First Total Synthesis of 5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one: A Cancer Chemopreventive Agent

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Abstract: The first total synthesis of 5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one, a newly discovered natural product with anticancer property is described by two different routes. A sequence involving an incorporation of a methyl group via a Gilman reagent and a chemoselective reduction of a cyclic anhydride functionality are the key steps. The methods proposed start from easily available starting materials and allow ready preparation of the final compound in good overall yield.

Key words: *Allium cepa*, synthesis, Gilman reagent, chemopreventive, selective

Cancer chemoprevention involves prevention, delay, or reversal of the process of carcinogenesis through ingestion of dietary or pharmaceutical agents.[1,2] It also involves suppression of carcinogen metabolic activation.[3] In particular, the induction of phase II enzymes can offer protection against toxic and reactive chemical species.[4] Many recent studies have shown that elevation of phase II enzymes, such as NAD(P)H:quinone reductase (QR) and glutathione *S*-transferase (GST), correlates with protection against chemically induced carcinogenesis in animal models,[5,6] in the stage of promotion[7] as well as initation.[5]

5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (**1**) (Figure 1), a γ-hydroxybutenolide derivative was first isolated from *Allium cepa* (green onion) by Xiao and Parkin in 2007.[8] The γ-hydroxybutenolide [5-hydroxy-2-(5*H*)-furanone] is an important moiety, found in many bioactive natural products.[9] The preliminary biological evaluation revealed that the target molecule **1** induced phase II drug metabolizing enzyme, QR up to 5.55-fold compared to the control (CD = 15.6 μg/ml). Moreover, compound **1** doubled GST activity at the upper end of the dose range. However, to the best of our knowledge, the synthesis of compound **1** has not been reported in the literature and taking into account the important biological activities, we initiated the development of a flexible strategy for the synthesis of this molecule.

Herein, we describe a concise and an efficient approach, designed to afford the first total synthesis of target molecule **1**, which could be useful for structure–activity relationship study.

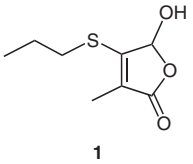

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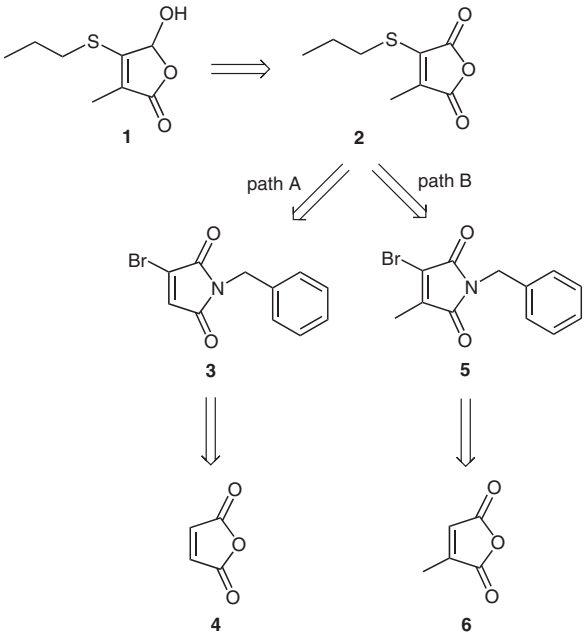
Figure 1 Structure of 5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (**1**)

In our retrosynthetic analysis (Scheme 1), we envisioned that the target molecule **1** could be obtained from commercially available maleic anhydride (**4**). The 5-hydroxy functionality in **1** could be prepared from cyclic anhydride **2** via selective reduction of carbonyl group. Cyclic anhydride **2** could be attained from bromomaleimide **3** as a key intermediate in path A, which could be obtained from maleic anhydride (**4**). In our other approach, cyclic anhydride **2** could be prepared from bromomethylmaleimide (**5**), which could be obtained from citraconic anhydride (**6**).



Scheme 1 Retrosynthetic analysis of **1**

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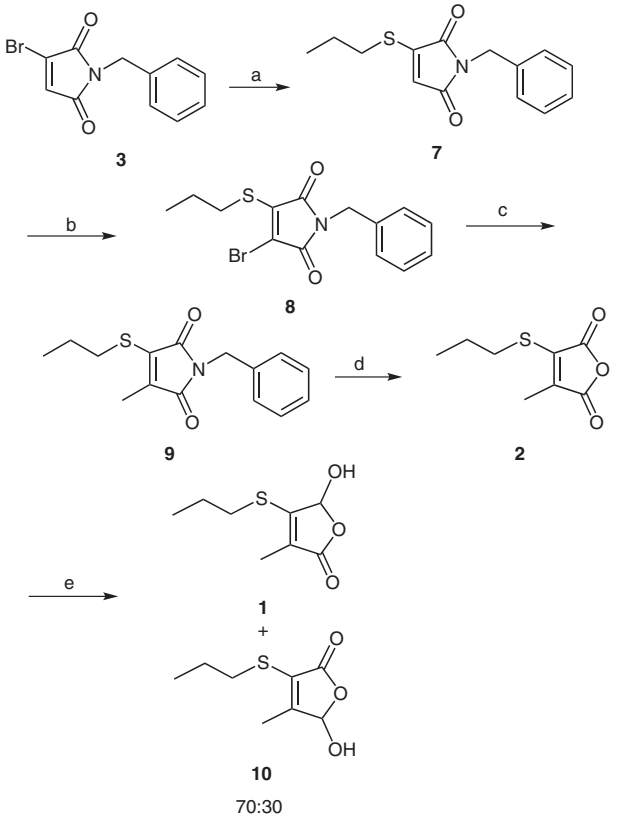
As illustrated in Scheme 2, the total synthesis of target molecule **1** commenced with the known compound **3**, which can be easily prepared from maleic anhydride **4** (path A).[10] Reaction of bromomaleimide **3** with propane-1-thiol in *N*,*N*-dimethylformamide at 90 °C afforded thiomaleimide **7** in 61% yield, as a consequence of a nucleophilic substitution. Subsequently, bromination of **7** with molecular bromine in the presence of triethylamine in dichloromethane at 0 °C to room temperature furnished the bromide **8** in 92% yield. The next step was the incorporation of the methyl group at the C-3 position, which was the key step for the synthesis of **1**. The displacement of the bromo group by a methyl group using Grignard reagent (MeMgCl) in anhydrous tetrahydrofuran afforded a complex reaction mixture and isolation of the desired product was difficult. Hence, we planned to introduce the methyl group using Gilman reagent. Freshly prepared Me_2CuLi[11] from copper(I) iodide and 1.6 M methyllithium in hexane at –78 °C in anhydrous tetrahydrofuran reacted with **8** to afford the key intermediate methyl thiomaleimide **9** in 63% yield. Alkaline hydrolysis of **9** with aqueous 5 M potassium hydroxide in absolute ethanol under reflux furnished the cyclic anhydride **2** in 60% yield.[12] Finally, the selective reduction of carbonyl group at C-5 position in cyclic anhydride **2** with 0.5 equivalent of sodium borohydride in anhydrous methanol gave a mixture of two regioisomers **1** (64%) and **10** (28%), which were separated by flash column chromatography. Compound **1** exhibited HRMS and ^{13}C NMR spectral data in full agreement with those reported in the literature.[8] In the ^1H NMR data for compound **1**, the hydroxyl proton appeared as a broad singlet at 4.27 ppm, instead of the reported doublet at 3.3 ppm. Also, H-5 proton of compound **1** appeared as a singlet instead of the reported doublet. Its structure was further confirmed by X-ray crystal structure analysis. The ORTEP diagram of **1** is given in Figure 2.



Scheme 2 *Reagents and conditions*: (a) propane-1-thiol, DMF, 90 °C, 61%; (b) Br_2, Et_3N, CH_2Cl_2, 0 °C to r.t., 92%; (c) Me_2CuLi, THF, –78 °C, 63%; (d) aq 5 M KOH, EtOH, reflux, 2 h, 60%; (e) $NaBH_4$, MeOH, 0 °C to r.t. (64% for **1**, 28% for **10**).

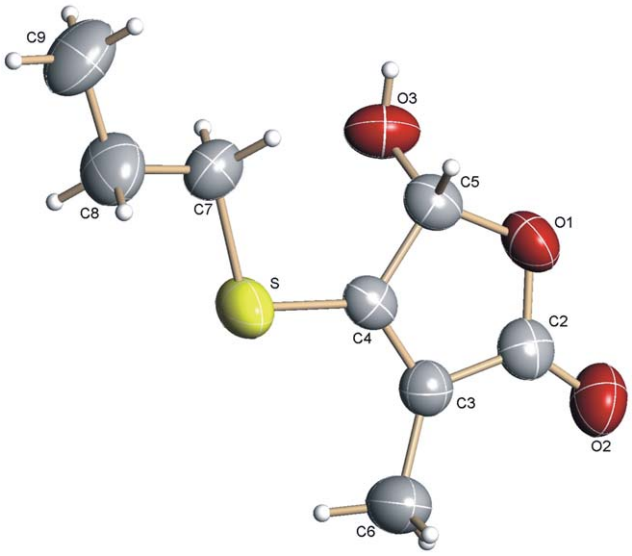


Figure 2 ORTEP plot of the X-ray crystal structure of **1**

Further, the confirmation of synthetic 5-hydroxy-4-methyl-3-proplysulfanyl-5*H*-furan-2-one (**10**) was accomplished on the basis of ^1H NMR, ^{13}C NMR, ^{13}C DEPT, and HMBC spectral data. In the HMBC spectrum (Figure 3), the H-6 proton of the methyl group is strongly correlated with the C-3, C-4 and C-5 carbons through two or three bonds. The H-5 proton is strongly correlated with C-2 and C-4 and weakly correlated with the C-6 carbon. Hence, we conclude that the methyl group is placed in between the hydroxy and sulfur groups with strong bonding.

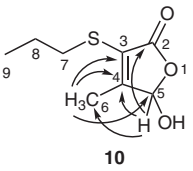
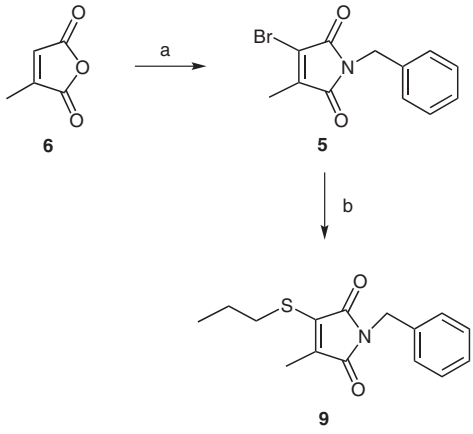


Figure 3 Significant ^1H–^{13}C long-range correlations observed from HMBC spectra of compound **10**

In retrosynthetic path B, bromomethylmaleimide (**5**) was prepared from commercially available citraconic anhydride (**6**) by simple bromination reaction followed by nucleophilic substitution reaction with propane-1-thiol affording methyl thiomaleimide **9** in good yield. Further alkaline hydrolysis of **9** and selective reduction of cyclic anhydride **2** gave final molecule **1** (Scheme 3). In this approach, we designed an alternative route, avoiding the use of a Gilman reagent.



Scheme 3 *Reagents and conditions*: (a) i. $BnNH_2$, AcOH, reflux, 3 h, NaOAc, ii. Br_2, 0 °C to r.t., 86%; (b) propane-1-thiol, DMF, 90 °C, 3 h, 92%.

In summary, we have achieved two facile routes for the first total synthesis of 5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (**1**) from readily available starting materials, in good overall yields. This methodology can be applied for the synthesis of new analogues of compound **1**.

All chemicals were purchased from commercial sources (Sigma-Aldrich, Lancaster, and Merck) and used without further purification. Solvents used as reaction media were purchased from local sources and used after distillation. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Reactions were monitored using analytical TLC plates (Merck, silica get 60 F254, 0.25 mm), and compounds were visualized with ultraviolet light. Silica gel (60–120 and 230–400 mesh) was used for column chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 and DPX 400 instrument operating at 300 MHz (^1H), and 75 MHz (^{13}C) and 400 MHz. Chemical shifts (δ) are reported in ppm using TMS as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP5050 instrument. IR spectra were recorded on a Perkin-Elmer FTIR 16PC spectrometer. Melting points were determined on a Büchi instrument and are uncorrected.

3-Bromo-1-benzyl-1*H*-pyrrole-2,5-dione (3)
A stirred mixture of maleic anhydride (**4**; 5.0 g, 51.0 mmol) and benzylamine (5.55 mL, 51.0 mmol) in glacial AcOH (50 mL) was refluxed for 2 h. After the solution was cooled to 0 °C, Br_2 (2.6 mL, 51 mmol) and NaOAc (4.18 g, 51.0 mmol) were added and the reaction mixture was stirred for 2 h at 0 °C to r.t. Then ice-water (100 g) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were separated and washed with H_2O (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 2% EtOAc in hexane to afford compound **3** as a yellow solid; yield: 4.9 g (36%).

IR ($CHCl_3$): 3059, 2938, 2848, 1955, 1907, 1776, 1651, 1600, 1494, 1402, 1288, 925 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.63 (s, 2 H), 6.79 (s, 1 H), 7.18–7.28 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.27, 128.03, 128.51, 128.70, 131.36, 131.84, 135.56, 164.93, 168.09.

MS (ESI): *m*/*z* = 266 (M + 1).

1-Benzyl-3-(propylthio)-1*H*-pyrrole-2,5-dione (7)
To a stirred solution of **3** (5.0 g, 18.8 mmol) in DMF (50 mL) was added propane-1-thiol (2.55 mL, 28.2 mmol). The resulting mixture was then heated at 90 °C for 4 h. H_2O (20 mL) was added to the reaction mixture and extracted with EtOAc (3 × 30 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and then concentrated in vacuo. The residue was purified by silica gel column chromatography using 2% EtOAc in hexane to afford compound **7** as a pale yellow crystal; yield: 3.0 g (61%).

IR ($CHCl_3$): 3143, 3032, 2926, 2873, 1762, 1556, 1497, 1433, 1397, 1354, 1241, 1141, 1054 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.32 Hz, 3 H), 1.76 (m, 2 H), 2.88 (t, *J* = 7.20 Hz, 2 H), 4.67 (s, 2 H), 6.05 (s, 1 H), 7.28–7.37 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.38, 21.10, 33.62, 41.59, 117.15, 127.73, 128.40, 128.57, 136.18, 151.64, 167.62, 169.26.

MS (ESI): *m*/*z* = 261 $(M)^+$.

1-Benzyl-3-bromo-4-(propylthio)-1*H*-pyrrole-2,5-dione (8)
To a stirred solution of **7** (2.69 g, 10.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added Br_2 (0.63 mL, 12.4 mmol) dropwise. The resulting solution was stirred for 5 min at 0 °C, and Et_3N (1.72 mL, 12.4 mmol) was added. Then, the reaction mixture was brought to r.t. and stirred for an additional 1 h. The progress of the reaction was monitored by TLC (10% EtOAc in hexane). H_2O (15 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers washed with H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using 1% EtOAc in hexane to afford compound **8** as a yellow solid; yield: 3.2 g (92%).

IR ($CHCl_3$): 2900, 1750, 1715, 1530, 1432, 1391, 1200, 1177, 1080, 1040, 759, 665 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.20 Hz, 3 H), 1.70 (m, 2 H), 3.36 (t, *J* = 7.46 Hz, 2 H), 4.69 (s, 2 H), 7.26–7.36 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.98, 23.84, 32.69, 42.56, 116.51, 128.00, 128.56, 128.70, 135.70, 143.54, 164.02, 165.65.

MS (ESI): *m*/*z* = 341 (M + 1).

1-Benzyl-3-methyl-4-(propylthio)-1*H*-pyrrole-2,5-dione (9)
Path A: The following reaction was carried out under an inert atmosphere. To a stirred solution of CuI (0.7 g, 3.68 mmol) in anhyd THF (20 mL) at –78 °C was added a 1.6 M solution of MeLi in hexane (5.75 mL, 9.2 mmol). The solution became dark black. The resulting mixture was stirred for 1 h. To the above solution, compound **8** (1.0 g, 3.06 mmol) in anhyd THF (5 mL) was added dropwise and stirred for 4 h at –78 °C. The progress of the reaction was monitored by TLC (10% EtOAc in hexane). The reaction mixture was quenched by the addition of sat. aq NH_4Cl (20 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a yellow residue. purification of the residue by silica gel flash column chromatography using 1% EtOAc in hexane afforded compound **9** as a yellow oil; yield: 0.51 g (63%).

Path B: To a stirred solution of **5** (5.0 g, 17.8 mmol) in DMF (40 mL) was added propane-1-thiol (2.42 mL, 26.7 mmol). The resulting mixture was then heated at 90 °C for 3 h. H_2O (20 mL) was added to the reaction mixture and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography using 2% EtOAc in hexane to afford compound **9** as pale yellow crystals; yield: 4.52 g (92%).

IR ($CHCl_3$): 3367, 2932, 1704, 1603, 1400, 1348, 1070 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.33 Hz, 3 H), 1.56 (m, 2 H), 1.92 (s, 3 H), 3.16 (t, *J* = 7.45 Hz, 2 H), 4.57 (s, 2 H), 7.19–7.28 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.56, 13.04, 23.91, 33.28, 41.77, 127.73, 128.38, 128.61, 135.92, 136.42, 138.29, 167.90, 169.70.

MS (ESI): *m*/*z* = 275 $(M)^+$.

3-Methyl-4-(propylthio)furan-2,5-dione (2)

To a stirred solution of **9** (0.1 g, 0.36 mmol) in absolute EtOH (5 mL) was added dropwise aq 5 M KOH (10 mL). The resulting mixture was then refluxed for 2 h with stirring. The mixture was concentrated and the residue was cooled to 0 °C and acidified with aq 2 M HCl and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with H_2O (2 × 5 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by column chromatography using 5% EtOAc in hexane afforded **2** as a dark yellow liquid; yield: 0.040 g (60%).

IR ($CHCl_3$): 3342, 2986, 2306, 1825, 1766, 1712, 1600, 1421, 1265, 1021, 896, 739, 705, 665 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.33 Hz, 3 H), 1.68 (m, 2 H), 2.05 (s, 3 H), 3.31 (t, *J* = 7.46 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.99, 12.86, 23.76, 33.04, 136.00, 142.43, 161.95, 163.84.

MS (ESI): *m*/*z* = 187 (M + 1).

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (1)

To a stirred solution of compound **2** (0.05 g, 0.268 mmol) in anhyd MeOH (1 mL) was added $NaBH_4$ (0.005 g, 0.0134 mmol) at 0 °C and stirred for 10 min. The reaction was monitored by TLC (30% EtOAc in hexane). After the reaction was complete, ice-water (5 mL) was added and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using 10% EtOAc in hexane to afford racemic **1** (0.032 g, 64%) as a white crystalline solid and racemic **10** (0.014 g, 27.5%) as a pale yellow liquid.

IR ($CHCl_3$): 3432, 2984, 1735, 1446, 1374, 1246, 939, 757 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.3 Hz, 3 H), 1.71 (m, 2 H), 1.84 (s, 3 H), 3.08 (m, 2 H), 4.27 (s, 1 H), 6.06 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.12, 13.16, 23.39, 32.32, 96.49, 122.55, 157.75, 170.94.

HRMS (ESI): *m*/*z* (M^+) calcd for $C_8H_{12}O_3S$: 188.05072; found: 188.05071.

Crystal Structure Determination

The X-ray diffraction data of **1** were carried out on a Bruker SMART APEX single crystal CCD diffractometer using graphite monochromated Mo Kα radiation with fine focus tube with 50 kV and 30mA. Data reduction was carried out with SAINTPLUS, and the structure was solved and refined SHELX-97 (ShelxTL)[13] was used for structure solution and full matrix least squares refinement on F^2.

Crystal Data for 1[14]

$C_8H_{12}O_3S$, MW = 188.24, orthorhombic, space group: Pbca, *a* = 11.1790(8) Å, *b* = 8.0910(6) Å, *c* = 21.1200(15) Å, *α* = 90°, *β* = 90°, *γ* = 90°, *V* = 1910.3(2) $Å^3$, Z = 8, D_{calcd} = 1.309 mg/m^3, *μ* = 0.305 mm^{-1}, *λ* = 0.71073 Å, crystal size 0.38 × 0.21 × 0.03 mm, *T* = 273(2) K, full matrix least squares, R_1 = 0.0674, wR_2 = 0.1570, for observed 1670 reflections [$I > 2s(I)$].

(±)-5-Hydroxy-4-methyl-3-propylsulfanyl-5*H*-furan-2-one (10)

IR ($CHCl_3$): 3393, 2965, 2932, 2873, 1746, 1707, 1635, 1456, 1381, 1339, 1294, 1128, 1087, 1009, 946, 755, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.34 Hz, 3 H), 1.59 (m, 2 H), 2.11 (s, 3 H), 2.97 (t, *J* = 7.45 Hz, 2 H), 5.93 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.73, 13.01, 23.51, 33.32, 98.07, 125.22, 160.71, 169.19.

MS (ESI): *m*/*z* = 188 $(M)^+$.

1-Benzyl-3-methyl-4-bromo-1*H*-pyrrole-2,5-dione (5)

To a stirred solution of citraconic anhydride (**6**; 15.0 mL, 167 mmol) in glacial AcOH (100 mL) was added benzylamine (18.0 mL, 167 mmol) dropwise in an ice-cooled bath. The mixture was then heated to reflux for 3 h. After cooling, NaOAc (13.7 g, 167 mmol) and Br_2 (12.9 mL, 251 mmol) were added at r.t. Then, the mixture was poured into ice-water (100 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed to give the crude product, which was purified by recrystallization from EtOAc to afford compound **5**; yield: 40.2 g (86%).

IR ($CHCl_3$): 3470, 3059, 2938, 2848, 1955, 1907, 1776, 1651, 1600, 1494, 1402, 1288, 925 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 4.68 (s, 2 H), 7.26–7.35 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.55, 42.18, 124.86, 128.45, 128.59, 128.88, 135.76, 142.18, 165.04, 168.88.

MS (ESI): *m*/*z* = 280 $(M)^+$.

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(14) CCDC 813937 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033, E-mail: deposit@ccdc.cam.ac.uk].