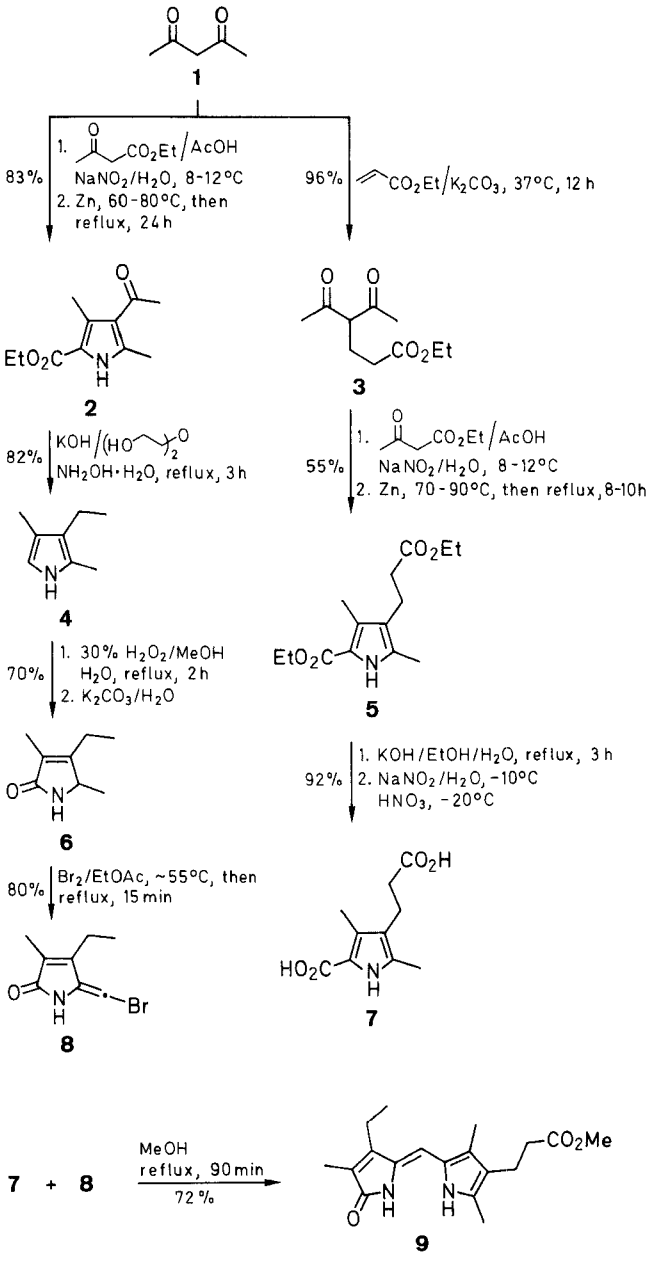
Structually interesting and complicated dipyrrinones, such as xanthobilirubic acid methyl ester (**9**), can be synthesized on a large scale from simple, inexpensive starting materials like ethyl acetoacetate, 2,4-pentanedione (**1**) and ethyl acrylate in 8 steps with an average yield of 80% at each step and an overall 17% yield.

Dipyrrinones are useful building blocks for the syntheses of biologically important tetrapyrrole pigments such as bilirubin (the yellow pigment of jaundice), the prosthetic groups of biliproteins such as phytochrome (the light sensory pigment that governs photomorphogenesis in plants), and heme (the red pigment of blood).[1] They have also found extensive use as model dipyrrole pigments for spectroscopic and photochemical studies of linear tetrapyrroles such as bilirubin and biliverdin. Some 15 years ago Grunewald et al,[2] focussing on the synthesis of xanthobilirubic acid, showed how the Fischer synthesis[3] of dipyrrinones could be improved by making one or two key steps more reliable and therefore give an overall yield of ~ 2.5%. Although xanthobilirubic acid and its methyl ester have been used repeatedly as relay intermediates in the total syntheses of important bilirubin analogs[1,4] and as a model pigment for investigating the structure, spectroscopy and photochemistry of bilirubin,[1,5,6] the total synthesis of this useful pigment has not been improved further in a major way.

In the following we report a modified, efficient total synthesis of xanthobilirubic acid methyl ester (**9**), with yields maximized at each step and an overall yield increased by a factor of ~ 7, up to a satisfactory 17%. The synthesis has considerable generality, as other dipyrrinones can be prepared from a common intermediate monopyrrole derivative, which is synthesized in four steps and represents half of the dipyrrole structure.

The synthesis outlined below is accomplished by the condensation of two monopyrrole intermediates **7** and **8** each of which is prepared in three or four steps. The left half **8**, an oxidized and brominated derivative of kryptopyrrole (**4**) is prepared in an overall yield of 38–44%. The *Organic Synthesis* preparation of kryptopyrrole derivative **4** from ethyl acetoacetate and 2,4-pentanedione (**1**) reported by Fischer[7] is improved from 27.5–35% yield to a 68% yield, when carried out on the same or larger scale. This substantial improvement was achieved by modifying the reaction temperature and avoiding excess water in the second reduction step. Neither Fischer and Hartmann[3] nor Grunewald et al[2] reported difficulties with the oxidation (hydrogen peroxide) of kryptopyrrole (**4**) but there are many, and the yields can vary widely depending on reaction conditions.

Fischer and Hartmann[3] report that 10 g of kryptopyrrole (**4**) are converted to "about 10 g" of distilled oxopyrrole **6** (corresponding to an approximate 88% yield). Whether the oxidized pyrrole material was purified is unclear. It is a distillable solid, but the melting point was not given, nor is the exact weight of product. On a considerably larger scale (380 g), we were able to convert kryptopyrrole (**4**) to 70% yield of isolated, crystalline oxopyrrole product **6** with a sharp melting point. On a smaller scale (5 g) we were able to achieve 82% yield. Grunewald et al.[2] encountered difficulty in Fischer's original procedure[8] for the bromination of the 2-oxo-2,5-dihydropyrrole **6** and found the later Fischer and Hartmann[3] procedure to give an adequate (54%) yield on a 20 g scale. We found the later procedure to be capricious, with yields varying considerably: to the ~ 50% yield reported down to ~ 30% or less. However, with suitable modification, 135 g of the pyrrolinone 2-oxo-2,5-dihydropyrrole **6** could be converted reliably in 80% yield to pure, solid bromo-product **8** with a sharp melting point. On a smaller



scale (20 g) the yield of product was even higher (92%). This substantial improvement was achieved by using a solvent, which favorably displaces the equilibrium between product and the dibromo intermediate.

Synthesis of right half monopyrrole **7** required ethyl 4-acetyl-5-oxohexanoate **(3)** for condensation with ethyl acetoacetate to give ethyl 4-(2-ethoxycarbonylethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate **(5)**. Bullock et al[9] showed how the ester **3** could be obtained in 70% yield from a Michael reaction of 2,4-pentane-dione **(1)** with ethyl acrylate in ethanol using sodium ethoxide as base. By changing the base to potassium carbonate, yields as high as 98% could be achieved on a 0.5 mole scale in 2,4-pentanedione **(1)** as solvent (4:1). Alternative Michael reaction procedures were not as effective. For example, when nickel acetylacetonate was used as catalyst for the Michael reaction,[10] for reactions scaled up to 0.6 mole, our yields varied from 40–50% in ten runs. A more satisfactory procedure for the Michael reaction involved the use of potassium fluoride as base,[11] however, even here the yields (40–60%) were less than those obtained with potassium carbonate. Condensation of the resultant ester **3** with ethyl acetoacetate afforded the pyrrole diester **5** in 57% yield. Although we made numerous attempts, e.g., changes in reaction temperature and stoichiometry, we were unable to improve the yield at this step. Saponification to the diacid **7** was accomplished in 92% yield. This pyrrole **7** could be condensed directly with the bromo-oxopyrrole **8** in 72% yield. Since decarboxylation of the α-carboxylic group is accomplished *in situ*, it is not necessary to decarboxylate and isolate the α-carboxylic group free pyrrole acid as a separate step.

Ethyl 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (2):
Freshly distilled ethyl acetoacetate (603 g, 4.6 mol) is dissolved in glacial AcOH (2 L) in a 5-L 3-neck round bottom flask equipped with a thermometer, mechanical stirrer and a condenser. The flask is cooled to 8 °C in an ice bath and $NaNO_2$ (492 g, 5.3 mol) in H_2O (600 mL) at 0 °C is added by pipette such that the reaction temperature remained between 8–12 °C. The addition time is 4 h and resulted in a yellow solution, which is stirred at 25 °C overnight. To the now orange solution is added freshly distilled 2,4-pentane-dione (**1**; 522 g, 5.2 mol) all at once followed by Zn dust (675 g, 10.3 gatom) in portions over a 7 h period. Since there is a considerable hazard of foaming, great care must be used in adding the Zn. The Zn is added in 3–5 g portions initially to increase the pot temperature to 60–80 °C ensuring that all the Zn has dissolved before the next addition. The flask is cooled in an ice bath and the additions are repeated until the reaction temperature is again between 60–80 °C. Cooling below 50 °C at this point causes product precipitation which render unpredictable the results of further Zn additions. Additions at this point are made only in the absence of foaming and are briefly terminated when foaming is obvious. After all the Zn has been added, the mixture is refluxed for 24 h, during which the progress is monitored by GC/MS until complete. The hot mixture is quenched by pouring onto ice/H_2O (8 L). The resulting grey solid is filtered and washed with H_2O (3 × 6 L) while being careful to mash clumps of product to effect good washing. The solid is then dissolved in boiling 95% EtOH (3 L), filtered while hot to remove unreacted Zn, then cooled to −30 °C. The resulting crystals are filtered and washed with cold 95% EtOH. The washings are combined with the mother liquors, and the volume is reduced to bring out a second crop of crystals; total yield: 795 g (83%); white crystals; mp 141–143 °C (Lit.[7] mp 143–144 °C).
IR (film): ν = 3302, 1678, 1646 cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 1.38 (t, 3H, J = 7.5 Hz), 2.50 (s, 3H), 2.56 (s, 3H), 2.60 (s, 3H), 4.35 (q, 2H, J = 7.5 Hz), 10.26 (br s, 1H, NH).
^{13}C-NMR ($CDCl_3$/TMS): δ = 12.76 ($CH_2\underline{C}H_3$), 14.45 (3-CH_3), 14.96 (5-CH_3), 31.27 ($\underline{C}H_3CO$), 60.46 (CH_2O), 118.16 (C-2), 123.53 (C-4), 129.51 (C-3), 138.94 (C-5), 162.26 (CO_2), 195.58 ($CH_3\underline{C}$=O).
GC-MS (DEI): m/z = 209 [M^+], 148, 65.

2,4-Dimethyl-3-ethyl-1*H*-pyrrole (Kryptopyrrole) (4):
The pyrrole **2** (795 g, 3.8 mol), KOH (639 g, 11.4 mol), and diethylene glycol (3 L) are added to a 5-L 3-neck round bottom flask equipped with a methanical stirrer, condenser, and an N_2 inlet tube fixed so that N_2 is fed just above the surface. With vigorous stirring, hydrazine monohydrate (250 g, 5 mol) is added and the mixture is heated to ~120 °C to effect distillation, which is aided by the N_2 flow. The distillate with bp below 105 °C is discarded and the desired product is collected over a 105–160 °C range. At 160 °C, the flow of N_2 is reduced and the mixture is refluxed for 3 h. More product is collected over the bp range 130–160 °C. The combined yellow brown product is taken up in Et_2O (1 L), washed with H_2O (3 × 100 mL), and dried ($MgSO_4$). Solvent is removed by distillation and the product distilled; yield: 380 g (82%); bp 57–70 °C/0.7 mbar (Lit.[7] bp 104–105 °C/17 mbar; light green liquid. The two-step yield from ethyl acetoacetate is 67%. (Note: Hydrazine monohydrate is currently cheaper than the 45% aq hydrazine and the excess H_2O does not have to be removed by distillation).
IR (film): ν = 3377, 1689, 1644 cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 1.14 (t, 3H, J = 7.2 Hz), 2.10 (s, 3H), 2.22 (s, 3H), 2.45 (q, 2H, CH_2, J = 7.2 Hz), 6.12 (s, 1H, =CH), 7.50 (s, NH).
^{13}C-NMR ($CDCl_3$/TMS): δ = 10.22 ($\underline{C}H_3CH_2$), 11.08 (pyrrole α-$\underline{C}H_3$), 15.52 (pyrrole β-$\underline{C}H_3$), 17.44 (CH_2), 112.77 (C-2), 117.79 (C-5), 120.46 (C-3), 123.17 (C-4).
GC/MS (DEI): m/z = 123 (M^+), 108 (M-CH_3), 92.

3,5-Dimethyl-4-ethyl-2-oxo-2,5-dihydropyrrole (6):
Kryptopyrrole (**4**; 380 g, 3.1 mol), N_2 purged MeOH (1 L) and N_2-purged H_2O (400 mL) are added to a 3-L 3-neck round bottom flask equipped with a N_2 inlet, thermometer, condenser with an addition funnel on top,[12] and stirred vigorously. The flask temperature is increased to 50 °C while maintaining a slight flow of N_2. 30% H_2O_2 (380 mL, 114 g, 3.35 mol) is added (1/8 portion per h) such that the reaction temperature does not exceed 60 °C. It is occasionally necessary to stop the addition and either remove the heating mantle or turn up the N_2 flow to cool the reaction. After all the H_2O_2 has been added, the mixture is stirred at 50 °C for 2 h, and refluxed for 2 h. After cooling, a solution of K_2CO_3[13] (80 g) in H_2O (180 g) is added to the mixture, which is stirred overnight. H_2O (1 L) is added, and the mixture is divided into 3 portions for ease in handling. The mixture is extracted with CH_2Cl_2 until the organic layer is light yellow. The aqueous layer is slowly and cautiously neutralized (not to acidity) with conc HCl and again extracted with CH_2Cl_2 until the organic layer is colorless. The combined CH_2Cl_2 extracts are washed with brine (100 mL), and dried ($MgSO_4$). The solvent is removed on a rotary evaporator to leave a red-brown oil. Distillation of the oil at 80–135 °C/0.7 mbar using dry ice-acetone to cool the distillate to −30 °C affords a yellow-brown oil, which solidifies on warming to r.t. in one large lump. Just enough cold (30 °C) hexane is added to break up the solid for filtration. The solid is washed with cold hexane until is becomes colorless. The hexane is removed from the combined washings and mother liquor, and the residue is distilled at 80–177 °C/0.7 mbar with the same results as before. This is repeated a third time when GC/MS shows that all product has been collected; yield: 306 g (70%, 48% from ethyl acetoacetate); white crystals; GC/MS pure; mp 76–77 °C (Lit.[2] mp 83 °C).
IR (film): ν = 3228, 1684 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.12 (t, 3H, J = 7.5 Hz), 1.23 (d, 3H, J = 6.8 Hz), 1.71 (s, 3H), 2.28 (q, 2H, J = 7.4 Hz), 4.00 (q, 1H, J = 6.8 Hz), 8.42 (s, NH).

^{13}C-NMR ($CDCl_3$/TMS): δ = 8.27 ($\underline{C}H_3CH$), 12.92 ($\underline{C}H_3CH_2$), 18.12 (CH), 19.61 (CH_2), 54.30 (=$C\underline{C}H_3$), 127.04 (C-3), 159.13 (C-4), 175.51 (C=O).

GC MS (DEI): m/z = 139 [M^+], 124 (M-CH_3), 110, 96, 80, 67, 53.

5-Bromomethylene-4-ethyl-3-methyl-2-oxo-2,5-dihydropyrrole (8):
3,5-Dimethyl-4-ethyl-2-oxo-2,5-dihydropyrrole (**6**; 135.5 g, 0.97 mol) and anhydrous EtOAc (1.5 L) are added to a 3-L 3-neck round bottom flask equipped with a thermometer, addition funnel, a latex tube with pipet for N_2 delivery with cooling. Br_2 (310 g, 1.94 mol)[14] is added over 45 min, using N_2 only briefly to keep the reaction temperature below 55 °C while the Br_2 is being added. After the addition is complete, a condenser is installed and the reaction is refluxed for 15 min until complete (as determined by GC/MS) and then cooled to 25 °C. The EtOAc phase is washed with 5% aq $NaHCO_3$ (3 × 150 mL) and then with 10% aq $NaHCO_3$ (3 × 150 mL). A heavy precipitate forms in the separatory funnel, which is filtered and washed with H_2O and cold EtOAc. The combined EtOAc phases are washed with H_2O (3 × 100 mL), then brine (100 mL), and dried ($MgSO_4$). The volume is reduced to 1.4 L using a rotary evaporator. After cooling to − 30 °C, the light yellow needles formed are collected by filtration and washed with cold EtOAc. The combined washings and mother liquor are reduced to 400 mL on a rotary evaporator and cooled to give more light yellow crystals, which are collected by filtration and washed as above. The solvent is then removed from these combined mother liquor and washings, and the resultant dark brown oil is dissolved in an equal volume of Et_2O and cooled to − 30 °C. Solid product precipitates and is collected by filtration and washed with Et_2O (− 30 °C) until pale yellow. GC/MS shows that only very little product is left in the washings and nother liquor; yield: 168 g (80%). This represents a 38% yield from ethyl acetoacetate; mp 138–139 °C (Lit.[3] mp 140–142 °C).

IR (film): ν = 3156, 3008, 2965, 1686, 1636 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.08 (t, 3H, J = 7.5 Hz), 1.81 (s, 3H), 2.36 (q, 2H, J = 7.5 Hz), 5.88 (s, 1H), 8.27 (s, 1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 8.35 (q), 14.22 (q), 17.83 (t), 86.82 (d), 129.47 (s), 141.56 (s), 145.13 (s), 171.88 (s).

GC/MS (DEI): m/z = 217 and 215 [M^+], 136, 108, 91, 53.

Ethyl 4-Acetyl-5-oxohexanoate (3):
A vigorously stirred mixture of ethyl acrylate (100 g, 1.0 mol) and 2,4-pentane-dione (**1**; 400 g, 4.0 mol) and K_2CO_3 (69 g, 0.5 mol) is heated to 37 °C in a 1 L round bottom flask. After 12 h, GC/MS analysis confirmed the reaction to be complete with 98% mono (C-3) and 2% (C-3) dialkylation. The solid residue is filtered and washed with $CHCl_3$ (3 × 100 mL). The solvent is removed under reduced pressure, and the excess of 2,4-pentanedione (**1**) is recovered by distillation at 22 °C/0.7 mbar; yield: 192 g (96%); bp 90–110 °C/0.7 mbar (Lit.[10] 150–151 °C/13 mbar); GC/MS pure.

IR (film): ν = 2987, 1730, 1703, 1360, 1186, 1028 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): keto form, δ = 0.93 (t, 3H, J = 7.2 Hz), 1.81 (m, 2H), 1.89 (s, 3H), 1.98 (t, 2H, J = 7.2 Hz), 3.49 (t, 3H, J = 6.9 Hz), 3.80 (q, 2H, J = 7.2 Hz); enol form, δ = 1.852 (s, CH_3), 2.11–2.3 (m, 1H), 16.3 (OH).

^{13}C-NMR ($CDCl_3$/TMS): keto form, δ = 13.767 (q), 22.52 (q), 31.19 (t), 34.30 (t), 59.98 (t), 68.22 (d), 172.01 (s), 203.33 (s); enol form, δ = 22.35 (t), 28.91 (q), 108.21 (s), 190.96 (s).

GC-MS (DEI): m/z = 200 [M^+], 158 (M-CH_2CO), 113 (M-$CH_2CO_2CH_2CH_3$), 84, 55.

Ethyl 2,4-Dimethyl-5-ethoxycarbonyl)-1*H*-pyrrole-3-propanoate (5):
To a solution of ethyl acetoacetate (130 g, 1 mol) in glacial AcOH (360 mL) in a 2 L, 3 neck round bottom flask equipped with a thermometer and mechanical stirrer, and cooled to 8 °C is added dropwise a cooled (0 °C) solution of $NaNO_2$ (90 g, 1.3 mol) in H_2O (150 mL) such that the temperature remained between 8–12 °C. When all the $NaNO_2$ has been added, the yellow mixture is stirred for 12 h at r.t., whereupon it slowly turned to orange. Alkylated 2,4-pentanedione **3** (160 g, 0.8 mol) is added all at once and then Zn dust (165 g, 2.5 mol) in 3–5 g portions to maintain the temperature between 70–90 °C. Zn is added only in the absence of foaming and only when previous additions have dissolved. After all the Zn has been added, the mixture is refluxed overnight. The reaction is quenched by adding the hot solution to ice/water (5 L) and a grey solid slowly precipitates on standing for 6 h. The solid is filtered (saving the mother liquor for later workup) and washed with H_2O (4 × 2 L), being careful to mash the solid into small particles with each wash. The solid is slowly added to hot 95% EtOH (350 mL) and filtered while hot to remove unreacted Zn. Cooling to − 30 °C and filtration gives an off-white solid. Reducing the volume of EtOH and cooling gives the same results. The mother liquor from above is extracted with $CHCl_3$ until the organic layer is colorless and the $CHCl_3$ is removed on a rotary evaporator leaving a dark brown oil. The oil is taken up in 95% EtOH (~ 250 mL), and water is added until the solution remains turbid. 95% EtOH (50 mL) is added and the solution is cooled in an ice bath. Scratching the flask with a glass rod facilitates the precipitation of the off-white product. The combined solids are dried overnight at 0.7 mbar in a dessicator over P_2O_5 to afford the pure diester; yield: 116 g (55%); mp 72–73 °C (Lit.[15] mp 73 °C).

IR (film): ν = 3313, 2976, 1736, 1665, 1442, 1267, 1169 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.19 (t, 3H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz), 2.18 (s, 3H), 2.23 (s, 3H), 2.37 (t, 2H, J = 7.0 Hz), 2.66 (t, 2H, J = 7.0 Hz), 4.07 (q, 2H, J = 7.2 Hz), 4.25 (q, 2H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$/TMS): δ = 10.60 (q), 11.15 (q), 14.11 (q), 14.49 (q), 19.58 (t), 35.16 (t), 59.64 (t), 60.28 (t), 116.77 (s), 119.75 (s), 126.66 (s), 130.44 (s), 162.08 (s), 173.05 (s).

GC-MS (DEI): m/z = 267 [M^+], 180 (M-$CH_2CO_2CH_2CH_3$), 134.

2,4-Dimethyl-5-carboxy-1*H*-pyrrole-3-propanoic Acid (7):
A mixture of **5** (15 g, 0.056 mol), NaOH (6.75 g, 0.17 mol), 95% EtOH (90 mL) and H_2O (30 mL) is refluxed for 3 h. EtOH is recovered by distillation and the flask is cooled. A solution of $NaNO_2$ (65.0 g, 0.76 mol) in water (100 mL) is added and the flask is cooled to − 10 °C in dry ice/acetone bath. Concentrated HNO_3 (15 mL) (− 20 °C) is added very slowly to keep the temperature at − 10 °C and the mixture is stirred an additional 30 min after the addition is complete. The product is filtered and washed with cold H_2O and dried a 0.7 mbar in a dessicator over P_2O_5 overnight to afford a lavender solid; yield: 10.8 g (92%); mp 114 °C (dec) (Lit.[16] mp not reported).

IR (film): ν = 3346, 2924, 1697, 1634, 1505, 1467 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.07 (s, 3H), 2.12 (s, 3H), 2.22 (t, 2H, J = 7.2 Hz), 2.53 (t, 2H, J = 7.2 Hz), 10.83 (s, 1H), 11.760 (s, 2H), 11.762 (s, 1H).

^{13}C-NMR (DMSO-d_6/TMS): δ = 10.70 (q), 11.21 (q), 19.77 (t), 35.35 (t), 116.90 (s), 119.61 (s), 125.83 (s), 130.19 (s), 162.79 (s), 174.43 (s).

Methyl 5-[2,5-Dihydro-3-ethyl-4-methyl-5-oxo-2-pyrrolylidene)-methyl]-2,4-dimethyl-1*H*-pyrrole-3-propanoate (9):
A mixture of **7** (9.7 g, 0.045 mol), **8** (9.9 g, 0.045 mol) and anhydrous MeOH (100 mL) is refluxed for 90 min. The flask is cooled in an ice bath and the contents are filtered to give a green-yellow solid. This is dissolved in $CHCl_3$ and then slowly precipitated with MeOH while cooling in an ice bath to give 10.3 g (0.032 moles) of bright yellow crystals after filtration and drying; yield: 10.3 g (72%); mp 217–218 °C (Lit.[2] mp 217–220 °C).

UV/vis: ($CHCl_3$)λ_{max} = 406 (ε = 34000); (MeOH)λ_{max} = 411 (ε = 37000); (DMSO)λ_{max} = 412 (ε = 34400).

IR (film): ν = 3346, 3161, 2965, 1736, 1676, 1632, 1267, 1775 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.17 (t, 3H, J = 7.5 Hz), 1.94 (s, 3H), 2.14 (s, 3H), 2.41 (s, 3H), 2.46 (t, 2H, J = 7.2 Hz), 2.54 (q, 2H, J = 7.5 Hz), 2.74 (t, 2H, J = 7.2 Hz), 3.68 (s, 3H), 6.13 (s, 1H), 10.41 (s, 1H), 11.36 (s, 1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 8.53 (q), 9.60 (q), 11.57 (q), 15.08 (q), 17.96 (t), 19.88 (t), 35.13 (t), 51.56 (q), 101.04 (d), 119.03 (s), 122.40 (s), 122.43 (s), 124.57 (s), 127.10 (s), 131.65 (s), 148.29 (s), 173.59 (s), 173.92 (s).

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(12) When the reaction was repeated using a syringe pump for adding H_2O_2 in exactly 1/8 equivalent per h, it was not necessary to cool the reaction. The reaction temperature remained 54 °C until the addition was almost complete and then began to fall. After the workup and removal of the CH_2Cl_2, the product precipitated. It was washed with hexane (−30 °C). The solvent was removed from the mother liquor and the brown oil distilled as above. This yield was again 70% but with fewer distillations.

(13) This is necessary (presumably) to destroy excess H_2O_2 and pyrrole-dipyrrole peroxides, which cause severe bumping at reduced pressure distillation. Also, before extraction with CH_2Cl_2, an unidentifiable byproduct, present as a black tar, is separable at this point with decantation.

(14) Addition of any excess Br_2 causes the reaction to proceed to an unwanted equilibrium between product and the dibromo intermediate, making the workup much more difficult.

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