**Synthesis of (–)-Picrotoxinin by Late-Stage Strong Bond Activation**

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**Table of Contents**

## 1. Materials and Methods

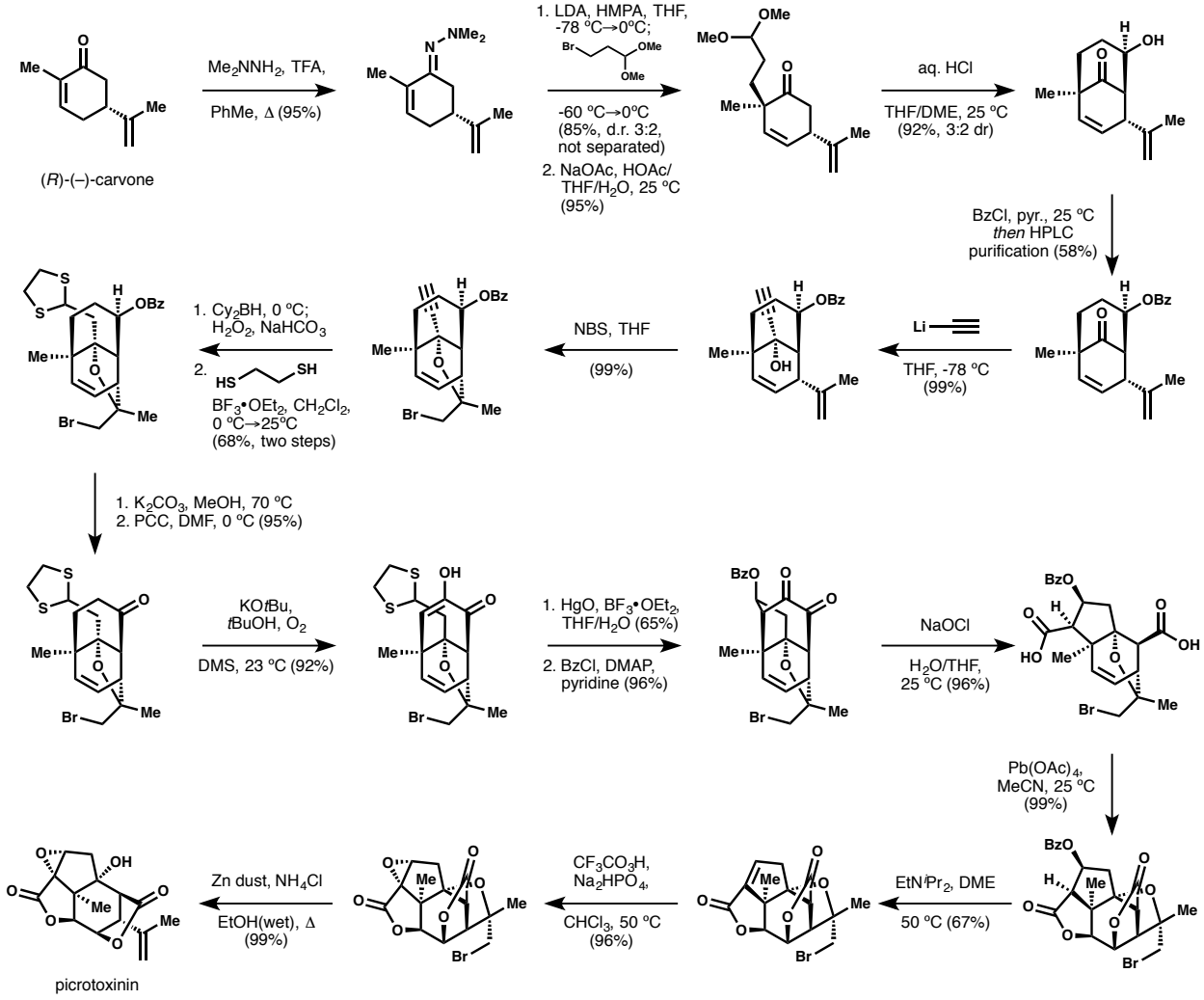
Pentane, hexanes, dichloromethane (DCM), toluene, ethyl acetate (EtOAc), diethyl ether, benzene, dimethylsulfoxide (DMSO), methanol (MeOH), *N*-dimethylformamide (DMF), dichloroethane (DCE), α, α, α – trifluorotoluene and triethylamine were purchased from Sigma Aldrich, EMD Chemicals, Fisher Chemicals or Acros Organics and used without further purification. All anhydrous solvents were purchased from Fisher Chemicals, Sigma Aldrich or Acros Organics and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) with precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F254, 250 $\mu$m thickness) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid (PMA), chromic acid, iodine vapor, Seebach's stain, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. Preparatory thin layer chromatography (PTLC) was performed using the aforementioned silica gel plates. Flash column chromatography was performed over silica gel 60 (particle size 0.035- 0.07 mm) from Acros Organics. NMR spectra were recorded on Bruker DRX-600 (equipped with a 5mm DCH Cryoprobe), AV-600, DRX-500 or DPX-400 and calibrated using residual non-deuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm $^1$H NMR, 77.16 ppm $^{13}$C NMR; $(CD_3)_2CO$ @ 2.05 ppm $^1$H NMR, 206.26 ppm $^{13}$C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, sep = septet m = multiplet, br = broad. LC/MS analysis was performed on an Agilent 1200 series HPLC/MS equipped with an Agilent SB-C18 2.1 mm x 50 mm column, with mass spectra recorded on a 6120 Quadrupole mass spectrometer (API-ES), using ACN and $H_2O$ as the mobile phase (0.1% formic acid). LC/MS runs used the following method unless otherwise specified: flow rate of 0.5 mL / min is used, initial equilibration of 5% ACN / $H_2O$ with a linear gradient to 95% ACN / $H_2O$ over 5 minutes, then a hold at 95% ACN / $H_2O$ for an additional 3 minutes. GC/MS analysis was performed on Agilent 7820A/5975 GC/MSD system with helium as a carrier gas. Unless otherwise specified, GC/MS runs were performed with the following method: GC/MSD; HP-5MS (30m x 0.25mm ID, part # 19091S-433); 139 KPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C for 0 min, then 20 °C/min to 280 °C, then held for 2 min. GC/FID analysis was conducted on an Agilent 7820A GC/FID system with nitrogen as a carrier gas and with air and hydrogen as combustion gasses. Unless otherwise specified, GC/FID runs were prepared with the following method: GC/FID; HP-5MS UI (20m x 0.180mm ID, part # 190915-577UI); inlet temperature 250 °C; column temperature 50 °C for 0 min, then 20 °C/min to 280 °C, then held for 2 min. Chiral HPLC analysis was performed on Agilent 1100 series equipped with a DAD detector. Chiralcel OZ-3, 3 µm particle size, 250 mm x 6 mm column; flow rate 1 mL/min with solvent mixture of 98% hexanes and 2% isopropanol; detection wavelength 210 nm. Optical rotations of arylated menthol derivatives were measured digitally on an Autopol III polarimeter from Rudolph Research Analytic, using a flow cell with a 0.5 decimeter pathlength and the sodium lamp D-line wavelength (λ=589.3 nm). High resolution mass spectrometric data were obtained on a Waters Xevo G2-XS TOF instrument (http://www.waters.com/webassets/cms/library/docs/720005089en.pdf). Calculated HRMS data were obtained by input of the (M+H) chemical formulae into the Exact Mass Calculator, Single Isotope Version at (https://www.sisweb.com/referenc/tools/exactmass.htm?formula).

Unless otherwise noted, all experiments were run in flame-dried glassware under an atmosphere of argon gas.

## 2. Prior Syntheses of Picrotoxinin

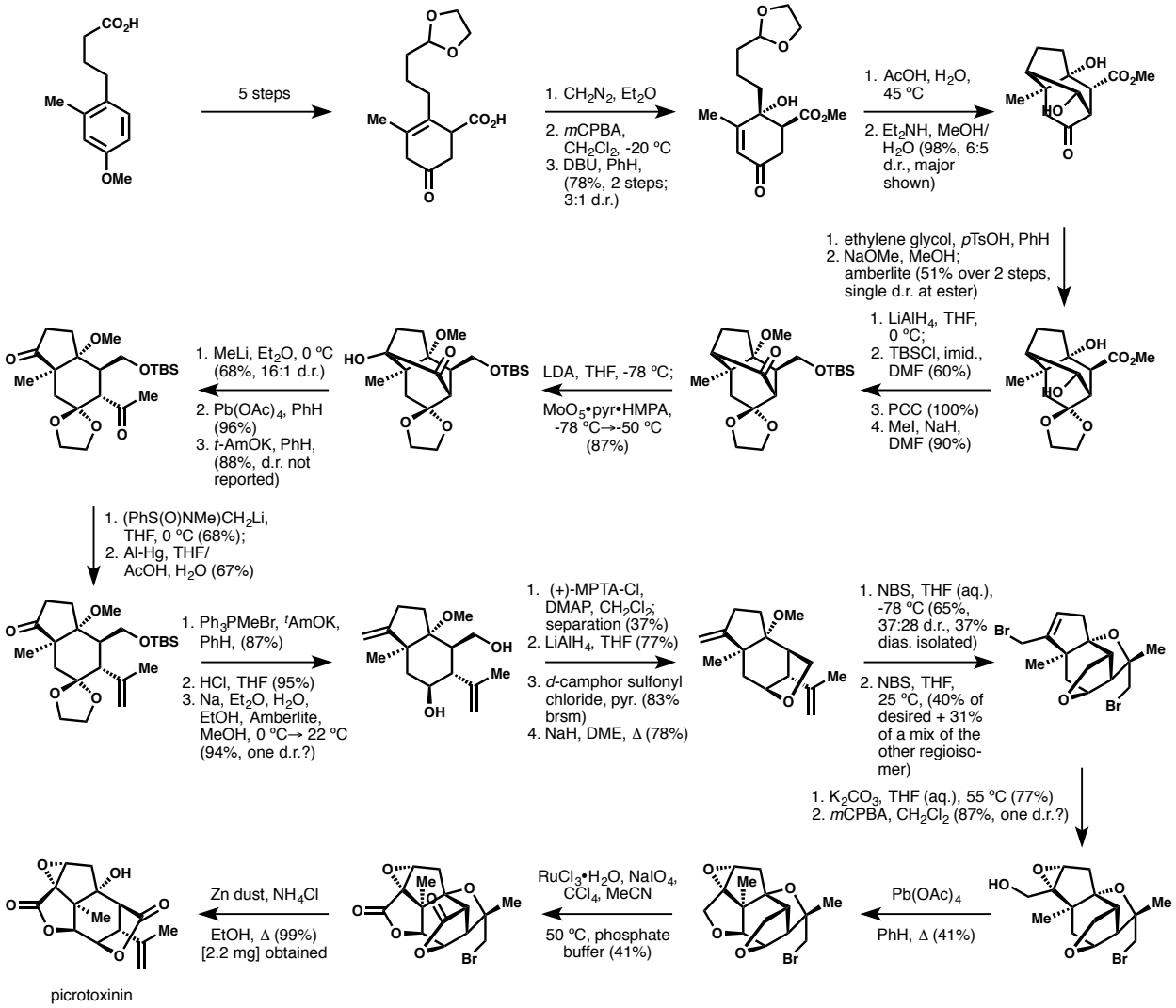
### 2.1 Corey (1979)

1. Corey, E. J.; Pearce, H. L. Total Synthesis of Picrotoxinin. *J. Am. Chem. Soc.* **1979**, *101*, 5841–5843.
2. Corey, E. J.; Pearce, H. L. Total Synthesis of Picrotin. *Tetrahedron Lett.* **1980**, *21*, 1823–1824.



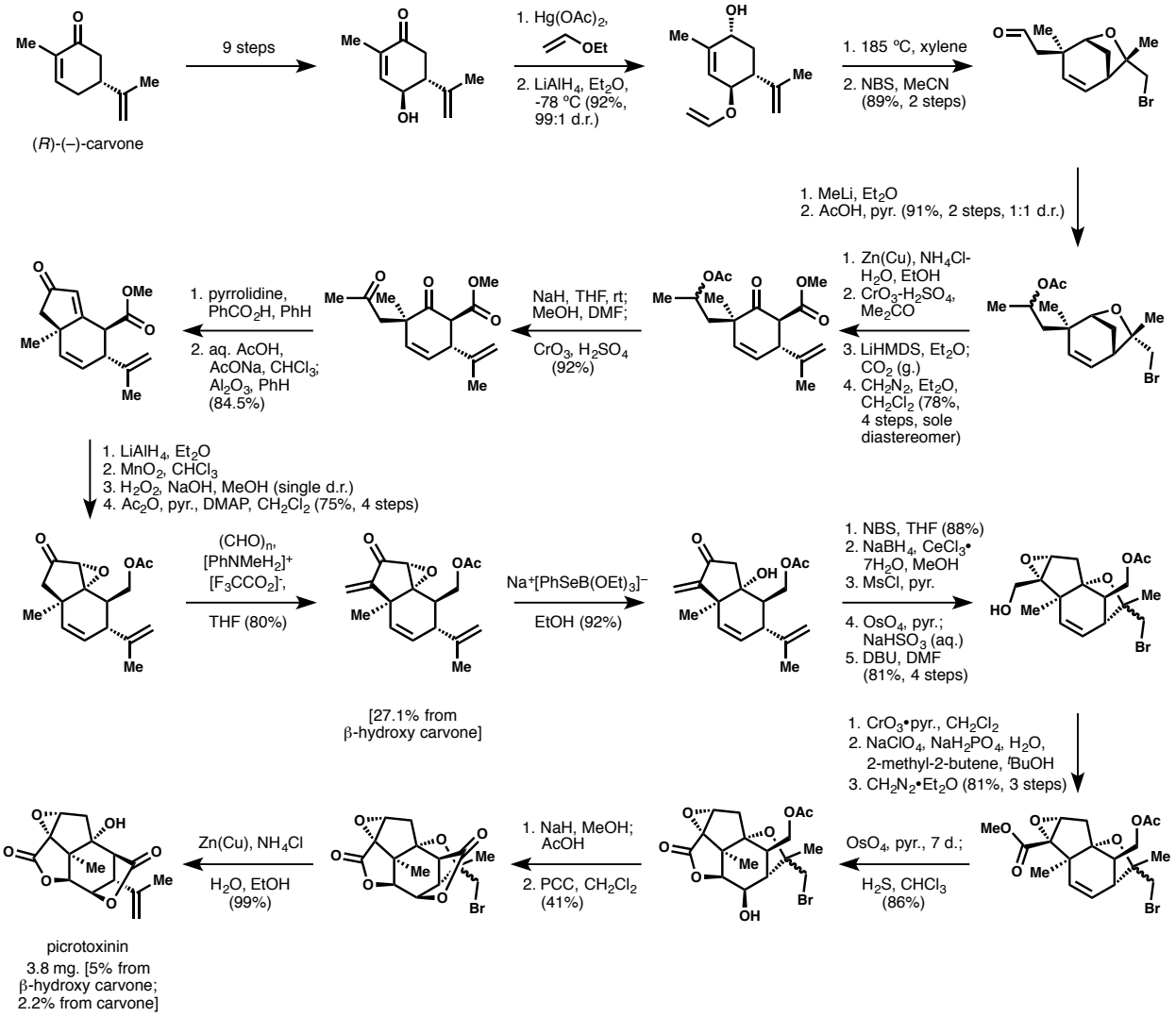
2.2 Yamada (1984)


1. Yamada, K.; K. Nagase, H.; Hayakawa, Y.; Aoki, K.; Hirata, Y. Synthetic Studies on Spirovetivanes. I. Spirocondensation of a 4-(3'-formylpropyl)-3-cyclohexenone and Stereospecific Total Synthesis of d1-β-vetivone. *Tetrahedron Lett.* **1973**, *14*, 4963–4966.
2. Niwa, N.; Wakamatsu, K.; Hida, T.; Niiyama, K.; Kigoshi, H.; Yamada, M.; Nagase, H.; Suzuki, M.; Yamada, K. Stereocontrolled Total Synthesis of (–)-Picrotoxinin and (+)-Coriamyrtin via a Common Isotwistane Intermediate. *J. Am. Chem. Soc.* **1984**, *106*, 4547–4552.

2.3 Yoshikishi (1989)

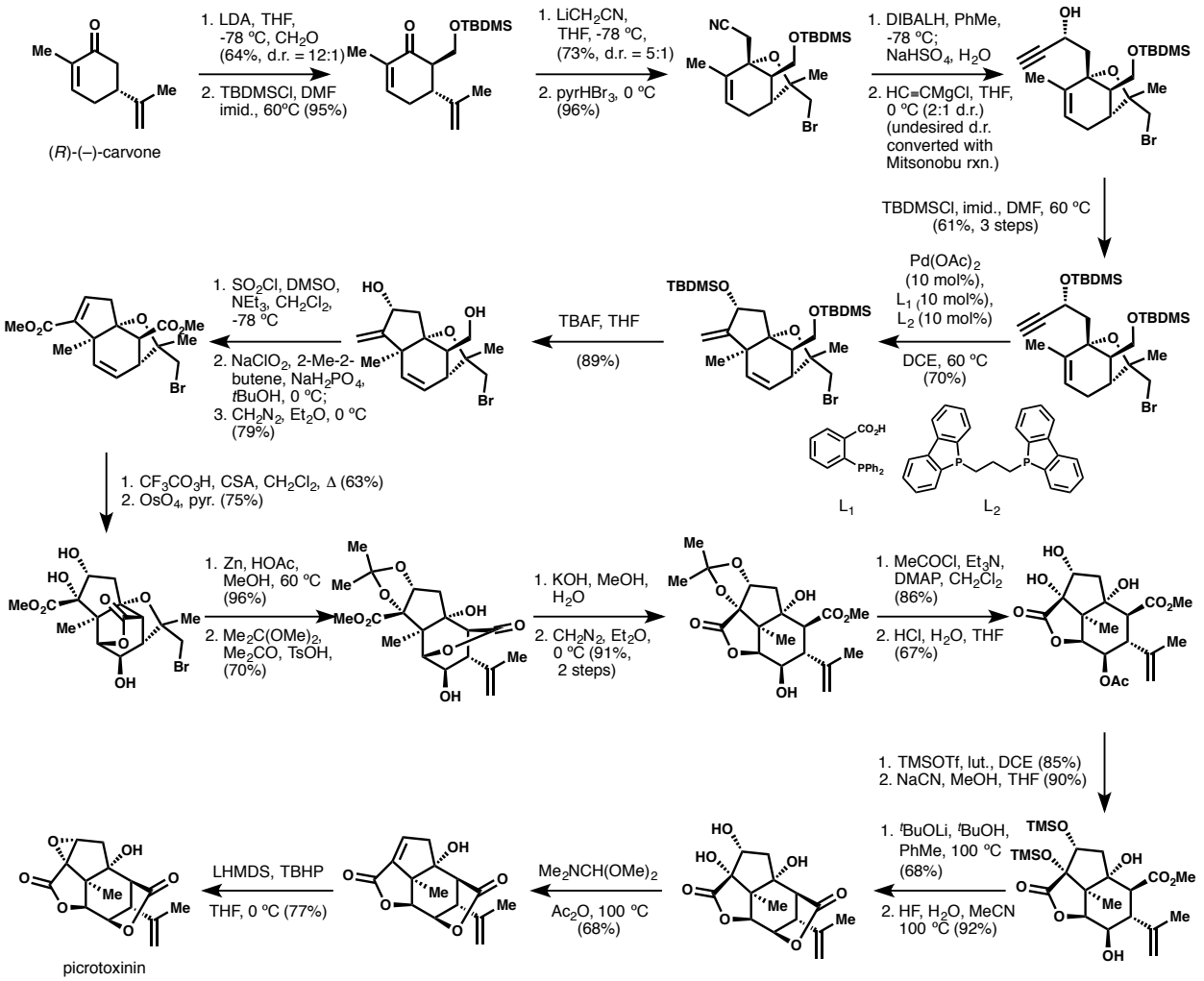
1. Miyashita, M.; Suzuki, T.; Yoshikishi, A. Stereoselective Total Synthesis of (–)-Picrotoxinin and (–)-Picrotin. *J. Am. Chem. Soc.* **1989**, *111*, 3728–3734.
2. Miyashita, M.; Sukuki, T.; Yoshikishi, A. Highly Efficient Conversion of (–)-carvone to (+)-β-hydroxycarvone. *J. Org. Chem.* **1985**, *50*, 3377–3380.



2.4 Trost (1996/1999)

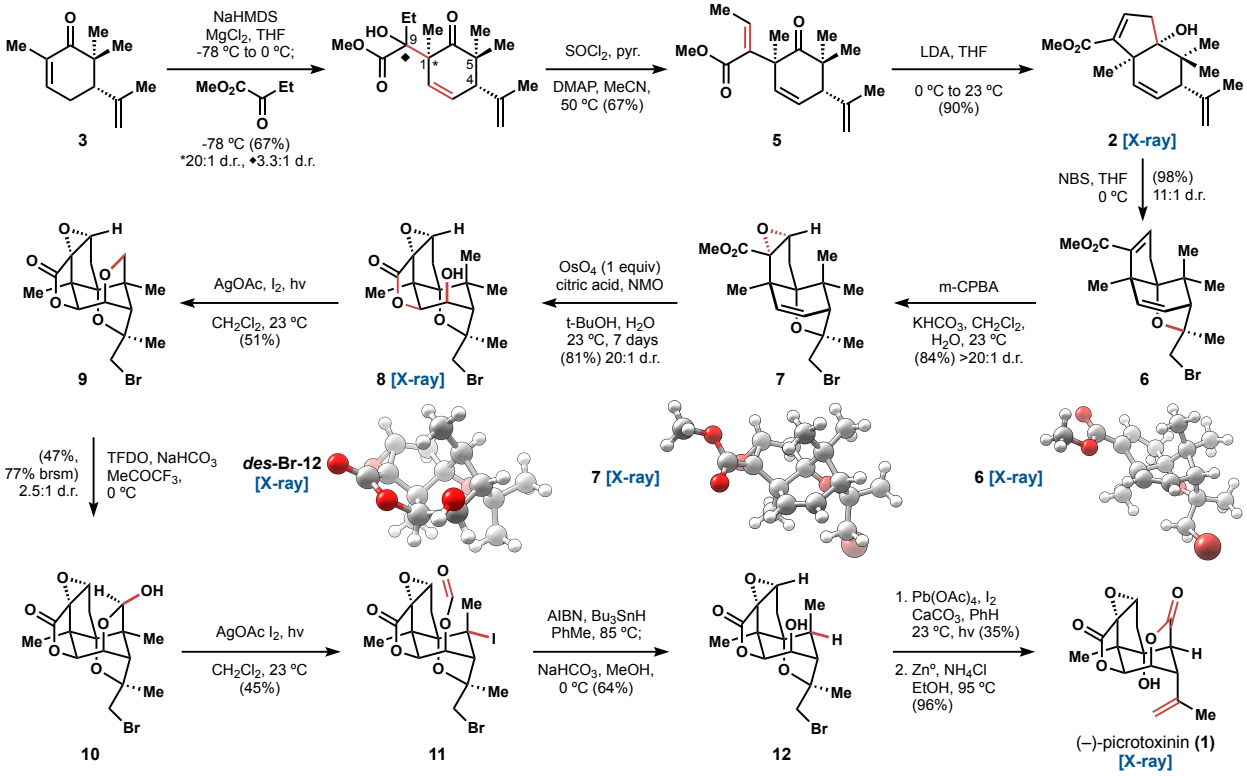
(Scheme depicts the first-generation synthesis)


1. Trost, B. M.; Krische, M. J. General Strategy for the Asymmetric Synthesis of the Picrotaxanes. *J. Am. Chem. Soc.* **1996**, *118*, 233–234.
2. Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krishe, M. J.; Thomas, A. P. The Palladium-Catalyzed Enyne Cycloisomerization Reaction in a General Approach to the Asymmetric Syntheses of the Picrotoxane Sesquiterpenes. Part 1. First-Generation Total Synthesis of Corianin and Formal Syntheses of Picrotoxinin and Picrotin. *J. Am. Chem. Soc.* **1999**, *121*, 6183–6192.
3. Trost, B.; Krische, M. J. Palladium-Catalyzed Enyne Cycloisomerization Reaction in an Asymmetric Approach to the Picrotoxane Sesquiterpenes. 2. Second-Generation Total Syntheses of Corianin, Picrotoxinin, Picrotin, and Methyl Picrotoxate. *J. Am. Chem. Soc.* **1999**, *121*, 6131–6141.

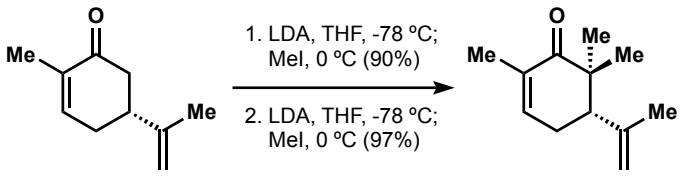



3. Experimental Procedures and Characterization Data

Scheme 1 from Main Text.



3.1 Dimethyl-carvone (**3**) formation




Procedure:

A [0.33 M] solution of LDA in THF was formed by addition of *n*BuLi in hexanes [2.67 M] (1.2 equiv, 240.0 mmol, 90 mL) to a solution of diisopropylamine (distilled off $CaH_2$) (1.5 equiv, 300.0 mmol, 42.0 ml) in THF (600 mL, [0.5 M] wrt $HN^iPr_2$) at -78 ºC. After addition, the solution was stirred at 0 ºC for 30 minutes before cooling back to -78 ºC.

To a flame-dried 500 mL round bottom flask containing a [0.33 M] solution of LDA in THF (1.2 equiv, 240.0 mmol, see above for preparation details) cooled to -78 ºC in a dry ice/acetone bath under an argon atmosphere was added via cannula a [1M (ignoring carvone volume)] solution of (*R*)-carvone (**SI-1**) (1 equiv, 200.0 mmol, 30 g, 31.3 mL) in THF (200 mL). The addition took ~ 10 minutes and the solution turned from clear and pale yellow to yellow over the course of the addition. The reaction was allowed to stir for 105 minutes, at which point methyl iodide (2.0 equiv, 200.0 mmol, 12.4 mL) was added neat in a slow but steady stream to the carvone enolate solution. The reaction was then stirred at 0 ºC in an ice water bath and monitored by TLC (5% EtOAc/hex). Full consumption of carvone was observed after 60 minutes.

After completion, the reaction was quenched by pouring the reaction onto a 1:1 mixture of saturated $NH_4Cl$ (aq.): $H_2O$ (500 mL). The aqueous layer was extracted with EtOAc (3x ~250 mL). The organic layer was washed 1x each with $Na_2S_2O_3$ (saturated, aq., ~250 mL) and brine (saturated, aq. ~250 mL), and then dried over $MgSO_4$, filtered, and concentrated. A white precipitate crashed out of the solution during concentration on the rotovap (presumably a diisopropylamine HI salt). The solid was filtered off over a plug of celite, rinsing with hexanes. The yellow solution became increasingly yellow/orange upon concentration. Therefore, the solution was diluted in 500 mL of hexanes, washed 1x with $Na_2S_2O_3$ (saturated, aq., ~100 mL) which removed most of the yellow color, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by fractional distillation on high vacuum. The desired mixture of α-methyl-carvone isomers was distilled over as a colorless to slightly pale-yellow oil at ~125-130 ºC (external temperature), ~90-91 ºC (internal temperature at distillation head) at a pressure of < 5 torr. α-methyl-carvone (1:1 *cis*:*trans*) was obtained 90% yield (29.4 g, 180.0 mmol).

A second [0.34 M] solution of LDA in THF was formed by addition of *n*BuLi in hexanes (1.25 equiv, 225.0 mmol, 84 mL of [2.67 M]) to a solution of diisopropylamine (distilled off $CaH_2$) (1.5 equiv, 270.0 mmol, 37.7 ml) in THF (540 mL, [0.5 M] with respect to $HN^iPr_2$) at -78 ºC. After addition, the solution was stirred at 0 ºC for 30 minutes before cooling back to -78 ºC.

To a flame-dried 500 mL round bottom flask containing the [0.34 M] solution of LDA in THF (1.2 equiv, 108.0 mmol, see above for preparation details) cooled to -78 ºC in a dry ice/acetone bath under an argon atmosphere was added via cannula a [1M (ignoring α-methyl-carvone volume)] solution of α-methyl-carvone (1 equiv, 180.0 mmol, 29.4 g) in THF (180 mL). The substrate solution was rinsed with a few mL of anhydrous THF after transfer. The solution was allowed to stir for 90 minutes, at which point methyl iodide (2.0 equiv, 180.0 mmol,

11.2 mL) was added neat in slow but steady stream to the α-methyl-carvone enolate solution. The reaction was then stirred at 0 ºC in an ice water bath and monitored by TLC (10% EtOAc/hex). After 1 hour, some starting material still remained by TLC (10% EtOAc/hex). After two hours, there appeared to be no further conversion, so the solution was quenched.

The reaction was poured onto a 1:1 mixture of saturated $NH_4Cl$ (aq.): $H_2O$ (500 mL). The aqueous layer was extracted with EtOAc (1x ~250 mL) and hexanes (2x ~250 mL). The organic layer was washed 1x each with $Na_2S_2O_3$ (saturated, aq., ~250mL) and brine (saturated, aq., ~250 mL) and then dried over $MgSO_4$, filtered, and concentrated. The residue turned increasingly yellow (NOTE 1) and cloudy during concentration, so the residue was dissolved in ~ 150 mL of hexanes and washed a second times with $Na_2S_2O_3$ (saturated, aq., ~ 100 mL). After separation, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction was purified by a fractional distillation on high vacuum. Dimethyl-carvone was distilled over as a colorless to slightly pale-yellow oil at ~120-130 ºC (external temperature), ~80 ºC (internal temperature at distillation head) at a pressure of < 5 torr. α-methyl-carvone was obtained in 97% yield (31.1 g, 174.0 mmol). NMR analysis indicated a 1.00:0.03:0.03 mixture of dimethyl-carvone to α-methyl-carvone isomers. This compound was used without further purification in the subsequent step and stored over solid copper in a tinted glass bottle (old $CDCl_3$ bottle) away from light at -20 ºC.

NOTE 1: We speculate that the yellow/orange color that appears during concentration of the crude reaction is due to formation of iodine from aerobic oxidation of iodide salt in the presence of both α-methyl-carvone and dimethylcarvone. The thiosulfate wash temporarily reduces the nascent iodine, but storage in air results in further oxidation. We recommend minimal storage time between work-up and purification by distillation.

Characterization data of dimethyl-carvone (**3**)**:**

*Description* clear or pale-yellow oil

$R_f$ 0.44 in 5% EtOAc/hex. 0.56 in 10% EtOAc/hex. Stains purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -10.7º, c=1.00 in $CH_2Cl_2$, T=22.9 ºC

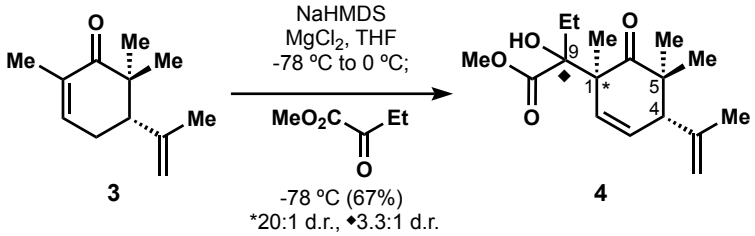
$^1$H NMR (600 MHz, Chloroform-*d*)
δ 6.61 (ddt, *J* = 6.2, 2.8, 1.4 Hz, 1H), 4.86 (p, *J* = 1.6 Hz, 1H), 4.77 – 4.65 (m, 1H), 2.53 (dd, *J* = 7.7, 5.4 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.44 – 2.35 (m, 1H), 1.77 (q, *J* = 1.8 Hz, 3H), 1.72 – 1.66 (m, 3H), 1.14 (s, 3H), 1.03 (s, 3H).

$^{13}$C NMR (151 MHz, Chloroform-*d*)
δ 204.7, 146.1, 142.4, 133.7, 113.9, 52.2, 44.8, 29.2, 24.6, 23.5, 20.5, 16.6.

HRMS Calculated $C_{12}H_{19}O$ [M+H]: 179.1436 | Found: 179.1432

X-ray N/A, oil

3.2 Aldol addition of methyl-2-oxobutanoate to **3** to form **4**



Procedure:

To a flame-dried round bottom flask charged with anhydrous $MgCl_2$ (1.9 g, 20.0 mmol, 2 equiv, NOTE 1) was added a solution of freshly distilled dimethyl-carvone **3** (1.78 g, 10.0 mmol, 1 equiv) in anhydrous THF (100 mL) at 23 ºC for 20 minutes. NaHMDS (1 M in THF, 15 mL, 15.0 mmol, 1.5 equiv) was added to the above mixture at -78 ºC. The reaction was vigorously stirred for an additional 30 minutes at -78 ºC. The solution was placed in a 0 ºC ice/water bath and stirred for 60 minutes at 0 ºC. Once the enolate was fully formed (NOTE 2), the solution was cooled back to -78 ºC and methyl-2-oxobutanoate (3.35 mL, 30.0 mmol, 3.0 equiv) was added neat to the enolate solution in a steady stream within a period of 5 minutes. After 75 minutes, the mixture was quenched by addition of saturated $NH_4Cl/H_2O$ (1:1, v:v, 20 mL) at -78 ºC (NOTE 3). The reaction was then warmed to room temperature and extracted with EtOAc (3 x 150 mL). The organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (5% EtOAc/hex to 10% EtOAc/hex). The desired aldol addition products **4** were collected together (1.91 g, 6.7 mmol, 67%, dr ~ 3.3:1 at C-9, NOTE 4) as a pale-yellow oil.

NOTE 1: $MgCl_2$ powder (weighed out assuming it is anhydrous) is further dried by heating with a heat gun under high vacuum until no more 'bubbling' of the powder occurs. The vessel is then placed under an argon atmosphere and other reagents are added to this reaction vessel.

NOTE 2: After 60 minutes, it is useful to TLC the enolate solution to confirm that the enolate has fully formed. Protonation at C-1 occurs upon TLC analysis to give the deconjugated isomer of dimethyl-carvone, which is less polar than dimethyl-carvone and not UV-active. Disappearance of the dimethyl-carvone spot is observed when the enolate has fully formed.

NOTE 3: The reaction must be quenched at -78 ºC because the retro-aldol reaction of the product occurs at warmer temperatures (*ca* >~ -20 ºC).

NOTE 4: The yield of this reaction between different runs ranged from 60-70% and the diastereoselectivity between 2-3.3:1 at the C-9 alcohol. The opposite diastereomer at C-1 was never observed. The C-9 diastereomers can be collected separately after chromatographic separation. A 2.2:1 diastereomeric mixture at C-9 were separated and used for characterization of the two C-9 diastereomers.

Characterization data of aldol addition adduct (**4**, **major** diastereomer)**:**

| | |
|---|---|
| *Description* | Faint yellow/colorless oil. Became a white waxy crystalline solid upon storage at -20 ºC. |
| $R_f$ | 0.23 in 15% EtOAc/hex. Weakly UV active. Stain purple in anisaldehyde. |
| Opt. Rot. | $\alpha_{obs}$ = +58.9º, c=1.00 in $CH_2Cl_2$, T=25.6 ºC |
| $^1$H NMR | (600 MHz, Chloroform-*d*)<br>δ 5.91 (dd, *J* = 10.3, 2.4 Hz, 1H), 5.80 (dd, *J* = 10.3, 3.1 Hz, 1H), 5.05 (dq, *J* = 2.0, 1.3 Hz, 1H), 4.77 (dt, *J* = 1.7, 0.8 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 1H), 3.15 (t, *J* = 2.8 Hz, 1H), 1.98 (dq, *J* = 13.7, 7.3 Hz, 1H), 1.81 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.67 (dq, *J* = 13.6, 7.4 Hz, 1H), 1.34 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 0.76 (t, *J* = 7.3 Hz, 3H). |
| $^{13}$C NMR | (151 MHz, Chloroform-*d*)<br>δ 218.4, 176.1, 144.7, 132.9, 130.6, 115.9, 83.3, 55.0, 53.0, 50.2, 48.4, 26.6, 24.7, 23.1, 23.0, 22.0, 7.6. |
| HRMS | Calculated $C_{17}H_{27}O_4$ [M+H]: 295.1909 \| Found: 295.1906 |
| X-ray | not obtained |
| 2D-NMR | NOESY |

Characterization data of aldol addition adduct (**4**, **minor** diastereomer)**:**

*Description* Faint yellow/colorless oil. Became a white waxy crystalline solid upon extended storage at -20 ºC.

$R_f$ 0.3 in 15% EtOAc/hex. Weakly UV active. Stain purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -45.9º, c=1.00 in $CH_2Cl_2$, T=24.2 ºC

$^1$H NMR (600 MHz, Chloroform-*d*)
δ 5.86 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.52 (dd, *J* = 10.4, 3.2 Hz, 1H), 5.11 – 4.98 (m, 1H), 4.75 (dq, *J* = 1.7, 0.8 Hz, 1H), 4.09 (d, *J* = 1.6 Hz, 1H), 3.76 (s, 3H), 3.18 (t, *J* = 2.8 Hz, 1H), 2.11 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.90 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.84 – 1.78 (m, 3H), 1.32 (s, 3H), 1.13 (s, 3H), 0.99 (s, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).

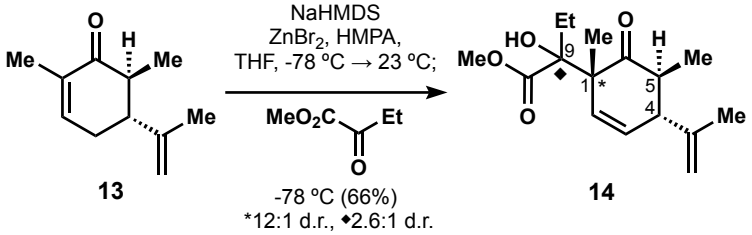
$^{13}$C NMR (151 MHz, Chloroform-*d*)
δ 218.5, 175.2, 144.7, 133.1, 130.4, 116.0, 84.3, 52.7, 52.4, 50.2, 48.5, 26.0, 24.5, 23.2, 22.6, 22.4, 8.1.

HRMS Calculated $C_{17}H_{27}O_4$ [M+H]: 295.1909 | Found: 295.1905

X-ray not obtained

2D-NMR NOESY

3.3 Aldol addition of methyl-2-oxobutanoate to **13** to form **14**




Procedure:

Trans-α-methyl-carvone (**13**) was obtained by chromatographic separation on silica gel with a 5% $Et_2O$/hexane solvent system after mono-alkylation of (*R*)-carvone according to the procedure described for the synthesis of **4** (see above). HMPA was dried by stirring over anhydrous $CaH_2$ for > 1 hour and purified via distillation through a simple short path distillation apparatus using a heat gun with mild heating under a vacuum. Zinc bromide was flame-dried on a high vacuum immediately prior to use and used to prepared 15 mL of a saturated zinc-bromide solution in anhydrous THF under an Argon atmosphere.

To a flame-dried 150 mL round bottom flask charged with a stir bar under an Argon atmosphere was added anhydrous THF (25 mL), anhydrous HMPA (2.00 mL, 11.5 mmol, 2.50 equiv.), and NaHMDS (1M in THF, 6.80 mL, 1.50 equiv.) at -78 ºC and stirred. To this was added at -78 ºC a solution of trans-α-methyl-carvone (**13**) (750 mg, 4.60 mmol, 1.00 equiv.) in anhydrous THF (25 mL). The reaction mixture was then removed from the -78 ºC acetone/dry ice bath and stirred at room temperature to obtain a clear yellow solution. After 75 min, the solution was cooled back to -78 ºC and 10 mL of a saturated $ZnBr_2$ solution in THF was added, causing the solution to become opaque. After stirring for 30 minutes, methyl-2-oxo-butanoate (1.50 mL, 13.8 mmol, 3.00 equiv.) was added neat to the solution at -78 ºC and the reaction was monitored by TLC (20% EtOAc/hex). Completion of the reaction was indicated by TLC analysis after 45 minutes, at which point the reaction was quenched by addition of a 1:1 mixture of saturated aq. $NH_4Cl$ and $H_2O$ (~50 ml) at -78 ºC, diluted with $Et_2O$

(~20 mL), and warmed to room temperature. The solution was extracted with $Et_2O$ (3x 50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mass (3.2 g) was purified by flash column chromatography on 400 g of silica with a solvent gradient of 10% EtOAc/hex to 35% EtOAc/hex to obtain **14** (851 mg, 3.04 mmol, 66% yield) as a ~12:1 mixture of diastereomers at C-1 and a 2.6:1 mixture at C-9.

For characterization purposes, the C-9 diastereomers were separated by silica gel-backed prep plate in 20% EtOAc/hex. The C-1 epimers with the same C-9 stereochemistry co-elute.

Characterization data of aldol addition adduct (**14, minor C-9 diastereomer**, 1.00:0.04 mix of C-1 epimers)**:**

*Description* Faint yellow oil

$R_f$ 0.48 in 20% EtOAc/hex. Weakly UV active. Stain peach in anisaldehyde.

Opt. Rot. Not obtained

$^1$H NMR (600 MHz, Chloroform-*d*); NMR data for major isomer
δ 5.69 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.46 (dd, *J* = 10.1, 2.7 Hz, 1H), 4.85 (p, *J* = 1.6 Hz, 1H), 4.80 (d, *J* = 2.1 Hz, 1H), 3.80 (s, 3H), 3.46 (d, *J* = 2.0 Hz, 1H), 2.96 (dq, *J* = 10.9, 6.4 Hz, 1H), 2.76 (dt, *J* = 11.0, 2.3 Hz, 1H), 1.96 (dqd, *J* = 14.4, 7.2, 2.0 Hz, 1H), 1.70 (t, *J* = 1.1 Hz, 3H), 1.55 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.15 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H).

$^{13}$C NMR (151 MHz, Chloroform-*d*); NMR data for major isomer
δ 212.8, 174.7, 145.2, 133.0, 131.1, 113.8, 80.9, 54.6, 53.5, 52.8, 45.7, 26.1, 20.4, 18.0, 11.8, 8.4.

LRMS Calculated $C_{16}H_{24}O_4$: 280.2 | Found: 280.1

X-ray N/A, oil

2D-NMR NOESY

Characterization data of aldol addition adduct (**14**, **major C-9 diastereomer**, 1.00:0.12 mix of C-1 epimers)**:**

*Description* Faint yellow oil

$R_f$ 0.39 in 20% EtOAc/hex. Weakly UV active. Stain peach in anisaldehyde.

Opt. Rot. Not obtained

$^1$H NMR (600 MHz, Chloroform-*d*); NMR data for major isomer
δ 5.86 (dd, *J* = 10.2, 2.7 Hz, 1H), 5.68 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.85 (p, *J* = 1.5 Hz, 1H), 4.81 – 4.79 (m, 1H), 3.79 (s, 3H), 3.48 (d, *J* = 0.8 Hz, 1H), 2.77 (dt, *J* = 11.2, 2.3 Hz, 1H), 2.66 (dq, *J* = 11.1, 6.4 Hz, 1H), 1.96 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.75 (dq, *J* = 13.6, 7.3 Hz, 1H), 1.69 – 1.68 (m, 3H), 1.20 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).

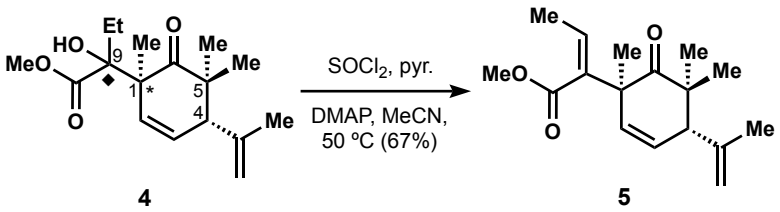
$^{13}$C NMR (151 MHz, Chloroform-*d*); NMR data for major isomer
δ 214.0, 175.4, 145.2, 131.6, 131.2, 113.8, 81.6, 54.8, 53.0, 51.8, 46.0, 26.6, 20.9, 17.9, 11.8, 8.0.

LRMS Calculated $C_{16}H_{24}O_4$: 280.2 | Found: 280.1

X-ray N/A, oil

2D-NMR NOESY

3.4 Dehydration of **4** to form **5**




**4** **5**

Procedure:

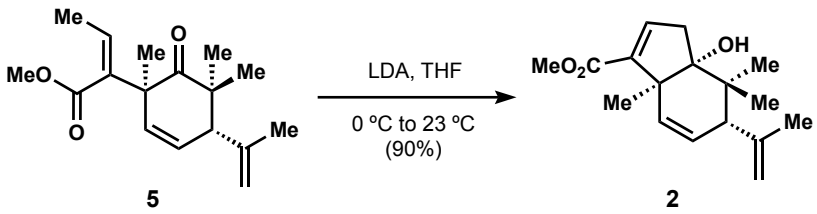
Two separate solutions were made: First, a solution of diastereomeric (3.3:1 d.r.) substrate **4** (1.47 g, 5.0 mmol, 1.0 equiv), DMAP (3.05 g, 25.0 mmol, 5.0 equiv), and non-anhydrous MeCN (50 mL, [0.1 M] with respect to substrate) was made in a 250 mL round bottom flask. Second, a solution of $SOCl_2$ (725 µL, 10.0 mmol, 2 equiv) in anhydrous pyridine (10 mL, [1 M] with respect to $SOCl_2$) under an argon atmosphere was made. The substrate/DMAP/MeCN solution was slowly added $SOCl_2$/pyr solution with vigorous stirring at 50 ºC (oil bath). The reaction was monitored by TLC. After 45 minutes, the resulting orange solution was cooled to room temperature, then poured onto a 1:1 mixture of $H_2O$:EtOAc (50 mL each). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with 1 M HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine. The combined organic layer was dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (5% EtOAc/hex to 10% EtOAc/hex) to obtain elimination product **5** (926 mg, 3.35 mmol, 67%) as a clear yellow oil.

NOTE: Toluene may be substituted for MeCN, but the reaction takes ~12 hours for a similar result.

Characterization data of dehydration product (**5**)**:**

| | |
|---|---|
| *Description* | viscous yellow oil |
| $R_f$ | 0.52 in 10% EtOAc/hex. UV active. Stains purple in anisaldehyde. |
| Opt. Rot. | $\alpha_{obs}$ = -289.5º, c=1.00 in $CH_2Cl_2$, T=22.3 ºC |
| $^1$H NMR | (600 MHz, Chloroform-*d*)<br>δ 5.84 (q, *J* = 7.1 Hz, 1H), 5.69 (dd, *J* = 10.1, 3.8 Hz, 1H), 5.66 (dd, *J* = 10.3, 0.7 Hz, 1H), 4.88 – 4.84 (m, 1H), 4.76 – 4.72 (m, 1H), 3.72 (s, 3H), 3.08 (dd, *J* = 3.7, 0.7 Hz, 1H), 1.72 (d, *J* = 7.1 Hz, 3H), 1.57 – 1.55 (m, 3H), 1.37 (s, 3H), 1.22 (s, 3H), 1.00 (s, 3H). |
| $^{13}$C NMR | (151 MHz, Chloroform-*d*)<br>δ 214.5, 168.7, 144.5, 137.3, 131.5, 129.4, 129.0, 115.4, 57.7, 51.6, 50.5, 47.5, 27.6, 26.4, 22.8, 21.2, 15.5. |
| HRMS | Calculated $C_{17}H_{25}O_3$ [M+H] 277.1804 \| Found: 277.1810 |
| X-ray | N/A, oil |
| 2D-NMR | NOESY |

3.5 Intramolecular aldol addition of **5** to form **2**




**5** **2**

Procedure:

A [0.5M] solution of LDA in THF was made by addition of *n*BuLi ([2.67M in hex], 12.0 mmol, 4.5 mL) to a solution of $HN^iPr_2$ (freshly distilled off $CaH_2$, 15.0 mmol, 2.10 mL) in anhydrous THF (17.4 mL) while cooled to -78 ºC under an argon atmosphere. After addition of *n*BuLi, the solution was stirred at 0 ºC for 20 minutes, then cooled back to -78 ºC.

A solution of substrate (>99% purity, 2.49 mmol, 687 mg) in anhydrous THF under an argon atmosphere in a flame-dried 100 mL round bottom flask was cooled to 0 ºC. The LDA solution ([0.5M], 1.1 equiv., 5.5 mL) was added in a slow but steady stream via syringe to this solution at 0 ºC, which caused the solution to turn from clear and pale yellow to clear and orange/red. The solution stirred at 0 ºC for 30 minutes, then warmed to 23 ºC and monitored by TLC (20% EtOAc/hex, Anis.). Starting material still remained after 3 hours, so 100 µL more [0.5 M] LDA was added dropwise at 23 ºC to this solution. TLC analysis indicated full consumption of starting material 1 hour after this (4 hours after the initial LDA addition).

The reaction was quenched by addition of $NH_4Cl$ (aq., saturated, ~20 mL) and dilution with EtOAc (~ 20 mL). The reaction was extracted with EtOAc (3x ~ 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mass (860 mg) was purified on silica gel (~250 mL) with 2L of 10% EtOAc/hex. The desired compound was isolated as a yellow-white solid. (620 mg, 90% yield; see NOTE 1).

NOTE 1: The yield drops significantly if the substrate is impure. The excess LDA solution is maintained at -78 ºC for the duration of the intramolecular aldol reaction. Use of a larger excess of LDA can lead to transposition of the α,β-unsaturated ester alkene and incorporation of molecular oxygen, so reaction monitoring by TLC and subsequent addition of small portions of LDA to drive the reaction to completion is preferable to use of more than 1.1 equivalents of LDA at the start of the reaction.

Characterization data of intramolecular aldol product (**2**)**:**

*Description* yellow-white solid

$R_f$ 0.52 in 10% EtOAc/hex. UV active and stains purple in anisaldehyde

Opt. Rot. $\alpha_{obs}$ = -27.6º, c=1.00 in $CH_2Cl_2$, T=21.0 ºC

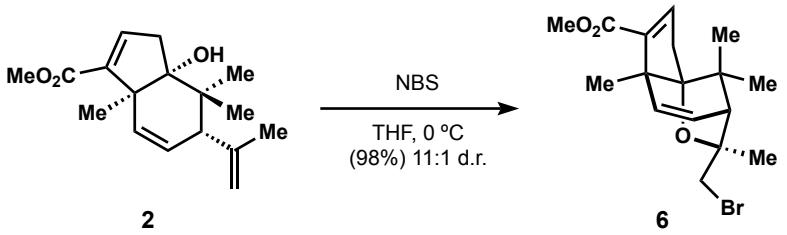
$^1$H NMR (600 MHz, Chloroform-*d*)
δ 6.67 (br dd, *J* = 3.2, 2.0 1H), 5.98 (br d, *J* = 10.3 Hz, 1H), 5.32 (br d, *J* = 10.3 Hz, 1H), 5.02 – 4.99 (br m, 1H), 4.73 (br s, 1H), 3.72 (s, 3H), 2.93 (br s, 1H), 2.92 (br d, *J* = 18.5 Hz, 1H), 2.31 (dd, *J* = 18.9, 3.2 Hz, 1H), 1.79 (s, 3H), 1.71 (br s, 1H), 1.42 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H).

$^{13}$C NMR (151 MHz, Chloroform-*d*)
δ 165.1, 145.8, 141.0, 140.6, 133.6, 126.7, 116.0, 85.4, 53.3, 52.1, 51.4, 42.6, 40.3, 24.0, 23.3, 18.8, 18.5.

HRMS Calculated $C_{17}H_{25}O_3$ [M+H]: 277.1804 | Found: 277.1810

X-ray X-ray quality crystals were grown by slow evaporation of hexanes layered on a $CDCl_3$ solution of **2** in a cylindrical recrystallization tube (~500 µL volume) placed vertically within a 20 mL scintillation vial and capped with aluminum foil.

3.6 Bromoetherification of **2** to form **6**




**2** **6**

Procedure:

A flame-dried 50 mL round bottom flask was charged with solid triene substrate **2** (1.0 equiv, 610 mg, 2.21 mmol) and a stir bar and placed under an argon atmosphere at 0 ºC in an ice-water bath. A separate flame-dried 50 mL round bottom flask was charged with NBS (recrystallized, 2.0 equiv, 4.42 mmol, 787 mg) and anhydrous THF ([0.2 M], wrt NBS) at 0 ºC in an ice-water bath and kept out of light (wrapped in foil and hood light turned off). Without stirring (See NOTE 1), the NBS/THF solution was then transferred by cannula (see NOTE 2) with differential pressure under an Argon atmosphere at 0 ºC. The solution after transfer was clear and pale yellow. The reaction was stirred at 0 ºC in the dark (fume hood lights off and the reaction flask was wrapped in foil) and monitored by TLC (15% EtOAc/hex, Anis.). No starting material remained after 2 hours.

The reaction was worked-up by addition to a mixture of $NH_4Cl$ (saturated, aq., ~50 mL) and EtOAc (~50 mL). The aqueous layer was extracted with EtOAc (3x ~ 100 mL) and then washed with $NaHCO_3$ (saturated, 1x ~ 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mass (~1.2 g) was dry-loaded with celite onto a silica column (~100 mL of silica) and purified by flash column chromatography with 15% EtOAc/hex. The desired compound was isolated as a yellow-tinged white solid. (776 mg, 98% yield, 11:1 diastereoselectivity in favor of the endo diastereomer shown above.). Isolated yields for this reaction ranged between 92 – 98% for different runs.

NOTE 1: Dissolution of the substrate in THF prior to addition of the NBS/THF solution diminishes the diastereoselectivity of the reaction. Although the diastereoselectivity of this step is technically inconsequential because the stereocenter is erased by the final zinc reduction step, low diastereoselectivity at this step complicates analysis and characterization of the products of subsequent steps.

NOTE 2: The cannula was cooled during transfer by contact with solid dry ice.

Characterization data of bromoetherification product (major diastereomer) (**6**)**:**

*Description* yellow-white powder. Can be obtained as white crystalline material by recrystallization

$R_f$ 0.37 in 10% EtOAc/hx. UV active and stains purple in anisaldehyde

Opt. Rot. $\alpha_{obs}$ = -14.7º, c=1.00 in $CH_2Cl_2$, T=21.5 ºC (on 11:1 diastereomeric mixture)

$^1$H NMR (600 MHz, Chloroform-*d*)

δ 6.53 (dd, *J* = 3.5, 2.2 Hz, 1H), 6.25 (d, *J* = 9.6 Hz, 1H), 5.97 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.72 (s, 3H), 3.66 (dd, *J* = 9.2, 1.1 Hz, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 2.59 (ddd, *J* = 18.1, 2.2, 0.7 Hz, 1H), 2.46 (ddd, *J* = 18.2, 3.6, 0.8 Hz, 1H), 2.21 (d, *J* = 6.9 Hz, 1H), 1.65 (d, *J* = 1.0 Hz, 3H), 1.29 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H).

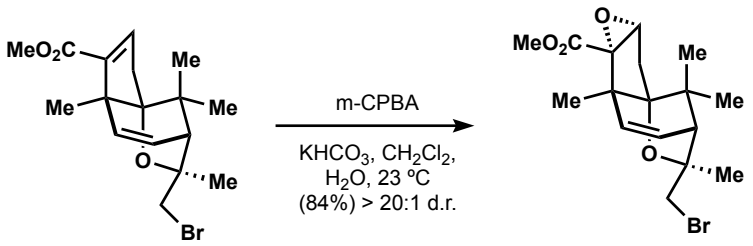
$^{13}$C NMR (151 MHz, Chloroform-*d*)

δ 164.3, 142.7, 139.1, 132.7, 128.0, 95.9, 85.2, 52.9, 52.8, 51.4, 46.2, 42.9, 32.1, 27.2, 27.0, 26.2, 20.6.

HRMS Calculated $C_{17}H_{24}BrO_3$ [M+H] 355.0909 | Found: 355.0907

X-ray Crystals were grown by slow evaporation from $CH_2Cl_2$ then hexanes in a cylindrical recrystallization (~ 500 μL volume) placed vertically within a 20 mL scintillation vial and capped with aluminum foil at room temperature. The starting material was a 7.25:1.00 diastereomeric mixture.

3.7 Epoxidation of **6** to form **7**




**6** **7**

Procedure:

To a suspension of substrate **6** (2.5 g, 7.0 mmol, 1 equiv) in $CH_2Cl_2/H_2O$ (5:1, v:v, 120 mL) was added $KHCO_3$ (5.6 g, 56.0 mmol, 8 equiv) and stirred vigorously for 15 min. The biphasic reaction mixture was then cooled to 0 ºC and *m*CPBA (50% purity, 9.66 g, 28.0 mmol, 4 equiv) was slowly added portion-wise. The solution was stirred vigorously for 2 hours at room temperature, during which time a white precipitate formed. TLC indicated starting material consumption. The reaction was quenched by slowly adding a saturated $Na_2S_2O_3$ solution (aq., 20 mL) at 0ºC, then diluted by $H_2O$ (100 mL) and $CH_2Cl_2$ (200 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (5% EtOAc/Hexane) to afford epoxide **7** (2.18 g, 5.88 mmol, 84%) as a single diastereomer.

Characterization data of epoxidation product (**7**)**:**

*Description* yellow-white powder. Can be obtained as white crystalline material by recrystallization

$R_f$ 0.28 in 10% EtOAc/hex. Stains purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -36.0º, c=1.00 in $CH_2Cl_2$, T=22.0 ºC

$^1$H NMR (600 MHz, Chloroform-*d*)

δ 6.20 (dd, *J* = 9.6, 0.7 Hz, 1H), 6.02 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.75 (dd, *J* = 4.1, 1.0 Hz, 1H), 3.71 (s, 3H), 3.60 (dd, *J* = 9.2, 1.1 Hz, 1H), 3.31 (d, *J* = 9.2 Hz, 1H), 2.23 (d, *J* = 6.9 Hz, 1H), 2.12 (ddd, *J* = 14.6, 4.2, 0.9 Hz, 1H), 1.84 (dt, *J* = 14.6, 1.0 Hz, 1H), 1.61 (d, *J* = 1.1 Hz, 3H), 1.29 (s, 4H), 1.16 (s, 3H), 1.14 (s, 3H).

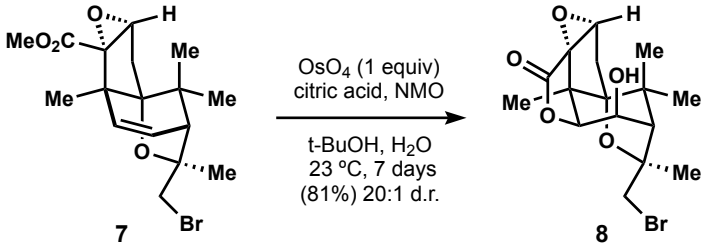
$^{13}$C NMR (151 MHz, Chloroform-*d*)

δ 168.1, 133.1, 127.6, 99.4, 85.9, 66.0, 61.5, 52.5, 52.0 (observed by HSQC), 48.2, 46.6, 42.6, 29.3, 28.1, 26.2, 24.2, 17.1.

HRMS Calculated $C_{17}H_{24}BrO_4$ [M+H]: 371.0858 | Found: 371.0856

X-ray Crystals were grown by slow evaporation at room temperature of a solution of **7** in hexanes from a cylindrical glass tube (~ 500 μL volume) placed vertically within a 20 mL glass vial capped with aluminum foil.

3.8 Dihydroxylation of **7** to form **8**




Procedure:

A 1 L round bottom flask was charged with a magnetic stir bar, the alkene substrate **7** (3.31 g, 8.92 mmol, 1 equiv), citric acid (3.43 g, 17.84 mmol, 2 equiv), NMO (3.13 g, 26.76 mmol, 3 equiv), and *t*-BuOH (57 mL). During this time, the fume hood lights were turned off and the reaction was wrapped with aluminum foil to minimize exposure to ambient light. $OsO_4$ (57 mL, 4 wt% in $H_2O$, 9.37 mmol, 1.05 equiv, NOTE 1) was then added at room temperature in the dark. The reaction was capped with a yellow cap (a 24/40 polyethylene flask stopper), sealed with duct tape, and stirred vigorously (>1000 rpm) for 7 days at room temperature. During the course of the reaction, the yellow cap was stained black by osmium tetroxide. The reaction was quenched by adding a saturated solution of $Na_2S_2O_3$ (20 mL) after cooling the reaction to 0 ºC. After stirring for 15 min, the dark yellow solution changed to black suspension, hood lamps were turned on, the reaction mixture was diluted with EtOAc (200 mL), then extracted with EtOAc (3 x 300 mL). The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel (30% EtOAc/Hexane to 50% EtOAc/Hexane) to afford desired dihydroxylation product **8** (2.7 g, 7.23 mmol, 81%, 89% brsm) as single diastereoisomer. Starting material **7** (298 mg, 0.8 mmol, 9%) was recovered.

NOTE 1: $OsO_4$ 4 wt% in $H_2O$ is a commercially available greenish solution. It may also be made from $OsO_4$ solid in deionized $H_2O$. $OsO_4$ is a highly toxic volatile solid so use of an efficient fume hood is strongly recommended for this procedure.

Characterization data of dihydroxylation product (**8**)**:**

*Description* white foam/powder

$R_f$ 0.41 in 50% EtOAc/Hex. Anis. Stains dark blue/purple.

Opt. Rot. $\alpha_{obs}$ = 2.4º, c=1.00 in $CH_2Cl_2$, T=20.7 ºC

$^1$H NMR (600 MHz, Chloroform-*d*)

δ 4.78 (d, *J* = 8.8 Hz, 1H), 4.70 (ddd, *J* = 8.9, 3.5, 1.5 Hz, 1H), 3.89 (dd, *J* = 3.9, 1.6 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 3.28 (d, *J* = 10.4 Hz, 1H), 2.23 (dd, *J* = 14.6, 3.9 Hz), 2.24 – 2.21 (m, 2H), 1.96 (ddd, *J* = 14.6, 1.6, 0.9 Hz, 1H), 1.65 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H).

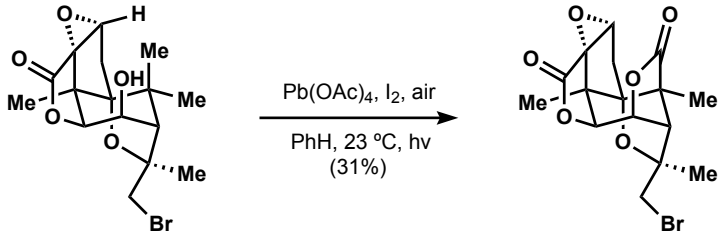
$^{13}$C NMR (151 MHz, Chloroform-*d*)

δ 170.7, 100.6, 82.4, 79.4, 68.4, 67.7, 63.1, 56.9, 44.3, 44.1, 40.9, 31.8, 29.8, 27.5, 22.7, 18.7.

HRMS(M+H) Calculated $C_{16}H_{22}BrO_5$ [M+H]: 373.0651 | Found: 373.0646

X-ray Crystals were grown by slow evaporation from hexanes/EtOAc (5:1) in a 5 mL vial covered with Teflon tape at room temperature.

3.9 Oxidation of **8** to **18**




**8** **18**

Procedure:

To a solution of $Pb(OAc)_4$ (592 mg, 1.34 mmol, 5 equiv, NOTE 1) in benzene (10 mL) was added $I_2$ (340 mg, 1.34 mmol, 5 equiv) in the dark (covered with aluminum foil and hood light turned-off) at room temperature and stirred for 30 min. To a suspension of **8** (100 mg, 0.27 mmol, 1 equiv) and $CaCO_3$ (270 mg, 2.7 mmol, 10 equiv) in benzene (5 mL) was added the $Pb(OAc)_4/I_2$/benzene solution at room temperature. The hood lamps were turned on and the reaction was vigorously stirred at room temperature under ambient light for 2.5 h. Consumption of **8** was monitored by TLC. The reaction was quenched by saturated $Na_2S_2O_3$ (5 mL) at 0 ºC then filtered through a short pad of Celite, washed with EtOAc (3 x 10 mL). The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (50% EtOAc/Hexane) to afford 5-methyl-bromopicrotoxinin **18** (32 mg, 0.084 mmol, 31%) as a white solid.

NOTE 1: Commercially available $Pb(OAc)_4$ is stabilized with AcOH, pure $Pb(OAc)_4$ could be freshly recrystallized from AcOH, then washed three times with hexane prior to use.

Characterization data of oxidation product (**18**)**:**

*Description* clear to white amphorous solid

$R_f$ 0.51 in 50% EtOAc/hex. Stains weakly grey/green in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -17.0º, c=0.50 in $CH_2Cl_2$, T=20.0 ºC

$^1$H NMR (600 MHz, Chloroform-*d*)

δ 5.22 (t, *J* = 5.3 Hz, 1H), 4.76 (d, *J* = 5.2 Hz, 1H), 3.96 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.52 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.41 (d, *J* = 10.7 Hz, 1H), 3.16 (dd, *J* = 5.5, 0.9 Hz, 1H), 2.46 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.94 (dt, *J* = 14.4, 1.3 Hz, 1H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.56 (s, 3H), 1.36 (s, 3H).

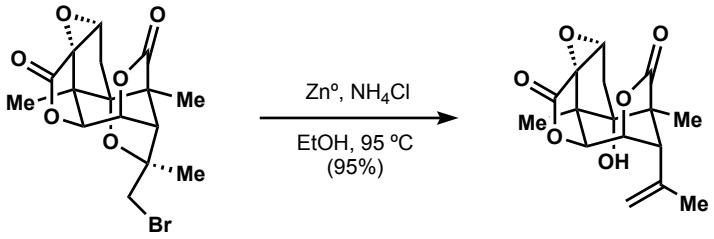
$^{13}$C NMR (151 MHz, Chloroform-*d*)

δ 173.6, 168.3, 97.3, 84.2, 78.3, 75.8, 67.7, 63.3, 60.5, 53.9, 47.8, 36.8, 33.9, 26.5, 19.7, 17.4.

HRMS Calculated $C_{16}H_{18}BrO_6$ [M+H]: 385.0287 | Found: 385.0279

X-ray Crystals were grown by slow evaporation from hexanes/$CH_2Cl_2$ (1:1) in a 5 mL vial covered with Teflon tape at room temperature.

3.10 Reductive debromination of **18** to form 5-methyl-picrotoxinin (**20**)




**18** **20**

Procedure:

Zinc powder (55 mg, 0.84 mmol, 10 equiv), $NH_4Cl$ (90 mg, 1.68 mmol, 20 equiv) were added into a solution of 5-methyl-bromopicrotoxinin **18** (32 mg, 0.084 mmol, 1 equiv) in EtOH/$H_2O$ (v:v, 10:1, 6.6 mL). Then the reaction was warmed up to 95 ºC and stirred at this temperature for 2 h. The reaction mixture was diluted by EtOAc (5 mL) then filtered through a short pad of Celite and washed with EtOAc (3 x 3 mL). The reaction mixture was concentrated and purified by column chromatography over silica gel (10% EtOAc/$CH_2Cl_2$) to give 5-methyl-picrotoxinin **20** (24.4 mg, 0.08 mmol, 95%) as a white solid.

Characterization data of 5-methyl-picrotoxinin (**20**):

*Description* white crystalline solid

$R_f$ 0.31 in 40% EtOAc/hex. Stains brown in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -1.2º, c=0.10 in $CH_2Cl_2$, T=20.0 ºC

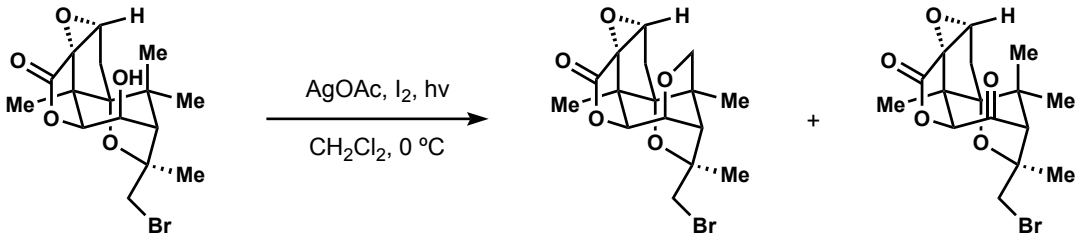
$^1$H NMR (600 MHz, Chloroform-*d*)
δ 5.11 (p, *J* = 1.6 Hz, 1H), 5.05 (d, *J* = 2.1 Hz, 1H), 5.02 (dd, *J* = 5.2, 3.4 Hz, 1H), 4.83 (d, *J* = 3.4 Hz, 1H), 3.70 (dd, *J* = 3.6, 0.7 Hz, 1H), 3.14 (d, *J* = 5.1 Hz, 1H), 2.97 (dd, *J* = 15.3, 3.6 Hz, 1H), 1.96 (dt, *J* = 1.6, 0.9 Hz, 3H), 1.88 (s, 1H), 1.75 (d, *J* = 15.3 Hz, 1H), 1.53 (s, 3H), 1.26 (s, 3H).

$^{13}$C NMR (151 MHz, Chloroform-*d*)
δ 177.2, 168.9, 139.4, 115.6, 88.7, 80.2, 76.1, 72.6, 62.0, 53.9, 51.0, 47.4, 42.5, 24.3, 17.1, 17.0.

HRMS Calculated $C_{16}H_{19}O_6$ [M+H]: 307.1182 | Found: 307.1178

X-ray Crystals were grown by slow evaporation of a solution of **20** in $CDCl_3$ in a small cylindrical glass recrystallization tube (~ 500 µL volume) placed vertically within a 20 mL scintillation vial and capped with aluminum foil at room temperature.

3.11 Etherification of **8** to form **9**




Procedure:

Two reactions were carried out in parallel. To a suspension of alcohol **8** (2 x (50 mg, 0.13 mmol, 1 equiv)) and AgOAc (2 x (109 mg, 0.65 mmol, 5 equiv)) in $CH_2Cl_2$ (2 x 5 mL) was added $I_2$ (2 x (165 mg, 0.65 mmol, 5 equiv) as solid at 0ºC. The reaction was vigorously stirred under ambient light for 1 hour, then quenched with saturated $Na_2S_2O_3$ (aq., 0.5 mL each) at 0 ºC. The two reactions were combined, filtered through a short pad of celite and washed with $CH_2Cl_2$ (3 x 10 mL). The crude product was concentrated *in vacuo* and then purified by column chromatography over silica gel (5% EtOAc/$CH_2Cl_2$ to 10% EtOAc/$CH_2Cl_2$) to give ether **9** (49 mg, 0.13 mmol, 51%) as colorless foam and the major byproduct, ketone **15** (17 mg, 0.047 mmol, 18%), as pale yellow solid.

Characterization data of ether **9**:

*Description* colorless oil/foam

$R_f$ 0.51 in 10% EtOAc/$CH_2Cl_2$. Stains dark blue in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -64.3º, c=2.00 in $CH_2Cl_2$, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)

δ 4.75 (dd, *J* = 5.8 Hz, *J* = 4.9 Hz, 1H), 4.63 (d, *J* = 5.8 Hz, 1H), 4.02 (d, *J* = 11.1 Hz, 1H), 3.93 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.71 (d, *J* = 11.1 Hz, 1H), 3.42 (d, *J* = 10.7 Hz, 1H), 3.34 (d, *J* = 10.7 Hz, 1H), 2.68 (d, *J* = 4.9 Hz, 1H), 2.32 (dd, *J* = 14.6, 3.8 Hz, 1H), 1.99 (d, *J* = 14.6 Hz, 1H), 1.59 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$)

δ 169.8, 100.1, 81.8, 81.6, 77.0 (overlaps with $CDCl_3$), 71.8, 69.0, 62.4, 60.6, 54.7, 46.1, 38.7, 33.5, 26.7, 21.6, 18.1.

HRMS Calculated $C_{16}H_{20}BrO_5$ [M+H]: 371.0494 | Found: 371.0489

X-ray not obtained

Characterization data of ketone **15**:

*Description* pale yellow solid

$R_f$ 0.57 in 5% EtOAc/$CH_2Cl_2$. Stains blue in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -43.0º, c=0.50 in $CH_2Cl_2$, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)

δ 4.51 (s, 1H), 3.94 (dd, *J* = 3.8, 1.6 Hz, 1H), 3.27 (d, *J* = 11.0 Hz, 1H), 3.22 (d, *J* = 11.0 Hz, 1H), 2.84 (s, 1H), 2.34 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.12 (ddd, *J* = 14.7, 1.6, 0.9 Hz, 1H), 1.62 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.13 (s, 3H).

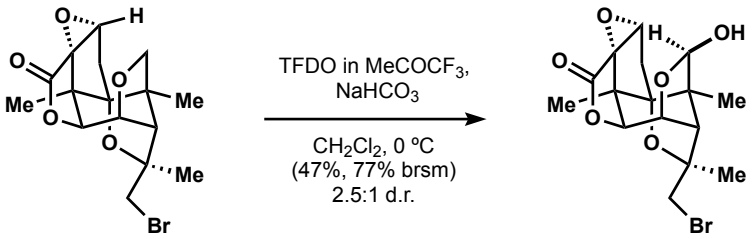
$^{13}$C NMR (150 MHz, $CDCl_3$)

δ 202.3, 169.4, 100.6, 82.8, 81.6, 69.4, 68.1, 63.0, 47.6, 45.2, 39.3, 32.1, 28.7, 26.8, 21.7, 18.1.

HRMS Calculated $C_{16}H_{20}BrO_5$ [M+H]: 371.0494 | Found: 371.0491.

X-ray Crystals were grown by slow evaporation from $CH_2Cl_2$ in a 5 mL vial covered with Teflon tape at room temperature.

3.12 TFDO oxidation of **9** to form **10**



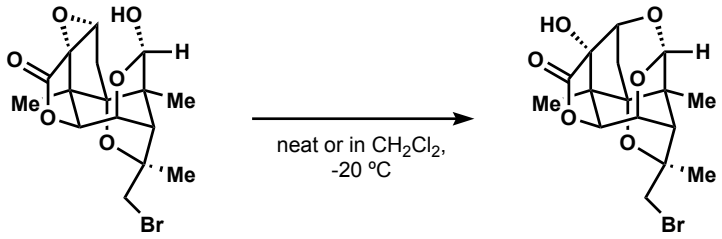

**9** **10**

Procedure:

To a 20 mL vial was charged ether **9** (60 mg, 0.16 mmol, 1 equiv) and $NaHCO_3$ (59 mg, 0.7 mmol, 4.4 equiv) in $CH_2Cl_2$ (1.5 mL). During this time, the fume hood lights were turned off and the reaction was wrapped with aluminum foil to minimize exposure to ambient light. A TFDO solution (~0.5 M in 1,1,1-trifluoroacetone, 3 mL, 1.5 mmol, 9.4 equiv, NOTE 1) was added dropwise at 0 ºC. The reaction was vigorously stirred for 6 h in the dark, then quenched with saturated $Na_2S_2O_3$ (0.5 mL) at 0 ºC. The mixture was warmed up slowly to room temperature and filtered through a short pad of Celite and washed with $CH_2Cl_2$ (2 x 10 mL). The crude product was concentrated *in vacuo* and then purified by column chromatography over silica gel (10% EtOAc/$CH_2Cl_2$ to 30% EtOAc/$CH_2Cl_2$). The desired lactol **10** (29 mg, 0.075 mmol, 47%, 77% brsm) was obtained as a colorless oil diastereomer mixture (dr~2.5:1), **9** (23.8 mg, 0.064 mmol, 40%) was recovered (NOTE 2).

NOTE 1: A methyl(trifluoromethyl)dioxirane (TFDO) solution in trifluoroacetone was prepared according to *Tetrahedron* **1996**, *52*, 2377–2384 or Baran's TFDO Synthesis Procedure (http://openflask.blogspot.com/2014/01/tfdo-synthesis-procedure.html). The TFDO solution should be titrated before use. A 0.1 mL TFDO solution was added into the mixture of 0.5 mL $H_2O$, 1.5 mL AcOH and 0.25 mL saturated KI at -78ºC. This dark red solution was then titrated with 0.05 M $Na_2S_2O_3$ at room temperature.

NOTE 2: The endo lactol epimer of **10** was observed to irreversibly decompose via intramolecular epoxide opening (***endo*-10** to **SI-2**) during storage either neat or as solution in $CH_2Cl_2$ in a -20 ºC freezer. The less polar **SI-2** could be isolated as a white solid. Due to decomposition, using lactol **10** directly with minimal storage time is strongly recommended.




***endo*-10** **SI-2**

Characterization data of lactol **10** (major diastereomer):

*Description* colorless oil

*$R_f$* 0.37 in 30% EtOAc/$CH_2Cl_2$. Stains red purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -42.5º, c=1.00 in $CH_2Cl_2$, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)
δ 5.33 (s, 1H), 4.88 (dd, *J* = 5.4 Hz, *J* = 5.2 Hz 1H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.11 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 3.35 (d, *J* = 10.6 Hz, 1H), 2.91 (d, *J* = 5.2 Hz, 1H), 2.47 (dd, *J* = 14.6, 3.8 Hz, 1H), 1.96 (d, *J* = 14.6 Hz, 1H), 1.58 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H).

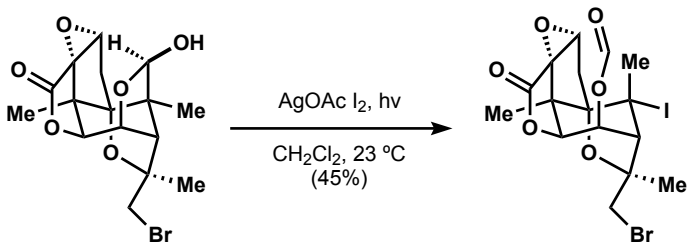
$^{13}$C NMR (150 MHz, $CDCl_3$)
δ 170.4, 98.7, 96.7, 82.7, 81.0, 76.6, 68.4, 62.4, 59.1, 57.6, 46.6, 38.6, 33.6, 26.5, 19.4, 17.8.

HRMS Calculated $C_{16}H_{20}BrO_6$ [M+H]: 387.0443 | Found: 387.0439.

X-ray N/A, oil

2D-NMR NOESY

3.13 Fragmentation of **10** to form **11**




**10** **11**

Procedure:

A 25 mL screw cap test tube was charged with a solution of lactol **10** (20 mg, 0.052 mmol, 1 equiv) in $CH_2Cl_2$ (3 mL), AgOAc (52 mg, 0.31 mmol, 6 equiv) and $I_2$ (79 mg, 0.31 mmol, 6 equiv) in the dark. (The hood lights were kept off during this process and the reaction was wrapped with aluminum foil). After stirring for 10 min in the dark, the hood lamps were turned on, and the reaction was vigorously stirred at room temperature under ambient light for 1 hour. The reaction was monitored by TLC for consumption of starting material. The reaction was quenched by saturated $Na_2S_2O_3$ (0.5 mL) then filtered through a short pad of Celite, washed with $CH_2Cl_2$ (3 x 5 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (15% EtOAc/Hexane) to afford iodide formate **11** (12 mg, 0.023 mmol, 45%) as a colorless oil.

NOTE: Due to the sensitivity of iodide formate **11** to light, storage of this compound in a $CH_2Cl_2$ solution covered with aluminum foil in the -20 ºC freezer is recommended.

Characterization data of iodide **11**:

*Description* colorless oil

*$R_f$* 0.63 in 33% EtOAc/Hexane. Stains brown in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = +24.0º, c=0.40 in $CHCl_3$, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)
δ 8.09 (d, *J* = 1.1 Hz, 1H), 5.55 (d, *J* = 8.7 Hz, 1H), 4.95 (d, *J* = 8.7 Hz, 1H), 4.01 (dd, *J* = 3.9, 1.6 Hz, 1H), 3.44 (d, *J* = 10.6 Hz, 1H), 3.36 (d, *J* = 10.6 Hz, 1H), 2.99 (d, *J* = 1.4 Hz, 1H), 2.81 (dd, *J* = 15.1, 4.0 Hz, 1H), 2.59 (s, 3H), 2.22 – 2.14 (m, 4H), 1.35 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$)

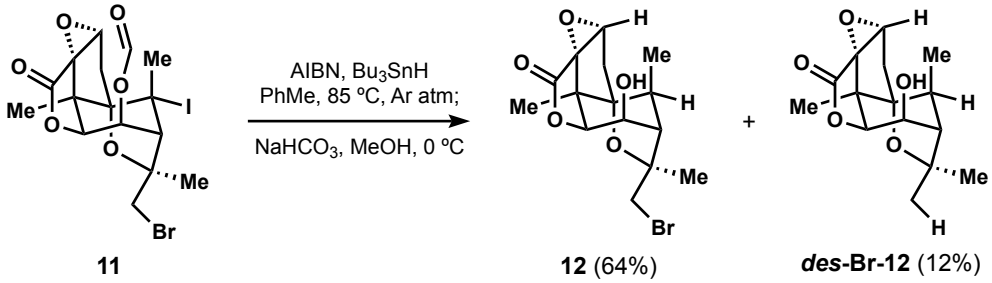
δ 169.7, 159.0, 102.8, 83.8, 76.5, 68.7, 68.1, 62.8, 60.5, 58.9, 44.1, 40.2, 39.7, 32.6, 28.9, 20.0.

HRMS Calculated $C_{16}H_{19}BrIO_6$ [M+H]: 512.9410 | Found: 512.9401.

X-ray N/A, oil

2D-NMR NOESY

3.14 Reductive deiodination and deformylation of **11** to **12**




Procedure:

To a 10 mL microwave tube were added a solution of iodide formate **11** (24 mg, 0.047 mmol, 1 equiv) in toluene (5 mL, freshly distilled over sodium and benzophenone), AIBN (3.8 mg, 0.023 mmol, 0.5 equiv) and *n*$Bu_3SnH$ (16 μL, 0.061 mmol, 1.3 equiv) in the dark. The reaction mixture was then degassed using 5 freeze-pump-thaw cycles. (Each freeze-pump-thaw cycle was conducted as described: the reaction mixture was frozen in liquid $N_2$ for 10 min, then evacuated under high vacuum and backfilled with argon gas three times. The mixture was then warmed up to room temperature to melt the solid.) The reaction mixture was heated at 85 ºC for 30 min and consumption of starting material was monitored by TLC. Upon completion, the solvent was removed under high vacuum to give a pale-yellow residue. The residue was cooled to 0 ºC, then methanol (4 mL) and a saturated $NaHCO_3$ (0.2 mL) solution were added. After stirring at 0ºC for 1 h, reaction was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (50% EtOAc/Hexane) to afford **12** (10.8 mg, 0.03 mmol, 64%) as a colorless oil and ***des*-Br-12** (1.5 mg, 0.006 mmol, 12%) as a white solid.

NOTE 1: To minimize decomposition of ambient light-sensitive iodide formate **11**, all manipulations of this reaction should be conducted with minimal exposure to light. The hood lights were kept off during this process and the reaction was wrapped with aluminum foil.

NOTE 2: Five freeze-pump-thaw cycles were found to be necessary for efficient reduction of the tertiary iodide **11**. Less thorough degassing procedures allow for oxygen incorporation at C5.

Characterization data of **12**:

*Description* colorless oil

$R_f$ 0.56 in 50% EtOAc/Hexane. Stains purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -3.2º, c=0.25 in $CHCl_3$, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)
δ 4.77 (d, *J* = 8.5 Hz, 1H), 4.64 (d, *J* = 8.4 Hz, 1H), 3.87 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.36 (d, *J* = 10.4 Hz, 1H), 3.20 (d, *J* = 10.4 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.33 (d, *J* = 3.9 Hz, 1H), 2.16 (d, *J* = 14.3 Hz, 1H), 2.06 (dd, *J* = 14.3, 3.8 Hz, 1H), 1.49 (s, 3H), 1.24 (d, *J* = 8.0 Hz, 3H), 1.13 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$)

δ 170.4, 97.2, 83.0, 78.8, 68.2, 66.2, 62.3, 51.4, 42.3, 42.1, 37.4, 35.9, 27.1, 17.8, 11.9.

HRMS Calculated $C_{15}H_{20}BrO_5$ [M+H]: 359.0494 | Found: 359.0497.

2D-NMR NOESY

Characterization data of ***des*-Br-12**:

*Description* white solid

$R_f$ 0.32 in 50% EtOAc/Hexane. Stains purple in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = +22.9º, c=0.14 in MeOH, T=20.0 ºC

$^1$H NMR (600 MHz, $CDCl_3$)

δ 4.75 (d, *J* = 8.5 Hz, 1H), 4.52 (d, *J* = 8.5 Hz, 1H), 3.86 (dd, *J* = 3.8, 1.4 Hz, 1H), 2.36 (ddd, *J* = 7.9, 4.0, 1.4 Hz, 1H), 2.13 (t, *J* = 7.5 Hz, 2H), 2.08 – 2.00 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.22 (d, *J* = 8.0 Hz, 3H), 1.14 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$)

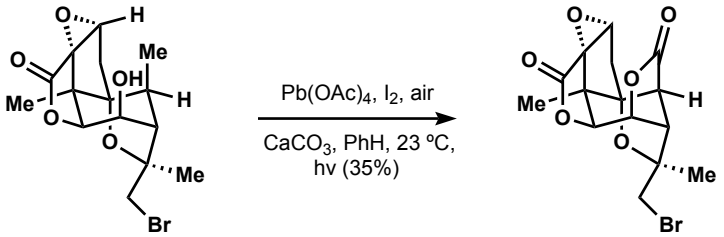
δ 170.8, 96.6, 81.7, 79.1, 68.3, 67.3, 62.6, 52.4, 42.4, 42.1, 35.9, 30.9, 25.9, 17.8, 12.0.

HRMS Calculated $C_{15}H_{21}O_5$ [M+H]: 281.1389 | Found: 281.1383.

X-ray Crystals were grown by slow evaporation from hexanes/EtOAc (2:1) in a 5 mL vial covered with Teflon tape at room temperature.

2D-NMR NOESY

3.15 Oxidation of **12** to bromopicrotoxinin (**SI-3**)




Procedure:

To a solution of $Pb(OAc)_4$ (53 mg, 0.12 mmol, 5 equiv, freshly recrystallized from AcOH, then washed three times with hexane) in benzene (2 mL) was added $I_2$ (30 mg, 0.12 mmol, 5 equiv) in the dark (covered with aluminum foil and hood light turned off) at room temperature and stirred for 30 min. To a suspension of **12** (8.6 mg, 0.024 mmol, 1 equiv), $CaCO_3$ (24 mg, 0.24 mmol, 10 equiv) in benzene (1 mL) was added the $Pb(OAc)_4/I_2$/PhH solution at room temperature under ambient atmosphere. The hood lamps were turned on, and the reaction was vigorously stirred at room temperature under ambient light for 2.5 hours. Consumption of starting material was monitored by TLC. The reaction was quenched with saturated $Na_2S_2O_3$ (0.5 mL) then filtered through a short pad of celite, washed with EtOAc (3 x 5 mL), and concentrated *in vacuo*. The crude product was purified by prep thin layer chromatography (50% EtOAc/Hexane) to afford bromopicrotoxinin **SI-3** (3.1 mg, 0.008 mmol, 35%) as a white solid.

Characterization data of **SI-3**:

*Description* white solid

$R_f$ 0.53 in 50% EtOAc/Hexane. Stains brown in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -123.6º, c=0.28 in $CH_2Cl_2$, T=20.0 ºC [*cf. JACS* **1989**, *111*, 3728: $[\alpha]^{27}_D$ = -126º (c=0.21, $CHCl_3$)]

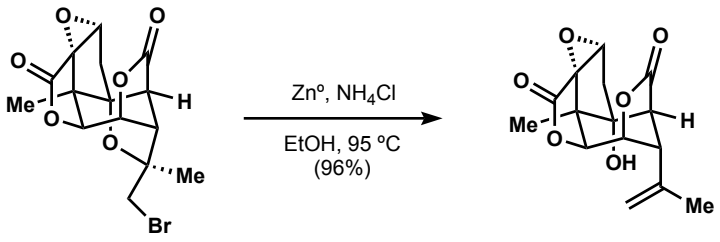
$^1$H NMR (600 MHz, $CDCl_3$)
δ 5.23 (td, *J* = 5.2, 1.0 Hz, 1H), 4.71 (d, *J* = 5.1 Hz, 1H), 4.06 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.51 – 3.40 (m, 3H), 3.06 (dd, *J* = 5.3, 0.8 Hz, 1H), 2.45 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.27 – 2.19 (m, 1H), 1.56 (s, 3H), 1.33 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$)
δ 170.3, 168.1, 94.7, 85.0, 77.63, 77.59, 67.7, 63.3, 55.7, 54.2, 47.2, 38.4, 35.4, 27.9, 16.9.

HRMS Calculated $C_{15}H_{16}BrO_6$ [M+H]: 371.0130 | Found: 371.0128.

X-ray Crystals were grown by slow evaporation of a solution of **SI-3** in hexanes, EtOAc, $CH_2Cl_2$, and MeOH at room temperature from a cylindrical glass recrystallization tube placed vertically within a 20 mL scintillation tube and capped with aluminum foil.

3.16 Reductive debromination of bromopicrotoxinin (**SI-3**) to form picrotoxinin (**1**)




**SI-3** (–)-picrotoxinin **(1)**

Procedure:

Zinc powder (10 mg, 0.15 mmol, 10 equiv), $NH_4Cl$ (16 mg, 0.3 mmol, 20 equiv) were added into a solution of bromopicrotoxinin (**SI-3**) (5.3 mg, 0.015 mmol, 1 equiv) in EtOH/$H_2O$ (v:v, 10:1, 2.2 mL). Then the reaction was warmed up to 95 ºC and stirred at this temperature for 2 hours. The reaction mixture was diluted by EtOAc then filtered through a short pad of Celite and washed with EtOAc (3 x 2 mL). The reaction mixture was concentrated and purified by prep thin layer chromatography (10% EtOAc/$CH_2Cl_2$) to give picrotoxinin (**1**) (4.2 mg, 0.014 mmol, 96%) as a white solid.

Characterization data of picrotoxinin (**1**):

*Description* white solid

$R_f$ 0.38 in 10% EtOAc/$CH_2Cl_2$. Stains dark blue in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -9.5º, c=0.20 in $CHCl_3$, T=20.0 ºC [*cf. JACS* **1984**, *106*, 4547: $[\alpha]^{27}_D$ = -6.7º (c=1.03, $CHCl_3$)]

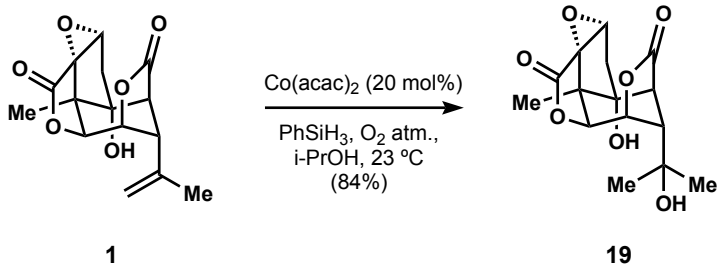
$^1$H NMR (600 MHz, $CDCl_3$) δ 5.17 – 5.01 (m, 2H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.85 (d, *J* = 1.9 Hz, 1H), 3.74 (d, *J* = 3.0 Hz, 1H), 3.44 (s, 1H), 2.97 (dd, *J* = 15.1, 3.6 Hz, 2H), 1.99 (d, *J* = 15.1 Hz, 1H), 1.96 – 1.89 (m, 3H), 1.25 (s, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$) δ 173.8, 168.7, 139.8, 113.6, 86.3, 79.6, 77.2, 72.4, 61.6, 50.8, 48.7, 46.7, 44.7, 23.3, 16.6.

HRMS Calculated: $C_{15}H_{17}O_6$ [M+H]: 293.1025 | Found: 293.1029.

X-ray Crystals were grown by slow evaporation of a solution of **1** in $CDCl_3$ at room temperature from a cylindrical glass recrystallization tube placed vertically within a 20 mL scintillation tube and capped with aluminum foil.

3.17 Mukaiyama hydration of picrotoxinin (**1**) to form picrotin (**19**)




**1** **19**

Procedure:

To a solution of **1** (18 mg, 0.062 mmol, 1 equiv) in iPrOH (0.4 mL) was added $Co(acac)_2$ (1.7 mg, 0.0068 mmol, 0.11 equiv) and $PhSiH_3$ (7.4 mg, 0.068 mmol, 1.1 equiv). The reaction was fitted with a balloon of $O_2$ and purged with sonication for 5 min. The reaction was stirred at room temperature for 2 hours at which time TLC analysis showed consumption of starting material. The reaction mixture was concentrated and purified by silica column chromatography to give picrotin (**19**) (16 mg, 84%) as a white solid.

Characterization data of picrotin (**19**):

*Description* white solid

$R_f$ 0.16 in 20% EtOAc/Hexane. Stains dark blue in anisaldehyde.

Opt. Rot. $\alpha_{obs}$ = -43.3º, c=0.24 in EtOH, T=20.0 ºC (*cf. JACS* **1989**, *111*, 3728: $[\alpha]^{25}_D$ = -69.9º (c=1.07, EtOH))

$^1$H NMR (600 MHz, Acetone-*d*) δ 5.91 (d, *J* = 3.5 Hz, 1H), 5.58 (d, *J* = 1.3 Hz 1H), 5.18 (ddd, *J* = 5.1, 3.4, 0.7 Hz, 1H), 4.98 (d, *J* = 3.4 Hz, 1H), 3.69 (d, *J* = 3.3 Hz, 1H), 3.06 (ddd, *J* = 5.2, 3.9, 1.1 Hz, 1H), 2.99 – 2.93 (m, 3H), 2.88 (ddd, *J* = 14.9, 3.6, 2.0 Hz, 1H), 2.13 (d, *J* = 14.3 Hz, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H).

$^{13}$C NMR (150 MHz, Acetone-*d*) δ 175.2, 170.1, 85.9, 81.3, 78.5, 74.1, 69.7, 62.3, 53.2, 51.3, 48.7, 44.0, 30.0, 28.8, 16.4. (*cf. Phytochem. Anal.* **2001**, *12*, 69. references the $^1$H NMR spectrum to 2.15 ppm, $^{13}$C NMR spectrum 206.15 ppm)

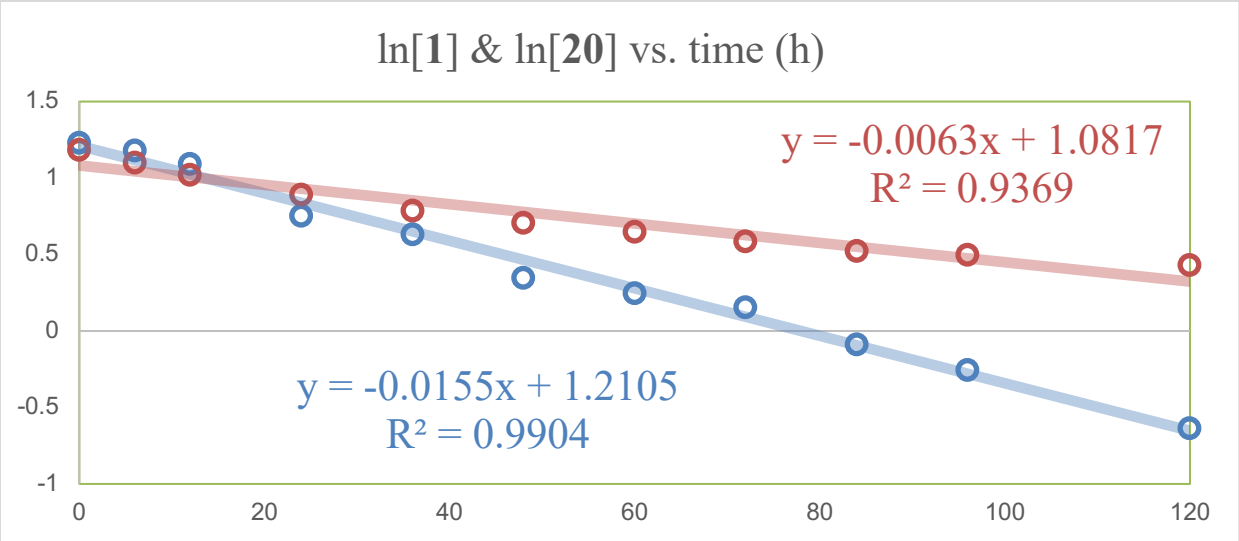
HRMS Calculated: $C_{15}H_{19}O_7$ [M+H]: 311.1131 | Found: 311.1134.

X-ray The crystal structure of PTN has previously been reported: *Acta Crystallographica, Section B: Structural Crystallography and Crystal Chemistry* (**1976**), *B32*(11), 2987-93.

3.18 Hydrolytic stability study of picrotoxinin (**1**) vs (**20**)

In separate 5 mm NMR tubes, picrotoxinin (**1**, 1 mg) or 5-methyl picrotoxinin (**20**, 1 mg) were dissolved in 1 mL of 100 mM phosphate buffer (pH = 8, prepared with $D_2O$). Spectra were acquired at 0, 6, 12, 24, 36, 48, 60, 72, 84, 96, and 120 h. and monitored for the amount of hydrolysis product.

| Time (h) | [PXN] (mM) | ln[PXN] | [5MePXN] (mM) | ln[5MePXN] |
|---|---|---|---|---|
| 0 | 3.42 | 1.229640551 | 3.27 | 1.184789985 |
| 6 | 3.25714286 | 1.180850387 | 3 | 1.098612289 |
| 12 | 2.97391304 | 1.089878609 | 2.771186441 | 1.019275546 |
| 24 | 2.1242236 | 0.753406372 | 2.440298507 | 0.892120371 |
| 36 | 1.87912088 | 0.63080405 | 2.194630872 | 0.786013865 |
| 48 | 1.41322314 | 0.345873011 | 2.031055901 | 0.708555806 |
| 60 | 1.28089888 | 0.247562079 | 1.912280702 | 0.648296614 |
| 72 | 1.16723549 | 0.154638128 | 1.796703297 | 0.585953484 |
| 84 | 0.9144385 | -0.08944506 | 1.68556701 | 0.522102012 |
| 96 | 0.7755102 | -0.254234138 | 1.64321608 | 0.496655346 |
| 120 | 0.52941176 | -0.635988767 | 1.535211268 | 0.428668005 |



3.19 Measurement of $IC_{50}$ value for 5-methyl-picrotoxinin (**20**)

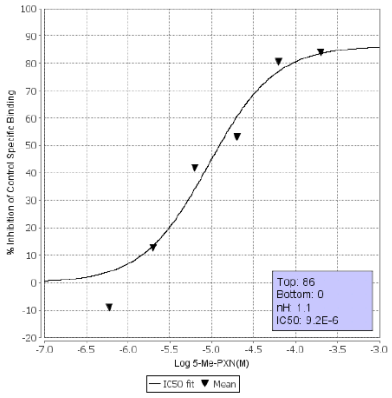
A Non-selective Rat $GABA_A$ Ion Channel [3H] TBOB Binding (Antagonist Radioligand) Assay (Catalog #3817) was conducted by Eurofins Pharma Discovery Service of Eurofins Cerep, France. (https://www.eurofinsdiscoveryservices.com/catalogmanagement/viewitem/Non-Selective-Rat-GABAA-Ion-Channel-3H-TBOB-Binding-Antagonist-Radioligand-Assay-Cerep/3817).

The assay is based on these publications:
Lewin, A. H. *et al*. *Mol. Pharmacol.* **1989**, *35*, 189.
Schwartz, R. D.; Mindlin, M. C. *J. Pharmacol. Exp. Ther.* **1987**, *244*, 963.

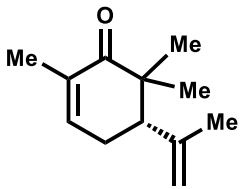
Compound binding was calculated as a % inhibition of the binding of the radioactive ligand [3H] TBOB (*t*-[$^3$H]Butylbicycloorthobenzoate) for **RAT** $GABA_A$ Ion Channels.

A 20.0 mM stock solution was prepared in DMSO from pure solid 5-methyl-picrotoxinin (**20**) to evaluate radioligand displacement of [3H] TBOB from rat cerebral cortex $GABA_A$ receptors at final concentrations of 200 μM, 63 μM, 20 μM, 6.3 μM, 2.0 μM, and 0.6 μM. An $IC_{50}$ value of 9.2 μM and a $K_i$ value of 8.2 μM were determined for compound **20**. Picrotoxinin (**1**) was used as a standard reference in this assay and exhibited an $IC_{50}$ value of 0.2 μM and a $K_i$ value of 0.2 μM.

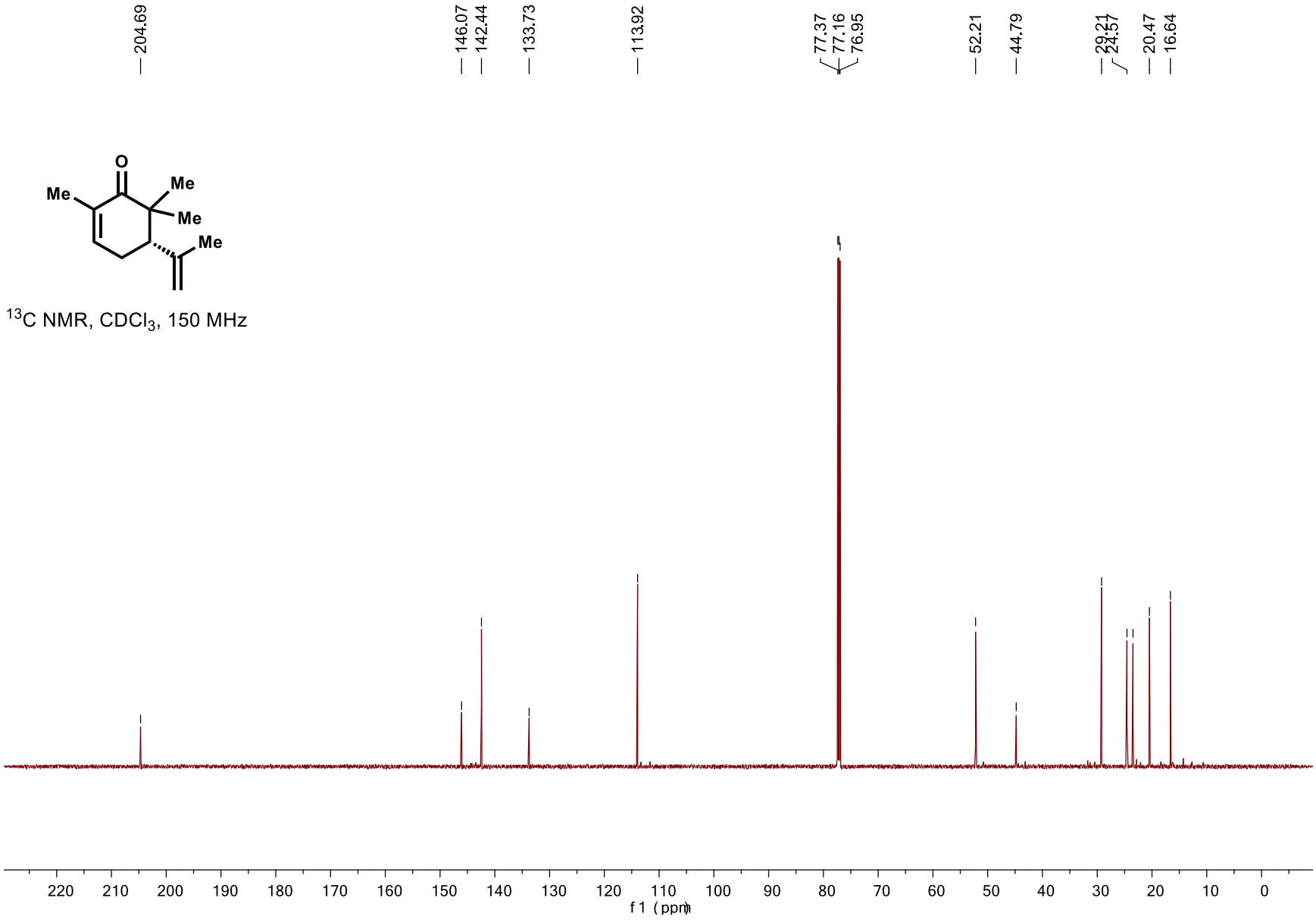
| Compound I.D. | Client Compound I.D. | $IC_{50}$ (M) | $K_i$ (M) | nH | Test Concentration | % Inhibition of Control Specific Binding 1st | Mean |
|---|---|---|---|---|---|---|---|
| **Cl- channel (GABA-gated) (TBOB site) (antagonist radioligand)** | | | | | | | |
| 100044035-1 | 5-Me-PXN | 9.2E-06 M | 8.2E-06 M | 1.1 | 6.0E-07 M | -8.8 | -8.8 |
| | | | | | 2.0E-06 M | 12.7 | 12.7 |
| | | | | | 6.3E-06 M | 41.9 | 41.9 |
| | | | | | 2.0E-05 M | 53.3 | 53.3 |
| | | | | | 6.3E-05 M | 80.8 | 80.8 |
| | | | | | 2.0E-04 M | 84.2 | 84.2 |

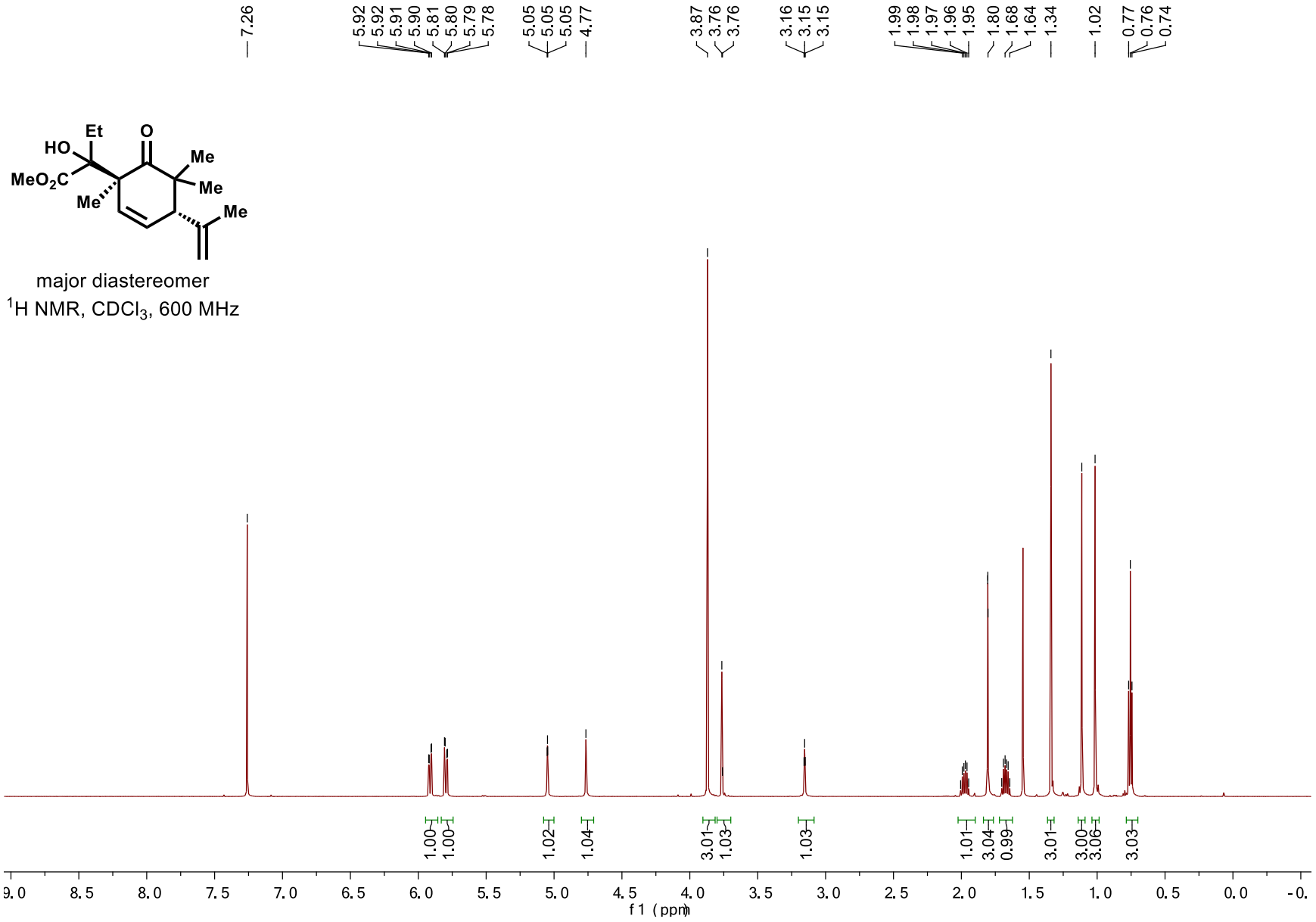


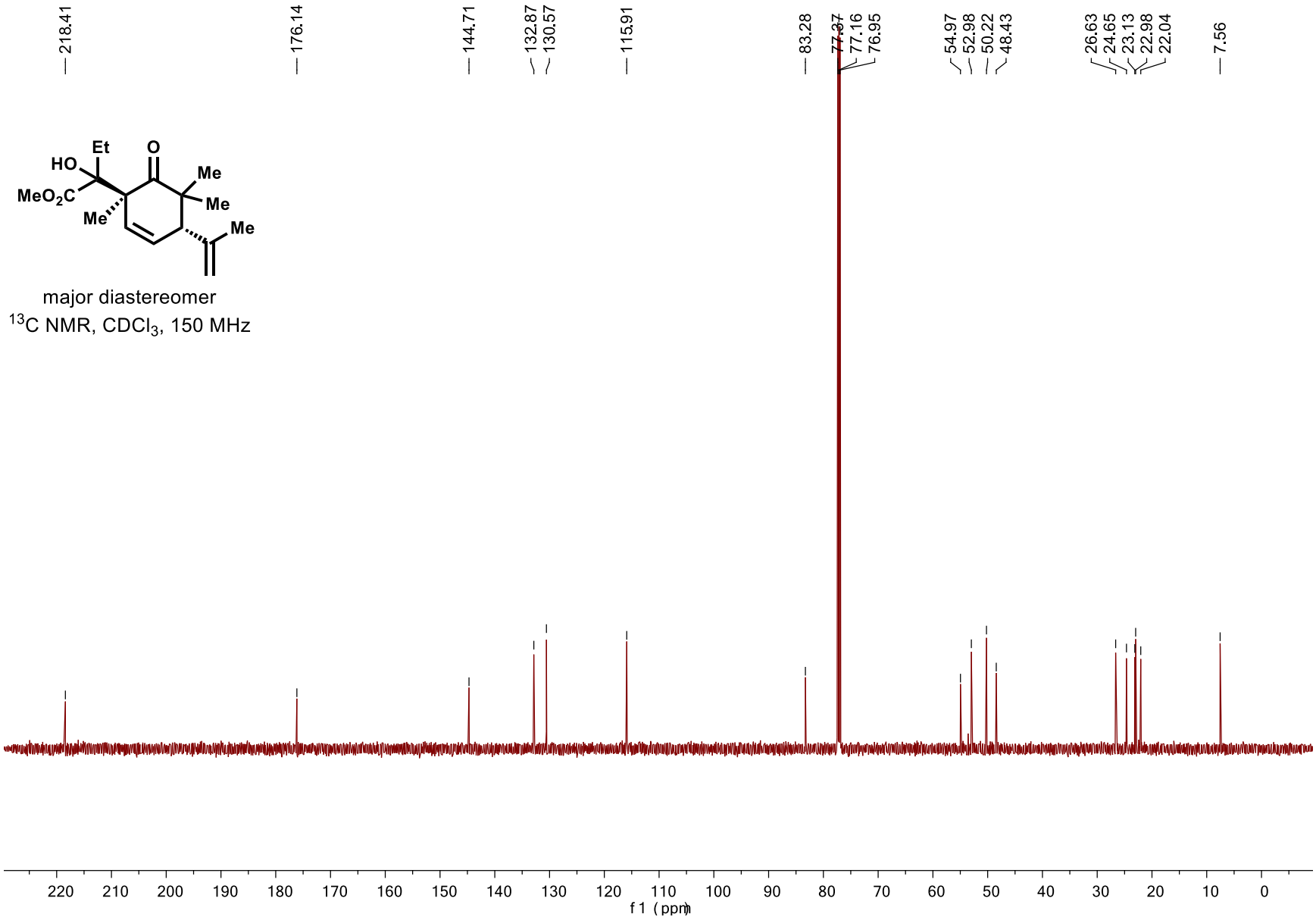
4. NMR spectra




$^1$H NMR, $CDCl_3$, 600 MHz

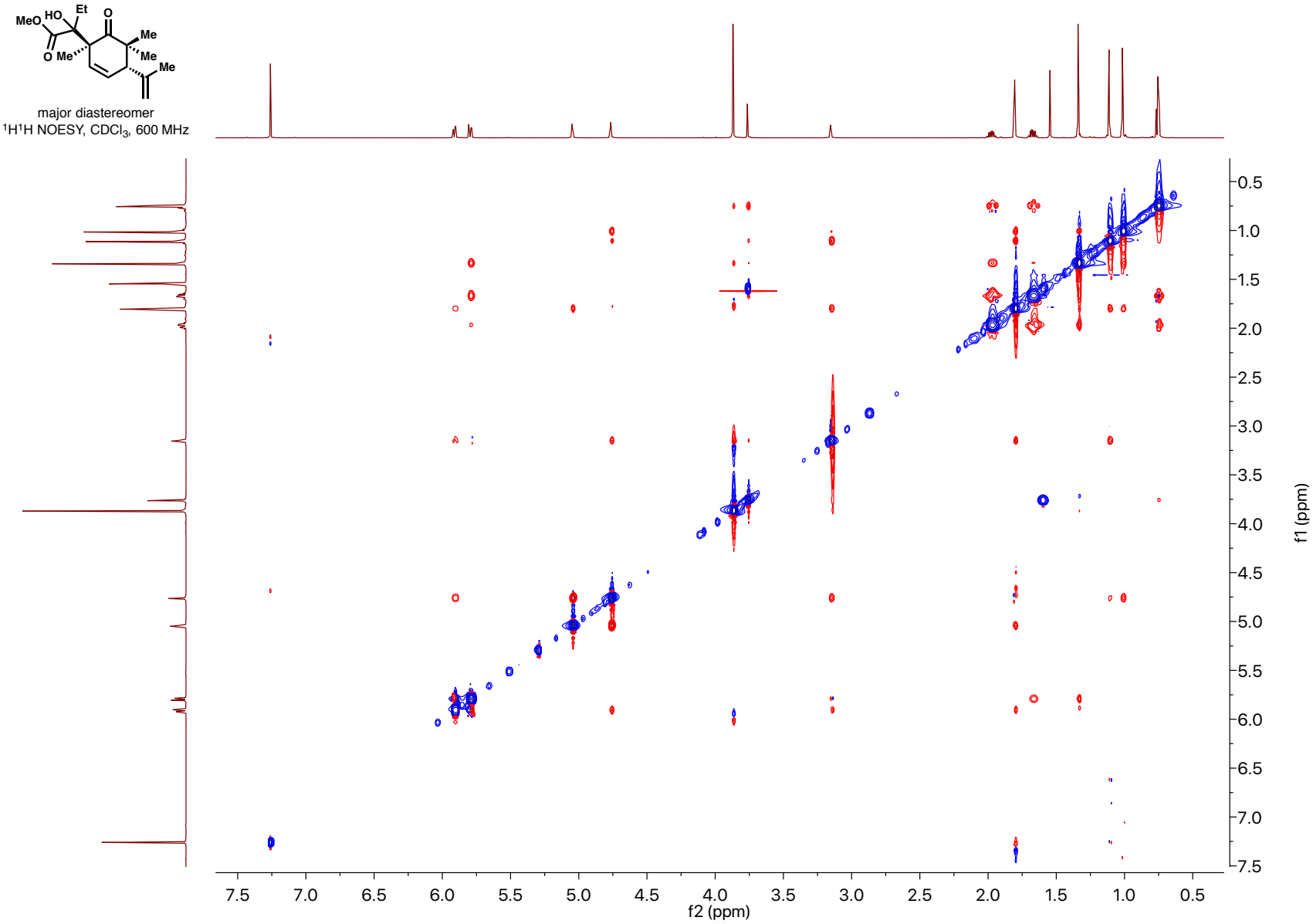

204.69
146.07
142.44
133.73
113.92
77.37
77.16
76.95
52.21
44.79
29.21
24.57
20.47
16.64
O
Me
Me
Me
Me
13C NMR, CDCl3, 150 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

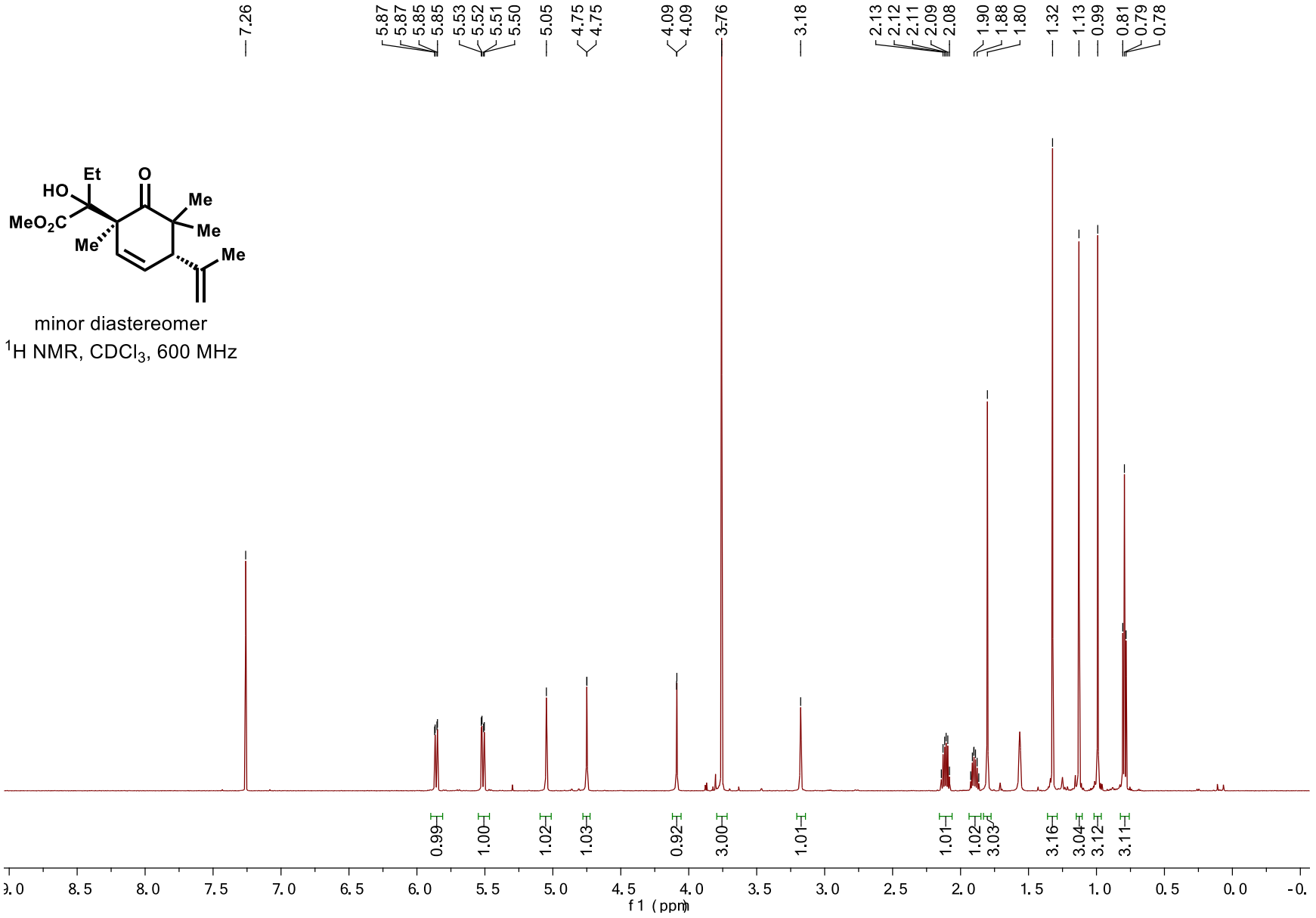

7.26
5.92
5.92
5.91
5.90
5.81
5.80
5.79
5.78
5.05
5.05
5.05
4.77
3.87
3.76
3.76
3.16
3.15
3.15
1.99
1.98
1.97
1.96
1.95
1.80
1.68
1.64
1.34
1.02
0.77
0.76
0.74
Et
O
HO
Me
MeO2C
Me
Me
Me
major diastereomer
1H NMR, CDCl3, 600 MHz
1.00
1.00
1.02
1.04
3.01
1.03
1.03
1.01
3.04
0.99
3.01
3.00
3.06
3.03
f1 (ppm)




major diastereomer

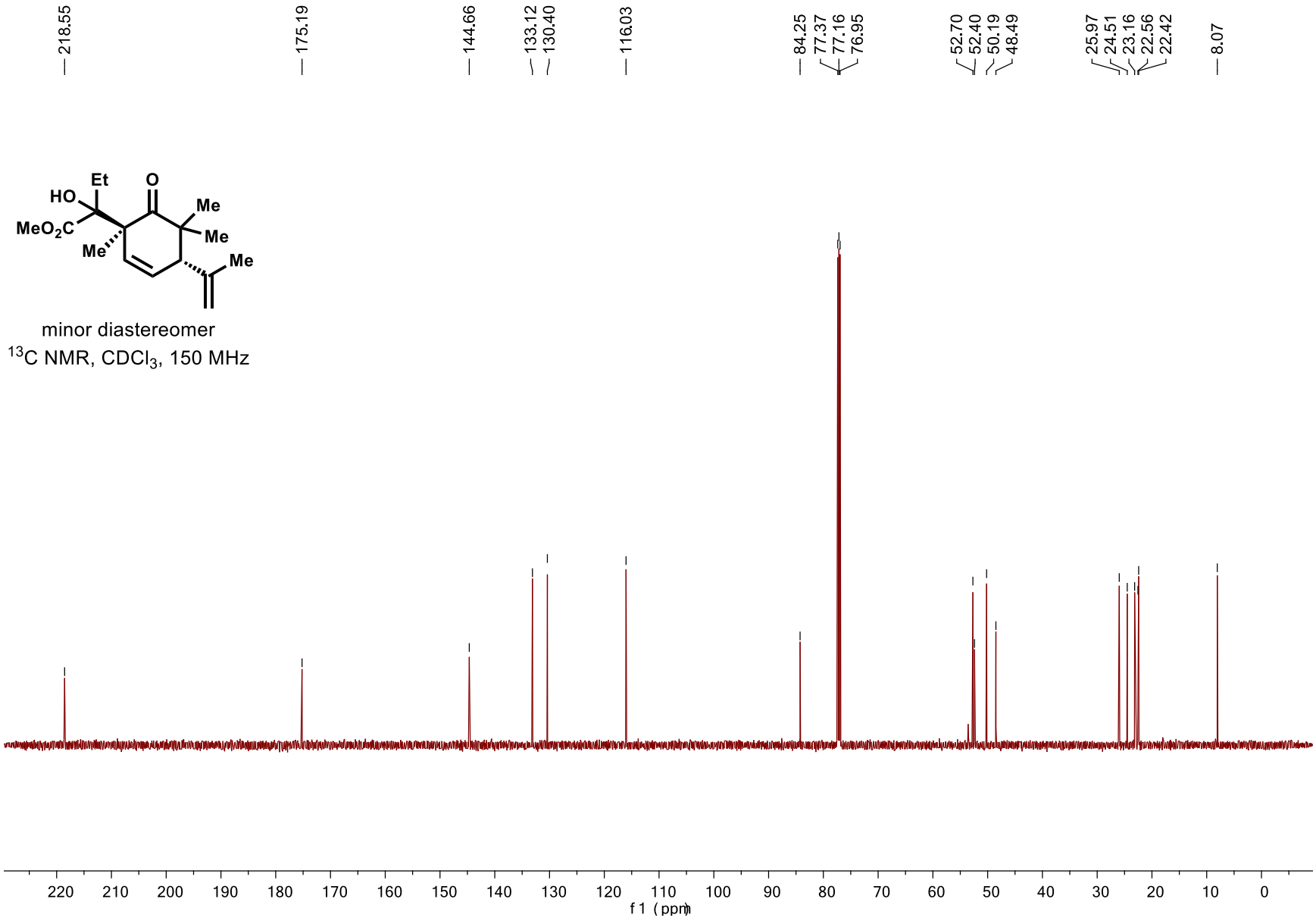
$^{13}C$ NMR, $CDCl_3$, 150 MHz

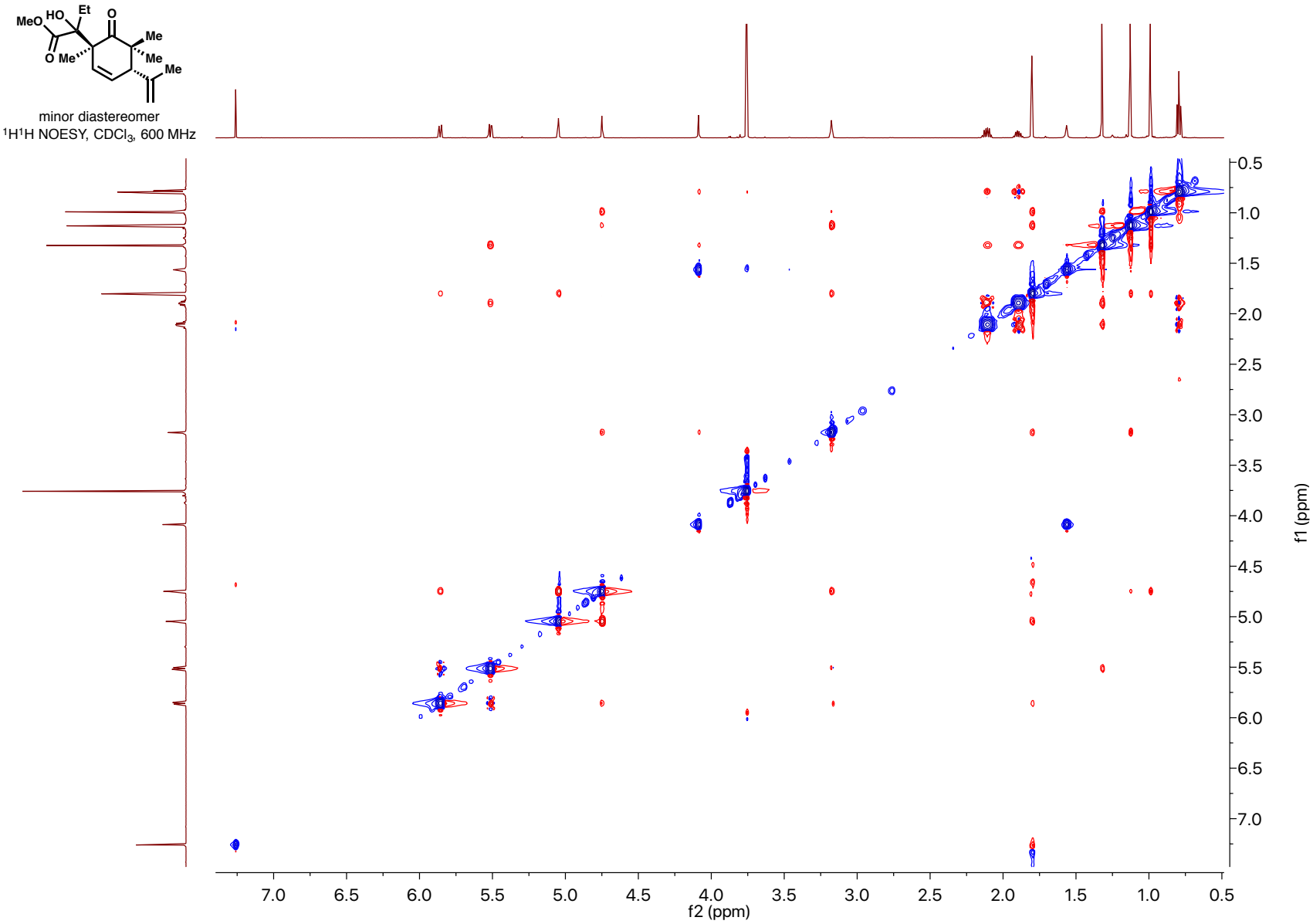

MeO
HO
Et
O
O Me
Me
Me
Me
major diastereomer
$^1H^1H$ NOESY, $CDCl_3$, 600 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)

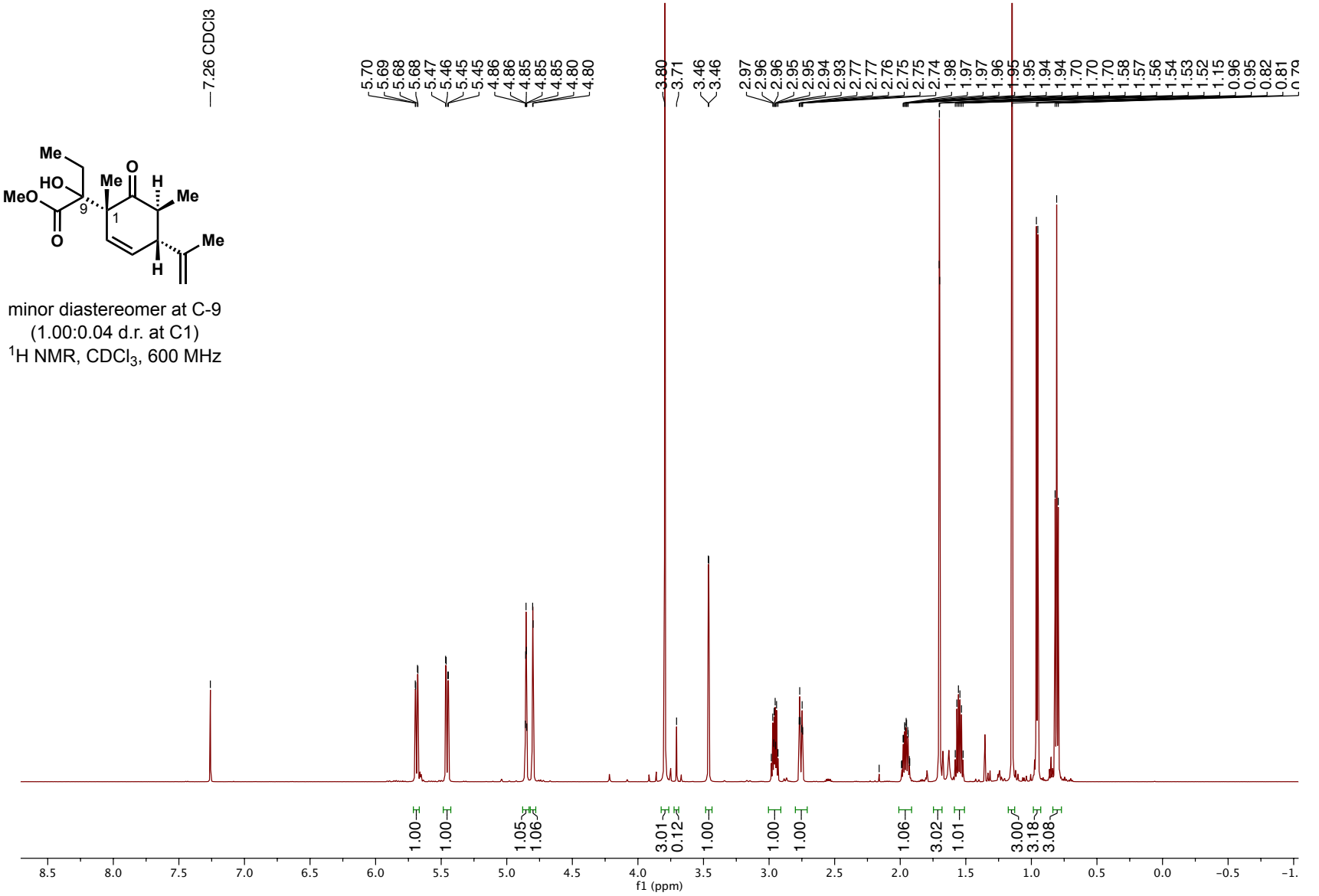



minor diastereomer

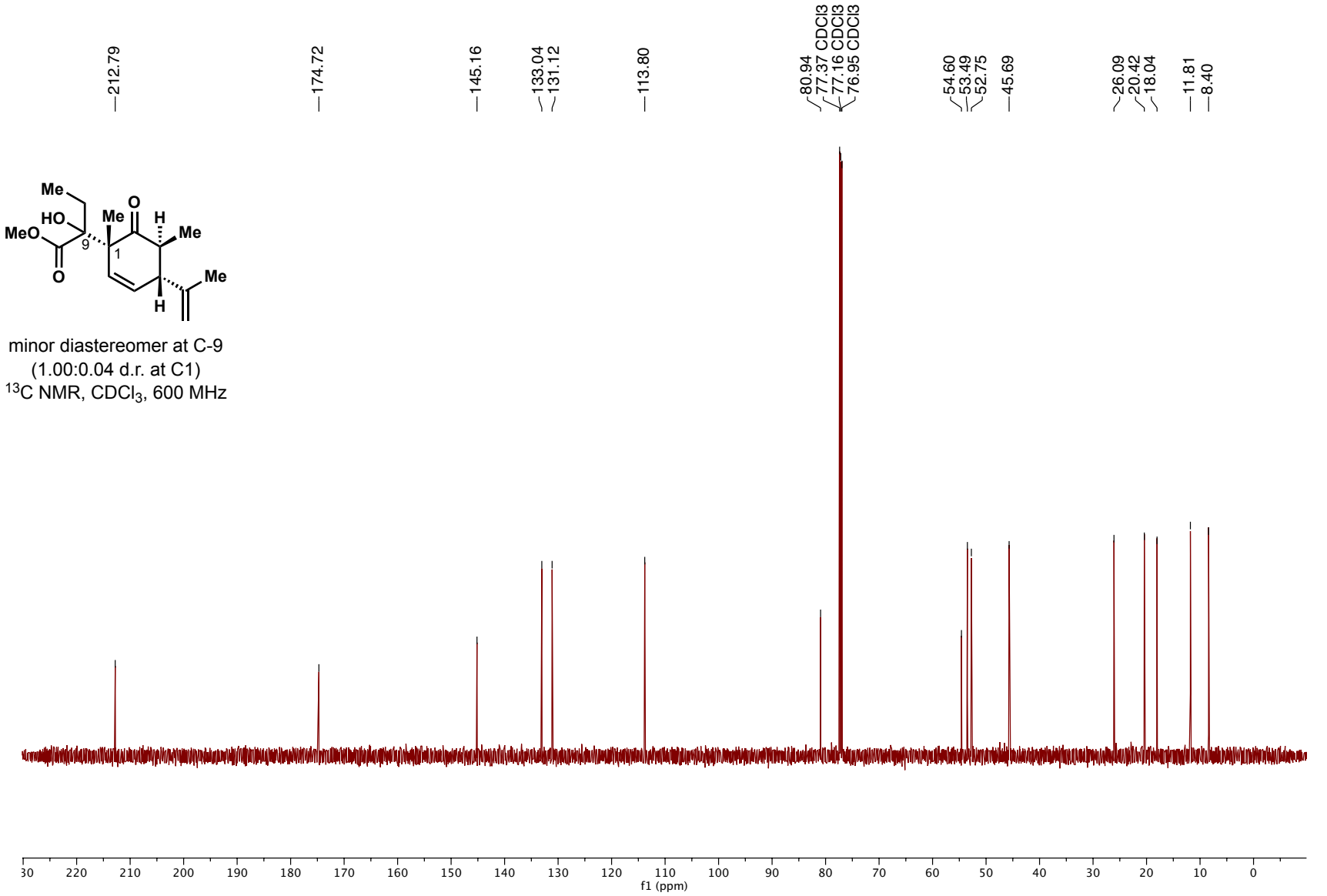
$^1$H NMR, $CDCl_3$, 600 MHz


218.55
175.19
144.66
133.12
130.40
116.03
84.25
77.37
77.16
76.95
52.70
52.40
50.19
48.49
25.97
24.51
23.16
22.56
22.42
8.07
Et
O
HO
Me
MeO2C
Me
Me
Me
minor diastereomer
13C NMR, CDCl3, 150 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

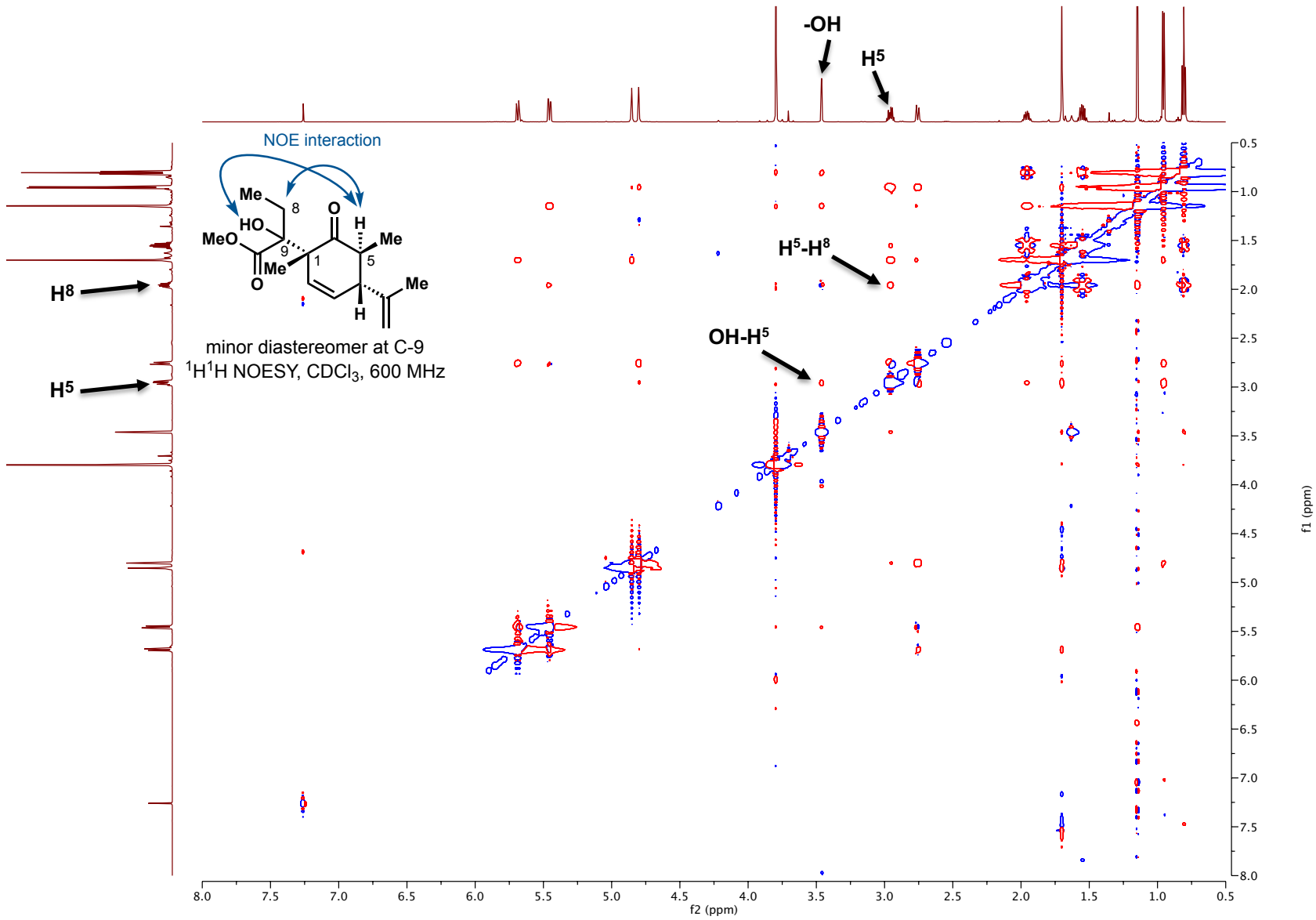

MeO
HO
Et
O
O
Me
Me
Me
Me
minor diastereomer
$^1H^1H$ NOESY, $CDCl_3$, 600 MHz
f2 (ppm)
f1 (ppm)

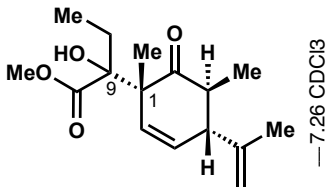



minor diastereomer at C-9
(1.00:0.04 d.r. at C1)
$^1$H NMR, $CDCl_3$, 600 MHz

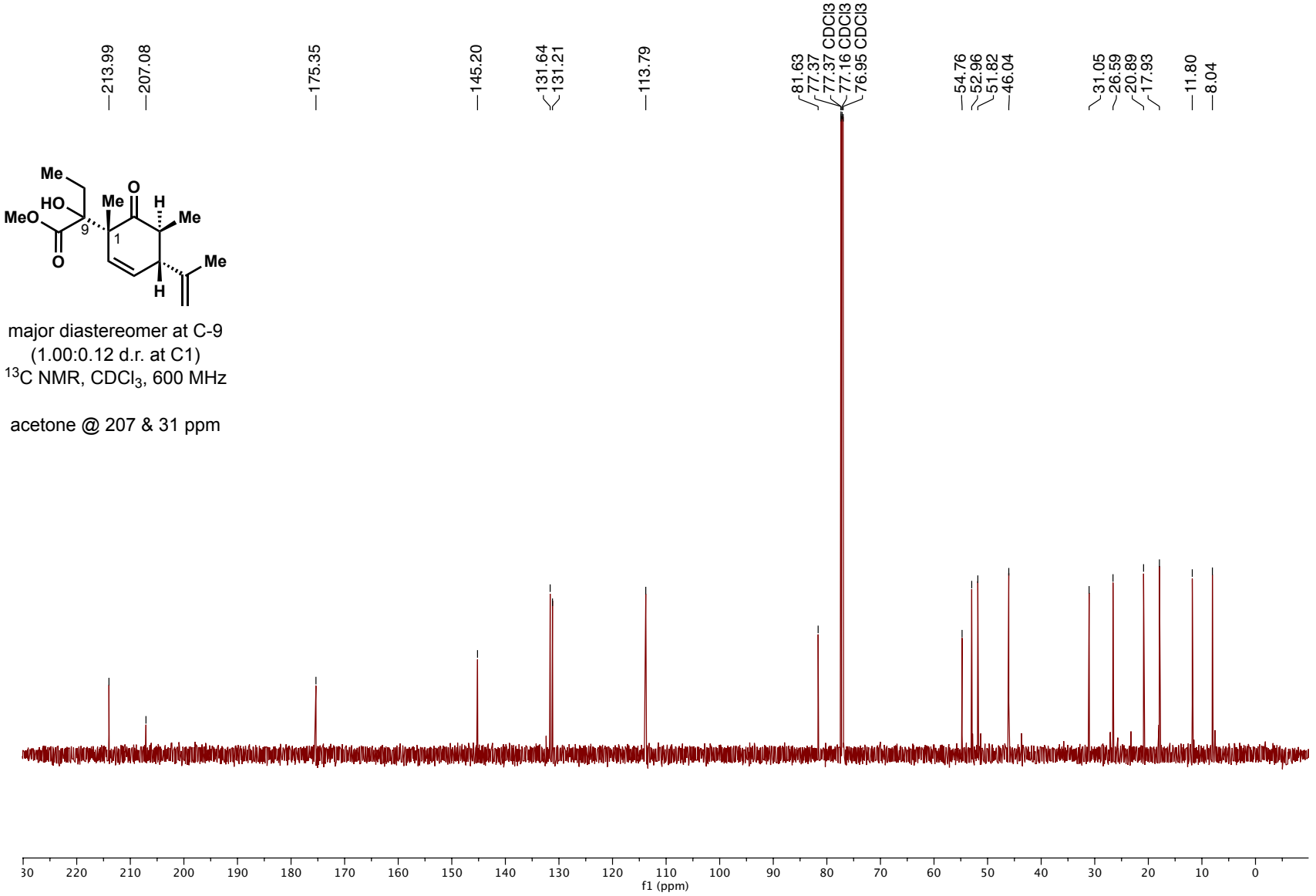



minor diastereomer at C-9
(1.00:0.04 d.r. at C1)
$^{13}C$ NMR, $CDCl_3$, 600 MHz


-OH
H5
NOE interaction
Me
8
O
HO
H
MeO
Me
9
1
5
Me
O
Me
H
H8
H5
minor diastereomer at C-9
1H1H NOESY, CDCl3, 600 MHz
H5-H8
OH-H5
f2 (ppm)
f1 (ppm)

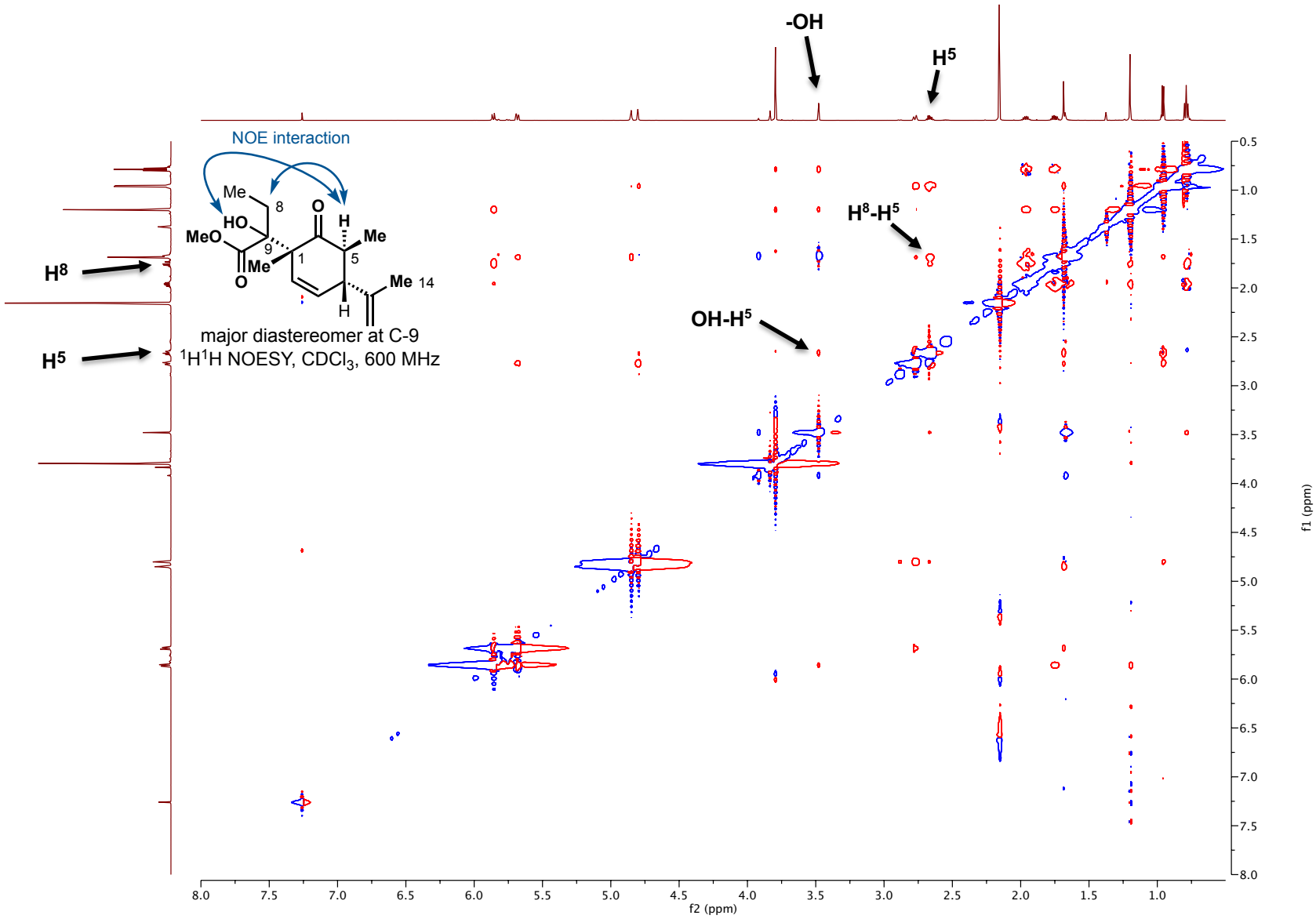


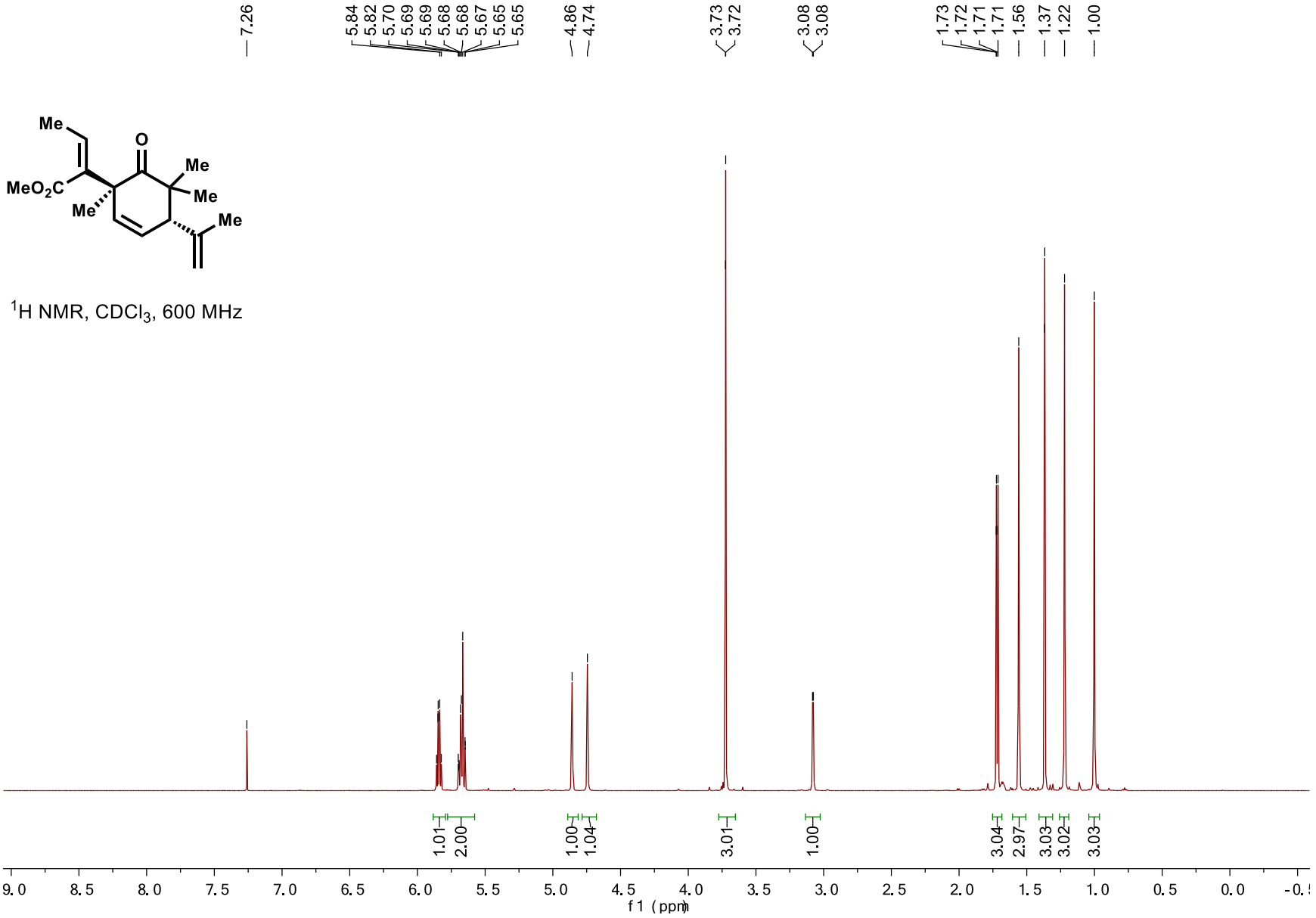

major diastereomer at C-9
(1.00:0.12 d.r. at C1)
$^1$H NMR, $CDCl_3$, 600 MHz

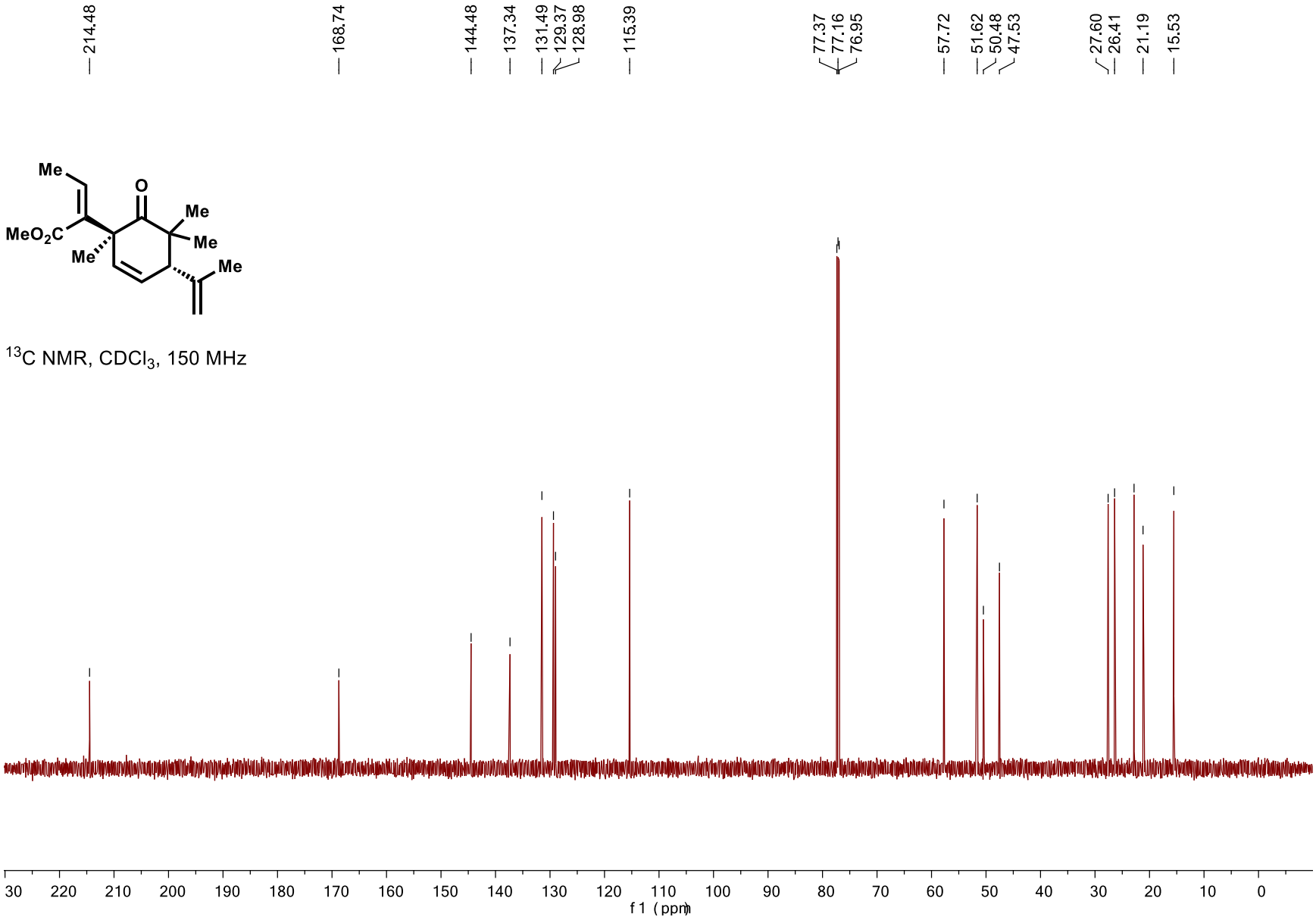


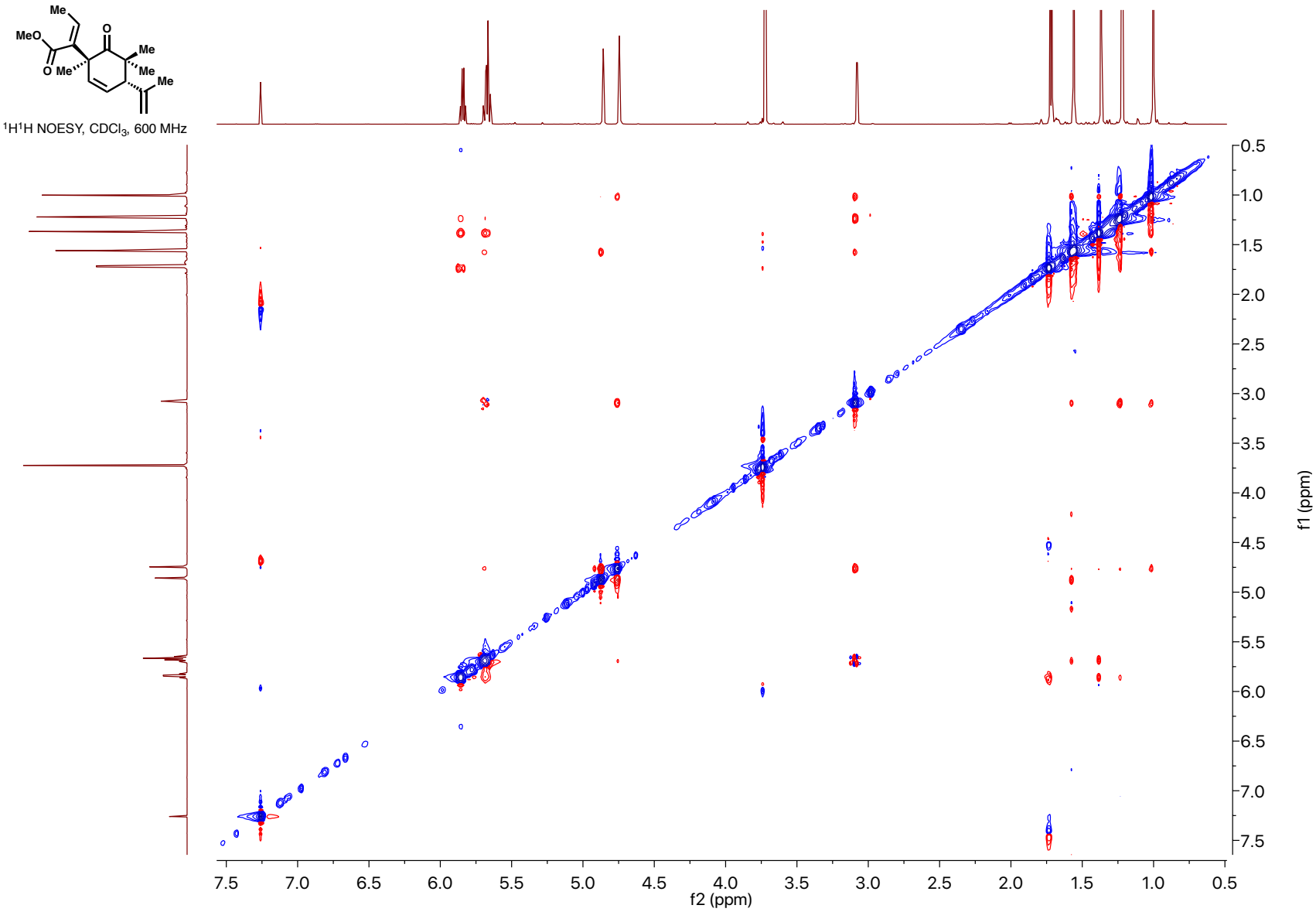

major diastereomer at C-9
(1.00:0.12 d.r. at C1)
$^{13}C$ NMR, $CDCl_3$, 600 MHz

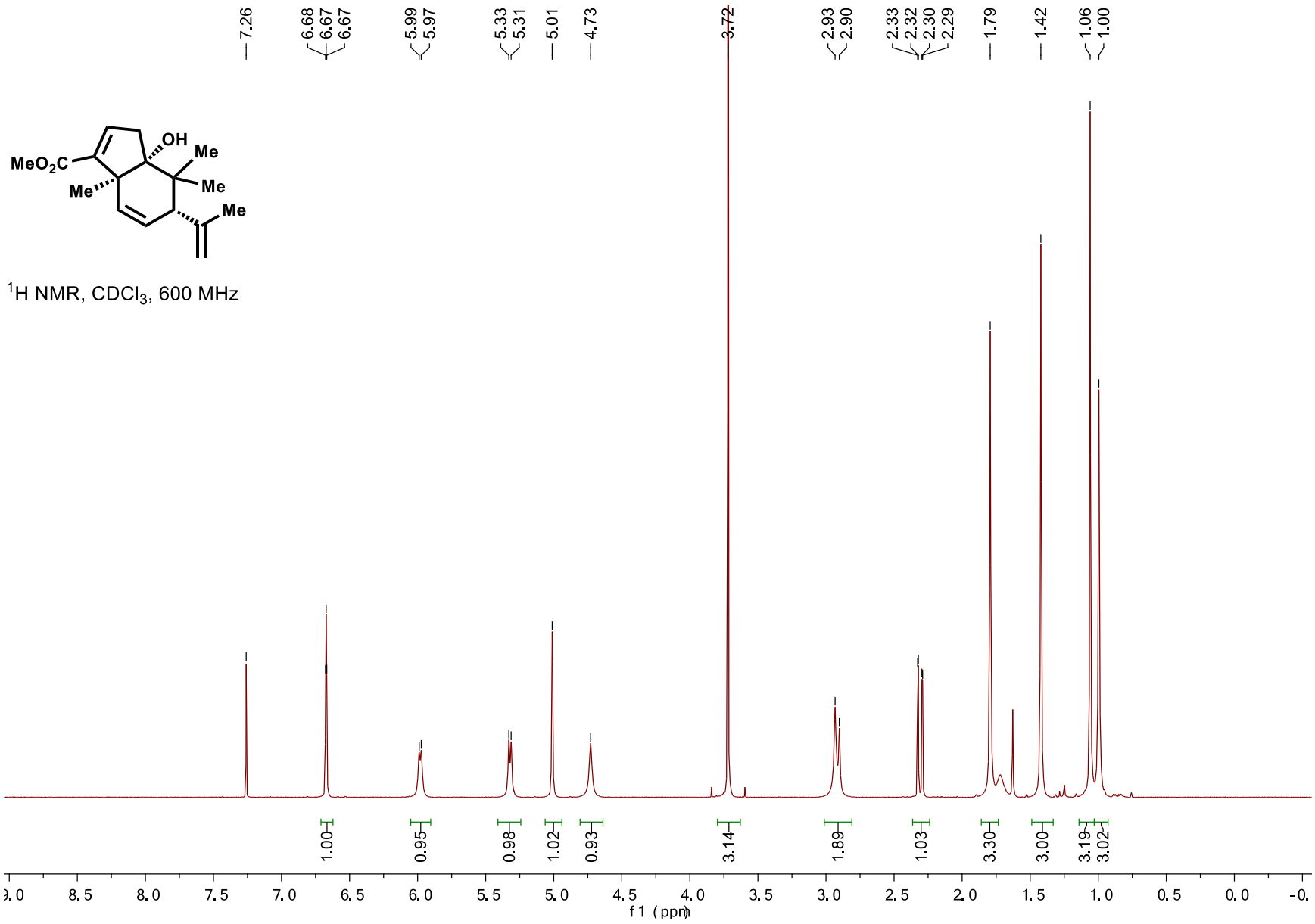
acetone @ 207 & 31 ppm

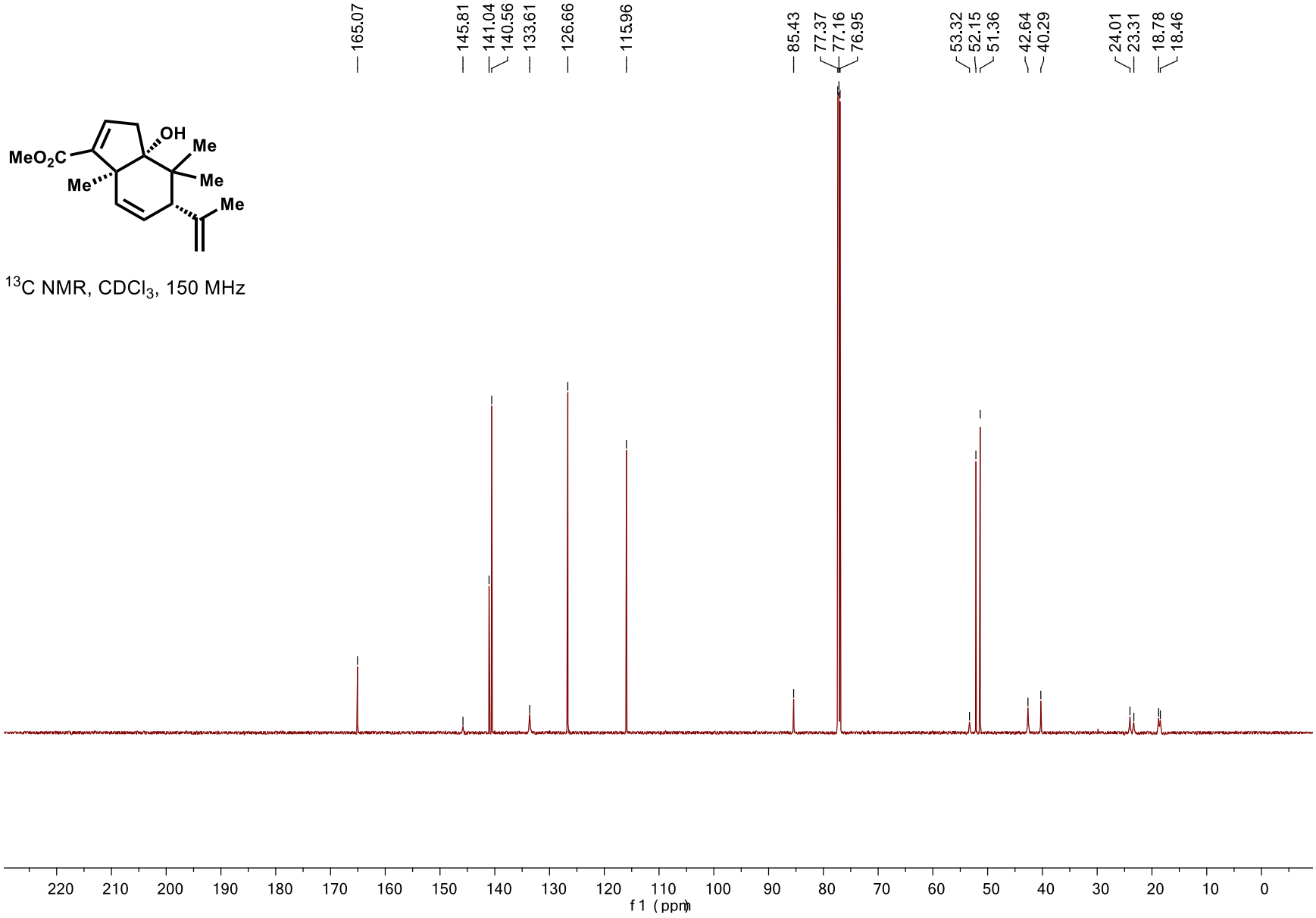

-OH
H5
NOE interaction
Me
8
O
H
HO
MeO
Me
9
1
5
Me
Me
O
Me 14
H
H8
H5
major diastereomer at C-9
1H1H NOESY, CDCl3, 600 MHz
H8-H5
OH-H5
f2 (ppm)
f1 (ppm)

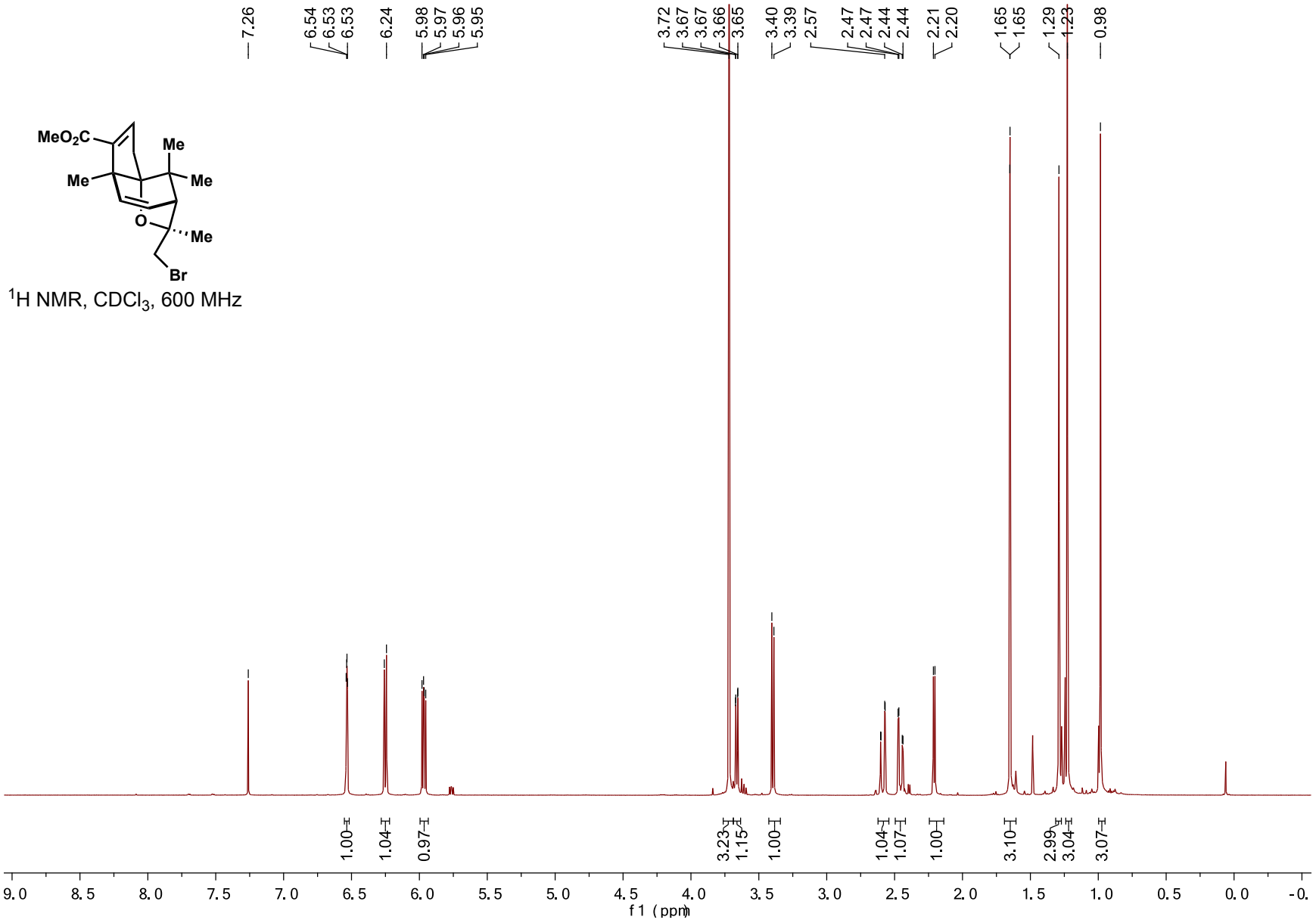

7.26
5.84
5.82
5.70
5.69
5.69
5.68
5.68
5.67
5.65
5.65
4.86
4.74
3.73
3.72
3.08
3.08
1.73
1.72
1.71
1.71
1.56
1.37
1.22
1.00
Me
O
Me
MeO2C
Me
Me
Me
1H NMR, CDCl3, 600 MHz
1.01
2.00
1.00
1.04
3.01
1.00
3.04
2.97
3.03
3.02
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

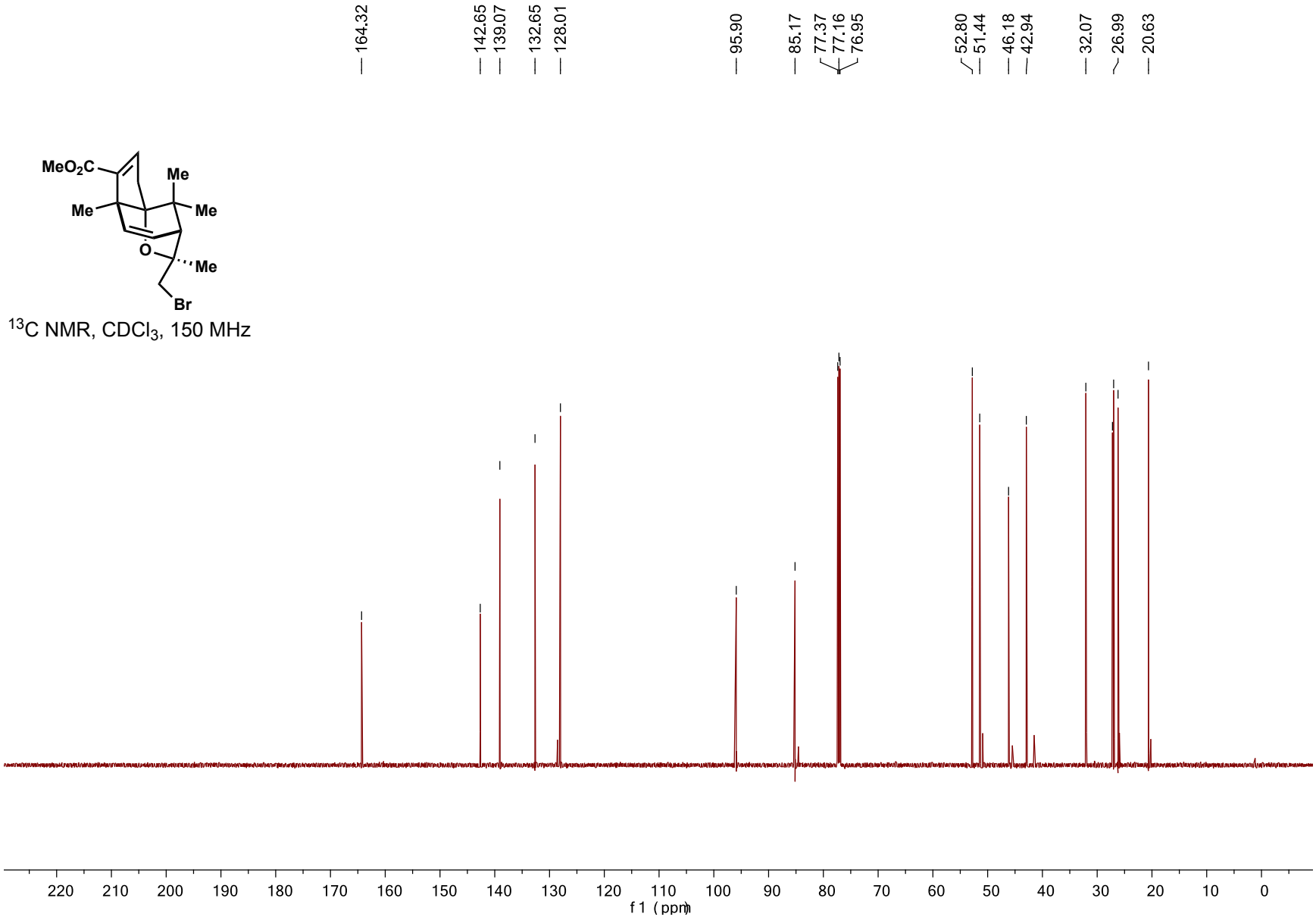

214.48
168.74
144.48
137.34
131.49
129.37
128.98
115.39
77.37
77.16
76.95
57.72
51.62
50.48
47.53
27.60
26.41
21.19
15.53
Me
O
Me
MeO2C
Me
Me
Me
13C NMR, CDCl3, 150 MHz
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

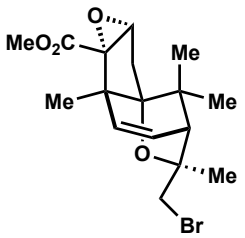

Me
MeO
O
Me
O
Me
Me
Me
$^1H^1H$ NOESY, $CDCl_3$, 600 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)


7.26
6.68
6.67
6.67
5.99
5.97
5.33
5.31
5.01
4.73
3.72
2.93
2.90
2.33
2.32
2.30
2.29
1.79
1.42
1.06
1.00
OH
Me
Me
Me
Me
MeO2C
1H NMR, CDCl3, 600 MHz
1.00
0.95
0.98
1.02
0.93
3.14
1.89
1.03
3.30
3.00
3.19
3.02
f1 (ppm)

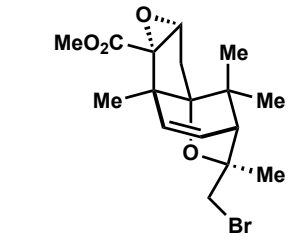

165.07
145.81
141.04
140.56
133.61
126.66
115.96
85.43
77.37
77.16
76.95
53.32
52.15
51.36
42.64
40.29
24.01
23.31
18.78
18.46
OH
Me
MeO2C
Me
Me
Me
13C NMR, CDCl3, 150 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO2C
Me
Me
Me
O
Me
Br
1H NMR, CDCl3, 600 MHz
7.26
6.54
6.53
6.53
6.24
5.98
5.97
5.96
5.95
3.72
3.67
3.67
3.66
3.65
3.40
3.39
2.57
2.47
2.47
2.44
2.44
2.21
2.20
1.65
1.65
1.29
1.23
0.98
1.00
1.04
0.97
3.23
1.15
1.00
1.04
1.07
1.00
3.10
2.99
3.04
3.07
f1 (ppm)

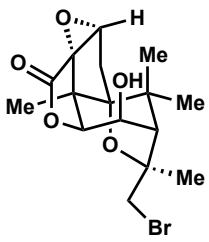

164.32
142.65
139.07
132.65
128.01
95.90
85.17
77.37
77.16
76.95
52.80
51.44
46.18
42.94
32.07
26.99
20.63
MeO2C
Me
Me
Me
O
Me
Br
13C NMR, CDCl3, 150 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



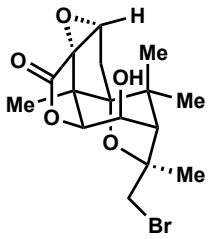

$^1$H NMR, $CDCl_3$, 600 MHz



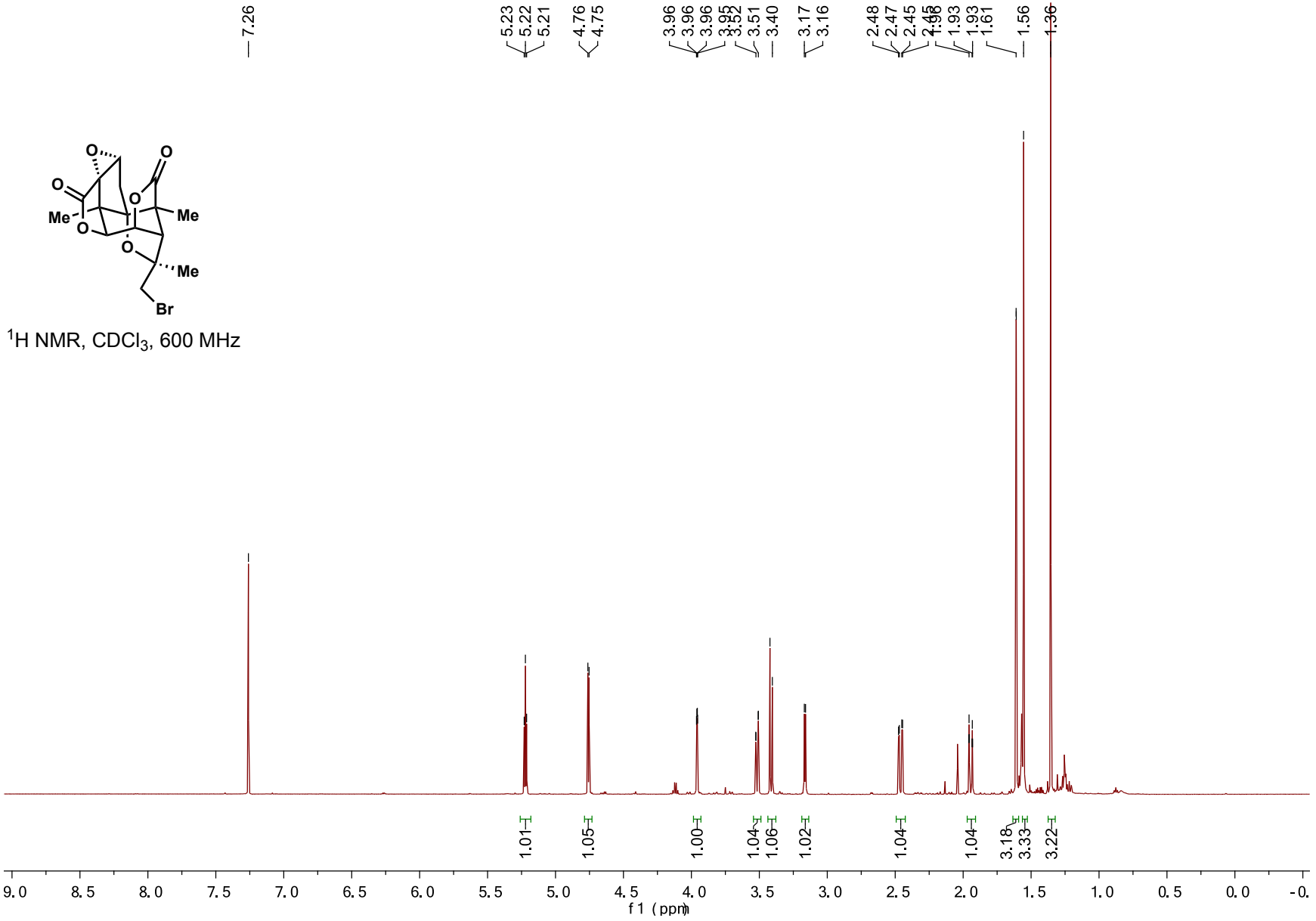

$^{13}C$ NMR, $CDCl_3$, 150 MHz



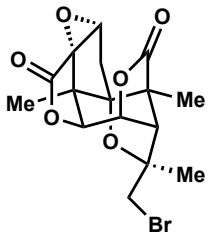

$^1$H NMR, $CDCl_3$, 600 MHz



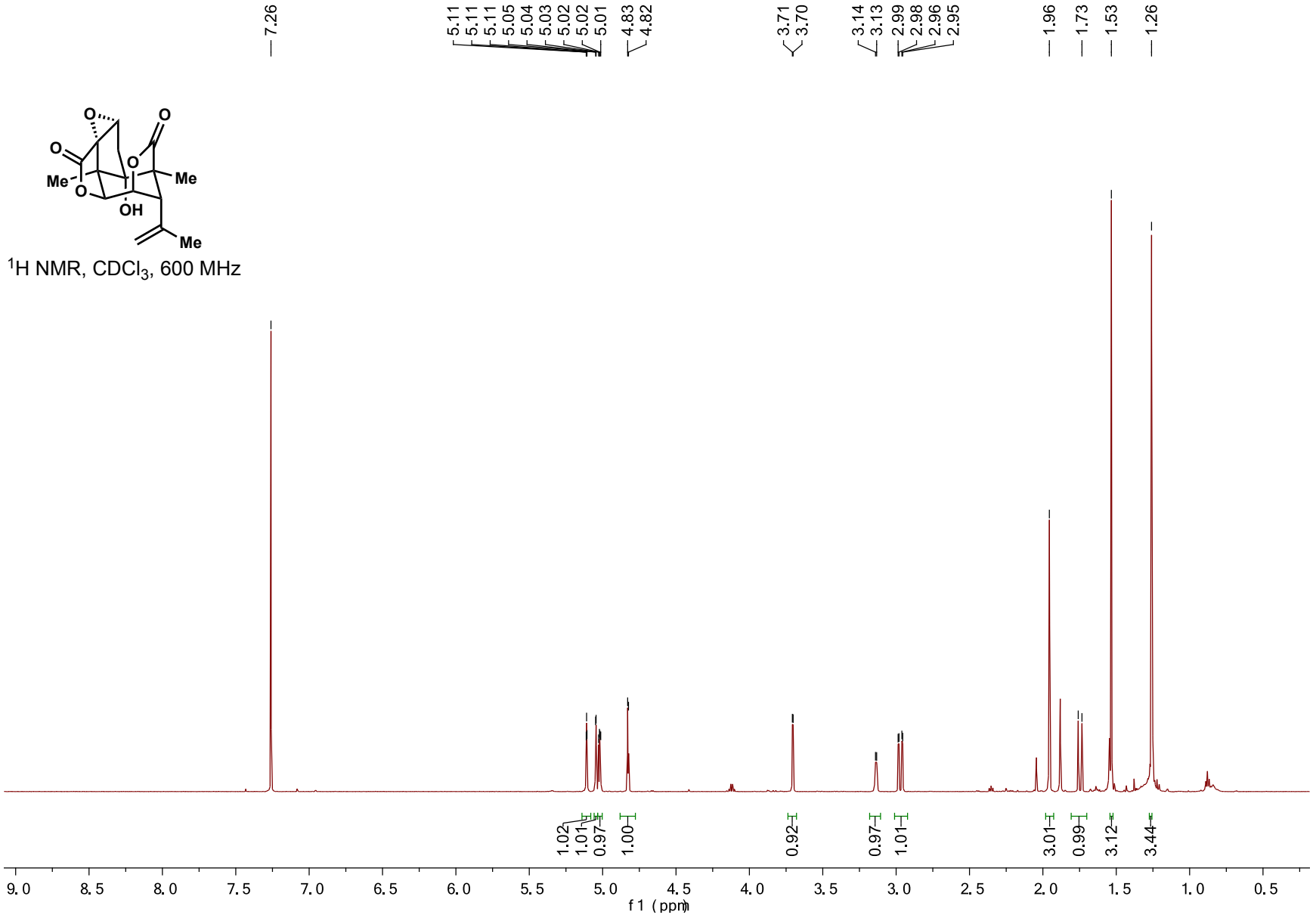

$^{13}C$ NMR, $CDCl_3$, 150 MHz

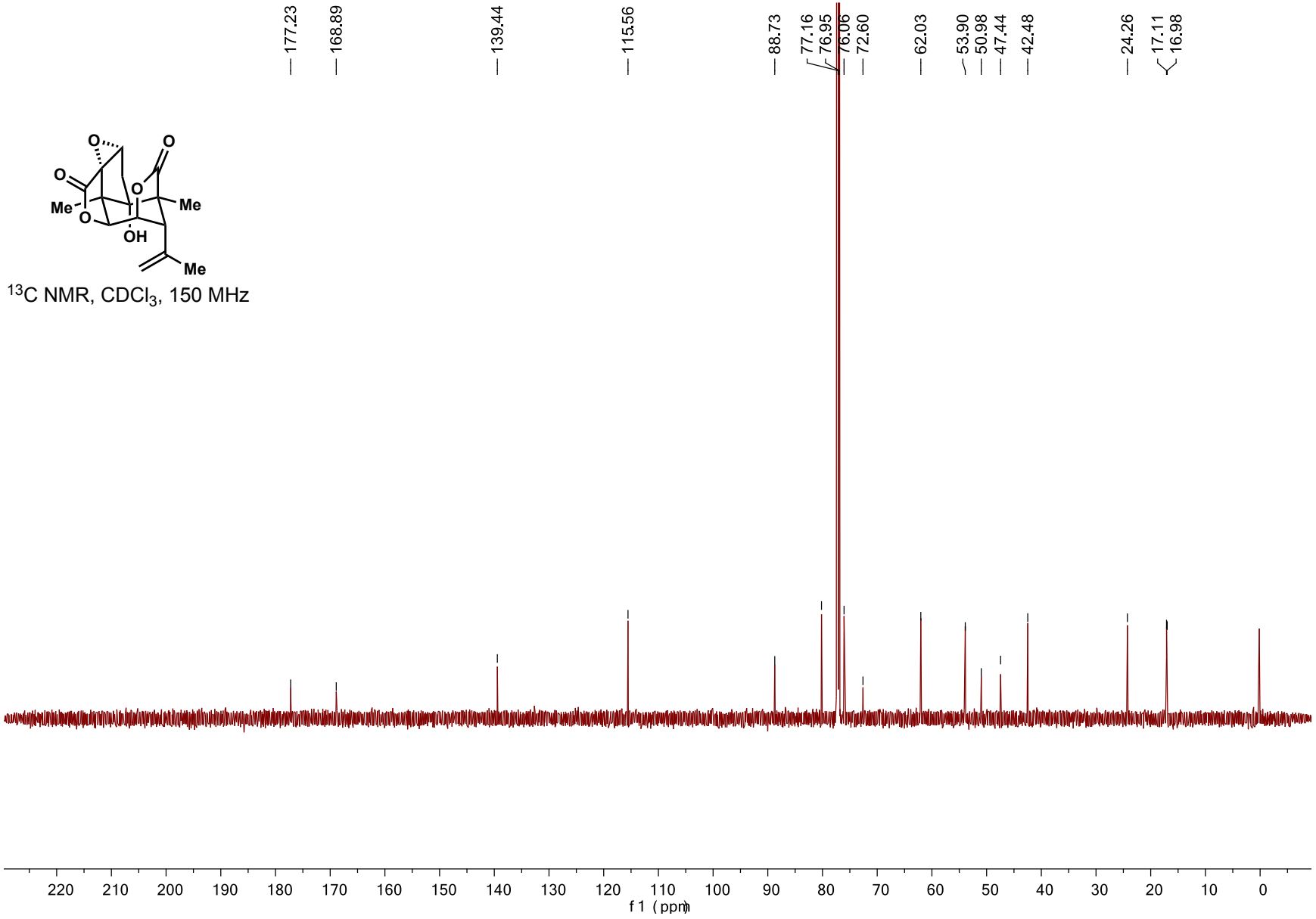



$^1$H NMR, $CDCl_3$, 600 MHz

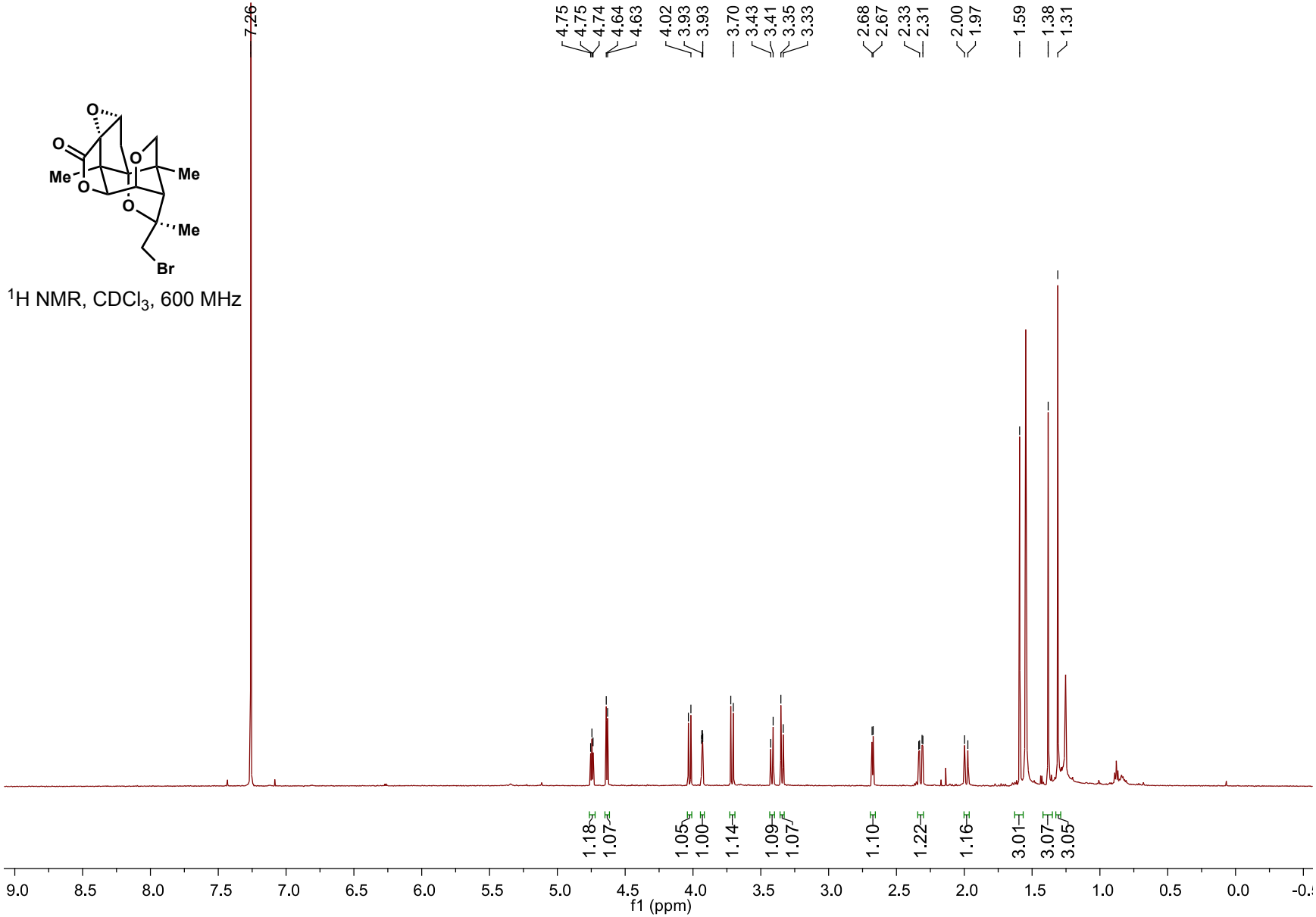


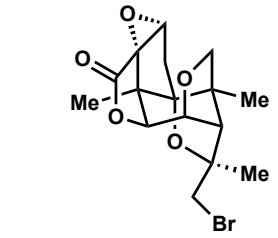

$^{13}C$ NMR, $CDCl_3$, 150 MHz


7.26
5.11
5.11
5.11
5.05
5.04
5.03
5.02
5.02
5.01
4.83
4.82
3.71
3.70
3.14
3.13
2.99
2.98
2.96
2.95
1.96
1.73
1.53
1.26
O
O
O
O
Me
Me
O
OH
Me
1H NMR, CDCl3, 600 MHz
1.02
1.01
0.97
1.00
0.92
0.97
1.01
3.01
0.99
3.12
3.44
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

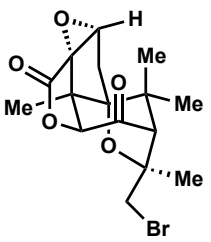



$^{13}C$ NMR, $CDCl_3$, 150 MHz

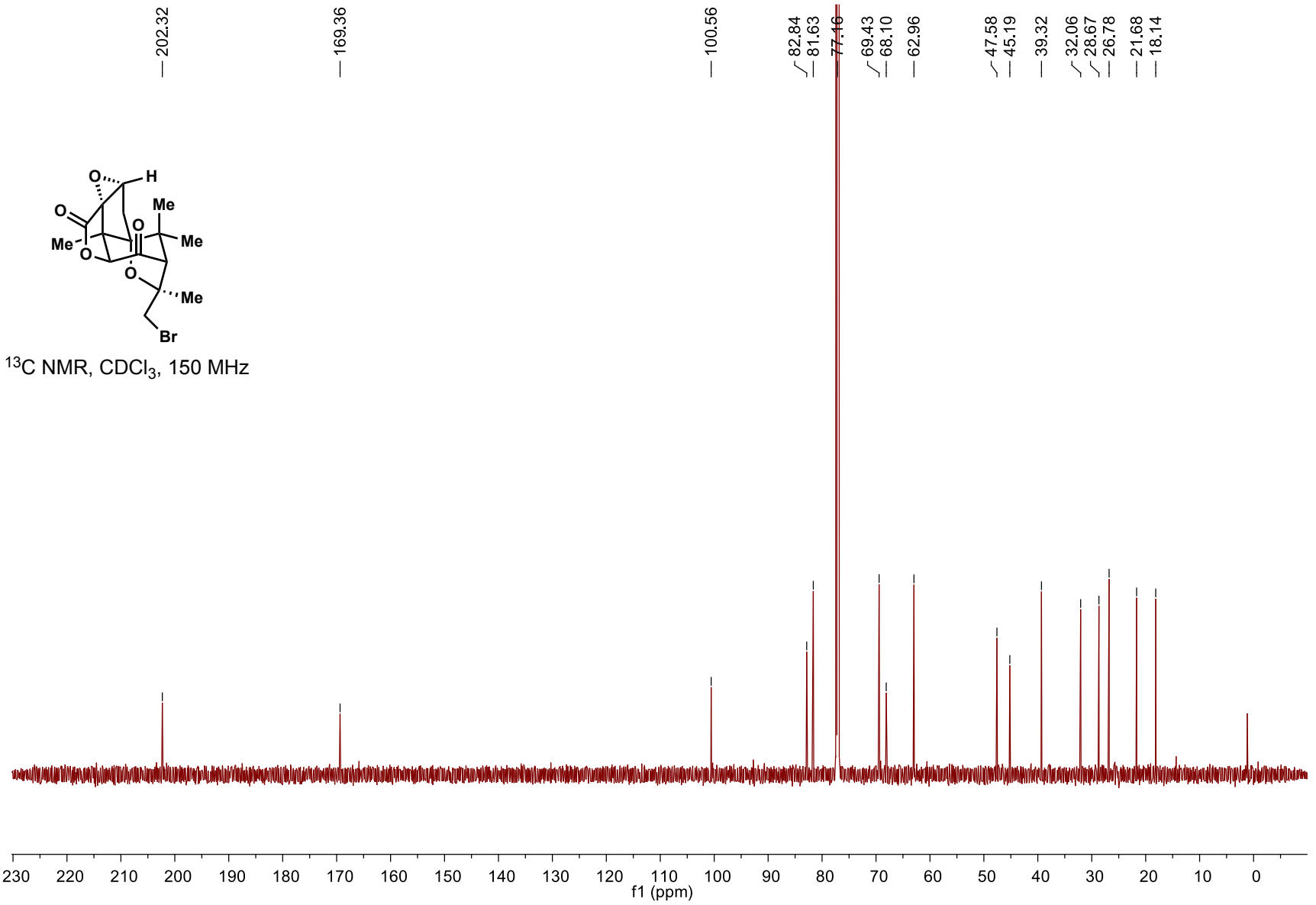

7.26
4.75
4.75
4.74
4.64
4.63
4.02
3.93
3.93
3.70
3.43
3.41
3.35
3.33
2.68
2.67
2.33
2.31
2.00
1.97
1.59
1.38
1.31
O
O
Me
O
O
O
Me
Me
Br
1H NMR, CDCl3, 600 MHz
1.18
1.07
1.05
1.00
1.14
1.09
1.07
1.10
1.22
1.16
3.01
3.07
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



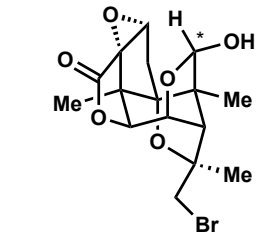

$^{13}C$ NMR, $CDCl_3$, 150 MHz




$^1$H NMR, $CDCl_3$, 600 MHz

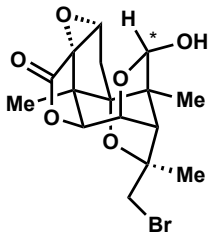



$^{13}C$ NMR, $CDCl_3$, 150 MHz



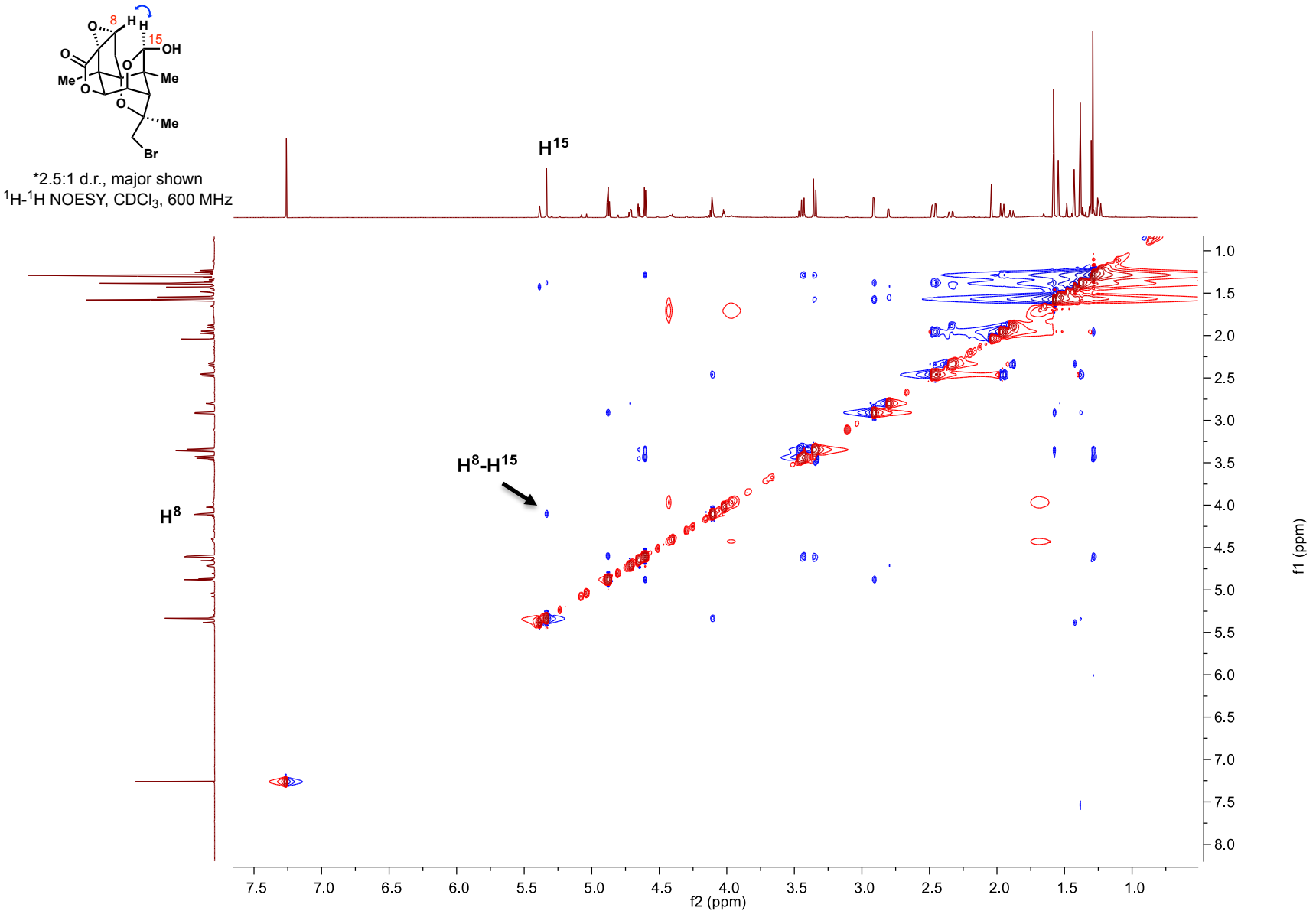

*2.5:1 d.r., major shown

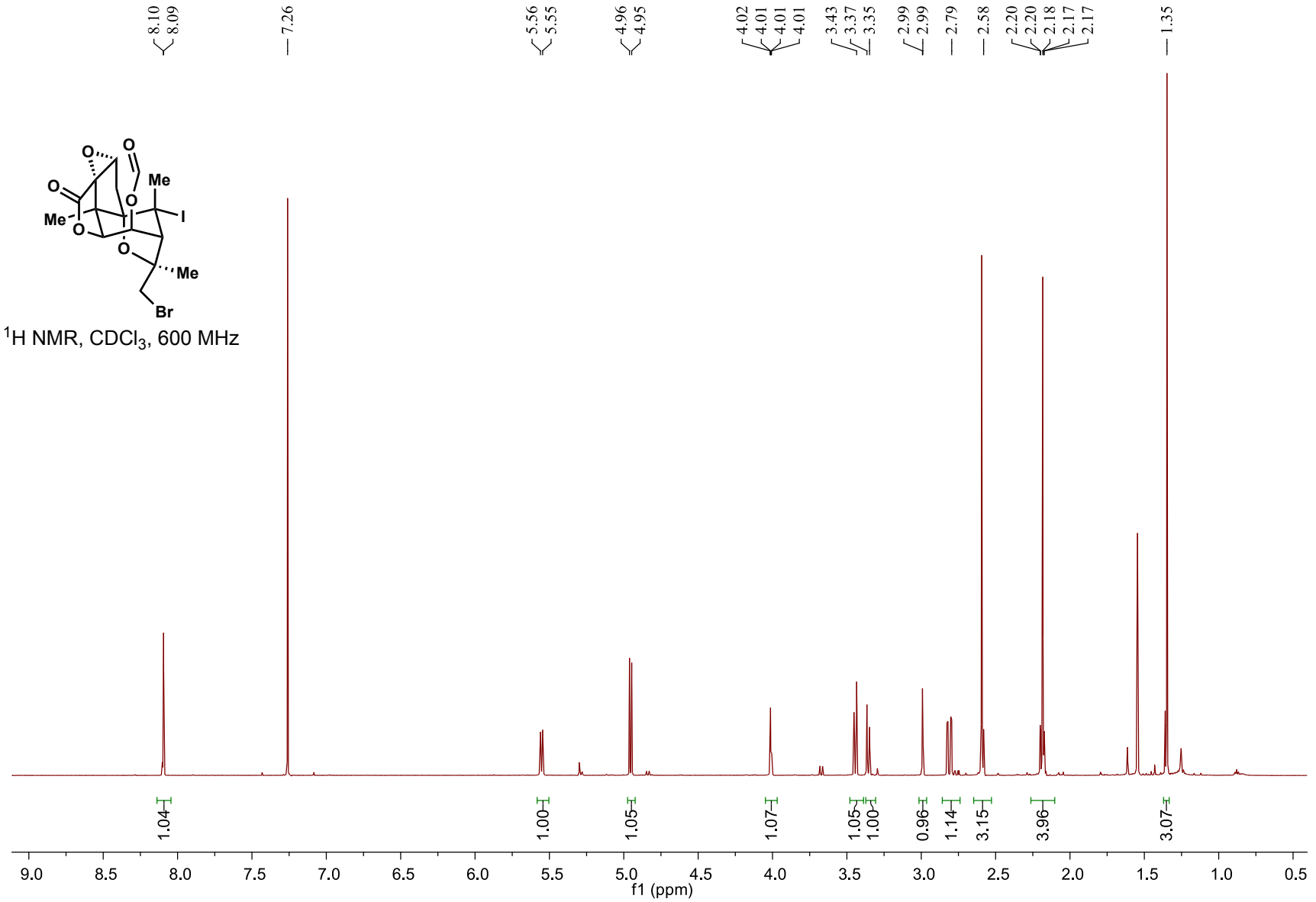
$^{1}$H NMR, $CDCl_3$, 600 MHz

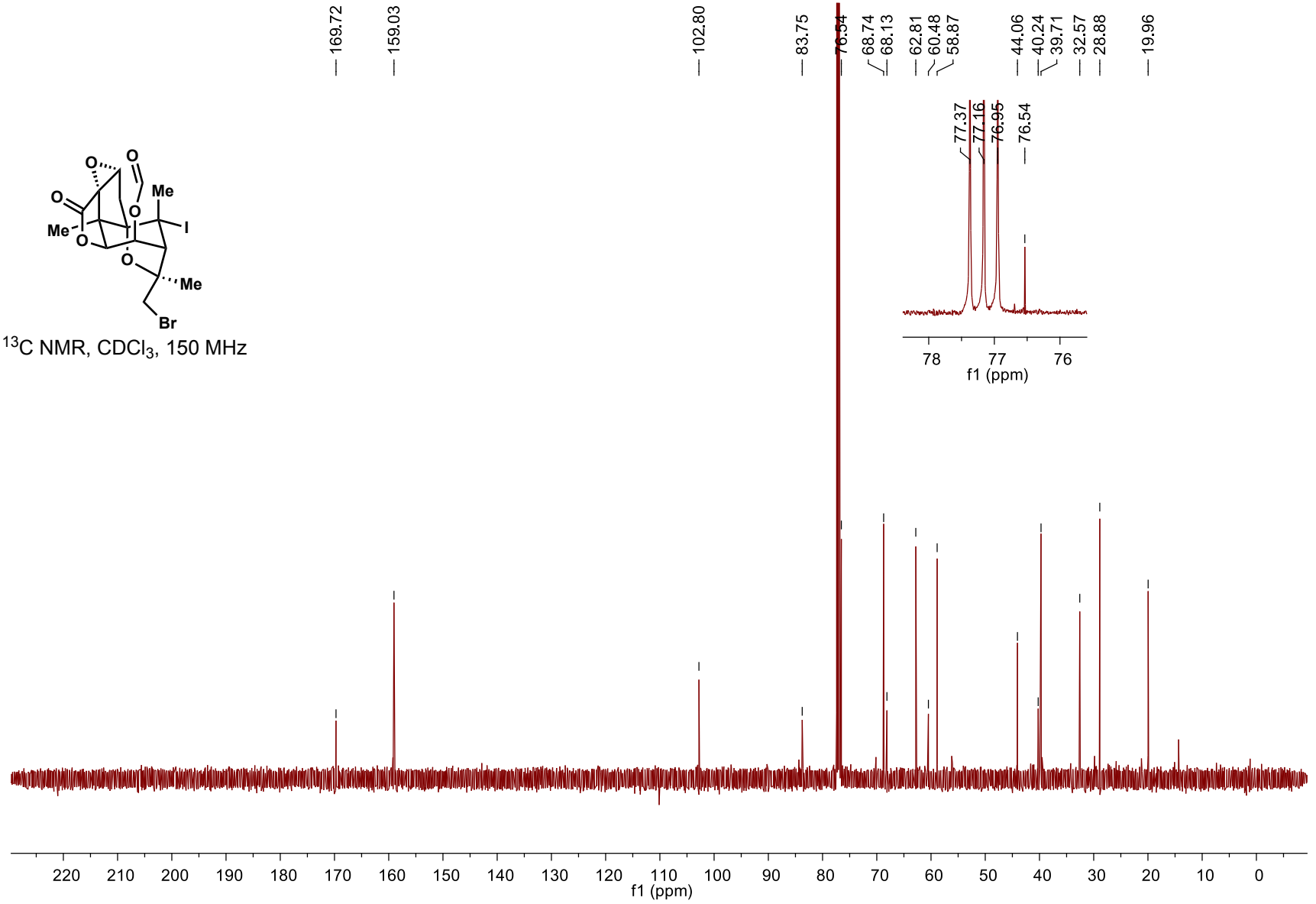



*2.5:1 d.r., major shown

$^{13}C$ NMR, $CDCl_3$, 150 MHz


8
H
H
15
OH
O
O
Me
Me
O
O
Me
Br
*2.5:1 d.r., major shown
1H-1H NOESY, CDCl3, 600 MHz
H15
H8
H8-H15
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
8.0

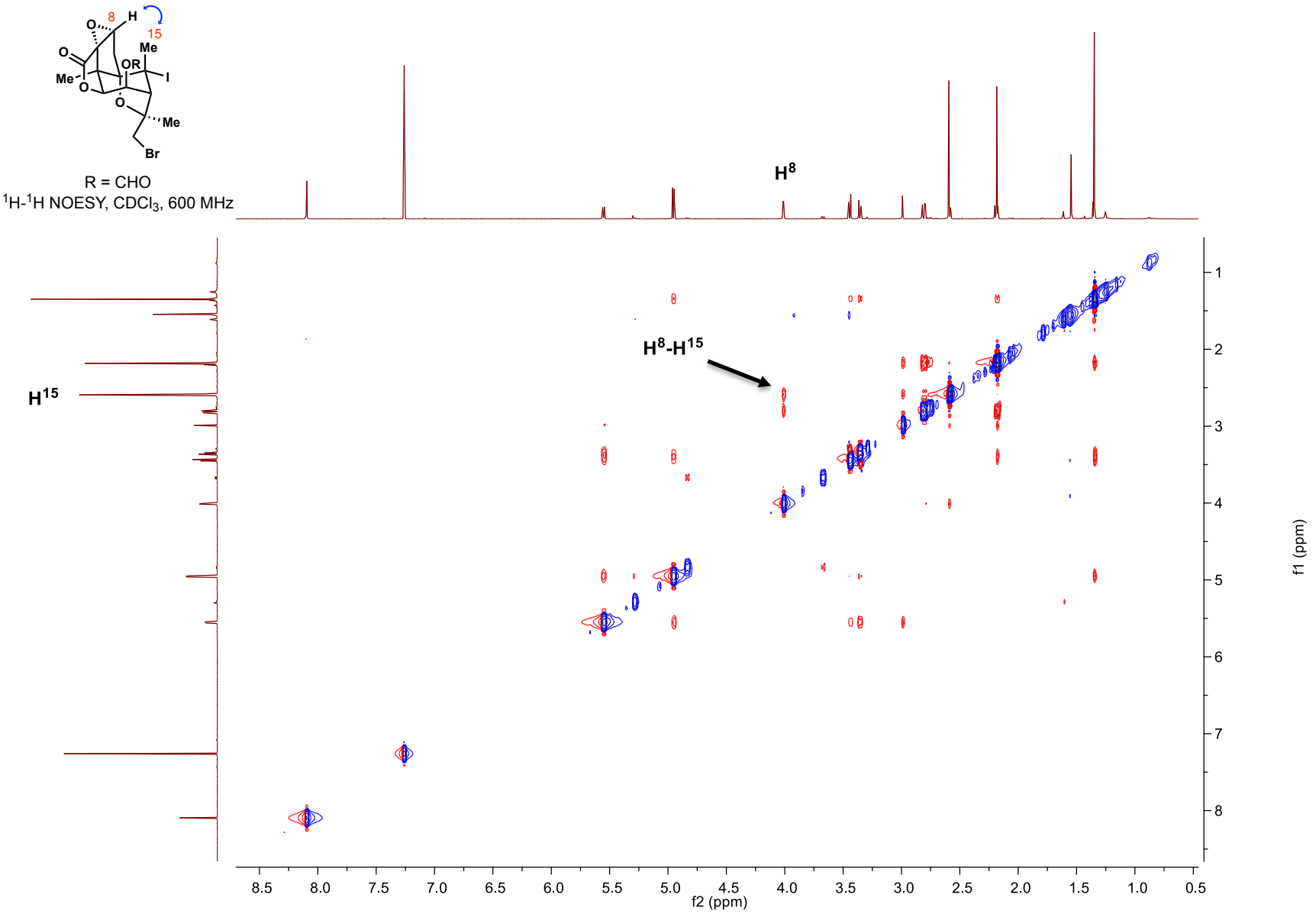

8.10
8.09
7.26
5.56
5.55
4.96
4.95
4.02
4.01
4.01
4.01
3.43
3.37
3.35
2.99
2.99
2.79
2.58
2.20
2.20
2.18
2.17
2.17
1.35
O
O
O
Me
O
Me
O
I
O
Me
Br
1H NMR, CDCl3, 600 MHz
1.04
1.00
1.05
1.07
1.05
1.00
0.96
1.14
3.15
3.96
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

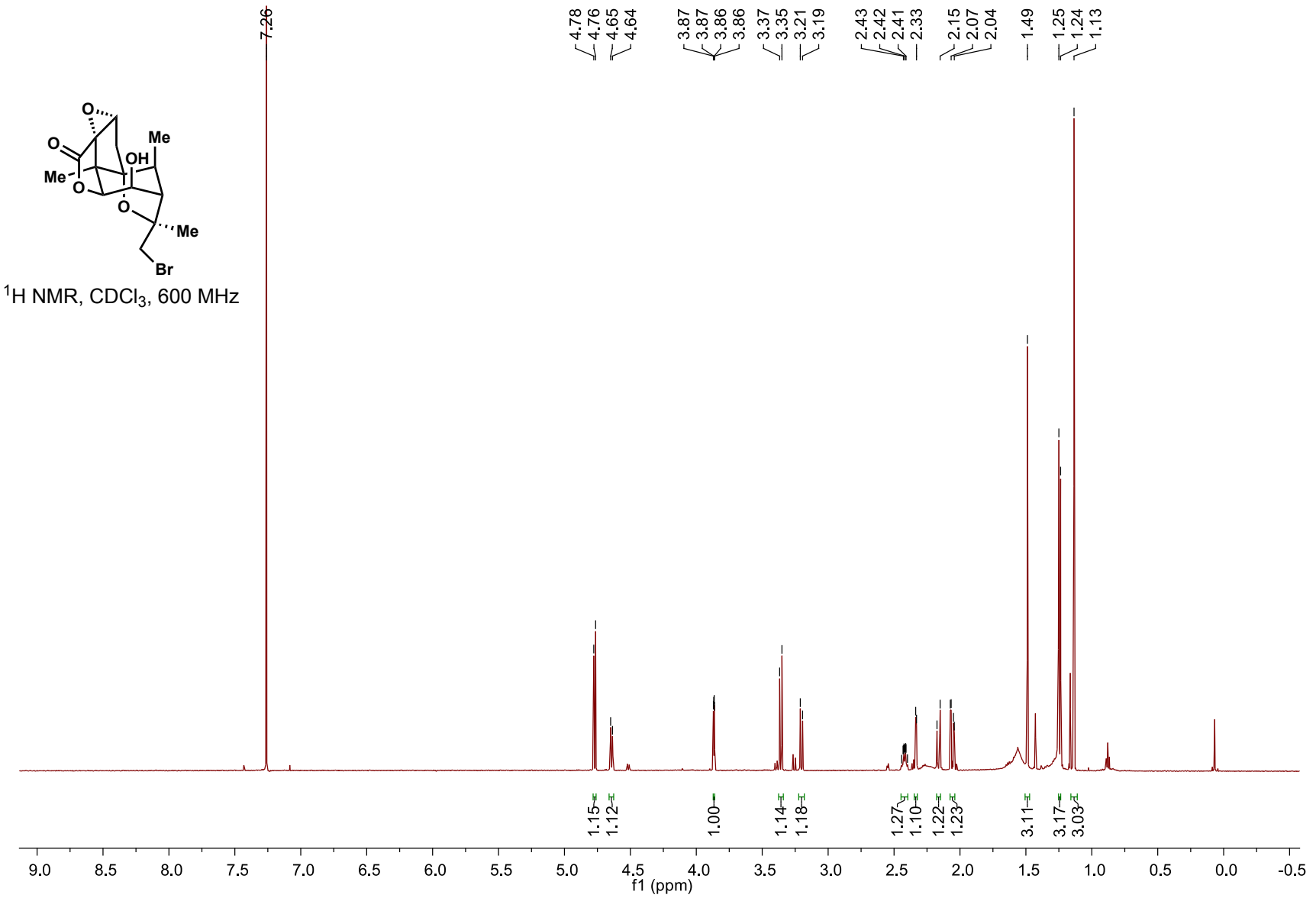


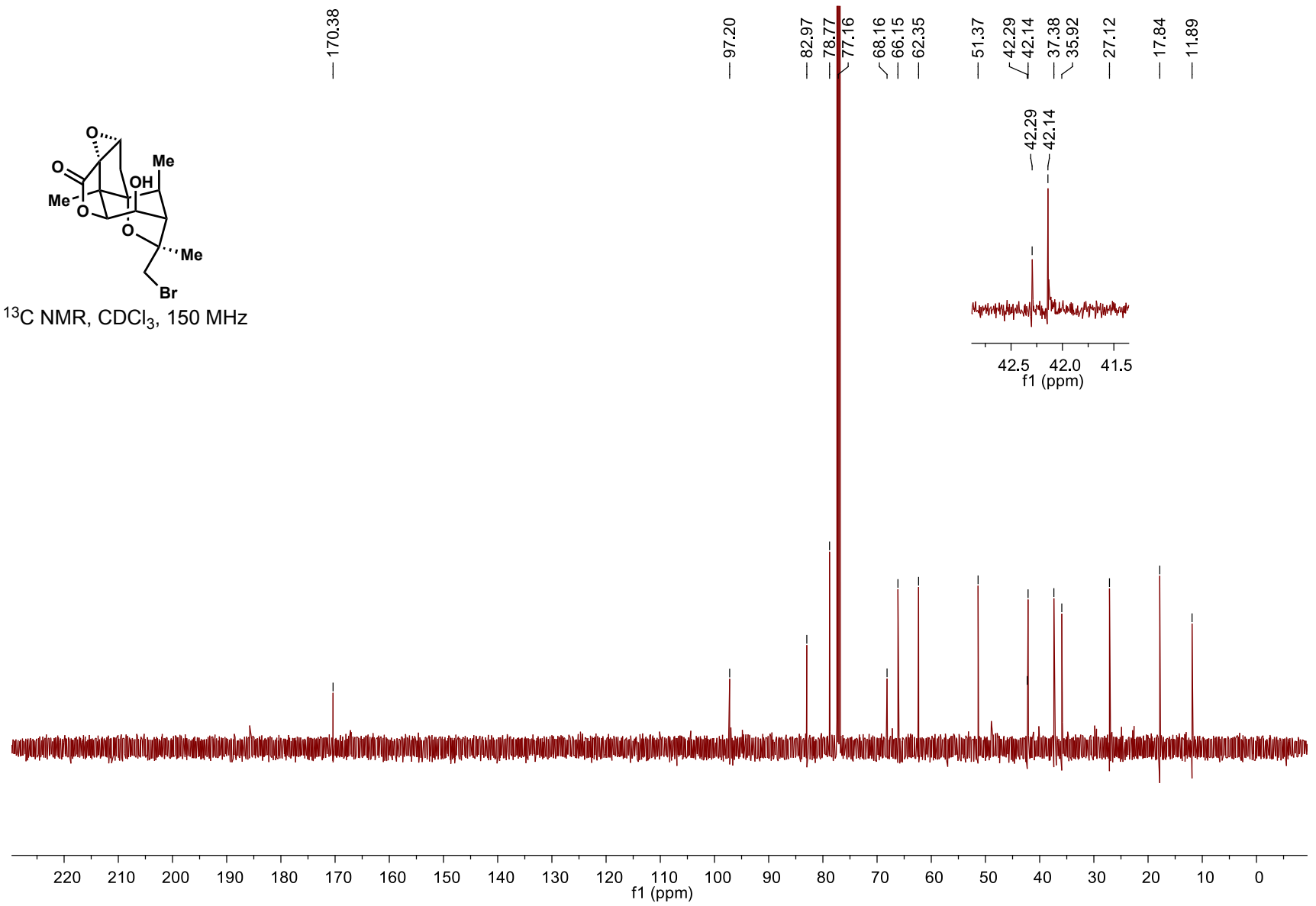


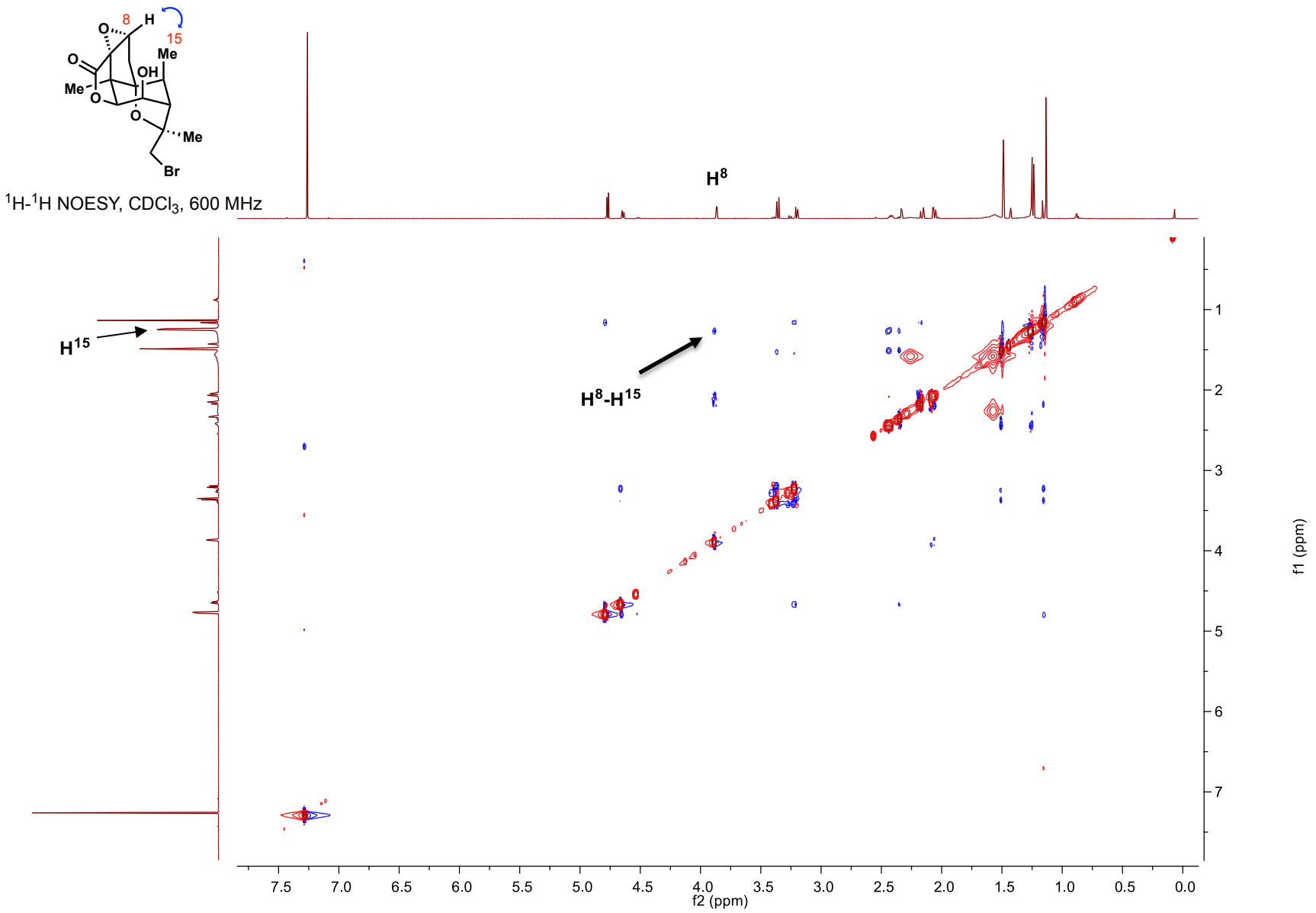


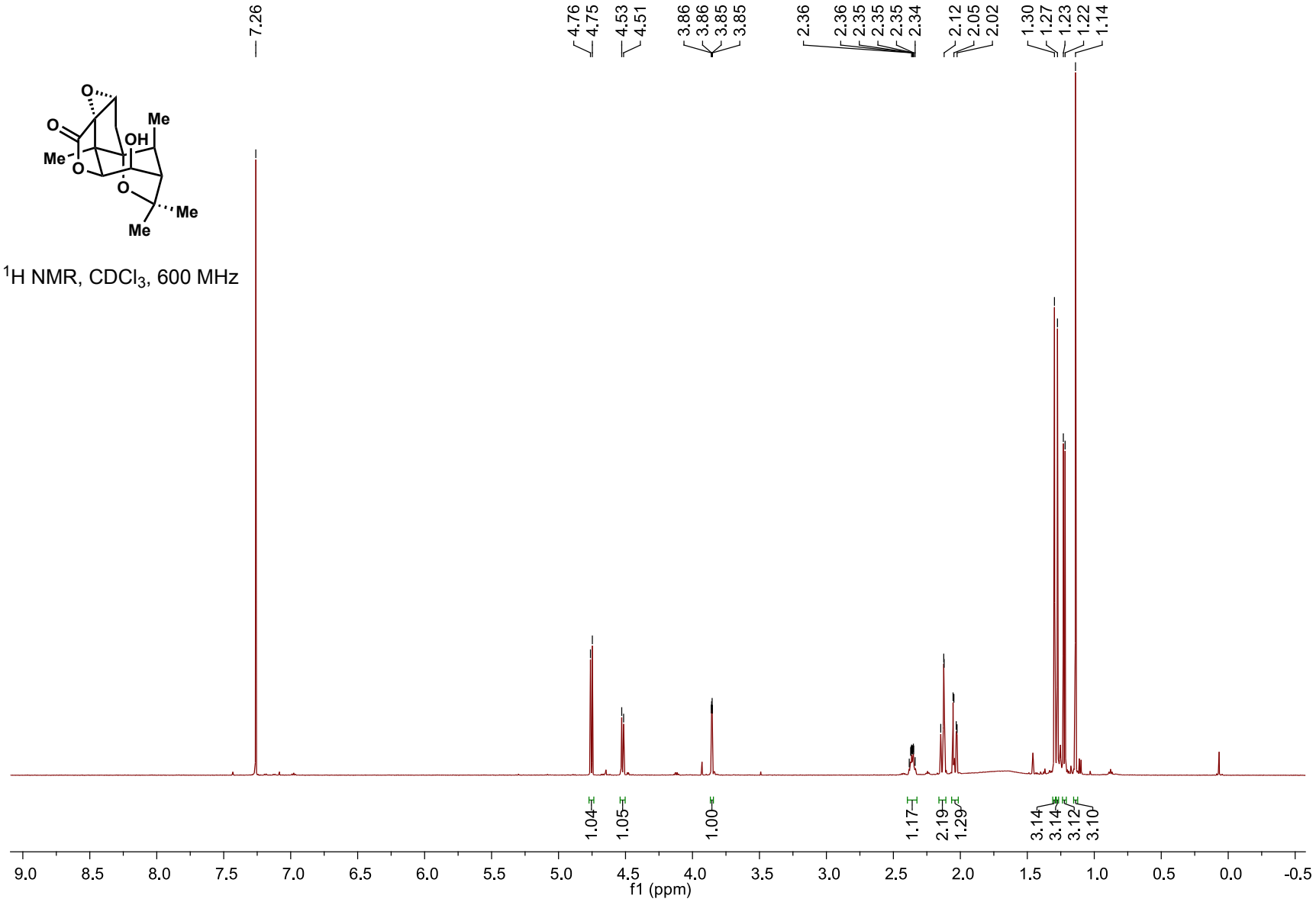
$^{13}C$ NMR, $CDCl_3$, 150 MHz

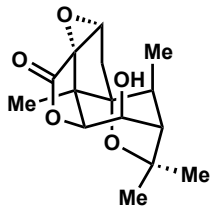

R = CHO
$^1$H-$^1$H NOESY, CDCl$_3$, 600 MHz
H$^8$
H$^{15}$
H$^8$-H$^{15}$
f2 (ppm)
f1 (ppm)


O
O
Me
OH
Me
O
O
Me
Br
$^1$H NMR, $CDCl_3$, 600 MHz
7.26
4.78
4.76
4.65
4.64
3.87
3.87
3.86
3.86
3.37
3.35
3.21
3.19
2.43
2.42
2.41
2.33
2.15
2.07
2.04
1.49
1.25
1.24
1.13
1.15
1.12
1.00
1.14
1.18
1.27
1.10
1.22
1.23
3.11
3.17
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

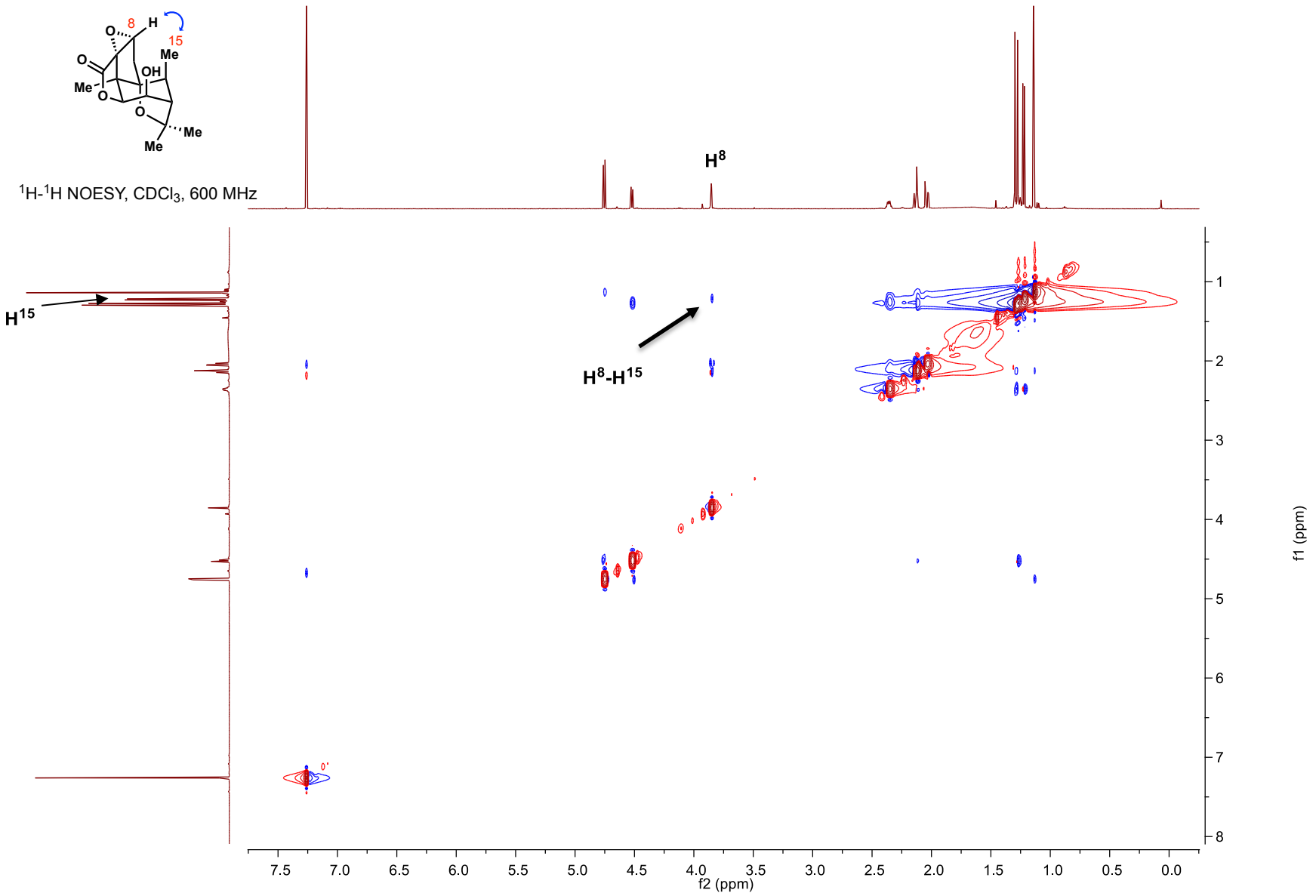

170.38
97.20
82.97
78.77
77.16
68.16
66.15
62.35
51.37
42.29
42.14
37.38
35.92
27.12
17.84
11.89
O
O
Me
OH
Me
O
O
Me
Br
13C NMR, CDCl3, 150 MHz
42.29
42.14
42.5
42.0
41.5
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

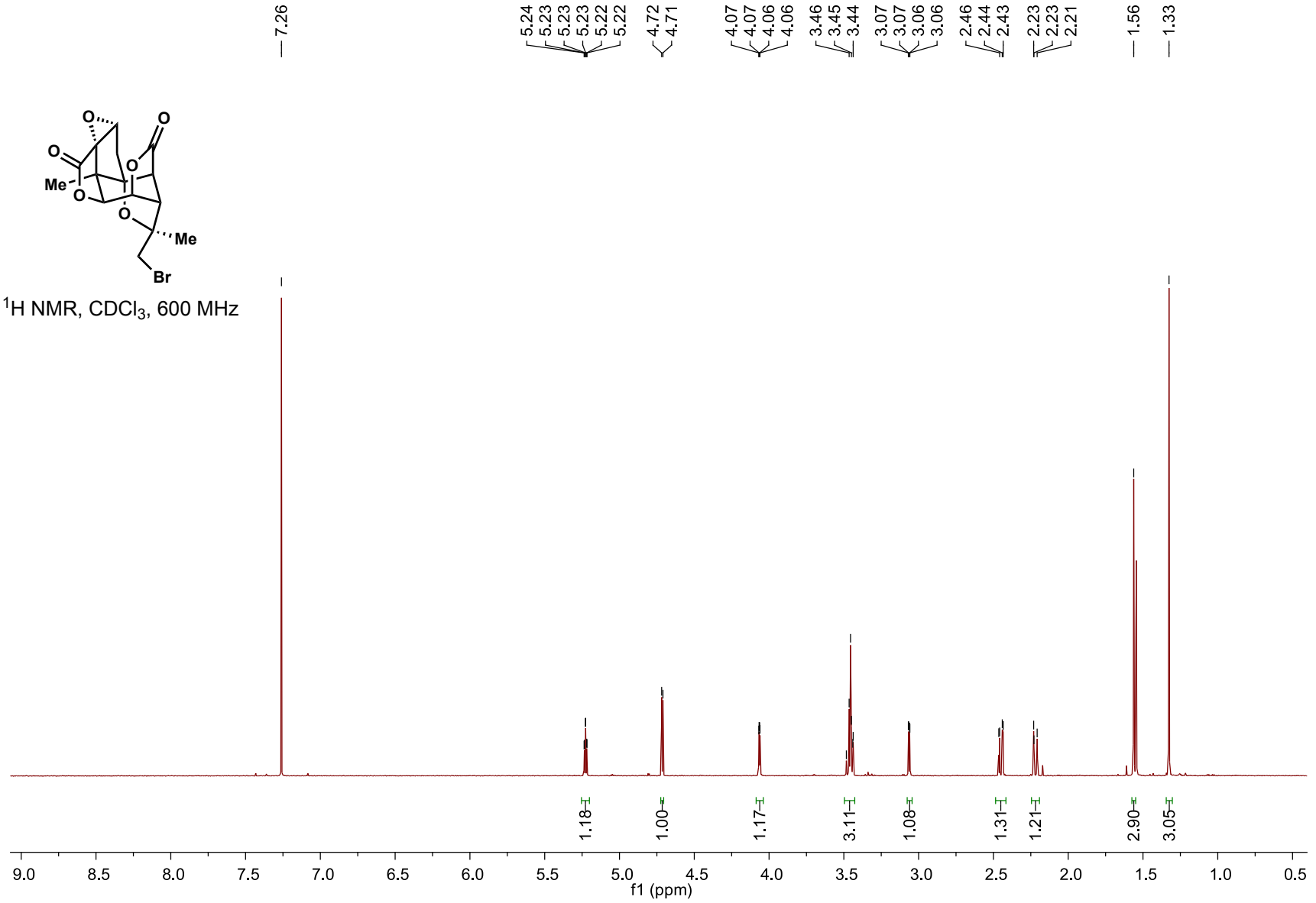

8
H
15
O
O
Me
OH
Me
O
O
Me
Br
$^1$H-$^1$H NOESY, CDCl$_3$, 600 MHz
H$^8$
H$^{15}$
H$^8$-H$^{15}$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
1
2
3
4
5
6
7
f1 (ppm)

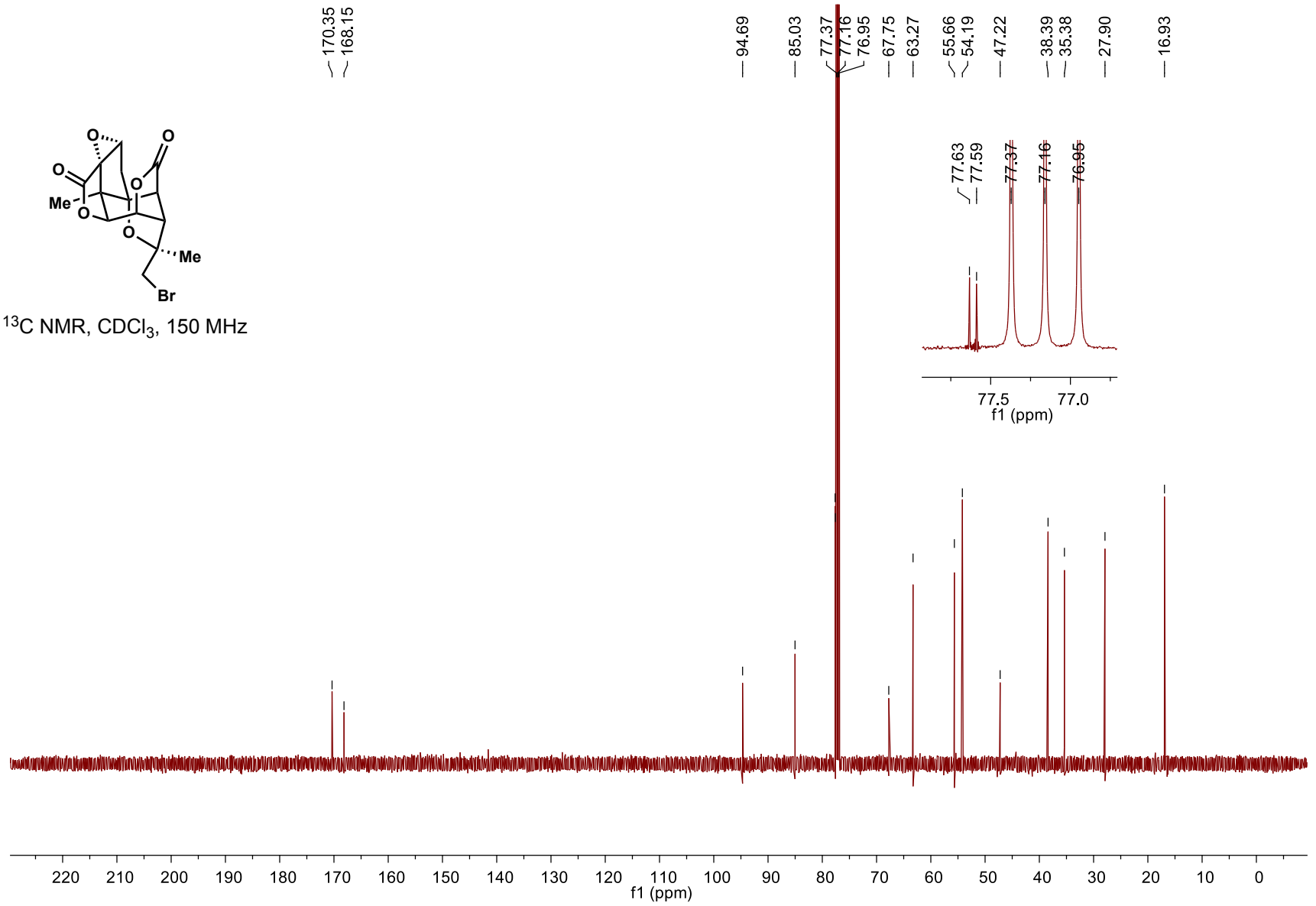

7.26
4.76
4.75
4.53
4.51
3.86
3.86
3.85
3.85
2.36
2.36
2.35
2.35
2.35
2.34
2.12
2.05
2.02
1.30
1.27
1.23
1.22
1.14
O
O
Me
OH
Me
O
O
Me
Me
1H NMR, CDCl3, 600 MHz
1.04
1.05
1.00
1.17
2.19
1.29
3.14
3.14
3.12
3.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



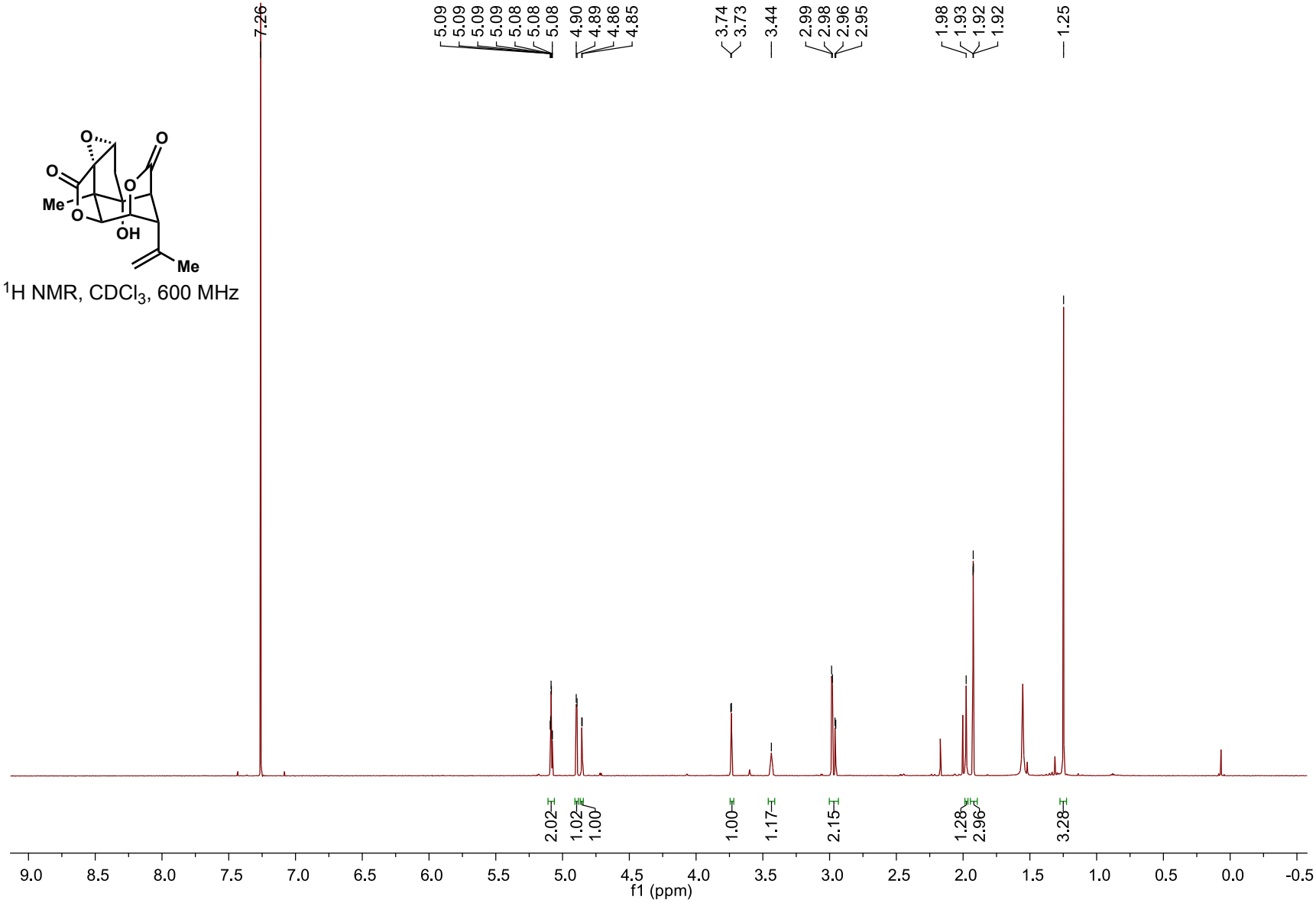

$^{13}C$ NMR, $CDCl_3$, 150 MHz


8
H
15
Me
O
OH
Me
O
O
Me
Me
$^1$H-$^1$H NOESY, CDCl$_3$, 600 MHz
H$^8$
H$^{15}$
H$^8$-H$^{15}$
f2 (ppm)
f1 (ppm)

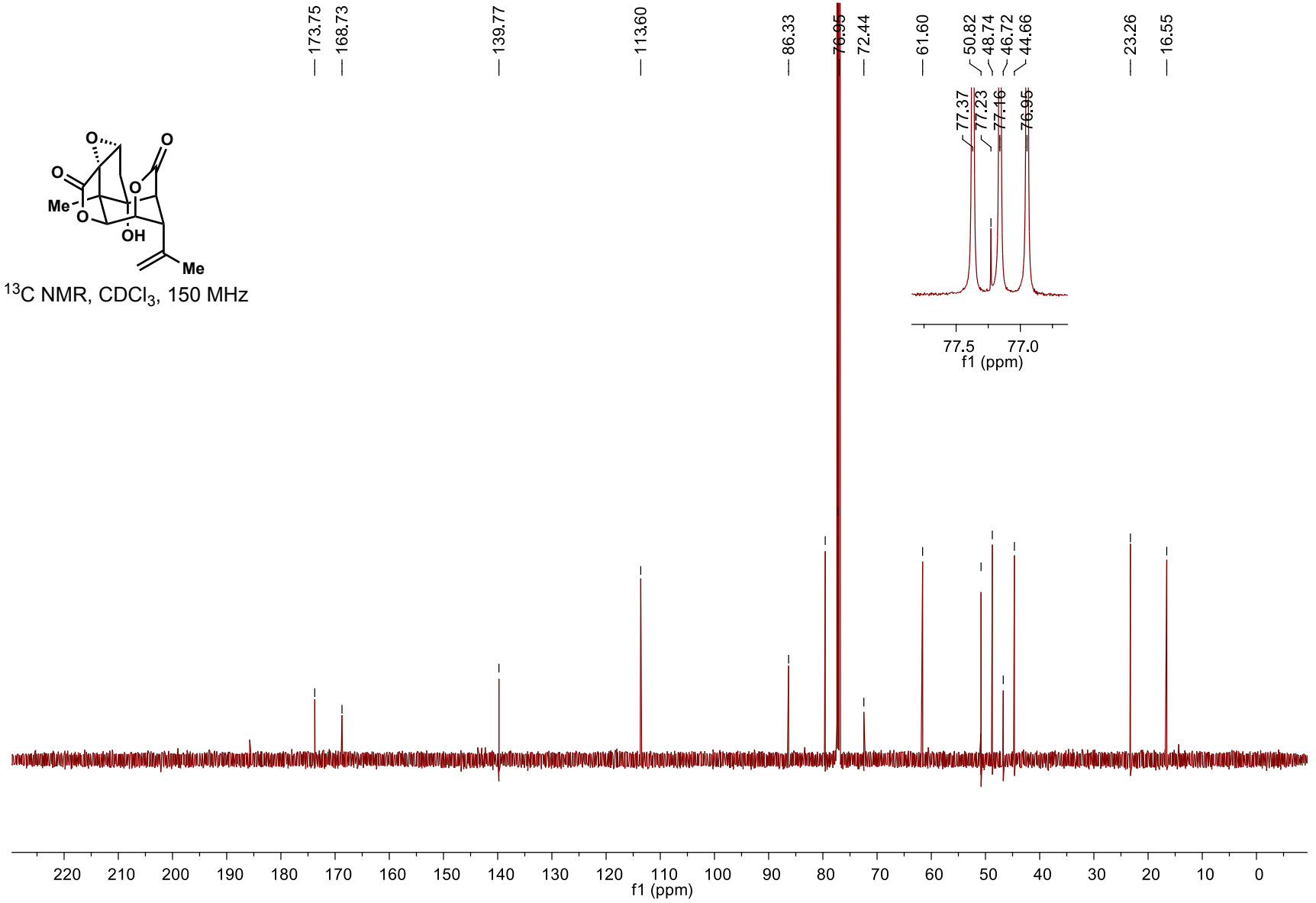

7.26
5.24
5.23
5.23
5.23
5.22
5.22
4.72
4.71
4.07
4.07
4.06
4.06
3.46
3.45
3.44
3.07
3.07
3.06
3.06
2.46
2.44
2.43
2.23
2.23
2.21
1.56
1.33
O
O
O
O
O
Me
O
Me
Br
1H NMR, CDCl3, 600 MHz
1.18
1.00
1.17
3.11
1.08
1.31
1.21
2.90
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

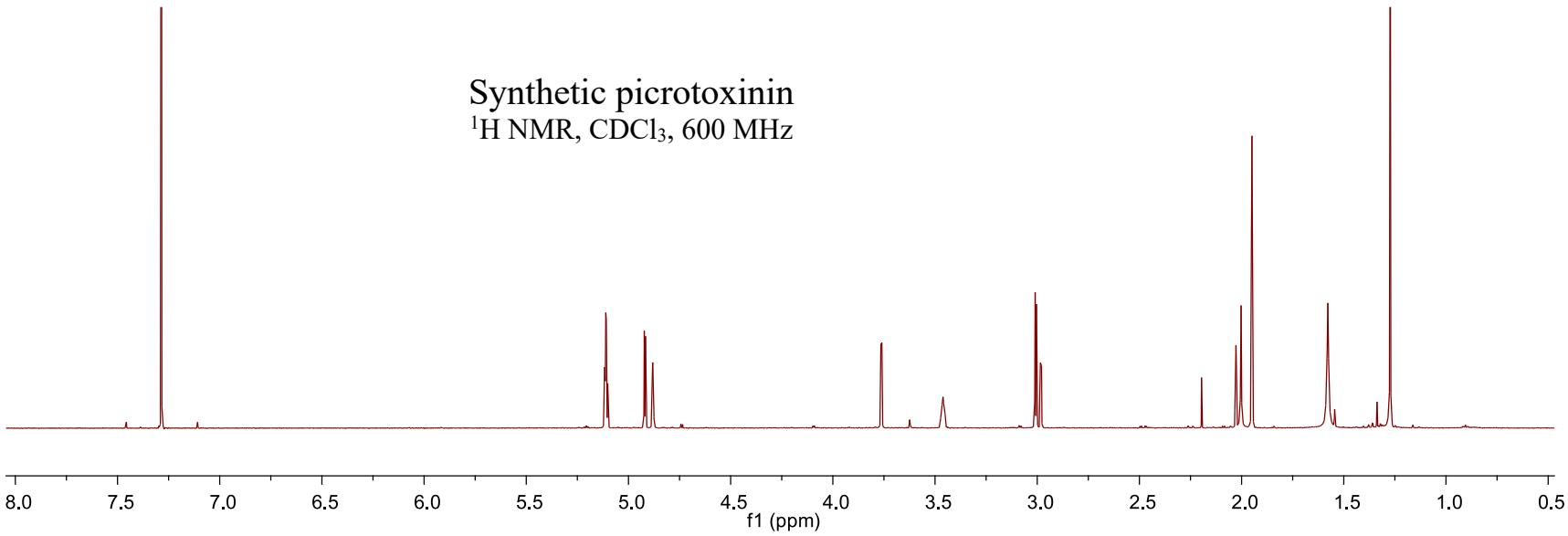


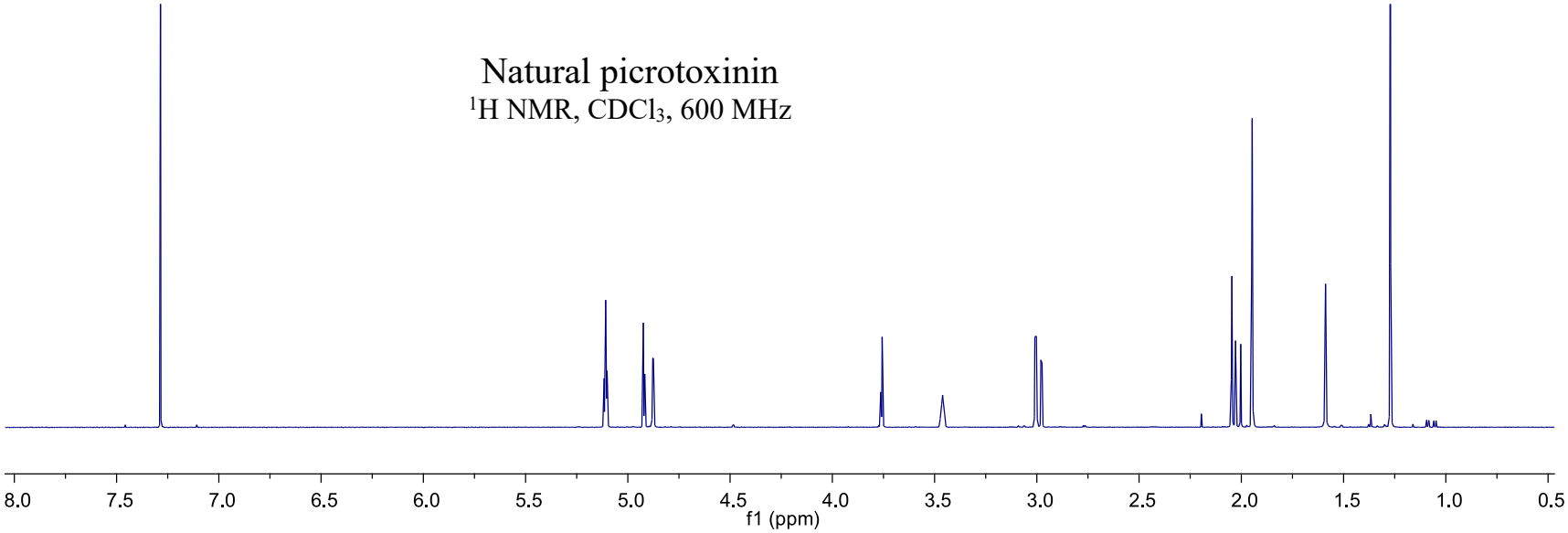

$^{13}C$ NMR, $CDCl_3$, 150 MHz




$^1$H NMR, $CDCl_3$, 600 MHz

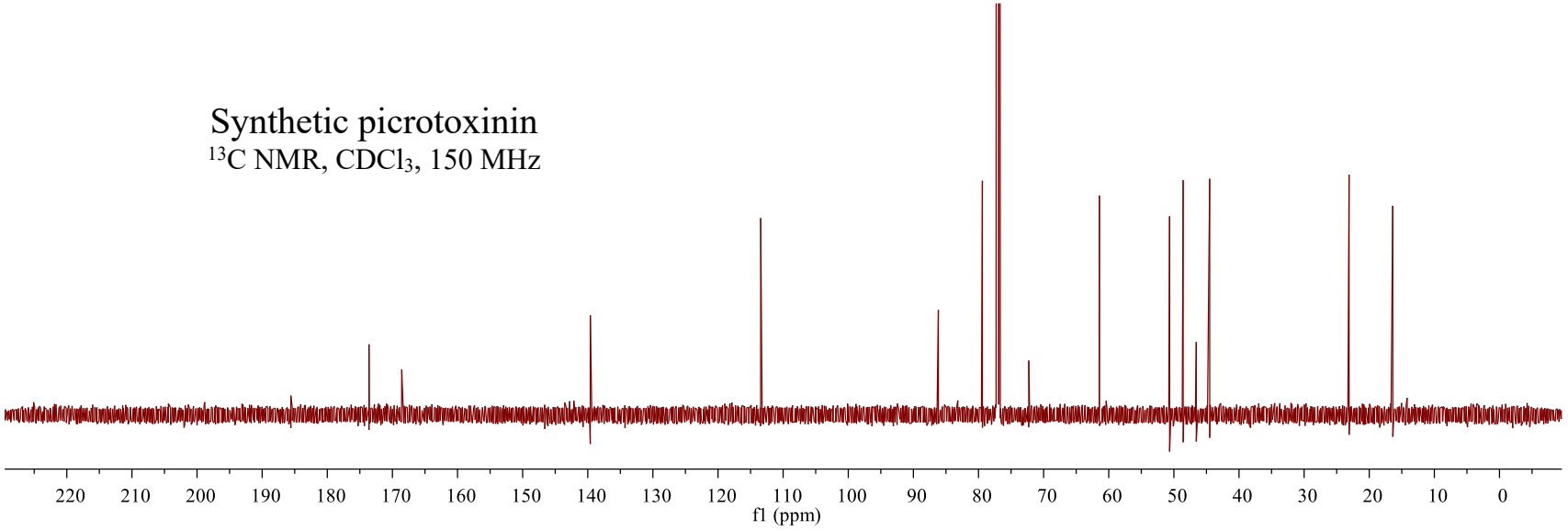

173.75
168.73
139.77
113.60
86.33
76.95
72.44
61.60
50.82
48.74
46.72
44.66
23.26
16.55
77.37
77.23
77.16
76.95
77.5
77.0
f1 (ppm)
O
O
O
Me
O
OH
Me
13C NMR, CDCl3, 150 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Synthetic picrotoxinin
$^1$H NMR, $CDCl_3$, 600 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Natural picrotoxinin
$^1$H NMR, $CDCl_3$, 600 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

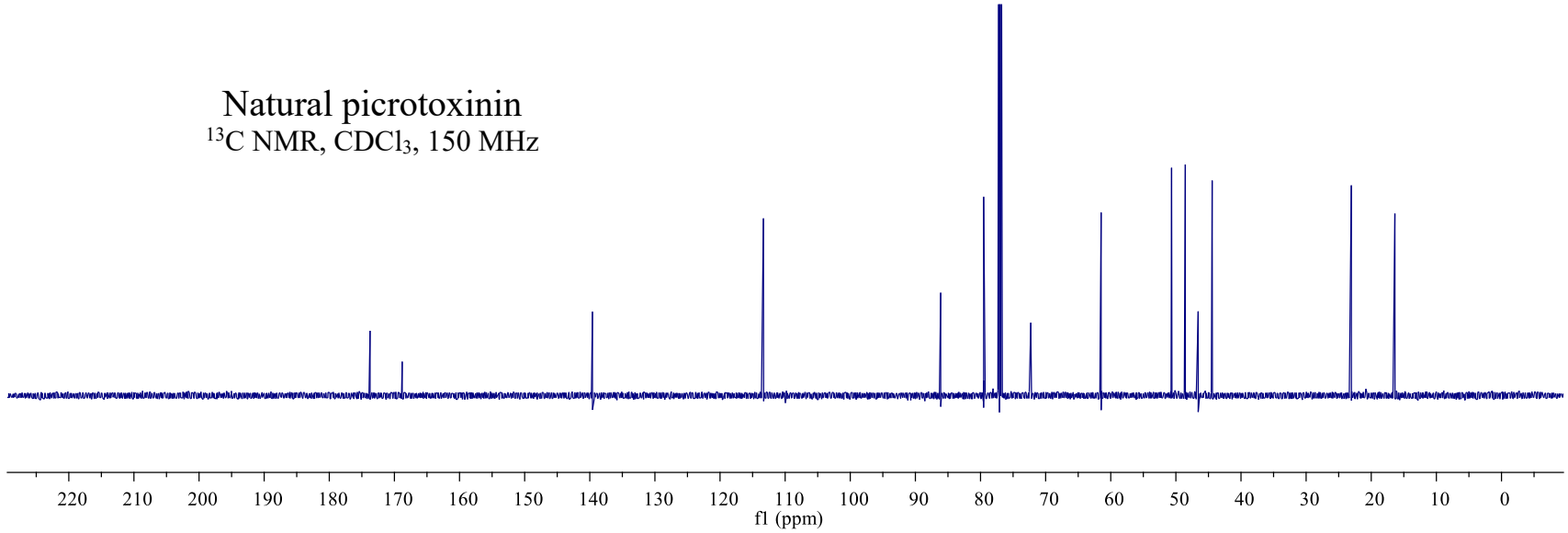
Synthetic picrotoxinin

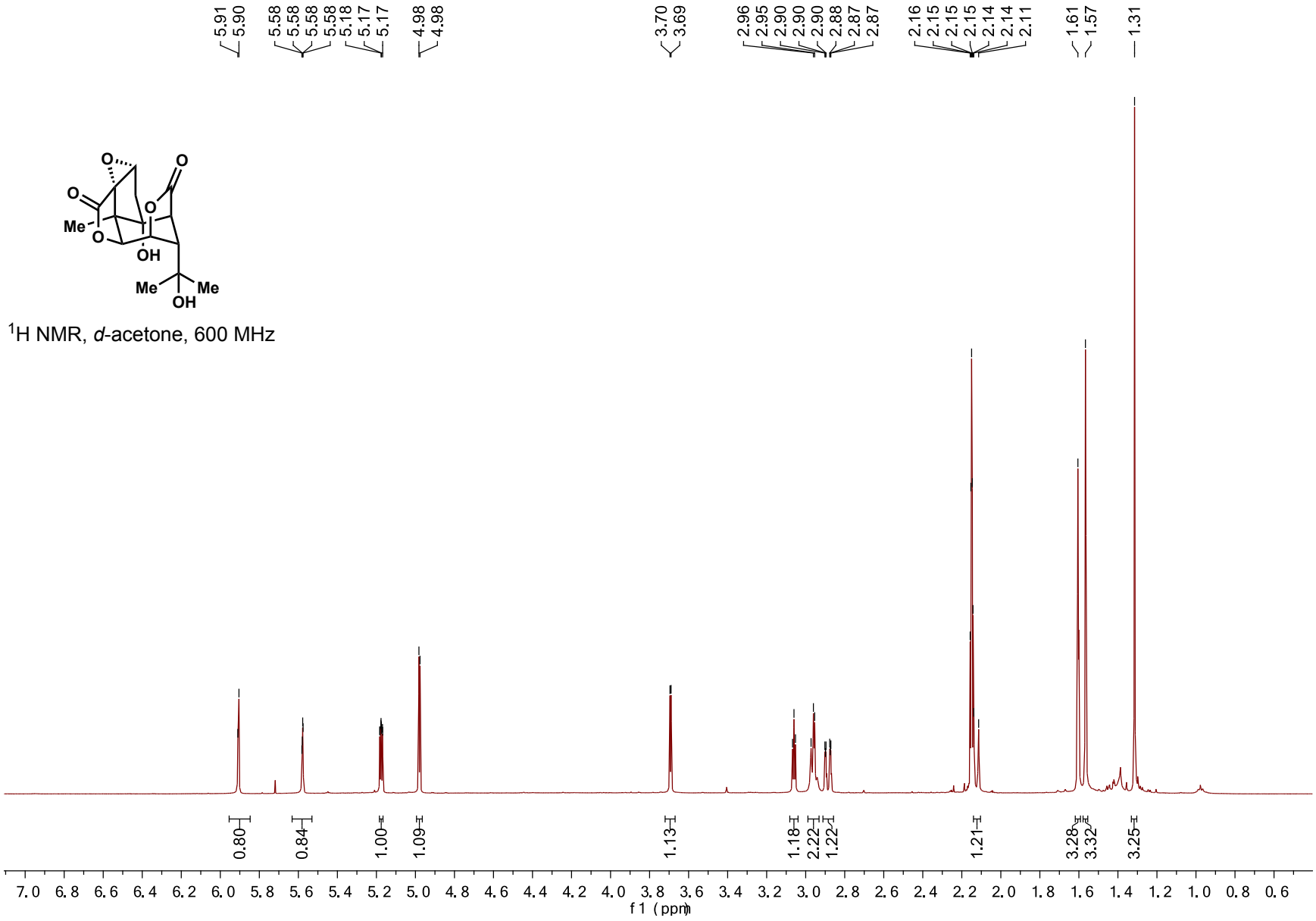
$^{13}C$ NMR, $CDCl_3$, 150 MHz



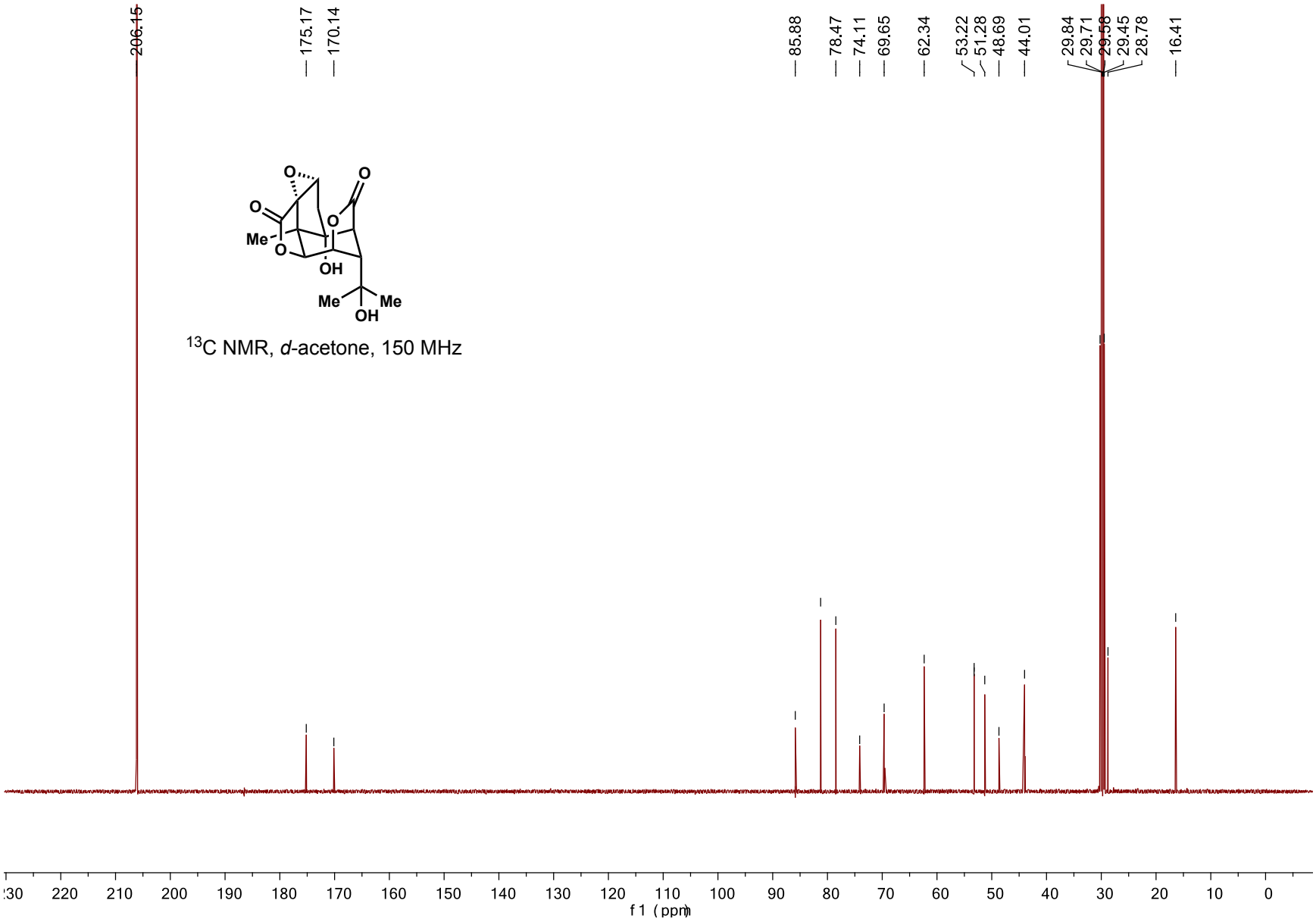

Natural picrotoxinin

$^{13}C$ NMR, $CDCl_3$, 150 MHz






$^1$H NMR, *d*-acetone, 600 MHz


206.15
175.17
170.14
85.88
78.47
74.11
69.65
62.34
53.22
51.28
48.69
44.01
29.84
29.71
29.58
29.45
28.78
16.41
O
O
O
O
Me
O
OH
Me
Me
OH
13C NMR, d-acetone, 150 MHz
f1 (ppm)

5. X-ray data

Intramolecular aldol product (**2**) (CCDC1999782)

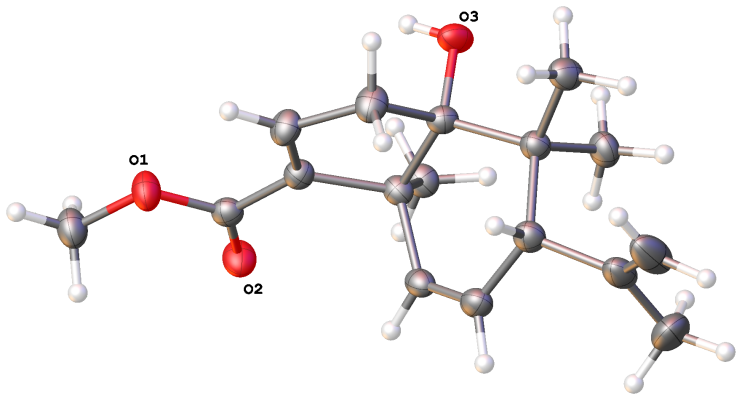



Table S1. Crystal data and structure refinement for shenvi124.

| | | |
|---|---|---|
| Identification code | SC2329 | |
| Empirical formula | C17 H24 O3 | |
| Formula weight | 276.36 | |
| Temperature | 100.15 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 7.1439(4) Å | α= 90°. |
| | b = 7.9679(5) Å | β= 90°. |
| | c = 27.4909(11) Å | γ = 90°. |
| Volume | 1564.83(15) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.173 $Mg/m^3$ | |
| Absorption coefficient | 0.628 $mm^{-1}$ | |
| F(000) | 600 | |
| Crystal size | 0.3 x 0.24 x 0.18 $mm^3$ | |
| Theta range for data collection | 3.215 to 68.388°. | |
| Index ranges | -8<=h<=8, -9<=k<=9, -32<=l<=33 | |
| Reflections collected | 9317 | |
| Independent reflections | 2856 [R(int) = 0.0338] | |
| Completeness to theta = 67.679° | 99.6 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.5210 and 0.4340 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2856 / 0 / 190 | |
| Goodness-of-fit on $F^2$ | 1.057 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0340, wR2 = 0.0857 | |
| R indices (all data) | R1 = 0.0360, wR2 = 0.0868 | |

| | |
|---|---|
| Absolute structure parameter | 0.00(9) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.246 and -0.139 e.Å$^{-3}$ |

Bromoetherification product (**6**) (CCDC1999783)

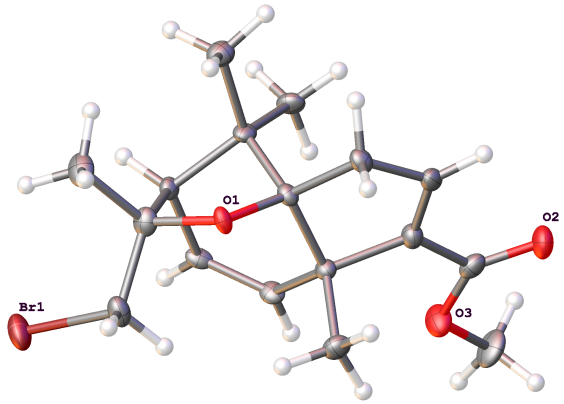



Table S2. Crystal data and structure refinement for shenvi118_0m_a.

| | | |
|---|---|---|
| Identification code | SC2385 | |
| Empirical formula | C17 H23 Br O3 | |
| Formula weight | 355.26 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Hexagonal | |
| Space group | $P6_1$ | |
| Unit cell dimensions | a = 8.8468(15) Å | α= 90°. |
| | b = 8.8468(15) Å | β= 90°. |
| | c = 35.599(6) Å | γ = 120°. |
| Volume | 2412.9(9) Å$^3$ | |
| Z | 6 | |
| Density (calculated) | 1.467 Mg/m$^3$ | |
| Absorption coefficient | 3.545 mm$^{-1}$ | |
| F(000) | 1104 | |
| Crystal size | 0.25 x 0.2 x 0.1 mm$^3$ | |
| Theta range for data collection | 5.775 to 68.204°. | |
| Index ranges | -10<=h<=10, -10<=k<=10, -42<=l<=42 | |
| Reflections collected | 16091 | |
| Independent reflections | 2947 [R(int) = 0.0625] | |
| Completeness to theta = 67.679° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.5849 and 0.4274 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2947 / 1 / 195 | |

| | |
|---|---|
| Goodness-of-fit on $F^2$ | 1.069 |
| Final R indices [I>2sigma(I)] | R1 = 0.0358, wR2 = 0.0825 |
| R indices (all data) | R1 = 0.0381, wR2 = 0.0835 |
| Absolute structure parameter | 0.052(13) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.318 and -0.539 e.Å$^{-3}$ |

Epoxidation product (**7**) (CCDC1999788)

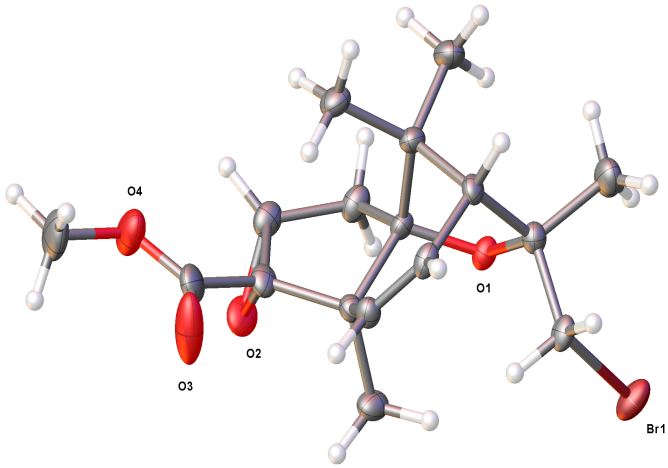



Table S3. Crystal data and structure refinement for Shenvi126.

| | | |
|---|---|---|
| Identification code | SC2425 | |
| Empirical formula | C17 H23 Br O4 | |
| Molecular formula | C17 H23 Br O4 | |
| Formula weight | 371.26 | |
| Temperature | 100.0 K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 9.9382(19) Å | α= 90°. |
| | b = 11.216(2) Å | β= 90°. |
| | c = 14.840(3) Å | γ = 90°. |
| Volume | 1654.2(5) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.491 Mg/m$^3$ | |
| Absorption coefficient | 2.500 mm$^{-1}$ | |
| F(000) | 768 | |
| Crystal size | 0.277 x 0.234 x 0.216 mm$^3$ | |

| | |
|---|---|
| Crystal color, habit | Colorless Block |
| Theta range for data collection | 2.276 to 26.423°. |
| Index ranges | -12<=h<=12, -14<=k<=14, -17<=l<=18 |
| Reflections collected | 24212 |
| Independent reflections | 3393 [R(int) = 0.0690, R(sigma) = 0.0538] |
| Completeness to theta = 25.000° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.0932 and 0.0571 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3393 / 0 / 214 |
| Goodness-of-fit on $F^2$ | 1.032 |
| Final R indices [I>2sigma(I)] | R1 = 0.0315, wR2 = 0.0620 |
| R indices (all data) | R1 = 0.0416, wR2 = 0.0643 |
| Absolute structure parameter | 0.032(6) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.304 and -0.343 e.Å$^{-3}$ |

Dihydroxylation product (**8**) (CCDC1999787)

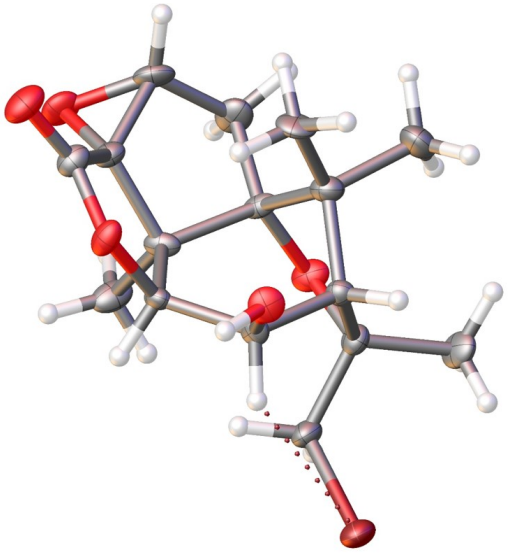


Table S4. Crystal data and structure refinement for shenvi178_0m_a_sq.

| | | |
|---|---|---|
| Identification code | shenvi178 | |
| Empirical formula | C16 H20.90 Br O5 | |
| Formula weight | 373.14 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 11.11210(10) Å | α= 90°. |
| | b = 11.34500(10) Å | β= 90°. |

| | |
|---|---|
| | c = 24.5785(3) Å γ = 90°. |
| Volume | 3098.53(5) $Å^3$ |
| Z, Z’ | 8, 2 |
| Density (calculated) | 1.600 $Mg/m^3$ |
| Absorption coefficient | 3.814 $mm^{-1}$ |
| F(000) | 1535 |
| Crystal size | 0.25 x 0.23 x 0.21 $mm^3$ |
| Theta range for data collection | 3.596 to 68.523°. |
| Index ranges | -13<=h<=13, -13<=k<=13, -25<=l<=29 |
| Reflections collected | 32068 |
| Independent reflections | 5664 [R(int) = 0.0582] |
| Completeness to theta = 67.679° | 99.5 % |
| Absorption correction | Multi-scan |
| Max. and min. transmission | 0.7503 and 0.6547 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 5664 / 0 / 418 |
| Goodness-of-fit on $F^2$ | 1.079 |
| Final R indices [I>2sigma(I)] | R1 = 0.0575, wR2 = 0.1518 |
| R indices (all data) | R1 = 0.0580, wR2 = 0.1523 |
| Absolute structure parameter | 0.074(8) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 3.120 and -0.514 $e.Å^{-3}$ |

Ketone **15** (CCDC1999786)

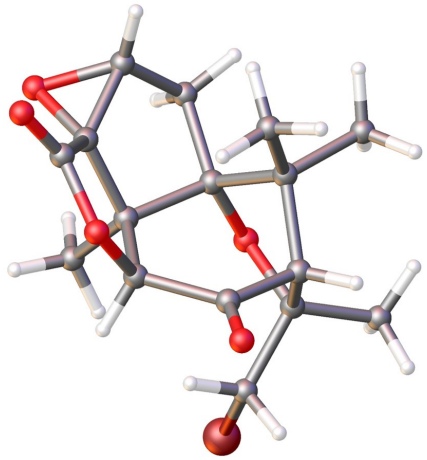


Table S5. Crystal data and structure refinement for shenvi197.

| | | |
|---|---|---|
| Identification code | shenvi197 | |
| Empirical formula | C16 H19 Br O5 | |
| Molecular formula | C16 H19 Br O5 | |
| Formula weight | 371.22 | |
| Temperature | 100.0 K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P 1 21 1 | |
| Unit cell dimensions | a = 8.7464(5) Å | α= 90°. |
| | b = 8.1031(6) Å | β= 100.894(2)°. |
| | c = 10.9434(8) Å | γ = 90°. |
| Volume | 761.61(9) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.619 $Mg/m^3$ | |
| Absorption coefficient | 2.720 $mm^{-1}$ | |
| F(000) | 380 | |
| Crystal size | 0.3 x 0.25 x 0.2 $mm^3$ | |
| Crystal color, habit | colourless block | |
| Theta range for data collection | 2.742 to 28.304°. | |
| Index ranges | -7<=h<=11, -10<=k<=10, -14<=l<=14 | |
| Reflections collected | 6171 | |
| Independent reflections | 3548 [R(int) = 0.0217] | |
| Completeness to theta = 25.242° | 98.3 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.4920 and 0.4421 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3548 / 1 / 203 | |
| Goodness-of-fit on $F^2$ | 1.051 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0280, wR2 = 0.0608 | |
| R indices (all data) | R1 = 0.0313, wR2 = 0.0622 | |

| | |
|---|---|
| Absolute structure parameter | -0.017(5) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.778 and -0.547 e.Å$^{-3}$ |

***des*-Br-12** (CCDC1999791)

Table S6. Crystal data and structure refinement for Shenvi220.

| | | |
|---|---|---|
| Identification code | shenvi220 | |
| Empirical formula | C15 H20 O5 | |
| Molecular formula | C15 H20 O5 | |
| Formula weight | 280.31 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P 1 21 1 | |
| Unit cell dimensions | a = 7.33000(10) Å | α= 90°. |
| | b = 10.37940(10) Å | β= 101.4390(10)°. |
| | c = 8.96710(10) Å | γ = 90°. |
| Volume | 668.674(14) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.392 $Mg/m^3$ | |
| Absorption coefficient | 0.862 $mm^{-1}$ | |
| F(000) | 300 | |
| Crystal size | 0.17 x 0.15 x 0.085 $mm^3$ | |
| Crystal color, habit | colorless block | |
| Theta range for data collection | 5.032 to 70.114°. | |
| Index ranges | -8<=h<=8, -12<=k<=12, -10<=l<=10 | |
| Reflections collected | 11000 | |
| Independent reflections | 2506 [R(int) = 0.0245] | |
| Completeness to theta = 67.500° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7533 and 0.6867 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2506 / 1 / 191 | |
| Goodness-of-fit on $F^2$ | 1.053 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0248, wR2 = 0.0637 | |
| R indices (all data) | R1 = 0.0250, wR2 = 0.0638 | |

| | |
|---|---|
| Absolute structure parameter | -0.04(4) |
| Extinction coefficient | 0.0044(9) |
| Largest diff. peak and hole | 0.220 and -0.146 e.Å$^{-3}$ |

5-methyl-bromopicrotoxinin (**18**) (CCDC1999789)

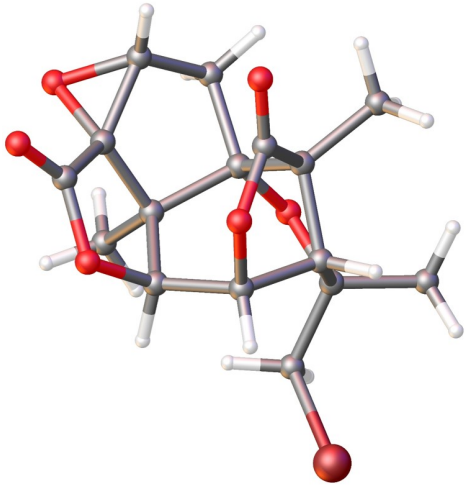


Table S7. Crystal data and structure refinement for Shenvi211_a.

| | | |
|---|---|---|
| Identification code | shenvi211 | |
| Empirical formula | C16 H17 Br O6 | |
| Formula weight | 385.20 | |
| Temperature | 100.0 K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 8.0004(4) Å | α= 90°. |
| | b = 11.8702(5) Å | β= 90°. |
| | c = 15.6494(7) Å | γ = 90°. |
| Volume | 1486.17(12) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.722 $Mg/m^3$ | |
| Absorption coefficient | 2.796 $mm^{-1}$ | |
| F(000) | 784 | |
| Crystal size | 0.25 x 0.2 x 0.175 $mm^3$ | |
| Theta range for data collection | 2.153 to 26.371°. | |
| Index ranges | -10<=h<=9, -14<=k<=14, -17<=l<=19 | |
| Reflections collected | 12668 | |
| Independent reflections | 3027 [R(int) = 0.0319] | |
| Completeness to theta = 25.242° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.4910 and 0.4261 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3027 / 0 / 211 | |
| Goodness-of-fit on $F^2$ | 1.064 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0255, wR2 = 0.0615 | |
| R indices (all data) | R1 = 0.0280, wR2 = 0.0623 | |
| Absolute structure parameter | -0.003(4) | |

| | |
|---|---|
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.461 and -0.246 e.Å$^{-3}$ |

5-methyl-picrotoxinin (**20**) (CCDC1999784)

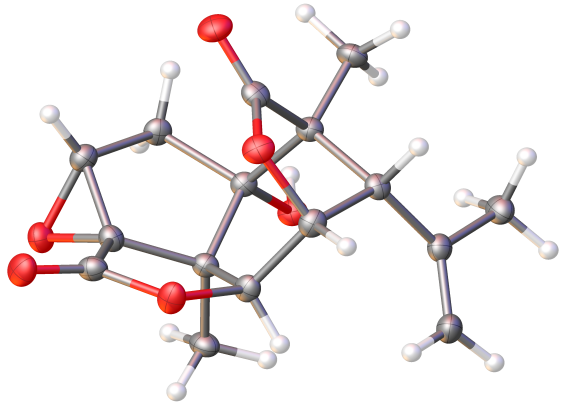


Table S8. Crystal data and structure refinement for Shenvi137.

| | | |
|---|---|---|
| Identification code | shenvi137 | |
| Empirical formula | C16 H18 O6 | |
| Molecular formula | C16 H18 O6 | |
| Formula weight | 306.30 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 8.1071(7) Å | α= 90°. |
| | b = 11.4912(10) Å | β= 90°. |
| | c = 14.8574(12) Å | γ = 90°. |
| Volume | 1384.1(2) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.470 Mg/m$^3$ | |
| Absorption coefficient | 0.946 mm$^{-1}$ | |
| F(000) | 648 | |
| Crystal size | 0.4 x 0.35 x 0.2 mm$^3$ | |
| Crystal color, habit | colorless block | |
| Theta range for data collection | 4.865 to 72.467°. | |
| Index ranges | -9<=h<=9, -14<=k<=14, -17<=l<=18 | |
| Reflections collected | 12109 | |
| Independent reflections | 2706 [R(int) = 0.0495] | |
| Completeness to theta = 67.500° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7536 and 0.6163 | |
| Refinement method | Full-matrix least-squares on F$^2$ | |

| | |
|---|---|
| Data / restraints / parameters | 2706 / 0 / 204 |
| Goodness-of-fit on $F^2$ | 1.070 |
| Final R indices [I>2sigma(I)] | R1 = 0.0290, wR2 = 0.0734 |
| R indices (all data) | R1 = 0.0291, wR2 = 0.0735 |
| Absolute structure parameter | -0.02(5) |
| Largest diff. peak and hole | 0.249 and -0.157 e.Å$^{-3}$ |

Bromo-picrotoxinin (**SI-3**) (CCDC1999792)

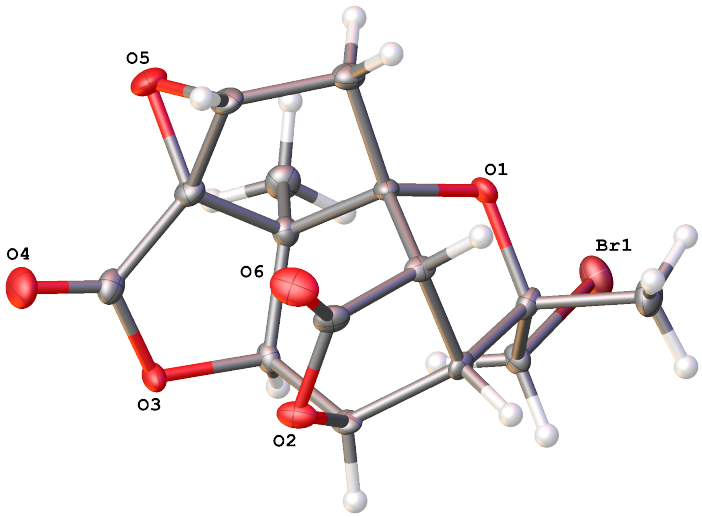



Table S9. Crystal data and structure refinement for shenvi140_0m_a.

| | | |
|---|---|---|
| Identification code | ASC2679 | |
| Empirical formula | C15 H15 Br O6 | |
| Formula weight | 371.18 | |
| Temperature | 100.0 K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Tetragonal | |
| Space group | $P4_3$ | |
| Unit cell dimensions | a = 7.0612(8) Å | α= 90°. |
| | b = 7.0612(8) Å | β= 90°. |
| | c = 28.368(3) Å | γ = 90°. |
| Volume | 1414.5(4) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.743 Mg/m$^3$ | |
| Absorption coefficient | 2.935 mm$^{-1}$ | |
| F(000) | 752 | |
| Crystal size | 0.34 x 0.34 x 0.32 mm$^3$ | |
| Theta range for data collection | 2.872 to 28.279°. | |
| Index ranges | -9<=h<=9, -9<=k<=8, -37<=l<=37 | |
| Reflections collected | 12634 | |
| Independent reflections | 3506 [R(int) = 0.0563] | |
| Completeness to theta = 25.242° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7457 and 0.6163 | |

| | |
|---|---|
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3506 / 1 / 201 |
| Goodness-of-fit on $F^2$ | 0.991 |
| Final R indices [I>2sigma(I)] | R1 = 0.0364, wR2 = 0.0833 |
| R indices (all data) | R1 = 0.0421, wR2 = 0.0845 |
| Absolute structure parameter | 0.015(13) [stereochemistry confirmed] |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.869 and -0.384 e.Å$^{-3}$ |

Picrotoxinin (**1**) (CCDC1999790)

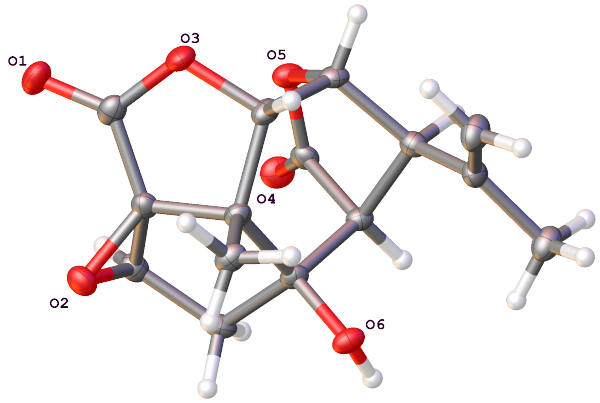



Table S10. Crystal data and structure refinement for shenvi145.

| | | |
|---|---|---|
| Identification code | 2711 | |
| Empirical formula | C15 H16 O6 | |
| Formula weight | 292.28 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21 | |
| Unit cell dimensions | a = 15.2385(5) Å | α= 90°. |
| | b = 11.3399(4) Å | β= 115.9850(10)°. |
| | c = 17.2881(5) Å | γ = 90°. |
| Volume | 2685.43(15) Å$^3$ | |
| Z, Z’ | 8, 4 | |
| Density (calculated) | 1.446 Mg/m$^3$ | |
| Absorption coefficient | 0.948 mm$^{-1}$ | |
| F(000) | 1232 | |
| Crystal size | 0.33 x 0.28 x 0.26 mm$^3$ | |
| Theta range for data collection | 2.843 to 72.608°. | |
| Index ranges | -18<=h<=18, -13<=k<=12, -21<=l<=18 | |
| Reflections collected | 30798 | |
| Independent reflections | 10212 [R(int) = 0.0451] | |
| Completeness to theta = 67.679° | 99.8 % | |
| Absorption correction | Semi-empirical from equivalents | |

| | |
|---|---|
| Max. and min. transmission | 0.7536 and 0.6661 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 10212 / 1 / 769 |
| Goodness-of-fit on $F^2$ | 1.023 |
| Final R indices [I>2sigma(I)] | R1 = 0.0317, wR2 = 0.0782 |
| R indices (all data) | R1 = 0.0329, wR2 = 0.0791 |
| Absolute structure parameter | 0.08(5) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.189 and -0.235 e.Å$^{-3}$ |

Picrotin (**19**) (CCDC1999785)

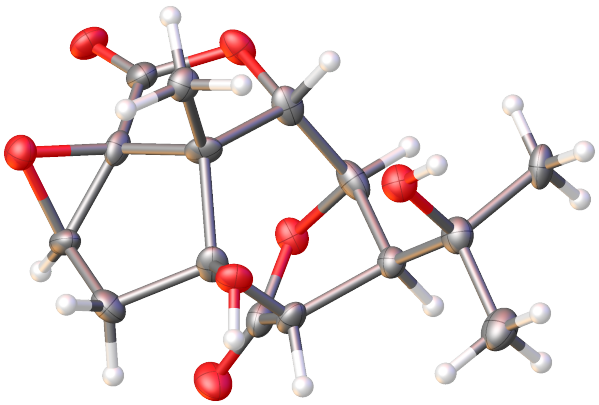


Table S11. Crystal data and structure refinement for shenvi146_0m_a.

| | | |
|---|---|---|
| Identification code | shenvi146 | |
| Empirical formula | C15 H18 O7 | |
| Formula weight | 310.29 | |
| Temperature | 100.0 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 7.0934(2) Å | α= 90°. |
| | b = 11.9278(4) Å | β= 90°. |
| | c = 32.7898(11) Å | γ = 90°. |
| Volume | 2774.30(15) Å$^3$ | |
| Z | 8 | |
| Density (calculated) | 1.486 Mg/m$^3$ | |
| Absorption coefficient | 1.006 mm$^{-1}$ | |
| F(000) | 1312 | |

| | |
|---|---|
| Crystal size | 0.26 x 0.07 x 0.05 $mm^3$ |
| Theta range for data collection | 3.944 to 68.275°. |
| Index ranges | -8<=h<=8, -14<=k<=14, -38<=l<=39 |
| Reflections collected | 16014 |
| Independent reflections | 4873 [R(int) = 0.0620] |
| Completeness to theta = 67.679° | 98.6 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7531 and 0.6369 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4873 / 0 / 416 |
| Goodness-of-fit on $F^2$ | 1.134 |
| Final R indices [I>2sigma(I)] | R1 = 0.0566, wR2 = 0.1356 |
| R indices (all data) | R1 = 0.0670, wR2 = 0.1424 |
| Absolute structure parameter | 0.20(12) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.320 and -0.319 $e.Å^{-3}$ |