Total Synthesis of the Cytotoxic Enehydrazide Natural Products Hydrazidomycins A and B by a Carbazate Addition / Peterson Olefination Approach

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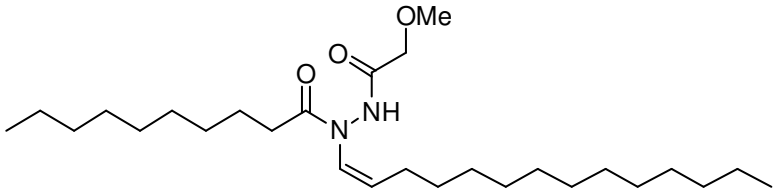
General Considerations

THF and Et_2O were dried over sodium benzophenone-ketyl and toluene and acetonitrile were dried over calcium hydride and solvents distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. All chemical manipulations were performed under a N_2 atmosphere unless otherwise stated. All reagents including tetradecyne, 3-octyn-1-ol, Lindlar's catalyst, Boc-carbazate, KHMDS (0.5M in toluene), Et_3N, acid chlorides, KO*t*Bu, TBS-Cl, TBAF (1M in THF), DIBAL (1M in hexanes), $Mg(ClO_4)_2$, $BF_3{\cdot}OEt_2$ were purchased from Aldrich or VWR and used as received unless otherwise stated. 6-heptyn-1-ol was purchased from Matrix Scientific. TMS-Cl was distilled from calcium hydride before use. 7-octyn-1-ol was prepared according to a modified literature procedure.[1] Ynehydrazide starting materials for synthesis of compounds **8**-**9** (scheme **1**) were prepared as described previously.[2] NMR solvents ($CDCl_3$ with TMS internal standard, d_6-DMSO, d_4-MeOH) were purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz, 400 MHz, 500 MHz or Bruker 400 MHz spectrometers. Chemical shifts are expressed in ppm values and ^{1}H NMR spectra are referenced to Me_4Si internal standard of 0.00 ppm for $CDCl_3$ and to residual solvent peaks for d_6-DMSO, d_4-MeOH (2.50 and 3.31 respectively). ^{13}C NMR spectra are referenced to residual solvent peaks: 77.00 ppm for $CDCl_3$, 39.52 for d_6-DMSO, and 49.00 for d_4-MeOH). ^{13}C NMR spectrum for Elaiomycin B (compound **3**) was referenced to a residual d_6-DMSO solvent peak of 39.7 for direct comparison with the isolation paper of the natural material.[3] ^{13}C NMR spectra for hydrazidomycin B and elaiomycin B (compounds **2**-**3**) were run on an Agilent DD2 500 MHz spectrometer with a HC 5-mm XSens cryogenically cooled probed. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; J, coupling constant in Hz. The coupling constant J (Hz) has been rounded to 0.5 Hz for all compounds except hydrazidomycins A-B and elaiomycin B (compounds **1**-**3**) where coupling constants are rounded to 0.1 Hz. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (i.e. dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH_2Cl_2 as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates

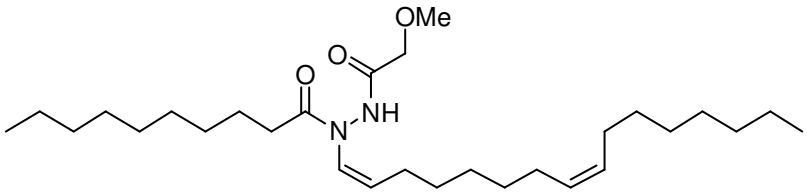
(Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized using $KMnO_4$, or ninhydrin and heating.

Spectral Data for Hydrazidomycins A-B and Elaiomycin B (Compounds 1-3)



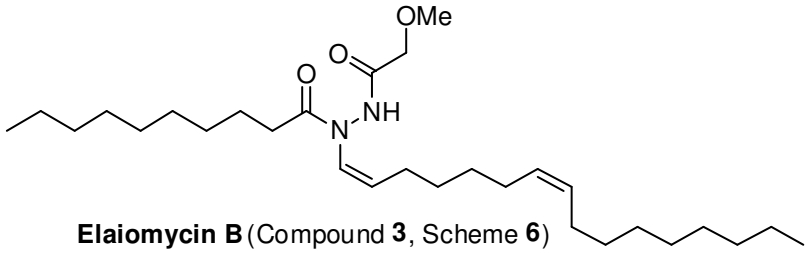
Hydrazidomycin A (Compound **1**, Scheme **4**)

White solid. m.p.= 38 – 40 ºC (CH_2Cl_2); R_f= 0.52 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3276, 2955, 2924, 2854, 1692, 1495, 1467, 1401, 1378, 1199, 1118; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.67 (1H, s), 6.40 (1H, dt, *J*=9.2, 1.6 Hz), 4.77 (1H, dt, *J*=9.2, 7.2 Hz), 3.97 (2H, s), 3.35 (3H, s), 1.94 - 2.38 (4H, m), 1.41 - 1.52 (2H, m), 1.19 - 1.31 (32H, m), 0.85 (6H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 173.18, 167.64, 124.26, 117.31, 70.67, 58.94, 31.28, 31.16, 29.07 (2 C's), 29.03 (3 C's), 29.00, 28.87, 28.84, 28.80, 28.69 (2 C's), 28.65, 28.57, 25.82, 23.84, 22.08 (2 C's), 13.94 (2 C's); HRMS (*m/z*): $[M + H]^+$ for $C_{27}H_{53}N_2O_3$, calcd, 453.4061; found, 453.4043.



Hydrazidomycin B (Compound **2**, Scheme **6**)

Clear oil at room temperature. White solid in a -15 ºC freezer. R_f= 0.48 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3265, 3003, 2955, 2925, 2855, 1692, 1680, 1498, 1466, 1401, 1378, 1284, 1245, 1199, 1160, 1118; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 6.41 (1H, dt, *J*=9.3, 1.6 Hz), 5.32 (2H, app t, *J*=5.0 Hz), 4.76 (1H, dt, *J*=9.3, 7.3 Hz), 3.97 (2H, s), 3.36 (3H, s), 2.31 (1H, t, *J*=7.3 Hz), 2.01 - 2.15 (3H, m), 1.92 - 2.01 (4H, m), 1.40 - 1.54 (2H, m), 1.14 - 1.36 (28H, m), 0.85 (6H, t, *J*=6.9 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 173.14, 167.60, 129.62, 129.55, 124.26, 117.09, 70.68, 58.94, 31.29, 31.27, 31.15, 29.12, 28.99, 28.89 (2 C's), 28.82 (2 C's), 28.67, 28.57, 28.54, 28.46, 26.62, 26.58, 25.81, 23.84, 22.09, 22.07, 13.93, 13.92; HRMS (*m/z*): $[M + H]^+$ for $C_{29}H_{55}N_2O_3$, calcd, 479.42127; found, 479.42290.



Elaiomycin B (Compound **3**, Scheme **6**)

Clear oil at room temperature. White solid in a -15 ºC freezer. R_f= 0.45 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3271, 3003, 2955, 2922, 2855, 1710, 1663, 1495, 1456, 1402, 1379, 1283, 1252, 1233, 1198, 1117; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 6.40 (1H, dt, *J*=9.3, 1.6 Hz), 5.31 (2H, app t, *J*=5.4 Hz), 4.75 (1H, dt, *J*=9.3, 7.2 Hz), 3.97 (2H, s), 3.34 (3H, s), 2.30 (1H, t, *J*=7.3 Hz), 2.01 - 2.19 (3H, m), 1.96 (4H, dt, *J*=6.1, 6.4 Hz), 1.38 - 1.53 (2H, m), 1.19 - 1.31 (28H, m), 0.84 (6H, t, *J*=7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 173.35, 167.80, 129.87, 129.67, 124.51, 117.25, 70.86, 59.13, 31.45, 31.34 (2 C's), 29.31, 29.12, 29.06, 29.04, 28.99, 28.91, 28.86, 28.84, 28.80, 28.75, 26.77, 26.68, 25.89, 24.02, 22.27, 22.26, 14.12, 14.12; HRMS (*m/z*): $[M + H]^+$ for $C_{29}H_{55}N_2O_3$, calcd, 479.42127; found, 479.42176.

Table 1. Synthetic vs. Natural ^{13}C NMR data for Hydrazidomycins A and B[a]

Hydrazidomycin A		**Hydrazidomycin B**	
Natural[4]	Synthetic	Natural[4]	Synthetic
173.3	173.2	173.2	173.1
167.8	167.6	167.7	167.6
124.3	124.3	129.6 (2 C's)	129.62, 129.55
117.2	117.3	124.3	124.3
70.7	70.7	117.1	117.1
59.0	58.9	70.7	70.7
31.4	31.3	59.0	58.9
31.2	31.2	31.3	31.3
29.2, 29.1 (5C's)	29.07, 29.03 (5C's)	31.2 (2C's)	31.27, 31.15
29.0 (2C's)	29.0, 28.87	29.1 (2C's)	29.12, 28.99
28.8 (2C's)	28.84, 28.80	28.9 (2C's)	28.89 (2C's)
28.7 (2C's)	28.69 (2C's)	28.8 (2C's)	28.82 (2C's)
28.6 (2C's)	28.65, 28.57	28.7	28.67
25.9	25.8	28.6 (3C's)	28.57, 28.54, 28.46
23.9	23.8	26.6 (2C's)	26.62, 26.58
22.2 (2C's)	22.1 (2C's)	25.9	25.8
14.1 (2C's)	13.9 (2C's)	23.9	23.8
		22.1 (2C's)	22.09, 22.07
		13.9 (2C's)	13.93, 13.92

a) δ in ppm; d6-DMSO at 25 °C relative to 39.52 solvent residual peak[4]

Table 2. Synthetic vs. Natural ^{13}C NMR data for Elaiomycin B[a]

Natural[3]	Synthetic
173.4	173.4
167.8	167.8
129.8	129.87
129.7	129.67
124.4	124.5
117.4	117.2
70.9	70.9
58.5	59.1
31.4	31.4
31.3, 31.2	31.3 (2C's)
29.3	29.3
29.2-28.6 (9C's)	29.12, 29.06, 29.04, 28.99, 28.91, 28.86, 28.84, 28.80, 28.75
26.8	26.8
26.7	26.7
26.0	25.9
23.9	24.0
22.3 (2C's)	22.27, 22.26
14.1 (2C's)	14.12, 14.12

a) δ in ppm; d6-DMSO at 25 °C relative to 39.7 solvent residual peak[3]

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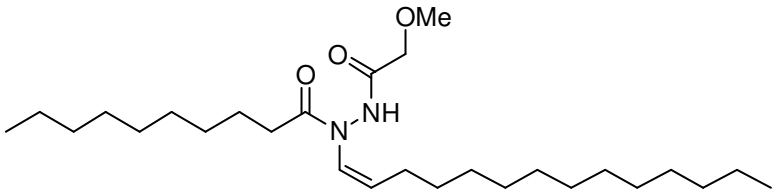

Hydrazidomycin A

(Compound **1**, Scheme **4,** ^{1}H NMR @ rm. temp. d6-DMSO)

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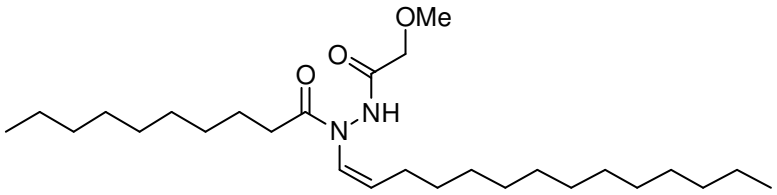

Hydrazidomycin A

(Compound **1**, Scheme **4,** ^{1}H NMR @ 55 C d6-DMSO)

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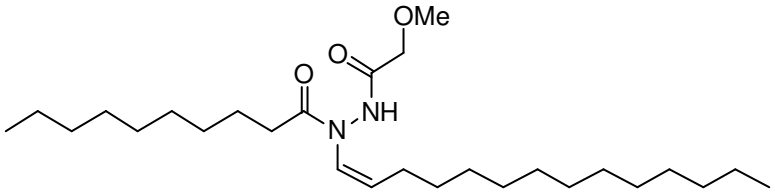
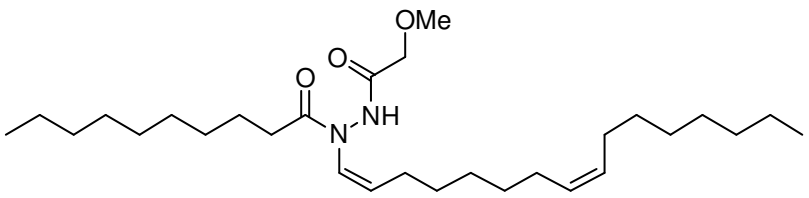


Hydrazidomycin A

(Compound **1**, Scheme **4**)

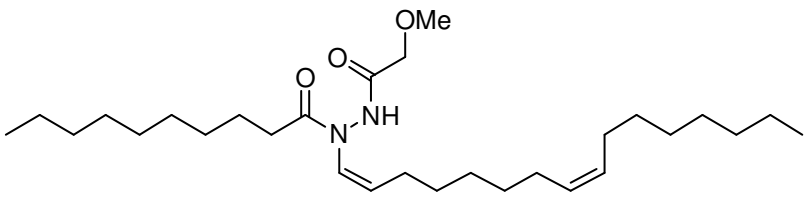
20130406_vnmrs_500_reb-9-159-fs39-41-PROTON_01



Hydrazidomycin B

(Compound **2**, Scheme **6,** ^{1}H NMR @ RT in *d6*-DMSO)

20130408_vnmrs_400_reb-9-159-55deg-PROTON_01



Hydrazidomycin B

(Compound **2**, Scheme **6,** ^{1}H NMR @ 55 C in *d6*-DMSO)

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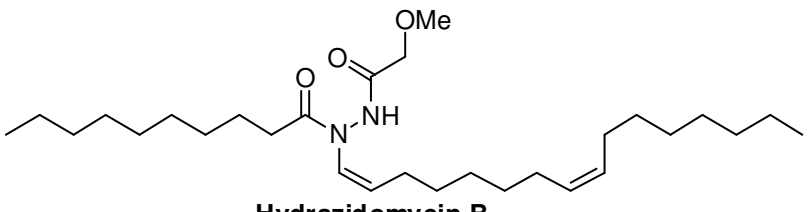

Hydrazidomycin B

(Compound **2**, Scheme **6**)

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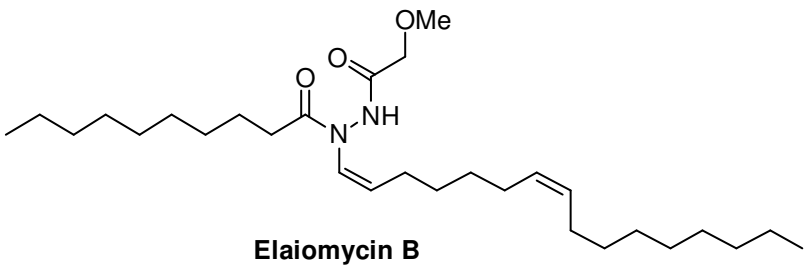

Elaiomycin B

(Compound **3**, Scheme **6,** ^{1}H NMR @ RT in *d6*-DMSO)

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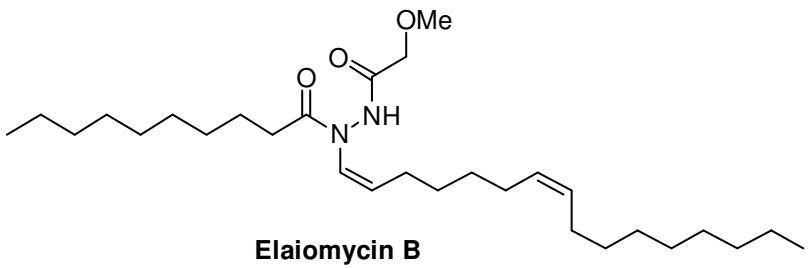

Elaiomycin B

(Compound **3**, Scheme **6,** ^{1}H NMR @ 55 C in *d6*-DMSO)

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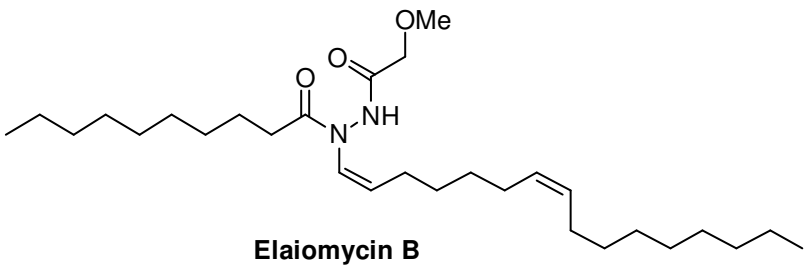
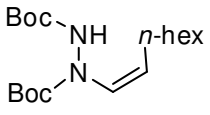


Elaiomycin B
(Compound **3**, Scheme **6**)

Experimental Procedures

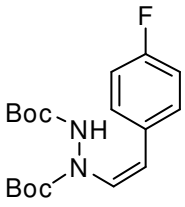
Synthesis of Z-enehydrazides from ynehydrazides via Lindlar hydrogenation (Scheme 1, Compounds 8-9):

(Z)-di-tert-butyl 1-(oct-1-en-1-yl)hydrazine-1,2-dicarboxylate (compound 8, scheme 1):



di-tert-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate ynehydrazide prepared according to the previously disclosed procedure[2] (0.2 mmol , 68 mg) in CH_2Cl_2 (20 mL) was charged with Lindlar's catalyst (22 mg 5 wt% Pd on $CaCO_3$ poisoned with Pb) and the flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by TLC (26 hours) the flask was purged with nitrogen for 5 mins then diluted with CH_2Cl_2 (40 mL) and filtered through a short celite plug and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 52 mg (76% yield) of (Z)-di-tert-butyl 1-(oct-1-en-1-yl)hydrazine-1,2-dicarboxylate (compound **8**, scheme **1**) as a clear oil with $\geq$ 10:1 Z:E olefin geometry by ^{1}H NMR. R_f= 0.42 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3308 (br), 2978, 2922, 2857, 1751-1655 (br m), 1506, 1381, 1323, 1249, 1165; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.46 (1H, br. s.), 6.08 - 6.36 (1H, m), 4.80 (1H, d, *J*=8.0 Hz), 2.15 (2H, q, *J*=6.0 Hz), 1.41 - 1.56 (18H, m), 1.19 - 1.38 (8H, m), 0.88 (3H, t, *J*=6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.90, 153.62, 125.29, 117.46, 81.97, 81.41, 31.74, 29.74, 29.06, 28.21, 28.13, 26.36, 22.63, 14.09; HRMS (*m/z*): $[M + H]^+$ for $C_{18}H_{35}N_2O_4$, calcd, 343.2591; found, 343.2607.

(Z)-di-tert-butyl 1-(4-fluorostyryl)hydrazine-1,2-dicarboxylate (compound 9, scheme 1):

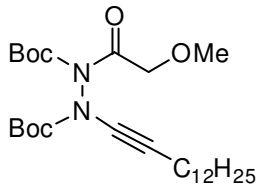


di-tert-butyl 1-((4-fluorophenyl)ethynyl)hydrazine-1,2-dicarboxylate ynehydrazide prepared according to the previously disclosed procedure[2] (0.12 mmol, 44 mg) in CH_2Cl_2 (12 mL) was charged with Lindlar's catalyst (13 mg 5 wt% Pd on $CaCO_3$ poisoned with Pb) and the flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by TLC (2 hours) the flask was purged with nitrogen for 5 mins then diluted with CH_2Cl_2 (40 mL) and filtered through a short celite plug and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 52 mg (76% yield) of (Z)-di-tert-butyl 1-(4-fluorostyryl)hydrazine-1,2-dicarboxylate (compound **9**, scheme **1**) as a clear oil with 6:1 Z:E olefin geometry by ^{1}H NMR. R_f= 0.45 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3313, 2979, 2935, 1888, 1722, 1656, 1603, 1511, 1368, 1316, 1155, 1052, 1023, 873, 849; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.24 (2H, m), 6.98

(2H, dd, *J*= 9.0, 9.0 Hz), 6.41-6.86 (1H, m), 6.17 (1H, br. s.), 5.79 (1H, d, *J*=9.5 Hz), 1.22 - 1.52 (18H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.8 (1C, d, *J* = 245 Hz), 154.08, 153.47, 132.46, 130.33, 127.06, 115.1 (1C , d, *J* = 21 Hz), 112.42, 82.99, 81.75, 28.29, 28.23; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -116.29 (1F, s, major cis isomer), -115.69 (1F, s, minor trans isomer); HRMS (*m/z*): $[M + H]^+$ for $C_{18}H_{26}FN_2O_4$, calcd, 353.18766; found, 353.18869.

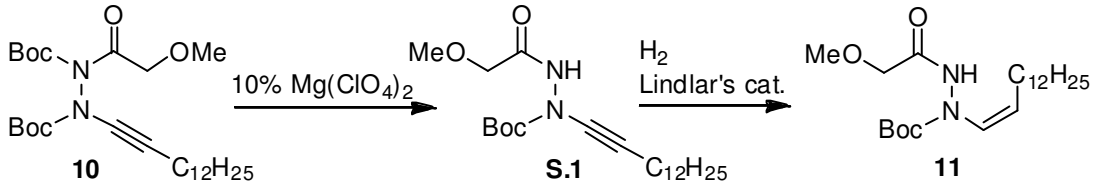
Synthesis of hydrazidomycin A analogues via an ynehydrazide approach (Scheme 2, Compounds 10-13):

di-tert-butyl 1-(2-methoxyacetyl)-2-(tetradec-1-yn-1-yl)hydrazine-1,2-dicarboxylate (compound 10, scheme 2):



A solution of 1-tetradecyne (2.0 mmol, 1.0 eq., 389 mg, 0.49 mL) in THF (8 mL) was cooled to 0 ºC and treated with n-BuLi (2.4 mmol, 1.2 eq., 0.96 mL of a 2.5 M sol'n in hexanes) and stirred for 10 mins. The mixture was then cooled to -78 ºC and a solution of di-tert-butyl-diazodicarboxylate (3.0 mmol, 1.5 eq., 690 mg) in THF (4 mL) was added quickly by syringe and the mixture removed from the cooling bath and warmed to room temperature. After stirring for 30 mins at room temperature, the mixture was re-cooled to -78 ºC and a solution of methoxyacetyl chloride (3.0 mmol, 1.5 eq., 326 mg, 0.27 mL) in THF (2 mL) was added and the cooling bath removed and warmed to room temperature. After stirring at room temperature for 14 hours the mixture was diluted with sat'd NH_4Cl(aq) (10 mL) and water (10 mL) and ethyl acetate (100 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* and the crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 616 mg (62% yield) of di-tert-butyl 1-(2-methoxyacetyl)-2-(tetradec-1-yn-1-yl)hydrazine-1,2-dicarboxylate (compound **10**, scheme **2**) as a yellow oil. R_f= 0.35 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 2980, 2926, 2855, 2830, 2266, 1802, 1740, 1456, 1395, 1371, 1151, 1130, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.42 – 4.56 (2H, m, r), 3.48 (3H, s), 2.23 – 2.35 (2H, m, r), 1.42 - 1.62 (20H, m), 1.18 - 1.41 (18H, m), 0.83 - 0.92 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm (major rotomer) 168.99, 151.72, 150.41, 85.13, 84.10, 73.04, 71.95, 71.59, 59.42, 31.93, 29.69, 29.64, 29.36, 29.18, 28.87, 28.76, 28.70, 27.89, 27.86, 27.80, 22.69, 18.45, 14.13; HRMS (*m/z*): $[M + Na]^+$ for $C_{27}H_{48}N_2O_6Na$, calcd, 519.3404; found, 519.3425.

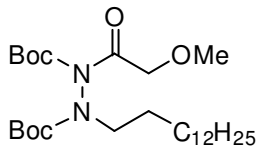
(Z)-tert-butyl 2-(2-methoxyacetyl)-1-(tetradec-1-en-1-yl)hydrazinecarboxylate (compound 11, scheme 2):



To compound **10** (0.207 mmol, 1.0 eq., 103 mg) dissolved in MeCN (5 mL) was added $Mg(ClO_4)_2$ and the mixture placed in a 55 ºC oil bath with a reflux condenser. After 2 hours the mixture was cooled to room temperature and concentrated *in vacuo* and the crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 64 mg (78% yield) of compound **S.1** as a clear oil. R_f= 0.11 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3299, 2979, 2925, 2855, 2264, 1748, 1714, 1489, 1370, 1318, 1253, 1156, 1117; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (1H, s), 4.04 (2H, s), 3.44 (3H, s), 2.28 (2H, t, *J*=7.0 Hz), 1.43 - 1.57 (11H, m), 1.33 - 1.41 (2H, m), 1.22 - 1.30 (16H, m), 0.88 (3H, t, *J*=7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.62, 152.51, 83.99, 72.65, 71.61, 71.10, 59.46, 31.88, 29.63, 29.61, 29.60, 29.51, 29.31, 29.14, 28.82, 28.66, 27.85, 22.64, 18.43, 14.07; HRMS (*m/z*): $[M + H]^+$ for $C_{22}H_{41}N_2O_4$, calcd, 397.30663; found, 397.30757.

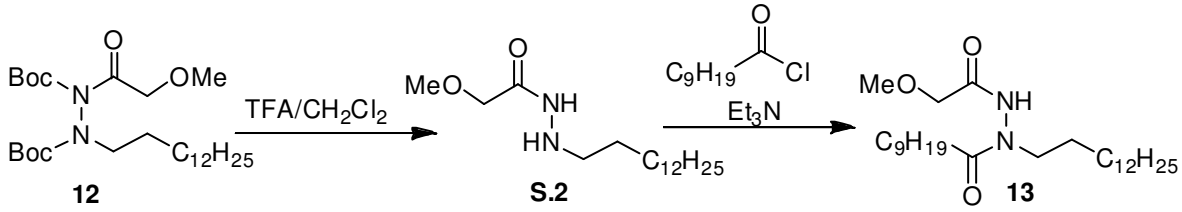
Compound **S.1** (0.096 mmol, 1.0 eq., 38 mg) was dissolved in CH_2Cl_2 (10 mL) and Lindlar's catalyst (11 mg 5 wt% Pd on $CaCO_3$ poisoned with Pb) was added. The flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by ^1H NMR (17 hours) the flask was purged with nitrogen for 5 mins then diluted with CH_2Cl_2 (40 mL) and filtered through a short celite plug and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 29 mg (76% yield, 59% over 2 steps) of (Z)-tert-butyl 2-(2-methoxyacetyl)-1-(tetradec-1-en-1-yl)hydrazinecarboxylate (compound **11**, scheme **2**) as a clear oil with ≥ 10:1 Z:E olefin geometry by ^1H NMR. R_f= 0.48 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3298, 2925, 2854, 1722, 1693, 1504, 1456, 1368, 1456, 1368, 1316, 1255, 1168, 1118; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.21 (1H, s), 6.22 - 6.51 (1H, m), 4.87 (1H, ddd, *J*=8.50, 7.50, 7.50 Hz), 4.01 (2H, s), 3.45 (3H, s), 2.08 (2H, qd, *J*=7.0, 1.5 Hz), 1.48 (9H, s), 1.19 - 1.38 (20H, m), 0.88 (3H, t, *J*=7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 167.79, 152.96, 125.45, 119.38, 82.65, 71.76, 59.53, 31.90, 29.66, 29.64, 29.62, 29.61, 29.53, 29.50, 29.39, 29.33, 28.07, 26.53, 22.67, 14.09; HRMS (*m/z*): $[M + Na]^+$ for $C_{22}H_{42}N_2O_4Na$, calcd, 421.3036; found, 421.3038.

di-tert-butyl 1-(2-methoxyacetyl)-2-(tetradecyl)hydrazine-1,2-dicarboxylate (compound 12, scheme 2):



Compound **11** (0.191 mmol, 1.0 eq., 95 mg) was dissolved in ethyl acetate (5 mL) and Pd/C (21 mg 10 wt% dry Pd/C) was added. The flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. After 18 hours the flask was purged with nitrogen for 5 mins then diluted with ethyl acetate (40 mL) and filtered through a short celite plug and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute providing 69 mg (72% yield) of di-tert-butyl 1-(2-methoxyacetyl)-2-(tetradecyl)hydrazine-1,2-dicarboxylate (compound **12**, scheme **2**) as a clear oil. R_f= 0.44 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3379, 2977, 2925, 2855, 1739, 1721, 1460, 1394, 1369, 1322, 1254, 1151, 1128, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.46 - 4.56 (2H, m), 3.46 - 3.57 (1H, m), 3.44 - 3.46 (3H, m), 3.23 - 3.36 (1H, m), 1.37 - 1.53 (21H, m), 1.21 - 1.30 (21H, m), 0.86 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm (major rotomer) 170.50, 153.57, 152.18, 84.30, 81.06, 73.39, 59.21, 49.04, 31.88, 29.61, 29.56, 29.39, 29.32, 28.19, 28.12, 28.04, 27.87, 27.82, 27.49, 26.87, 22.65, 14.08; HRMS (*m/z*): $[M + NH_4]^+$ for $C_{27}H_{56}N_3O_6$, calcd, 518.41691; found, 518.41786.

N'-(2-methoxyacetyl)-N-tetradecyldecanehydrazide (compound 13, scheme 2):



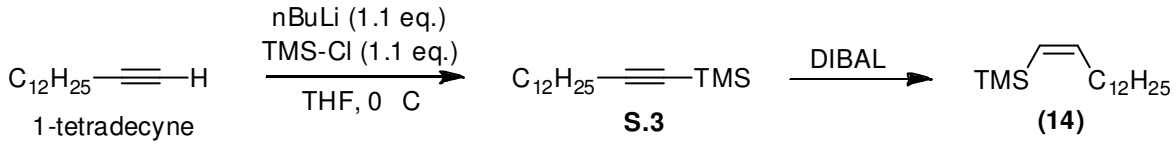
Compound **12** (0.133 mmol, 1.0 eq., 67 mg) dissolved in CH_2Cl_2 (3 mL) was cooled to 0 ºC and treated with TFA (0.20 mL) and stirred for 3 hours allowing to warm to room temperature. A further portion of TFA (0.60 mL) was then added and stirred at room temperature until complete by TLC (4 hours, 7 hours total). The mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat'd $NaHCO_3$(aq) (10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered concentrated *in vacuo* to provide 35 mg (88% yield) of crude intermediate **S.2** as a white solid.

Compound **S.2** (0.116 mmol, 1.0 eq., 35 mg) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 ºC before additioin of Et_3N (0.162 mmol, 1.4 eq., 16 mg) as a solution in CH_2Cl_2 (0.5 mL) followed by

addition of decanoyl chloride (0.128 mmol, 1.1 eq., 24 mg) as a solution in CH_2Cl_2 (0.5 mL). The mixture was stirred overnight allowing to warm to room temperature. After 16 hours the mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat'd $NaHCO_3$(aq) (10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute providing 41 mg (78% yield, 68% over 2 steps) of N'-(2-methoxyacetyl)-N-tetradecyldecanehydrazide (compound **13**, scheme **2**) as a white solid.. m.p.= 51-54 ºC (EtOAc/hexanes); R_f= 0.48 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3256, 2917, 2850, 1674, 1658, 1504, 1469, 1200, 1115, 989; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (1H, s), 4.04 (2H, s), 3.57 (2H, t, *J*=8.0 Hz), 3.48 (3H, s), 2.26 (2H, t, *J*=8.0 Hz), 1.47 - 1.65 (4H, m), 1.17 - 1.34 (34H, m), 0.88 (6H, td, *J*=7.0, 2.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 174.64, 167.73, 71.70, 59.48, 47.60, 32.25, 31.91, 31.87, 29.68, 29.66, 29.64, 29.57, 29.55, 29.44, 29.35, 29.32, 29.28, 27.05, 26.79, 24.62, 22.68, 22.66, 14.11, 14.10; $[M + H]^+$ for $C_{27}H_{55}N_2O_3$, calcd, 455.42127; found, 455.42142.

Silyl-epoxide ring opening with Boc-carbazate (Table 1, Compounds 14-16):

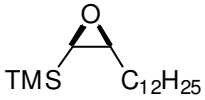
(Z)-trimethyl(tetradec-1-en-1-yl)silane (compound 14, table 1):



A solution of 1-tetradecyne (5.0 mmol, 1.0 eq., 972 mg, 1.23 mL) in THF (5 mL) was cooled to 0 ºC and treated with n-BuLi (5.5 mmol, 1.1 eq., 2.20 mL of a 2.5 M sol'n in hexanes) and stirred for 10 minutes before addition of distilled TMS-Cl (5.5 mmol, 1.1 eq., 598 mg, 0.70 mL). The mixture was removed from the cooling bath and stirred at room temperature for 1 hour then quenched by addition of sat'd NH_4Cl(aq.) (10 mL) and water (10 mL) and organics extracted with ethyl acetate (75 mL). The organic extract was dried ($MgSO_4$), filtered through a silica plug (3 cm x 3 cm) using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 1.30 g (98% yield) of 95% pure compound **S.3** as a clear oil. R_f= 0.33 (100% hexanes); IR (neat, cm^{-1}) 3316, 2957, 2926, 2855, 2176, 1468, 1248, 843; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.21 (2H, t, *J*=7.0 Hz), 1.45 - 1.56 (2H, m), 1.21 - 1.41 (18H, m), 0.88 (3H, t, *J*=7.0 Hz), 0.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 107.80, 84.21, 31.93, 29.67, 29.65, 29.60, 29.50, 29.36, 29.09, 28.81, 28.65, 22.69, 19.87, 14.12, 0.18; HRMS (*m/z*): $[M + H]^+$ for $C_{17}H_{35}Si$, calcd, 267.25080; found, 267.25060.

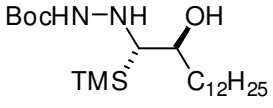
A solution of compound **S.3** prepared above (4.89 mmol, 1.0 eq., 1.30 g) and N-Me-Morpholine (5.87 mmol, 1.2 eq., 594 mg, 0.65 mL) in Et_2O (10 mL) was treated with DIBAL (5.87 mmol, 1.2 eq., 3.91 mL of a 1M sol'n in hexanes) at room temperature and stirred overnight. After 16 hours the mixture was diluted with Et_2O (75 mL) and poured slowly into a sep. funnel containing ice and 10% HCl(aq.) (10 mL). The organic phase was separated, washed with sat'd NaCl(aq) (10 mL), dried ($MgSO_4$), filtered through a celite plug and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 710 mg (53% yield over 2 steps) of pure (Z)-trimethyl(tetradec-1-en-1-yl)silane (compound **14**, table **1**) as a clear oil. R_f= 0.72 (100% hexanes); IR (neat, cm^{-1}) 2957, 2926, 2855, 1607, 1468, 1377, 1248, 858, 837, 762; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 6.01 - 6.43 (1H, dt, J_1=14.0 Hz, J_2=7.0 Hz), 5.46 (1H, d, J=14.0 Hz), 2.10 (2H, m), 1.19 - 1.40 (20H, m), 0.78 - 0.95 (3H, t, J=6.0 Hz), 0.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.35, 128.68, 33.56, 31.92, 29.78, 29.69, 29.67, 29.65, 29.61, 29.59, 29.38, 29.36, 22.70, 14.12, 0.24; HRMS EI (*m/z*): [M] for $C_{17}H_{36}Si$, calcd, 268.2586; found, 268.2590.

<u>*syn*-(3-dodecyloxiran-2-yl)trimethylsilane (compound 15, table 1):</u>



A solution of (Z)-trimethyl(tetradec-1-en-1-yl)silane (compound **14**, 2.05 mmol, 1.0 eq., 549 mg) in CH_2Cl_2 (10 mL) was treated with Na_2HPO_4 (3.90 mmol, 1.9 eq., 553 mg) followed by addition of m-CPBA (3.48 mmol, 1.7 eq., 600 mg of 70% pure reagent) and stirred at room temperature overnight. After 18 hours the mixture was diluted with Et_2O (75 mL) and sat'd $NaHCO_3$(aq) (30 mL) and stirred at room temperature for 30 minutes for transferring to a sep. funnel and separating the phases. The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 493 mg (85% yield) of pure *syn*-(3-dodecyloxiran-2-yl)trimethylsilane (compound **15**, table **1**) as a clear oil. R_f= 0.56 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 2957, 2926, 2855, 1468, 1418, 1250, 841, 754; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.98 - 3.16 (1H, m), 2.19 (1H, d, J=5.0 Hz), 1.40 - 1.55 (4H, m), 1.18 - 1.34 (18H, m), 0.81 - 0.94 (3H, t, J=6.0 Hz), 0.13 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 57.71, 50.64, 31.92, 31.59, 29.67, 29.64, 29.58, 29.56 (2C, s), 29.35 (2C, s), 27.06, 22.69, 14.11, -1.71; HRMS (*m/z*): $[M + H]^+$ for $C_{17}H_{37}OSi$, calcd, 285.26137; found, 285.26052.

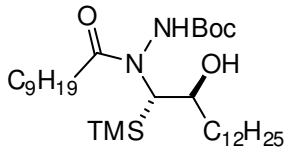
<u>tert-butyl 2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound 16, table 1):</u>



A 5 mL Biotage™ microwave vial was charged with *syn*-(3-dodecyloxiran-2-yl)trimethylsilane (compound **15**, 0.41 mmol, 1.0 eq., 118 mg) and Boc-carbazate (1.66 mmol, 4.0 eq., 216 mg) and the vial was capped with a rubber septa and purged with N_2 for 5 minutes before addition of THF (2 mL). The mixture was cooled to 0 ºC and $BF_3{\cdot}OEt_2$ added (0.041 mmol, 0.1 eq., 5.0 µL) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 ºC oil bath sealed (no N_2 bubbler) overnight. After 14 hours the reaction mixture was cooled to room temperature and sat'd NH_4Cl(aq) (10 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 40 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 127 mg (75% yield) of pure tert-butyl 2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound **16**, table **1**) as a clear oil. R_f= 0.11 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3445, 3308, 2953, 2922, 2855, 1709, 1456, 1367, 1250, 1165, 1045, 1017, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.02 (1H, br. s.), 4.22 (1H, br. s.), 3.50 - 3.78 (2H, m), 2.41 (1H, d, *J*=5.0 Hz), 1.40 - 1.49 (11H, m), 1.21 - 1.36 (19H, m), 0.88 (3H, t, *J*=7.0 Hz) 0.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.67, 80.85, 70.75, 57.42, 36.68, 31.90, 29.64 (6C), 29.33, 28.33, 26.36, 22.67, 14.10, -1.76; HRMS (*m/z*): $[M + H]^+$ for $C_{22}H_{49}N_2O_3Si$, calcd, 417.35124; found, 417.34925.

Synthesis of hydrazidomycin A (Scheme 3, Compounds 1 & 17):

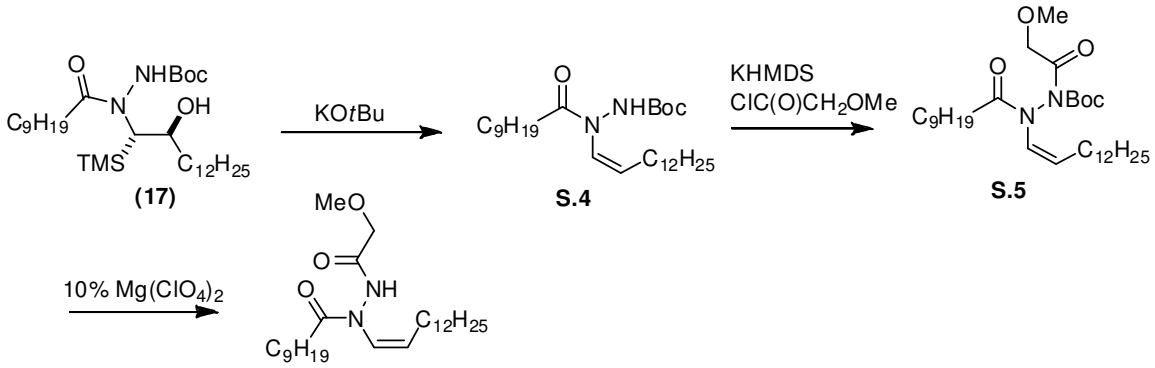
tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound 17, scheme 3):



A solution of tert-butyl 2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound **16**, 0.38 mmol, 1.0 eq., 160 mg) in CH_2Cl_2 (5 mL) was cooled to 0 ºC and treated with Et_3N (0.53 mmol, 1.4 eq., 54 mg, 0.074 mL) followed by addition of decanoyl-chloride (0.43 mmol, 1.15 eq., 83 mg) and the mixture was stirred overnight allowing to warm to room temperature. After 18 hours the mixture was diluted with CH_2Cl_2 (75 mL) and washed with sat'd $NaHCO_3$(aq) (20 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 191 mg (88% yield) of pure tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound **17**, scheme **3**) as a clear oil. R_f= 0.42 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3428, 3250, 2955, 2926, 2855, 1742, 1713, 1643, 1456, 1368, 1250, 1161, 843; ^{1}H NMR (400 MHz, DMSO-d_6, 55deg C) δ ppm 8.82 - 9.03 (1H, br.s), 4.37 - 4.53 (1H, m), 3.67 - 3.83 (1H, m), 3.38 - 3.55 (1H, m), 2.14 - 2.34 (4H, m), 1.45 (13H, m),

1.25 (30H, m), 0.86 (6H, t, *J*=7.0 Hz), 0.06 (9H, s); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.92, 155.48, 81.14, 70.10, 69.34, 34.91, 34.51, 31.98, 31.73, 29.43 (3 C), 29.38, 29.33, 29.22, 29.12 (2 C), 28.42 (2 C), 25.85, 25.71, 24.73, 24.61, 22.54, 14.39 (2 C), -0.40; HRMS (*m/z*): $[M + Na]^+$ for $C_{32}H_{66}N_2O_4SiNa$, calcd, 593.4695; found, 593.4701.

Hydrazidomycin A (compound 1, scheme 3):



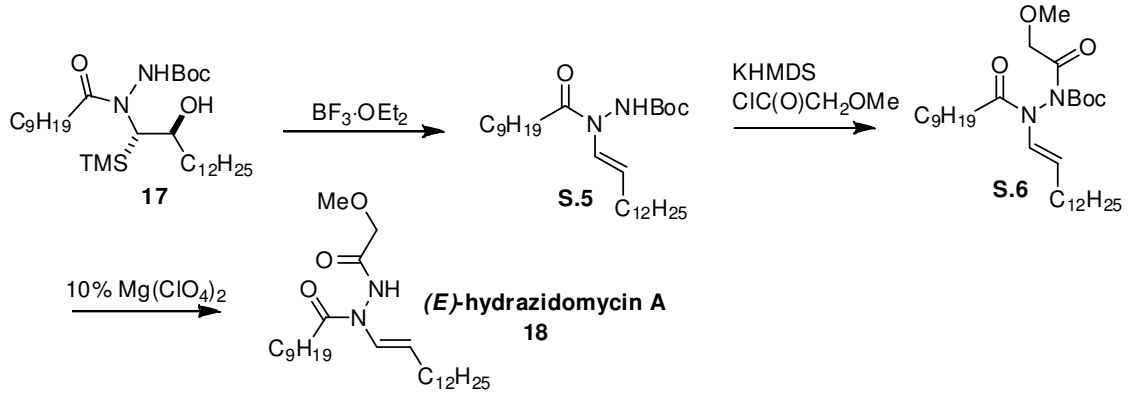
A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound **17**, 0.15 mmol, 1.0 eq., 87 mg) in THF (5 mL) was charged with KO*t*Bu (0.38 mmol, 2.5 eq., 43 mg) at room temperature then fitted with a reflux condenser and placed in a 45 ºC oil bath overnight. After 16 hours the mixture was cooled to room temperature and diluted with ethyl acetate (75 mL) and washed with a mixture of water (5 mL) and sat'd $NaHCO_3$(aq) (10 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 69 mg (96% yield) of crude **S.4** as a clear oil.

Crude **S.4** (0.14 mmol, 1.0 eq., 69 mg) was dissolved in THF (5 mL) and cooled to -78 ºC and treated with KHMDS (0.15 mmol, 1.1 eq., 0.30 mL of a 0.5 M sol'n in toluene) and stirred at -78 ºC for 15 minutes. To this was then added 2-methoxyacetyl chloride (0.17 mmol, 1.2 eq., 18 mg) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between ethyl acetate (75 mL) and sat'd $NaHCO_3$(aq) (20 mL) and the phases were separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (1 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 78 mg (100% yield) of crude **S.5** as a clear oil.

Crude **S.5** (0.14 mmol, 1.0 eq., 78 mg) was dissolved in MeCN (5 mL) and $Mg(ClO_4)_2$ (0.014 mmol, 0.1 eq., 3.0 mg) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 16 hours the mixture was cooled to room temperature and volatiles were removed *in vacuo* on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et_3N in hexanes) using ethyl acetate in hexanes to elute to provide 36 mg (53% yield over 3 steps) of pure hydrazidomycin A (compound **1**, scheme **3**) as a white solid. m.p.= 38 – 40 ºC (CH_2Cl_2); R_f= 0.52 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3276, 2955, 2924, 2854, 1692, 1495, 1467, 1401, 1378, 1199, 1118; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.67 (1H, s), 6.40 (1H, dt, *J*=9.2, 1.6 Hz), 4.77 (1H, dt, *J*=9.2, 7.2 Hz), 3.97 (2H, s), 3.35 (3H, s), 1.94 - 2.38 (4H, m), 1.41 - 1.52 (2H, m), 1.19 - 1.31 (32H, m), 0.85 (6H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 173.18, 167.64, 124.26, 117.31, 70.67, 58.94, 31.28, 31.16, 29.07 (2 C's), 29.03 (3 C's), 29.00, 28.87, 28.84, 28.80, 28.69 (2 C's), 28.65, 28.57, 25.82, 23.84, 22.08 (2 C's), 13.94 (2 C's); HRMS (*m/z*): $[M + H]^+$ for $C_{27}H_{53}N_2O_3$, calcd, 453.4061; found, 453.4043.

Synthesis of E-hydrazidomycin A analogue (Scheme 4, Compound 18):

E-Hydrazidomycin A (compound 18, scheme 4):



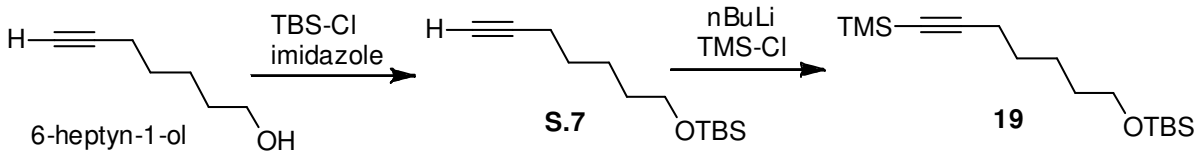
A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (compound **17**, 0.042 mmol, 1.0 eq., 24 mg) in THF (3 mL) was treated with $BF_3{\cdot}OEt_2$ (0.0882 mmol, 2.1 eq., 12.5 mg, 0.01 µL) at room temperature for 24 hours then fitted with a reflux condenser and placed in a 45 ºC oil bath for 16 hours. The mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with sat'd $NaHCO_3$(aq) (10 mL) and the phases separated. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* on the rotovap to give 23 mg (quantitative yield) of crude **S.5** as a clear oil.

Crude **S.5** (0.042 mmol, 1.0 eq., 20 mg) was dissolved in THF (2 mL) and cooled to -78 ºC and treated with KHMDS (0.0462 mmol, 1.1 eq., 0.09 mL of a 0.5 M sol'n in toluene) and stirred at -78 ºC for 15 minutes. To this was then added 2-methoxyacetyl chloride (0.0504 mmol, 1.2 eq., 5.5 mg) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between CH_2Cl_2 (50 mL) and sat'd $NaHCO_3$(aq) (10 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered through a short plug of silica gel (1 cm tall x 1 cm wide) using CH_2Cl_2 (10 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give crude **S.6** as a clear oil.

Crude **S.6** was dissolved in MeCN (3 mL) and $Mg(ClO_4)_2$ (0.0042 mmol, 0.1 eq., 1.0 mg) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 16 hours the mixture was cooled to room temperature and volatiles were removed *in vacuo* on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 9.5 mg (50% yield over 3 steps) of E-hydrazidomycin A (compound **18**, scheme **4**) as a white solid. m.p.= 31 – 33 ºC (EtOAc/hexanes); R_f= 0.19 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3269, 2955, 2925, 2854, 1697, 1677, 1456, 1397, 1116; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.48 (1H, s), 7.02 (1H, d, *J*=14.0 Hz), 4.93 (1H, dt, *J*=14.0, 7.0 Hz), 4.04 (2H, s), 3.37 (3H, s), 2.33 (1H, dt, *J*=16.5, 7.5 Hz), 2.11 (1H, dt, *J*=16.5, 7.5 Hz), 1.99 (2H, q, *J*=7.0 Hz), 1.41 - 1.51 (2H, m), 1.18 - 1.31 (32H, m), 0.85 (6H, t, *J*=7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 171.46, 168.06, 123.73, 109.66, 70.65, 58.92, 31.56, 31.29, 31.26, 29.44, 29.05, 29.02, 29.01, 28.85, 28.83, 28.78, 28.73, 28.70, 28.64, 28.57, 28.38, 23.80, 22.08, 13.94; HRMS (*m/z*): $[M + H]^+$ for $C_{27}H_{53}N_2O_3$, calcd, 453.40562; found, 453.40463.

Synthesis of Peterson precursors for hydrazidomycin B and elaiomycin B (Scheme 5, Compounds 19-28):

tert-butyldimethyl((7-(trimethylsilyl)hept-6-yn-1-yl)oxy)silane (compound 19, scheme 5):

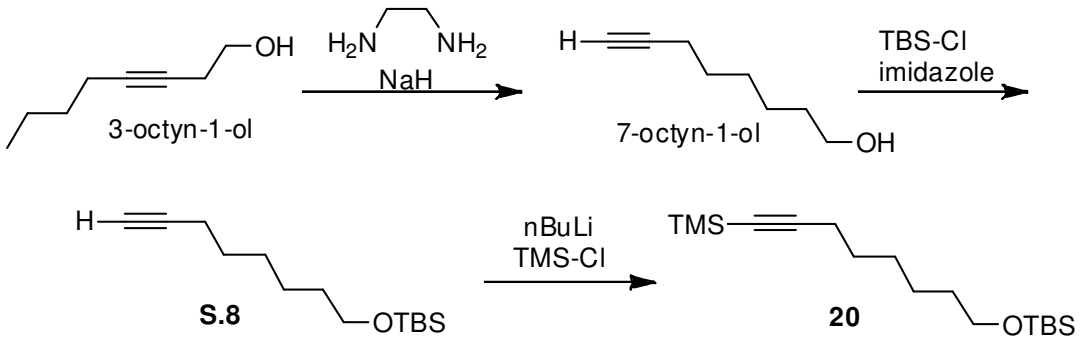


To a solution of 6-heptyn-1-ol (2.70 mmol, 1.0 eq., 302 mg) in DMF (3 mL) was added imidazole (3.78 mmol, 1.4 eq., 260 mg) followed by TBS-Cl (2.97 mmol, 1.1 eq., 448 mg) and the mixture stirred at room temperature overnight. After 16 hours the mixture was diluted with ethyl acetate (75 mL) and washed with sat'd $NaHCO_3$(aq) (15 mL) then with water (10 mL) and finally with 50%

sat'd NaCl(aq) (4 x 10 mL). The organic phase was dried ($MgSO_4$), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 602 mg (98%) of **S.7** as a clear oil.

The protected alcohol intermediate **S.7** obtained above (2.60 mmol, 1.0 eq., 590 mg) was dissolved in THF (15 mL) and cooled to -78 ºC and treated with n-BuLi (3.12 mmol, 1.2 eq., 1.25 mL of a 2.5 M sol'n in hexanes) and stirred 10 minutes before addition of TMS-Cl (3.64 mmol, 1.4 eq., 395 mg, 0.46 mL). The cooling bath was removed and warmed to room temperature and stirred for 45 minutes before addition of sat'd NH_4Cl(aq) (5 mL) and water (10 mL). Organics were extracted with ethyl acetate (75 mL), dried ($MgSO_4$), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap. This provided 688 mg (89% yield, 87% over 2 steps) of tert-butyldimethyl((7-(trimethylsilyl)hept-6-yn-1-yl)oxy)silane (compound **19**, scheme **5**) as a clear oil of sufficient purity to use without further purification. R_f= 0.30 (5% EtOAc/hexanes); IR (neat, cm^{-1}) 2957, 2930, 2899, 2859, 2176, 1472, 1250, 1109, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.61 (2H, t, *J*=6.5 Hz), 2.22 (2H, t, *J*=7.0 Hz), 1.48 - 1.57 (4H, m), 1.37 - 1.46 (2H, m), 0.89 (9H, s), 0.14 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 107.52, 84.34, 63.09, 32.35, 28.47, 25.97, 25.14, 19.86, 18.36, 0.17, -5.27; HRMS (*m/z*): $[M + H]^+$ for $C_{16}H_{35}OSi_2$, calcd, 299.2220; found, 299.2220.

<u>tert-butyldimethyl((8-(trimethylsilyl)oct-7-yn-1-yl)oxy)silane (compound 20, scheme 5):</u>



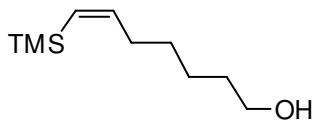
7-octyn-1-ol was prepared according to a modified literature procedure:[1] Ethylene diamine (9 mL) in a 3-neck flask fitted with a reflux condenser and rubber septa was cooled to 0 ºC and charged with NaH in one portion (20 mmol, 4.0 eq., 800 mg of a 60% dispersion in mineral oil). The mixture was stirred at 0 ºC for 5 minutes then 1 hour at room temperature before being transferred to a 65 ºC bath for 1 hour. The mixture was then cooled to 45 ºC before addition of 3-octyn-1-ol (5mmol, 1.0 eq., 631 mg, 0.72 mL) dropwise over 2 minutes. After warming back to 65 ºC the mixture was stirred at that temperature for 1 hour then cooled to 0 ºC and water (7.5 mL)

was slowly added followed by slow addition of 1N HCl(aq) (7.5 mL). A further portion of N HCl(aq) (10 mL) was then added and organics were extracted with Et_2O (3 x 25 mL) and washed with 1N HCl(aq) (10 mL), sat'd NaCl(aq) (5 mL), dried ($MgSO_4$), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using Et_2O (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 631 mg (100%) of 7-octyn-1-ol as a yellow oil in sufficient purity (>90% by ^{1}H NMR) to advance without further purification.

To a solution of 7-octyn-1-ol (5.0 mmol, 1.0 eq., 630 mg) in DMF (8 mL) was added imidazole (7.0 mmol, 1.4 eq., 476 mg) followed by TBS-Cl (5.5 mmol, 1.1 eq., 829 mg) and the mixture stirred at room temperature overnight. After 16 hours the mixture was diluted with ethyl acetate (75 mL) and washed with water (10 mL) then with 50% sat'd NaCl(aq) (4 x 10 mL). The organic phase was dried ($MgSO_4$), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 1.25 g (100%) of **S.8** as a yellow oil.

The protected alcohol intermediate **S.8** obtained above (5.0 mmol, 1.0 eq., 1.25 g) was dissolved in THF (40 mL) and cooled to -78 ºC and treated with n-BuLi (6 mmol, 1.2 eq., 2.4 mL of a 2.5 M sol'n in hexanes) and stirred 15 minutes before addition of TMS-Cl (7.0 mmol, 1.4 eq., 760 mg, 0.88 mL). The cooling bath was removed and warmed to room temperature and stirred for 1 hour before addition of sat'd NH_4Cl(aq) (10 mL) and water (10 mL). Organics were extracted with ethyl acetate (100 mL), dried ($MgSO_4$), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 25 mL) to wash/elute and concentrated *in vacuo* on the rotovap. This provided 1.40 g (89% yield, 89% over 3 steps) of tert-butyldimethyl((8-(trimethylsilyl)oct-7-yn-1-yl)oxy)silane (compound **20**, scheme **5**) as a slightly yellow oil of sufficient purity to use without further purification. R_f= 0.42 (5% EtOAc/hexanes); IR (neat, cm^{-1}) 2957, 2930, 2857, 2176, 1464, 1387, 1362, 1250, 1101, 839, 775, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.61 (2H, t, *J*=6.5 Hz), 2.22 (2H, t, *J*=7.0 Hz), 1.47 - 1.59 (4H, m), 1.31 - 1.44 (4H, m), 0.90 (9H, s), 0.15 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 107.65, 84.28, 63.16, 32.72, 29.70, 28.60, 25.98, 25.29, 19.81, 18.37, 0.18, -5.26; HRMS (*m/z*): $[M + H]^+$ for $C_{17}H_{37}OSi_2$, calcd, 313.23829; found, 313.23830.

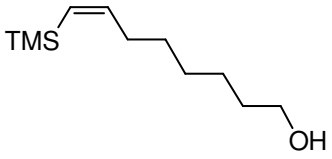
(Z)-7-(trimethylsilyl)hept-6-en-1-ol (compound 21, scheme 5):



A solution of compound **19** (1.84 mmol, 1.0 eq., 550 mg) and N-Me-Morpholine (12.9 mmol, 7.0 eq., 1.30 g, 1.41 mL) in Et_2O (25 mL) was treated with DIBAL (12.9 mmol, 7.0 eq., 12.93 mL of a 1M sol'n in hexanes) at room temperature and stirred overnight. After 16 hours the mixture was diluted

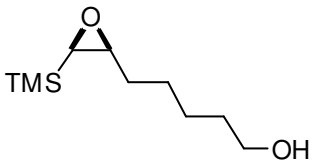
with Et_2O (75 mL) and poured slowly into a sep. funnel containing ice (~25 g) and 10% HCl(aq.) (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered through a celite plug and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 215 mg (63% yield) of pure (Z)-7-(trimethylsilyl)hept-6-en-1-ol (compound **21**, scheme **5**) as a clear oil. R_f= 0.23 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3331, 2955, 2934, 2858, 1607, 1248, 1074, 1053, 858, 837, 762; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.21 - 6.38 (1H, m), 5.48 (1H, dt, *J*=14.0, 1.0 Hz), 3.65 (2H, t, *J*=6.5 Hz), 2.05 - 2.22 (2H, m), 1.51 - 1.63 (2H, m), 1.36 - 1.47 (4H, m), 1.33 (1H, br. s.), 0.11 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 148.86, 129.06, 62.93, 33.42, 32.71, 29.54, 25.45, 0.21; HRMS (*m/z*): $[M + H]^+$ for $C_{10}H_{23}OSi$, calcd, 187.15182; found, 187.15100.

(Z)-8-(trimethylsilyl)oct-7-en-1-ol (compound 22, scheme 5):



A solution of compound **20** (1.69 mmol, 1.0 eq., 530 mg) and N-Me-Morpholine (11.8 mmol, 7.0 eq., 1.20 g, 1.30 mL) in Et_2O (25 mL) was treated with DIBAL (11.8 mmol, 7.0 eq., 11.8 mL of a 1M sol'n in hexanes) at room temperature and stirred overnight. After 16 hours the mixture was diluted with Et_2O (100 mL) and poured slowly into a sep. funnel containing ice (~25 g) and 10% HCl(aq.) (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered through a celite plug and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 184 mg (54% yield) of pure (Z)-8-(trimethylsilyl)oct-7-en-1-ol (compound **22**, scheme **5**) as a clear oil. R_f= 0.23 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3331 (br), 2955, 2929, 2857, 1744, 1724, 1607, 1248, 1057; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.22 - 6.35 (1H, m), 5.47 (1H, dt, *J*=14.0, 1.0 Hz), 3.64 (2H, t, *J*=6.5 Hz), 2.07 - 2.16 (2H, m), 1.53 – 1.62 (2H, m), 1.30 - 1.44 (7H, m), 0.11 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 149.07, 128.91, 63.02, 33.44, 32.74, 29.70, 29.11, 25.67, 0.23; HRMS (*m/z*): $[M + H]^+$ for $C_{11}H_{25}OSi$, calcd, 201.16747; found, 201.16690.

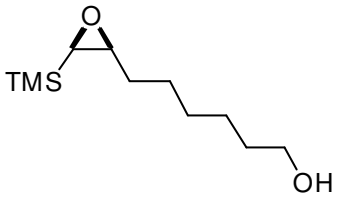
***syn*-5-(3-(trimethylsilyl)oxiran-2-yl)pentan-1-ol (compound 23, scheme 5):**



Compound **21** (1.07 mmol, 1.0 eq., 200 mg) was dissolved in CH_2Cl_2 (10 mL) and Na_2HPO_4 (2.03 mmol, 1.9 eq., 289 mg) was added followed by addition of m-CPBA (1.82 mmol, 1.7 eq., 406 mg of 70% pure reagent) and the mixture was stirred at room temperature overnight. After 14 hours the solution was partitioned between CH_2Cl_2 (75 mL) and sat'd $NaHCO_3$(aq) (10 mL) and the phases were separated. The organic phase was dried ($MgSO_4$),

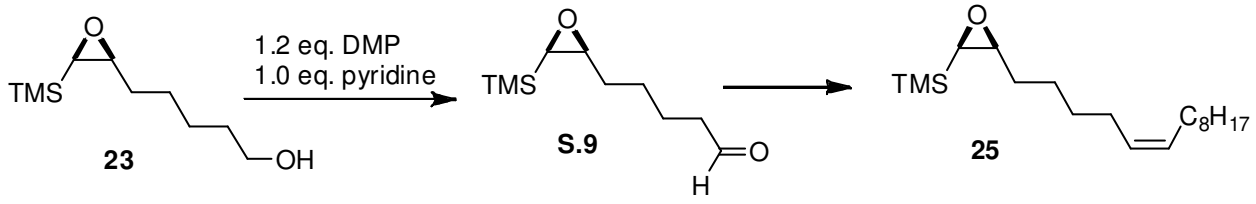
filtered and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 200 mg (92% yield) of pure *syn*-5-(3-(trimethylsilyl)oxiran-2-yl)pentan-1-ol (compound **23**, scheme **5**) as a clear oil. R_f= 0.32 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3402, 2955, 2934, 2860, 1719, 1456, 1418, 1250, 1055, 843, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.66 (2H, t, *J*=6.5 Hz), 3.01 - 3.18 (1H, m), 2.20 (1H, d, *J*=5.0 Hz) , 1.53 - 1.66 (4H, m), 1.37 - 1.51 (5H, m), 0.13 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 62.87, 57.59, 50.62, 32.65, 31.51, 26.93, 25.65, -1.73; HRMS (*m/z*): [M + NH_4]$^+$ for $C_{10}H_{26}O_2NSi$, calcd, 220.17328; found, 220.17315.

<u>*syn*-6-(3-(trimethylsilyl)oxiran-2-yl)hexan-1-ol (compound 24, scheme 5):</u>



Compound **22** (0.77 mmol, 1.0 eq., 154 mg) was dissolved in CH_2Cl_2 (10 mL) and Na_2HPO_4 (1.46 mmol, 1.9 eq., 208 mg) was added followed by addition of m-CPBA (1.31 mmol, 1.7 eq., 292 mg of 70% pure reagent) and the mixture was stirred at room temperature overnight. After 16 hours the solution was partitioned between CH_2Cl_2 (50 mL) and sat'd $NaHCO_3$(aq) (10 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 146 mg (88% yield) of pure *syn*-6-(3-(trimethylsilyl)oxiran-2-yl)hexan-1-ol (compound **24**, scheme **5**) as a clear oil. R_f= 0.26 (40% EtOAc/hexanes); IR (neat, cm^{-1}) 3393 (br), 2951, 2859, 1717, 1464, 1420, 1250, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.66 (2H, t, *J*=6.5 Hz), 3.05 - 3.13 (1H, m), 2.19 (1H, d, *J*=5.5 Hz), 1.51 - 1.63 (4H, m), 1.36 - 1.49 (7H, m), 0.13 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 62.92, 57.65, 50.60, 32.64, 31.45, 29.23, 27.07, 25.63, -1.71; HRMS (*m/z*): [M + H]$^+$ for $C_{11}H_{25}O_2Si$, calcd, 217.16238; found, 217.16293.

<u>(Z)-trimethyl(syn-3-(tetradec-5-en-1-yl)oxiran-2-yl)silane (compound 25, scheme 5):</u>

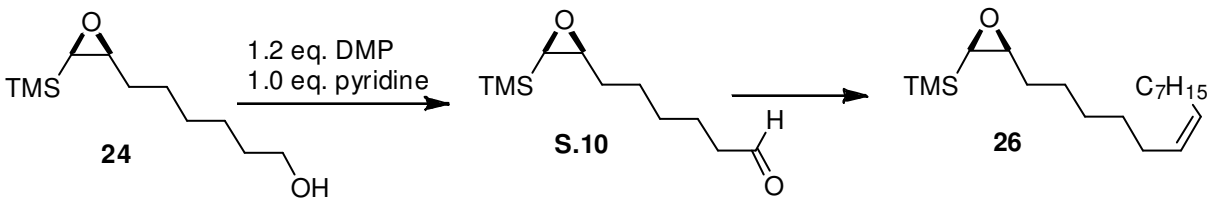


Compound **23** (0.40 mmol, 1.0 eq., 80 mg) and pyridine (0.40 mmol, 1.0 eq., 32 mg) were combined in un-distilled CH_2Cl_2 (5 mL) and Dess-Martin periodinane reagent (0.48 mmol, 1.2 eq., 212 mg) was added and the mixture stirred at room temperature until complete by TLC (90

minutes). The mixture was then diluted with ethyl acetate (75 mL) and washed with water (10 mL) followed by 1N NaOH(aq) (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered through a silica plug (1 cm tall x 1 cm wide) using ethyl acetate (2 x 5 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 75 mg (95%) of crude aldehyde intermediate **S.9** which was used *immediately* in the next step without further purification. R_f= 0.57 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.78 (1H, t, *J*=2.0 Hz), 2.96 - 3.18 (1H, m), 2.47 (2H, td, *J*=7.5, 2.0 Hz), 2.20 (1H, d, *J*=5.0 Hz), 1.66 - 1.78 (2H, m), 1.38 - 1.65 (4H, m), 0.13 (9H, s).

A solution of 1-nonyl-triphenylphosphonium bromide (0.412 mmol, 1.1 eq., 193 mg) in THF (5 mL) was cooled to 0 ºC and LiHMDS (0.412 mmol, 1.1 eq., 0.41 mL of a 1M sol'n in THF) was added and stirred at 0 ºC for 20 minutes. The solution was then cooled to -78 ºC and a solution of aldehyde intermediate **S.9** (0.375 mmol, 1.0 eq., 75 mg) in THF (3 mL) was added dropwise in 0.3 mL portions every 5 minutes. After complete addition, the mixture was stirred for 30 minutes at -78 ºC then warmed to room temperature and stirred for 30 minutes at which time TLC indicated complete conversion. The reaction mixture was treated with sat'd NH_4Cl(aq) (5 mL) and water (5mL) and organics extracted with 50 mL ethyl acetate. The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 69 mg (59% yield over 2 steps) of the desired (Z)-trimethyl(syn-3-(tetradec-5-en-1-yl)oxiran-2-yl)silane (compound **25**, scheme **5**) as a clear oil. Regardless of olefination conditions, this material always contained a single set of olefin peaks but was contaminated with an unknown impurity having a characteristic doublet at 3.36 ppm with a coupling constant J= 3.1 Hz. This peak correlates well with that of a trans epoxide, however, such a species is not observed in the previous starting materials. R_f= 0.61 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2955, 2926, 2855, 1462, 1250, 841; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.30 - 5.43 (2H, m), 2.98 - 3.18 (1H, m), 2.19 (1H, d, *J*=5.0 Hz), 1.92 - 2.11 (4H, m), 1.16 - 1.48 (18H, m), 0.88 (3H, t, *J*=7.0 Hz), 0.13 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 130.30, 129.36, 57.63, 50.61, 31.90, 31.51, 29.75, 29.64, 29.52, 29.33, 29.31, 27.24, 27.11, 26.73, 22.68, 14.11, -1.71; HRMS (*m/z*): $[M + H]^+$ for $C_{19}H_{39}OSi$, calcd, 311.27702; found, 311.27693.

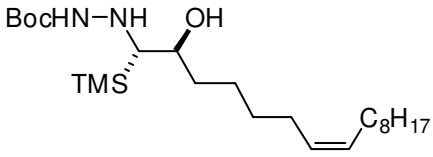
(Z)-trimethyl(syn-3-(tetradec-6-en-1-yl)oxiran-2-yl)silane (compound 26, scheme 5):



Compound **24** (0.268 mmol, 1.0 eq., 58 mg) and pyridine (0.268 mmol, 1.0 eq., 21 mg) were combined in un-distilled CH_2Cl_2 (5 mL) and Dess-Martin periodinane reagent (0.321 mmol, 1.2 eq., 136 mg) was added and the mixture stirred at room temperature until complete by TLC (90 minutes). The mixture was then diluted with ethyl acetate (50 mL) and washed with water (5 mL) followed by 1N NaOH(aq) (2 x 5 mL). The organic phase was dried ($MgSO_4$), filtered through a silica plug (1 cm tall x 1 cm wide) using ethyl acetate (2 x 5 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 56 mg (98%) of crude aldehyde intermediate **S.10** which was used *immediately* in the next step without further purification. R_f= 0.60 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.77 (1H, t, *J*=2.0 Hz), 3.08 (1H, dt, *J*=7.5, 5.0 Hz), 2.45 (2H, td, *J*=7.5, 2.0 Hz), 2.20 (1H, d, *J*=5.0 Hz), 1.66 (2H, quin, *J*=7.5 Hz), 1.51 - 1.61 (2H, m), 1.36 - 1.50 (4H, m), 0.13 (9H, s).

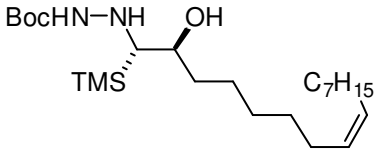
A solution of 1-octyl-triphenylphosphonium bromide (0.288 mmol, 1.1 eq., 131 mg) in THF (5 mL) was cooled to 0 ºC and n-BuLi (0.288 mmol, 1.1 eq., 0.11 mL of a 2.5M sol'n in hexanes) was added and stirred at 0 ºC for 20 minutes. The solution was then cooled to -78 ºC and a solution of aldehyde intermediate **S.10** (0.261 mmol, 1.0 eq., 56 mg) in THF (2 mL) was added dropwise in 0.2 mL portions every 5 minutes. After complete addition, the mixture was stirred for 30 minutes at -78 ºC then warmed to room temperature and stirred for 30 minutes at which time TLC indicated complete conversion. The reaction mixture was treated with sat'd NH_4Cl(aq) (5 mL) and water (5mL) and organics extracted with 50 mL ethyl acetate. The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 42 mg (51% yield over 2 steps) of the desired (Z)-trimethyl(syn-3-(tetradec-6-en-1-yl)oxiran-2-yl)silane (compound **26**, scheme **5**) as a clear oil. Regardless of olefination conditions, this material always contained a single set of olefin peaks but was contaminated with an unknown impurity having a characteristic doublet at 3.36 ppm with a coupling constant J= 3.1 Hz. This peak correlates well with that of a trans epoxide, however, such a species is not observed in the previous starting materials. R_f= 0.59 (20% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3003, 2955, 2926, 2855, 1722, 1464, 1417, 1250, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.35 (2H, appdt, *J*=6.0, 3.5 Hz), 3.03 - 3.13 (1H, m), 2.19 (1H, d, *J*=5.5 Hz), 1.96 - 2.08 (4H, m), 1.41 - 1.49 (2H, m), 1.20 - 1.40 (16H, m), 0.88 (3H, t, *J*=7.0 Hz), 0.14 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 130.11, 129.60, 57.66, 50.63, 31.87, 31.56, 29.76, 29.69, 29.28, 29.22, 29.21, 27.23, 27.11, 27.00, 22.68, 14.11, -1.71; HRMS (*m/z*): $[M + H]^+$ for $C_{19}H_{39}OSi$, calcd, 311.27702; found, 311.27698.

(Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-7-en-1-yl)hydrazinecarboxylate (compound 27, scheme 5):



A 5 mL Biotage™ microwave vial was charged with compound **25 (**0.10 mmol, 1.0 eq., 31 mg) and Boc-carbazate (0.4 mmol, 4.0 eq., 52 mg) and the vial was capped with a rubber septa and purged with N_2 for 5 minutes before addition of THF (0.5 mL). The mixture was cooled to 0 ºC and $BF_3{\cdot}OEt_2$ added (0.01 mmol, 0.1 eq., 1.2 µL) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 ºC oil bath sealed (no N_2 bubbler) overnight. After 20 hours the reaction mixture was cooled to room temperature and sat'd NH_4Cl(aq) (5 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 32 mg (73% yield) of pure (Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-7-en-1-yl)hydrazinecarboxylate (compound **27**, scheme **5**) as a clear oil. R_f= 0.24 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3445, 3287, 3003, 2957, 2926, 2855, 1713, 1537, 1456, 1393, 1368, 1250, 1169, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.00 (1H, br. s.), 5.26 - 5.44 (2H, m), 4.22 (1H, br. s.), 3.55 - 3.75 (2H, m), 2.37 - 2.43 (1H, m), 1.96 - 2.07 (4H, m), 1.42 - 1.52 (13H, m), 1.23 - 1.38 (14H, m), 0.88 (3H, t, *J*=7.0 Hz), 0.12 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 157.75, 130.06, 129.62, 80.87, 70.67, 57.52, 36.61, 31.90, 29.80, 29.78, 29.52, 29.34, 29.31, 28.34, 27.25, 27.24, 26.10, 22.68, 14.11, -1.75; HRMS (*m/z*): $[M + H]^+$ for $C_{24}H_{51}N_2O_3Si$, calcd, 443.36689; found, 443.36801.

(Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-8-en-1-yl)hydrazinecarboxylate (compound 28, scheme 5):

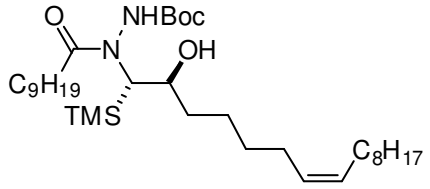


A 5 mL Biotage™ microwave vial was charged with compound **26 (**0.138 mmol, 1.0 eq., 43 mg) and Boc-carbazate (0.552 mmol, 4.0 eq., 72 mg) and the vial was capped with a rubber septa and purged with N_2 for 5 minutes before addition of THF (0.5 mL). The mixture was cooled to 0 ºC and $BF_3{\cdot}OEt_2$ added (0.0138 mmol, 0.1 eq., 1.7 µL) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 ºC oil bath sealed (no N_2 bubbler) overnight. After 14 hours the reaction mixture was cooled to room temperature and sat'd NH_4Cl(aq) (5 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by

flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 48 mg (79% yield) of pure (Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-8-en-1-yl)hydrazinecarboxylate (compound **28**, scheme **5**) as a clear oil. R_f= 0.18 (20% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3400, 3285 (br), 3005, 2926, 2855, 1709, 1456, 1392, 1368, 1250, 1167, 1047, 1022, 839; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.03 (1H, br. s.), 5.34 (2H, ddd, *J*=6.0, 3.5, 2.5 Hz), 4.22 (1H, br. s.), 3.70 (1H, br. s.), 3.57 - 3.65 (1H, m), 2.40 (1H, d, *J*=5.0 Hz), 1.97 - 2.05 (4H, m), 1.42 - 1.48 (11H, m), 1.22 - 1.39 (16H, m), 0.88 (3H, t, *J*=7.0 Hz), 0.11 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 157.75, 129.98, 129.73, 80.86, 70.71, 57.48, 36.66, 31.86, 29.77 (2C overlap), 29.31, 29.28, 29.22, 28.34, 27.21, 27.19, 26.30, 22.66, 14.10, -1.76; HRMS (*m/z*): $[M + H]^+$ for $C_{24}H_{51}N_2O_3Si$, calcd, 443.36689; found, 443.36654.

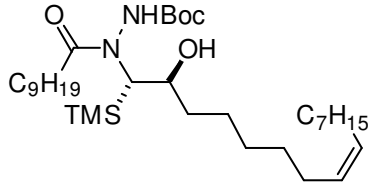
Synthesis of hydrazidomycin B and elaiomycin B (Scheme 6, Compounds 2 & 3):

tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-7-(Z)-en-1-yl)hydrazinecarboxylate (compound 29, scheme 6):



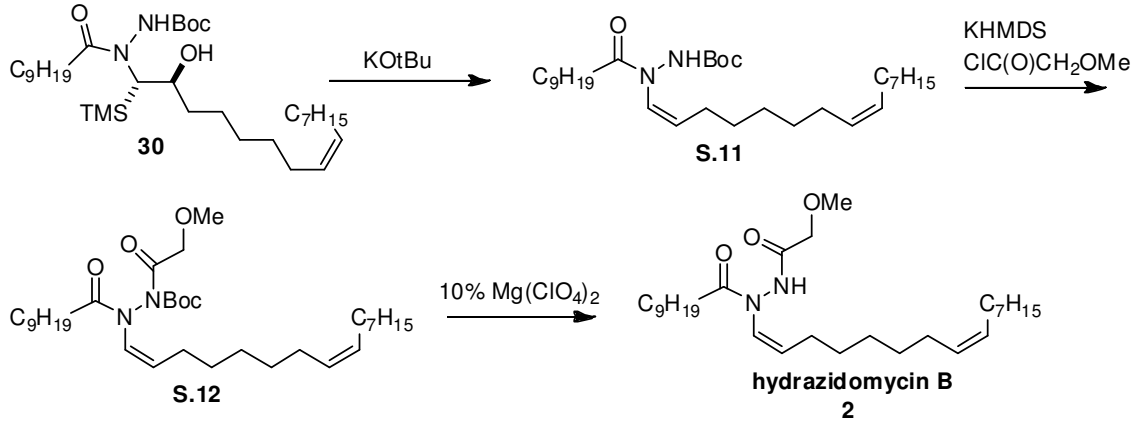
A solution of (Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-7-en-1-yl)hydrazinecarboxylate (compound **27**, 0.0858 mmol, 1.0 eq., 38 mg) in CH_2Cl_2 (2 mL) was cooled to 0 ºC and treated with Et_3N (0.12 mmol, 1.4 eq., 12 mg) in CH_2Cl_2 (0.5 mL) followed by addition of decanoyl-chloride (0.0944 mmol, 1.1 eq., 18 mg) in CH_2Cl_2 (0.5 mL) and the mixture was stirred overnight allowing to warm to room temperature. After 16 hours the mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat'd $NaHCO_3$(aq) (10 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 42 mg (82% yield) of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-7-(Z)-en-1-yl)hydrazinecarboxylate (compound **29**, scheme **6**) as a clear oil. R_f= 0.34 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3460, 3252, 3003, 2955, 2926, 2855, 1743-1640 (m), 1368, 1250, 1159, 841; ^{1}H NMR (400 MHz, DMSO-d_6, 55deg C) δ ppm 8.90 (1H, br. s), 5.26 - 5.39 (2H, m), 4.38 - 4.48 (1H, m), 3.68 - 3.81 (1H, m), 3.36 - 3.53 (1H, m), 2.10 - 2.40 (2H, m), 1.90 - 2.06 (4H, m), 1.37 - 1.59 (13H, m), 1.17 - 1.36 (28H, m), 0.87 (6H, t, *J*=7.0 Hz), 0.07 (9H, s); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.45, 155.09, 129.58, 129.55, 80.64, 69.43, 68.91, 34.32, 34.03, 31.93, 31.51, 31.26, 31.24, 29.09, 28.86, 28.83, 28.67, 28.64, 28.61, 27.95, 27.68, 26.61, 26.58, 25.00, 24.15, 22.07 (2C), 13.91, 13.54, -0.86; HRMS (*m/z*): $[M + H]^+$ for $C_{34}H_{69}N_2O_4Si$, calcd, 597.50266; found, 597.50165.

tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-8-(Z)-en-1-yl)hydrazinecarboxylate (compound 30, scheme 6):



A solution of (Z)-tert-butyl 2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-8-en-1-yl)hydrazinecarboxylate (compound **28**, 0.0903 mmol, 1.0 eq., 40 mg) in CH_2Cl_2 (2 mL) was cooled to 0 ºC and treated with Et_3N (0.126 mmol, 1.4 eq., 13 mg) in CH_2Cl_2 (0.5 mL) followed by addition of decanoyl-chloride (0.0994 mmol, 1.1 eq., 19 mg) in CH_2Cl_2 (0.5 mL) and the mixture was stirred overnight allowing to warm to room temperature. After 14 hours the mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat'd $NaHCO_3$(aq) (10 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 43 mg (80% yield) of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-8-(Z)-en-1-yl)hydrazinecarboxylate (compound **30**, scheme **6**) as a clear oil. R_f= 0.39 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3455, 3361, 3227, 3004, 2956, 2925, 2855, 1715, 1717, 1635, 1451, 1367, 1249, 1160, 842; ^{1}H NMR (400 MHz, DMSO-d_6, 55deg C) δ ppm 8.87 (1H, br. s.), 5.24 - 5.42 (2H, m), 4.34 - 4.49 (1H, m), 3.68 - 3.81 (1H, m), 3.37 - 3.53 (1H, m), 2.12 - 2.35 (2H, m), 1.89 - 2.07 (4H, m), 1.37 - 1.57 (13H, m), 1.13 - 1.36 (28H, m), 0.86 (6H, t, *J*=7.0 Hz), 0.07 (9H, s); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 174.44, 155.07, 129.61, 129.58, 80.65, 80.38, 69.48, 68.87, 34.48, 34.14, 31.26, 31.23, 29.11, 28.86, 28.64 (2 C's), 28.55, 28.52, 28.46, 27.95 (2 C's), 26.59, 26.56, 25.20, 24.15, 22.08, 22.07, 13.92 (2 C's), -0.86; HRMS (*m/z*): $[M + H]^+$ for $C_{34}H_{69}N_2O_4Si$, calcd, 597.50266; found, 597.50529.

Hydrazidomycin B (compound 2, scheme 6):



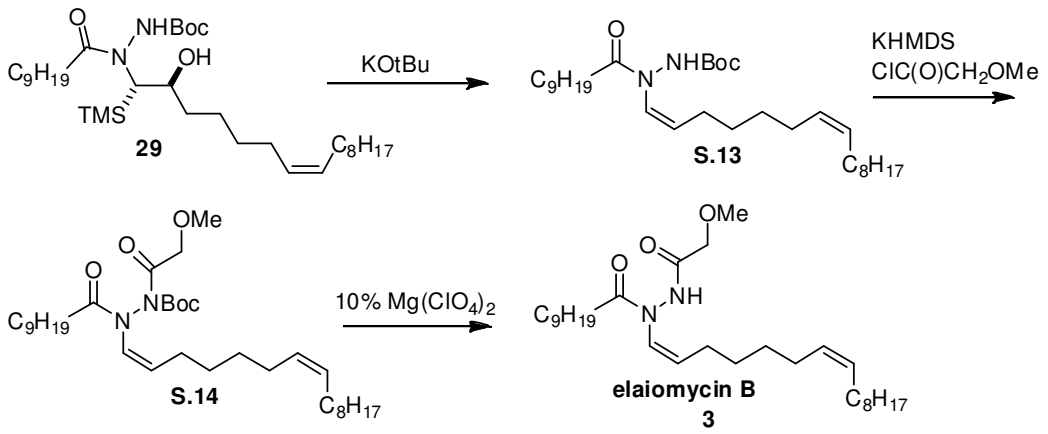
A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-8-(Z)-en-1-yl)hydrazinecarboxylate (compound **30**, 0.0905 mmol, 1.0 eq., 54 mg) in THF (3 mL) was charged

with KO*t*Bu (0.226 mmol, 2.5 eq., 25 mg) at room temperature then fitted with a reflux condenser and placed in a 45 ºC oil bath overnight. After 16 hours the mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with a mixture of water (5 mL) and sat'd $NaHCO_3$(aq) (5 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 40 mg (87% yield) of crude **S.11** as a clear oil.

Crude **S.11** (0.079 mmol, 1.0 eq., 40 mg) was dissolved in THF (3 mL) and cooled to -78 ºC and treated with KHMDS (0.0869 mmol, 1.1 eq., 0.17 mL of a 0.5 M sol'n in toluene) and stirred at -78 ºC for 15 minutes. To this was then added 2-methoxyacetyl chloride (0.0948 mmol, 1.2 eq., 10 mg) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between ethyl acetate (50 mL) and sat'd $NaHCO_3$(aq) (10 mL) and the phases were separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (1 cm tall x 1 cm wide) using ethyl acetate (2 x 10 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give crude **S.12** as a clear oil.

Crude **S.12** was dissolved in MeCN (3 mL) and $Mg(ClO_4)_2$ (0.00948 mmol, 0.12 eq., 2.1 mg) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 18 hours the mixture was cooled to room temperature and volatiles were removed *in vacuo* on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et_3N in hexanes) using ethyl acetate in hexanes to elute to provide 21.2 mg (49% yield over 3 steps) of pure hydrazidomycin B (compound **2**, scheme **6**) as a clear oil at room temperature and a white solid in a -15 ºC freezer. R_f= 0.48 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3265, 3003, 2955, 2925, 2855, 1692, 1680, 1498, 1466, 1401, 1378, 1284, 1245, 1199, 1160, 1118; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 6.41 (1H, dt, *J*=9.3, 1.6 Hz), 5.32 (2H, app t, *J*=5.0 Hz), 4.76 (1H, dt, *J*=9.3, 7.3 Hz), 3.97 (2H, s), 3.36 (3H, s), 2.31 (1H, t, *J*=7.3 Hz), 2.01 - 2.15 (3H, m), 1.92 - 2.01 (4H, m), 1.40 - 1.54 (2H, m), 1.14 - 1.36 (28H, m), 0.85 (6H, t, *J*=6.9 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 173.14, 167.60, 129.62, 129.55, 124.26, 117.09, 70.68, 58.94, 31.29, 31.27, 31.15, 29.12, 28.99, 28.89 (2 C's), 28.82 (2 C's), 28.67, 28.57, 28.54, 28.46, 26.62, 26.58, 25.81, 23.84, 22.09, 22.07, 13.93, 13.92; HRMS (*m/z*): $[M + H]^+$ for $C_{29}H_{55}N_2O_3$, calcd, 479.42127; found, 479.42290.

Elaiomycin B (compound 3, scheme 6):



A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-7-(Z)-en-1-yl)hydrazinecarboxylate (compound **29**, 0.100 mmol, 1.0 eq., 60 mg) in THF (3 mL) was charged with KO*t*Bu (0.25 mmol, 2.5 eq., 28 mg) at room temperature then fitted with a reflux condenser and placed in a 45 ºC oil bath overnight. After 13 hours the mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with a mixture of water (5 mL) and sat'd $NaHCO_3$(aq) (5 mL) and the phases separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give 40 mg (80% yield) of crude **S.13** as a clear oil.

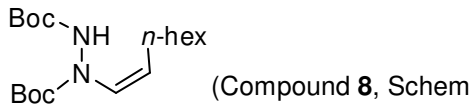
Crude **S.13** (0.079 mmol, 1.0 eq., 40 mg) was dissolved in THF (3 mL) and cooled to -78 ºC and treated with KHMDS (0.0869 mmol, 1.1 eq., 0.17 mL of a 0.5 M sol'n in toluene) and stirred at -78 ºC for 15 minutes. To this was then added 2-methoxyacetyl chloride (0.0948 mmol, 1.2 eq., 10 mg) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between ethyl acetate (75 mL) and sat'd $NaHCO_3$(aq) (20 mL) and the phases were separated. The organic phase was dried (Na_2SO_4), filtered through a short plug of basic Al_2O_3 (1 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated *in vacuo* on the rotovap to give crude **S.14** as a clear oil.

Crude **S.14** was dissolved in MeCN (3 mL) and $Mg(ClO_4)_2$ (0.010 mmol, 0.13 eq., 2.3 mg) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 19 hours the mixture was cooled to room temperature and volatiles were removed *in vacuo* on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et_3N in hexanes) using ethyl acetate in hexanes to elute to provide 19.1 mg (40% yield over 3 steps) of pure elaiomycin B (compound **3**, scheme **6**) as a

clear oil at room temperature and a white solid in a -15 ºC freezer. R_f= 0.45 (40% EtOAc/hexanes); IR (CH_2Cl_2 thin film, cm^{-1}) 3271, 3003, 2955, 2922, 2855, 1710, 1663, 1495, 1456, 1402, 1379, 1283, 1252, 1233, 1198, 1117; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 6.40 (1H, dt, *J*=9.3, 1.6 Hz), 5.31 (2H, app t, *J*=5.4 Hz), 4.75 (1H, dt, *J*=9.3, 7.2 Hz), 3.97 (2H, s), 3.34 (3H, s), 2.30 (2H, t, *J*=7.3 Hz), 2.01 - 2.11 (2H, m), 1.96 (4H, dt, *J*=6.1, 6.4 Hz), 1.38 - 1.53 (2H, m), 1.19 - 1.31 (28H, m), 0.84 (6H, t, *J*=7.0 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 173.35, 167.80, 129.87, 129.67, 124.51, 117.25, 70.86, 59.13, 31.45, 31.34 (2 C's), 29.31, 29.12, 29.06, 29.04, 28.99, 28.91, 28.86, 28.84, 28.80, 28.75, 26.77, 26.68, 25.89, 24.02, 22.27, 22.26, 14.12, 14.12; HRMS (*m/z*): $[M + H]^+$ for $C_{29}H_{55}N_2O_3$, calcd, 479.42127; found, 479.42176.

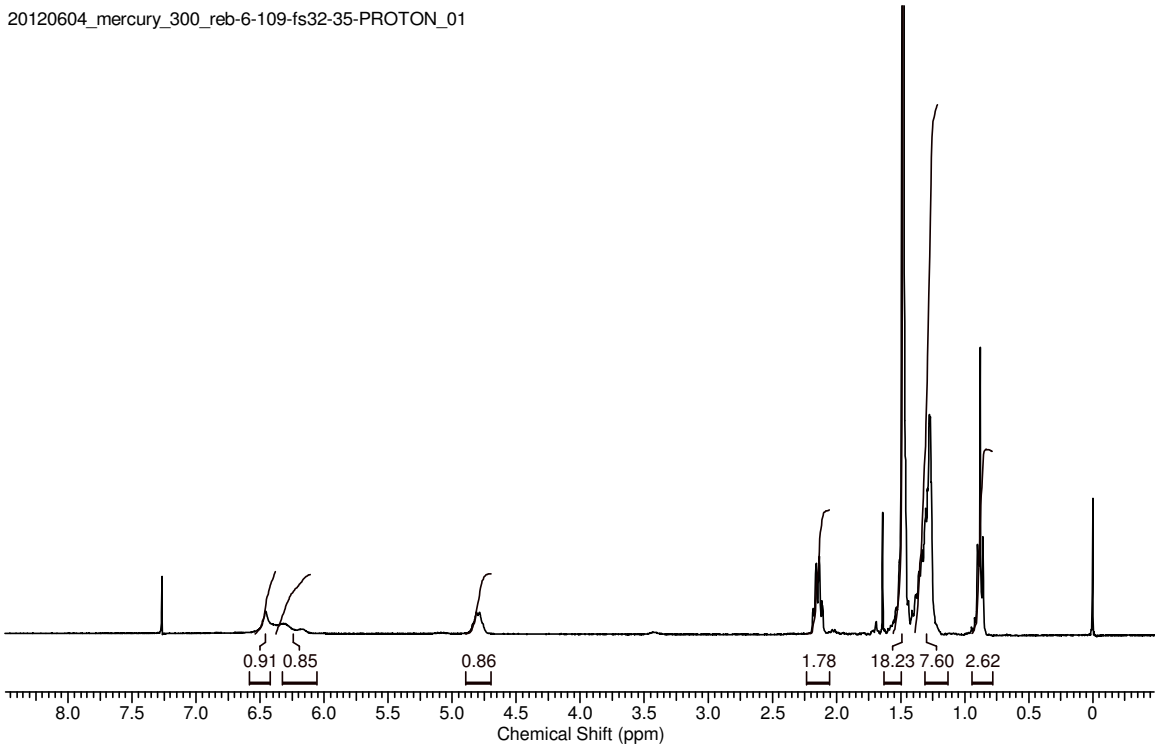
References:

1. Shi, C.; Aldrich, C. C. *J. Org. Chem.* **2012**, *77*, 6051-6058.
2. Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540-543.
3. Helaly, S. E.; Pesic, A.; Fiedler, H-P.; Sussmuth, R. D. *Org. Lett.* **2011**, *13*, 1052-1055.
4. Ueberschaar, N.; Le Sage Tchize Ndejouong, B.; Ding, L.; Maier, A.; Fiebig, H-H.; Hertweck, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5839-5841.

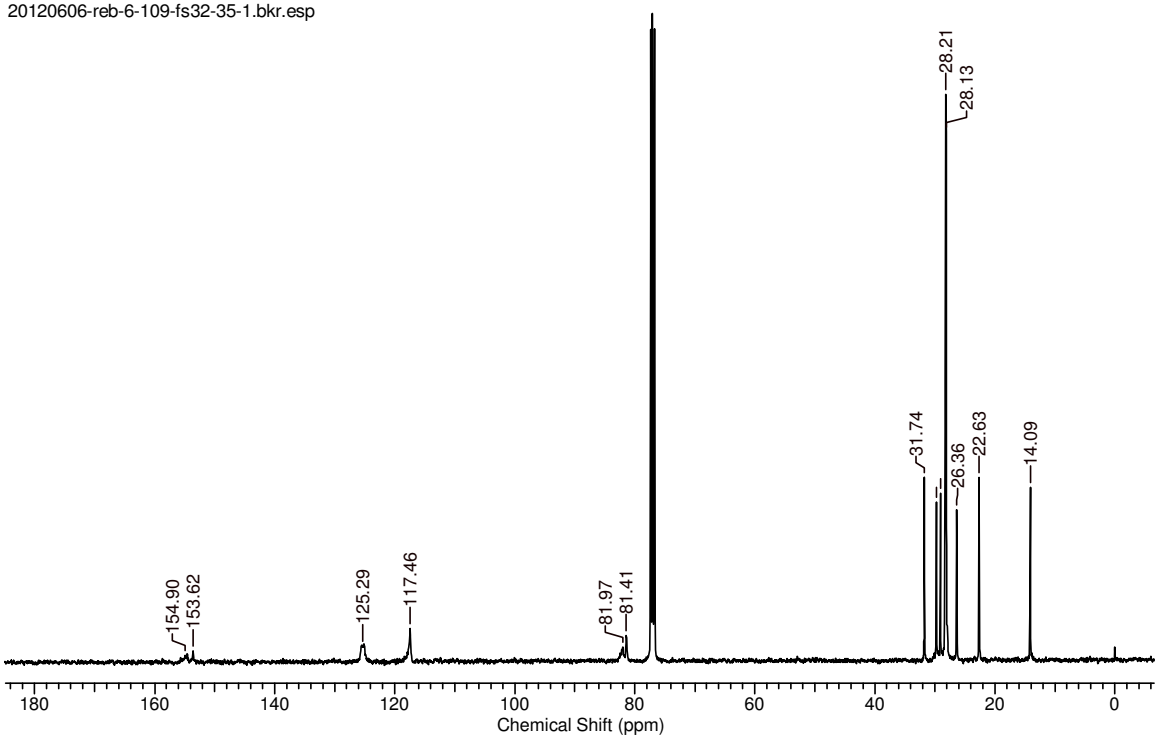


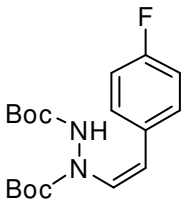
(Compound **8**, Scheme **1**)

20120604_mercury_300_reb-6-109-fs32-35-PROTON_01



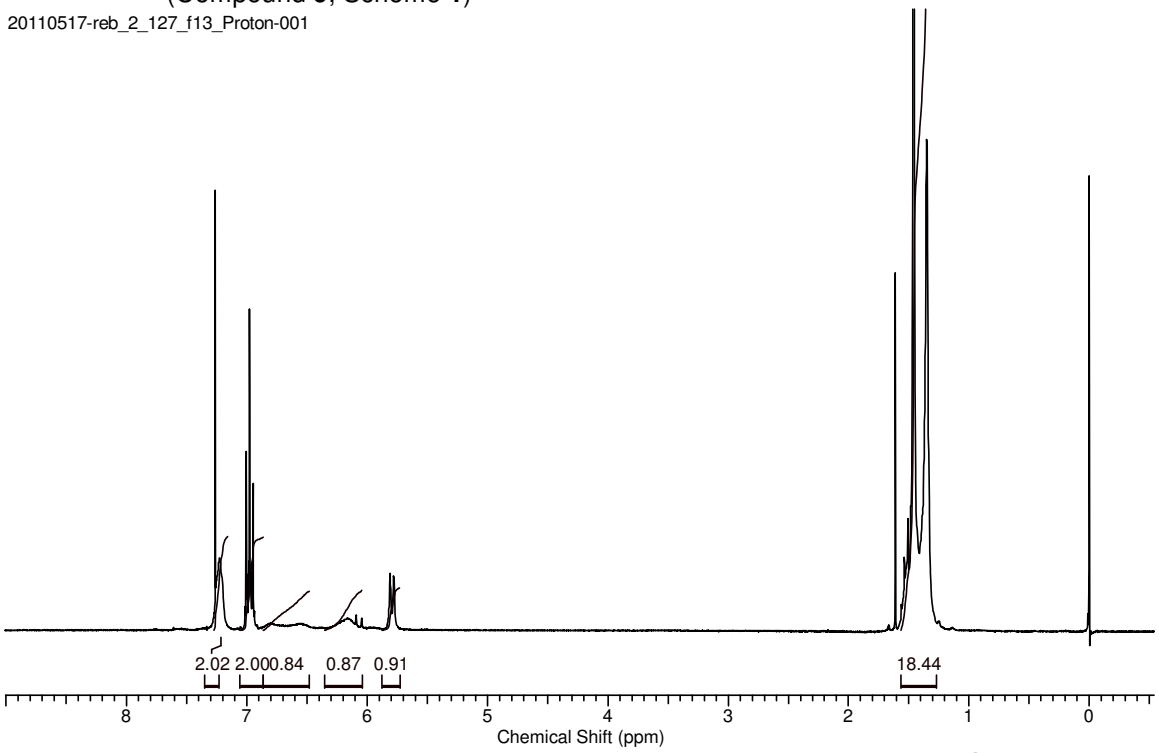
20120606-reb-6-109-fs32-35-1.bkr.esp



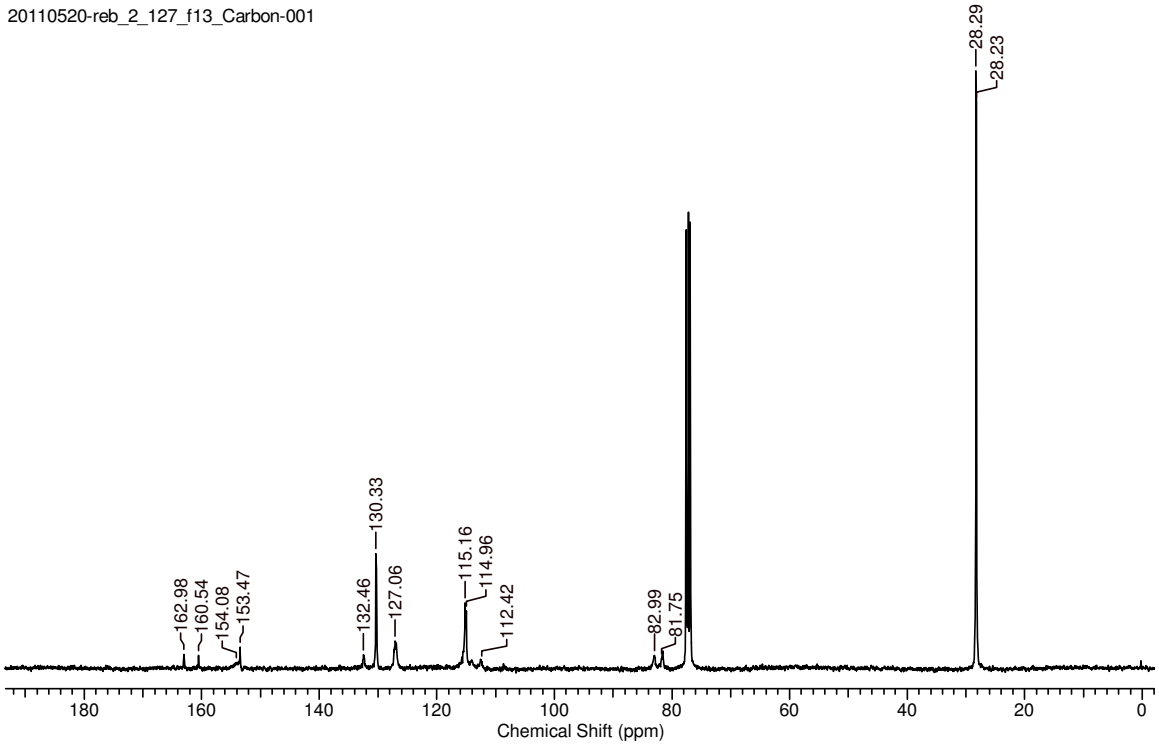


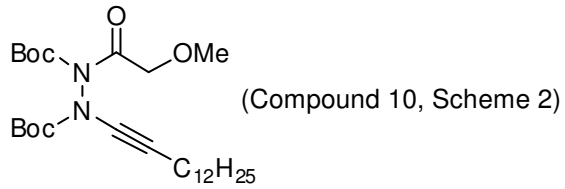
(Compound **9**, Scheme **1**)

20110517-reb_2_127_f13_Proton-001



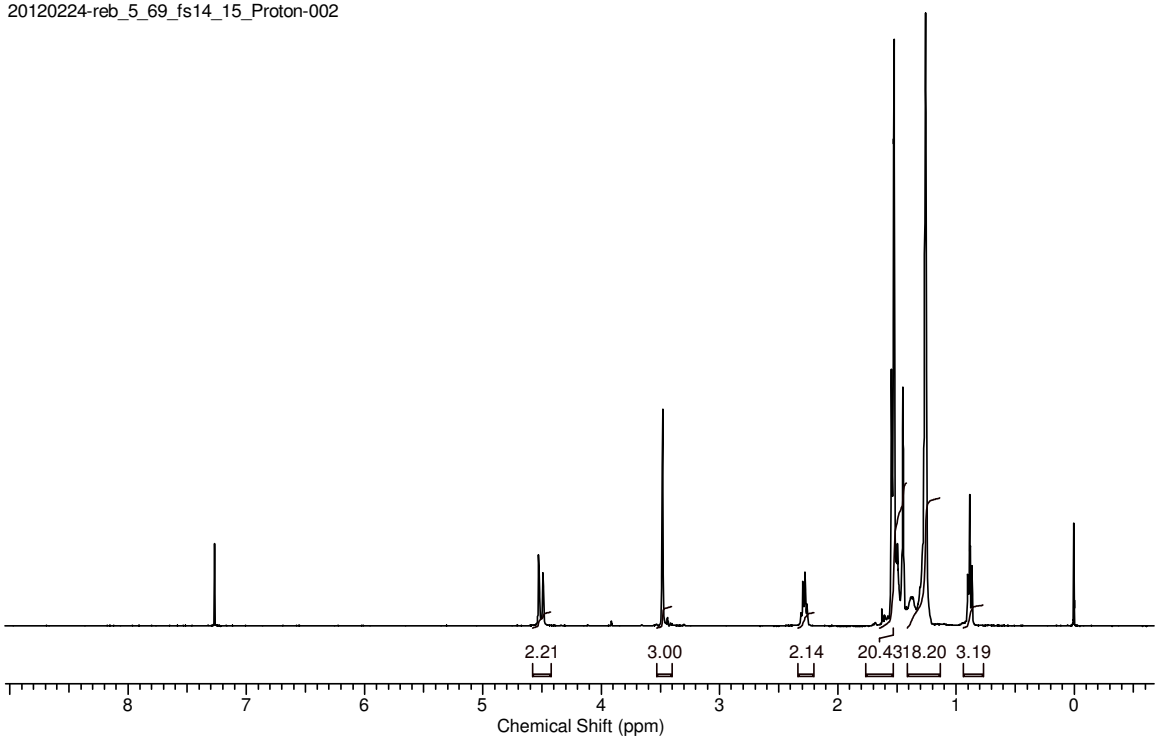
20110520-reb_2_127_f13_Carbon-001





(Compound 10, Scheme 2)

20120224-reb_5_69_fs14_15_Proton-002



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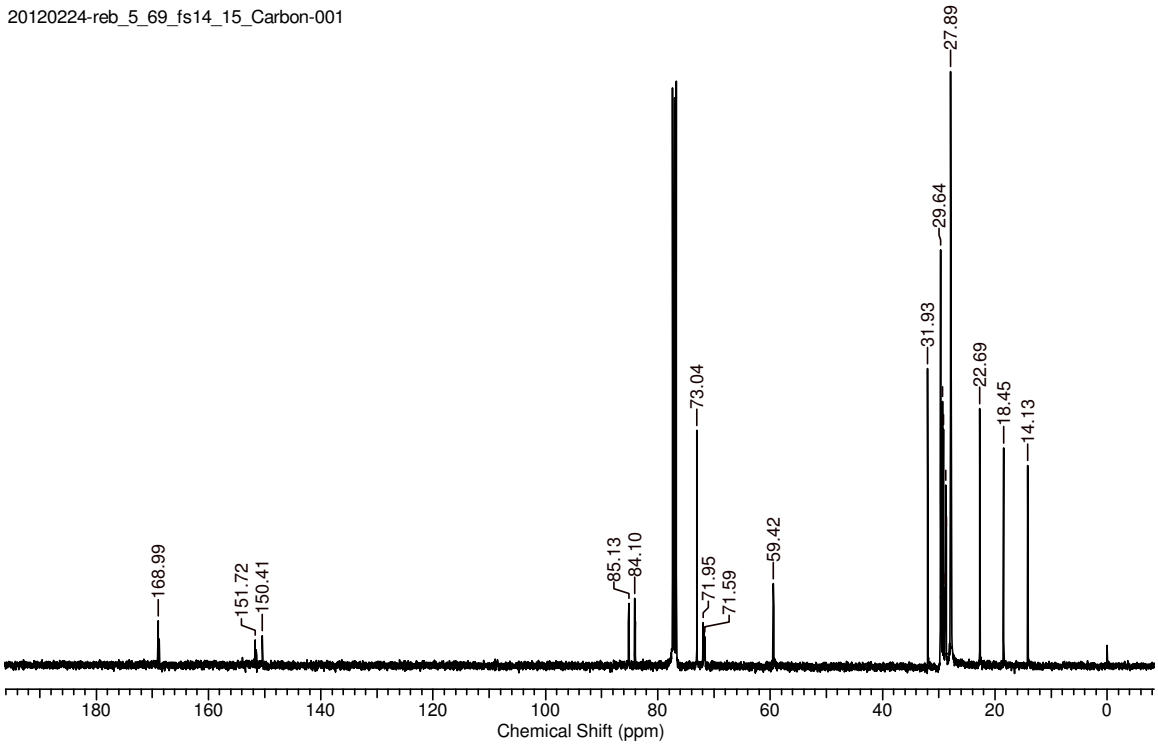
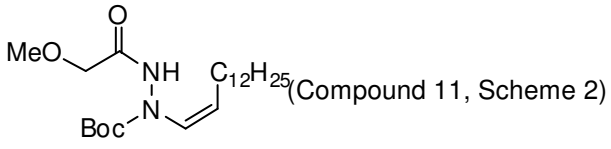
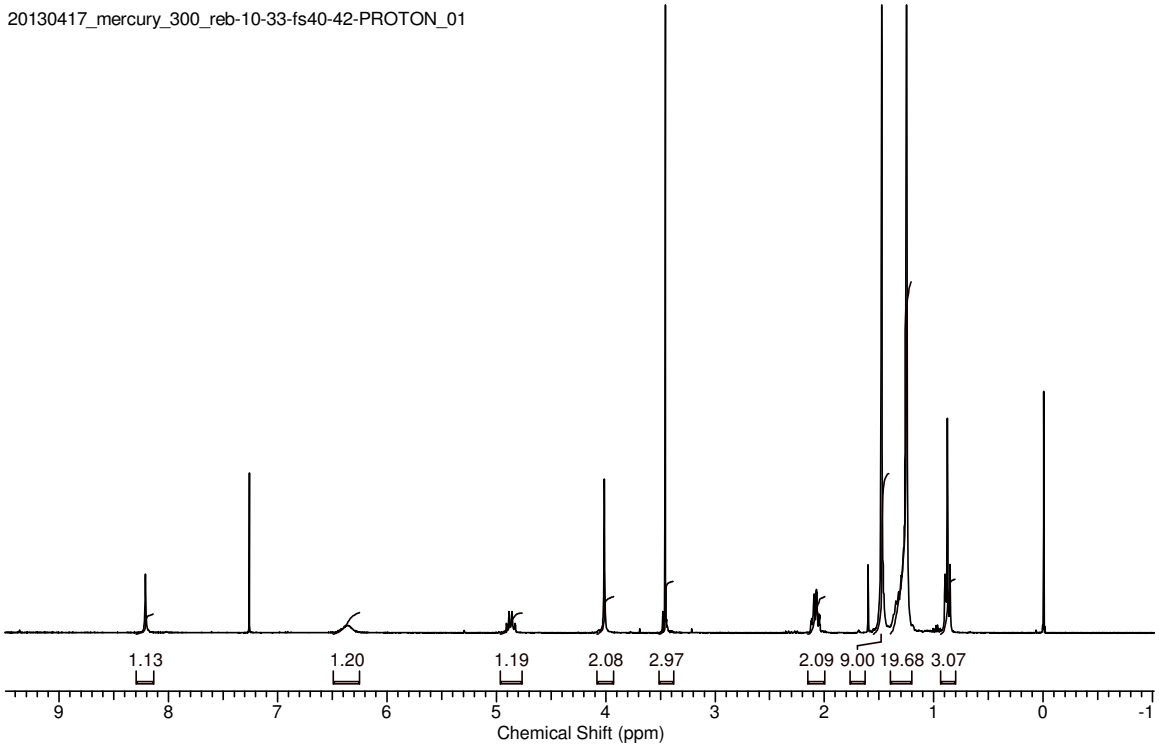
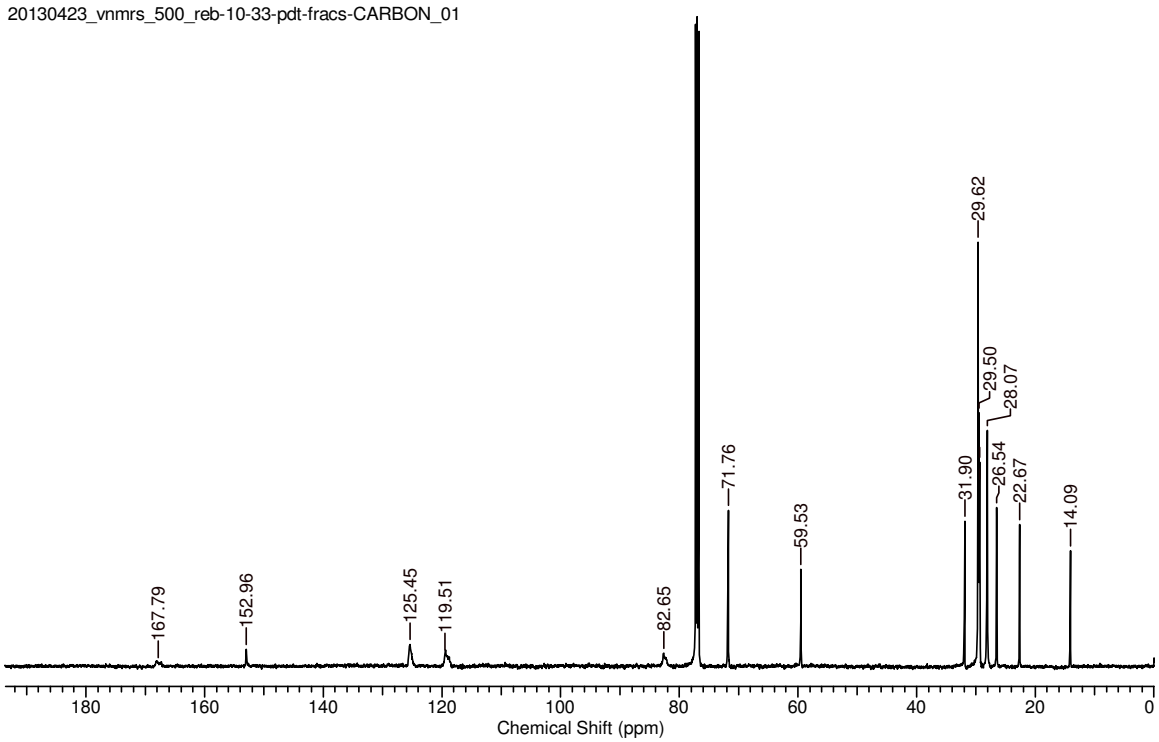
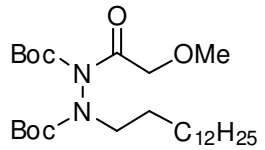




(Compound 11, Scheme 2)

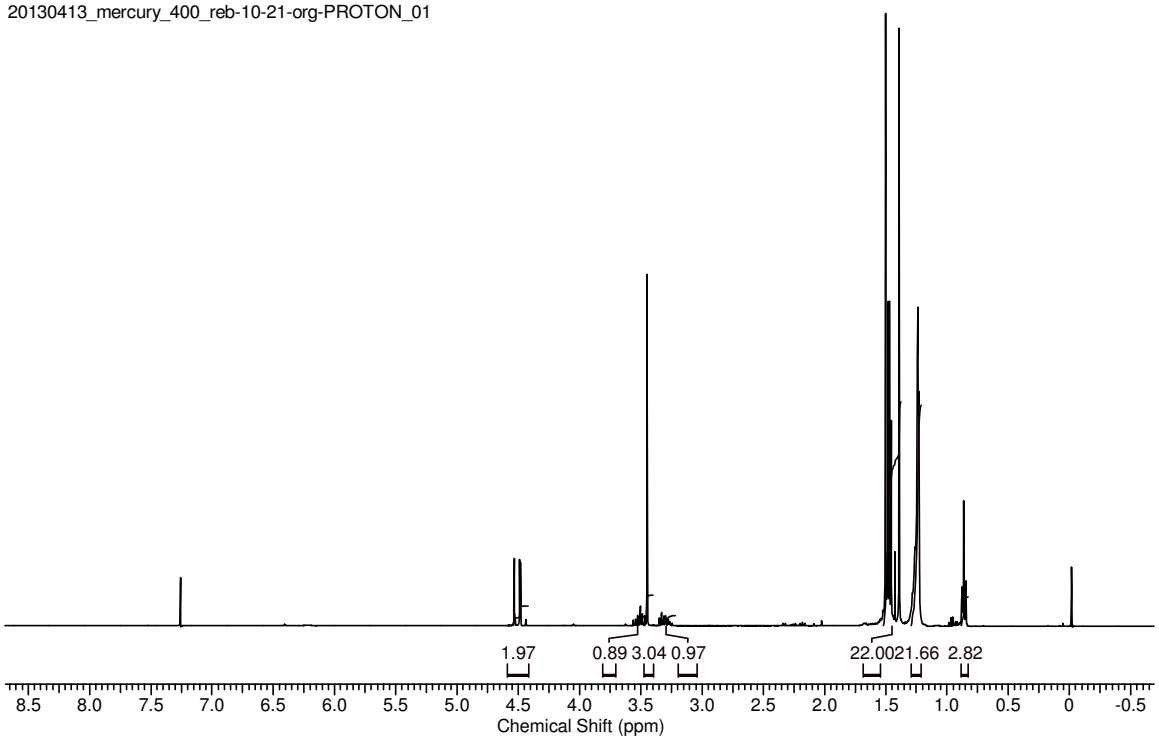






(Compound 12, Scheme 2)

20130413_mercury_400_reb-10-21-org-PROTON_01



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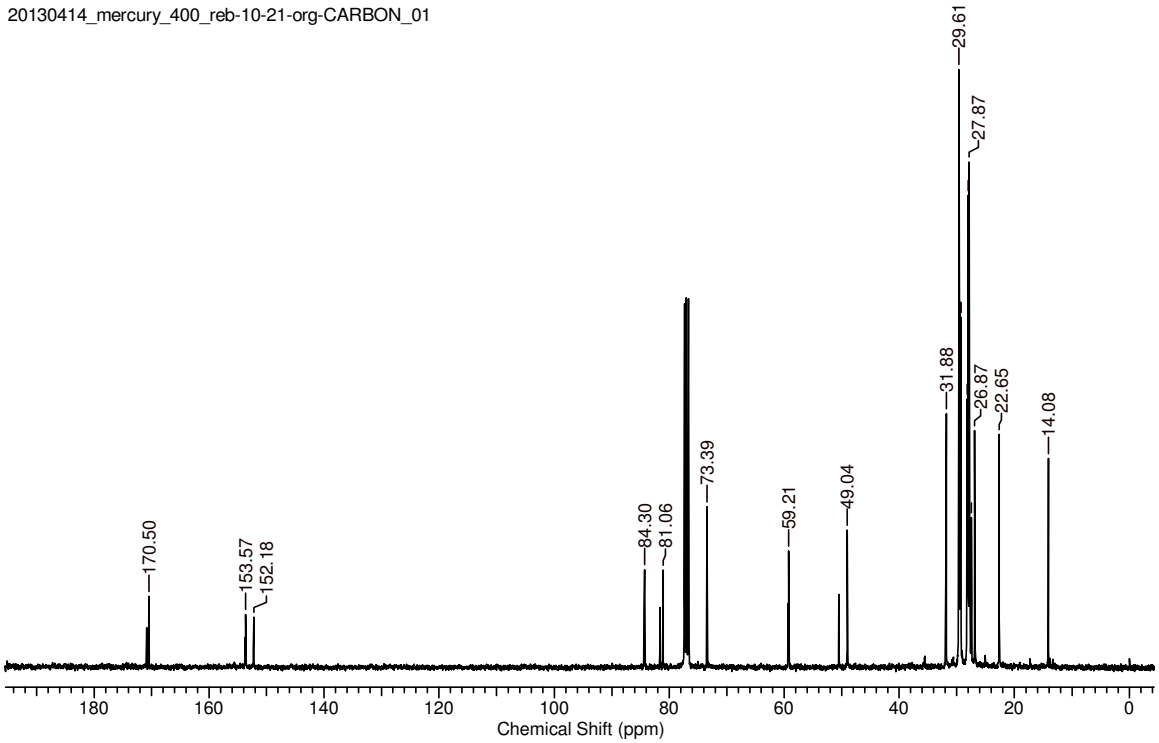

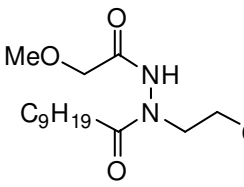

(Compound **13**, Scheme **2**)

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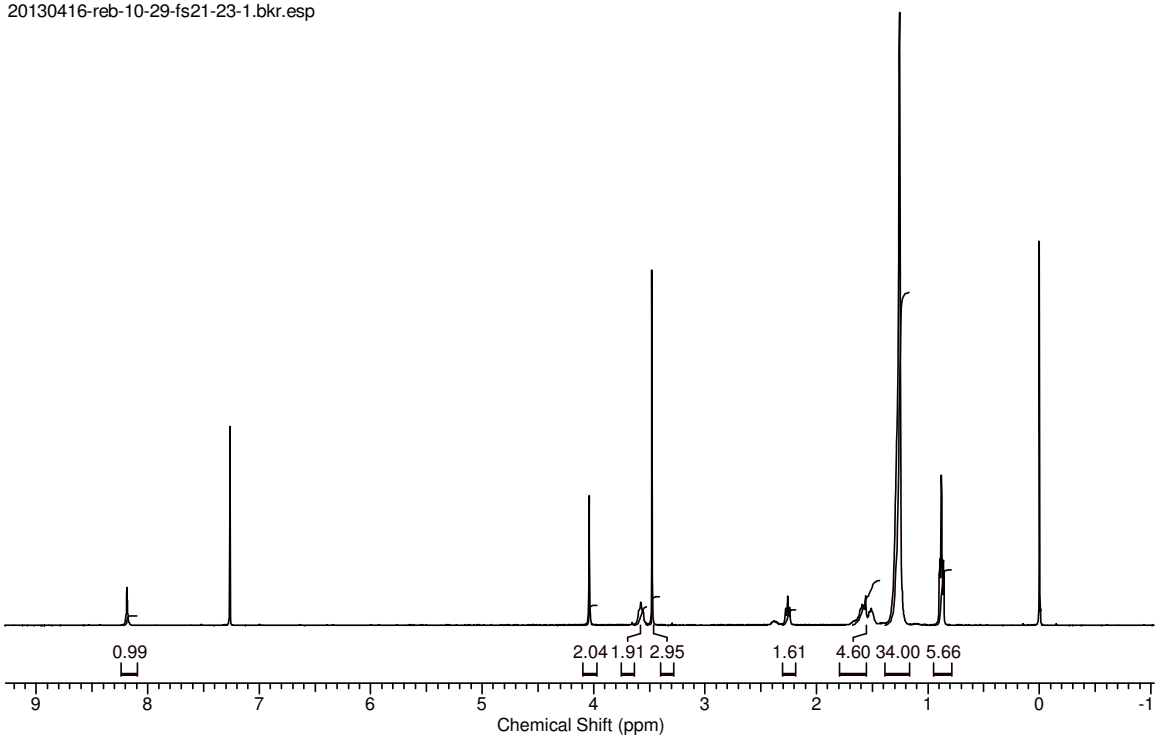

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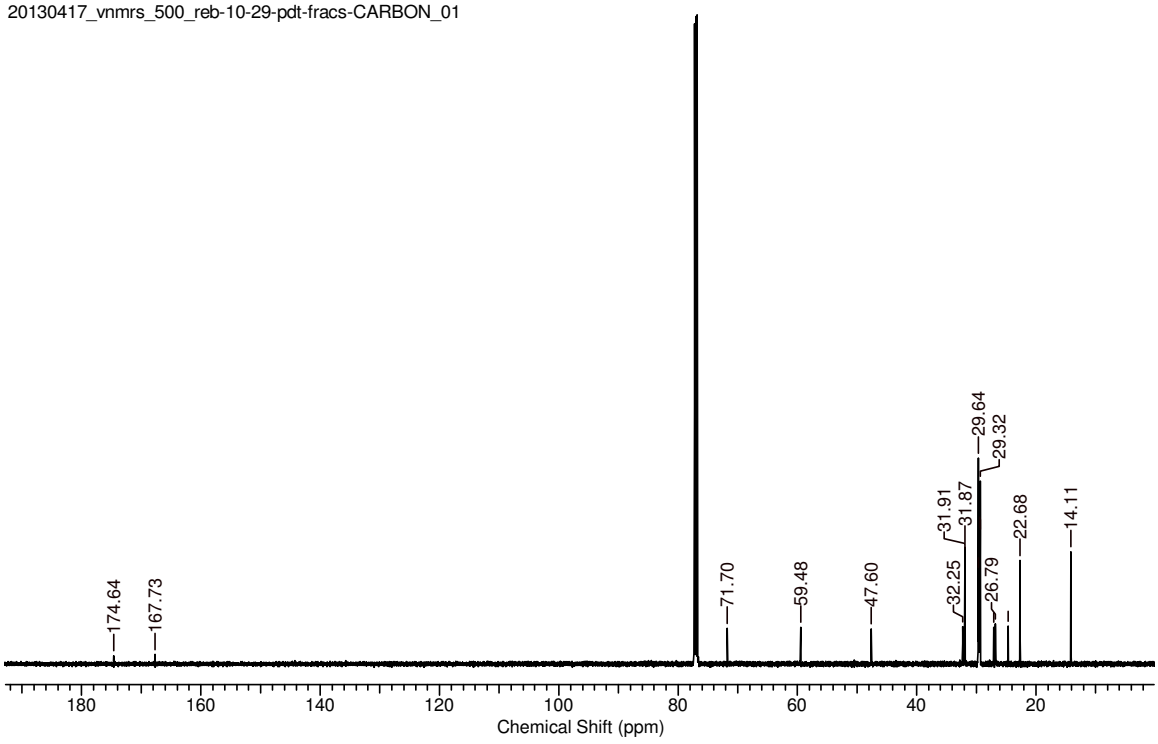
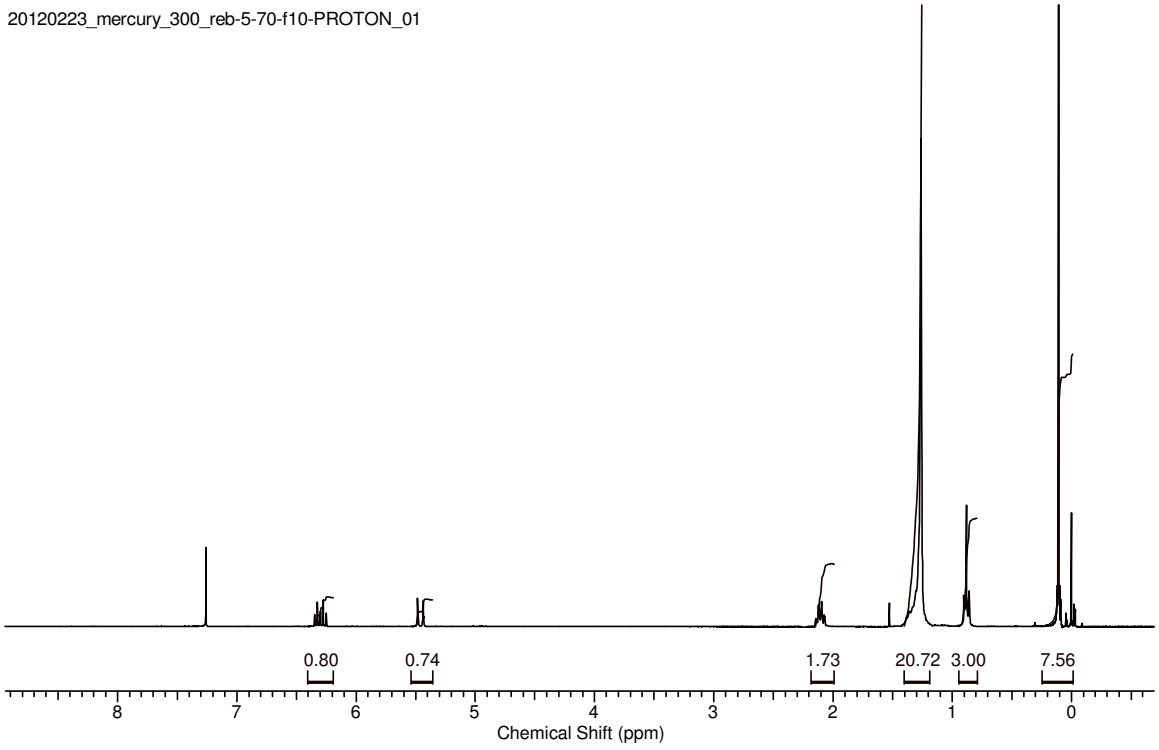
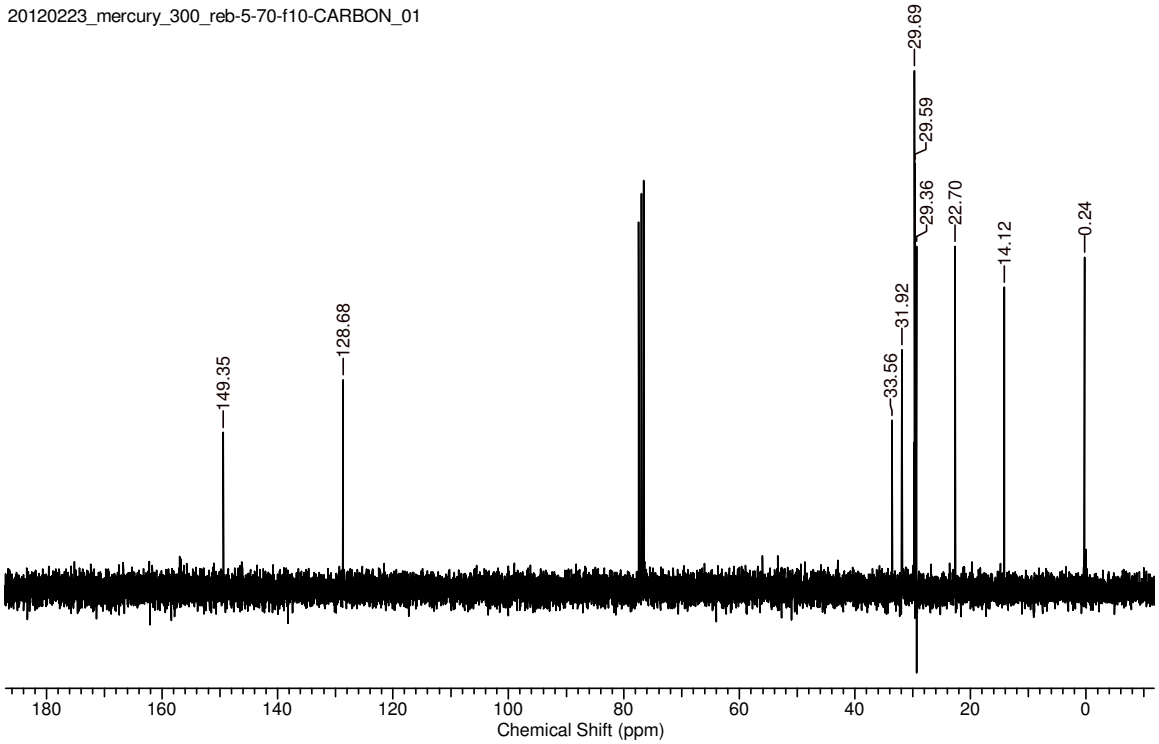
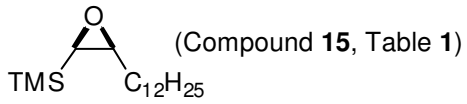


(Compound **14**, Table **1**)

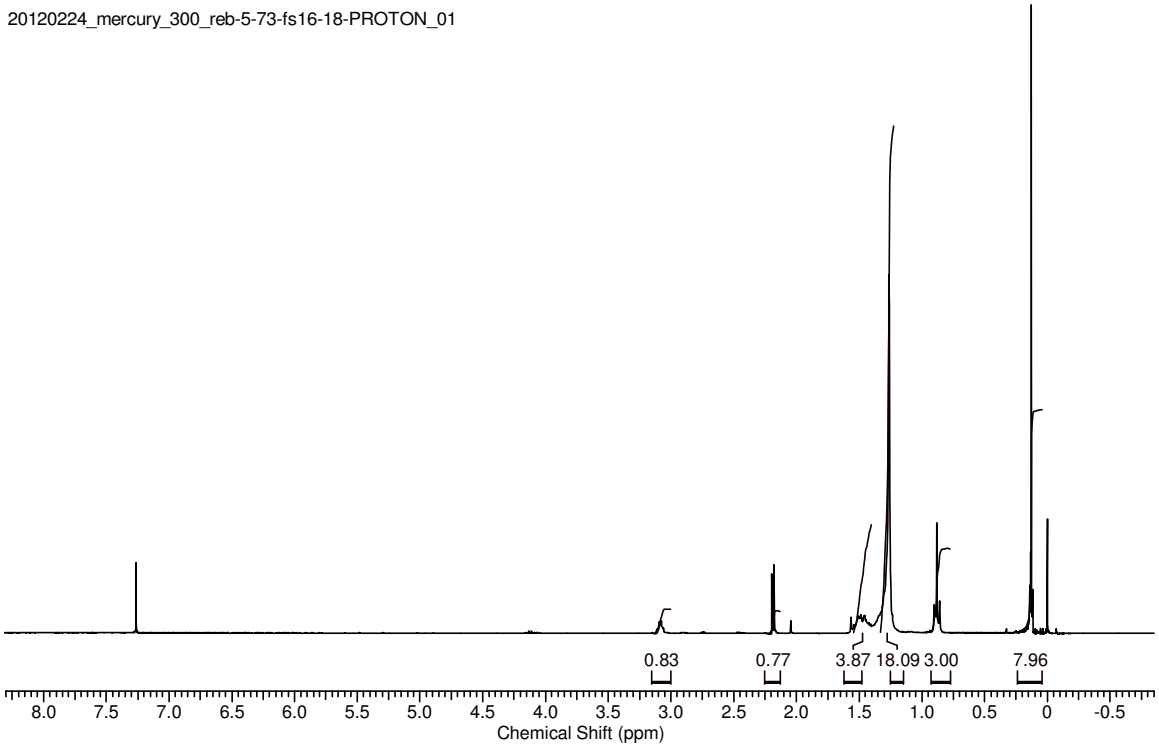






(Compound **15**, Table **1**)

20120224_mercury_300_reb-5-73-fs16-18-PROTON_01



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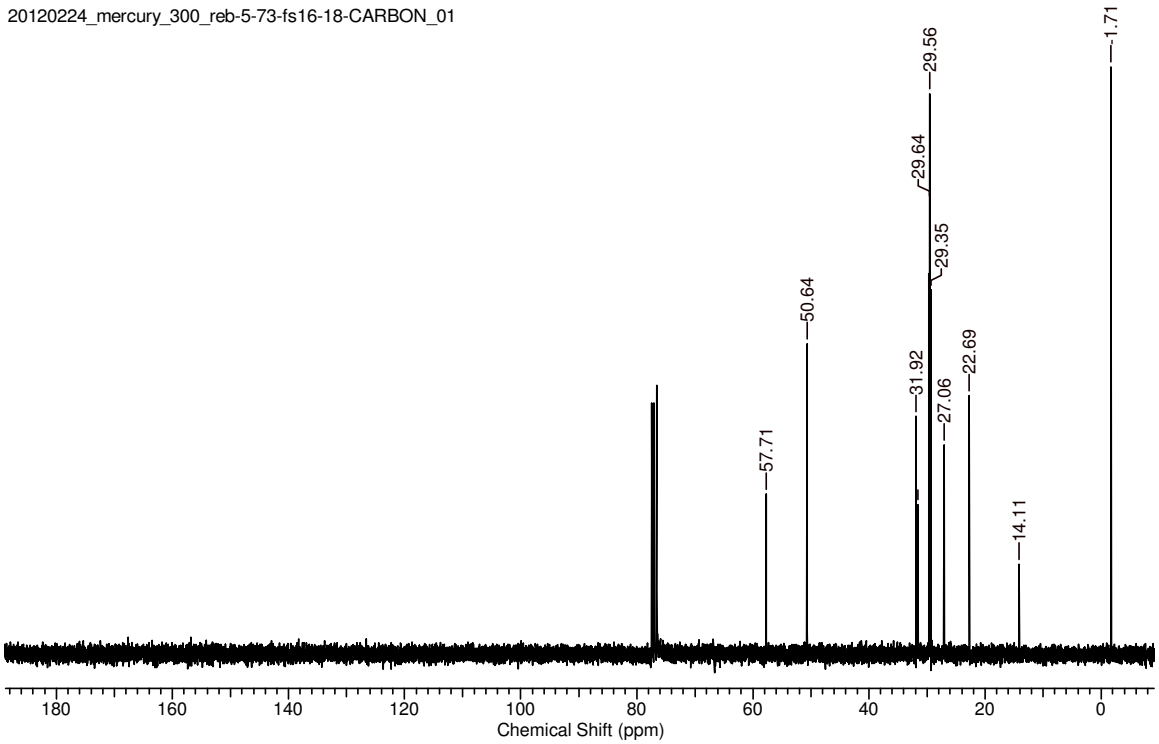
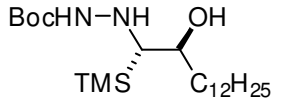
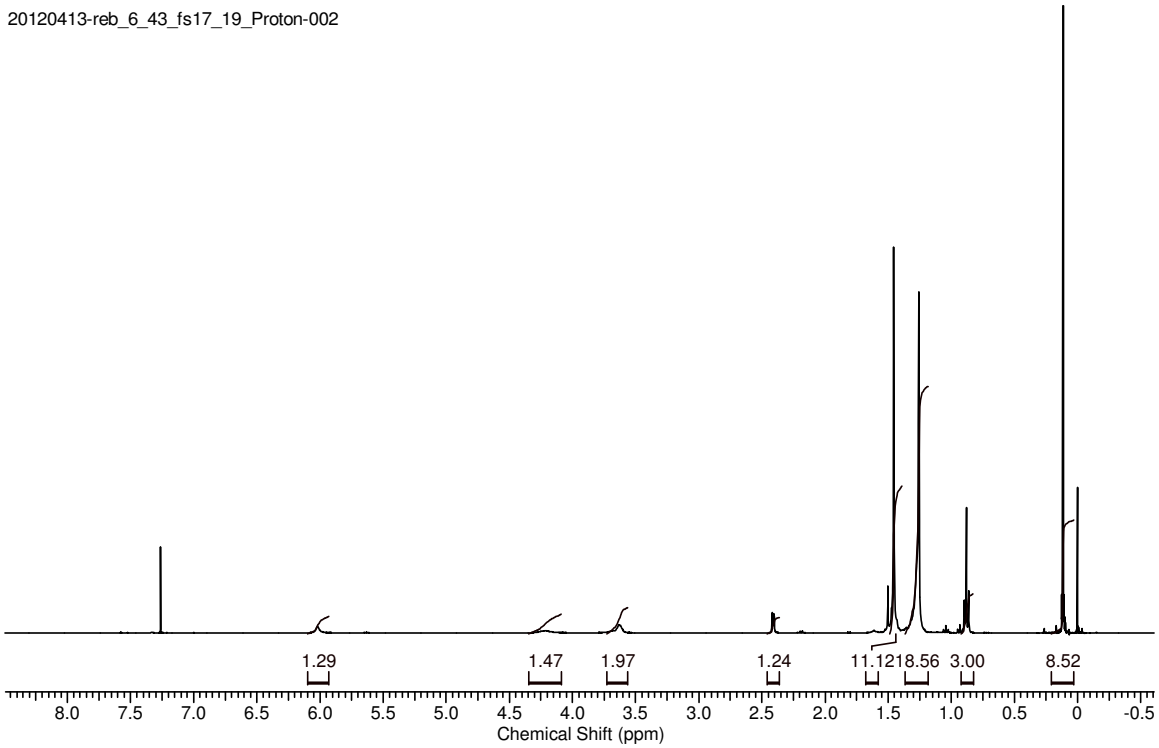
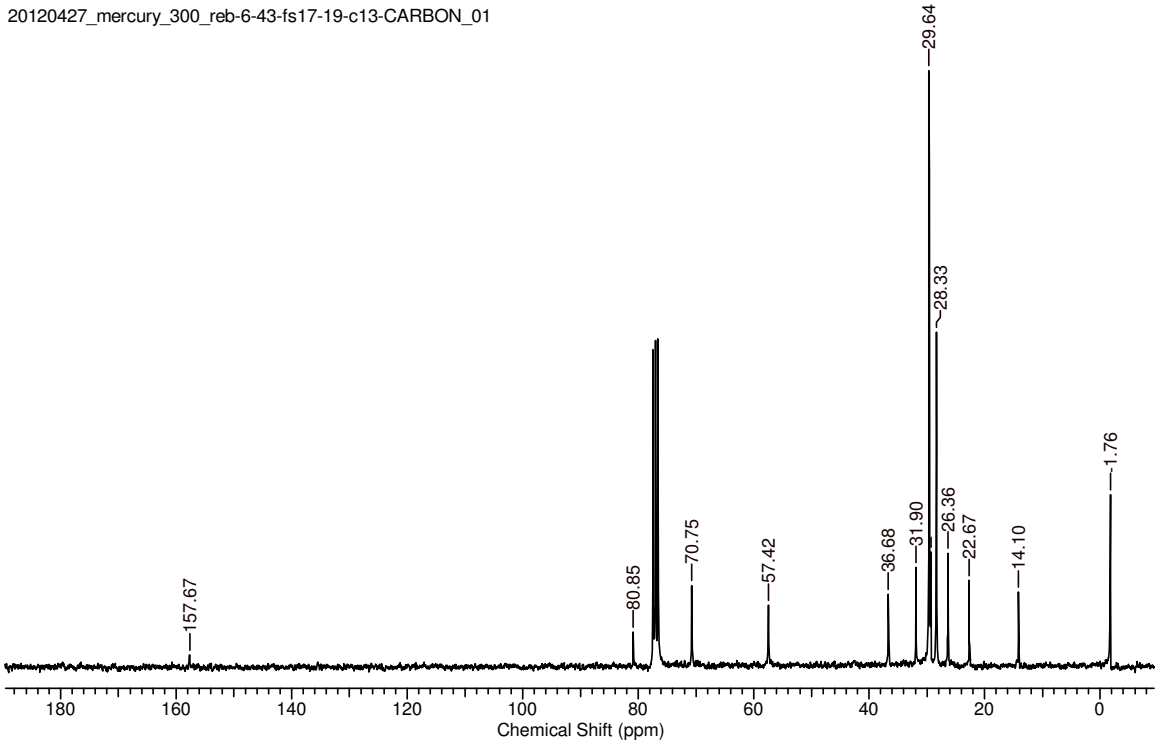
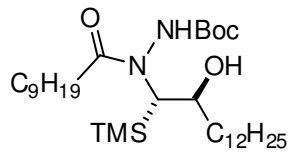




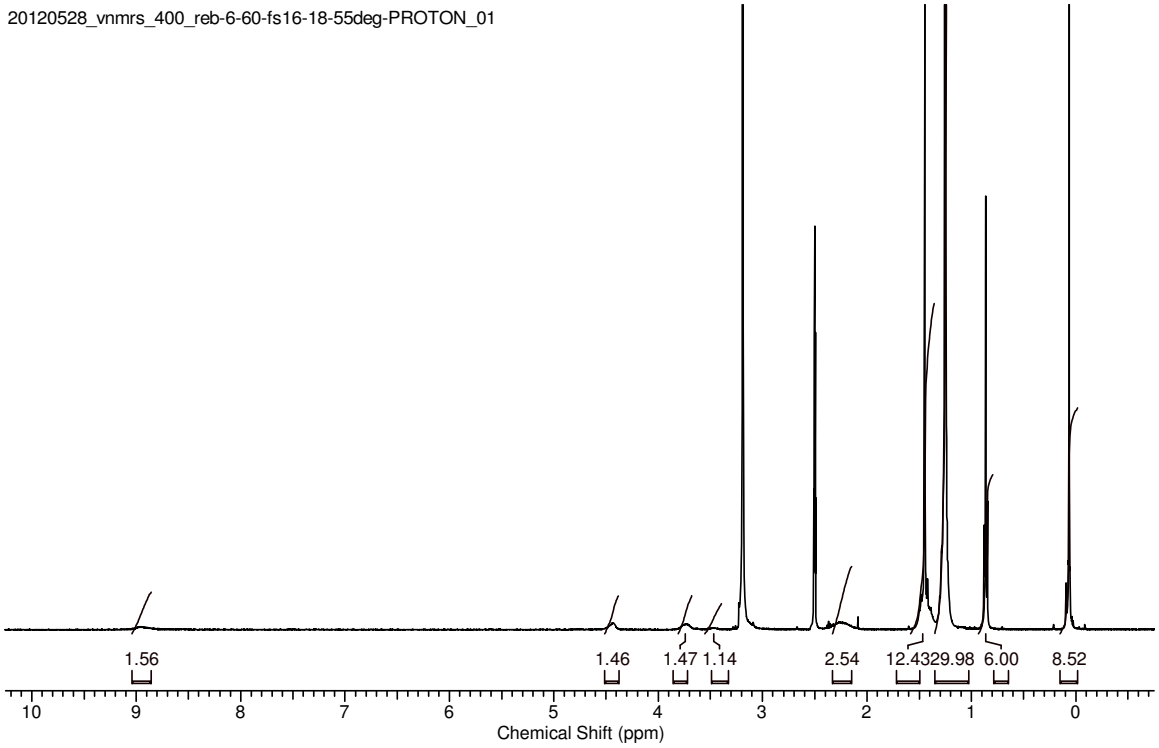
(Compound **16**, Table **1**)

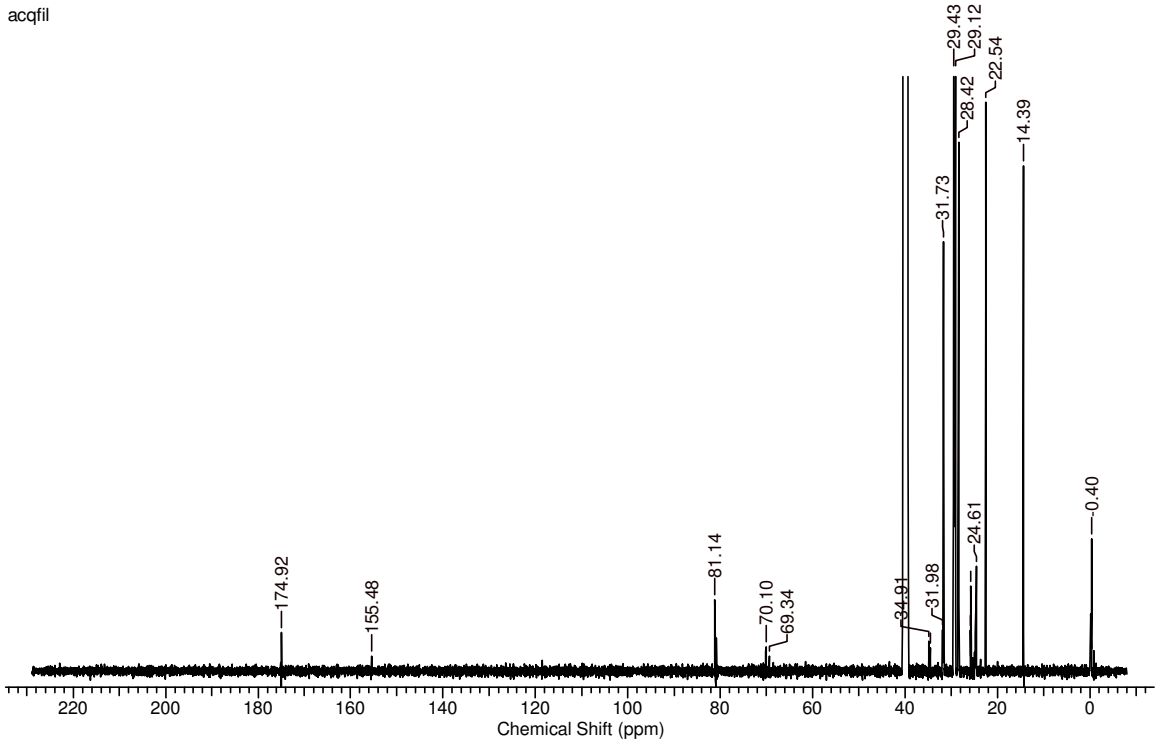


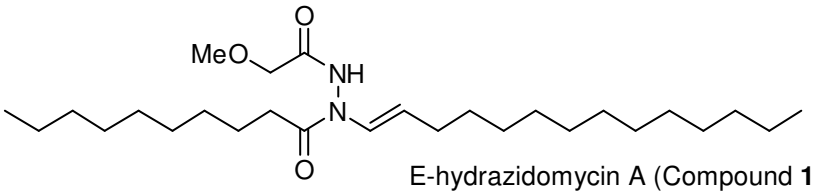




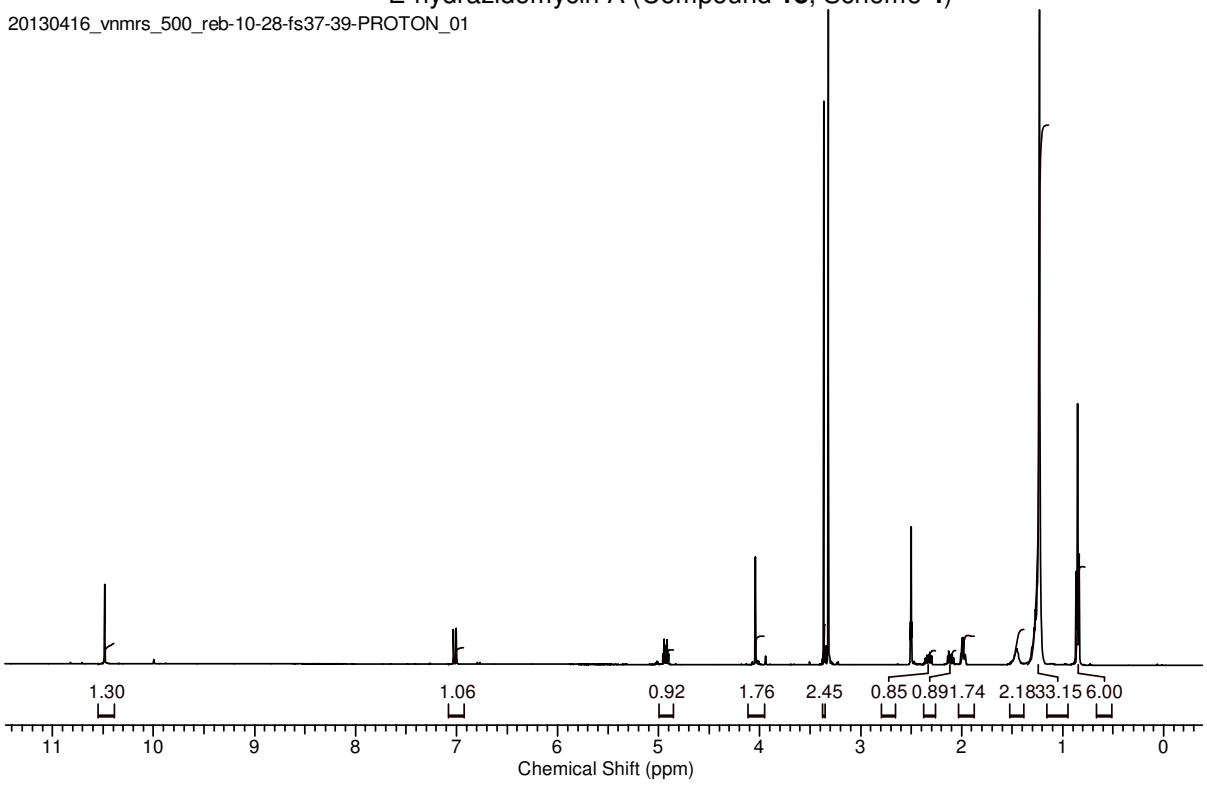
(Compound **17**, Scheme 3**)**

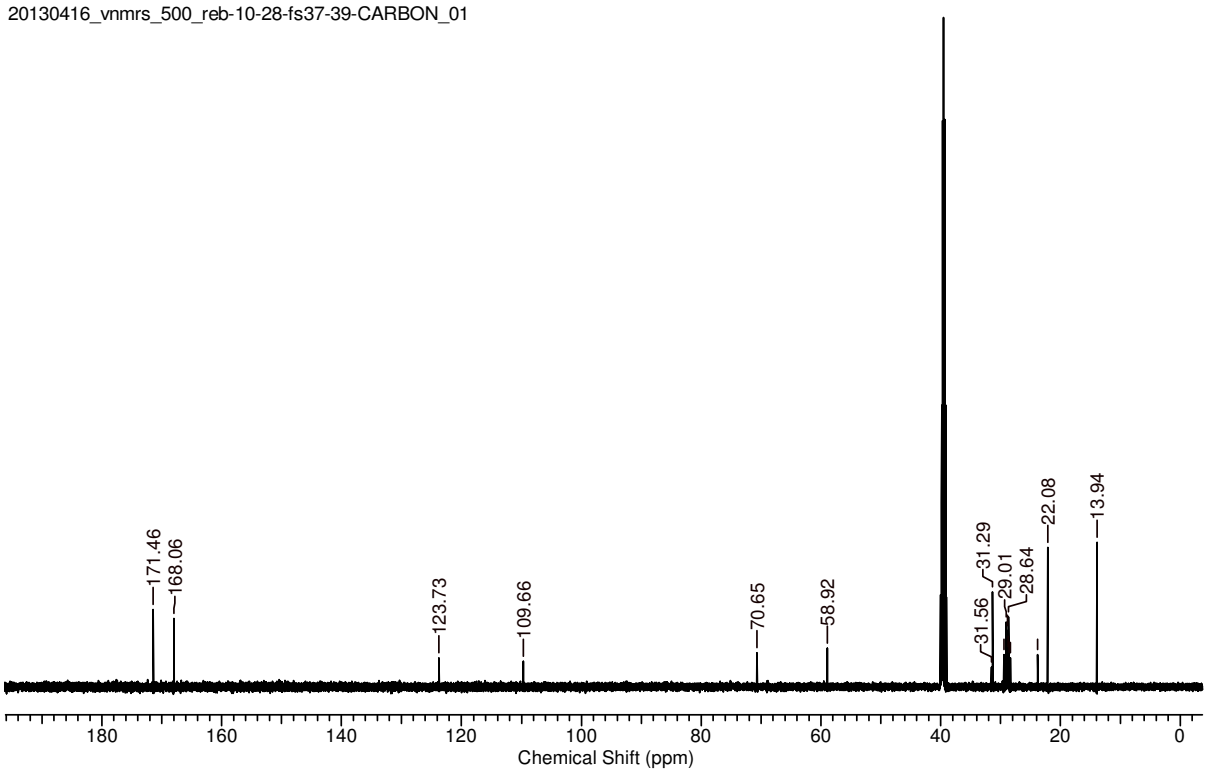


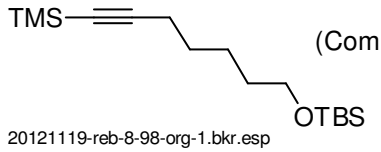




E-hydrazidomycin A (Compound **18**, Scheme **4**)

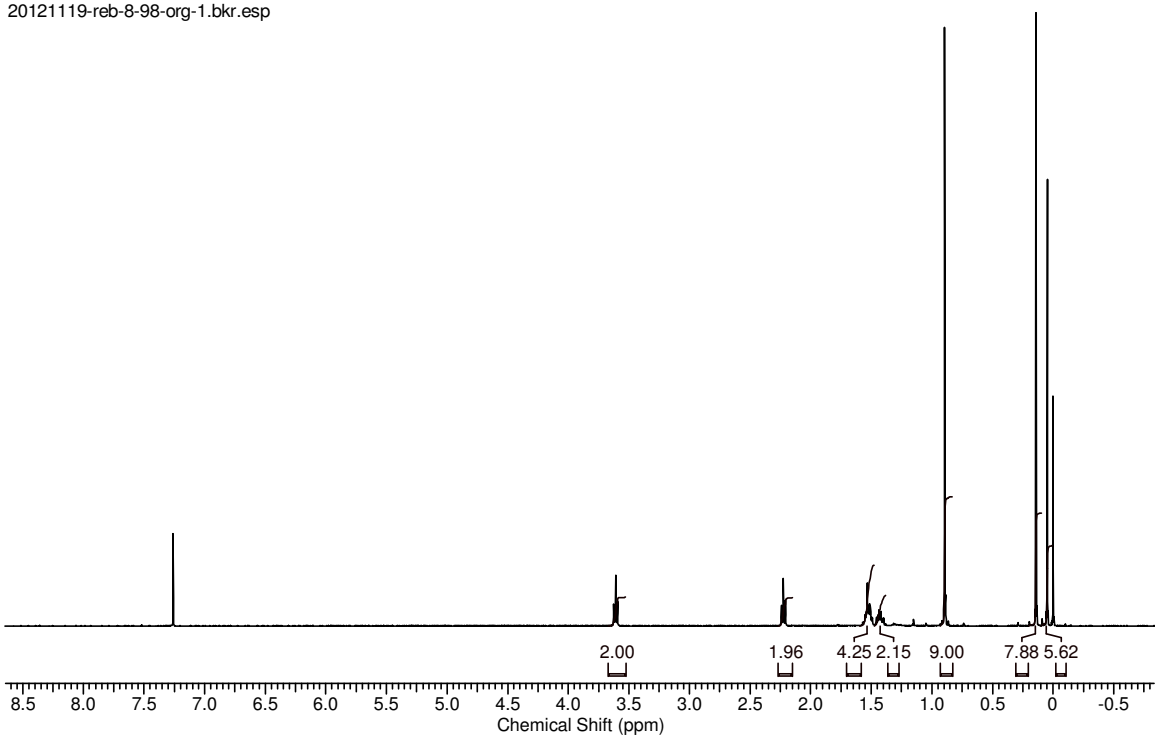






(Compound **19**, Scheme **5**)

20121119-reb-8-98-org-1.bkr.esp



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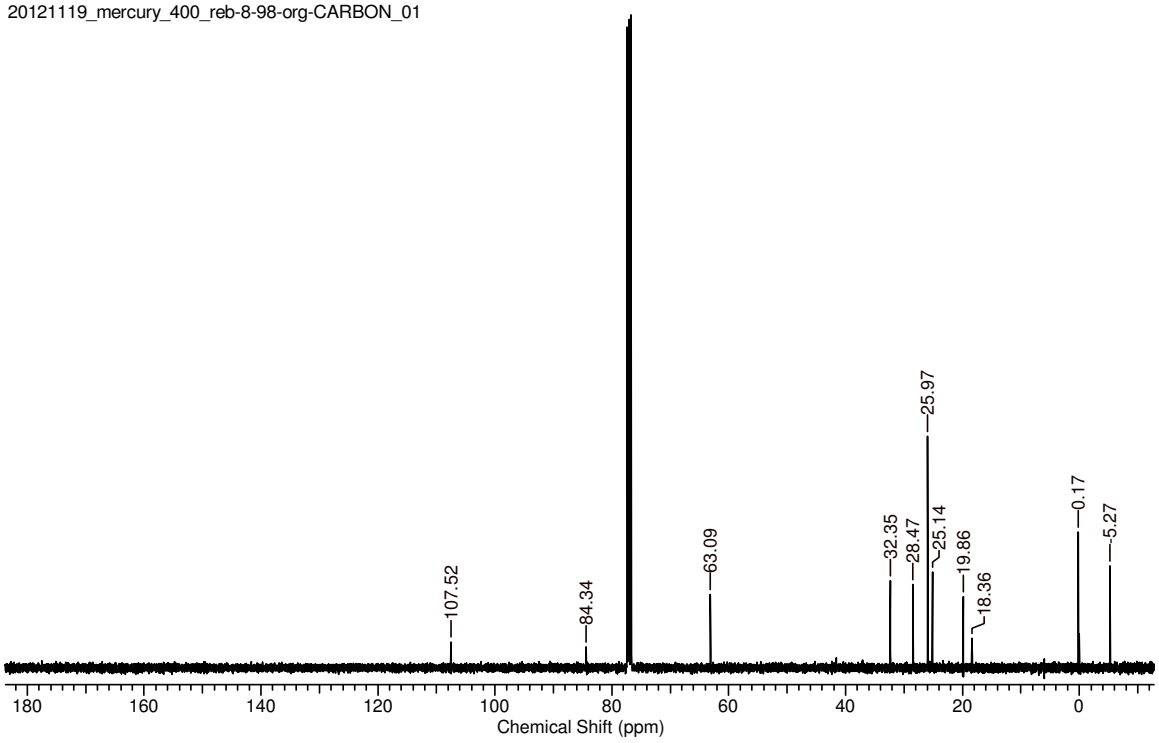
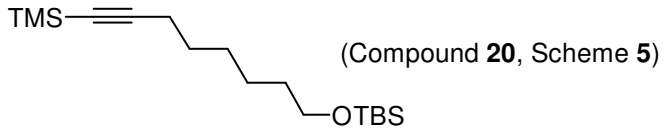
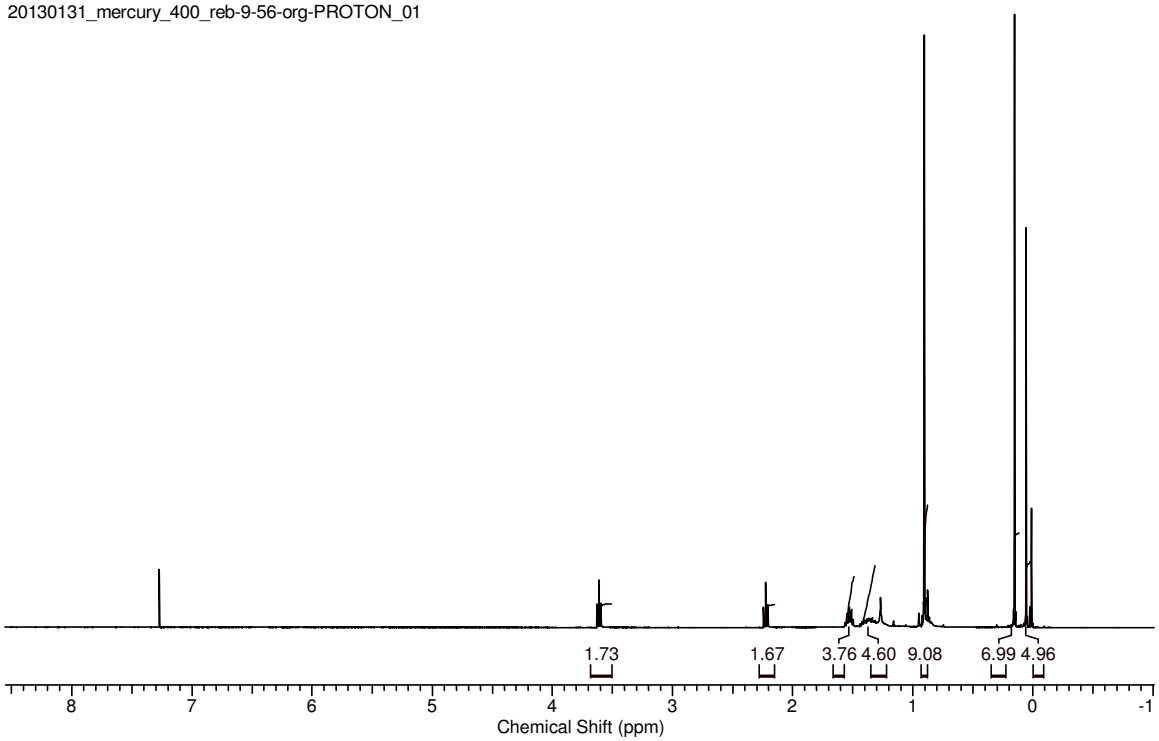




(Compound **20**, Scheme **5**)

20130131_mercury_400_reb-9-56-org-PROTON_01



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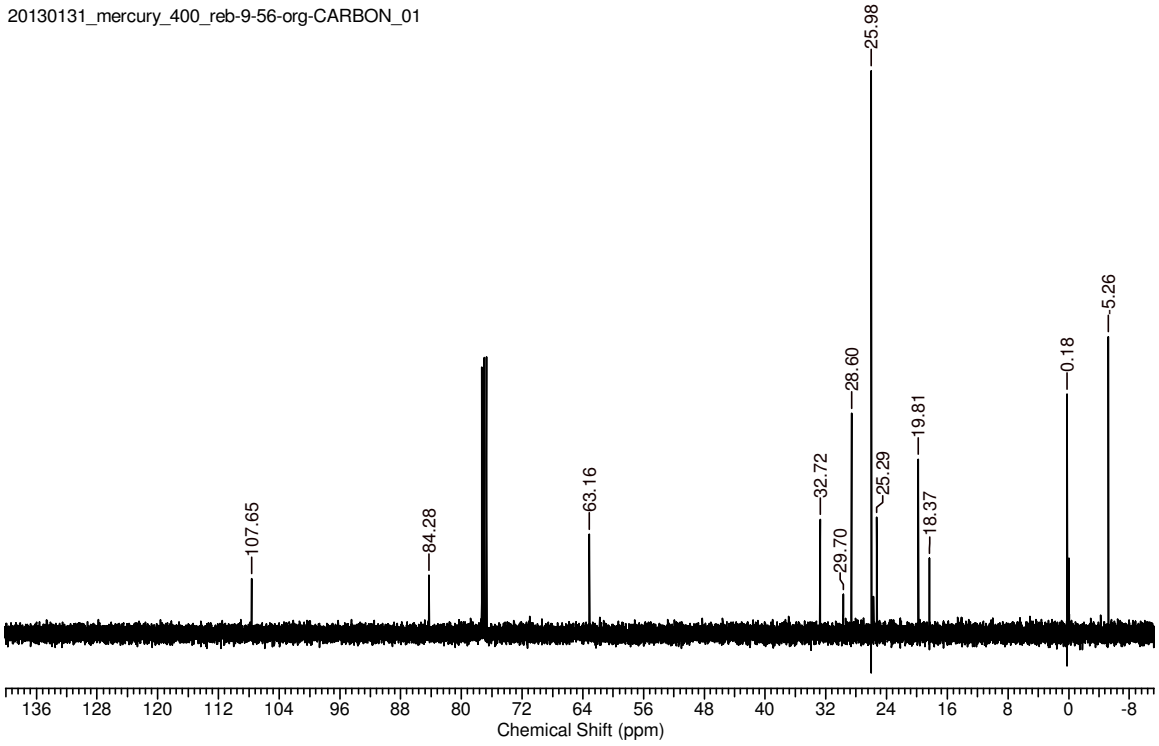

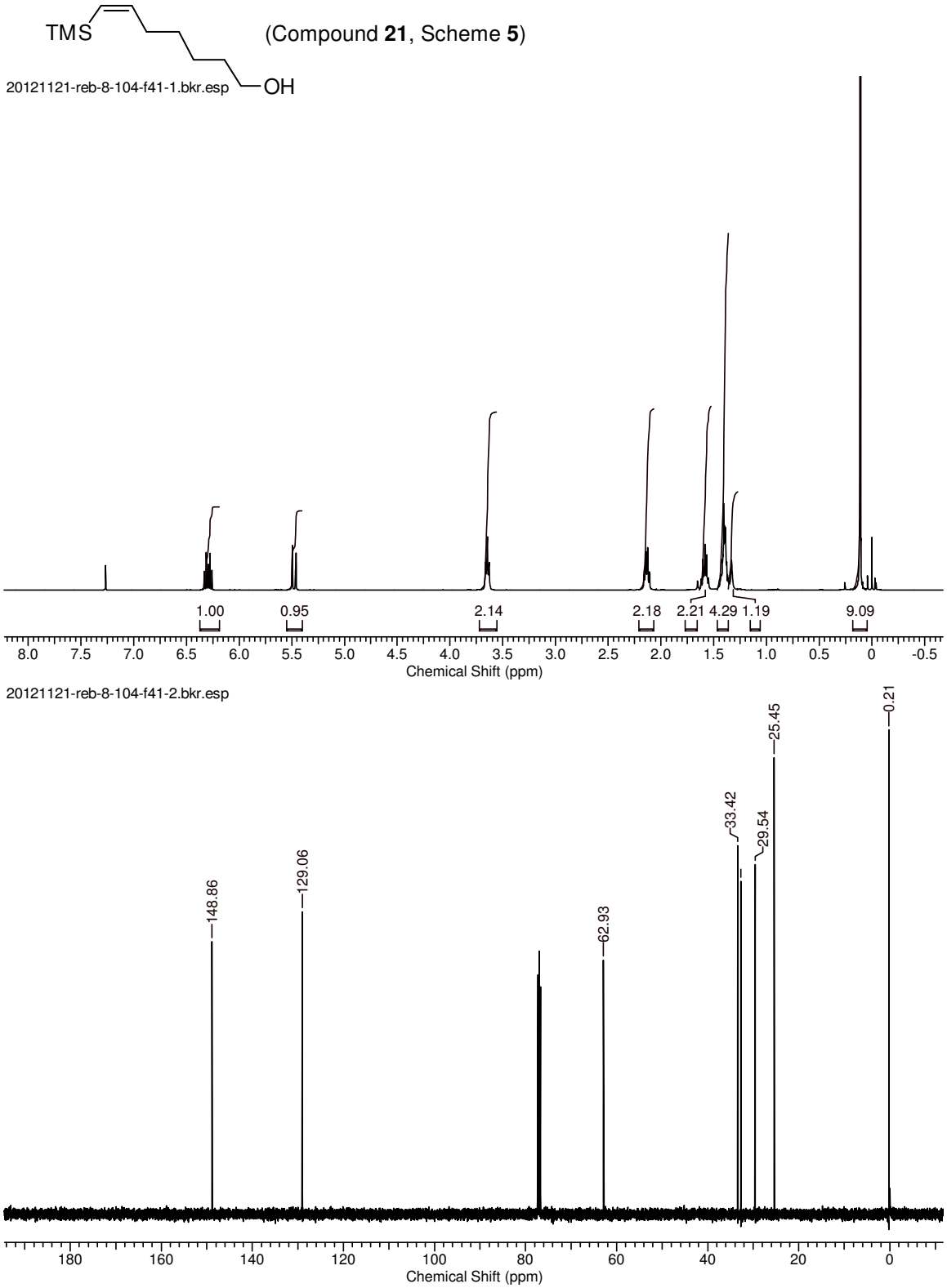
TMS
OH
(Compound 21, Scheme 5)
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1.19
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20121121-reb-8-104-f41-2.bkr.esp
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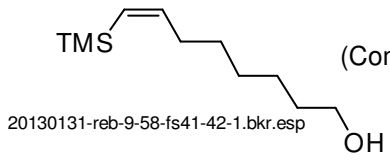

(Compound **22**, Scheme **5**)

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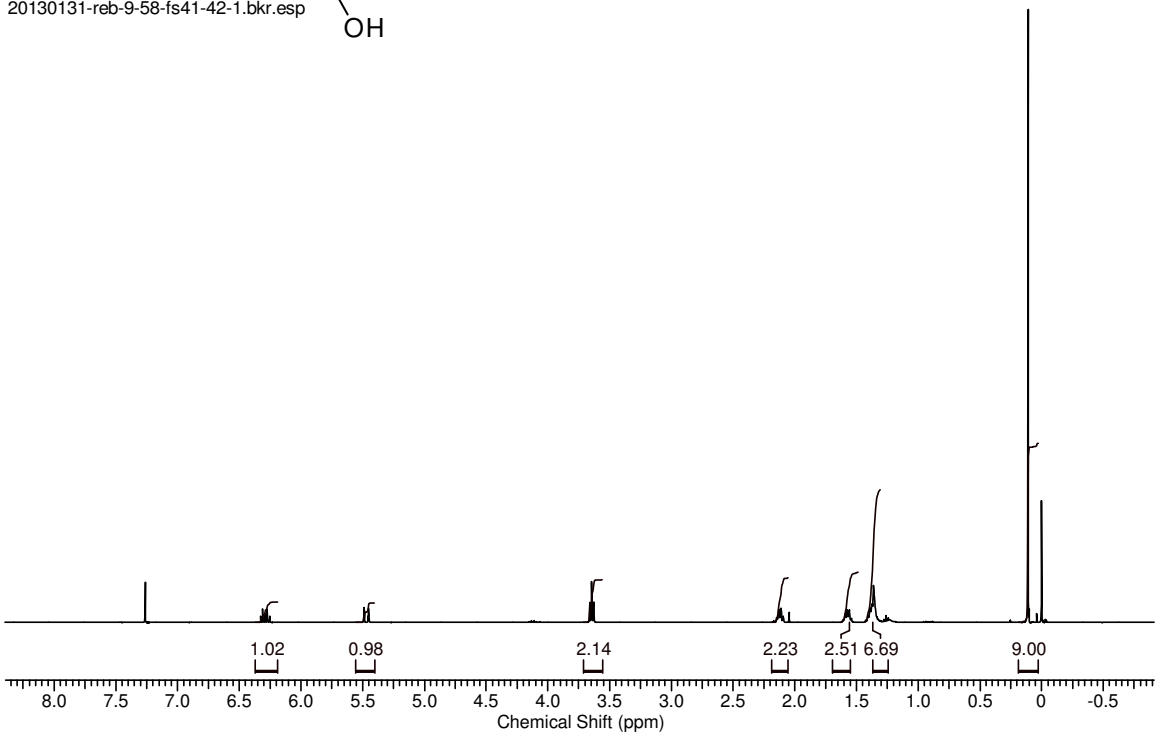
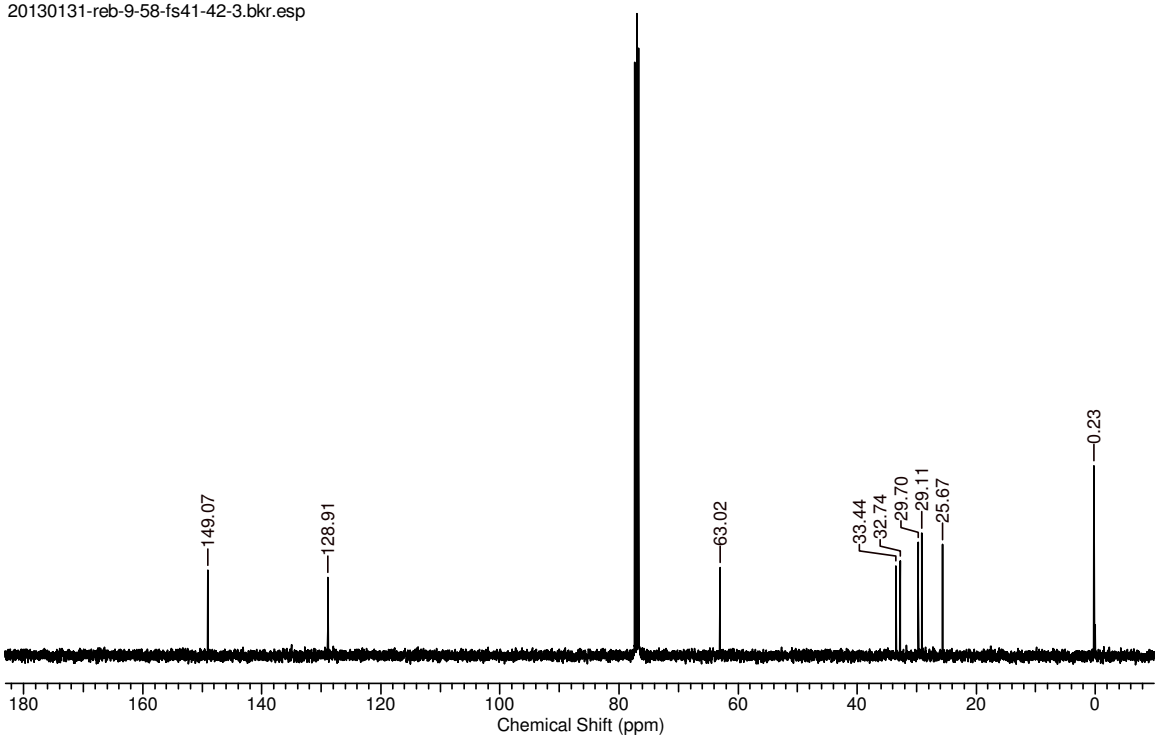
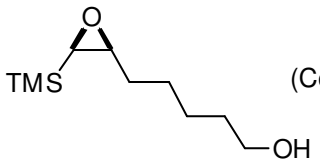
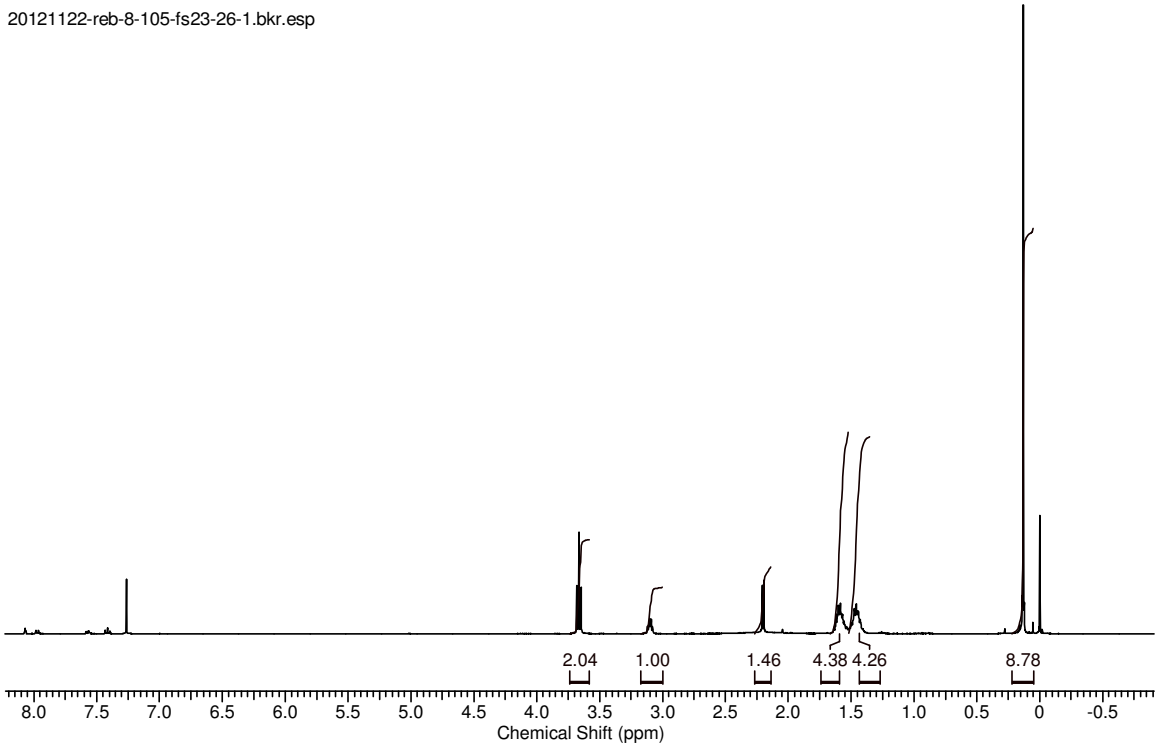


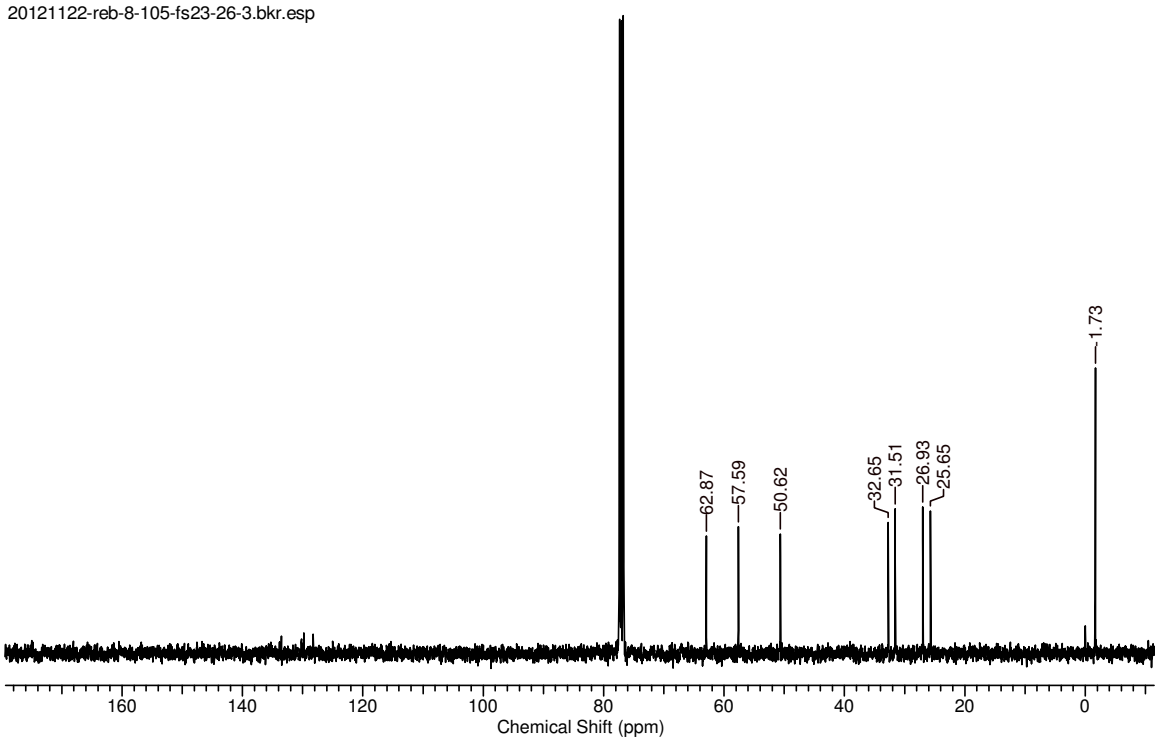
20130131-reb-9-58-fs41-42-3.bkr.esp

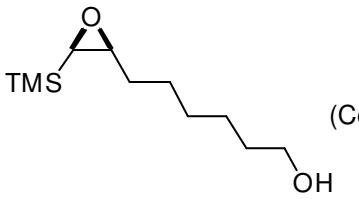




(Compound **23**, Scheme **5**)

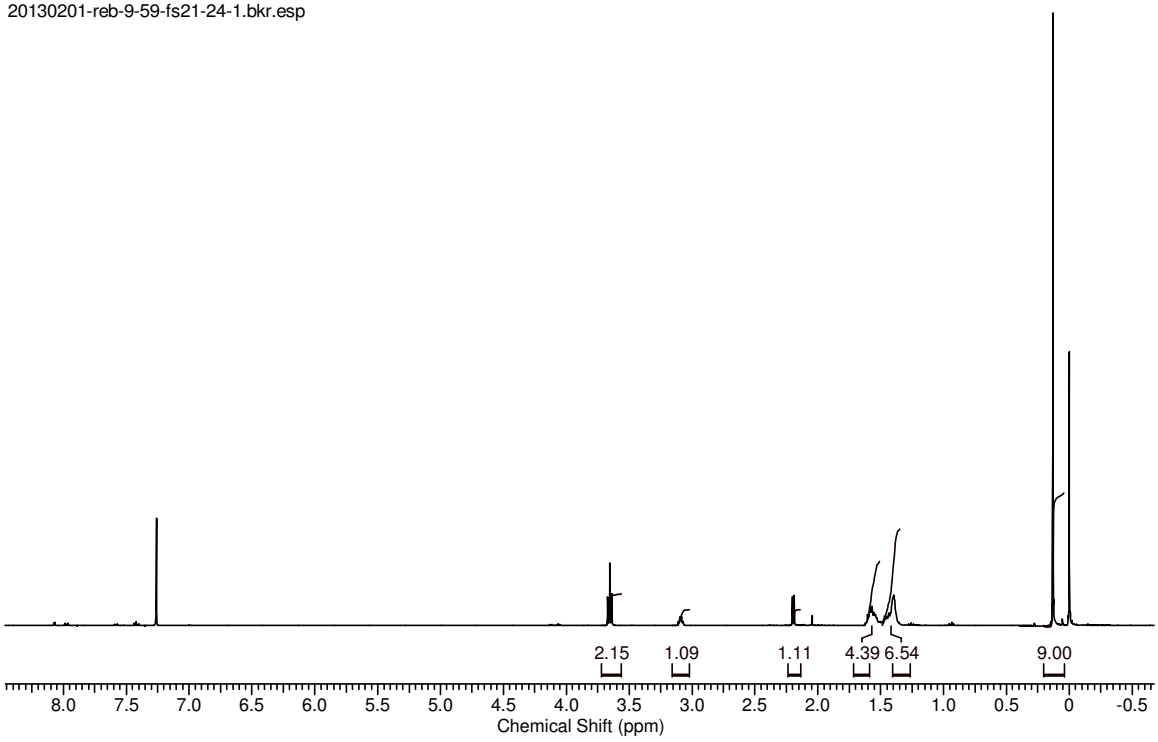




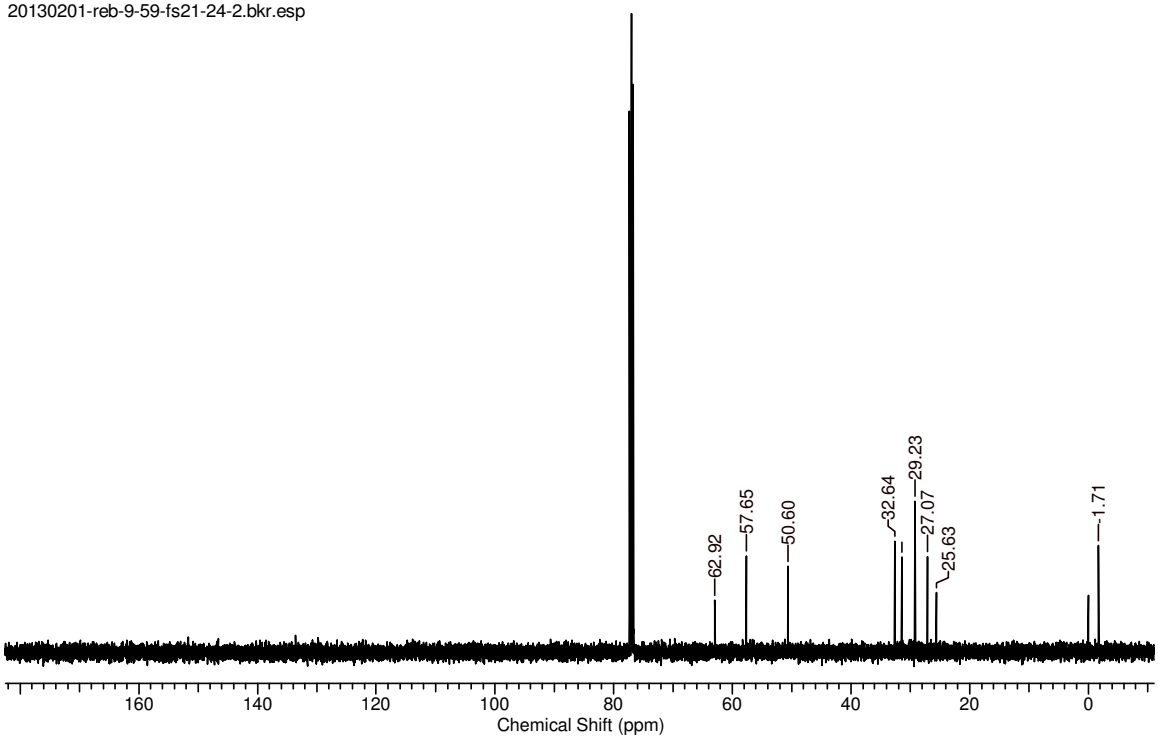


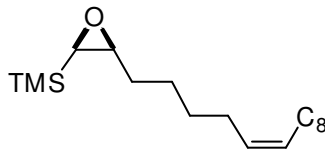
(Compound **24**, Scheme **5**)

20130201-reb-9-59-fs21-24-1.bkr.esp



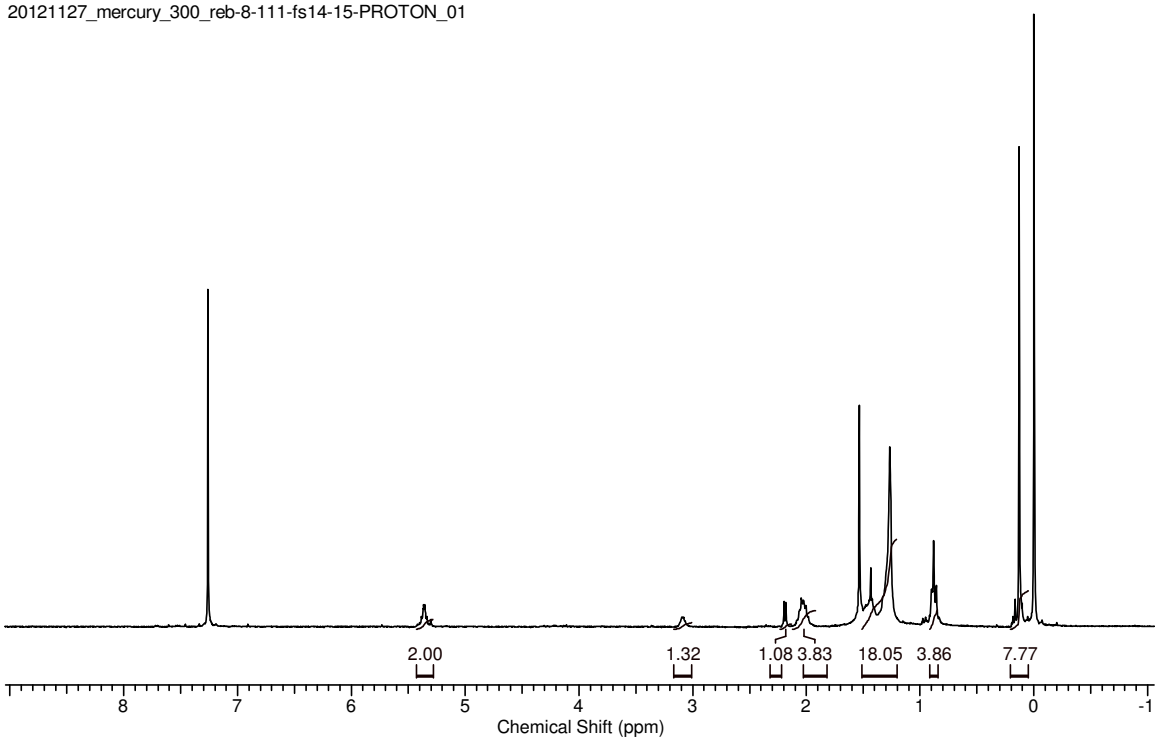
20130201-reb-9-59-fs21-24-2.bkr.esp



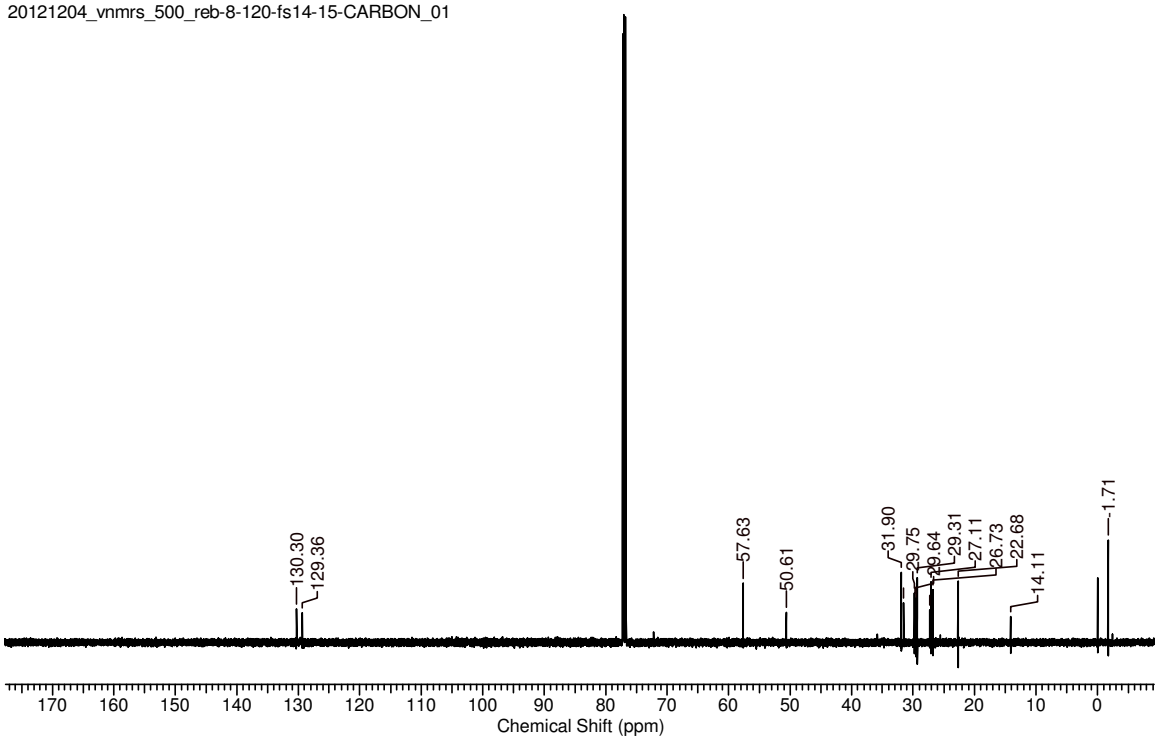


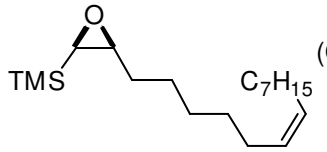
(Compound **25**, Scheme **5**)

20121127_mercury_300_reb-8-111-fs14-15-PROTON_01



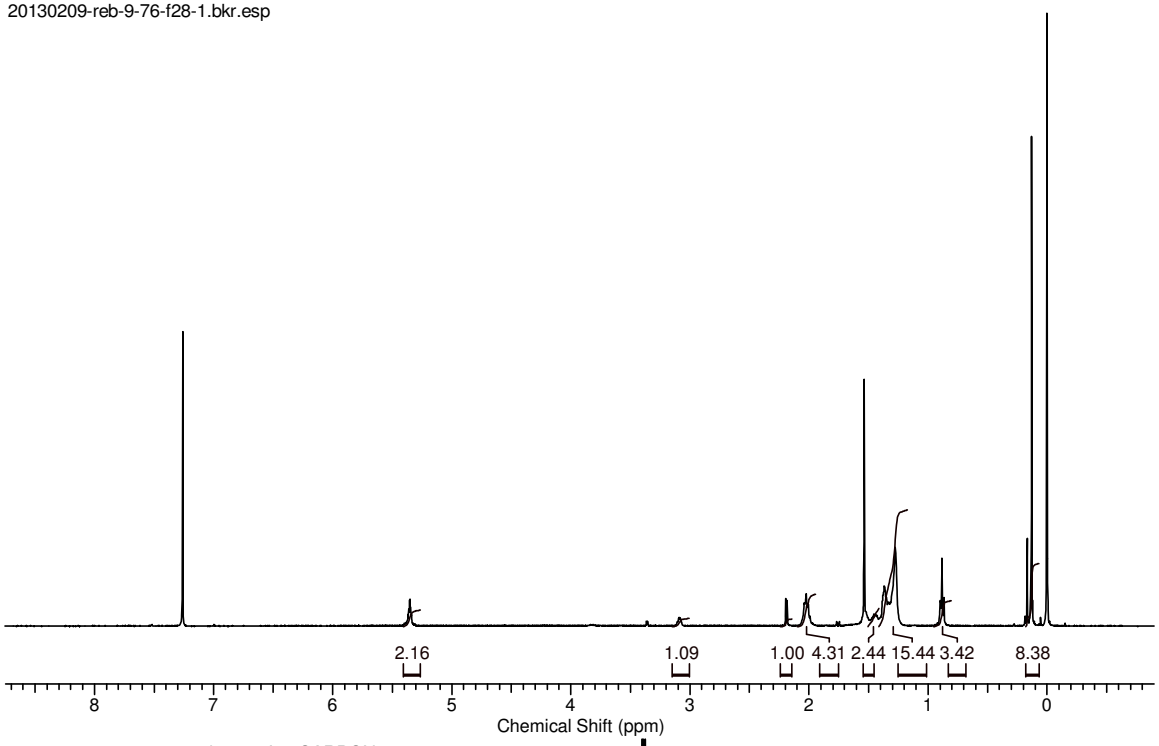
20121204_vnmrs_500_reb-8-120-fs14-15-CARBON_01



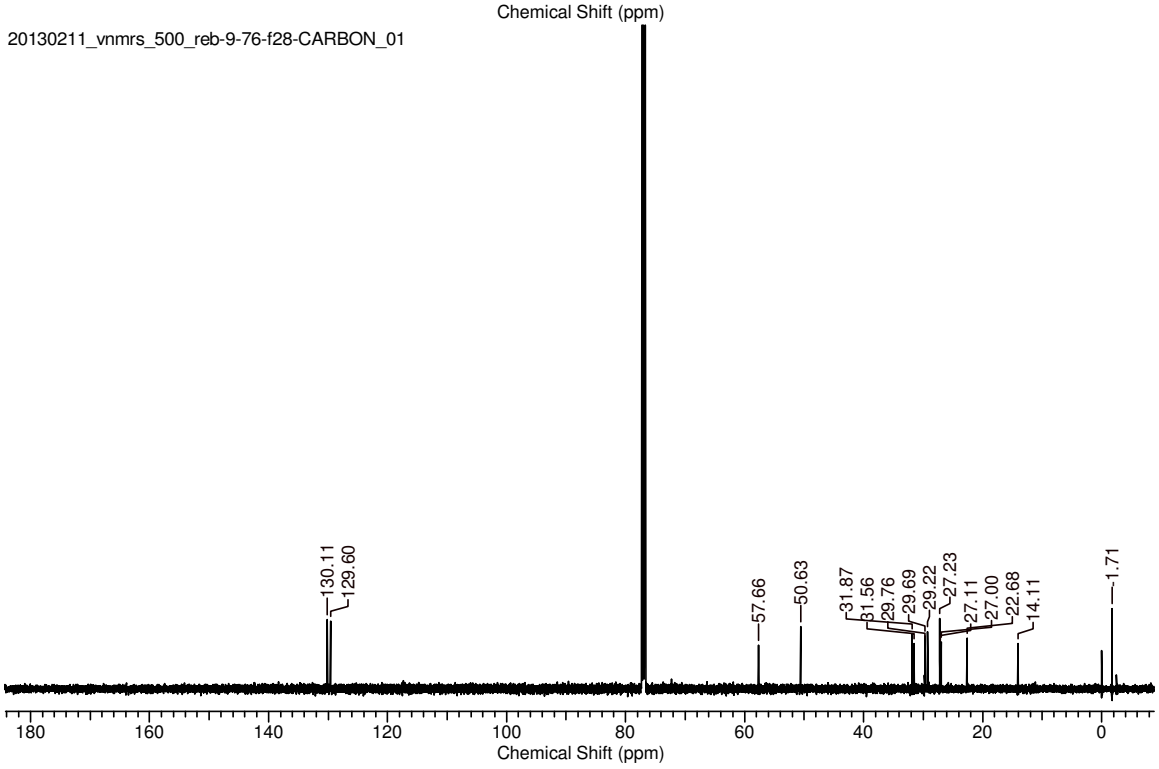


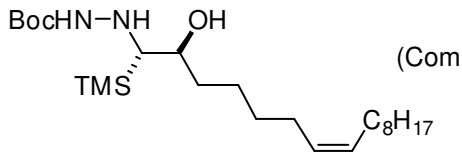
(Compound **26**, Scheme **5**)

20130209-reb-9-76-f28-1.bkr.esp



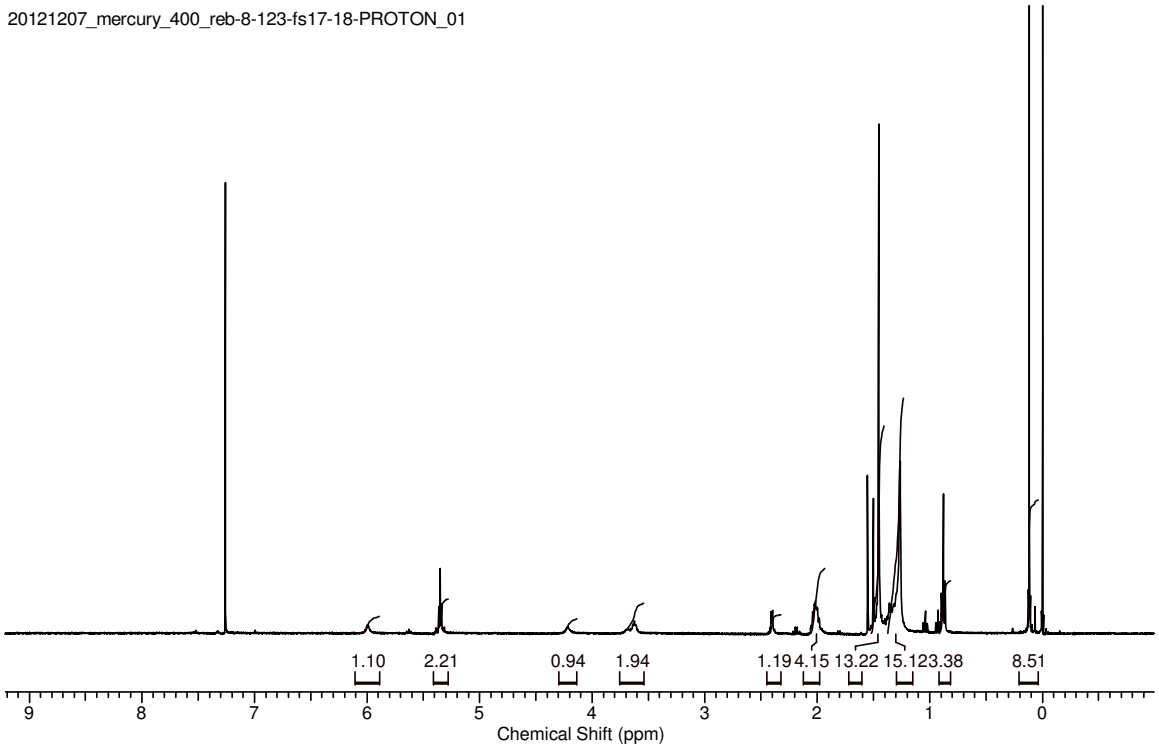
20130211_vnmrs_500_reb-9-76-f28-CARBON_01



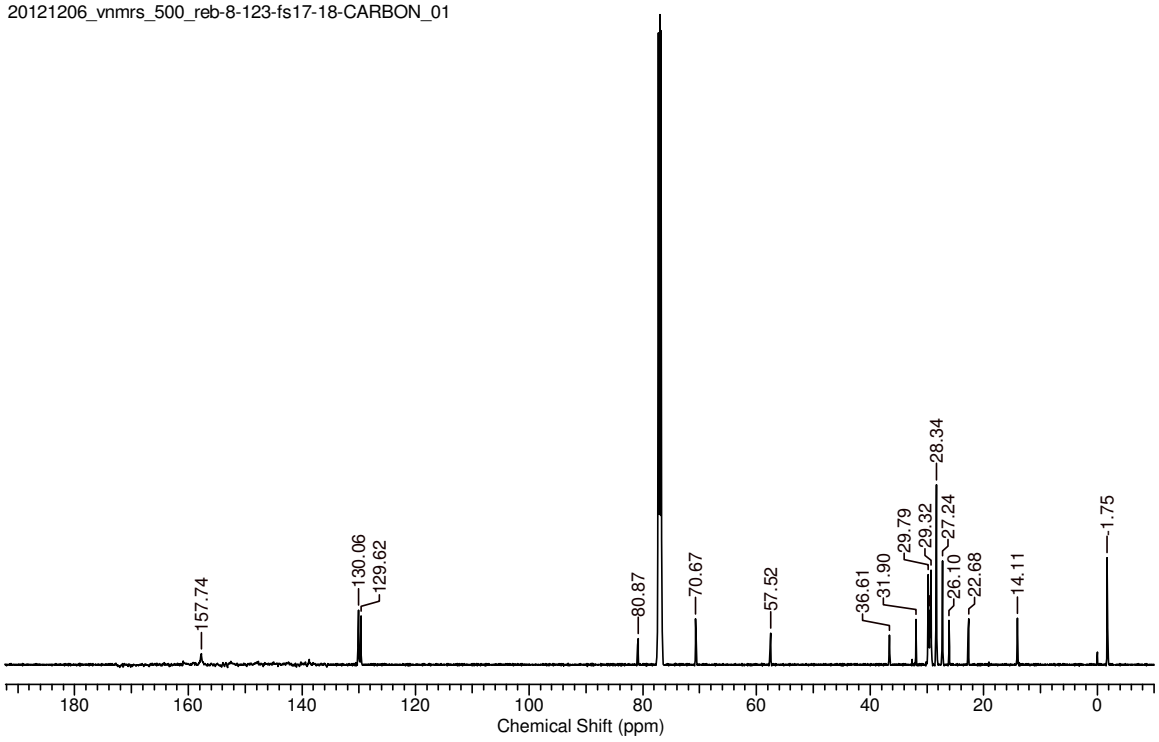


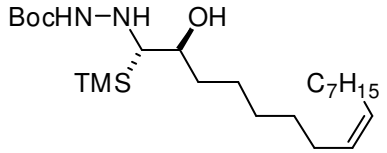
(Compound **27**, Scheme **5**)

20121207_mercury_400_reb-8-123-fs17-18-PROTON_01



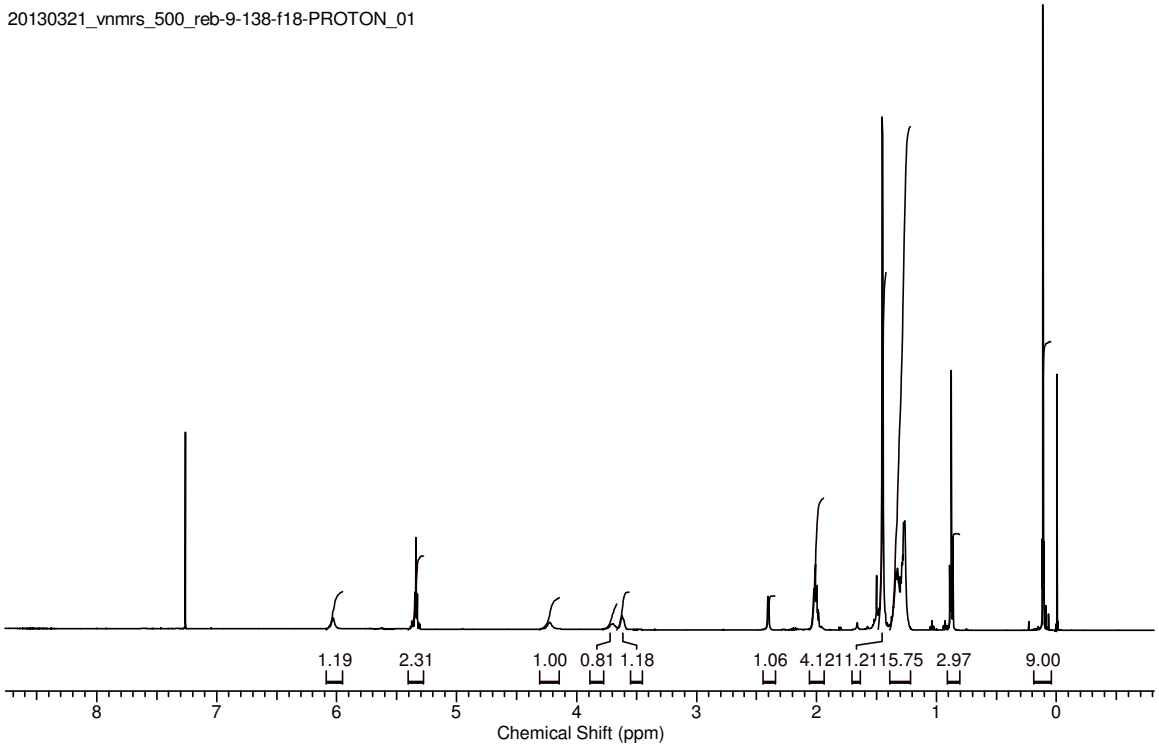
20121206_vnmrs_500_reb-8-123-fs17-18-CARBON_01



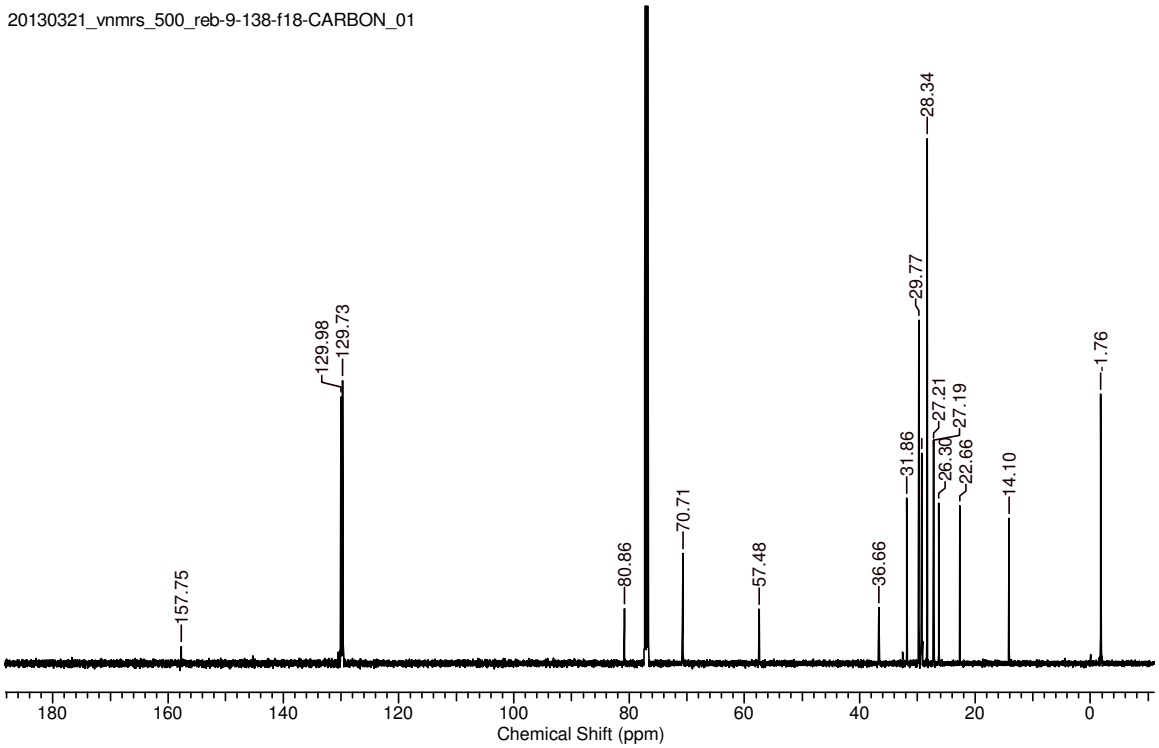


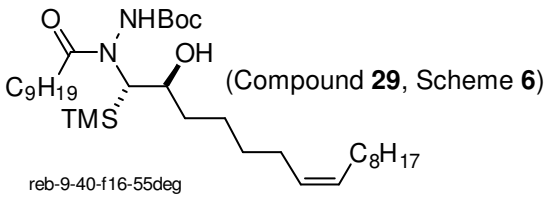
(Compound **28**, Scheme **5**)

20130321_vnmrs_500_reb-9-138-f18-PROTON_01



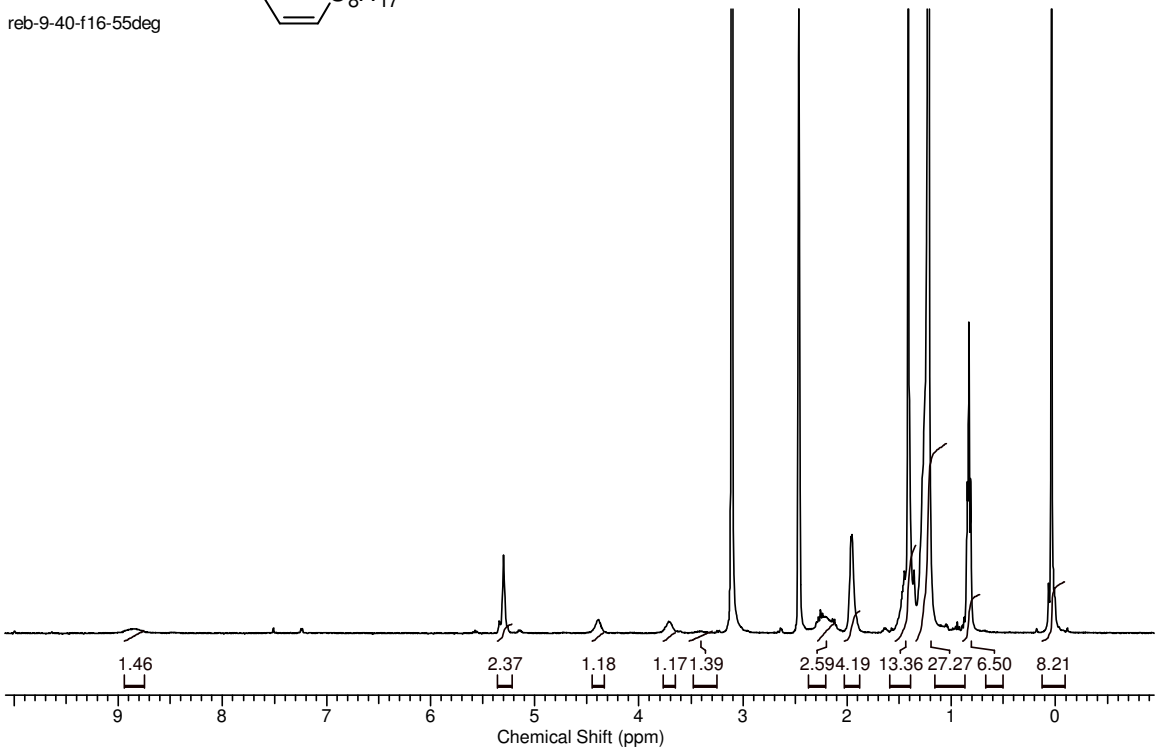
20130321_vnmrs_500_reb-9-138-f18-CARBON_01



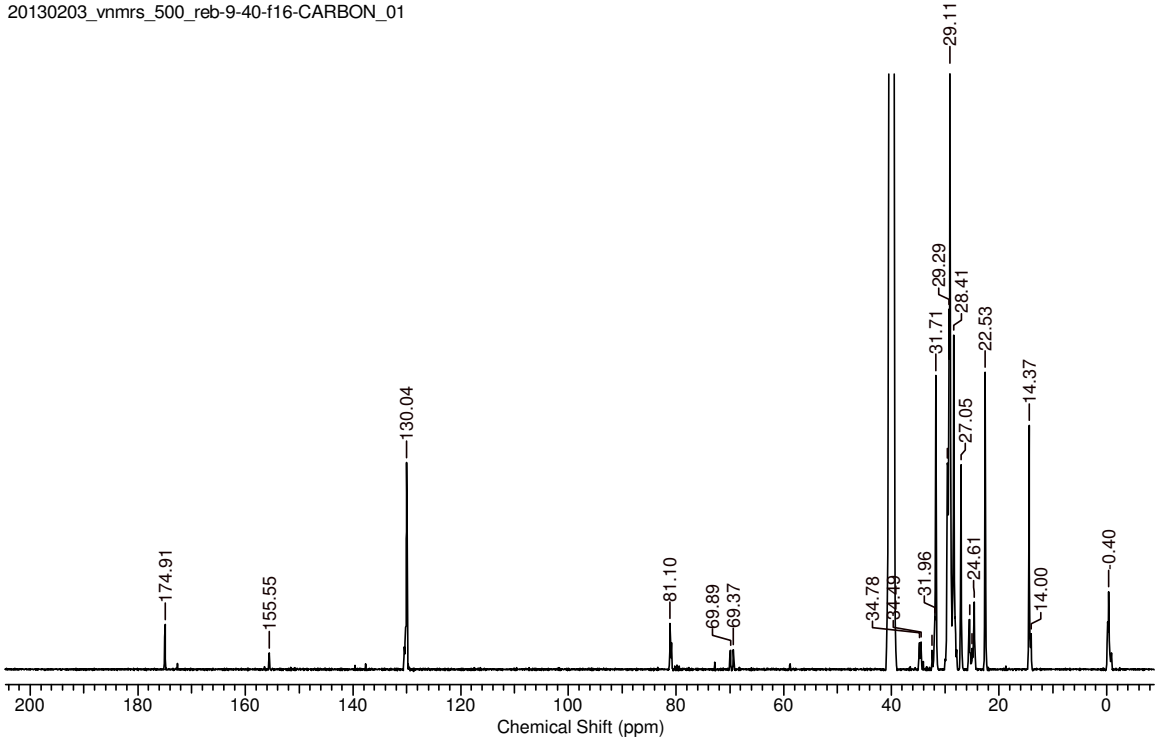


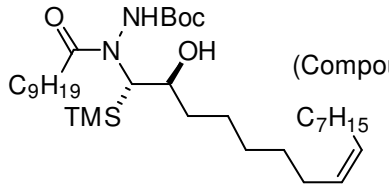
(Compound **29**, Scheme **6**)

reb-9-40-f16-55deg



20130203_vnmrs_500_reb-9-40-f16-CARBON_01





(Compound **30**, Scheme **6**)