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Supporting Information

Enantioselective Total Synthesis of Avarol and Avarone

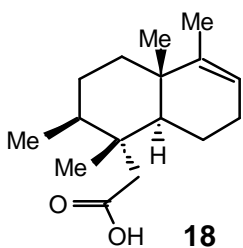
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General techniques. All reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium/benzophenone; dichloromethane (CH₂Cl₂), HMPA and toluene from calcium hydride; DMF from calcium chloride. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 or 500 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High

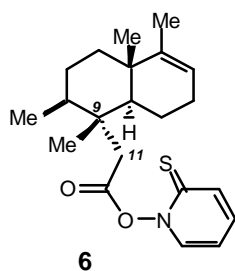
resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Carboxylic acid **18**



18: white solid; $R_f = 0.2$ (silica, 50% ethyl acetate in hexanes); $[\alpha]_D^{25} : 18.1$ ($c = 0.6$, CH_2Cl_2); IR (film) ν_{max} 2922, 2686, 1700, 1451, 1406, 1383, 1311, 1229, 1120, 948; ^1H NMR (400 MHz, CDCl_3) δ 5.20 (s, 1H), 2.46 (d, 1H, $J = 13.6$ Hz), 2.30 (d, 1H, 13.6 Hz), 2.08 (bs, 2H), 1.8-1.2 (m, 12H), 1.0 (s, 3H), 0.91 (d, 3H, $J = 6.8$ Hz), 0.79 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.5, 143.5, 120.8, 48.0, 43.1, 41.2, 38.5, 37.5, 36.4, 27.4, 26.7, 20.0, 19.3, 18.1, 17.5, 16.3; HRMS, calcd for $\text{C}_{16}\text{H}_{26}\text{O}_2$ ($\text{M}^+ \text{Cs}^+$) 383.0985, found 383.0979.

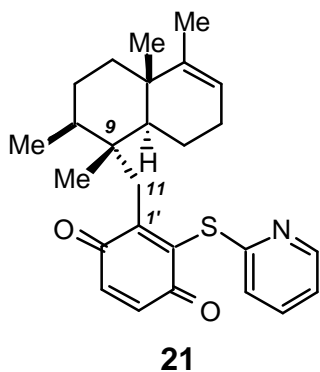
Ester **6**



To a solution of acid **18** (0.13 g, 0.52 mmol) and 2-mercaptopyridine *N*-oxide (66 mg, 0.52 mmol) in dichloromethane (3 ml) was added DCC (107 mg, 0.52 mmol) and the mixture was stirred at 25 °C in the dark (flask was covered with aluminum foil) for 12 h. The mixture was diluted with dichloromethane (5 ml), subjected to filtration over cotton to remove the DCU and the filtrate was partitioned with aqueous saturated sodium bicarbonate (10 ml) and extracted with dichloromethane (3 x 10 ml). The organic layer was collected, dried (MgSO_4), concentrated and the residue was chromatographed (silica, 10-20% ether and 10% dichloromethane in hexanes) to afford ester **6** (170 mg, 0.47 mmol, 91 %).

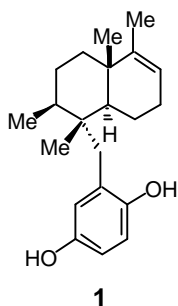
Note: the above procedure needs to be performed in a semi-dark room, since thiohydroxamate esters such as **6** are light-sensitive. **6**: yellow solid; $R_f = 0.7$ (silica, 50% ethyl ether in hexanes); IR (film) ν_{\max} 1780, 1610; ^1H NMR (400 MHz, CDCl_3) δ 7.66 (m, 1H), 7.48 (m, 1H), 7.18 (m, 1H), 6.60 (m, 1H), 5.17 (s, 1H), 2.86 (d, 1H, $J = 13.2$ Hz), 2.70 (d, 1H, $J = 13.2$ Hz), 2.11 (bs, 2 H), 1.81-1.2 (m, 11 H), 1.01 (s, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.5, 166.5, 143.5, 137.6, 137.3, 133.2, 120.4, 112.4, 47.7, 41.6, 39.9, 38.4, 37.8, 36.3, 27.3, 26.8, 19.9, 19.3, 18.1, 17.3, 16.4.

Thioether **21**



A solution of ester **6** (63.1 mg, 0.17 mmol) and 1,4-benzoquinone (**7**) (56 mg, 0.51 mmol) in dichloromethane (5 ml) was cooled at 0 °C and irradiated with one tungsten lamp (GE, 300W) for 2 h. The reaction mixture was concentrated and subjected to flash chromatography (silica, 10-30% ether in hexanes) to afford thioether **21** (58.5 mg, 0.14 mmol, 81%). **21**: colorless liquid; $R_f = 0.45$ (silica, 50% ether in hexanes); $[\alpha]_D^{25}$: +28.6 ($c = 0.9$, CH_2Cl_2); IR (film) ν_{\max} 2926, 2360, 2341, 1654, 1417, 1274; ^1H NMR (400 MHz, CDCl_3) δ 8.3 (bs, 1H), 7.6 (m, 1H), 7.31 (d, 1H, $J = 8$ Hz), 7.03 (m, 1H), 6.83 (s, 2H), 5.15 (bs, 1H), 3.01 (d, 1H, $J = 12.4$ Hz), 2.84 (d, 1H, $J = 12.4$ Hz), 2.1-1.2 (m, 13H), 1.00 (s, 3H), 0.85 (s, 3H), 0.75 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 185.1, 181.7, 153.3, 149.4, 144.0, 142.1, 137.4, 136.9, 136.7, 122.9, 120.7, 120.4, 51.9, 45.5, 42.2, 39.7, 38.9, 36.1, 28.4, 27.1, 20.9, 20.0, 19.0, 18.2, 16.0. HRMS, calcd for $\text{C}_{26}\text{H}_{31}\text{NO}_2\text{S}$ (M^+ Cs^+) 554.1128, found 554.1142.

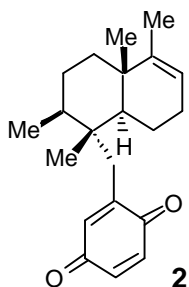
Avarol (1)



1

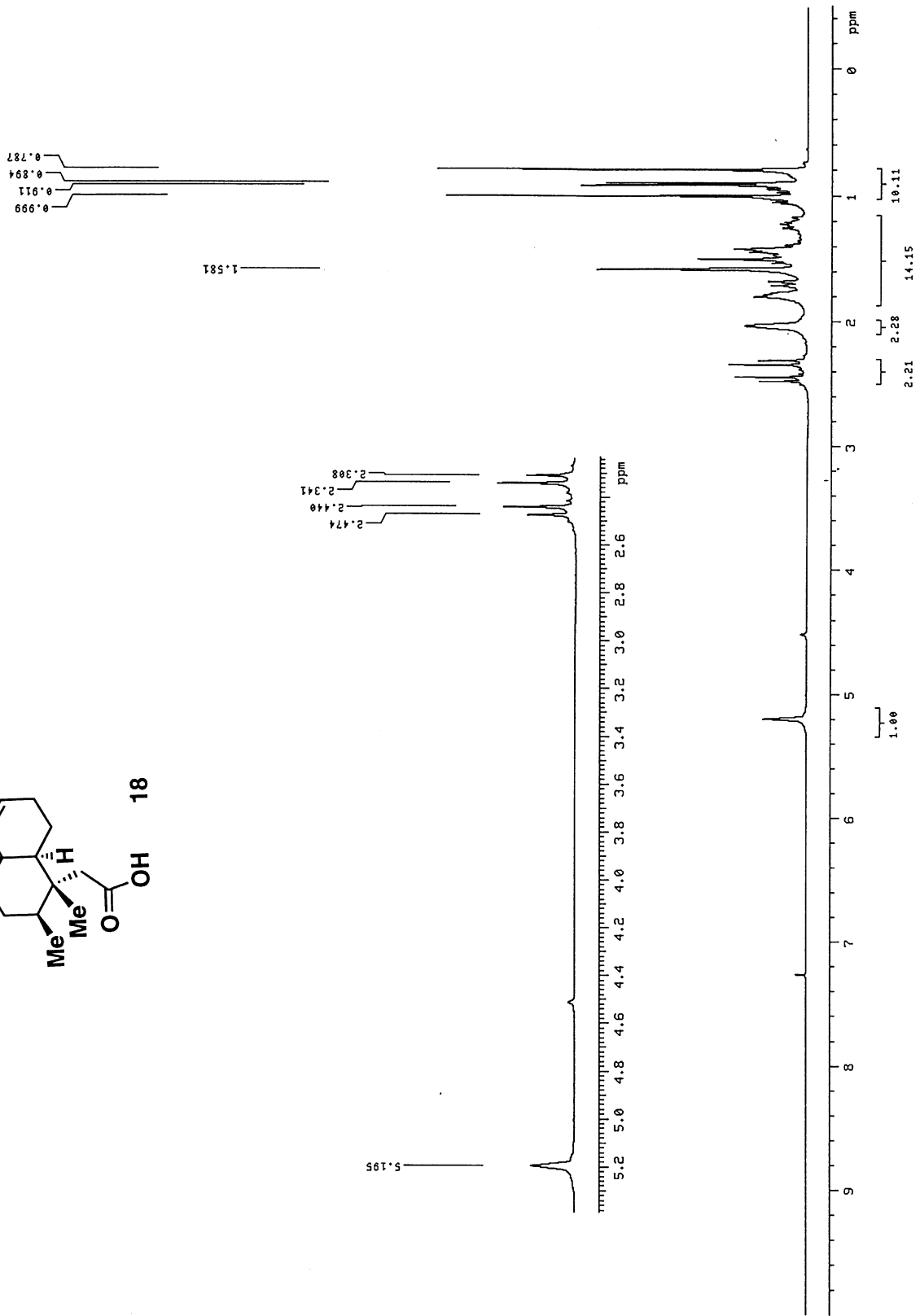
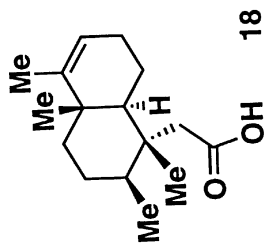
A solution of thioether **21** (13.0 mg, 31 μ mol) in dichloromethane (3 ml) was treated with excess of Raney[®] Nickel for 10 min. The reaction mixture was then filtered, the filtrate concentrated and the residue purified by a preparative thin layer chromatography plate (silica, 40% ether in hexanes) to produce avarol (**1**) (8.1 mg, 26 μ mol, 84%). **1**: light yellow liquid; $R_f = 0.5$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D : +10.2$ (c= 0.8, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.59 (m, 3H), 5.14 (bs, 1H), 2.66 (d, 1H, $J = 14.5$ Hz), 2.57 (d, 1H, $J = 14.5$ Hz), 2.10-2.0 (m, 4H), 1.6-1.2 (m, 11 H), 1.2 (s, 3H), 1.02 (d, 3H, $J = 6.8$ Hz), 0.86 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.7, 125.6, 120.5, 119.7, 116.2, 113.9, 110.0, 101.3, 45.8, 37.5, 36.0, 35.7, 30.2, 29.6, 27.6, 26.6, 20.0, 19.7, 18.0, 17.6, 17.4.

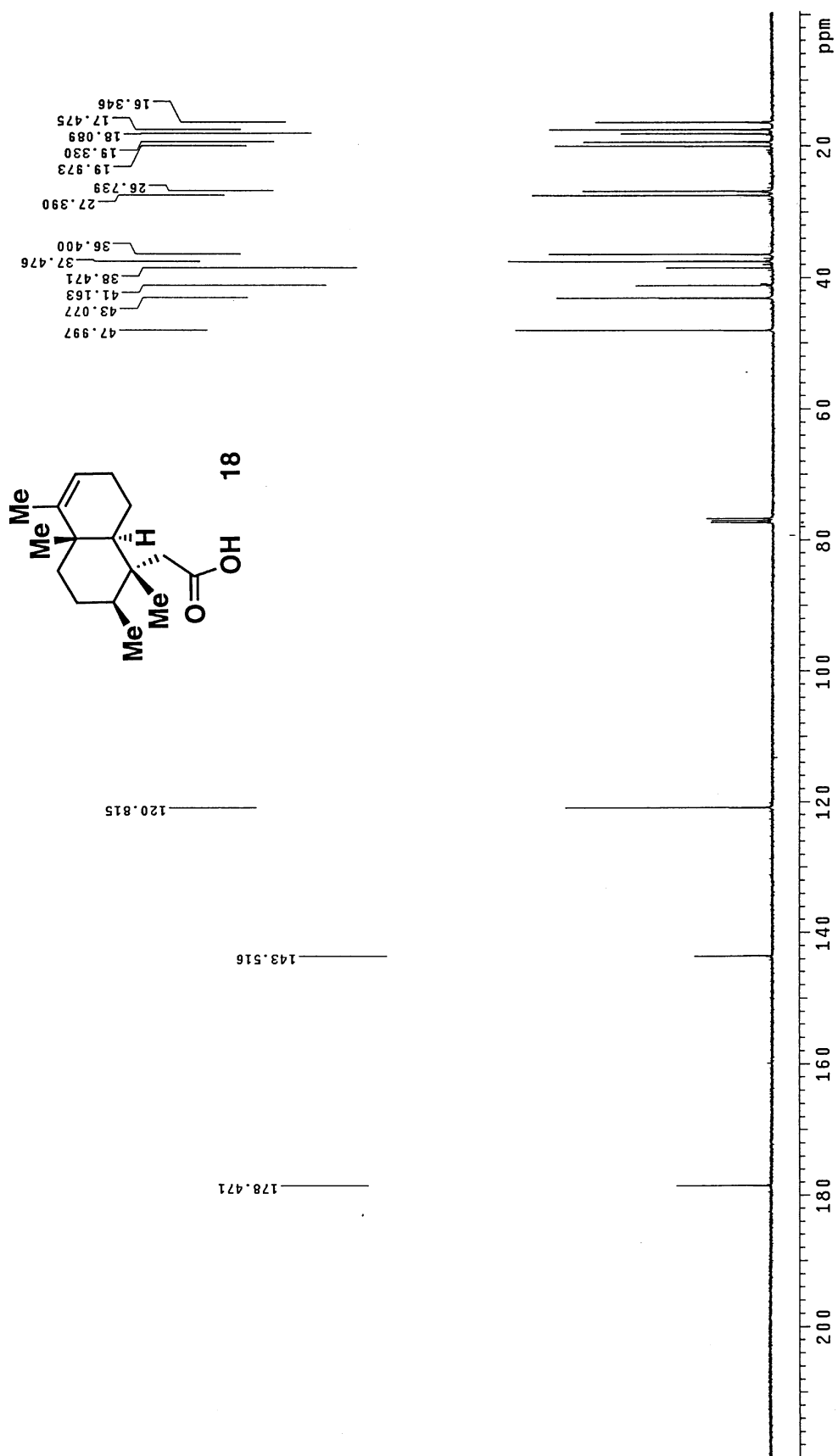
Avarone (2)

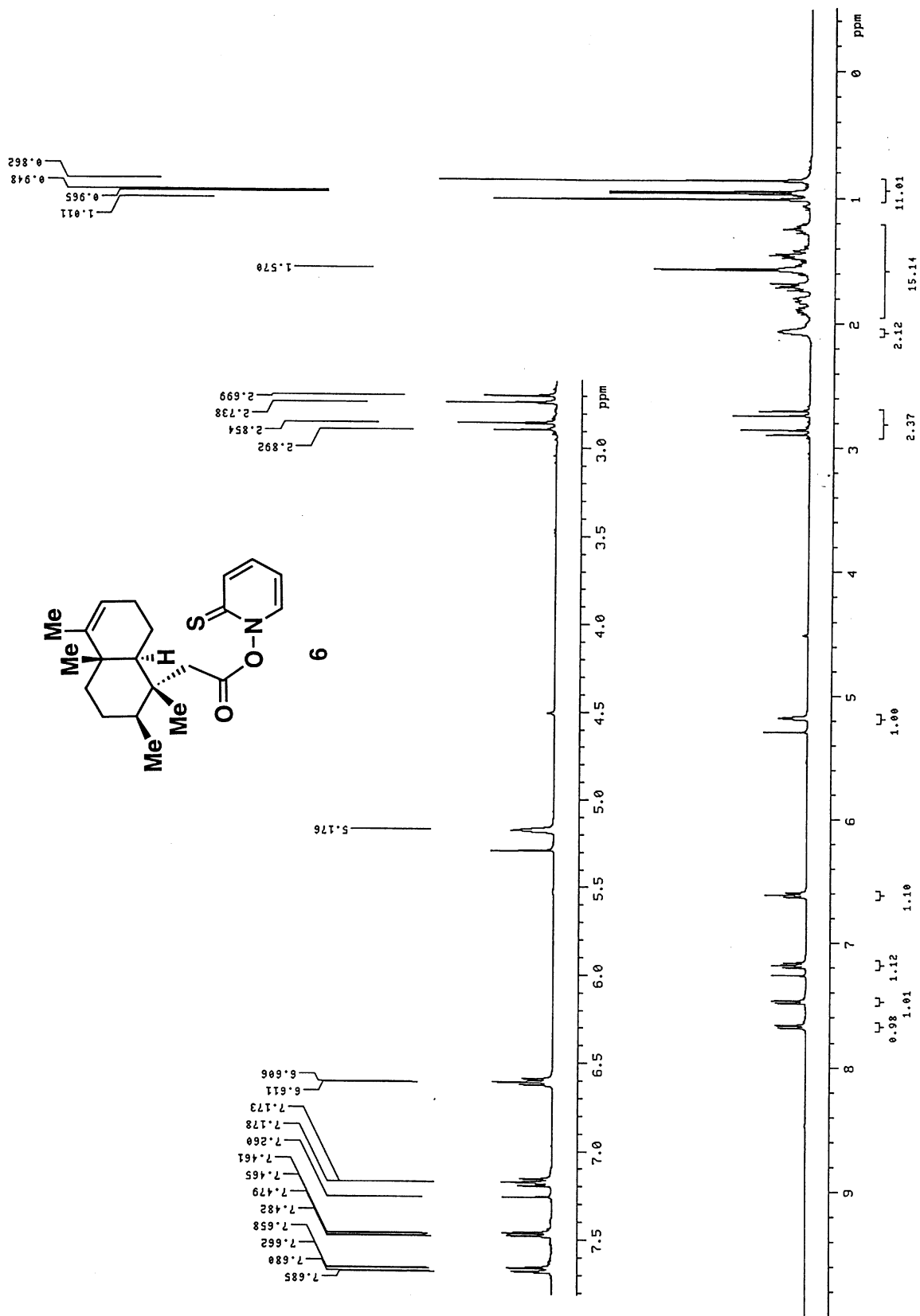


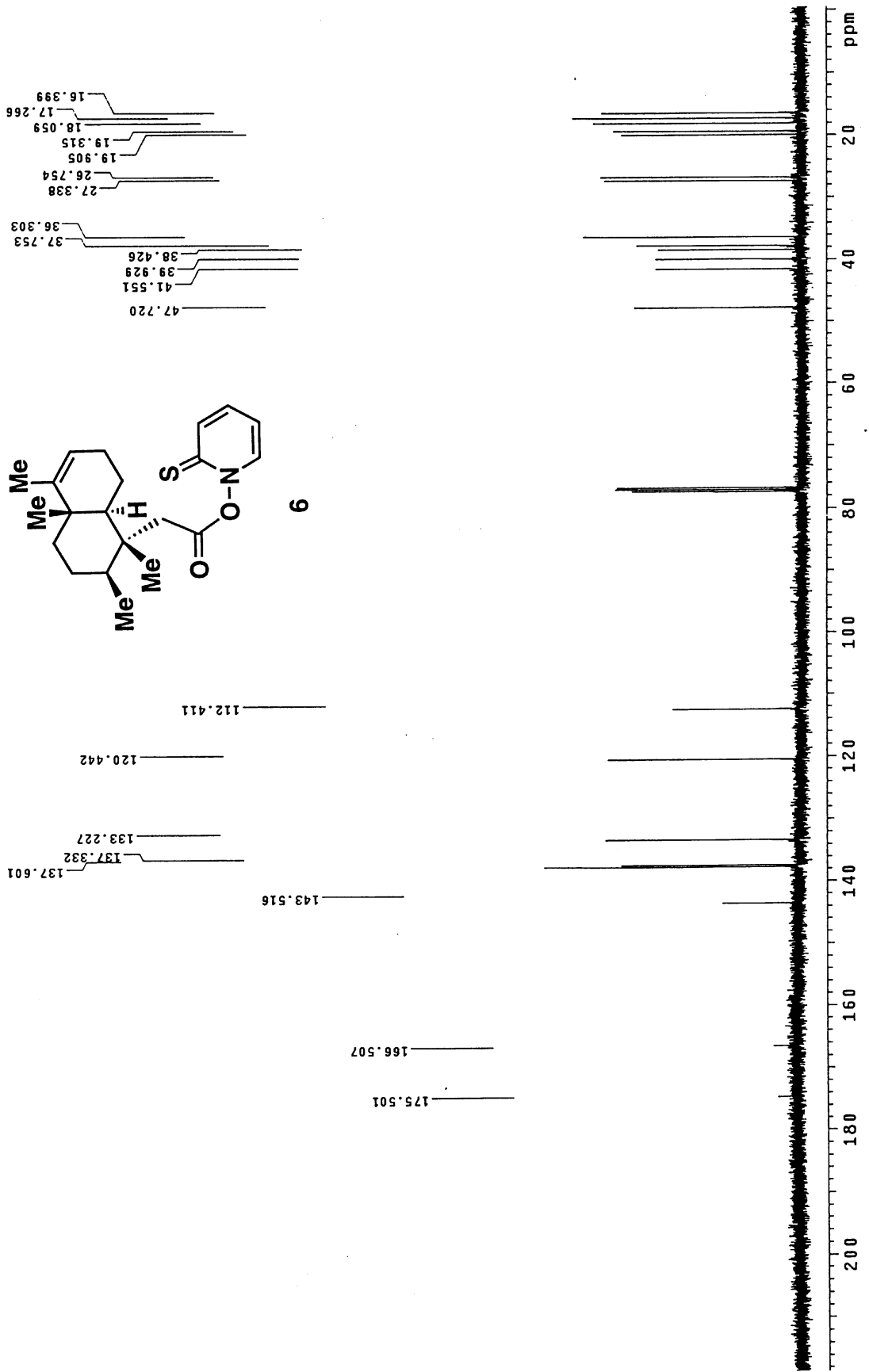
2

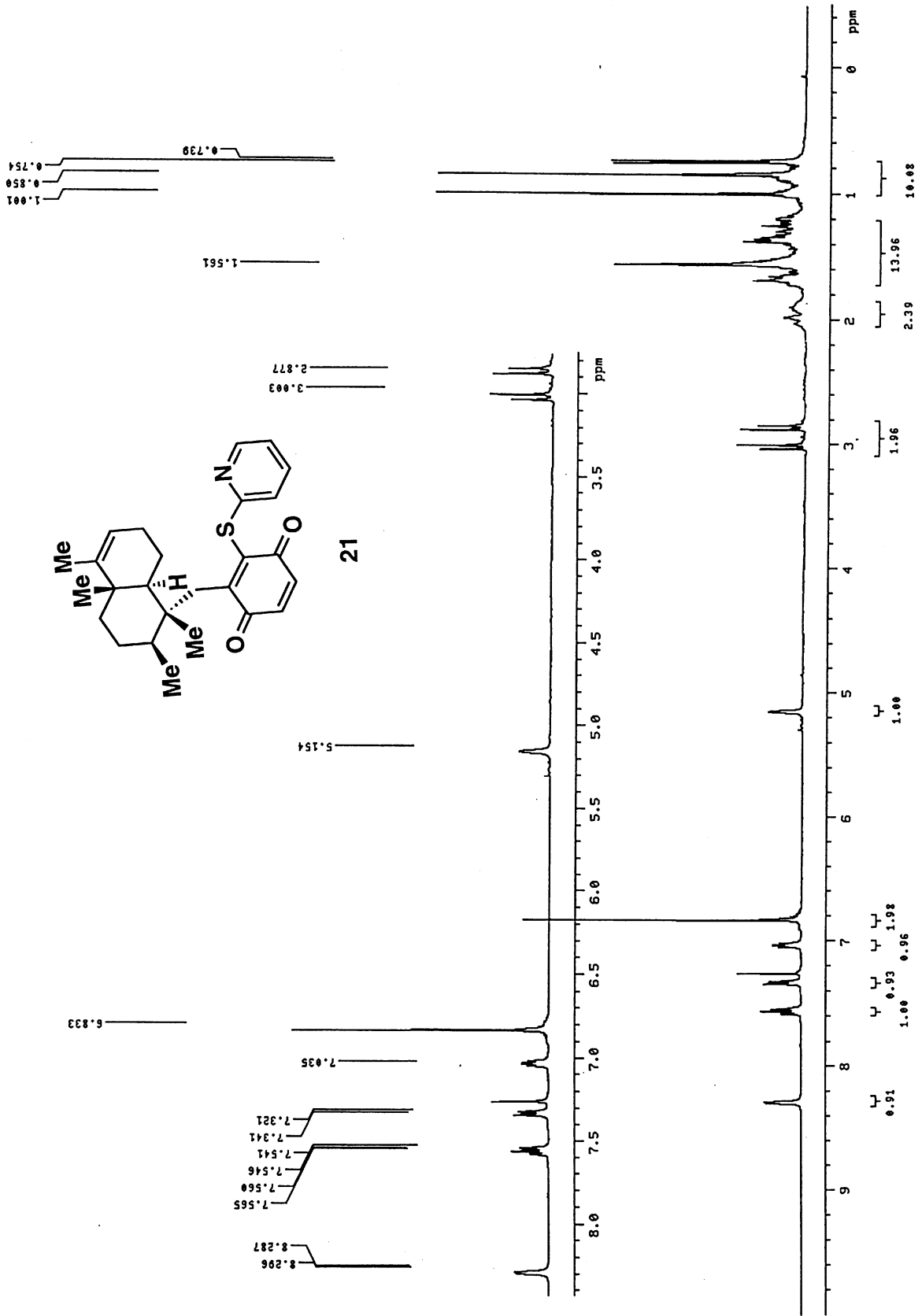
A solution of avarol (**1**) (5.2 mg, 17 μ mol) in ethyl ether (0.5 ml) was treated with manganese (IV) oxide (10 mg, 84 17 μ mol) for 10 min at 25 °C. The reaction mixture was filtered through cotton, the filtrate concentrated and the residue purified by a preparative thin layer chromatography plate (silica, 30% ether in hexanes) to produce avarone (**2**) (5.1 mg, 16.5 μ mol, 97%). **2**: purple liquid; $R_f = 0.85$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D : +13.1$ (c= 0.5, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.71 (m, 2H), 6.5 (s, 1H), 5.13 (bs, 1H), 2.64 (d, 1H, $J = 13.5$ Hz), 2.43 (d, 1H, $J = 13.5$ Hz), 2.10-2.0 (m, 2H), 1.82-1.78 (m, 2H), 1.6-1.2 (m, 9H), 1.0 (s, 3H), 0.93 (d, 3H, $J = 6.5$ Hz), 0.84 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 187.5, 187.4, 147.5, 144.1, 137.2, 136.2, 136.0, 120.7, 47.0, 42.6, 38.4, 36.9, 36.0, 35.3, 27.3, 26.3, 19.9, 19.2, 17.9, 17.7, 16.6.

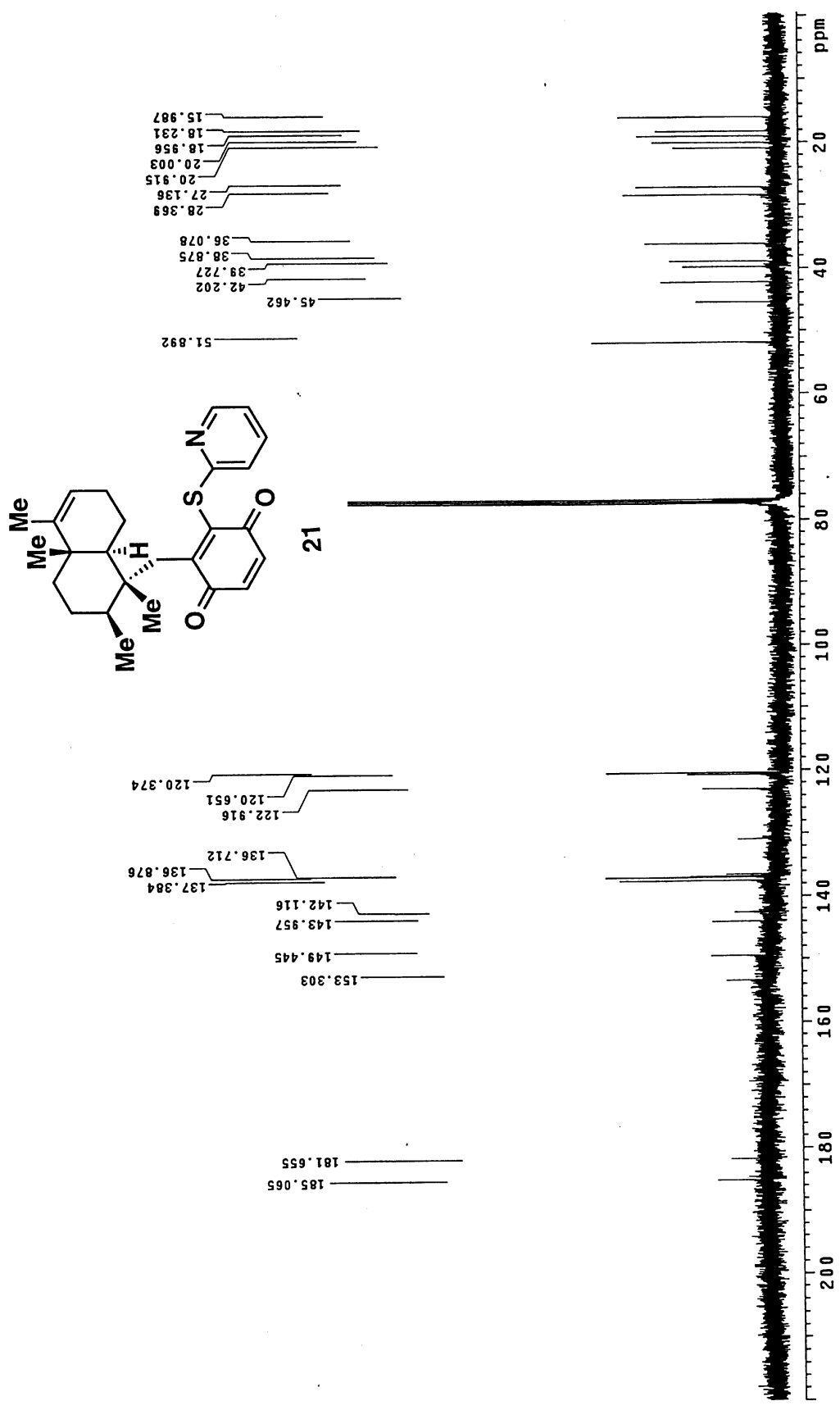


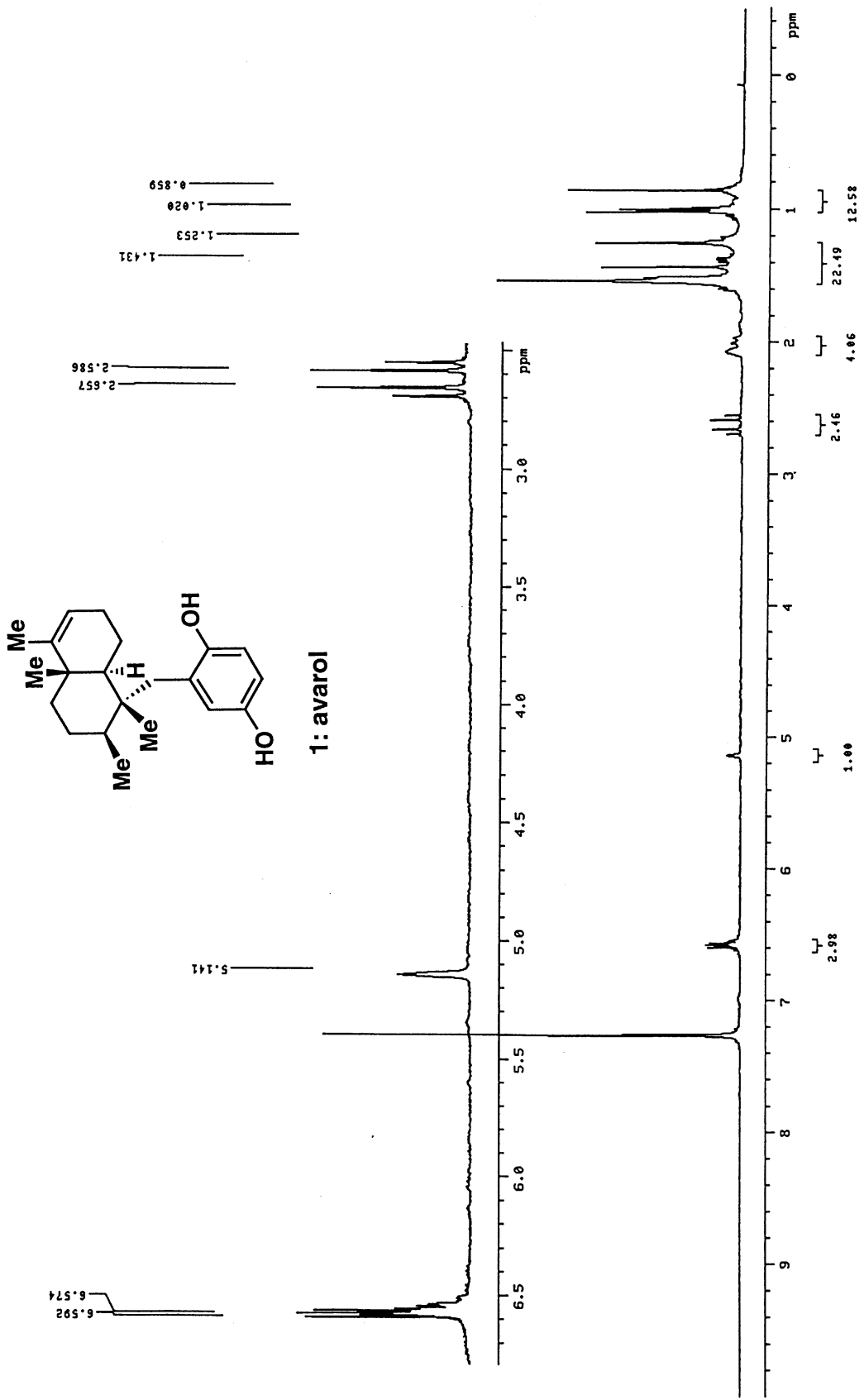


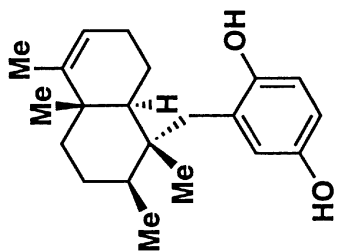












1: avarol

