Asymmetric Total Syntheses of Euphol and Tirucallol

Joshua Nicholson and Glenn Micalizio*

Supporting Information

Table of Contents

1. Materials and Methods

A. Reagents and Solvents

All reagents and starting materials were purchased from commercial sources and used as received, unless otherwise indicated. Anhydrous tetrahydrofuran (THF) and toluene (PhMe) were obtained by passing HPLC grade solvents through a column of activated alumina using a Glass Contour Solvent Purification System by Pure Process Technology, LLC. Anhydrous pyridine and anhydrous benzene (PhH) were purchased in a Sure-Seal™ bottle from Sigma-Aldrich, and used as received. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, and used as received. For flash column chromatography, HPLC grade solvents were used without further purification. Solutions of *n*-BuLi were purchased from Sigma-Aldrich and titrated against *N*-benzylbenzamide in accordance with the procedure reported by Chong.[1]

B. Reaction Set-Up and Purification

All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen unless otherwise indicated. Reaction mixtures were magnetically stirred, and their progress was monitored by thin layer chromatography (TLC) on EMD TLC silica gel 60 F_{254} glass-backed plates. Compounds were visualized by initial exposure of TLC plates to UV-light (254 nm), followed by staining with *p*-anisaldehyde.

Purification of crude isolates was achieved by flash column chromatography on a Biotage® Isolera One™ Automated Liquid Chromatography System using Biotage® SNAP Ultra HP-Sphere 5–100 g or Biotage® KP-Sil 5–100 g silica gel cartridges. Concentration of reaction product solutions and chromatography fractions was accomplished by rotary evaporation at 30–35 ºC under the appropriate pressure, followed by concentration at room temperature on a vacuum pump (approx. 0–1 mbar). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise indicated.

C. Characterization Data for New Compounds

i. Nuclear Magnetic Resonance Spectroscopy

^{1}H-NMR data were recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe). ^{1}H chemical shifts are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the residual protium in $CDCl_3$ (7.26 ppm) and CD_3OD (3.31ppm). NMR coupling constants are measured in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{13}C {1H decoupled} NMR data were recorded at 150 MHz on a Bruker Avance III 600 MHz spectrometer (BBFO probe). ^{13}C chemical shifts are reported in parts per million (ppm, δ scale) and are referenced to the central line of the carbon

[1] Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281-283.

resonances of the solvents: $CDCl_3$ (77.16 ppm) and CD_3OD (49.86 ppm) unless otherwise noted.

Structural assignments for new compounds were supported by two-dimensional NMR experiments (COSY, HSQC, HMBC and NOESY) recorded on a Bruker Avance III 600 MHz spectrometer (BBFO probe).

ii. Infrared Spectroscopy

Infrared spectra were collected on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer.

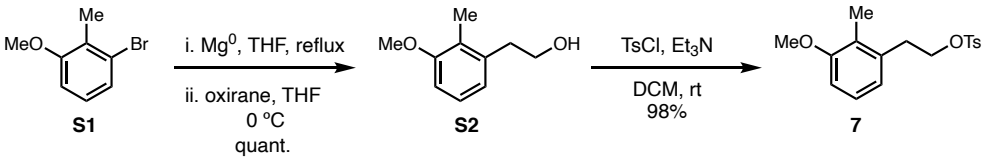
iii. Accurate Mass Determination

HRMS (EI-TOF) analyses were performed at the Mass Spectrometry Laboratory of the University of Illinois at Urbana-Champaign.

iv. Optical Rotation

Optical rotations (α) were obtained on a JASCO-P-2000 polarimeter equipped with a tungsten-halogen lamp (WI) and interface filter set to 589 nm, using a sample cell with a pathlength of 100 nm. Specific rotations are reported as: $[\alpha]_{589}^{T\,(^\circ C)}$ (*c*, solvent) and are based on the equation $[\alpha]_{589}^{T\,(^\circ C)}$ = (100•α)/(*l*•*c*), where the concentration (*c*) is reported as g/100 ml and the pathlength (*l*) is in decimeters.

2. Experimental Procedures



Synthesis of alcohol S2: To a round bottom flask equipped with a stir bar and Mg^0 (725 mg, 29.84 mmol, 1.2 equiv) was added a small amount of commercially available aryl bromide **S1** in THF (~5 mL) from a stock solution of aryl bromide (5.0 g, 24.86 mmol, 1 equiv) in THF (55 mL). After the color of the mixture faded the rest of the solution of aryl bromide in THF was added dropwise via addition funnel. The mixture was stirred at reflux for 2 hours. The resulting solution was cooled to 0 ºC, and a 2.9 M solution of oxirane in THF (11 mL, 32.33 mmol, 1.3 equiv) was added dropwise. Upon completion of the addition of oxirane, the reaction was monitored by TLC, when the reaction was complete (approximately 1 hour), the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 90:10 hexanes–ethyl acetate gradient elution to afford alcohol **S2** (4.13 g, 24.87 mmol, 100%) as a colorless oil.

Analytical data for alcohol S2:

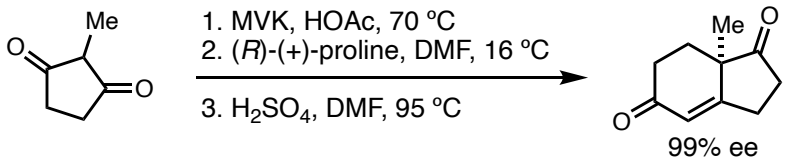
Analytical data for alcohol **S2** was consistent with previously reported data.[1]

Synthesis of tosylate 7: To a round bottom flask equipped with a stirring solution of alcohol **S2** (4.22 g, 25.4 mmol, 1 equiv) in CH_2Cl_2 (60 mL) was added Et_3N (5.66 mL, 40.64 mmol, 1.6 equiv) followed by TsCl (7.26 g, 38.1 mmol, 1.5 equiv). The resulting mixture was monitored by TLC, and when the reaction was complete (approximately 6 hours), the mixture was washed with a 1:1 mixture of DI water: brine. The aqueous layer was extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 90:10 hexanes–ethyl acetate gradient elution to afford tosylate **7** (8.10 g, 25.0 mmol, 98%) as a colorless oil.

Analytical data for tosylate 7:

TLC (SiO_2) R_f = 0.57 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2, 2H), 7.06 (t, J = 7.9 Hz, 1H), 6.71 (dd, J = 20.9, 7.9, 2H), 4.14 (t, J = 7.6 Hz, 2H), 3.80 (s, 3H), 2.98 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 2.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.0, 144.8, 135.5, 133.1, 129.9, 128.0, 126.4, 125.3, 122.2, 109.0, 69.8, 55.6, 33.2, 21.8, 11.4; **IR** (thin film, cm^{-1}): 2956, 1597, 1359, 961, 554; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{20}O_4SNa$ 343.0980; found, 343.0977.

Synthesis of (*R*)-HPK:

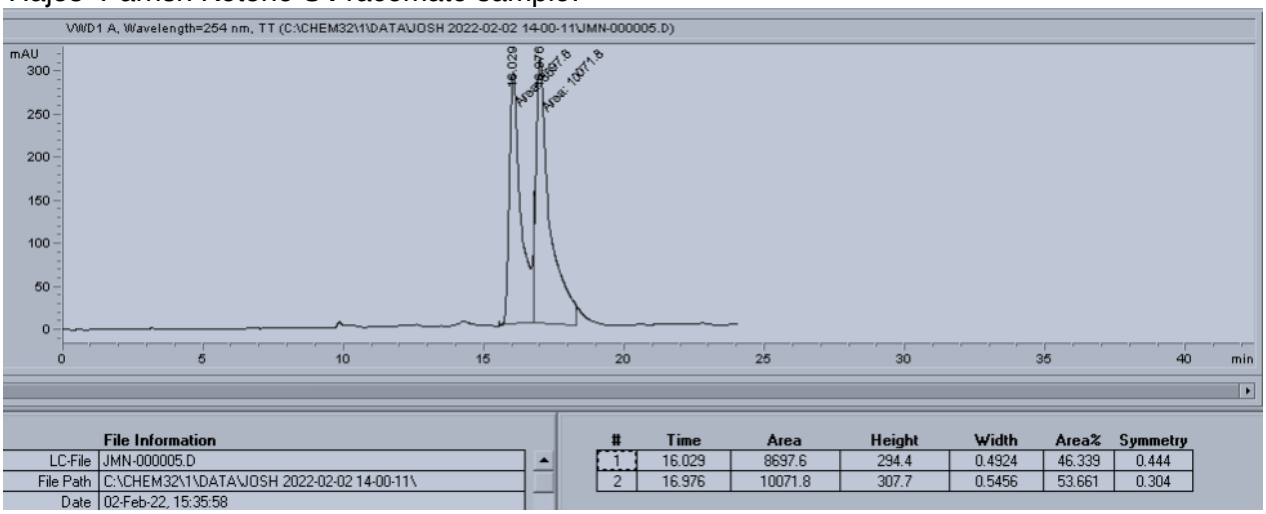


S3 **S4**

**All Hajos–Parrish ketone was prepared following the known 3-step sequence.[2]
Enantio-enrichment was determined by chiral HPLC (Daicel Chiralpak AD-H, hexanes/*i*-PrOH = 94:6), flow rate 1.0 mL/min, λ = 254 nm): t_R (*S*) = 16.0 min (minor) and t_R (*R*) = 16.9 min (major) (ee = 99%).[3]

Chromatograms are shown below:

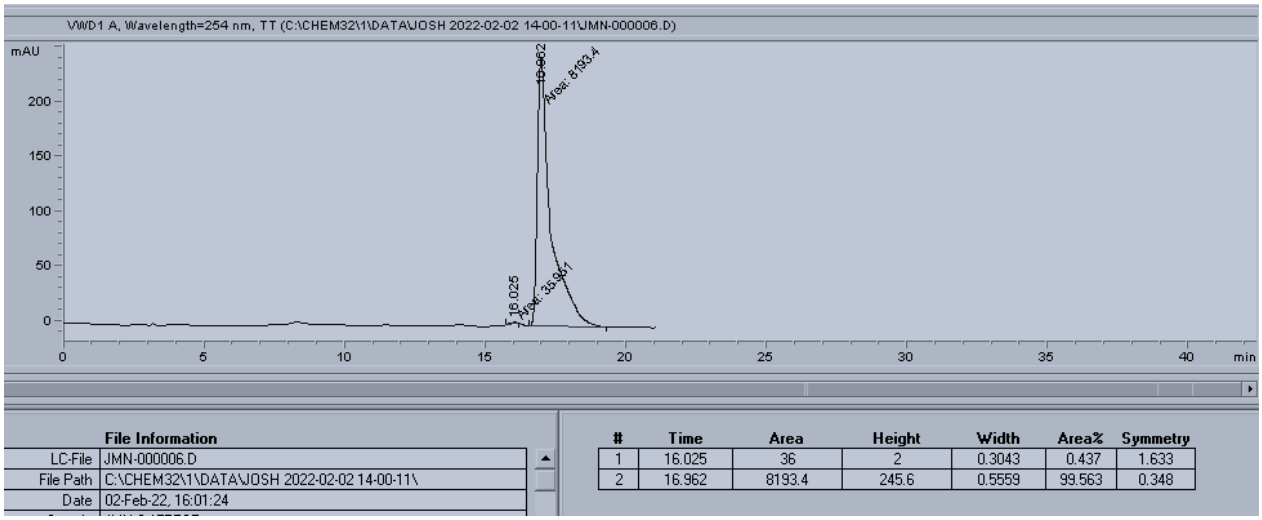
Hajos–Parrish Ketone **S4** racemate sample:



File Information	
LC-File	JMN-000005.D
File Path	C:\CHEM32\1\DATA\JOSH 2022-02-02 14-00-11\
Date	02-Feb-22, 15:35:58

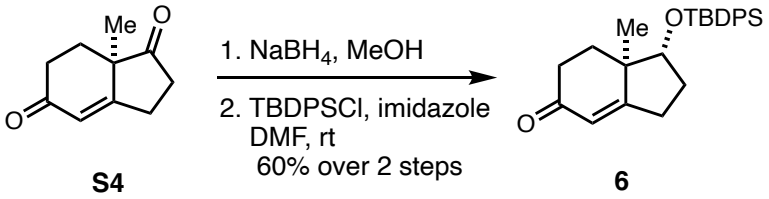
#	Time	Area	Height	Width	Area%	Symmetry
1	16.029	8697.6	294.4	0.4924	46.339	0.444
2	16.976	10071.8	307.7	0.5456	53.661	0.304

Hajos–Parrish ketone **S4** enantio-enriched sample:



File Information	
LC-File	JMN-000006.D
File Path	C:\CHEM32\1\DATA\JOSH 2022-02-02 14-00-11\
Date	02-Feb-22, 16:01:24

#	Time	Area	Height	Width	Area%	Symmetry
1	16.025	36	2	0.3043	0.437	1.633
2	16.962	8193.4	245.6	0.5559	99.563	0.348



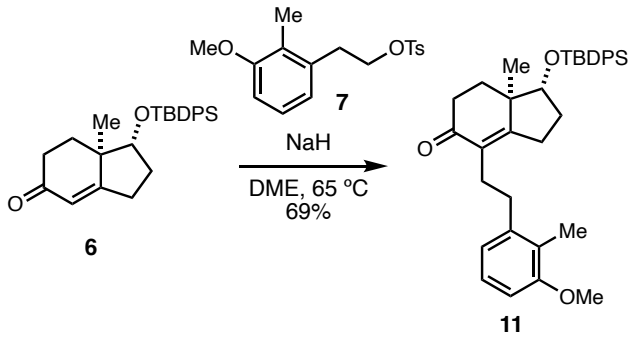
S4 **6**

Synthesis of alcohol S5: To a stirring solution of ketone **S4** (69.6 g, 424 mmol, 1 equiv) in methanol (1.7 L) at –5 ºC was added $NaBH_4$ (4.0 g, 106 mmol, 0.25 equiv) portion wise. The reaction was monitored by TLC while maintaining a temperature of –5 ºC. Once the reaction was complete (approximately 4 hours), the mixture was neutralized with an aqueous 10% HCl solution to reach a pH of 6. The solution was then diluted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was subjected to silyl protection without further purification.

Synthesis of silyl ether 6: To a solution of crude alcohol (70.4 g, 424 mmol, 1 equiv) in DMF (750 mL) was added imidazole (43.3 g, 636 mmol, 1.5 equiv) and TBDPSCl (230 mL, 509 mmol, 1.2 equiv). The resulting mixture was allowed to stir for 48 hours at room temperature. The reaction was poured into DI water and extracted with PhMe (x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes–ethyl acetate gradient elution to afford silyl ether **6** (103 g, 254 mmol, 60% over 2 steps) as a colorless oil.

Analytical data for silyl ether 6:

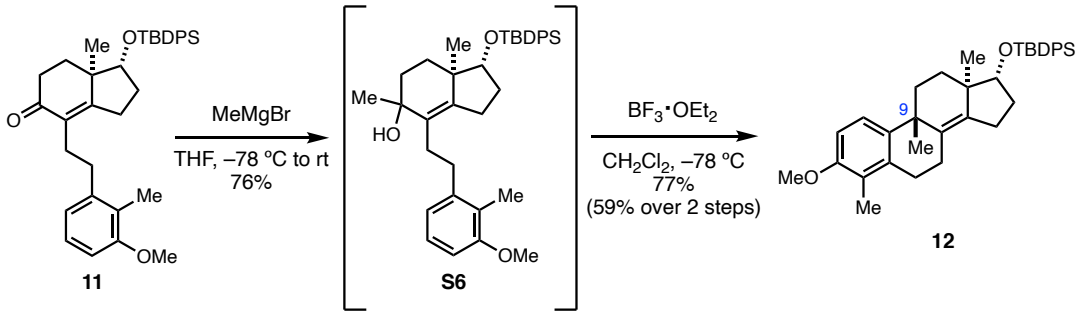
Analytical data for silyl ether **6** was consistent with previously reported data.[4]



Synthesis of enone 11: To a round bottom flask equipped with a stir bar and NaH (60% dispersion in oil; 14.2 g, 355.5 mmol, 1.5 equiv) was added a solution of enone **6**[4] (96 g, 237 mmol, 1.0 equiv.) in freshly degassed DME (500 mL). The resulting yellow mixture was heated to 65 ºC in an oil bath and allowed to stir overnight (14 hours). The resulting black mixture was cooled to room temperature. A solution of tosylate **7** (79.1 g, 247 mmol, 1.04 equiv) in freshly degassed DME (400 mL) was added dropwise over 2 hours. The mixture was heated to 65 ºC in an oil bath and allowed to stir overnight (approximately 14 hours). When the reaction was complete by TLC the mixture was cooled to 0 ºC and quenched with saturated aqueous sodium phosphate monobasic under a stream of N_2. The aqueous layer was extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 90:10 hexanes–ethyl acetate gradient elution to afford enone **11** (90.9 g, 164 mmol, 69%) as a colorless oil.

Analytical data for enone 11:

TLC (SiO_2) R_f = 0.68 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.67 – 7.63 (m, 4H), 7.46 – 7.42 (m, 2H), 7.40 – 7.36 (m, 4H), 6.93 (app t, *J* = .9 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1 H), 3.76 (s, 3H), 3.62 (dd, *J* = 10.3, 7.2 Hz, 1H), 2.62 – 2.49 (m, 3H), 2.35 – 2.22 (m, 3H), 2.15 (s, 3H), 2.11 – 2.03 (m, 1H), 1.94 (ddd, *J* = 12.8, 5.5, 2.0 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.71 – 1.63 (m, 1H), 1.52 – 1.42 (m, 2H), 1.16 (s, 3H), 1.07 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 198.6, 168.7, 157.8, 141.6, 136.1, 136.0, 135.0, 134.5, 133.8, 132.3, 130.0, 129.9, 127.8, 127.7, 125.8, 124.9, 122.5, 108.0, 81.6, 55.7, 46.0, 34.2, 33.8, 32.3, 29.8, 27.2, 26.7, 26.6, 25.1, 19.5, 15.9, 14.4, 11.4; **IR** (thin film, cm^{-1}): 3003, 1715, 1422, 1362, 1221, 530; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{45}O_3Si$ 553.3138; found, 553.3127; $[\alpha]_{589}^{21.1}$**:** +7.8 (*c* 0.25, $CHCl_3$).



Synthesis of alcohol S6: To a round bottom flask equipped with a stirring solution of 3M MeMgBr in THF (18.6 mL, 55.8 mmol, 3 equiv) was added THF (150 mL). The resulting solution was cooled to –78 °C and a solution of enone **11** (10.3 g, 18.6 mmol, 1 equiv) in THF (50 mL) was then added dropwise. The mixture was allowed to warm to room temperature overnight (approximately 14 hours). When the reaction was complete (as judged by TLC), the mixture was cooled to 0 °C and slowly quenched with aqueous saturated NH_4Cl, diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (x 2). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 90:10 hexanes–ethyl acetate gradient elution to afford alcohol **S6** (8.0 g, 14.1 mmol, 76%) as a white foam. The foam was immediately moved on to the subsequent step.

Analytical data for alcohol S6:

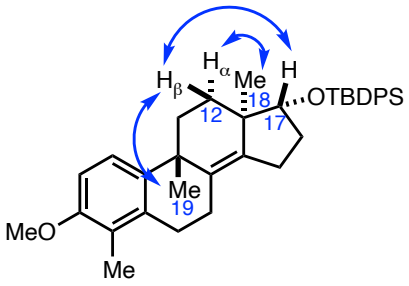
TLC (SiO_2) R_f = 0.47 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.86 – 7.67 (m, 4H), 7.44 – 7.41 (m, 2H), 7.38 – 7.36 (m, 4H), 7.06 (app t, *J* = 7.8 Hz, 1H), 6.70 (dd, *J* = 9.0, 2.8 Hz, 2H), 3.79 (s, 3H), 3.57 (dd, *J* = 9.7, 7.8 Hz, 1H), 2.66 – 2.64 (m, 2H), 2.30 – 2.20 (m, 2H), 2.18 (s, 3H), 2.14 – 2.08 (m, 1H), 2.01 (ddd, *J* = 17.1, 9.7, 7.6 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.75 – 1.65 (m, 3H), 1.63 – 1.58 (m, 1H), 1.15 (s, 3H), 1.09 – 1.07 (m, 13 H). 0.84 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.9, 142.3, 141.6, 136.2, 136.1, 129.8, 129.7, 127.7, 127.6, 126.1, 124.9, 122.0, 108.1, 82.3, 73.8, 55.6, 45.5, 37.6, 34.1, 33.8, 30.4, 28.6, 27.7, 27.2, 24.1, 19.6, 17.9, 11.5

Synthesis of tetracycle 12: To a round bottom flask equipped with a stir bar was added a solution of allylic alcohol **S6** (8.01 g, 14.1 mmol, 1 equiv) in CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and BF_3•OEt_2 (5.2 mL, 42.24 mmol, 3 equiv) was then added dropwise. The resulting mixture was stirred at –78 °C and monitored by TLC. When the reaction was complete, as judged by TLC analysis (4 hours, however reaction length widely varied depending on scale), the mixture was quenched with aqueous saturated $NaHCO_3$ then warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (x 2). The combined organic layers were washed with DI water and brine. The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 90:10 hexanes–ethyl acetate gradient elution to afford tetracycle **12** (5.95 g, 10.8 mmol, 77%) as a white foam. No evidence of a C9 diastereomer was found.

Analytical data for tetracycle 12:

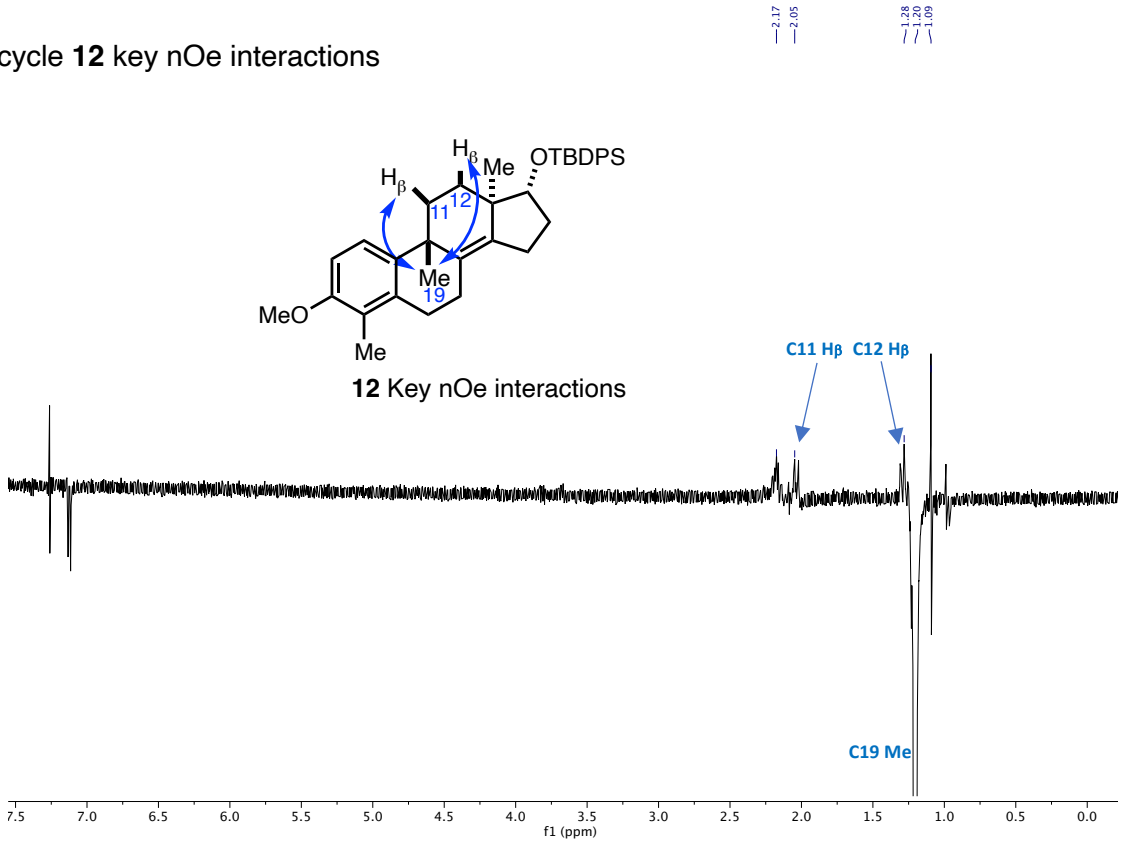
TLC (SiO_2) R_f = 0.75 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.71 – 7.68 (m, 4H), 7.44 – 7.41 (m, 2H), 7.39 – 7.36 (m, 4H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.66 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.85 – 2.82 (m, 1H), 2.47 – 2.41 (m, 2H), 2.25 (app t, *J* = 14.3 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.08 (s, 3H), 2.06 – 2.01 (m, 1H), 1.80 – 1.63 (m, 3H), 1.65 – 1.57 (m, 2H), 1.31 – 1.23 (m, 1H), 1.20 (s, 3H), 1.08 (s, 9H), 0.98 (s, 3H); **^{13}C NMR**

(150 MHz, $CDCl_3$) δ 155.0, 140.6, 136.3, 136.2, 136.1, 136.0, 135.1, 134.5, 132.8, 129.7, 129.6, 127.6, 127.5, 124.2, 123.7, 108.7, 82.8, 55.7, 44.6, 38.5, 35.3, 32.1, 31.4, 30.5, 29.5, 27.3, 23.9, 23.7, 19.6, 18.1; **IR** (thin film, cm^{-1}): 2930, 1715, 1408, 1105, 485; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{47}O_2Si$ 551.3345; found 551.3332; $[\alpha]_{589}^{21.3}$: –27.6 (*c* 0.27, $CHCl_3$).

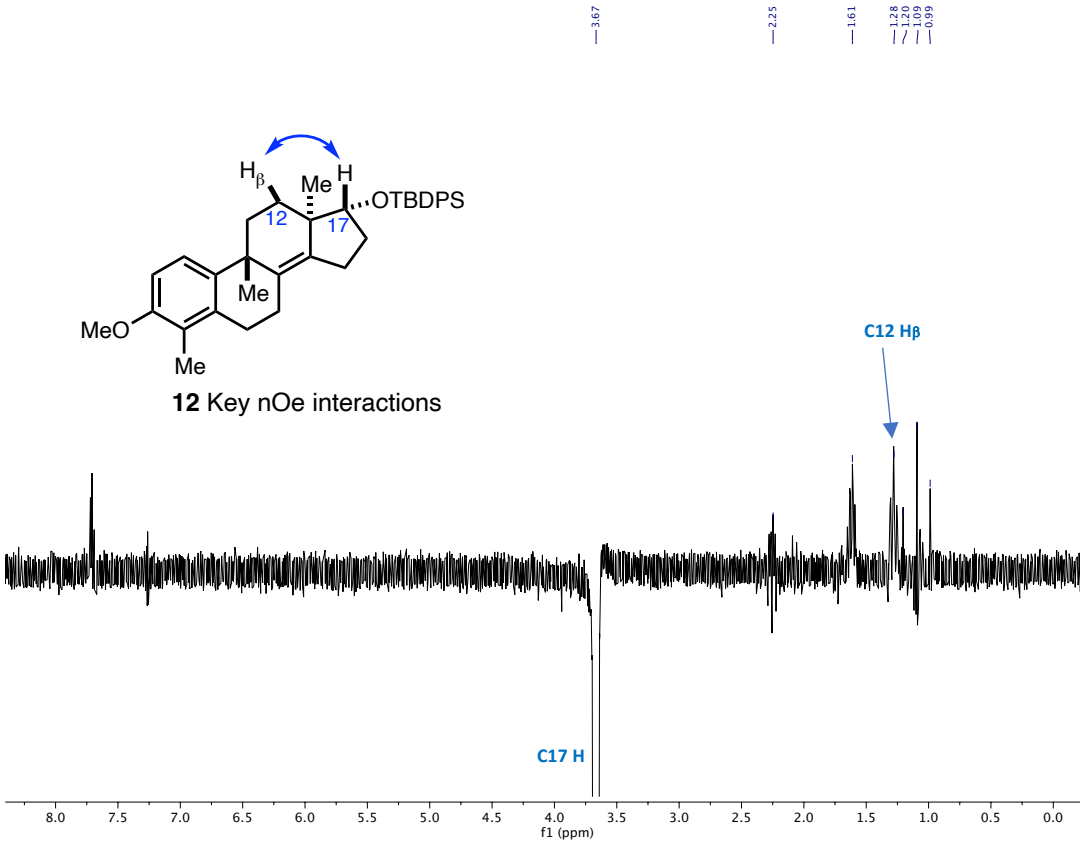


12 Key nOe interactions

Tetracycle **12** key nOe interactions

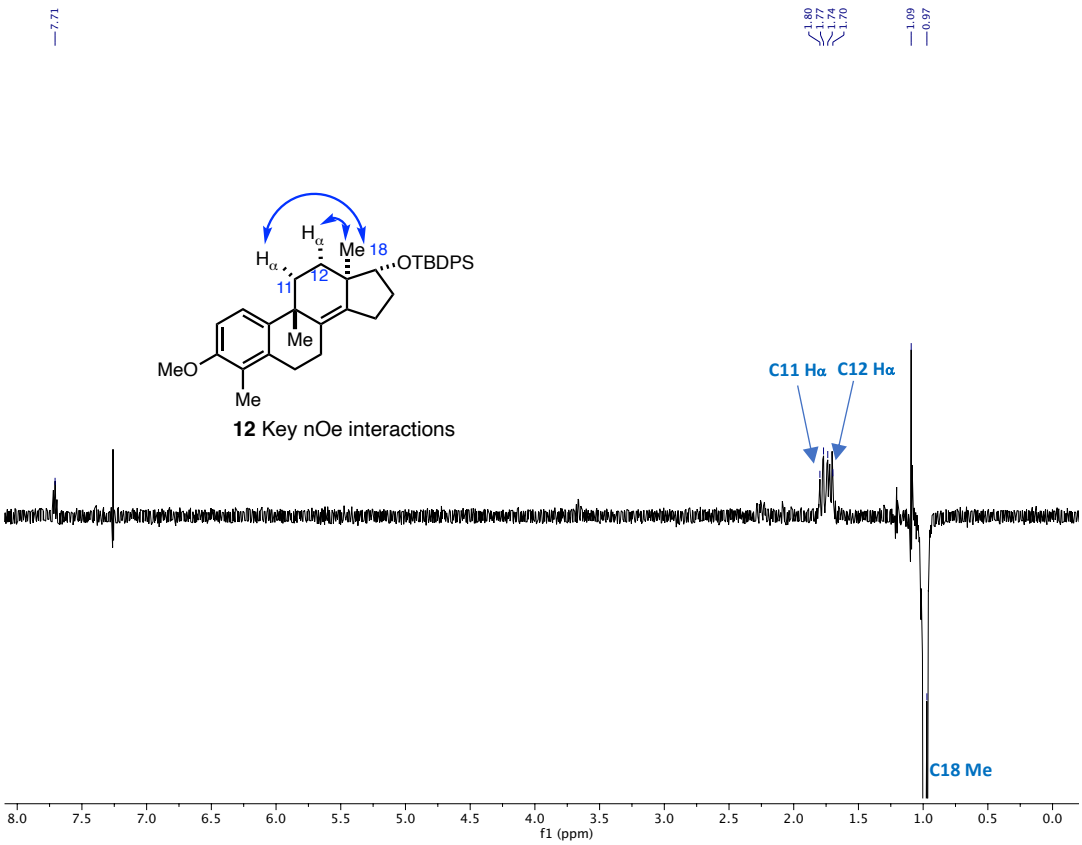


12 Key nOe interactions

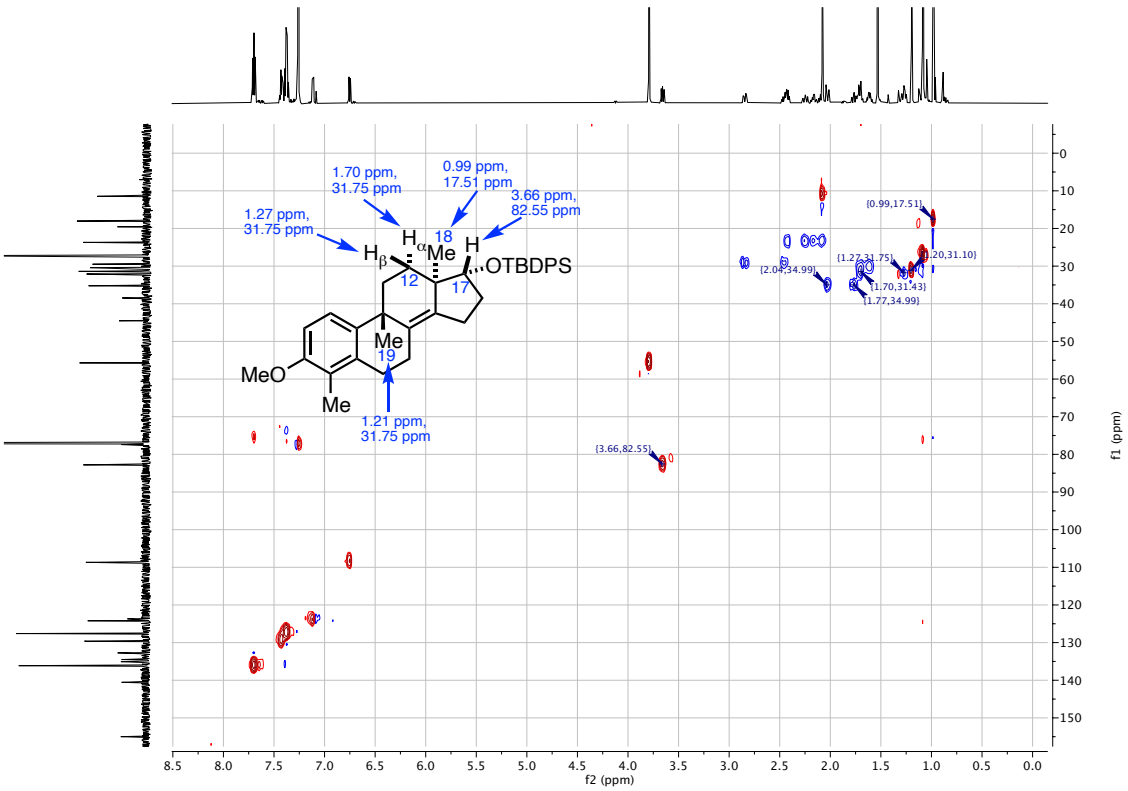


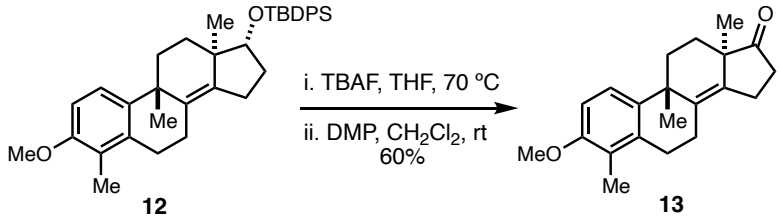
12 Key nOe interactions

Tetracycle **12** key nOe interactions



Tetrayle **12** key HSQC interactions



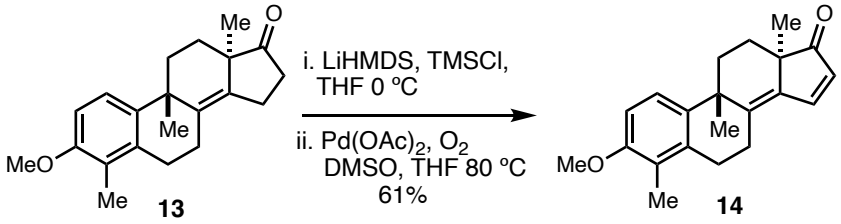


Synthesis of ketone 13: To a round bottom flask equipped with a stir bar and silyl ether **12** (5.95 g, 10.8 mmol, 1 equiv) was added a solution of 1M TBAF in THF (41 mL, 41 mmol, 3.8 equiv). The resulting solution was heated to reflux in an oil bath and stirred for 3 hours. When the reaction was judged to be complete by TLC analysis, the reaction mixture was poured into DI water. The aqueous layer was extracted with EtOAc (x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product which was immediately subjected to subsequent oxidation with the Dess-Martin periodinane (DMP).

To a round bottom flask equipped with a stirring solution of the crude alcohol (2.6 g, 8.3 mmol, 1 equiv) in CH_2Cl_2 (200 mL) was added pyridine (1.32 mL, 16.6 mmol, 2 equiv) followed by DMP (7.1 g, 16.6 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 4 hours. When the reaction was judged to be complete by TLC analysis, the reaction was quenched with a 1:1 mixture of NaS_2O_3:$NaHCO_3$ saturated aqueous solutions. The organic layer was washed with DI water then brine. The combined aqueous layers were extracted with Et_2O (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 85:15 hexanes–ethyl acetate gradient elution to afford ketone **13** (2.02 g, 6.51 mmol, 60%) as a white foam.

Analytical data for ketone 13:

TLC (SiO_2) R_f = 0.65 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 3.81 (s, 3H), 2.97 (ddd, *J* = 16.4, 5.8, 2.2 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.71 (ddd, *J* = 12.9, 5.9, 2.1 Hz, 1H), 2.66 – 2.51 (m, 3H), 2.34 (tdd, *J* = 12.7, 5.7, 1.8 Hz, 1H), 2.27 (ddd, *J* = 18.0, 10.0, 8.4 Hz, 1H), 2.18 (app dt, *J* = 13.0, 3.3 Hz, 1H), 2.12 (s, 3H), 1.82 (td, *J* = 13.6, 3.5Hz, 1H), 1.77 – 1.69 (m, 2H), 1.34 (s, 3H), 1.07 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 221.1, 155.2, 139.8, 135.7, 135.2, 132.2, 124.1, 123.8, 108.9, 55.8. 48.7, 38.7, 36.8, 34.7, 31.4, 29.8, 23.2, 24.1, 23.2, 23.1, 11.5; **IR** (thin film, cm^{-1}): 2934, 1739, 1482, 1263, 1099, 497; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{27}O_2$ 311.2011; found, 311.2000; $[\alpha]_{589}^{21.5}$**:** –309.3 (*c* 0.29, $CHCl_3$).

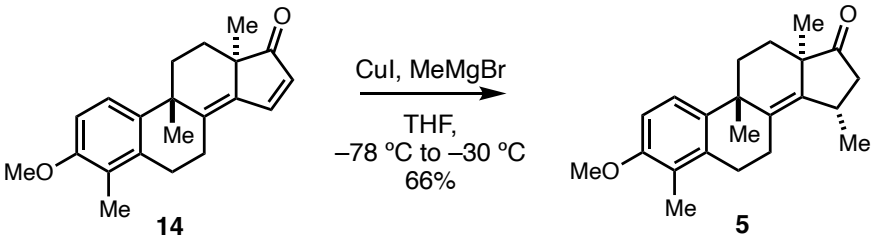


Synthesis of enone 14: To a round bottom flask was added a solution of ketone **13** (2.02 g, 6.44 mmol, 1 equiv) in THF (65 mL). The solution was cooled to 0 °C and a solution of LiHMDS in THF (13 mL of 1M solution, 13 mmol, 2 equiv) was then added dropwise, followed by the addition of TMSCl (2.45 mL, 19.3 mmol, 3 equiv). The reaction was warmed to room temperature and monitored by TLC. Upon completion, the reaction was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product as a colorless oil which was immediately used in the next step.

The crude enol silane was redissolved in a mixture of DMSO:THF (52 mL:13 mL) and $Pd(OAc)_2$ (580 mg, 2.58 mmol, 0.4 equiv) was added. The resulting mixture was aerated with a balloon of O_2 gas and heated to 80 °C in an oil bath. The solution was stirred at 80 °C under an atmosphere of O_2 for 14 hours. When the reaction was complete by TLC the mixture was diluted with Et_2O and washed with 2:1 mixture of DI water:brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 100:0 to 80:20 hexanes–ethyl acetate gradient elution to afford enone **14** (1.2 g, 3.89 mmol, 61%) as a yellow foam.

Analytical data for enone 14:

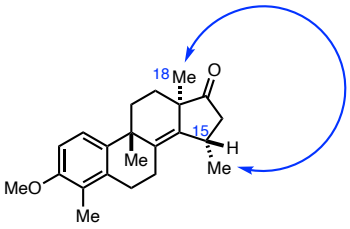
TLC (SiO_2) R_f = 0.58 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 8.03 (d, J = 5.7 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.07 (d, J = 5.7 Hz, 1H), 3.82 (s, 3H), 3.09 – 3.05 (m, 1H), 2.94 – 2.90 (m, 1H), 2.67 – 2.56 (m, 2H), 2.28 (app dt, J = 13.6, 3.3 Hz, 1H), 2.13 (s, 3H), 2.07 – 2.02 (m, 1H) 1.90 (app dt, J = 13.6, 3.3 Hz, 1H), 1.70 (td, J = 13.6, 3.2 Hz, 1H), 1.36 (s, 3H), 1.15 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 212.0, 155.5, 153.4, 139.4, 138.9, 137.1, 134.9, 129.4, 124.0, 109.2, 55.8, 46.4, 39.9, 33.9, 33.2, 29.9, 25.6, 25.0, 24.3, 11.6; **IR** (thin film, cm^{-1}): 2936, 1699, 1448, 1105, 822, 791, 487; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{25}O_2$ 309.1855; found, 309.1845; $[\alpha]_{589}^{21.7}$**:** +61.7 (*c* 2.24, $CHCl_3$).



Synthesis of ketone 5: In a round bottom flask, a stirring solution of CuI (1.33 g, 7.0 mmol, 1.8 equiv) in THF (40 mL) was cooled to –78 °C, and a solution of MeMgBr in THF (3.9 mL of 3M stock solution, 11.67 mmol, 3 equiv) was then added dropwise. The resulting mixture was warmed to –30 °C and allowed to stir for 10 minutes. A solution of enone **14** (1.2 g, 3.89 mmol, 1 equiv) in THF (30 mL) was then added dropwise to the solution. The reaction mixture was allowed to stir at –30 °C until the reaction was judged to be complete by TLC analysis (30 minutes). The reaction was then quenched at –30 °C with an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 100:0 to 80:20 hexanes–ethyl acetate gradient elution to afford ketone **5** (833 mg, 2.57 mmol, 66%) as a yellow foam.

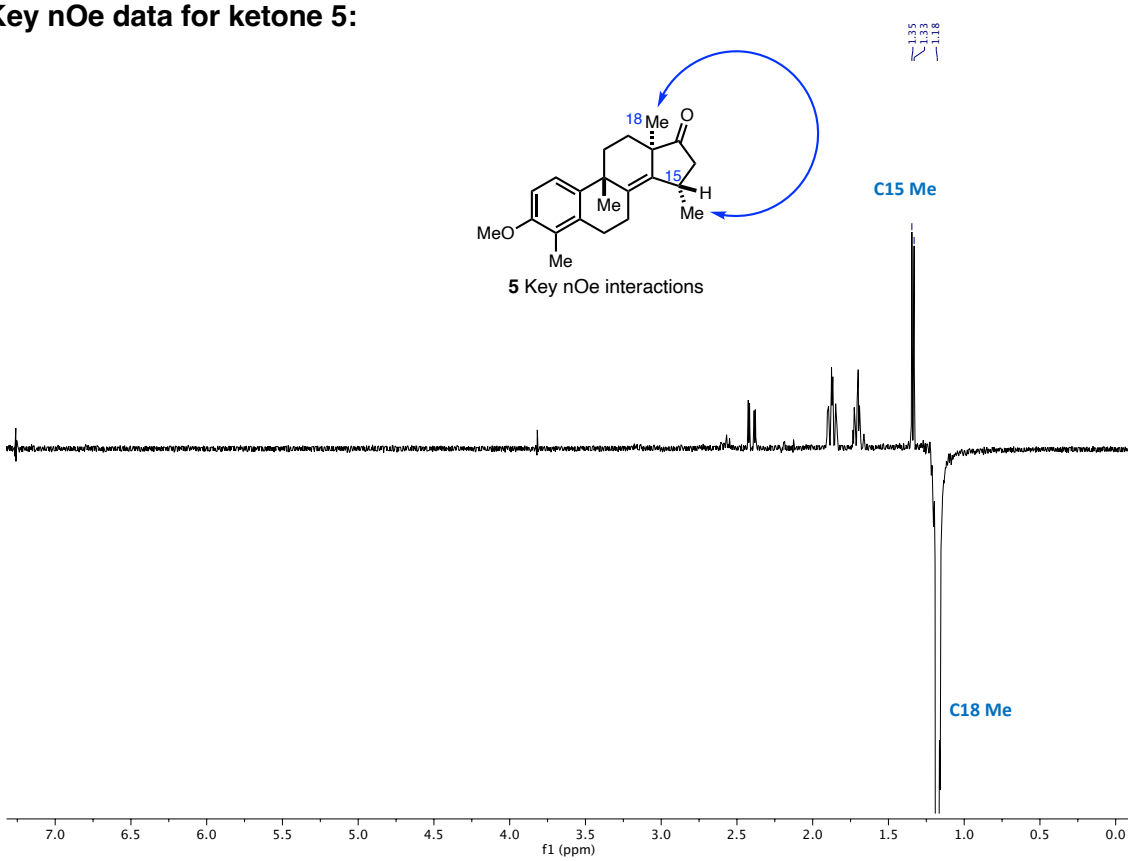
Analytical data for ketone 5:

TLC (SiO_2) R_f = 0.67 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 3.82 (s, 3H), 3.19 – 3.13 (m, 1H), 3.03 (ddd, J = 16.4, 5.9, 1.9 Hz, 1H), 2.73 (ddd, J = 12.9, 6.0, 2.0 Hz, 1H), 2.60 – 2.54 (m, 2H), 2.44 – 2.33 (m, 2H), 2.20 (app dt, J = 14.6, 7.3, 4.2 Hz, 1H), 2.13 (s, 3H), 1.87 (td, J = 13.7, 3.6 Hz, 1H), 1.73 – 1.64 (m, 2H), 1.35 – 1.33 (m, 6H), 1.18 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 220.9, 155.3, 140.1, 136.3, 136.2, 135.5, 124.0, 108.9, 55.7, 48.8, 44.2, 38.8, 34.5, 31.9, 31.0, 30.5, 27.1, 26.1, 23.6, 23.5, 11.5. **IR** (thin film, cm^{-1}): 2923, 1743, 1481, 1265, 1101, 472; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{29}O_2$ 325.2168; found, 325.2160; $[\alpha]_{589}^{21.7}$**:** –240.5 (*c* 3.55, $CHCl_3$).



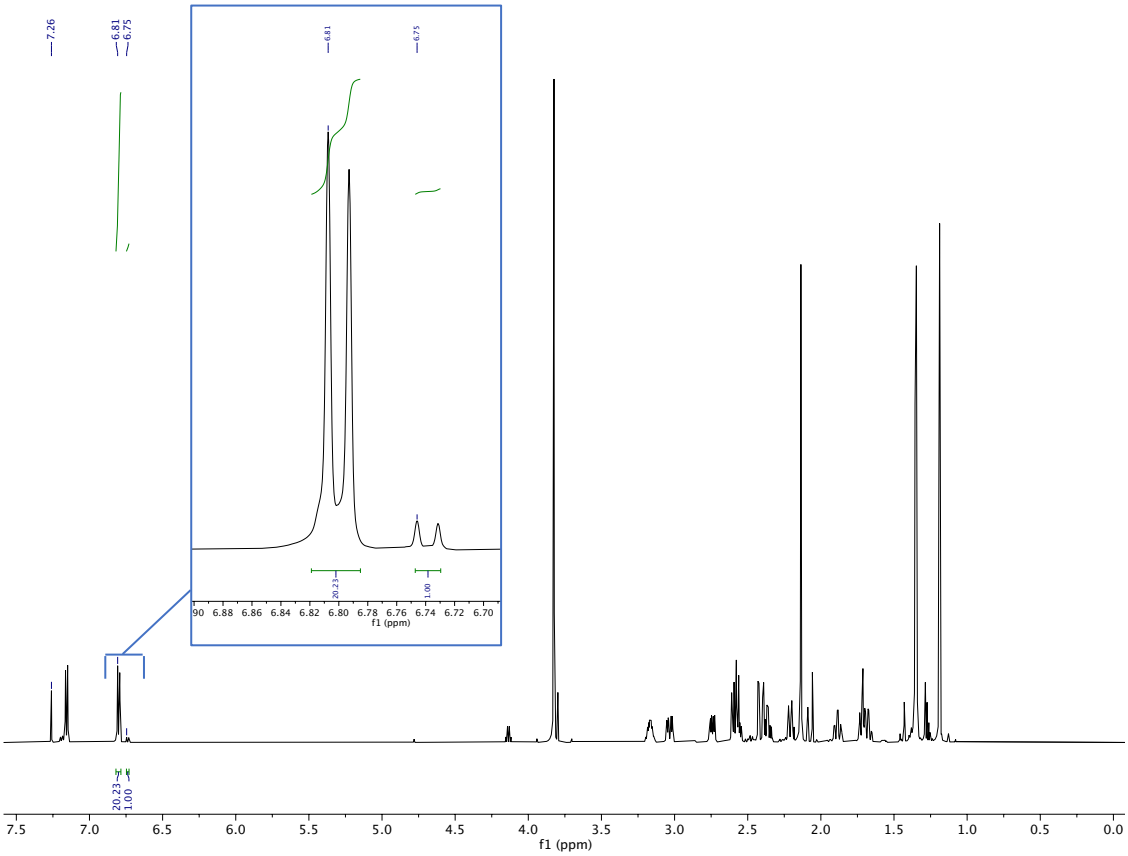
5 Key nOe interactions

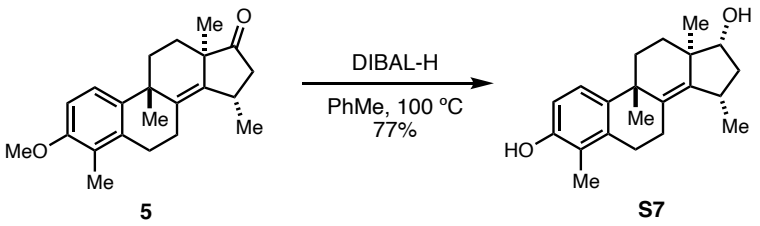
Key nOe data for ketone 5:



5 Key nOe interactions

Diastereomeric ratio of ketone 5



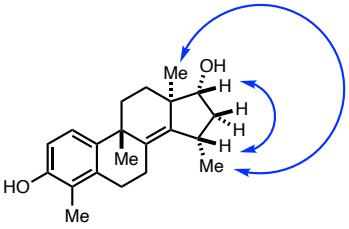


5 **S7**

Synthesis of phenol S7: To a stirring solution of aryl methyl ether **5** (830 mg, 2.56 mmol, 1 eqiuv) in PhMe (5 mL) was added a solution of DIBAL-H in PhMe (25.6 mL of 1M solution, 25.6 mmol, 10 equiv) at room temperature. The resulting mixture was heated to 100 °C in an oil bath and stirred overnight (14 hours). When the reaction was judged to be complete by TLC analysis, the mixture was cooled to room temperature and slowly quenched with DI water. Once bubbling stopped, the mixture was washed with 1M HCl. The aqueous layer was extracted with EtOAc (x 3) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 100:0 to 70:30 hexanes–ethyl acetate gradient elution to afford phenol **S7** (614 mg, 1.97 mmol, 77%) as a white foam.

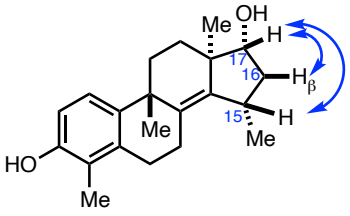
Analytical data for phenol S7:

TLC (SiO_2) R_f = 0.43 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.05 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.66 (dd, J = 10.6, 7.5 Hz, 1H), 2.96 (ddd, J = 16.3, 5.8, 1.8 Hz, 1H), 2.75 – 2.69 (m, 1H), 2.62 (dd, J = 12.8, 6.0 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.37 – 2.33 (m, 1H), 2.31 – 2.25 (m, 1H), 2.14 – 2.10 (m, 4H), 1.81 (td, J = 13.8, 3.0 Hz, 1H), 1.74 (app dt, J = 12.8, 3.5 Hz, 1H), 1.52 – 1.48 (m, 1H), 1.45 – 1.40 (m, 1H), 1.33 (s, 3H), 1.20 (d, J = 7.2 Hz, 3H), 0.97 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 151.2, 140.6, 139.6, 136.1, 134.4, 124.5, 121.3, 113.4, 81.8, 44.1, 39.6, 38.8, 35.1, 32.6, 31.9, 31.7, 30.6, 23.4, 23.2, 18.7, 11.5; **IR** (thin film, cm^{-1}): 3388, 2959, 1705, 1362, 1073, 512; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{29}O_2$ 313.2168; found, 313.2154; $[\alpha]_{589}^{21.8}$**:** –115.2 (*c* 6.0, $CHCl_3$).

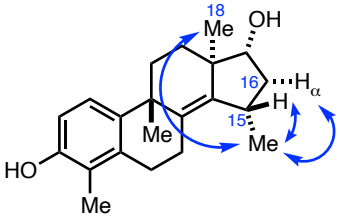


S7 Key nOe interactions

Key nOe data for phenol S7:

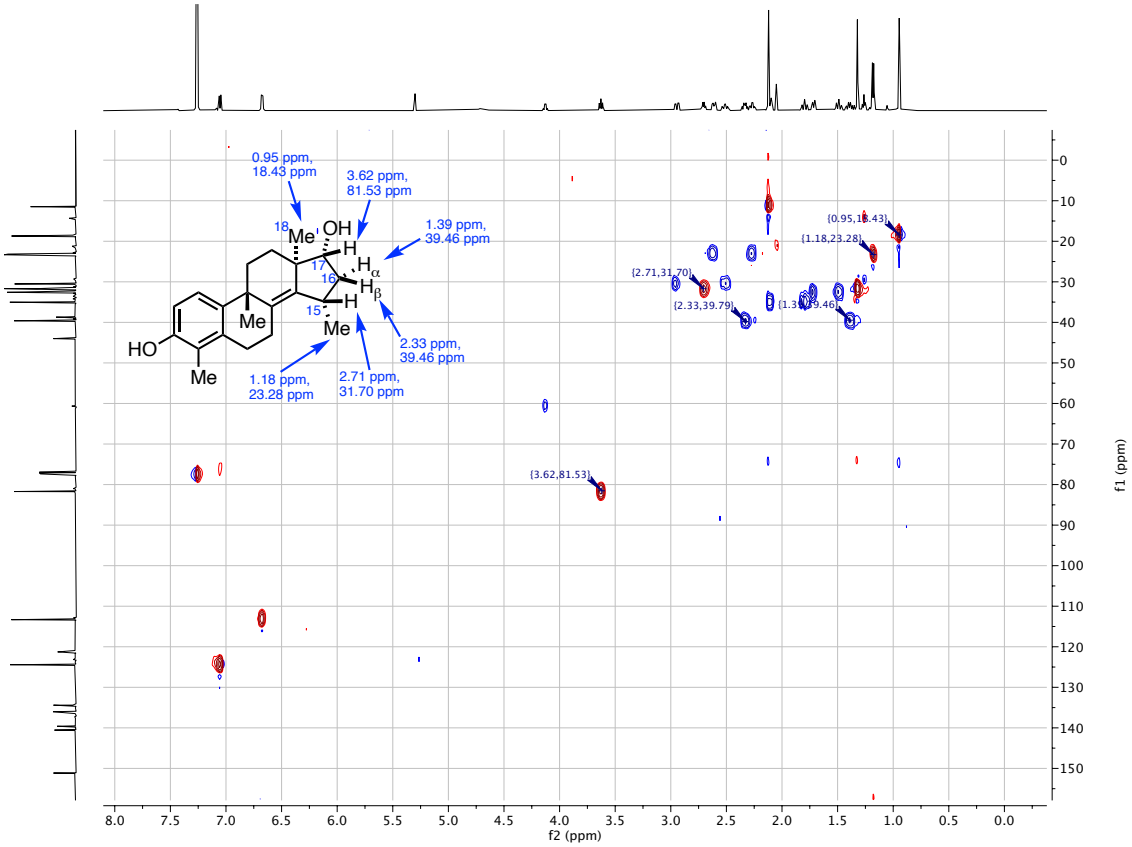


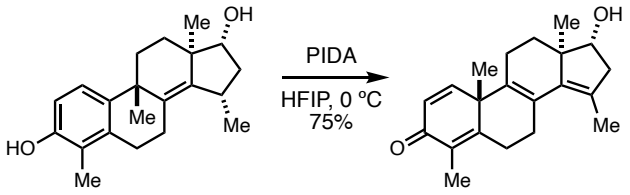
S7 Key nOe interactions



S7 Key nOe interactions

HSQC for phenol S7



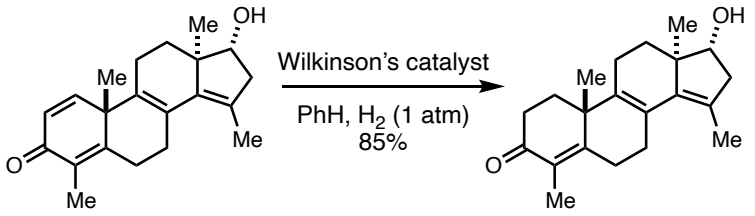


S7 **15**

Synthesis of dienone 15: To a stirring solution of phenol **S7** (614 mg, 1.96 mmol, 1 equiv) in HFIP (20 mL) at 0 °C was added PIDA (631 mg, 1.96 mmol, 1 equiv) in one portion. After 1 minute of stirring at 0 °C the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature and the phases were separated. The aqueous layer was extracted with EtOAc (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 100:0 to 40:60 hexanes–ethyl acetate gradient elution to afford dienone **15** (457 mg, 1.47 mmol, 75%) as a yellow foam.

Analytical data for dienone 15:

TLC (SiO_2) R_f = 0.23 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.16 (d, *J* = 10.1 Hz, 1H), 6.26 (d, *J* = 10.1 Hz, 1H), 3.89 (app t, *J* = 8.5 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.50 – 2.38 (m, 5H), 2.32 – 2.26 (m, 1H), 1.94 (s, 3H), 1.90 – 1.87 (m, 4H), 1.44 (s, 3H), 1.31 (td, *J* = 12.4, 5.2 Hz, 1H), 0.87 (s, 1H), 0.79 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 185.5, 159.7, 152.6, 136.9, 135.7, 128.7, 127.9, 127.8, 127.4, 79.6, 47.6, 46.4, 45.0, 34.1, 31.3, 28.7, 25.8, 25.1, 17.7, 14.7, 10.5; **IR** (thin film, cm^{-1}): 3398, 2924, 1658, 1602, 1081, 463; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{27}O_2$ 311.2011; found, 311.2010; $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20.6}}$**:** +46.21 (*c* 0.125, $CHCl_3$).

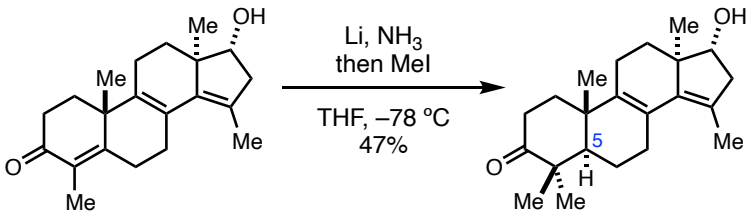


15 **S8**

Synthesis of enone S8: To a stirring solution of dienone **15** (2.90 g, 9.34 mmol, 1 equiv) in benzene (65 mL) was added Wilkinson's catalyst [$RhCl(PPh_3)_3$] (1.7 g, 1.87 mmol, 0.2 equiv). H_2 gas was bubbled into the solution and the reaction was stirred under an atmosphere of H_2 gas for 4 hours. When the reaction was judged to be complete by TLC analysis, the solution was diluted in EtOAc and filtered through a pad of celite. The organic layer was concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 25 g cartridge with 100:0 to 40:60 hexanes–ethyl acetate gradient elution to afford enone **S8** (2.47 g, 7.91 mmol, 85%) as a yellow foam.

Analytical data for enone S8:

TLC (SiO_2) R_f = 0.33 (hexanes–ethyl acetate, 50:50); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 3.89 (app t, *J* = 7.2 Hz, 1H), 2.95 – 2.90 (m, 1H), 2.81 (ddd, *J* = 13.0, 5.1, 2.4 Hz, 1H), 2.56 – 2.39 (m, 4H), 2.37 – 2.31 (m,1H), 2.21 – 2.14 (m, 1H), 2.12 – 2.08 (m, 2H), 1.94 – 1.92 (m, 1H), 1.90 (s, 3H), 1.86 – 1.83 (m, 1H), 1.80 – 1.78 (m, 4H), 1.79 – 1.74 (m, 1H), 1.38 (s, 3H), 1.28 (td, *J* = 12.0, 6.0 Hz, 1H), 0.83 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 198.5, 162.8, 139.3, 137.3, 127.7, 127.2, 126.6, 79.7, 47.7, 46.4, 40.7, 34.0, 33.9, 33.8, 29.6, 26.2, 23.3, 22.5, 17.6, 14.9, 10.8; **IR** (thin film, cm^{-1}): 3418, 2921, 1654, 1080, 735, 496; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{29}O_2$ 313.2168; found, 313.2164; $[\alpha]_{589}^{20.8}$**:** +156.85 (*c* 0.10, $CHCl_3$).



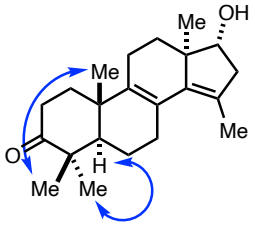
S8 **16**

Synthesis of ketone 16: To a stirring solution of NH_3 (7 mL) at –78 °C was added Li^0 metal (56 mg, 8.0 mmol, 12.5 equiv). The resulting dark blue solution and was stirred at –78 °C for 10 minutes. A solution of enone **S8** (200 mg, 0.64 mmol, 1 equiv) in THF (7 mL) was then added dropwise to the stirring solution over 5 minutes. The resulting dark blue mixture was allowed to stir for 25 minutes at –78 °C, then MeI was added, and the resulting yellow mixture was warmed to –33 °C and refluxed for 30 minutes. The mixture was warmed to room temperature and NH_3 was removed by evaporation under a positive pressure of N_2 gas (25 minutes). The resulting mixture was washed with saturated aqueous NH_4Cl and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 100:0 to 40:60 hexanes–ethyl acetate gradient elution to afford ketone **16** (98 mg, 0.301 mmol, 47%) as a yellow foam.

Note: this reaction resulted in a complex mixture of products favoring desired ketone **16 which could be isolated through careful chromatography (0-40% ethyl acetate in hexanes over 30 column volumes with a flowrate of 20mL/min). Attempts to isolate and identify a C5 diastereomer were unsuccessful.

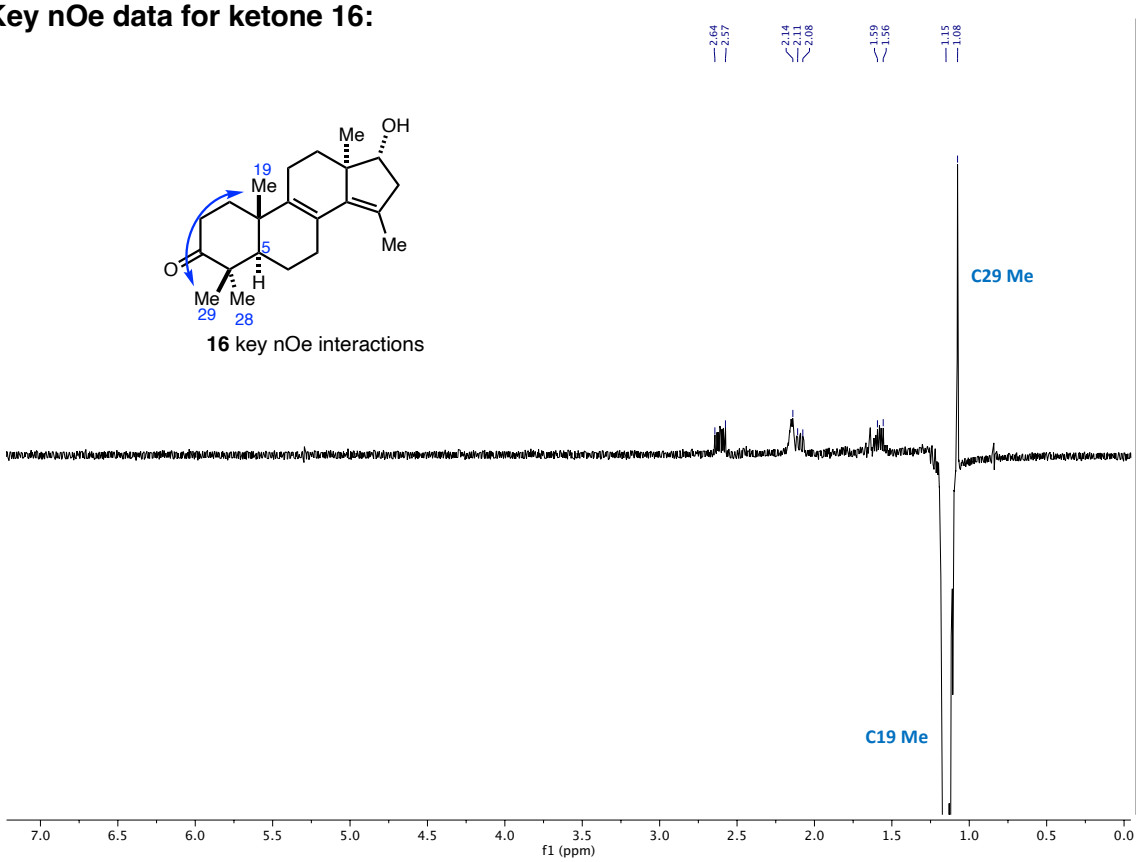
Analytical data for ketone 16:

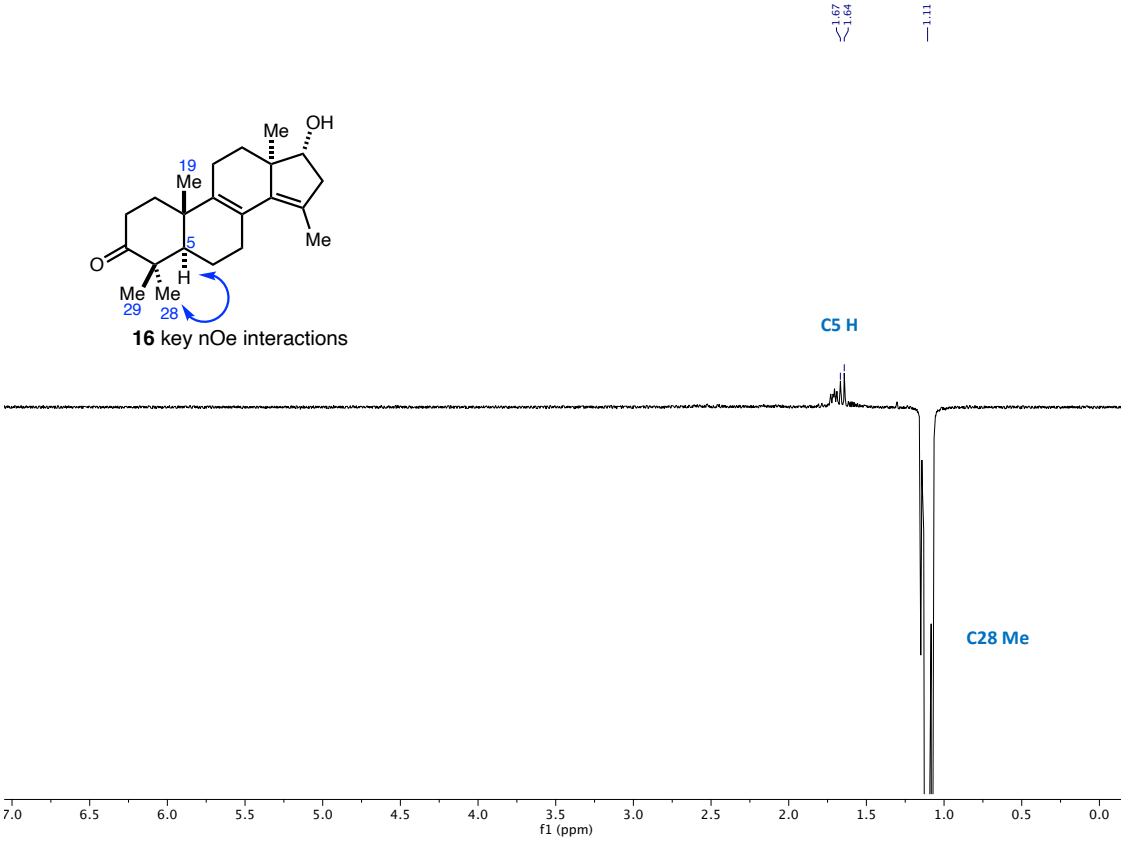
TLC (SiO_2) R_f = 0.33 (hexanes–ethyl acetate, 60:40); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 3.87 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.61 (ddd, *J*= 16.0, 11.3, 7.1 Hz, 1H), 2.51 – 2.36 (m, 3H), 2.35 – 2.28 (m, 1H), 2.19 – 2.06 (m, 3H), 1.91 (s, 3H), 1.82 – 1.79 (m, 1H), 1.73 – 1.56 (m, 5H), 1.26 – 1.19 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.84 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.6, 141.0, 137.6, 126.9, 125.6, 79.9, 60.6, 50.6, 47.7, 47.4, 46.5, 38.2, 35.6, 34.7, 34.2, 26.5, 22.7, 21.5, 19.9, 18.9, 17.7, 14.8; **IR** (thin film, cm^{-1}): 3400, 2930, 1704, 1383, 1078, 475; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{33}O_2$ 329.2481; found, 329.2473; $[\alpha]_{589}^{20.9}$**:**+54.27 (*c* 1.05, $CHCl_3$).



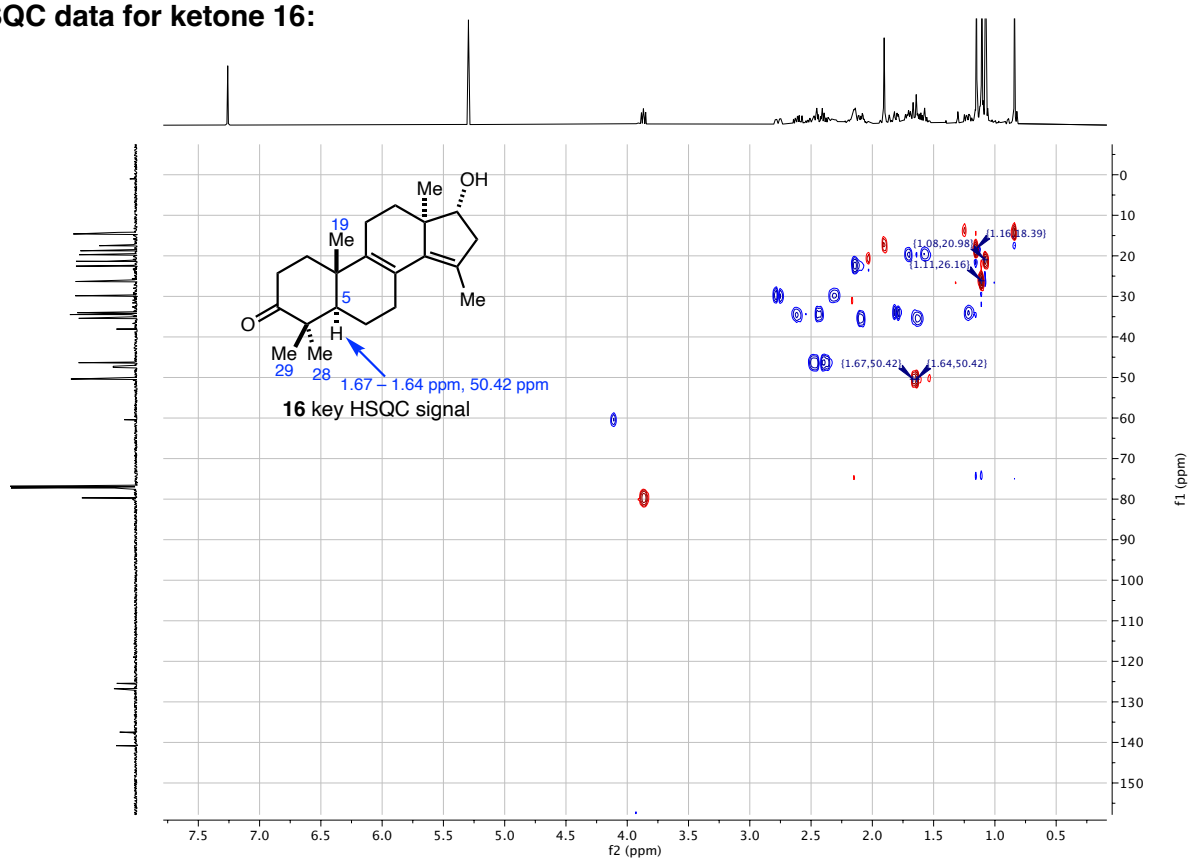
16 key nOe interactions

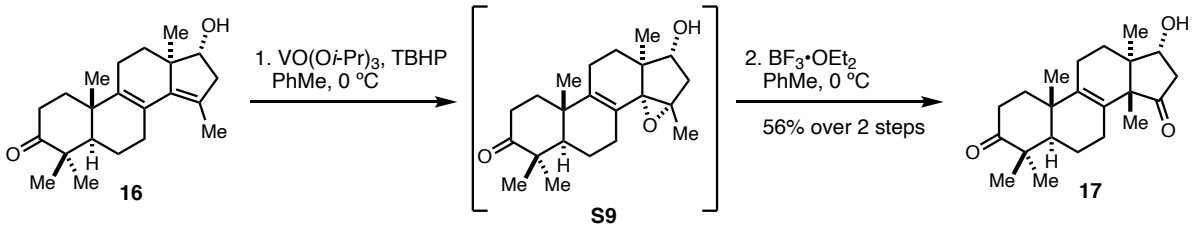
Key nOe data for ketone 16:





HSQC data for ketone 16:



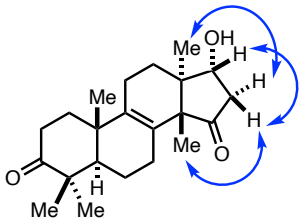


Synthesis of ketone 17: To a stirring solution of homoallylic alcohol **16** (120 mg, 0.365 mmol, 1 equiv) in PhMe (3 mL) at 0 °C was added VO(O*i*-Pr)$_3$ (43 μL, 0.183 mml, 0.5 equiv) followed by dropwise addition of TBHP (365 μL, 1.83 mmol, 5.5 equiv). The resulting mixture was stirred at 0 °C for 5 hours, after which time a few drops of DMS were added to quench the reaction. The solution was concentrated *in vacuo* to afford the crude product, which was filtered through a pad of silica with a hexanes wash followed by elution at 30% ethyl acetate in hexanes to afford epoxide **S9** (48.8 mg, 0.13 mmol, 70%) as a white foam which was immediately subjected to the subsequent Lewis acid-mediated semi–Pinacol reaction.

To a stirring solution of epoxide **S9** in PhMe (3 mL) at 0 °C was added BF_3•OEt_2 (90 μL, 0.73 mmol, 2 equiv). Within 5 minutes the reaction was judged to be complete by TLC analysis. The mixture was then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (x 3), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 5 g cartridge with 100:0 to 40:60 hexanes–ethyl acetate gradient elution to afford ketone **17** (70 mg, 0.203 mmol, 56% over 2 steps) as a white foam.

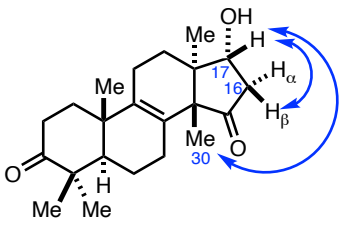
Analytical data for ketone 17:

TLC (SiO_2) R_f = 0.28 (hexanes–ethyl acetate, 30:70); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 4.35-4.30 (m, 1H), 2.82 (dd, *J* = 19.0, 8.5 Hz, 1H), 2.61 – 2.40 (m, 4H), 2.20 (dd, *J* = 19.0, 8.5 Hz, 1H), 2.15 – 2.09 (m, 2H), 2.06 – 1.98 (m, 1H), 1.86 – 1.57 (m, 6H), 1.44 (qd, *J* = 12.4, 5.8 Hz, 1H), 1.10 (s, 6H), 1.06 (s, 3H), 1.05 (s, 3H), 0.90 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.9, 212.8, 135.0, 132.2, 72.1, 60.6, 57.5, 51.3, 47.4, 44.7, 43.9, 37.7, 35.7, 34.6, 27.9, 26.9, 26.0, 21.3, 20.1, 14.8; **IR** (thin film, cm^{-1}): 3456, 2938, 1739, 1702, 1457, 1379, 1078, 735, 505; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{33}O_3$ 345.2430; found, 345.2421; $[\alpha]_{589}^{20.3}$: +53.4 (*c* 0.97, $CHCl_3$).

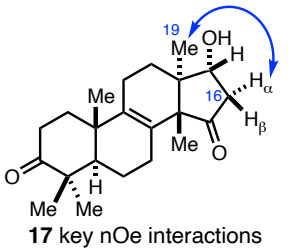


17 key nOe interactions

Key nOe data for ketone 17:

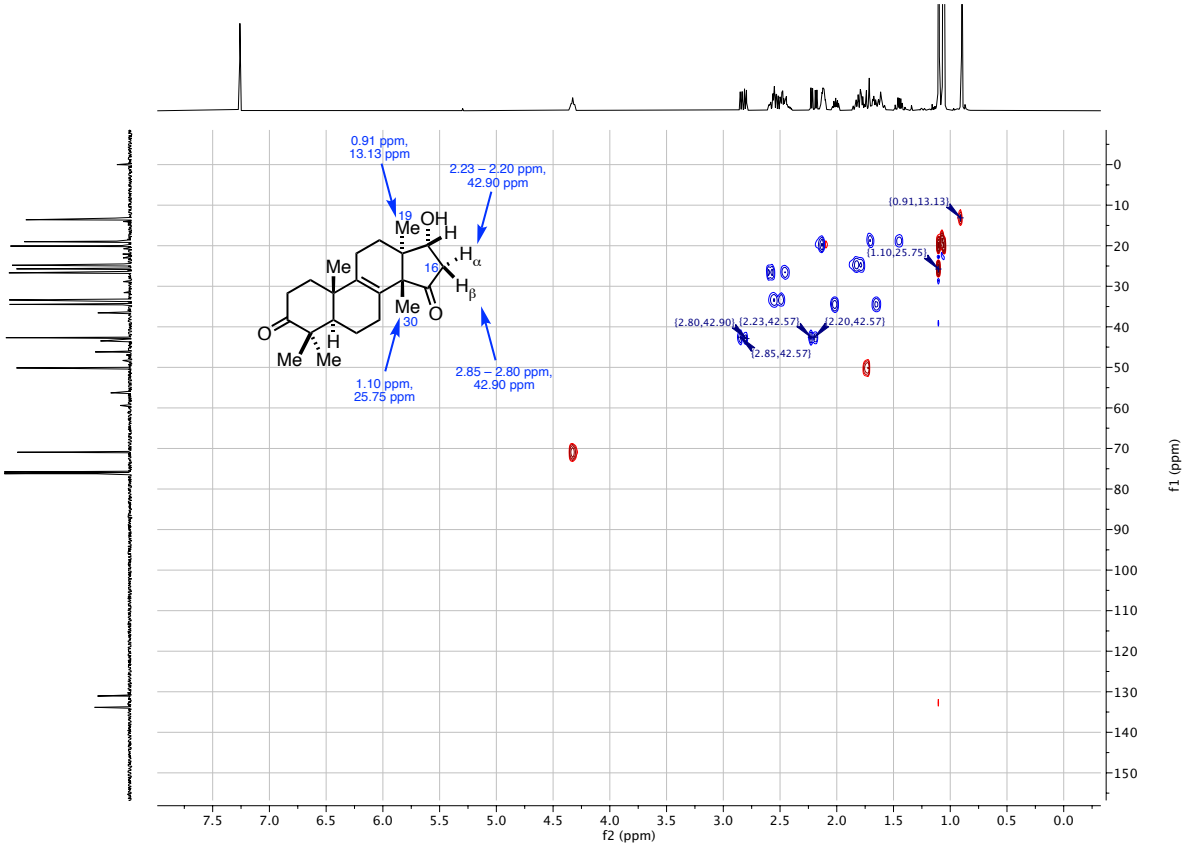


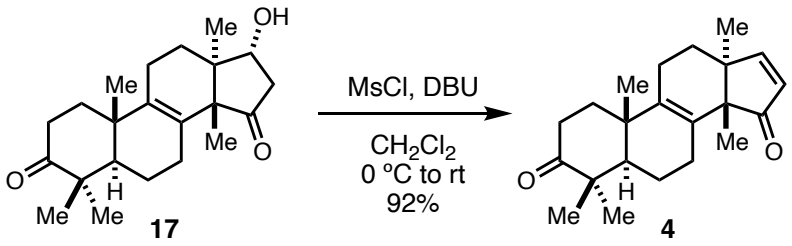
17 key nOe interactions



17 key nOe interactions

HSQC data for ketone 17:



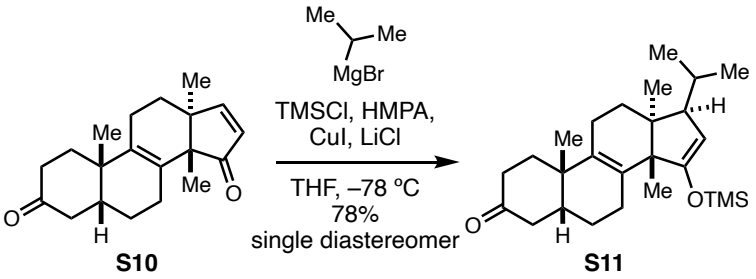


Synthesis of enone 4: To a stirring solution of alcohol **17** (27.6 mg, 0.0801 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 0 ºC was added DBU (32 μL, 0.203 mmol, 2.5 equiv), followed by MsCl (8 μL, 0.098 mmol, 1.2 equiv). Once all starting material was consumed, the reaction mixture was slowly warmed to room temperature and additional DBU was added (128μL, 0.812 mmol, 10 equiv). When the reaction was judged to be complete by TLC analysis (3 hours), a saturated aqueous solution of $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 5 g cartridge with 100:0 to 40:60 hexanes–ethyl acetate gradient elution to afford enone **4** (24.0 mg, 0.0737 mmol, 92%) as a white foam.

Analytical data for enone 4:

TLC (SiO_2) R_f = 0.67 (hexanes–ethyl acetate, 80:20); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 7.41 (d, *J* = 5.9 Hz, 1H), 5.83 (d, *J* = 5.9 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.58 – 2.46 (m, 2H), 2.34 – 2.08 (m, 4H), 2.03 (ddd, *J* = 12.3, 7.5, 4.4 Hz, 1H), 1.77 – 1.62 (m, 4H), 1.54 – 1.45 (m, 1H), 1.25 (s, 3H), 1.11 (s, 3H), 1.07 (s, 6H), 0.96 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.9, 210.4, 165.2, 134.9, 133.3, 130.7, 56.5, 51.4, 48.3, 47.4, 37.8, 35.9, 34.5, 29.9, 28.9, 27.6, 27.0, 24.7, 21.2, 20.4, 20.1, 19.9; **IR** (thin film, cm^{-1}): 2966, 1707, 1455, 1377, 816, 499; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{31}O_2$ 327.2324; found, 327.2315; $[\alpha]_{589}^{20.5}$**:** +40.60 (*c* 0.25, $CHCl_3$).

Initial study into the stereoselectivity of cuprate addition:

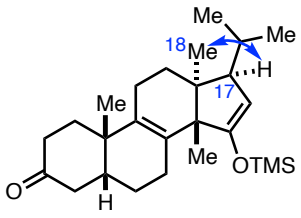


Synthesis of enol silane S11:

To a round bottom flask equipped with CuI (958 mg, 5.03 mmol, 30 equiv) and LiCl (426 mg, 10.05 mmol, 60 equiv) was added THF (20 mL). The resulting mixture was stirred at room temperature until the solution became clear. The mixture was then cooled to –78 °C and *i*-PrMgCl (1.68 mL, 3.0 M in THF, 20 equiv) was added dropwise. The mixture was stirred for 5 minutes at –78 °C, after which time HMPA (583 μL, 3.35 mmol, 20 equiv) was added. In a separate flask, enone **S10** (50 mg, 0.168 mmol, 1 equiv) was dissolved in THF (10 mL) and cooled to –78 °C. Once cold, TMSCl (425 μL, 3.35 mmol, 20 equiv) was added and the resulting solution was stirred for 5 minutes at –78 °C. The solution of enone **S10** and TMSCl was then cannulated dropwise into the stirring solution containing the cuprate. The reaction was kept at –78 °C and monitored by TLC. The reaction was judged to be complete by TLC analysis within 15 minutes and was then quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (x 3), and the combined organic layers were washed with brine, dried under Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 5 g cartridge with 100:0 to 80:20 hexanes-ethyl acetate gradient to afford enone **S11** (54 mg, 0.130 mmol, 78%) as a white solid.

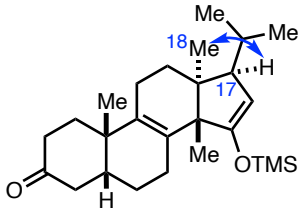
Analytical data for enol silane S11:

TLC (SiO_2) R_f = 0.78 (hexanes–ethyl acetate, 60:40); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 4.51 (d, J = 3.2 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.26 – 2.05 (m, 8H), 1.89 – 1.80 (m, 3H), 1.71 (dd, J = 9.7, 3.3 Hz, 1H), 1.62 – 1.52 (m, 2H), 1.41 – 1.37 (m, 1H), 1.21 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.90 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.22 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.5, 160.5, 137.1, 129.1, 104.3, 57.3, 53.0, 44.6, 44.2, 43.4, 39.2, 36.9, 35.9, 29.1, 28.8, 27.9, 26.7, 24.7, 24.6, 23.2, 22.1, 22.0, 0.2



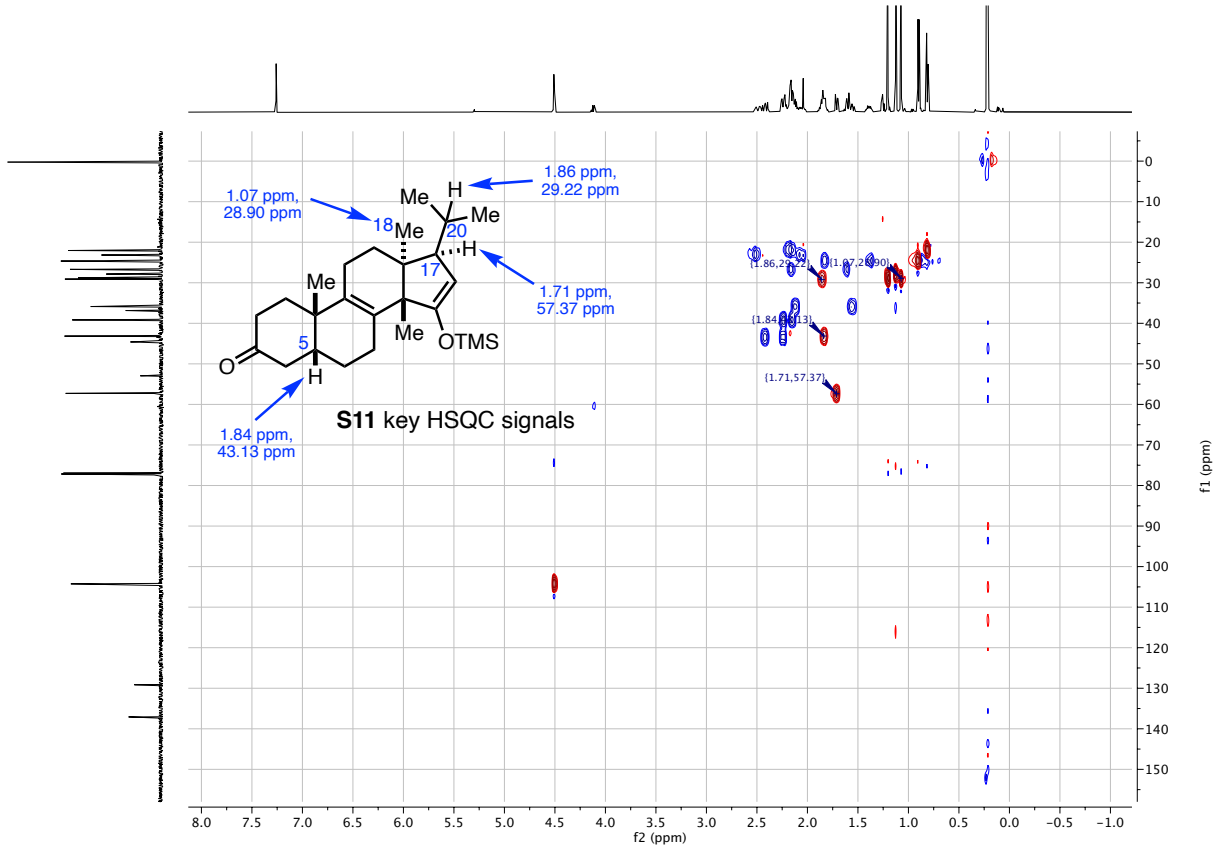
S11 key nOe interactions

S11 key nOe interactions

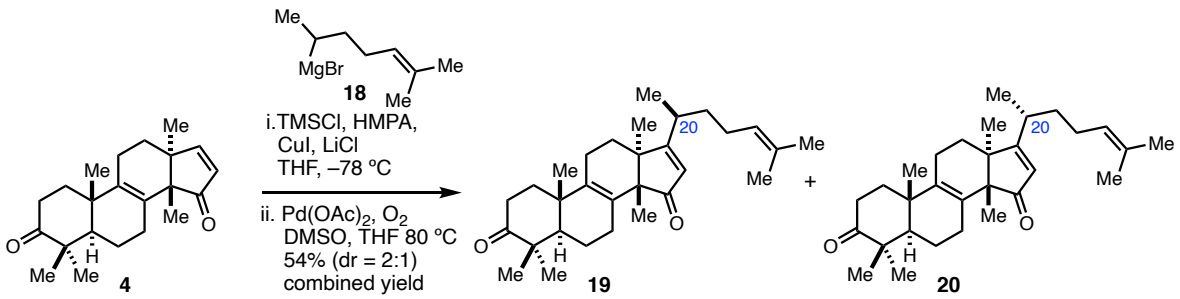


S11 key nOe interactions

S11 key HSQC interactions



S11 key HSQC signals

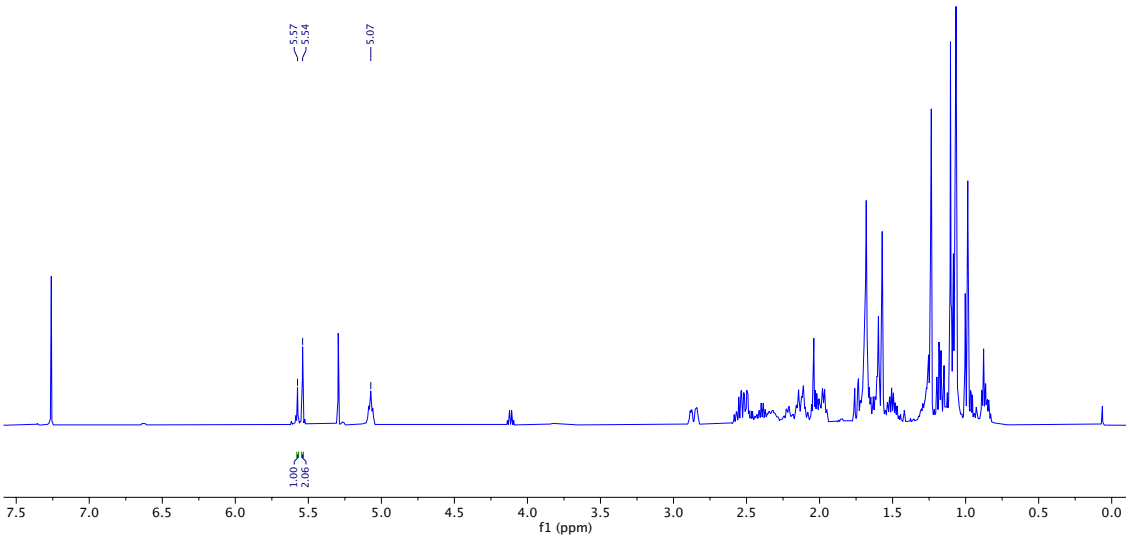


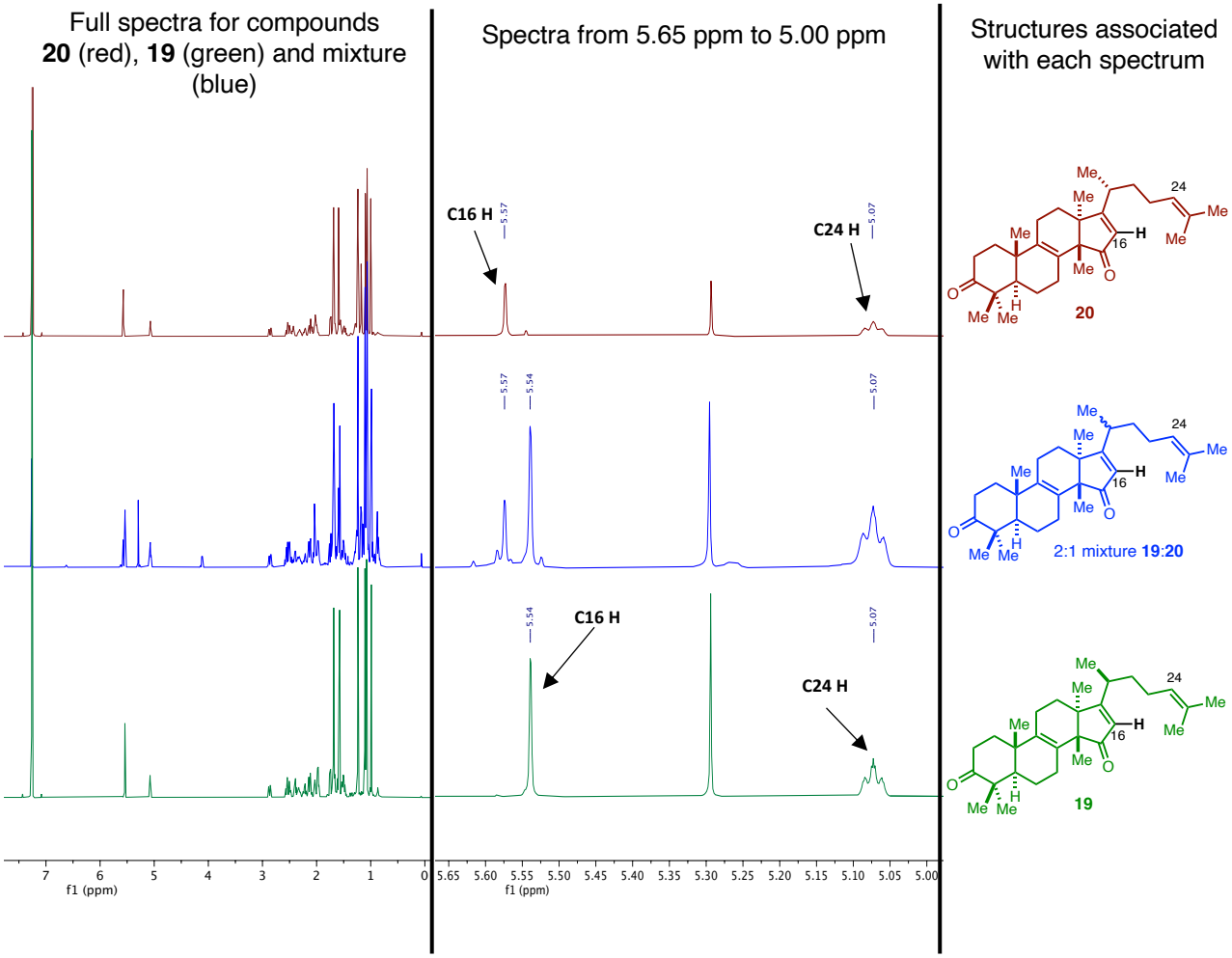
Synthesis of enones 19 and 20: To a round bottom flask equipped with CuI (397 mg, 2.08mmol, 13.33 equiv) and LiCl (176 mg, 4.16 mmol, 26.7 equiv) was added THF (20 mL). The resulting mixture was stirred at room temperature until the solution became clear. The solution was then cooled to –78 ºC and Grignard reagent **18**[5] (13.7 mL, 0.152 M in THF, 13.3 equiv) was added dropwise. The mixture was stirred for 5 minutes at –78 ºC, after which time HMPA (240 μL, 1.38 mmol, 8.86 equiv) was added. In a separate flask, enone **4** (51 mg, 0.156 mmol, 1 equiv) was dissolved in THF (10 mL) and cooled to –78 ºC. TMSCl (175 μL, 1.38 mmol, 8.86 equiv) was then added to this mixture and the resulting solution was allowed to stir for 5 minutes at –78 ºC. The solution of enone **4** and TMSCl was then cannulated dropwise into the stirring cuprate solution. The reaction mixture was kept at –78 ºC and monitored by TLC. The reaction was judged to be complete by TLC analysis within 5 minutes and was then quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (x 3), and the combined organic layers were washed with brine, dried under Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then subjected to a Saegusa–Ito oxidation.
The crude material was dissolved in a mixture of DMSO:THF (3 mL:1 mL) in a round bottom flask. $Pd(OAc)_2$ (35 mg, 0.156 mmol, 1 equiv) was added to the mixture and the solution became a dark red color. The reaction flask was sealed, heated to 80 ºC in an oil bath and stirred overnight (approximately 14 hours). The reaction mixture was then cooled to room temperature, diluted with EtOAc, filtered through a pad of celite and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 5 g cartridge with 100:0 to 80:20 hexanes-ethyl acetate gradient to afford a 2:1 mixture of enones **19** and **20** (36.5 mg, 0.0836 mmol, 54% combined yield) as a white solid. The resulting mixture was separated by HPLC on a slow ramp from 100:0 to 88:12 hexanes-ethyl acetate gradient over 30 minutes at a flowrate of 20 mL/min to afford the enones **19** and **20** as white solids.
**Note: C20 stereochemistry was assigned after completing the syntheses of both natural products

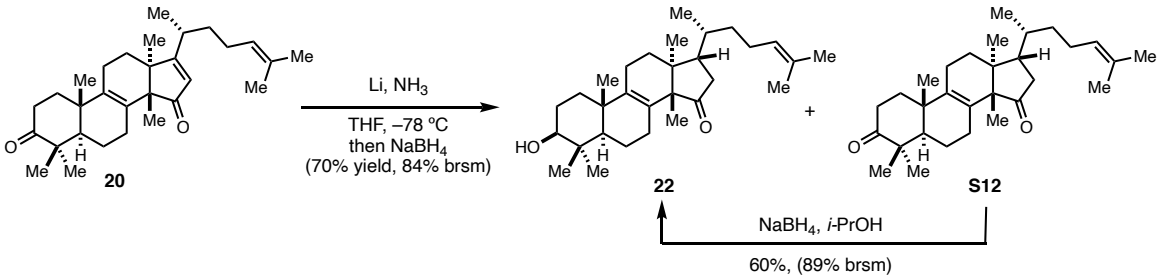
Analytical data for enone 19:
TLC (SiO_2) R_f = 0.54 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.08 (app t, J = 7.0Hz, 1H), 2.86 (dd, J =18.5, 5.1 Hz, 1H), 2.58 – 2.46 (m, 2H), 2.42 – 2.28 (m, 2H), 2.26 – 2.18 (m, 1H), 2.17 – 2.08 (m, 2H), 2.06 – 1.95 (m, 3H), 1.75 (dd, J = 12.6, 2.2 Hz, 1H), 1.72 – 1.64 (m, 6H), 1.64 – 1.56 (m, 5H), 1.55 – 1.47 (m, 2H), 1.24 (s, 3H), 1.11 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 218.0, 210.3, 186.9, 134.3, 133.6, 132.3, 124.0, 123.3, 57.1, 51.5, 50.5, 47.5, 37.7, 35.9, 35.7, 34.6, 33.4, 31.8, 27.0, 26.1, 25.9, 23.4, 22.9, 21.2, 20.5, 20.3, 20.2, 20.1, 18.0, 14.3; **IR**: (thin film, cm^{-1}): 2966, 1705, 1596, 1455, 1376, 1092, 699, 496; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{45}O_2$ 437.3420; found, 437.3411; $[\alpha]_{589}^{20.2}$**:** +73.29 (*c* 0.685, $CHCl_3$).

Analytical data for enone 20:
TLC (SiO_2) R_f = 0.54 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.07 (app t, *J* = 7.2 Hz, 1H), 2.87 (dd, *J* = 18.2, 5.8 Hz, 1H), 2.59 – 2.42 (m, 3H), 2.36 – 2.14 (m, 3H), 2.12 – 1.96 (m, 4H), 1.75 (dd, *J* = 12.6, 2.2 Hz, 1H), 1.72 – 1.65 (m, 6H), 1.63 – 1.59 (m, 4H), 1.58 – 1.54 (m, 1H), 1.32 – 1.24 (m, 2H), 1.24 (s, 3H), 1.18 (d, *J* = 6.8Hz, 3H), 1.11 (s, 3H), 1.08 (s, 6H), 1.01 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.8, 210.0, 187.1, 134.1, 133.3, 132.3, 123.8, 123.7, 56.8, 51.3, 47.3, 37.5, 35.9, 35.7, 34.4, 32.7, 31.6, 29.4, 29.3, 27.6, 26.8, 25.7, 23.3, 22.7, 21.0, 20.0, 19.9, 19.3, 17.7, 14.1; **IR** (thin film, cm^{-1}): 2965, 1706, 1596, 1456, 1378, 1093, 480; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{45}O_2$ 437.3420; found, 437.3405; $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20.3}}$**:** +62.39 (*c* 0.35, $CHCl_3$).

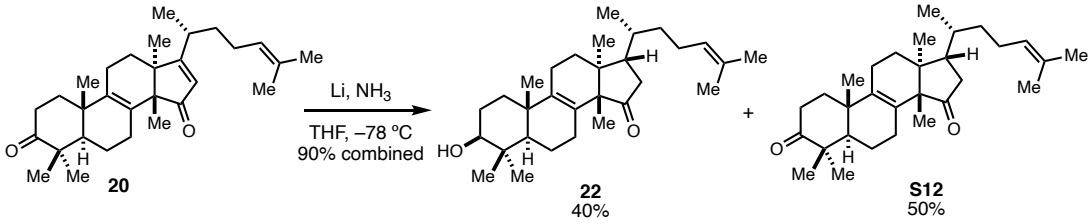
^{1}HNMR spectrum of product mixture following Saegusa–Ito oxidation:







Reduction of enone **20 was carried out by a dissolving metal reduction; the resulting two products (**22** and **S12**) were easily separated. The undesired dione **S12** was subjected to $NaBH_4$ reduction to access the desired alcohol **22**. The reported yield reflects the combined yields of the dissolving metal reduction and $NaBH_4$ reduction to give the desired alcohol **22**.



Synthesis of alcohol 22 and ketone S12: To a round bottom flask equipped with a stirring solution of NH_3 (3 mL) at –78 °C was added Li^0 metal (2 mg, 0.32 mmol, 20 equiv). The resulting mixture became a dark blue color, and after 10 minutes of stirring enone **20** (7 mg, 0.016 mmol, 1 equiv) in THF (2 mL) was added. The resulting mixture was stirred at –78 °C for 5 minutes before saturated aqueous NH_4Cl was added (resulting in a clear solution). The mixture was warmed to room temperature and NH_3 was evaporated under a stream of N_2. The organic layer was extracted with EtOAc (x 3). The combined organic layers were dried, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford alcohol **22** (2.8 mg, 0.0063 mmol, 40% yield) and dione **S12** (3.5 mg, 0.008 mmol, 50%) as white solids.

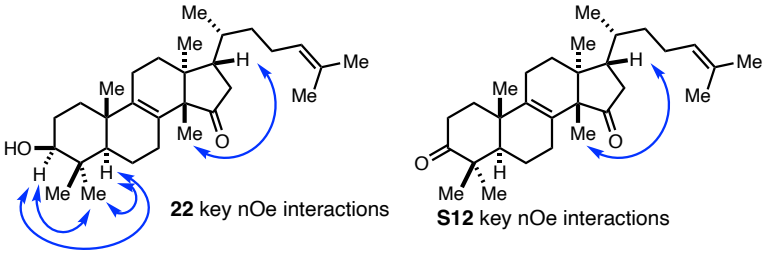
Analytical data for alcohol 22:

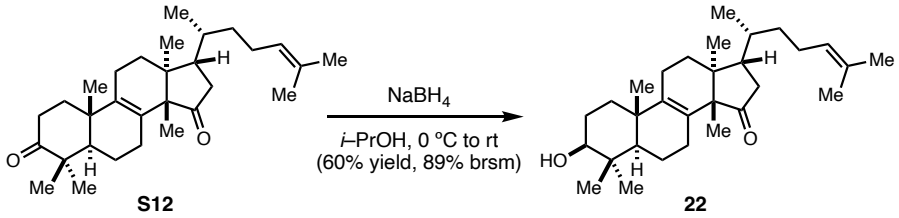
TLC (SiO_2) R_f = 0.40 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.09 (app t, *J* = 7.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.54 (dd, *J* = 18.7, 8.3 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.11 – 1.96 (m, 4H), 1.94 – 1.80 (m, 5H), 1.77 – 1.72 (m, 2H), 1.69 – 1.65 (m, 3H), 1.61 (s, 3H), 1.60 – 1.55 (m, 2H), 1.42 – 1.33 (m, 2H), 1.22 – 1.16 (m, 3H), 1.13 – 1.09 (m, 4H), 1.00 (s, 3H), 0.96 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.82 (s, 3H), 0.80 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.6, 136.1, 131.6, 131.1, 124.8, 79.0, 57.9, 50.8, 44.9, 43.4, 42.1, 39.0, 37.8, 35.8, 35.4, 35.1, 29.3, 28.3, 28.2, 27.9, 25.9, 24.8, 21.9, 21.6, 20.3, 19.0, 18.9, 17.9, 15.7. 15.5; **IR** (thin film, cm^{-1}): 3451, 2927, 1737, 1455, 1376, 1027; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{49}O_2$ 441.3733; found, 441.3716; $[\alpha]_{589}^{20.8}$**:** +18.36 (*c* 0.14, $CHCl_3$).

Analytical data for ketone S12:

TLC (SiO_2) R_f = 0.59 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.09 (app t, *J* = 7.0Hz, 1H), 2.61 – 2.42 (m, 5H), 2.10 – 1.96 (m, 4H), 1.94 – 1.81 (m, 5H), 1.72 – 1.62 (m, 6H), 1.61 – 1.59 (m, 4H), 1.47 – 1.38 (m, 1H), 1.22 – 1.16 (m, 1H), 1.15 (s, 3H), 1.09 (s, 3H), 1.05 (s, 6H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.82 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 218.0, 216.3, 134.7, 132.2, 131.6, 124.7, 57.8, 51.3, 47.4, 45.0, 43.4, 42.1, 37.6, 35.8, 35.7, 35.1, 34.6, 29.3, 28.0,

26.9, 25.9, 24.8, 21.7, 21.5, 21.2, 20.3, 20.0, 18.9, 17.9, 15.6; **IR** (thin film, cm^{-1}): 2925, 1738, 1706, 1455, 1378, 1058, 471; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{46}O_2$ 438.3498; found, 438.3496; $[\alpha]_{589}^{20.3}$: +43.76 (*c* 0.315, $CHCl_3$).

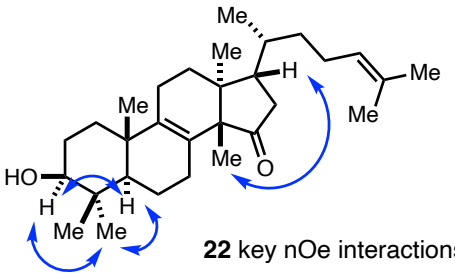




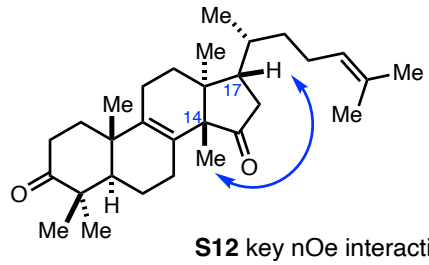
Synthesis of alcohol 22: To a stirring solution of dione **S12** (3.5 mg, 0.0080 mmol, 1 equiv) in *i*–PrOH (2 mL) at 0 °C was added $NaBH_4$ (1.0 mg, 0.026 mmol, 3.3 equiv). The mixture was warmed to room temperature and allowed to stir for 4 hours. The reaction mixture was then diluted with EtOAc and washed with dilute HCl (0.2M). The organic layer was dried, filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford alcohol **22** (2.1 mg, 0.0048 mmol, 60% yield) as well as starting material (1.0 mg, 0.024 mmol) (89% yield of **22** based on recovered starting material).

Analytical data for alcohol 22:

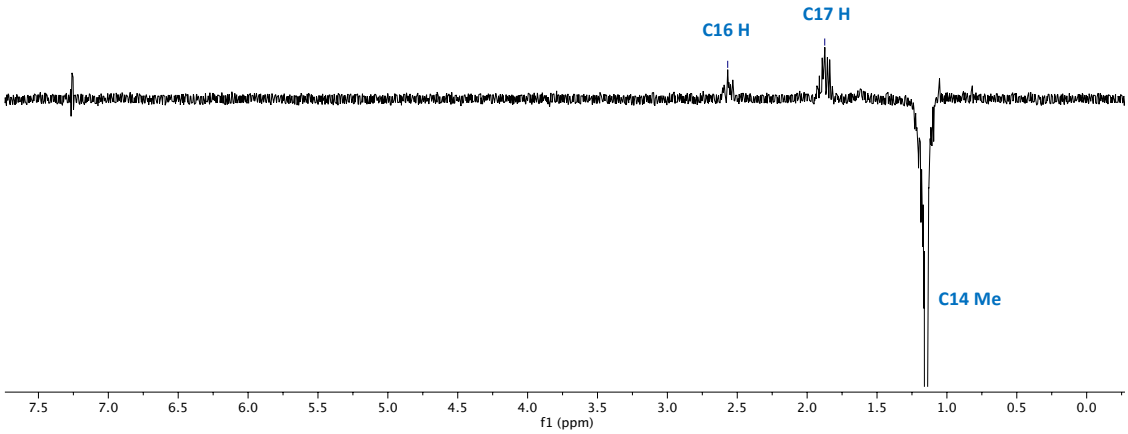
TLC (SiO_2) R_f = 0.40 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.09 (app t, *J* = 7.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.54 (dd, *J* = 18.7, 8.3 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.11 – 1.96 (m, 4H), 1.94 – 1.80 (m, 5H), 1.77 – 1.72 (m, 2H), 1.69 – 1.65 (m, 3H), 1.61 (s, 3H), 1.60 – 1.55 (m, 2H), 1.42 – 1.33 (m, 2H), 1.22 – 1.16 (m, 3H), 1.13 – 1.09 (m, 4H), 1.00 (s, 3H), 0.96 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.82 (s, 3H), 0.80 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.6, 136.1, 131.6, 131.1, 124.8, 79.0, 57.9, 50.8, 44.9, 43.4, 42.1, 39.0, 37.8, 35.8, 35.4, 35.1, 29.3, 28.3, 28.2, 27.9, 25.9, 24.8, 21.9, 21.6, 20.3, 19.0, 18.9, 17.9, 15.7. 15.5; **IR** (thin film, cm^{-1}): 3451, 2927, 1737, 1455, 1376, 1027; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{49}O_2$ 441.3733; found, 441.3716; $[\alpha]_{589}^{20.8}$: +18.36 (*c* 0.14, $CHCl_3$).



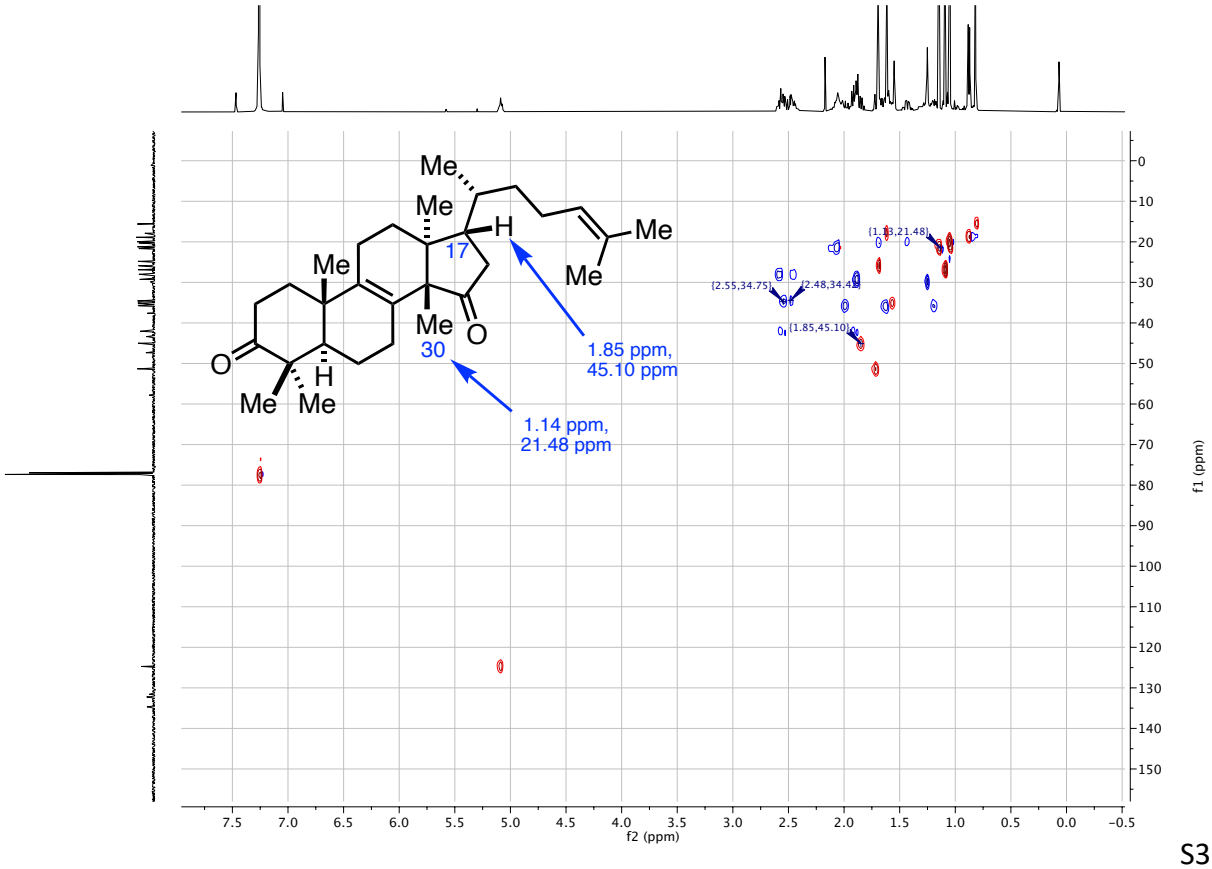
Key nOe data for ketone S12:



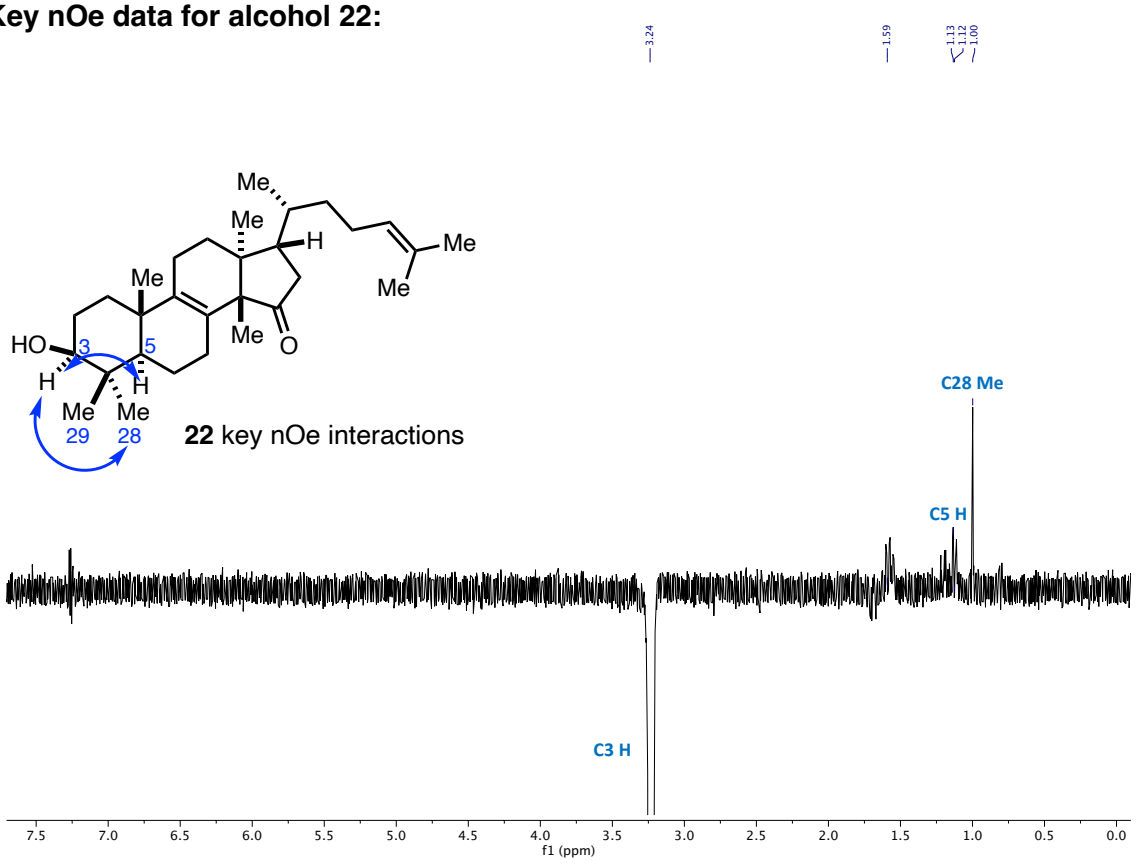
S12 key nOe interactions

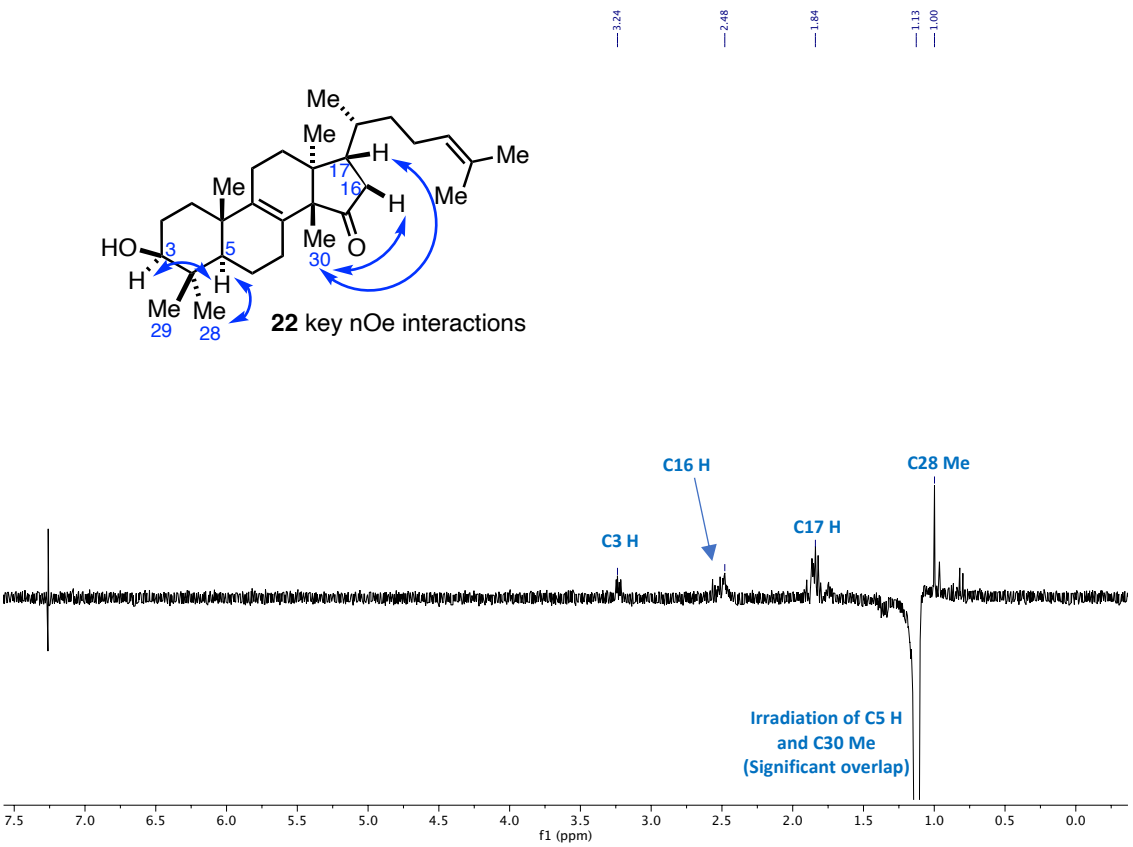


HSQC data for ketone S12:

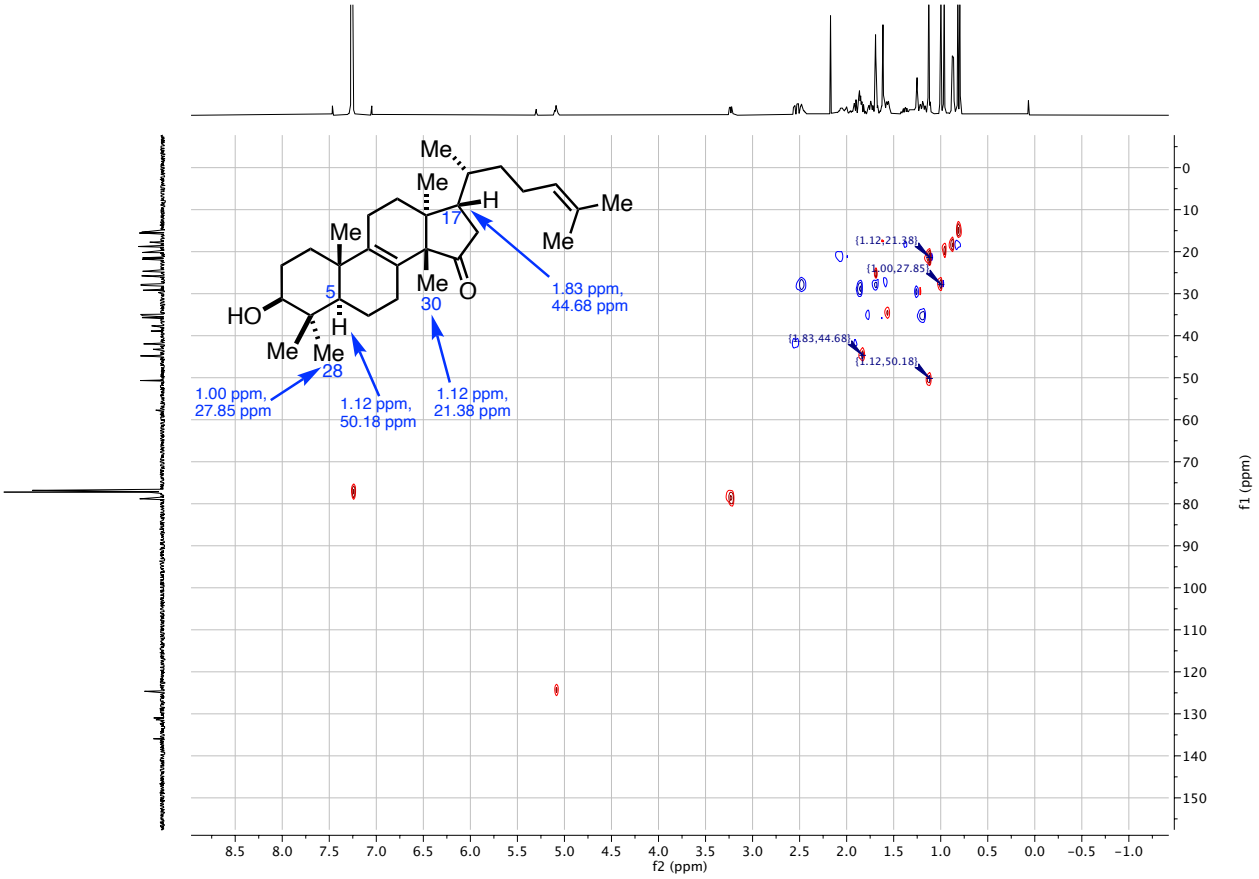


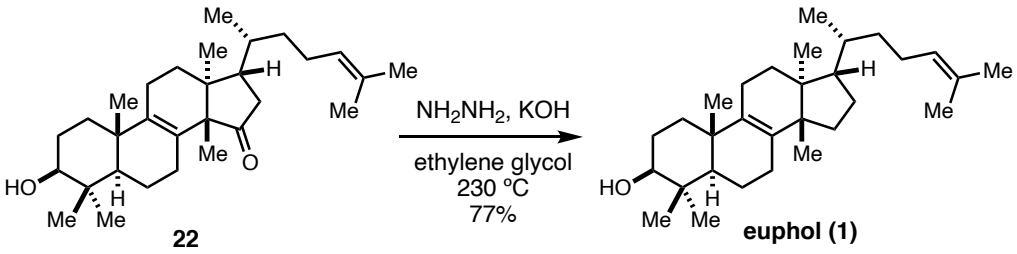
Key nOe data for alcohol 22:





HSQC data for alcohol 22:





Synthesis of euphol (1): To a round bottom flask was added a solution of ketone **22** (2 mg, 0.0045 mmol, 1 equiv) in ethylene glycol (2 mL), KOH (7 mg, 0.125 mmol, 28 equiv) and $(N_2H_4)\bullet H_2O$ (5 μL, 0.156 mmol, 35 equiv). The mixture was heated to 230 ºC in a sand bath and stirred at this temperature for 48 hours. When the reaction was judged to be complete by TLC analysis, the mixture was cooled to room temperature, diluted with EtOAc, washed with dilute HCl (0.2M) until a pH of 6 was obtained. The combined organic layers were dried, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford euphol (**1**) (1.5 mg, 0.0035 mmol, 77% yield).

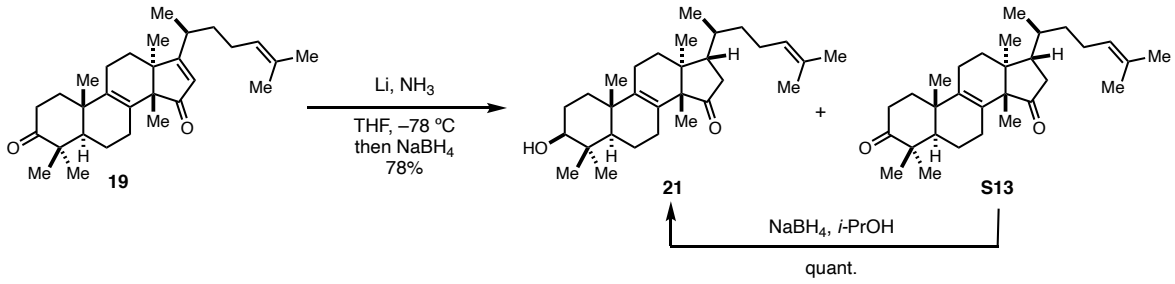
Analytical data for euphol (1):

TLC (SiO_2) R_f = 0.49 (hexanes–ethyl acetate, 80:20); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.09 (app. t, J = 7.1 Hz, 1H), 3.24 (dd, J = 11.8, 4.5 Hz, 1H), 2.11 – 2.00 (m, 3 H), 1.96 – 1.82 (m, 4H), 1.79 – 1.66 (m, 6H), 1.68 (s, 3H), 1.63 – 1.36 (m, 4H), 1.60 (s, 3H), 1.35 – 1.16 (m, 4H). 1.12 (m, 1H), 1.07 – 1.00 m, 2H), 1.00 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H), 0.86 (d, J = 6.0 Hz, 3H), 0.80 (s, 3H), 0.75 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 134.0, 133.7, 131.0, 125.4, 79.2, 51.1, 50.2, 49.8, 44.3, 39.1, 37.4, 36.0, 35.6, 35.4, 31.0, 29.9, 28.3, 28.2, 28.1, 27.8, 25.9, 24.9, 24.6, 21.7, 20.3, 19.10, 19.07, 17.8, 15.8, 15.7; **IR** (thin film, cm^{-1}): 3399, 2943, 1453, 1027, 472; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{50}O$ 426.3817; found, 426.3860; $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20.9}}$**:** +29.50 (*c* 0.04, $CHCl_3$). All analytical data matched previously reported literature.[6]

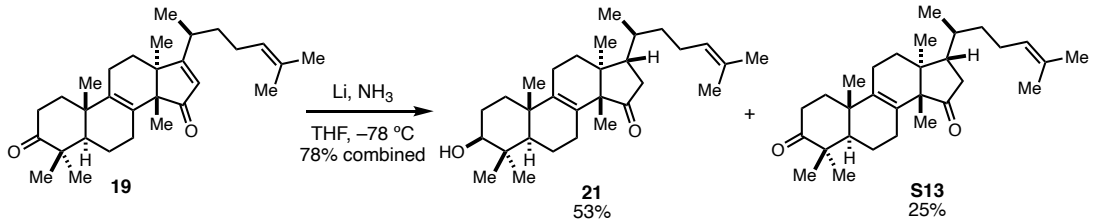
Euphol ^{13}CNMR in $CDCl_3$

C#	Experimental	Literature[6]	Difference
1	35.4	35.4	0.0
2	28.1	28.1	0.0
3	79.2	79.1	+0.1
4	39.1	39.1	0.0
5	51.1	51.1	0.0
6	19.1	19.1	0.0
7	27.8	27.8	0.0
8	133.7	133.7	0.0
9	134.2	134.1	+0.1
10	37.4	37.4	0.0
11	21.7	21.7	0.0
12	31.0	31.0	0.0
13	44.3	44.2	+0.1
14	50.2	50.2	0.0
15	29.9	29.9	0.0
16	28.3	28.3	0.0
17	49.8	49.8	0.0
18	15.7	15.7	0.0
19	20.3	20.3	0.0
20	36.0	36.0	0.0
21	19.1	19.1	0.0
22	35.6	35.5	+0.1
23	24.9	24.9	0.0
24	125.4	125.4	0.0
25	131.0	131.1	–0.1
26	17.8	17.7	+0.1
27	25.9	25.9	0.0
28*	28.2	28.2	0.0
29*	15.8	15.8	0.0
30	24.6	24.6	0.0

**Note: Carbon numbering of this reference puts C28 on the β face of the molecule and C29 on the α face; for consistency, we changed the carbon numbering of the reference to match typical numbering convention



Reduction of enone **19 was carried out through a dissolving metal reduction; the resulting two products (**21** and **S13**) were easily separated. The undesired dione **S13** was subjected to $NaBH_4$ reduction to access the desired alcohol **21**. The reported yield reflects the combined yields of the dissolving metal reduction and $NaBH_4$ reduction to give the desired alcohol **21.**



Synthesis of alcohol 21 and ketone S13: To a round bottom flask equipped with a stirring solution of NH_3 (3 mL) at –78 °C was added Li^0 metal (2 mg, 0.153 mmol, 10 equiv). The resulting mixture became a dark blue color and after 10 minutes of stirring, enone **19** (13.3 mg, 0.0307 mmol, 1 equiv) in THF (2 mL) was added. The resulting mixture was stirred at –78 °C for 5 minutes before saturated aqueous NH_4Cl was added (resulting in a clear solution). The mixture was warmed to room temperature and NH_3 was evaporated under a stream of N_2. The organic layer was extracted with EtOAc (x 3) and the combined organic layers were dried, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford alcohol **21** (7.0 mg, 0.0159 mmol, 53% yield) and dione **S13** (3.3 mg, 0.0075 mmol, 25%) as white solids.

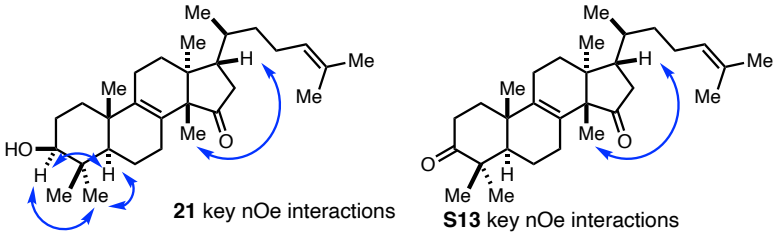
Analytical data for alcohol 21:

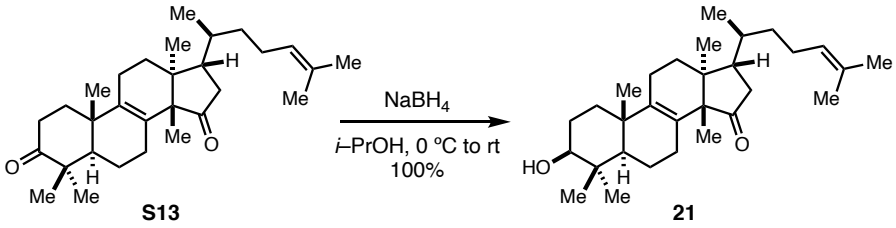
TLC (SiO_2) R_f = 0.40 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.08 (app t, *J* = 7.5 Hz, 1H), 3.23 (dd, *J* = 11.9, 4.5 Hz, 1H), 2.58 (dd, *J* = 18.8, 8.5 Hz, 1H), 2.48 – 2.43 (m, 1H), 2.10 – 1.95 (m, 3H), 1.91 –1.85 (m, 3H), 1.81 – 1.70 (m, 9H), 1.68 (s, 3H), 1.62 – 1.55 (m, 4H), 1.52 – 1.45 (m, 1H), 1.40 – 1.32 (m, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.96 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.6, 136.1, 131.7, 131.1, 124.7, 79.0, 50.8, 45.5, 43.3, 42.2, 39.0, 37.8, 36.4, 35.8, 35.4, 29.3, 28.3, 28.2, 27.9, 25.9, 24.9, 21.9, 21.5, 20.3, 19.0, 18.9, 17.8, 15.7, 15.3; **IR** (thin film, cm^{-1}): 3451, 2965, 1737, 1454, 1375, 1026, 480; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{49}O_2$ 441.3733; found, 441.3712; $[\alpha]_{589}^{20.5}$**:** –7.99 (*c* 0.35, $CHCl_3$).

Analytical data for ketone S13:

TLC (SiO_2) R_f = 0.59 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.07 (app t, *J* = 7.4 Hz, 1H), 2.62 – 2.50 (m, 3H), 2.49 – 2.42 (m, 2H), 2.11 – 1.97 (m, 4H), 1.91 – 1.85 (m, 4H), 1.80 (q, *J* = 8.9, 8.4 Hz, 1H), 1.73 – 1.66 (m, 5H), 1.65 – 1.61 (1H), 1.60 (s, 3H), 1.52 – 1.41 (m, 2H), 1.38 – 1.28 (m, 2H), 1.14 (s, 3H), 1.09 (s, 3H), 1.05 (s, 6H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.82 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.9, 216.2, 134.6, 132.1, 131.6, 124.5, 51.2, 47.2, 45.4, 43.2, 42.1, 37.5, 36.2, 35.6, 35.5, 34.4, 29.7, 29.1, 27.9, 26.8, 25.7, 24.8, 24.5, 21.5, 21.3, 21.1,

20.1, 19.8, 18.9, 17.7, 15.3; **IR** (thin film, cm^{-1}): 2925, 1737, 1705, 1455, 1380, 480; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{47}O_2$ 439.3576; found, 439.3564; $[\alpha]_{589}^{20.2}$**:** +27.19 (*c* 0.165, $CHCl_3$).



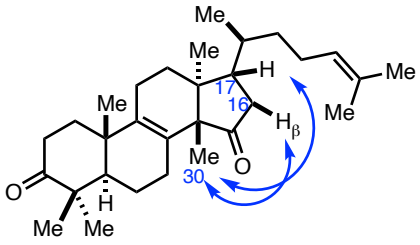


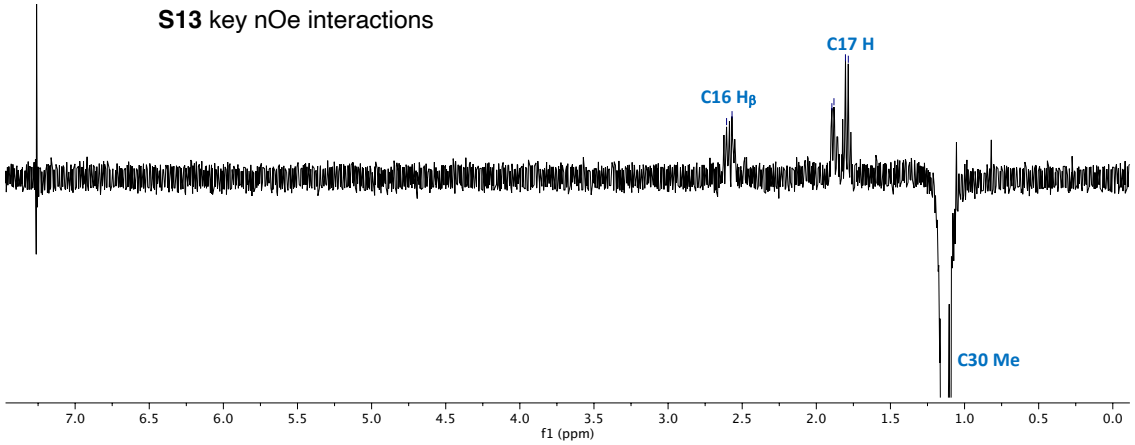
Synthesis of alcohol 21: To a stirring solution of dione **S13** (3.3 mg, 0.0075 mmol, 1 equiv) in *i*–PrOH (2 mL) at 0 °C was added $NaBH_4$ (1.0 mg, 0.026 mmol, 3.5 equiv). The mixture was warmed to room temperature and monitored by TLC, after 3 hours the reaction was judged to be complete. The reaction mixture was then diluted with EtOAc and washed with dilute HCl (0.2M). The organic layer was dried, filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford alcohol **21** (3.3 mg, 0.0075 mmol, 100% yield).

Analytical data for alcohol 21:

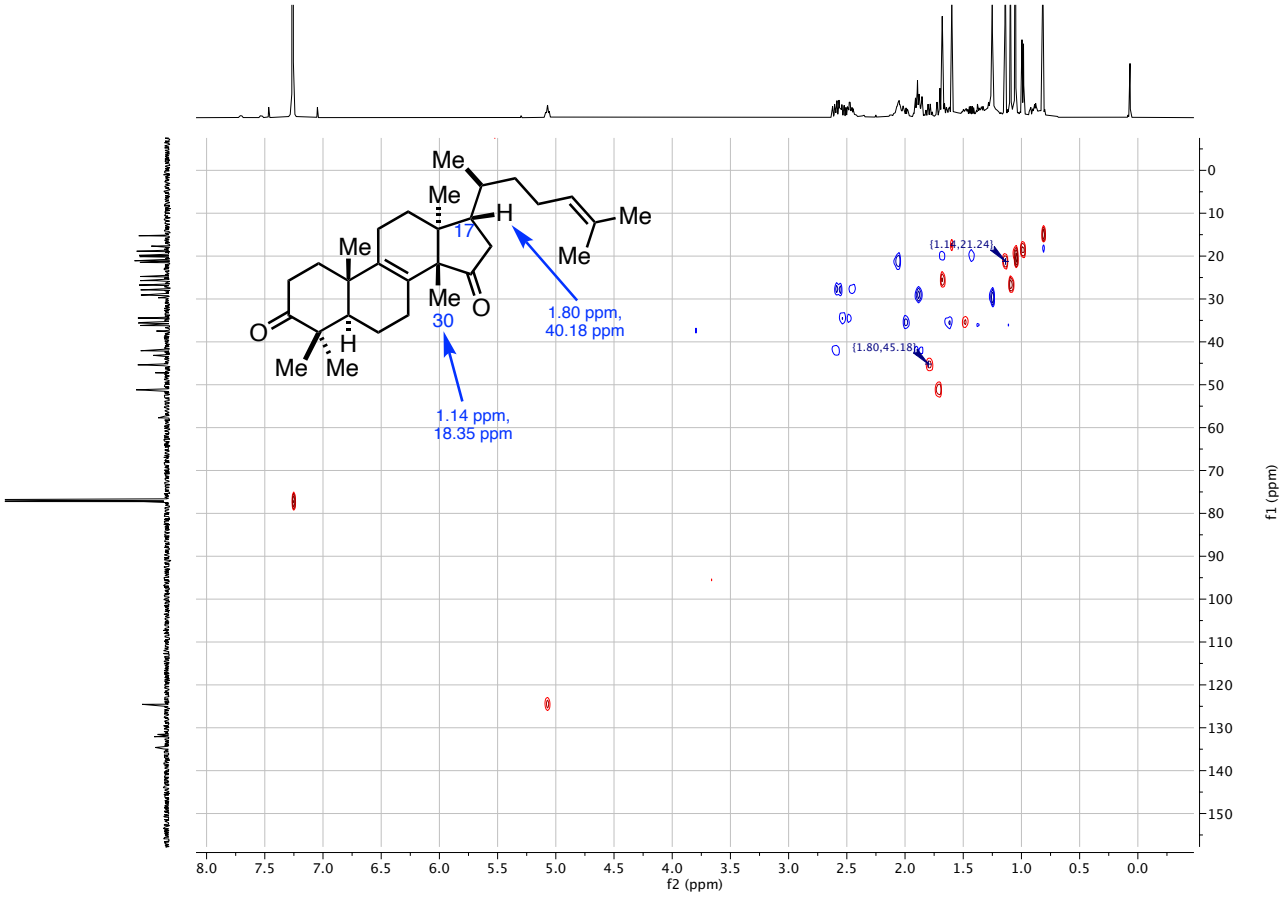
TLC (SiO_2) R_f = 0.40 (hexanes–ethyl acetate, 70:30); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.08 (app t, *J* = 7.5 Hz, 1H), 3.23 (dd, *J* = 11.9, 4.5 Hz, 1H), 2.58 (dd, *J* = 18.8, 8.5 Hz, 1H), 2.48 – 2.43 (m, 1H), 2.10 – 1.95 (m, 3H), 1.91 –1.85 (m, 3H), 1.81 – 1.70 (m, 9H), 1.68 (s, 3H), 1.62 – 1.55 (m, 4H), 1.52 – 1.45 (m, 1H), 1.40 – 1.32 (m, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.96 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.6, 136.1, 131.7, 131.1, 124.7, 79.0, 50.8, 45.5, 43.3, 42.2, 39.0, 37.8, 36.4, 35.8, 35.4, 29.3, 28.3, 28.2, 27.9, 25.9, 24.9, 21.9, 21.5, 20.3, 19.0, 18.9, 17.8, 15.7, 15.3; **IR** (thin film, cm^{-1}): 3451, 2965, 1737, 1454, 1375, 1026, 480; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{49}O_2$ 441.3733; found, 441.3712; $[\alpha]_{589}^{20.5}$**:** –7.99 (*c* 0.35, $CHCl_3$).

Key nOe data for ketone S13:

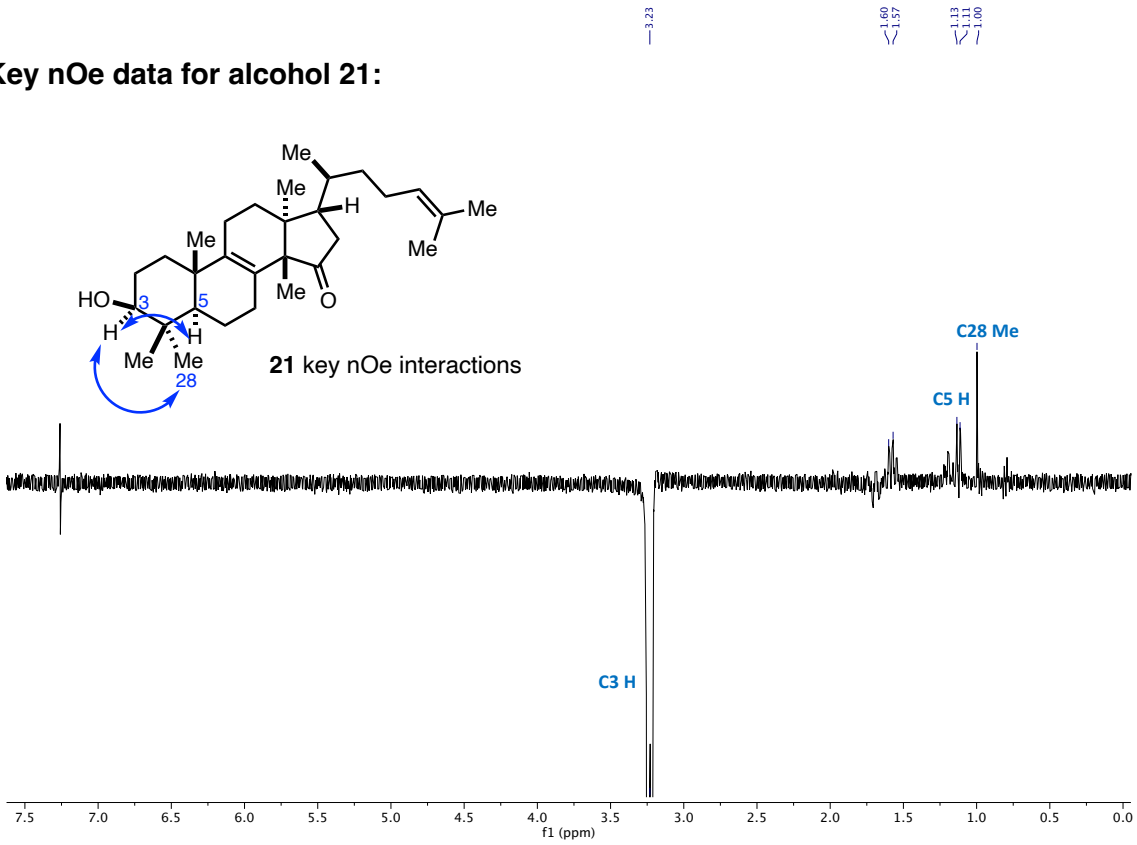


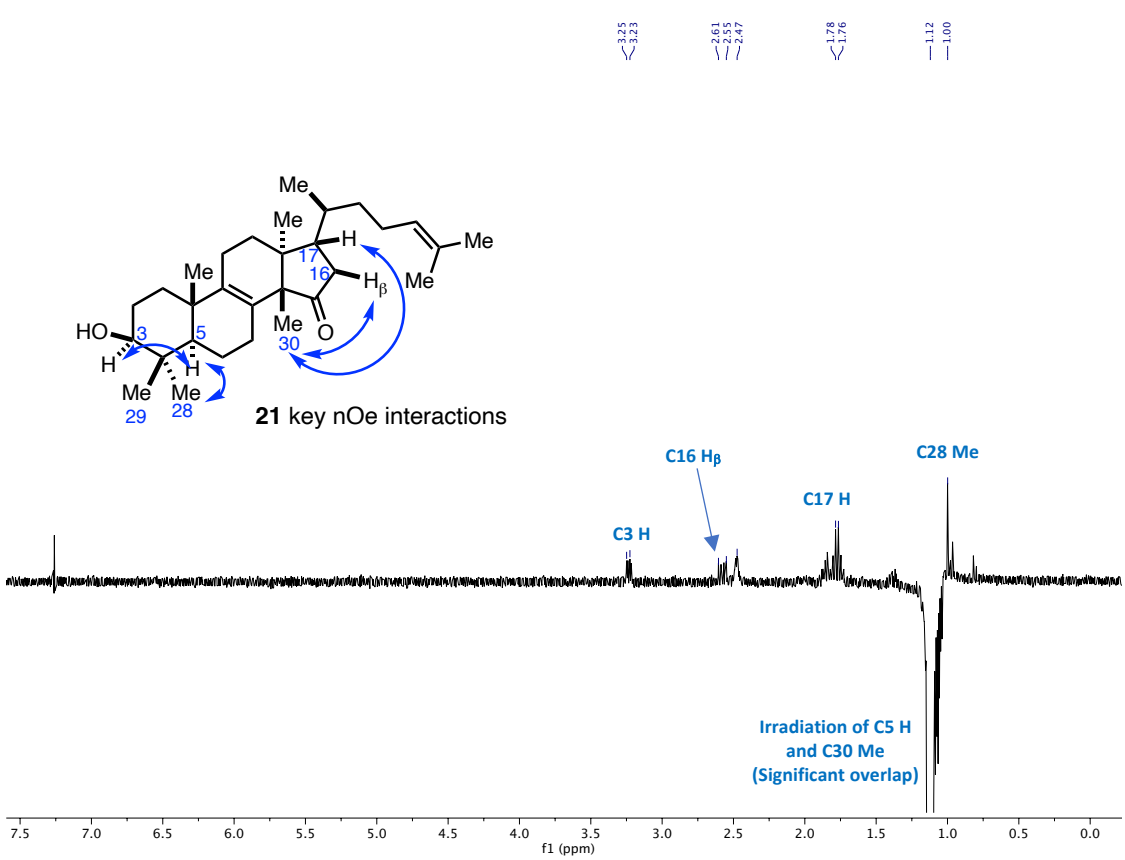


HSQC data for ketone S13:

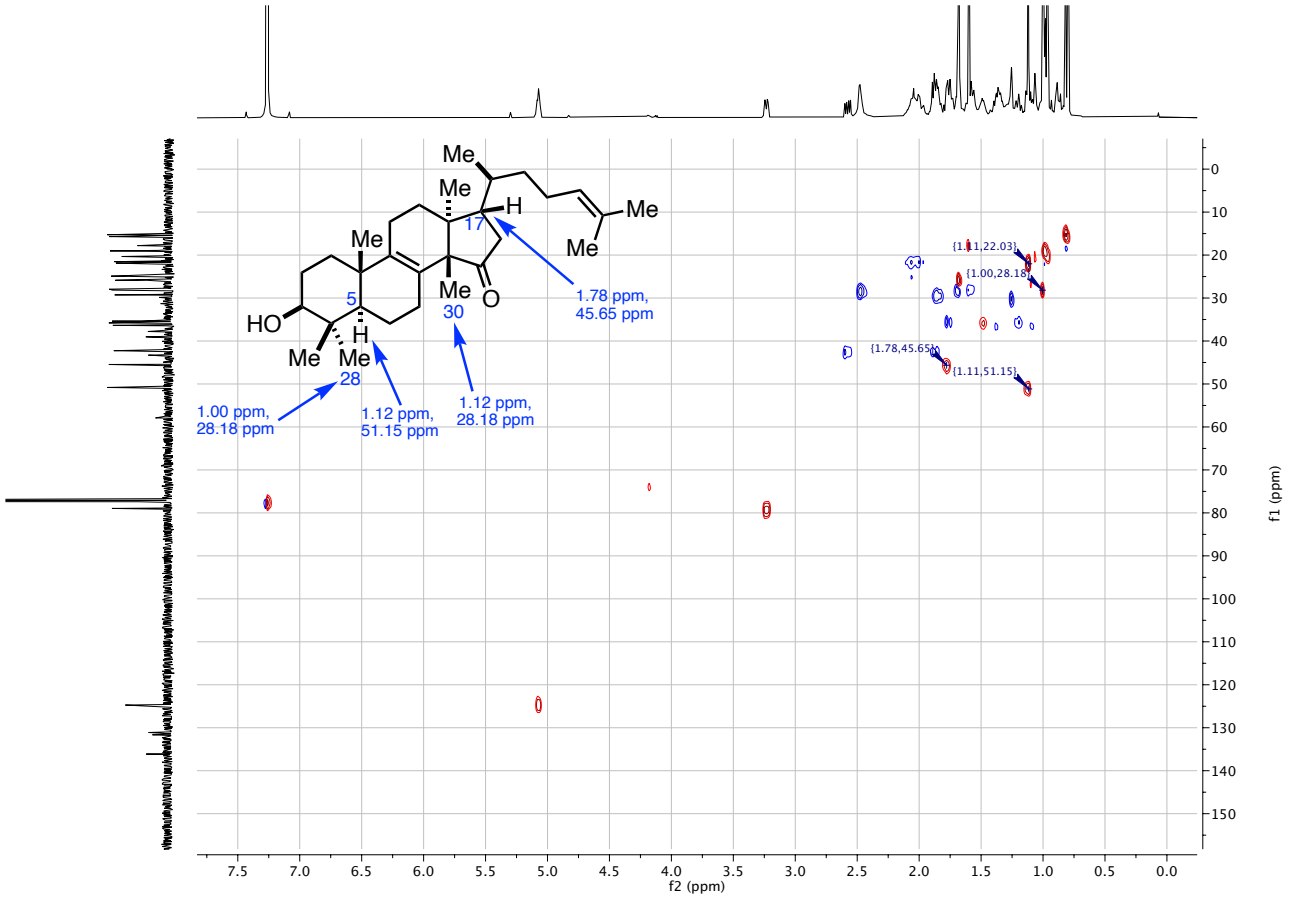


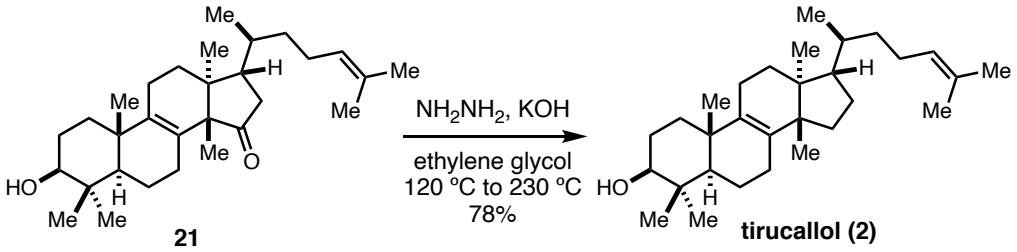
Key nOe data for alcohol 21:





HSQC data for alcohol 21:





Synthesis of tirucallol (2): To a round bottom flask was added a solution of ketone **21** (8 mg, 0.0182 mmol, 1 equiv) in ethylene glycol (3 mL), KOH (38 mg, 0.68 mmol, 37 equiv) and $(N_2H_4)\bullet H_2O$ (15 μL, 0.4538 mmol, 25 equiv). The mixture was heated to 230 ºC in a sand bath and allowed to stir at this temperature for 72 hours. When the reaction was judged to be complete by TLC analysis, the reaction mixture was cooled to room temperature, diluted with EtOAc, washed with dilute HCl (0.2M) until a pH of 6 was obtained. The combined organic layers were dried, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel with 100:0 to 80:20 hexanes-ethyl acetate gradient elution to afford tirucallol (**2**) (6 mg, 0.0141 mmol, 78% yield).

Analytical data for tirucallol (2):

TLC (SiO_2) R_f = 0.49 (hexanes–ethyl acetate, 80:20); **^{1}H NMR** (600 NMR, $CDCl_3$) δ 5.10 (app. t, J = 7.2 Hz, 1H), 3.24 (dd, J = 11.8, 4.7 Hz, 1H), 2.11 – 2.00 (m, 3 H), 1.96 – 1.82 (m, 4H), 1.79 – 1.66 (m, 6H), 1.68 (s, 3H), 1.63 – 1.36 (m, 4H), 1.60 (s, 3H), 1.35 – 1.16 (m, 4H). 1.12 (m, 1H), 1.07 – 1.00 m, 2H), 1.00 (s, 3H), 0.95 (s, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.87 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 134.1, 133.6, 131.0, 125.3, 79.0, 51.0, 50.1, 50.0, 44.1, 39.0, 37.3, 36.5, 36.4, 35.3, 30.8, 29.9, 29.8, 28.1, 28.0, 27.7, 25.8, 25.0, 24.4, 21.5, 20.2, 19.0, 18.7, 17.7, 15.6, 15.5. **IR** (thin film, cm^{-1}): 3330, 2926, 1453, 1027, 496; **HRMS** (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{51}O$ 427.3940; found 427.3928; $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20.4}}$**:** +4.44 (*c* 0.13, PhH).

^{13}CNMR was referenced to 77.20 ppm for the most downfield chloroform peak to match the reported literature reference peak[7]

Tirucallol ^{13}CNMR in $CDCl_3$

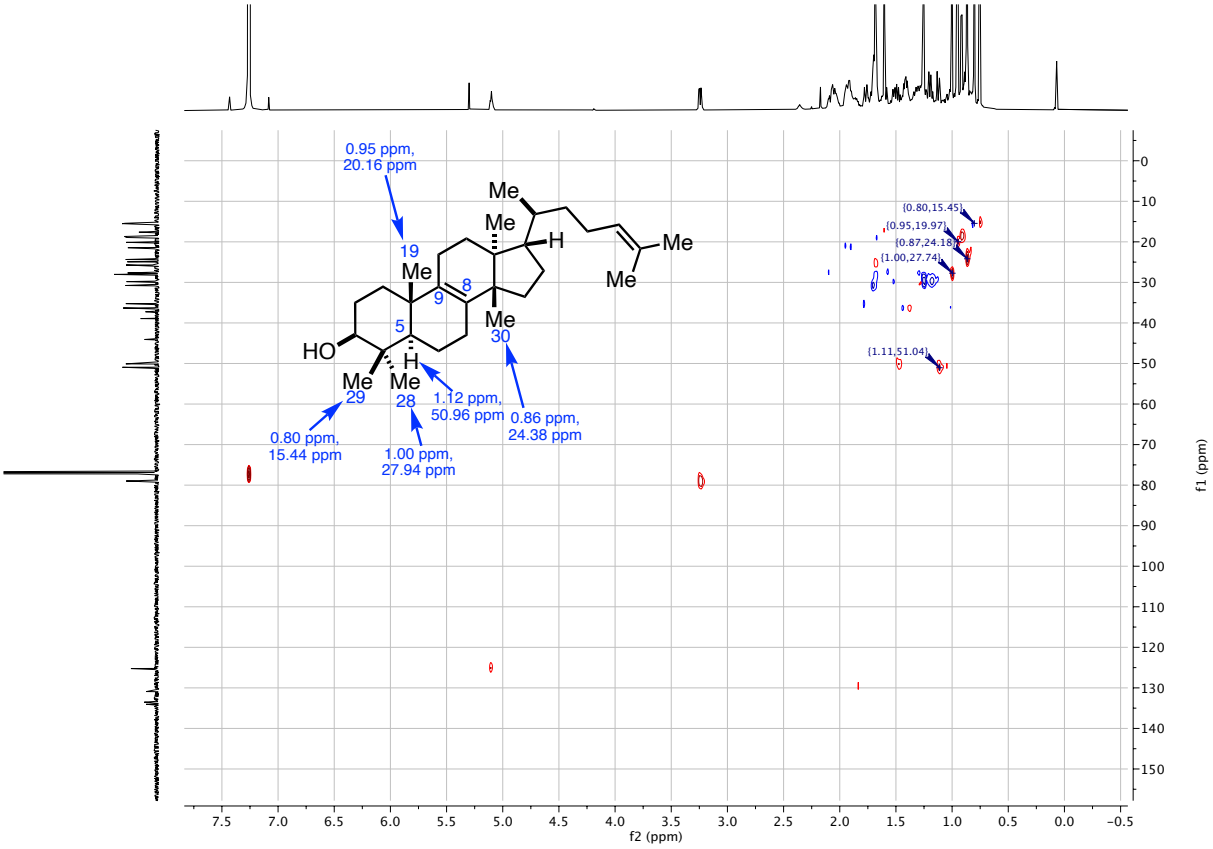
C#	Difference	Literature[7]	Experimental	Authentic Sample	Difference
1	–0.1	35.3	35.2	35.2	0.0
2	+0.1	27.9	28.0	28.0	0.0
3	0.0	79.0	79.0	79.0	0.0
4	0.0	38.9	38.9	38.9	0.0
5	–0.1	51.0	50.9	50.9	0.0
6	–0.1	19.0	18.9	18.9	0.0
7	0.0	27.7	27.7	27.7	0.0
8*	NA	134.1	133.5	133.5	0.0
9*	NA	133.5	134.0	134.0	0.0
10	–0.1	37.3	37.2 (37.24)	37.3 (37.25)	–0.1
11	–0.1	21.5	21.4	21.4	0.0
12	0.0	30.8	30.8	30.8	0.0
13	0.0	44.1	44.1	44.1	0.0
14	0.0	50.1	50.1	50.1	0.0
15*	+1.0	28.8	29.8	29.8	0.0
16	–0.1	28.0	27.9	27.9	0.0
17	–0.1	50.0	49.9	49.9	0.0
18	0.0	15.5	15.5	15.5	0.0
19	0.0	20.1	20.1	20.1	0.0
20	0.0	36.3	36.3	36.3	0.0
21	0.0	18.7	18.7	18.7	0.0
22	0.0	36.4	36.4	36.4	0.0
23	0.0	24.9	24.9	24.9	0.0
24	–0.1	125.3	125.2	125.2	0.0
25	0.0	130.9	130.9	130.9	0.0
26	0.0	17.6	17.6	17.6	0.0
27	0.0	25.7	25.7	25.7	0.0
28	+0.1	27.9	28.0	28.0	0.0
29	0.0	15.4	15.4	15.4	0.0
30	0.0	24.4	24.4	24.4	0.0

**C8 and C9 assigned based off key HMBC and nOe interactions

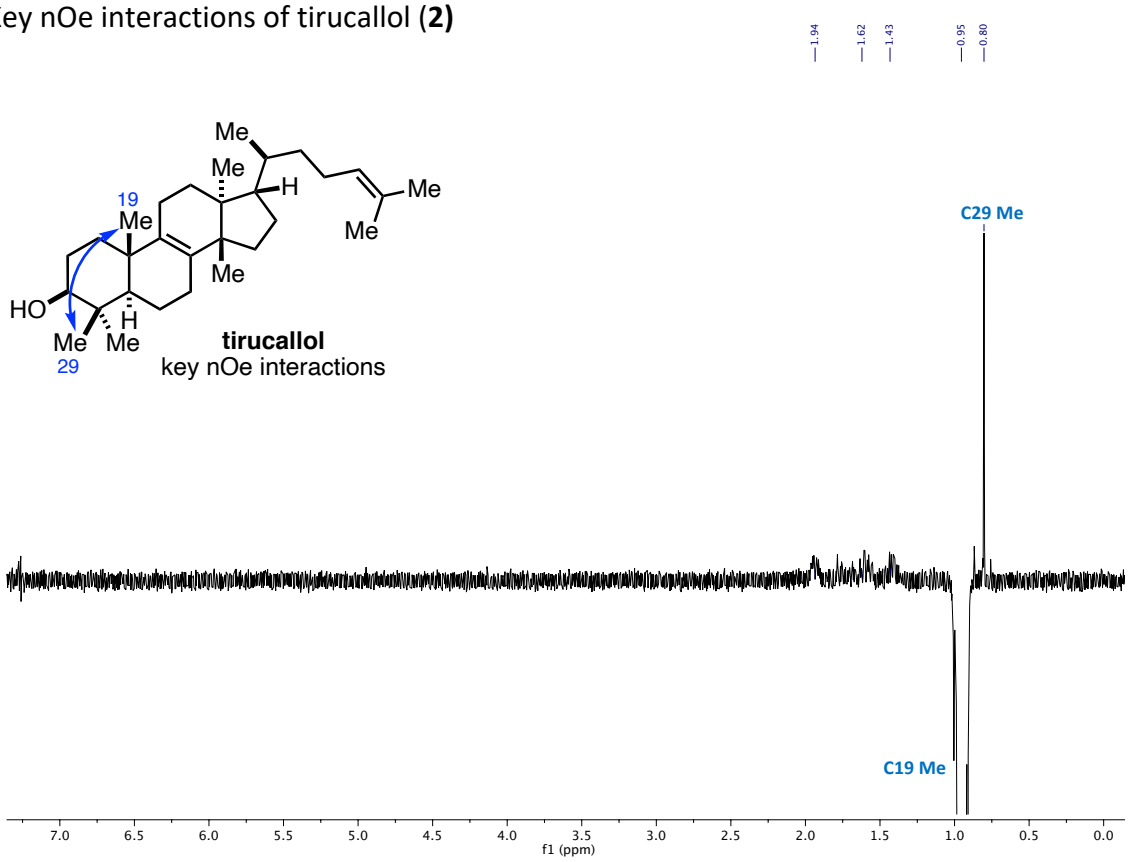
**Note that our experimental CNMR data for C15 varied from the previously reported value by 1.0 ppm. In addition, our assignment of C8 and C9 differed from reported literature assignment. To determine whether we had successfully made the natural product, an authentic sample of tirucallol was obtained from MedChemExpress. All CNMR shifts of the authentic sample matched the experimental values obtained, including C15 that differed from previously reported literature.

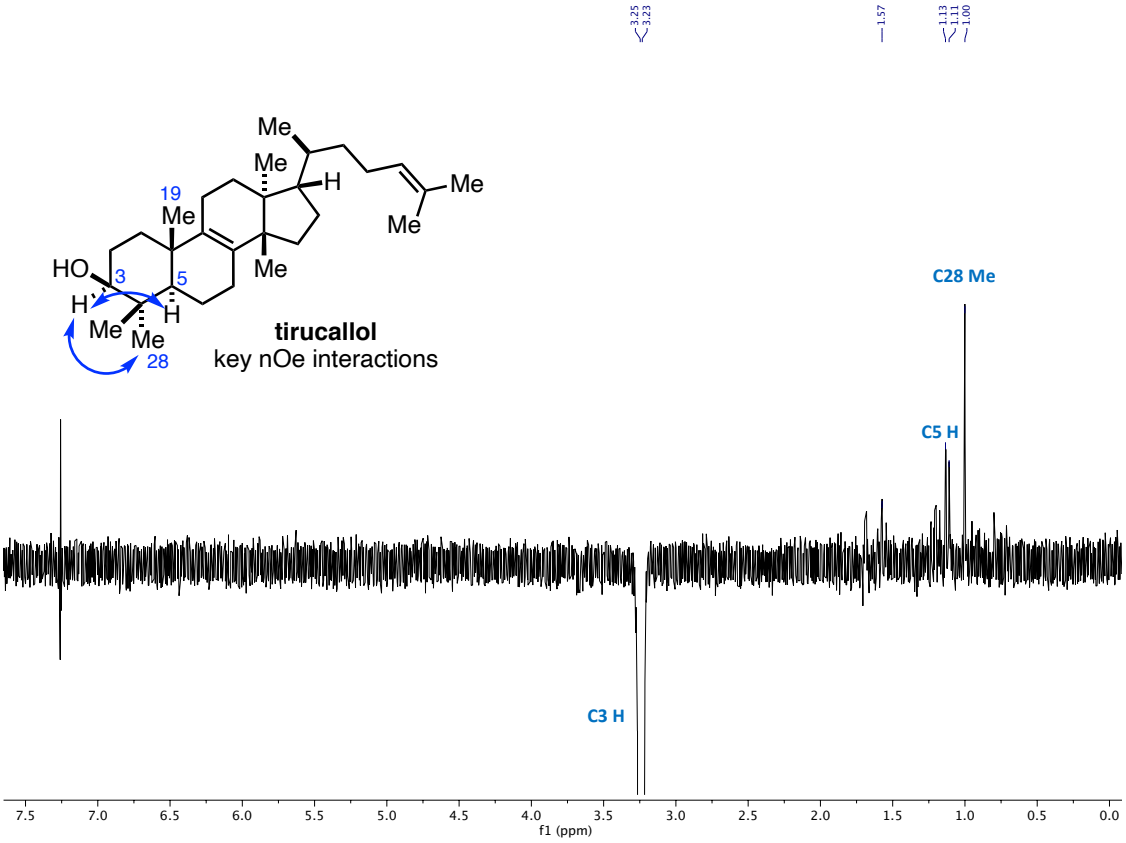
**Note: $CDCl_3$ referenced to 77.2 ppm on the most downfield chloroform peak to match literature reference peak

Key HSQC signals of tirucallol (**2**)



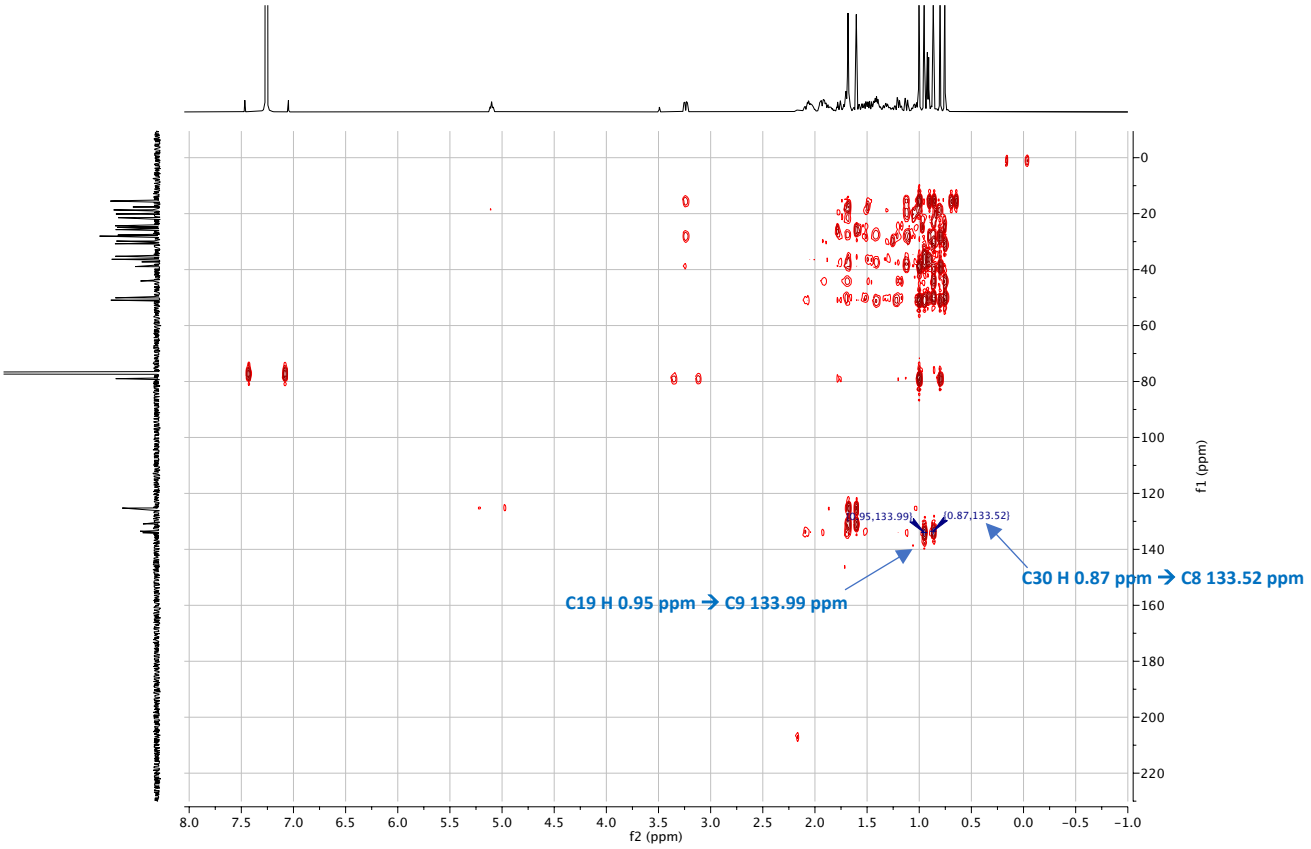
Key nOe interactions of tirucallol (**2**)

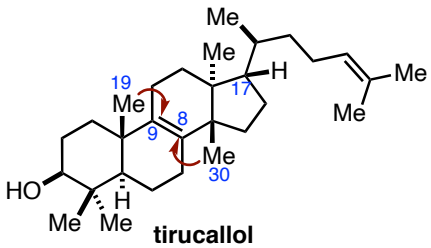




Assignment of C8 and C9

Key HMBC interactions of tirucallol (**2**)



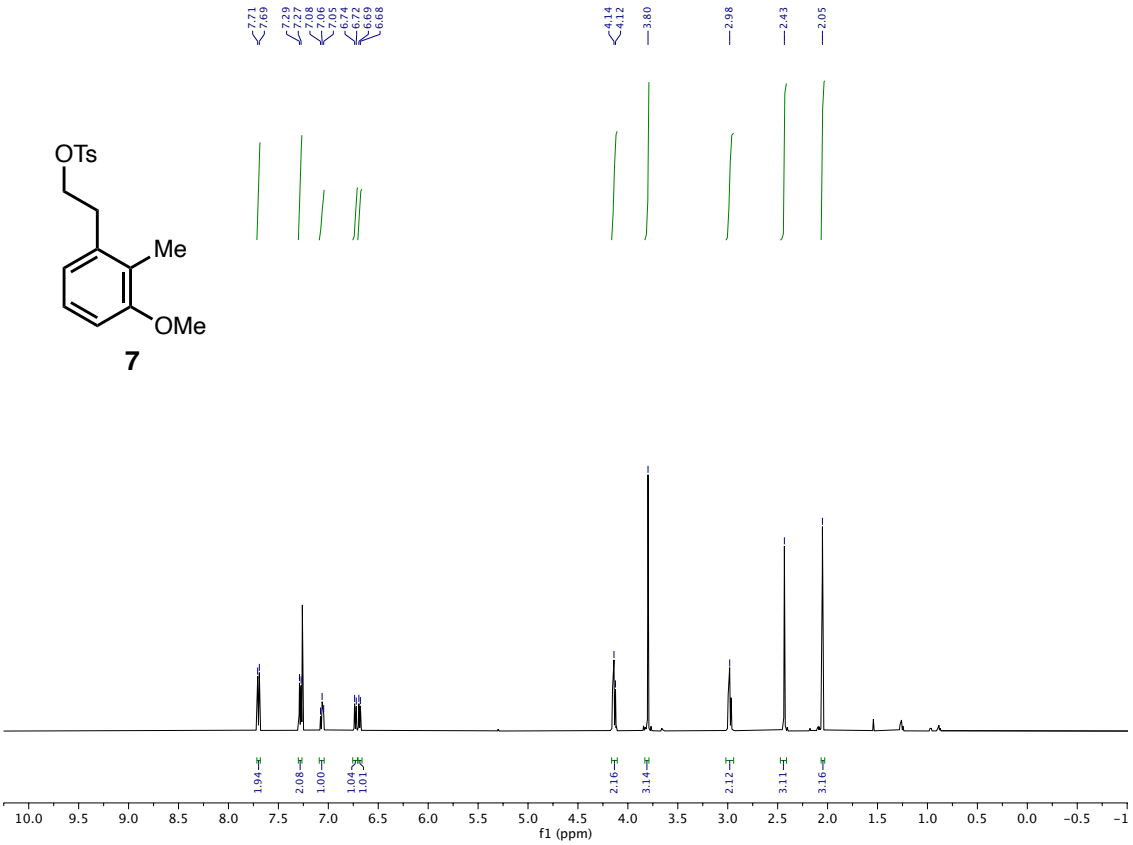


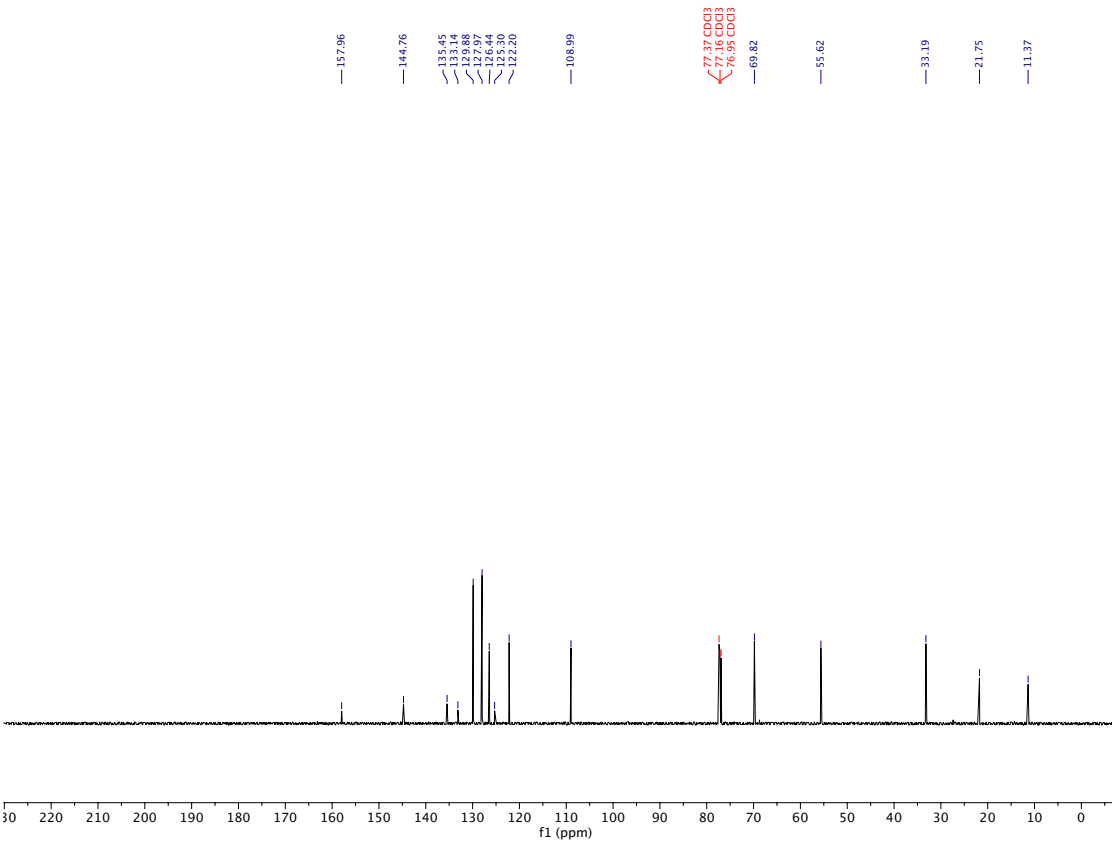
tirucallol

= HMBC interaciton

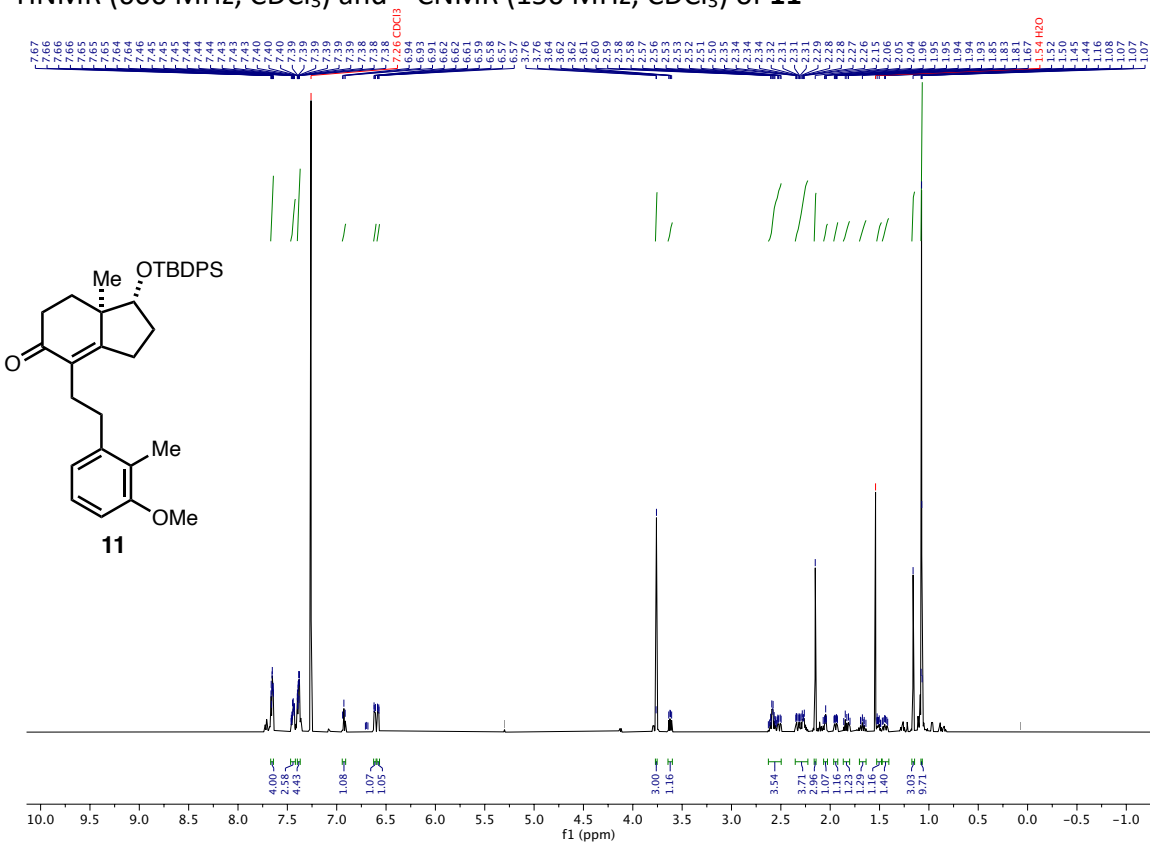
NMR Spectra

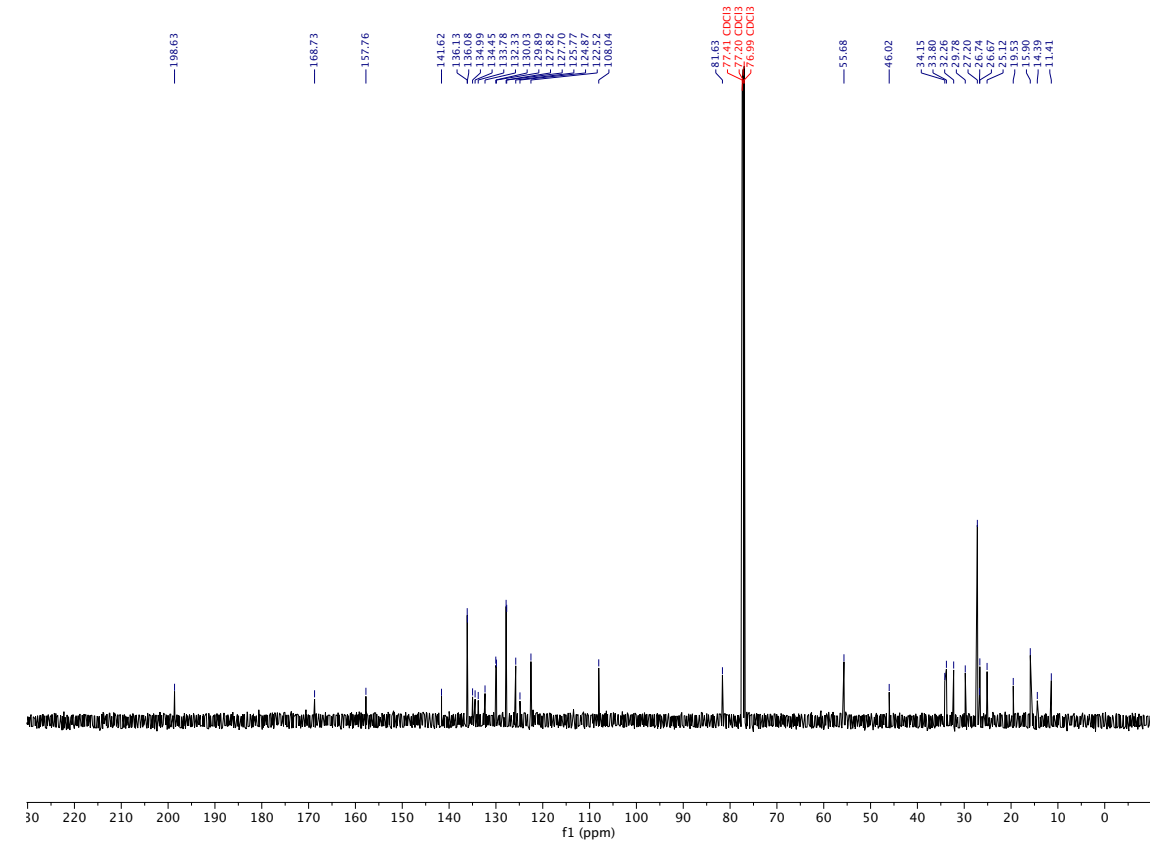
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **7**



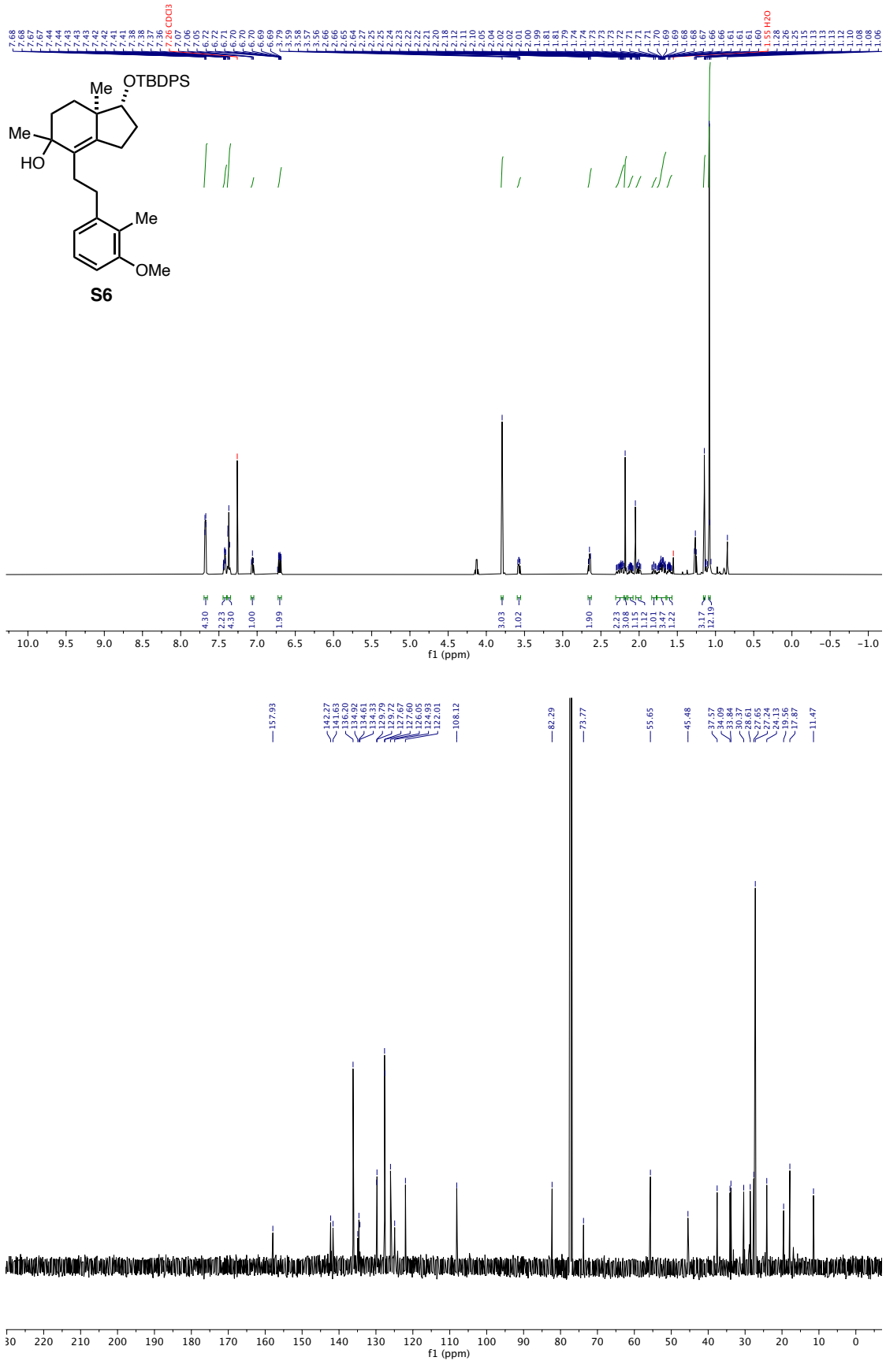


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **11**

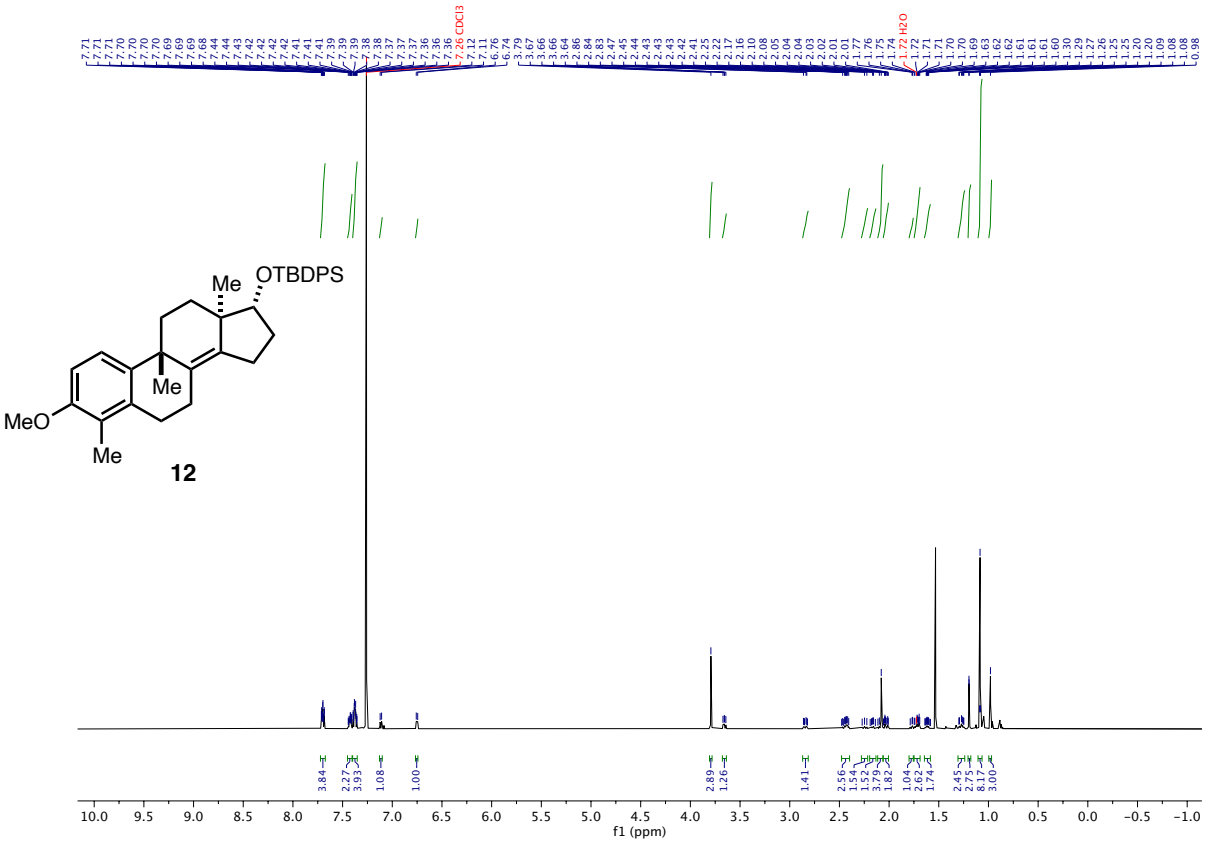


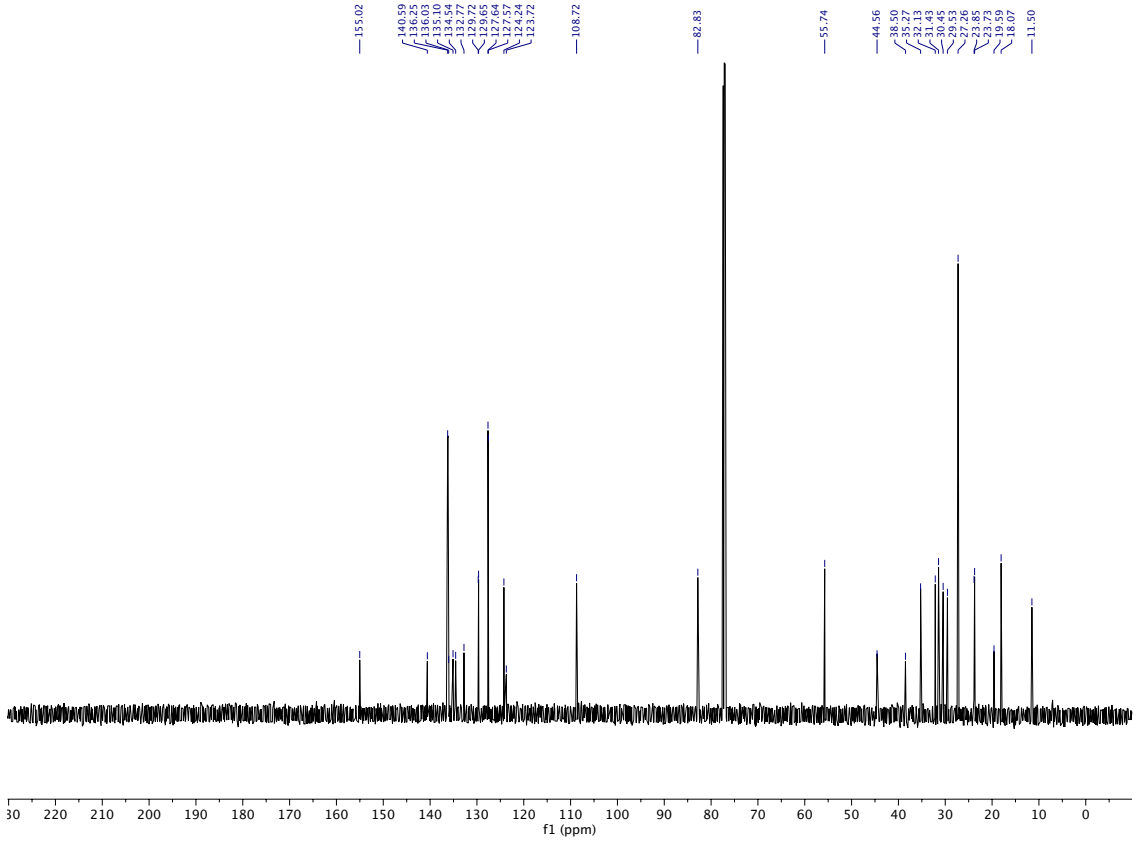


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S6**



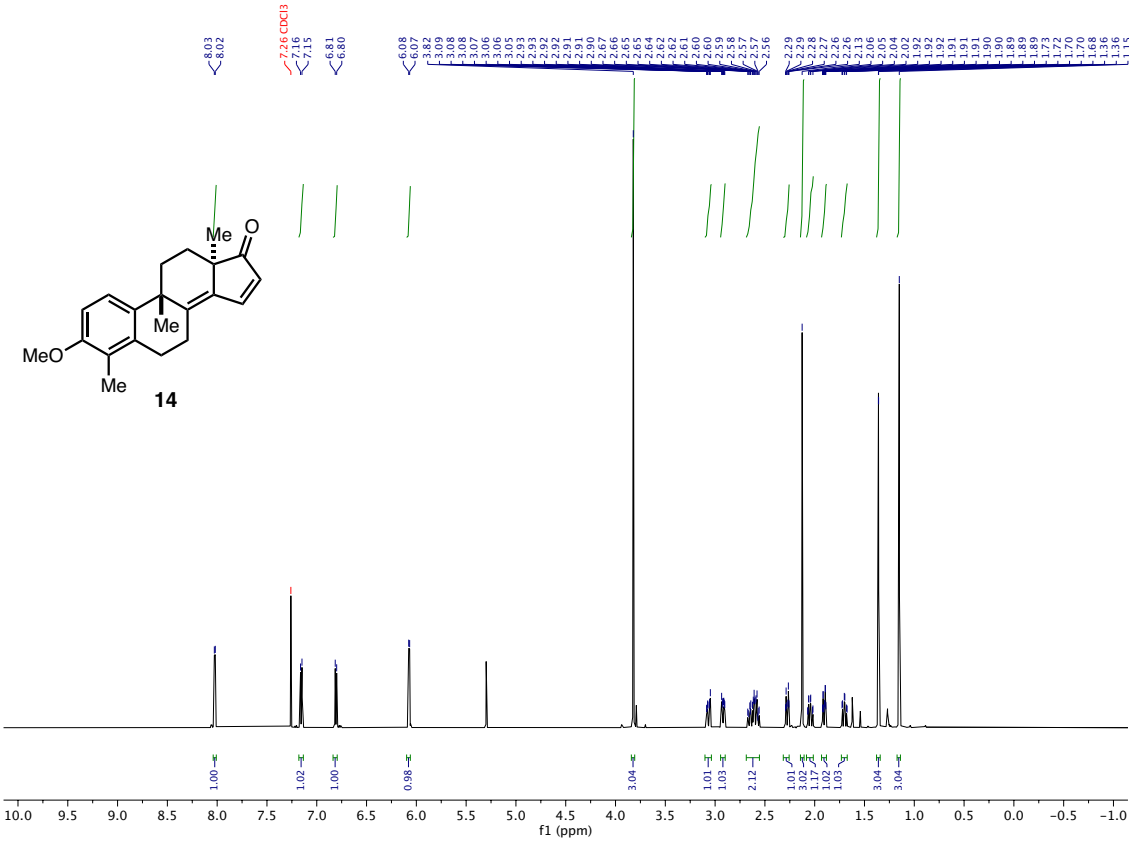
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **12**

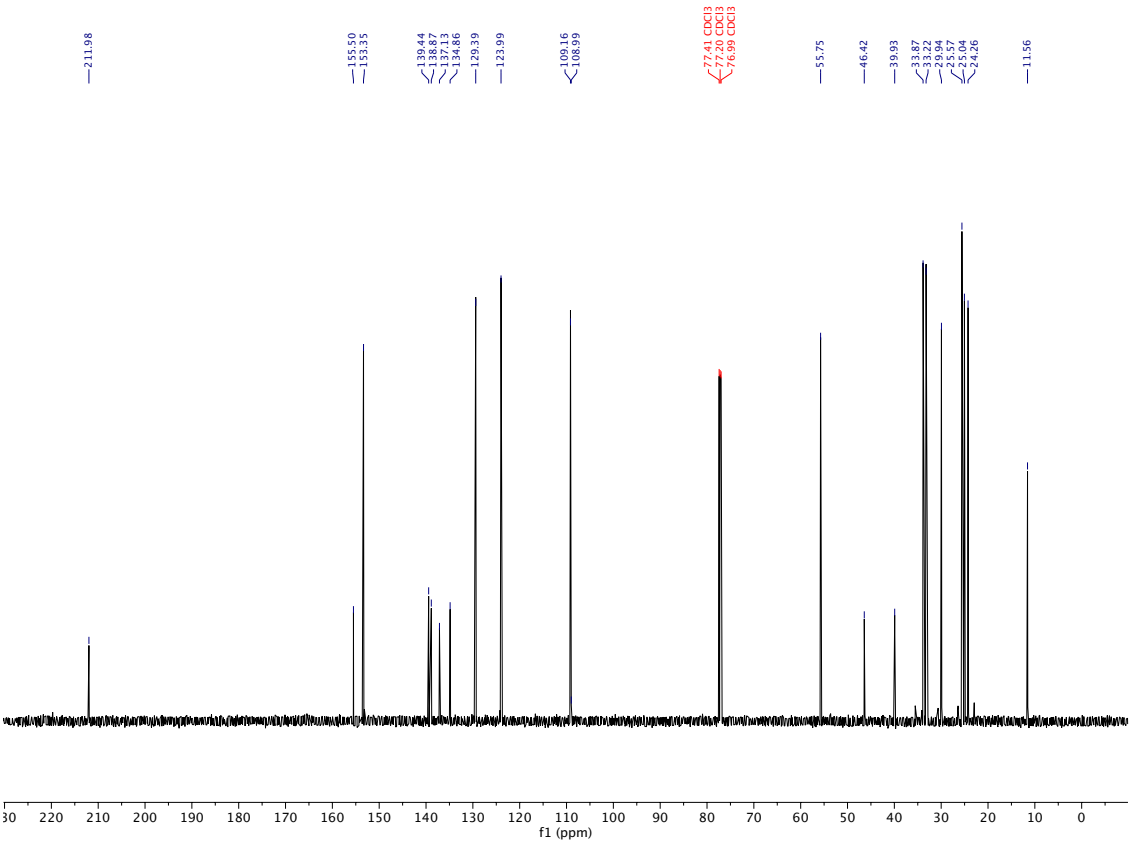




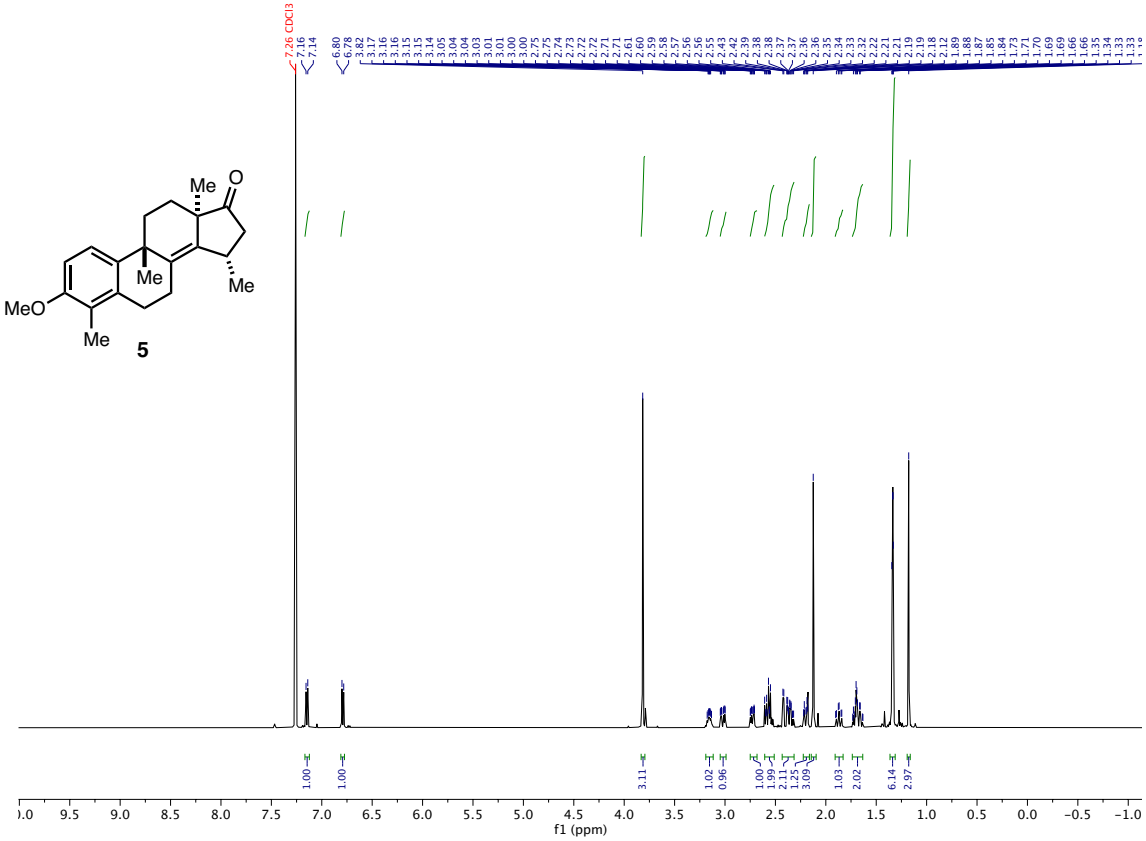
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **13**

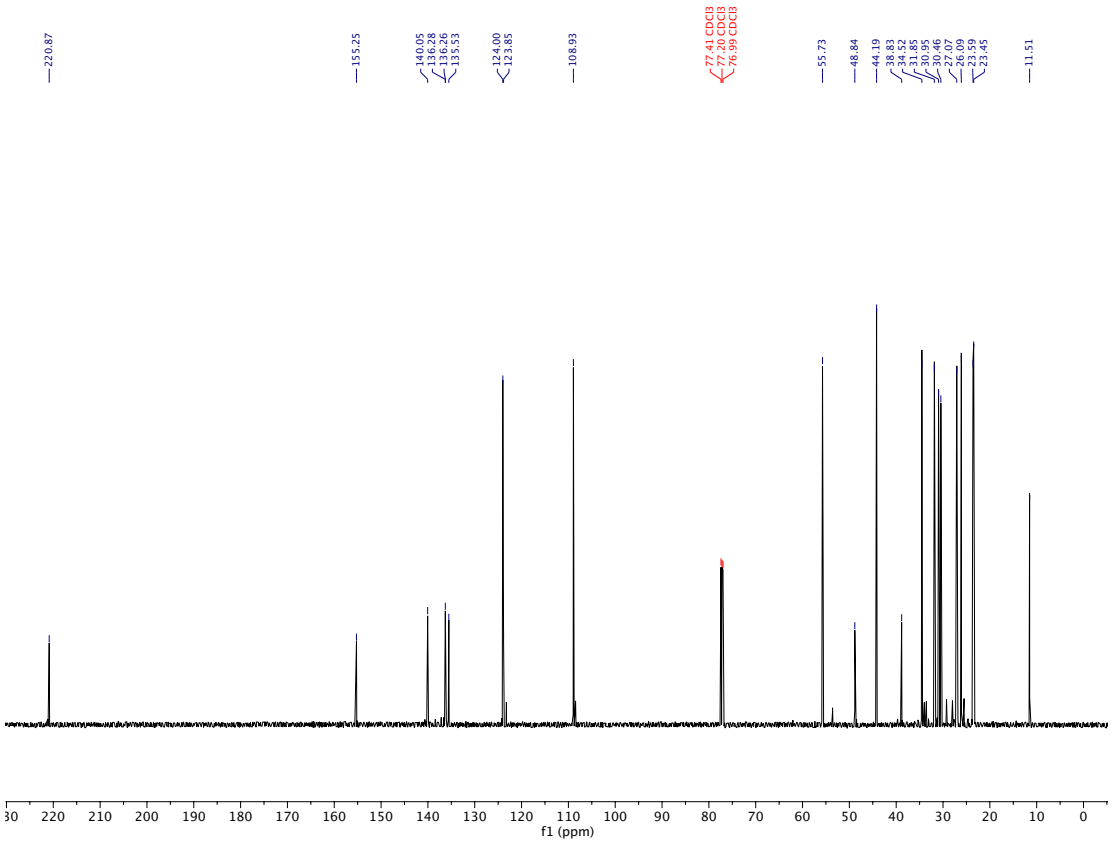
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **14**



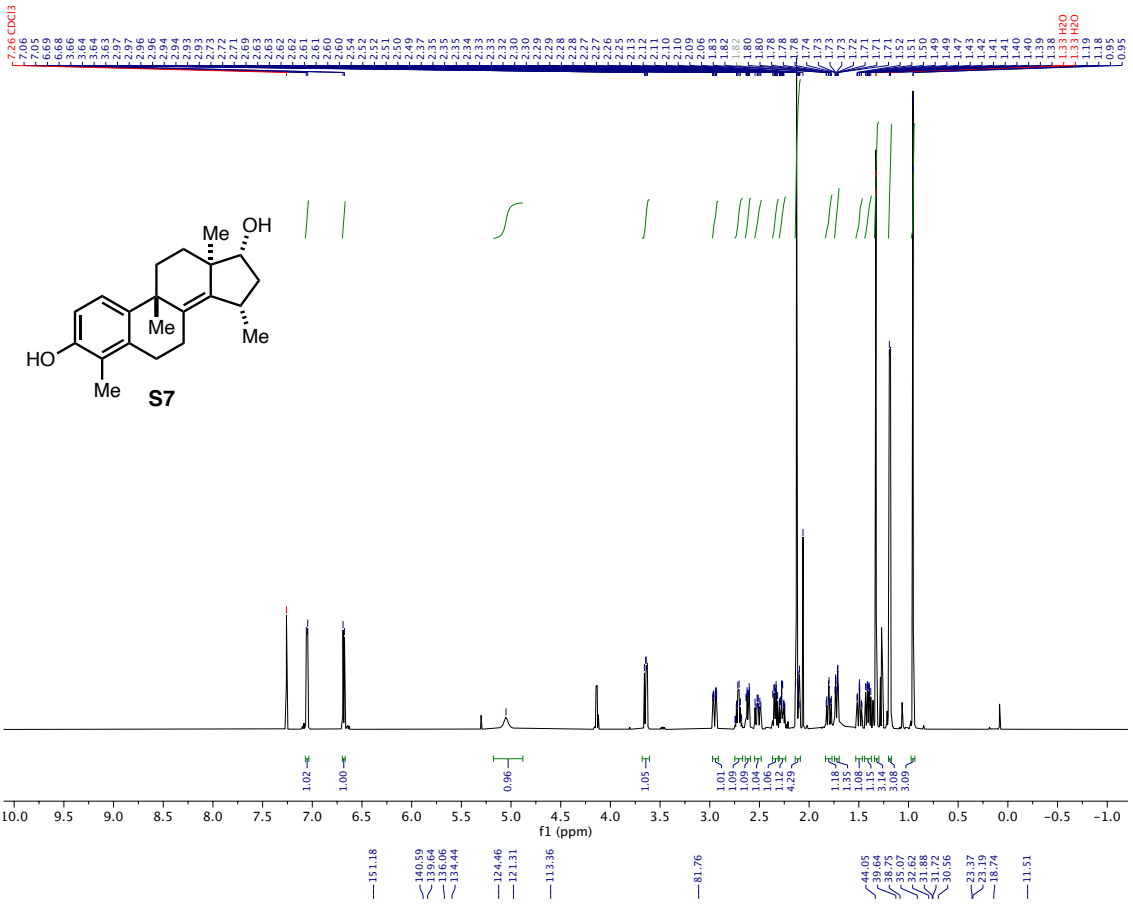


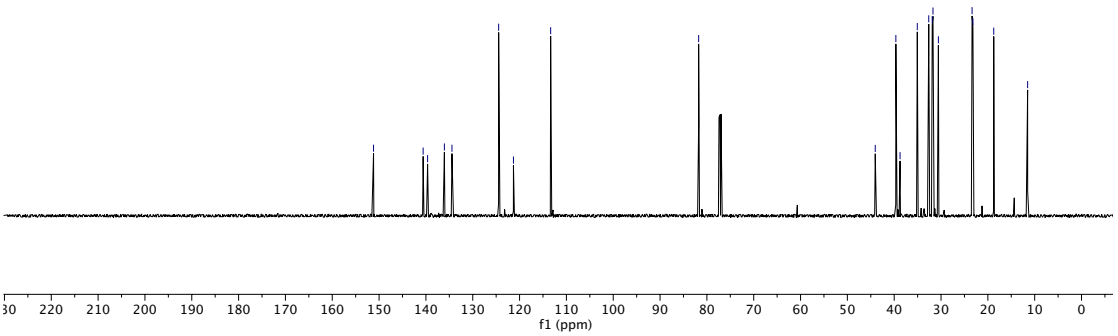
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **5**



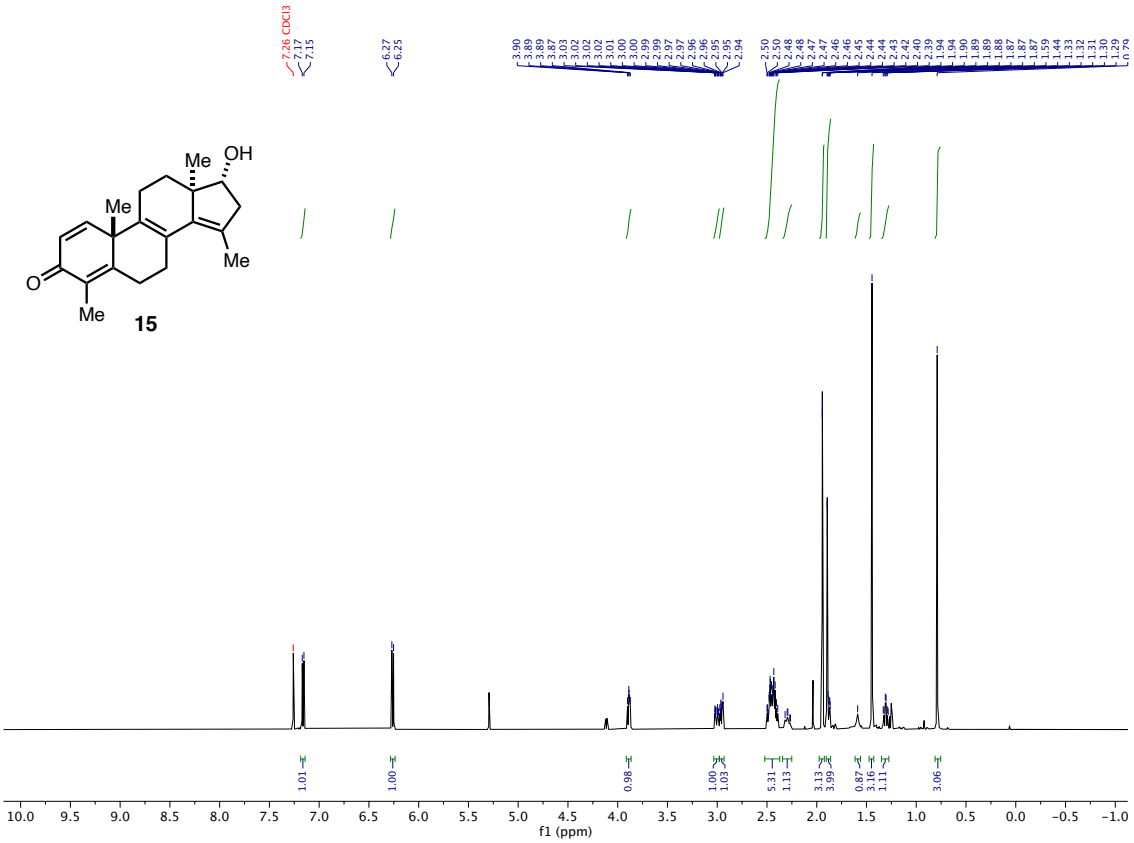


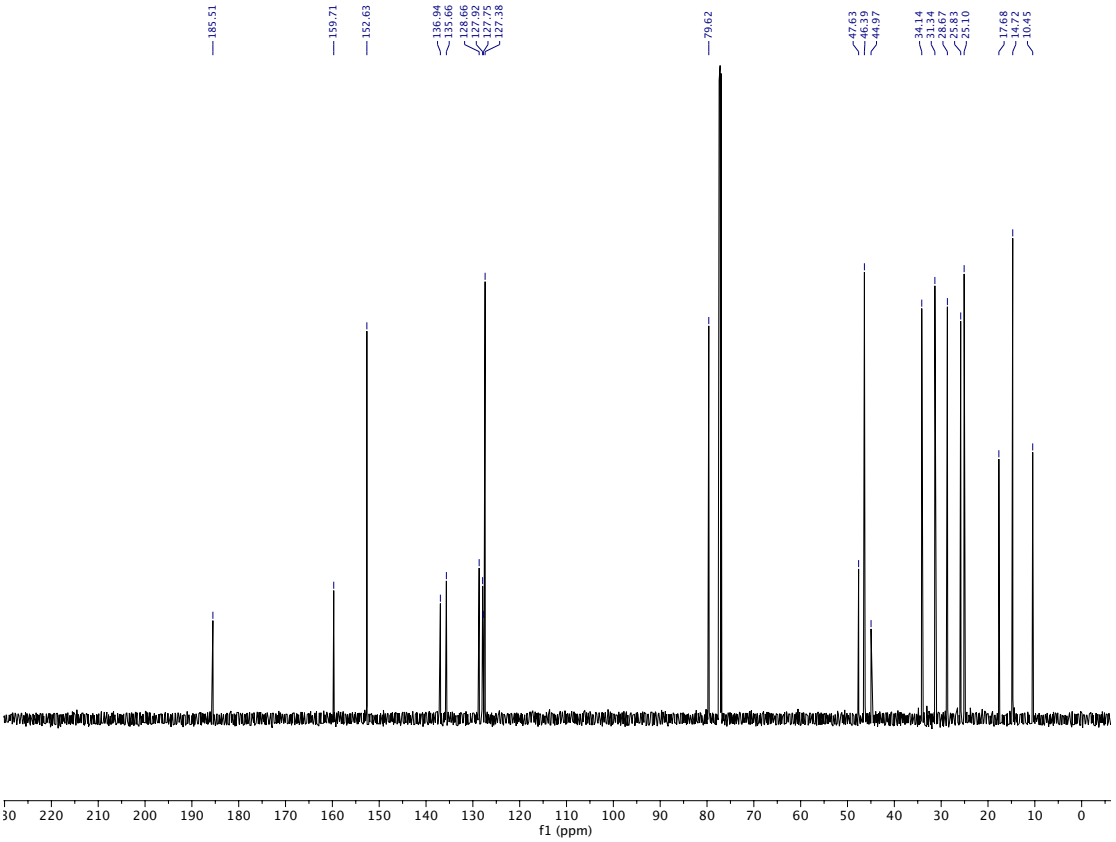
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S7**



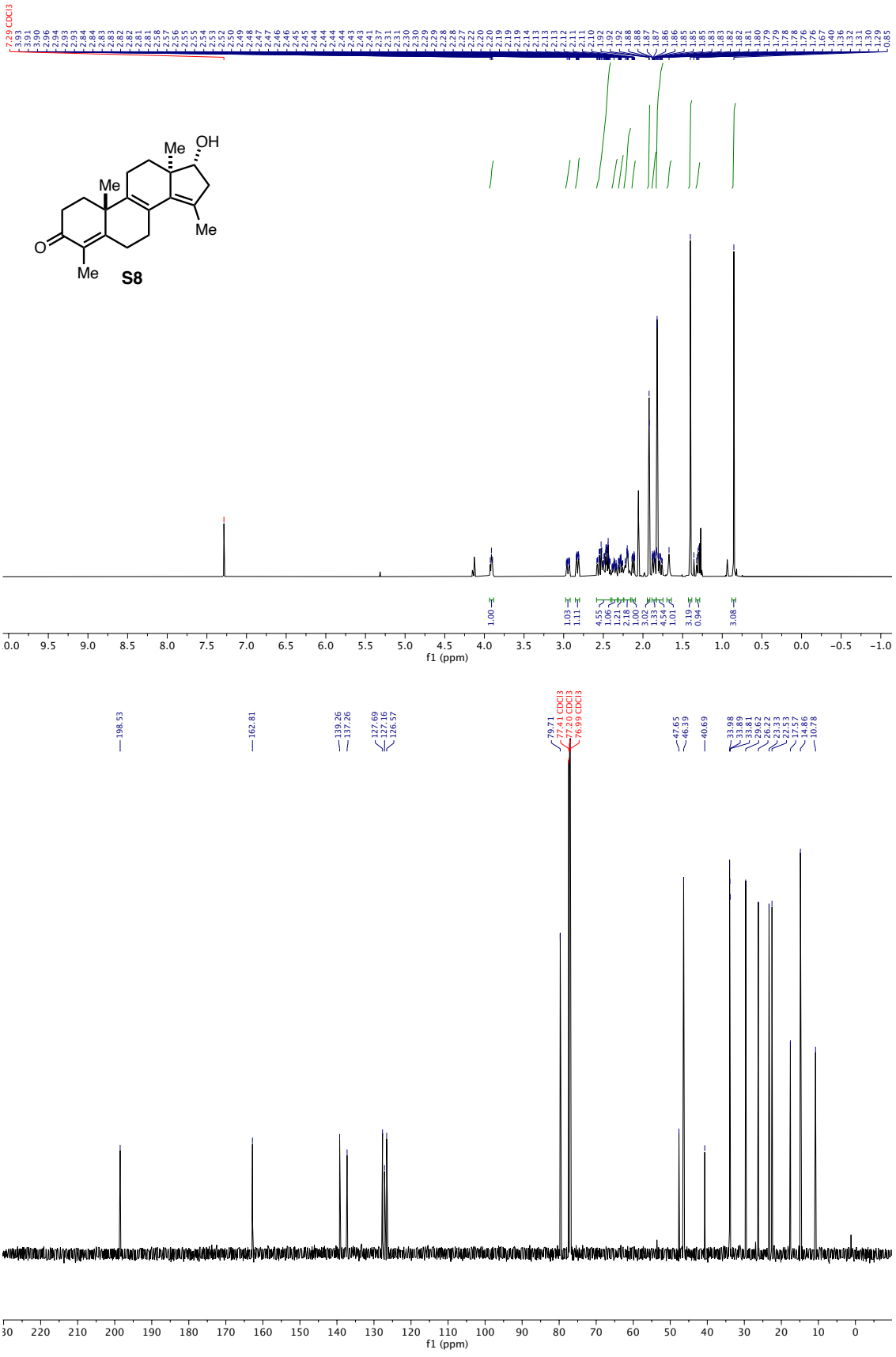


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **15**

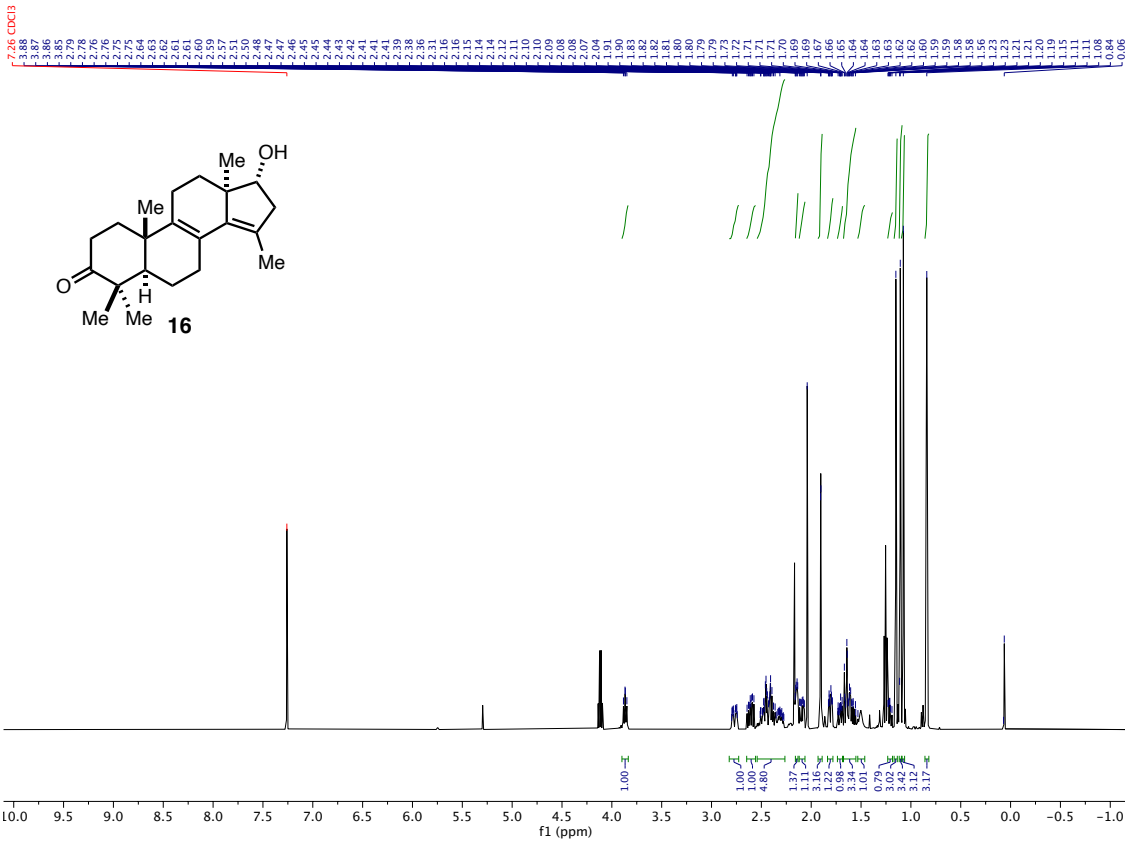


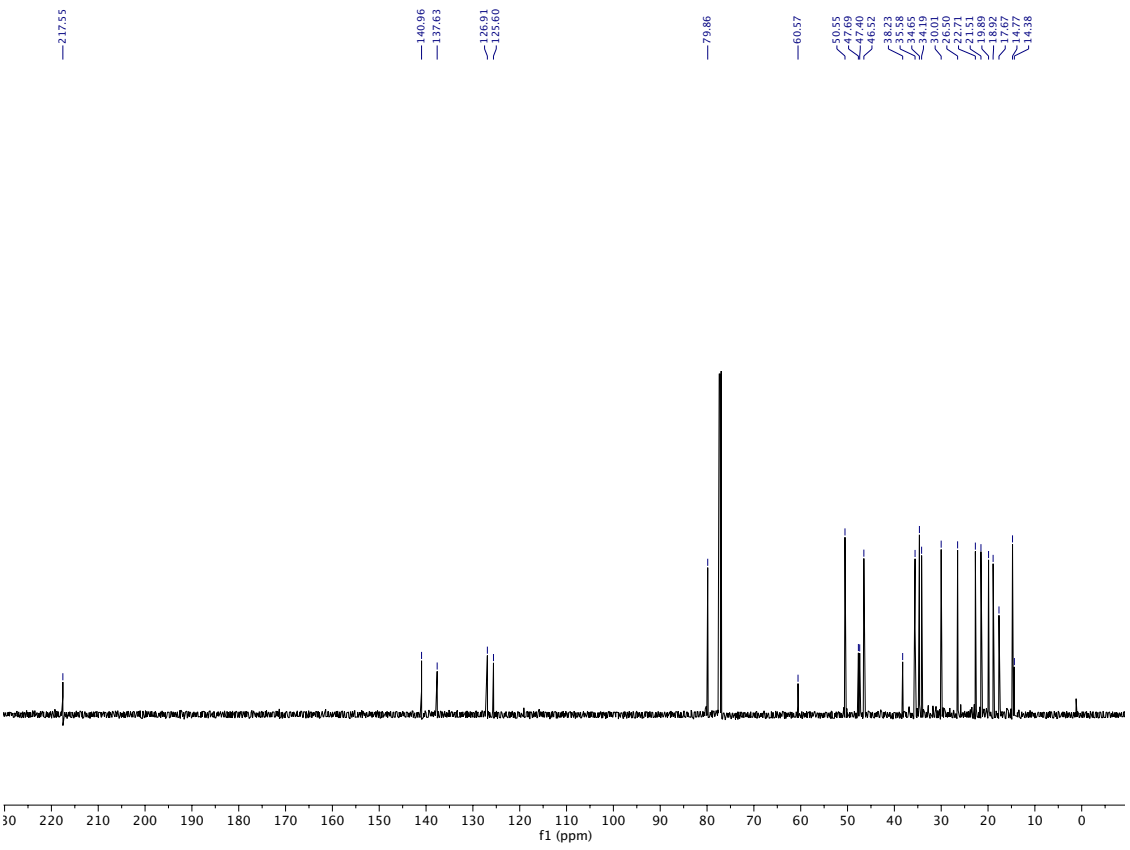


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S8**

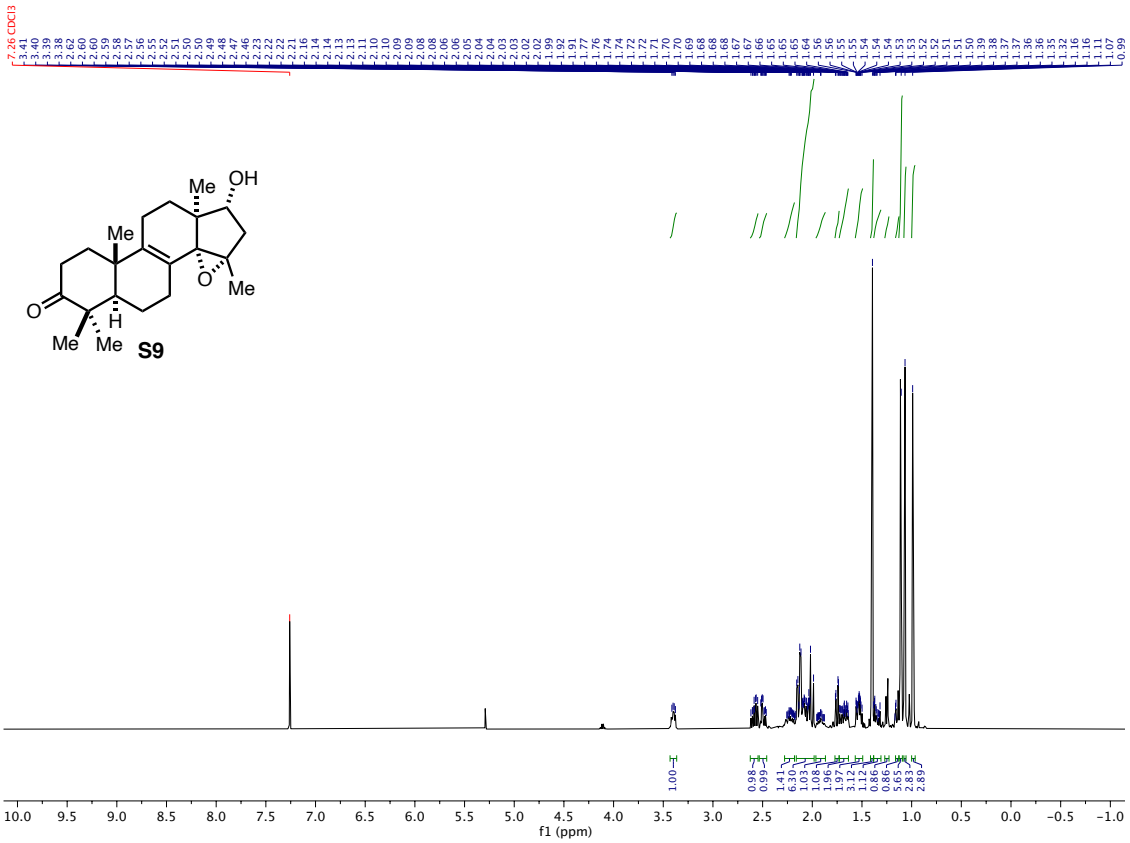


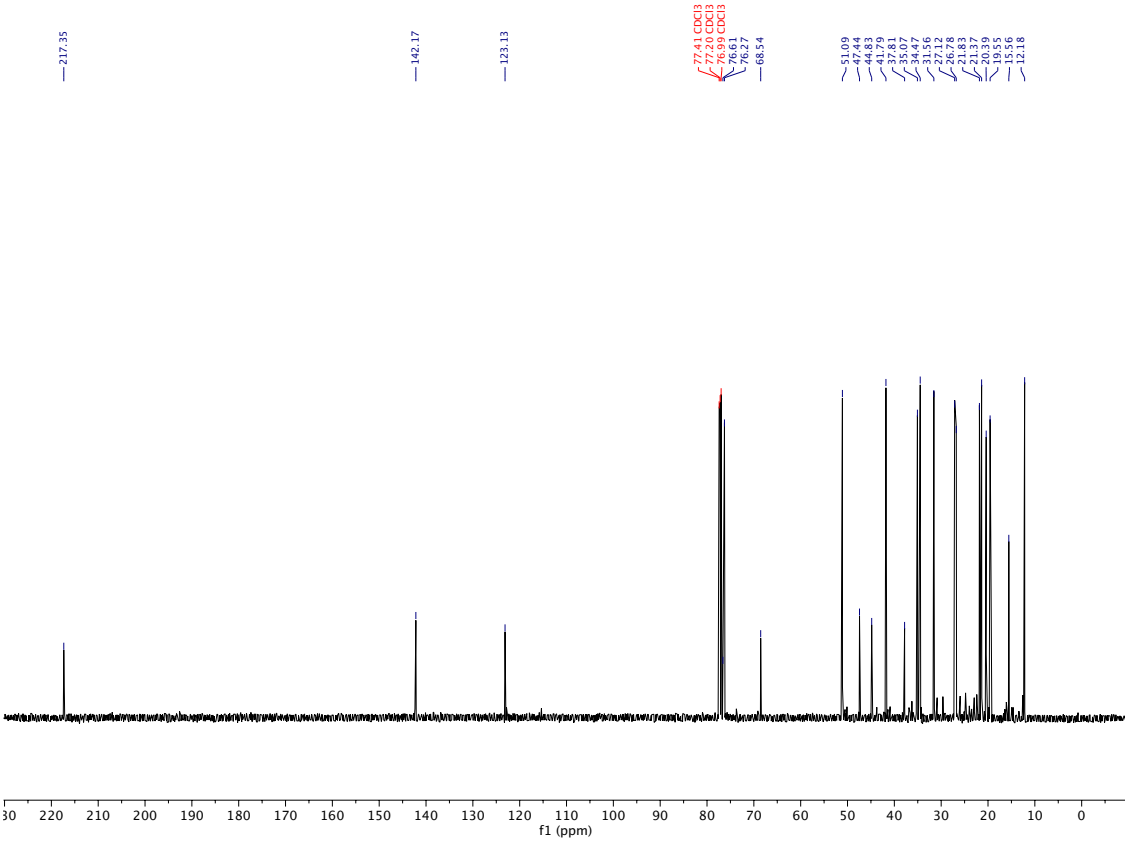
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **16**



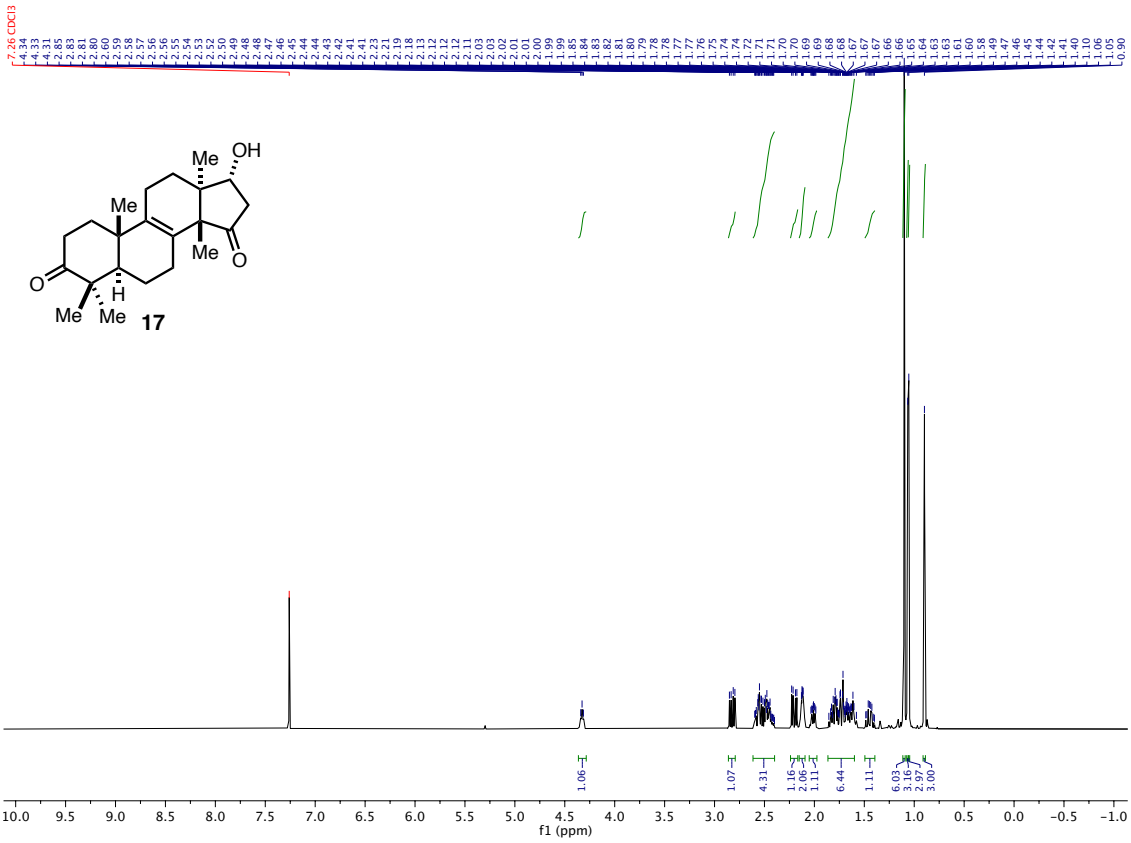


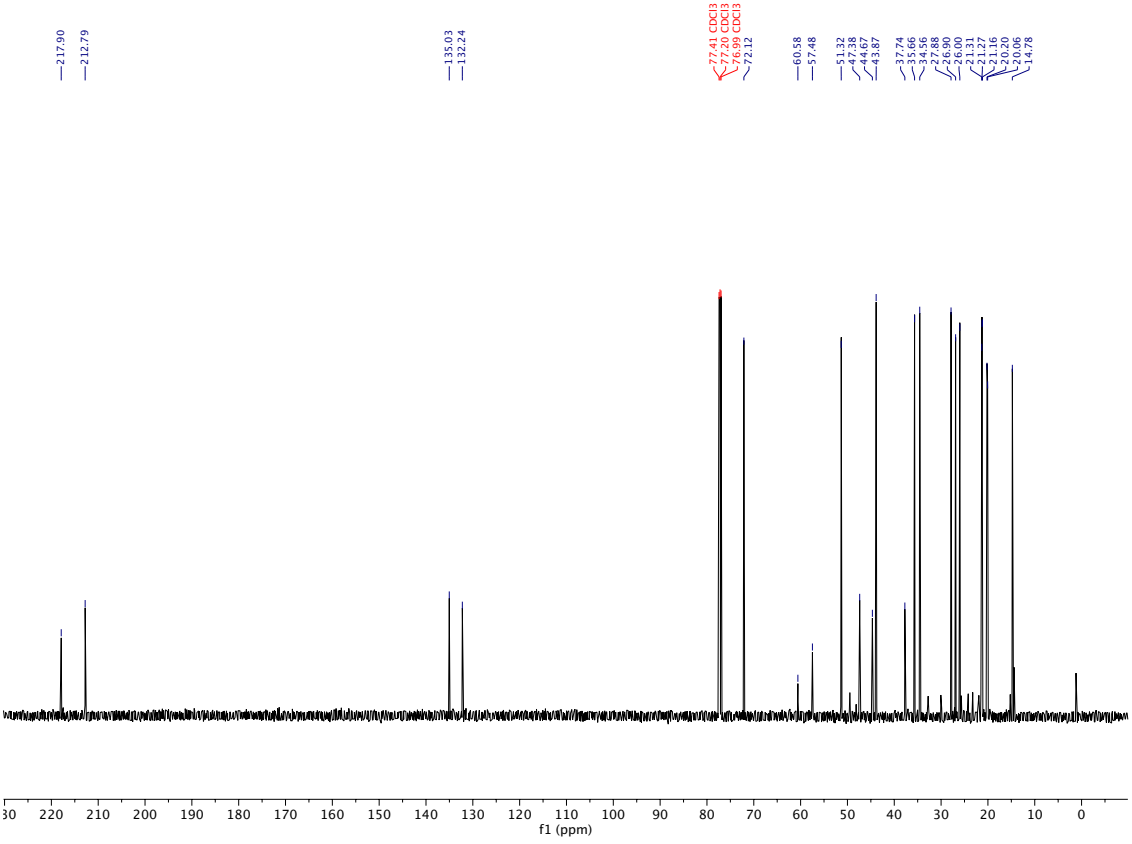
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S9**



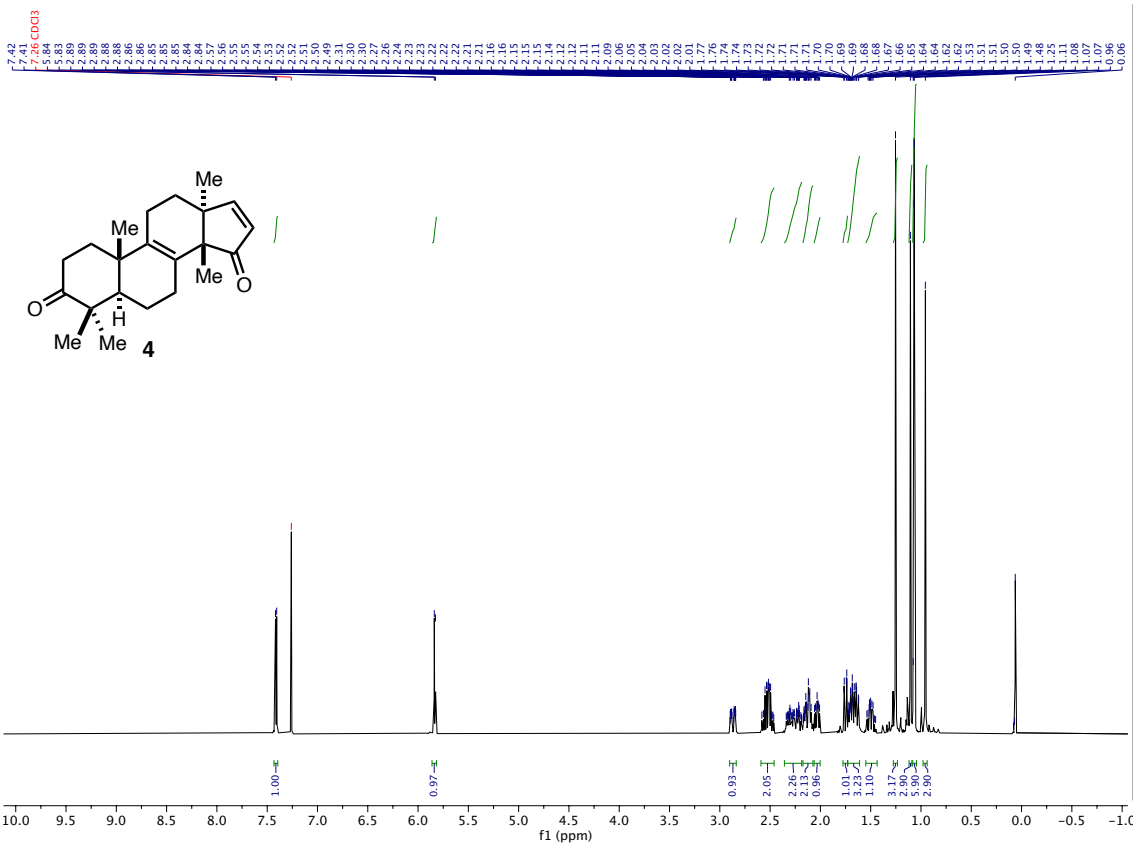


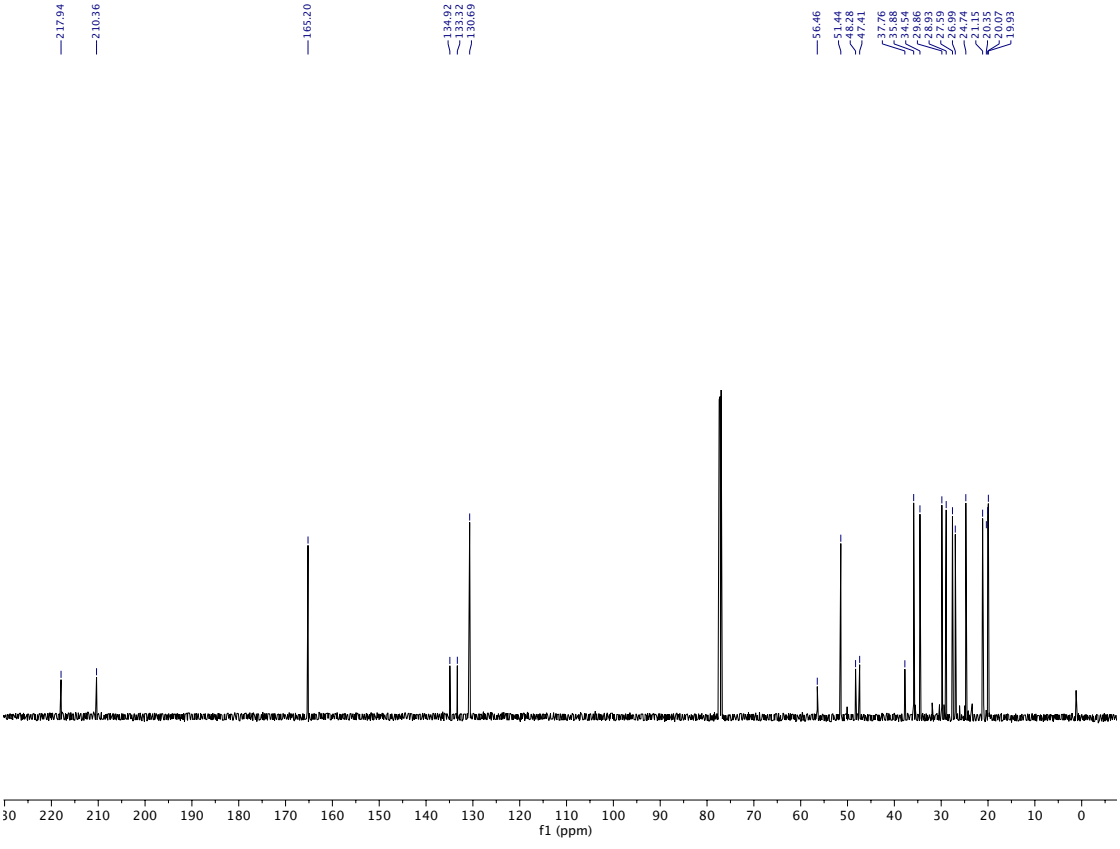
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **17**



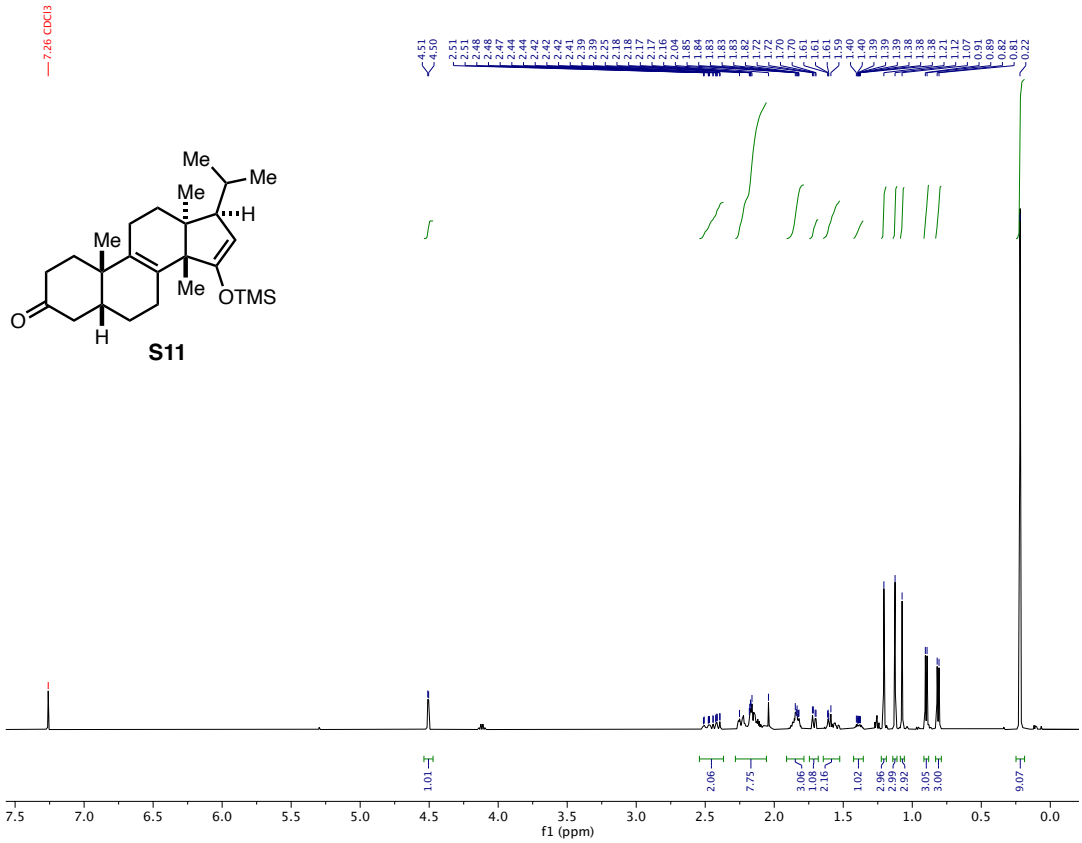


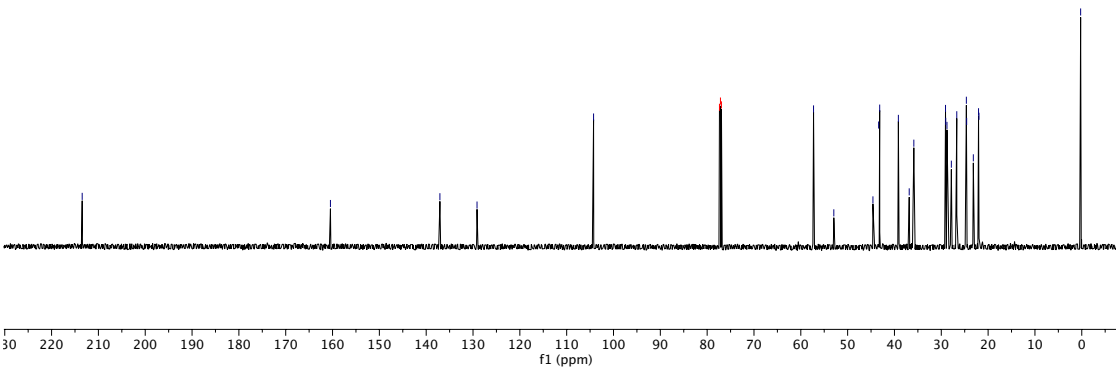
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **4**



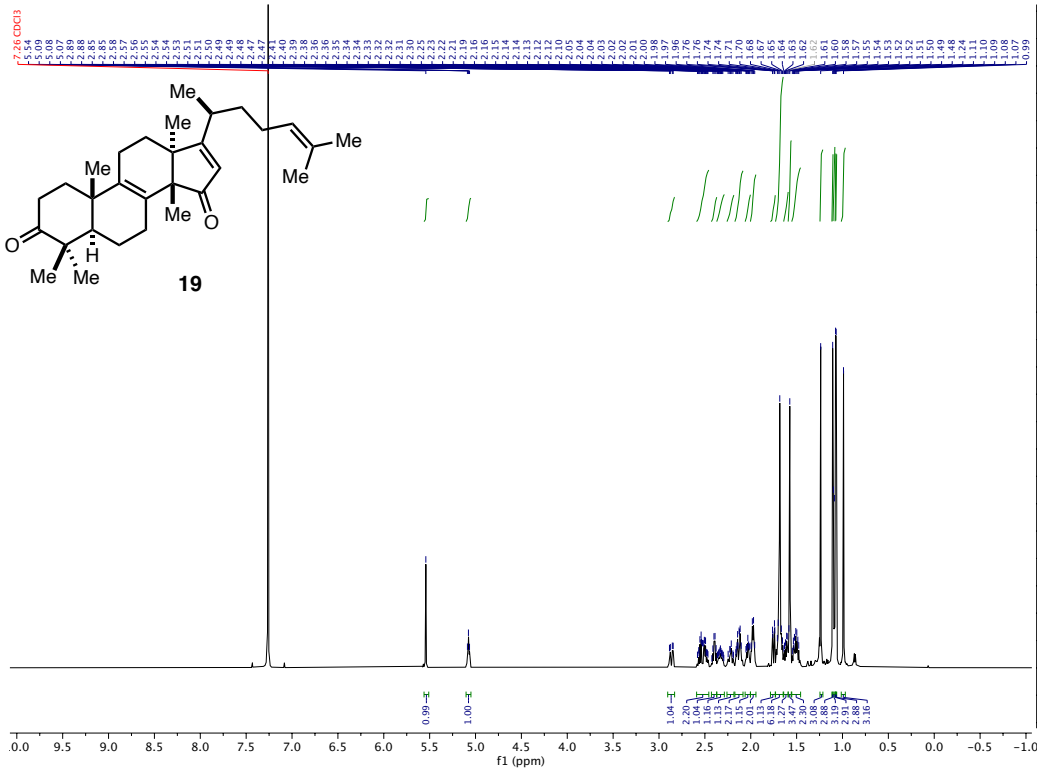


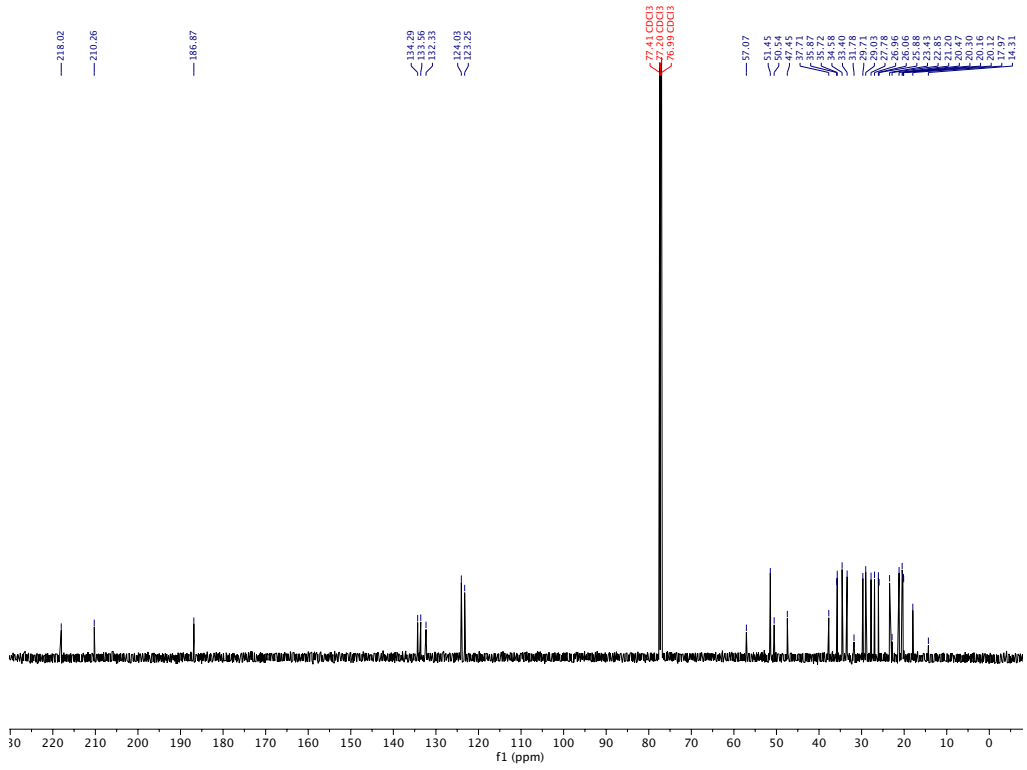
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S11**



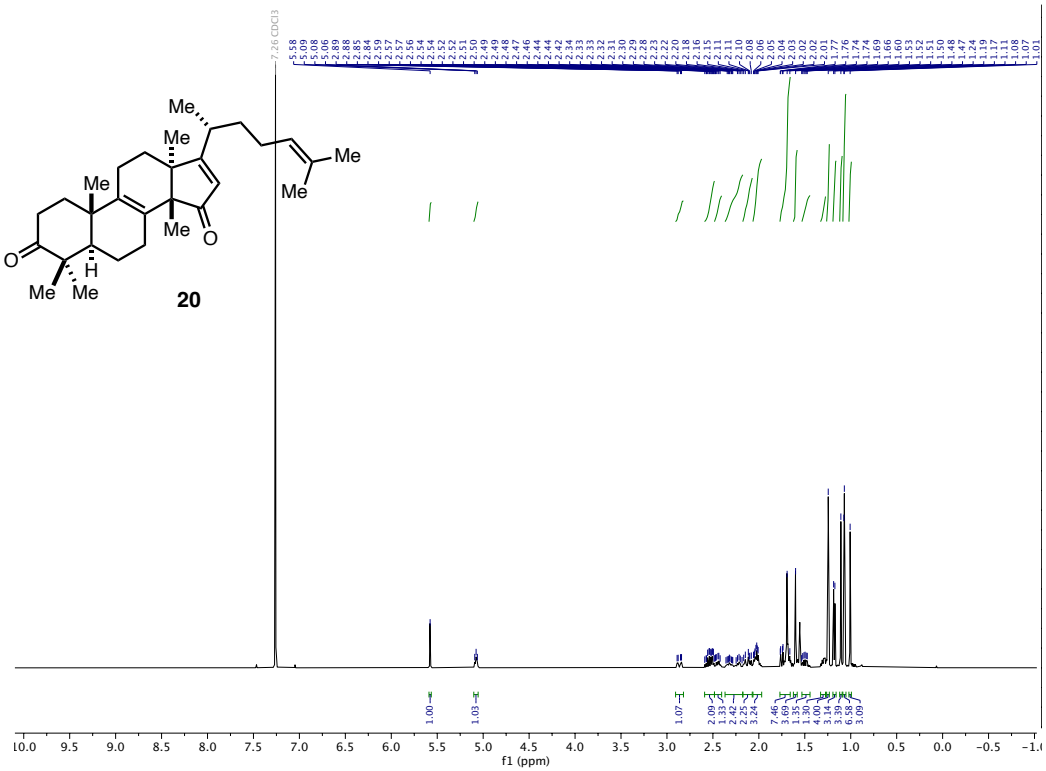


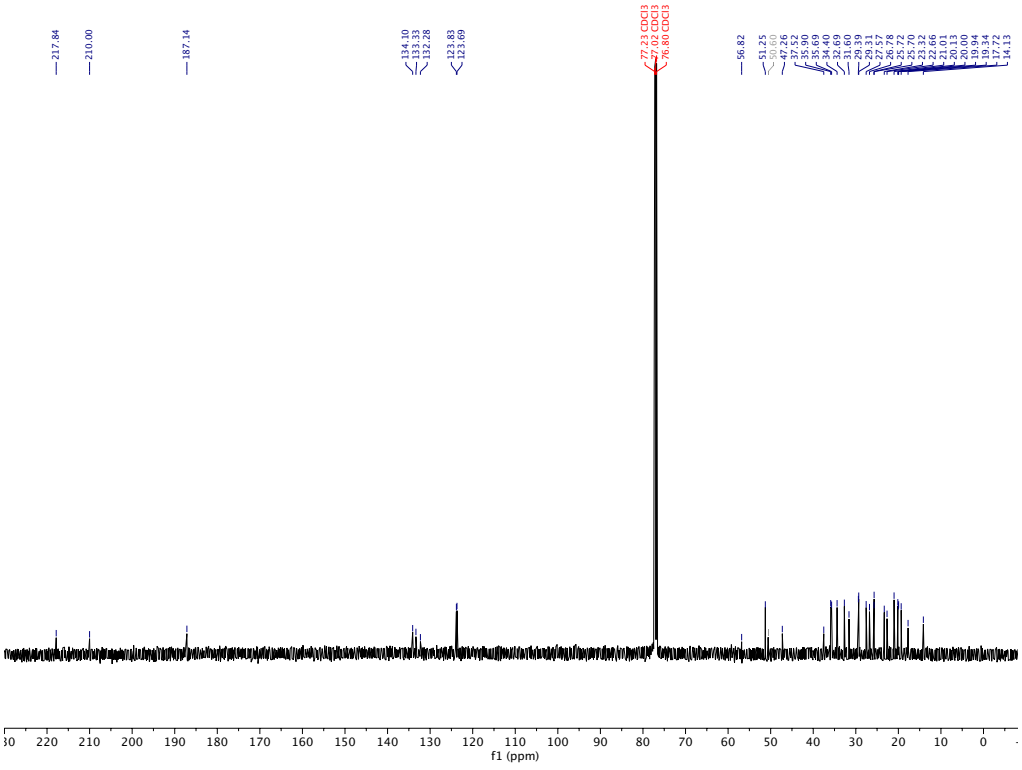
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **19**



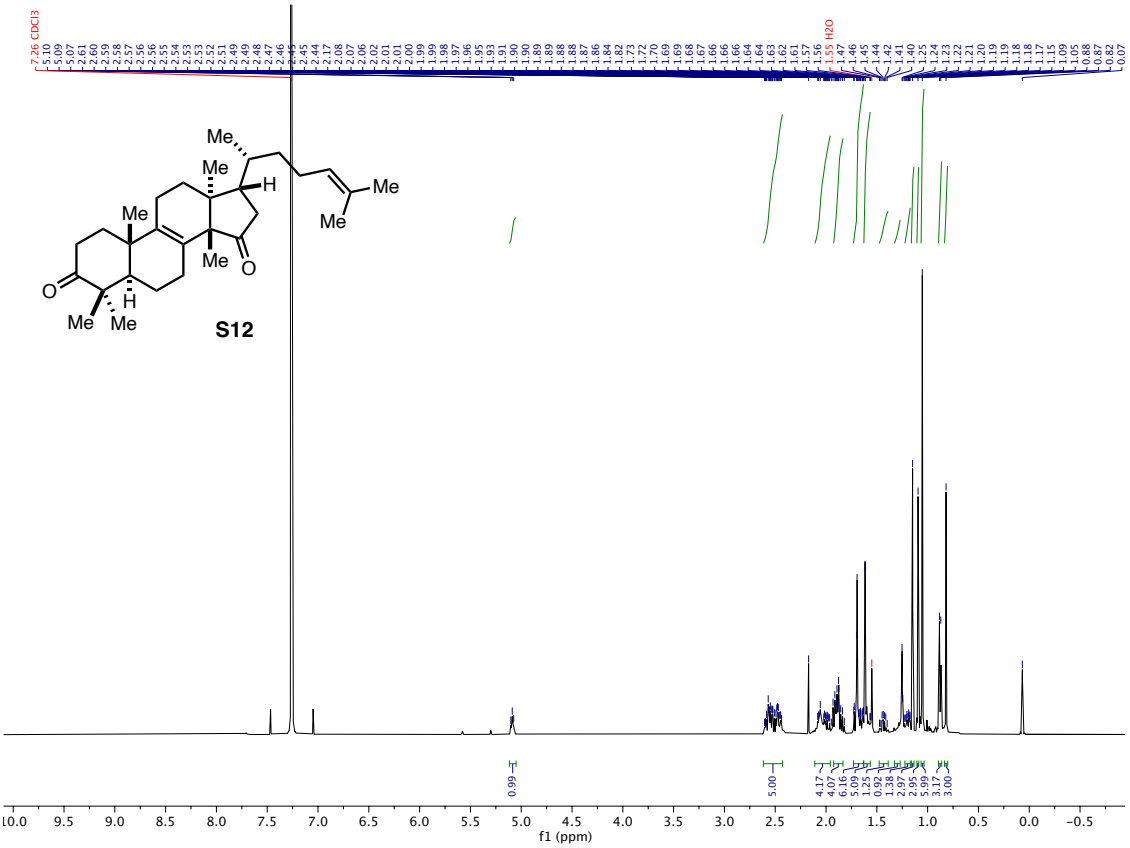


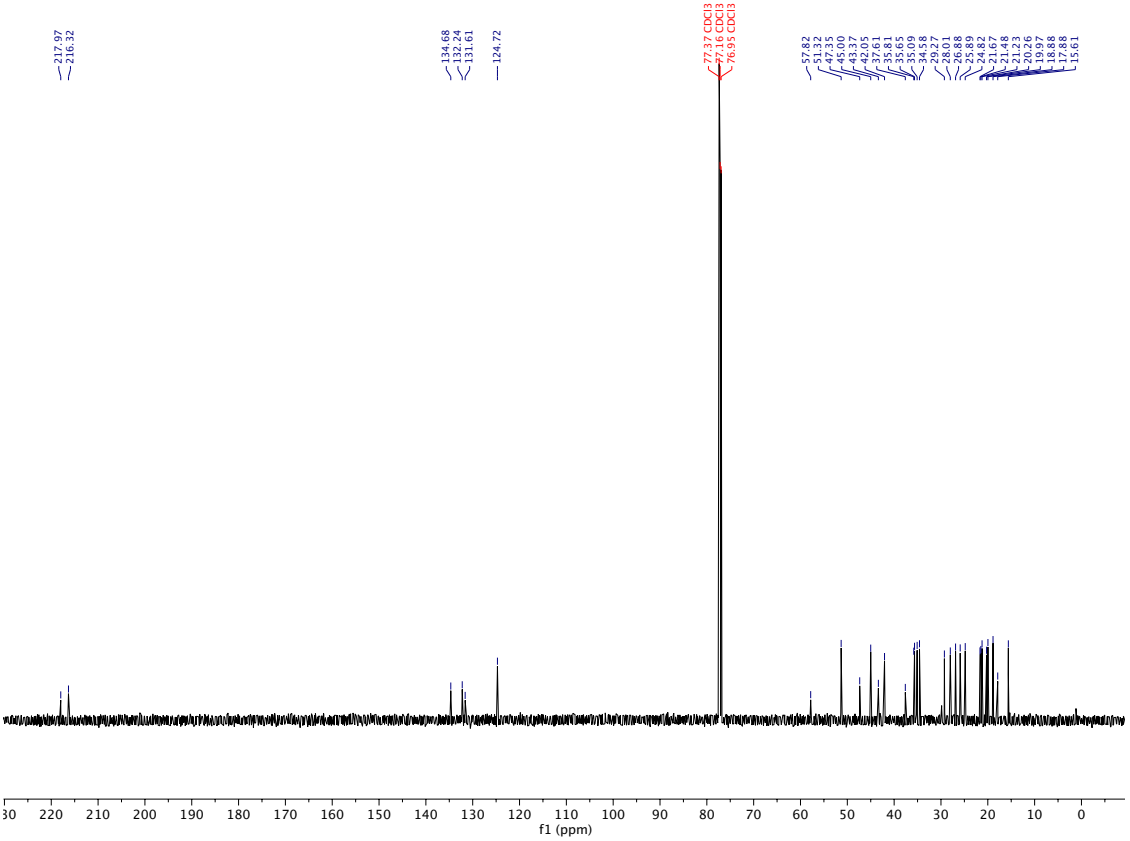
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **20**



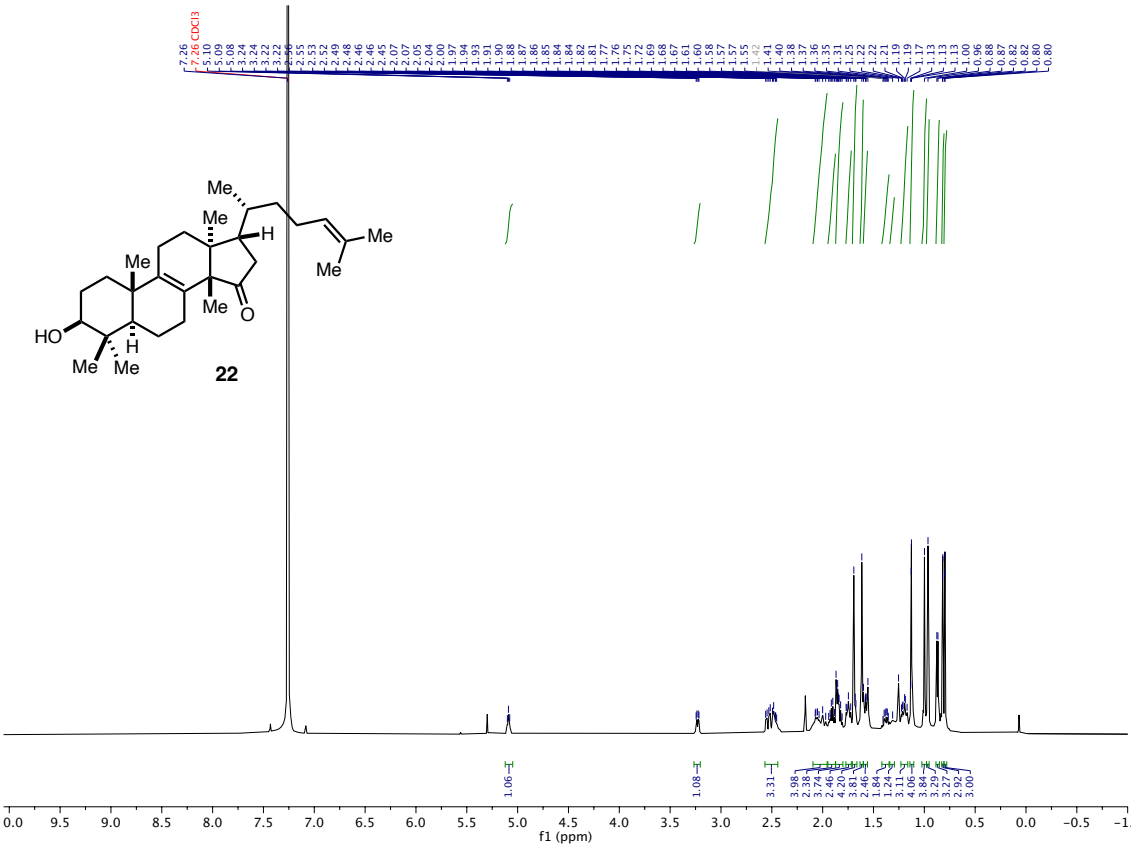


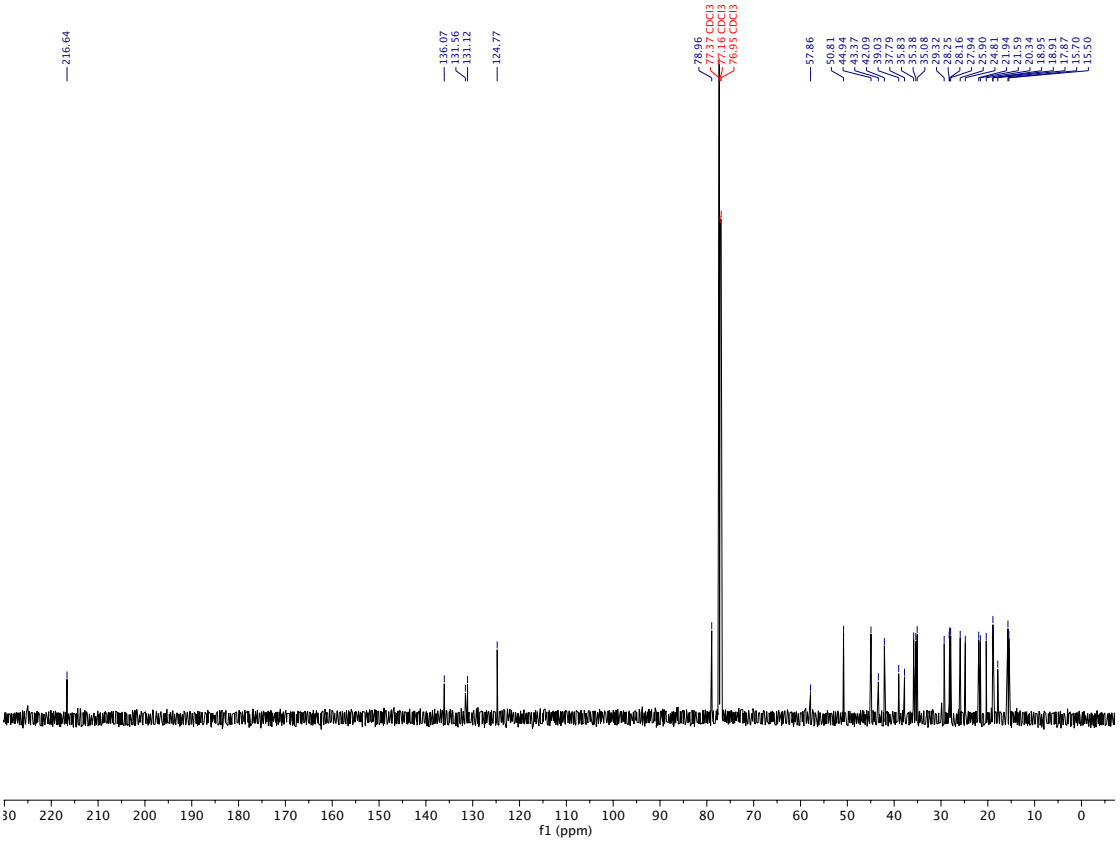
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S12**



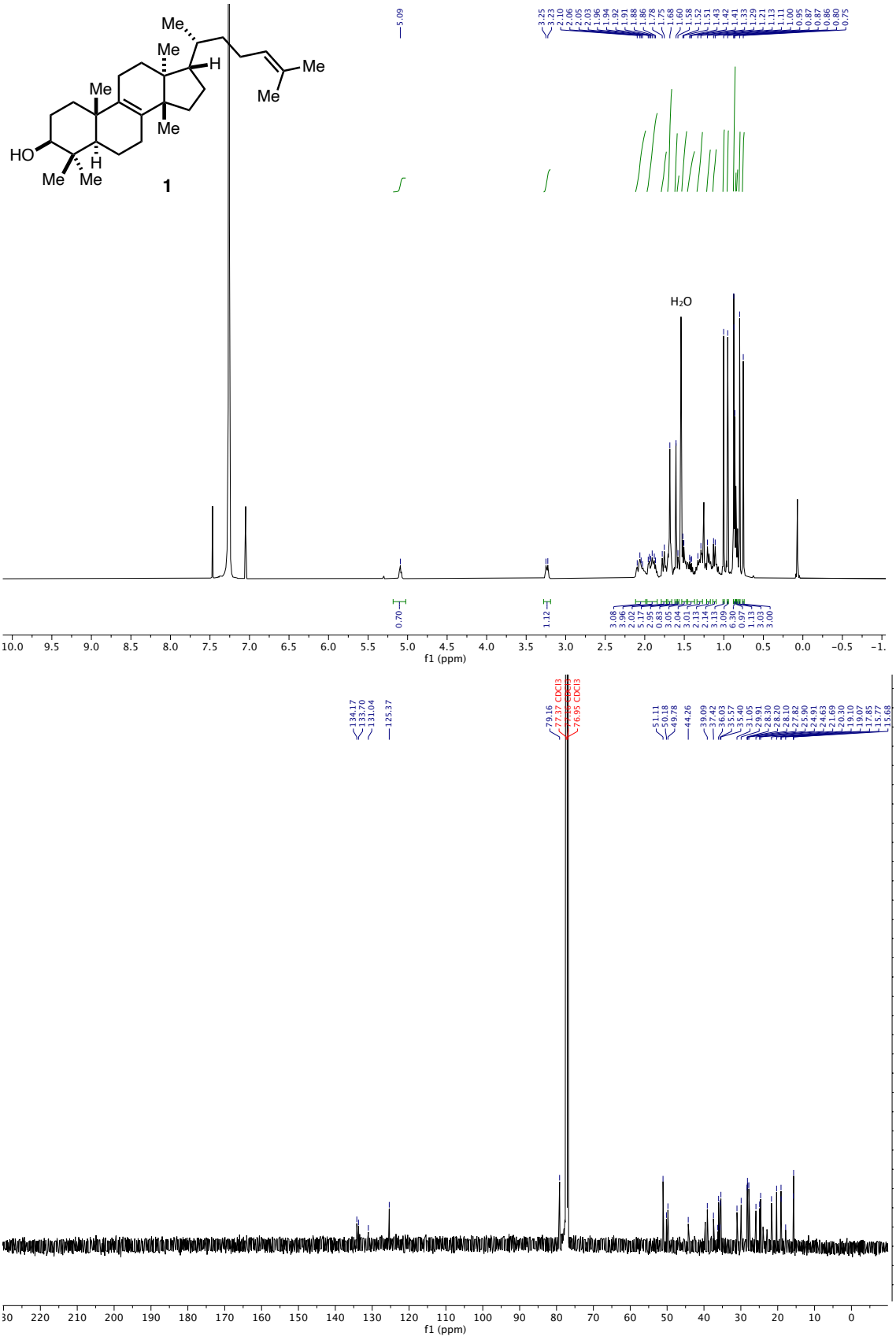


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **22**

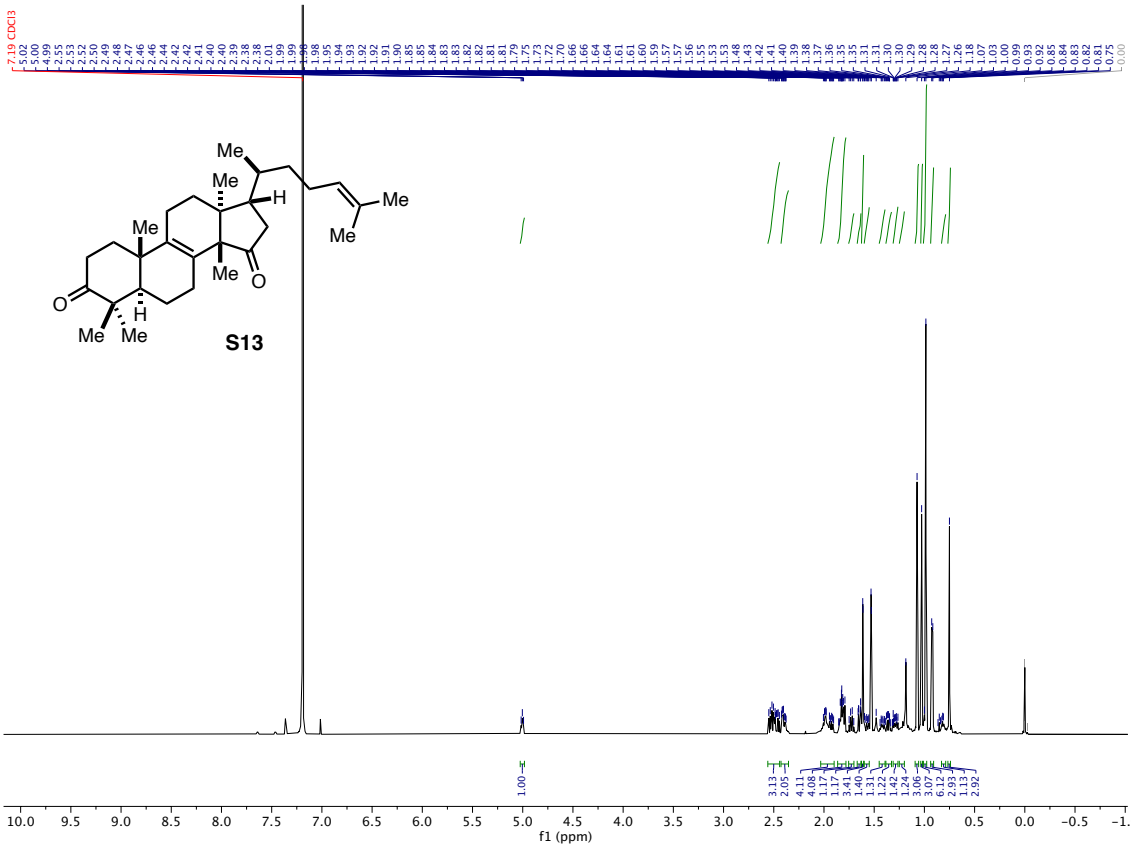


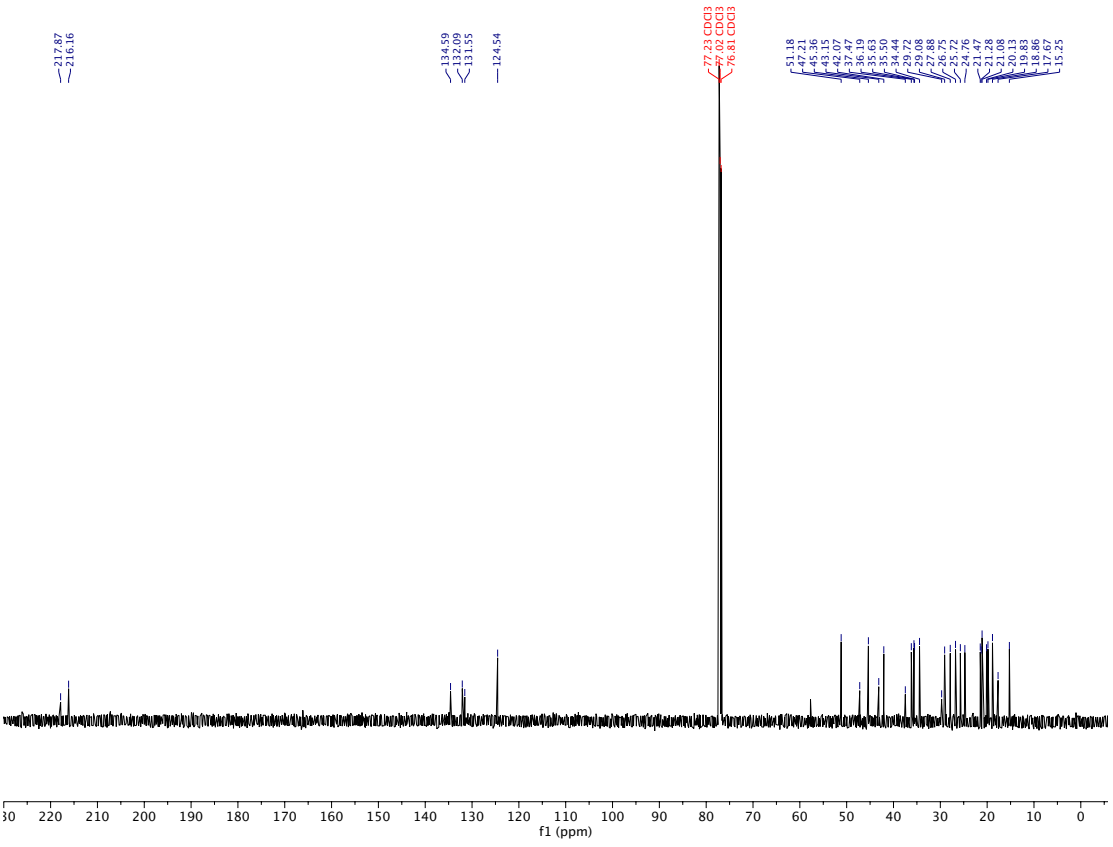


^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of Euphol (**1**)

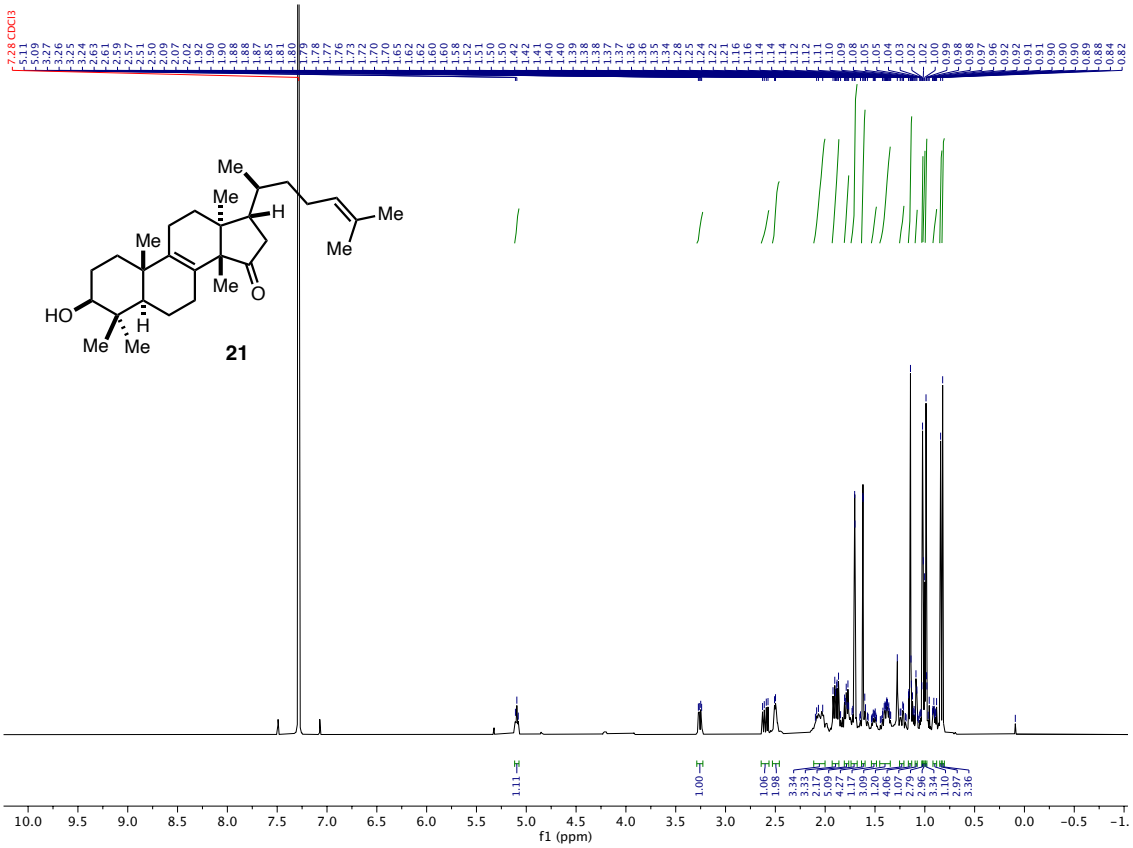


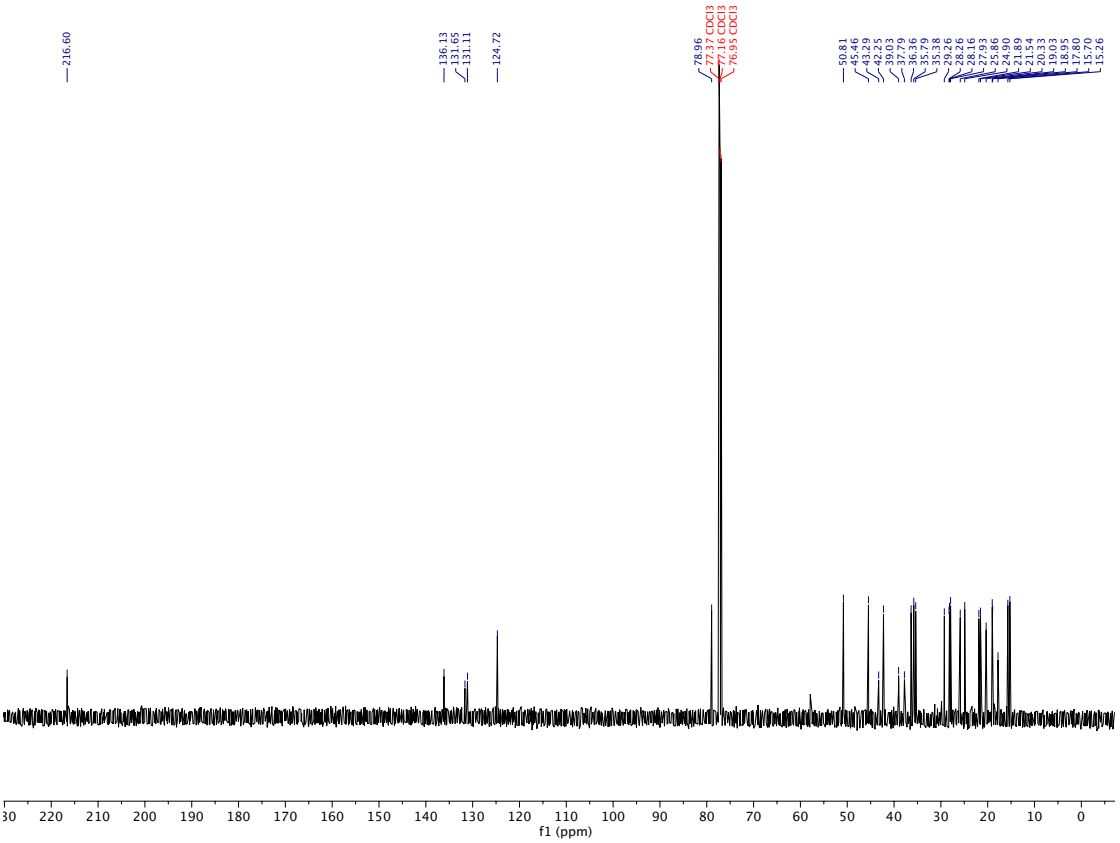
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **S13**



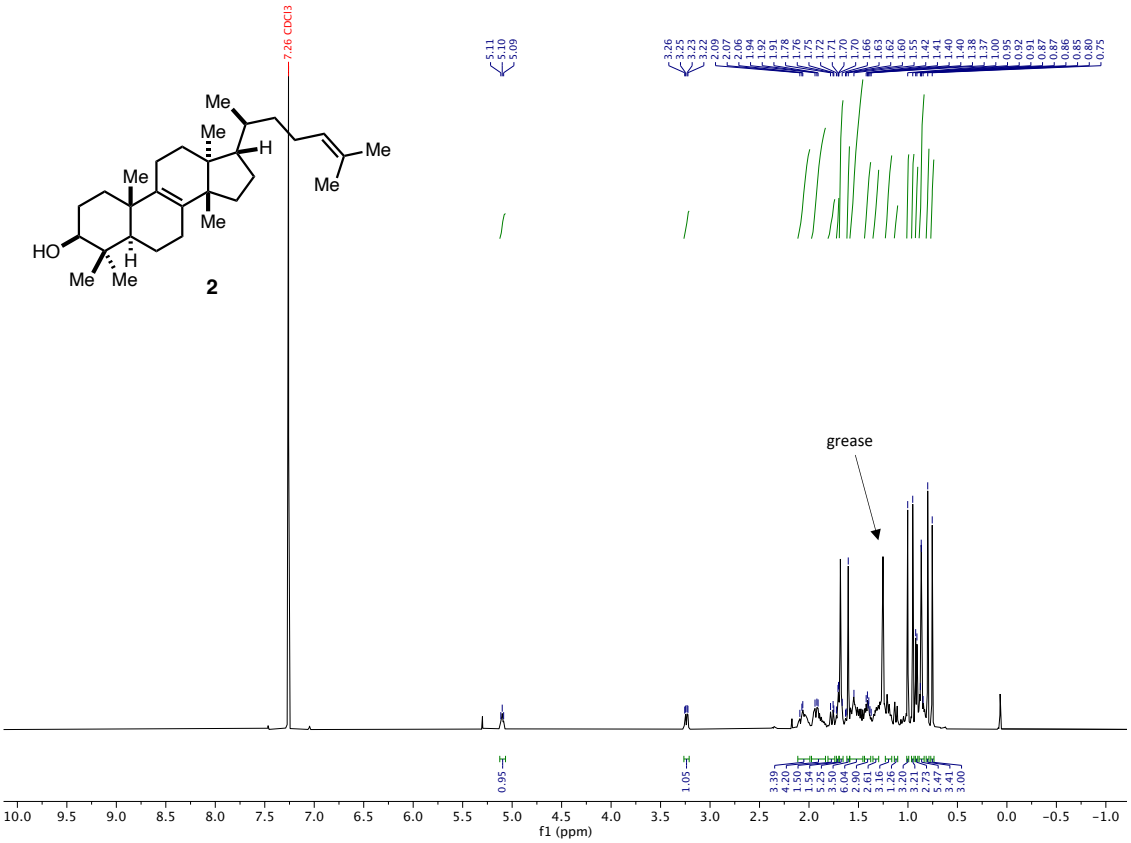


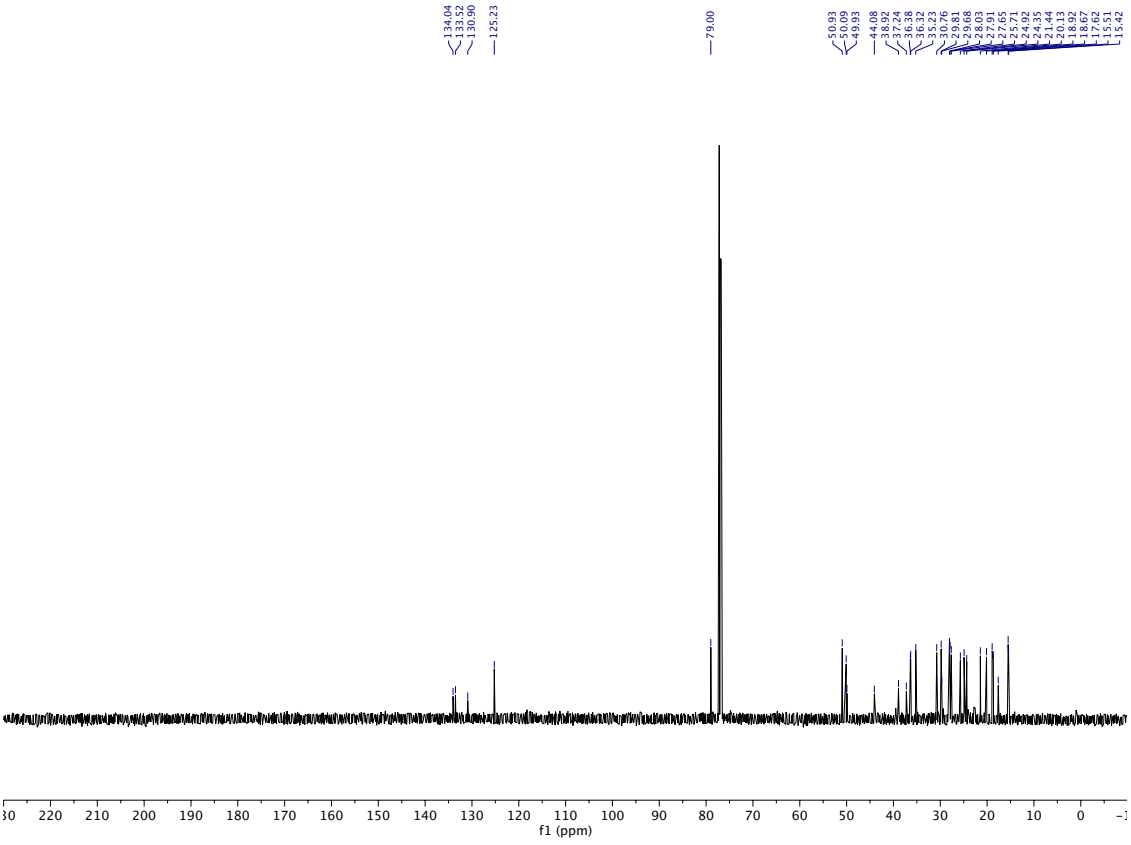
^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of **21**



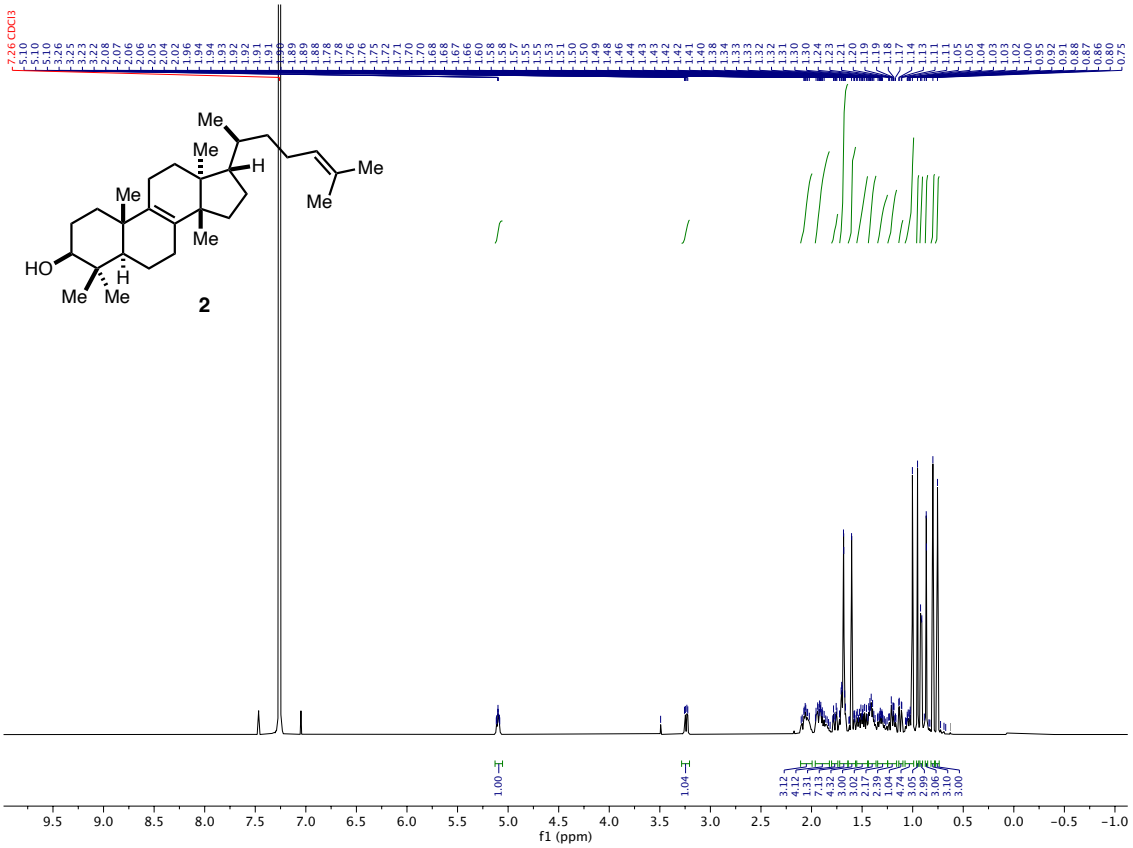


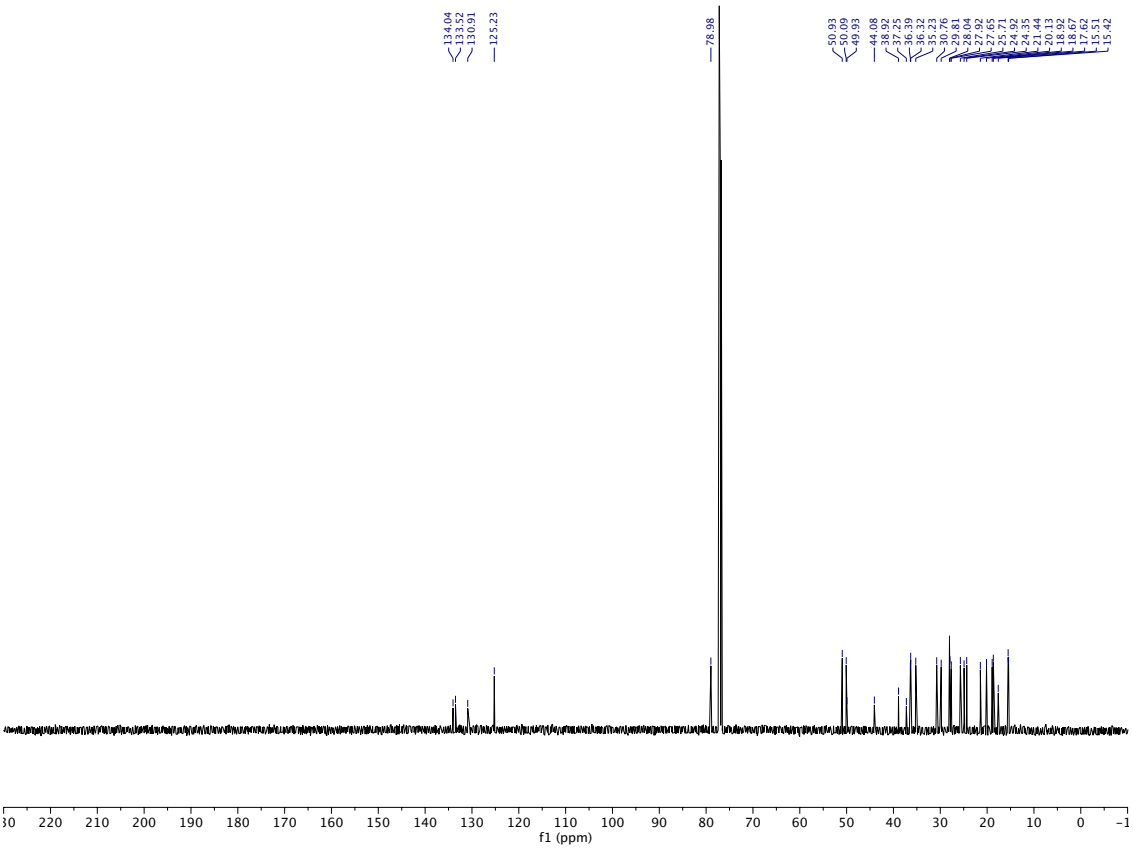
Experimental ^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of tirucallol (**2**)





^{1}HNMR (600 MHz, $CDCl_3$) and ^{13}CNMR (150 MHz, $CDCl_3$) of tirucallol authentic sample (**2**)





References:

1. Alvarado, J., Fournier, J., Zakarian, A. Synthesis of Funcitonalized Dihydrobenzofurans by Direct Aryl C-O Bind Formation under Mild Conditions. *Angew. Chem. Int. Ed.* **2016**, *55*, 11625 - 11628
2. Hajos, Z., Parrish, D. (+)-(7aS)-7a-methyl-2,3,7,7a-tetrahydro-1-H-indene-1,5-(6H-dione). *Org. Synth.* **1985**, *63*, 26
3. Cañellas, S., Ayats, C., Henseler, A., Pericàs, M. A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow. *ACS Catal.* **2017**, *7*, 1383–1391)
4. Caine, D., Kotian, P., McGuiness, M. Synthesis and Photochemical Rearrangements of Bicyclic Cross-Conjugated Cyclohexadienones Containing δ-Oxy Substituents *J. Org. Chem*. **1991**, *56*, 6307 – 6313
5. Liu, G., Mei, G.,Chen, R., Yuan, H., Yang, Z., Li, C. Total Synthesis of Aplykurodinone-1 *Org. Lett*. **2014**, *16*, 4380-4383
6. Romero-Morán, L., Ramírez-Apan, M., Hernández-Ortega, S., Martínez-Otero, D., Delgado, G. Tris *nor*-Euphane-Type Triterpenoid and Other Constituents Isolated from *Euphorbia tenquahuete* Sessé & Moc.: Preparation and Cytotoxic Evaluation of Semisynthetic Derivatives of Euphol. *ACS Omega* **2022**, *7*, 35077-35082
7. Zhang, Q., Zhou, Q., Lou, J., Chen, P., Yao, W., Tao, W., Tang, Y., Dai, G., Wang, K., Zhang, L. Chemical Constituents from *Euphorbia kansui*. *Molecules* **2017**, *22*, 2176