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Supporting Information

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The Total Synthesis of (+)-Isomigrastatin

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General Information:

Analytical Equipment: Optical rotations were measured on a JASCO DIP-370 digital polarimeter at rt. Concentration (c) in g/100 ml and solvent are given in parentheses. Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer neat or as a film in $CHCl_3$ (NaCl plates). Absorption bands are noted in cm^{-1}. ^1H- and ^{13}C NMR spectra were recorded on a Bruker AMX-400, a Bruker DRX-500, or a Bruker AVII+-600 spectrometer in $CDCl_3$. Chemical shifts (δ-values) are reported in ppm with residual undeuterated $CHCl_3$ as the internal standard (referenced to 7.26 ppm for ^1H-NMR and 77.2 ppm for ^{13}C-NMR). Coupling constants (J) (H,H) are given in Hz, spectral splitting patterns are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintet (qunit), multiplet or more overlapping signals (m), apparent (app), broad signal (br). Low resolution mass spectra (ionspray, a variation of electrospray) were acquired on a Perkin-Elmer Sciex API 100 spectrometer. Samples were introduced by direct infusion. Flash chromatography (FC) was performed with E. Merck silica gel (60, particle size 0.040-0.063 mm). Preparative thin layer chromatography (TLC) was performed with Whatman Partisil Plates (20 x 20 cm, 60 Å, 200 μm).

Techniques, Solvents, and Reagents: Reactions involving air or moisture-sensitive reagents or intermediates were performed under argon or nitrogen atmosphere in glassware which had been heat gun or flame-dried under high vacuum. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 22 °C. Preparative reactions were stirred magnetically. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), and toluene were obtained from a dry solvent system (activated alumina columns, positive pressure of argon). All other solvents were used as received in Sure/Seal bottles (Aldrich). Triethylamine (Et_3N), diisopropylethylamine (i-Pr_2NEt), pyridine, 2,6-lutidine, and chlorotrimethylsilane (TMSCl) were distilled from CaH_2 immediately prior to use. All other reagents were purchased from Aldrich at the highest commercial quality and used without further purification, with the exception of Grubbs 2nd-generation catalyst, which was purchased from both Strem and Aldrich.

Synthetic procedures:

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Lactol **10**: To a room temperature solution of **8**[1] (1.00 g, 5.10 mmol) in 20 mL MeOH was added $CeCl_3$-H_2O (2.28 g, 6.11 mmol), which was dissolved by vigorous stirring over 15 min. The reaction was then cooled in a -15ºC bath before addition of solid $NaBH_4$ (212 mg, 5.61 mmol), giving vigorous gas evolution. After 2.5 hours, the reaction was quenched by addition of sat. aq. NaOAc, followed by extraction with 3 x 40 mL Et_2O. The combined organics were dried over $MgSO_4$, filtered concentrated *in vacuo*, to give **9** as a colorless oil which was pure by ^{1}HNMR. (500 MHz, $CDCl_3$): δ 1.00 (d, *J* = 7.0 Hz, 3H), 1.61 (s, 3H), 2.23 (m, 1H), 3.31 (s, 3H), 3.75 (dd, *J* = 8.1 Hz, *J* = 6.2 Hz, 1H), 3.86 (dd, *J* = 6.2 Hz, *J* = 3.4 Hz, 1H) 4.12 (m, 1H), 5.35 (d, *J* = ~17 Hz, 1H), 5.38 (d, *J* = ~11 Hz, 2H) 5.73 (m, 1H), 6.19 (s, 1H).

A solution of crude **9** (~ 1 g, 5.1 mmol, from above) in 500 mL 10% H_2O/THF was heated to 65ºC, and camphorsulfonic acid (2.70 g, 11.5 mmol) was added. (This reaction must be run dilute in starting material to avoid formation of dimeric byproducts). After 2 hr, the mixture was poured into separatory funnel containing 500mL $NaHCO_3$. The mixture was extracted with 3 x 500 mL CH_2Cl_2, the organics combined and briefly dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil was immediately purified by flash column chromatography on SiO_2 (10 % to 33 % EtOAc/Hex) to give 829 mg (82 %) lactol **10** (inseparable 9:1 anomeric mixture) as a colorless oil. ^{1}HNMR. (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 7.0 Hz, 3H), 1.60 (s, 3H), 2.23 (m, 1H), 2.31 (br s, 1H), 3.31 (s, 3H), 3.70 (dd, *J* = 8.3 Hz, *J* = 6.3 Hz, 1H), 3.85 (dd, *J* = 6.3 Hz, *J* = 3.4 Hz, 1H), 4.03 (app t, *J* = ~6 Hz,1H), 5.34 (d, *J* = 17.3 Hz, 1H), 5.37 (d, *J* = 10.2 Hz, 1H), 5.72 (ddd, *J* = 17.3 Hz, *J* = 10.2 Hz, *J* = 8.5 Hz, 1H), 6.18 (s, 1H).

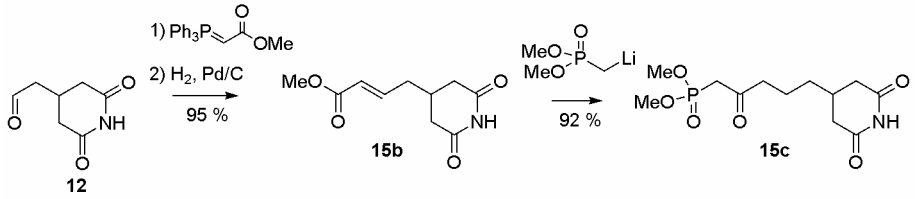
Epoxy-lactol **11**: Prepurified (~95%) mCPBA (9.0 g, 52.5 mmol) and solid K_2CO_3 (4.35 g, 31.5 mmol) were suspended in 500 mL CH_2Cl_2 and stirred at room temperature for 15 minutes, then cooled to 0ºC. Lactol **10** (2.07 g, 10.4 mmol) was added as a solution, and the reaction was allowed to stir in a cold room at 4ºC for 13 hours. The cold reaction mixture was filtered through a medium frit into a flask containing 200 mL sat. aq. Na_2CO_3, transferred to a separatory funnel, and the organic layer washed with 2 more 200-mL portions of sat. aq. Na_2CO_3. The organics were dried over $MgSO_4$, filtered, concentrated and immediately purified by flash column chromatography on SiO_2 (25 % to 33 % to 50 % EtOAc/Hex) to give 1.28 g of a 9:1:.5 mixture of three epoxy lactols. Recrystallization from hot hexanes gave 840 mg of the major lactol as a colorless solid, along with 400 mg of material from the mother liquor and rinses, which was subjected to partial purification by flash column chromatography on SiO_2 (33 % to 50 % EtOAc/Hex) to remove 116 mg of a minor isomer, then recrystallized from hot hexanes to give a further 125 mg pure major isomer. Colorless crystals of the major isomer **11** (965 mg, 43 %), were analyzed by X-ray diffraction and shown to possess the alpha configuration for both epoxide and hydroxyl groups. $[\alpha]_D$ = - 29º (c = 1, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (d, *J* = 6.9, 3H), 1.43 (s, 3H), 2.05 (m, 1H), 3.11 (d, *J* = 2.2 Hz, 1H) 3.29 (s, 3H), 3.52 (t, *J* = 8.5 Hz, 1H) 3.56 (br s or d, *J* = 9.8 Hz, 1 H), 3.73 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H) 5.14 (d, *J* = 9.8 Hz, 1H) 5.35 (app d, *J* = ~13 Hz, 2H), 5.56 (m, 1H). ^{13}C HNMR (100 MHz, $CDCl_3$): δ 9.68, 20.30, 29.87, 56.48, 58.73, 65.45, 67.60, 83.13, 91.52,

[1] Gaul, C.; Njardarson J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D.; Tong, W. P.; Huang, X.-Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326-11337.

120.55, 133.66. MS (ESI): 236.9 [M + Na]. IR (neat): 3483, 3081, 2987, 1454, 1284, 1078, 1038, 731.

Glutarimide phosphorane **14**: A solution of acetone bisphosphorane **13** was prepared by addition of potassium t-butoxide (1.0 M in THF, 9.40 mL, 9.40 mmol), to a room-temperature solution of acetone bis-1,3-triphenylphosphonium chloride[2] (2.45 g, 3.76 mmol) in 90 mL DMSO. After 30 minutes, glutarimide aldehyde **12**[3] was added as a solid. After 5 hours, the reaction mixture was poured into a separatory funnel containing 200 mL CH_2Cl_2 and 200 mL sat. aq. $NaHCO_3$. The organic layer was washed with 2 x 200 mL sat. aq. $NaHCO_3$, then 200 mL water, then dried over MgSO4, filtered and concentrated *in vacuo* to give a brownish solid, which was purified by flash column chromatography on SiO_2 (4 % MeOH/CH_2Cl_2), giving 1.19g (70 %) of unsaturated phosphorane **14** as a pale yellow solid. This product was occasionally contaminated with variable amounts of acetone-1-triphenylphosphorane. Because of the difficulty of removing this contaminant, the analogous Horner-Emmons reagent **15c** was more conveniently employed for olefination to afford **18** (see below). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22-2.39 (m, 5H), 2.69-2.77 (app d, ~16 Hz, 2H), 3.84 (d, J_{PH} = 25.0 Hz, 1H), 6.25 (d, J = 15.3 Hz, 1H), 6.45 (dt, J = 15.3 Hz, J = 7.1 Hz, 1H), 7.47 (t, J = 7.5 Hz, 6H), 7.56 (t, J = 7.2 Hz, 3H), 7.65 (dd, J = 12.4 Hz, J = 7.5 Hz, 6H), 7.86 (br s, 1H).

Glutarimide phosphorane **15**: Phosphorane **14** (1.19 g, 2.61 mmol) was dissolved in 50 mL of THF/MeOH (1:1). The solution was purged with nitrogen, then Pd/C catalyst (5 % wt. Pd, 120 mg) was added. The reaction was then purged with hydrogen and stirred for 48 hr, then purged again with nitrogen, filtered, concentrated, and purified by flash column chromatography on SiO_2 (4 % MeOH/CH_2Cl_2) to give 1.15 g (96 %) **15** as a light brown powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.70 (app quint, J = 7.7 Hz, 2H), 2.14 (m, 1H), 2.23 (app dd, J = 16.7 Hz, J = 10.9 Hz, 2H), 2.32 (t, 7.2 Hz, 2H), 2.70 (dd, J = 16.7 Hz, J = 3.3 Hz, 2H), 3.70 (br d, J_{PH} = 23.8 Hz, 1H), 7.45 (td, J = 7.8 Hz, J = 2.5 Hz, 6H), 7.55 (t, J = 7.2 Hz, 3H), 7.63 (dd, J = 12.5 Hz, J = 7.7 Hz, 6H), 8.08 (br s, 1H). The following glutarimide β-ketophosphonate (**15c**) was easier to obtain in pure form, and was thus used more often for preparation of **18**.



Glutarimide β-ketophosphonate **15c**: To a room-temperature suspension of glutarimide aldehyde **12**[3] (500 mg, 3.22 mmol) in 25 mL CH_2Cl_2 was added 1.08 g methyl (triphenylphosphoranylidene)acetate. After 5 minutes, all solids had dissolved. After 2 hours, the reaction was complete by TLC (80 % EtOAc/Hex). The solution was

[2] Denney, D. B.; Song, J. *J. Org. Chem.* **1964**, *29*, 495.
[3] Egawa, Y.; Okuda, T.; Suzuki, M. *Chem. Pharm. Bull.* **1963**, *11*, 589.

concentrated *in vacuo* and the resulting beige solid redissolved in 25 mL THF. The solution was purged with Argon, 10 % wt. Pd/C (170 mg, .161 mmol Pd) was added, and the solution was purged with H_2. After 20 hours under an H_2 baloon, the reaction was not complete, so it was purged with Ar, and additional 170 mg Pd/C was added, the reaction was purged with H_2 again and allowed to react for an additional 24 hours. After filtration, concentration *in vacuo*, and purification of the residue by flash column chromatography on SiO_2 (40 % EtOAc/Hex) 651 mg (95 % yield) of the corresponding homologated ester **15b** was obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (m, 2H), 1.66 (m, 2H), 2.15 (m, 1H), (dd, J = 16.8 Hz, J = 10.6 Hz, 2H), 2.33 (app t, 7.3 Hz, 2H), 2.71 (dd, J = 16.8 Hz, J = 4.5 Hz, 2H) 3.67 (s, 3H), 8.24 (br s, 1H).

To a -78ºC solution of dimethyl methylphosphonate (4.42 mL, 41.4 mmol) in 400 mL THF was added n-BuLi solution (1.6 M in Hex, 22.7 mL, 36.3 mmol). After 30 min, the above glutarimide ester **15b** was added *via cannula* as a solution in 4 mL THF over 2 minutes (followed by 3 x 1 mL THF rinse). After 40 min, TLC (5 % MeOH/EtOAc) showed complete consumption of the glutarimide ester, and the reaction was quenched at -78ºC by addition of glacial acetic acid (2.22mL, 38.9 mmol) and allowed to warm to room temperature. $MgSO_4$ was added and the resulting suspension filtered and concentrated *in vacuo*. Nearly all dimethyl methylphosphonate was distilled off at 60ºC / ~1 mm Hg, and the remaining oil was purified by flash column chromatography on SiO_2 (4 % MeOH/EtOAc) to give 1.45 g (92 %) **15c** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (m, 2H), 1.62 (m, 2H), 2.13 (m, 1H), 2.24 (dd, J = 16.8 Hz, J = 11.1 Hz, 2H), 2.64 (app t, J = 6.9 Hz, 2H), 2.69 (dd, J = 16.8 Hz, J = 4.0 Hz, 2H), 3.07 (d, J_{PH} = 22.9 Hz, 2H), 3.77 (d, J_{PH} = 11.3 Hz, 6H), 8.39 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.31, 30.46, 34.05, 37.90, 41.67 (d, J_{CP} = 127 Hz), 43.62, 53.28 (d, J_{CP} = 6 Hz), 172.39, 201.28 (d, J_{CP} = 6 Hz). MS (ESI): 328.0 [M+Na]. IR (neat): 3194, 3090, 2956, 2854, 1698, 1261, 1029, 811.

Diol **16**: To a solution of **11** (960 mg, 4.48 mmol) in 35 mL THF was added H_2O (2.42 mL, 134 mmol). $LiBH_4$ solution (2.0M in THF, 2.69 mL, 5.38 mmol) was added over 15 min by syringe pump, while the reaction was stirred vigorously in a room-temperature water bath. Vigorous gas evolution was observed throughout. 15 minutes after addition was complete, TLC (40 % EtOAc/Hex) showed complete conversion. The reaction was quenched by addition of a few drops (very carefully!) of sat. aq. NH_4Cl. More NH_4Cl was added and the mixture was extracted with 4 x 100 mL CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (46 % EtOAc/Hex) to give 938 mg (97 %) of diol **16** as a clear colorless oil. $[\alpha]_D$ = +46º (c = 1, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 7.1 Hz, 3H), 1.42 (s, 3H), 1.78 (m, 1H) 2.81 (d, J = 9.9 Hz, 1H) 2.90 (dd, J = 8.0 Hz, J = 5.1 Hz, 1H) 3.03 (s, 1H), 3.30 (s, 3H), 3.53 (m, 2H), 3.57 (dd, J = 11.8 Hz, J = 4.9 Hz, 1H), 3.65 (dd, J = 11.8 Hz, J = 8.0 Hz, 1H), 5.39 (dd, J = 10.4 Hz, J = 1.4 Hz, 1H), 5.33 (dd, J = 17.2 Hz, J = 1.2 Hz, 1H), 5.66 (m , 1H). ^{13}C HNMR (100 MHz, $CDCl_3$): δ 13.44, 20.63, 35.31, 56.20, 62.04, 64.51, 66.84, 75.64, 83.84, 120.97, 134.52. MS (ESI): 239.0 [M + Na]. IR (neat): 3443, 2978, 1456, 1092.

Alcohol **17**: To a -15ºC solution of Diol **16** (893 mg, 4.13 mmol) and pyridine (1.34 mL, 16.5 mmol) in 3 mL CH_2Cl_2 was added Ac_2O (273 μL, 2.89 mmol), and the reaction

was stored in a -20ºC freezer for 10 hr. TLC (50 % EtOAc/Hex) showed ~50 % conversion. The reaction was quenched with sat. aq. NH_4Cl, extracted with 4 x 5 mL CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude concentrate was purified by flash column chromatography on SiO_2 (15% to 40 % to 50 % EtOAc/Hex) to give 519 mg 1º-monoacetylated product (49 %), 348 mg recovered **16** (39 %), and 138 mg of a mixture of 2º-monoacetylated product and diacetylated material, which were recycled by stirring for 3 hours in 5 mL MeOH with 150 mg K_2CO_3 (see procedure below for details) giving 106 mg additional recovered **16**, which was combined with the other recovered material and resubjected to the acetylation conditions. After 3 cycles of resubjection, a total of 906 mg (85 % from **16**) 1º-monoacetylated material was obtained. 1H NMR (400 MHz, CDCl3): δ 1.10 (d, *J* = 6.7 Hz, 3H), 1.38 (s, 3H), 1.54 (m, 1H), 2.10 (s, 3H), 2.72 (d, *J* = .8 Hz, 1H) 2.96 (d, *J* = 9.7 Hz, 1H), 3.31 (s, 3H), 3.49 (m, 2H), 4.03 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.8 Hz, 1H), 5.32 (dd, *J* = 16.7 Hz, *J* = .8 Hz, 1H), 5.37 (dd, *J* = 10.5 Hz, *J* = 1.1 Hz, 1H), 5.55 (m, 1H).

To a 0ºC solution of the resulting 1º-monoacetate (906 mg, 3.51 mmol) in 6 mL CH_2Cl_2 and 12.2 mL iPr_2NEt (70.2 mmol) was added MOMCl (1.33 mL, 17.55 mmol) dropwise. After the ice bath melted (~1 hr), the reaction was allowed to warm to room temperature and stir for 16 hours. The reaction was quenched by addition of 50 mL sat. aq. $NaHCO_3$, then extracted with 4 x 100 mL CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography on SiO_2 (50 % EtOAc/Hex) to give 1.02 g (96 %) of the MOM-acetate product as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.61 (m, 1H), 2.02 (s, 3H), 2.87 (d, *J* = 9.4 Hz, 1H), 3.25 (s, 3H), 3.38 (s, 3H), 3.50 (dd, *J* = 7.0 Hz, *J* = 2.7 Hz, 1H), 3.60 (app t, *J* = ~7.5 Hz, 1H), 4.00 (d, *J* = 11.8 Hz, 1H), 4.17 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 5.27 (d, *J* = 17.3 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 5.58 (ddd, *J* = 17.3 Hz, *J* = 10.0 Hz, *J* = 7.9 Hz, 1H).

To a 0ºC solution of the above MOM-acetate (1014 mg, 3.35 mmol) in 75 mL MeOH was added K_2CO_3 (1.85 g, 13.4 mmol). After 2 hr, TLC (33 % EtOAc/Hex) showed full conversion. Mixture was concentrated *in vacuo*, redissolved in 50 mL CH_2Cl_2 and 50 mL $NaHCO_3$ and extracted with 4 x 50 mL CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (50 % EtOAc/Hex), giving 858 mg (98 %) of alcohol **17** as a colorless oil. $[\alpha]_D$ = -6.4º (c = 1, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.41 (s, 3H), 1.79 (m, 1H), 2.77 (d, *J* = 9.6 Hz, 1H), 2.83 (m, 1H), 3.28 (s, 3H), 3.39 (s, 3H), 3.57 (m, 2H), 3.68 (m, 2H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 9.7 Hz, 1H), 5.72 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.95, 20.60, 34.92, 56.36, 56.59, 62.16, 64.57, 68.01, 81.26, 83.67, 97.73, 119.63, 134.79. MS (ESI): 283.1 [M + Na]. IR (neat): 3458, 2979, 2937, 2892, 2823, 1451, 1033, 920.

Vinyl epoxide **18**: To a -78ºC solution of $(COCl)_2$ (848 μL, 9.87 mmol) in 45 mL CH_2Cl_2 was added DMSO (1403 μL, 19.8 mmol) dropwise. After 5 minutes, **17** was cannulated in as a solution in 2 mL CH_2Cl_2, followed by 4 x 1 mL CH_2Cl_2 rinse, giving a cloudy solution. After 45 minutes at -78ºC, triethylamine (4.12 mL, 29.6 mmol) was added dropwise, giving a clear solution. 15 minutes later, the solution was allowed to warm to 0ºC, giving white precipitate. After 1 hour at 0ºC, the reaction was quenched by

addition of 100 mL sat. aq. $NaHCO_3$, extracted with 4 x 100 mL, and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude aldehyde **17b** as a golden oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 3H), 1.95 (m, 1H), 3.10 (d, *J* = 9.8 Hz, 1H), 3.21 (s, 3H), 3.38 (s, 3H), 3.41 (m, 1H) 3.61 (dd, *J* = 7.7 Hz, *J* = 5.6 Hz, 1H), 4.63 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 5.28 (d, *J* = 17.7 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 5.64 (ddd, *J* = 17.7 Hz, *J* = 10.5 Hz, *J* = 7.7 Hz, 1H), 9.32 (s, 1H).

To a room-temperature solution of β-ketophosphonate **15c** (1104 mg, 3.62 mmol) in 19 mL DMF was added LiCl solid (146 mg, 3.45 mmol), then DBU (516 μL, 3.45 mmol). After 10 min, the above crude aldehyde **17b** was added *via cannula* as a solution in 1.5 mL DMF, followed by 5 x 1 mL DMF rinses. After 30 min, TLC (50 % EtOAc/Hex) showed full conversion, and the reaction mixture was poured into a bilayer of 50 mL CH_2Cl_2 / 50 mL sat. aq. NH_4Cl and extracted with 4 x 50 ml CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil, which was purified by flash column chromatography on SiO_2 (50 % to 80 % EtOAc/Hex) to give product contaminated with a small amount of DMF, which was removed by treatment under < 1 mm Hg vacuum in a large flask overnight, to give 1.40 g (93 % from **17**) pure **18** as a pale yellow glass. $[\alpha]_D$ = +2.4º (c = 1, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.51 (m, 2H), 1.48 (s, 3H), 1.55 (m, 1H), 1.66 (m, 2H), 2.13 (m, 1H), 2.27 (dd, *J* = 17.0 Hz, *J* =10.8 Hz, 2H), 2.55 (app t, *J* = 7.0 Hz, 2H), 2.72 (dd, *J* = 17.0 Hz, *J* = 4.0 Hz, 2H), 3.04 (d, *J* = 9.3 Hz, 1H), 3.24 (s, 3H), 3.35 (m, 1H), 3.37 (s, 3H), 3.57 (app t, *J* = 7.1 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 5.24 (app d, *J* = 13.0 Hz, 2H), 5.50 (m, 1H), 6.26 (d, *J* = 15.9 Hz 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 8.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.04, 20.65, 21.36, 30.45, 34.35, 34.38, 37.82, 40.38, 56.17, 56.59, 60.83, 70.30, 81.10, 84.57, 98,02, 119.48, 130.74, 134.83, 144.02, 172.52, 198.38. MS (ESI): 460.2 [M + Na]. IR (neat): 3222, 3095, 1702 (br), 1377, 1261, 1150, 1103, 1030.

TBS-alcohol vinyl epoxide **19**: *S*-Me-CBS catalyst (824 mg, 2.97 mmol) was weighed out in a glove box into an empty flask, which was sealed with a septum stopper and brought out into the hood. The flask was charged with 8 mL toluene to dissolve the catalyst at room temperature. The resulting solution was cooled to -20ºC and Me_2S-BH_3 (2.0M in THF, 1257 μL, 2.51 mmol) was added dropwise. Vinyl epoxide **18** (954 mg, 2.18 mmol) was added as a solution in 2 mL toluene *via cannula* over 1 minute down the inside wall of the flask, followed by 3 x 2 mL toluene rinses. After 15 min, TLC (100 % EtOAc) showed full conversion, and reaction was quenched by addition of 2 mL MeOH down inside wall of flask. After 1 min, added 40 mL sat. aq. NH_4Cl and allowed reaction to warm to room temperature. The mixture was extracted with 4 x 40 mL EtOAc, the combined organics were combined, dried over $MgSO_4$, concentrated in vacuo, and purified by flash column chromatography on SiO_2 (67 % to 100 % EtOAc/Hex). Some product fractions were contaminated with catalyst-derived impurities which hydrolyzed to a baseline spot on TLC, and these fractions were combined and re-purified by Prep TLC (1 mm x 20 cm x 20 cm, 100 % EtOAc), to give additional pure product. Combined allylic alcohol product (10:1 epimeric mixture at C15-OH) was obtained as 769 mg (80 %) of a colorless glass. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, *J* = 6.9 Hz, 3H), 1.35-

1.65 (m, 11H), 2.12 (m, 1H), 2.26 (dd, *J* = 16.7 Hz, *J* = 10.4 Hz, 2H), 2.71 (dd, *J* = 16.7 Hz, *J* = 3.9 Hz, 2H), 2.94 (d, *J* = 9.1 Hz, 1H), 3.25 (s, 3H), 3.39 (s, 3H), 3.43 (dd, *J* = 7.0 Hz, *J* = 2.8 Hz, 1H), 3.60 (app t, *J* = 7.7 Hz, 1H), 4.11 (m, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 5.27 (m, 2H), 5.58 (ddd, *J* = 17.6 Hz, *J* = 12.0 Hz, *J* = 7.7 Hz), 5.65 (d, *J* = 15.7 Hz, 2H), 5.76 (dd, *J* = 15.7 Hz, *J* = 6.5 Hz, 1H), 7.87 (br s, 1H).

To a room-temperature solution of the above crude allylic alcohol (769 mg, 1.75 mmol) in 10 mL DMF was added DMAP (428 mg, 3.50 mmol), then Et_3N (488 μL, 3.50 mmol), then TBSCl (396 mg, 2.62 mmol). After stirring for 16 hr, the reaction was cooled to 0ºC, quenched with 10 mL sat. aq. $NaHCO_3$, extracted with 4 x 10 mL EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (50 % EtOAc/Hex) to give 820 mg (85 %) of **19** (a ~10:1 epimeric mixture with **20**) as a colorless glass. $[\alpha]_D$ = +0.0º (c = 1, $CDCl_3$) ^{1}H NMR (400 MHz, CDCl3) : (major isomer) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.89 (s, 9H), 1.08 (d, *J* = 5.8 Hz, 3H), 1.27-1.50 (m, 9H), 1.55 (m, 1H), 2.03 (m, 1H), 2.25 (ddd, *J* = 16.7 Hz, *J* = 10.9 Hz, *J* = 2.4 Hz, 2H), 2.68 (dd, *J* = 16.7 Hz, *J* = 3.8 Hz, 2H), 2.94 (d, *J* = 9.1 Hz, 1H) 3.23 (s, 3H), 3.37 (s, 3H), 3.42 (dd, *J* = 6.9 Hz, *J* = 3.4 Hz, 1H), 3.57 (app t, 7.6 Hz, 1H), 4.11 (m, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 5.25 (d, *J* = 17.8 Hz, 1H), 5.52 (m, 2H), 5.71 (dd, *J* = 15.7 Hz, *J* = 5.7 Hz, 1H), 8.14 (br, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.51, -3.92, 11.76, 18.35, 22.34, 22.42, 26.06, 30.51, 34.38, 35.14, 38.01 ,38.45, 56.29, 56.69, 61.12, 69.15, 72.59, 81.05, 85.38, 98.29, 119.44, 128.01, 134.95, 137.18, 172.39.

Alcohol **21**: Methyllithium solution was freshly titrated (addition of reagent to THF solution of menthol with 2,2'-dipyriyl indicator at 0ºC). To a -78ºC suspension of CuCN (3.98 g, 44.4 mmol) in 250 mL Et_2O, was added MeLi solution (1.4M in Et_2O, 20 mL, 28.0 mmol). The suspension was placed in a -15ºC bath and stirred vigorously for 1 hr, giving a yellow-orange slurry. **19** (a ~10:1 mixture with **20**, 820 mg) was added via cannula as a solution in 5 mL Et_2O, with 4 x 1 mL rinses. The reaction was allowed to warm to 0ºC and stir for 16 hours (for monitoring the reaction, aliquots must be hydrolyzed before TLC analysis). The reaction was then quenched by syringe addition of 1:1 (sat. aq. NH_4Cl / 3% aq. NH_3OH) under argon. Mixture was then poured into large Erlenmeyer flask containing 250 mL of the quench mixture and stirred vigorously until most Cu salts had oxidized and dissolved. The mixture was then extracted with 4 x 250 mL EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo*, to give a colorless oil, which by ^{1}HNMR appeared to be a ~13:1:.5 mixture of products. Purification by prep TLC (50 % EtOAc/Hex) afforded 675 mg (80 %) of diastereomerically pure **21** as a colorless glass. $[\alpha]_D$ = +0.0º (c = 1, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ .033 (s, 3H), .063 (s, 3H), .88 (d, *J* = 7.1 Hz, 3H), .90 (s, 9H), .94 (d, *J* = 6.8 Hz, 3H), 1.22 (m, 1H), 1.40 (m, 5H), 1.56 (s, 3H), 1.90 (m, 1H), 2.13 (m, 1H), 2.22 (dd, *J* = 15.6 Hz, *J* = 9.8 Hz, 2H), 2.56 (m, 1H), 2.69 (dd, *J* = 6.7 Hz, *J* = 3.8 Hz, 2H), 2.88 (br s, 1H) 3.30 (s, 3H), 3.41 (s, 3H), 3.53 (m, 2H), 3.71 (app t, J ~7 Hz ,1H) 4.17 (d, *J* = 3.4 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 1H), 5.31 (d, *J* = 17.4 Hz, 1H) 5.33 (d, *J* = 10.4 Hz, 1H), 5.40 (d, *J* = 9.6 Hz, 1H), 5.68 (m, 1H), 7.82 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.15, -4.11, 8.18, 13.64, 15.60, 18.30, 23.32, 26.09, 30.54, 33.15, 35.25, 37.08, 37.88, 38.01, 38.09, 56.29, 56.76, 75.38, 77.11, 83.09, 85.05, 98.34, 119.43, 128.60, 135.04,

135.15, 172.78. MS (ESI): 592.5 [M+Na]. IR (neat): 3500, 3212, 3093, 2930, 2857, 1698, 1258, 1039.

Acid **23**: To a -78ºC solution of iPr_2NH (3.3 mL, 23.7 mmol) in 80 mL THF was added n-BuLi solution (1.6 M in Hexanes, 12.5 mL, 20.1 mmol). After 20 minutes, the mixture was warmed to room temperature, then re-cooled to -78ºC. Ethyl-6-heptenoate (2.85 g, 18.2 mmol) was added as a solution in 10 mL THF over 5 minutes (addition funnel), with 3 x 2 mL toluene rinse. After 40 minutes, diphenyl diselenide solid (6.25g, 20.0 mmol) was added over 1 minute. After 90 minutes at -78ºC, TLC (100 % toluene) showed virtually complete conversion. The reaction was quenched with NH_4Cl, extracted with 3 x 100 mL EtOAc, dried over MgSO4, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (5 % EtOAc/Hex) to give product contaminated with a small amount (~5 %) starting material, which was removed by vacuum treatment overnight at ~1 mm Hg / 30ºC, giving 4.64 g (82 %) of the corresponding phenylseleno-heptenoate as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.1 Hz, 3H), 1.53 (m, 2H), 1.78 (m, 1H) 1.92 (m, 1H), 2.05 (app q, *J* = ~7 Hz, 2H), 3.60 (dd, *J* = 8.7 Hz, *J* = 6.6 Hz, 1H), 4.09 (q, 7.1 Hz, 2H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.99 (d, *J* = 17.5 Hz, 1H), 5.75 (m, 1H), 7.31 (m, 3H), 7.60 (d, *J* = 6.9 Hz, 2H).

The phenylselenoheptenoate (4.64 g, 14.9 mmol) was suspended in 250 mL of a 2/1/2 mixture of MeOH/THF/H_2O. LiOH (6.11 g, 149 mmol) was added as a solid, the mixture was sonicated for 3 minutes to give a cloudy suspension, then stirred vigorously for 3 hours. A 100-µL aliquot was neutralized with a 1N HCl/CH_2Cl_2 bilayer and TLC (50 % EtOAc/Hex) showed full conversion. The reaction mixture was poured in to 150 mL 1N HCl, then extracted with 3 x 300 mL EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo* to give an oil containing a coarse solid. This oil was resuspended in 200 mL CH_2Cl_2, filtered and concentrated again to give 4.22 g (100 %) acid **23** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (m, 2H), 1.78 (m, 1H), 1.89 (m, 1H), 2.07 (q, *J* = 7.1 Hz, 2H), 3.57 (app t, *J* ~8 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 5.00 (d, *J* = 17.7 Hz, 1H), 5.75 (m, 1H), 7.33 (m, 3H), 7.62 (d, *J* = 6.8 Hz, 2H), 11.1 (v br s, ~1H). ^{13}C NMR (125 MHz, 27.42, 31.14, 33.24, 43.32, 115.34, 127.88, 128.92, 129.35, 136.82, 138.11, 179.21. MS (ESI): 307.1 [M + Na]. IR (neat): 3700-2500 (v br), 1690, 1279, 908.

Selenoester **24**: EDCI (181 mg, .943 mmol) was added to a -78ºC solution of **21** (100 mg, .175 mmol), DMAP (115 mg, .943 mmol), and Acid **23** (267 mg, .943 mmol) in 1 mL CH_2Cl_2. The solution was allowed to warm to 0ºC, and the reaction was complete after 3 hr. The reaction was quenched by addition of .3 mL MeOH, then sat. aq. $NaHCO_3$ was added and the mixture extracted with 4 x 5 mL CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale yellow oil, which was purified by prep TLC (50 % EtOAc/Hex) to give 136 mg (91 %) of **24** as an ~8:1 mixture of epimers at the selenium-bearing carbon. *Note:for all intermediates containing the phenyl selenide, absorption onto silica gel followed by passage of oxygenated, weakly-eluting solvents resulted in oxidation and deselenation. Flash chromatography using solvents in which the Rf of the substrate is less than .5 is not recommended unless the solvent has been degassed and saturated with Argon prior to use. Alternatively, prep TLC (using solvent systems in which the substrate Rf is greater than .4) consistently afforded products without oxidation.* ^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.04

(s, 3H) , 0.07 (s, 3H), 0.91 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.14 (m, 1H), 1.29-1.50 (m, 7H), 1.52 (s, 3H), 1.76 (m, 1H), 1.87 (m, 1H), 1.97-2.13 (m, 4H), 2.19 (ddd, *J* = 17.0 Hz, *J* = 10.7 Hz, *J* = ~2.2 Hz, 2H), 2.53 (m, 1H), 2.66 (dm, *J* = 17.0 Hz, 2H), 3.27 (s, 3H), 3.27-3.32 (m, 1H), 3.42 (s, 3H), 3.48 (m, 1H), 3.54 (m, 1H), 3.62 (app t, *J* = 7.4 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.96 (d, *J* = 17.0 Hz, 1H), 5.21-5.37 (m, 3H), 5.49-5.62 (m, 2H), 5.72 (m, 1H), 7.23-7.33 (m, 3H), 7.54 (app d, *J* = 7.3 Hz, 2H), 7.75 (br s, 1H).

Metathesis precursor **25**: **24** (143 mg, .171 mmol) was transferred to a 15mL conical plastic vial equipped with triangular stirring vane and dried at ~1 mm Hg / 22ºC overnight. A 1.1/1 mol/mol solution of pyridine/HF was prepared by mixing 882 µl of pyridine with 260 µl of Aldrich 70 % wt HF-pyridine solution. This mixture was then diluted to a volume of 2 mL with THF, and transferred to the vial containing **24**. The solution was heated to 40ºC for 16 hr. The reaction was cooled to 0ºC, quenched with sat. aq. $NaHCO_3$, extracted with 4 x 5 mL EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a colorless glass. This crude material was purified by prep TLC (80 % EtOAc/Hex) to give 108 mg (88%) of the free alcohol. Major isomer ^{1}HNMR (500 MHz, $CDCl_3$) (major isomer): δ 0.95 (app t, *J* = 6.5 Hz, 6H), 1.27-1.36 (m, 1H), 1.36-1.48 (m, 5H), 1.50 (d, *J* = 1.0 Hz, 3H), 1.52-1.56 (m, 1H), 1.57-1.65 (m, 1H), 1.76 (m, 1H), 1.87 (m, 1H), 1.97-2.03 (m, 3H), 2.14 (m, 1H), 2.26 (ddd, *J* = 17.1 Hz, *J* = 10.8 Hz, *J* = 2.8 Hz, 2H), 2.38 (m, 1H), 2.71 (dd, *J* = 17.1 Hz, *J* = 3.9 Hz, 2H), 3.14 (d, *J* = 5.4 Hz, 1H), 3.23 (s, 3H), 3.31 (m, 1H), 3.36 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 3.47 (s, 3H), 3.53 (dd, *J* = 9.4 Hz, *J* = 6.2 Hz, 1H), 3.60 (app t, *J* = 8.1 Hz, 1H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.93 (d, *J* = ~11 Hz, 1H), 4.96 (dq, *J* = 17.0 Hz, *J* = 1.7 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 17.3 Hz, 1H), 5.33 (dd, *J* = 10.4 Hz, *J* = 1.5 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 5.55 (ddd, *J* = 17.3 Hz, *J* = 10.4 Hz, *J* = 8.1 Hz, 1H), 5.72 (m, 1H), 7.21-7.33 (m, 3H), 7.53 (app d, *J* = ~7.8 Hz, 2H), 7.82 (br s, 1H).

The free alcohol was dried at ~1mm Hg / 22ºC overnight in a glass vial prior to the next reaction. To a -78ºC solution of DMSO (106 µL, 1.50 mmol) in 5 mL CH_2Cl_2 was added oxalyl chloride (64 µl, .750 mmol) dropwise. After 15 minutes, the free alcohol starting material (108 mg, .150 mmol) was added as a solution in 500 µl CH_2Cl_2 (with 4 x .5mL rinses) over 5 minutes via syringe down the inside wall of the flask. After 1 hour, iPr_2NEt (392 µl, 2.25 mmol) was added slowly. After an additional 30 minutes, the reaction was allowed to warm to 0ºC and stirred 1.5 hours. The reaction was quenched with sat. aq. NH_4Cl, extracted with 4 x 5 mL CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by prep TLC (40 % acetone/Hex) to give 104 mg (97 %) of the resulting ketone. ^{1}HNMR (500 MHz, $CDCl_3$): (major isomer) δ .92 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.34 (m, 2H), 1.32-1.51 (m, 2H), 1.51-1.59 (m, 2H), 1.60 (d, *J* = 1.2 Hz, 3H), 1.76 (m, 1H), 1.88 (m, 1H), 1.98-2.15 (m, 4H), 2.22 (ddd, *J* = 17.1 Hz, *J* = 10.9 Hz, *J* = 2.1 Hz, 2H), 2.39 (dt, *J* = 18.0 Hz, *J* = 7.1 Hz, 1H), 2.52 (dt, *J* = 18.0 Hz, *J* = 7.1 Hz, 1H), 2.68 (dd, *J* = 17.1 Hz, *J* = 4.1 Hz, 2H), 3.26 (s, 3H), 3.26-3.30 (m, 1H), 3.33 (m, 1H), 3.41 (s, 3H), 3.55 (m, 1H), 3.62 (app t, *J* = ~7.4 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.93 (dm, *J* = 11.4 Hz, 1H), 4.97 (dq, *J* = 17.0 Hz, *J* = 1.8 Hz, 1H), 5.24 (d, *J* = 8.7 Hz, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 5.33 (dd, *J* = 10.4 Hz, *J* = 1.6 Hz, 1H), 5.49 (d, *J* = 9.6 Hz, 1H), 5.59 (ddd, *J* = 17.4 Hz, *J* = 10.4 Hz, *J* = 7.8 Hz, 1H), 5.73 (m, 1H), 7.24-7.34 (m, 3H), 7.52 (app d, *J* = ~8 Hz, 2H), 7.77 (br s, 1H).

To a -78ºC solution of the ketone (dried overnight at ~1 mmHg / 22ºC) in 5 mL CH_2Cl_2 was added iPr_2NEt (303 µl, 1.74 mmol), then Me_2BBr (85 µl, .870 mmol). TLC (80 % EtOAc/Hex) after 5 min showed complete conversion. 1 mL of a 1/1/1 v/v/v mixture of sat. aq. $NaHCO_3/H_2O$/THF was added at -78ºC with vigorous stirring. The mixture was then allowed to warm to room temperature and immediately extracted with 4 x 5 mL CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by prep TLC (80 % EtOAc/Hex) to give 79 mg (80 %) **25** as an ~8:1 mixture of epimers at the selenium-bearing carbon. $[\alpha]_D$ = +44º (c = 1, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.32 (app q, *J* = 7.7 Hz, 2H), 1.37-1.51 (m, 2H), 1.51-1.60 (m, 2H), 1.62 (s, 3H), 1.75 (m, 1H), 1.88 (m, 2H), 2.02 (app q, *J* = 7.5 Hz, 2H) 2.09 (m, 1H), 2.23 (dd, *J* = 17.0 Hz, *J* = 10.9 Hz, 2H), 2.36 (dt, *J* = 17.7 Hz, *J* = 7.0 Hz, 1H), 2.47 (dt, *J* = 17.7 Hz, *J* = 7.1 Hz, 1H) 2.53 (br s, 1H), 2.68 (dd, *J* = 17.0 Hz, *J* = 4.2 Hz, 2H), 3.28 (m, 1H), 3.30 (s, 3H), 3.33 (m, 1H), 3.49 (t, *J* = 8.2 Hz, 1H), 3.55 (dd, *J* = 9.2 Hz, *J* = 6.2 Hz, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 5.20 (d, *J* = 9.4 Hz, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.38 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 5.45-5.55 (m, 1H), 5.67-5.77 (m, 1H), 7.23-7.34 (m, 3H), 7.52 (app d, 7.9 Hz, 2H), 7.84 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.19, 12.77, 16.33, 20.53, 27.48, 30.56, 31.61, 33.33, 34.40, 36.18, 37.89, 37.91, 39.92, 43.59, 46.55, 56.61, 73.00, 81.85, 85.10, 115.21, 120.95, 128.30, 128.44, 129.28, 129.92, 134.27, 134.68, 134.95, 135.03, 138.13, 172.09, 172.31, 172.33, 210.52. MS (ESI): 698.3 [M + Na], IR (neat): 3479, 3220, 3075, 2976, 2930, 1715, 1359, 1262, 1147.

26: In a 2000-mL flask, **25** (79 mg, .116 mmol, ~8:1 C2-epimeric mixture) was dried by 4 cycles of dissolution in 1 mL toluene and concentration at 1 mm Hg / 22ºC. The starting material was then dissolved in 1000 mL of toluene, heated to 110ºC, and Grubbs 2nd-generation catalyst added (20 mg, .0232 mmol). After 1 minute, the flask was submerged (carefully) in a large -78ºC bath, cooled for 15 minutes, and allowed to warm up during concentration *in vacuo*. The concentrate was immediately redissolved in 1 mL CH_2Cl_2 and filtered (with 5 x 1 mL rinsing) by gravity through a 500 mg SPE StratoSpheres (PL-Thiourea MP SPE+) column to remove most ruthenium. The resulting crude solution was reconcentrated and purified by prep TLC (50 % Acetone/Hexanes) to afford 28 mg impure trans material (less polar) and 35 mg impure cis material (more polar). The trans material was further purified by prep TLC (80 % EtOAc/Hexanes) to afford 5 mg impure minor C2-epimer (less polar) and 21 mg impure major C2-epimer (more polar). The minor C2-epimer was further purified by prep TLC (30 % Acetone/Toluene) to give 1.7 mg (2.3 %) pure minor C2-epimer. The impure major C2-epimer was purified again by prep TLC (30 % Acetone/Toluene) to afford 14.0 mg (19 %) pure major C2-epimer. $[\alpha]_D$ = +40º (c = 1, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (d, *J* = 7.1 Hz, 3H), 1.07, (d, *J* = 6.8 Hz, 3H), 1.33 (m, 2H), 1.55 (m, 2H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.64-1.71 (m, 2H), 1.86 (m, 1H), 2.01 (m, 2H), 2.14 (m, 3H), 2.22 (dd, *J* = 17.1 Hz, *J* = 11.0 Hz, 2H), 2.33 (dt, *J* = 17.8 Hz, *J* = 6.9 Hz, 1H), 2.51 (dt, *J* = 17.8 Hz, *J* = 7.2 Hz, 1H), 2.69 (dd, *J* = 17.1 Hz, *J* = 4.0 Hz, 2H), 3.23 (br s, 1H), 3.27 (s, 3H), 3.25-3.38 (m, 2H), 3.50 (dd, *J* = 9.3 Hz, *J* = 5.4 Hz, 1H), 3.67 (dd, *J* = 8.3 Hz, *J* = 5.8 Hz, 1H), 4.84 (d, *J* = 2.9 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 5.30 (dd, *J* = 16.0 Hz, *J* = 7.2 Hz, 1H), 5.70 (dt, *J* = 16.0 Hz, *J* = 6.4 Hz, 1H), 7.25-7.31 (m, 3H), 7.53 (app d, *J* ~6 Hz, 2H), 7.89 (br s, 1H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.60, 14.16, 16.06, 20.48, 25.90, 30.38,

30.92, 32.31, 34.42, 37.99, 38.00, 38.78, 39.87, 42.84, 46.27, 56.32, 73.53, 79.19, 82.62, 126.35, 127.99, 128.43, 128.69, 129.43, 133.91, 134.64, 136.84, 172.05, 172.37, 211.00. MS (ESI): 670.3 [M + Na]. IR (neat): 3483, 3236, 3095, 2919, 1708, 1355, 1261, 1096.

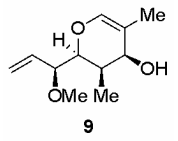
Isomigrastatin (**1**): To a -78ºC solution of **26** (14.0 mg, 21.6 μmol) in 2 mL CH_2Cl_2 was added mCPBA (95% pre-purified, 4.1 mg, 23.8 μmol) as a solution in 2 mL CH_2Cl_2. After 30 minutes at -78ºC, TLC (80 % EtOAc/Hex) showed only baseline material. iPr_2NEt (4.1 μL, 23.8 μmol) was added and the mixture was allowed to warm to room temperature over 10 minutes. After 1 hour at room temperature, TLC (80 % EtOAc/Hex) showed robust reappearance of non-baseline material. The mixture was concentrated *in vacuo* and purified by prep TLC (80 % EtOAc/Hex) to give 9.9 mg (93 %) Isomigrastatin as a 9:1 mixture with its 2,3-*Z* isomer.

The 2,3-*E* and 2,3-*Z* isomers were cleanly separated by preparative reversed-phase HPLC (Varian 21 x 250 mm C18 Microsorb 5 μm particle size - 300Å pore size column, 20 ml/min flow rate, 214 nm detection. Gradient: 15-35 % B over 1 minute, followed by 35-55 % B over 20 minutes, A = H2O/.1% HOAc, B = MeCN/.1% HOAc). The sample was dissolved in .3 mL methanol, which was diluted 3-fold with 15% B immediately before injection. The *trans* isomer eluted at 18.6 minutes, the *cis* isomer at 19.5 minutes. The fraction containing isomigrastatin was collected from the HPLC directly into a flask containing 200 mL of 200-proof ethanol, then 100 mL toluene was added and the mixture was immediately concentrated *in vacuo* to give pure isomigrastatin as a colorless glass. $[\alpha]_D$ = +178º (c = .18, $CDCl_3$) (vs. +170º for natural material, reported by Shen group) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.36 (m, 2H), 1.59 (m, 2H), 1.86 (m, 1H), 1.91 (d, *J* = 1.2 Hz, 3H), 1.96 (qd, *J* = 12.0 Hz, *J* = 4.7 Hz, 1H) 2.09-2.20 (m, 2H), (dd, *J* = 17.0 Hz, *J* = 10.8 Hz, 2H), 2.39 (dt, *J* = 17.8 Hz, *J* = 6.9 Hz, 1H), 2.43-2.48 (m, 1H), 2.57-2.66 (m, 2H), 2.70 (dd, *J* = 17.0 Hz, *J* = 4.0 Hz, 2H), 2.84 (br s, 1H), 3.33 (s, 3H), 3.42-3.49 (m, 2H), 3.74 (d, *J* = 9.2 Hz, 1H), 5.10 (dd, *J* = 15.7 Hz, *J* = 3.9 Hz, 1H), 5.20 (m, 2H), 5.60 (ddd, *J* = 15.7 Hz, *J* = 10.9 Hz, *J* = 4.7 Hz, 1H), 5.68 (d, *J* = 16.0 Hz, 1H), 6.65 (ddd, *J* = 16.0 Hz, *J* = 9.1 Hz, *J* = 7.2 Hz, 1H) 7.71 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.73, 13.49, 15.93, 20.48, 30.28, 30.35, 32.94, 34.36, 37.94, 38.00, 38.28, 40.15, 46.18, 57.29, 73.37, 81.78, 82.38, 125.16, 128.18, 129.31, 130.52, 134.33, 150.80, 167.82, 172.24, 210.95. MS (ESI): 512.3 [M+Na]. IR (neat): 3483, 3213, 3084, 2931, 1708, 1261, 1102, 997. This material was identical with natural material by 1H and 13C NMR, and showed an identical solvolytic decomposition pattern in water/DMSO, as monitored by LC/MS. [4]

2,3-Z-Isomigrastatin (**27**): A sample of Isomigrastatin (**1**) (1.1 mg, 2.2 μmol) was dried under vacuum for several hours, then transferred as a solution in 4Å-mol-seive-dried d_8-toluene (150 μl + 3 x 150μl rinses), by syringe, into an argon-filled NMR tube fitted with a rubber septum. Trimethylphosphine (1.0 M in THF, .3 μL, .3μmol) was added and the rubber septum was quickly replaced with a plastic cap and wrapped tightly with teflon tape. After 30 minutes at 22ºC, ^{1}HNMR showed only **1**. The NMR tube was placed in a 40ºC-oil bath and checked periodically by ^{1}HNMR. After 40 minutes, ~10 % new product (**27**) appeared. The reaction reached ~85% conversion within 16 hours, but

[4] Ju, J. H.; Lim, S. K.; Jiang, H.; Shen, B. *J. Am. Chem. Soc.* **2005**, *127*, 1622-1623.

stalled. An additional .3 μL catalyst solution was added, and the reaction reached full conversion after 16 more hours. The product solution was transferred in the open air to a vial, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 to afford 1.1 mg of **27** as a colorless glass. α_D = +194 (c = .18, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (d, *J* = 7.3 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.36 (m, 2H), 1.58 (m, 2H), 1.80 (app q, ~11 Hz, 1H), 1.90 (s, 3H), 2.09-2.18 (m, 2H), 2.18-2.56 (m, 1H), 2.24 (dd, *J* = 17.0 Hz, *J* = 10.9 Hz, 2H), 2.34-2.41 (m, 1H), 2.38 (dt, *J* = 17.8 Hz, *J* = 6.9 Hz, 1H), 2.59 (dt, *J* = 17.8 Hz, *J* = 7.1 Hz, 1H), 2.70 (dd, *J* = 17.0 Hz, *J* = 3.9 Hz, 2H), 2.85 (br s, 1H), 3.01 (app q, ~11.5 Hz, 1H) 3.15 (app t, *J* = ~8.6 Hz, 1H) 3.30 (s, 3H), 3.35 (dq, *J* = 9.8 Hz, *J* = 6.7 Hz, 1H), 3.68 (d, *J* = 9.4 Hz, 1H) 5.02 (d, *J* = 4.4 Hz, 1H), 5.04 (dd, *J* = 15.6 Hz, *J* = 8.1 Hz, 1H), 5.20 (d, *J* = 9.5 Hz, 1H), 5.55 (ddd, *J* = 15.6 Hz, *J* = 9.6 Hz, *J* = 6.0 Hz, 1H), 5.96 (d, *J* = 11.7 Hz, 1H), 6.02 (ddd, *J* = 11.7 Hz, *J* = ~10.4 Hz, *J* = 6.3 Hz, 1H), 7.70 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.81, 13.38, 16.04, 20.51, 26.67, 30.40, 30.67, 34.39, 36.25 (br), 37.94, 38.00, 40.23, 46.19, 56.64, 69.23 (br), 80.74 (br), 83.93, 123.11, 128.55 (br), 130.90, 134.27, 134.57, 142.52, 166.31, 172.20, 210.84. MS (ESI) : 512.2 [M + Na]. IR (neat): 3483, 3213, 3096, 2966, 2930, 2872, 1713, 1449, 1407, 1367, 1261, 1185, 1100, 988.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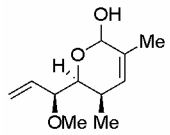
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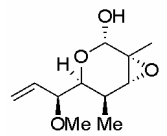
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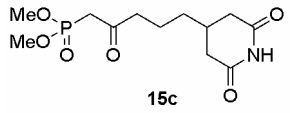
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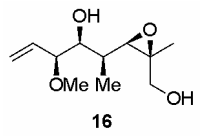
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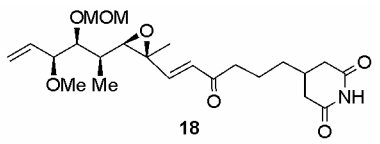
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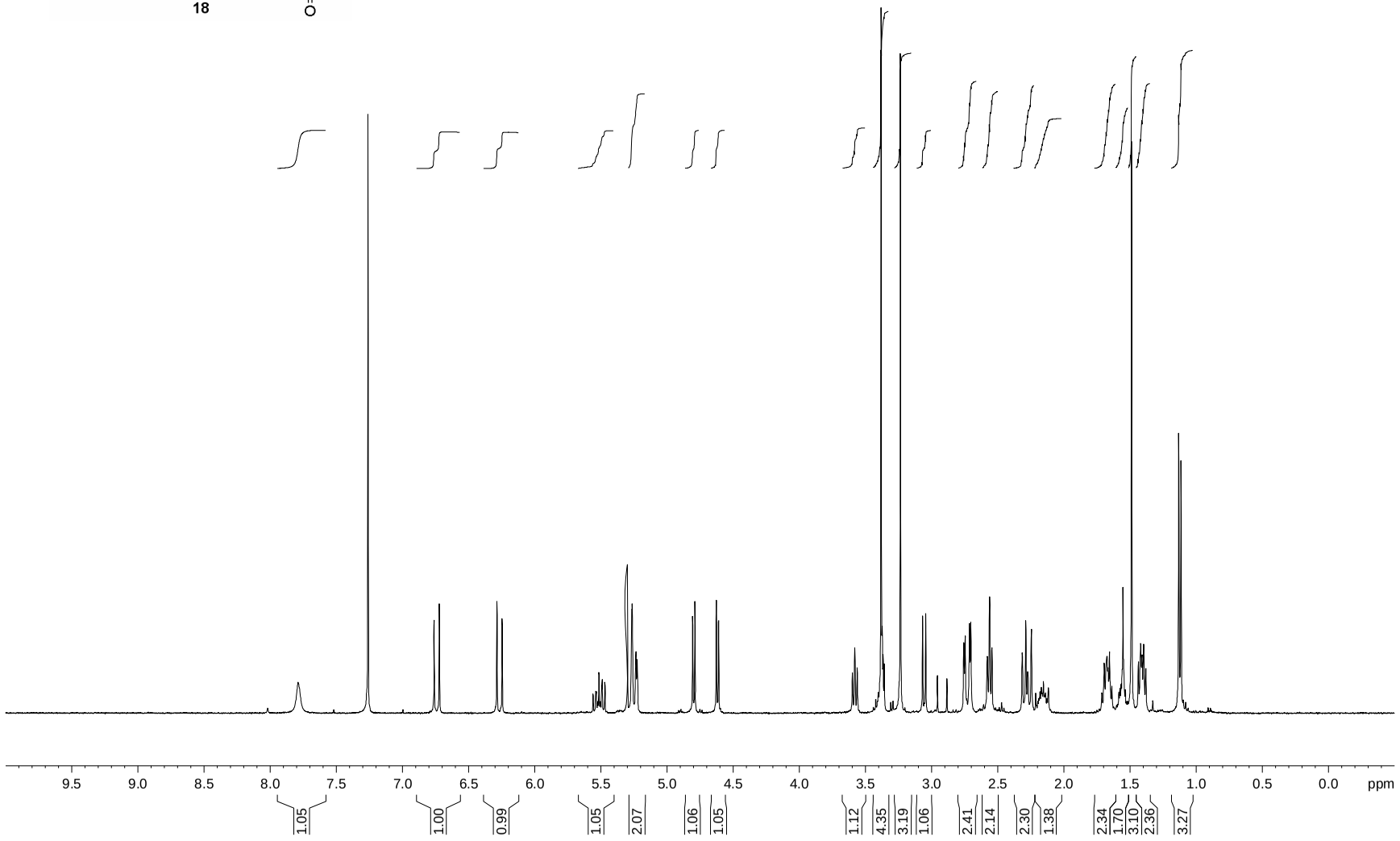
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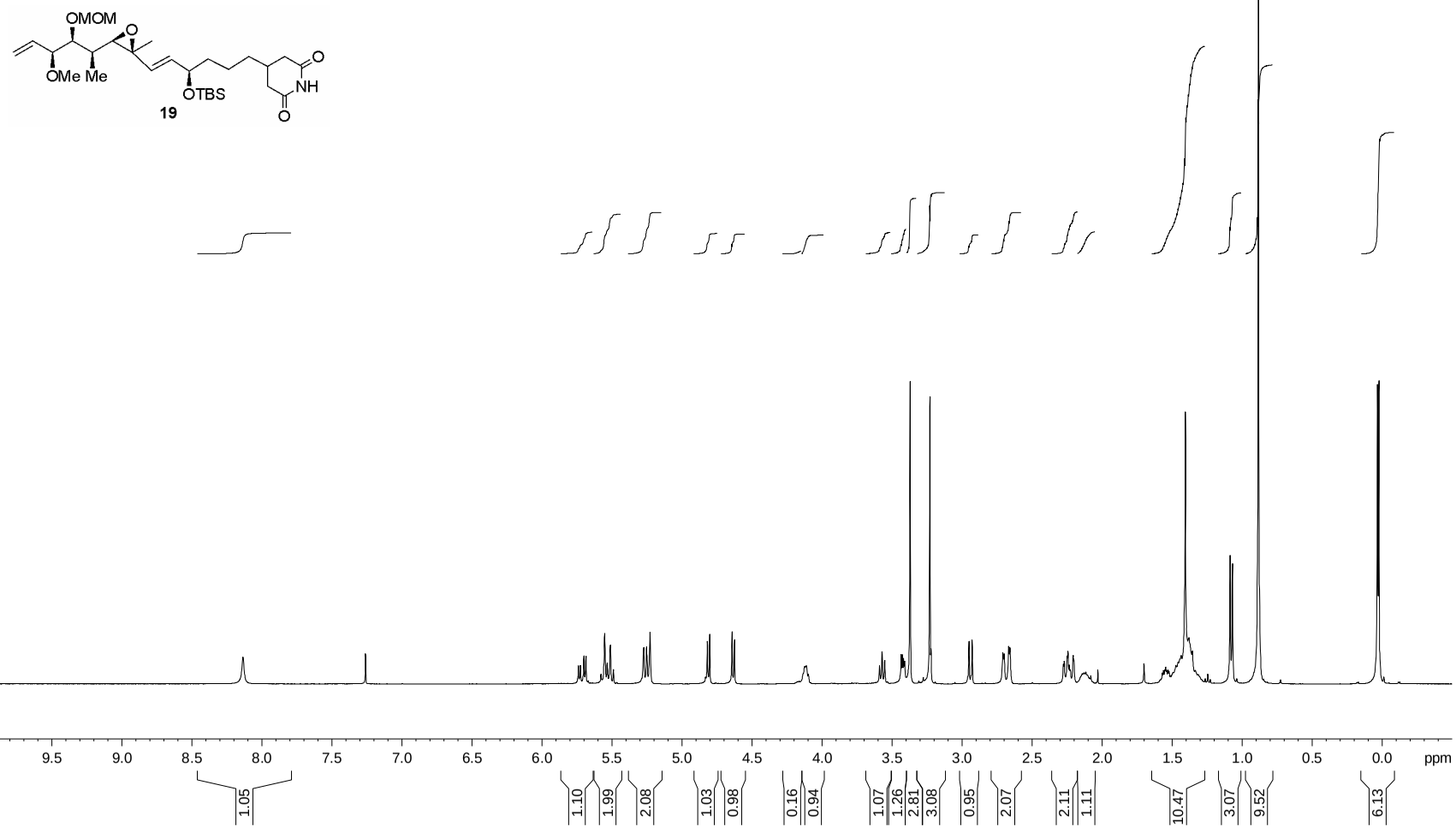
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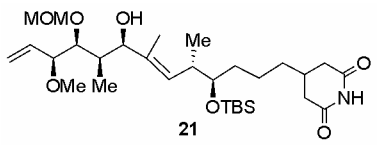
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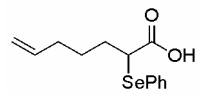
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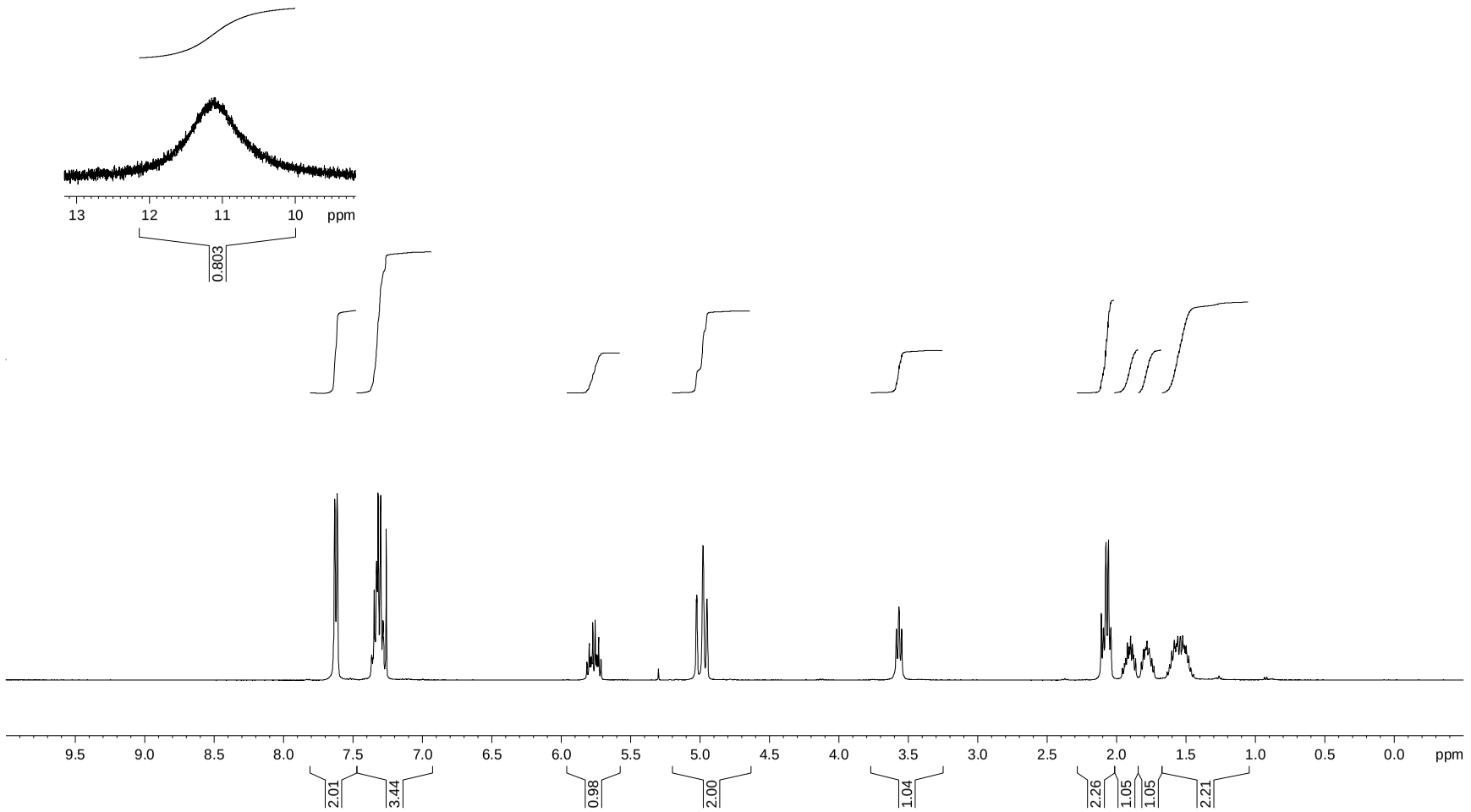
23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11
10
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8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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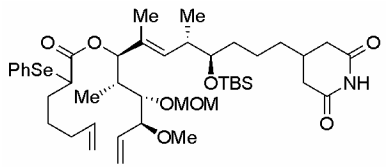
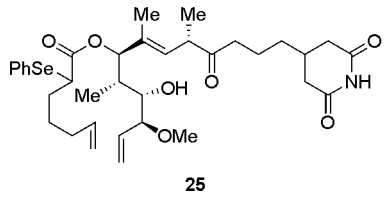
3.44
0.98
2.00
1.04
2.26
1.05
1.05
2.21


Me
Me
O
O
PhSe
Me
OMOM
OTBS
O
NH
O
OMe

24

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.19
3.57
1.03
2.13
3.29
2.17
2.17
1.21
2.19
3.21
4.39
2.10
1.07
2.17
4.42
1.14
1.06
5.48
7.73
1.13
16.67
6.39


Me
Me
O
O
PhSe
Me
OH
O
NH
O
OMe

25

9.5
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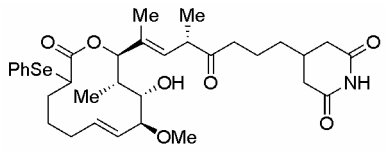
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.94
1.86
0.48
0.98
2.07
2.16
0.89
0.16
1.97
1.02
1.05
5.24
2.09
1.01
1.10
1.09
2.13
1.08
2.15
2.13
1.12
0.47
2.66
4.55
2.09
2.70
0.46
3.20


Me
Me
O
O
PhSe
Me
OH
O
NH
O
O
OMe

26

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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.11
2.19
2.84
1.10
1.08
1.11
1.04
1.10
1.10
1.74
3.90
0.91
2.26
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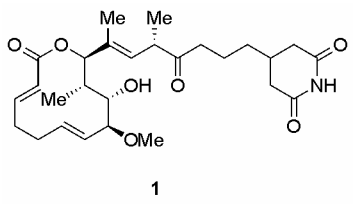
2.88
15.58
2.49
1.41
5.53
2.52
2.51
3.27
3.54


Me
Me
O
O
O
OH
O
NH
O
Me
OMe

1

9.5
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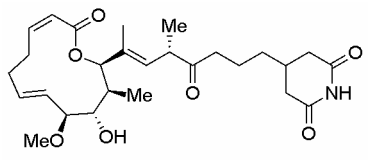
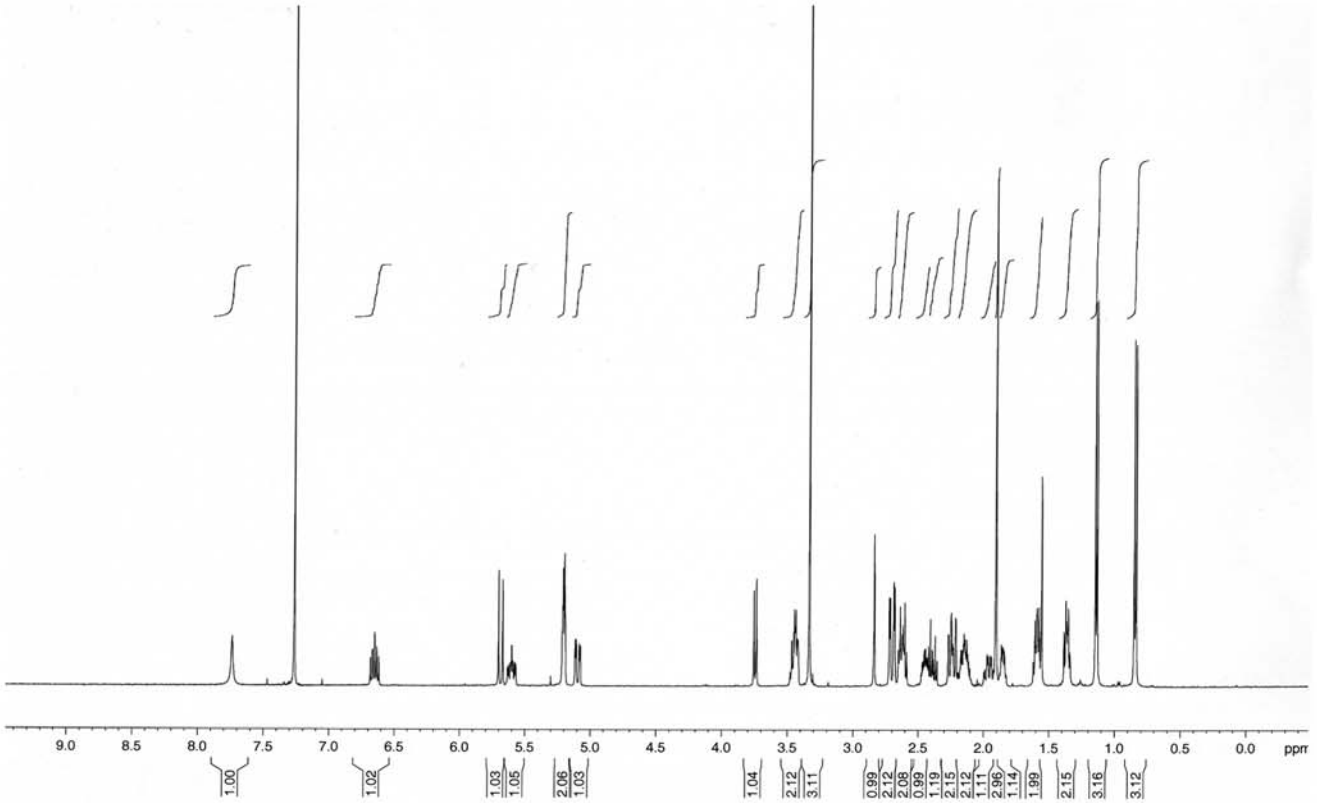
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.98
1.00
1.01
1.03
2.02
1.02
1.02
2.08
3.04
0.97
2.08
2.04
0.98
1.17
2.12
2.08
1.09
2.90
1.12
1.95
2.10
3.09
3.05


Me
O
O
Me
O
NH
O
MeO
OH

27

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.92
0.95
0.97
1.04
1.00
2.03
1.10
1.03
2.95
0.95
1.04
0.91
2.05
1.01
2.06
3.14
2.14
4.28
2.18
2.27
3.13
2.95

synthetic isomigrastatin:



natural isomigrastatin: