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Synthesis of three *tricholoma*-derived indoles via an *ortho*-quinone methide

Joshua A. Homer and Jonathan Sperry*

School of Chemical Sciences, University of Auckland, 23 Symonds St., Auckland, New Zealand
Email: j.sperry@auckland.ac.nz

Dedicated to Professor Gordon Gribble in celebration of his many outstanding contributions to organic synthesis

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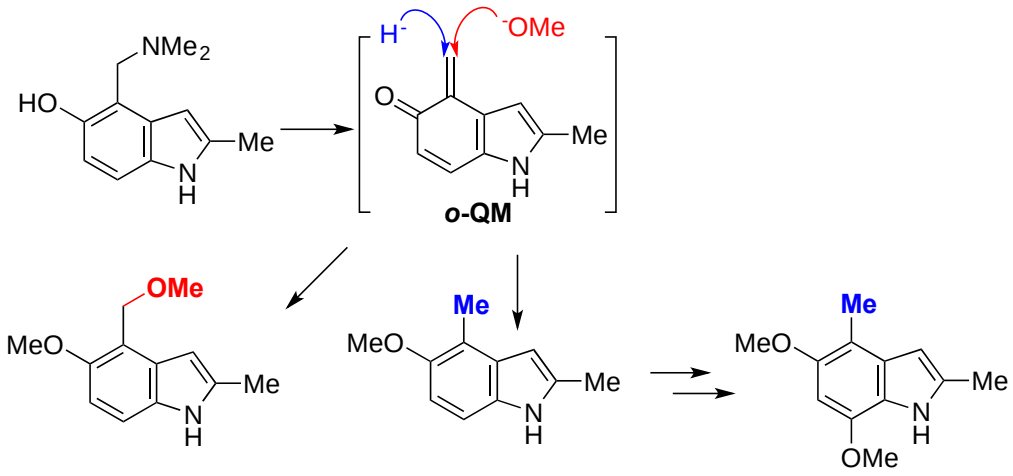
Abstract

Three *Tricholoma*-derived indole natural products have been synthesised via an *ortho*-quinone methide (*o*-QM), itself generated from a phenolic Mannich base.



Tricholoma-derived indoles

Keywords: Natural product, *ortho*-quinone methide, indole, C-H borylation

Introduction

Tricholoma is a large genus of white-spored, gilled mushrooms notable for their distinctive pungency and bitter taste.[1,2] Several indole alkaloids harbouring a methyl group at the C2-position have been isolated from species of *Tricholoma*, a selection of which (**1**-**4**) can be seen in Figure 1A.[3-6] Unlike most indole alkaloids, the *Tricholoma* indoles are not biosynthetically derived from tryptophan, but instead assembled via a biosynthetic pathway that involves lascivol (**5**), a bitter component isolated from *Tricholoma lascivum* that likely serves as a predation deterrent.[7] Tellingly, lascivol degrades into the natural product 5-methoxy-2,4-dimethylindole (**1**) and dimethylglutamate upon treatment with acid in methanol (Figure 1B).[7] As part of an ongoing synthetic study towards the bisindole natural product sciodole (**4**), we required a supply of the 'lower half' of this alkaloid, specifically 5-methoxy-2,4-dimethylindole (**1**). Although 5-methoxy-2,4-dimethylindole (**1**) has been synthesized previously,[8] this route starts with a trifluoromethylbenzoquinone that is not readily attainable. Here, we report a synthesis of **1** via an *ortho*-quinone methide (*o*-QM) that has enabled access to grams of the natural product. Furthermore, the *Tricholoma* indoles **2** and **3** were also accessed via the same *o*-QM.

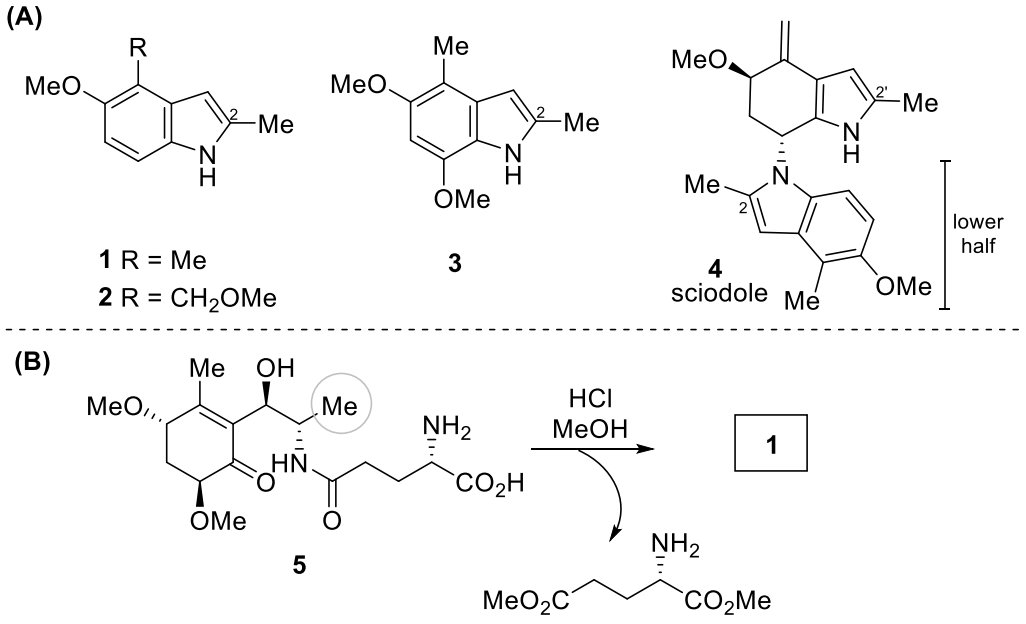
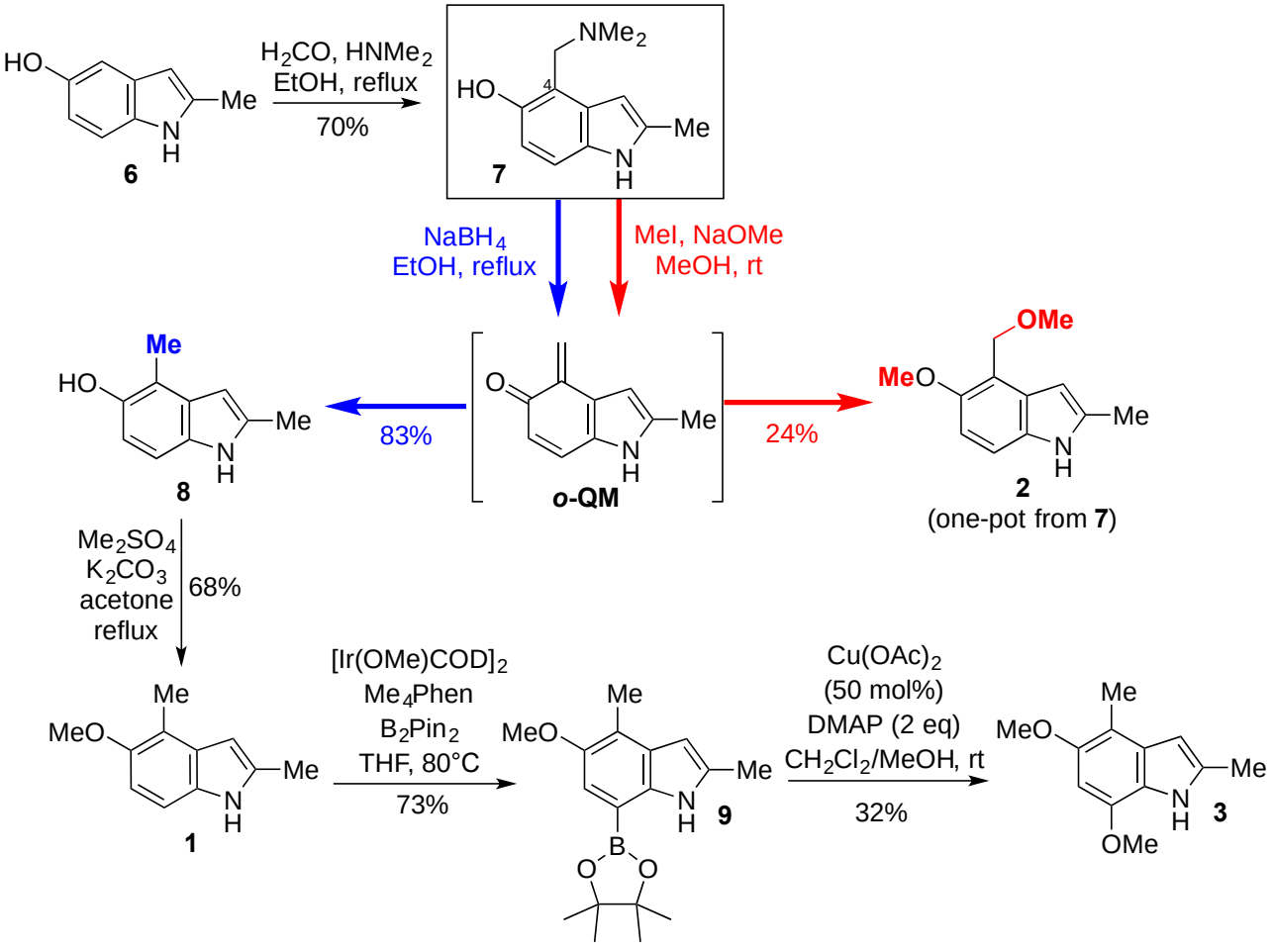


Figure 1. (**A**) *Tricholoma*-derived 2-methylindole derivatives (**1**-**4**); (**B**) lascivol (**5**) and its conversion into 5-methoxy-2,4-dimethylindole (**1**).

Result and Discussion

The known[9] 5-hydroxy-2-methylindole **6** was subjected to a regioselective aminomethylation to give the phenolic Mannich base **7**,[10] which would serve as an *o*-QM precursor.[11] Upon reaction of the *o*-QM with an appropriate nucleophile, functionalization of the indole C4-site would occur and thus provide access to the targets **1**-**3** (Scheme 1). Upon treating Mannich base **7** with sodium borohydride in ethanol at reflux, the desired product **8** was isolated. In this instance, thermal generation of the *o*-QM is followed by reduction/aromatization[12] to give the indole **8** bearing a methyl group at C4. Selective O-methylation of **8** gave the natural product 5-methoxy-2,4-dimethylindole **1**, a key intermediate in our ongoing efforts towards the

synthesis of sciodole (**4**). Our next target was the natural product **2**, which required the introduction of a methoxymethyl group at C4. In this instance, the dimethylamino group of **7** was quaternized with iodomethane to allow a base-mediated *o*-QM formation at ambient temperature;[13,14] trapping of the *o*-QM with methoxide and concomitant phenol alkylation (MeI) occurred to give the natural product **2** in a single-pot from **7**. Finally, natural product **3** was targeted, which required introduction of a methoxy group at C7 in **1**. This desired transformation aligns perfectly with the iridium-catalyzed C-H borylation reaction,[15] the regiochemical outcome of which is reliably dictated by the directing ability of the indole N-H. Subjecting **1** to an iridium-catalyzed C-H borylation using the 3,4,7,8-tetramethylphenanthroline as ligand (Me_4Phen)[16,17] gave the 7-borylindole **9** in good yield. A DMAP-assisted[18] Chan-Evans-Lam coupling of **9** with methanol gave the natural product 5,7-dimethoxy-2,4-dimethylindole (**3**). The modest yield for this step can be attributed to the instability of the electron-rich indole **3**.



Scheme 1. Synthesis of *Tricholoma*-derived indoles **1**-**3** via an *o*-QM.

Conclusions

The synthesis of three *Tricholoma*-derived indole natural products has been achieved. The Mannich base **7** served as a precursor to an *o*-QM that upon reaction with an appropriate nucleophile, led to efficient installation of a methyl group and a methoxymethyl group at the indole C4-position. The utility of the iridium

catalyzed C-H borylation reaction for selective functionalization of the indole C7-site has also been demonstrated.

Experimental Section

General. Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. All reactions were routinely carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using silica plates and compounds were visualized at 254 and/or 360 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded using either a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual chloroform (δ 7.26 ppm) and DMSO (δ 2.50 ppm) peaks. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm) and DMSO (δ 39.5 ppm) peaks. ^{13}C NMR values are reported as chemical shift, δ, multiplicity and assignment. ^{1}H NMR shift values are reported as chemical shift, δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), and assignment. Assignments are made with the aid of NOESY and HMBC experiments. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a Bruker micrOTOF-QII mass spectrometer.

5-Hydroxy-4-(dimethylamino)methyl-2-methylindole (7). Prepared according to the procedure reported by Monti and Johnson,[10] but with changes to purification. The product **7** was not completely characterised in the literature.[10] A solution of formaldehyde (37% aqueous, 1.53 mL) and dimethylamine (40% aqueous, 2.84 mL) in EtOH (30 mL) was prepared and warmed to 80 °C for 30 min. This solution was then cooled to rt before 5-hydroxy-2-methylindole (**6**)[9] (3.30 g, 22.42 mmol) in EtOH (70 mL) was added. The mixture was stirred under reflux for 1 h, during which time a colour change from yellow to dark red was observed. The reaction mixture was concentrated *in vacuo* and the resulting crude material was purified by flash column chromatography on silica gel eluting with CH_2Cl_2MeOH/NH_4OH (94:5:1) to afford the *title compound* (3.187 g, 15.60 mmol, 70%) as a light brown solid, mp 128-132 °C (lit.[10] 130-131 °C); ν_{max} (neat)/cm^{-1} 3392, 2981, 2949, 2826, 2780, 1706, 1621, 1596, 1555, 1511, 1439, 1427, 1361, 1319, 1270, 1202, 1055, 1039, 1000, 991, 837, 794, 774, 748, 737, 674; δ_H (400 MHz, $CDCl_3$) 7.71 (1 H, s, NH), 7.07 (1 H, d, *J* 9.2, ArH), 6.69 (1 H, d, *J* 8.8, ArH), 6.08 (1 H, m, ArH), 3.83 (2 H, s, $C\underline{H}_2NMe_2$), 2.42 (3 H, s, Me), 2.36 (6 H, s, NMe_2); δ_C (100 MHz, $CDCl_3$) 151.4 (C), 135.7 (C), 130.4 (C), 128.4 (C), 111.2 (CH), 110.02 (C), 109.97 (CH), 97.4 (CH), 59.4 (CH_2), 44.8 (NMe_2), 13.8 (Me); HRMS (ESI) found: 205.1333 $[C_{12}H_{16}N_2O + H]^+$ requires 205.1335.

5-Hydroxy-2,4-dimethylindole (8). To a stirred solution of **7** (2.886 g, 14.07 mmol) in EtOH (150 mL) cooled to 0 °C, was slowly added $NaBH_4$ (2.660 g, 70.35 mmol). The resulting slurry was stirred under reflux for 6 h, after which time the solution was cooled back to 0 °C and an additional portion of $NaBH_4$ (1.064 g, 28.14 mmol) was added. The reaction mixture was stirred under reflux for a further 1 h before being cooled again to 0 °C and quenched by the slow addition of H_2O (100 mL). The resulting slurry was allowed to gradually warm to rt. The

aqueous phase was extracted with EtOAc (5 × 75 mL). The organic extracts were combined, washed with brine (100 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified via flash column chromatography on silica gel eluting with EtOAc/petroleum ether (2:3) to afford the *title compound* (1.875 g, 11.70 mmol, 83%) as an off-white solid, mp 65-67 °C; ν_{max} (neat)/cm^{-1} 3503, 3380, 2921, 1590, 1498, 1425, 1386, 1360, 1330, 1302, 1279, 1206, 1161, 1129, 1112, 1060, 1015, 897, 790, 755, 739; δ_H (400 MHz, $CDCl_3$) 7.72 (1 H, s, NH), 7.00 (1 H, d, *J* 8.5, ArH), 6.66 (1 H, d, *J* 8.5, ArH), 6.16 (1 H, s, ArH), 4.31 (1 H, s, OH), 2.43 (3 H, d, *J* 0.8, Me), 2.38 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 146.8 (C), 135.7 (C), 131.1 (C), 130.3 (C), 112.7 (C), 110.7 (CH), 108.1 (CH), 99.0 (CH), 14.0 (Me), 11.9 (Me); HRMS (ESI) found: 184.0735 [$C_{10}H_{11}NO$ + Na]$^+$ requires 184.0733.

5-Methoxy-2,4-dimethylindole (1). To a stirred solution of **8** (1.00 g, 6.20 mmol) and K_2CO_3 (2.143 g, 15.51 mmol) in Me_2CO (60 mL) was added dimethyl sulfate (0.880 mL, 9.30 mmol). The mixture was stirred under reflux for 36 h after which the reaction was quenched by the addition of aq NaOH (1 M, 10 mL). The resulting aqueous phase was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified via flash column chromatography on silica gel eluting with EtOAc/petroleum ether (1:4) to afford the *title compound* (742 mg, 4.24 mmol, 68%) as a colourless solid, mp 56-59 °C (lit.[8] 50-52 °C); ν_{max} (neat)/cm^{-1} 3394, 2920, 1593, 1497, 1424, 1324, 1260, 1228, 1168, 1097, 1007, 774, 736, 666; δ_H (400 MHz, $CDCl_3$) 7.71 (1 H, s, NH), 7.07 (1 H, d, *J* 8.7, ArH), 6.80 (1 H, d, *J* 8.7, ArH), 6.18 (1 H, m, ArH), 3.84 (3 H, s, OMe), 2.43 (3 H, d, *J* , Me), 2.39 (3 H, s, Me); δ_C (75 MHz, $CDCl_3$) 151.4 (C), 136.0 (C), 131.7 (C), 130.5 (C), 116.8 (C), 108.5 (CH), 107.7 (CH), 99.2 (CH), 58.0 (OMe), 14.1 (Me), 12.2 (Me); HRMS (ESI) found: 176.1067 [$C_{11}H_{13}NO$ + H]$^+$ requires 176.1070; spectroscopic data consistent with isolation report.[3,7]

5-Methoxy-4-methoxymethyl-2-methylindole (2). Sodium metal (101 mg, 4.41 mmol) was added portionwise to MeOH (10 mL) at 0 °C. The resulting solution was allowed to stir for 15 min until the consumption of the sodium was complete. Mannich base **7** (300 mg, 1.47 mmol) was then slowly added, followed by the dropwise addition of MeI (0.275 mL, 4.41 mmol). The resulting solution was allowed to warm to rt and a nitrogen stream was gently bubbled through the solution for 1 h. After this time, an additional portion of MeI (0.460 mL, 7.35 mmol) was added and the resulting reaction was sealed and stirred at rt for 12 h. The mixture was concentrated *in vacuo* and the crude material purified by flash column chromatography on silica gel eluting with EtOAc/petroleum ether (2:3) to afford the *title compound* (73 mg, 0.36 mmol, 24%) as a light brown solid, mp 85-88 °C; ν_{max} (neat)/cm^{-1} 3270, 2940, 1592, 1497, 1449, 1429, 1362, 1325, 1279, 1253, 1225, 1171, 1152, 1097, 1065, 1049, 894, 765, 740; δ_H (300 MHz, $CDCl_3$) 7.94 (1 H, br s, NH), 7.14 (1 H, d, *J* 8.7, ArH), 6.81 (1 H, d, *J* 8.7, ArH), 6.32 (1 H, m, ArH), 4.82 (2 H, d, *J* 1.5, CH_2), 3.87 (3 H, s, OMe), 3.43 (3 H, s, OMe), 2.38 (3 H, s, Me); δ_C (75 MHz, $CDCl_3$) 152.1 (C), 136.9 (C), 131.8 (C), 130.5 (C), 115.7 (C), 110.5 (CH), 107.6 (CH), 99.0 (CH), 66.9 (CH_2), 58.0 (OMe), 57.8 (OMe), 13.8 (Me); HRMS (ESI) found: 228.0997 [$C_{12}H_{15}NO_2$ + Na]$^+$ requires 228.0995.
The natural product **2** was only detected by mass spectrometry in the isolation report.[4]

5-Methoxy-2,4-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (9). [Ir(OMe)COD]$_2$ (68 mg, 0.10 mmol, 6 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (47 mg, 0.20 mmol, 12 mol%) and bis(pinacolato)diboron (652 mg, 2.57 mmol) in THF (1.5 mL) was stirred under a heavy stream of nitrogen for approximately 5 min at rt, during which time the solution became deep green in colour. A solution of **1** (300 mg, 1.71 mmol) in THF (1.5 mL) was subsequently added and the resulting mixture sealed under nitrogen and stirred at 80 °C for 24 h. The mixture was then diluted with EtOAc (10 mL) and concentrated *in vacuo.* The resulting crude material was purified via flash column chromatography on silica gel eluting with EtOAc/petroleum ether (1:9) to afford the *title compound* (376 mg, 1.25 mmol, 73%) as a colourless solid, mp 124-127 °C; ν_{max} (neat)/cm^{-1} 3445, 2976, 2928, 1607, 1561, 1503, 1445, 1388, 1370, 1292, 1211, 1167, 1137,

1108, 971, 846, 792, 757, 684; δ_H (300 MHz, $CDCl_3$) 8.69 (1 H, s, NH), 7.18 (1 H, s, ArH), 6.15 (1 H, m, ArH), 3.88 (3 H, s, OMe), 2.47 (3 H, s, Me), 2.40 (3 H, s, Me), 1.39 (12 H, s, BPin); δ_C (75 MHz, $CDCl_3$) 151.1 (C), 137.2 (C), 135.8 (C), 129.6 (C), 121.2 (C), 113.8 (CH), 98.3 (CH), 83.8 (2 × C, BPin), 57.7 (OMe), 25.1 (4 × Me, BPin), 14.1 (Me), 12.6 (Me), 1 × C not observed; HRMS (ESI) found: 324.1732 $[C_{17}H_{24}BNO_3 + Na]^+$ requires 324.1744.

5,7-Dimethoxy-2,4-dimethylindole (3). To a solution of 7-borylindole **9** (10 mg, 0.033 mmol) in a mixture of CH_2Cl_2 (0.75 mL) and MeOH (0.25 mL) was added $Cu(OAc)_2{\cdot}H_2O$ (3.3 mg, 0.016 mmol), 4-dimethylaminopyridine (8.0 mg, 0.066 mmol) and molecular sieves (100 mg). The reaction mixture was allowed to stir at rt under an atmosphere of air for 1 h. The mixture was filtered through a plug of Celite and concentrated *in vacuo*. The resulting crude material was purified via flash column chromatography on silica gel eluting with EtOAc/petroleum ether (1:9) to afford the *title compound* (2.2 mg, 0.011 mmol, 32% yield) as an off white solid; mp 172-177 °C (lit.[5] 178-180 °C, dec.); ν_{max} (neat)/cm^{-1} 3360, 2926, 2851, 1598, 1514, 1451, 1398, 1319, 1200, 1125, 1018; δ_H (300 MHz, $CDCl_3$) 7.93 (1 H, br s, NH), 6.38 (1 H, s, ArH), 6.16 (1 H, m, ArH), 3.93 (3 H, s, OMe), 3.84 (3 H, s, OMe), 2.43 (3 H, d, *J* 0.8, Me), 2.32 (3 H, s, Me); δ_C (75 MHz, $CDCl_3$) 151.3 (C), 143.6 (C), 135.1 (C), 130.7 (C), 121.8 (C), 109.3 (C), 99.5 (CH), 92.4 (CH), 58.8 (OMe), 55.7 (OMe), 13.9 (Me), 11.6 (Me); HRMS (ESI) found: 228.0997 $[C_{12}H_{15}NO_2 + Na]^+$ requires 228.0995; Spectroscopic data consistent with isolation report.[5]

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Supplementary Material

^{1}H NMR and ^{13}C NMR spectra of **1**-**3** and **7**-**9**.

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