Supporting Information

Asymmetric Syntheses of (-)-Mitorubrin and Related Azaphilone Natural Products

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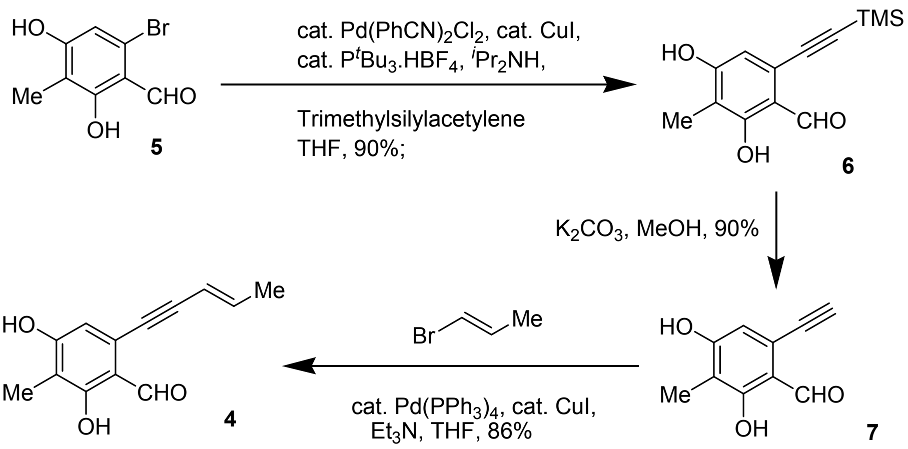
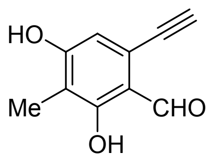
General Information: ^{1}H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 75.0 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0), acetone-d_6 (^{1}H, δ 2.05; ^{13}C, δ 207.6, 30.0), DMSO-d_6 (^{1}H, δ 2.50; ^{13}C, δ 39.51). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D^{22}$ (concentration in grams/100 mL solvent). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Preparative TLC plates were purchased from Silicycle (20X20 cm, thickness: 1000 μm). C18 cartridges were purchased from Waters (Sep-Pak® Vac 12cc, 2g). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. All other reagents were purchased from Sigma-Aldrich, Lancaster, Alfa Aesar, and Strem Chemicals. Methylene chloride, acetonitrile, methanol, and benzene were purified by passing through two packed columns of neutral alumina (Innovative Technology etc). All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. HPLC analysis was performed on an Agilent 1100 series HPLC (*Chiralcel OD*) using UV detection at 320 nm.

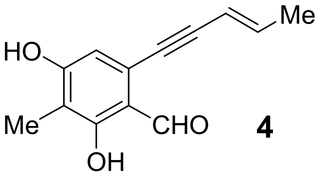




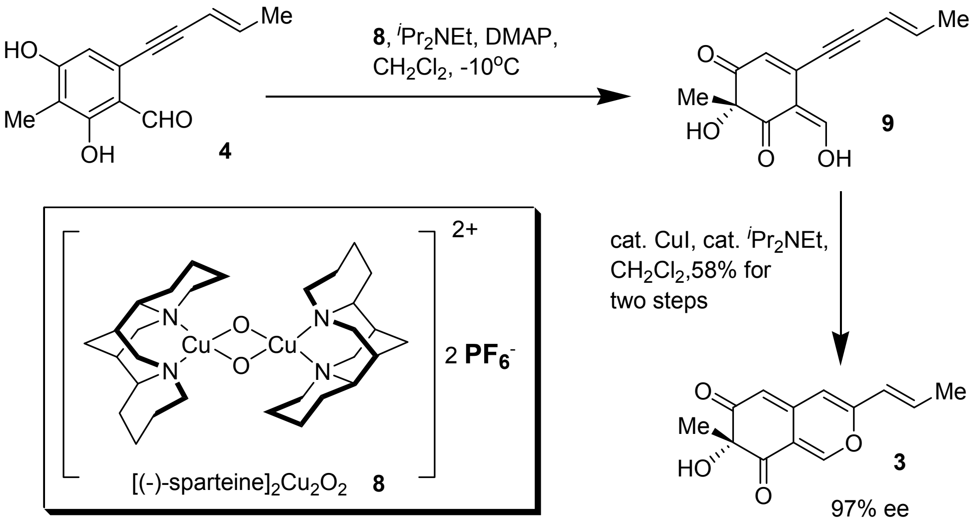
7

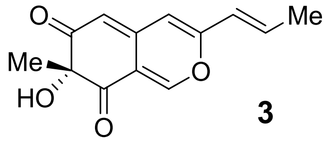
Alkynylbenzaldehyde 7 An oven-dried round-bottom flask containing a mixture of 2-bromo-4,6-dihydroxy-5-methylbenzaldehyde **5**[S1] (500 mg, 2.16 mmol), $Pd(PhCN)_2Cl_2$ (50.0 mg, 0.13 mmol), $[HP(^tBu)_3]BF_4$ (75.0 mg, 0.26 mmol), and CuI (17 mg, 0.09 mmol) was evacuated and refilled with argon. Anhydrous THF 4.0 mL, trimethylsilylacetylene (550 μL, 3.90 mmol) and diisopropylamine (485 μL, 3.46 mmol) were sequentially added under argon. The resulting mixture was stirred at room temperature under argon atmosphere until full disappearance of starting material **5** (TLC). The reaction mixture was diluted with water, carefully neutralized with 0.1 N aqueous HCl, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 16 : 1 to 10 : 1) provided 484 mg (90%) of TMS-alkynylbenzaldehyde **6** as a yellow solid which was used without further purification. To compound 6 (484 mg, 1.95 mmol), in 6.0 mL anhydrous methanol solution was added anhydrous K_2CO_3 (404 mg, 2.92 mmol) in one portion, the resulting mixture was stirred at room temperature until starting material **6** was totally consumed (TLC analysis). The reaction mixture was diluted with water, carefully neutralized with 1.0 N aqueous HCl, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 10 : 1 to 8 : 1) provided 309 mg (90%) of alkynylbenzaldehyde **7** as a yellow solid. mp 165°C (decomp.); ^{1}H NMR (400 MHz, acetone-d_6) δ 12.39 (1H, s), 10.20 (1H, s), 9.79 (1H, s), 6.73 (1H, s), 4.07 (1H, s), 2.07 (3H, s); ^{13}C NMR (75.0 MHz, acetone-d_6) δ 195.3, 164.0, 163.3, 125.9, 114.9, 114.0, 85.5, 79.5, 7.7; IR (thin film) 3283, 3152 (br), 2118, 1599, 1480, 1323, 1254, 1124, 844, 710 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{10}H_9O_3$ 177.0552, found 177.0523.

[S1] Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239.



Enyne-benzaldehyde 4 An oven-dried round-bottom flask containing a mixture of alkynylbenzaldehyde **7** (286 mg, 1.62 mmol), $Pd(PPh_3)_4$ (94 mg, 0.08 mmol), and CuI (15 mg, 0.08 mmol) was evacuated and refilled with argon. Anhydrous THF 3.0 mL, (*E*)-1-bromo-1-propene (176 μL, 2.04 mmol) and triethylamine (452 μL, 3.25 mmol) was sequentially added under argon. The resulting mixture was stirred at room temperature until complete conversion of **7** was observed (TLC analysis). The reaction mixture was diluted with water, carefully neutralized with 0.1 N aqueous HCl, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 10 : 1) provided 302 mg (86%) of enyne benzaldehyde **4** as a yellow solid. mp 195°C (decomp.); ^{1}H NMR (400 MHz, acetone-d_6) δ 12.40 (1H, s), 10.16 (1H, s), 9.69 (1H, s), 6.62 (1H, s), 6.37 (1H, dq, *J* = 16.0, 6.8 Hz), 5.83 (1H, dq, *J* = 16.0, 2.0 Hz), 2.04 (3H, s), 1.85 (3H, dd, *J* =6.8, 2.0 Hz); ^{13}C NMR (75.0 MHz, acetone-d_6) δ 195.5, 164.0, 163.4, 142.9, 127.5, 114.4, 113.2, 112.9, 111.1, 95.2, 83.6, 19.0, 7.7; IR (thin film) 3107 (br), 2196, 1598, 1453, 1248, 1115, 946, 837, 730 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{13}H_{13}O_3$ 217.0865, found 217.0866.



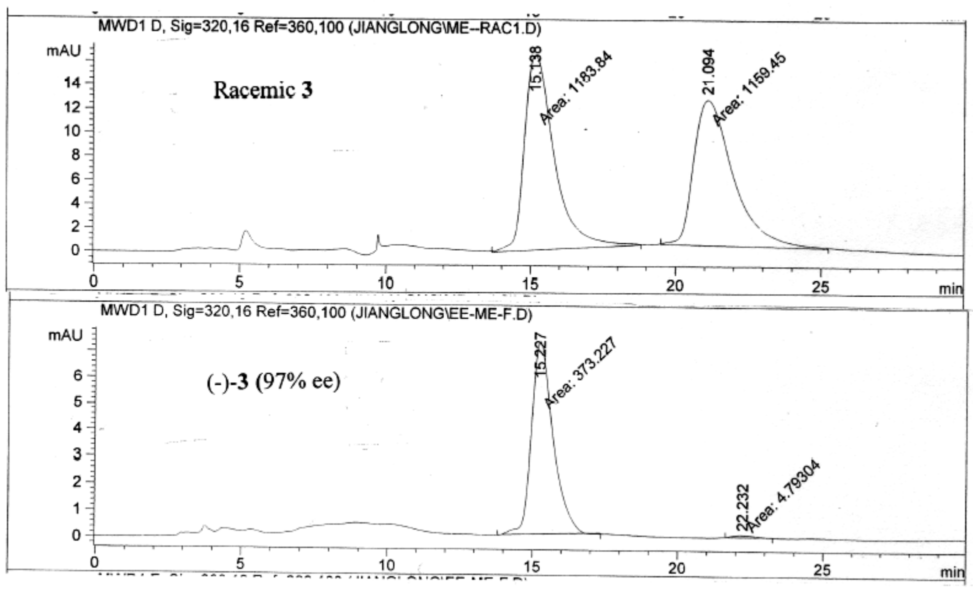


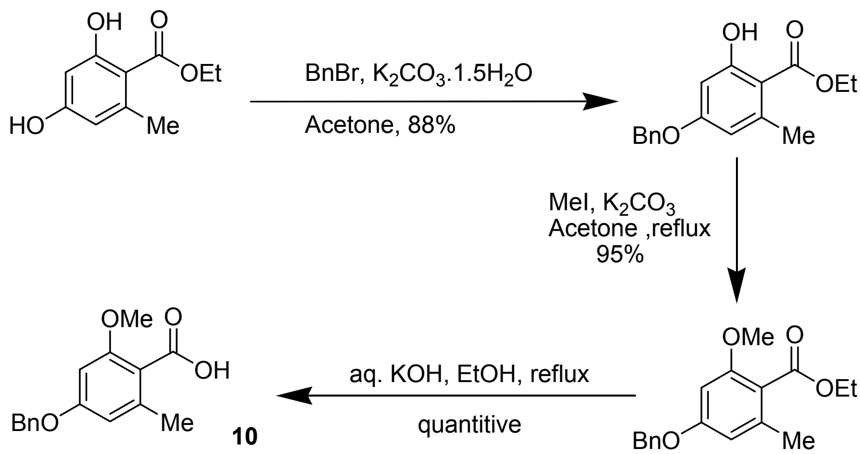
Azaphilone core 3 $[(-)\text{-sparteine}]_2Cu_2O_2$ complex **8** was prepared from $Cu(CH_3CN)_4PF_6$ (1010 mg, 2.71 mmol) and (-)-sparteine (646 μL, 2.81 mmol) in 8.0 mL anhydrous CH_2Cl_2 under an oxygen atmosphere at -78°C following our previously reported procedure.[S2] To complex **8** in CH_2Cl_2 at -78 °C was added dropwise a mixture of

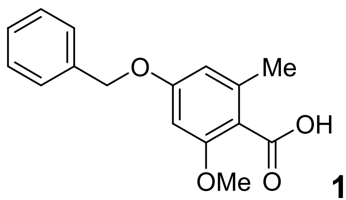
[S2] Zhu, J.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342.

enyne benzaldehyde **4** (217 mg, 1.0 mmol) and diisopropylethylamine (DIEA) (280 μL, 1.6 mmol) in 1.5 mL CH_2Cl_2. After 5 min, 4-dimethylaminopyridine (331 mg, 2.71 mmol) in 1.5 mL was added and the resulting reaction mixture was slowly warmed up and stirred at -10 ^oC for 30 h under an oxygen atmosphere. The reaction mixture was quenched at -10^oC with 20 mL of 10% sulfuric acid and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford 175 mg (75%) of vinylogous acid **9**, which was found to be unstable and therefore used immediately in the next step. To the crude vinylogous acid **9** (175 mg, 0.75 mmol) and CuI (36 mg, 0.19 mmol) in 4.0 mL anhydrous CH_2Cl_2 was added diisopropylethylamine (DIEA) (33 μL, 0.19 mmol). The resulting heterogeneous mixture was stirred at room temperature for 1 h before 4.0 mL 10% sulfuric acid was added. The resulting mixture was quickly extracted twice with EtOAc and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford 135 mg (77%, 58% for two steps) of mitorubrin core **3** as a yellow solid. mp 157-158 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, s), 6.56 (1H, dd, J =15.6, 6.8 Hz), 6.07 (1H, s), 5.97 (1H, dd, J =15.6, 1.2 Hz), 5.54 (1H, s), 3.89 (1H, broad), 1.90 (1H, dd, J =6.8, 1.2 Hz), 1.51 (1H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 196.1, 195.6, 155.8, 152.4, 144.0, 136.0, 122.3, 115.5, 108.1, 105.8, 83.4, 28.5, 18.6; IR (thin film) 3425 (br), 2924, 2854, 1716, 1659, 1443, 1170, 967 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{13}H_{12}O_4Na$ 255.0633, found 255.0613. The 97% e.e. of azaphilone core **3** was determined on an Agilent 1100 series HPLC (*Chiralcel OD*, 25% ^{i}PrOH in hexane, 1.0 mL/min) using UV detection at 320 nm. $[\alpha]_D^{22}$ = -88.0^o (c = 0.3, $CHCl_3$).

Enantiomeric excess determined by HPLC analysis
(25% iPrOH in hexanes, 1.0 mL/min, Chiral cel OD) with UV detection (320 nm).

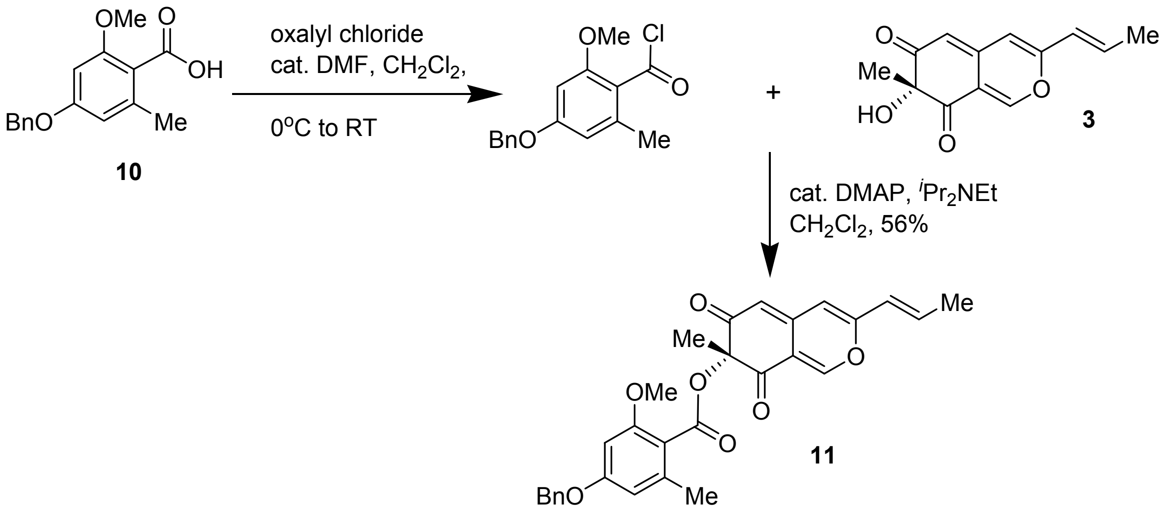


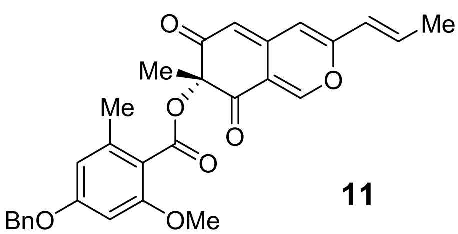




4-Benzyloxy-2-methoxy-6-methylbenzoic aicd 10 A mixture of commercially available ethyl 2,4-dihydroxy-6-methylbenzoate (5.0 g, 25.5 mmol), potassium carbonate sesquihydrate (6.35 g, 38.2 mmol), and benzyl bromide (3.18 mL, 26.8 mmol) in 70 mL distilled acetone was heated at reflux until for 24 hours. The mixture was cooled down, diluted with water, neutralized with 1.0 N aqueous HCl, and extracted three times with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1 to 15 : 1) provided 6.42 g (88%) of the corresponding 4-benzyloxy-2-hydroxy-6-methylbenzoate as a white solid which was used directly in the next step without further purification. A mixture of ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate (5.80 g, 20.2 mmol), anhydrous potassium carbonate (8.40 g, 60.8 mmol), and methyl iodide (3.78 mL, 60.8 mmol) in 50 mL distilled acetone was heated at reflux until complete conversion of the starting material was observed (TLC analysis). The mixture was cooled to rt, diluted with water, neutralized with 1.0 N aqueous HCl, and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 15 : 1 to 6 : 1) provided 5.78 g (95%) of the corresponding ethyl 4-benzyloxy-2-methoxy-6-methylbenzoate as a white solid which was used directly in the next step. A mixture of this ethyl 4-benzyloxy-2-methoxy-6-methylbenzoate (5.60 g, 18.6 mmol) and potassium hydroxide (4.18 g, 74.6 mmol) in 40 mL ethanol and 20 mL water was heated at reflux until complete conversion of the starting material was observed (TLC analysis). The mixture was cooled to room temperature, diluted with water, and extracted with diethyl ether. The water layer was separated, acidified with concentrated HCl and extracted with diethyl ether. The ether extracts were washed with brine and concentrated to afford 5.07 g (100%) of 4-benzyloxy-2-

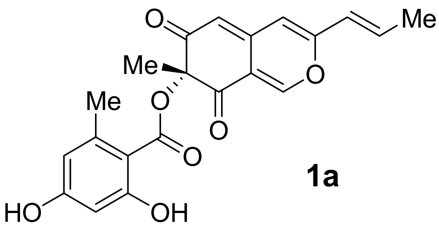
methoxy-6-methylbenzoic aicd **10** as a white solid which was sufficiently pure for characterization. mp 129-130°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42~7.32 (5H, m), 6.52 (1H, d, *J* = 2.0 Hz), 6.46 (1H, d, *J* = 2.0 Hz), 5.08 (2H, s), 3.92 (3H, s), 2.57 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.1, 161.7, 159.7, 143.3, 136.6, 129.1, 128.6, 127.9, 113.4, 109.8, 97.6, 70.5, 56.7, 22.5; IR (thin film) 3028, 2908, 1699, 1592, 1345, 1287, 738 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{16}H_{17}O_4$ 273.1127, found 273.1103.





Azaphilone 11 To 4-benzyloxy-2-methoxy-6-methylbenzoic aicd **10** (204 mg, 0.75 mmol) in 2.0 mL of anhydrous dichloromethane cooled to 0°C under argon were added freshly distilled oxalyl chloride (76 μL, 0.90 mmol) and one drop of anhydrous DMF. The reaction mixture was stirred for 15 min at 0°C and 1.5 h at rt. The reaction was recooled to 0°C and treated sequentially with diisopropylethylamine (313 μL, 1.80 mmol), azaphilone core **3** (116 mg, 0.50 mmol) in 3.0 mL dichloromethane, and 4-dimethylaminopyridine (6.1 mg, 0.05 mmol). The reaction mixture was slowly warmed to rt and stirred until full disappearance of **3** by TLC analysis. The reaction mixture was quenched with 1.0 N aqueous HCl and extracted with ethyl acetate. The organic layer was separated, sequentially washed twice with 1.0 N aqueous HCl, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc : HOAc = 15 : 1 : 1 to 15 : 5 : 1) provided 136 mg (56%) of azaphilone **11**. mp 208-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.45~7.28 (5H, m), 6.52 (1H, dd, *J* =15.6, 6.8 Hz), 6.38 (1H, d, *J* = 2.0 Hz), 6.36 (1H, d, *J* = 2.0 Hz), 6.07 (1H, s), 5.97 (1H, dd, *J* =6.8, 1.2 Hz), 5.61 (1H, s), 5.03 (2H, s), 3.78 (1H, s), 2.47 (3H, s), 1.90 (3H, dd, *J* =6.8, 1.2 Hz), 1.58 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.6, 193.0,

167.1, 161.4, 160.1, 155.7, 153.8, 143.0, 140.9, 136.9, 135.6, 129.0, 128.4, 127.9, 122.8, 115.4, 114.3, 108.9, 108.3, 97.6, 84.9, 70.4, 56.6, 22.8, 20.8, 18.9; IR (thin film) 2929, 1715, 1630, 1447, 1160, 1092, 752 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{29}H_{27}O_7$ 487.1757, found 487.1769. $[\alpha]_D^{22}$ = -146^o (c = 0.25, $CHCl_3$).



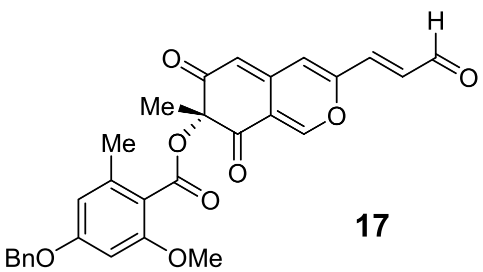
1a

(-)-Mitorubrin 1a To azaphilone **11** (20.0 mg, 0.041 mmol) in 2.0 mL dichloromethane cooled at -78^{o}C was added dropwise boron trichloride (250 μL, 1.0 M in CH_2Cl_2, 0.25 mmol). The reaction was warmed slowly and stirred at -20^{o}C for 2h. Water and ethyl acetate were sequentially added, and the resulting mixture was stirred at room temperature for 15 minutes before being extracted with ethyl acetate. The EtOAc extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by preparative TLC plate (Hexane : EtOAc = 2 : 1, with 2% HOAc) afforded 11 mg (70%) of the desired product (-)-mitorubrin **1a** as a yellow solid. mp 212-214 ^{o}C (decomp.) (lit.: 218 ^{o}C) [S3]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (1H, s), 10.31 (1H, s), 8.29 (1H, d, *J* = 0.8 Hz), 6.61 (1H, s), 6.55 (1H, dq, *J* =15.6, 6.8 Hz), 6.26 (1H, dq, partial overlapping, *J* =15.6, 1.2 Hz), 6.24 (1H, d, *J* =2.0 Hz), 6.15 (1H, d, *J* =2.0 Hz), 5.61 (1H, d, *J* = 0.8 Hz), 2.45 (3H, s), 1.90 (3H, dd, *J* =6.8, 1.2 Hz), 1.54 (3H, s); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 192.4, 191.2, 168.2, 162.8, 162.4, 157.6, 155.2, 143.3, 142.5, 135.3, 122.6, 114.3, 111.2, 108.5, 106.5, 104.8, 100.6, 85.1, 22.7, 22.1, 18.4; IR (thin film) 3233 (br), 1708, 1662, 1590, 1537, 1445, 1310, 1262, 1233, 1213, 1155, 1110 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{21}H_{19}O_7$ 383.1131, found 383.1144. $[\alpha]_D^{22}$ = -417^o (c = 0.25, dioxane). Natural (-)-mitorubrin: 1. $[\alpha]_D^{25}$ = -405^o (c = 1.02, dioxane);[S3] 2. $[\alpha]_D^{20}$ = -422^o (c = 0.3, solvent not indicated).[S4] Natural (+)-mitorubrin: $[\alpha]_D^{25}$ = +586^o (c = 0.5, dioxane);[S5]

[S3] Buchi, G.; White, J. D.; Wogan, G. N. *J. Am. Chem. Soc.* **1965**, *87*, 3484.
[S4] Suzuki, S.; Hosoe, T.; Nozawa, K.; Yaguchi, T.; Udagawa, S.; Kawai, K. *J. Nat. Prod.* **1999**, *62*, 1328.
[S5] Steglich, W.; Klaar, M.; Furtner, W. *Phytochemistry* **1974**, *13*, 2874.

^{1}H NMR comparison of natural and synthetic (-)-mitorubrin **1a**

Chemical shift (ppm) (integration, multiplicity, coupling constants *(J,* Hz))			
Natural (not indicated)[S3]	Natural (60 MHz, $CDCl_3$)[S6]	**Synthetic (400 MHz, d$_6$-DMSO)**	Natural (+)-mitorubrin **1a** (d$_6$-acetone)[S5]
10.4 (1H, s)	10.4 (1H, s)	10.33 (1H, s)	10.70 (1H, s)
10.3 (1H, s)	10.3 (1H, s)	10.31 (1H, s)	9.06 (1H, s)
8.25 (1H, d, 1)	8.25 (1H, d, 0.7)	8.29 (1H, d, 0.8)	8.05 (1H, d, 1.5)
6.57 (1H, s)	not indicated	6.61 (1H, s)	6.45 (1H, s)
6.55(1H, dd, 16, 6)	6.55 (1H, m, 16, 6)	6.55 (1H, dq, 15.6, 6.8)	6.58 (1H, dq, 16, 6)
6.21 (1H, d, 16)	6.21 (1H, m, 16)	6.26 (1H, dq, 15.6, 1.2)	6.22 (1H, dq, 16, 1.2)
6.28 (1H, d, 2)	6.28 (1H, d, 2)	6.24 (1H, d, 2.0)	6.33 (1H, dq, 2.0, 0.6)
6.19 (1H, d, 2)	6.18(1H, d, 2)	6.15 (1H, d, 2.0),	6.23 (1H, d, 2.0)
5.61 (1H, d, 1)	5.61 (1H, d, 0.7)	5.61 (1H, d, 0.8)	5.59 (1H, d, 1.2)
2.48 (3H, s)	2.60 (3H, s)	2.45 (3H, s)	2.61 (3H, s)
1.89 (3H, d, 6)	1.89 (3H, d, 6)	1.90 (3H, dd, 6.8, 1.2)	1.92 (3H, dd, 6, 1.2)
1.67 (3H, s)	1.67 (3H, s)	1.54 (3H, s)	1.64 (3H, s)

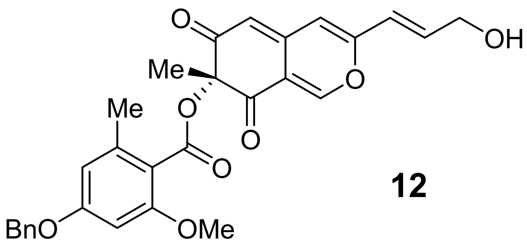


17

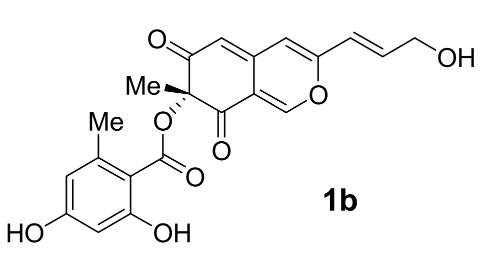
Aldehyde 17 To azaphilone **11** (80.0 mg, 0.16 mmol) and acrolein (33 μL, 0.49 mmol) in 2.5 mL freshly distilled and degassed CH_2Cl_2 was added a solution of Hoveyda-Grubbs 2nd generation catalyst (11.0 mg, 0.016 mmol, 0.1 equiv.) in 0.5 mL freshly distilled and degassed CH_2Cl_2. The reaction was then heated at reflux under an argon atmosphere. After 12 h, a solution of acrolein (33 μL, 0.49 mmol) and Hoveyda-Grubbs 2nd generation catalyst (11.0 mg, 0.016 mmol, 0.1 equiv) in 0.5 mL degassed freshly distilled CH_2Cl_2 was added into the reaction mixture at reflux. The reaction mixture was further refluxed for additional 12 h before being concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 1 : 1 to 1 : 2) provided 62 mg (76%) of aldehyde **17**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, d, *J* = 7.6 Hz), 7.92 (1H, s), 7.42~7.28 (5H, m), 6.93 (1H, d, *J* =

[S6] Locci, R.; Merlini, L.; Nasini, G.; Locci, J. R. *Giorn. Microbio.* **1967**, *15*, 93.

16.0 Hz), 6.72 (1H, dd, J = 16.0 Hz, 7.6 Hz), 6.56 (1H, s), 6.38 (1H, d, J = 2.0 Hz), 6.36 (1H, d, J = 2.0 Hz), 5.77 (1H, s), 5.04 (2H, s), 3.79 (3H, s), 2.46 (3H, s), 1.59 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 192.8, 192.3, 191.7, 166.8, 161.2, 159.8, 153.2, 152.5, 140.6, 140.3, 139.0, 136.5, 132.1, 128.6, 128.1, 127.5, 117.2, 115.0, 113.5, 111.3, 108.0, 97.3, 84.5, 70.0, 56.2, 22.1, 20.4; IR (thin film) 2929, 1683, 1620, 1454, 1333, 1270, 1160, 1115, 751 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{29}H_{24}O_8Na$ 523.1369, found 523.1426. $[\alpha]_D^{22}$ = -149^o (c = 0.30, $CHCl_3$).



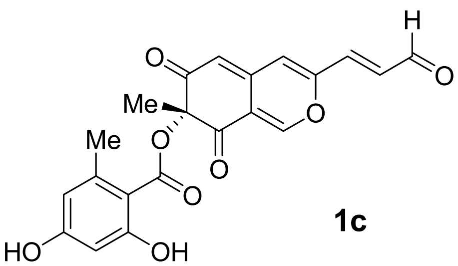
Allylic alcohol 12 To a solution of aldehyde **17** (50 mg, 0.10 mmol) in 2.5 mL dry dichloromethane cooled at -78^{o}C was added boron trifluoride diethyl etherate (38 μL, 0.30 mmol), then the mixture was stirred at that temperature for 30 minutes. DIBAL-H (110 μL, 1.0 M in hexanes, 0.11 mmol) was then added dropwise into the cold mixture and the reaction was stirred at -78^{o}C for additional 30 minutes before being quenched with 1.0 N aqueous HCl. The resulting mixture was diluted with ethyl acetate, slowly warmed up to room temperature and extracted with ethyl acetate. The EtOAc extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by preparative TLC (Hexane : EtOAc = 1 : 3, with 2% HOAc) afforded 33 mg (66%) of allylic alcohol **12**. ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (1H, s), 7.41~7.28 (5H, m), 6.60 (1H, dt, J = 15.6 Hz, 4.0 Hz), 6.39 (1H, d, J = 2.0 Hz), 6.36 (1H, d, J = 2.0 Hz), 6.28 (1H, d, J = 15.6 Hz), 6.17 (1H, s), 5.64 (1H, s), 5.04 (2H, s), 4.37 (2H, m), 3.79 (3H, s), 2.47 (3H, s), 1.58 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.1, 192.7, 166.8, 161.1, 159.7, 155.0, 153.5, 142.4, 140.6, 137.6, 136.5, 128.6, 128.1, 127.5, 120.0, 115.0, 113.7, 110.0, 108.4, 108.0, 97.3, 84.6, 70.0, 62.1, 56.2, 22.4, 20.4; IR (thin film) 3413 (br), 2931, 1713, 1609, 1455, 1331, 1271, 1160, 1092, 753 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{29}H_{27}O_8$ 503.1706, found 503.1694. $[\alpha]_D^{22}$ = -136^o (c = 0.30, $CHCl_3$).



(-)-Mitorubrinol 1b To allylic alcohol **12** (26 mg, 0.052 mmol) in 2.0 mL dichloromethane cooled at -78^{o}C was added dropwise boron trichloride (310 μL, 1.0 M in CH_2Cl_2, 0.31 mmol). The reaction was slowly warmed and stirred at -20^{o}C for 2h. Water and ethyl acetate were sequentially added, and the resulting mixture was stirred at room temperature for 15 minutes before being extracted with ethyl acetate. The EtOAc extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by preparative TLC (Hexane : EtOAc = 1 : 4, with 2% HOAc) afforded 15 mg (72%) of the desired product (-)-mitorubrinol **1b**. mp 215-216 ^{o}C (decomp.) (lit.: 219-221 ^{o}C)[S3]; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.75 (1H, s), 9.24 (1H, s), 8.14 (1H, s), 6.73 (1H, dt, *J* = 15.6 Hz, 4.0 Hz), 6.60 (1H, s), 6.47 (1H, dt, *J* = 15.6 Hz, 2.0 Hz), 6.35 (1H, d, *J* = 2.0 Hz), 6.23 (1H, d, *J* = 2.0 Hz), 5.62 (1H, s), 4.34 (2H, br), 4.25 (1H, m), 2.60 (3H, s), 1.66 (3H, s); ^{13}C NMR (75.0 MHz, acetone-d_6) δ 193.3, 192.2, 170.7, 166.2, 164.0, 156.7, 155.3, 145.0, 144.1, 140.4, 120.3, 115.9, 112.8, 110.4, 108.3, 105.3, 101.9, 86.8, 62.2, 24.1, 22.9; IR (thin film) 3239 (br), 2928, 1711, 1620, 1451, 1324, 1265, 1169, 1106 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{21}H_{19}O_8$ 399.1080, found 399.1082. $[\alpha]_D^{22}$ = -408^{o} (c = 0.30, dioxane). Natural (-)-mitorubrinol: 1. $[\alpha]_D^{25}$ = -375^{o} (c = 1.70, dioxane);[S3] 2. $[\alpha]_D^{20}$ = -455^{o} (c = 0.2, solvent not indicated).[S4]

^{1}H NMR comparison of natural and synthetic (-)-mitorubrinol **1b**

Chemical shift (ppm) (integration, multiplicity, coupling constants *(J,* Hz))	
Natural (d_6-DMSO)[S3]	**Synthetic (400 MHz, d_6-acetone)**
10.3 (1H, s)	10.75 (1H, s)
10.2 (1H, s)	9.24 (1H, s)
8.27 (1H, d, *J* =1 Hz)	8.14 (1H, s)
6.70(1H, d, *J* =16 Hz)	6.73 (1H, dt, *J* = 15.6 Hz, 4.0 Hz)
not indicated	6.60 (1H, s)
6.35 (1H, d, *J* =16 Hz)	6.47 (1H, dt, *J* = 15.6 Hz, 2.0 Hz)
6.27 (1H, *J* =d, 2 Hz)	6.35 (1H, d, *J* = 2.0 Hz)
6.18 (1H, *J* =d, 2 Hz)	6.23 (1H, d, *J* = 2.0 Hz)
5.62 (1H, *J* =d, 1 Hz)	5.62 (1H, s)
4.20 (2H, m)	4.34 (2H, br)
5.1 (1H, br, OH)	4.25 (1H, m, OH)
2.47 (3H, s)	2.60 (3H, s)
1.58 (3H, s)	1.66 (3H, s)

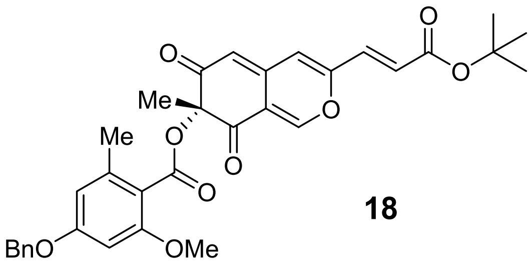


1c

(-)-Mitorubrinal 1c To (-)-mitorubrinol **1b** (10.0 mg, 0.025 mmol) in 2.5 mL distilled acetone was added freshly activated manganese dioxide (45 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 25 minutes before being filtered through a pad of Celite®. The Celite layer was washed with acetone and the combined organic elutes were concentrated and subjected to purification by preparative TLC (CH_2Cl_2 : EtOAc = 1 : 1) to afford 4.6 mg (46%) of (-)-mitorubrinal **1c**. mp 190-192 °C (decomp.) (lit.: 188.5-191 °C, decomp.)[S4]; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.74 (1H, s), 9.79 (1H, d, *J* = 7.6 Hz), 9.32 (1H, br), 8.17 (1H, s), 7.44 (1H, d, *J* = 15.6 Hz), 7.11 (1H, s), 6.68 (1H, dd, *J* = 15.6 Hz, 7.6 Hz), 6.36 (1H, d, *J* = 2.0 Hz), 6.23 (1H, d, *J* = 2.0 Hz), 5.80 (1H, s), 2.61 (3H, s), 1.68 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 193.5, 192.8, 192.6, 170.8, 166.4, 164.2, 155.3, 154.2, 145.0, 142.6, 141.0, 132.9, 118.1, 115.8, 112.8, 110.9, 105.0, 101.8, 86.9, 24.2, 22.6; IR (thin film) 3195 (br), 2929, 1683, 1619, 1448, 1325, 1266, 1113, 970 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{21}H_{16}O_8Na$ 419.0743, found 419.0767. $[\alpha]_D^{22}$ = -510° (c = 0.30, dioxane). Natural (-)-mitorubrinal: $[\alpha]_D^{20}$ = -541° (c = 0.16, solvent not indicated).[S4]

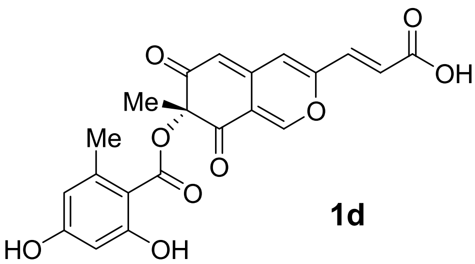
NMR (in d_6-acetone) comparison of natural [S4] and synthetic (-)-mitorubrinal **1c**

^{1}H NMR (Hz)		^{13}C NMR (Hz)	
Natural (400 MHz) [S4]	**Synthetic (400 MHz)**	Natural (90 MHz) [S4]	**Synthetic (75 MHz)**
10.63 (1H, s)	10.74 (1H, s)	193.2	193.5
9.66 (1H, d, *J* = 7.6 Hz)	9.79 (1H, d, *J* =7.6 Hz)	192.5	192.8
9.16 (1H, br)	9.32 (1H, br)	192.3	192.6
8.04 (1H, s)	8.17 (1H, s)	170.6	170.8
7.30 (1H, d, *J* = 15.6 Hz)	7.44 (1H, d, *J* =15.6 Hz)	166.2	166.4
6.98 (1H, s)	7.11 (1H, s)	163.9	164.2
6.56 (1H, dd, *J* = 15.6, 7.6 Hz)	6.68 (1H, dd, *J* = 15.6, 7.6 Hz)	155.0	155.3
6.23 (1H, d, *J* = 2.3 Hz)	6.36 (1H, d, *J* = 2.0 Hz)	153.9	154.2
6.10 (1H, d, *J* = 2.3 Hz)	6.23 (1H, d, *J* = 2.0 Hz)	144.8	145.0
5.67 (1H, d, *J* = 1 Hz)	5.80 (1H, s)	142.3	142.6
2.49 (3H, s)	2.61 (3H, s)	140.8	141.0
1.61 (3H, s)	1.68 (3H, s)	132.6	132.9
		117.9	118.1
		115.6	115.8
		112.6	112.8
		110.7	110.9
		104.7	105.0
		101.6	101.8
		86.6	86.9
		24.9	24.2
		22.4	22.6



18

***tert*-Butyl ester 18** To a mixture of azaphilone **11** (20 mg, 0.041 mmol) and *tert*-butyl acrylate (24 μL, 0.16 mmol) in 1.5 mL freshly distilled and degassed CH_2Cl_2 was added a solution of ((N,N'-mesityl)imidazolidin-2-yl)(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Grubbs 2nd Generation catalyst, , 7.0 mg, 0.008 mmol) in 0.5 mL freshly distilled and degassed CH_2Cl_2. The reaction mixture was heated at reflux until full disappearance of starting material **11** by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (hexane : EtOAc = 10 : 1 to 2 : 1) to afford 21 mg (90%) of *tert*-butyl ester **18**. ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (1H, s), 7.42~7.28 (5H, m), 7.01 (1H, d, J = 15.2 Hz), 6.45 (1H, d, J = 15.2 Hz), 6.43 (1H, s), 6.38~6.36 (2H, m), 5.72 (1H, s), 5.03 (2H, s), 3.78 (3H, s), 2.46 (3H, s), 1.58 (3H, s), 1.50 (9H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.1, 167.2, 164.9, 161.5, 160.1, 153.7, 153.4, 141.3, 141.0, 136.9, 132.7, 129.0, 128.5, 127.9, 126.9, 115.7, 115.4, 114.0, 110.8, 108.4, 97.7, 84.9, 82.2, 70.4, 56.6, 28.4, 22.6, 20.8; IR (thin film) 2929, 1711, 1630, 1452, 1316, 1157, 697, 752 cm^{-1}; ESIHRMS $[M+H]^+$ calculated for $C_{33}H_{33}O_9$ 573.2125, found 573.2181. $[\alpha]_D^{22}$ = -140^o (c = 0.30, $CHCl_3$).



1d

(-)-Mitorubrinic acid 1d To *tert*-butyl ester **18** (15 mg, 0.026 mmol) in 1.0 mL dichloromethane cooled at -78^{o}C was added dropwise boron trichloride (160 μL, 1.0 M in CH_2Cl_2, 0.16 mmol). The reaction was slowly warmed and stirred at -20^{o}C for 2h. Water and ethyl acetate were sequentially added, and the resulting mixture was stirred at room temperature for 15 minutes before being extracted with ethyl acetate. The EtOAc extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by preparative TLC (Hexane : EtOAc = 1 : 4, with 4% AcOH) followed by a C18 cartridge (10-30% CH_3CN in H_2O) afforded 8.8 mg (82%) of the desired product (-)-mitorubrinic acid **1d** as a yellow solid. mp 219-221 ^{o}C (decomp.) (lit.: 160-165 ^{o}C[S6]; 222-225 ^{o}C;[S7] (+)-mitorubrinic acid: 225-227 ^{o}C, decomp.[S6]); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.75 (1H, s), 8.17 (1H, s), 7.33 (1H, d, J = 16.0 Hz), 7.03 (1H, s), 6.54 (1H, d, J = 16.0 Hz), 6.37 (1H, d, J = 2.0 Hz), 6.24 (1H, d, J = 2.0 Hz), 5.76 (1H, s), 2.61 (3H, s), 1.68 (3H, s); ^{13}C NMR (75.0 MHz, acetone-d_6) δ 196.2, 195.8, 174.0, 169.9, 169.6, 167.5, 158.5,

[S7] Natsume, M.; Takahashi, Y. Marumo, S. *Agric. Biol. Chem.* **1985**, *49*, 2517.

157.4, 148.3, 146.1, 138.3, 128.5, 120.1, 119.1, 116.1, 113.7, 109.3, 105.1, 90.1, 27.4, 25.9; IR (thin film) 3191 (br), 1710, 1621, 1324, 1265, 1171, 11083, 971 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{21}H_{16}O_9Na$ 435.0692, found 435.0687. $[\alpha]_D^{22}$ = -428^o (c = 0.30, EtOH). Natural (-)-mitorubrinic acid: 1. $[\alpha]_D^{20}$ = -426^o (c = 0.112, solvent not indicated);[S4] 2. $[\alpha]_D^{20}$ = -465^o (c = 0.112, EtOH);[S6] 3. $[\alpha]_D^{22}$ = -450^o (c = 0.025, EtOH).[S7]

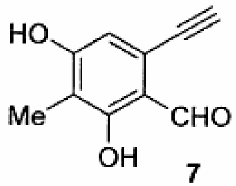
^{1}H NMR (in d_6-acetone) comparison of natural and synthetic (-)-mitorubrinic acid **1d**

Chemical shift (ppm) (integration, multiplicity, coupling constants *(J,* Hz))		
Natural (60 MHz)[S6]	Synthetic sample by Pettus and co-workers (400 MHz)[S8]	**Synthetic (400 MHz)**
not indicated	10.76 (1H, s)	10.75 (1H, s)
8.16 (1H, d, *J* = 0.7 Hz)	8.17 (1H, s)	8.17 (1H, s)
7.30 (1H, d, *J* = 16.0 Hz)	7.34 (1H, d, *J* = 15.9 Hz)	7.33 (1H, d, *J* = 16.0 Hz)
5.1-6.0 (3H, broad)	7.04 (1H, s)	7.03 (1H, s)
6.53 (1H, d, *J* = 16.0 Hz)	6.54 (1H, d, *J* = 15.9 Hz)	6.54 (1H, d, *J* = 16.0 Hz)
6.36 (1H, d, *J* = 2.0 Hz)	6.36 (1H, s)	6.37 (1H, d, *J* = 2.0 Hz)
6.23 (1H, d, *J* = 2.0 Hz)	6.23 (1H, s)	6.24 (1H, d, *J* = 2.0 Hz)
5.82 (1H, d, *J* = 0.7 Hz)	5.76 (1H, s)	5.76 (1H, s)
	5.63 (1H, s, OH)	
2.67 (3H, s)	2.61 (3H, s)	2.61 (3H, s)
1.68 (3H, s)	1.68 (3H, s)	1.68 (3H, s)

TLC comparison of natural and synthetic (-)-mitorubrinic acid **1d**

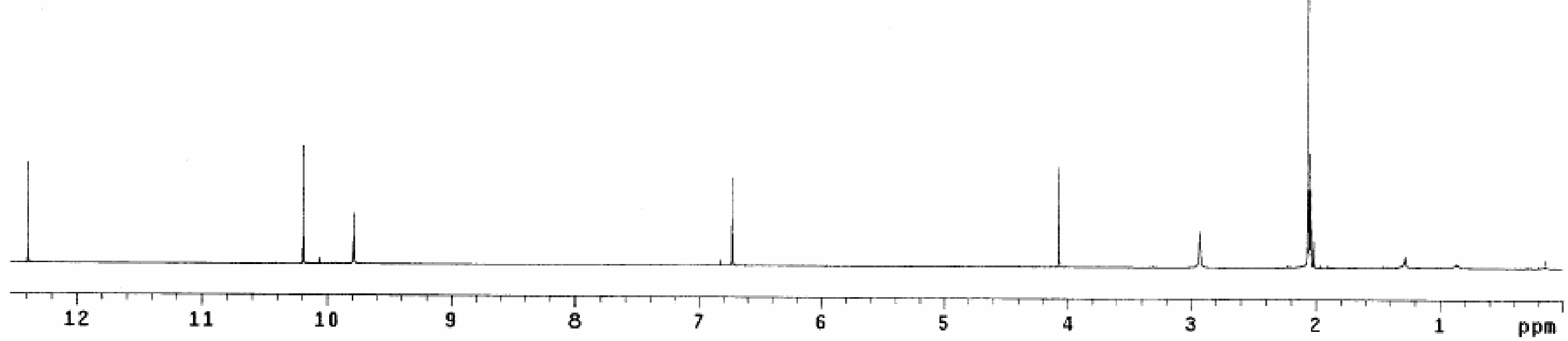
TLC solvents	R_f	
	Natural (-)-mitorubrinic acid	**Synthetic (-)-mitorubrinic acid**
EtOAc (100%)	0.49	0.49
CH_2Cl_2 : EtOAc = 1 : 1	0.17	0.17
CH_2Cl_2 : HOAc = 5 : 1	0.35	0.35

[S8] Marsini, M. A.; Gowin, K. M.; Pettus T. R. R. *Org. Lett.* **2006**, *8*, 3481.

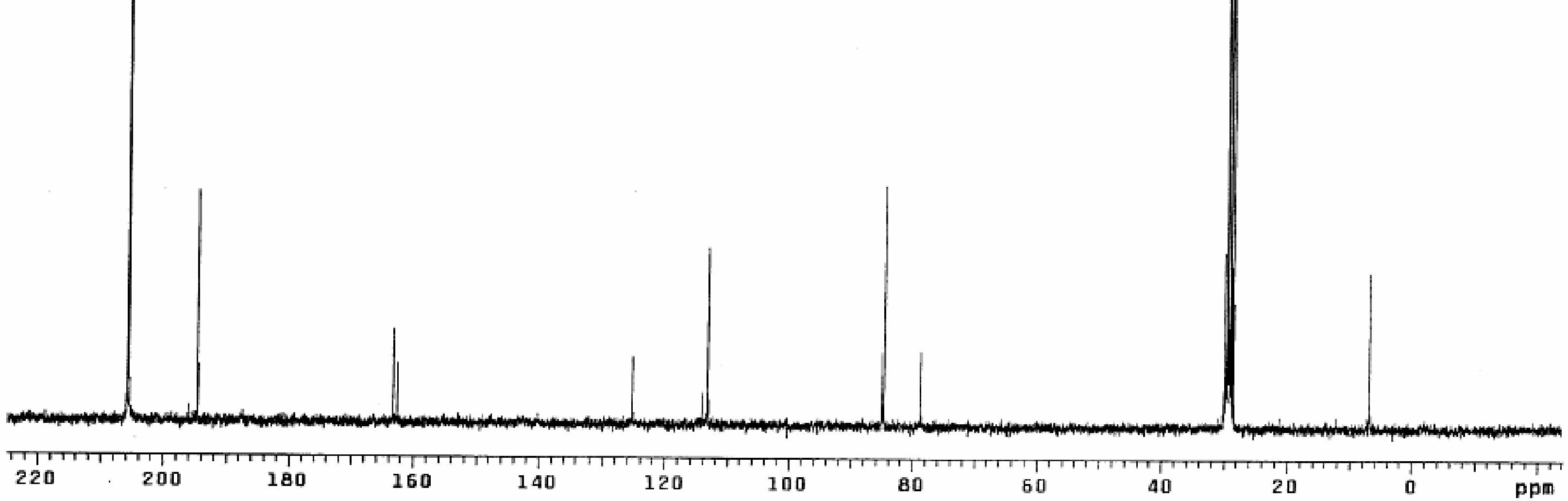


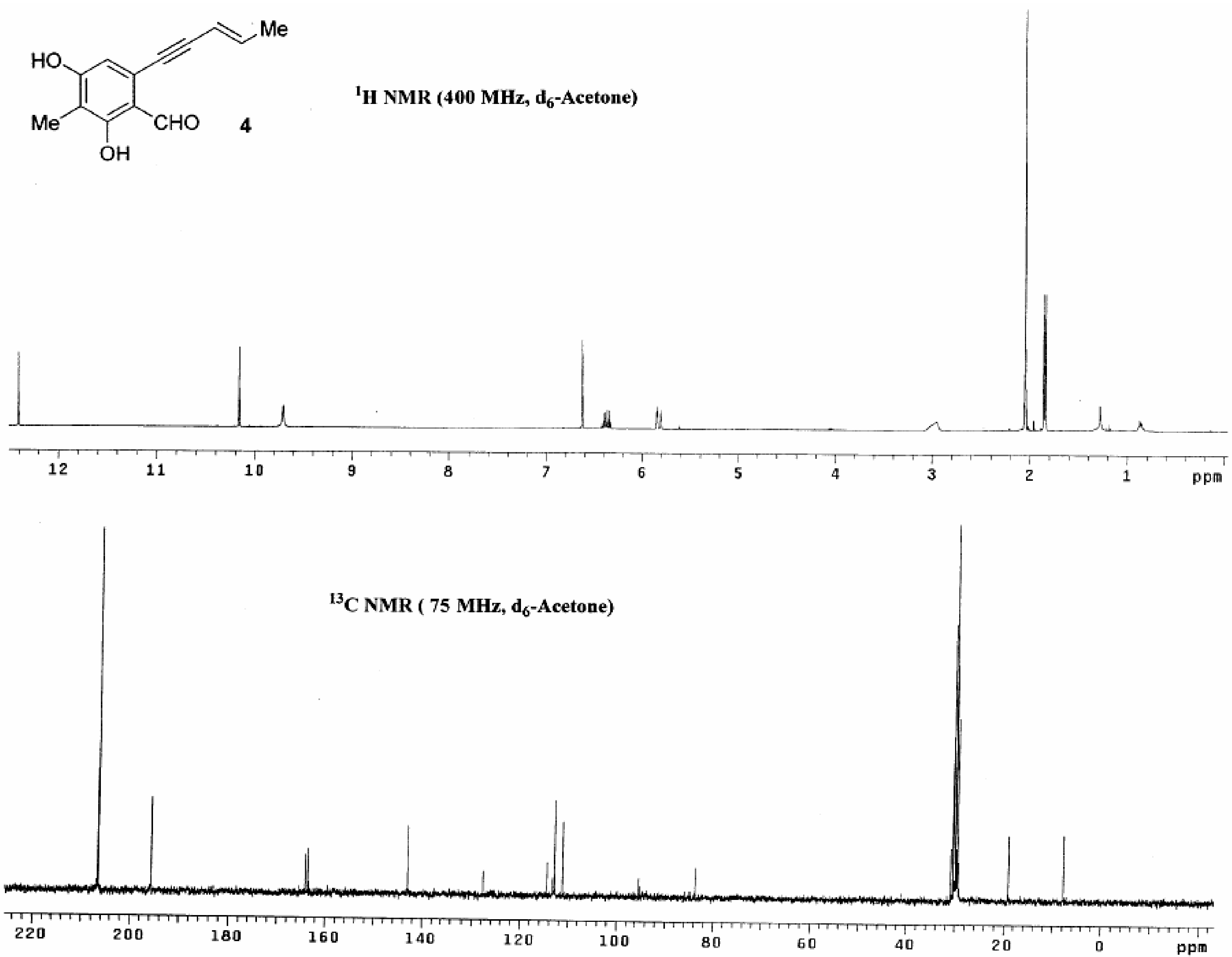
7

^{1}H NMR (400 MHz, d_6-Acetone)

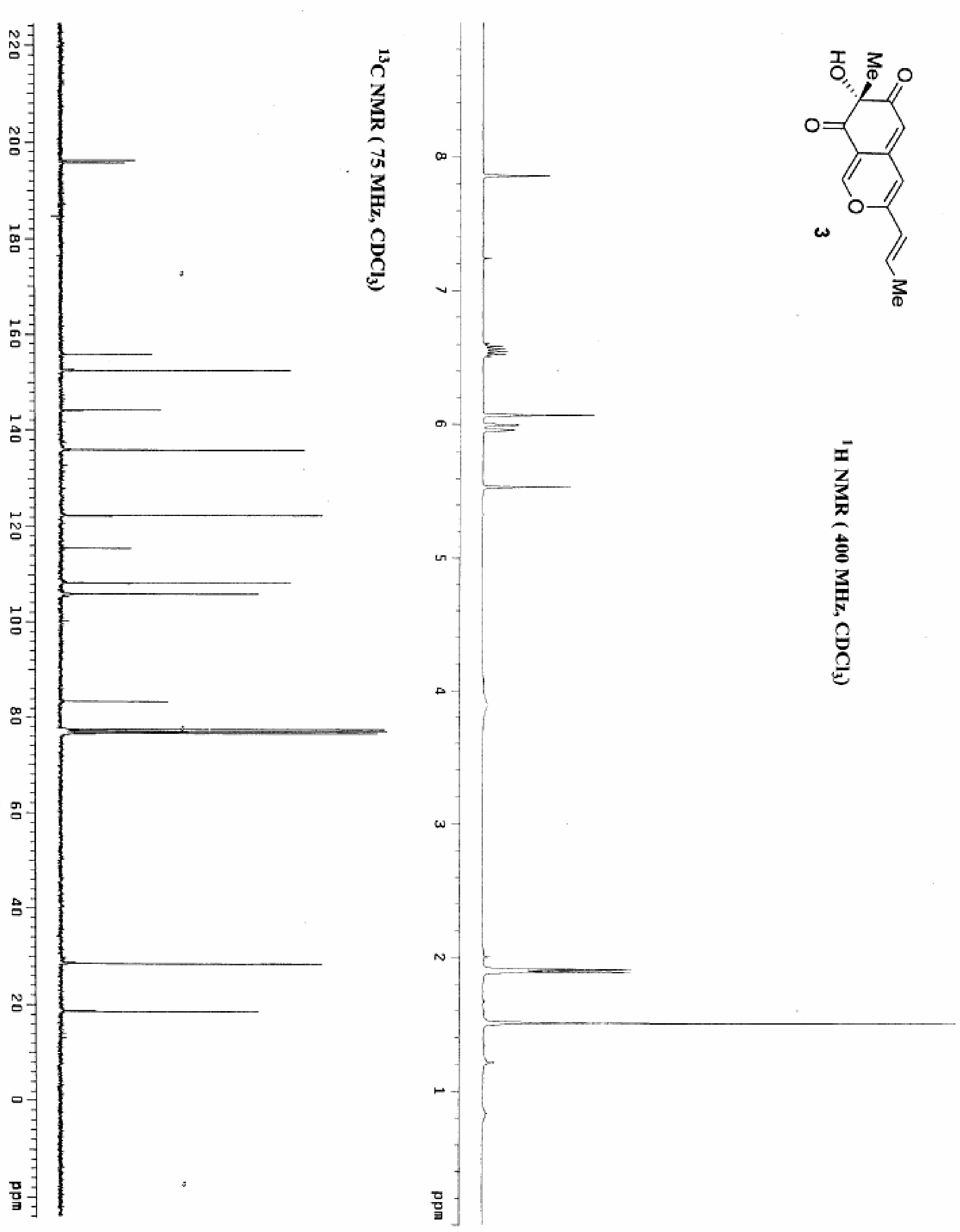


^{13}C NMR (75 MHz, d_6-Acetone)

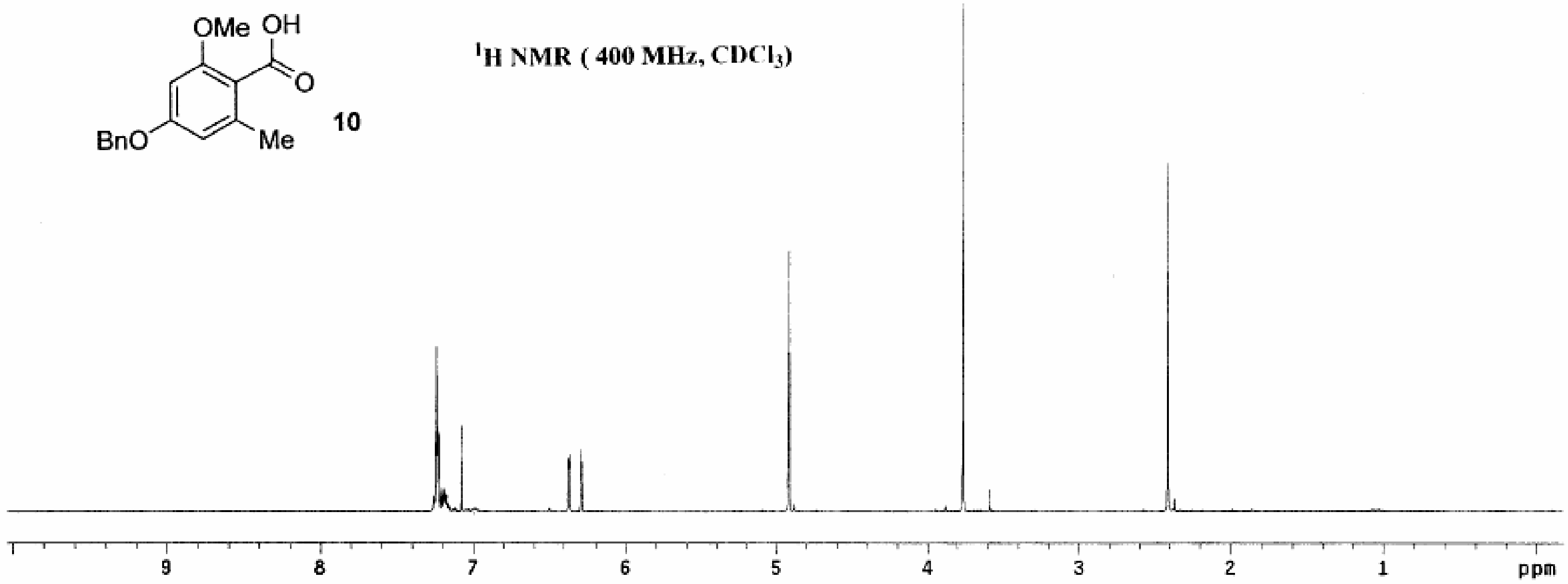




HO
Me
OH
CHO
Me
4
^{1}H NMR (400 MHz, d_6-Acetone)
12 11 10 9 8 7 6 5 4 3 2 1 ppm
^{13}C NMR (75 MHz, d_6-Acetone)
220 200 180 160 140 120 100 80 60 40 20 0 ppm

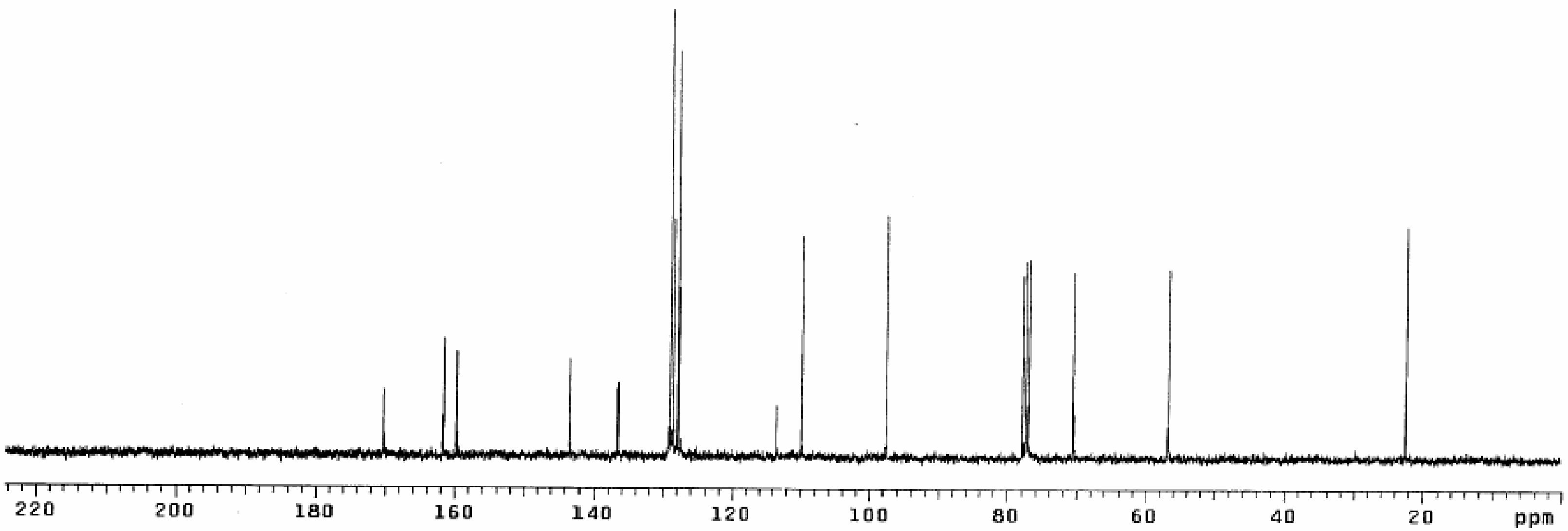


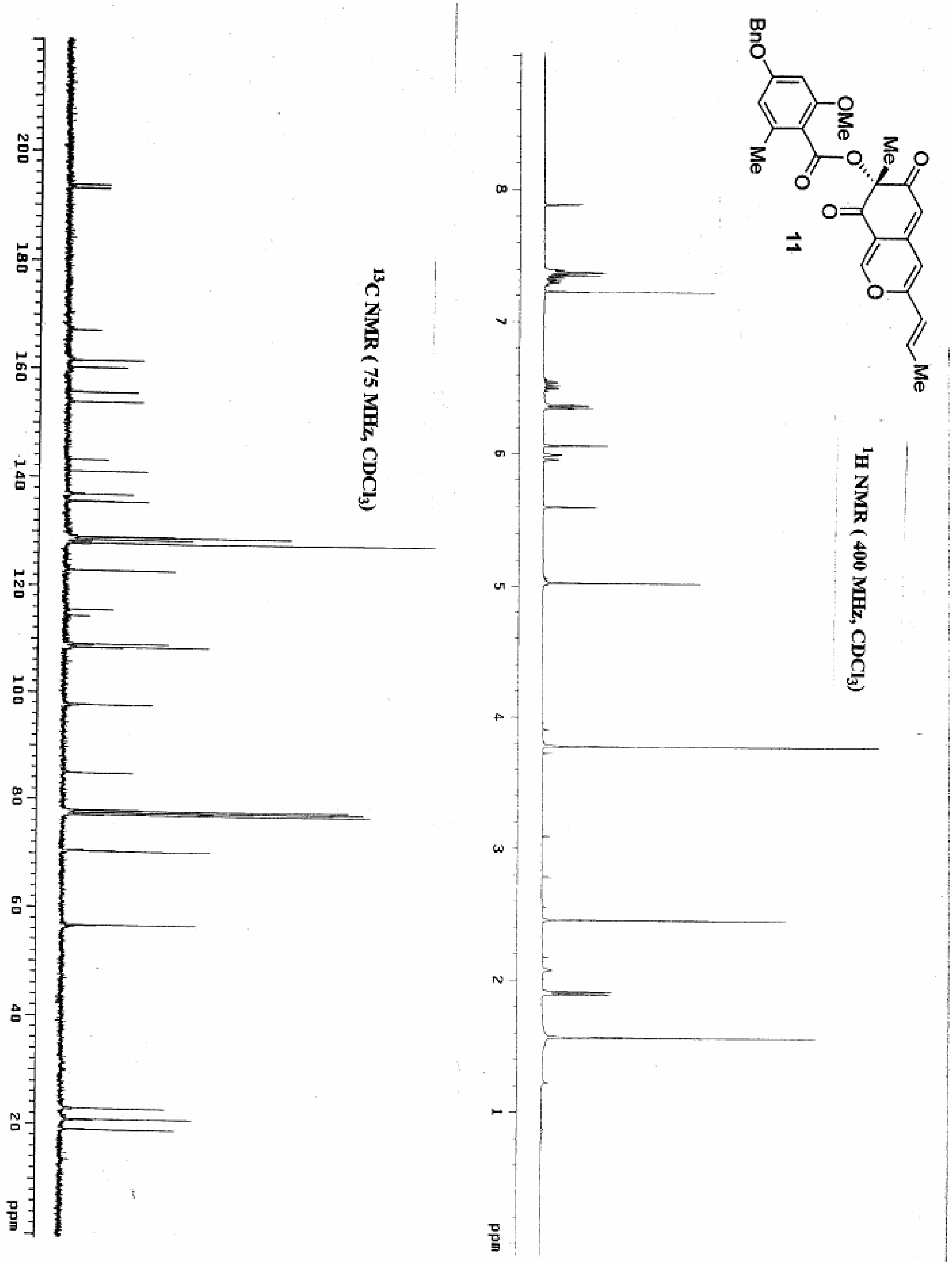
3
1H NMR (400 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
ppm



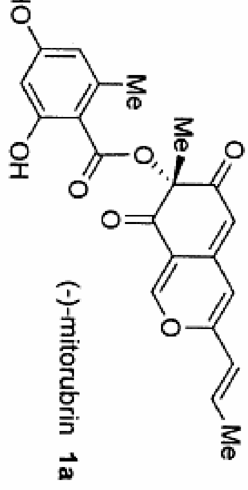
^{1}H NMR (400 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)



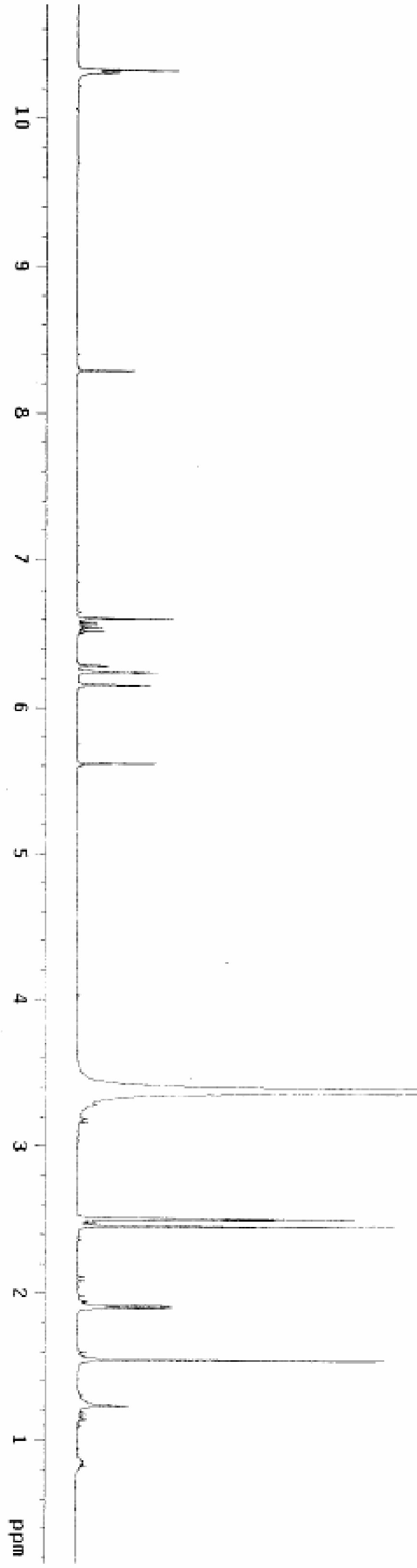


BnO
OMe
Me
O
11
1H NMR (400 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
ppm

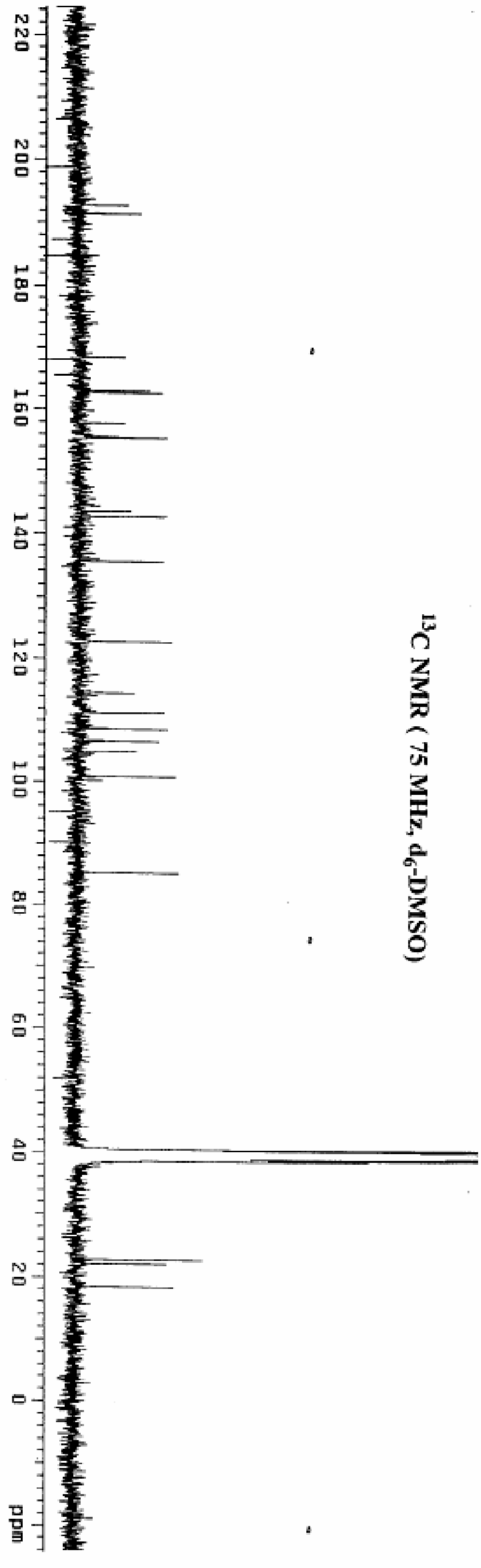


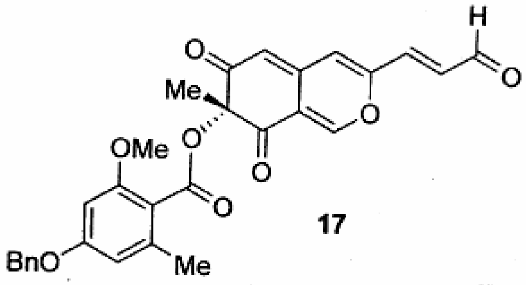
(-)-mitorubrin **1a**

^{1}H NMR (400 MHz, d_6-DMSO)



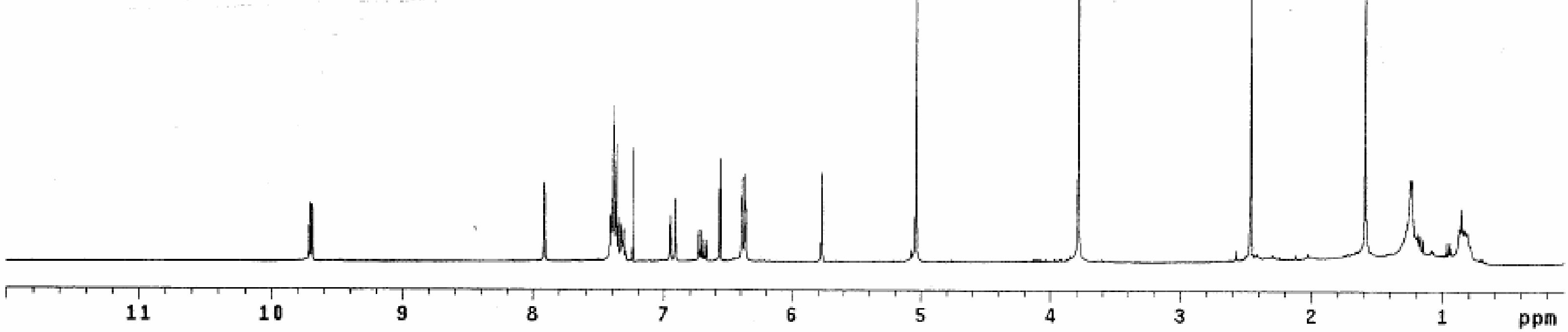
^{13}C NMR (75 MHz, d_6-DMSO)



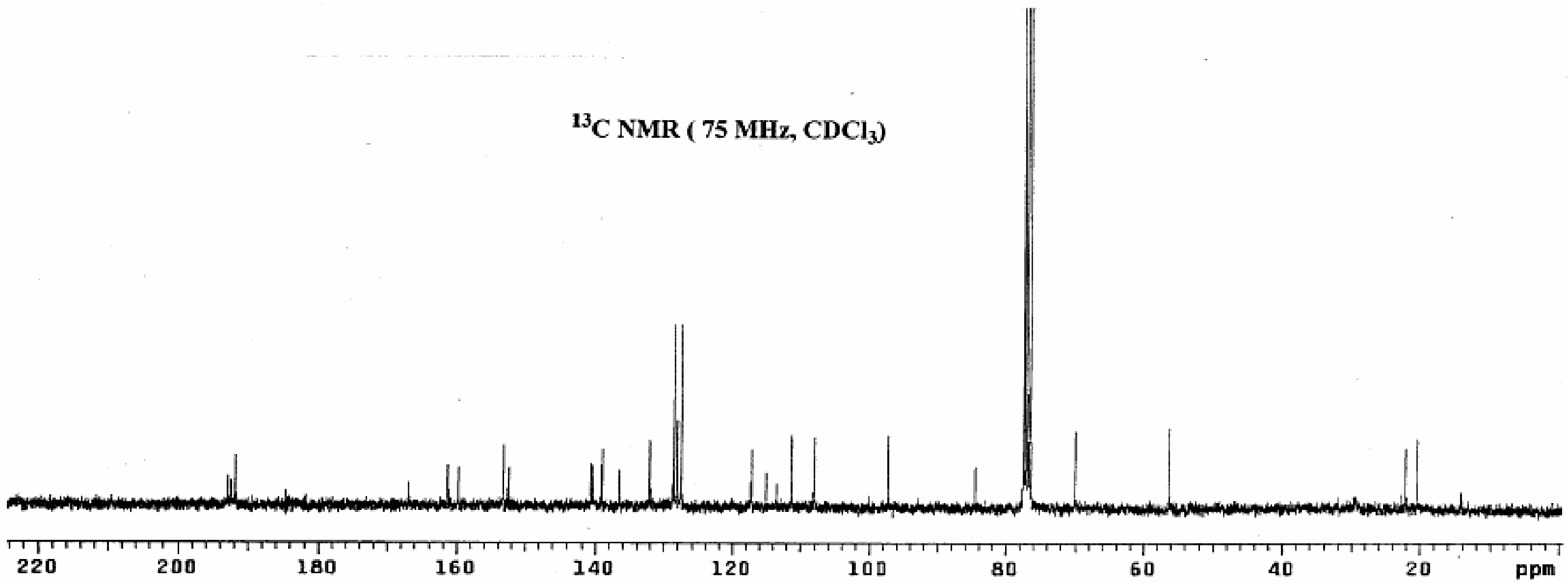


Me
OMe
BnO
Me
H

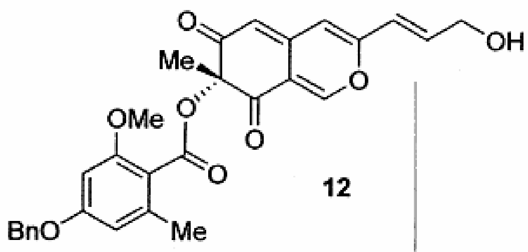
17



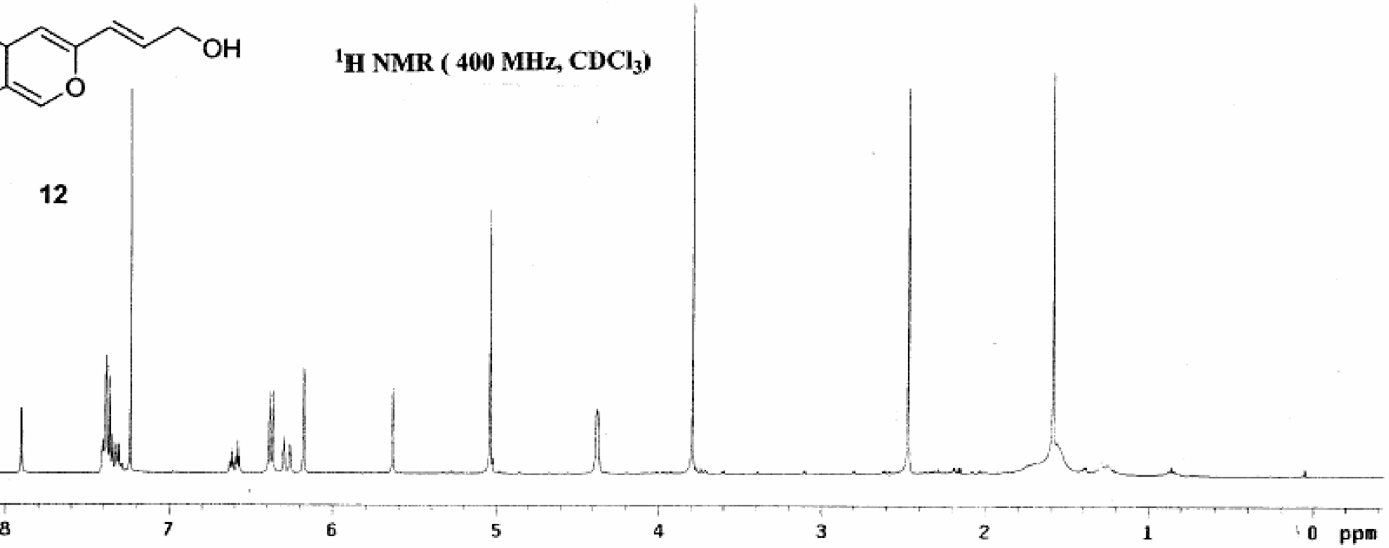
^{1}H NMR (400 MHz, CDCl$_3$)
11
10
9
8
7
6
5
4
3
2
1
ppm



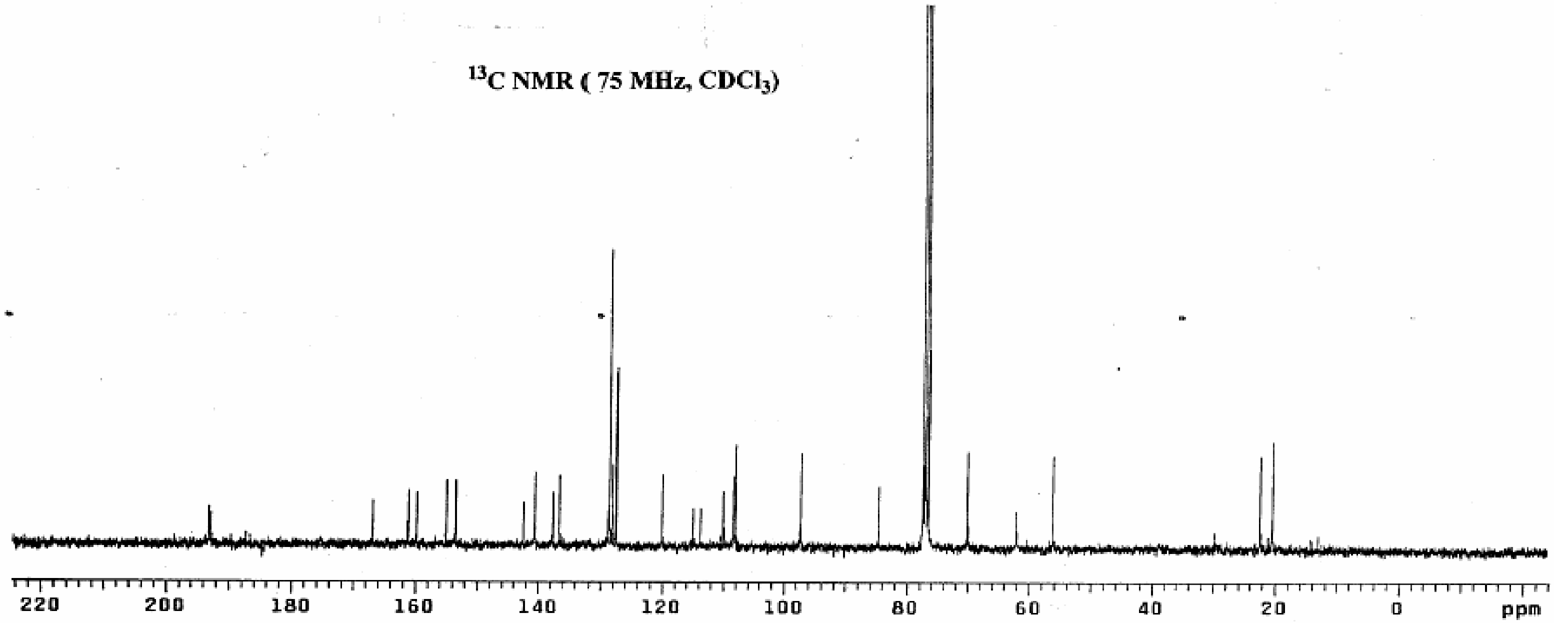
^{13}C NMR (75 MHz, CDCl$_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm



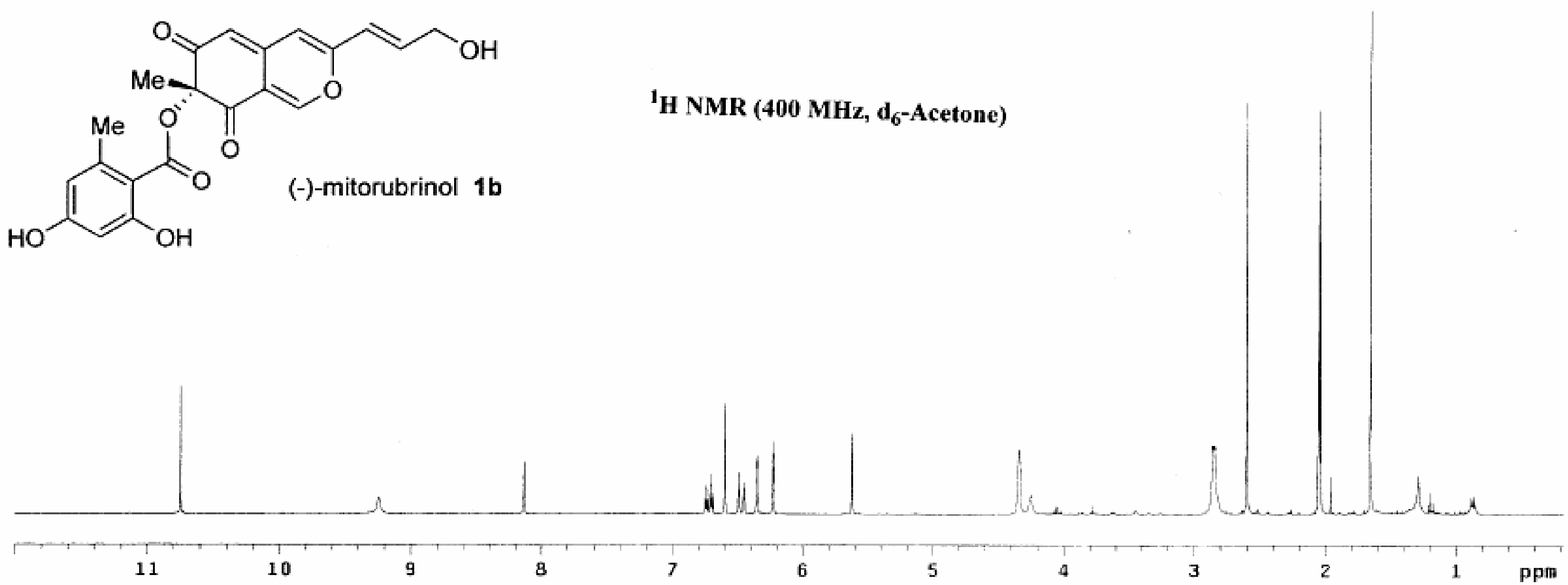
12

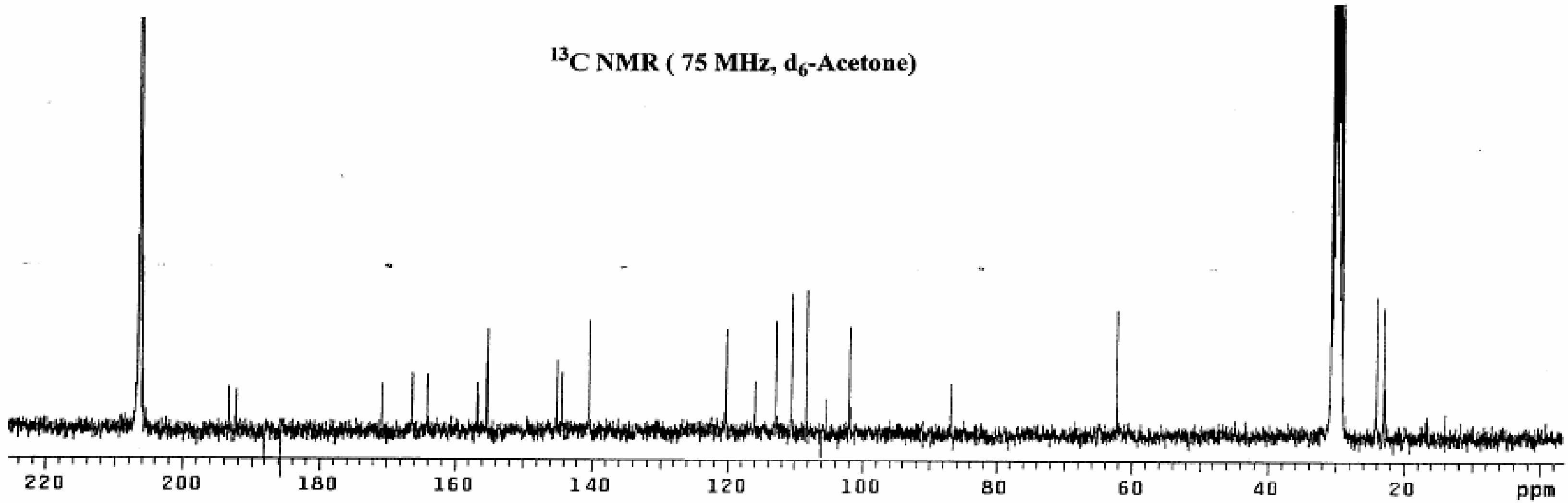


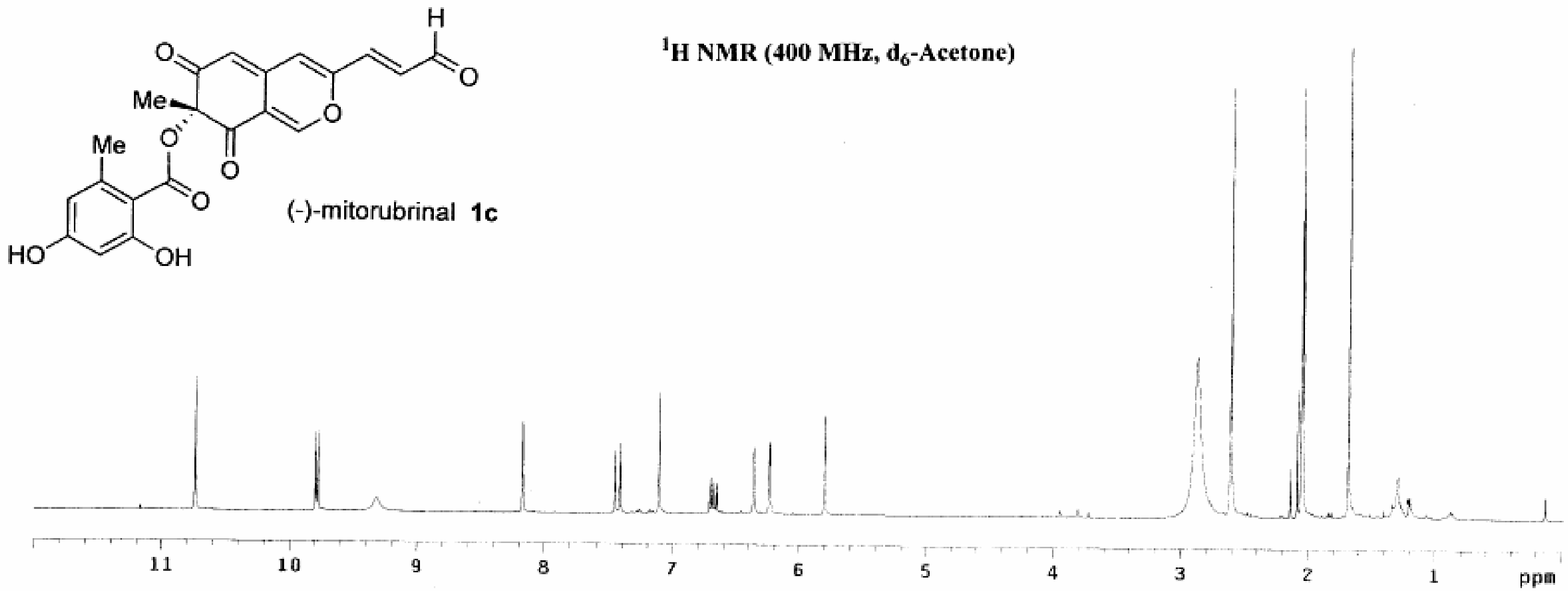
^{1}H NMR (400 MHz, CDCl$_3$)
8 7 6 5 4 3 2 1 0 ppm



^{13}C NMR (75 MHz, CDCl$_3$)
220 200 180 160 140 120 100 80 60 40 20 0 ppm


(-)-mitorubrinol **1b**
^{1}H NMR (400 MHz, d_6-Acetone)
11 10 9 8 7 6 5 4 3 2 1 ppm

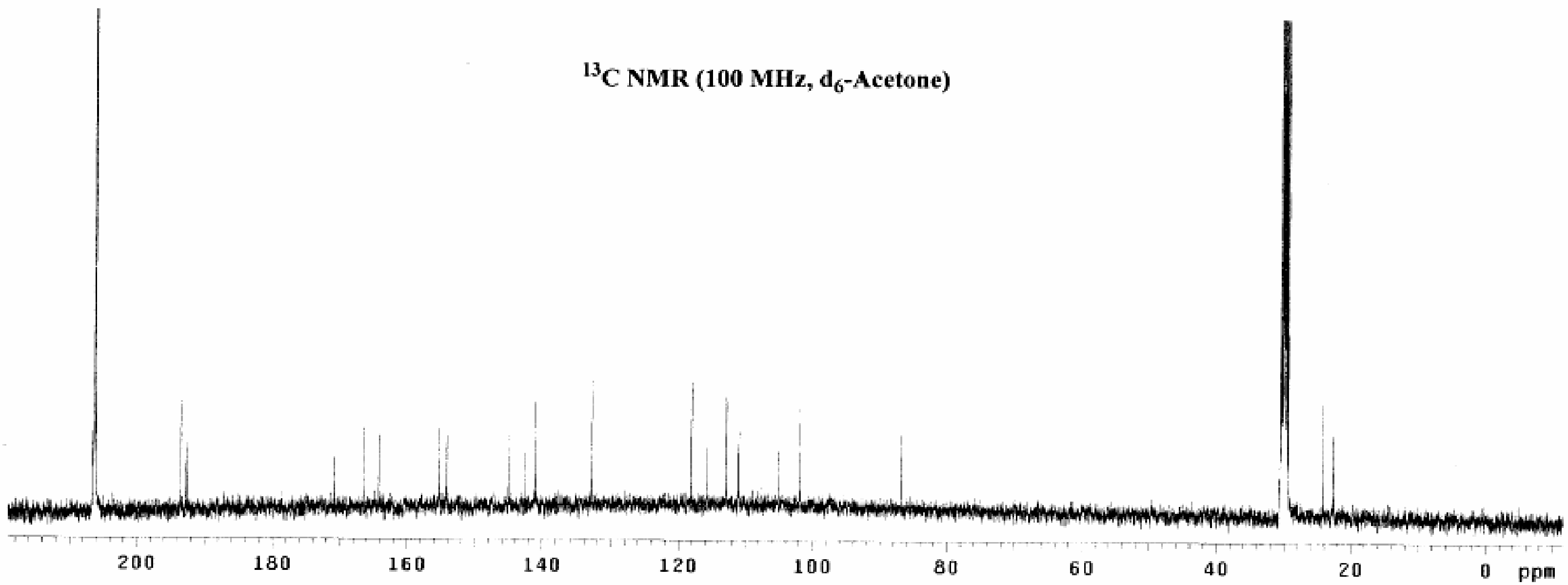

^{13}C NMR (75 MHz, d_6-Acetone)
220 200 180 160 140 120 100 80 60 40 20 ppm

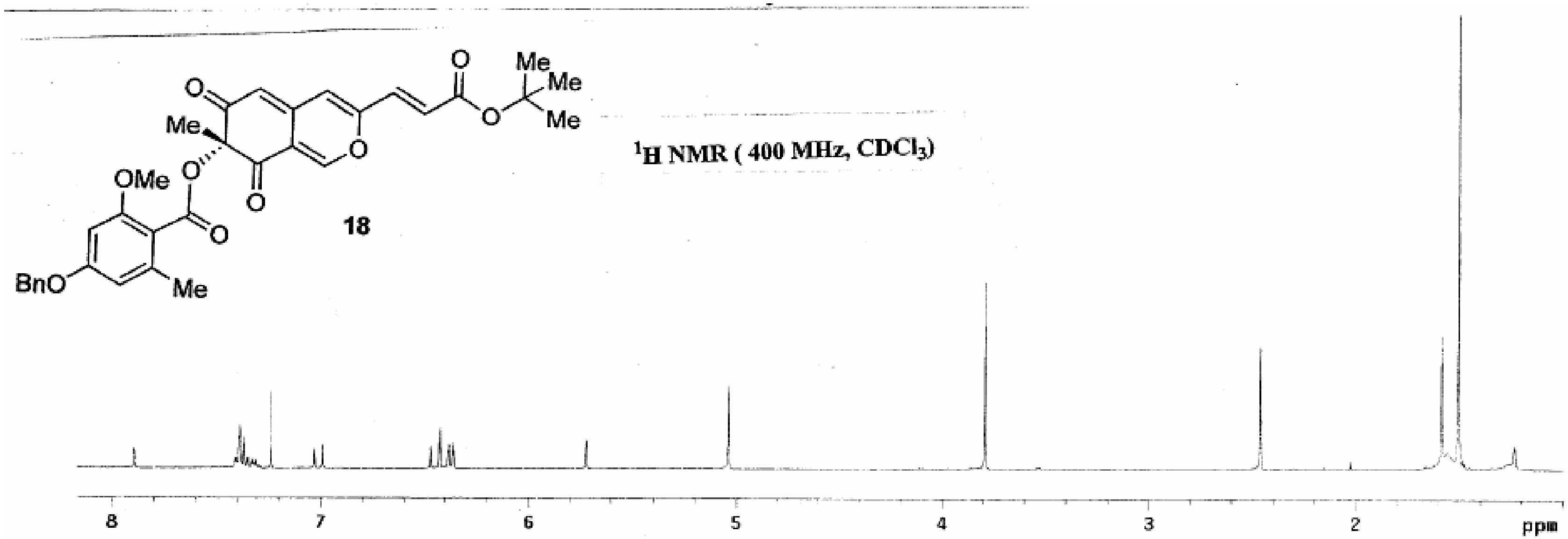


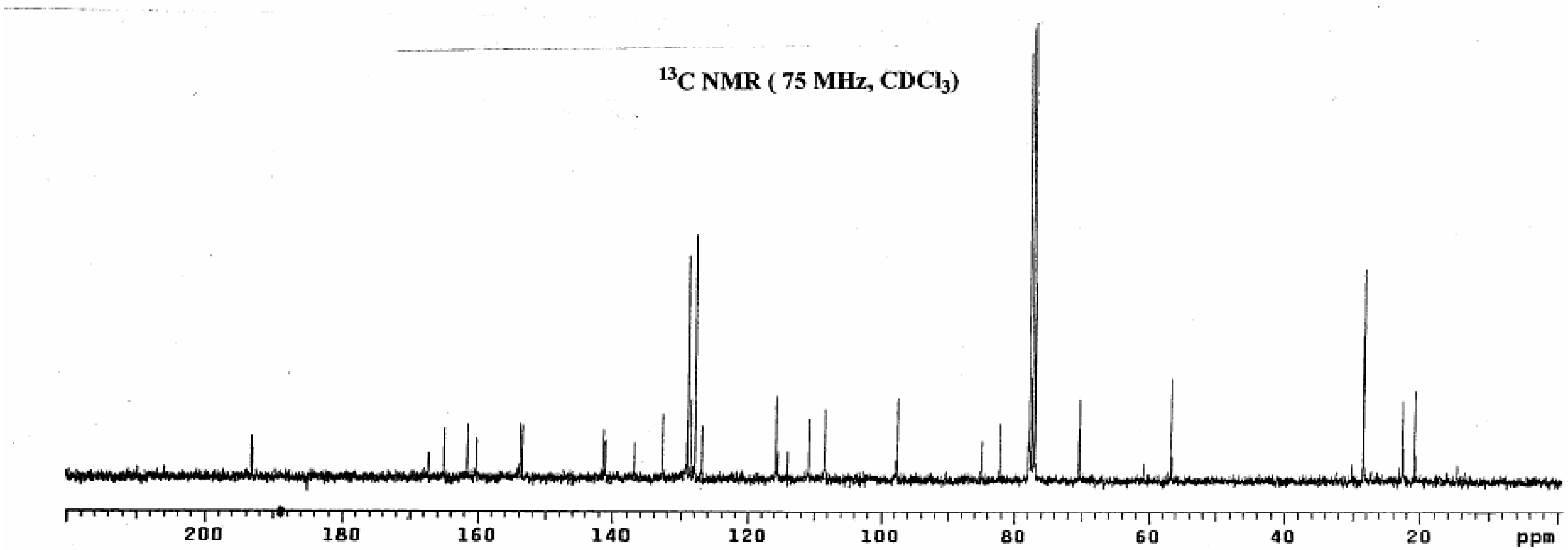
(-)-mitorubrinal **1c**

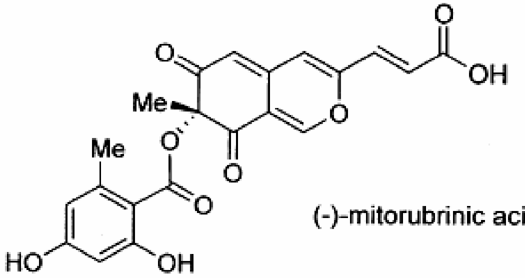
^{1}H NMR (400 MHz, d_6-Acetone)

^{13}C NMR (100 MHz, d_6-Acetone)



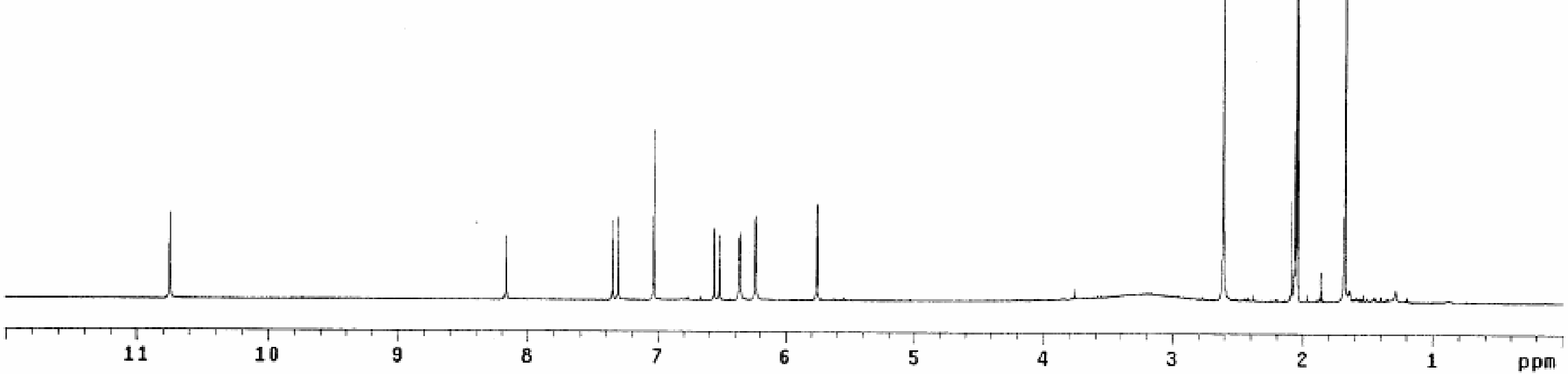

OMe
Me
BnO
Me
Me
Me
Me
18
^{1}H NMR (400 MHz, CDCl$_3$)
8
7
6
5
4
3
2
ppm


^{13}C NMR (75 MHz, CDCl$_3$)
200
180
160
140
120
100
80
60
40
20
ppm

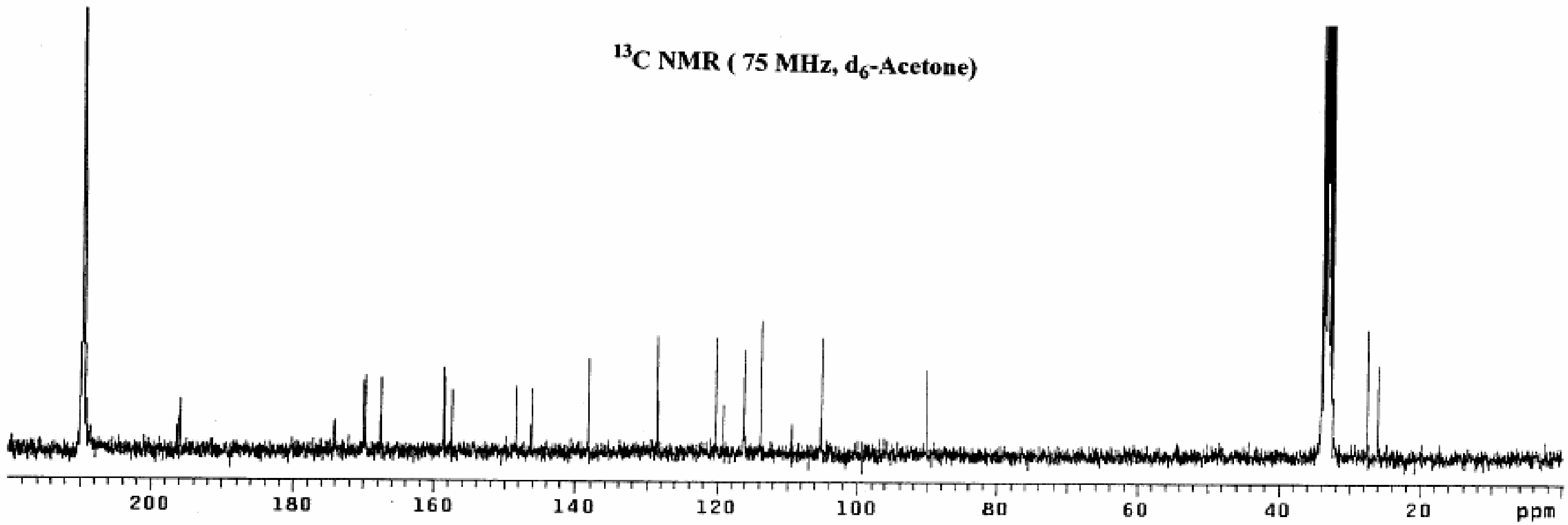


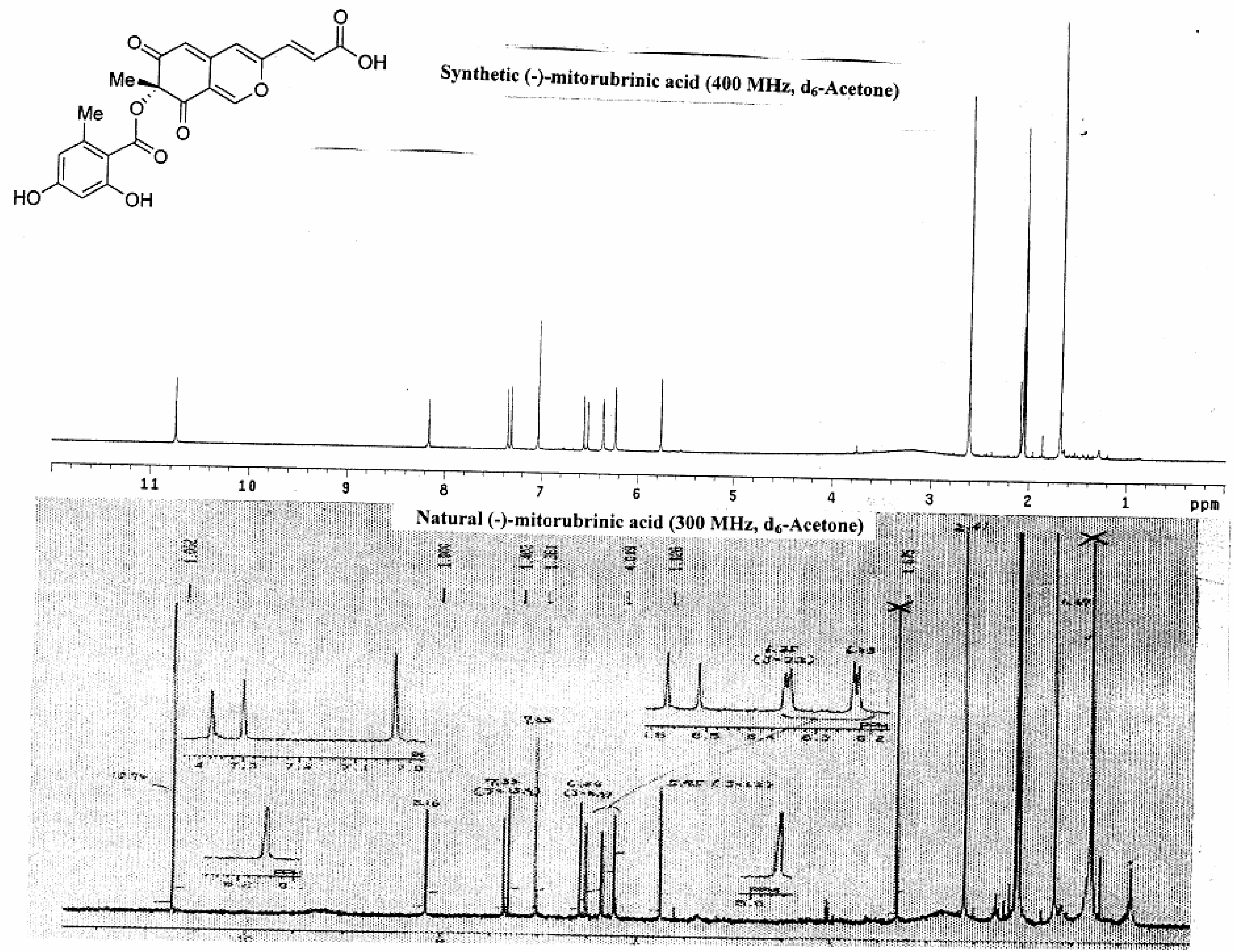
(-)-mitorubrinic acid **1d**

^{1}H NMR (400 MHz, d_6-Acetone)



^{13}C NMR (75 MHz, d_6-Acetone)




Synthetic (-)-mitorubrinic acid (400 MHz, d_6-Acetone)
Natural (-)-mitorubrinic acid (300 MHz, d_6-Acetone)
Me
Me
O
OH
HO
OH
ppm
11
10
9
8
7
6
5
4
3
2
1