

# Total Synthesis of (-)-Penifulvin A, an Antiinsectan with a Dioxafenestrane Skeleton.

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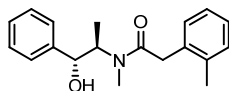
## Supporting Information

### 1. Procedures

#### General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous  $\text{CH}_2\text{Cl}_2$  (DCM) was distilled from  $\text{CaH}_2$  under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofuran) was purchased (99.85%, water < 50 ppm). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel (0.04-0.063mm, 240-400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in  $\text{CDCl}_3$  solutions and referenced to the residual  $\text{CHCl}_3$  signal ( $^1\text{H}$ ,  $\delta$  = 7.26 ppm;  $^{13}\text{C}$ ,  $\delta$  = 77.00 ppm). All  $^1\text{H}$  and  $^{13}\text{C}$  shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured at 20°C. High resolution mass spectra (HRMS) were performed with a resolution of 10000. Compound names were generated using AutoNom.

#### *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-*o*-tolylacetamide (**A**)

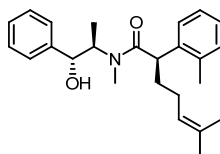


*o*-Tolylacetic acid (1.00 g, 6.7 mmol, 1 eq.), (*R,R*)-pseudoephedrine (1.20 g, 7.3 mmol, 1.1 eq.), and *N,N*-dimethyl-4-amino pyridine were dissolved in DCM (40 mL) at room temperature. After the starting materials had dissolved, the solution was cooled to 0°C in an ice bath and diisopropyl carbodiimide (1.1 mL, 7.3 mmol, 1.1 eq.) was added dropwise. After 20 min a precipitate was formed, and the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated on the rotatory evaporator and directly submitted to flash column chromatography (hexane:ethylacetate=3:1) yielding 1.95 g (98%) of the desired amide **A**.

$^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.39-7.26 p.p.m. (m, 5H), 7.20-7.04 (m, 4H), 4.65 (t,  $J$ =7.3 Hz, 1H), 4.55-4.48 (m, 1H), 4.34 (s, br 1H), 3.64 (d,  $J$ =2.3 Hz, 2H), 2.86 (s, 3H), 2.25 (s, 3H), 1.18 (d,  $J$ =6.8 Hz, 3H).

$^{13}\text{C}$ -NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.70 p.p.m., 142.83, 136.84, 133.81, 130.63, 129.28, 128.79, 128.04, 127.42, 126.72, 126.65, 76.88, 75.97, 59.09, 39.83, 20.02, 14.85. IR (film): 3383, 2971, 1699, 1617, 1558, 1452, 1404, 1118, 1051, 743, 702, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{19}\text{H}_{23}\text{NO}_2$  297.1729; found, 297.1715.  $[\alpha]_D$  = -96 (c 1.05g/100mL,  $\text{CHCl}_3$ ).

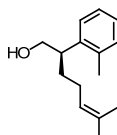
#### *(R)*-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,6-dimethyl-2-*o*-tolylhept-5-enamide (**5**)



A solution of *n*-butyllithium (5.9 mL, 2.5M, 2.2 eq.) was added to a suspension of LiCl (1.65 g, 39.9 mmol, 6 eq.) and diisopropylamine (2 mL, 14.6 mmol, 2.2 eq.) in THF (7 mL) at  $-78^{\circ}\text{C}$ . The resulting suspension was briefly warmed to  $0^{\circ}\text{C}$  and then cooled to  $-78^{\circ}\text{C}$ . Amide **A** (1.95 g, 6.5 mmol, 1 eq.) was added to this mixture *via* cannula and stirred at that temperature for 1 h, then at  $0^{\circ}\text{C}$  for 15 min and at  $23^{\circ}\text{C}$  for 5 min. The mixture was cooled to  $0^{\circ}\text{C}$  and 5-bromo-2-methyl-2-pentene (1.44 g, 8.9 mmol) was added neat to this reaction mixture. After stirring at room temperature for 24 h the mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3x100 mL). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (hexane:ethylacetate=3:1) afforded 1.47 g (58%) of amide **5**.

$^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.38-7.04 p.p.m. (m, 9H), 5.18-5.10 (m, 1H), 4.59-4.50 (m, 1H), 4.47-4.26 (s br, 1H), 3.71-3.66 (m, 1H), 2.92 (s, 1H minor rotamer), 2.54 (s, 1H major rotamer), 2.36 (s, 1H minor rotamer), 2.30 (s, 2H major rotamer), 2.24-2.21 (m, 1H), 2.11-2.04 (m, 1H), 1.98-1.89 (m, 1H), 1.69 (s, 2H major rotamer), 1.68 (s, 1H minor rotamer), 1.59 (s, 1H minor rotamer), 1.56 (s, 2H major rotamer), 1.51-1.41 (m, 1H), 1.13 (d,  $J$ =4.9 Hz, 2H major rotamer), 0.39 (d,  $J$ =6 Hz, 1H).  $^{13}\text{C}$ -NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 138.67 p.p.m., 134.82, 132.60, 130.70, 128.78, 128.44, 127.65, 127.00, 126.90, 126.64, 126.45, 124.45, 124.08, 76.60, 75.68, 58.06, 45.28, 34.50, 34.23, 27.58, 26.74, 25.84, 19.35, 17.81, 14.19. IR (film): 3383, 2924, 1713, 1621, 1454, 1404, 1376, 1228, 1119, 1051, 895, 838, 757, 726, 702, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_2$  379.2511; found, 379.2510  $[\alpha]_{\text{D}} = -137^{\circ}$  (c 0.75g/100mL,  $\text{CHCl}_3$ ).

### (R)-6-Methyl-2-*o*-tolylhept-5-en-1-ol (3a)

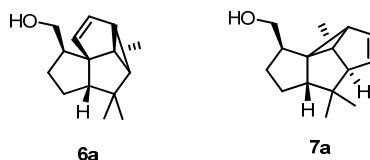


A solution of *n*-butyllithium (5.9 mL, 2.5M, 14.8 mmol, 4 eq.) in hexanes was added to a solution of diisopropylamine (2.1 mL, 14.8 mmol, 4 eq.) in THF (10 mL) at  $-78^{\circ}\text{C}$ . The resulting solution was stirred at this temperature for 10 min, then warmed to  $0^{\circ}\text{C}$  and held at that temperature for 10 min. Borane-ammonia complex (456 mg, 14.8 mmol, 4 eq.) was added in one portion. The suspension was stirred at  $0^{\circ}\text{C}$  for 15 min, then at  $23^{\circ}\text{C}$  for 15 min, cooled again to  $0^{\circ}\text{C}$  and a solution of amide **5** (1.40 g, 3.7 mmol, 1 eq.) in THF (6 mL) was added *via* cannula. The reaction mixture was warmed to room temperature and stirred for 2 h before it was cooled to  $0^{\circ}\text{C}$  again and carefully quenched with 1M hydrochloric acid (40 mL). The mixture was diluted with water (100 mL) and extracted with ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **3a** (734 mg, 91%) as a yellow oil which was directly used in the next step. An analytical sample was purified by chromatography (hexane:ethyl acetate 5:1).

$^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.21-7.10 p.p.m. (m, 4H), 5.07 (dt,  $J$ =6.9, 0.6 Hz, 1H), 3.76-3.69 (m, 2H), 3.19-3.15 (m, 1H), 2.33 (s, 3H), 1.89 (dd,  $J$ =14.9, 7.3 Hz, 2H), 1.78-1.72 (m, 1H), 1.69-1.61 (m, 1H), 1.66 (d,  $J$ =1.1 Hz, 3H), 1.44 (s, 3H).  $^{13}\text{C}$ -NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 140.73 p.p.m., 137.71, 132.32, 130.90, 126.74, 126.62, 126.27, 124.66, 67.78, 42.66, 32.55, 26.12, 25.98, 20.29, 17.97. IR (film): 3241, 2928, 2857, 1653, 1559, 1463, 1256, 1101, 836, 775, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{O}$  218.1671; found, 218.1665.  $[\alpha]_{\text{D}} = +18$  (c 1.05g/100mL,  $\text{CHCl}_3$ ).

**((1a*S*,4*R*,4a*R*,6*bS*,6*cS*)-1,1,6*c*-Trimethyl-1,1a,2,3,4,6a,6*b*,6*c*-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalen-4-yl)-methanol (6a)**

**((2a*S*,3a*S*,6*R*,6*bS*,6*cR*)-3,3,6*c*-Trimethyl-2a,3,3a,4,5,6,6*b*,6*c*-octahydro-cyclopenta[*a*]cyclopropa[*gh*]pentalen-6-yl)-methanol (7a)**

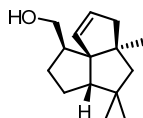


Compound **3a** (1.00 g, 3.0 mmol) in pentane (100 mL) was irradiated with a Hannovia 700W medium pressure mercury lamp with a quartz filter at room temperature for 2 h. The reaction mixture was concentrated and the crude residue was submitted to flash column chromatography (hexane) yielding **6a** and **7a** (350 mg each, total 70%) in a 1:1 ratio.

**6a**:  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.76 p.p.m. (dd,  $J$ =5.3, 2.0 Hz, 1H), 5.44 (d,  $J$ =5.3 Hz, 1H), 3.68-3.61 (m, 1H), 3.58-3.48 (m, 1H), 2.47-2.38 (m, 1H), 2.01-1.85 (m, 2H), 1.84-1.74 (m, 1H), 1.67 (d  $J$ =1.3 Hz, 1H), 1.63-1.50 (m, 3H), 1.48-1.43 (m, 1H), 1.34 (s, 3H), 1.31 (d,  $J$ =7.6 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 3H).  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 133.61 p.p.m., 130.69, 70.95, 66.14, 64.83, 60.47, 49.77, 48.55, 42.50, 38.42, 31.09, 29.64, 29.36, 28.51, 19.15. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{O}$  218,1671; found, 218,1679.  $[\alpha]_D = -79$  (c 1.35g/100mL,  $\text{CHCl}_3$ ).

**7a**:  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.66 p.p.m. (dd,  $J$ =5.6, 2.2 Hz, 1H), 5.46 (dd,  $J$ =5.6, 2.5 Hz, 1H), 3.44 (dd  $J$ =10.6, 4.3 Hz, 1H), 3.36 (dd,  $J$ =9.3, 4.3 Hz, 1H), 2.40, (d,  $J$ =2.5 Hz, 1H), 2.07 (s, br, 1H), 1.90 (dd,  $J$ =9.5, 3.4 Hz, 1H), 1.86-1.77 (m, 3H), 1.72-1.59 (m, 2H), 1.51 (d,  $J$ =2.3 Hz, 1H), 1.49-1.42 (m, 1H), 0.94, (s, 3H), 0.74 (s, 3H).  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 131.70 p.p.m., 129.84, 68.40, 64.77, 55.25, 50.85, 50.75, 46.71, 41.22, 38.16, 31.25, 23.78, 23.14, 23.03, 16.02. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{O}$  218,1671; found, 218,1681  $[\alpha]_D = +58$  (c 2.56g/100mL,  $\text{CHCl}_3$ ).

**((1*R*,3a*S*,5a*S*,8a*R*)-4,4,5a-Trimethyl-1,2,3,3a,4,5,5a,6-octahydro-cyclopenta[*c*]pentalen-1-yl)-methanol (8)**

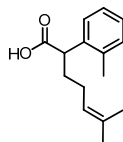


A solution of **6a** (120 mg, 0.36 mmol, 1 eq.) in absolute THF (500  $\mu\text{L}$ ) was cooled to  $-78^\circ\text{C}$  and ethylamine (3 mL) was condensed in. Small pieces of lithium (15 mg, 2.16 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h until a deep blue color formed. The excess lithium was quenched with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **8** (118 mg, 97%) as a yellow oil which was directly subjected to the next step. A purified sample was obtained by chromatography (hexanes:ethyl acetate 10:1).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.68 p.p.m. (dt,  $J$ =5.7, 2.2 Hz, 1H), 5.54 (dt,  $J$ =5.6, 2.4 Hz, 1H), 3.55 (dd,  $J$ =11.0, 7.2 Hz, 1H), 3.49-3.42 (m, 2H), 2.36 and 2.24 (AB dt,  $J$ =17.0, 2.2 Hz, 2H), 1.95-1.87 (m, 2H),

1.69 (dd,  $J=4.8$ , 2.2 Hz, 3H), 1.67-1.62 (m, 3H), 1.15 (s, 3H), 0.98 (m, 3H), 0.92 (s, 3H).  $^{13}\text{C}$ -NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  = 137.51 p.p.m., 127.87, 65.31, 63.90, 58.52, 53.82, 51.12, 46.78, 42.12, 39.58, 32.20, 30.77, 28.43, 28.02, 27.57. HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{24}\text{O}$  220,1827; found, 220,1820.

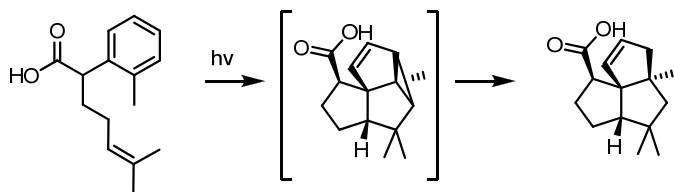
### 6-Methyl-2-*o*-tolyl-hept-5-enoic acid (**3b**)



Diisopropyl amine (1.5 mL, 10.5 mmol, 2.1 eq) was dissolved in 4 mL THF and cooled to 0°C. *n*-Butyllithium (2.5M, 4.2 mL 10.5 mmol, 2.1 eq) was added dropwise and the solution was stirred for 30 min at that temperature. The reaction mixture was cooled to -78°C and *o*-tolyl acetic acid (750 mg, 5 mmol) in THF (1 mL) was added at -78°C. The reaction was moved to a NaCl/ice bath and stirred at -20°C for 2h. After this time the reaction was cooled to -78°C and 5-bromo-2-methyl-pent-2-ene (1.21 g, 7.5 mmol) was added crude to this solution. The reaction was warmed to rt over night and quenched with aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted two times with  $\text{Et}_2\text{O}$  (50 mL). Then the aqueous phase was acidified to pH 2 and extracted four times with 100 mL of DCM. The combined DCM fractions were dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. Crude **3b** was used without any further purification. Yield 1.16g (quant).

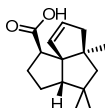
$^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.01 p.p.m. (s, br 1H), 7.38-7.35 (m, 1H), 7.26-7.18 (m, 3H), 5.14 (dd,  $J=7.1\text{Hz}$ , 1H), 3.91 (t,  $J=7.3\text{Hz}$ , 1H), 2.41 (s, 3H), 2.20 (ddd,  $J=14.1, 7.1\text{Hz}$ , 1H), 2.04 (dd,  $J=14.4, 7.1\text{Hz}$ , 2H), 1.90-1.81 (m, 1H), 1.73 (s, 3H), 1.55 (s, 3H).

### (1a*S*,4*R*,6*cS*)-1,1,6*c*-Trimethyl-1,1*a*,2,3,4,6*a*,6*b*,6*c*-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalene-4-carboxylic acid (**9**)



Acid **3b** (1.14 g, 4.9 mmol) in pentane (100 mL) was irradiated with a Hanovia 700W medium pressure mercury lamp with a quartz filter at room temperature for 1 h. The reaction mixture was concentrated and the crude mixture of **6b/7 b** was dissolved in THF (1 mL), cooled to -78°C and ethylamine (3 mL) was condensed in. Small lithium pieces (15 mg, 2.16 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h as a deep blue color formed. The excess lithium was destroyed with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **9** (along with its regioisomer, 707 mg, 62 %) as a yellow oil.

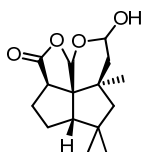
### (1*R*,3*aS*,5*aS*,8*aR*)-4,4,5*a*-Trimethyl-1,2,3,3*a*,4,5,5*a*,6-octahydro-cyclopenta[*c*]pentalene-1-carboxylic acid (**9**)



Alcohol **8** was dissolved in DMSO (1 mL) and IBX (302 mg, 1.1 mmol, 3 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 20 min until TLC control revealed full consumption of the starting material. The reaction mixture was diluted with diethyl ether (20 mL) and the solids were filtered off through a silica pad. The solvents were removed *in vacuo* and the crude aldehyde was dissolved in *tert*-butanol (5 mL) and 2-methyl-2-butene (500  $\mu$ L) was added. A solution of sodium chlorite (537 mg, 5.4 mmol, 15 eq.) and sodium dihydrogenphosphate (537 mg) in water (2 mL) was added dropwise under vigorous stirring. The reaction mixture was stirred at room temperature for 1 h and quenched with a 1M solution of potassium hydrogen sulfate in brine. The mixture was extracted with methylene chloride (3 x 50 mL), dried over magnesium sulfate and the solvents were removed *in vacuo*. Flash column chromatography (hexane:ethyl acetate=5:1) furnished 73 mg (86%) of **9** as a viscous oil.

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$ = 5.60-5.47 p.p.m. (m, 2H), 2.98 (dd,  $J$ =10.7, 7.0 Hz, 1H), 2.48-2.42 (m, 1H), 2.32-2.25 (m, 1H), 2.03-1.81 (m, 4H), 1.77-1.67 (m, 3H), 1.23 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H).  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$ = 180.32 p.p.p.m., 137.28, 128.60, 63.39, 58.51, 54.06, 61.32, 50.10, 45.96, 39.74, 31.29, 30.82, 28.84, 28.42, 27.95. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{O}$  218,1671; found, 218,1681.  $[\alpha]_{\text{D}} = -76$  (c 1.05g/100mL,  $\text{CHCl}_3$ ).

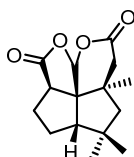
## Lactol **11**



Acid **9** (25 mg, 0.11mmol, 1 eq) was dissolved in dichloromethane (50 mL) in a three necked round bottom flask equipped with a gas outlet and a gas inlet-tube. The solution was cooled to  $-78^\circ\text{C}$  and ozonized for 2 min (flow 100mL/min) until the solution was dark blue. The excess ozone was driven out with air until the solution became colorless again. Then thiourea (9 mg, 0.12 mmol, 1.1 eq.) was added in one portion and the suspension was warmed to room temperature and stirred for 40 min giving a cloudy solution. The solvent was removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethyl acetate=3:1) yielding 15 mg (56%) of lactol **11**.

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$ = 5.69 p.p.m. (s, 1H), 5.37 (dd,  $J$ =8.9, 5.8 Hz, 1H), 3.24 (s, br 1H), 2.93 (d,  $J$ = 7.5 Hz, 1H) 2.25 (dd,  $J$ =9.3, 1.3 Hz, 1H) 2.16 (dd,  $J$ =13, 7.0 Hz, 1H), 2.01 (dd,  $J$ =14.2, 8.9 Hz, 1H), 1.89-1.85 (m, 2H), 1.76-1.65 (m, 1H), 1.74 (d,  $J$ =14 Hz, 1H), 1.54-1.47 (m, 1H), 1.47 (d,  $J$ =13.6 Hz, 1H), 1.22 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H).  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$ = 179.83 p.p.p.m., 101.09, 91.81, 66.90, 60.10, 58.16, 46.56, 42.39, 41.06, 40.06, 34.50, 31.21, 29.37, 28.33, 28.00. IR(film): 3449, 2958, 1792, 1559, 1457, 1132, 997, 884, 738, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_4$  266,1518; found, 266,1509.  $[\alpha]_{\text{D}} = -65$  (c 0.6g/100mL,  $\text{CHCl}_3$ )

## Penifulvin A (**1**)

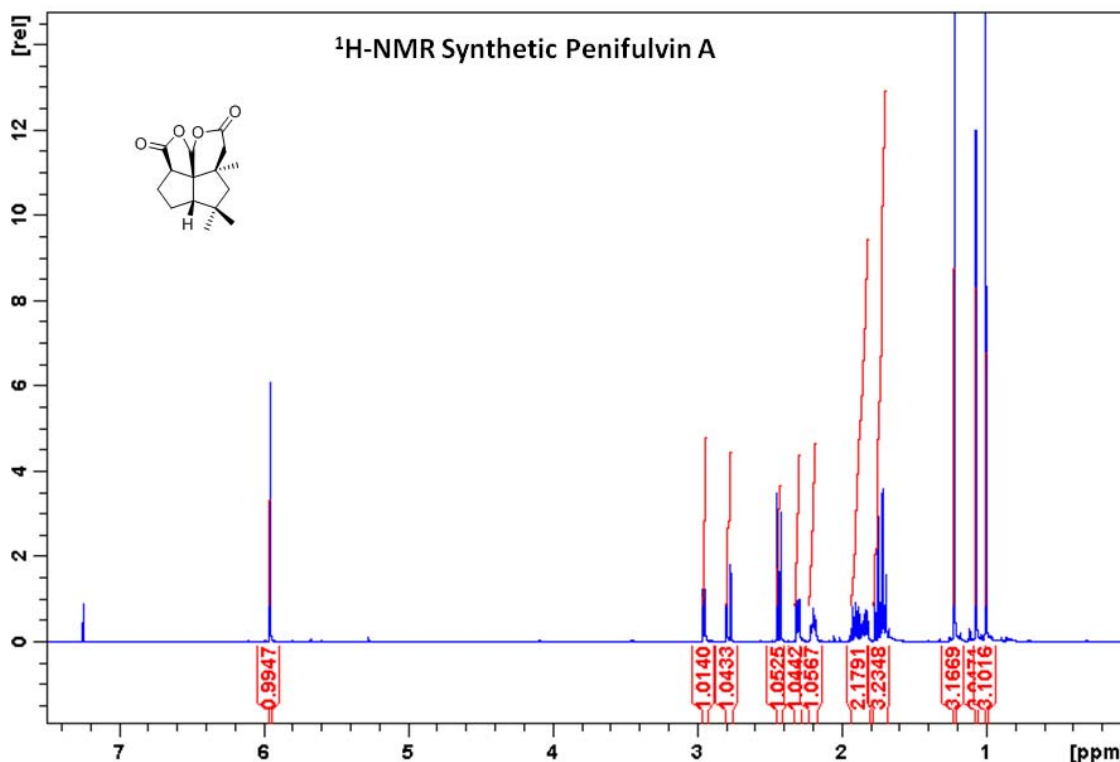


Lactol **11** (15 mg, 56  $\mu$ mol, 1eq) was dissolved in dichloromethane (0.5 mL) at room temperature. PDC (84 mg, 0.22 mmol, 4 eq.) was added in one portion. After 20 min concentrated acetic acid (67  $\mu$ L, 1.12 mmol, 20 eq.) was added dropwise. The reaction mixture was stirred for another hour and then diluted with diethyl ether. The suspension was filtered through a silica pad and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 12 mg (80%) of pure penifulvin A (**1**).

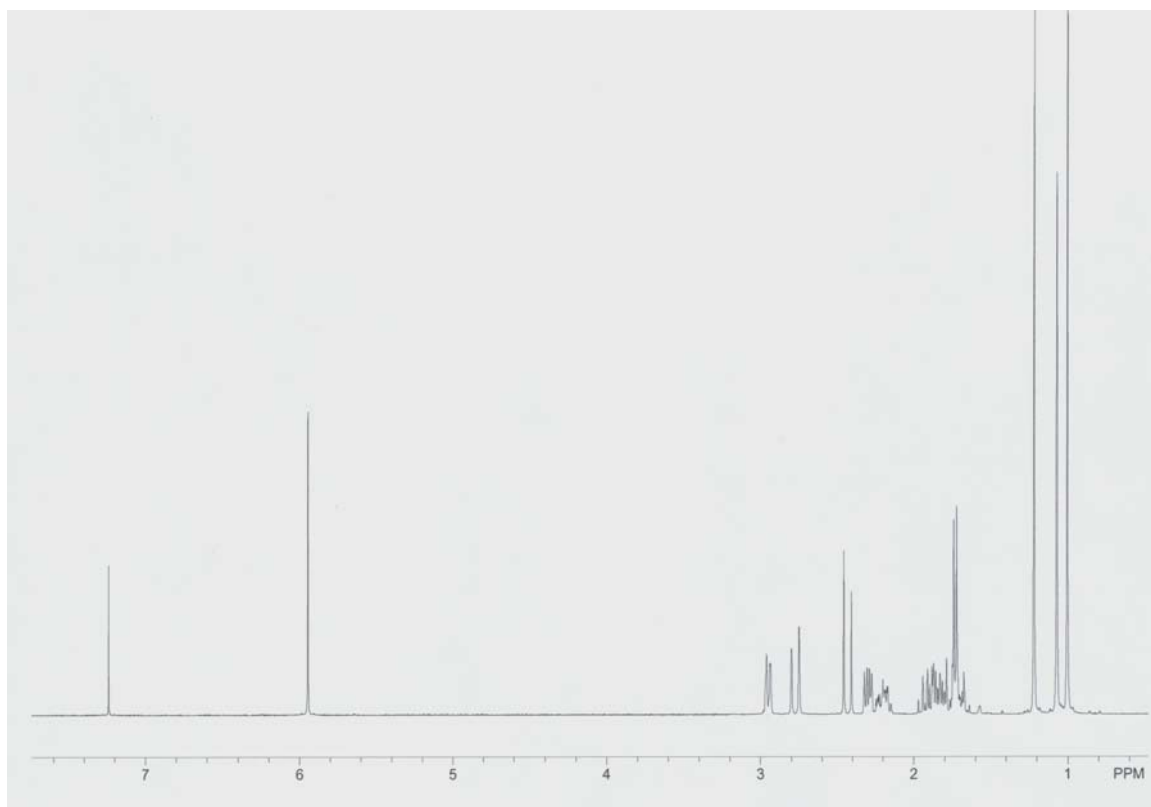
$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$ = 5.96 p.p.m. (s, 1H), 2.97 (dd,  $J$ =8.0, 1.0 Hz, 1H), 2.79 (d,  $J$ =15 Hz, 1H), 2.46 (dd,  $J$ =15 Hz, 1H), 2.32 (dd,  $J$ =9.7, 5.0 Hz, 1H), 2.23 (ddd,  $J$ =13.3, 8.0, 3.9, 1.8 Hz, 1H), 1.91 (ddt,  $J$ =14.0, 8.1, 8.2 Hz, 1H), 1.82 (m, 1H), 1.78 (d,  $J$ =14 Hz, 1H), 1.73 (d,  $J$ =14 Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H).  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$ = 178.04 p.p.m., 168.65, 103.88, 66.73, 60.86, 55.62, 46.43, 44.10, 42.07, 40.32, 32.83, 30.11, 28.18, 27.58, 27.42. IR (film): 2960, 1799, 1771, 1653, 1559, 1507, 1458, 1367, 1115, 1043, 995, 905, 738, 610  $\text{cm}^{-1}$ . HRMS (ESI) ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4$  264,1362; found, 264,1368.  $[\alpha]_D^{25}$  = -127 (c 0.35g/100mL,  $\text{CHCl}_3$ ).  $[\alpha]_D^{25}$  = -97 (c 0.35g/100mL, MeOH).

In the racemic series, the operations from **9** to **1** were performed without isolation of the intermediates. The chromatography (hexanes:ethyl acetate 5:1) of the final mixture gave pure crystalline *rac*-**1** (23% from the **6b/7b**- mixture).

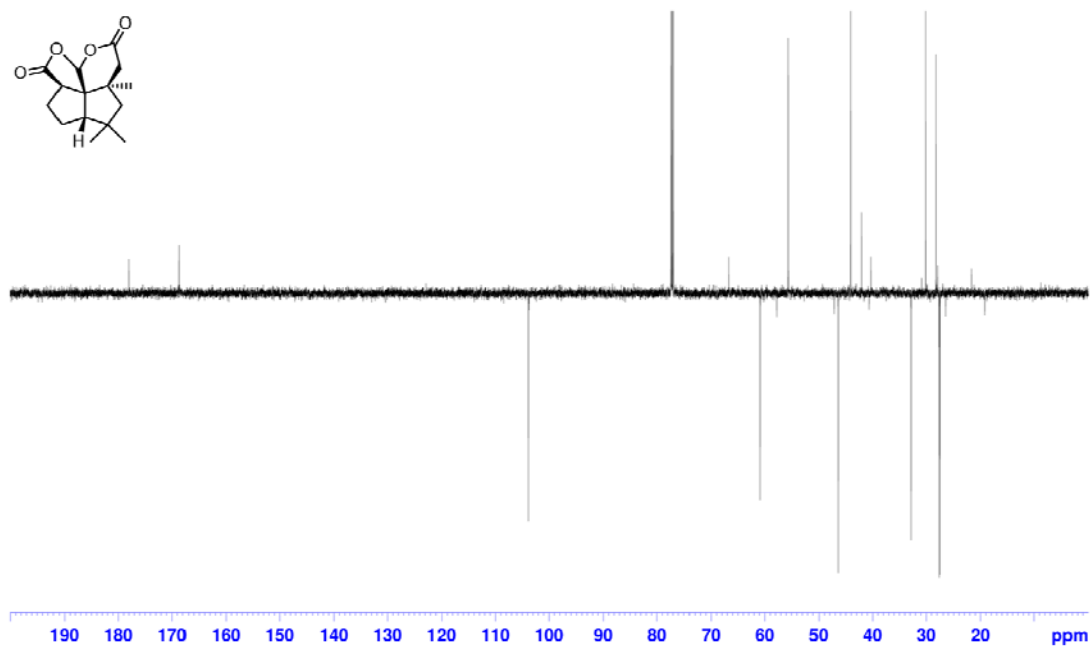
## 2. NMR Spectra



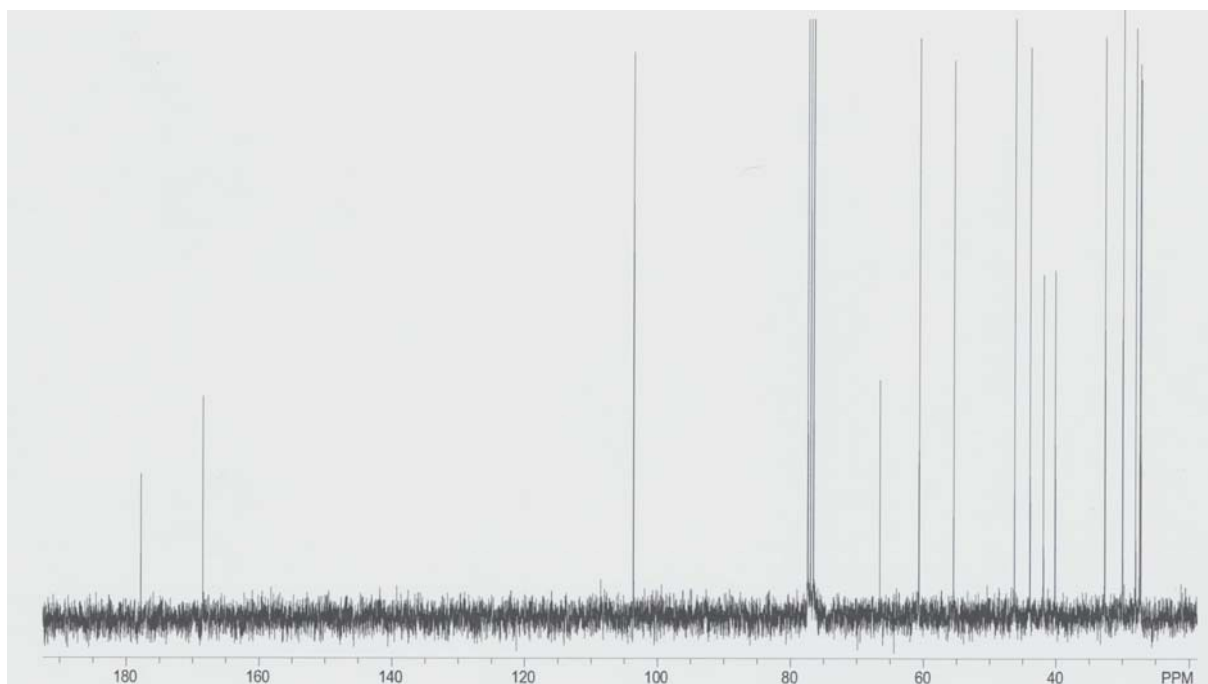
## Natural Penifulvin A<sup>2</sup>



<sup>13</sup>C-NMR Synthetic Penifulvin A

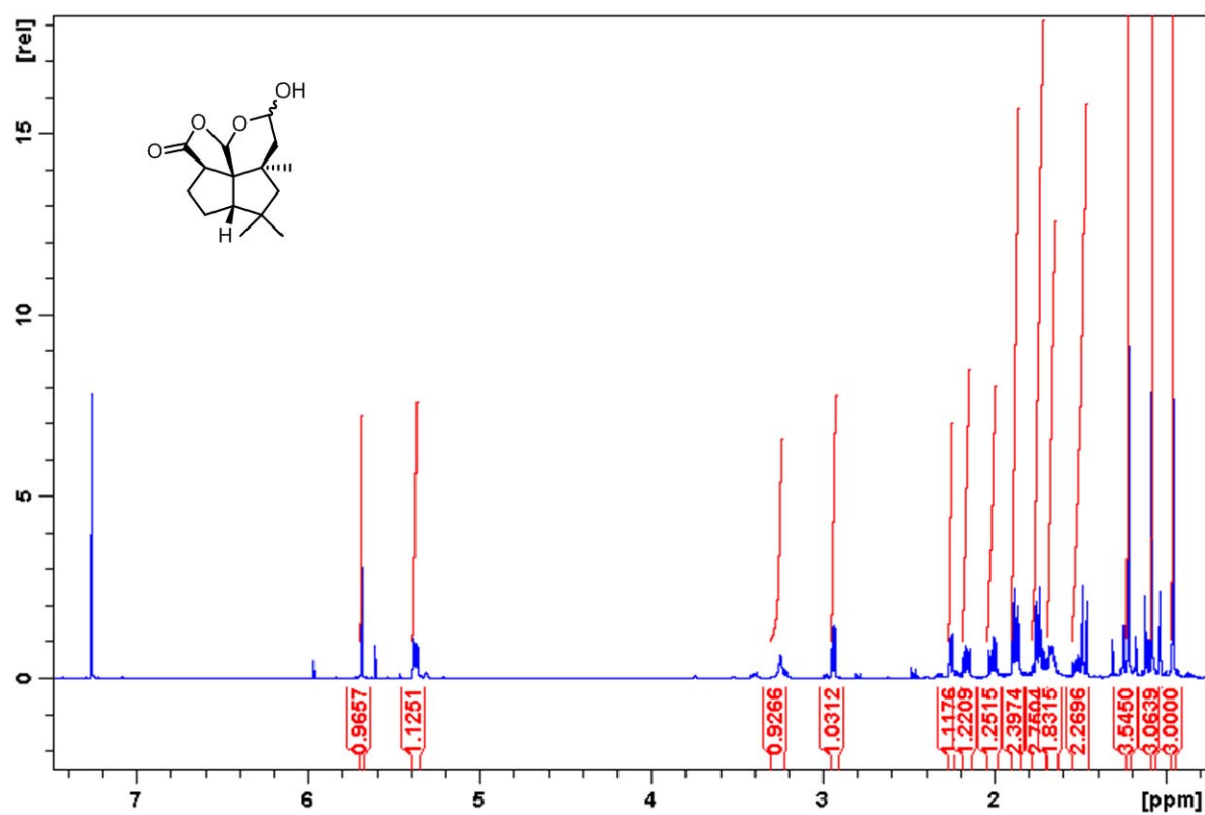


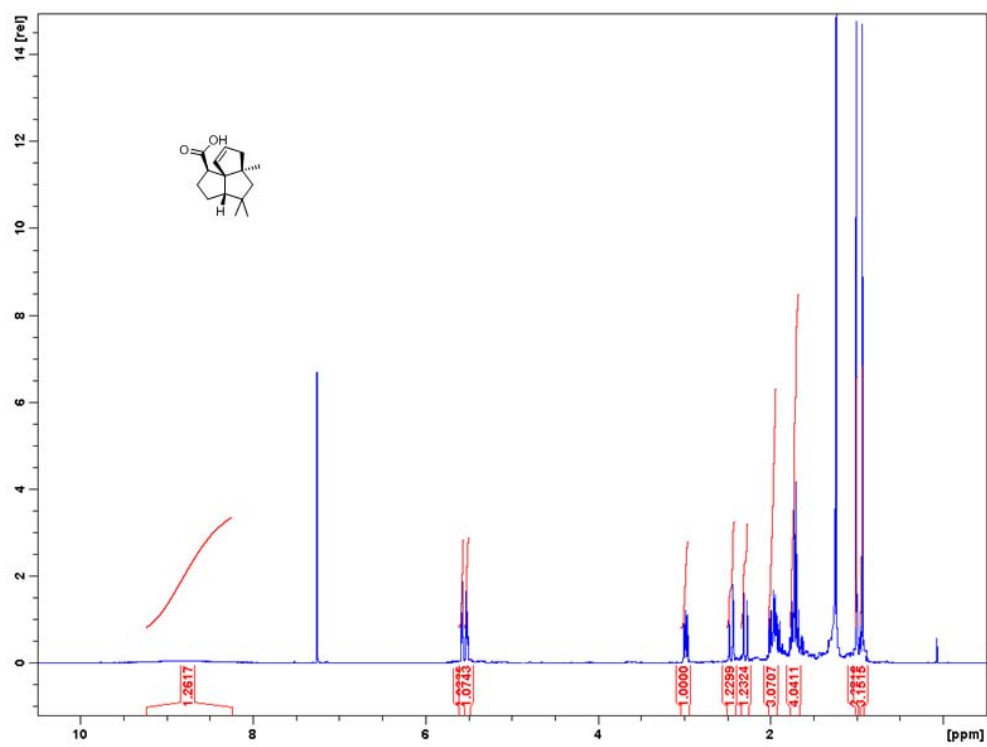
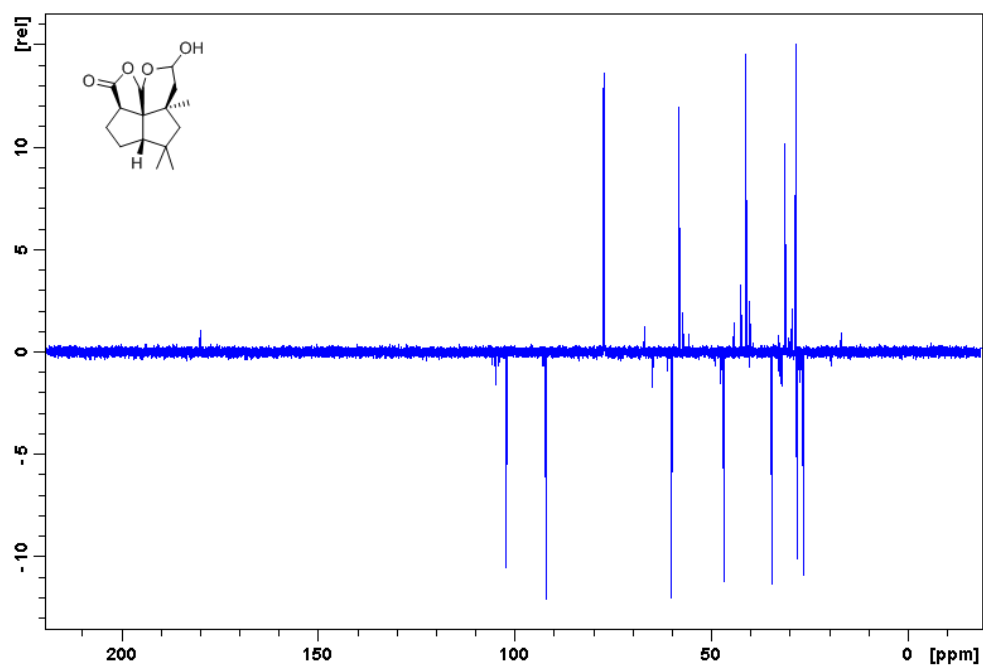
Natural Penifulvin A<sup>2</sup>

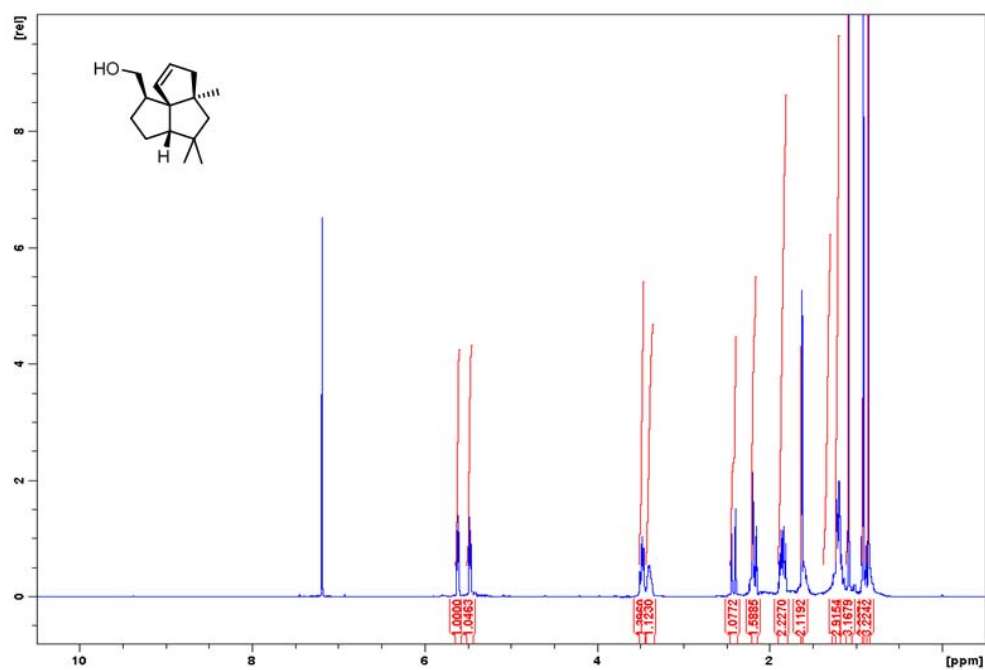
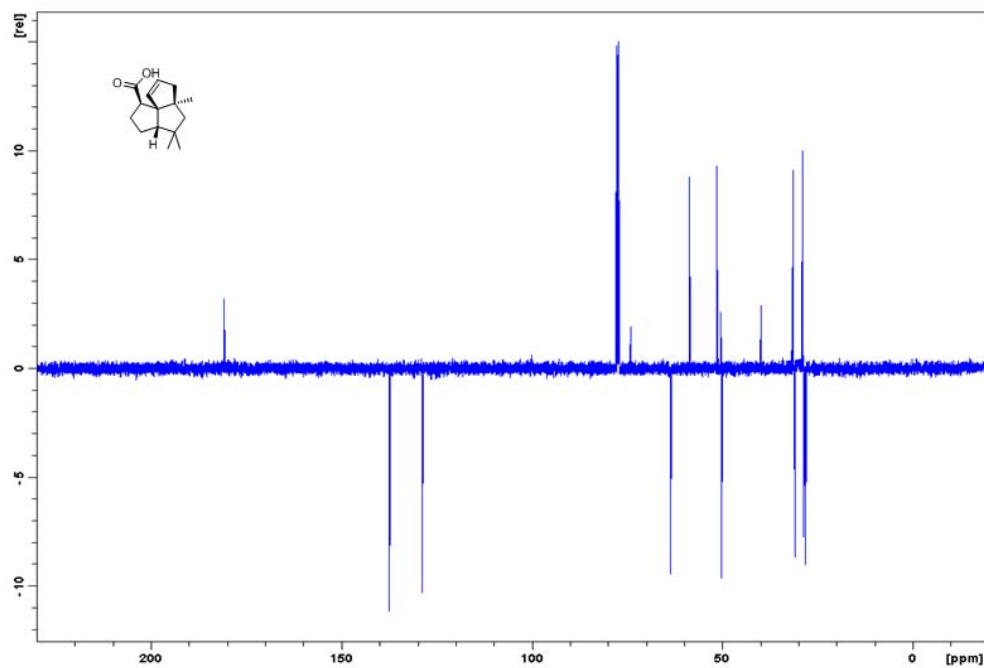


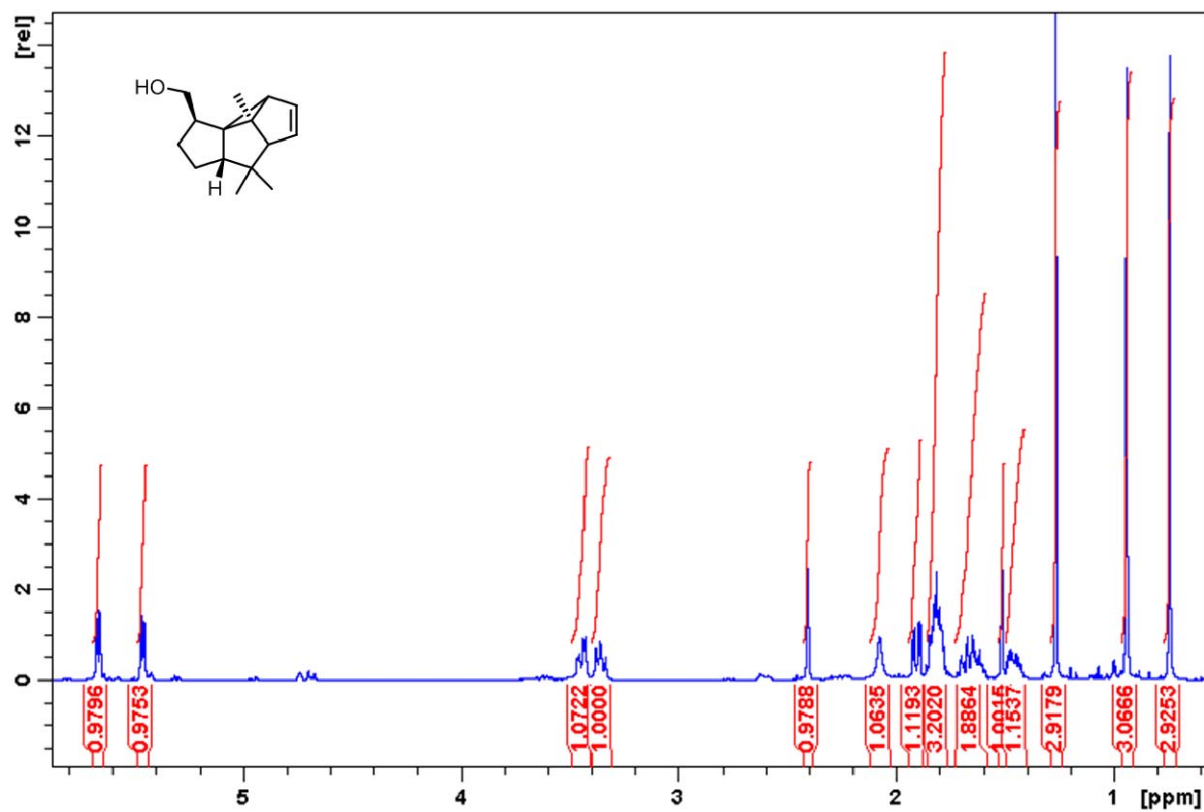
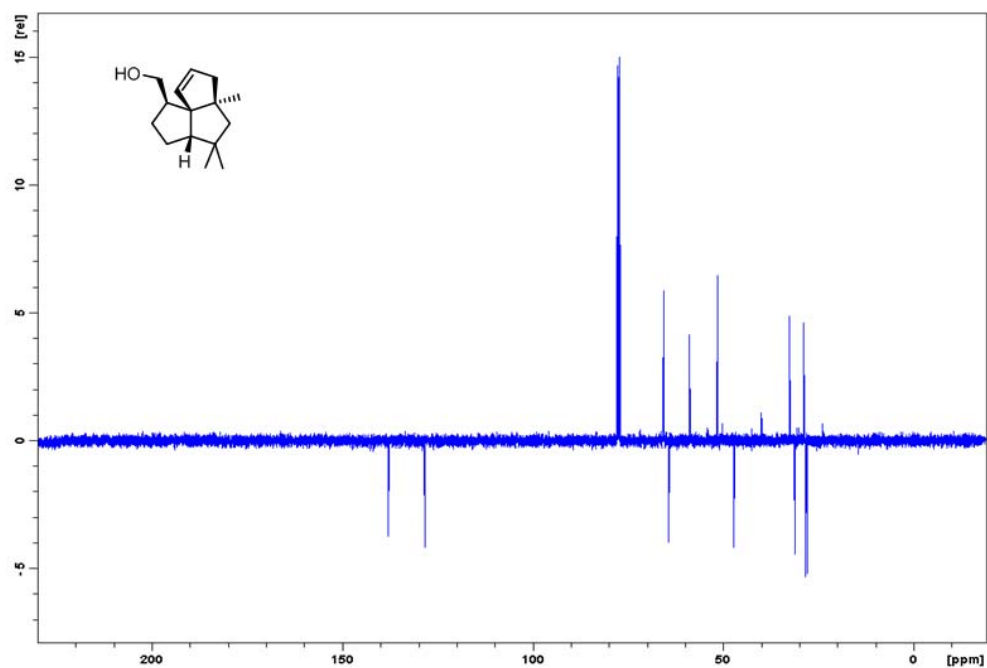
	COMPARISON of $^1\text{H}$ -NMR DATA		COMPARISON of $^{13}\text{C}$ -NMR DATA	
	natural	synthetic	natural	synthetic
Position	$\delta_{\text{H}}$ (mult, $J$ in Hz)		$\delta_{\text{C}}$	$\delta_{\text{C}}$
1	5.95 (s)	5.96 (s)	103.7	103.88
2			168.3	168.65
3 $\alpha$	2.77 (d, 16)	2.79 (d, 15)	43.9	44.10
3 $\beta$	2.43 (d, 16)	2.46 (d, 15)		
4			41.9	42.07
5 $\alpha$	1.76 (d, 14)	1.78 (d, 14)	55.4	55.62
5 $\beta$	1.71 (d, 14)	1.73 (d, 14)		
6			40.2	40.32
7	2.30 (dd, 5.1, 9.8)	2.32 (dd, 5.0, 9.7)	60.7	60.86
8			66.7	66.73
9	2.95 (dd, 1.2, 8.0)	2.97 (dd, 1.0, 8.0)	46.2	46.43
10 $\alpha$	2.20 (dddd, 2.0, 3.4, 8.0, 14)	2.23 (dddd, 1.8, 3.9, 8.0, 13.6)	29.9	30.11
10 $\beta$	1.90 (ddt, 8.0, 8.0, 14)	1.91 (ddt, 8.1, 8.1, 13.6)		
11 $\alpha$	1.71 (m)	1.74 (m)	28.0	28.18
11 $\beta$	1.83 (m)	1.83 (m)		
12	1.22 (s)	1.24 (s)	32.6	32.83
13	1.00 (s)	1.03 (s)	27.4	27.58
14	1.07 (s)	1.10 (s)	27.2	27.42
15			177.8	178.04

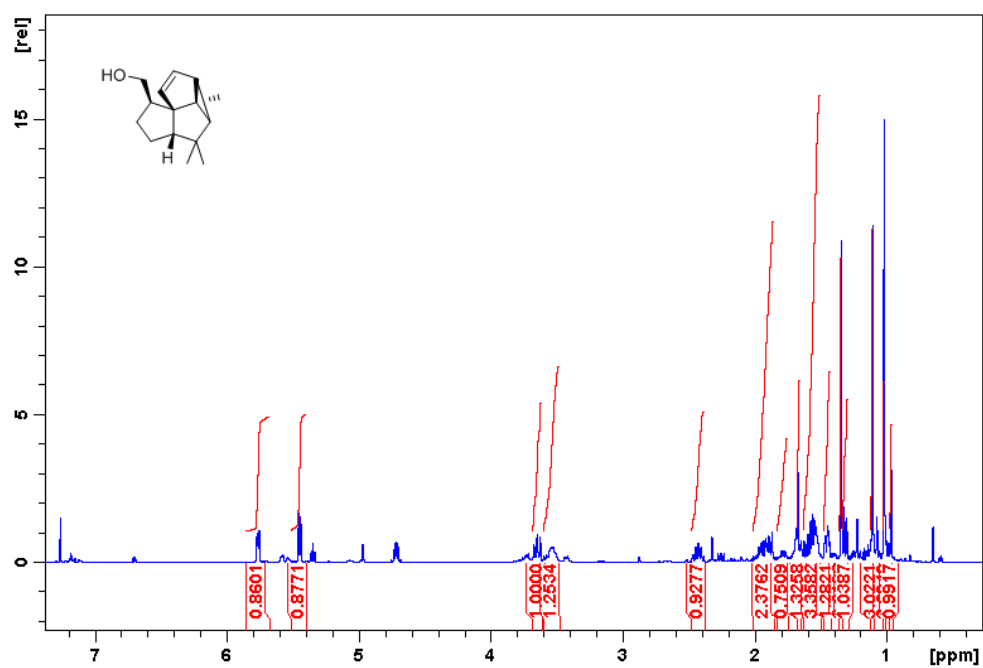
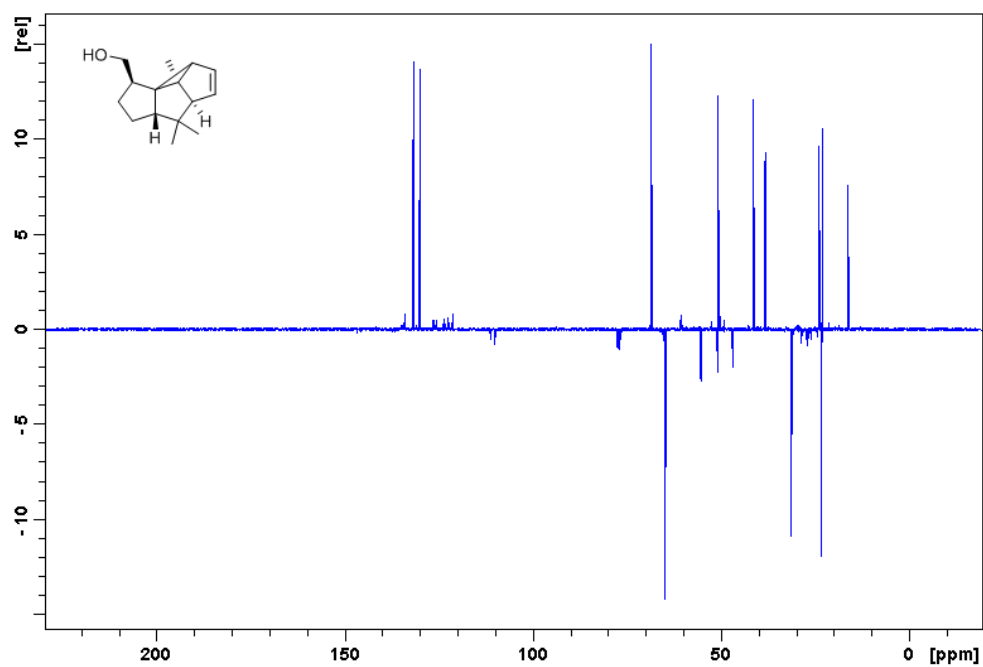


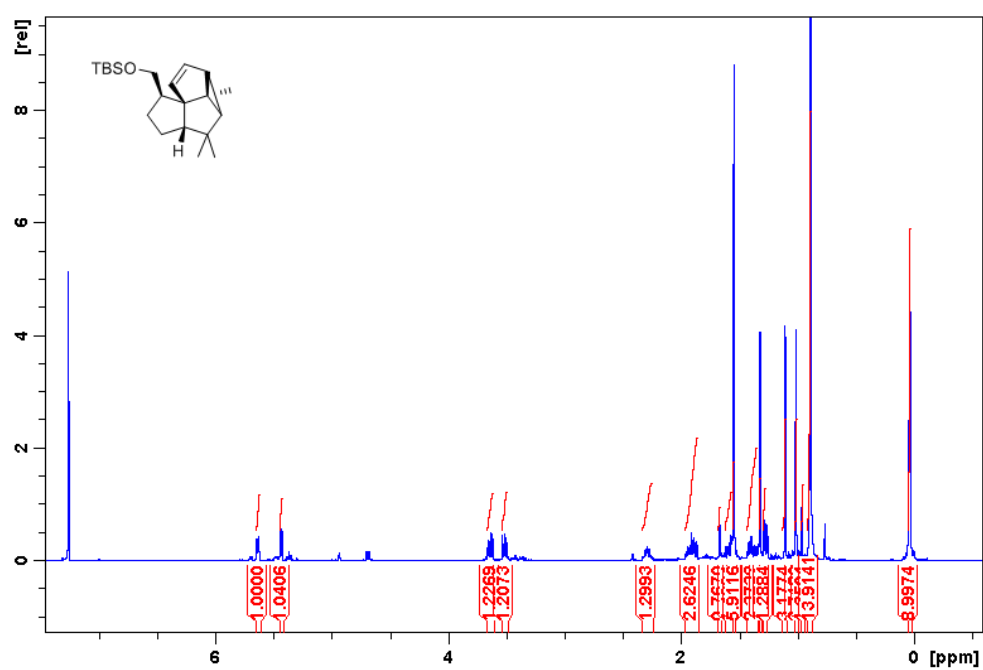
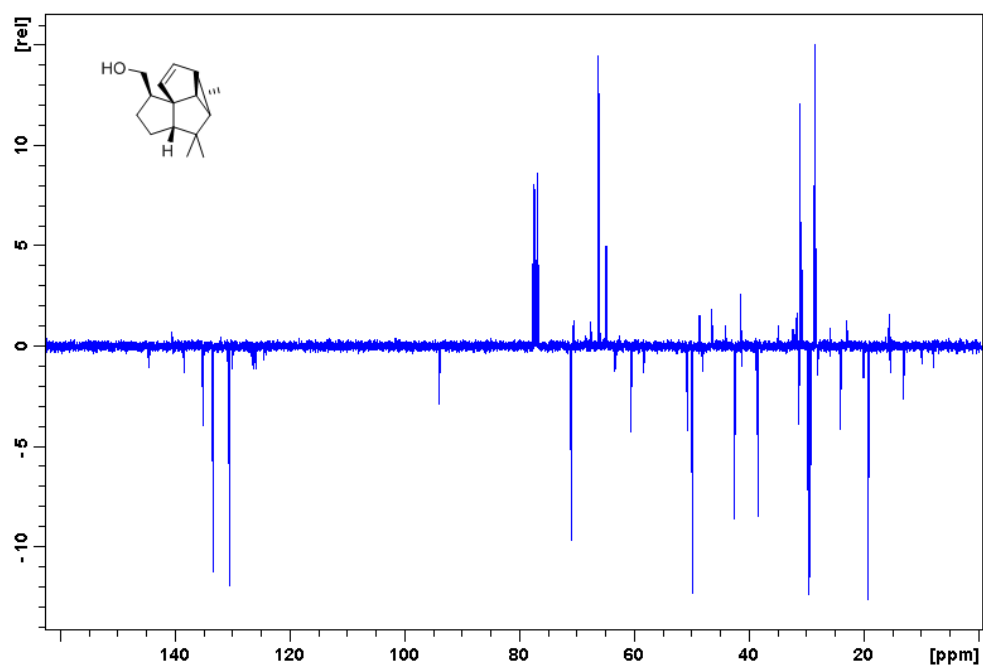


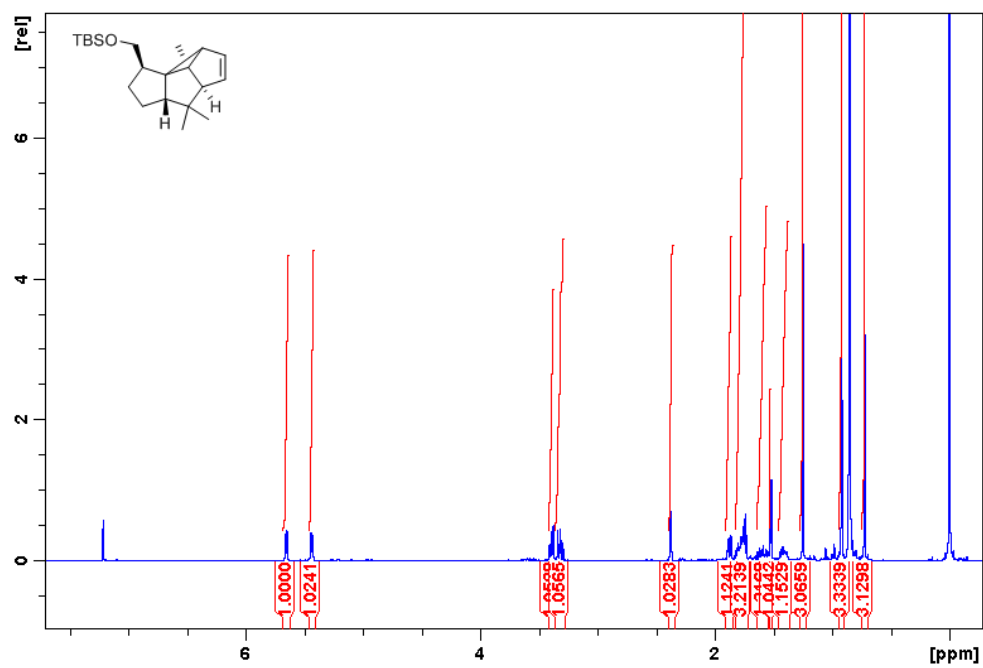
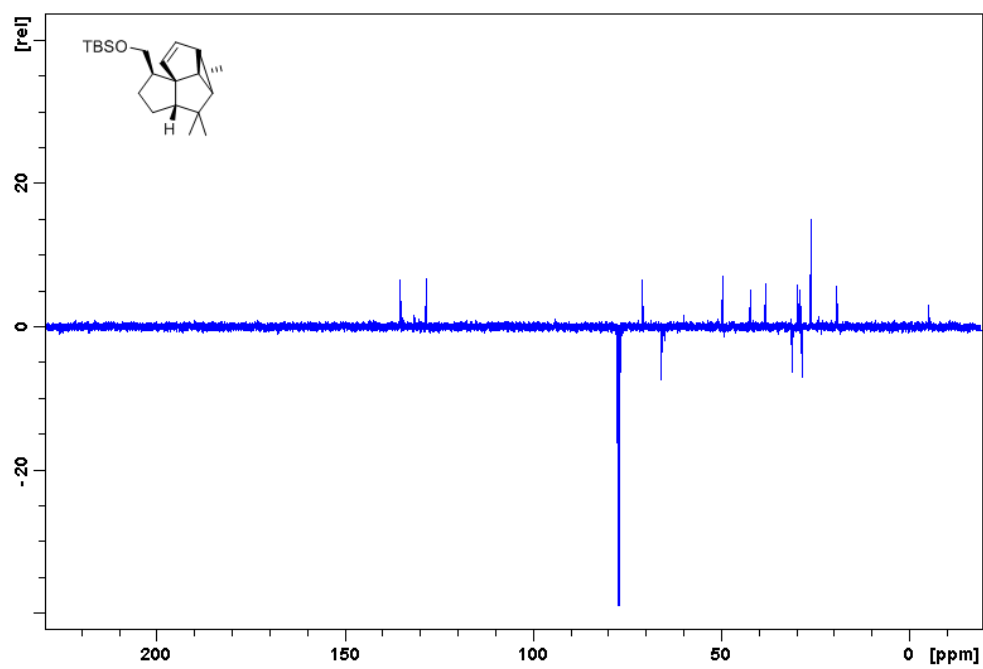


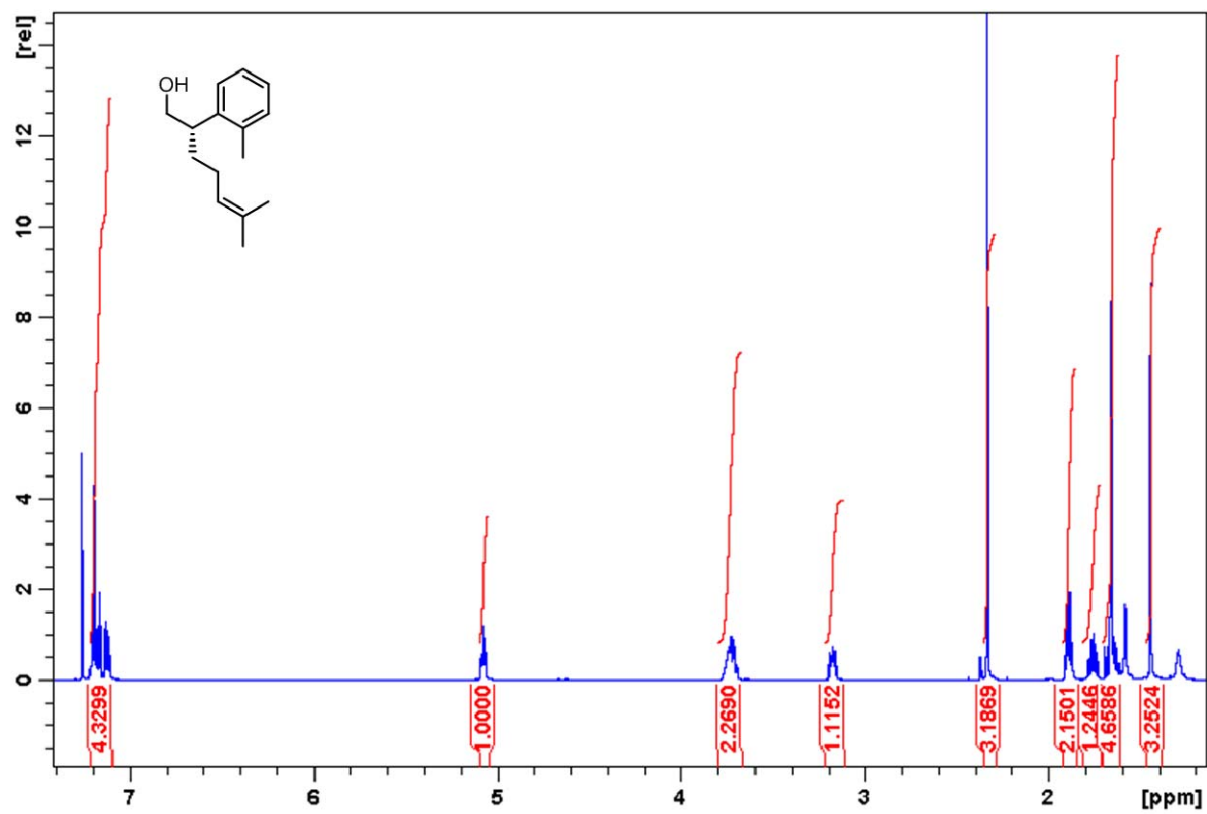
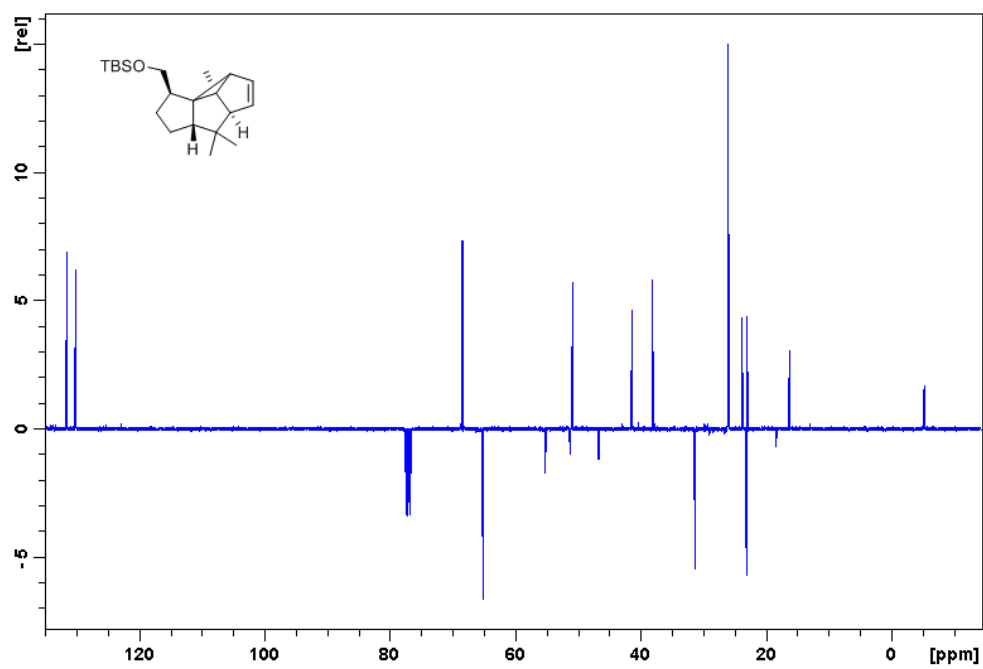




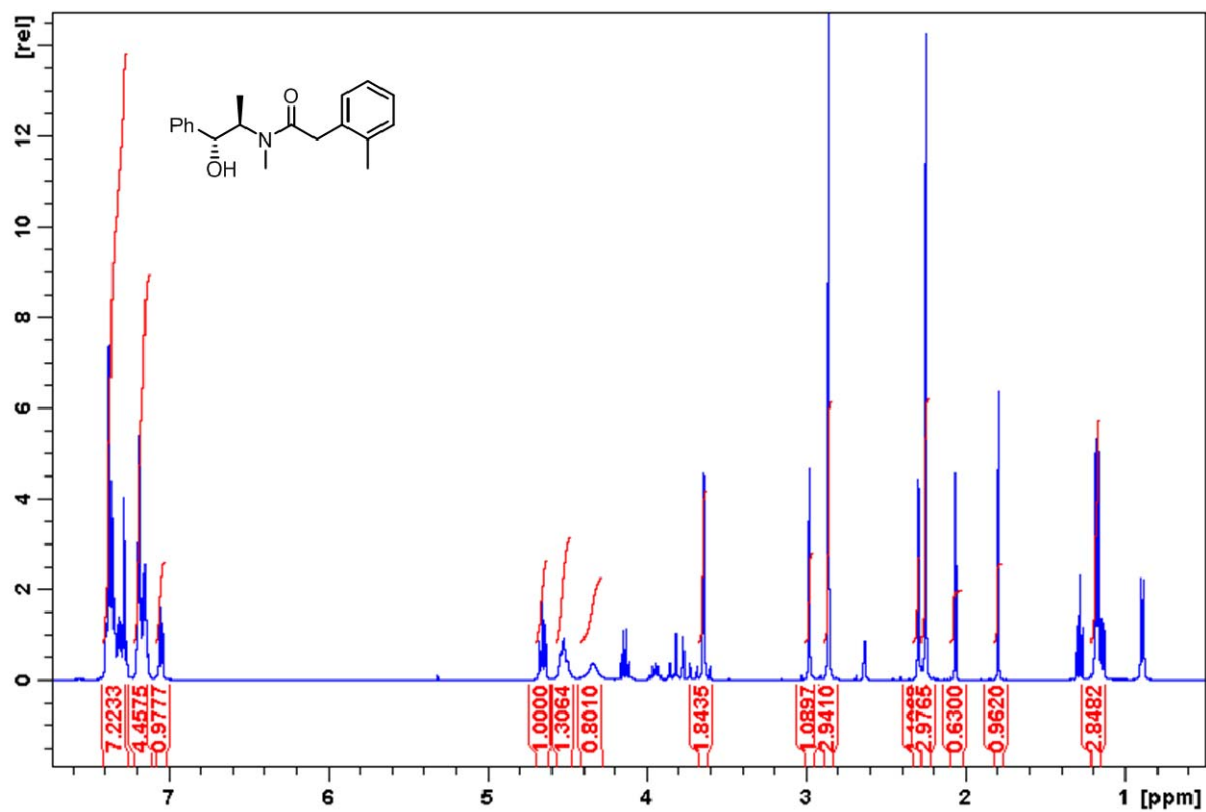
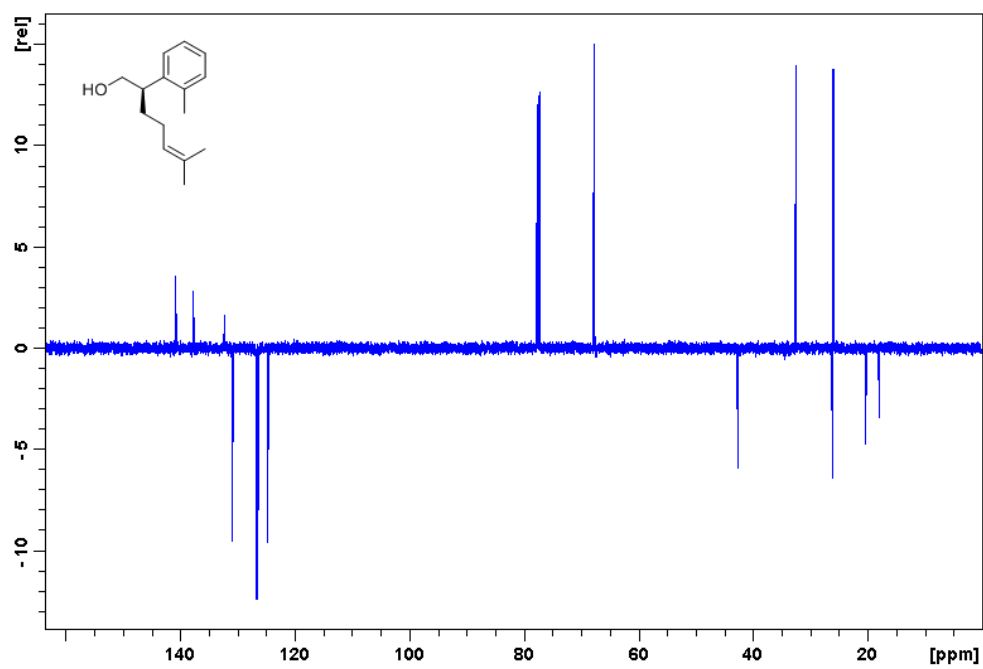


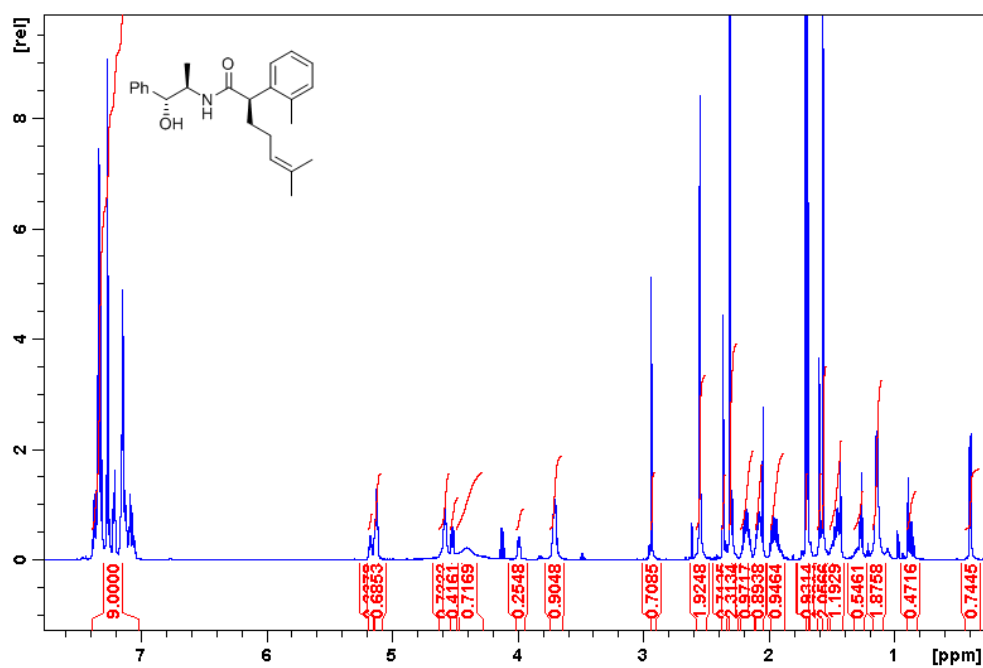
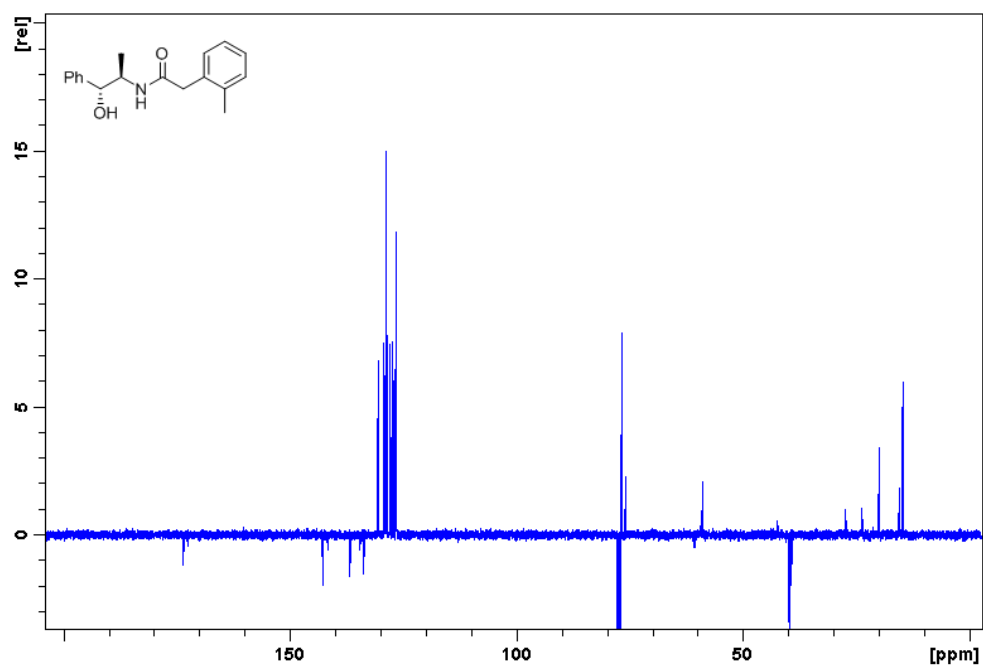


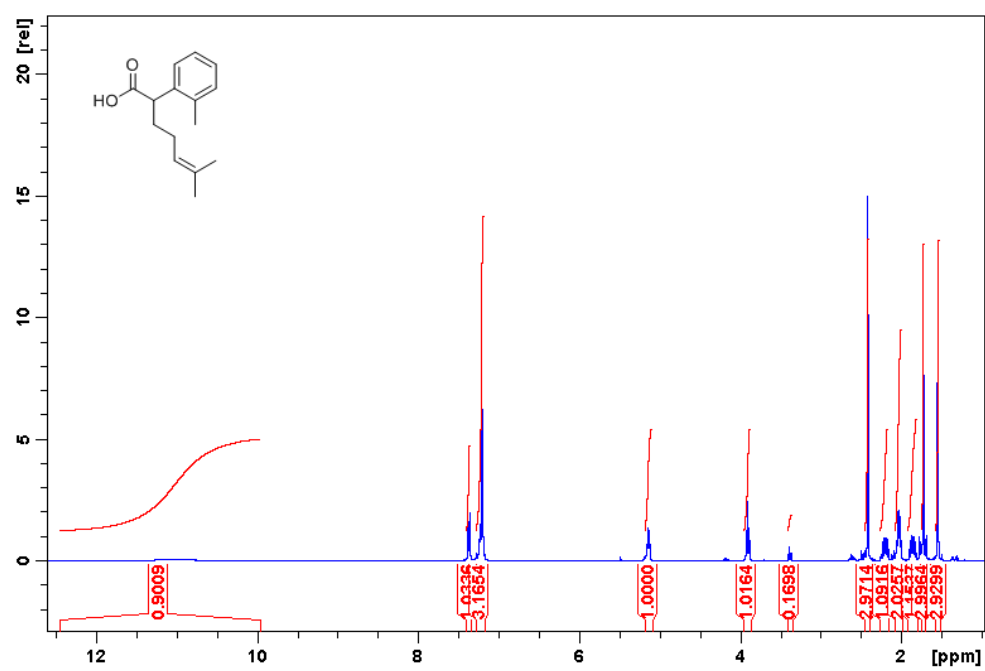












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