

**Asymmetric Total Synthesis of (+)-Phainanoid A, and Biological Evaluation of the Natural Product and Its Synthetic Analogues**

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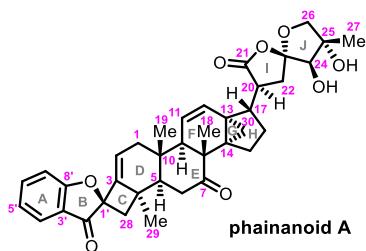
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## 1. General Information

Unless otherwise noted, reactions were performed under an inert atmosphere (dry N<sub>2</sub> or Ar) with dry solvents processed by filtration through a Pure-Solv MD-5 Solvent Purification System (Innovative Technology) or distillation in the presence of an appropriate desiccant. Glassware was dried utilizing propane flame under high vacuum. Reaction temperatures were reported as the temperatures of the bather surrounding the flasks or vials. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical) and visualized by UV (254 nm), and/or CAM or KMnO<sub>4</sub> staining. Flash column chromatography was performed using silica gel (Silica 60M, particle size 0.04–0.063 mm) purchased from Macherey-Nagel. Vials (15 × 45 mm 1 dram (4 mL) / 17 × 60 mm 3 drams (7.5 mL) with PTFE lined cap attached) were purchased from Qorpak. High-resolution mass spectra (HRMS) were recorded on an Agilent 6223 TOF mass spectrometer using electrospray ionization with fragmentation voltage set at 130 V or 70 V, processed with an Agilent MassHunter Operating System, and were reported for the molecular ion [M+H]<sup>+</sup> or [M+Na]<sup>+</sup>. X-ray diffraction data were collected at 100(2) K on a Bruker APEX-II CCD diffractometer. Infrared spectra were recorded as frequencies in reciprocal centimeters (cm<sup>-1</sup>) on a Nicolet iS5 FT-IR Spectrometer using neat thin film technique with potassium bromide (KBr) salt plates. Nuclear magnetic resonance spectra (<sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>31</sup>P-NMR, <sup>1</sup>H-<sup>1</sup>H COSY, NOESY) were recorded with a Bruker Model DMX 400 (400 MHz, <sup>1</sup>H at 400 MHz, <sup>13</sup>C at 101 MHz, <sup>31</sup>P at 162 MHz) and DMX 500 (500 MHz, <sup>1</sup>H at 500 MHz, <sup>13</sup>C at 126 MHz). Chemical shifts were reported in parts per million (ppm, δ) and were referenced to residual solvent (CDCl<sub>3</sub>, δ = **7.26** ppm (<sup>1</sup>H) and **77.16** ppm (<sup>13</sup>C); C<sub>6</sub>D<sub>6</sub>, δ = **7.16** ppm (<sup>1</sup>H) and **128.06** ppm (<sup>13</sup>C)). Coupling constants were reported in Hertz (Hz). Data for <sup>1</sup>H NMR spectra were reported as follows: chemical shift (ppm, referenced to protium, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, dq = doublet of quartets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration). Analytical chiral HPLC was carried out on an Agilent 1260 infinity HPLC with DAD, Chiraldak IB and IF served as columns, and mixtures of *n*-hexane and *i*-PrOH were used for elution. Optical rotations were measured on an Anton Paar's MCP 200 polarimeter using a 10 mm pathlength cell or a Jasco DIP-1000 digital polarimeter using a 100 mm pathlength cell at 589 nm. Circular dichroism spectroscopy of (+)-phainanoid A was recorded on a Jasco J-1500 spectrometer. All other materials were obtained from Sigma-Aldrich, Fisher Scientific, Combi-blocks, Strem or Oakwood and were used as received.

## 2. Positional Numbering



The carbon numbering system as outlined by Yue and coworkers<sup>1</sup> and the ring assignment shown above are utilized throughout this Supporting Information.

## 3. Abbreviations

Ac, acetyl

acac, acetylacetone

Bn, benzyl

*n*-Bu, *normal*-butyl

*t*-Bu, *tert*-butyl

Bz, benzoyl

CBS, Corey-Bakshi-Shibata

CDI, 1,1'-carbonyldiimidazole

cod, 1,5-cyclooctadiene

Cp, cyclopentadienyl

*m*-CPBA, *meta*-chloroperoxybenzoic acid

DCM, dichloromethane

DIBAL-H, diisobutylaluminum hydride

DIPEA, diisopropylethylamine

DMAP, 4-dimethylaminopyridine

DMP, Dess-Martin periodinane

DMSO, dimethyl sulfoxide

dppp, 1,3-bis(diphenylphosphino)propane

ESI, electrospray ionization

Et, ethyl

HMDS, hexamethyldisilazane

HRMS, high-resolution mass spectrometry

KHMDS, potassium bis(trimethylsilyl)amide

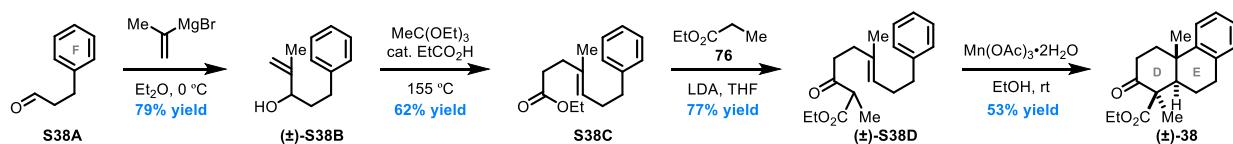
LDA, lithium diisopropylamide

Me, methyl  
MOM, methoxymethyl  
MP, melting point  
MS, molecular sieves  
NCS, *N*-chlorosuccinimide  
NIS, *N*-iodosuccinimide  
NMO, *N*-methylmorpholine *N*-oxide  
NMR, nuclear magnetic resonance  
Ph, phenyl  
*n*-Pr, *normal*-propyl  
rsm, recovery of starting material  
TBAF, tetrabutylammonium fluoride  
TBAI, tetrabutylammonium iodide  
TBHP, *tert*-butyl hydroperoxide  
TBS, *tert*-butyldimethylsilyl  
TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl  
TES, triethylsilyl  
Tf, trifluomethanosulfonyl  
TFA, trifluoroacetic acid  
THF, tetrahydrofuran  
TIPS, triisopropylsilyl  
TLC, thin-layer chromatography  
TMS, trimethylsilyl  
TOF, time-of-flight  
Ts, *para*-toluenesulfonyl

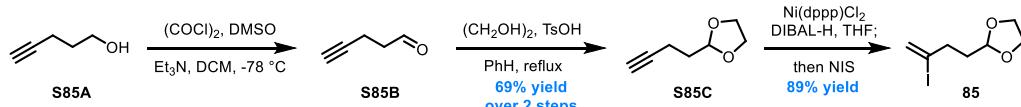
## 4. Synthesis of Fragments and Intermediates

**Scheme S1.** Synthesis of ( $\pm$ )-38, 85, 126 and 136

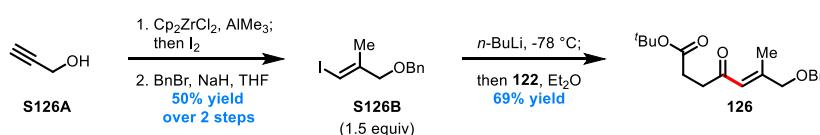
A. Modified synthetic route to the known ketoester ( $\pm$ )-38



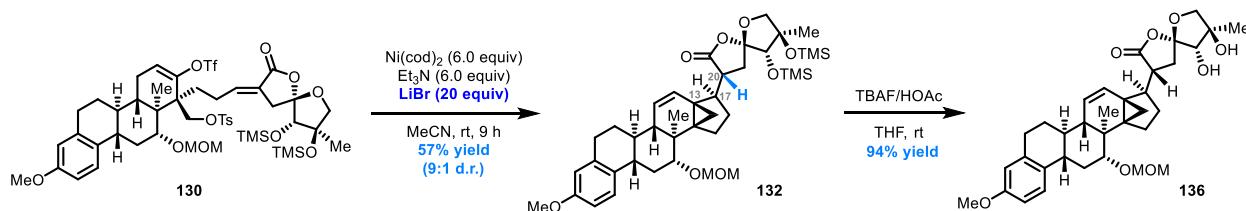
B. Synthesis of vinyl iodide 85



C. Synthesis of enone 126

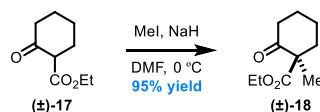


D. Synthesis of pure [4.3.1]propellane 136



## 5. Synthetic Procedures and Characterization of New Compounds

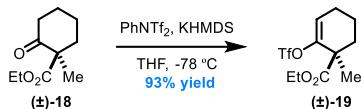
### Synthesis of $\beta$ -ketoester ( $\pm$ )-18



To a suspension of NaH (440 mg, 60% dispersion in mineral oil, 11 mmol) in DMF (20 mL) was added ( $\pm$ )-17 (1.6 mL, 10 mmol) dropwise. The reaction mixture was stirred at 0 °C until a light-yellow solution was obtained without any H<sub>2</sub> evolution. MeI (0.75 mL, 12 mmol) was then added at the same temperature dropwise. The reaction mixture was allowed to warm up to room temperature and keep stirring for 1 hour, after which it was quenched with a saturated NH<sub>4</sub>Cl solution and extracted with ether (20 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) gave ( $\pm$ )-18 as a colorless oil (1.75 g, 95% yield). The experimental NMR data of ( $\pm$ )-18 recorded were consistent with those reported by Shneider and co-

workers.<sup>2</sup>

### Synthesis of vinyl triflate ( $\pm$ )-19



A flame-dried round bottle flask was charged with KHMDS (2.83 g, 14.2 mmol) and THF (20 mL). The clear solution was cooled down to -78 °C, after which a solution of ( $\pm$ )-18 (1.75 g, 9.5 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 40 minutes, and then solid PhNTf<sub>2</sub> (4.07 g, 11.4 mmol) was added to the solution in one portion. The reaction mixture was stirred for another 60 minutes, then quenched with a saturated NH<sub>4</sub>Cl solution and extracted with ethyl acetate (20 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 80:1) gave ( $\pm$ )-19 as a pale-yellow oil (2.81 g, 93% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.6 (KMnO<sub>4</sub>)

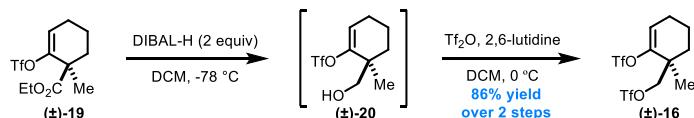
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.85 (t, J = 4.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.31–2.18 (m, 3H), 1.70–1.60 (m, 3H), 1.42 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 173.59, 149.65, 118.94, 118.44 (q, J = 319.2 Hz), 61.70, 46.84, 36.05, 24.51, 22.17, 18.67, 14.04 ppm

**IR (neat):** ν 2987, 2945, 1735, 1415, 1210, 1143, 1027, 901, 606 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>11</sub>H<sub>15</sub>F<sub>3</sub>NaO<sub>5</sub>S<sup>+</sup> [M+Na]<sup>+</sup> 339.0484, found 339.0484

### Synthesis of ditriflate ( $\pm$ )-16



To a solution of ( $\pm$ )-19 (3.16 g, 10 mmol) in DCM (50 mL) was slowly added a solution of DIBAL-H in hexanes (1 M, 20 mL, 20 mmol) at -78 °C. The reaction mixture was stirred at the same temperature for 30 minutes before the addition of a saturated solution of Rochelle's salt (50 mL). The reaction mixture was warmed up to room temperature and stirred for another 3 hours. The layers were separated, and the aqueous layer was extracted with DCM (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give the crude alcohol ( $\pm$ )-20 intermediate as a colorless oil. In practice, the crude ( $\pm$ )-20 is analytically pure and can be directly used in the next reaction.

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.3 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  5.90 (t,  $J$  = 4.2 Hz, 1H), 3.70 (d,  $J$  = 11.3 Hz, 1H), 3.35 (d,  $J$  = 11.3 Hz, 1H), 2.34–2.13 (m, 2H), 2.05 (ddd,  $J$  = 13.4, 10.2, 3.3 Hz, 1H), 1.78 (ddtd,  $J$  = 13.2, 7.6, 5.5, 3.3 Hz, 1H), 1.72 (s, 1H), 1.68–1.58 (m, 1H), 1.51 (dddd,  $J$  = 13.3, 7.6, 3.3, 0.6 Hz, 1H), 1.08 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  152.63, 120.71, 118.48 (q,  $J$  = 319.3 Hz), 67.70, 41.04, 33.89, 24.94, 21.36, 18.49 ppm

**IR (neat):**  $\nu$  3397, 2944, 2882, 1676, 1411, 1211, 1143, 1021, 875, 608 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>9</sub>H<sub>13</sub>O<sub>4</sub>SF<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 297.0379, found 297.0370

The crude ( $\pm$ )-**20** was directly dissolved in DCM (50 mL), followed by sequential addition of 2,6-lutidine (1.6 mL, 14 mmol) and Tf<sub>2</sub>O (2 mL, 12 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for another 15 minutes. The reaction mixture was quenched with a saturated solution of NaHCO<sub>3</sub>. The layers were separated, and the aqueous layer was extracted with DCM (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 30:1) gave ditriflate ( $\pm$ )-**16** as a pale-yellow oil (3.5 g, 86% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.5 (KMnO<sub>4</sub>)

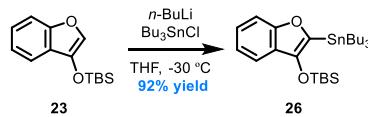
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  5.97 (t,  $J$  = 4.2 Hz, 1H), 4.48 (d,  $J$  = 9.8 Hz, 1H), 4.27 (d,  $J$  = 9.8 Hz, 1H), 2.26 (td,  $J$  = 6.1, 4.2 Hz, 2H), 1.97 (ddd,  $J$  = 12.8, 8.5, 3.9 Hz, 1H), 1.77–1.62 (m, 3H), 1.24 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  148.87, 121.45, 118.76 (d,  $J$  = 319.7 Hz), 118.43 (d,  $J$  = 319.3 Hz), 78.80, 39.50, 33.23, 24.60, 21.05, 17.83 ppm

**IR (neat):**  $\nu$  2950, 1417, 1249, 1209, 1143, 1041, 950, 877, 613 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>10</sub>H<sub>12</sub>O<sub>6</sub>F<sub>6</sub>S<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 428.9872, found 428.9849

### Synthesis of arylstannane **26**



To a solution of known compound **23**<sup>3</sup> (100 mg, 0.4 mmol) in dry THF (1 mL) was slowly added a solution of *n*-BuLi in hexanes (2.5 M, 0.18 mL, 0.44 mmol) at -30 °C. The reaction mixture was stirred at the same

temperature for 60 minutes before the addition of  $\text{Bu}_3\text{SnCl}$  (0.12 mL, 0.44 mL). The reaction mixture was stirred at the same temperature for another 3 hours before it was quenched with a saturated solution of  $\text{NaHCO}_3$ . The layers were separated, and the aqueous layer was extracted with ethyl acetate ( $5 \text{ mL} \times 3$ ). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (neutral alumina, hexanes) gave **26** as a pale-yellow oil (200 mg, 92% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 8:1, neutral  $\text{Al}_2\text{O}_3$ ):**  $R_f$  0.9 (UV,  $\text{KMnO}_4$ )

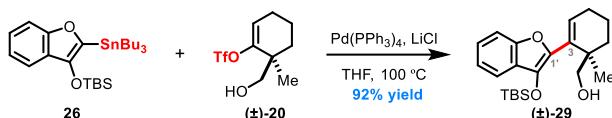
**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.48 (br d,  $J = 7.6 \text{ Hz}$ , 1H), 7.37 (br d,  $J = 8.1 \text{ Hz}$ , 1H), 7.22–7.18 (m, 1H), 7.15 (br t,  $J = 7.3 \text{ Hz}$ , 1H), 1.68–1.52 (m, 6H), 1.36 (h,  $J = 7.3 \text{ Hz}$ , 6H), 1.29–1.12 (m, 6H), 1.09 (s, 9H), 0.91 (t,  $J = 7.3 \text{ Hz}$ , 9H), 0.21 (s, 6H) ppm

**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  158.25, 149.81, 149.57, 123.94, 123.50, 121.39, 118.53, 111.54, 29.15 (t,  $J = 10.3 \text{ Hz}$ ), 27.39 (t,  $^{119}\text{Sn}J = 31.4 \text{ Hz}$ ,  $^{117}\text{Sn}J = 30.2 \text{ Hz}$ ), 26.02, 18.36, 13.83, 10.34 (t,  $^{119}\text{Sn}J = 181 \text{ Hz}$ ,  $^{117}\text{Sn}J = 173 \text{ Hz}$ ), -3.82 ppm

**IR (neat):**  $\nu$  2957, 2929, 2857, 1543, 1445, 1348, 1252, 1229, 1100, 885, 840, 782, 744, 692  $\text{cm}^{-1}$

**HRMS (ESI-TOF):** molecular ion peak not found despite extensive efforts.

### Synthesis of alcohol $(\pm)$ -**29**



In the glovebox, a 4-mL vial, equipped with a magnetic stir bar and fitted with a Teflon screw-up, was charged with  $(\pm)$ -**20** (82.3 mg, 0.3 mmol), **26** (403 mg, 0.75 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (34.7 mg, 0.03 mmol),  $\text{LiCl}$  (38.2 mg, 0.9 mmol) and THF (2 mL). The vial was then sealed, taken out of the glovebox, and heated to  $100^\circ\text{C}$  for 24 hours. The reaction mixture was cooled down to room temperature and quenched with water. The layers were separated, and the aqueous layer was extracted with ethyl acetate ( $2 \text{ mL} \times 3$ ). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 25:1 → 10:1) gave alcohol  $(\pm)$ -**29** as a pale-yellow solid (103 mg, 92% yield).

**Physical state:** pale-yellow solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.5 (UV, CAM)

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.49–7.45 (m, 1H), 7.36–7.31 (m, 1H), 7.25–7.21 (m, 1H), 7.19 (td,  $J = 7.4, 1.2 \text{ Hz}$ , 1H), 6.36 (t,  $J = 4.0 \text{ Hz}$ , 1H), 3.77 (d,  $J = 11.2 \text{ Hz}$ , 1H), 3.49 (d,  $J = 11.2 \text{ Hz}$ , 1H), 2.26–2.16

(m, 2H), 2.04 (ddd,  $J$  = 13.4, 10.4, 3.3 Hz, 1H), 1.89–1.77 (m, 2H), 1.79–1.67 (m, 1H), 1.47 (ddd,  $J$  = 13.2, 7.4, 3.2 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H) ppm

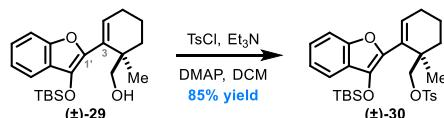
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.53, 143.61, 136.24, 134.66, 131.60, 124.82, 124.08, 122.30, 118.56, 111.51, 70.39, 40.23, 33.82, 26.18, 25.86, 23.19, 18.65, 18.35, -3.69, -3.93 ppm

**MP:** 73–75 °C

**IR (neat):**  $\nu$  3366, 2959, 2930, 2859, 1597, 1453, 1388, 1252, 1137, 879, 840, 782, 743  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{22}\text{H}_{33}\text{O}_3\text{Si}^+$  [M+H]<sup>+</sup> 373.2193, found 373.2195

### Synthesis of tosylate ( $\pm$ )-30



A 4-mL vial, equipped with a magnetic stir bar and fitted with a Teflon screw-up, was charged with ( $\pm$ )-29 (24 mg, 0.0644 mmol), DMAP (1.6 mg, 0.013 mmol), Et<sub>3</sub>N (27  $\mu$ L, 0.193 mmol) and DCM (1 mL). TsCl (18.5 mg, 0.097 mmol) was added to the resulting solution at room temperature. The vial was then sealed, and the reaction mixture was stirred at room temperature for 16 hours before it was directly loaded on a silica gel column. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 15:1) gave tosylate ( $\pm$ )-30 as a colorless oil (29 mg, 85% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.65 (UV, CAM)

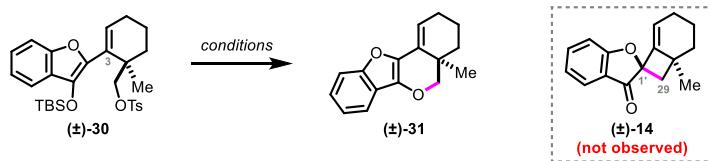
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.73 (d,  $J$  = 8.3 Hz, 2H), 7.46–7.40 (m, 1H), 7.24–7.11 (m, 5H), 6.43 (t,  $J$  = 4.0 Hz, 1H), 4.28 (d,  $J$  = 9.3 Hz, 1H), 4.20 (d,  $J$  = 9.3 Hz, 1H), 2.39 (s, 3H), 2.27–2.11 (m, 2H), 2.02–1.92 (m, 1H), 1.72–1.60 (m, 2H), 1.49–1.41 (m, 1H), 1.11 (s, 3H), 1.03 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H) ppm

**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.08, 144.56, 142.68, 134.73, 134.46, 133.04, 129.85, 129.76, 128.09, 124.87, 123.97, 122.24, 118.52, 111.37, 75.28, 37.69, 33.34, 25.80, 25.74, 23.20, 21.73, 18.29, 17.92, -3.84, -3.96 ppm

**IR (neat):**  $\nu$  2931, 2859, 1598, 1453, 1389, 1362, 1253, 1177, 1140, 876, 842, 814, 784, 746, 666, 555  $\text{cm}^{-1}$

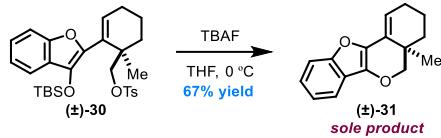
**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{29}\text{H}_{38}\text{O}_5\text{SiNa}^+$  [M+Na]<sup>+</sup> 549.2101, found 549.2100

**Table S1.** Evaluation of reaction conditions for the intramolecular alkylation of ( $\pm$ )-30



entry	reagents	additives	solvent	temperature	time	results
1	TBAF	none	THF	rt	< 10 min	( $\pm$ )-31 only
2	TBAF	LiOTf (2 equiv)	THF	rt	< 10 min	( $\pm$ )-31 only
3	TBAF	LiOTf (4 equiv)	THF	rt ~ 100 °C	2.5 h	no reaction
4	Et <sub>3</sub> N	none	THF/MeOH	60 ~ 100 °C	30 h	no reaction
5	KF	none	THF	rt	72 h	no reaction
6	CsF	none	THF	rt	72 h	( $\pm$ )-31 + unknown products
7	Bu <sub>3</sub> SnF	none	THF	rt	72 h	no reaction
8	CuF <sub>2</sub>	none	THF	rt	72 h	low conv.
9	ZnF <sub>2</sub>	none	THF	rt	72 h	low conv.
10	NH <sub>4</sub> HF <sub>2</sub>	none	THF	rt	3 h	no reaction
11	LiOH·H <sub>2</sub> O	none	THF/MeOH	rt ~ 45 °C	30 h	( $\pm$ )-31 only
12	LiOH·H <sub>2</sub> O	none	THF/H <sub>2</sub> O	rt	24 h	( $\pm$ )-31 + unknown products
13	NaOH	none	THF/H <sub>2</sub> O	rt	24 h	( $\pm$ )-31 + unknown products
14	KOH	none	THF/H <sub>2</sub> O	rt	24 h	( $\pm$ )-31 + unknown products

### Synthesis of benzofuran ( $\pm$ )-31



To a solution of ( $\pm$ )-30 (29 mg, 0.055 mmol) in dry THF (2 mL) was added a solution of TBAF in THF (1.0 M, 0.08 mL, 0.08 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 5 minutes before it was quenched with a pH 7 buffer solution (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 30:1) gave ( $\pm$ )-31 as a white solid (8.8 mg, 67% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.8 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.52–7.48 (m, 1H), 7.37 (dt, J = 8.2, 0.9 Hz, 1H), 7.24 (ddd, J = 8.2, 7.3, 1.5 Hz, 1H), 7.19 (td, J = 7.4, 1.1 Hz, 1H), 5.90 (t, J = 4.0 Hz, 1H), 3.96 (d, J = 10.2 Hz, 1H), 3.79 (d, J = 10.3 Hz, 1H), 2.40–2.22 (m, 2H), 1.96 (tddd, J = 13.8, 10.3, 6.8, 3.3 Hz, 1H), 1.88–1.81 (m, 1H), 1.52 (dt, J = 12.5, 3.4 Hz, 1H), 1.35 (td, J = 13.2, 3.6 Hz, 1H), 1.27 (s, 3H) ppm

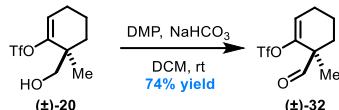
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 153.06, 137.15, 136.78, 129.47, 124.62, 122.54, 121.53, 117.98, 115.61, 111.60, 79.27, 33.49, 30.78, 24.99, 22.87, 17.67 ppm

**MP:** 70–72 °C

**IR (neat):**  $\nu$  2933, 2867, 1664, 1604, 1448, 1204, 1134, 1102, 980 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 241.1223, found 241.1224

### Synthesis of aldehyde ( $\pm$ )-32



To a solution of alcohol ( $\pm$ )-20 (8 mmol) in DCM (40 mL) was added NaHCO<sub>3</sub> (6.72 g, 80 mmol) and Dess-Martin periodinane (3.39 g, 8.00 mmol) at room temperature. After 10 minutes, the reaction mixture was quenched by addition of a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and extracted with DCM (30 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ ethyl acetate = 20:1) gave ( $\pm$ )-32 as a colorless oil (1.62 g, 74% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.4 (CAM, KMnO<sub>4</sub>)

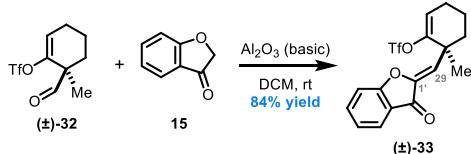
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.49 (s, 1H), 6.06 (t,  $J$  = 4.2 Hz, 1H), 2.28 (q,  $J$  = 5.8 Hz, 2H), 2.10–2.04 (m, 1H), 1.72–1.55 (m, 3H), 1.33 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  199.47, 148.18, 121.46, 118.46 (q,  $J$  = 319.6 Hz), 50.88, 32.42, 24.59, 18.65, 18.14 ppm

**IR (neat):**  $\nu$  2945, 1734, 1415, 1212, 1142, 1036, 873, 614 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>9</sub>H<sub>11</sub>F<sub>3</sub>NaO<sub>4</sub>S<sup>+</sup> [M+Na]<sup>+</sup> 295.0222, found 295.0212

### Synthesis of enone ( $\pm$ )-33



To a solution of ( $\pm$ )-32 (1.36 g, 5.00 mmol) and 15 (738 mg, 5.50 mmol) in DCM (10 mL) was added activated basic alumina (10 g, 98 mmol). The mixture was stirred at room temperature overnight, and then filtered through a plug of silica gel to give pure ( $\pm$ )-33 as an orange viscous oil (1.63 g, 84% yield).

**Physical state:** orange viscous oil

**TLC (hexanes/ethyl acetate 8:1):** R<sub>f</sub> 0.3 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.76 (br d,  $J$  = 7.6 Hz, 1H), 7.68–7.57 (m, 1H), 7.21 (br d,  $J$  = 8.4 Hz, 1H),

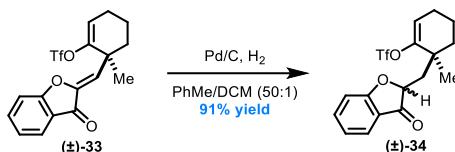
7.19 (t,  $J$  = 7.8 Hz, 1H), 6.03 (s, 1H), 5.88 (t,  $J$  = 4.1 Hz, 1H), 2.31–2.24 (m, 2H), 2.19 (ddd,  $J$  = 13.4, 7.0, 3.2 Hz, 1H), 1.85 (ddd,  $J$  = 13.4, 10.2, 3.3 Hz, 1H), 1.75–1.64 (m, 2H), 1.55 (s, 3H) ppm

**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  184.63, 166.51, 152.02, 147.71, 137.45, 124.88, 123.46, 121.39, 118.51 (q,  $J$  = 319.5 Hz), 118.27, 117.76, 113.10, 39.94, 38.10, 24.76, 24.62, 18.73 ppm

**IR (neat):**  $\nu$  2942, 2874, 1717, 1668, 1606, 1477, 1413, 1210, 1141, 879, 759, 603  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{17}\text{H}_{15}\text{F}_3\text{NaO}_5\text{S}^+$  [M+Na]<sup>+</sup> 411.0484, found 411.0484

### Synthesis of ketone ( $\pm$ )-34



To a mixture of ( $\pm$ )-33 (422 mg, 1.09 mmol) and 5% Pd/C (40 mg) in a round-bottom flask under  $\text{H}_2$  atmosphere was added dry toluene (10 mL) and DCM (0.2 mL). The reaction mixture was stirred at room temperature for 2 hours, then filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-34 as a yellow oil and an inseparable but inconsequential mixture of diastereomers (384 mg, 91% combined yield, d.r. = 1.1:1). The synthesized ( $\pm$ )-34 was always contaminated by a small amount of unknown impurities (purity ca. >95%). It should be noted that ( $\pm$ )-34 is quite unstable in air, for which it was used in the next step of reaction right after isolation.

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 8:1):**  $R_f$  0.3 (UV,  $\text{KMnO}_4$ )

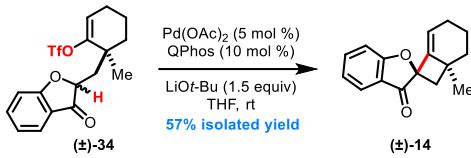
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): (major)**  $\delta$  7.66 (d,  $J$  = 7.7 Hz, 1H), 7.62 (t,  $J$  = 7.8 Hz, 1H), 7.15–7.04 (m, 2H), 5.81 (t,  $J$  = 4.2 Hz, 1H), 4.55 (dd,  $J$  = 10.3, 1.7 Hz, 1H), 2.28–2.19 (m, 2H), 2.14 (dd,  $J$  = 15.1, 1.7 Hz, 1H), 2.07–1.99 (m, 1H), 1.76 (dd,  $J$  = 15.3, 10.3 Hz, 1H), 1.79–1.64 (m, 3H), 1.32 (s, 3H) ppm; **(minor)**  $\delta$  7.66 (d,  $J$  = 7.7 Hz, 1H), 7.62 (t,  $J$  = 7.8 Hz, 1H), 7.15–7.04 (m, 2H), 5.82 (t,  $J$  = 4.3 Hz, 1H), 4.62 (dd,  $J$  = 10.8, 1.9 Hz, 1H), 2.28–2.19 (m, 2H), 2.14 (dd,  $J$  = 15.1, 1.9 Hz, 1H), 2.07–1.99 (m, 1H), 1.83 (dd,  $J$  = 15.1, 10.8 Hz, 1H), 1.79–1.64 (m, 3H), 1.31 (s, 3H) ppm

**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  201.90, 201.64, 172.75, 172.64, 154.30, 153.96, 138.27, 138.20, 124.51, 124.49, 122.32, 122.15, 122.13, 120.50, 120.41, 118.50 (q,  $J$  = 319.4 Hz), 117.94, 117.23, 113.80, 113.74, 82.78, 82.74, 40.43, 40.34, 38.08, 37.72, 36.18, 35.88, 25.08, 24.89, 24.84, 18.35, 18.27 ppm

**IR (neat):**  $\nu$  2942, 1723, 1615, 1478, 1464, 1412, 1247, 1212, 1142, 1024, 874, 761  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{F}_3\text{NaO}_5\text{S}^+$  [M+Na]<sup>+</sup> 413.0641, found 413.0640

### Synthesis of 4,5-spirocycle ( $\pm$ )-14



In the glovebox, to a mixture of **(±)-34** (388 mg, 0.99 mmol) and LiOt-Bu (119 mg, 1.49 mmol) in a vial (25 mL) was added a solution of Pd(OAc)<sub>2</sub> (11.2 mg, 0.050 mmol) and QPhos (71.1 mg, 0.10 mmol) in THF (20 mL). The reaction mixture was divided and placed in 3 vials (ca. 6.7 mL for each vial). It was stirred at room temperature for 60 hours, then filtered through a plug of silica gel and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave **(±)-14** as a yellow oil and a single diastereomer (137 mg, 57% yield). It should be noted that in practice, this reaction is very sensitive to reaction scales.

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.6 (UV, KMnO<sub>4</sub>)

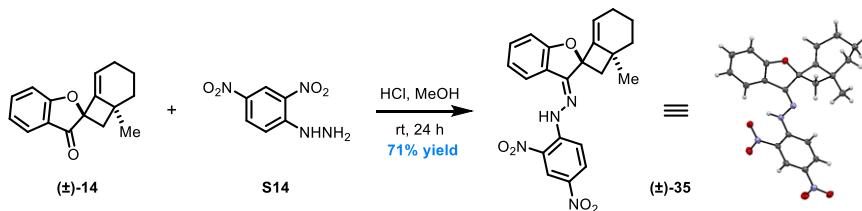
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.66 (br d, J = 7.6 Hz, 1H), 7.61–7.55 (m, 1H), 7.09–7.05 (m, 2H), 5.63 (dd, J = 4.3, 2.8 Hz, 1H), 2.56 (d, J = 11.4 Hz, 1H), 2.37 (d, J = 11.4 Hz, 1H), 2.24–2.03 (m, 2H), 1.80–1.75 (m, 3H), 1.59 (s, 3H), 1.42–1.33 (m, 1H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 199.16, 170.94, 142.79, 137.83, 124.94, 121.99, 120.72, 119.60, 112.95, 93.22, 46.64, 38.99, 36.67, 24.70, 21.78, 19.13 ppm

**IR (neat):** ν 2931, 2869, 1720, 1610, 1463, 1301, 895, 756 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 241.1223, found 241.1211

### Synthesis of hydrazone **(±)-35**



To a mixture of **(±)-14** (24 mg, 0.1 mmol) and **S14** (21 mg, 0.11 mmol) in MeOH (4 mL) was added concentrated hydrochloric acid (ca. 2 μL). The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate = 25:1) to give **(±)-35** as an orange solid (30 mg, 71% yield).

**Physical state:** orange solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.55 (UV, KMnO<sub>4</sub>)

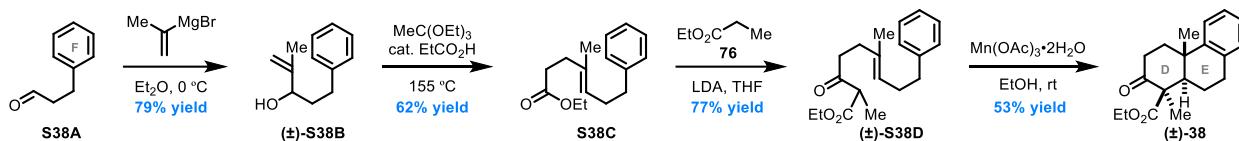
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  11.82 (s, 1H), 9.19 (d,  $J$  = 2.5 Hz, 1H), 8.40 (dd,  $J$  = 9.5, 2.4 Hz, 1H), 8.10 (br d,  $J$  = 7.8 Hz, 1H), 8.08 (d,  $J$  = 9.6 Hz, 1H), 7.51 (br t,  $J$  = 7.6 Hz, 1H), 7.15 (t,  $J$  = 7.6 Hz, 1H), 7.06 (br d,  $J$  = 8.2 Hz, 1H), 5.75 (dd,  $J$  = 4.3, 2.7 Hz, 1H), 2.69 (d,  $J$  = 11.8 Hz, 1H), 2.56 (d,  $J$  = 11.9 Hz, 1H), 2.28–2.12 (m, 2H), 1.86–1.77 (m, 3H), 1.68 (s, 3H), 1.43 (td,  $J$  = 13.0, 6.0 Hz, 1H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  164.77, 156.90, 145.43, 145.42, 138.50, 134.93, 130.36, 129.71, 124.84, 123.64, 122.06, 121.29, 117.35, 116.66, 112.24, 93.39, 50.01, 38.90, 36.81, 24.61, 23.08, 19.17 ppm

**IR (neat):**  $\nu$  3338, 2925, 2851, 1617, 1590, 1501, 1465, 1336, 1318, 1085, 741 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>22</sub>H<sub>21</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 421.1506, found 421.1509

### Modified synthesis of known $\beta$ -ketoester ( $\pm$ )-38



A modified synthetic route to the known  $\beta$ -ketoester ( $\pm$ )-38 is described as follows. The known ester S38C was prepared according to the procedures reported by Li and co-workers.<sup>4</sup> The Claisen condensation from S38C to ( $\pm$ )-S38D was realized using Baran's protocol.<sup>5</sup>

A flame dried round bottle flask equipped with a magnetic stir bar under Ar atmosphere was charged with a solution of isopropenyl magnesium bromide in THF (0.5 M, 40.8 mL, 20.4 mmol). The solution was cooled down to 0 °C before a slow addition of commercial aldehyde S38A (1.37 g, 10.2 mmol) in ether (5 mL). The reaction mixture was stirred at 0 °C for 10 minutes, after which it was quenched with a 1 N HCl solution (25 mL) and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaHCO<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give the crude alcohol ( $\pm$ )-S38B as a colorless to pale-yellow oil (1.387 g, 79% yield).

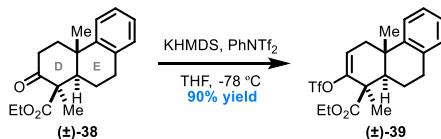
A pressure vessel was sequentially charged with the above crude ( $\pm$ )-S38B, triethyl orthoacetate (10 mL) and propionic acid (0.1 mL). The vessel was sealed off and heated under a 155 °C oil bath for 3 hours. The reaction mixture was cooled down to room temperature and then placed under an ice-water bath, followed by the addition of ether (10 mL) and a 1 N HCl solution (10 mL). The reaction mixture was then stirred at the same temperature for 15 minutes and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ether (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 15:1) gave the ester S38C as a yellow oil (1.205 g, 62% yield). The experimental NMR data of S38C recorded

were consistent with those reported by Li and co-workers.<sup>4</sup>

Diisopropylamine (1.7 mL, 12.2 mmol) was dissolved in THF (6 mL) and the solution was cooled to 0 °C. n-BuLi (1.6 M in hexanes, 7.6 mL, 12.2 mmol) was added slowly and the resulting yellow solution was stirred for 1 h at 0 °C and then cooled to -78 °C. Ethyl propionate (**76**, 1.4 mL, 12.2 mmol) was added dropwise (over 15 min) and the solution was stirred for additional 45 min at -78 °C. The ester **S38C** (1.205 g, 4.87 mmol) in THF (4 mL) was added dropwise (over 15 min) to the solution. The reaction mixture was stirred at -78 °C for additional 1 h and then warmed up to room temperature overnight. After 12 h, the reaction was diluted with Et<sub>2</sub>O and quenched with a 1 N HCl solution until pH < 3. The layers were separated, and the aqueous layer was extracted with ether (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-**S38D** as a pale-yellow oil (1.449 g, 77% yield). The experimental NMR data of ( $\pm$ )-**S38D** recorded were consistent with those reported by Snider and co-workers.<sup>6</sup>

( $\pm$ )-**S38D** (1.449 g, 4.79 mmol) was dissolved in ethanol (45 mL), and the solution was sparged with continuous flow of N<sub>2</sub> or Ar for 3 hours. Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (2.823 g, 10.5 mmol) was added in one portion and the resulting dark slurry was stirred for 16 h at room temperature under N<sub>2</sub> or Ar. The reaction was diluted with ethyl acetate (100 mL) and water (100 mL) before it was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution to give a yellow organic layer and a colorless aqueous layer. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by recrystallization from DCM/pentane in two batches gave ( $\pm$ )-**38** as a white crystalline solid (763 mg, 53% yield). The experimental NMR data of ( $\pm$ )-**38** recorded were consistent with those reported by Snider and co-workers.<sup>6</sup>

#### *Synthesis of vinyl triflate ( $\pm$ )-39*



To a solution of ( $\pm$ )-**38** (150 mg, 0.5 mmol) and PhNTf<sub>2</sub> (268 mg, 0.75 mmol) in THF (3 mL) was slowly added a solution of KHMDS (150 mg, 0.75 mmol) in THF (1 mL) at -78 °C. The reaction mixture was stirred at the same temperature until TLC indicating full consumption of ( $\pm$ )-**38** (ca. 45 minutes) and then quenched with a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 40:1 → 25:1) gave vinyl triflate ( $\pm$ )-

**39** as a colorless oil (237 mg, 90% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 8:1):**  $R_f$  0.5 (CAM, KMnO<sub>4</sub>)

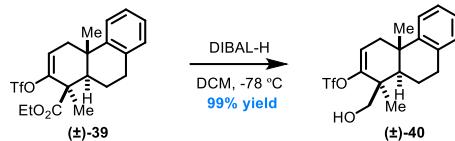
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.24 (dd,  $J$  = 7.9, 1.4 Hz, 1H), 7.18 (ddd,  $J$  = 8.0, 6.8, 1.4 Hz, 1H), 7.11 (td,  $J$  = 7.3, 1.4 Hz, 1H), 7.06 (dd,  $J$  = 7.7, 1.5 Hz, 1H), 5.89 (dd,  $J$  = 6.3, 2.3 Hz, 1H), 4.25–4.15 (m, 2H), 2.95 (ddd,  $J$  = 16.9, 5.2, 1.9 Hz, 1H), 2.87–2.74 (m, 2H), 2.38–2.32 (m, 1H), 2.32–2.26 (m, 1H), 1.89 (dd,  $J$  = 12.6, 1.9 Hz, 1H), 1.75 (dtd,  $J$  = 13.8, 12.7, 5.1 Hz, 1H), 1.55 (s, 3H), 1.28 (t,  $J$  = 7.2 Hz, 3H), 1.26 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.91, 149.62, 145.53, 134.90, 129.15, 126.51, 126.13, 126.11, 118.46 (q,  $J$  = 319.2 Hz), 116.84, 61.67, 51.50, 48.89, 38.88, 36.83, 31.39, 24.11, 23.84, 21.13, 13.89 ppm

**IR (neat):**  $\nu$  2963, 2925, 2853, 1735, 1414, 1211, 1142, 1023, 1005, 899, 761, 601 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>20</sub>H<sub>23</sub>F<sub>3</sub>O<sub>5</sub>SnNa<sup>+</sup> [M+Na]<sup>+</sup> 455.1111, found 455.1104

### Synthesis of alcohol ( $\pm$ )-40



To a solution of ( $\pm$ )-39 (102 mg, 0.19 mmol) in DCM (1 mL) was slowly added a solution of DIBAL-H in hexanes (1 M, 0.4 mL, 0.4 mmol) at -78 °C. The reaction mixture was stirred at the same temperature for 30 minutes before the addition of a saturated solution of Rochelle's salt (10 mL). The reaction mixture was warmed up to room temperature and stirred for another 3 hours. The layers were separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 25:1 → 10:1) gave alcohol ( $\pm$ )-40 as a colorless viscous oil (73 mg, 99% yield).

**Physical state:** colorless viscous oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.5 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.25 (dd,  $J$  = 8.0, 1.5 Hz, 1H), 7.20–7.16 (m, 1H), 7.12 (td,  $J$  = 7.3, 1.4 Hz, 1H), 7.07 (dd,  $J$  = 7.6, 1.5 Hz, 1H), 5.91 (dd,  $J$  = 6.6, 2.2 Hz, 1H), 3.87 (d,  $J$  = 12.0 Hz, 1H), 3.78 (d,  $J$  = 11.9 Hz, 1H), 2.98 (ddd,  $J$  = 17.0, 5.5, 1.8 Hz, 1H), 2.90–2.82 (m, 1H), 2.79 (dd,  $J$  = 17.2, 6.7 Hz, 1H), 2.36 (ddd,  $J$  = 17.3, 2.2, 1.0 Hz, 1H), 2.04 (ddt,  $J$  = 12.8, 6.5, 1.8 Hz, 1H), 1.92 (dd,  $J$  = 12.6, 1.7 Hz, 1H), 1.82 (qd,  $J$  = 12.5, 5.4 Hz, 1H), 1.66 (s, 1H), 1.36 (s, 3H), 1.31 (s, 3H) ppm

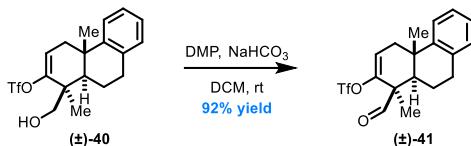
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  153.58, 146.17, 134.79, 129.16, 126.44, 126.06, 125.95, 118.50 (q,  $J$  =

319.5 Hz), 117.41, 64.01, 50.39, 43.72, 38.84, 36.58, 31.32, 26.36, 22.47, 20.25 ppm

**IR (neat):**  $\nu$  3432, 2970, 2943, 1685, 1410, 1206, 1141, 1037, 997, 878, 761, 603  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{18}H_{21}F_3O_4SNa^+ [M+Na]^+$  413.1005, found 413.1006

### *Synthesis of aldehyde ( $\pm$ )-41*



Alcohol ( $\pm$ )-**40** (56 mg, 0.143 mmol) was dissolved in DCM (1.5 mL), followed by sequential addition of NaHCO<sub>3</sub> (120 mg, 1.43 mmol) and Dess-Martin periodinane (73 mg, 0.172 mmol) at room temperature. After 30 minutes, the reaction mixture was quenched by addition of a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ ethyl acetate = 10:1) gave ( $\pm$ )-**41** as a white solid (51 mg, 92% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.7 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 9.81 (s, 1H), 7.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.22–7.18 (m, 1H), 7.13 (td, *J* = 7.3, 1.4 Hz, 1H), 7.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.13 (dd, *J* = 6.6, 2.2 Hz, 1H), 2.97 (ddd, *J* = 17.0, 5.5, 1.9 Hz, 1H), 2.91–2.82 (m, 2H), 2.43 (ddd, *J* = 17.5, 2.2, 1.0 Hz, 1H), 2.14 (ddt, *J* = 13.2, 5.9, 2.0 Hz, 1H), 2.01 (dd, *J* = 13.1, 2.0 Hz, 1H), 1.70 (qd, *J* = 13.0, 5.4 Hz, 1H), 1.45 (s, 3H), 1.29 (s, 3H) ppm

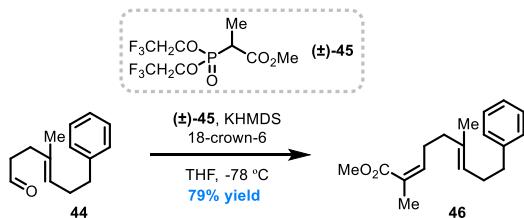
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 200.53, 148.83, 144.52, 134.49, 129.27, 126.69, 126.42, 125.97, 119.19, 118.45 (d, *J* = 319.5 Hz), 53.89, 51.81, 38.51, 36.65, 31.18, 25.99, 20.22, 19.45 ppm

**MP:** 90–92 °C

**IR (neat):**  $\nu$  2928, 2851, 1728, 1415, 1213, 1141, 1022, 879, 762, 603  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{18}H_{19}F_3O_4SNa^+ [M+Na]^+$  411.0848, found 411.0843

### Synthesis of ester 46



To a solution of ( $\pm$ )-45 (2.19 g, 6.6 mmol) and 18-crown-6 (8.3 g, 31.4 mmol) in THF (30 mL) at -78 °C

was added a solution of KHMDS (1.32 g, 6.6 mmol) in THF (10 mL) dropwise. The reaction mixture was stirred for 10 minutes, after which a solution of **44**<sup>7</sup> (1.27 g, 6.3 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at the same temperature for another 20 minutes, then quenched with a saturated NH<sub>4</sub>Cl solution and extracted with ether (30 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave **46** as a colorless oil (1.36 g, 79% yield, Z/E > 19:1).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.7 (UV, KMnO<sub>4</sub>)

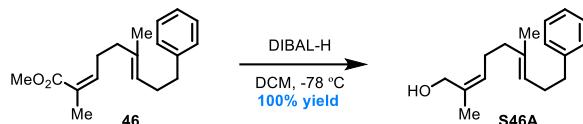
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.30–7.25 (m, 2H), 7.21–7.15 (m, 3H), 5.94–5.87 (m, 1H), 5.20 (br t, J = 6.8 Hz, 1H), 3.74 (s, 3H), 2.67–2.60 (m, 2H), 2.59–2.52 (m, 2H), 2.31 (q, J = 7.5 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.90–1.86 (m, 3H), 1.55 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 168.61, 143.25, 142.46, 135.13, 128.60, 128.35, 126.95, 125.81, 124.41, 51.33, 39.26, 36.22, 30.03, 28.12, 20.77, 15.98 ppm

**IR (neat):** ν 3026, 2926, 2856, 1718, 1453, 1435, 1243, 1197, 1128, 748, 699 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>18</sub>H<sub>25</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 273.1849, found 273.1851

### Synthesis of alcohol S46A



To a solution of **46** (1.04 g, 3.84 mmol) in DCM (10 mL) at -78 °C was added DIBAL-H (1.0 M solution in hexane, 8.4 mL, 8.4 mmol) dropwise. Upon finishing addition, the reaction mixture was slowly warmed up to room temperature and stirred for another 10 minutes, then quenched with a saturated Rochelle salt solution and extracted with DCM (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/DCM/ethyl acetate = 5:1:1) gave **S46A** as a colorless oil (935 mg, 100% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.7 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.32–7.26 (m, 2H), 7.22–7.17 (m, 3H), 5.30–5.24 (m, 1H), 5.22–5.15 (m, 1H), 4.12 (s, 2H), 2.67–2.62 (m, 2H), 2.32 (q, J = 7.4 Hz, 2H), 2.14 (q, J = 7.4 Hz, 2H), 2.01 (t, J = 7.6 Hz, 2H), 1.82–1.78 (m, 3H), 1.56 (s, 3H), 1.29 (br s, 1H) ppm

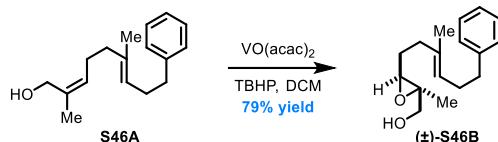
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 142.41, 135.37, 134.51, 128.59, 128.34, 128.31, 125.81, 124.29, 61.76,

39.96, 36.21, 30.00, 26.30, 21.38, 16.12 ppm

**IR (neat):**  $\nu$  3328, 3026, 2922, 2855, 1496, 1453, 1379, 1004, 748, 699 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>17</sub>H<sub>25</sub>O<sup>+</sup> [M+H]<sup>+</sup> 245.1900, found 245.1900

### Synthesis of epoxide ( $\pm$ )-S46B



To a stirred solution of **S46A** (92 mg, 0.38 mmol) in DCM (2 mL) at 0 °C was added VO(acac)<sub>2</sub> (5 mg, 0.02 mmol), followed by addition of TBHP solution (~5.5 M in decane, 0.1 mL, ~0.55 mmol) dropwise. The reaction mixture was stirred at 0 °C until TLC (hexanes/ethyl acetate = 2:1) indicated complete consumption of **S46A**. It was then quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and a saturated NaHCO<sub>3</sub> solution and extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/DCM/ethyl acetate = 4:1:1 → 2:1:1) gave ( $\pm$ )-**S46B** as a colorless oil (78 mg, 79% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.2 (KMnO<sub>4</sub>)

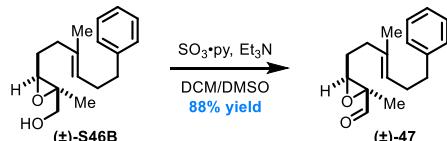
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 5.23 (t,  $J$  = 7.0 Hz, 1H), 3.73–3.60 (m, 2H), 2.82 (t,  $J$  = 6.3 Hz, 1H), 2.65 (t,  $J$  = 7.8 Hz, 2H), 2.32 (q,  $J$  = 7.4 Hz, 2H), 2.17 (dt,  $J$  = 14.6, 7.4 Hz, 1H), 2.09 (dt,  $J$  = 14.4, 7.7 Hz, 1H), 1.75–1.62 (m, 3H), 1.57 (s, 3H), 1.37 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 142.30, 134.80, 128.59, 128.38, 125.88, 124.72, 64.69, 64.16, 60.99, 36.55, 36.12, 30.02, 26.81, 20.33, 16.09 ppm

**IR (neat):**  $\nu$  3432, 2968, 2926, 2856, 1452, 1031, 749, 699 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>17</sub>H<sub>24</sub>NaO<sub>2</sub><sup>+</sup> [M+Na]<sup>+</sup> 283.1669, found 283.1669

### Synthesis of aldehyde ( $\pm$ )-47



To a stirred solution of ( $\pm$ )-**S46B** (664 mg, 2.55 mmol) in DCM (10 mL) at 0 °C was added DMSO (2 mL) and Et<sub>3</sub>N (2.1 mL, 15.3 mmol), followed by addition of SO<sub>3</sub>·py (1.22 g, 7.65 mmol) in one portion. The reaction mixture was stirred at 0 °C and naturally warmed up to room temperature until TLC (hexanes/ethyl

acetate = 4:1) indicated complete consumption of ( $\pm$ )-**S46B**. It was then quenched with a saturated NH<sub>4</sub>Cl solution and extracted with DCM (10 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-**47** as a colorless oil (578 mg, 88% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.7 (KMnO<sub>4</sub>)

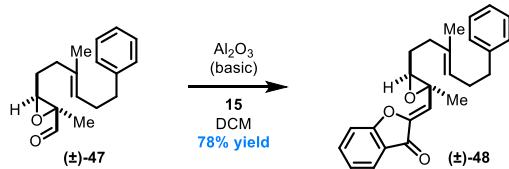
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.37 (s, 1H), 7.31–7.24 (m, 2H), 7.20–7.15 (m, 3H), 5.25–5.19 (m, 1H), 3.03 (t, *J* = 6.5 Hz, 1H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 2.20 (dt, *J* = 14.4, 7.4 Hz, 1H), 2.10 (dt, *J* = 14.3, 7.6 Hz, 1H), 1.93–1.69 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  200.62, 142.21, 133.89, 128.58, 128.39, 125.91, 125.40, 65.43, 62.89, 36.44, 36.00, 29.96, 26.58, 16.01, 15.99 ppm

**IR (neat):**  $\nu$  3026, 2973, 2931, 2855, 1723, 1496, 1453, 1383, 750, 700 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>17</sub>H<sub>23</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 259.1693, found 259.1690

### *Synthesis of enone ( $\pm$ )-48*



To a solution of ( $\pm$ )-**47** (320 mg, 1.24 mmol) and **15** (166 mg, 1.24 mmol) in DCM (6 mL) was added activated basic alumina (1.2 g, 11.8 mmol). The mixture was stirred at room temperature for 24 hours, then filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1  $\rightarrow$  15:1) gave ( $\pm$ )-**48** as a yellow oil (362 mg, 78% yield).

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (UV, KMnO<sub>4</sub>)

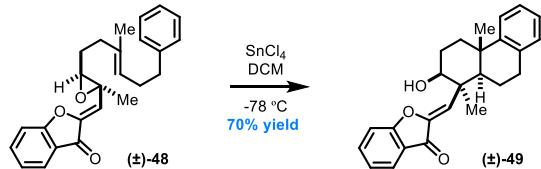
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.79–7.76 (m, 1H), 7.65 (ddd, *J* = 8.5, 7.4, 1.4 Hz, 1H), 7.27–7.12 (m, 7H), 6.05 (s, 1H), 5.24–5.16 (m, 1H), 2.97 (t, *J* = 6.2 Hz, 1H), 2.64–2.57 (m, 2H), 2.27 (q, *J* = 7.4 Hz, 2H), 2.20–2.06 (m, 2H), 1.67 (s, 3H), 1.66–1.60 (m, 2H), 1.51 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  183.94, 166.53, 149.60, 142.32, 137.53, 134.59, 128.55, 128.34, 125.82, 125.00, 124.72, 123.62, 121.50, 113.54, 113.15, 66.06, 58.47, 36.34, 36.08, 30.00, 28.31, 22.45, 16.03 ppm

**IR (neat):**  $\nu$  3026, 2969, 2928, 2855, 1716, 1670, 1606, 1461, 1299, 1188, 1129, 756 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>25</sub>H<sub>26</sub>NaO<sub>3</sub><sup>+</sup> [M+Na]<sup>+</sup> 397.1774, found 397.1773

*Synthesis of alcohol ( $\pm$ )-49 from ( $\pm$ )-48*



To a solution of ( $\pm$ )-48 (604 mg, 1.61 mmol) in DCM (10 mL) at -78 °C was added  $\text{SnCl}_4$  (1.0 M in heptane, 1.6 mL, 1.6 mmol) dropwise. The mixture was stirred at -78 °C for 15 minutes, then quenched with a saturated  $\text{NaHCO}_3$  solution, and extracted with DCM (10 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Flash chromatography (silica gel, hexanes/DCM/ethyl acetate = 4:1:1) gave ( $\pm$ )-49 as a pale-yellow solid (425 mg, 70% yield).

**Physical state:** pale-yellow solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.1 (UV,  $\text{KMnO}_4$ )

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.79 (br d,  $J$  = 7.6 Hz, 1H), 7.64 (br t,  $J$  = 7.8 Hz, 1H), 7.29–7.22 (m, 2H), 7.20 (br t,  $J$  = 7.4 Hz, 1H), 7.13 (br t,  $J$  = 7.4 Hz, 1H), 7.09 (br t,  $J$  = 7.2 Hz, 1H), 7.05 (br d,  $J$  = 7.4 Hz, 1H), 6.37 (s, 1H), 3.44 (dd,  $J$  = 11.8, 4.3 Hz, 1H), 3.00–2.87 (m, 2H), 2.39 (br d,  $J$  = 13.3 Hz, 1H), 2.31 (dd,  $J$  = 13.0, 6.6 Hz, 1H), 2.19 (br s, 1H), 2.15–1.98 (m, 2H), 1.82–1.59 (m, 3H), 1.62 (s, 3H), 1.14 (s, 3H) ppm

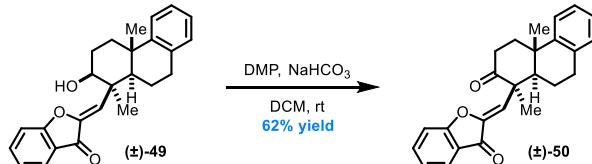
**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  183.86, 166.04, 148.43, 148.02, 137.08, 134.86, 129.13, 126.01, 125.75, 125.04, 124.79, 123.41, 121.74, 118.47, 113.01, 79.22, 53.23, 45.76, 37.85, 37.18, 30.67, 28.40, 25.32, 24.39, 19.92 ppm

**MP:** 224–225 °C

**IR (neat):**  $\nu$  3449, 2935, 2872, 1706, 1655, 1601, 1477, 1460, 1300, 1192, 1174, 1100, 757, 728  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{25}\text{H}_{26}\text{NaO}_3^+$  [M+Na]<sup>+</sup> 397.1774, found 397.1781

*Synthesis of ketone ( $\pm$ )-50*



Alcohol ( $\pm$ )-49 (37.4 mg, 0.10 mmol) was dissolved in DCM (1 mL), followed by sequential addition of  $\text{NaHCO}_3$  (84 mg, 1.0 mmol) and Dess-Martin periodinane (46.7 mg, 0.11 mmol) at room temperature. After 15 minutes, the reaction mixture was quenched by addition of a saturated  $\text{Na}_2\text{S}_2\text{O}_3$  solution and extracted

with DCM (10 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) gave ( $\pm$ )-**50** as a white crystalline solid (23 mg, 62% yield).

**Physical state:** white crystalline solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.3 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.77–7.73 (m, 1H), 7.63 (ddd, *J* = 8.6, 7.4, 1.4 Hz, 1H), 7.26–7.06 (m, 6H), 6.41 (s, 1H), 3.11–2.90 (m, 3H), 2.65–2.52 (m, 2H), 2.15 (ddt, *J* = 18.3, 11.9, 6.2 Hz, 1H), 2.08–2.00 (m, 1H), 1.95–1.87 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H) ppm

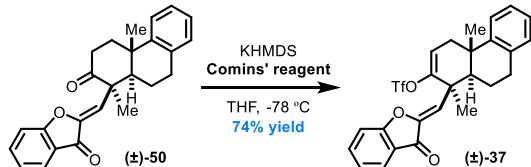
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  211.14, 184.01, 166.41, 146.79, 146.61, 137.45, 134.59, 129.33, 126.30, 126.23, 124.96, 124.86, 123.55, 121.67, 116.66, 113.33, 54.75, 52.62, 40.03, 38.17, 36.79, 30.74, 24.20, 22.18, 20.13 ppm

**MP:** 215–217 °C

**IR (neat):**  $\nu$  2928, 2863, 1712, 1664, 1602, 1460, 1299, 1189, 758 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>25</sub>H<sub>25</sub>O<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 373.1798, found 373.1796

### Synthesis of vinyl triflate ( $\pm$ )-**37**



A flame-dried round bottle flask was charged with KHMDS (296 mg, 1.48 mmol) and THF (2 mL). The clear solution was cooled down to -78 °C, after which a solution of ( $\pm$ )-**50** (460 mg, 1.24 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred for 15 minutes, and then solid Comins' reagent (582 mg, 1.48 mmol) was added to the solution in one portion. The reaction mixture was stirred for another 3 hours, quenched with a saturated NH<sub>4</sub>Cl solution, and extracted with ethyl acetate (30 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-**37** as a white solid (466 mg, 74% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.76 (br d, *J* = 7.6 Hz, 1H), 7.67–7.63 (m, 1H), 7.29–7.15 (m, 4H), 7.12 (br t, *J* = 6.9 Hz, 1H), 7.06 (br d, *J* = 7.5 Hz, 1H), 6.02 (s, 1H), 5.98 (dd, *J* = 6.5, 2.0 Hz, 1H), 2.99–2.87 (m, 2H), 2.85 (dd, *J* = 17.3, 6.6 Hz, 1H), 2.40 (br d, *J* = 17.1 Hz, 1H), 2.13 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.03

(dd,  $J = 12.6, 1.5$  Hz, 1H), 1.77 (dq,  $J = 12.6, 5.9$  Hz, 1H), 1.67 (s, 3H), 1.29 (s, 3H) ppm

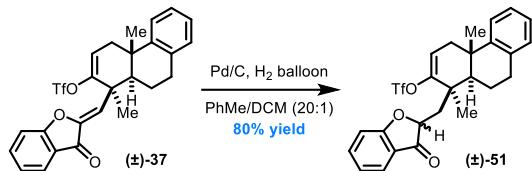
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  184.16, 166.57, 151.97, 147.93, 145.38, 137.48, 134.66, 129.18, 126.58, 126.19, 125.98, 124.98, 123.53, 121.36, 118.55 (q,  $J = 319.6$  Hz), 114.86, 114.38, 113.19, 52.68, 43.11, 38.69, 36.71, 30.93, 25.50, 24.88, 20.74 ppm

**MP:** 140–142 °C

**IR (neat):**  $\nu$  2940, 1718, 1668, 1605, 1413, 1299, 1210, 1141, 881, 758, 604 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{26}\text{H}_{23}\text{F}_3\text{NaO}_5\text{S}^+$  [M+Na]<sup>+</sup> 527.1111, found 527.1110

### Synthesis of ketone ( $\pm$ )-51



To a mixture of ( $\pm$ )-37 (25 mg, 0.050 mmol) and 5% Pd/C (25 mg) under  $\text{H}_2$  atmosphere was added dry toluene (1 mL) and DCM (0.05 mL). The reaction mixture was stirred at room temperature for 12 hours, then filtered through a plug of silica gel, washed with ether, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-51 as a white solid and an inseparable but inconsequential mixture of diastereomers (20 mg, 80% yield, d.r. = 2:1). The synthesized ( $\pm$ )-51 was always contaminated by a small amount of unknown impurities (purity ca. >95%) that did not influence the next step of reaction. In practice, the crude ( $\pm$ )-51 was sufficiently pure to be directly used for the next step without further purification.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.5 (UV,  $\text{KMnO}_4$ )

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): (major)**  $\delta$  7.69–7.60 (m, 2H), 7.25–7.03 (m, 6H), 5.90 (dd,  $J = 4.0, 2.3$  Hz, 1H), 4.73 (dd,  $J = 10.6, 1.4$  Hz, 1H), 3.03–2.83 (m, 2H), 2.77 (dd,  $J = 17.4, 6.3$  Hz, 1H), 2.38 (d,  $J = 17.7$  Hz, 1H), 2.16 (dd,  $J = 15.6, 1.3$  Hz, 1H), 2.07 (dd,  $J = 15.6, 10.7$  Hz, 1H), 2.02 (dd,  $J = 12.7, 5.8$  Hz, 1H), 1.94 (d,  $J = 11.1$  Hz, 1H), 1.80 (dd,  $J = 12.6, 5.3$  Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H) ppm; **(minor)**  $\delta$  7.69–7.60 (m, 2H), 7.25–7.03 (m, 6H), 5.91 (dd,  $J = 4.0, 2.2$  Hz, 1H), 4.80 (dd,  $J = 11.2, 1.4$  Hz, 1H), 3.03–2.83 (m, 2H), 2.80 (dd,  $J = 17.4, 6.6$  Hz, 1H), 2.40 (d,  $J = 16.7$  Hz, 1H), 2.55 (d,  $J = 15.5$  Hz, 1H), 1.95–1.90 (m, 1H), 1.92 (dd,  $J = 15.4, 1.4$  Hz, 1H), 1.83 (dd,  $J = 12.6, 5.2$  Hz, 1H), 1.70 (dd,  $J = 15.4, 11.2$  Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H) ppm

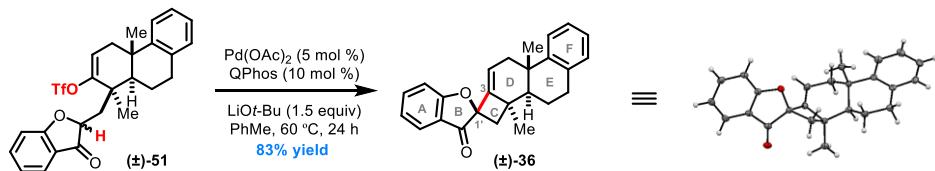
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ): (major)**  $\delta$  201.95, 172.79, 154.02, 145.81, 138.32, 134.75, 129.14, 126.54, 126.12, 126.06, 124.45, 122.06, 120.55, 118.59 (q,  $J = 319.8$  Hz), 114.48, 113.95, 83.05, 51.15, 39.80,

39.05, 36.83, 35.76, 31.27, 25.95, 24.55, 20.31 ppm; (**minor**)  $\delta$  201.59, 172.62, 154.73, 145.93, 138.20, 134.80, 129.11, 126.56, 126.14, 126.11, 124.57, 122.08, 120.52, 118.52 (q,  $J = 319.7$  Hz), 115.55, 113.85, 83.96, 51.78, 40.79, 39.05, 36.79, 35.76, 31.39, 26.20, 25.23, 20.55 ppm

**IR (neat):**  $\nu$  3060, 2973, 2942, 1718, 1615, 1477, 1464, 1412, 1212, 1142, 999, 908, 760, 734, 605 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>26</sub>H<sub>26</sub>F<sub>3</sub>O<sub>5</sub>S<sup>+</sup> [M+H]<sup>+</sup> 507.1448, found 507.1448

### Synthesis of 4,5-spirocycle ( $\pm$ )-36



In the glovebox, 0.1 mL of a 1-mL stock solution of Pd(OAc)<sub>2</sub> (5.2 mg, 0.023 mmol) and QPhos (32.6 mg, 0.046 mmol) in dry toluene was added to LiOt-Bu (5.4 mg, 0.068 mmol), followed by addition of a solution of **(±)-51** (24 mg, 0.047 mmol) in dry toluene (0.8 mL). The reaction mixture was then heated to 60 °C for 24 hours, after which it was cooled down, filtered through a plug of silica gel, washed with ether, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave **(±)-36** as a white solid (14 mg, 83% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.7 (UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.68 (br d,  $J = 7.3$  Hz, 1H), 7.64–7.58 (m, 1H), 7.30–7.25 (m, 1H), 7.17–7.12 (m, 3H), 7.11–7.06 (m, 2H), 5.93 (dd,  $J = 8.6, 4.3$  Hz, 1H), 3.11–2.98 (m, 2H), 2.76 (dd,  $J = 14.4, 8.6$  Hz, 1H), 2.61 (d,  $J = 11.2$  Hz, 1H), 2.31 (d,  $J = 11.2$  Hz, 1H), 2.07 (dd,  $J = 14.3, 4.2$  Hz, 1H), 1.88–1.80 (m, 3H), 1.72 (s, 3H), 1.19 (s, 3H) ppm

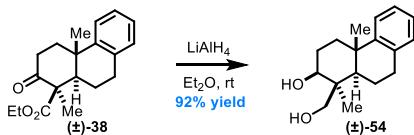
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  199.09, 170.94, 147.74, 144.71, 137.91, 136.08, 129.56, 125.91, 125.73, 124.92, 123.67, 121.97, 120.96, 120.67, 112.96, 92.74, 49.81, 44.79, 41.98, 40.40, 35.63, 29.66, 26.08, 22.83, 18.81 ppm

**MP:** 174–177 °C

**IR (neat):**  $\nu$  2930, 2869, 1717, 1612, 1476, 1463, 1300, 1253, 754, 728 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>25</sub>H<sub>25</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 357.1849, found 357.1855

### Synthesis of diol ( $\pm$ )-54



To a suspension of LiAlH<sub>4</sub> (78 mg, 2.08 mmol) in anhydrous ether (5 mL) was slowly added a solution of ( $\pm$ )-38 (260 mg, 0.866 mmol) in ether (5 mL) at 0 °C. The reaction was stirred at room temperature until TLC indicated full conversion of ( $\pm$ )-38. The reaction was carefully quenched with a saturated NaCl solution followed by addition of a 3 N HCl solution to reach an acidic pH ~ 1. The layers were separated, and the aqueous layer was extracted with ether (10 mL  $\times$  3). The combined extracts were washed sequentially with saturated NaHCO<sub>3</sub> and NaCl solutions, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 1:1:1) gave ( $\pm$ )-54 as a white solid (207 mg, 92% yield). In practice, the crude diol is sufficiently pure to be used directly in the next step without further purification.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.2 (CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.23 (dd, J = 7.8, 1.5 Hz, 1H), 7.12 (tdt, J = 7.8, 1.6, 0.7 Hz, 1H), 7.08 (td, J = 7.3, 1.4 Hz, 1H), 7.05–7.01 (m, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.53 (ddd, J = 11.8, 4.6, 1.4 Hz, 1H), 3.43 (dd, J = 11.3, 1.4 Hz, 1H), 2.99–2.93 (m, 1H), 2.86 (ddd, J = 17.6, 11.6, 7.2 Hz, 1H), 2.64 (br s, 2H), 2.35 (dt, J = 13.3, 3.5 Hz, 1H), 2.07–1.94 (m, 2H), 1.91 (ddt, J = 13.3, 4.7, 3.7 Hz, 1H), 1.67 (tdd, J = 13.0, 11.6, 6.5 Hz, 1H), 1.58–1.50 (m, 1H), 1.46 (dd, J = 12.6, 2.0 Hz, 1H), 1.32 (s, 3H), 1.17 (s, 3H) ppm

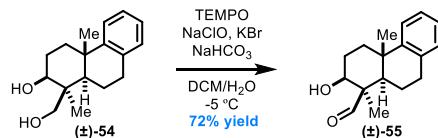
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  148.88, 134.79, 129.18, 126.01, 125.71, 124.72, 80.71, 64.33, 50.73, 43.03, 37.50, 36.87, 31.09, 28.58, 26.06, 22.63, 19.04 ppm

**MP:** 144–146 °C

**IR (neat):**  $\nu$  3336, 2967, 2935, 2876, 1489, 1447, 1380, 1010, 1037, 909, 762, 728 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>17</sub>H<sub>25</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 261.1849, found 261.1842

### Synthesis of aldehyde ( $\pm$ )-55



To a solution of diol ( $\pm$ )-54 (130 mg, 0.5 mmol) in DCM (5 mL) was added a saturated NaHCO<sub>3</sub> solution (5 mL), TEMPO (3.9 mg, 0.025 mmol) and KBr (6 mg, 0.05 mmol). The reaction mixture was cooled down with an ice-water-acetone bath (-5 °C by thermometer) and then a NaClO solution (13% chlorine) was added batch-wise (0.11 mL per batch) every 20 minutes (0.44 mL, 1.0 mmol) until TLC indicated full

conversion of ( $\pm$ )-**54**. During this period, the reaction mixture turned red after addition of a NaClO solution and faded to light yellow before addition of the next batch. The reaction mixture was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 4:1) gave ( $\pm$ )-**55** as a white solid (93.4 mg, 72% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.5 (CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.87 (d, J = 2.4 Hz, 1H), 7.28–7.24 (m, 1H), 7.18–7.11 (m, 1H), 7.11 (td, J = 7.3, 1.5 Hz, 1H), 7.08–7.05 (m, 1H), 3.34–3.25 (m, 1H), 3.19 (br s, 1H), 3.01 (ddd, J = 17.1, 6.3, 1.9 Hz, 1H), 2.91 (ddd, J = 17.2, 11.9, 6.8 Hz, 1H), 2.38 (dt, J = 13.3, 3.6 Hz, 1H), 2.25–2.18 (m, 1H), 2.10–1.92 (m, 3H), 1.62–1.51 (m, 2H), 1.39 (s, 3H), 1.13 (s, 3H) ppm

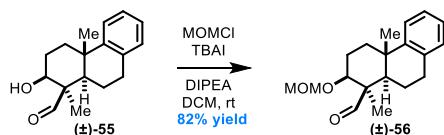
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  208.10, 146.90, 134.47, 129.24, 126.22, 126.01, 125.18, 77.22, 52.90, 51.86, 37.91, 37.01, 31.25, 29.00, 24.37, 19.42, 19.16 ppm

**MP:** 110–112 °C

**IR (neat):**  $\nu$  3448, 2926, 2854, 1713, 1489, 1404, 1383, 1089, 1037, 761, 726 cm<sup>-1</sup>

**HRMS (APCI-TOF):** m/z calcd for C<sub>17</sub>H<sub>23</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 259.1693, found 259.1693

### Synthesis of aldehyde ( $\pm$ )-**56**



To a solution of ( $\pm$ )-**55** (93.4 mg, 0.362 mmol), DIPEA (0.32 mL, 1.81 mmol) and TBAI (27 mg, 0.0724 mmol) in DCM (3 mL) was added MOMCl (0.1 mL, 1.32 mmol). The reaction mixture was stirred at room temperature overnight and quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave ( $\pm$ )-**56** as a white solid (90 mg, 82% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.15 (s, 1H), 7.28–7.27 (m, 1H), 7.17–7.12 (m, 1H), 7.10 (td, J = 7.3, 1.4 Hz, 1H), 7.05 (br d, J = 7.3 Hz, 1H), 4.83 (d, J = 7.0 Hz, 1H), 4.65 (d, J = 7.0 Hz, 1H), 3.45–3.39 (m, 1H),

3.41 (s, 3H), 2.95 (dd,  $J$  = 17.2, 6.3 Hz, 1H), 2.84 (ddd,  $J$  = 17.7, 11.4, 7.3 Hz, 1H), 2.45 (dt,  $J$  = 13.5, 3.6 Hz, 1H), 2.26 (dt,  $J$  = 13.8, 4.3 Hz, 1H), 2.21–2.09 (m, 2H), 1.75–1.63 (m, 1H), 1.63–1.56 (m, 2H), 1.28 (s, 3H), 1.10 (s, 3H) ppm

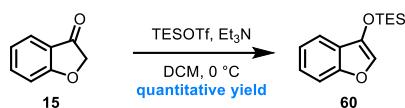
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  206.02, 147.01, 134.94, 129.26, 126.02, 125.92, 124.79, 96.04, 82.61, 55.91, 53.15, 52.65, 37.47, 36.25, 30.70, 26.12, 25.61, 21.57, 19.42 ppm

**MP:** 96–98 °C

**IR (neat):**  $\nu$  2946, 2888, 1718, 1489, 1472, 1448, 1146, 1105, 1044, 971, 917, 761, 726  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_3\text{Na}^+$  [M+Na]<sup>+</sup> 325.1774, found 325.1773

### Synthesis of 3-triethylsiloxybenzofuran 60



To a solution of **15** (1.34 g, 10.0 mmol) in DCM (30 mL) was sequentially added triethylamine (2.8 mL, 20.0 mmol) and TESOTf (2.5 mL, 11.0 mmol) at 0 °C. The reaction mixture was stirred for 30 minutes before work-up with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous solution was extracted with DCM (15 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 40:1) gave **60** as a yellow oil (2.48 g, quantitative yield).

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.8 (UV, KMnO<sub>4</sub>)

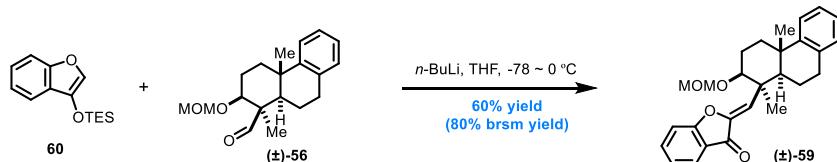
**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.56 (d,  $J$  = 7.6 Hz, 1H), 7.38 (d,  $J$  = 8.2 Hz, 1H), 7.29 (s, 1H), 7.30–7.25 (m, 1H), 7.21 (t,  $J$  = 7.4 Hz, 1H), 1.03 (t,  $J$  = 8.0 Hz, 9H), 0.78 (q,  $J$  = 7.9 Hz, 6H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  153.67, 139.18, 129.89, 124.62, 124.21, 122.22, 118.77, 111.76, 6.72, 4.86 ppm

**IR (neat):**  $\nu$  2957, 2915, 2878, 1622, 1599, 1584, 1452, 1352, 1200, 1089, 862, 742  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{14}\text{H}_{21}\text{O}_2\text{Si}^+$  [M+H]<sup>+</sup> 249.1305, found 249.1308

### Synthesis of enone ( $\pm$ )-59



To a solution of **60** (81 mg, 0.33 mmol) in dry THF (1 mL) was slowly added a solution of *n*-BuLi in hexane

(2.5 M, 0.13 mL, 0.33 mmol) at -78 °C. The reaction mixture was kept at the same temperature for 10 minutes and then warmed up to 0 °C for 15 minutes to complete the deprotonation process, resulting in formation of the corresponding aryllithium agent. The reaction mixture was then cooled back to -78 °C. A solution of ( $\pm$ )-**56** (82.5 mg, 0.27 mmol) in dry THF (1 mL) was added at this point and the reaction mixture was warmed up to 0 °C and stirred for another 2.5 hours before it was quenched with a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 15:1:1 → 10:1:1 → 5:1:1) gave ( $\pm$ )-**59** as a yellow solid (67.9 mg, 60% yield) and recovered ( $\pm$ )-**56** as a yellow solid (20.6 mg, 25% yield).

**Physical state:** yellow solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.4 (UV, CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.77 (ddd, J = 7.5, 1.4, 0.6 Hz, 1H), 7.62 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 7.27–7.22 (m, 2H), 7.17 (td, J = 7.5, 0.8 Hz, 1H), 7.14–7.10 (m, 1H), 7.07 (td, J = 7.3, 1.4 Hz, 1H), 7.03 (dd, J = 7.6, 1.6 Hz, 1H), 6.48 (s, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.64 (d, J = 7.0 Hz, 1H), 3.41 (s, 3H), 3.31 (dd, J = 11.6, 4.7 Hz, 1H), 3.04–2.84 (m, 2H), 2.46–2.32 (m, 2H), 2.18–2.01 (m, 2H), 1.73–1.62 (m, 2H), 1.66 (s, 3H), 1.57 (td, J = 13.4, 4.1 Hz, 1H), 1.13 (s, 3H) ppm

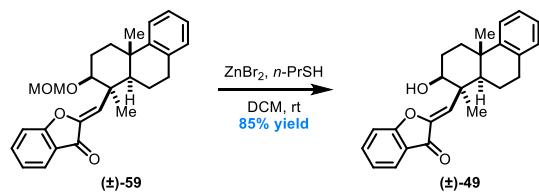
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 184.25, 166.32, 149.14, 147.95, 136.88, 134.92, 129.12, 125.98, 125.71, 124.92, 124.84, 123.07, 121.89, 119.26, 113.00, 95.82, 85.19, 55.88, 53.98, 44.91, 37.62, 36.75, 30.64, 25.79, 24.88, 24.14, 20.24 ppm

**MP:** 169–171 °C

**IR (neat):** ν 2938, 2888, 1711, 1661, 1603, 1476, 1462, 1299, 1191, 1145, 1098, 1041, 916, 885, 758, 727 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>27</sub>H<sub>30</sub>O<sub>4</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 441.2036, found 441.2035

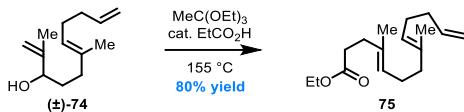
#### Synthesis of alcohol ( $\pm$ )-**49** from ( $\pm$ )-**59**



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with ZnBr<sub>2</sub> (22.5 mg, 0.10 mmol), ( $\pm$ )-**59** (21 mg, 0.05 mmol), DCM (0.5 mL) and n-PrSH (18  $\mu$ L, 0.20 mmol). The reaction mixture was sealed and stirred at room temperature for 2 hours before it was quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined

extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1) gave  $(\pm)$ -49 as a white solid (16 mg, 85% yield). The spectroscopic data of  $(\pm)$ -49 are consistent with those of our previous sample prepared from  $(\pm)$ -48.

### Synthesis of ester 75



To a mixture of the known allyl alcohol  $(\pm)$ -74<sup>8</sup> (38.6 g, 199 mmol) and triethyl orthoacetate (91 mL, 500 mmol) was added propionic acid (0.75 mL, 10 mmol). The reaction mixture was sealed in a pressure vessel and heated to  $155^\circ\text{C}$  for 2.5 hours when TLC indicated full conversion of  $(\pm)$ -74. The reaction mixture was cooled down to room temperature and poured to an ice-cold mixture of a 1 N HCl solution (50 mL) and ether (100 mL). After continuously stirring for 30 minutes at  $0^\circ\text{C}$ , the layers were separated, and the aqueous layer was extracted with ether (50 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 100:1) gave 75 as a yellow liquid (36.28 g, 80% yield). In practice, the crude 75 can be directly used in the next reaction without further purification.

**Physical state:** yellow liquid

**TLC (hexanes/ether 4:1):**  $R_f$  0.75 ( $\text{KMnO}_4$ )

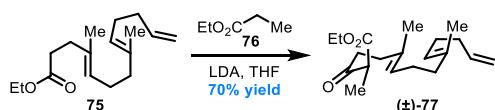
**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.93–5.71 (m, 1H), 5.18–5.10 (m, 2H), 5.05–4.97 (m, 1H), 4.98–4.91 (m, 1H), 4.12 (q,  $J$  = 7.1 Hz, 2H), 2.43–2.36 (m, 2H), 2.31–2.26 (m, 2H), 2.10–2.05 (m, 6H), 2.01–1.94 (m, 2H), 1.61 (br s, 3H), 1.59 (br s, 3H), 1.25 (t,  $J$  = 7.1 Hz, 3H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  173.60, 138.83, 135.29, 133.40, 125.15, 124.04, 114.49, 60.32, 39.65, 34.80, 34.09, 33.41, 27.51, 26.66, 16.15, 16.04, 14.38 ppm

**IR (neat):**  $\nu$  3077, 2978, 2921, 2855, 1738, 1640, 1446, 1371, 1158, 1097, 1036, 911  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{17}\text{H}_{29}\text{O}_2^+$   $[\text{M}+\text{H}]^+$  265.2162, found 265.2158

### Synthesis of $\beta$ -ketoester $(\pm)$ -77



Diisopropylamine (35 mL, 250 mmol) was dissolved in THF (500 mL), and the solution was cooled to  $0^\circ\text{C}$ . *n*-BuLi (2.5 M in hexanes, 100 mL, 250 mmol) was added slowly and the resulting yellow solution was stirred for 1 h at  $0^\circ\text{C}$  and then cooled to  $-78^\circ\text{C}$ . Ethyl propionate (76, 29 mL, 250 mmol) was added

dropwise (over 15 min) and the solution was stirred for additional 45 min at -78 °C. The ester **75** (26.44 g, 100 mmol) in THF (50 mL) was added dropwise (over 15 min) to the solution. The reaction mixture was stirred at -78 °C for additional 1 h and then warmed up to ambient temperature overnight. After 12 h, the reaction was diluted with Et<sub>2</sub>O and quenched with a 1 N HCl solution until pH < 3. The layers were separated, and the aqueous layer was extracted with ether (200 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 60:1 → 40:1) gave ( $\pm$ )-**77** as a pale-yellow oil (22.43 g, 70% yield).

**Note:** This Claisen condensation procedure was adopted from Baran's work<sup>5</sup> on a similar substrate. During the preparation of the LDA solution, stirring at 0 °C for at least 1 h is necessary to ensure a full conversion of **76** in a reproducible manner.

**Physical state:** pale-yellow oil

**TLC (hexanes/ether 4:1):** R<sub>f</sub> 0.6 (KMnO<sub>4</sub>)

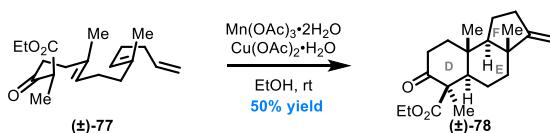
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.88–5.76 (m, 1H), 5.17–5.07 (m, 2H), 5.01 (dd, J = 16.9, 2.0 Hz, 1H), 4.94 (dd, J = 10.1, 2.0 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 3.51 (q, J = 7.1 Hz, 1H), 2.71–2.54 (m, 2H), 2.25 (t, J = 7.7 Hz, 2H), 2.13–2.03 (m, 6H), 2.01–1.94 (m, 2H), 1.59 (s, 6H), 1.33 (d, J = 7.1 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 205.59, 170.64, 138.77, 135.24, 133.41, 125.12, 124.04, 114.47, 61.36, 52.98, 40.27, 39.62, 34.07, 33.39, 27.50, 26.66, 16.14, 16.12, 14.19, 12.84 ppm

**IR (neat):** ν 3077, 2980, 2917, 2850, 1746, 1717, 1640, 1449, 1377, 1238, 1191, 911 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>20</sub>H<sub>31</sub>O<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 321.2424, found 321.2427

### Synthesis of $\beta$ -ketoester ( $\pm$ )-**78**



$\beta$ -Ketoester ( $\pm$ )-**77** (10.58 g, 33.0 mmol) was dissolved in ethanol (330 mL), and the solution was degassed by continuously bubbling through N<sub>2</sub> or Ar for 3 hours. Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (19.46 g, 72.6 mmol) and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (6.59 g, 33.0 mmol) were added in one portion and the resulting dark slurry was stirred for 16 h at ambient temperature under N<sub>2</sub> or Ar and eventually turned green (the color of Cu(OAc)<sub>2</sub>). The reaction was diluted with ethyl acetate (200 mL) and water (200 mL) before it was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution to give a yellow organic layer and a colorless aqueous layer. The layers were separated, and the aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined extracts

were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 40:1) gave  $(\pm)$ -**78** as a pale-yellow oil (5.29 g, 50% yield), which eventually became a white solid. Alternatively,  $(\pm)$ -**78** could also be purified by recrystallization of the crude from DCM/pentane.

**Note:** During the workup, dilution with ethyl acetate and water **BEFORE** the addition of saturated  $\text{Na}_2\text{S}_2\text{O}_3$  solution is necessary to avoid formation of a dark-colored emulsion. With this simple maneuver, a nicely separated bilayer system will show up in the separatory funnel quickly after the addition of  $\text{Na}_2\text{S}_2\text{O}_3$ .

**Physical state:** white solid

**TLC (hexanes/ether 4:1):**  $R_f$  0.5 ( $\text{KMnO}_4$ )

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.57 (br s, 1H), 4.56 (br s, 1H), 4.19–4.10 (m, 2H), 2.98 (td,  $J$  = 14.7, 6.6 Hz, 1H), 2.51 (ddt,  $J$  = 17.4, 9.9, 2.5 Hz, 1H), 2.39 (ddd,  $J$  = 14.9, 4.9, 2.2 Hz, 1H), 2.29–2.09 (m, 2H), 1.96–1.81 (m, 3H), 1.64–1.48 (m, 2H), 1.37 (s, 3H), 1.39–1.31 (m, 1H), 1.27 (t,  $J$  = 7.1 Hz, 3H), 1.29–1.14 (m, 2H), 1.06–1.01 (m, 1H), 1.02 (s, 3H), 0.97 (s, 3H) ppm

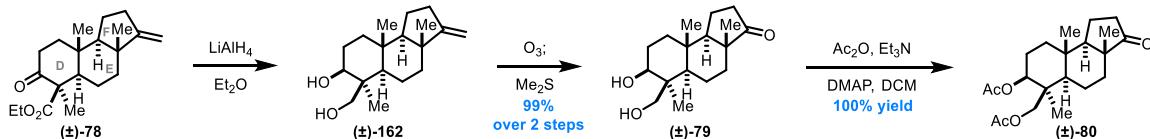
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  208.46, 173.70, 162.07, 100.46, 61.09, 59.94, 58.23, 57.85, 44.42, 40.54, 37.42, 37.38, 36.65, 28.91, 21.39, 21.37, 21.15, 20.25, 14.06, 13.39 ppm

**MP:** 93–95 °C

**IR (neat):**  $\nu$  3066, 2962, 2918, 2851, 1739, 1713, 1452, 1222, 1141, 1093, 876  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{20}\text{H}_{29}\text{O}_3^+$  [M+H]<sup>+</sup> 319.2268, found 319.2270

### Synthesis of ketone $(\pm)$ -**80**



To a suspension of  $\text{LiAlH}_4$  (4.37 g, 115 mmol) in anhydrous ether (350 mL) was slowly added a solution of  $(\pm)$ -**78** (36.67 g, 115 mmol) in ether (50 mL) over 15 minutes at 0 °C. The reaction was stirred at room temperature until TLC indicated full conversion of  $(\pm)$ -**78**. The reaction was carefully quenched with a saturated  $\text{NaCl}$  solution followed by addition of a 3 N  $\text{HCl}$  solution to reach an acidic pH ~ 1. The layers were separated, and the aqueous layer was extracted with ether (100 mL × 3). The combined extracts were washed sequentially with saturated  $\text{NaHCO}_3$  and  $\text{NaCl}$  solutions, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give crude diol  $(\pm)$ -**162** as a white solid (32.02 g, 100% yield). In practice, the crude  $(\pm)$ -**162** is spectroscopically pure enough and can be directly used in the next reaction without further purification. Enantio-enriched **162** and *ent*-**162** were also prepared from **163** and *ent*-**163** using the same

procedure, respectively (vide infra).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 1:1):**  $R_f$  0.25 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  4.57–4.50 (m, 2H), 4.20 (d,  $J$  = 11.1 Hz, 1H), 3.42 (dd,  $J$  = 12.0, 4.6 Hz, 1H), 3.38 (d,  $J$  = 11.2 Hz, 1H), 2.58 (br s, 2H), 2.49 (ddq,  $J$  = 17.3, 10.1, 2.4 Hz, 1H), 2.26–2.14 (m, 1H), 1.91–1.79 (m, 2H), 1.78–1.65 (m, 2H), 1.60–1.49 (m, 2H), 1.50–1.33 (m, 2H), 1.23 (s, 3H), 1.23–1.16 (m, 1H), 1.10–0.99 (m, 2H), 0.90–0.86 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  162.66, 100.04, 81.09, 64.38, 61.03, 56.71, 44.58, 42.81, 38.09, 38.00, 36.75, 29.02, 27.59, 22.77, 21.70, 20.19, 19.24, 16.41 ppm

**MP:** 154–156 °C

**IR (neat):**  $\nu$  3362, 3283, 2966, 2932, 2850, 1653, 1482, 1378, 1061, 1031, 999, 878 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 301.2138, found 301.2135

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (162 at 91% ee):** -22 (*c* = 1.0, CHCl<sub>3</sub>)

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (ent-162 at 92% ee):** +16 (*c* = 1.0 in CHCl<sub>3</sub>)

Diol ( $\pm$ )-**162** (32.02 g, 115 mmol) was dissolved in 600 mL DCM/MeOH (1:1), and the solution was cooled to -78 °C. In a well-ventilated fume hood, a continuous O<sub>3</sub>/O<sub>2</sub> flow was introduced into the solution until a persistent blue color of O<sub>3</sub> was observed in the solution. N<sub>2</sub> flow was then introduced to remove the residual O<sub>3</sub> from the solution until the blue color disappeared. Dimethyl sulfide (17 mL, 230 mmol) was added in one portion and the reaction mixture was warmed up to room temperature overnight. The reaction mixture was concentrated *in vacuo* to give ( $\pm$ )-**79** as a white solid (32.2 g, quantitative yield). In practice, the crude ( $\pm$ )-**79** is spectroscopically pure enough and can be directly used in the next reaction without further purification. Enantio-enriched **79** was also prepared from **162** using the same procedure.

**Physical state:** white solid

**TLC (DCM/acetone 4:1):**  $R_f$  0.5 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  4.20 (d,  $J$  = 11.1 Hz, 1H), 3.45 (dd,  $J$  = 11.7, 4.5 Hz, 1H), 3.39 (d,  $J$  = 11.2 Hz, 1H), 2.44 (ddd,  $J$  = 19.3, 9.0, 1.5 Hz, 1H), 2.08 (dt,  $J$  = 19.2, 8.9 Hz, 1H), 1.92–1.62 (m, 9H), 1.40 (qd,  $J$  = 14.2, 3.9 Hz, 1H), 1.24 (s, 3H), 1.27–1.22 (m, 2H), 1.10 (td,  $J$  = 13.4, 3.9 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 3H), 0.90 (dd,  $J$  = 12.2, 2.2 Hz, 1H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  220.74, 80.92, 64.21, 58.32, 56.49, 48.22, 42.86, 37.26, 35.73, 33.56, 27.41, 22.77, 18.61, 18.42, 16.96, 16.94 ppm

**MP:** 182–184 °C

**IR (neat):**  $\nu$  3378, 2932, 2856, 1735, 1452, 1064, 1045, 1013, 734 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>17</sub>H<sub>28</sub>O<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 303.1931, found 303.1932

$[\alpha]_D^{22}$  (**79**): -97 ( $c = 0.58$ , CHCl<sub>3</sub>)

To a solution of ( $\pm$ )-**79** (4.38 g, 15.6 mmol), DMAP (953 mg, 7.8 mmol) and Et<sub>3</sub>N (8.7 mL, 62.4 mmol) in DCM (60 mL) was added Ac<sub>2</sub>O (5.2 mL, 54.6 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes before it was quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude ( $\pm$ )-**80** as a white solid (5.63 g, 100% yield). ( $\pm$ )-**80** could be further purified by recrystallization from DCM/pentane to give white crystalline.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.5 (KMnO<sub>4</sub>, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.56 (dd,  $J = 10.0, 6.7$  Hz, 1H), 4.33 (d,  $J = 11.8$  Hz, 1H), 4.19 (d,  $J = 11.8$  Hz, 1H), 3.66 (dd,  $J = 11.5, 4.0$  Hz, 1H), 2.76 (br s, 1H), 2.54–2.41 (m, 1H), 2.20–2.11 (m, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 1.98–1.92 (m, 1H), 1.88–1.79 (m, 2H), 1.77–1.66 (m, 4H), 1.27–1.13 (m, 2H), 1.11–1.07 (m, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H) ppm

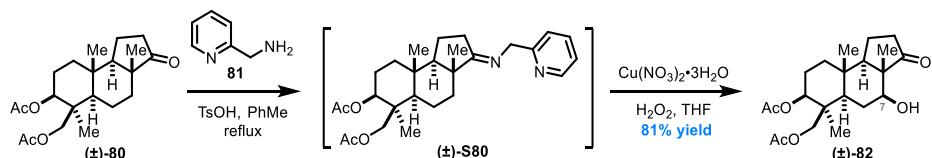
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 220.39, 171.11, 170.62, 80.18, 65.46, 58.32, 56.55, 48.20, 41.19, 37.38, 37.36, 35.69, 33.74, 23.39, 22.79, 21.31, 21.27, 19.67, 18.36, 16.81, 16.28 ppm

**MP:** 158–160 °C

**IR (neat):**  $\nu$  2955, 2922, 2857, 1738, 1374, 1237, 1034 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>21</sub>H<sub>33</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 365.2323, found 365.2322

### Synthesis of alcohol ( $\pm$ )-**82**



A round bottle flask was charged with ( $\pm$ )-**80** (365 mg, 1.0 mmol), **81** (238 mg, 2.2 mmol), TsOH·H<sub>2</sub>O (10 mg, cat.) and toluene (10 mL). The reaction mixture was heated to reflux under a Dean-Stark apparatus overnight, and then it was diluted with ether (10 mL), sequentially washed with a saturated NH<sub>4</sub>Cl solution (10 mL × 3), a saturated NaHCO<sub>3</sub> solution (10 mL), and brine (10 mL). The remaining solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude imine ( $\pm$ )-**80** as a yellow solid (454 mg, 100% yield). The crude imine was dissolved in THF (5 mL) and then Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (266 mg, 1.1 mmol)

was added. The heterogeneous mixture was stirred vigorously for 30 minutes during which all the solids initially dissolved giving a deep blue solution, followed by the formation of a heavy pale blue precipitate. Hydrogen peroxide (30 wt % in water, 0.51 mL, 5.0 mmol) was then added to the reaction mixture slowly which resulted in the dissolution of the precipitate to give a blue green solution. The reaction mixture was then stirred for another 90 minutes at room temperature. Then ethyl acetate (10 mL) and a saturated Na<sub>4</sub>EDTA solution (10 mL) were added, and the reaction mixture was stirred overnight. The layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, DCM/acetone = 8:1 → 6:1) gave ( $\pm$ )-**82** as a white solid (307 mg, 81% yield).

**Physical state:** white solid

**TLC (DCM/acetone 4:1):**  $R_f$  0.5 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.56 (dd, *J* = 10.3, 6.4 Hz, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 4.19 (d, *J* = 11.8 Hz, 1H), 3.66 (dd, *J* = 11.0, 3.4 Hz, 1H), 2.76 (s, 1H), 2.54–2.42 (m, 1H), 2.19–2.10 (m, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 1.98–1.91 (m, 1H), 1.88–1.79 (m, 2H), 1.77–1.66 (m, 4H), 1.24–1.13 (m, 2H), 1.11–1.07 (m, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H) ppm

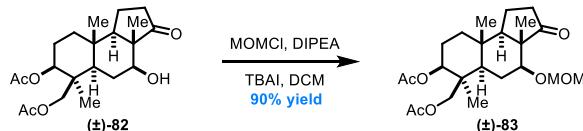
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 222.03, 171.16, 170.61, 79.95, 74.53, 65.74, 56.03, 54.47, 52.51, 41.05, 36.99, 36.97, 35.58, 27.52, 23.32, 22.96, 21.30, 21.29, 18.55, 16.33, 11.43 ppm

**MP:** 191–193 °C

**IR (neat):**  $\nu$  3544, 2965, 2933, 2873, 1732, 1373, 1244, 1053, 1035  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{21}H_{32}O_6Na^+ [M+Na]^+$  403.2091, found 403.2092

### Synthesis of ketone ( $\pm$ )-84 from ( $\pm$ )-82

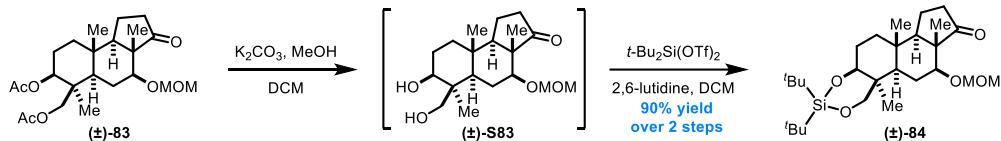


To a solution of ( $\pm$ )-**82** (170 mg, 0.447 mmol), DIPEA (0.9 mL, 5.2 mmol) and TBAI (170 mg, 0.46 mmol) in DCM (2 mL) was added MOMCl (0.16 mL, 2.11 mmol). The reaction mixture was stirred at room temperature overnight and quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 2:1) gave ( $\pm$ )-**83** as a white solid (171 mg, 90% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.2 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.96 (d,  $J = 6.8$  Hz, 1H), 4.73 (d,  $J = 6.8$  Hz, 1H), 4.55 (dd,  $J = 11.1, 5.6$  Hz, 1H), 4.34 (d,  $J = 11.7$  Hz, 1H), 4.18 (d,  $J = 11.8$  Hz, 1H), 3.50 (dd,  $J = 11.1, 4.4$  Hz, 1H), 3.44 (s, 3H), 2.49–2.40 (m, 1H), 2.08 (s, 3H), 2.08–1.98 (m, 2H), 2.05 (s, 3H), 1.87–1.64 (m, 6H), 1.25–1.11 (m, 2H), 1.08–1.04 (m, 1H), 1.06 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H) ppm



To a solution of ( $\pm$ )-83 (2.94 g, 6.93 mmol) in MeOH/DCM (1:1 v/v, 30 mL) was added  $\text{K}_2\text{CO}_3$  (1.92 g, 13.86 mmol). The reaction mixture was stirred at room temperature overnight and diluted with  $\text{H}_2\text{O}$ . The reaction mixture was extracted with DCM (30 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give the crude alcohol ( $\pm$ )-S83 as a white solid (2.28 g). To a solution of crude ( $\pm$ )-S83 and 2,6-lutidine (3.1 mL, 26.8 mmol) in DCM (30 mL) was added  $t'\text{Bu}_2\text{Si}(\text{OTf})_2$  (2.62 mL, 8.04 mmol) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 60 minutes before it was quenched with a saturated  $\text{NaHCO}_3$  solution. The layers were separated, and the aqueous layer was extracted with DCM (30 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) gave ( $\pm$ )-84 as a white solid (3.01 g, 90% yield over two steps). In practice, enantio-enriched 84 was also prepared from 101 (vide infra).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.5 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.98 (d,  $J = 6.7$  Hz, 1H), 4.70 (d,  $J = 6.7$  Hz, 1H), 4.36 (d,  $J = 11.4$  Hz, 1H), 3.64 (dd,  $J = 11.4, 5.9$  Hz, 1H), 3.53 (d,  $J = 11.6$  Hz, 1H), 3.43 (s, 3H), 2.43 (ddd,  $J = 19.2, 7.9, 2.5$  Hz, 1H), 2.05 (dt,  $J = 19.1, 8.8$  Hz, 1H), 2.00–1.91 (m, 3H), 1.84–1.74 (m, 2H), 1.64 (dt,  $J = 13.4, 3.6$  Hz, 1H), 1.42 (dd,  $J = 24.5, 13.1$  Hz, 1H), 1.40 (s, 3H), 1.18 (dd,  $J = 11.7, 7.0$  Hz, 1H), 1.11 (s, 9H), 1.07 (s, 9H), 1.04 (s, 3H), 1.04–0.95 (m, 2H), 0.96 (s, 3H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  218.06, 96.65, 81.53, 78.46, 65.84, 56.49, 55.72, 55.16, 52.69, 41.52, 36.56, 36.31, 35.34, 28.82, 28.76, 28.43, 26.48, 26.19, 22.74, 21.38, 17.98, 16.39, 12.08 ppm

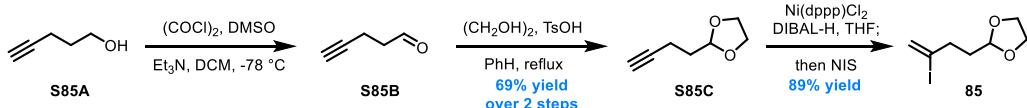
**MP:** 187–189 °C

**IR (neat):**  $\nu$  2965, 2946, 2894, 2859, 1740, 1479, 1101, 1070, 1038, 826, 792, 734, 642  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{27}\text{H}_{49}\text{O}_5\text{Si}^+$  [M+H]<sup>+</sup> 481.3344, found 481.3348

**$[\alpha]_D^{22}$  (84):** -131 ( $c = 0.48$ ,  $\text{CHCl}_3$ )

*Synthesis of vinyl iodide 85*



To a solution of oxalyl chloride (12.9 mL, 150 mmol) in dry DCM (500 mL) at -78 °C was added DMSO (21.3 mL, 300 mmol) very slowly via syringe, during which vigorous gas evolution was observed and the pressure was carefully released with a needle. Upon finishing addition of DMSO, the reaction mixture was stirred for 10 minutes before the slow addition of **S85A** (8.41 g, 100 mmol) at -78 °C. Then the reaction mixture was stirred for 30 minutes at the same temperature to give a white slurry. Triethylamine (55.8 mL, 400 mmol) was then added slowly, and the reaction mixture was kept stirring for another 30 minutes before the cooling bath was removed. After TLC indicated full conversion of **S85A**, water (500 mL) was added, and the layers were separated. The aqueous layer was extracted with DCM (200 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and carefully concentrated *in vacuo* to give crude aldehyde **S85B**, which is practically pure enough to be directly used in the next step.

**Note:** The aldehyde **S85B** is somewhat volatile. When concentrated using rotary evaporator under vacuum, the heat bath temperature should be maintained below 10 °C while pressure above 100 Torr is preferable.

The crude **S85B** was dissolved in benzene (500 mL) followed by addition of ethylene glycol (31 g, 500 mmol) and TsOH·H<sub>2</sub>O (190 mg, 1 mmol). The reaction mixture was heated to reflux under Dean-Stark conditions overnight and was cooled down to room temperature. The organic solution was washed with a saturated NaHCO<sub>3</sub> solution (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 8:1) gave **S85C** as a pale-yellow oil (8.7 g, 69% overall yield). The experimental NMR data of **S85C** recorded were consistent with those reported by Fleming and co-workers.<sup>9</sup>

A 1-L round bottle flask was charged with Ni(dppp)Cl<sub>2</sub> (2.7 g, 4.98 mmol) in the glove box. The flask was then sealed and taken out of the glove box. Dry THF (400 mL) was then cannulated into the flask followed by addition of DIBAL-H solution (1 M in hexane, 185 mL, 185 mmol) at room temperature. The resulting dark red reaction mixture was then placed in an ice-water bath followed by slow addition of a THF solution (50 mL) containing **S85C** (15.82 g, 125 mmol). Upon finishing addition, the cooling bath was removed, and the reaction mixture was stirred until TLC indicated full conversion of **S85C** (ca. 2.5 hours). Then it was cooled down to 0 °C again before slow addition of NIS (56 g, 249 mmol) as solid. The cooling bath

was removed, and the resulting brownish slurry was stirred for 30 minutes. A saturated Rochelle's salt solution was carefully added to the reaction mixture under cooling with an ice-water bath. The resulting reaction mixture was stirred for 6 hours. The layers were separated, and the aqueous layer was extracted with diethyl ether (200 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 10:1) gave **85** as a pale-yellow oil (28.33 g, 89% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (UV, KMnO<sub>4</sub>)

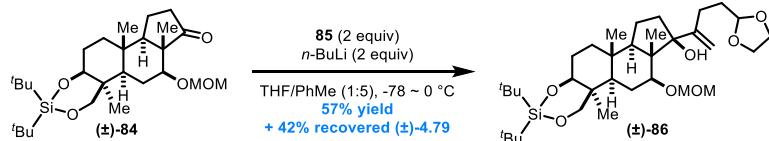
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 6.07 (br s, 1H), 5.70 (br s, 1H), 4.90 (t, J = 4.6 Hz, 1H), 4.02–3.92 (m, 2H), 3.91–3.82 (m, 2H), 2.57–2.50 (m, 2H), 1.95–1.84 (m, 2H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 125.89, 111.01, 103.14, 65.12, 40.01, 33.65 ppm

**IR (neat):** ν 3088, 2955, 2882, 1617, 1405, 1197, 1142, 1037, 898 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>7</sub>H<sub>12</sub>O<sub>2</sub>I<sup>+</sup> [M+H]<sup>+</sup> 254.9876, found 254.9879

### Synthesis of alcohol ( $\pm$ )-86



To a solution of **85** (2.10 g, 8.25 mmol) in dry THF (3.3 mL) at -78 °C was added an *n*-BuLi solution (2.5 M in hexane, 3.3 mL, 8.25 mmol) dropwise via syringe. The reaction mixture was stirred for 1 hour at the same temperature, during which time white precipitates were observed. A solution of ( $\pm$ )-**84** (1.98 g, 4.11 mmol) in toluene (16.5 mL) was then added via syringe and the cool bath was replaced by an ice-water bath. The reaction mixture was stirred for another 1 hour and then quenched by addition of a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined extracts were washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1 → 6:1 → 2:1) gave ( $\pm$ )-**86** as a white solid (1.43 g, 57% yield) and recovered ( $\pm$ )-**84** as a white solid (812 mg, 42% yield). In practice, enantio-enriched **86** was also prepared from **84** using the same procedure.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.3 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.13 (s, 1H), 4.89 (t, J = 4.6 Hz, 1H), 4.80 (s, 1H), 4.69 (s, 2H), 4.36 (d, J = 11.4 Hz, 1H), 3.99–3.92 (m, 2H), 3.88–3.82 (m, 2H), 3.61 (dd, J = 11.7, 5.6 Hz, 1H), 3.51 (d, J = 11.3

Hz, 1H), 3.33 (s, 3H), 3.04 (dd,  $J = 10.8, 4.4$  Hz, 1H), 2.33 (ddd,  $J = 15.6, 10.7, 5.1$  Hz, 1H), 2.17 (ddd,  $J = 15.6, 11.0, 5.2$  Hz, 1H), 2.12–2.07 (m, 1H), 2.03–1.84 (m, 6H), 1.78 (ddt,  $J = 13.6, 10.6, 5.0$  Hz, 1H), 1.64–1.54 (m, 1H), 1.49 (dt,  $J = 13.2, 3.6$  Hz, 1H), 1.42–1.32 (m, 3H), 1.35 (s, 3H), 1.10 (s, 9H), 1.07 (s, 3H), 1.06 (s, 9H), 0.93 (s, 3H), 0.92–0.85 (m, 1H), 0.71 (d,  $J = 11.8$  Hz, 1H) ppm

**$^{13}\text{C}$ -NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  154.32, 112.89, 104.28, 96.41, 87.61, 84.81, 81.74, 65.99, 64.99, 55.52, 55.13, 53.55, 51.43, 41.52, 37.10, 37.04, 35.68, 34.35, 28.86, 28.81, 28.41, 26.50, 26.36, 25.30, 22.73, 21.34, 19.33, 16.01, 12.25 ppm

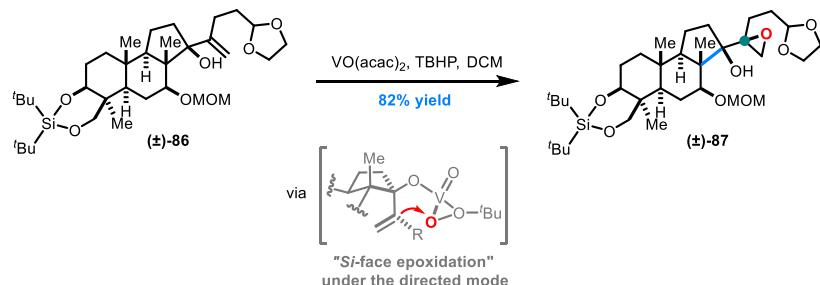
**MP:** 125–127 °C

**IR (neat):**  $\nu$  3494, 2938, 2860, 1478, 1142, 1101, 1038, 908, 826, 797, 734, 642  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{34}\text{H}_{61}\text{O}_7\text{Si}^+ [\text{M}+\text{H}]^+$  609.4181, found 609.4180

$[\alpha]_D^{22}$  (**86**): -46 ( $c = 1.0$ ,  $\text{CHCl}_3$ )

### Synthesis of epoxide ( $\pm$ )-**87**



To a stirred solution of ( $\pm$ )-**86** (122 mg, 0.20 mmol) in DCM (3 mL) at 0 °C was added  $\text{VO}(\text{acac})_2$  (10.6 mg, 0.040 mmol), followed by addition of a TBHP solution (~5.5 M in decane, 0.1 mL, ~0.55 mmol) dropwise. The reaction mixture was stirred at room temperature until TLC (DCM/ether = 5:1) indicated complete consumption of ( $\pm$ )-**86**. It was then quenched with a saturated  $\text{Na}_2\text{S}_2\text{O}_3$  solution and a saturated  $\text{NaHCO}_3$  solution and extracted with DCM (2 mL × 3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, DCM/ether = 5:1) gave ( $\pm$ )-**87** as a white solid (102 mg, 82% yield).

**Physical state:** white solid

**TLC (DCM/ether 4:1):**  $R_f$  0.5 (CAM)

**$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.90 (dd,  $J = 4.9, 3.9$  Hz, 1H), 4.71 (d,  $J = 6.7$  Hz, 1H), 4.64 (d,  $J = 6.7$  Hz, 1H), 4.37 (d,  $J = 11.4$  Hz, 1H), 4.01–3.91 (m, 2H), 3.89–3.84 (m, 2H), 3.63 (dd,  $J = 11.6, 5.7$  Hz, 1H), 3.53 (d,  $J = 11.3$  Hz, 1H), 3.49 (dd,  $J = 11.6, 5.3$  Hz, 1H), 3.34 (s, 3H), 3.09 (d,  $J = 4.7$  Hz, 1H), 2.74 (br s, 1H), 2.69 (d,  $J = 4.7$  Hz, 1H), 2.21–2.09 (m, 2H), 2.07–1.86 (m, 4H), 1.82–1.61 (m, 3H), 1.56–1.40 (m, 5H), 1.39 (s, 3H), 1.11 (s, 9H), 1.08 (d,  $J = 1.2$  Hz, 12H), 0.93 (s, 3H), 0.88–0.79 (m, 1H) ppm

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ 104.01, 96.70, 84.20, 83.35, 81.73, 65.92, 65.16, 61.29, 56.56, 55.55, 55.54, 51.67, 48.49, 41.58, 37.77, 36.25, 35.08, 28.91, 28.82, 28.42, 28.37, 26.47, 26.45, 25.83, 22.74, 21.36, 20.18, 16.46, 12.74 ppm

**MP:** 68–70 °C

**IR (neat):** ν 3496, 2938, 2859, 1101, 1041, 826, 797, 732, 643 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>34</sub>H<sub>60</sub>O<sub>8</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 647.3950, found 647.3951

### Synthesis of alcohol ( $\pm$ )-C14-*epi*-88



To a solution of ( $\pm$ )-87 (31.2 mg, 0.05 mmol) in DCM (0.4 mL) was added an AlMe<sub>3</sub> solution (2 M in hexane, 0.1 mL, 0.20 mmol) at -78 °C. After stirring at the same temperature for 10 minutes, the reaction mixture was warmed up to -20 °C and stirred for 6 hours. A saturated Rochelle's salt solution (5 mL) was added, and the reaction mixture was stirred at room temperature overnight. The layers were separated, and the aqueous solution was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 2:1) gave ( $\pm$ )-C14-*epi*-88 as a white solid (22.4 mg, 72% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 1:1):** R<sub>f</sub> 0.2 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.88–4.83 (m, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.02–3.91 (m, 3H), 3.89–3.79 (m, 3H), 3.74 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.68 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.53 (dd, *J* = 9.2, 5.5 Hz, 1H), 3.48 (d, *J* = 11.3 Hz, 1H), 3.38 (s, 3H), 2.48 (td, *J* = 13.4, 6.8 Hz, 1H), 2.28 (ddd, *J* = 13.3, 4.6, 2.2 Hz, 1H), 2.12 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.04–1.85 (m, 6H), 1.82 (dt, *J* = 13.2, 3.8 Hz, 1H), 1.72 (dd, *J* = 12.6, 2.6 Hz, 1H), 1.65 (td, *J* = 13.8, 13.4, 4.7 Hz, 1H), 1.41 (s, 3H), 1.36–1.27 (m, 1H), 1.22–1.12 (m, 1H), 1.10 (s, 9H), 1.08 (s, 9H), 0.97 (s, 3H), 0.97–0.93 (m, 1H), 0.90 (s, 3H), 0.88–0.82 (m, 1H) ppm

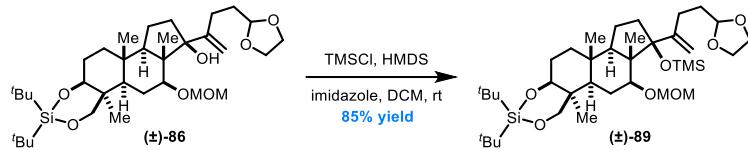
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 215.89, 104.66, 95.08, 81.28, 80.19, 65.83, 65.02, 64.99, 61.44, 60.44, 56.52, 52.97, 50.74, 49.99, 41.57, 39.60, 38.19, 37.51, 29.44, 29.03, 28.79, 28.39, 26.06, 24.41, 23.80, 22.73, 22.00, 21.37, 16.83, 12.57 ppm

**MP:** 93–95 °C

**IR (neat):** ν 3536, 2946, 2892, 2860, 1699, 1478, 1147, 1105, 1066, 826, 797, 733, 642 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 647.3950, found 647.3949

Synthesis of alkene ( $\pm$ )-89



To a solution of ( $\pm$ )-**86** (5.45 g, 8.95 mmol) in DCM (50 mL) was sequentially added HMDS (5 mL, 35.8 mmol), TMSCl (3.4 mL, 17.9 mmol) and imidazole (1.22 g, 17.9 mmol) at room temperature. After stirring at the same temperature for 12 hours, the reaction mixture was quenched by addition of a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous solution was extracted with DCM (20 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) gave ( $\pm$ )-**89** as a white solid (5.30 g, 85% yield). In practice, enantio-enriched **89** was also prepared from **86** using the same procedure.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.75 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.07 (s, 1H), 4.90 (t, *J* = 4.6 Hz, 1H), 4.77 (s, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 3.98–3.94 (m, 2H), 3.87–3.83 (m, 2H), 3.60 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.34 (s, 3H), 3.00 (dd, *J* = 10.6, 4.5 Hz, 1H), 2.32 (ddd, *J* = 16.7, 11.8, 4.9 Hz, 1H), 2.23 (ddd, *J* = 16.7, 12.0, 5.0 Hz, 1H), 2.04–1.84 (m, 6H), 1.77 (ddt, *J* = 13.5, 11.9, 4.9 Hz, 1H), 1.59–1.50 (m, 1H), 1.46 (dt, *J* = 13.1, 3.7 Hz, 1H), 1.38–1.24 (m, 3H), 1.34 (s, 3H), 1.10 (s, 9H), 1.07 (s, 9H), 1.02 (s, 3H), 0.91 (s, 3H), 0.89–0.83 (m, 1H), 0.69 (dd, *J* = 13.1, 2.0 Hz, 1H), 0.07 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 155.33, 111.34, 104.61, 96.18, 90.12, 83.32, 81.83, 66.04, 65.03, 55.36, 54.85, 52.44, 52.25, 41.44, 37.04, 36.73, 35.71, 33.69, 28.96, 28.83, 28.43, 26.42, 26.32, 25.88, 22.74, 21.36, 19.64, 15.73, 12.75, 2.16 ppm

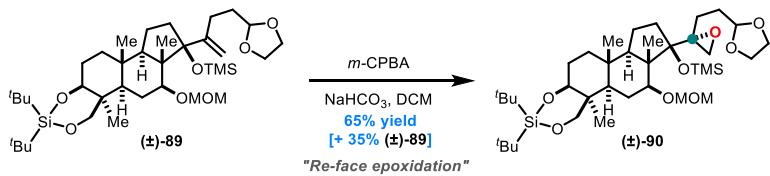
**MP:** 192–194 °C

**IR (neat):**  $\nu$  2950, 2892, 2860, 1478, 1251, 1144, 1103, 1065, 1044, 909, 839, 825, 734, 643  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{37}H_{69}O_7Si_2^+ [M+H]^+$  681.4576, found 681.4575

$[\alpha]_D^{22}$  (89): -58 ( $c = 0.64$ ,  $\text{CHCl}_3$ )

### Synthesis of epoxide ( $\pm$ )-90



To a solution of (±)-89 (6.81 g, 10.0 mmol) in DCM (50 mL) was added NaHCO<sub>3</sub> (1.68 g, 20.0 mmol). Purified *m*-CPBA (3.00 g, 15.0 mmol) was added in three batches (0.5 equiv each time) every 30 minutes. After complete addition of *m*-CPBA, the reaction mixture was stirred at room temperature for another 3 hours and then quenched with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub> solutions. The layers were separated, and the aqueous layer was extracted with DCM (20 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1 → 6:1) gave (±)-90 as a white solid (4.51 g, 65% yield) and recovered (±)-89 as a white solid (2.36 g, 35% yield). In practice, enantio-enriched 90 was also prepared from 89 using the same procedure.

**Note:** Anhydrous *m*-CPBA ensures a higher yield and better mass balance for this epoxidation reaction. Commercial *m*-CPBA (ca. 77% purity and usually contaminated with water and *m*-chlorobenzoic acid) was purified according to literature<sup>10</sup> and the final purity was usually assessed to be 85–87% (contaminated only by *m*-chlorobenzoic acid) by <sup>1</sup>H-NMR. Extra precautions should be exercised when attempting this purification protocol, as peroxides can be explosives by shock or heat. Purification of a large amount (>20 g) in one batch is NOT recommended.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.65 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.81 (dd, J = 5.4, 3.9 Hz, 1H), 4.74 (d, J = 6.4 Hz, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 3.98–3.91 (m, 2H), 3.86–3.81 (m, 2H), 3.62 (dd, J = 11.6, 5.5 Hz, 1H), 3.52 (d, J = 11.3 Hz, 1H), 3.47 (dd, J = 10.5, 4.4 Hz, 1H), 3.36 (s, 3H), 2.80 (d, J = 3.8 Hz, 1H), 2.55 (d, J = 3.9 Hz, 1H), 2.36 (ddd, J = 14.8, 12.3, 4.8 Hz, 1H), 2.12 (dd, J = 13.5, 4.1 Hz, 1H), 2.02–1.78 (m, 4H), 1.63 (tt, J = 12.1, 4.4 Hz, 1H), 1.55–1.38 (m, 5H), 1.38 (s, 3H), 1.28–1.13 (m, 2H), 1.10 (s, 9H), 1.07 (s, 9H), 1.01 (s, 3H), 0.89 (s, 3H), 0.81 (dd, J = 13.4, 3.8 Hz, 1H), 0.76 (d, J = 13.5 Hz, 1H), 0.12 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 104.63, 95.99, 90.45, 83.88, 81.75, 65.96, 64.97, 64.93, 60.54, 55.38, 55.27, 55.08, 53.09, 49.51, 41.48, 37.54, 36.15, 29.33, 28.96, 28.93, 28.82, 28.42, 26.35, 25.91, 23.88, 22.74, 21.36, 20.10, 16.03, 13.47, 2.38 ppm

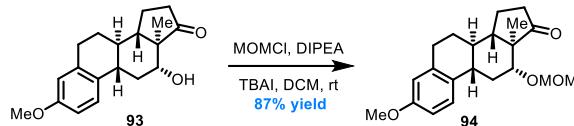
**MP:** 211–213 °C

**IR (neat):** ν 2949, 2890, 2860, 1478, 1251, 1144, 1104, 1065, 1043, 825, 798, 734, 642 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>37</sub>H<sub>69</sub>O<sub>8</sub>Si<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 697.4525, found 697.4524

$[\alpha]_D^{22}$  (**90**): -39 ( $c = 1.11$ ,  $\text{CHCl}_3$ )

### Synthesis of ketone **94**



To a solution of **93**<sup>11</sup> (2.76 g, 9.19 mmol), DIPEA (9.59 mL, 55.2 mmol) and TBAI (682 mg, 1.85 mmol) in DCM (30 mL) was added MOMCl (2.76 mL, 36.3 mmol). The reaction mixture was stirred at room temperature overnight and quenched with a saturated  $\text{NaHCO}_3$  solution. The layers were separated, and the aqueous layer was extracted with DCM (30 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1) gave **94** as a white solid (2.75 g, 87% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.5 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.18 (d,  $J = 8.6$  Hz, 1H), 6.73 (dd,  $J = 8.6, 2.8$  Hz, 1H), 6.65 (d,  $J = 2.8$  Hz, 1H), 5.03 (d,  $J = 6.9$  Hz, 1H), 4.80 (d,  $J = 6.9$  Hz, 1H), 3.81 (dd,  $J = 11.2, 4.8$  Hz, 1H), 3.78 (s, 3H), 3.50 (s, 3H), 2.94–2.87 (m, 2H), 2.61 (dt,  $J = 13.1, 4.6$  Hz, 1H), 2.49 (dd,  $J = 18.5, 9.1$  Hz, 1H), 2.35–2.28 (m, 1H), 2.16–1.97 (m, 3H), 1.77–1.64 (m, 1H), 1.59–1.34 (m, 4H), 1.00 (s, 3H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  218.64, 157.78, 137.67, 131.24, 126.21, 113.96, 111.73, 96.68, 77.14, 55.72, 55.27, 52.07, 49.09, 42.25, 37.41, 35.72, 33.56, 29.65, 26.12, 21.05, 9.06 ppm

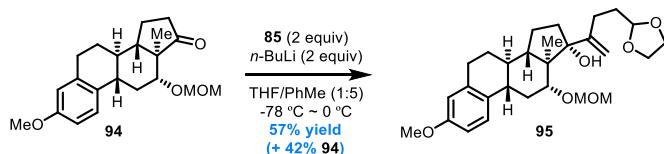
**MP:** 112–113 °C

**IR (neat):**  $\nu$  2931, 2888, 2837, 1739, 1610, 1501, 1255, 1033 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{21}\text{H}_{28}\text{NaO}_4^+$  [M+Na]<sup>+</sup> 367.1880, found 367.1889

$[\alpha]_D^{22}$ : +134.6 ( $c = 0.5$ ,  $\text{CHCl}_3$ )

### Synthesis of alcohol **95**



To a solution of **85** (3.44 g, 13.5 mmol) in dry THF (7 mL) at -78 °C was added an *n*-BuLi solution in hexane (2.5 M, 5.4 mL, 13.5 mmol) dropwise via syringe. The reaction mixture was stirred for 1 hour at the same temperature, during which time white precipitates were observed. A solution of **94** (2.33 g, 6.76

mmol) in toluene (35 mL) was then added via syringe and the cool bath was replaced by an ice-water bath. The reaction mixture was stirred for another 1 hour and then quenched by addition of a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined extracts were washed with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1 → 6:1 → 2:1) gave **95** as a white solid (1.82 g, 57% yield) and recovered **94** as a white solid (979 mg, 42% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.25 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.16 (d, J = 8.6 Hz, 1H), 6.70 (dd, J = 8.6, 2.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 5.11 (s, 1H), 4.92 (t, J = 4.7 Hz, 1H), 4.84 (s, 1H), 4.80 (d, J = 6.9 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 3.99–3.94 (m, 2H), 3.88–3.84 (m, 2H), 3.77 (s, 3H), 3.40 (s, 3H), 3.38 (dd, J = 11.0, 4.9 Hz, 1H), 2.92–2.80 (m, 2H), 2.75 (dt, J = 13.0, 4.6 Hz, 1H), 2.51 (s, 1H), 2.42 (ddd, J = 15.8, 11.2, 5.0 Hz, 1H), 2.25 (ddd, J = 15.8, 11.2, 5.1 Hz, 1H), 2.17–1.96 (m, 4H), 1.89 (ddt, J = 12.6, 5.5, 2.7 Hz, 1H), 1.79 (ddt, J = 13.6, 10.7, 5.0 Hz, 1H), 1.71–1.61 (m, 1H), 1.56–1.40 (m, 4H), 1.34–1.22 (m, 1H), 1.06 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.62, 154.37, 138.00, 131.82, 126.25, 113.91, 112.28, 111.56, 104.38, 96.51, 88.11, 83.13, 64.99, 64.98, 55.64, 55.28, 51.29, 46.76, 41.97, 38.67, 37.92, 34.24, 32.93, 29.90, 27.15, 26.68, 23.36, 10.79 ppm

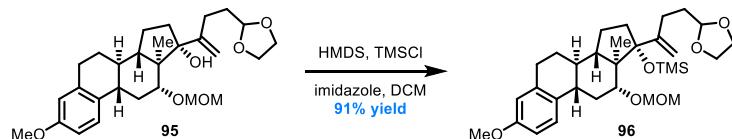
**MP:** 66–68 °C

**IR (neat):** ν 3578, 3512, 2932, 2882, 1610, 1500, 1255, 1147, 1037, 907 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>28</sub>H<sub>40</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup> 495.2717, found 495.2719

[α]<sub>D</sub><sup>22</sup>: +59.8 (c = 0.5, CHCl<sub>3</sub>)

### Synthesis of alkene **96**



To a solution of **95** (10.0 g, 21.2 mmol) in DCM (20 mL) was sequentially added HMDS (17.5 mL, 83.5 mmol), TMSCl (5.3 mL, 41.8 mmol) and imidazole (2.83 g, 41.6 mmol) at room temperature. After stirring at the same temperature for 12 hours, the reaction mixture was quenched by addition of a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous solution was extracted with DCM (20 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1) gave **96** as a viscous oil (10.53 g, 91% yield).

**Physical state:** viscous oil

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.7 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.16 (d,  $J = 8.6$  Hz, 1H), 6.70 (dd,  $J = 8.6, 2.8$  Hz, 1H), 6.62 (d,  $J = 2.8$  Hz, 1H), 5.06 (s, 1H), 4.92 (t,  $J = 4.6$  Hz, 1H), 4.82 (s, 1H), 4.80 (d,  $J = 6.5$  Hz, 1H), 4.69 (d,  $J = 6.5$  Hz, 1H), 4.01–3.94 (m, 2H), 3.89–3.84 (m, 2H), 3.77 (s, 3H), 3.41 (s, 3H), 3.29 (dd,  $J = 10.7, 4.9$  Hz, 1H), 2.92–2.78 (m, 2H), 2.70 (dt,  $J = 13.0, 4.6$  Hz, 1H), 2.43–2.27 (m, 2H), 2.14–1.98 (m, 3H), 1.98–1.83 (m, 2H), 1.84–1.72 (m, 1H), 1.70–1.59 (m, 1H), 1.54–1.32 (m, 4H), 1.31–1.19 (m, 1H), 0.99 (s, 3H) ppm

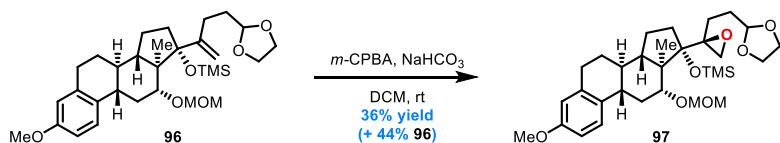
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  157.60, 155.26, 138.05, 132.17, 126.33, 113.91, 111.55, 110.81, 104.69, 96.62, 90.65, 82.18, 65.04, 65.03, 55.41, 55.30, 52.07, 45.70, 41.85, 38.87, 37.66, 33.81, 33.71, 29.97, 27.09, 26.45, 23.66, 11.11, 2.19 ppm

**IR (neat):**  $\nu$  2952, 2882, 1610, 1501, 1251, 1131, 1105, 1041, 911, 839  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{31}\text{H}_{48}\text{NaO}_6\text{Si}^+$  [M+Na]<sup>+</sup> 567.3112, found 567.3114

$[\alpha]_D^{22}$ : +55.6 ( $c = 0.5$ ,  $\text{CHCl}_3$ )

### Synthesis of epoxide 97



To a solution of **96** (952 mg, 1.75 mmol) in DCM (17 mL) was added NaHCO<sub>3</sub> (1.47 g, 17.5 mmol). Purified *m*-CPBA (522 mg, 2.62 mmol) was added in three batches (0.5 equiv each time) every 30 minutes. After complete addition of *m*-CPBA, the reaction mixture was stirred at room temperature for another 3 hours and then quenched with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub> solutions. The layers were separated, and the aqueous layer was extracted with DCM (20 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1 → 6:1) gave **97** as a white solid (351 mg, 36% yield) and recovered **96** as a viscous oil (419 mg, 44% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.55 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.19 (d,  $J = 8.6$  Hz, 1H), 6.72 (dd,  $J = 8.6, 2.8$  Hz, 1H), 6.63 (d,  $J = 2.8$  Hz, 1H), 4.86 (d,  $J = 6.6$  Hz, 1H), 4.84 (dd,  $J = 5.4, 4.0$  Hz, 1H), 4.74 (d,  $J = 6.5$  Hz, 1H), 3.98–3.93 (m, 2H), 3.88–3.83 (m, 2H), 3.77 (s, 3H), 3.74 (dd,  $J = 10.7, 4.9$  Hz, 1H), 3.42 (s, 3H), 2.85–2.76 (m, 3H), 2.79 (d,  $J = 3.9$  Hz, 1H), 2.59 (d,  $J = 3.8$  Hz, 1H), 2.44 (ddd,  $J = 14.7, 12.3, 4.8$  Hz, 1H), 2.21–2.12 (m, 1H), 2.06–1.98 (m, 1H), 1.91 (ddd,  $J = 14.9, 9.8, 5.4$  Hz, 1H), 1.87–1.80 (m, 1H), 1.70–1.35 (m, 6H), 1.34–1.16

(m, 3H), 1.01 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.70, 137.98, 131.82, 126.35, 113.94, 111.66, 104.74, 96.18, 91.02, 82.33, 64.97, 64.94, 60.32, 55.46, 55.32, 52.90, 48.92, 48.13, 41.91, 39.18, 33.72, 30.07, 29.91, 28.95, 27.15, 24.19, 23.84, 11.64, 2.35 ppm

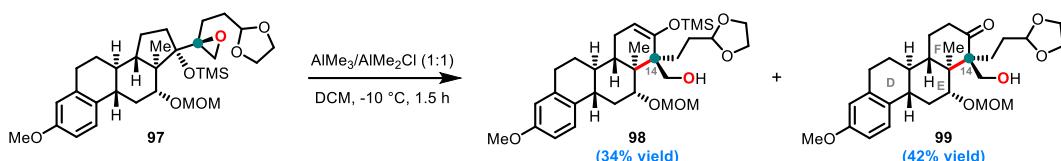
**MP:** 49–51 °C

**IR (neat):** ν 2953, 2882, 1609, 1500, 1251, 1133, 1105, 1039, 839 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>31</sub>H<sub>49</sub>O<sub>7</sub>Si<sup>+</sup> [M+H]<sup>+</sup> 561.3242, found 561.3239

[α]<sub>D</sub><sup>22</sup>: +56.9 (*c* = 0.2, CHCl<sub>3</sub>)

### Synthesis of alcohols 98 and 99



A round bottle flask was charged with DCM (2.7 mL) under N<sub>2</sub>, and the flask was cooled to -78 °C. An AlMe<sub>3</sub> solution (2 M in hexane, 0.21 mL, 0.42 mmol) and an AlMe<sub>2</sub>Cl solution (1 M in hexane, 0.42 mL, 0.42 mmol) were sequentially added to the flask. After stirring at the same temperature for 5 minutes, a solution of **97** (216 mg, 0.385 mmol) in DCM (5 mL) was added. The reaction mixture was warmed up to -10 °C and stirred for 1.5 hours. A saturated Rochelle's salt solution was added, and the reaction mixture was stirred at room temperature until all the aluminum gel was dissolved (ca. 3 hours). The layers were separated, and the aqueous solution was extracted with DCM (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 8:1:1 → 4:1:1 → 0:1:0) gave **98** as a white amorphous solid (64 mg, 34% yield) and **99** as a white solid (91 mg, 42% yield).

### Analytical data for 98:

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.4 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 4.95 (dd, *J* = 6.0, 2.0 Hz, 1H), 4.86 (s, 2H), 4.76 (t, *J* = 4.5 Hz, 1H), 4.09 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.99–3.90 (m, 2H), 3.88–3.77 (m, 4H), 3.77 (s, 3H), 3.44 (s, 3H), 2.88–2.77 (m, 2H), 2.67 (dt, *J* = 12.8, 4.0 Hz, 1H), 2.37–2.29 (m, 1H), 2.29–2.22 (m, 1H), 2.14–2.06 (m, 2H), 2.05–1.97 (m, 1H), 1.95–1.85 (m, 2H), 1.83–1.65 (m, 3H), 1.52 (q, *J* = 12.2 Hz, 1H), 1.34–1.27 (m, 1H), 1.00 (s, 3H), 0.23 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.68, 151.50, 138.10, 132.23, 126.24, 113.58, 111.68, 106.31, 103.81, 96.17, 82.24, 66.15, 64.96, 64.83, 56.12, 55.34, 51.07, 44.66, 41.46, 40.22, 39.93, 32.53, 31.67, 30.23, 26.80, 26.16, 25.04, 11.14, 0.51 ppm

**IR (neat):** ν 3486, 2951, 2928, 1746, 1672, 1609, 1501, 1253, 1146, 1039, 904, 845 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>31</sub>H<sub>49</sub>O<sub>7</sub>Si<sup>+</sup> [M+H]<sup>+</sup> 561.3242, found 561.3243

[α]<sub>D</sub><sup>22</sup>: -5.6 (*c* = 0.77, CHCl<sub>3</sub>)

#### Analytical data for 99:

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 1:1):** R<sub>f</sub> 0.1 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.18 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.9 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 4.89 (d, *J* = 6.7 Hz, 1H), 4.87 (dd, *J* = 5.6, 3.4 Hz, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.30 (dd, *J* = 12.2, 7.8 Hz, 1H), 4.14 (dd, *J* = 11.3, 4.4 Hz, 1H), 4.02–3.95 (m, 2H), 3.92–3.85 (m, 3H), 3.77 (s, 3H), 3.43 (s, 3H), 2.99 (dd, *J* = 7.8, 5.5 Hz, 1H), 2.92–2.77 (m, 2H), 2.70 (dt, *J* = 13.0, 4.2 Hz, 1H), 2.44–2.17 (m, 5H), 2.13–2.03 (m, 2H), 2.02–1.90 (m, 2H), 1.55–1.39 (m, 3H), 1.37–1.28 (m, 2H), 0.93 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 213.52, 157.85, 137.86, 131.75, 126.17, 113.58, 111.84, 105.46, 96.58, 81.71, 65.05, 65.01, 62.06, 61.38, 56.01, 55.35, 49.27, 43.85, 40.56, 39.77, 39.10, 33.52, 30.04, 29.58, 26.92, 25.67, 22.77, 10.70 ppm

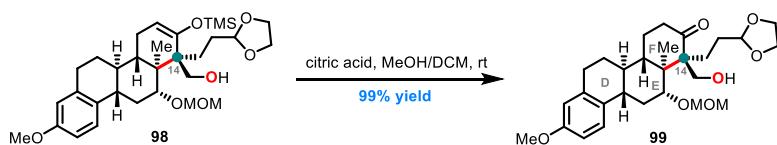
**MP:** 137–138 °C

**IR (neat):** ν 3467, 2951, 2886, 1736, 1707, 1610, 1502, 1256, 1240, 1146, 1037 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>28</sub>H<sub>41</sub>O<sub>7</sub><sup>+</sup> [M+H]<sup>+</sup> 489.2847, found 489.2851

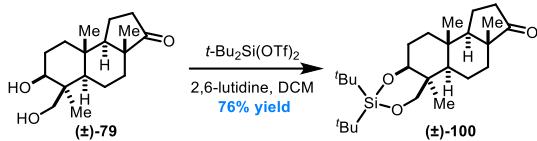
[α]<sub>D</sub><sup>22</sup>: +6.1 (*c* = 1.09, CHCl<sub>3</sub>)

#### Synthesis of alcohol 99 from 98



To a solution of **98** (387 mg, 0.69 mmol) in methanol/DCM (8 mL, 1:1 *v/v*) at room temperature was added a solution of citric acid (0.7 mL, 1 N in water). The reaction mixture was stirred for 60 minutes before it was quenched with a saturated NaHCO<sub>3</sub> solution (*Caution! CO<sub>2</sub> gas evolution occurs during workup*). The layers were separated, and the aqueous solution was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give **99** as a white solid (334 mg, 99% yield).

#### Synthesis of ketone ( $\pm$ )-100



To a solution of **(±)-79** (730 mg, 2.6 mmol) and 2,6-lutidine (1.2 mL, 10.4 mmol) in DCM (15 mL) was added  $t\text{-Bu}_2\text{Si}(\text{OTf})_2$  (0.93 mL, 2.86 mmol) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 60 minutes and warmed up to room temperature before it was quenched with a saturated  $\text{NaHCO}_3$  solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1) gave **(±)-100** as a white solid (827 mg, 76% yield). In practice, enantio-enriched **100** was also prepared from **79** using the same procedure.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.7 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.36 (d,  $J$  = 11.4 Hz, 1H), 3.64 (ddd,  $J$  = 11.6, 5.7, 1.4 Hz, 1H), 3.54 (dd,  $J$  = 11.3, 1.5 Hz, 1H), 2.44 (ddd,  $J$  = 19.2, 9.0, 1.4 Hz, 1H), 2.07 (dt,  $J$  = 19.3, 8.9 Hz, 1H), 2.05–1.90 (m, 2H), 1.84–1.62 (m, 5H), 1.38 (s, 3H), 1.39–1.29 (m, 1H), 1.27–1.18 (m, 2H), 1.11 (s, 9H), 1.07 (s, 9H), 1.09–1.03 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.91 (dd,  $J$  = 12.5, 2.3 Hz, 1H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  220.35, 81.74, 66.04, 58.19, 57.44, 48.20, 41.75, 37.24, 36.73, 35.75, 33.76, 28.84, 28.79, 28.44, 26.59, 22.75, 21.38, 18.41, 18.38, 17.08, 16.60 ppm

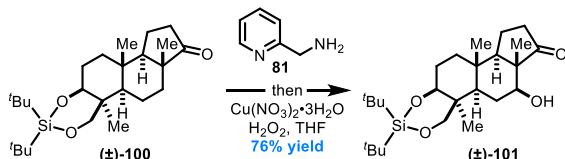
**MP:** 163–165 °C

**IR (neat):**  $\nu$  2939, 2859, 1740, 1478, 1098, 1071, 826, 792, 734, 641  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{25}\text{H}_{45}\text{O}_3\text{Si}^+$  [M+H]<sup>+</sup> 421.3132, found 421.3127

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (100):** -95 ( $c$  = 0.66,  $\text{CHCl}_3$ )

### Synthesis of alcohol **(±)-101**



A round bottle flask was charged with **(±)-100** (827 mg, 1.97 mmol), 2-(aminomethyl)pyridine (**81**, 425 mg, 3.93 mmol),  $\text{TsOH}\cdot\text{H}_2\text{O}$  (20 mg, cat.) and toluene (30 mL). The reaction mixture was heated to reflux under a Dean-Stark apparatus overnight, and then it was diluted with ether (20 mL), sequentially washed with a saturated  $\text{NH}_4\text{Cl}$  solution (10 mL), a saturated  $\text{NaHCO}_3$  solution (10 mL), and brine (10 mL). The remaining solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to afford the crude imine

(1.00 g, 1.97 mmol) as a yellow solid. The crude imine was then dissolved in THF (10 mL) and then Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (522 mg, 2.16 mmol) was added. The heterogeneous mixture was stirred vigorously for 30 minutes, during which all the solids were initially dissolved to give a deep blue solution, followed by the formation of a heavy pale blue precipitate. Hydrogen peroxide (30 wt % in water, 1.0 mL, 9.83 mmol) was then added to the reaction mixture slowly, which dissolved the precipitate to give a blue-green solution. The reaction mixture was then stirred for another 90 minutes at room temperature to give a blue-green slurry. Then ethyl acetate (10 mL) and a saturated Na<sub>4</sub>EDTA solution (10 mL, prepared from Na<sub>2</sub>EDTA and NaOH in water) were added, and the reaction mixture was stirred overnight. The layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 5). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1 → 4:1) gave ( $\pm$ )-**101** as a white solid (653 mg, 76% yield). In practice, enantio-enriched **101** was also prepared from **100** using the same procedure.

**Note:** After the Na<sub>4</sub>EDTA workup, extensive extraction with ethyl acetate is necessary to ensure a reproducible and high isolated yield of ( $\pm$ )-**5.2** due to its potential ligation with Cu(II) in aqueous media.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.45 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.36 (d, J = 11.3 Hz, 1H), 3.69 (dd, J = 11.1, 4.2 Hz, 1H), 3.64 (dd, J = 11.0, 5.7 Hz, 1H), 3.53 (dd, J = 11.3, 1.5 Hz, 1H), 2.72 (br s, 1H), 2.45 (ddd, J = 19.5, 8.5, 1.8 Hz, 1H), 2.10 (dt, J = 19.6, 8.8 Hz, 1H), 2.06–1.91 (m, 2H), 1.92–1.75 (m, 3H), 1.65 (dt, J = 13.3, 3.6 Hz, 1H), 1.44–1.34 (m, 1H), 1.39 (s, 3H), 1.20 (dd, J = 12.5, 6.3 Hz, 1H), 1.11 (s, 9H), 1.07 (s, 9H), 1.07–0.99 (m, 1H), 1.04 (s, 3H), 0.98 (dd, J = 13.0, 2.2 Hz, 1H), 0.95 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 221.90, 81.45, 74.51, 65.98, 55.91, 55.45, 52.59, 41.64, 36.84, 36.30, 35.61, 28.82, 28.76, 28.42, 26.67, 26.07, 22.74, 21.38, 18.57, 16.71, 11.69 ppm

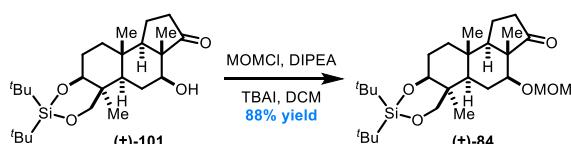
**MP:** 191–193 °C

**IR (neat):** ν 3482, 2967, 2939, 2859, 1734, 1479, 1100, 1057, 827, 793, 643 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>25</sub>H<sub>44</sub>O<sub>4</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 459.2901, found 459.2897

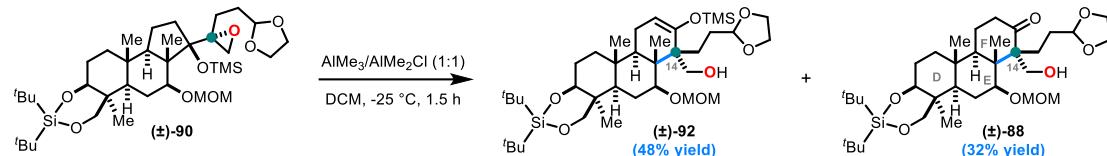
**[α]<sub>D</sub><sup>22</sup> (101):** -105 (c = 0.6, CHCl<sub>3</sub>)

#### Synthesis of ketone ( $\pm$ )-**84** from ( $\pm$ )-**101**



To a solution of ( $\pm$ )-**101** (653 mg, 1.50 mmol), DIPEA (1.3 mL, 7.5 mmol) and TBAI (111 mg, 0.3 mmol) in DCM (10 mL) was added MOMCl (0.34 mL, 4.5 mmol). The reaction mixture was stirred at room temperature overnight and quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (10 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1) gave ( $\pm$ )-**84** as a white solid (631 mg, 88% yield). In practice, enantio-enriched **84** was also prepared from **101** using the same procedure (vide supra).

### Synthesis of alcohols ( $\pm$ )-**92** and ( $\pm$ )-**88**



A round bottle flask was charged with DCM (10 mL) under N<sub>2</sub> and the flask was cooled to -78 °C. An AlMe<sub>3</sub> solution (2 M in hexane, 0.8 mL, 1.6 mmol) and an AlMe<sub>2</sub>Cl solution (1 M in hexane, 1.6 mL, 1.6 mmol) were sequentially added to the flask. After stirring at the same temperature for 5 minutes, a solution of ( $\pm$ )-**90** (1 g, 1.43 mmol) in DCM (18 mL) was added. The reaction mixture was warmed up to -25 °C and stirred for 1.5 hours. A saturated Rochelle's salt solution was added, and the reaction mixture was stirred at room temperature until all the aluminum gel was dissolved (ca. 3 hours). The layers were separated, and the aqueous solution was extracted with DCM (10 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 8:1:1  $\rightarrow$  6:1:1  $\rightarrow$  4:1:1  $\rightarrow$  1:2:1) gave ( $\pm$ )-**92** as a white solid (478 mg, 48% yield) and ( $\pm$ )-**88** as a white solid (290 mg, 32% yield). In practice, enantio-enriched **92** and **88** were also prepared from **90** using the same procedure.

### Analytical data for ( $\pm$ )-**92**:

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.5 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.89 (dd, J = 5.8, 2.4 Hz, 1H), 4.77 (d, J = 6.6 Hz, 1H), 4.76–4.73 (m, 2H), 4.35 (d, J = 11.4 Hz, 1H), 3.98–3.90 (m, 3H), 3.86–3.80 (m, 2H), 3.77 (dd, J = 11.6, 5.3 Hz, 1H), 3.70 (dd, J = 11.7, 6.4 Hz, 1H), 3.64 (dd, J = 11.3, 5.6 Hz, 1H), 3.48 (dd, J = 11.4, 1.4 Hz, 1H), 3.37 (s, 3H), 2.14 (t, J = 6.3 Hz, 1H), 2.03–1.83 (m, 7H), 1.80–1.68 (m, 3H), 1.56–1.52 (m, 1H), 1.39 (s, 3H), 1.39–1.30 (m, 1H), 1.09 (s, 9H), 1.07 (s, 9H), 0.99 (s, 3H), 1.00–0.95 (m, 1H), 0.93 (s, 3H), 0.93–0.86 (m, 1H), 0.20 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 150.86, 106.16, 103.97, 96.33, 83.78, 81.63, 66.17, 66.14, 64.98, 64.85, 56.03, 52.98, 52.32, 49.82, 46.10, 41.56, 38.32, 37.10, 31.56, 29.23, 28.82, 28.44, 26.04, 25.57, 24.85, 22.74, 21.38, 20.83, 17.17, 12.43, 0.51 ppm

**MP:** 85–87 °C

**IR (neat):** ν 3482, 2938, 2894, 2859, 1146, 1106, 1064, 1041, 902, 844, 827, 798, 641 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>37</sub>H<sub>68</sub>O<sub>8</sub>Si<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 719.4345, found 719.4342

[α]<sub>D</sub><sup>22</sup> (**92**): -25 (c = 1.26, CHCl<sub>3</sub>)

#### *Analytical data for (±)-88:*

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.1 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.85 (dd, J = 5.6, 3.0 Hz, 1H), 4.80 (d, J = 6.5 Hz, 1H), 4.65 (d, J = 6.5 Hz, 1H), 4.32 (d, J = 11.4 Hz, 1H), 4.26 (d, J = 12.5 Hz, 1H), 4.00–3.93 (m, 3H), 3.89–3.83 (m, 2H), 3.77 (d, J = 12.3 Hz, 1H), 3.67 (dd, J = 10.6, 6.1 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 3.36 (s, 3H), 2.34–2.26 (m, 1H), 2.20 (td, J = 12.7, 6.7 Hz, 1H), 2.12 (tdt, J = 14.1, 8.3, 2.9 Hz, 1H), 2.08–1.92 (m, 6H), 1.92–1.85 (m, 1H), 1.80 (dt, J = 12.4, 2.8 Hz, 1H), 1.73 (dd, J = 12.7, 2.9 Hz, 1H), 1.61 (dt, J = 12.9, 6.4 Hz, 1H), 1.47–1.36 (m, 1H), 1.40 (s, 3H), 1.36–1.28 (m, 1H), 1.10 (s, 9H), 1.08 (s, 9H), 1.07–0.94 (m, 2H), 0.92 (s, 3H), 0.89 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.50, 105.30, 96.73, 83.12, 81.35, 65.91, 65.04, 65.01, 62.36, 61.92, 55.85, 53.19, 51.81, 50.30, 41.51, 39.82, 38.33, 37.59, 29.37, 29.09, 28.79, 28.41, 26.07, 25.81, 22.70, 22.30, 21.60, 21.35, 16.82, 11.63 ppm

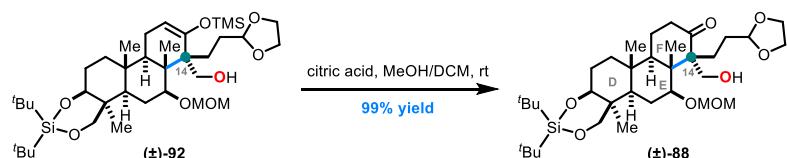
**MP:** 132–134 °C

**IR (neat):** ν 3436, 2967, 2939, 2892, 2859, 1705, 1477, 1147, 1109, 1033, 826, 797, 736, 641 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>34</sub>H<sub>60</sub>O<sub>8</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 647.3950, found 647.3950

[α]<sub>D</sub><sup>22</sup> (**88**): -20 (c = 1.82, CHCl<sub>3</sub>)

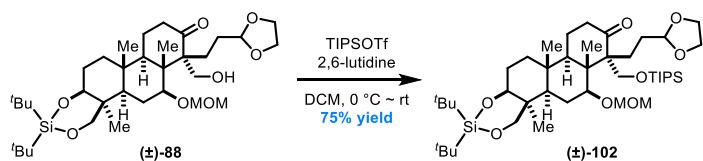
#### *Synthesis of alcohol (±)-88 from (±)-92*



To a solution of (±)-**92** (478 mg, 0.686 mmol) in methanol/DCM (8 mL, 1:1 v/v) at room temperature was added a solution of citric acid (0.7 mL, 1 N in water). The reaction mixture was stirred for 60 minutes before it was quenched with a saturated NaHCO<sub>3</sub> solution (Caution! CO<sub>2</sub> gas evolution occurs during

*workup*). The layers were separated, and the aqueous solution was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give ( $\pm$ )-**88** as a white solid (424 mg, 99% yield). In practice, enantio-enriched **88** was also prepared from **92** using the same procedure.

**Synthesis of ketone ( $\pm$ )-**102****



To a solution of ( $\pm$ )-**88** (1.65 g, 2.64 mmol) in DCM (130 mL) was sequentially added 2,6-lutidine (0.92 mL, 7.92 mmol) and TIPSOTf (1.06 mL, 3.96 mmol) at -78 °C. The reaction mixture was warmed up to room temperature and stirred for 1 hour before work-up with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1 → 6:1) gave ( $\pm$ )-**102** as a white foam (1.55 g, 75% yield). In practice, enantio-enriched **102** was also prepared from **88** using the same procedure.

**Note:** A low concentration of this reaction (<0.05 M, 0.02 M optimal) is crucial for a high yield of ( $\pm$ )-**102** presumably by suppressing potential side reactions of the dioxolane moiety in the presence of TIPSOTf.

**Physical state:** white foam

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.4 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.82 (t, J = 4.8 Hz, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.32 (d, J = 11.4 Hz, 1H), 4.12 (d, J = 10.3 Hz, 1H), 4.08 (d, J = 10.4 Hz, 1H), 3.96–3.85 (m, 2H), 3.86–3.76 (m, 3H), 3.64 (dd, J = 11.3, 5.8 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 3.37 (s, 3H), 2.48–2.33 (m, 2H), 2.07–1.90 (m, 5H), 1.89–1.75 (m, 4H), 1.68–1.49 (m, 2H), 1.39 (s, 3H), 1.33 (dd, J = 24.2, 13.2 Hz, 1H), 1.11–1.01 (m, 41H), 0.96 (s, 3H), 0.89 (s, 3H) ppm

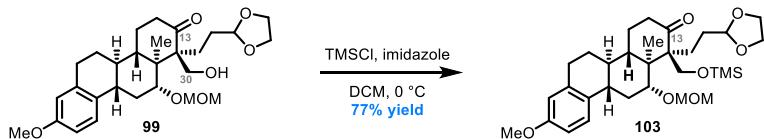
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.57, 105.79, 96.20, 82.50, 81.47, 66.15, 65.92, 64.85, 64.83, 60.39, 56.13, 53.11, 51.71, 49.53, 41.54, 40.30, 38.24, 37.61, 30.37, 29.09, 28.82, 28.41, 26.02, 25.61, 25.26, 22.73, 21.57, 21.37, 18.39, 18.36, 16.87, 12.44, 12.20 ppm

**IR (neat):** ν 2943, 2865, 1710, 1464, 1388, 1147, 1104, 1063, 826, 797, 738, 641 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>43</sub>H<sub>81</sub>O<sub>8</sub>Si<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 781.5464, found 781.5465

**[α]<sub>D</sub><sup>22</sup> (102):** -22 (c = 1.78, CHCl<sub>3</sub>)

*Synthesis of ketone 103*



To a solution of imidazole (358 mg, 5.26 mmol) and **99** (644 mg, 1.32 mmol) in DCM (65 mL) was added TMSCl (0.39 mL, 3.07 mmol) at 0 °C. The reaction mixture was stirred for 30 minutes at the same temperature and white precipitates were crashed out during the period. The reaction mixture was quenched with water. The layers were separated, and the aqueous solution was extracted with DCM. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1 → 4:1) gave **103** as a white foam (569 mg, 77% yield).

**Note:** A low concentration of this reaction (<0.05 M, 0.02 M optimal) is crucial for a high yield of **103** presumably by suppressing potential side reactions of the dioxolane moiety.

**Physical state:** white foam

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.45 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.18 (d, J = 8.6 Hz, 1H), 6.72 (dd, J = 8.6, 2.7 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 4.84 (t, J = 4.2 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.78 (d, J = 7.0 Hz, 1H), 4.06 (d, J = 10.3 Hz, 1H), 4.03 (d, J = 10.3 Hz, 1H), 3.99–3.90 (m, 3H), 3.87–3.80 (m, 2H), 3.78 (s, 3H), 3.46 (s, 3H), 2.92–2.77 (m, 2H), 2.65 (dt, J = 12.9, 4.1 Hz, 1H), 2.46 (td, J = 12.8, 6.8 Hz, 1H), 2.40–2.27 (m, 3H), 2.24–2.15 (m, 1H), 2.12–2.06 (m, 1H), 1.99 (ddd, J = 13.3, 9.9, 3.8 Hz, 1H), 1.95–1.83 (m, 2H), 1.54–1.41 (m, 2H), 1.38–1.27 (m, 3H), 0.93 (s, 3H), 0.12 (s, 9H) ppm

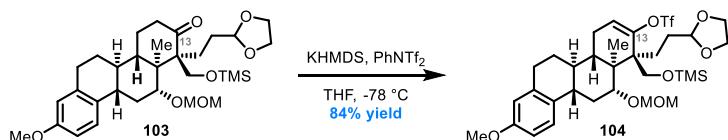
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.75, 157.81, 137.93, 131.72, 126.12, 113.56, 111.82, 105.98, 96.26, 81.13, 64.84, 64.82, 63.49, 59.33, 56.30, 55.35, 48.96, 44.09, 40.78, 39.59, 39.55, 33.21, 30.22, 30.06, 26.99, 25.48, 25.36, 10.89, -0.54 ppm

**IR (neat):** ν 2953, 2934, 1707, 1609, 1501, 1255, 1146, 1036 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>31</sub>H<sub>48</sub>NaO<sub>7</sub>Si<sup>+</sup> [M+Na]<sup>+</sup> 583.3062, found 583.3060

[α]<sub>D</sub><sup>22</sup>: +1.6 (c = 0.23, CHCl<sub>3</sub>)

*Synthesis of vinyl triflate 104*



To a solution of **103** (569 mg, 1.0 mmol) and PhNTf<sub>2</sub> (500 mg, 1.4 mmol) in THF (5 mL) was added a solution of KHMDS (300 mg, 1.5 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred at the same temperature until TLC indicating full consumption of **103** (ca. 1.5 hours) and then quenched with a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 8:1 → 6:1) gave vinyl triflate **104** as a white amorphous solid (582 mg, 84% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.7 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.21 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 8.6, 2.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 5.95 (dd, J = 6.3, 2.0 Hz, 1H), 4.88 (d, J = 6.7 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.76 (t, J = 4.8 Hz, 1H), 4.13 (dd, J = 11.4, 4.3 Hz, 1H), 3.98–3.88 (m, 2H), 3.85–3.79 (m, 3H), 3.78 (s, 3H), 3.67 (d, J = 10.9 Hz, 1H), 3.44 (s, 3H), 2.89–2.80 (m, 2H), 2.70 (dt, J = 12.9, 4.0 Hz, 1H), 2.45 (dt, J = 17.8, 5.7 Hz, 1H), 2.35 (td, J = 10.7, 4.7 Hz, 1H), 2.32–2.22 (m, 2H), 2.05–1.98 (m, 1H), 1.90–1.76 (m, 2H), 1.68–1.59 (m, 2H), 1.55–1.46 (m, 1H), 1.34–1.17 (m, 2H), 1.02 (s, 3H), 0.11 (s, 9H) ppm

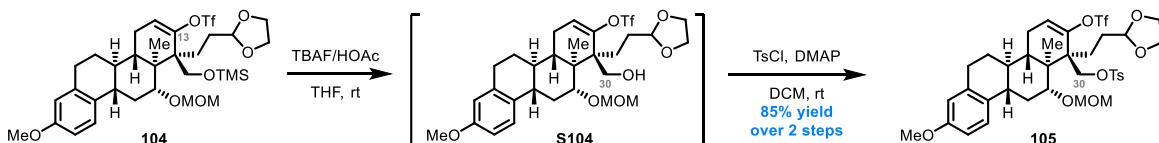
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.87, 151.77, 137.97, 131.68, 126.16, 118.45 (q, J = 319.4 Hz), 117.47, 113.66, 111.84, 105.41, 95.97, 81.38, 64.93, 64.87, 64.62, 56.20, 55.34, 49.99, 45.86, 40.61, 40.36, 39.61, 32.22, 30.96, 30.06, 27.05, 26.31, 25.34, 11.24, -0.58 ppm

**IR (neat):** ν 2953, 2892, 1611, 1502, 1411, 1249, 1211, 1146, 1039, 895, 873, 844, 735, 609 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>32</sub>H<sub>47</sub>O<sub>9</sub>SF<sub>3</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 715.2554, found 715.2547

[α]<sub>D</sub><sup>22</sup>: -30.4 (c = 0.34, CHCl<sub>3</sub>)

### Synthesis of tosylate **105**



To a solution of **104** (612 mg, 0.883 mmol) in THF (10 mL) was added TBAF solution (1 M, 3.0 mL, 3 mmol) that was pre-buffered with acetic acid (0.22 mL, 3.83 mmol). The reaction mixture was stirred at room temperature for 2 hours. Upon full conversion of **104** indicated by TLC analysis, the reaction mixture was quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude **S104** as a white foam to be used in the next step without further purification. The crude **S104** was dissolved in DCM (10 mL) followed by addition of DMAP (161 mg, 1.32

mmol), TsCl (252 mg, 1.32 mmol), and Et<sub>3</sub>N (0.25 mL, 1.77 mmol) at room temperature. The reaction mixture was stirred at 30 °C until TLC analysis showed full conversion of **S104** (ca. 12 hours). The solution was directly loaded on silica gel column, and purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 4:1:1) gave **105** as a white amorphous solid (582 mg, 85% overall yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate/DCM 2:1:1):** R<sub>f</sub> 0.5 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.80 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 8.5, 2.7 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 5.98 (d, J = 6.0 Hz, 1H), 4.77 (d, J = 6.6 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 4.72 (t, J = 4.7 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 3.96 (d, J = 10.5 Hz, 1H), 3.93–3.85 (m, 3H), 3.84–3.79 (m, 2H), 3.78 (s, 3H), 3.41 (s, 3H), 2.90–2.75 (m, 2H), 2.67–2.60 (m, 1H), 2.47 (dt, J = 17.3, 4.9 Hz, 1H), 2.41 (s, 3H), 2.32–2.19 (m, 2H), 2.00–1.94 (m, 1H), 1.92–1.76 (m, 3H), 1.76–1.67 (m, 1H), 1.48 (q, J = 12.3 Hz, 1H), 1.32–1.26 (m, 2H), 1.02 (s, 3H) ppm

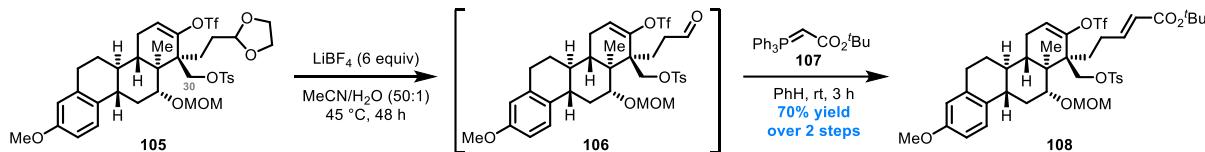
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.83, 148.99, 145.25, 137.77, 132.44, 131.25, 129.92, 128.30, 126.12, 118.52, 118.25 (q, J = 320.2 Hz), 113.59, 111.84, 104.81, 95.94, 81.15, 70.14, 64.95, 64.89, 56.18, 55.32, 48.58, 45.88, 40.73, 39.96, 39.64, 32.09, 30.69, 29.95, 26.72, 26.45, 25.20, 21.70, 11.28 ppm

**IR (neat):** ν 2926, 1609, 1501, 1412, 1367, 1190, 1178, 1144, 1037 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>36</sub>H<sub>49</sub>O<sub>11</sub>S<sub>2</sub>F<sub>3</sub>N<sup>+</sup> [M+NH<sub>4</sub>]<sup>+</sup> 792.2694, found 792.2692

[α]<sub>D</sub><sup>22</sup>: -42.6 (c = 0.05, CHCl<sub>3</sub>)

### Synthesis of ester **108**



To a solution of **105** (23.2 mg, 0.03 mmol) in MeCN/H<sub>2</sub>O (50:1 v/v, 3.06 mL) was added LiBF<sub>4</sub> (8.4 mg, 0.09 mmol). The reaction mixture was heated to 45 °C for 48 hours before it was diluted with DCM and quenched with a pH 7 buffer solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude residue could also be purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 6:1:1) to give **106** as a white amorphous solid. In practice, the crude **106** could be directly used in the next reaction without further purification.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.5 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.64 (s, 1H), 7.81 (d,  $J$  = 8.3 Hz, 2H), 7.35 (d,  $J$  = 8.0 Hz, 2H), 7.16 (d,  $J$  = 8.6 Hz, 1H), 6.73 (dd,  $J$  = 8.6, 2.8 Hz, 1H), 6.63 (d,  $J$  = 2.7 Hz, 1H), 6.01 (dd,  $J$  = 6.3, 1.6 Hz, 1H), 4.77 (d,  $J$  = 6.6 Hz, 1H), 4.73 (d,  $J$  = 6.6 Hz, 1H), 4.34 (d,  $J$  = 10.6 Hz, 1H), 4.00 (d,  $J$  = 10.5 Hz, 1H), 3.87 (dd,  $J$  = 11.2, 4.3 Hz, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.90–2.76 (m, 2H), 2.69–2.58 (m, 2H), 2.55–2.44 (m, 3H), 2.42 (s, 3H), 2.29–2.19 (m, 1H), 2.10–2.01 (m, 1H), 2.01–1.94 (m, 1H), 1.89–1.80 (m, 2H), 1.47 (td,  $J$  = 12.7, 11.3 Hz, 1H), 1.33–1.27 (m, 1H), 1.27–1.19 (m, 1H), 1.00 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  200.66, 157.91, 148.42, 145.46, 137.72, 132.31, 131.11, 130.03, 128.35, 126.17, 119.19, 118.22 (q,  $J$  = 319.6 Hz), 113.67, 111.91, 96.02, 81.16, 69.99, 56.22, 55.38, 48.75, 45.87, 41.20, 40.57, 39.94, 39.70, 32.16, 29.95, 26.72, 25.30, 23.10, 21.77, 11.21 ppm

**IR (neat):**  $\nu$  2925, 2851, 1726, 1610, 1501, 1216, 1178, 1144, 1097, 1037, 772 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>34</sub>H<sub>41</sub>O<sub>10</sub>S<sub>2</sub>F<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 753.1985, found 753.1991

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>:** -43 (*c* = 0.325, CHCl<sub>3</sub>)

To a mixture of the above crude and **107** (12 mg, 0.0318 mmol) was added benzene (0.6 mL). The solution was stirred until full consumption of **106** indicated by TLC. The reaction mixture was directly loaded on silica gel column, and purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1 → 4:1) gave **108** as a white amorphous solid (17.3 mg, 70% overall yield). **105** was recovered as a white foam (4.4 mg, 19% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.7 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.80 (d,  $J$  = 8.2 Hz, 2H), 7.34 (d,  $J$  = 8.0 Hz, 2H), 7.16 (d,  $J$  = 8.6 Hz, 1H), 6.74 (dd,  $J$  = 8.7, 2.7 Hz, 1H), 6.69 (dt,  $J$  = 15.3, 6.9 Hz, 1H), 6.63 (d,  $J$  = 2.7 Hz, 1H), 5.98–5.93 (m, 1H), 5.66 (d,  $J$  = 15.6 Hz, 1H), 4.76 (d,  $J$  = 6.6 Hz, 1H), 4.73 (d,  $J$  = 6.6 Hz, 1H), 4.33 (d,  $J$  = 10.5 Hz, 1H), 4.01 (d,  $J$  = 10.5 Hz, 1H), 3.86 (dd,  $J$  = 11.3, 4.2 Hz, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.92–2.75 (m, 2H), 2.64 (dt,  $J$  = 12.9, 3.6 Hz, 1H), 2.47 (dd,  $J$  = 13.3, 6.2 Hz, 1H), 2.42 (s, 3H), 2.37–2.27 (m, 1H), 2.27–2.14 (m, 2H), 2.12–2.02 (m, 1H), 2.01–1.94 (m, 1H), 1.90–1.77 (m, 3H), 1.50–1.46 (m, 1H), 1.47 (s, 9H), 1.33–1.24 (m, 2H), 1.01 (s, 3H) ppm

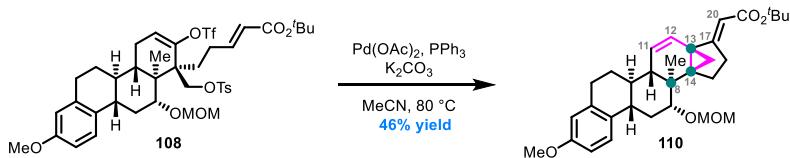
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  166.07, 157.87, 149.02, 147.12, 145.40, 137.75, 132.37, 131.16, 129.99, 128.30, 126.13, 123.30, 118.62, 118.26 (q,  $J$  = 319.8 Hz), 113.63, 111.87, 95.94, 81.22, 80.33, 69.89, 56.19, 55.35, 48.69, 45.90, 40.65, 39.95, 39.71, 32.05, 30.67, 29.94, 28.65, 28.26, 26.72, 25.25, 21.75, 11.14 ppm

**IR (neat):**  $\nu$  2932, 1712, 1654, 1611, 1502, 1413, 1368, 1213, 1178, 1145, 1037, 985 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>40</sub>H<sub>51</sub>O<sub>11</sub>S<sub>2</sub>F<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 851.2717, found 851.2713

$[\alpha]_D^{22}$ : -22.2 ( $c = 0.2$ , CHCl<sub>3</sub>)

*Synthesis of [4.3.1]propellane 110 from 108*



A 4-mL vial equipped with a magnetic stir bar was sequentially charged with **108** (30.9 mg, 0.0373 mmol), Pd(OAc)<sub>2</sub> (2.2 mg, 0.01 mmol), PPh<sub>3</sub> (5.2 mg, 0.02 mmol), K<sub>2</sub>CO<sub>3</sub> (15.5 mg, 0.112 mmol) and MeCN (3 mL) at room temperature. The vial was sealed and stirred for 1 minute before it was heated to 80 °C for 1 h to give a dark solution where Pd black formation was observed. The reaction mixture was cooled down to room temperature, diluted with DCM, and filtered through a short plug of silica gel. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate = 12:1 → 8:1) to give **110** as a white amorphous solid (8.6 mg, 46% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.7 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.19 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 8.6, 2.7 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 6.25 (dd, J = 10.2, 3.0 Hz, 1H), 5.78 (s, 1H), 5.48 (dd, J = 10.2, 2.2 Hz, 1H), 4.85 (d, J = 6.8 Hz, 1H), 4.83 (d, J = 6.8 Hz, 1H), 3.78 (s, 3H), 3.61 (dd, J = 11.4, 4.3 Hz, 1H), 3.48 (s, 3H), 3.41–3.31 (m, 1H), 2.95–2.83 (m, 2H), 2.67 (dt, J = 12.7, 4.3 Hz, 1H), 2.43–2.34 (m, 1H), 2.33–2.13 (m, 4H), 2.01–1.91 (m, 1H), 1.85 (d, J = 4.9 Hz, 1H), 1.67 (dt, J = 11.5, 2.6 Hz, 1H), 1.63–1.52 (m, 2H), 1.49 (s, 9H), 1.36–1.27 (m, 2H), 1.01 (d, J = 5.0 Hz, 1H) ppm

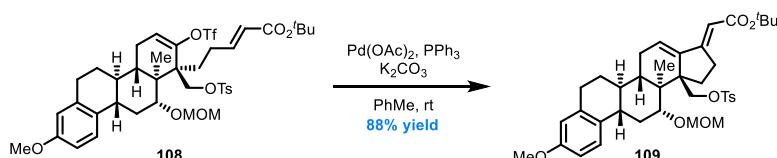
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 167.35, 166.77, 157.87, 138.04, 132.05, 126.42, 125.93, 121.99, 113.75, 111.72, 110.46, 97.24, 84.87, 79.50, 55.83, 55.37, 45.79, 44.53, 41.81, 38.03, 38.00, 37.46, 32.82, 30.09, 29.26, 29.19, 28.51, 27.51, 24.10, 12.07 ppm

**IR (neat):** ν 2947, 2930, 2884, 1702, 1644, 1501, 1256, 1144, 1040 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>32</sub>H<sub>43</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 507.3105, found 507.3094

$[\alpha]_D^{22}$ : -36.8 ( $c = 0.33$ , CHCl<sub>3</sub>)

*Synthesis of tosylate 109*



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with **108** (8.3 mg, 0.01 mmol), Pd(OAc)<sub>2</sub> (1.1 mg, 0.005 mmol), PPh<sub>3</sub> (2.6 mg, 0.01 mmol), K<sub>2</sub>CO<sub>3</sub> (4.1 mg, 0.03 mmol) and toluene (0.2 mL) at room temperature. The vial was sealed, and the resulting yellow solution was stirred at room temperature for 12 hours during which the color turned red. The reaction mixture was then directed loaded on a silica gel column and purified by flash chromatography (silica gel, toluene/ether = 15:1) to give **109** as a white amorphous solid (6.0 mg, 88% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.7 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.77 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 8.6, 2.8 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.27 (t, J = 3.9 Hz, 1H), 5.88 (d, J = 2.6 Hz, 1H), 4.84 (d, J = 6.7 Hz, 1H), 4.72 (d, J = 6.7 Hz, 1H), 4.05 (d, J = 11.0 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.62 (dd, J = 11.3, 4.2 Hz, 1H), 3.40 (s, 3H), 2.96–2.88 (m, 1H), 2.89–2.76 (m, 2H), 2.68 (dt, J = 12.7, 4.0 Hz, 1H), 2.46–2.39 (m, 1H), 2.38 (s, 3H), 2.37–2.27 (m, 1H), 2.16–2.08 (m, 1H), 2.02–1.92 (m, 2H), 1.91–1.80 (m, 1H), 1.78 (ddd, J = 20.0, 10.5, 3.5 Hz, 1H), 1.70–1.52 (m, 1H), 1.48 (s, 9H), 1.47–1.40 (m, 1H), 1.32–1.28 (m, 1H), 1.23–1.19 (m, 1H), 0.78 (s, 3H) ppm

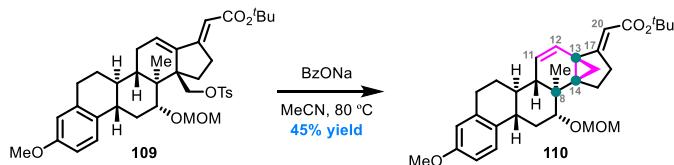
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 166.58, 157.78, 157.47, 145.25, 141.79, 137.80, 132.74, 131.65, 130.00, 128.20, 126.31, 124.64, 113.69, 111.80, 110.87, 96.67, 81.45, 79.79, 69.78, 55.75, 55.35, 52.66, 42.89, 40.40, 40.28, 40.06, 32.69, 30.15, 29.69, 28.46, 28.40, 28.32, 26.93, 21.76, 10.42 ppm

**IR (neat):** ν 2955, 2927, 1745, 1701, 1624, 1501, 1366, 1177, 1144, 1041, 838, 666 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>39</sub>H<sub>50</sub>O<sub>8</sub>SnNa<sup>+</sup> [M+Na]<sup>+</sup> 701.3119, found 701.3122

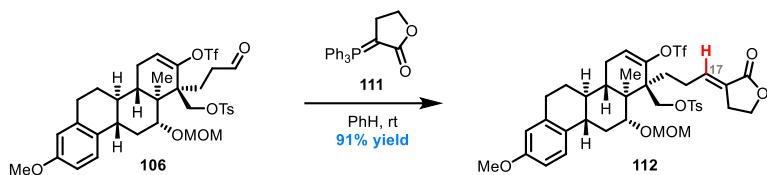
[α]<sub>D</sub><sup>22</sup>: -75 (c = 1.0, CHCl<sub>3</sub>)

### Synthesis of [4.3.1]propellane **110** from **109**



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with **109** (6.0 mg, 0.0088 mmol), BzONa (6.4 mg, 0.044 mmol) and MeCN (0.1 mL) at room temperature. The vial was sealed and heated to 80 °C for 1 h before it was cooled down to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate = 8:1) to give **110** as a white amorphous solid (2.0 mg, 45% yield).

*Synthesis of lactone 112*



An 8-mL vial equipped with a magnetic stir bar was sequentially charged with **106** (84 mg, 0.115 mmol), **111** (60 mg, 0.173 mmol) and benzene (4 mL). The vial was sealed and stirred for 24 hours when full consumption of **106** was indicated by TLC. The reaction mixture was directly loaded on silica gel column, and purification by flash chromatography (silica gel, hexanes/ethyl acetate = 3:1) gave **112** as a white amorphous solid (84 mg, 91% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.25 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.80 (d,  $J$  = 8.0 Hz, 2H), 7.35 (d,  $J$  = 8.0 Hz, 2H), 7.15 (d,  $J$  = 8.6 Hz, 1H), 6.74 (dd,  $J$  = 8.4, 2.6 Hz, 1H), 6.63 (d,  $J$  = 2.7 Hz, 1H), 6.60–6.53 (m, 1H), 5.97 (d,  $J$  = 5.9 Hz, 1H), 4.74 (d,  $J$  = 6.5 Hz, 1H), 4.68 (d,  $J$  = 6.5 Hz, 1H), 4.39–4.33 (m, 3H), 4.08 (d,  $J$  = 10.5 Hz, 1H), 3.81 (dd,  $J$  = 11.4, 4.3 Hz, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.89–2.79 (m, 4H), 2.63 (dt,  $J$  = 13.0, 3.4 Hz, 1H), 2.48 (dd,  $J$  = 13.6, 6.8 Hz, 1H), 2.42 (s, 3H), 2.41–2.34 (m, 1H), 2.25–2.10 (m, 3H), 2.05–1.93 (m, 2H), 1.87–1.79 (m, 2H), 1.47 (q,  $J$  = 12.2 Hz, 1H), 1.33–1.19 (m, 2H), 1.02 (s, 3H) ppm

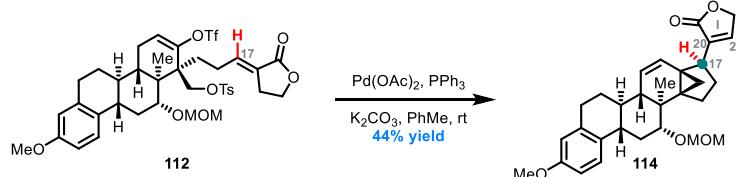
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.32, 157.93, 149.40, 145.50, 140.02, 137.71, 132.47, 131.07, 130.02, 128.27, 126.10, 125.67, 118.62, 118.32 (q,  $J$  = 319.7 Hz), 113.68, 111.91, 95.87, 81.17, 69.64, 65.58, 56.11, 55.37, 48.54, 46.00, 40.63, 39.96, 39.77, 31.99, 30.66, 29.91, 26.98, 26.74, 25.30, 25.04, 21.75, 11.02 ppm

**IR (neat):**  $\nu$  2925, 2853, 1756, 1438, 1413, 1369, 1211, 1177, 1119, 1032  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{38}\text{H}_{46}\text{O}_{11}\text{S}_2\text{F}_3^+$  [M+H]<sup>+</sup> 799.2428, found 799.2431

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>:** -25 ( $c$  = 0.48,  $\text{CHCl}_3$ )

*Synthesis of [4.3.1]propellane 114*



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with **112** (16 mg, 0.02 mmol),  $\text{Pd}(\text{OAc})_2$  (1.1 mg, 0.005 mmol),  $\text{PPh}_3$  (2.6 mg, 0.01 mmol),  $\text{K}_2\text{CO}_3$  (5.5 mg, 0.04 mmol) and toluene (0.4 mL) at room temperature. The vial was sealed, and the resulting yellow solution was stirred at room

temperature for 18 hours during which the color turned red. The reaction mixture was then directed loaded on a silica gel column and purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1) to give **114** as a white amorphous solid (4.2 mg, 44% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.25 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):**  $\delta$  7.28 (d,  $J$  = 8.5 Hz, 1H), 6.79 (dd,  $J$  = 8.5, 2.8 Hz, 1H), 6.71 (d,  $J$  = 2.7 Hz, 1H), 6.31 (q,  $J$  = 1.7 Hz, 1H), 6.09 (dd,  $J$  = 9.9, 2.9 Hz, 1H), 5.38 (dd,  $J$  = 10.0, 2.2 Hz, 1H), 4.76 (d,  $J$  = 6.6 Hz, 1H), 4.73 (d,  $J$  = 6.6 Hz, 1H), 3.87 (q,  $J$  = 1.6 Hz, 2H), 3.52 (dd,  $J$  = 11.4, 4.2 Hz, 1H), 3.42 (s, 3H), 3.33 (s, 3H), 2.90 (t,  $J$  = 9.5 Hz, 1H), 2.78 (dt,  $J$  = 12.6, 4.2 Hz, 1H), 2.74–2.68 (m, 2H), 2.27–2.14 (m, 2H), 2.12 (dt,  $J$  = 12.8, 8.0 Hz, 1H), 2.01–1.92 (m, 2H), 1.66 (q,  $J$  = 12.5 Hz, 1H), 1.48–1.38 (m, 2H), 1.14 (d,  $J$  = 5.6 Hz, 1H), 1.14–1.03 (m, 2H), 0.93 (s, 3H), 0.69 (d,  $J$  = 5.5 Hz, 1H) ppm

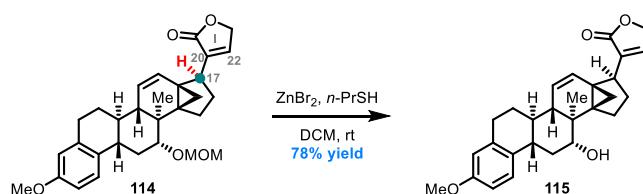
**$^{13}\text{C-NMR}$  (101 MHz,  $\text{C}_6\text{D}_6$ ):**  $\delta$  173.68, 158.55, 142.78, 138.02, 136.51, 132.36, 130.45, 126.20, 122.61, 114.09, 112.05, 97.08, 84.74, 69.62, 55.45, 54.83, 44.84, 41.97, 40.48, 39.77, 38.17, 37.83, 34.00, 32.95, 30.49, 30.28, 28.25, 27.95, 12.58, 12.23 ppm

**IR (neat):**  $\nu$  2925, 2880, 2851, 1753, 1610, 1500, 1383, 1143, 1105, 1040  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{30}\text{H}_{36}\text{NaO}_5^+$  [M+Na]<sup>+</sup> 499.2455, found 499.2459

$[\alpha]_D^{22}$ : +27 ( $c$  = 0.15,  $\text{CHCl}_3$ )

### Synthesis of alcohol **115**



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with **114** (7.9 mg, 0.0166 mmol),  $\text{ZnBr}_2$  (4.0 mg, 0.018 mmol), DCM (0.1 mL) and *n*-PrSH (4.5  $\mu\text{L}$ , 0.05 mmol). The reaction mixture was sealed and stirred at room temperature for 2.5 hours before it was quenched with a saturated  $\text{NaHCO}_3$  solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 1:1) gave **115** as a white amorphous solid (5.6 mg, 78% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 1:2):**  $R_f$  0.5 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 6.05 (dd, *J* = 9.9, 3.0 Hz, 1H), 5.50 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.85 (dt, *J* = 17.8, 1.9 Hz, 1H), 4.80 (dt, *J* = 17.8, 1.7 Hz, 1H), 3.80 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.78 (s, 3H), 2.96–2.83 (m, 3H), 2.50 (dt, *J* = 12.4, 4.3 Hz, 1H), 2.44–2.35 (m, 1H), 2.26–2.16 (m, 3H), 2.08–1.99 (m, 1H), 1.59 (dt, *J* = 11.4, 2.9 Hz, 1H), 1.57–1.51 (m, 1H), 1.51–1.42 (m, 1H), 1.36–1.27 (m, 1H), 1.30 (d, *J* = 5.8 Hz, 1H), 1.23–1.17 (m, 1H), 0.89 (d, *J* = 5.7 Hz, 1H), 0.83 (s, 3H) ppm

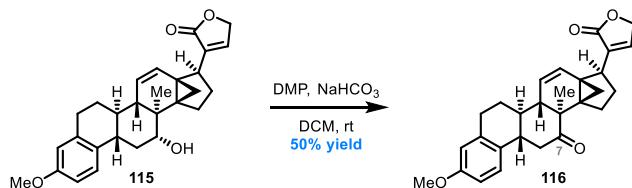
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 174.59, 157.91, 143.39, 138.06, 136.66, 131.97, 130.06, 125.93, 122.87, 113.84, 111.70, 77.80, 70.54, 55.39, 44.42, 42.00, 39.89, 39.55, 38.20, 37.42, 35.36, 33.73, 30.51, 30.08, 28.56, 27.59, 12.70, 10.88 ppm

**IR (neat):** *v* 3488, 2927, 2878, 2853, 1747, 1610, 1501, 1384, 1255, 1201, 1139, 1091, 757 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>28</sub>H<sub>33</sub>O<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup> 433.2373, found 433.2378

[*α*]<sub>D</sub><sup>22</sup>: +10 (*c* = 1.44, CHCl<sub>3</sub>)

### Synthesis of ketone 116



Alcohol **115** (8.6 mg, 0.02 mmol) was dissolved in DCM (0.5 mL), followed by sequential addition of NaHCO<sub>3</sub> (16.8 mg, 0.2 mmol) and Dess-Martin periodinane (8.5 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 30 minutes and quenched by addition of a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 3:1:1) gave **116** as a white solid (4.3 mg, 50% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.25 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.25 (q, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.74 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 6.14 (dd, *J* = 9.9, 3.0 Hz, 1H), 5.53 (dd, *J* = 10.0, 2.3 Hz, 1H), 4.88–4.78 (m, 2H), 3.79 (s, 3H), 3.04–2.89 (m, 4H), 2.79–2.65 (m, 2H), 2.35–2.23 (m, 2H), 2.17 (dt, *J* = 13.3, 8.0 Hz, 1H), 2.06–1.88 (m, 3H), 1.39 (dtd, *J* = 13.0, 10.8, 7.7 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 1H), 1.27–1.19 (m, 1H), 1.13 (s, 3H), 1.08 (d, *J* = 6.0 Hz, 1H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 213.45, 174.60, 158.25, 143.42, 137.87, 136.54, 131.44, 130.99, 125.96, 121.55, 114.00, 111.95, 70.58, 55.41, 48.03, 45.94, 44.40, 42.68, 39.90, 37.85, 36.91, 32.38, 30.05, 28.45,

28.17, 27.36, 17.15, 13.97 ppm

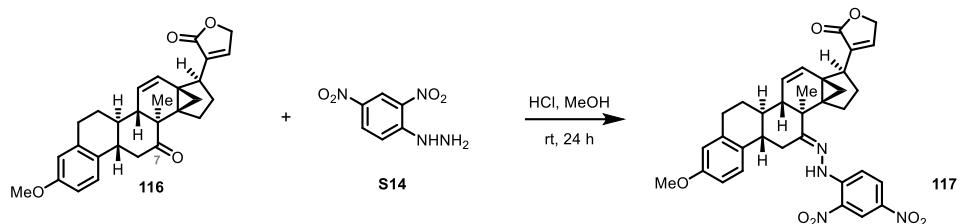
**MP:** 129–131 °C

**IR (neat):**  $\nu$  2925, 2851, 1752, 1707, 1610, 1501, 1256, 1075, 909, 734 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>28</sub>H<sub>30</sub>O<sub>4</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 453.2036, found 453.2037

$[\alpha]_D^{22}$ : +109 ( $c = 0.8$ , CHCl<sub>3</sub>)

### Synthesis of the DNP-hydrazone of 117



Ketone **116** (2.0 mg, 0.0046 mmol) was dissolved in methanol (0.2 mL), followed by sequential addition of **S14** (1 mg, 0.0050 mmol) and concentrated HCl solution (0.4  $\mu$ L, 0.0048 mmol). The reaction mixture was stirred at room temperature for 12 hours before evaporation of the solvent under vacuum. The resulting red solid was suspended in methanol (0.1 mL) and filtered through cotton. The solid on cotton was washed by methanol 3 times and then collected by dissolving it in DCM and evaporation of DCM under vacuum. The resulting red solid was recrystallized to give orange crystalline **117** for X-ray crystallography. Yield was not determined.

**Physical state:** orange crystalline solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.3 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  11.51 (s, 1H), 9.17 (d,  $J$  = 2.6 Hz, 1H), 8.36 (dd,  $J$  = 9.5, 2.6 Hz, 1H), 7.97 (d,  $J$  = 9.6 Hz, 1H), 7.31 (q,  $J$  = 1.6 Hz, 1H), 7.29 (d,  $J$  = 8.6 Hz, 1H), 6.82 (dd,  $J$  = 8.6, 2.8 Hz, 1H), 6.70 (d,  $J$  = 2.7 Hz, 1H), 6.18 (dd,  $J$  = 9.9, 3.0 Hz, 1H), 5.54 (dd,  $J$  = 10.0, 2.3 Hz, 1H), 4.92–4.81 (m, 2H), 3.81 (s, 3H), 3.51 (dd,  $J$  = 14.0, 4.2 Hz, 1H), 3.03 (t,  $J$  = 9.6 Hz, 1H), 2.99–2.89 (m, 2H), 2.63–2.51 (m, 1H), 2.40–2.20 (m, 4H), 2.19–2.08 (m, 1H), 2.02–1.97 (m, 1H), 1.92–1.81 (m, 1H), 1.47–1.33 (m, 3H), 1.21 (d,  $J$  = 6.0 Hz, 1H), 1.16 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  174.52, 164.34, 158.40, 145.96, 143.62, 138.19, 137.83, 136.47, 131.38, 130.43, 130.28, 129.28, 125.67, 123.85, 121.92, 116.28, 114.27, 112.11, 70.60, 55.44, 46.93, 43.74, 43.05, 40.29, 38.66, 37.88, 32.88, 30.05, 29.06, 28.27, 27.69, 27.42, 18.16, 14.42 ppm

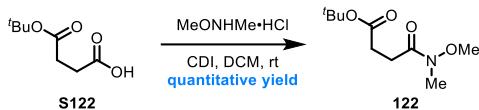
**MP:** 253–255 °C (decomposition)

**IR (neat):**  $\nu$  3312, 3114, 2925, 2853, 1749, 1617, 1593, 1517, 1501, 1334, 1095 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>34</sub>H<sub>35</sub>N<sub>4</sub>O<sub>7</sub><sup>+</sup> [M+H]<sup>+</sup> 611.2500, found 611.2500

$[\alpha]_D^{22}$ : -15 ( $c = 0.68$ ,  $\text{CHCl}_3$ )

### Synthesis of Weinreb amide 122



A flame-dried round bottle flask was charged with **S122** (16.67 g, 95.7 mmol) and DCM (150 mL). CDI (16.29 g, 100.5 mmol) was added portionwise as  $\text{CO}_2$  continuously evolved. The reaction mixture was stirred for 60 minutes, and then solid MeONHMe·HCl (18.67 g, 191.0 mmol) was added to the solution in one portion. The reaction mixture was stirred overnight, then quenched with water (150 mL) and extracted with DCM (50 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 4:1:1) gave **122** as a pale-yellow oil (20.79 g, quantitative yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.15 ( $\text{KMnO}_4$ )

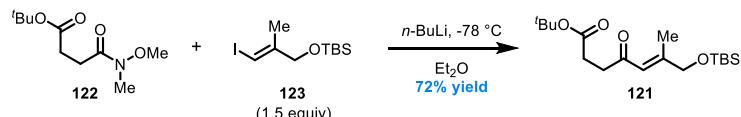
**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  3.69 (s, 3H), 3.15 (s, 3H), 2.67 (t,  $J = 6.9$  Hz, 2H), 2.53 (t,  $J = 6.9$  Hz, 2H), 1.42 (s, 9H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  173.01, 172.14, 80.29, 61.12, 32.18, 29.70, 28.02, 26.91 ppm

**IR (neat):**  $\nu$  2978, 2936, 1730, 1670, 1366, 1155, 997, 849  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{10}\text{H}_{19}\text{O}_4\text{NNa}^+$  [M+Na]<sup>+</sup> 240.1206, found 240.1208

### Synthesis of enone 121



A flame-dried round bottle flask was charged with known vinyl iodide **123**<sup>12</sup> (468 mg, 1.5 mmol) and ether (1 mL). The clear solution was cooled down to -78 °C, after which an *n*-BuLi solution (2.5 M in hexane, 0.6 mL, 1.5 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes at -78 °C, and then a solution of **122** (217 mg, 1.0 mmol) in ether (1 mL) was added to the solution dropwise. The reaction mixture was stirred for another 2 hours, then quenched with a saturated  $\text{NH}_4\text{Cl}$  solution and extracted with ethyl acetate (5 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 25:1) gave **121** as a pale-yellow oil (247 mg, 72% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.6 (UV, KMnO<sub>4</sub>)

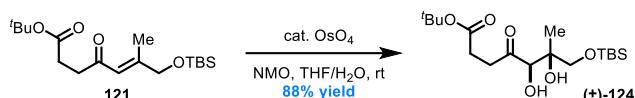
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 6.47–6.35 (m, 1H), 4.10 (s, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 2.01 (s, 3H), 1.44 (s, 9H), 0.93 (s, 9H), 0.09 (s, 6H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 199.08, 172.37, 155.89, 119.95, 80.45, 67.10, 39.09, 29.49, 28.19, 25.98, 18.47, 16.07, -5.32 ppm

**IR (neat):**  $\nu$  2956, 2930, 2858, 1732, 1694, 1634, 1367, 1253, 1155, 1128, 1092, 840, 778 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{18}H_{34}O_4SiNa^+ [M+Na]^+$  365.2119, found 365.2120

### Synthesis of diol ( $\pm$ )-124



A round bottle flask was charged with **121** (500 mg, 1.46 mmol), NMO (180 mg, 1.53 mmol) and THF (4 mL). An aqueous solution of OsO<sub>4</sub> (0.08 M, 1 mL, 0.08 mmol) was added. The reaction mixture was stirred for 5 hours at ambient temperature, and then a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (4 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 4:1:1) gave ( $\pm$ )-**124** as a yellow oil (485 mg, 88% yield).

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.5 (CAM, KMnO<sub>4</sub>)

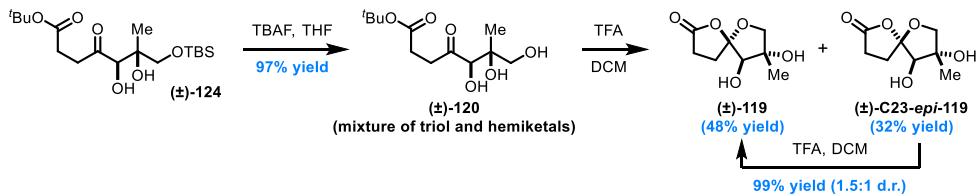
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.05 (d, *J* = 4.8 Hz, 1H), 3.76 (d, *J* = 4.9 Hz, 1H), 3.64 (d, *J* = 9.9 Hz, 1H), 3.48 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 1H), 3.02–2.86 (m, 2H), 2.64–2.45 (m, 2H), 1.43 (s, 9H), 1.22 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 211.80, 172.28, 80.90, 80.77, 74.17, 67.76, 35.54, 29.41, 28.17, 25.98, 21.96, 18.42, -5.46, -5.48 ppm

**IR (neat):** v 3458, 2956, 2931, 2858, 1731, 1709, 1634, 1368, 1253, 1158, 1094, 839, 779 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{18}H_{36}O_6SiNa^+ [M+Na]^+$  399.2173, found 399.2175

### Synthesis of 5,5-oxaspirolactone ( $\pm$ )-119 and ( $\pm$ )-C23-epi-119



A round bottle flask was charged with **(±)-124** (624 mg, 1.66 mmol) and THF (5 mL). A solution of TBAF in THF (1.0 M, 1.8 mL, 1.8 mmol) was added. The reaction mixture was stirred at ambient temperature for 20 minutes, and then a saturated NH<sub>4</sub>Cl solution (4 mL) was added. The aqueous solution was extracted with ethyl acetate (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, DCM/acetone = 4:1) gave **(±)-120** initially as a pale-yellow oil, later a white solid (424 mg, 97% yield). The <sup>1</sup>H-NMR shows that **(±)-120** is in equilibrium with its hemiketals.

To a solution of **(±)-120** (424 mg, 1.62 mmol) in DCM (1 mL) was added a solution of TFA in DCM (1 N, 8.1 mL, 8.1 mmol), after which the solution instantly turned pink. The reaction mixture was stirred for 10 minutes and directly loaded on a silica gel column. Purification by flash chromatography (silica gel, toluene/acetone = 4:1) gave **(±)-119** as a white solid (146 mg, 48% yield) and **(±)-C23-epi-119** as a colorless oil (98 mg, 32% yield). In practice, enantio-enriched **119** and **ent-119** were also prepared from **127** and **ent-127**, respectively (*vide infra*).

**Note:** Treatment of pure **(±)-C23-epi-119** with a 1 N TFA solution in DCM for 10 minutes will deliver a 1.5:1 diastereomeric mixture of **(±)-119** and **(±)-C23-epi-119** in almost quantitative yield, which could be separated by flash column chromatography using the above protocol.

#### Analytical data for **(±)-119**:

**Physical state:** white solid

**TLC (toluene/acetone 2:1):** R<sub>f</sub> 0.25 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.04 (d, J = 10.0 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 3.93 (d, J = 9.6 Hz, 1H), 2.77 (dt, J = 17.8, 9.6 Hz, 1H), 2.57 (ddd, J = 17.6, 9.6, 3.0 Hz, 1H), 2.48 (dt, J = 13.4, 9.6 Hz, 1H), 2.44 (d, J = 10.2 Hz, 1H), 2.36 (ddd, J = 13.0, 9.6, 3.0 Hz, 1H), 2.20 (s, 1H), 1.42 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 175.47, 113.85, 83.55, 78.74, 77.59, 30.42, 28.33, 21.69 ppm

**MP:** 117–119 °C

**IR (neat):** ν 3388, 2973, 2930, 2915, 1768, 1156, 1091, 1017, 911 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>8</sub>H<sub>13</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 189.0757, found 189.0751

**[α]<sub>D</sub><sup>22</sup> (119 at 76% ee):** +70 (c = 0.04, CHCl<sub>3</sub>)

$[\alpha]_D^{22}$  (*ent*-**119** at 91% ee): -100 ( $c = 0.02$ , CHCl<sub>3</sub>)

**Analytical data for ( $\pm$ )-C23-*epi*-**119**:**

**Physical state:** colorless oil

**TLC (toluene/acetone 2:1):**  $R_f$  0.3 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  4.07 (d,  $J = 5.6$  Hz, 1H), 4.01 (d,  $J = 9.4$  Hz, 1H), 3.96 (d,  $J = 9.4$  Hz, 1H), 3.35 (s, 1H), 3.30 (d,  $J = 5.6$  Hz, 1H), 2.75 (dt,  $J = 17.0, 8.4$  Hz, 1H), 2.66–2.49 (m, 2H), 2.29–2.20 (m, 1H), 1.38 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  175.99, 117.64, 82.05, 79.84, 79.55, 28.46, 27.93, 19.09 ppm

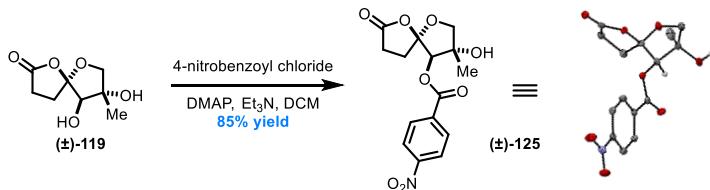
**IR (neat):**  $\nu$  3404, 2975, 1770, 1288, 1253, 1156, 1079, 1010, 992, 913 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>8</sub>H<sub>13</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 189.0757, found 189.0752

$[\alpha]_D^{22}$  (C23-*epi*-**119** at 76% ee): -49 ( $c = 0.61$ , CHCl<sub>3</sub>)

$[\alpha]_D^{22}$  (*ent*-C23-*epi*-**119** at 91% ee): +56 ( $c = 1.0$ , CHCl<sub>3</sub>)

*Synthesis of p-nitrobenzoate of ( $\pm$ )-**125***



A round bottle flask was charged with ( $\pm$ )-**119** (19 mg, 0.1 mmol), DMAP (5 mg, 0.04 mmol), Et<sub>3</sub>N (30 mg, 0.30 mmol) and DCM (1 mL). The clear solution was cooled down to 0 °C, after which 4-nitrobenzoyl chloride (27.8 mg, 0.15 mmol) was added. The reaction mixture was stirred for 30 minutes, and then it was directly loaded on silica gel column. Purification by flash chromatography (silica gel, toluene/acetone = 6:1) gave the corresponding *p*-nitrobenzoate ( $\pm$ )-**125** as a white crystalline solid (28.6 mg, 85% yield).

**Physical state:** white crystalline solid

**TLC (toluene/acetone 4:1):**  $R_f$  0.4 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.33 (d,  $J = 8.9$  Hz, 2H), 8.22 (d,  $J = 8.9$  Hz, 2H), 5.21 (s, 1H), 4.15 (d,  $J = 9.6$  Hz, 1H), 4.07 (d,  $J = 9.6$  Hz, 1H), 2.88–2.74 (m, 1H), 2.67–2.45 (m, 3H), 1.42 (s, 3H) ppm

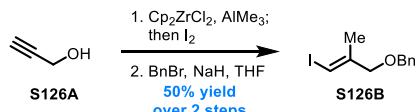
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  174.90, 165.42, 151.31, 133.75, 131.28, 124.06, 112.76, 86.25, 79.51, 77.65, 30.53, 28.19, 22.42 ppm

**MP:** 136–138 °C

**IR (neat):**  $\nu$  3456, 3113, 2981, 2958, 2938, 2894, 1786, 1732, 1608, 1530, 1277, 1123, 1102, 1021, 913, 719  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_8^+$  [M+H]<sup>+</sup> 338.0870, found 338.0871

*Synthesis of vinyl iodide S126B*



A round bottle flask was charged with  $\text{Cp}_2\text{ZrCl}_2$  (2.92 g, 10 mmol) and DCM (80 mL) at room temperature before it was placed under a positive  $\text{N}_2$  or Ar atmosphere using Schlenk technique. To the flask was then added a solution of  $\text{AlMe}_3$  in hexanes (2 M, 62.5 mL, 125 mmol) at 0 °C, after which the resulting yellow solution was stirred for 10 minutes. A solution of **S126A** (2.8 g, 50 mmol) in DCM (20 mL) was added dropwise while maintaining the cooling bath temperature, and then it was stirred at room temperature for 24 hours with the flask covered with aluminum foil to avoid light. The reaction mixture was placed under a -25 °C cooling bath before the addition of a solution of  $\text{I}_2$  (15.23 g, 60 mmol) in THF (50 mL). The reaction mixture was then carefully quenched with a saturated solution of Rochelle's salt (*Caution! Rapid evolution of methane gas during the workup*). The layers were separated, and the aqueous layer was extracted with DCM (50 mL × 3). The combined extracts were washed with saturated  $\text{Na}_2\text{S}_2\text{O}_3$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether/DCM = 2:1:1) gave the alcohol [(*E*)-3-iodo-2-methylprop-2-en-1-ol] as a yellow oil (5.38 g, 54% yield). The experimental NMR data of the alcohol recorded were consistent with those reported by Lipshutz and co-workers.<sup>12</sup>

To a suspension of  $\text{NaH}$  (1.3 g, 60% dispersion in mineral oil, 32.6 mmol) in THF (40 mL) was added a solution of the above alcohol (5.38 g, 27.2 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 30 minutes at the same temperature followed by addition of  $\text{BnBr}$  (3.6 mL, 30 mmol). The reaction mixture was warmed up to room temperature and stirred for 12 hours. The reaction mixture was quenched with a saturated  $\text{NH}_4\text{Cl}$  solution. The layers were separated, and the aqueous solution was extracted with ethyl acetate. The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 50:1) gave **S126B** as a colorless to pale-yellow oil (7.33 g, 93% yield).

**Physical state:** pale-yellow oil

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.75 (UV,  $\text{KMnO}_4$ )

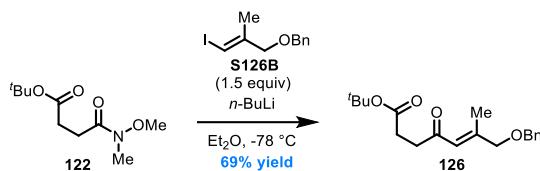
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.41–7.27 (m, 5H), 6.29 (q, *J* = 1.3 Hz, 1H), 4.48 (s, 2H), 4.01 (d, *J* = 1.4 Hz, 2H), 1.86 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 144.89, 137.90, 128.51, 127.82, 127.76, 78.78, 74.00, 72.03, 21.68 ppm

**IR (neat):** ν 3063, 3030, 2915, 2850, 1619, 1453, 1353, 1281, 1096, 736, 697 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>11</sub>H<sub>14</sub>O<sup>+</sup> [M+H]<sup>+</sup> 289.0084, found 289.0069

### Synthesis of enone 126



A flame-dried round bottle flask was charged with **S126B** (2.16 g, 7.5 mmol) and anhydrous ether (7 mL). The clear solution was cooled down to -78 °C, after which *n*-BuLi solution (2.5 M in hexane, 3 mL, 7.5 mmol) was added dropwise. The reaction mixture was stirred for 45 minutes at -78 °C, and then a solution of **122** (1.086 g, 5 mmol) in ether (3 mL) was added to the solution dropwise. The reaction mixture was stirred for another 2 hours, then quenched with a saturated NH<sub>4</sub>Cl solution and extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1 → 6:1) gave **126** as a colorless to yellow oil (1.10 g, 69% yield).

**Physical state:** colorless to yellow oil

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.7 (UV, KMnO<sub>4</sub>)

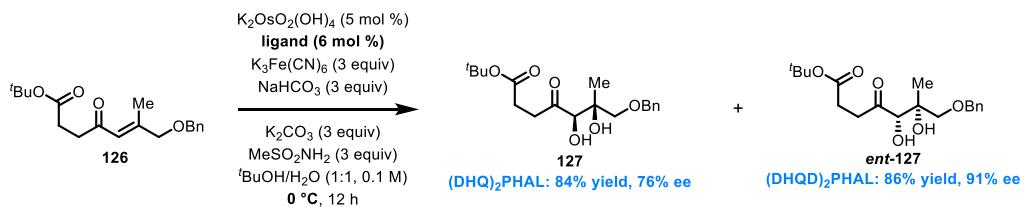
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.42–7.27 (m, 5H), 6.41 (q, *J* = 1.5 Hz, 1H), 4.55 (s, 2H), 3.99–3.98 (m, 2H), 2.76 (t, *J* = 6.7 Hz, 2H), 2.52 (t, *J* = 6.7 Hz, 2H), 2.06 (d, *J* = 1.4 Hz, 3H), 1.44 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 199.06, 172.28, 153.10, 137.84, 128.59, 127.93, 127.74, 121.53, 80.48, 74.10, 72.77, 39.10, 29.48, 28.17, 16.52 ppm

**IR (neat):** ν 2978, 2917, 2850, 1729, 1692, 1632, 1367, 1153, 1094, 850, 739, 699 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>19</sub>H<sub>26</sub>O<sub>4</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 341.1723, found 341.1723

### Synthesis of chiral diol 127 and ent-127



A 40-mL vial equipped with a magnetic stir bar was charged with  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (23.6 mg, 0.064 mmol), Cinchona alkaloid ligand (59.2 mg, 0.076 mmol),  $\text{K}_3\text{Fe}(\text{CN})_6$  (1.58 g, 4.8 mmol),  $\text{NaHCO}_3$  (403 mg, 4.8 mmol),  $\text{K}_2\text{CO}_3$  (663 mg, 4.8 mmol),  $\text{MeSO}_2\text{NH}_2$  (457 mg, 4.8 mmol) and *t*-BuOH/ $\text{H}_2\text{O}$  (1:1 *v/v*, 16 mL). The mixture was stirred at room temperature for 30 minutes until all the solids were completely dissolved. The resulting yellow solution was cooled down to 0 °C before the addition of a solution of **126** (510 mg, 1.6 mmol) in toluene (1 mL). The reaction mixture was stirred at the same temperature for 12 hours. As TLC indicated full conversion of **126**, the reaction was then quenched with a saturated  $\text{Na}_2\text{S}_2\text{O}_3$  solution. The layers were separated, and the aqueous solution was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 3:1:1) gave **127** as a colorless to pale-yellow oil (946 mg, 84% yield, 76% ee) [ligand = (DHQ)<sub>2</sub>PHAL] and *ent*-**127** as a colorless to pale-yellow oil (968 mg, 86% yield, 91% ee) [ligand = (DHQD)<sub>2</sub>PHAL]. The ee of the products was determined by chiral HPLC analysis using Chiralpak IB column (hexane:isopropanol = 98:2, 0.7 mL/min, 214 nm,  $t_{127} = 31.9$  min,  $t_{\text{ent}-127} = 29.2$  min).

**Physical state:** colorless to yellow oil

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.4 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.37–7.27 (m, 5H), 4.52–4.45 (m, 2H), 4.06 (s, 1H), 3.78 (br s, 1H), 3.51 (d, *J* = 9.4 Hz, 1H), 3.39 (d, *J* = 9.4 Hz, 1H), 3.23 (br s, 1H), 2.95 (ddd, *J* = 18.5, 6.9, 5.5 Hz, 1H), 2.84 (ddd, *J* = 18.5, 8.0, 5.5 Hz, 1H), 2.54 (ddd, *J* = 17.3, 7.9, 5.6 Hz, 1H), 2.42 (ddd, *J* = 17.3, 6.9, 5.6 Hz, 1H), 1.42 (s, 9H), 1.27 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 211.63, 172.40, 137.47, 128.55, 128.02, 128.00, 80.87, 80.78, 74.38, 74.13, 73.73, 35.43, 29.37, 28.13, 22.64 ppm

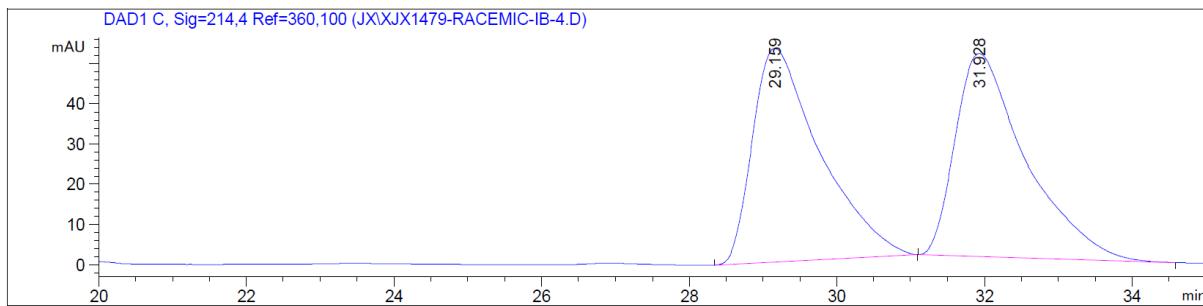
**IR (neat):**  $\nu$  3448, 2978, 2932, 2868, 1727, 1707, 1368, 1156, 1096, 848, 751, 699 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>19</sub>H<sub>28</sub>O<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 375.1778, found 375.1779

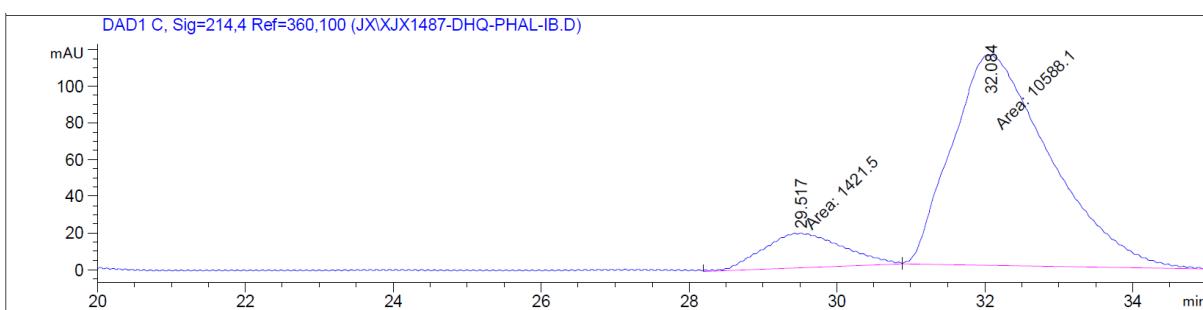
**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (127 at 76% ee):** -8.9 (*c* = 0.27, CHCl<sub>3</sub>)

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (*ent*-127 at 91% ee):** +11.4 (*c* = 0.29, CHCl<sub>3</sub>)

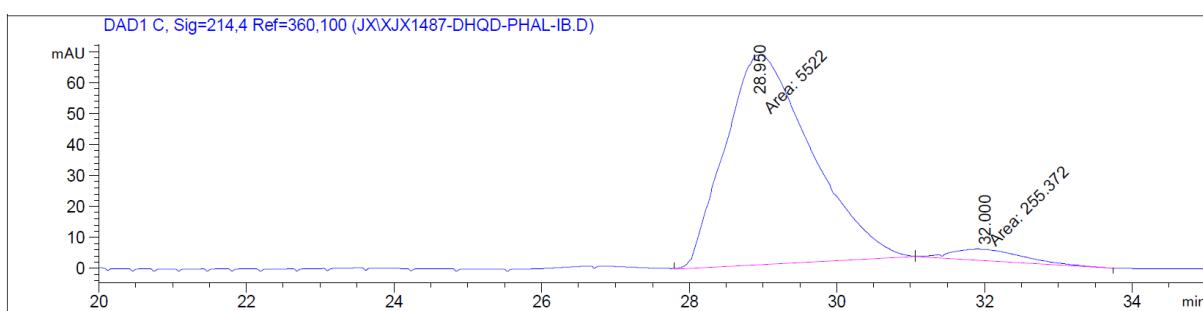
**Table S2.** HPLC trace for the racemic sample ( $\pm$ )-**127** (prepared from **126** using Upjohn dihydroxylation conditions: cat. OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O, rt)



**Table S3.** HPLC trace for the enantiomeric sample **127**



**Table S4.** HPLC trace for the enantiomeric sample **ent-127**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.950	MM	1.3573	5522.00439	67.80735	95.5798
2	32.000	MM	1.1559	255.37186	3.68227	4.4202

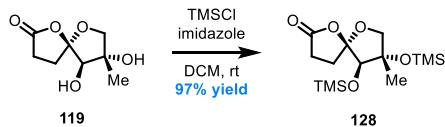
### Synthesis of chiral 5,5-oxaspirolactone **119** and *ent*-**119**



A round bottle flask was charged with **127** or *ent*-**127**, 5% Pd on carbon (ca. 0.05 equiv of Pd) and EtOH (0.2 M). The reaction mixture was degassed with a hydrogen balloon at room temperature for 60 minutes and stirred under the hydrogen atmosphere for another 12 hours. The reaction mixture was filtered and concentrated *in vacuo* to give the crude triol intermediates as a pale-yellow oil.

To the above crude triol was added a solution of TFA in DCM (1 N, 6 equiv), after which the solution instantly turned pink. The reaction mixture was stirred for 10 minutes and directly loaded on a silica gel column. Purification by flash chromatography (silica gel, toluene/acetone = 4:1) gave **119** or *ent*-**119** as a white solid (48% yield) along with **C23-epi-119** or *ent*-**C23-epi-119** as a colorless oil.

### Synthesis of 5,5-oxaspirolactone **128**



To a suspension of **119** (268 mg, 1.42 mmol) in DCM (10 mL, solubility of **119** is very poor in DCM) was sequentially added imidazole (388 mg, 5.70 mmol) and TMSCl (0.54 mL, 4.27 mmol). The reaction mixture was stirred for 20 minutes when TLC indicated completion of the reaction. The reaction mixture was then directed loaded on a silica gel column and purified by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) to give **128** as a white solid (458 mg, 97% yield). In practice, *ent*-**128** and ( $\pm$ )-**128** were also prepared from *ent*-**119** and ( $\pm$ )-**119** using the same procedure, respectively.

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.7 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.04 (s, 1H), 3.94 (s, 2H), 2.71–2.58 (m, 1H), 2.49 (ddd,  $J = 17.7, 8.7, 7.0$  Hz, 1H), 2.32–2.21 (m, 2H), 1.39 (s, 3H), 0.17 (s, 9H), 0.13 (s, 9H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  175.29, 112.77, 85.05, 79.98, 79.19, 30.80, 28.59, 22.75, 2.12, 0.39 ppm

**MP:** 52–54 °C

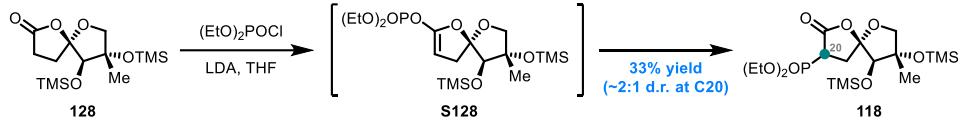
**IR (neat):**  $\nu$  2958, 2898, 1790, 1253, 1143, 1020, 915, 887, 842, 755  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{14}\text{H}_{29}\text{O}_5\text{Si}_2^+$  [ $\text{M}+\text{H}]^+$  333.1548, found 333.1548

**[ $\alpha$ ]D<sup>22</sup> (128 at 76% ee):** +52 ( $c = 0.58$ ,  $\text{CHCl}_3$ )

**[ $\alpha$ ]D<sup>22</sup> (ent-128 at 91% ee):** -78 ( $c = 0.18$ ,  $\text{CHCl}_3$ )

### Synthesis of phosphonate 118



To a solution of freshly prepared LDA (0.15 mmol) in THF (0.2 mL) was added a solution of **128** (33.3 mg, 0.10 mmol) in THF (0.3 mL) at -78 °C. The reaction mixture was kept at the same temperature for 30 minutes before diethylchlorophosphite (22  $\mu\text{L}$ , 0.15 mmol) was added. The reaction mixture was maintained at -78 °C for another 15 minutes and then immediately warmed up to 0 °C in an ice/water bath. About 25 minutes later, TLC analysis of the reaction mixture should indicate a very high conversion of **128** to a putative phosphonate intermediate **S128** ( $R_f \sim 0.5$ , hexanes/ethyl acetate 2:1), at which point the reaction mixture was cooled back to -78 °C. A solution of freshly prepared LDA (0.22 mmol) in THF (0.3 mL) was added and then the reaction mixture was maintained at the same temperature. Upon full conversion of **S128** indicated by TLC (ca. 30 minutes), the reaction was quickly quenched with a solution of HOAc in ether (1 M, 0.5 mL, 0.5 mmol). The resulting white precipitates were filtered off with a plug of celite and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 1:1) gave **118** as a yellow oil and an inconsequential 2:1 mixture of diastereomers (15.4 mg, 33% yield). In practice, *ent*-**118** and  $(\pm)$ -**118** were also prepared from *ent*-**128** and **128** using the same procedure, respectively.

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.2 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ): (major)**  $\delta$  4.29–4.15 (m, 4H), 4.00 (s, 1H), 3.93–3.85 (m, 2H), 3.34 (ddd,  $J = 23.0, 11.3, 9.1$  Hz, 1H), 2.72–2.42 (m, 2H), 1.40–1.32 (m, 9H), 0.19 (s, 9H), 0.14 (s, 9H) ppm; **(minor)**  $\delta$  4.29–4.15 (m, 4H), 4.06 (s, 1H), 4.00–3.95 (m, 2H), 3.14 (ddd,  $J = 23.6, 10.6, 8.8$  Hz, 1H), 2.72–2.42 (m,

2H), 1.40–1.32 (m, 9H), 0.17 (s, 9H), 0.13 (s, 9H) ppm

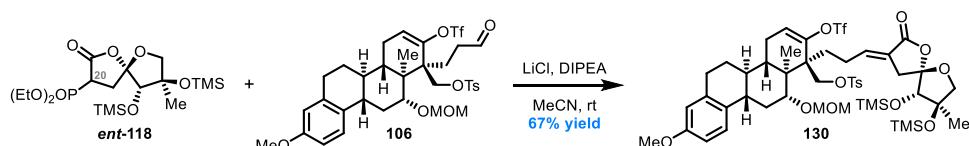
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>): (major)** δ 170.44 (d, *J* = 2.1 Hz), 111.73 (d, *J* = 12.8 Hz), 83.69, 80.25, 78.74, 63.40 (d, *J* = 6.6 Hz), 63.18 (d, *J* = 6.5 Hz), 38.73 (d, *J* = 152.0 Hz), 33.33 (d, *J* = 2.9 Hz), 21.99, 16.54 (d, *J* = 1.5 Hz), 16.49 (d, *J* = 1.3 Hz), 2.11, 0.38 ppm; **(minor)** δ 169.24 (d, *J* = 3.4 Hz), 111.49 (d, *J* = 9.0 Hz), 85.68, 79.60, 79.58, 63.68 (d, *J* = 6.7 Hz), 63.27 (d, *J* = 6.6 Hz), 40.13 (d, *J* = 147.0 Hz), 33.16 (d, *J* = 3.3 Hz), 22.82, 16.50, 16.45, 2.07, 0.36 ppm

**<sup>31</sup>P-NMR (202 MHz, CDCl<sub>3</sub>): (major)** δ 20.24 ppm; **(minor)** δ 19.71 ppm

**IR (neat):** *v* 2958, 2916, 1785, 1253, 1141, 1026, 843, 757 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>18</sub>H<sub>37</sub>O<sub>8</sub>PSi<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 491.1657, found 491.1658

### Synthesis of 5,5-oxaspirolactone 130



To a mixture of **106** (16.4 mg, 0.022 mmol), **ent-118** (14.2 mg, 0.030 mmol), LiCl (1.3 mg, 0.030 mmol) and DIPEA (7 μL, 0.040 mmol) was added dry MeCN (0.5 mL) in the glove box at room temperature. The reaction mixture was stirred at room temperature for 18 hours before it was filtered through a plug of silica gel, which was extensively washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1 → 4:1) gave **130** as a white amorphous solid (15.7 mg, 67% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.7 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.74 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.54–6.49 (m, 1H), 5.98 (dd, *J* = 6.3, 1.5 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.35 (d, *J* = 10.5 Hz, 1H), 4.05 (d, *J* = 10.5 Hz, 1H), 4.02 (s, 1H), 3.98–3.93 (m, 2H), 3.82 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 2.90–2.76 (m, 4H), 2.63 (dt, *J* = 12.5, 3.6 Hz, 1H), 2.53–2.41 (m, 1H), 2.42 (s, 3H), 2.40–2.27 (m, 1H), 2.24–2.15 (m, 2H), 2.16–2.05 (m, 1H), 2.01–1.94 (m, 1H), 1.91–1.78 (m, 3H), 1.46 (q, *J* = 13.1, 12.6 Hz, 1H), 1.41 (s, 3H), 1.33–1.26 (m, 1H), 1.25–1.16 (m, 1H), 1.01 (s, 3H) ppm

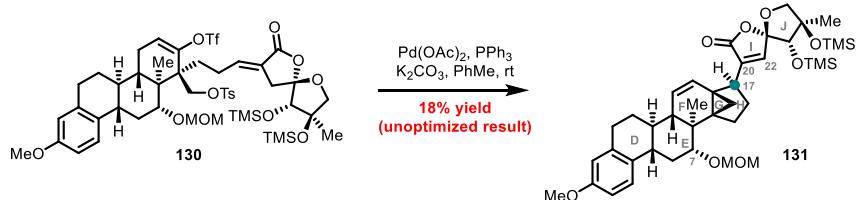
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 169.02, 157.92, 149.13, 145.48, 139.38, 137.72, 132.47, 131.09, 130.01, 128.29, 126.53, 126.12, 118.66, 118.31 (q, *J* = 319.8 Hz), 113.68, 111.90, 110.13, 95.86, 85.36, 81.18, 79.98, 79.34, 69.71, 56.14, 55.38, 48.61, 45.96, 40.67, 39.95, 39.71, 34.48, 32.01, 30.55, 29.93, 26.90, 26.74, 25.26, 22.87, 21.76, 11.16, 2.14, 0.32 ppm

**IR (neat):**  $\nu$  2955, 2928, 2855, 1767, 1685, 1610, 1502, 1413, 1370, 1252, 1212, 1178, 1143, 1034, 986, 889, 844, 735  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{48}\text{H}_{67}\text{O}_{14}\text{S}_2\text{F}_3\text{Si}_2\text{Na}^+$  [M+Na]<sup>+</sup> 1067.3355, found 1067.3362

$[\alpha]_D^{22}$ : -23 ( $c = 0.79$ ,  $\text{CHCl}_3$ )

### Synthesis of [4.3.1]propellane 131



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with **130** (10.7 mg, 0.010 mmol),  $\text{Pd}(\text{OAc})_2$  (0.56 mg, 0.0025 mmol),  $\text{PPh}_3$  (1.3 mg, 0.005 mmol),  $\text{K}_2\text{CO}_3$  (2.8 mg, 0.020 mmol) and toluene (0.2 mL) at room temperature. The vial was sealed, and the resulting yellow solution was stirred at room temperature for 24 hours. The reaction mixture was then directed loaded on a silica gel column and purified by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1) to give **131** as a white amorphous solid (1.3 mg, 18% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.85 (CAM)

**<sup>1</sup>H-NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):**  $\delta$  7.27 (d,  $J = 8.2$  Hz, 1H), 6.79 (dd,  $J = 8.5, 2.8$  Hz, 1H), 6.71 (d,  $J = 2.7$  Hz, 1H), 6.63 (d,  $J = 1.5$  Hz, 1H), 6.02 (dd,  $J = 9.9, 2.9$  Hz, 1H), 5.34 (dd,  $J = 10.0, 2.2$  Hz, 1H), 4.72 (d,  $J = 6.6$  Hz, 1H), 4.68 (d,  $J = 6.6$  Hz, 1H), 4.20 (s, 1H), 3.98 (d,  $J = 8.9$  Hz, 1H), 3.95 (d,  $J = 8.9$  Hz, 1H), 3.49 (dd,  $J = 11.3, 4.2$  Hz, 1H), 3.42 (s, 3H), 3.30 (s, 3H), 2.91 (dd,  $J = 10.7, 8.2$  Hz, 1H), 2.77 (dt,  $J = 12.7, 4.2$  Hz, 1H), 2.74–2.68 (m, 2H), 2.25 (dt,  $J = 12.3, 7.9$  Hz, 1H), 2.23–2.13 (m, 2H), 2.00–1.93 (m, 2H), 1.65 (q,  $J = 12.5$  Hz, 1H), 1.45 (s, 3H), 1.43–1.34 (m, 2H), 1.27–1.20 (m, 1H), 1.18 (d,  $J = 5.7$  Hz, 1H), 1.15–1.06 (m, 1H), 0.89 (s, 3H), 0.79 (d,  $J = 5.6$  Hz, 1H), 0.12 (s, 9H), 0.07 (s, 9H) ppm

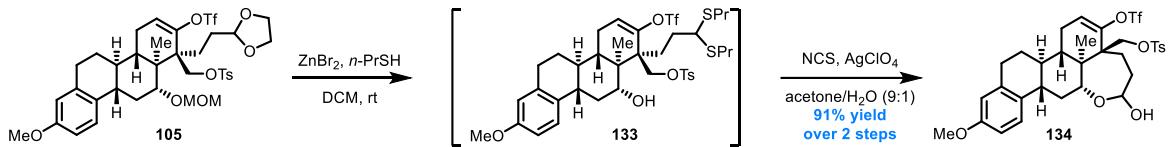
**<sup>13</sup>C-NMR (101 MHz, C<sub>6</sub>D<sub>6</sub>):**  $\delta$  170.52, 158.56, 142.12, 141.32, 138.03, 132.37, 130.19, 126.21, 122.65, 114.09, 112.06, 110.36, 97.15, 84.89, 83.35, 81.11, 79.30, 55.40, 54.83, 44.83, 41.98, 40.45, 39.77, 38.15, 37.82, 33.74, 33.04, 30.54, 30.29, 28.64, 27.93, 22.50, 12.68, 12.18, 2.02, 0.31 ppm

**IR (neat):**  $\nu$  2955, 2925, 2853, 1774, 1611, 1501, 1253, 1129, 1106, 1039, 1012, 891  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{40}\text{H}_{59}\text{O}_8\text{Si}_2^+$  [M+H]<sup>+</sup> 723.3743, found 723.3742

$[\alpha]_D^{22}$ : -8.7 ( $c = 0.23$ ,  $\text{CHCl}_3$ )

### Synthesis of hemiacetal 134



A 2-mL vial equipped with a stir bar was sequentially charged with **105** (357 mg, 0.461 mmol), ZnBr<sub>2</sub> (208 mg, 0.922 mmol), *n*-PrSH (0.42 mL, 4.61 mmol) and DCM (1 mL) at room temperature. The reaction mixture was stirred until TLC indicated full conversion of **105** (ca. 2 hours). It was quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude **133** as a white foam.

To the above crude **133** in a round-bottom flask was added a clear solution of NCS (185 mg, 1.38 mmol) and AgClO<sub>4</sub> (315 mg, 1.52 mmol) in acetone/H<sub>2</sub>O (9:1 *v/v*, 10 mL), which immediately formed a white to pale-yellow slurry. The reaction mixture was stirred for another 5 minutes before it was quenched with saturated solutions of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub> and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1) gave **134** as a white amorphous solid (287 mg, 91% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.25 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.61 (d, *J* = 2.9 Hz, 1H), 5.63 (t, *J* = 3.9 Hz, 1H), 5.22 (t, *J* = 7.2 Hz, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.38–4.31 (m, 2H), 4.13 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.77 (s, 3H), 2.90–2.74 (m, 3H), 2.52–2.46 (m, 1H), 2.44 (s, 3H), 2.38 (ddd, *J* = 13.2, 5.4, 3.6 Hz, 1H), 2.30–2.20 (m, 1H), 2.11–2.03 (m, 1H), 1.99–1.85 (m, 3H), 1.73 (t, *J* = 13.6 Hz, 1H), 1.60 (td, *J* = 14.5, 13.3, 8.3 Hz, 1H), 1.54–1.42 (m, 2H), 1.29–1.18 (m, 2H), 1.00 (s, 3H) ppm

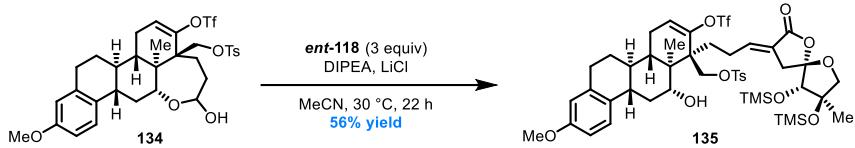
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 157.80, 151.86, 145.30, 137.63, 132.63, 130.70, 129.91, 128.04, 126.53, 118.44, 118.34 (q, *J* = 319.9 Hz), 113.70, 112.05, 94.59, 73.48, 69.09, 55.33, 48.52, 46.04, 40.27, 39.81, 39.05, 35.78, 29.94, 29.13, 27.20, 25.90, 21.77, 20.73, 11.47 ppm

**IR (neat):** ν 3462, 2926, 1610, 1502, 1414, 1213, 1177, 1141, 1003, 965, 844, 732 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>32</sub>H<sub>37</sub>O<sub>9</sub>S<sub>2</sub>F<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 709.1723, found 709.1727

[*α*]<sub>D</sub><sup>22</sup>: -20 (*c* = 1.0, CHCl<sub>3</sub>)

### Synthesis of 5,5-oxaspirolactone **135**



To a mixture of **134** (19.2 mg, 0.028 mmol), **ent-118** (32.8 mg, 0.070 mmol), LiCl (3.0 mg, 0.070 mmol) and DIPEA (12  $\mu$ L, 0.070 mmol) was added dry MeCN (0.25 mL) in the glove box at room temperature. The reaction mixture was stirred at 30 °C for 21 hours before it was filtered through a plug of silica gel, which was extensively washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1 → 4:1) gave **135** as a white amorphous solid (15.6 mg, 56% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.45 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.80 (d,  $J$  = 8.3 Hz, 2H), 7.36 (d,  $J$  = 8.0 Hz, 2H), 7.13 (d,  $J$  = 8.6 Hz, 1H), 6.73 (dd,  $J$  = 8.6, 2.8 Hz, 1H), 6.63 (d,  $J$  = 2.8 Hz, 1H), 6.57–6.49 (m, 1H), 5.97 (dd,  $J$  = 6.2, 2.1 Hz, 1H), 4.35 (d,  $J$  = 10.5 Hz, 1H), 4.09 (d,  $J$  = 10.5 Hz, 1H), 4.02 (s, 1H), 3.99–3.92 (m, 3H), 3.78 (s, 3H), 2.94–2.76 (m, 4H), 2.52–2.44 (m, 1H), 2.43 (s, 3H), 2.36–2.22 (m, 3H), 2.19–2.06 (m, 2H), 2.01–1.90 (m, 2H), 1.88–1.80 (m, 1H), 1.74 (td,  $J$  = 10.3, 4.5 Hz, 1H), 1.58 (q,  $J$  = 11.9 Hz, 1H), 1.40 (s, 3H), 1.34–1.27 (m, 1H), 1.26–1.19 (m, 1H), 0.96 (s, 3H), 0.13 (s, 9H), 0.13 (s, 9H) ppm

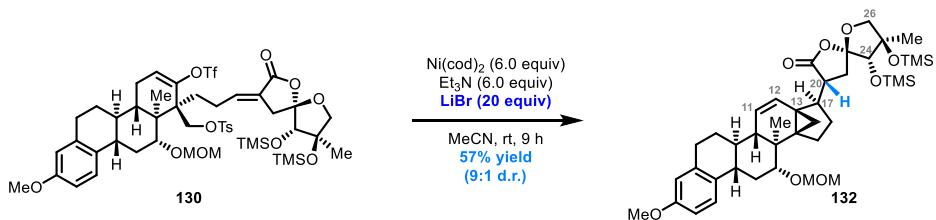
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  168.97, 157.97, 149.08, 145.58, 139.38, 137.67, 132.22, 131.01, 130.08, 128.23, 126.53, 125.98, 119.00, 118.29 (q,  $J$  = 320.0 Hz), 113.75, 111.89, 110.11, 85.39, 80.00, 79.35, 73.45, 69.90, 55.38, 48.48, 46.19, 40.43, 40.35, 39.70, 34.49, 31.51, 30.57, 29.88, 26.74, 26.72, 25.40, 22.87, 21.79, 10.17, 2.14, 0.31 ppm

**IR (neat):**  $\nu$  3528, 2956, 2928, 1767, 1685, 1610, 1501, 1413, 1252, 1211, 1177, 1141, 983, 888, 843, 756 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>46</sub>H<sub>63</sub>O<sub>13</sub>S<sub>2</sub>F<sub>3</sub>Si<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 1023.3093, found 1023.3095

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>:** -27 (*c* = 0.78, CHCl<sub>3</sub>)

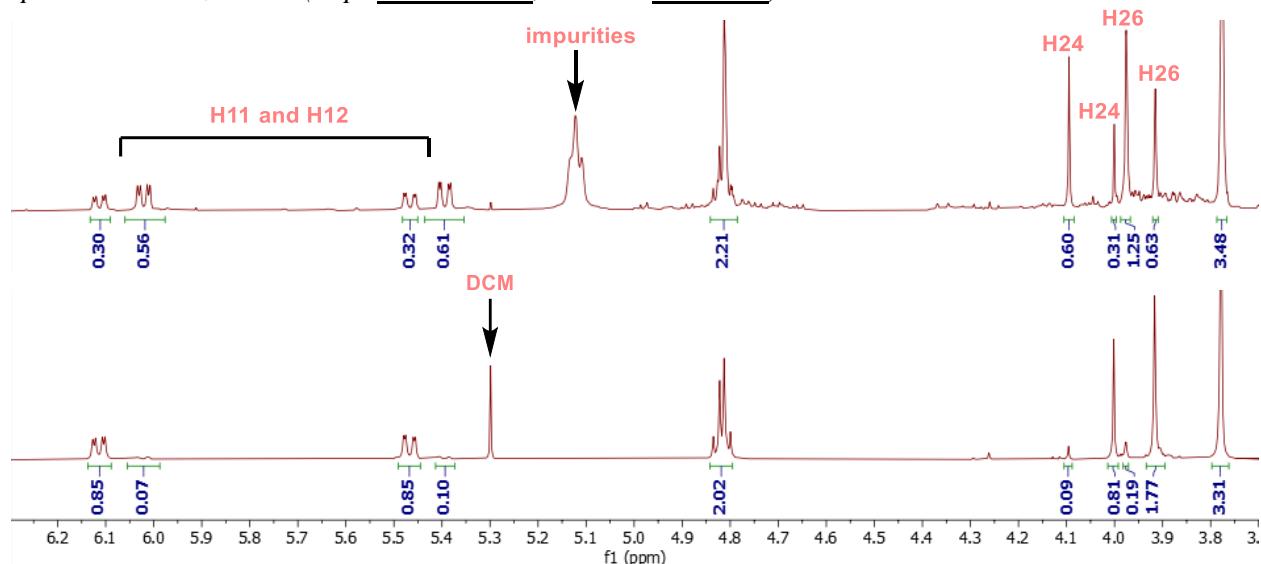
### Synthesis of [4.3.1]propellane **132**



To a mixture of **130** (13.1 mg, 0.0125 mmol), Ni(cod)<sub>2</sub> (20.6 mg, 0.075 mmol), LiBr (21.7 mg, 0.25 mmol)

and Et<sub>3</sub>N (10 µL, 0.075 mmol) in a 4-mL vial with a PTFE-lined cap was added dry MeCN (1.3 mL) in the glove box, after which the vial was sealed and taken out of the glove box. The reaction mixture was stirred at room temperature for 5 hours before it was filtered through a plug of silica gel, which was extensively washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1) to give **132** as a white amorphous solid (5.2 mg, 57% yield, 9:1 d.r.), which could be further purified to give the single diastereomeric **132** (>20:1 d.r.).

**Note:** Without LiBr, the diastereoselectivity is inverted as evidenced in the key region of their <sup>1</sup>H-NMR spectra in CDCl<sub>3</sub> below. (Top: without LiBr; Bottom: with LiBr)



**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (CAM)

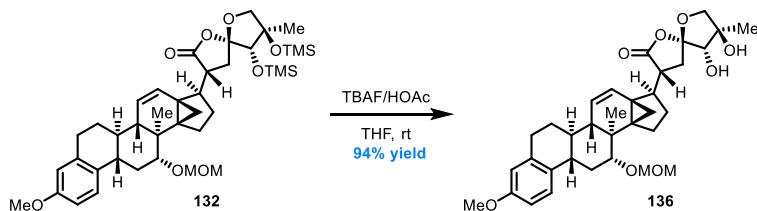
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.19 (d, J = 8.6 Hz, 1H), 6.72 (dd, J = 8.6, 2.8 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.11 (dd, J = 10.0, 3.0 Hz, 1H), 5.47 (dd, J = 10.0, 2.3 Hz, 1H), 4.83 (d, J = 6.6 Hz, 1H), 4.81 (d, J = 6.7 Hz, 1H), 4.00 (s, 1H), 3.92 (s, 2H), 3.78 (s, 3H), 3.55 (dd, J = 11.4, 4.3 Hz, 1H), 3.47 (s, 3H), 3.25 (ddd, J = 11.2, 8.8, 5.1 Hz, 1H), 2.92–2.85 (m, 2H), 2.63 (dt, J = 12.8, 4.4 Hz, 1H), 2.57–2.49 (m, 1H), 2.39–2.31 (m, 1H), 2.24 (dd, J = 13.3, 8.8 Hz, 1H), 2.20–2.07 (m, 3H), 1.82 (dd, J = 13.4, 8.1 Hz, 1H), 1.68–1.58 (m, 1H), 1.59–1.51 (m, 2H), 1.50–1.41 (m, 1H), 1.39 (s, 3H), 1.34–1.29 (m, 1H), 1.19 (d, J = 5.6 Hz, 1H), 1.01–0.92 (m, 1H), 0.82 (s, 3H), 0.61 (d, J = 5.6 Hz, 1H), 0.18 (s, 9H), 0.13 (s, 9H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 177.94, 157.83, 138.12, 132.20, 129.78, 125.94, 122.30, 113.73, 111.70, 110.85, 97.27, 85.01, 84.21, 79.92, 78.81, 55.78, 55.37, 44.59, 41.89, 41.36, 40.21, 38.55, 37.81, 37.51, 32.80, 32.59, 31.96, 30.15, 29.20, 27.62, 22.83, 22.64, 12.48, 11.89, 2.16, 2.13, 0.56 ppm

**IR (neat):** ν 2954, 1784, 1611, 1501, 1253, 1141, 1108, 1041, 843, 753, 734 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{40}H_{61}O_8Si_2^+ [M+H]^+$  725.3899, found 725.3899  
 $[\alpha]_D^{22}$ : -9.6 ( $c = 0.52$ , CHCl<sub>3</sub>)

*Synthesis of [4.3.1]propellane 136*



A 2-mL vial equipped with a stir bar was sequentially charged with **132** (4 mg, 0.0055 mmol) and a solution of 1:1 TBAF/HOAc in THF (0.033 M, 0.5 mL, 0.0165 mmol) at room temperature. The reaction mixture was stirred at the same temperature until TLC analysis indicated full conversion of **132** (ca. 15 minutes) and was diluted with 1 mL toluene. The whole reaction mixture was directly loaded on a silica gel column and purified by flash chromatography (silica gel, toluene/acetone = 6:1 → 4:1) to give **136** as a white solid (3.0 mg, 94% yield).

**Physical state:** white amorphous solid

**TLC (toluene/acetone 2:1):**  $R_f$  0.5 (CAM)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.19 (d,  $J = 8.7$  Hz, 1H), 6.72 (dd,  $J = 8.6, 2.8$  Hz, 1H), 6.64 (d,  $J = 2.7$  Hz, 1H), 6.12 (dd,  $J = 10.0, 3.0$  Hz, 1H), 5.48 (dd,  $J = 10.0, 2.3$  Hz, 1H), 4.81 (s, 2H), 4.04 (br s, 1H), 3.97 (d,  $J = 9.8$  Hz, 1H), 3.93 (d,  $J = 9.6$  Hz, 1H), 3.78 (s, 3H), 3.56 (dd,  $J = 11.4, 4.3$  Hz, 1H), 3.46 (s, 3H), 3.37–3.30 (m, 1H), 2.91–2.86 (m, 2H), 2.63 (dt,  $J = 12.5, 4.1$  Hz, 1H), 2.54 (dt,  $J = 11.9, 6.6$  Hz, 1H), 2.37 (d,  $J = 10.2$  Hz, 2H), 2.36–2.30 (m, 1H), 2.22–2.10 (m, 2H), 1.85 (dd,  $J = 13.3, 8.1$  Hz, 1H), 1.66–1.58 (m, 3H), 1.51–1.44 (m, 1H), 1.43 (s, 3H), 1.34–1.27 (m, 1H), 1.20 (d,  $J = 5.7$  Hz, 1H), 1.07–0.99 (m, 1H), 0.83 (s, 3H), 0.66 (d,  $J = 5.7$  Hz, 1H) ppm

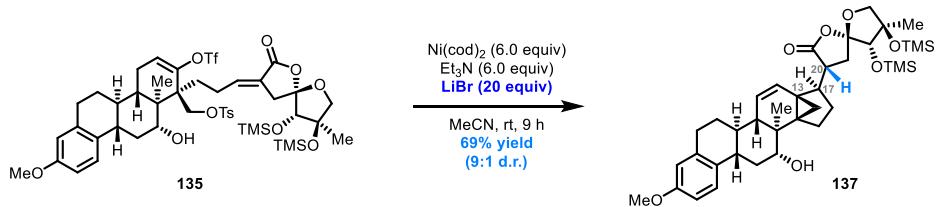
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  177.38, 157.84, 138.10, 132.19, 129.59, 125.93, 122.48, 113.74, 111.81, 111.69, 97.08, 84.72, 83.29, 78.58, 77.51, 55.80, 55.37, 44.59, 41.86, 41.28, 40.61, 38.69, 37.79, 37.50, 32.63, 32.54, 32.07, 30.13, 29.18, 27.63, 22.89, 21.70, 12.48, 11.92 ppm

**IR (neat):**  $\nu$  3422, 2930, 1780, 1610, 1501, 1142, 1104, 1039, 912, 733 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for  $C_{34}H_{45}O_8^+ [M+H]^+$  581.3109, found 581.3112

$[\alpha]_D^{22}$ : -6.7 ( $c = 0.3$ , CHCl<sub>3</sub>)

*Synthesis of [4.3.1]propellane 137*



To a mixture of **135** (10 mg, 0.01 mmol),  $\text{Ni}(\text{cod})_2$  (16.6 mg, 0.06 mmol),  $\text{LiBr}$  (17.4 mg, 0.2 mmol) and  $\text{Et}_3\text{N}$  (8.4  $\mu\text{L}$ , 0.06 mmol) in a 4-mL vial with a PTFE-lined cap was added dry  $\text{MeCN}$  (1.0 mL) in the glove box, after which the vial was sealed and taken out of the glove box. The reaction mixture was stirred at room temperature for 9 hours before it was filtered through a plug of silica gel, which was extensively washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 8:1:1) to give **137** as a white amorphous solid (4.8 mg, 69% yield, 9:1 d.r.), which could be further purified to give the single diastereomeric **137**.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate/DCM 4:1:1):**  $R_f$  0.45 (CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.18 (d,  $J$  = 8.6 Hz, 1H), 6.72 (dd,  $J$  = 8.6, 2.9 Hz, 1H), 6.65 (d,  $J$  = 2.8 Hz, 1H), 6.13 (dd,  $J$  = 10.0, 2.9 Hz, 1H), 5.49 (dd,  $J$  = 10.0, 2.3 Hz, 1H), 4.01 (s, 1H), 3.92 (s, 2H), 3.78 (s, 3H), 3.77–3.74 (m, 1H), 3.25 (ddd,  $J$  = 11.1, 8.8, 5.1 Hz, 1H), 2.94–2.82 (m, 2H), 2.55 (dt,  $J$  = 11.9, 7.0 Hz, 1H), 2.48 (dt,  $J$  = 12.5, 4.2 Hz, 1H), 2.42–2.34 (m, 1H), 2.24 (dd,  $J$  = 13.4, 8.8 Hz, 1H), 2.21–2.10 (m, 3H), 1.94 (dd,  $J$  = 12.8, 8.1 Hz, 1H), 1.67 (dt,  $J$  = 12.9, 7.9 Hz, 1H), 1.53–1.43 (m, 2H), 1.39 (s, 3H), 1.34–1.27 (m, 2H), 1.19 (d,  $J$  = 5.6 Hz, 1H), 1.08–0.98 (m, 1H), 0.79 (s, 3H), 0.67 (d,  $J$  = 5.6 Hz, 1H), 0.18 (s, 9H), 0.13 (s, 9H) ppm

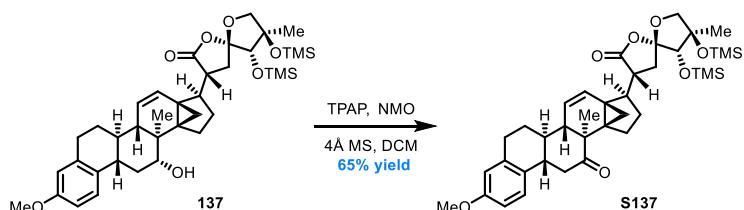
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  177.91, 157.89, 138.10, 131.99, 129.76, 125.92, 122.49, 113.82, 111.69, 110.84, 84.23, 79.85, 78.87, 77.91, 55.38, 44.41, 42.00, 41.25, 40.15, 38.65, 37.97, 37.42, 35.35, 32.66, 31.81, 30.10, 29.51, 27.54, 23.00, 22.70, 12.66, 10.80, 2.16, 0.57 ppm

**IR (neat):**  $\nu$  3529, 2957, 2924, 2853, 1782, 1610, 1501, 1253, 1141, 1020, 843, 753  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{38}\text{H}_{57}\text{O}_7\text{Si}_2^+$  [ $\text{M}+\text{H}]^+$  681.3637, found 681.3636

**$[\alpha]_D^{22}$ :** -8.3 ( $c$  = 0.48,  $\text{CHCl}_3$ )

### Synthesis of [4.3.1]propellane S137



To a mixture of **137** (5.4 mg, 0.0079 mmol), TPAP (1 mg, 0.0028 mmol), NMO (1.1 mg, 0.0095 mmol) and 4Å MS (27 mg) in a 2-mL vial with a PTFE-lined cap was added dry DCM (0.2 mL). The reaction mixture was stirred at room temperature for 3 hours before it was directly loaded on a silica gel column. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1) gave **S137** as a white amorphous solid (3.5 mg, 65% yield).

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 4:1):**  $R_f$  0.45 (CAM)

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.06 (d,  $J$  = 8.7 Hz, 1H), 6.73 (dd,  $J$  = 8.6, 2.8 Hz, 1H), 6.68 (d,  $J$  = 2.7 Hz, 1H), 6.21 (dd,  $J$  = 9.9, 2.9 Hz, 1H), 5.52 (dd,  $J$  = 10.0, 2.2 Hz, 1H), 4.01 (s, 1H), 3.92 (s, 2H), 3.78 (s, 3H), 3.24 (ddd,  $J$  = 11.2, 8.7, 5.2 Hz, 1H), 3.04–2.86 (m, 3H), 2.76–2.65 (m, 2H), 2.56 (dt,  $J$  = 11.8, 6.3 Hz, 1H), 2.32–2.12 (m, 4H), 2.03–1.96 (m, 1H), 1.95–1.85 (m, 2H), 1.66 (dt,  $J$  = 13.1, 7.9 Hz, 1H), 1.39 (s, 3H), 1.45–1.32 (m, 2H), 1.16 (d,  $J$  = 6.4 Hz, 1H), 1.10 (s, 3H), 0.88 (d,  $J$  = 6.0 Hz, 1H), 0.18 (s, 9H), 0.13 (s, 9H) ppm

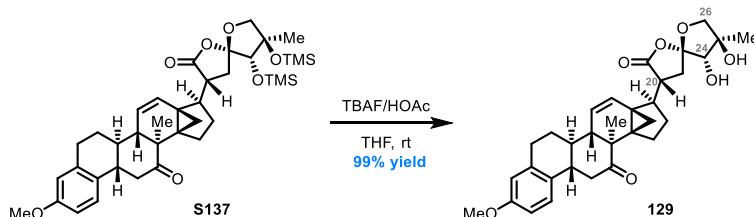
**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  213.70, 177.83, 158.23, 137.91, 131.18, 131.02, 125.96, 121.20, 113.98, 111.94, 110.87, 84.17, 79.86, 78.86, 55.40, 47.88, 45.98, 44.45, 42.68, 41.51, 40.29, 37.87, 36.05, 31.98, 31.19, 30.07, 27.33, 27.19, 22.89, 22.66, 17.09, 13.92, 2.16, 0.57 ppm

**IR (neat):**  $\nu$  2957, 2853, 1783, 1708, 1610, 1577, 1502, 1457, 1253, 1199, 1140, 1022, 843, 734, 649  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{38}\text{H}_{55}\text{O}_7\text{Si}_2^+$  [ $\text{M}+\text{H}]^+$  679.3481, found 679.3480

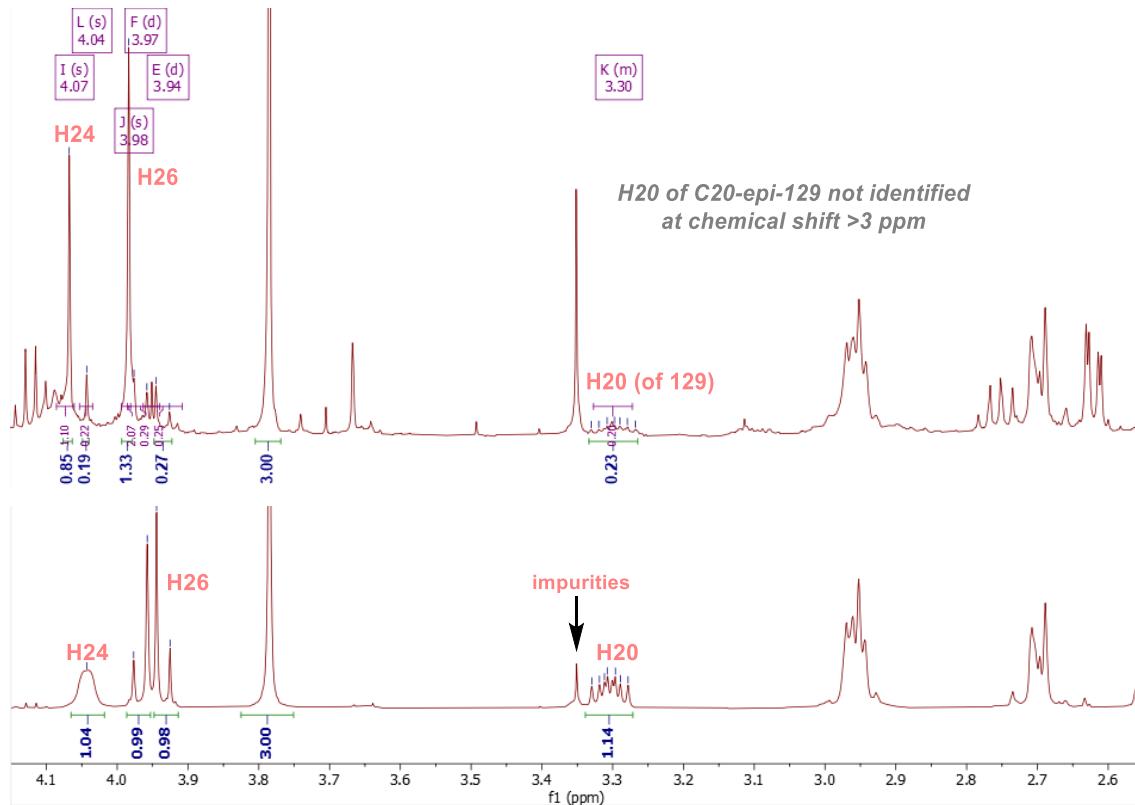
$[\alpha]_D^{22}$ : +31 ( $c$  = 0.70,  $\text{CHCl}_3$ )

### *Synthesis of 5,5-oxaspirolactone 129*



A 2-mL vial equipped with a stir bar was sequentially charged with **S137** (3.5 mg, 0.00515 mmol) and a solution of 1:1 TBAF/HOAc in THF (0.1 M, 0.2 mL, 0.02 mmol) at room temperature. The reaction mixture was stirred at the same temperature until TLC analysis indicated full conversion of the substrate (ca. 15 minutes) and was diluted with 1 mL toluene. The whole reaction mixture was directly loaded on a silica gel column and purified by flash chromatography (silica gel, toluene/acetone = 6:1 → 4:1) to give **129** as a white solid (2.7 mg, 99% yield).

**Note:** Without LiBr for the Ni-mediated reductive Heck cyclization cascade (NRHCC), the diastereoselectivity is inverted as evidenced in the key region of their  $^1\text{H-NMR}$  spectra in  $\text{CDCl}_3$  below. (Top: crude derived from NRHCC without LiBr; Bottom: purified **129** derived from NRHCC with LiBr)



**Physical state:** white amorphous solid

**TLC (toluene/acetone 2:1):**  $R_f$  0.5 (CAM)

**$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.06 (d,  $J = 8.6$  Hz, 1H), 6.73 (dd,  $J = 8.6, 2.8$  Hz, 1H), 6.68 (d,  $J = 2.7$  Hz, 1H), 6.26 (dd,  $J = 10.0, 2.9$  Hz, 1H), 5.53 (dd,  $J = 10.0, 2.3$  Hz, 1H), 4.04 (s, 1H), 3.97 (d,  $J = 9.6$  Hz, 1H), 3.93 (d,  $J = 9.5$  Hz, 1H), 3.79 (s, 3H), 3.30 (ddd,  $J = 11.2, 9.0, 5.5$  Hz, 1H), 3.03–2.89 (m, 3H), 2.75–2.65 (m, 2H), 2.54 (dt,  $J = 12.5, 6.6$  Hz, 1H), 2.42–2.32 (m, 2H), 2.32–2.24 (m, 1H), 2.20–2.15 (m, 1H), 2.00 (dt,  $J = 11.5, 2.7$  Hz, 1H), 1.95–1.85 (m, 2H), 1.70–1.60 (m, 1H), 1.43 (s, 3H), 1.43–1.33 (m, 2H), 1.17 (d,  $J = 5.8$  Hz, 1H), 1.10 (s, 3H), 0.91 (d,  $J = 6.1$  Hz, 1H) ppm

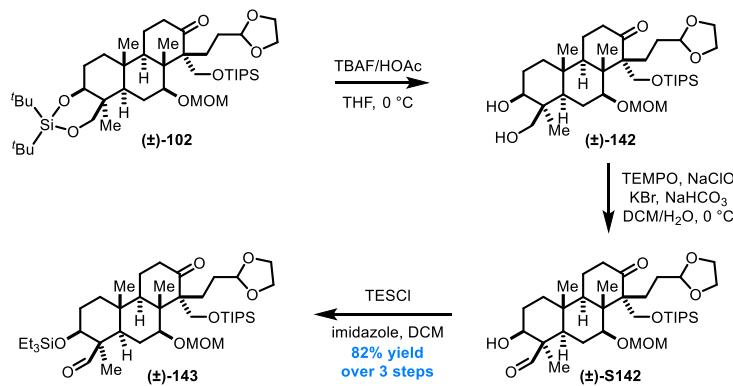
**$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  213.49, 177.19, 158.23, 137.90, 131.17, 131.02, 125.96, 121.29, 113.99, 111.94, 111.83, 83.22, 78.55, 77.56, 55.41, 47.85, 45.91, 44.37, 42.68, 41.55, 40.90, 37.86, 36.44, 32.51, 31.30, 30.06, 27.32, 27.19, 23.39, 21.65, 17.11, 14.03 ppm

**IR (neat):**  $\nu$  3398, 2959, 2926, 1781, 1707, 1611, 1501, 1139, 1094, 1036, 911  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{32}\text{H}_{39}\text{O}_7^+ [\text{M}+\text{H}]^+$  535.2690, found 535.2686

$[\alpha]_D^{22}$ : +36 ( $c = 0.28$ , CHCl<sub>3</sub>)

*Synthesis of aldehyde ( $\pm$ )-143*



To a solution of ( $\pm$ )-102 (3 g, 3.84 mmol) in THF (80 mL) at 0 °C was added a TBAF solution (1 M, 7.7 mL, 7.7 mmol) that was buffered with acetic acid (0.45 mL, 7.87 mmol). The reaction mixture was stirred for 15 minutes and quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude ( $\pm$ )-142 as a viscous oil to be used in the next step without further purification. Alternatively, ( $\pm$ )-142 could be purified by flash chromatography (silica gel, hexanes/ethyl acetate = 1:2).

**Physical state:** viscous oil

**TLC (hexanes/ethyl acetate 1:1):** R<sub>f</sub> 0.1 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 4.83 (dd, J = 5.3, 4.4 Hz, 1H), 4.74 (d, J = 6.9 Hz, 1H), 4.68 (d, J = 6.9 Hz, 1H), 4.16 (dd, J = 11.3, 2.4 Hz, 1H), 4.14 (d, J = 10.4 Hz, 1H), 4.10 (d, J = 10.3 Hz, 1H), 3.96–3.88 (m, 2H), 3.85–3.78 (m, 3H), 3.44 (dt, J = 10.4, 3.8 Hz, 1H), 3.39 (s, 3H), 3.36–3.30 (m, 1H), 2.62 (dd, J = 8.7, 2.6 Hz, 1H), 2.46 (ddd, J = 13.3, 12.0, 6.9 Hz, 1H), 2.41–2.34 (m, 2H), 2.08–2.01 (m, 2H), 1.94 (dd, J = 12.6, 3.5 Hz, 1H), 1.92–1.72 (m, 6H), 1.64 (td, J = 12.7, 5.9 Hz, 1H), 1.61–1.50 (m, 1H), 1.38 (td, J = 13.0, 11.0 Hz, 1H), 1.26 (s, 3H), 1.16–1.05 (m, 23H), 0.96 (s, 3H), 0.86 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.66, 105.77, 95.98, 82.10, 80.39, 66.10, 64.80, 64.78, 64.16, 60.30, 56.21, 52.42, 52.01, 49.63, 42.62, 40.35, 38.87, 37.63, 30.35, 27.71, 25.57, 25.24, 22.38, 21.75, 18.33, 18.32, 17.21, 12.17, 12.15 ppm

**IR (neat):** ν 3405, 2943, 2867, 1708, 1464, 1147, 1105, 1035, 863, 734 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>35</sub>H<sub>64</sub>O<sub>8</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 663.4263, found 663.4271

To a solution of the above crude diol ( $\pm$ )-142 in DCM (40 mL) was added a saturated NaHCO<sub>3</sub> solution (40

mL), TEMPO (32 mg, 0.20 mmol) and KBr (48 mg, 0.40 mmol). The reaction mixture was cooled down with an ice-water bath and then a NaClO solution (13% chlorine) was added batch-wise (1 mL per batch) every 20 minutes (4 mL, 17.7 mmol) until TLC indicated full conversion of ( $\pm$ )-**142**. During this period, the reaction mixture turned red after addition of a NaClO solution and faded to light yellow before addition of the next batch. The reaction mixture was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (50 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude ( $\pm$ )-**S142** as a yellow oil to be used in the next step without further purification. Alternatively, ( $\pm$ )-**S142** could be purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1).

**Physical state:** yellow oil

**TLC (hexanes/ethyl acetate 1:1):** R<sub>f</sub> 0.45 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.75 (d, J = 2.6 Hz, 1H), 4.82 (t, J = 4.8 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.15 (d, J = 10.3 Hz, 1H), 4.12 (d, J = 10.3 Hz, 1H), 3.97–3.85 (m, 3H), 3.85–3.78 (m, 2H), 3.41 (s, 3H), 3.22–3.14 (m, 1H), 3.02 (d, J = 10.5 Hz, 1H), 2.51–2.36 (m, 2H), 2.26 (dd, J = 12.4, 4.1 Hz, 1H), 2.04 (td, J = 13.4, 12.8, 4.6 Hz, 1H), 1.98 (dd, J = 12.7, 3.5 Hz, 1H), 1.94–1.80 (m, 6H), 1.76–1.62 (m, 2H), 1.29 (s, 3H), 1.21–1.03 (m, 24H), 1.02 (s, 3H), 0.83 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  212.27, 207.15, 105.69, 96.10, 82.05, 77.11, 66.12, 64.84, 64.82, 60.25, 56.27, 52.96, 52.35, 50.75, 49.13, 39.94, 38.76, 38.06, 30.30, 28.11, 25.80, 25.16, 21.59, 19.11, 18.34, 18.32, 15.68, 12.45, 12.19 ppm

**IR (neat):**  $\nu$  3475, 2943, 2867, 1709, 1464, 1147, 1104, 1036, 882, 734, 681 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>35</sub>H<sub>62</sub>O<sub>8</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 661.4106, found 661.4106

To a solution of the above crude aldehyde ( $\pm$ )-**S142** in DCM (30 mL) was added imidazole (654 mg, 9.6 mmol) and TESCl (1.3 mL, 7.75 mmol). The reaction mixture was stirred for 2 hours and quenched with water. The layers were separated, and the aqueous layer was extracted with DCM (15 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 6:1) gave ( $\pm$ )-**143** as a viscous oil (2.38 g, 82% overall yield). In practice, enantio-enriched **143** was also prepared from **102** using the same procedure.

**Physical state:** viscous oil

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.6 (CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.00 (s, 1H), 4.81 (dd, J = 5.3, 4.3 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 7.0 Hz, 1H), 4.19 (d, J = 10.2 Hz, 1H), 4.11 (d, J = 10.2 Hz, 1H), 3.96–3.86 (m, 2H), 3.84–3.79 (m,

2H), 3.79–3.75 (m, 1H), 3.44–3.39 (m, 1H), 3.40 (s, 3H), 2.53–2.35 (m, 2H), 2.17–1.93 (m, 4H), 1.93–1.79 (m, 5H), 1.72–1.60 (m, 1H), 1.55–1.49 (m, 1H), 1.49–1.38 (m, 1H), 1.17 (s, 3H), 1.15–1.03 (m, 23H), 0.95 (s, 3H), 0.95 (t,  $J$  = 7.9 Hz, 9H), 0.76 (s, 3H), 0.60 (q,  $J$  = 8.1 Hz, 6H) ppm

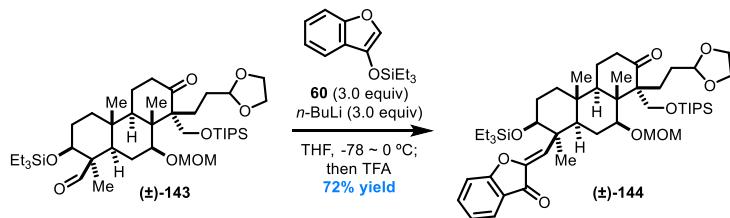
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  212.45, 206.70, 105.77, 95.65, 81.54, 77.64, 66.40, 64.85, 64.84, 60.17, 56.37, 53.32, 52.80, 50.83, 49.21, 40.03, 38.37, 37.72, 30.40, 28.61, 26.09, 25.28, 21.73, 21.64, 18.39, 18.36, 17.34, 12.41, 12.28, 6.99, 5.29 ppm

**IR (neat):**  $\nu$  2950, 2874, 1714, 1464, 1147, 1108, 882, 827, 800, 741, 681  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{41}\text{H}_{77}\text{O}_8\text{Si}_2^+ [\text{M}+\text{H}]^+$  753.5151, found 753.5148

$[\alpha]_D^{22}$  (**143**): +9.2 ( $c$  = 2.06,  $\text{CHCl}_3$ )

### Synthesis of enone ( $\pm$ )-**144**



To a solution of **60** (460 mg, 1.85 mmol) in dry THF (1.5 mL) at -78 °C was slowly added a solution of *n*-BuLi in hexane (2.5 M, 0.73 mL, 1.83 mmol). The reaction mixture was kept at the same temperature for 5 minutes and then warmed up to 0 °C for 25 minutes to complete the deprotonation process, resulting in formation of the corresponding aryllithium agent. The reaction mixture was then cooled back to -78 °C. A solution of ( $\pm$ )-**143** (460 mg, 0.61 mmol) in THF (2 mL) was added at this point and the reaction mixture was warmed up to 0 °C and stirred for another 1.5 hours before it was quenched with a saturated  $\text{NH}_4\text{Cl}$  solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 10:1 → 6:1 → 4:1) gave ( $\pm$ )-**144** as a yellow to red amorphous solid ( $R_f$  = 0.45, hexanes/ethyl acetate 2:1) and two proposed premature intermediates ( $R_f$  = 0.55 and 0.65, respectively, hexanes/ethyl acetate 2:1). Both premature intermediates were treated with trifluoroacetic acid (1 N in DCM, 0.5 mL) in DCM, and the reaction mixtures were stirred for 60 minutes. After TLC indicated high conversion of these intermediates to ( $\pm$ )-**144**, purification of these reaction mixtures eventually resulted in total isolation of ( $\pm$ )-**144** (382 mg, 72% combined yield). In practice, enantio-enriched **144** was also prepared from **143** using the same procedure.

**Physical state:** yellow to red amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.45 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.77 (d, *J* = 6.9 Hz, 1H), 7.59 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.36 (s, 1H), 4.81 (t, *J* = 4.9 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.18–4.09 (m, 2H), 3.96–3.84 (m, 3H), 3.85–3.76 (m, 2H), 3.46 (s, 3H), 3.30 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.51–2.34 (m, 3H), 2.05–1.77 (m, 8H), 1.73–1.60 (m, 2H), 1.53 (s, 3H), 1.45 (dd, *J* = 24.6, 13.0 Hz, 1H), 1.19–1.07 (m, 23H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 3H), 0.79 (s, 3H), 0.61–0.54 (m, 6H) ppm

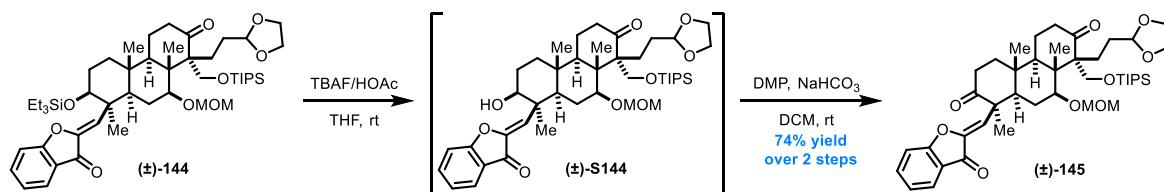
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.49, 184.02, 166.15, 149.09, 136.78, 124.92, 122.96, 121.97, 119.83, 112.73, 105.77, 96.17, 82.25, 80.03, 66.28, 64.83, 64.82, 60.36, 56.12, 54.78, 51.14, 49.27, 45.08, 40.01, 38.95, 37.83, 30.35, 27.99, 27.09, 25.74, 24.00, 21.59, 18.40, 18.37, 16.96, 12.38, 12.27, 7.06, 5.35 ppm

**IR (neat):** *v* 2947, 2874, 1711, 1663, 1602, 1462, 1299, 1103, 1038, 877, 756 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>49</sub>H<sub>81</sub>O<sub>9</sub>Si<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 869.5414, found 869.5415

**[α]<sub>D</sub><sup>22</sup>(144):** +125 (*c* = 1.0, CHCl<sub>3</sub>)

### Synthesis of ketone (±)-145



To a solution of (±)-144 (884 mg, 1.02 mmol) in THF (3 mL) was added a TBAF solution (1 M, 3 mL, 3.0 mmol) that was buffered with acetic acid (0.2 mL, 3.5 mmol). The reaction mixture was stirred at room temperature for 12 hours and quenched with a saturated NaHCO<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude (±)-S144 as a yellow to red solid to be used in the next step without further purification. Alternatively, (±)-S144 could be purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1) to give a yellow solid.

**Physical state:** yellow solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.25 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.78 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.62 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.20 (td, *J* = 7.5, 0.8 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.20 (s, 1H), 4.82 (dd, *J* = 5.3, 4.3 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 10.4 Hz, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 3.94–3.87 (m, 3H), 3.84–3.77 (m, 2H), 3.44 (s, 3H), 3.34 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.49–2.34 (m, 3H), 2.04–1.80 (m, 9H), 1.67–1.44 (m, 2H), 1.55 (s, 3H), 1.19–1.04 (m, 23H), 0.93 (s, 3H), 0.82 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.38, 183.86, 165.98, 148.44, 137.13, 125.04, 123.38, 121.65, 118.14,

112.77, 105.74, 96.22, 82.07, 79.11, 66.12, 64.81, 64.79, 60.37, 56.13, 54.68, 51.16, 49.35, 44.96, 40.10, 39.05, 37.97, 30.31, 27.43, 26.53, 25.58, 23.96, 21.60, 18.36, 18.34, 16.76, 12.28, 12.20 ppm

**MP:** 98–100 °C

**IR (neat):**  $\nu$  3463, 2943, 2867, 1709, 1660, 1602, 1461, 1300, 1103, 1036, 884, 757 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>43</sub>H<sub>67</sub>O<sub>9</sub>Si<sup>+</sup> [M+H]<sup>+</sup> 755.4549, found 755.4549

The above crude alcohol ( $\pm$ )-**S144** was dissolved in DCM (5 mL), followed by sequential addition of NaHCO<sub>3</sub> (840 mg, 10.0 mmol) and Dess-Martin periodinane (848 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 6 hours and quenched by addition of a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The layers were separated, and the aqueous layer was extracted with DCM (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 3:1:1) gave ( $\pm$ )-**145** as a pale-yellow solid (566 mg, 74% overall yield). In practice, enantio-enriched **145** was also prepared from **144** using the same procedure.

**Physical state:** pale-yellow solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.35 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.74 (dd,  $J$  = 7.9, 1.4 Hz, 1H), 7.61 (ddd,  $J$  = 8.6, 7.3, 1.5 Hz, 1H), 7.22–7.15 (m, 2H), 6.26 (s, 1H), 4.83 (t,  $J$  = 4.8 Hz, 1H), 4.75 (d,  $J$  = 7.1 Hz, 1H), 4.71 (d,  $J$  = 7.1 Hz, 1H), 4.14 (d,  $J$  = 10.3 Hz, 1H), 4.11 (d,  $J$  = 10.3 Hz, 1H), 3.98–3.87 (m, 3H), 3.85–3.78 (m, 2H), 3.41 (s, 3H), 2.84 (td,  $J$  = 13.9, 6.2 Hz, 1H), 2.52–2.37 (m, 3H), 2.15–1.97 (m, 4H), 1.95–1.79 (m, 4H), 1.74 (td,  $J$  = 12.4, 6.0 Hz, 1H), 1.61–1.51 (m, 1H), 1.49 (dd,  $J$  = 12.7, 2.1 Hz, 1H), 1.43–1.36 (m, 1H), 1.35 (s, 3H), 1.14 (s, 3H), 1.13–1.03 (m, 24H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  211.87, 210.92, 183.95, 166.30, 146.52, 137.46, 124.84, 123.55, 121.54, 116.18, 113.20, 105.70, 96.23, 81.68, 66.16, 64.83, 64.81, 60.37, 56.27, 55.73, 52.05, 50.82, 49.27, 42.03, 40.03, 38.39, 35.78, 30.31, 26.30, 25.79, 22.02, 21.79, 18.30, 18.28, 15.78, 12.42, 12.15 ppm

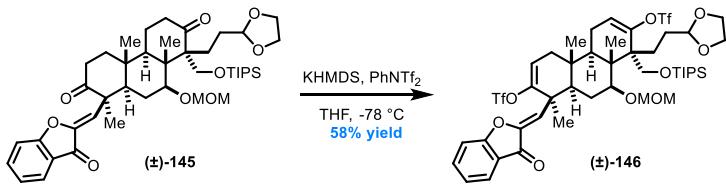
**MP:** 181–183 °C

**IR (neat):**  $\nu$  2944, 2866, 1712, 1664, 1602, 1462, 1299, 1100, 1036, 883, 759, 737 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>43</sub>H<sub>65</sub>O<sub>9</sub>Si<sup>+</sup> [M+H]<sup>+</sup> 753.4392, found 753.4393

**[ $\alpha$ ]<sub>D</sub><sup>22</sup>(**145**):** -9.8 (*c* = 0.92, CHCl<sub>3</sub>)

### *Synthesis of vinyl triflate ( $\pm$ )-**146***



To a solution of **(±)-145** (52.3 mg, 0.069 mmol) and PhNTf<sub>2</sub> (74.4 mg, 0.208 mmol) in THF (1 mL) was slowly added a solution of KHMDS (55.3 mg, 0.277 mmol) in THF (1 mL) at -78 °C. The reaction mixture was stirred at the same temperature until TLC indicated full consumption of **(±)-145** (ca. 2 hours), and then it was quenched with a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 10:1 → 4:1) gave vinyl triflate **(±)-146** as a white foam (41 mg, 58% yield).

**Physical state:** white foam

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.6 (UV, CAM)

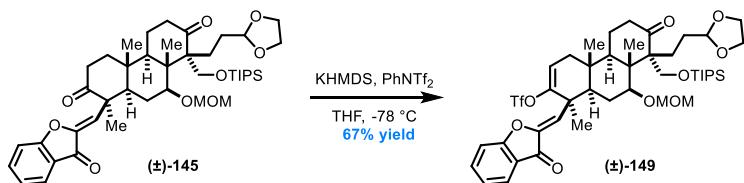
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.77 (dd, J = 7.7, 1.4 Hz, 1H), 7.64 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 7.23–7.18 (m, 2H), 5.95 (dd, J = 6.5, 2.2 Hz, 1H), 5.93 (s, 1H), 5.78 (dd, J = 6.5, 2.1 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.74 (d, J = 6.8 Hz, 1H), 4.74–4.72 (m, 1H), 4.20 (dd, J = 11.3, 4.2 Hz, 1H), 3.90 (ddd, J = 8.7, 3.7, 2.6 Hz, 3H), 3.84–3.77 (m, 3H), 3.33 (s, 3H), 2.46 (dd, J = 11.7, 4.4 Hz, 1H), 2.30–2.16 (m, 3H), 2.08–1.92 (m, 2H), 1.89–1.72 (m, 4H), 1.59 (s, 3H), 1.58–1.49 (m, 2H), 1.14–1.05 (m, 21H), 1.02 (s, 3H), 1.00 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 184.08, 166.48, 151.69, 151.60, 148.28, 137.51, 129.65, 124.99, 123.56, 121.23, 118.45 (q, J = 319.5 Hz), 118.34 (q, J = 319.6 Hz), 116.19, 114.19, 113.00, 105.20, 95.80, 81.11, 65.84, 64.90, 64.87, 56.21, 52.92, 50.62, 46.84, 46.08, 42.52, 39.91, 35.95, 30.33, 26.56, 25.96, 25.03, 21.42, 18.20, 18.14, 16.85, 12.21, 12.18 ppm

**IR (neat):** ν 2945, 2892, 2869, 1718, 1690, 1668, 1606, 1462, 1414, 1300, 1209, 1143, 1036 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>45</sub>H<sub>62</sub>O<sub>13</sub>SiS<sub>2</sub>F<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 1039.3198, found 1039.3197

### Synthesis of vinyl triflate **(±)-149**



To a solution of **(±)-145** (300 mg, 0.398 mmol) in THF (3 mL) was added a solution of KHMDS (112 mg, 0.561 mmol) in THF (3 mL) at -78 °C. After stirring for 15 minutes at this temperature to ensure full

deprotonation, PhNTf<sub>2</sub> (200 mg, 0.560 mmol) in THF (2 mL) was added. The reaction mixture was stirred at the same temperature until TLC indicated full consumption of ( $\pm$ )-145 (ca. 30 minutes), and then it was quenched with a saturated NH<sub>4</sub>Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL  $\times$  3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 10:1  $\rightarrow$  4:1) gave vinyl triflate ( $\pm$ )-149 as a white amorphous solid (235 mg, 67% yield). In practice, enantio-enriched 149 was also prepared from 145 using the same procedure.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.4 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.79–7.73 (m, 1H), 7.63 (td, *J* = 7.7, 1.5 Hz, 1H), 7.23–7.16 (m, 2H), 5.91 (s, 1H), 5.79 (dd, *J* = 6.5, 2.1 Hz, 1H), 4.82 (t, *J* = 4.7 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 10.2 Hz, 1H), 4.08 (d, *J* = 10.2 Hz, 1H), 3.96–3.76 (m, 5H), 3.35 (s, 3H), 2.53 (td, *J* = 12.8, 6.8 Hz, 1H), 2.45–2.35 (m, 2H), 2.21 (ddd, *J* = 13.2, 4.2, 2.3 Hz, 1H), 2.13–2.02 (m, 2H), 1.95–1.78 (m, 4H), 1.74 (td, *J* = 12.7, 5.3 Hz, 1H), 1.67 (dd, *J* = 13.2, 2.2 Hz, 1H), 1.62 (s, 3H), 1.59–1.48 (m, 2H), 1.17–1.02 (m, 24H), 0.97 (s, 3H), 0.94 (s, 3H) ppm

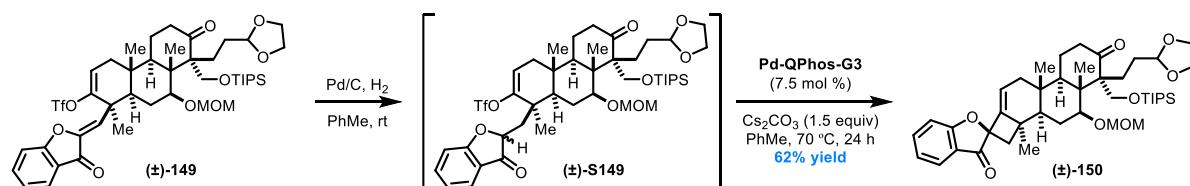
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  211.84, 184.01, 166.45, 151.76, 148.21, 137.50, 125.00, 123.58, 122.26, 121.24, 119.72, 117.17, 114.63, 114.07, 113.98, 112.97, 105.74, 96.07, 80.88, 66.26, 64.83, 64.82, 60.21, 56.37, 53.35, 49.88, 49.20, 42.59, 40.61, 40.39, 36.64, 30.41, 26.57, 25.81, 25.08, 21.90, 18.32, 18.31, 16.48, 12.19, 12.01 ppm

**IR (neat):**  $\nu$  2945, 2890, 2868, 1714, 1667, 1606, 1461, 1414, 1212, 1146, 1036, 881, 734, 604 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>44</sub>H<sub>63</sub>O<sub>11</sub>SiSF<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 907.3705, found 907.3704

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (149):** +77 (*c* = 1.73, CHCl<sub>3</sub>)

### Synthesis of 4,5-spirocycle ( $\pm$ )-150



A 10-mL round bottle flask was charged with 5% Pd/C (88.5 mg) followed by addition of a solution of ( $\pm$ )-149 (88.5 mg, 0.10 mmol) in toluene (5 mL). The flask was sealed by rubber septum and H<sub>2</sub> was bubbled through the reaction mixture for 60 minutes using a double-layer balloon. The reaction was kept under H<sub>2</sub> atmosphere and stirred at room temperature until crude <sup>1</sup>H-NMR indicated full conversion of ( $\pm$ )-149 (ca. 16 hours). The reaction mixture was filtered through a plug of silica gel and washed with ether. The filtrate

was concentrated *in vacuo* to give crude vinyl triflate ( $\pm$ )-**S149** as a white foam (85.5 mg). The crude ( $\pm$ )-**S149** was then transferred to a flame-dried 20-mL vial and taken into the glovebox. To the vial with ( $\pm$ )-**S149** was sequentially charged with **Pd-QPhos-G3** (8.1 mg, 0.0075 mmol), Cs<sub>2</sub>CO<sub>3</sub> (48.9 mg, 0.15 mmol) and anhydrous toluene (10 mL). The vial was then sealed, taken out of the glove box, and heated to 70 °C for 24 hours. The reaction mixture was cooled down and directly loaded on silica gel column. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 4:1) gave ( $\pm$ )-**150** as a white to pink amorphous solid (45.5 mg, 62% yield). In practice, enantio-enriched **150** was also prepared from **149** using the same procedure.

**Note:** Carefully monitoring the hydrogenation reaction by crude <sup>1</sup>H-NMR is highly recommended because ( $\pm$ )-**149** and ( $\pm$ )-**S149** have the same R<sub>f</sub> on TLC. Full conversion of ( $\pm$ )-**149** must be confirmed by <sup>1</sup>H-NMR as remaining ( $\pm$ )-**149** can significantly impede the conversion of ( $\pm$ )-**S149** to ( $\pm$ )-**150** in the alkenylation event.

**Physical state:** white to pink amorphous solid

**TLC (hexanes/ethyl acetate 2:1):** R<sub>f</sub> 0.5 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.65 (dd, J = 8.1, 1.5 Hz, 1H), 7.59 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 7.11–7.03 (m, 2H), 5.69 (dd, J = 8.7, 4.1 Hz, 1H), 4.84 (t, J = 4.7 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 6.7 Hz, 1H), 4.23 (d, J = 10.4 Hz, 1H), 4.10 (d, J = 10.4 Hz, 1H), 4.06 (dd, J = 10.1, 4.9 Hz, 1H), 3.96–3.88 (m, 2H), 3.86–3.77 (m, 2H), 3.39 (s, 3H), 2.47–2.43 (m, 2H), 2.29–2.22 (m, 2H), 2.18 (dd, J = 12.7, 3.8 Hz, 1H), 2.06–1.99 (m, 1H), 1.95–1.76 (m, 6H), 1.69 (s, 3H), 1.54–1.37 (m, 4H), 1.13–1.04 (m, 24H), 1.01 (s, 3H) ppm

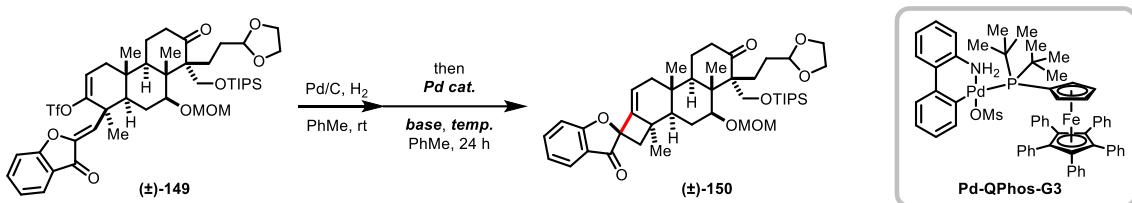
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.62, 198.87, 170.82, 144.08, 137.95, 124.91, 121.99, 120.86, 120.80, 112.92, 105.78, 95.89, 93.22, 81.75, 66.14, 64.89, 64.86, 60.73, 56.26, 52.20, 49.62, 49.28, 44.57, 42.41, 40.10, 39.76, 38.39, 30.34, 29.85, 25.78, 24.77, 21.42, 18.38, 18.34, 14.25, 12.92, 12.23 ppm

**IR (neat):** ν 2944, 2867, 1718, 1711, 1612, 1464, 1145, 1097, 1038 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>43</sub>H<sub>64</sub>O<sub>8</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 759.4263, found 759.4264

**[α]<sub>D</sub><sup>22</sup>(150):** +73 (c = 1.64, CHCl<sub>3</sub>)

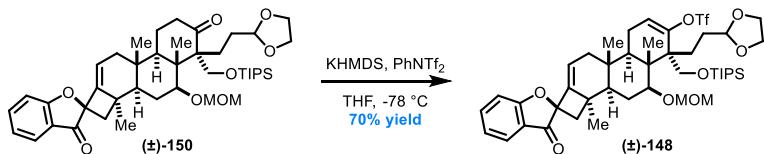
**Table S5. Reaction optimization for the 4,5-spirocycle formation from ( $\pm$ )-149**



entry	[Pd] cat. (mol %)	ligand (mol %)	base (equiv)	concentration/M	temperature	isolated yield/%
1	$Pd(OAc)_2$ (5)	QPhos (10)	$LiOt-Bu$ (1.5)	0.050	60 °C	<20
2	$Pd(QPhos)_2$ (5)	none	$LiOt-Bu$ (1.5)	0.050	60 °C	22
3	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.050	60 °C	29
4	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.050	70 °C	45
5	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.050	80 °C	38
6	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (3.0)	0.050	70 °C	32
7	$Pd(QPhos)_2$ (5)	none	$Na_2CO_3$ (1.5)	0.050	70 °C	<5
8	$Pd(QPhos)_2$ (5)	none	$K_2CO_3$ (1.5)	0.050	70 °C	<5
9	$Pd(QPhos)_2$ (5)	none	$K_3PO_4$ (2.0)	0.050	70 °C	44
10	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.025	70 °C	41
11	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.010	70 °C	46
12	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.005	70 °C	37
13	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.010	60 °C	37
14	$Pd(QPhos)_2$ (5)	none	$Cs_2CO_3$ (1.5)	0.010	65 °C	43
15	<b>Pd-QPhos-G3 (5)</b>	none	$Cs_2CO_3$ (1.5)	0.010	70 °C	48
16	<b>Pd-QPhos-G3 (7.5)</b>	<b>none</b>	<b><math>Cs_2CO_3</math> (1.5)</b>	<b>0.010</b>	<b>70 °C</b>	<b>62</b>

Note: This table is adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

### Synthesis of vinyl triflate ( $\pm$ )-148 from ( $\pm$ )-150



To a solution of ( $\pm$ )-150 (100 mg, 0.135 mmol) and  $PhNTf_2$  (72.5 mg, 0.203 mmol) in THF (2 mL) was added a solution of KHMDS (53.9 mg, 0.270 mmol) in THF (1 mL) at -78 °C. The reaction mixture was stirred at the same temperature until TLC indicated full consumption of ( $\pm$ )-150 (ca. 1.5 hours), and then it was quenched with a saturated  $NH_4Cl$  solution. The layers were separated, and the aqueous layer was extracted with  $EtOAc$  (5 mL  $\times$  3). The combined extracts were dried over  $Na_2SO_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate 6:1  $\rightarrow$  4:1) gave vinyl triflate ( $\pm$ )-148 as a white amorphous solid (82 mg, 70% yield). In practice, enantio-enriched 148 was also prepared from 150 using the same procedure.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.7 (UV, CAM)

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.65–7.61 (m, 1H), 7.60–7.55 (m, 1H), 7.09–7.01 (m, 2H), 5.94 (dd, *J* = 6.1, 2.5 Hz, 1H), 5.67 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.81 (d, *J* = 6.5 Hz, 1H), 4.75 (t, *J* = 4.5 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.27–4.19 (m, 1H), 3.94–3.87 (m, 3H), 3.86–3.76 (m, 3H), 3.38 (s, 3H), 2.48–2.42 (m, 1H), 2.42 (d, *J* = 11.1 Hz, 1H), 2.22 (d, *J* = 11.1 Hz, 1H), 2.20–2.03 (m, 4H), 1.94–1.77 (m, 4H), 1.64 (s, 3H), 1.62–1.56 (m, 1H), 1.48–1.38 (m, 2H), 1.12 (s, 3H), 1.10–1.03 (m, 2H), 1.02 (s, 4H) ppm

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ 198.94, 170.83, 151.90, 143.90, 137.97, 124.92, 122.01, 121.05, 120.85, 116.78, 112.92, 105.39, 95.60, 93.28, 81.88, 65.92, 64.94, 56.24, 51.60, 51.15, 47.54, 45.88, 44.53, 41.77, 40.15, 37.98, 30.53, 26.58, 25.68, 24.15, 21.44, 18.32, 18.19, 14.77, 12.86, 12.26 ppm

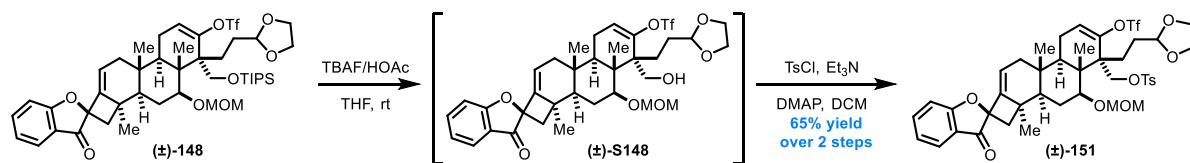
**<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>):** δ -74.99 ppm

**IR (neat):** *v* 2945, 2918, 2870, 2851, 1718, 1617, 1211, 1143, 1097, 1034 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>44</sub>H<sub>63</sub>O<sub>10</sub>F<sub>3</sub>SSiNa<sup>+</sup> [M+Na]<sup>+</sup> 891.3756, found 891.3754

**[α]<sub>D</sub><sup>22</sup> (148):** +83 (*c* = 1.48, CHCl<sub>3</sub>)

### Synthesis of tosylate (±)-151



To (±)-148 (93 mg, 0.107 mmol) in a 2-mL vial was added a TBAF solution (1 M, 0.54 mL, 0.54 mmol) that was pre-buffered with acetic acid (18 μL, 0.32 mmol). The reaction mixture was stirred at 30 °C for 6 hours and quenched with a saturated NaHCO<sub>3</sub> solution when TLC indicated full conversion of (±)-148. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give crude (±)-S148 as a white foam to be used in the next step without further purification. The crude (±)-S148 was dissolved in DCM (2 mL) followed by addition of DMAP (13.1 mg, 0.107 mmol), TsCl (30.6 mg, 0.161 mmol), and Et<sub>3</sub>N (30 μL, 0.214 mmol) at room temperature. The reaction mixture was stirred at room temperature until TLC analysis showed full conversion of (±)-S148 (ca. 12 hours). The solution was directly loaded on silica gel column and purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 3:1:1) to give (±)-151 as a white amorphous solid (60 mg, 65% overall yield). In practice, enantio-enriched 151 was also prepared from 148 using the same procedure.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate/DCM 2:1:1):** R<sub>f</sub> 0.5 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.68–7.64 (m, 1H), 7.59 (ddd, *J* = 8.5, 7.2, 1.5

Hz, 1H), 7.38–7.32 (m, 2H), 7.10–7.03 (m, 2H), 6.03 (dd,  $J$  = 5.4, 3.2 Hz, 1H), 5.66 (dd,  $J$  = 8.6, 4.1 Hz, 1H), 4.74 (t,  $J$  = 4.7 Hz, 1H), 4.69 (d,  $J$  = 6.4 Hz, 1H), 4.60 (d,  $J$  = 6.4 Hz, 1H), 4.24 (d,  $J$  = 10.6 Hz, 1H), 4.02 (d,  $J$  = 10.6 Hz, 1H), 3.94–3.88 (m, 2H), 3.86 (dd,  $J$  = 10.1, 4.2 Hz, 1H), 3.83–3.79 (m, 2H), 3.37 (s, 3H), 2.44 (s, 3H), 2.44–2.41 (m, 1H), 2.32–2.22 (m, 2H), 2.17–2.06 (m, 3H), 1.89–1.82 (m, 2H), 1.83–1.75 (m, 1H), 1.72 (s, 3H), 1.63–1.57 (m, 2H), 1.51–1.41 (m, 1H), 1.37 (dd,  $J$  = 14.4, 4.3 Hz, 1H), 1.33–1.29 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  198.72, 170.79, 148.54, 145.33, 144.03, 137.94, 132.60, 130.03, 128.29, 124.96, 122.04, 120.89, 120.60, 119.46, 112.87, 104.83, 95.89, 93.20, 82.19, 69.94, 65.01, 64.95, 56.31, 51.95, 50.11, 47.53, 46.70, 44.49, 41.64, 40.17, 38.50, 30.71, 26.10, 25.82, 24.10, 21.79, 21.46, 14.67, 13.00 ppm

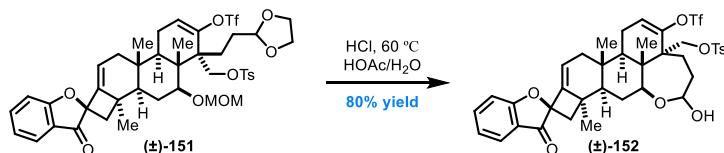
**$^{19}\text{F-NMR}$  (470 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -74.76 ppm

**IR (neat):**  $\nu$  2918, 2849, 1718, 1612, 1212, 1143, 1030, 986  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{42}\text{H}_{49}\text{O}_{12}\text{F}_3\text{S}_2\text{Na}^+$   $[\text{M}+\text{Na}]^+$  889.2510, found 889.2512

$[\alpha]_D^{22}$  (**151**): +84 ( $c$  = 1.0,  $\text{CHCl}_3$ )

### Synthesis of hemiacetal ( $\pm$ )-**152**



To a solution of ( $\pm$ )-**151** (17.3 mg, 0.020 mmol) in HOAc/H<sub>2</sub>O (4:1 v/v, 0.75 mL) was added a 6 N HCl solution (10  $\mu\text{L}$ , 0.060 mmol). The reaction mixture was heated to 60 °C and maintained for 3 hours before it was cooled down and diluted with DCM (5 mL). The solution was transferred to a separatory funnel and carefully quenched with a Na<sub>2</sub>CO<sub>3</sub> solution (~0.45 equiv) and then a saturated NaHCO<sub>3</sub> solution until CO<sub>2</sub> evolution ceased. The layers were separated, and the aqueous layer was extracted with DCM. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 2:1:1) gave ( $\pm$ )-**152** as a white amorphous solid (12.6 mg, 80% yield). In practice, enantio-enriched **152** was also prepared from **151** using the same procedure.

**Note:** Neutralization of HOAc with addition of a Na<sub>2</sub>CO<sub>3</sub> solution should be very slow to maintain an acidic pH such that undesired cyclization via an intramolecular nucleophilic substitution of tosylate by the hemiacetal hydroxy group is avoided.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.4 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.79 (d,  $J$  = 8.3 Hz, 2H), 7.66 (dd,  $J$  = 7.7, 1.4 Hz, 1H), 7.59 (ddd,  $J$  = 8.6, 7.2, 1.5 Hz, 1H), 7.35 (d,  $J$  = 8.1 Hz, 2H), 7.10–7.03 (m, 2H), 5.71–5.64 (m, 2H), 5.14 (dd,  $J$  = 8.6, 6.0 Hz, 1H), 4.44 (d,  $J$  = 9.5 Hz, 1H), 4.35 (d,  $J$  = 9.6 Hz, 1H), 4.01 (dd,  $J$  = 10.5, 5.7 Hz, 1H), 2.46 (s, 3H), 2.43 (d,  $J$  = 11.3 Hz, 1H), 2.26–2.18 (m, 3H), 2.06–1.97 (m, 2H), 1.88–1.74 (m, 2H), 1.70 (s, 3H), 1.67–1.59 (m, 2H), 1.57–1.40 (m, 3H), 1.25–1.20 (m, 1H), 1.01 (s, 3H), 0.98 (s, 3H) ppm

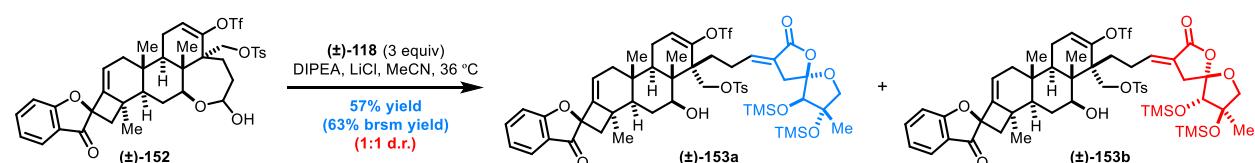
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  198.69, 170.76, 150.76, 145.38, 144.28, 138.01, 132.67, 129.99, 128.06, 124.95, 122.09, 120.80, 120.17, 119.12, 118.37 (q,  $J$  = 319.8 Hz), 114.55, 112.87, 94.88, 92.96, 73.01, 70.62, 52.82, 49.17, 46.98, 44.85, 44.18, 41.33, 40.03, 37.10, 28.70, 27.27, 25.98, 23.19, 21.85, 20.97, 15.54, 13.16 ppm

**IR (neat):**  $\nu$  3422, 2937, 1717, 1612, 1414, 1212, 1177, 1142, 1006, 970, 734 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>38</sub>H<sub>42</sub>O<sub>10</sub>S<sub>2</sub>F<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 779.2166, found 779.2170

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (152):** +49 ( $c$  = 1.24, CHCl<sub>3</sub>)

### Synthesis of 5,5-oxaspirolactone ( $\pm$ )-153a



To a mixture of (±)-152 (15.5 mg, 0.020 mmol), (±)-118 (28 mg, 0.060 mmol), LiCl (2.6 mg, 0.061 mmol) and DIPEA (21  $\mu$ L, 0.12 mmol) was added dry MeCN (0.14 mL) in the glove box at room temperature. The reaction mixture was stirred at 36 °C for 48 hours and filtered through a plug of silica gel, which was extensively washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 4:1 → 2:1) gave an inseparable 1:1 diastereomeric mixture (±)-153a and (±)-153b as a white amorphous solid (12.5 mg, 57% combined yield) and recovered (±)-152 as a white amorphous solid (1.6 mg, 10% yield). In practice, enantio-enriched 153a was also prepared from 152 using the same procedure.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.55 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.85–7.77 (m, 2H), 7.66 (dd,  $J$  = 7.8, 1.4 Hz, 1H), 7.59 (ddd,  $J$  = 8.5, 7.2, 1.5 Hz, 1H), 7.36 (d,  $J$  = 8.0 Hz, 2H), 7.10–7.03 (m, 2H), 6.58–6.50 (m, 1H), 6.05–5.98 (m, 1H), 5.70–5.63 (m, 1H), 4.23 (d,  $J$  = 10.5 Hz, 0.5H), 4.22 (d,  $J$  = 10.5 Hz, 0.5H), 4.12 (d,  $J$  = 10.5 Hz, 0.5H), 4.10 (d,  $J$  = 10.4 Hz, 0.5H), 4.05–4.00 (m, 2H), 3.99–3.94 (m, 2H), 2.89–2.75 (m, 2H), 2.44 (s, 3H), 2.42 (d,  $J$  = 11.2

Hz, 1H), 2.36–2.29 (m, 1H), 2.25 (d,  $J$  = 11.1 Hz, 1H), 2.20–2.06 (m, 5H), 1.71 (s, 3H), 1.61–1.55 (m, 2H), 1.40 (s, 3H), 1.38–1.29 (m, 4H), 1.09 (s, 3H), 1.01 (s, 3H), 0.13 (s, 9H), 0.12 (s, 9H) ppm

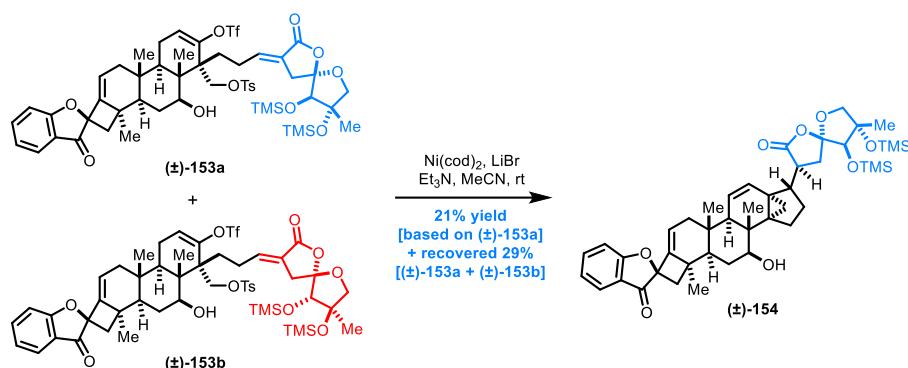
**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  198.65, 198.64, 170.75, 168.95, 148.71, 148.52, 145.63, 145.61, 144.05, 144.04, 139.33, 139.31, 138.01, 132.35, 132.29, 130.16, 130.13, 128.15, 126.53, 124.97, 122.10, 120.83, 120.48, 119.75, 119.73, 118.29 (d,  $J$  = 319.6 Hz), 112.86, 110.11, 110.09, 93.18, 85.53, 85.40, 80.00, 79.92, 79.44, 79.38, 74.83, 74.81, 69.69, 52.52, 49.91, 49.79, 47.92, 47.89, 46.30, 46.23, 44.31, 41.83, 41.80, 40.14, 38.28, 34.51, 34.46, 30.30, 30.28, 28.78, 28.72, 26.84, 26.76, 25.84, 22.95, 22.88, 21.82, 21.63, 21.61, 14.65, 14.62, 11.83, 11.66, 2.14, 0.31 ppm

**IR (neat):**  $\nu$  3361, 2959, 2929, 2851, 1763, 1719, 1617, 1252, 1209, 1142, 1095, 1019, 888, 843  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{52}\text{H}_{68}\text{O}_{14}\text{S}_2\text{F}_3\text{Si}_2^+$  [M+H]<sup>+</sup> 1093.3536, found 1093.3535

$[\alpha]_D^{22}$  (**153a + 153b**): +45 ( $c$  = 1.0,  $\text{CHCl}_3$ )

### Synthesis of [4.3.1]propellane ( $\pm$ )-**154**



To a mixture of [**(±)-153a + (±)-153b**] (14 mg, 0.013 mmol),  $\text{Ni}(\text{cod})_2$  (21.3 mg, 0.077 mmol),  $\text{LiBr}$  (22.5 mg, 0.26 mmol) and  $\text{Et}_3\text{N}$  (20  $\mu\text{L}$ , 0.14 mmol) in a 4-mL vial with a PTFE-lined cap was added dry  $\text{MeCN}$  (1.2 mL) in the glove box, after which it was sealed and taken out of the glove box. The reaction mixture was stirred at room temperature for 9 hours before it was filtered through a plug of silica gel, which was extensively washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate/DCM = 7:1:1) to give **(±)-154** as a white amorphous solid (1.0 mg, 21% yield based on **(±)-153a**) and recovered [**(±)-153a + (±)-153b**] as a white amorphous solid (4.0 mg, 29% total yield). In practice, enantio-enriched **154** was also prepared from a 1:1 mixture of **153a** and **153b** using the same procedure.

**Physical state:** white amorphous solid

**TLC (hexanes/ethyl acetate 2:1):**  $R_f$  0.5 (UV, CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ , characteristic peaks):**  $\delta$  7.65 (dd,  $J$  = 7.8, 1.5 Hz, 1H), 7.59 (ddd,  $J$  = 8.6,

7.2, 1.5 Hz, 1H), 7.09–7.03 (m, 2H), 6.14 (dd,  $J$  = 10.0, 2.9 Hz, 1H), 5.71 (dd,  $J$  = 8.6, 4.2 Hz, 1H), 5.40 (dd,  $J$  = 10.0, 2.6 Hz, 1H), 4.00 (s, 1H), 3.91 (s, 2H), 3.75–3.68 (m, 1H), 3.24 (ddd,  $J$  = 11.0, 8.8, 5.2 Hz, 1H), 2.46 (d,  $J$  = 10.9 Hz, 1H), 1.70 (s, 3H), 1.39 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.60 (d,  $J$  = 5.8 Hz, 1H), 0.18 (s, 9H), 0.13 (s, 9H) ppm

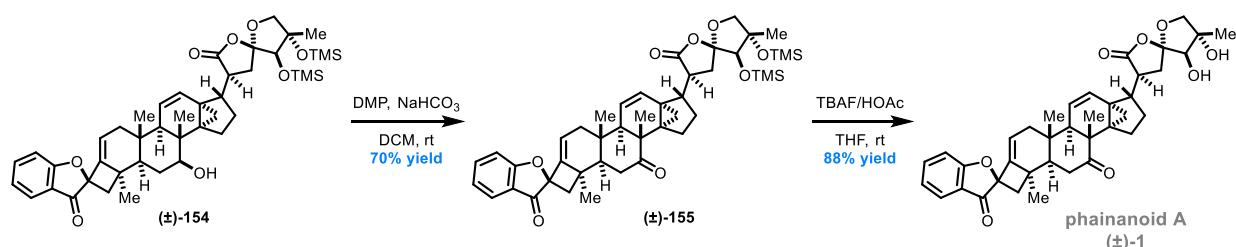
**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  198.89, 177.94, 170.82, 144.19, 137.97, 129.92, 124.91, 122.31, 121.99, 121.01, 120.90, 112.94, 110.86, 93.61, 84.23, 79.85, 79.08, 78.86, 53.72, 49.87, 44.55, 41.07, 40.10, 39.91, 38.76, 38.47, 38.11, 33.03, 29.52, 28.60, 28.02, 25.72, 23.21, 22.84, 22.68, 14.79, 14.27, 11.77, 2.16, 0.56 ppm

**IR (neat):**  $\nu$  3409, 2957, 2926, 2854, 1782, 1719, 1613, 1464, 1253, 1141, 1020, 890, 844, 757  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{44}\text{H}_{60}\text{O}_8\text{Si}_2\text{Na}^+$  [M+Na]<sup>+</sup> 795.3719, found 795.3718

$[\alpha]_D^{22}$  (**154**): +43 ( $c$  = 0.4,  $\text{CHCl}_3$ )

### Synthesis of ( $\pm$ )-Phainanoid A



Alcohol ( $\pm$ )-**154** (1.0 mg, 0.0013 mmol) was dissolved in DCM (0.2 mL), followed by sequential addition of  $\text{NaHCO}_3$  (2 mg, 0.024 mmol) and Dess-Martin periodinane (1 mg, 0.0024 mmol). The reaction mixture was stirred at room temperature for 25 minutes and directed loaded on silica gel column after TLC analysis indicated full conversion of ( $\pm$ )-**154**. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 5:1) gave the corresponding ketone ( $\pm$ )-**155** as a white foam (0.7 mg, 70% yield). The ketone was then treated with a solution of 1:1 TBAF/HOAc (0.3 mL, 0.01 M in THF) at room temperature. The reaction mixture was stirred at the same temperature until TLC analysis indicated full conversion of the substrate (ca. 15 minutes), and it was diluted with 1 mL toluene. The whole reaction mixture was directly loaded on a silica gel column and purification by flash chromatography (silica gel, toluene/acetone = 5:1 → 3:1) delivered the racemic natural product ( $\pm$ )-**1** as a white solid (0.5 mg, 88% yield). In practice, enantio-enriched **1** was also prepared from **154** using the same procedure.

**Physical state:** white solid

**TLC (toluene/acetone 2:1):**  $R_f$  0.55 (UV, CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.66 (dd,  $J$  = 8.0, 1.4 Hz, 1H), 7.61 (ddd,  $J$  = 8.6, 7.2, 1.5 Hz, 1H), 7.10–7.06 (m, 2H), 6.24 (dd,  $J$  = 9.9, 3.0 Hz, 1H), 5.77 (dd,  $J$  = 8.6, 4.1 Hz, 1H), 5.43 (dd,  $J$  = 9.9, 2.6 Hz, 1H),

4.04 (d,  $J = 10.1$  Hz, 1H), 3.96 (d,  $J = 9.6$  Hz, 1H), 3.93 (d,  $J = 9.5$  Hz, 1H), 3.30 (td,  $J = 10.1, 5.4$  Hz, 1H), 2.73 (dd,  $J = 14.7, 13.7$  Hz, 1H), 2.55–2.49 (m, 1H), 2.47 (d,  $J = 11.1$  Hz, 1H), 2.36 (d,  $J = 10.1$  Hz, 2H), 2.31 (dd,  $J = 14.9, 8.8$  Hz, 1H), 2.24 (dd,  $J = 13.3, 2.7$  Hz, 1H) 2.23 (d,  $J = 11.1$  Hz, 1H), 2.21–2.16 (m, 1H), 2.08–1.98 (m, 3H), 1.85 (br s, 1H), 1.71 (dd,  $J = 15.0, 2.7$  Hz, 1H), 1.69 (s, 3H), 1.68–1.64 (m, 1H), 1.51 (dd,  $J = 14.9, 4.1$  Hz, 1H), 1.43 (s, 3H), 1.24 (s, 3H), 1.24 (d,  $J = 6.3$  Hz, 1H), 1.18 (s, 3H), 1.13–1.07 (m, 1H), 0.82 (d,  $J = 6.2$  Hz, 1H) ppm

**$^{13}\text{C}$ -NMR (126 MHz, CDCl<sub>3</sub>):** δ 212.8, 198.5, 177.2, 170.8, 144.3, 138.1, 131.2, 125.0, 122.2, 120.9, 120.8, 120.7, 112.9, 111.8, 93.0, 83.2, 78.6, 77.5, 55.6, 51.0, 48.4, 44.6, 41.4, 41.1, 40.8, 39.6, 37.9, 36.3, 35.7, 32.3, 32.1, 27.4, 25.3, 23.5, 21.7, 17.2, 14.4, 14.1 ppm

**IR (neat):**  $\nu$  3421, 2959, 2926, 2854, 1777, 1712, 1612, 1464, 1259, 1139, 1093, 1028, 973, 909, 803, 759 cm<sup>-1</sup>

**HRMS (ESI-TOF):**  $m/z$  calcd for C<sub>38</sub>H<sub>43</sub>O<sub>8</sub><sup>+</sup> [M+H]<sup>+</sup> 627.2952, found 627.2952

**[ $\alpha$ ]<sub>D</sub><sup>22</sup> (1):** +6.3 ( $c = 0.32$ , CHCl<sub>3</sub>)

**Table S6.** Comparison of  $^1\text{H}$ -NMR data for phainanoid A

Proton #	Natural Phainanoid A <sup>1</sup> $^1\text{H}$ -NMR, 400 MHz, $\text{CDCl}_3$ $^1\text{H} [\delta, \text{multi.}, J (\text{Hz})]$	Synthetic Phainanoid A (This Work) $^1\text{H}$ -NMR, 500 MHz, $\text{CDCl}_3$ $^1\text{H} [\delta, \text{multi.}, J (\text{Hz})]$
1 $\alpha$	1.51 (dd, 14.9, 4.1)	1.52 (dd, 14.9, 4.1)
1 $\beta$	2.31 (dd, 14.9, 8.6)	2.31 (dd, 14.9, 8.8)
2	5.77 (dd, 8.6, 4.1)	5.77 (dd, 8.6, 4.1)
5	1.71 (dd, 14.9, 2.6)	1.71 (dd, 14.5, 2.7)
6 $\alpha$	2.24 (dd, 13.4, 2.6)	2.25 (dd, 13.3, 2.7)
6 $\beta$	2.73 (dd, 14.9, 13.4)	2.73 (dd, 14.7, 13.7)
9	2.01 (dd, 2.9, 2.5)	2.01 (m)
11	5.43 (dd, 9.9, 2.5)	5.43 (dd, 9.9, 2.6)
12	6.24 (dd, 9.9, 2.9)	6.24 (dd, 9.9, 3.0)
15 $\alpha$	2.19 (m)	2.19 (m)
15 $\beta$	2.01 (m)	2.01 (m)
16 $\alpha$	1.11 (m)	1.10 (m)
16 $\beta$	1.67 (m)	1.67 (m)
17	2.52 (m)	2.52 (m)
18	1.18 (s)	1.18 (s)
19	1.23 (s)	1.24 (s)
20	3.30 (td, 10.1, 5.4)	3.30 (td, 10.1, 5.4)
22	2.36 (d, 10.1, 2H)	2.36 (d, 10.1, 2H)
24	4.04 (d, 10.9)	4.04 (d, 10.1)
26 $\alpha$	3.96 (d, 9.6)	3.96 (d, 9.6)
26 $\beta$	3.93 (d, 9.6)	3.93 (d, 9.5)
27	1.43 (s)	1.43 (s)
28	1.69 (s)	1.69 (s)
29 $\alpha$	2.23 (d, 11.2)	2.23 (d, 11.2)
29 $\beta$	2.47 (d, 11.2)	2.47 (d, 11.1)
30a	0.82 (d, 6.2)	0.82 (d, 6.2)
30b	1.24 (d, 6.2)	1.24 (d, 6.3)
4'	7.66 (dd, 7.7, 1.4)	7.66 (dd, 8.0, 1.4)
5'	7.08 (br dd, 7.7, 7.3)	7.08 (m)
6'	7.61 (ddd, 8.3, 7.3, 1.4)	7.61 (ddd, 8.6, 7.2, 1.5)
7'	7.08 (br d, 8.3)	7.08 (m)

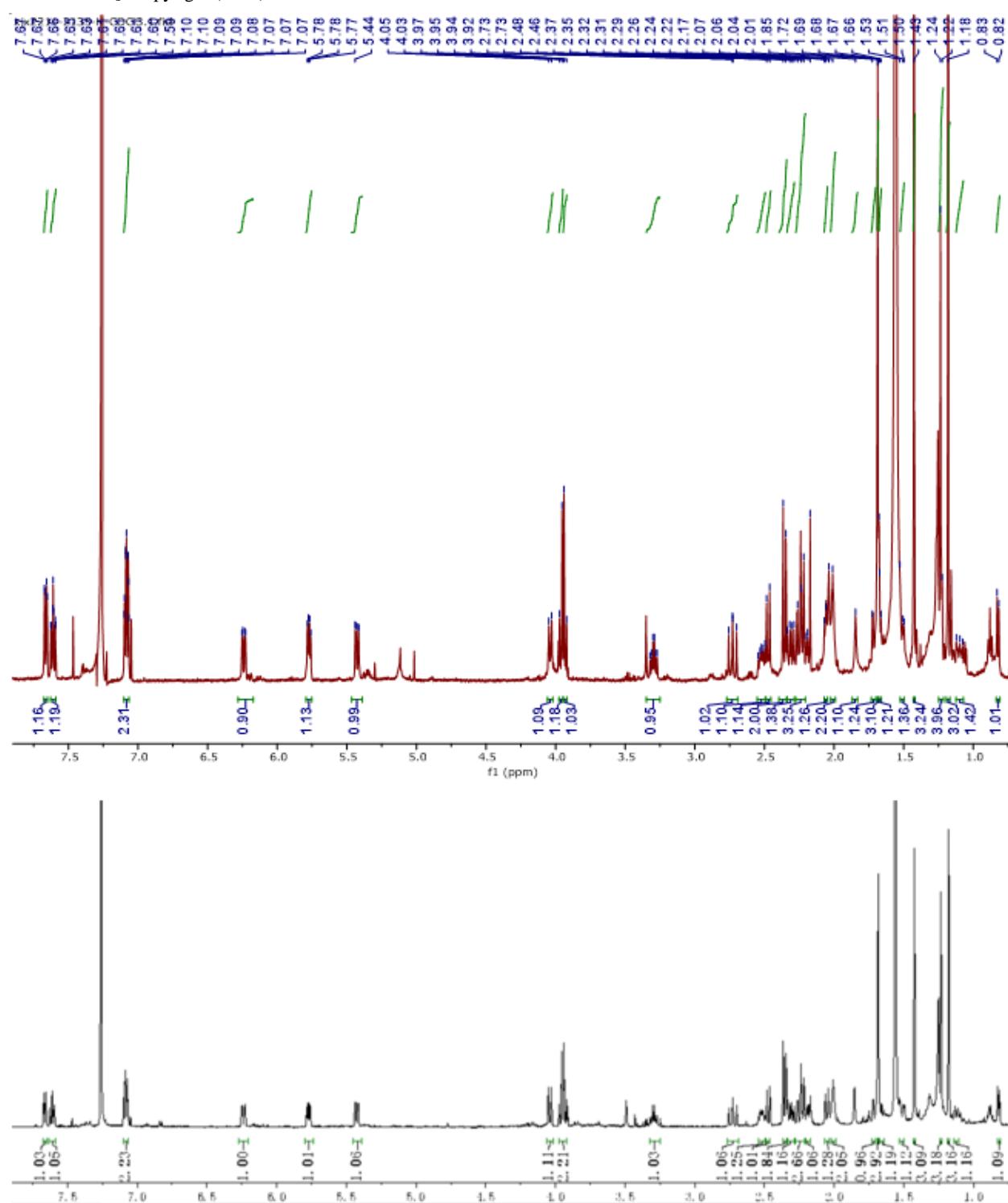
Note: This table is adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

**Table S7.** Comparison of  $^{13}\text{C}$ -NMR data for phainanoid A

Carbon #	Natural Phainanoid A <sup>1</sup> $^{13}\text{C}$ -NMR, 125 MHz, $\text{CDCl}_3$ $^{13}\text{C}$ ( $\delta$ ) ppm	Synthetic Phainanoid A (This Work) $^{13}\text{C}$ -NMR, 126 MHz, $\text{CDCl}_3$ $^{13}\text{C}$ ( $\delta$ ) ppm	Chemical Shift Difference, $\Delta\delta$ , ppm
1	37.8	37.9	0.1
2	120.7	120.7	0
3	144.3	144.3	0
4	44.6	44.6	0
5	55.6	55.6	0
6	35.7	35.7	0
7	212.8	212.8	0
8	48.4	48.4	0
9	51.0	51.0	0
10	41.1	41.1	0
11	120.9	120.9	0
12	131.2	131.2	0
13	32.0	32.1	0.1
14	36.2	36.3	0.1
15	27.3	27.4	0.1
16	23.5	23.5	0
17	41.3	41.4	0.1
18	17.2	17.2	0
19	14.4	14.4	0
20	40.8	40.8	0
21	177.2	177.2	0
22	32.3	32.3	0
23	111.8	111.8	0
24	83.2	83.2	0
25	77.5	77.5	0
26	78.6	78.6	0
27	21.7	21.7	0
28	25.3	25.3	0
29	39.6	39.6	0
30	14.1	14.1	0
1'	93.0	93.0	0
2'	198.5	198.5	0
3'	120.8	120.8	0
4'	125.0	125.0	0
5'	122.2	122.2	0
6'	138.1	138.1	0
7'	112.9	112.9	0
8'	170.8	170.8	0

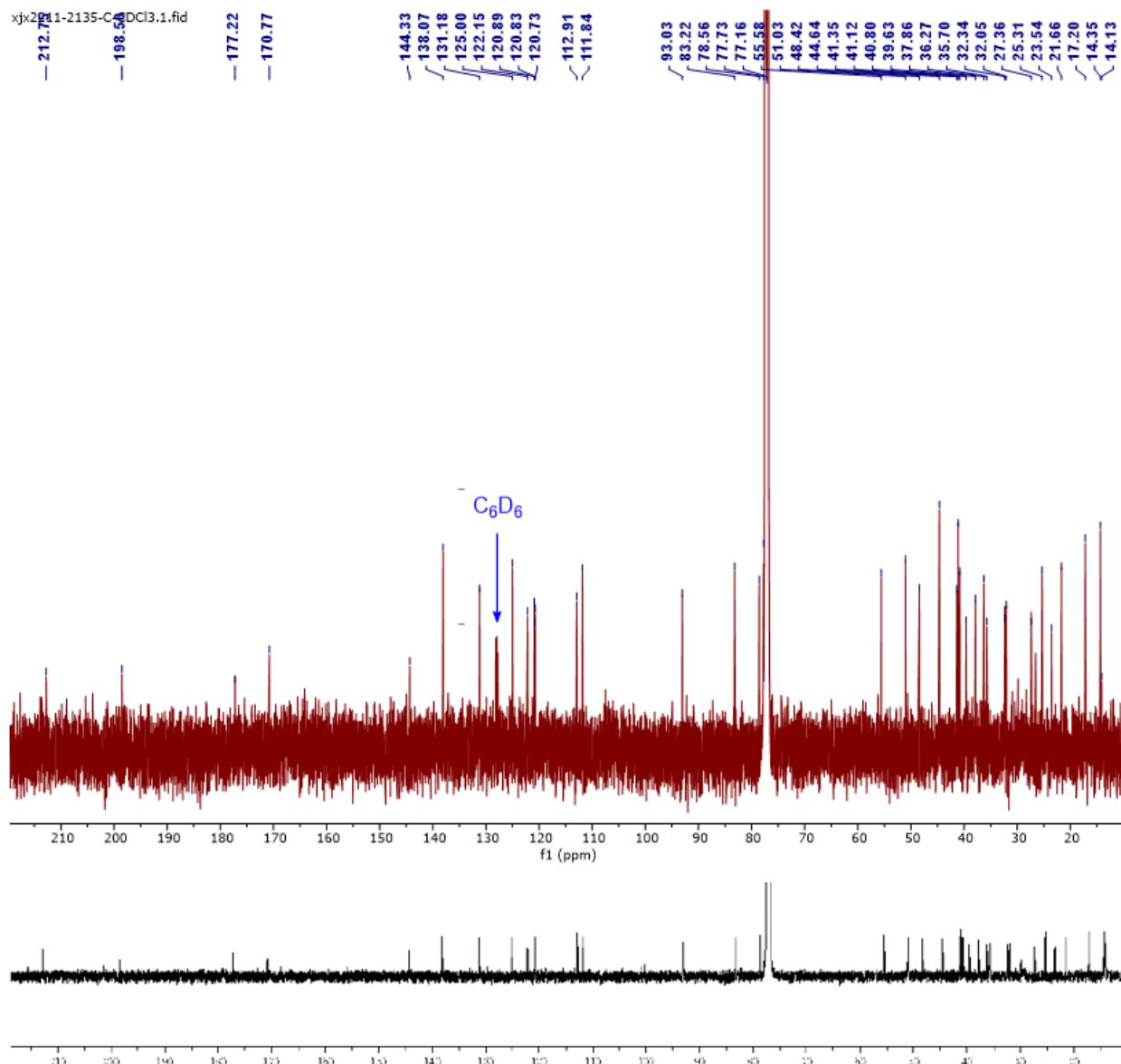
Note: This table is adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, 143,

19311–19316]. Copyright (2021) of ACS Publications.



**Figure S1.** Comparison of <sup>1</sup>H-NMR spectra for phainanoid A. (Top: <sup>1</sup>H-NMR spectrum of synthetic phainanoid A; Bottom: <sup>1</sup>H-NMR spectrum of natural phainanoid A<sup>1</sup>)

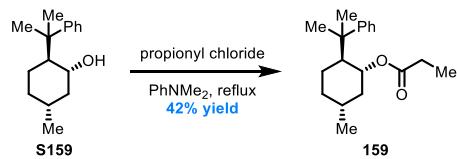
Note: This figure is adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.



**Figure S2.** Comparison of <sup>13</sup>C-NMR spectra for phainanoid A. (Top: <sup>13</sup>C-NMR spectrum of synthetic phainanoid A; Bottom: <sup>13</sup>C-NMR spectrum of natural phainanoid A<sup>1</sup>)

Note: This figure is adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

### Synthesis of ester 159



To a solution of **S159** (20.75 g, 89.3 mmol) in ether (100 mL) was sequentially added PhNMe<sub>2</sub> (14.07 g,

116 mmol) and propionyl chloride (9.3 mL, 107 mmol). The reaction mixture was heated to reflux for 12 hours before it was cooled down and transferred to a separatory funnel. It was sequentially washed with a 1 N HCl solution and saturated NaHCO<sub>3</sub> solution. The resulting solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave **159** as a colorless oil (10.85 g, 42% yield).

**Physical state:** colorless oil

**TLC (hexanes/ethyl acetate 4:1):** R<sub>f</sub> 0.5 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.29–7.26 (m, 4H), 7.17–7.09 (m, 1H), 4.82 (td, J = 10.7, 4.5 Hz, 1H), 2.01 (ddd, J = 12.3, 10.6, 3.6 Hz, 1H), 1.87–1.76 (m, 2H), 1.72–1.60 (m, 3H), 1.52–1.40 (m, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 1.10 (qd, J = 13.0, 3.4 Hz, 1H), 0.99–0.81 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H) ppm

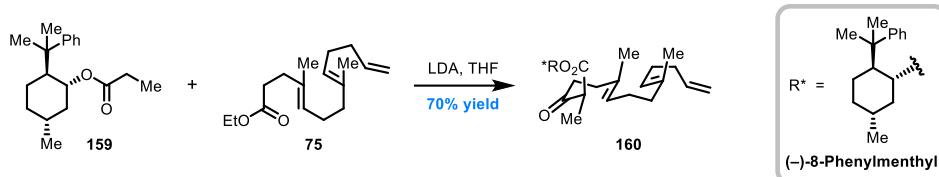
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 173.80, 151.79, 127.97, 125.49, 125.13, 73.95, 50.51, 41.95, 39.81, 34.71, 31.40, 28.11, 27.64, 26.70, 25.03, 21.92, 8.88 ppm

**IR (neat):** ν 3057, 3021, 2955, 2918, 2872, 1732, 1600, 1457, 1368, 1197, 1086, 764 cm<sup>-1</sup>

**HRMS (ESI-TOF):** m/z calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 311.1982, found 311.1986

[α]<sub>D</sub><sup>22</sup>: -2.2 (c = 1.34, CHCl<sub>3</sub>)

### Synthesis of β-ketoester **160**



Diisopropylamine (0.29 mL, 2.08 mmol) was dissolved in THF (2 mL), and the solution was cooled to 0 °C. n-BuLi (2.5 M in hexanes, 0.83 mL, 2.08 mmol) was added slowly and the resulting yellow solution was stirred for 1 h at 0 °C and then cooled to -78 °C. A solution of **159** (600 mg, 2.08 mmol) in THF (4 mL) was added dropwise and the reaction mixture was stirred for additional 45 min at -78 °C. The ester **75** (220 mg, 0.832 mmol) in THF (2 mL) was added dropwise to the solution. The reaction mixture was stirred at -78 °C for additional 1 h and then warmed up to room temperature overnight. After 12 h, the reaction was diluted with Et<sub>2</sub>O and quenched with a 1 N HCl solution until pH < 3. The layers were separated, and the aqueous layer was extracted with ether (10 mL × 3). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ether = 40:1) gave **160** as a colorless to pale-yellow oil (295 mg, 70% yield).

**Physical state:** colorless to pale-yellow oil

**TLC (hexanes/ether 10:1):**  $R_f$  0.4 (UV, CAM)

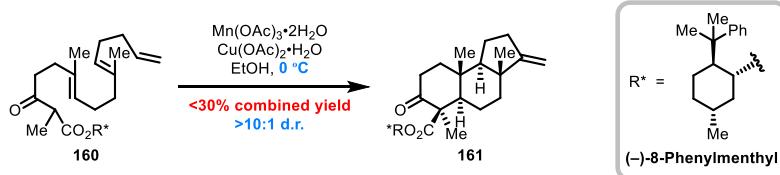
**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ , mixture of diastereomers and tautomers):**  $\delta$  7.33–7.26 (m, 4H), 7.19–7.08 (m, 1H), 5.90–5.76 (m, 1H), 5.21–5.06 (m, 2H), 5.02 (d,  $J = 17.2$  Hz, 1H), 4.98–4.92 (m, 1H), 4.89–4.79 (m, 1H), 2.67–2.45 (m, 1H), 2.39–2.19 (m, 2H), 2.15–2.01 (m, 8H), 2.02–1.95 (m, 2H), 1.91–1.77 (m, 1H), 1.71–1.64 (m, 1H), 1.63–1.55 (m, 6H), 1.50–1.41 (m, 1H), 1.33–1.26 (m, 3H), 1.24–1.13 (m, 4H), 1.13–1.04 (m, 3H), 0.98–0.83 (m, 6H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  206.08, 205.94, 170.34, 169.49, 152.15, 151.35, 138.80, 138.78, 135.31, 135.30, 133.60, 133.45, 128.08, 128.00, 125.57, 125.45, 125.34, 125.12, 124.97, 124.03, 124.02, 114.54, 114.51, 75.80, 74.91, 52.72, 52.18, 50.40, 50.20, 41.56, 41.35, 40.75, 40.38, 39.96, 39.71, 39.68, 39.60, 34.62, 34.57, 34.09, 33.33, 33.20, 31.39, 31.34, 29.32, 27.52, 26.95, 26.89, 26.74, 26.72, 26.53, 26.42, 23.50, 21.88, 21.87, 16.20, 12.75, 12.44 ppm

**IR (neat):**  $\nu$  3432, 3058, 2955, 2918, 1739, 1713, 1640, 1455, 1375, 1198, 809, 765, 701  $\text{cm}^{-1}$

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{34}\text{H}_{51}\text{O}_3^+$  [M+H]<sup>+</sup> 507.3833, found 507.3834

### Synthesis of chiral $\beta$ -ketoester **161**



$\beta$ -Ketoester **160** was dissolved in ethanol (0.1 M), and the solution was sparged with a continuous flow of N<sub>2</sub> or Ar for 3 hours. Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (2 equiv) and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 equiv) were added in one portion and the resulting dark slurry was stirred for 16 h at 0 °C under N<sub>2</sub> or Ar and eventually turned green (the color of Cu(OAc)<sub>2</sub>). The reaction was diluted with ethyl acetate and water before it was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution to give a yellow organic layer and a colorless aqueous layer. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 40:1) and multiple rounds of preparative TLC gave **161** as a colorless to pale-yellow oil.

**Physical state:** colorless to pale-yellow oil

**TLC (hexanes/ethyl acetate 8:1):**  $R_f$  0.5 (UV, CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.30–7.27 (m, 4H), 7.18–7.14 (m, 1H), 4.91 (td,  $J = 10.5, 4.3$  Hz, 1H), 4.59–4.58 (m, 1H), 4.59–4.54 (m, 1H), 2.91 (td,  $J = 14.6, 6.4$  Hz, 1H), 2.52 (ddq,  $J = 17.2, 9.8, 2.5$  Hz, 1H), 2.36 (ddd,  $J = 14.9, 4.7, 2.3$  Hz, 1H), 2.24 (dtt,  $J = 17.2, 8.9, 2.0$  Hz, 1H), 2.13–1.97 (m, 3H), 1.92 (dt,  $J =$

12.9, 3.3 Hz, 1H), 1.87 (ddd,  $J$  = 13.2, 6.5, 2.4 Hz, 1H), 1.72 (dq,  $J$  = 14.2, 3.3 Hz, 1H), 1.65–1.58 (m, 1H), 1.57–1.48 (m, 2H), 1.46–1.37 (m, 1H), 1.35 (s, 3H), 1.34–1.30 (m, 2H), 1.28 (s, 3H), 1.27–1.25 (m, 1H), 1.24 (s, 3H), 1.23–1.17 (m, 2H), 1.09 (s, 3H), 1.06–1.01 (m, 1H), 1.00 (s, 3H), 0.96–0.91 (m, 1H), 0.86 (d,  $J$  = 6.5 Hz, 3H), 0.83–0.71 (m, 1H) ppm

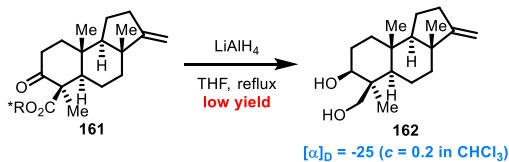
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 208.60, 173.46, 162.23, 150.61, 128.25, 125.86, 125.60, 100.41, 77.29, 59.99, 58.50, 58.47, 49.95, 44.50, 41.88, 40.39, 40.38, 37.53, 37.52, 36.83, 34.41, 31.51, 30.19, 28.95, 27.77, 24.47, 21.95, 21.73, 21.59, 21.28, 20.25, 14.37 ppm

**IR (neat):**  $\nu$  2954, 2923, 2872, 2853, 1719, 1458, 1384, 1228, 1189, 1138, 1088, 912, 733, 701 cm<sup>-1</sup>

**HRMS (ESI-TOF):** *m/z* calcd for C<sub>34</sub>H<sub>48</sub>O<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 527.3496, found 527.3496

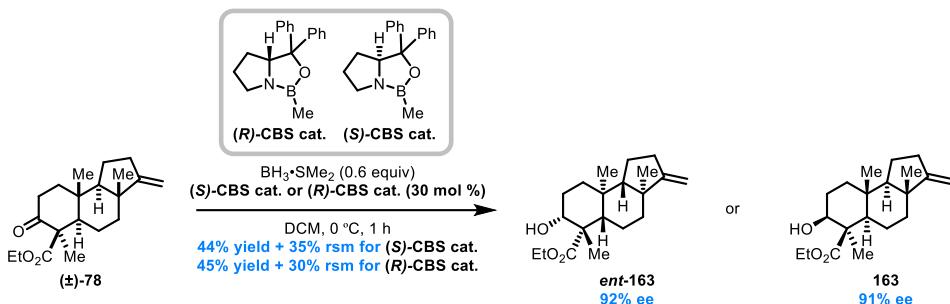
**[ $\alpha$ ]<sub>D</sub><sup>22</sup>:** -8.9 (*c* = 1.68, CHCl<sub>3</sub>)

### Synthesis of diol 162 from 161



To a suspension of LiAlH<sub>4</sub> (3.3 mg, 0.088 mmol) in anhydrous THF (0.5 mL) was slowly added a solution of **161** (22 mg, 0.044 mmol) in THF (0.5 mL) at 0 °C. The reaction was heated to reflux overnight. The reaction was carefully quenched with saturated NaCl solution followed by addition of a 3 N HCl solution to reach acidic pH ~ 1. The layers were separated, and the aqueous layer was extracted with ether (5 mL × 3). The combined extracts were washed sequentially with saturated NaHCO<sub>3</sub> and NaCl solutions, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 15:1 → 1:1) gave diol **162** as a colorless oil (2.4 mg, 20% yield), which displayed a specific rotation of -25 (*c* = 0.2, CHCl<sub>3</sub>).

### Synthesis of chiral alcohols *ent*-163 and 163



A flame-dried 500-mL round bottom flask equipped with a magnetic stir bar was charged with (*R*)-CBS catalyst (1.3 g, 4.71 mmol) in the glovebox. The flask was taken out the glovebox before the sequential

addition of dry DCM (250 mL) and a solution of  $\text{BH}_3\cdot\text{SMe}_2$  in THF (2 M, 4.4 mL, 8.8 mmol). The reaction mixture was stirred at room temperature for 20 minutes and cooled down to 0 °C in an ice-water bath. A solution of ( $\pm$ )-**78** (5 g, 15.7 mmol) in DCM (60 mL) was slowly added via dropping funnel over 20 minutes. The reaction mixture was stirred at the same temperature for another 1 hours and quenched with the sequential addition of methanol and water, during which the evolution of  $\text{H}_2$  was observed. The layers were separated, and the aqueous layer was extracted with DCM (100 mL  $\times$  3). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexanes/ethyl acetate = 20:1) gave **163** as a colorless oil (2.242 g, 45% yield), which turned into a white solid in the freezer, and recovered **78** as a colorless oil (1.489 g, 30% yield). By using the (*S*)-CBS catalyst, the preparation of *ent*-**163** was accomplished at 1 mmol scale under otherwise identical conditions (44% yield + 35% recovery of **78**). The ee of the products was determined by chiral HPLC analysis of their *p*-bromobenzoate derivatives **164** and *ent*-**164**, respectively, using Chiraldpak IF column (hexane:isopropanol = 99:1, 0.7 mL/min, 260 nm,  $t_{5.31} = 12.3$  min,  $t_{\text{ent-}5.31} = 10.6$  min).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 8:1):**  $R_f$  0.5 ( $\text{KMnO}_4$ , CAM)

**$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.57–4.53 (m, 2H), 4.19–4.11 (m, 2H), 3.41 (br s, 1H), 3.06 (dd,  $J = 11.7$ , 3.5 Hz, 1H), 2.49 (ddq,  $J = 17.3$ , 10.1, 2.3 Hz, 1H), 2.26–2.16 (m, 1H), 2.08–1.84 (m, 4H), 1.82–1.72 (m, 1H), 1.62 (ddd,  $J = 13.3$ , 4.3, 2.8 Hz, 1H), 1.59–1.53 (m, 1H), 1.50–1.44 (m, 1H), 1.41 (s, 3H), 1.31 (t,  $J = 7.2$  Hz, 3H), 1.22–1.15 (m, 1H), 1.11–1.03 (m, 1H), 1.00 (dd,  $J = 13.0$ , 6.4 Hz, 1H), 0.95–0.92 (m, 1H), 0.91 (s, 3H), 0.76 (s, 3H) ppm

**$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  178.05, 162.71, 100.16, 78.74, 60.57, 60.42, 56.99, 49.07, 44.41, 39.14, 37.76, 37.43, 29.03, 28.25, 23.87, 21.36, 21.06, 20.22, 14.24, 13.69 ppm

**IR (neat):**  $\nu$  3537, 3066, 2951, 2912, 2852, 1701, 1654, 1457, 1375, 1236, 1181, 1051, 1024, 877  $\text{cm}^{-1}$

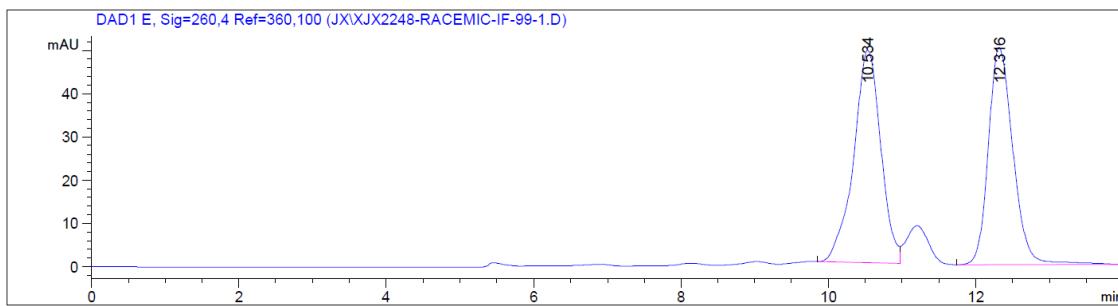
**MP:** 53–55 °C

**HRMS (ESI-TOF):**  $m/z$  calcd for  $\text{C}_{20}\text{H}_{33}\text{O}_3^+$  [M+H]<sup>+</sup> 321.2424, found 321.2424

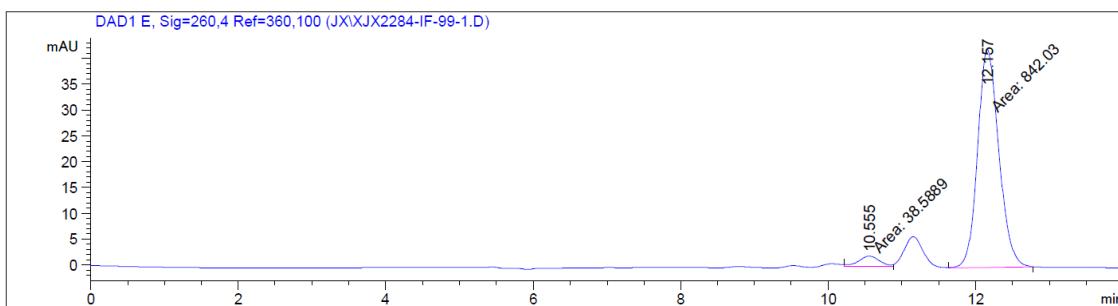
**$[\alpha]_D^{22}$  (**163** at 91% ee):** +11 ( $c = 0.45$ ,  $\text{CHCl}_3$ )

**$[\alpha]_D^{22}$  (*ent*-**163** at 92% ee):** -17 ( $c = 1.0$ ,  $\text{CHCl}_3$ )

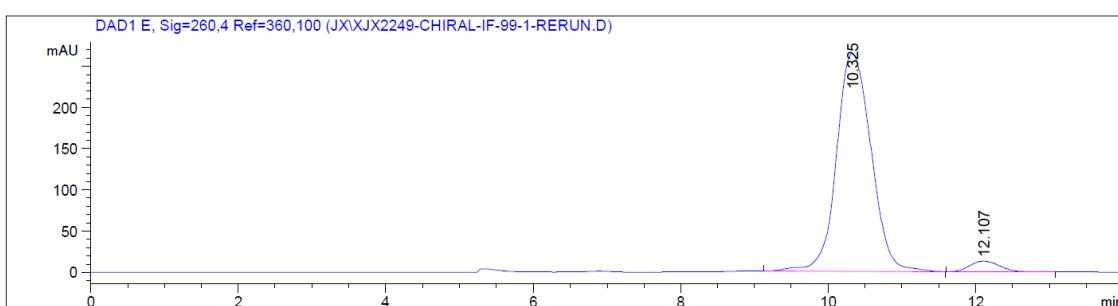
**Table S8.** HPLC trace for the racemic sample ( $\pm$ )-**163** (prepared from **78** using the following conditions:  $\text{NaBH}_4$ , MeOH, 0 °C)



**Table S9.** HPLC trace for the enantiomeric sample **163**

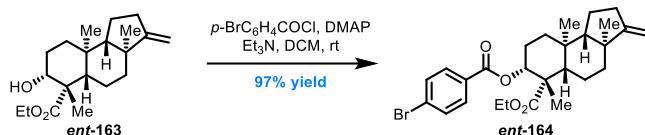


**Table S10.** HPLC trace for the enantiomeric sample **ent-163**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.325	BB	0.5217	8652.68066	264.49484	95.9841
2	12.107	BB	0.4523	362.01865	12.86334	4.0159

### Synthesis of ester *ent*-164



A 2-mL vial equipped with a magnetic stir bar was sequentially charged with *ent*-163 (14.4 mg, 0.045 mmol), DMAP (0.5 mg, 0.054 mmol), Et<sub>3</sub>N (15 µL, 0.108 mmol), *p*-bromobenzoyl chloride (11.9 mg, 0.054 mmol) and DCM (0.4 mL). The vial was sealed and stirred at room temperature for 4 hours, during which the resulting white slurry gradually turned yellow. Upon indication of full conversion of *ent*-163 by TLC, the reaction mixture was directly loaded on a silica gel column and purified by flash chromatography to give *ent*-164 as a white solid (22.0 mg, 97% yield).

**Physical state:** white solid

**TLC (hexanes/ethyl acetate 8:1):** R<sub>f</sub> 0.7 (UV, CAM)

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.91 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 4.75 (dd, J = 12.0, 4.7 Hz, 1H), 4.60–4.55 (m, 2H), 4.27 (dq, J = 10.9, 7.1 Hz, 1H), 4.16 (dq, J = 10.9, 7.2 Hz, 1H), 2.56–2.43 (m, 2H), 2.25 (dddd, J = 17.2, 9.1, 5.1, 1.9 Hz, 1H), 1.99–1.77 (m, 4H), 1.69 (ddd, J = 13.3, 4.2, 2.9 Hz, 1H), 1.63–1.45 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.28–1.18 (m, 2H), 1.14 (dd, J = 12.0, 2.7 Hz, 1H), 1.10–1.03 (m, 1H), 0.92 (s, 3H), 0.84 (s, 3H) ppm

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ 174.07, 165.70, 162.55, 131.82, 131.38, 129.65, 128.13, 100.26, 80.26, 60.63, 60.31, 57.15, 48.32, 44.50, 38.46, 37.73, 37.41, 29.04, 24.19, 24.13, 21.46, 20.80, 20.24, 14.41, 13.76 ppm

**IR (neat):** ν 2957, 2923, 2851, 1718, 1384, 1273, 1174, 1114, 1101, 1012 cm<sup>-1</sup>

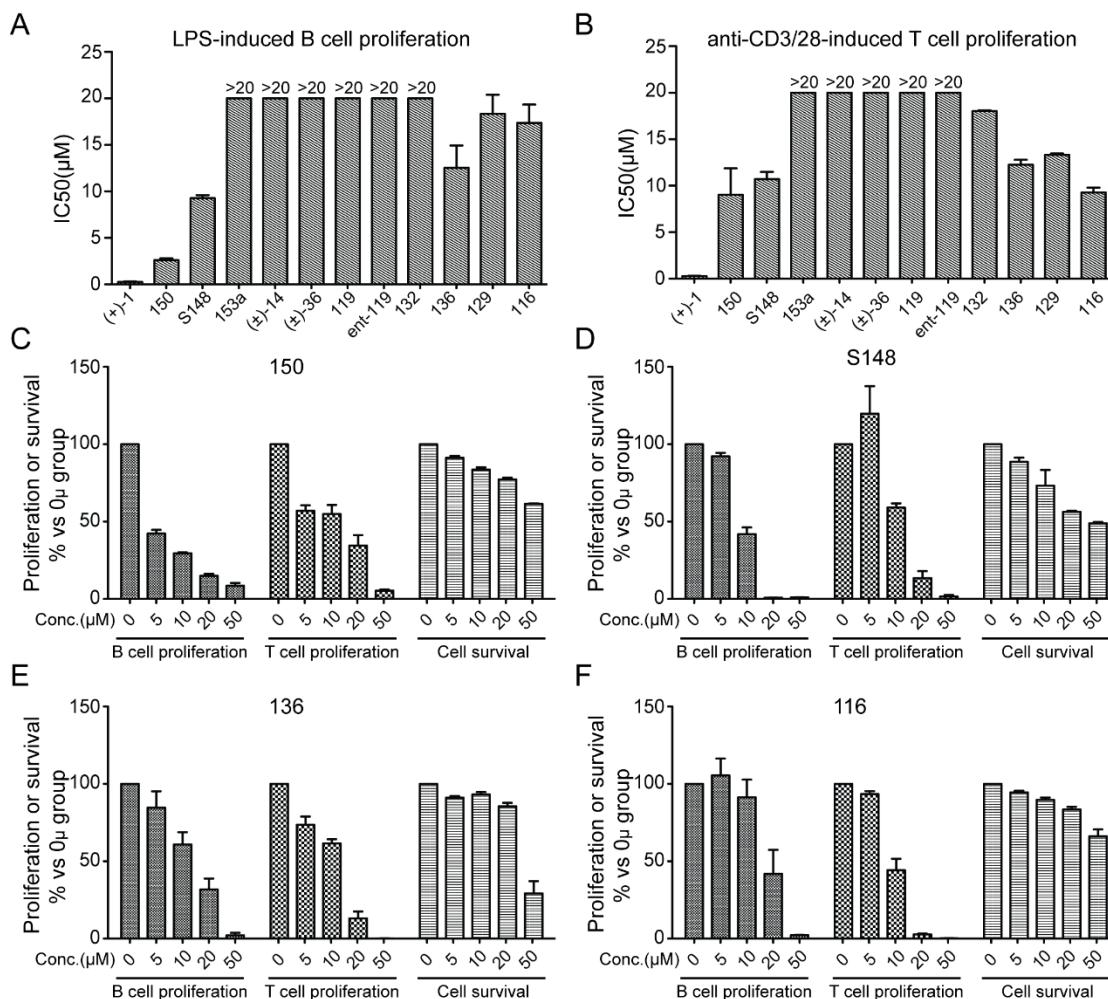
**MP:** 127–129 °C

**HRMS (ESI-TOF):** m/z calcd for C<sub>27</sub>H<sub>36</sub>O<sub>4</sub><sup>81</sup>Br<sup>+</sup> [M+H]<sup>+</sup> 505.1771, found 505.1769

**[α]<sub>D</sub><sup>22</sup>:** -22 (c = 1.0, CHCl<sub>3</sub>)

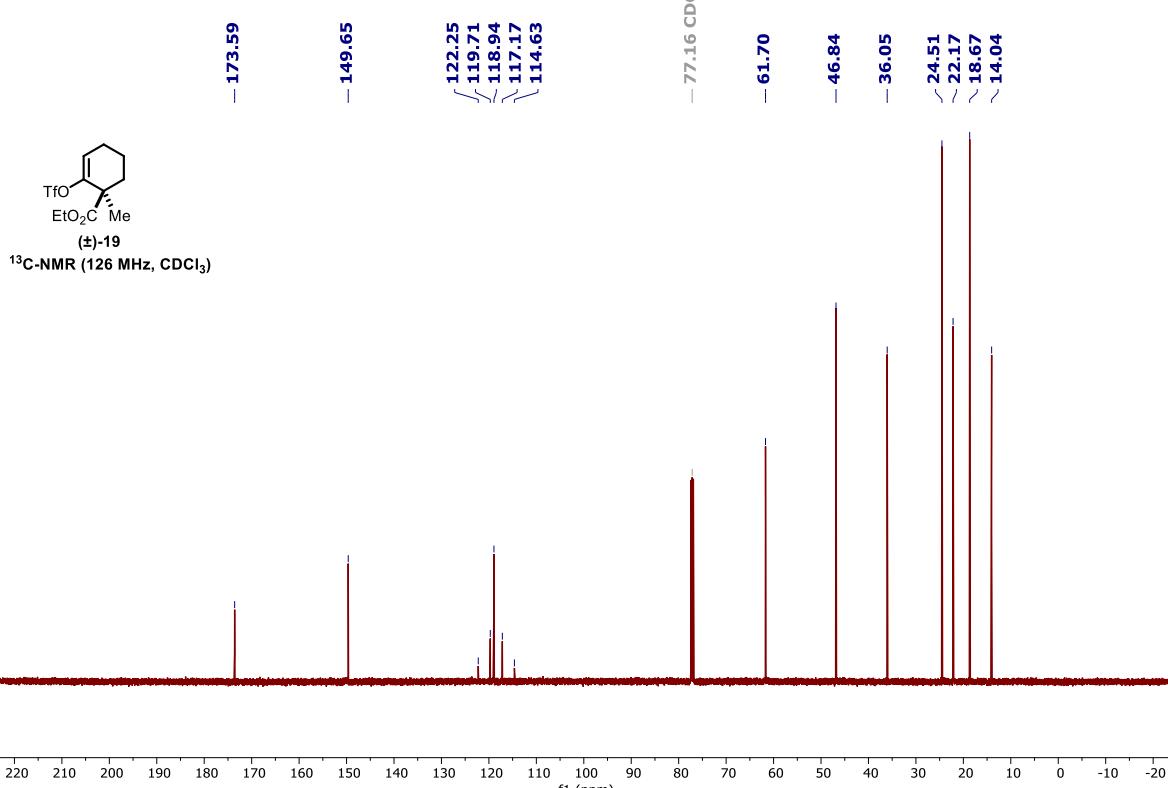
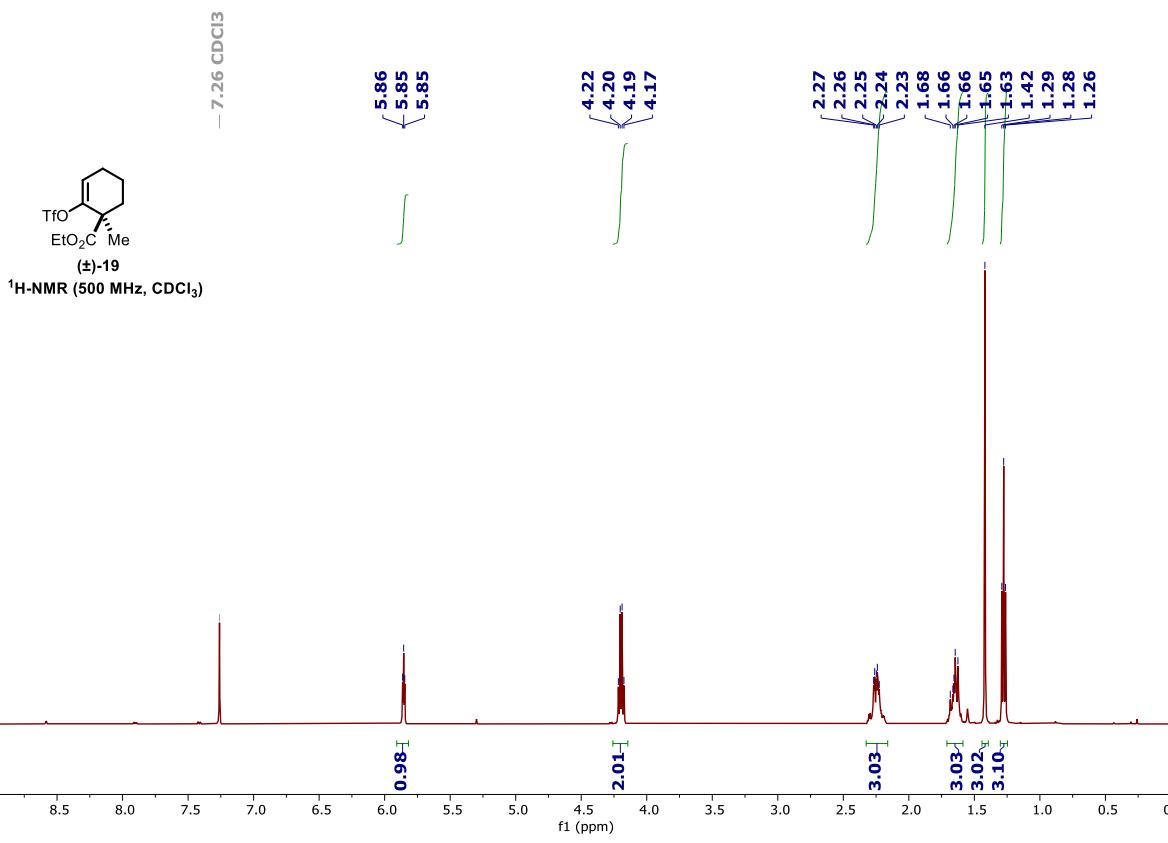
## 6. Bioassays of the Natural Product and Its Synthetic Analogues

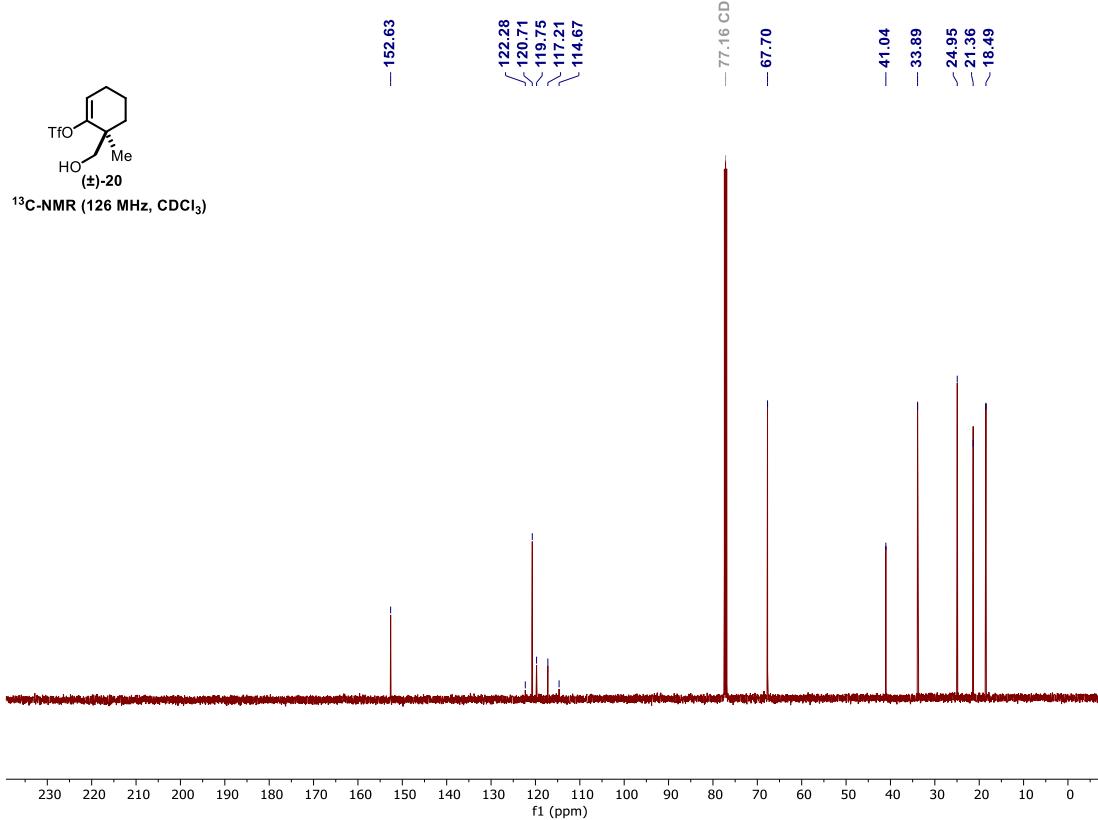
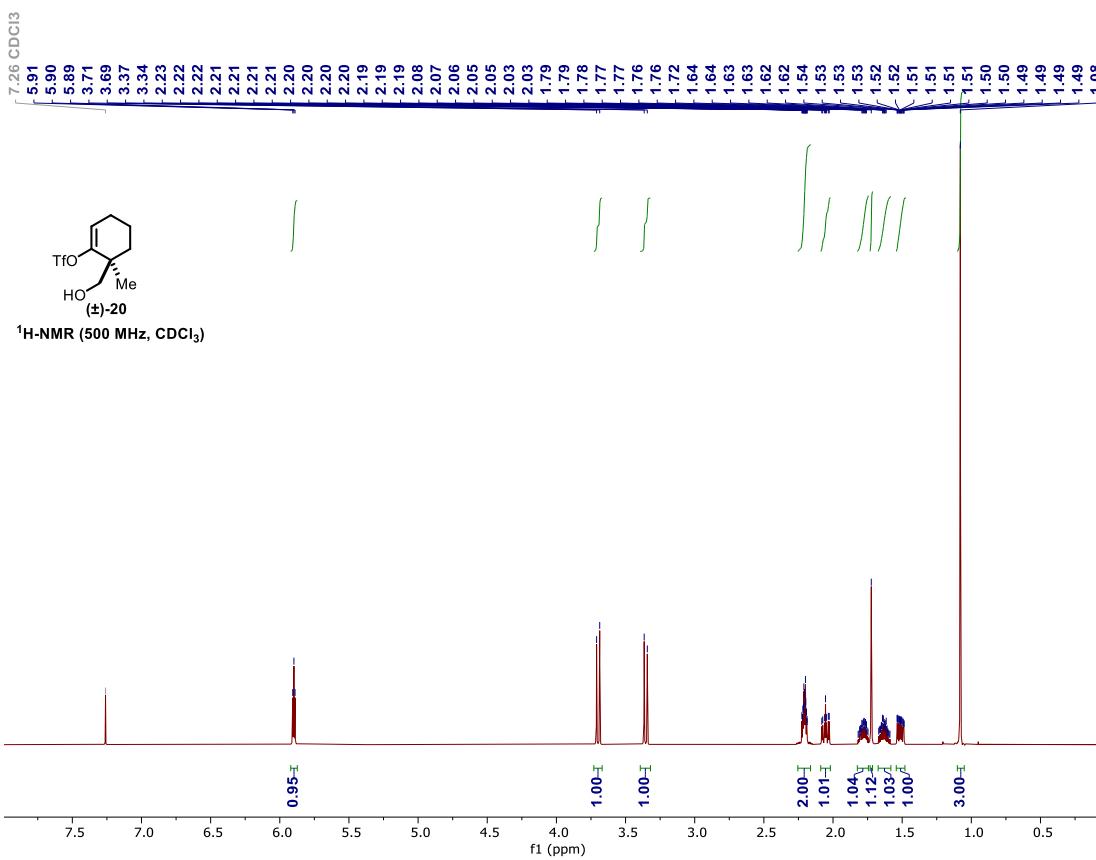
C57Bl6/j mice were originally purchased from the Jackson Laboratory and bred in house. All mice were housed in a specific pathogen-free facility and used at 6~12 weeks of age. Both males and females were used. All the experiments were approved by the University of Chicago Institutional Animal Care and Use Committee (IACUC). For evaluating B cell or CD4 T cell proliferation, whole splenocytes from mice were labeled with CFSE (CellTrace) and cultured in presence of 10  $\mu$ g/mL LPS or 1 $\mu$ g/mL pre-coated anti-CD3 (BioLegend) +0.5 $\mu$ g/mL anti-CD28 (BioLegend) for 72 hours, before CFSE dilution was evaluated in CD19 $^+$ B220 $^+$  B cells or CD3 $^+$ CD4 $^+$  T cells, respectively, by flow cytometry. Monoclonal antibodies for flow cytometry against mouse B220 (RA3-6B2), CD19 (1D3), Ig $\kappa$  (RMK-45), CD4 (GK1.5) and CD3 (17A2) were all from Biolegend. For evaluating the effect of chemicals on cell survival, CD4 T cells were enriched with a commercial kit (Miltenyi Biotech) and cultured without stimulation for 24 hours. The live and death of cells were evaluated by 7-AAD (BioLegend) staining.

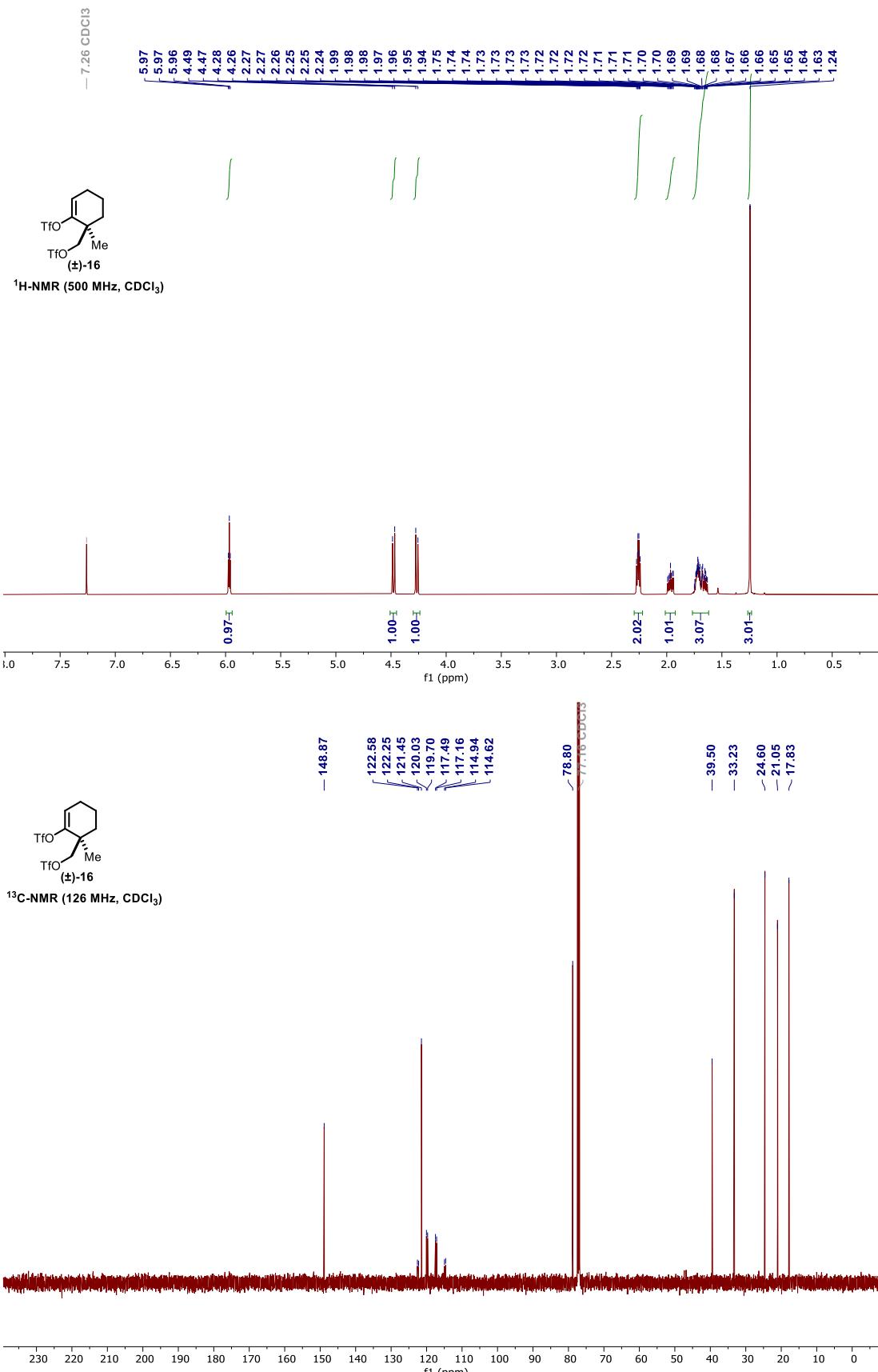


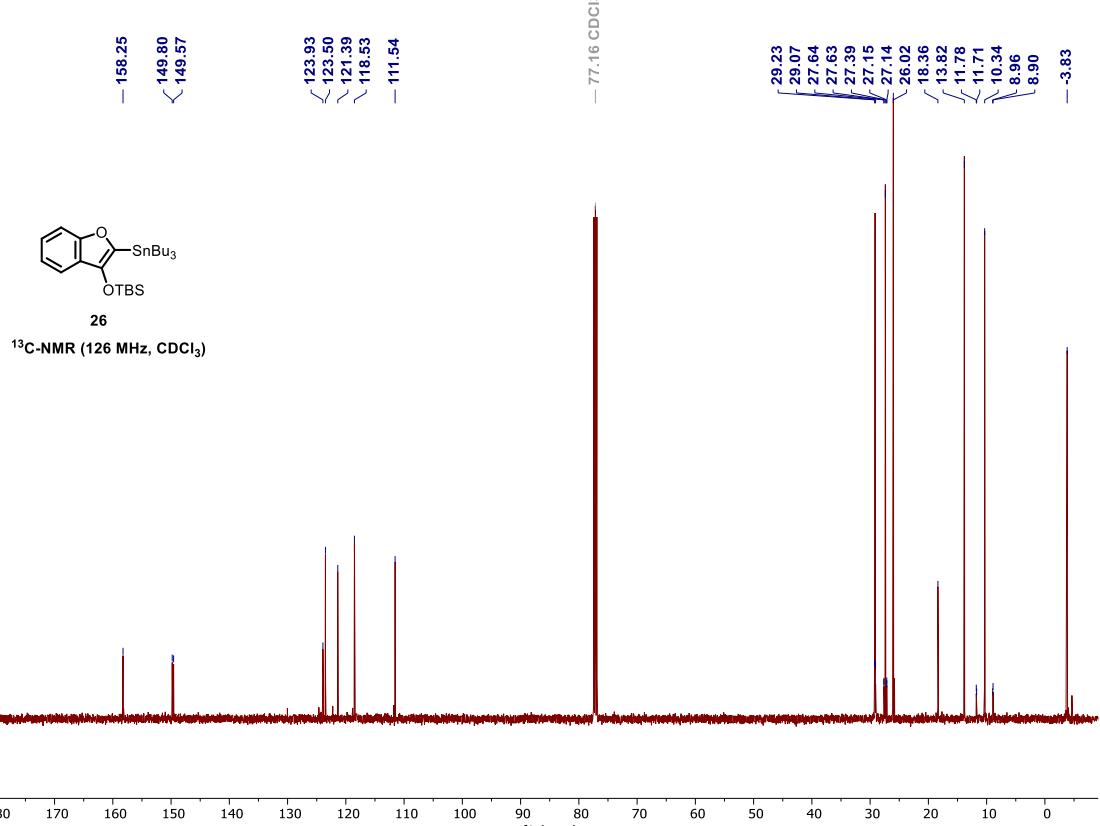
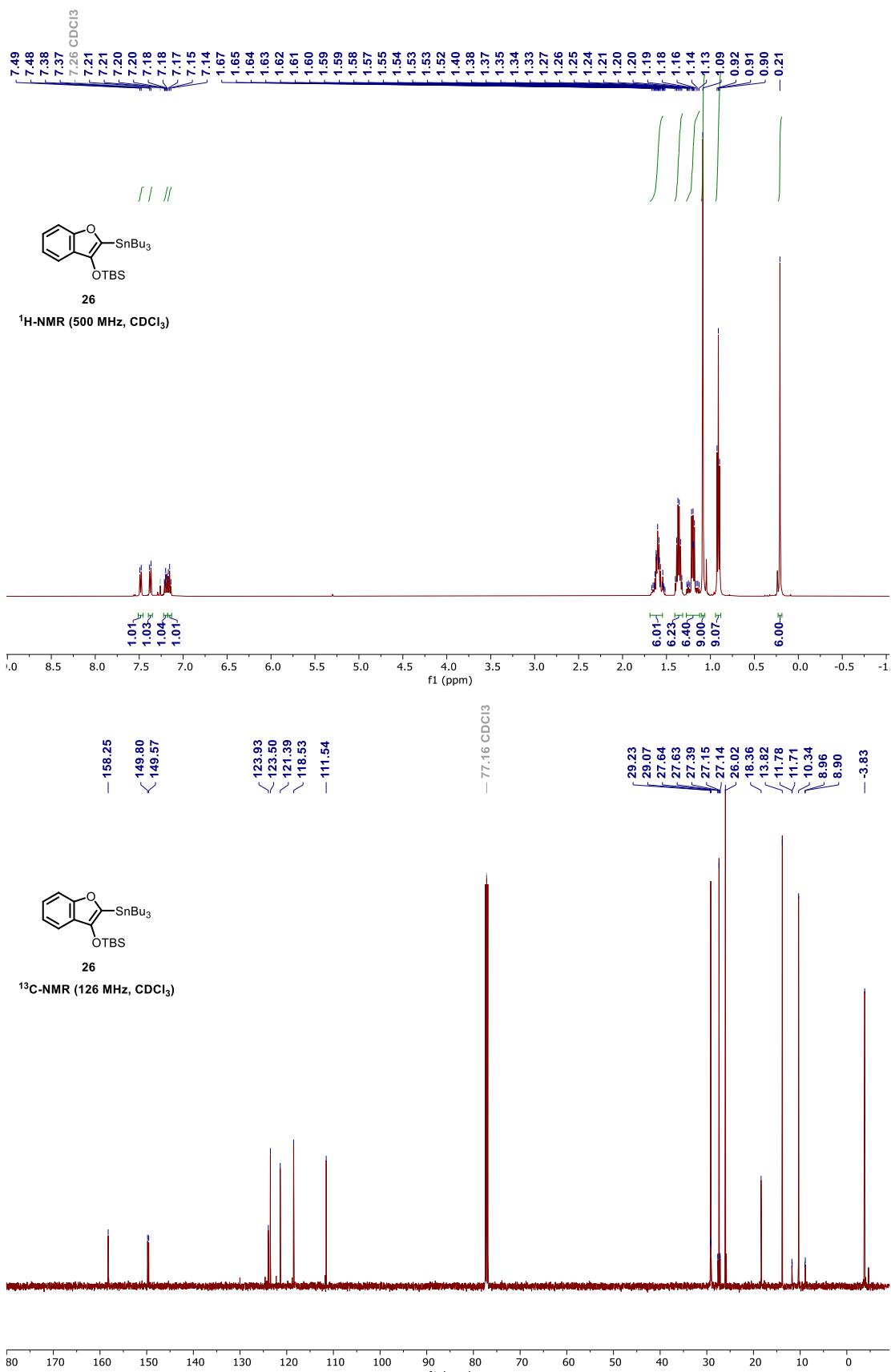
**Figure S3.** Immunosuppressive and cell survival assays of selected synthetic analogues

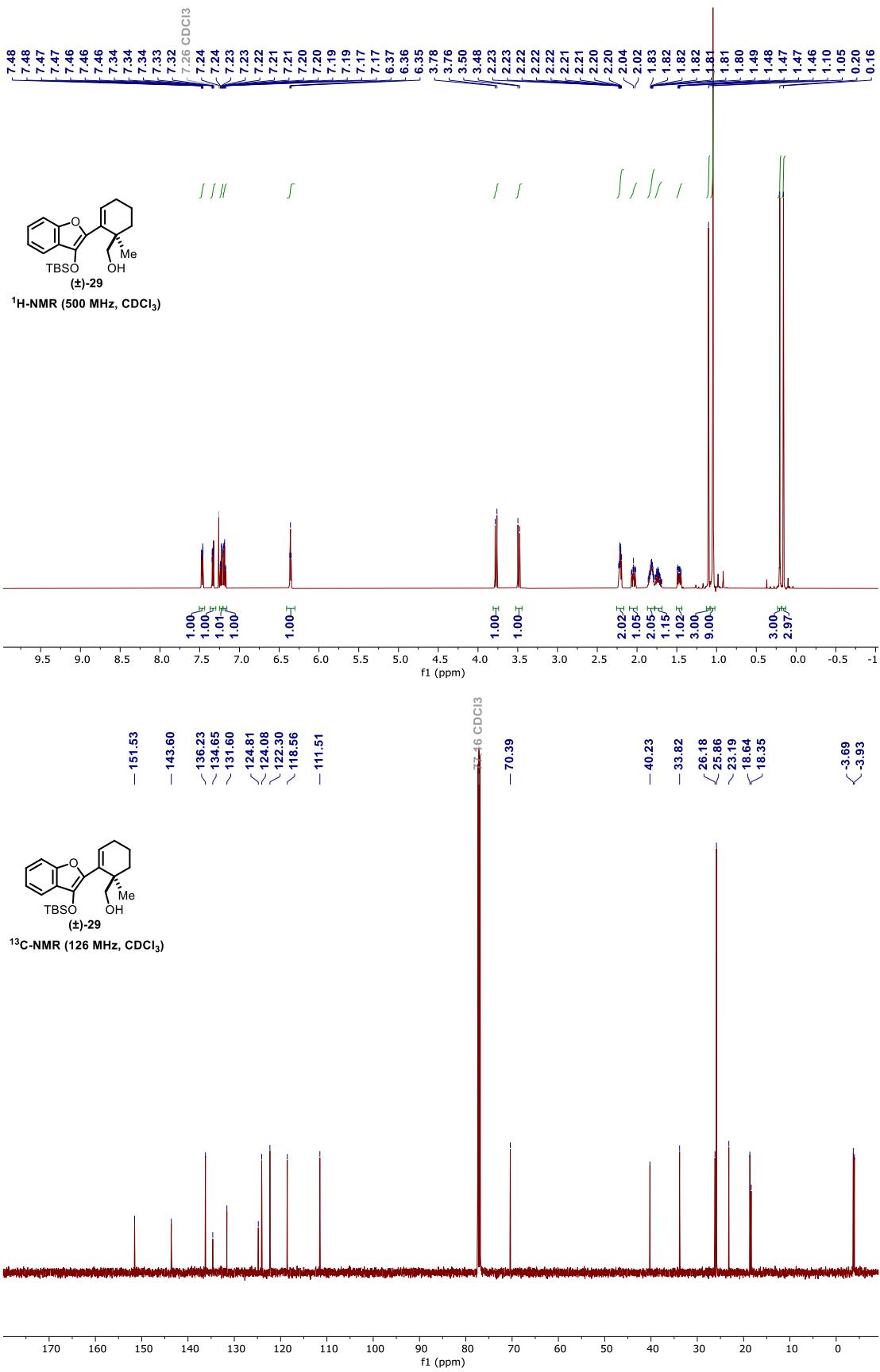
## 7. NMR Spectra

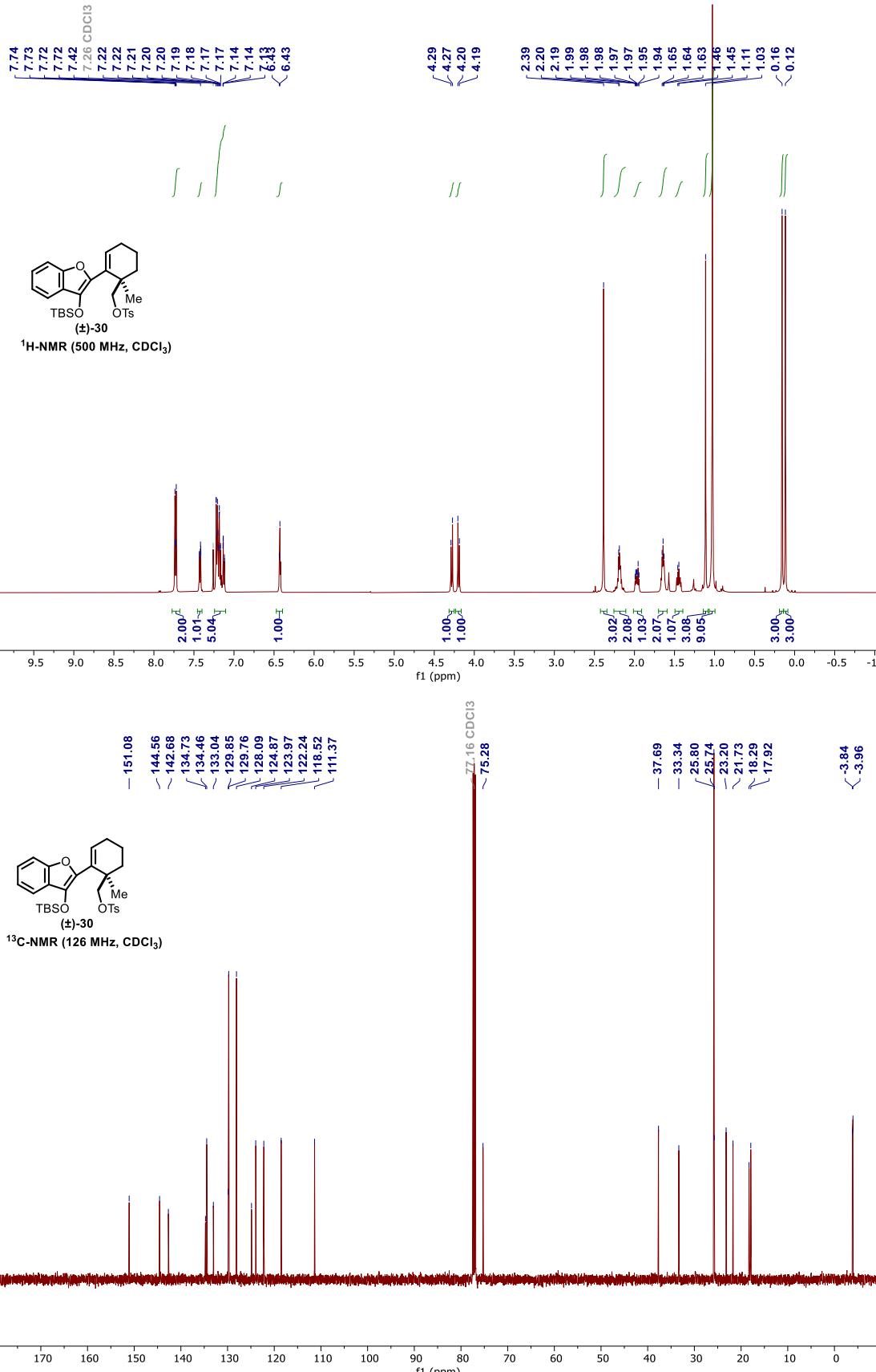


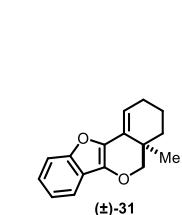
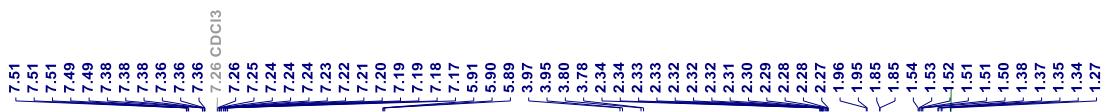




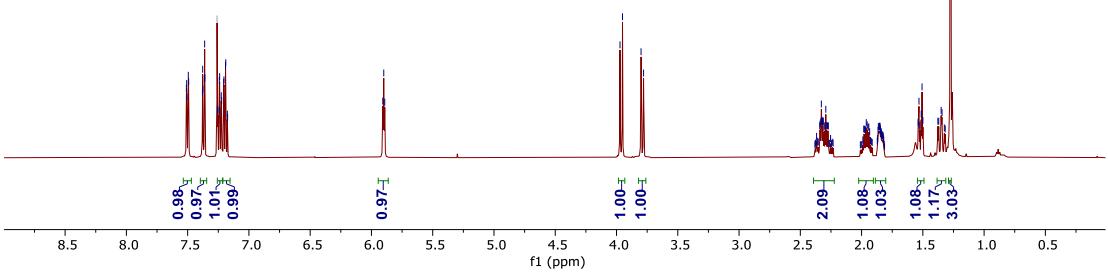




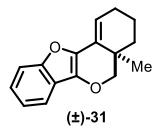




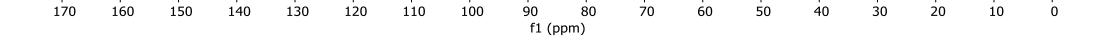
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)

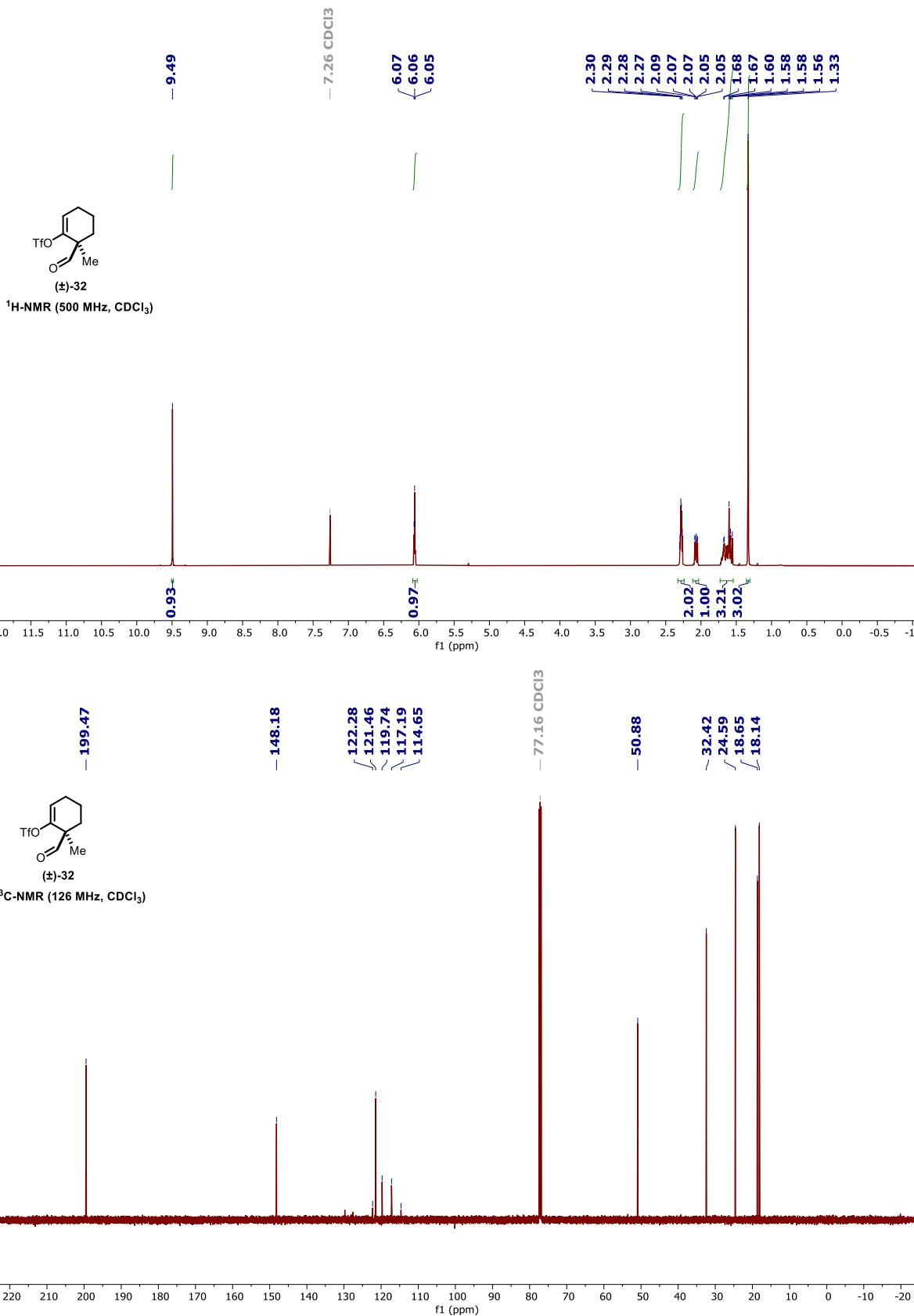


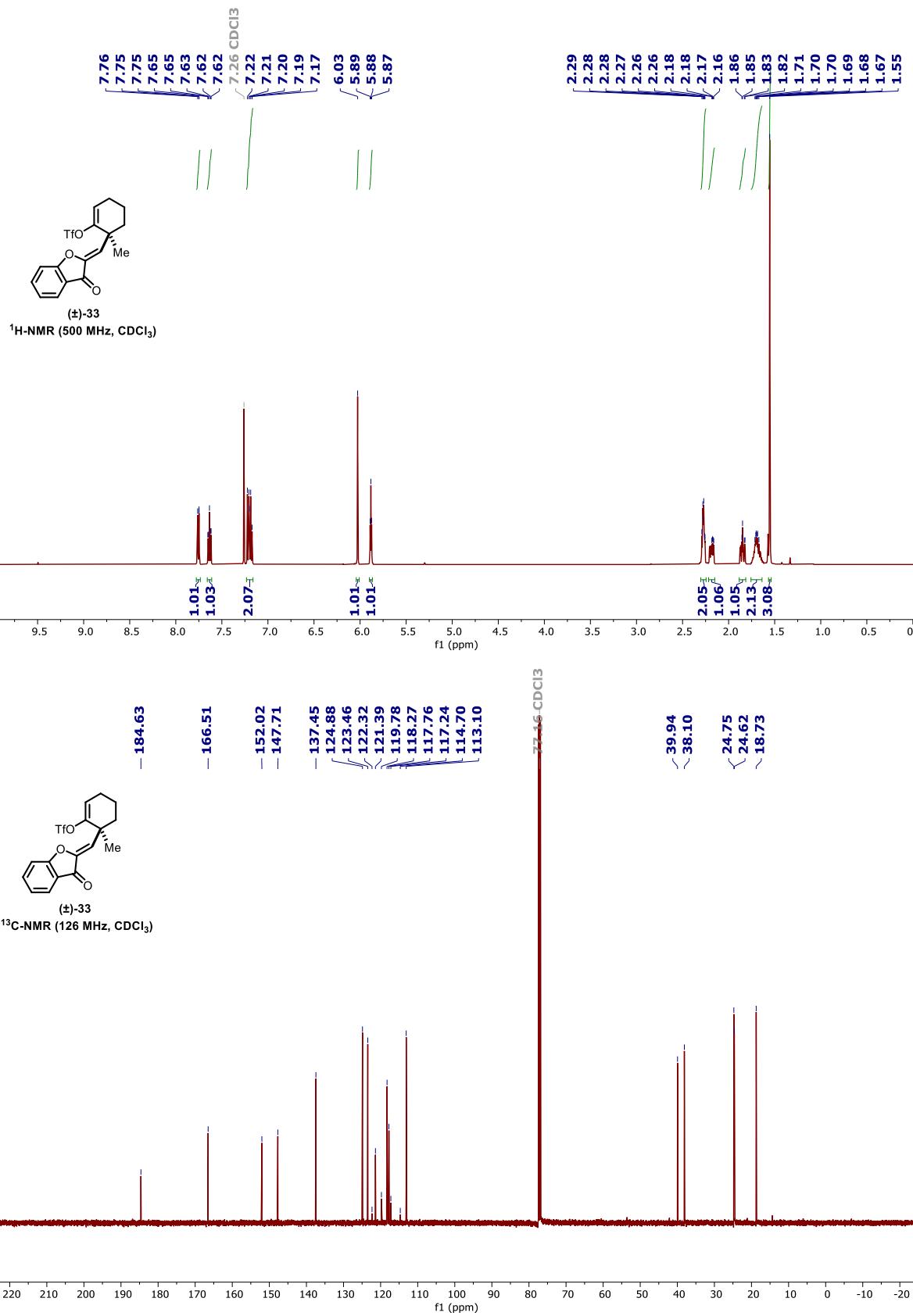
— 153.05  
 < 137.15  
 < 136.78  
 — 129.47  
 / 124.61  
 / 122.54  
 > 121.53  
 > 117.98  
 > 115.61  
 > 111.60

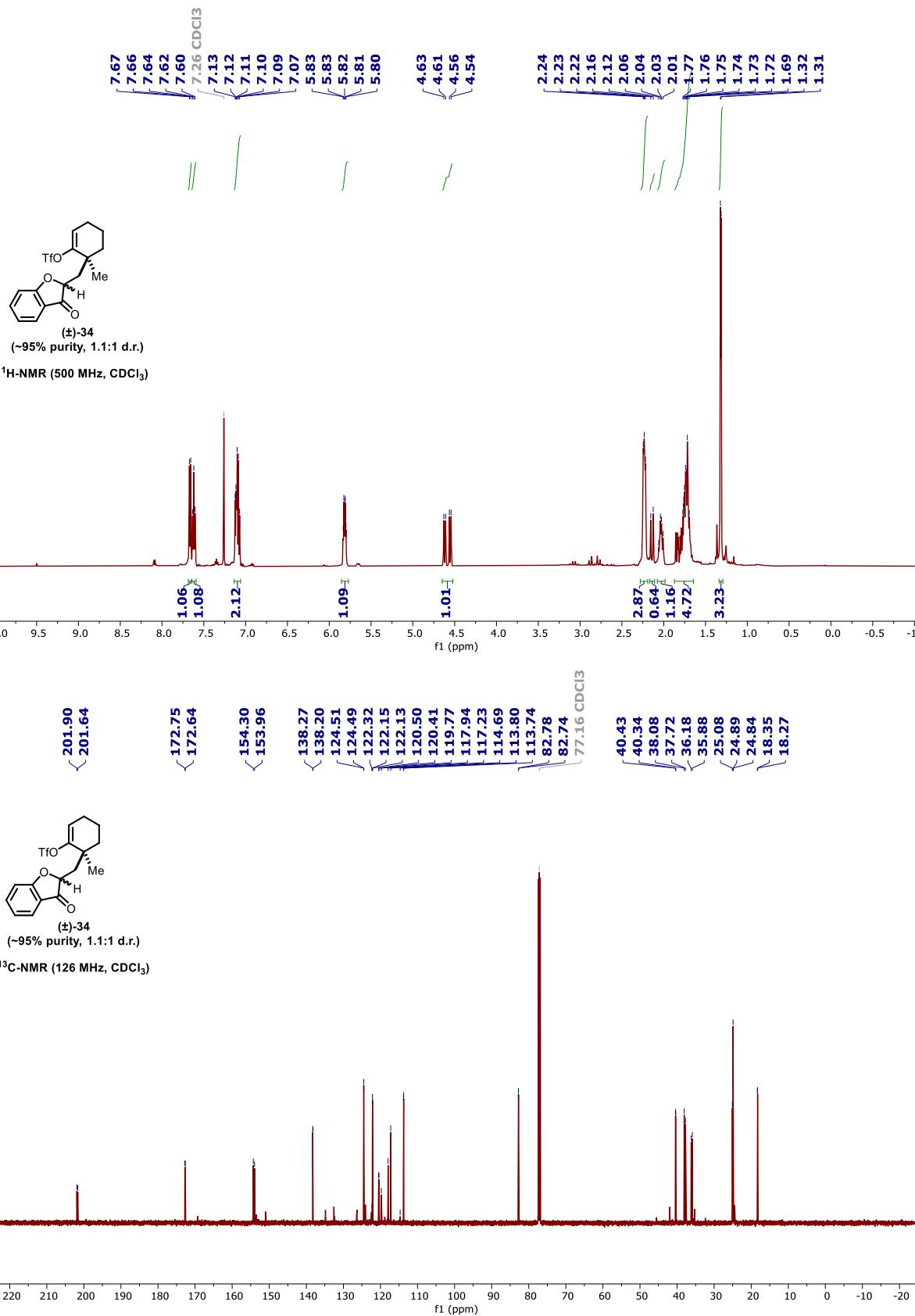


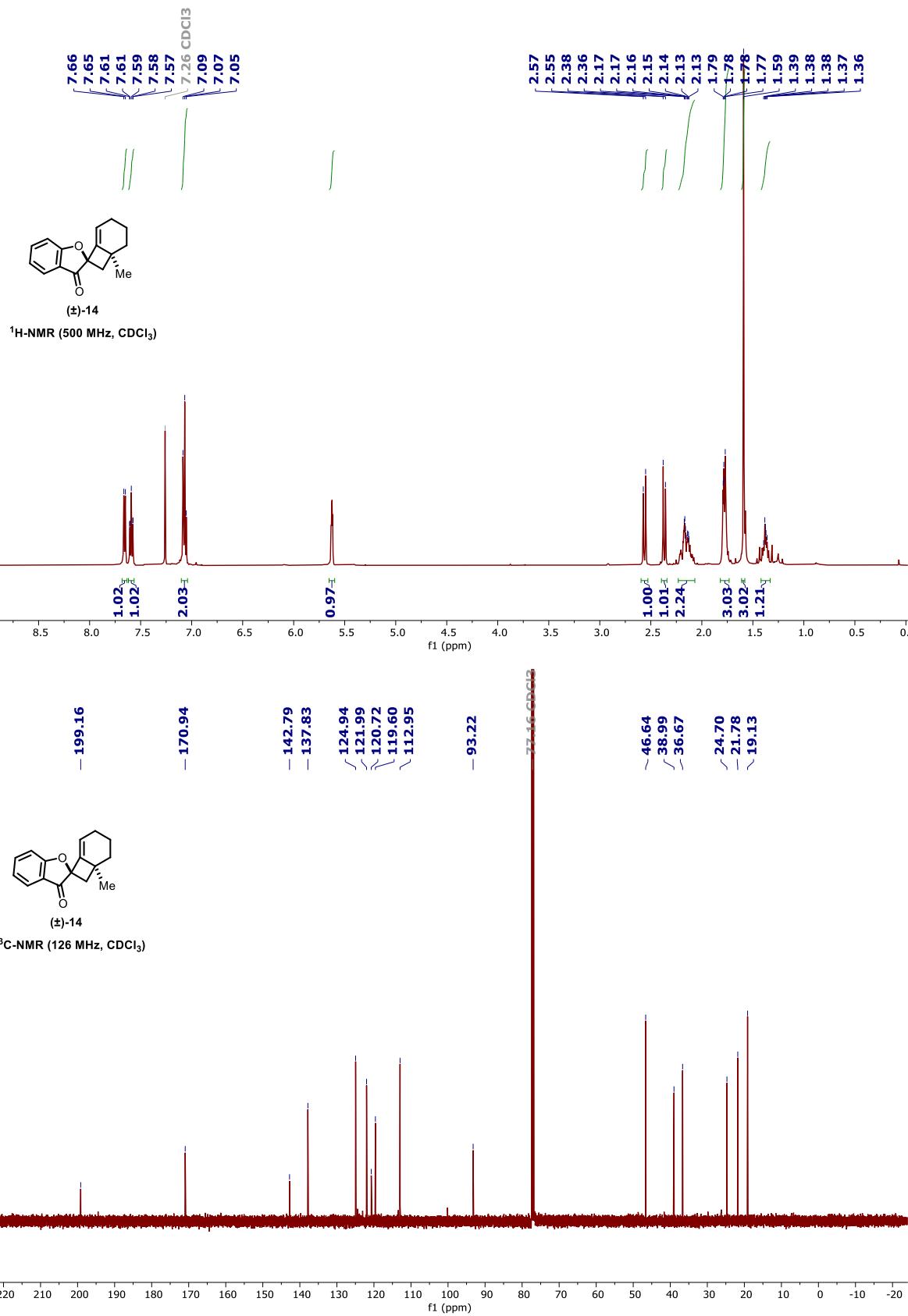
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)

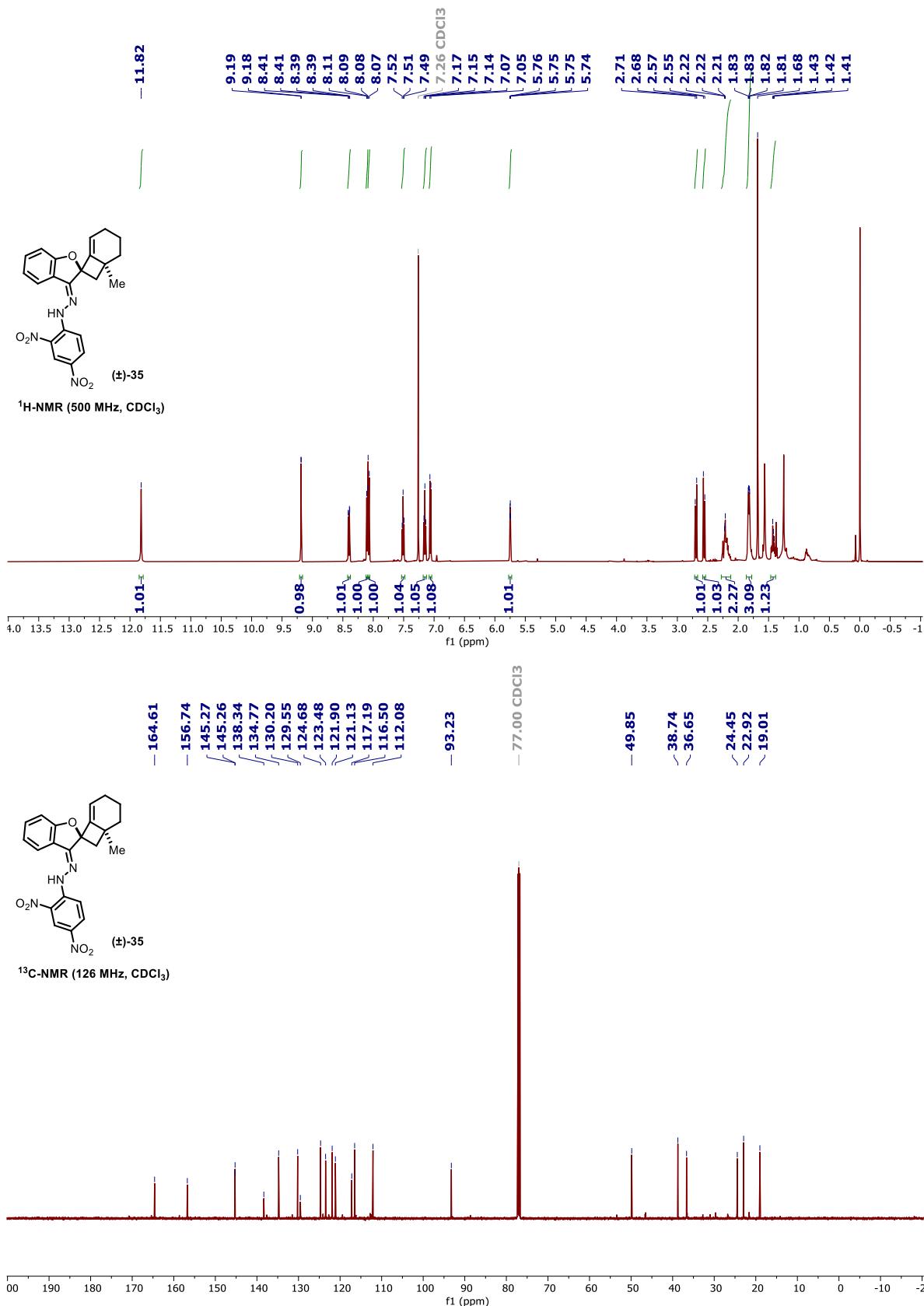






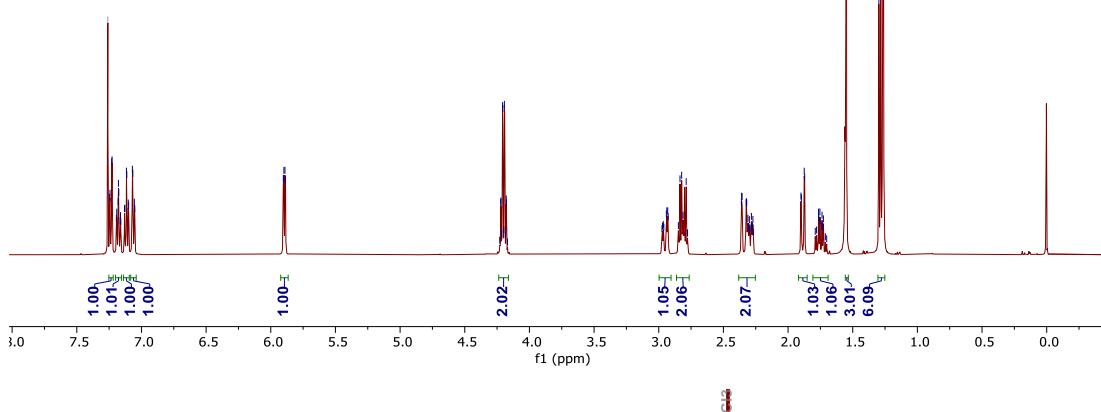








<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)

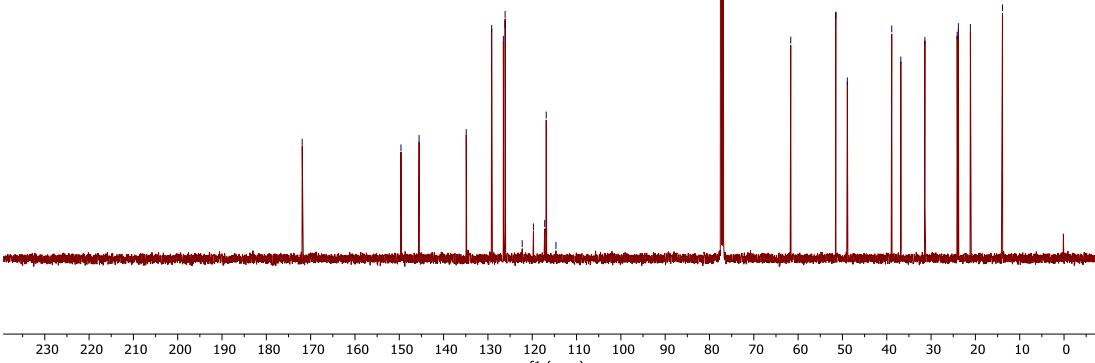


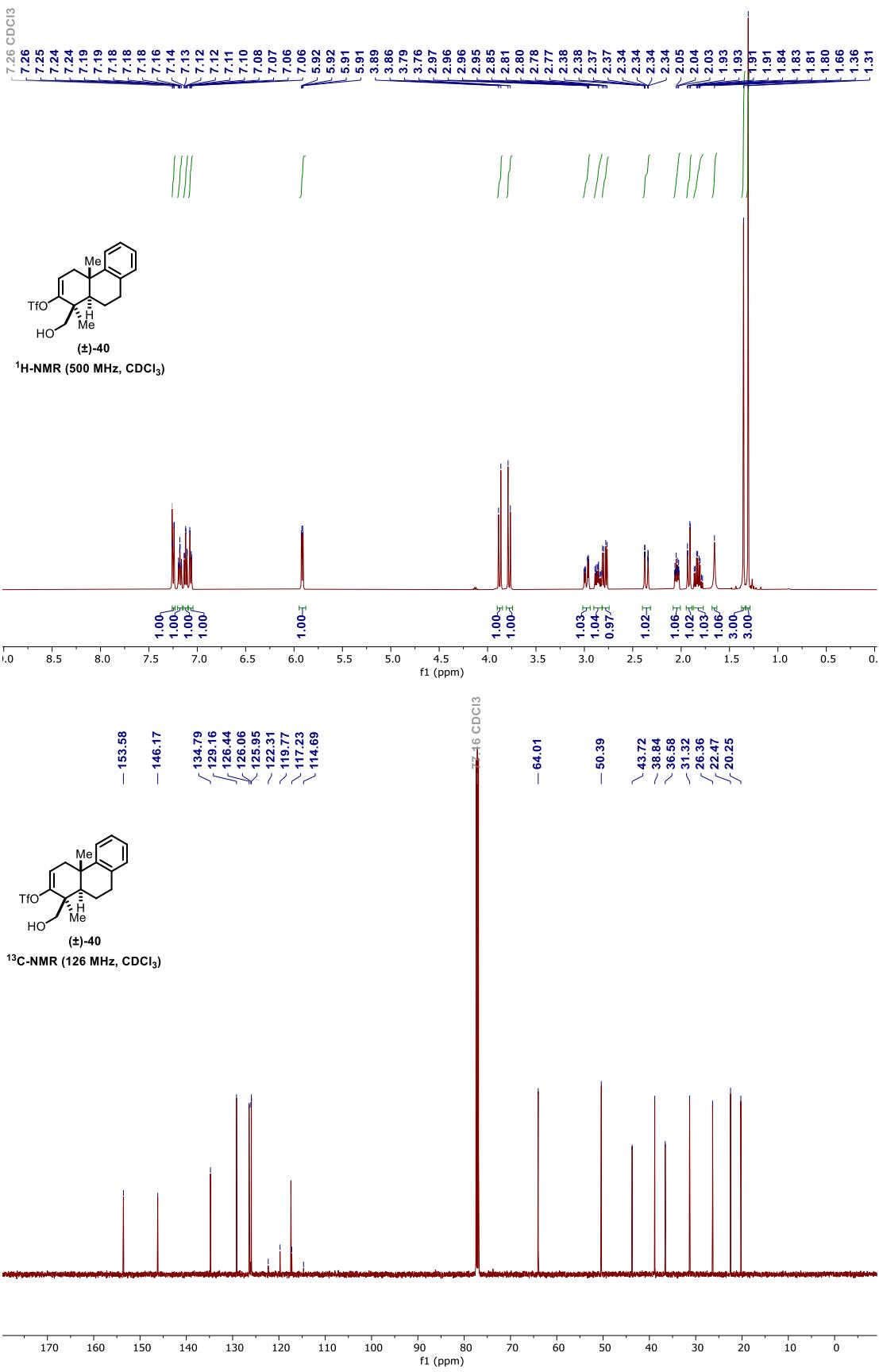
— 171.91

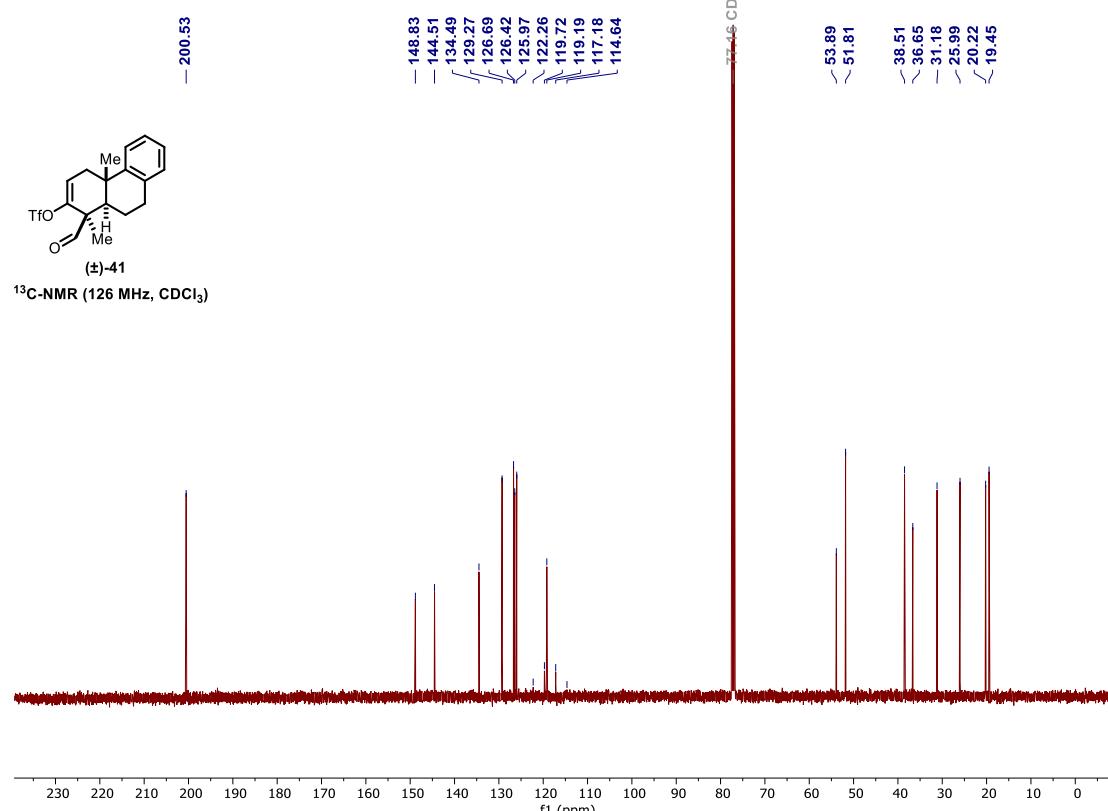
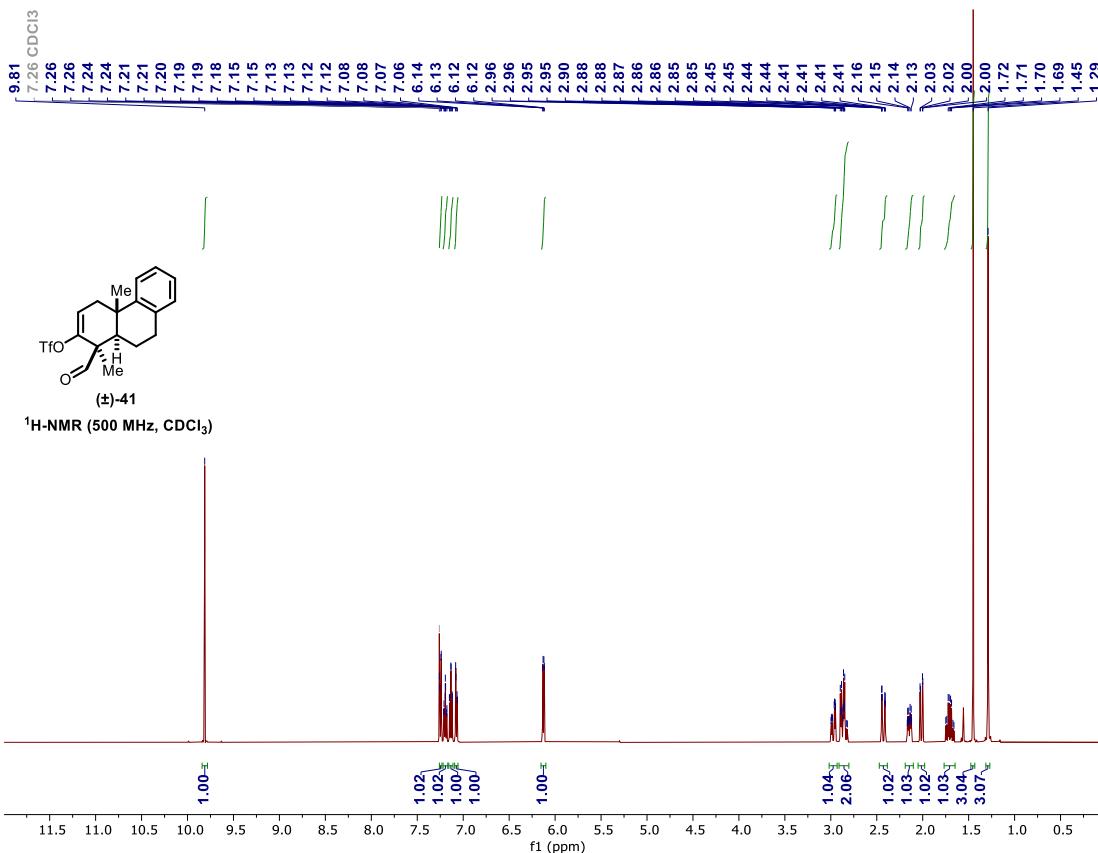
— 149.62  
— 145.53  
— 134.90  
— 129.15  
— 126.51  
— 126.13  
— 126.12  
— 122.27  
— 119.73  
— 117.19  
— 116.84  
— 114.65

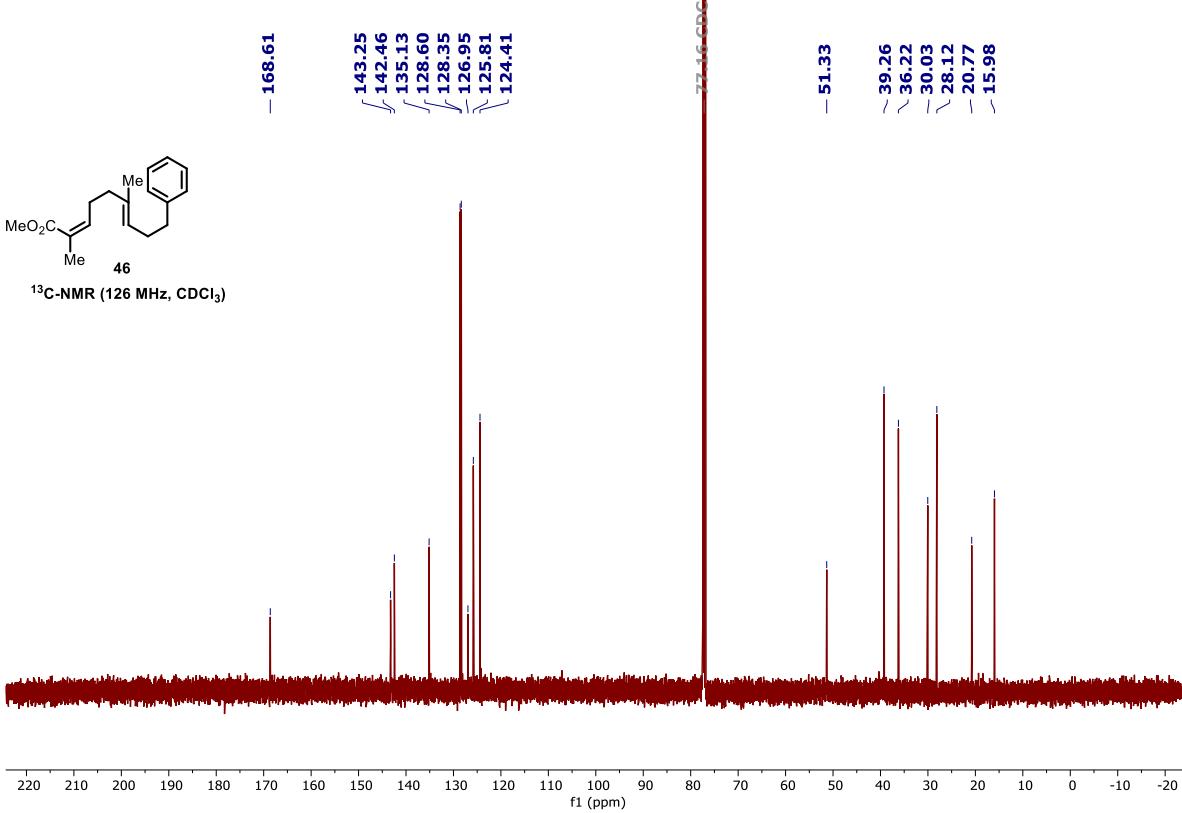
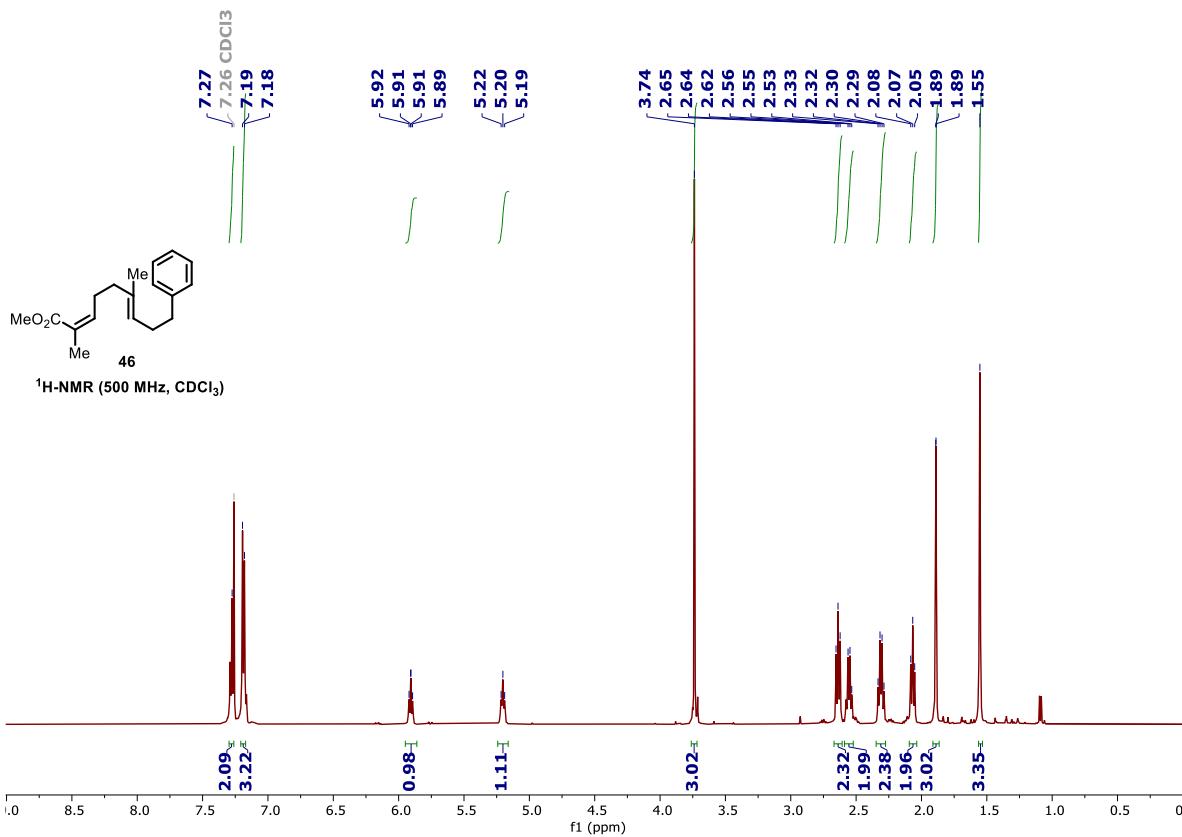
— 61.67  
— 51.50  
— 48.90  
— 38.88  
— 36.83  
— 31.40  
— 24.11  
— 23.84  
— 21.13  
— 13.89

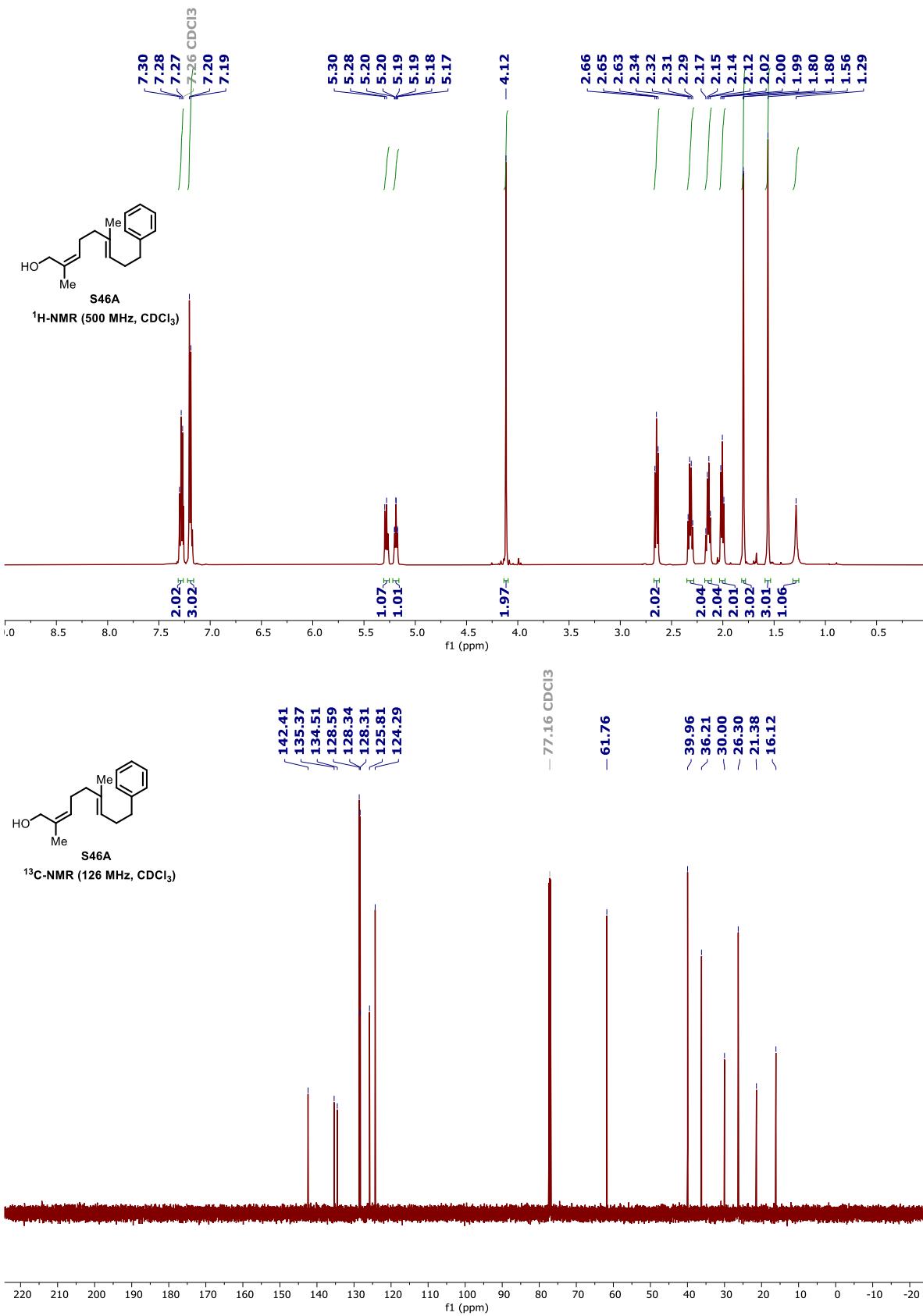
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)

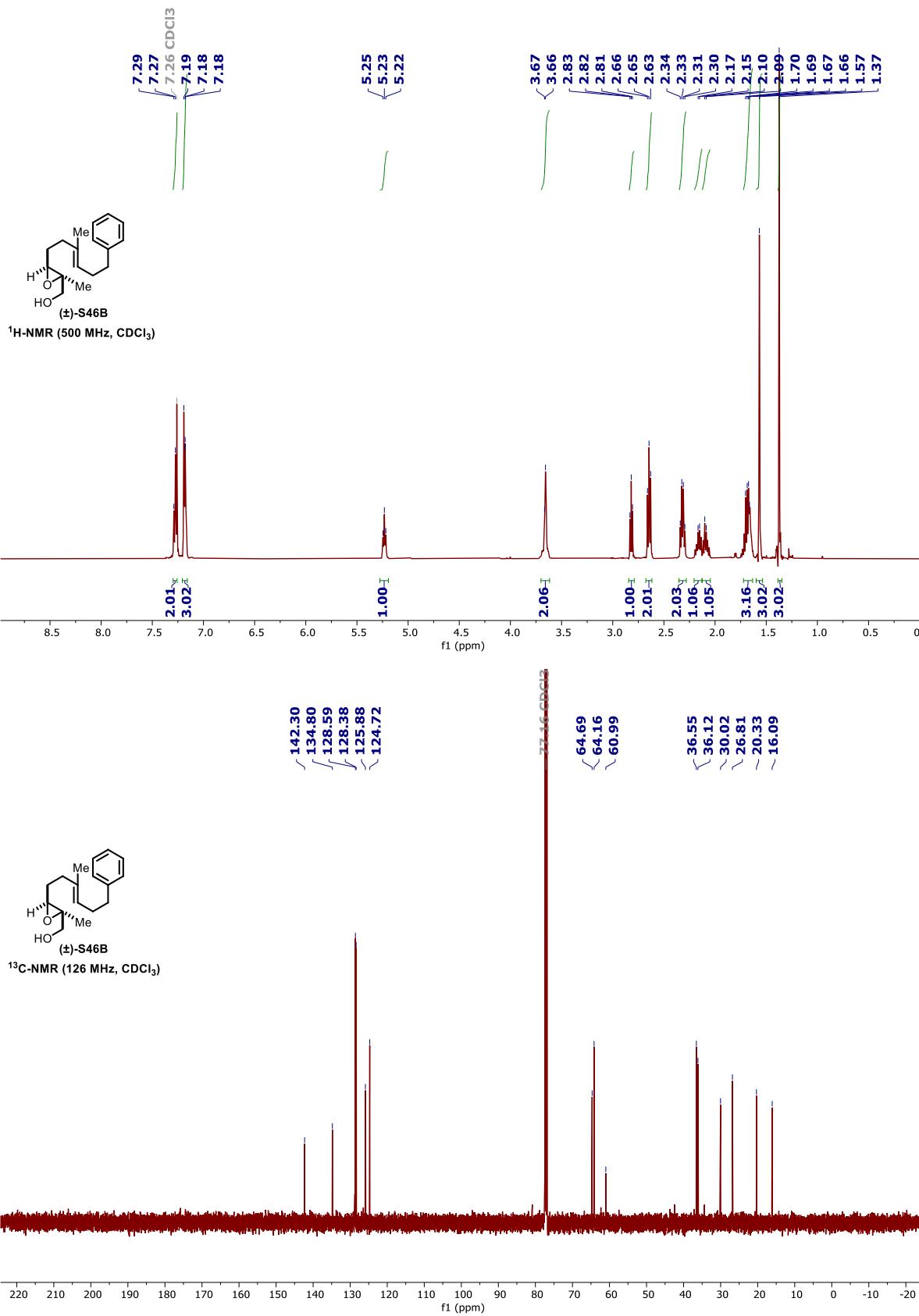


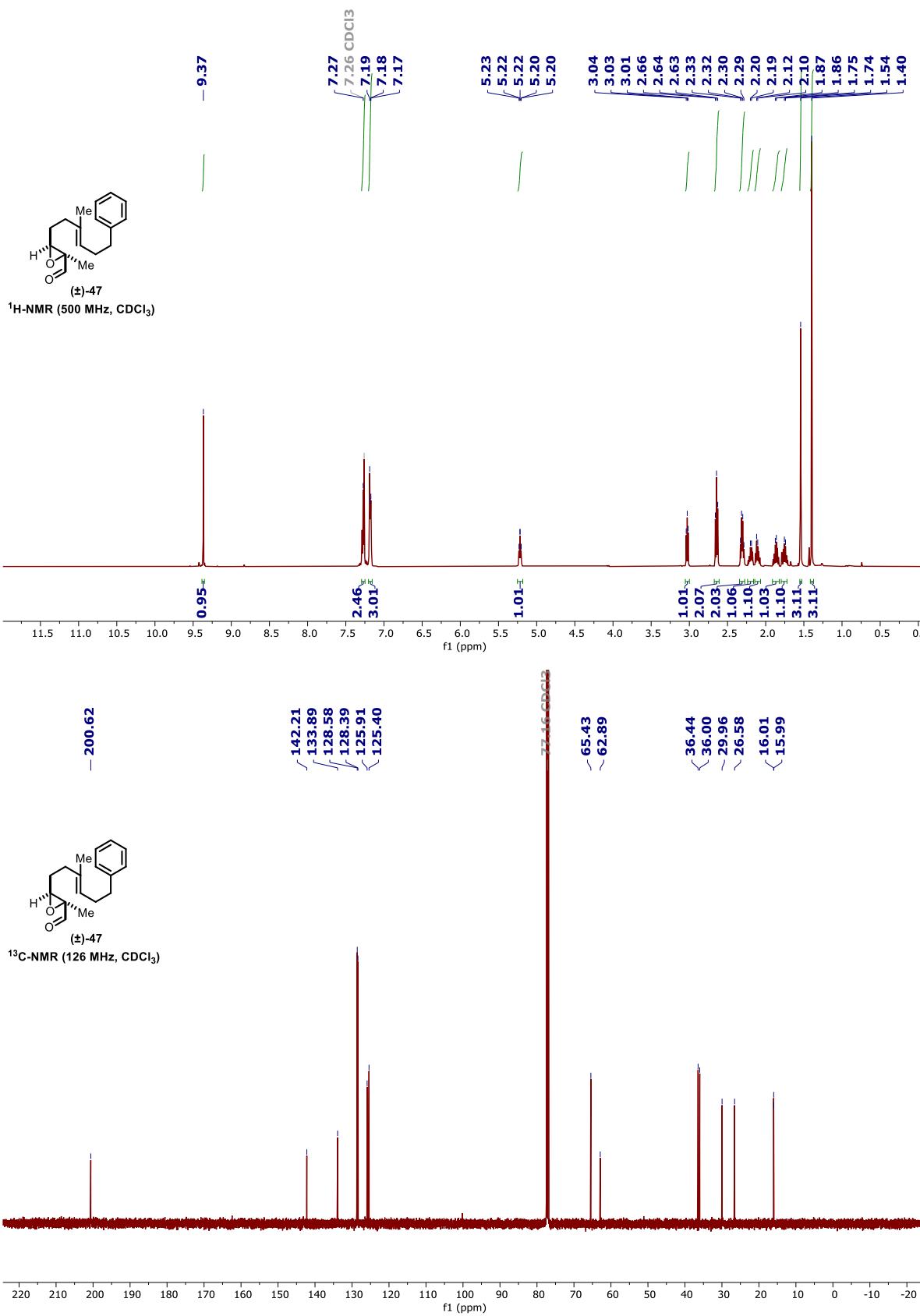


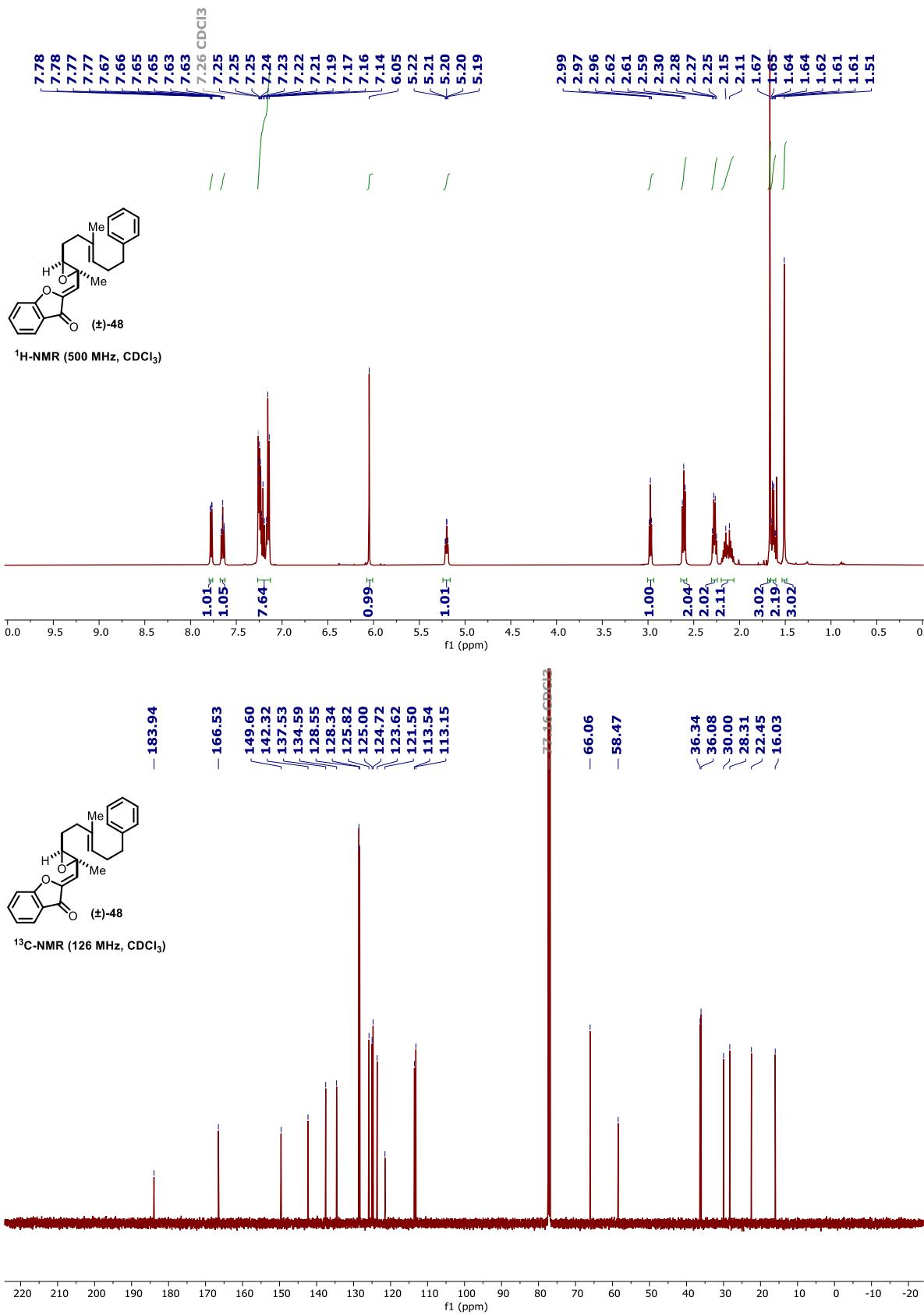


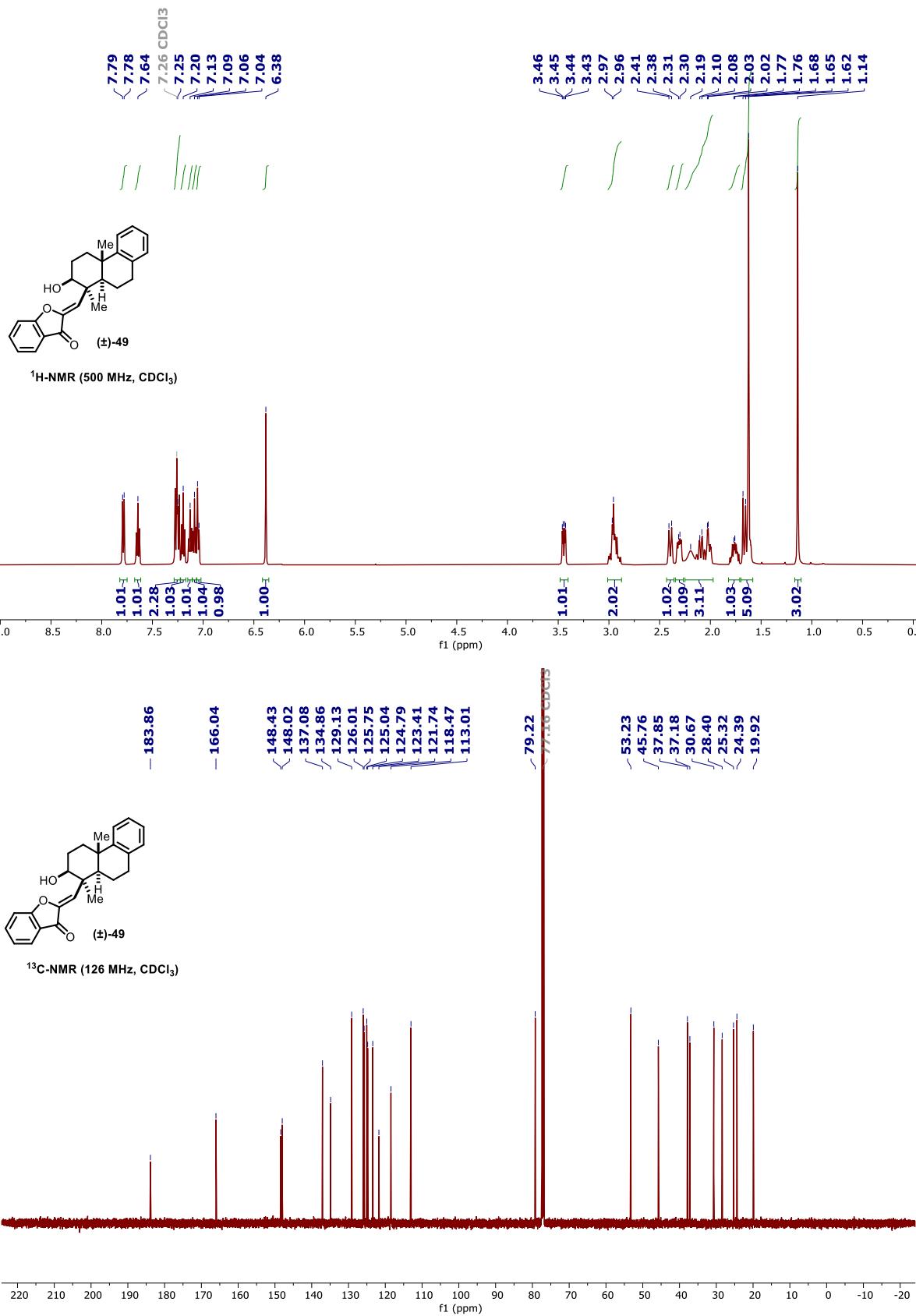


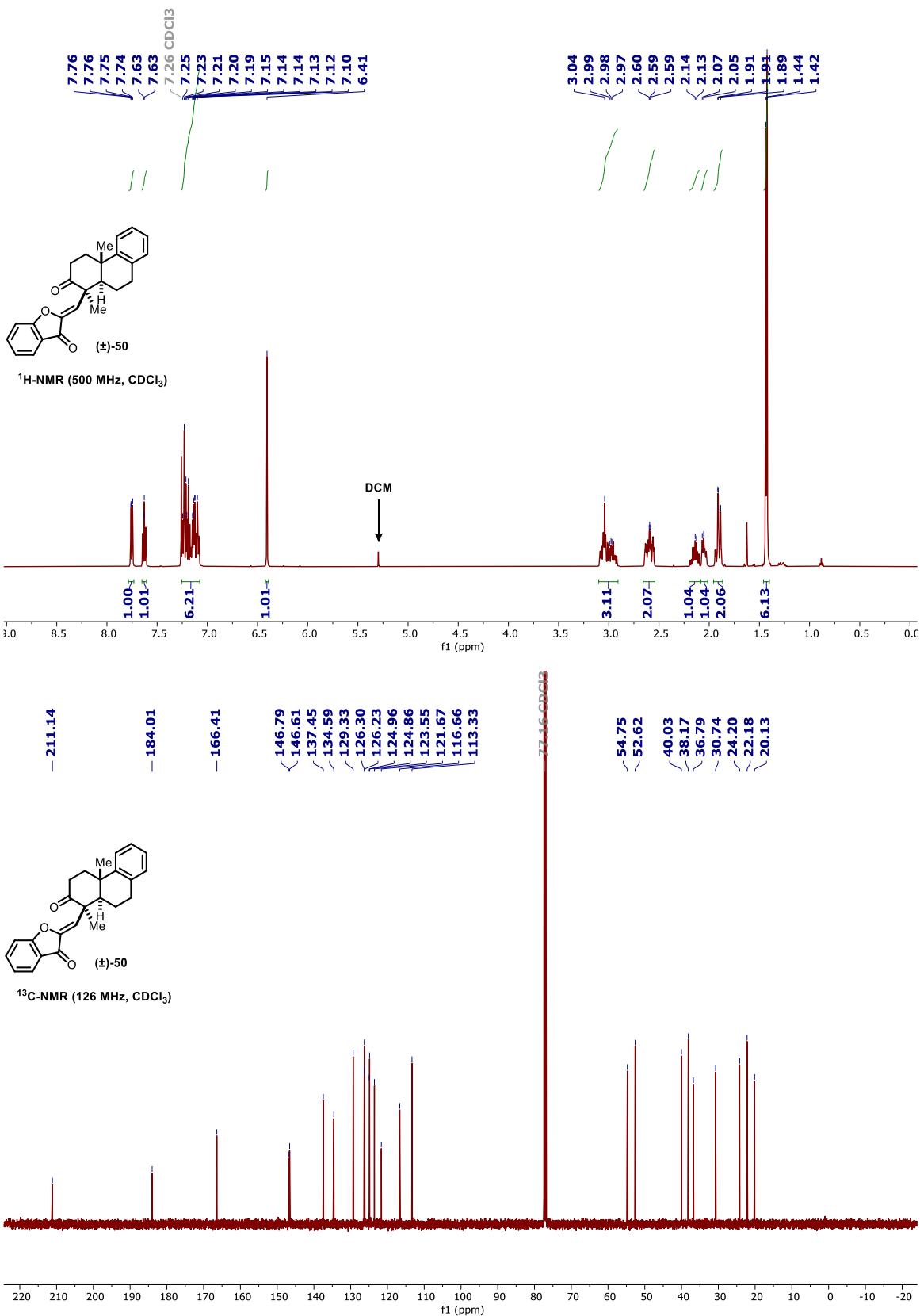


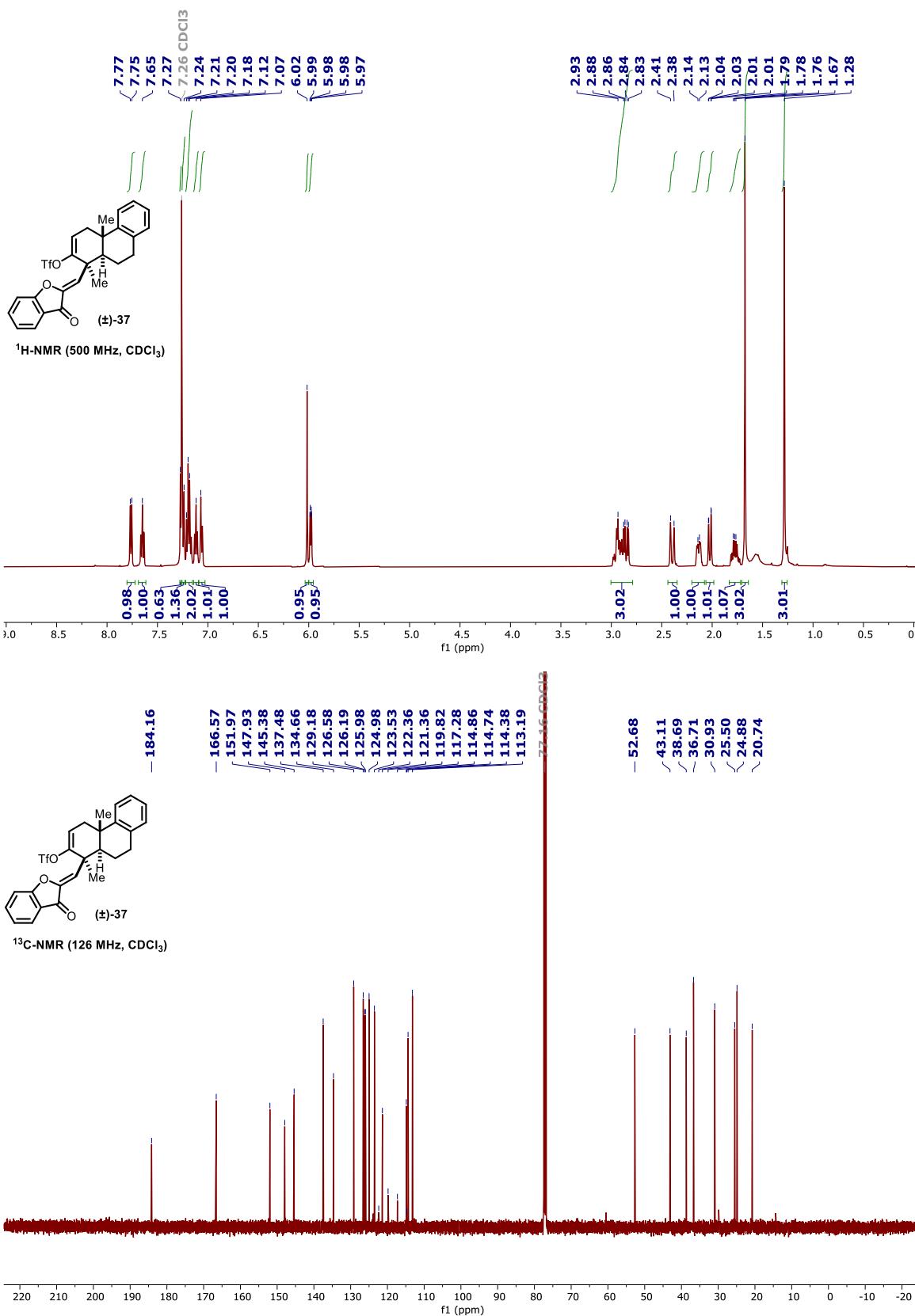


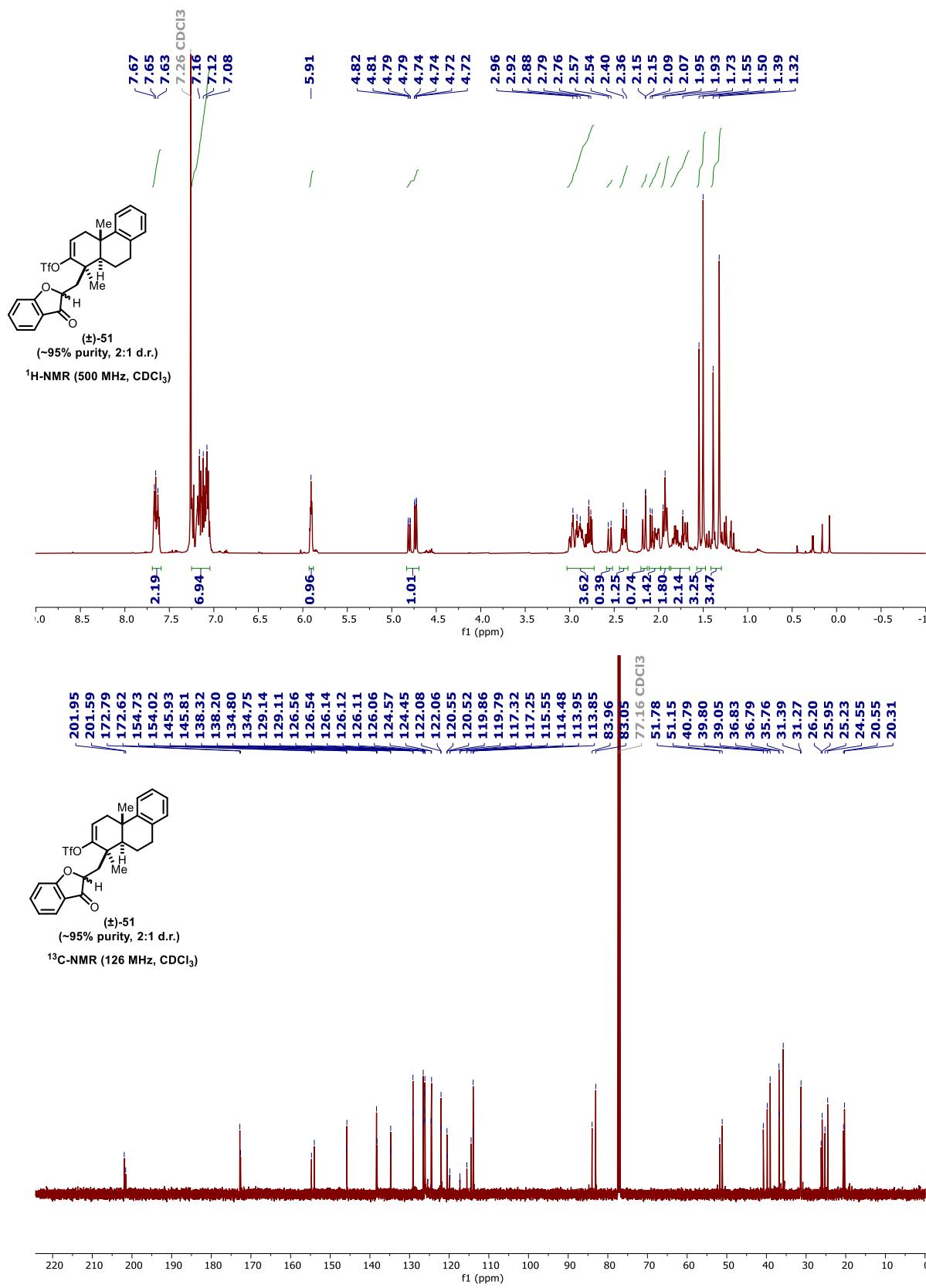


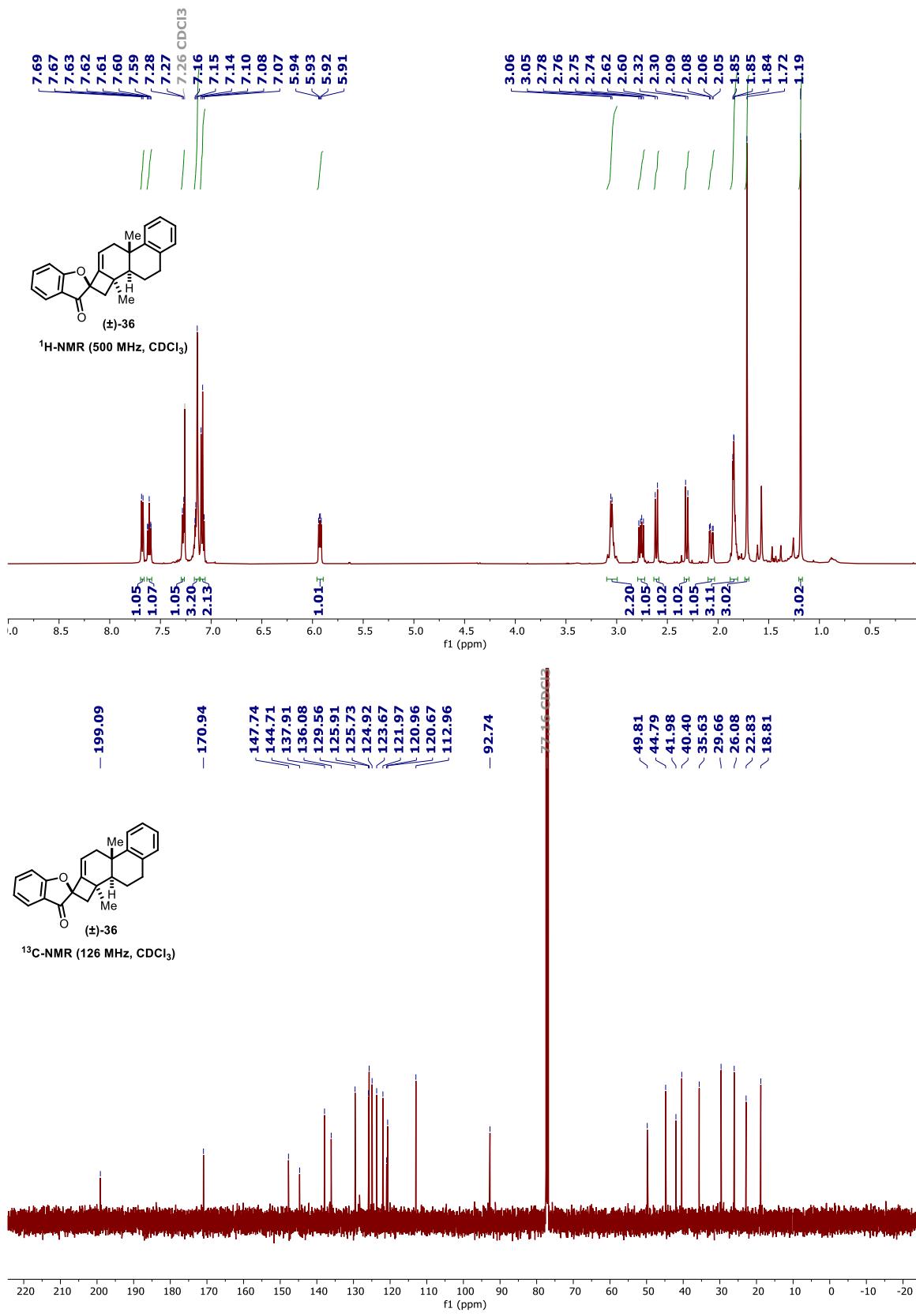


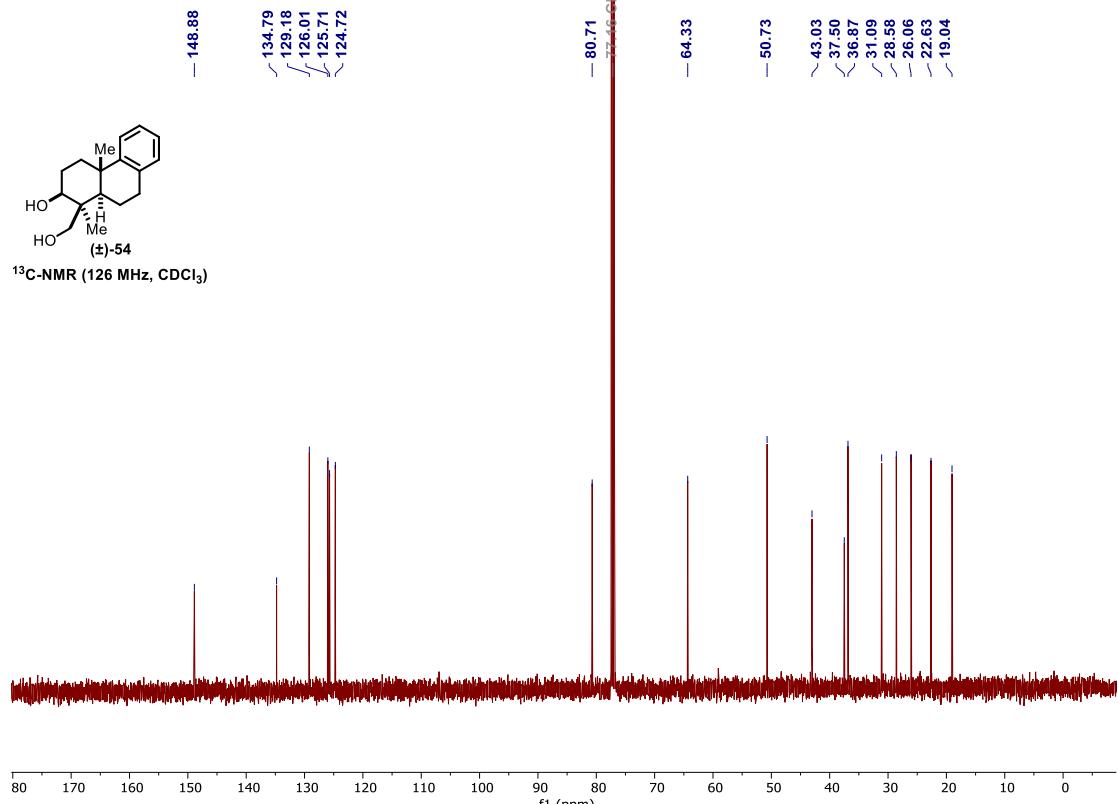
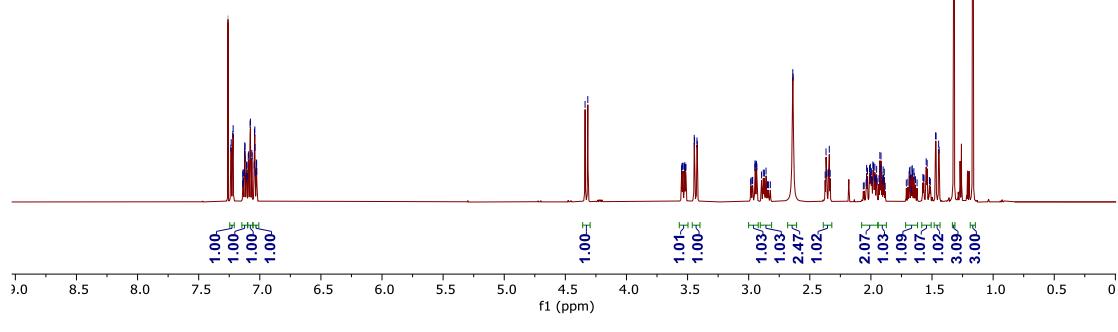
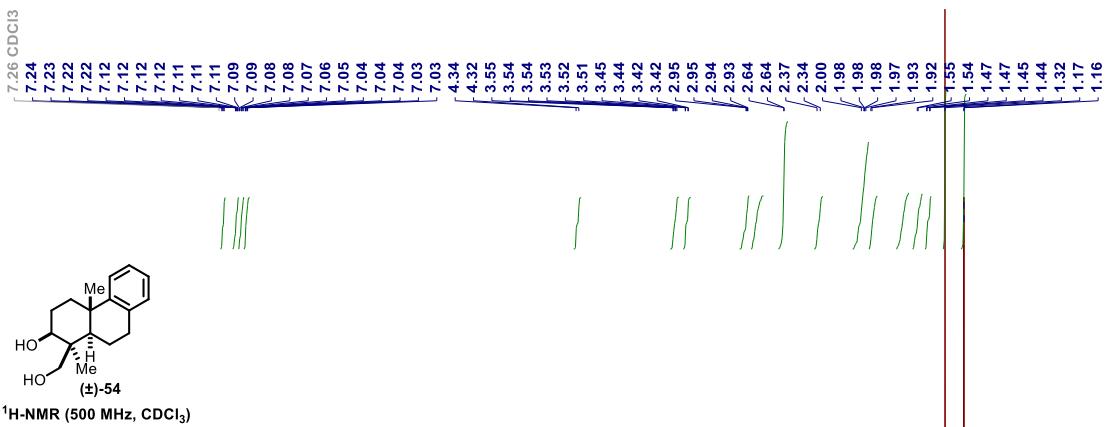


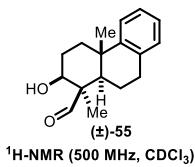
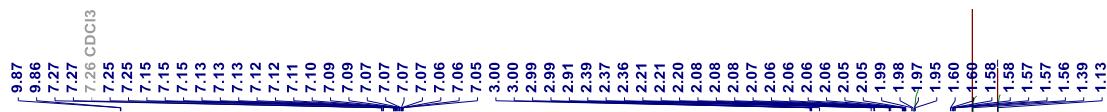




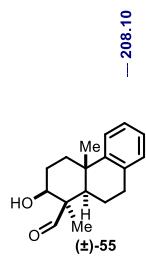
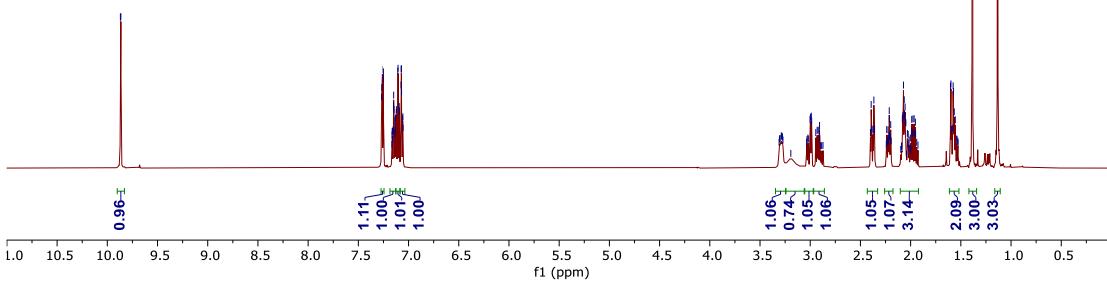




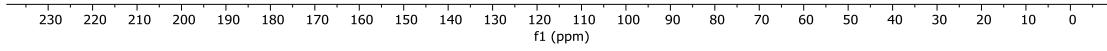


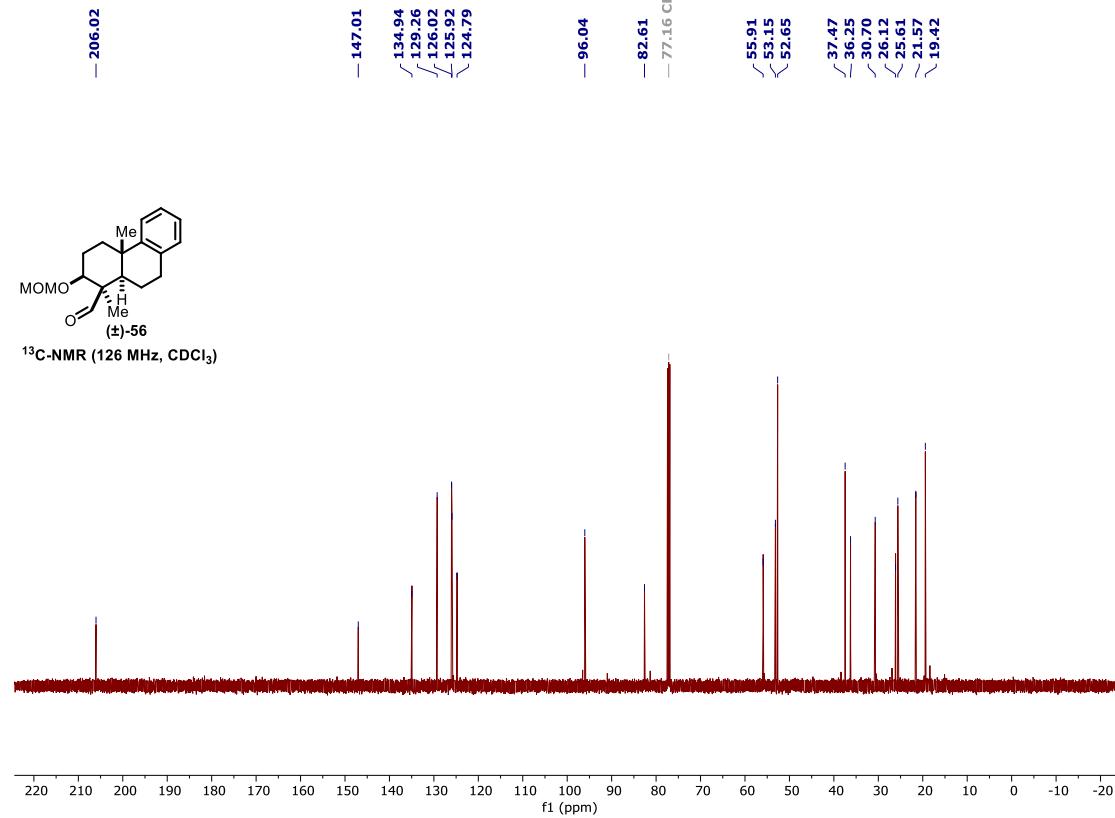
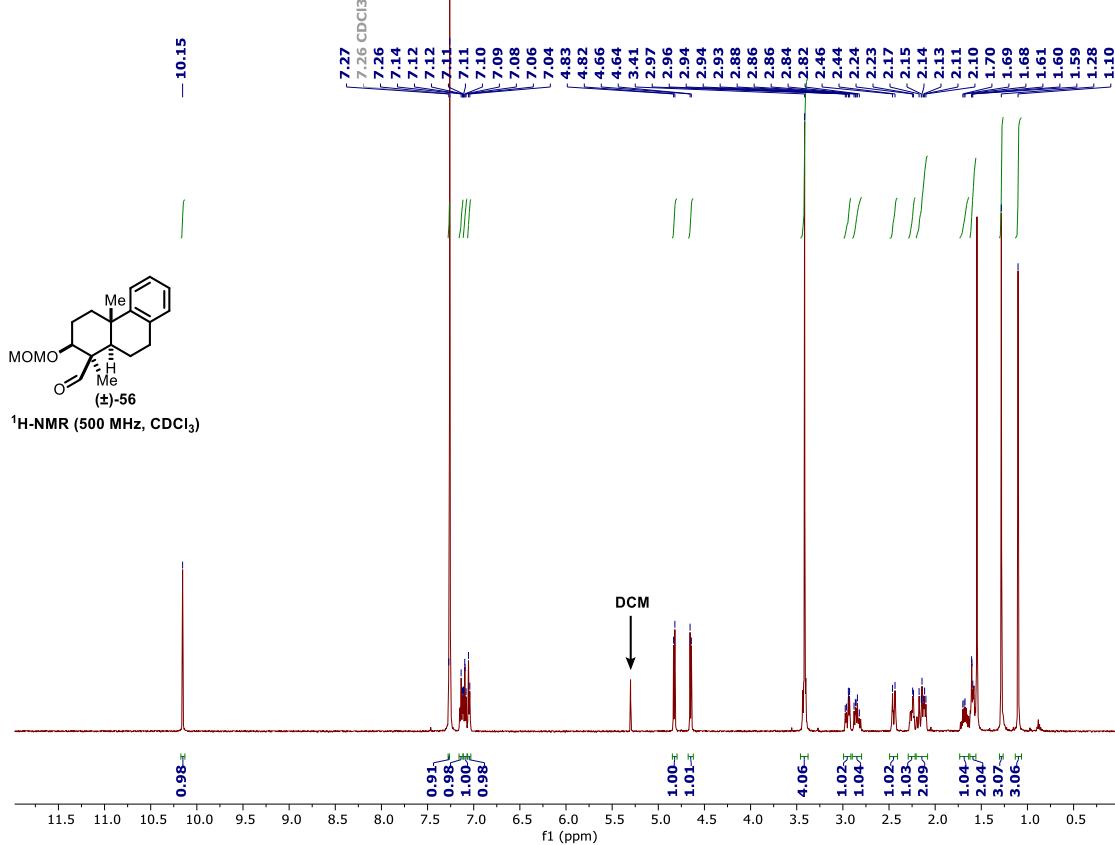


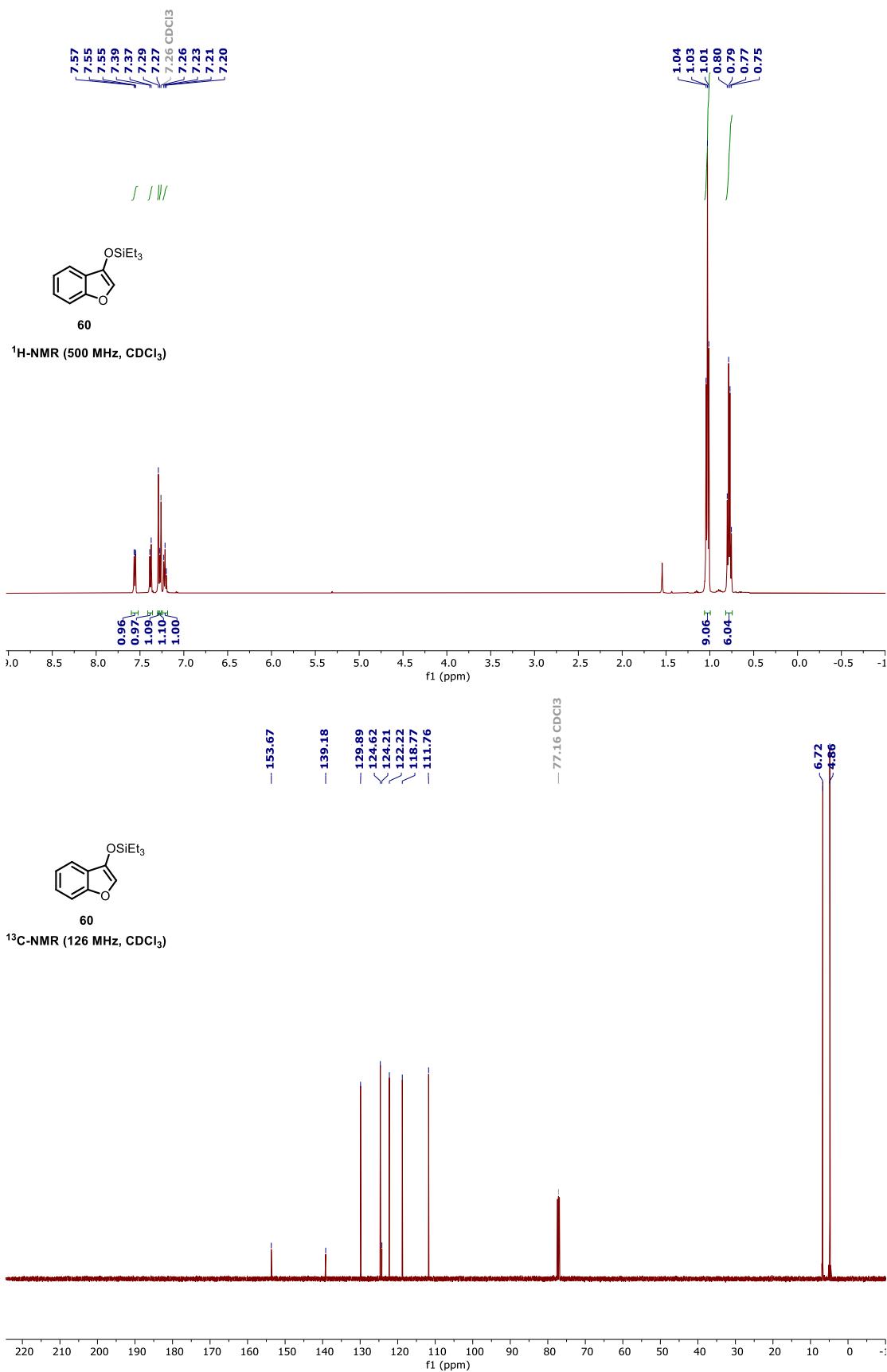
$^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )

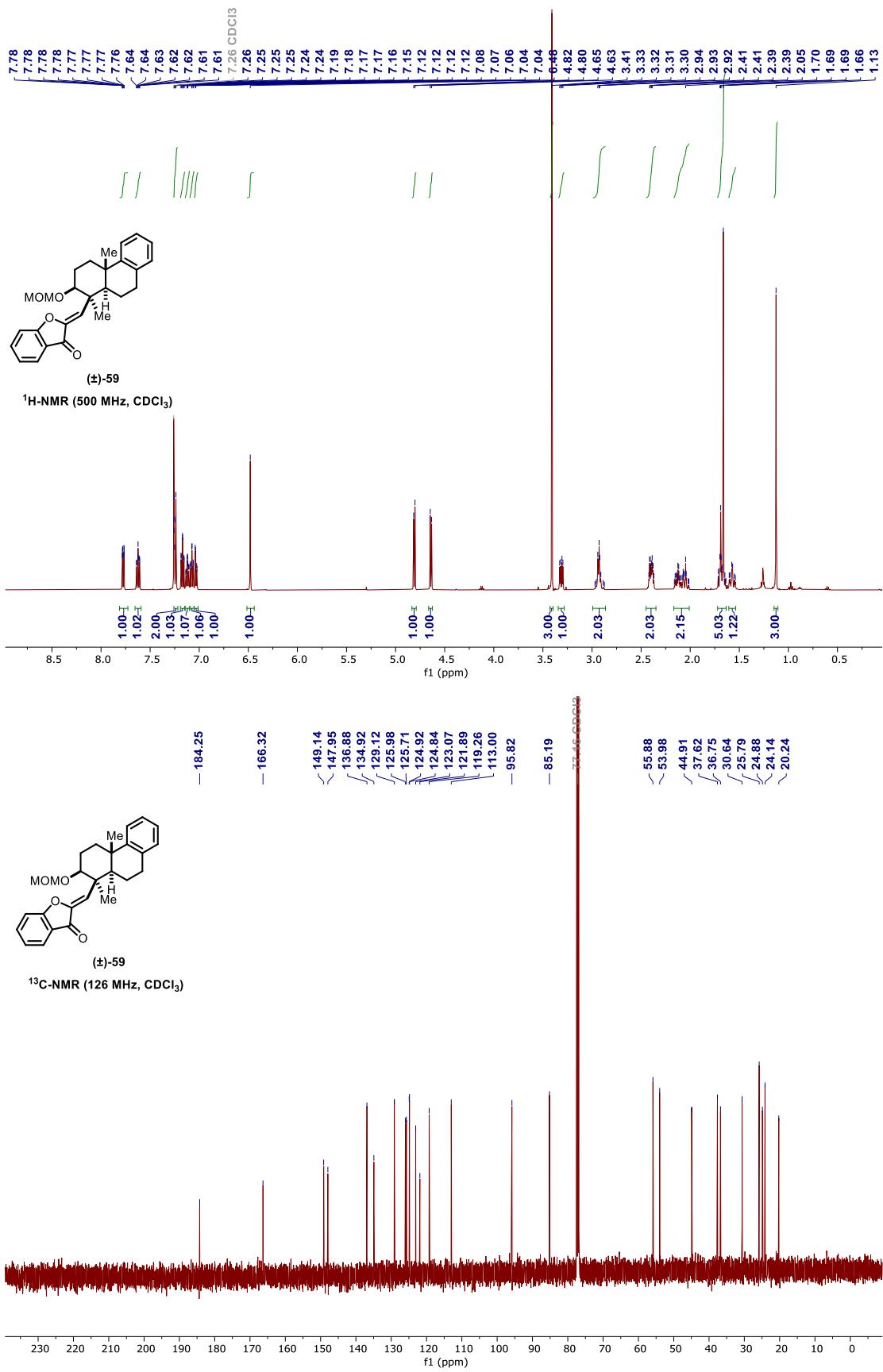


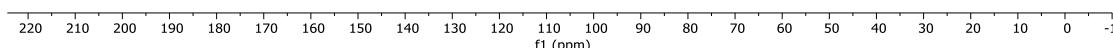
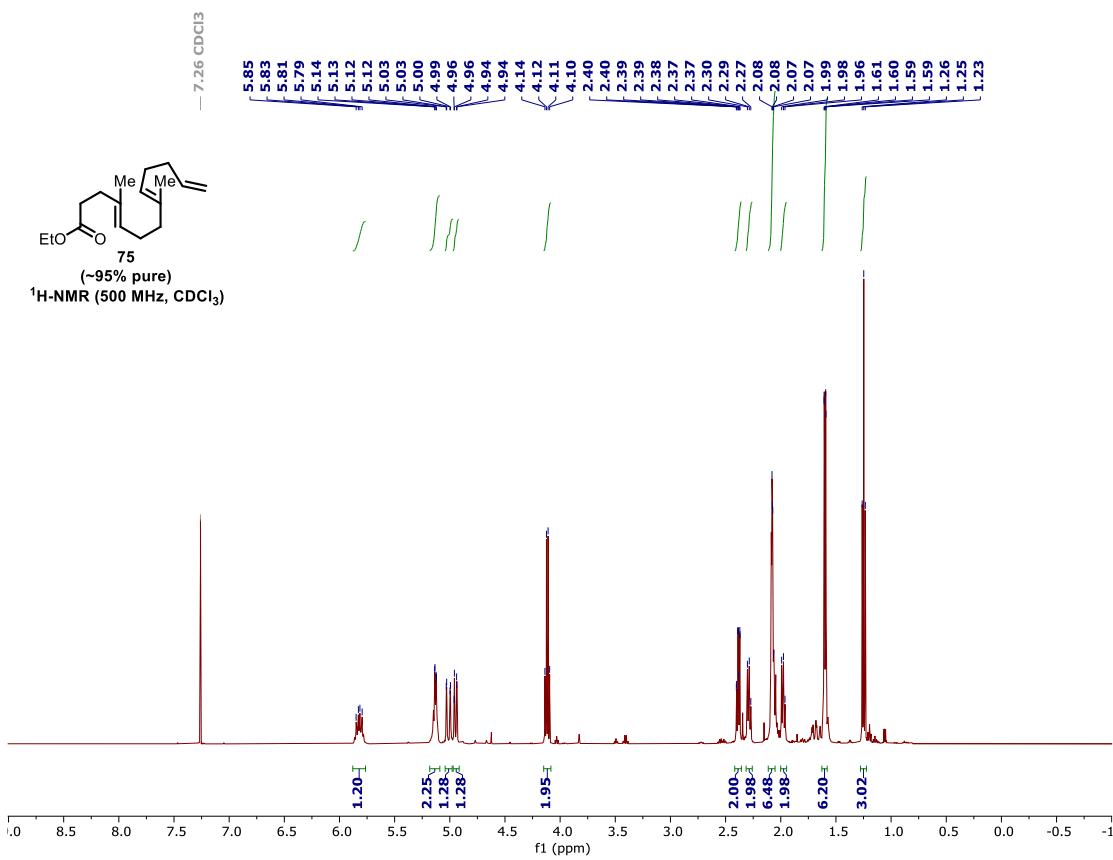
$^{13}\text{C}$ -NMR (126 MHz,  $\text{CDCl}_3$ )

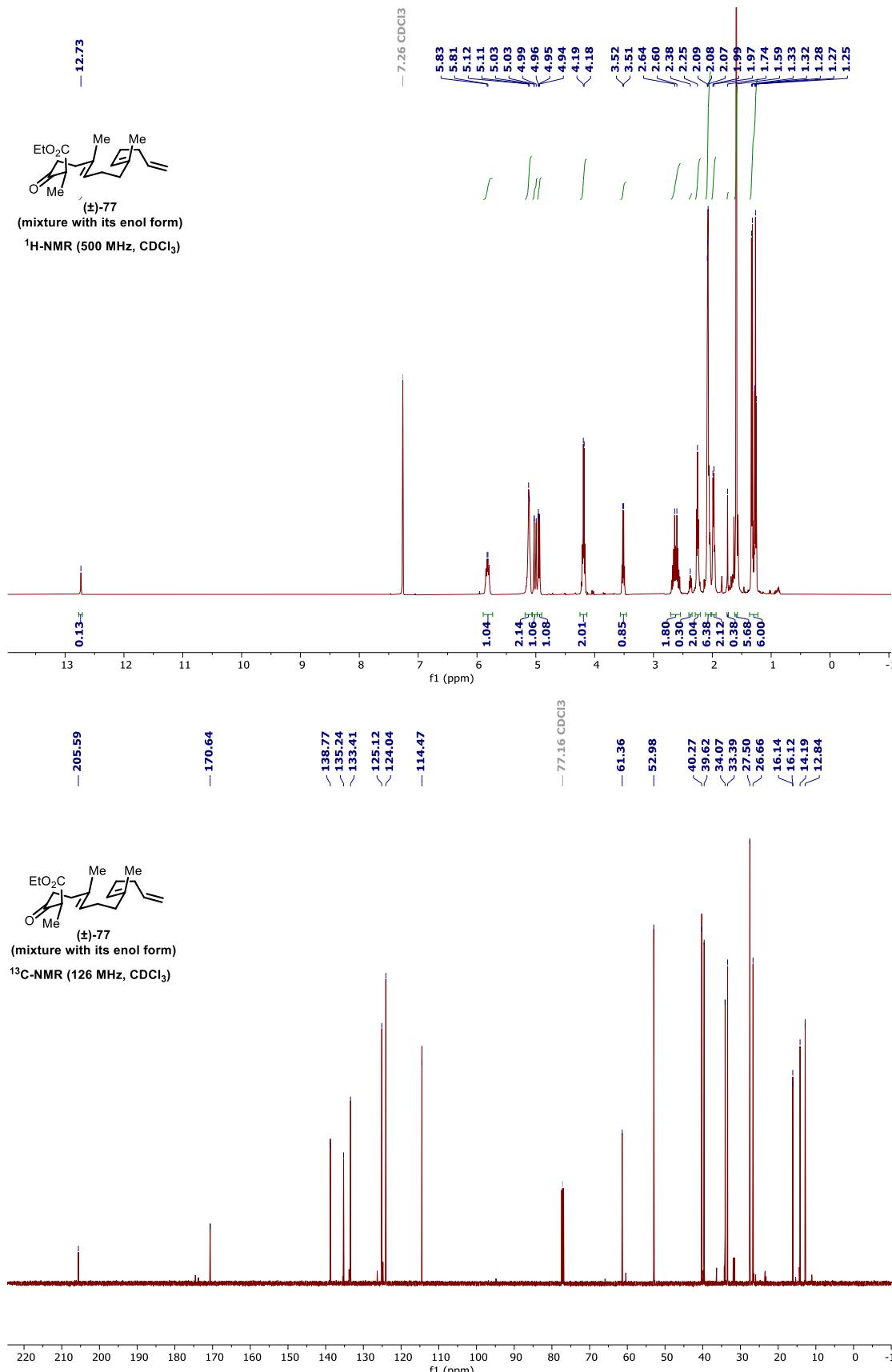


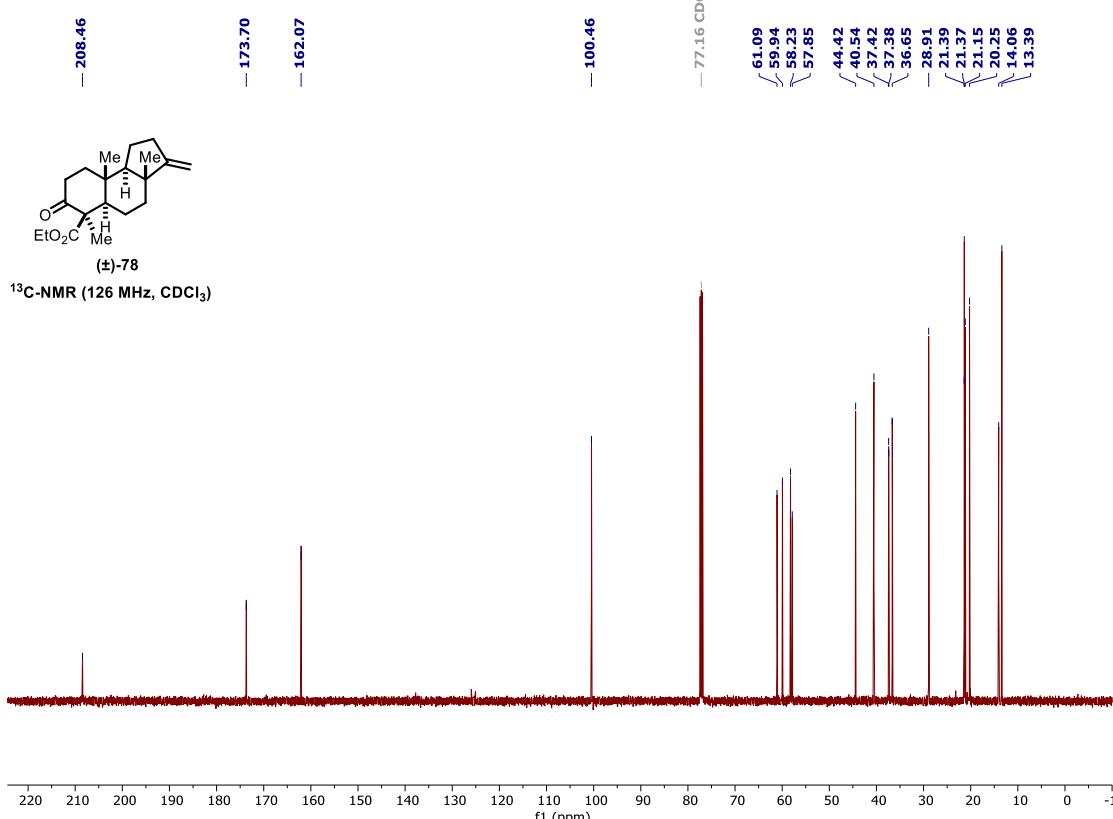
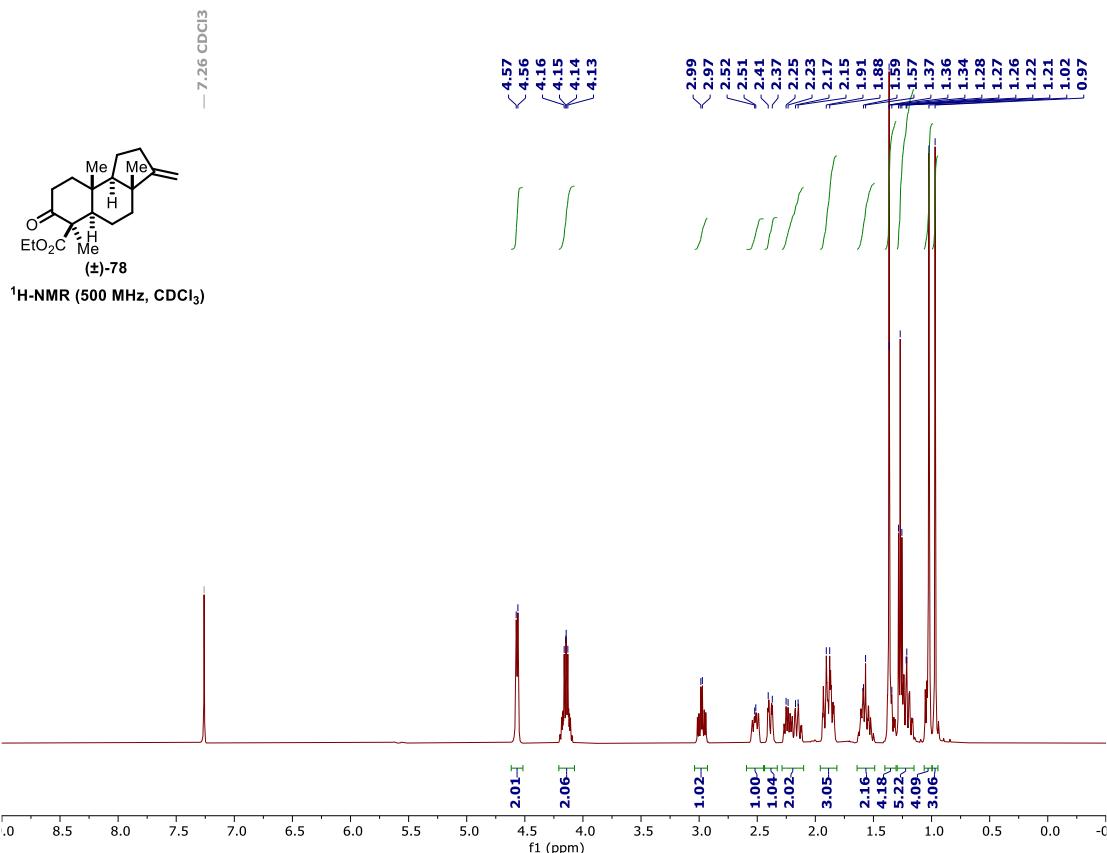


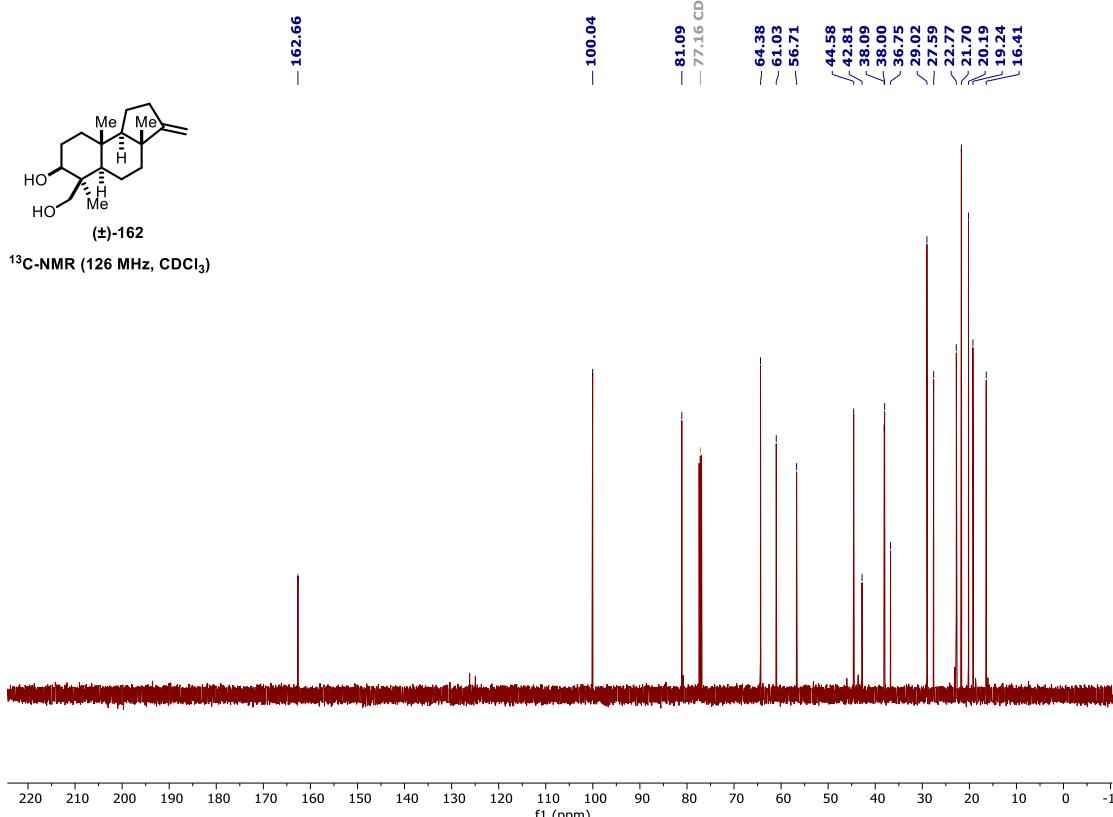
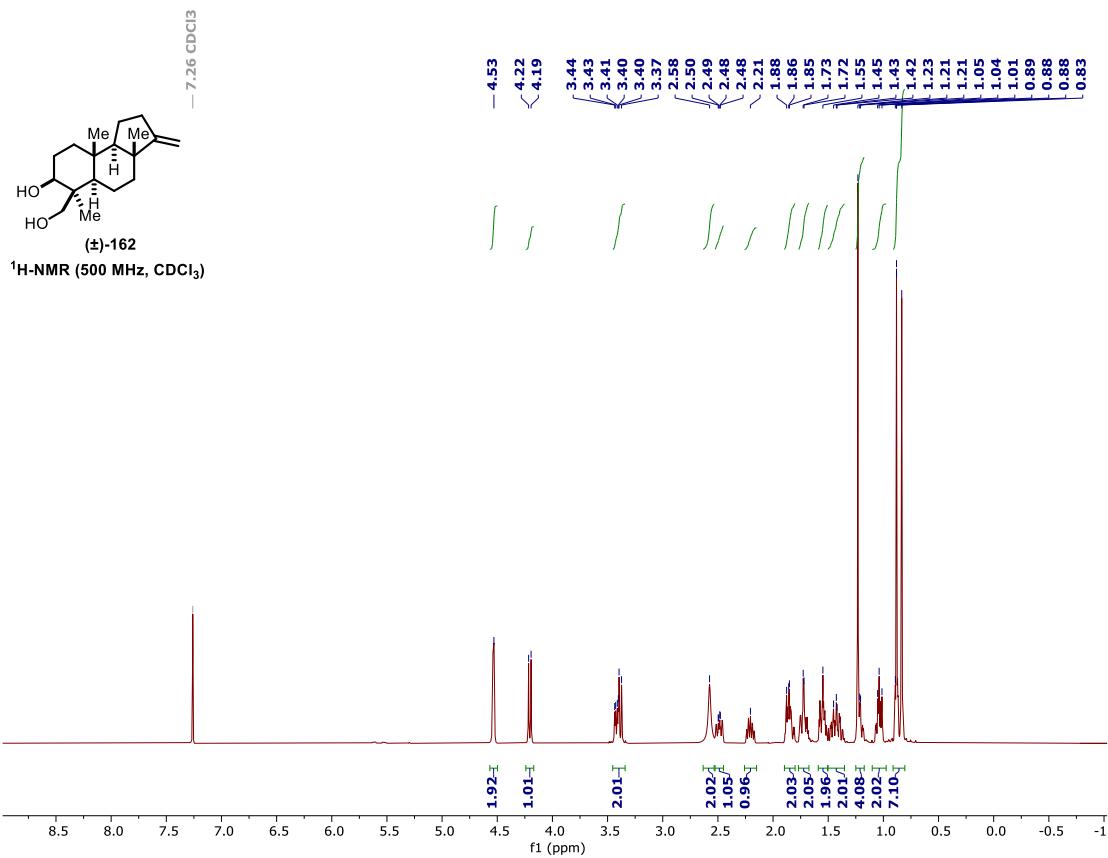


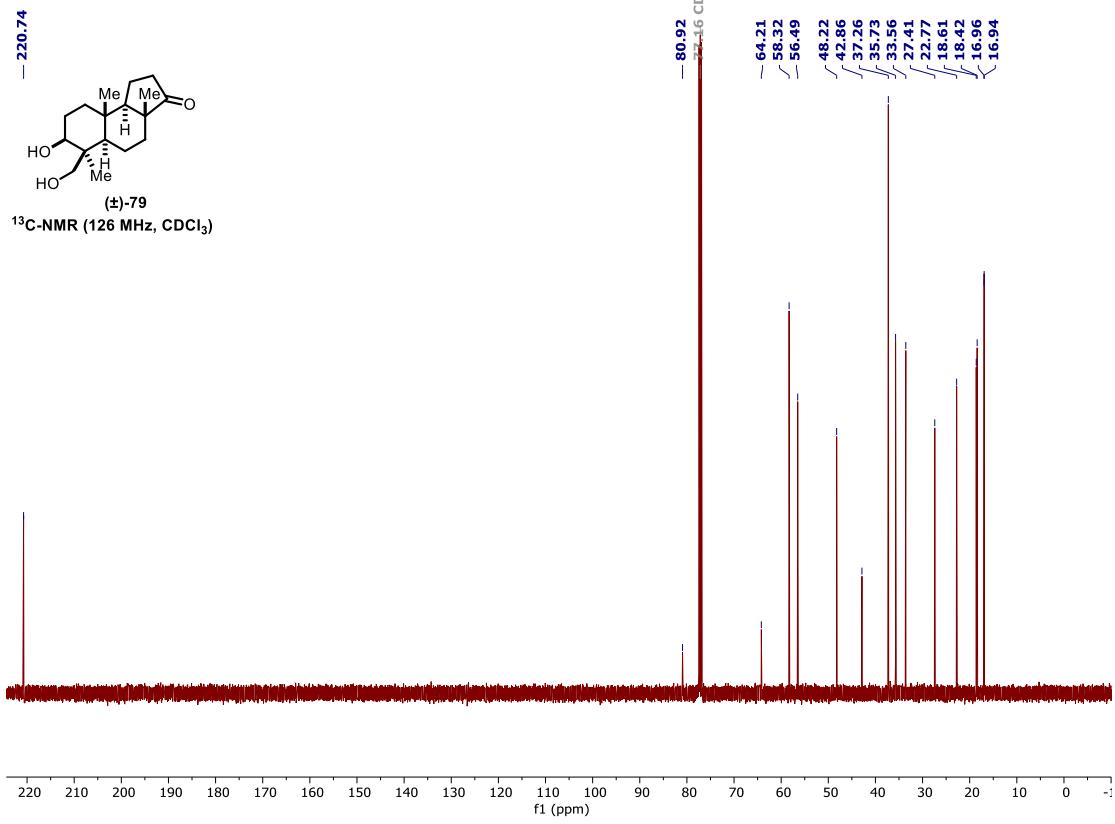
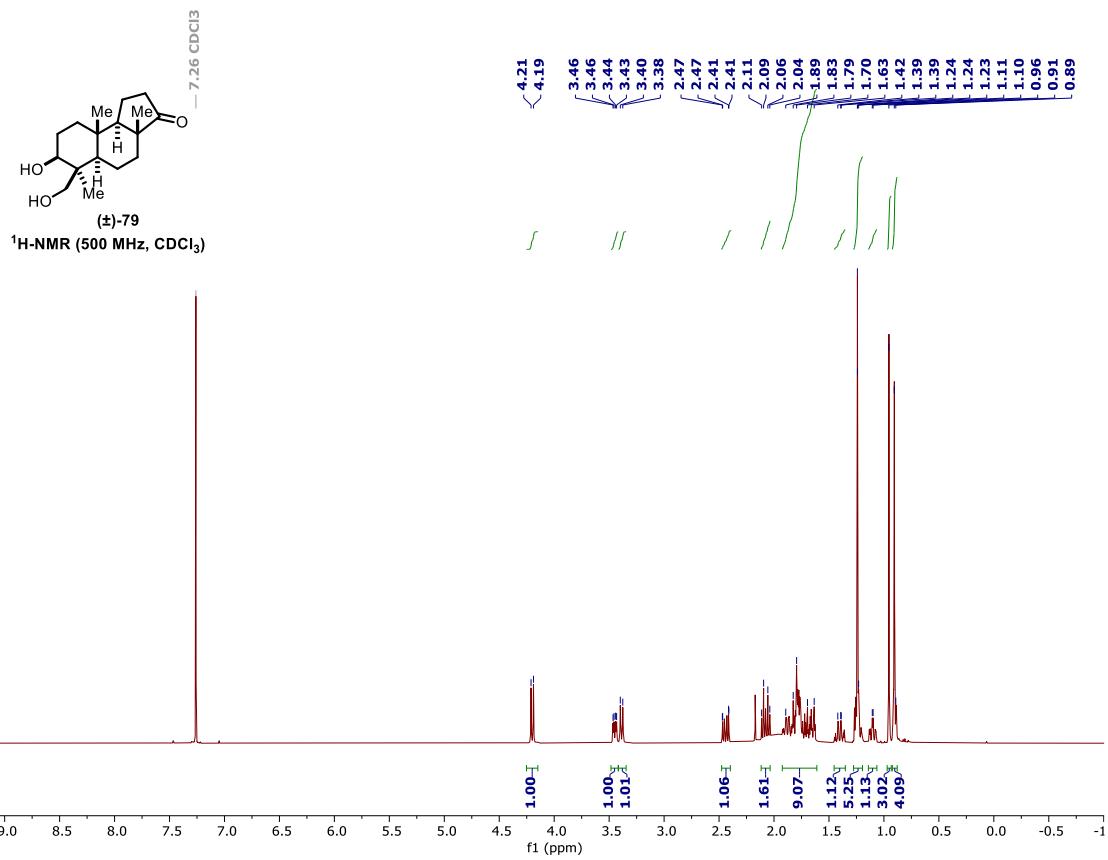


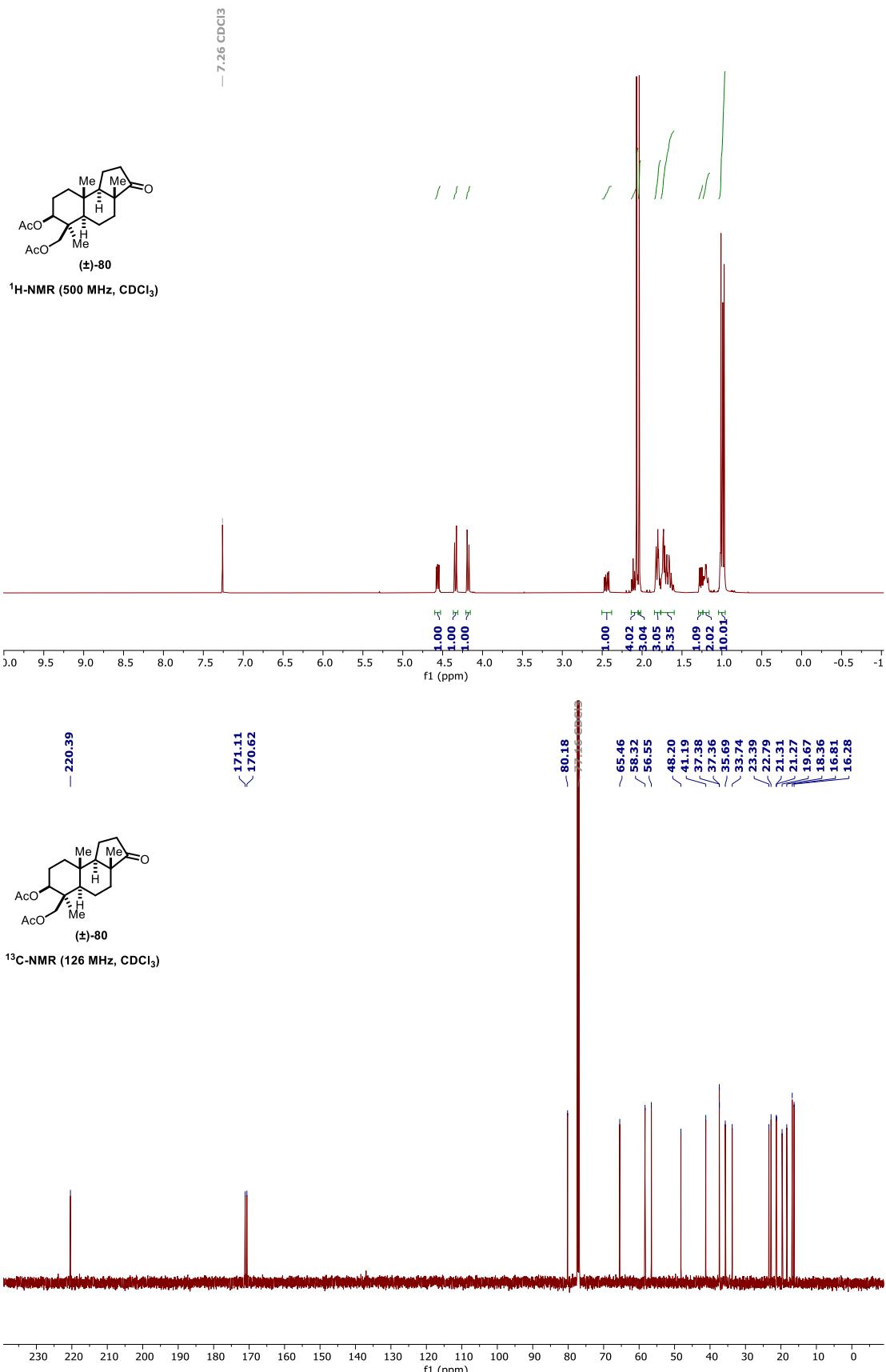


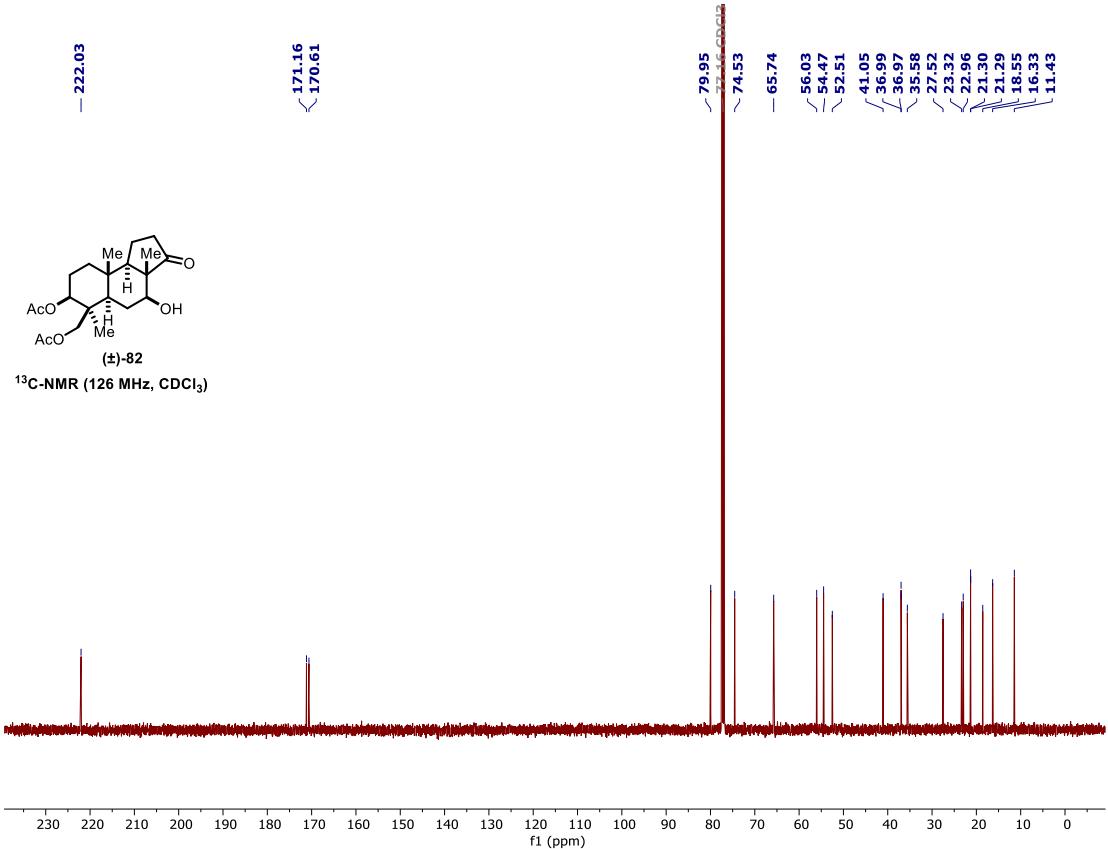
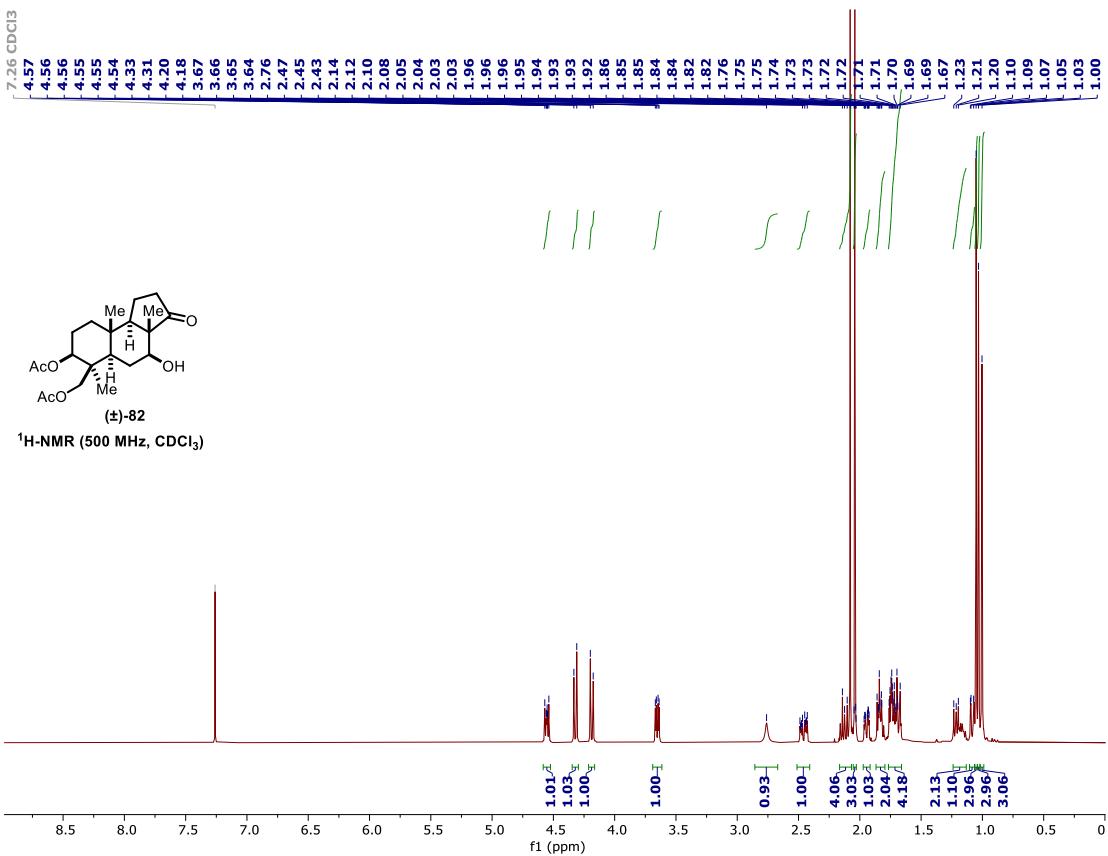


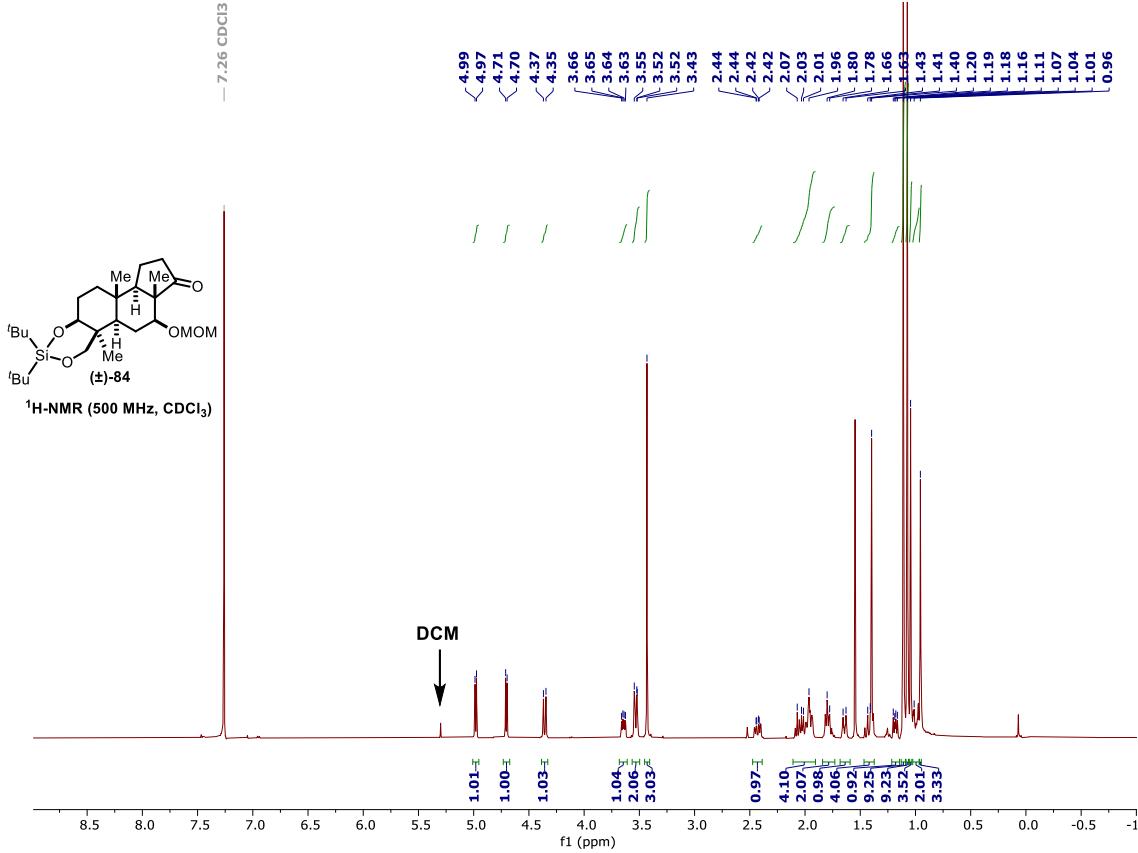
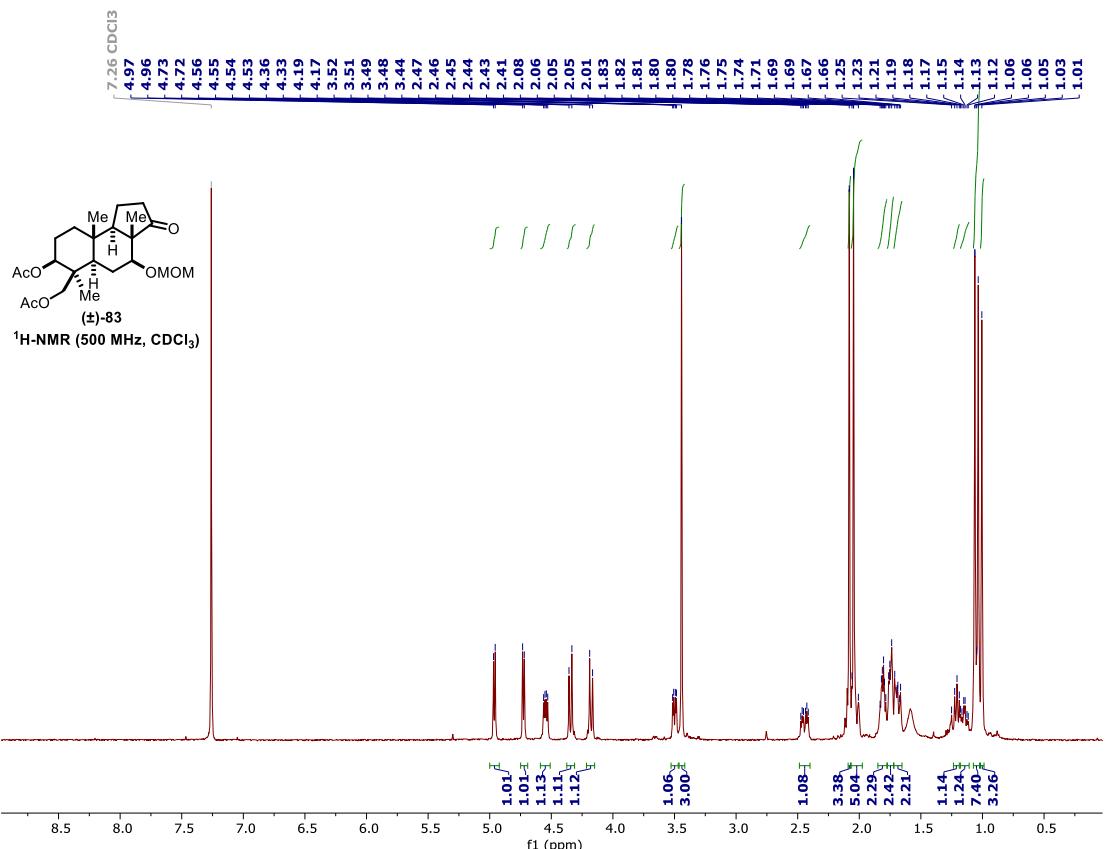


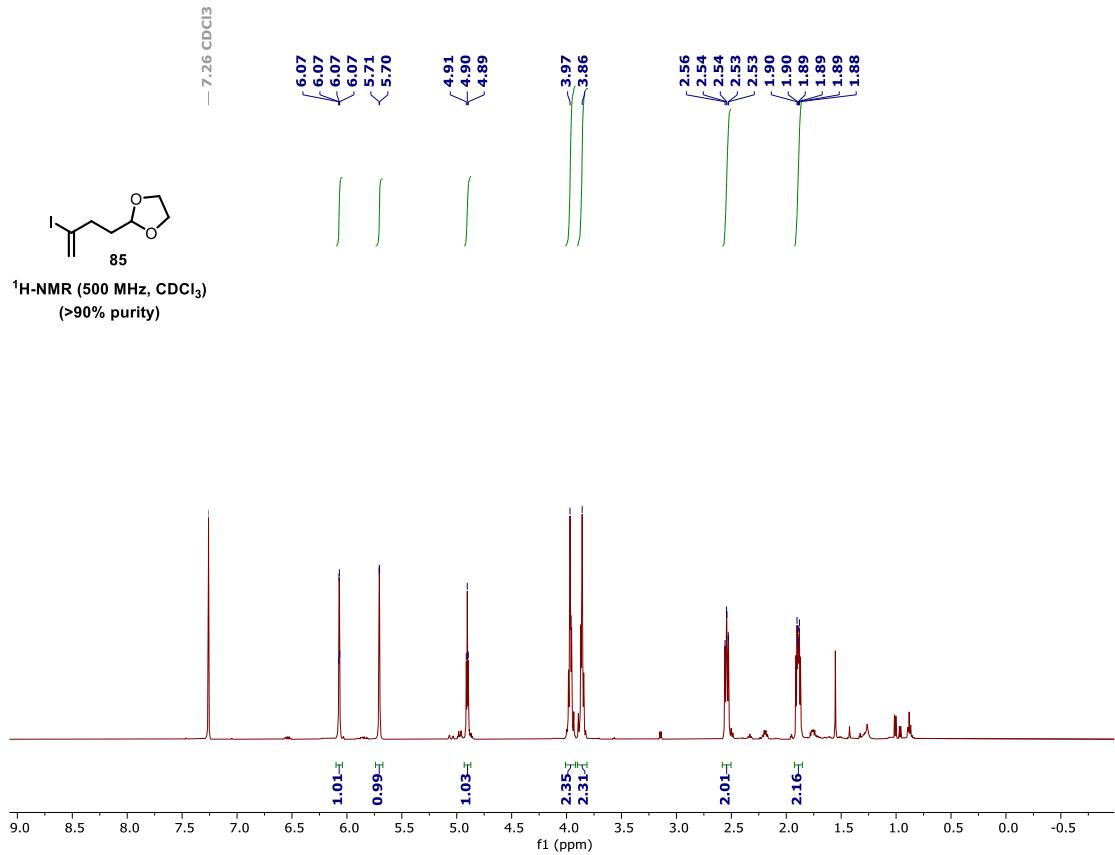
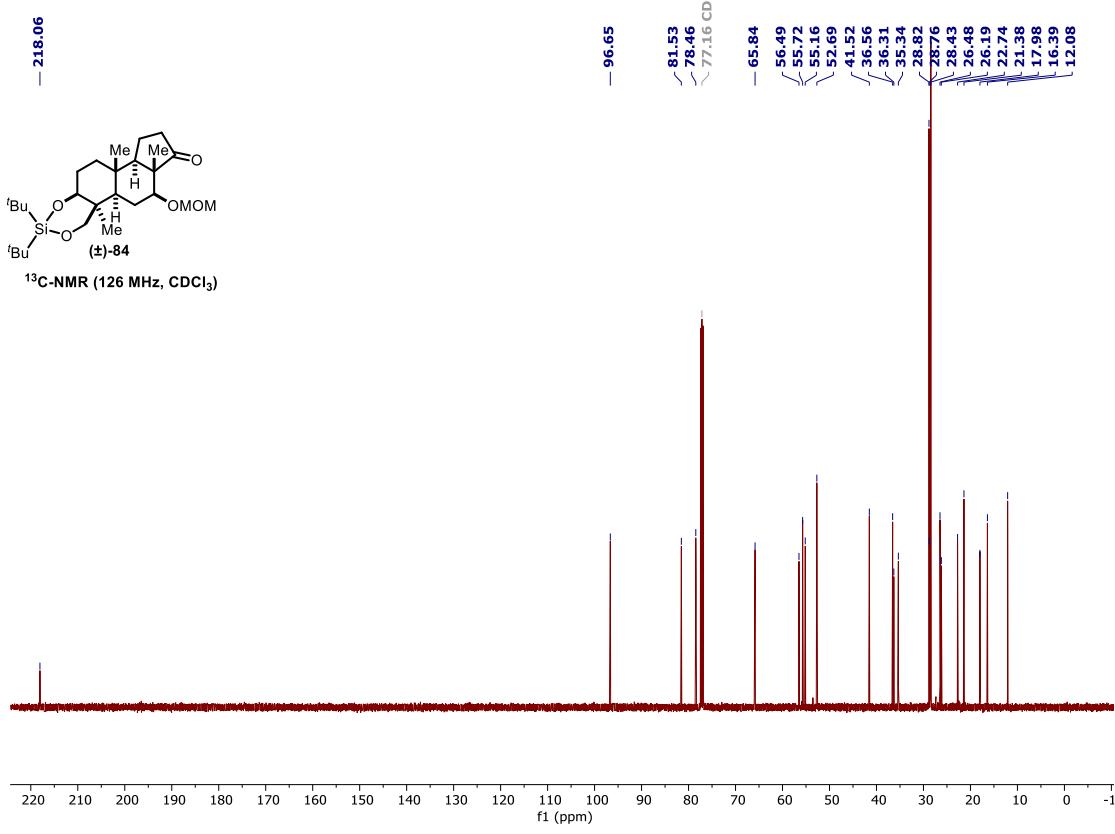


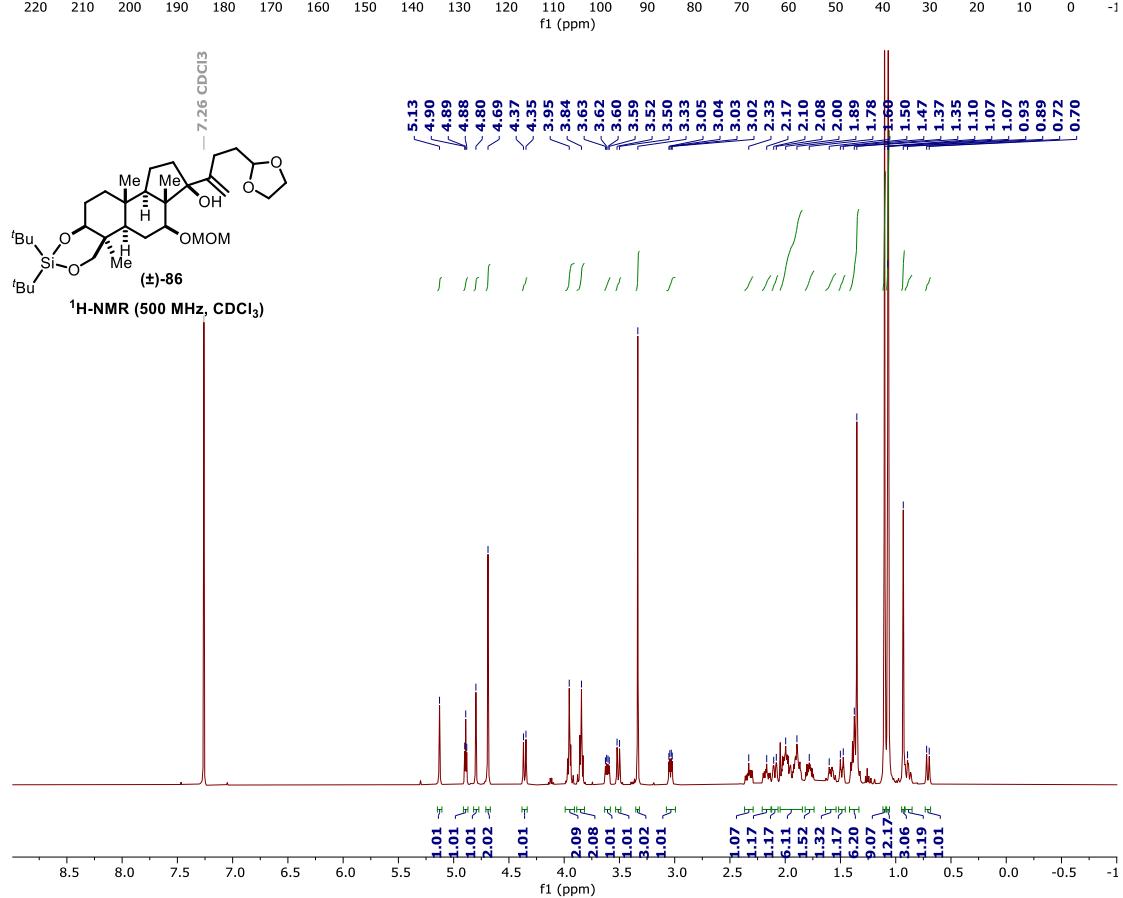
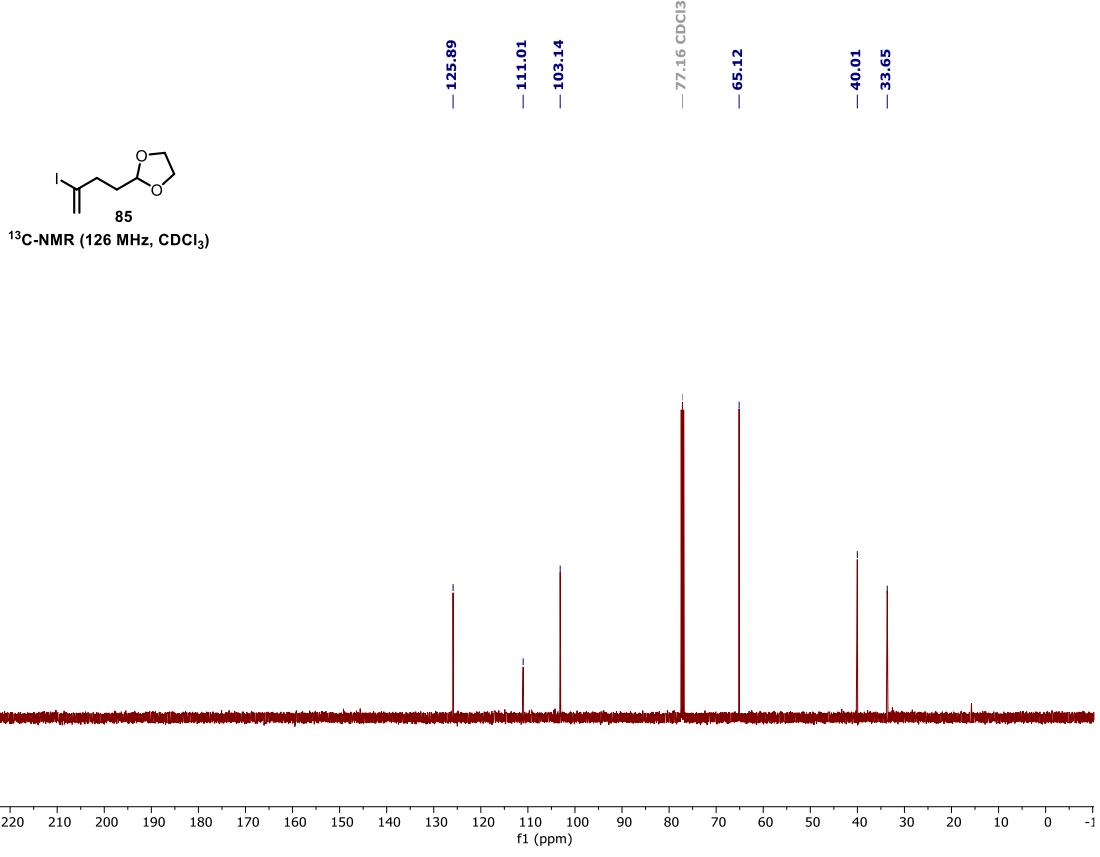


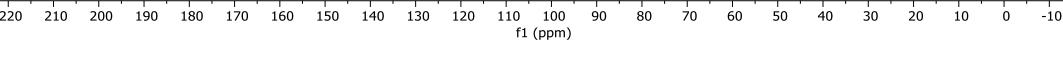
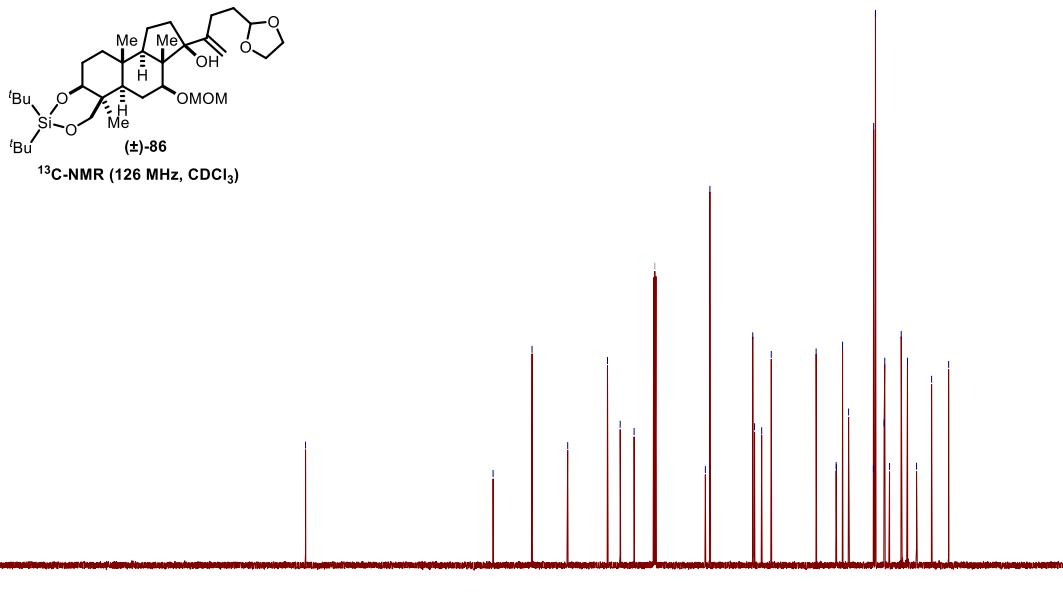


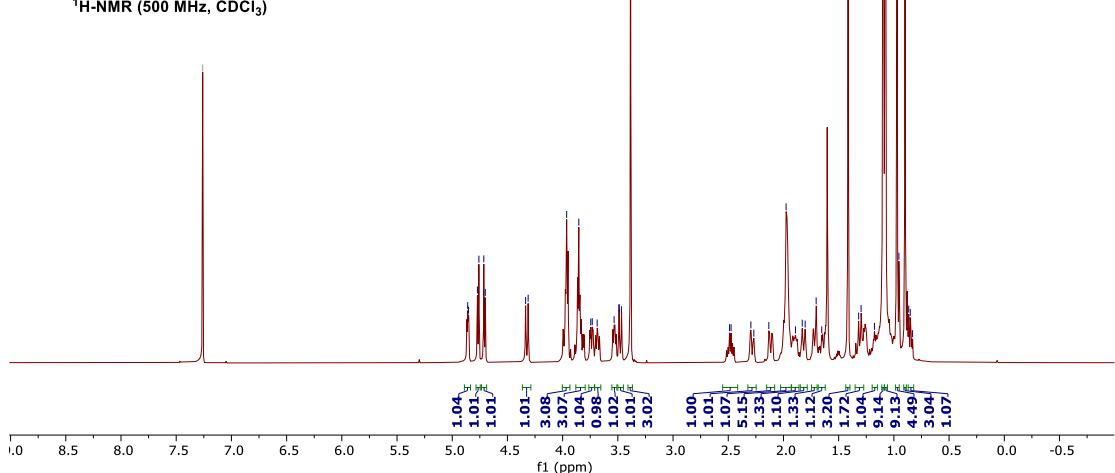
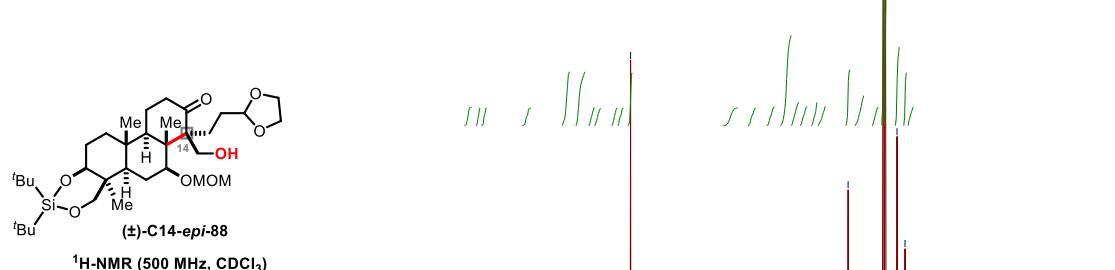
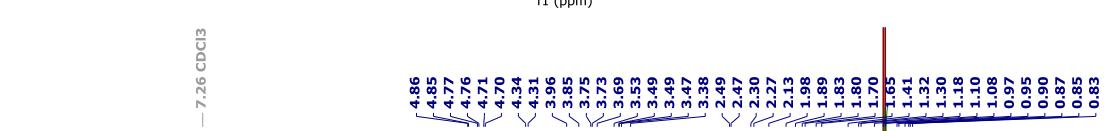
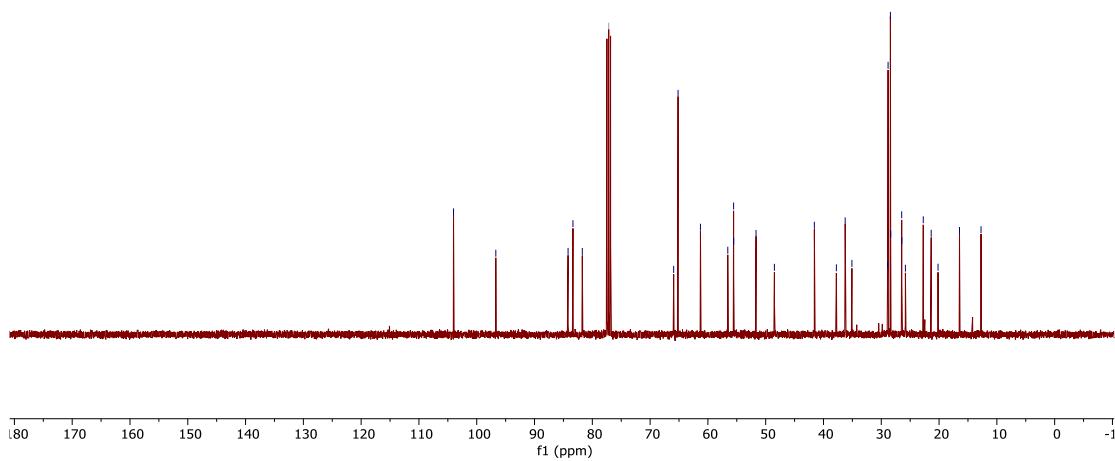
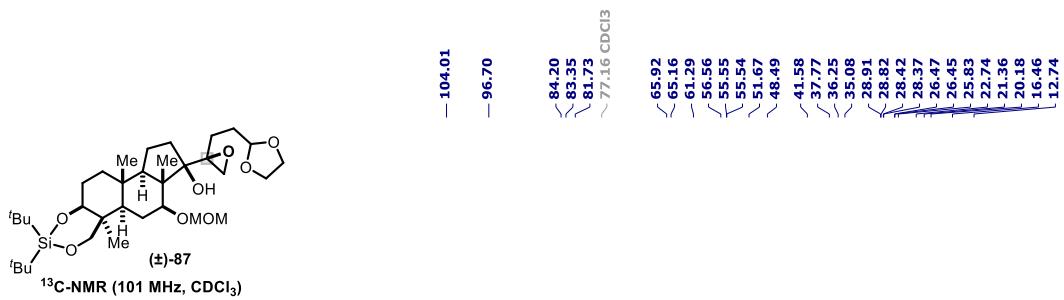


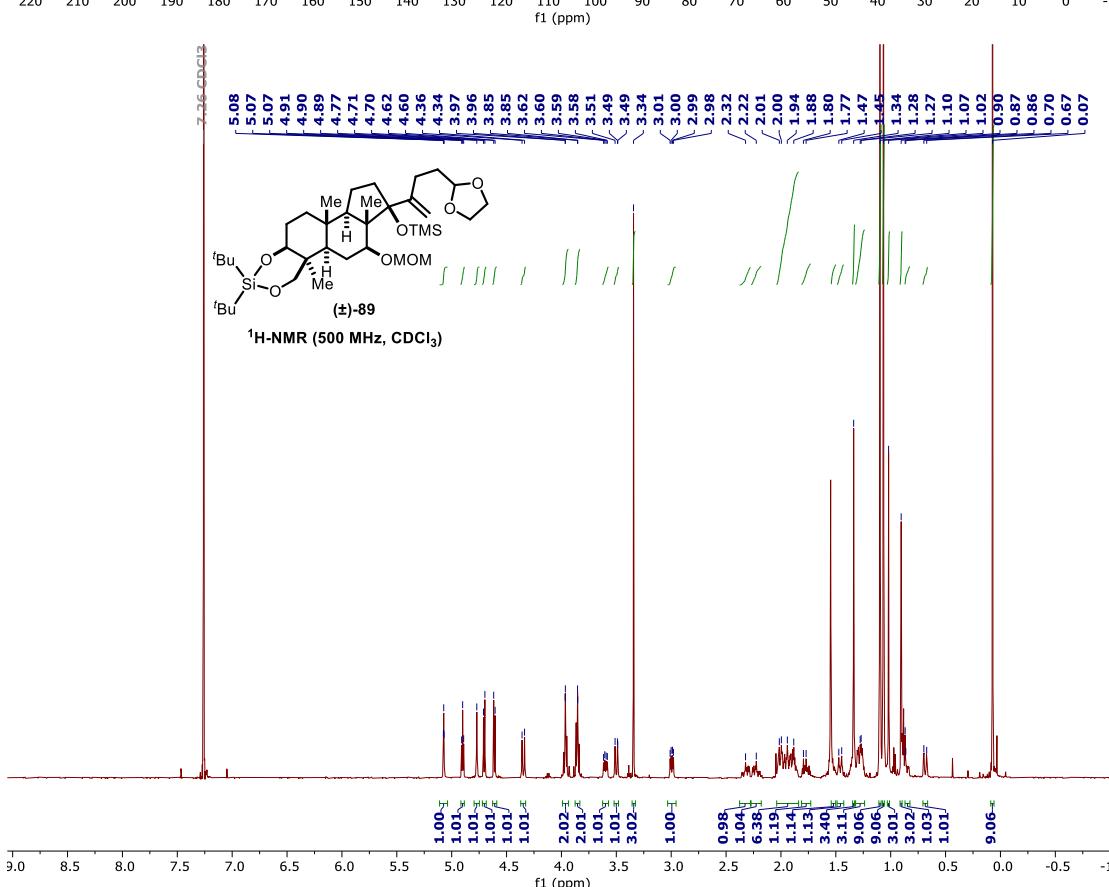
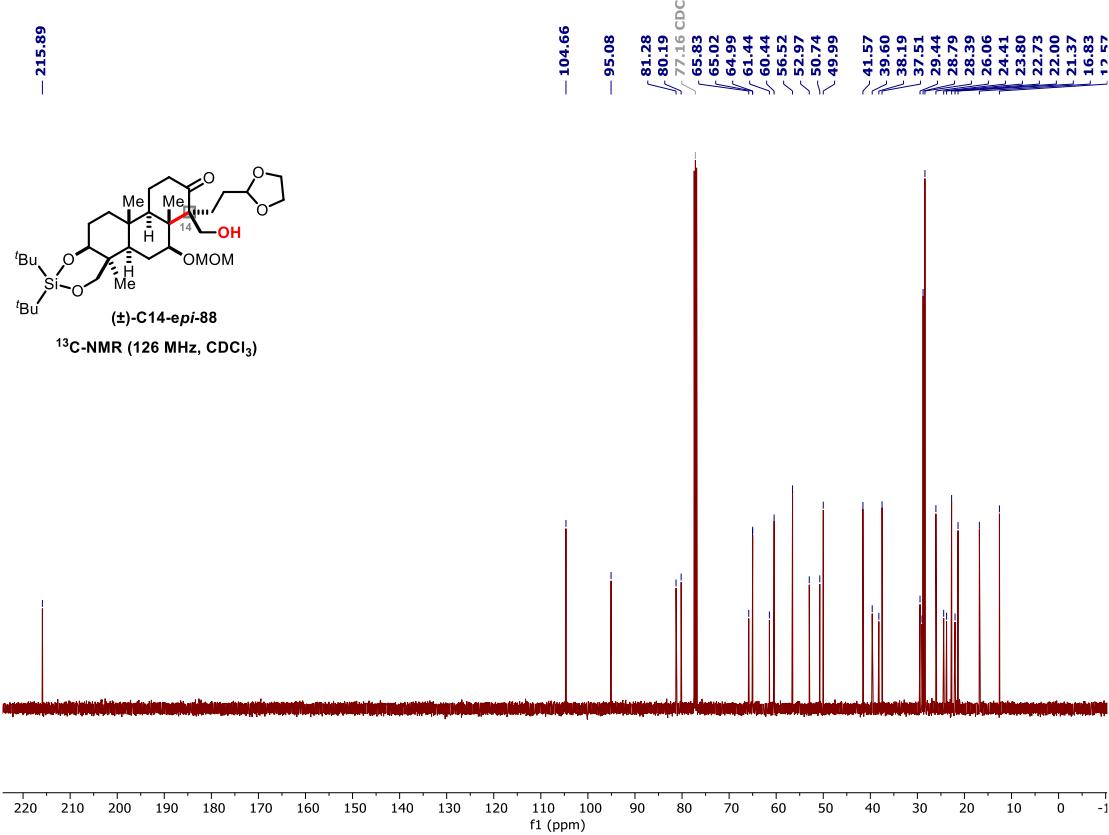


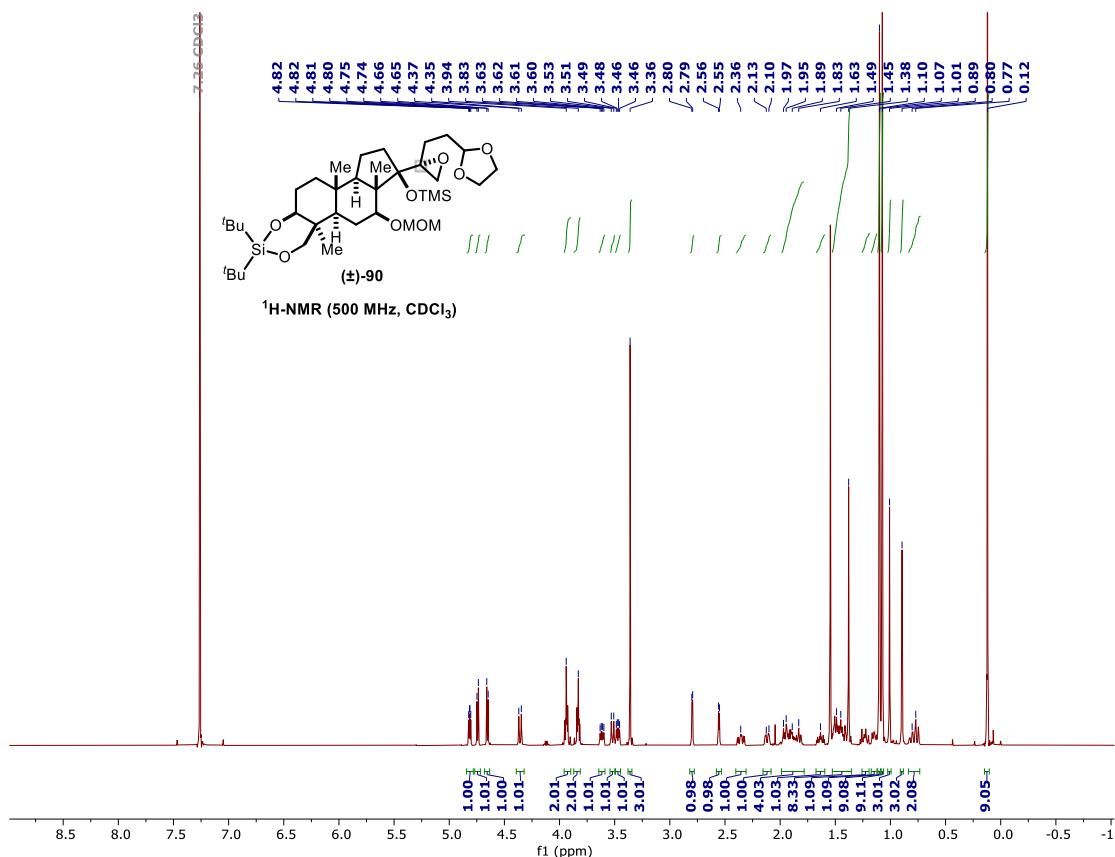
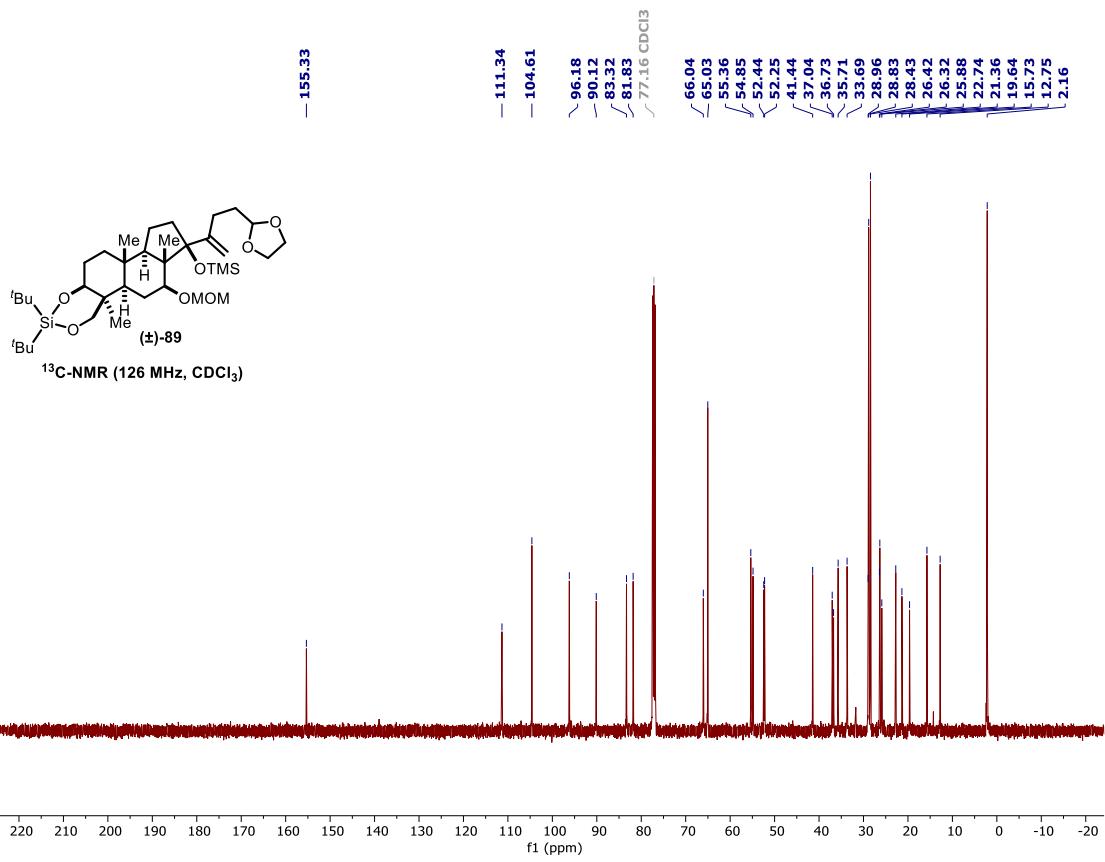


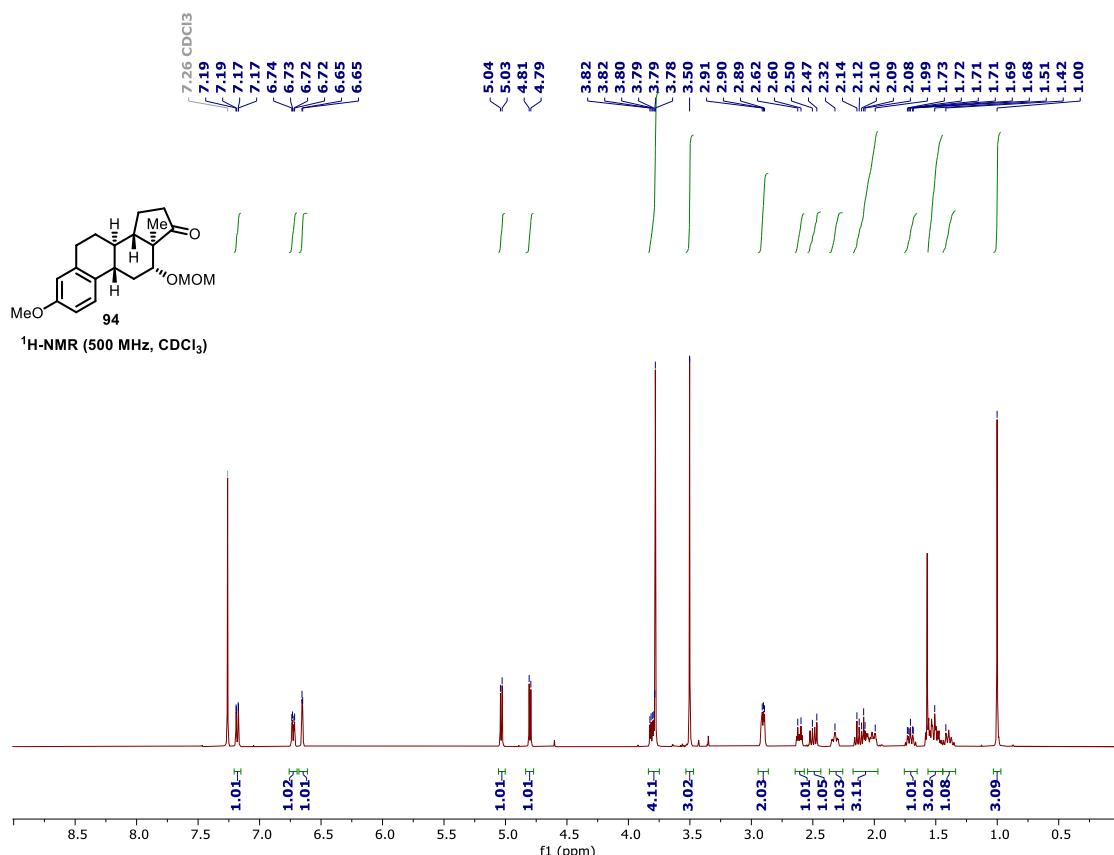
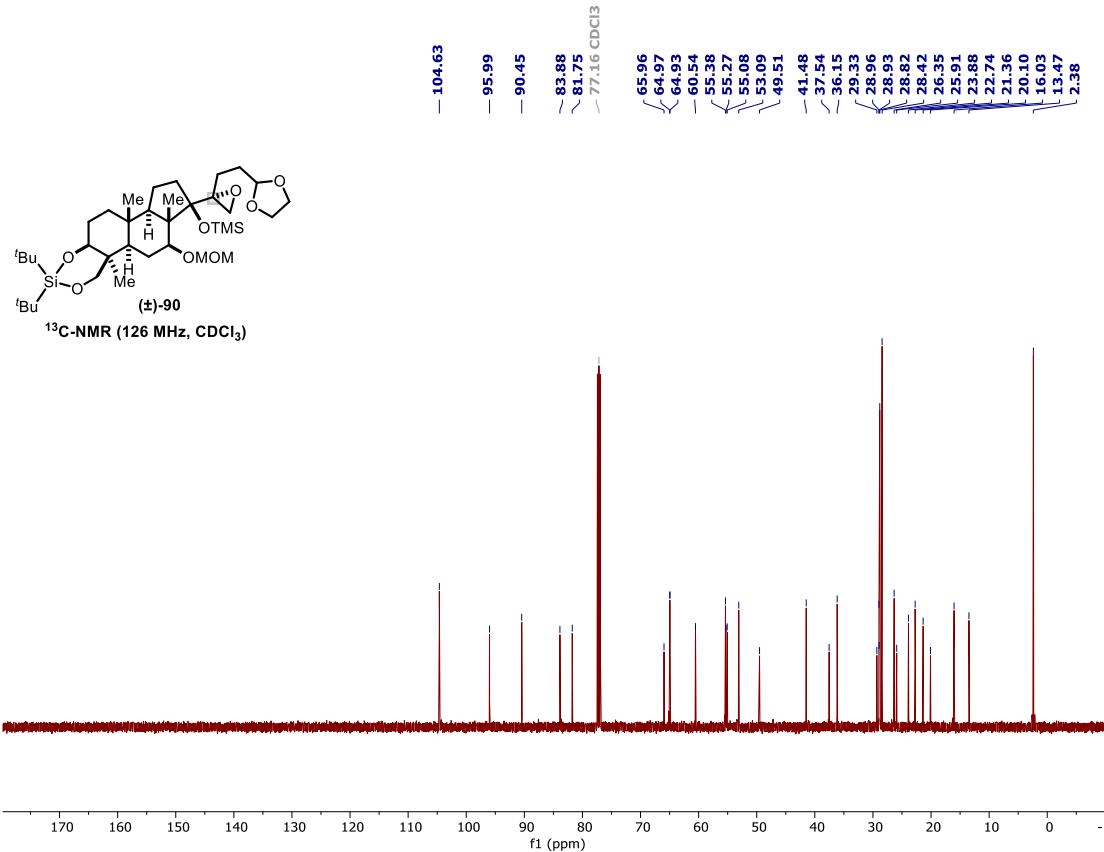


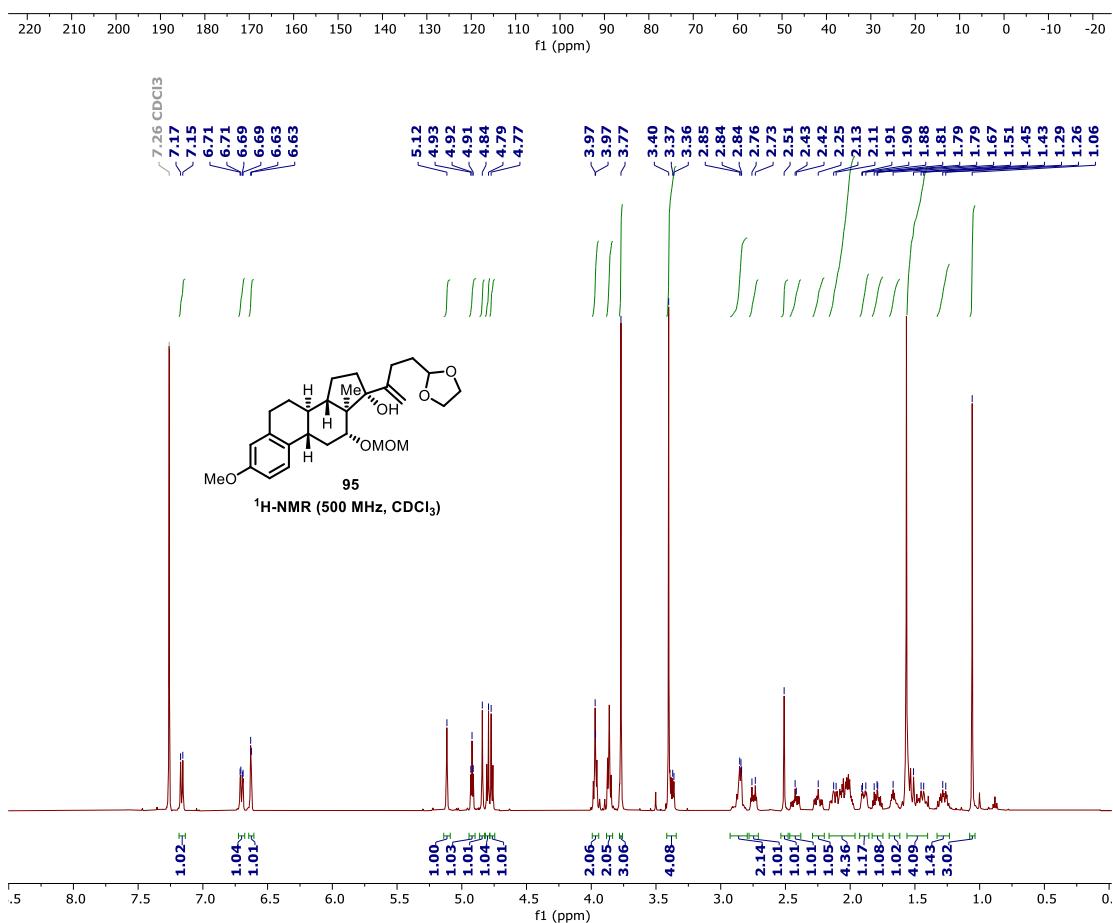
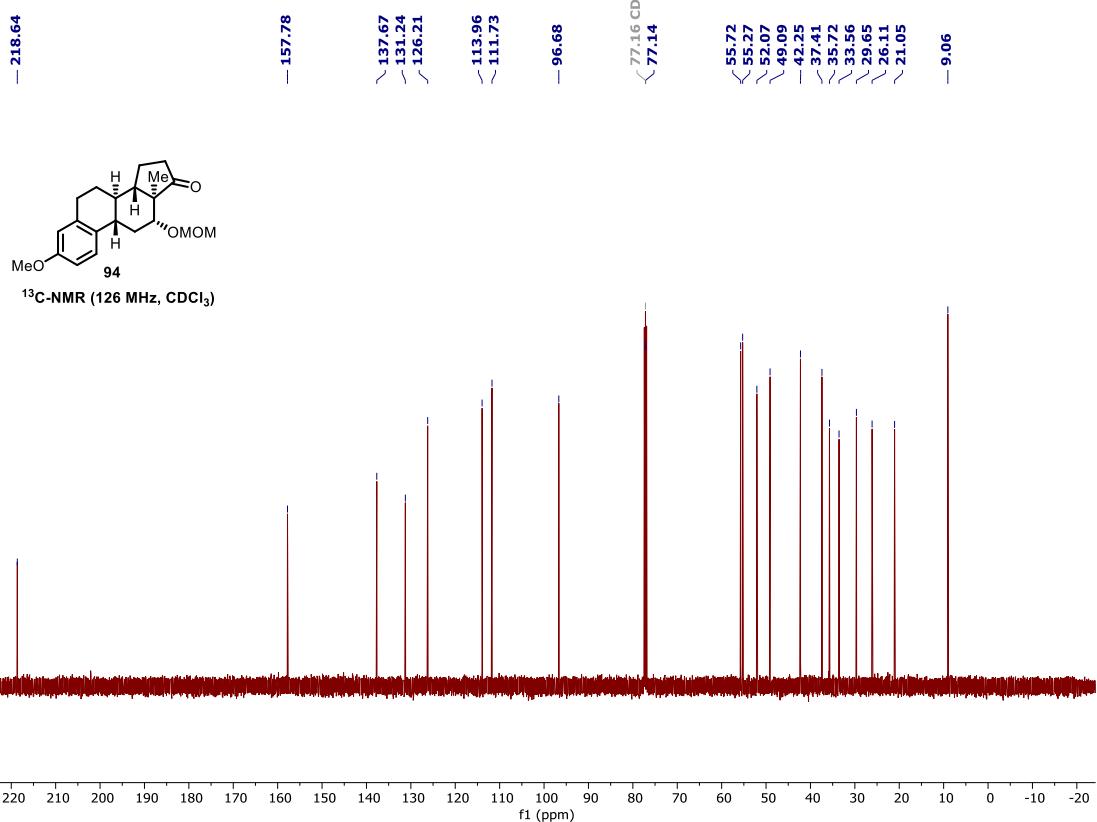


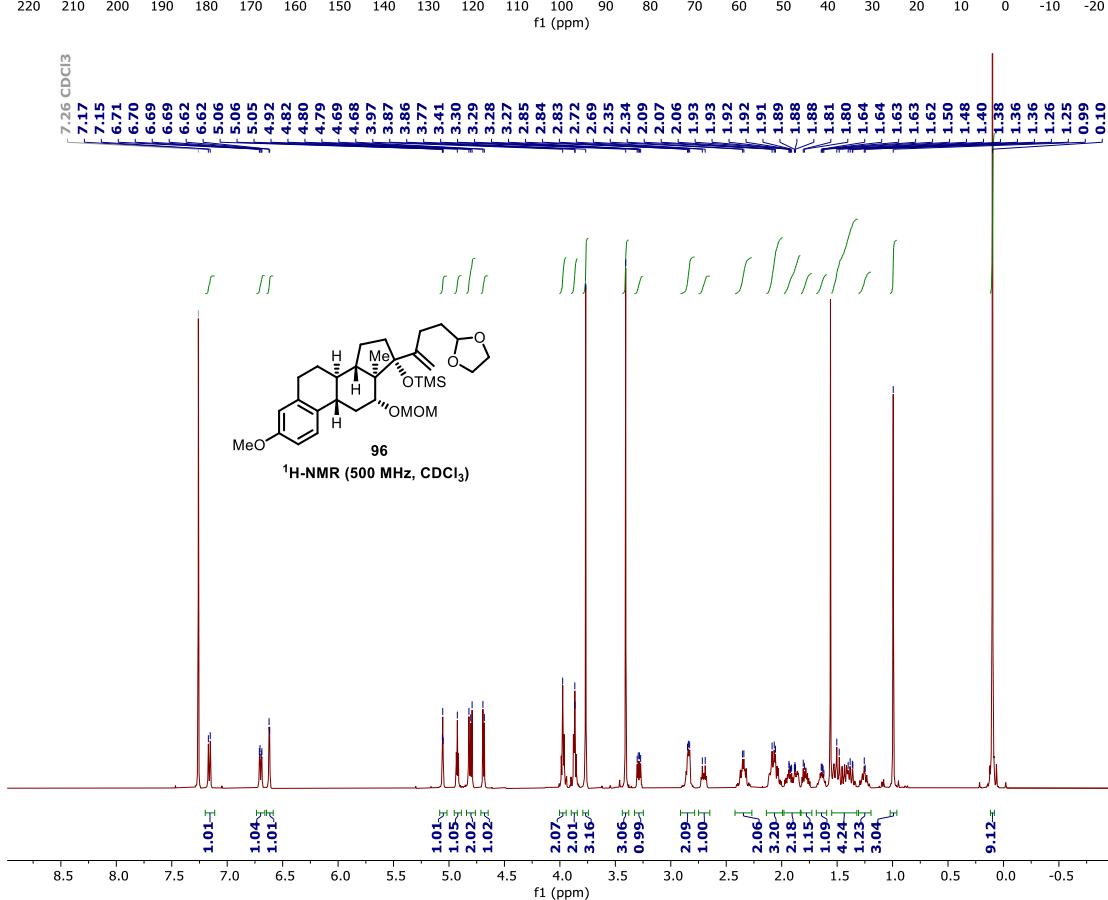
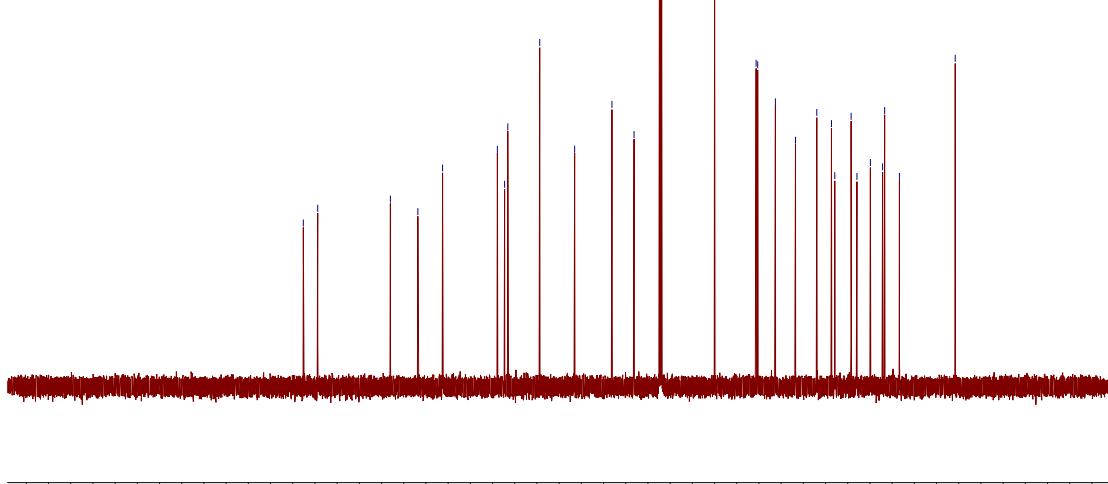
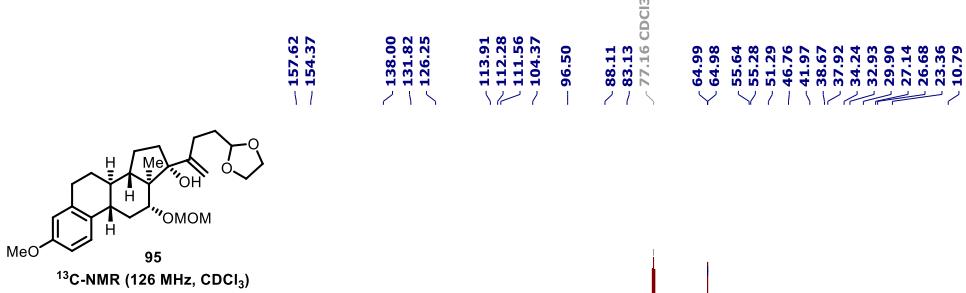


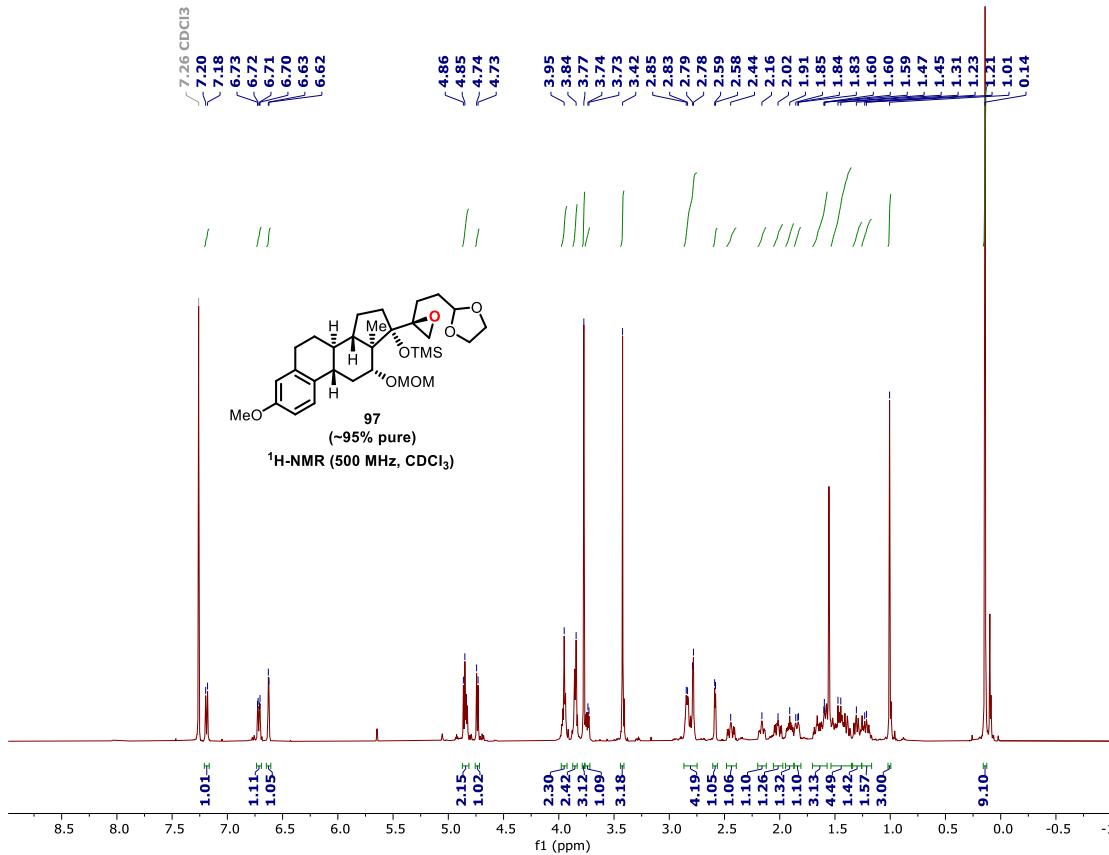
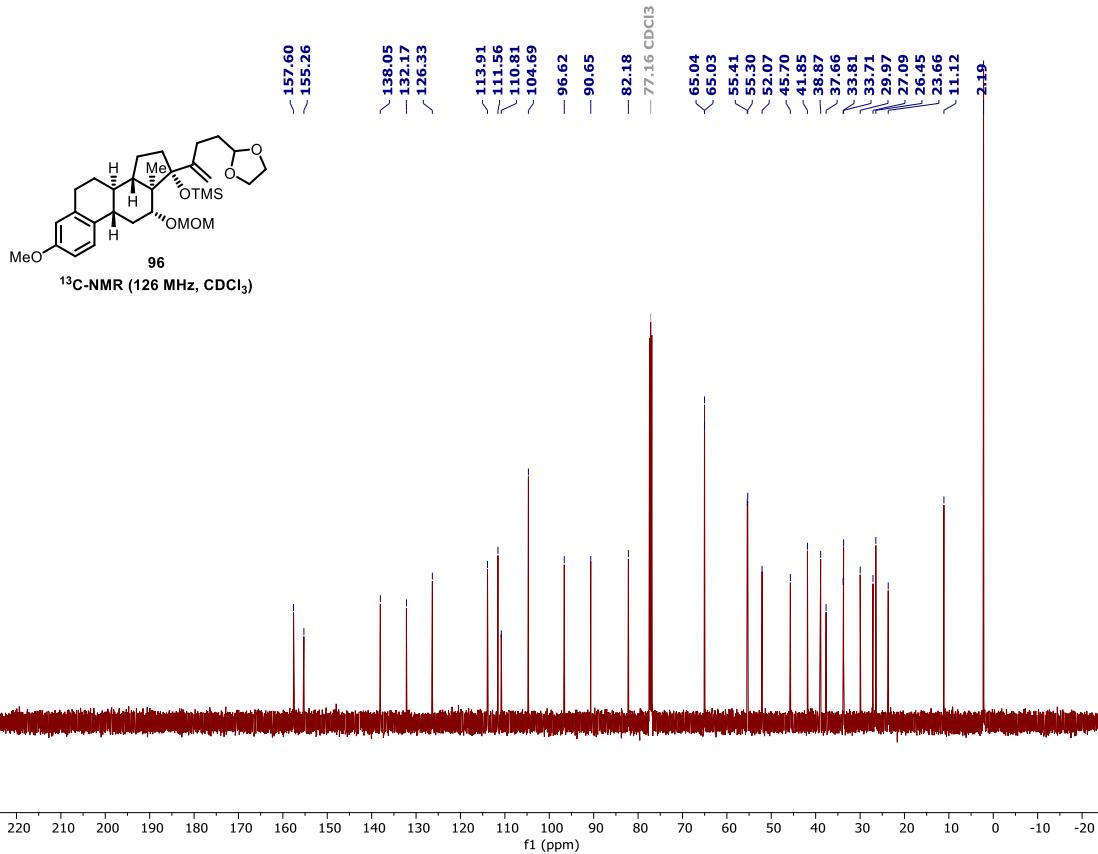


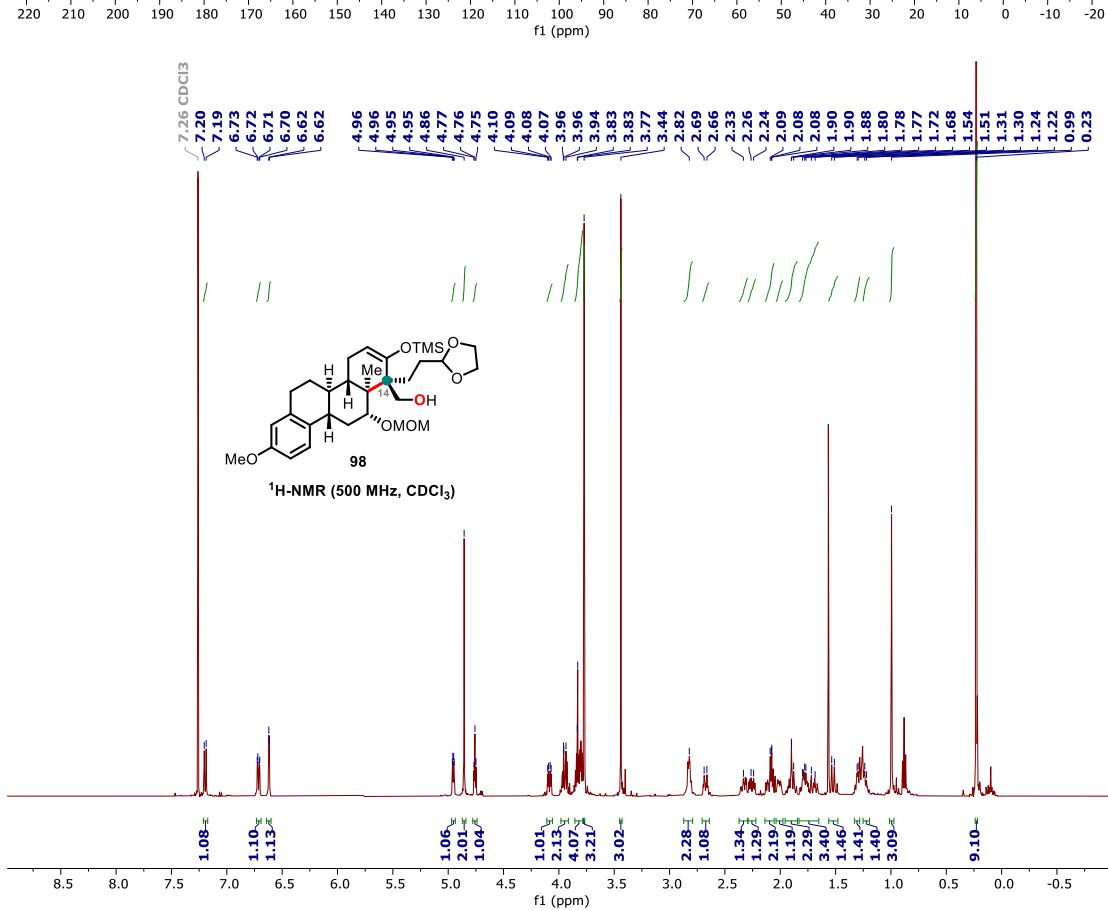
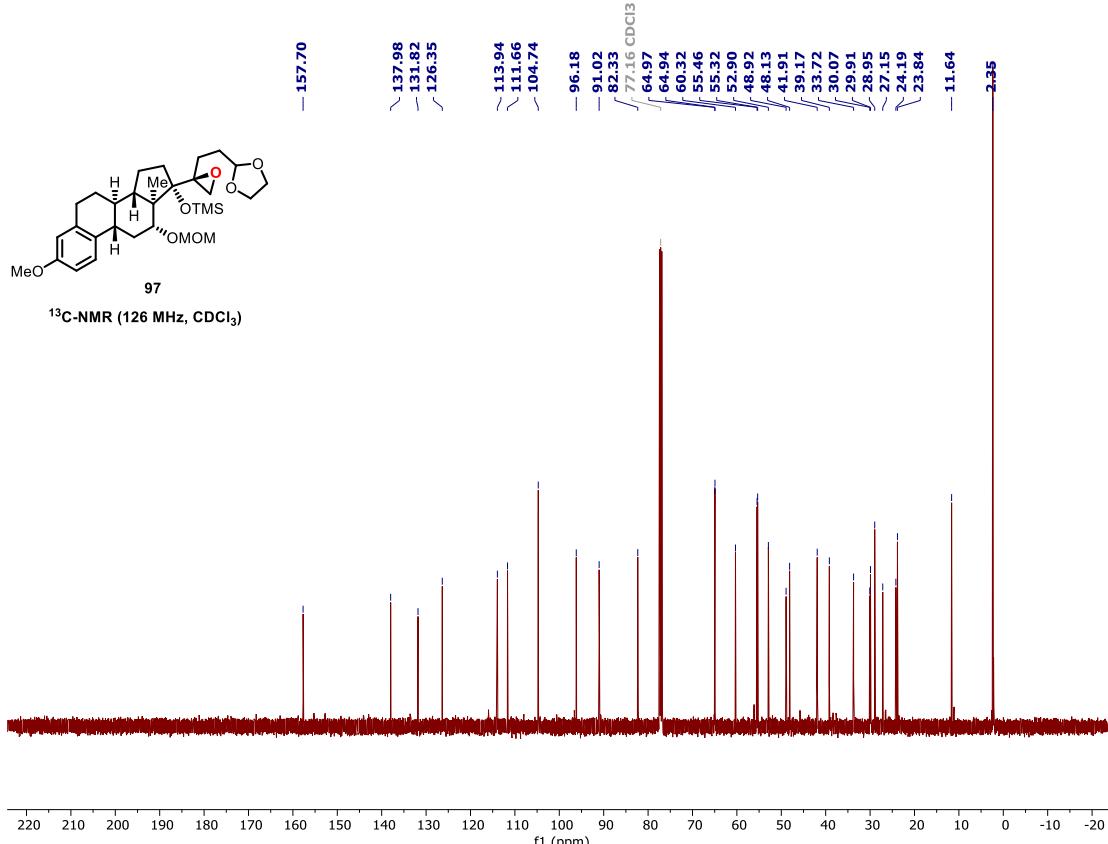


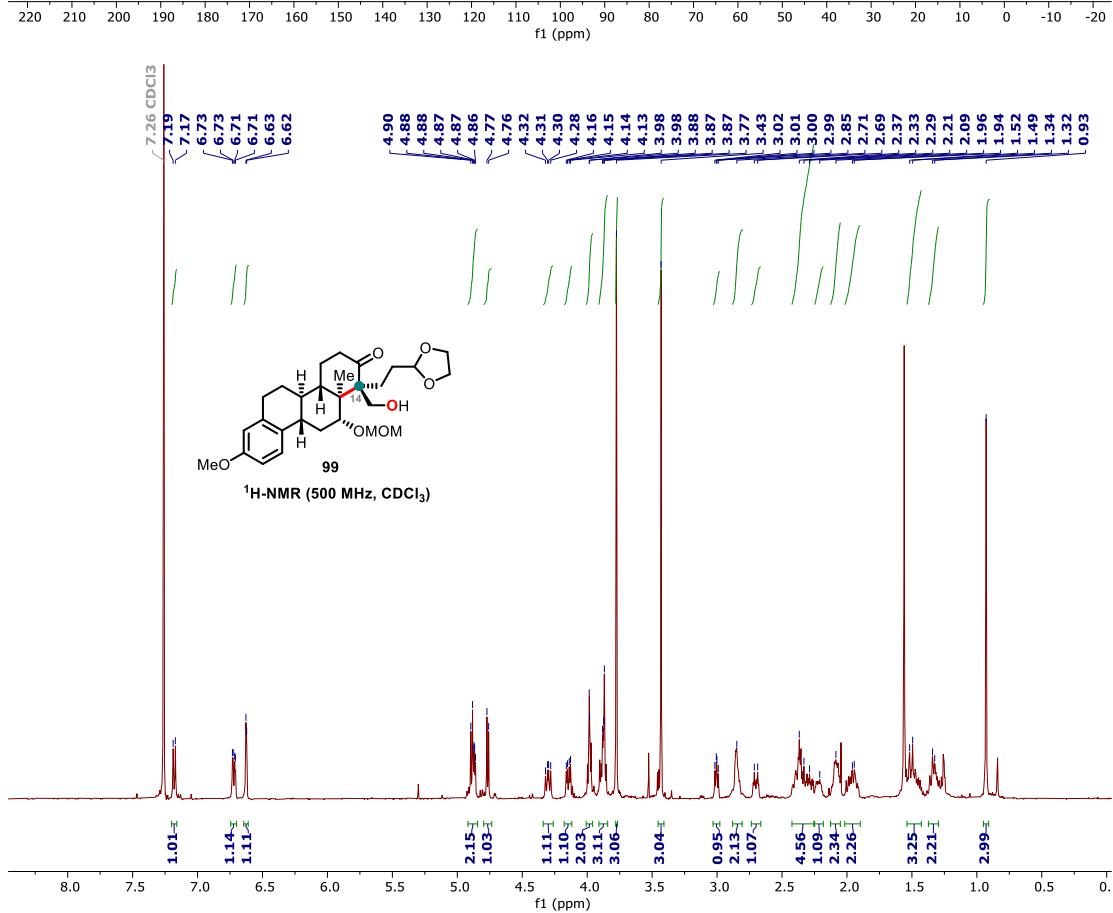
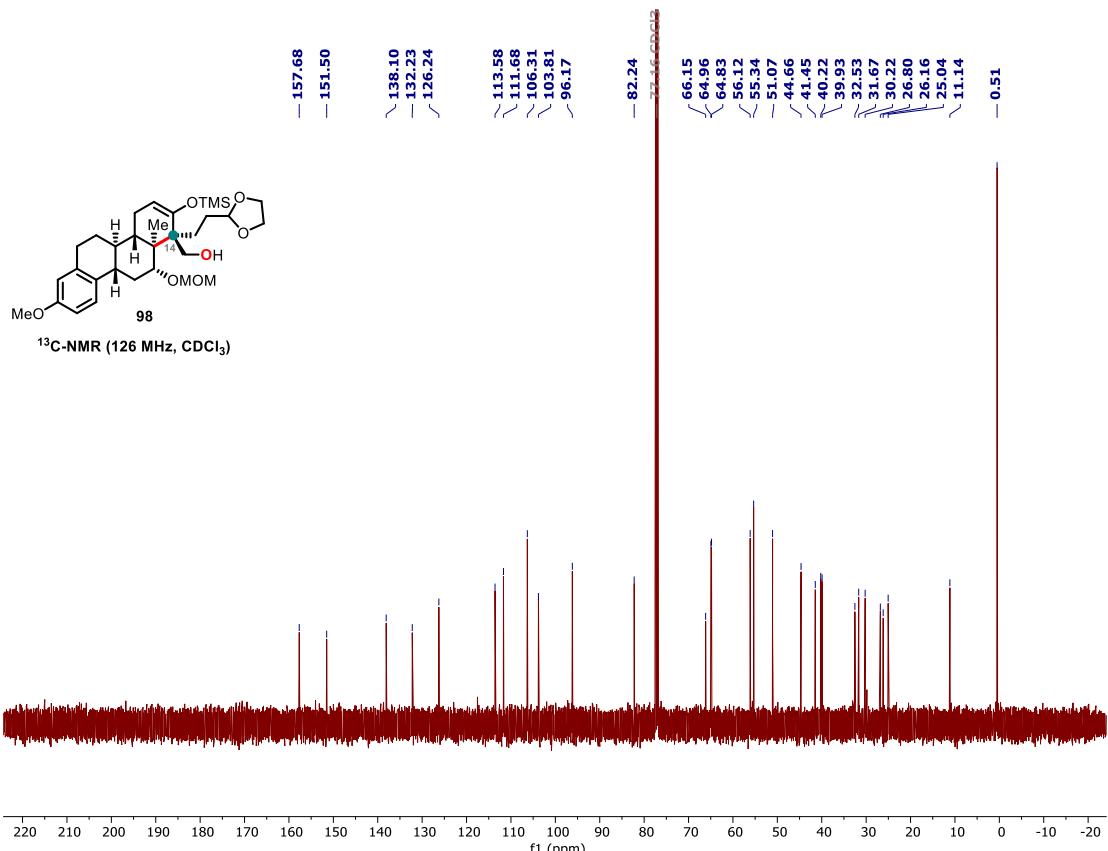


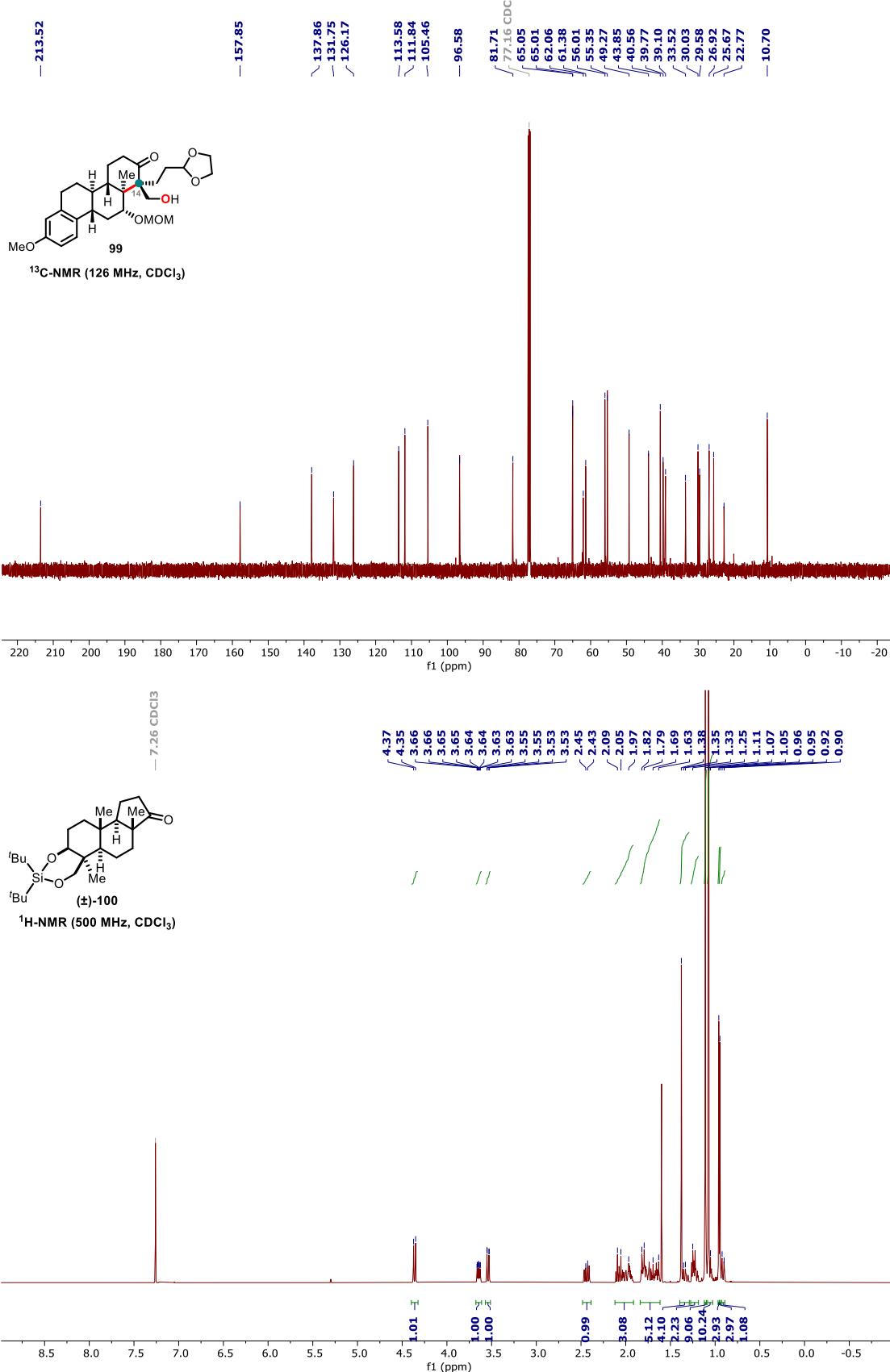


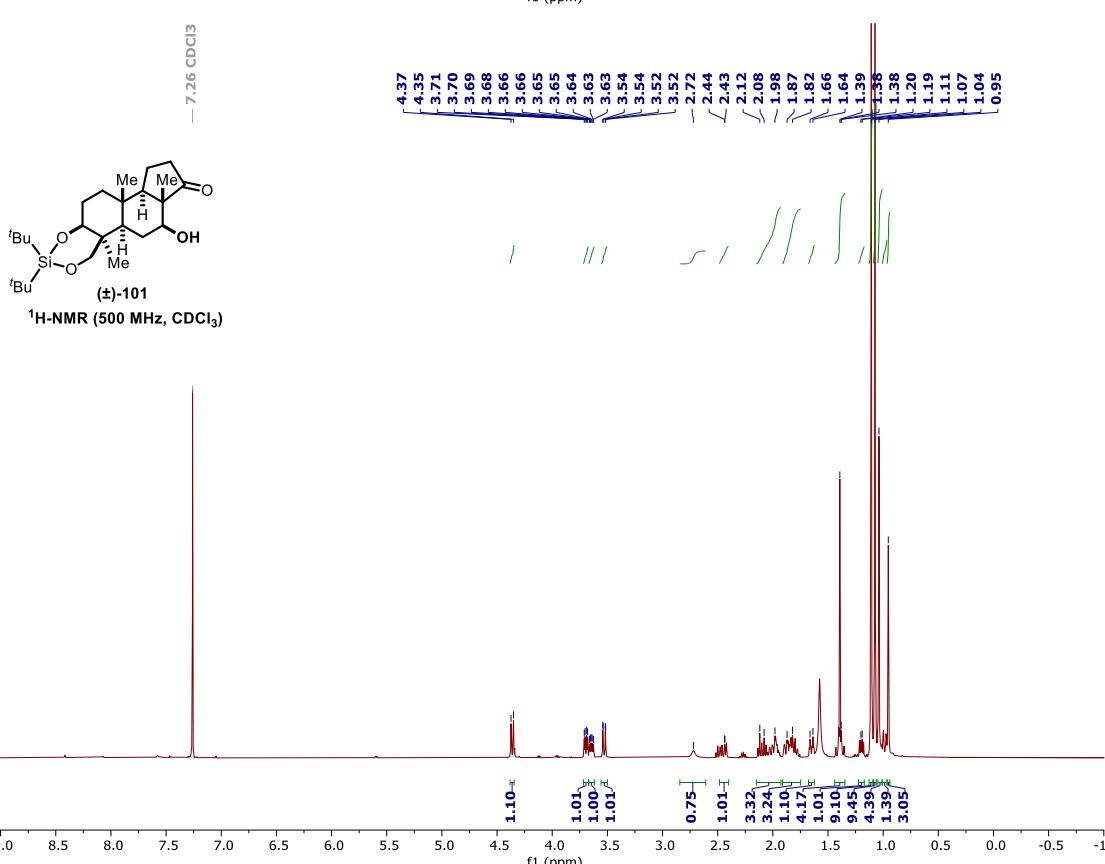
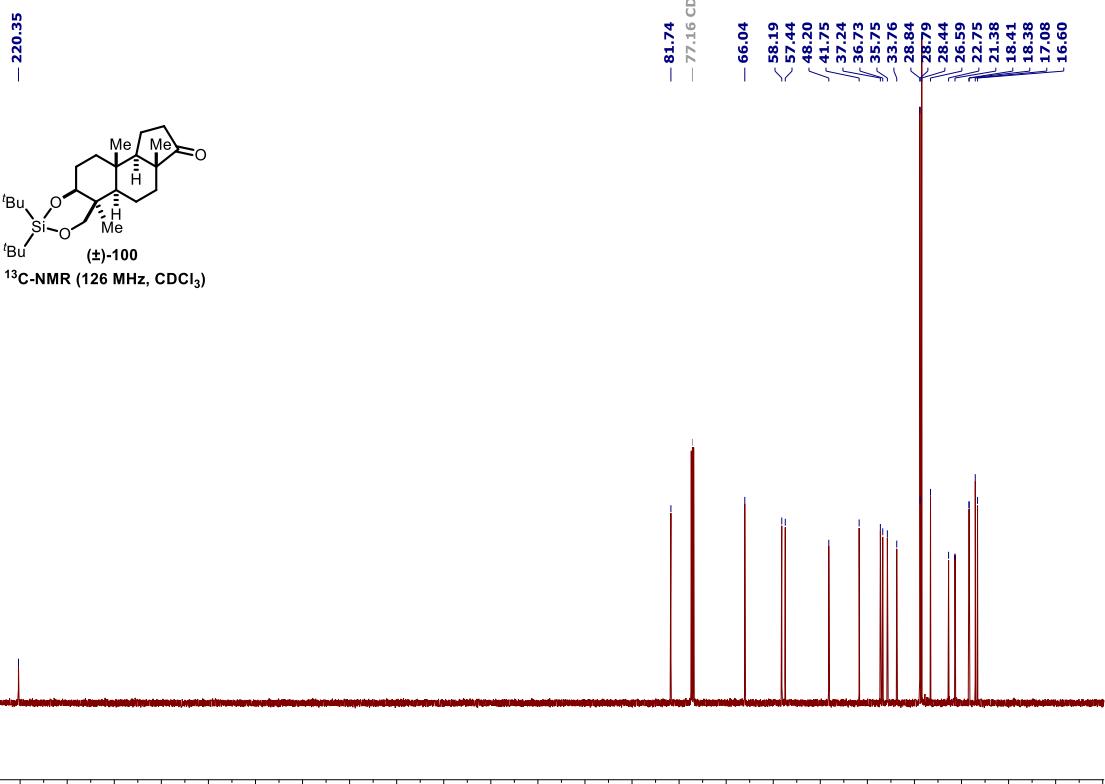


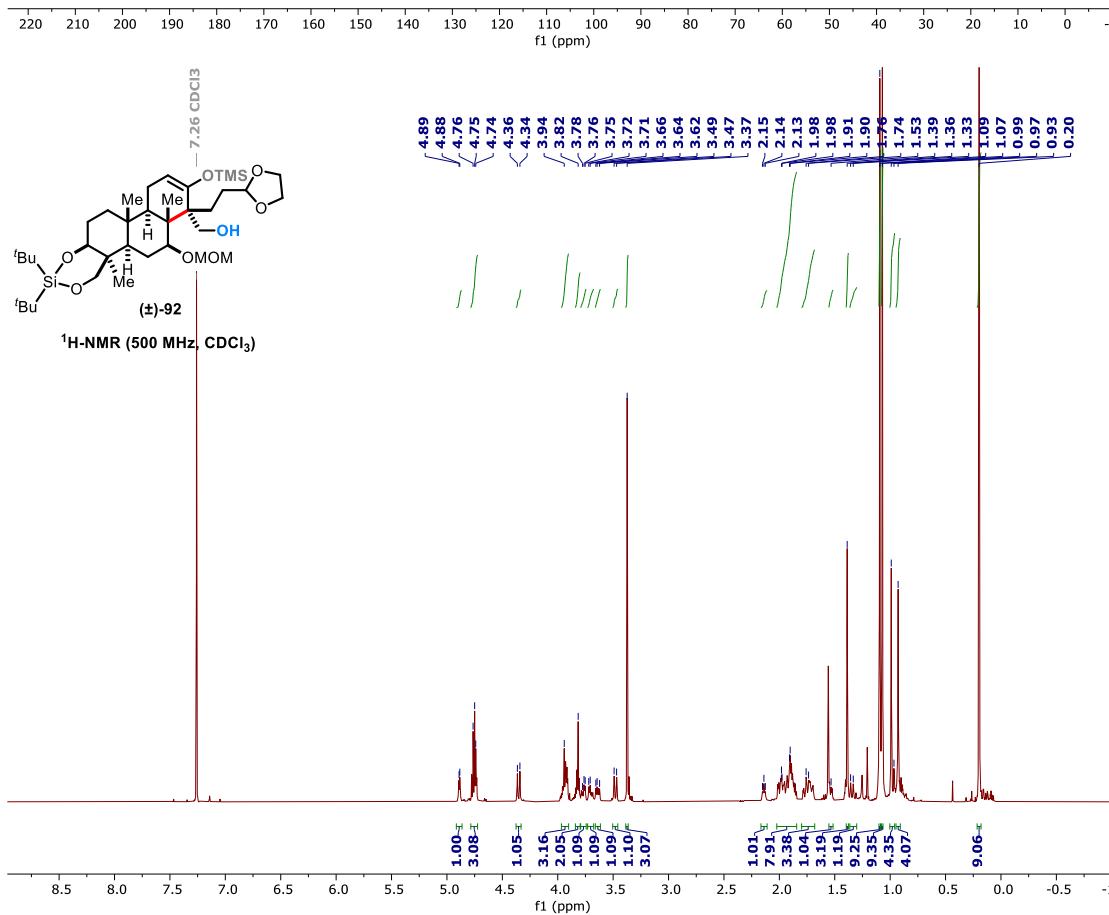
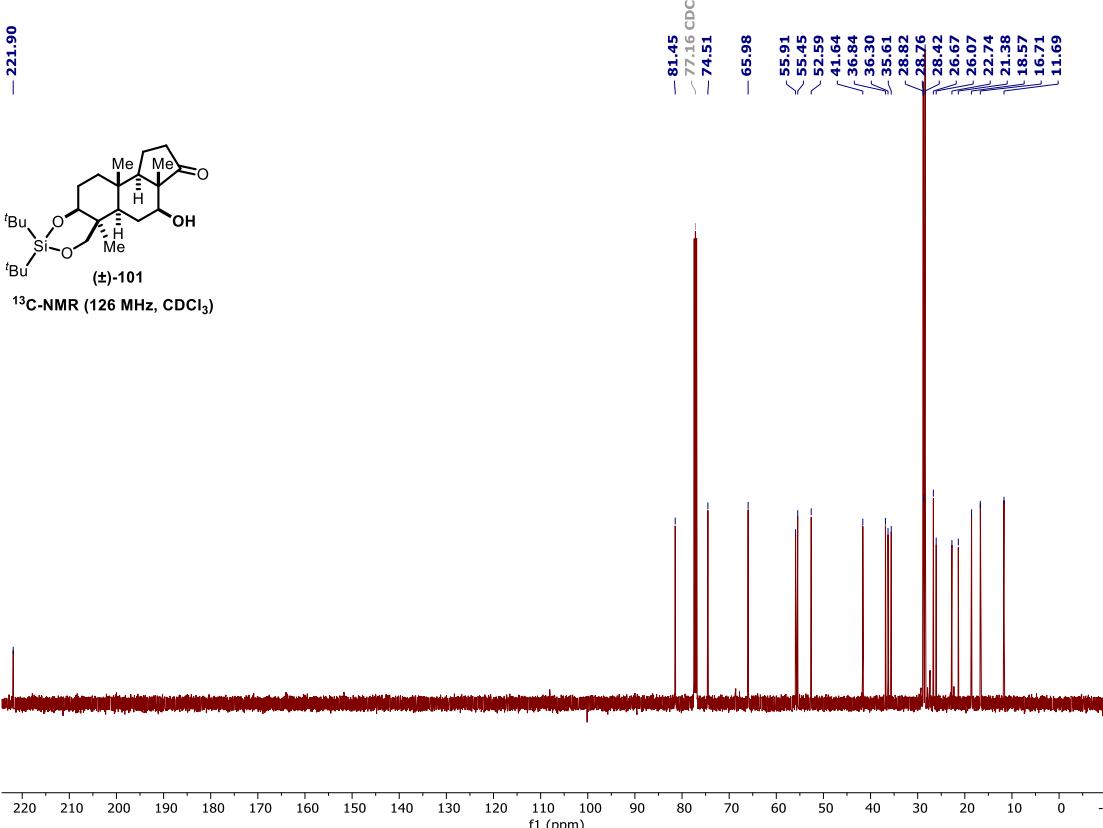


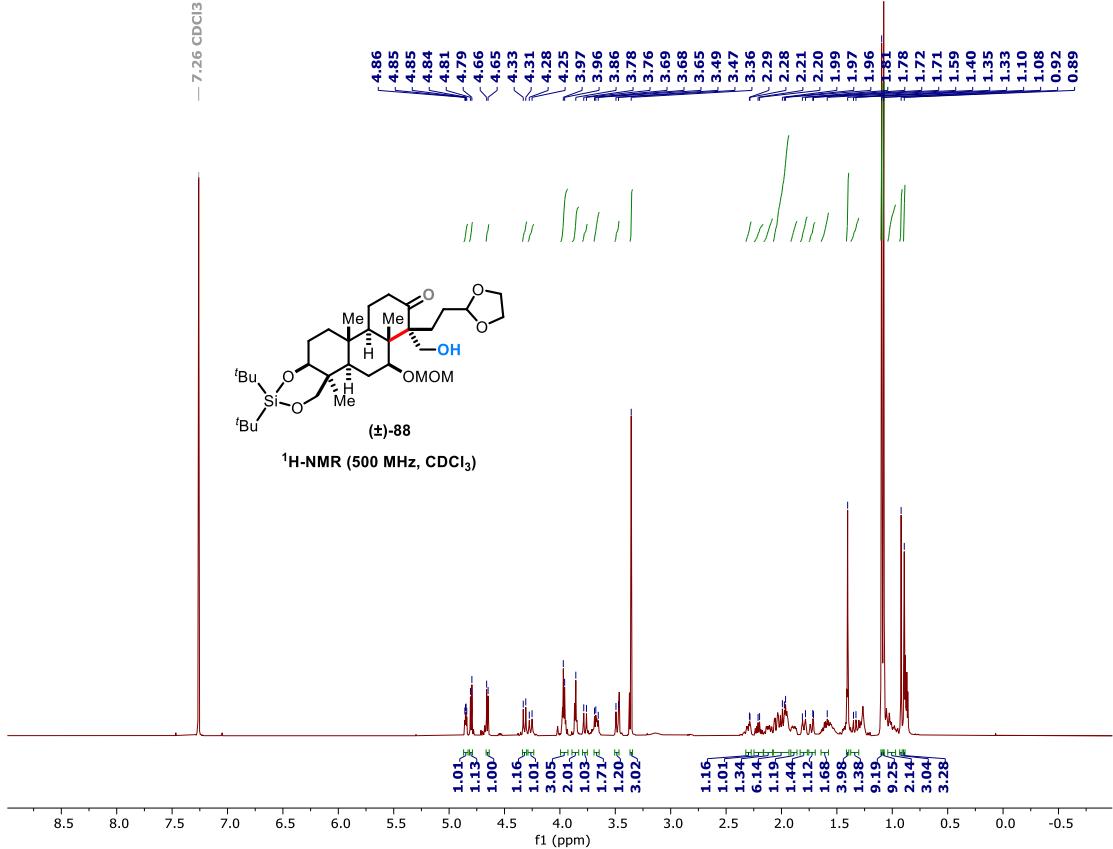
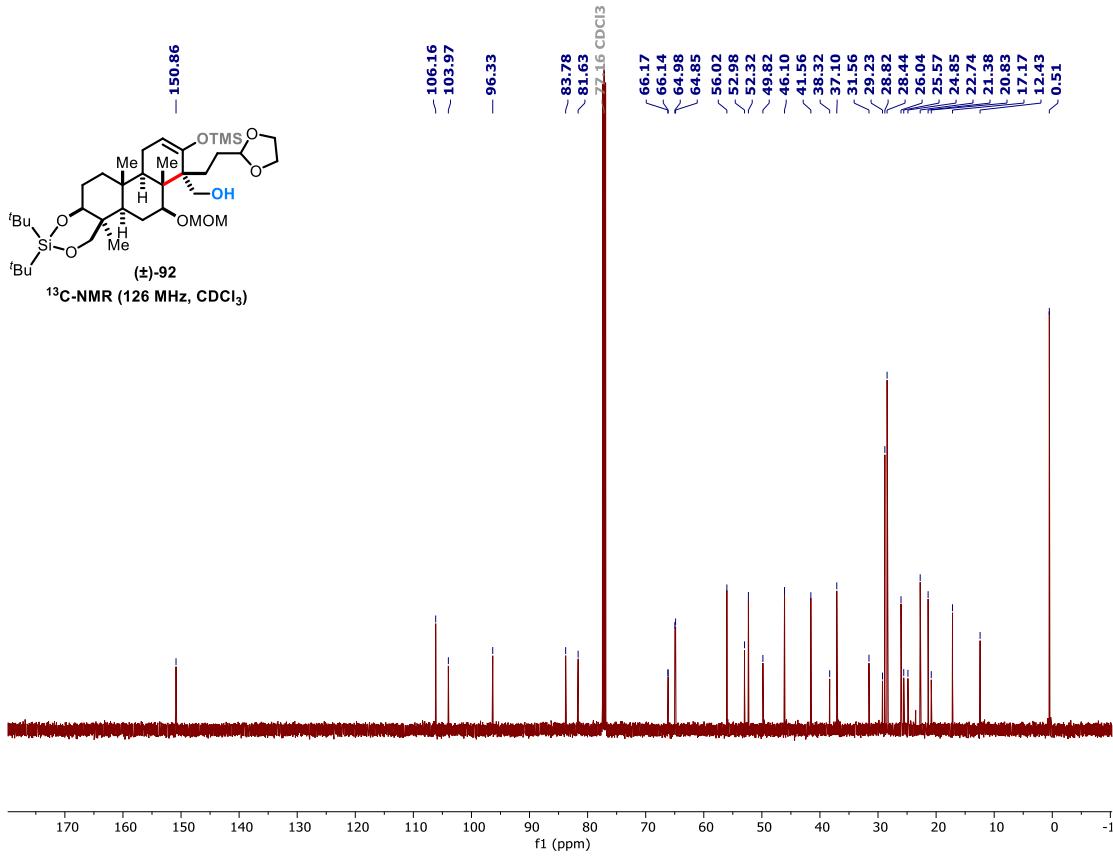


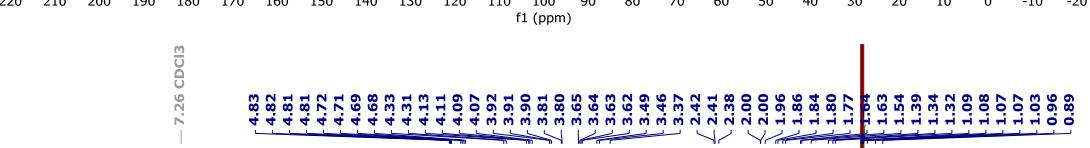
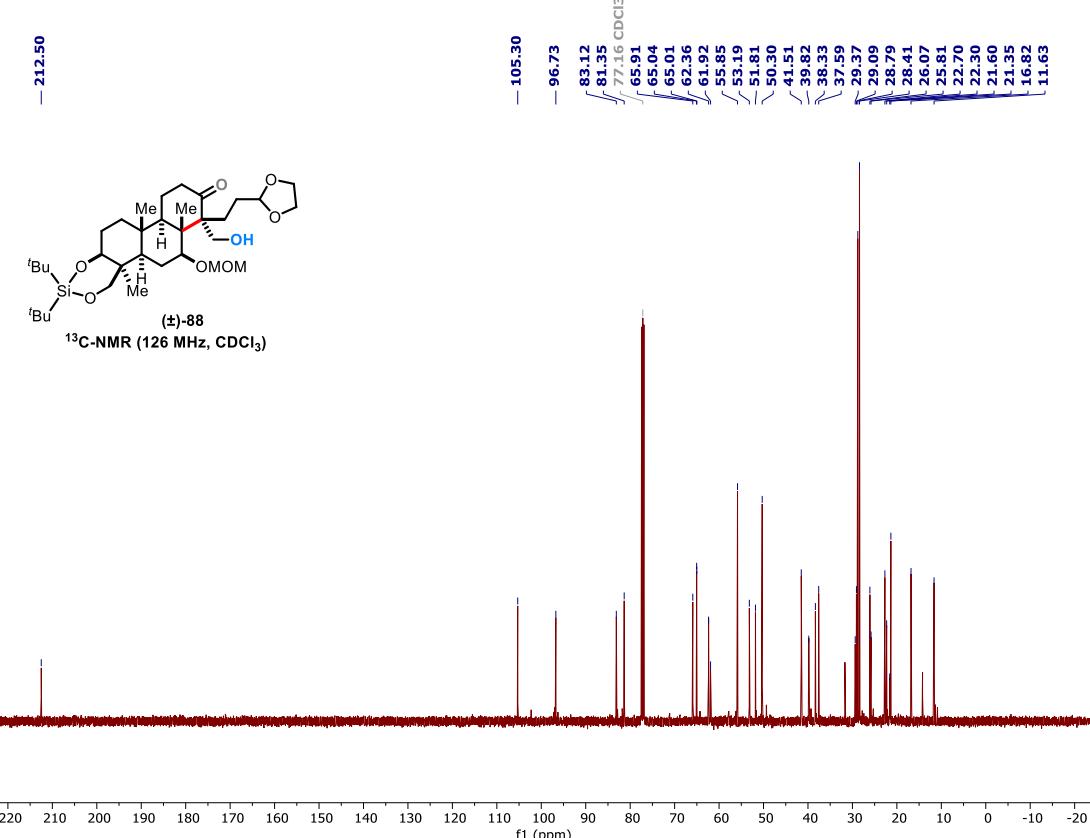




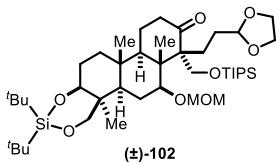






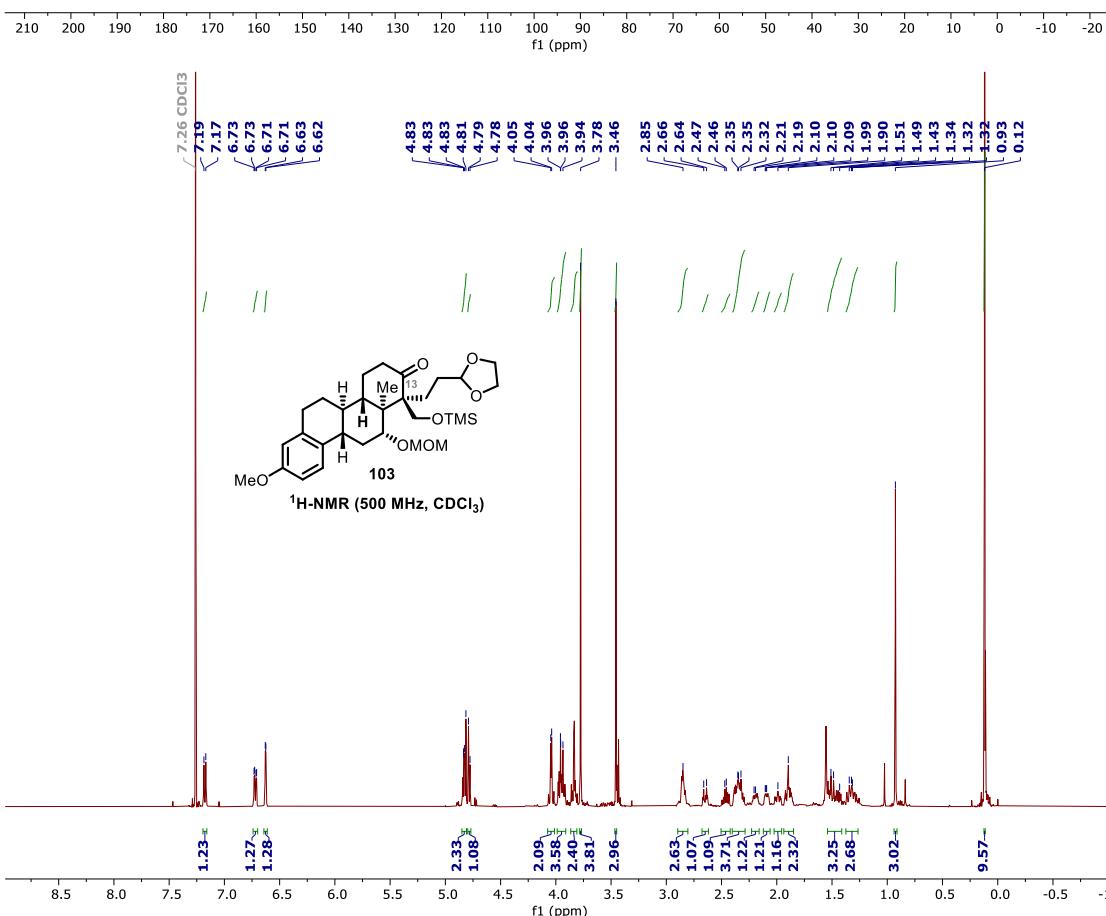


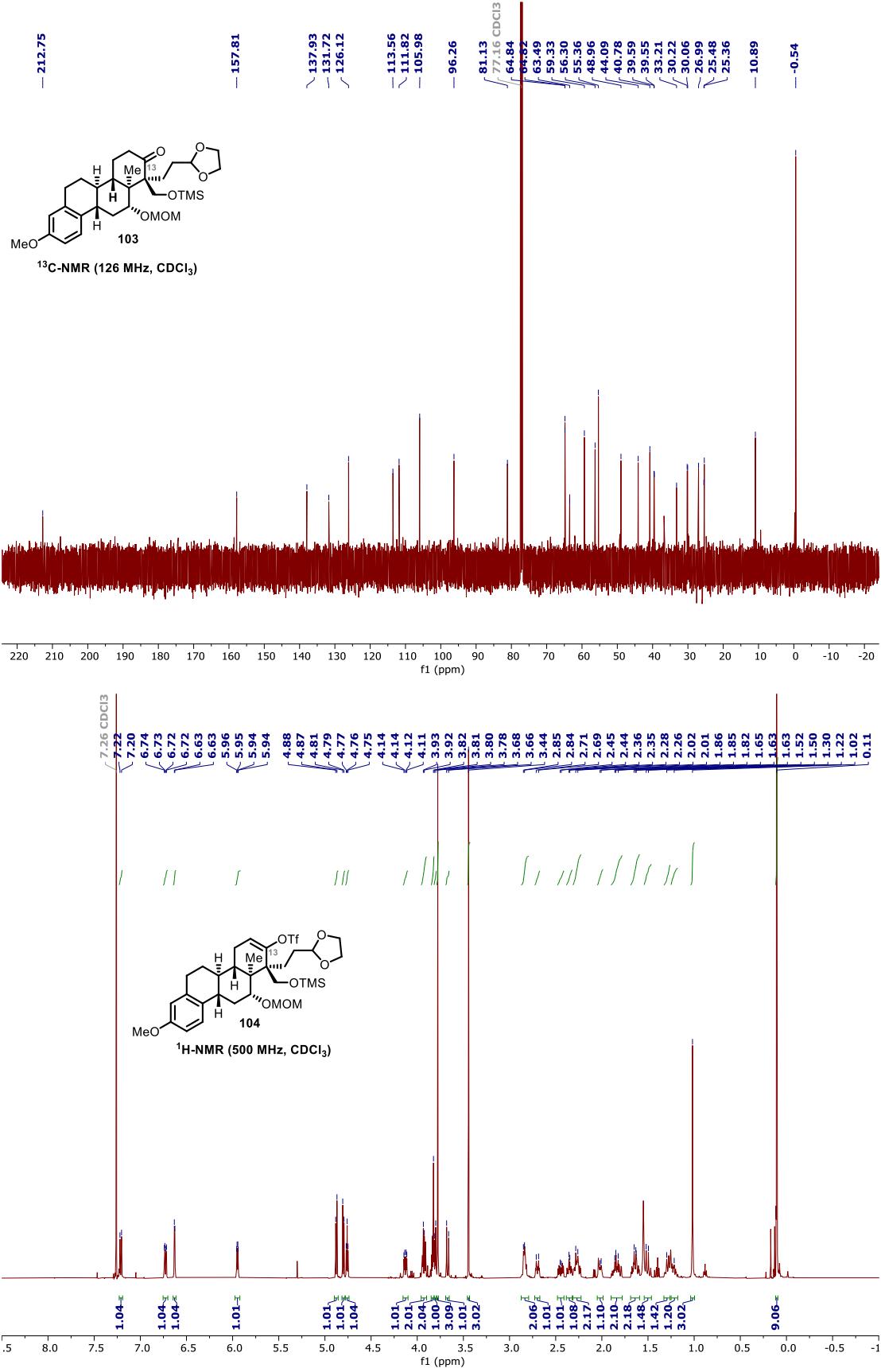
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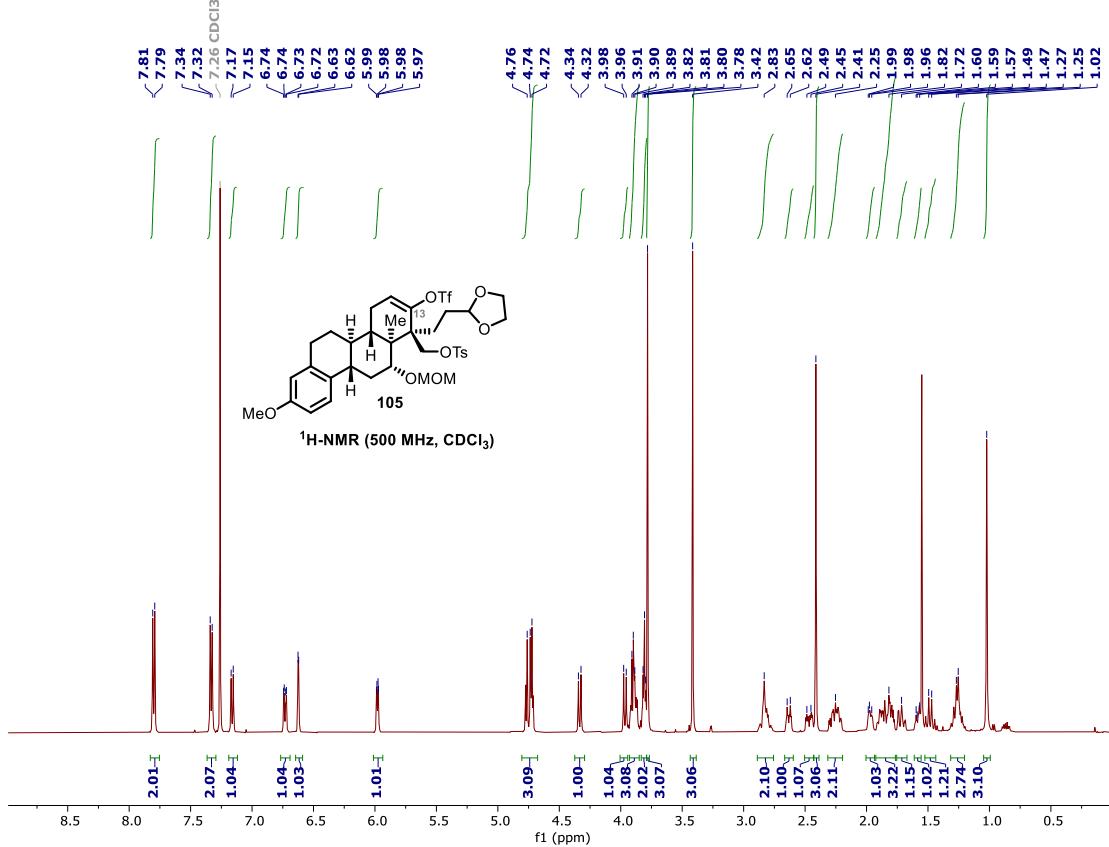
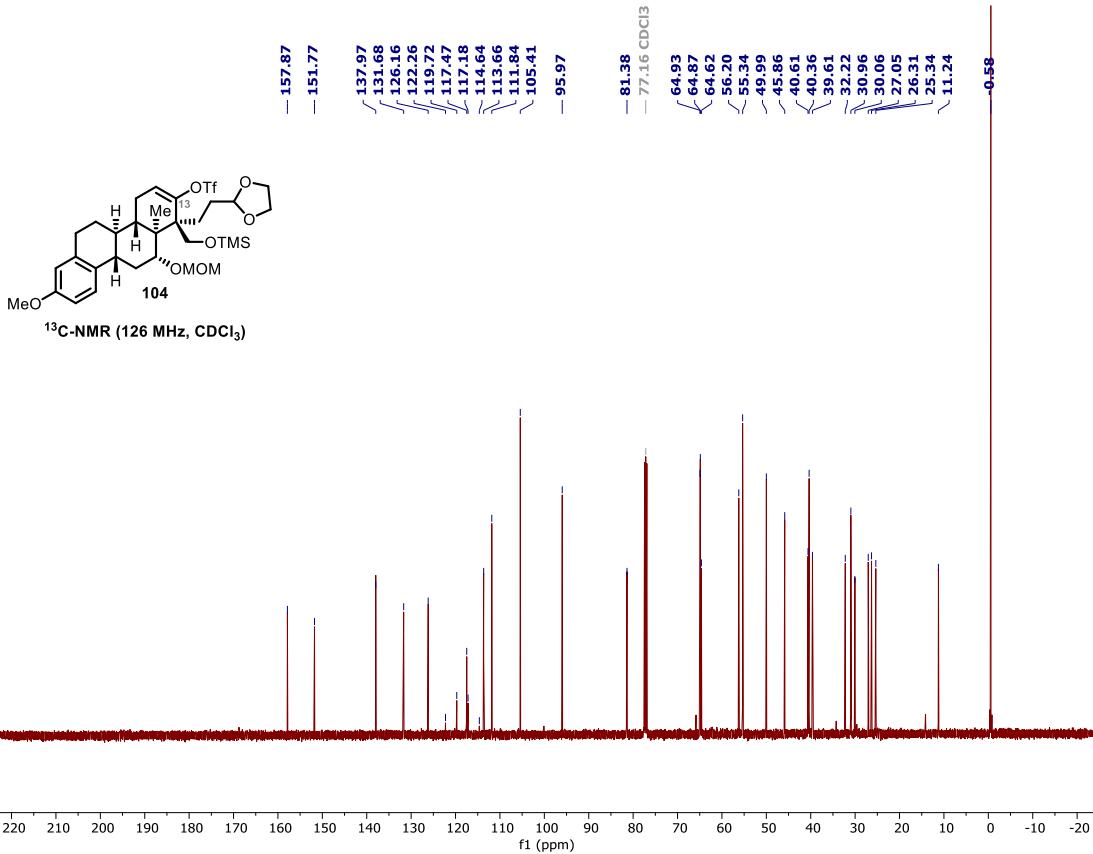


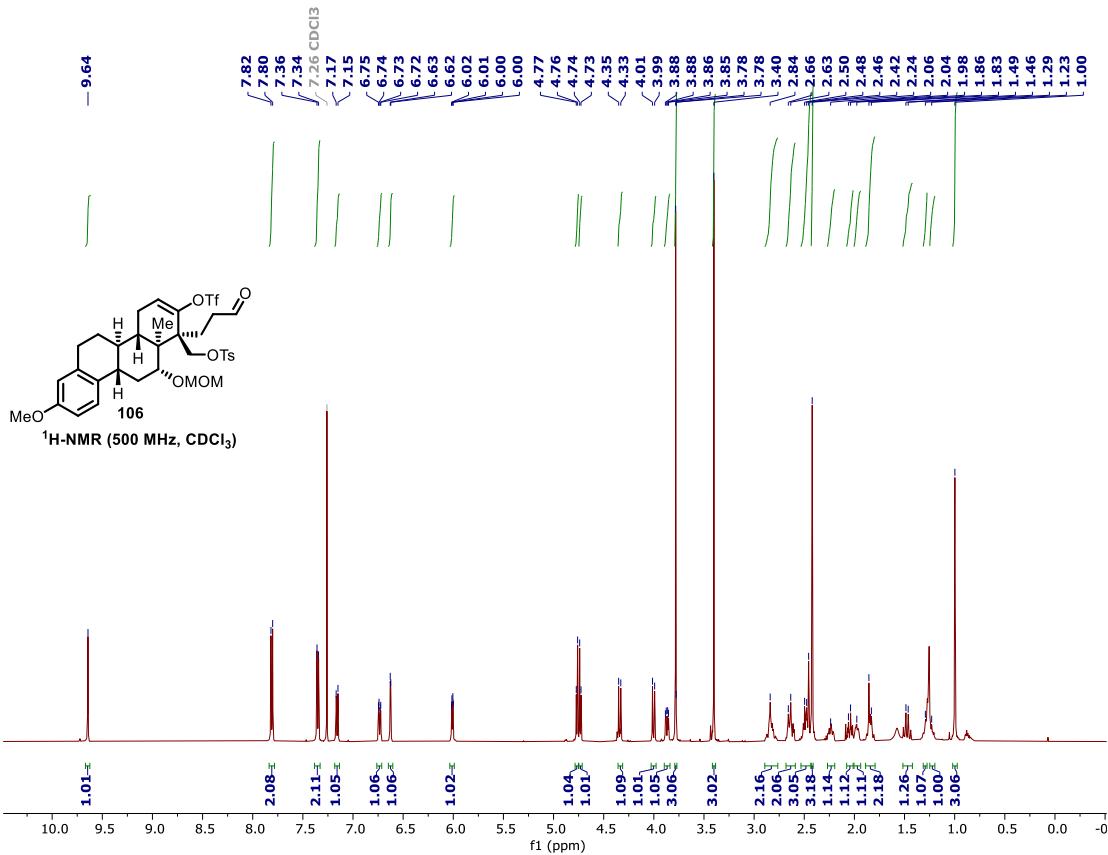
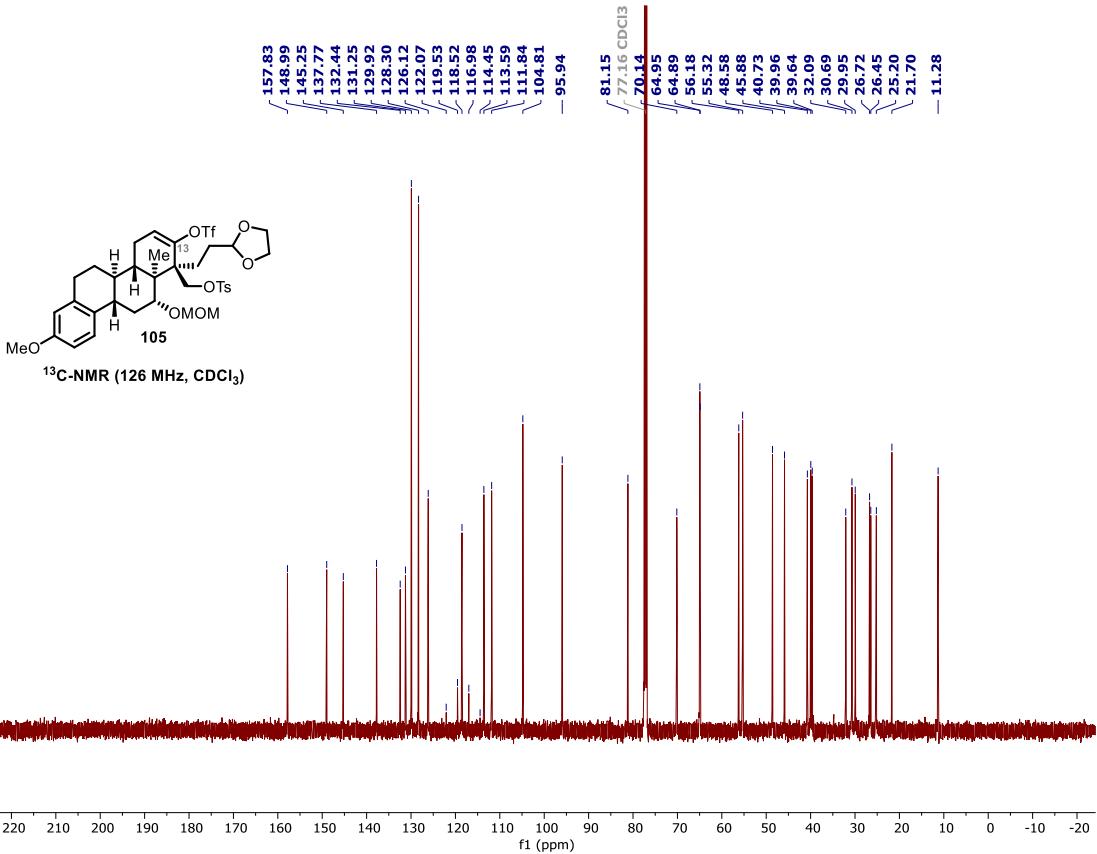
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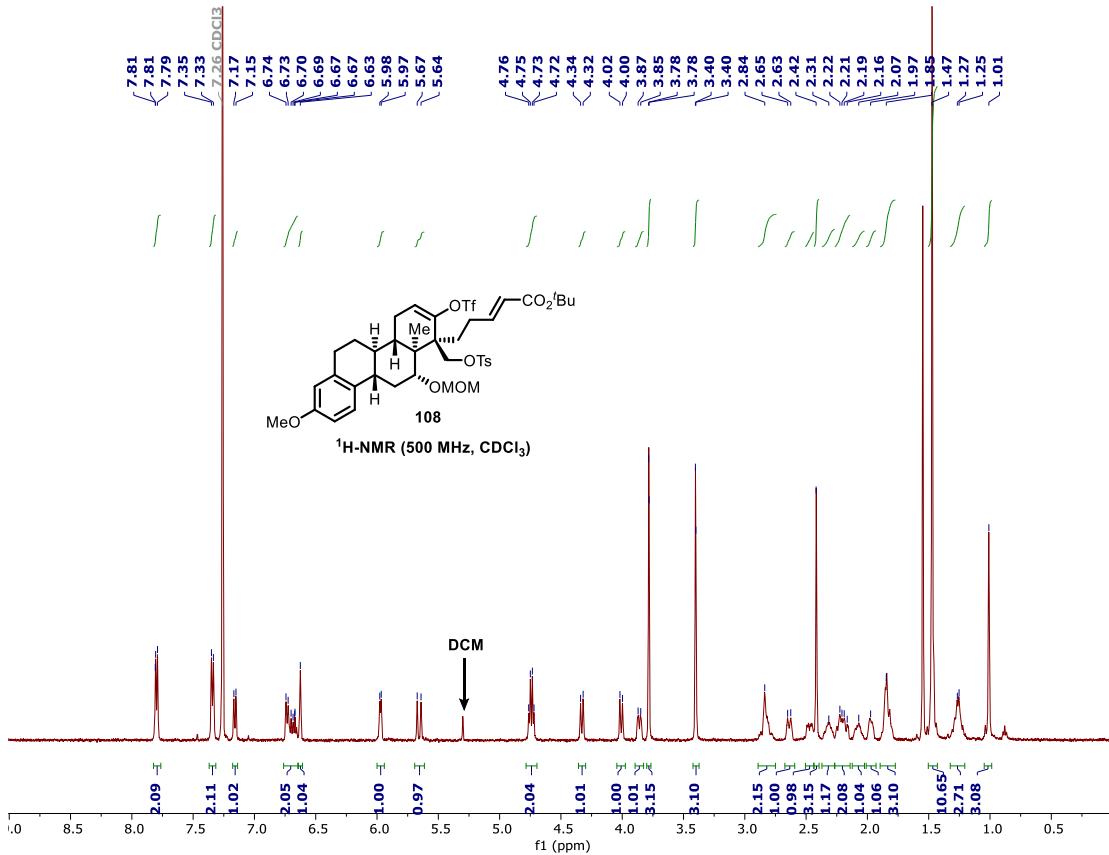
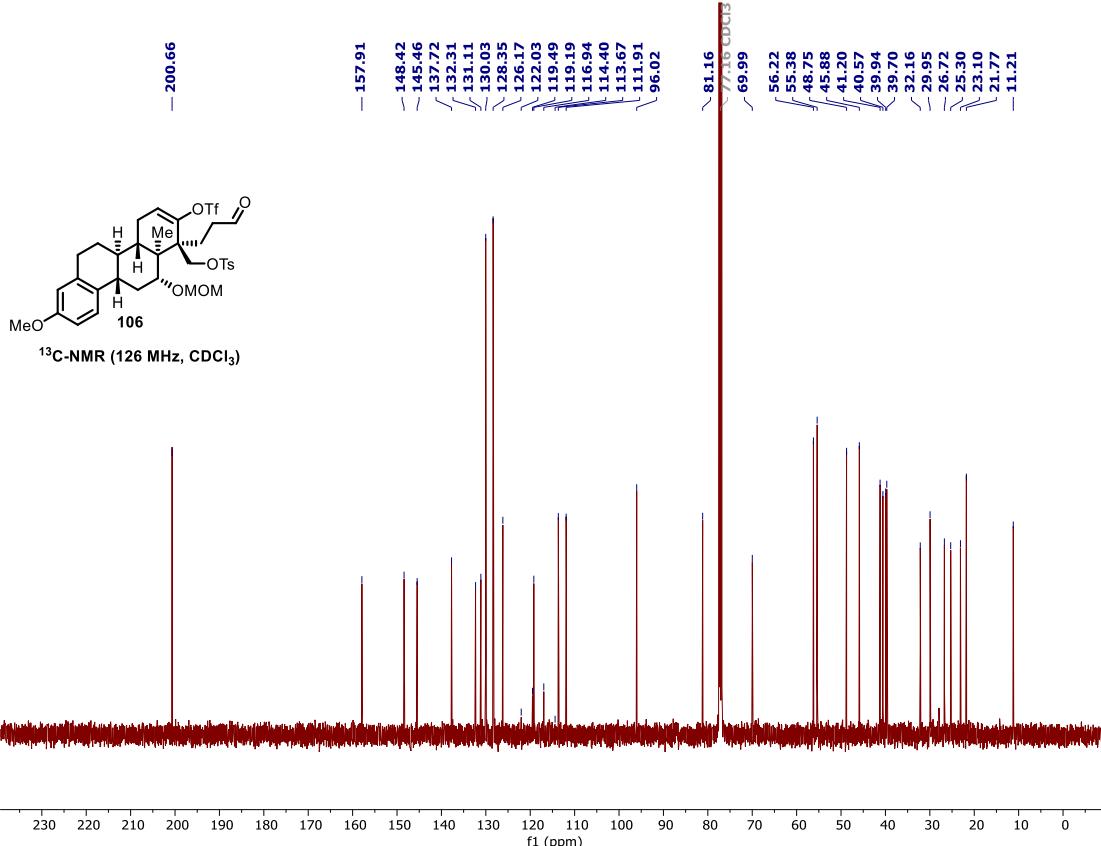
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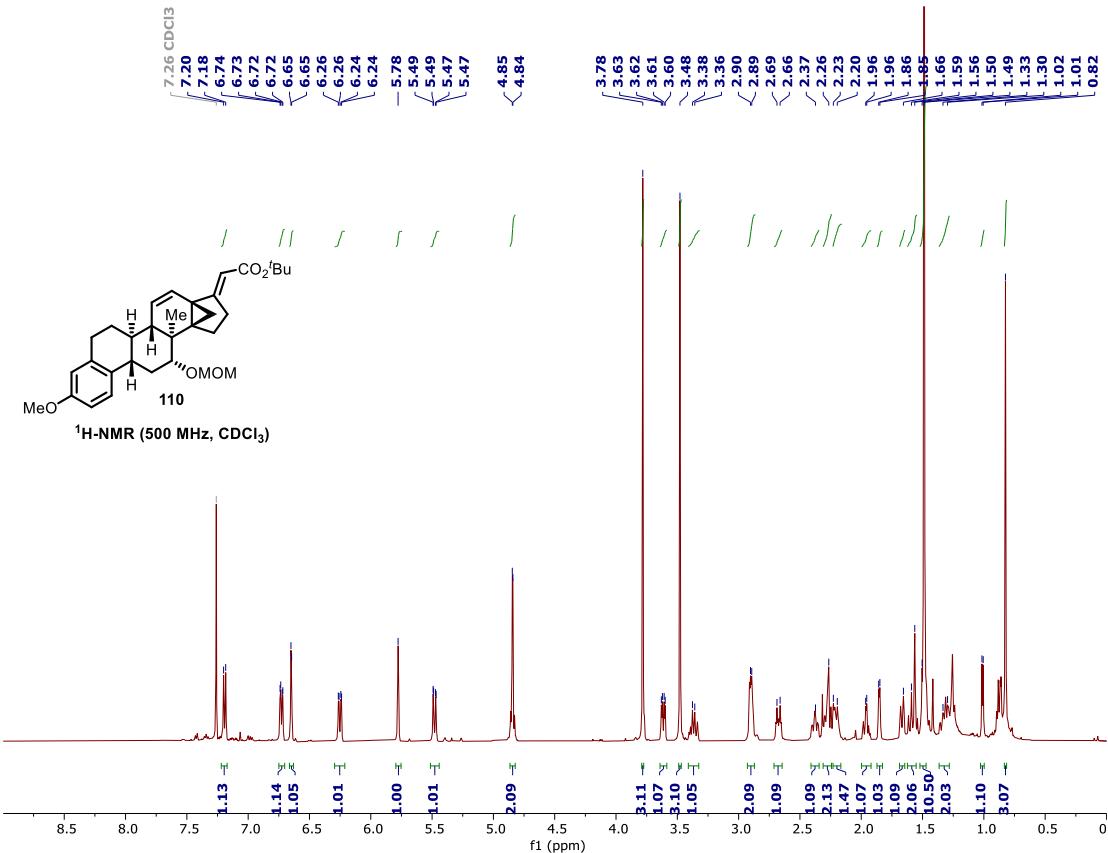
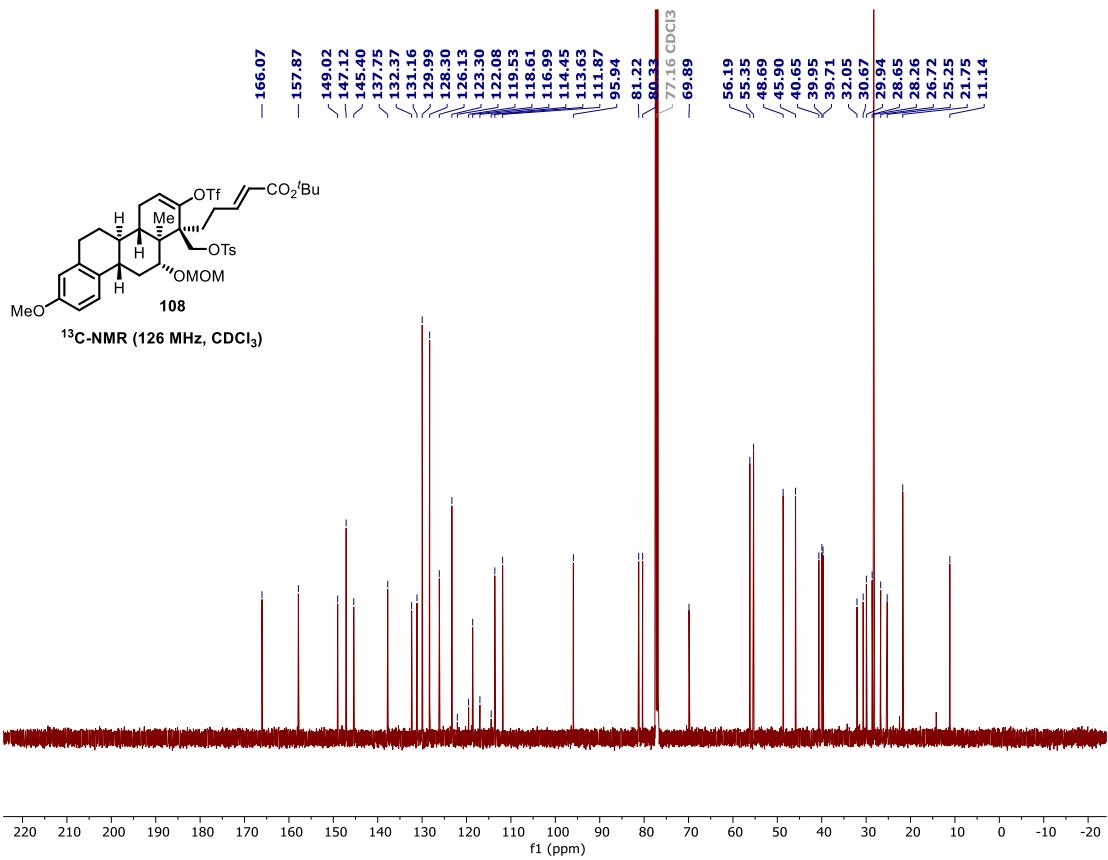


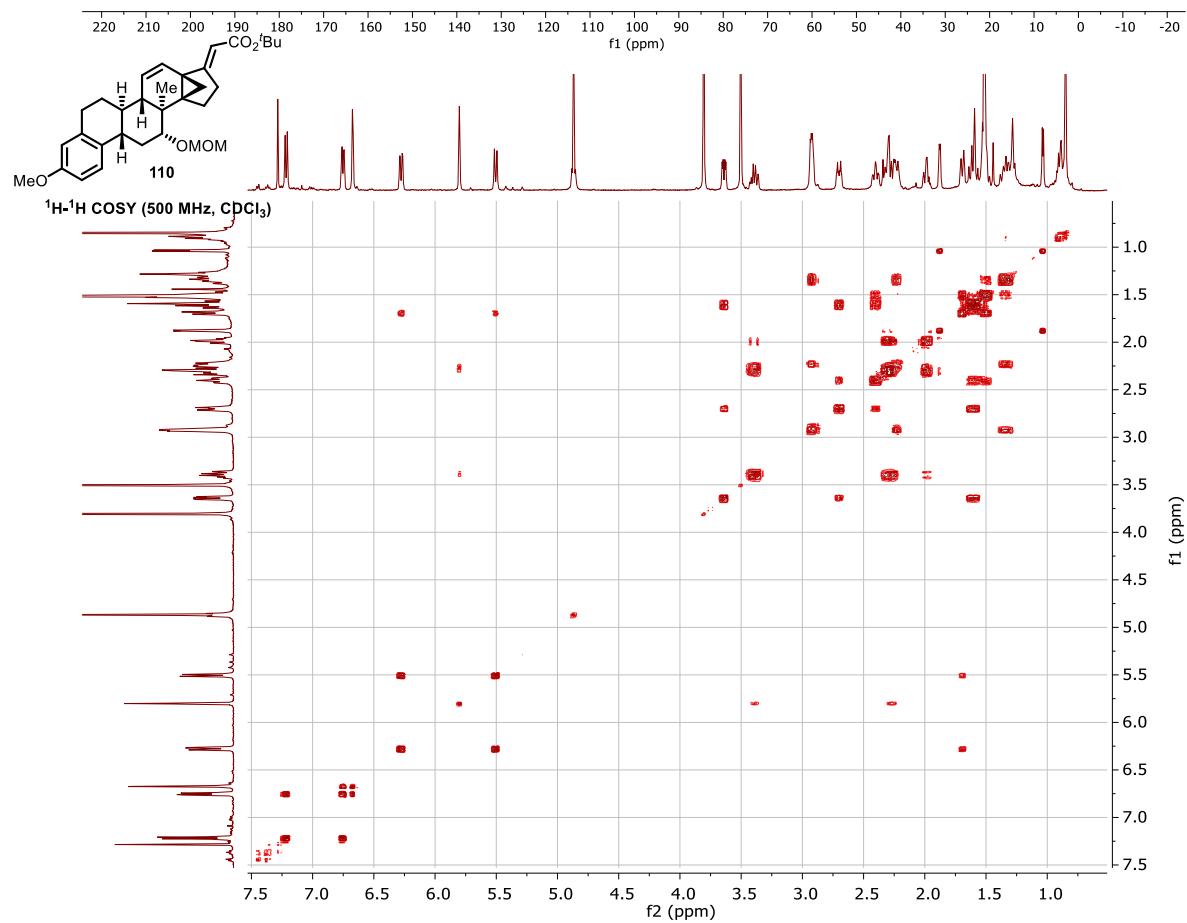
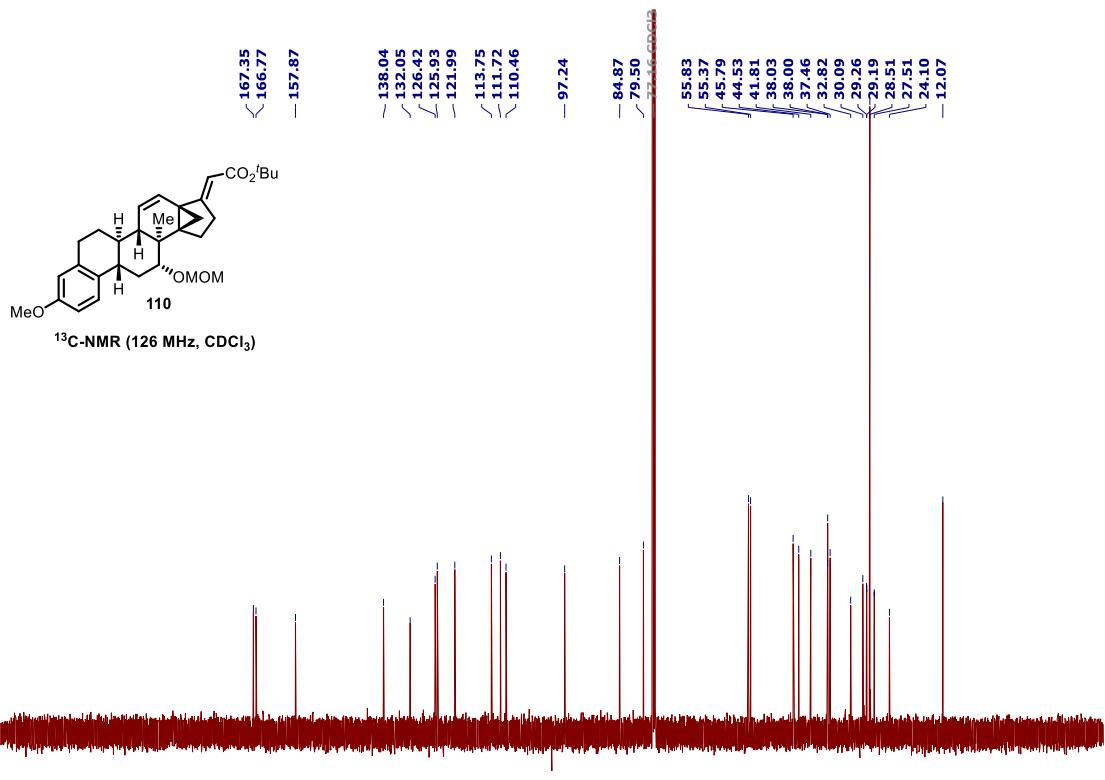


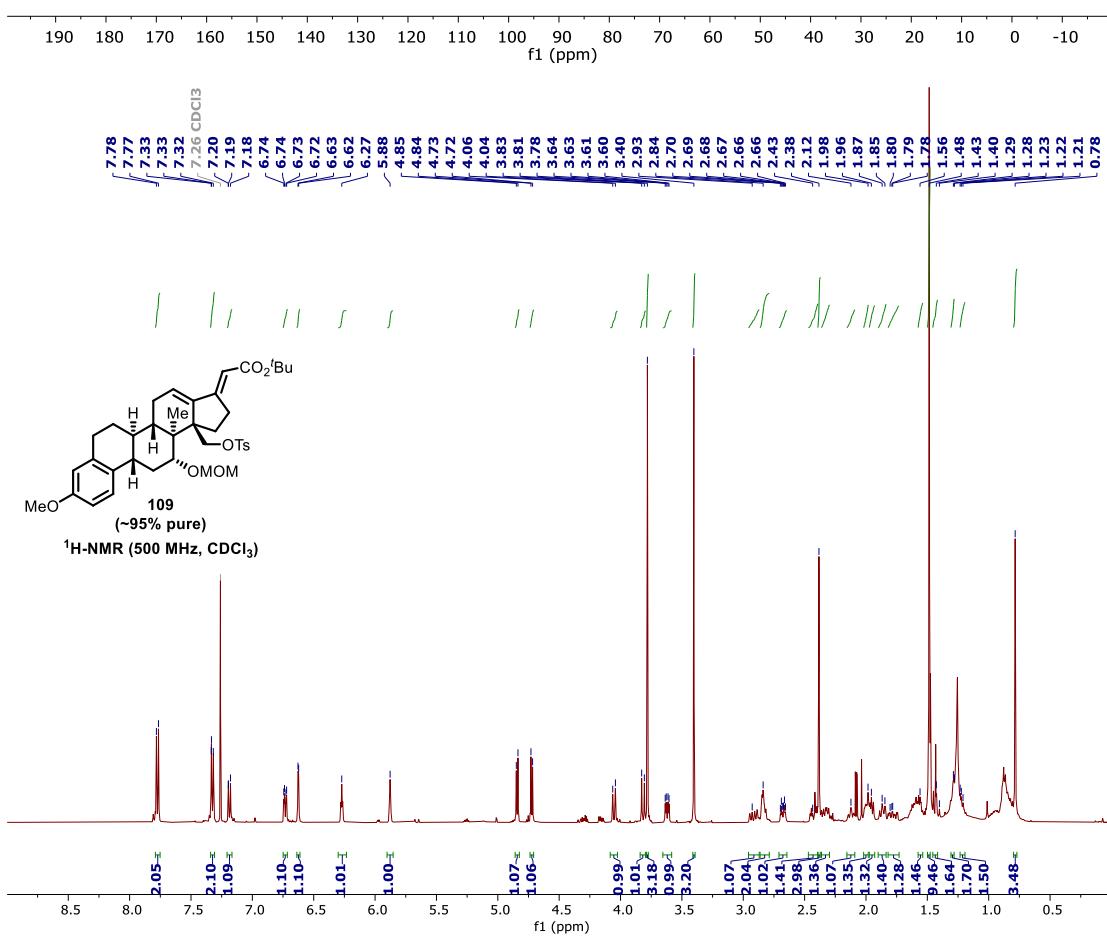
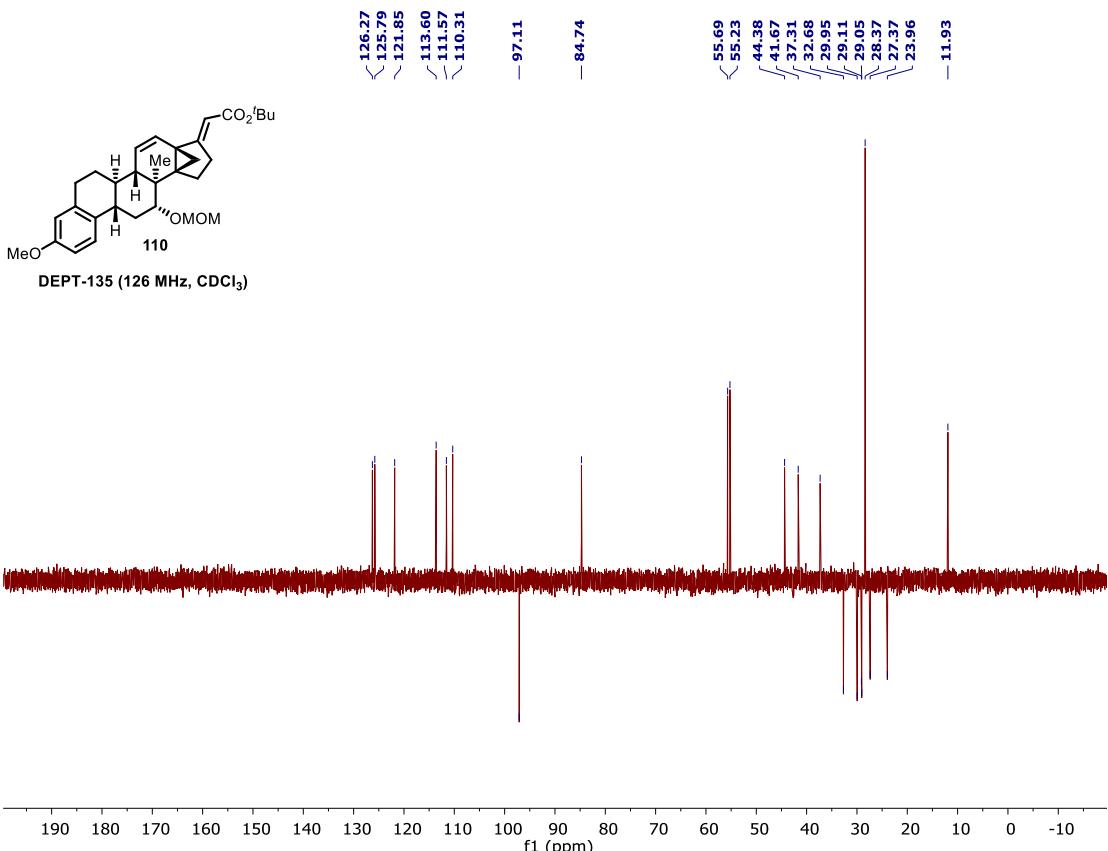


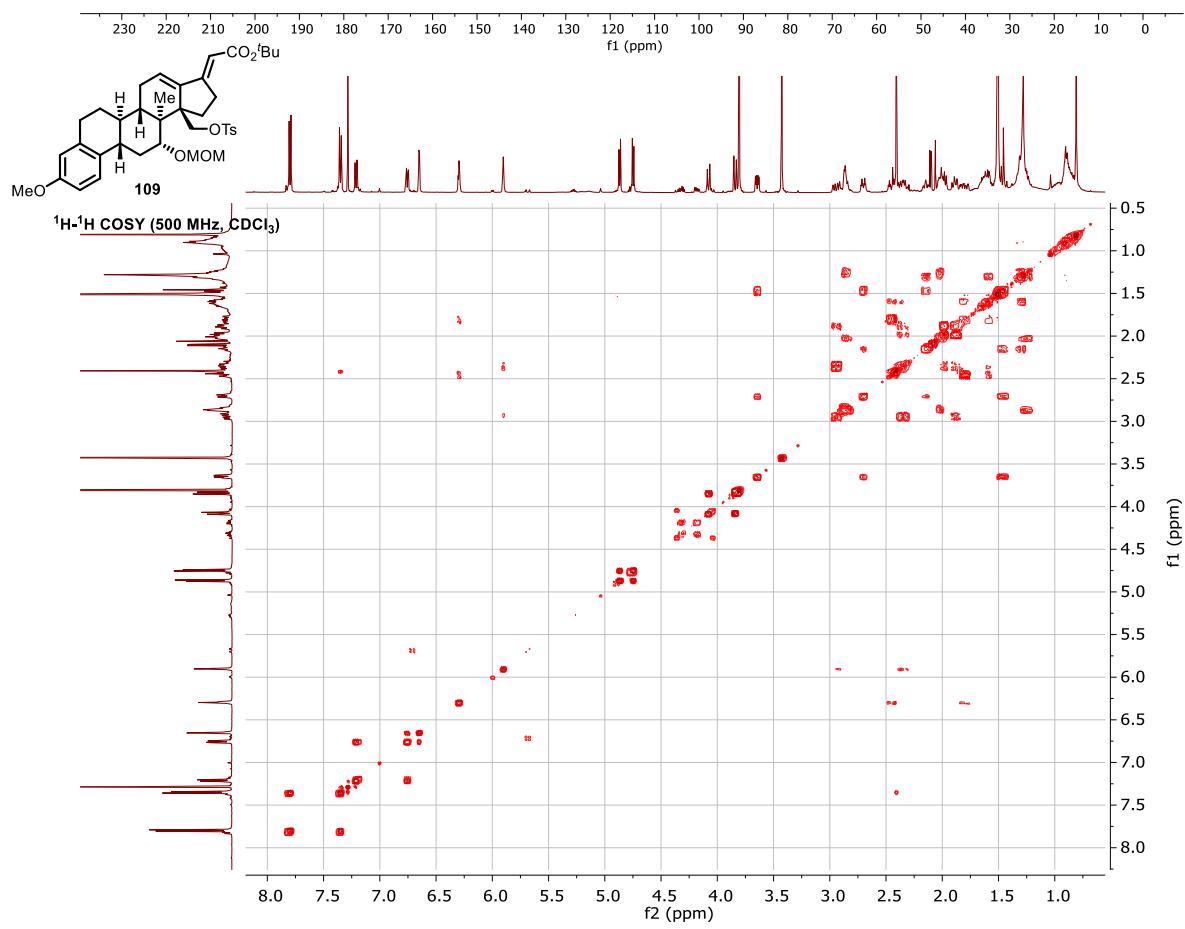
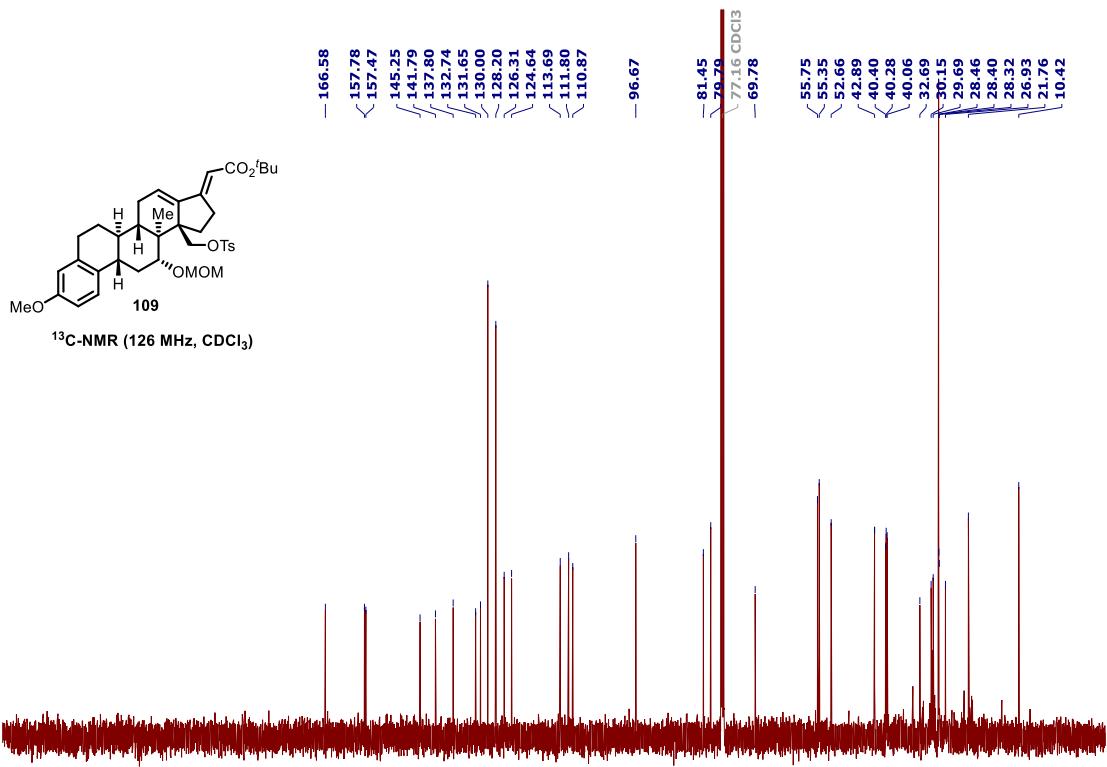


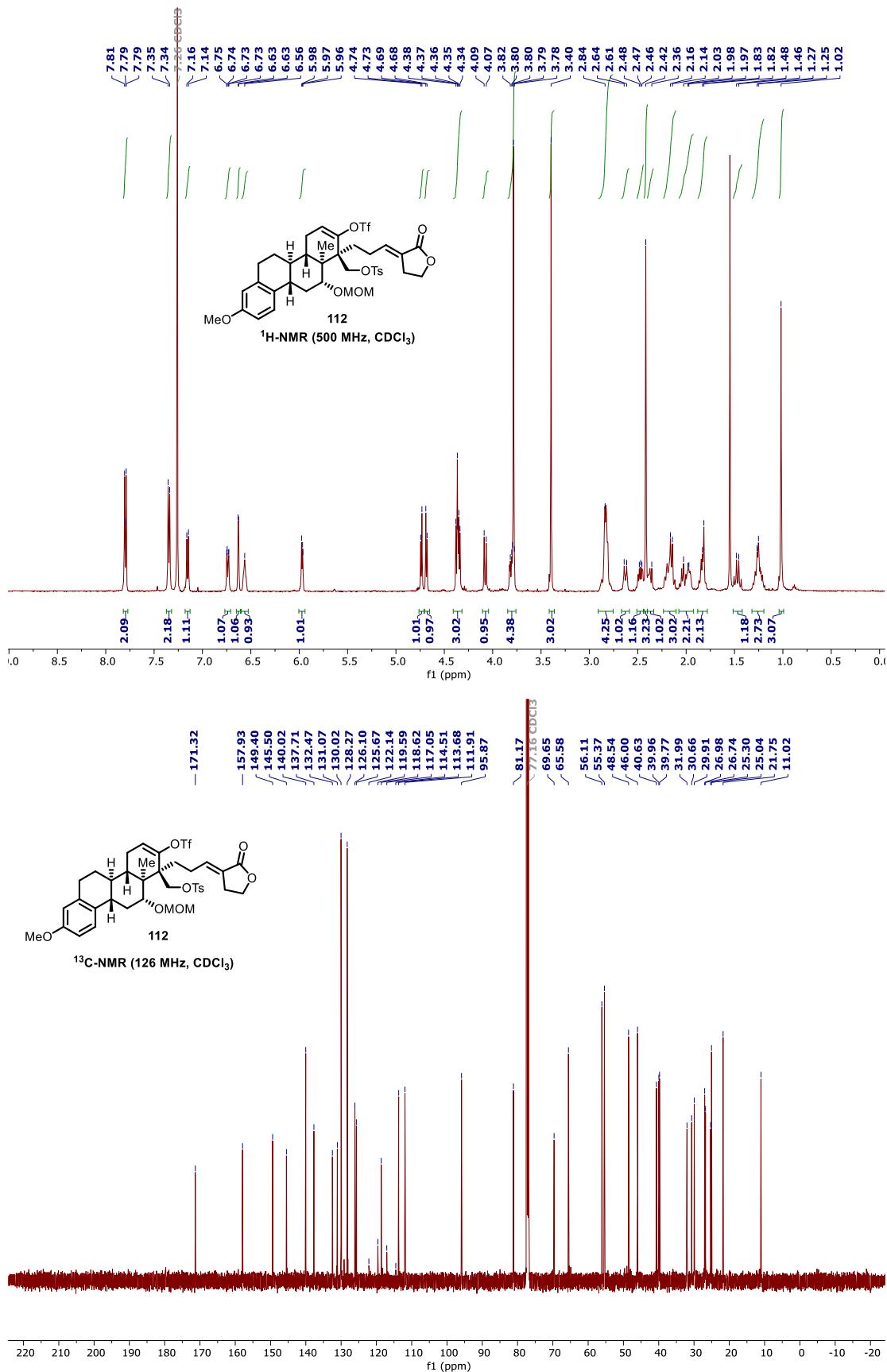


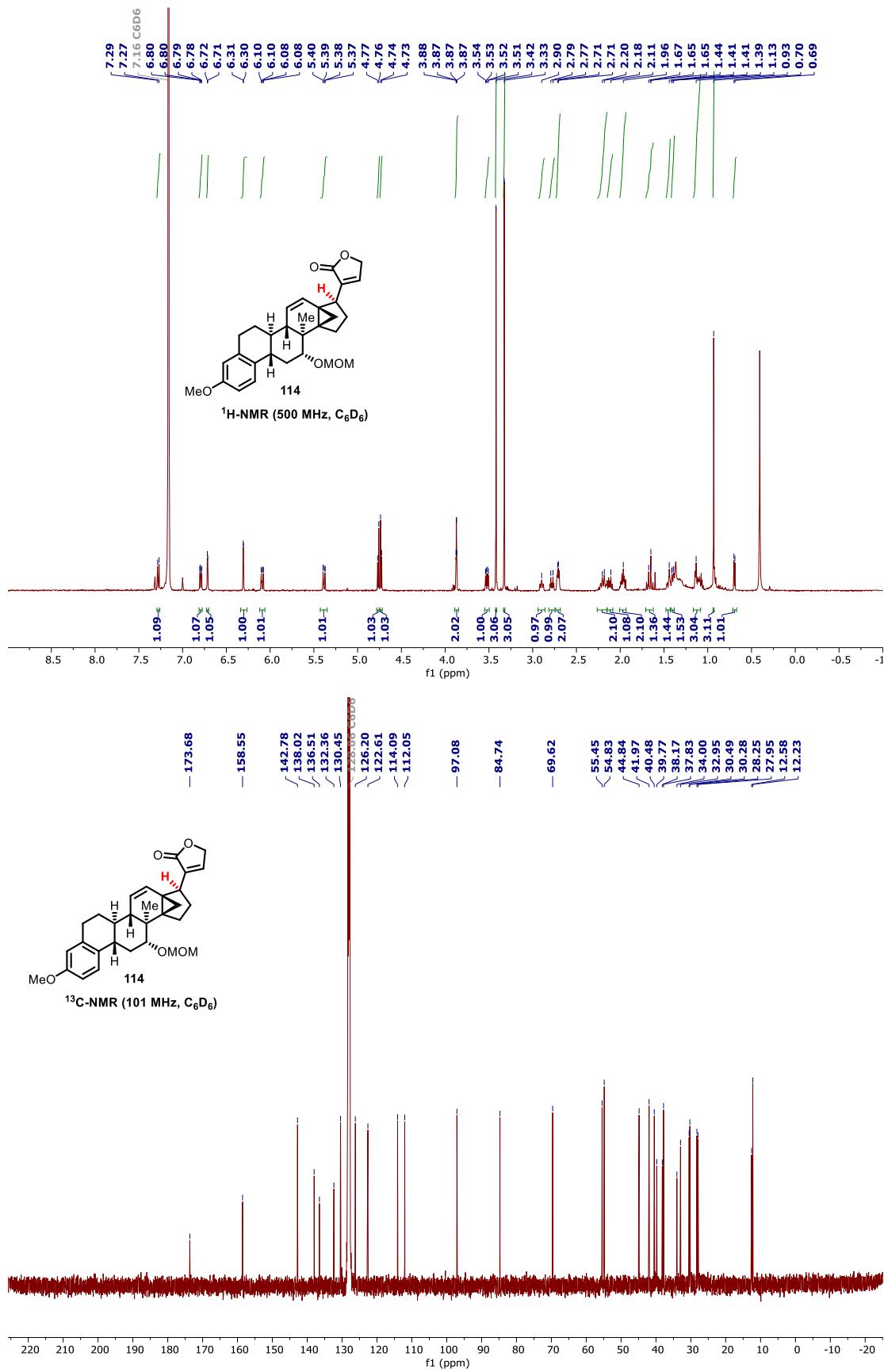


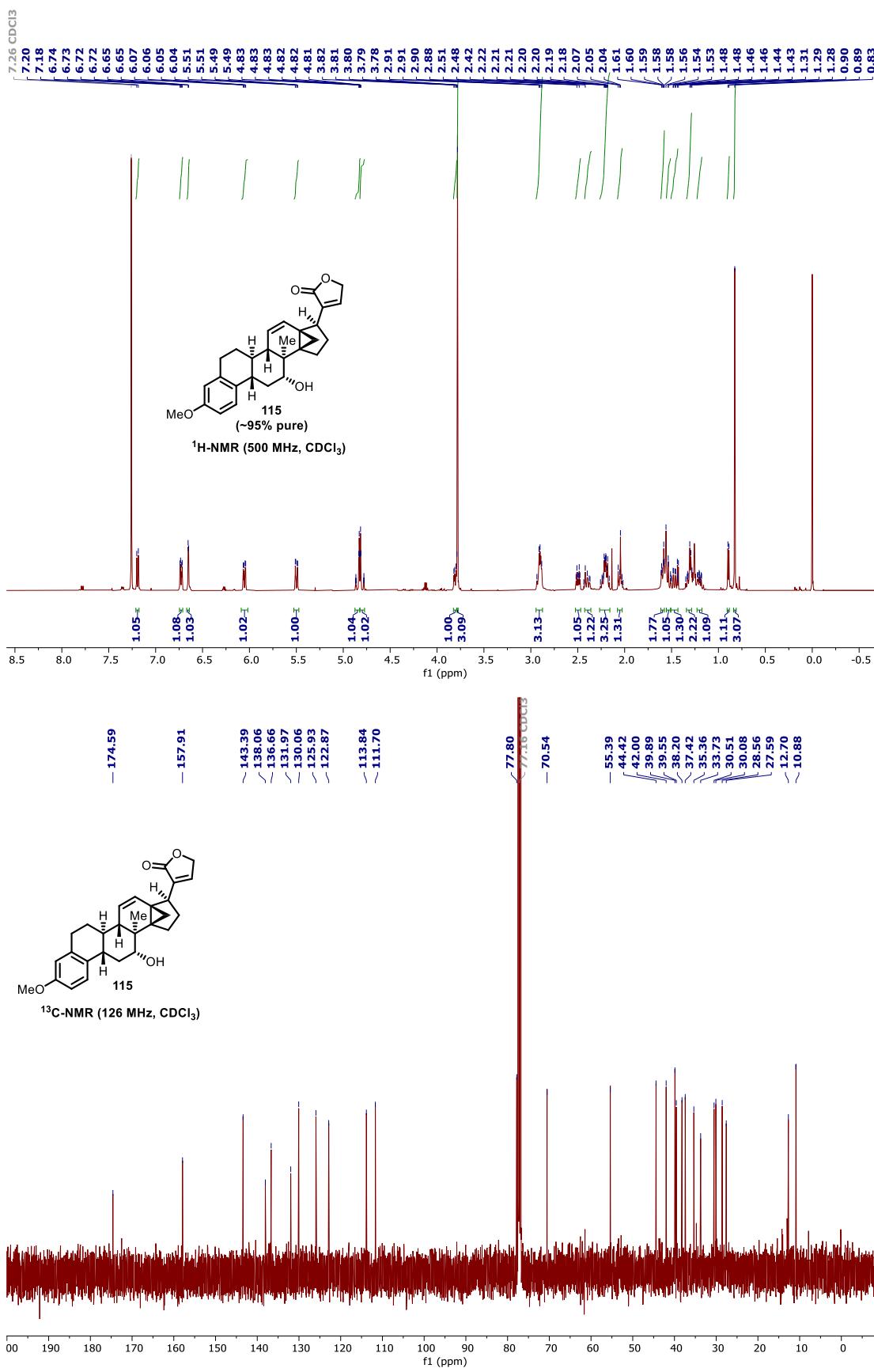


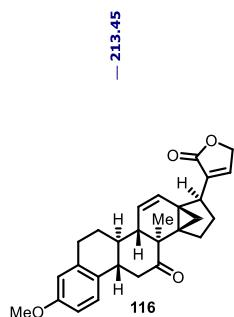
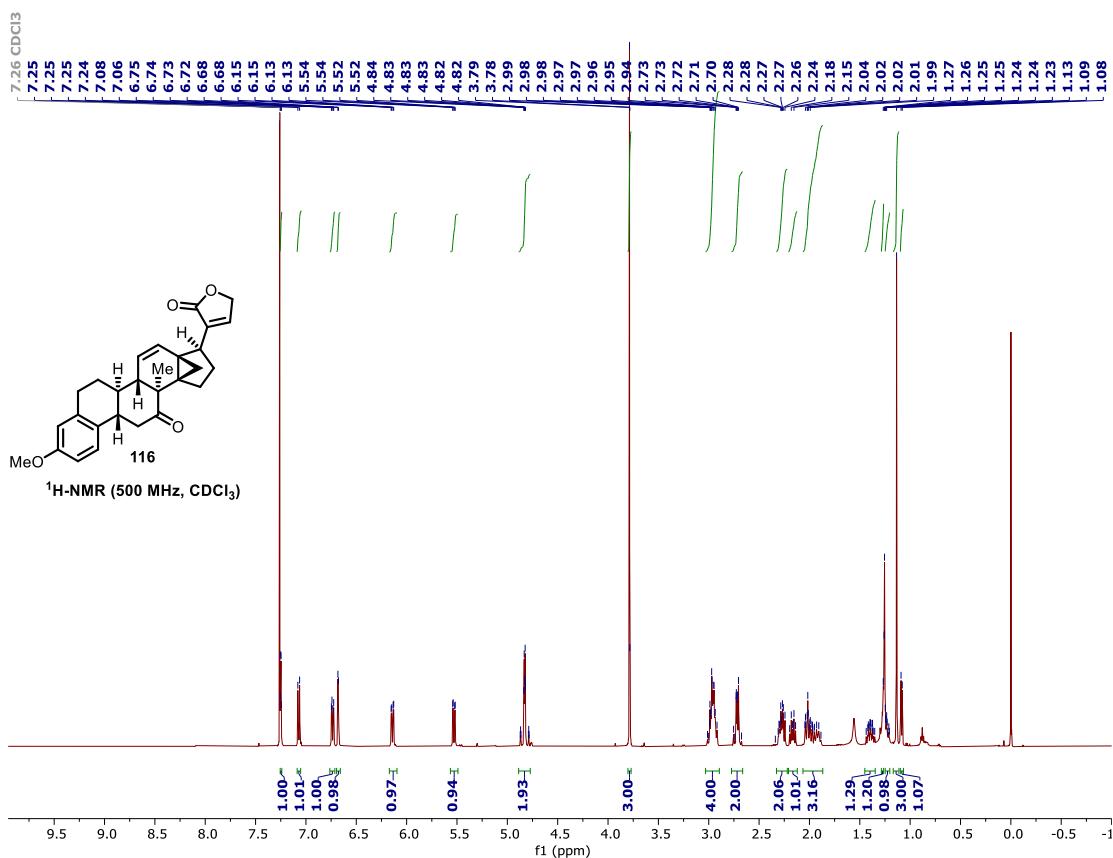




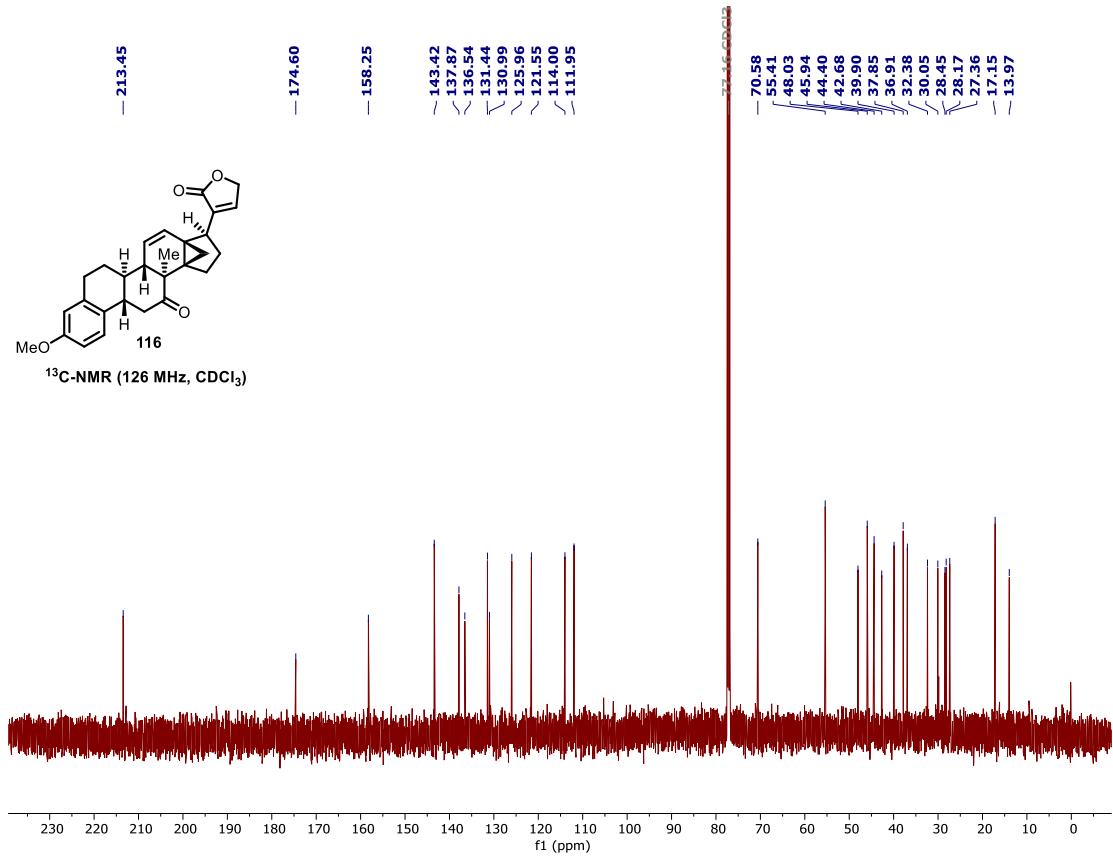


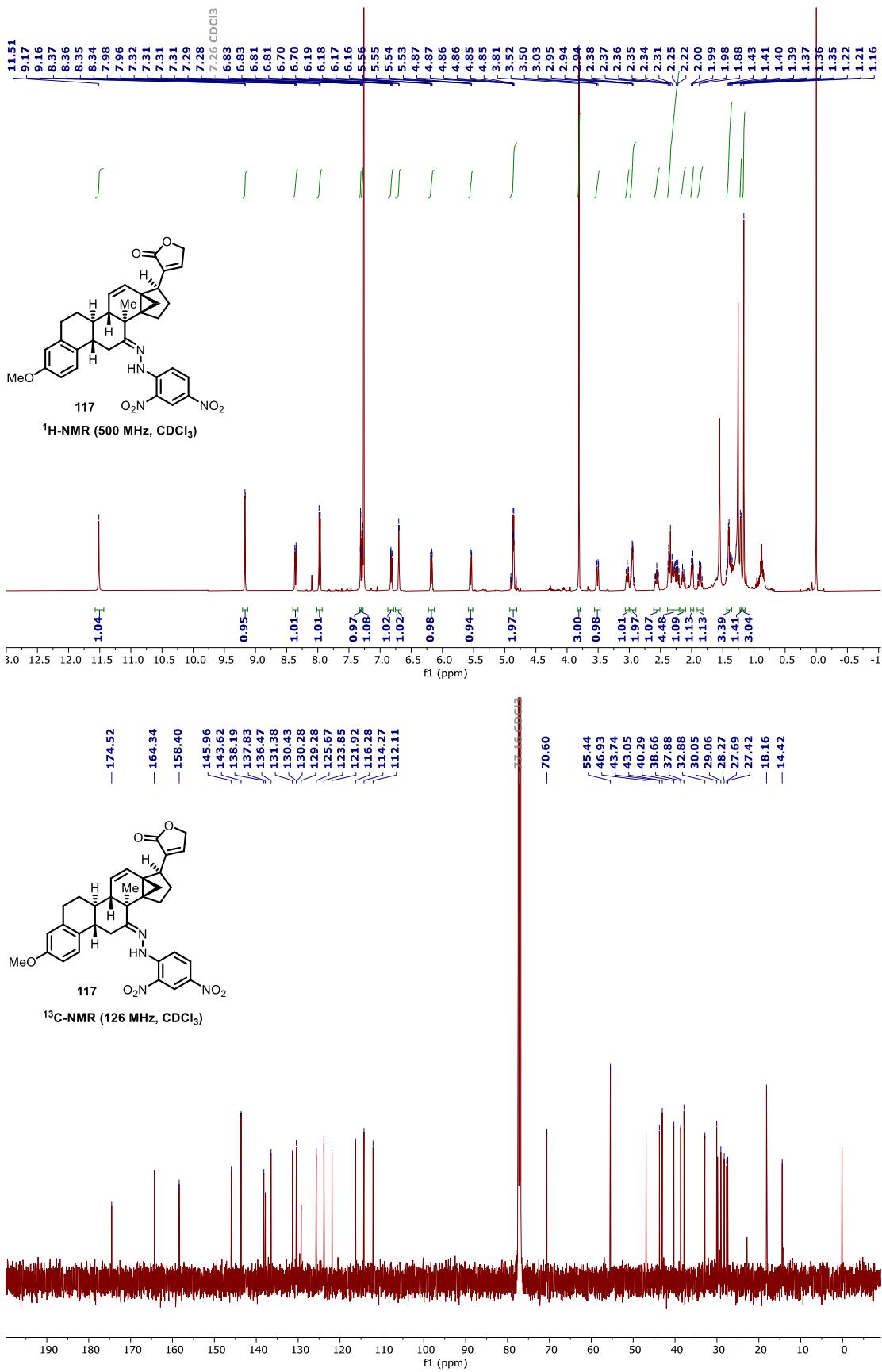


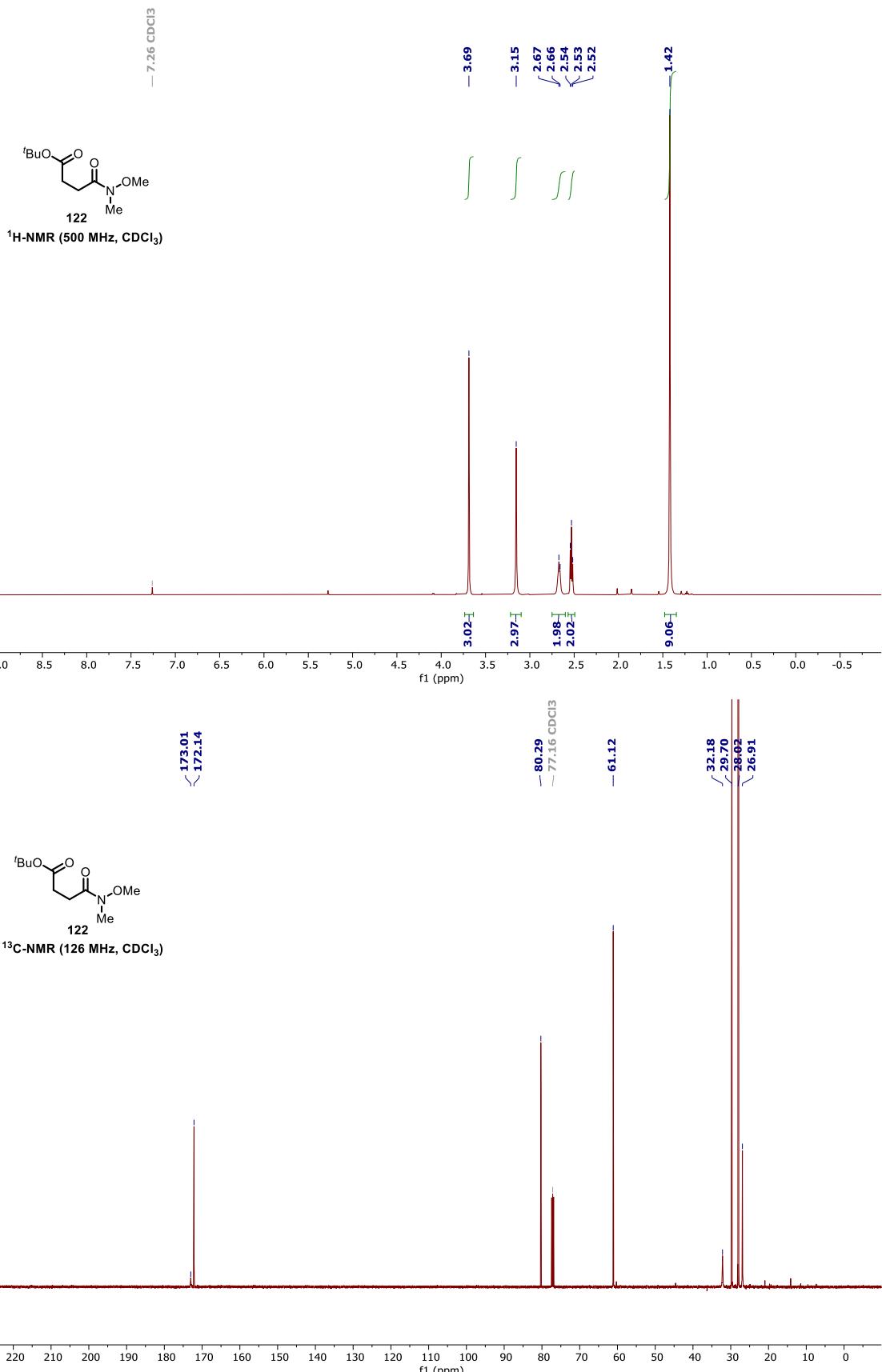


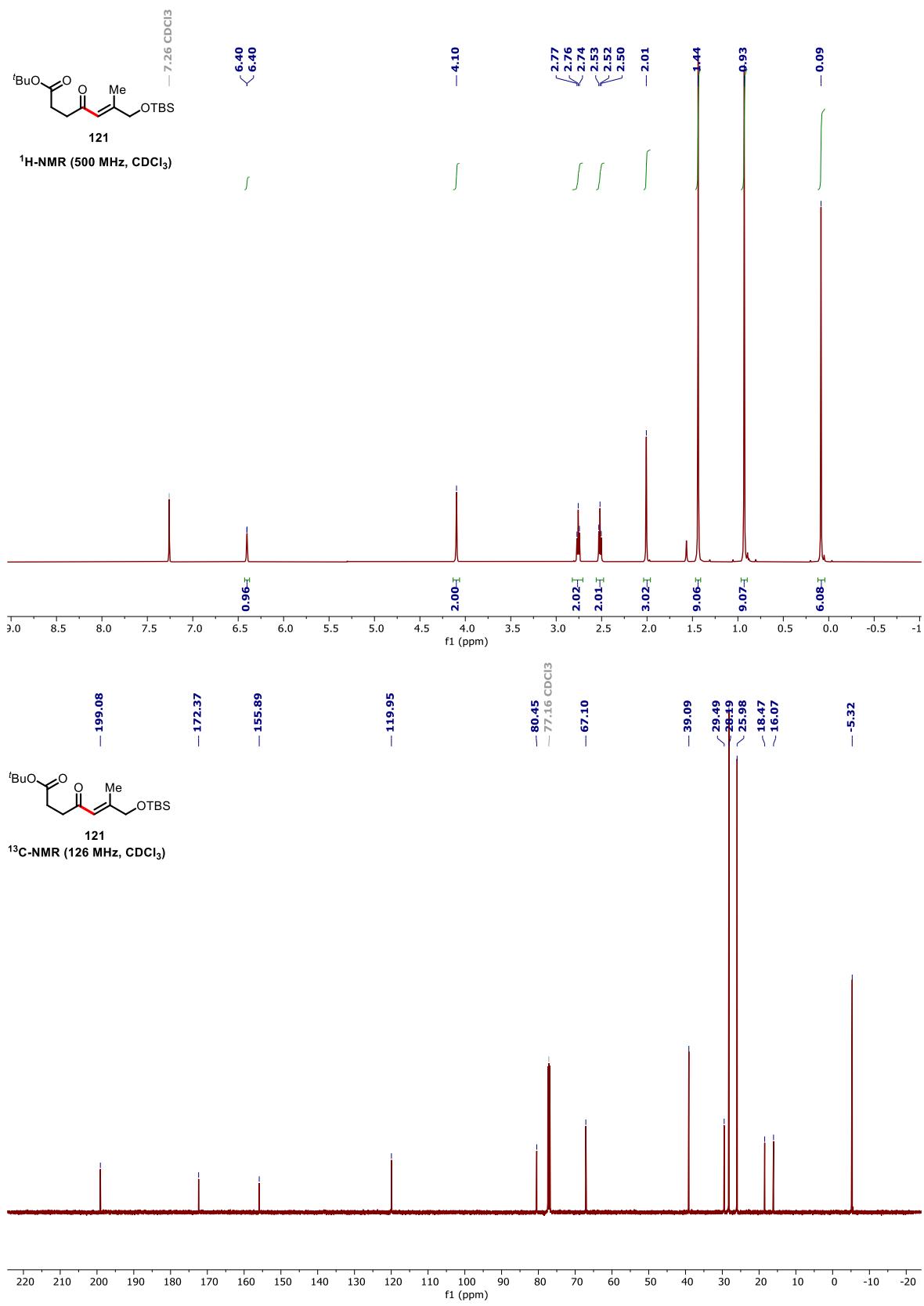


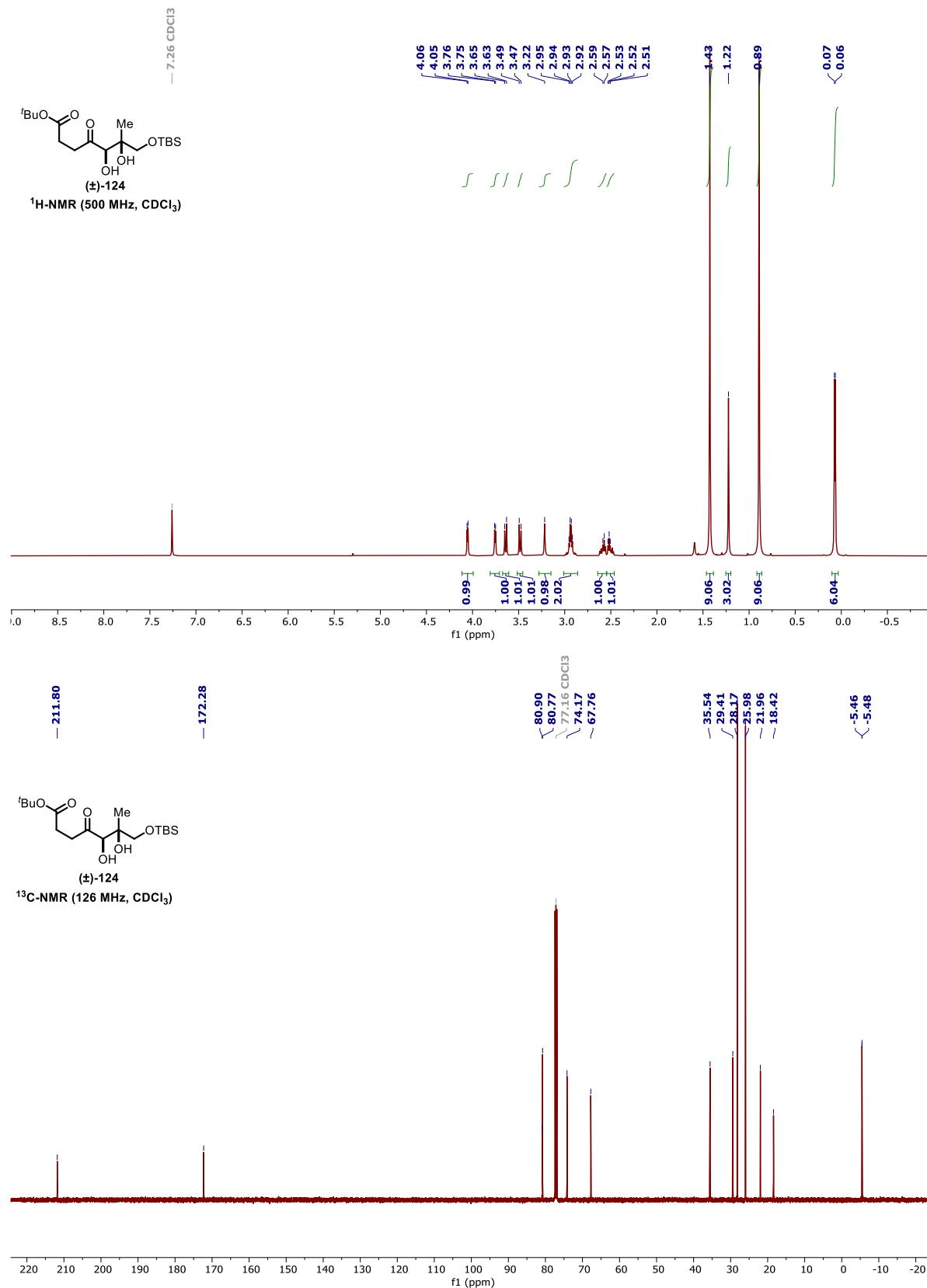
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)

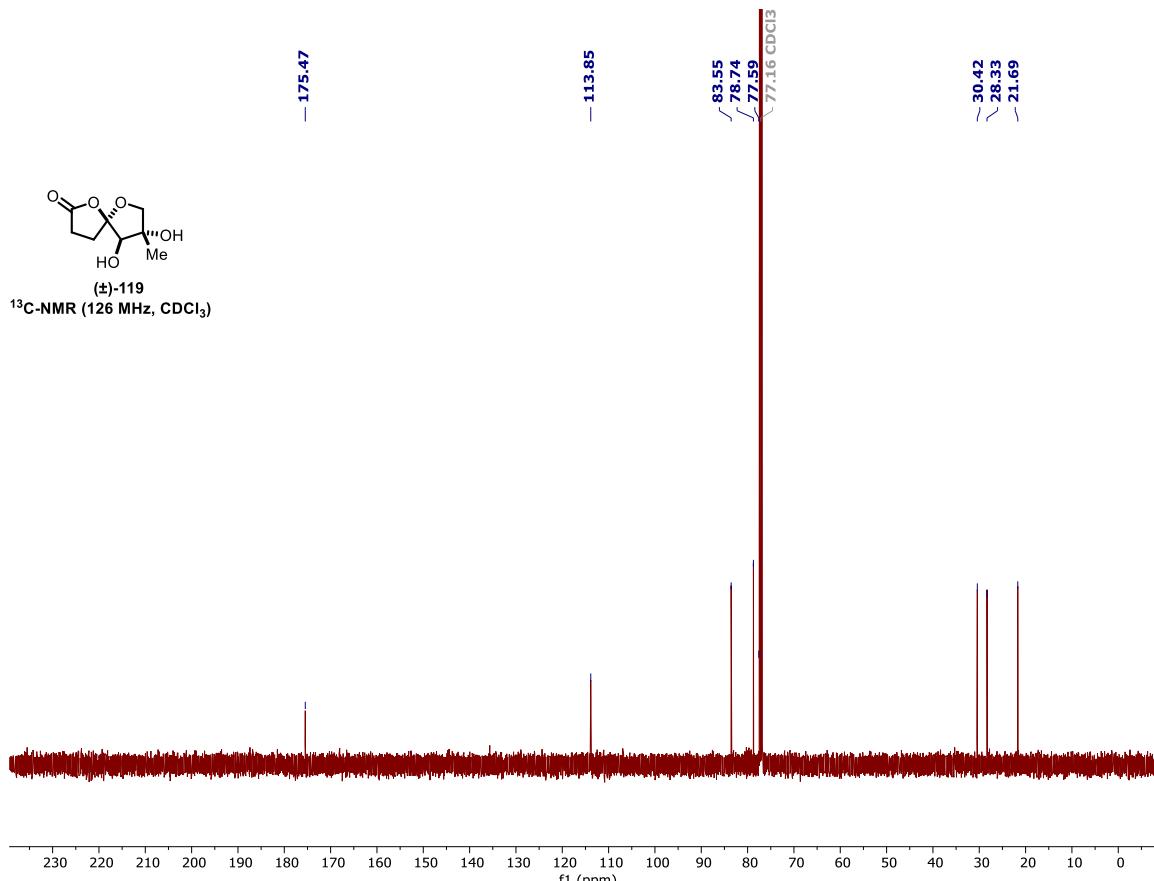
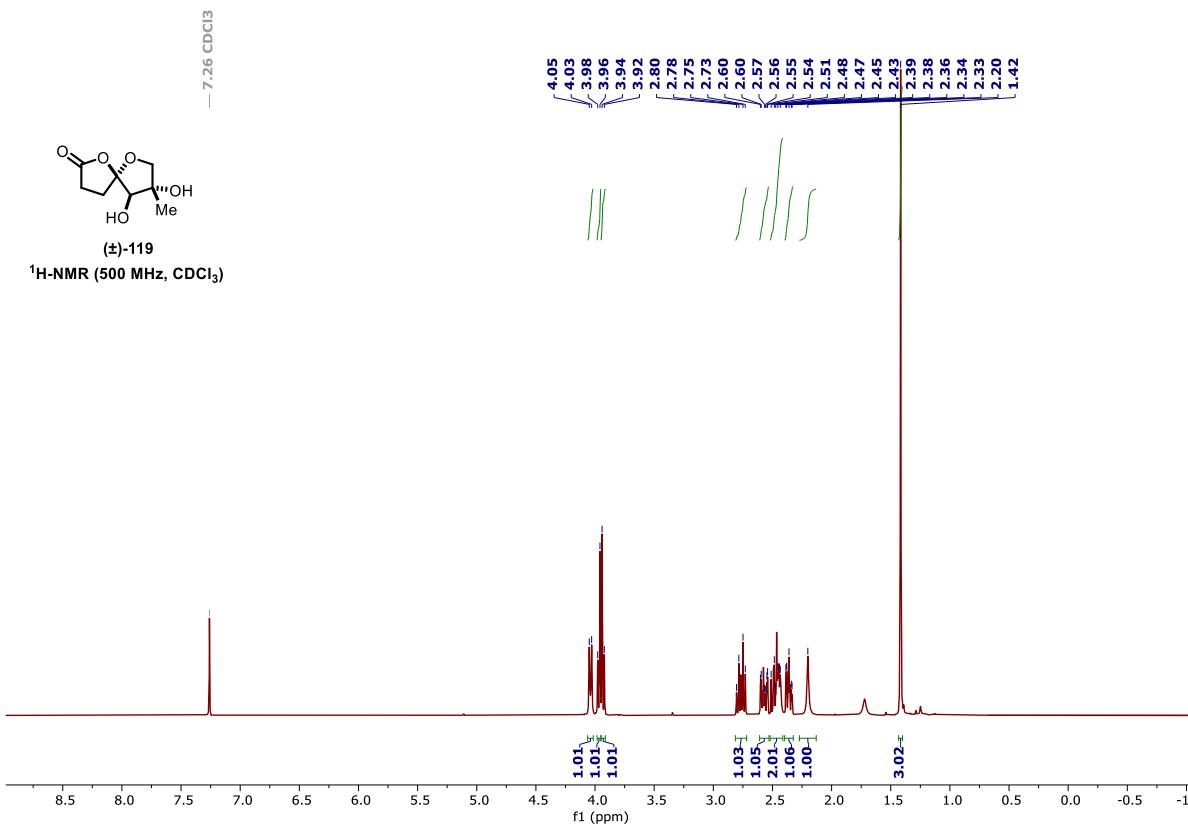


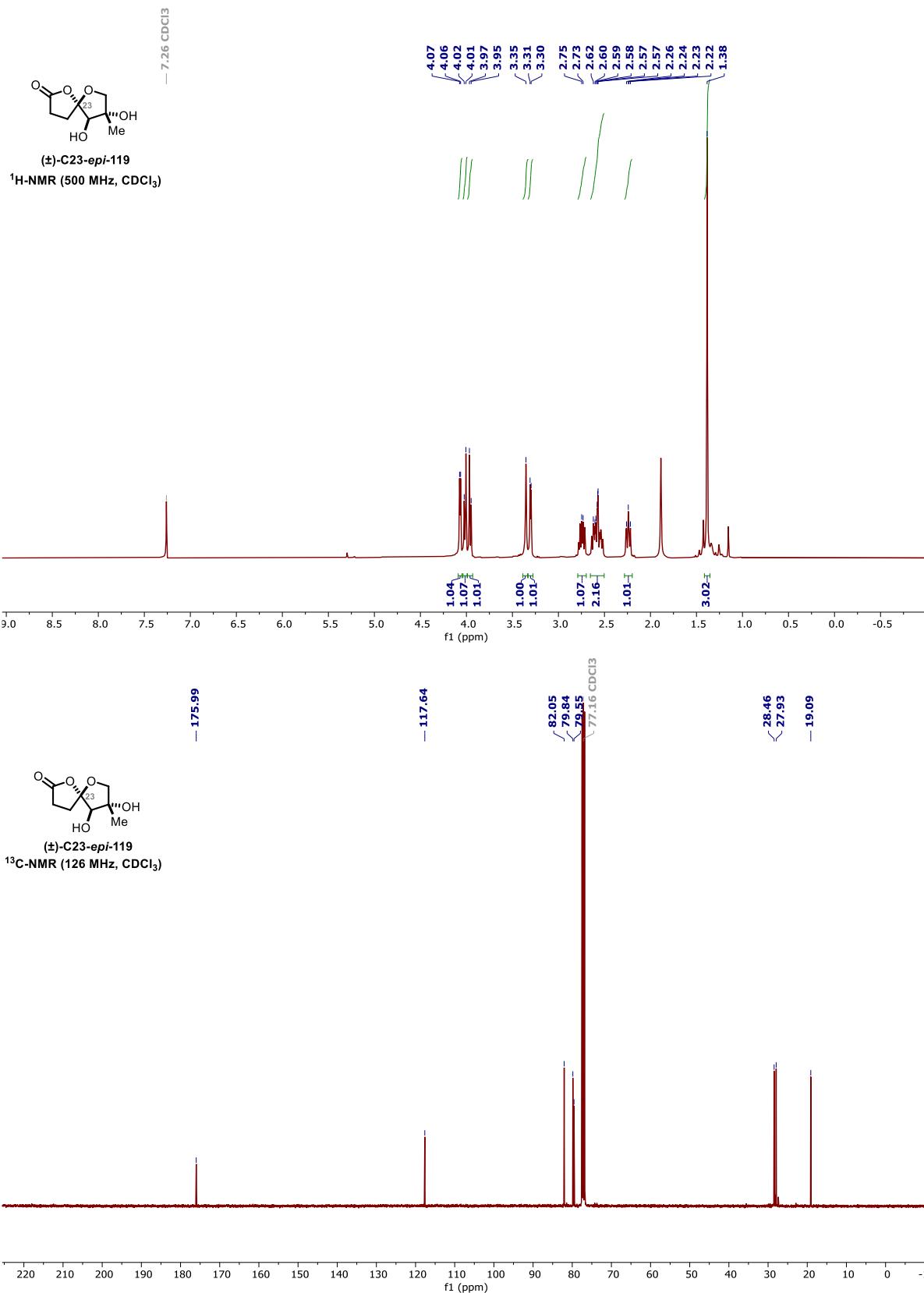


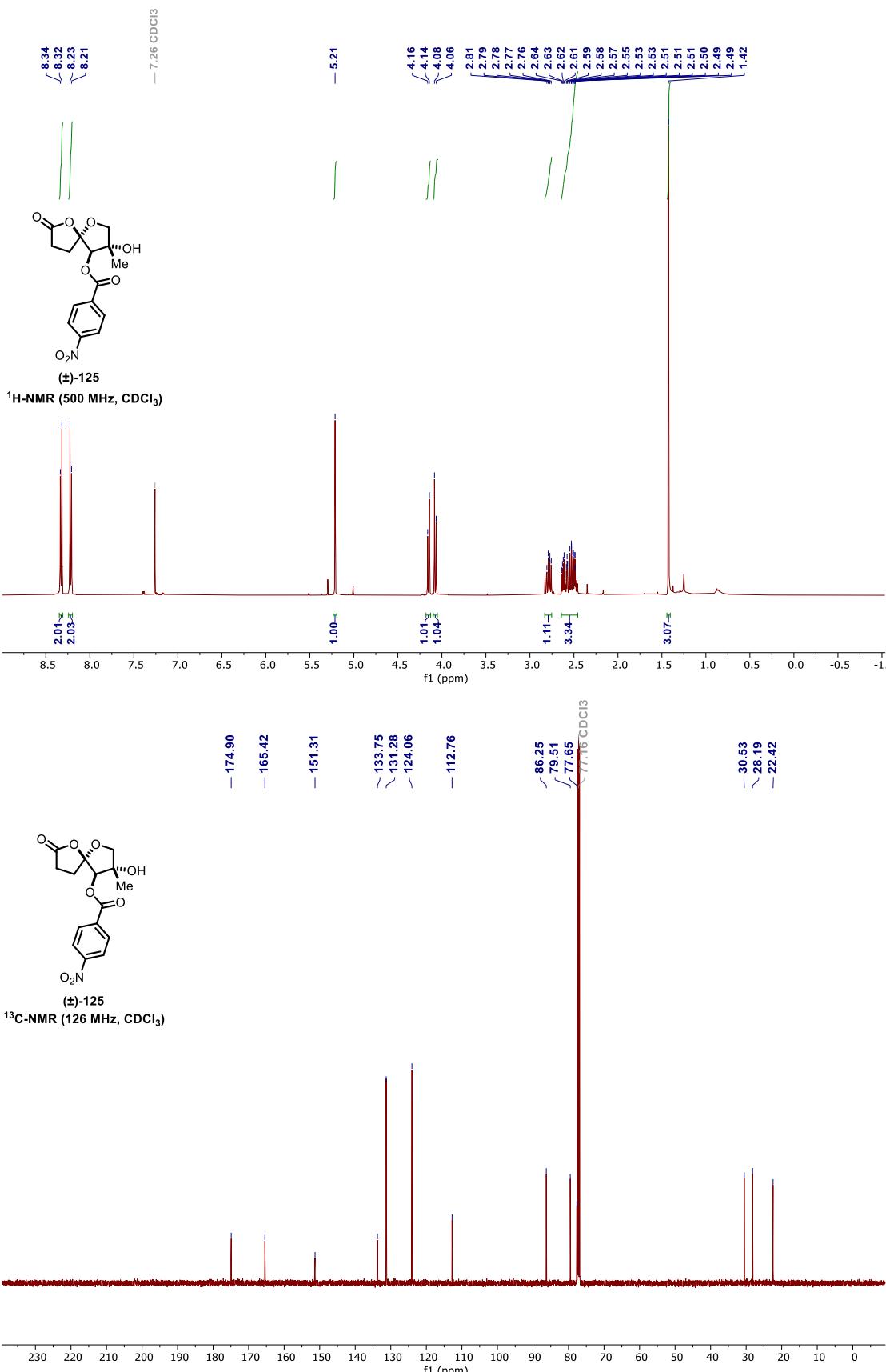


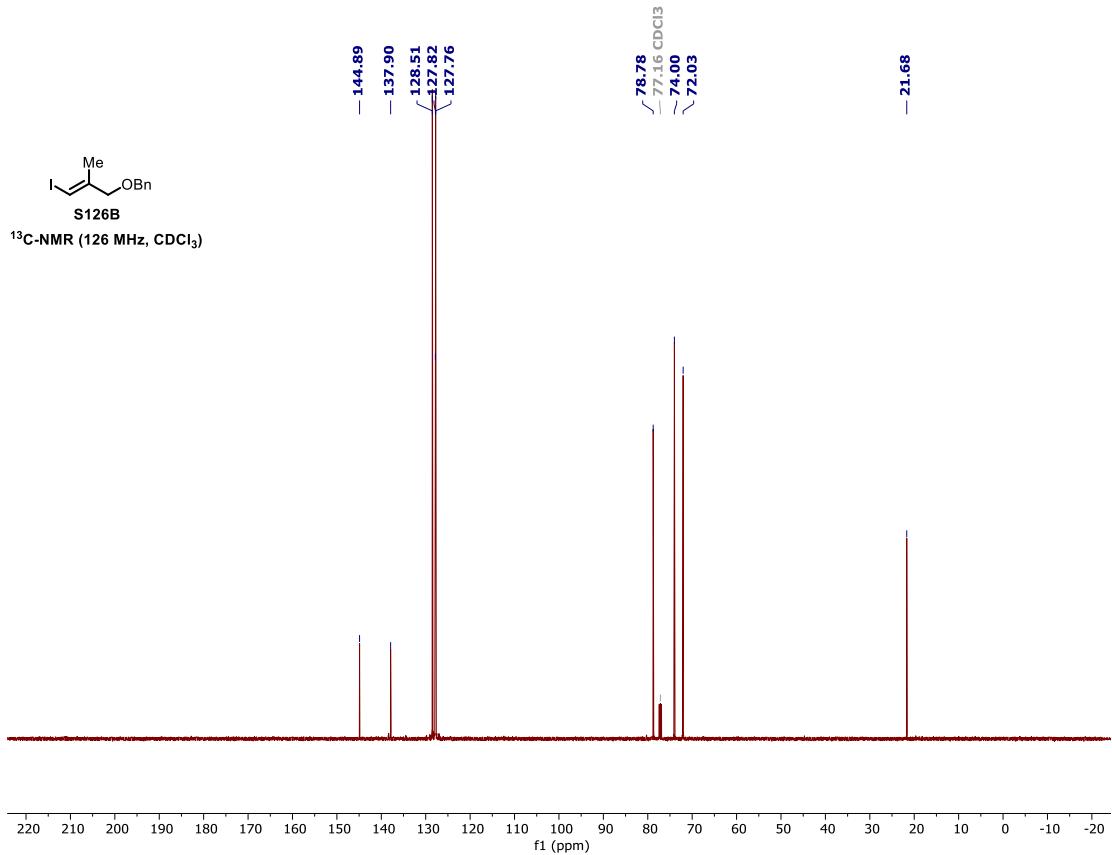
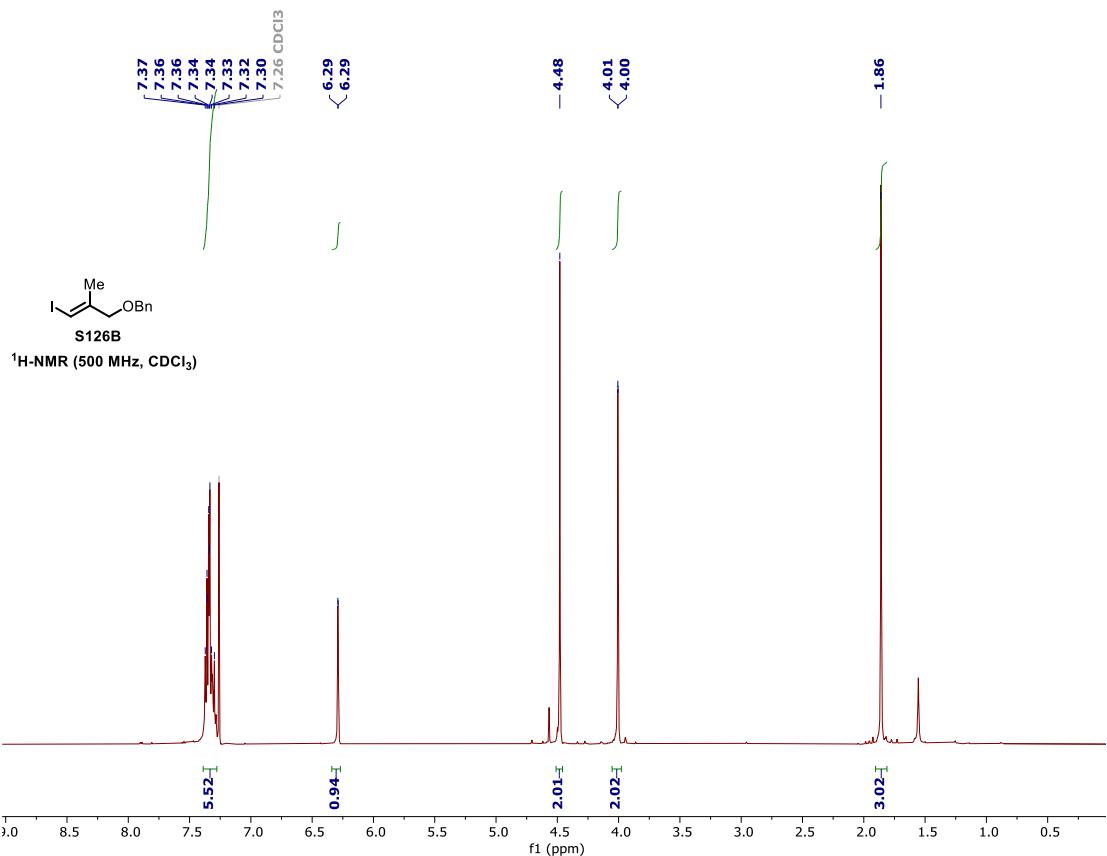


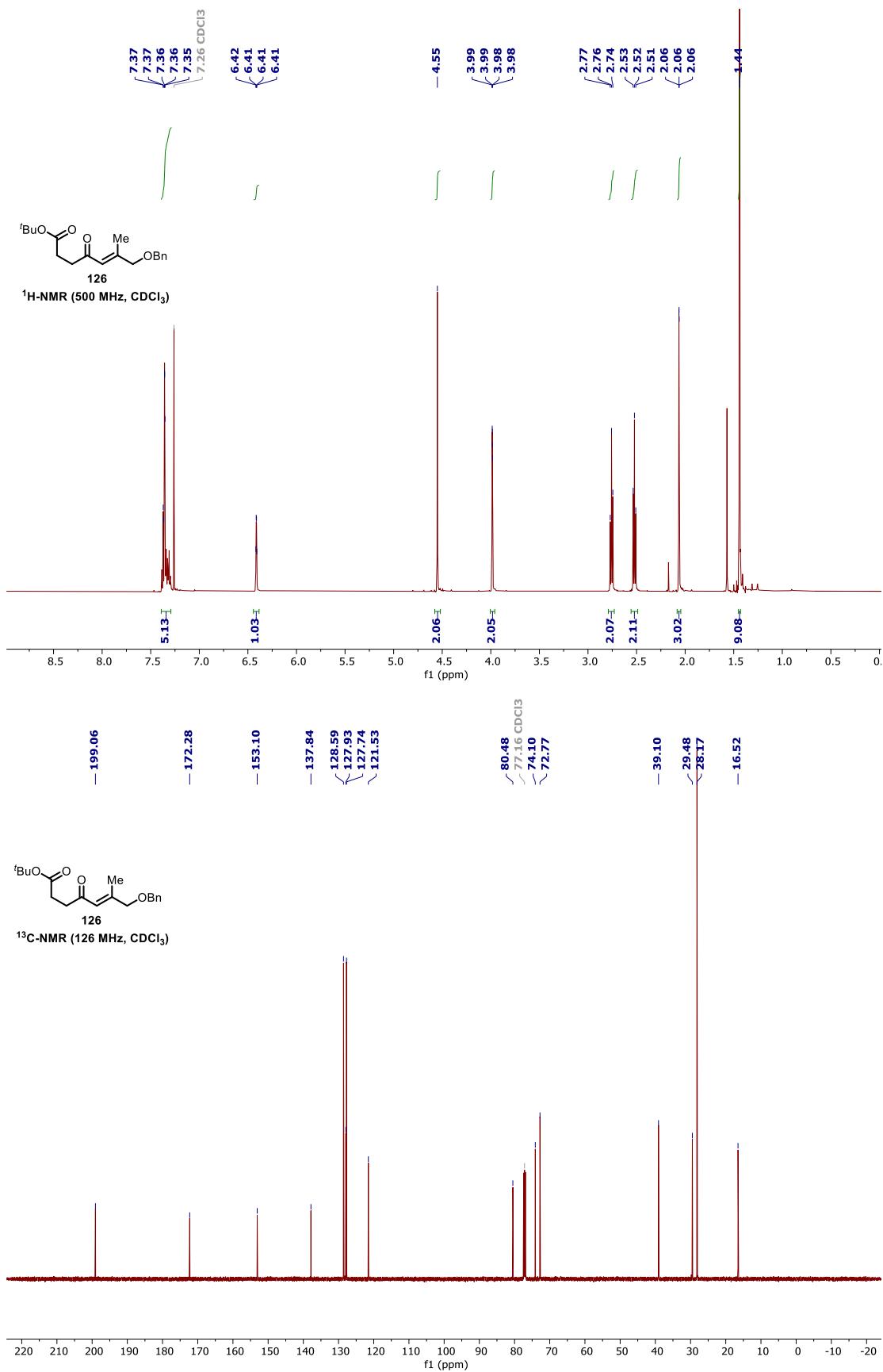


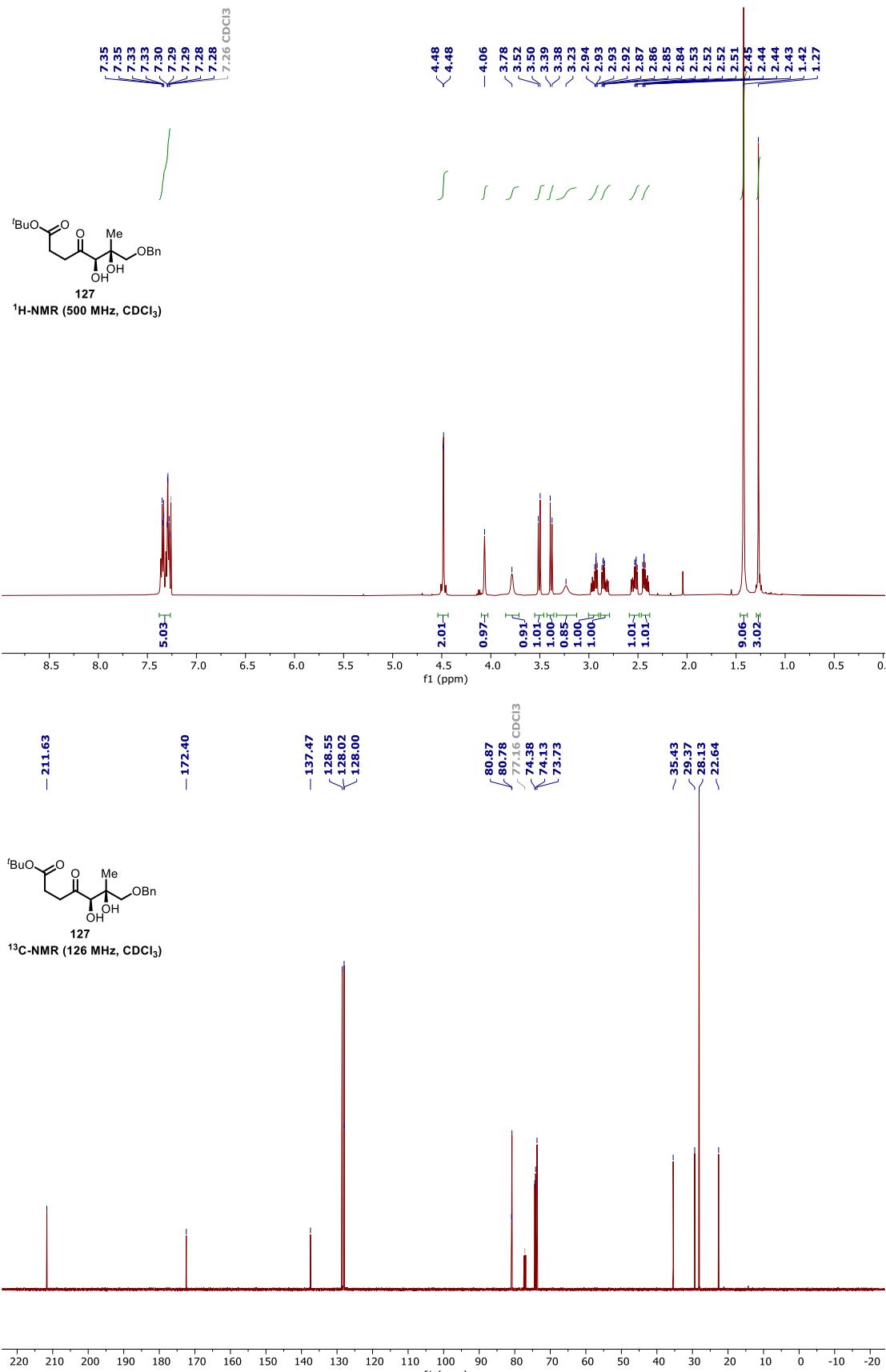


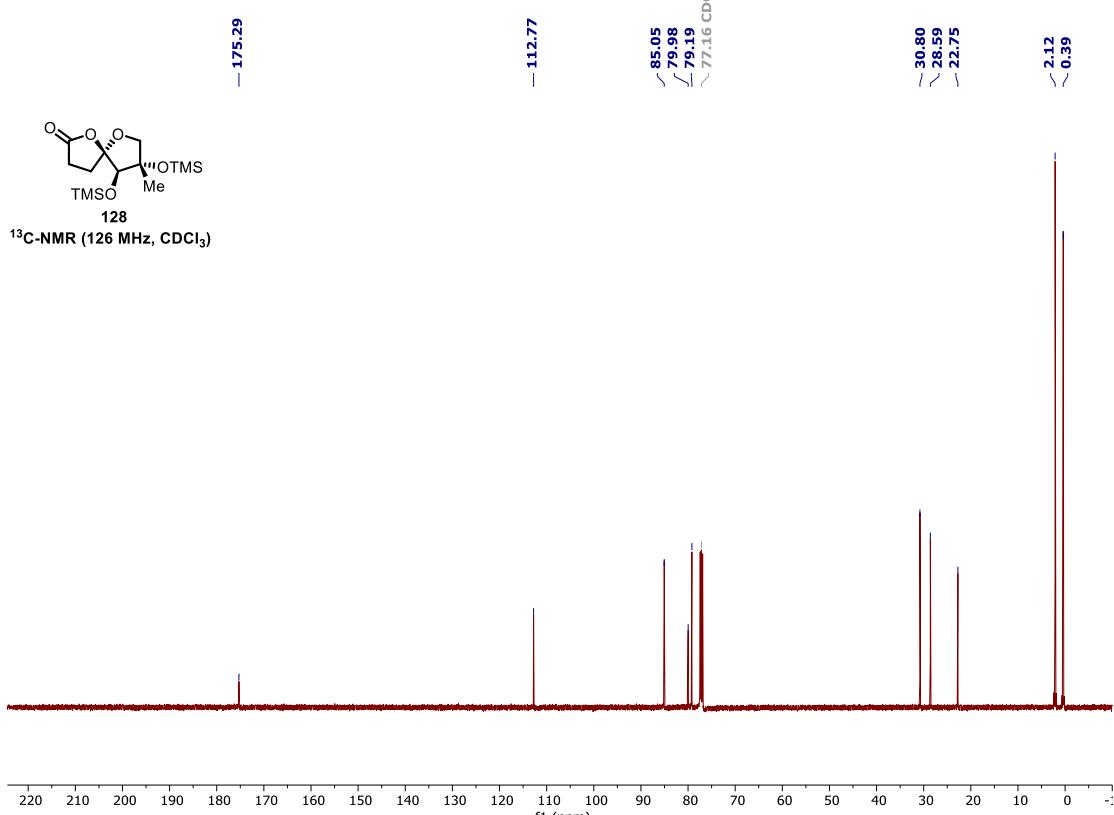
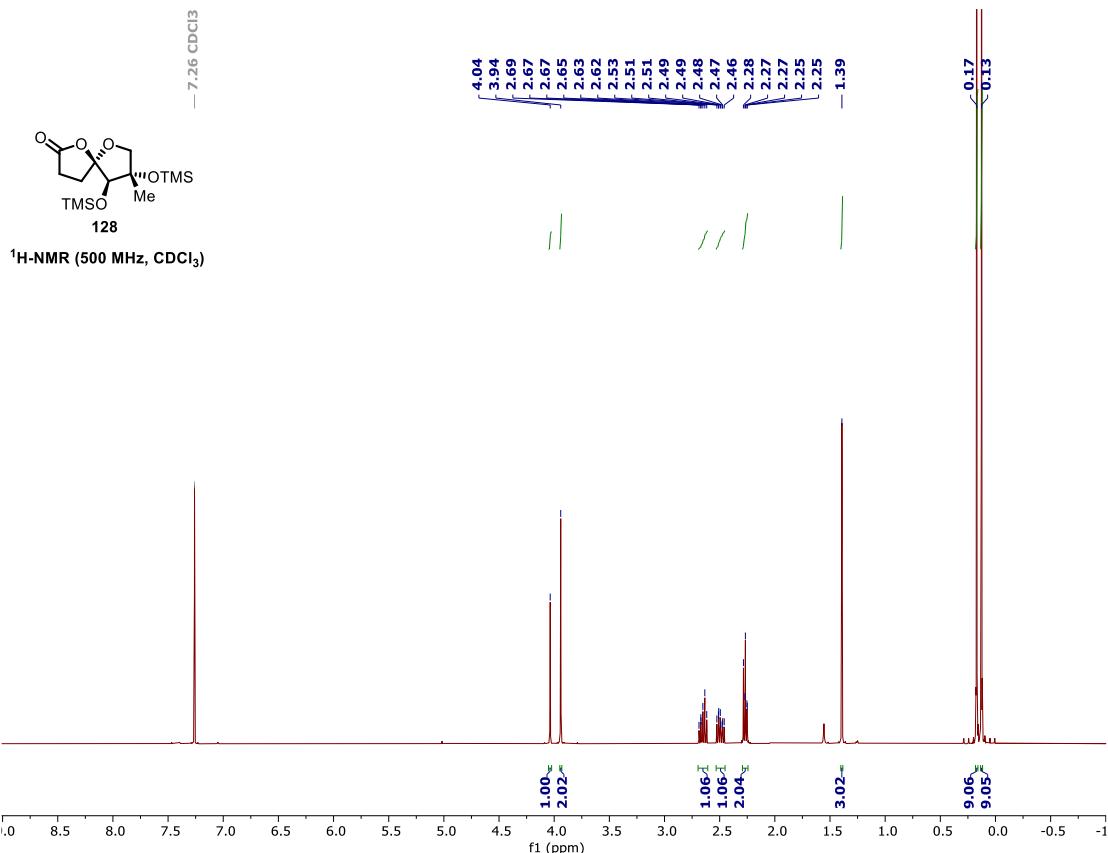


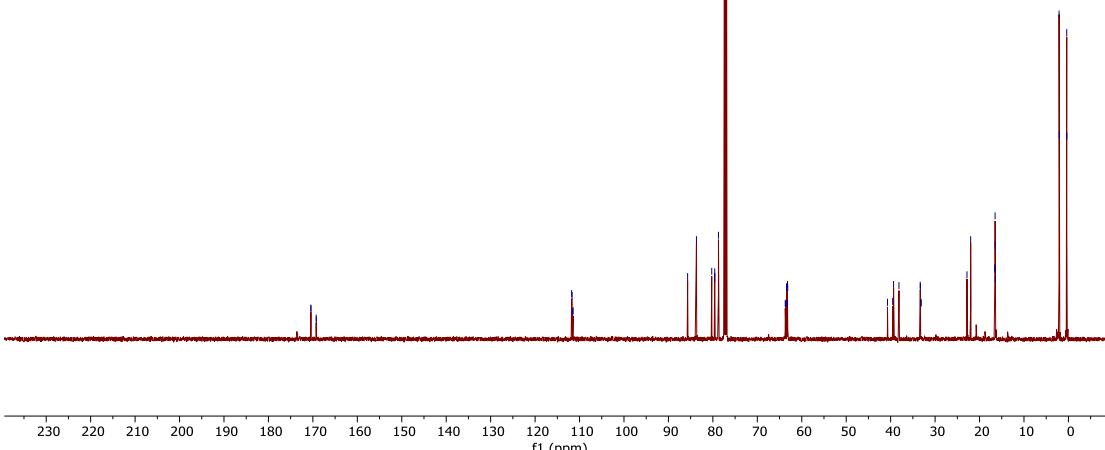
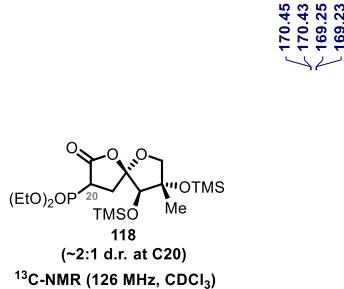
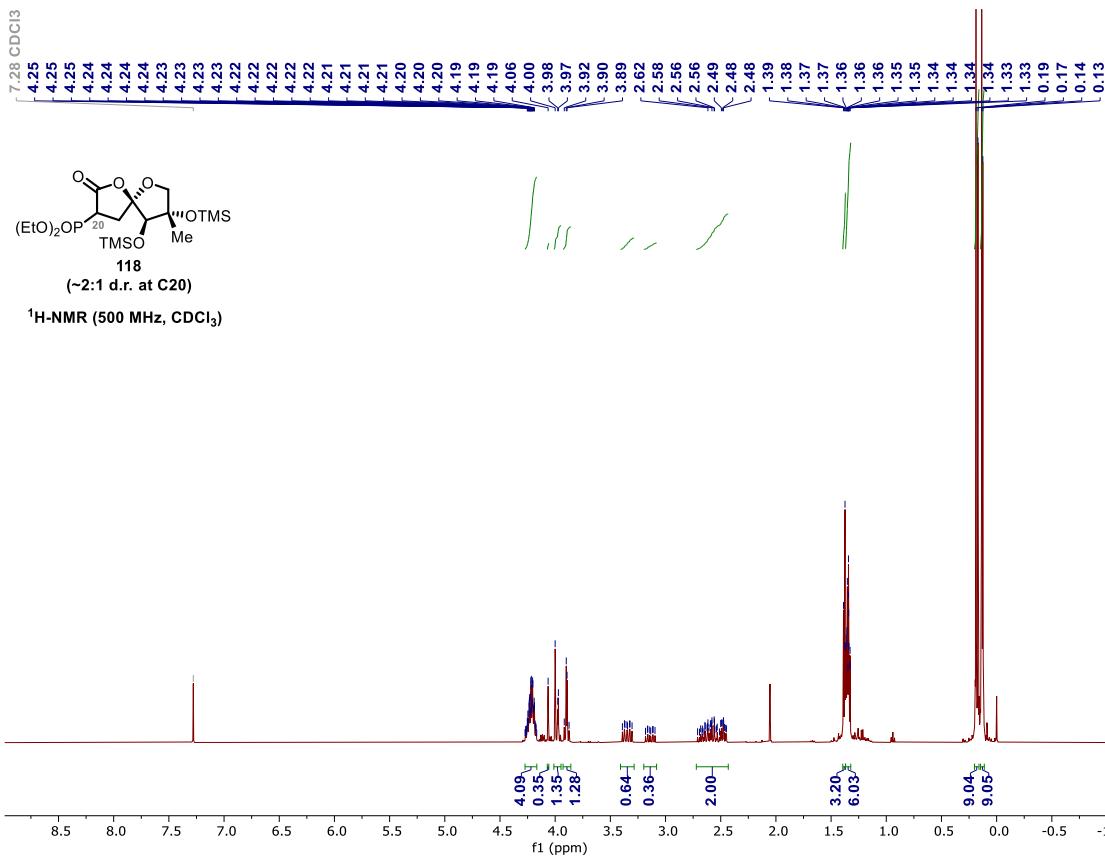


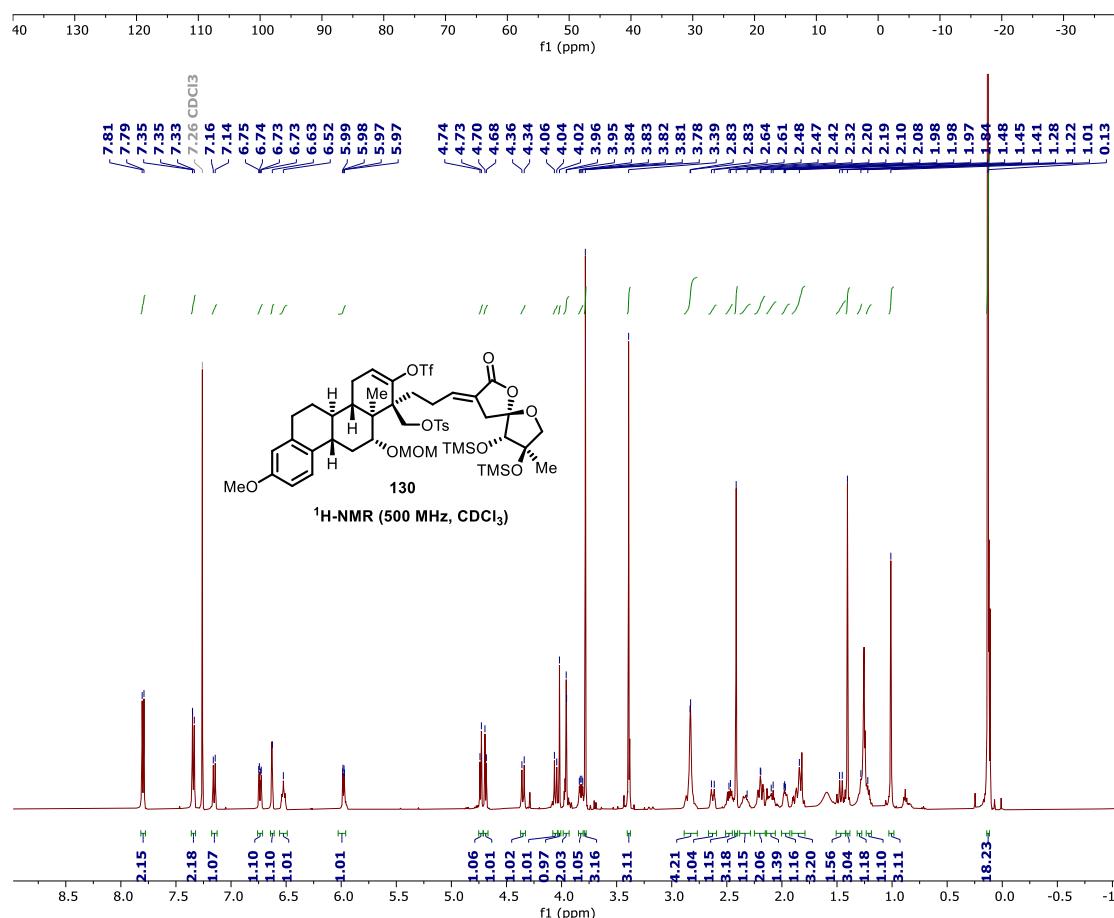
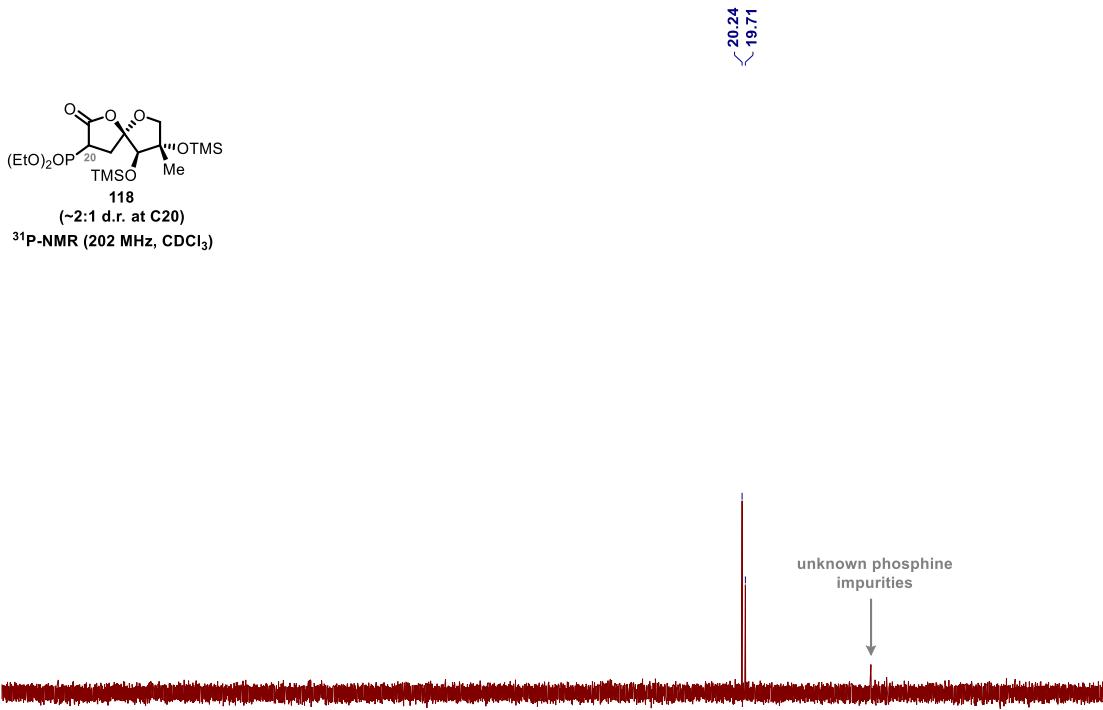


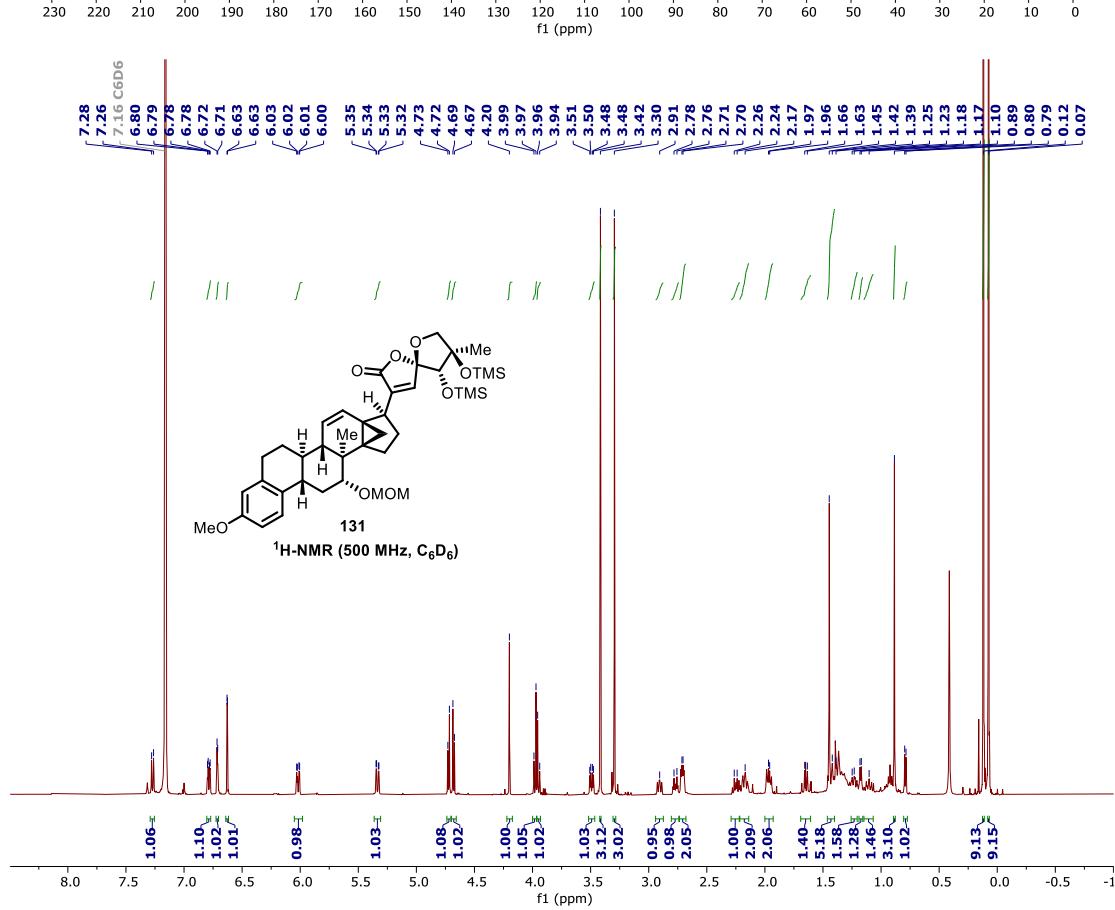
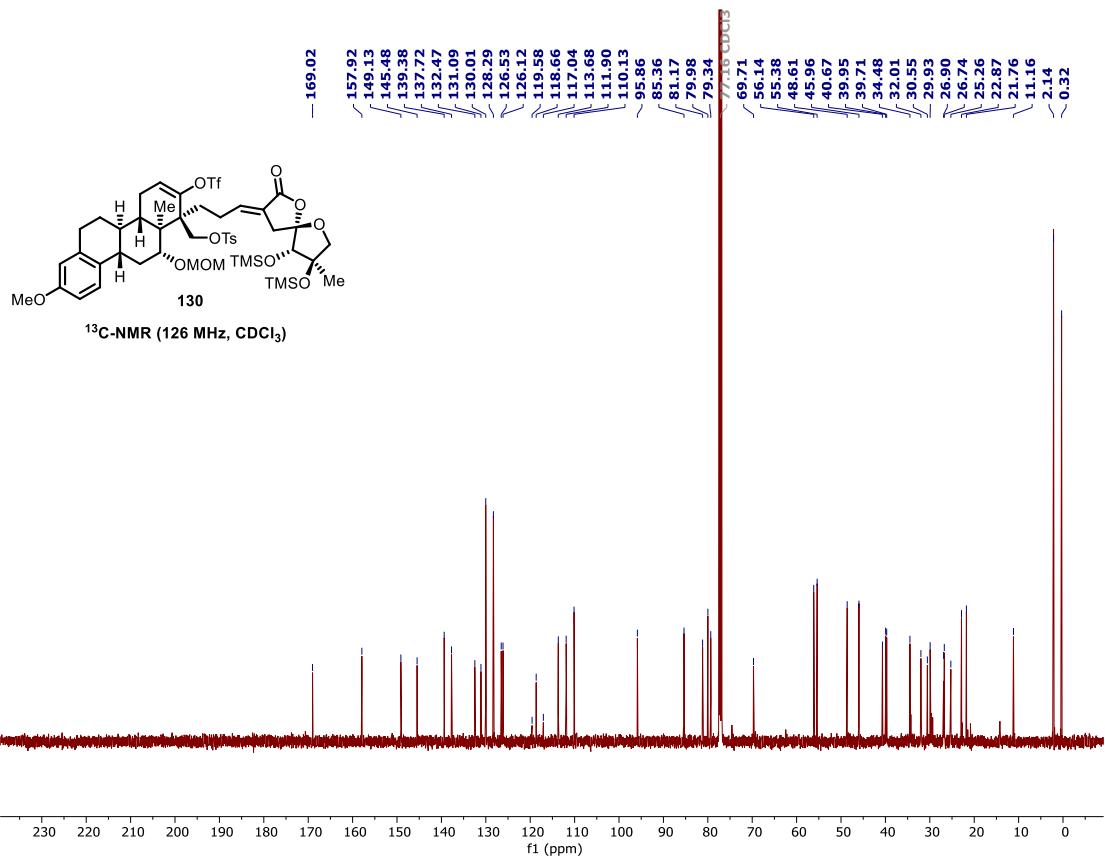


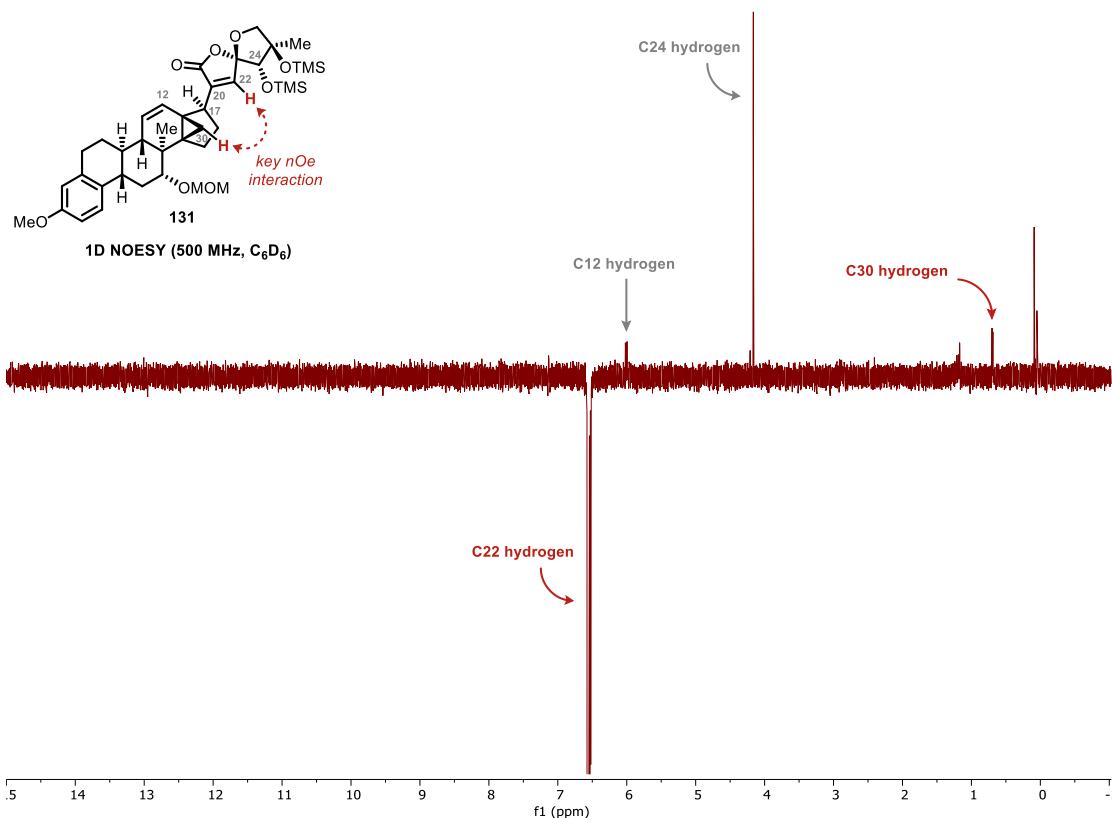
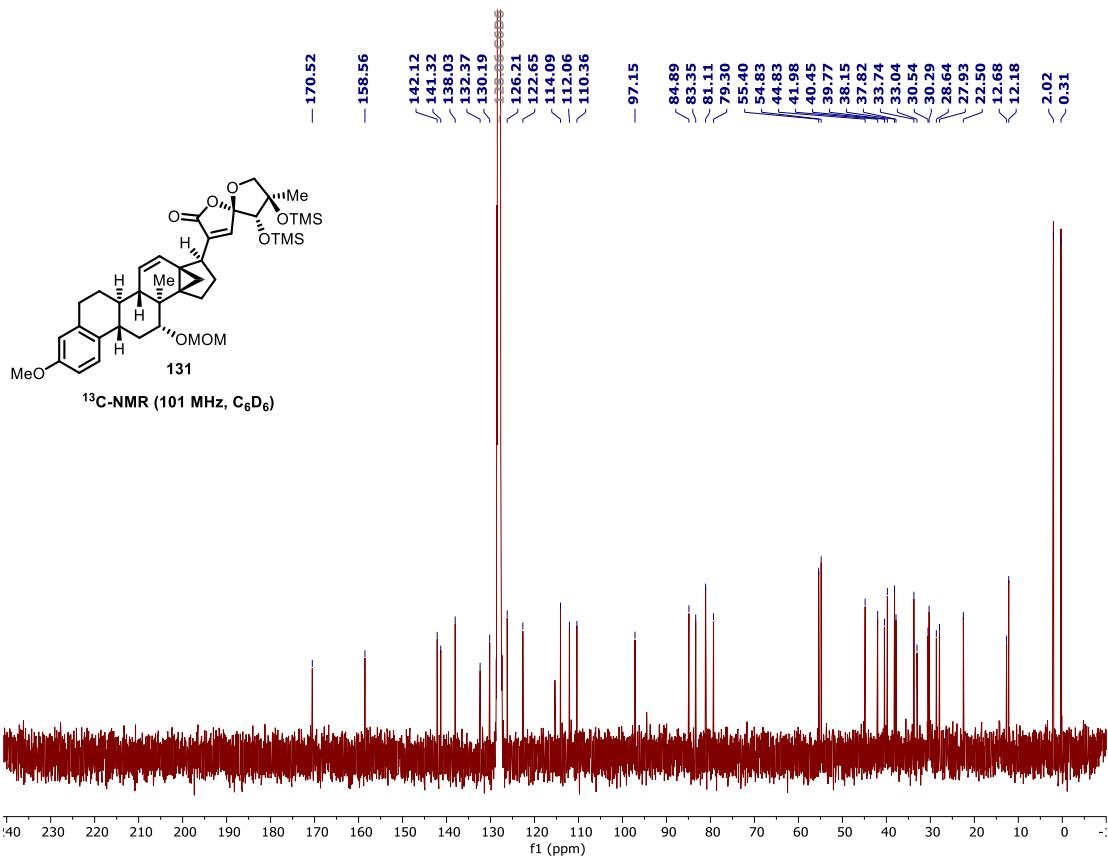


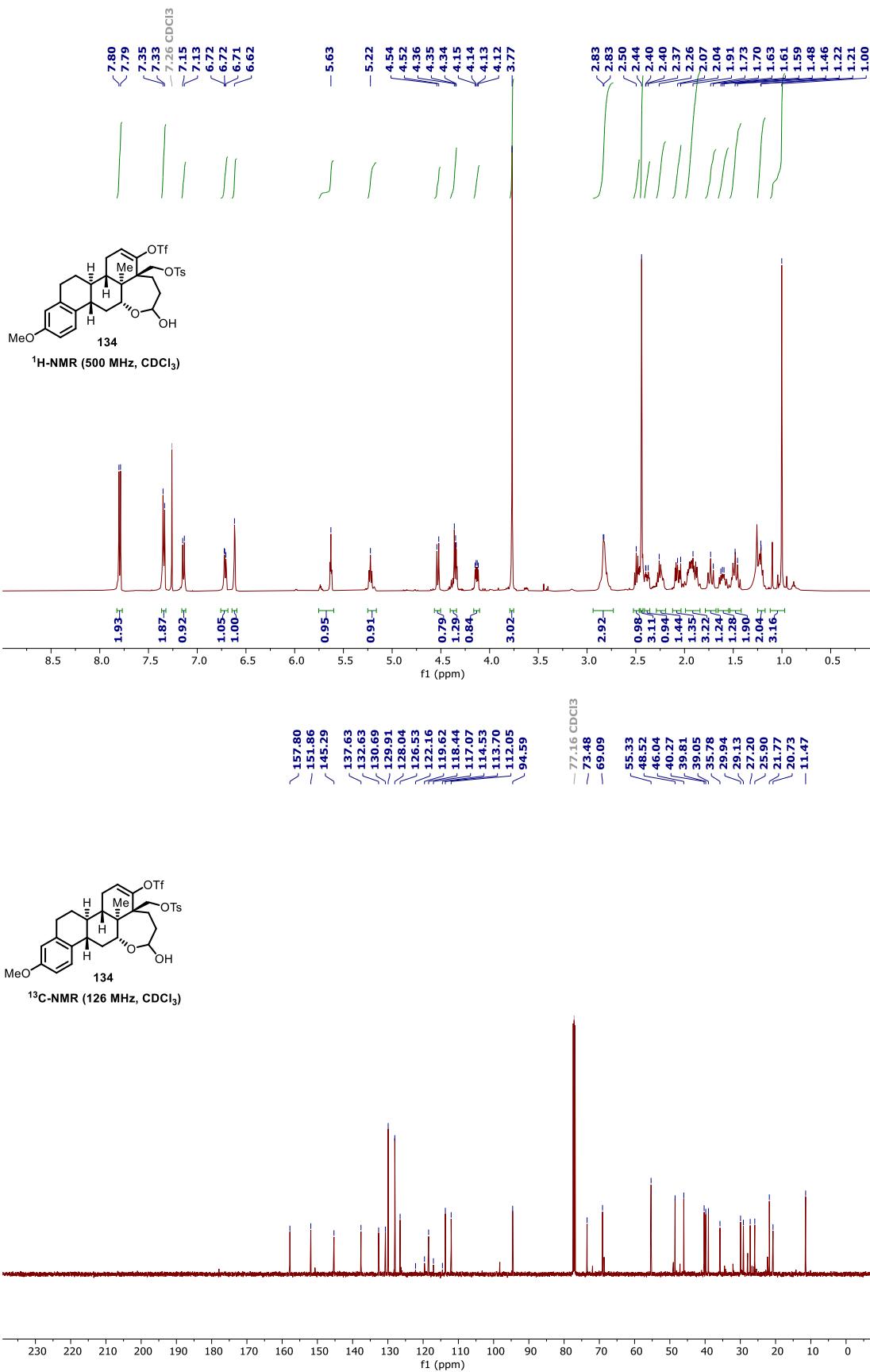


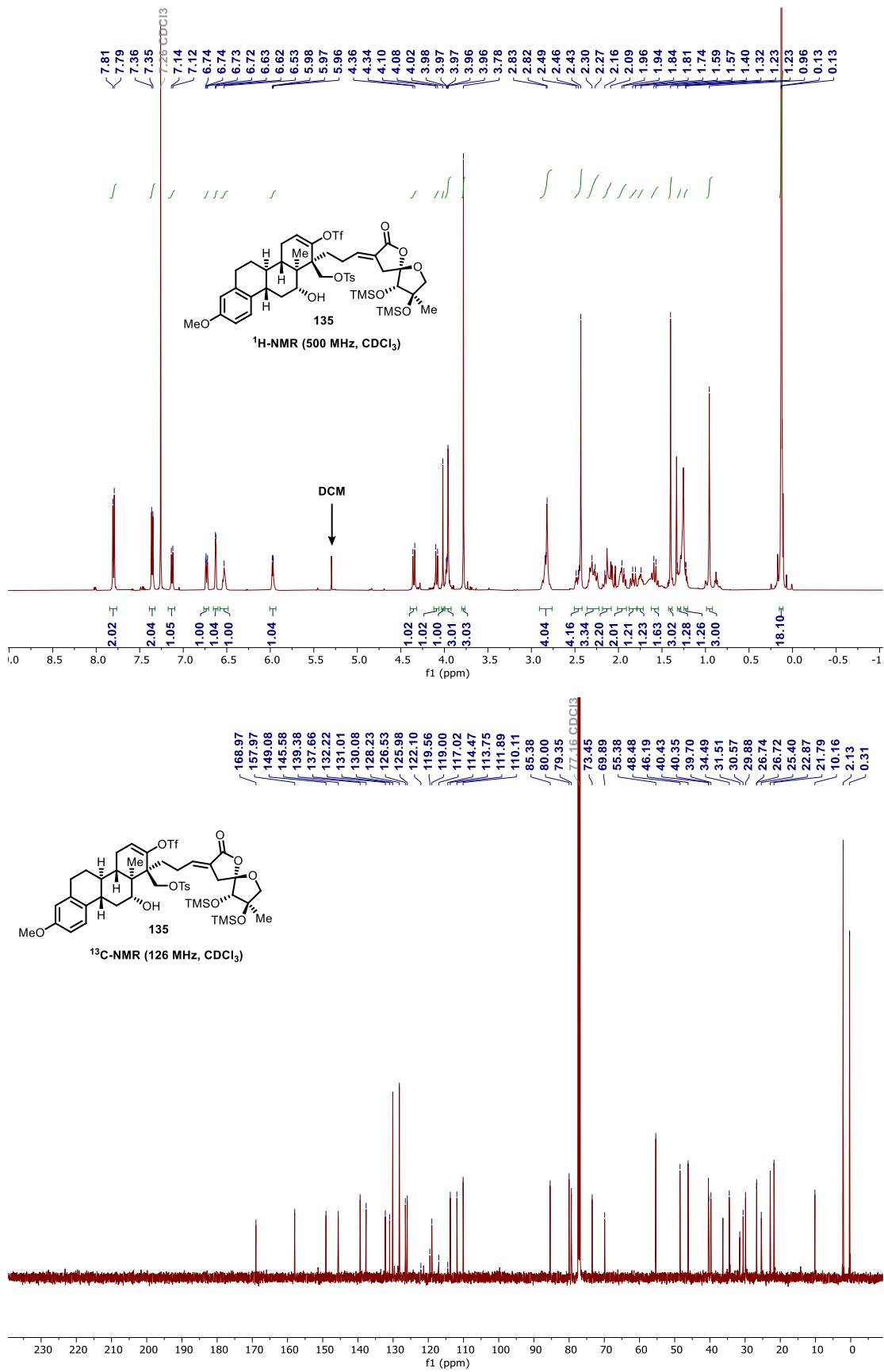


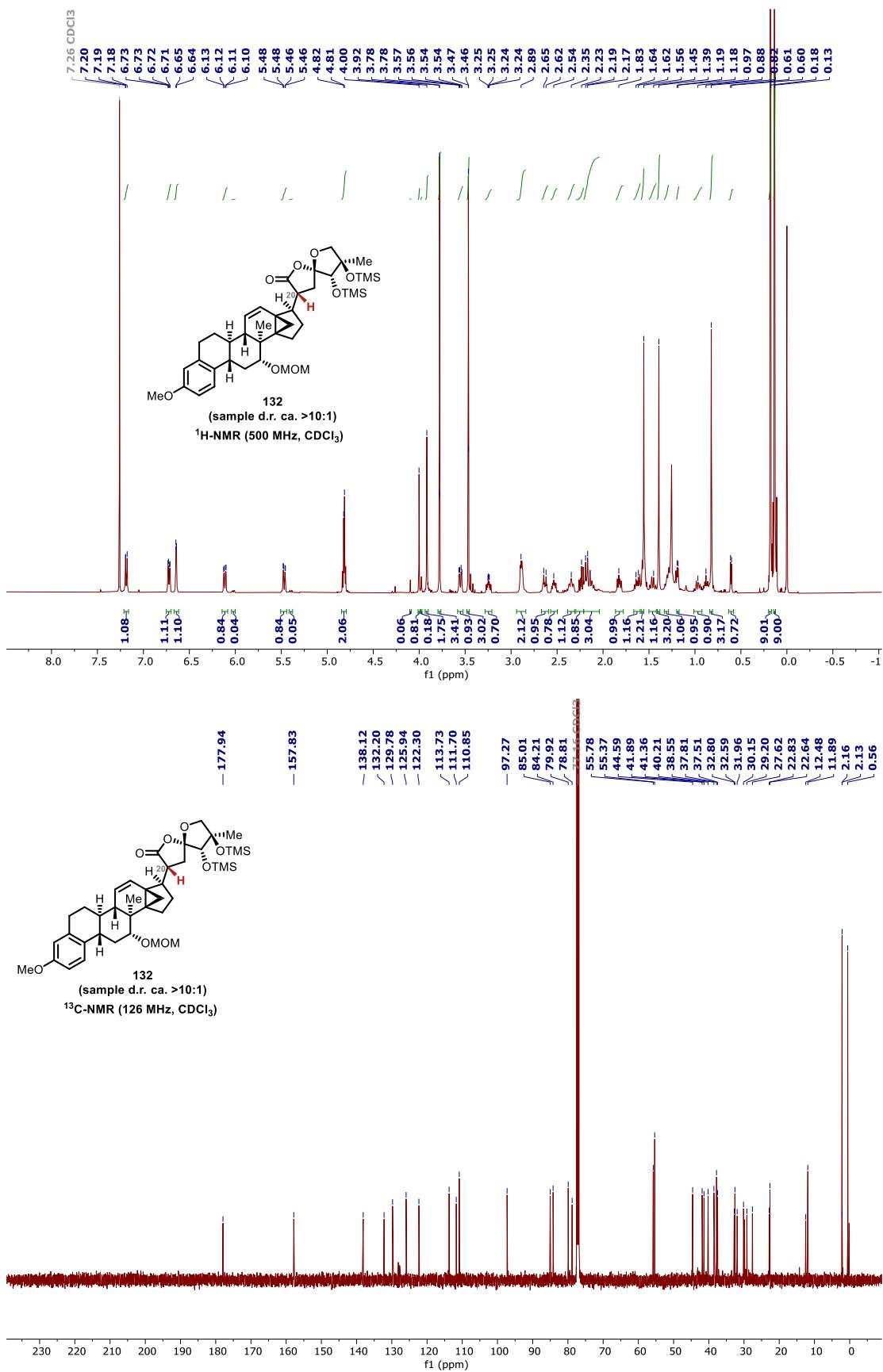


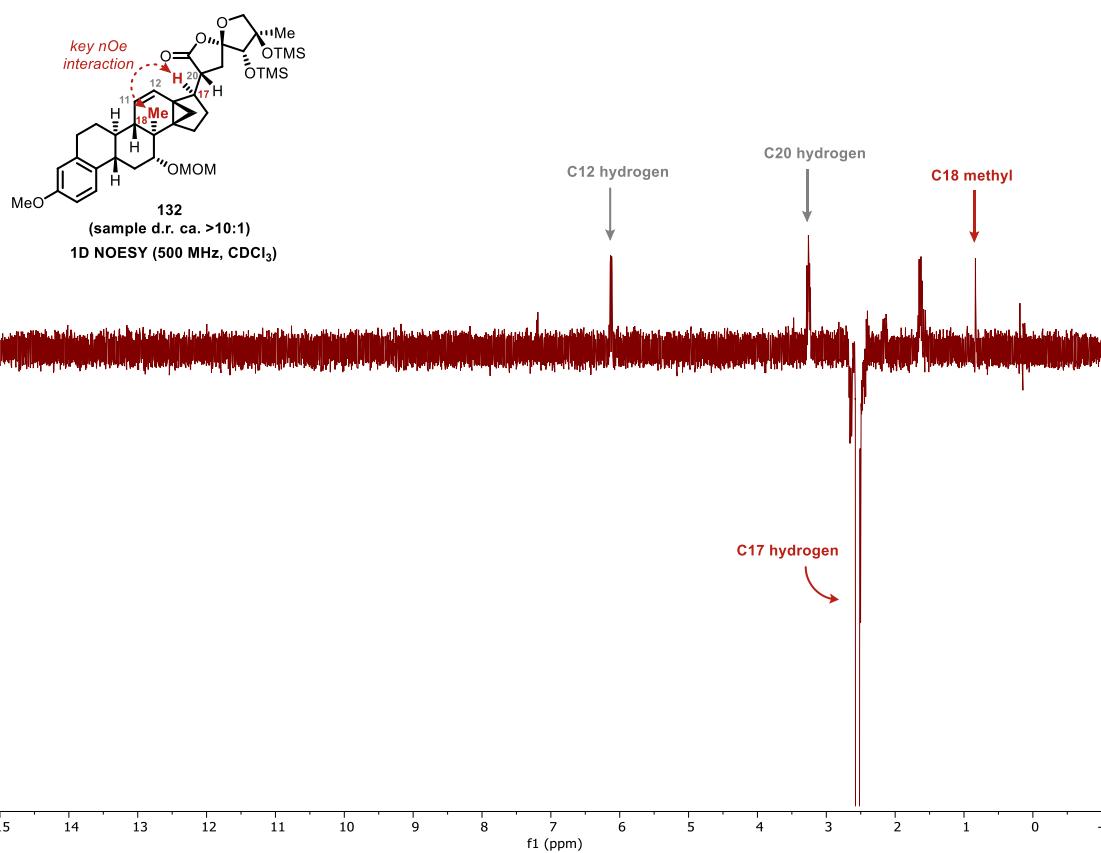
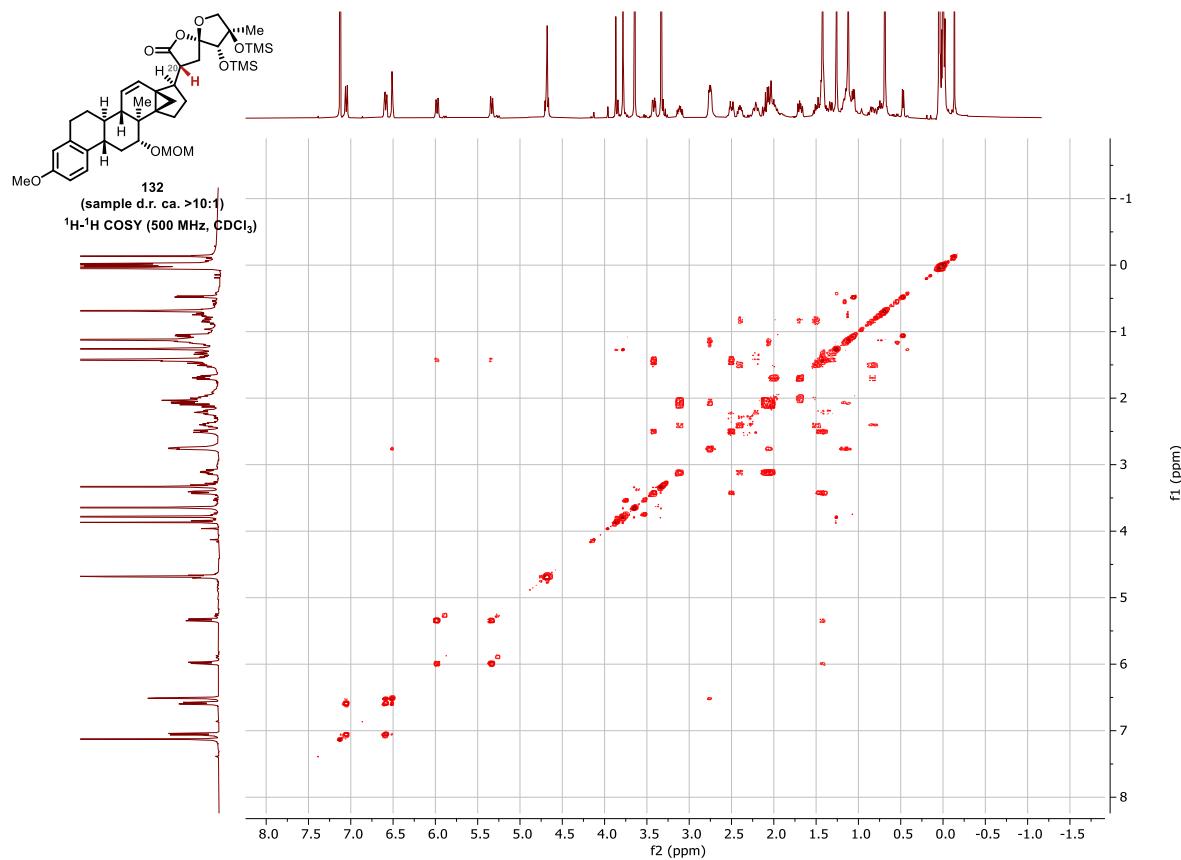


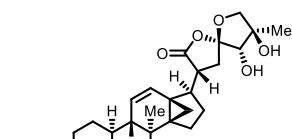
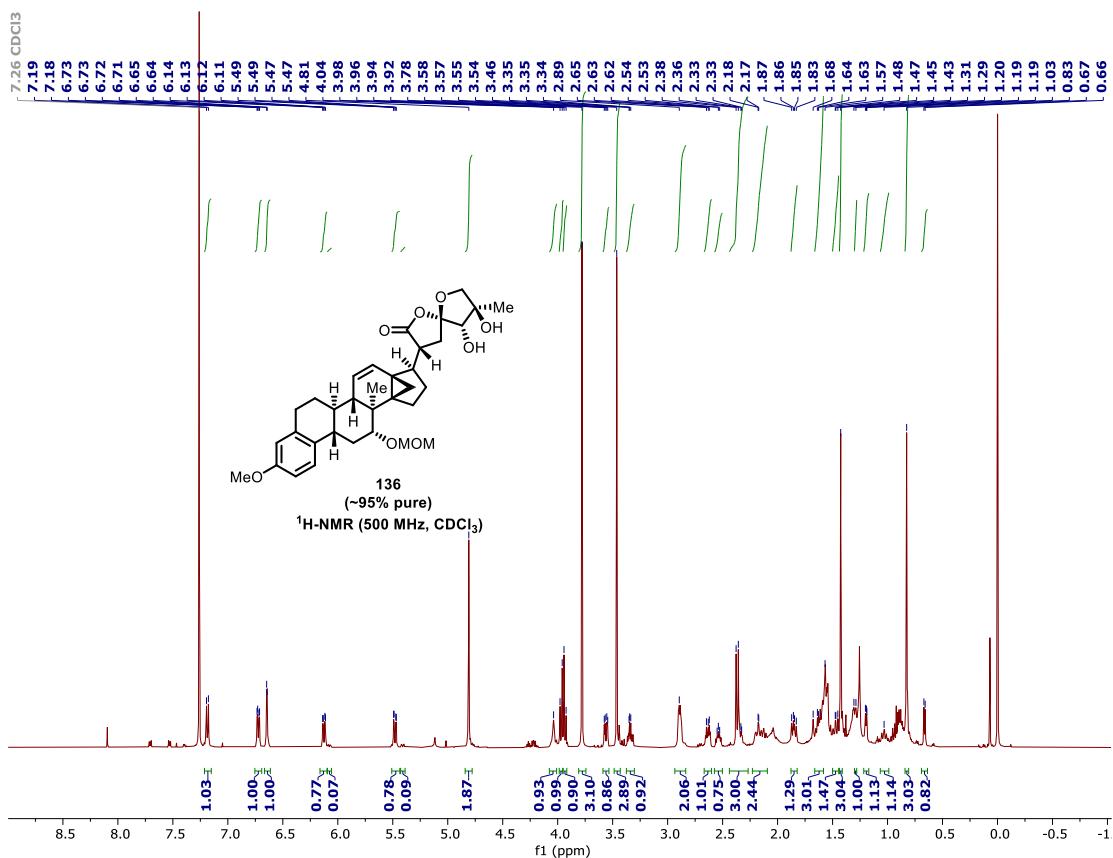




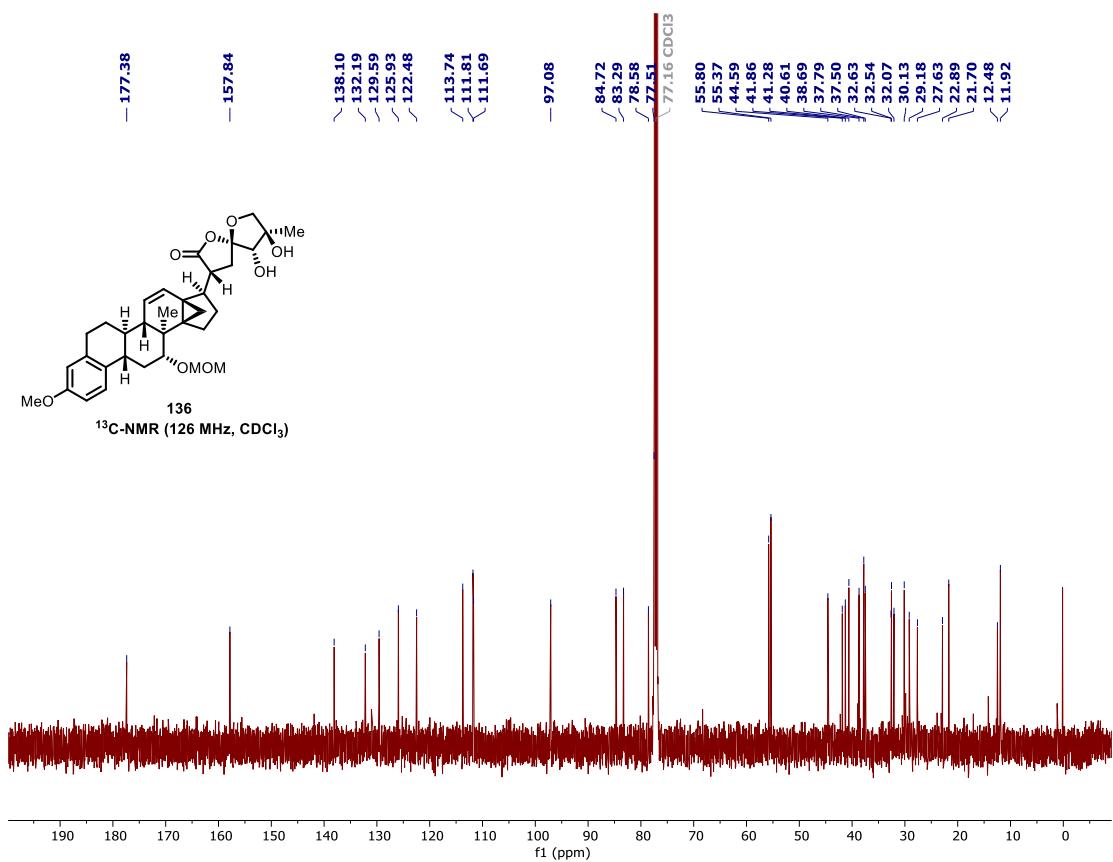


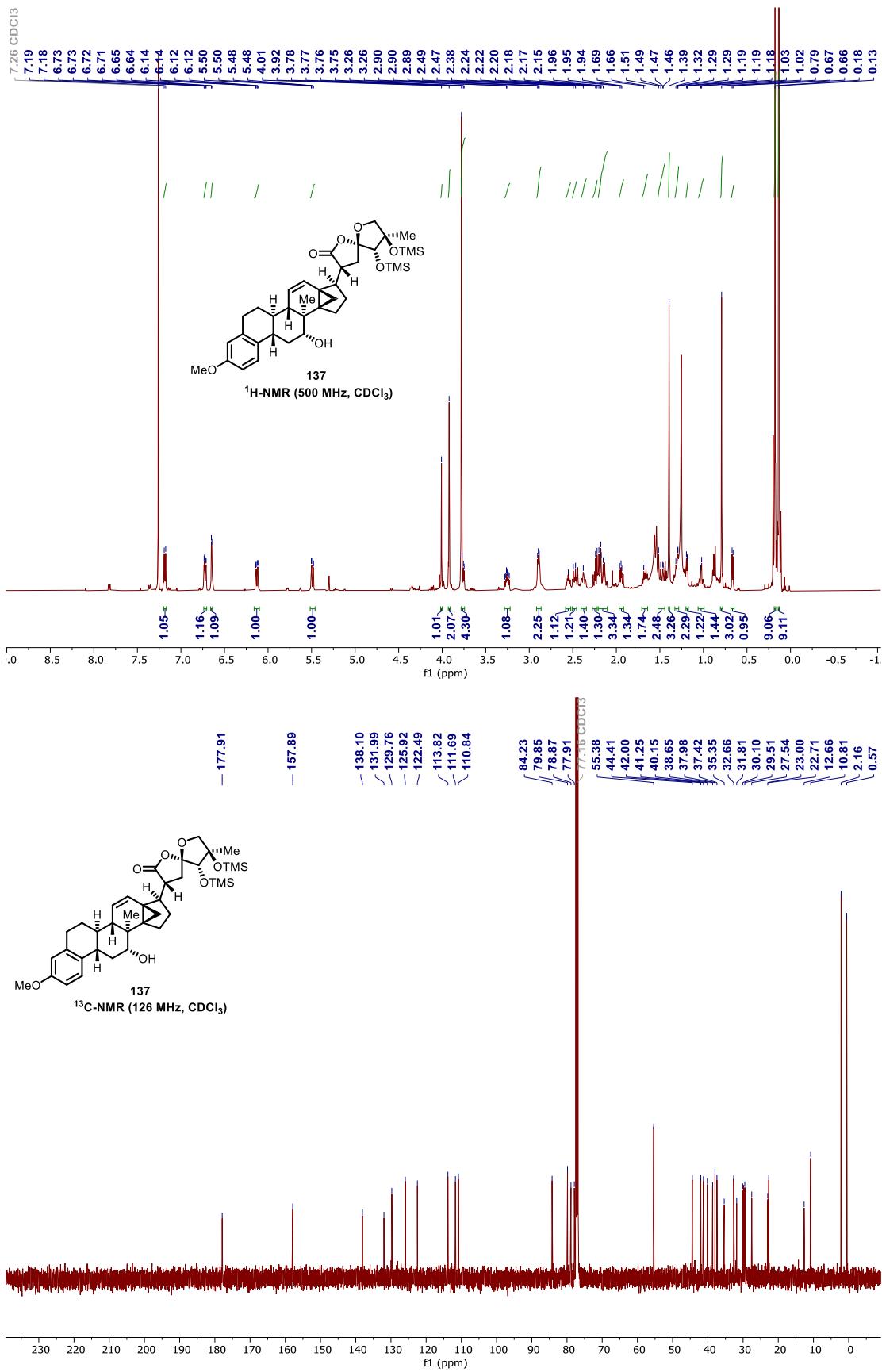


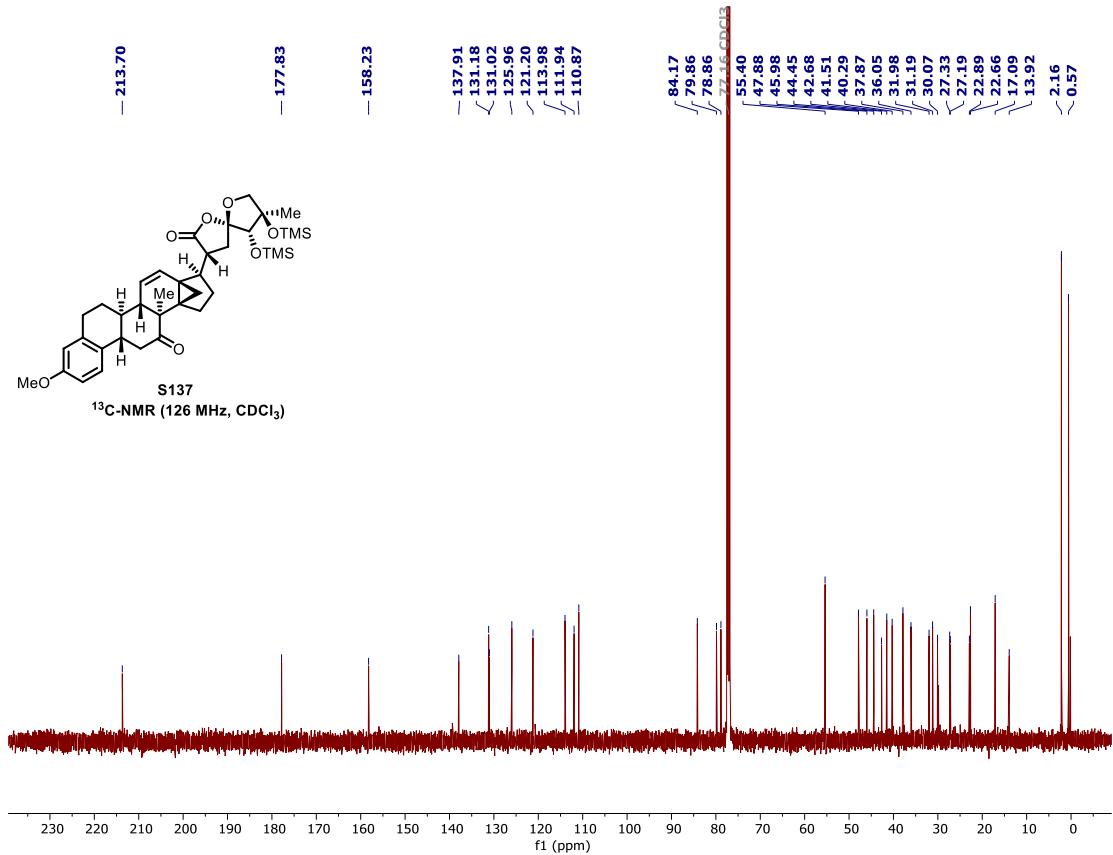
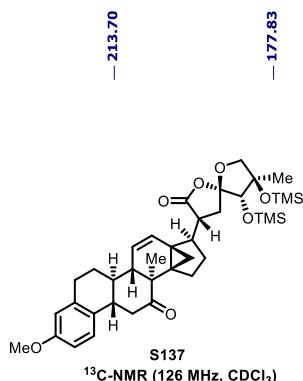
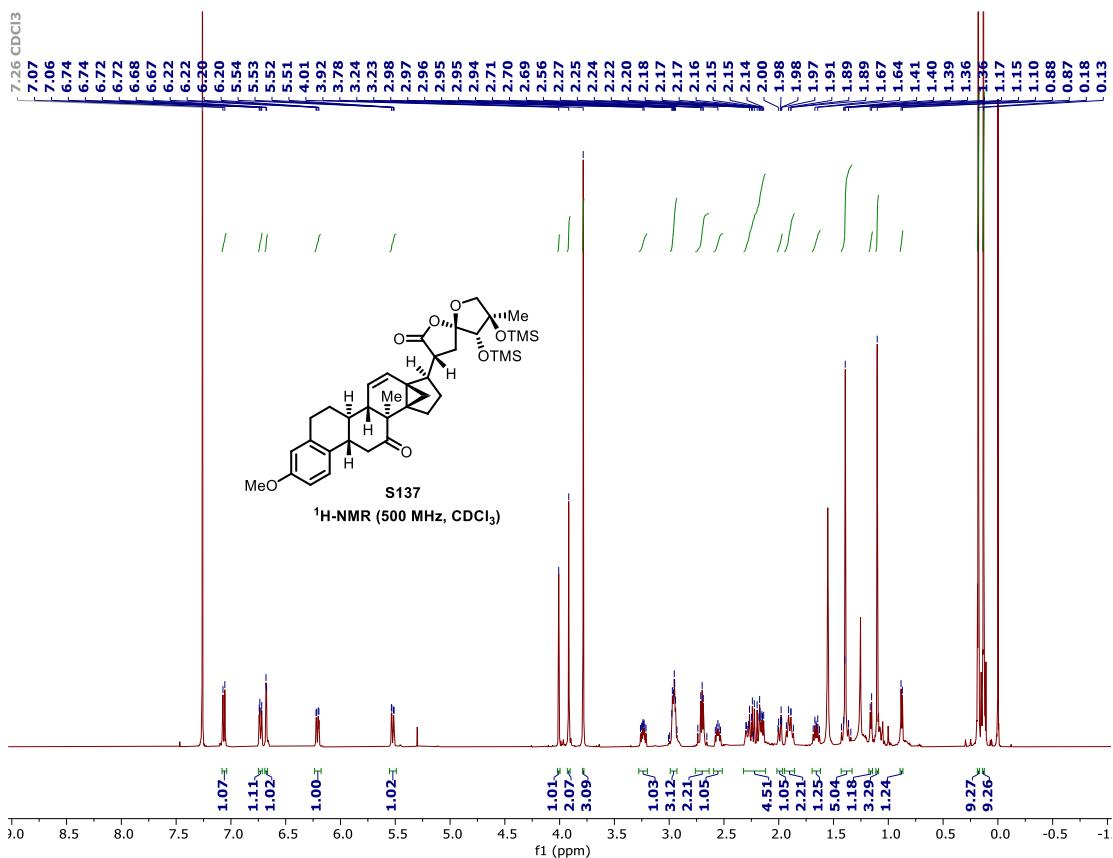


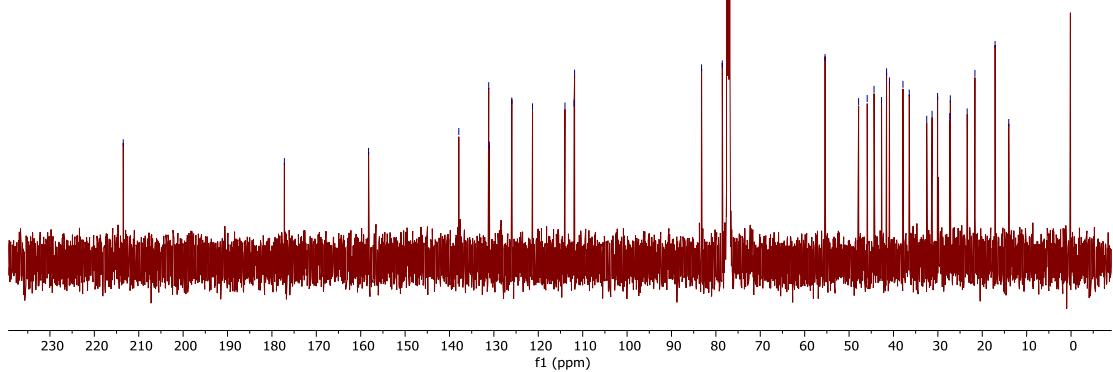
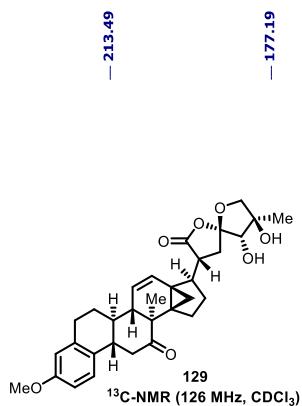
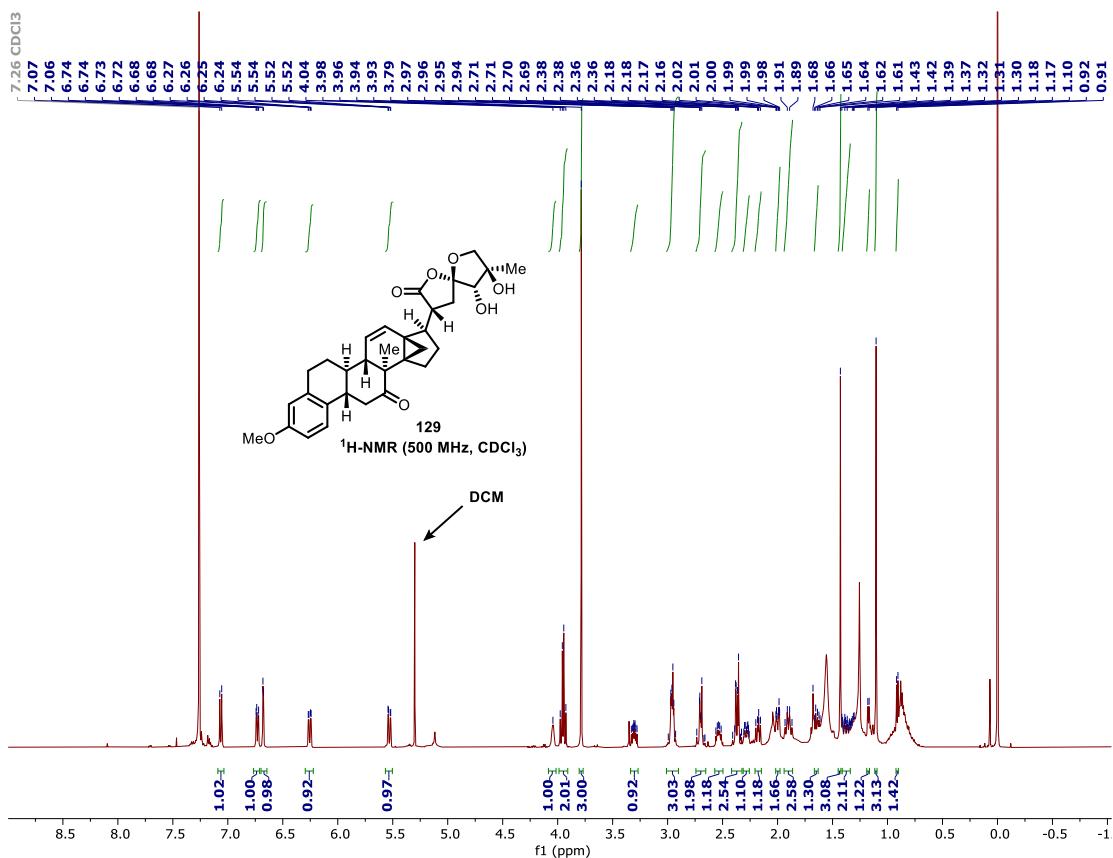


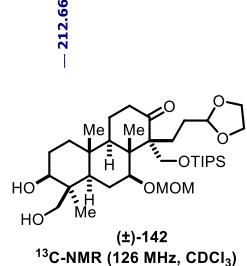
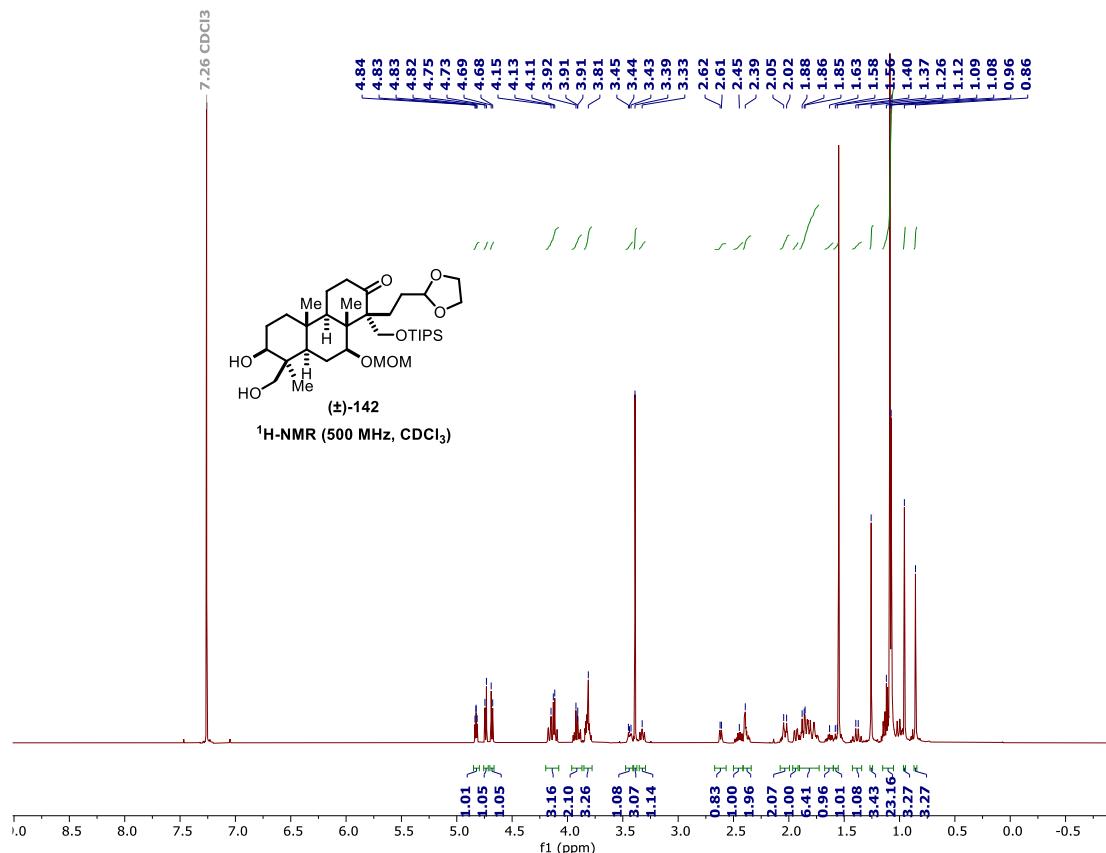
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



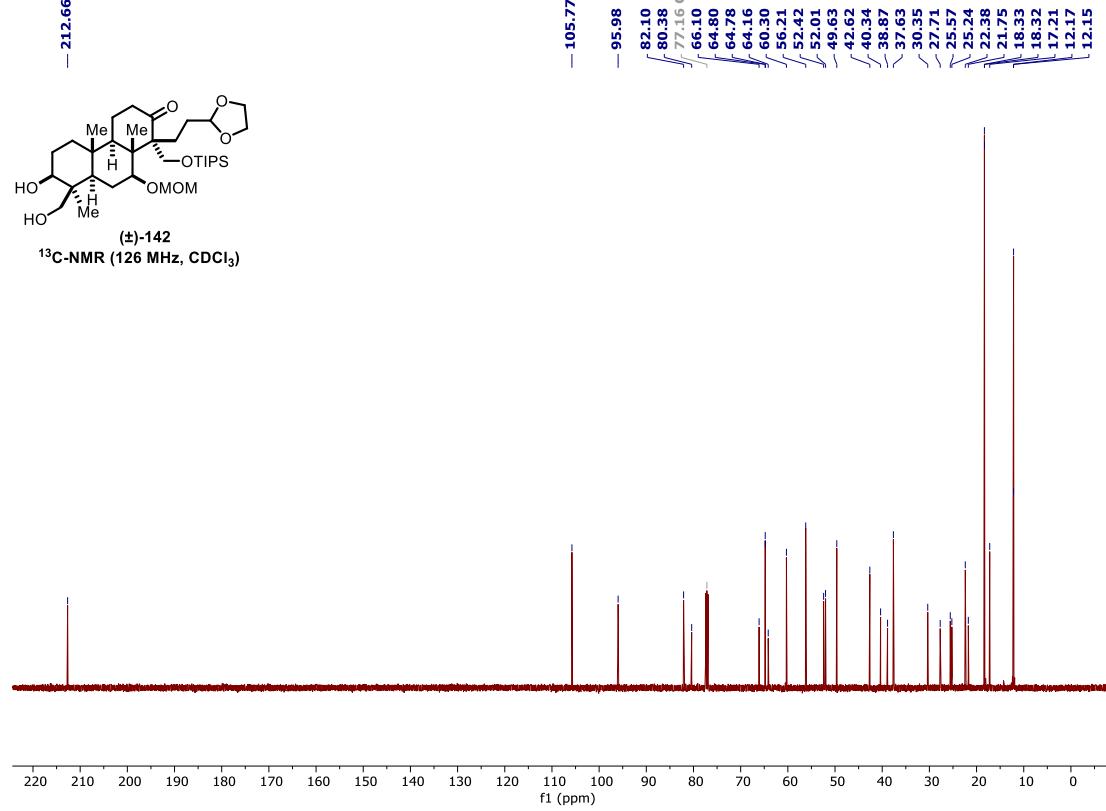


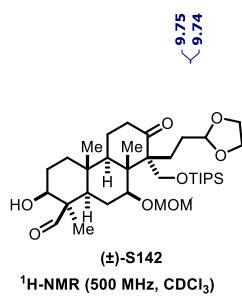




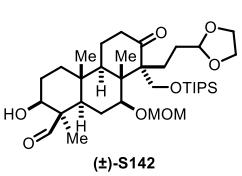
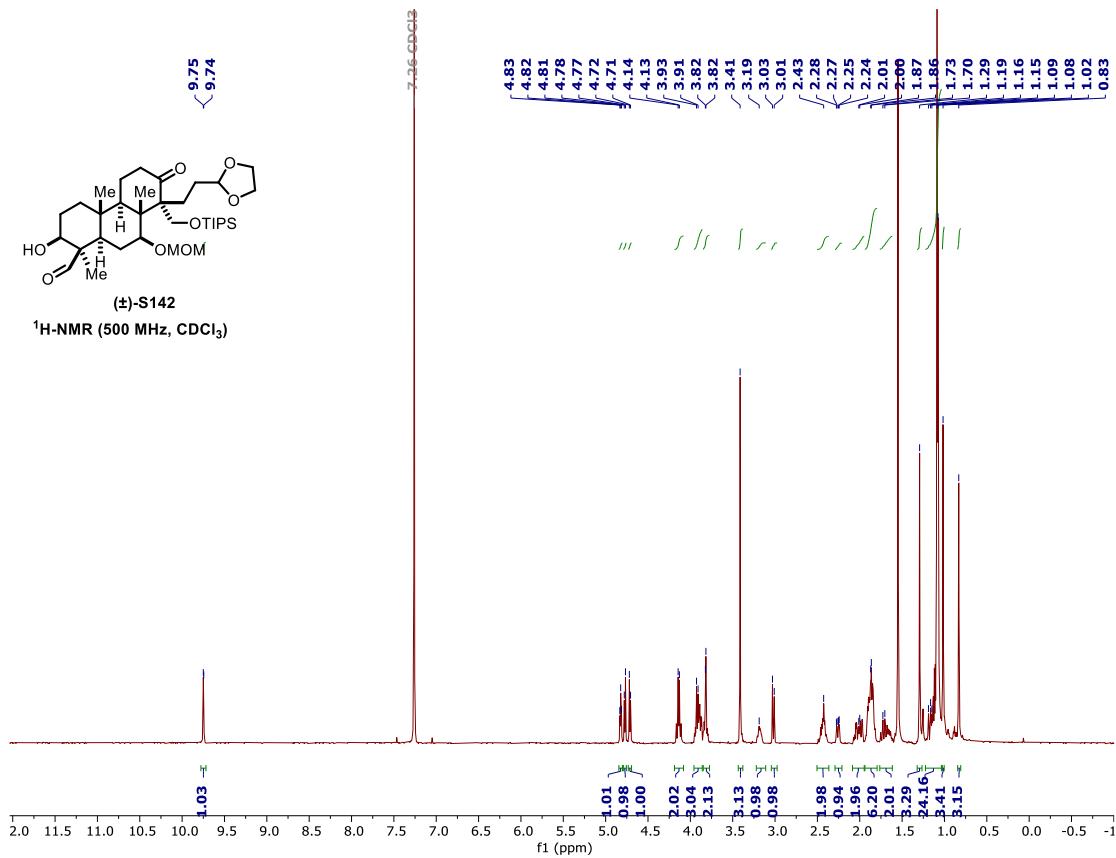


<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)

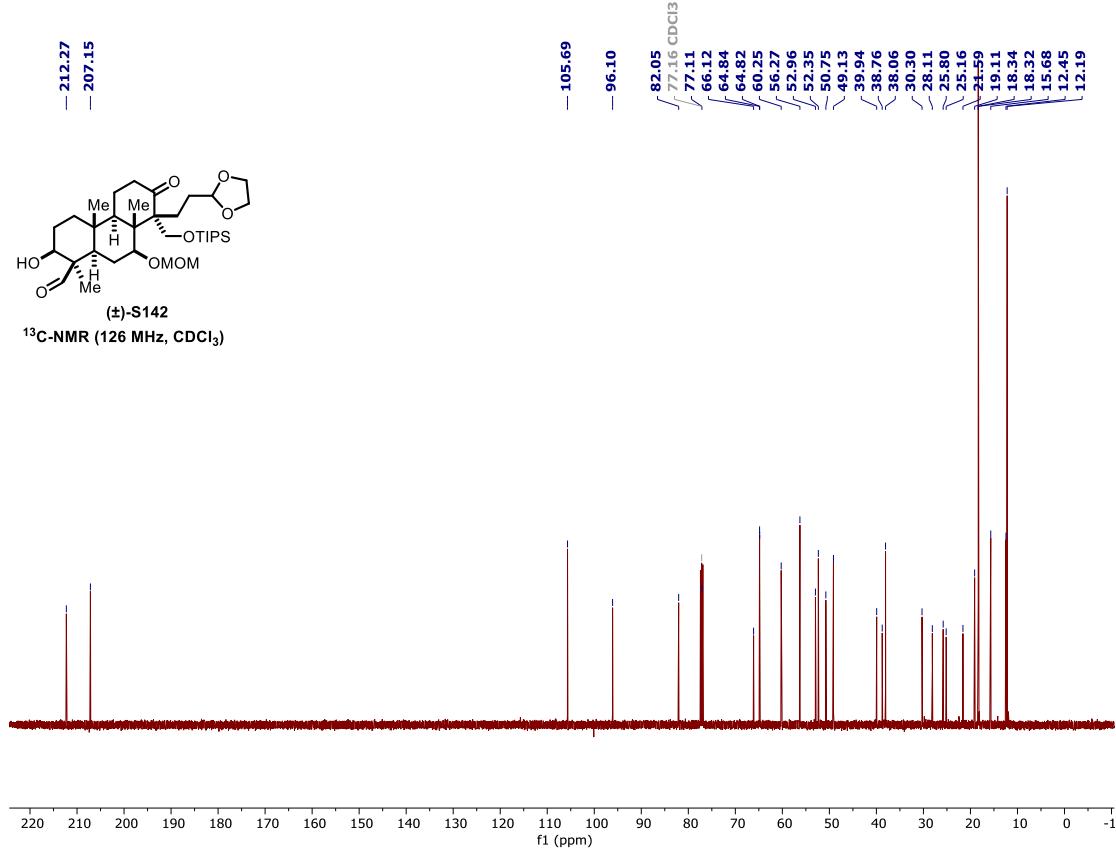


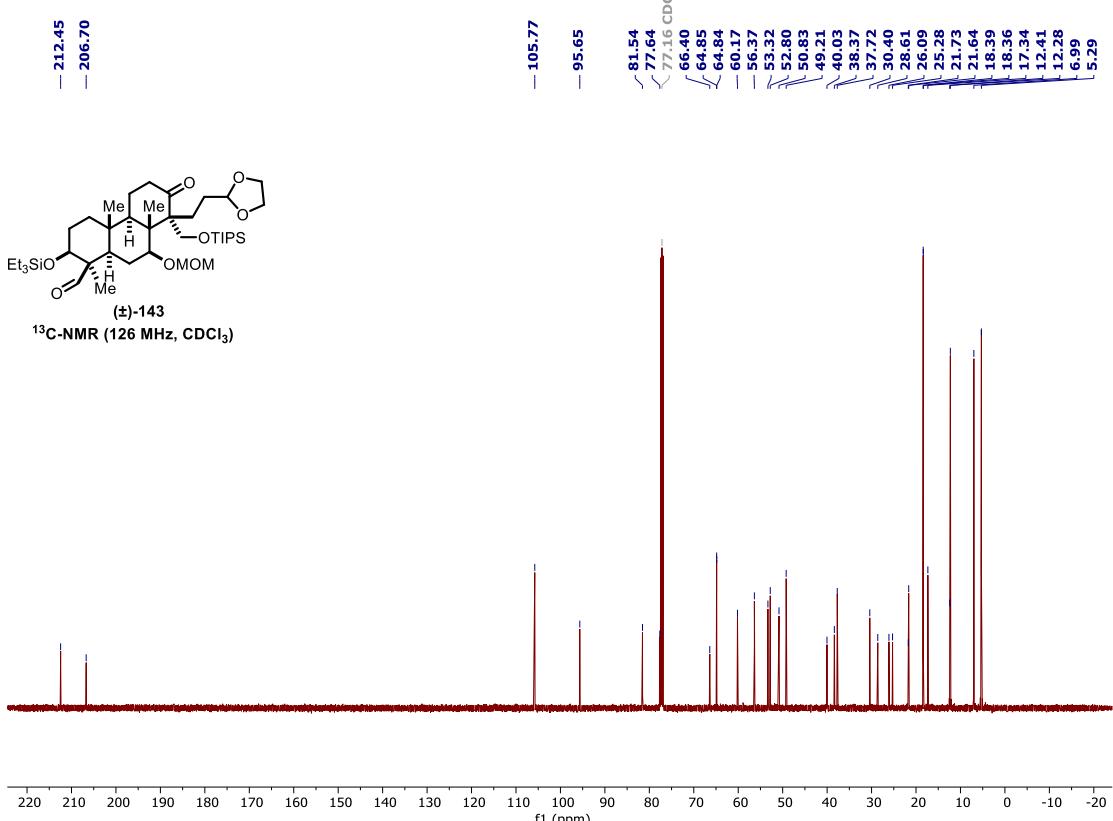
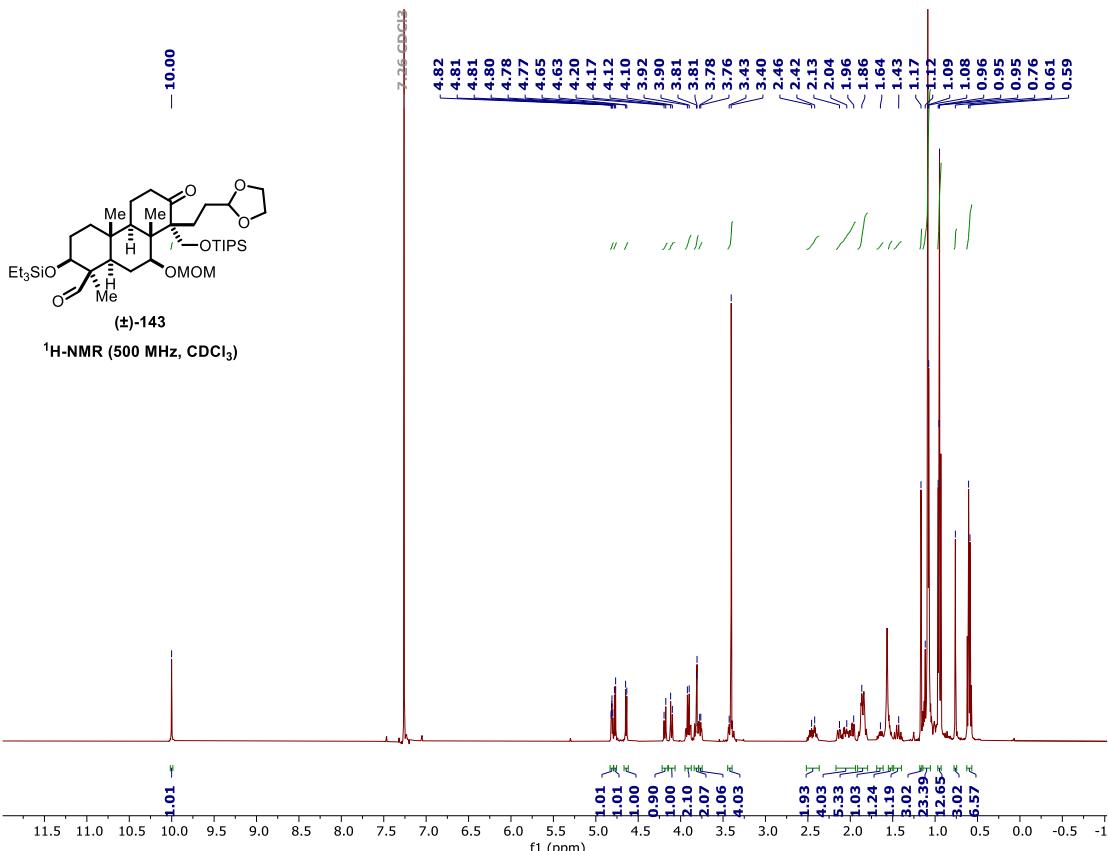


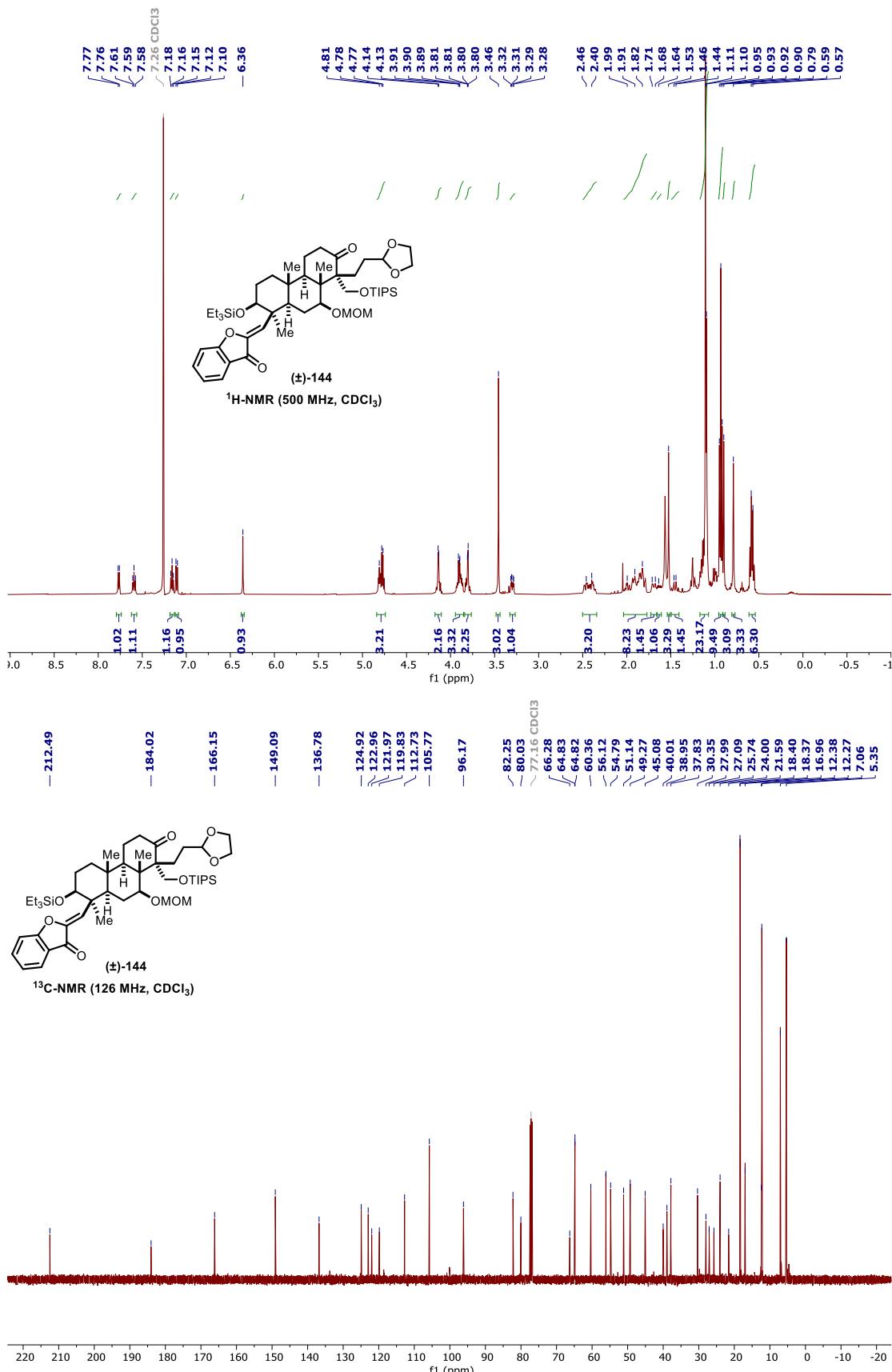
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)**

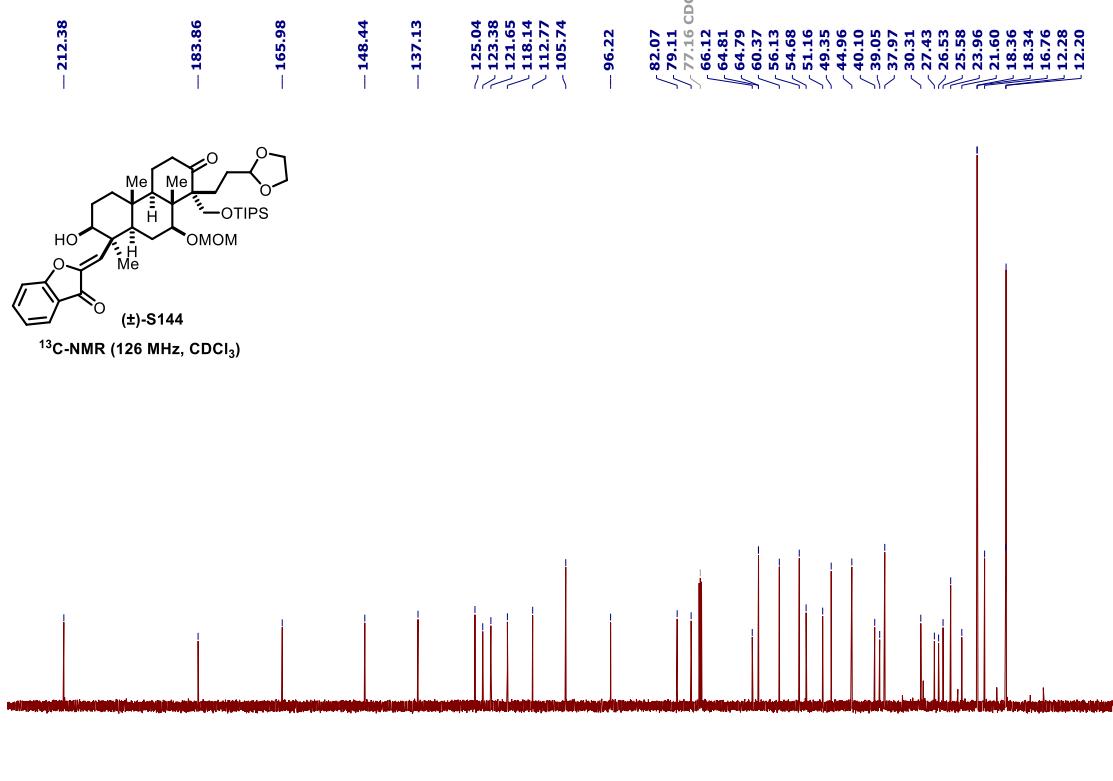
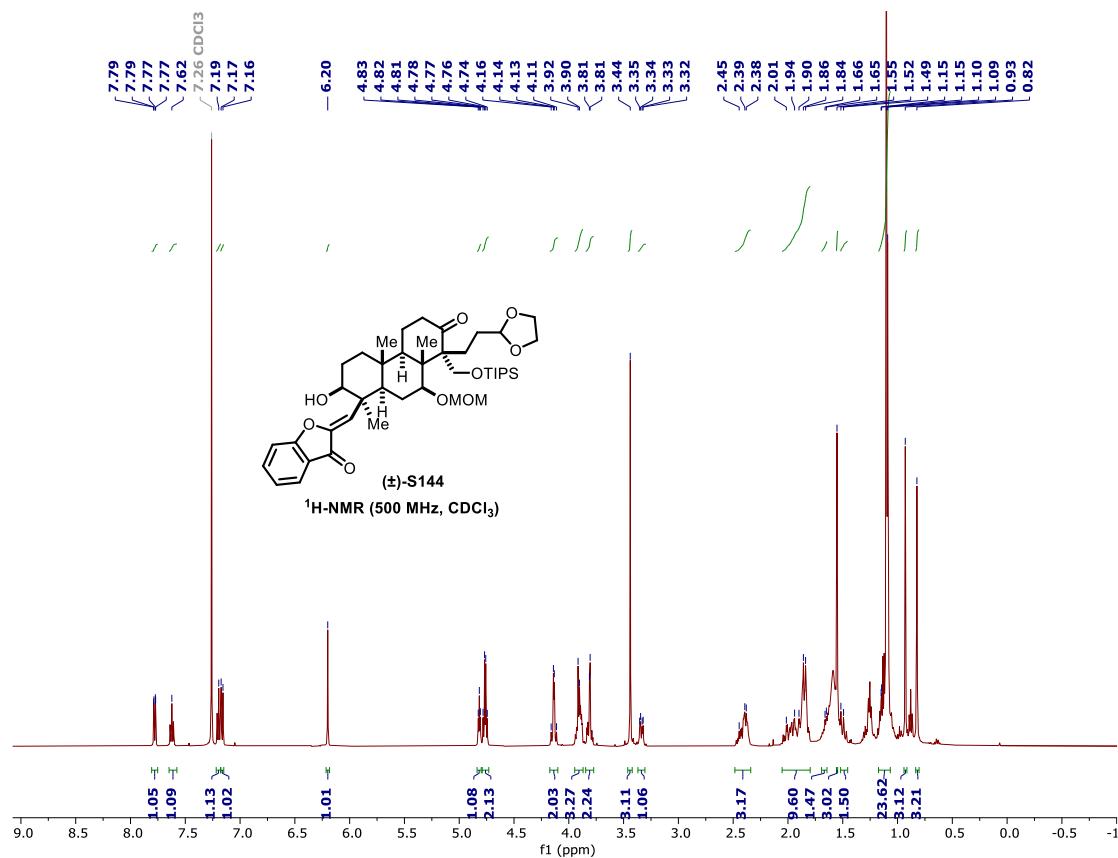


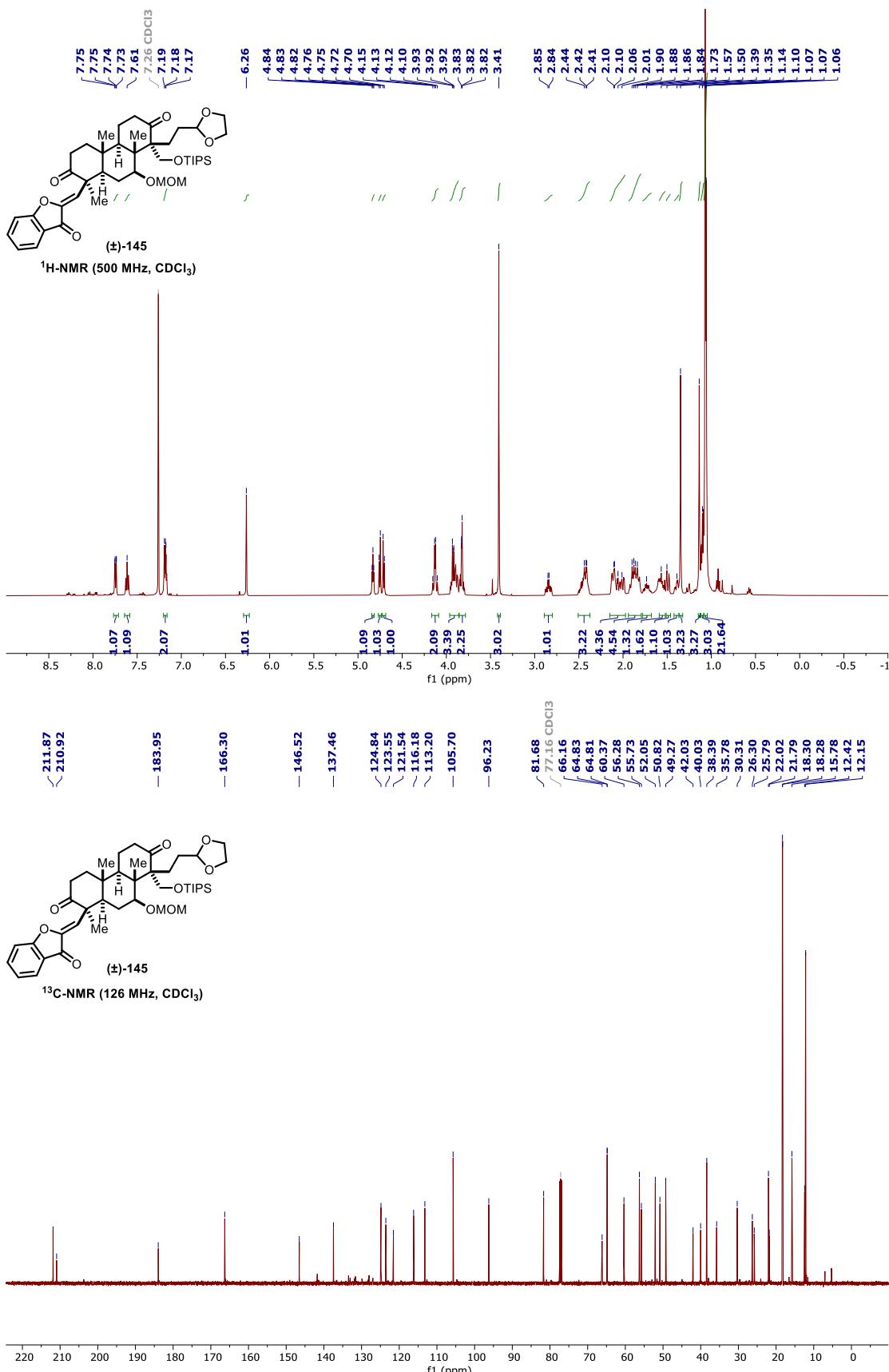
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)

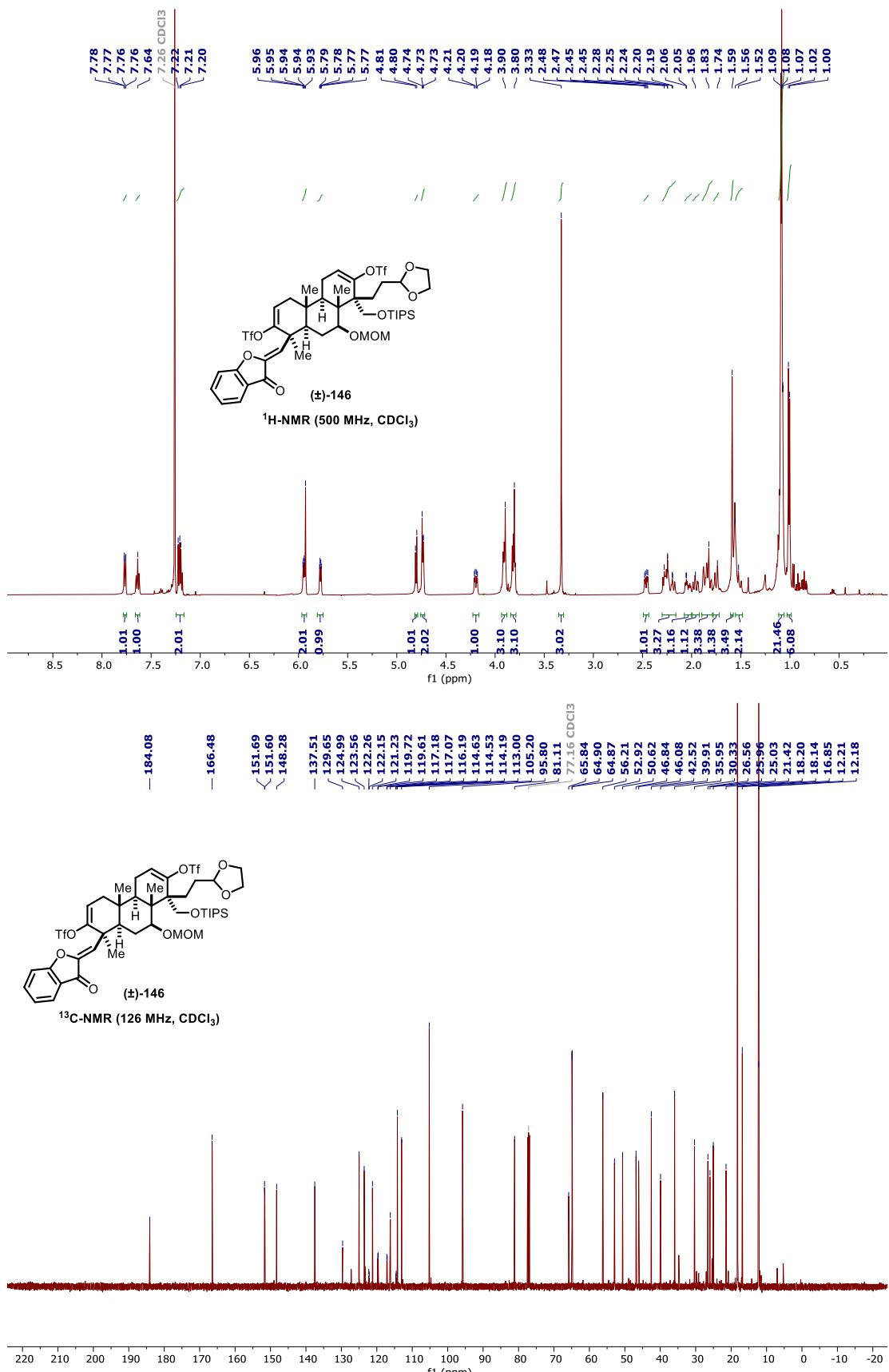


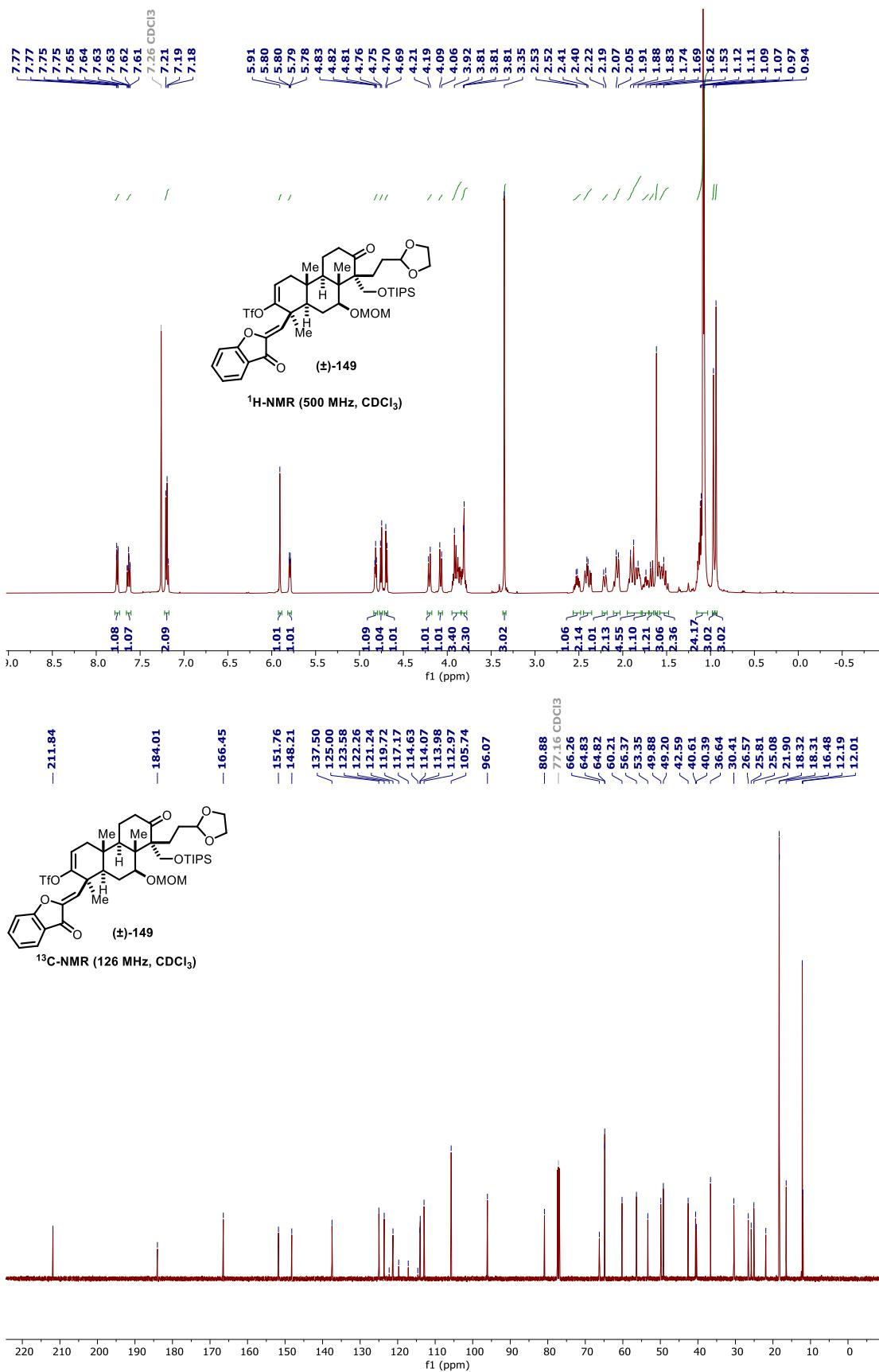


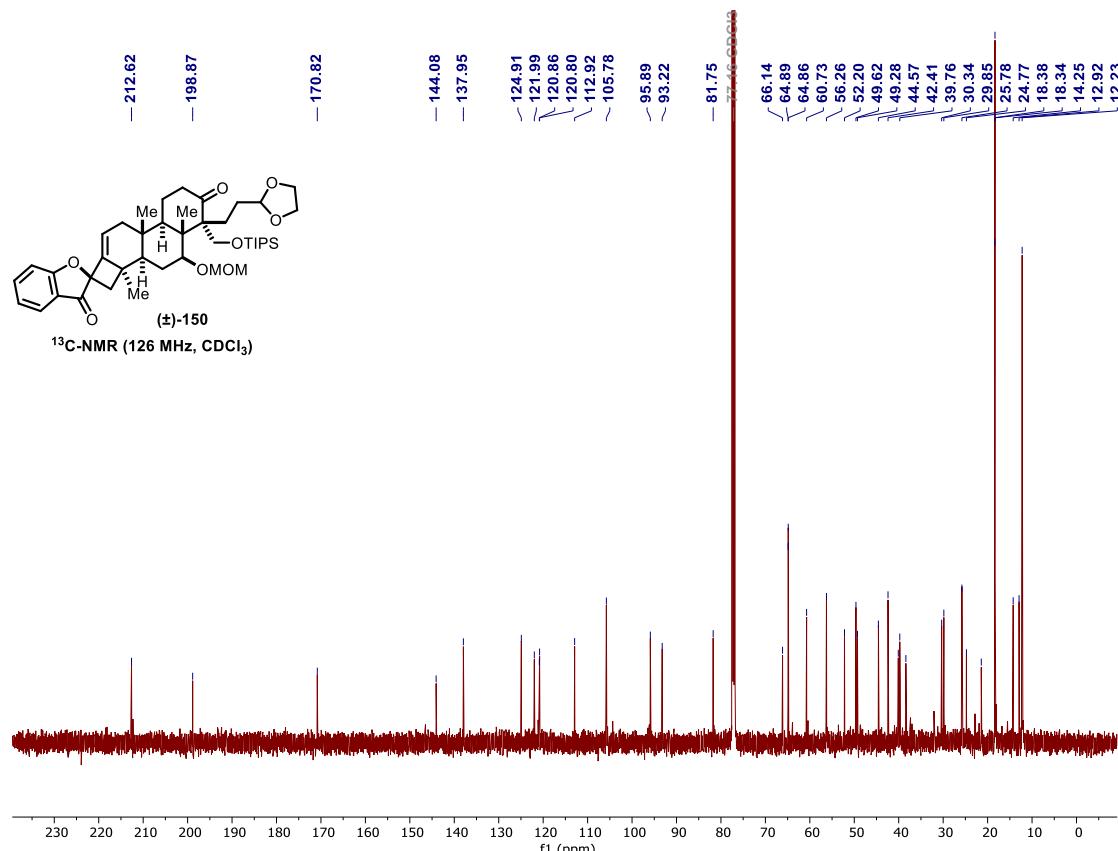
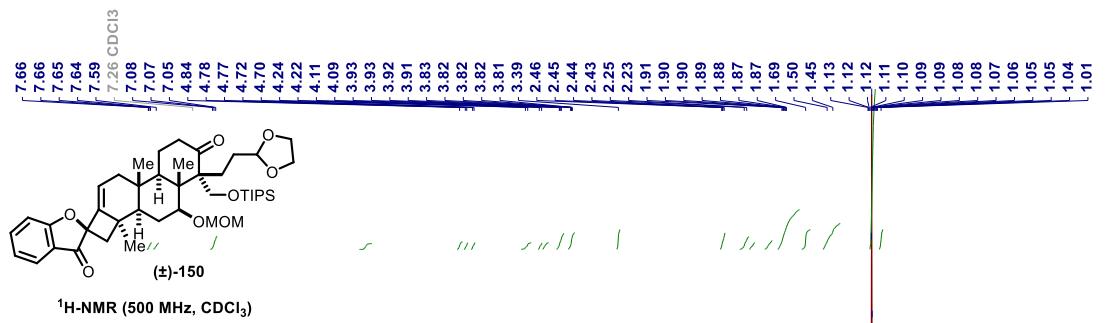


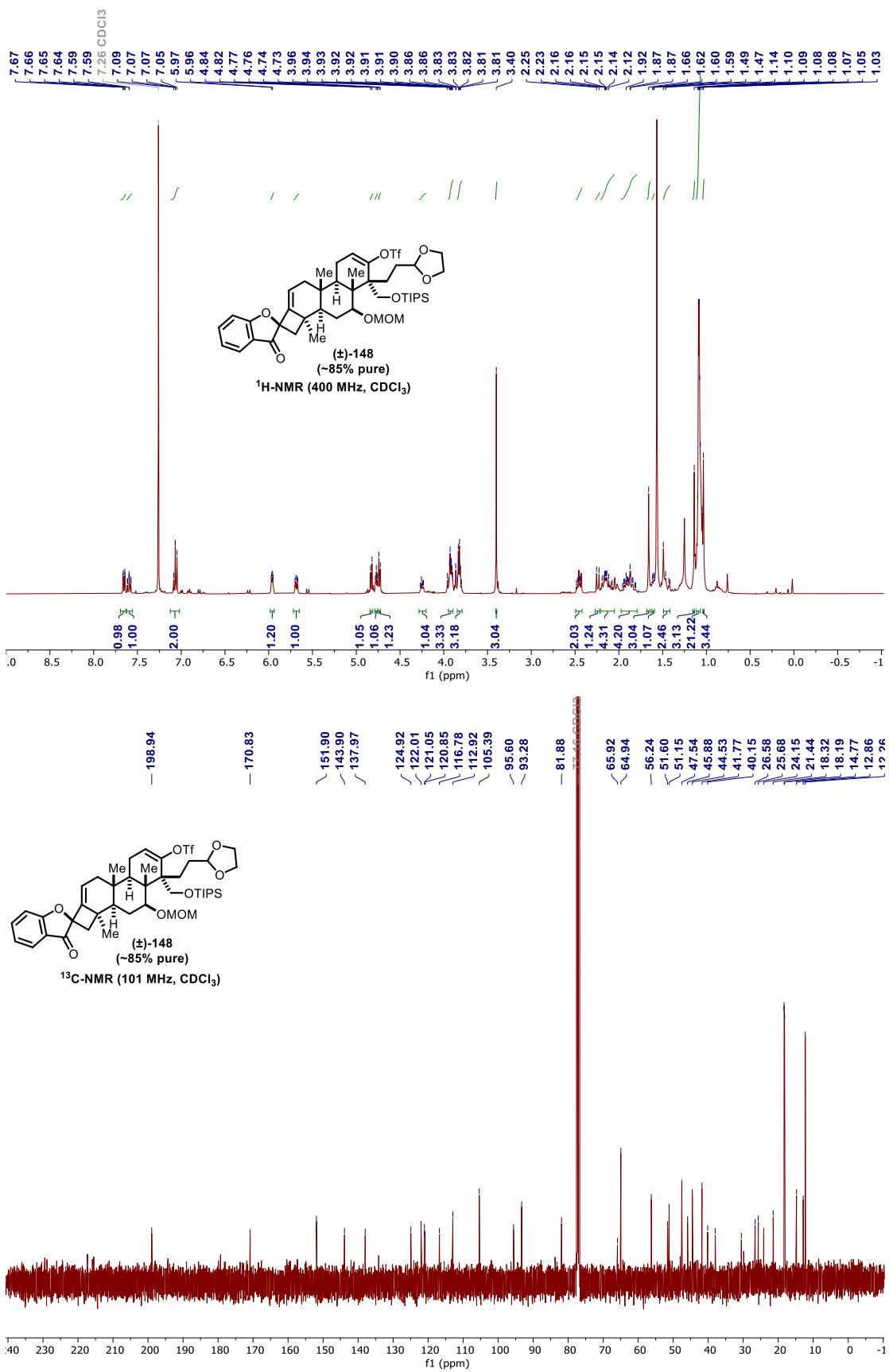


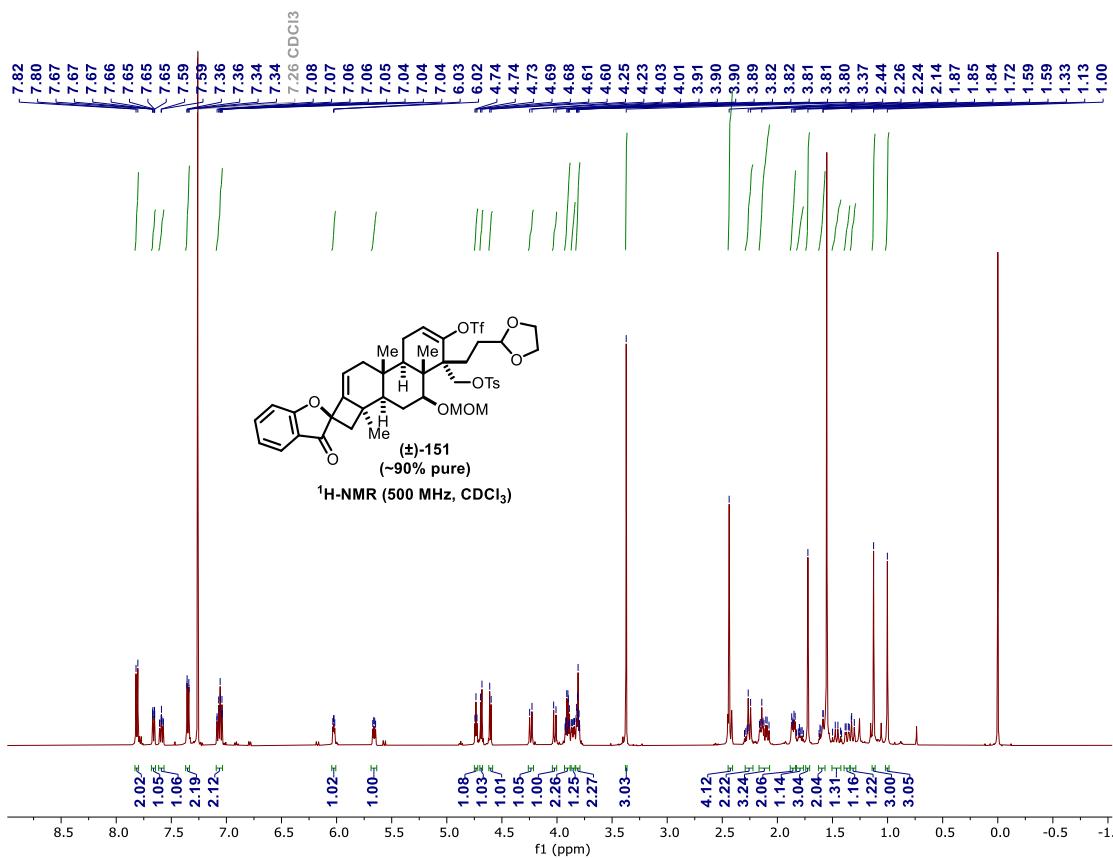
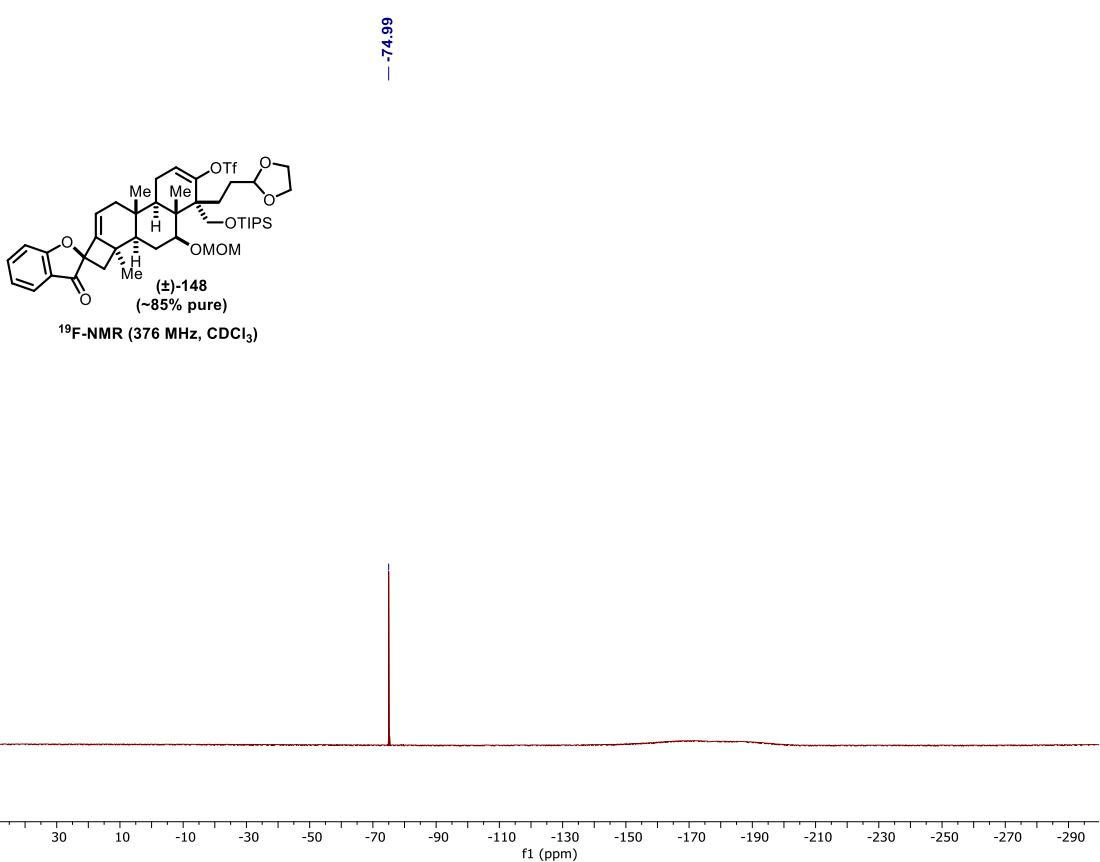


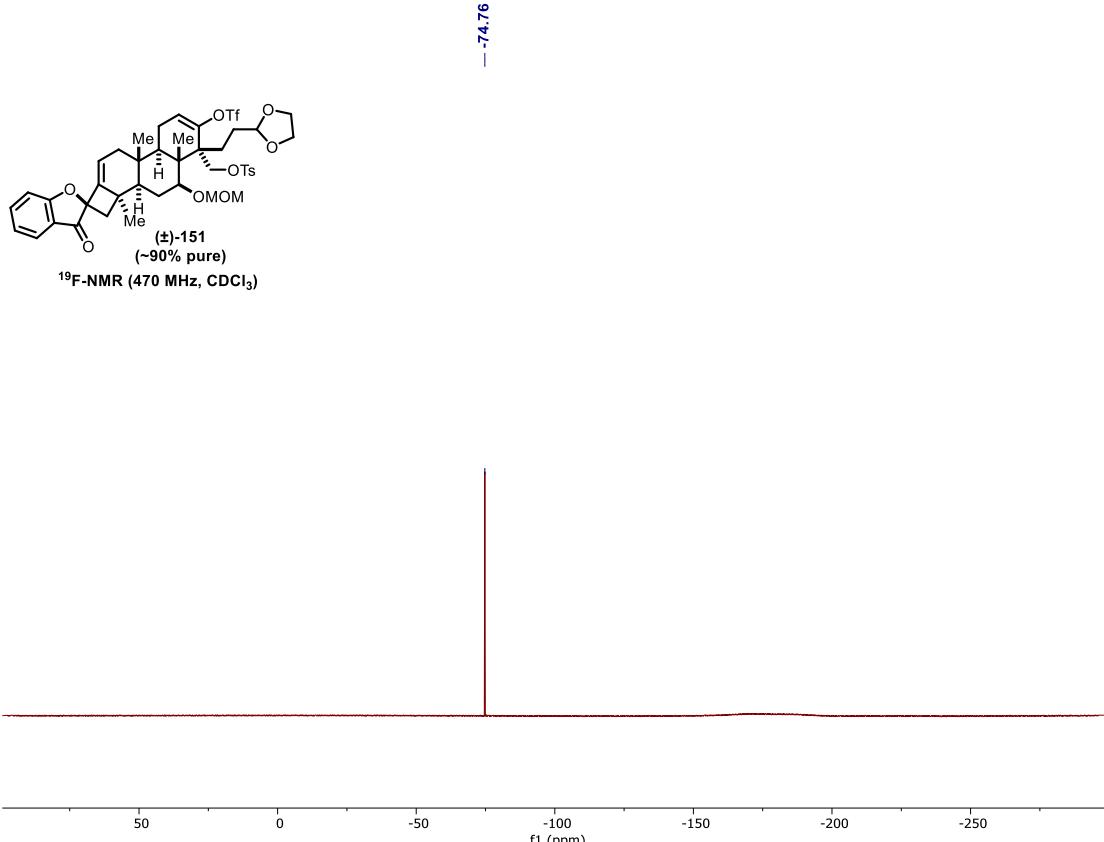
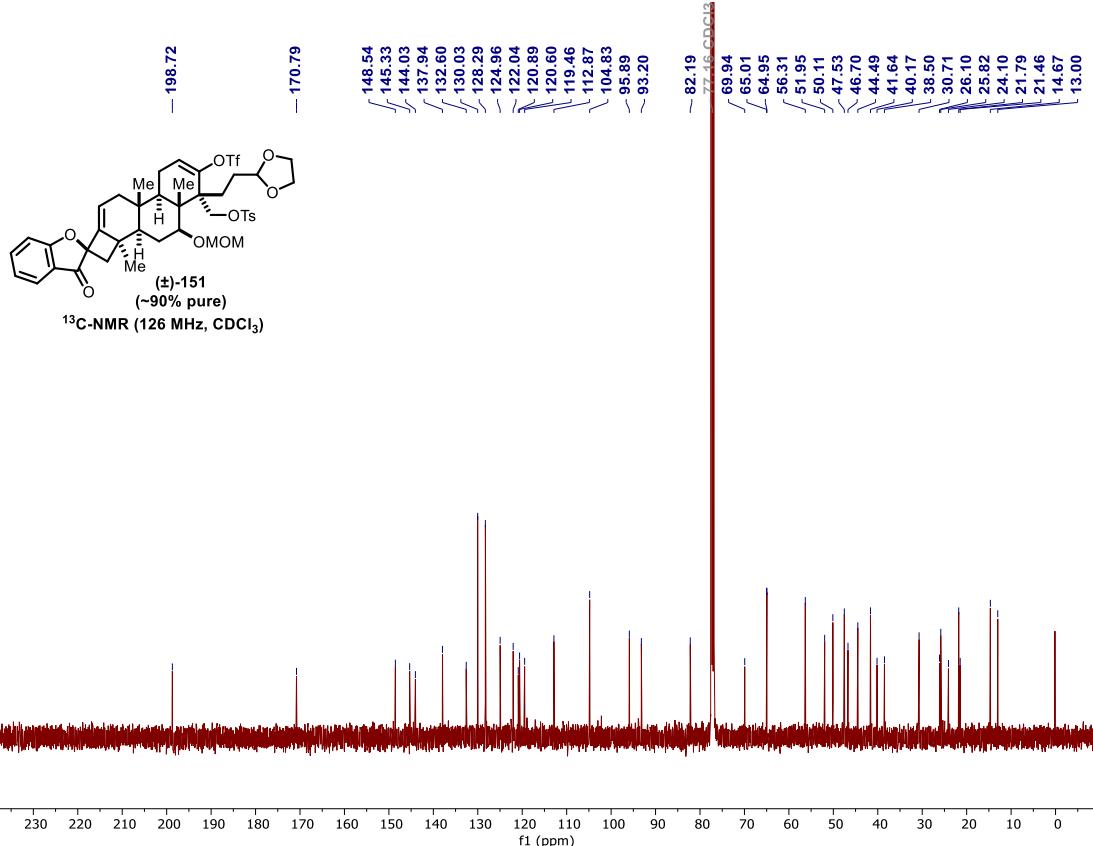


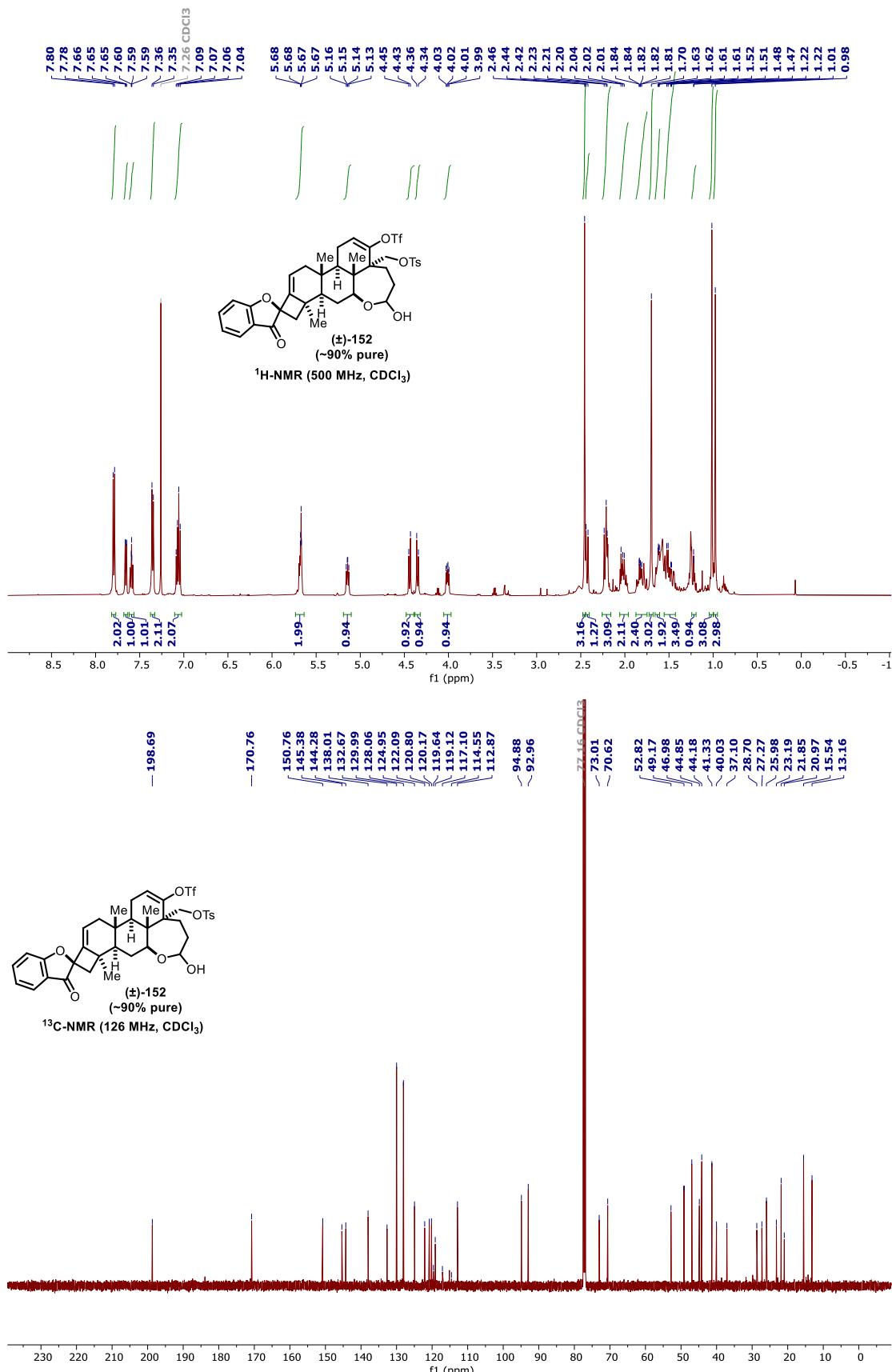


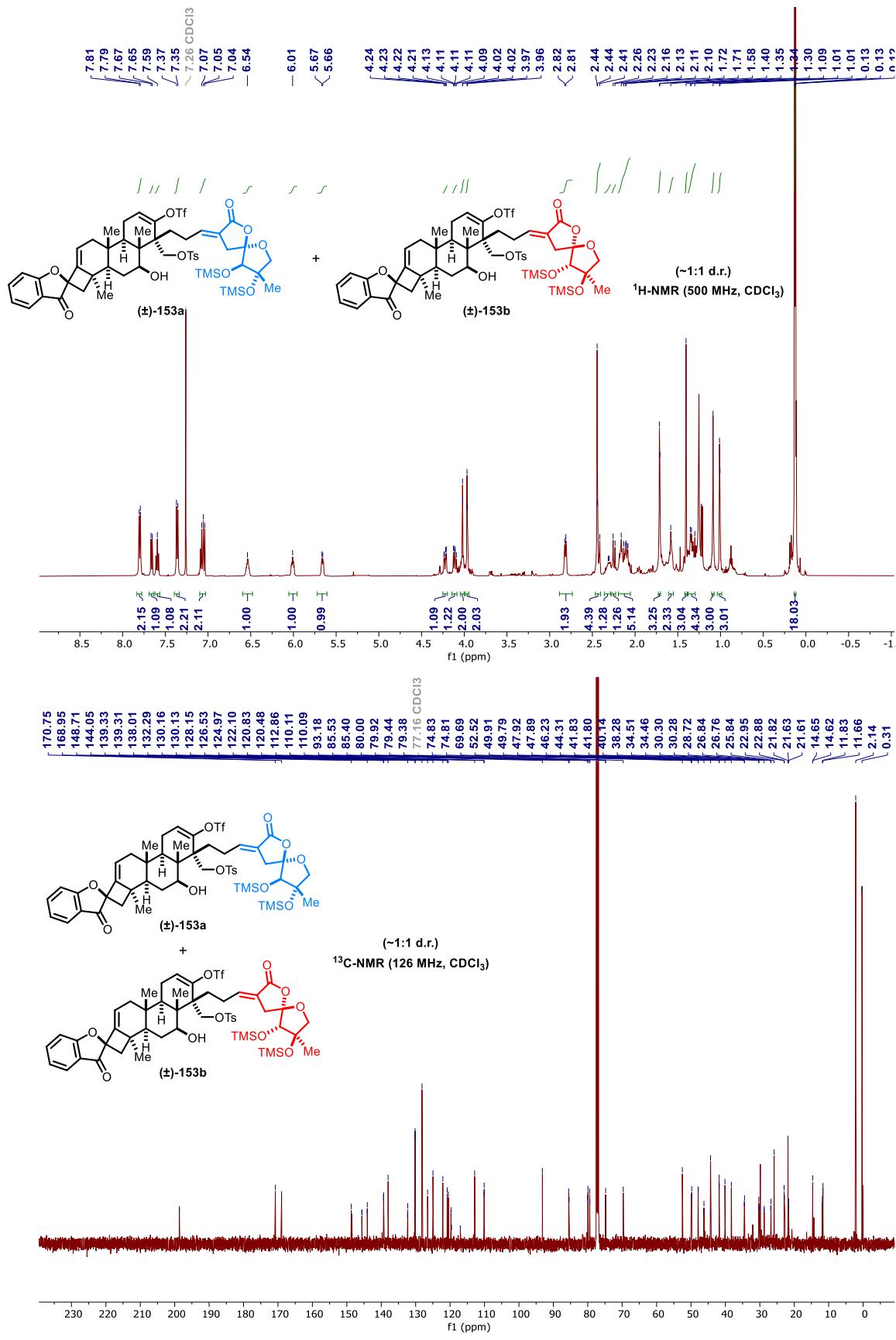


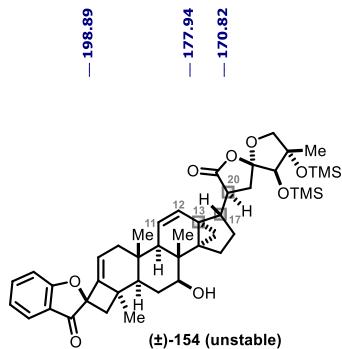
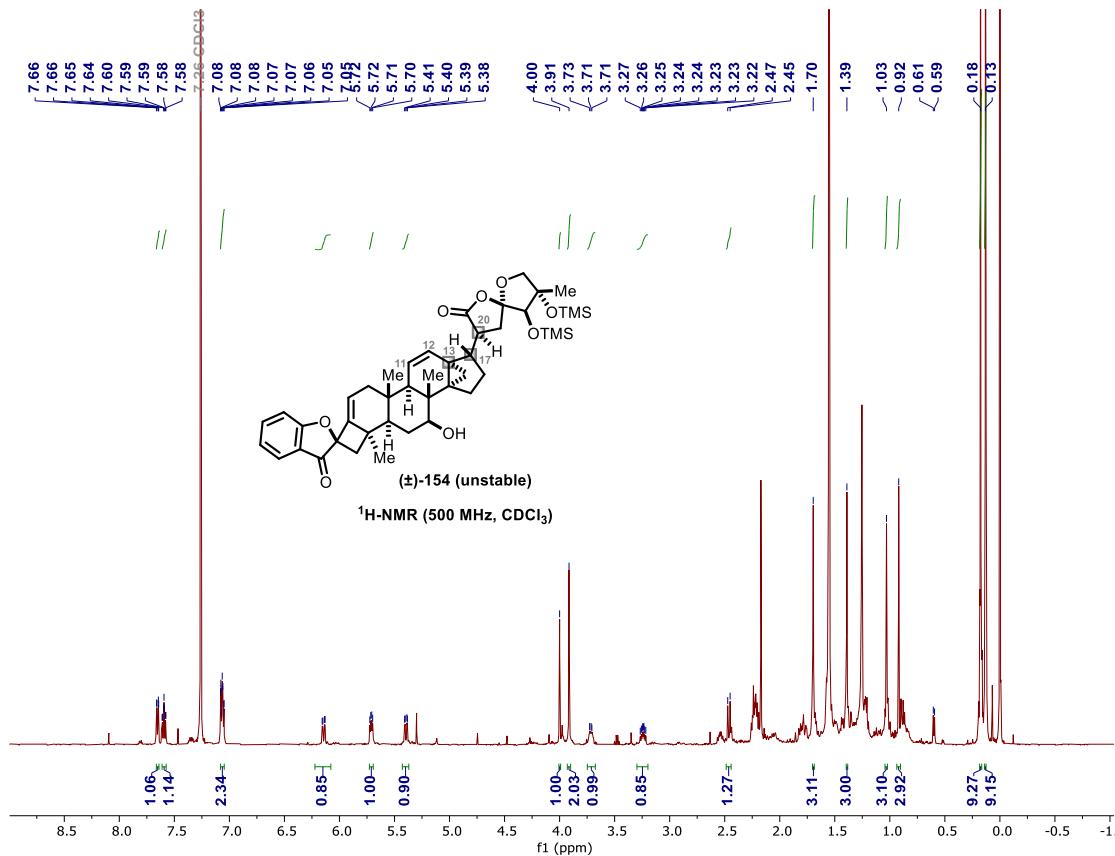




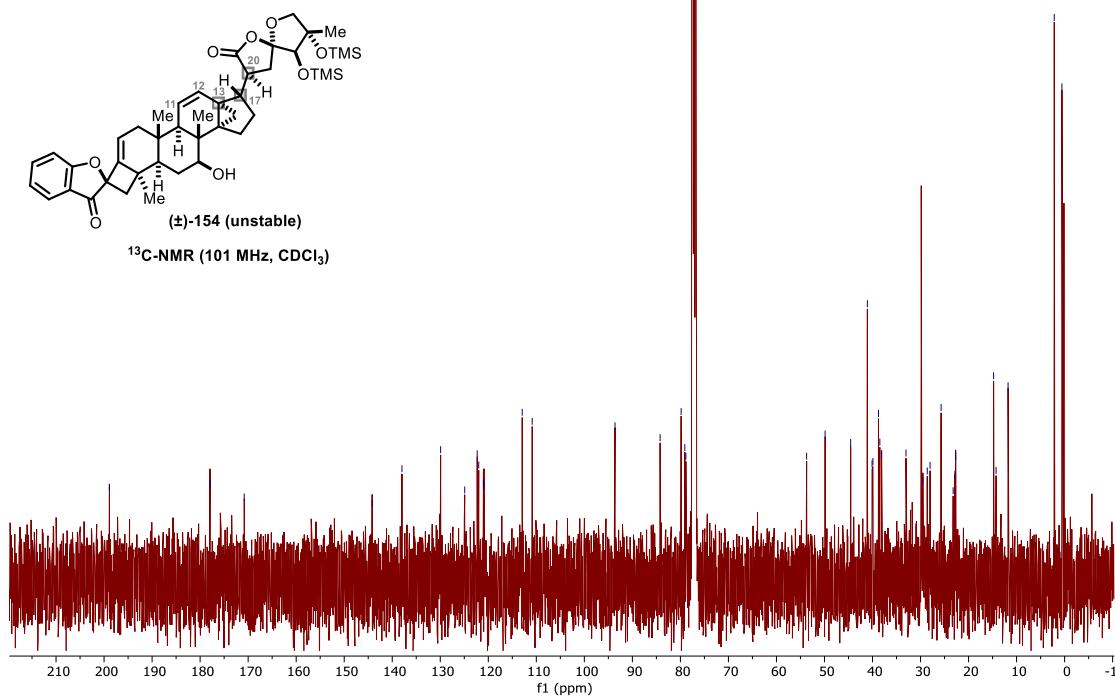


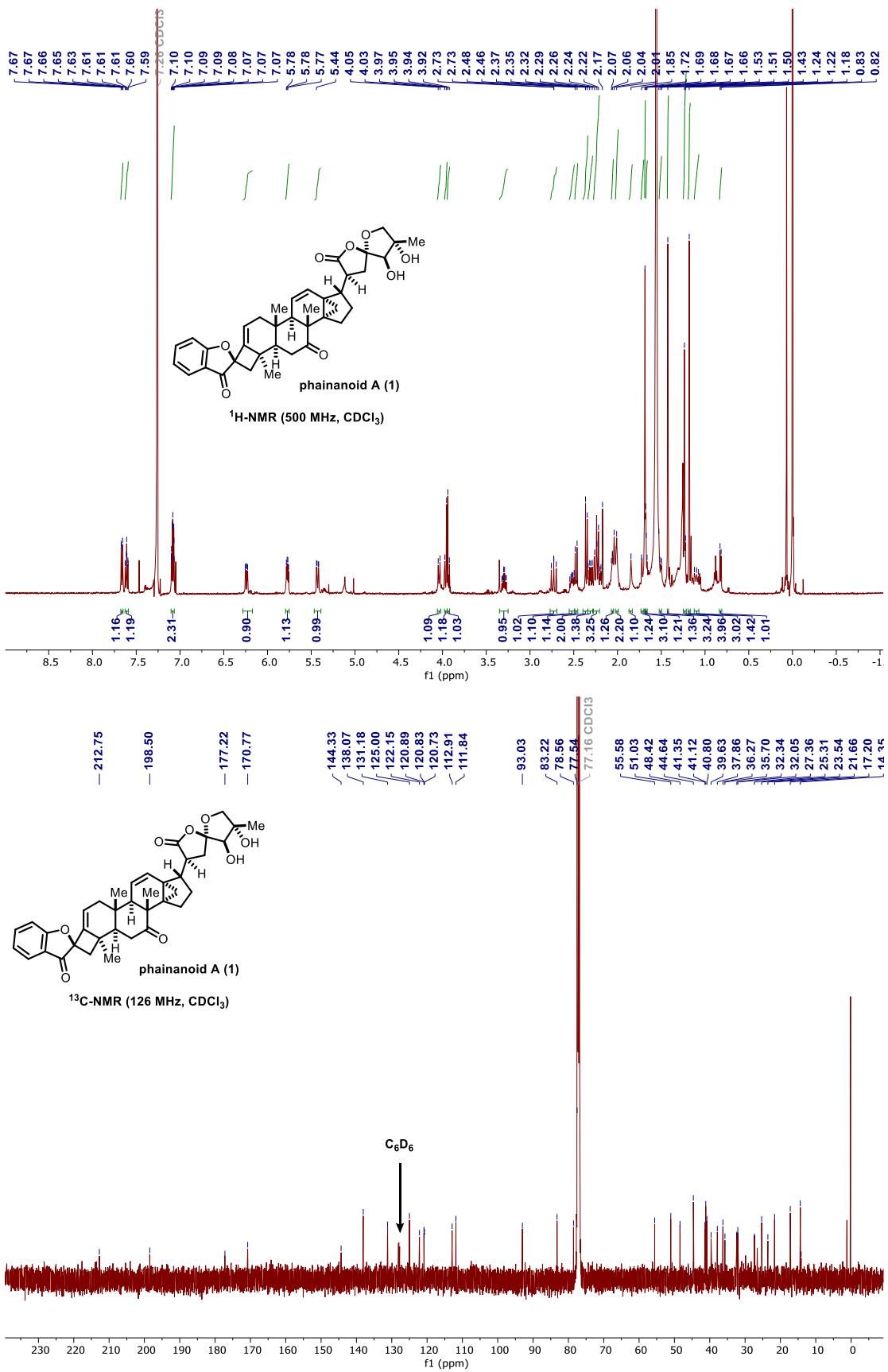


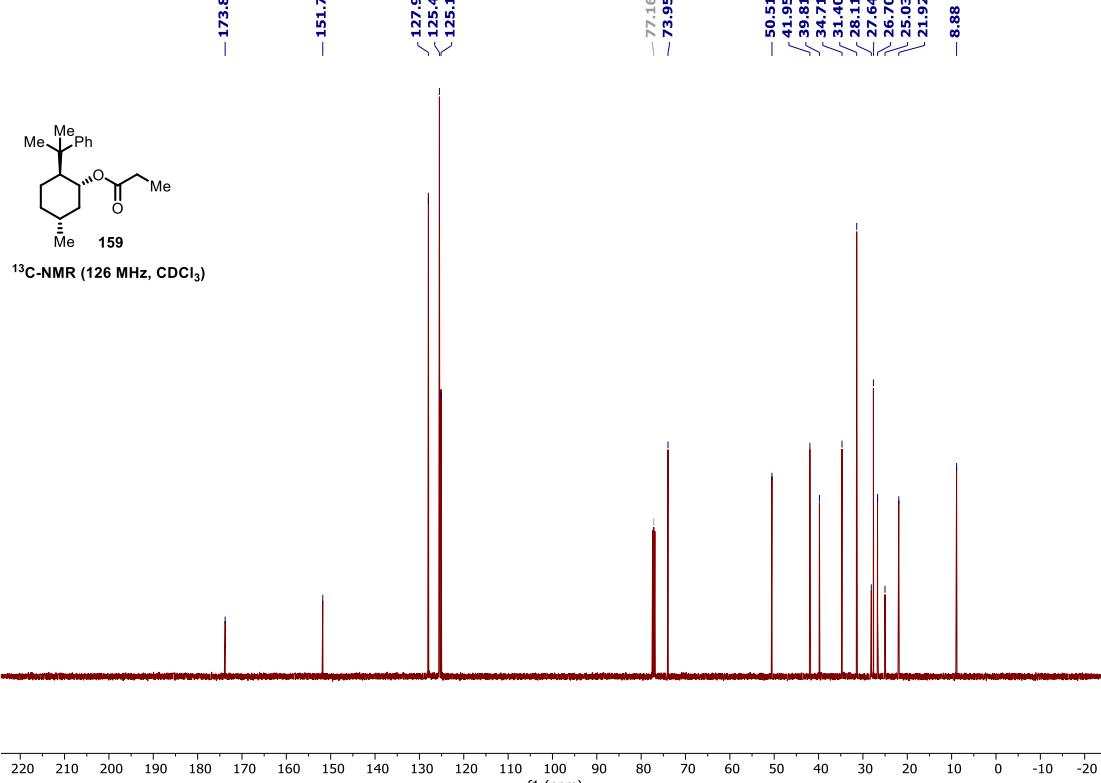
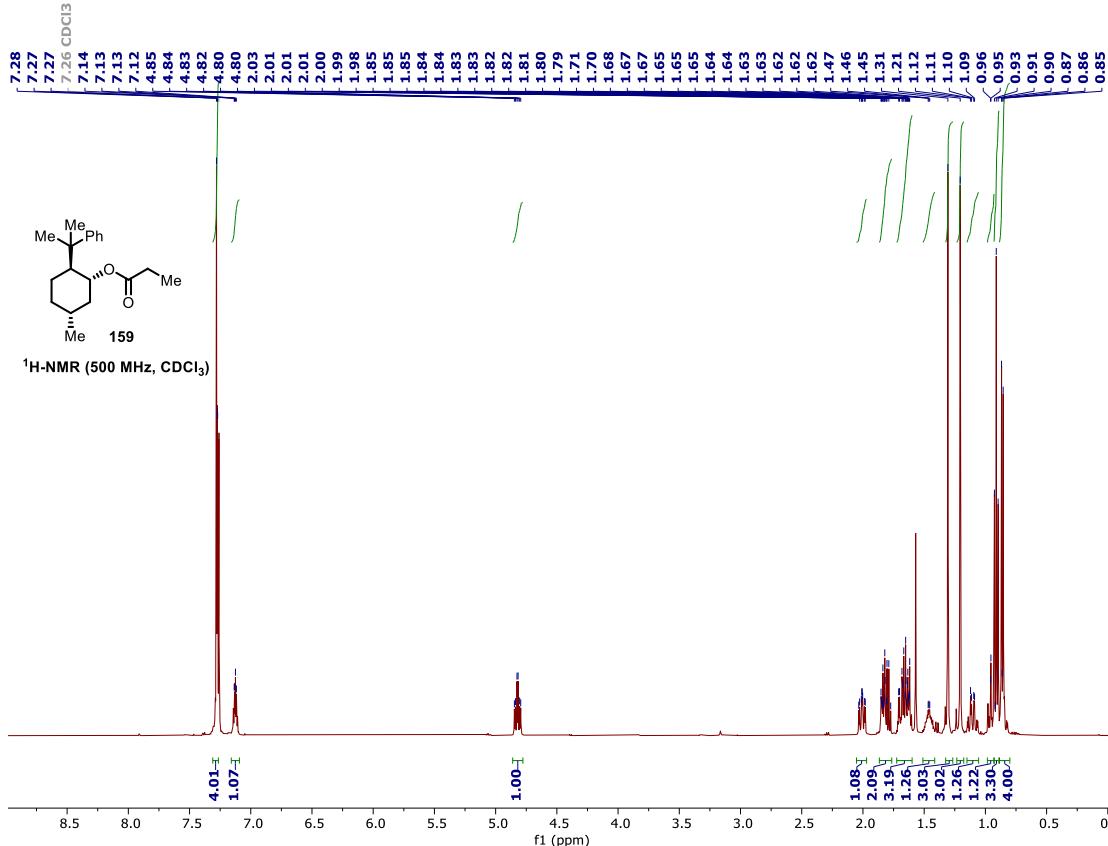


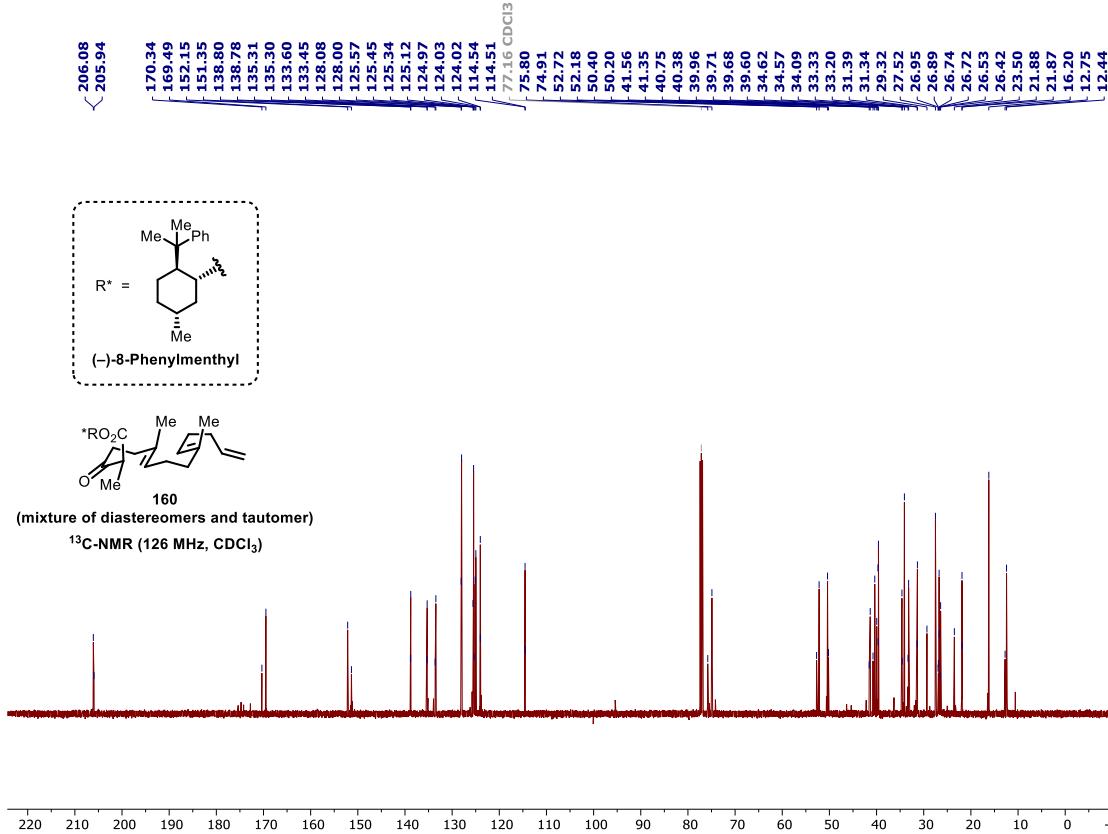
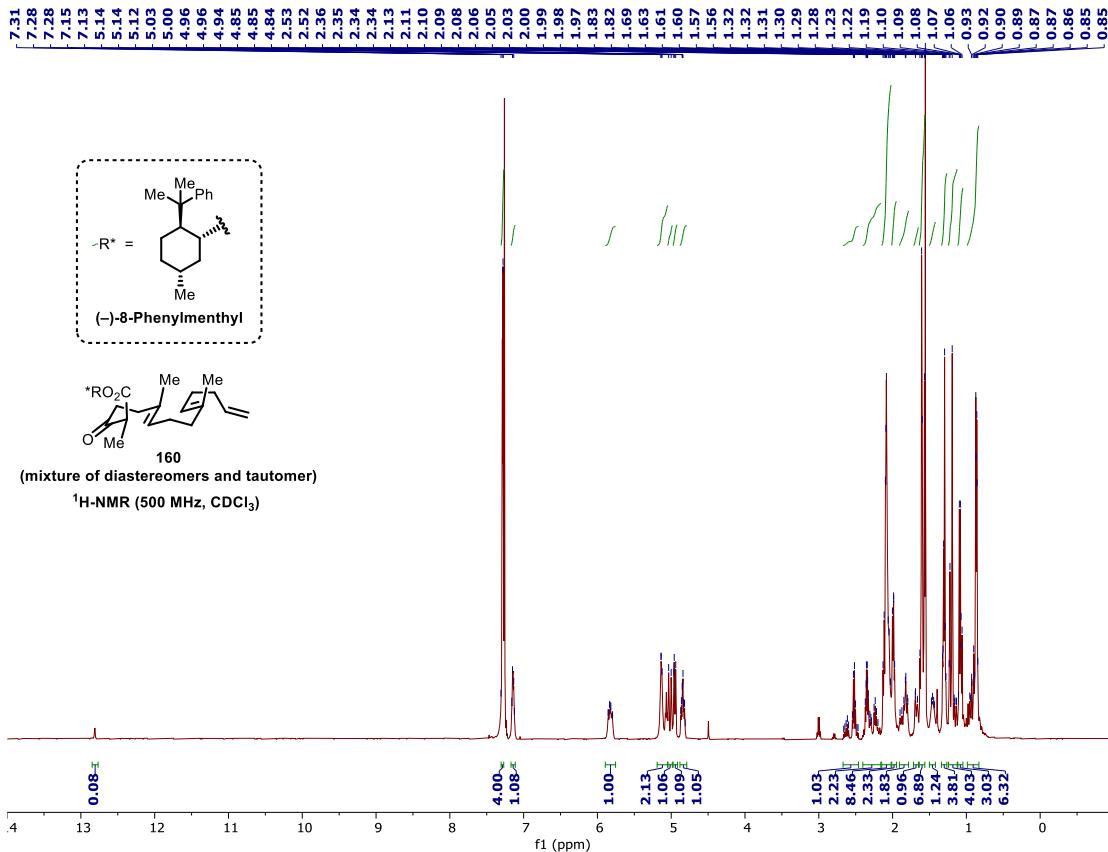


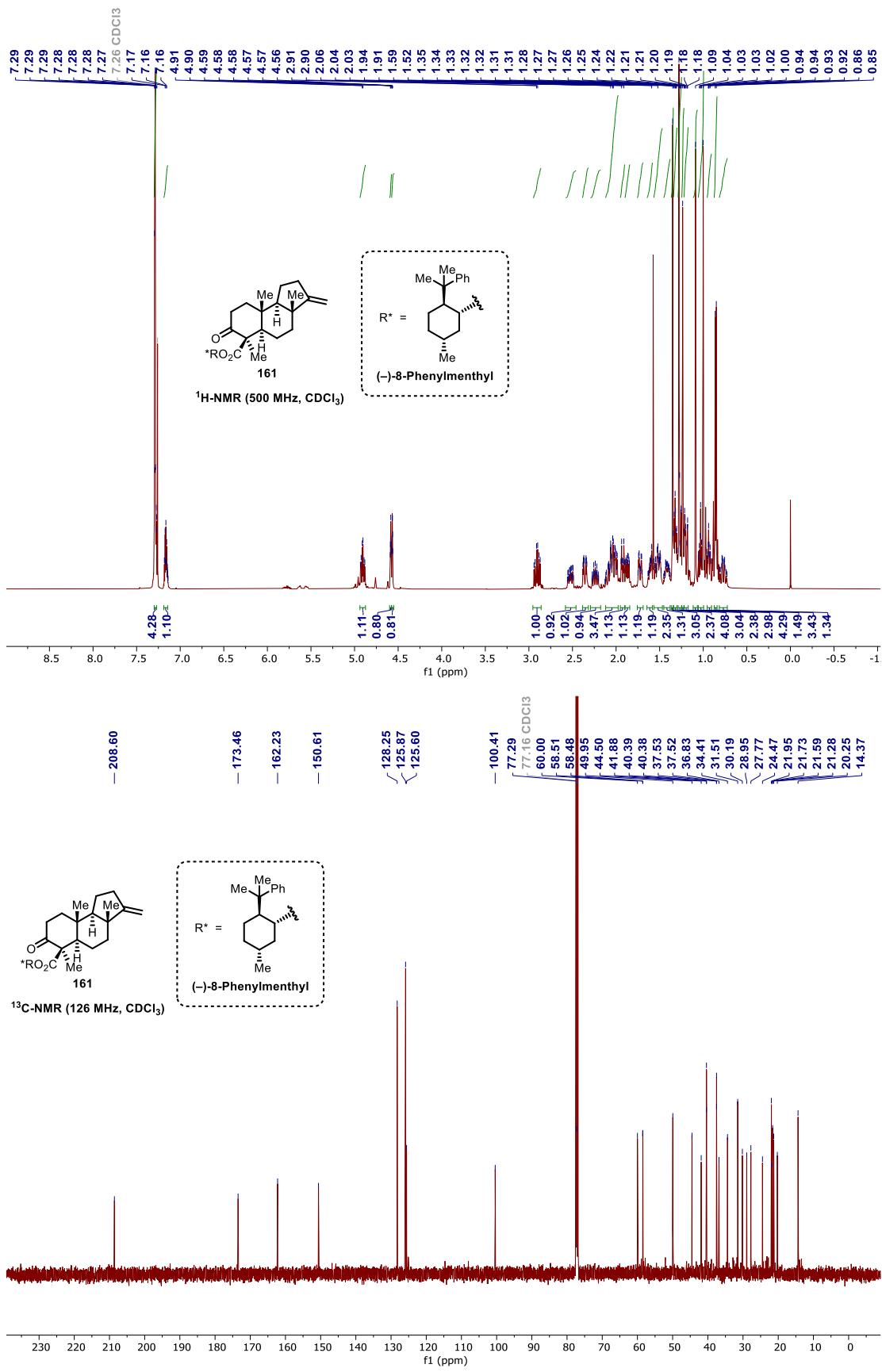
<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)

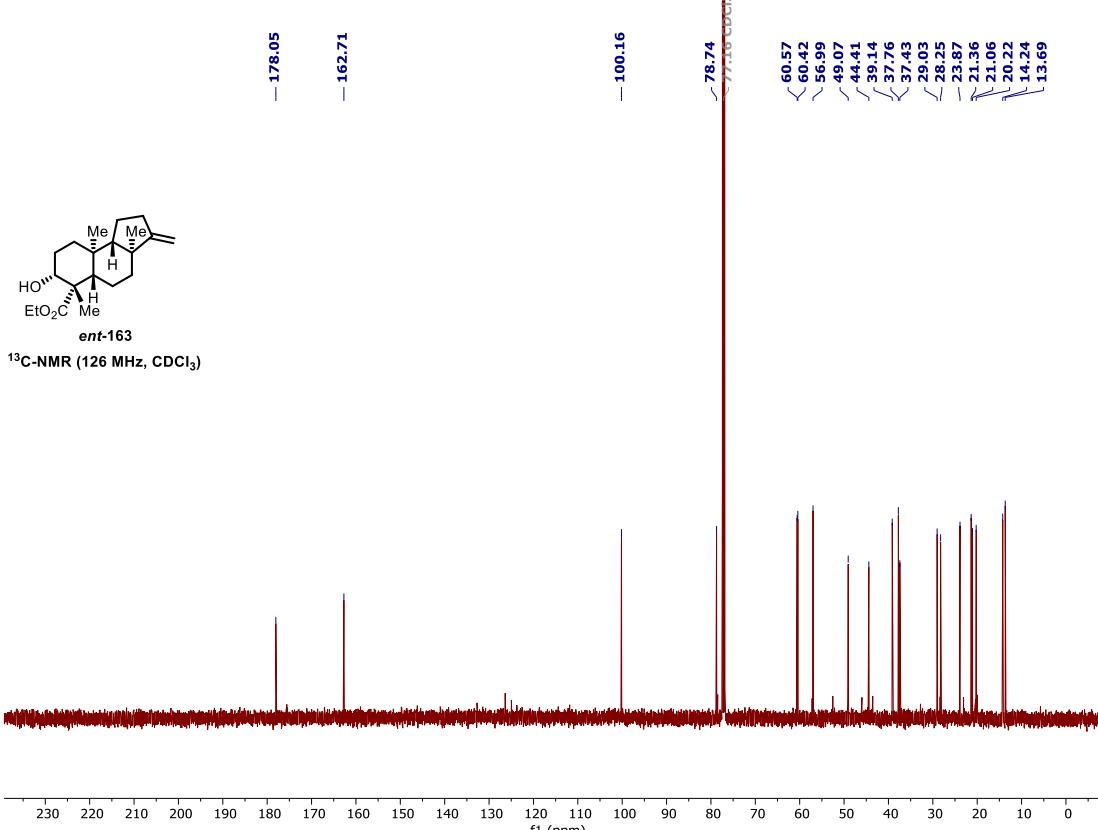
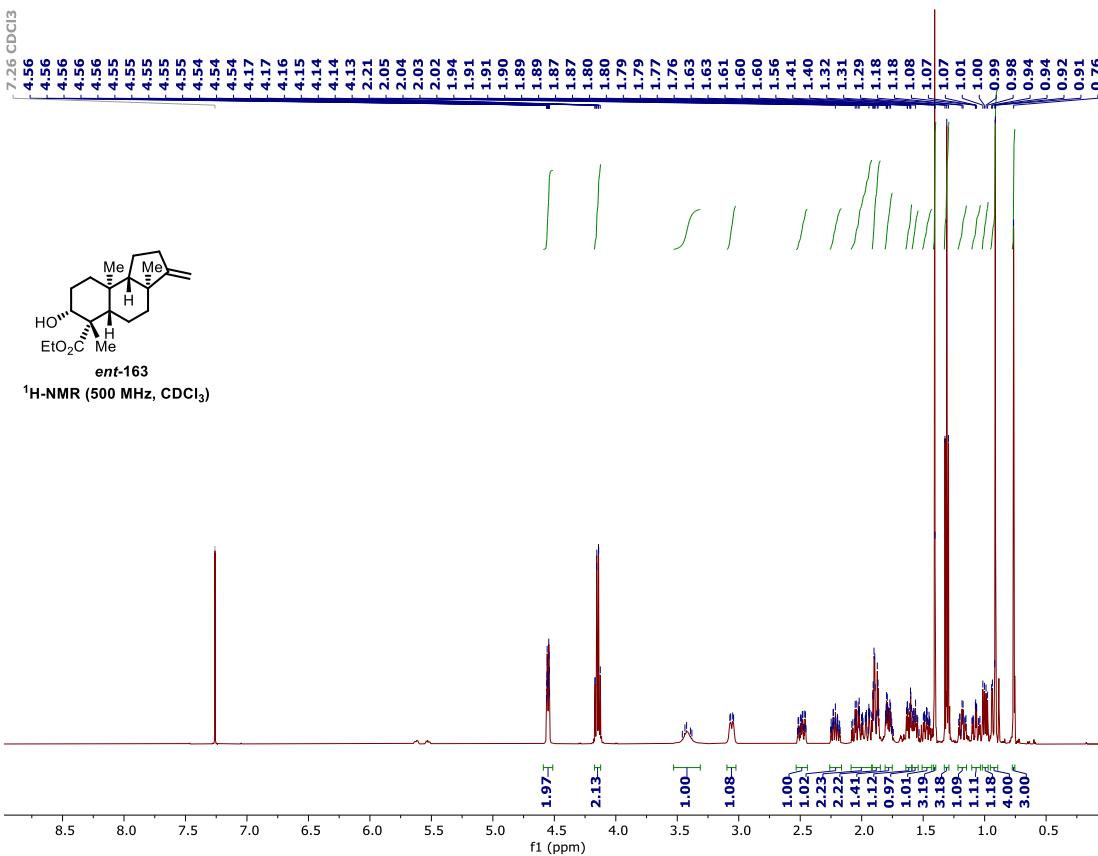


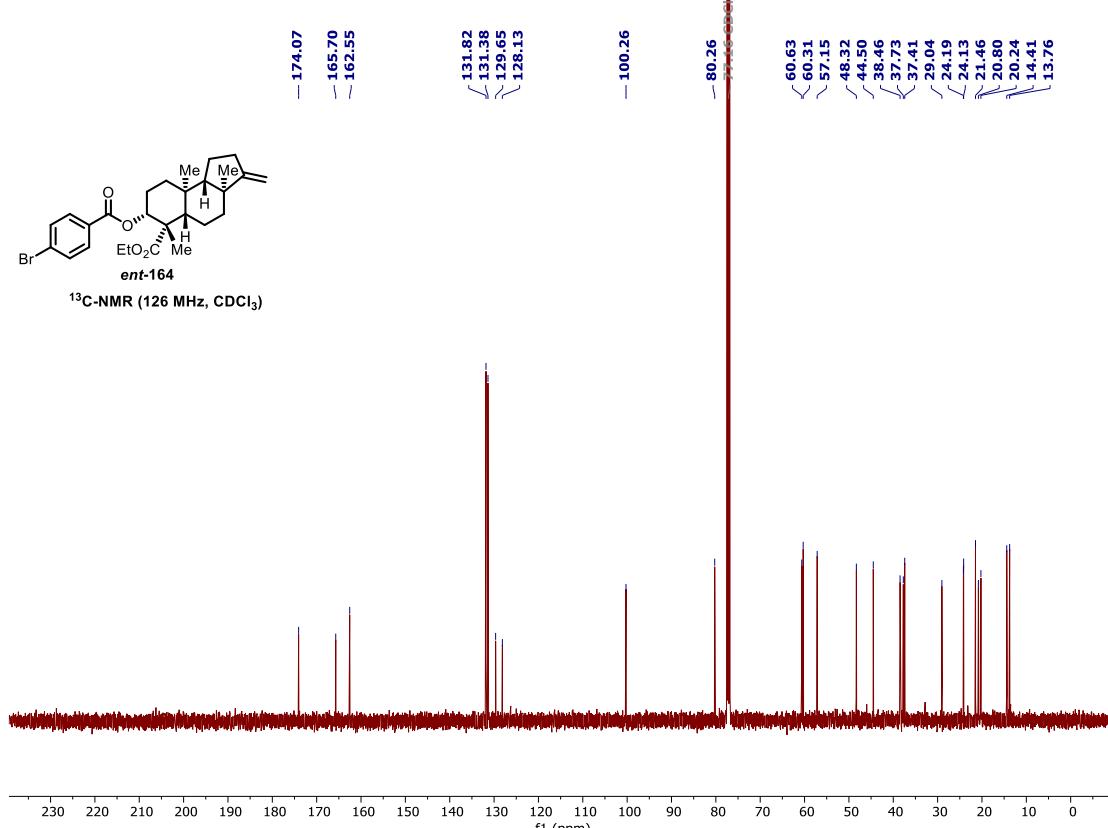
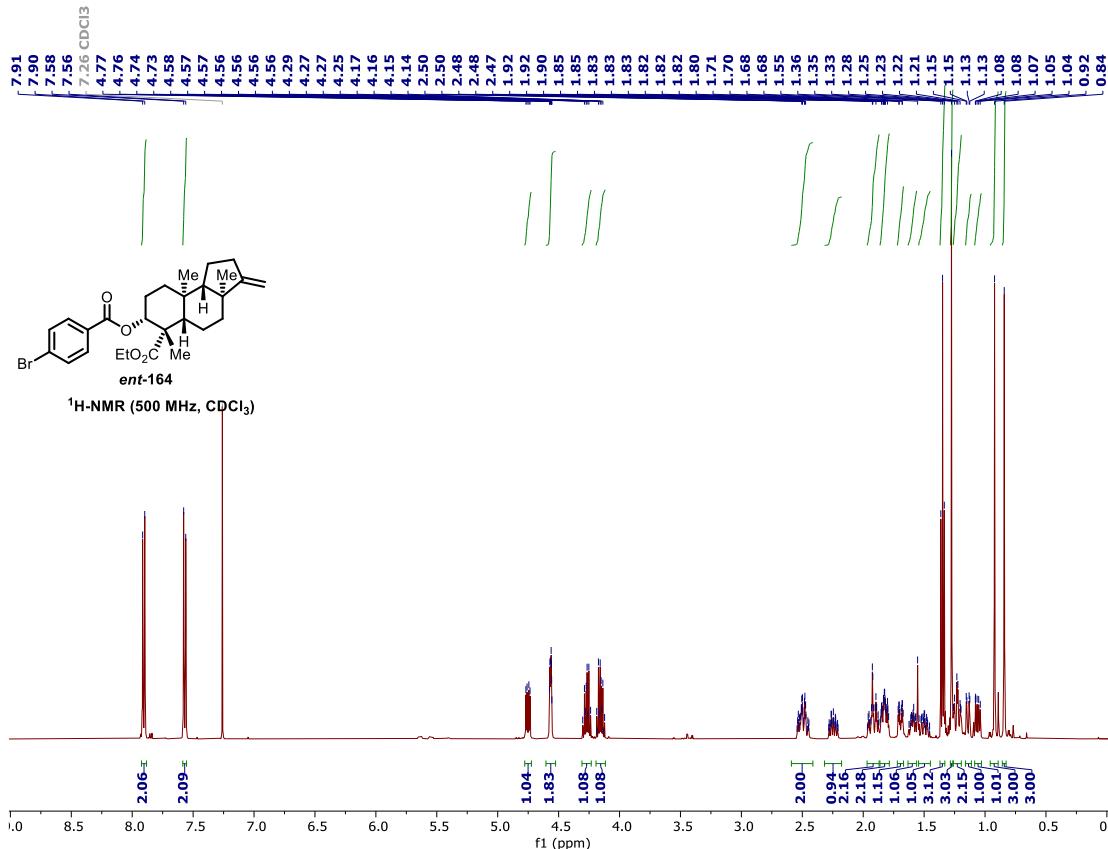










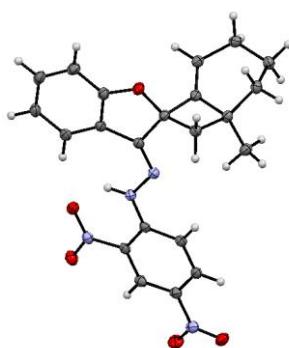


## **8. Single Crystal X-Ray Diffraction Data**

X-ray diffraction data were collected at 100(2) K on a Bruker APEX-II CCD diffractometer. Using Olex2<sup>13</sup>, the structures were solved with the ShelXT<sup>14</sup> structure solution program using Intrinsic Phasing and refined with the ShelXL<sup>15</sup> refinement package using Least Squares minimization. Crystallography data for **(±)-35**, **(±)-50**, **(±)-36**, **(±)-82**, **(±)-C14-*epi*-88**, **(±)-88, 99, 117**, **(±)-125**, and ***ent*-164** can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via [www.ccdc.com.ac.uk/data\\_request/cif](http://www.ccdc.com.ac.uk/data_request/cif) under CCDC deposition numbers 1554711, 1554710, 1554712, 2203374, 2109818, 2109816, 2203375, 2203376, 2109817 and 2203377, respectively. Graphical representation of **(±)-35**, **(±)-50**, **(±)-36**, **(±)-82**, **(±)-C14-*epi*-88**, **(±)-88, 99, 117**, **(±)-125**, and ***ent*-164** with 50% probability thermal ellipsoids was generated using Mercury visualization software.

**Table S11.** Crystal data and structure refinement for ( $\pm$ )-35

Identification code	shelx
Empirical formula	C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O <sub>5</sub>
Formula weight	420.42
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 7.3583(3) Å a = 94.049(3)° b = 8.6653(3) Å b = 95.948(3)° c = 15.7812(5) Å g = 105.631(3)°
Volume	958.70(6) Å <sup>3</sup>
Z	2
Density (calculated)	1.456 mg/m <sup>3</sup>
Absorption coefficient	0.877 mm <sup>-1</sup>
F(000)	440
Crystal size	0.220 x 0.100 x 0.060 mm <sup>3</sup>
Theta range for data collection	2.830 to 73.547°
Index ranges	-9<=h<=9, -10<=k<=10, -18<=l<=19
Reflections collected	12068
Independent reflections	3754 [R(int) = 0.0246]
Completeness to theta = 67.684°	99.4 %
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3754 / 0 / 289
Goodness-of-fit on F <sup>2</sup>	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR2 = 0.0986
R indices (all data)	R1 = 0.0406, wR2 = 0.1012
Extinction coefficient	n/a
Largest diff. peak and hole	0.349 and -0.214 e.Å <sup>-3</sup>



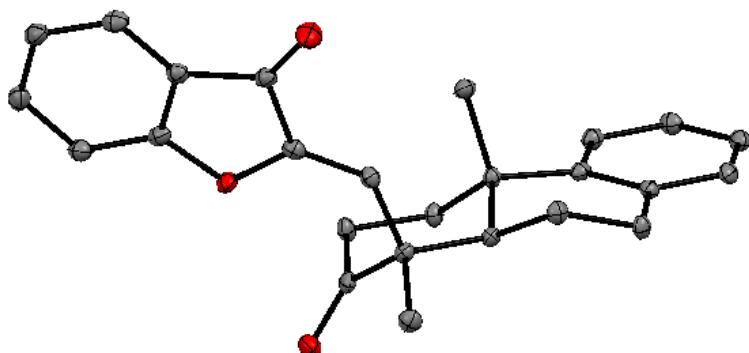
**Figure S4.** Structure of ( $\pm$ )-35 with 50% probability thermo ellipsoids

Note: Table S11 and Figure S4 are adapted with permission from [Xie, J.; Wang, J.; Dong, G. *Org. Lett.* **2017**, *19*, 3017–3020].

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**Table S12.** Crystal data and structure refinement for  $(\pm)$ -**50**

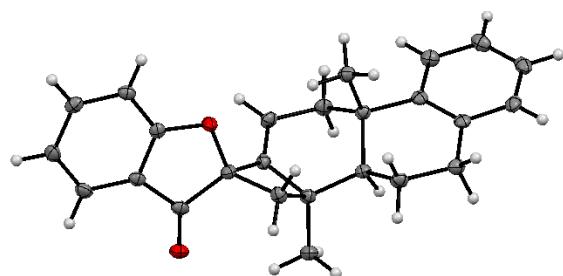
Identification code	mo_0345_KY_JX
Empirical formula	C <sub>25</sub> H <sub>24</sub> O <sub>3</sub>
Formula weight	372.44
Temperature	100.01 K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P2 <sub>1</sub> /c
Unit cell dimensions	a = 10.0189(8) Å $\alpha$ = 90° b = 25.362(2) Å $\beta$ = 102.290(3)° c = 7.4147(6) Å $\gamma$ = 90°
Volume	1840.9(3) Å <sup>3</sup>
Z	4
Density (calculated)	1.344 mg/m <sup>3</sup>
Absorption coefficient	0.087 mm <sup>-1</sup>
F(000)	792.0
Crystal size	0.05 x 0.03 x 0.03 mm <sup>3</sup>
Theta range for data collection	3.212 to 56.19°
Index ranges	-13 <= h <= 12, -33 <= k <= 33, -7 <= l <= 9
Reflections collected	4449
Independent reflections	4449 [R(sigma) = 0.0361]
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4449 / 0 / 256
Goodness-of-fit on F <sup>2</sup>	1.040
Final R indices [I > 2sigma(I)]	R1 = 0.0611, wR2 = 0.1659
R indices (all data)	R1 = 0.0758, wR2 = 0.1741
Extinction coefficient	n/a
Largest diff. peak and hole	0.45 and -0.35 e.Å <sup>-3</sup>

**Figure S5.** Structure of  $(\pm)$ -**50** with 50% probability thermo ellipsoids (H atoms omitted for clarity)Note: Table S12 and Figure S5 are adapted with permission from [Xie, J.; Wang, J.; Dong, G. *Org. Lett.* **2017**, *19*, 3017–3020].

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**Table S13.** Crystal data and structure refinement for ( $\pm$ )-**36**

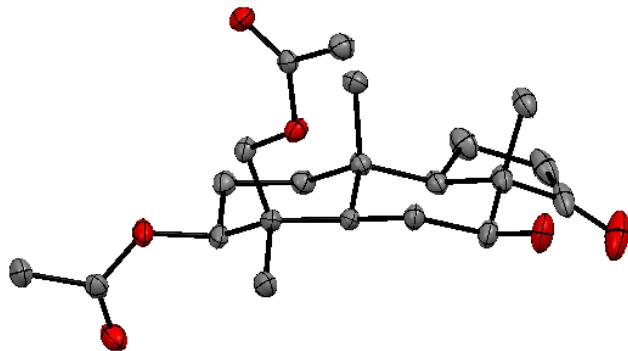
Identification code	xjx-mod2
Empirical formula	C <sub>25</sub> H <sub>24</sub> O <sub>2</sub>
Formula weight	356.44
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 7.611(2) Å $\alpha$ = 105.352(9) $^{\circ}$ b = 11.490(3) Å $\beta$ = 94.190(9) $^{\circ}$ c = 11.506(3) Å $\gamma$ = 109.278(8) $^{\circ}$ 901.5(4) Å <sup>3</sup>
Volume	901.5(4) Å <sup>3</sup>
Z	2
Density (calculated)	1.313 mg/m <sup>3</sup>
Absorption coefficient	0.082 mm <sup>-1</sup>
F(000)	380
Crystal size	0.170 x 0.120 x 0.070 mm <sup>3</sup>
Theta range for data collection	3.104 to 26.023 $^{\circ}$
Index ranges	-9<=h<=9, -14<=k<=14, -14<=l<=13
Reflections collected	13140
Independent reflections	3518 [R(int) = 0.0518]
Completeness to theta = 25.242 $^{\circ}$	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.850
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3518 / 162 / 250
Goodness-of-fit on F <sup>2</sup>	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.1034
R indices (all data)	R1 = 0.0661, wR2 = 0.1114
Extinction coefficient	n/a
Largest diff. peak and hole	0.266 and -0.230 e.Å <sup>-3</sup>

**Figure S6.** Structure of ( $\pm$ )-**36** with 50% probability thermo ellipsoidsNote: Table S13 and Figure S6 are adapted with permission from [Xie, J.; Wang, J.; Dong, G. *Org. Lett.* **2017**, *19*, 3017–3020].

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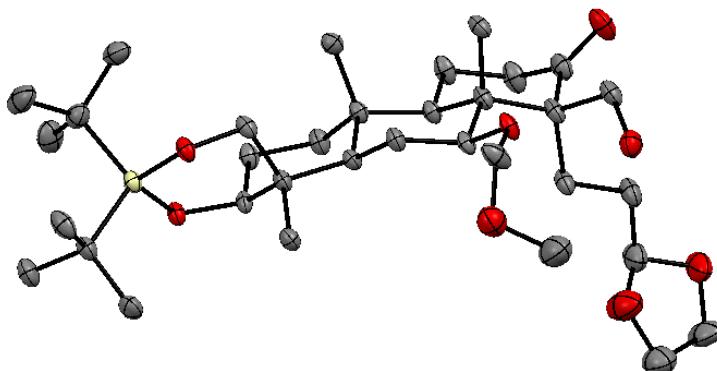
**Table S14.** Crystal data and structure refinement for ( $\pm$ )-**82**

Identification code	xjx999
Empirical formula	C <sub>21</sub> H <sub>32</sub> O <sub>6</sub>
Formula weight	380.46
Temperature/K	100.01
Crystal system	orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
a/Å	7.8188(4)
b/Å	14.4047(7)
c/Å	17.1125(9)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å <sup>3</sup>	1927.34(17)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.311
$\mu/\text{mm}^{-1}$	0.095
F(000)	824.0
Crystal size/mm <sup>3</sup>	0.1 × 0.05 × 0.05
Radiation	MoK $\alpha$ ( $\lambda = 0.71073$ )
2 $\Theta$ range for data collection/°	4.76 to 57.426
Index ranges	-8 ≤ h ≤ 10, -19 ≤ k ≤ 19, -23 ≤ l ≤ 18
Reflections collected	15712
Independent reflections	4930 [ $R_{\text{int}} = 0.0262$ , $R_{\text{sigma}} = 0.0340$ ]
Data/restraints/parameters	4930/0/250
Goodness-of-fit on F <sup>2</sup>	1.057
Final R indexes [I >= 2 $\sigma$ (I)]	$R_1 = 0.0403$ , wR <sub>2</sub> = 0.0914
Final R indexes [all data]	$R_1 = 0.0529$ , wR <sub>2</sub> = 0.0972
Largest diff. peak/hole / e Å <sup>-3</sup>	0.29/-0.17
Flack parameter	-0.1(3)

**Figure S7.** Structure of ( $\pm$ )-**82** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

**Table S15.** Crystal data and structure refinement for ( $\pm$ )-C14-*epi*-88

Identification code	xyx
Empirical formula	C <sub>34</sub> H <sub>60</sub> O <sub>8</sub> Si·0.5H <sub>2</sub> O
Formula weight	633.96
Temperature/K	103.99
Crystal system	triclinic
Space group	P-1
a/Å	14.7591(10)
b/Å	15.7156(10)
c/Å	16.7228(11)
$\alpha/^\circ$	76.534(2)
$\beta/^\circ$	64.490(2)
$\gamma/^\circ$	75.258(2)
Volume/Å <sup>3</sup>	3351.5(4)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.253
$\mu/\text{mm}^{-1}$	0.121
F(000)	1382.0
Crystal size/mm <sup>3</sup>	0.1232 × 0.1125 × 0.0254
Radiation	MoK $\alpha$ ( $\lambda = 0.71073$ )
2 $\Theta$ range for data collection/°	4.464 to 56.738
Index ranges	-19 ≤ h ≤ 19, -21 ≤ k ≤ 20, -22 ≤ l ≤ 22
Reflections collected	93522
Independent reflections	16684 [R <sub>int</sub> = 0.0516, R <sub>sigma</sub> = 0.0538]
Data/restraints/parameters	16684/0/809
Goodness-of-fit on F <sup>2</sup>	1.029
Final R indexes [I>=2σ (I)]	R <sub>1</sub> = 0.0797, wR <sub>2</sub> = 0.2075
Final R indexes [all data]	R <sub>1</sub> = 0.1207, wR <sub>2</sub> = 0.2322
Largest diff. peak/hole / e Å <sup>-3</sup>	2.29/-0.63

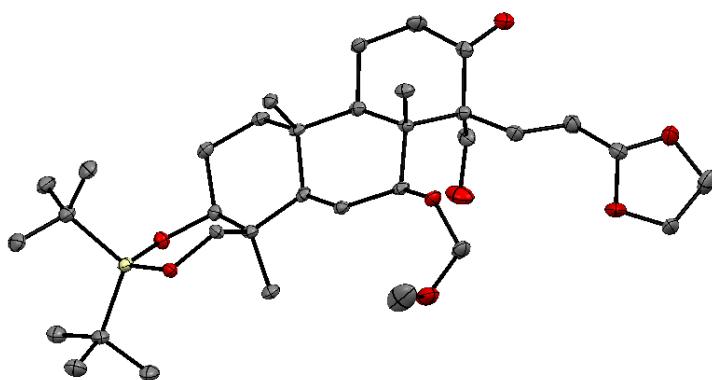


**Figure S8.** Structure of ( $\pm$ )-C14-*epi*-88 with 50% probability thermo ellipsoids (H atoms omitted for clarity)

Note: Table S15 and Figure S8 are adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

**Table S16.** Crystal data and structure refinement for ( $\pm$ )-**88**

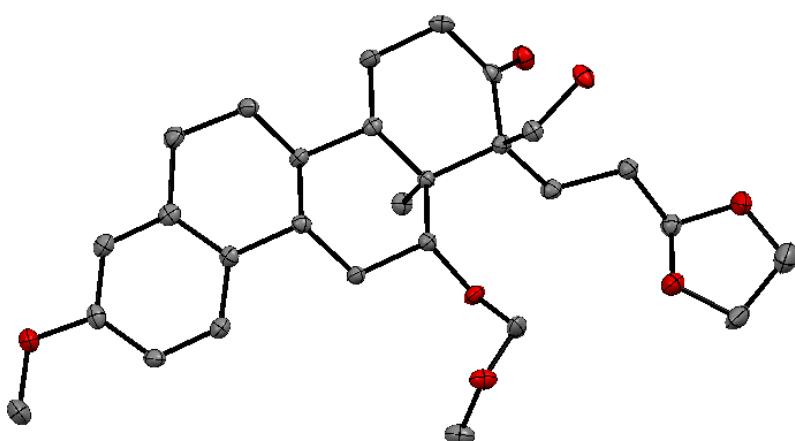
Identification code	test4
Empirical formula	C <sub>34</sub> H <sub>60</sub> O <sub>8</sub> Si·H <sub>2</sub> O
Formula weight	642.92
Temperature/K	100(2)
Crystal system	monoclinic
Space group	P2 <sub>1</sub> /n
a/Å	8.4467(6)
b/Å	47.031(3)
c/Å	8.8360(6)
$\alpha/^\circ$	90
$\beta/^\circ$	104.832(2)
$\gamma/^\circ$	90
Volume/Å <sup>3</sup>	3393.2(4)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.259
$\mu/\text{mm}^{-1}$	0.122
F(000)	1408.0
Crystal size/mm <sup>3</sup>	0.445 × 0.11 × 0.084
Radiation	MoK $\alpha$ ( $\lambda = 0.71073$ )
2 $\Theta$ range for data collection/°	4.846 to 48.916
Index ranges	-9 ≤ h ≤ 9, -54 ≤ k ≤ 54, -10 ≤ l ≤ 10
Reflections collected	54510
Independent reflections	5606 [ $R_{\text{int}} = 0.0894$ , $R_{\text{sigma}} = 0.0517$ ]
Data/restraints/parameters	5606/0/448
Goodness-of-fit on F <sup>2</sup>	1.134
Final R indexes [I>=2σ (I)]	$R_1 = 0.0654$ , $wR_2 = 0.1399$
Final R indexes [all data]	$R_1 = 0.0956$ , $wR_2 = 0.1509$
Largest diff. peak/hole / e Å <sup>-3</sup>	0.49/-0.32

**Figure S9.** Structure of ( $\pm$ )-**88** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

Note: Table S16 and Figure S9 are adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

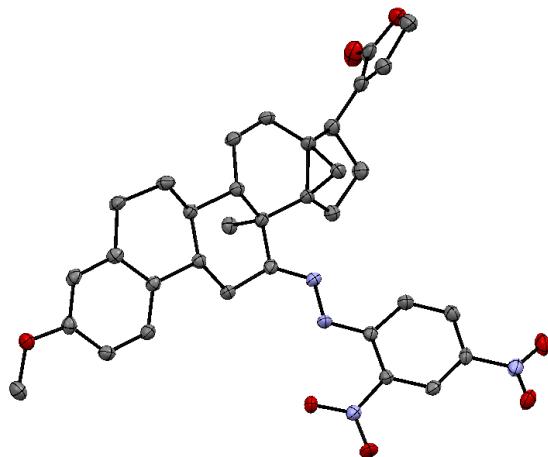
**Table S17.** Crystal data and structure refinement for **99**

Identification code	xjx-model-semipinacol
Empirical formula	C <sub>28</sub> H <sub>39</sub> O <sub>7</sub>
Formula weight	487.59
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
a/Å	8.2265(7)
b/Å	13.6935(12)
c/Å	22.0938(18)
α/°	90
β/°	90
γ/°	90
Volume/Å <sup>3</sup>	2488.9(4)
Z	4
ρ <sub>calc</sub> g/cm <sup>3</sup>	1.301
μ/mm <sup>-1</sup>	0.092
F(000)	1052.0
Crystal size/mm <sup>3</sup>	0.2 × 0.1 × 0.05
Radiation	MoKα ( $\lambda = 0.71073$ )
2Θ range for data collection/°	4.738 to 54.812
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 17, -28 ≤ l ≤ 28
Reflections collected	22059
Independent reflections	5643 [ $R_{\text{int}} = 0.0369$ , $R_{\text{sigma}} = 0.0371$ ]
Data/restraints/parameters	5643/0/320
Goodness-of-fit on F <sup>2</sup>	1.015
Final R indexes [I>=2σ (I)]	$R_1 = 0.0435$ , $wR_2 = 0.0982$
Final R indexes [all data]	$R_1 = 0.0554$ , $wR_2 = 0.1040$
Largest diff. peak/hole / e Å <sup>-3</sup>	0.52/-0.40
Flack parameter	0.3(3)

**Figure S10.** Structure of **99** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

**Table S18.** Crystal data and structure refinement for **117**

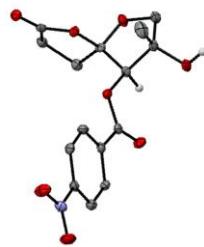
Identification code	mo_1004_SHO_JX_0m
Empirical formula	C <sub>34</sub> H <sub>34</sub> N <sub>4</sub> O <sub>7</sub>
Formula weight	610.65
Temperature/K	100(2)
Crystal system	monoclinic
Space group	P2 <sub>1</sub>
a/Å	14.1637(8)
b/Å	12.6742(7)
c/Å	16.9602(9)
α/°	90
β/°	109.048(2)
γ/°	90
Volume/Å <sup>3</sup>	2877.9(3)
Z	4
ρ <sub>calc</sub> g/cm <sup>3</sup>	1.409
μ/mm <sup>-1</sup>	0.100
F(000)	1288.0
Crystal size/mm <sup>3</sup>	0.263 × 0.237 × 0.093
Radiation	MoKα ( $\lambda = 0.71073$ )
2Θ range for data collection/°	4.556 to 53.358
Index ranges	-17 ≤ h ≤ 17, -15 ≤ k ≤ 15, -21 ≤ l ≤ 21
Reflections collected	52477
Independent reflections	10374 [R <sub>int</sub> = 0.0322, R <sub>sigma</sub> = 0.0363]
Data/restraints/parameters	10374/1/815
Goodness-of-fit on F <sup>2</sup>	1.039
Final R indexes [I>=2σ (I)]	R <sub>1</sub> = 0.0358, wR <sub>2</sub> = 0.0782
Final R indexes [all data]	R <sub>1</sub> = 0.0525, wR <sub>2</sub> = 0.0836
Largest diff. peak/hole / e Å <sup>-3</sup>	0.22/-0.21
Flack parameter	-0.5(2)



**Figure S11.** Structure of **117** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

**Table S19.** Crystal data and structure refinement for ( $\pm$ )-**125**

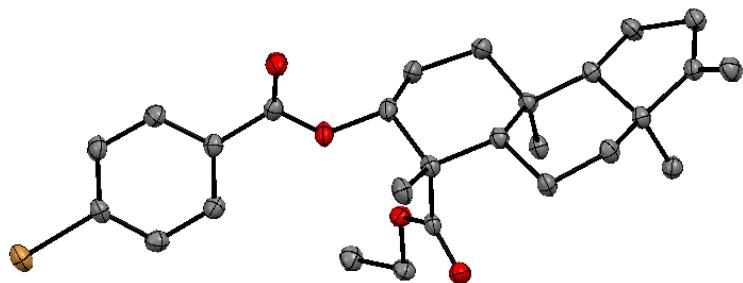
Identification code	xjx790
Empirical formula	C <sub>15</sub> H <sub>15</sub> NO <sub>8</sub>
Formula weight	337.28
Temperature/K	100.0
Crystal system	orthorhombic
Space group	Pna <sub>2</sub> <sub>1</sub>
a/Å	11.6783(9)
b/Å	8.2327(6)
c/Å	30.711(2)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å <sup>3</sup>	2952.7(4)
Z	8
$\rho_{\text{calc}}/\text{g/cm}^3$	1.517
$\mu/\text{mm}^{-1}$	0.125
F(000)	1408.0
Crystal size/mm <sup>3</sup>	0.06 × 0.05 × 0.05
Radiation	MoK $\alpha$ ( $\lambda = 0.71073$ )
2 $\Theta$ range for data collection/°	5.122 to 48.956
Index ranges	-13 ≤ h ≤ 13, -9 ≤ k ≤ 9, -35 ≤ l ≤ 35
Reflections collected	42033
Independent reflections	4878 [ $R_{\text{int}} = 0.0599$ , $R_{\text{sigma}} = 0.0390$ ]
Data/restraints/parameters	4878/1/437
Goodness-of-fit on F <sup>2</sup>	1.073
Final R indexes [I >= 2 $\sigma$ (I)]	$R_1 = 0.0375$ , $wR_2 = 0.0746$
Final R indexes [all data]	$R_1 = 0.0551$ , $wR_2 = 0.0806$
Largest diff. peak/hole / e Å <sup>-3</sup>	0.27/-0.20
Flack parameter	0.2(4)

**Figure S12.** Structure of ( $\pm$ )-**125** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

Note: Table S19 and Figure S12 are adapted with permission from [Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316]. Copyright (2021) of ACS Publications.

**Table S20.** Crystal data and structure refinement for *ent*-**164**

Identification code	xjx2249-chiral
Empirical formula	C <sub>27</sub> H <sub>35</sub> BrO <sub>4</sub>
Formula weight	503.480
Temperature/K	99.99
Crystal system	monoclinic
Space group	P2 <sub>1</sub>
a/Å	10.9210(7)
b/Å	18.0460(11)
c/Å	12.5617(8)
α/°	90
β/°	97.775(2)
γ/°	90
Volume/Å <sup>3</sup>	2452.9(3)
Z	4
ρ <sub>calc</sub> g/cm <sup>3</sup>	1.363
μ/mm <sup>-1</sup>	2.522
F(000)	1056.2
Crystal size/mm <sup>3</sup>	0.602 × 0.472 × 0.273
Radiation	Cu Kα ( $\lambda = 1.5417800000000002$ )
2Θ range for data collection/°	7.1 to 158.92
Index ranges	-13 ≤ h ≤ 13, -22 ≤ k ≤ 22, -15 ≤ l ≤ 14
Reflections collected	80320
Independent reflections	10280 [ $R_{\text{int}} = 0.0345$ , $R_{\text{sigma}} = 0.0201$ ]
Data/restraints/parameters	10280/1/601
Goodness-of-fit on F <sup>2</sup>	1.036
Final R indexes [I>=2σ (I)]	$R_1 = 0.0273$ , $wR_2 = 0.0692$
Final R indexes [all data]	$R_1 = 0.0278$ , $wR_2 = 0.0696$
Largest diff. peak/hole / e Å <sup>-3</sup>	0.82/-0.32
Flack parameter	0.072(3)



**Figure S13.** Structure of *ent*-**164** with 50% probability thermo ellipsoids (H atoms omitted for clarity)

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