

Total Synthesis of Nigellicine and Nigeglanine Hydrobromide

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Supporting Information

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General Information

¹H- and ¹³C NMR spectra were recorded on either a Varian Gemini 400 MHz spectrometer or a Varian Unity INOVA 500 MHz spectrometer and chemical shifts are reported relative to tetramethylsilane as the internal standard. NOe difference, NOESY1D, and gHMBC spectra were recorded on a Varian Unity INOVA 500 MHz spectrometer. High-resolution mass spectra were obtained from the University of Illinois, Urbana-Champaign spectrometry facility. Infrared spectra were recorded using a Nicolet Avatar 360 FT-IR. Uv-Vis spectra were recorded on an Agilent 8453 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed at Atlantic Microlab, Inc (Norcross, GA).

Tetrahydrofuran (THF) and dichloromethane (DCM) were dried by passage through a column of activated alumina under a positive pressure of nitrogen.¹ Triethylamine (NEt₃) was purchased from Aldrich and distilled from calcium hydride prior to use. Methanol (MeOH) was purchased anhydrous from Acros and used as supplied. Acetone, dibromobutane and diethyl oxalate were dried over 4Å molecular sieves for a minimum of 1 day and stored at ambient temperature under an atmosphere of argon. Diphenylphosphinic chloride was purchased from Strem and used without further purification. *O*-(Diphenylphosphinyl)hydroxylamine was prepared² in advance and stored under argon at -26 °C. All other reagents were obtained from either Aldrich or Acros and used without further purification. Unless otherwise noted, all reactions were carried out in flame-dried glassware under an atmosphere of argon. The following abbreviations are used throughout the subsequent sections: EtOAc (ethyl acetate), Et₂O (diethyl ether), DME (1,2-dimethoxyethane).

Experimental Procedures

2-Chloro-5-methylanisole (8).³

2-Chloro-5-methylphenol (25.0 g, 175 mmol) was dissolved in a mixture of acetone (175 mL) and iodomethane (13.0 mL, 209 mmol). Anhydrous K₂CO₃ (30.0 g, 217 mmol) was added and the resulting suspension was heated at reflux for 3.5 h. After cooling to ambient temperature, the solvent was removed by rotary evaporation and the resulting mixture of product and unreacted K₂CO₃ was partitioned between water (100 mL) and EtOAc (130 mL). The organic layer was separated, washed with brine (2 x 100 mL), dried over MgSO₄ and evaporated to yield a pale yellow liquid (26.9 g, 98%). ¹H NMR (400 MHz, CDCl₃, δ): 2.33 (s, 3H), 3.88 (s, 3H), 6.71 (d, *J* = 8Hz, 1H), 6.74 (s, 1H), 7.22 (d, *J* = 8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 21.3 (1C), 55.8 (1C), 112.8 (1C), 118.9 (1C), 121.6 (1C), 129.4 (1C), 137.7 (1C), 154.3 (1C).

3-Methoxy-5-methylaniline (9).⁴

Anhydrous ammonia was passed into a pre-cooled (-78 °C) three-neck 250 mL flask equipped with a dry ice condenser. After collecting approximately 100 mL of liquid ammonia, a small chunk of sodium metal (approximately 0.10 g) was added (solution turned from clear to blue), followed by a catalytic amount of iron (III) nitrate nonahydrate (0.121 g, 0.300 mmol). Once no trace of blue color remained (solution now brown), additional chunks of sodium metal (approximately 0.10 g each) were added over 2 h until a total of 2.1 molar equivalents of sodium had been added (3.02 g, 131 mmol total), waiting after each addition for the blue color to disappear (10–15 min). After the last piece of sodium had been added, the reaction was allowed to warm to reflux (dry ice bath removed). After an additional 2 h, **8** (9.92 g, 63.4 mmol) was added neat in one portion via syringe and the reaction was allowed to reflux for an

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

² Boche, G; In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 4, 2240–2242.

³ 2-Chloro-5-methylanisole (**8**) was prepared by a modification of literature methods: a) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5397–5400.; b) Claudi, F.; Giorgioni, G.; Di Stefano, A.; Abbracchio, M. P.; Paoletti, A. M.; Balduini, W. *J. Med. Chem.* **1992**, *35*, 4408–4414.

⁴ 3-Methoxy-5-methylaniline (**9**) was prepared by a modification of literature methods: Saari, W. S. (Merck). U.S. Patent 3671636, 1972.; *Chem. Abstr.* **1972**, *77*, 88083.

additional 2 h. The dry ice condenser was then removed and the ammonia was allowed to evaporate under a rapid stream of argon. The resulting residue was diluted with Et₂O (150 mL) and saturated NH₄Cl (40 mL) was added and the layers were separated. The aqueous layer was then extracted with Et₂O (2 x 50 mL) and the Et₂O extracts were combined, washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over MgSO₄ and evaporated to yield a brown liquid (8.05 g). The crude product was purified by flash chromatography using silica gel (5 x 15.5 cm) with a hexanes:EtOAc solvent gradient [4:1 hexanes:EtOAc (250 mL); 3:1 hexanes:EtOAc (250 mL); 2:1 hexanes:EtOAc (750 mL)] to yield a pale yellow solid (5.08 g, 58%). Mp 44–46 °C (lit.^{5,6} 46–47 °C). ¹H NMR (400 MHz, CDCl₃, δ): 2.25 (s, 3H), 3.63 (bs, 2H), 3.76 (s, 3H), 6.08 (s, 1H), 6.14 (s, 1H), 6.18 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 21.7 (1C), 55.0 (1C), 98.1 (1C), 104.8 (1C), 108.6 (1C), 140.0 (1C), 147.3 (1C), 160.4 (1C).

***N*-(3-Methoxy-5-methylphenyl)-2,2-dimethylpropionamide (10).**

Aniline **9** (8.86 g, 64.6 mmol) was dissolved in a mixture of DCM (104 mL) and NEt₃ (9.0 mL, 65 mmol). The solution was cooled to 0 °C in an ice bath and trimethylacetyl chloride (8.8 mL, 71 mmol) was added dropwise over 5 min. The solution rapidly began to reflux on the walls of the flask. After the addition was complete, the ice bath was removed and the reaction was stirred for 30 min at ambient temperature. The solvent was then evaporated and the resulting white solid was dissolved in a 1:1 (v/v) mixture of Et₂O:H₂O (460 mL). The organic layer was washed with 0.25 M HCl (1 x 250 mL), saturated NaHCO₃ (1 x 250 mL), and brine (1 x 250 mL), dried over MgSO₄ and evaporated to yield a white solid (13.5 g, 94%). An analytical sample was obtained by crystallization from a minimum amount of hexanes yielding white needles. Mp 107–108.5 °C. ¹H NMR (400 MHz, CDCl₃, δ): 1.35 (s, 9H), 2.33 (s, 3H), 3.82 (s, 3H), 6.52 (s, 1H), 6.88 (s, 1H), 7.19 (t, *J* = 2 Hz, 1H), 7.33 (bs, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 21.7 (1C), 27.7 (3C), 39.7 (1C), 55.3 (1C), 102.3 (1C), 111.1 (1C), 112.6 (1C), 138.8 (1C), 139.6 (1C), 159.9 (1C), 176.3 (1C). I.R.: (KBr) (cm⁻¹): 3307 (s), 2961 (m), 2930 (w), 2871 (w), 1649 (vs), 1618 (vs), 1591 (m), 1544 (s), 1478 (m), 1455 (m). Anal. Calcd for C₁₃H₁₉NO₂: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.53; H, 8.58; N, 6.20. HR-ESI *m/z*: [M + H]⁺ calcd for C₁₃H₂₀NO₂, 222.1494; found, 222.1493.

Ethyl [2-(2,2-Dimethylpropanonylamino)-6-methoxy-4-methylphenyl]oxoacetate (12).

Amide **10** (2.22 g, 10.0 mmol), dried by gentle heating (with a heat gun) under vacuum (0.1 mm Hg) until the solid had just begun to melt and then cooling under argon, was dissolved in THF (85 mL). The resulting solution was then cooled to 0 °C and TMEDA (3.4 mL, 22 mmol) was added. After 30 min at 0 °C, *n*-butyllithium⁷ (8.8 mL, 2.48 M in hexanes, 22 mmol) was added dropwise over 3 min and the reaction was stirred for 2 h at 0 °C. After cooling the mixture to –78 °C, neat diethyl oxalate (1.7 mL, 11 mmol) was added over 2 min and the reaction was stirred for 1 h. The cold bath was removed and the solution was allowed to warm to ambient temperature. After an additional 1.5 h, the reaction was quenched by addition of saturated NH₄Cl (30 mL) followed by addition of Et₂O (250 mL). The layers were separated and the aqueous layer was extracted with additional Et₂O (50 mL). The organic portions were combined, dried over MgSO₄, and evaporated to yield a mixture of **10** and **12** as a yellow solid (3.7 g). The crude mixture was purified by flash chromatography using silica gel (7 mm x 20 mm) with 10% EtOAc in hexanes as eluent to yield **12** (1.54 g, 48%) as a yellow solid and recovered starting material (1.06, 48%). An analytical sample was obtained by crystallization from a minimum amount of hexanes to yield fine yellow needles. Mp 83–85 °C. ¹H NMR (400 MHz, CDCl₃, δ): 1.33 (s, 9H), 1.40 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 3.83 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.46 (s, 1H), 8.30 (s, 1H), 11.45 (bs, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 14.2 (1C), 23.0 (1C), 27.5 (3C), 40.5 (1C), 56.2 (1C), 61.7 (1C), 106.4 (1C), 106.7 (1C), 113.6 (1C), 143.5 (1C), 150.1 (1C), 161.4 (1C), 164.3 (1C), 178.1 (1C), 188.9 (1C). I.R.: (KBr) (cm⁻¹): 3272 (w), 2976 (m), 1747 (s), 1688 (m), 1626 (s), 1579 (s), 1532 (w), 1470 (m). Anal. Calcd for C₁₇H₂₃NO₅: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.64; H, 7.24; N, 4.30. HR-ESI *m/z*: [M + Na]⁺ calcd for C₁₇H₂₃NO₅Na, 344.1474; found, 344.1474

⁵ While this compound has been reported in the literature, no spectral data are available.

⁶ Haworth, R. D.; Lapworth, A. *J. Chem. Soc.* **1923**, 123, 2982–2996; Saari, W. S. (Merck). U.S. Patent 3671636, 1972.; *Chem. Abstr.* **1972**, 77, 88083.

⁷ Titrated using the method described in Duhamel, L.; Plaquevent, J. *J. Organomet. Chem.* **1993**, 448, 1–3.

4-Methoxy-6-methyl-1H-indole-2,3-dione (13).

Oxoacetate **12** (2.00 g, 6.22 mmol) was dissolved in DME (6.2 mL) yielding a pale yellow solution. Concentrated HCl (6.2 mL) was added (yellow ppt) and the resulting suspension was heated to reflux (yellow ppt dissolves with heating and the solution slowly turns orange). After 5h, the reaction mixture was cooled to ambient temperature and carefully neutralized with 1M aqueous NaOH (~65 mL) to a pH = 6–7⁸ and then basified with saturated NaHCO₃ (~5 mL) to a pH = 8–9.⁹ The basic solution was extracted with DCM (4 x 150 mL) and the organic extracts were combined, dried over MgSO₄ and evaporated to yield an orange solid (1.18 g, 99%). An analytically pure sample was obtained by crystallization of a 0.300 g sample from isopropanol (10.3 mL). Mp 198–199°C. ¹H NMR (400 MHz, DMSO, δ): 2.31 (s, 3H), 3.86 (s, 3H), 6.26 (s, 1H), 6.52 (s, 1H), 10.93 (s, 1H). ¹³C NMR (100 MHz, DMSO, δ): 22.7 (1C), 55.8 (1C), 103.8 (1C), 104.9 (1C), 107.0 (1C), 151.1 (1C), 152.5 (1C), 157.8 (1C), 159.8 (1C), 179.3 (1C). I.R.: (KBr) (cm⁻¹) 3552 (w), 3478 (w), 3296 (m), 3190 (w), 1750 (s), 1715 (s), 1626 (s), 1591 (s), 1509 (w), 1459 (m). Anal. Calcd. for C₁₀H₉NO₃: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.99; H, 4.66; N, 7.27. HR-ESI m/z: [M + Na]⁺ calcd for C₁₀H₉NO₃Na, 214.0477; found, 214.0477.

3,3,4-Trimethoxy-6-methylindolin-2-one (14).

Isatin **13** (1.16 g, 6.07 mmol) was stirred as a suspension in anhydrous MeOH (6 mL). Trimethylorthoformate (0.8 mL, 7 mmol) and *p*-toluenesulfonic acid monohydrate (0.0357 g, 0.188 mmol) were added and the mixture was heated to reflux. After 6 h at reflux, the resulting homogeneous solution was cooled to ambient temperature, diluted with Et₂O (70 mL) and washed with sat. Na₂CO₃ (1 x 20 mL). The aqueous layer was then back-extracted with Et₂O (1 x 20 mL). The two organic layers were combined, dried over MgSO₄ and evaporated to yield an orange solid (1.40 g). The crude product was purified by flash chromatography on deactivated alumina (1.5 x 10 cm, Brockman III¹⁰) using 50% EtOAc in Hexanes as eluent to yield an orange solid (1.29 g, 90%). An analytically pure sample was obtained by crystallization from DCM:hexanes by stirring a 0.500 g sample in refluxing hexanes (5 mL) and adding DCM dropwise until all solid had dissolved. Mp 117–119 °C. ¹H NMR (400 MHz, CDCl₃, δ): 2.33 (s, 3H), 3.53 (s, 6H), 3.87 (s, 3H), 6.33 (s, 1H), 6.44 (s, 1H), 7.90 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 22.2 (1C), 52.1 (2C), 55.6 (1C), 99.7 (1C), 104.9 (1C), 107.1 (1C), 108.0 (1C), 142.2 (1C), 143.2 (1C), 156.6 (1C), 173.5 (1C). I.R.: (KBr) (cm⁻¹) 3338 (s), 2976 (w), 2949 (w), 2829 (w), 1731 (s), 1630 (s), 1602 (s), 1513 (m), 1466 (m), 1424 (w). Anal. Calcd for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.75; H, 6.36; N, 5.88. HR-ESI m/z: [M + Na]⁺ calcd for C₁₂H₁₅NO₄Na, 260.0899; found, 260.0896.

1-Amino-3,3,4-trimethoxy-6-methylindolin-2-one (15).

Isatin **14** (1.48 g, 6.26 mmol) was ground gently with a spatula under argon and then dried under reduced pressure (0.1 torr) in the reaction flask for 30 min. The resulting orange powder was dissolved in THF (68 mL) and the solution was cooled to 0 °C. A 60% dispersion of NaH in oil (0.277 g, 6.9 mmol) was added, resulting in a rapid production of hydrogen gas. After 5 min, *O*-(diphenylphosphinyl)hydroxylamine (1.70 g, 7.29 mmol) was added and the reaction was warmed to ambient temperature. After 45 min, the crude reaction mixture was filtered through a plug of Celite (washed with Et₂O until the filtrate was colorless) and evaporated to yield a brown oil (2.02 g). The crude product was purified by flash chromatography using deactivated alumina (4 x 7 cm, Brockman III¹⁰) and 60% EtOAc in hexanes as eluent to yield a yellow solid (1.43 g, 91%). An analytically pure sample was obtained by crystallization of a 0.340 g sample from a mixture of hexanes (0.7 mL) and ¹PrOH (1.7 mL). Mp 109.5–110.5 °C. ¹H NMR (400 MHz, CDCl₃, δ): 2.37 (s, 3H), 3.52 (s, 6H), 3.87 (s, 3H), 4.18 (s, 2H), 6.46 (s, 1H), 6.63 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 22.4 (1C), 52.1 (2C), 55.7 (1C), 98.7 (1C), 103.2 (1C), 106.1 (1C), 107.5 (1C), 143.2 (1C), 144.8 (1C), 156.1 (1C), 170.2 (1C). I.R.: (KBr) (cm⁻¹) 3323 (m), 2973 (w), 2945 (w), 2836 (w), 1712 (s), 1634 (m), 1599 (m), 1509 (w), 1474 (w). Anal. Calcd for C₁₂H₁₆N₂O₄: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.13; H, 6.61; N, 10.94. HR-ESI m/z: [M + Na]⁺ calcd for C₁₂H₁₆N₂O₄Na, 275.1008; found, 275.1004.

⁸ Determined by colorpHast indicating strips.

⁹ The solution should remain orange throughout the workup. A purple color indicates the presence of isatin anion that will hydrolyze at ambient temperature over a period of hours.

¹⁰ Furniss, B. S.; Hanneford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th Edition, John Wiley and Sons, Inc.: NY, 1989; 212.

4-Methoxy-6-methyl-1H-indazole-3-carboxylic acid (**16**).

To a suspension of **15** (1.04 g, 4.13 mmol) in water (200 mL) was added concentrated sulfuric acid (14 mL) dropwise over 3 min (this reaction was carried out in undried glassware and open to the atmosphere). After stirring the resulting orange solution for 1 h at ambient temperature, the mixture was heated to 85 °C and stirred at that temperature for an additional 3 h. The reaction was then allowed to cooled to ambient temperature and then cooled to 0 °C in an ice/water bath. The resulting precipitate was collected by vacuum filtration and the filter cake was washed with a small amount of Et₂O to yield a yellow-orange solid (0.761 g, 89%). Mp 230–232 °C. ¹H NMR (400 MHz, DMSO, δ): 2.41 (s, 3H), 3.85 (s, 3H), 6.49 (s, 1H), 6.92 (s, 1H).¹¹ ¹³C NMR (100 MHz, DMSO, δ): 21.8 (1C), 55.4 (1C), 102.3 (1C), 103.6 (1C), 110.5 (1C), 136.3 (1C), 137.9 (1C), 143.1 (1C), 152.3 (1C), 163.4 (1C). I.R.: (KBr) (cm⁻¹) 3459 (m), 3178 (m), 3097 (m), 2957 (m), 2871 (m), 1719 (s), 1634 (m), 1587 (m), 1532 (w), 1443 (s), 1412 (s). HR-ESI *m/z*: [M+H]⁺ calcd for C₁₀H₁₁N₂O₃, 207.0770; found, 207.0765.

Methyl 4-Methoxy-6-methyl-1H-indazole-3-carboxylate (**17**).

Crude **16** (0.760 g, 3.69 mmol) was dissolved in anhydrous methanol (40 mL). The solution was cooled to 0 °C and thionyl chloride (1.4 mL, 19 mmol) was added dropwise over 5 min. The resulting mixture was heated to reflux. After 1.5 h, the reaction was cooled to ambient temperature and the volatiles were removed by rotary evaporation. The resulting residue was diluted with EtOAc (100 mL) and brine (100 mL). The brine layer was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, dried over MgSO₄ and evaporated to yield a yellow-orange solid (0.820 g). The crude product was purified by flash chromatography on deactivated alumina (5 x 7 cm, Brockman III¹⁰) using 3% MeOH in chloroform as eluent to yield a yellow-orange powder (0.642 g, 79%). An analytically pure sample was obtained by crystallization of a 0.217 g sample from toluene (1 mL). Mp 144–145 °C. ¹H NMR (400 MHz, CDCl₃, δ): 2.44 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 6.43 (s, 1H), 6.97 (s, 1H), 11.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 22.3 (1C), 52.3 (1C), 55.8 (1C), 102.7 (1C), 104.5 (1C), 111.6 (1C), 136.1 (1C), 139.2 (1C), 143.8 (1C), 153.1 (1C), 162.9 (1C). I.R.: (KBr) (cm⁻¹) 3261 (s), 3000 (m), 2949 (m), 2840 (w), 1739 (m), 1703 (s), 1622 (s), 1579 (s), 1532 (s), 1455 (s). Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found, C, 60.08; H, 5.44; N, 12.56. HR-ESI *m/z*: [M+H]⁺ calcd for C₁₁H₁₃N₂O₃, 221.0926; found, 221.0925.

Nigellidine (**1**).

Indazole **17** (0.515 g, 2.34 mmol) was dissolved in THF (600 mL). The resulting solution was cooled to 0 °C and NaH (0.137 g, 3.4 mmol) was added as a 60% dispersion in oil. After the visible evolution of gas had stopped (~10 min), 1,4-dibromobutane (6.3 mL, 53 mmol) was added rapidly in one portion. The ice bath was then removed and the reaction allowed to warm to ambient temperature. After 22 h, excess NaH was quenched by the addition of wet Et₂O (100 mL). Deactivated alumina was then added (12 g, Brockman III¹⁰) and the solvent was removed by rotary evaporation.¹² The resulting solid was purified by flash chromatography using deactivated alumina (4 cm x 9 cm, Brockman III¹⁰) using a stepwise solvent gradient from pure hexanes to 25% EtOAc in hexanes as the eluent to yield **18** as a pale yellow oily solid (0.555 g, ~67%). Crude **18** is always contaminated with trace amounts of both cyclized product **21** and further decomposition products resulting from the hydrolysis and decarboxylation of **21** to yield **22**. ¹H NMR (400 MHz, CDCl₃, δ): 1.83–1.91 (m, 2H), 2.07–2.14 (m, 2H), 2.49 (s, 3H), 3.40 (t, *J* = 7 Hz, 2H), 3.99 (s, 3H), 4.00 (s, 3H), 4.42 (t, *J* = 7 Hz, 2H), 6.45 (s, 1H), 6.80 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 22.2 (1C), 28.0 (1C), 29.5 (1C), 32.7 (1C), 48.5 (1C), 52.0 (1C), 55.6 (1C), 101.2 (1C), 104.2 (1C), 112.3 (1C), 134.5 (1C), 138.8 (1C), 142.6 (1C), 153.2 (1C), 162.2 (1C). HR-ESI *m/z*: [M+H]⁺ calcd for C₁₅H₂₀N₂O₃Br, 355.0657; found, 355.0690.

Crude **18** (0.555 g, 1.56 mmol) was dissolved in methanol (55 mL) under a rapid stream of Ar and the solution was sealed in a thick-walled pressure flask. The yellow solution was heated at 85 °C for 48 h, at which time the flask was cooled to 0 °C and the solvent was evaporated on a rotary evaporator to yield crude **21** as a yellow-white solid (0.554 g, ~99%).¹³ ¹H NMR (400 MHz, CDCl₃, δ): 2.48 (m, 4H), 2.56 (s,

¹¹ Peaks for the NH and COOH were not visible.

¹² It should be noted that excess heating during solvent removal can cause cyclization and spontaneous decarboxylation, thus all evaporation steps were performed using a chilled water bath.

¹³ It should be noted that heating in the presence of trace (atmospheric) water during solvent removal can cause spontaneous decarboxylation, thus all evaporation steps were performed using a ice/water bath.

3H), 3.97 (s, 3H), 4.11 (s, 3H), 4.90 (t, $J = 6.0$, 2H), 4.99 (t, $J = 6.0$, 2H), 6.62 (s, 1H), 7.20 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 19.1 (1C), 19.7 (1C), 23.3 (1C), 48.1 (1C), 50.8 (1C), 54.3 (1C), 56.4 (1C), 101.8 (1C), 107.4 (1C), 109.7 (1C), 131.4 (1C), 141.5 (1C), 147.8 (1C), 153.1 (1C), 157.8 (1C).

The crude **21** (0.554 g, 1.56 mmol) was dissolved in DCM (65 mL) and the solution was cooled to 0 °C. Boron tribromide (10.6 mL, 1.0 M solution in hexanes, 11 mmol) was added dropwise (2 min). The cold bath was removed and the reaction was allowed to warm to ambient temperature. After 3.5 h, the reaction was cooled back down to 0 °C and the excess boron tribromide was quenched by slow addition (5 min) of water (35 mL). The resulting biphasic mixture was extracted with 10% MeOH in DCM (4 x 60 mL). The organic layers were combined, dried over MgSO_4 and evaporated to yield nigellidine (**1**) as a yellow solid (0.347 g, 60% over 3 steps). Mp dec over large range. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ (5:1), δ): 2.26–2.38 (m, 4H), 2.49 (s, 3H), 4.52 (t, $J = 6.0$ Hz, 2H), 5.20 (t, $J = 6.0$ Hz, 2H), 6.60 (s, 1H), 6.68 (s, 1H). ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ (5:1), δ): 19.4 (1C), 20.1 (1C), 22.7 (1C), 46.8 (1C), 50.1 (1C), 97.9 (1C), 110.59 (1C), 110.63 (1C), 138.1 (1C), 141.9 (1C), 148.3 (1C), 153.6 (1C), 159.8 (1C). I.R.: (KBr) (cm^{-1}) 3424 (w), 3042 (w), 2922 (w), 2875 (w), 1665 (m), 1633 (s), 1622 (s), 1580 (s), 1513 (s), 1451 (m), 1404 (m), 1357 (m), 1284 (s), 1256 (s). UV (EtOH) λ_{max} , nm (log ϵ): 241 (4.3), 288 (3.6), sh. 296 (3.6), 355 (3.5). HR-ESI m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3$, 247.1083; found, 247.1079.

Natural 1 ¹⁴	Synthetic 1	Natural 1 ¹⁴	Synthetic 1
$^1\text{H-NMR}^{15}$ (δ)		UV (EtOH) λ_{max} , nm (log ϵ)	
2.32 (m, 4H)	2.26–2.38 (m, 4H)	240 (4.30)	241 (4.3)
2.48 (s, 3H)	2.49 (s, 3H)	288 (3.52)	288 (3.6)
4.46 (t, $J = ?$, ¹⁶ 2H)	4.52 (t, $J = 6.0$ Hz, 2H)	296 (3.51)	296 (3.6)
5.18 (t, $J = ?$, ¹⁶ 2H)	5.20 (t, $J = 6.0$ Hz, 2H)	353 (3.53)	355 (3.5)
6.58 (s, 1H)	6.60 (s, 1H)	IR (KBr) (cm^{-1})	
6.75 (s, 1H)	6.68 (s, 1H)	3405	3424
$^{13}\text{C-NMR}^{15,17}$ (δ)		3055	3042
19.2	19.4	2910	2922
20.0	20.1	2890	2875
22.4	22.7	1670	1665
46.8	46.8	1650	
49.5	50.1	1637	1633
97.6	97.9	1625	1622
110.5	110.59	1576	1580
	110.63		1513
138.3	138.1		1451
141.9	141.9	1406	1404
148.2	148.3		1357
153.7	153.6	1286	1284
159.6	159.8	1266	1260

Table 1. Comparison of the spectral properties of synthetic 1 and natural 1.

Nigeglanine hydrobromide (2b)

Crude **18** (0.475 g, 1.34 mmol) was dissolved in a mixture of 10% H_2O in acetone (v/v; 55 mL) and the solution was sealed in a thick-walled pressure flask. The yellow solution was heated at 80 °C for 40 h, at which time the flask was cooled to ambient temperature and the solvent was evaporated to yield **22** as a yellow-white solid (0.377 g, ~95%). Mp dec over large range. ^1H NMR (400 MHz, CDCl_3 , δ): 2.30–2.38 (m, 2H), 2.40–2.46 (m, 2H), 2.54 (s, 3H), 3.96 (s, 3H), 4.56 (t, $J = 6$ Hz, 2H), 5.15 (t, $J = 6$ Hz, 2H), 6.52 (s, 1H), 6.98 (s, 1H), 9.39 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3 , δ): 19.8 (1C), 20.3 (1C), 23.3 (1C), 46.9 (1C), 51.3 (1C), 56.0 (1C), 100.9 (1C), 106.0 (1C), 111.4 (1C), 132.2 (1C), 142.4 (1C), 147.7 (1C),

¹⁴ Atta-ur-Rahman; Malik, S; He, C.; Clardy, J. *Tetrahedron Lett.* **1985**, 26, 2759–2762.

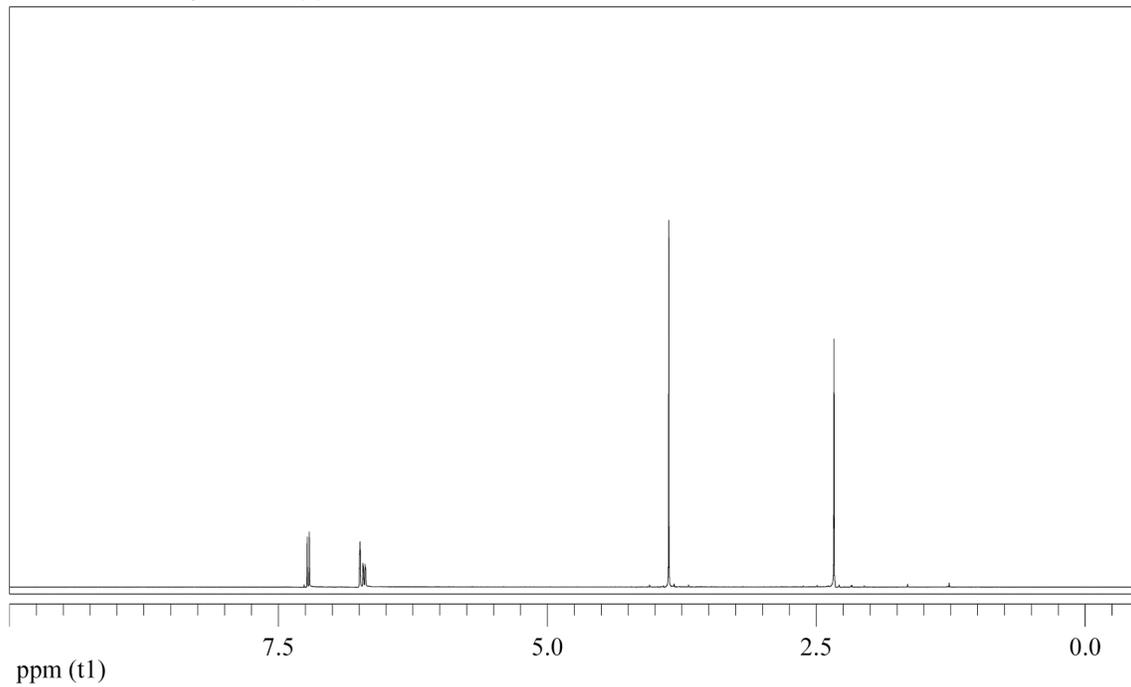
¹⁵ It should be noted that while all NMR spectra of synthetic **1** were obtained in a mixture of 5:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, ref. 14 does not indicate the relative amounts of CD_3OD and CDCl_3 used. Unfortunately, an authentic sample of natural **1** could not be located.

¹⁶ Value not reported.

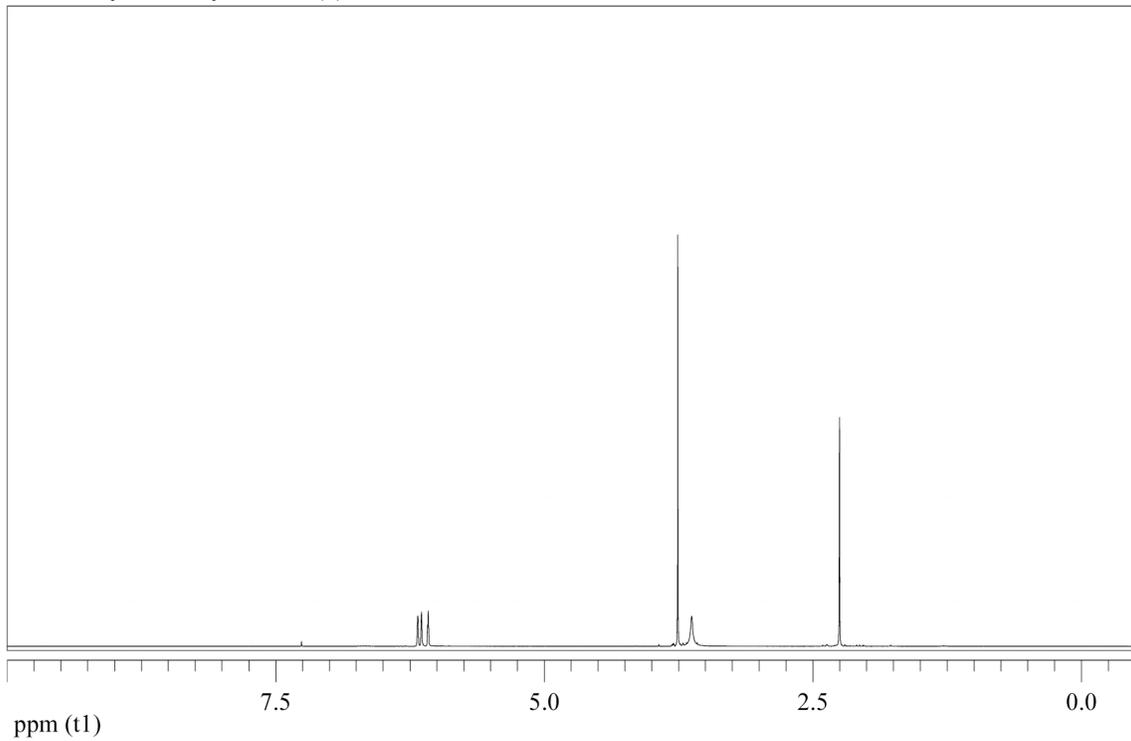
¹⁷ Synthetic **1** ^{13}C NMR (125 MHz); Natural **1** ^{13}C NMR (100 MHz).

Selected Spectra

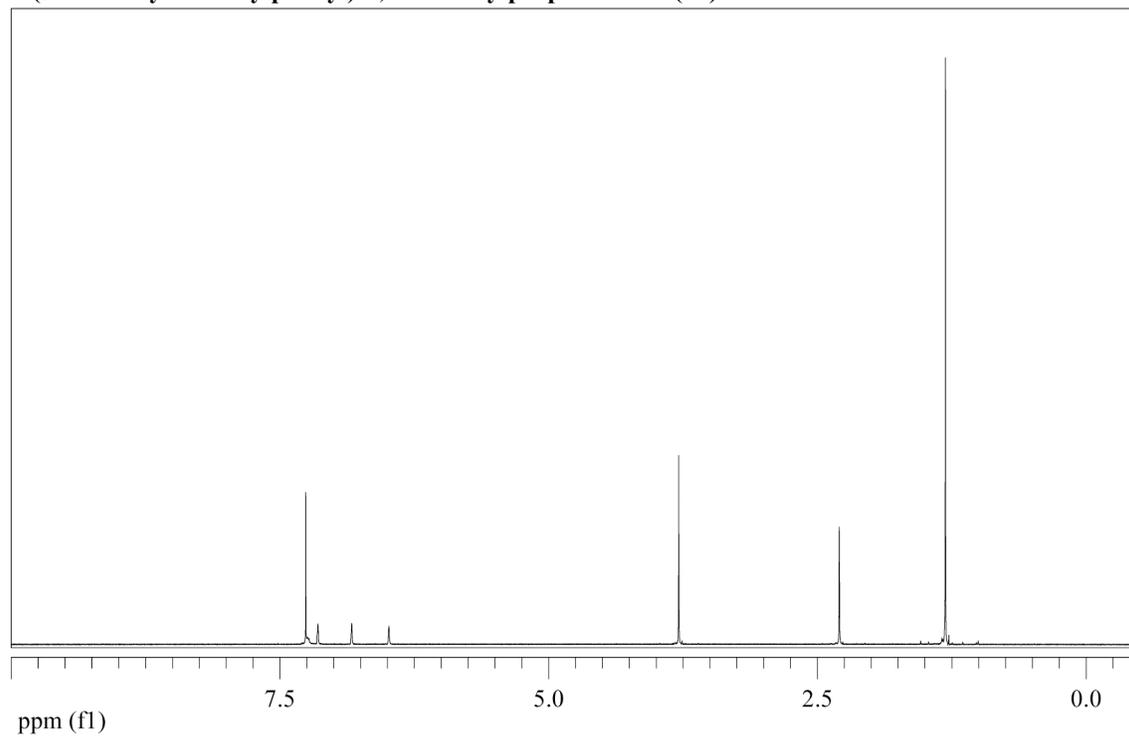
2-Chloro-5-methylanisole (8).



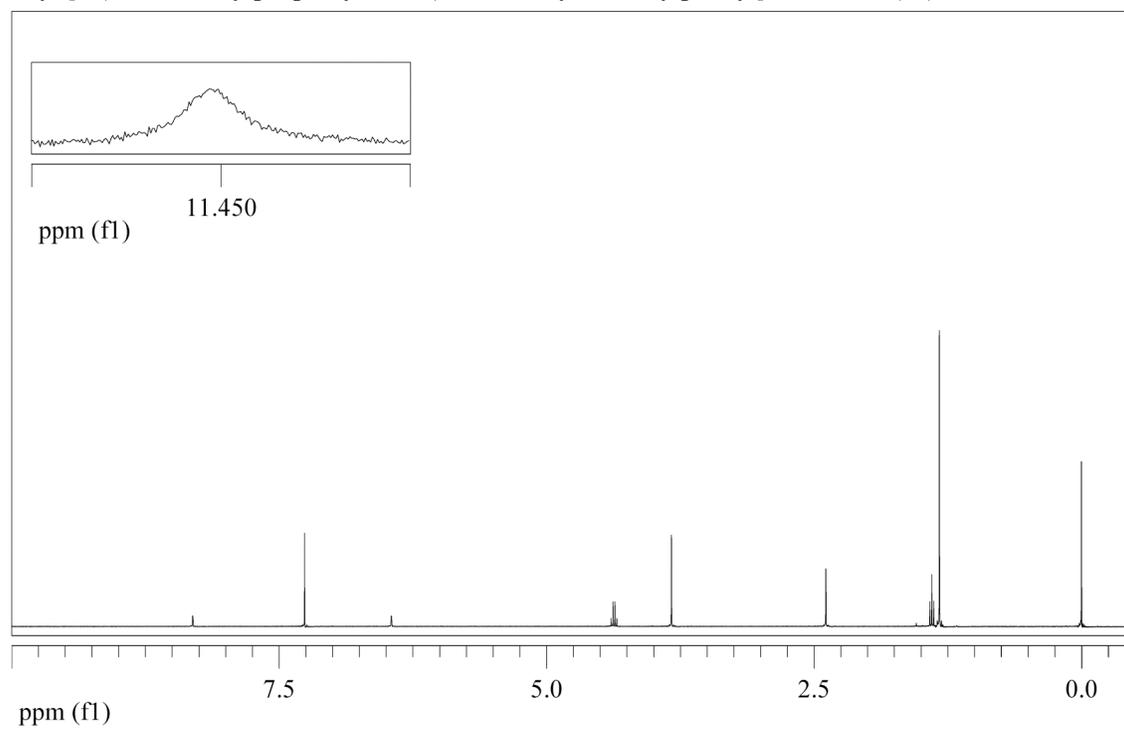
3-Methoxy-5-methylaniline (9).



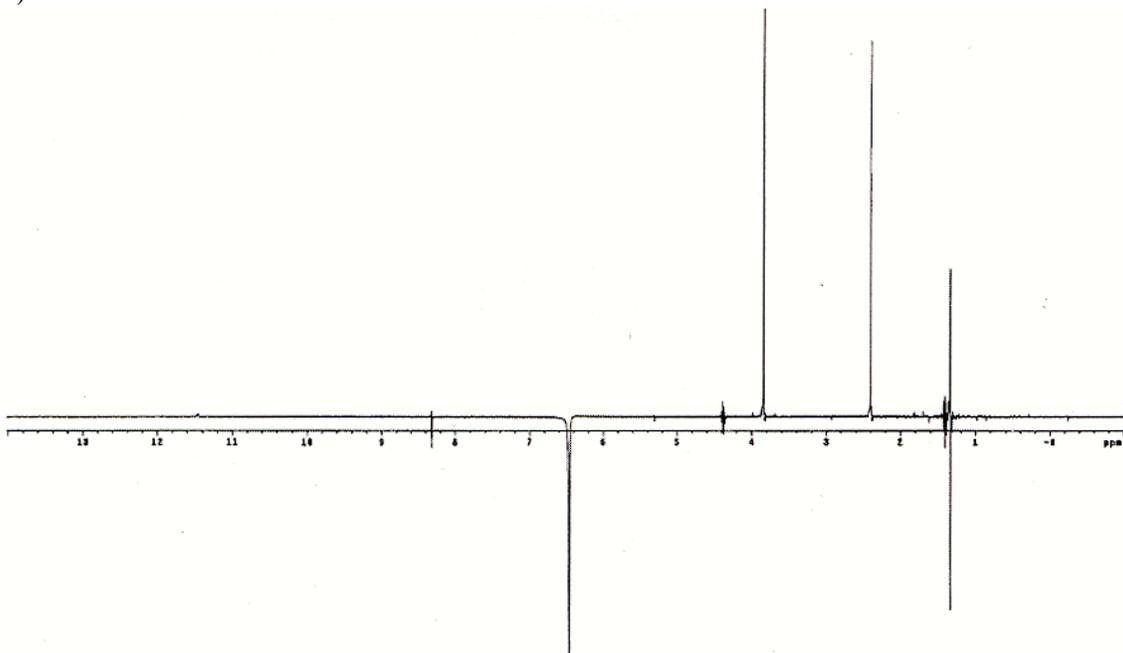
***N*-(3-Methoxy-5-methylphenyl)-2,2-dimethylpropionamide (10).**



Ethyl [2-(2,2-Dimethylpropionylamino)-6-methoxy-4-methylphenyl]oxoacetate (12).



a)



b)

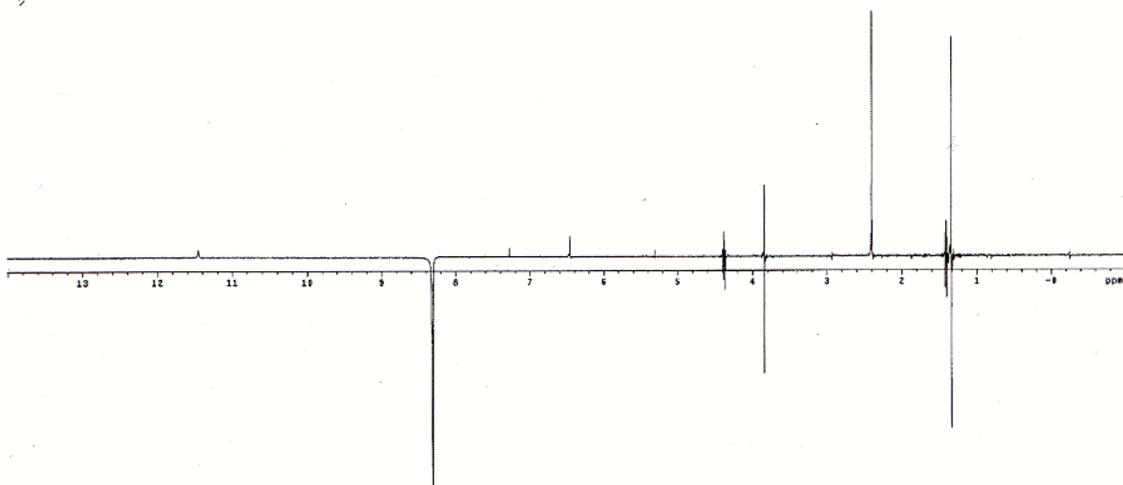
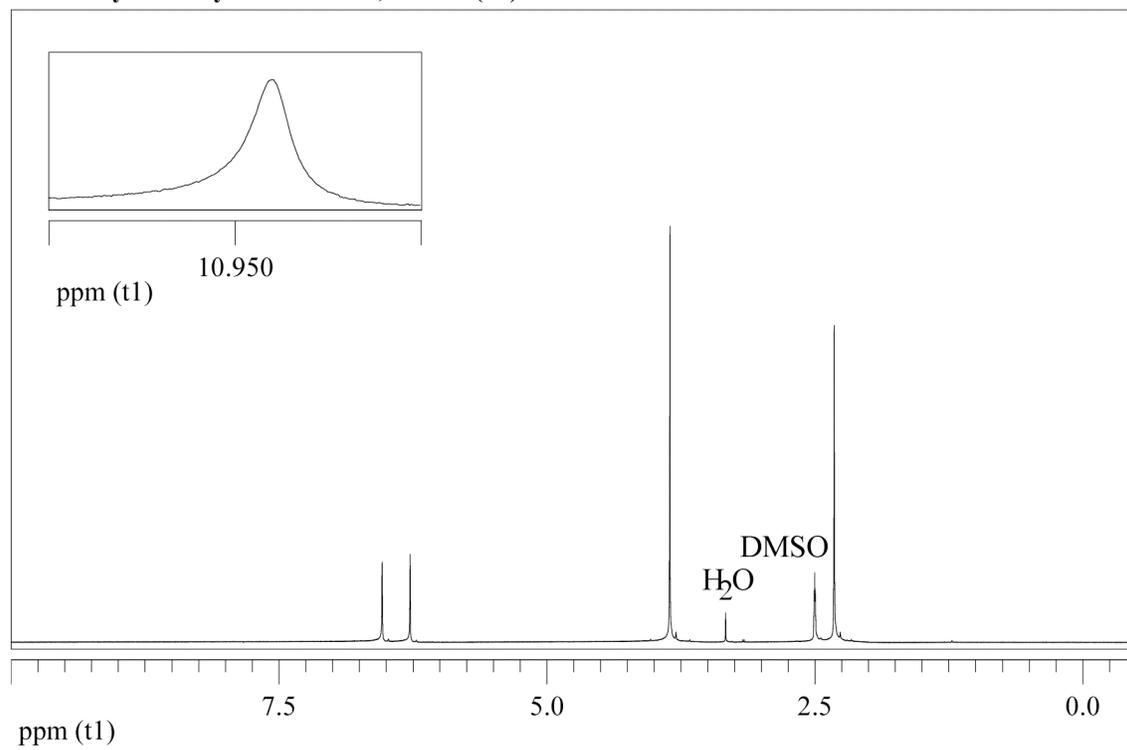


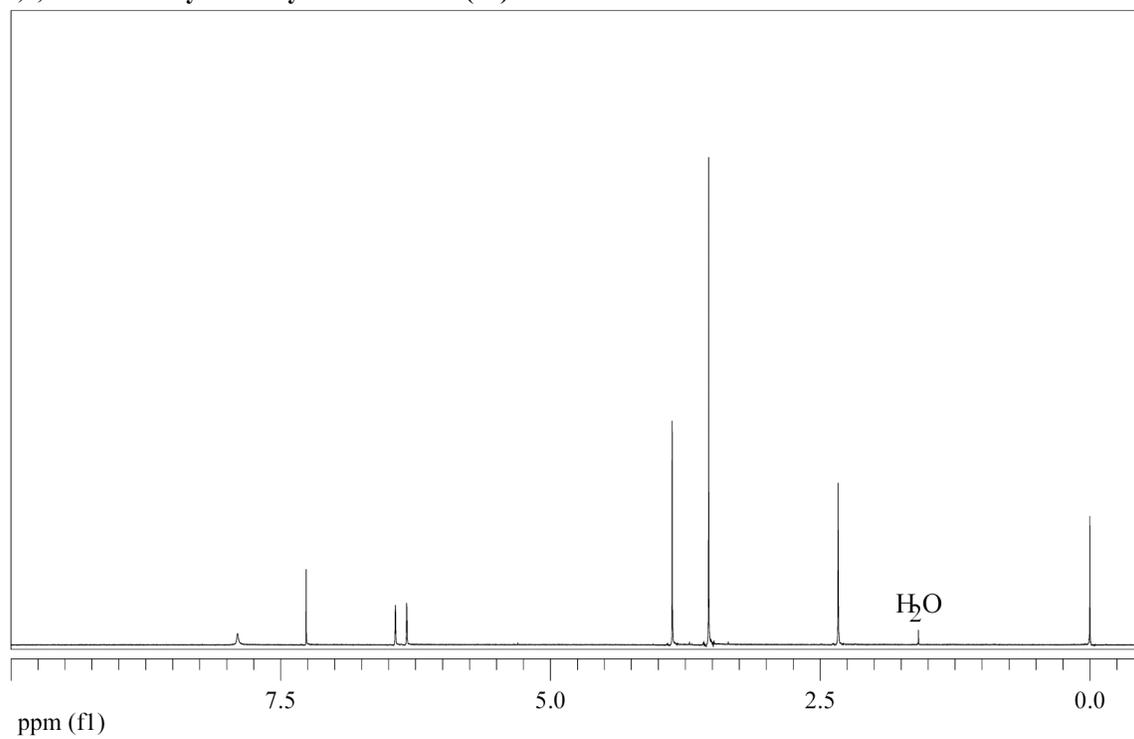
Figure 1. nOe difference spectra of 12.

The nOe's observed to the methyl signal (2.39 ppm) and the methoxy signal (3.83 ppm) as a result of irradiation of the aromatic resonance at 6.46 ppm (spectrum a) combined with the nOe observed to the methyl signal (2.39 ppm) as a result of irradiation of the aromatic resonance at 8.30 ppm (spectrum b) confirm the assigned structure.

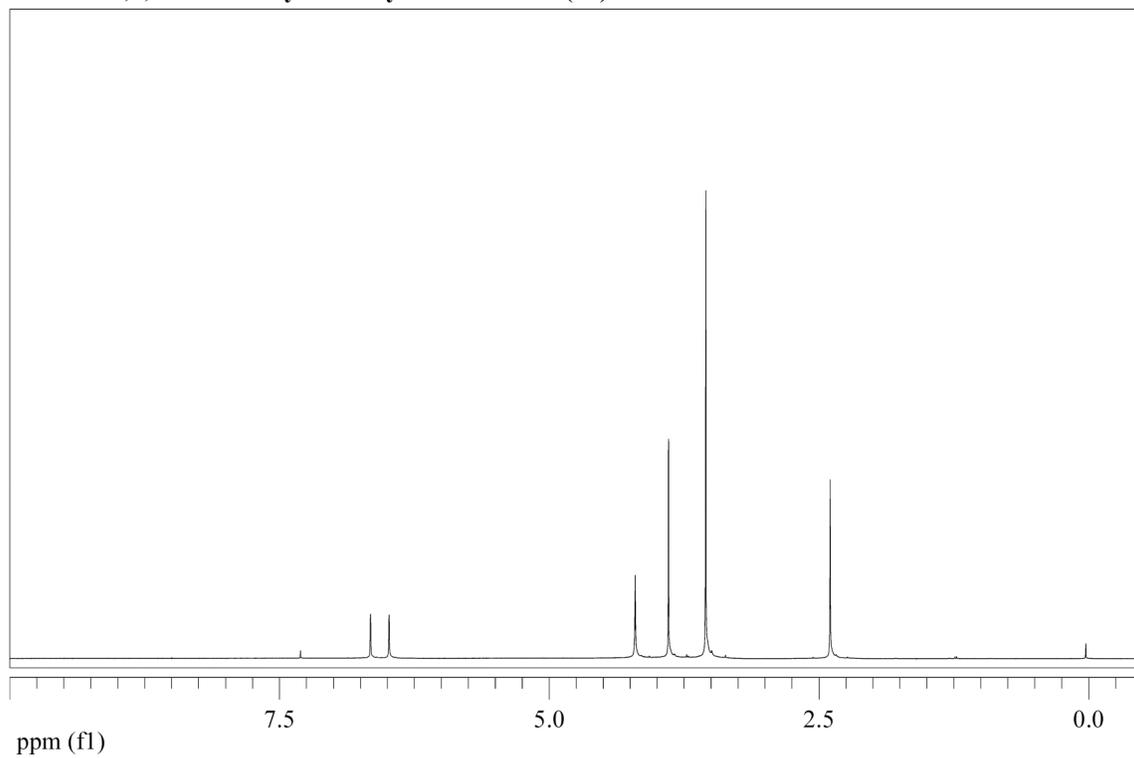
4-Methoxy-6-methyl-1H-indole-2,3-dione (13).



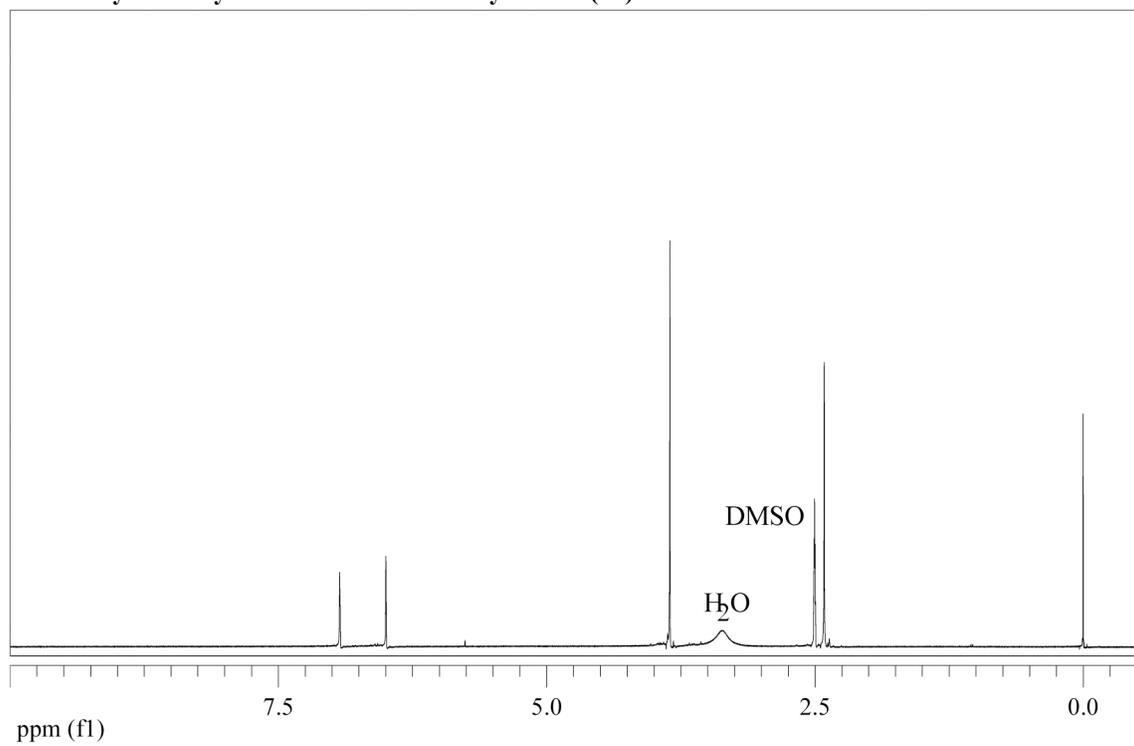
3,3,4-Trimethoxy-6-methylindolin-2-one (14).



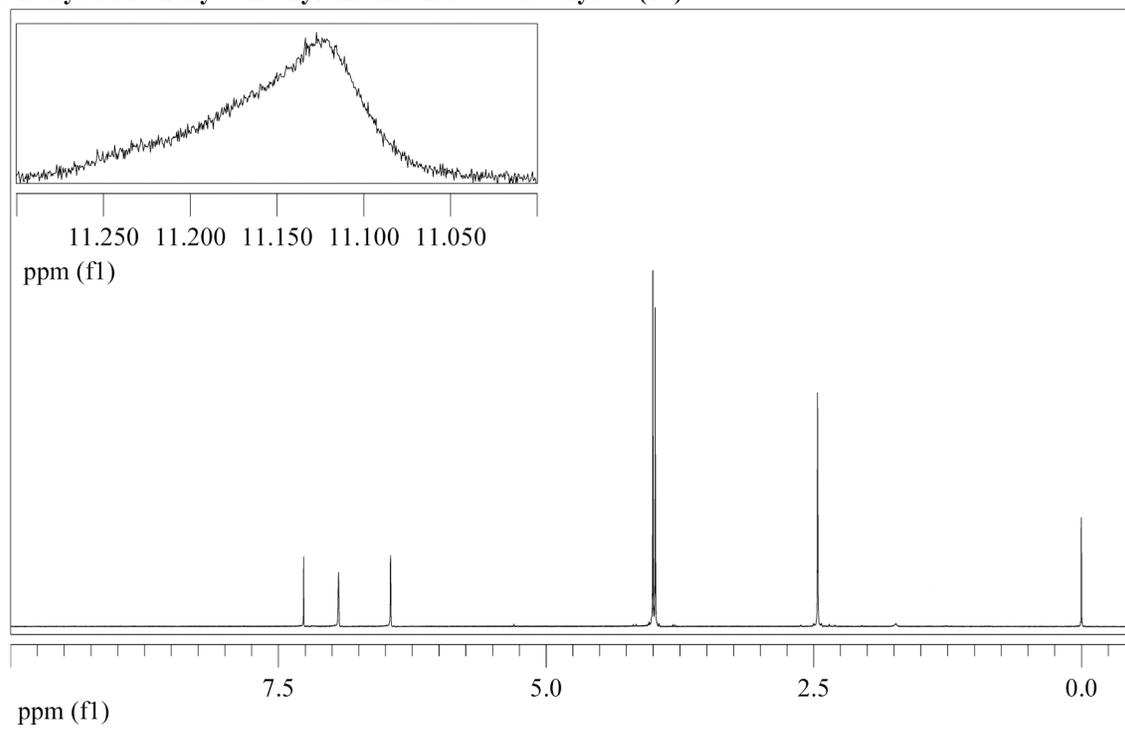
1-Amino-3,3,4-trimethoxy-6-methylindolin-2-one (15).



4-Methoxy-6-methyl-1H-indazole-3-carboxylic acid (16)



Methyl 4-Methoxy-6-methyl-1*H*-indazole-3-carboxylate (17).



Methyl 1-(4-Bromobutyl)-4-methoxy-6-methyl-1*H*-indazole-3-carboxylate (18)

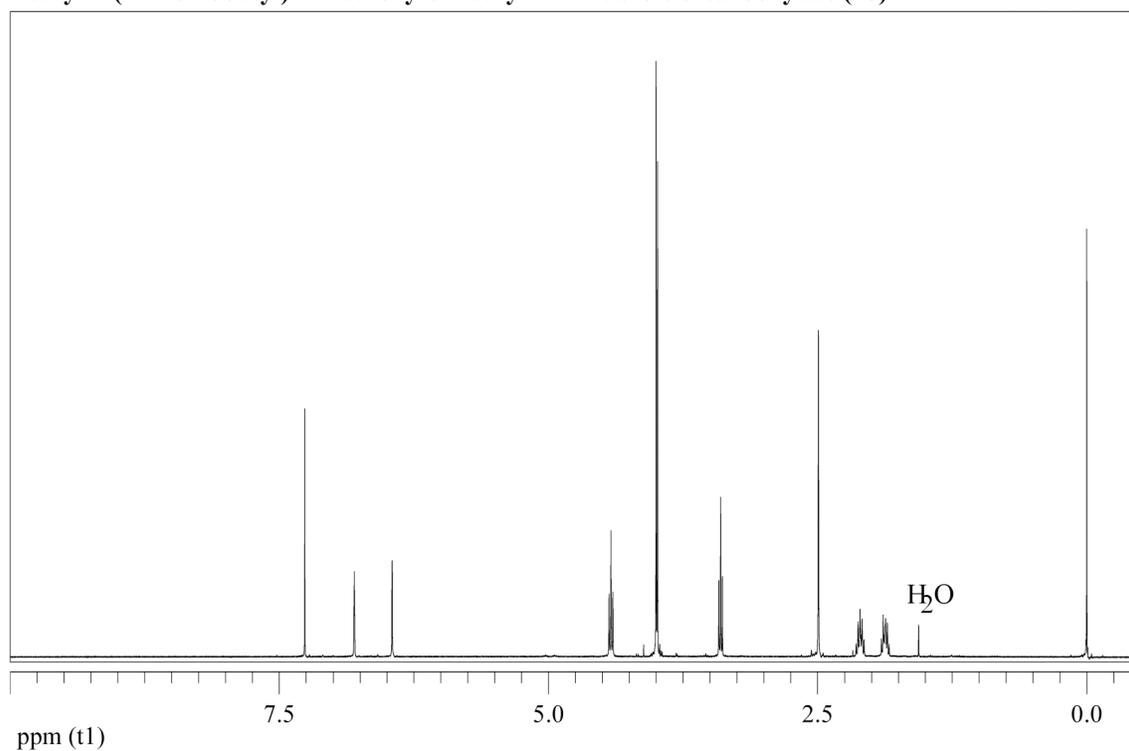
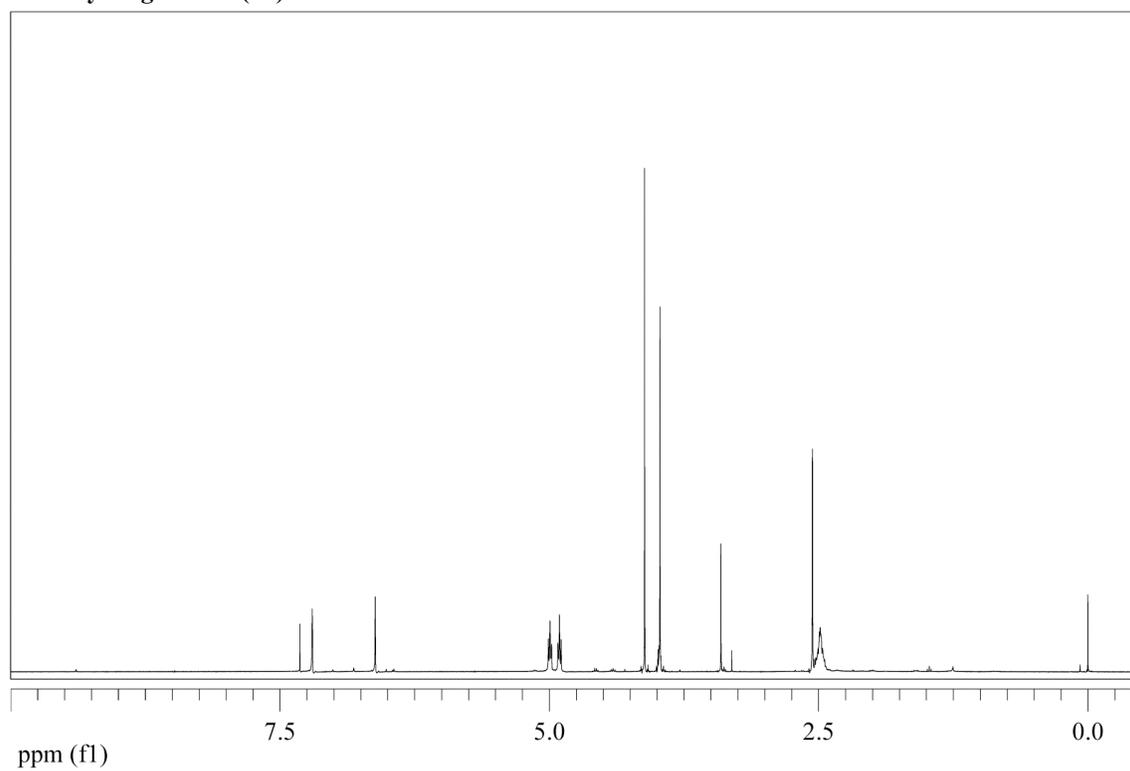




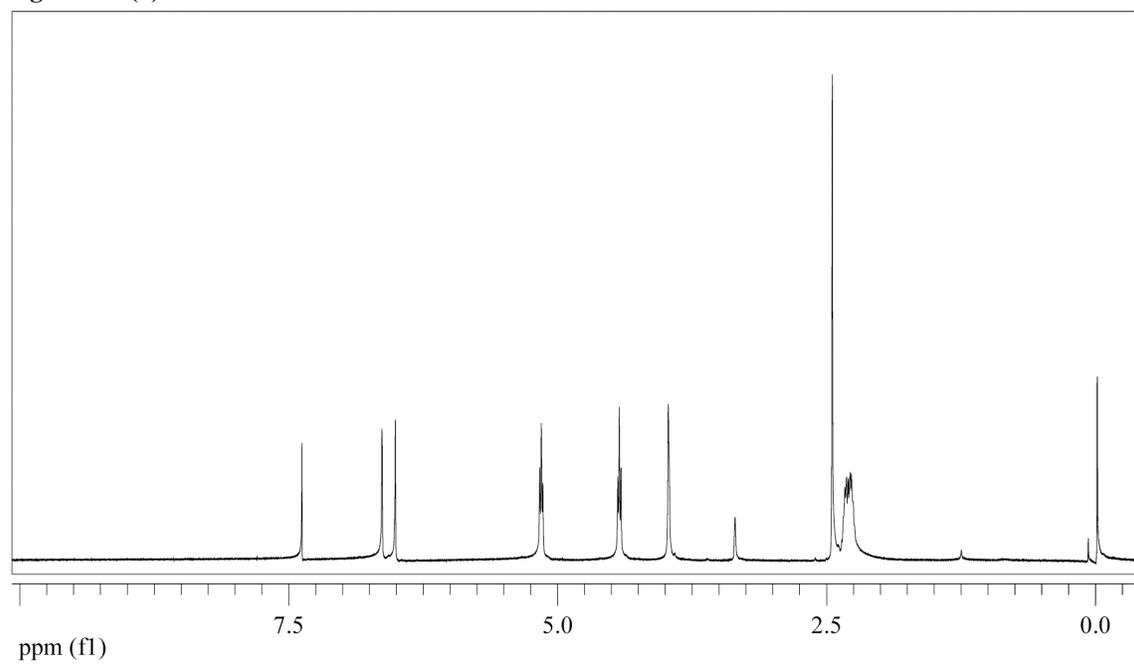
Figure 2: 1-D NOESY spectrum of 18.

The nOe observed to the aromatic signal (6.80 ppm) as a result of irradiation of the alkyl resonance at 4.42 ppm confirms alkylation at N1.

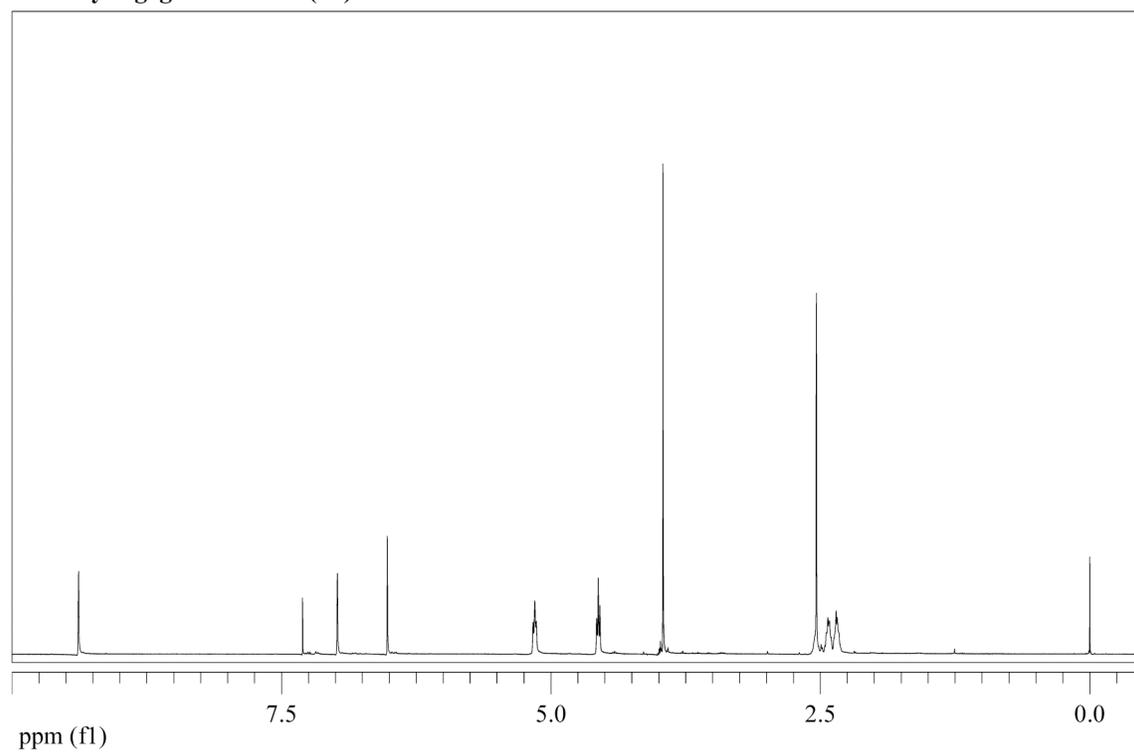
Dimethyl Nigellidine (21).



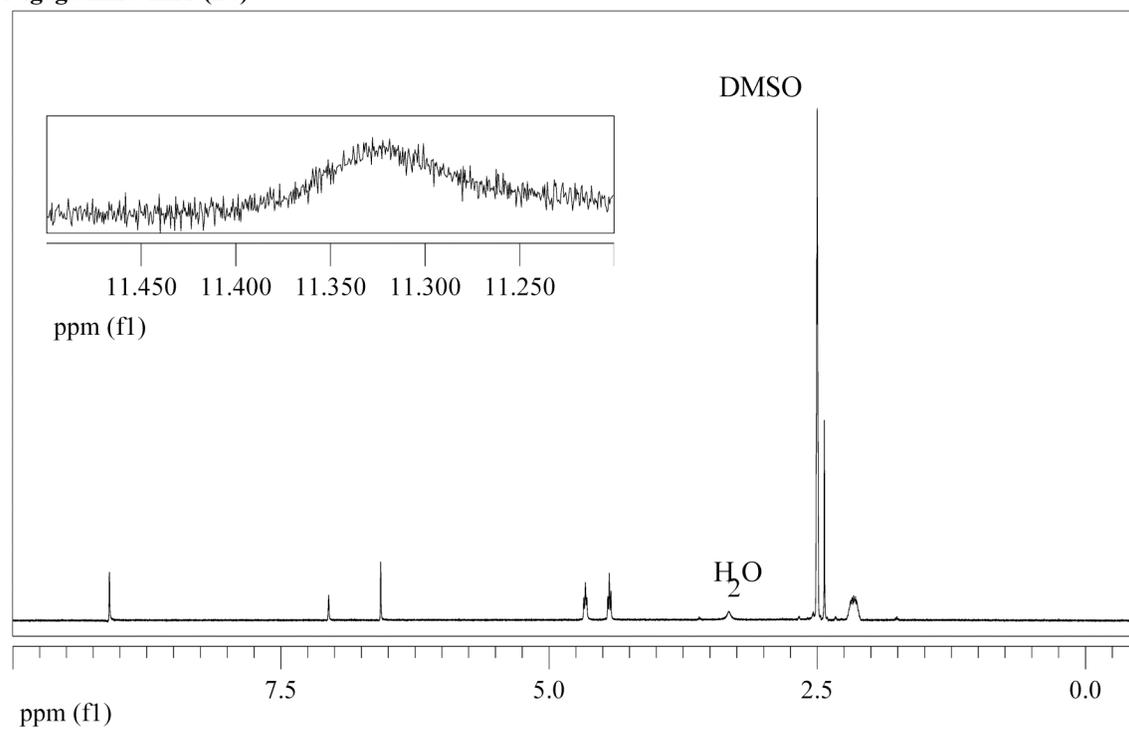
Nigellicine (1)



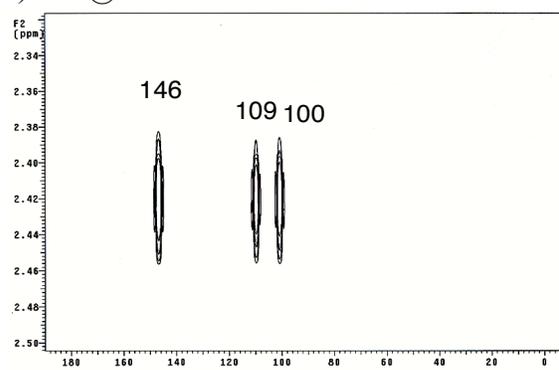
***O*-Methylnigeglanine•HBr (22).**



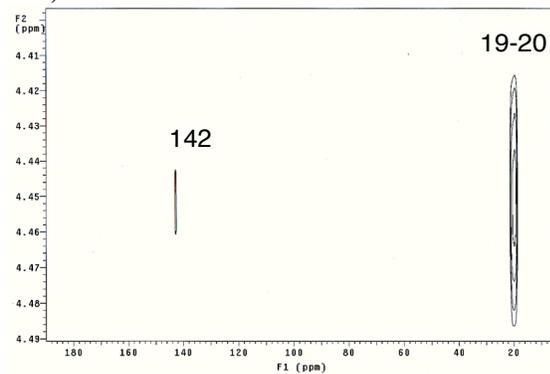
Nigeglanine•HBr (2b).



a) Me @ C 6



b) H 10



c) H 13

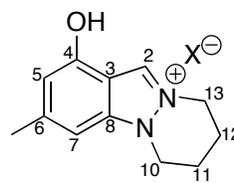
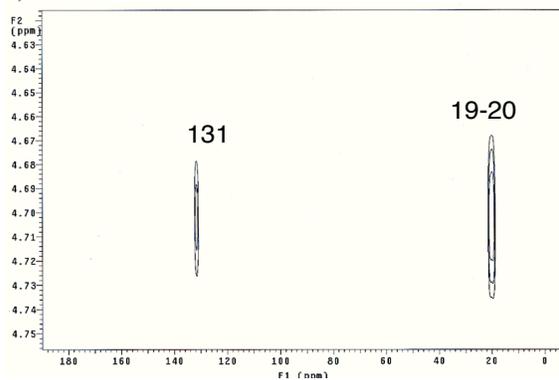


Figure 3. HMBC spectrum²¹ of 2b (J_{CH} filter set to 140 Hz).

²¹ Due to the large difference in one-bond J_{CH} between the aliphatic signals and the heteroaromatic signals, it was necessary to acquire two separate HMBC spectra (one with the one-bond J_{CH} filter set to 140 Hz and the other with the J_{CH} filter set to 165 Hz).

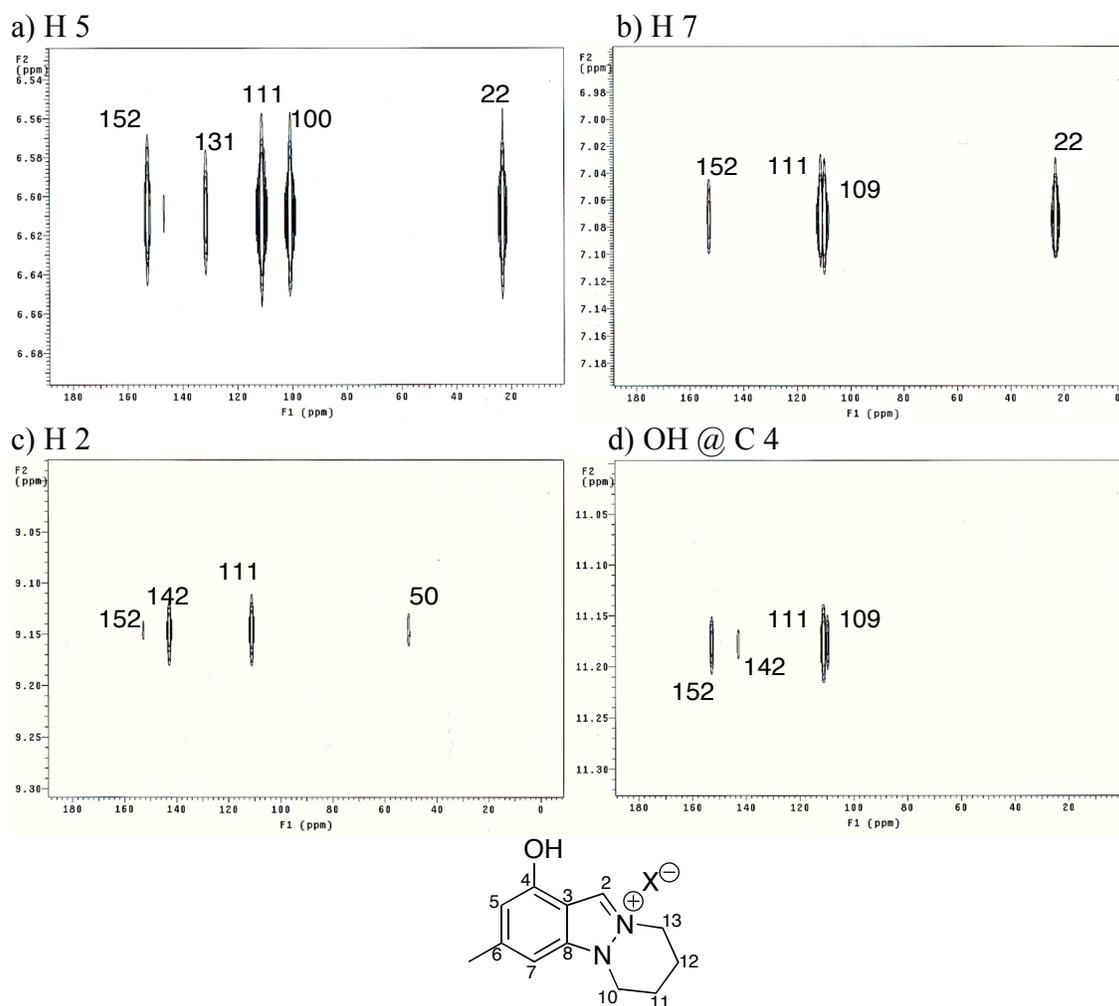


Figure 3. HMBC spectrum²¹ of 2b (J_{CH} filter set to 165 Hz).