Regioselective Reduction of 3-Methoxymaleimides: an Efficient Method for the Synthesis of Methyl 5-Hydroxytetramates

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SUPPORTING INFORMATION

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General Experimental

Solvents and reagents were dried and purified according to literature methods, prior to use, and reactions were conducted under an inert atmosphere of dry nitrogen, unless otherwise stated. Thin layer chromatography was performed using 0.2 mm thick pre-coated aluminium-backed silica gel plates. Compounds were visualised by ultraviolet absorption or by staining with vanillin in ethanolic sulfuric acid or potassium permanganate. Flash chromatography was performed using 40–63 μ m silica gel with the specified solvents. Preparative HPLC was performed using a 10 μ m, 21.5 $\times$ 25 cm column with UV detection at 254 nm.

Only strong absorptions are reported for IR spectra and absorption maxima are expressed in wavenumbers (cm^{-1}). Compounds were prepared as thin films between sodium chloride plates or as KBr discs. NMR spectra were recorded at 300 K in deuteriochloroform, unless otherwise stated. Data are expressed in parts per million downfield shift from tetramethylsilane and are reported as chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad and app = apparent), coupling constant (*J* Hz) and relative integral. Low resolution mass spectra were recorded using positive electrospray ionization (ESI+). High resolution mass spectra

were recorded using electron impact (EI+) at 70 eV in magnetic scan with PFK as standard or ESI+. Melting points were determined in open glass capillaries and are uncorrected.

Experimental Procedures and Characterization Data

3-Methoxy-1-methyl-1*H*-pyrrole-2,5-dione (5b). Method A in acetone, using methyl iodide, provided **5b** as a colourless solid (87%): mp 126-127 °C, lit.¹ mp 129-130 °C; IR (thin film) 3113, 1705, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.41 (s, 1H), 3.93 (s, 3H), 3.00 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.2 (C), 165.7 (C), 161.1 (C), 96.2 (CH), 58.9 (CH₃), 23.5 (CH₃). Spectroscopic data matched that previously reported.¹

1-Ethyl-3-methoxy-1*H*-pyrrole-2,5-dione (5c). Method A in acetone, using ethyl iodide, provided **5c** as a colourless solid (92%): mp 69-70 °C; IR (thin film) 3109, 1709, 1636 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.40 (s, 1H), 3.93 (s, 3H), 3.56 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.0 (C), 165.4 (C), 160.9 (C), 96.1 (CH), 58.8 (CH₃), 32.5 (CH₂), 13.9 (CH₃); MS (ESI) *m/z* 156 [M + H]⁺; HRMS (ESI) calcd for C₇H₁₀NO₃ [M + H]⁺ 156.0655, found 156.0654.

3-Methoxy-1-(4-methoxybenzyl)-1*H*-pyrrole-2,5-dione (5f). Method A in acetone, using PMBCl, provided **5f** as a colourless solid (91%): mp 104-105 °C; IR (thin film) 3101, 3013, 1713, 1636 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.39 (s, 1H), 4.59 (s, 2H), 3.90 (s, 3H), 3.77 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 169.8 (C), 165.3 (C), 161.0 (C), 159.2 (C), 129.9 (CH), 128.6 (C), 114.0 (CH), 96.3 (CH), 58.8 (CH₃), 55.2 (CH₃), 40.7 (CH₂); MS (ESI) *m/z* 270 [M + Na]⁺; HRMS (ESI) calcd for C₁₃H₁₃NO₄Na [M + Na]⁺ 270.0737, found 270.0736.

5-Hydroxy-4-methoxy-1*H*-pyrrol-2(5*H*)-one (6a). Purification by flash chromatography (MeOH/CH₂Cl₂ 10:90) afforded **6a** (87%) as a colourless solid: mp 175-178 °C, lit.² mp 163 °C; IR (KBr disc) 3223 (br), 3175 (br), 1645, 1626 cm⁻¹; ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.73 (br s, 1H), 6.18 (d, *J* = 8.5 Hz, 1H), 5.21 (dd, *J* = 8.5 Hz, *J* = 1.7 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.74 (s, 3H); ¹³C NMR (75.7 MHz, *d*₆-DMSO) δ 176.5 (C), 172.4 (C), 93.6 (CH), 77.8 (CH),

58.8 (CH₃); MS (EI) m/z 129 [M]⁺, 112 [M-OH]⁺, 97 (34), 69 (100); HRMS (EI) calcd for C₅H₇NO₃ [M]⁺ 129.0426, found 129.0427. Spectroscopic data matched that previously reported.²

5-Hydroxy-4-methoxy-1-methyl-1H-pyrrol-2(5H)-one (6b). Purification by flash chromatography (EtOAc/acetone 95:5) afforded **6b** as a colourless solid (87%): mp 130-131 °C, lit.³ mp 140-141 °C; IR (thin film) 3267, 3107, 1693, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.09 (br d, J = ~8 Hz, 1H), 4.95 (s, 1H), 4.30 (br d, J = ~9 Hz, 1H), 3.83 (s, 3H), 2.90 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 173.7 (C), 170.8 (C), 93.2 (CH), 82.4 (CH), 58.4 (CH₃), 25.6 (CH₃); MS (ESI) m/z 166 [M + Na]⁺; HRMS (ESI) calcd for C₆H₉NO₃Na [M + Na]⁺ 166.0475, found 166.0475.

1-Ethyl-5-hydroxy-4-methoxy-1H-pyrrol-2(5H)-one (6c). Purification by flash chromatography (EtOAc/acetone 95:5) afforded **6c** as a colourless solid (84%): mp 79-83 °C; IR (thin film) 3337, 1653, 1637 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 5.21 (d, J = 10.0 Hz, 1H), 4.98 (s, 1H), 3.83 (s, 3H), 3.59 (sextet, J = 7.0 Hz, 1H), 3.28 (sextet, J = 7.0 Hz, 1H), 2.64 (d, J = 10.1 Hz, 1H), 1.17 (t, J = 7.2 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 173.8 (C), 170.5 (C), 93.2 (CH), 80.3 (CH), 58.4 (CH₃), 33.5 (CH₂), 13.6 (CH₃); MS (ESI) m/z 180 [M + Na]⁺, 158 [M + H]⁺; HRMS (ESI) calcd for C₇H₁₁NO₃Na [M + Na]⁺ 180.0631, found 180.0629.

1-Allyl-5-hydroxy-4-methoxy-1H-pyrrol-2(5H)-one (6d). Purification by flash chromatography (EtOAc/acetone 95:5) afforded **6d** as a colourless solid (85%): mp 70-71 °C; IR (thin film) 3275, 1666, 1636 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.77 (dddd, J = 17.2, 11.6, 7.0, 4.6 Hz, 1H), 5.21 (br s, 1H), 5.16 (dq, J = ~18, 1 Hz, 1H), 5.15 (dq, J = ~10, 1 Hz, 1H), 5.09 (br s, 1H), 4.96 (s, 1H), 4.23 (ddt, J = 15.8, 4.6, 1.6 Hz, 1H), 3.82 (s, 3H), 3.70 (ddt, J = 15.8, 7.0, 1.0 Hz, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 174.1 (C), 170.6 (C), 133.0 (CH), 117.3 (CH₂), 92.9 (CH), 80.1 (CH), 58.4 (CH₃), 41.0 (CH₂); MS (ESI) m/z 192 [M + Na]⁺, 170 [M + H]⁺, 152 [M - OH]⁺; HRMS (ESI) calcd for C₈H₁₁NO₃Na [M + Na]⁺ 192.0631, found 192.0637.

5-Hydroxy-4-methoxy-1-(4-methoxybenzyl)-1H-pyrrol-2(5H)-one (6f). Purification by flash chromatography (EtOAc/CH₂Cl₂ 50:50) afforded **6f** as a colourless solid (76%): mp 167-169 °C; IR (thin film) 3115, 1643 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.21 (d, J = 8.6 Hz, 2H), 6.84 (d, J

= 8.6 Hz, 2H), 5.04 (d, J = 8.8 Hz, 1H), 5.00 (s, 1H), 4.88 (d, J = 14.9 Hz, 1H), 4.12 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.13 (br s, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.6 (C), 170.0 (C), 159.0 (C), 129.6 (CH), 129.4 (C), 114.1 (CH), 93.4 (CH), 80.0 (CH), 58.4 (CH_3), 55.3 (CH_3), 41.9 (CH_2); MS (ESI) m/z 272 $[\text{M} + \text{Na}]^+$, 250 $[\text{M} + \text{H}]^+$, 121 $[\text{C}_8\text{H}_9\text{O}]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 272.0893, found 272.0883.

5-Hydroxy-4-methoxy-1-phenyl-1H-pyrrol-2(5H)-one (6g). Purification by flash chromatography (hexane/EtOAc 40:60) afforded **6g** as a colourless solid (70%): mp 138-139 °C; IR (thin film) 3271, 1676, 1641 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.67 (dd, J = 8.7, 1.0 Hz, 2H), 7.33 (app t, J = 7.5 Hz, 2H), 7.11 (app t, J = 7.5 Hz, 1H), 5.67 (br s, 1H), 4.89 (s, 1H), 4.63 (br s, 1H), 3.70 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.3 (C), 170.1 (C), 137.3 (C), 128.9 (CH), 124.3 (CH), 120.5 (CH), 93.9 (CH), 81.7 (CH), 58.5 (CH_3); MS (ESI) m/z 228 $[\text{M} + \text{Na}]^+$, 206 $[\text{M} + \text{H}]^+$, 188 $[\text{M} - \text{OH}]^+$, 174 $[\text{M} - \text{OCH}_3]^+$; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 206.0812, found 206.0811.

4,5-Dimethoxy-1H-pyrrol-2(5H)-one (7). To a cooled (0 °C) solution of **6a** (500 mg, 3.87 mmol) in MeOH (20 mL) was added anhydrous HCl in MeOH (1.0 M, 775 μL , 0.775 mmol, 0.20 equiv.), generated by adding TMSCl (256 μL , 2.00 mmol) to MeOH (2.0 mL). The resulting solution was allowed to stir whilst warming to rt. After 3.5 h, the solvent was removed *in vacuo* to give **7** (554 mg, 100%) as a light yellow solid. A small portion of **7** was purified by flash chromatography (EtOAc/ CH_2Cl_2 /MeOH 50:50:1 to 50:50:5) to afford an analytically pure sample of **7** as a white solid: mp 105-106 °C, lit.² mp 107 °C; IR (KBr disc) 3246 (br), 3092, 1701, 1666, 1632 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.11 (br s, 1H), 5.33 (d, J = 1.9 Hz, 1H), 5.08 (d, J = 1.3 Hz, 1H), 3.85 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 173.6 (C), 173.4 (C), 95.0 (CH), 83.9 (CH), 58.7 (CH_3), 52.3 (CH_3); MS (+ESI) m/z 144 $[\text{M} + \text{H}]^+$, 112 $[\text{M} - \text{OCH}_3]^+$; HRMS (+ESI) calcd for $\text{C}_6\text{H}_{10}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 144.0655, found 144.0656. Spectroscopic data matched that previously reported.²

Reduction of 5e with DIBAL-H to give 6e and S1. To a 0 °C solution of 1-benzyl-3-methoxy-1*H*-pyrrole-2,5-dione (**5e**) (95.5 mg, 0.440 mmol, 1.0 equiv.) in THF (2.2 mL) was added DIBAL-H (1.0 M in heptane, 0.46 mL, 0.46 mmol, 0.462 mmol, 1.05 equiv.) dropwise. The resultant brown solution was stirred at 0 °C for 4 h after which time t.l.c analysis revealed incomplete consumption of the starting material. The reaction was quenched with half-saturated aq. NaHCO₃ solution then diluted with H₂O and extracted with EtOAc (3 ×). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to give a crude brown oil. The products **6e** and **S1** were separated from the starting material by flash chromatography (EtOAc/acetone 90:10). Separation of a small portion of **S1** (*R*_t ~12.5 min) and **6e** (*R*_t ~14.0 min) was achieved by preparative HPLC (EtOAc/*i*-PrOH 97.5:2.5, 13.5 mLmin⁻¹), providing **S1** as a colourless solid: ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.25 (m, 5H), 5.57 (d, *J* = 2.1 Hz, 1H), 5.17 (d, *J* = 1.9 Hz, 1H), 4.94 (d, *J* = 14.8 Hz, 1H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 3H), OH signal not visible; ¹³C NMR (75.5 MHz, CDCl₃) δ 164.2 (C), 153.0 (C), 136.8 (C), 128.7 (CH), 128.4 (CH), 127.6 (CH), 106.8 (CH), 78.9 (CH), 57.4 (CH₃), 42.9 (CH₂); MS (ESI) *m/z* 242 [M + Na]⁺, 220 [M + H]⁺, 202 [M - OH]⁺; HRMS (ESI) calcd for C₁₂H₁₃NO₃Na [M + Na]⁺ 242.0788, found 242.0787.

Single crystal x-ray diffraction experimental for compound 6e

A colourless block-like crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from a commercial cryosystem. A CCD detector equipped diffractometer employing graphite monochromated MoK α radiation generated from a rotating anode was used for the data collection. Cell constants were obtained from a least squares refinement against 8777 reflections located between 6 and 56° 2 θ . Data were collected at 150(2) Kelvin with ω and ϕ scans to 61° 2 θ . The data integration and reduction were undertaken with SAINT and XPREP,⁴ and subsequent computations were carried out with the WinGX⁵ XTAL⁶ graphical user interfaces. Absorption was not sufficient to require a correction.

The structure was solved in the space group *Pna*2₁(#33) by direct methods with SIR97,⁷ and extended and refined with SHELXL-97.⁸ The asymmetric unit contains two crystallographically independent molecules. The non-hydrogen atoms were modelled with anisotropic displacement parameters, and a riding atom model with group displacement parameters was used for the hydrogen atoms. Anomalous dispersion effects were not sufficient to determine the absolute structure and accordingly Friedel pairs were merged. An ORTEP⁹ depiction of the molecule with 50% displacement ellipsoids is provided in Figure S1.

Figure S1: ORTEP Depiction of **6e**, with 50% displacement ellipsoids.

Formula $C_{12}H_{13}NO_3$, M 219.23, Orthorhombic, space group $Pna2_1$ (#33), a 8.6992(3), b 6.3159(2), c 39.6797(15) Å, V 2180.13(13) Å³, D_c 1.336 g cm⁻³, Z 8, crystal size 0.472 by 0.130 by 0.117 mm, colour colourless, habit block, temperature 150(2) Kelvin, $\lambda(\text{MoK}\alpha)$ 0.71073 Å, $\mu(\text{MoK}\alpha)$ 0.097 mm⁻¹, $2\theta_{\text{max}}$ 60.92, hkl range -12 12, -8 8, -52 50, N 30509, N_{ind} 5902(R_{merge} 0.0946), N_{obs} 3707($I > 2\sigma(I)$), N_{var} 293, residuals* $R1(F)$ 0.0365, $wR2(F^2)$ 0.0689, GoF(all) 1.184, $\Delta\rho_{\text{min,max}}$ -0.272, 0.168 e⁻ Å⁻³.

* $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\sum w(F_o^2 - F_c^2)^2 / \sum w(F_c^2)^2)^{1/2}$ all reflections
 $w = 1 / [\sigma^2(F_o^2) + (0.02P)^2]$ where $P = (F_o^2 + 2F_c^2) / 3$

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5e

75.5 MHz, CDCl₃

300 MHz, CDCl₃

6e

6f

6g