Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 15 May 2009, Revised 21 August 2009, Accepted 27 October 2009 Published online 4 January 2010 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1704

Novel synthesis of [$^{13}C_4$,^{15}N]1H-pyrrole-2,3,5-tricarboxylic acid: an important biomarker for melatonin metabolism

Marc B. Skaddan*

1H-pyrrole-2,3,5-tricarboxylic acid is a breakdown product of melatonin. A labeled version of this compound would serve as a key biomarker for drug candidates which track this substance to monitor their effectiveness (e.g. hyperpigmentation drugs). A Hantzsch synthesis using readily available starting materials was used to generate [$^{13}C_4$,^{15}N]1H-pyrrole-2,3,5-tricarboxylic acid in six steps (12% overall yield).

Keywords: stable label; ^{13}C; ^{15}N; C-13; N-15; melatonin; pyrrole; biomarker

Introduction

1H-pyrrole-2,3,5-tricarboxylic acid (**1a**) is a breakdown product of melatonin. To monitor the effectiveness of a new hyperpigmentation drug, a request was made for 200 mg of stable isotope labeled **1a** (with a minimum mass increase of 3 AMU and preferably 4 or 5 AMU). At least 3 Da mass difference had to be present in the ring itself, since it was known that at least one carboxylic acid residue was lost under the MS ionization conditions used to track the biomarker.

The discovery chemistry group had previously synthesized a small amount of **1a** via degradation of a commercially available starting material, 5-hydroxyindole-2-carboxylic acid (Scheme 1). Yields were extremely poor and the final compound was difficult to separate from reaction by-products by normal chromatographic methods. Importantly, the synthesis was not clearly amenable to the production of labeled **1a**. Therefore, a new route was sought to provide an analog with a mass increase of 5 AMU from commercially available stable isotope starting materials.

Results and discussion

A thorough search of the literature revealed that no synthetic routes to **1a** had been published. A myriad of methods are available for synthesizing substituted pyrroles, including the Paal–Knorr, Hantzsch and Kenner syntheses, and 1,3-dipolar cycloadditions to alkynes.[1] Since the labeled synthesis required at least three stable labels in the ring itself, simple substitution of readily accessed pyrrole starting materials was not feasible. Moreover, many of the aforementioned methods rely on precursors that are difficult to produce using known labeled starting materials. The Hantzsch synthesis, however, was attractive due to the fact that it used inexpensive, readily available labeled precursors.

Our envisioned route uses the Hantzsch reaction to construct the 2,3-disubstituted pyrrole nucleus from [1,2,3,4-$^{13}C_4$]ethyl acetoacetate, $^{15}NH_4OH$, and chloroacetaldehyde (Scheme 2). The use of these labeled precursors satisfies the mass and regiochemical requirements of the desired compound. At this point, the electronics of the ring should direct substitution with a carboxy electrophile to the 5-position.[1] Subsequent oxidation of the 2-methyl group, followed by hydrolysis, produces the final compound.

The synthesis was first performed with unlabeled material for optimization purposes. Using a slightly modified literature procedure,[2] NH_4OH was added to an aqueous mixture of ethyl acetoacetate and chloroacetaldehyde, resulting in an exothermic reaction (Scheme 3, yields in parentheses refer to stable-labeled product). Acidification and extractive workup provided pyrrole **2a**.

Yields were modest due to a competing Feist–Benary reaction that produced an equimolar amount of furan **3** (Scheme 4). While the furan can be removed by flash chromatography, it was found that trituration of the crude oily extract with cold hexanes provided product that was pure by NMR.

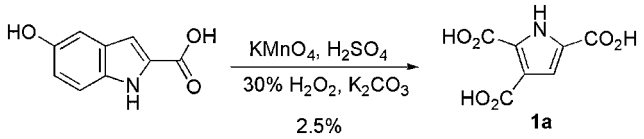
Installation of the 5-carboxy group was accomplished by heating **2a** with trichloroacetyl chloride in dioxane, which provided crude **4a** quantitatively following workup. Ethanolysis of the trichloromethyl ketone generated the 2,4,5-trisubstituted pyrrole **5a** in excellent yield after purification. Oxidation of the 5-methyl group to the carboxylic acid presents a special challenge. Pyrroles are, in general, easily attacked by oxidizing reagents, frequently with complete decomposition.[1] Moreover, oxidation of alkyl substituents alpha to the nitrogen in pyrroles are usually sluggish unless activated by an electron-withdrawing group in the second alpha position. In the present case,

Pfizer Global Research and Development, Pfizer Inc., Eastern Point Road, Groton, CT 06340, USA

**Correspondence to: Marc B. Skaddan, Pfizer Inc., Eastern Point Road, Mail Stop 8274-1342, Groton, CT 06340, USA.*
E-mail: mskaddan@yahoo.com

carboethoxy moieties in the 2 and 4 positions set up pyrrole **5a** nicely for oxidation of the 5-methyl group. Direct conversion of α-methyl substituents to the acid/ester with SO_2Cl_2 are known; however, the literature substrates consist of tetrasubstituted pyrroles.[3–6] The open 3-position in **5a** would almost certainly be halogenated under these conditions. The better approach is to perform a stepwise oxidation of the alkyl moiety to the aldehyde, then to the acid. Cerric ammonium nitrate (CAN) oxidations of activated α-methyl substituents have been shown to proceed in good yields;[7–9] therefore, we proceeded by reacting **5a** with 6 equivalents of CAN in MeOH. This provided aldehyde **6a** in modest yield, the main by-product being the analogous 5-methoxymethyl pyrrole. Oxidation of the aldehyde side chain using sodium chlorite failed to produce appreciable amounts of the desired acid. On the contrary, slow addition of potassium permanganate to a dilute acetone solution of **6a**, followed by heating at 55°C, provided acid **7a** in good yield. Basic hydrolysis furnished the desired triacid **1a** quantitatively (extractive workup only). The entire sequence gave an overall yield of 12%.

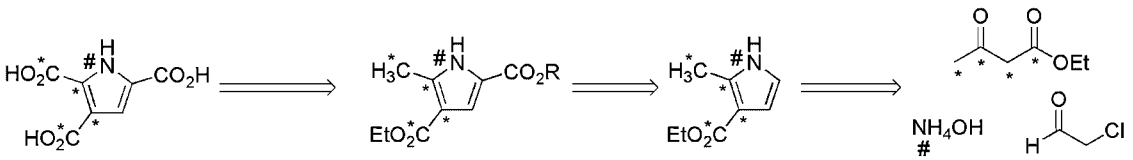
Even though we predicted that reaction of **2a** would occur alpha to the nitrogen (*vide supra*), empirical evidence was required to prove that we did, in fact, get 5- vs 4-substitution for the final compound **1a**. Unfortunately, with only one aromatic proton, ^{1}H NMR was unsupportive in this regard. Other NMR experiments, including ^{13}C NMR, HMBC, and ^{15}N-^{1}H IMPEACH experiments on **1a** and other trisubstituted intermediates in this sequence, were also inconclusive (for ^{13}C experiments, the resonances of the carbon signals did not closely match the predicted resonances of either regioisomer). The definitive answer came from a ^{13}C 2D INADEQUATE experiment (Figure 1), which unambiguously showed coupling of the pyrrole ring C-H carbon to two other pyrrole ring carbons (the 4-substituted regioisomer would have showed only 1 other carbon coupling).



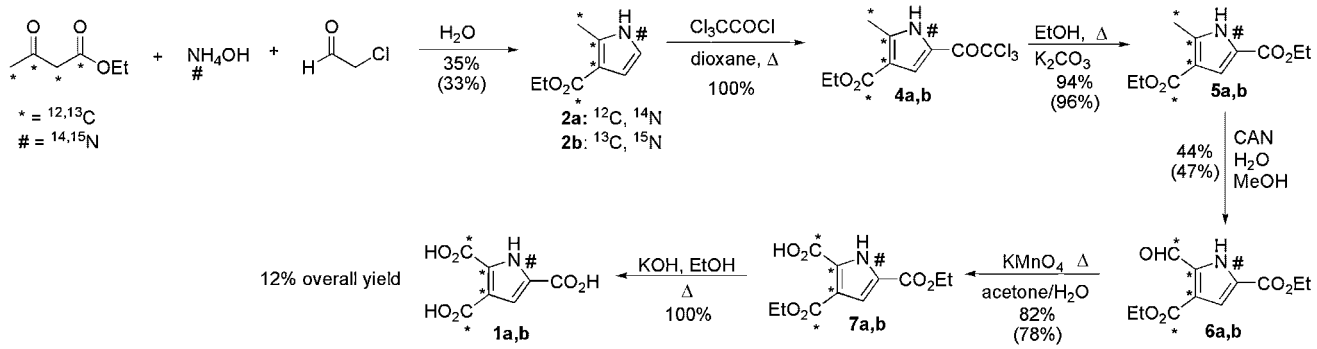
Scheme 1. Degradation route to **1a**.

With the successful implementation of the synthetic strategy on unlabeled **1a**, attention was turned to synthesizing the labeled analog **1b**. The synthesis proceeded without any noticeable deviations from the unlabeled synthesis, using the aforementioned labeled precursors (Scheme 3). Starting with 3.1 g (23.0 mmol) of [1,2,3,4-$^{13}C_4$]ethyl acetoacetate and 120 mmol $^{15}NH_4OH$, 560 mg of **1b** was produced in an overall yield of 12%, which matched what was achieved with **1a**. Mass spectrometry clearly showed the molecular ion associated with the M+5 species, with no M+0 evident. The purity of the final compound (92% by UV-HPLC) was sufficient for the project team's needs.

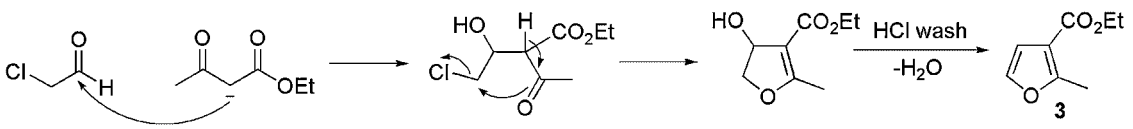
In conclusion, we have synthesized the M+5 melatonin biomarker [$^{13}C_4$,^{15}N]1H-pyrrole-2,3,5-tricarboxylic acid in a six step 12% overall yield from relatively inexpensive and readily available stable label starting materials. While some of the transformations have modest yields, the chemistry is very reproducible. This compound will serve as a valuable tool to track melatonin metabolism in drug therapies designed to treat various ailments involving this important hormone.



Scheme 2. Retrosynthetic route for [$^{13}C_4$,^{15}N]1H-pyrrole-2,3,5-tricarboxylic acid.



Scheme 3. Synthesis of **1a/b** via Hantzsch reaction.



Scheme 4. Competing Feist–Benary reaction to produce furan **3**.

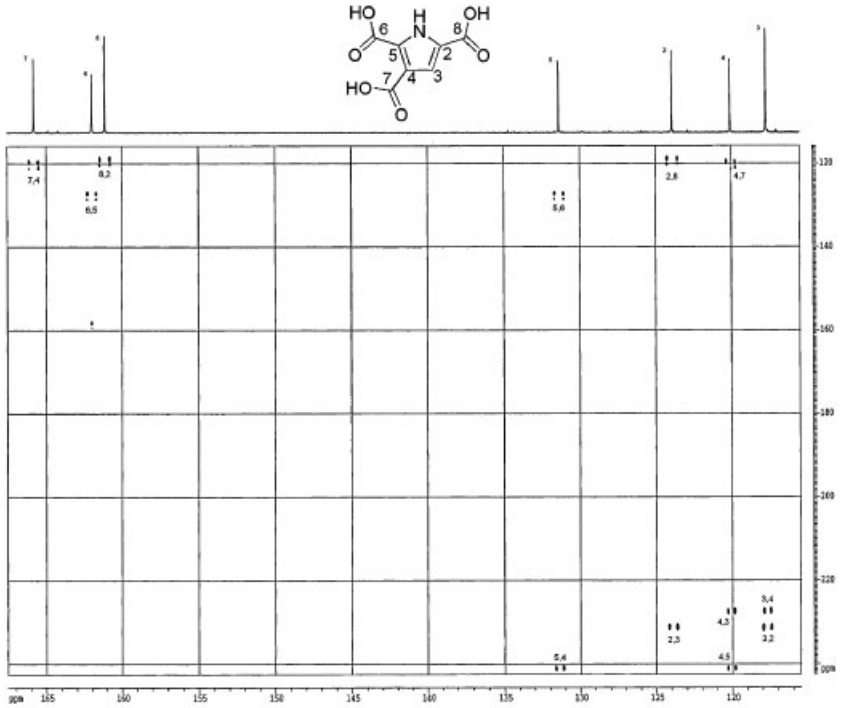


Figure 1. INADEQUATE spectrum of **1a**.

Experimental

All unlabeled reagents and solvents were obtained from Acros and Aldrich and used without further purification. The [1,2,3,4-$^{13}C_4$]ethyl acetoacetate was purchased from Cambridge Isotopes (CLM-3297, 99%) and the [^{15}N]NH_4OH was purchased from Aldrich (cat# 485454, 6 N, 98%). Mass spectrometric data were collected on a PerkinElmer Sciex API 150EX (electrospray). Reaction progress was monitored by analytical thin-layer chromatography (Analtech scored glass 10 cm × 20 cm hard TLC plates). TLC plates were visualized using short wave UV light (254 nm) or potassium permanganate. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 300, 400, or 500 MHz spectrometer. Resonances are reported in parts per million relative to the incomplete deuteration signal from the NMR solvent. HPLC analyses were performed on an Agilent 1100 LC system, using a Phenomenex Luna C-18(2) 4.6 × 250 mm column, UV = 254 nm, flow = 1.0 ml/min.

1H-Pyrrole-2,3,5-tricarboxylic acid (1a)

Following a slightly modified literature procedure,[2] compound **7a** (949 mg, 3.72 mmol) was dissolved in 2 M KOH (30 ml of a 90:10 water:EtOH solution). The reaction was followed by MS, which showed steady but sluggish hydrolysis. After 24 h, the reaction was heated for 1.5 h at 51°C and this resulted in complete conversion to the triacid. The reaction was cooled in an ice bath and acidified with 6 M HCl. A precipitate formed from the yellow solution. The solid was filtered, and the filter cake was washed with cold water, diethyl ether, hexanes, and EtOAc. The yellow solid was dried on a high vacuum line to provide **1** (802 mg, 108%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.03 (s, 1H), 11.72 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 117.6, 120.2, 123.8, 131.4, 161.1, 161.8, 165.7. ESIMS (neg. ion): *m/z* 198 (M-H, 100), 154 (M-CO_2H, 50).

[$^{13}C_4$,^{15}N]1H-Pyrrole-2,3,5-tricarboxylic acid (1b)

The procedure used to prepare **1a** was followed using 0.669 g **7b** (2.57 mmol) and 21 ml of the KOH solution (55.8 mmol). After 1.5 h at 51°C, the reaction mixture was worked up as described for **1a** to provide **1b** (560 mg, 107%) as a slightly yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.00 (s, 1H), 11.31 (d, $J_{H-^{13}C}$ = 98.2 Hz, 1H), 12.71 (bs, 1H). ESIMS (neg. ion): *m/z* 203 (M-H, 100), 159 (M-CO_2H, 47). HPLC conditions (A = 5:95 CH_3CN:0.1% TFA in water; B = 70:30 CH_3CN:0.1% TFA in water): 0–10 min 100% A, 10–11 min 100% A to 100% B, 11–16 min 100% B, 16–17 min 100%B to 100% A, 17–20 min 100% A. HPLC purity = 92% (t_R = 9.40 min). Minor impurity at t_R = 14.2 min (8%).

Ethyl 2-methyl-1H-pyrrole-3-carboxylate (2a)

To a vigorously stirred solution of ethyl acetoacetate (2.60 g, 20.0 mmol) in water (10 ml) was added chloroacetaldehyde (2.80 ml of a 50 wt% in water solution, 22.0 mmol), followed immediately by ammonium hydroxide (9.70 ml of a 28 wt% water solution, 144 mmol). The reaction exothermed and was stirred overnight, providing an oily, globular precipitate. Analysis of the reaction by TLC (40% EtOAc/hexanes) showed the presence of product (R_f = 0.41) and a single, more polar impurity (equal intensity under UV light, R_f = 0.26). The heterogeneous solution was extracted with 20 ml diethyl ether. The aqueous phase was extracted with another 10 ml of ether, and the organics were combined. The combined organics were washed sequentially with 10 ml 10% NaOH, 10 ml water, and 10 ml 5% HCl. Following the HCl wash, the TLC analysis showed complete conversion of the 0.26 R_f impurity to a less polar impurity (R_f = 0.62), presumably compound **3** from the competing Feist–Benary reaction. The organic layer was dried with sodium sulfate and evaporated to an oily residue with crystalline solids in it. Ten milliliters of hexanes was added, and the mixture was stirred for 30 min in an ice bath

to triturate the product. The cold mixture was filtered and the filter cake washed with a few milliliters of cold hexanes. This provided a slightly off-white, pinkish powder and an oily filtrate. The powder was dried *in vacuo* for 2 h to provide **2** (1.02 g, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, J = 7.3 Hz, 3H), 2.56 (s, 3H), 4.30 (q, J = 7.3 Hz, 2H), 6.59 (s, 1H), 8.40 (bs, 1H). ESIMS: *m/z* 176 ($M+H+Na^+$, 100), 154 ($M+H^+$, 79), 126 (27). Isolation of **3** from the filtrate by flash chromatography (SiO_2, 20–30% EtOAc/hexanes) provided a pungent-smelling, volatile oil (1.17 g, with some EtOAc still present). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, J = 7.3 Hz, 3H), 2.59 (s, 3H), 4.31 (q, J = 7.3 Hz, 2H), 6.66 (s, 1H), 7.24 (s, 1H).

[$^{13}C_4$, ^{15}N]Ethyl 2-methyl-1H-pyrrole-3-carboxylate (2b)

The procedure used to prepare **2a** was followed, using 20 ml (119.6 mmol) 6 N [^{15}N]NH_4OH, 3.10 g (23.0 mmol) [1,2,3,4-$^{13}C_4$]ethyl acetoacetate, and 3.20 ml (25.3 mmol) chloroacetaldehyde. After 6 h, the reaction was worked up as described for **2a** to afford **2b** as a white powder (1.26 g, 35%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, J = 7.5 Hz, 3H), 2.56 (d, $J_{H-^{13}C}$ = 129 Hz, 3H), 4.29 (q, J = 7.0 Hz, 2H), 6.59 (m, 2H), 8.17 (d, $J_{H-^{15}N}$ = 129 Hz, 1H). ESIMS: *m/z* 181 ($M+H+Na^+$, 100), 159 ($M+H^+$, 80), 131 (20).

Ethyl 2-methyl-5-(2,2,2-trichloroacetyl)-1H-pyrrole-3-carboxylate (4a)

To a solution of **2a** (1.89 g, 12.3 mmol) in dioxane (20 ml) and 2,6-lutidine (1.58 ml, 13.5 mmol) was added the trichloroacetyl chloride (1.51 ml, 13.5 mmol) at room temperature. The turbid mixture was heated to 85°C. After 1 h, a milky white precipitate formed, and TLC showed complete disappearance of the starting material. The reaction was cooled and half of the dioxane was removed *in vacuo*. The remaining mixture was partitioned between 50 ml EtOAc and 10 ml water. The EtOAc layer was washed with 10 ml saturated NaCl. The combined aqueous washes were back-extracted with EtOAc (20 ml+10 ml). The combines organics were washed with 4 ml saturated NaCl, then dried with Na_2SO_4 and evaporated *in vacuo* to provide **4a** as an orange solid (4.16 g, >100%). This crude material was used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, J = 7.0 Hz, 3H), 2.65 (s, 3H), 4.34 (q, J = 7.0 Hz, 2H), 7.73 (s, 1H), 9.39 (bs, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 13.81, 14.44, 60.29, 94.46, 115.89, 120.57, 123.29, 143.58, 164.01, 173.49. MS (APCI): *m/z* 339 ($M+CH_3CN$, 48), 298 (M^+, 100), 270 (7).

[$^{13}C_4$, ^{15}N]Ethyl 2-methyl-5-(2,2,2-trichloroacetyl)-1H-pyrrole-3-carboxylate (4b)

The procedure used to prepare **4a** was followed, using 1.24 g (7.85 mmol) of **2b**, 0.997 ml (8.64 mmol) of 2,6-lutidine,13 ml dioxane, and 0.964 ml (8.64 mmol) of trichloroacetyl chloride. After 1 h, TLC revealed the presence of starting material. An additional 100 µl (0.896 mmol) of trichloroacetyl chloride was added, and the solution was heated for an additional 30 min, with no change in the progress of the reaction. The reaction was worked up as described for **4a** to provide **4b** as a light brown solid (2.54 g, 107%), which was used in the next step without further purification.

Diethyl 5-methyl-1H-pyrrole-2,4-dicarboxylate (5a)

To a solution of **4a** (3.66 g, 12.2 mmol) in 23 ml EtOH was added the K_2CO_3 (952 mg, 6.89 mmol). The slurry was heated at 90°C for 2 h, during which the reaction mixture turned brown. TLC showed complete conversion of the starting material. The reaction was cooled to room temperature and then filtered. The K_2CO_3 cake was washed with 3 ml EtOH, and the filtrate was evaporated *in vacuo* to afford a brown solid. The solid was purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to provide **5a** as a slightly yellow fluffy solid (2.64 g, 96%). ^{1}H NMR (DMSO-d_6, 500 MHz, 5 mm Cryoprobe) δ 1.24 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 6.99 (s, 1H), 12.33 (s, 1H). ESIMS: *m/z* 248 ($M+H+Na^+$, 94), 226 ($M+H^+$, 100), 198 (21).

[$^{13}C_4$, ^{15}N]Diethyl 5-methyl-1H-pyrrole-2,4-dicarboxylate (5b)

The procedure used to prepare **5a** was followed, using 2.54 g (~7.85 mmol) **4b**, 15 ml EtOH, and 1.08 g (7.85 mmol) K_2CO_3. The reaction was worked up and purified as described for **5a** to provide **5b** as a slightly yellow, fluffy solid (1.70 g, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (m, 6H) 2.59 (d, $J_{H-^{13}C}$ = 129.6 Hz, 3H), 4.33 (m, 4H), 7.26 (s, 1H), 9.23 (d, $J_{H-^{15}N}$ = 97.0 Hz, 1H). ESIMS: *m/z* 253 ($M+H+Na^+$, 100), 231 ($M+H^+$, 85), 203 (15).

Diethyl 5-formyl-1H-pyrrole-2,4-dicarboxylate (6a)

Following Bobal's procedure,[7] a solution of **5a** (2.57 g, 11.4 mmol) in MeOH (50 ml) was cooled in an ice bath. To this was added a solution of CAN (25.6 g, 46.7 mmol) in water (25 ml). The reaction turned a deep claret color and the ice bath was removed. After 25 min, the reaction had changed to a yellow color. After 1 h, analysis by TLC showed incomplete conversion of starting material to the aldehyde. After 1.5 h, an additional 12.5 g (22.8 mmol) of CAN was added to the reaction mixture and the reaction mixture turned claret. After another 70 min (total reaction time = 2.5 h), the reaction was an orange color and TLC showed complete disappearance of the starting material. The MeOH was evaporated *in vacuo*, during which time a solid formed. The aqueous suspension was extracted with CH_2Cl_2 (1 × 50 ml, 2 × 35 ml), and the combined extracts were dried with Na_2SO_4 and evaporated to an orange solid. Purification by flash chromatography (SiO_2, 20% EtOAc/hexanes) provided **6a** as a white fluffy solid (1.29 g, 47%) containing a minor impurity by TLC (2.5% acetone/CH_2Cl_2). This was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 6H), 4.41 (m, 4H), 7.34 (s, 1H), 10.10 (bs, 1H), 10.35 (s, 1H). ESIMS: *m/z* 262 ($M+H+Na^+$, 100), 240 ($M+H^+$, 31).

[$^{13}C_4$, ^{15}N]Diethyl 5-formyl-1H-pyrrole-2,4-dicarboxylate (6b)

The procedure used to prepare **6a** was followed, using 1.69 g (7.34 mmol) **5b**, 33 ml MeOH, 16.5 g (30.1 mmol) CAN in 16 ml water, and 8.00 g (14.6 mmol) of additional CAN. The reaction was worked up as described for **6a**, then purified by flash chromatography (SiO_2, 1.5% acetone/CH_2Cl_2) to give **6b** as a white solid (787 mg, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 6H), 4.41 (m, 4H), 7.34 (s, 1H), 10.0 (d, $J_{H-^{15}N}$ = 101 Hz, 1H), 10.29 (dd, $J_{H-^{13}C}$ = 192.0, 30.2 Hz, 1H). ESIMS: *m/z* 267 ($M+H+Na^+$, 100), 245 ($M+H^+$, 33).

3,5-*Bis*(ethoxycarbonyl)-1H-pyrrole-2-carboxylic acid (7a)

Using a slightly modified literature procedure,[10] a solution of $KMnO_4$ (2.44 g, 15.4 mmol) in 125 ml water and 125 ml acetone was added dropwise via addition funnel to a solution of **6a** (1.23 g, 5.14 mmol) in acetone (150 ml) over the course of 3 h.

The reaction was monitored by MS, and showed slow but steady progress. After 6 h, MS showed a 58:42 ratio of compound **7a**:**6a**. The reaction mixture was heated at 55°C for 1 h, then room temperature overnight. The reaction was checked again by MS, showing a 92:8 ratio of compound **7a**:**6a**, and the reaction was heated again for 1 h at 55°C. The ratio of **7a**:**6a** was now 97:3, and the acetone was removed *in vacuo*. The purple solution was treated with 10% sodium metabisulfite in 1 M HCl solution (95 ml). The purple solution turned clear and exothermed. It was extracted with CH_2Cl_2 (3 × 50 ml), and the organics were dried with Na_2SO_4 and evaporated *in vacuo* to a slightly yellow solid (1.02 g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (m, 6H), 4.43 (m, 4H), 7.37 (s, 1H), 10.43 (bs, 1H). ESIMS (neg. ion): *m/z* 254 (M-H, 100), 210 (M-CO_2H, 87).

[$^{13}C_4$, ^{15}N]3,5-*Bis*(ethoxycarbonyl)-1H-pyrrole-2-carboxylic acid (7b)

The procedure used to prepare **7a** was followed, using 777 mg (3.18 mmol) **6b**, 93 ml acetone, and 1.51 g (9.54 mmol) $KMnO_4$ in 77 ml water and 77 ml acetone. The reaction mixture was heated to 55°C for 3 h. An additional 251 mg (1.59 mmol) $KMnO_4$ was added and the reaction mixture was stirred for 1 h. The heat was removed and the reaction allowed to stir overnight at room temperature. The solution was evaporated *in vacuo* (~130 ml acetone removed), and the resulting aqueous solution was poured into 60 ml 10% sodium metabisulfite in 1 M HCl (cooled to 5°C). The clear solution was worked up as described in **7a** to provide **7b** as a white solid (679 mg, 82%), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (m, 6H), 4.44 (m, 4H), 7.36 (s, 1H), 10.29 (d, $J_{H-^{13}C}$ = 98.7 Hz, 1H). ESIMS (neg. ion): *m/z* 259 (M-H, 81), 214 (M-CO_2H, 100).

Acknowledgements

We thank Stephen Grode from the Rapid ID Lab (Portage, MI) for his work on the INADEQUATE experiments, as well as David J. Russell and Gary Martin from the Structure Elucidation Group (Portage, MI) for their help in the HMBC and ^{15}N-^{1}H IMPEACH NMR experiments. We also thank the members of the Kalamazoo Radiosynthesis Lab for their scientific input and support.

References

[1] J. A. Joule, K. Mills, G. F. Smith, Pyrroles: reactions and synthesis, *Heterocyclic Chemistry* 3rd ed., Chapman & Hall, New York, **1995**, pp. 229–258.
[2] A. Treibs, W. Ott, *Justus Liebigs Ann. Chem.* **1958**, 615, 137.
[3] U. Eisner, R. P. Linstead, E. A. Parkes, E. Stephen, *J. Chem. Soc.* **1956**, 1655.
[4] B. Morgan, D. Dolphin, R. H. Jones, T. Jones, F. W. B. Einstein, *J. Org. Chem.* **1987**, 52, 4628.
[5] M. Scarsella, G. Sleiter, *Gazzetta Chimica Italiana* **1988**, 118, 757.
[6] E. Vogel, M. Balci, K. Pramod, P. Koch, J. Lex, O. Ermer, *Angewandte Chemie* **1987**, 99, 909.
[7] P. Bobal, D. A. Lightner, *J. Heterocycl. Chem.* **2001**, 38, 1219.
[8] A. J. Moreno-Vargas, J. G. Fernandez-Bolanos, J. Fuentes, I. Robina, *Tetrahedron: Asymmetry* **2001**, 12, 3257.
[9] T. Thyrann, D. A. Lightner, *Tetrahedron Lett.* **1996**, 37, 315.
[10] P. Barker, P. Gendler, H. Rapoport, *J. Org. Chem.* **1978**, 43, 4849.