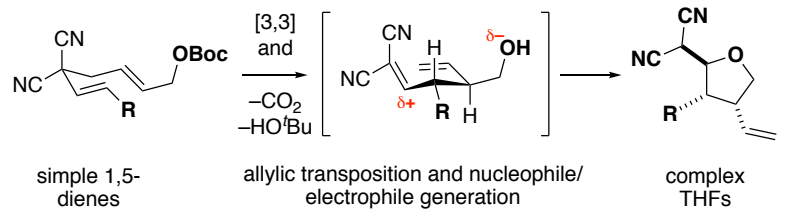
Convergent synthesis of trisubstituted tetrahydrofurans *via bis*-thermally reactive 1,5-diene-*tert*-butyl carbonates.

Fabien Emmetiere and Alexander J. Grenning*

Department of Chemistry, University of Florida, PO Box 117200
E-mail: grenning@ufl.edu

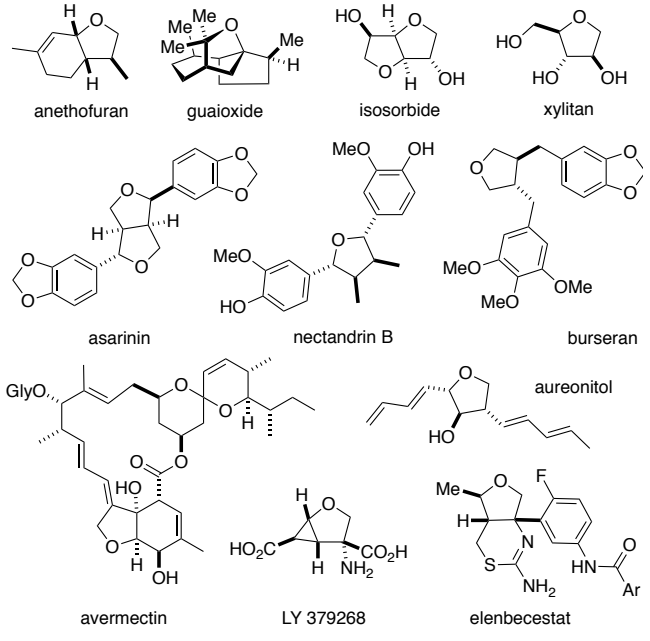
Abstract: Cascade reactions (also known as domino- or tandem reactions) are an efficient strategy for generating molecular complexity. We report that synergizing the thermal reactivity of 3,3-dicyano-1,5-dienes and *tert*-butyl carbonates result in stereospecific 2,3,4-trisubstituted tetrahydrofuran synthesis. While substituted tetrahydrofurans can be challenging to synthesize, this discovery converts readily available 1,5-dienes derived from aldehydes, malononitrile, and *cis*-buten-1,4-diol into complex tetrahydrofurans *via* a process involving *thermal* Cope rearrangement, Boc-deprotection, and *oxy*-Michael addition. Described herein includes background related to the discovery, optimization and scope, and representative functional group interconversion chemistry for the scaffolds.



Introduction

Substituted tetrahydrofurans (THFs) are a common heterocyclic core found in diverse, bioactive natural products such as terpenes, (anethofuran,[1] guaioxide[2]), furanose-derivatives (isosorbide[3], xylitan[4]), lignans[5,6] (asarinin, nectandrin B, burseran), macrolides (avermectin), fungal metabolites[7–10] (aureonitol), and pharmaceutical drug leads (LY 379268[11] and elenbecestat[12]).

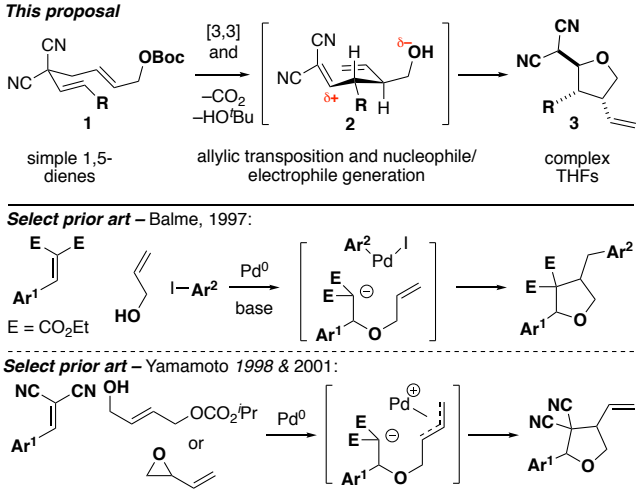
Figure 1. *Representative THF-containing natural products and pharmaceuticals*



Considering the relevance of tetrahydrofurans to drug discovery, a variety of strategies have been developed to access them in efficient ways.[13] Synthesis strategies fall into one of two subcategories: (a) *constructive* synthesis, where the THF scaffold is assembled[14–23] or (b) by an approach that *functionalizes* a preexisting THF core (*e.g* C-H functionalization, cross-coupling reactions.[24–31] The former category is of particular relevance to this report. We have been advancing the *classic* Cope rearrangement

(that of 3,3-dicyano-1,5-dienes) for application in modern chemical synthesis.[32–37] Considering that Cope rearrangement results in allylic transposition and an electrophilic alkylidenemalononitrile, we hypothesized that "trapping" with tethered nucleophiles could result in additional bond formation and structural complexity. Specifically, it was proposed that 1,5-dienes **1** derived from alkylidenemalononitrile and a *cis*-buten-1,4-diol derivative could undergo *polythermal* transformation involving Cope rearrangement, Boc-deprotection, and intramolecular *oxy*-Michael addition. Reviews of furan synthesis literature[13-31] and "domino reactions[38,39]" in general reveal that this proposal is unique and would access novel trisubstituted THFs. The most relevant prior art is summarized in Scheme 1, which demonstrates the likelihood of *oxy*-Michael additions to alkylidenemalonic acid derivatives. Interestingly our proposal and these methods for comparison result in furans where the malonate/malononitrile functional group are at complementary locations about the THF core.

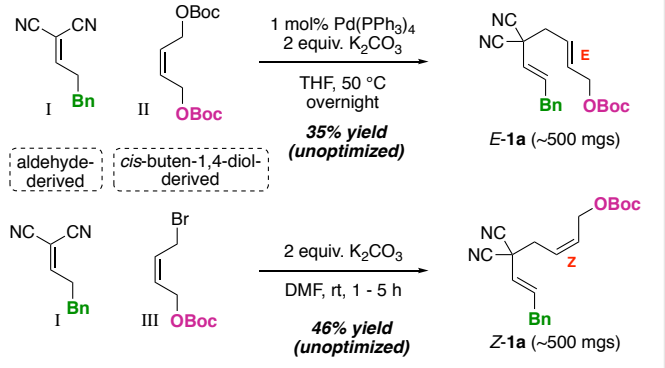
Scheme 1. *This proposal for THF synthesis and representative state of the art protocols.*



Results and Discussion

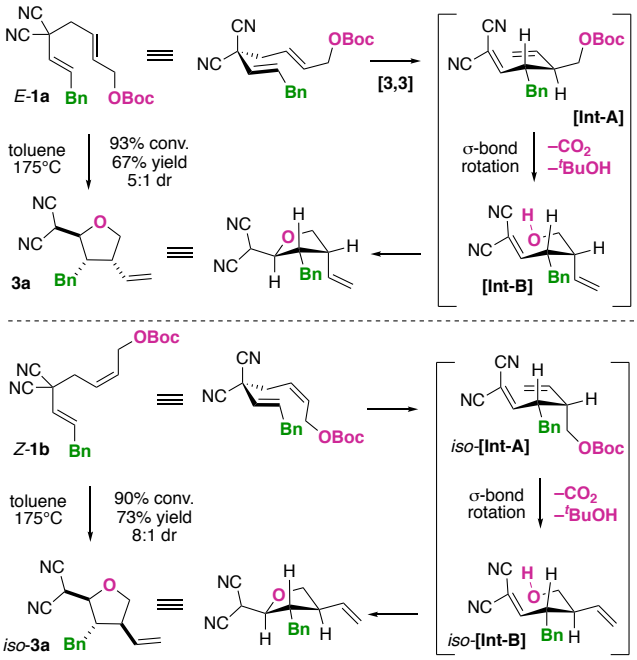
We began our studies by synthesizing diastereomeric 1,5-dienes *E*-**1a** and *Z*-**1a** from their corresponding aldehyde-derived Knoevenagel adduct and a *cis*-buten-1,4-diol derivative (Scheme 2). Specifically, *E*-**1a** is prepared in 35% *unoptimized* yield *via* Tsuji-Trost reaction between alkylidenemalononitrile **I** and the *bis*-boc-protected *cis*-buten-1,4-diol derivative **II** where *Z*-**1a** is derived from the allyl bromide **III** and prepared in 46% yield. Notably, *via* Pd-catalysis the *cis*-olefin on **II** is isomerized to the *trans*-isomer during the deconjugative alkylation process.[40] Finally, all 1,5-dienes in this disclosure were prepared by this method in unoptimized yields ranging from 25 – 75% (See the supporting information for details).

Scheme 2. *Representative synthesis of either E- or Z-1,5-dienes.*

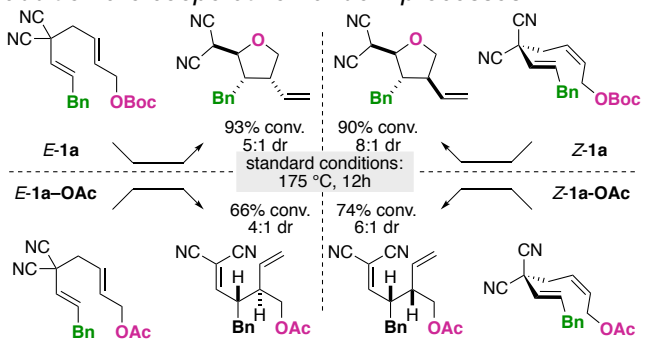


With *E*-**1a** and *Z*-**1a** in hand, we began examining the substrates for the desired thermal cascade to tetrahydrofurans. The desired products **3a** and **3b** could be formed when heated at 175 °C in toluene with good yield and diastereoselectivity (Scheme 3.). Interestingly, **3a** and **3b** were the only products detected in the crude mixture; none of the suspected intermediates such as **[Int-A]**, **[Int-B]**, or their isomers were observed. The different diastereomers *E*-**1a** and *Z*-**1a** react distinctly and diastereoselectively to yield their respective products. In both cases, the stereochemical outcomes can be rationalized *via* a Zimmerman-Traxler model and an *oxy*-Michael addition yielding a *pseudo*-equatorial malononitrile functional group. Notably, the elevated temperatures in this transformation's current form are necessary: at 150 °C or lower in toluene, we observed diminished conversion of the 1,5-dienes. In this case, both Cope rearrangement and Boc-deprotection were sluggish over the same time period.

Scheme 3. *Stereospecific furan synthesis via a thermal cascade.*



Scheme 4. *The Cope rearrangement and oxy-Michael addition are cooperative Tandem processes.*

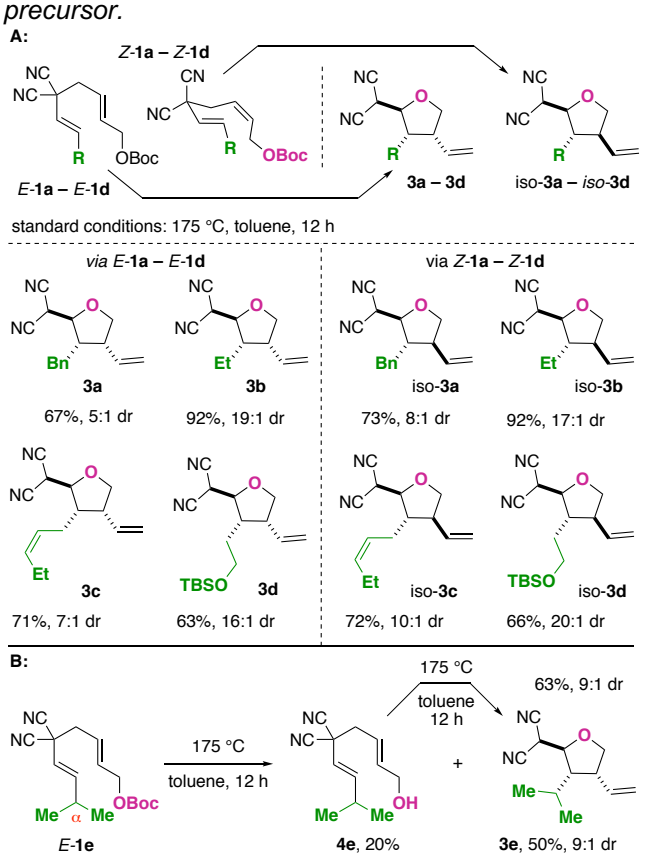


From our previous work on related 1,5-dienes, it was found that the *classic* Cope rearrangement often does not favor the *product* side of the equilibrium.[34,36] Rather it was demonstrated that the Cope rearrangement could be promoted by a stoichiometric reductant that intermolecularly reacted with the *product* side of the equilibrium *via* chemoselective alkylidenemalononitrile reduction (the "reductive Cope rearrangement"). It was hypothesized that *oxy*-Michael addition was having a similar effect here. To examine this, we compared *E*-**1a** and *Z*-**1a** to substrates *E*-**1a-OAc** and *Z*-**1a-OAc** that have similar structure and electronics but cannot generate the nucleophilic hydroxyl group under the standard reaction conditions (Scheme 4). While *E*-**1a** transforms to the furan scaffolds with 93% conversion under standard conditions, *E*-**1a-OAc** had lower conversion (66%). A similar trend was observed for the *Z*-**1a** and *Z*-**1a-OAc,** though with slightly different ratios. This suggests that the tandem transformation is *cooperative*: The

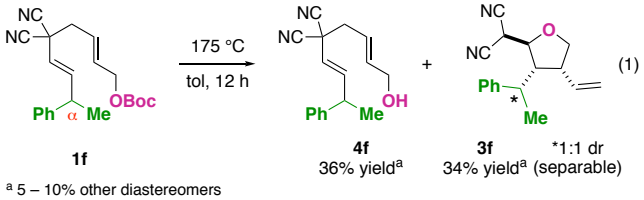
Cope equilibrium process will not reach full conversion on its own during the reaction time, rather is driven forward and rendered irreversible by the nucleophilic addition; the *oxy*-Michael reaction.

The scope of the furan synthesizing reaction was examined next (Scheme 5). It was found that the transformation was successful with a variety of substrates and could tolerate the incorporation of functional groups such as alkenes and TBS-protected alcohols. Furthermore, the yield and diastereoselectivity remained consistent with the previously optimized yields. It should be noted that sterics about the 1,5-diene termini have an impact on the kinetics of the transformation. For example, **1e** having an α-isopropyl group reacted under the standard conditions to produce a mixture of the desired product (50% yield, 9:1 dr) along with the Boc-deprotected substrate **4e**. However, you can re-subject the 1,5-diene-alcohol to the conditions and yield additional product. As a final note, this suggests that the order of events for the tandem reaction might be Boc-deprotection then Cope rearrangement.

Scheme 5. *Reaction scope: variation of the aldehyde precursor.*

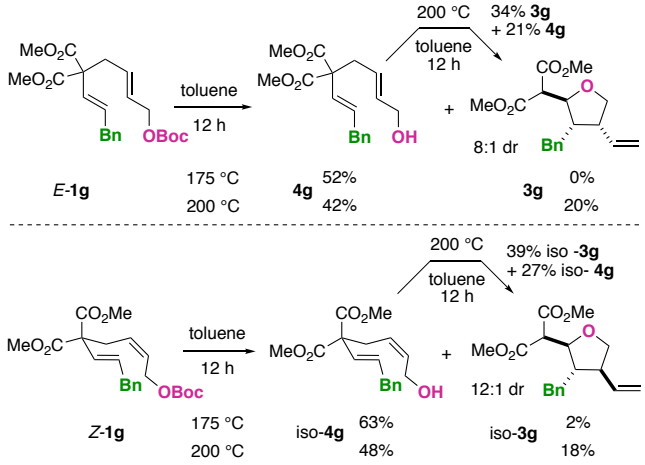


Having an understanding of the scope of the transformation, we next examined chirality transfer from an existing stereocenter on the 1,5-diene for the cascade sequence. Unfortunately, in limited studies (only the one substrate disclosed herein has currently been examined to date), the existing stereocenter on **1f** did not influence the diastereoselectivity of the Cope rearrangement (equation 1). Thus, two epimers (**3f**) were prepared *via* the thermal cascade reaction. Notably, both epimers can be separated by silica gel chromatography and each individual epimer is >20:1 dr from the tandem thermal transformation.



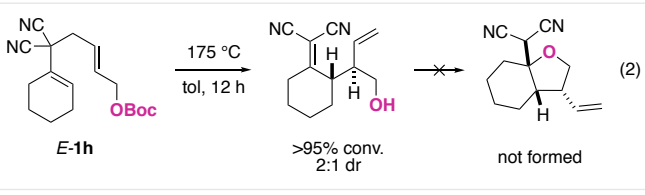
We next examined malonate-containing 1,5-dienes for tetrahydrofuran synthesis. Generally speaking, the malonate-1,5-dienes are less reactive to Cope rearrangement than malononitrile substrates. For example,

Scheme 6. *Reactivity of malonate-containing-1,5-dienes.*



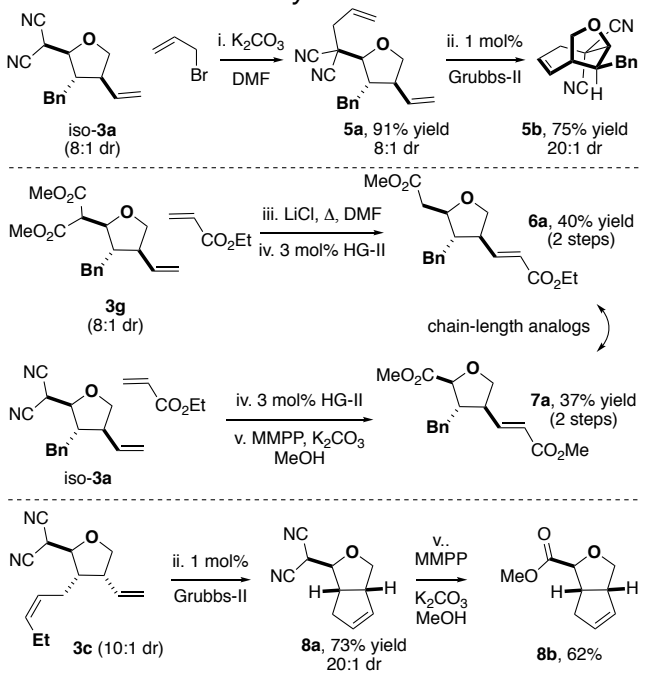
heating *E*-**1g** at 175 °C only produced the Boc-deprotected starting material **4g** in 52% yield (Scheme 6). At 200 °C, the desired product **3g** was prepared in 20% yield as an 8:1 mixture of diastereomers along with 42% of the alcohol **4g**, which upon re-subjection to the standard conditions produced an additional 21% of the desired furan. Similar reactivity was observed with *Z*-**1g**.

As final results related to scope, we have identified a current limitation of this furan synthesis (equations 2). In its current form, the transformation is limited to aldehyde- and butene-1,4-diol-derived 1,5-dienes, as outlined in the aforementioned schemes and equations. We encountered challenges when utilizing ketone-derived substrates (equation 2). Under the standard conditions, *E*-**1h** underwent Cope rearrangement (with significant epimerization; 2:1 dr) and Boc deprotection but no furan product was detected. The potential reasons for the lack of *oxy*-Michael reactivity are many. For example, there could be steric or conformation issues with the nucleophilic attack. Alternatively, the reduced electrophilicity of the tetrasubstituted alkylidene may also play a role in the undesired outcome. In any case, more studies are needed to expand the reactivity to ketones.



For our final studies, we examined functional group interconversions on the THF scaffolds (Scheme 7). As a result of the reaction design, trisubstituted THFs with complementary and orthogonal functional groups are prepared. This allows for rapid structural diversification. For example, we prepared a bicyclic THF-containing architecture **5b** *via* malononitrile allylation (to **5a**) followed by ring-closing metathesis[41] in 68% yield over 2 steps.

Scheme 7. *Representative functional group interconversion chemistry.*



Conditions: i. 2 eq K_2CO_3, DMF, rt, 1 h. ii. 1 mol% Grubbs II, toluene, 80 °C, 12 h. iii. 1 eq LiCl, 1 eq H_2O, DMF, 150 °C, 4 h. iv.) 3 mol% Hoveyda-Grubbs II, 10 eq ethyl acrylate, toluene, 80 °C, 12 h. v.) 1 eq MMPP, 2 eq K_2CO_3, MeOH, rt, 1 h.

The malonate-containing THF scaffold can be converted to **6a** via Krapcho decarboxylation[42] followed by cross-metathesis[43] with ethyl acrylate in 40% yield over 2 steps. Interestingly, the analogous malononitrile scaffold iso-**3a** can be converted into a chain-length analog (**6a** *vs* **7a**) *via* oxidative decyanation[44–46] then cross-metathesis. Finally, **3c** was converted into the bicycloalkanes **8b** *via* ring-closing metathesis (to **8a**) and oxidative decyanation.

In conclusion, we have developed a new methodology to synthesize trisubstituted and functionally dense tetrahydrofurans from readily available 1,5-dienes *via* a *cooperative* tandem process involving Cope rearrangement, OBoc-deprotection, and *oxy*-Michael addition. The transformation occurs with good yields and diastereoselectivities within the current scope. These discoveries set the stage for numerous follow-up studies related to increasing the scope and diversity of the transformation, developing asymmetric variants, and finding unique opportunities for the transformation in complex natural product and pharmaceutical molecule synthesis.

Experimental Section

Experimental procedures, compound characterization (^{1}NMR, ^{13}C NMR, HRMS), and spectral reprints are available in the Supporting Information.

Acknowledgements

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Supporting Information

Convergent synthesis of trisubstituted tetrahydrofurans *via bis*-thermally reactive 1,5-diene-*tert*-butyl carbonates.

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1. General experimental details

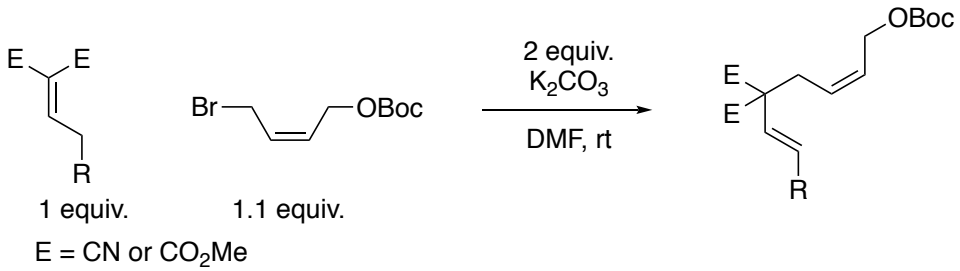
All commercial materials were used without further purification. Knoevenagel adducts were synthesized from modified reported literature procedures that are referenced along the way. All other synthetic protocols are outlined below. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 400 MHz or 600 MHz Varian VNMRS spectrometer (with $CHCl_3$ residual peak as an internal standard) unless specified otherwise. All ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS data were recorded on Agilent Time of Flight 6200 spectrometer. Reaction progress was monitored by thin-layer chromatography

(TLC) and visualized by UV light, phosphomolybdic acid stain, and $KMnO_4$ stain. Compounds were purified via silica gel column chromatography using Hexanes/Ethyl Acetate (Hex/EtOAc) solvent mixture. All reactions were carried out using anhydrous solvents obtained dried by passing through activated alumina columns. Notation: Hex/EtOAc X % reads "mixture of 10 % ethyl acetate (EtOAc) in hexanes (Hex)".

2. General procedures

a. Knoevenagel adduct S_N2 alkylation

i. Procedure A-1



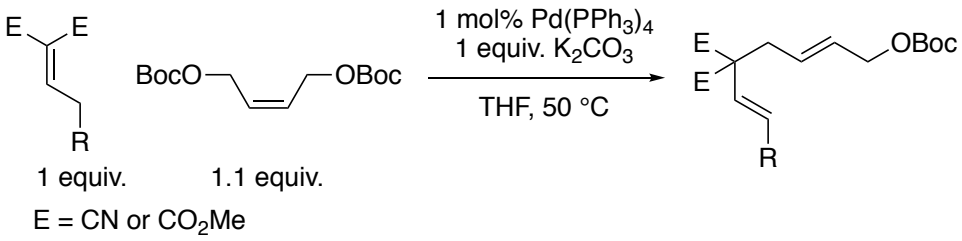
Pulverized K_2CO_3 (2 equiv.) was suspended in dry DMF in a flame-dried Schlenk flask under N_2. A mixture of Knoevenagel adduct (1 equiv.) and (*Z*)-4-bromobut-2-en-1-yl *tert*-butyl carbonate [Bulletin of the Chemical Society of Japan, 92(5), 937-940; 2019] (1.1 equiv.) in DMF (resulting in 0.1 M concentration) was then added at room temperature. The reaction mixture was monitored by TLC. Once the reaction reached completion, the reaction mixture was quenched slowly using a 2M $HCl_{(aq)}$ solution until no more effervescence was observed. The resulting aqueous mixture was extracted with EtOAc three times. The organic layers were then combined and washed sequentially with 2M $HCl_{(aq)}$ and brine before being dried over Na_2SO_4. The excess solvent was removed under reduced pressure and the crude mixture was purified via silica gel column chromatography (Hex/EtOAc).

ii. Procedure A-2

Same procedure as above but with NaH (1 equiv.) as base.

b. Knoevenagel adduct Tsuji-Trost alkylation

i. Procedure B-1



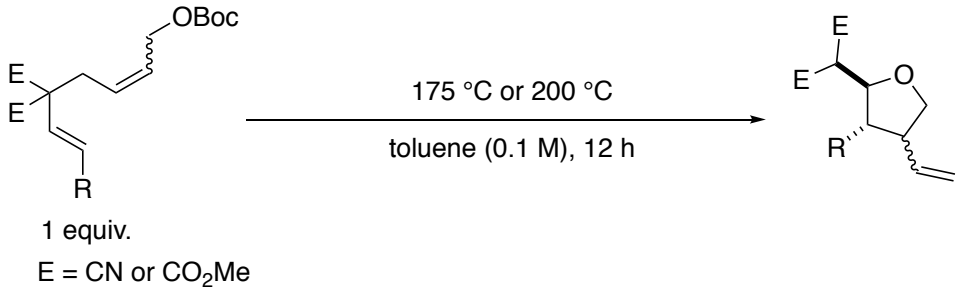
$Pd(PPh_3)_4$ (1 mol%) and K_2CO_3 (1 equiv.) were charged in a flame-dried Schlenk flask under N_2 and suspended in THF (0.1 M). *bis*-Boc protected (Z)-but-2-ene-1,4-diol[Angewandte Chemie, International Edition, 49(48), 9270-9273, S9270/1-S9270/106; 2010] (1.1 equiv.) and Knoevenagel adduct (1 equiv.) were added sequentially in this order. The reaction mixture was heated at 50 °C until completion (monitored by TLC). After completion, the reaction mixture was filtered through a short pad of silica eluted with EtOAc. The filtrate was concentrated down and the crude mixture was purified via silica column chromatography (Hex/EtOAc).

ii. Procedure B-2

$Pd(PPh_3)_4$ (1 mol%) and NaH (1 equiv.) were charged in a flame-dried Schlenk flask under N_2 and suspended in DMF (0.1 M). *bis*-Boc protected (Z)-but-2-ene-1,4-diol [Angewandte Chemie, International Edition, 49(48), 9270-9273, S9270/1-S9270/106; 2010] (1.1 equiv.) and Knoevenagel adduct (1 equiv.) were added sequentially in this order. The reaction mixture was stirred at room temperature until completion (monitored by TLC). Once the reaction reached completion, the reaction mixture was quenched slowly using a 2M $HCl_{(aq)}$ solution until no more effervescence was observed. The resulting aqueous mixture was extracted with EtOAc three times. The organic layers were then combined and washed sequentially with 2M $HCl_{(aq)}$ and brine before being dried over Na_2SO_4. The excess solvent was removed under reduced pressure and the crude mixture was purified via silica gel column chromatography (Hex/EtOAc).

c. Cope rearrangement/Oxy Michael addition cascade

i. Procedure C-1



Alkylated Knoevenagel precursor was charged in a flame-dried microwave pressured flask under N_2. Toluene is added (0.1 M) and the pressured flask was sealed. The reaction mixture was heated at 175 °C for 12 h. After 12 h reaction, the flask was cooled down to room temperature and toluene was removed under reduced pressure. The resulting crude mixture was purified via silica gel column chromatography (Hex/EtOAc).

ii. Procedure C-2

Same as Procedure C-1 but at 200 °C.

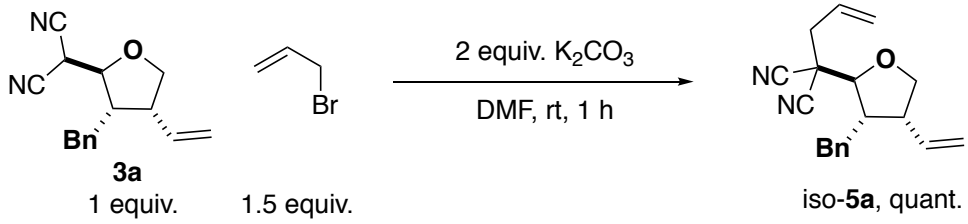
d. Specific experimental procedures

i. Allylation of iso-**3a** and **3a**

K_2CO_3 (2 equiv., 22 mg, 0.16 mmol) was charged in a flame-dried Schlenk flask under N_2 and suspended in DMF (0.5 mL). iso-**3a** (1 equiv., 20 mg, 0.079 mmol) in 0.5 mL DMF was then added immediately followed by allyl bromide (1.5 equiv., 10 µL, 0.12 mmol) at room temperature. The reaction was stirred for 1 h at room temperature and was then quenched slowly using a 2M $HCl_{(aq)}$ (3 mL) solution until no more effervescence was observed. The resulting aqueous mixture was extracted with EtOAc three times (3 x 10 mL). The organic layers were then combined and washed sequentially with 2M $HCl_{(aq)}$ (10 mL) and brine (10 mL) before being dried over Na_2SO_4. The excess solvent was removed under reduced pressure and **5a** was sufficiently pure to be used in the next step without further purification (21 mg, 91 % yield, colorless oil, 8:1 d.r., major reported below).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.17 (m, 3H), 5.91 (ddt, *J* = 17.3, 10.4, 7.3 Hz, 1H), 5.60 (dt, *J* = 17.9, 9.2 Hz, 1H), 5.46 – 5.36 (m, 2H), 5.05 (d, *J* = 6.1 Hz, 1H), 5.02 (s, 1H), 3.94 (dd, *J* = 7.6, 3.2 Hz, 2H), 3.82 (t, *J* = 9.2 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.93 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.86 – 2.75 (m, 2H), 2.66 – 2.49 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.28, 135.42, 130.14, 128.67, 127.00, 123.36, 118.26, 114.58, 114.11, 83.57, 73.32, 50.29, 49.57, 42.91, 39.64, 37.31.

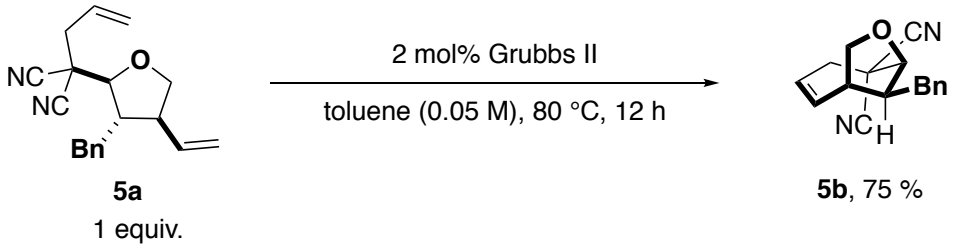


K_2CO_3 (2 equiv., 22 mg, 0.16 mmol) was charged in a flame-dried Schlenk flask under N_2 and suspended in DMF (0.5 mL). **3a** (1 equiv., 19 mg, 0.078 mmol) in 0.5 mL DMF was then added immediately followed by allyl bromide (1.5 equiv., 10 µL, 0.12 mmol) at room temperature. The reaction was stirred for 1 h at room temperature and was then quenched slowly using a 2M $HCl_{(aq)}$ (3 mL) solution until no more effervescence was observed. The resulting aqueous mixture was extracted with EtOAc three times (3 x 10 mL). The organic layers were then combined and washed sequentially with 2M $HCl_{(aq)}$ (10 mL) and brine (10 mL) before being dried over Na_2SO_4. The excess solvent was removed under reduced pressure and **5a** was sufficiently pure to be used in the next step without further purification (22 mg, quantitative yield, colorless oil, 5:1 d.r., major reported below).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.20 (m, 3H), 5.80 (tq, *J* = 16.7, 8.4, 7.3 Hz, 2H), 5.37 (d, *J* = 10.2 Hz, 1H), 5.33 (d, *J* = 17.0 Hz, 1H), 5.26 (d, *J* = 10.3 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 4.19 (dd, *J* = 8.6, 5.9 Hz, 1H), 3.96 (d, *J* = 4.6 Hz, 1H), 3.86 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.21 (p, *J* = 6.7 Hz, 1H), 2.93 – 2.87 (m, 1H), 2.84 – 2.77 (m, 2H), 2.58 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.45 (dd, *J* = 13.9, 7.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.65, 133.97, 129.27, 128.87, 128.63, 126.90, 123.18, 119.02, 114.48, 113.81, 83.70, 73.47, 48.58, 46.32, 43.17, 39.37, 34.79.

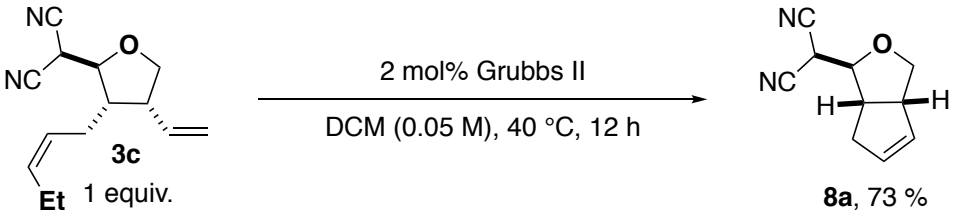
ii. Ring-closing metathesis of **5a** / **5b** and **3c** / **8a**



5a
1 equiv.

5b, 75 %

Grubbs 2nd generation catalyst (2 mol%, 1 mg, 0.0014 mmol) was charged in a flame-dried Schlenk flask under N_2 and dissolved in toluene (0.4 mL). **5a** (1 equiv., 20 mg, 0.068 mmol) in 1 mL toluene (0.05 M final concentration) was added at room temperature. The reaction mixture was then stirred at 80 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude residue was purified via silica gel column chromatography (Hex/EtOAc 10 %) yielding bicyclic **5b** as a colorless oil (13.5 mg, 75 %, 8:1 d.r., major reported below).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 6.28 (ddd, *J* = 11.5, 8.7, 3.1 Hz, 1H), 5.64 (ddd, *J* = 11.7, 8.6, 3.5 Hz, 1H), 4.63 (s, 1H), 4.39 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.17 (dd, *J* = 8.7, 1.3 Hz, 1H), 3.10 (dt, *J* = 15.9, 3.3 Hz, 1H), 2.79 (q, *J* = 9.0, 8.5 Hz, 1H), 2.74 (q, *J* = 5.9 Hz, 2H), 2.71 (d, *J* = 5.9 Hz, 1H), 2.70 – 2.66 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 140.49, 137.97, 129.07, 129.04, 127.16, 122.70, 115.96, 114.38, 85.72, 75.42, 50.04, 41.13, 38.94, 38.15, 31.22.
HRMS (ESI – TOF) m/z: Calcd for $C_{17}H_{15}N_2O$ $[M–H]^-$ 263.1179, found 263.1183.

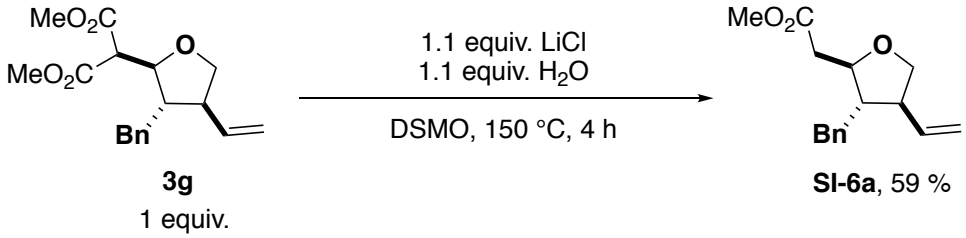


3c
Et 1 equiv.

8a, 73 %

Grubbs 2nd generation catalyst (2 mol%, 1.5 mg, 0.0017 mmol) was charged in a flame-dried Schlenk flask under N_2 and dissolved in DCM (0.7 mL). **3c** (1 equiv., 20 mg, 0.086 mmol) in 1 mL DCM (0.05 M final concentration) was added at room temperature. The reaction mixture was then stirred at 40 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude residue was purified via silica gel column chromatography (Pentanes/Et_2O 20 %) yielding bicyclic **8a** as a colorless oil (11 mg, 73 %, 7:1 d.r., major reported below).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.74 (dq, *J* = 4.7, 2.2 Hz, 1H), 5.66 (dq, *J* = 5.7, 2.1 Hz, 1H), 4.28 (dd, *J* = 8.9, 7.3 Hz, 1H), 3.96 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.92 (d, *J* = 5.2 Hz, 1H), 3.83 (dd, *J* = 8.9, 3.6 Hz, 1H), 3.63 (dddq, *J* = 9.8, 5.9, 3.9, 2.2 Hz, 1H), 2.91 (tdd, *J* = 8.0, 6.3, 1.6 Hz, 1H), 2.75 (ddq, *J* = 17.2, 7.8, 2.4 Hz, 1H), 2.40 (dp, *J* = 17.2, 2.1 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 132.20, 130.35, 111.30, 110.97, 84.25, 74.33, 52.60, 46.43, 37.25, 28.33.
HRMS (ESI – TOF) m/z: Calcd for $C_{10}H_9N_2O$ $[M–H]^-$ 173.0720, found 173.0715.

iii. Krapcho decarboxylation of **3g**



3g
1 equiv.

SI-6a, 59 %

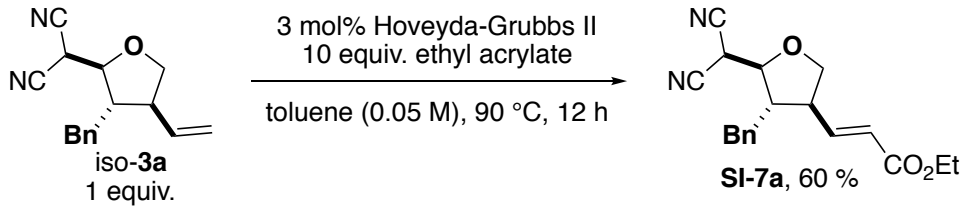
3g (1 equiv., 35 mg, 0.11 mmol) was dissolved in 0.5 mL DMSO is a microwave pressured flask. LiCl (1.1 equiv. 5 mg, 0.12 mmol) and H_2O (~1.1 equiv., 7 µL, ~0.12 mmol) were added and the flask was sealed. The reaction mixture was heated at 150 °C for 4 h. After completion, the reaction mixture was cooled down to room temperature and diluted with a 2M $HCl_{(aq)}$ (5 mL) solution. The resulting aqueous mixture was extracted with EtOAc three times (3 x 5 mL). The organic layers were then combined and washed sequentially with 2M $HCl_{(aq)}$ (10 mL) and brine (10 mL) before being dried over Na_2SO_4. The excess solvent was removed under reduced pressure and the crude residue was purified via silica gel column chromatography (Hex/EtOAc 10 %). **SI-6a** was obtained as a colorless oil (17 mg, 59 %, 8:1 d.r., major reported below).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, 3H), 7.23 – 7.18 (m, 1H), 7.18 – 7.13 (m, 2H), 5.72 – 5.59 (m, 1H), 5.15 – 5.00 (m, 2H), 4.17 – 4.05 (m, 1H), 4.01 – 3.91 (m, 1H), 3.70 – 3.57 (m, 3H), 2.94 (dt, *J* = 13.6, 5.5 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.22 (dd, *J* = 15.3, 8.9 Hz, 1H), 2.11 – 2.06 (m, 1H), 1.94 (qt, *J* = 8.9, 3.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 139.42, 137.61, 129.15, 129.13, 128.63, 126.52, 116.99, 80.89, 71.75, 51.96, 51.79, 50.98, 40.03, 37.40.

HRMS (ESI – TOF) m/z: Calcd for $C_{16}H_{20}NaO_3$ $[M+Na]^+$ 283.1305, found 283.1293.

iv. Cross-metathesis of iso-**3a** and **SI-6a**



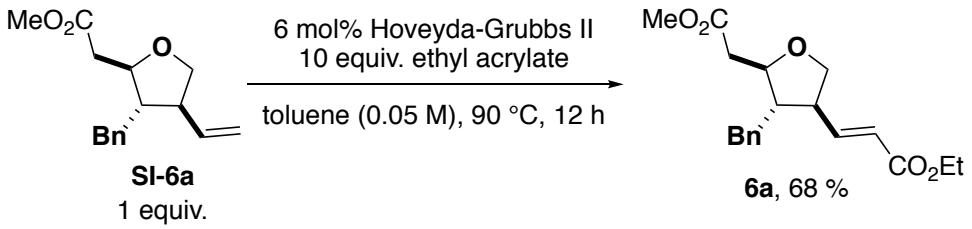
iso-**3a**
1 equiv.

SI-7a, 60 %

Hoveyda-Grubbs 2nd generation catalyst (3 mol%, 1.5 mg, 0.0024 mmol) was charged in a flame-dried Schlenk flaks under N_2 and dissolved in 1 mL toluene. iso-**3a** (1 equiv., 20 mg, 0.08 mmol) was added in 0.5 mL toluene (0.05 M final concentration) followed by ethyl acrylate (10 equiv., 84 µL, 0.8 mmol). The reaction flask was sealed and heated at 90 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude residue was purified via silica gel column chromatography (Hex/EtOAc 20 %) yielding **SI-7a** as a yellowish oil (15 mg, 60 %, 8:1 d.r., major reported below).

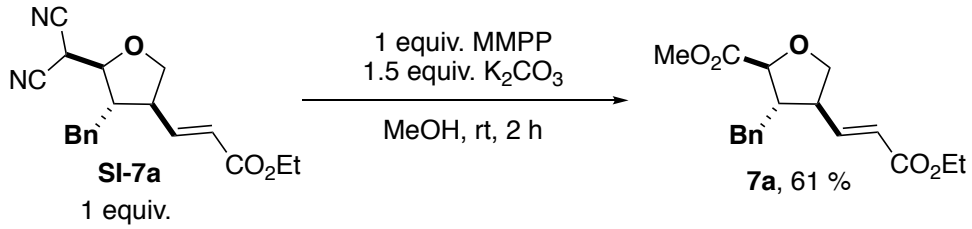
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.28 (m, 1H), 7.17 (d, *J* = 6.9 Hz, 2H), 6.79 (dd, *J* = 15.6, 9.0 Hz, 1H), 5.94 (d, *J* = 15.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.14 (dd, *J* = 8.9, 7.7 Hz, 1H), 4.09 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.91 (dd, *J* = 9.9, 8.9 Hz, 1H), 3.12 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.96 – 2.89 (m, 1H), 2.73 (d, *J* = 2.6 Hz, 1H), 2.57 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.41 (tdd, *J* = 10.0, 8.5, 5.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.65, 143.60, 137.45, 129.64, 128.64, 127.91, 125.17, 111.35, 110.75, 82.00, 72.87, 60.89, 50.36, 49.29, 36.94, 28.61, 14.37.
HRMS (ESI – TOF) m/z: Calcd for $C_{19}H_{20}N_2NaO_3$ $[M+Na]^+$ 347.1366, found 347.1375.



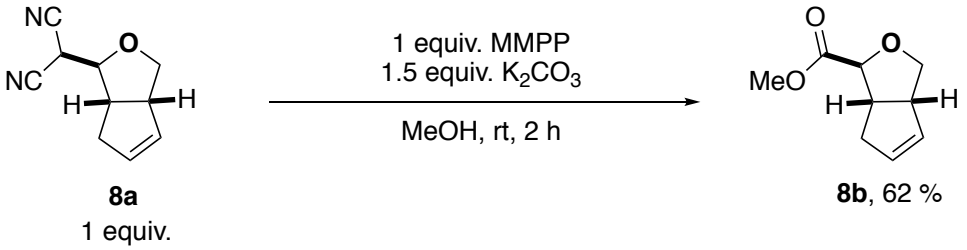
Hoveyda-Grubbs 2nd generation catalyst (6 mol%, 2 mg, 0.0029 mmol) was charged in a flame-dried Schlenk flaks under N_2 and dissolved in 0.5 mL toluene. **SI-a** (1 equiv., 15 mg, 0.057 mmol) was added in 0.5 mL toluene (0.05 M final concentration) followed by ethyl acrylate (10 equiv., 80 µL, 0.57 mmol). The reaction flask was sealed and heated at 90 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude residue was purified via silica gel column chromatography (Hex/EtOAc 15 %) yielding **6a** as a yellow oil (13.5 mg, 68 %, 6:1 d.r., major reported below).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.27 (m, 2H), 7.22 – 7.16 (m, 1H), 7.16 – 7.11 (m, 2H), 6.72 (dd, *J* = 15.6, 9.2 Hz, 1H), 5.73 (dd, *J* = 15.6, 0.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.14 – 4.07 (m, 1H), 3.96 (dd, *J* = 8.9, 7.6 Hz, 1H), 3.70 – 3.65 (m, 2H), 3.65 (s, 3H), 2.85 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.76 (tt, *J* = 8.6, 0.9 Hz, 1H), 2.66 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.29 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.15 (dd, *J* = 15.4, 3.5 Hz, 1H), 2.08 (qd, *J* = 8.4, 6.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.56, 166.16, 147.13, 138.73, 129.10, 128.76, 126.79, 122.93, 81.05, 71.20, 60.52, 51.99, 51.88, 49.17, 39.73, 37.60, 14.37.
HRMS (ESI – TOF) m/z: Calcd for $C_{19}H_{24}NaO_5$ $[M+Na]^+$ 355.1516, found 355.1503.

v. Oxidative esterification of **SI-7a** and **8a**



SI-7a (1 equiv., 10 mg, 0.031 mmol) was dissolved in dry MeOH (1 mL) in a flame-dried Schlenk flask under N_2. K_2CO_3 (1.5 equiv., 6 mg, 0.046 mmol) and MMPP (magnesium monoperoxyphthalate 80 %, 1 equiv., 12 mg, 0.031 mmol) were added sequentially in this order at room temperature. After 2 h at room temperature, MeOH is removed under reduced pressure. The residue is diluted with EtOAc and was filtered through a short pad of silica to remove MMPP solid byproducts. The filtrate was then concentrated down and **7a** was obtained clean without further purification. (6 mg, 61 %, colorless oil, 8:1 d.r., major reported below).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.6 Hz, 3H), 7.20 (tt, *J* = 7.6, 1.4 Hz, 1H), 7.16 (d, *J* = 6.7 Hz, 2H), 6.65 (dd, *J* = 15.6, 9.0 Hz, 1H), 5.72 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.24 (d, *J* = 7.5 Hz, 1H), 4.16

(q, *J* = 7.2 Hz, 2H), 4.07 (dd, *J* = 8.8, 7.4 Hz, 1H), 3.82 (t, *J* = 8.9 Hz, 1H), 3.65 (s, 3H), 2.89 (h, *J* = 7.0 Hz, 2H), 2.81 – 2.74 (m, 1H), 2.57 (dq, *J* = 8.7, 7.1 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.87, 165.95, 145.59, 137.93, 129.55, 128.63, 126.86, 123.63, 81.55, 72.93, 60.58, 52.29, 51.23, 48.08, 37.62, 14.37.
HRMS (ESI – TOF) m/z: Calcd for $C_{18}H_{22}NaO_5$ $[M+Na]^+$ 341.1359, found 341.1360.

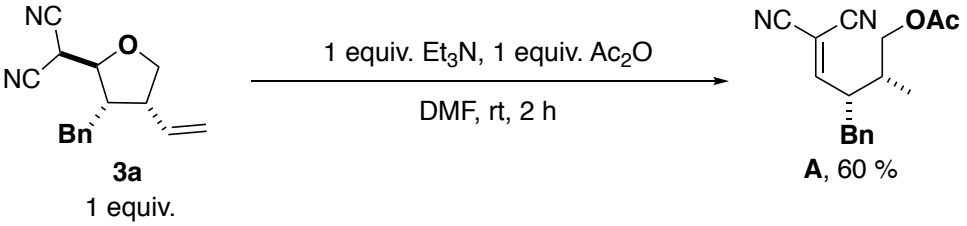


8a
1 equiv.

8b, 62 %

8a (1 equiv., 10 mg, 0.057 mmol) was dissolved in dry MeOH (1 mL) in a flame-dried Schlenk flask under N_2. K_2CO_3 (1.5 equiv., 12 mg, 0.086 mmol) and MMPP (magnesium monoperoxyphthalate 80 %, 1 equiv., 22 mg, 0.057 mmol) were added sequentially in this order at room temperature. After 2 h at room temperature, MeOH is removed under reduced pressure. The residue is diluted with EtOAc and was filtered through a short pad of silica to remove MMPP solid byproducts. The filtrate was then concentrated down and **8b** was obtained clean without further purification. (6 mg, 62 %, yellowish oil, 7:1 d.r., major reported below).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.73 (dq, *J* = 4.6, 2.2 Hz, 1H), 5.62 – 5.59 (m, 1H), 4.18 (dd, *J* = 8.7, 7.1 Hz, 1H), 4.09 (d, *J* = 5.7 Hz, 1H), 3.79 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.77 (s, 3H), 3.46 (dtd, *J* = 10.8, 4.9, 2.4 Hz, 1H), 2.98 (tdd, *J* = 8.1, 5.7, 2.0 Hz, 1H), 2.71 (ddq, *J* = 17.2, 8.3, 2.3 Hz, 1H), 2.45 (dp, *J* = 17.3, 2.2 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.39, 132.04, 130.62, 84.67, 73.57, 52.19, 51.95, 46.40, 38.62.
HRMS (ESI – TOF) m/z: Calcd for $C_9H_{12}NaO_3$ $[M+Na]^+$ 191.0679, found 191.0671.

vi. Retro-Oxy-Michael addition on **3a**



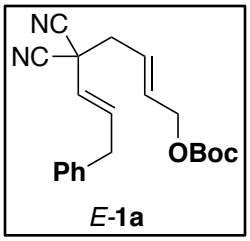
3a
1 equiv.

A, 60 %

3a (1 equiv., 10 mg, 0.04 mmol) was dissolved in DMF (1 mL) at room temperature in a 4 mL vial under air. Et_3N (1.1 equiv., 6 µL, 0.043 mmol) was added and the reaction was stirred for 5 min before Ac_2O (1.1 equiv., 4 µL, 0.043 mmol) was added. The reaction mixture was stirred at room temeprature for 2 h. After completion, the reaction mixture was diluted with 2 M $HCl_{(aq)}$ (3 mL) and extracted with EtOAc three times (3 x 1 mL). The combined organic layers were washed with 2 M $HCl_{(aq)}$ (3 mL), brine (6 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via sílica gel column chromatography yielding compound **A** (7 mg, 60 %).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 3H), 7.18 – 7.08 (m, 3H), 5.72 (ddd, *J* = 17.0, 10.4, 9.0 Hz, 1H), 5.39 (dd, *J* = 10.3, 1.2 Hz, 1H), 5.29 (dt, *J* = 17.1, 1.0 Hz, 1H), 4.19 (dd, *J* = 11.4, 5.6 Hz, 1H), 4.00 (dd, *J* = 11.4, 7.7 Hz, 1H), 3.38 (dddd, *J* = 11.2, 9.1, 5.8, 4.7 Hz, 1H), 3.03 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.80 – 2.76 (m, 1H), 2.72 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.12 (s, 3H).

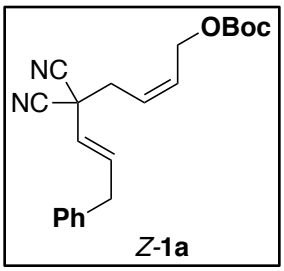
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.81, 169.28, 136.62, 132.67, 129.15, 128.97, 127.50, 121.16, 111.82, 110.31, 91.27, 64.77, 46.25, 46.06, 38.27, 20.99.

3. ^{1}H, ^{13}C NMR & mass spectrometry data



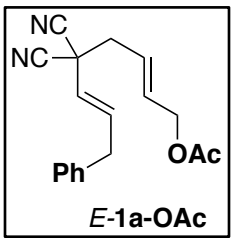
E-**1a**

Synthesized according to Procedure B-1 (384 mg, 25 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.33 (tt, *J* = 7.8, 1.6 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.38 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.90 (dtt, *J* = 15.4, 5.7, 0.8 Hz, 1H), 5.79 (dtt, *J* = 15.4, 7.2, 1.3 Hz, 1H), 5.38 (dt, *J* = 15.1, 1.6 Hz, 1H), 4.57 (dd, *J* = 5.5, 0.8 Hz, 2H), 3.48 (dd, *J* = 6.4, 1.6 Hz, 2H), 2.75 (dd, *J* = 7.2, 0.7 Hz, 2H), 1.50 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 153.21, 137.59, 137.47, 133.00, 128.97, 128.78, 127.01, 124.10, 121.56, 113.98, 82.65, 66.05, 42.19, 38.94, 38.11, 27.89.
HRMS (ESI – TOF) m/z: Calcd for $C_{21}H_{24}N_2NaO_3$ $[M+Na]^+$ 375.1679, found 375.1675.



Z-**1a**

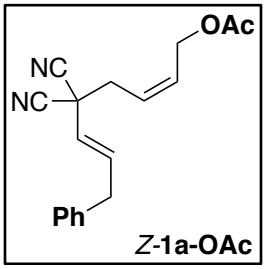
Synthesized according to Procedure A-1 (337 mg, 41 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 7.19 – 7.14 (m, 3H), 6.40 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.98 (dtt, *J* = 11.2, 6.9, 1.4 Hz, 1H), 5.71 (dtt, *J* = 10.8, 7.7, 1.4 Hz, 1H), 5.40 (dt, *J* = 15.2, 1.7 Hz, 1H), 4.62 (dd, *J* = 6.8, 1.5 Hz, 2H), 3.48 (dd, *J* = 6.5, 1.7 Hz, 2H), 2.88 (dd, *J* = 7.7, 1.4 Hz, 2H), 1.48 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 153.34, 137.56, 131.30, 128.98, 128.80, 127.03, 124.29, 121.51, 114.02, 82.78, 61.91, 38.69, 38.12, 37.39, 27.88.
HRMS (ESI – TOF) m/z: Calcd for $C_{21}H_{24}N_2NaO_3$ $[M+Na]^+$ 375.1679, found 375.1675.



E-**1a-OAc**

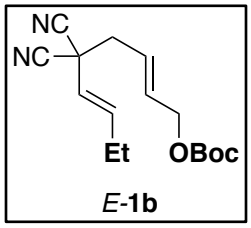
Synthesized according to Procedure B-1 with Ac_2O instead of Boc_2O (236 mg, 49 %).

Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 2H), 7.29 – 7.26 (m, 1H), 7.18 – 7.13 (m, 2H), 6.38 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.89 (dtt, *J* = 15.3, 5.6, 1.1 Hz, 1H), 5.75 (dtt, *J* = 15.6, 7.3, 1.4 Hz, 1H), 5.38 (dt, *J* = 15.2, 1.7 Hz, 1H), 4.58 (dd, *J* = 5.6, 1.2 Hz, 2H), 3.49 (dd, *J* = 6.6, 1.6 Hz, 2H), 2.74 (dd, *J* = 7.3, 1.0 Hz, 2H), 2.08 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.67, 137.59, 137.47, 133.20, 128.96, 128.77, 127.03, 123.79, 121.57, 113.98, 63.69, 42.19, 39.05, 38.12, 21.00.



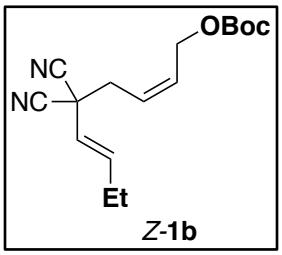
Z-**1a-OAc**

Synthesized according to Procedure A-1 with (*Z*)-4-bromobut-2-en-1-yl acetate (135 mg, 40 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.23 – 7.09 (m, 2H), 6.40 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.96 (dtt, *J* = 11.0, 6.9, 1.4 Hz, 1H), 5.70 (dtt, *J* = 10.7, 7.8, 1.4 Hz, 1H), 5.40 (dt, *J* = 15.2, 1.7 Hz, 1H), 4.63 (dd, *J* = 7.0, 1.4 Hz, 2H), 3.49 (dd, *J* = 6.6, 1.6 Hz, 2H), 2.87 (dd, *J* = 7.6, 1.4 Hz, 2H), 2.06 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.80, 137.53, 137.52, 131.44, 128.98, 128.79, 127.04, 124.20, 121.53, 114.01, 59.58, 38.78, 38.11, 37.41, 21.00.



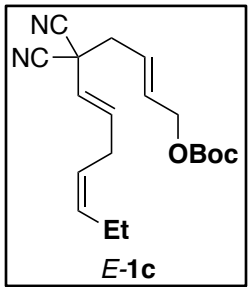
E-**1b**

Synthesized according to Procedure B-1 (90 mg, 25 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.24 (dt, *J* = 15.3, 6.4 Hz, 1H), 5.92 (dtt, *J* = 15.4, 5.5, 1.0 Hz, 1H), 5.80 (dtt, *J* = 15.5, 7.3, 1.3 Hz, 1H), 5.36 (dt, *J* = 15.3, 1.7 Hz, 1H), 4.59 (dq, *J* = 5.7, 0.9 Hz, 2H), 2.74 (dd, *J* = 7.2, 1.0 Hz, 2H), 2.23 – 2.14 (m, 2H), 1.49 (s, 9H), 1.06 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.23, 140.15, 132.82, 124.33, 119.52, 114.19, 82.64, 66.09, 42.28, 39.08, 27.88, 25.14, 12.83.
HRMS (ESI – TOF) m/z: Calcd for $C_{16}H_{22}N_2NaO_3$ $[M+Na]^+$ 313.1523, found 313.1522.



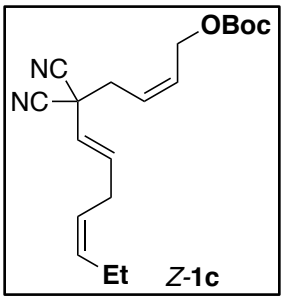
Z-**1b**

Synthesized according to Procedure A-1 (54 mg, 31 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.25 (dt, *J* = 15.3, 6.3 Hz, 1H), 5.98 (dtt, *J* = 11.2, 6.9, 1.4 Hz, 1H), 5.72 (dtt, *J* = 10.7, 7.7, 1.5 Hz, 1H), 5.38 (dt, *J* = 15.3, 1.7 Hz, 1H), 4.63 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.87 (dd, *J* = 7.7, 1.4 Hz, 2H), 2.18 (qdd, *J* = 7.5, 6.3, 1.7 Hz, 2H), 1.48 (s, 9H), 1.05 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.32, 140.18, 131.13, 124.43, 119.46, 114.21, 82.72, 61.91, 38.74, 37.44, 27.85, 25.10, 12.75.
HRMS (ESI – TOF) m/z: Calcd for $C_{16}H_{22}N_2NaO_3$ $[M+Na]^+$ 313.1523, found 313.1522.



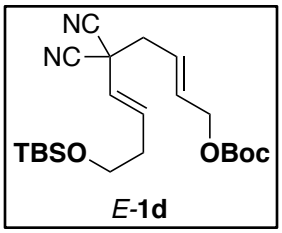
E-**1c**

Synthesized according to Procedure B-1 (100 mg, 49 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.20 (dt, *J* = 15.3, 6.0 Hz, 1H), 5.91 (dtt, *J* = 15.4, 5.6, 0.5 Hz, 1H), 5.84 – 5.74 (m, 1H), 5.56 (dtt, *J* = 10.6, 7.4, 1.2 Hz, 1H), 5.39 (dt, *J* = 15.2, 1.8 Hz, 1H), 5.31 (dtt, *J* = 10.7, 7.3, 1.7 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.73 (d, *J* = 7.1 Hz, 2H), 2.11 – 1.96 (m, 2H), 1.49 (s, 9H), 0.98 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.21, 137.02, 135.00, 132.86, 124.24, 123.51, 120.51, 114.09, 82.63, 66.07, 42.24, 39.06, 29.46, 27.88, 20.67, 14.26.
HRMS (ESI – TOF) m/z: Calcd for $C_{19}H_{26}N_2NaO_3$ $[M+Na]^+$ 353.1836, fouond 353.1827.



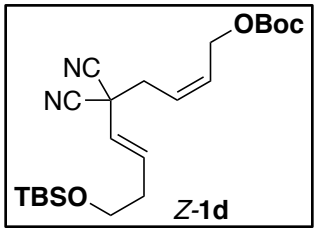
Z-**1c**

Synthesized according to Procedure A-2 (51 mg, 12 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.22 (dt, *J* = 15.2, 6.1 Hz, 1H), 5.98 (dtt, *J* = 11.0, 6.8, 1.4 Hz, 1H), 5.71 (dtt, *J* = 10.7, 7.7, 1.5 Hz, 1H), 5.56 (dtt, *J* = 10.3, 7.3, 1.5 Hz, 1H), 5.41 (dt, *J* = 15.3, 1.8 Hz, 1H), 5.31 (dtt, *J* = 10.6, 7.3, 1.6 Hz, 1H), 4.63 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.94 – 2.84 (m, 4H), 2.03 (pd, *J* = 7.5, 1.6 Hz, 3H), 1.48 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.31, 137.09, 134.99, 131.20, 124.34, 123.46, 120.46, 114.11, 82.73, 61.91, 38.74, 37.41, 29.44, 27.85, 20.66, 14.23.
HRMS (ESI – TOF) m/z: Calcd for $C_{19}H_{26}N_2NaO_3$ $[M+Na]^+$ 353.1836, fouond 353.1827.



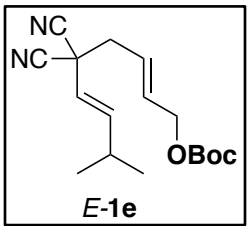
E-**1d**

Synthesized according to Procedure B-1 (122 mg, 58 %).
Solvent system for column chromatography: Hex/EtOAc 5 % → 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.23 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.93 (dtt, *J* = 15.4, 5.5, 1.0 Hz, 1H), 5.80 (dtt, *J* = 15.4, 7.2, 1.0 Hz, 1H), 5.46 (dt, *J* = 15.3, 1.5 Hz, 1H), 4.59 (dd, *J* = 5.5, 1.2 Hz, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.36 (dtd, *J* = 7.6, 6.2, 1.5 Hz, 2H), 1.49 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.21, 135.68, 132.86, 128.12, 124.29, 121.98, 114.02, 82.63, 66.08, 62.41, 61.60, 42.27, 39.21, 35.36, 27.89, 26.00, 18.39, -5.20.
HRMS (ESI – TOF) m/z: Calcd for $C_{22}H_{36}N_2NaO_4Si$ $[M+Na]^+$ 443.2337, found 443.2335.



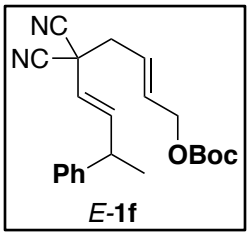
Z-**1d**

Synthesized according to Procedure A-2 (60 mg, 30 %*).
***<u>Note:</u>** *Z*-**1d** was isolated along with 10 % SM, inseparable.
Solvent system for column chromatography: Hex/EtOAc 5 % → 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.24 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.98 (dtt, *J* = 11.2, 6.9, 1.4 Hz, 1H), 5.73 (dtt, *J* = 11.1, 7.5, 1.4 Hz, 1H), 5.48 (dt, *J* = 15.3, 1.5 Hz, 1H), 4.64 (dd, *J* = 6.9, 1.4 Hz, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 2.88 (dd, *J* = 7.7, 1.4 Hz, 2H), 2.41 – 2.31 (m, 2H), 1.48 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.33, 135.82, 131.19, 124.43, 121.93, 114.07, 82.74, 61.91, 61.62, 38.88, 37.42, 35.38, 27.88, 26.01, 18.40, -5.20.
HRMS (ESI – TOF) m/z: Calcd for $C_{22}H_{36}N_2NaO_4Si$ $[M+Na]^+$ 443.2337, found 443.2335.



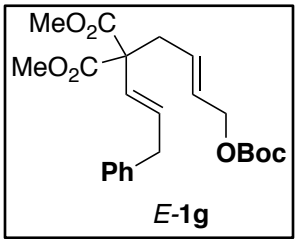
E-**1e**

Synthesized according to Procedure B-1 (97 mg, 30 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.16 (dd, *J* = 15.3, 6.7 Hz, 1H), 5.92 (dt, *J* = 15.5, 5.5 Hz, 1H), 5.79 (dtt, *J* = 15.4, 7.1, 1.2 Hz, 1H), 5.32 (dd, *J* = 15.3, 1.4 Hz, 1H), 4.59 (d, *J* = 5.5 Hz, 2H), 2.74 (d, *J* = 7.3 Hz, 2H), 2.47 – 2.37 (m, 1H), 1.49 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.22, 145.16, 132.82, 124.31, 117.96, 114.21, 82.62, 66.07, 42.31, 39.05, 31.00, 27.88, 21.78.
HRMS (ESI – TOF) m/z: Calcd for $C_{17}H_{24}N_2NaO_3$ $[M+Na]^+$ 327.1679, found 327.1662.



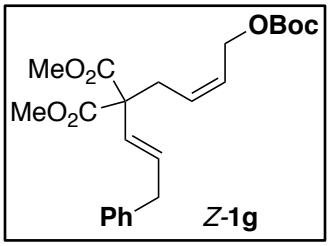
E-**1f**

Synthesized according to Procedure B-1 (186 mg, 50 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 2H), 6.37 (dd, *J* = 15.3, 6.5 Hz, 1H), 5.89 (dt, *J* = 15.2, 5.7 Hz, 1H), 5.77 (dtt, *J* = 15.3, 7.3, 1.4 Hz, 1H), 5.33 (dd, *J* = 15.1, 1.6 Hz, 1H), 4.56 (d, *J* = 5.2 Hz, 2H), 3.69 – 3.51 (m, 1H), 2.74 (d, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.42 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.22, 143.19, 142.97, 132.98, 128.96, 127.30, 127.07, 124.13, 119.66, 114.06, 114.02, 82.64, 66.04, 42.25, 41.90, 38.96, 27.89, 20.76.
HRMS (ESI – TOF) m/z: Calcd for $C_{22}H_{26}N_2NaO_3$ $[M+Na]^+$ 389.1836, found 389.1842.



E-**1g**

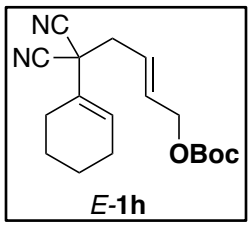
Synthesized according to Procedure B-2 (73 mg, 43 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.27 (m, 2H), 7.19 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.16 – 7.12 (m, 2H), 5.99 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.71 (dt, *J* = 16.0, 6.9 Hz, 1H), 5.66 – 5.61 (m, 2H), 4.44 (d, *J* = 4.7 Hz, 2H), 3.73 (s, 6H), 3.42 (d, *J* = 6.7 Hz, 2H), 2.80 (d, *J* = 5.5 Hz, 1H), 1.48 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.66, 153.40, 139.68, 132.08, 129.85, 128.63, 128.61, 128.34, 127.65, 126.36, 82.21, 67.12, 59.48, 52.86, 39.14, 38.52, 27.92.
HRMS (ESI – TOF) m/z: Calcd for $C_{23}H_{30}NaO_7$ $[M+Na]^+$ 441.1884, found 441.1888.



Z-**1g**

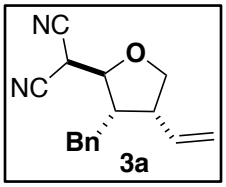
Synthesized according to Procedure A-2 (112 mg, 46 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 2H), 7.19 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.74 (dt, *J* = 16.0, 6.9 Hz, 1H), 5.66 (dtt, *J* = 11.1, 6.8, 1.5 Hz, 1H), 5.52 (dtt, *J* = 10.7, 7.6, 1.5 Hz, 1H), 4.57 (dd, *J* = 6.7, 1.5 Hz, 2H), 3.73 (s, 6H), 3.43 (d, *J* = 6.7 Hz, 2H), 2.86 (dd, *J* = 7.5, 1.6 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.64, 153.52, 139.61, 132.21, 128.62, 128.22, 127.53, 127.17, 126.36, 82.27, 62.64, 59.24, 52.93, 39.12, 33.62, 27.91.
HRMS (ESI – TOF) m/z: Calcd for $C_{23}H_{30}NaO_7$ $[M+Na]^+$ 441.1884, found 441.1888.



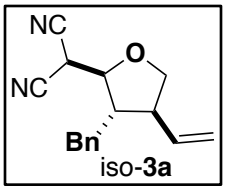
E-**1h**

Synthesized according to Procedure B-1 (73 mg, 22 %).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.21 (tt, *J* = 3.8, 1.5 Hz, 1H), 5.91 (dtt, *J* = 15.3, 5.6, 1.0 Hz, 1H), 5.76 (dtt, *J* = 15.6, 7.3, 1.3 Hz, 1H), 4.58 (dd, *J* = 5.7, 1.2 Hz, 2H), 2.76 (dd, *J* = 7.2, 1.0 Hz, 2H), 2.22 – 2.07 (m, 4H), 1.77 – 1.69 (m, 2H), 1.66 – 1.58 (m, 2H), 1.49 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.24, 132.32, 130.19, 127.48, 124.83, 114.29, 82.58, 66.16, 43.73, 40.07, 27.89, 25.38, 24.70, 22.38, 21.43.
HRMS (ESI – TOF) m/z: Calcd for $C_{18}H_{24}N_2NaO_3$ $[M+Na]^+$ 339.1679, found 339.1674.



3a

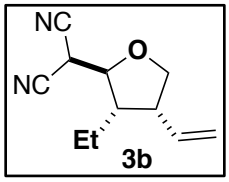
Synthesized according to Procedure C-1 (48 mg, 67 %, 5:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 20 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 7.19 (dd, *J* = 6.8, 1.6 Hz, 2H), 5.84 (ddd, *J* = 17.0, 10.4, 9.1 Hz, 1H), 5.29 – 5.19 (m, 2H), 4.20 (dd, *J* = 8.8, 5.5 Hz, 1H), 4.06 (dd, *J* = 7.7, 3.0 Hz, 1H), 3.90 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.12 (dtd, *J* = 9.3, 6.0, 3.7 Hz, 1H), 2.99 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.87 (d, *J* = 2.9 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.54 (dd, *J* = 13.6, 10.5 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.47, 134.49, 129.45, 128.60, 127.50, 118.72, 111.58, 110.88, 80.76, 73.95, 48.16, 47.34, 34.86, 28.82.
HRMS (ESI – TOF) m/z: Calcd for $C_{16}H_{15}N_2O$ $[M–H]^–$ 251.1190, found 251.1182.



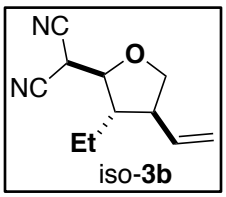
iso-**3a**

Synthesized according to Procedure C-1 (52 mg, 73 %, 8:1 d.r.), (Scale-up: 180 mg, 84 %, 8:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 20 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.18 (dd, *J* = 6.9, 1.7 Hz, 2H), 5.73 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.28 – 5.20 (m, 2H), 4.12 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.05 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.83 (dd, *J* = 10.1, 8.7 Hz, 1H), 3.17 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.77 (tt, *J* = 10.0, 8.0 Hz, 1H), 2.66 (d, *J* = 2.5 Hz, 1H), 2.49 (dd, *J* = 13.7, 10.3 Hz, 1H), 2.28 (tdd, *J* = 10.2, 8.5, 4.4 Hz, 1H).

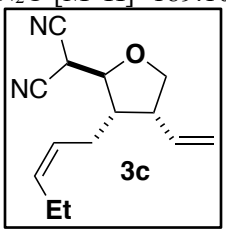
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.12, 134.83, 129.56, 128.62, 127.69, 119.29, 111.59, 110.95, 81.96, 73.43, 51.10, 50.36, 36.77, 28.72.
HRMS (ESI – TOF) m/z: Calcd for $C_{16}H_{15}N_2O$ $[M–H]^-$ 251.1190, found 251.1182.



Synthesized according to Procedure C-1 (12 mg, 92 %, 19:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 20 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.74 (ddd, *J* = 16.8, 10.6, 9.2 Hz, 1H), 5.21 (dt, *J* = 2.3, 1.0 Hz, 1H), 5.20 – 5.16 (m, 1H), 4.14 (dd, *J* = 8.7, 5.5 Hz, 1H), 4.07 (dd, *J* = 7.3, 4.0 Hz, 1H), 3.89 (d, *J* = 4.0 Hz, 1H), 3.84 (dd, *J* = 8.7, 3.8 Hz, 1H), 3.07 (dtd, *J* = 9.4, 6.0, 3.7 Hz, 1H), 2.26 (p, *J* = 7.3 Hz, 1H), 1.56 – 1.45 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.08, 118.30, 111.57, 111.02, 80.71, 74.07, 48.93, 46.34, 28.77, 21.07, 12.21, 1.16.
HRMS (ESI – TOF) m/z: Calcd for $C_{11}H_{13}N_2O$ $[M–H]^-$ 189.1033, found 189.1023.

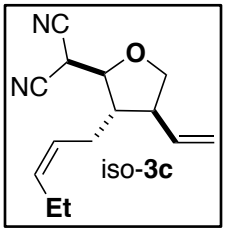


Synthesized according to Procedure C-1 (18 mg, 92 %, 17:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.72 (ddd, *J* = 17.1, 10.2, 8.5 Hz, 1H), 5.18 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.89 (d, *J* = 4.1 Hz, 1H), 3.80 (t, *J* = 9.1 Hz, 1H), 2.73 (q, *J* = 8.1 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.64 (qdd, *J* = 7.4, 6.3, 3.9 Hz, 2H), 1.01 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.18, 118.15, 111.58, 111.07, 81.78, 73.67, 50.56, 50.48, 28.88, 24.20, 11.75.
HRMS (ESI – TOF) m/z: Calcd for $C_{11}H_{13}N_2O$ $[M–H]^-$ 189.1033, found 189.1023.

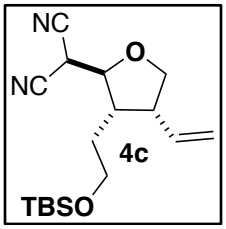


Synthesized according to Procedure C-1 (25 mg, 72 %, 7:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.76 (ddd, *J* = 17.0, 10.4, 8.9 Hz, 1H), 5.54 (dtt, *J* = 10.5, 7.3, 1.5 Hz, 1H), 5.28 (dtt, *J* = 10.8, 6.5, 1.7 Hz, 1H), 5.21 (dd, *J* = 5.5, 0.9 Hz, 1H), 5.18 (dt, *J* = 14.1, 1.1 Hz, 1H), 4.17 (dd, *J* = 8.7, 5.8 Hz, 1H), 4.04 (dd, *J* = 6.9, 3.7 Hz, 1H), 3.92 (d, *J* = 3.7 Hz, 1H), 3.85 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.14 – 3.03 (m, 1H), 2.39 (dq, *J* = 8.3, 7.1 Hz, 1H), 2.28 – 2.13 (m, 2H), 2.10 – 1.99 (m, 3H), 0.98 (t, *J* = 7.5 Hz, 3H).

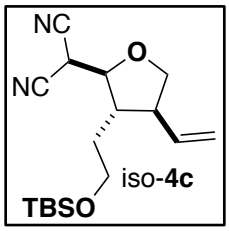
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.28, 134.07, 124.94, 118.54, 111.63, 111.05, 80.94, 73.74, 46.84, 46.76, 29.10, 26.19, 20.96, 14.21.
HRMS (ESI – TOF) m/z: Calcd for $C_{14}H_{17}N_2O$ $[M–H]^-$ 229.1335, found 229.1339.



Synthesized according to Procedure C-1 (15 mg, 71 %, 7:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.69 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.57 (dtt, *J* = 11.0, 7.3, 1.5 Hz, 1H), 5.31 (dtt, *J* = 10.6, 6.7, 1.3 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.09 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.03 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.97 (d, *J* = 3.2 Hz, 1H), 3.81 (dd, *J* = 9.8, 8.7 Hz, 1H), 2.78 – 2.66 (m, 1H), 2.43 – 2.33 (m, 1H), 2.24 (dtd, *J* = 14.4, 8.6, 1.2 Hz, 1H), 2.10 – 2.02 (m, 3H), 0.98 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.89, 135.24, 124.19, 118.85, 111.66, 111.06, 81.75, 73.41, 50.51, 48.74, 29.08, 27.72, 20.87, 14.23.
HRMS (ESI – TOF) m/z: Calcd for $C_{14}H_{17}N_2O$ $[M–H]^-$ 229.1335, found 229.1339.

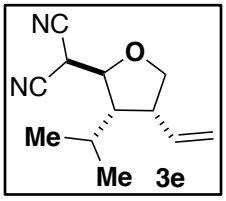


Synthesized according to Procedure C-1 (24 mg, 63 %, 16:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 10 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.74 (ddd, *J* = 17.0, 10.4, 9.4 Hz, 1H), 5.21 – 5.11 (m, 2H), 4.44 (d, *J* = 2.7 Hz, 1H), 4.17 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.13 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.85 (dd, *J* = 8.7, 2.8 Hz, 1H), 3.77 (dt, *J* = 10.9, 4.9 Hz, 1H), 3.64 (ddd, *J* = 10.7, 8.8, 3.7 Hz, 1H), 3.08 – 2.93 (m, 1H), 2.54 – 2.42 (m, 1H), 1.76 (dtd, *J* = 14.4, 5.3, 3.7 Hz, 1H), 1.55 (ddt, *J* = 14.4, 8.8, 4.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.02, 118.15, 112.17, 111.55, 81.32, 73.95, 62.06, 47.94, 45.19, 31.78, 28.51, 26.05, 18.44, -5.21, -5.30.
HRMS (ESI – TOF) m/z: Calcd for $C_{17}H_{27}N_2O_2Si$ $[M–H]^-$ 319.1836, found 319.1836.



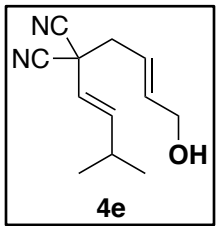
Synthesized according to Procedure C-1 (25 mg, 66 %*, 20:1 d.r.).
***Note:** product iso-**4c** was isolated with 15 % Knoevenagel adduct starting material, inseparable.
Solvent system for column chromatography: Hex/EtOAc 10 %.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.65 (ddd, *J* = 17.0, 10.1, 8.6 Hz, 1H), 5.21 – 5.13 (m, 2H), 4.65 (d, *J* = 2.2 Hz, 1H), 4.17 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.08 (dd, *J* = 8.6, 7.7 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.62 (ddd, *J* = 11.0, 9.5, 2.9 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.11 – 2.00 (m, 1H), 1.90 (ddt, *J* = 14.6, 5.0, 3.2 Hz, 1H), 1.58 – 1.49 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.19, 118.98, 112.36, 111.85, 82.78, 73.12, 62.53, 52.03, 48.41, 33.70, 28.52, 26.06, 18.47, -5.22, -5.31.
HRMS (ESI – TOF) m/z: Calcd for $C_{17}H_{27}N_2O_2Si$ $[M–H]^-$ 319.1836, found 319.1836.



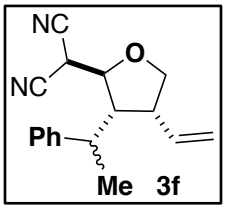
3e

Synthesized according to Procedure C-1 (4.2 mg, 63 % after 2 reaction cycle, 9:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 20 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.80 (dt, *J* = 17.3, 9.8 Hz, 1H), 5.22 – 5.18 (m, 1H), 5.17 (s, 1H), 4.23 (dd, *J* = 7.4, 2.6 Hz, 1H), 4.19 (dd, *J* = 8.6, 5.3 Hz, 1H), 3.87 (d, *J* = 2.9 Hz, 1H), 3.85 (d, *J* = 2.5 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.10 (dt, *J* = 9.0, 7.1 Hz, 1H), 1.81 (dp, *J* = 9.0, 6.7 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.74, 118.03, 111.90, 111.39, 79.63, 74.75, 53.77, 47.41, 30.28, 27.30, 21.88, 21.28.
HRMS (ESI – TOF) m/z: Calcd for $C_{12}H_{15}N_2O$ $[M–H]^-$ 203.1179, found 203.1179.



4e

Deprotected *E*-**1e** recovered after Procedure C-1 on **3e**.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.17 (dd, *J* = 15.3, 6.7 Hz, 1H), 5.99 (dtt, *J* = 15.3, 5.0, 1.1 Hz, 1H), 5.77 (dtt, *J* = 15.1, 7.3, 1.7 Hz, 1H), 5.34 (dd, *J* = 15.3, 1.4 Hz, 1H), 4.22 (ddt, *J* = 5.1, 1.8, 0.9 Hz, 2H), 2.73 (dq, *J* = 7.4, 1.1 Hz, 2H), 2.43 (dqd, *J* = 13.5, 6.8, 1.5 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 6H).



3f

Synthesized according to Procedure C-1 (7.5 mg, 34 %, 1:1 d.r., separable diastereomers).
Solvent system for column chromatography: Hex/EtOAc 20 %.
Diastereomer 1:
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 7.22 – 7.18 (m, 2H), 5.92 (dt, *J* = 17.4, 9.9 Hz, 1H), 5.32 (dd, *J* = 3.5, 1.3 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 4.17 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.95 (d, *J* = 2.4 Hz, 1H), 3.93 (d, *J* = 1.9 Hz, 1H), 3.10 (ddd, *J* = 10.1, 6.0, 4.2 Hz, 1H), 2.68 (dq, *J* = 11.2, 6.7 Hz, 1H), 2.44 (ddd, *J* = 11.3, 9.4, 6.1 Hz, 1H), 1.84 (d, *J* = 1.9 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H).

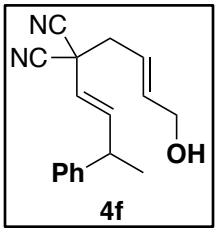
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.00, 134.62, 129.83, 128.24, 126.93, 118.44, 111.88, 111.24, 80.11, 74.62, 53.88, 47.07, 39.35, 28.53, 19.86.

Diastereomer 2:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 7.20 – 7.16 (m, 2H), 5.79 (ddd, *J* = 17.2, 10.4, 8.9 Hz, 1H), 5.14 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.88 (dt, *J* = 17.2, 1.2 Hz, 1H), 4.33 (dd, *J* = 7.4, 2.5 Hz, 1H), 4.19 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.86 (dd, *J* = 8.7, 3.1 Hz, 1H), 3.80 (d, *J* = 2.5 Hz, 1H), 2.96 (dq, *J* = 9.7, 7.0 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.72 (dt, *J* = 9.4, 7.1 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.29, 134.19, 128.91, 127.29, 127.05, 118.67, 111.75, 111.23, 79.43, 74.52, 52.69, 47.12, 38.70, 30.43, 21.15.

HRMS (ESI – TOF) m/z: Calcd for $C_{17}H_{17}N_2O$ $[M–H]^-$ 265.1335, found 265.1339.

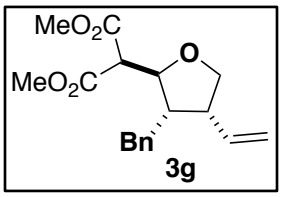


4f

Deprotected *E*-**1f** recovered after Procedure C-1 on **3f**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 2H), 7.28 – 7.25 (m, 1H), 7.20 – 7.15 (m, 2H), 6.37 (dd, *J* = 15.3, 6.6 Hz, 1H), 5.95 (dtt, *J* = 15.4, 5.0, 1.2 Hz, 1H), 5.72 (dtt, *J* = 15.1, 7.4, 1.7 Hz, 1H), 5.36 (dd, *J* = 15.3, 1.5 Hz, 1H), 4.17 (dd, *J* = 5.0, 1.6 Hz, 2H), 3.59 (pd, *J* = 7.0, 1.5 Hz, 1H), 2.74 (dt, *J* = 7.4, 1.0 Hz, 2H), 1.43 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.28, 142.79, 138.34, 128.95, 127.30, 127.07, 120.78, 119.78, 114.23, 114.17, 62.68, 42.29, 41.92, 39.31, 20.77.



3g

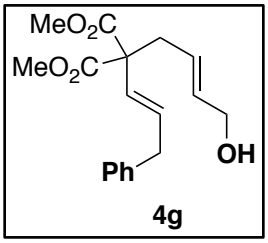
Synthesized according to Procedure C-2 (3 mg, 36 % after 2 reaction cycle, 8:1 d.r.).

Solvent system for column chromatography: Hex/EtOAc 20 %.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (t, *J* = 7.6 Hz, 3H), 7.21 – 7.18 (m, 1H), 7.16 (d, *J* = 6.6 Hz, 2H), 5.87 (ddd, *J* = 17.1, 10.3, 8.8 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.09 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.39 (dd, *J* = 7.2, 5.8 Hz, 1H), 3.98 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.79 – 3.76 (m, 1H), 3.72 (s, 3H), 3.56 (s, 3H), 3.36 (d, *J* = 7.2 Hz, 1H), 2.94 (dq, *J* = 8.5, 6.2 Hz, 1H), 2.79 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.50 (dd, *J* = 13.7, 8.2 Hz, 1H).

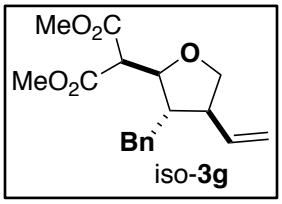
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.73, 167.53, 139.92, 135.37, 129.11, 128.60, 126.36, 117.88, 80.75, 72.33, 56.70, 52.69, 52.66, 47.97, 46.48, 34.43.

HRMS (ESI – TOF) m/z: Calcd for $C_{18}H_{22}NaO_5$ $[M+Na]^+$ 341.1559, found 341.1351.

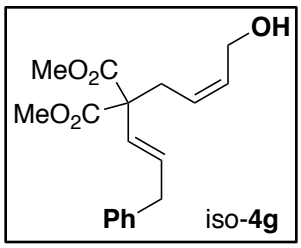


4g

Deprotected *E*-**1g** recovered after Procedure C-1 on **3g**.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 5.99 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.73 (dt, *J* = 16.0, 7.0 Hz, 1H), 5.67 (dtt, *J* = 15.4, 5.7, 1.3 Hz, 1H), 5.54 (dtt, *J* = 15.6, 7.2, 1.4 Hz, 1H), 4.02 (dd, *J* = 5.7, 1.4 Hz, 2H), 3.73 (s, 6H), 3.43 (d, *J* = 7.0 Hz, 2H), 2.80 (dd, *J* = 7.3, 1.3 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.79, 139.76, 133.76, 132.11, 128.64, 128.60, 127.65, 126.39, 126.28, 63.45, 59.62, 52.84, 39.16, 38.36.



Synthesized according to Procedure C-2 (1.5 mg, 39 % after 2 reaction cycle, 12:1 d.r.).
Solvent system for column chromatography: Hex/EtOAc 20 %.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.12 (m, 2H), 5.59 (ddd, *J* = 17.8, 9.9, 8.2 Hz, 1H), 5.03 – 4.97 (m, 1H), 4.96 (t, *J* = 1.1 Hz, 1H), 4.36 (t, *J* = 6.7 Hz, 1H), 3.95 (dd, *J* = 8.7, 7.4 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.61 (t, *J* = 8.6 Hz, 1H), 3.26 (d, *J* = 6.4 Hz, 1H), 2.80 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.72 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.64 (p, *J* = 8.1 Hz, 1H), 2.37 – 2.26 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.90, 167.74, 139.12, 137.44, 129.33, 128.61, 126.58, 116.82, 82.06, 72.21, 56.19, 52.74, 52.62, 50.21, 50.14, 38.37.
HRMS (ESI – TOF) m/z: Calcd for $C_{18}H_{22}NaO_5$ $[M+Na]^+$ 341.1559, found 341.1351.

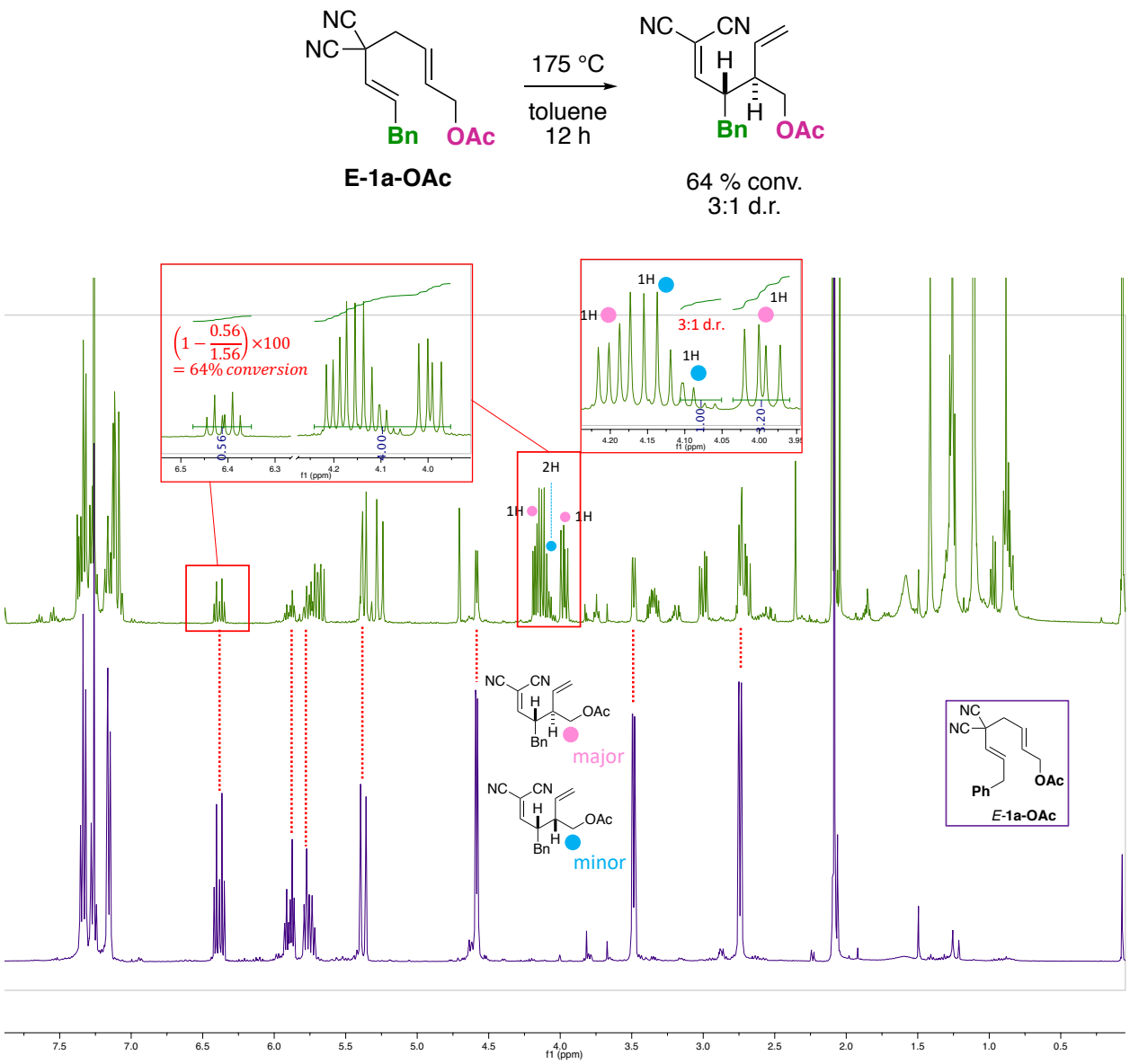


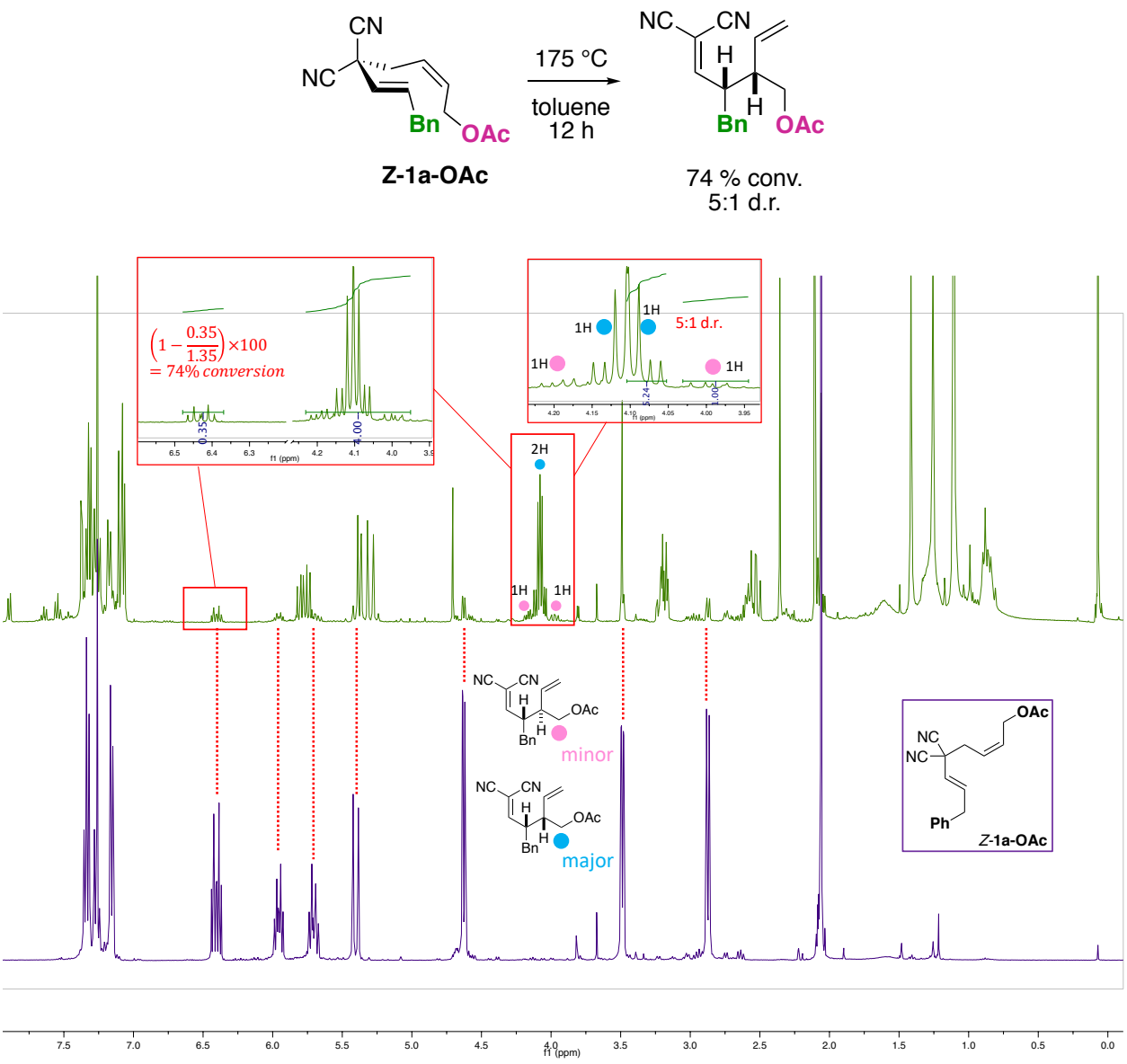
Deprotected *Z*-**1g** recovered after Procedure C-1 on iso-**3g**.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.29 (m, 2H), 7.26 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 6.03 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.81 – 5.70 (m, 2H), 5.44 (dtt, *J* = 10.6, 7.7, 1.4 Hz, 1H), 4.15 (d, *J* = 6.8 Hz, 2H), 3.76 (s, 6H), 3.45 (d, *J* = 6.9 Hz, 2H), 2.86 (dd, *J* = 7.7, 1.5 Hz, 2H).

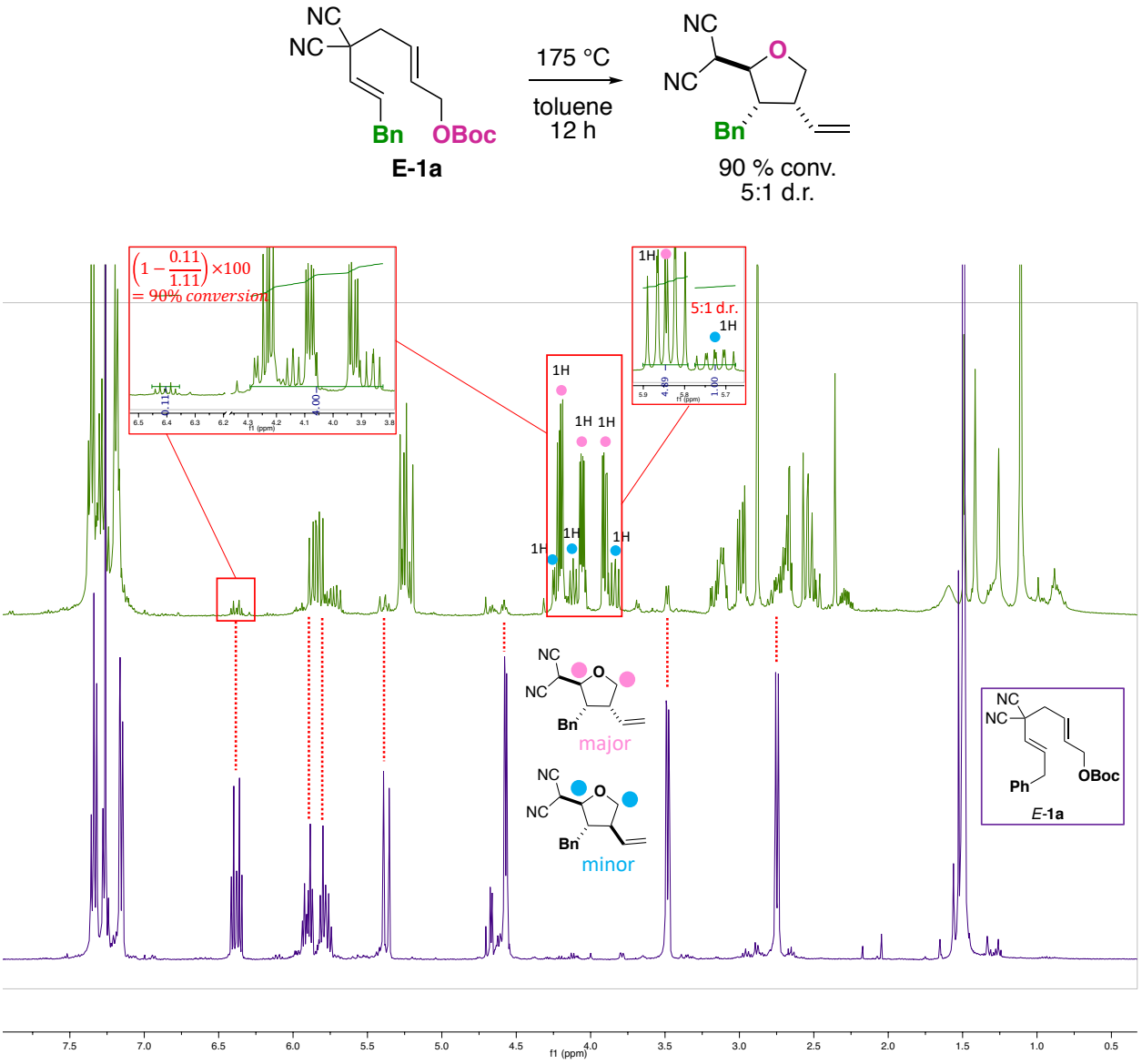
4. Structural and Stereochemical assignment control experiments

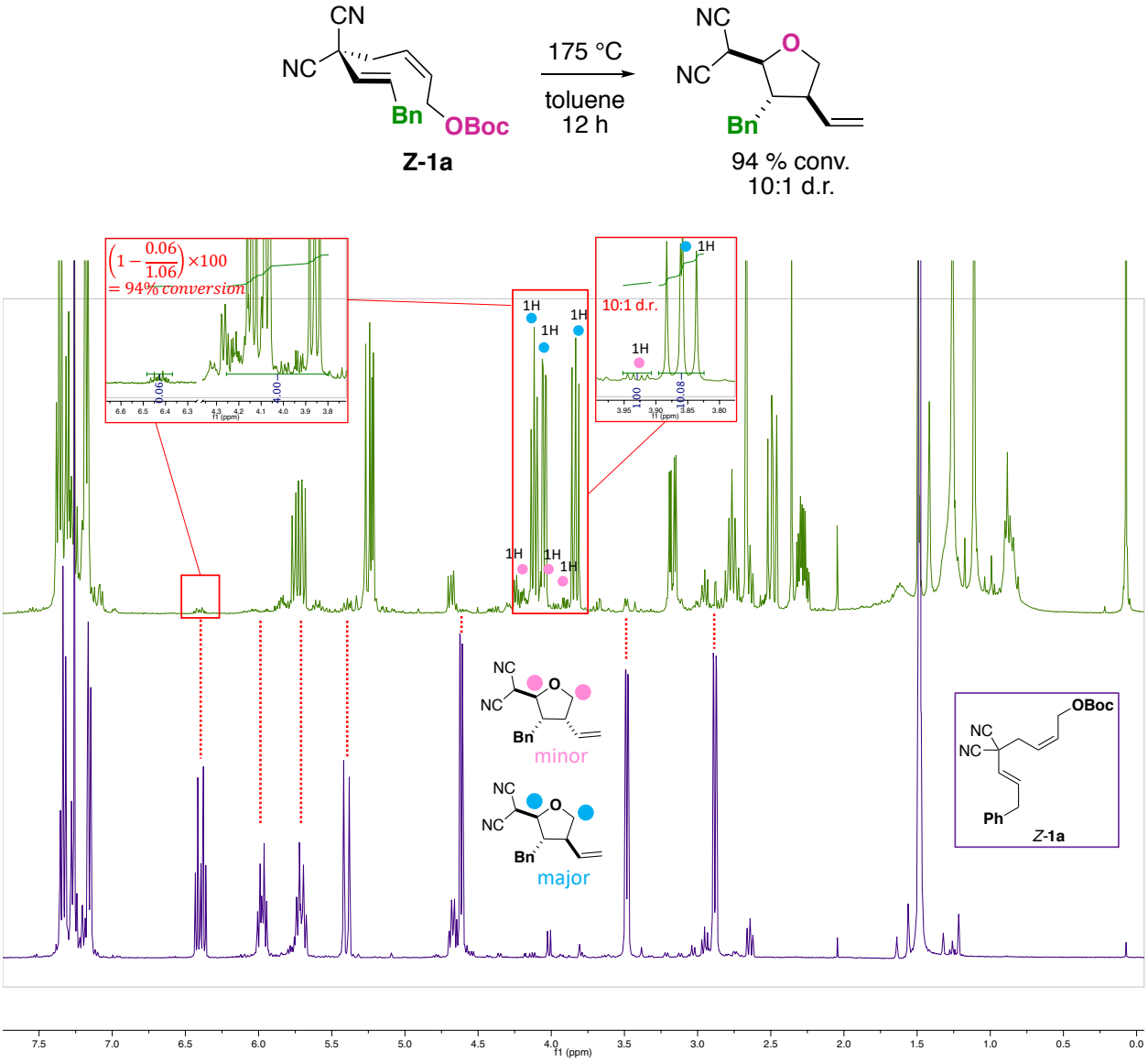
a. Conversion and diastereoselectivity ratio for Scheme 4

Below are crude NMRs for **3a**, iso-**3a** and their respective Cope products. An overlay of the starting material (in purple) is presented against the crude mixture (in green). All peaks from each diastereomers (pink and blue) and starting material could be clearly assigned. Each red box demonstrate how conversion and diastereoselective was determined.


NC
NC
Bn
OAc
E-1a-OAc
175 °C
toluene
12 h
NC
CN
H
H
Bn
OAc
64 % conv.
3:1 d.r.
$\left(1-\frac{0.56}{1.56}\right)\times 100$
$= 64\%\ conversion$
0.56
1.00
3:1 d.r.
1H
1H
1H
1H
2H
1H
1H
major
minor
NC
NC
Ph
OAc
E-1a-OAc
f1 (ppm)

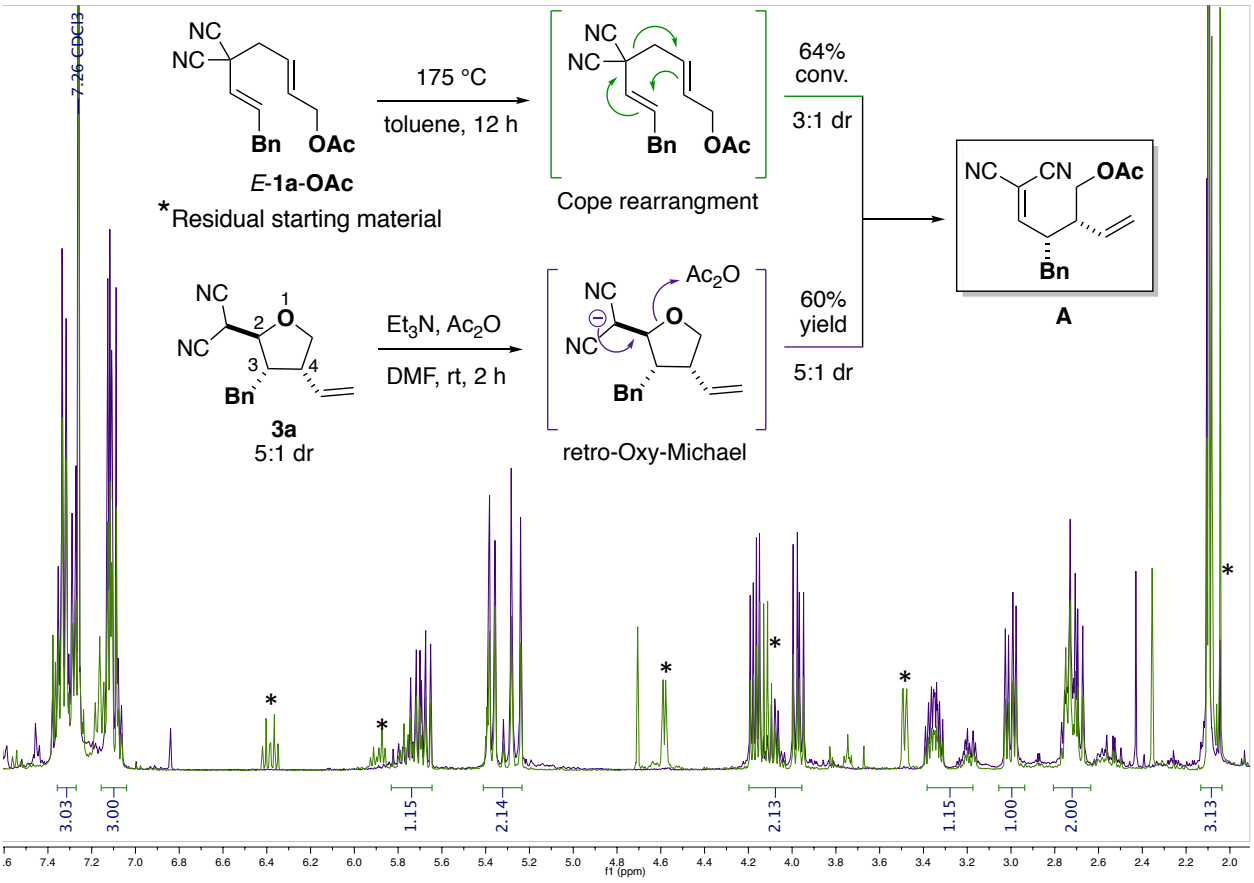

CN
NC
Bn
OAc
175 °C
toluene
12 h
NC
CN
H
H
Bn
OAc
Z-1a-OAc
74 % conv.
5:1 d.r.
$\left(1-\frac{0.35}{1.35}\right)\times 100$
$= 74\%\ conversion$
0.35
1.00
1H
1H
5:1 d.r.
1H
1H
5.24
1.00
2H
1H
1H
NC
CN
H
OAc
H
Bn
minor
major
OAc
NC
NC
Ph
Z-1a-OAc
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


NC
NC
Bn
OBoc
E-1a
175 °C
toluene
12 h
NC
NC
O
Bn
90 % conv.
5:1 d.r.
$\left(1-\frac{0.11}{1.11}\right)\times 100$
$= 90\%\ conversion$
5:1 d.r.
1H
major
minor
Ph
OBoc
E-1a
f1 (ppm)

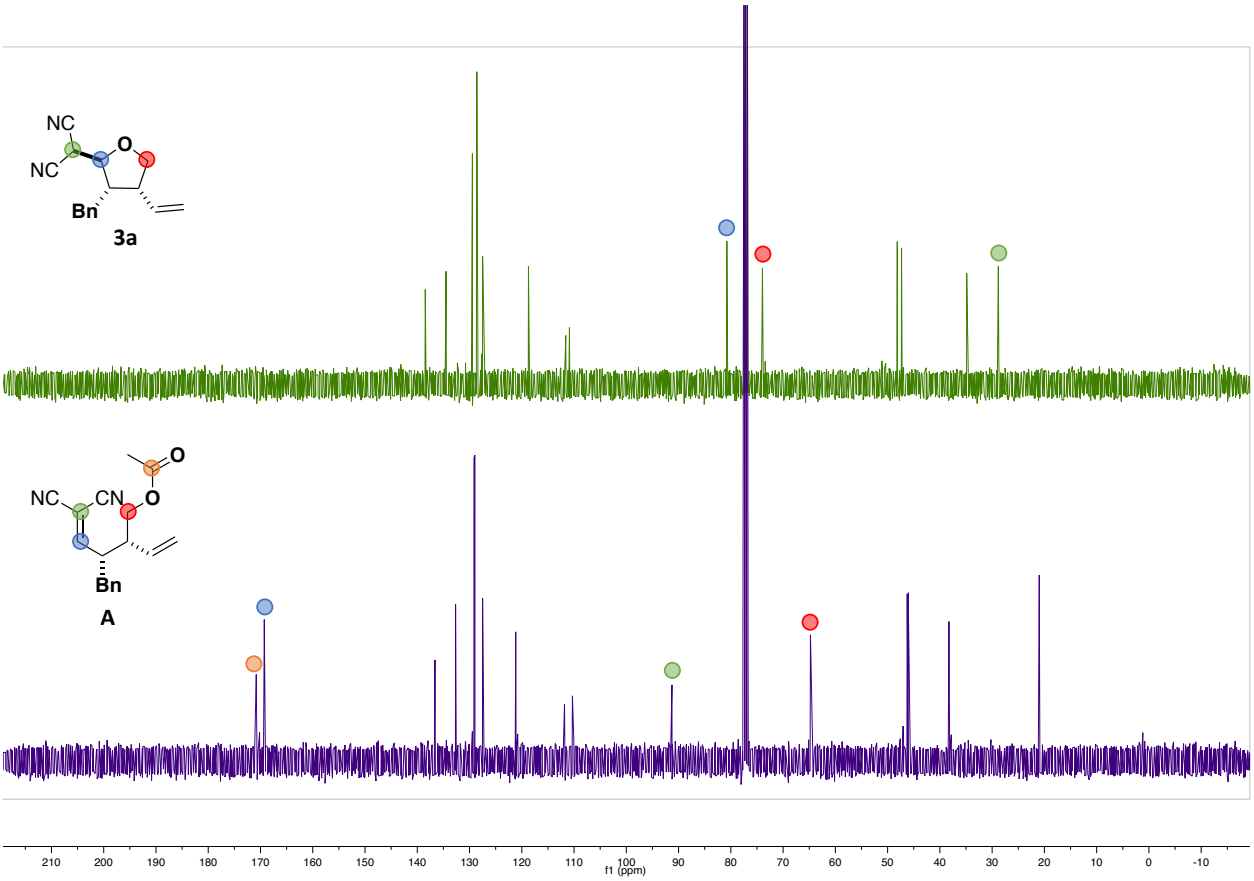


b. Stereochemical outcome of the Cope rearrangement (3 and 4 position)

In order to confirm the stereochemical outcome predicted by the Zimmerman-Traxler model, we performed the following experiment: *E*-**1a-OAc** was subjected to the Cope rearrangement conditions (175 °C, 12 h in toluene). The expected Cope rearranged product **A** was observed (green pathway).
Starting from **3a** (made from **1a**), we performed a retro-Oxy-Michael addition as depicted in the figure below using Et_3N, Ac_2O in DMF at room temperature. The same product **A** was obtained in 60 % (purple pathway). Since both reactions converge to the same product **A**, we are confident about the assigned stereochemistry of **3a** and iso-**3a** at the 3 and 4 position. (both ^1H NMR spectra clearly show that the same product is formed although with slightly different diastereomer ratios).

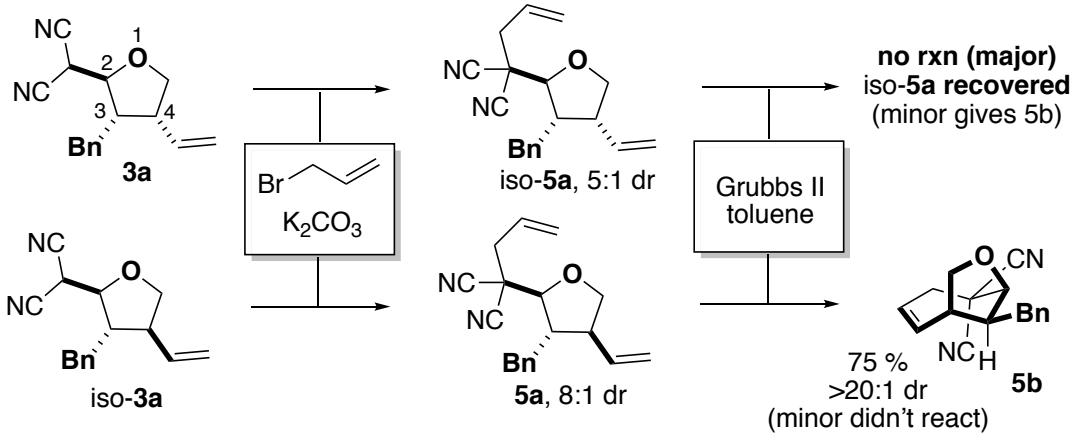


^{13}C NMR comparison of **3a** and **A** demonstrate that they can unambiguously and easily be differentiated (please see next figure).

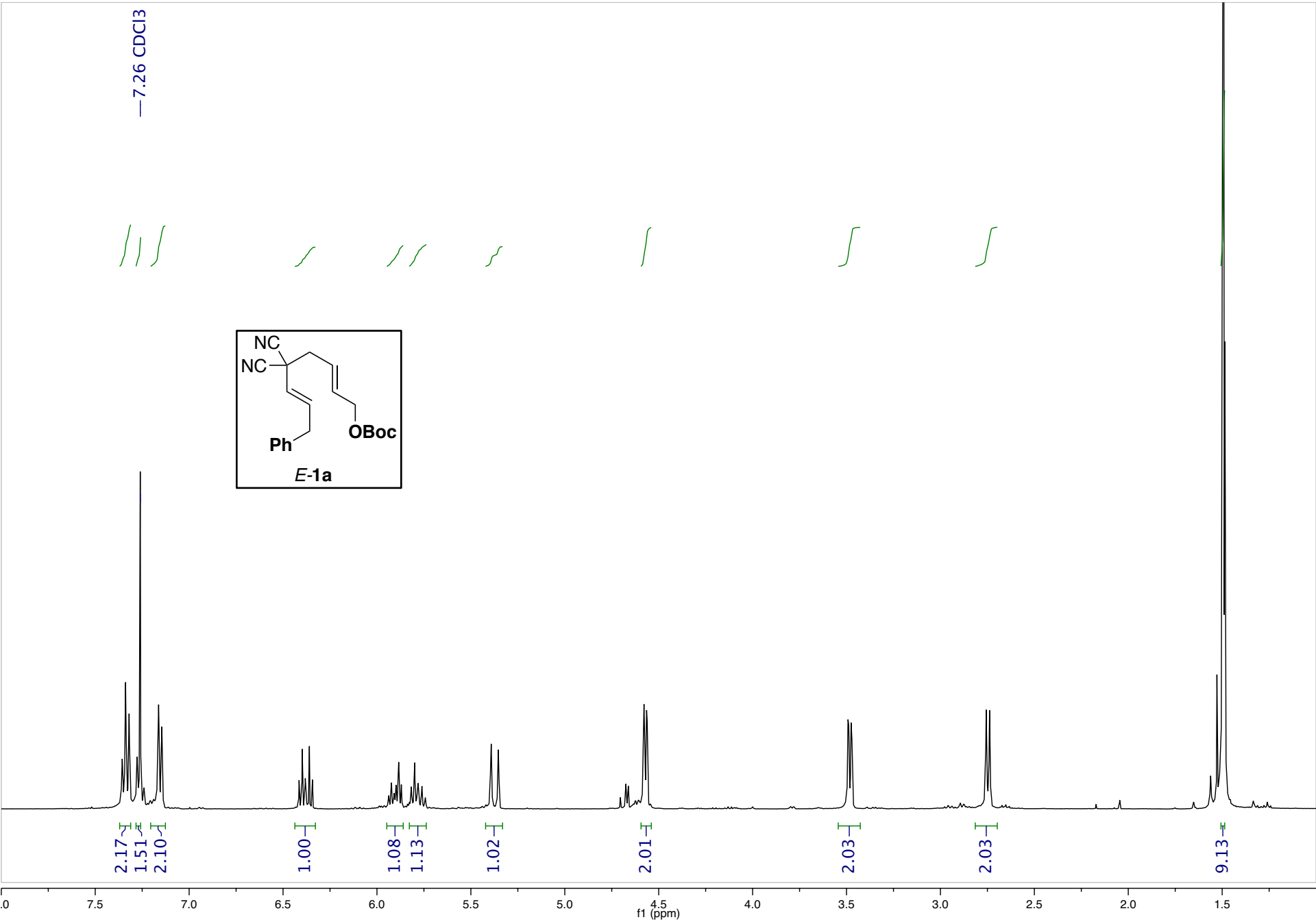


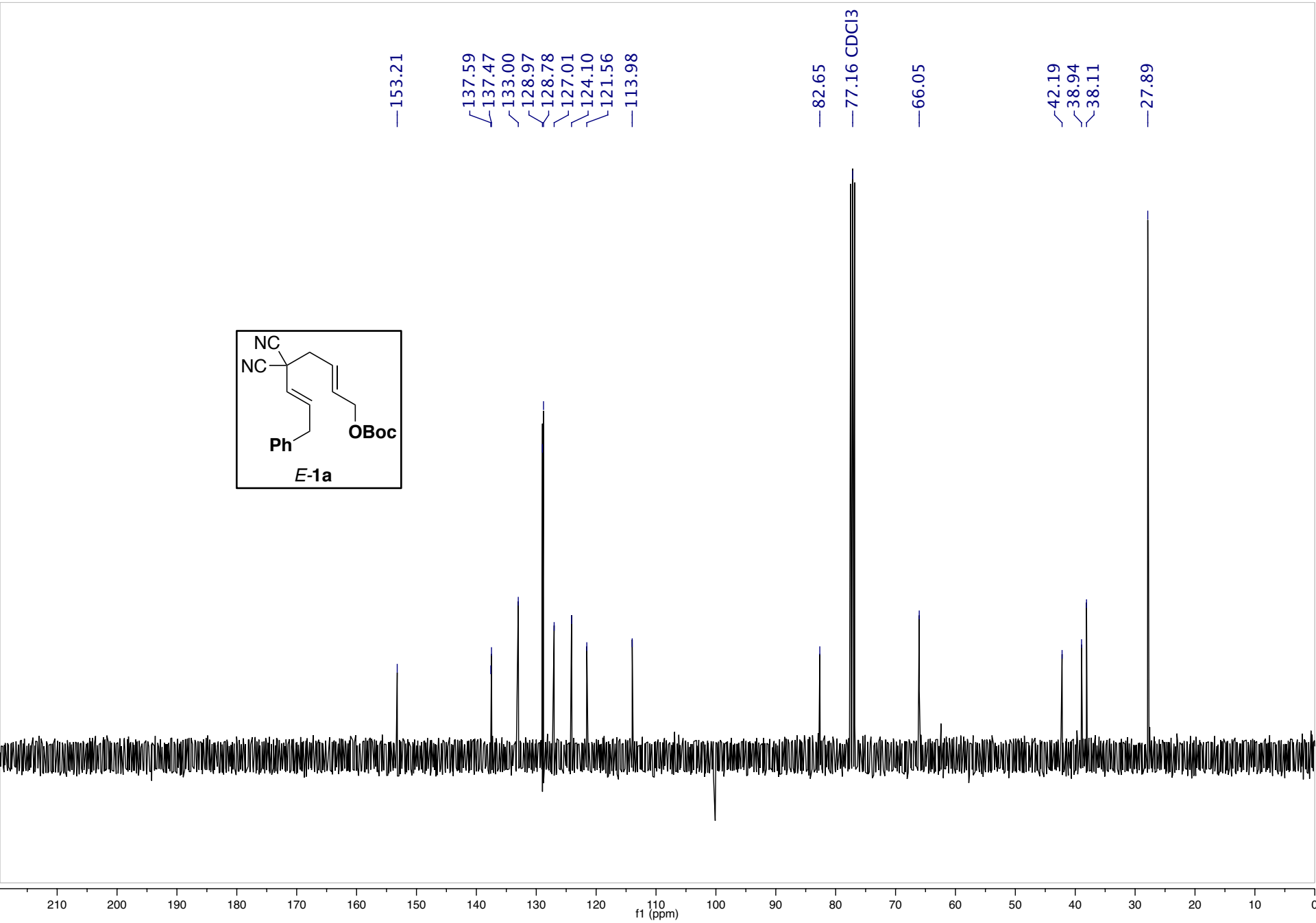
c. Stereochemical outcome of the Cope rearrangement/Oxy-Michael (2 position)

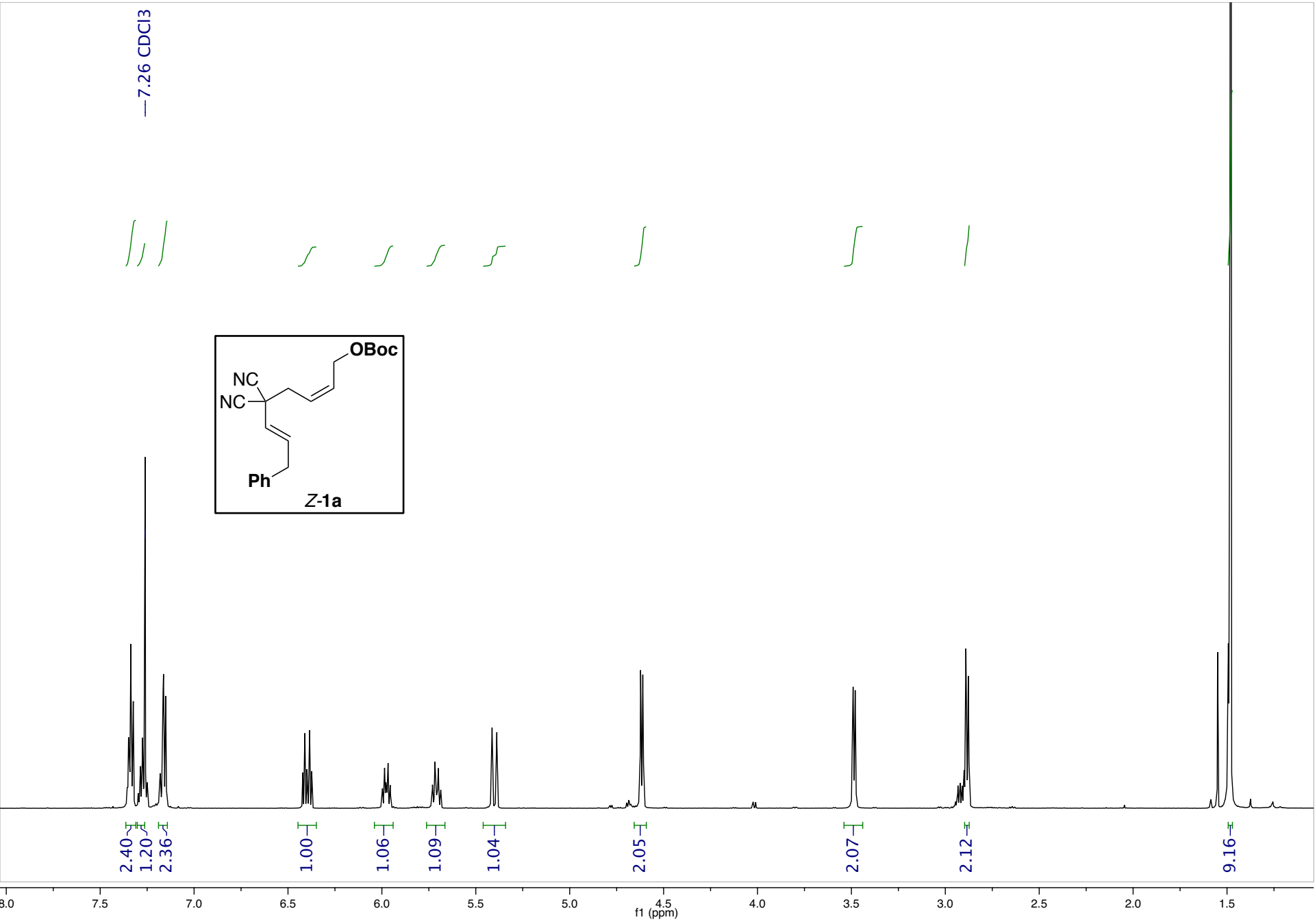
3a and iso-**3a** were both subjected to the same allylation conditions (described in detail in section **2.d.i.**). Then, product **5a** and iso-**5a** were subjected to ring-closing metathesis conditions (described in detail in section **2.d.ii.**). While **5a** gave the expected product **5b**, iso-**5a** didn't react at all under these conditions and was entirely recovered. In this system, only one diastereomer, presenting the appropriate geometry, can react. This experiment allowed us to confirm the assigned stereochemistry of **3a** and iso-**3a** at the 2 position.

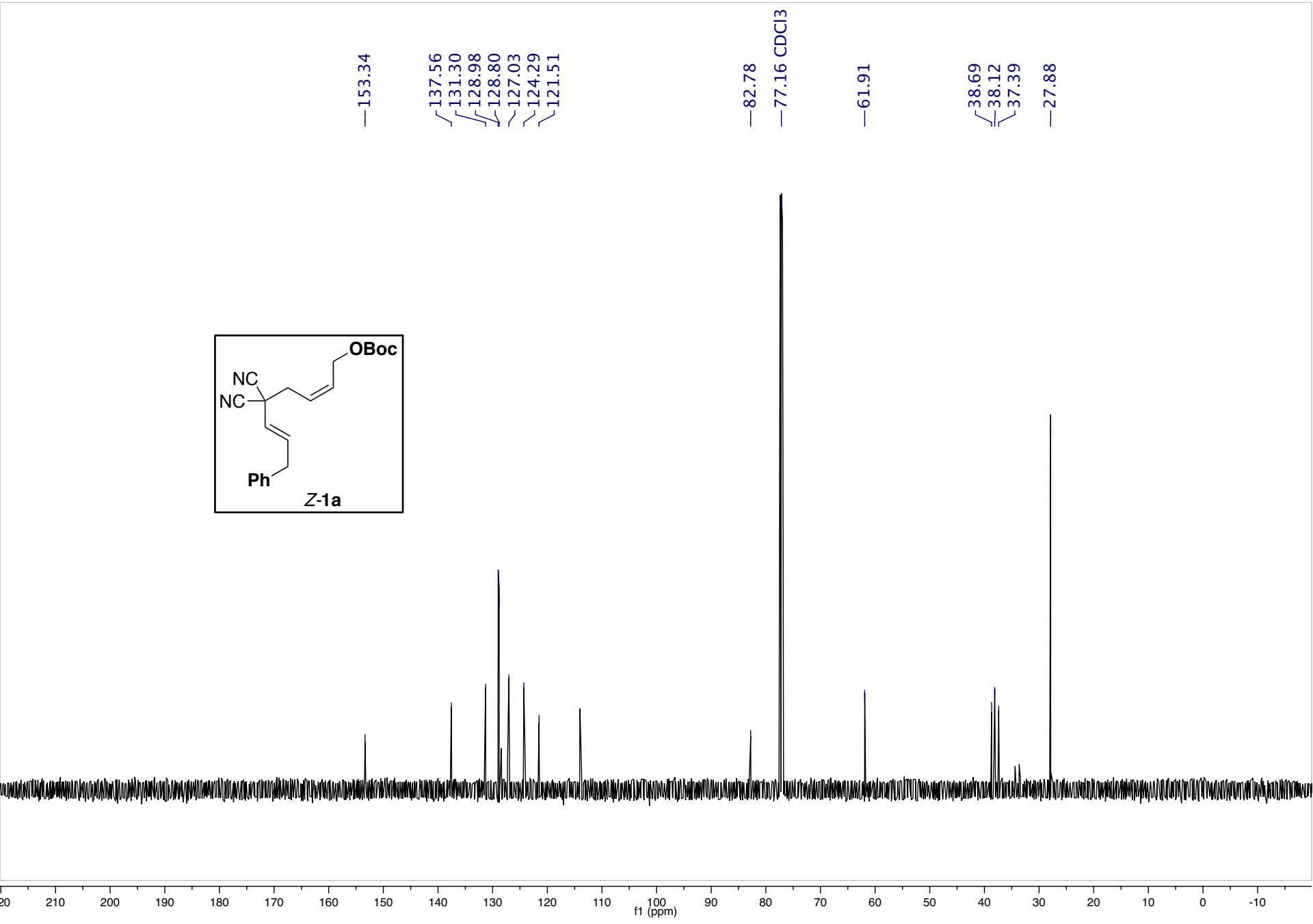


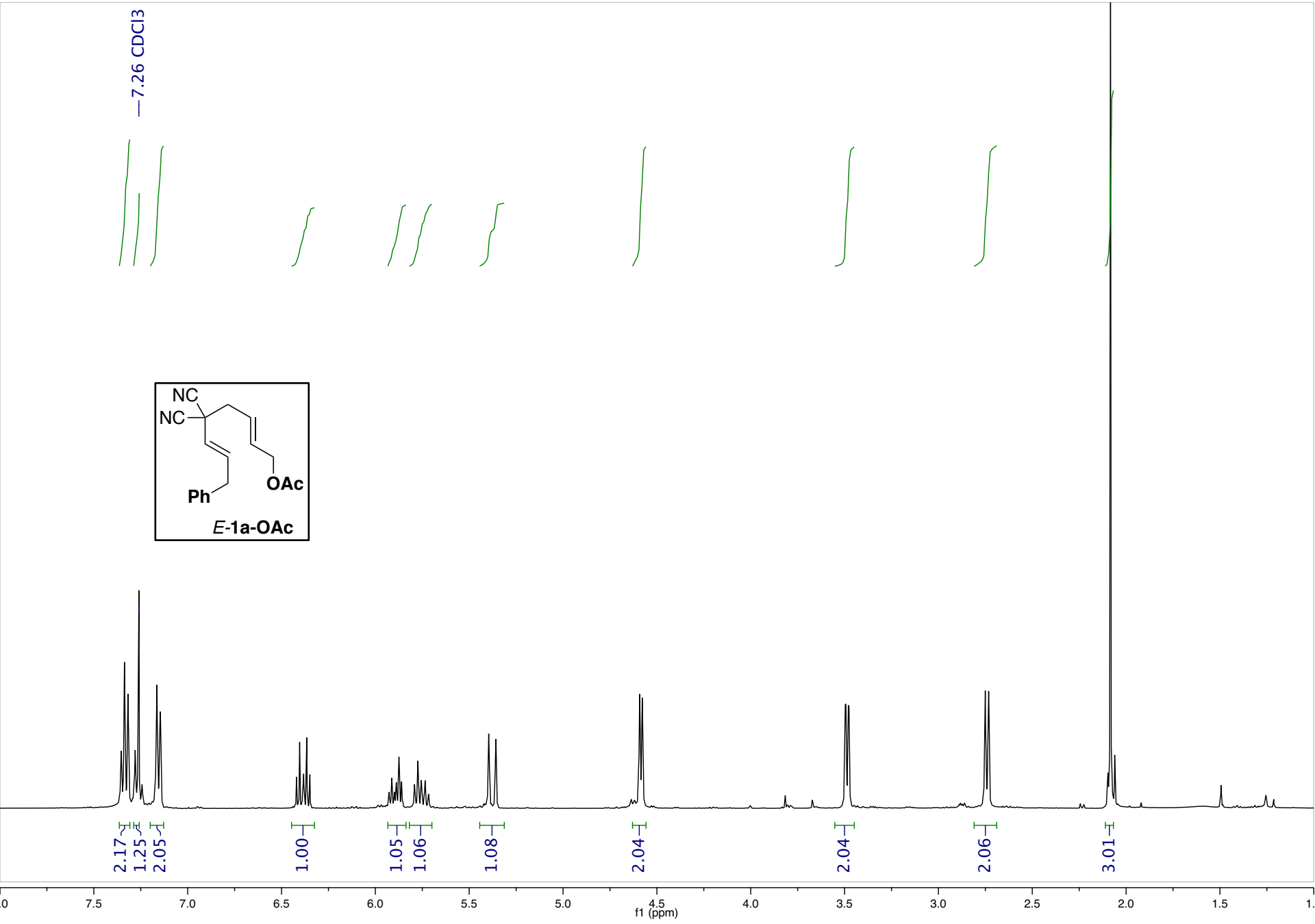
^{1}H & ^{13}C NMR spectra

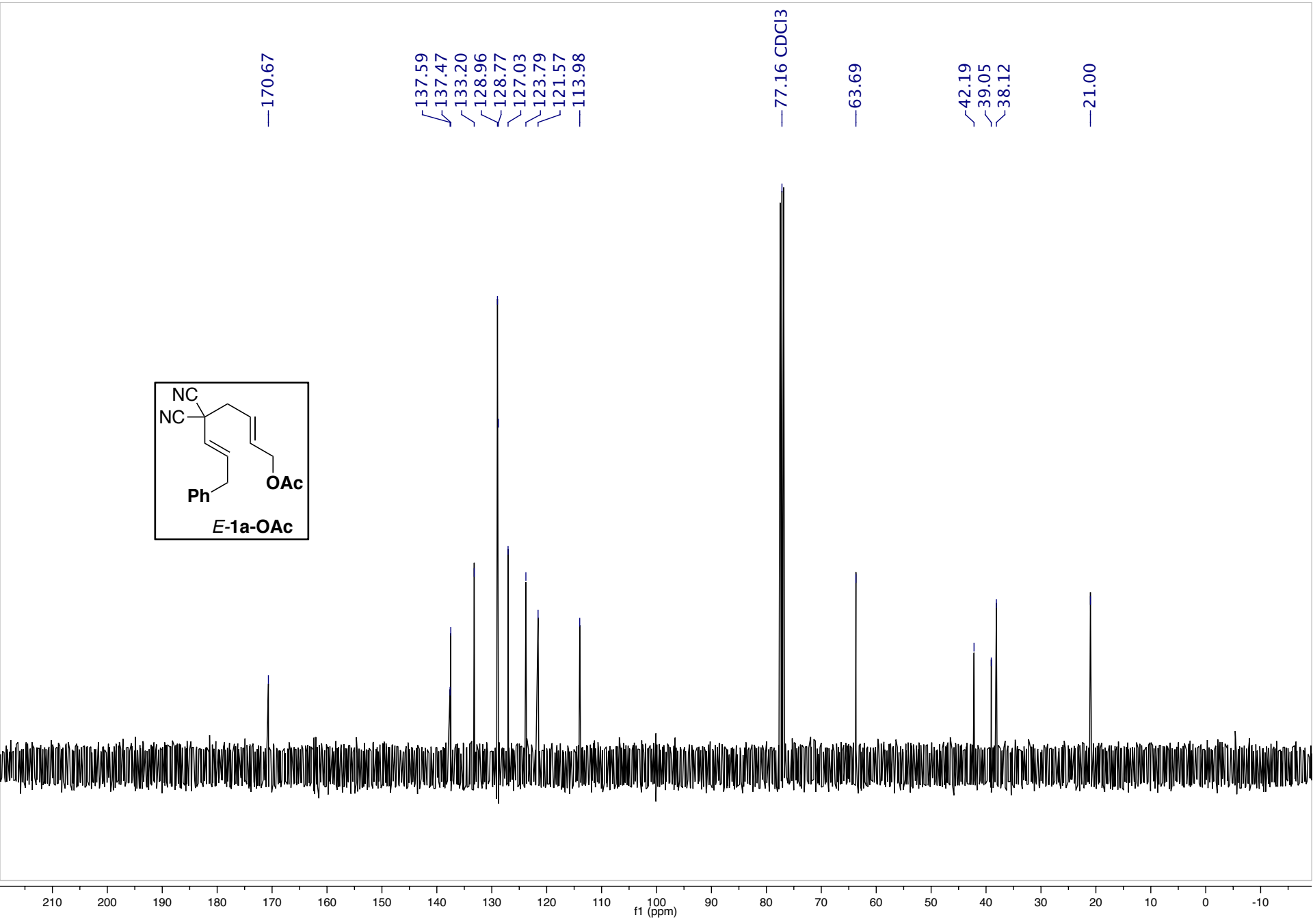

7.26 CDCl3
NC
NC
Ph
OBoc
E-1a
2.17
1.51
2.10
1.00
1.08
1.13
1.02
2.01
2.03
2.03
9.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

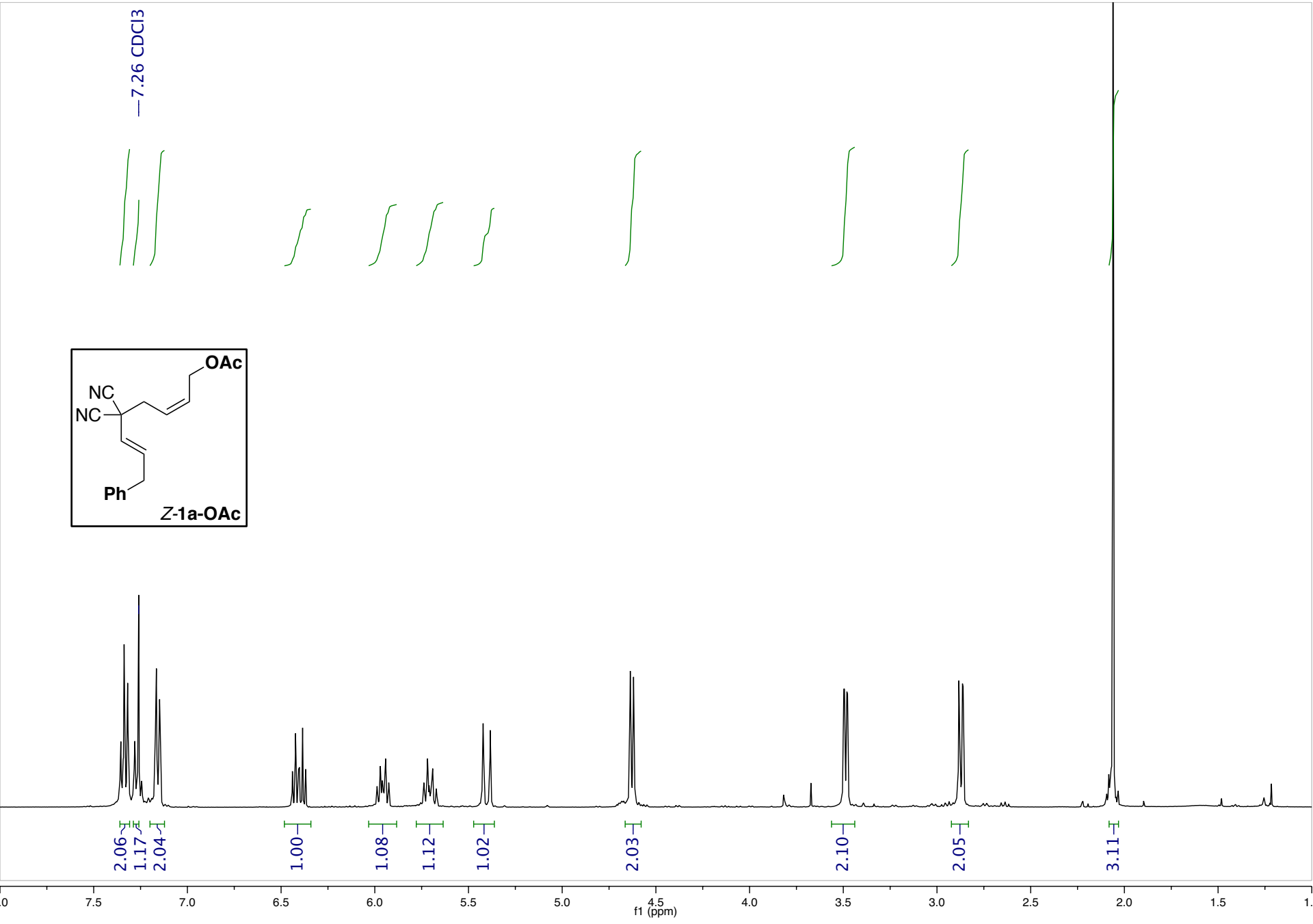

153.21
137.59
137.47
133.00
128.97
128.78
127.01
124.10
121.56
113.98
82.65
77.16 CDCl3
66.05
42.19
38.94
38.11
27.89
NC
NC
Ph
OBoc
E-1a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

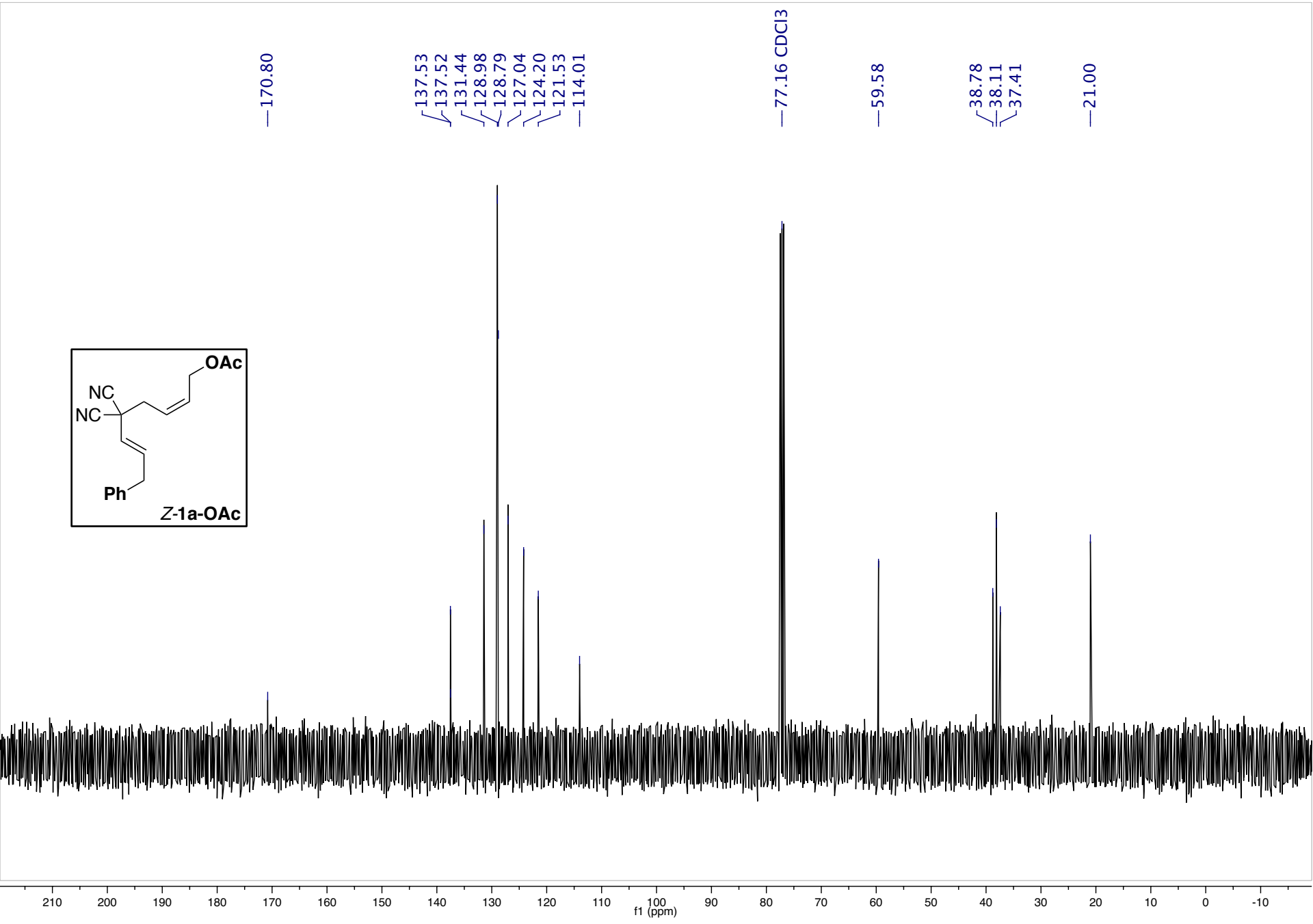

7.26 CDCl3
OBoc
NC
NC
Ph
Z-1a
2.40
1.20
2.36
1.00
1.06
1.09
1.04
2.05
2.07
2.12
9.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

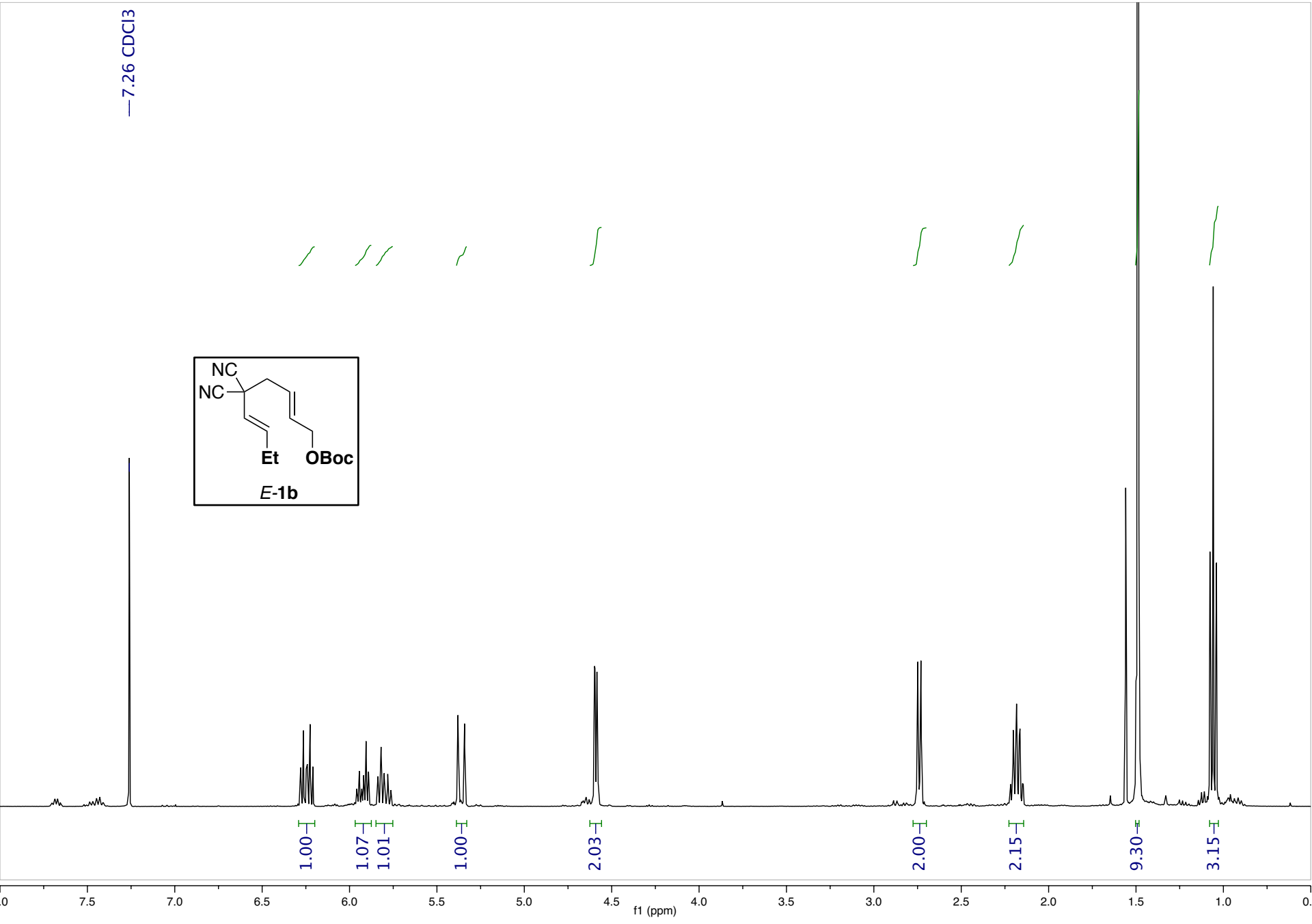

153.34
137.56
131.30
128.98
128.80
127.03
124.29
121.51
82.78
77.16 CDCl3
61.91
38.69
38.12
37.39
27.88
OBoc
NC
NC
Ph
Z-1a
f1 (ppm)

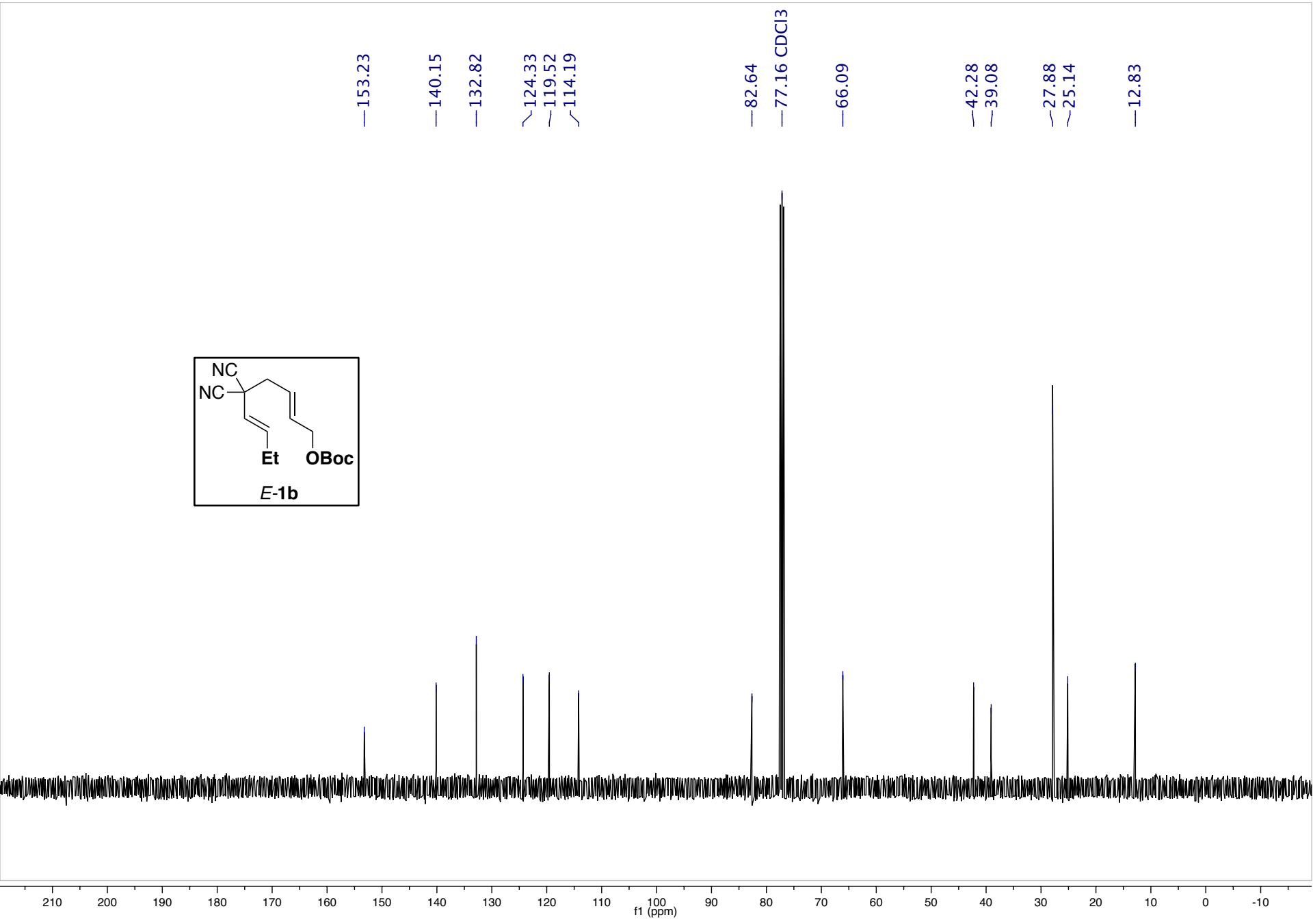

7.26 CDCl3
NC
NC
Ph
OAc
E-1a-OAc
2.17
1.25
2.05
1.00
1.05
1.06
1.08
2.04
2.04
2.06
3.01
f1 (ppm)

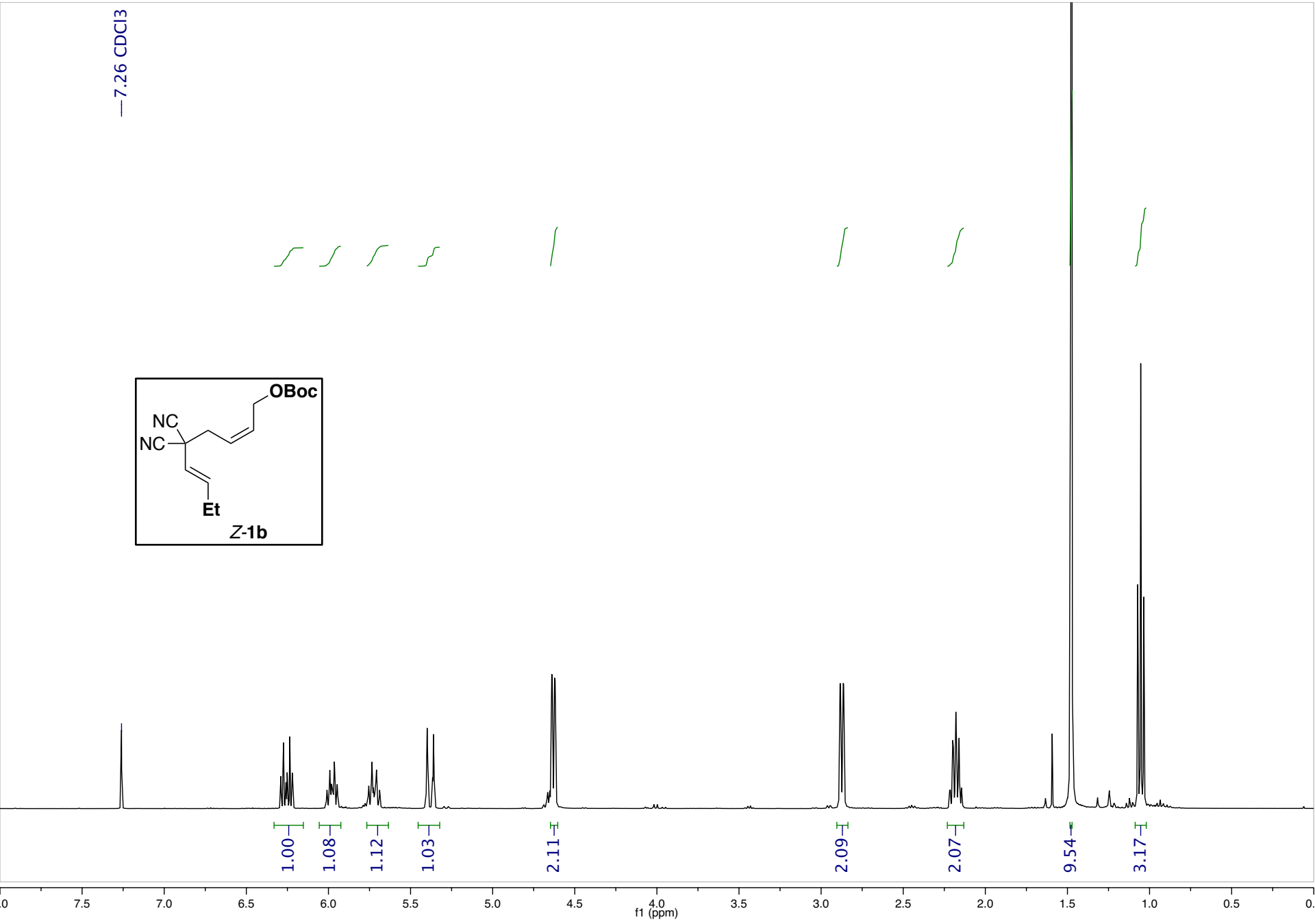

170.67
137.59
137.47
133.20
128.96
128.77
127.03
123.79
121.57
113.98
77.16 CDCl3
63.69
42.19
39.05
38.12
21.00
NC
NC
Ph
OAc
E-1a-OAc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

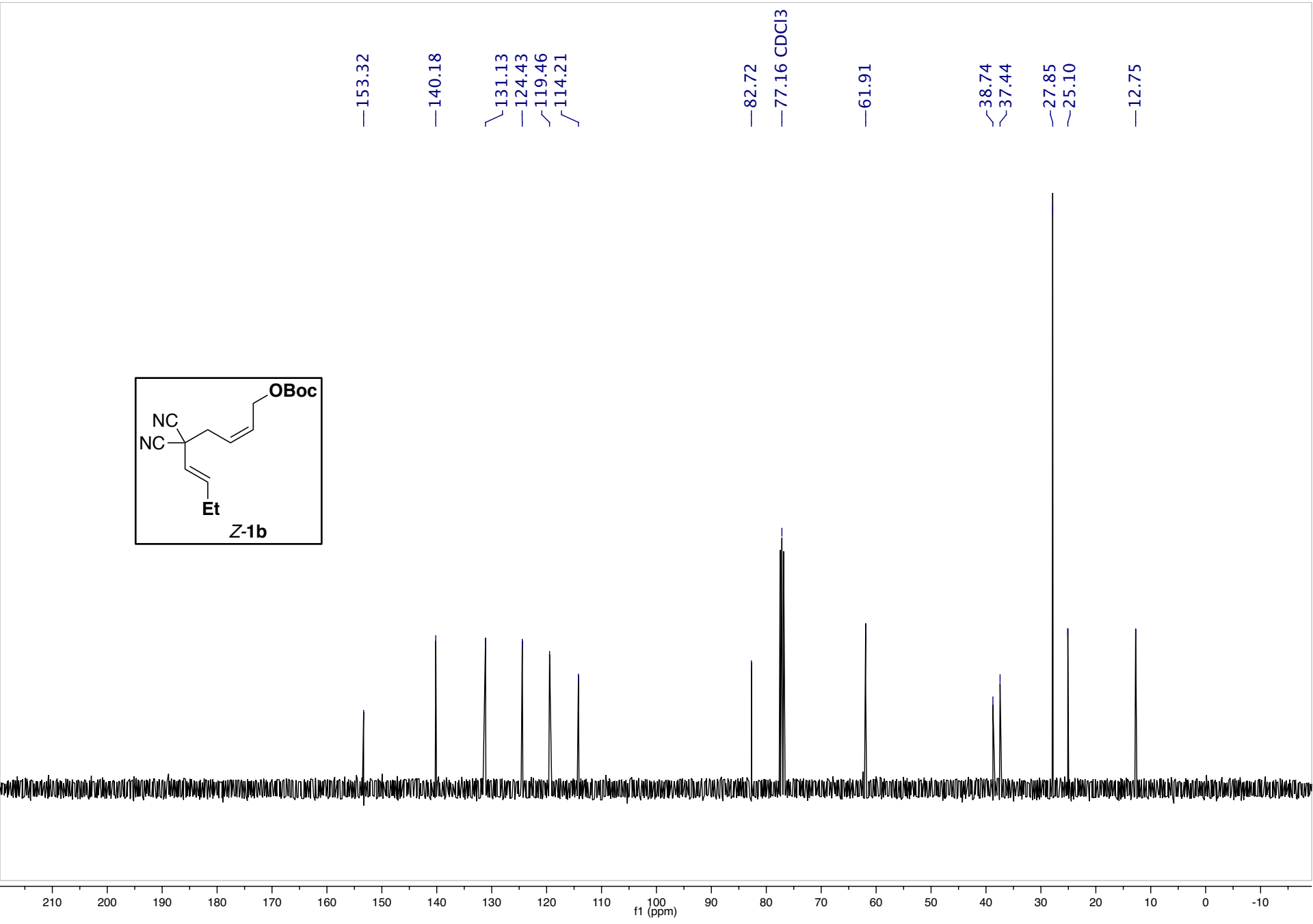

7.26 CDCl3
OAc
NC
NC
Ph
Z-1a-OAc
2.06
1.17
2.04
1.00
1.08
1.12
1.02
2.03
2.10
2.05
3.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

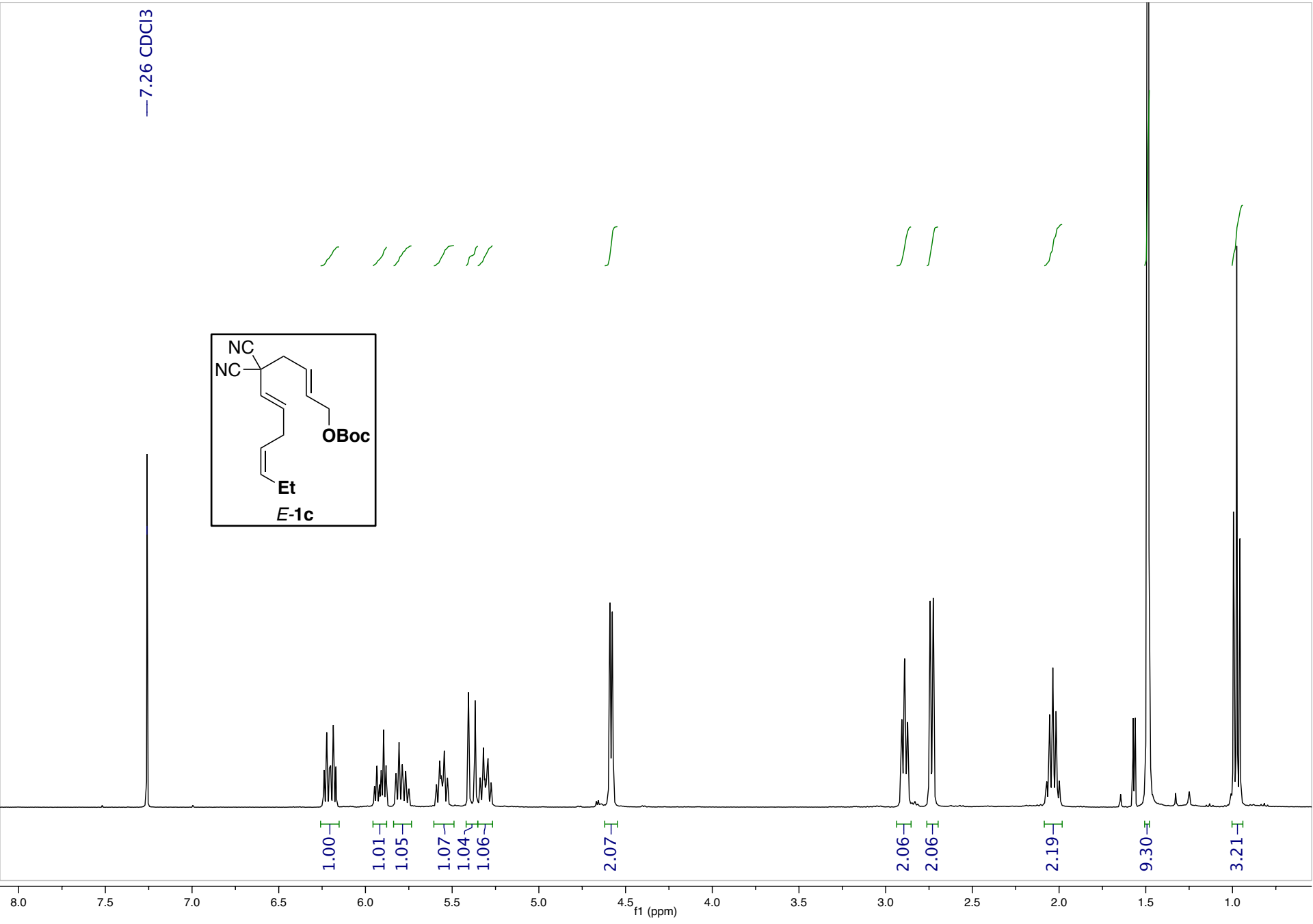

170.80
137.53
137.52
131.44
128.98
128.79
127.04
124.20
121.53
114.01
77.16 CDCl3
59.58
38.78
38.11
37.41
21.00
OAc
NC
NC
Ph
Z-1a-OAc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

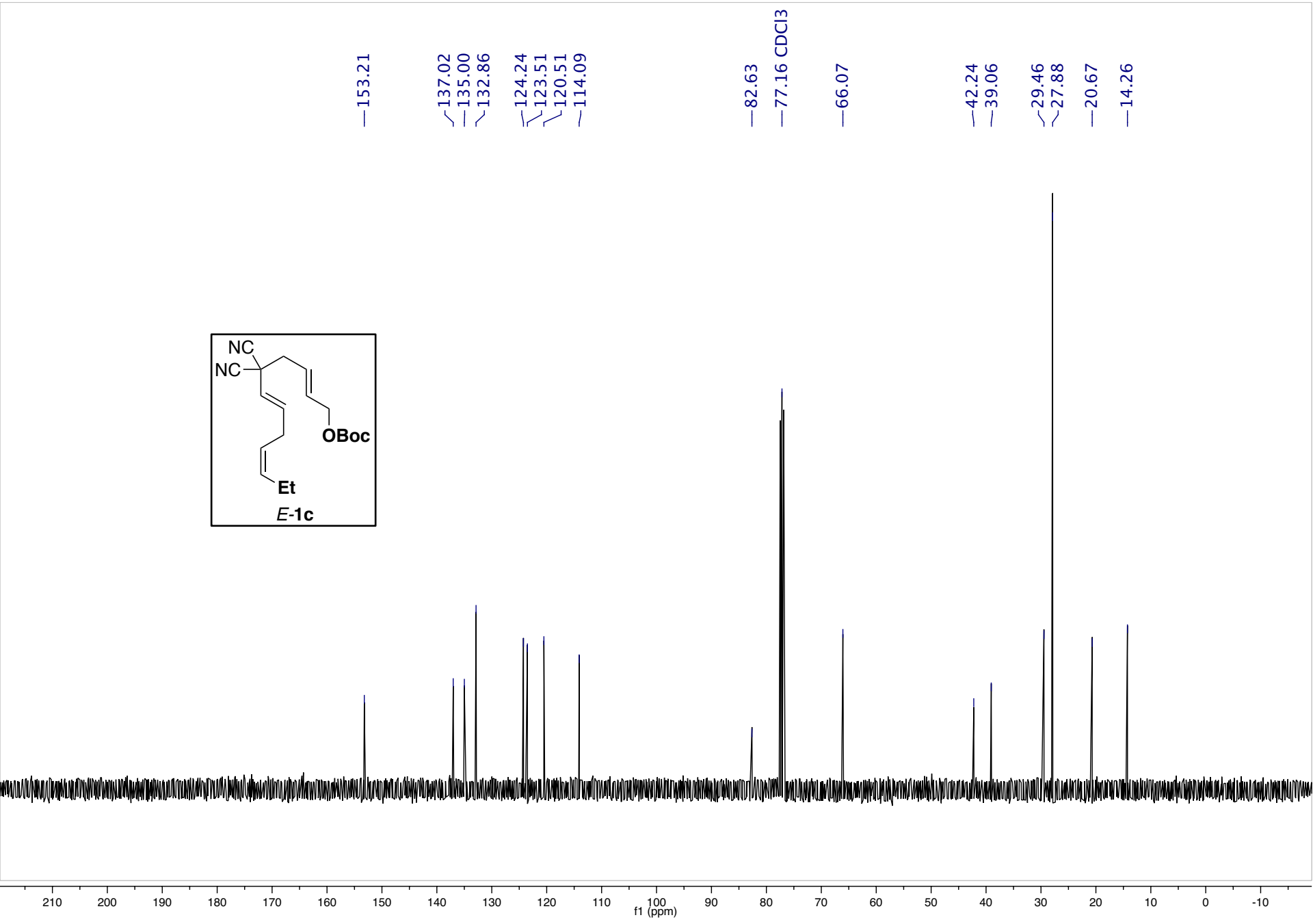

7.26 CDCl3
NC
NC
Et
OBoc
E-1b
1.00
1.07
1.01
1.00
2.03
2.00
2.15
9.30
3.15
f1 (ppm)

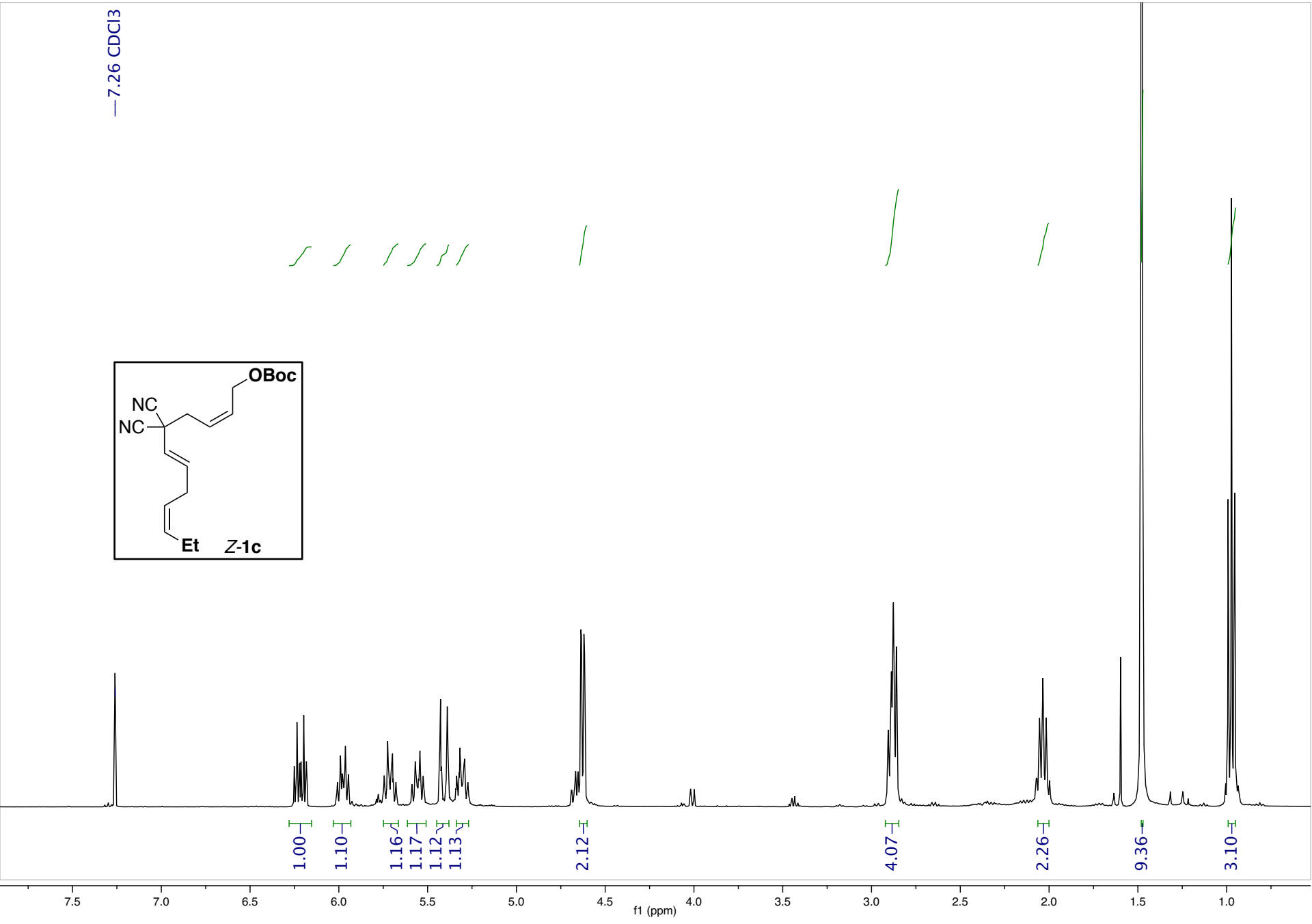

153.23
140.15
132.82
124.33
119.52
114.19
82.64
77.16 CDCl3
66.09
42.28
39.08
27.88
25.14
12.83
NC
NC
Et
OBoc
E-1b
f1 (ppm)

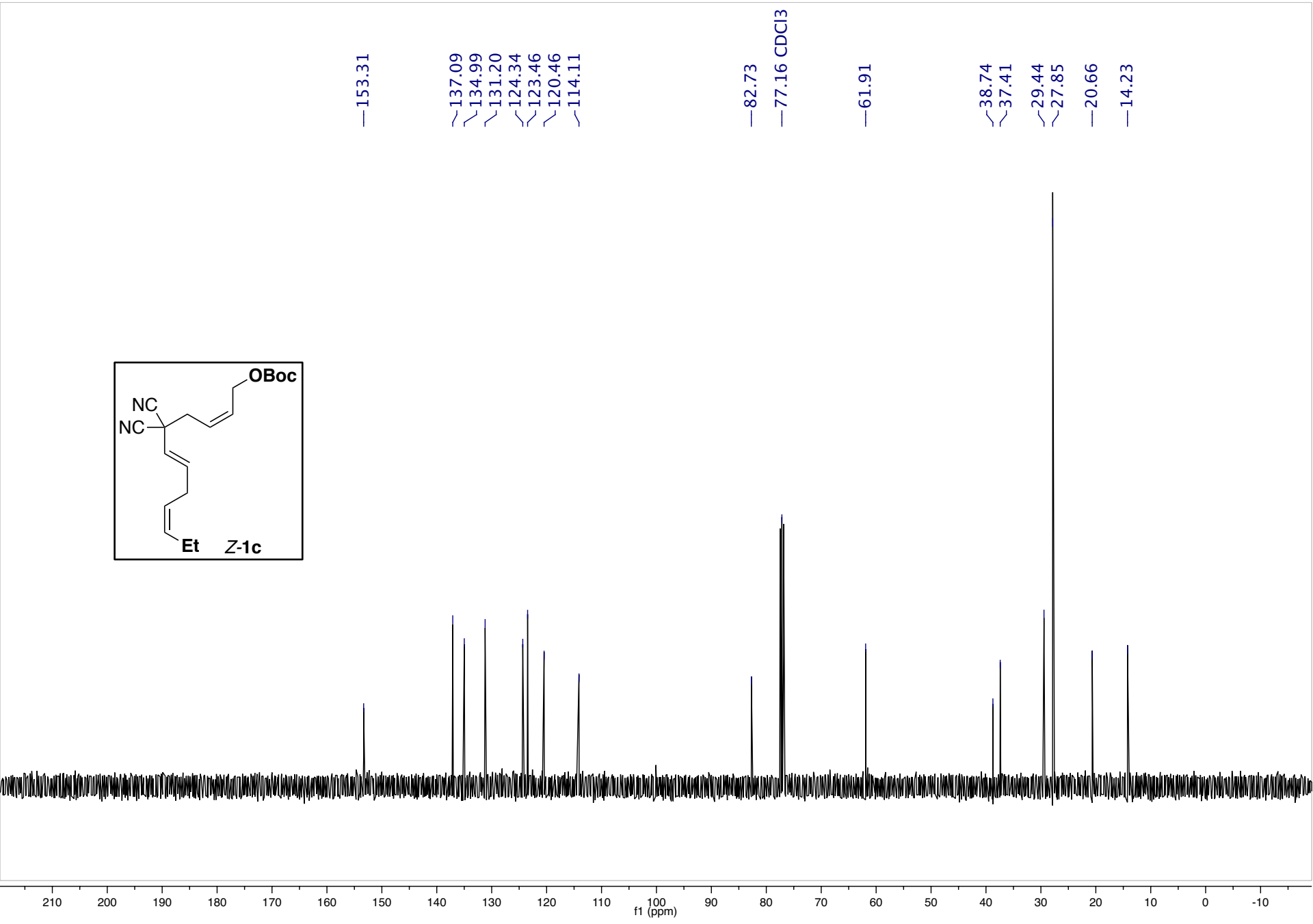

7.26 CDCl3
OBoc
NC
NC
Et
Z-1b
1.00
1.08
1.12
1.03
2.11
2.09
2.07
9.54
3.17
f1 (ppm)

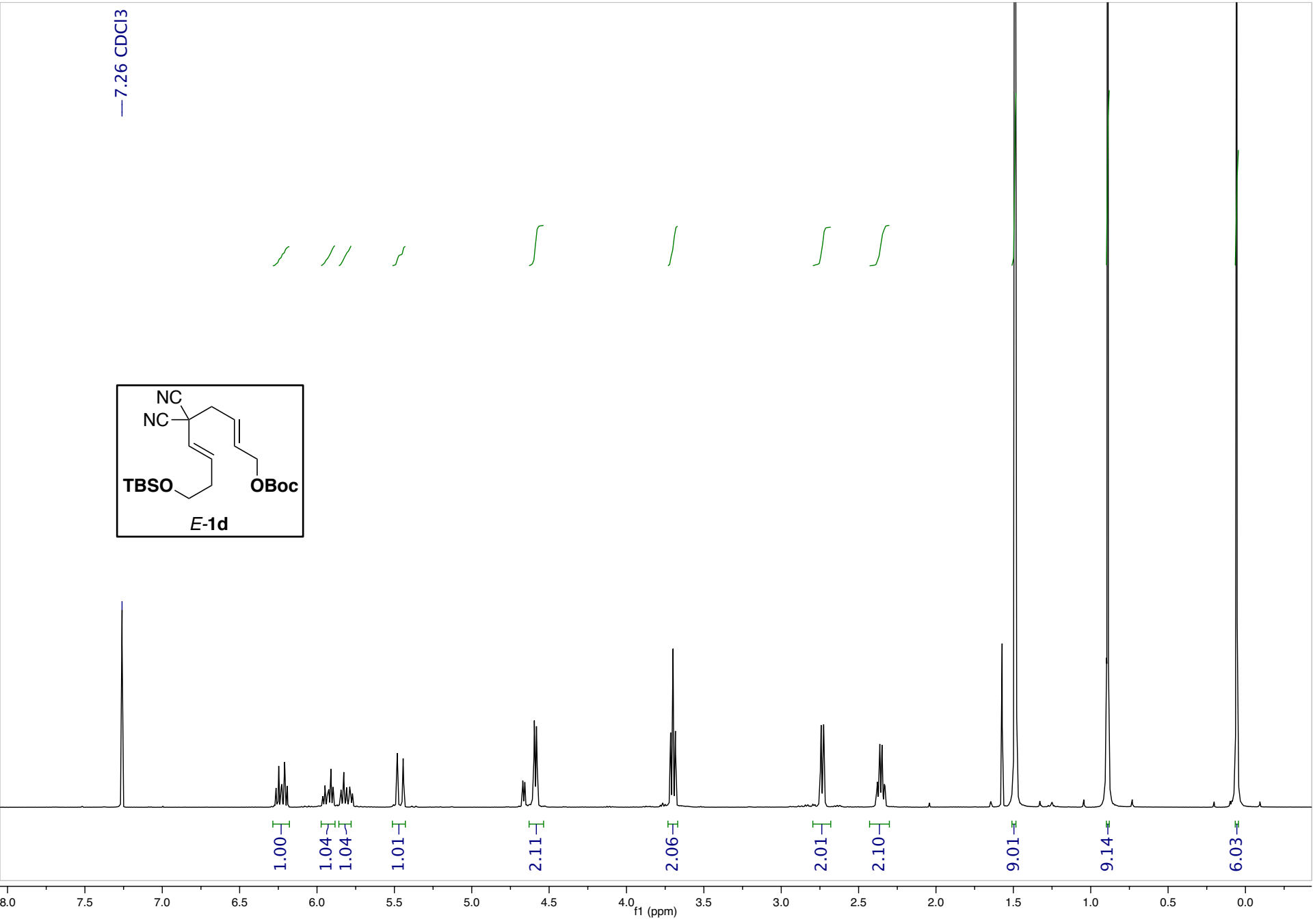

153.32
140.18
131.13
124.43
119.46
114.21
82.72
77.16 CDCl3
61.91
38.74
37.44
27.85
25.10
12.75
OBoc
NC
NC
Et
Z-1b
f1 (ppm)

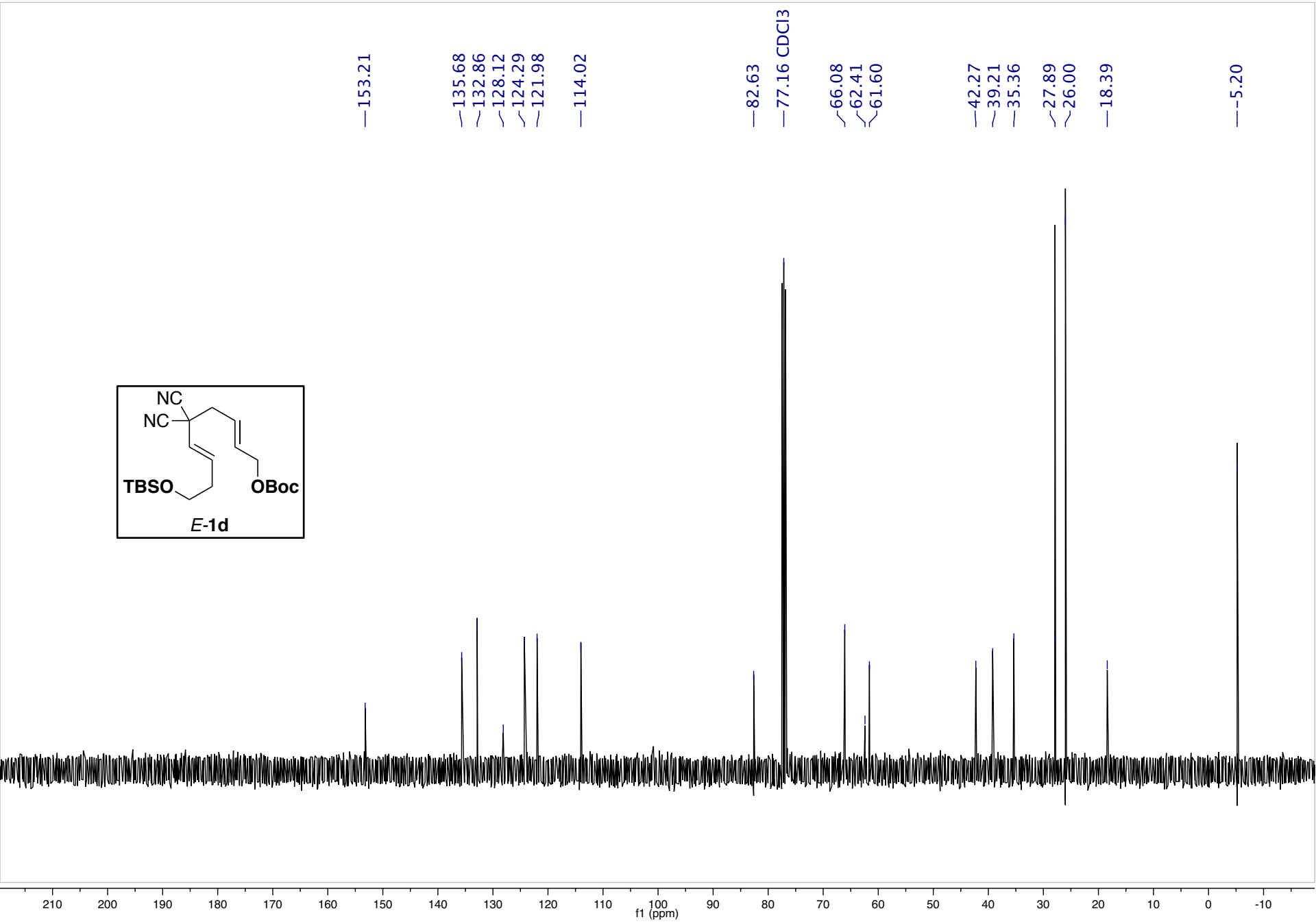

7.26 CDCl3
NC
NC
OBoc
Et
E-1c
1.00
1.01
1.05
1.07
1.04
1.06
2.07
2.06
2.06
2.19
9.30
3.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


153.21
137.02
135.00
132.86
124.24
123.51
120.51
114.09
82.63
77.16 CDCl3
66.07
42.24
39.06
29.46
27.88
20.67
14.26
NC
NC
OBoc
Et
E-1c
f1 (ppm)

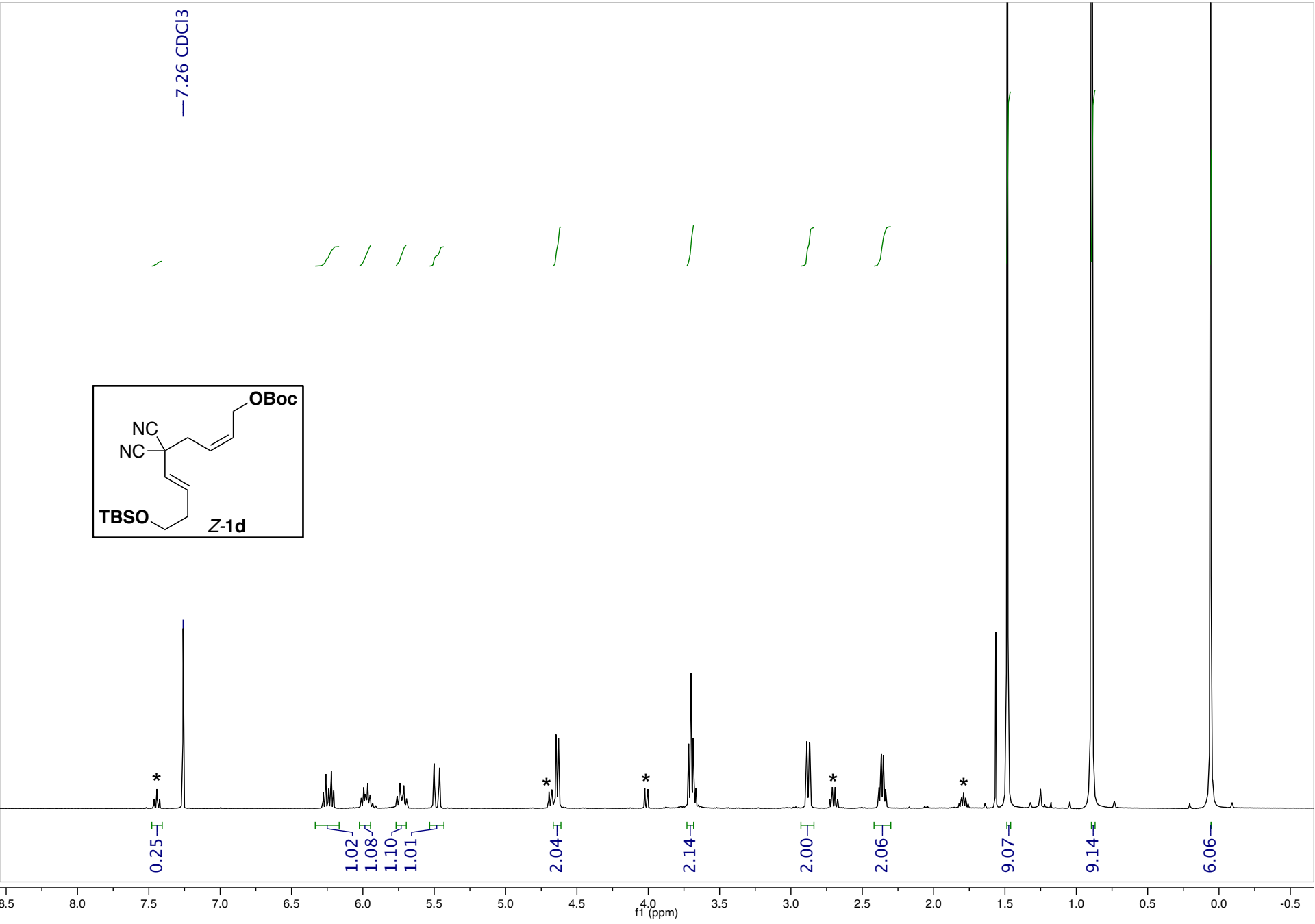

7.26 CDCl3
OBoc
NC
NC
Et
Z-1c
1.00
1.10
1.16
1.17
1.12
1.13
2.12
4.07
2.26
9.36
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

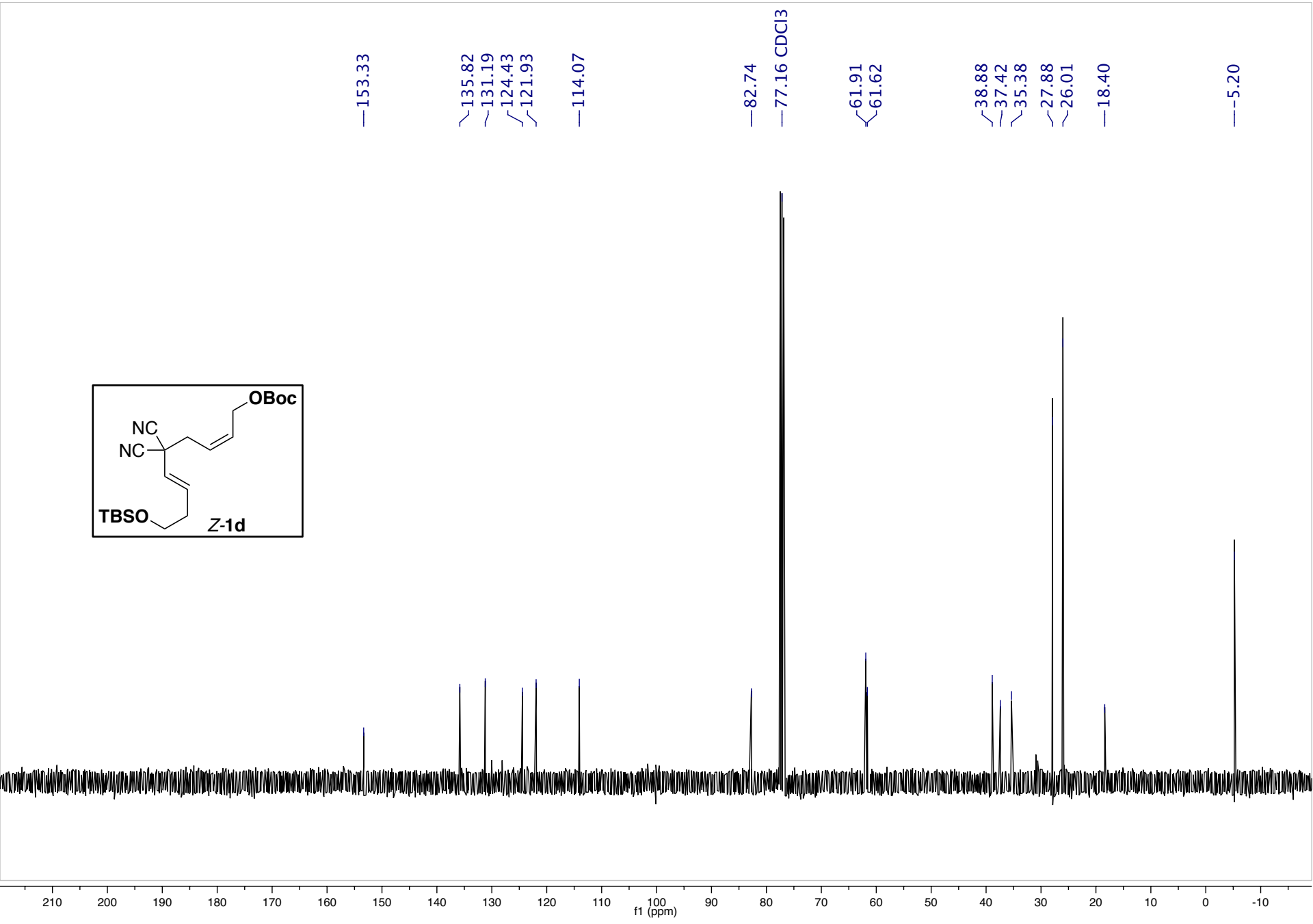

153.31
137.09
134.99
131.20
124.34
123.46
120.46
114.11
82.73
77.16 CDCl3
61.91
38.74
37.41
29.44
27.85
20.66
14.23
OBoc
NC
NC
Et
Z-1c
f1 (ppm)

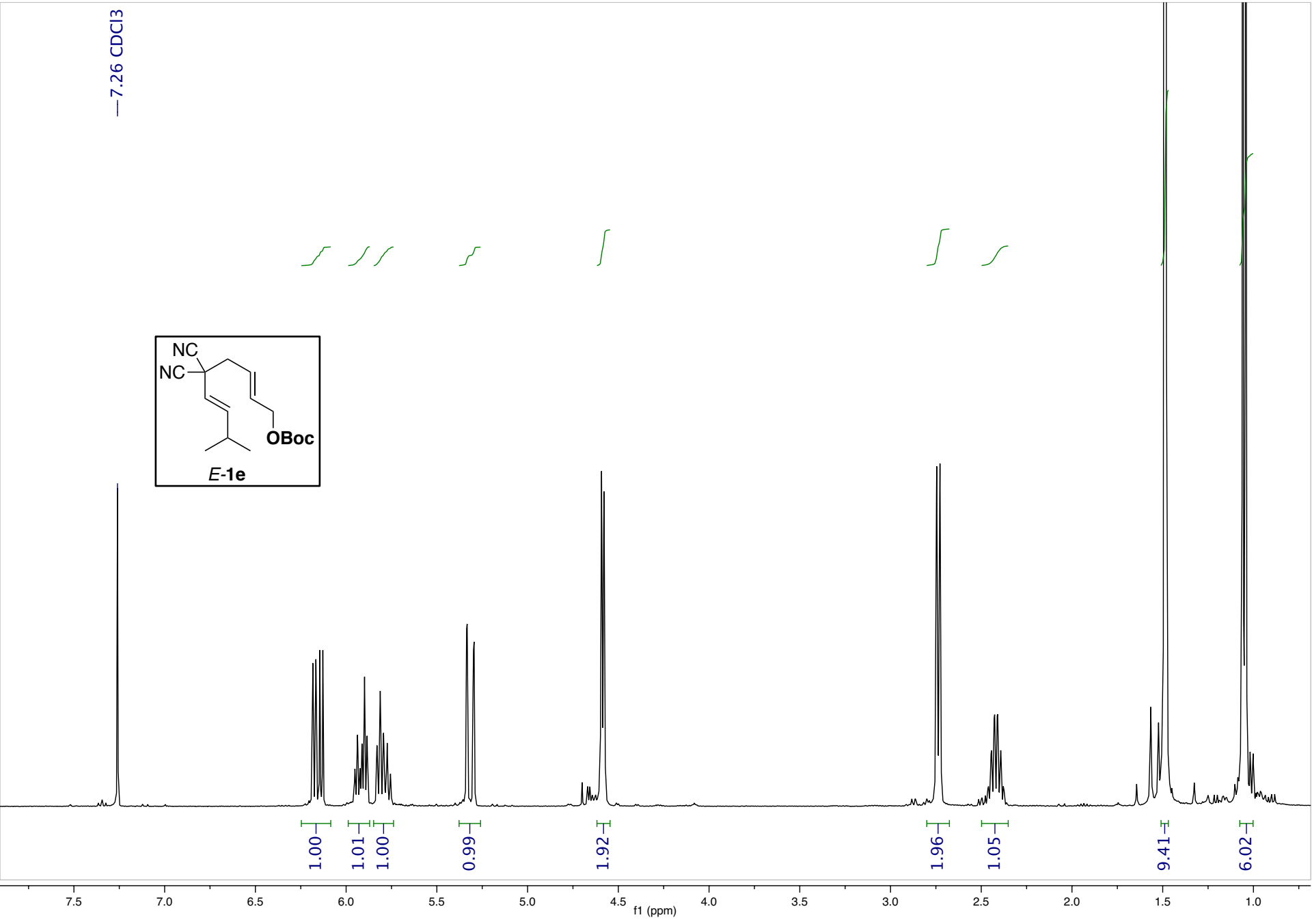

7.26 CDCl3
NC
NC
TBSO
OBoc
E-1d
1.00
1.04
1.04
1.01
2.11
2.06
2.01
2.10
9.01
9.14
6.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

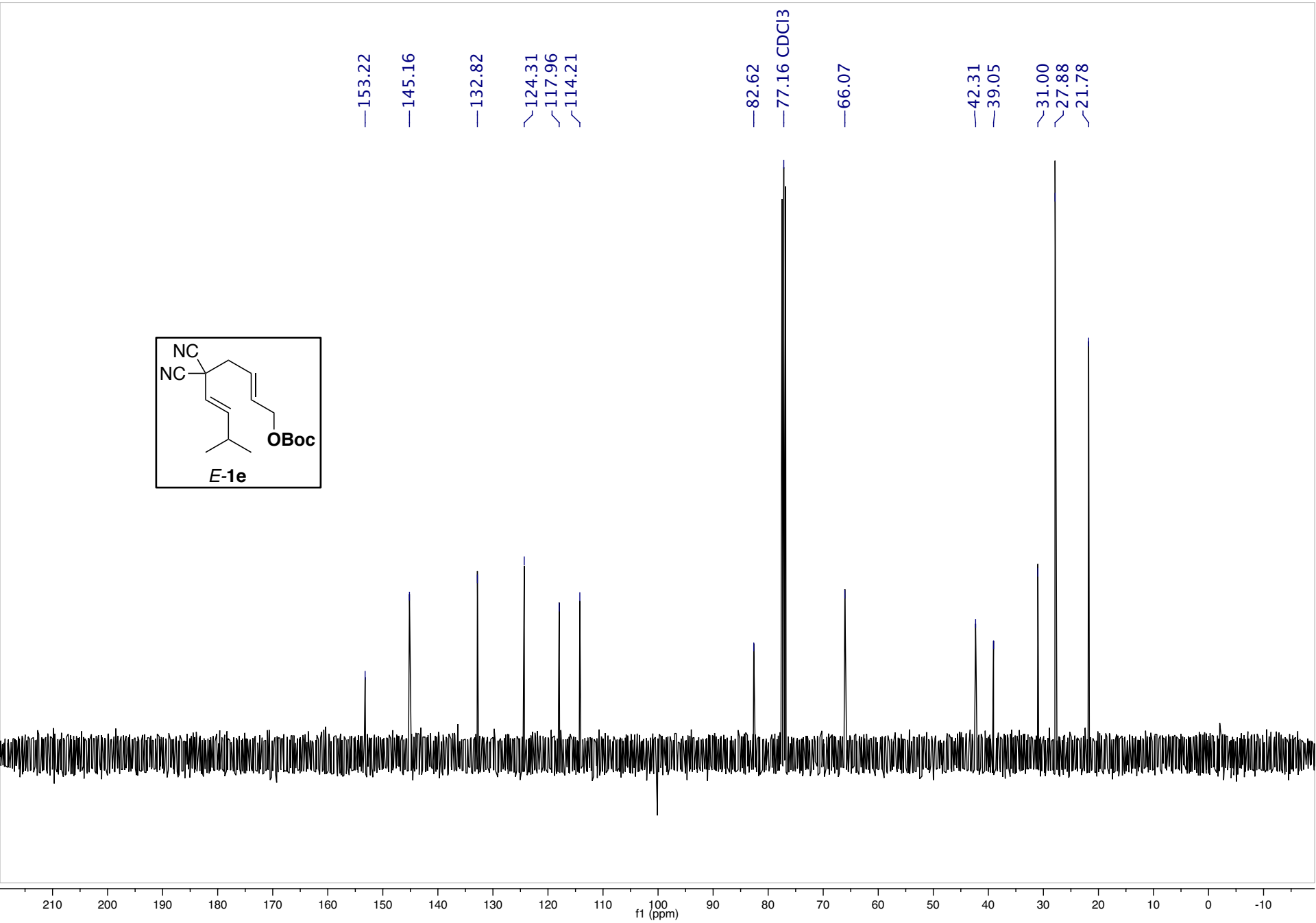

153.21
135.68
132.86
128.12
124.29
121.98
114.02
82.63
77.16 CDCl3
66.08
62.41
61.60
42.27
39.21
35.36
27.89
26.00
18.39
5.20
NC
NC
TBSO
OBoc
E-1d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

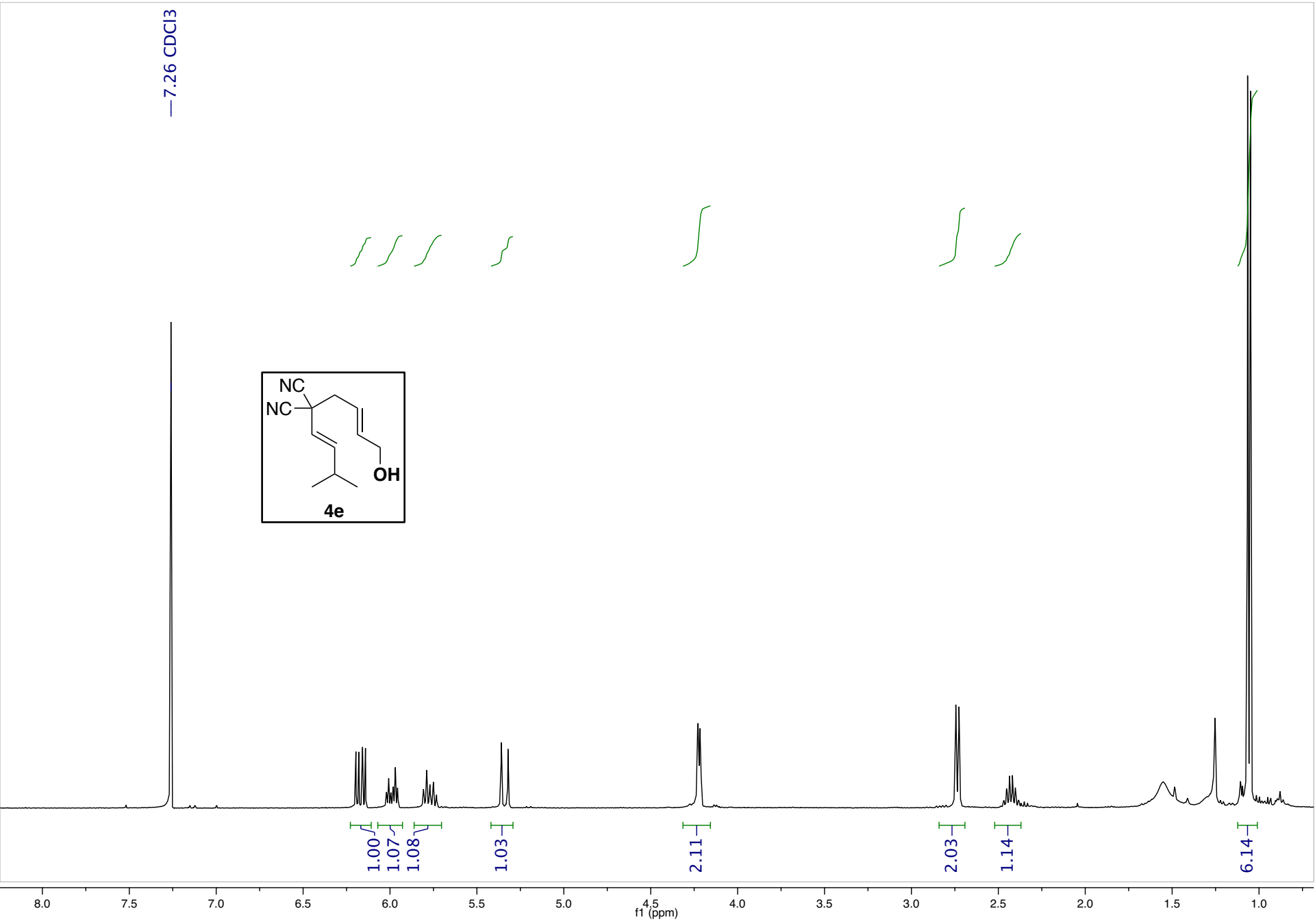
* Trace of Knoevenagel starting material

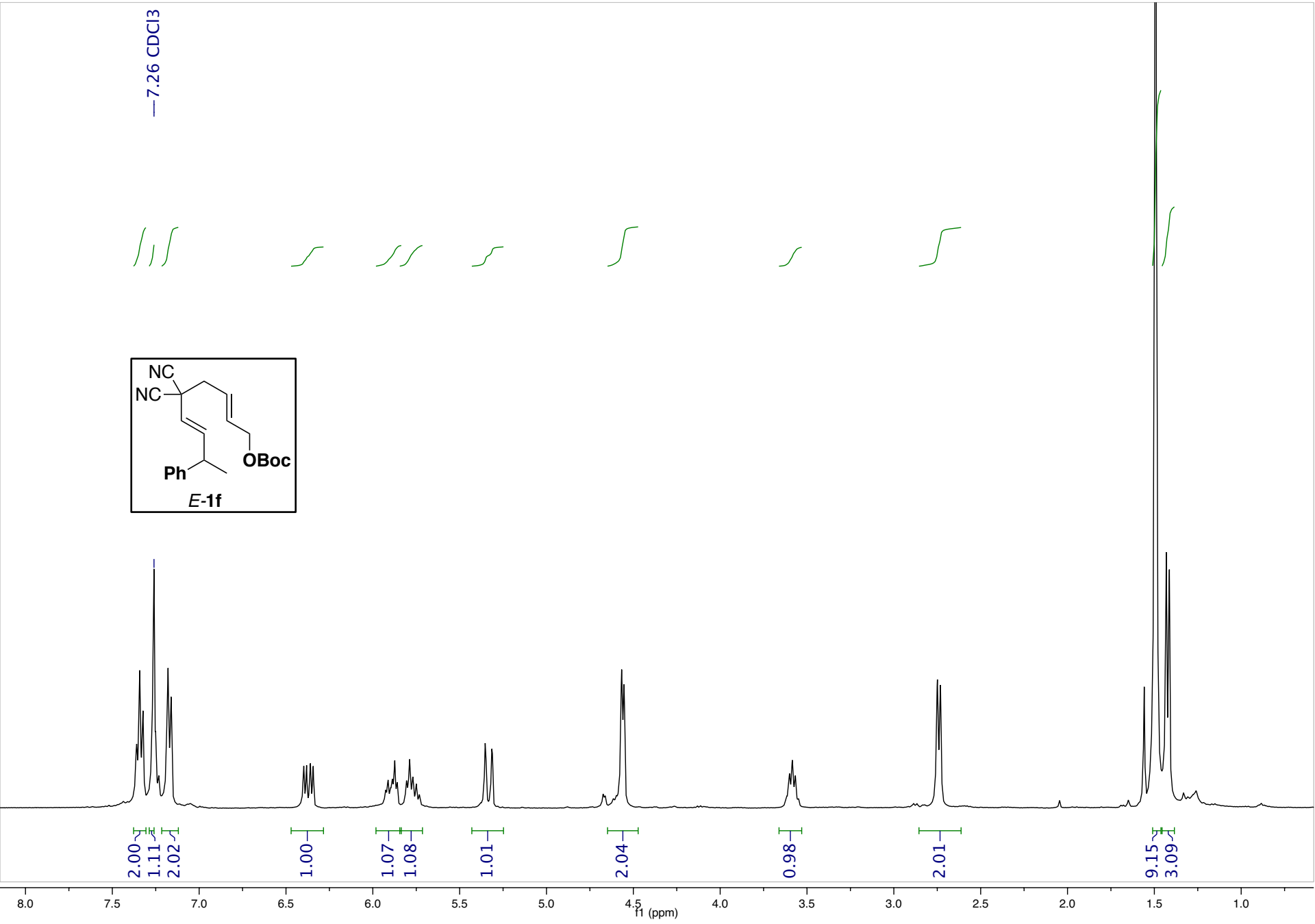


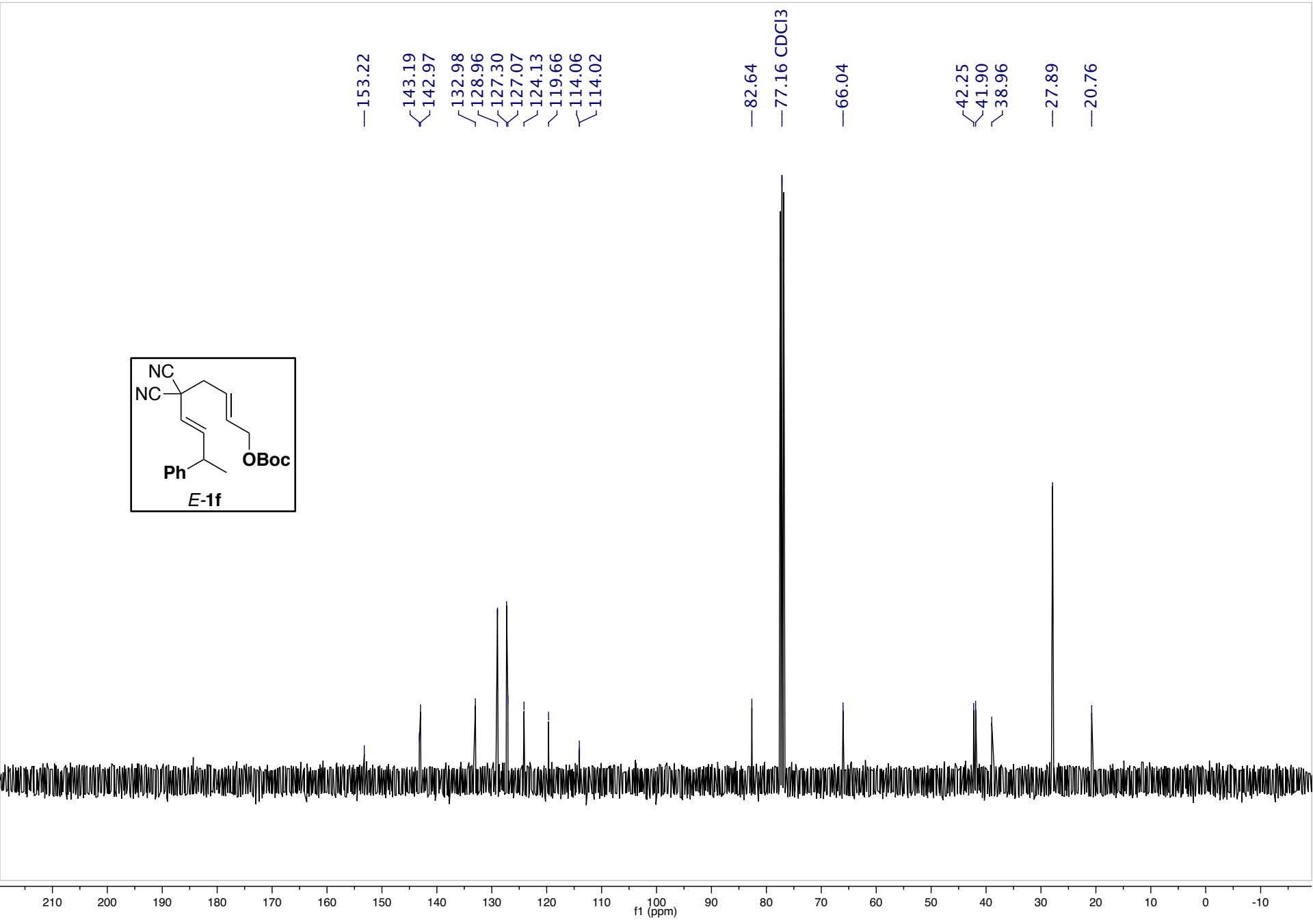

153.33
135.82
131.19
124.43
121.93
114.07
82.74
77.16 CDCl3
61.91
61.62
38.88
37.42
35.38
27.88
26.01
18.40
-5.20
OBoc
NC
NC
TBSO
Z-1d
f1 (ppm)

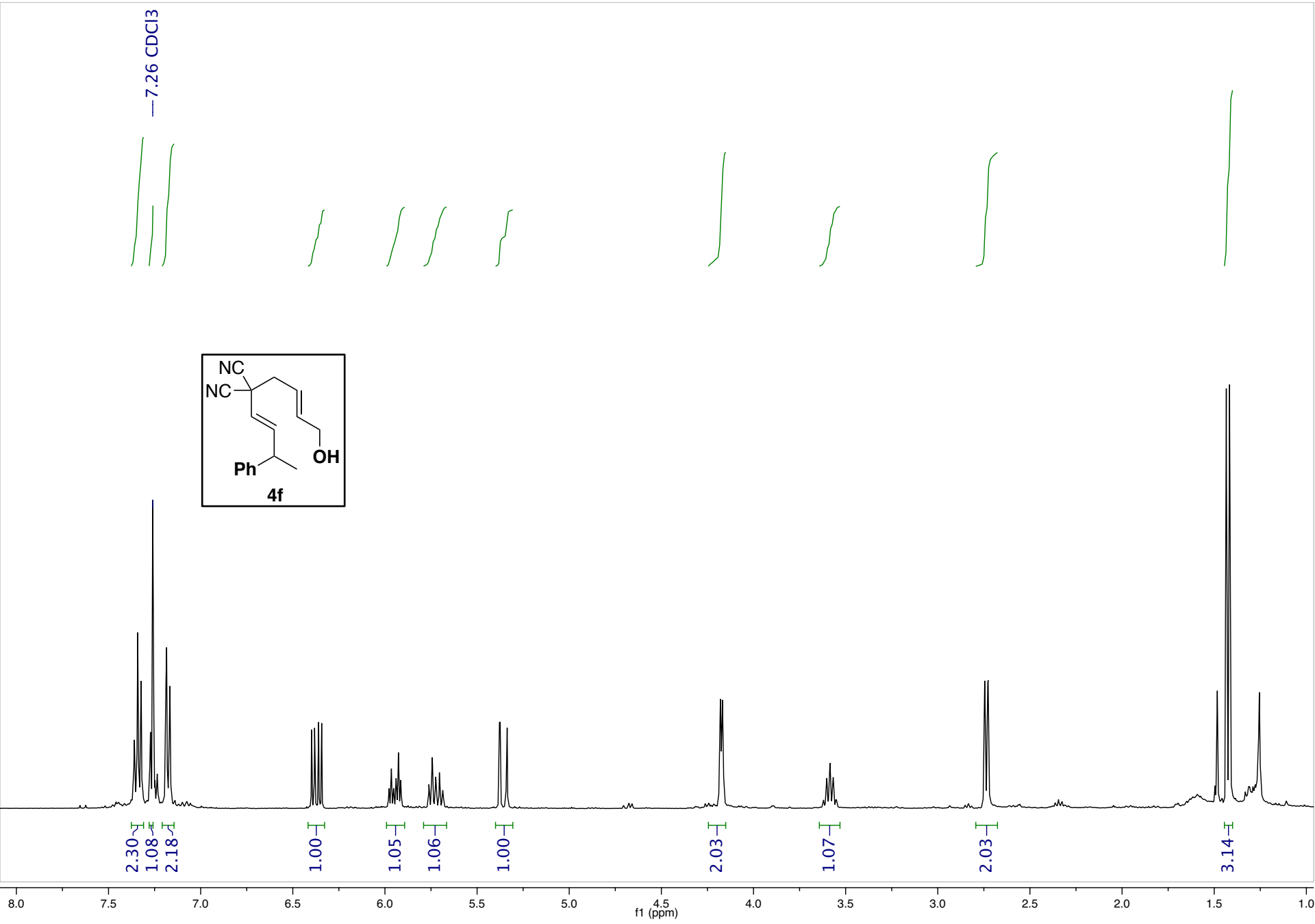

7.26 CDCl3
NC
NC
OBoc
E-1e
1.00
1.01
1.00
0.99
1.92
1.96
1.05
9.41
6.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

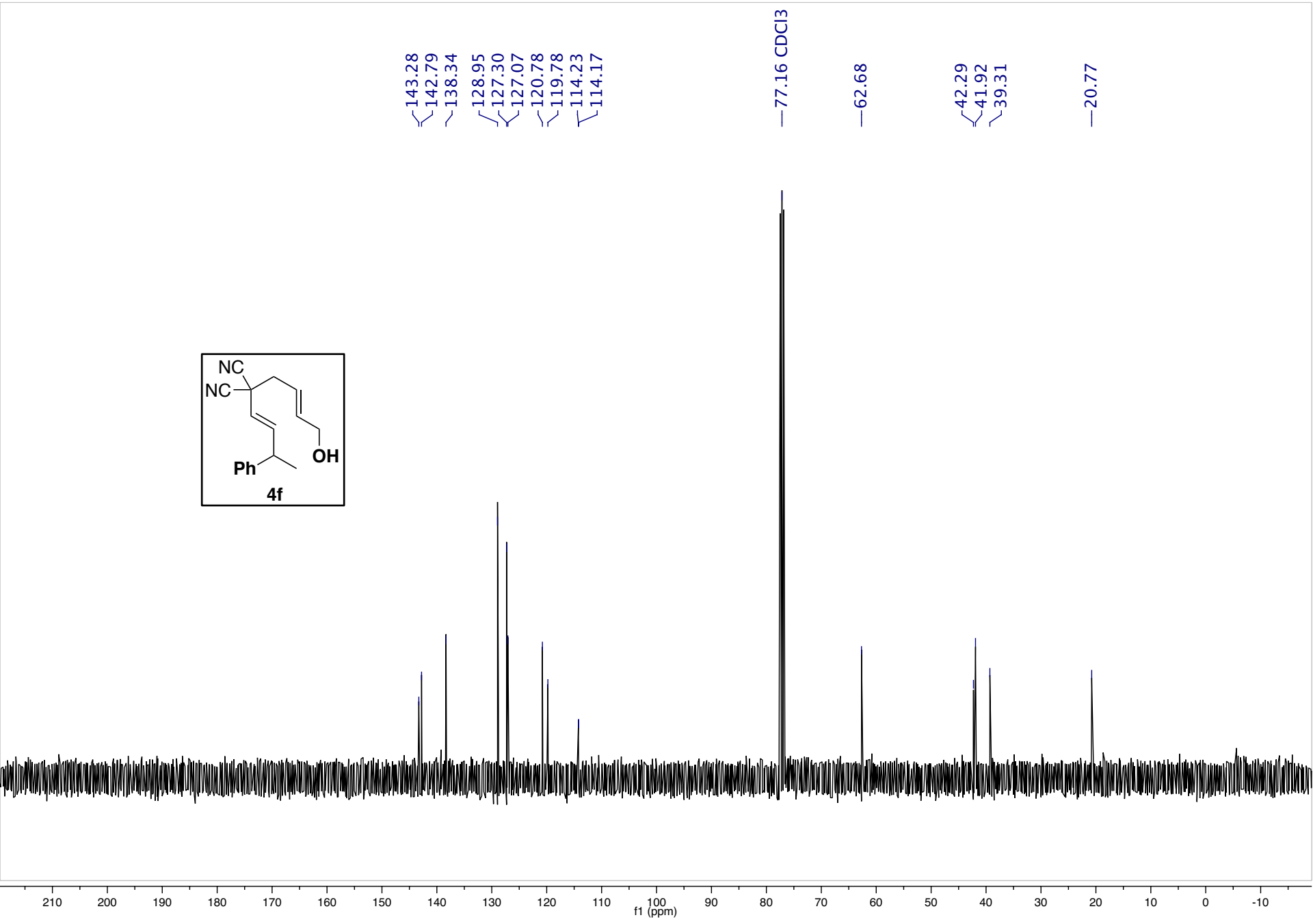

153.22
145.16
132.82
124.31
117.96
114.21
82.62
77.16 CDCl3
66.07
42.31
39.05
31.00
27.88
21.78
NC
NC
OBoc
E-1e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

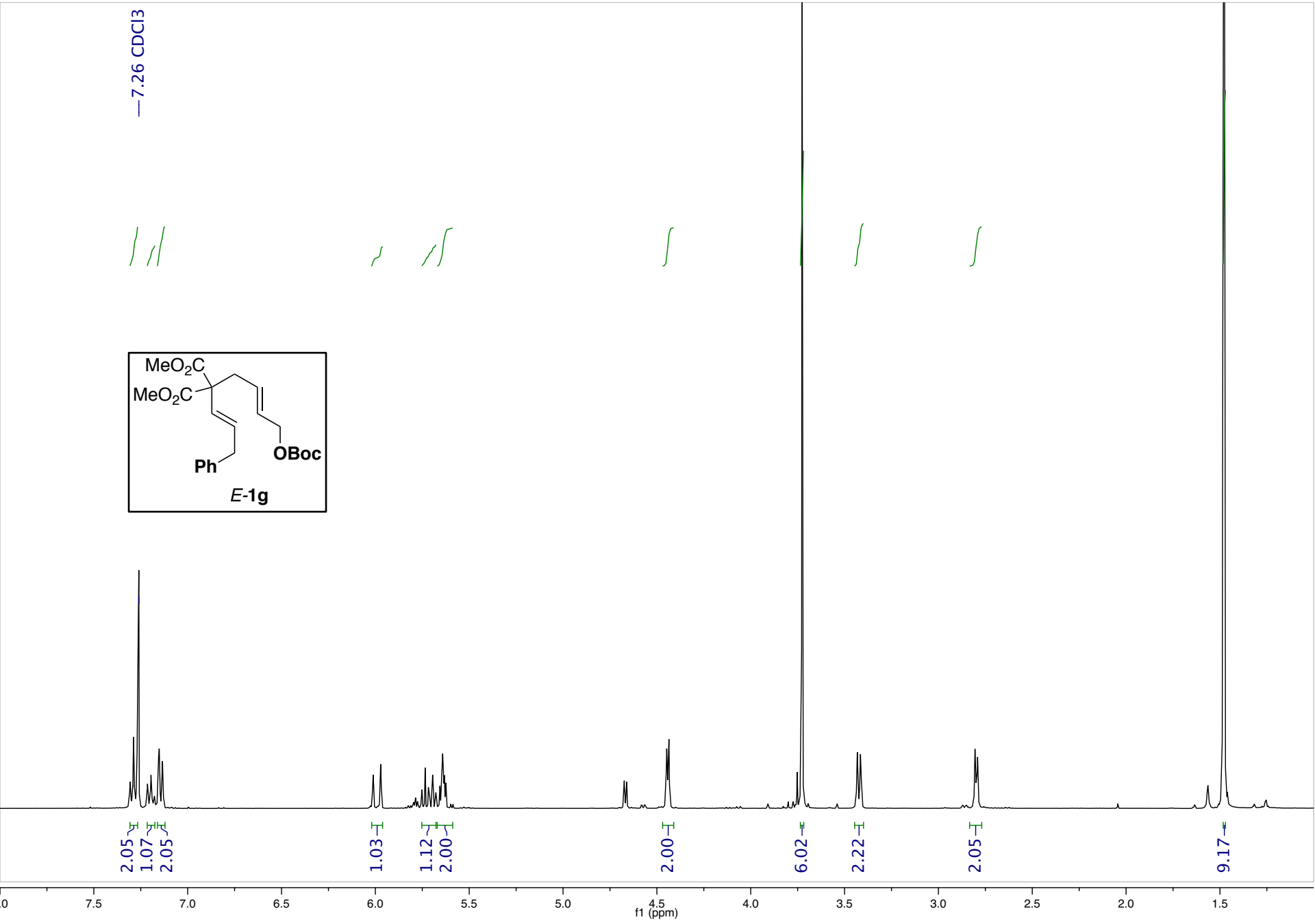

7.26 CDCl3
NC
NC
OH
4e
1.00
1.07
1.08
1.03
2.11
2.03
1.14
6.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

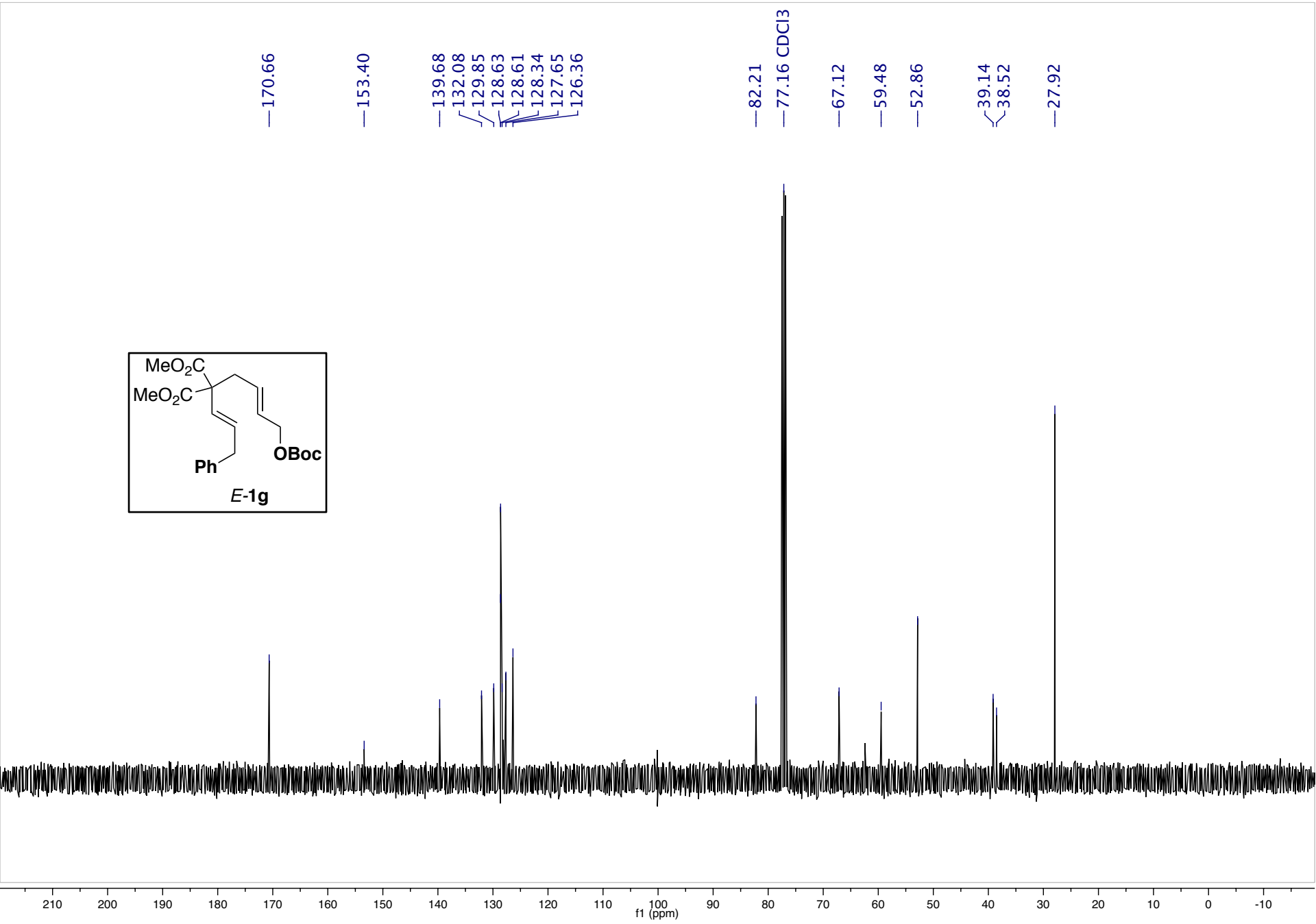

7.26 CDCl3
NC
NC
OBoc
Ph
E-1f
2.00
1.11
2.02
1.00
1.07
1.08
1.01
2.04
0.98
2.01
9.15
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

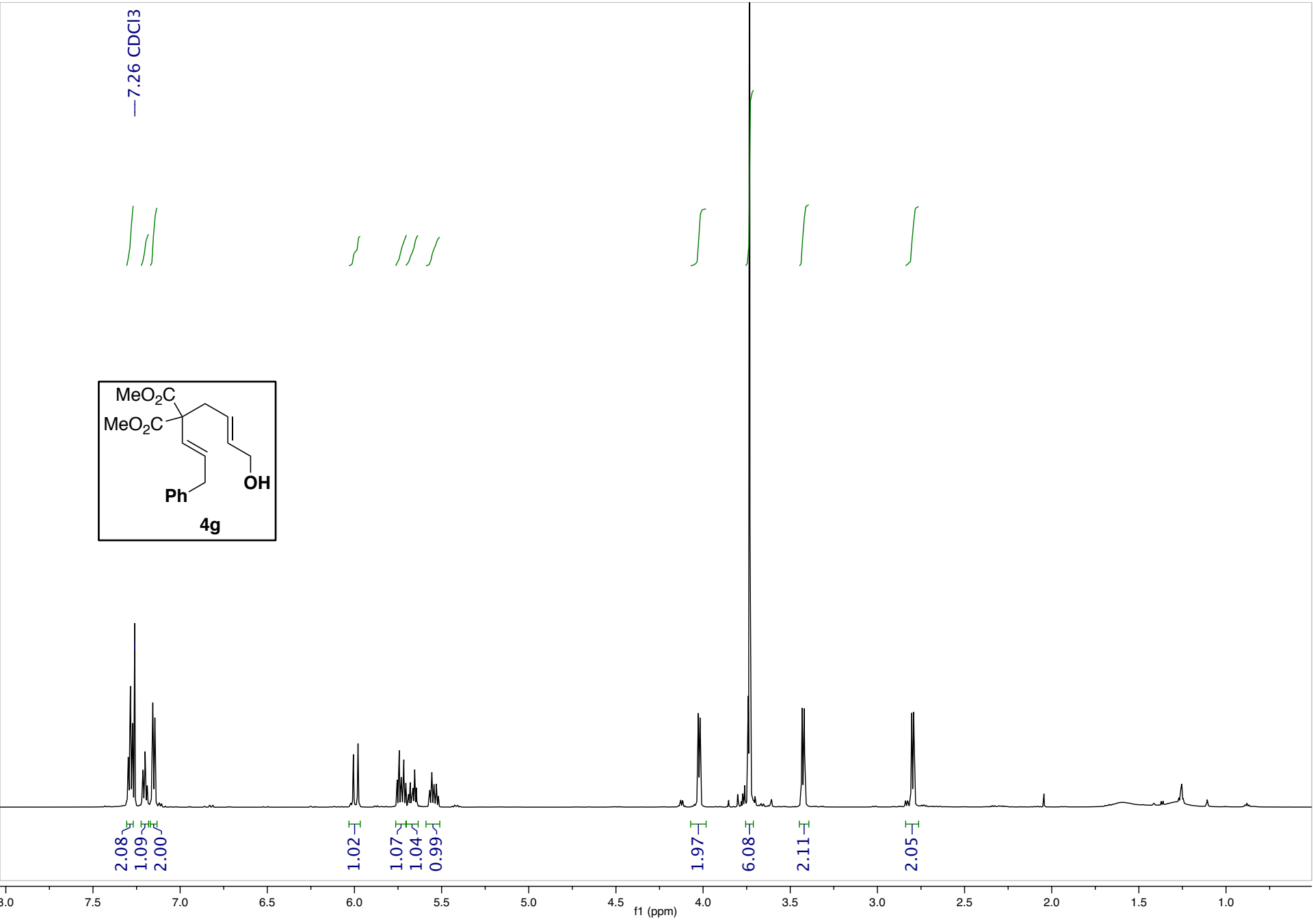

153.22
143.19
142.97
132.98
128.96
127.30
127.07
124.13
119.66
114.06
114.02
82.64
77.16 CDCl3
66.04
42.25
41.90
38.96
27.89
20.76
NC
NC
OBoc
Ph
E-1f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

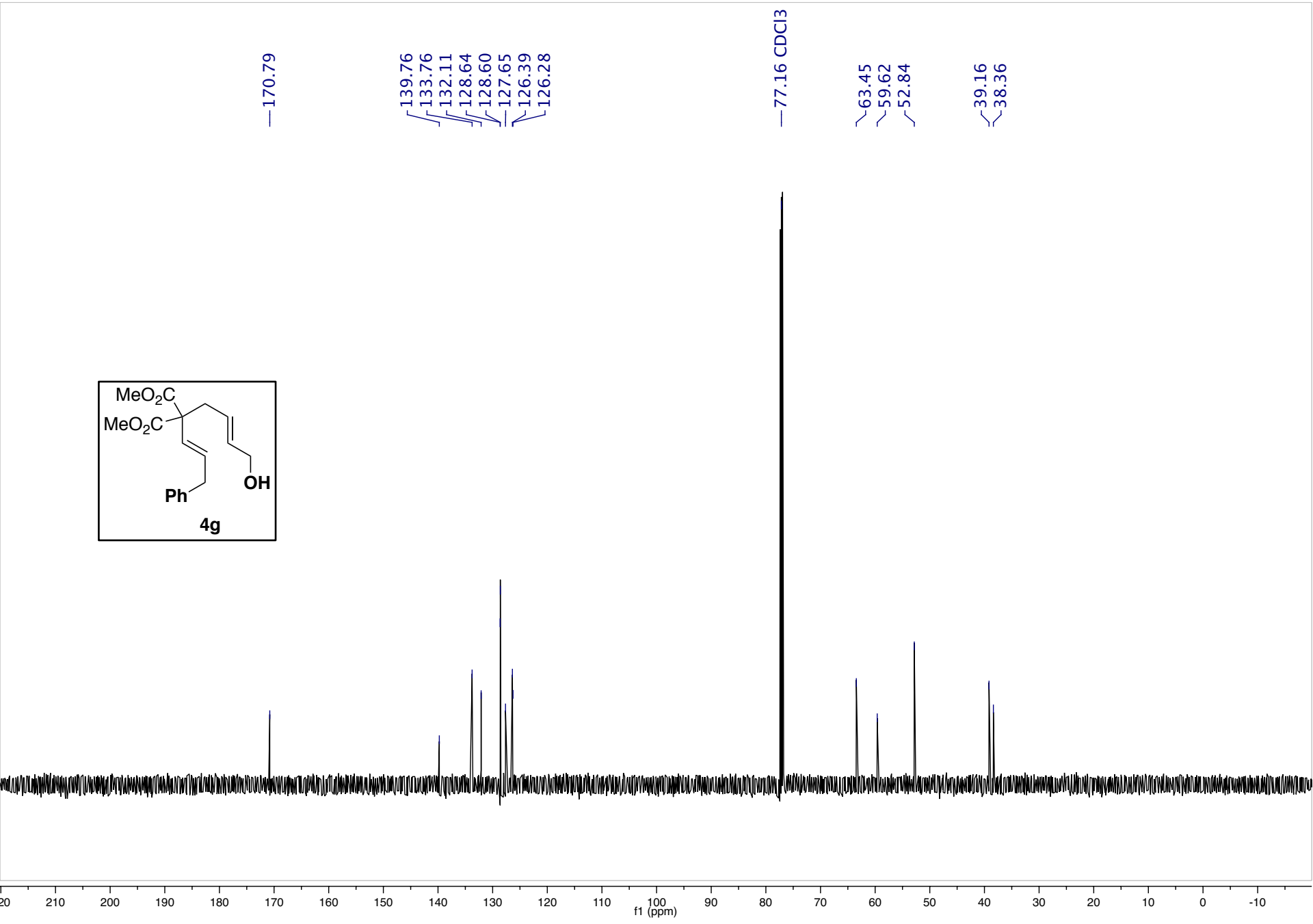

7.26 CDCl3
NC
NC
OH
Ph
4f
2.30
1.08
2.18
1.00
1.05
1.06
1.00
2.03
1.07
2.03
3.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

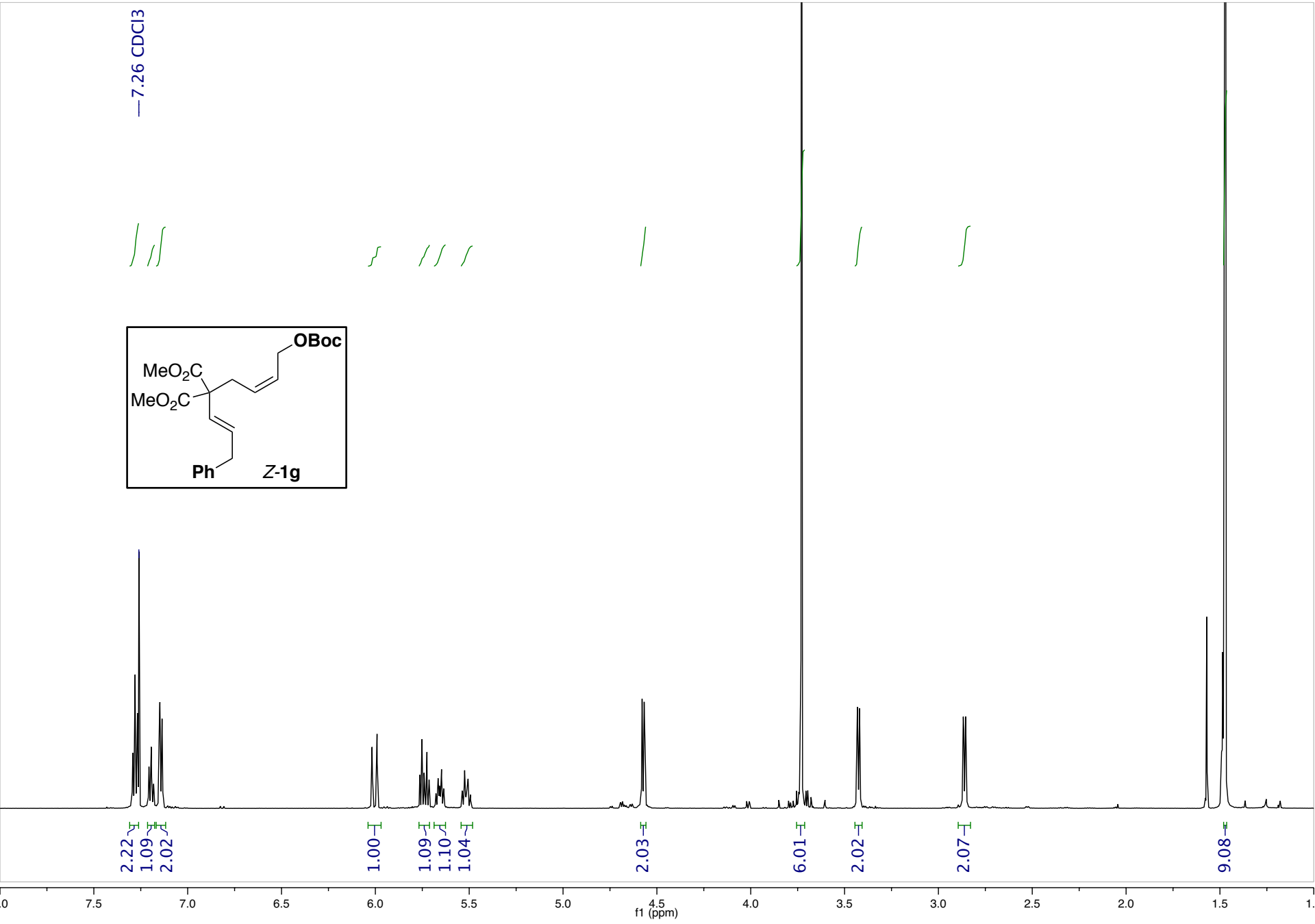

143.28
142.79
138.34
128.95
127.30
127.07
120.78
119.78
114.23
114.17
77.16 CDCl3
62.68
42.29
41.92
39.31
20.77
NC
NC
Ph
OH
4f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

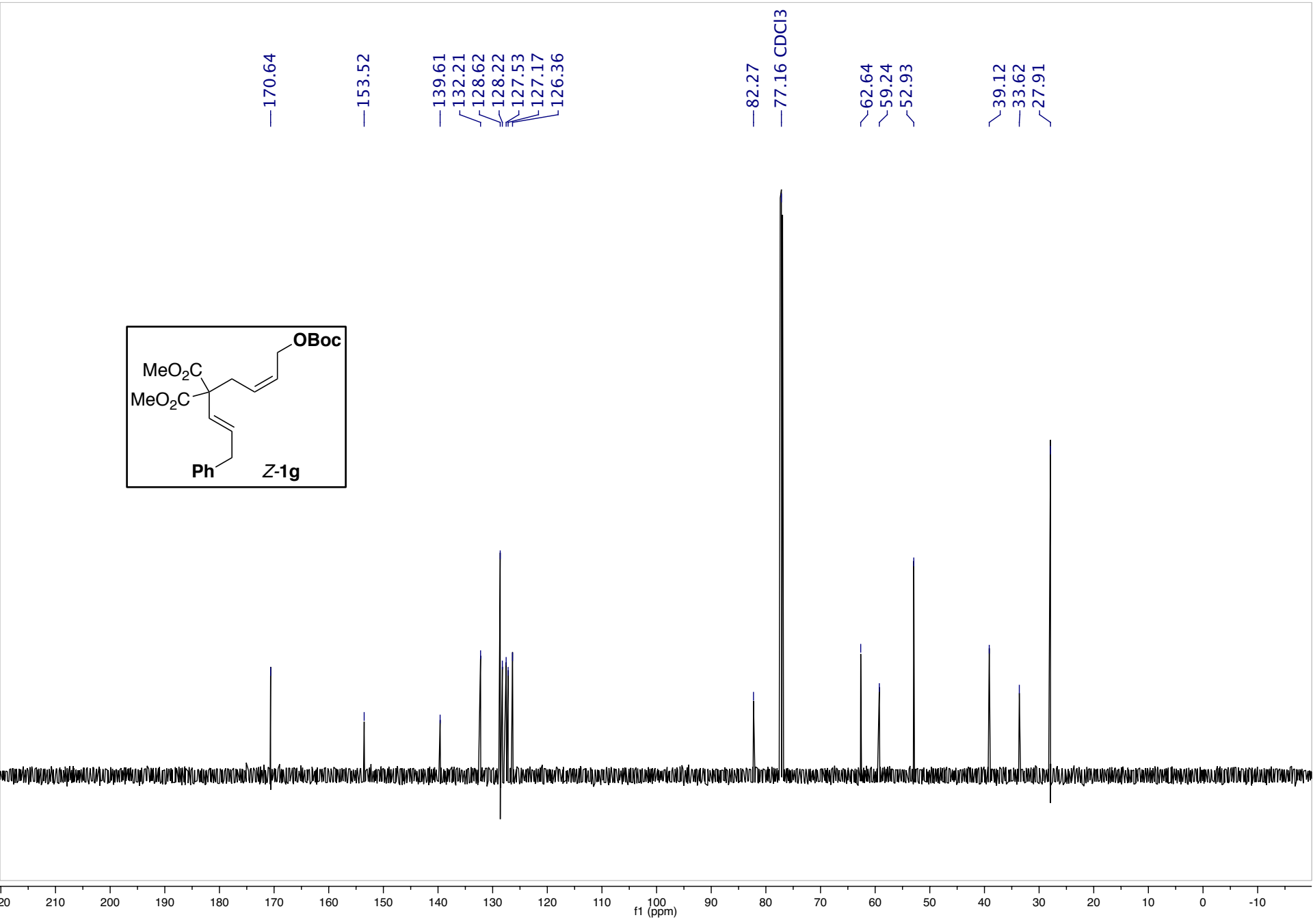

7.26 CDCl3
MeO2C
MeO2C
Ph
OBoc
E-1g
2.05
1.07
2.05
1.03
1.12
2.00
2.00
6.02
2.22
2.05
9.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

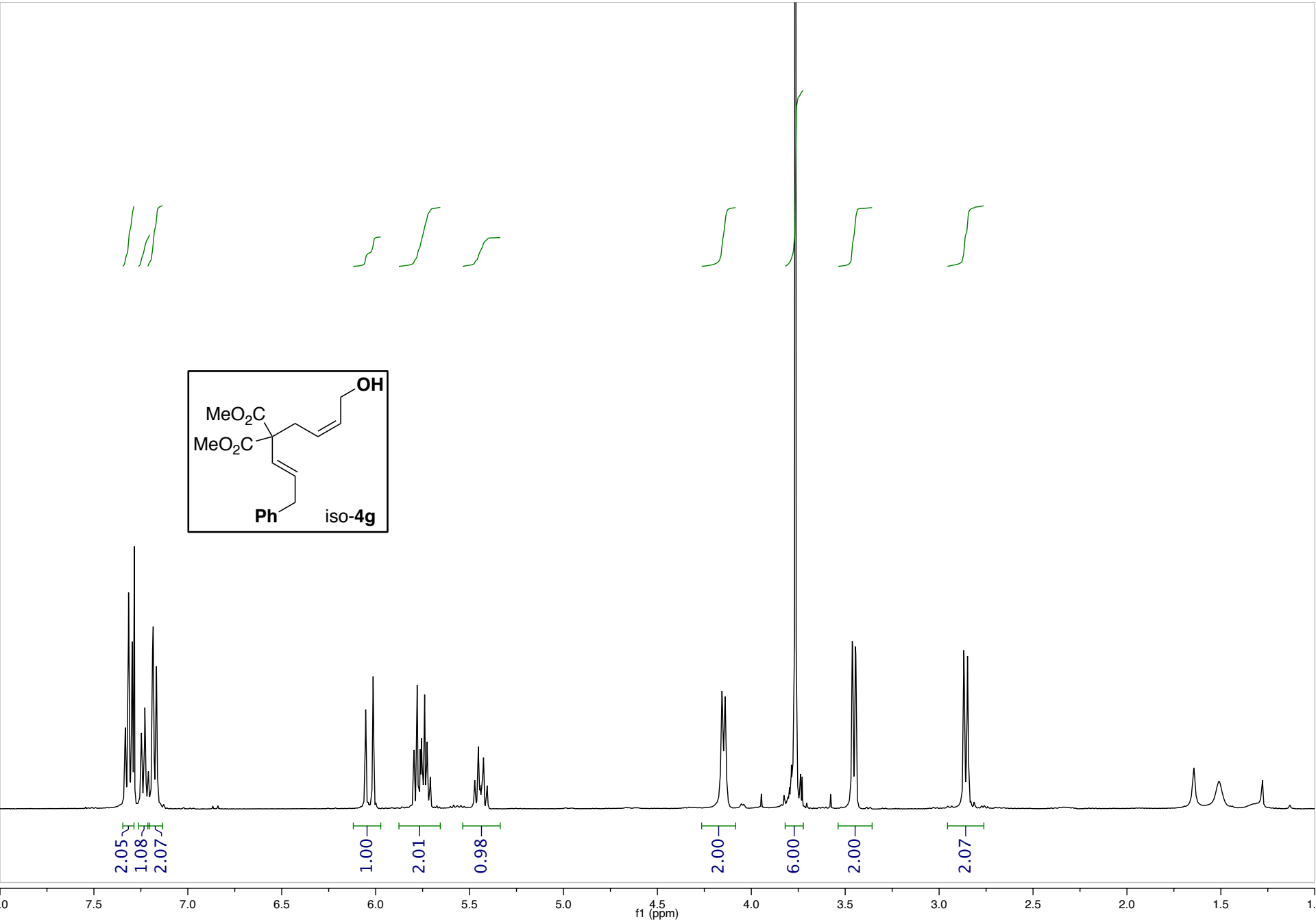

170.66
153.40
139.68
132.08
129.85
128.63
128.61
128.34
127.65
126.36
82.21
77.16 CDCl3
67.12
59.48
52.86
39.14
38.52
27.92
MeO2C
MeO2C
Ph
OBoc
E-1g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

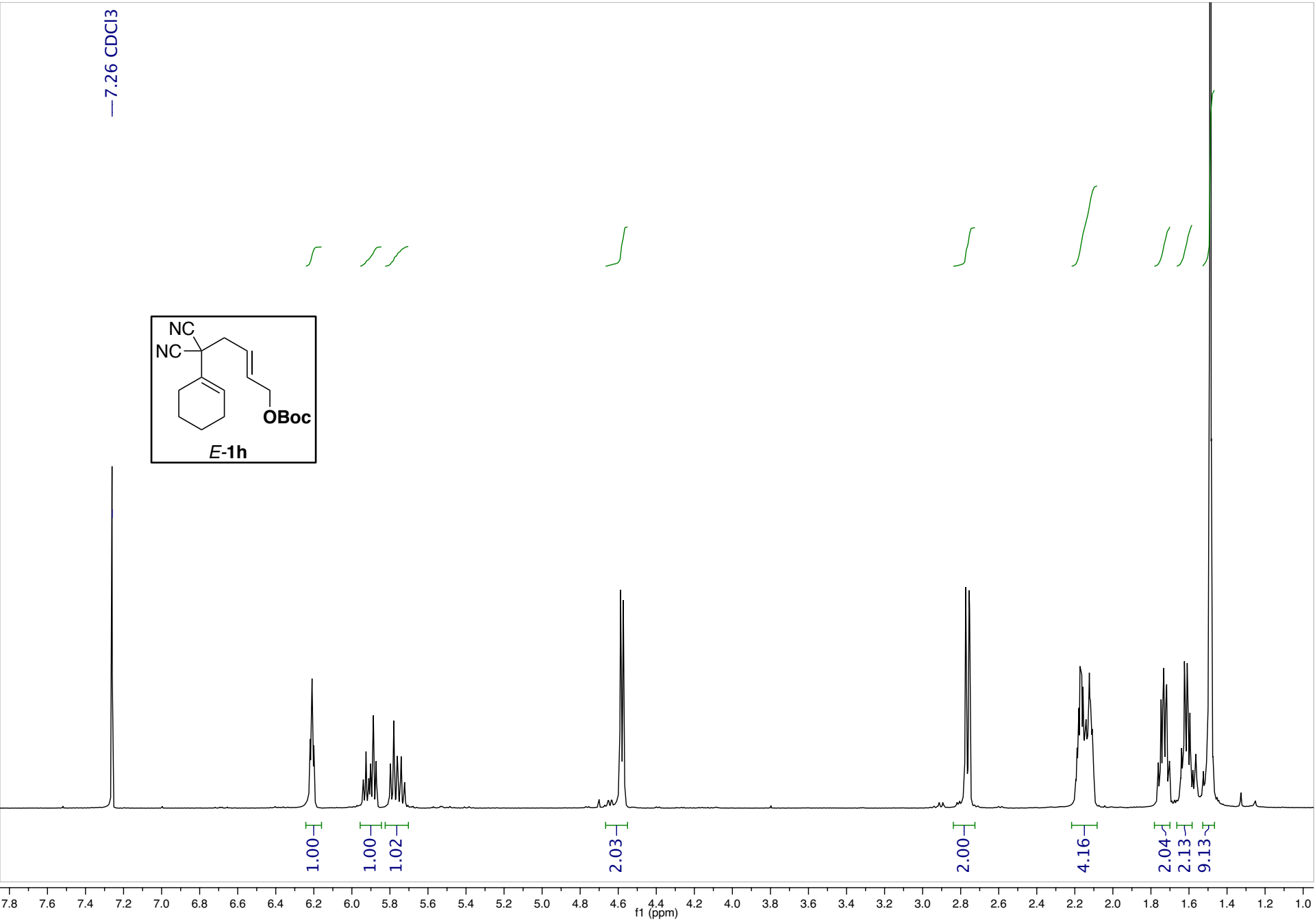

7.26 CDCl3
MeO2C
MeO2C
Ph
OH
4g
2.08
1.09
2.00
1.02
1.07
1.04
0.99
1.97
6.08
2.11
2.05
f1 (ppm)

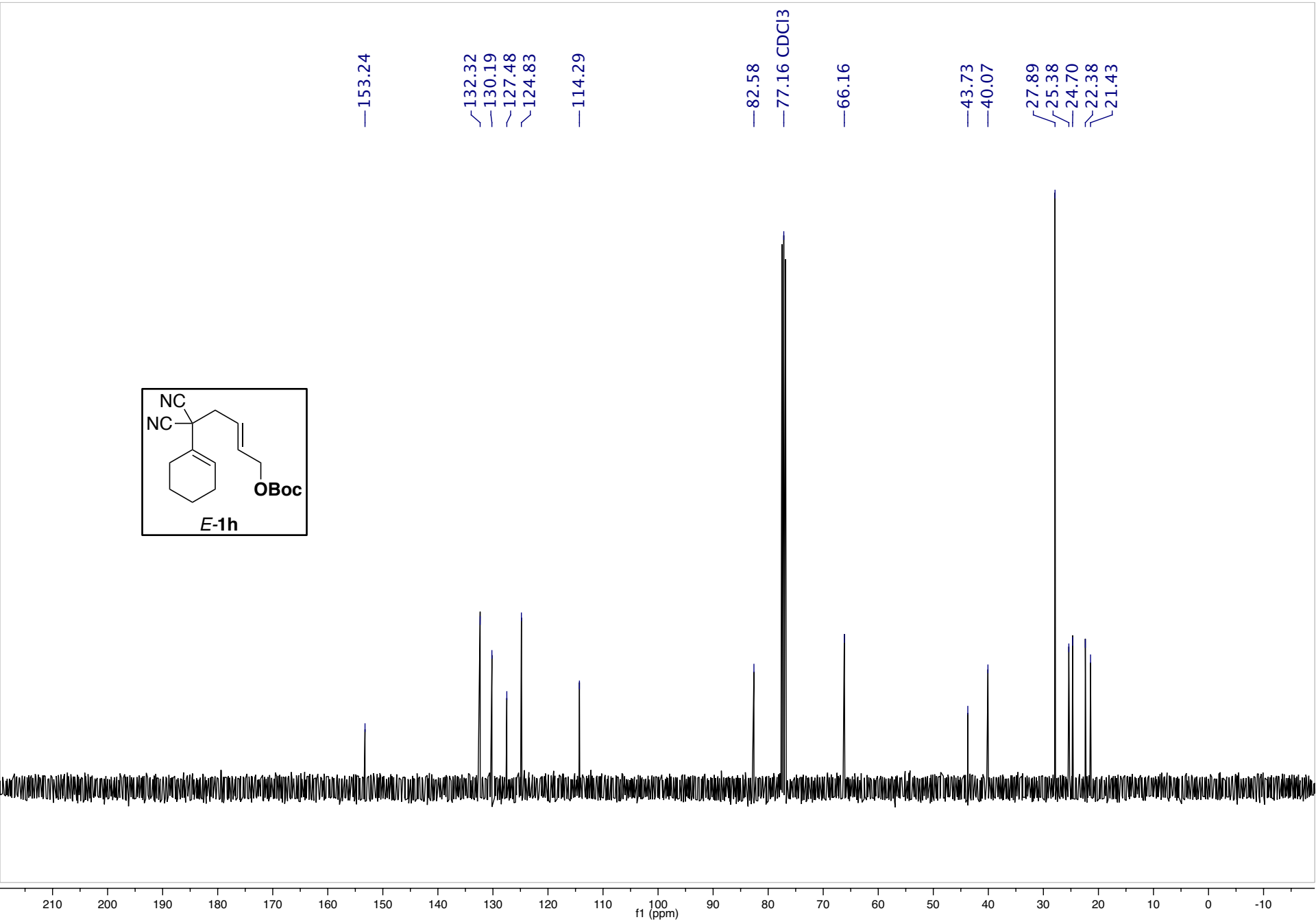

170.79
139.76
133.76
132.11
128.64
128.60
127.65
126.39
126.28
77.16 CDCl3
63.45
59.62
52.84
39.16
38.36
MeO2C
MeO2C
Ph
OH
4g
f1 (ppm)

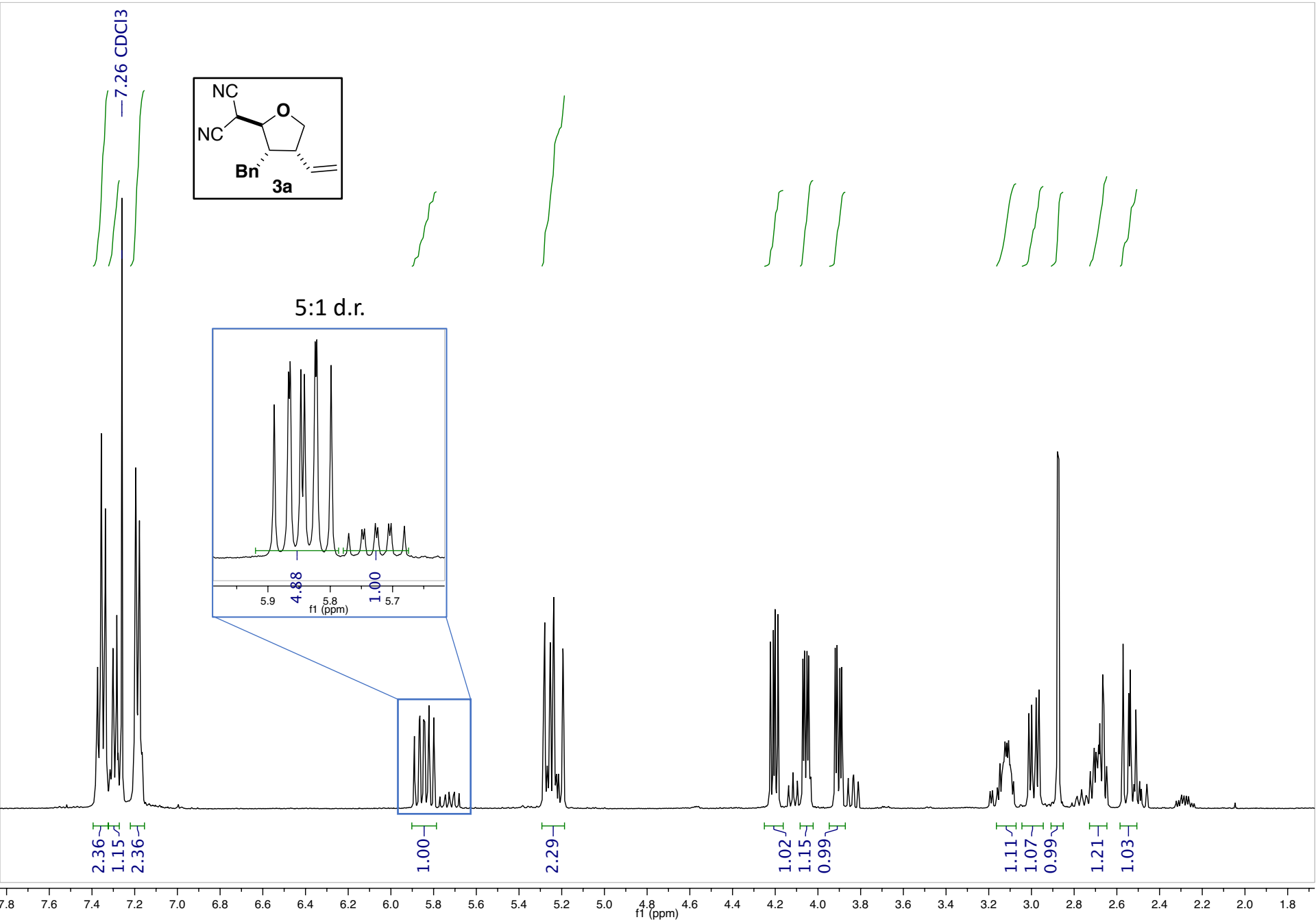

7.26 CDCl3
OBoc
MeO2C
MeO2C
Ph
Z-1g
2.22
1.09
2.02
1.00
1.09
1.10
1.04
2.03
6.01
2.02
2.07
9.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

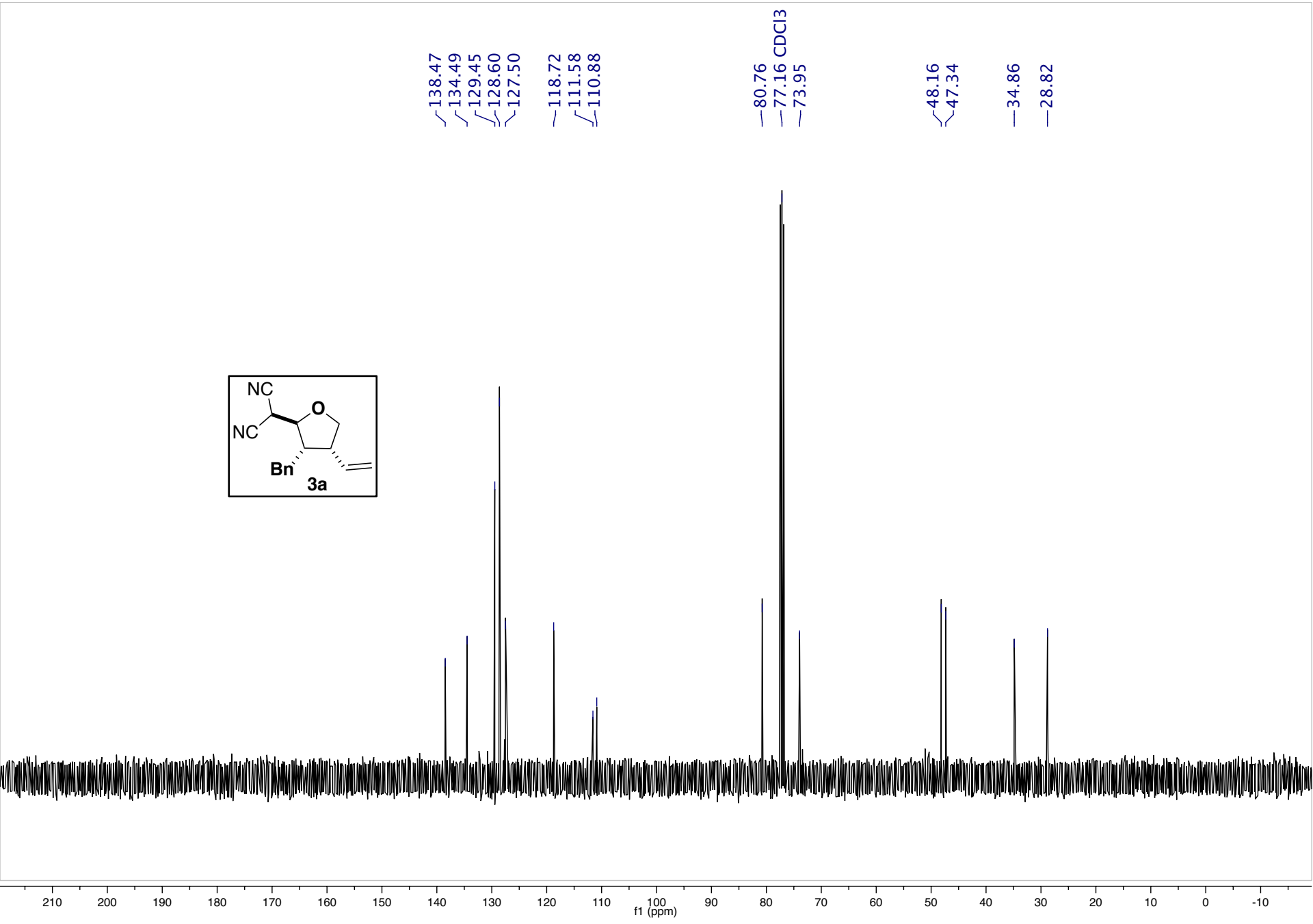

170.64
153.52
139.61
132.21
128.62
128.22
127.53
127.17
126.36
82.27
77.16 CDCl3
62.64
59.24
52.93
39.12
33.62
27.91
OBoc
MeO2C
MeO2C
Ph
Z-1g
f1 (ppm)

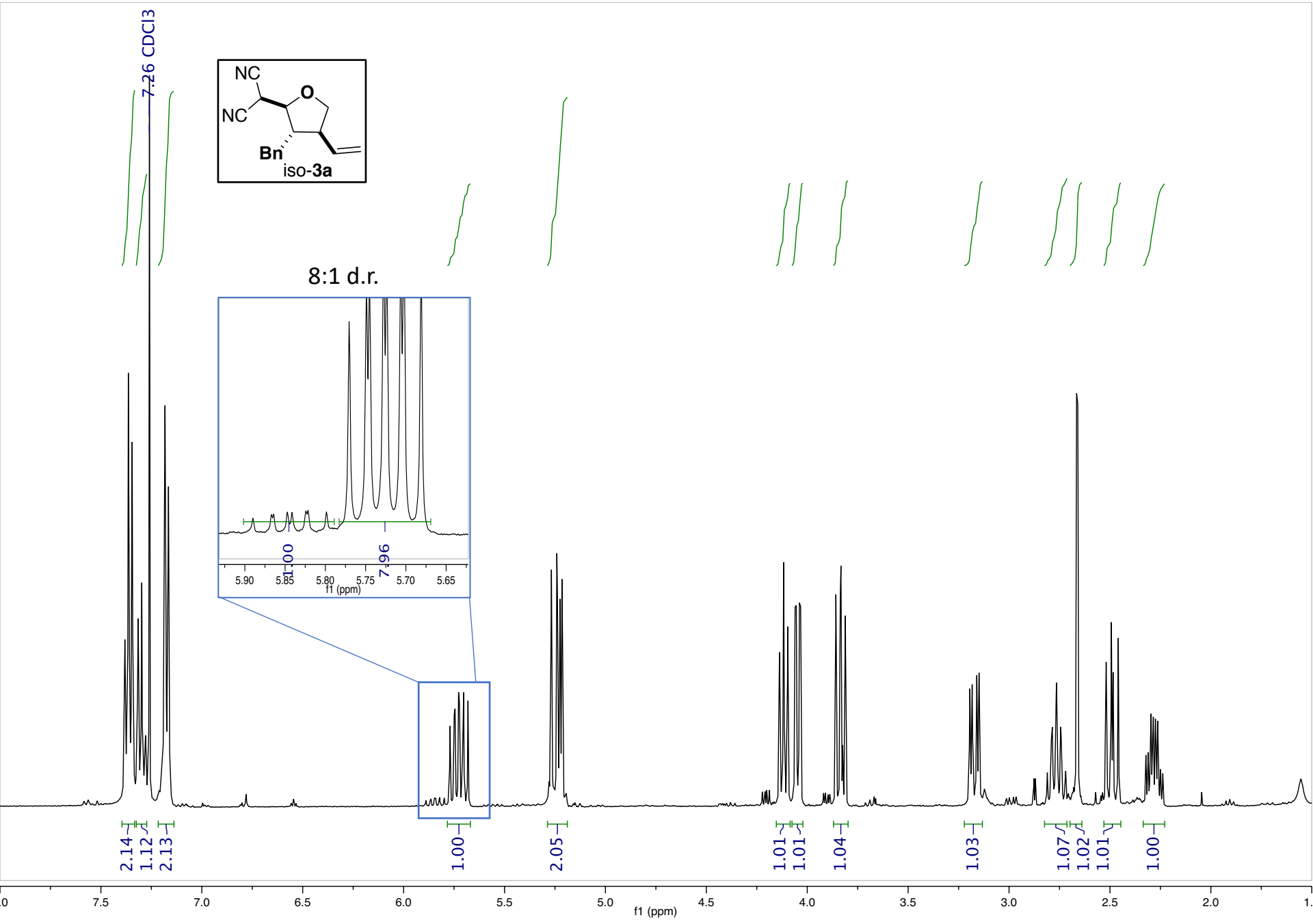

OH
MeO2C
MeO2C
Ph
iso-4g
2.05
1.08
2.07
1.00
2.01
0.98
2.00
6.00
2.00
2.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

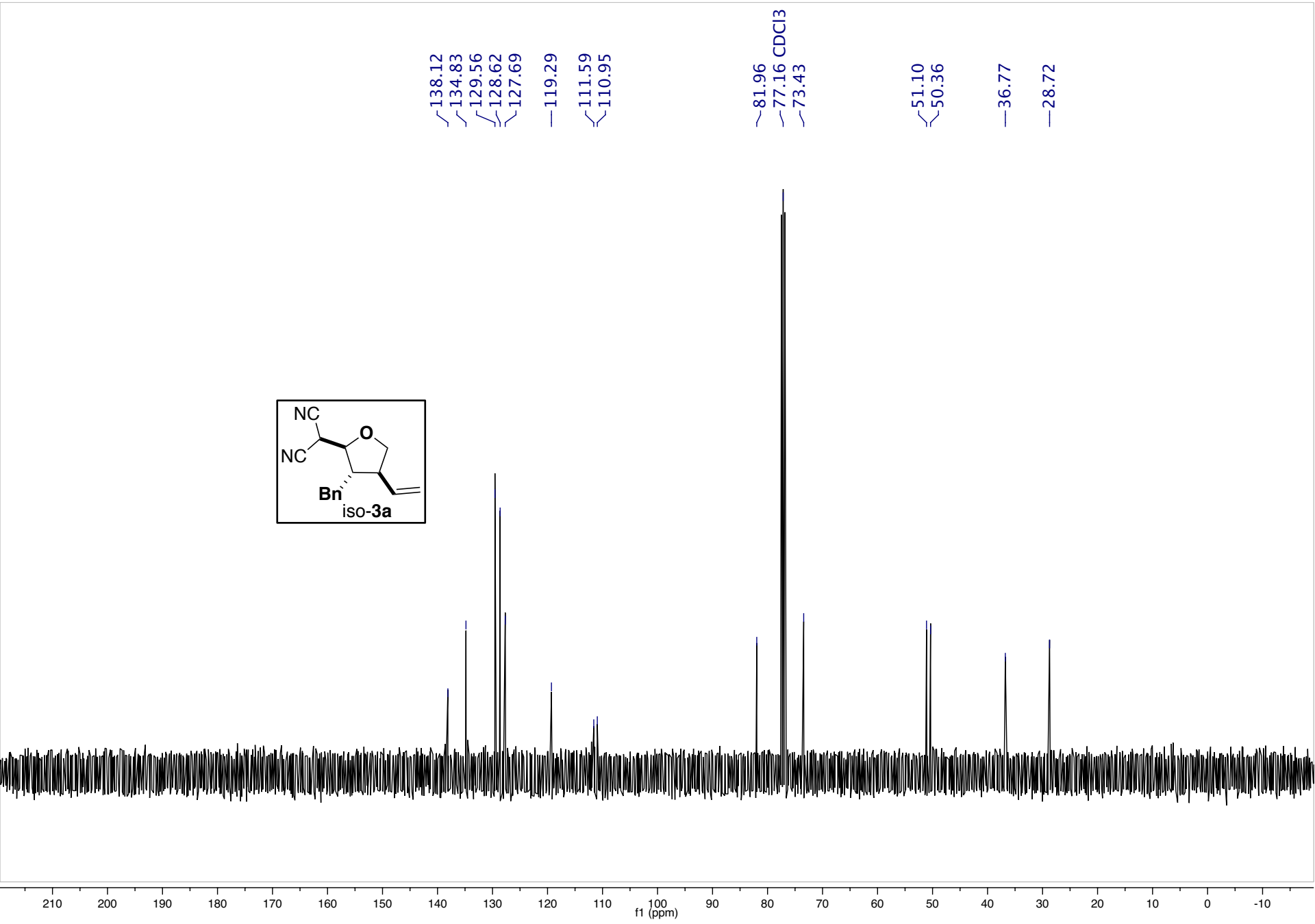

7.26 CDCl3
NC
NC
OBoc
E-1h
1.00
1.00
1.02
2.03
2.00
4.16
2.04
2.13
9.13
f1 (ppm)

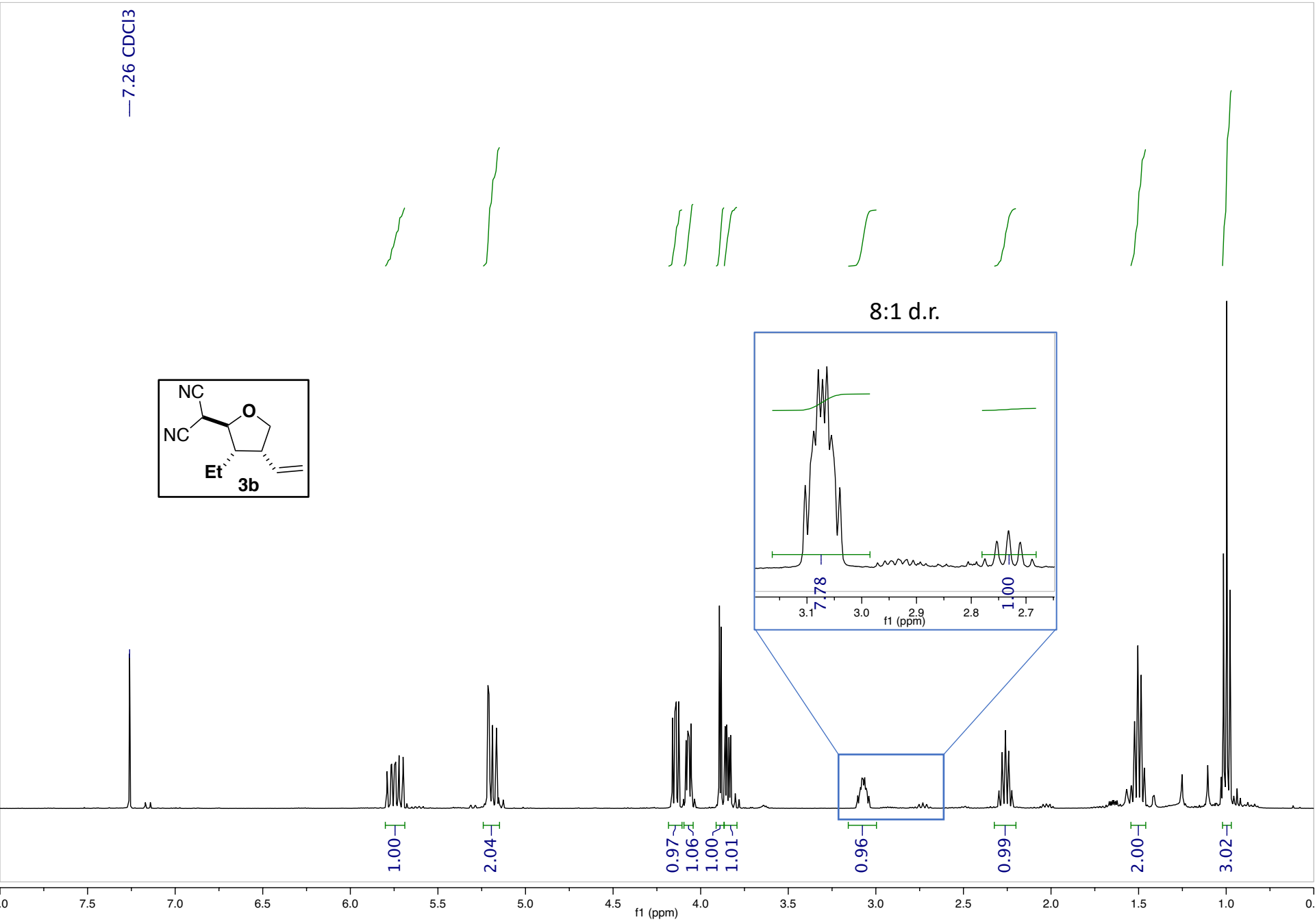

153.24
132.32
130.19
127.48
124.83
114.29
82.58
77.16 CDCl3
66.16
43.73
40.07
27.89
25.38
24.70
22.38
21.43
NC
NC
OBoc
E-1h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

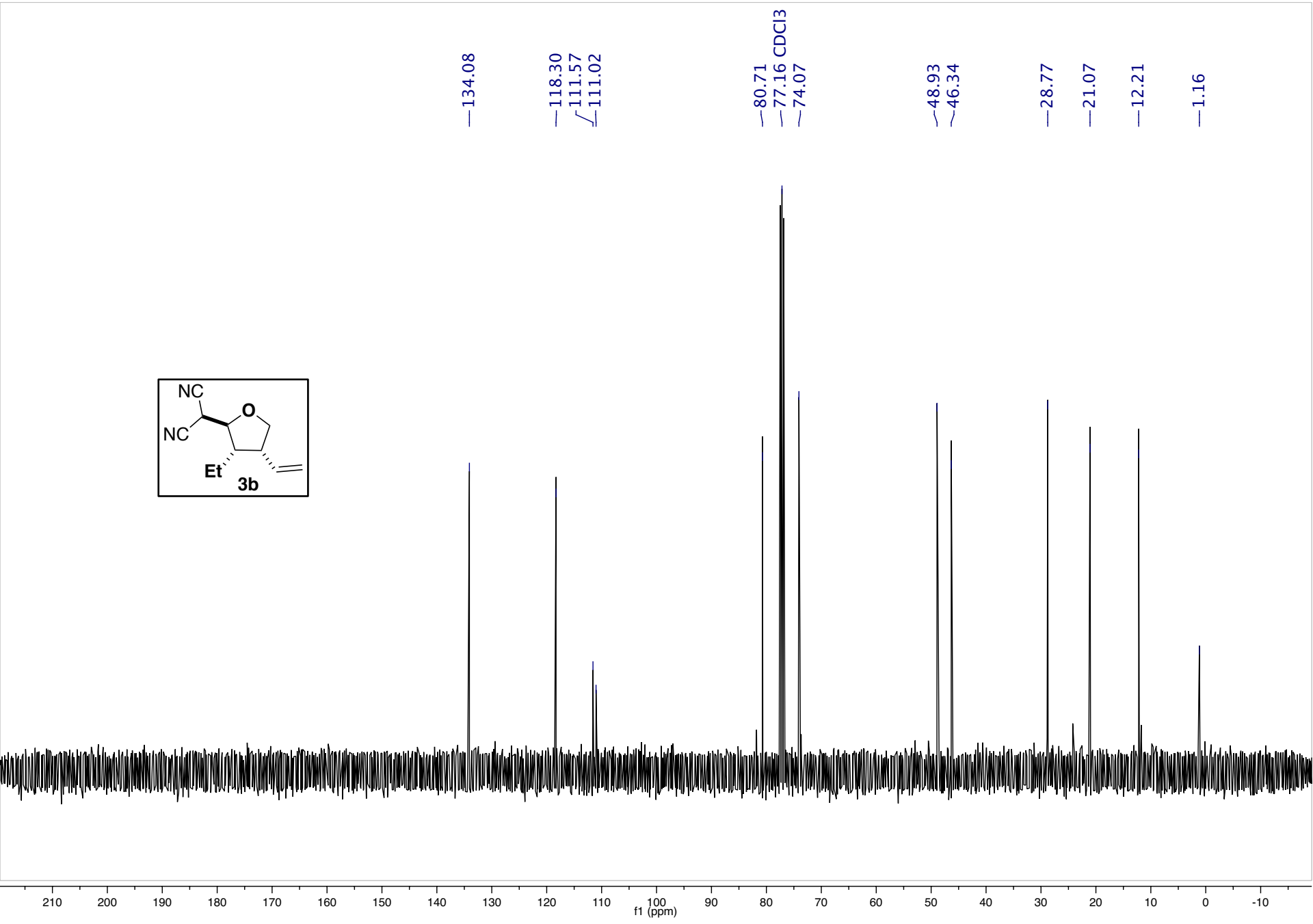

7.26 CDCl3
NC
NC
O
Bn
3a
5:1 d.r.
4.88
1.00
5.9
5.8
5.7
f1 (ppm)
2.36
1.15
2.36
1.00
2.29
1.02
1.15
0.99
1.11
1.07
0.99
1.21
1.03
f1 (ppm)

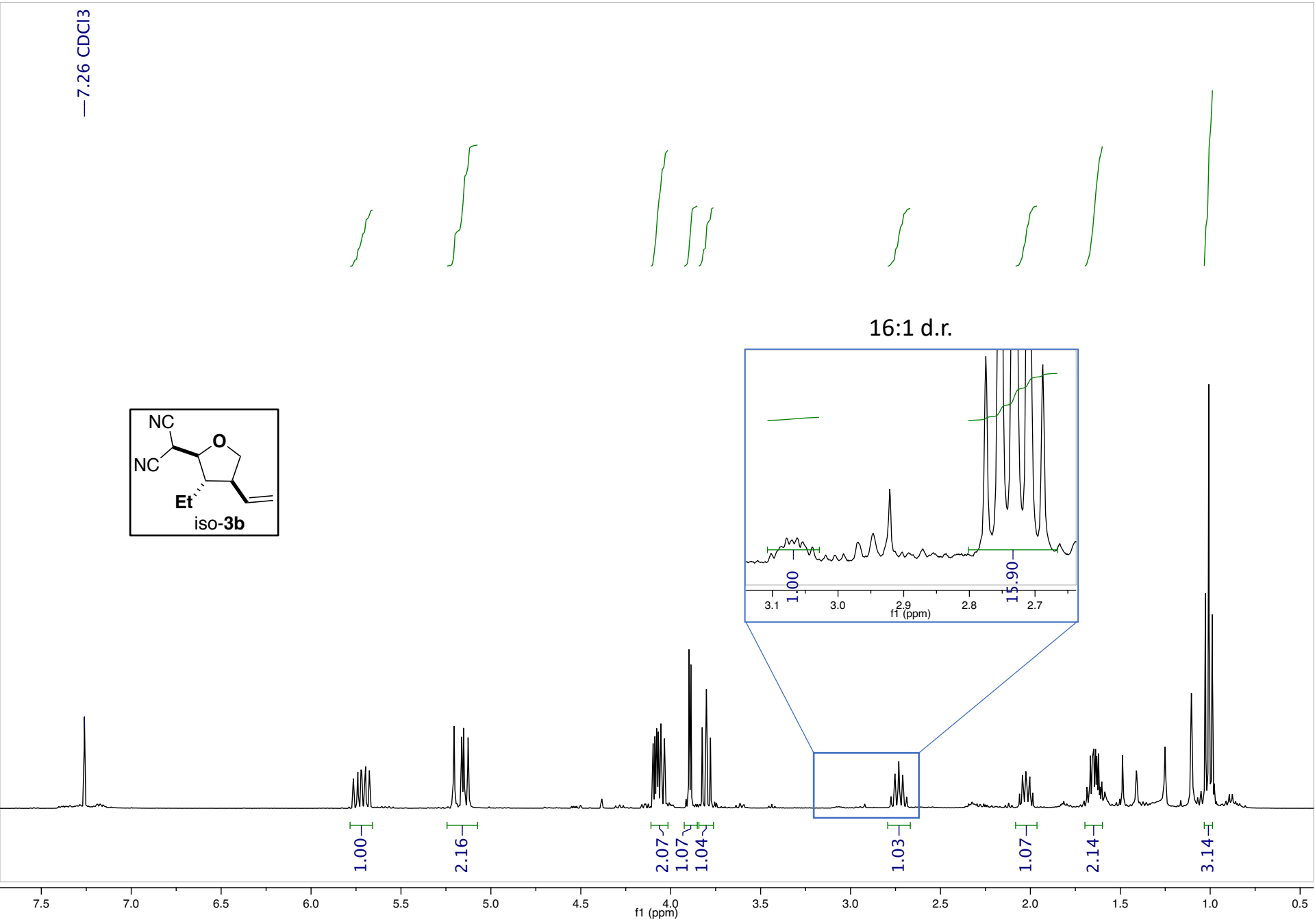

138.47
134.49
129.45
128.60
127.50
118.72
111.58
110.88
80.76
77.16 CDCl3
73.95
48.16
47.34
34.86
28.82
NC
NC
O
Bn
3a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

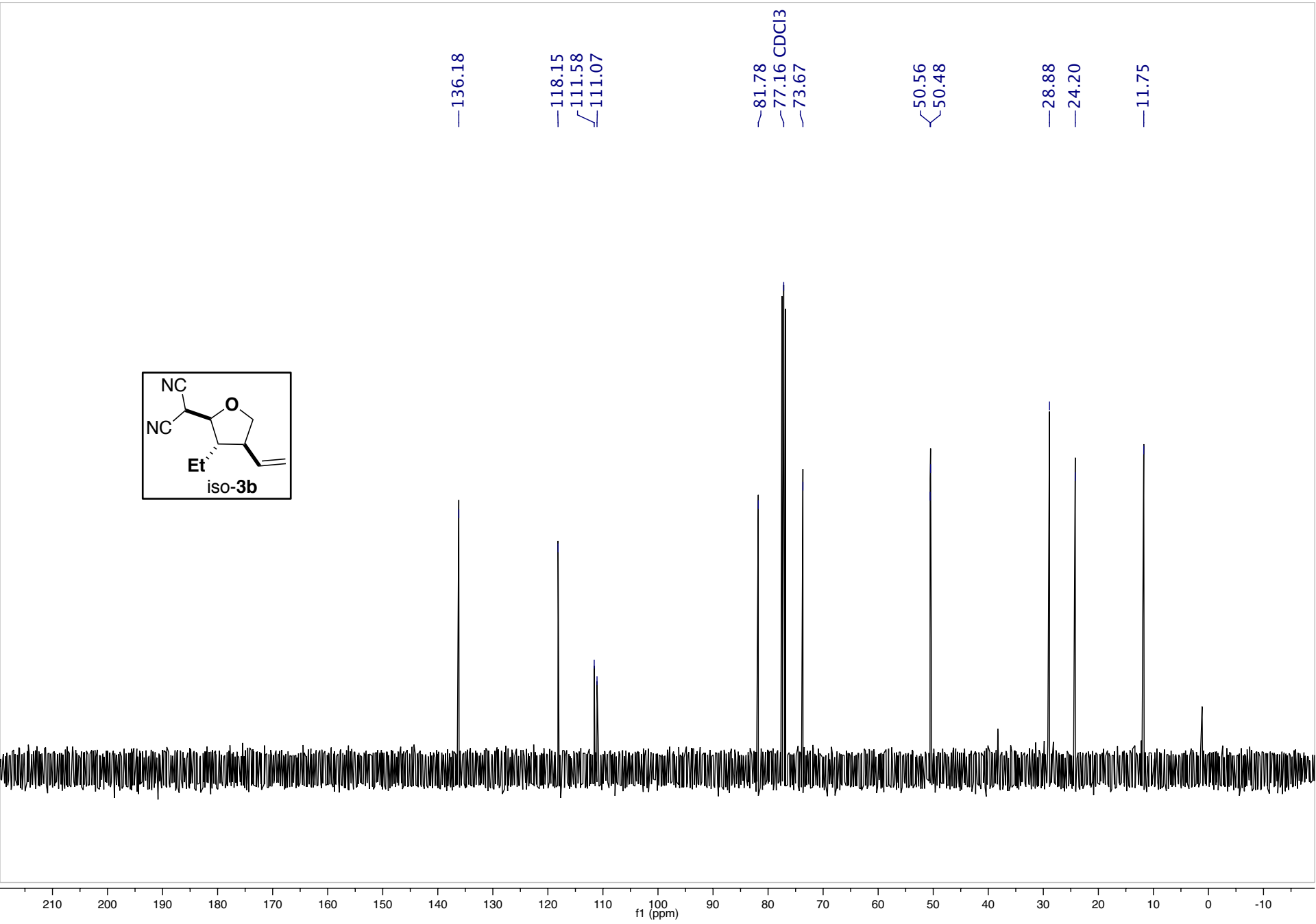

7.26 CDCl3
NC
NC
O
Bn
iso-3a
8:1 d.r.
1.00
7.96
5.90
5.85
5.80
5.75
5.70
5.65
f1 (ppm)
2.14
1.12
2.13
1.00
2.05
1.01
1.01
1.04
1.03
1.07
1.02
1.01
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

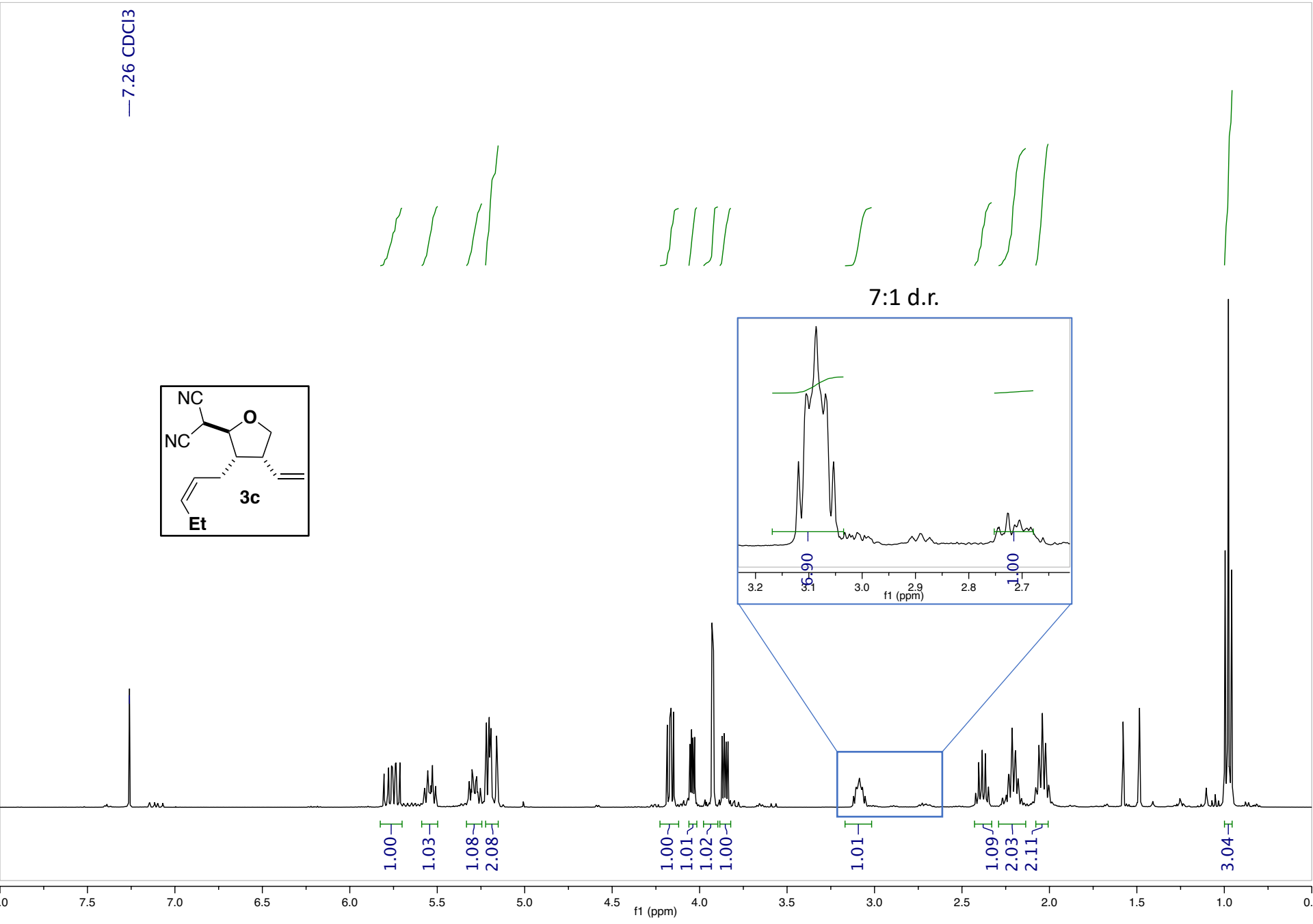

138.12
134.83
129.56
128.62
127.69
119.29
111.59
110.95
81.96
77.16 CDCl3
73.43
51.10
50.36
36.77
28.72
NC
NC
O
Bn
iso-3a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

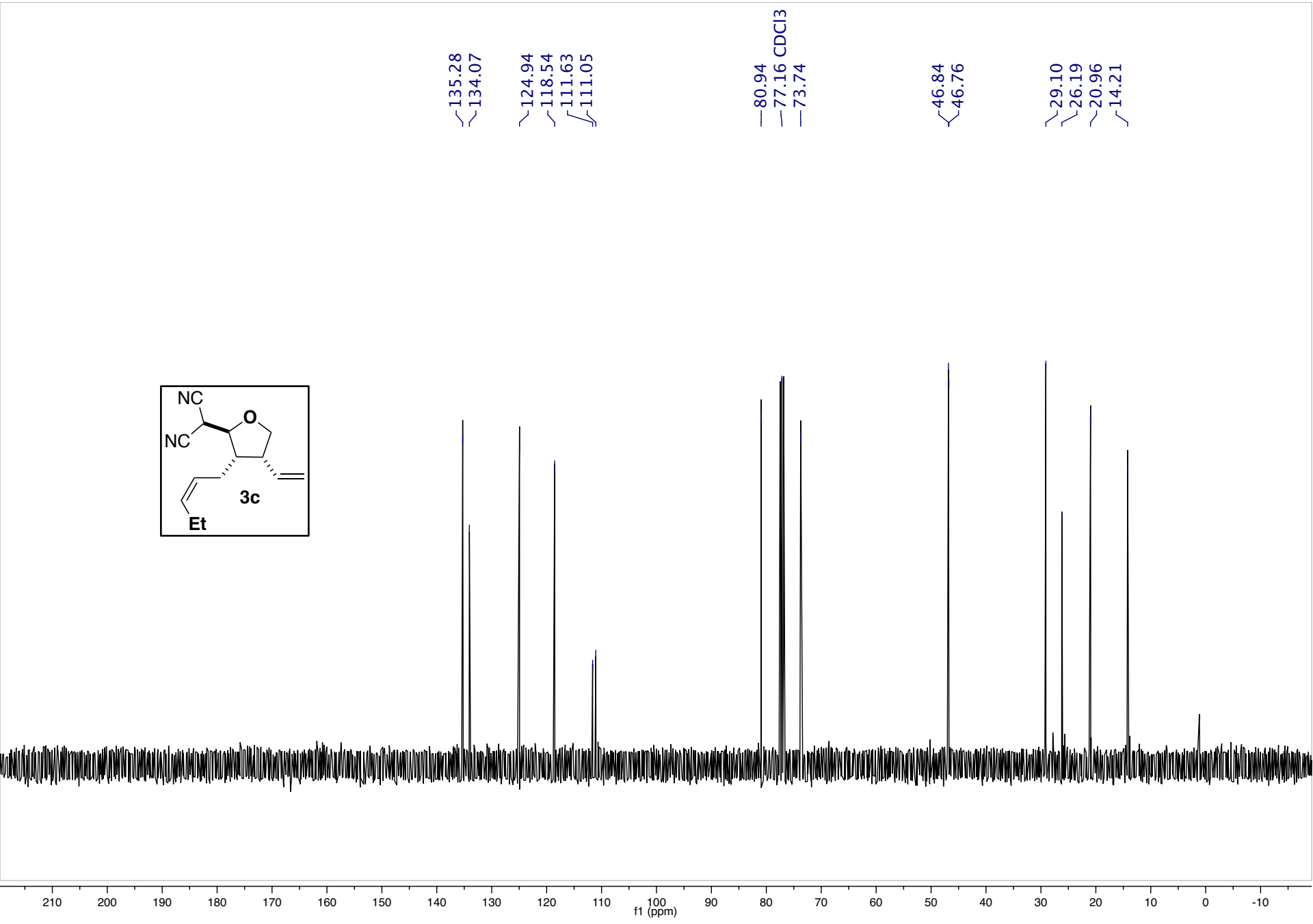

7.26 CDCl3
8:1 d.r.
NC
NC
O
Et
3b
7.78
1.00
3.1
3.0
2.9
2.8
2.7
f1 (ppm)
1.00
2.04
0.97
1.06
1.00
1.01
0.96
0.99
2.00
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

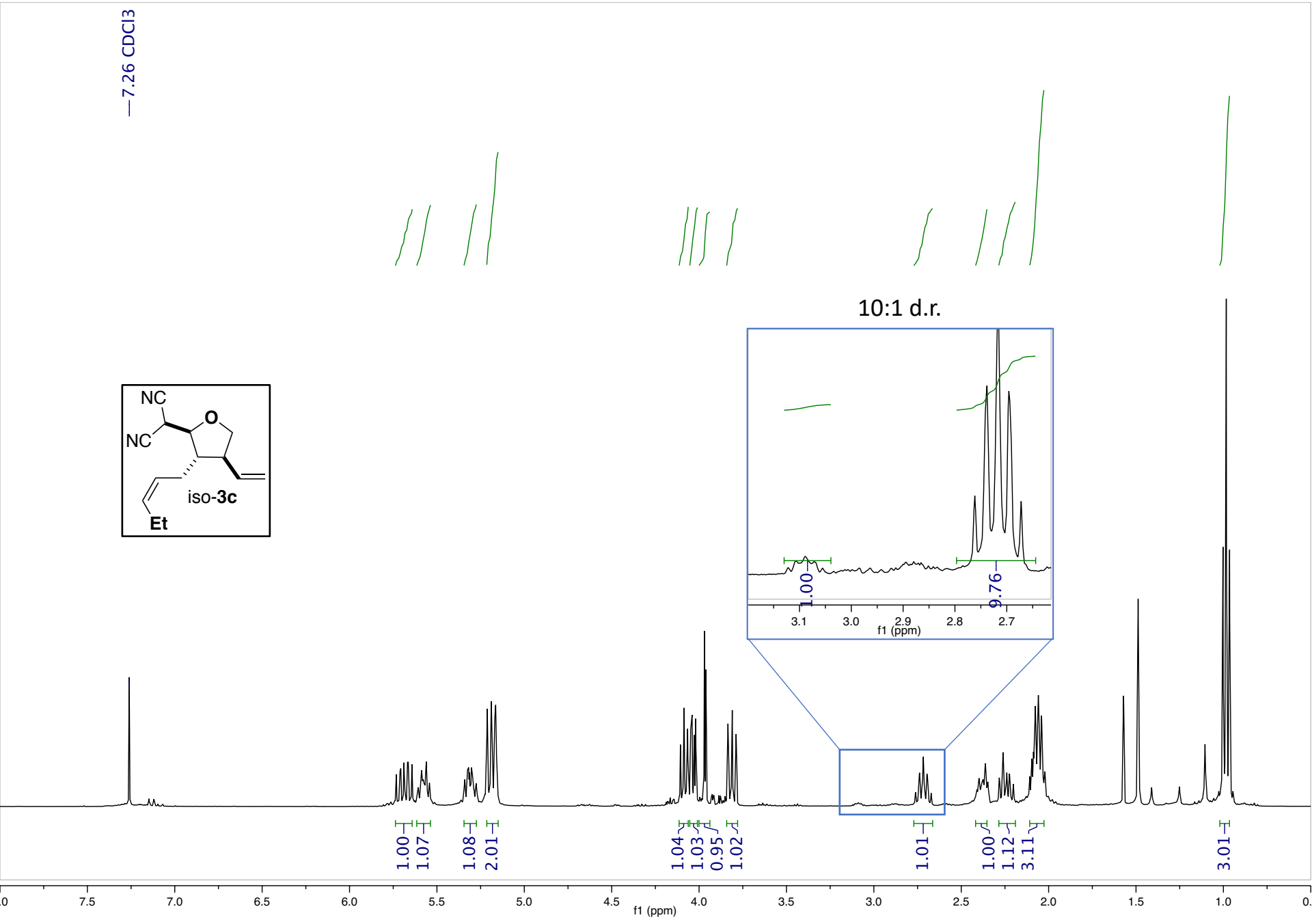

134.08
118.30
111.57
111.02
80.71
77.16 CDCl3
74.07
48.93
46.34
28.77
21.07
12.21
1.16
NC
NC
O
Et
3b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

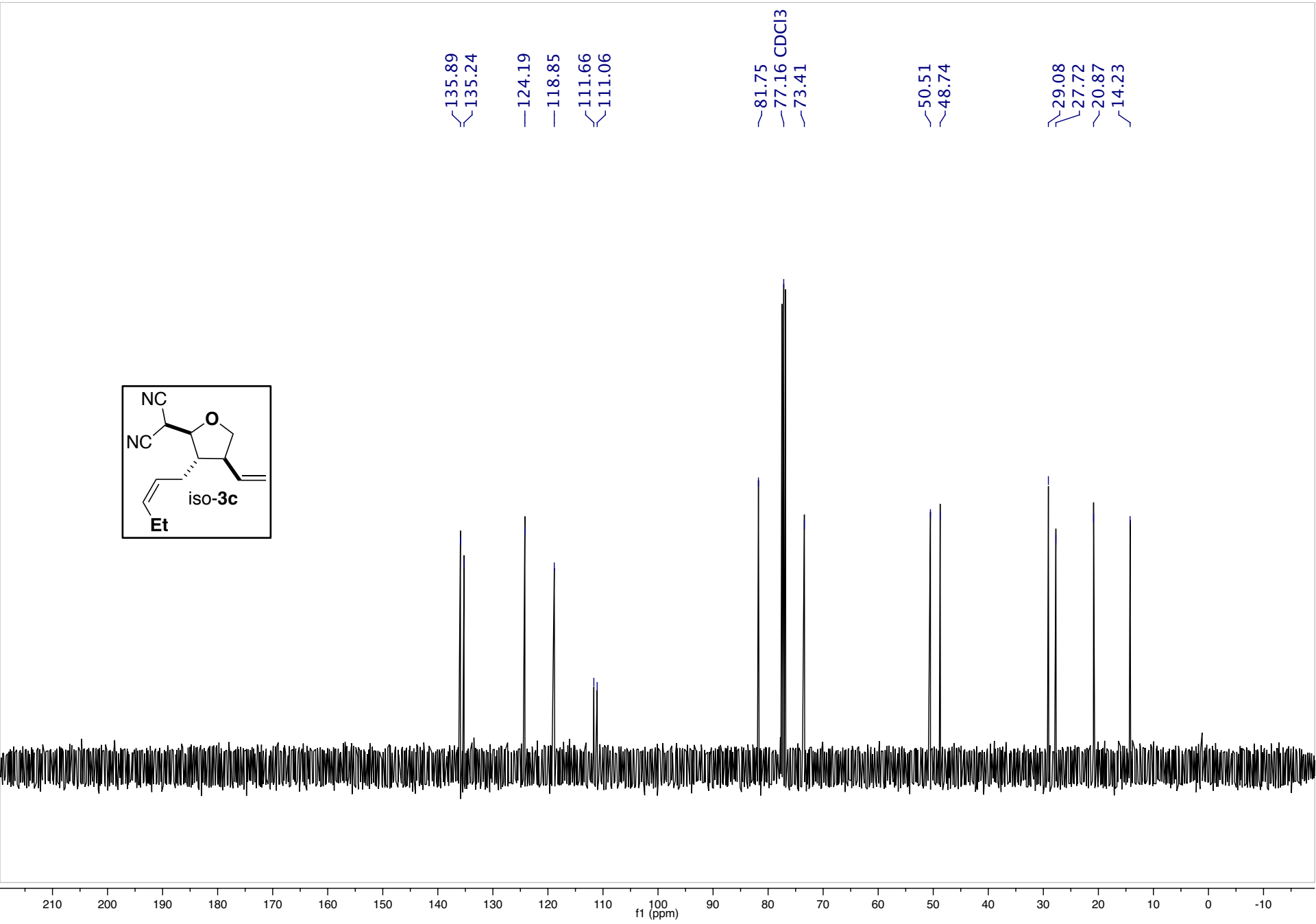

7.26 CDCl3
16:1 d.r.
NC
NC
O
Et
iso-3b
1.00
2.16
2.07
1.07
1.04
1.03
1.07
2.14
3.14
1.00
15.90
f1 (ppm)
f1 (ppm)

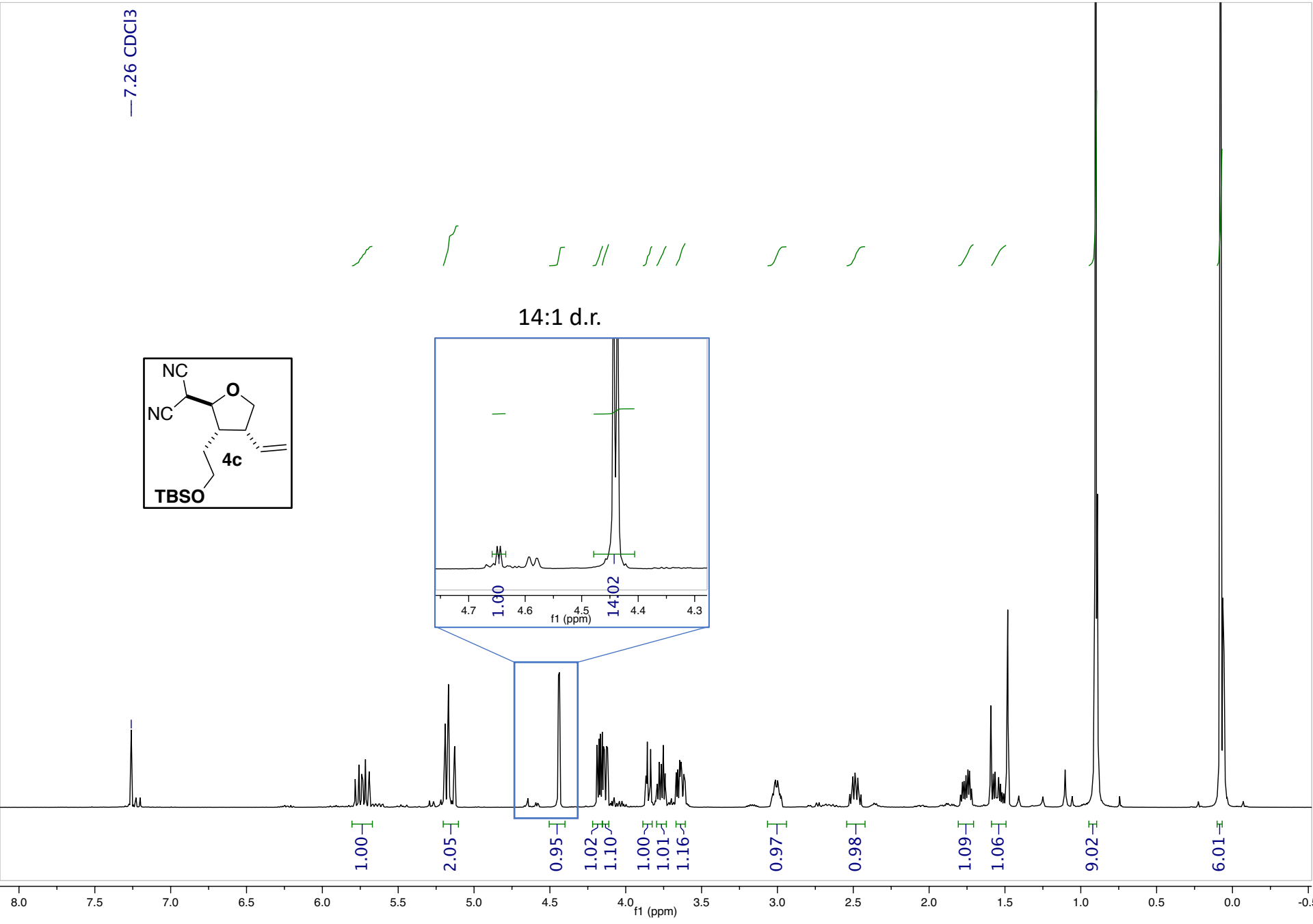

136.18
118.15
111.58
111.07
81.78
77.16 CDCl3
73.67
50.56
50.48
28.88
24.20
11.75
NC
NC
O
Et
iso-3b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

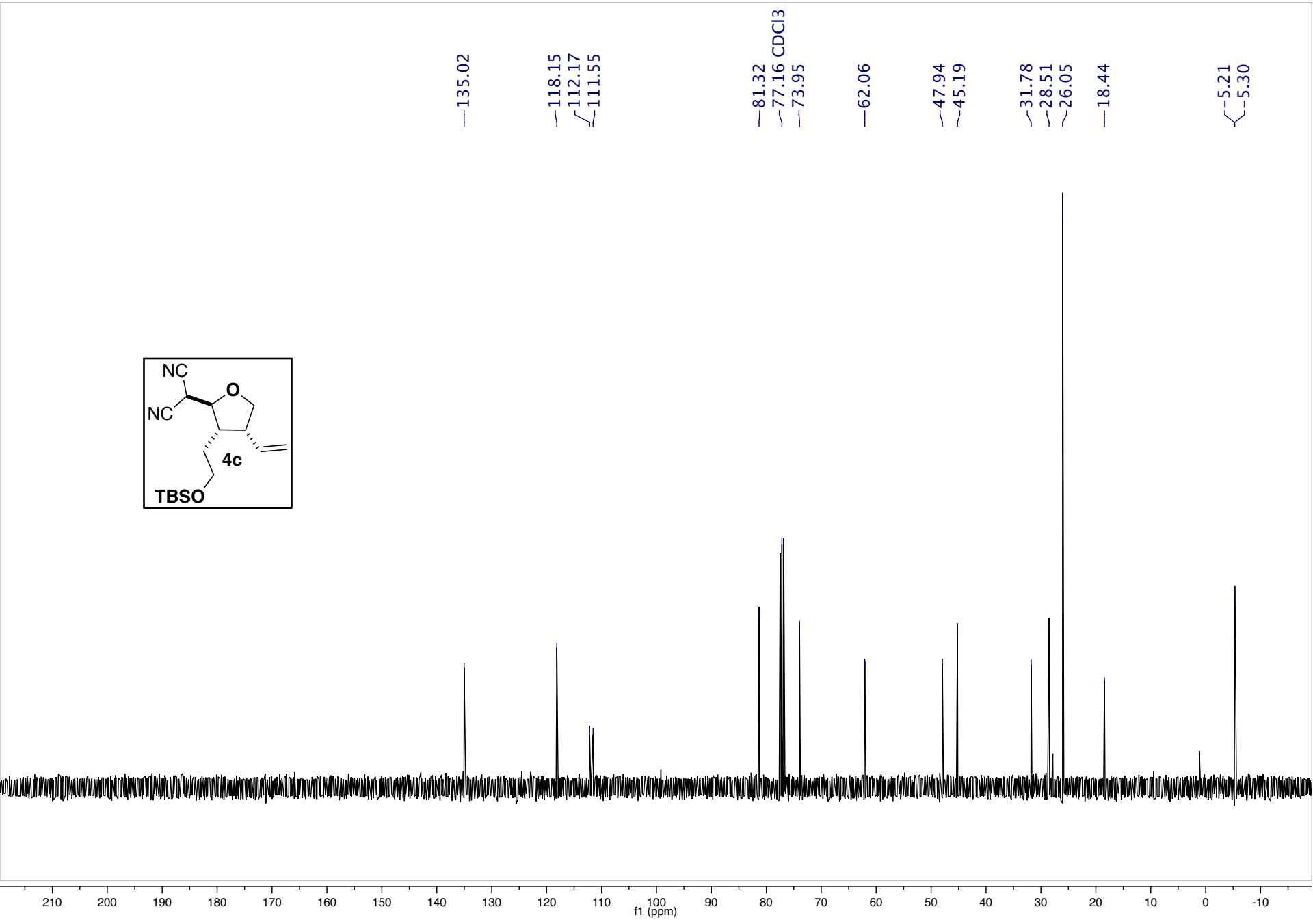

7.26 CDCl3
7:1 d.r.
NC
NC
O
3c
Et
6.90
1.00
3.2
3.1
3.0
2.9
2.8
2.7
f1 (ppm)
1.00
1.03
1.08
2.08
1.00
1.01
1.02
1.00
1.01
1.09
2.03
2.11
3.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


135.28
134.07
124.94
118.54
111.63
111.05
80.94
77.16 CDCl3
73.74
46.84
46.76
29.10
26.19
20.96
14.21
NC
NC
O
3c
Et
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

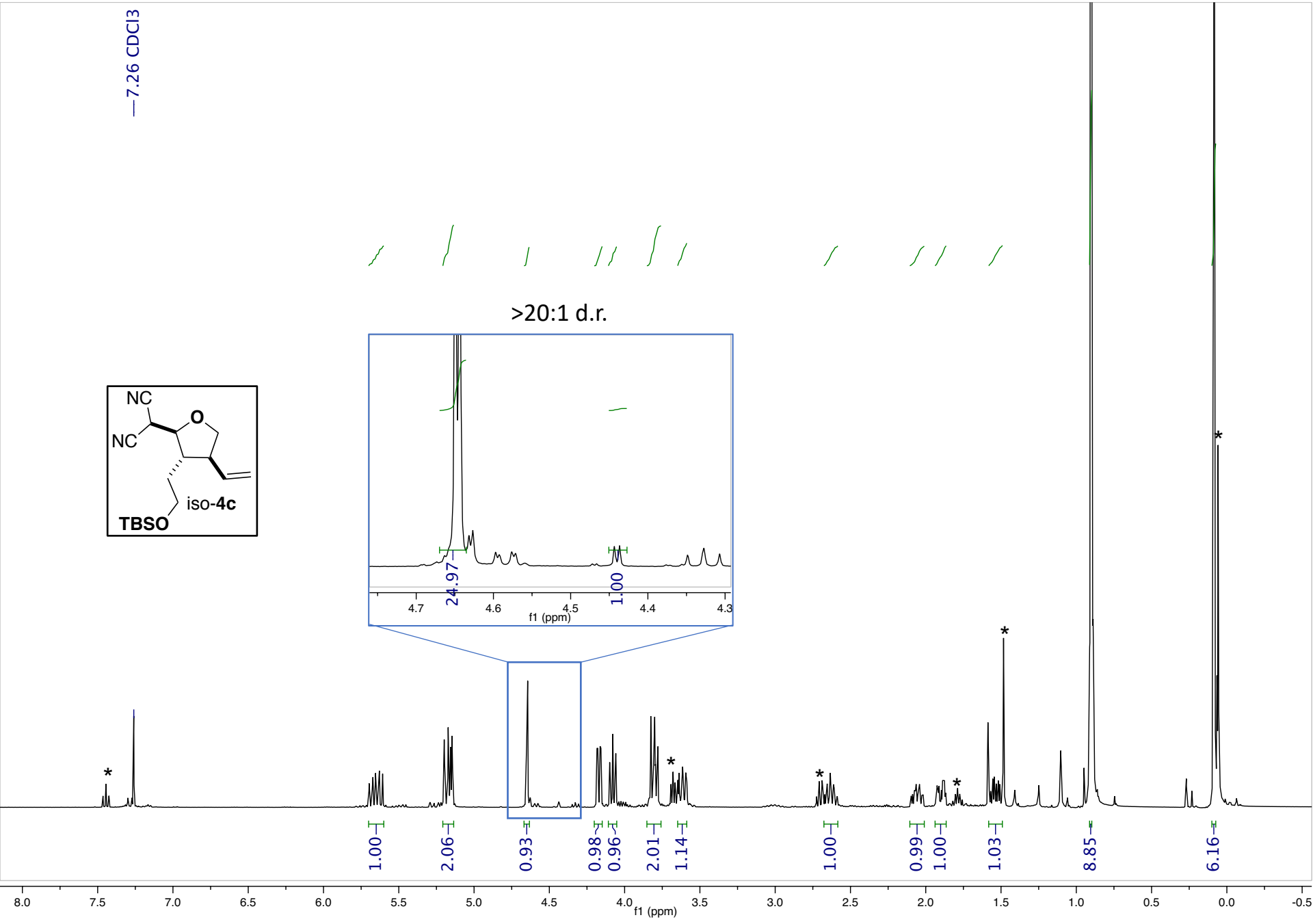

7.26 CDCl3
10:1 d.r.
NC
NC
O
iso-3c
Et
1.00
1.07
1.08
2.01
1.04
1.03
0.95
1.02
1.01
1.00
1.12
3.11
3.01
1.00
9.76
3.1
3.0
2.9
2.8
2.7
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

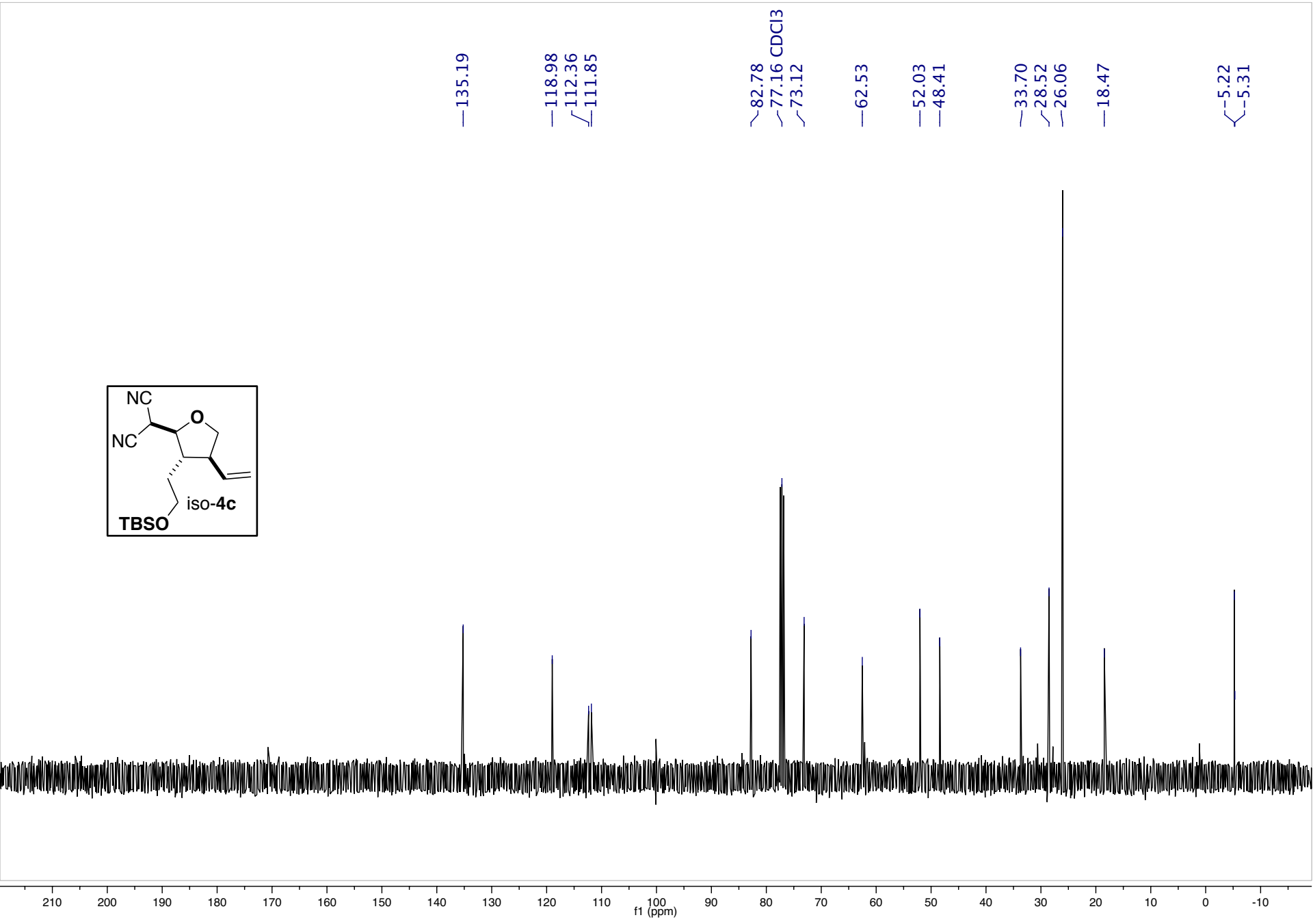

135.89
135.24
124.19
118.85
111.66
111.06
81.75
77.16 CDCl3
73.41
50.51
48.74
29.08
27.72
20.87
14.23
NC
NC
O
iso-3c
Et
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

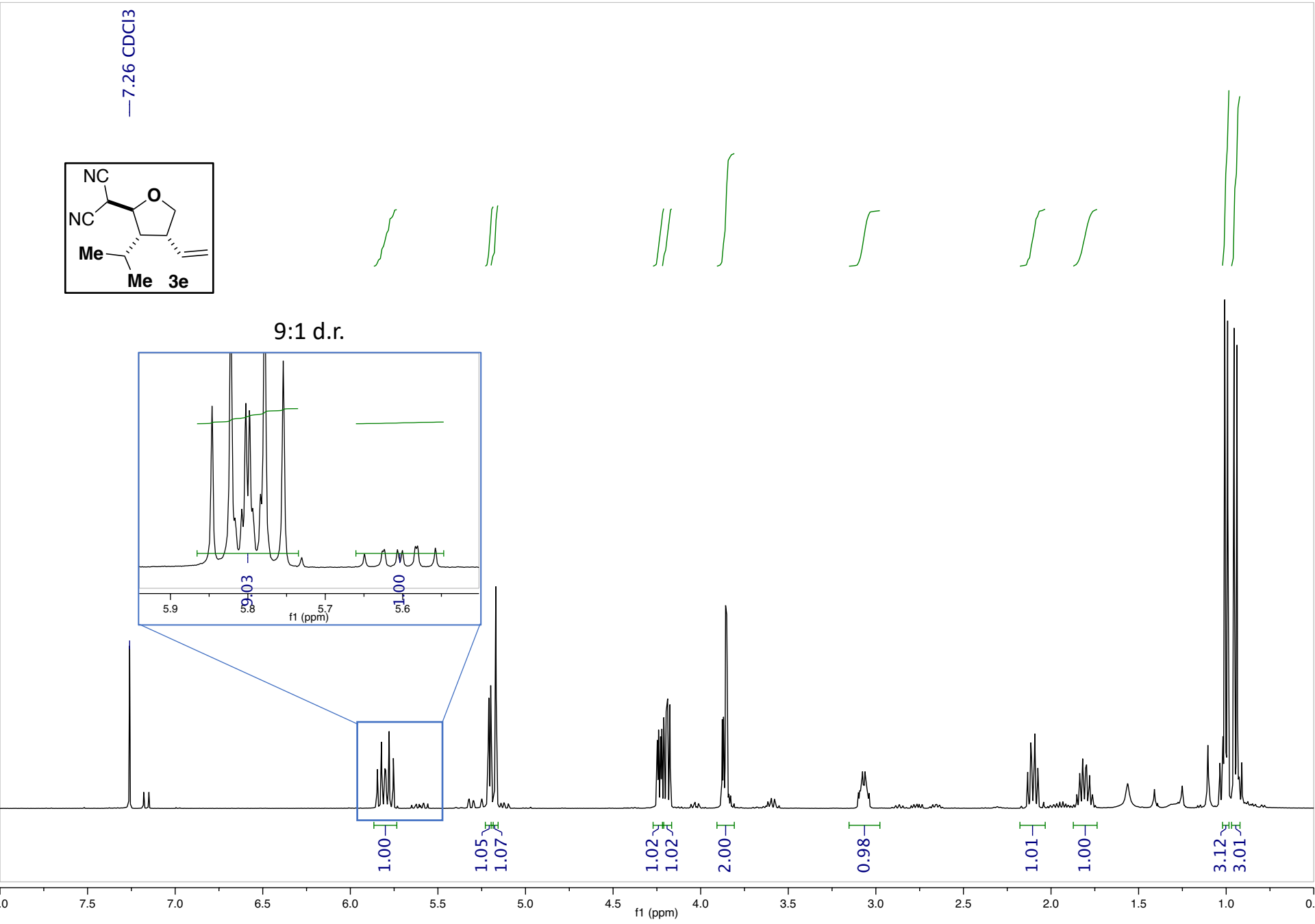

7.26 CDCl3
14:1 d.r.
NC
NC
O
4c
TBSO
1.00
14.02
4.7
4.6
4.5
4.4
4.3
f1 (ppm)
1.00
2.05
0.95
1.02
1.10
1.00
1.01
1.16
0.97
0.98
1.09
1.06
9.02
6.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

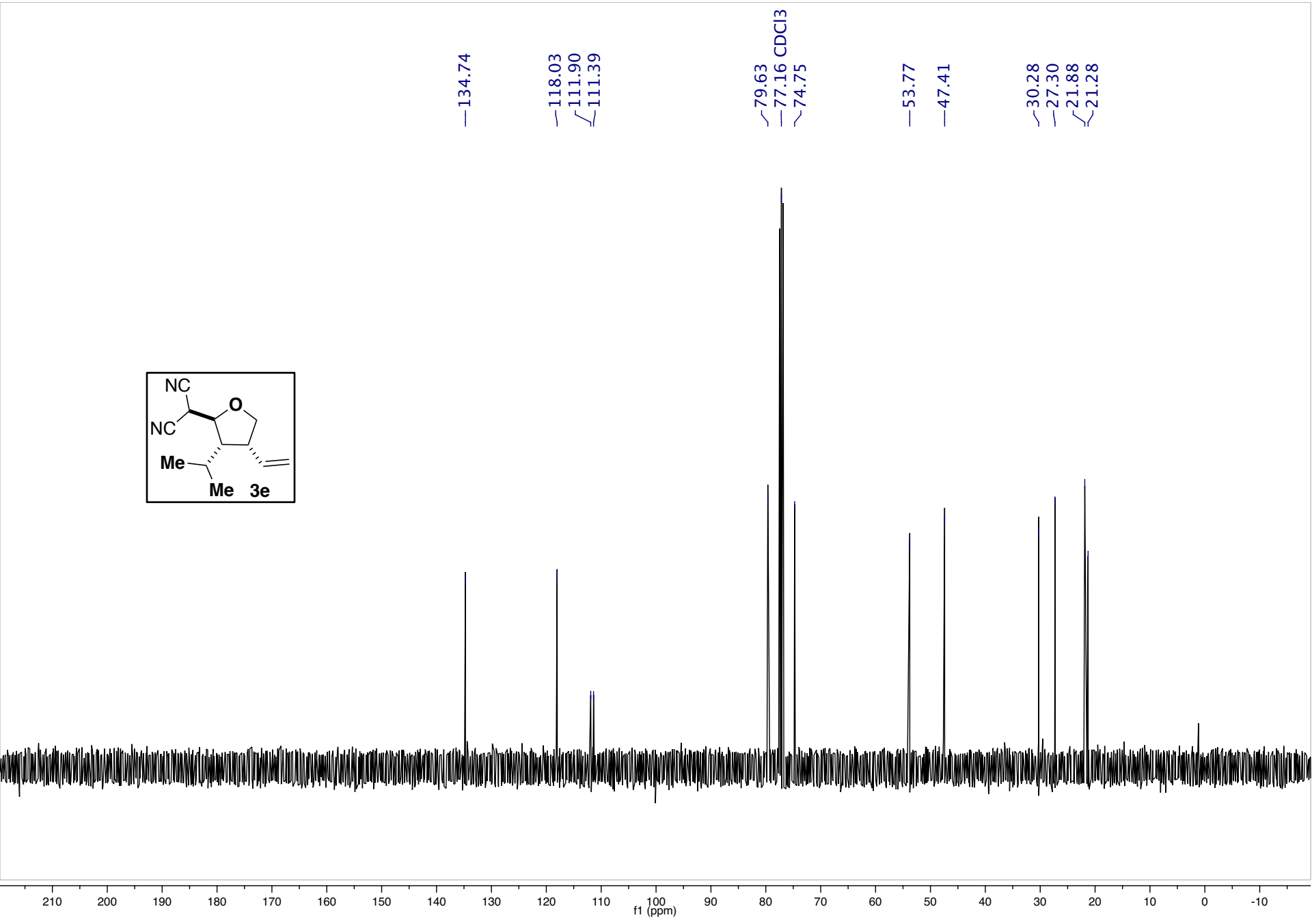

135.02
118.15
112.17
111.55
81.32
77.16 CDCl3
73.95
62.06
47.94
45.19
31.78
28.51
26.05
18.44
5.21
5.30
NC
NC
O
4c
TBSO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

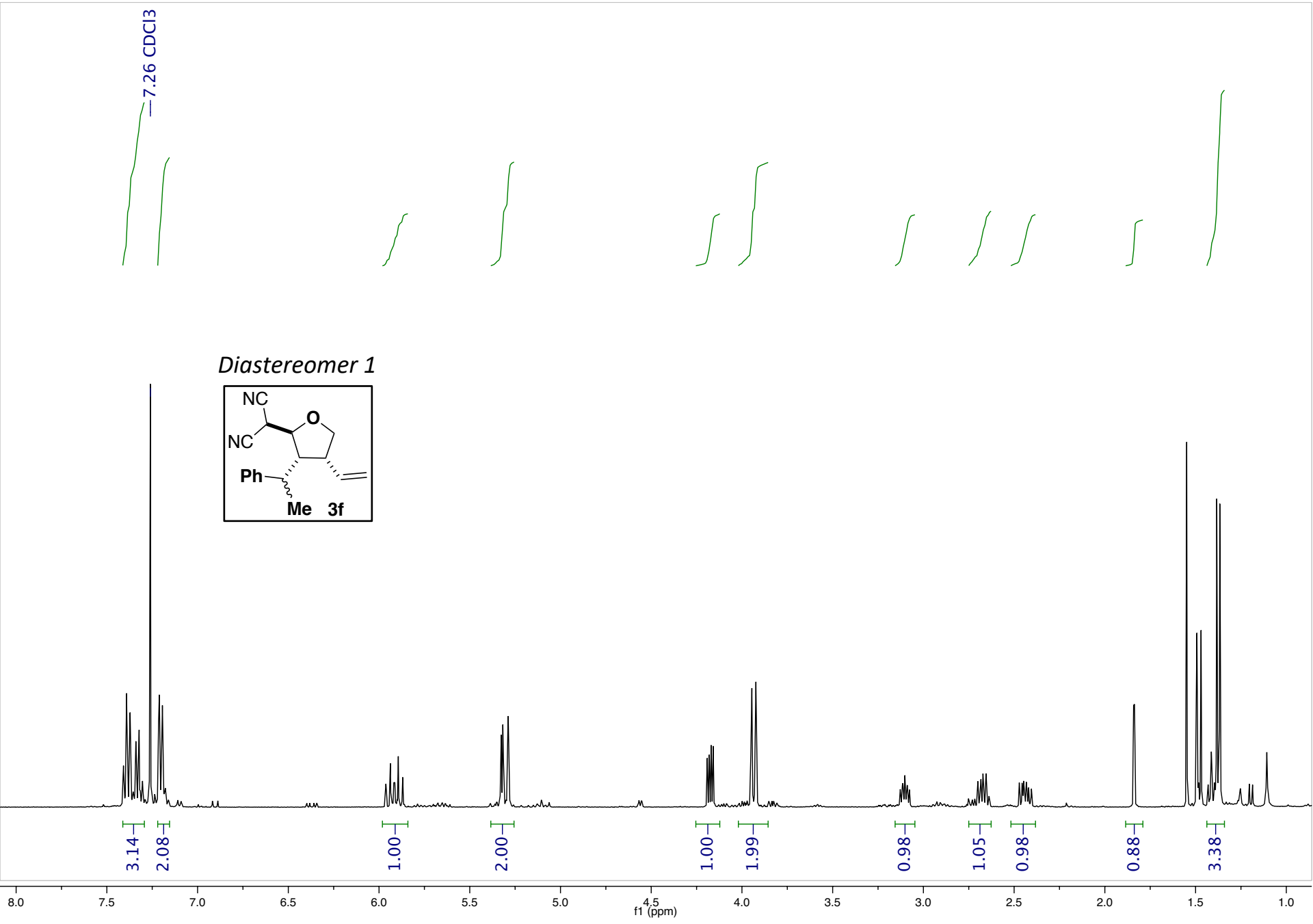
* Trace of Knoevenagel starting material

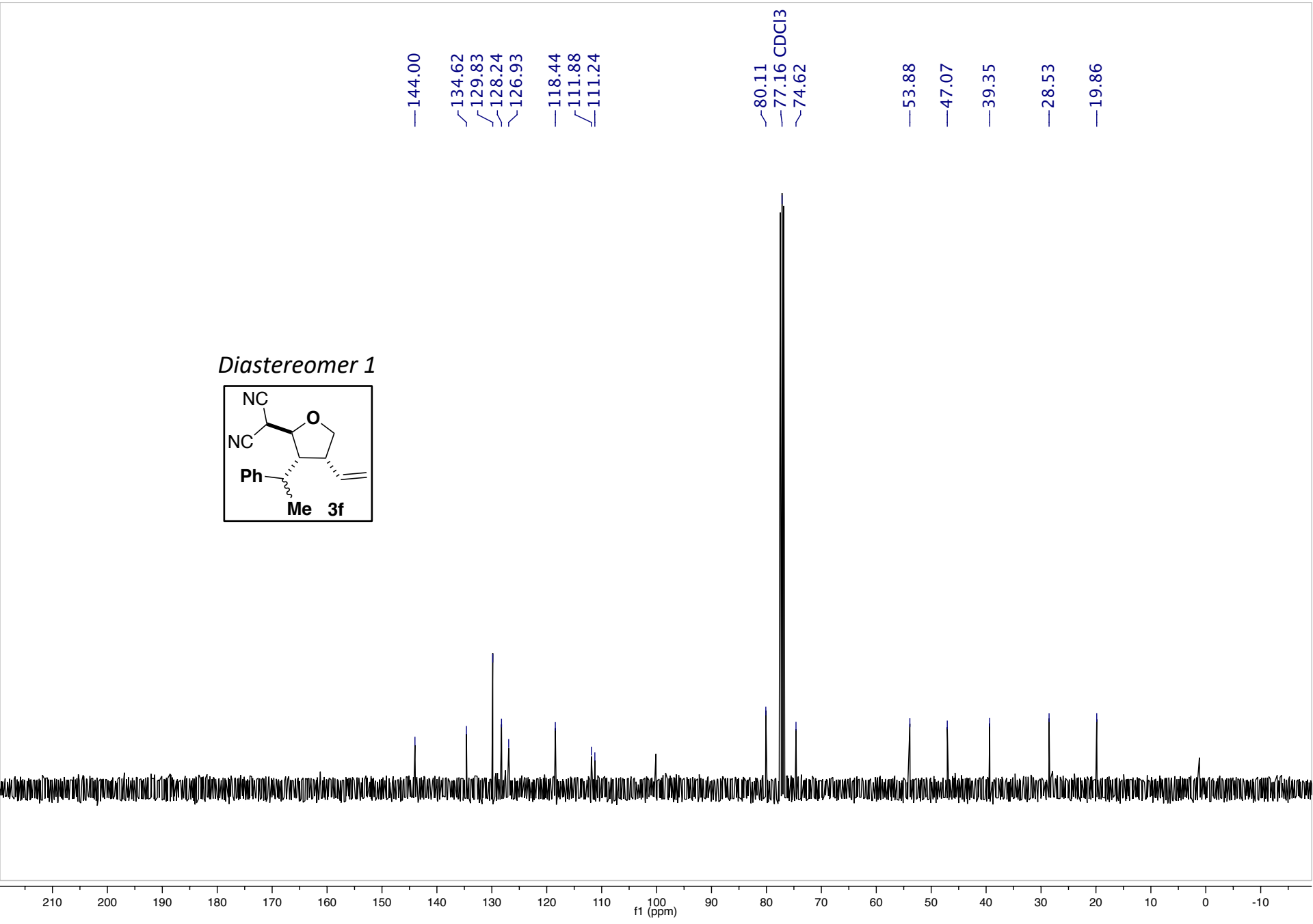


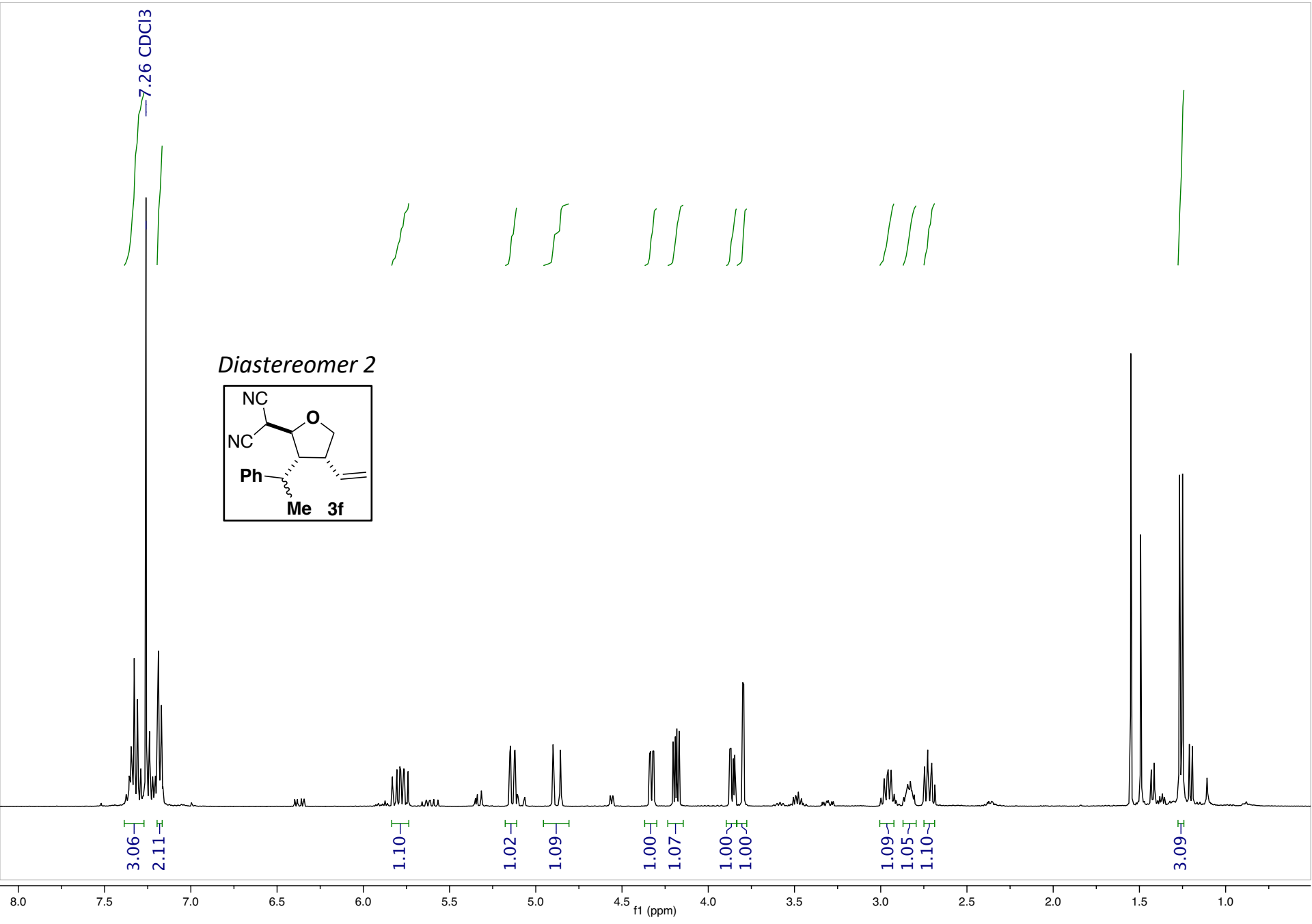

135.19
118.98
112.36
111.85
82.78
77.16 CDCl3
73.12
62.53
52.03
48.41
33.70
28.52
26.06
18.47
5.22
-5.31
NC
NC
O
iso-4c
TBSO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

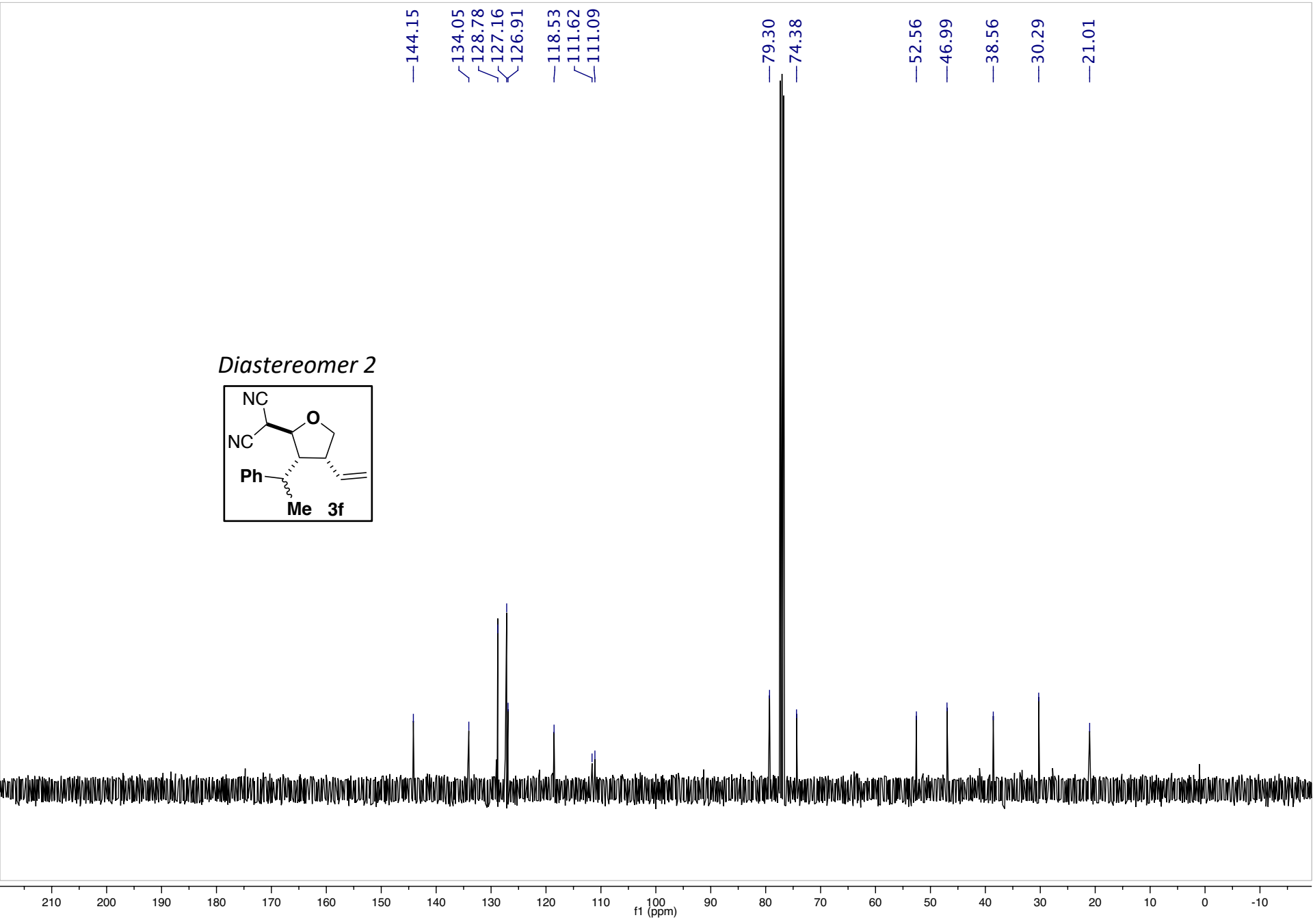

7.26 CDCl3
NC
NC
O
Me
Me
3e
9:1 d.r.
9.03
1.00
5.9
5.8
5.7
5.6
f1 (ppm)
1.00
1.05
1.07
1.02
1.02
2.00
0.98
1.01
1.00
3.12
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0

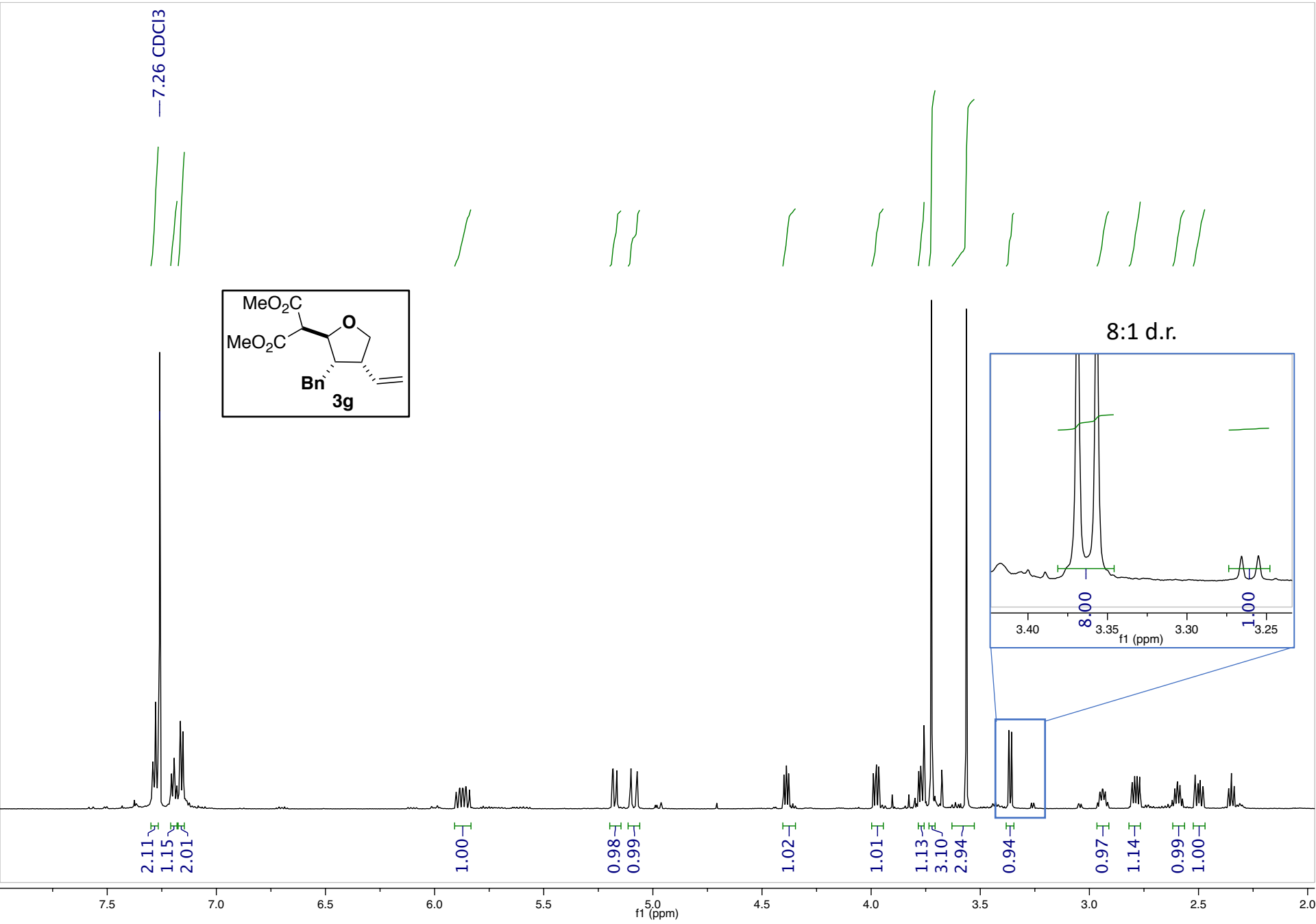

134.74
118.03
111.90
111.39
79.63
77.16 CDCl3
74.75
53.77
47.41
30.28
27.30
21.88
21.28
NC
NC
O
Me
Me
3e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

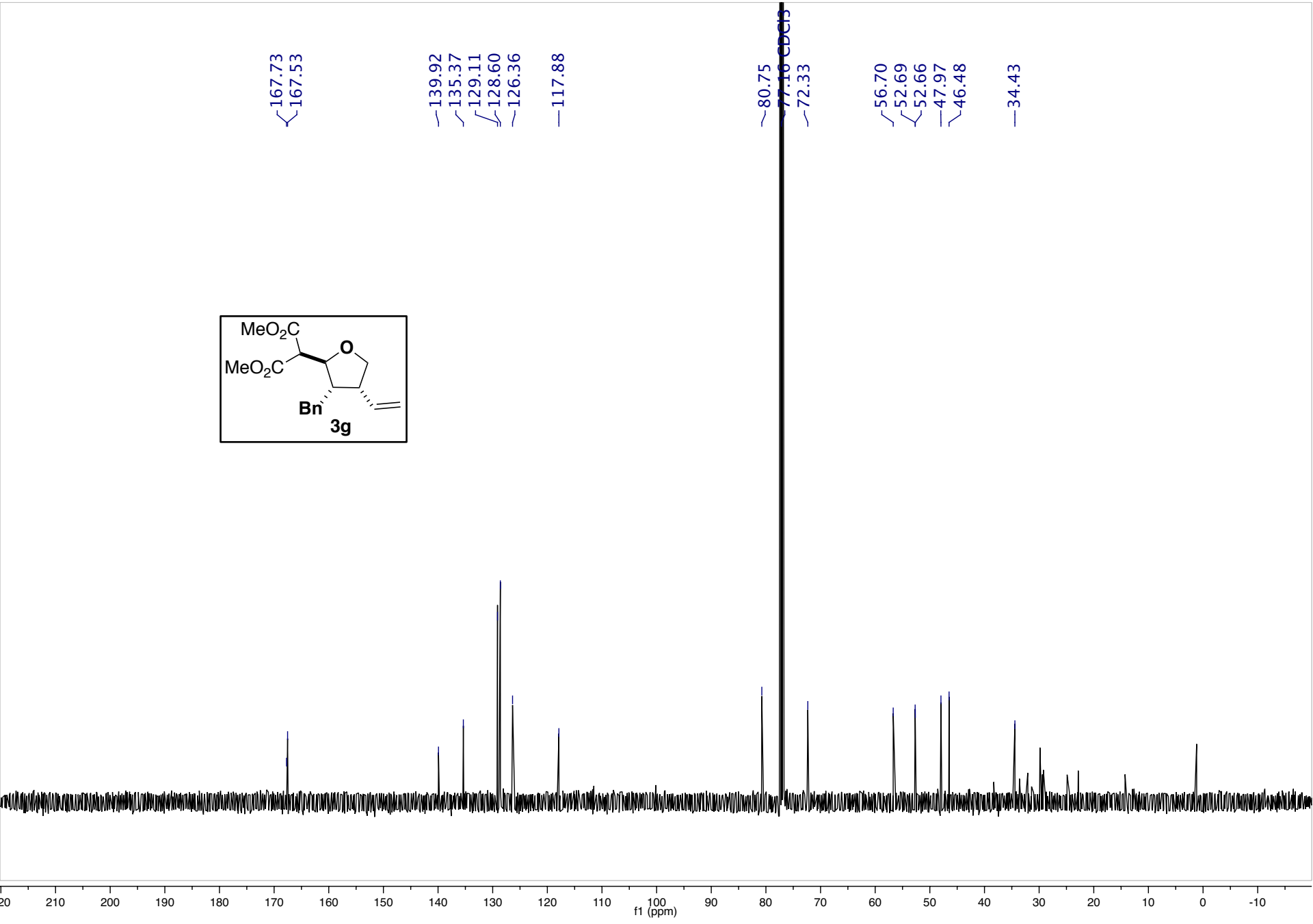

7.26 CDCl3
Diastereomer 1
NC
NC
O
Ph
Me
3f
3.14
2.08
1.00
2.00
1.00
1.99
0.98
1.05
0.98
0.88
3.38
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

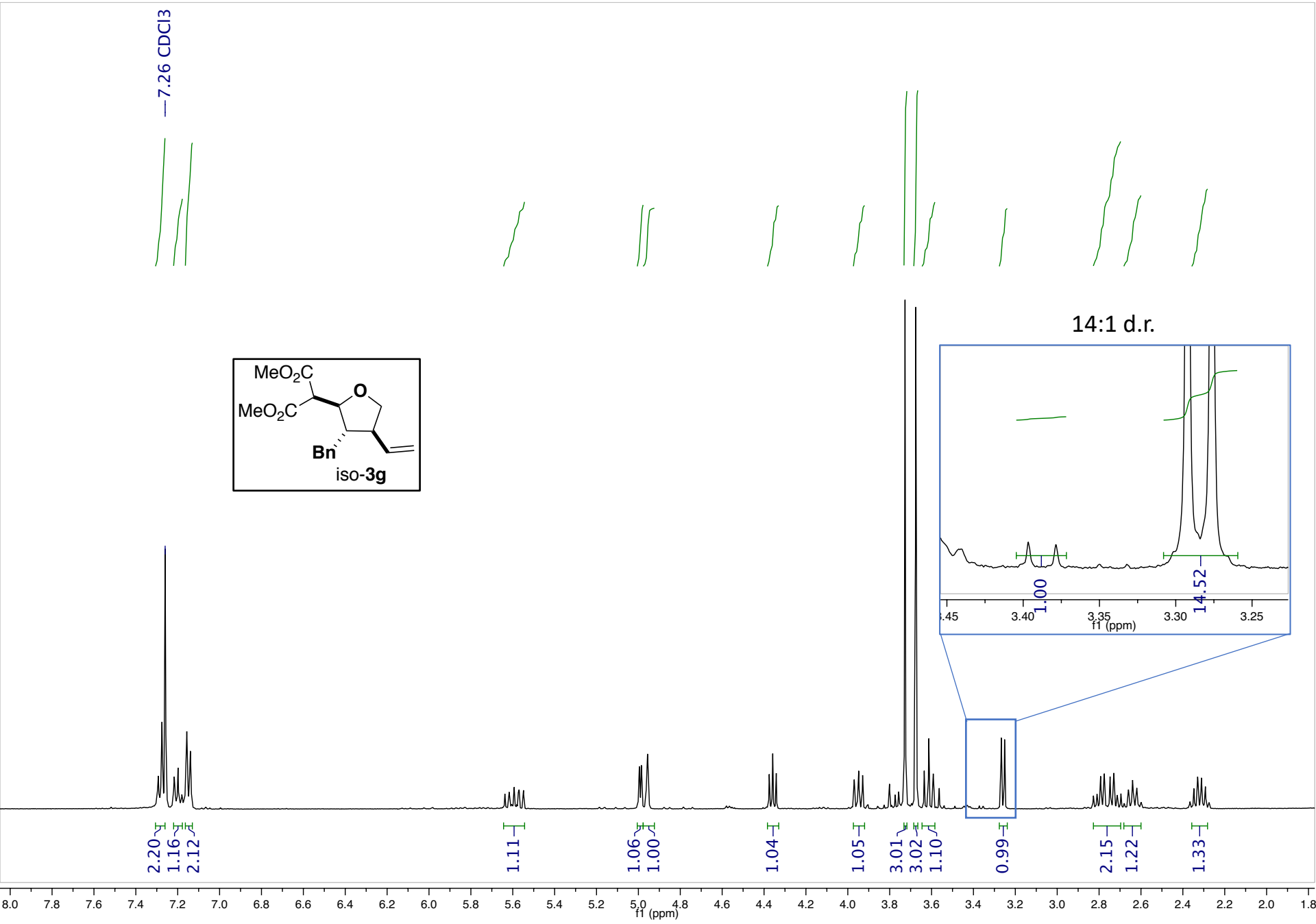

144.00
134.62
129.83
128.24
126.93
118.44
111.88
111.24
80.11
77.16 CDCl3
74.62
53.88
47.07
39.35
28.53
19.86
Diastereomer 1
NC
NC
O
Ph
Me
3f
f1 (ppm)

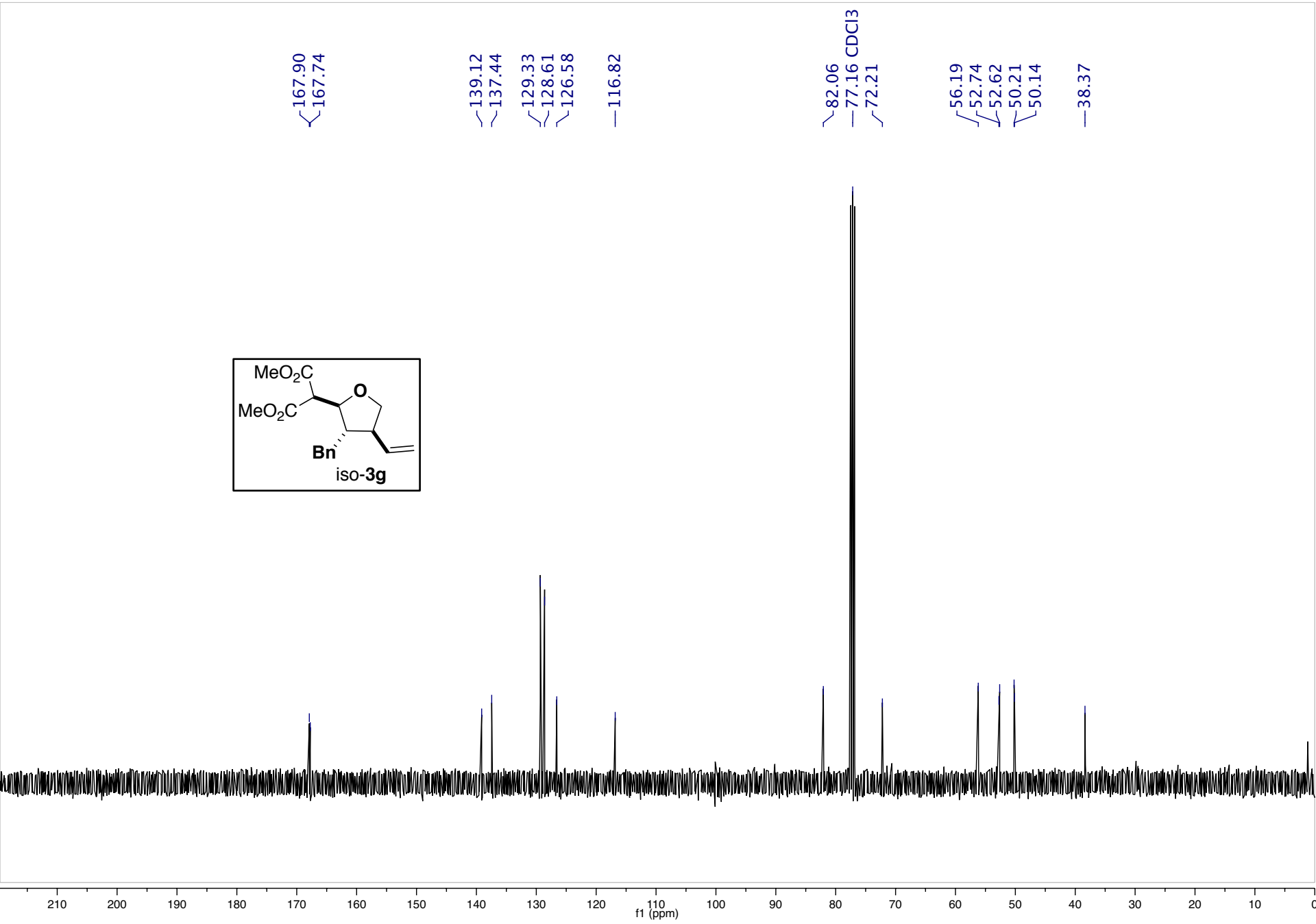

7.26 CDCl3
Diastereomer 2
NC
NC
O
Ph
Me
3f
3.06
2.11
1.10
1.02
1.09
1.00
1.07
1.00
1.00
1.09
1.05
1.10
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

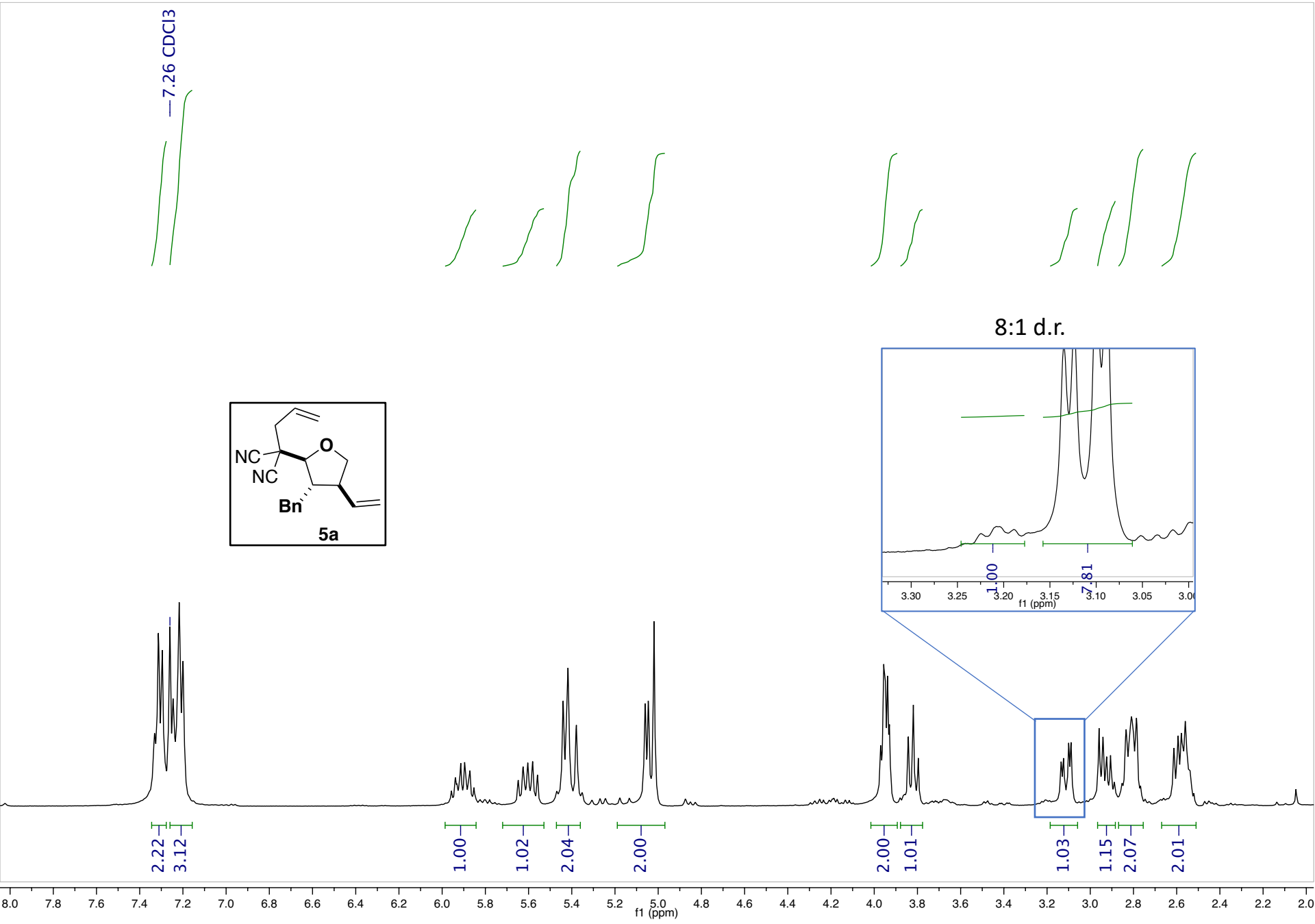

144.15
134.05
128.78
127.16
126.91
118.53
111.62
111.09
79.30
74.38
52.56
46.99
38.56
30.29
21.01
Diastereomer 2
NC
NC
O
Ph
Me
3f
f1 (ppm)

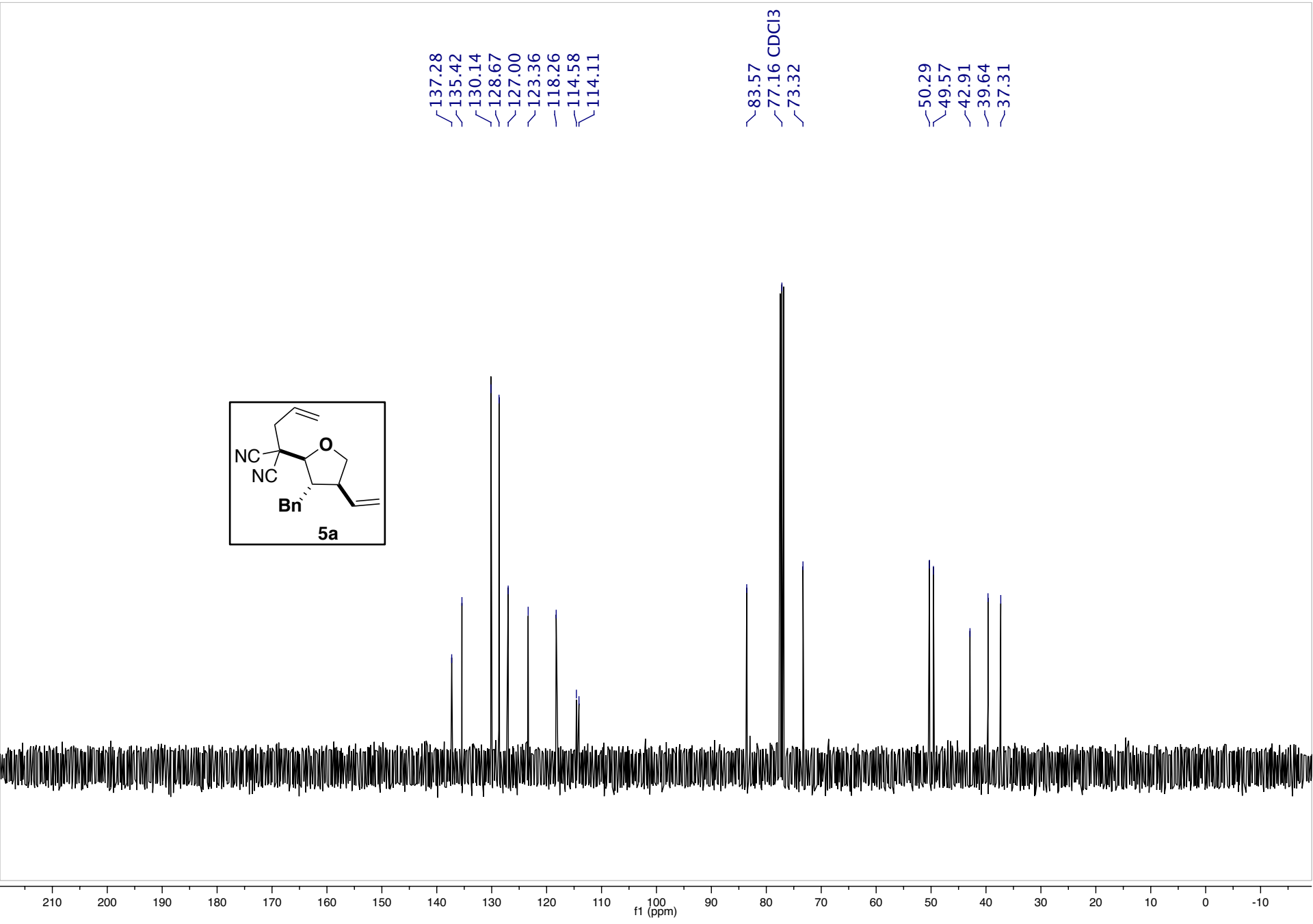

7.26 CDCl3
MeO2C
MeO2C
O
Bn
3g
8:1 d.r.
8.00
1.00
3.40
3.35
3.30
3.25
f1 (ppm)
2.11
1.15
2.01
1.00
0.98
0.99
1.02
1.01
1.13
3.10
2.94
0.94
0.97
1.14
0.99
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

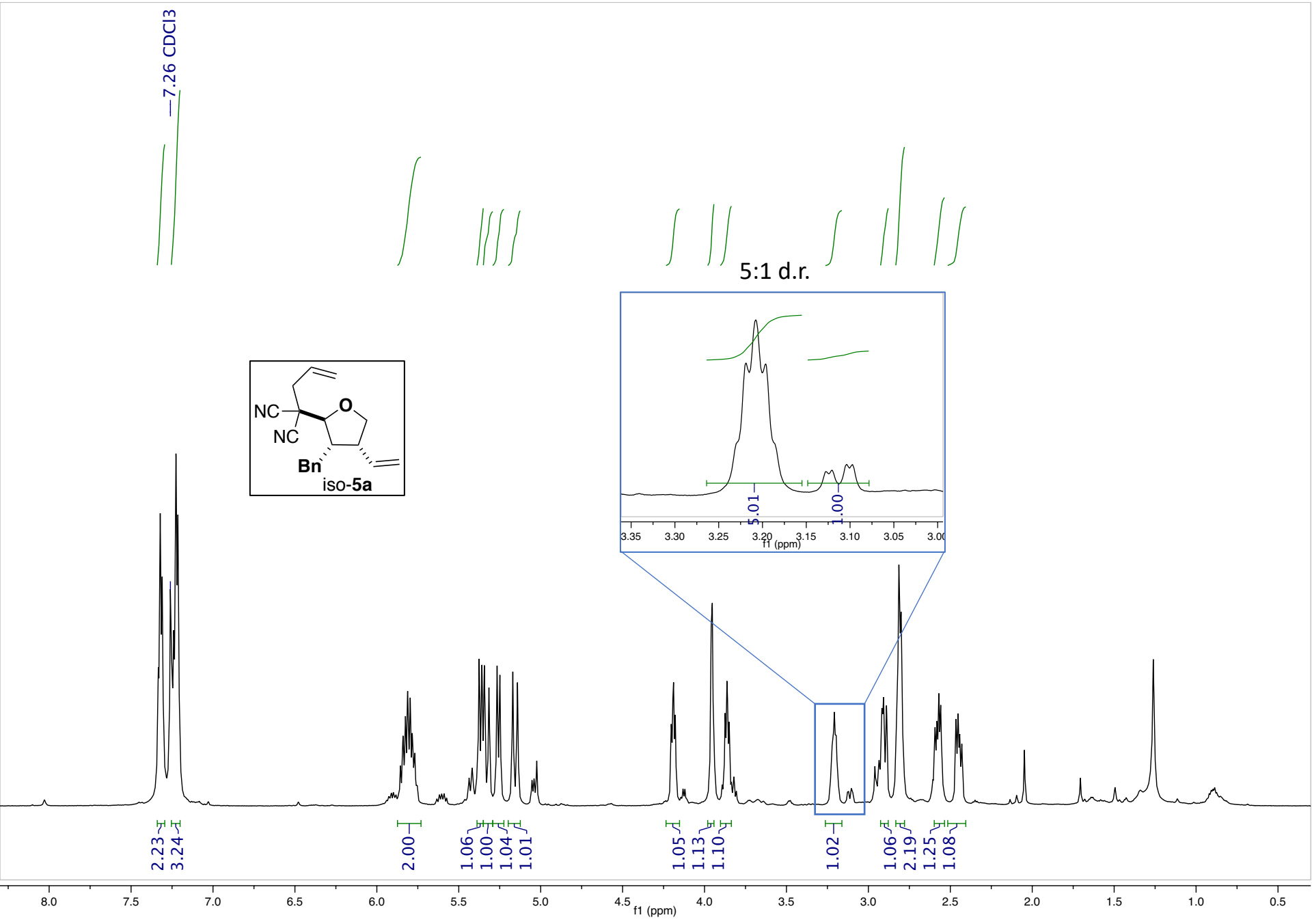

167.73
167.53
139.92
135.37
129.11
128.60
126.36
117.88
80.75
77.16 CDCl3
72.33
56.70
52.69
52.66
47.97
46.48
34.43
MeO2C
MeO2C
O
Bn
3g
f1 (ppm)

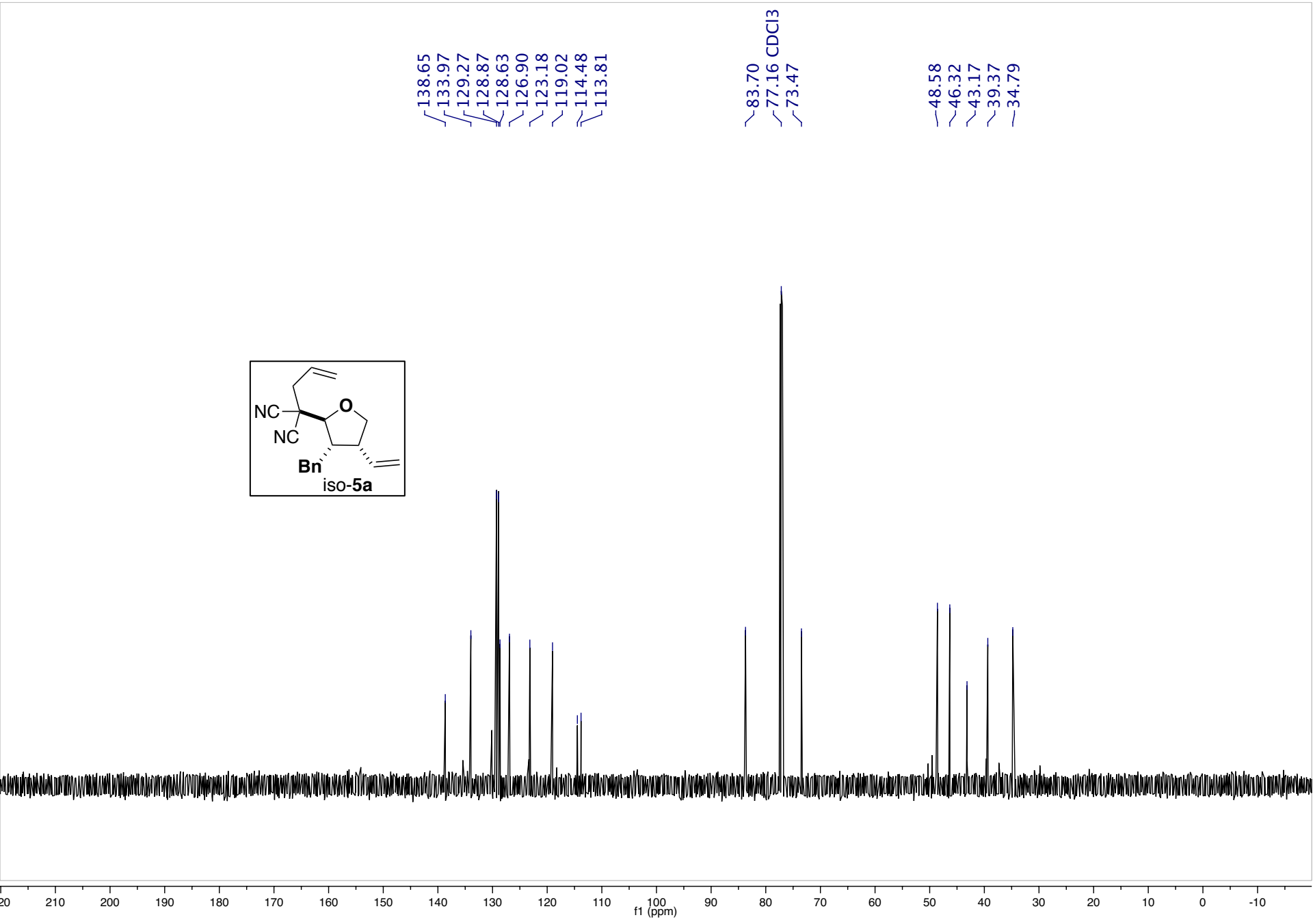

7.26 CDCl3
MeO2C
MeO2C
O
Bn
iso-3g
14:1 d.r.
1.00
14.52
3.45
3.40
3.35
3.30
3.25
f1 (ppm)
2.20
1.16
2.12
1.11
1.06
1.00
1.04
1.05
3.01
3.02
1.10
0.99
2.15
1.22
1.33
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

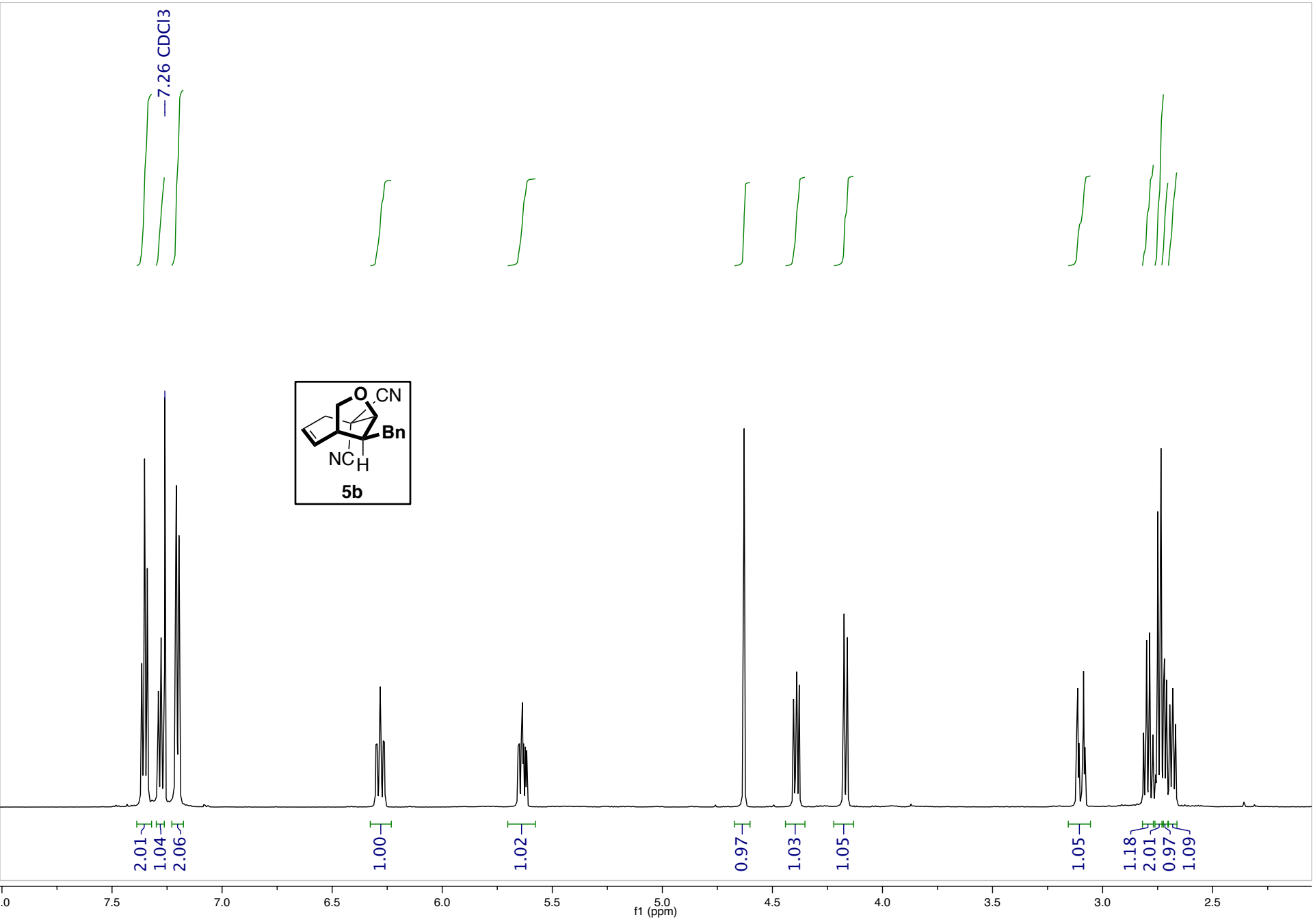

167.90
167.74
139.12
137.44
129.33
128.61
126.58
116.82
82.06
77.16 CDCl3
72.21
56.19
52.74
52.62
50.21
50.14
38.37
MeO2C
MeO2C
O
Bn
iso-3g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

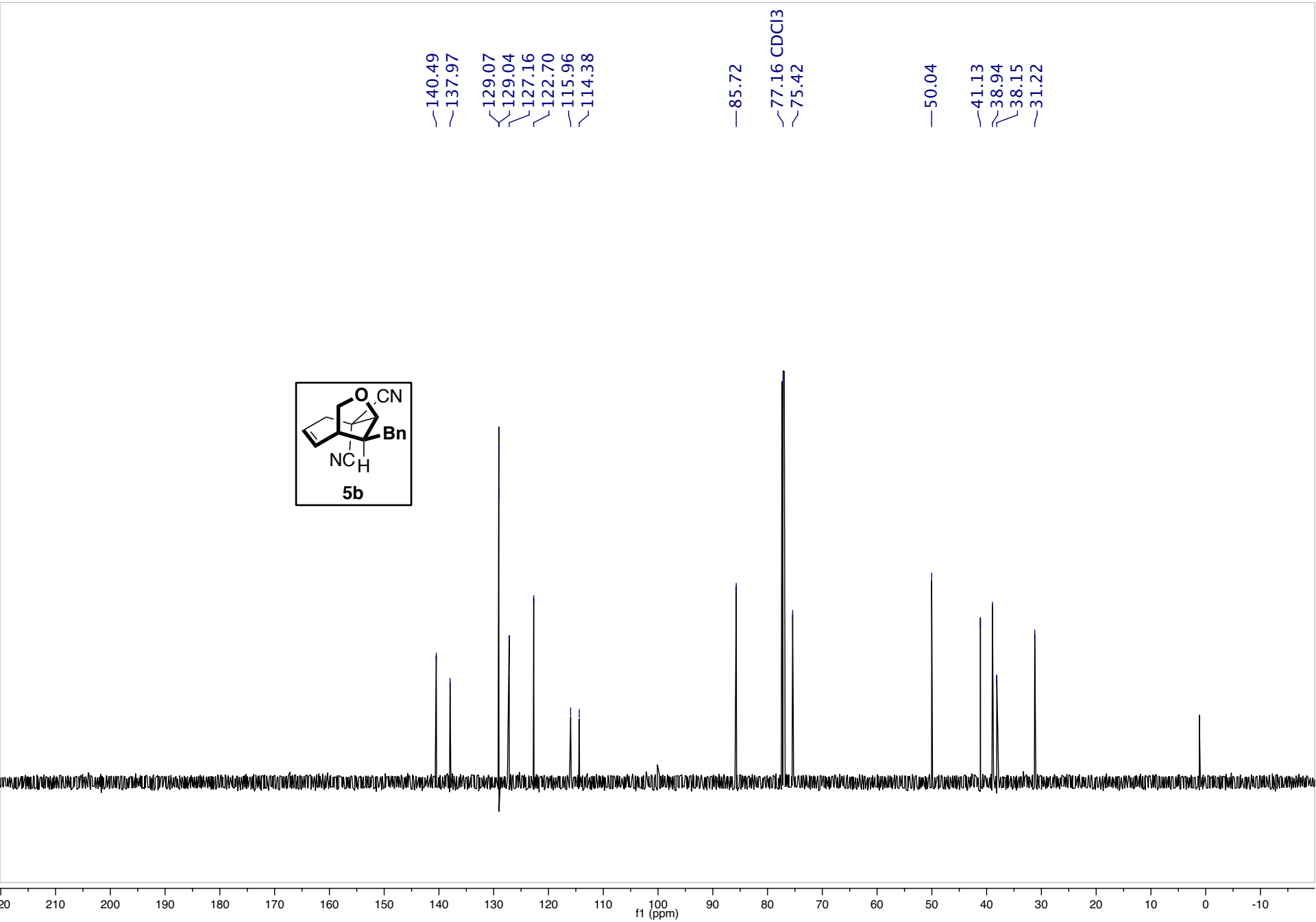

7.26 CDCl3
8:1 d.r.
NC
NC
O
Bn
5a
1.00
7.81
f1 (ppm)
2.22
3.12
1.00
1.02
2.04
2.00
2.00
1.01
1.03
1.15
2.07
2.01
f1 (ppm)

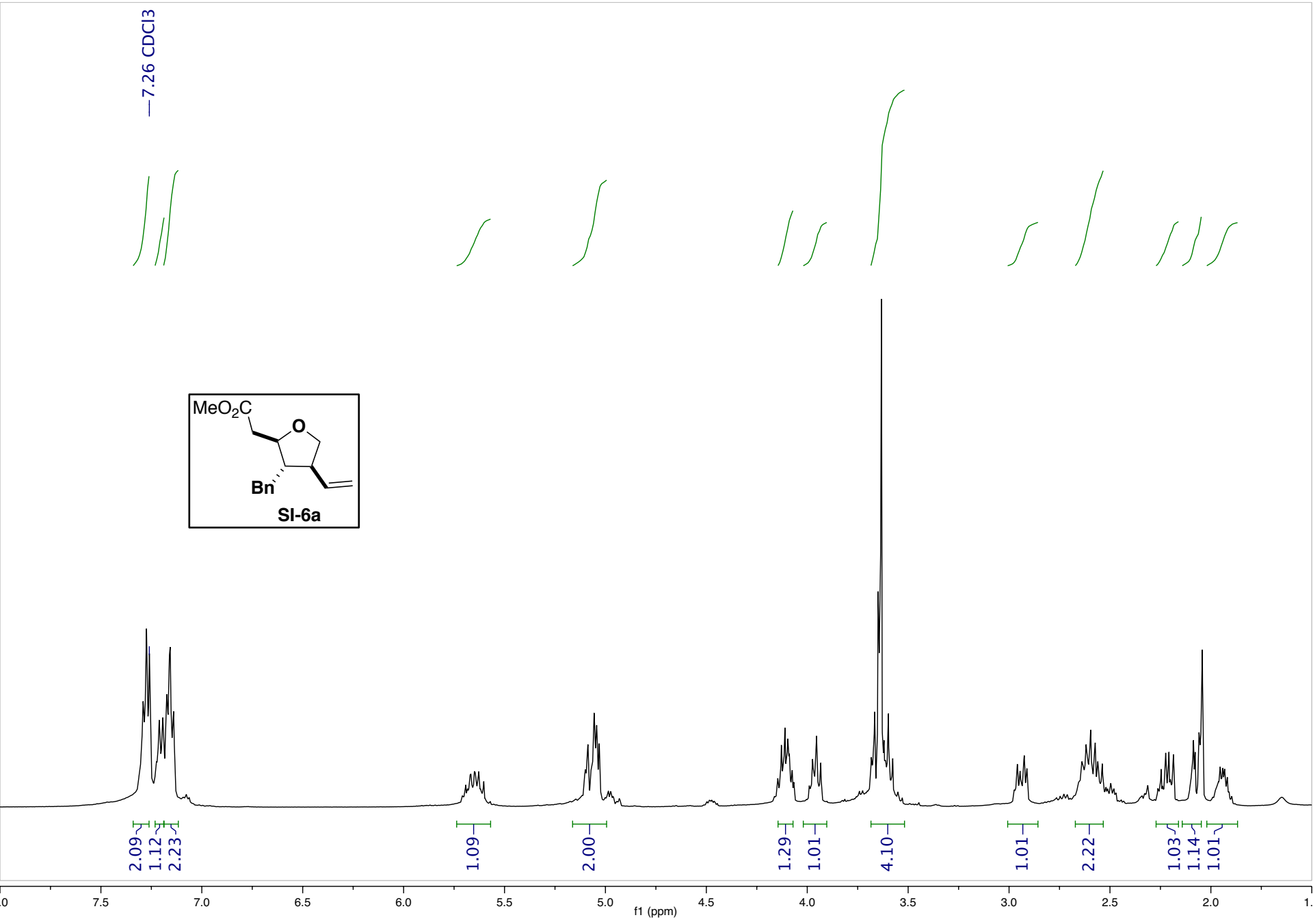

137.28
135.42
130.14
128.67
127.00
123.36
118.26
114.58
114.11
83.57
77.16 CDCl3
73.32
50.29
49.57
42.91
39.64
37.31
NC
NC
O
Bn
5a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

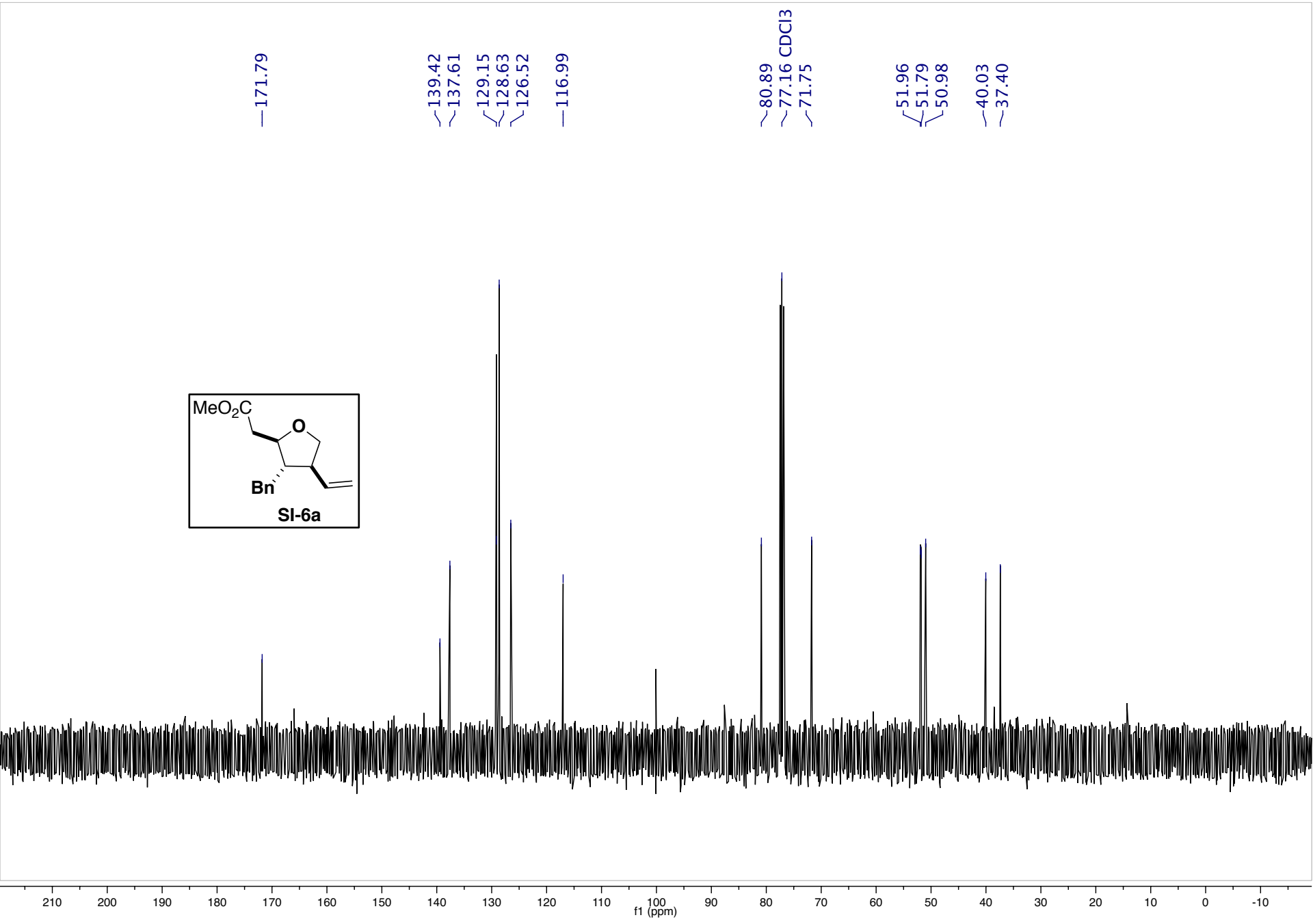

7.26 CDCl3
5:1 d.r.
NC
NC
O
Bn
iso-5a
5.01
1.00
3.35 3.30 3.25 3.20 3.15 3.10 3.05
f1 (ppm)
2.23
3.24
2.00
1.06
1.00
1.04
1.01
1.05
1.13
1.10
1.02
1.06
2.19
1.25
1.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

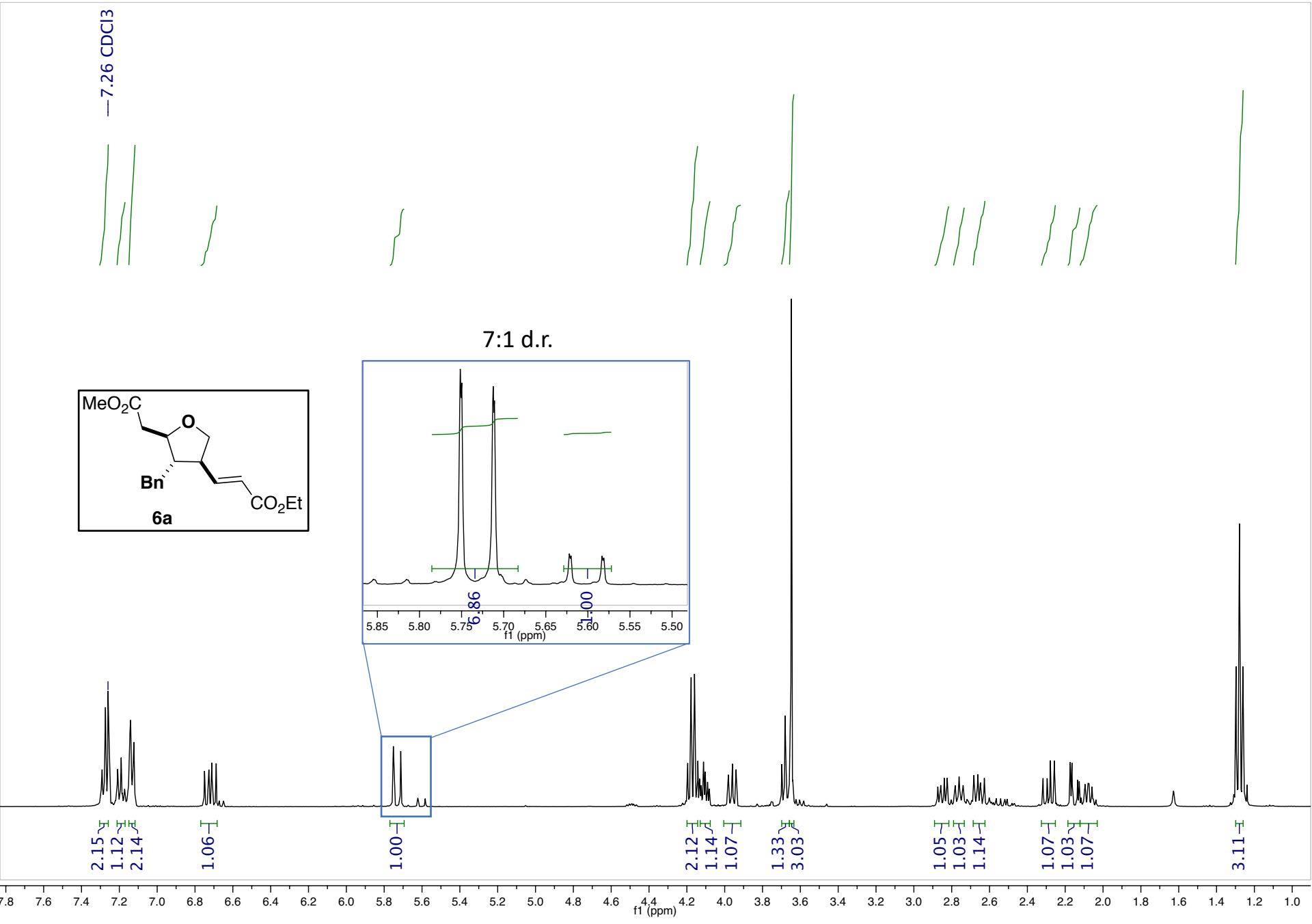

138.65
133.97
129.27
128.87
128.63
126.90
123.18
119.02
114.48
113.81
83.70
77.16 CDCl3
73.47
48.58
46.32
43.17
39.37
34.79
NC
NC
O
Bn
iso-5a
f1 (ppm)

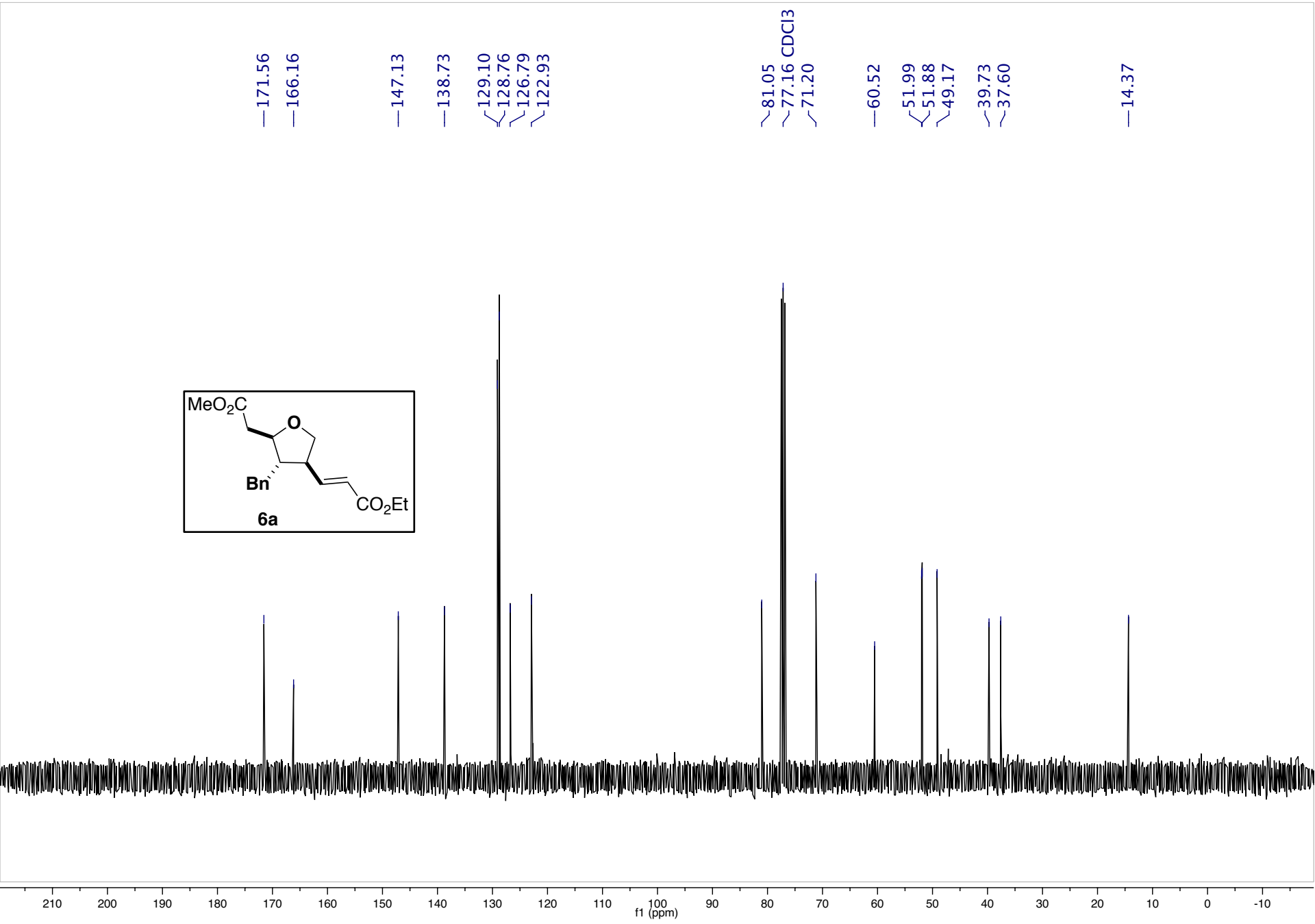

7.26 CDCl3
O
CN
Bn
NC
H
5b
2.01
1.04
2.06
1.00
1.02
0.97
1.03
1.05
1.05
1.18
2.01
0.97
1.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

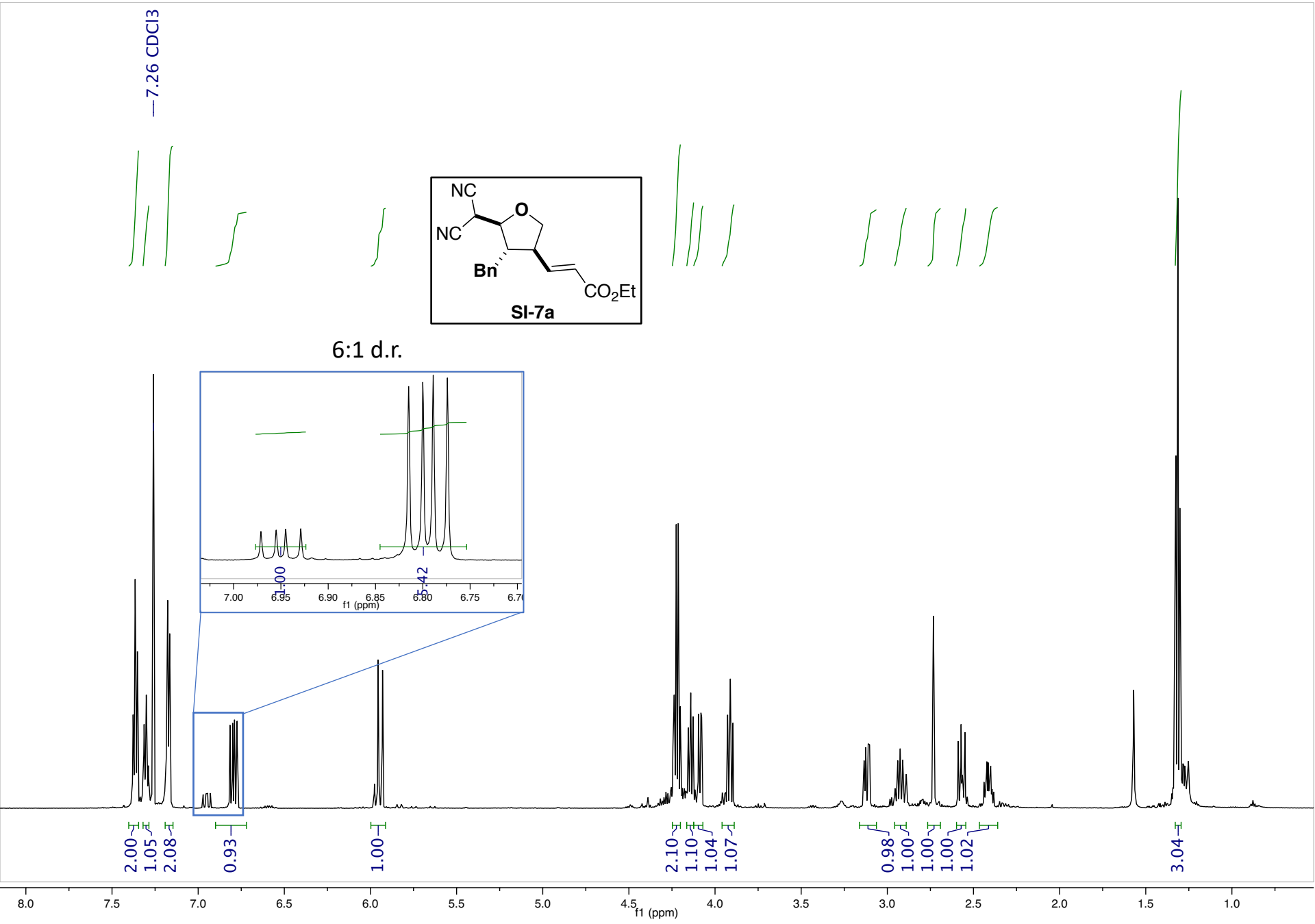

140.49
137.97
129.07
129.04
127.16
122.70
115.96
114.38
85.72
77.16 CDCl3
75.42
50.04
41.13
38.94
38.15
31.22
O
CN
Bn
NC
H
5b
f1 (ppm)

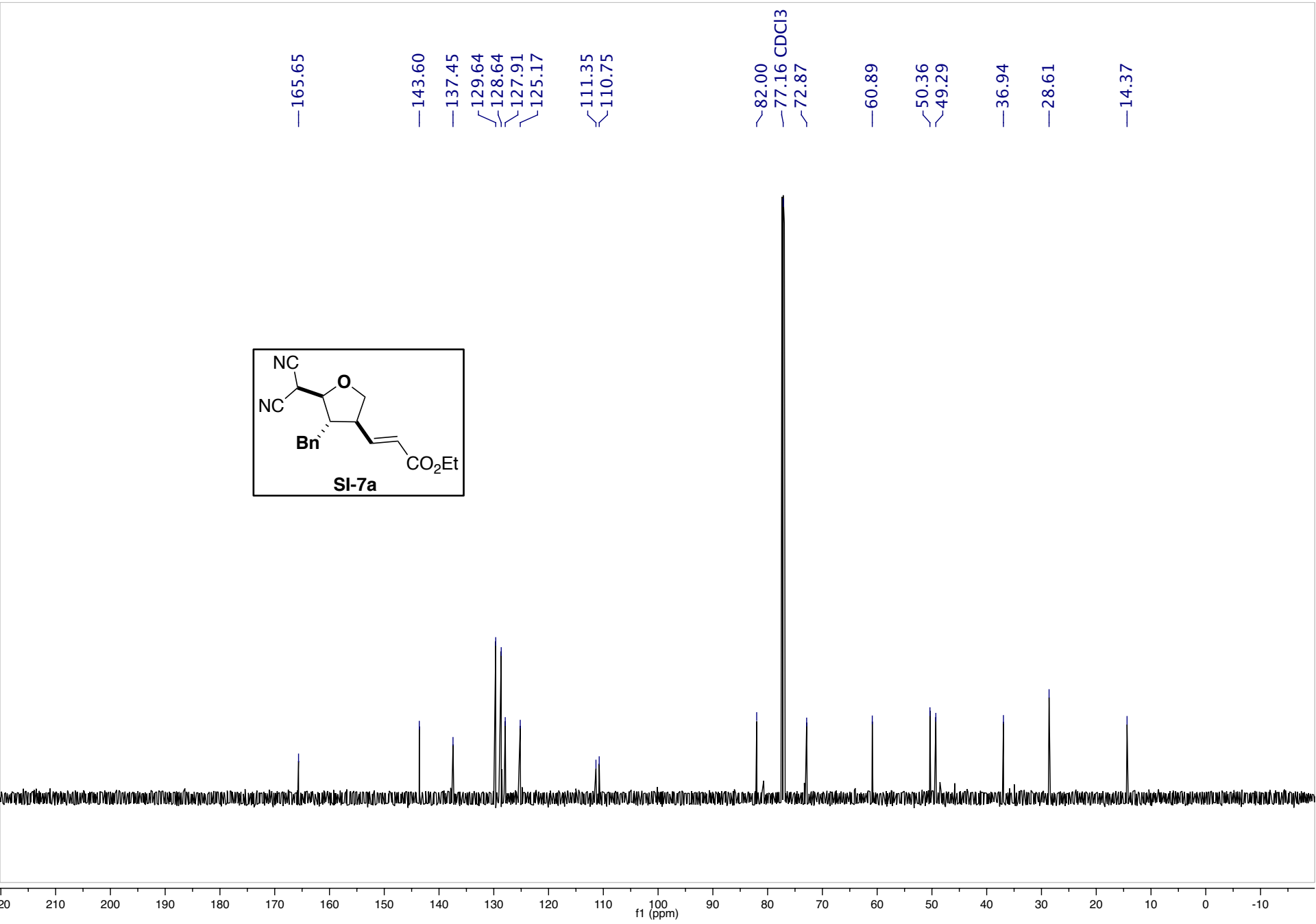

7.26 CDCl3
MeO2C
O
Bn
SI-6a
2.09
1.12
2.23
1.09
2.00
1.29
1.01
4.10
1.01
2.22
1.03
1.14
1.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

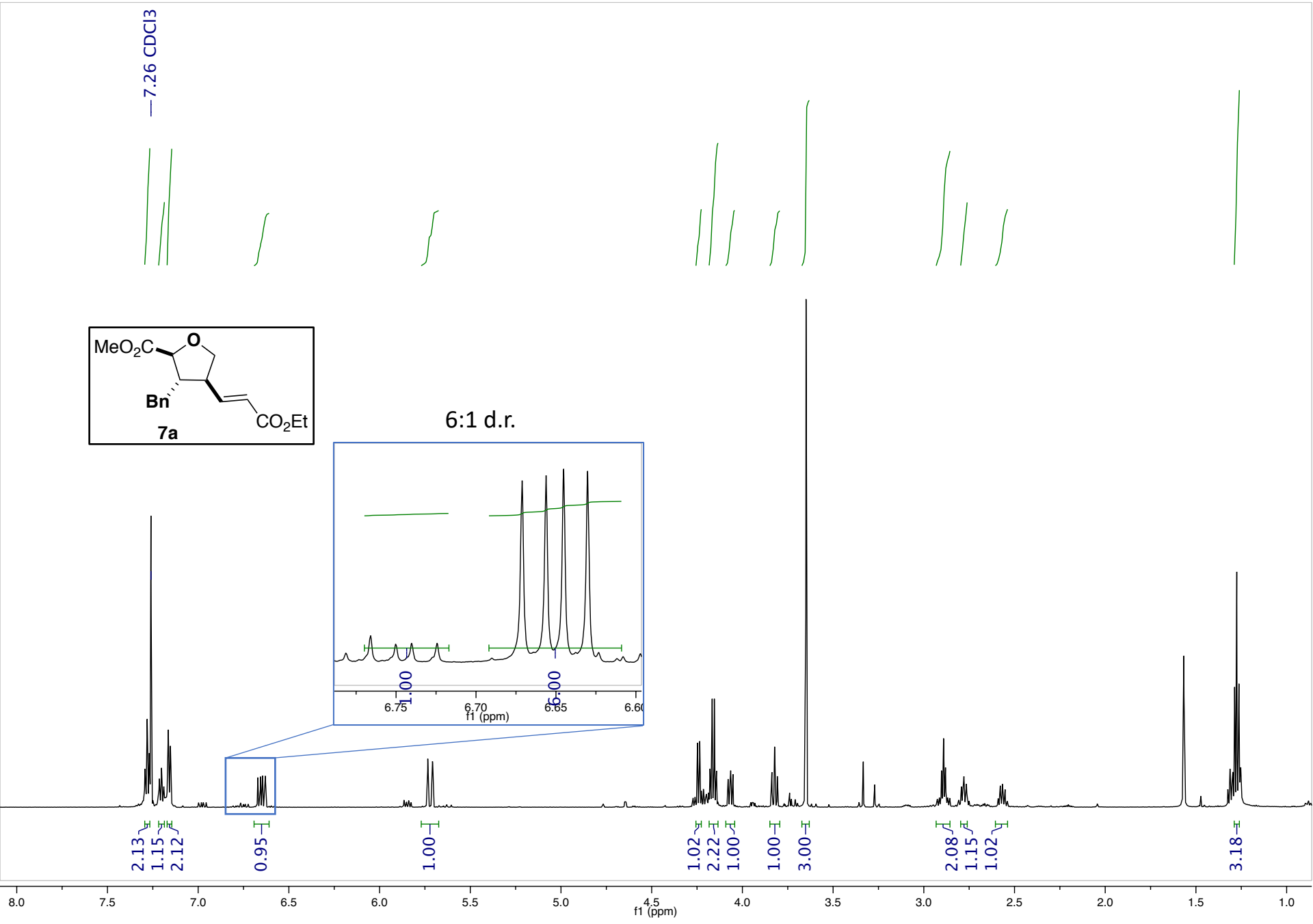

171.79
139.42
137.61
129.15
128.63
126.52
116.99
80.89
77.16 CDCl3
71.75
51.96
51.79
50.98
40.03
37.40
MeO2C
O
Bn
SI-6a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

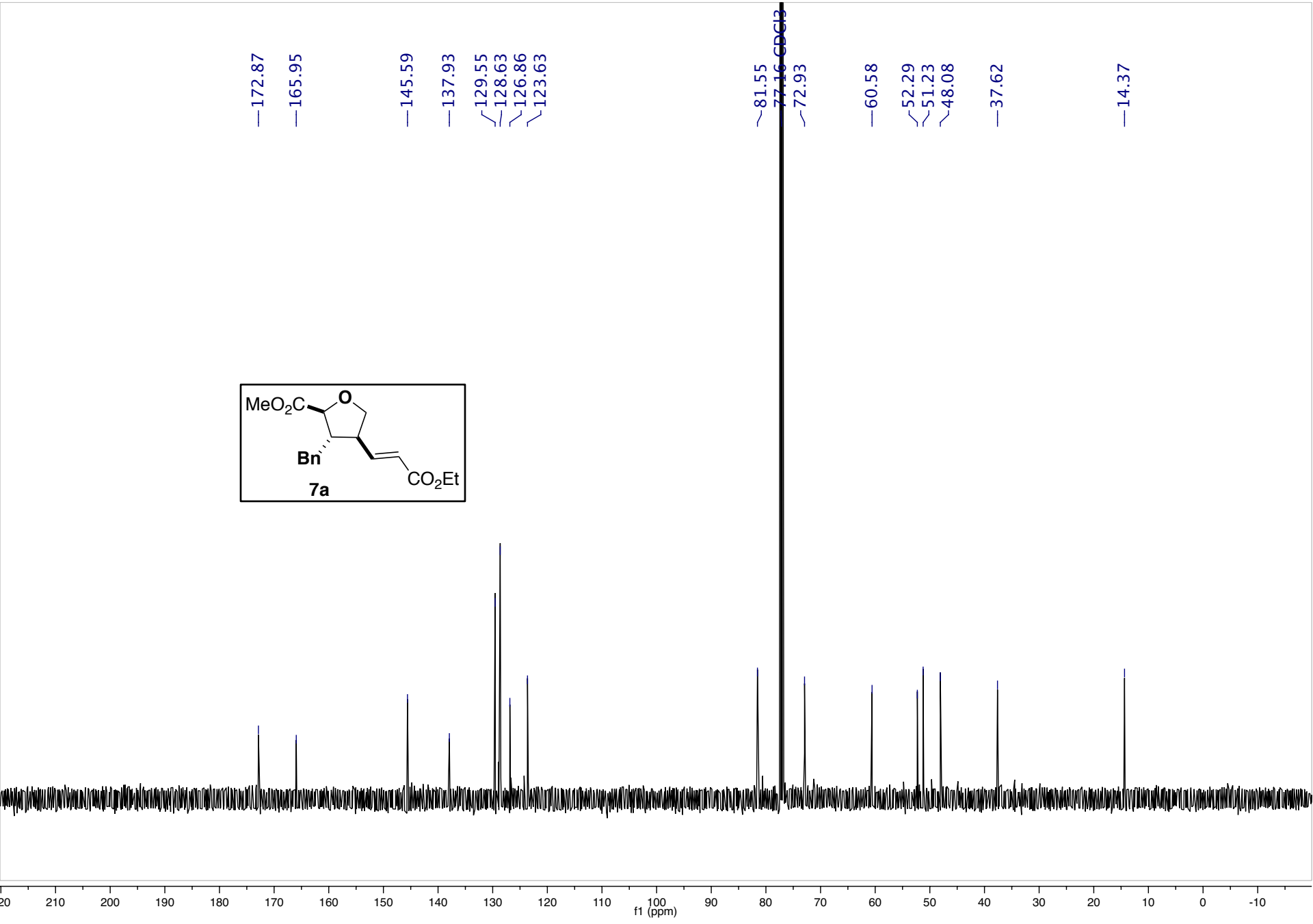

7.26 CDCl3
7:1 d.r.
MeO2C
O
Bn
CO2Et
6a
6.86
1.00
5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50
f1 (ppm)
2.15 1.12 2.14 1.06 1.00 2.12 1.14 1.07 1.33 3.03 1.05 1.03 1.14 1.07 1.03 1.07 3.11
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)

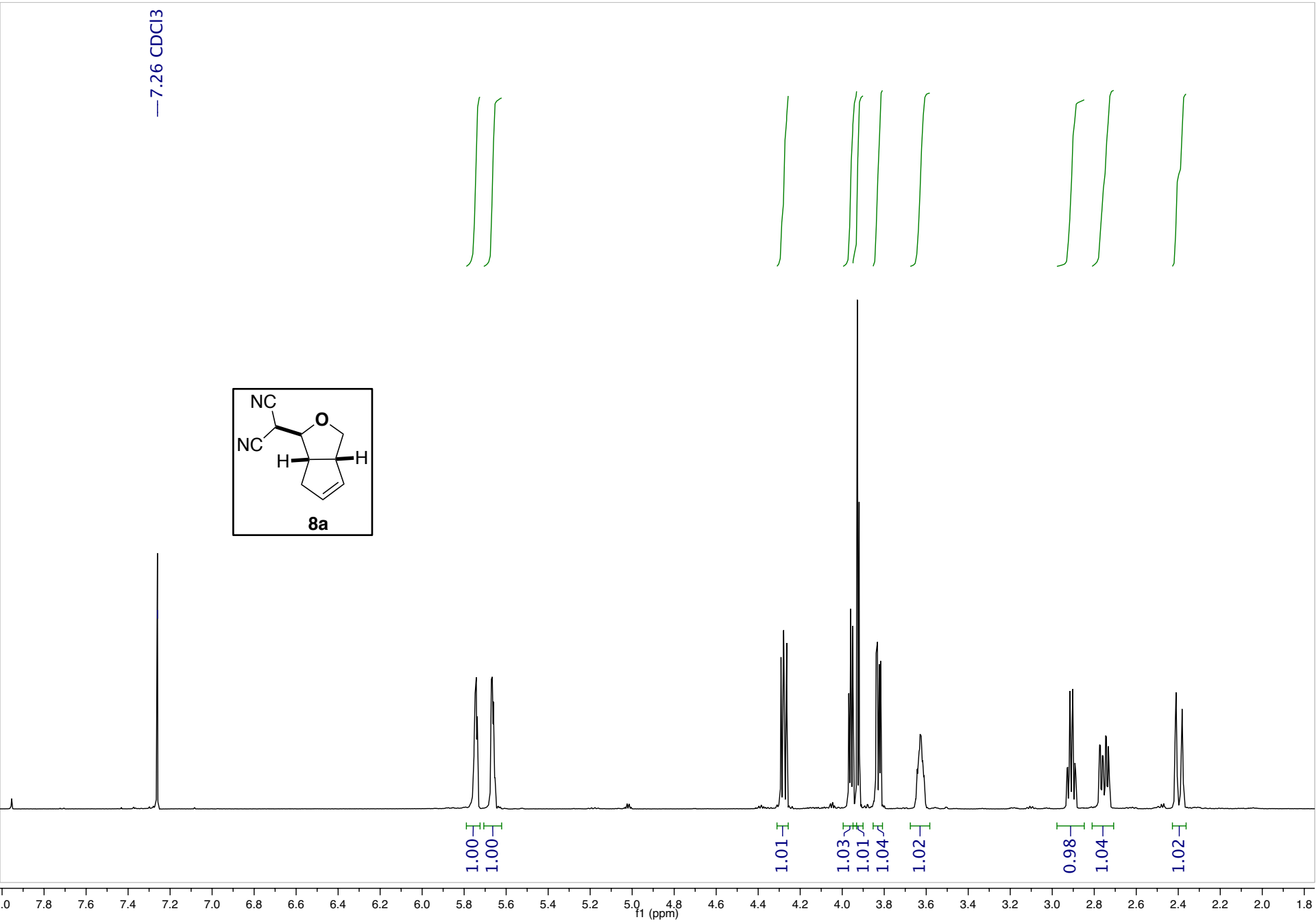

171.56
166.16
147.13
138.73
129.10
128.76
126.79
122.93
81.05
77.16 CDCl3
71.20
60.52
51.99
51.88
49.17
39.73
37.60
14.37
MeO2C
O
Bn
CO2Et
6a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

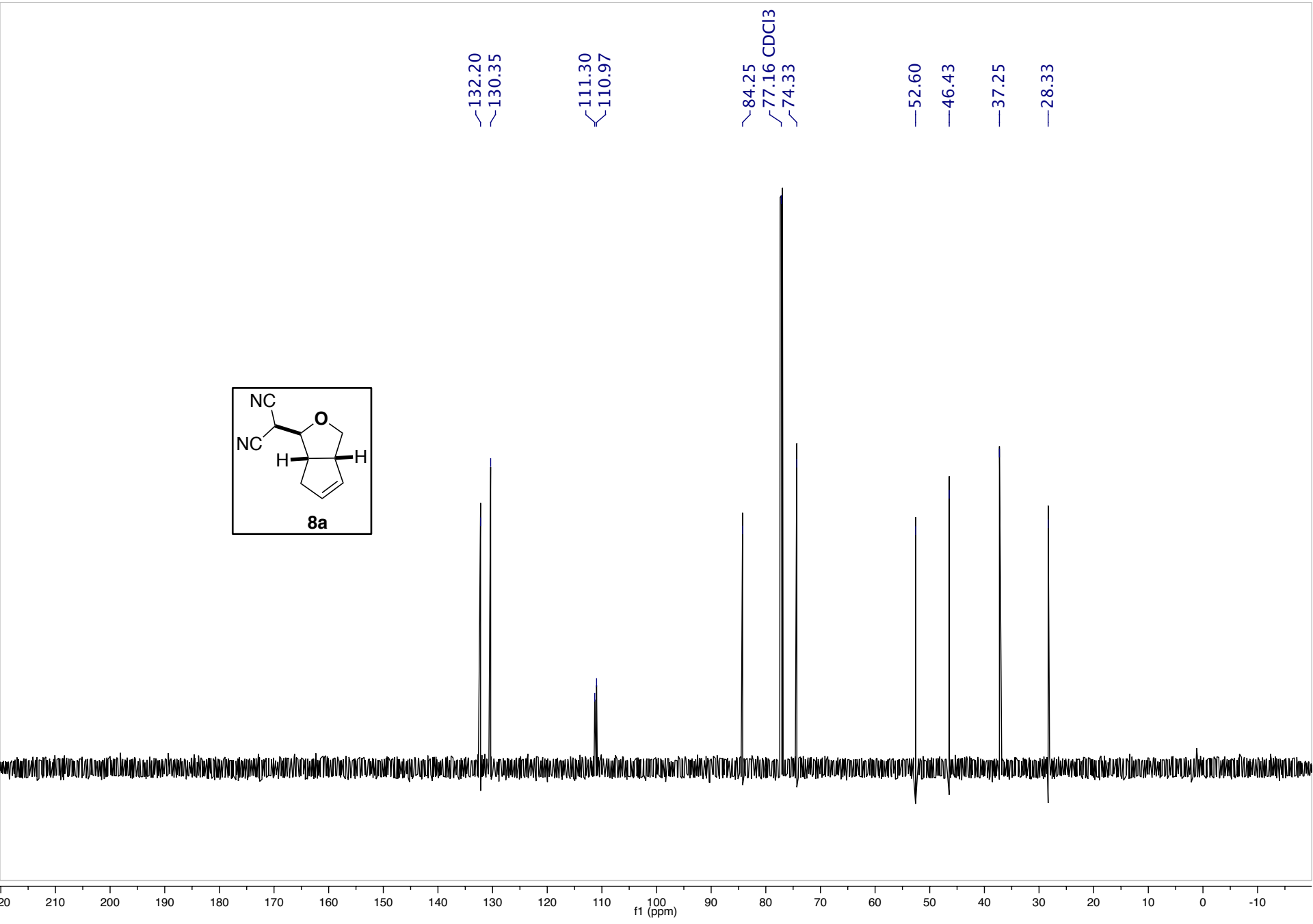

7.26 CDCl3
NC
NC
O
Bn
CO2Et
SI-7a
6:1 d.r.
1.00
5.42
f1 (ppm)
2.00
1.05
2.08
0.93
1.00
2.10
1.10
1.04
1.07
0.98
1.00
1.00
1.00
1.02
3.04
f1 (ppm)

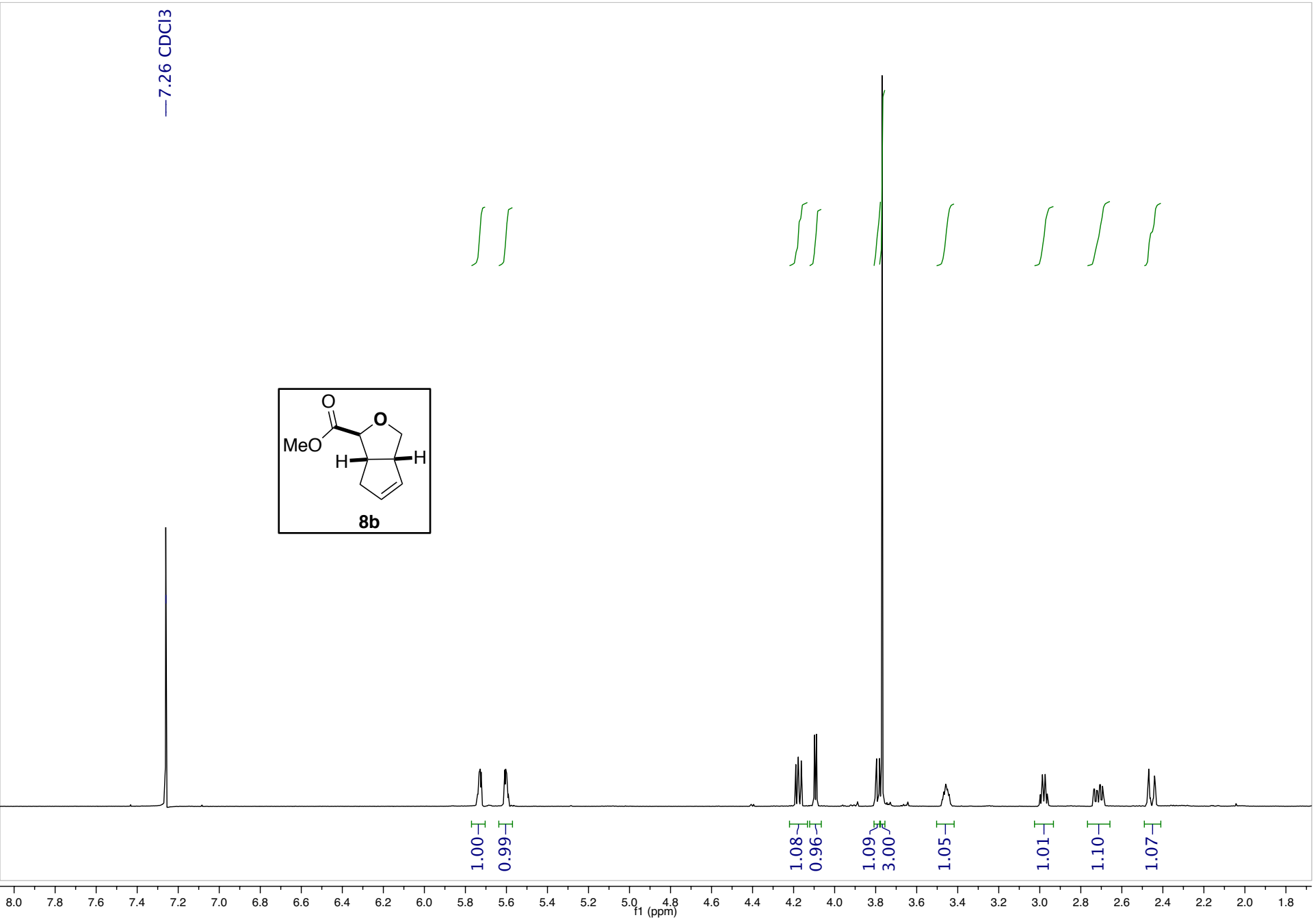

165.65
143.60
137.45
129.64
128.64
127.91
125.17
111.35
110.75
82.00
77.16 CDCl3
72.87
60.89
50.36
49.29
36.94
28.61
14.37
NC
NC
O
Bn
CO2Et
SI-7a
f1 (ppm)

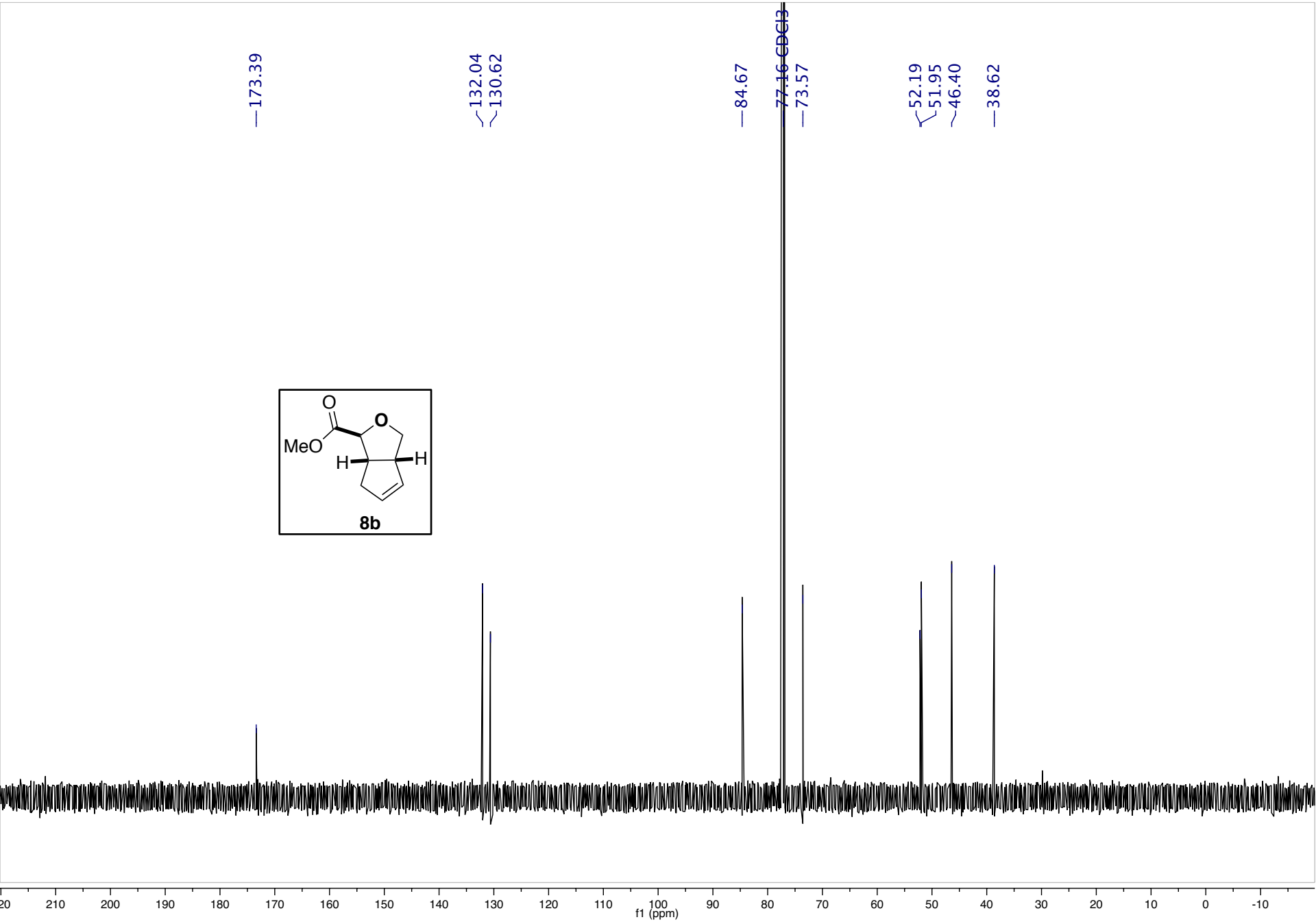

7.26 CDCl3
MeO2C
O
Bn
CO2Et
7a
6:1 d.r.
1.00
6.00
6.75
6.70
6.65
f1 (ppm)
2.13
1.15
2.12
0.95
1.00
1.02
2.22
1.00
1.00
3.00
2.08
1.15
1.02
3.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


172.87
165.95
145.59
137.93
129.55
128.63
126.86
123.63
81.55
77.16 CDCl3
72.93
60.58
52.29
51.23
48.08
37.62
14.37
MeO2C
O
Bn
CO2Et
7a
f1 (ppm)


7.26 CDCl3
NC
NC
O
H
H
8a
1.00
1.00
1.01
1.03
1.01
1.04
1.02
0.98
1.04
1.02
f1 (ppm)


132.20
130.35
111.30
110.97
84.25
77.16 CDCl3
74.33
52.60
46.43
37.25
28.33
NC
NC
O
H
H
8a
f1 (ppm)


7.26 CDCl3
O
O
MeO
H
H
8b
1.00
0.99
1.08
0.96
1.09
3.00
1.05
1.01
1.10
1.07
f1 (ppm)


173.39
132.04
130.62
84.67
77.16 CDCl3
73.57
52.19
51.95
46.40
38.62
O
O
MeO
H
H
8b
f1 (ppm)