SUPPORTING INFORMATION

Catalytic Enantioselective Total Synthesis of (+)-Torrubiellone C

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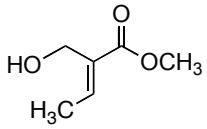
General Methods and Materials:

Unless otherwise stated, chemicals were purchased from Sigma-Aldrich, ABCR, Acros or Lancaster and used without further purification. Solvents for work-up and chromatography were distilled from technical quality. Solvents used for chemical transformations were either puriss. quality or dried by filtration through activated aluminium oxide under argon or nitrogen. Reactions involving air or moisture sensitive reagents or intermediates were performed under argon or nitrogen in glassware which had been oven dried or dried by a heat gun under high vacuum. Concentration under reduced pressure was performed by rotary evaporation at 40 °C (unless otherwise specified). Yields refer to purified, dried and spectroscopically pure compounds. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) precoated with fluorescent indicator. The developed plates were examined under UV light and stained with ceric ammonium molybdate followed by heating. Flash chromatography was performed using silica gel 60 (230-240 mesh) from Fluka using a forced flow eluant at 0.3-0.5 bar pressure. All ^{1}H and ^{13}C NMR spectra were recorded either using Bruker Avance 400 MHz (^{1}H) & 101 MHz (^{13}C) or Bruker Avance DRX 500 MHz (^{1}H) & 126 MHz (^{13}C) spectrometers at room temperature. Chemical shifts (δ-values) are reported in ppm, spectra were calibrated related to solvent's residual proton and carbon chemical shift,[1] multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextet, hept. = heptet, m = multiplet or unresolved and coupling constant J in Hz. IR spectra were recorded using a Varian 800 FT-IR ATR Spectrometer. The absorptions are reported in cm^{-1}. Analytical High Performance Liquid Chromatography (HPLC) were performed on a *Dionex Chromatography System* (Interface Chromeleon, ASI 100 automatic sample injector, PDA 100 (USB) PD detector, pump P680, degaser, MSQ-ESI mass spectrometric detector) at a flow rate of 1 mL/min with a Phenomenex Gemini 5 μm C18 110A column (150 x 4.6 mm) or on a *Dionex Chromatography System* (Interface Chromeleon, UVD 170 U UV detector, pump P580) at a flow rate of 1 mL/min with a Chiralpak® IC column (250 x 4.6 mm). Optical rotations $[\alpha]_D^T$ were measured at the sodium D line using a 1 mL cell with a 1 dm path length on a Jasco P-2000 digital polarimeter. The concentration c is given in g/100mL and the used solvent is $CHCl_3$. All mass spectra (HRMS-ESI) were

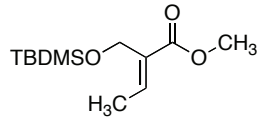
recorded by the Mass spectrometric Service of University of Bern on Sciex QSTAR Pulsar mass spectrometer using electrospray ionization. GC experiments were conducted on a CE Instruments GC 8000 Top with a chiral γ-Cyclodextrin, Trifluoroacetyl (Chiraldex), 30 m×0.25 mm column. Hydrogenation experiments were conducted in a HPM-005 autoclave by PREMEX Reactor AG (Lengnau, Switzerland).

(*E*)-Methyl 2-(hydroxymethyl)but-2-enoate (S6a)



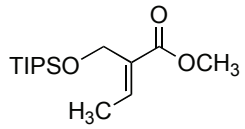
Hydroxyester **S6a** was prepared in 4 steps starting from methyl acrylate according to a literature procedure.[2] All analytical data were found to be in full agreement with the previously published values.[2]

(*E*)-Methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)but-2-enoate (S6b)



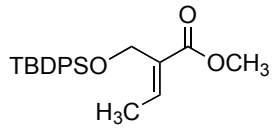
A suspension of (*E*)-methyl 2-(hydroxymethyl)but-2-enoate (2.00 g, 15.4 mmol, 1.0 equiv.), 1H-imidazole (1.57g, 23.1 mmol, 1.5 equiv.) and *tert*-butyldimethylsilyl chloride (2.55 g, 16.5 mmol, 1.1 equiv.) in dry dichloromethane (45 mL) was stirred at rt under an argon atmosphere and monitored by TLC (SiO_2, pentane/Et_2O 12:1 v/v). After 14 h, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2x70 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed. Flash chromatography (SiO_2, pentane/Et_2O 12:1) gave the product as a colorless oil (2.48 g, 10.1 mmol, 66%).**^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 6.95 (q, *J* = 7.2 Hz, 1H), 4.39 (s, 2H), 3.72 (s, 3H), 1.89 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.74, 141.44, 132.57, 57.01, 51.67, 25.99, 18.47, 14.51, -5.21.). **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 2953, 2858, 1718, 1469, 1436, 1298, 1246, 1037, 836, 776, 727, 662, 627. R_f = 0.34 (SiO_2, pentane/Et_2O 12:1) **HR-MS** (ESI) calc. for $[C_{12}H_{25}O_3Si]^+$: $[M+H]^+$ 245.1573; found: 245.1567.

(*E*)-Methyl 2-(((triisopropylsilyl)oxy)methyl)but-2-enoate (S6c)



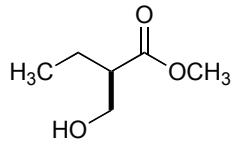
Silyl protected ester **S6c** was prepared according to literature procedures. All analytical data were found in full agreement with the previously published values.[3]

(*E*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)but-2-enoate (6)



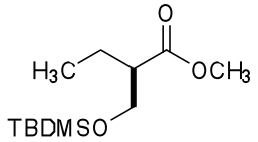
TBDPS protected hydroxyester **6** was prepared according to literature procedures.[2] All analytical data were in full agreement with the previously published values.[2]

(*R*)-Methyl 2-(hydroxymethyl)butanoate (S7a)



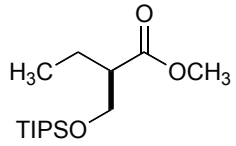
General Asymmetric Hydrogenation Procedure:[4] A high pressure steel autoclave (Premex Reactor AG; Lengnau, Switzerland; Model HPM-005) with a dry glass insert and a magnetic stir bar was charged with the appropriate catalyst (0.002 mmol) and 0.5 mL of a 0.2M degassed substrate solution freshly prepared from the corresponding substrate and dichloromethane. The autoclave was closed and attached to a high pressure hydrogen line and purged with H_2. The autoclave was sealed under the appropriate H_2 pressure and the mixture was stirred at 900 rpm for 2 hours at the appropriate pressure and temperature. After release of H_2 the solution was concentrated in a stream of nitrogen, diluted with 1 mL of hexane/MTBE (4:1), and passed through a short plug of silica gel in a Pasteur pipette and the filtrate was concentrated in a stream of nitrogen.

(*R*)-Methyl 2-((tert-butyldimethylsilyloxy)methyl)butanoate (S7b)



According to the general procedure for the asymmetric hydrogenation, enoate **S6b** was reduced at room temperature under 50 bar hydrogen pressure in 2 h. The enantiomeric purity for compound **S7b** was determined by GC analysis of the free alcohol on a chiral column. Removal of the TBDMS protecting group was accomplished by adding Dowex 50W-X8 (10 mg) in MeOH to the reaction mixture after filtration of the catalyst over silica gel in hexane/MTBE (4:1).[5] After 12 hours at room temperature, the reaction mixture was filtered over Celite in hexane and the free alcohol was analyzed by GC.[4] **GC** (chiral, γ-Cyclodextrin, Trifluoroacetyl (Chiraldex), 30 m×0.25 mm, 60 kPa H_2, 50 °C, 10 min, 5 K/min, 120 °C, 10 K/min, 160 °C, 2 min): $t_{R(S)}$ = 23.2 min, $t_{R(R)}$ = 23.7 min. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.84-3.71 (m, 2H), 3.73 (s, 3H), 2.53 (ddd, *J* = 14.2, 7.2, 4.4 Hz, 1H), 1.73-1.57 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

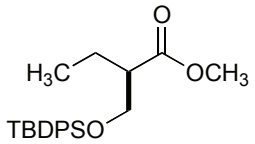
(*R*)-Methyl 2-(((triisopropylsilyl)oxy)methyl)butanoate (S7c)



According to the general procedure for the asymmetric hydrogenation, enoate **S6c** was reduced at room temperature under 50 bar hydrogen pressure in 2 h. The enantiomeric purity for compound **S7c** was determined by analysis of the free alcohol on a chiral GC column. Removal of the TIPS protecting group was accomplished by adding TBAF (1M in THF, 0.2 mL) to the reaction mixture after filtration of the catalyst over silica gel in hexane/MTBE (4:1). After 2 hours at room temperature, the reaction mixture was filtered over silica gel in hexane/MTBE (4:1) and the free alcohol was analyzed by GC.[4] **GC** (chiral, γ-Cyclodextrin, Trifluoroacetyl (Chiraldex), 30 m×0.25 mm, 60 kPa H_2, 50 °C, 10 min, 5 K/min, 120 °C, 10 K/min, 160 °C, 2 min): $t_{R(S)}$ = 23.2 min, $t_{R(R)}$ = 23.7 min. **^{1}H-**

NMR (400 MHz, $CDCl_3$) δ 3.84-3.71 (m, 2H), 3.73 (s, 3H), 2.53 (ddd, *J* = 14.2, 7.2, 4.4 Hz, 1H), 1.73-1.57 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

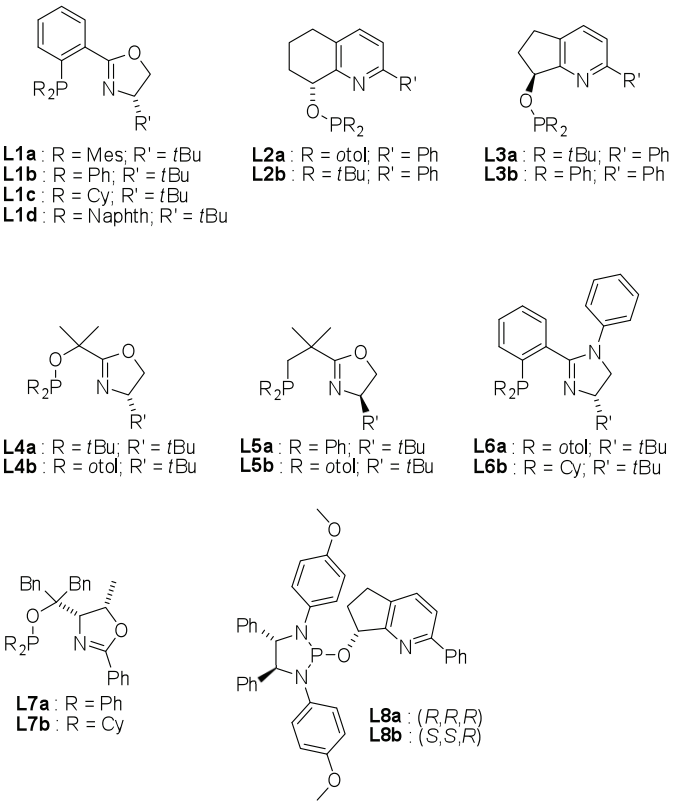
(*R*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butanoate (7)



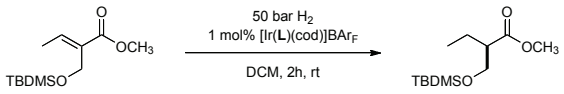
According to the general procedure for the asymmetric hydrogenation, enoate **6** was reduced at room temperature under 50 bar hydrogen pressure in 2 h. The enantiomeric purity for compound **7** was determined by analysis of the free alcohol on a chiral GC column. Removal of the TBDPS protecting group was accomplished by adding TBAF (1M in THF, 0.2 mL) to the reaction mixture after filtration of the catalyst over silica gel in hexane/MTBE (4:1). After 2 hours at room temperature, the reaction mixture was filtered over silica gel in hexane/MTBE (4:1) and the free alcohol was analyzed by GC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 4H), 7.46-7.35 (m, 6H), 3.84 (dd, *J* = 9.8, 7.9 Hz, 1H), 3.73 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.70 (s, 3H), 2.58 (tt, *J* = 8.0, 5.6 Hz, 1H), 1.68-1.46 (m, 2H), 1.02 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.0, 135.6, 135.5, 133.5, 133.4, 129.7, 129.6, 127.6, 64.5, 51.4, 50.0, 29.7, 21.5, 19.2, 11.7; **IR** $\tilde{\nu}$ [cm^{-1}] = 3071, 3049, 2958, 2933, 2856, 1735, 1472, 1462, 1427, 1388, 1362, 1265, 1235, 1197, 1174, 1111, 1105, 1091, 998, 909, 824, 798, 737, 700; $\mathbf{R_f}$ = 0.67 (SiO_2, cyclohexane/ EtOAc 10:1); **GC-MS** t_R = 19.2 min (EI, 70 eV, PhMeSi, 100/2/10-270/10/0,), *m/z* (%) = 370 (M^+, 1), 313 (100), 283 (65), 213 (96), 183 (48), 153 (28), 135 (14), 105 (21), 77 (14), 41 (17). **EA** Analyses calculated for $C_{22}H_{30}O_3Si$ requires: C = 71.31, H = 8.16, N = 0.00, found: C = 71.58, H = 8.22, N = 0.00; *The free alcohol was injected after removal of the protecting group*:[4] **GC** (chiral, γ-Cyclodextrin, Trifluoroacetyl (Chiraldex), 30 m×0.25 mm, 60 kPa H_2, 50 °C, 10 min, 5 K/min, 120 °C, 10 K/min, 160 °C, 2 min): $t_{R(S)}$ = 23.2 min, $t_{R(R)}$ = 23.7 min. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.84-3.71 (m, 2H), 3.73 (s, 3H), 2.53 (ddd, *J* = 14.2, 7.2, 4.4 Hz, 1H), 1.73-1.57 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

Catalyst Screening and Optimization of the Ir-Catalyzed Asymmetric Hydrogenation



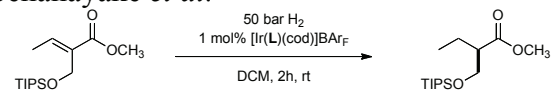
Scheme 1. Ligands evaluated in the Ir-catalyzed asymmetric hydrogenation of enoates **6**, **S6b** and **S6c**.



S6b **S7b**

Ligand L	Conversion [a] [%]	*ee* [a] [%]
1a	>99	81 (+) (*R*)
1b	>99	74 (+) (*R*)
1c	>99	62 (+) (*R*)
1d	>99	79 (+) (*R*)
2a	>99	59 (-) (*S*)
***ent*-2b**	30	52 (-) (*S*)
3a	21	<2 (+) (*R*)
3b	>99	82 (+) (*R*)
4a	>99	36 (+) (*R*)
4b	>99	71 (+) (*R*)
5a	>99	79 (-) (*S*)
5b	>99	85 (-) (*S*)
6a	>99	83 (+) (*R*)
6b	>99	70 (+) (*R*)
7a	>99	49 (+) (*R*)
7b	>99	72 (+) (*R*)
8a	>99	79 (-) (*S*)

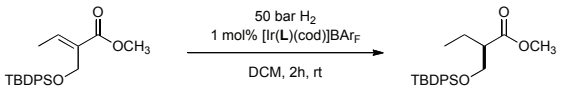
a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.*[4]



S6c **S7c**

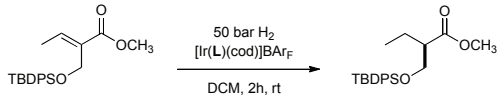
Ligand L	Conversion [a] [%]	*ee* [a] [%]
1a	>99	72 (+) (*R*)
2a	>99	67 (-) (*S*)
3b	>99	87 (+) (*R*)
4b	>99	69 (+) (*R*)
5b	>99	76 (-) (*S*)
6a	>99	80 (+) (*R*)
8a	>99	86 (-) (*S*)
8b	>99	83 (-) (*S*)

a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.*[4]



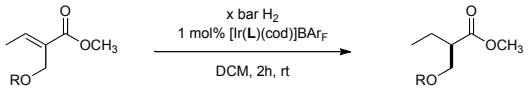
Ligand L	Conversion [a] [%]	*ee* [a] [%]
1a	>99	57 (+) (*R*)
2a	>99	76 (-) (*S*)
3b	>99	88 (+) (*R*)
4b	>99	72 (+) (*R*)
5b	>99	73 (-) (*S*)
6a	>99	76 (+) (*R*)
7a	>99	40 (+) (*R*)
8a	>99	86 (-) (*S*)

a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.* [4]



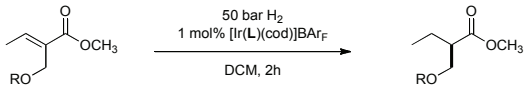
Ligand L	Cat. load.	[M]	Conversion [a] [%]	*ee* [a] [%]
3b	1 mol%	0.2	>99	87 (+) (*R*)
3b	0.5 mol%	0.2	>99	87 (+) (*R*)
3b	1 mol%	0.4	>99	86 (+) (*R*)
***ent*-3b**	1 mol%	0.2	>99	84 (-) (*S*)

a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.* [4]



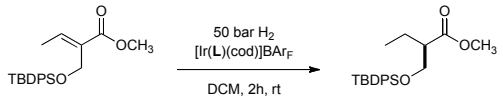
Ligand L	R	[p]	Conversion [a] [%]	*ee* [a] [%]
3b	TBDPS	75 bar	>99	87 (+) (*R*)
3b	TIPS	75 bar	>99	87 (+) (*R*)
3b	TBDPS	25 bar	>99	86 (+) (*R*)
3b	TIPS	25 bar	>99	86 (+) (*R*)

a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.* [4]



Ligand L	R	[T]	Conversion [a] [%]	*ee* [a] [%]
3b	TBDPS	0 °C	>99	90 (+) (*R*)
3b	TIPS	0 °C	>99	89 (+) (*R*)
3b	TBDPS	40 °C	>99	85 (+) (*R*)
3b	TIPS	40 °C	>99	86 (+) (*R*)

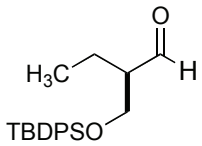
a) Determined for the free hydroxyester on a chiral GC column; absolute configuration assigned according to Senanayake *et al.* [4]



Ligand L	Cat. load.	[M]	Conversion [a] [%]	*ee* [a] [%]
3b	1 mol%	0.4	>99	89 (+) (*R*)
3b	0.5 mol%	0.2	86	90 (+) (*R*)
3b	0.25 mol%	0.2	<5	-
***ent*-3b**	1 mol%	0.2	>99	87 (-) (*S*)

a) Determined for the free alcohol on a chiral GC column; absolute configuration referred to Senanayake *et al.* [4]

(*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)butanal (S8a)

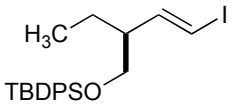


To a stirred solution of **7** (650 mg, 1.75 mmol, 1.0 equiv.) in DCM (6 mL) at -78°C was added DIBAH (1.0 M in hexanes, 4.03 mL, 4.03 mmol, 2.3 equiv.) under argon. The solution was stirred 10 min and subsequently the reaction was quenched by addition of methanol. Diethylether (30 mL) and a saturated solution of Rochelle's salt (15 mL) were added. The biphasic mixture was stirred vigorously for 1h. The layers were separated and the aqueous phase was extracted once with diethylether (20 mL). The combined organic phases were washed with brine (2x20 mL) dried over sodium sulfate, filtered and

evaporated under reduced pressure. The residue was used without further purification in the next step.

To a stirred slurry of the alcohol (589 mg, 1.72 mmol, 1.0 equiv.) and powdered molecular sieves (50 mg, 4Å) in dry DCM (5 mL) were added tetrapropylammonium perruthenate (15.1 mg, 0.04 mmol, 2.5 mol%) and *N*-methylmorpholine-*N*-oxide (302 mg, 2.58 mmol, 1.5 equiv.) at 0 °C. After 15 min the ice bath was removed and the mixture stirred at rt for 2 h. The slurry was filtered through a small plug of silica (rinse with 20 mL DCM) and the solvents removed *in vacuo*. The crude product was purified by FC (pent/Et_2O 12:1, v/v) to give compound **S8a** (410 mg, 1.20 mmol, 69% over two steps) as a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 2.4 Hz, 1H), 7.70 – 7.61 (m, 4H), 7.49 – 7.36 (m, 6H), 3.93 – 3.87 (m, 2H), 2.43 – 2.33 (m, 1H), 1.81 – 1.67 (m, 1H), 1.61 – 1.46 (m, 1H), 1.04 (s, 9H), 0.89 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 204.7, 135.7, 133.3, 129.9, 127.9, 62.5, 56.0, 26.9, 19.4, 18.6, 11.6; **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 3071, 2932, 2859, 2710, 1728, 1469, 1428, 1108, 832, 702; $\mathbf{R_f}$ = 0.55 (*n*-pentane/Et_2O 9:1); **HR-MS** (ESI) calc. for $[C_{21}H_{29}O_2Si]^+$: $[M+Na]^+$ 363.1756; found: 363.1751; $[\alpha]_D^{25}$ = - 16.2° (c 1.00, $CHCl_3$).

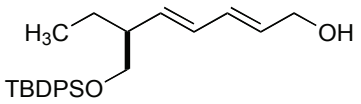
(*S*,*E*)-*tert*-butyl((2-ethyl-4-iodobut-3-en-1-yl)oxy)diphenylsilane (8)



A solution of aldehyde **S8a** (185 mg, 0.543 mmol, 1.0 equiv.) and CHI_3 (1.28 g, 3.26 mmol, 6 equiv.) in dry THF (5 mL) was added dropwise at -5 °C to a solution of chromium(II)chloride (1.34 g, 10.9 mmol, 20 equiv.) in dry THF (5 mL). and stirred for 2 h at -5 °C. The reaction was then quenched by the addition of water. The resulting mixture was diluted with diethylether (70 mL) and washed twice with water (20 mL). The solvents were removed *in vacuo*. The crude product was purified by FC (pentane + 0.1% Et_2O) yielding iodoalkene **8** (240 mg, 0.517 mmol, 95%, *E*/*Z* ca. 6:1) as colorless oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.69-7.62 (m, 4H), 7.46 – 7.35 (m, 6H), 6.37 (dd, *J* = 14.4, 9.0 Hz, 1H), 6.03 (d, *J* = 14.4 Hz, 1H), 3.64 – 3.51 (m, 2H), 2.20 – 2.12 (m, 1H), 1.57 – 1.47 (m, 1H), 1.35 – 1.23 (m, 1H), 1.05 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (126

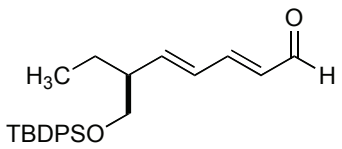
MHz, $CDCl_3$) δ 148.3, 135.8, 129.8, 127.8, 75.8, 66.1, 50.9, 27.0, 23.3, 19.4, 11.7; **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 3070, 2931, 2858, 1606, 1463, 1387, 1254, 1109, 823; $\mathbf{R_f}$ = 0.20 (*n*-pentane); **HR-MS** (ESI) calc. for $[C_{22}H_{30}IOSi]^+$: $[M+H]^+$ 465.1111; found: 465.1105**.**

(*S*,2*E*,4*E*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)octa-2,4-dien-1-ol (10)



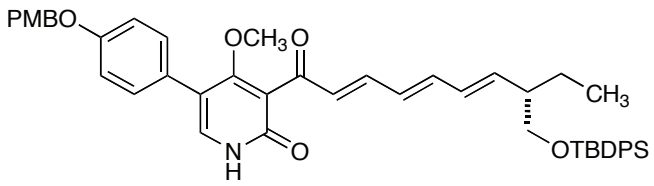
To a solution of iodoalkene **8** (100 mg, 0.215 mmol, 1.0 equiv.) and stannane **9**[6] in degassed *N*-methyl-2-pyrrolidone (0.5 mL) was added bis(acetonitrile)dichloropalladium (11.2 mg, 43.1 mmol 20 mol%). The mixture was stirred 1.5 h at rt after which a saturated solution of Rochelle's salt (10 mL) was added. The mixture was diluted with diethylether (30 mL). The organic layer was washed once with Rochelle's salt solution (5 mL) and twice with brine (10 mL). The organic layer was dried over sodium sulfate, filtered and the solvents removed *in vacuo*. TLC analysis revealed a slight difference in R_f – values of the *E*/*Z* isomers with the *Z*-isomer eluting first. After flash chromatography (*n*-pentane/Et_2O 1:1), mixed fractions were collected separately, yielding alcohol **10** (41.0 mg, 0.104 mmol, 48%) with an *E*/*Z* ratio of 15:1 as yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 4H), 7.46 – 7.34 (m, 6H), 6.23 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.75 (dt, *J* = 15.1, 6.0 Hz, 1H), 5.55 (dd, *J* = 15.2, 8.6 Hz, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 3.64 – 3.55 (m, 2H), 2.25 – 2.12 (m, 1H), 1.71 – 1.57 (m, 1H), 1.44 – 1.20 (m, 1H), 1.06 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 136.8, 135.7, 133.9, 132.1, 130.6, 129.8, 129.6, 127.6, 67.0, 63.5, 47.1, 26.9, 24.0, 19.3, 11.7; **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 3339, 2959, 2930, 2858, 2361, 1463, 1428, 1111, 989, 704, 631; $\mathbf{R_f}$ = 0.35 (*n*-pentane/Et_2O 1:1); **HR-MS** (ESI) calc. for $[C_{25}H_{35}O_2Si]^+$: $[M+H]^+$ 395.2406; found: 395.2401; $[\alpha]_D^{25}$ = + 21.7° (c 1.00, $CHCl_3$).

(*S*,2*E*,4*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)octa-2,4-dienal (11)



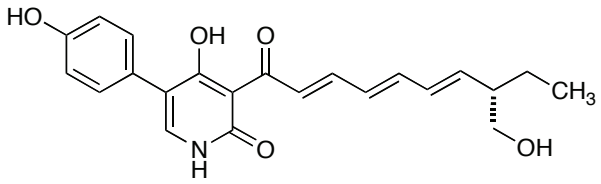
To a stirred slurry of alcohol **10** (30 mg, 0.076 mmol, 1.0 equiv.) and powdered molecular sieves (4 mg, 4Å) in dry DCM (1 mL) were added tetrapropylammonium perruthenate (2.4 mg, 6.8 mmol, 9 mol%) and *N*-methylmorpholine-*N*-oxide (11.6 mg, 0.099 mmol, 1.3 equiv.) at 0 °C. After 15 min the ice bath was removed and the mixture stirred at rt for 1 h. The slurry was filtered through a small plug of silica (rinse with 5 mL DCM) and the solvents removed *in vacuo* (bath temperature 25 °C). The crude product was purified by FC (*n*-pentane with a gradient of Et_2O 0-5%) yielding **11** (25 mg, 0.064 mmol, 84%, *E*/*Z* 18:1) as a yellowish oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 6.7 Hz, 4H), 7.45 – 7.32 (m, 6H), 7.07 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.34 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.17 – 6.05 (m, 2H), 3.69 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.62 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.38 – 2.24 (m, 1H), 1.68 – 1.54 (m, 1H), 1.47 – 1.32 (m, 1H), 1.05 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 194.1, 152.8, 148.8, 135.8, 133.7, 130.5, 129.8, 129.8, 127.8, 66.4, 47.8, 27.0, 23.8, 19.4, 11.8; **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 3048, 2950, 2810, 1744, 1727, 1680, 1591, 1441, 1366, 1292, 1116, 1060, 977, 859, 743, 698; $\mathbf{R}_f$ = 0.45 (*n*-pentane/Et_2O 1:1); **HR-MS** (ESI) calc. for $[C_{25}H_{33}O_2Si]^+$: $[M+H]^+$ 393.2250; found: 393.2244; $[\alpha]_D^{25}$ = + 24.7° (c 1.00, $CHCl_3$).

3-((*S*,2*E*,4*E*,6*E*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)deca-2,4,6-trienoyl)-4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)pyridin-2(1*H*)-one (13)



To a solution of LiOH*H_2O (4.6 mg, 0.11 mmol, 2.0 equiv.) and phosphonate **12**[7] (21 mg, 54 μmol, 1.0 equiv.) in distilled and degassed THF/H_2O (5:1 / 1 mL) was added aldehyde **11** (31 mg, 64 μmol, 1.2 eq.). The mixture was stirred in the dark for 3 days under argon. The orange solution was diluted with saturated aqueous ammonium chloride solution (5 mL) and the resulting mixture extracted 3x with DCM (5 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The residue was purified by FC (DCM/MeOH 15:1 to 12:1) yielding protected torrubiellone C (**13**) as a yellow oil (18 mg, 24 μmol, 45%, *E*/*Z* >12:1). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 13.17 (s, 1H), 7.63 (d, *J* = 6.7 Hz, 4H), 7.44 – 7.34 (m, 9H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.26 – 7.20 (m, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.60 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.54 (d, *J* = 15.3 Hz, 1H), 6.33 (dd, *J* = 14.8, 11.3 Hz, 1H), 6.18 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.79 (dd, *J* = 15.2, 8.7 Hz, 1H), 5.00 (s, 2H), 3.82 (s, 3H), 3.65 – 3.53 (m, 5H), 2.27 – 2.17 (m, 1H), 1.65 – 1.53 (m, 1H), 1.37 – 1.27 (m, 1H), 1.04 (s, 9H), 0.83 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 193.4, 165.8, 164.6, 159.7, 158.6, 146.0, 143.1, 142.9, 135.8 , 133.9 , 131.2, 130.7, 130.2, 129.7, 129.4, 129.0, 128.9, 127.8, 126.5, 117.6, 117.5, 115.0, 114.2, 70.0, 66.8, 60.9, 55.4, 47.7, 29.8, 27.0, 24.0, 19.4, 11.8; **FTIR** (ATR) $\tilde{\nu}$ [cm^{-1}] = 2931, 2858, 2361, 1636, 1609, 1513, 1462, 1386, 1239, 1175, 1110, 1031, 1004, 825, 702; $\mathbf{R_f}$ = 0.55 (DCM/MeOH 12:1); **HR-MS** (ESI) calc. for $[C_{47}H_{52}NO_6Si]^+$: $[M+H]^+$ 754.3564; found=754.3558; $[\alpha]_D^{25}$ = + 9.2° (c 0.75, $CHCl_3$).

4-hydroxy-3-((*S*,2*E*,4*E*,6*E*)-8-(hydroxymethyl)deca-2,4,6-trienoyl)-5-(4-hydroxyphenyl) pyridin-2(1*H*)-one, (+)-Torrubiellone C (*ent*-1)



Freshly crystallized LiI*3H_2O (5.6 mg, 37 μmol, 2.0 equiv.), pyridonpolyene **13** (14 mg, 19 μmol, 1.0 equiv.) and pyridiniumchloride (4.3 mg, 37 μmol, 2 equiv.) were suspended in degassed THF (1 mL), purged with argon and heated to 65 °C for 10 h in the dark. After cooling to rt, the mixture was diluted with Et_2O (15 mL) and washed twice with water (5 mL). The organic layer was dried over sodium sulfate, filtered and the solvents removed *in vacuo*. Exposure to light was minimized during the work-up procedure. The crude material was purified by FC (DCM/MeOH 30:1) allowing for the recovery of 2 mg unreacted starting material. The obtained *E*/*Z* mixture (ca. 5:1) was directly used in the next deprotection step.

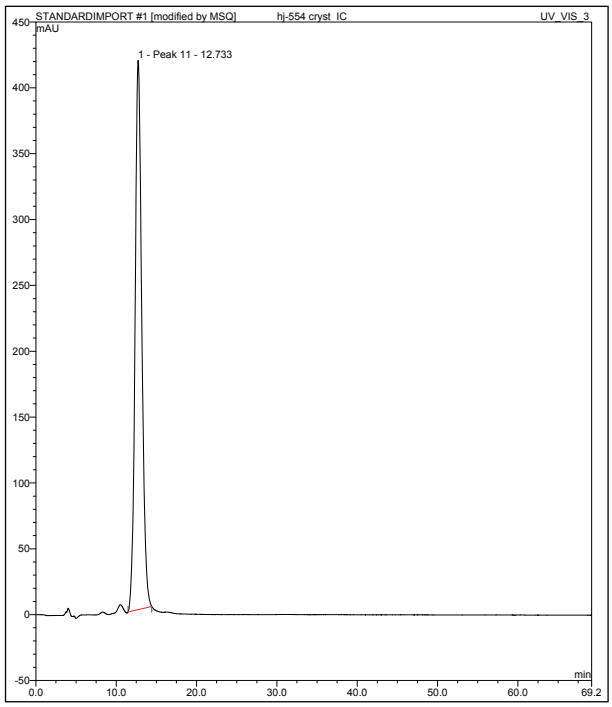
To a solution of the crude material from the former step (9 mg, 12 μmol, 1.0 equiv.) in THF (0.5 mL) was added TBAF*3H_2O (5.8 mg, 18 μmol, 1.5 equiv.). The mixture was stirred 5 h at rt in the dark. Diethylether (10 mL) and water (5 mL) were added. The aqueous phase was washed 2x with diethylether (5 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The obtained crude product was purified by FC (DCM/MeOH 10:1) giving a mixture of inseparable *E*/*Z* isomers (6 mg, 12 μmol, 100%, ca. 5:1).

The PMB-protected pyridonpolyene from the former step (5 mg, 10 μmol) was stirred 10 minutes under exclusion of light with 5% trifluoroacetic acid in DCM at room temperature (0.5 mL). The reaction mixture was poured into saturated $NaHCO_3$ solution (5 mL) and extracted three times with DCM (10 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The product was purified by repeated fractional crystallization MeOH/DCM/pentane (1:4:16 ; 1.5 mL) at 0 °C and collected by centrifugation giving (+)-torrubiellone C, (+)-**1**) as an amorphous

bright yellow solid (2.8 mg, 7.3 μmol, 54% over three steps, *E*/*Z* >30:1). The spectroscopic data were found to be in full agreement with those published for the naturally occurring torrubiellone C (**1**)[8], except for the inverted optical rotation.

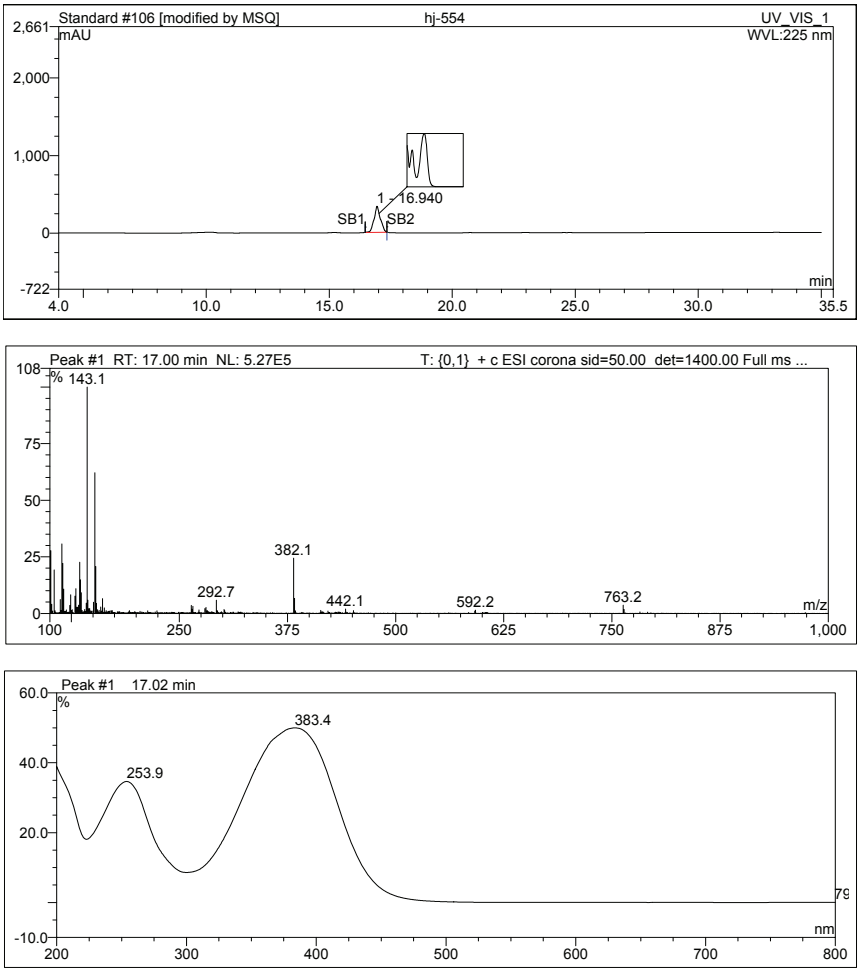
^{1}H-NMR (500 MHz, Acetone-d_6) δ 8.45 (s, 1H), 8.14 (d, *J* = 15.0 Hz, 1H), 7.67 – 7.57 (m, 1H), 7.61 (s, 1H), 7.37 – 7.32 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.83 (dd, *J* = 14.8, 11.0 Hz, 1H), 6.52 (dd, *J* = 14.8, 11.5 Hz, 1H), 6.36 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.95 (dd, *J* = 15.2, 8.7 Hz, 1H), 3.60 (s, 1H), 3.53 (d, *J* = 5.9 Hz, 2H), 2.26 – 2.19 (m, 1H), 1.67 – 1.57 (m, 1H), 1.38 – 1.31 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (126 MHz, Acetone-d_6) δ 194.5, 178.8, 162.5, 157.7, 145.3, 143.8, 143.3, 140.3, 131.7, 130.8, 130.1, 128.5, 125.2, 115.3, 114.5, 65.1, 49.7, 48.2, 24.1, 11.4; **R_f** = 0.41 (DCM/MeOH 9:1); **HR-MS** (ESI) calc. for $[C_{22}H_{24}NO_5]^+$: $[M+Na]^+$ 404.1474; found: 404.1468; **HPLC** t_R = **12.7** min (Hexane/*i*PrOH 60:40 1 mL/min, Chiralpak® IC 250x4.6 mm), t_R = **16.9** min (Acetonitrile/H_2O 10:90 to 100:0 in 30 min, 1 mL/min, Phenomenex Gemini 5 μm C18 110A 150 x 4.6 mm); **UV** λ_{max} = 254, 383 nm; $[\alpha]_D^{25}$ = + 18.4 ° (c 0.08, MeOH).

Overlay of Samples from Integration View



HPLC trace of (+)-torrubiellone C, (+)-**1** (Hexane/*i*PrOH 60:40 1 mL/min, Chiralpak® IC 250x4.6 mm)

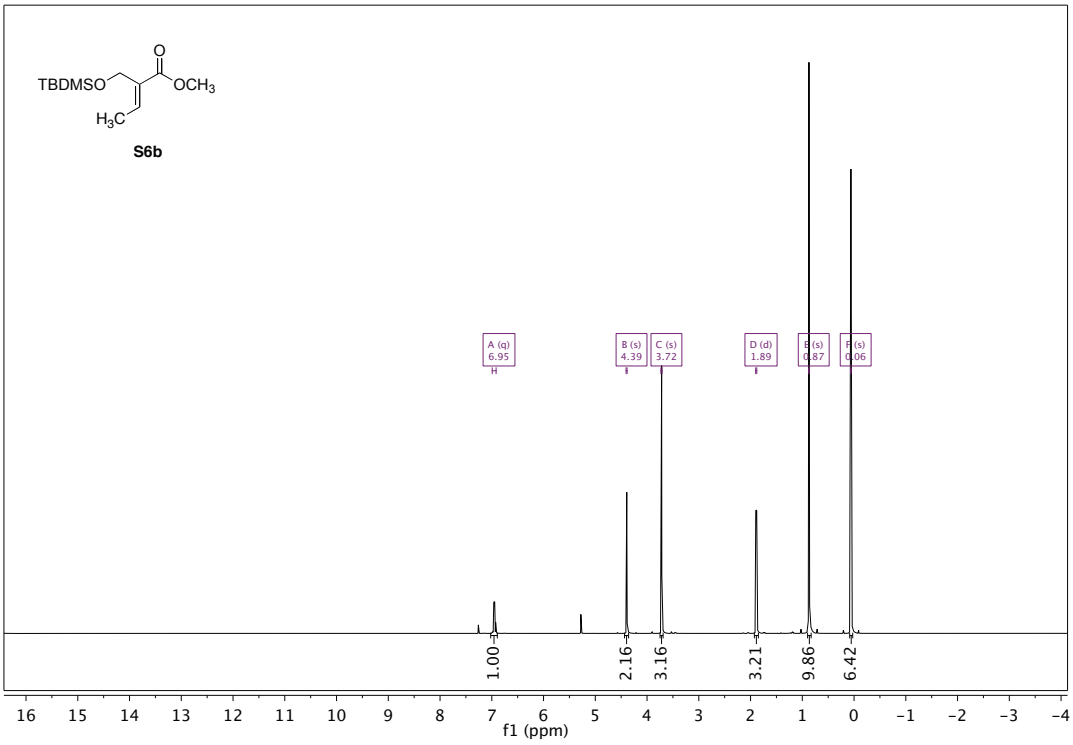
Overlay of Samples and Spectra from Integration View

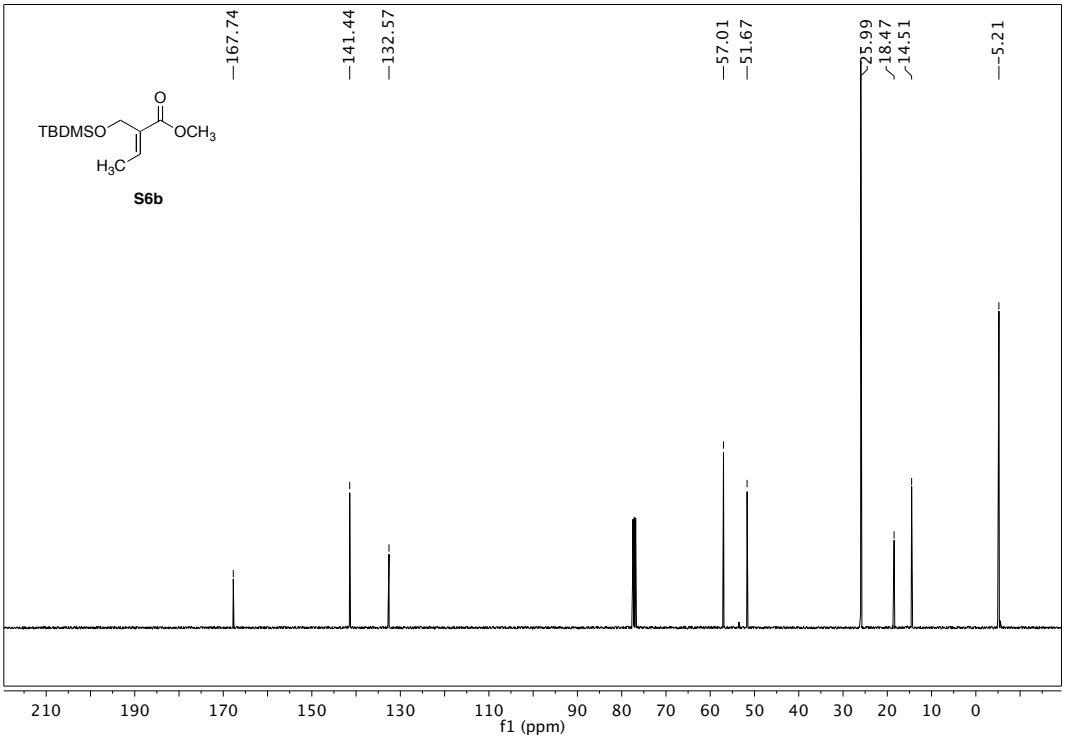


HPLC trace, MS and UV-Vis spectra of of (+)-torrubiellone C, (+)-**1** (Acetonitrile/H_2O 10:90 to 100:0 in 30 min, 1 mL/min, Phenomenex Gemini 5 μm C18 110A 150 x 4.6 mm)

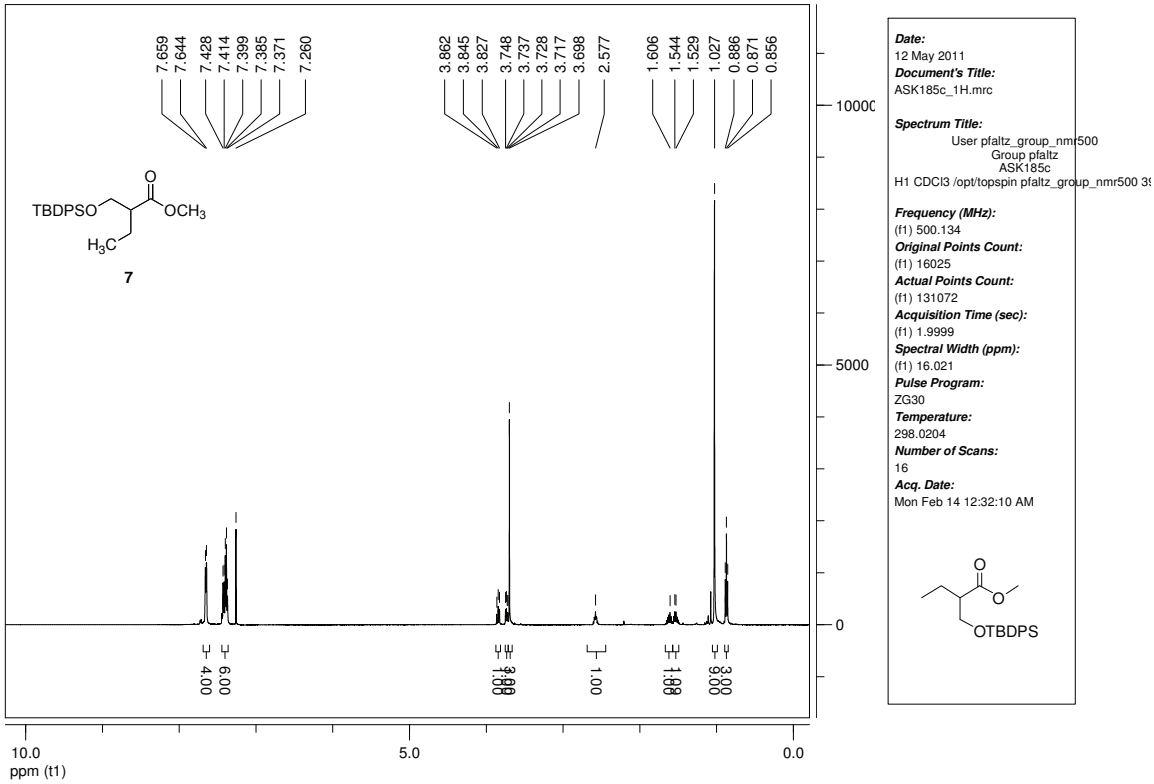
Copies of NMR Spectra:

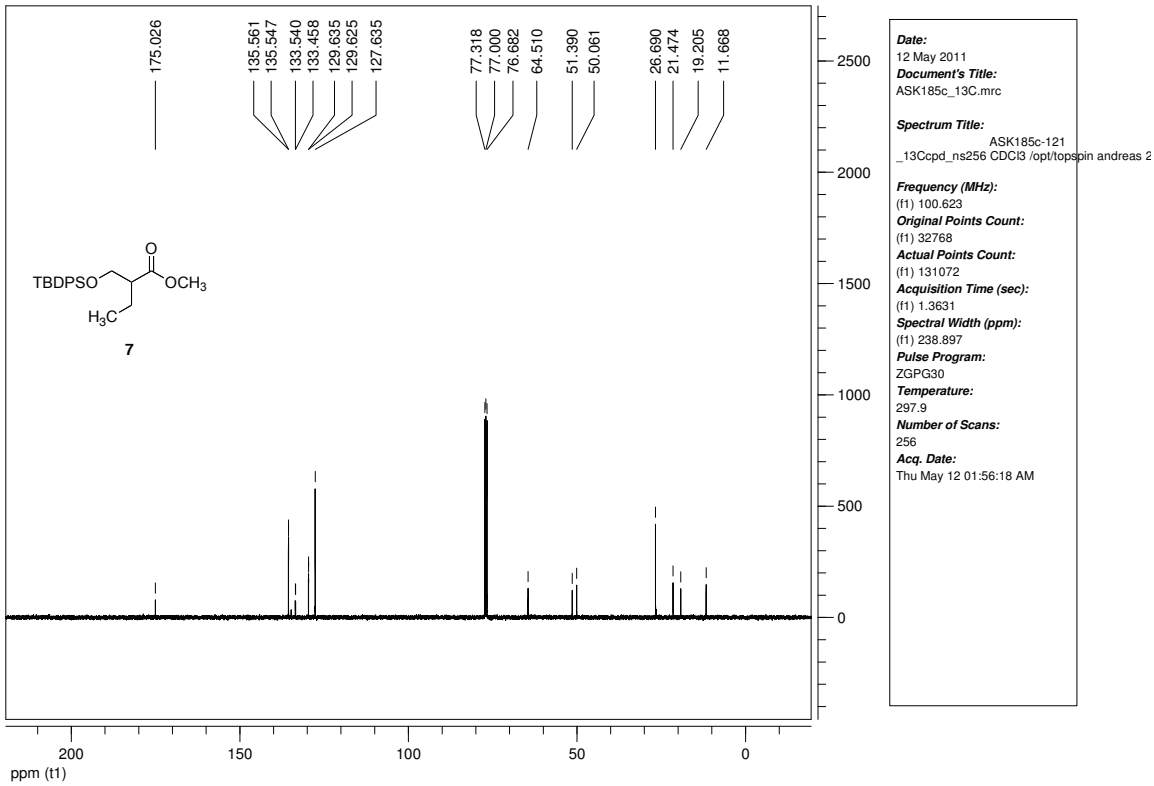
(*E*)-Methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)but-2-enoate (S6b)



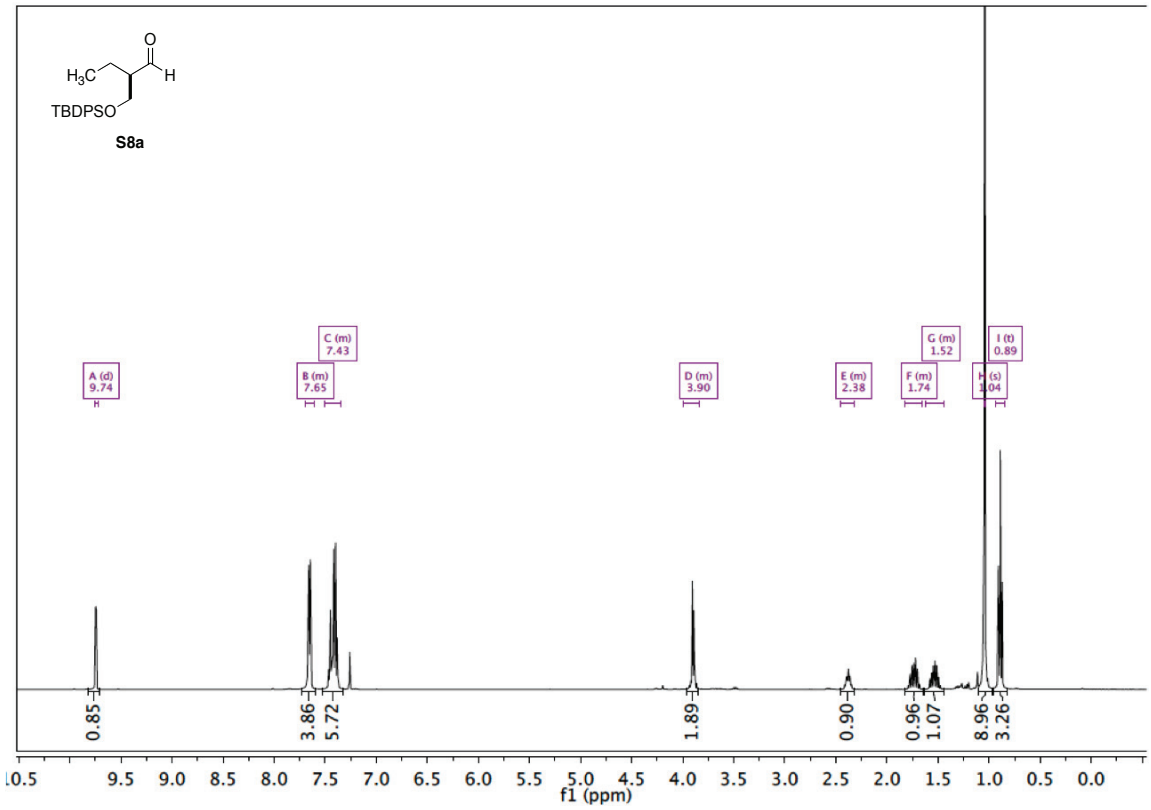


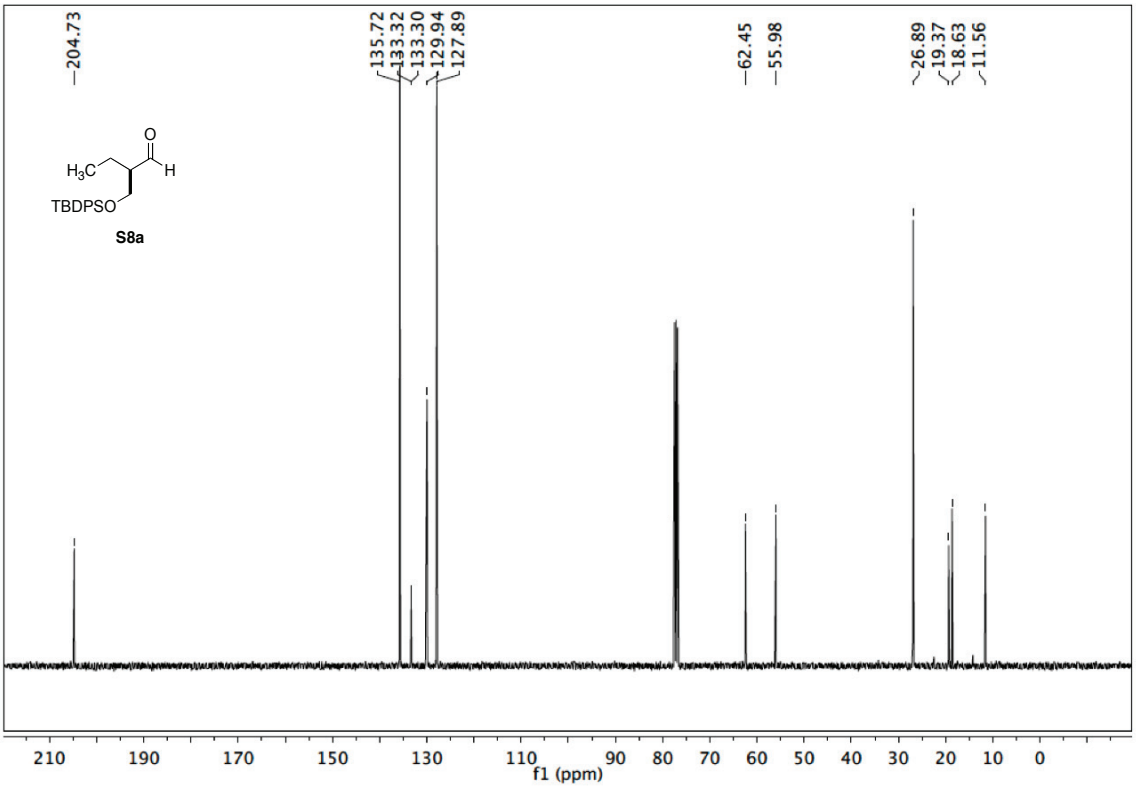
(*R*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butanoate (7)



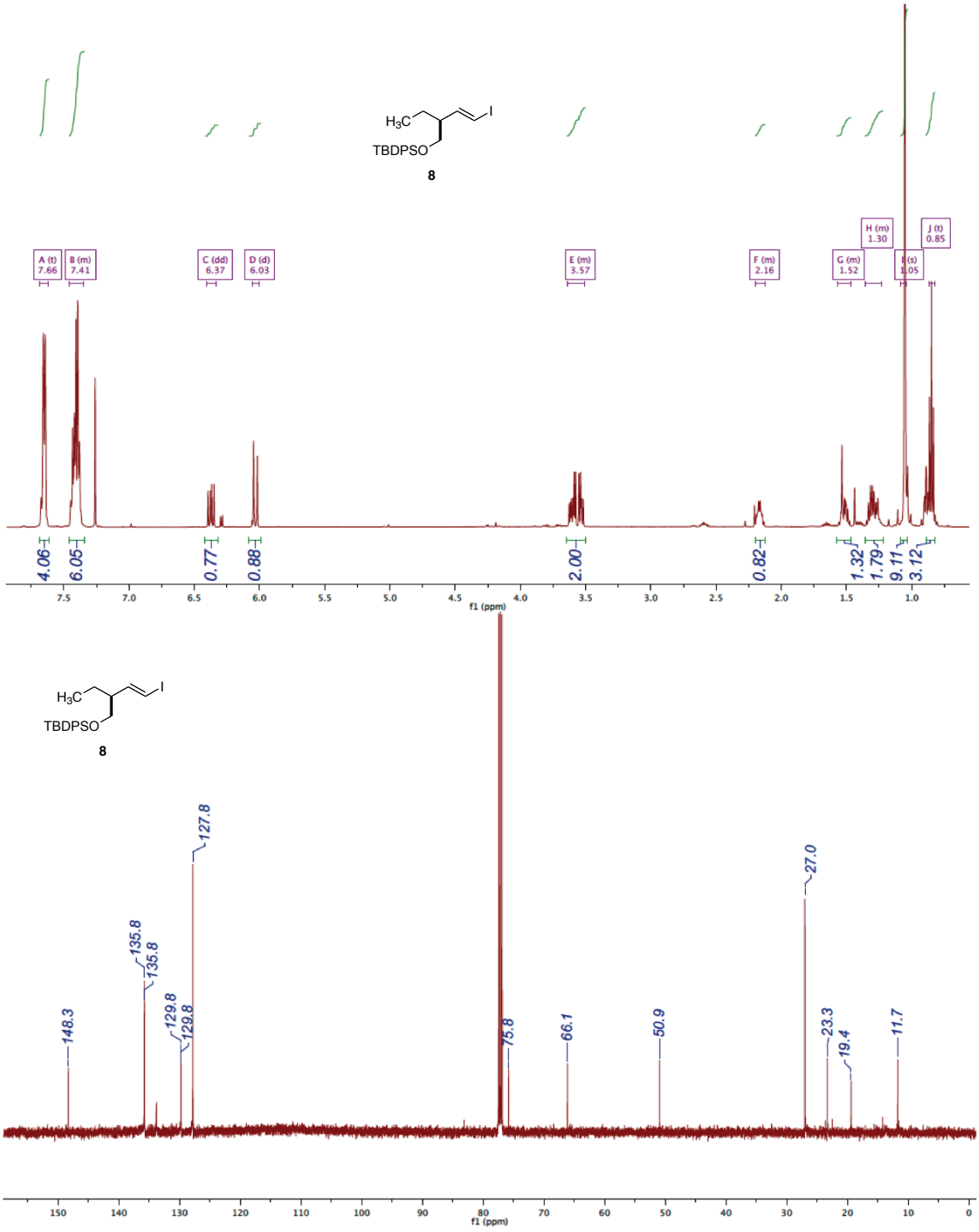


(*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)butanal (S8a)

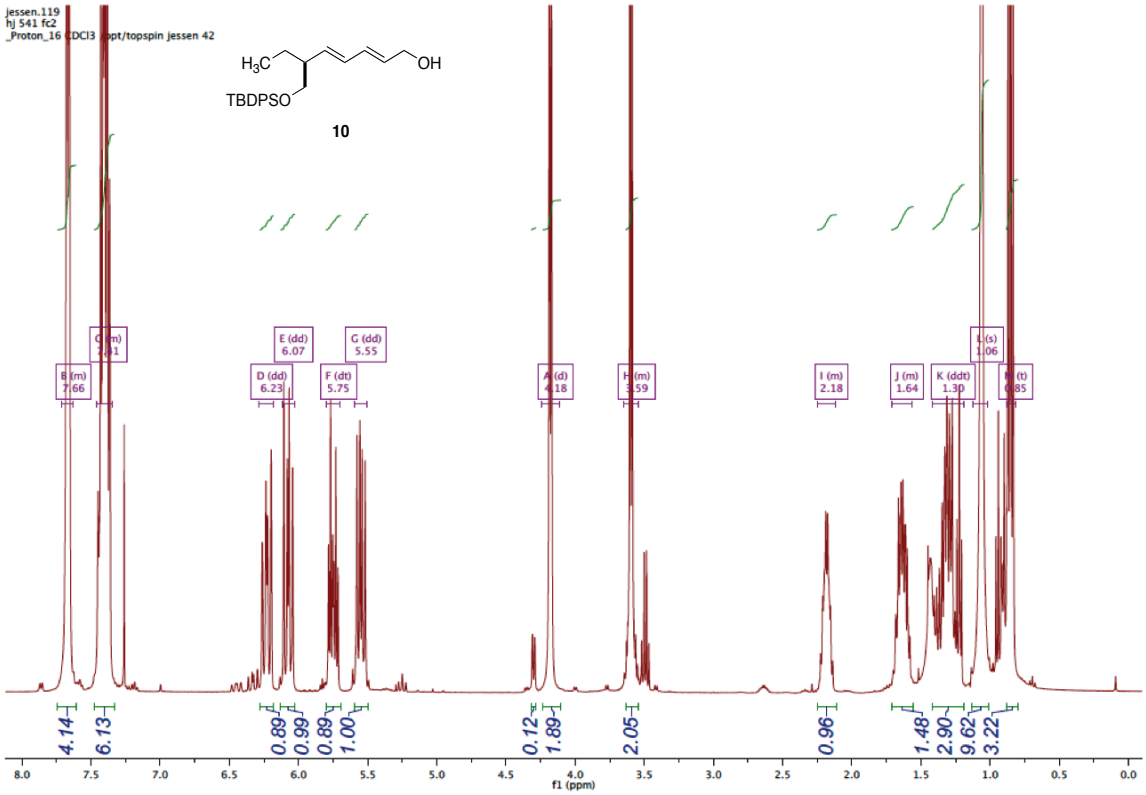


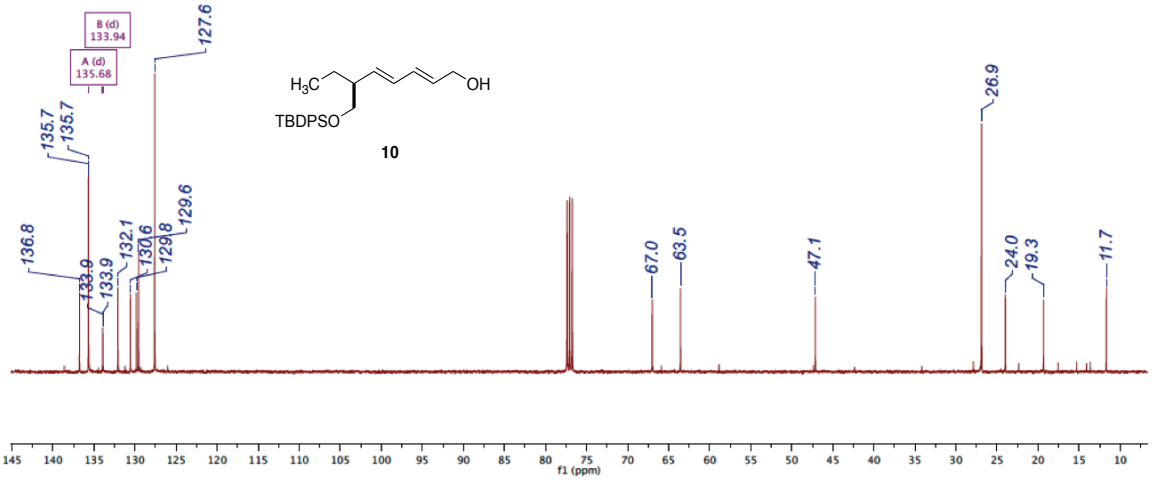


(*S*,*E*)-*tert*-Butyl((2-ethyl-4-iodobut-3-en-1-yl)oxy)diphenylsilane (8)

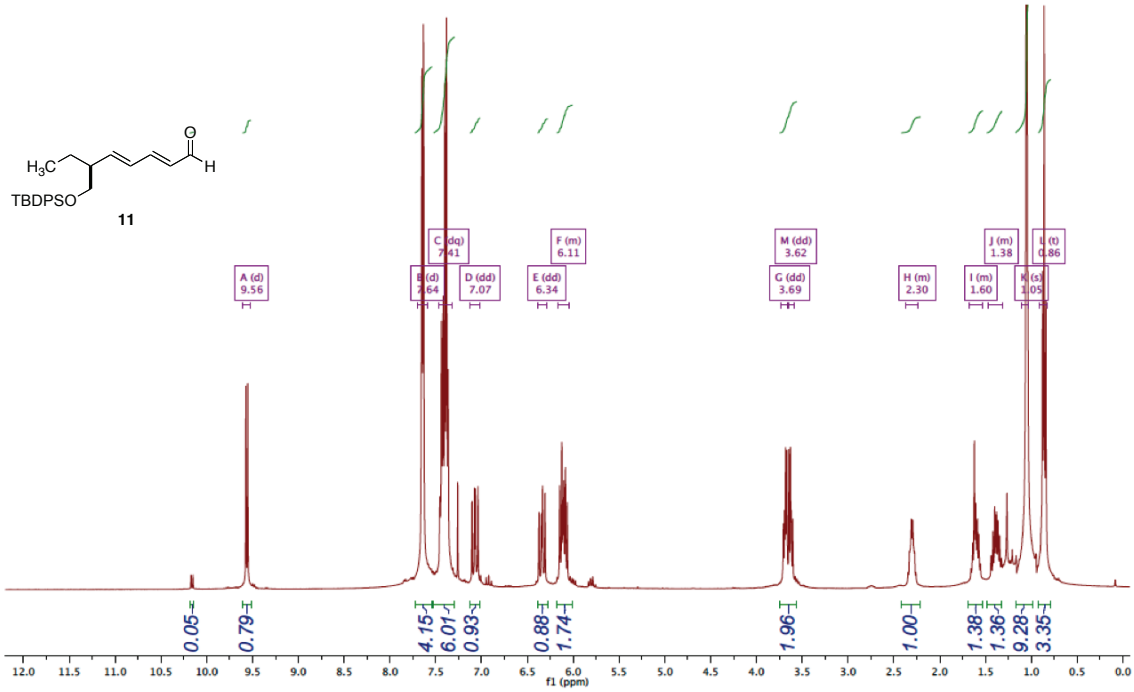


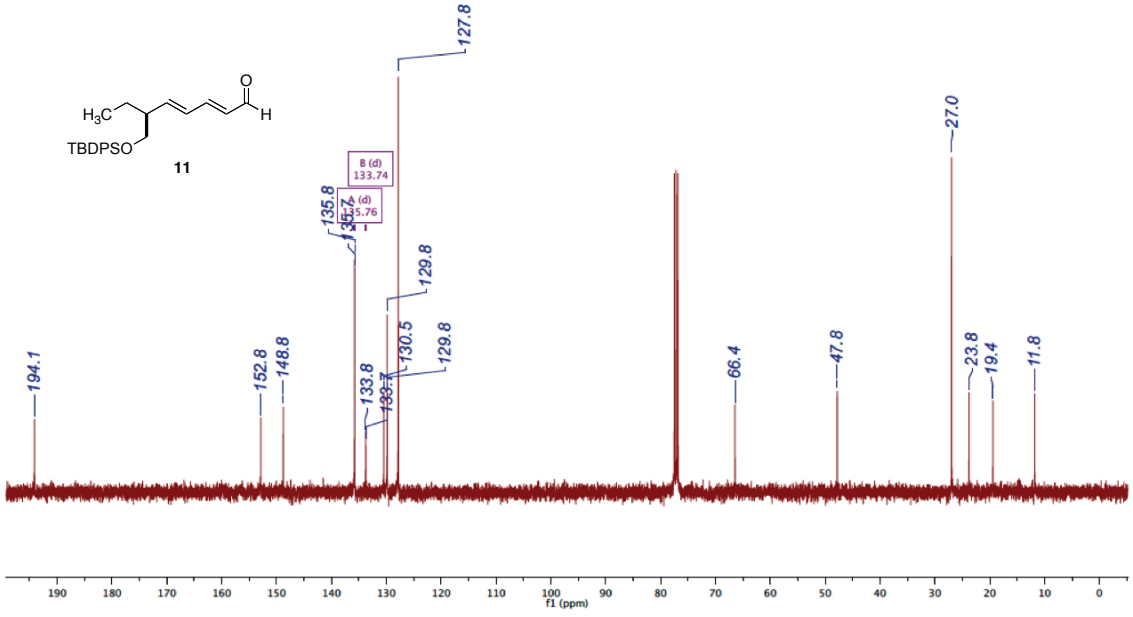
(*S*,2*E*,4*E*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)octa-2,4-dien-1-ol (10)



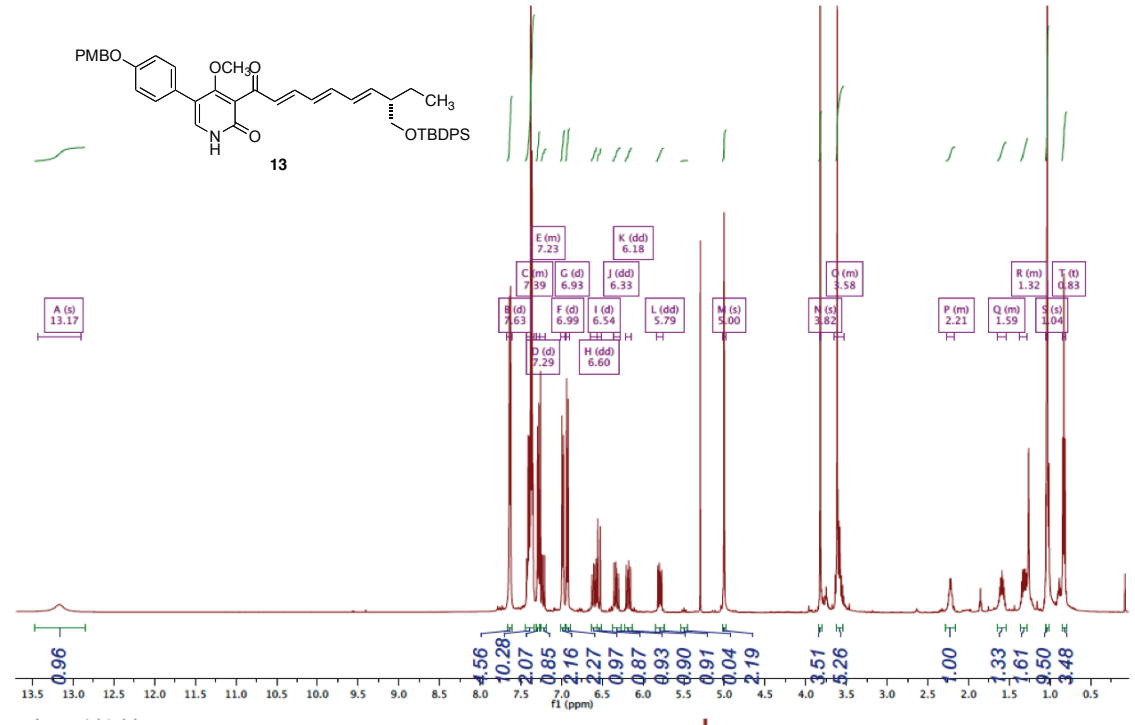


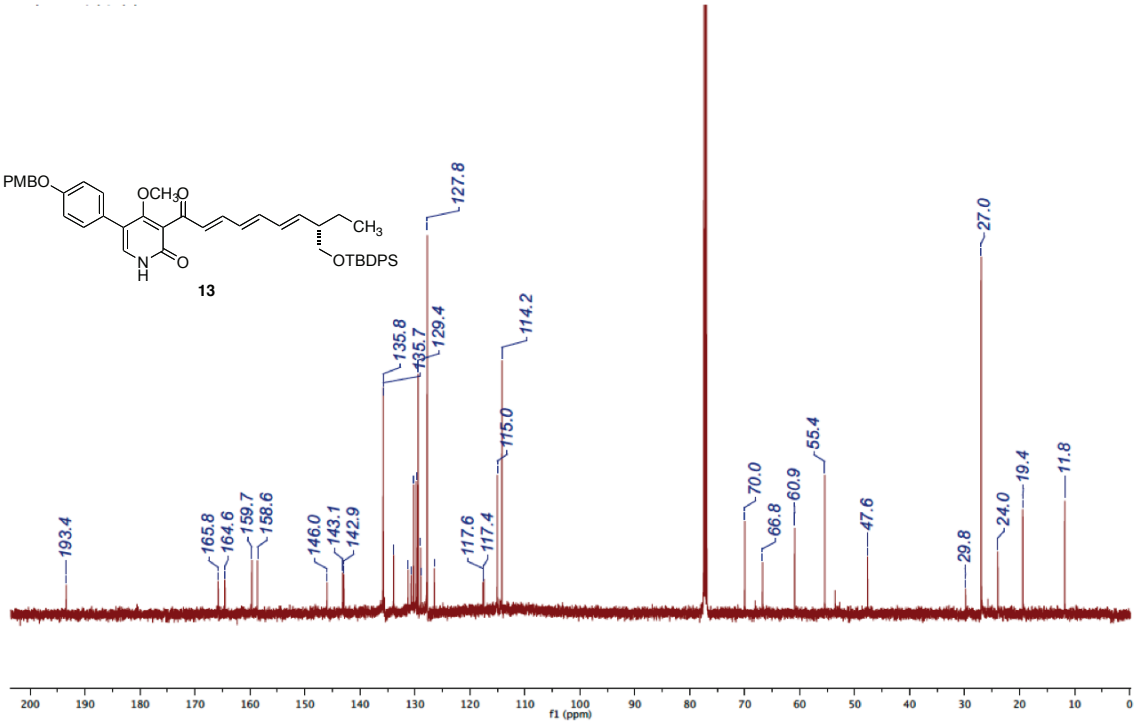
(*S*,2*E*,4*E*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)octa-2,4-dienal (11)



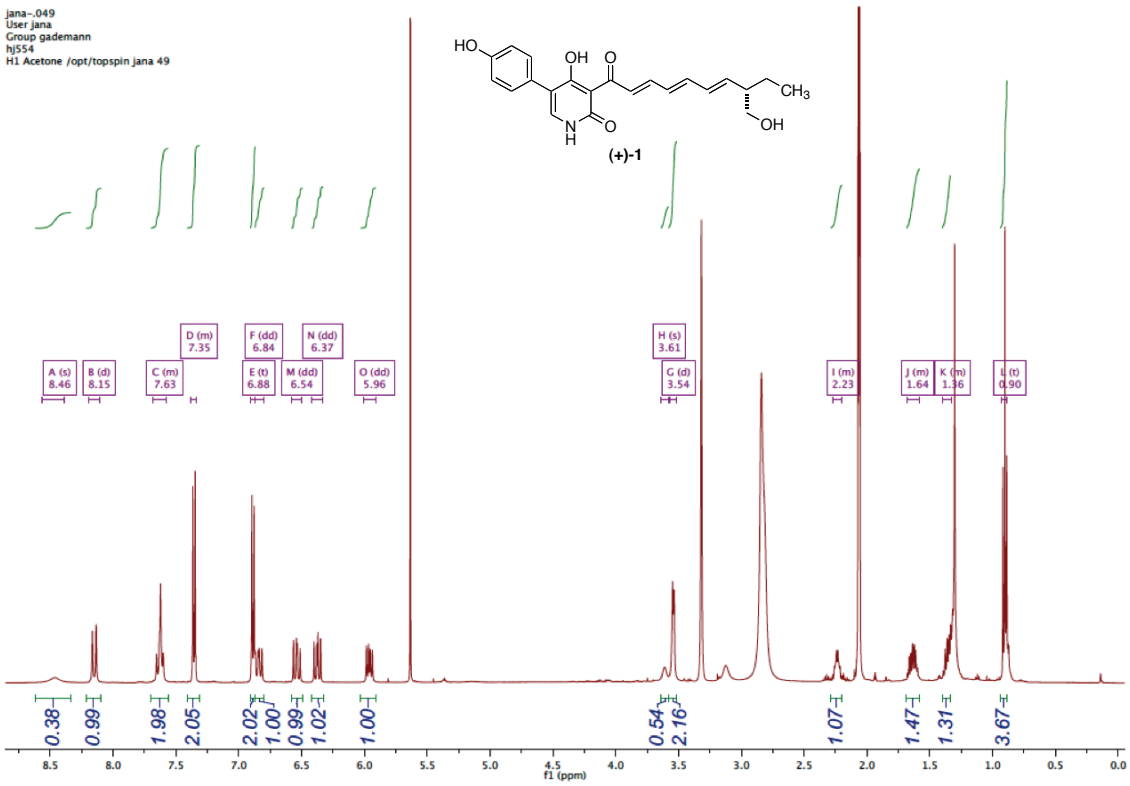


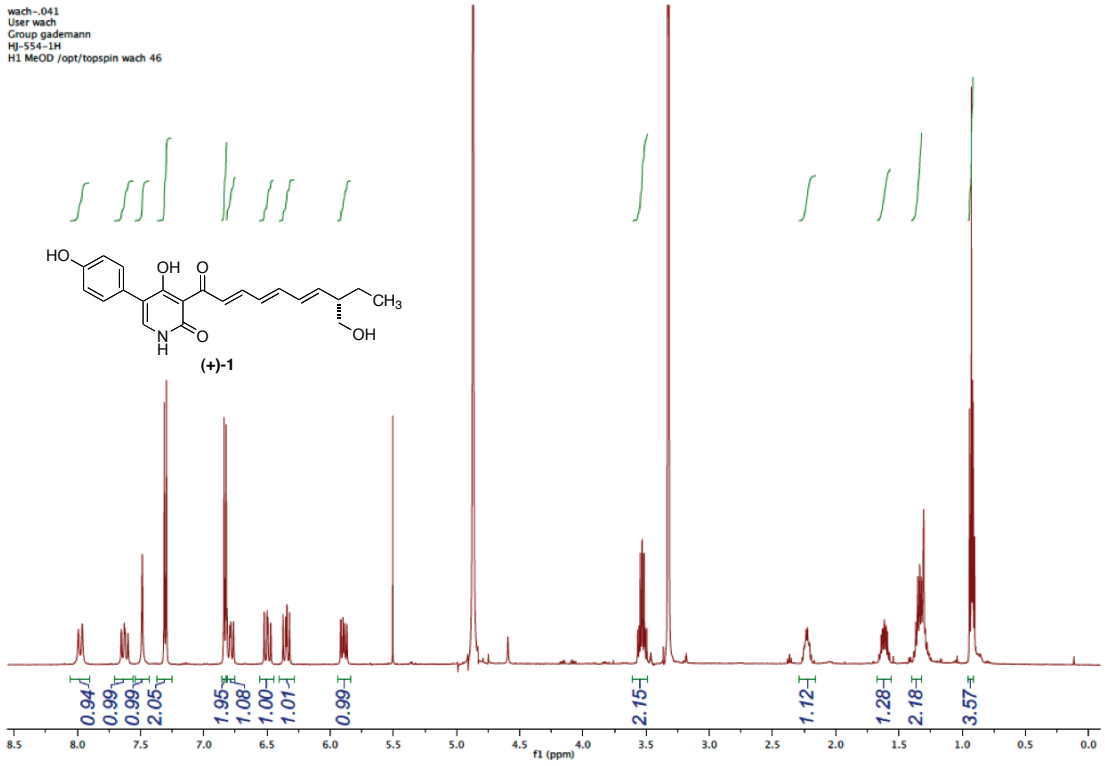
3-((*S*,2*E*,4*E*,6*E*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)deca-2,4,6-trienoyl)-4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)pyridin-2(1*H*)-one (13)

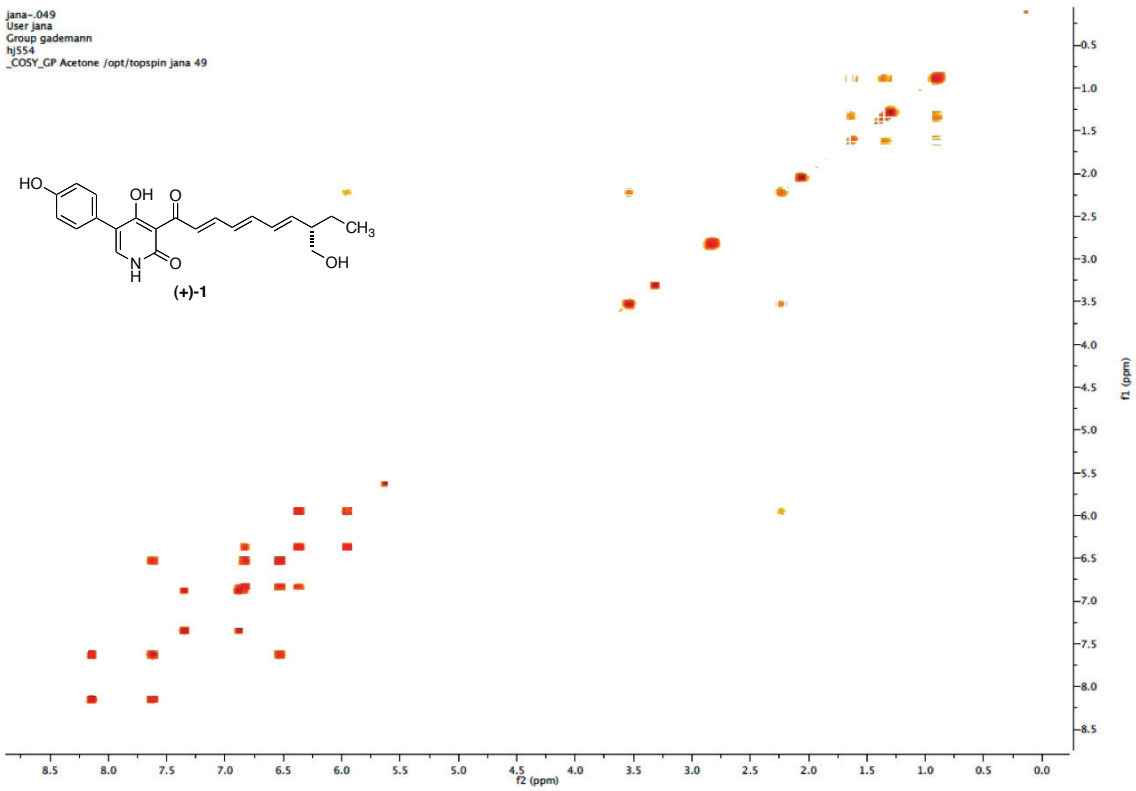




Synthetic (+)-Torrubiellone C, (+)–1



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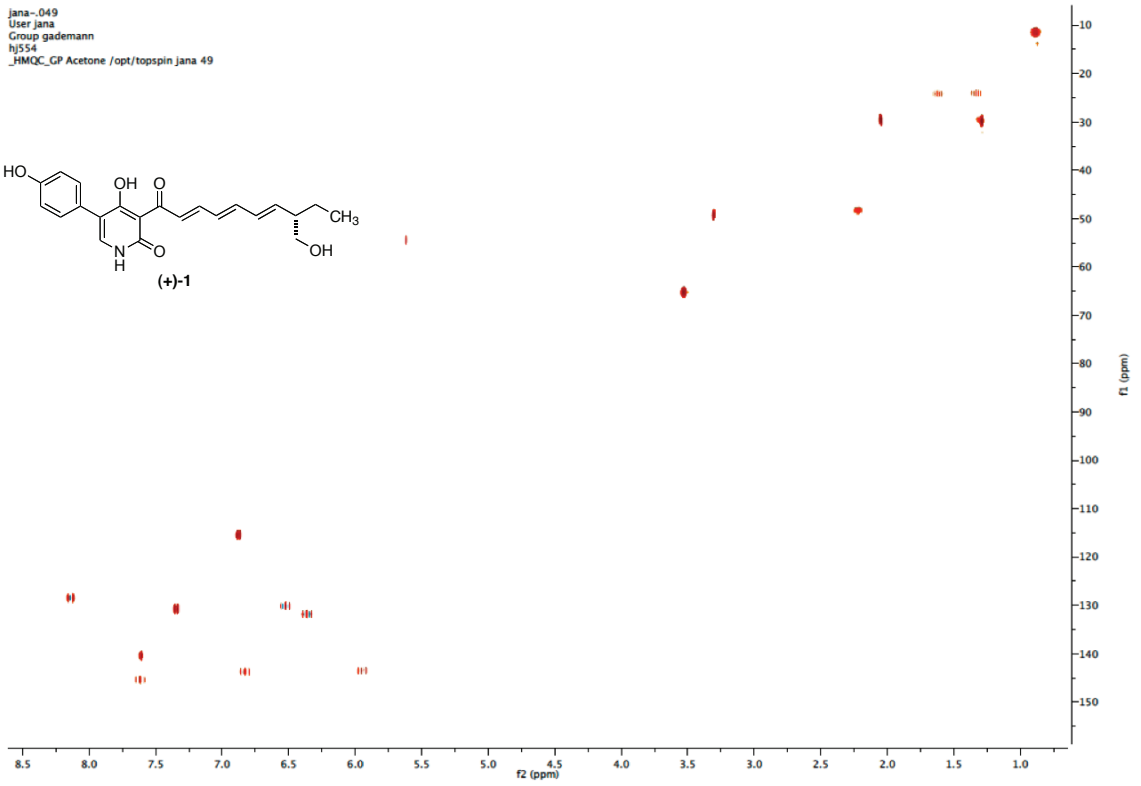
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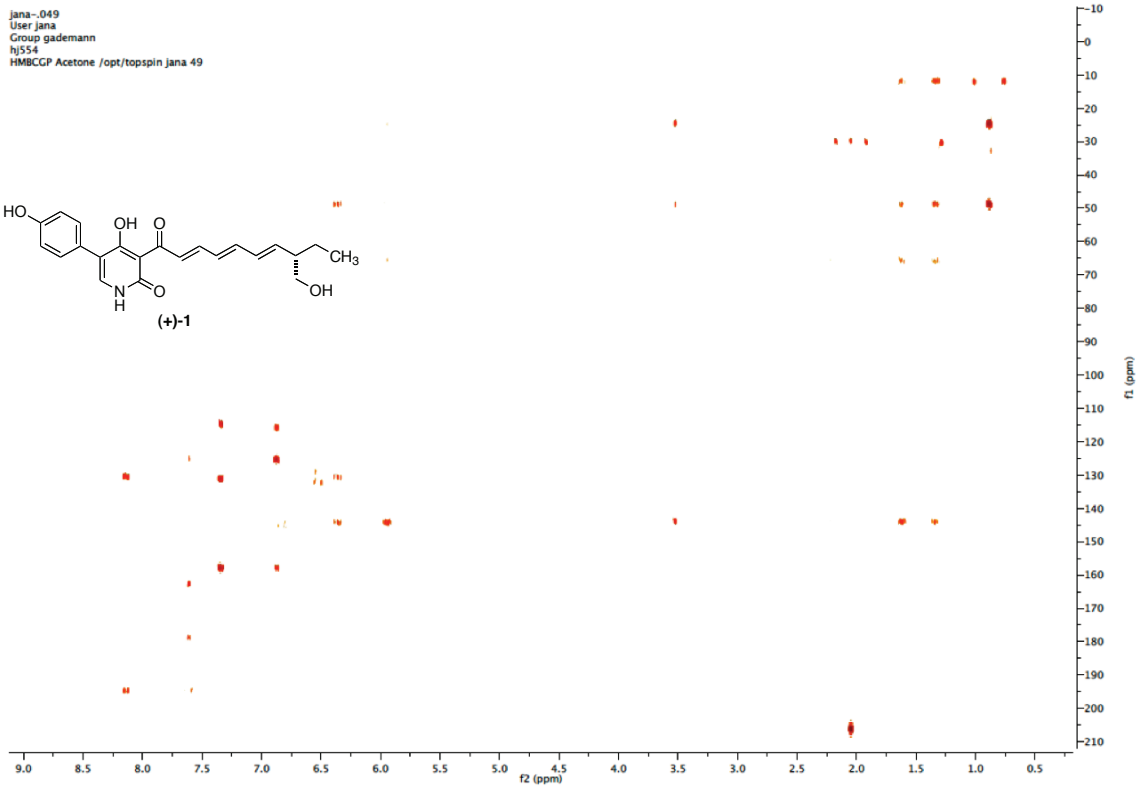
f1 (ppm)
f2 (ppm)


jana-.049
User jana
Group gademann
hj554
HMBCGP Acetone /opt/topspin jana 49
HO
OH
O
CH3
OH
N
H
O
(+)-1
f1 (ppm)
f2 (ppm)

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