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Synthesis of Coupling Substrates for Use in a Highly Enantioselective Conjugated Triene Cyclization Enabled by a Chiral N-Heterocyclic Carbene

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SYNTHESIS OF COUPLING SUBSTRATES FOR USE IN A HIGHLY ENANTIOSELECTIVE CONJUGATED TRIENE CYCLIZATION ENABLED BY A CHIRAL *N*-HETEROCYCLIC CARBENE

by

CHRISTOPHER A. TOTH

Under the Direction of Professor Hao Xu

ABSTRACT

The ability to generate chiral building blocks is of paramount importance to organic chemists. This problem presents itself most notably at the interface of chemistry and biology, where molecules of only a single enantiomer can induce function to many biological systems. In this context, recent developments in the field of organocatalysis, most notably the employment of chiral *N*-heterocyclic carbenes (NHCs) have shown much promise.

Our group has recently shown that one possible chiral NHC catalyzed Stetter cyclization product of a conjugated triene, a highly functionalized cyclopentenone, contains both a chiral center and an adjacent conjugated diene. This structure can be easily elaborated to a bicyclic structural motif present in some biologically active natural products from the ginkgolide family, and is difficult to access by other means. The synthesis of novel vinyl stannanes and other coupling substrates involved in the development of the aforementioned reaction discovery are described in this report.

INDEX WORDS: Asymmetric catalysis, N-heterocyclic carbene, Synthesis, Triene, Enantioselective, Intramolecular stetter reaction

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

in the College of Arts and Sciences

Georgia State University

2012

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May 2012

DEDICATION

I would like to dedicate this work to my loving father and mother, Glenn and Jean Toth. They encouraged me to pursue an education in something that I truly enjoy, without this I would not be where I am today.

ACKNOWLEDGEMENTS

I would like to first acknowledge Professor Hao Xu, for mentoring me and giving me the opportunity to work successfully in his laboratory. I would also like to acknowledge Dr. Guansai Liu for his helpful guidance over the past two years, and Phillip Wilkerson for being an excellent friend and co-worker.

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1. INTRODUCTION (LITERATURE OVERVIEW)

1.1 Carbenes in Organocatalysis

The demand for catalytic methods to effect efficient chemical transformations cannot be understated. Catalysis offers reduction in waste and expense via sub-stoichiometric amounts of reagents. In comparison to the expensive transition metal catalysts pioneered in the early 1970's, organocatalytic methods have received an enormous amount of attention in recent years.[1] These methods have been shown to be highly efficient for the carbon-carbon bond formations that play such an important role in modern organic syntheses. In addition, organocatalyic processes are environmentally friendly, selective and easy to use. In this context, much effort has been taken to mimic the seemingly effortless methods by which natural biochemical processes occur. One particularly pertinent example, the coenzyme thiamine (vitamin B_1), utilizes a nucleophilic carbene as its active species (Figure 1).[2]

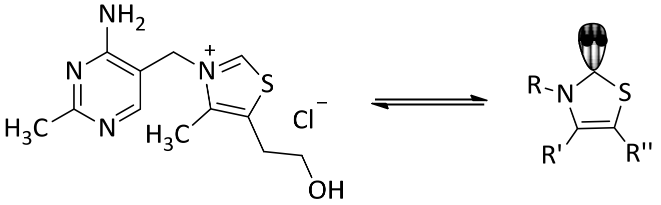


Figure 1. Structure of thiamine (left) and a general carbene species (right)

Carbenes are the most investigated reactive species in the field of organic chemistry.[1] These neutral species contain a bivalent carbon atom with only six valence electrons (Figure 1). As a consequence of these unique characteristics, many carbenes are highly reactive. Evidence for their existence was first discovered by Buchner and Curtis in the late 19th century.[3] It was not until the late

1980's that Bertrand and co-workers isolated and characterized the first stable carbene.[4] This was followed closely by Arduengo *et al.* in their isolation of a kinetically and thermodynamically stable N-heterocyclic carbene based on the imidazole moiety (Figure 2).[5]

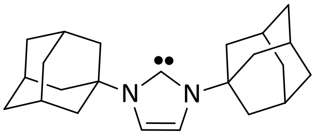
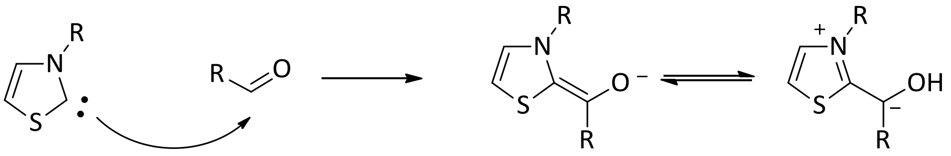


Figure 2. First stable crystalline carbene prepared by Arduengo et al.

Even before the isolation of the first persistent carbene, thiazolium salts had been known to catalyze the condensation of benzaldehyde to benzoin products.[6] The *umpolung* or polarity reversed reactivity of aldehydes promoted by a carbene intermediate was proposed by Breslow in 1958.[7]

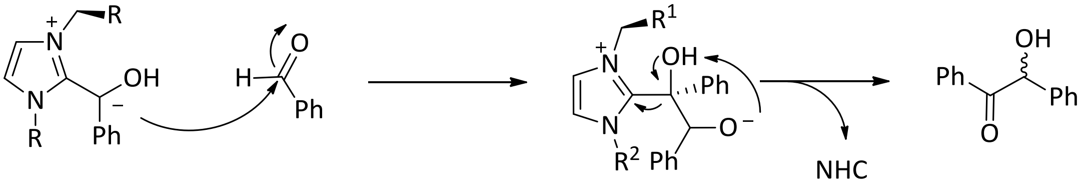
Scheme 1



Breslow Intermediate

Attack of the nucleophilic carbene on the carbonyl carbon, generates an acyl-anion equivalent (Scheme 1). This nucleophilic species (Breslow Intermediate) inverts the normal reactivity of the aldehyde. This subsequently promotes nucleophilic attack on an electrophilic species, another equivalent of benzaldehyde (Scheme 2). The generation of the 1,2 addition product, an α-hydroxyketone, also creates a new stereogenic center.

Scheme 2



In an effort to generate an asymmetric product by this method, an array of novel chiral heterazolium carbene precursors have been used with great success.[8-10] Enders et al. were the first to generate good enantioselectivities for this transformation using their chiral triazolium salt **7** (Figure 3).[8]

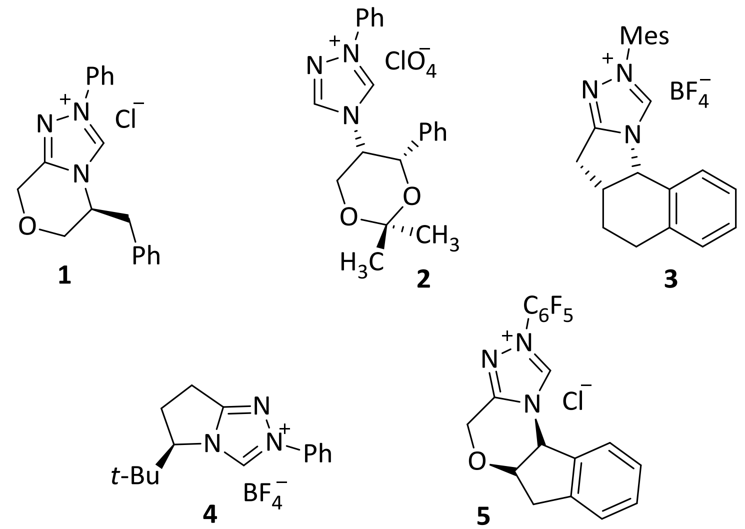


Figure 3. Examples of chiral triazolium carbene precursors

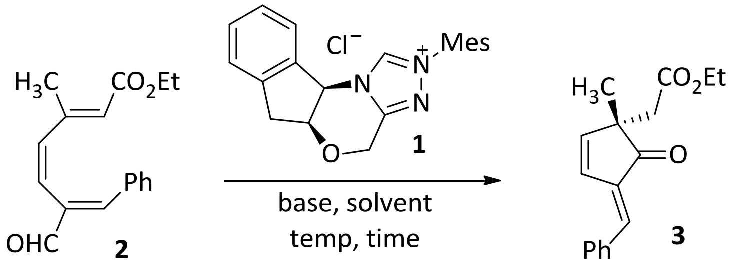
Besides self condensations, *N*-heterocyclic carbenes have been used effectively to catalyze cross condensations between aldehydes and other various electrophiles including aliphatic or aromatic aldehydes[11], ketones[12], imines[13] and even activated double bonds (*Stetter* reaction).[15]

Since its initial discovery in 1976, the *Stetter* reaction has evolved into one of the most important procedures for the synthesis of 1,4-dicarbonyl compounds.[15] This transformation consists of a nucleophile catalyzed conjugate addition of an aldehyde to a Michael accepter such as an enone. The active catalyst is a thiazolium, imidazolium or triazolium salt, which forms a N-heterocyclic carbene *in situ* upon deprotonation (Figure 4). In addition to intermolecular Stetter products, intramolecular 1,4-additions have the ability to form highly functionalized cyclic products.

Enders and co-workers were the first to report an asymmetric variant of the intramolecular *Stetter* reaction using chiral triazolium salts.[16] This facet was later expounded upon most notably by Rovis *et al.*, in their design and functional assessment of polycyclic pyrrolidine and aminoindanol-derived triazolium salts.[17] He successfully showed in subsequent reports that these catalyst frameworks were versatile and suitable for a variety of other asymmetric Stetter-type transformations.[18] The aforementioned catalysts of type **4** and **5** (Figure 3) have proved exceptional in generating some products in excellent enantioselectivies. The multiple applications of these privileged NHC's has prompted much investigation in the scientific community and consequently the number of asymmetric transformations mediated by *N*-heterocyclic carbenes is growing by the day.[19]

1.2 Discovery of a Novel Asymmetric Stetter Cyclization

Our group was initially interested in solving an elusive problem faced by synthetic chemists, the selective catalysis of triene cyclizations. Conjugated trienes can contain many unique functional groups and their cyclic derivatives could prove to be useful synthetic intermediates. Inspired by the results by Rovis involving intramolecular *Stetter* reactions[17-18], we hypothesized that a catalytic amount of chiral NHC could be employed to facilitate an asymmetric triene cyclization provided that the substrates possessed suitable reactivities.



(1)

A preliminary study by Guansai Liu, involving activated triene **2** (Equation 1) showed great promise in converting the acyclic substrate to the corresponding cyclopentenone **3**. This method employed the use of an aminoindanol-derived triazolium salt **1** as catalyst and generated this unique product with high enantioselectivity (>97 % ee). The proposed catalytic cycle is shown in Figure 4.

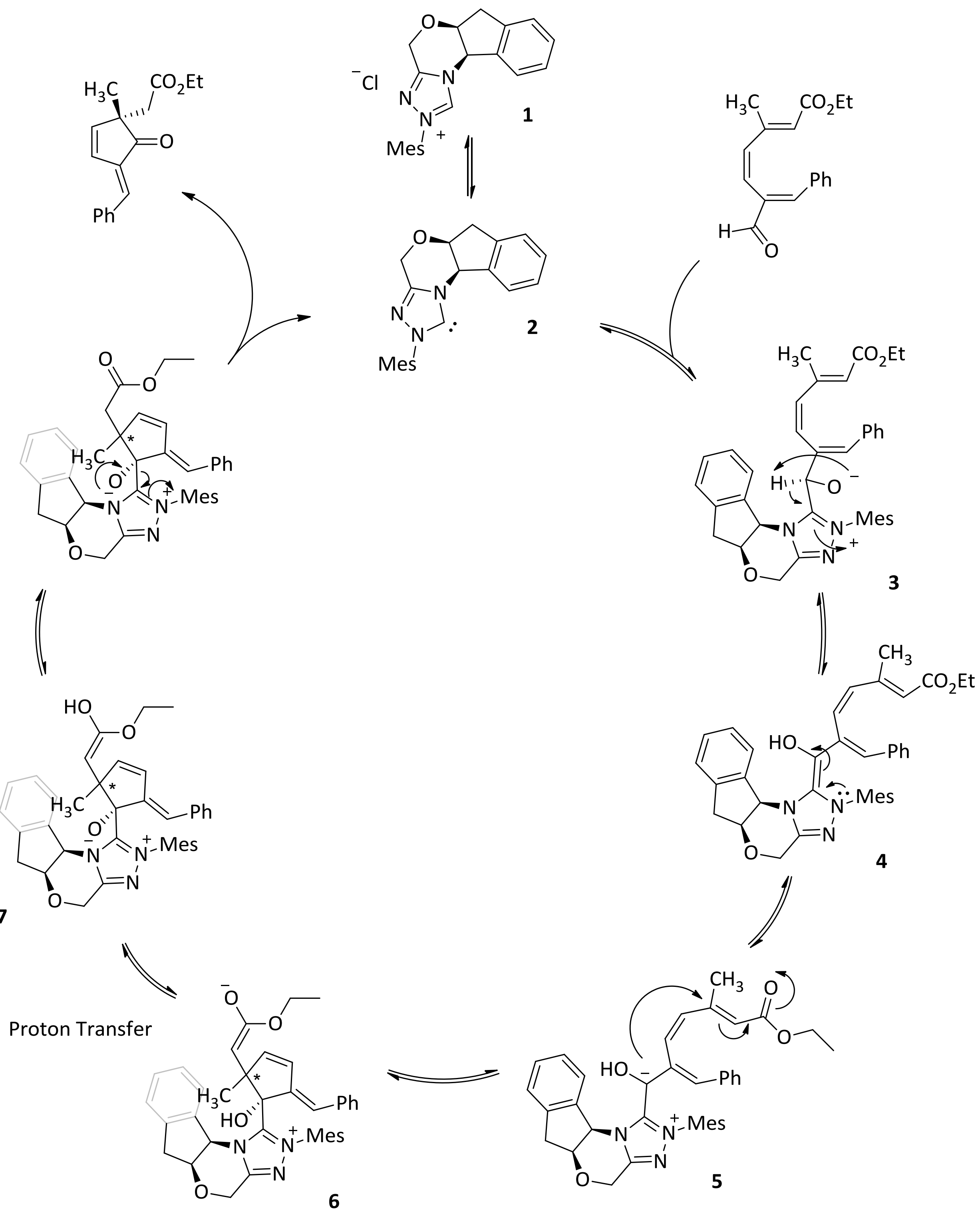
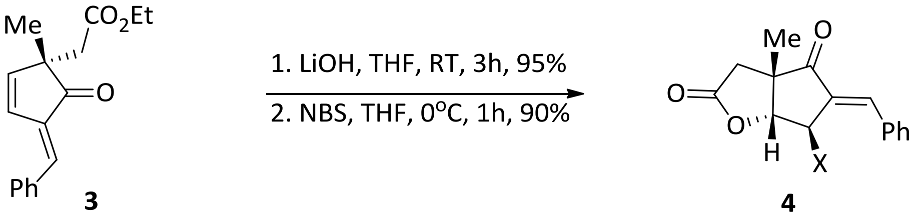


Figure 4. Proposed Catalytic Cycle. Chiral aminoindanol derived triazolium salt **1**, is deprotonated upon addition of base to generate active carbene species **2**. Nucleophilic attack of carbene on aldehyde generates intermediate **3**, followed by proton transfer to form enol **4**. Equilibration with breslow intermediate **5**, forms an acyl-anion, which readily undergoes intramolecular attack on the Michael acceptor to form cyclic intermediate **6**. Intermolecular proton transfer yields species **7**, which readily equilibrates to form **8**, followed by reformation of the carbonyl and release of active catalyst.



(2)

This previously unreported structure contains an enantio-enriched quaternary steriogenic center and an adjacent conjugated diene, thus can be a useful synthetic intermediate for further transformations. The immediate synthetic application of this discovery later became apparent after following a two-step transformation, to deliver enantiopure bicyclic lactone (Equation 2). This bicyclic moiety can be identified in a variety of biologically active natural products in the ginkgolide family.[20]

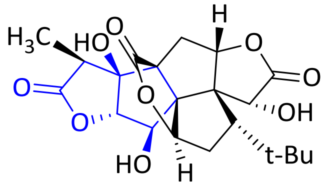


Figure 5. Structure of ginkgolide B

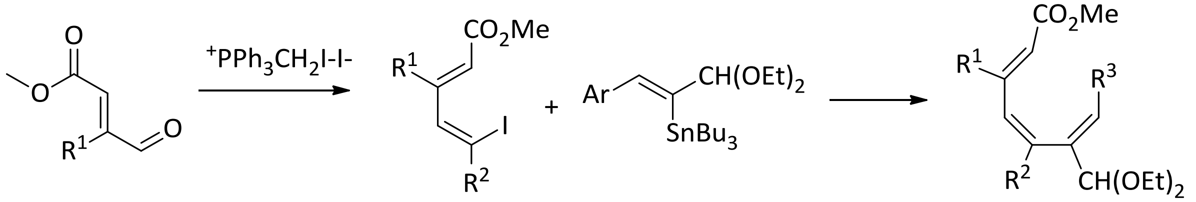
Terpenelactones such as ginkgolide B (Figure 5) have been established as potent PAF receptor antagonists.[21] Platelet-activating factor (PAF) is an important factor for inflammation and a mediator of bronchoconstriction in the body, stressing the value of new synthetic routes towards their structural analogs.[22] In addition, ginkgolide natural products have been shown to inhibit neurotoxicity of amyloid-β plaques that are responsible for Alzheimer's disease.[23] The aforementioned structure **4** is difficult to access by other means (Equation 2). In addition, the enatio-pure bicyclic allylic halides are versatile intermediates for further transformations and may prove useful in future drug discovery and natural product total syntheses.

1.3 Synthesis of Conjugated Trienes

To fully realize the overall scope and relevancy of this reaction discovery, a variety of substrate trienes with different steric and electronic properties were needed. Ideally the product triene would have a formyl group at the 5’-position and a Michael acceptor at the 1’ carbon to direct the *Stetter* cyclization towards its β carbon. It was already known that methyl or ethyl ester would be sufficient to activate the double bond at that position.[24] The incorporation of aliphatic and aromatic substituents positioned along the polyene chain must also be tolerated (Figure 6). The route chosen to procure the desired conjugated trienes was to link them together in a series of coupling reactions.

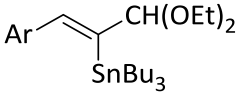
Since the geometry of the conjugated double bonds could play a significant role in the outcome of a successful result, the synthetic steps were designed after procedures known to maximize the yield of select isomers. It was determined that a geometrically defined (2E, 4Z, 6E) hepatriene could be prepared by *Stille* coupling of a vinyl stannane and a (2E, 4Z) vinyl iodide, and formerly the vinyl iodide could be prepared by a *Witteg* reaction from a (2E) vinyl aldehyde and methyltriphenylphosphonium iodide (Scheme 3).

Scheme 3

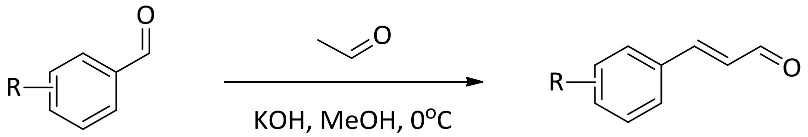


2. SYNTHESIS OF COUPLING SUBSTRATES

2.1 Synthesis of Vinyl Stannanes



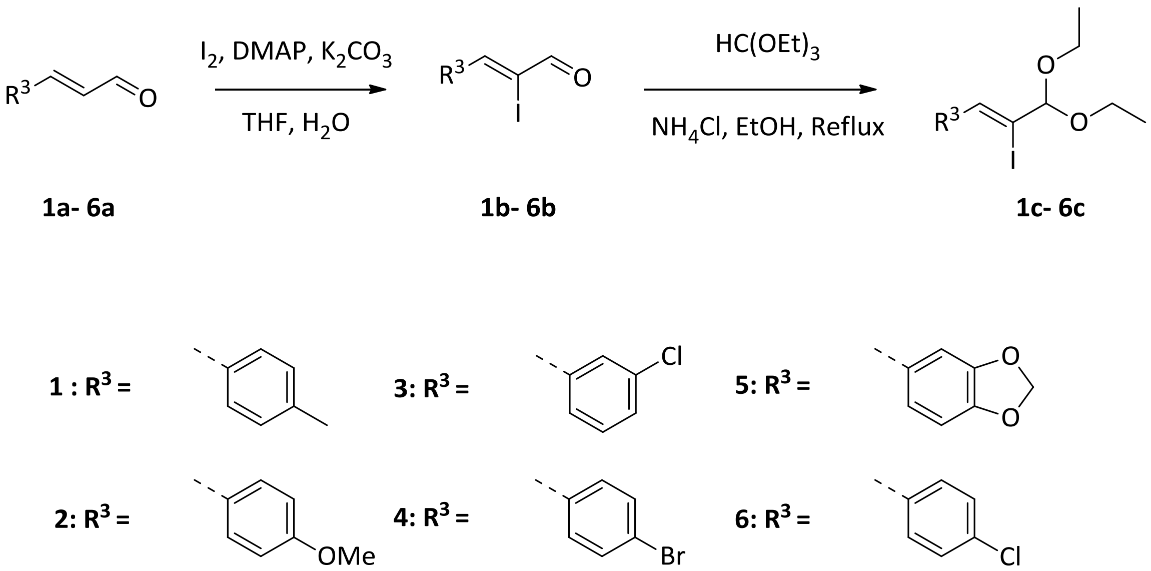
The earliest work focused on procuring of a variety of aryl vinyl stannanes with different electronic properties. When finally coupled to form a conjugated triene, these properties would be used to tune the reactivity and define the overall scope of the asymmetric cyclization reaction. Both electron withdrawing and some moderately donating groups on the aromatic ring were sought after. The starting material moiety was determined by cost factor as derivatives of cinnamaldehyde. Many of these compounds were known and a few were commercially available. Those that were not readily available were synthesized from their corresponding benzaldehyde derivative via Aldol condensation with acetaldehyde in MeOH and strong base such as KOH (Equation 3).



(3)

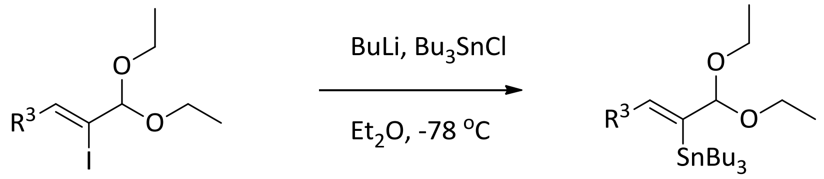
This procedure was adequate for moderately donating groups **1a**, **2a**, and **5a** (Scheme 4) but proved too reactive when applied to substrates with strong electron withdrawing capabilities. A modified procedure was developed to use a slightly weaker base (DBU) and by decreasing the reaction time period. This proved adequate to furnish the desired products **3a**, **4a** and **6a** in acceptable yields.

Scheme 4



The α,β-unsaturated aldehydes **1a-6a** (Scheme 2) were next converted to their corresponding vinyl iodide. Dimethylaminopyridine (DMAP) catalyzed a mild vinylic halogenation in aqueous THF. This procedure proved effective for all the substrates investigated and led to the desired α-iodoaldehydes

1b-6b in moderate yield. A facile acetal protection of compounds **1b-6b** via triethylorthoformate in refluxing EtOH delivered the desired products **1c-6c** in excellent yields. All unreported compounds were fully characterized before use in subsequent steps.

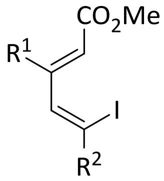


(4)

1c - 6c **1d - 6d**

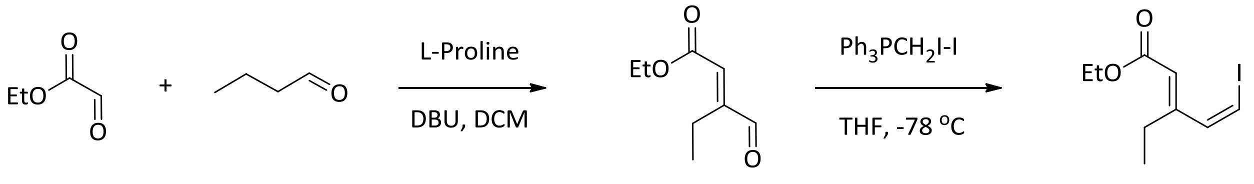
The next step was done concurrently with Jing Huang. Compounds **1c - 6c** were lithiated by n-BuLi to displace iodine, then the corresponding organolithium reagent was used *in situ*. A solution of Bu_3SnCl was added dropwise to the reaction mixture and stirred overnight at -78 °C. Due to their liable nature vinyl stannanes **1d-6d** were not fully purified or characterized, instead the crude coupling substrates were used directly in the Leibskind modified Stille coupling procedure reported by Xu *et al.*[26]

2.2 Synthesis of Vinyl Iodides



This work focused on procuring of a variety of ethyl ester substituted (2E, 4Z) vinyl iodides with different steric and electronic properties. When finally coupled to form a conjugated triene, these functional groups would be used to help tune the reactivity and define the overall scope of the asymmetric cyclization reaction.

Both aliphatic and aromatic 3'- substituted (2E) 4-oxobut-2-enoates, were desired. As Wilkerson, P. began synthesis aromatic derivatives, work began on an ethyl (2E) 3-ethyl -4-oxobut-2-enoate, compound **14**.



14 **15**

For the synthesis of ethyl (2E) 3-ethyl -4-oxobut-2-enoate, compound **14**, a novel procedure had to be developed. It was hypothesized that ethyl glyoxylate could cross condense with butyraldehyde via a proline catalyzed Aldol condensation, followed by dehydration to yield the desired vinyl aldehyde. An initial procedure was developed using a catalytic amount L-proline in DCM at 0 ^{o}C that yielded the desired product in acceptable yield without the need for dehydration. Before this discovery, compound **14** had never been synthesized by this method and although it is reported as a byproduct from another mechanism (REF), has never been fully characterized until now. Compound **14** was also taken one step further by reaction with a previously prepared methyltriphenylphosphonium iodide *Witteg* reagent in dry THF at -78 ^{o}C to furnish the previously unreported compound **15** in moderate yield and good diastereoselectivity - 10:1/Z:E.

3. RESULTS

The array of novel vinyl stannanes and vinyl iodides were passed on to Guansai Liu, to form fourteen distinct substrate variants. A Liebeskind modified Stille coupling procedure was adopted that involved $Pd(PPh_3)_4$ catalyst and CuTC, to join distinct vinyl tin and vinyl iodides together. These compounds were then de-protected to generate the reactive conjugated trienes in good yield. These substrates were then successfully applied in the novel asymmetric *Stetter* cyclization reaction.[26]

4. CONCLUSION

An efficient one step procedure for the synthesis of (*E*)-ethyl 3-formylpent-2-enoate from commercially available starting materials has been developed herein. The absolute configuration was determined by NOESY 2-D NMR. This procedure has not been fully optimized and may prove useful in the development of other 3' substituted (*E*)-ethyl 4-oxobut-2-enoates. These vinyl aldehydes are useful synthetic intermediates for a variety of transformations. One example used herein, the Stork-Zhao Witteg Olefination method[25] generated the corresponding ethyl (2E, 4Z)-3-ethyl-5-iodopenta-2, 4-dienoate in good yield and selectivity. These vinyl iodides may prove useful in cross-coupling reactions such as Suzuki-Miyaura, Stille, and Heck coupling. A series of novel aromatic vinyl tin compounds were also synthesized and fully characterized herein. These compounds were successfully applied in a Stille coupling reaction by Xu *et al.* to generate conjugated trienes [26] and may prove useful in other Stille type transformations.

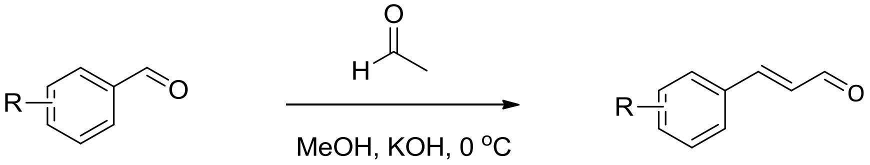
5. EXPERIMENTAL

5.1 General

All solvents used were dehydrated by an SG Water solvent drying system. All reagents were purchased from Sigma Aldrich and used without further purification unless otherwise noted. Glassware was either flame dried under vacuum or dried in an oven at 120 ^{o}C, assembled hot under a continuous argon atmosphere and capped with a rubber septum. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at 27 ˚C on a Bruker 400 MHz instrument. Chloroform peaks for ^{1}H NMR and ^{13}C NMR spectra were referenced at 7.27 and 77.0 ppm respectively. All final products were fully characterized by ^{1}H NMR, $_{13}$C NMR, mass spectrometry, and infrared spectroscopy.

5.2 Synthesis of Vinyl Tin Compounds

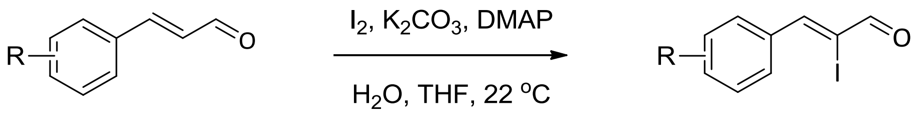
General procedure for the preparation of (2E)-(3-phenyl-substituted)-prop-2-enals 1a-6a



To a solution of substituted benzaldehyde (100 mmol) and acetaldehyde (150 mmol) at 0 °C, KOH (110 mmol) in MeOH (250 mL) was added dropwise via gradutated addition funnel over the course of several hours. This solution was allowed to warm to RT over 12 h. The solution was quenched by 0.1 M HCl and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (pure DCM) afforded products **1a**, **2a** and **5a** in moderate (40-55%) yield.

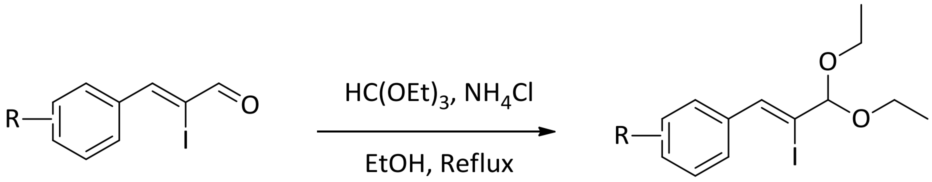
Compounds **3a**, **4a** and **6a**, were prepared as previously described with slight modifications. To a solution of substituted benzaldehyde (35 mmol) and acetaldehyde (40 mmol) at 0 °C, DBU (70 mmol) was added dropwise and the solution stirred for 1 h. This solution was allowed to warm to room temperature over the course of 4 h after which the solution was quenched with 0.1 M HCl and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (pure DCM) afforded products in (35-40%) yield, all spectra agreed with reported data.

General procedure for synthesis of (Z)-2-iodo-(phenyl-substituted)acrylaldehydes 1b-6b



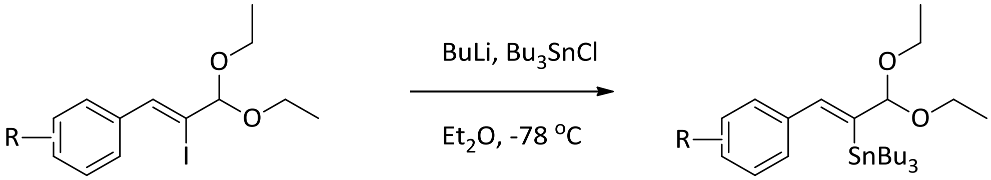
Compounds were prepared by dissolving α,β- unsaturated aldehyde **1a-6a** (1 mmol) in a mixture of THF/H_2O (5 mL, 1:1). K_2CO_3 (0.17 g, 1.2 mmol), iodine (0.38 g, 1.5 mmol) and DMAP (0.024 g, 0.2 mmol) were added in succession. The reaction mixture was stirred at RT for 24 h, then diluted with DCM and washed with saturated Na_2S2O_3. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Column chromatography on silica gel (hexanes : DCM = 1:2) afforded product α-iodoaldehydes in (50-70%) yield.

General procedure for acetal protection of α-iodoaldehydes 1c-6c



To a solution of (2Z)-2-iodo-(3-phenyl-substituted)-prop-2-enal, **1b-6b** (2 mmol) and triethylorthoformate (0.2 mL, 1.2 mmol) in EtOH (2 mL) was added a catalytic amount of NH_4Cl (4.3 mg, 0.08 mmol). The resultant mixture was stirred under reflux until all the starting material was consumed as monitored by TLC. The solvent was then removed *in vacuo,* column chromatography on silica gel (hexanes : EtOAc : Et_3N = 1 : 4 : 0.2) afforded product in (90-98%) yield.

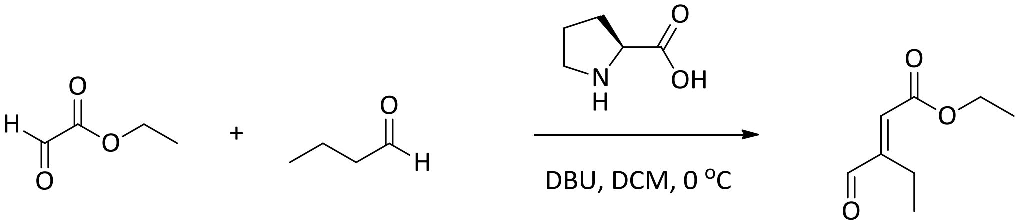
General procedure for the synthesis of vinyl stannanes 1d-6d



To a flame dried flask was charged vinyl iodide **1c-6c** (3 mmol) and Et_2O (35 mL). The resultant solution was cooled to -78 °C and n-BuLi (2.5 M in hexanes, 1.4 mL, 3.3 mmol) was added dropwise. The reaction mixture was stirred for 10 min and Bu_3SnCl (0.9 mL, 3.3 mmol) was added dropwise. After stirring for an additional 2 h at -78 °C, H_2O (2 mL) was added to quench the reaction. The organic solution was washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography by a short silica gel column (hexanes : Et_3N = 19 : 1) afforded vinyl tin compound that was found adequate to allow progression to the next step without further purification (83-91%).

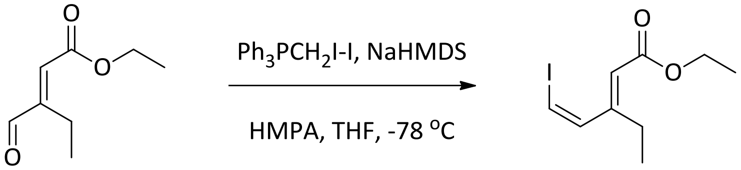
5.2 Synthesis of Vinyl Iodides

General Procedure for the Synthesis of Vinyl Aldehydes via Proline Catalyzed Aldol Condensation



To a solution of butyraldehyde (1 mmol) in dry DCM (10 mL) was added ethyl glyoxylate (50% in toluene, 2.5 mmol) and L-proline (0.5 mmol). The resultant solution was cooled to 0 °C and DBU (1.1 mmol) was added dropwise. The mixture was stirred for 1 h then allowed to warm to RT and stirred for an additional 2 h. The organic solution was washed with H_2O and the combined organic layers dried over Na_2SO_4 before being concentrated *in vacuo*. Column chromatography by a short silica gel column (hexanes : EA = 20 : 1) afforded product **14** in (42%) yield.

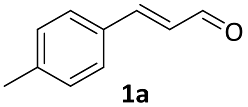
General Procedure for the Synthesis of (2E, 4Z) Vinyl Iodides via Stork-Zhao Witteg Olefination[25]



To a flame-dried round bottom flask was charged THF (15 mL) and (iodomethyl) triphenylphosphonium iodide (1.6 g, 3 mmol). NaHMDS (1.0 M in THF, 3.0 mL, 3 mmol) was added dropwise at RT. After the solid was dissolved, the solution was stirred for an additional 10 min then cooled to -60 °C. HMPA (3.8 mmol) was added dropwise. The reaction mixture was cooled to -78 °C and stirred for 15 min. Vinyl aldehyde **14** (2.5 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to stir for 30 min. Hexanes (50 mL) was added to quench the reaction and the resultant suspension was filtered through celite. The filtrate was washed by H_2O x 5 (25 mL) and brine.

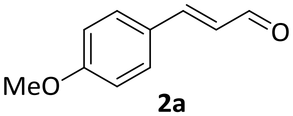
The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography on silica gel (hexanes : EtOAc = 20 : 1) afforded vinyl iodide **15** (Z/E = 10/1) in (55-60%) yield.

5.4 Compound Characterization



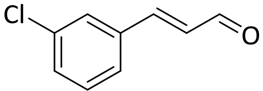
1a

(E)-3-(p-tolyl)acrylaldehyde (**1a**): known compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.71 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 2.5 Hz, 2H), 7.43 (d, J = 16 Hz, 1H), 7.24 (d, J = 8 Hz, 2H), 6.72 (dd, J = 7.6, 16 Hz, 1H), 2.39 (s, 3H)



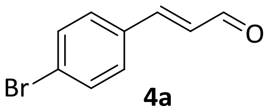
2a

(*E*)-3-(4-methoxyphenyl)acrylaldehyde (**2a**): known compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.64 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 16 Hz, 1H) 6.94 (d, *J* =8 Hz, 2H), 6.60 (dd, *J* = 7.6, 16 Hz, 1H) 3.86 (s, 3H)



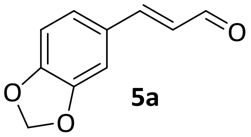
3a

(*E*)-3-(3-chlorophenyl)acrylaldehyde (**3a**): known compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (d, *J* = 7.5 Hz, 1H), 7.28-7.44 (m, 5H), 6.60 (dd, *J* = 16, 7.5 Hz, 1H)



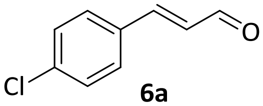
4a

(*E*)-3-(4-bromophenyl)acrylaldehyde (**4a**): known compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.71 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* =8.5 Hz, 1H), 7.45–7.40 (m, *3*H), 6.70 (dd, *J* = 16.0, 7.5 Hz, 1H)



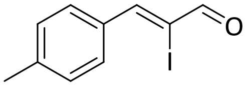
5a

(*E*)-3-(benzo[d][1,3]dioxol-5-yl)acrylaldehyde (**5a**): known compound: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.65 (d, *J* = 7.6 Hz, 1H) 7.38 (d, *J* = 16.0 Hz, 1H), 7.06-7.08 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.56 (dd, *J* = 16.0, 7.6 Hz, 1H) 6.05 (s, 2H)



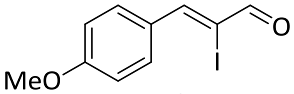
6a

(*E*)-3-(4-chlorophenyl)acrylaldehyde: known compound: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.70 (d, *J* = 7.6 Hz, 1H), 7.52−7.40 (m, 5H), 6.68 (dd, *J* = 16.0 Hz, 7.6 Hz, 1H)



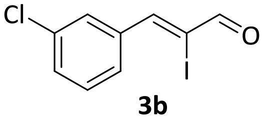
1b

(*Z*)-2-iodo-3-p-tolylacrylaldehyde (**1b**): known compound: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.76 (s, 1 H), 8.06 (s, 1 H), 8.95 (d, *J* = 12.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H)



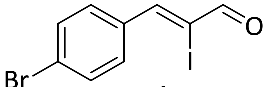
2b

(*Z*)-2-iodo-3-(4-methoxyphenyl)acrylaldehyde (**2b**): known compound: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.74 (s, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 8.04 (s, 1 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H)

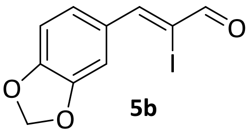


3b

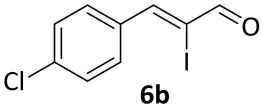
(*Z*)-3-(3-chlorophenyl)-2-iodoacrylaldehyde (**3b**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.80 (s, 1 H), 8.04 (s, 1 H), 7.99 (s, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.55–7.38 (m, 2 H); $_{13}$C NMR (100 MHz, CDCl$_3$): 188.7, 153.9, 135.9, 131.3, 129.9, 128.3, 107.7 ; IR (film) vmax, 3065 (w), 2827 (m), 1685 (s), 1587 (m), 1559 (m), 1469 (m), 1412 (m), 1265 (m), 1204 (m), 1086 (s) cm-1; HRMS (ESI-TOF) for $C_9H_3O_3I$ [M + H+] calculated 292.9230, found 292.9233


4b

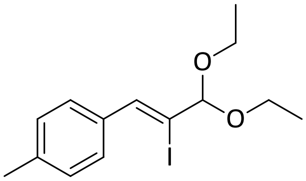
(*Z*)-3-(4-bromophenyl)-2-iodoacrylaldehyde (**4b**): m.p. 105–107 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.78 (s, 1 H), 8.03 (s, 1 H), 7.88 (d, *J* = 12.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H); $_{13}C$ NMR (100 MHz, $CDCl_3$): 188.8, 154.2, 133.0, 132.0, 131.7, 126.1, 106.8; IR (film) vmax, 2829 (w), 1674 (s), 1595 (m), 1579 (s), 1557 (m), 1485 (m), 1407 (m), 1278 (m), 1078 (s), 1091 (s) cm-1; HRMS (ESI-TOF) for C_9H_7OBrI [M + H+] calculated 336.8725, found 336.8735


5b

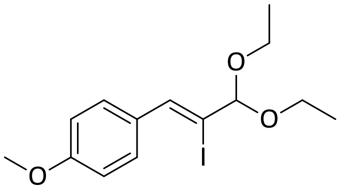
(*Z*)-3-(benzo[d][1,3]dioxol-5-yl)-2-iodoacrylaldehyde (**5b**): ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (s, 1 H), 7.98 (s, 1 H), 7.85 (s, 1 H), 7.46 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.08 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): 189.0, 155.2, 150.84, 147.83, 128.07, 128.04, 109.4, 108.6, 102.93, 102.0; IR (film) vmax, 2923 (s), 2853 (m), 1679 (s), 1572 (s), 1501 (s), 1486 (s), 1449 (s), 1361 (m), 1314 (w), 1255 (s), 1090 (s), 1035 (s) cm-1; HRMS (ESI-TOF) for $C_9H_3O_3I$ [M + H+] calculated 302.9518, found 302.9576


6b

(*Z*)-3-(4-chlorophenyl)-2-iodoacrylaldehyde (**6b**): known compound: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.81 (s, 1 H), 8.07 (s, 1 H), 7.98 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H)

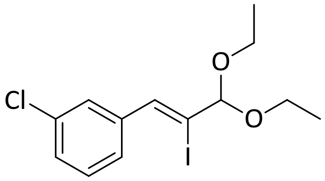

1c

(*Z*)-1-(3,3-diethoxy-2-iodoprop-1-enyl)-4-methylbenzene (**1c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.52 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 4.0 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 4.72 (s, 1 H), 3.70–3.56 (m, 4 H), 2.36 (s, 3 H), 1.29 (t, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$): 138.4, 136.2, 133.6, 128.80, 128.76, 105.1, 103.8, 61.9, 21.4, 15.1; IR (film) vmax, 3057 (w), 2975 (m), 2928 (w), 2878 (m), 1480 (w), 1445 (m), 1329 (m), 1116 (s), 1055 (s) cm-1; HRMS (ESI-TOF) for $C_{14}H_{19}O_2INa$ [M + Na+] calculated 369.0328, found 369.0313



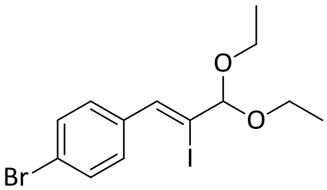
2c

(*Z*)-1-(3,3-diethoxy-2-iodoprop-1-enyl)-4-methoxybenzene (**2c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.64 (d, *J* = 12.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 4.71 (s, 1 H), 3.84 (s, 3 H), 3.71–3.57 (m, 4 H), 1.30 (t, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$): 159.7, 135.7, 130.4, 128.0, 113.4, 105.2, 102.4, 61.9, 55.2, 15.1; IR (film) vmax, 2829 (w), 1674 (s), 1595 (m), 1579 (s), 1557 (m), 1485 (m), 1407 (m), 1278 (m), 1078 (s), 1091 (s) cm-1; HRMS (ESI-TOF) for $C_{14}H_{19}O_3INa$ [M + Na+] calculated 385.0277, found 385.0267



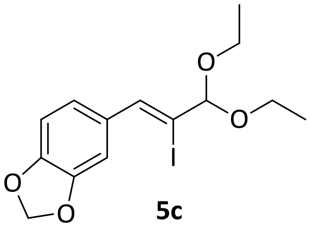
3c

(*Z*)-1-chloro-3-(3,3-diethoxy-2-iodoprop-1-enyl)benzene (**3c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.58 (s, 1 H), 7.48–7.46 (m, 1 H), 7.33–7.28 (m, 3 H), 4.79 (s, 1 H), 3.73–3.58 (m, 4 H), 1.31 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$): 138.7, 135.1, 129.4, 128.8, 128.3, 127.0, 106.5, 104.8, 62.0, 15.1; IR (film) vmax, 2976 (m), 2919 (m), 1593 (w), 1564 (w), 1473 (m), 1119 (s), 1061 (s) cm-1; HRMS (ESI-TOF) for $C_{13}H_{16}O_2ClINa$ [M + Na+] calculated 388.9781, found 388.9772



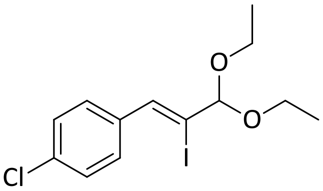
4c

(*Z*)-1-bromo-4-(3,3-diethoxy-2-iodoprop-1-enyl)benzene (**4c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.51–7.45 (m, 4 H), 7.24 (s, 1 H), 4.75 (s, 1H), 3.72–3.54 (m, 4 H), 1.28 (t, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$): 135.6, 135.2, 131.3, 130.4, 9 122.4, 105.7, 104.8, 62.0, 15.1; IR (film) vmax, 2974 (m), 2928 (w) 2878 (m), 1485 (m), 1396 (m), 1329 (m), 1115 (s), 1048 (s), 1009 (s) cm-1; HRMS (ESI-TOF) for $C_{13}H_{16}O_2BrINa$ [M + Na+] calculated 432.9276, found 432.9266



5c

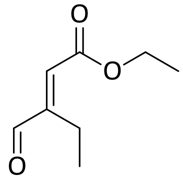
(*Z*)-5-(3,3-diethoxy-2-iodoprop-1-enyl)benzo[d][1,3]dioxole (**5c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.28 (s, 1 H), 7.20 (s, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 5.99 (s, 1 H), 4.70 (s, 1 H), 3.69–3.54 (m, 4 H), 1.28 (t, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$): 146.3, 135.7, 123.7, 108.7, 108.0, 105.2, 103.1, 101.2, 61.9, 15.1; IR (film) vmax, 2977 (m), 2888 (m), 2247 (w), 1605 (w), 1504 (m), 1489 (s), 1445 (m), 1259 (m), 1117 (m), 1059 (s), 1041 (s) cm-1; HRMS (ESI-TOF) for $C_{14}H_{17}O_4INa$ [M + Na+] calculated 399.0069, found 399.0061



6c

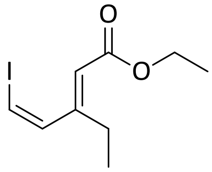
(*Z*)-1-chloro-4-(3,3-diethoxy-2-iodoprop-1-enyl)benzene(**6c**): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.55 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.29 (s, 1 H), 4.78 (s, 1 H), 3.74–3.56 (m, 4 H), 1.31 (t, *J* = 7.2 Hz, 6

H); ^{13}C NMR (100 MHz, $CDCl_3$): 135.16, 135.15, 134.17, 130.2, 128.3, 105.7 104.9, 62.0, 15.1 ; IR (film) vmax, 2976 (m), 2928 (w), 2879 (m), 1593 (m), 1564 (m), 1473 (m), 1409 (w), 1333 (w), 1257 (w), 1116 (s), 1055 (s) cm-1; HRMS (ESI-TOF) for $C_{13}H_{16}O_2ClINa$ [M + Na+] calculated 388.9781, found 388.9777



14

ethyl (2E)-formylpent-2-enoate (**14**): ^{1}H NMR (400 MHz, $CDCl_3$) 9.52 (s, 1H), 6.44 (s, 1H), 4.31-4.26 (q, J = 7 Hz, 2H), 2.73-2.67 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCL_3$): 194.34, 165.24, 155.8, 135.2, 61.05, 18.3, 14.1, 13.15; HRMS (ESI-TOF) for $C_8H_{13}O_3$[M + H+] calculated 157.0865, found 157.0863



15

ethyl (2E, 4Z)-3-ethyl-5-iodopenta-2, 4-dienoate (**15**)(Z/E = 10/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.73 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H) 5.98 (s, 1H), 4.23-4.18 (q, J = 7.1 Hz, 2H), 2.81-2.75 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.24 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCL_3$): 166.0, 157.65, 140.1, 119.1, 82.64, 60.0, 24.34, 14.25, 12.73; HRMS (ESI-TOF) for $C_9H_{14}O_2I$ [M + H+] calculated 281.0039, found 281.0029

6. REFERENCES

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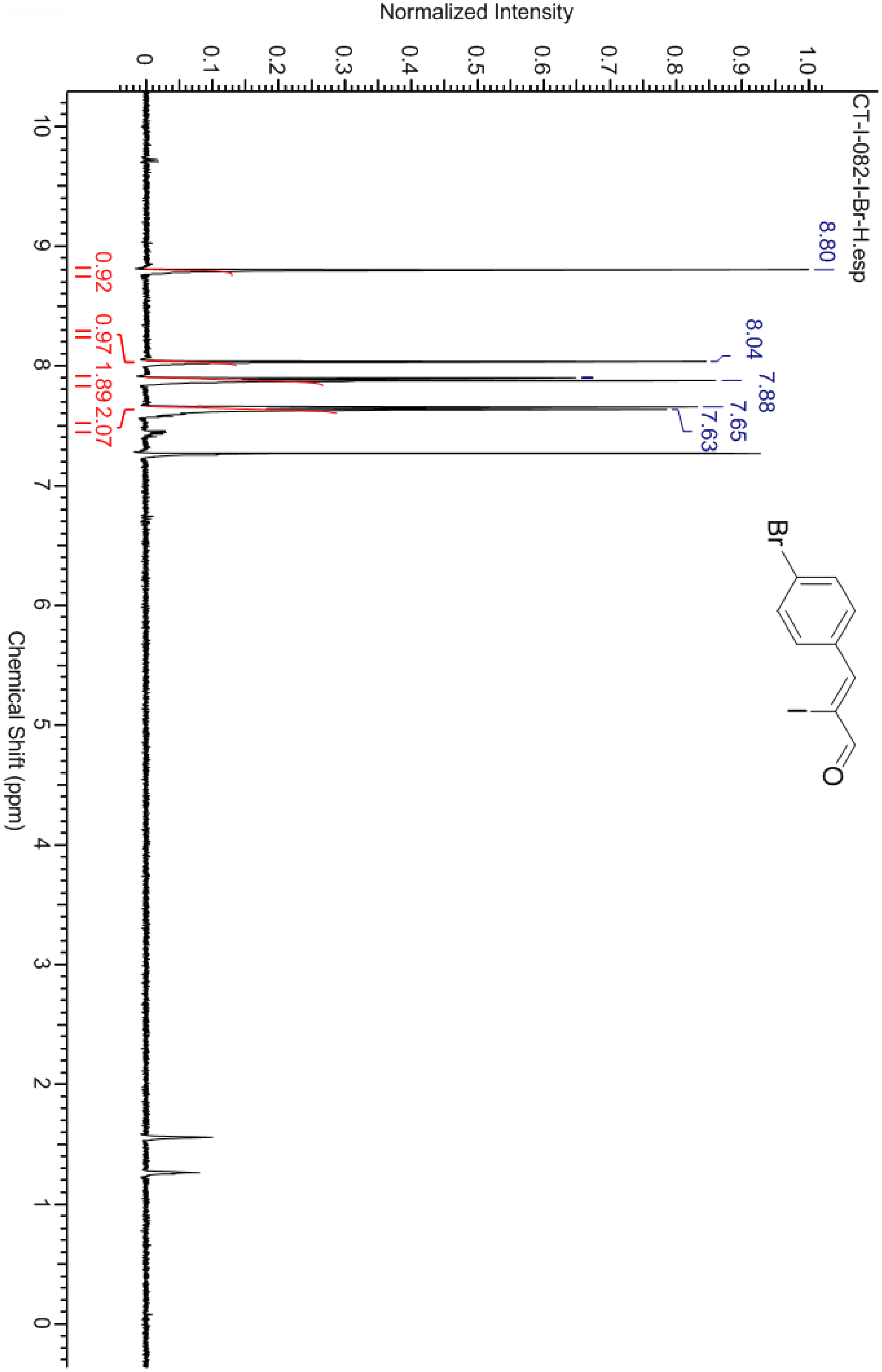
7. SPECTRA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0.9
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8.80
8.04
7.88
7.65
7.63
0.92
0.97
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4
3
2
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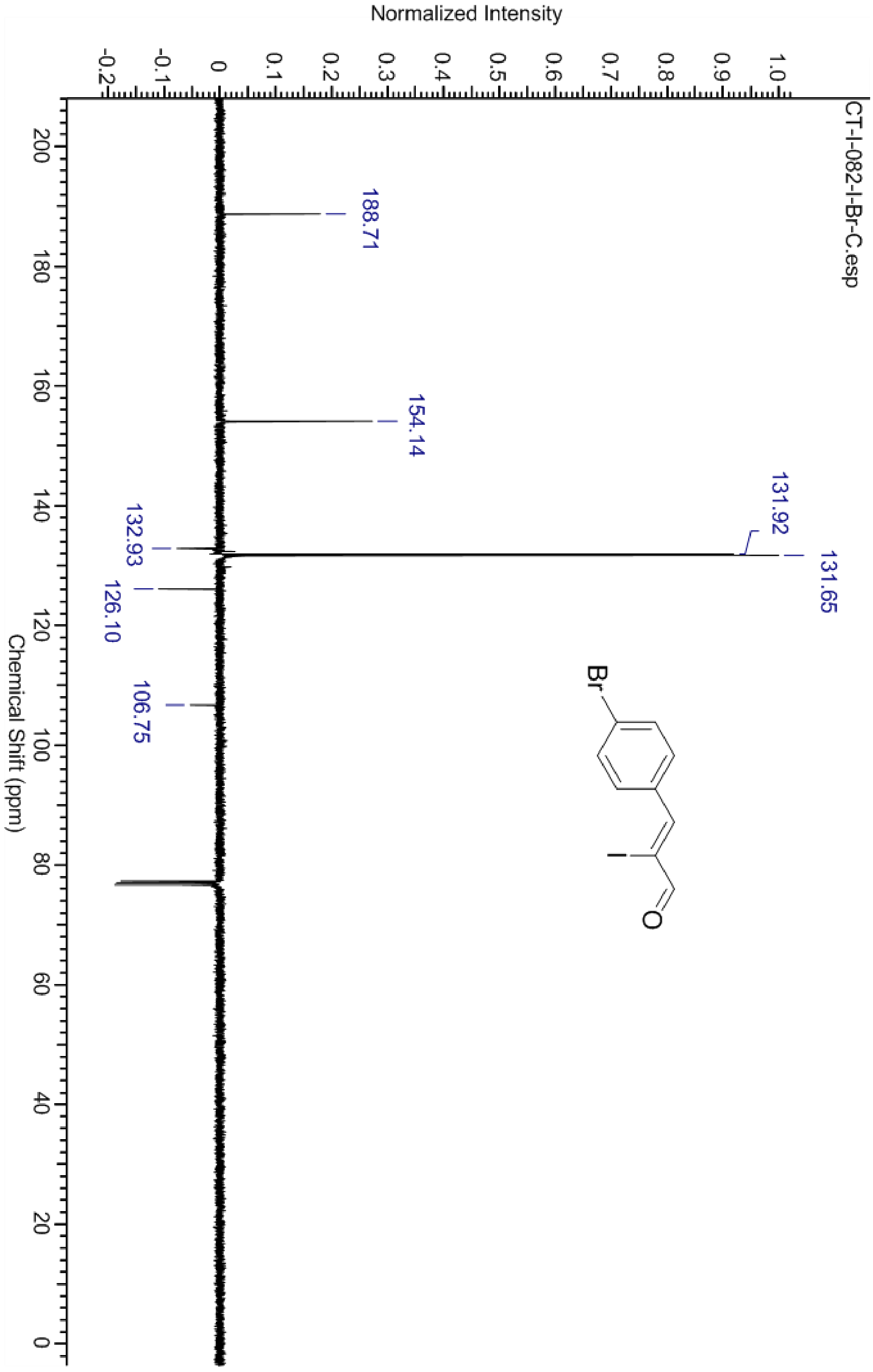
0
Chemical Shift (ppm)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Br
I
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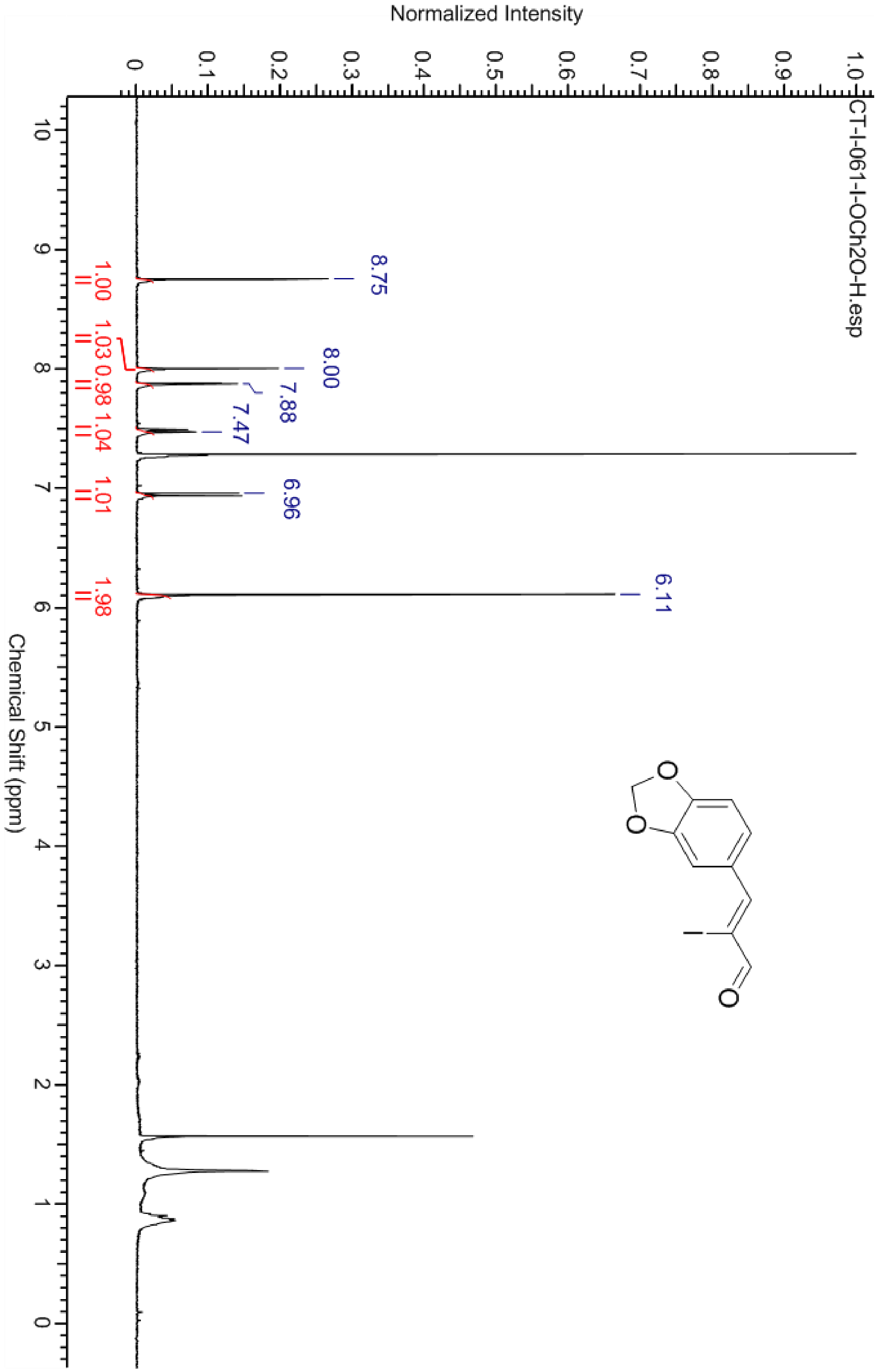
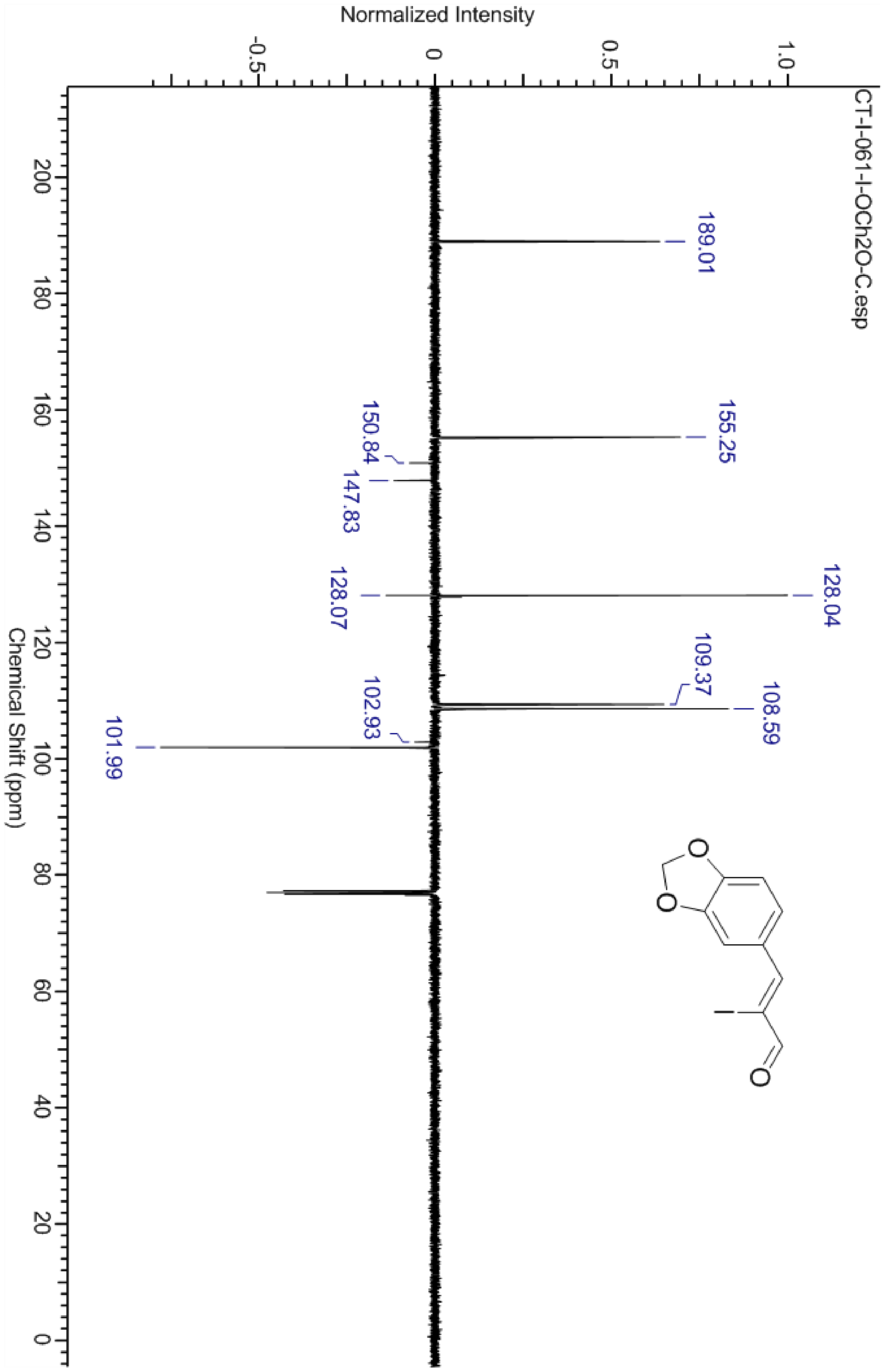
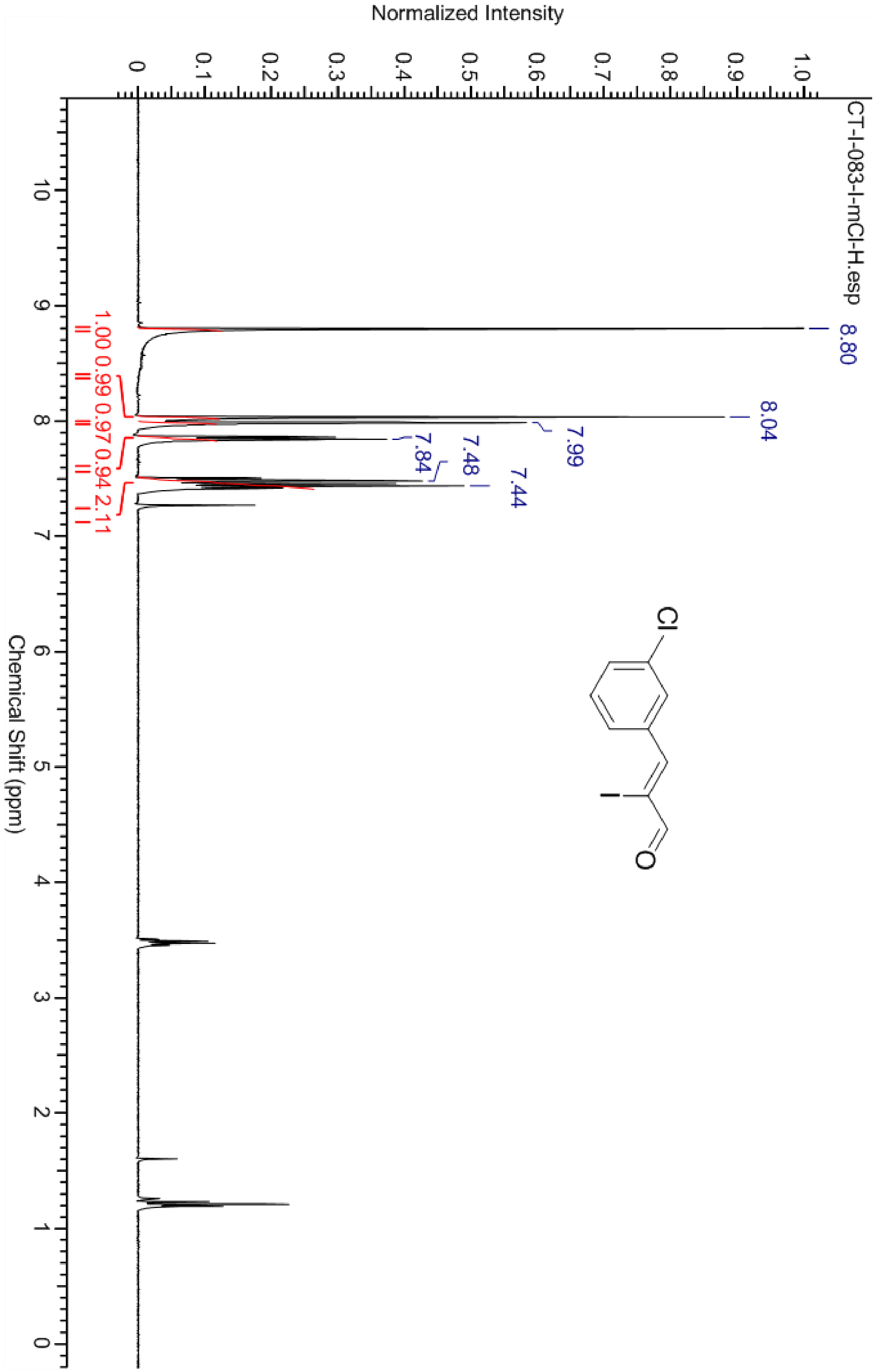
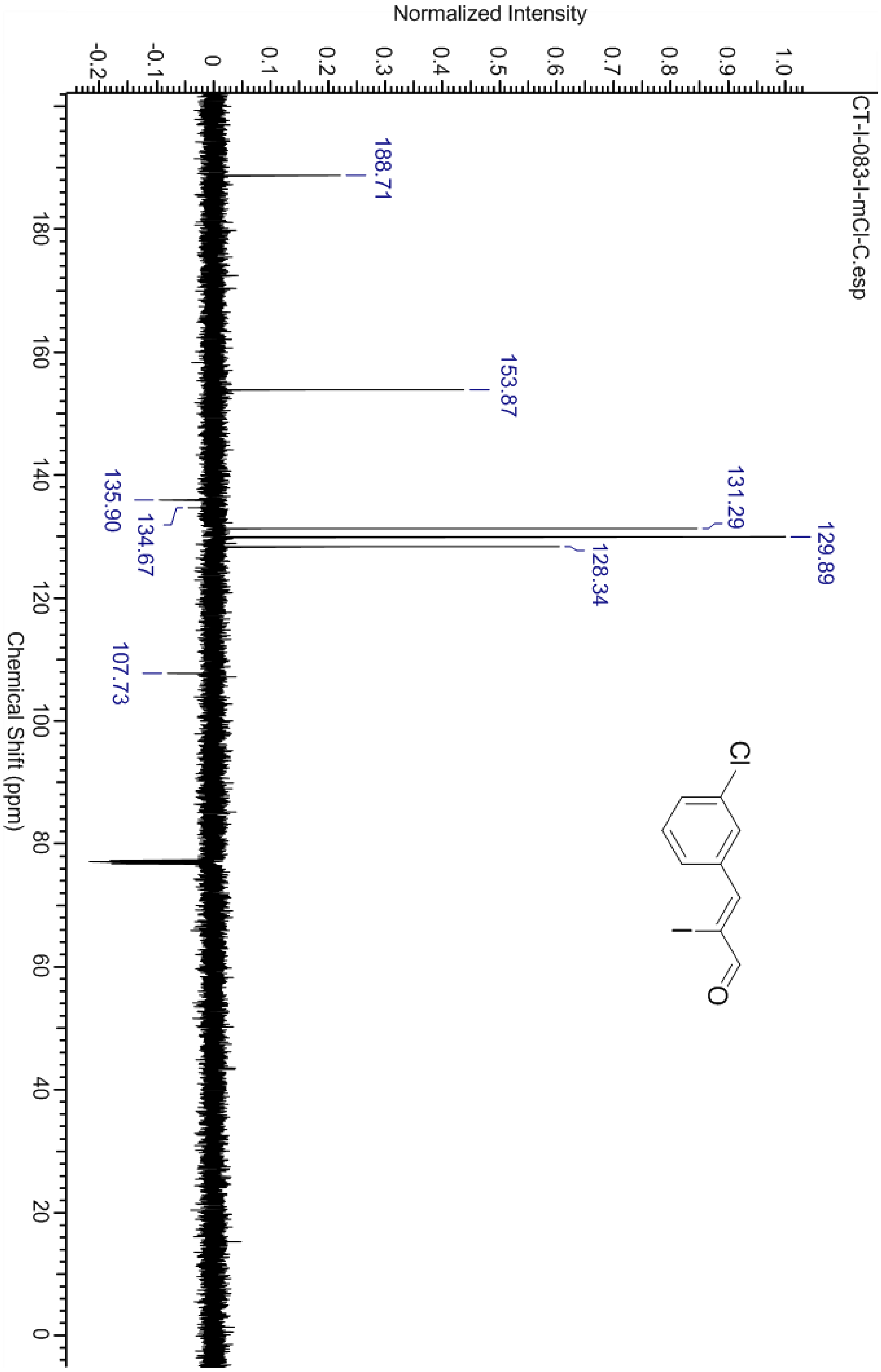
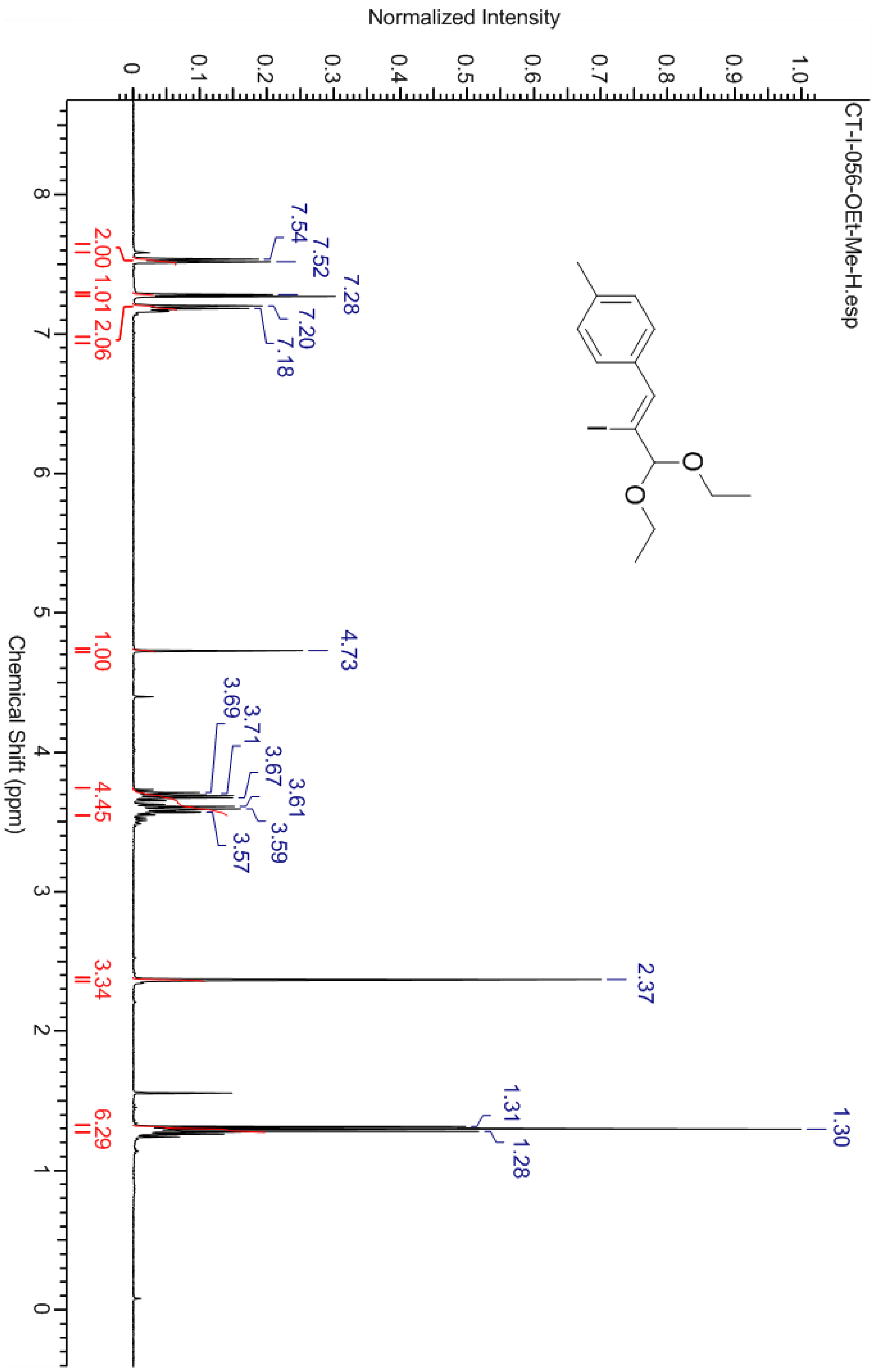
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

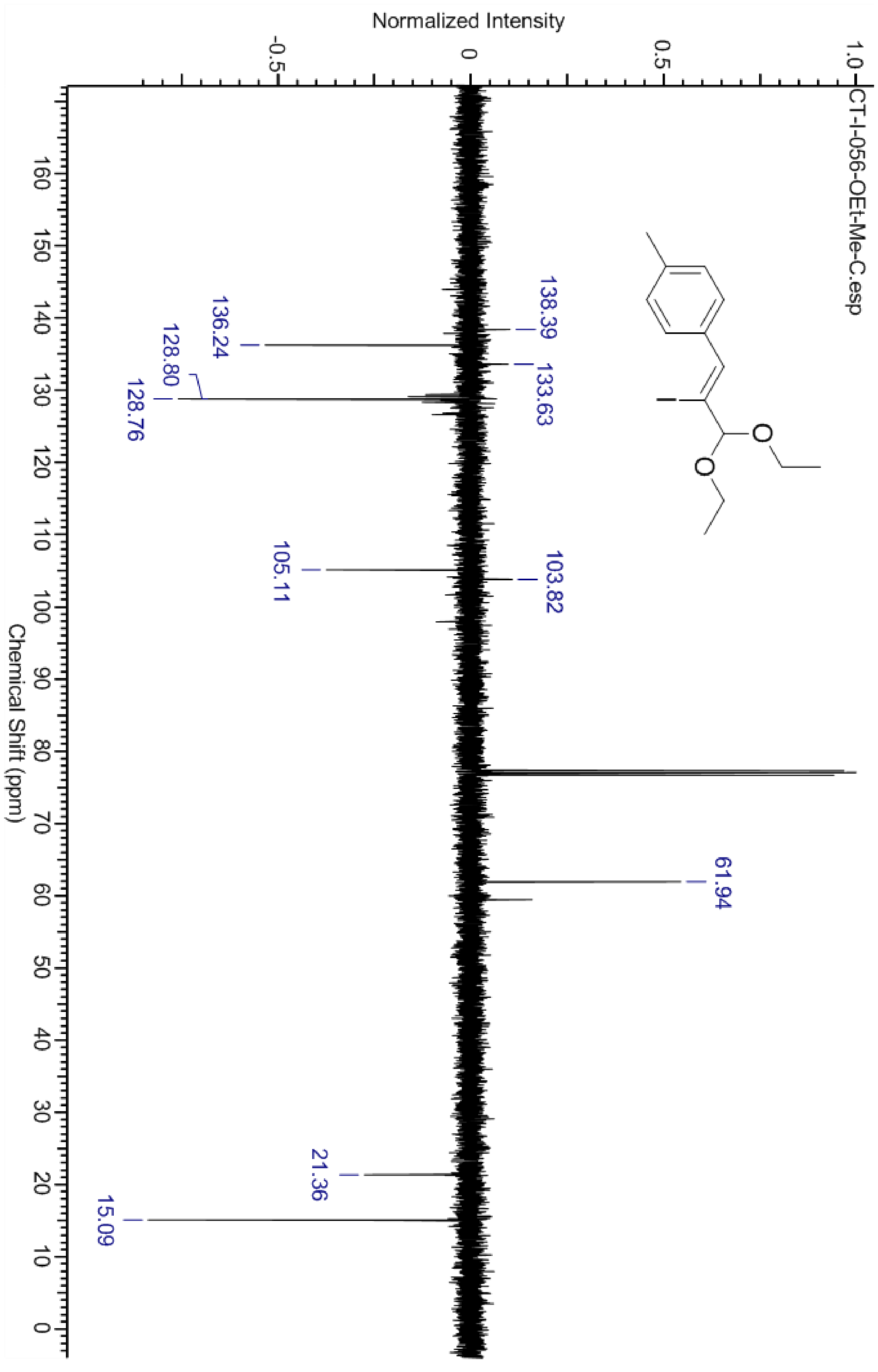

CT-I-061-I-OCh2O-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
8.75
8.00
7.88
7.47
6.96
6.11
1.00
1.03
0.98
1.04
1.01
1.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
O
I
O

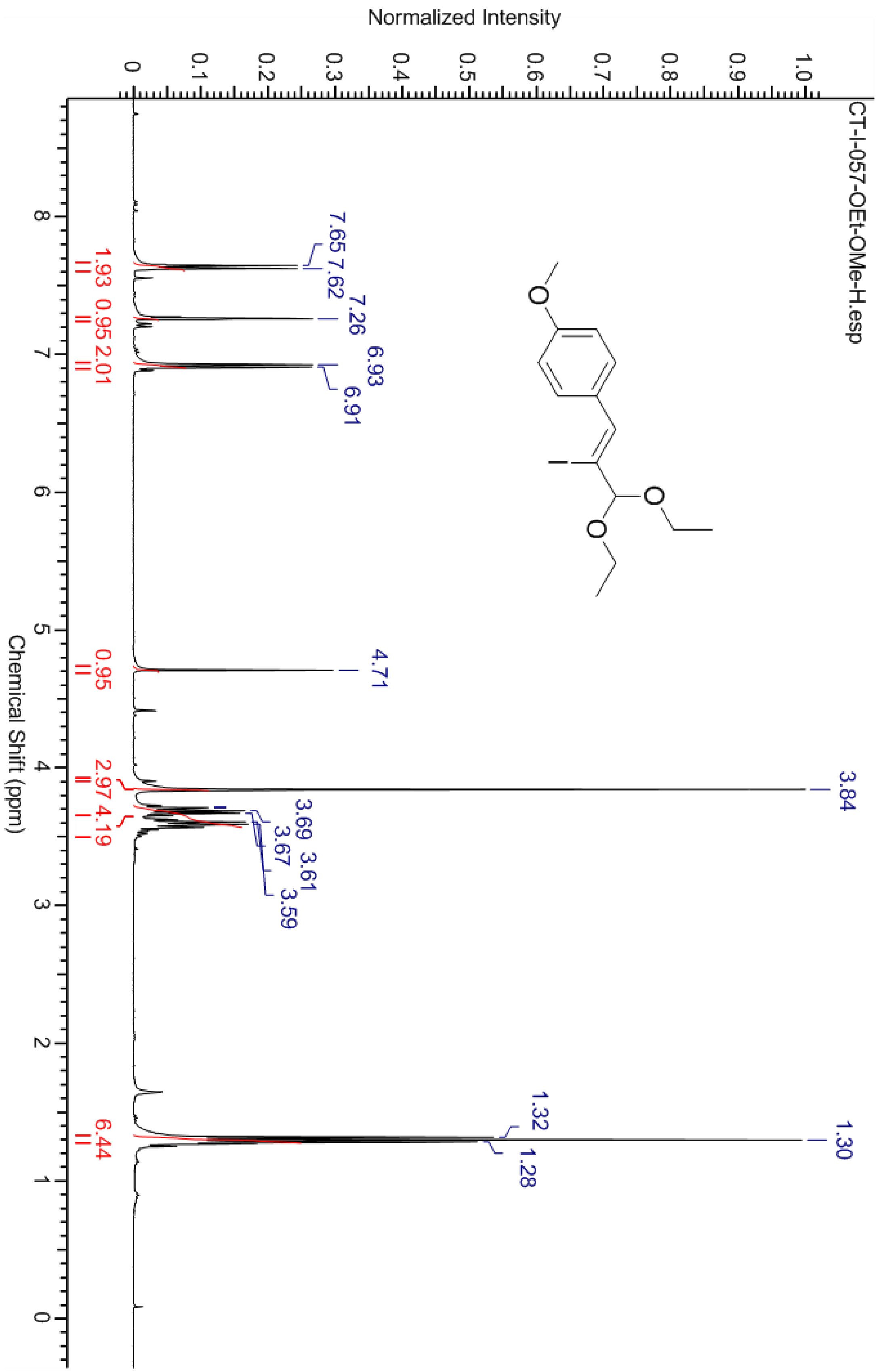

CT-I-061-I-OCh2O-C.esp
Normalized Intensity
1.0
0.5
0
-0.5
189.01
155.25
150.84
147.83
128.04
128.07
109.37
108.59
102.93
101.99
O
O
O
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

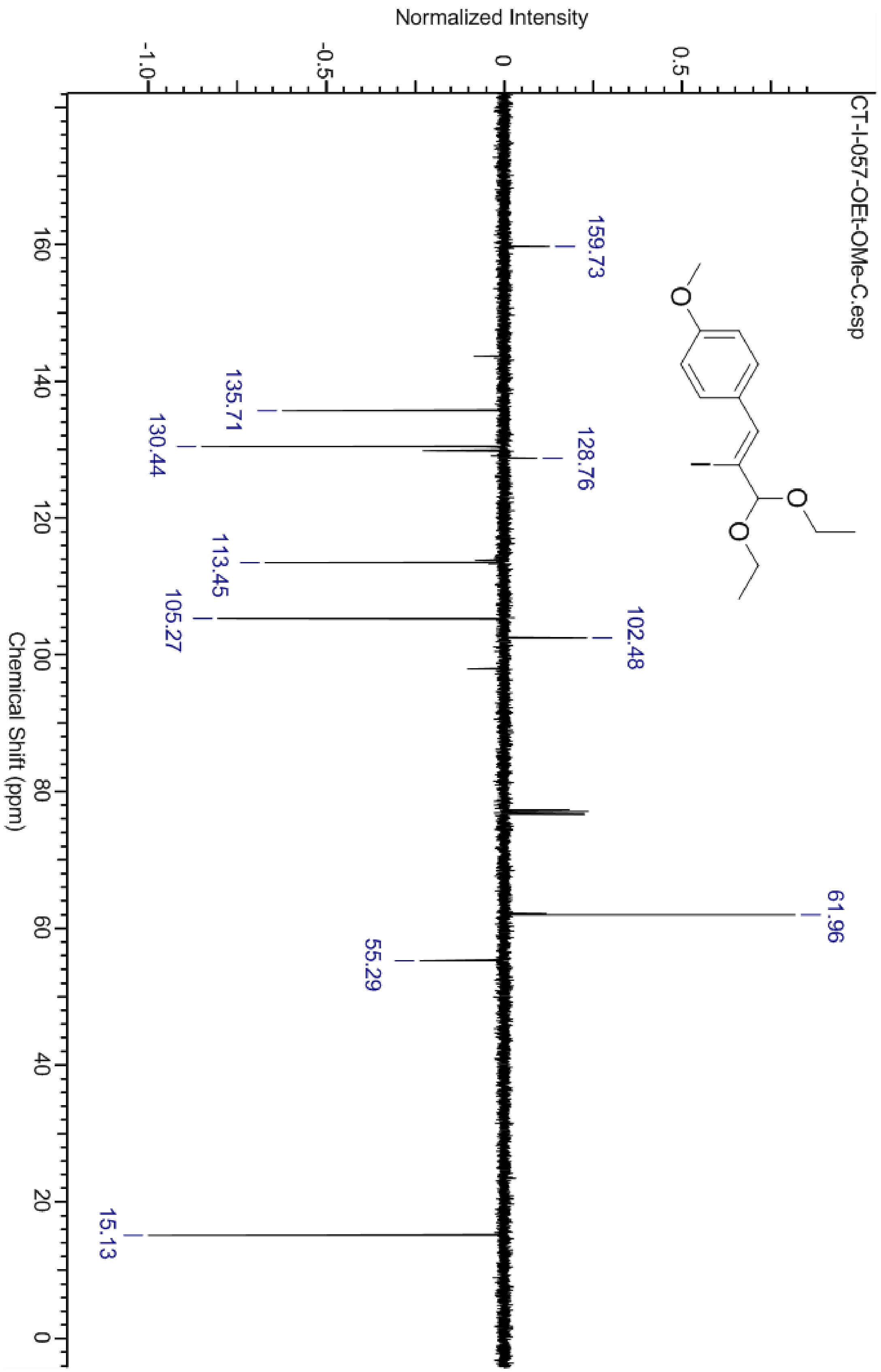

CT-I-083-I-mCl-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
8.80
8.04
7.99
7.84
7.48
7.44
1.00
0.99
0.97
0.94
2.11
Cl
I
O
Chemical Shift (ppm)
10
9
8
7
6
5
4
3
2
1
0

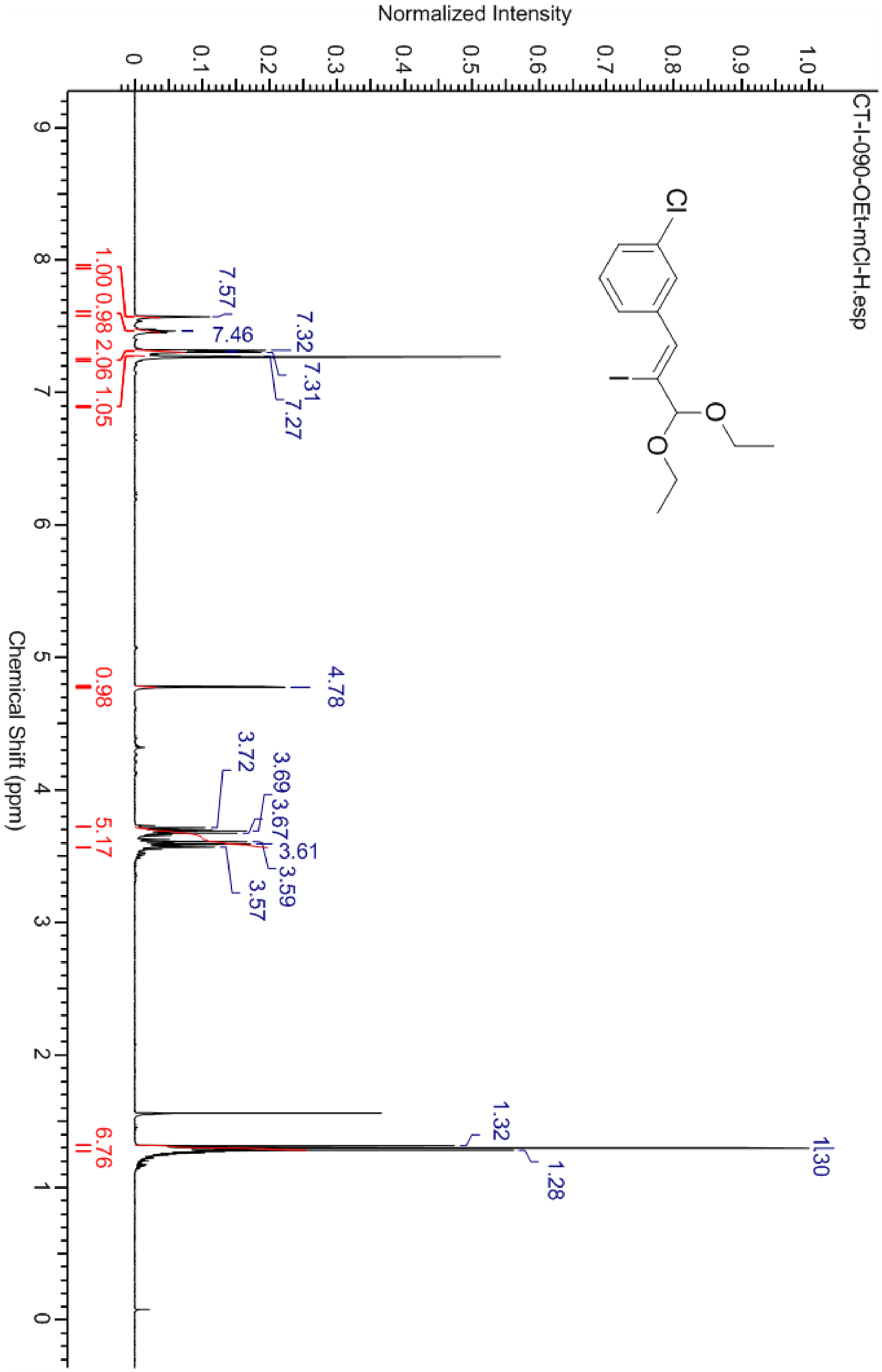

CT-I-083-I-mCl-C.esp
Normalized Intensity
-0.2
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
188.71
153.87
135.90
134.67
131.29
129.89
128.34
107.73
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
Cl
O

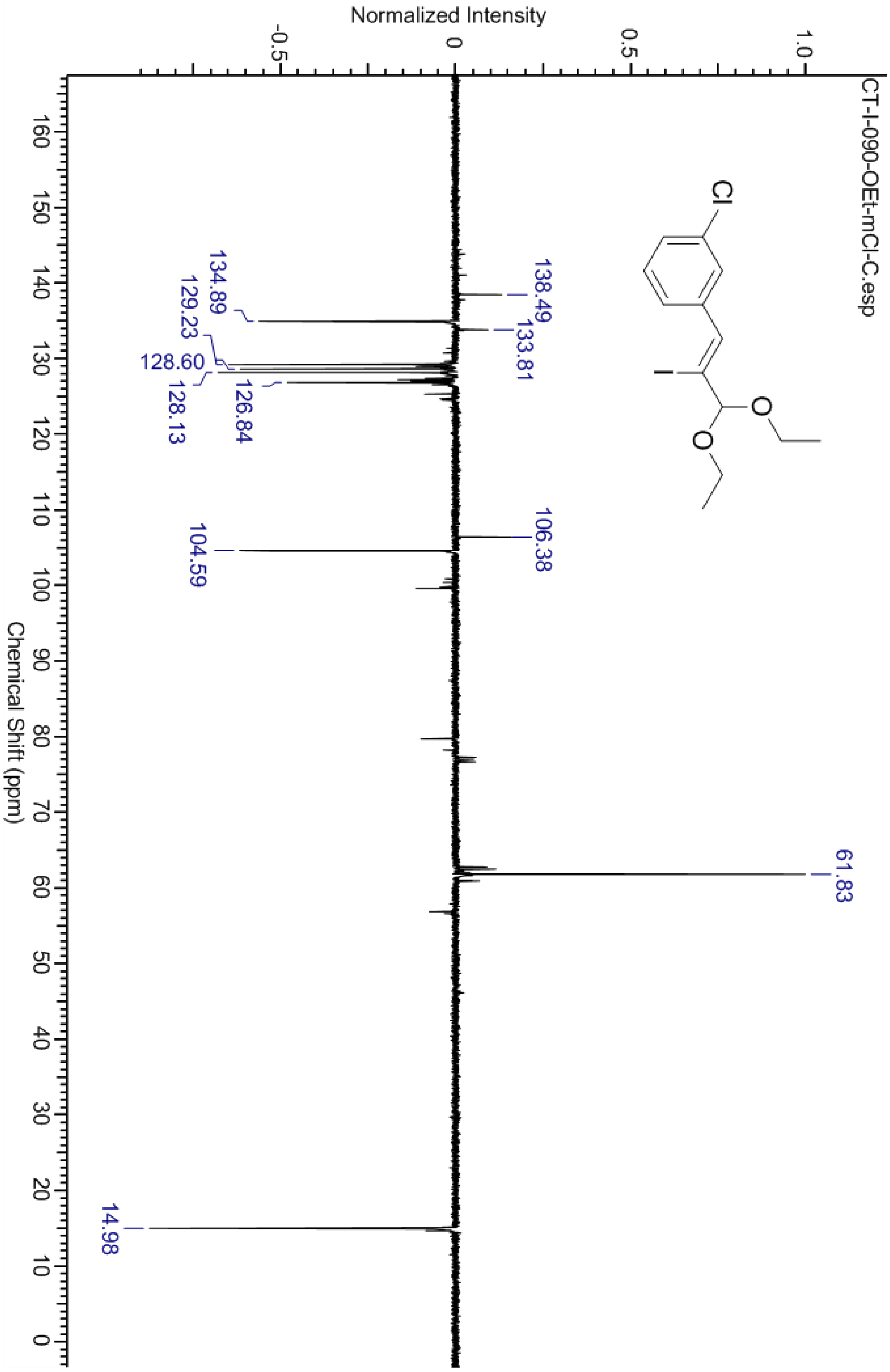

CT-I-056-OEt-Me-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
7.54
7.52
7.28
7.20
7.18
4.73
3.69
3.71
3.67
3.61
3.59
3.57
2.37
1.31
1.30
1.28
2.00
1.01
2.06
1.00
4.45
3.34
6.29
I
O
O
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

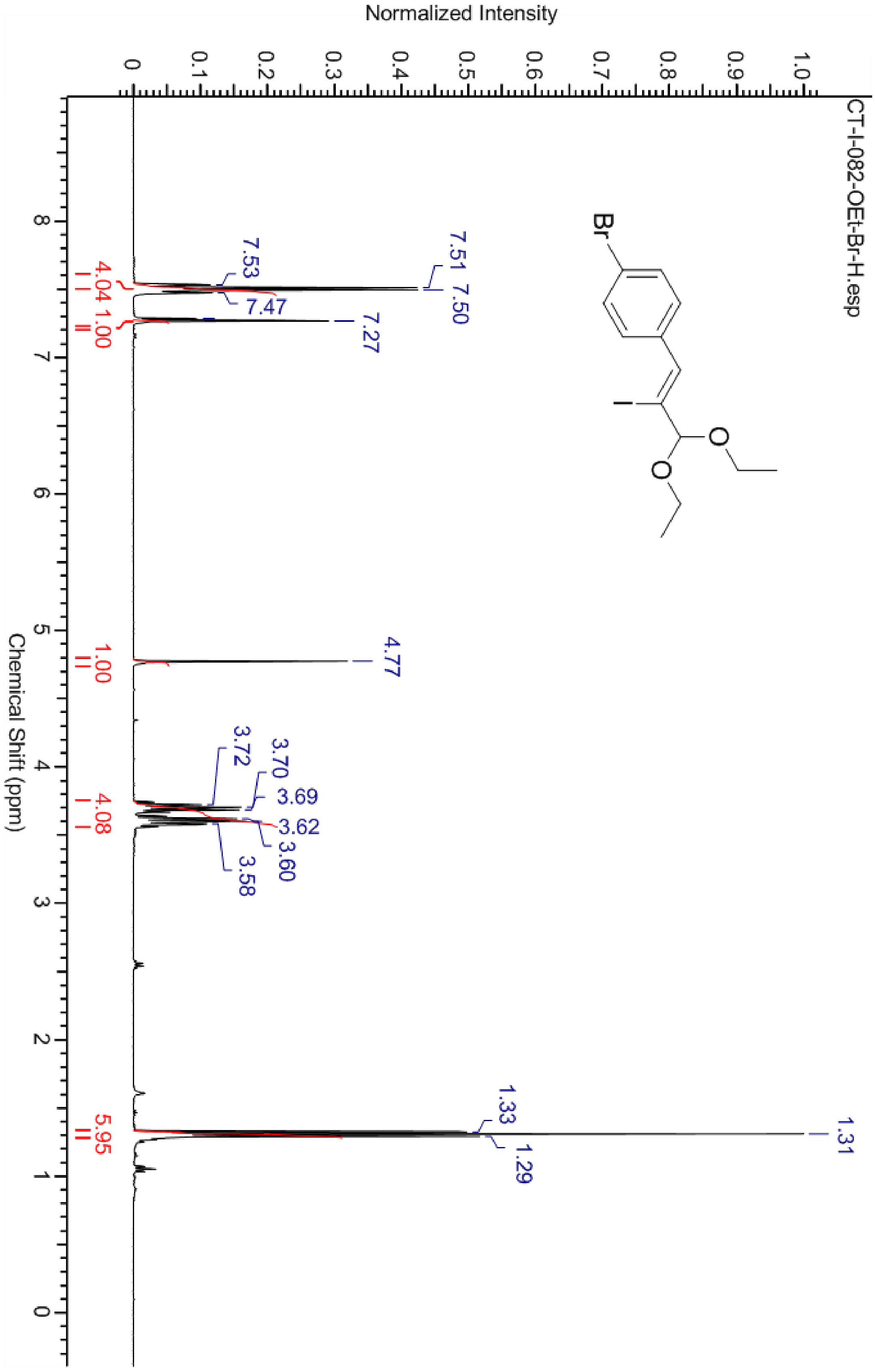

CT-I-056-OEt-Me-C.esp
Normalized Intensity
1.0
0.5
0
-0.5
138.39
136.24
133.63
128.80
128.76
105.11
103.82
61.94
21.36
15.09
O
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

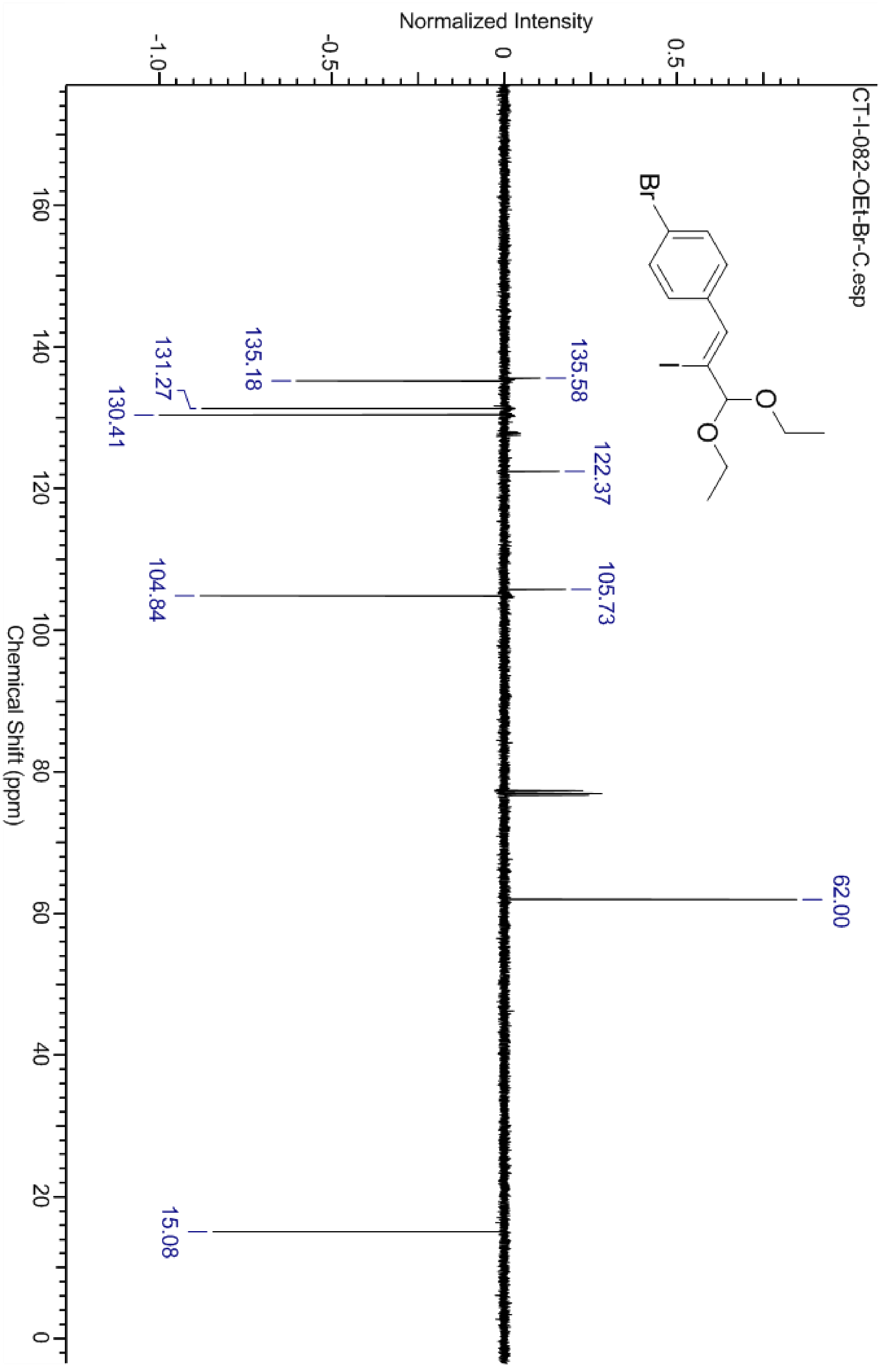

CT-I-057-OEt-OMe-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Chemical Shift (ppm)
8
7
6
5
4
3
2
1
0
7.65
7.62
7.26
6.93
6.91
4.71
3.84
3.69
3.67
3.61
3.59
1.32
1.30
1.28
1.93
0.95
2.01
0.95
2.97
4.19
6.44
O
O
O

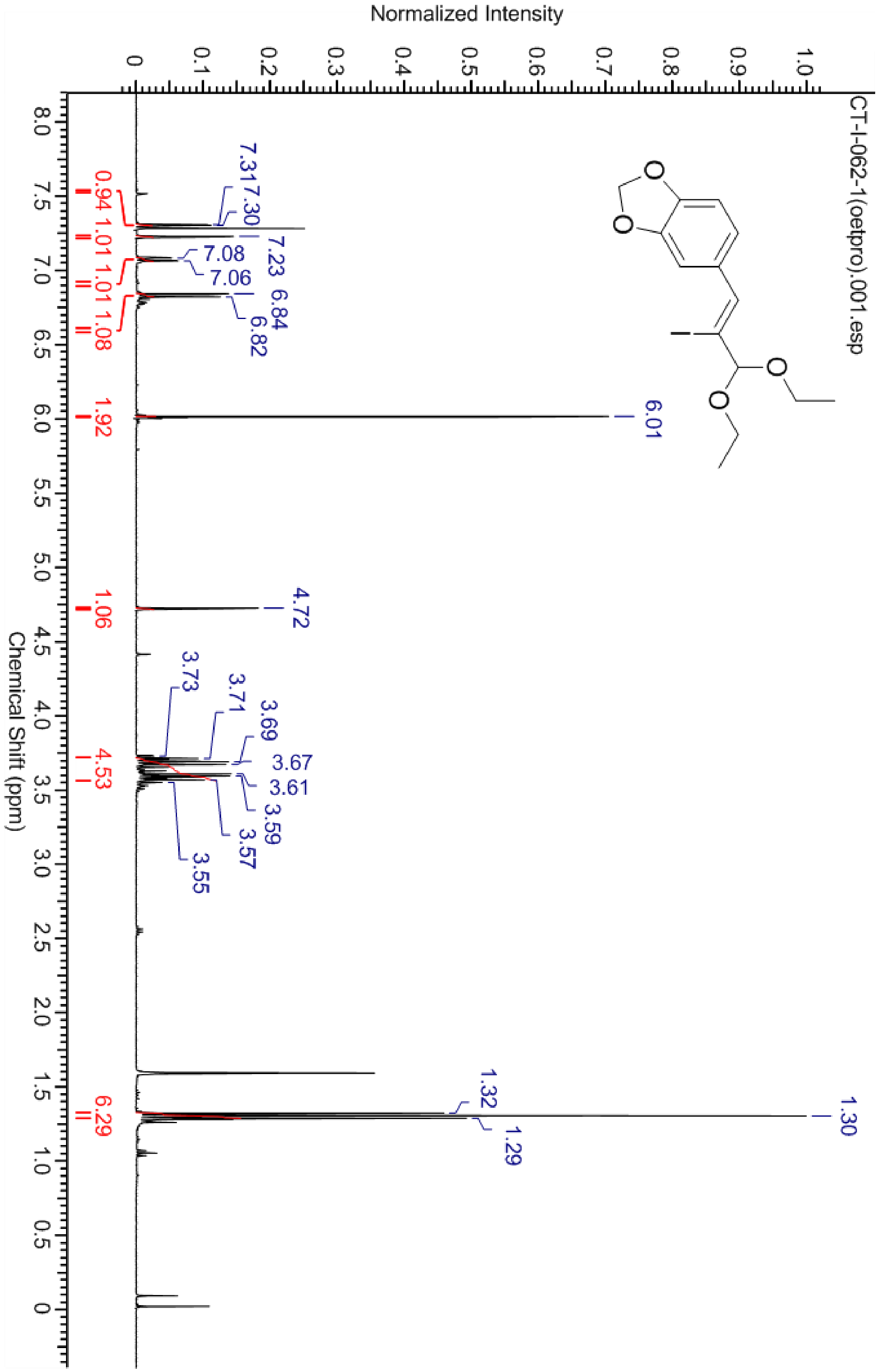

CT-I-057-OEt-OMe-C.esp
Normalized Intensity
0.5
0
-0.5
-1.0
159.73
135.71
130.44
128.76
113.45
105.27
102.48
61.96
55.29
15.13
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
O
O
O

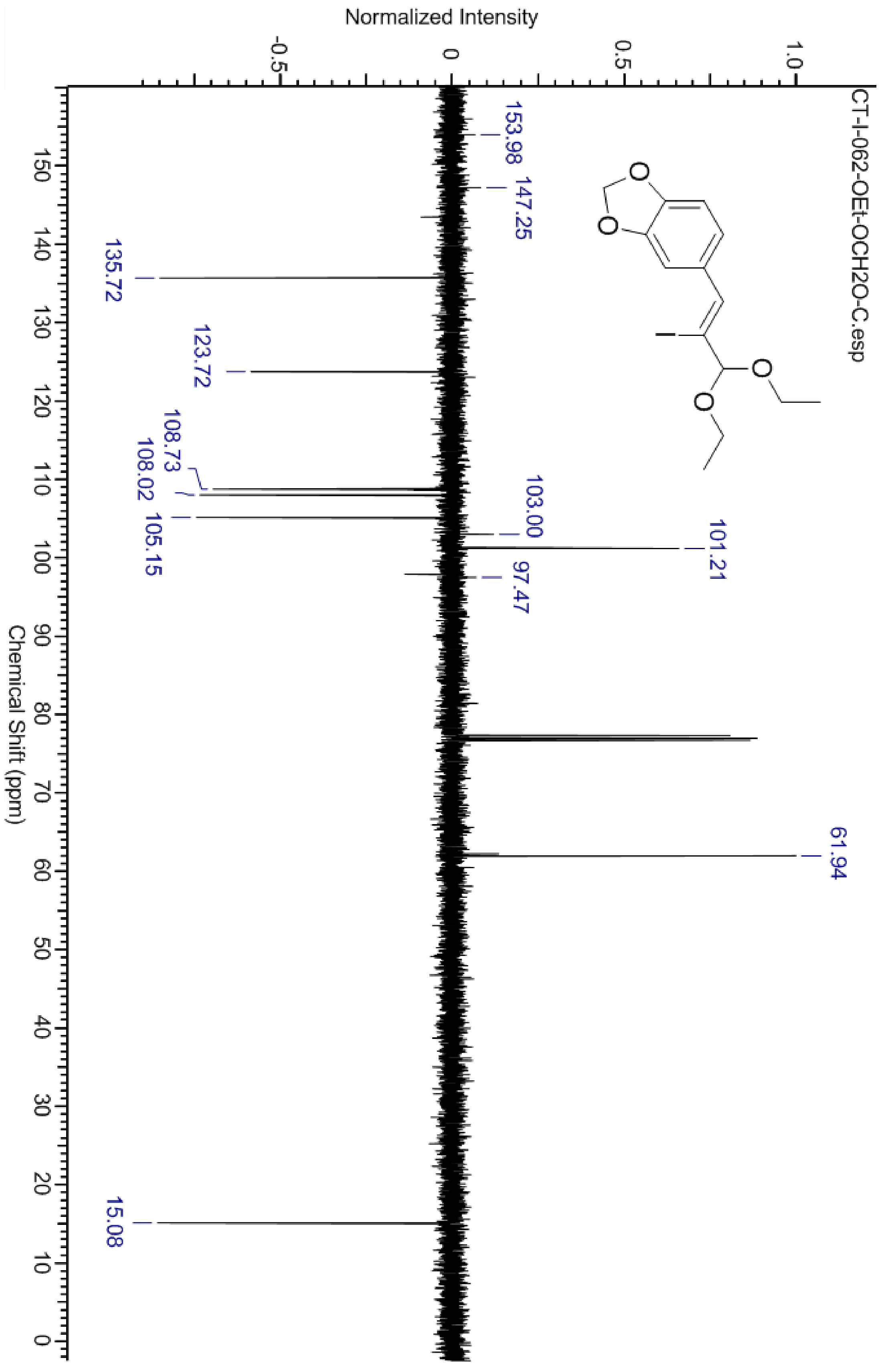

CT-I-090-OEt-mCl-H.esp
Cl
I
O
O
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Chemical Shift (ppm)
9
8
7
6
5
4
3
2
1
0
7.57
7.46
7.32
7.31
7.27
4.78
3.72
3.69
3.67
3.61
3.59
3.57
1.32
1.30
1.28
1.00
0.98
2.06
1.05
0.98
5.17
6.76

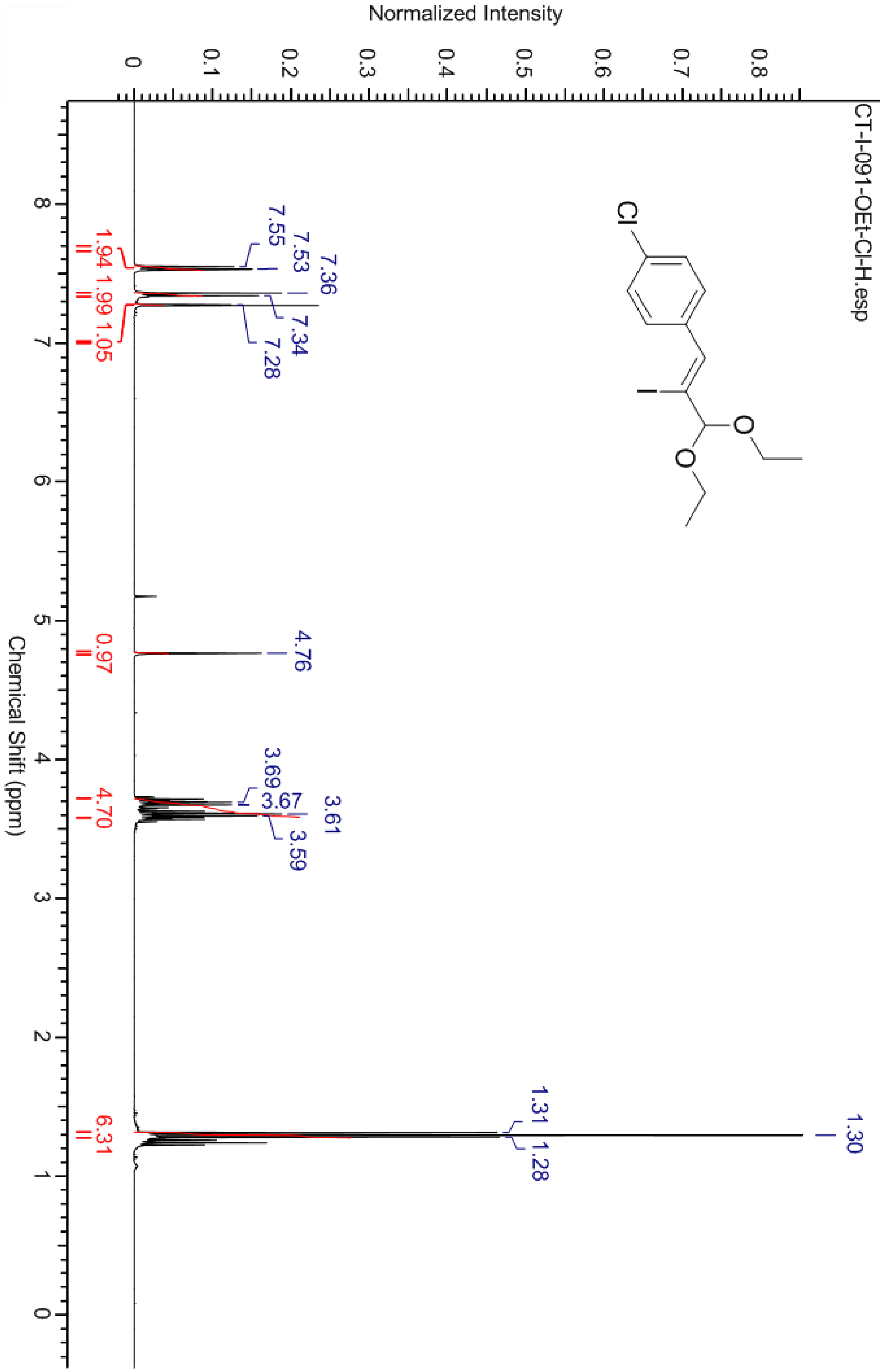

CT-I-090-OEt-mCl-C.esp
Cl
I
O
O
Normalized Intensity
1.0
0.5
0
-0.5
138.49
133.81
134.89
129.23
128.60
128.13
126.84
106.38
104.59
61.83
14.98
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

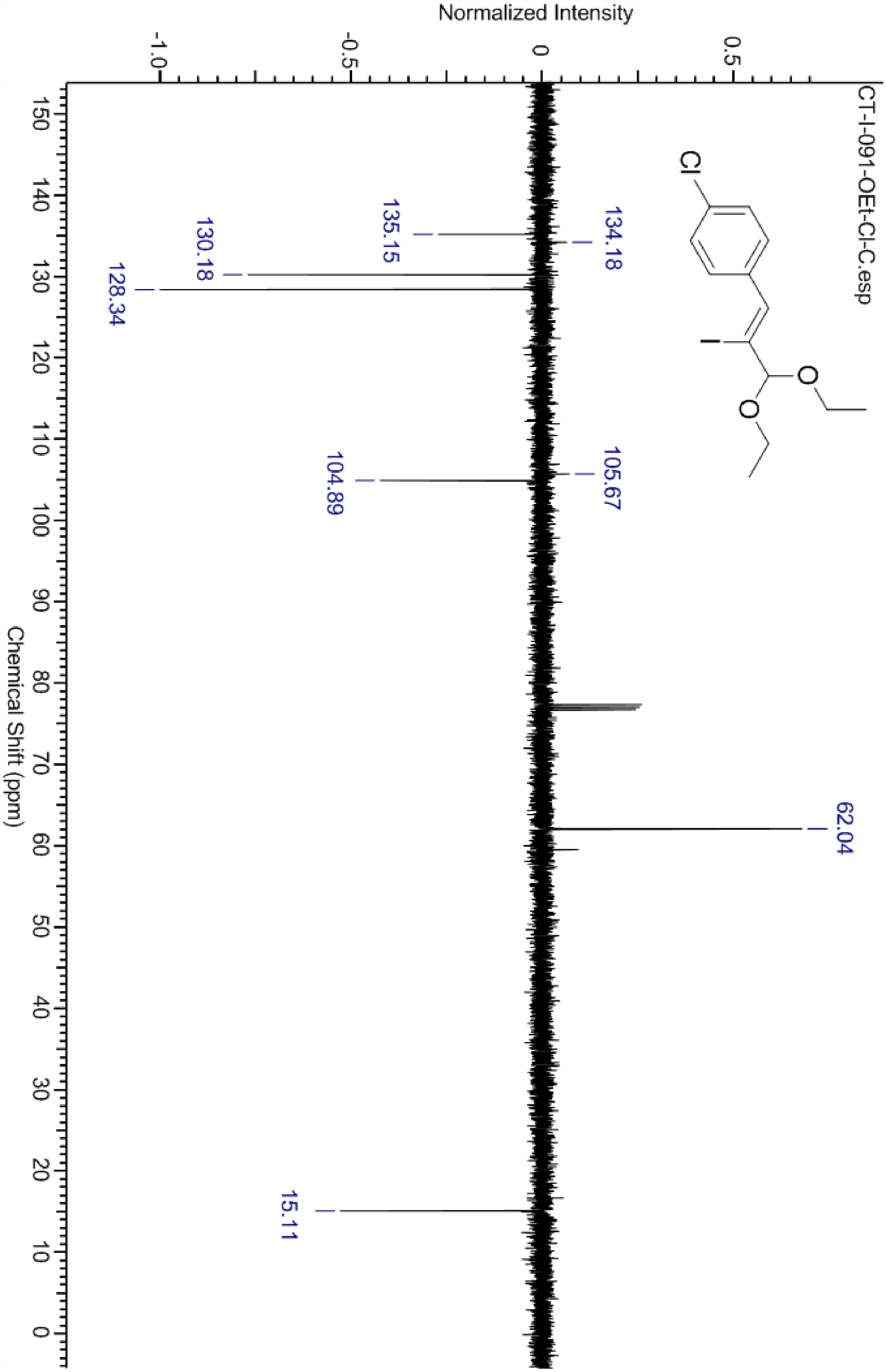

CT-I-082-OEt-Br-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Br
O
O
7.51 7.50
7.53
7.47
7.27
4.77
3.70
3.72
3.69
3.62
3.60
3.58
1.33
1.31
1.29
4.04
1.00
1.00
4.08
5.95
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

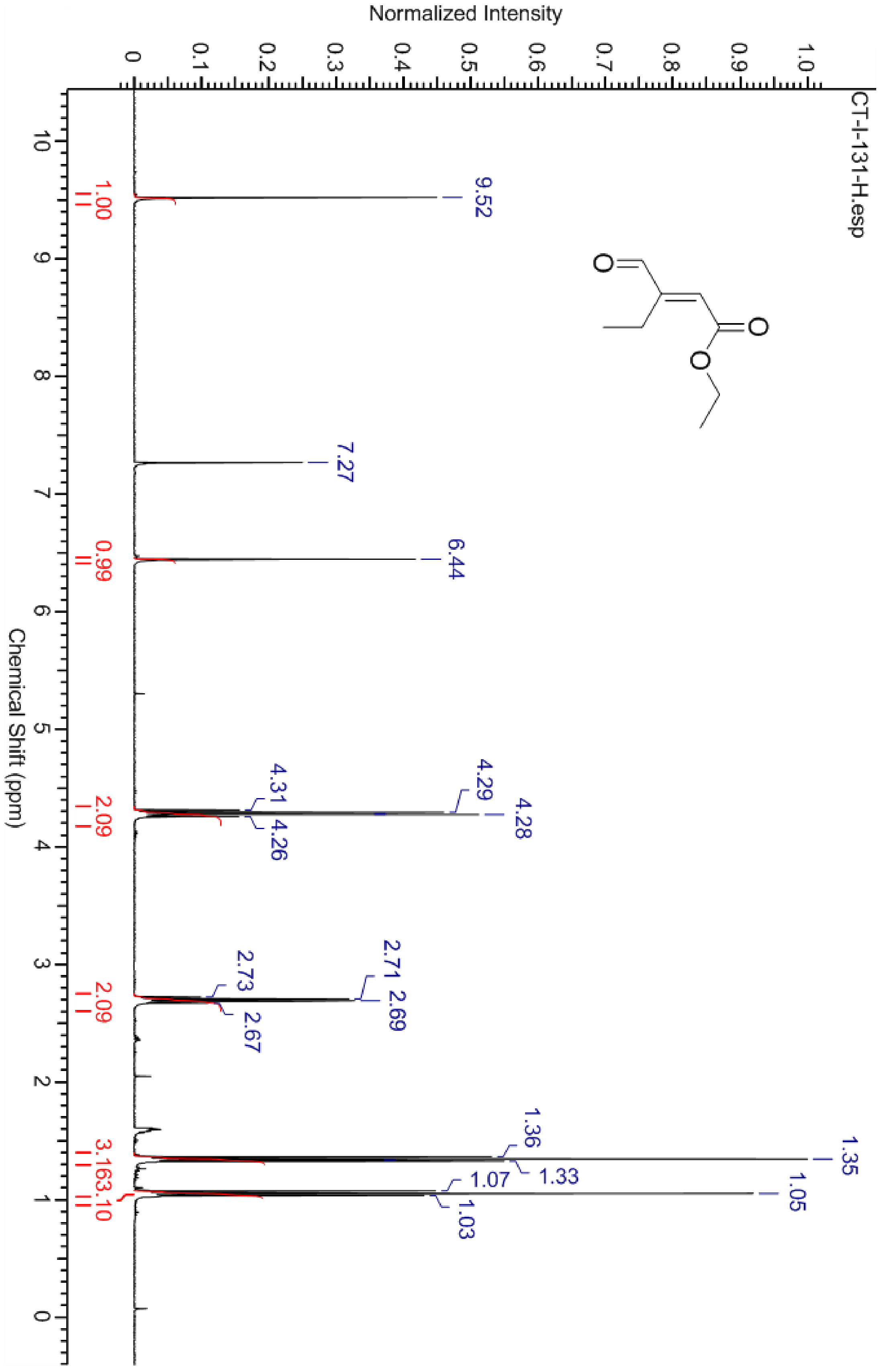

CT-I-082-OEt-Br-C.esp
Br
I
O
O
Normalized Intensity
0.5
0
-0.5
-1.0
135.58
135.18
131.27
130.41
122.37
105.73
104.84
62.00
15.08
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

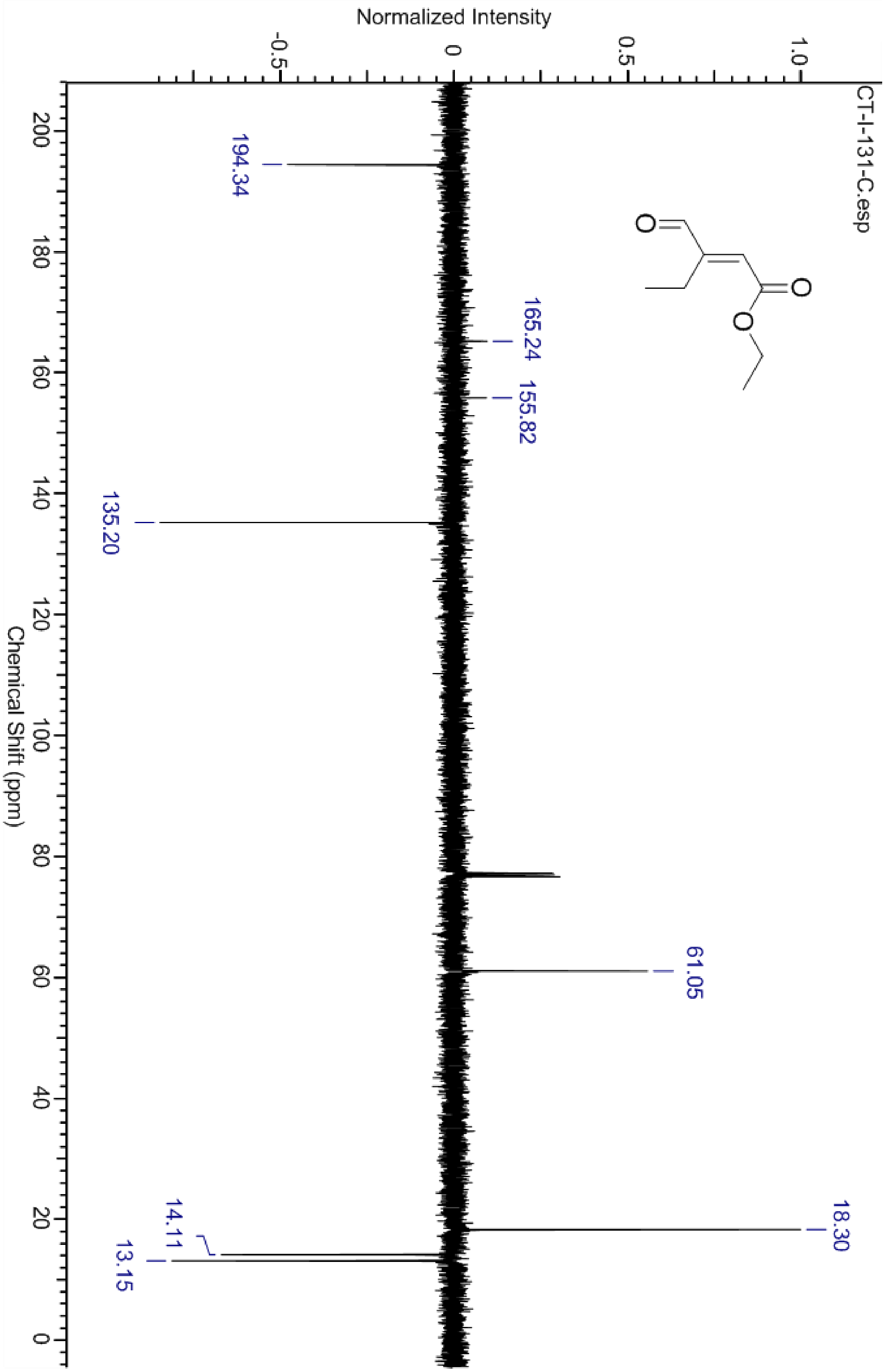

CT-I-062-1(oetpro).001.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
O
O
O
O
7.31
7.30
7.23
7.08
7.06
6.84
6.82
6.01
4.72
3.73
3.71
3.69
3.67
3.61
3.59
3.57
3.55
1.32
1.30
1.29
0.94
1.01
1.01
1.08
1.92
1.06
4.53
6.29
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

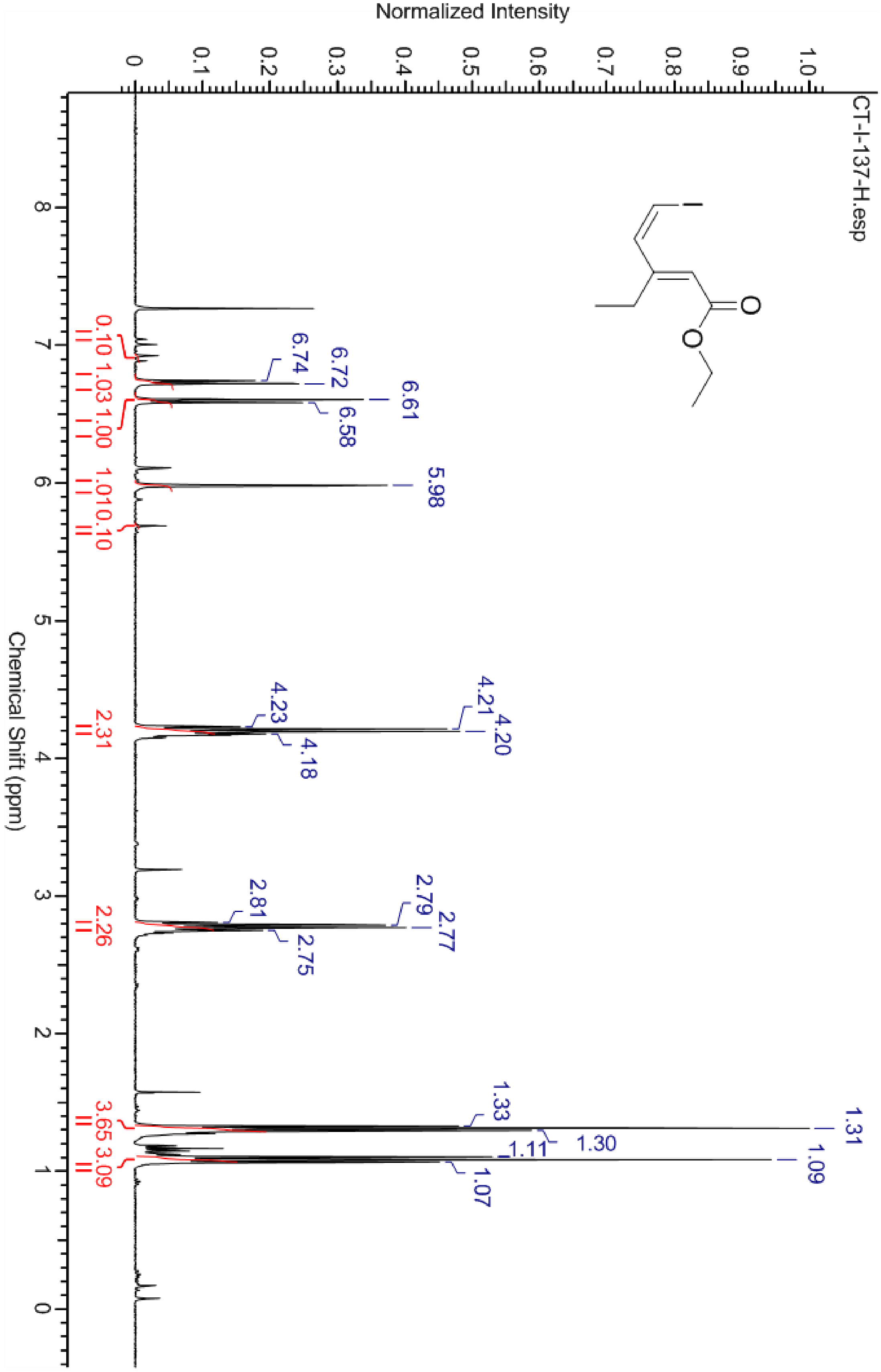

CT-I-062-OEt-OCH2O-C.esp
Normalized Intensity
Chemical Shift (ppm)
1.0
0.5
0
-0.5
153.98
147.25
135.72
123.72
108.73
108.02
105.15
103.00
101.21
97.47
61.94
15.08
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
O
O
O
O

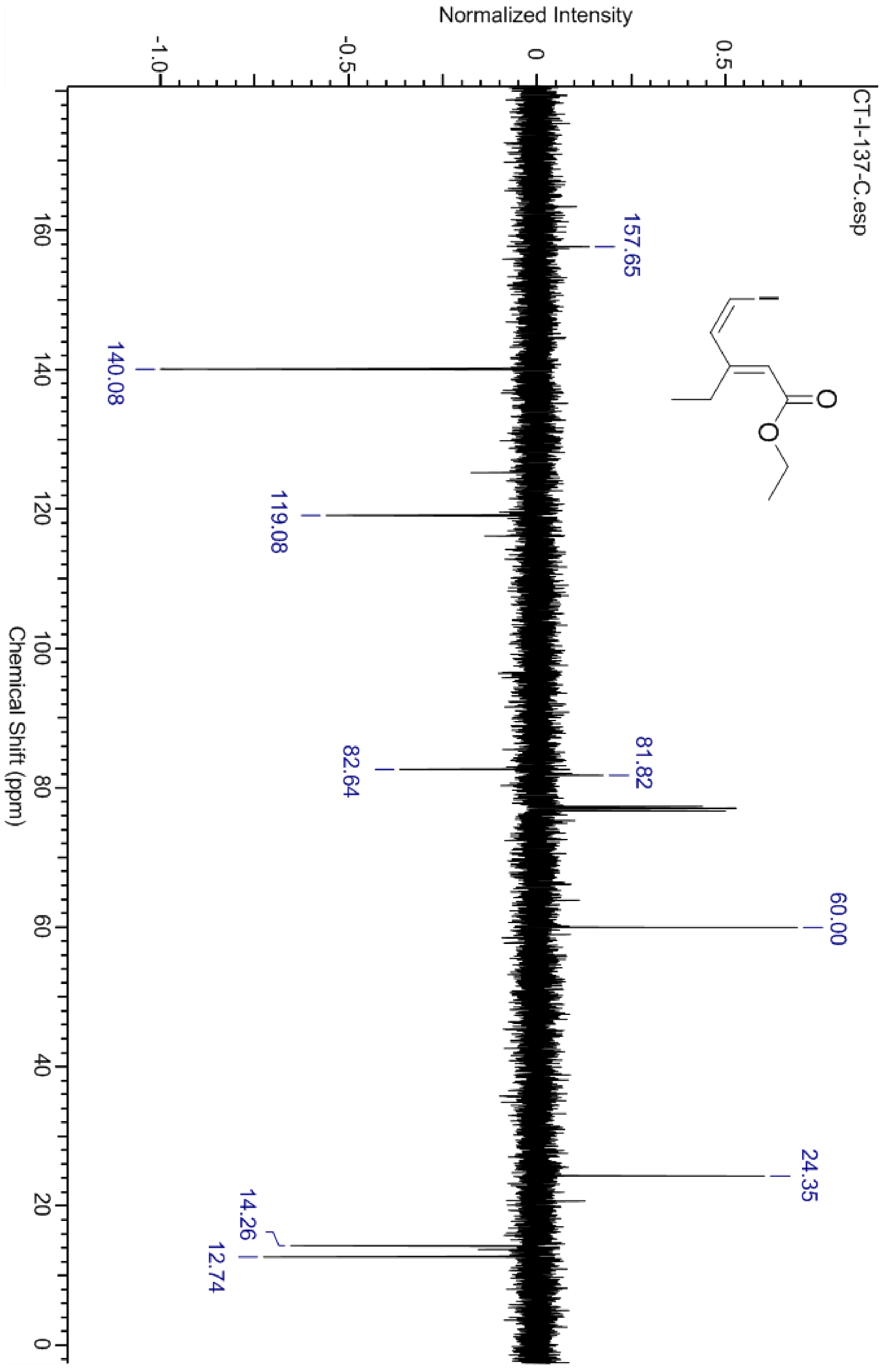

CT-I-091-OEt-Cl-H.esp
Cl
I
O
O
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Chemical Shift (ppm)
8
7
6
5
4
3
2
1
0
7.55
7.53
7.36
7.34
7.28
4.76
3.69
3.67
3.61
3.59
1.31
1.30
1.28
1.94
1.99
1.05
0.97
4.70
6.31

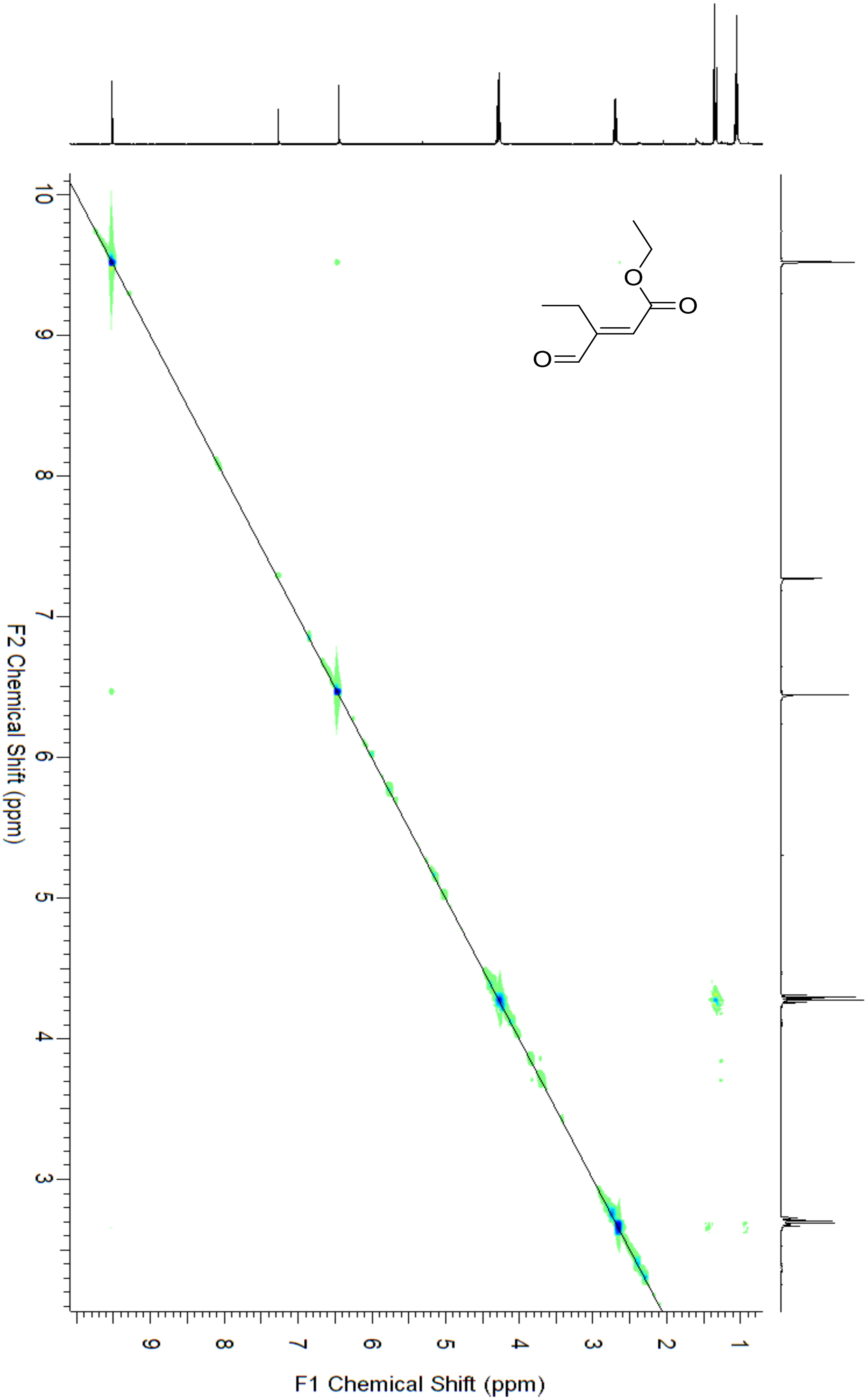

CT-I-091-OEt-Cl-C.esp
Cl
I
O
O
Normalized Intensity
0.5
0
-0.5
-1.0
134.18
135.15
130.18
128.34
105.67
104.89
62.04
15.11
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


CT-I-131-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
9.52
7.27
6.44
4.31
4.29
4.28
4.26
2.73
2.71
2.69
2.67
1.36
1.35
1.33
1.07
1.05
1.03
1.00
0.99
2.09
2.09
3.16
3.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
O
O


CT-I-131-C.esp
O
O
O
Normalized Intensity
1.0
0.5
0
-0.5
194.34
165.24
155.82
135.20
61.05
18.30
14.11
13.15
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CT-I-137-H.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
O
O
I
6.74
6.72
6.61
6.58
5.98
4.23
4.21
4.20
4.18
2.81
2.79
2.77
2.75
1.33
1.31
1.30
1.11
1.09
1.07
0.10
1.03
1.00
1.01
0.10
2.31
2.26
3.65
3.09
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


CT-I-137-C.esp
Normalized Intensity
0.5
0
-0.5
-1.0
I
O
O
157.65
140.08
119.08
82.64
81.82
60.00
24.35
14.26
12.74
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
O
O
F2 Chemical Shift (ppm)
10
9
8
7
6
5
4
3
F1 Chemical Shift (ppm)
9
8
7
6
5
4
3
2
1