

**Total Synthesis of (+)-Anhydrohavellockate and the Tetracyclic
Core of *Cembranoid* Natural Products**

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....*he who dares, wins.*

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ABSTRACT

Polycyclic cembranoid and norcembranoid natural products are congested, highly oxygenated natural products found in multiple marine sponges, and as of today, their synthesis remains a significant challenge for organic chemists. As well as being of great interest to biologists and medicinal chemists for their interesting medicinal applications, these natural products can certainly pique curiosity for the curious synthetic chemist seeking a challenge. In that optic, havellockate, one of the most complex members of this family of natural products, was chosen for the target of this research thesis.

We herein report a highly efficient enantioselective gram-scale synthesis of the tetracyclic core of (+)-havellockate as well as the total synthesis of (+)-anhydrohavellockate. The chemistry developed in this thesis can also be applied to the divergent synthesis of other higher order cembranoid and norcembranoid natural products such as mandapamate, confertdiatate, dissectolide and plumarellide. Stemming off of the Barriault laboratory's expertise in gold catalysis, an initial racemic model substrate was targeted, seeking to construct a simplified version of the tetracyclic core of these natural products. The initial hypothesis was to build a linear fragment that would react multiple times with itself in a stereocontrolled manner upon treatment with an Au^I catalyst. During the assembly of this linear fragment, the desired tetracyclic core target could be isolated, a serendipitous discovery that skyrocketed the efficiency of this synthesis.

Upon this discovery, an enantioselective synthesis of this tetracyclic structure was initiated, and after much optimisation, the enantiopure polycyclic structure could be accessed in a stereocontrolled manner. A linear substrate was assembled, and when exposed to Sonogashira cross-coupling conditions, a spectacular reaction cascade was observed. This cascade was thoroughly studied and underwent five chemical transformations in a single pot, which generated the tetracyclic core of the natural product havellockate in a single operation. This chemistry was developed to be applied on gram-scale and furnished plenty of material for the required late-stage transformations.

The last two transformations required to access the natural product, however, proved challenging, and multiple strategies were explored. Multiple protocols for the required penultimate alkene isomerisation were developed and ultimately succeeded, yielding the product (+)-anhydrohavellockate in 11 steps in the longest linear sequence from commercially-available TMS acetylene. The installation of the last oxygen atom, however, resisted all of our efforts, so far.

In total, this work sums of five years of efforts, where we studied a spectacular reaction cascade that stereoselectively constructed the tetracyclic core of the natural product (+)-havellockate through 5 distinctive steps that were carefully choreographed by clever chemical design and rationale. This work effectively achieved the enantioselective total synthesis of (+)-anhydrohavellockate in 11 steps from commercial reagents.

RÉSUMÉ

Les cembranoïdes et norcembranoïdes polycycliques sont des produits naturels complexes possédant un haut niveau d'oxygénation jusqu'à aujourd'hui, leur synthèse reste un défi de taille pour les chimistes organiciens. En même temps que d'être d'intérêt pour les biologistes et les chimistes médicaux pour leurs applications médicales, ces produits naturels ont certainement le pouvoir de piquer la curiosité du chimiste de chimie de synthèse cherchant un défi de taille. Dans cette optique, havellockate, un des membres uniques de cette famille de produits naturels, a été choisi comme cible pour les efforts de recherche de cette thèse.

Ici donc sera présentée une synthèse énantiosélective hautement efficace et à grande échelle du cœur tétracyclique du (+)-havellockate, ainsi que la synthèse totale de (+)-désoxyhavellockate. La chimie développée dans cette thèse peut également être appliquée à la synthèse divergente d'autres produits naturels cembranoïdes complexes, tels que le mandapamate, le confertdiolate, le dissectolide et le plumarellide. En se basant sur l'expertise du laboratoire Barriault en catalyse à l'or, un substrat modèle racémique a été initialement ciblé dans le but de construire un modèle du noyau tétracyclique du produit naturel. L'hypothèse initiale était de construire un fragment linéaire qui pourrait ensuite réagir en cascade avec lui-même de manière stéréocontrôlée par traitement avec un catalyseur Au^I. Pendant la synthèse de ce substrat, le noyau tétracyclique cible souhaité a pu être synthétisé par sérendipité, augmentant considérablement l'efficacité de cette synthèse.

Suite à cette découverte, une synthèse énantiosélective de cette structure tétracyclique a été entreprise. Après de nombreuses optimisations, la structure polycyclique énantio pure a pu être obtenue avec un haut degré de stéréocontrôle. Un substrat linéaire a été préparé et, soumis aux conditions de couplage croisé de Sonogashira, permettant d'observer une cascade réactionnelle spectaculaire. Cette cascade a été étudiée en détail et a permis d'effectuer cinq transformations chimiques distinctes, générant ainsi le noyau tétracyclique du produit naturel (+)-havellockate en un seul pot réactionnel. Cette chimie a pu être appliquée à l'échelle du gramme et a fourni une quantité importante de produit pour les transformations finales requises.

Les deux dernières transformations nécessaires afin d'obtenir le produit naturel se sont avérées complexes, et plusieurs stratégies ont été explorées. Différents protocoles pour l'isomérisation de l'alcène ont été développés et ont permis d'obtenir (+)-anhydrohavellockate en 11 étapes en séquence linéaire la plus longue à partir du réactif commercial TMS acétylène. L'introduction du dernier atome d'oxygène, en revanche, a résisté à tous nos efforts jusqu'à présent.

Ce travail représente cinq années d'efforts, durant lesquelles nous avons étudié une cascade réactionnelle spectaculaire permettant la construction stéréosélective du noyau tétracyclique du produit naturel (+)-havellockate. Cette opération se déroule en cinq étapes distinctes, soigneusement orchestrées grâce à un design chimique ingénieux et rationnel. Ce travail a permis de compléter la synthèse totale énantiosélective de (+)-anhydrohavellockate en onze étapes à partir de réactifs commerciaux.

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DECLARATION ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used a single time for grammatical revision, creative writing, translation, generation of outlines or resumes, conceptualisation, idea generation, definition of research objective, formulation of research hypotheses, assessment and risk, methodology, data analysis, data management, generation of images or text, interpretation or conclusions during the five years that this project has spanned.

Any and all text present in this thesis is solely the product of the author.

LIST OF ABBREVIATIONS

AD	asymmetric dihydroxylation
anh.	anhydrous
aq.	aqueous
Ar	argon
ATP	adenosine triphosphate
BDE	bond dissociation energy
br	broad
BRSM	based on recovered starting material
Bu	butyl
°C	degrees celcius
calcd.	calculated
CCDC	Cambridge crystallographic data centre
CDP	cytidine diphosphate
cm ⁻¹	wavenumber
CoA	coenzyme A
cod	1,5-cyclooctadiene
concd.	concentrated
COSY	correlation spectroscopy
CuTC	copper(I) 2-thiophenecarboxylate
δ	chemical shift
d	doublet / day
DA	Diels-Alder
dba	dibenzylideneacetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCB	dichlorobenzene

DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
decomp.	decomposition
DFT	density functionnal theory
DIBAL-H	diisobutylaluminium hydride
DIPA	<i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethylallyl diphosphate
DMF	<i>N,N</i> -dimethylformamide
dmg	dimethylglyme
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNB	dinitrobenzene
dpg	diphenylglyme
d.r.	diastereomeric ratio
DXP	1-deoxy-d-xylulose 5-phosphate
E ⁺	electrophile
<i>E</i>	entgegen (alkene nomenclature)
EA	energy of activation
<i>ee</i>	enantiomeric excess
<i>endo</i>	endocyclic
<i>ent</i>	enantiomer
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
Et ₃ N	triethylamine

EtOAc	ethyl acetate
EtOH	ethanol
<i>exo</i>	exocyclic
FPT	freeze-pump-thaw
g	gram
G-I	Grubbs catalyst, first generation
<i>gem</i>	geminal
[H ⁻]	reduction
h	hour
HAT	hydrogen atom transfer
HDDA	hydroxy-directed Diels-Alder
HG-II	Hoveyda-Grubbs catalyst, second generation
HMBC	heteronuclear multiple-bond correlation
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
hν	light irradiation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
<i>i</i>	iso
IC ₅₀	half maximum inhibition concentration
IEDDA	Invese Electron Demand Diels-Alder
imid.	imidazole
<i>i</i> -PrOH	<i>iso</i> -propanol
IPP	isopentenyl diphosphate
IR	infrared

<i>J</i>	coupling constant
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L-Selectride	lithium tri- <i>sec</i> -butylborohydride
L	litre / ligand
LD ₅₀	median lethal dose
LDA	lithium diisopropylamide
KHMDS	lithium hexamethyldisilazide
LPS	lipopolysaccharide
m/z	mass to charge ratio
M	molar
[M]	metal
[M] ⁺	molecular ion
<i>m</i>	meta
m	multiplet
Me	methyl
MeOH	methanol
mg	milligram
M+H ⁺	protonated parent mass adduct
M+Na ⁺	sodium parent mass adduct
MeCN	acetonitrile
MEP	mevalonate-independant pathway
MHz	megahertz
min	minutes
mL	milliliter
MOM	methoxymethyl
μg	microgram
μL	microliter

μM	micromolar
μmol	micromole
mmol	millimole
mol	mole
Ms	methanesulfonyl
MS	molecular sieves
MVA	mevalonate
MW	microwave
NaDT	sodium decatungstate
NaHMDS	sodium hexamethyldisilazide
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NHC	<i>N</i> -hetereocyclic carbene
nm	nanometer
nM	nanomolar
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NP	natural product
[O]	oxidation
<i>o</i>	ortho
OBO	4-Methyl-2,6,7-trioxabicyclo[2,2,2]octyl
obs.	observed
π	pi
<i>p</i>	para
PG	protecting group

pH	hydrogen ion concentration
Ph	phenyl
PhMe	toluene
pin	pinacolato
Piv	pivaloyl
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
ppm	parts per million
PPTS	<i>para</i> -toluenesulfonic acid
Pr	propyl
py	pyridine
q	quartet
quant.	quantitative
quint.	quintet
R	generic carbon chain
<i>R</i>	rectus
r.r.	regiomeric ratio
<i>rac.</i>	racemic
RCM	ring-closing metathesis
recryst.	recrystallization
R_f	retention factor
rt	room temperature
rsm	recovered starting material
σ^*	antibonding sigma orbital
s	singlet
<i>S</i>	sinister
satd.	saturated
SCXRD	single crystal x-ray diffraction

SM	starting material
SFC	silica flash chromatography
S _N 2	bimolecular nucleophilic substitution
t	triplet
<i>t</i>	tert
TBADT	tetra- <i>N</i> -butylammonium decatungstate
TBAF	tetra- <i>N</i> -butylammonium fluoride
TBAI	tetra- <i>N</i> -butylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TFP	trifurylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Triton B	trimethylbenzylammonium hydroxide
Ts	<i>para</i> -toluenesulfonyl
xs	excess
<i>Z</i>	zusammen (alkene nomenclature)

CHAPTER 1

The *Cembranoid* diterpenes and havellockate

1.1 – Introduction

Nature has always been the greatest source of inspiration for scientists. From observing natural phenomena to trying to recreate them within the confines of a laboratory, the products of evolution continue to fascinate researchers and curious minds alike. Along the evolutionary chain, organisms have evolved to gain an edge over their competitors, and do so by creating and secreting secondary metabolites, which are complex molecules built up from small carbon-based fragments that are available to them to assist in their survival, stress adaptation and defense against predators. These fascinating organic molecules provide a vital source of motivation for scientists in the search for remedies to diseases and sicknesses. Thus, we need to make it an essential science to study these captivating products of nature. One of the greater example of this necessity is the discovery of Paclitaxel as a treatment for cancer, which is still widely used to this day. In 1960, in California, plants were collected at random and screened against a wide range of cancer cell lines, and a hit, Taxol®, was identified, which stemmed from ethanolic extracts of trees of the *T. brevifolia* genus. From 12 kg of dried stem of the plant, only 0.5 g of Taxol® were collected, representing a 0.004% yield (Figure 1.1).¹ As the identity and the mechanism of action of the unknown promising future drug were determined, a chemical *gold rush* ensued in the early 1990's, where the molecule obtained the status of “*Holy grail*” by the synthetic chemistry community – with entire research groups halting their undergoing research to redirect their enterprise towards this natural product (NP) due to its highly complex structure and promising pharmacologic properties.²

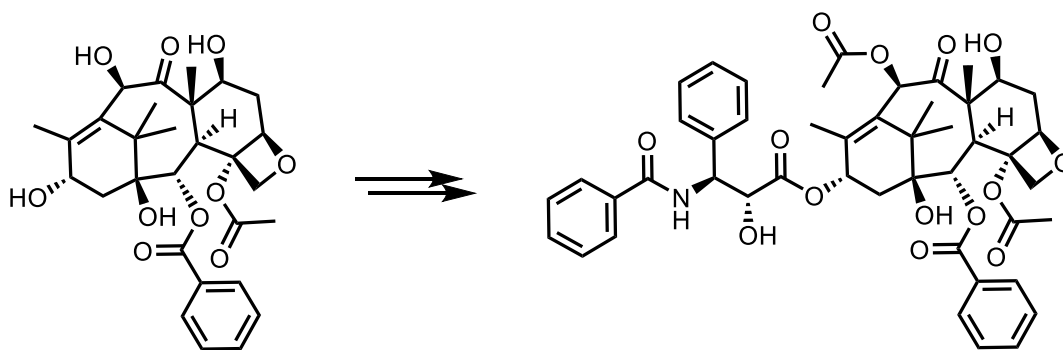


Figure 1.1. Structure of 10-deacetylbaccatin III (*left*) and Paclitaxel (Taxol®, *right*).

As a result, the Nicolaou research group reported the first total synthesis of Taxol in 1994.³ The scientific community has now developed over 15 syntheses (total & formal) of this important natural product. This, however, has failed to yield sufficient quantities of the drug for mass use in cancer treatment, as multiple hundreds of pacific yew trees needed to be felled to obtain the

quantity required to treat a single patient.² To remedy this problem, chemists cleverly came up with the idea to use a biosynthetic intermediate to pave a scalable access to the drug. The first large-scale approach involved the semi synthesis of Taxol® from 10-deacetylbaccatin III, isolated in higher concentrations from the needles and twigs of the European Yew tree. This offered a renewable source, as needles and twigs could be harvested periodically, and lessened the environmental impact of large-scale felling of the trees. The story of the discovery, isolation, use and large-scale production of Taxol® remains a fascinating tale that enlightens chemists in their synthetic efforts to this day. Learning from this story, it is of central importance to continue to invest efforts in the isolation, characterization and synthetic access to new natural products, which will hopefully enable a full biological activity screening and, in the end, pave a synthetic pathway to potential new pharmaceutical treatments to heal ailments.

1.1.1 – The cembranoid diterpenes

The cembranoid natural products, which are the derivatives of the diterpene cembrene A (**1.1**), are a vast family of diterpene natural products found in marine species and terrestrial species alike. Interestingly, they are also found in tobacco and insects.⁴ The structural diversity and complexity of these polyoxygenated 20 carbon secondary metabolites have made them an interesting area of study for biologists and chemists. Since the isolation of the main initial biosynthetic progenitor diterpene cembrene A (**1.1**, Figure 1.2) isolated from the trunk of a pine tree in 1962, hundreds of downstream natural products have been isolated in the last 60 years, especially from marine sources.⁵

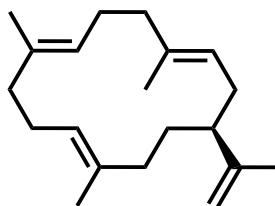


Figure 1.2. Structure of cembrene A (**1.1**).

The name given to these natural products and their congeners generally reflect the genus or species they were isolated from, *i.e.* “rubifolide” and “gersemolide” were isolated from the soft coral *Gersemia rubiformis* and “bipinnatin” isolated from the soft coral *Pseudopterogorgia bipinatta*. Other names reflect the site or collection point of the originating coral, *i.e.* “pukalide”

comes from *Puka*, the Hawaiian name for *hole*, since the coral was collected at the Blowhole rock formation in Hawaii; “rameswaralide” and “mandapamate” originate from Rameswaran, a mythological site on the Mandapam coast in India. Likewise, “havellockate” is a natural product that was isolated around the island of Havellock in the Indian ocean, and so on.⁶

Terrestrial cembranoids are primarily distributed in plants of the *Nicotiana*, *Boswellia* and *Pinus* genera. The *Nicotiana* genus is reported to contain the highest concentrations of cembranoids found in nature. In tobacco plant, it is contributing to the continuous cropping obstacle of plants, effectively reducing yield and lowering quality of the plant when it is continuously planted on the same land.⁷ Simultaneously, other compounds of this family are reported to be important aroma precursors in tobacco, which are synthesized in tobacco gland hairs during its growth.⁸ Interestingly, the flavour profile of tobacco was found not to stem from cembranoid natural products themselves but from their natural degradation to solanone, solanofuran and other natural products during the tobacco curing aging process.⁷ Cembranoids can be found in the trees of the *Boswellia* genus, where they are in high concentrations and make up the active ingredient, along with other compounds, in the traditional Chinese medicine “frankincense”, made from the gum resin of these trees. This indigenous medicine has been used to treat rheumatic arthralgia, chest obstruction, dysmenorrhea and amenorrhea.⁹ Frankincense also possesses analgesic, anti-inflammatory, sedative, antihyperlipidemic and antibacterial activities, and has historically been used to treat rheumatoid arthritis, osteoarthritis and ulcers.⁹

The Cembranoid natural products are also found in marine species, namely octocorals and soft coral species. The marine cembranoids, usually higher in complexity than terrestrial ones, help defend against competing and predatory organisms. The Indo Pacific reefs are populated largely by soft corals, especially from the *Sinularia* species. Despite their abundance in reef biomass, soft corals seem to have very few predators, believed to stem from the defensive action of cembranoids.¹⁰ The range of interesting biological properties from these secondary metabolites, *i.e.* antitumoral, antimicrobial and anti-inflammatory action, offers a great opportunity for their study and application to new therapeutics.⁶ For example, Uchio’s toxin (**1.2**) was found to protect *Sinularia flexibilis* soft corals from mosquitofish by poisoning upon fish feeding on the coral (Figure 1.3).¹¹ High concentrations of “cembranolid” **1.3** was found in *Sinularia maxima* corals, which was found to be able to deter local fish species feeding on *Sinularia maxima* corals.¹²

Allelopathy, a biological phenomenon where species release chemicals to inhibit and influence the growth of other organisms, was found to be the mechanism of action of flexibilide (**1.4**) in *Sinularia flexibilis*, which was able to kill neighboring hard corals at low exposures (5-10 ppm) over 8 hours.¹³ Sinulariolide (**1.5**), also found in *S. flexibilis*, was found to have antifouling properties, protecting against and controlling the growth of a number of algae on the coral.¹⁴

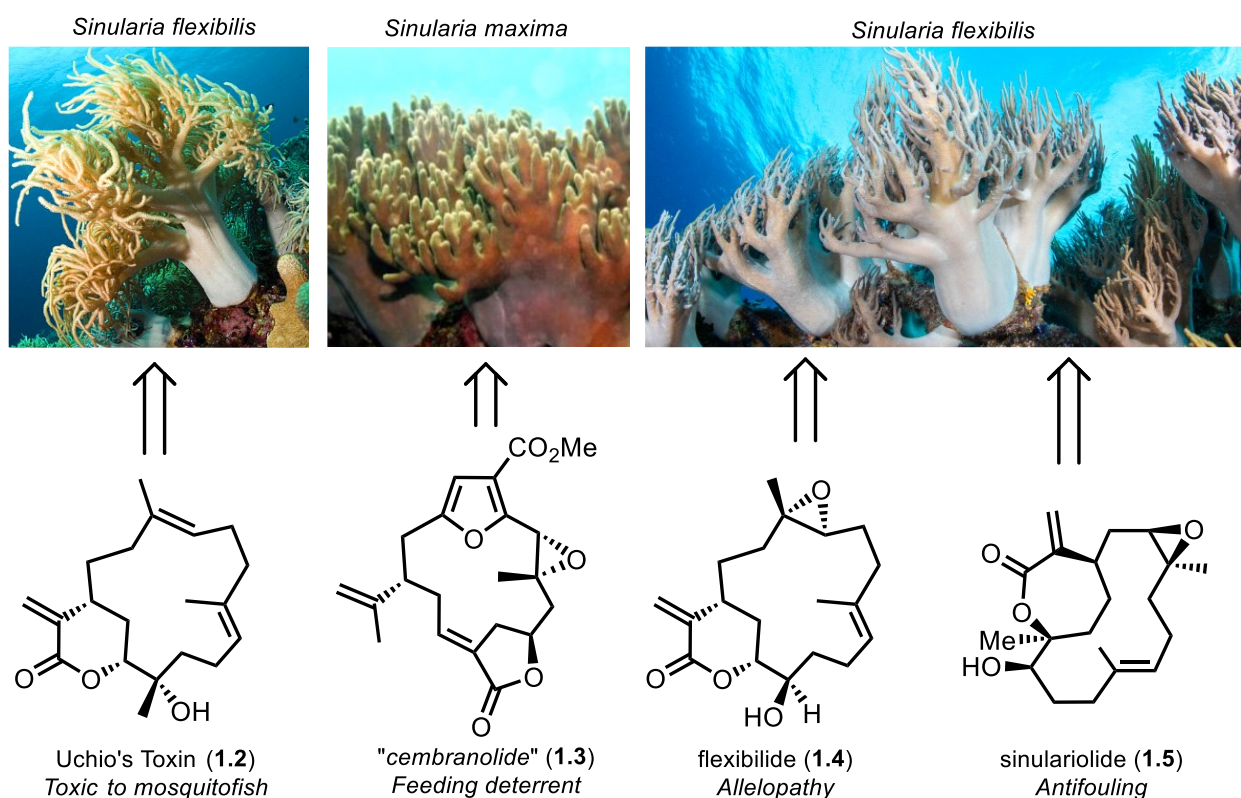


Figure 1.3. Cembranoid marine natural products and their biological role in coral colonies.

Cembranoid natural products have a wide range of structural diversification the further along they evolve along the biosynthetic ladder. As the complexity increases, additional oxygen incorporation and ring formation is observed. There are 14 membered macrocyclic diterpenes that can generally be structurally divided into 4 greater subfamilies. Due to the very wide breadth of natural products isolated, different representations of the cembrene core appear in the literature for different families of cembranoids. In the interest of an easier discussion, carbon numbering will stay identical but the spatial representation made by authors of the reporting work will be used.

The first are derivatives of the cembrene C₁₄ macrocycle **1.6**, which is directly derived from the geranylgeranyl diphosphate (GGPP), and is represented by the member β -cembratrien-diol **1.7**

(Figure 1.4). These simpler natural products are highly represented in terrestrial plants and trees, especially tobacco.⁸ Cyclisation and further oxidation of the latter unveils a step up in complexity in form of bicyclic substrates, namely 2,11-cyclized cembranoids (**1.8**), which have been extensively studied and observed in marine species of soft corals and is represented by Eunicellin (**1.9**).¹⁵ Undergoing further oxidation at C₁₀, C₆ and C₃ give rise to the furanobutenolide-derived cembranoids **1.10** and norcembranoids **1.11**. Interestingly, the norcembranoid furanobutenolides consist of a 19-carbon framework, having lost a carbon unit. It has been postulated that the loss of C₁₈ typically occurs by oxidation and subsequent hydrolysis along the biogenesis from GGPP.⁶ The tricyclic natural products are represented with bipinnatin J (**1.12**), a member of the cembranoids (C₂₀) which has gained a lot of attention from the synthetic community recently for its proposed role as a pivotal intermediate in the biosynthesis of higher order polycyclic cembranoid and norcembranoid natural products.^{16–19} Further oxidation, cyclisations and rearrangement of simpler biosynthetic precursors (*i.e.* **1.12**) afford rearranged polycyclic furanobutenolide cembranoid natural products (**1.13**) and norcembranoid natural products (**1.14**). These natural products continue to retain the C₁₄ macrocyclic scaffold have undergone photorearrangements, cyclizations, cycloadditions and 1,3-dipolar cycloadditions.^{19,20} These polycyclic species are also classified within the cembranoid and norcembranoid subcategories.^a One such member is dissectolide A (**1.15**), a tetracyclic polyoxygenated norcembranoid.^{21,22}

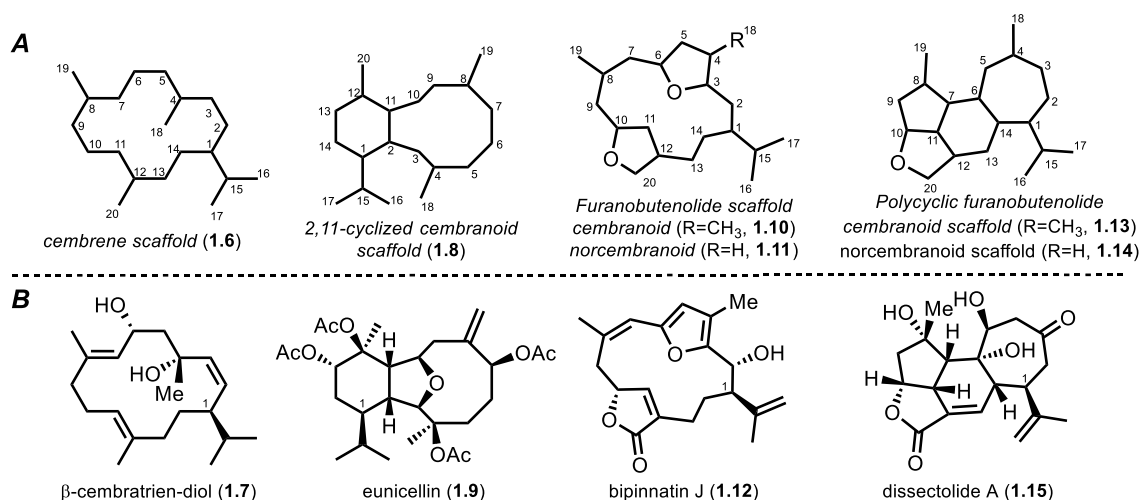


Figure 1.4. (A) Subfamilies of cembranoid natural products & (B) representative natural products.

^a To keep this monograph concise, the term “cembranoid” will be used to describe both of the *cembranoids* (C₂₀) and *norcembranoids* (C₁₉) natural products when not specified further.

Along the described subfamilies of cembranoids described above, the polycyclic furanobutenolide cembranoids offer a wide breadth of natural products that have captivated chemists and biologists alike for their complexity and biosynthetic origins. Every year, new natural products of this family are isolated, which continues to puzzle chemists and biochemists alike, who try to interlink the NPs to probe biosynthetic connections. The polycyclic natural products can be separated into two categories : cembranoid and norcembranoid. As previously discussed, the former is derived from the macrocyclic scaffold **1.13** and has retained all 20 carbons. Complementarily, the norcembranoid polycyclic natural products stem from scaffold **1.14** and contains 19 carbons in its core structure. To this day, 12 polycyclic furanobutenolide cembranoid natural products have been isolated (Figure 1.5). They are : intricarene (**1.16**)²³, havellockate (**1.17**)²⁴, bielschowskysin (**1.18**)²⁵, rameswaralide (**1.19**)²⁶, verrillin (**1.20**)²⁷, and the suite of related furan-bridged related natural products plumarellide (**1.21**)²⁸, plumarellate (**1.22**)²⁸, mandapamate (**1.23**)²⁹, isomandapamate (**1.24**)³⁰, bishomoisomandapamate (**1.25**)³¹, confertdiat (**1.26**)³² and pavidolide B (**1.27**).³³

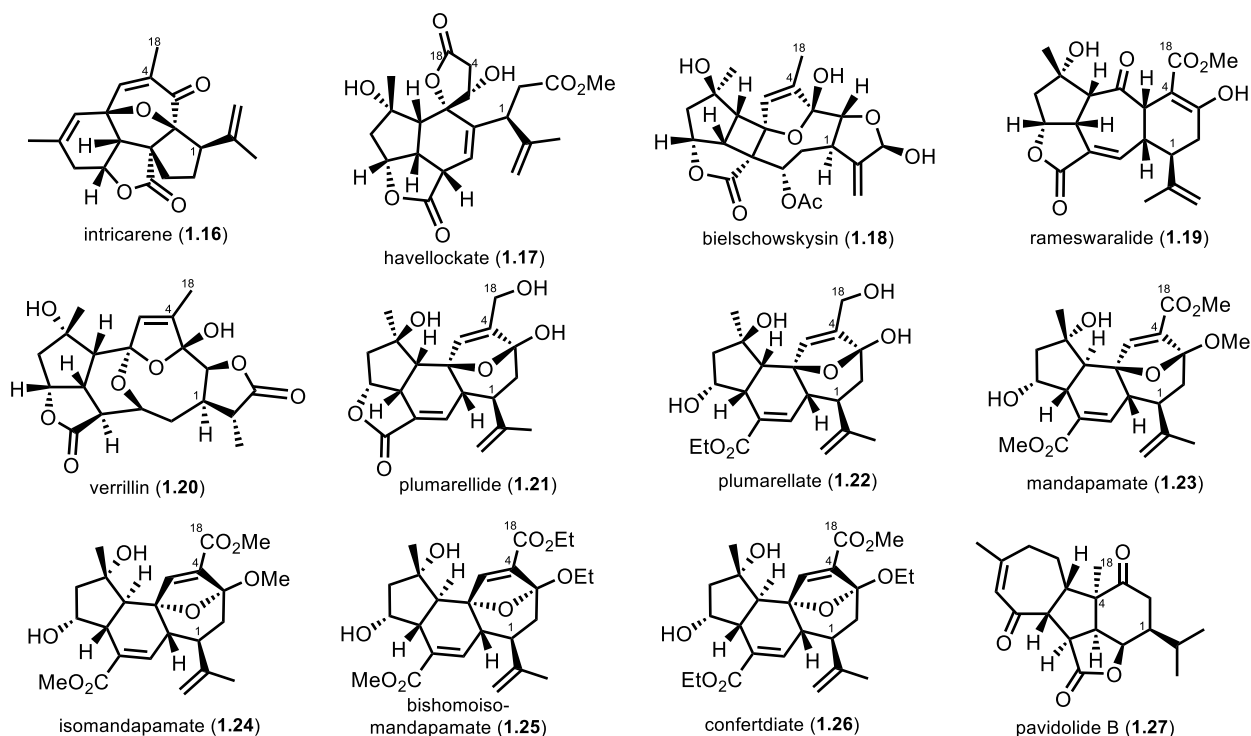


Figure 1.5. Polycyclic furanobutenolide cembranoid natural products.

The norcembranoid polycyclic natural products are comprised of 11 members (Figure 1.6). They are : ineleganolide (**1.28**)³⁴, horiolide (**1.29**)³⁵, kavaranolide (**1.30**)³⁶, dissectolide A (**1.15**)²¹, sinulochmodin C (**1.31**)³⁷, scabrolide A (**1.32**)³⁸, scabrolide B³⁸ (**1.33**, *structure reassigned in 2024*)³⁹, yonarolide (**1.34**)⁴⁰, 12-hydroxy-scabrolide A (**1.35**)⁴¹, sinulanorcembranolid A (**1.36**)⁴² and 1-epi-sinulanorcembranolid A (**1.37**)⁴³.

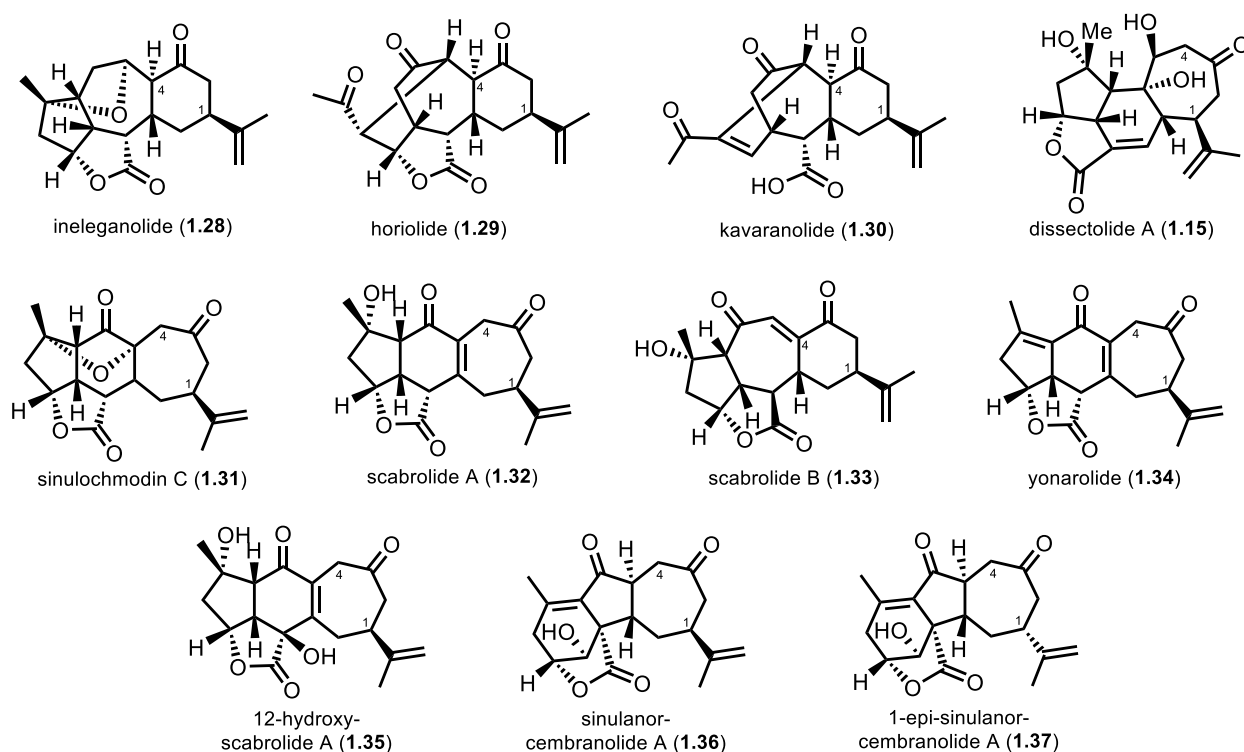


Figure 1.6. Polycyclic furanobutenolide norcembranoid natural products.

As a sum, these natural products offer a wide variety of complex, compact, dense architecture that are all biosynthetically related, and opens the possibility that accessing a single common synthetic precursor could give an access to many of these NPs.

Interestingly, most of the isolated cembranoids (**Figure 1.5**) are closely related, often separated by a different methanol or ethanol ester or acetal. Chemical handles such as esters and acetals can be prone to facile transformation during handling to yield new “un-natural” products.⁴⁴ This can be further inferred by looking at their isolation studies, usually reported in the same isolation article (*i.e.* Plumarellide **1.21** and Plumarellate **1.22**) in which the NPs are found in the ethanolic and methanolic extracts.

1.1.2 – Havellockate

Havellockate (**1.17**) was isolated in 1998 by Anjaneyulu and colleagues from ethyl acetate extracts of dried *Sinularia granosa* soft corals collected around the Havelock island, located in the Indian ocean (Figure 1.7, A).²⁴ It is a prime example of complex polycyclic cembranoid natural products, which belongs to the cembranoid subfamily owing to its C₂₀ core. which is not as obvious as the other members of this subfamily as it does not contain a 7-member ring compared the rest of the cembranoid NPs. The latter is owed to its unique structure resulting from its biogenesis, which reveals unique oxidation pattern and skeletal disposition (Figure 1.7, B). Structurally, it contains a fused [5,5,6] all-*cis* “bowl-like” ABC tricyclic core flanked with a spiro γ -lactone D ring and a pendant linear ester. The structure features 8 stereocenters, 7 of them being contiguous. The densely functionalized, highly oxygenated structure featuring the spirolactone motif is not observed in other cembranoids, making it an unique member of this family of NPs. Anjayanulu *et al.* were able assign the absolute and relative stereochemistry of havellockate by completing a single crystal X-ray crystallography (SCXRD) analysis of the crystalline substance, isolated in an unknown quantity. The data is available at the Cambridge crystallographic data centre (CCDC) with the deposition number 1228703.⁴⁵

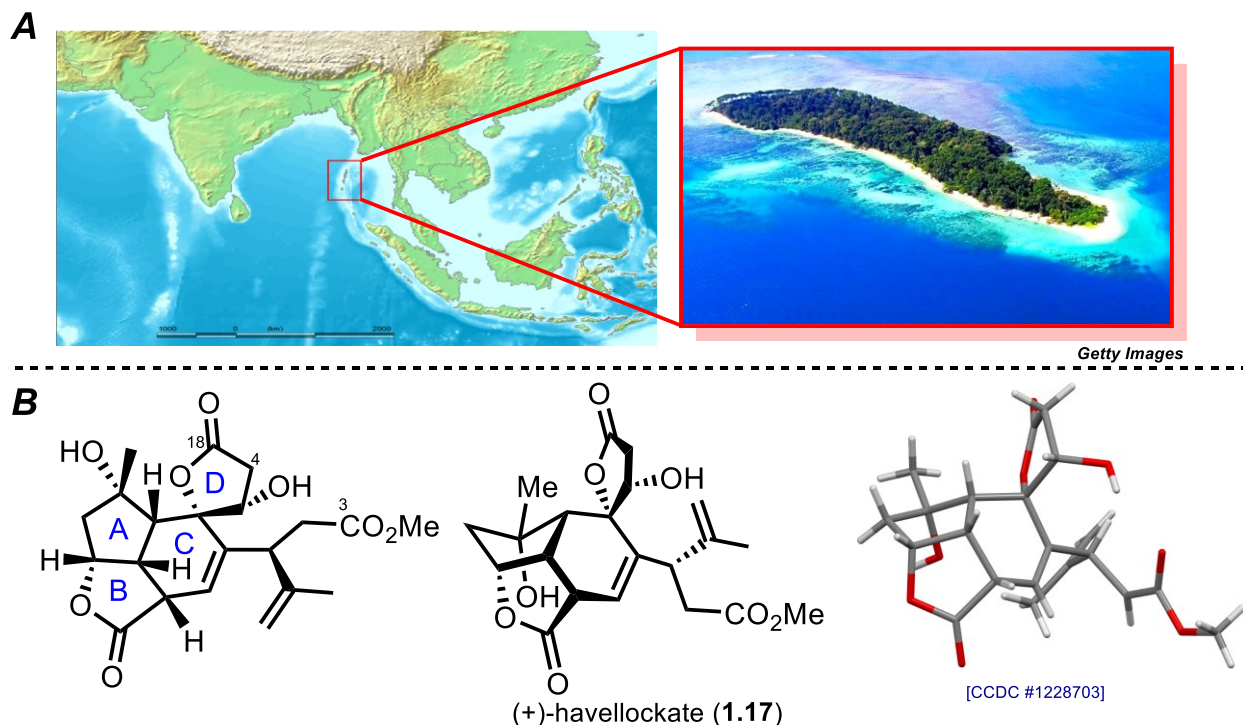


Figure 1.7. (A) The location of Havelock Island and (B) Structure of havellockate (**1.17**).

The apparent breadth of structural complexity found in polycyclic cembranoid and norcembranoid natural products has captivated chemists ever since their discovery. With now over 400 natural products in this family, there has been a continuous interest from both the biological and chemical community. In the last 8 years, there has been a very strong resurgence in the interest for these natural products by synthetic community, such as the research groups of Trauner, Pattenden, Stoltz, Vanderwal, Baran, Nicolaou, Romo, Wood, Sarlah, Fürstner, Sulikowski, Rawal, Hu, Liang, Moeller, Romiti, Roche and Zhang. All of those researchers have published their efforts towards the total synthesis of these NPs since 2018, noting a considerable uptick in activity.

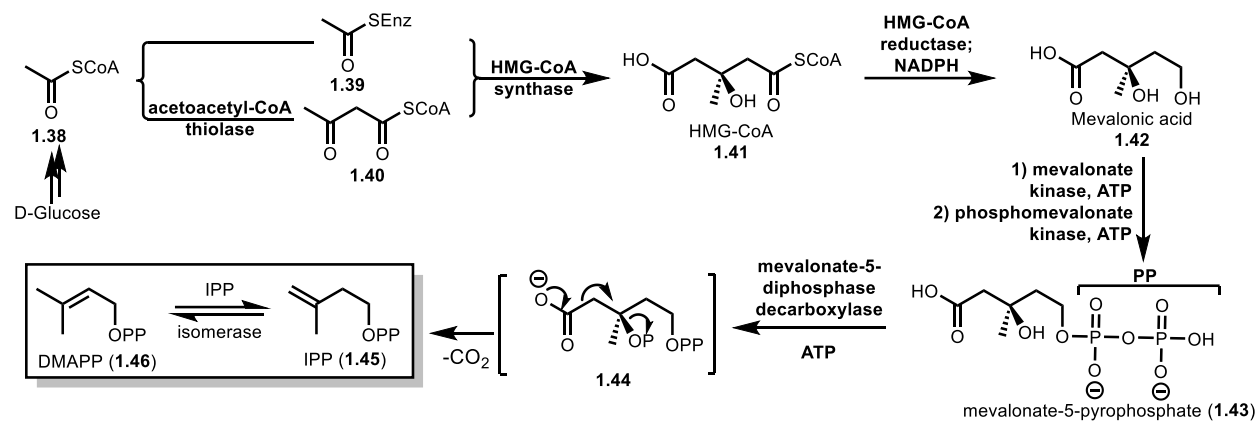
1.2 – Biosynthetic origins of polycyclic cembranoid natural products.

1.2.1 – Biosynthesis of cembrene A

All the polycyclic cembranoids of interest are derived of cembrene A (**1.1**). To fully understand the biosynthetic origins of the latter, we must pay special interest to the origin of cembrene A. Biosynthetically, cembrene A, and multiple other diterpenes, are derivatives of geranylgeranyl diphosphate (GGPP), an oligomeric product of isopentyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). The biosynthesis of IPP and DMAPP originates from two distinct pathways, depending on the origin of the biological organism (*i.e. terrestrial versus marine*). These two pathways are the Mevalonate (MVA) pathway⁴⁶ and the Methylerythritol Phosphate (MEP) pathway, referred to as mevalonate-independent pathway.⁴⁷ Since the common cembrene A, and thus polycyclic cembranoids, are found in both terrestrial and marine species, both pathways will be detailed. It is interesting to note that the MVA pathway, formerly regarded as the universal route to terpenoids, is much less prevalent in secondary metabolism than the mevalonate-independent pathway (MEP).

The MVA path is a prevalent biological pathway leading to steroids, triterpenoids, sesquiterpenoids and takes place in the cytosol of the bacteria of terrestrial species (Scheme 1.1).⁴⁶ In this pathway, D-Glucose is broken down to Acetyl-CoA (**1.38**) subunits, which can undergo a condensation with acetyl-bound thiolase enzyme **1.39** to give rise to acetoacetyl-CoA (**1.40**). Then, HMG-CoA synthase catalyses a second condensation with **1.39** to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, **1.41**). The reduction of HMG-CoA using HMH-CoA reductase and reduced nicotinamide adenine dinucleotide phosphate (NADPH) gives rise to mevalonic acid (**1.42**), which can undergo diphosphorylation to mevalonate-5-diphosphate (**1.43**) by help of two kinase enzymes.

Then, the mevalonate-5-diphosphate decarboxylate formally decarboxylates **1.43** (through intermediate **1.44**) to give rise to IPP (**1.45**). IPP can be isomerized to DMAPP (**1.46**) using the IPP isomerase enzyme.

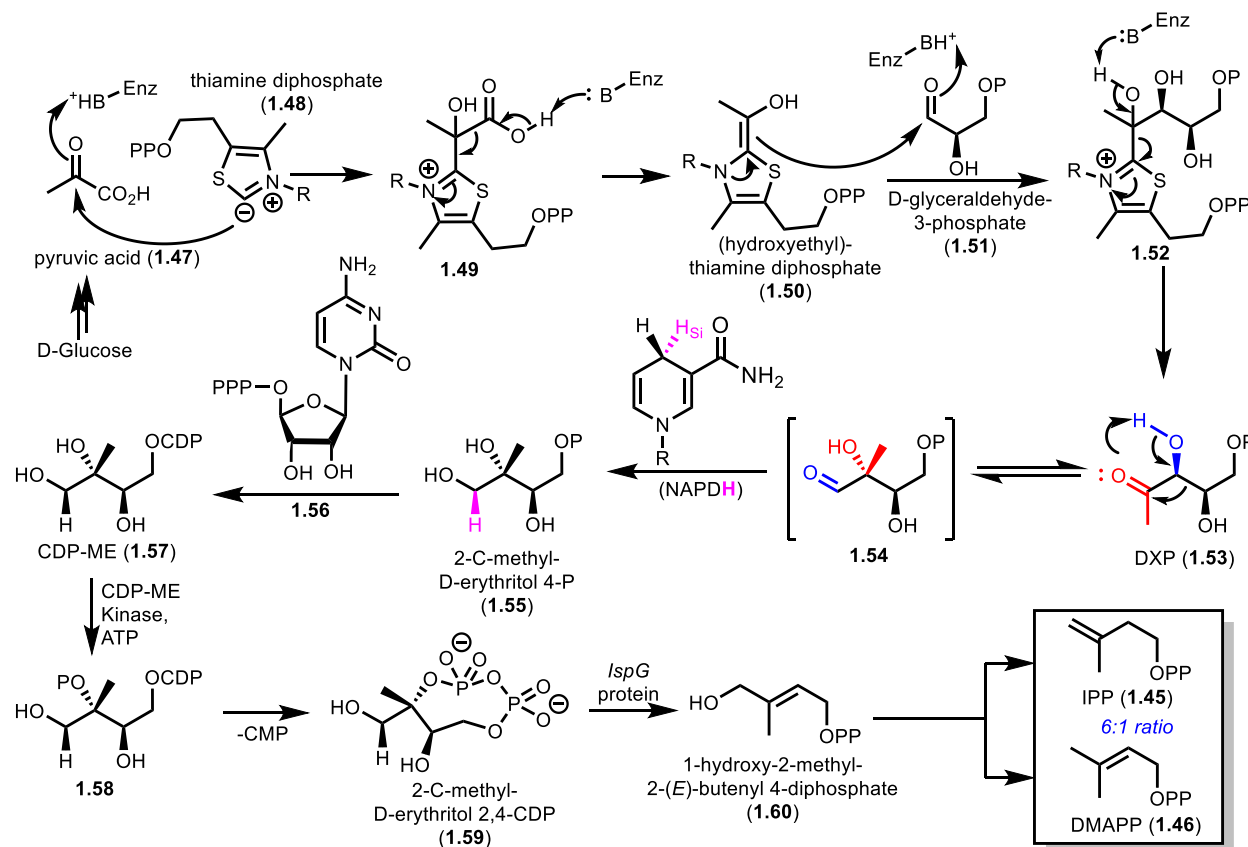


Scheme 1.1. The mevalonate (MVA) pathway towards IPP and DMAPP.

Complementarily, the MEP pathway is mostly prevalent in plastids, which are organelles found in plant and also algae cells. This pathway is mostly responsible for secondary metabolite production in green algae, and produces monoterpenes, diterpenes, sesquiterpenes and tetraterpenes. The pathway starts from the transformation of D-glucose into pyruvic acid **1.47** (Scheme 1.2). Activation of the latter and attack from thiamine diphosphate (**1.48**) affords α -hydroxy adduct **1.49**. Then, decarboxylation affords the C₂-substituted (hydroxyethyl)thiamine diphosphate (**1.50**). Condensation of this nucleophile with D-glyceraldehyde-3-phosphate (**1.51**) affords triol **1.52**. Then, an enzyme enables the ejection of thiamine to give rise to 5 carbon subunit 1-deoxy-d-xylulose 5-phosphate DXP (**1.53**). This pivotal intermediate can then rearrange to aldehyde intermediate **1.54**, which is thermodynamically favored in physiological conditions. This aldehyde is then reduced from the *Re* face by NADPH to afford 2-C-Methyl-D-erythritol-4-P (**1.55**). This reaction was studied using ²H-labelled substrates through NMR studies and concluded that the enzyme enabling this transformation favor the transfer of H_{Si} from C₄ of NADPH to aldehyde **1.54**.

Subsequently, the phosphorylation of 2-C-methyl-d-erythritol-4-P (**1.55**) with with cytidine triphosphate (**1.56**) affords cytidine diphosphate-2-C (CDP-ME, **1.57**). Further phosphorylation with CDP-Me kinase affords triphosphorilated substrate **1.58**. A cyclase enzyme promotes the release of cytidine and affords 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (**1.59**). An IspG protein then catalyzes its conversion to 1-hydroxy-2-methyl-2-(E)-butenyl-4-diphosphate

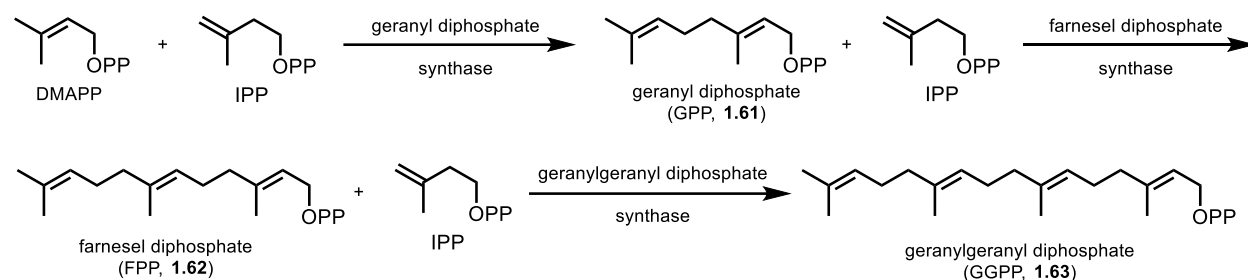
1.60. The latter is then transformed to IPP (**1.45**) and DMAPP (**1.46**) through an overall reductive mechanism presumably involving the presence of allylic radicals and Fe^{II}-Heme dependant enzymes. *In vivo* and *in vitro* replication assays of the last described steps, as well as with ¹³C-labelled substrates, reveals that IPP and DMAPP are produced in a 6:1 ratio respectively. This is interesting, as the synthetic intermediate precursor to all diterpenes is GGPP, and requires a 3:1 ratio of IPP to DMAPP to build (*vide infra*).



Scheme 1.2. Methylerythritol phosphate (MEP) pathway towards IPP and DMAPP.

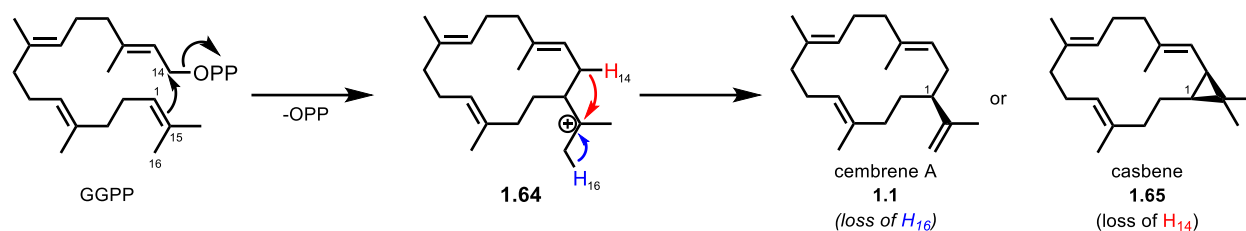
To resume, nature has multiple accesses to the important building blocks IPP and DMAPP. Depending on the origin source of the species, multiple organisms use different tools to construct the building blocks. The MVA pathways uses 3 Acetyl-CoA units (**1.38**) and loses 1 carbon unit through decarboxylation to build its C₅ subunits, a pathway prevalent in animals, archaea and fungi. In contrast, the MEP pathway uses a 2-carbon unit (pyruvic acid **1.47**) which attaches to a 3-carbon unit (D-glyceraldehyde **1.51**) to build its important C₅ units IPP and DMAPP.

From the available building blocks IPP and DMAPP, the more complex terpenes and diterpenes are constructed (Scheme 1.3). From this, the geranyl diphosphate synthase assembles both units of IPP and DMAPP into geranyl diphosphate (GPP, **1.61**), the first C₁₀ unit and a monoterpene precursor. Further building this fragment, farnesyl diphosphate synthase stitches an additional IPP fragment onto **1.61** to afford C₁₅ fragment farnesyl diphosphate (FPP, **1.62**). Ultimately, geranylgeranyl diphosphate synthase adds a third IPP fragment to **1.62** to afford GGPP (**1.63**), the universal C₂₀ unit responsible for the biosynthesis of all diterpenes.



Scheme 1.3. Biosynthesis of GGPP from DMAPP and IPP.

From GGPP, the $\Delta^{1,15}$ alkene can displace the terminal C₁₄ diphosphate group to create the carbocation **1.64** (Scheme 1.4). The latter is a biosynthetic precursor to two distinct macrocyclic diterpenoids. Abstraction of H₁₄ affords the cyclopropane-fused 14-member macrocycle casbene (**1.65**), a common precursor to all lathyrane, tiglane, ingenane diterpenoid natural products.⁴⁸ Abstraction of H₁₆ affords cembrene A (**1.1**), the precursor to all cembranoid and norcembranoid natural products.^{49–52} Interestingly, carbocation **1.64** is the precursor to taxane natural products, including Taxol®. As Taxol® and taxanes have had a much greater success in their use as therapeutic agents, most studies describing the downstream biosynthesis of **1.64** revolves around its transformation to the taxane diterpene, through multiple carbocationic rearrangements.⁵³ Since **1.64** can lead to multiple different terpenes, many different nomenclatures and numbering of **1.64**, thus **1.1**, exist. In the case of Cembrene A, Scott et al. note that “the term cembrene refers to the monocyclic diterpene with double bonds at $\Delta^{2,4Z,7,11}$, using the numbering system used in [our] Figure 1. Structure **8** in this work, with double bonds at $\Delta^{3,7,11,15}$ had previously been referred to as “cembrene” or “cembrene A” by others. We chose the term isocembrene because it is a single word”.⁵² It is now clear that a discrepancy exists in the literature, and from now on, “cembrene”, “cembrene A” “neo-cembrene”⁶ and “isocembrene” will all be referred to “Cembrene A” and defined by structure **1.1** with numbering mentioned in Figure 1.4A.



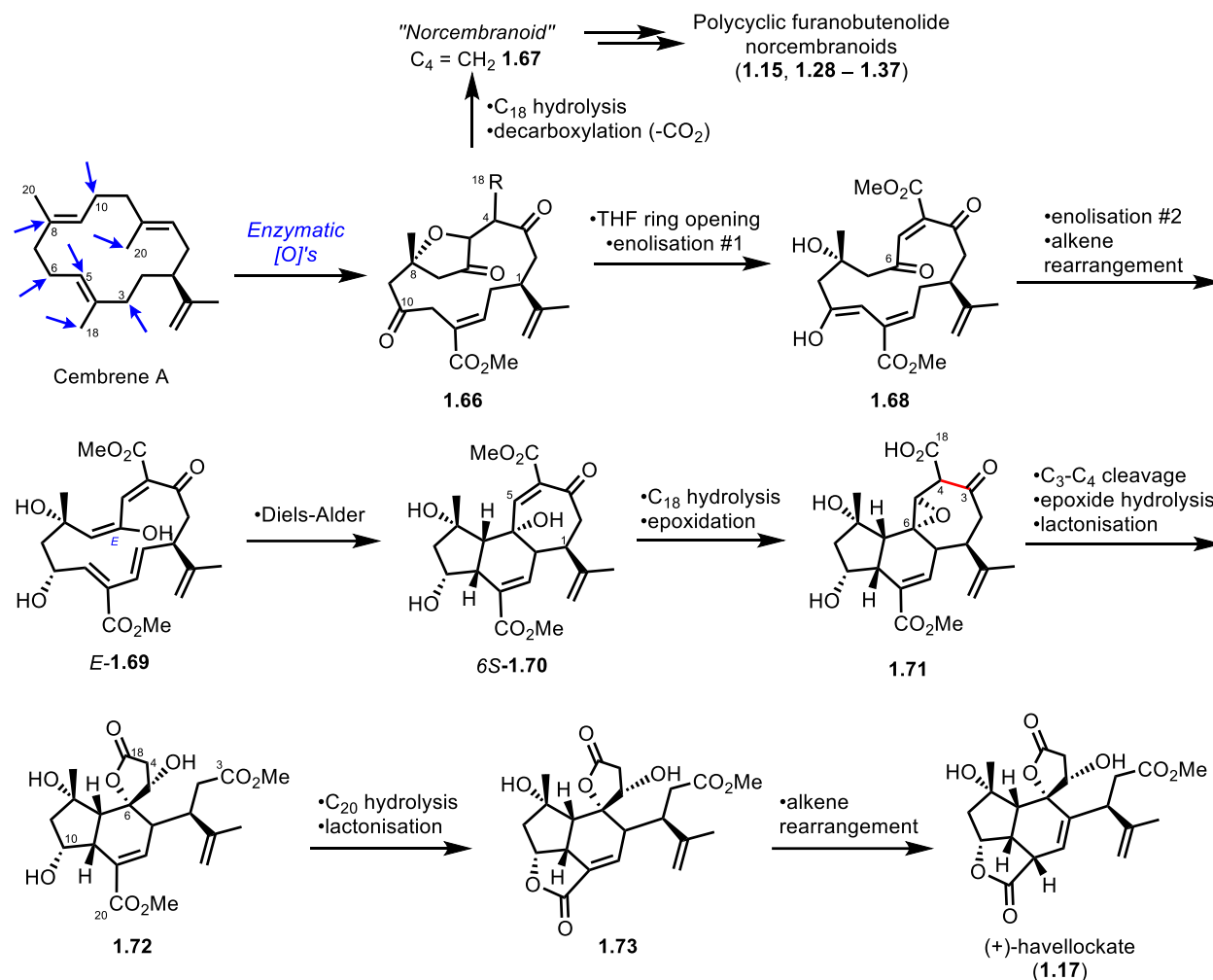
Scheme 1.4. Biosynthetic pathway to cembrene A (**1.1**) and casbene (**1.65**).

Despite both terrestrial and marine metabolism being able to create the same common precursor diterpenes, there exist a striking differences between both. Halogens and isocyanide groups appear frequently as substituents in the secondary metabolites of algae or sponges and are rarely observed in terrestrial species. Interestingly, marine metabolites often differ in absolute stereochemistry from their terrestrial counterparts, where **1.64** is mostly found in marine species, and *ent*-**1.64** is mainly found in terrestrial species.^{51,52} The different biosynthetic conditions found in marine species (pH between 8.2 – 8.5) offered by bicarbonate buffering, high sea water salt content (up to 40%) and high osmotic pressure (15 – 25 atm) give the marine species specialized cell structures and membrane composition – conditions perfectly enabling for a wider breadth of metabolites.⁵⁴

1.2.2 – Biosynthesis of havellockate

While biosynthetic interconversion from simpler to higher order polycyclic natural products has been studied in some cases¹⁹, the biosynthetic precursor to all cembranoid and norcembranoid products can only be left to speculation.^{6,55,56} A sequence of enzymatic oxidations at C₃, C₅, C₆, C₈, C₁₀, C₁₈ and C₂₀, presumably mediated by sunlight and cytochrome P450 monooxygenases, could then lead to hypothetical intermediate **1.66**. The latter is a speculative species, as it was never found from isolation studies. However, its C₁₈-desmethyl intermediate has been isolated in *Sinularia granosa* corals and is proposed to go through hydrolysis of the C₁₈ methyl ester and decarboxylated to yield C₁₉ diterpenoid **1.67**. The latter is named simply as “*Norcembranoid*” in the literature and is hypothesized to be the general precursor of all polycyclic furanobutenolides isolated, which are highlighted in Figure 1.6.⁵⁷

The biosynthesis of havellockate was hypothesized by the isolation team of Anjaneyulu *et al.* (Scheme 1.5).⁵⁷ Following multiple enzymatic oxidations, **1.66** is proposed to go through an E_{1CB} elimination of the tetrahydrofuran and C₁₀ enolization to yield macrocycle **1.68**. This macrocyclic structure is proposed to undergo another alkene enolization at C₆, generating an *E*-



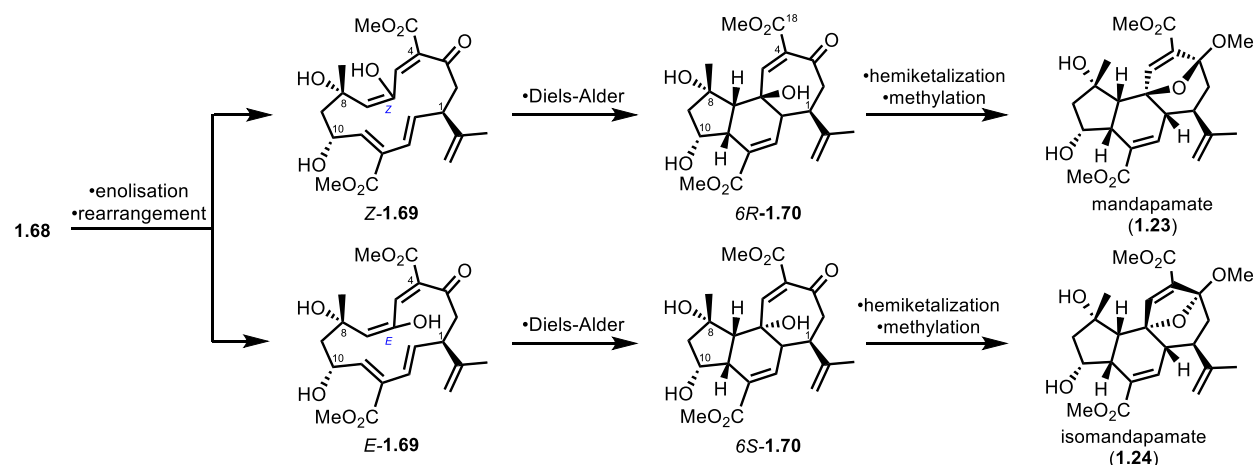
Scheme 1.5. Proposed biosynthesis of havellockate.

enol, followed by alkene rearrangement^b of $\Delta^{10,11}/\Delta^{12,13}$ to $\Delta^{11,12}/\Delta^{13,14}$ affording the ester-conjugated diene **E-1.69**. This diene is then proposed to undergo a Diels-Alder (DA) reaction that can generate the common core of cembranoids **1.70**, *sans* the B ring lactone. The C_{18} is then hydrolyzed to its carboxylic acid and the C_6 alcohol can then engage in a conjugate addition to generate the C_5 - C_6 epoxide **1.71**. The next transformation, a C_3 - C_4 oxidative bond cleavage is what sets havellockate **1.17** apart from the other cembranoid natural products, as the 7-member fused ring is present in all other structures. **1.71** is proposed to also undergo epoxide hydrolysis to its diol, followed by lactonization of the C_6 -OH to C_{18} - CO_2H , affording the spirolactone system **1.72**. With the main scaffold of the natural product constructed, it proposed that C_{20} ester hydrolysis and

^b The term « Rearrangement » is used by the authors to define alkene shifts.

lactonization with the C₁₀ alcohol affords the fully build tetracyclic ABCD core of the natural product **1.73**, which after $\Delta^{12,13}$ to $\Delta^{13,14}$ alkene rearrangement, gives rise to havellockate (**1.17**).

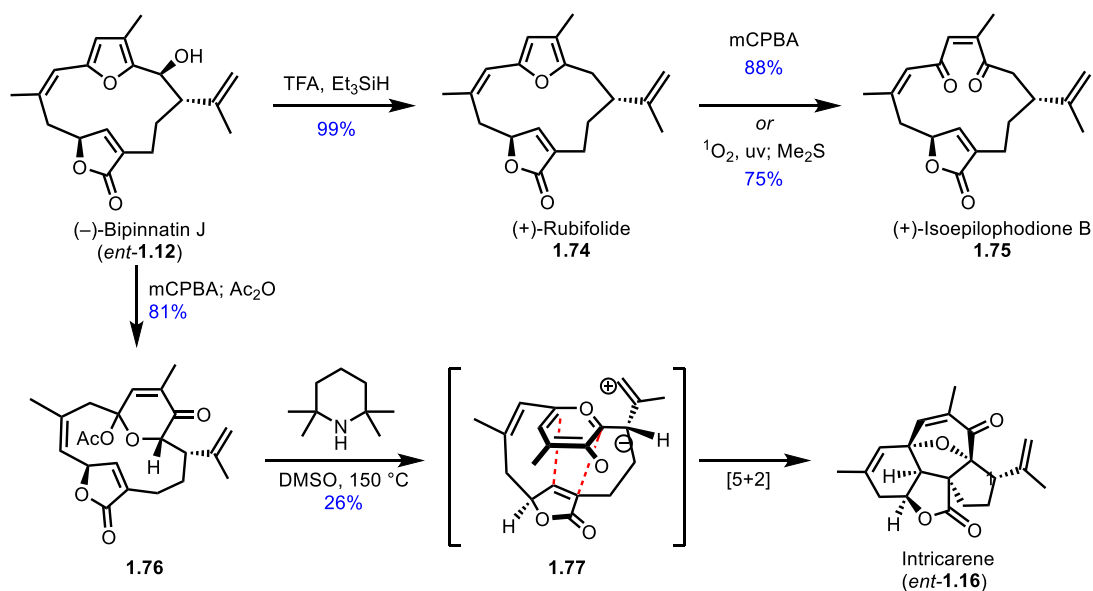
To show the interconnectivity of common intermediate **1.68** in the proposed biosynthesis of these natural products, the authors also present a plausible pathway to other complex polycyclic norcembranoid natural products, such as mandapamate **1.23** and isomandapamate **1.24** (Figure 1.5). It is thought that the intermediate **1.68** can be enolized into two alkene isomers (*Z*)-**1.69** and (*E*)-**1.69** (Scheme 1.6). Both geometrical isomers can undergo a Diels-Alder reaction, affording both (*6R*)-**1.70** and (*6S*)-**1.70** diastereomers respectively. Both structures then undergo hemiketalization with C₁₀-ketone and methylation of their acetal to afford mandapamate (**1.23**) and isomandapamate (**1.24**) respectively. This biosynthetic speculation of interconnectivity is important and show that multiple natural products stem from common intermediates, and dozens of highly complex polycyclic cembranoids are proposed to stem from lightly oxidated macrocyclic systems like **1.66** and their congeners.⁵⁸



Scheme 1.6. Proposed divergent biosynthetic pathway to mandapamate and isomandapamate.

Moreover, this interconnectivity has not only been described theoretically but also experimentally. For example, Trauner and colleagues have shown that a simple macrocyclic cembranoid can be synthetically transformed into 3 other natural products of the same family, one of them being a polycyclic furanobutenolide cembranoid (Scheme 1.7).⁵⁹ In this study, synthetic Bipinnatin J (*ent*-**1.12**), is rearranged through simple synthetic manipulations into rubifolide (**1.74**), isoepilophodione B (**1.75**) and intricarene (*ent*-**1.16**). Deoxygenation of *ent*-**1.12** using a silyl hydride and TFA affords (+)-rubifolide (**1.74**). This species can undergo oxidation of its furan

moiety with the help of mCPBA to yield (+)-isoepilophodione B (**1.75**) in 88% yield. Interestingly, the authors also reported biomimetic conditions of this oxidation by using singlet oxygen, a photosensitizer and UV light. The reduction of the intermediate endoperoxide (*not shown*) also affords **1.75** in 75% yield. Moreover, intricarene (*ent*-**1.16**) was also synthesized from Bipinnatin J by subjecting it to Achmatowicz oxidation (mCPBA), a reaction proposed to be biosynthetically operated by $^1\text{O}_2$, to afford hydroxypyranone acetate **1.76** after acetylation with Ac_2O . An esterification of the intermediate hydroxypyranone was required as unprotected the hemiketal intermediate decomposed upon attempts at purification, but it is this hemiketal that is proposed as the biosynthetic intermediate. Upon heating in the presence of 2,2,6,6-tetramethylpiperidine, acetate **1.76** is subjected to elimination to afford oxidopyrylium **1.77**, which can undergo a transannular 1,3-dipolar cycloaddition to yield intricarene (*ent*-**1.16**). This biosynthetic speculative pathway from *ent*-**1.12** to *ent*-**1.16** was also independently confirmed by Pattenden and colleagues using similar synthetic chemistry.⁶⁰ Bielschowskysin (**1.18**) is also proposed to be originating from bipinnatin J.⁶¹ Interestingly, both of these studies were published within 15 days of each other, demonstrating the high interest in these biosynthetic speculations from the scientific community.



Scheme 1.7. Trauner's biomimetic total synthesis of intricarene from bipinnatin J.

1.3 - Biological activity of the cembranoid natural products.

Given the well-documented use of *Boswellia* containing plants species in traditional folk medicines, it is not surprising that their cembranoid metabolites have been thoroughly probed for biological activities. These medicinal properties have pushed chemists and biologists alike to continue to extract these metabolites from other sources and identify their components to isolate pharmaceutically relevant compounds. As a result, many cembranoids have been found to exhibit interesting pharmacological profiles. Regardless of this fact, connections between the medicinal properties of these natural products remain scarce – as there are many, and that the latter can only be isolated in very minute amounts. Moreover, this section is by no means a comprehensive review of the medicinal properties of the > 400 natural products of this family, as this work was already thoroughly reported.^{62–64} This section aims to give an overview of their potential as pharmaceutical properties, more specifically of the high order polycyclic furanobutanolide cembranoids and norcembranoids. Doing as such aims to interest the reader in the profound value in trying to synthetically access these natural products to pave a way towards more complete biological evaluations.

1.3.1 – Oncological Activity

Many polycyclic cembranoid and norcembranoid natural products have been probed for their cytotoxic effect on many different cancer cell lines. Of those studied, bielschowskysin (**1.18**), pavidolide B (**1.27**) and ineleganolide (**1.28**) showed promising activities. After being isolated, bielschowskysin was tested and showed promising antiparasmodial activity (*vide infra*).²⁵ Considering its ability to inhibit *Plasmodium falciparum*, the isolation team also evaluated bielschowskysin for cytotoxicity using an anticancer screening panel (NCI-60) from the National Institute of Cancer, a standardized drug discovery tool established in 1989. This panel is designed to screen small molecules against 60 human tumor cell lines. Bielschowskysin was found to display strong and specific *in vitro* cytotoxicity against the EKVX nonsmall cell lung cancer ($GI_{50} < 0.01 \mu M$) and CAKI-1 renal cancer ($GI_{50} = 0.51 \mu M$).^c Pavidolide B was screened against another panel of common tumor cell lines including IL-60, HCT-8, HePG2, BGC-823, A549 and A375.³³ The results showed that it showed selective inhibition against human promyelocytic leukemia cell

^c GI_{50} defines the concentration of a drug required to reduce the growth of cancer cells by 50%.

lines HL-60 and HCT-8 with an IC_{50} of 2.7 $\mu\text{g/mL}$ and 5.3 $\mu\text{g/mL}$ respectively.^d Ineleganolide (**1.28**) was found to boast antileukemic activity upon isolation.³⁴ The authors have demonstrated that ineleganolide demonstrated *in vitro* cytotoxicity against murine lymphocytic leukemia P388 cell lines with an ED_{50} of 3.82 $\mu\text{g/mL}$. Other natural products of this family have been tested for their oncological properties but found no activity. Upon isolation the cytotoxicity of scabrolide A (**1.32**) and scabrolide B (**1.33**) have been tested against the growth of KB and Hepa59T/VGH cell lines, which are human oral and murine liver tumor cell lines respectively. The two natural products were shown to be inactive ($ED_{50} > 20 \mu\text{g/mL}$) for both cell lines.^e

1.3.2 – Anti inflammatory activity

The inflammatory response of bone marrow-derived dendritic cells was tested upon isolation of ineleganolide (**1.28**), scabrolide A (**1.32**) and yonanolide (**1.34**).⁴¹ After confirming that these three compounds had no effect on cell viability, an inflammatory response in cells was induced by secreting cytokines IL-12, IL-6 and TNF- α upon lipopolysaccharide (LPS) treatment of dendritic cells. Upon treatment of the inflicted cells, compound scabrolide A was found to exhibit moderate inhibitory activity on IL-12 and IL-6 production with IC_{50} values of 23.5 and 69.9 μM , respectively. **1.28**, **1.32** and **1.34** did not exhibit inhibitory activity on TNF- α production. These results show the potential use of cembranoids as treatment for autoimmune diseases. Additionally, the polycyclic cembranoid rameswarellide (**1.19**) was also found to be a potent anti-inflammatory. An isolation team based at the Indian Institute of Chemical Technology in Hyderabad, India teamed up with researchers from the University of California in Berkeley, United states to isolate, derive and test rameswaralide for its potency in inhibiting anti-inflammatory response (Figure 1.8). In a patent filed in 2001, they describe over 20 derivatives of Rameswaralide (i.e. **1.78** – **1.82**) and their application in inflammatory response, though no concrete values were described in the reporting patent.⁶⁵

1.3.3 – Antiviral activity

Chikungunya (CHIKV) is a viral disease that spreads through mosquito bites, and can cause sudden fever, rash, joint pain and headaches. When marine-derived substances were tested in a cell

^d IC_{50} defines the concentration of a drug required to inhibit 50% of the biological function of cancer cells.

^e ED_{50} (*median effective dose*) defines the concentration of a drug required to affect 50% of the population study sample.

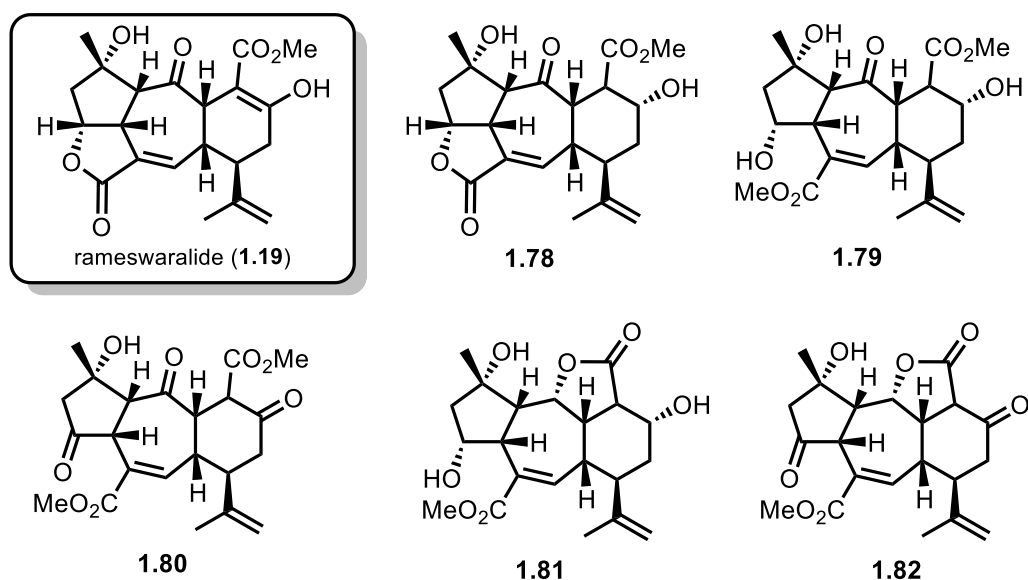


Figure 1.8. Patented rameswaralide derivatives for treatment of inflammation.

based CHIKV virus replicon and anti-inflammatory assay, extracts from *Sinularia kavarattiensis* showed promising activity against CHIKV replication.³⁶ After isolating ineleganolide (**1.28**) and kavaranolide (**1.30**) from the extract, both compounds were tested individually, along with other cembranoids isolated. The measurement of replication marker levels of CHIKV was evaluated for the pure compounds, and revealed that, at 100 μ M concentration, ineleganolide showed 14% inhibition of the virus replication, while kavaranolide showed < 2% replication. Both compounds **1.28** and **1.30** were also tested for cytotoxic activity but revealed none to very low cytotoxicity in the assay.³⁶

1.3.4 – Hemolytic activity

In 2002, two new cytotoxic diterpenoids, plumarellide (**1.21**) and plumarellate (**1.22**) were isolated from *Plumarella* sp.²⁸ Upon purification, both compounds were tested for multiple bioassays, including their capacity to destroy red blood cells (erythrocytes). It was shown that plumarellide and plumarellate show moderate hemolytic activity, inducing 50% hemolysis of mice blood erythrocytes at concentrations of 140 and 250 μ M respectively. Of interest, the authors report that **1.22** may be an isolation artifact of **1.21**, resulting from the ethanolysis of the B-ring lactone during the extraction and storage processes, which were completed using ethanol.

1.3.5 – Antibacterial activity

Tuberculosis is a contagious infection caused by *Mycobacterium tuberculosis* bacteria. This infection is transmitted through the air and can affect the lungs, causing persistent coughing, fever and weight loss. Upon its isolation from the Caribbean gorgonian corals *Pseudoptegorgia kallos*, intricarene (**1.16**) was tested for inhibitory activity toward the growth of the *Mycobacterium tuberculosis* H37Rv cell line, a widely used virulent laboratory strain. The Alamar Blue assay, a high-throughput cell viability reagent that measures metabolic stability, revealed a mere 15% inhibition of the strain at the high concentration of 128 µg/mL.

1.3.6– Antiplasmodial activity

Between 300 and 500 million clinical cases of malaria occur every year, with over 1.2–2.7 million deaths. Prevention and treatment of *Plasmodium falciparum*, its most severe form, are becoming more difficult because *P. falciparum* is increasingly resistant to various antimalarial drugs. Bielschowskysin (**1.18**), while also possessing oncological activity, possesses antiplasmodial activity. When the compound was tested against two chloroquine-resistant *P. falciparum* strains (Sierra Leone clone D6 and Tanzania F32), it showed moderate inhibition, with an IC₅₀ of 10 µg/mL.

In view of their interesting and important biological activities, it remains important to continue to further test polycyclic furanobutenolide cembranoid natural products for their role as potential future starting point in the development of new medicines. Often, these compounds are isolated in milligram quantities from multikilogram scale of the originating species. As a result, many biological assays needed to be cut short due to the paucity of the natural product. Intricarene (**1.16**) was isolated in very low quantities (4.0 mg) from 1.07 kg of *P. kallos* corals. Although it showed interesting antibacterial activity (*vide supra*), the authors note that “*unfortunately, the paucity of this material prevented us from conducting further biological testings*”.²³ Only 2.7 mg of verrillin (**1.20**) were isolated from 2.1 kg of *P. bipinnata* corals in 1996. Although had no antibacterial activity when tested against *M. tuberculosis* H₃₇Rv strains, the authors stopped the biological assays short because : “*unfortunately, scarcity of material precluded more extensive probing of the biological properties of [1.20]*”. Sinulanorcembranolide A (**1.36**) was isolated in very minute quantities (1.7 mg) from *S. Gaweli* (328 g dry wt) octocorals in 2013. This new cembranoid was tested in multiple biological assays, including its anti-inflammatory activity but

was found to have no activity up to 20 μ M in the LPS assay (*vide supra*). The authors ran out of material, and subsequently, synthetically transplanted *S. Gaweli* in culture tanks in the hopes of farming more of this material “*in order to establish a stable supply of material for study*”.⁴² In the light of these remarks, it is imperative that scientists establish short and efficient synthetic accesses to these important natural products.

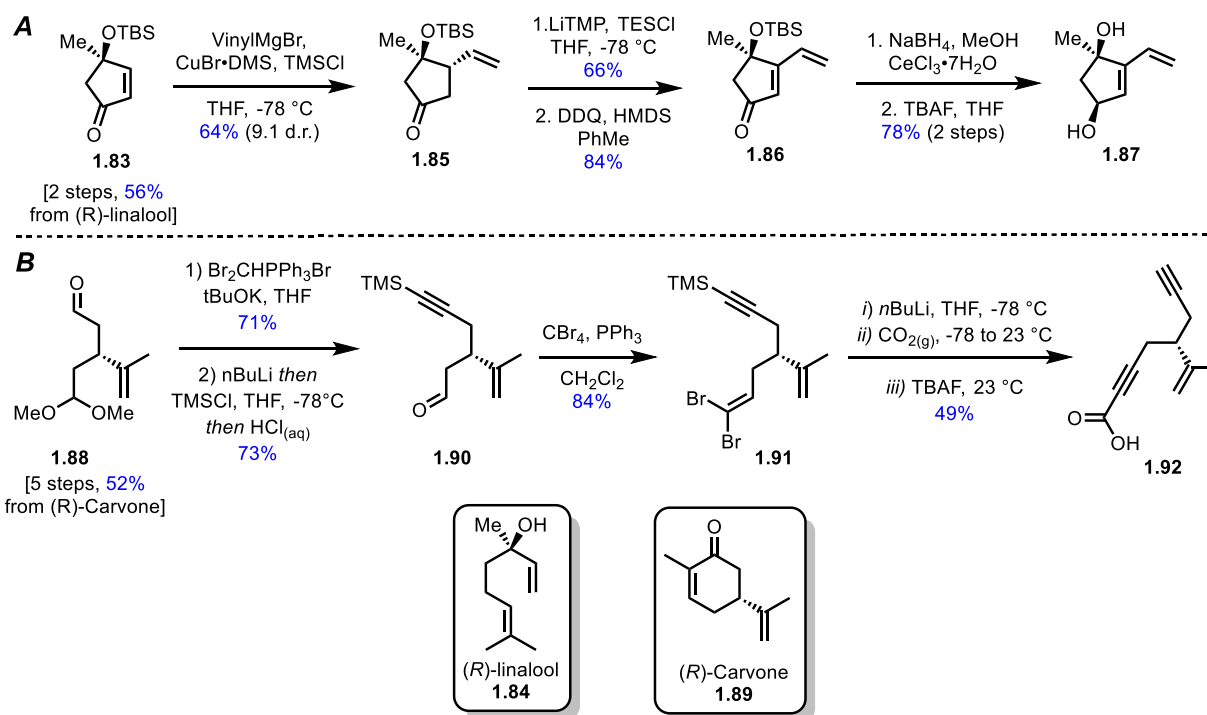
1.4 – Total syntheses of cembranoid natural products.

In the light of the remarks made by scientists that highlight the lack of raw material needed to complete thorough biological assays, it is imperative that scientists continue to establish short and efficient synthetic accesses to these important natural products. The fascinating structural features and reported bioactivities of the cembranoid natural products have sparked significant interest from the synthetic chemistry community, leading to many elegant total syntheses. The section is not a comprehensive review of these synthetic effort as it is not the goal, but the reader is directed to excellent reviews that have already been published on this subject.^{20,66} This section will present selected milestones in the synthetic approaches to a handful of polycyclic cembranoid natural products that utilize the Diels-Alder reaction, which will help the reader understand the logical synthetic disconnections to the common core they all carry. This logical thinking, which make use of the Diels-Alder pericyclic reaction to construct the core of these natural products, will lay the groundwork on our approach towards the total synthesis of (+)-havellockate (**1.17**).

1.4.1. Stoltz’s enantioselective synthesis of (–)-scabrolide A.

The collective efforts and the start of a resurgence of interests towards the total synthesis of cembranoid natural products were initiated by the Stoltz group in 2020, which reported the first total synthesis of any member of the polycyclic furanobutenolide-derived cembranoid natural products.⁶⁷ This work set the stage for all future work by other investigators in the coming years. The group developed a convergent enantiospecific synthesis of unnatural enantiomer of (–)-scabrolide A (*ent*-**1.32**). The first fragment **1.83** was synthesized in 2 steps and 56% yield from the commercially available, optically pure building block (*R*)-linalool **1.84**, (Scheme 1.8).⁶⁸ A conjugate addition using the divinyl Gilman reagent afforded ketone **1.85** in 64% and 9:1 d.r. Treatment of this ketone with LiTMP afforded an enolate that was trapped with triethylsilyl (TES) chloride which was oxidized using DDQ to afford dienone **1.86** in 66% and 84% yields respectively. Subjecting this dienone to Luche reduction and subsequent *tert*-butyldimethylsilyl

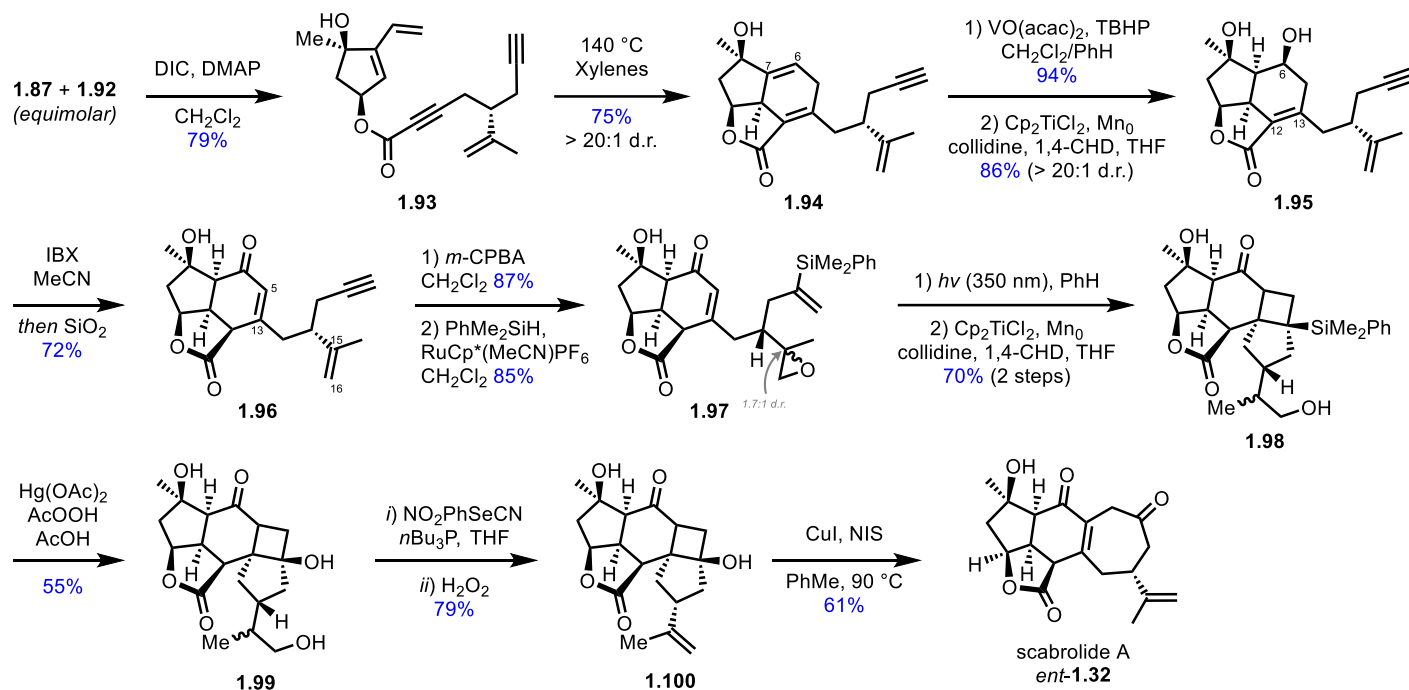
(TBS) deprotection to afford the cyclopentadiol **1.87** in 78% and >20:1 d.r. over 2 steps. The synthesis of second fragment, a nearly symmetric octynoic acid, was achieved in 4 steps from the known aldehyde **1.88**, which itself was known to be a 5 step sequence and 52% from (*R*)-Carvone (**1.89**).⁶⁹ A standard Corey-Fuchs olefination of **1.88** followed by treatment of the dibromoalkene with *n*BuLi, quench of the lithium acetylide with trimethylsilyl (TMS) chloride and *in situ* cleavage of the acetal in the same pot gave aldehyde **1.90** in 71% and 73% yield respectively. With the second aldehyde now unveiled, another Corey-Fuchs sequence was employed to introduce the ynoic acid, this time by a Ramirez dibromoolefination of **1.90** to give **1.91** in 84%. The treatment of the latter with *n*-BuLi generated a lithium acetylide that was quenched with CO_{2(g)} to integrate the carboxylic acid moiety. The TMS moiety was removed *in situ* using tetrabutylammonium fluoride (TBAF) to afford ynoic acid **1.92** in 49% on multigram scale.



Scheme 1.8. (A) Synthesis of the cyclopentadiene fragment **1.87** and (B) Synthesis of the ynoic acid fragment **1.92**.

With both pure fragments in hand, the authors stitched the latter together and entered the late stage of the synthesis (Scheme 1.9). Using DIC-mediated Steglich coupling between **1.87** and **1.92**, the authors were able to obtain ester **1.93** in 79%. By heating the diene-dienophile containing adduct, a thermal [4+2] Diels-Alder reaction was promoted, furnishing the cycloadduct **1.94** in

79% yield in a single detectable diastereoisomer. This transformation was crucial to fully construct the ABC ring system of the natural product. A vanadium-mediated C₆/C₇ alkene epoxidation followed by a Ti-catalyzed reductive epoxide opening furnished C₆-hydroxide **1.95** in 94% and 86% respectively. The treatment of this alcohol with iodoxybenzoic acid (IBX) afforded enone **1.96**, gratifyingly also enabling a spontaneous $\Delta^{12,13}$ - $\Delta^{13,5}$ olefin migration upon silica purification, correctly installing the insaturation present in the natural product. After realizing that the $\Delta^{15,16}$ alkene caused chemoselectivity problems, the latter was protected as its epoxide using *m*-CPBA and a following Ru-catalyzed hydrosilylation of the alkyne yielded **1.97** in 87% and 85% yields respectively. A [2+2] photocycloaddition produced the desired cyclobutane adduct, which was followed by another Ti-mediated epoxide reduction to afford **1.98** in 70% over 2 steps.



Scheme 1.9. Stoltz's total synthesis of scabrolide A (*ent*-**1.32**).

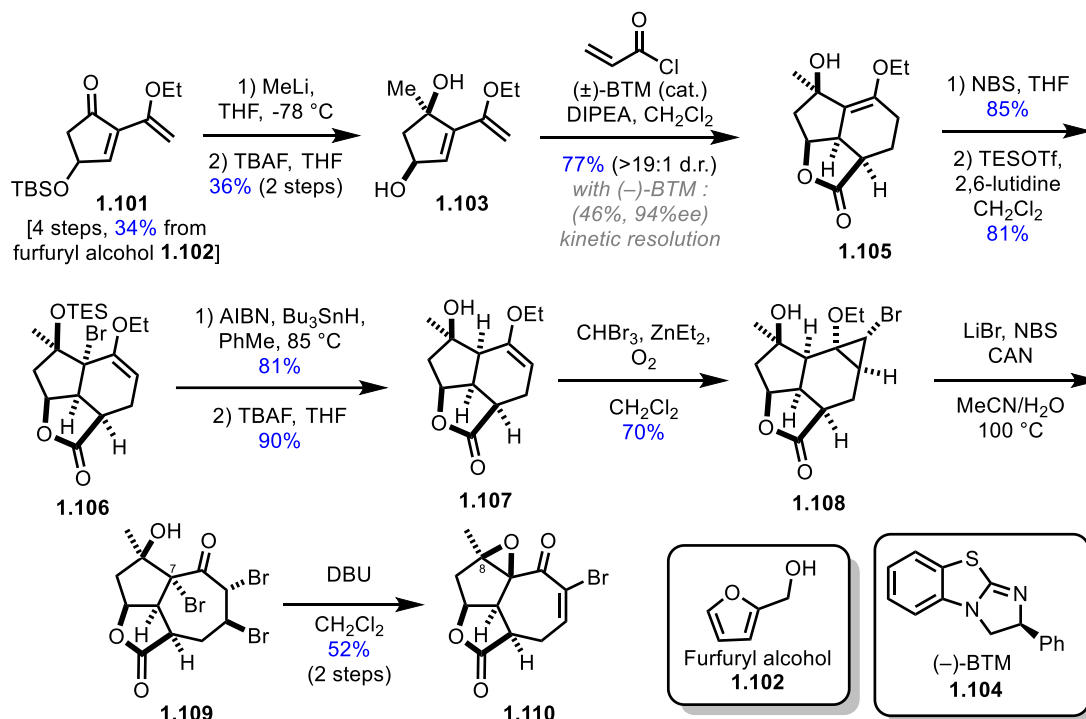
A Hg-mediated Tamao-Fleming oxidation yielded cyclobutanol **1.99** (55 %), which was followed by unmasking of the isopropenyl group through a Grieco elimination to give **1.100** in 79%, which set the stage for the last and crucial step of the synthesis. To trigger the oxidative ring-opening fragmentation of **1.100**, a mixture of CuI and NIS was used, presumably going through an alkoxy hypoiodite (RO-I) intermediate, effectively cleaving the [2,0,3] ring system to unveil the fused 7-member ring of scabrolide A (*ent*-**1.32**) in 61%. In total, this synthesis spanned 21 steps. and 0.52%

in the longest linear sequence from (*R*)-carvone. It is important to note that, aside from achieving a milestone that had evaded synthetic efforts for two decades since its isolation, this enantiospecific synthesis did not lead to the correct enantiomer of the natural product. Indeed, since only one enantiomer of linalool (*R*, **1.84**) is commercially available, this pathway cannot access the natural enantiomer of scabrolide A (**1.32**).

1.4.2 – Romo's total synthesis of (±)-rameswaralide.

In 2022, the group of Daniel Romo published the first total synthesis of rameswarelide (±-**1.19**) as its racemate through a pharmacophore-directed strategy.⁷⁰ The synthesis was initiated from diene **1.101**, available in 4 steps and 34% overall yield from furfuryl alcohol **1.102** (Scheme 1.10). A ketone methylation and subsequent TBS deprotection afforded the *syn*-diol **1.103** in 36% for 2 steps, which set the stage for the Diels-Alder reaction / lactonization sequence. The latter was completed using enantiomerically-pure benztetramisole ((-)-BTM, **1.104**) to kinetically resolve the enantiomers of racemic (±)-**1.103** to afford (-)-**1.105** in 46% and 94% e.e. as a single diastereoisomer. However, to maximise throughput, the authors decided to employ (±)-BTM, and in that matter, could obtain a yield of 77% for the tricyclic (±)-**1.105**. A subsequent treatment with *N*-bromosuccinimide (NBS) affected the required alkene transposition to afford and TES protection gave α-bromoalkene **1.106** in 85% and 81% respectively. A radical debromination (81%) and TBAF treatment (90%) subsequently afforded enol ether **1.107**, which was primed to undergo a Simmons-Smith cyclopropanation, which gave [4,0,1]-bromocyclopropane **1.108** in 70% yield. The subsequent bromine radical-mediated ring-opening (Br• from CAN & Br-) afforded the ring- expanded tribromide product **1.109**. Interestingly, C₇ bromination was not expected but proved to be very useful in further transformations since it allows the temporary protection the C₈ tertiary alcohol (*vide infra*), which when left unprotected^f, caused problems in further synthetic transformations.⁷¹ The E2 elimination of the tribromide **1.109** with DBU afforded the α-bromoenone **1.110** in 52% in 2 steps, priming the substrate for a cross-coupling, while also protecting C₈-OH as its epoxide. A Liebeskind modified Stille-cross coupling between **1.110** and **1.111** afforded adduct **1.112** in 70% (Scheme 1.11). Exposure of this adduct to triethylsilyl trifluoromethanesulfonate (TESOTf) with triethylamine resulted in the extension of the π system

^f The α-bromoketone **1.109** (C₇ = Br) was isolated as a major product (46%), while the analog ketone (C₇ = H) was a minor product in the reaction (10%).

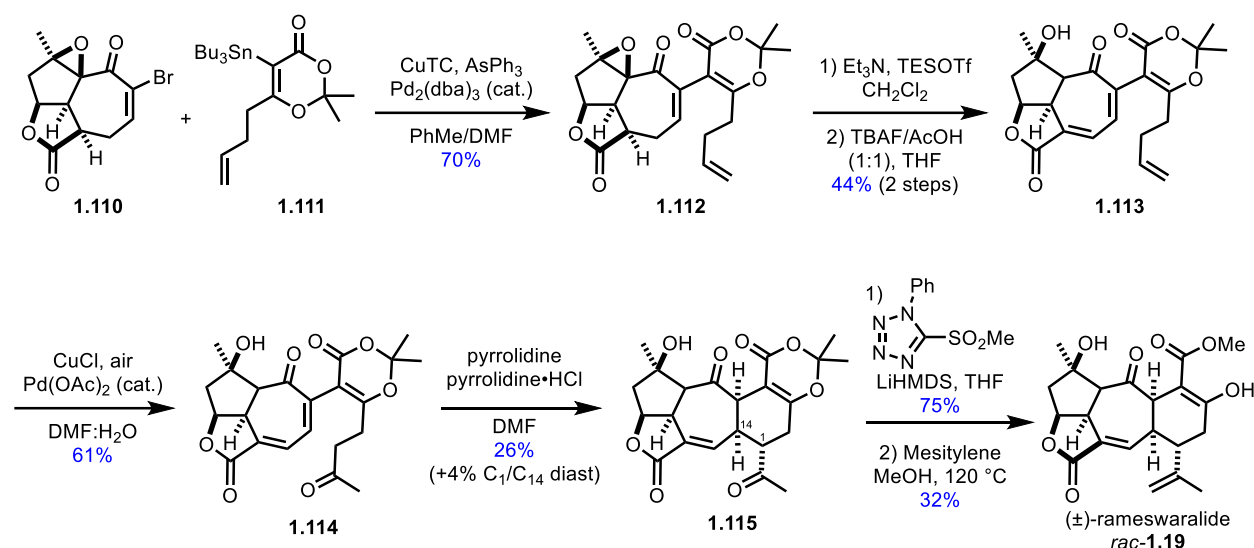


Scheme 1.10. Romo's synthesis of tricyclic [5,5,7] intermediate (±)-1.110.

by oxidative transposition / desilylation and concomitant epoxide opening to afford α -methylene butyrolactone **1.113** in 44% over 2 steps. A Wacker oxidation of the terminal alkene afforded ketone **1.114** in 61%. This substrate was now primed to undergo a Stork enamine cyclization, which was accomplished using a combination of pyrrolidine and its HCl salt and afforded the desired cyclization product **1.115** (26%) along with its C₁/C₁₄ diastereoisomer (4%). An olefination of the ketone was accomplished using Julia-Kocienski conditions in 75%, and of the acetonide using methanol at high temperature revealed the β -keto ester moiety in low yield (32%), completing the racemic total synthesis of rameswaralide (±-**1.19**). The completion of this synthesis was supported by the synthesis and testing of multiple reactions on model substrates, which proved crucial to the success of this total synthesis.^{70,71} Overall, this synthesis spanned 21 steps and 0.02% in its longest linear sequence from furfuryl alcohol, can lead to enantiopure rameswarelide if desired.

Throughout their work, the synthetic intermediates were tested for their oncological properties against HCT116 cells, a colon cancer cell line. These tests showed that an intermediate

of this synthesis, tricyclic epoxy α -bromocycloheptenone **1.110**, displayed the highest cytotoxicity, with an EC₅₀ of 0.39 μ M



Scheme 1.11. Romo's racemic total synthesis of rameswaralide (*rac*-1.19).

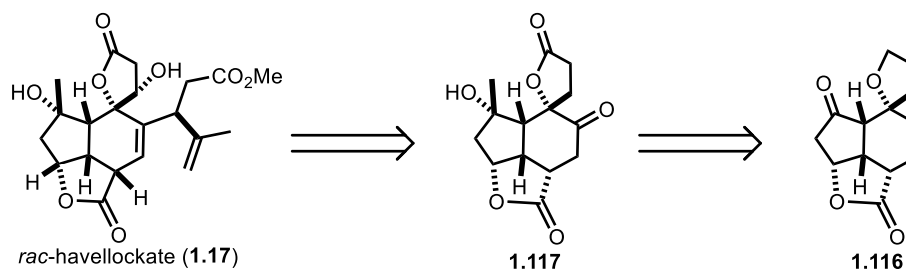
In total, over 20 total syntheses of the cembranoid polycyclic natural products have been reported between 2020 and 2026, which is a very considerable amount of attention since these natural products have been known for, on average, over 20 years. In between these dozens of syntheses, only two natural products (that are not havellockate) have used the [4+2] Diels-Alder reactions to synthesize the tetracyclic core of these natural products.

1.5 – Synthetic efforts towards the total synthesis of havellockate.

We have previously explored the use of the Diels-Alder reaction to synthesize these natural products. As described previously, (+)-havellockate (**1.17**) is a unique natural product of this family, as it contains the spirolactone moiety, absent in all other polycyclic furanobutenolide cembranoid and norcembranoid natural products. As such, this natural product has received considerably more attention than other members. This section will chronologically present all the work that has been completed towards the synthesis of this natural product and lay the groundwork for the challenges most often encountered during the synthesis of its caged, polycyclic, highly oxygenated core.

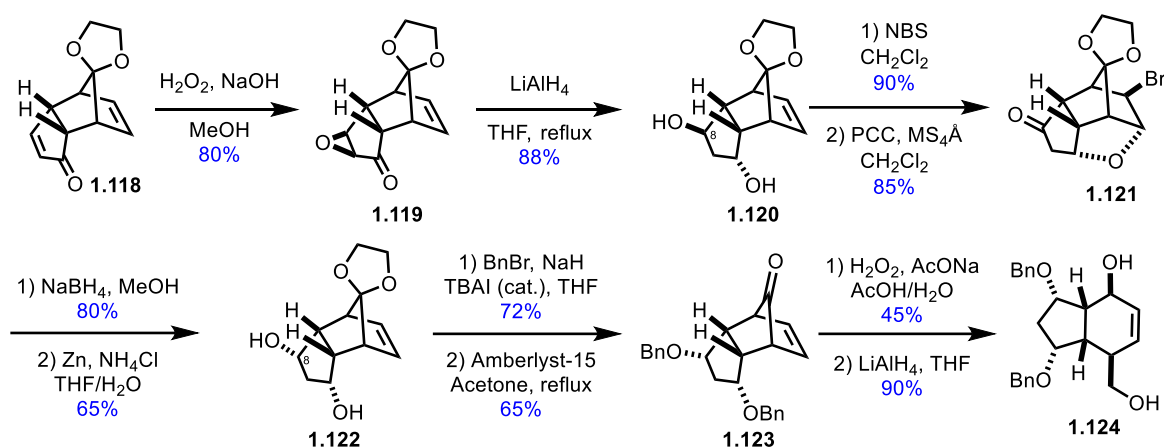
1.5.1 – Mehta’s pioneering work on *rac*-havellockate.

It took just 3 years after its isolation report for the synthetic community to report efforts on the natural product havellockate (**1.17**). In 2001, the Mehta group had envisioned, as a first objective, to target the tetracyclic core structure **1.116** (Scheme 1.12). By acquiring this substructure, the overall strategy could be tactically modified and adopted to obtain the bislactone **1.117**, which the latter could be further improved to pave a path towards the synthesis of havellockate (**1.17**) in racemic form.



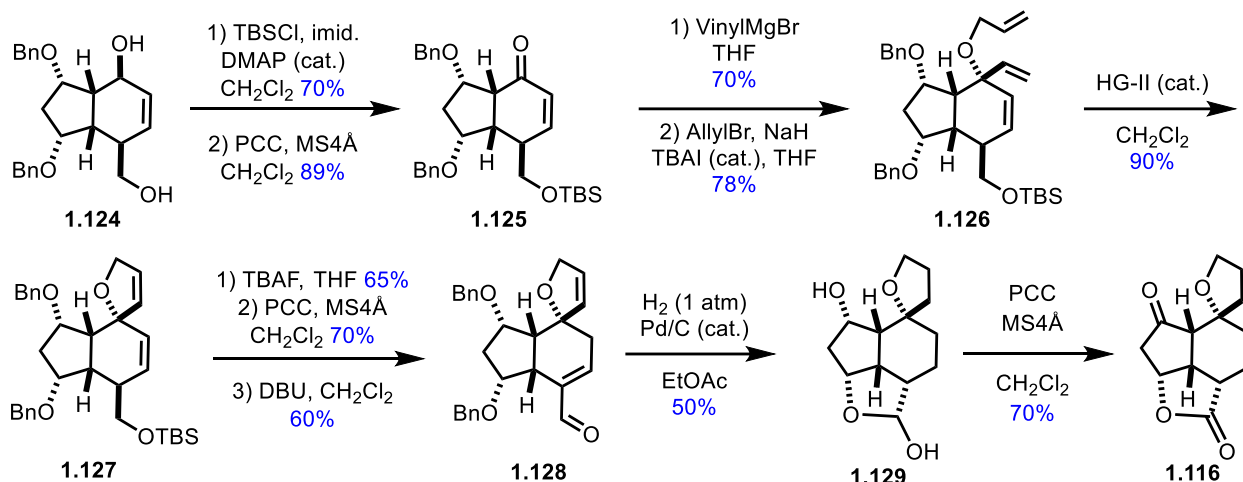
Scheme 1.12. Mehta’s retrosynthetic analysis of the ABCD core of havellockate (**1.116**).

The synthesis of tetracyclic structure **1.116** was envisioned to start from *endo* dicyclopentadienone **1.118**, available in 2 steps from cyclopentanone ethylene ketal (Scheme 1.13).⁷² The latter was subjected to a Weitz-Scheffer epoxidation to afford epoxide **1.119** in 80%. The epoxide was then reduced to its diol using LiAlH_4 in 88%. Unfortunately, all reduction attempts led the undesired the *R* stereochemistry at C_8 . To obtain the *S* stereochemistry required at C_8 , leading the authors to rely on a sequence of reactions to obtain the desired *S* alcohol. To remedy this, the *endo* hydroxy group of **1.120** was transformed to the bromoether with NBS (90%), and the resulting substrate oxidied with PCC in 85% yield to afford **1.121**. Now that the concave face of the substrate was exposed, a reduction using NaBH_4 allowed the formation of the desired alcohol in 80% (*not shown*). The regeneration of the original alcohol moiety was completed by exposure to zinc metal, forming the required symmetrical *cis* diol **1.122** in 65% yield. A protection of both alcohols as their benzyl ethers (72%) and subsequent ketal deprotection (65%) afforded ketone **1.123**. Then, a carefully controlled Baeyer-Villiger oxidation delivered the corresponding lactone in 45%, which was subsequently reduced using LiAlH_4 to furnish the diol **1.124** in 90% yield. This sequence delivered the desired adduct and secured the stereochemistry at six stereogenic centers.



Scheme 1.13. Mehta's synthesis of fused bicyclic diol **1.124**.

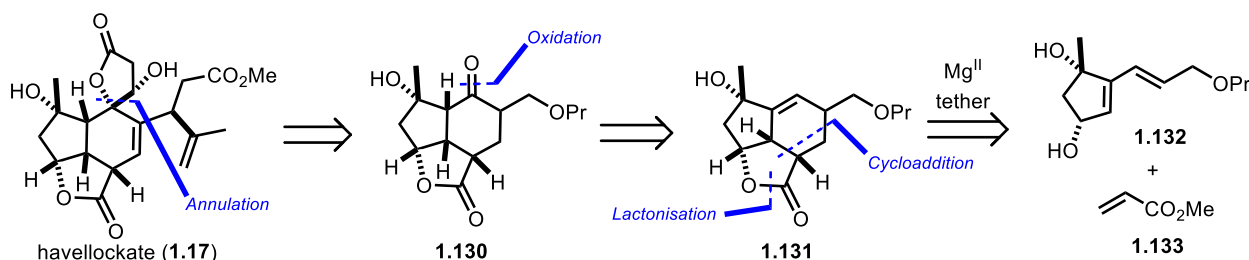
Further building on bicyclic substrate **1.124** (Scheme 1.14), a selective primary alcohol TBS protection and secondary alcohol oxidation afforded the enone **1.125** in 70% and 89% respectively. From this substrate, a ring-closing metathesis (RCM) protocol was employed to complete the annulation. To that effect, the addition of vinylmagnesium bromide occurred exclusively on the convex face of the molecule in 70% yield. An allylation of the resulting tertiary alcohol afforded dialkene substrate **1.126**. A RCM using the Hoveyda-Grubbs 2nd generation (HG-II) catalyst afforded the spiro-annulated dihydrofuran **1.127** in excellent yield (90%). To form the B ring lactone of the natural product, the authors removed the TBS group using TBAF (65%), oxidized the resulting primary alcohol to its aldehyde using PCC (70%). A subsequent isomerization of the alkene to the α - β unsaturated aldehyde using DBU afforded substrate **1.128** in 60%. This substrate was fully reduced using H₂ and Pd/C to remove both benzyl groups, reduce the α - β unsaturated aldehyde alkene and the dihydrofuran, which spontaneously cyclized to generate the hemiacetal **1.129** in 50%. This substrate was then oxidized to its lactone to furnish the target molecule **1.130**, which fully built the tetracyclic core of havellockate, *sans* a handful of oxidized carbons found in the natural product. This synthesis, although representing the first work in the field and building critical knowledge, build the tetracyclic ABCD core of the natural product in 22 steps and 0.10% yield in the longest linear sequence from cyclopentanone ethylene ketal.⁷²



Scheme 1.14. Mehta's synthesis of the ABCD core of havellockate (**1.116**).

1.5.2 – Barriault's efforts towards the total synthesis of (+)-havellockate.

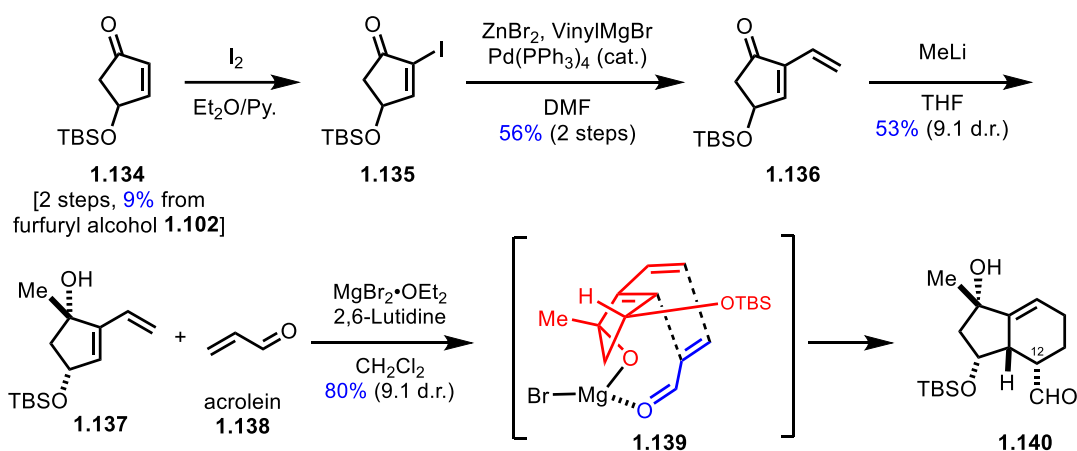
Also starting a handful of years after its discovery, the Barriault group initiated its efforts towards the total synthesis of havellockate in the early 2000's, with work that spanned from 2002 to 2010.^{73–75} A careful retrosynthetic analysis revealed that the application of a hydroxy-directed Diels-Alder (HDDA) reaction could be exploited to synthesize the ABCD core of the natural product (Scheme 1.15). Indeed, the general retrosynthetic analysis of the core was traced back to tricyclic ketone **1.130**, which could stem from alkene **1.131**, which is itself traced back to diene **1.132** and dienophile **1.133**, which would be added regio- and stereoselectively with the help of the magnesium tethering unit.



Scheme 1.15. Barriault's retrosynthetic analysis of the ABC core of havellockate.

The synthesis started from *rac*-enone **1.134**, which was synthesized in 2 steps and 9% from furfuryl alcohol **1.102** (Scheme 1.16). An α -iodination was completed to give iodoenone **1.135**, which was then taken as a crude in the Negishi coupling with divinylzincate to afford dienone **1.136** in 56% over 2 steps. The latter was then treated with methyllithium, which completed the

nucleophilic attack *anti* from the silyl ether, and delivered the *syn* tertiary alcohol **1.137** in 53% yield. The latter was subjected to multiple different conditions (bases, magnesium source, dienophile), and the only combination that gave a high yield of the desired adduct was using acrolein (**1.138**) as a dienophile instead of methyl acrylate (**1.133**). In that manner, the desired *endo* HDDA (**1.139**) reaction took place and gave fused bicyclic aldehyde **1.140** in 80% yield and high regio- and stereoselectivity. With the fused bicyclic system in hand, a synthetic pathway to construct the B and D ring of havellockate was developed.

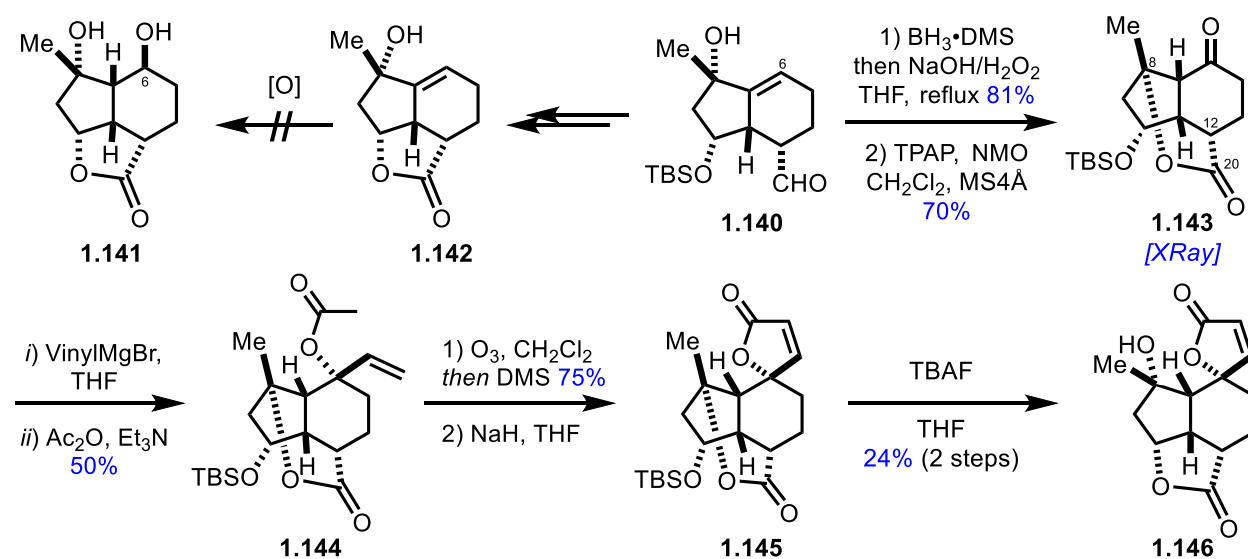


Scheme 1.16. Barriault's hydroxy-directed Diels-Alder synthesis of **1.141**.

The authors initially sought to construct the B-ring lactone from **1.141** through intermediate **1.142**, where the installation of the D ring would follow (Scheme 1.17). Starting from bicyclic structure **1.140**, the lactone moiety was elaborated in two steps and afforded **1.142**. After the extensive attempts trying to obtain **1.141** through various hydroboration conditions failed, it was apparent that the synthetic strategy would require modifications. Thus, the hydroboration of **1.140** was done first in 81% yield, and required oxidative treatment of the intermediate organoborane to be completed at reflux overnight in THF, highlighting the difficulty of this transformation. Along with the oxidation at C₈, a concomitant C₂₀ reduction from aldehyde to alcohol was observed. As a result, this intermediate was oxidized using the Ley-Griffith protocol and afforded **1.143** in 70% yield. Along with C₈ oxidation to the ketone, the tertiary alcohol and intermediate C₂₀ aldehyde cyclized to form a lactol, which was further oxidized in the reaction to afford the lactone. The structure of **1.143** was conformed by X-ray crystallography and provided a good platform for the

construction of the D spiro lactone ring as the authors decided to construct it through an aldol condensation strategy rather than a RCM reaction, another powerful method for construction of α - β unsaturated spiro lactones. This rigid structure proved to nicely shield the concave face of the molecule, and as a result, the reaction of the latter structure with vinylmagnesium bromide, and quenching of the intermediate magnesium alkoxide with acetic anhydride afforded the acetate **1.144** in 50% yield as the only detectable diastereoisomer. Bubbling ozone and quenching with dimethyl sulfide afforded the corresponding aldehyde in 75% (*not shown*). This intermediate aldehyde was treated with NaH to complete the intramolecular aldol and afforded **1.145**.

This intermediate was immediately treated with TBAF, after which the secondary alcohol spontaneously attacked the rigid 6-member lactone, which relieved ring-strain through a trans-lactonization and afforded the fully completed ABCD ring of havellockate **1.146** in 24% over 2 steps. This methodology has enabled a concise construction of the tetracyclic structure **1.146** in a total of 12 steps and 0.11% overall yield from furfuryl alcohol.

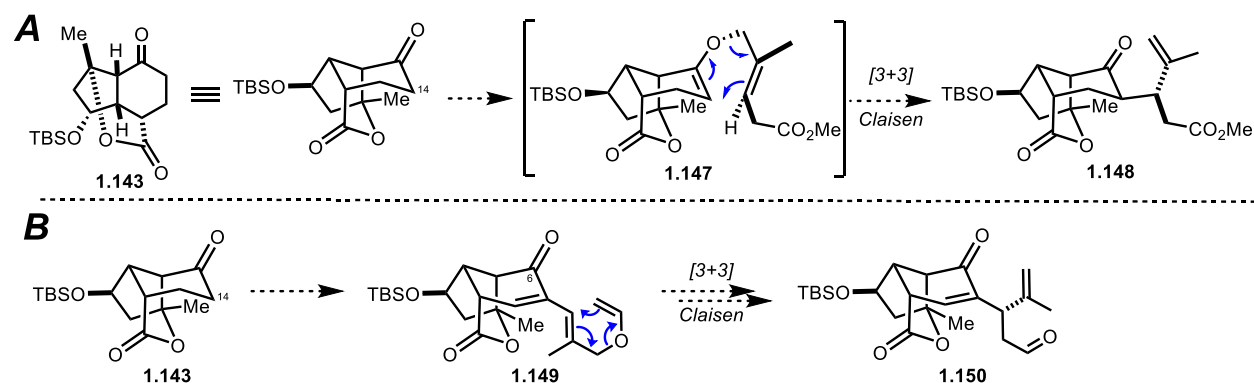


Scheme 1.17. Barriault's synthesis of the ABCD core of havellockate (**1.146**).

With a complete protocol that enabled the synthesis of the spiro lactone moiety of havellockate, the authors used the intermediate ketone **1.143** to install the side-chain on C₁₄ of the structure through a sigmatropic [3,3] Claisen rearrangement, which would also correctly install the C₁ isopropenyl unit (Scheme 1.18, A).⁷³ Initial efforts were made to attempt to kinetically transform ketone **1.143** into its enolate using a strong base, and trap the latter with an alkene-

containing electrophile to affect O-alkylation, (intermediate **1.147**). Unfortunately, all attempts at obtaining the Claisen-rearranged product **1.148** failed, presumably due to the reaction system being unable to form the O-alkylated adduct **1.147** *in situ*.

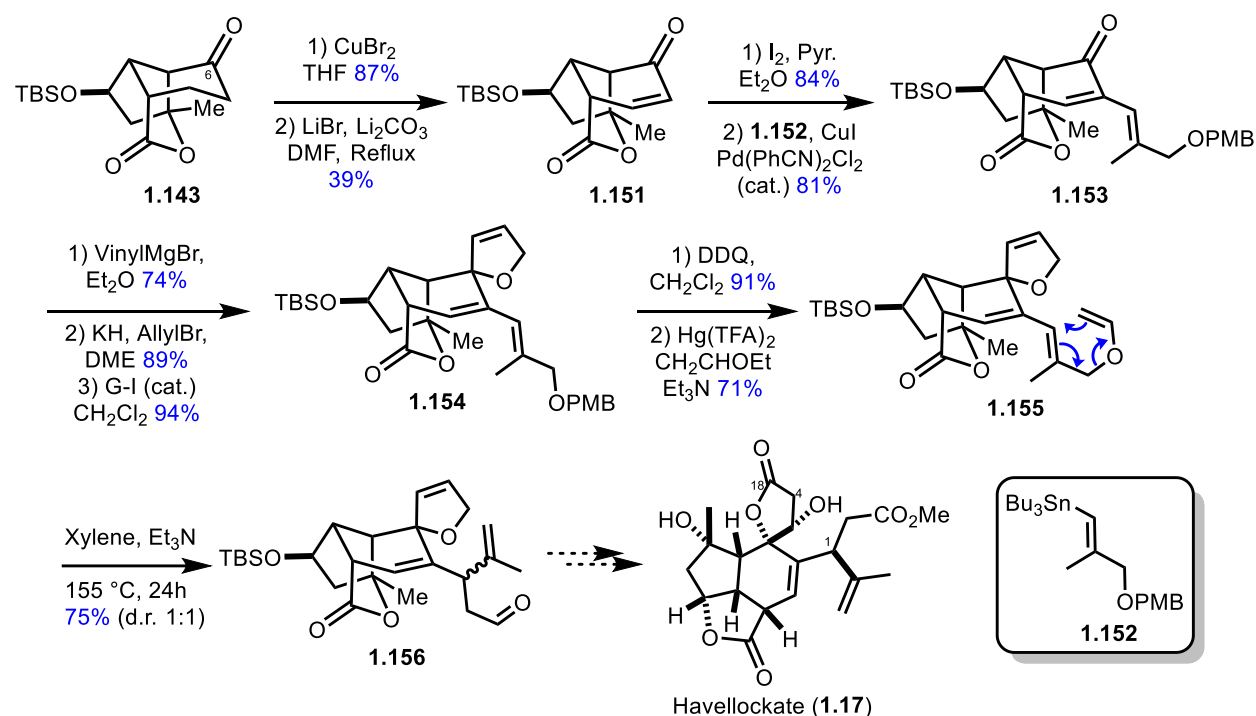
In order to create the desired C-C bond at C₁₄, the authors then shifted to a cross-coupling strategy. The ketone **1.143** was transformed to its α -haloenone (*not shown*), and cross-coupled using Stille conditions. This transformation appended the required sidechain, but attempting to transform the latter into the desired Claisen rearrangement product **1.150** from precursor **1.149** (Scheme 1.18, B) could not be completed. The authors reflected that the C₆ ketone might be antagonistic to the formation of **1.149**.



Scheme 1.18. Barriault's failed attempts at the desired Claisen rearrangement.

A successful work-around was found when the C₆ ketone was transformed into a potential D-ring spirolactone precursor that the natural product possesses (Scheme 1.19). The treatment of **1.143** with CuBr₂ enabled an α -bromination, and subsequent elimination afforded enone **1.151** in 87% and 39% yield respectively. This was followed by enone α -iodination in 84%, creating a cross-coupling handle which was exploited in a Stille cross-coupling with vinyl stannane **1.152** to afford dienone **1.153** in 81%. At this point, **1.153** was modified by the earlier-developed sequential stereospecific vinylation (74%), allylation of the tertiary alcohol (89%) and ring-closing metathesis using the Grubbs 1st generation catalyst (G-I) to afford the annulated dihydrofuran **1.154** in 94% yield. At this point, the transformation of the sidechain to its desired Claisen-rearrangement precursor was completed through PMB deprotection (91%) and reacting the resulting allylic alcohol with vinyl ethyl ether in presence of Hg^{II} to afford vinyl ether **1.155** in

71%. The Claisen [3,3] sigmatropic rearrangement was then affected by refluxing the substrate in xylenes to deliver the rearranged product **1.156** in 75% and in an equimolar diastereomeric ratio.



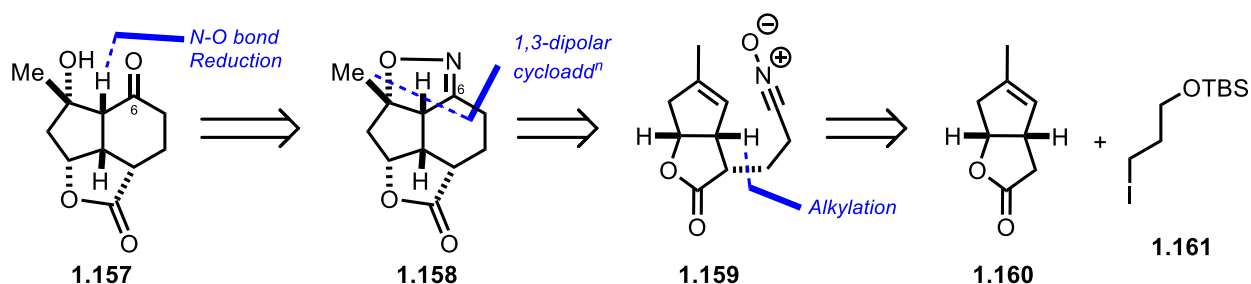
Scheme 1.19. Barriault's synthesis of Claisen rearrangement product **1.156**.

To conclude, these efforts represented the best advancements towards the total synthesis of havellockate **1.17** to date by the Barriault group, and probed multiple new methodologies to construct the critical stereocenters of the molecule, notably through the hydroxy-directed Diels-Alder and Claisen rearrangement reactions. The material could have been brought to the natural product upon separation of the isopropenyl diastereoisomers of **1.156** but efforts were stopped at this stage. In total, the efforts to build the penultimate intermediate **1.156** spanned 18 steps in 0.08% in the longest linear sequence from furfuryl alcohol.

1.5.3 – Liang's efforts towards the total synthesis of (+)-havellockate.

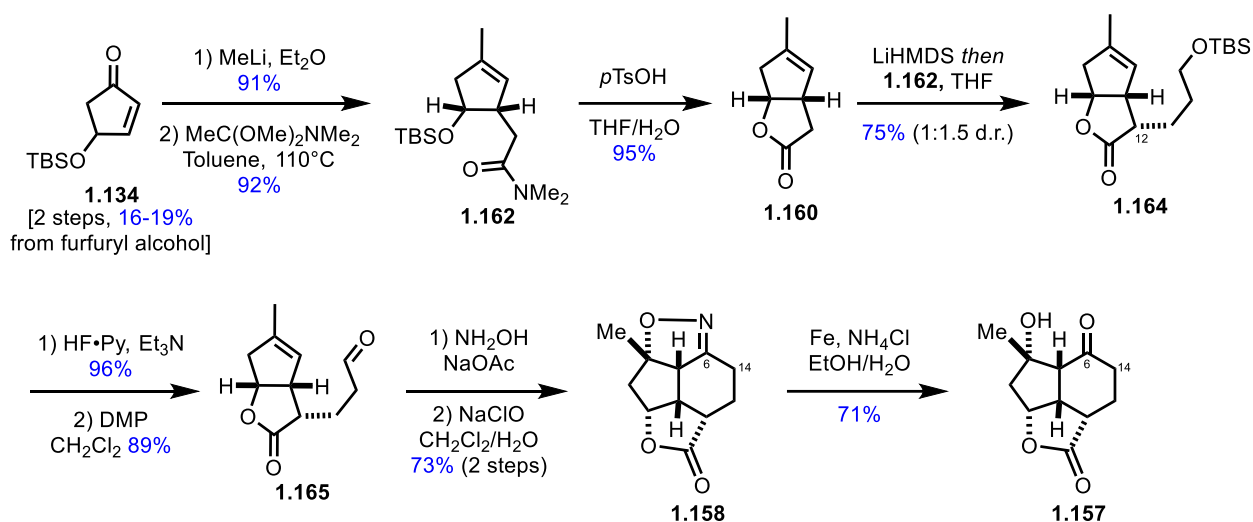
In 2019, the Liang group reported an intramolecular 1,3-dipolar cycloaddition to quickly access the functionalized tricyclic core of havellockate and other cembranoid natural products (Scheme 1.20). The authors proposed that the [5,5,6] tricyclic core **1.157** could be a precursor to all cembranoid natural products. This intermediate, which has the C₈-OH and the C₆ ketone installed, possesses the required chemical handles to be advanced to natural products or their

intermediates (See Mehta's and Barriault's synthesis of the D ring spirolactone through a C₆ cyclohexanone intermediate, Scheme 1.14 and 1.17 respectively.) This hydroxyketone was thought to stem from the hydrolysis of a cyclic N-O bond, tracing back to intermediate **1.158**, which is a substitution pattern easily accessed through an 1,3-dipolar cycloaddition of a nitrile oxide and alkene-containing substrate, such as **1.159**. The nitrile oxide can be accessed from an aldehyde through an oximation/oxidation sequence. This aldehyde is then easily traced back to an α -alkylated lactone, which can be prepared from the **1.160** and **1.161**.



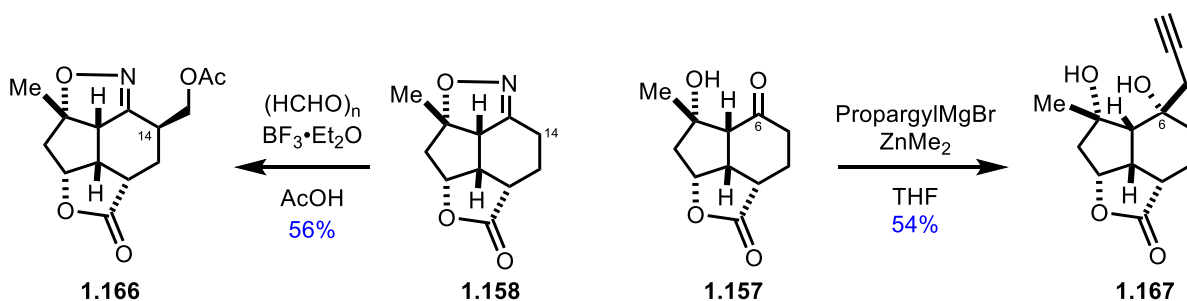
Scheme 1.20. Liang's retrosynthetic analysis of the ABC core of cembranoid natural products.

The authors used the racemic TBS enone **1.134**, available in 2 steps and 16-19% from furfuryl alcohol **1.102** as a starting material, which was methylated using MeLi in 91% yield (Scheme 1.21). Following this was a treatment with *N,N*-dimethylacetamide dimethoxy acetal at high temperatures, which concomitantly regioselectively eliminated the tertiary alcohol and generated the amide **1.162** in 92% yield. An acid hydrolysis accorded the bicyclic lactone **1.160** in 95% yield. The alkylation of the latter using LiHMDS and iodoalkane **1.161** afforded **1.164** as the minor diastereoisomer, as the concave face is less sterically available. However, its diastereoisomer, C₁₂-*epi*-**1.164** could be isomerized back in high yields through a deprotonation/kinetic protonation procedure (*not shown*). The desired aldehyde **1.165** was obtained upon removal of the TBS group (96%) and oxidation of the corresponding primary alcohol using the DMP oxidation (89%). This aldehyde was transformed into its oxime and subsequently oxidized into the intermediate nitrile oxide **1.159**, which was highly reactive and underwent the desired 1,3-dipolar cycloaddition to afford the desired tetracyclic isooxazoline **1.158** as a single diastereoisomer and in high yield (73% over 2 steps). The treatment of this tetracyclic intermediate with Fe⁰ in protic aqueous conditions afforded the β -hydroxyketone **1.157** in high yield of 80%.



Scheme 1.21. Liang's synthesis of the ABC tricyclic core of havellockate **1.157**.

After having developed an efficient pathway to the ABC tricyclic core of havellockate and other cembranoid natural products, the authors sought to further functionalize this scaffold (Scheme 1.22). After some effort, they were able to affect the C₄ functionalization by exploiting the imine-enamine tautomerism of **1.158**, enabling the synthesis of acetate **1.166** in 56% yield. Furthermore, the organometallic addition of a propargyl zincate afforded **1.167** in a highly stereospecific manner, effectively controlling the creation of the C₆ stereocenter of havellockate while generating chemical handles that can be precursors to a spirolactone.

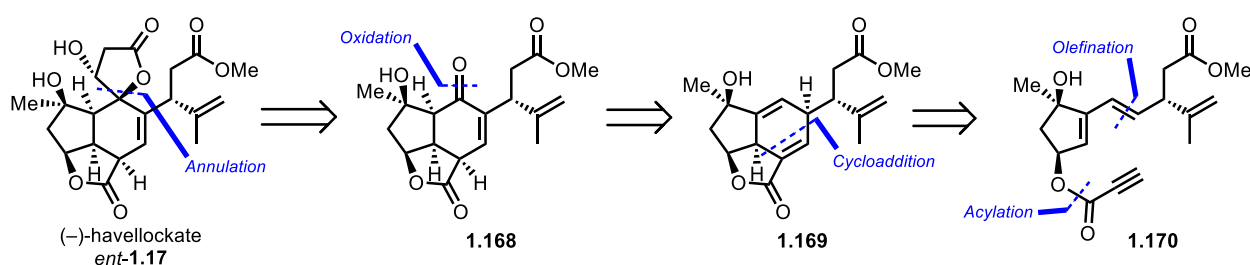


Scheme 1.22. Liang's late-stage transformations of cycloadducts **1.157** and **1.158**.

In conclusion, the Liang group developed a cycloaddition method complimentary to the widely used [4+2] Diels-Alder cycloaddition reaction, which is able to rapidly and efficiently synthesize the [5,5,6] framework of havellockate and other cembranoid natural products. In total, the efforts to build the penultimate intermediate **1.157** spanned 11 steps in 1.1% in the longest linear sequence from furfuryl alcohol.

1.5.4 – Stoltz’s total synthesis of (–)-havellockate.

In 2022, the Stoltz group disclosed the first and only enantiospecific total synthesis of havellockate using a chiral pool strategy, 24 years after its discovery.⁷⁶ The authors based their disconnection strategy from findings during their previous synthesis of other cembranoid natural product, such as scabrolide A (**1.32**, see section 1.4.1), electing to use a convergent route during their retrosynthetic strategy (Scheme 1.23). Based on the previous work by Mehta and Barriault, they opted to introduce the D ring spirolactone towards the end of the synthesis, leading them back to the C₆ ketone-containing late intermediate **1.168**. The latter, much like seen in their synthesis of scabrolide A, could stem from the tricyclic structure **1.169**, which itself can stem from **1.170** via an intramolecular [4+2] cycloaddition between an alkyne and diene. The Diels-Alder reaction adduct would be constructed from an acylation and a Julia-Kociensky olefination, building **1.170** from three simple building blocks (*not shown*) synthesized independently in a handful of steps using chiral pool and chiral auxiliary strategies.

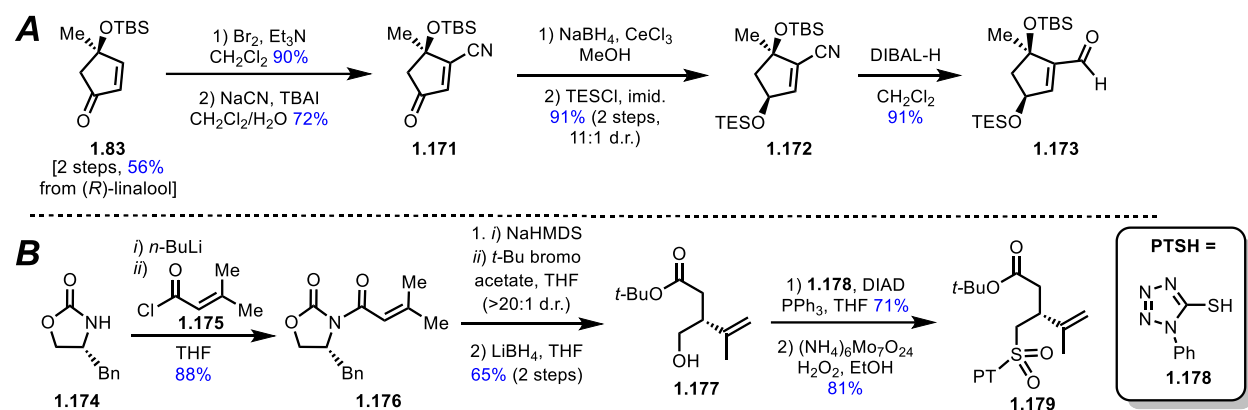


Scheme 1.23. Stoltz’s retrosynthetic analysis of (–)-havellockate (*ent*-**1.17**).

Starting from the same building block as previously used in their work on scabrolide A, the authors started their synthesis by using enantiopure enone **1.83**, built in two steps from (*R*)-linalool in 56% yield (Scheme 1.24, A). This molecule was exposed to bromine, undergoing an α -bromination, which was then subjected to cyanide conjugate addition/elimination to afford β -cyanoenone **1.171** in 90% and 72% respectively. The ketone moiety was then reduced and protected as its TES ether to afford acrylonitrile **1.172** in 91% over 2 steps and in a good diastereomeric ratio (11:1). This nitrile moiety was then reduced using diisobutylaluminium hydride (DIBAL-H) to give aldehyde **1.173** in 91% yield, creating one of the chemical handles required for the planned olefination.

The authors then turned to creating the synthesis of the required sulfone partner for the planned Julia-Kociensky olefination (Scheme 1.24, B). The required sulfone coupling partner was

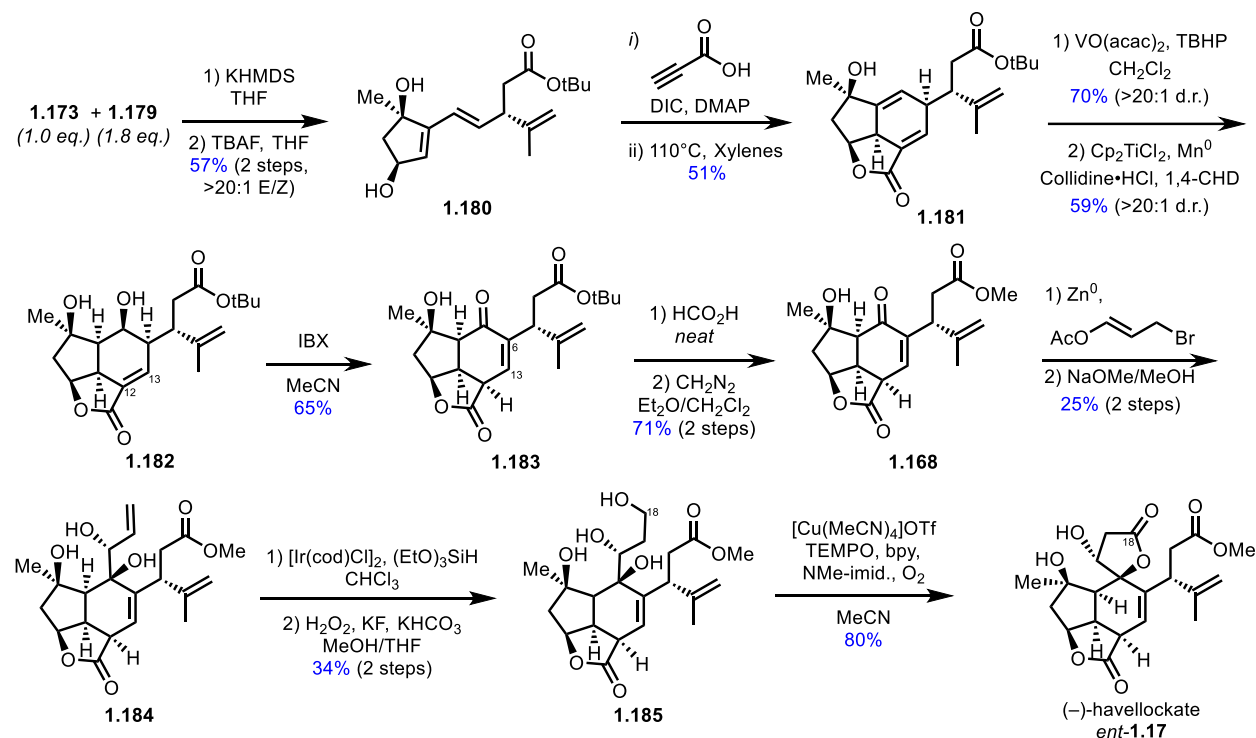
accessed first by coupling Evans' auxiliary **1.174** to the acyl fragment **1.175** to obtain **1.176** in high (88%) yield. The latter was then subjected to γ -deprotonation and α -alkylation using *tert*-butyl bromoacrylate as the electrophile, giving a crude mixture with high diastereocontrol (>20:1 d.r.). This crude mixture was subjected to reductive auxiliary cleavage to afford the enantioenriched alcohol **1.177** in 65% over 2 steps. Then, a Mitsunobu reaction with 1-phenyltetrazole thiol (PTSH, **1.178**) and subsequent oxidation using H₂O₂ and ammonium heptamolybdate as the catalyst delivered sulfone **1.179** in 71% and 81% yields respectively.



Scheme 1.24. (A) Synthesis of the aldehyde **1.173** and (B) Synthesis of the sulfone **1.179**.

With both coupling partners **1.173** and **1.179** in hand, the convergent alliance of these two was completed using potassium bis(trimethylsilyl)amine (KHMDs) as the base in THF at low temperatures and following TBAF treatment afforded the adduct **1.180** in high selectivity (> 20:1 *E/Z*) and 57% yield (Scheme 1.25). The coupling of alcohol **1.180** and propiolic acid under Steglich conditions afforded the ester intermediate (*not shown*), which was heated, after a short silica plug, in xylenes to afford the cycloadduct **1.181** as a single detectable diastereoisomer in modest yield (51%). With the [5,5,6] framework of havellockate now created, the authors used their previously-developed strategy to install the C₈ oxidation required to install the D ring spirolactone at a later stage. Subjecting the cycloadduct to vanadium-catalyzed epoxidation and titanium-mediated reduction afforded alcohol **1.182** in high diastereocontrol in 70% and 59% respectively. Then, an IBX-mediated oxidation afforded the corresponding ketone **1.183**, which spontaneously migrated the $\Delta^{12,13}$ alkene to the desired $\Delta^{6,13}$ alkene. At this point, the authors sought to perform the required transesterification to replace the *tert*-butyl ester to the methyl ester, which was accomplished by the consecutive treatment of the **1.183** in formic acid (*neat*) then

diazomethane, which afforded the desired methyl ester **1.168** in 71% yield over two steps. The installation of the last 3 carbons was completed using a zinc-mediated allylation using 3-bromo-1-acetoxypentene as the pronucleophile, as other usual nucleophiles were found to be incompetent for this transformation. This alkylation was followed by deacetylation using sodium methoxide in methanol and afforded the triol **1.184** in 25% yield over 2 steps. The authors attribute the low yield to the formation of intramolecular transesterification byproducts during the reaction. What followed is the elaboration of this allyl system using anti-Markovnikov iridium-catalyzed hydrosilylation of the $\Delta^{4,18}$ alkene, which yields the tetraol **1.185** after a subsequent Tamao-Fleming oxidation. Finally, a Stahl oxidation completed in aerobic conditions afforded the C₁₈-aldehyde, which turns into its lactol after C₆-OH interception. The latter was further oxidized to its lactone counterpart in 80% which completed the total synthesis of (–)-havellockate (*ent*-**1.17**).



Scheme 1.25. Stoltz's total synthesis of (–)-havellockate (*ent*-**1.17**).

In total, this synthesis spanned 20 steps with an overall yield of 0.11% in its longest linear sequence from commercially available (*R*)-linalool. This work constituted the first efforts that enabled a synthetic access to the complex polycyclic cembranoid natural product. As it was the case with the synthesis of scabrolide A (**1.32**), the authors opted for a chiral-pool approach, deciding to choose

the stereocenter at C₈ to be the first, which is the unnatural chiral center for all the natural products of this family. As such, their synthesis enabled the synthesis of the unnatural enantiomer of the natural product (–)-havellockate (*ent*-**1.17**). Interestingly, the authors noted that :

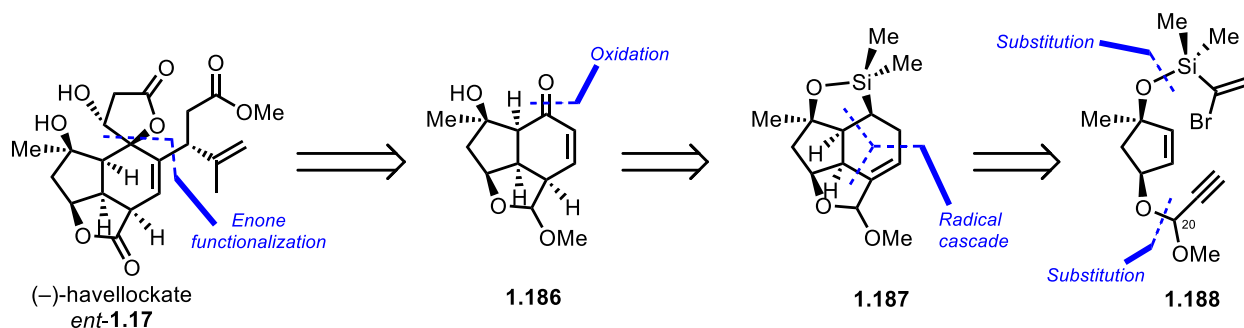
“Unfortunately, the optical rotation of our synthetic sample of [ent-1.17] did not match that reported in the literature in either sign of magnitude[...]. To date, attempts to secure a sample of the natural product have been met with failure. With no authentic material for comparison, we are left in the unenviable situation of not knowing, and potentially never knowing, whether there was an error in the original measurement or whether the absolute stereochemistry of the natural product could be enantiomeric to that depicted as [ent-1.17].”

This statement is conflicting and deserves some clarification for two reasons. The first reason is, the synthesis was started from (*R*)-linalool (**1.84**), which sets the C₈ stereocenter with an *R* absolute configuration, and by design, can only lead to the unnatural enantiomer of havellockate, *ent*-**1.17**, since the natural enantiomer, **1.17** has the *S* configuration at C₈. The second reason relates to the relative assignation of natural **1.17** and the synthetic *ent*-**1.17**. The relative and absolute configurations of both of these molecules were confirmed by single crystal x-ray diffraction of both the isolated natural product **1.17** (Anjaneyulu, 1998)²⁴ and the synthetic sample *ent*-**1.17** (Stoltz, 2022).⁷⁶ This SCXRD analysis is a proof that the authors truly synthesized the unnatural enantiomer, barring the fact that the magnitude of the measured optical rotation the rotations varied slightly due to purity, instrumentation or user error.

1.5.5 – Hu’s formal synthesis of (–)-havellockate and total synthesis of scabrolide A.

In 2024, the Hu group disclosed a divergent synthetic pathway that enabled a formal synthesis of (–)-havellockate (*ent*-**1.17**) and the total synthesis of scabrolide A (*ent*-**1.32**).⁷⁷ With the goal of accessing multiple members within the cembranoid natural product family, the common ABC core **1.186** was targeted, which was thought to be a precursor to *ent*-**1.17** through an enone functionalization (Scheme 1.26). The common core **1.186** could be traced back, after a Tamao-Fleming oxidation, to the silicon-bearing structure **1.187**. The latter was thought to be accessible through an *exo-exo-endo* radical cascade, initiated from silicon-tethered alkene **1.188** in a [2+2+2] addition fashion. Interestingly, this interesting synthetic methodology is somewhat reminiscent of

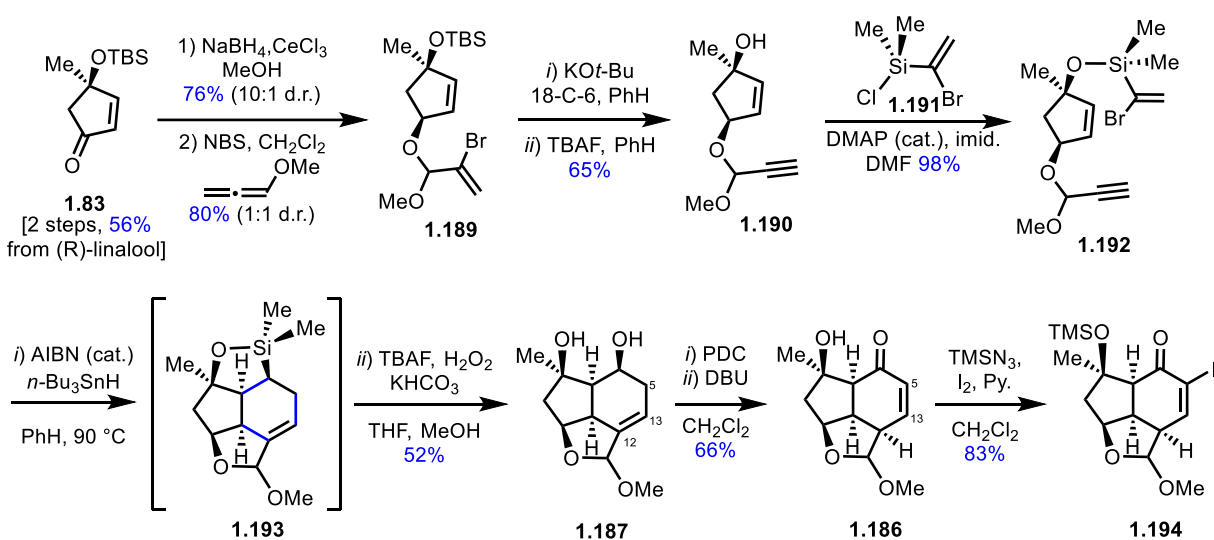
the radical-initiated polyolefinic cyclisations that were used in the 1980's towards the total synthesis of linear and angular triquinane natural products such as hirsutene and isocomene, and might be inspired from this work, although this was not discussed or cited in this publication.^{78,79} The monocyclic substrate **1.188** could easily be accessed through a series of substitutions between three simpler fragments. Fascinatingly, the authors decided to “protect” the C₂₀ carbon carbonyl as its methyl acetal, as carrying a lactone moiety at this position throughout the synthesis would likely cause chemoselectivity problems. This has the advantage of better chemoselectivity but carries the caveat that the two diastereomers at C₂₀ would have to be carried together throughout the synthesis when inseparable. This strategy also creates characterization and reaction tracking hardships, especially using thin-layer chromatography (TLC), a problem akin to sugar chemistry where both anomers react independently and are hardly separable. This acetal can readily be transformed to its carbonyl counterpart using acidic oxidative reaction conditions (*i.e.* Jones). On the other hand, carrying this carbon as its methylene equivalent would make it difficult to bring it to the ester moiety through oxidation, as recently demonstrated by Stoltz *et al.*⁸⁰



Scheme 1.26. Hu's retrosynthetic analysis of (-)-havellockate.

In an analogous way to Stoltz *et al.*, the synthesis starts from enantioenriched enone **1.83**, made from (*R*)-linalool in 2 steps (Scheme 1.27). A Luche reduction and subsequent treatment of the corresponding alcohol with methoxyallene in the presence of NBS afforded the acetals **1.189** in 80% yield and an uncontrolled (1:1) diastereomeric ratio. This equimolar mixture could not be separated and was carried as is throughout the next steps. This bromide was first eliminated to the alkyne using potassium *tert*-butoxide and 18-crown-6, and subsequently, the silyl ether was desilylated using TBAF to yield alkyne **1.190** in 65% yield. At this point, the silyl bromoalkene tether **1.191** was installed in high (98%) yield to afford **1.192**, which set the stage for the radical cascade cyclization. By treating this substrate with amounts of *n*-Bu₃SnH, an *exo-exo-endo* radical

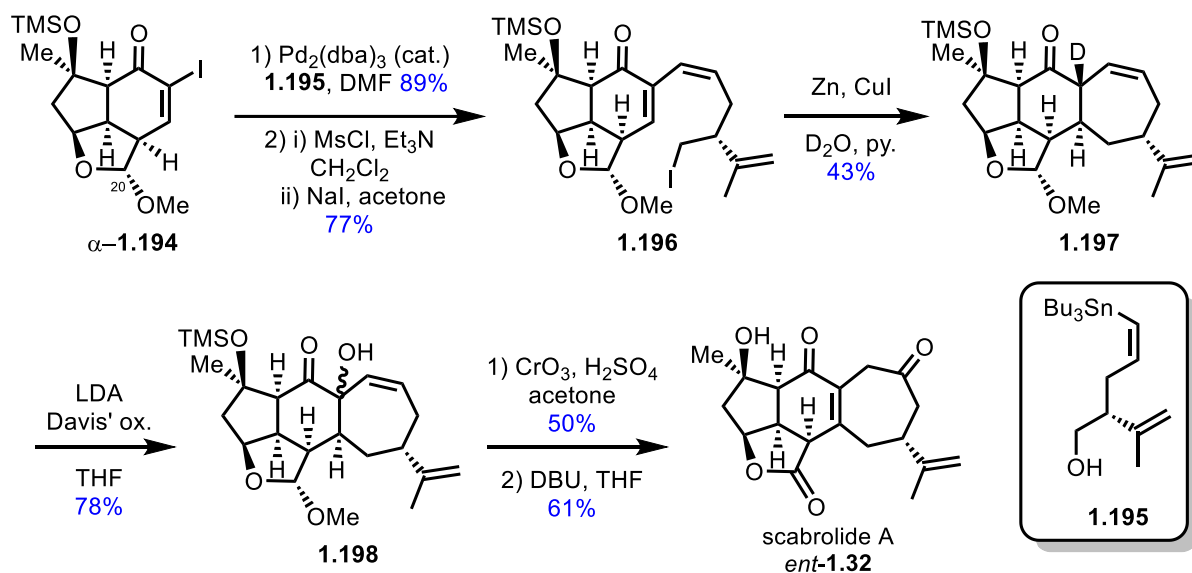
cascade is triggered and delivered cyclization product **1.193**, which was oxidized *in situ* using Tamao-Fleming conditions to afford diol **1.187** in 52%. At this point, the diastereoisomers at C₂₀ were separable, and were carried forward separately, and gave identical yields until late-stage transformations were performed (*vide infra*). At this point, a PDC-mediated oxidation and subsequent *in situ* migration of the $\Delta^{12,13}$ alkene to the desired $\Delta^{5,13}$ alkene using DBU afforded enone **1.186** in 66% yield. The reaction of the latter with TMSN₃ protected the tertiary alcohol, while subsequent treatment with iodine gave the α -iodoenone **1.194** in 83%. At this point, the ABC core of the cembranoid products was built, and ready for the divergent functionalization towards multiple members of this family of natural product.



Scheme 1.27. Hu's synthesis of the ABC tricyclic core of havellockate.

From this point on, the authors took a divergent approach towards the total synthesis of (–)-havellockate (*ent*-**1.17**). To highlight the divergent access that iodoenone **1.194** provided, the authors also developed a synthetic pathway towards scabrolide A (*ent*-**1.32**) (Scheme 1.28).⁷⁷ As mentioned previously, the C₂₀ methoxyacetal diastereoisomers could be isolated, and the synthesis towards both natural products was carried out using the separate diastereoisomers. Going forward, the methoxy acetal diastereomer α -**1.194** was cross coupled with vinylstannane **1.195** (made in 5 steps in 45% yield from **1.176**) and gave the corresponding dienone, which was subsequently turned into its alkyl iodide **1.196** in 77% over 2 steps through sequential mesylation and Finkelstein reaction with sodium iodide. The subsequent cyclization to give **1.197** was completed using Zn and CuI and used D₂O as a cosolvent, lowering the amount of side-product and giving a slight

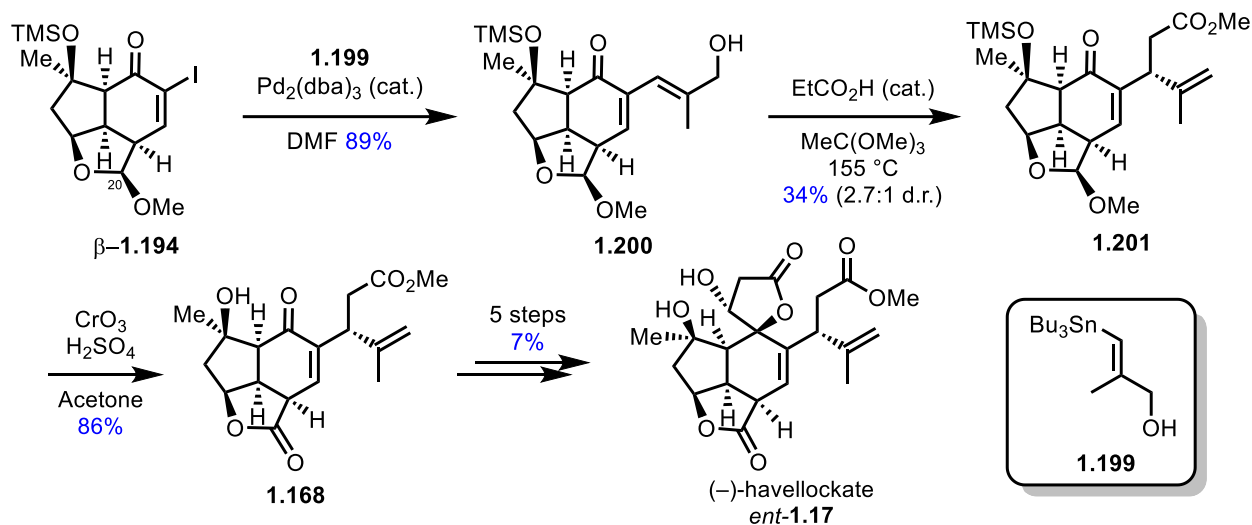
bump in yield (10%) as compared to H₂O. Finally, treatment with Davis' oxaziridine gave the α -hydroxylated ketone **1.198** in 78% yield, which after CrO₃-mediated oxidative rearrangement with concomitant TMS deprotection (50%) and DBU-mediated isomerisation (61%), afforded the natural product scabrolide A (*ent*-**1.32**). In total, this synthesis spanned 15 steps and 0.43% yield in its longest linear sequence from commercially available (*R*)-linalool, which represents an improvement in the total number of steps (15 steps versus 21 steps) and a slight decrease in overall yield (0.43% versus 0.52%) when compared to Stoltz's work.



Scheme 1.28. Hu's total synthesis of scabrolide A (*ent*-**1.32**).

The authors used the common intermediate iodoenone β -**1.194** in a divergent synthetic route towards another product of the cembranoid natural product family (Scheme 1.29). The methoxy acetal diastereomer β -**1.194** was engaged into Stille cross-coupling with vinyl stannane **1.199** to afford the cross-coupled dienone **1.200** in high yield (89%). Drawing inspiration from the work of Barriault *et al.* (Scheme 1.19), this allylic alcohol was setup to be engaged into a Johnson-Claisen rearrangement catalyzed by propionic acid in trimethyl orthoacetate (*neat*) at high temperatures to afford the desired β -isopropenylester **1.201** in 34% yield in 2.7:1 d.r. Following this step, exposing the substrate to Jones' reagent oxidized the acetal group to its ester and simultaneously removed the TMS group and yielded **1.168**. This synthetic intermediate was previously reported by the Stoltz group and transformed into (–)-havellockate (*ent*-**1.17**) in a sequence of 5 steps (*vide supra*). In total, this formal synthesis of (–)-havellockate spanned 17

steps and 0.11% yield in its longest linear sequence from commercially available (*R*)-linalool, which represents a great improvement in the total number of steps (17 steps versus 20 steps) in an equal total yield (0.11%) versus Stoltz's synthesis.

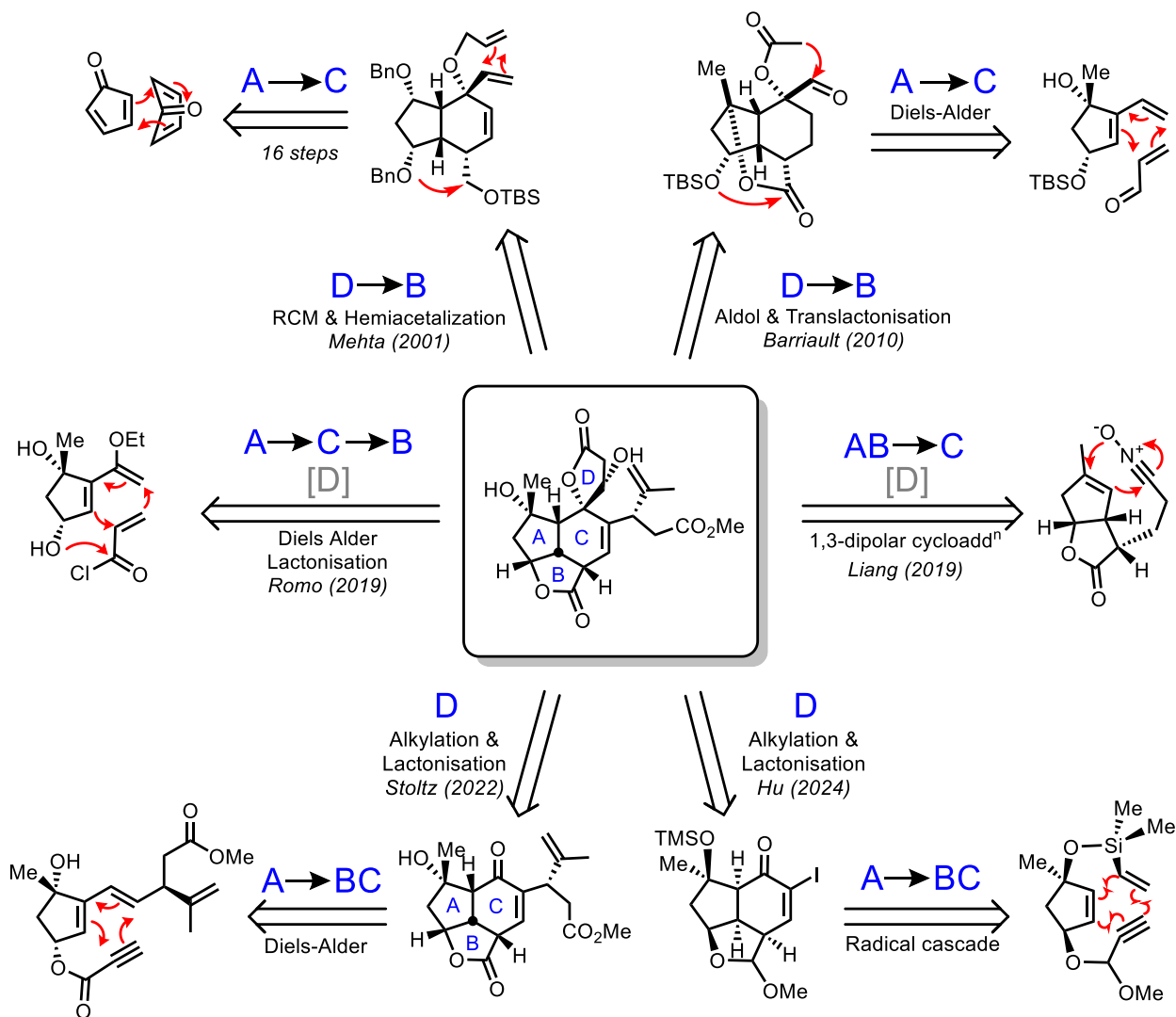


Scheme 1.29. Hu's formal synthesis of (-)-havellockate (*ent*-1.17).

To date, these two last syntheses represent the only reported accesses to the natural product havellockate. It is important to note that, since both total and formal syntheses start from the same building block (*R*)-linalool and yield the unnatural enantiomer of the natural products (-)-havellockate (*ent*-1.17) and scabrolide A (*ent*-1.32). It would then be operationally simple to switch to using (*S*)-linalool, since this enantiomer is also sparingly commercially available at reasonable prices, though slightly more costly than (*R*)-linalool.

Despite having been known for over almost 30 years, a surge of interest in cembranoid diterpenoids have resulted in many elegant total syntheses, again, with over 20 research groups having published their efforts towards these natural products since 2018. The structural complexity of these complex natural products continues to puzzle chemists and their challenging structures present an immense opportunity in the development of new reactions and synthesis of derivatives to probe the viability of their derivatives. Undoubtedly, multiple members of these interesting natural products will continue to be isolated and characterised in the coming years, feeding additional inspiration for synthetic and isolation chemists around the world.

As (+)-havellockate remains one of the more complex natural product of the cembranoid family, this thesis will discuss the laborious investigations that were undertaken by myself from 2021 to 2026, which will build onto the previously developed knowledge developed in previous synthetic pathways to the core of havellockate (Scheme 1.30).



Scheme 1.30. Overview of the strategies used in the synthesis of cembranoid natural products.

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CHAPTER 2

Retrosynthetic analysis and model substrate synthesis of the tetracyclic core of (+)-havellockate.

2.1 – Introduction.

Having now fully explored the background on Cembranoids and (+)-Havellockate (**1.17**), the molecule will be explored synthetically, as it contains multiple interesting features making it unique in its family of natural product and attractive target for the synthetic chemist (Figure 2.1). This structure contains 20 carbon atoms and possesses a high density of stereochemical information around the all-*cis* fused ABC tricycle that makes up its core. This feature has the distinct advantage that diastereotopic faces of this molecule, as it is constructed, makes it almost effortless to predict diastereoselectivity of chiral center-building events. On the other hand, its rigidity and packed structure could make it challenging to engage certain functional groups into otherwise easy transformations, as steric bulk and stereoelectronic factors will need to be carefully considered upon retrosynthetic analysis. Furthermore, a unique γ -butyrospirolactone moiety adorns this tricycle, which itself is substituted by a β -hydroxy group. The standard C₈ tertiary alcohol of *Cembranoids* also decorates the tricyclic core of this natural product. This structure also contains a side-chain ester on its eastern part, containing the chiral isopropenyl motif. The structure's identity was confirmed by crystallography in 1998 by the isolation team.

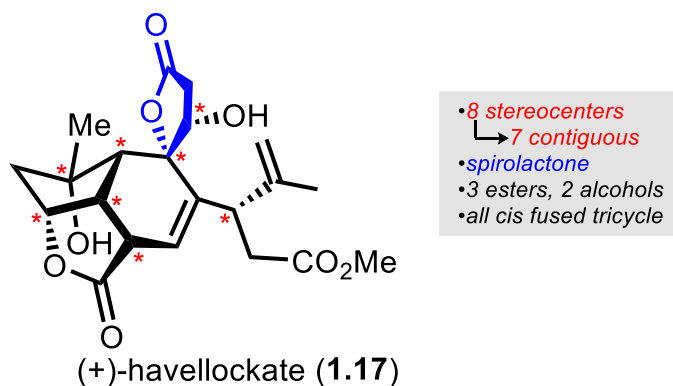


Figure 2.1. Notable structural features of (+)-havellockate (**1.17**).

Another interesting fact is that this molecule has only been isolated and reported once, and it was not mentioned in any other isolation reports since 1998. Knowing this, we now contemplate the arduous task of preparing a synthetic sample of this unique natural product and tackle the challenging structure that it imposes. As with previous reports and endeavors spent on this class of molecules, it was believed that a biomimetic [4+2] cycloaddition would enable an efficient and concise construction of the central C ring of this natural product. This chapter will discuss the intricacies of this molecule and a logical retrosynthetic analysis that would enable an efficient

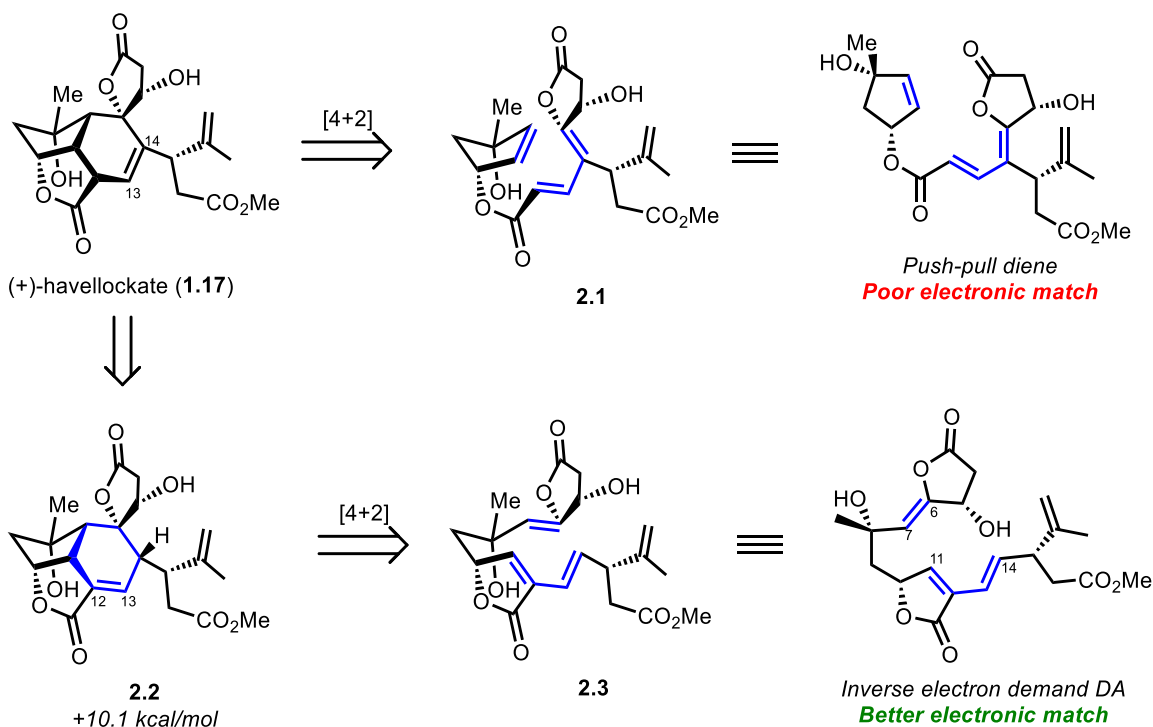
construction of its architecture. The development of a strategy to access the natural product will be based on studies of a model system, discussed below, that was crucial to an avenue towards the natural product.

2.2 – Retrosynthetic analysis of (+)-havellockate.

With the knowledge acquired previously in the Barriault laboratory utilizing Au^I for π -Lewis acid activation of alkynes, the same strategy was applied to the disconnection of havellockate.¹⁻³ The strategy revolved around a biomimetic construction of the central C ring of the natural product through a [4+2] Diels-Alder (DA) reaction. Herein, this strategy will be discussed in further details. A direct disconnection of the central C ring of **1.17** into its precursor diene & dienophile partners gives **2.1**, which, when flattened into a two-dimensional plane, reveals its DA partners. Looking over at the electronic system of **2.1**, it can be observed that the diene has an electron-rich system on the north-eastern end (*ether*), and an electron-poor substitution on the west end (*ester*). These diene systems are referred to as “*Push-Pull*” dienes. These dienes are not well electronically defined, and in many cases, a dramatic drop in diene reactivity is observed, even at higher pressures & temperatures.⁴ Other systems have been shown to undergo stepwise additions, which give rise to the possibility of stereocenter scrambling versus a concerted addition pathway.⁵ Fundamentally, these outcomes are the consequences of a higher HOMO-LUMO gap, as well as high distortion energies required to offset unfavorable reactions.^{6,7}

As this strategy did not give us enough confidence to embark onto a full synthetic campaign, a revision was needed and as such, a simple solution was proposed. It was proposed that shifting the Δ^{13-14} alkene to a Δ^{12-13} alkene could alleviate the problems associated with diene-dienophile electronic matching (Scheme 2.1). Indeed, this new retrosynthetic target **2.2**, when opened up into its diene-dienophile pair **2.3**, and flattened into a two-dimensional plane, offered an elegant solution to this problem. It is now evident that the diene-dienophile pair is much better matched electronically, according to Frontier-Molecular Orbital (FMO) theory and the Klopman-Salem equation^{8,9}, through use of an electron-rich dienophile and an electron-pool diene. Having bigger electronic lobes at C₇ and C₁₁ and smaller lobes at C₆ and C₁₄, an asynchronous, concerted Diels-Alder was expected to take place on this system. Another advantage of this now alkene-shifted system is the fact that the substrate **2.22** contains an alkene in a *pseudo* bridge-head

position, imparting a lot of strain energy on the system (+10.1 kcal/mol).^a With this unstable product, it was envisioned to be able to access the C₁₄ proton easily through deprotonation, to shift the alkene away from conjugation. This would be a process that is thermodynamically regulated and drastically stabilize the system in its ground state conformation. This strain energy release can be visualized by the proposed alkene shift, which would break the conjugated π bonds and fully open the *bowl-like* shape of the ABC fused ring system.



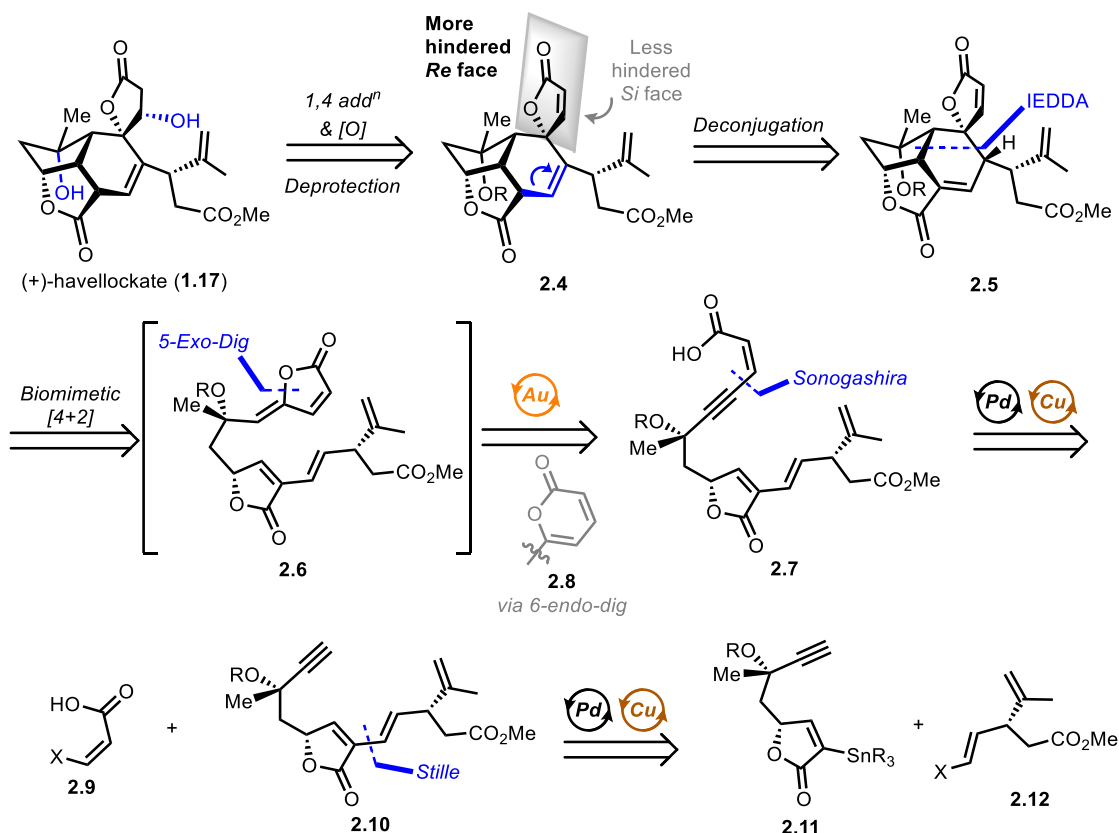
Scheme 2.1. General strategic deconstruction of the core of (+)-havellockate.

Now having a plan in hand, a full retrosynthetic analysis centered around this biomimetic C- ring construction of the natural product was completed (Scheme 2.2). First, it was decided to reveal the two free alcohols of havellockate at a late stage, protecting the tertiary C₈ alcohol with a protecting group (“R”), and introducing the C₅ secondary alcohol through nucleophilic conjugate addition of a boron or silicon cuprate, which could then be oxidized to the corresponding alcohol. The stereochemical outcome of this addition was important, and it was understood that the prochiral *Si* face of the system was less hindered than the *Re* face, by virtue of having a single alkane-like chain on its face versus the *Re* face, which contains the fused ABC tricyclic system on

^a Level of theory : B3LYP and basis set : 6-31G(d) in the gas phase.

that face. It is very likely that this nucleophile would add on the desired *Si* face of the molecule. These two operations lead back to **2.4**, which would need to undergo the thermodynamically favored deconjugation event from **2.5**.

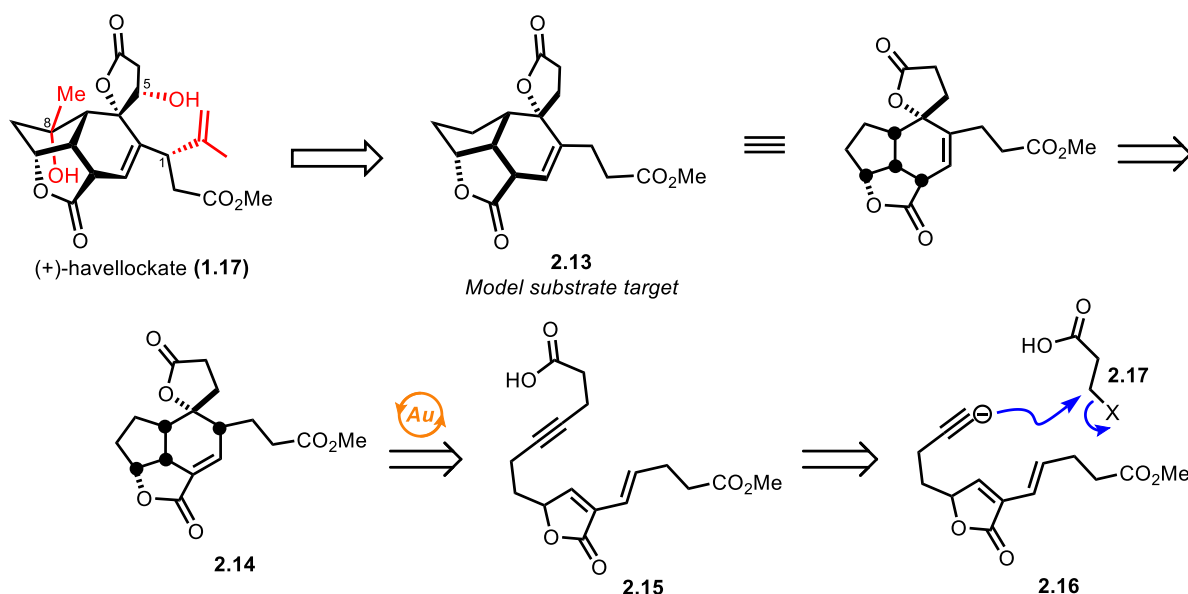
At this point, this substrate was set to undergo the crucial inverse electron demand Diels-Alder (IEDDA) reaction, which traced back to the internal diene-dienophile **2.6**. More importantly, it was hypothesized that this molecule would not be isolated, but would react in the cycloaddition, as the reacting parts were well matched electronically, though IEDDA reactions are notoriously more difficult than their normal electron demand homologues. By virtue of treatment with an Au^I catalyst, the exomethylenelactone dienophile could stem from a *5-exo-dig* cyclisation of carboxylic acid **2.7** onto the central alkyne to yield, after protodemetalation of the intermediate alkylgold species (*not shown*), the dienophile part of **2.6**. Although this desired reaction has been reported on similar systems, *6-endo-dig* products (**2.8**) were anticipated to be formed, as this transformation had been reported multiple times on simpler substrates, yielding this parasitic cyclisation product.^{10–12} The precursor of the planned reaction cascade **2.6** was now simplified to



Scheme 2.2. Retrosynthetic analysis of (+)-havellockate.

2.3.1 – Retrosynthetic analysis of a model system.

In that manner, a synthesis of a racemic model system was initiated (Scheme 2.3). The chemistry developed during this model substrate synthesis would guide much of the chemistry that would be used during the synthesis of the natural product. In that manner, the C₈ tertiary alcohol, C₅ secondary alcohol and isopropenyl group at C₁ were all ablated. These simplifications lead us back to racemic model substrate **2.13**, which can be traced back to its conjugated congener **2.14**, which could originate from the planned Au^I-mediated cascade of **2.15** in an analogous manner seen in Scheme 2.2. For the model system, carboxylic acid **2.15** could originate from a nucleophilic attack of dienyne anion **2.16** onto carboxylic acid electrophile fragment **2.17**.

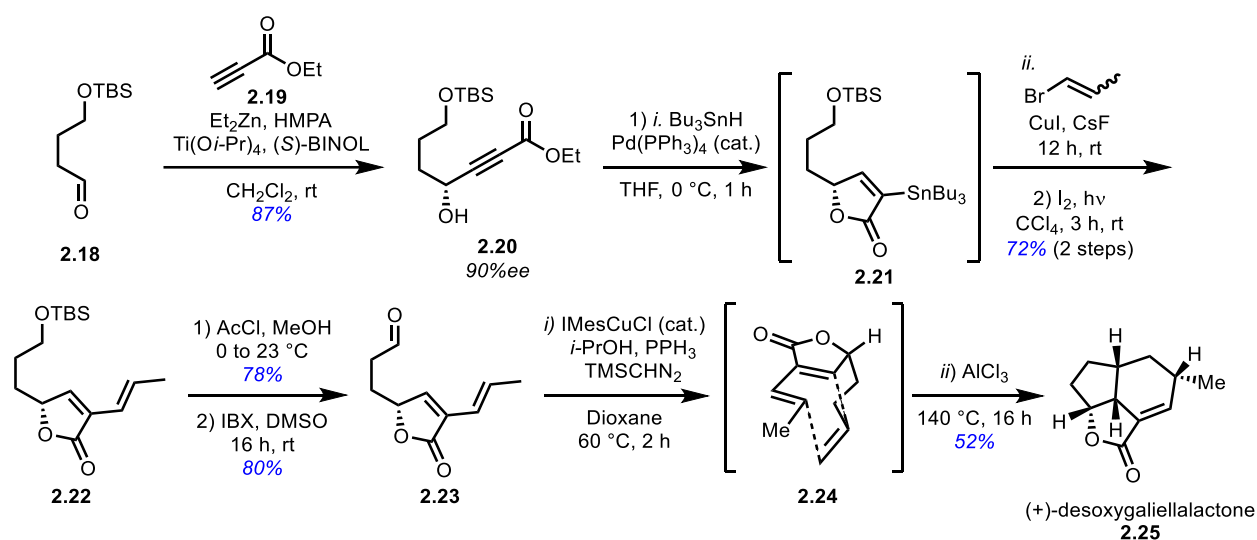


Scheme 2.3. Retrosynthetic synthesis of a model system through simplifications.

2.3.2 – Total synthesis of (+)-desoxygaliellalactone by Parmentier and Lebel.

Having now the simple diyne fragment **2.15** as a target, strategies that would enable an efficient synthesis of the butanolide part of the molecule were researched. A thorough search of the literature revealed to us that a very similar overall strategy had been used towards the total synthesis of (+)-desoxygaliellalactone by Pr. Hélène Lebel and Michael Parmentier at the University of Montreal (Scheme 2.4).^{15,16} The authors first subjected aldehyde **2.18** to asymmetric alkynylation with ethyl propiolate **2.19** and chiral (*S*)-BINOL to obtain propargylic alcohol **2.20** in 87% yield and high enantiopurity. This alcohol was subjected to palladium-catalyzed hydrostannylation in tetrahydrofuran (THF), generating the tin butanolide **2.21** *in situ*, which they

coupled to 1-bromopropene via a CsF-accelerated^{15,17} Stille cross-coupling to access the desired diene product (*not shown*) in a 1:1 *E/Z* mixture. This diene was quantitatively photoisomerized with iodine to give **2.22** in 72% over 3 steps. The TBS group was removed using methanolic hydrochloric acid (HCl, 78%) and the corresponding primary alcohol was oxidized to aldehyde **2.23** using IBX (80%). As multiple olefination attempts failed to yield **2.24**, a unique copper-catalyzed olefination process using diazomethane, known as the Lebel olefination¹⁸, was used to install the olefin and generated **2.24**, which was heated *in situ* in presence of the Lewis acid AlCl₃ to finally deliver the cycloadduct (+)-desoxygaliellalactone **2.25** in 52% over 2 steps. This work heavily inspired our strategy, as both of the ABC tricyclic carbon frameworks of (+)-desoxygaliellalactone (**2.25**) and (+)-havellockate (**1.17**) are identical.



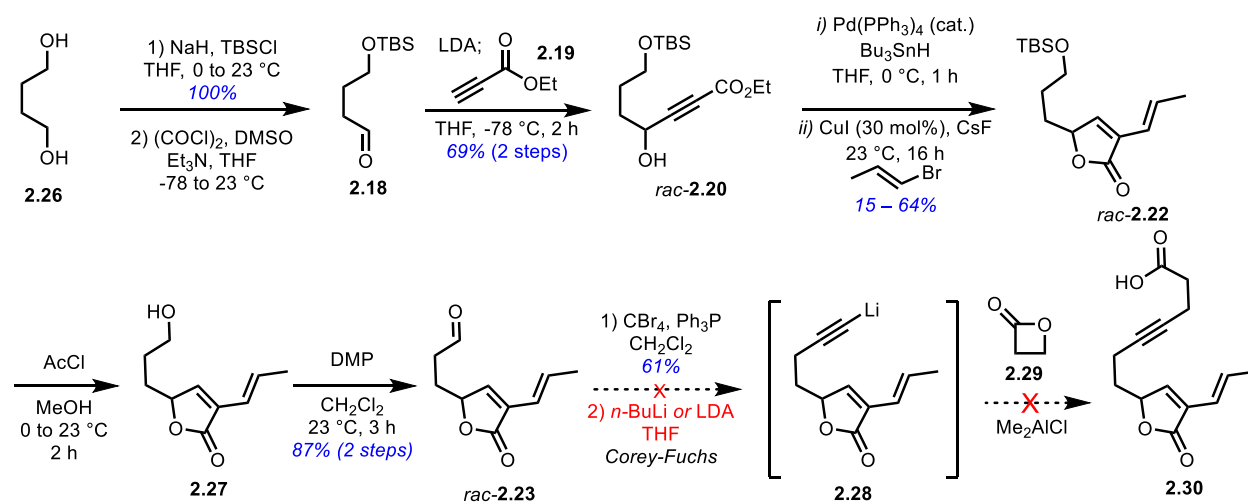
Scheme 2.4. Lebel and Parmentier's total synthesis of (+)-desoxygaliellalactone.

2.4 – Model substrate synthesis – First generation.

Efforts towards a synthesis of the target carboxylic acid **2.15** were initiated from butane-1,4-diol (**2.26**, Scheme 2.5). Firstly, one of the two alcohol groups of **2.26** was protected as its TBS silyl ether (100%) and the second alcohol was oxidized to aldehyde **2.18** using the Swern oxidation. Next, the treatment of ethyl propiolate (**2.19**) with lithium diisopropylamide (LDA) afforded the corresponding lithium acetylide, to which was added **2.18** slowly, to give propargylic alcohol *rac*-**2.20** in 69% over 2 steps. This alcohol was engaged in the aforementioned hydrostannylation / lactonization sequence, generating the vinyl tin intermediate *rac*-**2.21** *in situ*, which was cross-coupled with (*E*)-1-bromopropene under CsF-accelerated Stille conditions to

afford diene **rac-2.22** in 64%. It is important to note here that this one-pot cross-coupling protocol was hardly reproducible with yields ranging from 15-64%. As a result, it was later decided to isolate the intermediate vinyl tin **rac-2.21** and engage it in Stille cross-coupling in two steps instead to boost yields and reproducibility. This diene was then deprotected at the primary alcohol **2.27** using methanolic HCl and oxidized to its aldehyde **rac-2.23** using the Dess-Martin Periodinane (DMP) in 87% yield over 2 steps. It was envisioned to install the alkyne moiety through a Seyferth-Gilbert homologation¹⁹ of this aldehyde using the Bestmann-Ohira reagent, but the conditions needed for the deprotonation of the corresponding alkyne were thought to be too harsh for the substrate. To remedy this possible problem, generating the lithium acetylide *in situ* using the Corey-Fuchs two-step protocol at low temperature gave better odds.²⁰

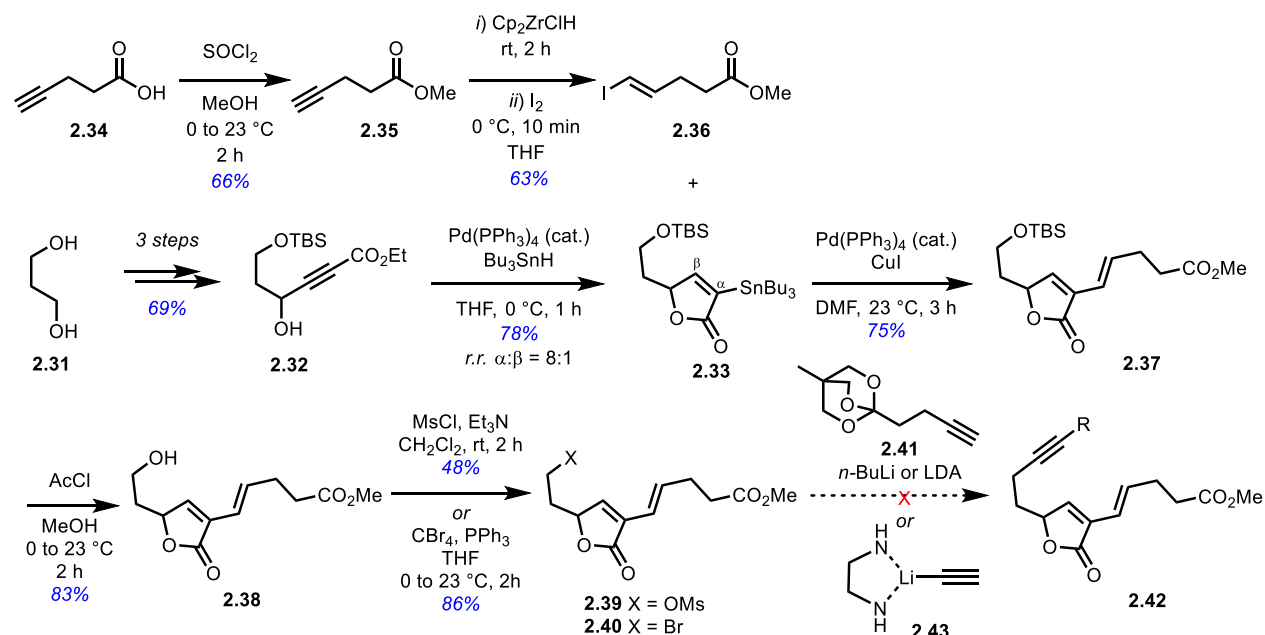
The intermediate acetylide **2.28** could then be homologated with β -propiolactone **2.29** in presence of a Lewis acid (*i.e.* Me_2AlCl)²¹ to give **2.30**. As such, a Ramirez olefination of aldehyde **rac-2.23** afforded the corresponding homologated dibromoolefin (*not shown*) in 61% yield. The treatment of this dibromoolefin with two equivalents of strong bases typically used in the Corey-Fuchs protocol [*n*-butyl lithium (*n*-BuLi) or LDA] and engagement of the putative acetylide **2.28** in the 3-carbon homologation protocol failed to give the desired product **2.30**, a truncated version of **2.15**. It was later determined that **2.28** failed to form, as a deuteration quench (MeOD) failed to yield the deuterated alkyne or any starting material, confirming the substrate's sensitivity to strongly basic conditions.



Scheme 2.5. Failed attempt at obtaining carboxylic acid **2.30**.

2.5 – Model substrate synthesis – Second generation.

In light of the lessons learned upon the first attempts at obtaining **2.30**, a new strategy that installed the alkyne and carboxylic acid moieties in a single step was conceived. This involved the nucleophilic addition of an alkyne-bearing 4-methyl-2,6,7-trioxabicyclo[2,2,2]octyl (OBO) orthoester onto the substrate bearing an electrophilic position at C₈ (Scheme 2.6). OBO orthoesters are transient protecting group for carboxylic acids and can withstand strongly basic conditions required for alkyne deprotonation.²² As the two carbon units would now come from the alkyne nucleophile, the OTBS-bearing carbon chain had to be shortened. In such manner, the protection-oxidation-sequence of butane-1,4-diol **2.26** (*vide supra*) was repeated onto the propane-1,3-diol **2.31** to give **2.32** in 69% yield over 3 steps. A hydrostannylation yielded the vinyl tin **2.33**, which was isolated in 78% yield in an 8:1 ratio of regioisomers, which could be separated by silica flash chromatography (SFC).²³ After isolating this substrate, introducing the ester moiety seen in the natural product was desired, to better test the robustness of this methodology by emulating the natural product as much as possible. As such, 4-pentynoic acid **2.34** was esterified to give **2.35** in 66% yield, which was subsequently transformed it into a transient vinyl zirconate using Schwartz's reagent (Cp₂ZrClH) and quenched with iodine to afford vinyl iodide **2.36** in 63% yield. This substrate and **2.33** were then engaged in the Stille cross-coupling to afford the diene **2.37** in 75%.



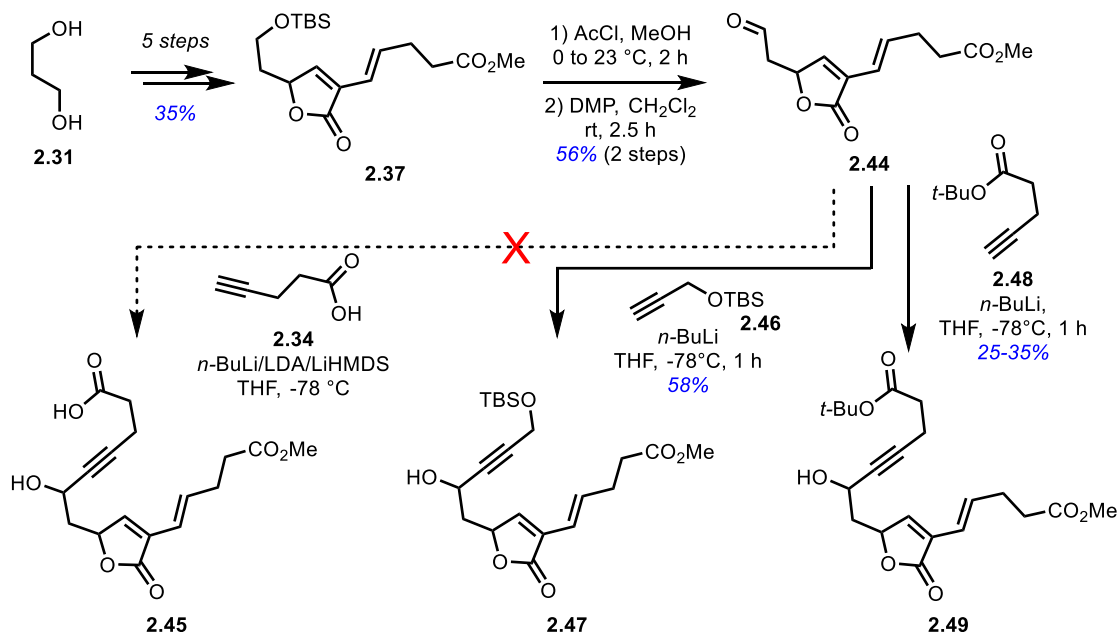
Scheme 2.6. Failed attempt at obtaining dienyne **2.42**.

By utilizing a two-step protocol with a vinyl iodide versus the one pot and vinyl bromide method, the reproducibility and yields for this reaction were greatly improved. An acid-mediated TBS clivage then yielded alcohol **2.38** in 83% yield, which was then activated into a leaving group as its mesylate (**2.39**, 48%) or as its alkyl bromide derivative (**2.40**, 86%) through an Appel reaction. These two substrates now set the stage for the desired installation of the alkyne/carboxylic acid functionalities on the diene. The known OBO ester **2.41**²⁴ was transformed to its lithium acetylide by treatment of *n*-BuLi or LDA, to which **2.39** or **2.40** was added at low temperature.

Unfortunately, the desired S_N2 product **2.42** was not observed in either case after multiple attempts, and lead to the decomposition of the electrophile. Other attempts to salvage this route such as installing the alkyne moiety with no OBO ester or affecting the S_N2 reaction using the commercially available lithium acetylide ethylenediamine complex **2.43** were also met with failure, yielding no desired addition product at C₈.

2.6 – Model substrate synthesis – Third generation.

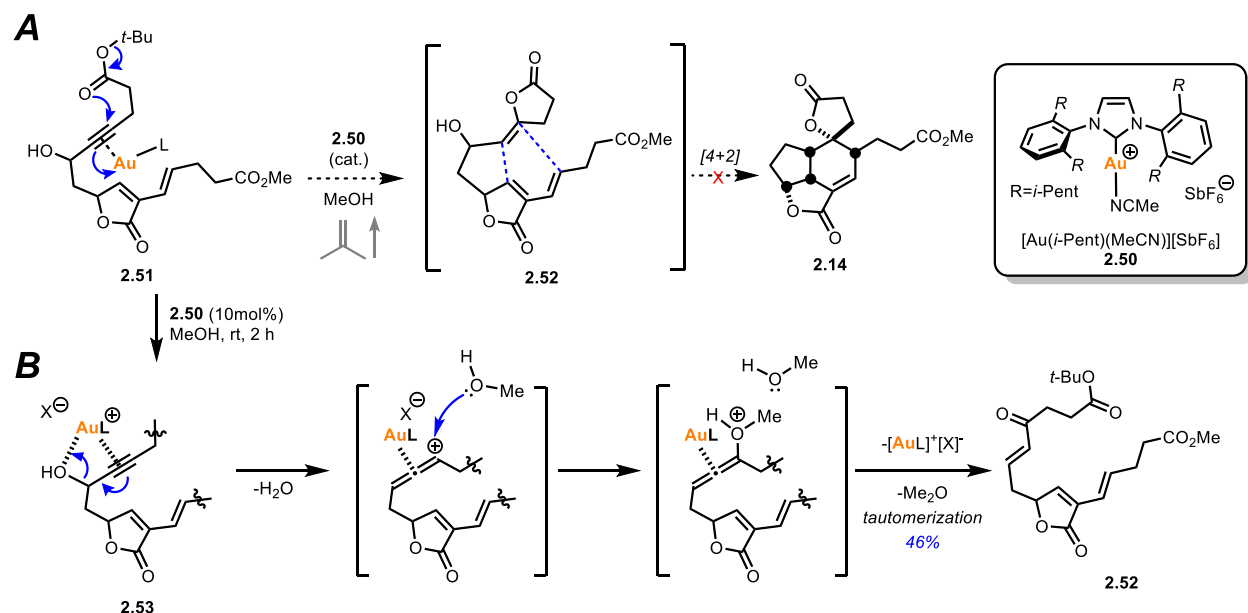
In light of these failed attempts, it was understood that the substrate was prone to decomposition when exposed to strongly basic conditions, but the idea that a nucleophilic substitution could couple the diene and alkyne/carboxylic acid fragments together was still very much alive. As such, the substrate would need a much more electrophilic moiety than an alkyl bromide/mesylate, and an aldehyde perfectly fit the bill. Fortunately, a previous intermediate would enable us to quickly access a competent aldehyde for this transformation (Scheme 2.7). From the diene **2.37**, an acid-mediated TBS deprotection and subsequent oxidation with DMP gave aldehyde **2.44** in 56% over 2 steps. A direct access to alkynoic acid **2.45** without protection/deprotection would be possible from the double deprotonation of alkynoic acid **2.34** and its exposure to the aldehyde **2.44**. This double deprotonation-alkynylation of an aldehyde had been reported previously and was thought to be applicable in this synthesis.^{25,26} Unfortunately, multiple attempts to obtain **2.45** failed. To confirm the aldehyde was a good electrophile, the alkynylation of the latter using OTBS-protected **2.46** as a surrogate was completed, yielding the adduct **2.47** in 58% yield. By confirming that the alkynylation was possible, the addition of alkyne **2.48** onto this aldehyde delivered the propargylic alcohol **2.49** in 25-35% yields.



Scheme 2.7. Successful synthesis of dienyne **2.49**.

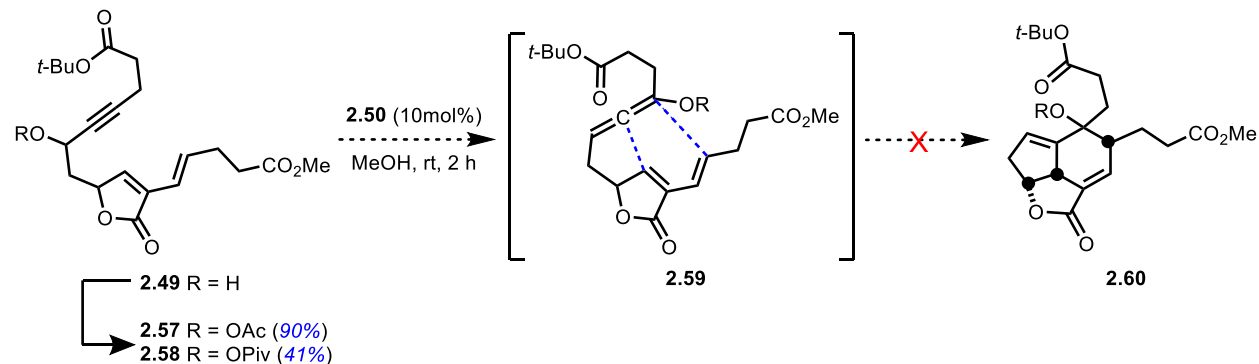
Having now installed the carboxylic acid, alkyne and diene moieties on a substrate **2.49**, the initial hypothesis (Scheme 2.2) was ready to be tested. Upon treatment of **2.49** with Au^I catalyst **2.50**, the *tert*-butyl ester in gold-bound **2.51** was anticipated to be a competent nucleophile in the *5-exo-dig* cyclisation, forming the 5 membered ring with a concomitant release of isobutylene (from the *tert*-butyl cation). Following this, the exomethylenelactone dienophile moiety would be created (**2.52**), following protodemetalation, and hopefully undergo the desired [4+2] Diels-Alder reaction to give **2.14** (Scheme 2.8, A)

Alas, **2.14** or any of its proposed pathway intermediates could not be isolated or observed by ¹H NMR, with the only product isolated being the enone **2.52**. This molecule is proposed to have undergone a *Meyer-Schuster* rearrangement, an acid-mediated (Lewis or Brønsted) formal 1,3 shift of the hydroxyl moiety (Scheme 2.8, B).²⁷ Mechanistically, the Au^I-bound alkyne **2.53** can favor the loss of the hydroxyl to give allenic cation **2.54** (Figure 2.8, B). This cation can then get trapped by a methanol molecule to form **2.55**, which after loss of a methane by another methanol molecule, afford an allenol, which can tautomerize to give enone **2.56** in 46% yield. In an effort to encourage this pathway, **2.49** was also exposed to protic acids (MsOH, TFA)²⁸, but this ended up only promoting decomposition of the starting material.



Scheme 2.8. (A) Desired reactive pathway and (B) Proposed mechanism for the observed Meyer-Schuster rearrangement.

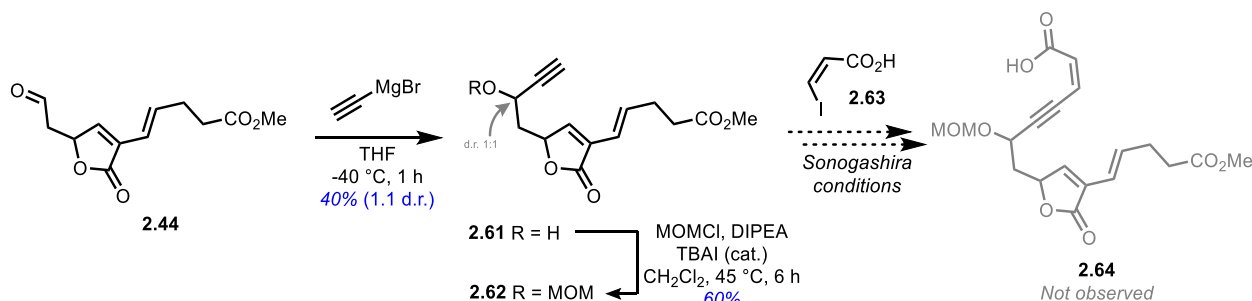
Alternatively, the Schuster-Meyer rearrangement can also be applied to propargylic acetates and pivalates to obtain the 1,3-rearranged allene esters (Scheme 2.9).^{29,30} In order to fully exploit the possibilities of this scaffold, propargylic alcohol **2.49** was transformed into its acetate (Ac₂O, Et₃N, DMAP (cat.), 90%) and pivalate (PivCl, DIPEA, DMAP (cat.), 41%) derivatives **2.57** and **2.58**. This reported rearrangement was thought to potentially afford allene ester **2.59**, which could undergo a [4+2] cycloaddition, as allenes are also known potent dienophiles in the Diels-Alder reactions.³¹ When **2.57** and **2.58** were exposed to the same conditions (10 mol% **2.50**, MeOH) neither **2.59** nor **2.60** could be isolated or observed by ¹H NMR.



Scheme 2.9. Failed Meyer-Schuster rearrangement of propargylic esters **2.57** and **2.58**.

2.7 – Model substrate synthesis – Fourth generation.

With a new understanding of this chemical scaffold, the fact that the C₈ of aldehyde **2.44** could be alkynylated was further taken advantage of. Instead of installing the carboxylic acid and alkyne in one fell swoop, the substrate would be modified sequentially. The Sonogashira Cross-coupling usually requires soft conditions that allow for a broad functional group tolerance. As a consequence, aldehyde **2.44** was exposed to ethynylmagnesium bromide, which afforded **2.61** as a 1:1 mixture of diastereoisomers in 40% yield (Scheme 2.10). As it was anticipated that the secondary alcohol could cause problems in the downstream transformations, it was protected as its methoxymethyl (MOM) ether **2.62** in 60% as an inseparable mixture of diastereoisomers. At this point, the carboxylic acid-bearing 3 carbon fragment could be installed directly without interference usually associated with its acidity.¹¹ However, the hybridization of the coupling partner would need to be adjusted, as sp-sp³ cross-couplings usually require an activated electrophile (allylic / benzylic halide).³² This problem was easily solved by engaging the terminal alkyne in a sp-sp² cross-coupling, which require softer conditions. As such, (*Z*)-3-iodoacrylic acid (**2.63**) was chosen as a coupling partner for this reaction in hopes of obtaining **2.64**, the desired cascade reaction precursor.



Scheme 2.10. Synthesis of propargylic MOM ether **2.62**.

2.7.1 – Construction of the tetracyclic core of (+)-havellockate through a spectacular reaction cascade.

Just as final preparations to affect this last sp-sp² cross-coupling were underway, more literature search yielded an interesting paper, which described the consecutive coupling of (*Z*)-3-iodoacrylic acid (**2.63**) to terminal alkynes and their subsequent cyclisation onto alkynes in a one-pot fashion.³³ This work described the transformation that was about to be attempted on dienyne **2.62**. This work described the exclusive formation of the 5-*exo-dig* cyclisation product versus the 6-*endo-dig*

product, which gave hope that no regioselectivity problems would arise. By slightly changing the reported protocol (Pd/C, PPh₃, CuI, Et₃N) to one where the active catalyst wasn't generated *in situ* (Pd(PPh₃)₄, CuI, Et₃N), diyne **2.62** and (*Z*)-3-iodoacrylic acid **2.63** were cross-coupled in the prescribed conditions at slightly lower temperature (55 °C, versus reported 80 °C). After a first attempt, the ¹H NMR data from this experiment looked very rough and over 3 different products could be observed by TLC analysis (Figure 2.2). In a project where clean transformations are expected and where less selective reactions are not desired, this crude mixture (*ran on 15 mg scale*) was almost discarded. But in the spirit of further understanding the reactive behavior of this molecule, these three products were purified by preparative TLC and fully characterized on a fateful late evening in May of 2022.

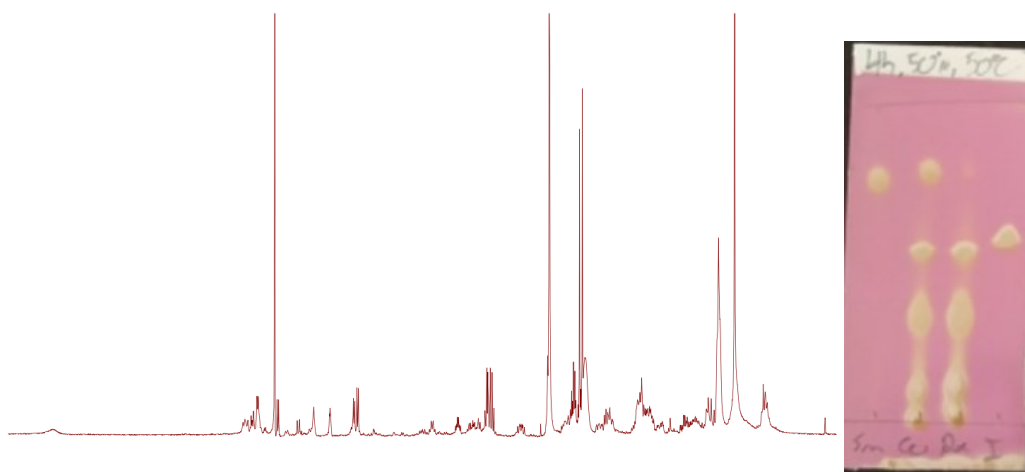
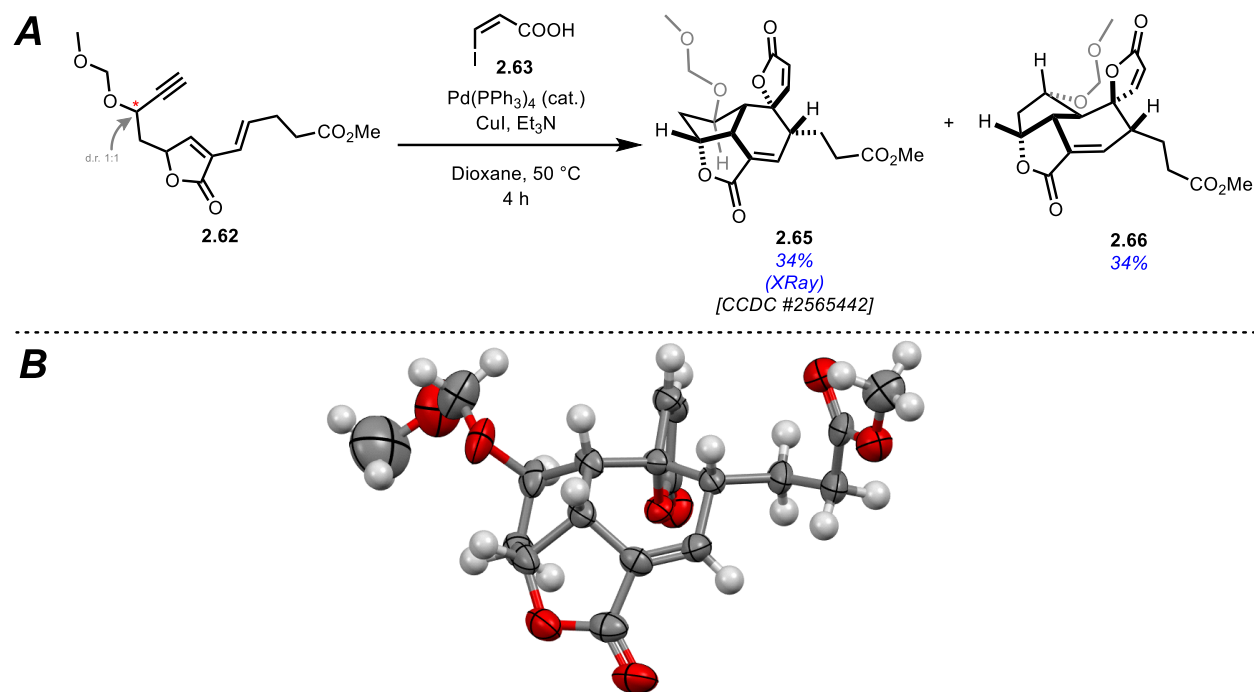


Figure 2.2. Crude ¹H NMR spectra and TLC data of the cross-coupling attempt between **2.62** and **2.63**.

After carefully isolating two compounds of interest, a full two-dimensional NMR analysis was completed on these two compounds and revealed not only that the cross-coupling and 5-*exo-dig* cyclisation happened, but this resulting exomethylenelactone intermediate successfully underwent the desired [4+2] Diels-Alder cycloaddition, all in one-pot fashion. As a result, the cycloadducts **2.65** and **2.66** were isolated in 34% yield each on 15 mg scale (Scheme 2.11, A). After this unexpected result, it was concluded that the stereochemical outcome of the Diels-Alder reaction (*endo* vs. *exo*) seemed to be solely guided by the stereocenter of the OMOM-bearing C₈, the β-**2.62** underwent an *exo* [4+2] and α-**2.62** underwent an *endo* [4+2] cycloaddition. Fortunately, leaving these purified samples in the freezer for multiple months afforded crystals of **2.65** which

were suitable for single crystal X-ray diffraction analysis. The results of this analysis enabled us to confirm the previous NMR analysis and confirm the structure of **2.65** (Scheme 2.11, B). The crystal structure of **2.65** was deposited at the Cambridge Crystallographic Data Centre (CCDC) with the deposition number #2565442.



Scheme 2.11. (A) Observed reaction cascade and (B) ORTEP diagram of **2.65** at 50% probability thermal ellipsoids.

While we were initially stunned by this result, the mechanism of this sequence of reactions was proposed (Scheme 2.12). First, the Sonogashira cross-coupling reaction between **2.62** and **2.63** was proposed. While palladium and copper are required for the cross-coupling, they can also both possibly act as π -Lewis acid activators of the alkyne towards electrophilic attack. While copper isn't known to be competent for this reaction, metals such as zinc³⁴, palladium³⁵, silver³⁶ and other agents such as iodine³⁷, acids³⁸ and bases³⁸ have been reported to affect the *5-exo-dig* and/or the *6-endo-dig* cyclisation in different ratios, depending on the reagent and the nature of the substrate. In all cases, no *6-endo-dig* products were observed, which is fortuitous as this was a proposed parasitic pathway in the initial synthesis design (**2.8**, Scheme 2.2). In presence of an excess of triethylamine, the deprotonated carboxylates α -**2.67** and β -**2.67** predominate the acid-base

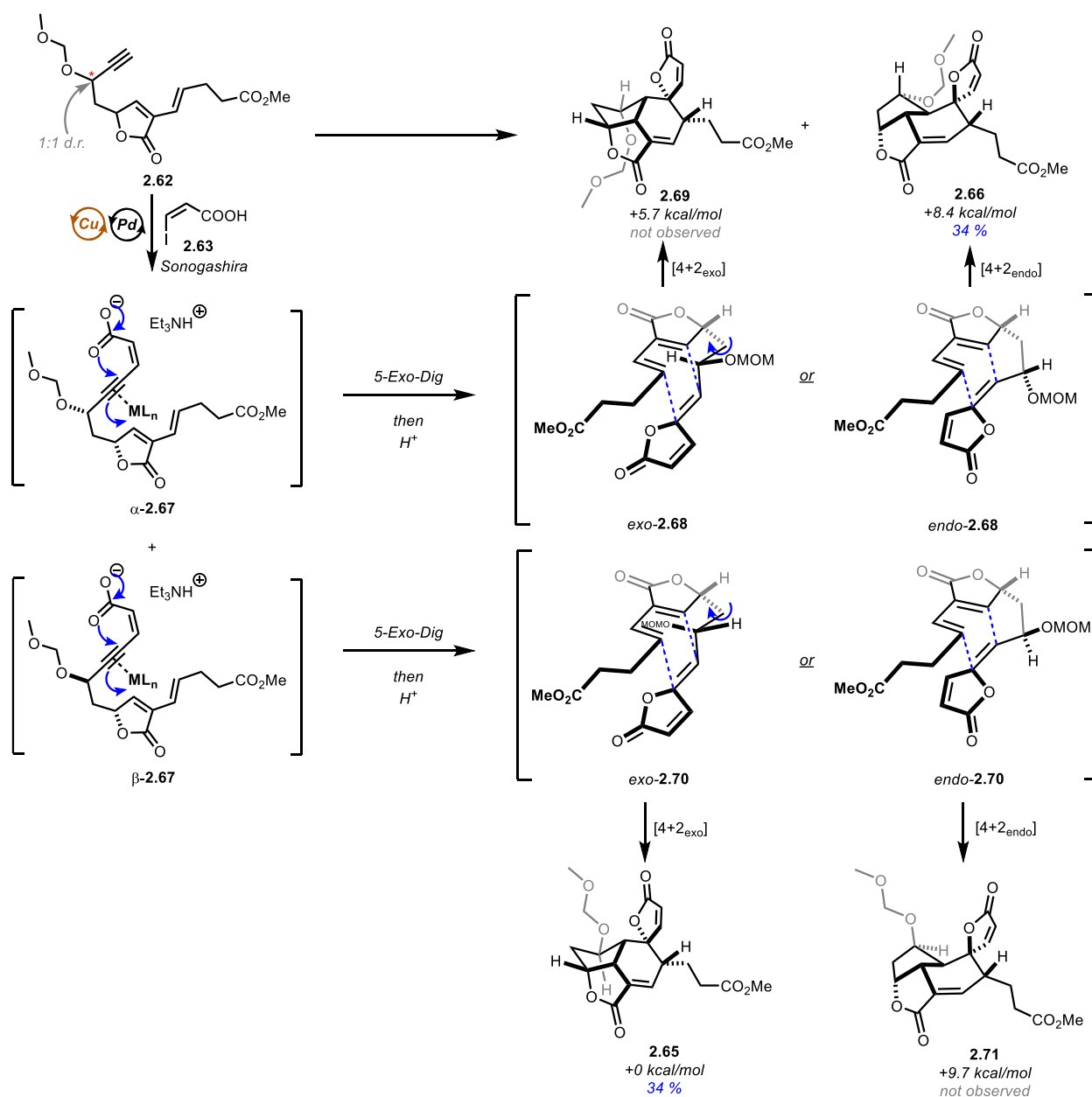
equilibrium, making them nucleophilic towards the activated alkyne and able to complete the desired *5-exo-dig* cyclisation.

To rationalize the stereochemical outcome of this reaction, DFT and a conformational analysis were performed. One of the diastereoisomer present, *syn* diol α -**2.67**, can undergo the proposed *5-exo-dig* & protodemetalation steps to give two transition states of its diene-dienophile pair **2.68**, namely *exo*-**2.68** and *endo*-**2.68**. The ground-state energies of both of the possible products of this reactions were calculated by DFT^b, and the values of +5.7 kcal/mol and +8.4 kcal/mol were found for both of these products, respectively. Theoretically, if the proportionating of these products was done under thermodynamic control, only *exo* adduct **2.69** would be observed, having a moderately lower ground state energy $\Delta\Delta G(\mathbf{2.69-2.66}) = \underline{-2.7 \text{ kcal/mol}}$. Experimentally, only **2.65** is observed, and thus, the stereochemical outcome of this reaction can be attributed to kinetic control, though transition state energies were not calculated for neither this system nor for the anti diol β -**2.67**. For the latter, the same possible outcomes were possible, affording two transition states of its diene-dienophile pair **2.70**, namely *exo*-**2.70** and *endo*-**2.70**. The conformer *exo*-**2.70** would lead to **2.65**, having a +0 kcal/mol ground state energy, while *endo*-**2.70** led to adduct **2.71**. In this case, a large discrepancy of ground-state energy $\Delta\Delta G(\mathbf{2.65-2.71}) = \underline{-9.7 \text{ kcal/mol}}$ is observed, favoring **2.65**, which is the sole diastereoisomer observed in the reaction, leading to the probationary conclusion that this reaction is under kinetic control, though more investigations would be required to confidently say so.

In both cases, the DFT analyses of the possible outcomes of engaging both diastereoisomers of **2.62** create a discrepancy : one is putatively under kinetic control, while one is under thermodynamic control. Since no control experiments were done to outright affirm or deny this proposition, one can still ponder how does this reaction behave. A thorough DFT analysis of the transition state of both of the reactions could provide valuable insights on the energy barriers to both diastereoisomers, while experiments could also lead to valuable insights in the mechanism of this transformation. This reaction control could be wielded depending on the desired outcome, and it is postulated that this reaction, when operated at this temperature, operates under kinetic control, a proposition that will become very useful in the synthesis of the core of the natural product

^bLevel of theory : B3LYP and basis set : 6-31G(d,p) in the gas phase.

(*vide infra*, chapter 3). Theoretically, a thermal isomerisation from **2.66** to **2.69** might be possible, but due to the lack of material at this stage, this reaction was not attempted.



Scheme 2.12. DFT-guided mechanism for the formation of **2.65** and **2.66**.

2.8. Conclusion.

As a sum, these efforts opened up a path towards the desired linear carboxylic acid **2.64**, which was found to be only transient, and conditions that further refined it into the fully build tetracyclic core of havellockate (**1.17**) in a spectacular fashion were identified. This reaction

cascade underwent three consecutive reactions one pot (Sonogashira, 5-*exo-dig*, Diels-Alder) in a stereospecific way, forging 3 carbocycles and 4 chiral centers of the natural product in a singular step. Furthermore, no 6-*endo-dig* cyclisation products were observed, and surprisingly, no Au^I catalyst was required. This platform will enable a strong entry into the enantioselective synthesis of (+)-havellockate (**1.17**).

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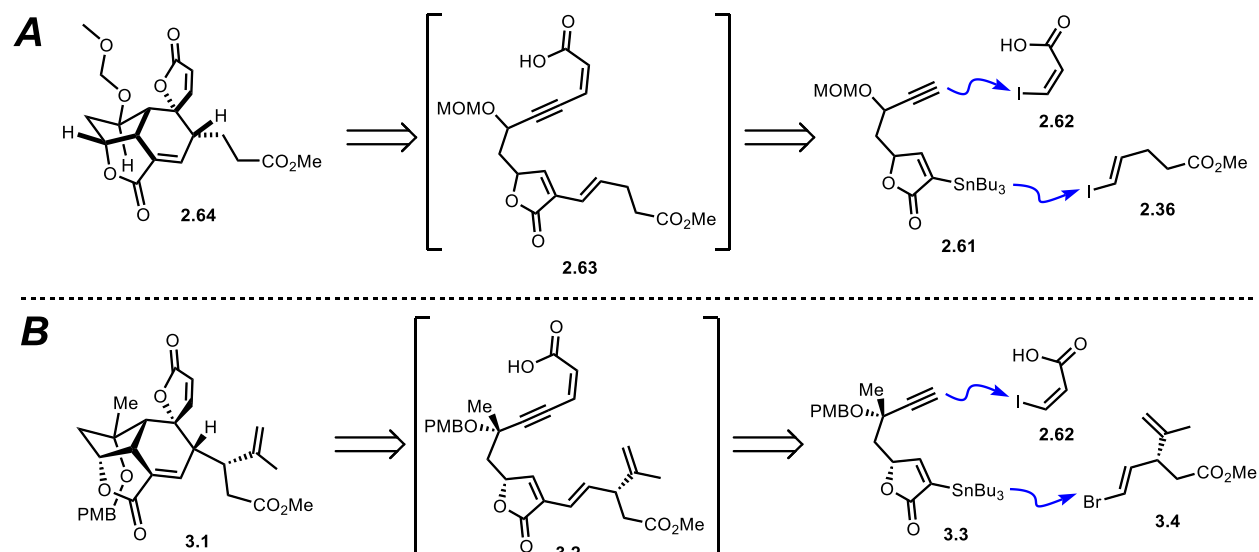
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CHAPTER 3

Enantioselective synthesis of the tetracyclic core of (+)-havellockate.

3.1 – Overview of the strategy.

As the reaction cascade was discovered in Chapter 2, we now endeavored to develop an enantioselective synthesis that would pave an access to the natural enantiomer of (+)-havellockate (**1.17**). The scalability of this synthesis was highly valued, with having set an objective of obtaining > 100 mg of the natural product (**1.17**) after completion of the synthesis. In that manner, the stereocenters would need to be installed at the positions where they were previously ablated in the model system (Scheme 2.3). In analogy on how the aforementioned reaction cascade leading to **2.64** was achieved from the intermediacy of **2.63** by using building blocks **2.61**, **2.36** and **2.62** (scheme 3.1, A), tetracycle **3.1** would be obtained from intermediate **3.2**, itself built from the building blocks **3.3**, **3.4** and **2.62** (scheme 3.2, B). It was known, from experiments seen in Chapter 2, that the stereocenter at C₈ controlled the outcome of the Diels-Alder reaction. Having a secondary OH at C₈, as seen in **2.64**, would require the stereoselective installation of the C₁₉ methyl at a later stage. Strategically, it was decided to install the tertiary α -OH center early, not knowing if it would lead to the *exo* or *endo* diastereoselectivity in the IEDDA reaction. This stereocenter would first be installed enantioselectively, guiding most of the other stereochemical outcomes of this synthesis at later stages. The protecting group (PG) strategy at C₈ would also play a critical role in this endeavor. The *p*-methoxybenzyl (PMB) was chosen, a freely rotating methylene similar to MOM, but could be selectively deprotected in mild oxidative conditions, versus to the MOM group's requirement for acidic or demethylating conditions (Scheme 3.1, B).¹



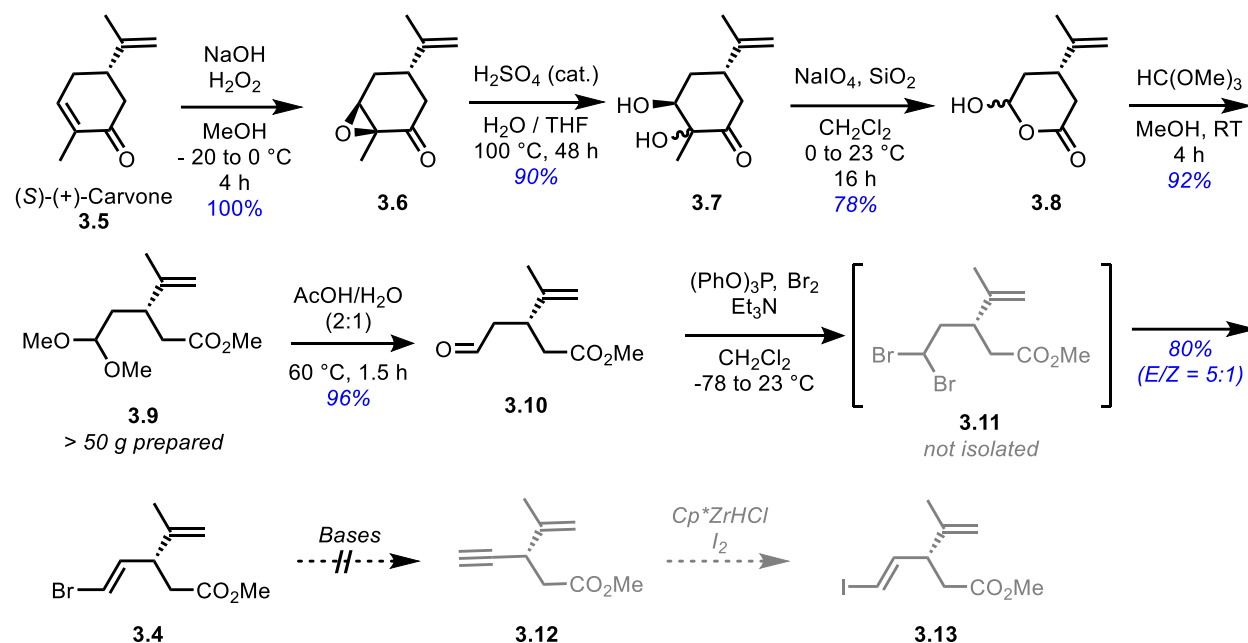
Scheme 3.1. (A) Retrosynthesis of **2.64**. (B) Retrosynthesis tetracyclic core of havellockate **3.1**.

3.2 – First generation synthesis and exploratory work towards the tetracyclic core of (+)-Havellockate.

3.2.1 – Synthesis of the vinyl halide coupling partner, (*first generation*) : vinyl bromide.

Initially, efforts were dedicated to access the enantiopure vinyl bromide **3.4**. It was thought that the stereochemical information of this fragment could be accessed based on a chiral pool-based approach. As such, (+)-carvone (**3.5**) was chosen for due to its availability and affordability (USD \$1.90 / gram)^a. While carvone has 7 carbon atoms on its methylcyclohexene mainframe, two of those would need to be deleted to forge the 5-carbon chain found in **3.4**. In 2004, Theodorakis *et al.* reported a synthesis of isocarvone from (+)-carvone **3.5** in a sequence of 8 steps, where we took interest in one of the intermediates (Scheme 3.2).² The sequence of reactions goes as follow : a Weitz-Scheffer epoxidation of (+)-carvone **3.5** afforded α,β -epoxyketone **3.6** in quantitative yield, which was hydrolyzed to diol **3.7** in 90% yield. This diol was oxidatively cleaved using sodium *meta*-periodate to afford a carboxylic acid-aldehyde (*not shown*), which acetalized *in situ* to the acylal **3.8** in 78%. This acylal was treated with trimethyl orthoacetate in methanol to afford dimethoxyacetal **3.9**. This acetal was obtained in a total of 4 steps in 64% overall yield in decagram scale and offered a great platform for the synthesis of vinyl bromide **3.4**. A literature search revealed that aldehydes could be transformed into geminal (*gem*) dibromides in a single step, which could then be eliminated with the base 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to selectively obtain the corresponding *E*-vinyl bromide.³ As such, the dimethoxyacetal was hydrolyzed to aldehyde **3.10** in 92% yield, and treated with the reported conditions (Br₂, triphenyl phosphite, Et₃N), only to directly afford the vinyl bromide **3.4** derivative directly from this reaction mixture. Surprisingly, it was not possible to observe or isolate the *gem*-dibromide **3.11** even when running the reaction at cryogenic temperatures, while the authors required hyperthermic conditions (DBU, DMF, reflux) to affect the elimination. Thus, without being able to control the elimination step, the observed *E/Z* ratio ranged between 5:1 and 2:1 depending on the scale, and on the largest scale ran (> 3 gram), **3.4** was obtained in 80% yield in a 5:1 *E/Z* ratio of inseparable geometrical isomers. Interestingly, vinyl bromide **3.4** resisted further elimination to the corresponding alkyne when treated with reported conditions using strong bases (*t*-BuOK, *t*-BuOK+18-C-6, LiHMDS).⁴ Being able to access alkyne **3.12** would offer a pathway to a selective synthesis of the *E*-vinyl halide **3.13**, *e.g.* through treatment with Schwartz reagent and molecular iodine (Scheme 2.6), but that proved impossible in this case. With a first successful, though not very optimal, synthesis of enantioenriched vinyl bromide **3.4**, efforts were then redirected towards the construction of the vinyl tin coupling partner **3.3**.

^a Toronto Chemical Industries, product code C0704.



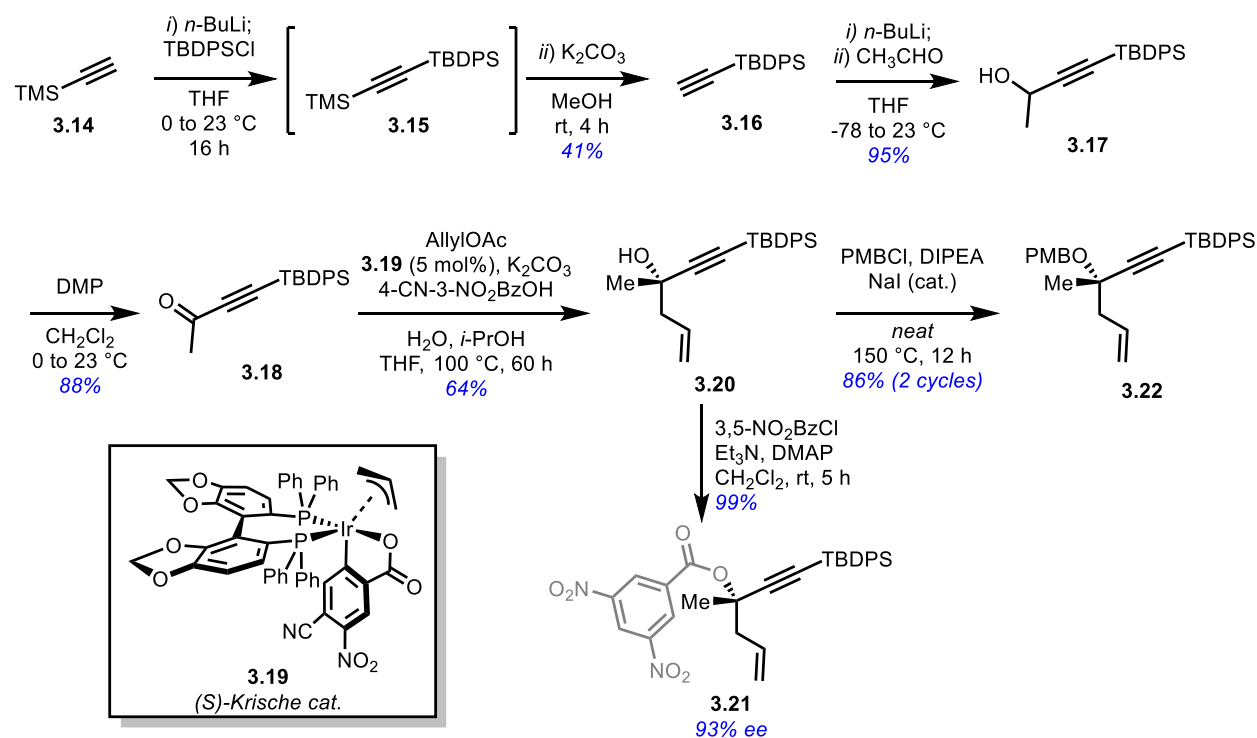
Scheme 3.2. Synthesis of vinyl bromide **3.4**.

3.2.2 – Synthesis of the vinyl tin coupling partner.

As the first coupling partner was synthesized, attention was shifted to the synthesis of the central vinyl tin fragment **3.3**. As it was learned during the synthesis of the model system in Chapter 2 of this thesis, the installation of the alkyne moiety proved troublesome at later stages. Thus, during this synthesis, the alkyne moiety would need to be introduced at an early stage, perhaps carried through the synthetic steps as a silicon-protected alkyne. Next to the alkyne moiety was the tertiary alcohol center that would guide the stereochemical outcome of the critical IEDDA reaction and thus, careful consideration on how to bring those two moieties together was taken. Krische *et al.* reported the enantioselective Ir-catalyzed allylation of acetylenic ketones to enantiopure allylic alcohols through transfer hydrogenation.⁵ Furthermore, the substrates required a bulky Si-based tri-*iso*-propylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups at the acetylenic position to inhibit poisoning of the Ir catalyst by the acetylenic C-H position. This work provided an excellent platform for the synthesis of **3.3**, with the malleable allyl moiety while carrying a Si-protected alkyne, which would be unveiled right before the critical cascade reaction.

Firstly, TMS acetylene (**3.14**) was treated with *n*-BuLi and TBDPSCl sequentially, to transiently afford bis-silylated alkyne **3.15**, after which the TMS group was selectively cleaved using slightly basic conditions in the same pot to afford **3.16** in 41% yield. This alkyne was further

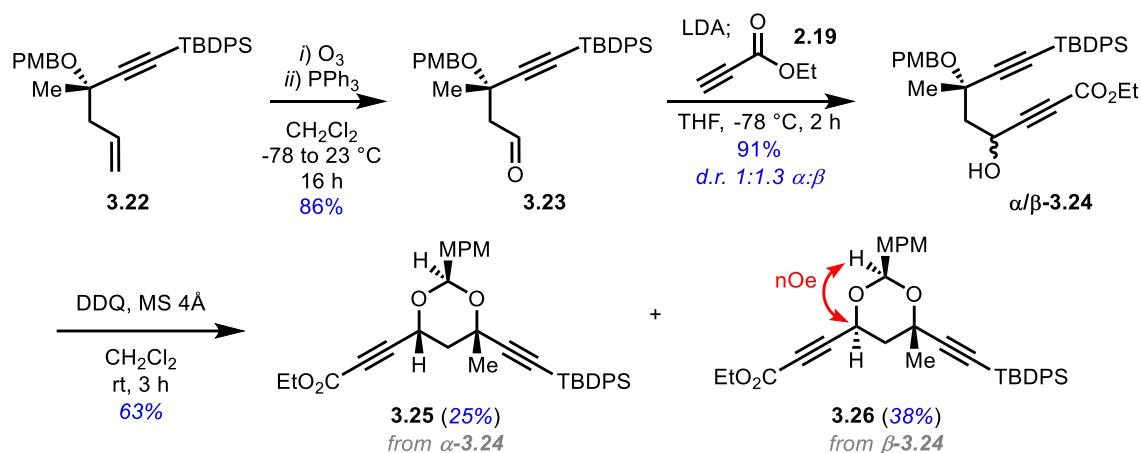
functionalized by treatment with *n*-BuLi and acetaldehyde to afford propargylic alcohol **3.17** in 95% yield, which was further oxidized to the propargylic ketone **3.18** in 88% yield with the use of DMP, whereas allylic MnO₂-mediated oxidation attempts failed to yield the ketone. After obtaining **3.18**, the substrate was subjected to the asymmetric allylation protocol reported by Krische, by first synthesizing the Ir catalyst **3.19** in house from (*S*)-SEGPHOS and [Ir(cod)Cl]₂, which is stable on silica gel and could be purified by SFC (scheme 3.3).⁶ The resulting propargylic alcohol **3.20** was obtained in 64% yield. The chemical derivatization of this alcohol to its 3,5-dinitrobenzoate derivative **3.21** (99%) using chiral column HPLC analysis revealed a 93% enantiomeric excess (*e.e.*) of **3.20**. The values for yield and *e.e.* for **3.20** were very similar to the reported (66 % yield, 94% *e.e.*) for this transformation and enabled further derivatization of this building block.⁵ Interestingly, the Ir catalyst **3.19** could be recovered from the reaction after SFC and was re-used in subsequent runs without loss of enantiopurity of the product. The resulting tertiary propargylic alcohol moiety was then protected as its PMB adduct in neat DIPEA to afford **3.22** in 86%.



Scheme 3.3. Enantioselective synthesis of tertiary alcohol **3.20**.

After the successful enantioselective construction the propargylic alcohol moiety, the allyl group was further functionalized to allow the introduction of another propargylic alcohol moiety, precursor group of the vinyl tin segment. As such, alkene **3.22** was treated with ozone and the

intermediate ozonide was reduced by triphenylphosphine to afford aldehyde **3.23** in 86%. To test the feasibility of the addition of an alkyne nucleophile to this aldehyde, the latter was treated with the lithium acetylide of **2.19** to afford the propargylic alcohols α/β -**3.24** in high yield (91%) but low diastereoselectivity (1:1.3), where the ratio was verified by ^1H NMR. Although alcohol diastereoisomers can usually be separated by SFC due to their more polar character, their separation by SFC on large-scale proved impossible. To obtain a pure sample of each, a preparative TLC had to be eluted 8 times to afford pure fractions. To confirm the identity of each of these propargylic alcohol diastereoisomers, the PMB group's capacity to be oxidized and trapped intramolecularly by the newly created alcohol was exploited (Scheme 3.4). As such, the mixture of α/β -**3.24** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of molecular sieves (MS 4Å) to afford the cyclic (4-methoxyphenyl)methyl (MPM) acetals in a representative 1:1.5 ratio of **3.25** (25%, from α -**3.24**) and **3.26** (38%, from β -**3.24**). These acetals could now be separated and fully characterized as their cyclized 6-membered ring derivatives with the help of nuclear Overhauser effect (nOe) and $^3J_{\text{HH}}$ couplings within the ring.

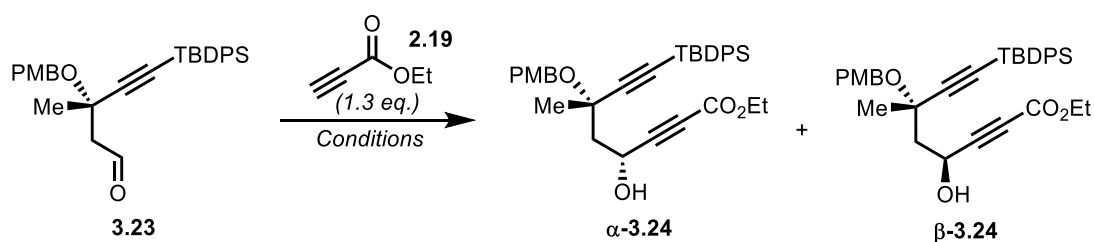


Scheme 3.4. Synthesis and derivatization of propargylic alcohols α -**3.24** and β -**3.24**.

A careful analysis of the acetals revealed that the major diastereoisomer of the alkynylation was β -**3.24**, and the minor diastereoisomer was the desired α -**3.24**. A short survey of the literature revealed that the alkynylation of 3-alkoxyaldehydes (this system) usually gave poor diastereoselectivity in most cases (avg. $\sim 2:1$ d.r.).⁷ In hope to obtain better stereoselectivity, a short optimisation of this addition of ethyl propiolate **2.19** to aldehyde **3.23** was carried out (Table 3.1). With the initial result of addition of the lithium acetylide (entry 1), the base was changed to

LiHMDS and multiple solvents competent for this reaction were screened based on an optimisation performed with a similar reaction.⁸ With hopes of changing the stereoselective outcome, multiple solvents were screened such as the less polar toluene to ether-based solvents (Et₂O, MBTE) with no immediate effect on the diastereomeric ratio (*d.r.*) (entry 2-4). Changing the base to LiHMDS in THF afforded an identical yield and *d.r.* (entry 5), but when hexamethylphosphoramide (HMPA) was added as an additive (entry 6), a reversal of the stereochemical outcome was observed, though minor and in lower conversion. After these unsatisfactory results, the use an external chiral source was explored to supplement these results. The majority of protocols describing the asymmetric addition of alkynes to aldehydes were mostly all done using electron-

Table 3.1. Alkynylation of aldehyde **3.23**.



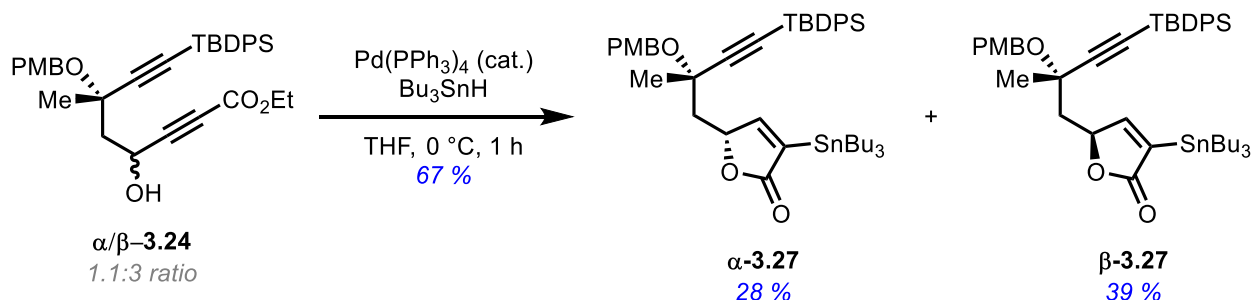
Entry ^a	Conditions	Additive	Conversion ^b	<i>d.r.</i> α - 3.24 : β - 3.24 ^b
1 ^c	LDA, THF, -78 °C, 1 h	-	89%	1 : 1.2
2 ^c	LiHMDS, toluene, - 78 °C, 1 h	-	93%	1 : 1.1
3 ^c	LiHMDS, Et ₂ O, -78 °C, 1 h	-	97%	1 : 1.5
4 ^c	LiHMDS, MTBE, -78 °C, 1 h	-	97%	1 : 1.2
5 ^c	LiHMDS, THF, -78 °C, 1 h	-	95%	1 : 1.2
6 ^c	LiHMDS, THF, -78 °C, 1 h	HMPA	61%	1.5 : 1
7	Me ₂ Zn, toluene, -20 °C, 48 h	(<i>S,S</i>)-Prophenol	0%	-
8	Et ₂ Zn, CH ₂ Cl ₂ , 23 °C, 24 h	(<i>S</i>)-Br ₂ -BINOL	0%	-
9	Et ₂ Zn, CH ₂ Cl ₂ , 23 °C, 24 h	(<i>S</i>)-BINOL	40%	2:1

^aRan on 0.1 mmol scale. ^bDetermined by ¹H NMR analysis of the reaction crude. ^c*rac*-**3.23** was used.

rich alkynes (R₃Si⁹, H¹⁰, Alk/Ar¹¹), but electron poor alkynes were less described. Despite this, some reports described the stereoselective addition of electron poor alkynes to aldehydes using BINOL^{12–17}, prolinol¹⁸, hydroxamide^{19,20} and prophenol²¹ chiral agents, making us confident that

a plausible diastereoselective construction of the C₁₀ stereocenter of this natural product was possible. As such, the three most promising asymmetric alkynylation methods were tested the intermediacy of chiral alkynyl zincates using (*S,S*)-Prophenol (entry 7), (*S*)-Br₂-BINOL (entry 8), which yielded no desired product. Interestingly, in entry 9, the use of (*S*)-BINOL gave only 40% conversion after 24 hours, and a meager 2:1 diastereomeric ratio of **α-3.24** to **β-3.24**, which was not efficient enough to pursue further.

Following these disappointing results, it was decided that this inseparable mixture of diastereoisomers would be carried into the next step in hope of being able to separate them at a later stage (Scheme 5). Moving on, the mixture of propargylic alcohols **α/β-3.24** was engaged in the previously developed hydrostannylation & lactonisation reaction, which cleanly delivered the vinyl tins **α-3.27** (28%) and **β-3.27** (39%) after a thorough solvent system screening and lengthy SFC separation (Scheme 3.5).



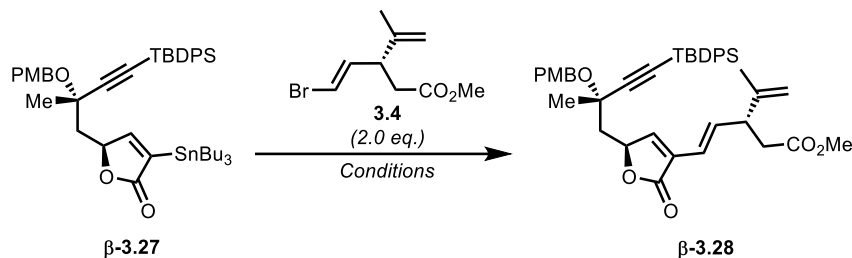
Scheme 3.5. Synthesis of vinyl tins **α-3.27** and **β-3.27**.

3.2.3 – Cross-coupling between vinyl bromide **3.4** and vinyl tin **β-3.27**.

As more material was available, and to test-run the following steps on this substrate that could not be used in the synthesis, **β-3.27** was first engaged into the Stille cross-coupling reaction with vinyl bromide **3.4** (table 3.2) in a round of optimisation. First, conditions similar to the reported conditions by Lebel and Parmentier were tested.^{22,23} Variation of the CuI loading with 5% mol. Pd (entry 1-3) afforded up to 25% yield only. Bringing the Pd loading up to 20% (entry 4) and changing the solvent for THF (entry 5) did not increase the yields, neither did employing the use of CsF (entry 6) to accelerate the turnover of the catalyst.²⁴ Employing monometallic²⁵ systems with either only Pd or the Cu metals (entries 7-8) resulted in no product formation even at higher temperatures. Thinking that the vinyl tin **β-3.27** was being decomposed or consumed in side

reactions^b too quickly for it to be cross coupled to **3.4**, attempt to slowly inject it over 30 minutes (entry 9) in the reaction mixture and observed a slight bump in yield (37%). The change to a different solvent system (DMSO/THF) with a different catalyst system ((Pd₂(dba)₃, CuTC) and use of LiCl as an additive²⁴ and addition of the trifurylphosphine (TFP)²⁶ ligand (entries 10-13) yielded minute amounts of desired product **β-3.28**.

Table 3.2. Optimisation of the Stille cross-coupling between **3.4** and **β-3.27**.



Entry ^a	Catalyst	Cocatalyst	Additive/Note	Conditions	Yield β-3.28 ^b
1	Pd(PPh ₃) ₄ (5mol%)	CuI (10 mol%)	-	DMF, RT	19 %
2	Pd(PPh ₃) ₄ (5mol%)	CuI (50 mol%)	-	DMF, RT	20 %
3	Pd(PPh ₃) ₄ (5mol%)	CuI (150 mol%)	-	DMF, RT	25 %
4	Pd(PPh ₃) ₄ (20mol%)	CuI (150 mol%)	-	DMF, RT	< 5 %
5	Pd(PPh ₃) ₄ (5mol%)	CuI (20 mol%)	-	THF, RT	< 5 %
6	Pd(PPh ₃) ₄ (5mol%)	CuI (20 mol%)	CsF (300 mol%)	THF, RT	0 %
7	Pd(PPh ₃) ₄ (5mol%)	-	-	Toluene, 90 °C	0 %
8	-	CuCl (200 mol%)	-	THF, RT	0 %
9^c	Pd(PPh₃)₄ (1mol%)	CuI (150 mol%)	-	DMF, RT	37 %
10	Pd(PPh ₃) ₄ (20mol%)	CuCl (1000 mol%)	LiCl (1200 mol%)	DMSO/THF ^d , 60 °C	< 5 %
11	Pd ₂ (dba) ₃ (20mol%)	CuI (150 mol%)	TFP (80 mol%) ^e	DMSO/THF ^d , RT	0 %
12	Pd ₂ (dba) ₃ (20mol%)	CuTC (1000 mol%)	TFP (80 mol%) ^e	DMSO/THF ^d , 60 °C	0 %
13	Pd ₂ (dba) ₃ (20mol%)	CuTC (1000 mol%)	TFP (80 mol%) ^e	DMSO/THF ^d , 60 °C	0 %

^aAll reactions ran on 0.03 mmol scale for 16 hours. ^bDetermined by ¹H NMR analysis of the reaction crude using mesitylene as an internal standard. ^c**β-3.27** added slowly over 30 minutes. ^dDMSO/THF (1:1). ^eTFP : trifurylphosphine.

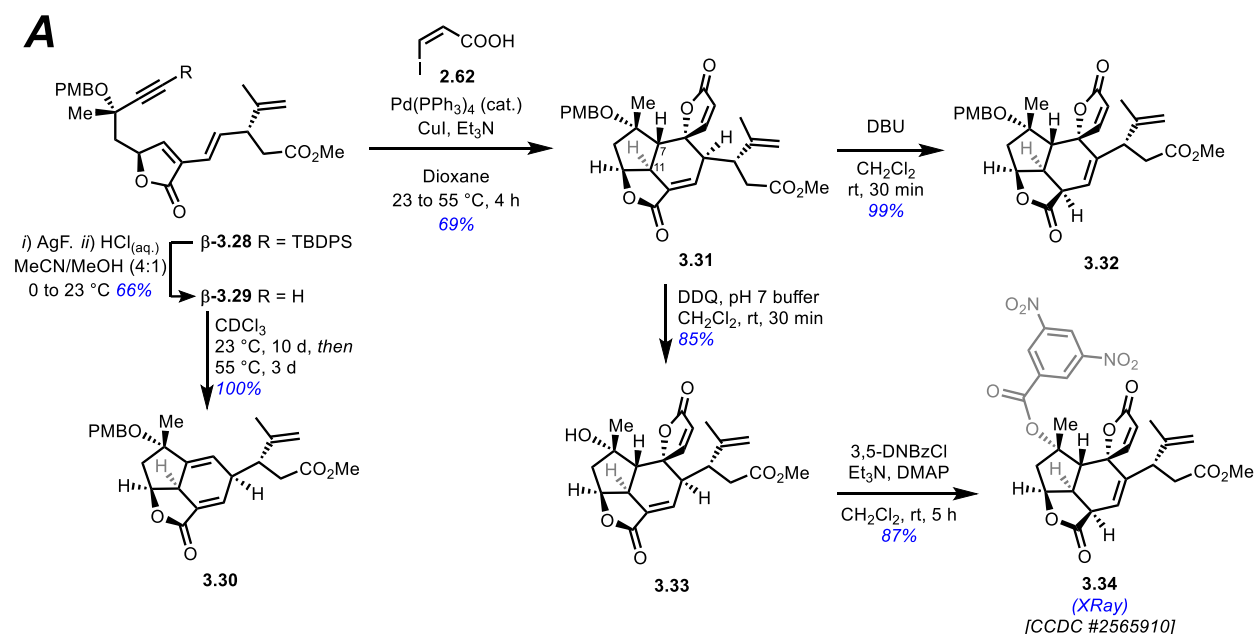
^b Homodimerisation (*vide infra*).

3.2.4 – Successful cascade reaction with β diastereoisomer – *endo* adduct.

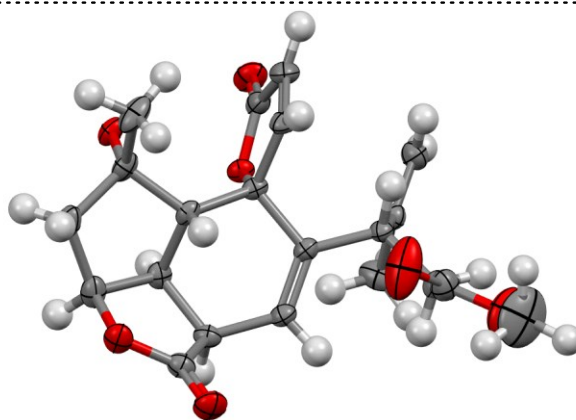
In the light of these results, it was decided to continue to explore the route with a subpar yield for this cross-coupling (36%), knowing this reaction could be optimized at a later time if need be. With now having diene β -3.28 in hand, the TBDPS protecting group needed to be removed to expose the reactive site of the substrate for the desired Sonogashira cross-coupling reaction (Scheme 3.6, A). It was reported in the literature that the butenolide moiety of this substrate was known to be sensitive to TBAF^{22,23}, so other desilylation protocols would be required. A method employing silver(I) fluoride as desilylating agent, which is selective towards alkyne-bound silyl groups (*via* Ag^I Lewis acid activation of the π bond) and inert towards C(sp³)-Si or O-Si bonds was known, and fit perfectly for this methodology.²⁷ As such, β -3.28 was treated with AgF in acetonitrile and methanol, then the intermediate Ag^I acetylide was reprotonated using HCl_(aq.) to afford dienyn β -3.29 in 66% yield. By looking at its structure, an early Diels-Alder reaction was expected to be possible between the diene and alkyne groups of this structure, and this phenomenon was readily observed, noting that dienyn β -3.29 underwent 20 % conversion towards cycloadduct 3.30 in under 48 hours in an NMR tube (CDCl₃). After 10 days in the tube, about 50% conversion to 3.30 was observed. To fully convert β -3.29, the NMR tube was heated in a water bath to 55 °C for 72 hours to fully convert the dienyn and give 3.30 in quantitative yield. This intrinsic early intramolecular reactivity was certainly worrisome, as it meant that the transient alkyne was sensitive at room temperature and would need to be entered in the cascade reaction very quickly after it was synthesized.

When a freshly synthesized sample of β -3.29 was submitted to the cascade reaction conditions developed in section 2.6, we were ecstatic to observe that the same sequence of reactions (Sonogashira, 5-*exo*-dig and Diels-Alder) smoothly delivered tetracycle 3.31 in 69%, now as a single diastereoisomer. As the *wrong* diastereoisomer at C₁₀ (from β -3.24) was being used, it was observed that the sole diastereoisomer observed in this reaction was *endo* (*trans* junction at C₇-C₁₁, ³J_{HH} = 12.0 Hz) and with a little bit of luck, this undesired stereochemical outcome would be different when this sequence would be repeated using α -3.24. After obtaining this interesting result, attempts at the planned late-stage transformation were performed. The planned deconjugation reaction was probed first, which was very well described in the literature for this [3,0,4] bicyclic lactone system using DBU^{28–32}, KHMDS³³, LiHMDS³⁴, LDA³⁵,

dimethylamine³⁶ or NaOMe³⁷. First, **3.31** was treated with DBU in CH₂Cl₂, as it seemed the most competent base for this reaction, and pleasantly delivered the deconjugated product **3.32** in an almost quantitative yield after only 30 minutes at room temperature. This positive result led us



B



Scheme 3.6. (A) Synthesis and derivation of **3.31** and (B) ORTEP diagram of **3.34** at 50% probability thermal ellipsoids.^c

to believe that the deconjugation for the desired *exo* adduct would also be trivial, though that would not be the case. With this favorable result, the core structure of **3.31** was confirmed by crystallography. Multiple attempts at recrystallization of **3.31** failed, and as such, chemical derivation was used, knowing that nitrobenzoate esters can aid at crystallization.³⁸ The initial

^c Dinitrobenzoate ester has been omitted for clarity.

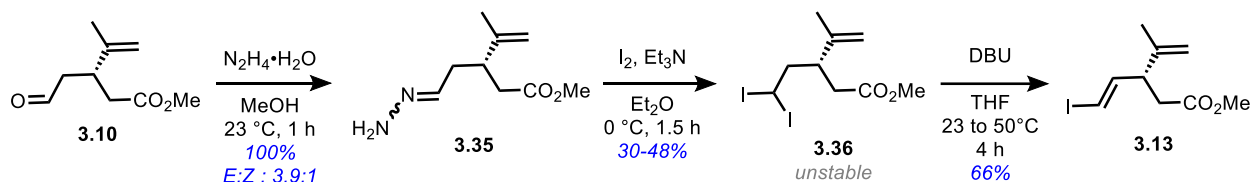
hypothesis that the PMB group could be selectively deprotected at a later stage (section 3.1) was proven by treating **3.31** with DDQ in buffered (pH=7) conditions to cleanly afford tertiary alcohol **3.33** in 85%. This tertiary alcohol was also not crystalline, and so the chemical derivatization was continued by treatment of the latter with 3,5-dinitrobenzoyl chloride (3,5-DNBzCl), triethylamine and 4-dimethylaminopyridine (DMAP) to afford the dinitrobenzoate ester **3.34**, obtained with a concomitant alkene isomerisation (*presumably by action of DMAP as the base*) in 87% yield. A controlled crystal growth by slow evaporation afforded crystals suitable for SCXRD and a crystal structure was found, confirming its structure (Scheme 3.6, B). This crystal structure was available by uploading the data to the CCDC with the deposition number #2565910. With these satisfactory results, the application of the same sequence of reactions with **α -3.24** was undertaken to stereoselectively build the tetracyclic core of (+)-havellockate (**1.17**) in a similar manner, with hopes that the outcome of the [4+2] reaction would favor the *exo* adduct.

3.3 – Optimised synthesis of diene **α -3.29** and its use in the cascade reaction.

3.3.1 – Synthesis of the vinyl halide coupling partner (*second generation*) : vinyl iodide.

As efforts were spent trying to find a synthetic pathway towards the tetracyclic core of (+)-havellockate, an optimisation of the aforementioned chemistry was due. First, the chemistry of the cross-coupling between vinyl tin **3.27** and vinyl bromide **3.4** had to be optimized. A standard rationale in Stille cross-couplings is that vinyl bromides are less reactive than vinyl iodides since the C-I bond is weaker ($\Delta G=58$ kcal / mol) than the C-Br bond ($\Delta G=72$ kcal / mol). Having a C-I bond in this catalytic cycle would kinetically favor the oxidative addition step and turn over the catalytic cycle more efficiently.³⁹ As observed in the model cross-coupling between **2.33** and **2.36** (Scheme 2.6), the yields are much higher and thus, the synthesis of vinyl iodide **3.13** was undertaken (Scheme 3.7). From aldehydes, vinyl iodides are usually synthesized either through Stork-Zhao⁴⁰ or Takai⁴¹ olefination protocols to obtain a homologated product. But since aldehyde **3.10**'s full synthetic potential needed to be exploited due to its easy to access in large quantities, homologative protocols were dismissed. In 1962, Barton and colleagues reported the transformation of hydrazones towards *gem*-iodoalkanes in good yields.^{42,43} Knowing this, aldehyde **3.10** (5 steps and 63% overall yield from (+)-carvone **3.5**) was treated with hydrazine hydrate to afford hydrazone **3.35** in quantitative yield in an inconsequential *E/Z* ratio of 3.9:1. This hydrazone was then treated with the reagents in absence of light to afford the *gem*-diiodo ester **3.36**, which

was very unstable due to its sensitivity to light, in yields typically ranging between 30 and 48% yield depending on the scale. After a short work-up and silica plug, **3.36** was treated with DBU to afford vinyl iodide **3.13** in 66% and the sole *E* geometrical isomer, which relinquished its instability after the elimination reaction and could be stored safely over long periods of time.



Scheme 3.7. Synthesis of vinyl iodide **3.13**.

3.3.2 – Optimisation of the synthesis of the vinyl tin coupling partner.

With a newly developed eight step sequence to make vinyl iodide **3.13** from (+)-carvone, the optimisation of the synthesis of allylic alcohol **3.24**, to favor the desired a diastereoisomer α -**3.24**, became the main focus. After failing to construct this critical chiral center through alkynylation, attempts at saving this route by obtaining α -**3.24** through reduction of the corresponding ketone were attempted (Table 3.3). To this effect, the quasi equimolar, inseparable diastereomeric mixture of α/β -**3.24** was oxidized using DMP in CH_2Cl_2 and afforded ketone **3.37** in 91% yield. Ketone **3.37** was then engaged in known propargylic ketone reductions to hopefully afford α -**3.24** as the principal diastereoisomer. The initial idea was to engage **3.37** with another reagent bearing chiral information, which usually can deliver the propargylic alcohol in very high stereoselectivity (> 20:1 *d.r.*). This chiral hydride delivery to propargylic ketones has been pioneered by Noyori *et al.*, who developed multiple systems capable of this transformations. As such, **3.37** was treated with (*R*)-BINOL/ LiAlH_4 ⁴⁴ (Entry 1) and using Ru^{II} -catalyzed asymmetric hydrogen transfer (Entry 2-4)⁴⁵ but to no productive means, effectively only succeeding at completing conjugate hydride reduction to afford enone products (not shown). The ketone **3.37** was then subjected to standard Luche⁴⁶ reduction conditions, hoping the substrate would guide the delivery of the external hydride through complexation with the PMB moiety (much akin to a Narasaka-Prasad reduction).^{47,48} Delightfully, using these conditions, α -**3.24** was delivered as the major diastereoisomer in a 2.8:1 ratio and quantitative yield (entry 5). Lowering the temperature (down to -100 °C, entry 6-7) did not improve the yield or selectivity. A thorough screen of all the lanthanide hydrates that were available in the laboratory (entries 8-14) determined that the best

results were obtained when **3.37** was used in conjunction with $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ in methanol, which gave a quantitative yield on 0.03 mmol scale in 3.0:1 *d.r.* (entry 8) and quantitative yields and 2.8:1 *d.r.* at 5 and 15 mmol scales respectively (entries 13-14). With this success, other achiral reductants known to reduce propargylic ketones were explored (entries 15-20), but with no improvement.

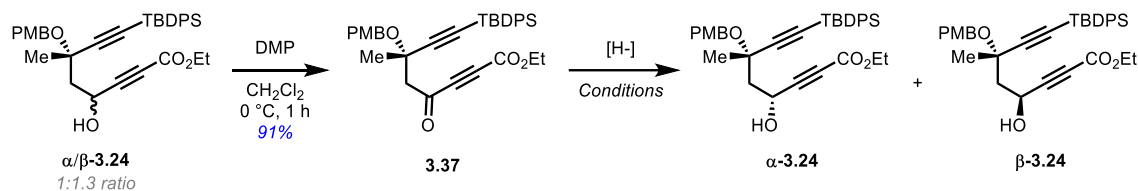


Table 3.3. Optimisation of the reduction of ketone **3.37**.

Entry ^a	Reductant	Temp. (°C)	Conv. (%) ^b	Yield (%) ^b	<i>d.r.</i> α : β 3.24 ^b
1	(R)-BINOL, LiAlH_4 , THF	-78	10	0	-
2 ^d	(R,R)-TsDPEN RuCl, <i>i</i> PrOH	23 to 60	100	0	-
3	$\text{RuCl}[(\text{R,R})\text{-TsDPEN}](\text{mesitylene})$, $\text{Et}_3\text{N}/\text{HCOOH}$	-78 to 0	100	0	-
4 ^d	$\text{RuCl}[(\text{R,R})\text{-TsDPEN}](\text{mesitylene})$, <i>i</i> -PrOH	0 to 60	100	0	-
5 ^c	NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-78	100	100	2.8 : 1
6 ^c	NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-90	100	100	2.7 : 1
7 ^c	NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-100	57	55	1.4 : 1
8 ^c	NaBH_4 , $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-78	100	100	3.0 : 1
9 ^c	NaBH_4 , $\text{SmCl}_3 \cdot 6\text{H}_2\text{O}$, MeOH	-78	100	100	1.9 : 1
10 ^c	NaBH_4 , $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$, MeOH	-78	100	100	1.9 : 1
11 ^c	NaBH_4 , $\text{YbCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-78	100	100	1.7 : 1
12 ^c	NaBH_4 , $\text{YCl}_3 \cdot 6\text{H}_2\text{O}$, MeOH	-78	100	100	1.9 : 1
13 ^c	NaBH_4 , $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-78	100	100	2.8 : 1
14^f	NaBH_4, $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH	-78	100	100	2.8 : 1
15 ^d	$\text{LiAlH}(\text{OtBu})_3$, THF	0	100	39	2.2 : 1
16	LiBHEt_3 , THF	-78	100	99	2.1 : 1
17	LiBHEt_3 , CH_2Cl_2	-78	100	100	1.5 : 1
18	$\text{LiBH}(\text{s-Bu})_3$ (<i>L-Selectride</i>), THF	-78	100	82	1 : 1
19 ^d	(<i>R</i>)-Alpine Borane, THF	23	100	0	-
20	(<i>R</i>)-CBS, $\text{BH}_3 \cdot \text{THF}$, THF	-78 to 0	0	-	-

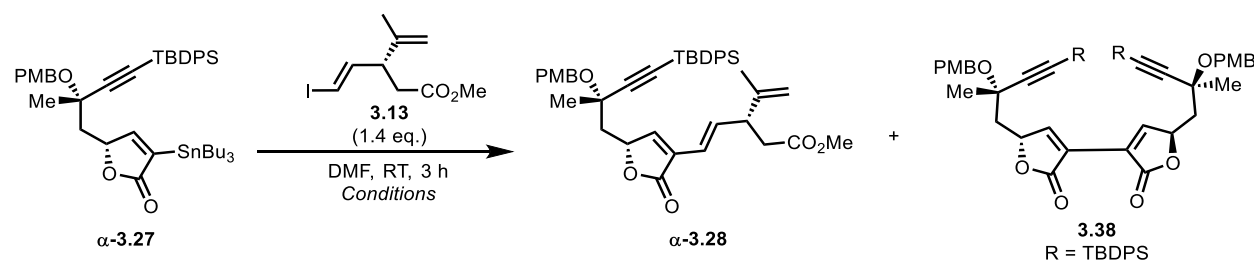
^aRan on 0.03 mmol scale. ^bDetermined using mesitylene as an internal standard. ^cUsed *rac*-**3.37** as substrate. ^dConjugate addition products detected. ^e5mmol scale. ^f15 mmol scale.

3.3.3 – Cross-coupling of vinyl iodide **3.13** and vinyl tin α -**3.27**.

Now in possession of a synthetic route of the more reactive vinyl iodide **3.13** and an enhanced pathway to α -**3.24**, the latter was transformed to its vinyl tin α -**3.27** and a small optimisation round was completed in order to obtain diene α -**3.28** in the most effective way

possible. To optimize the overall efficiency of this reaction, the loading of **3.13** was lowered from 2.0 to 1.4 equivalents (Table 3.4). Importantly, reducing the equivalents of **3.13** had the effect of saving the precious vinyl halide, but rendered the effective concentration of **α -3.27** higher *in situ*, and as a result, non-negligible amounts of homodimerization product **3.38** were observed during the cross-coupling attempts. The first attempt consisted of using identical conditions as seen during in model synthesis (Scheme 2.6), and netted **α -3.28** in 67% yield, which was already a great improvement over the use of vinyl bromide **3.4** as the electrophile. Attempts to reduce the amount of produced homodimer **3.38** by lowering Pd loading (entry 2), slow addition of **α -3.27** to the reaction mixture (entry 3) or late addition of CuI (entry 4) failed to lower the amount of **3.38** produced. A complete removal of either Pd or Cu (entries 5-6) yielded no product, highlighting the

Table 3.4. Optimisation of the Stille cross-coupling between **α -3.27** and **3.13**.



Entry ^a	Catalyst	Cocatalyst	Additive/Note	Yield α-3.28 ^b	Yield 3.38 ^b
1	Pd(PPh ₃) ₄ (5 mol%)	CuI (140 mol%)	-	67 %	12 %
2	Pd(PPh ₃) ₄ (1 mol%)	CuI (140 mol%)	-	49 %	9%
3	Pd(PPh ₃) ₄ (5 mol%)	CuI (140 mol%)	α-3.27 added slowly over 30 min	57 %	9 %
4	Pd(PPh ₃) ₄ (5 mol%)	CuI (50 mol%)	Stir 2 h, then add CuI	22 %	22 %
5	Pd(PPh ₃) ₄ (5 mol%)	-	-	0 %	0 %
6	-	CuI (200 mol%)	-	0 %	0 %
7	Pd(PPh ₃) ₄ (10 mol%)	CuI (140 mol%)	-	48 %	14 %
8 ^c	Pd(PPh ₃) ₄ (5 mol%)	CuI (140 mol%)	-	77 %	13 %
9 ^d	Pd(PPh ₃) ₄ (5 mol%)	CuI (140 mol%)	DMF degassed by freeze-pump-thaw (3x 5min cycles)	77%	12 %
10 ^e	Pd(PPh ₃) ₄ (5 mol%)	CuI (140 mol%)	DMF degassed by Ar(g) sparging (30 min)	83%	9 %

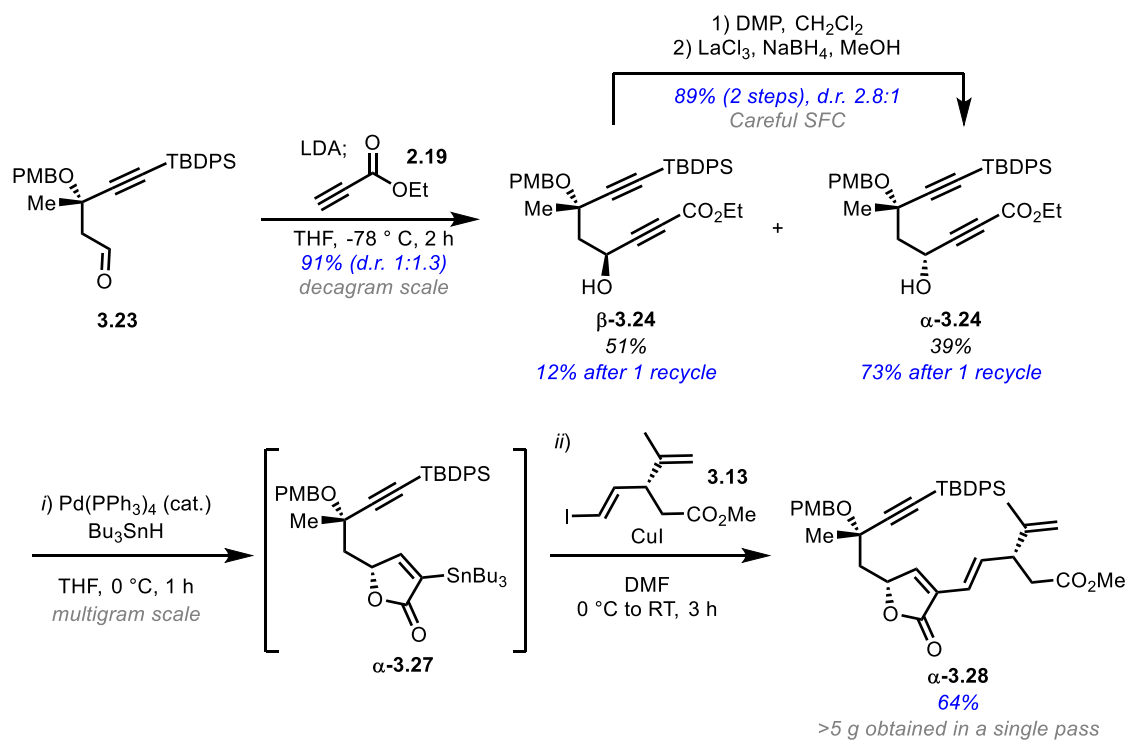
^aAll reactions ran on 0.03 mmol scale. ^bDetermined by ¹H NMR analysis of the reaction crude using TMS benzene as an internal standard. ^c0.3 mmol scale. ^d3 mmol scale, isolated yield. ^e8 mmol scale, isolated yield.

dependence of both metals for this reaction.^{25,39} A higher Pd loading also did not improve the amount of ***α*-3.28** produced over **3.38** (entry 7). Continuing with the original conditions of entry 1, the yield was slightly improved when the reaction was scaled 10x (0.3 mmol vs 0.03 mmol, entry 8). This effect was heightened when it was scaled 100x (3 mmol, entry 9), with a yield identical to the previous entry. It was proposed that **3.38** was the result of an oxidative dimerization of the intermediate vinyl cuprate (from transmetallation of vinyl tin ***α*-3.27**)²⁵ and as such, the reaction solvent *N,N*-dimethylformamide (DMF) was thoroughly degassed using freeze-pump-thaw (FPT) method and canulations (entry 9), with no positive effect on the amount of **3.38** produced. In other attempts, FPT degassing led to even worse ratios, up to 3:1 (*not shown*) and as such, the solvent was sparged with Ar_(g) to displace the solubilized O_{2(g)} in the solvent, which led to a slight improvement in yield of ***α*-3.28** (83%, entry 10) on multigram scale.

With this success in hand, the long-lasting challenge of separating the diastereoisomers of **3.24** by SFC was revisited, and after a more thorough screening of 60 different solvent systems, a combination of solvents that was able to separate the latter by SFC was finally identified. With a newfound ability to separate the propargylic alcohol diastereoisomers upon alkynylation, it would be possible to recycle the undesired stereoisomer ***β*-3.24**, as the reduction of ketone **3.27** was favorable towards ***α*-3.27**. The separation of these diastereoisomers, however, was very difficult and labor intensive on scale, but the outcome was worth the effort. Thus, when the alkynylation of aldehyde **3.23** was ran on decagram scale (20 mmol), ***α*-3.24** (39%) and ***β*-3.24** (51%) could be isolated (Scheme 3.8). The latter was then re-oxidized to **3.37** and reduced back using the best conditions (table 3.3, entry 14) to afford ***α*-3.24** as the major diastereoisomer. As a sum, the recycling of ***β*-3.24** netted another 34% of the precious ***α*-3.14** (from aldehyde **3.23**), and 12% of ***β*-3.24**. If desired, the yield of ***α*-3.24** could be theoretically brought in the 80's if a second recycling of this 12% left of ***β*-3.24** was completed.

With a now very robust access to propargylic alcohol ***α*-3.24** (and thus diene ***α*-3.28**), the one-pot, hydrostannylation / Stille cross-coupling was revisited (Scheme 2.4).^{23,49} As such, the hydrostannylation of ***α*-3.24** was completed using standard conditions (Scheme 3.5), and after 1 hour, the cross-coupling partner **3.13** in DMF and CuI were added to the reaction mixture. This reaction was found to be solvent-sensitive : it required the initial hydrostannylation in THF then addition of DMF to work effectively. As a sum, diene ***α*-3.28** was obtained in 64% on multigram

scale (5.7 g), along with 9% of **3.38**, from **α -3.24** (7.5 g, 13 mmol), considerably increasing the substrate's complexity in a single pot.

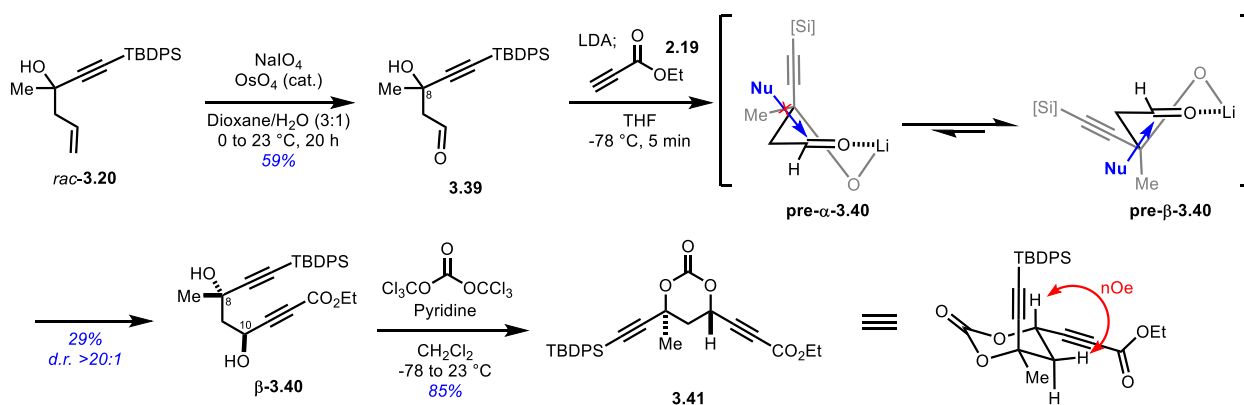


Scheme 3.8. Optimized synthesis of diene **α -3.28**.

3.3.4 – A protecting group-free strategy.

After having secured a highly efficient route toward diene **α -3.28**, efforts to improve the overall efficiency of this synthesis were spent by investing time towards a strategy that would require no protecting group manipulations. Protecting group manipulations impart two additional steps which hinders efficiency, and doing so strays a synthetic methodology away from an ideal synthesis.^{50,51} In an effort to be as efficient as possible, a synthetic route that did not include the PMB protecting group was explored (Scheme 3.9), with much of this exploratory work has been completed in a racemic way, as *rac*-**3.20** was accessible more rapidly and used cheaper reagents (AllylMgBr, 1 h vs Ir catalyst, 60 h). First, the ozonolysis of *rac*-**3.20** was attempted in hope to obtain β -hydroxyaldehyde **3.39**, but failed, as no product could be observed. This challenge was overcome by performing a Lemieux-Johnson oxidation, which yielded **3.39** in 59% yield. Then, the treatment with lithium acetylide of ethyl propiolate **2.19** in THF yielded diol **β -3.40** in 29% yield, obtained after a short round of optimisation of the reaction (not discussed). Interestingly, this diol was obtained as a single diastereoisomer, versus a *quasi* 1:1 ratio when the 3° OH at C₈

was protected with the PMB. This result can be rationalized by a now much stronger ionic interaction between the C₈ lithium alkoxide and the aldehyde oxygen after initial deprotonation of the first equivalent of **3.39** and adopt either conformations as seen by the Zimmerman-Traxler conformations **pre- α -3.40** and **pre- β -3.40**. As **pre- β -3.40** placed the major substituent (TBDPS alkyne) in a *pseudo*-equatorial position, the nucleophilic attack with a second equivalent of the nucleophile from the bottom face of **pre- β -3.40** delivers **β -3.40** as the only product, albeit in low yield. The relative configuration at this newly created stereocenter was confirmed by derivatizing the diol into its carbonate derivative **3.41** by treating it with triphosgene and pyridine (85%) and assigning the structure with the help of nOe and ³J_{HH} couplings within the ring.

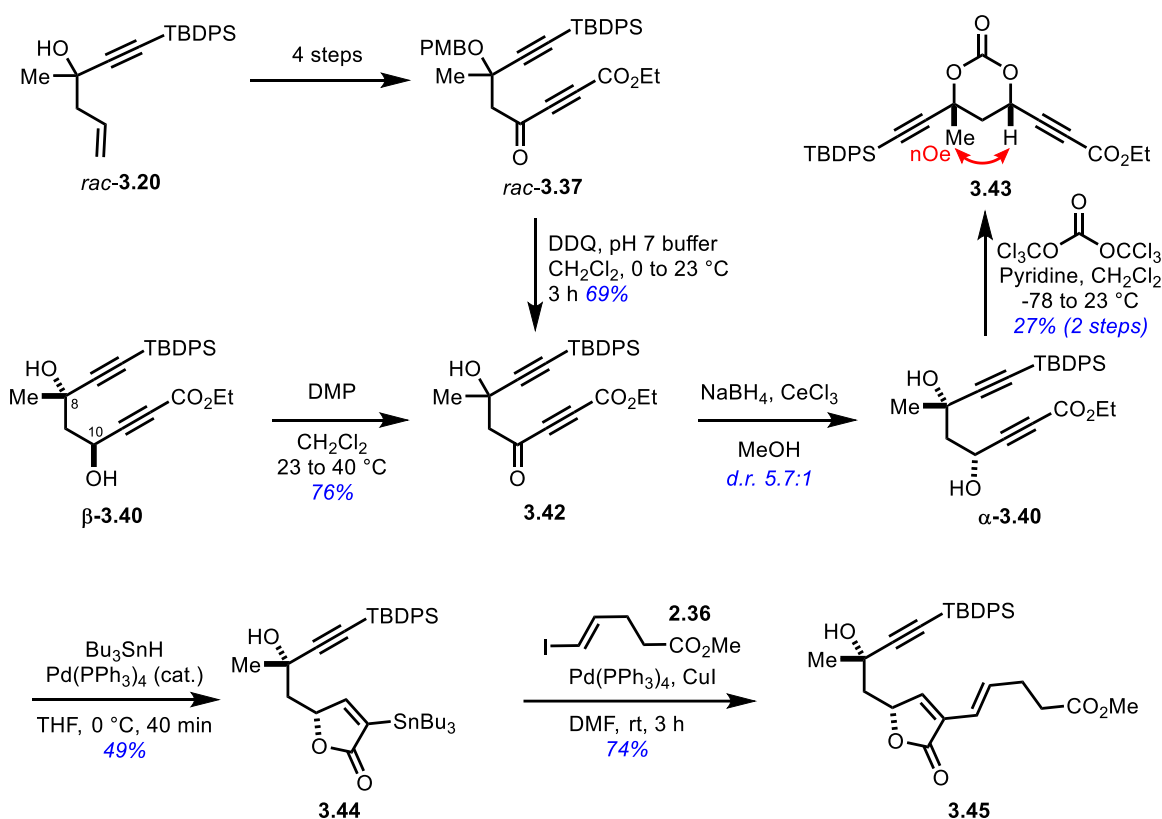


Scheme 3.9. Synthesis and structure determination of diol **β -3.40**.

As the undesired diastereoisomer at C₁₀ was again obtained, an alternative synthetic pathway to obtain **α -3.40** was sought. This work was completed in collaboration with Elliott Jackson, a talented undergraduate student taking on a summer internship in the laboratory. It is important to note that a serious hurdle to this protecting group-free chemistry was the instability of aldehyde **3.39**, and diol **β -3.40**, which were unstable and would decompose when attempting to purify them using SFC. As a consequence, the telescoping of multiple intermediates, without purification, would be necessary, which would lead to diminished overall yields. To obtain more material for further testing, a synthesis of ketone *rac*-**3.37** was undertaken through the same sequence of 4 steps from *rac*-**3.20**, after which a deprotection of the PMB group to finally obtain β -hydroxyketone **3.42** in 69% yield (Scheme 3.10). The latter could also be obtained by DMP oxidation of **β -3.40** with DMP in refluxing CH₂Cl₂ in 76% yield. Gratifyingly, when **3.42** was reduced using standard Luche reduction conditions, alcohol **α -3.40** was obtained as the major

diastereoisomer (5.7:1 d.r.). The stereochemistry at C₁₀ was confirmed by turning this diol into its corresponding carbonate **3.43** using triphosgene in 27% yield over 2 steps. This inversion protocol was developed after multiple attempts at a Mitsunobu inversion⁵² or chelation-directed Narasaka-Prasad reduction^{47,48} also failed to invert the C₁₀ stereocenter of **β-3.40**.

With a protecting group-free route of the desired propargylic alcohol **α-3.40** now in hand, attempts the hydrostannylation-Stille reaction to afford the diene moiety were at hand (scheme 3.10). Though this protocol was already planned beforehand, causes for concern were raised, since the substrate now contained two distinct propargylic alcohol moieties, though one was much more sterically hindered (TBDPS) and less reactive 3° alcohol, which was thought to be less likely participate in the alkoxide-directed binding^d of the intermediate H-Pd-SnR₃ intermediate.²² Interestingly, when **α-3.40** was exposed to the hydrostannylation reaction medium,



Scheme 3.10. Protecting group-free synthesis of diene **3.45**.

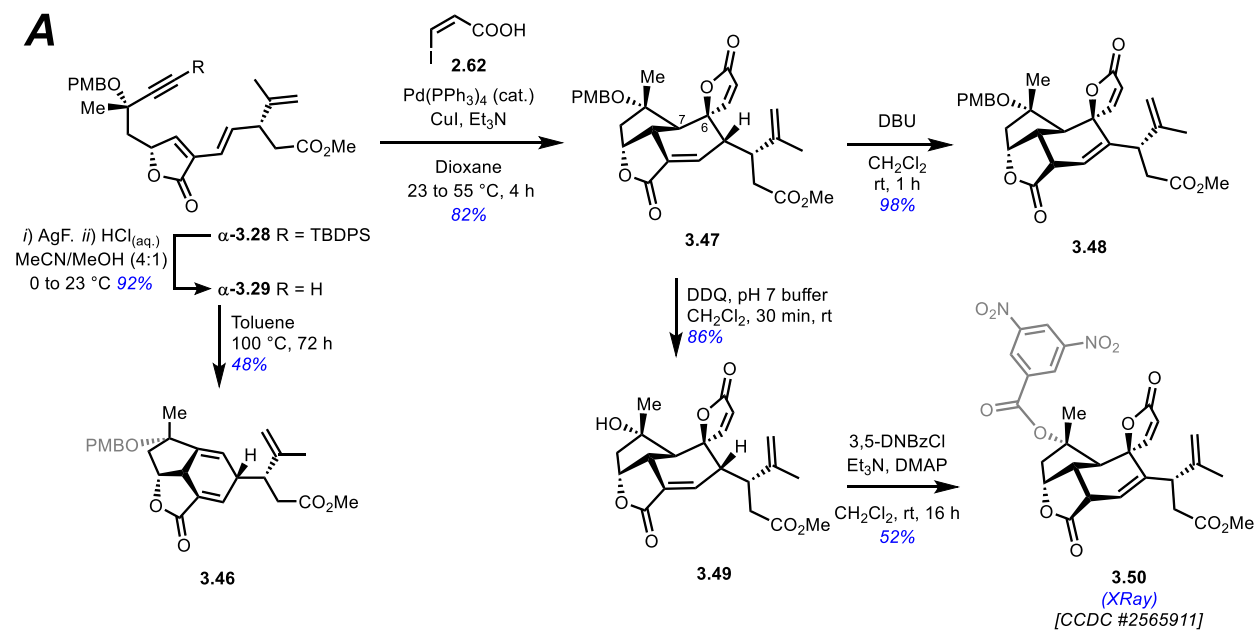
^d In his thesis, Michael Parmentier proposes that the regioselectivity of α - or β -stannylation of the butenolide is the result of a O-Pd monodentate interaction, ultimately favoring an α -stannylation product.

only the vinyl tin **3.44** was isolated in 49% yield. To confirm that the free tertiary alcohol would not interfere with the Stille cross-coupling reaction, **3.44** was then reacted with vinyl iodide **2.36** in previously developed conditions and cleanly afford diene **3.45** in 74% yield. Overall, this synthetic route offered a protecting group-free access to diene **3.45**, but due to the instability of certain intermediates on silica and a required oxidation/reduction sequence, it was decided that this route would not be scaled up, since the sequence requiring the PMB group yielded a much greater output of the corresponding diene (> 5 g in a single pass). Perhaps this route could be revisited in the future to fine-tune the chemistry and obtain an overall more efficient and ideal synthesis^{50,51} of the tetracyclic core of (+)-havellockate (**1.17**).

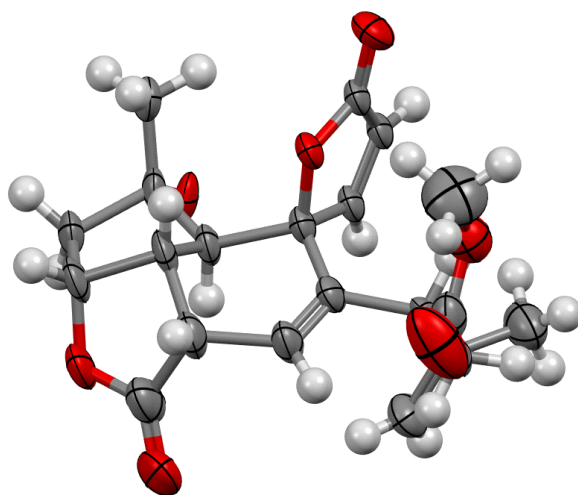
3.3.5 – Successful cascade reaction with the α diastereoisomer – *endo* adduct.

As it was concluded that the route using the PMB-protected alcohol was higher yielding overall, the latter was ultimately chosen over the PG-free one.. As it was previously done with β -**3.28**, the TBDPS substituent on α -**3.28** was removed using AgF to yield dienyne α -**3.29** (Scheme 3.11, A). A small sample of this intermediate was heated in toluene to observe its tendency to cyclize prematurely. Surprisingly, α -**3.29** was found to be much more resistant to early [4+2] cycloaddition when compared to β -**3.29**, and required heating at 100 °C for 3 d in toluene to yield the cycloadduct **3.46** in 48% yield and incomplete (85%) conversion. This result offered some relief as working with this intermediate would not require as much urgency between steps, especially during scale-up, as α -**3.29** seemed to be stable at room temperature. The dienyne α -**3.29** was then engaged in the previously developed cyclisation reaction, and again, with great fidelity, offered the tetracyclic structure **3.47** in 82% yield, requiring only very mild reaction temperature (55 °C) to undergo the critical Diels-Alder reaction. As much as we were delighted that the cascade chemistry could also be transposed to α -**3.29**, only the *endo* Diels-Alder adduct was observed, which sets the incorrect stereochemistry at C₆ and C₇ of the natural product. Despite this result, the exploration of late-stage transformations that would be required were also attempted and explored. As such, the deconjugation of the Δ^{12-13} alkene of **3.47** went, again, without a hitch and delivered **3.48** in 98% yield in, again, mild conditions versus what was previously described.^{28–37} To confirm the structure of **3.47**, chemical derivatization was also applied, akin to what has been done for **3.31**. First, the PMB group was removed using DDQ in buffered (pH=7) water to afford the tertiary alcohol **3.49** in 86% yield. Then, the attachment of a dinitrobenzoyl ester using 3,5-DNBzCl, Et₃N and DMAP afforded ester **3.50** in 52% yield, again with concomitant Δ^{12-13} to Δ^{13-}

¹⁴ alkene migration. A controlled crystal growth by slow evaporation afforded crystals suitable for SCXRD and a crystal structure was found, confirming its structure (Scheme 3.11, B), and the full crystal data was uploaded to the CCDC with the deposition number #2565911.



B



Scheme 3.11. (A) Synthesis and derivation of **3.47** and (B) ORTEP diagram of **3.50** at 50% probability thermal ellipsoids.^c

^c Dinitrobenzoate ester has been omitted for clarity.

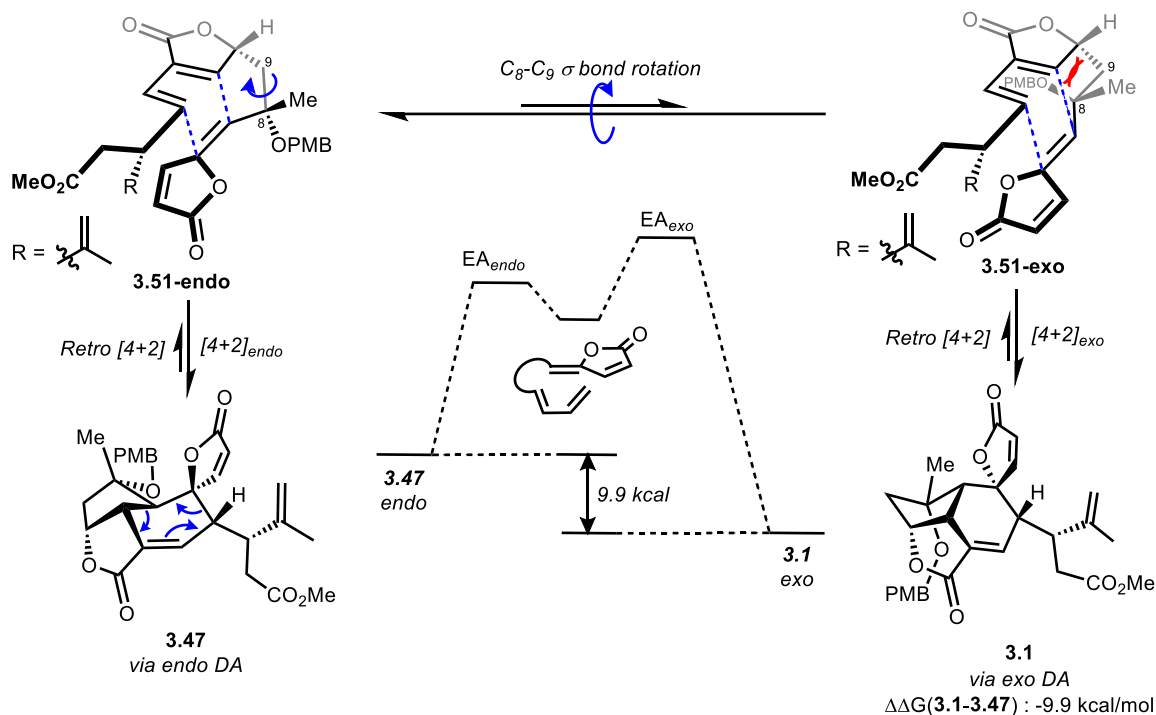
While the tetracyclic core of (+)-havellockate was fully constructed in terms of connectivity, this time with the right stereochemistry at C₁₀, the stereocenters at C₆ and C₇ were inverted, which was the result of a fully substrate-controlled *endo* [4+2] cycloaddition, and alas, yielded the wrong diastereoisomer. To correct this problem, two avenues were possible, either it would be required to go back and dramatically change the overall strategy or make full use of tetracycle **3.47**'s potential and correct the erroneous stereochemistry, which would require luck, fundamental knowledge and strategic thinking in order to pull off this Hail-Mary.

3.4 – Stereoselective synthesis of tetracyclic core of (+)-havellockate.

3.4.1 – Theoretical considerations : Is the cycloadduct **3.47** the kinetic product?

With all the right bond connectivity found in *endo* cycloadduct **3.47**, having to abandon this route because the wrong outcome of the [4+2] cycloaddition was hard to accept. Our gamble to introduce a tertiary alcohol at C₈ instead of a secondary alcohol, which was successful in the model study, was a losing one in this case. As a last resort, assuming that **3.47** was a kinetic product that could be thermally isomerized to the more stable *exo* thermodynamic product could be a saving grace. This was a bold assumption, since to the best of our knowledge, the reversibility of the IEDDA reaction had never been or observed studied previously in these systems. The question was, which of the adducts, *endo* or *exo*, was the thermodynamic product, and could the putative kinetic adduct isomerize towards the more stable one? This proposition is laid out in Scheme 3.12. Putatively, heating *endo* adduct **3.47** could make it undergo a retro [4+2] to revert back to its diene-dienophile pair **3.51-endo** upon heating. Then, a rotation along the C₈-C₉ σ bond could align the dienophile in the *exo* diene-dienophile alignment **3.51-exo** to finally afford the desired *exo* adduct **3.1** after a [4+2] cycloaddition. By imaging these putative intermediates, it is easy to observe that the alignment of both the methyl and OPMB groups of the C₈ tertiary alcohol in **3.51-endo** are pointed *away* from the core of the diene, while in **3.51-exo**, these two substituents are pointed directly *under* the rest of the molecule. This steric clash observed in **3.51-exo** would certainly impart a higher energy of activation (EA) when rotating the C₈-C₉ σ bond of **3.51-endo**, and offered hope that the higher energy of activation towards the *exo* pathway could be achieved by heating without the substrate undergoing side reactions or decomposition. Along with this proposition, the ground-state energies for both **3.47** and **3.1** were calculated using DFT, which revealed that *exo*

adduct **3.1** was 9.9 kcal/mol more stable than *endo* adduct **3.47**.^f Thus, the theoretical argument was in favor of the desired *exo* adduct, meaning that if the system was able to cycloreverse and align itself as seen in **3.51-*exo***, **3.1** would be accumulated as the sole product.



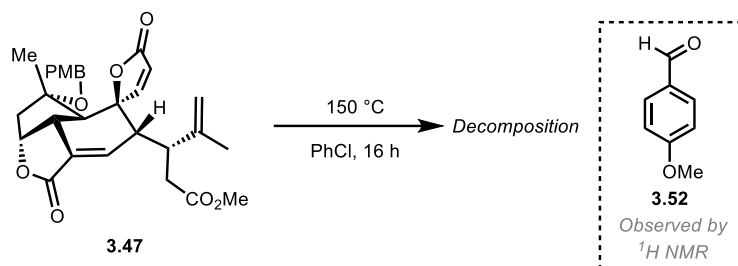
Scheme 3.12. Theoretical considerations of the desired retro[4+2]_{endo} / [4+2]_{exo} reaction of **3.47**.

3.4.2 – Thermal treatment of *endo* cycloadduct **3.47**.

Now having a strong theoretical backing that the isomerisation would be favorable, uncharted territory was explored in hopes of saving this synthetic route. Accordingly, the *endo* adduct **3.47** was dissolved in chlorobenzene, chosen for its polarity and high boiling point, and heated to reflux overnight (Scheme 3.13). After removing the solvent and looking at the ¹H NMR data, full decomposition of the substrate was observed. What was very interesting was that an aldehyde peak ($\delta = 9.69 \text{ ppm}$, C₆D₆) was present in the crude mixture and was correlated to *p*-methoxybenzaldehyde **3.52** from the literature. From this result, it was concluded that the PMB group had been oxidatively cleaved with the help of dissolved O_{2(g)} in the reaction, perhaps akin to an oxidative cleavage with DDQ, as no measures had been taken to run this reaction under inert

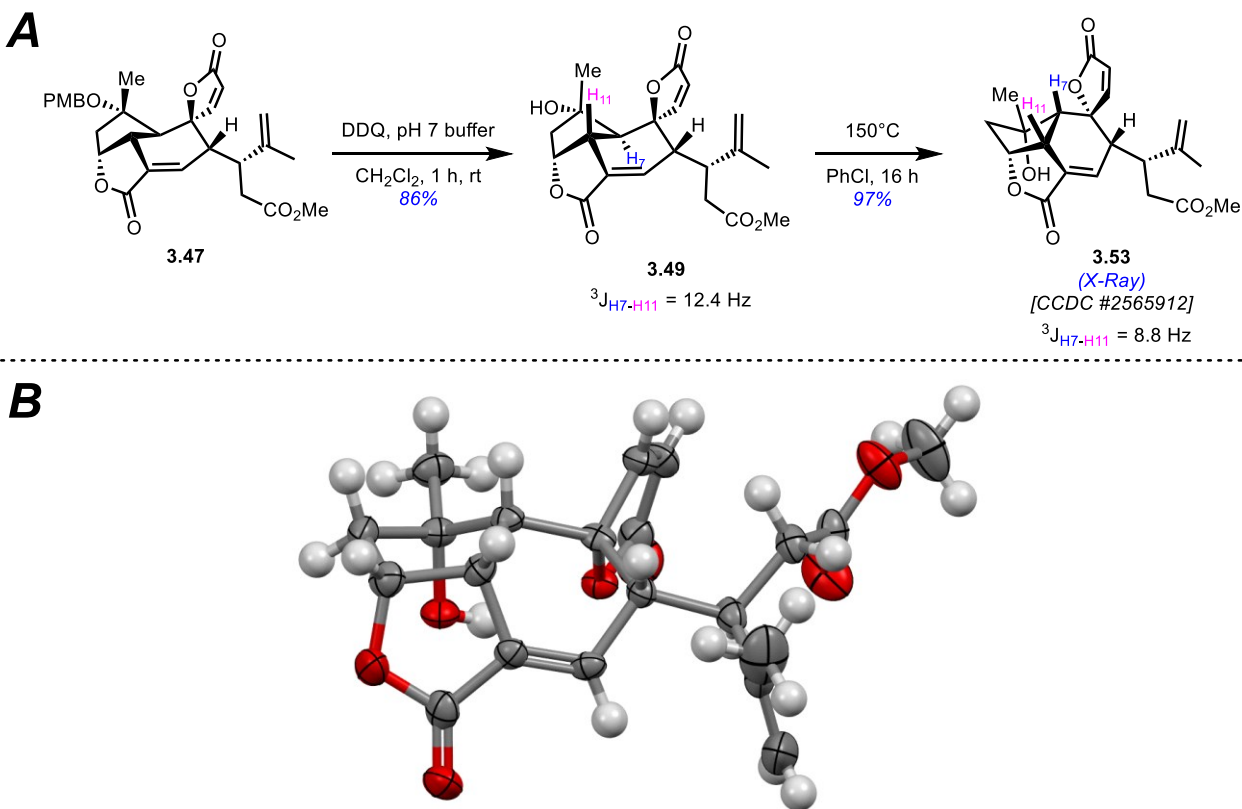
^f Level of theory : B3LYP and basis set : 6-31G(d) in the gas phase.

atmosphere. The first thought was not to exclude oxygen from the reaction, but to conclude that the PMB group was effectively hindering the desired isomerisation. This rationale can be qualitatively observed by substituent's bulkiness, which might be disabling the rotation from **3.51-endo** to **3.51-exo** (scheme 3.12) due to steric clashing.



Scheme 3.13. Observed decomposition of **3.47** upon heating.

In order to prove our theory that the PMB group was hindering a free rotation, the same experiment was completed using substrate **3.49**, where the PMB group of **3.47** was removed in standard conditions (DDQ, 86%). This *endo* adduct, in which the trans relationship between H₇-H₁₁ has a characteristic ³J_{HH} coupling constant of a trans junction predicted by the Karplus equation^{53,54} ($\varphi = 173.9^{\circ}$ in SCXRD structure of **3.50**, ³J_{HH} calcd. 10.7 Hz, obs. 12.4 Hz), was again heated to 150 °C in chlorobenzene overnight (Scheme 3.14, A). Following by the solvent removal and ¹H NMR in C₆D₆, we were ecstatic to conclude that the planned *endo-exo* isomerisation had not only actually succeeded, but that the only detectable product in ¹H NMR was *exo* adduct **3.53**!

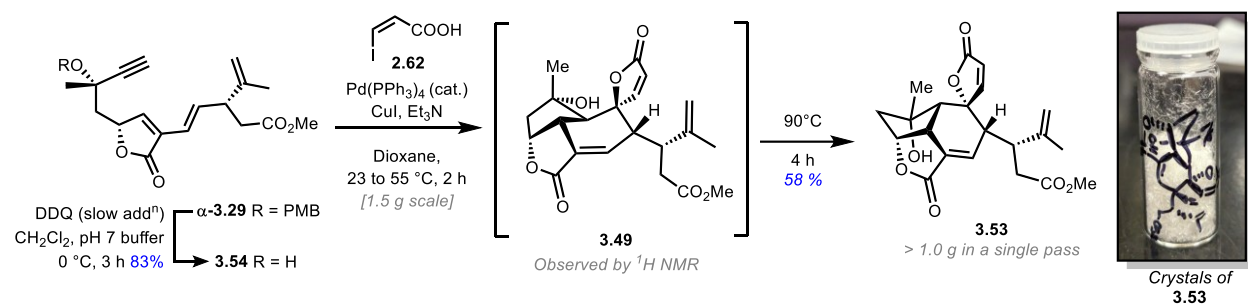


Scheme 3.14. (A) Synthesis of the tetracyclic core of (+)-havellockate **3.53**. (B) ORTEP diagram of **3.53** at 50% probability thermal ellipsoids.

This has revealed that the sole observed reactivity had presumably closely followed the theoretical predictions done above, with no detectable decomposition, side-reactions or *endo* adduct **3.49** present. After re-running this reaction on slightly larger scale, crystals of **3.53** were obtained from recrystallization in ethyl acetate (EtOAc) and its structure was unambiguously confirmed by SCXRD (Scheme 3.14, B). Interestingly, the observable $^3J_{\text{HH}}$ between H₇-H₁₁ did not correlate as well with the value the Karplus equation predicted ($\varphi = 33.6^\circ$ in SCXRD structure of **3.53**, $^3J_{\text{HH}}$ calcd. 5.9 Hz, obs. 8.8 Hz).^{53,54} This incredible discovery saved the route that was developed and enabled a deeper understanding of the reactivity of this type of IEDDA reaction. This is also, to the best of our knowledge, the first reported example of the *endo-exo* reversibility in the inverse demand Diels-Alder reaction and represents an efficient and straightforward synthetic pathway to the core of (+)-havellockate (**1.17**).

3.4.3 – Optimized synthesis of the tetracyclic core of (+)-havellockate.

With a synthetic pathway that now was able to forge the tetracyclic core of the natural product with the right stereochemistry at C₆ and C₇, an optimization of this sequence of events was needed to maximize throughput. As the transformation of *endo* adduct **3.49** to *exo* adduct **3.53** required the C₈ oxygen to be free of any substitution, we envisioned a pathway where this retro[4+2] / σ bond rotation / [4+2] sequence of events could be achieved in the same pot that generated the *endo* adduct. To do so, it would be required to remove the PMB group from dienyne **α -3.29** before trying the reaction cascade, and hope that a free alcohol group would not interfere with the spectacular reactivity that the reaction cascade provided. In this context, it was important to know that performing a PMB deprotection using an oxidant (*e.g.* DDQ) on substrates that contain the 1,3-diene or 1,4-diene motifs has been a hard roadblock during multiple total synthesis campaigns¹. This roadblock has been previously reported during the total synthesis of fumagillol⁵⁵, curacin A^{56,57} and delactonmycin⁵⁸, where a late-stage PMB removal on substrates containing a diene or triene failed. Treading carefully, OPMB dienyne **α -3.29** was exposed to small portionwise additions of DDQ in CH₂Cl₂ and buffered water over 3 hours at 0 °C, which delivered the deprotected dienyne **3.54** in 83% (Scheme 3.15). This deprotected dienyne was now primed for the reaction cascade, and when exposed to the standard conditions, afforded the *endo* adduct **3.49** *in situ* as the major diastereoisomer after 2 hours at 55 °C, as observed by NMR of an aliquot. This mixture was then heated to the boiling point of 1,4-dioxane (90 °C) for 4 additional hours to hopefully effect the retro [4+2] / σ bond rotation / [4+2] and obtain *exo* adduct **3.53**. Pleasingly, the *endo* adduct could be fully converted to the *exo* adduct at these lower temperatures (90 °C vs

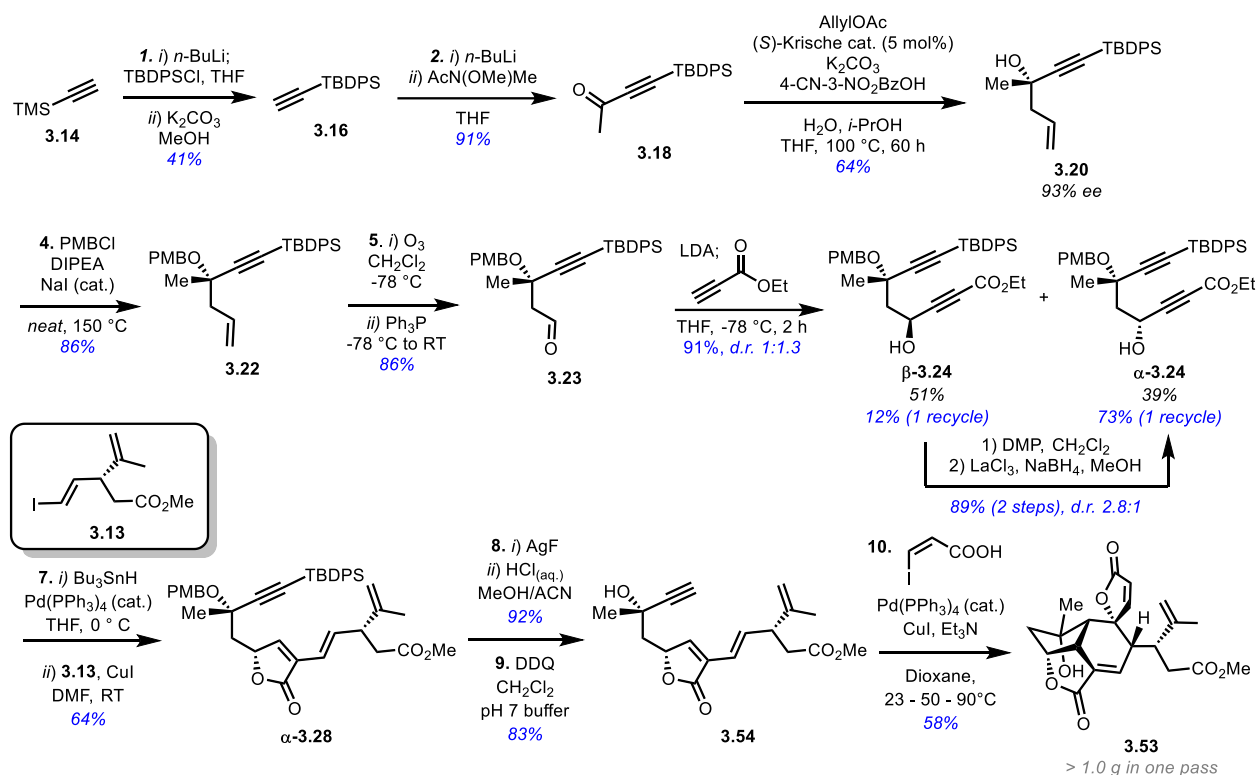


Scheme 3.15. One-pot synthesis of the tetracyclic core of havellockate **3.53** from **3.54**.

150 °C, Scheme 3.14), delivering the polycyclic structure **3.53**. This spectacular reaction cascade, comprised of 5 distinct steps in the same pot (*Sonogashira* – 5-*exo-dig* – [4+2]_{*endo*} – retro[4+2] – [4+2]_{*exo*}), enabled the construction of 3 carbocycles and forged 3 stereocenters found in the natural

product in one pot. This spectacular reaction cascade was also brought up to gram-scale (1.5 g of **3.54**), which could deliver over a gram of **3.53** (58%).

Overall, the synthesis of the tetracyclic structure **3.53** spanned 10 steps and an overall yield of 3.7% from TMS acetylene **3.14** (scheme 3.16). Furthermore, supplementary exploratory work showed that propargylic ketone **3.18** could be accessed in 2 steps (previously : 3 steps) from **3.14** by treating the lithium acetylide of **3.16** with Weinreb amide AcN(OMe)Me.



Scheme 3.16. A 10-step enantioselective synthesis of tetracyclic core of havellockate **3.53**.

This achievement represented a monumental advancement in our efforts to finish the total synthesis of (+)-havellockate (**1.17**), and its sheer scalability furnished more than enough material to undergo multiple attempts late-stage, allowing hundreds of reaction conditions to be attempted when ran on 1-5 milligram scale. This platform then enabled a focus on the late-stage transformations of this substrate, requiring only the $\Delta^{12,13}$ alkene deconjugation and oxidation at C₅ to complete the total synthesis of the natural product (+)-havellockate (**1.17**).

3.5. Conclusion.

To conclude, not only had a highly efficient enantioselective synthesis of **3.53** been developed, but by understanding the behaviour of the central [4+2] cycloaddition, it was revealed that its stereochemical outcome can be controlled by the substitution pattern of the C₈ alcohol. This chemical control enabled a divergent synthesis of *endo* adduct **3.47** or *exo* adduct **3.53**. The power of this divergency has not gone unrecognized, as both of these tetracyclic structures are also represented in multiple natural products, plus or minus one or two C-C bonds (*in red*) as seen in figure 3.1 and could pave the way for a divergent total synthesis of multiple members of the cembranoid family of natural products.

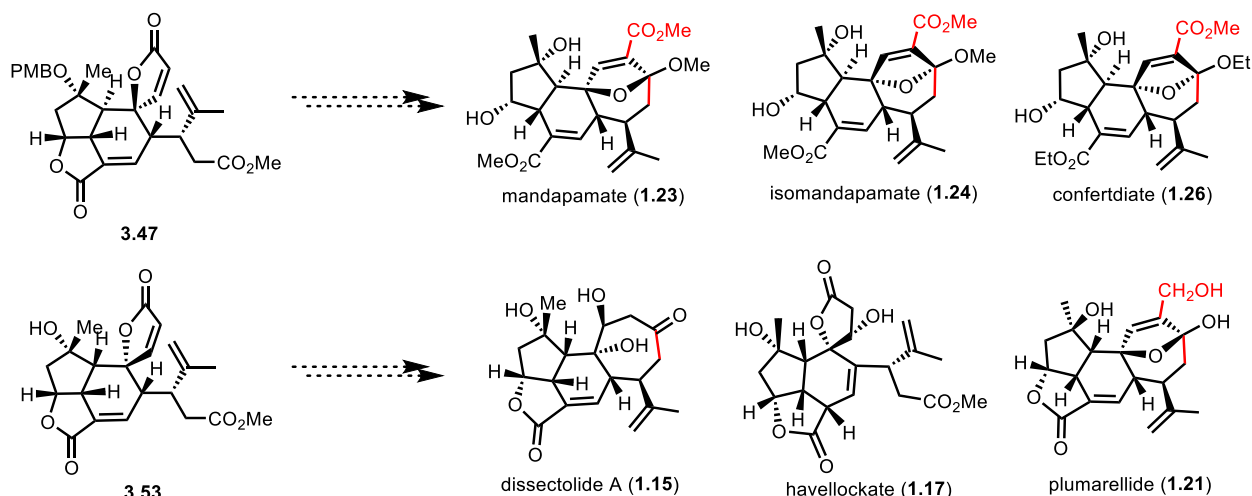


Figure 3.1. Divergent access to multiple cembranoid natural products.

3.6. Bibliography.

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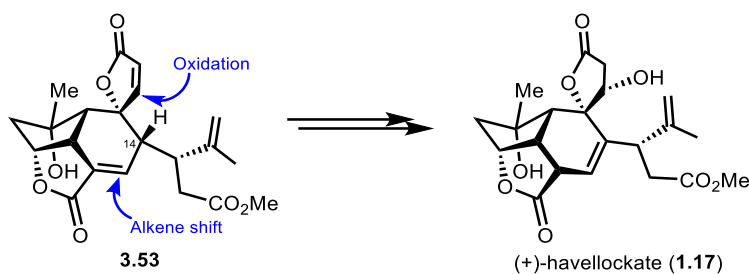
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CHAPTER 4

**Total synthesis of (+)-anhydrohavellockate and late-stage transformations
towards the total synthesis of (+)-havellockate**

4.1 – Strategy and theoretical predictions.

Coming off of the success of successfully controlling the outcome of the critical Diels-Alder reaction, seeking a way to complete the total synthesis was at hand. To do so, only two transformations remained on **3.53** : the alkene Δ^{12-13} to Δ^{13-14} alkene isomerisation and the installation of the C₅ alcohol moiety through an oxidation (Scheme 4.1).



Scheme 4.1. Transformations required to complete the total synthesis of (+)-havellockate (**1.17**).

As such, the first operation that was targeted was the alkene isomerisation operation. To do so would be thermodynamically favored, as seen in scheme 2.1, the deconjugation of the alkene would generate a “deconjugated” substrate that is *ca.* 10 kcal lower in energy in its ground-state form due to reduced strain. The accessibility of the proton at C₁₄ was also studied. Indeed, from looking at the crystal structure of **3.53**, it was observed that the desired proton’s C-H bond would allow an orbital alignment and overlap between its $\sigma_{(C-H)}$ and the $\pi^*_{(C=C)}$ of the alkene, known as the “90° rule” when considering stereoelectronic effects (figure 4.1).

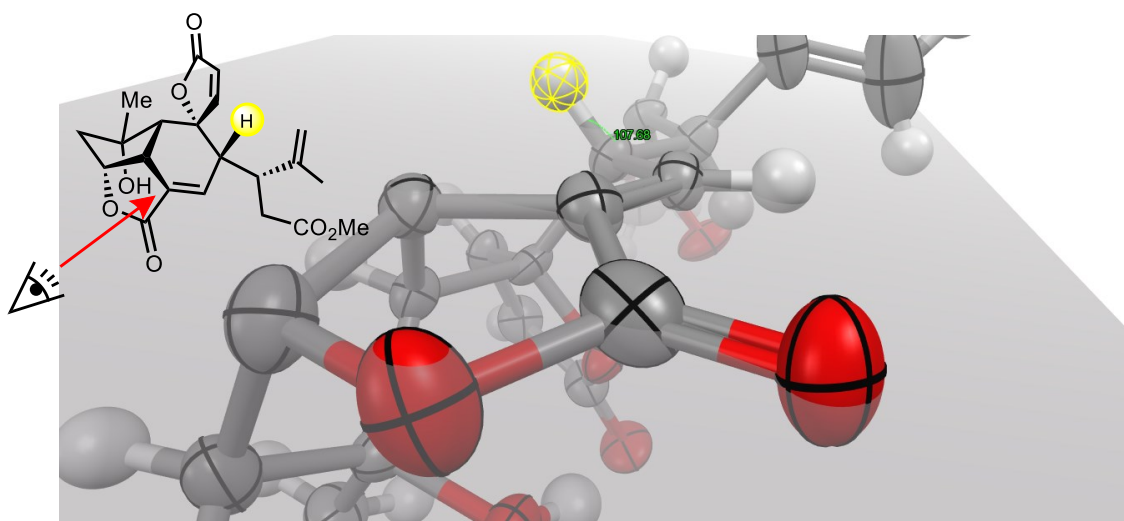
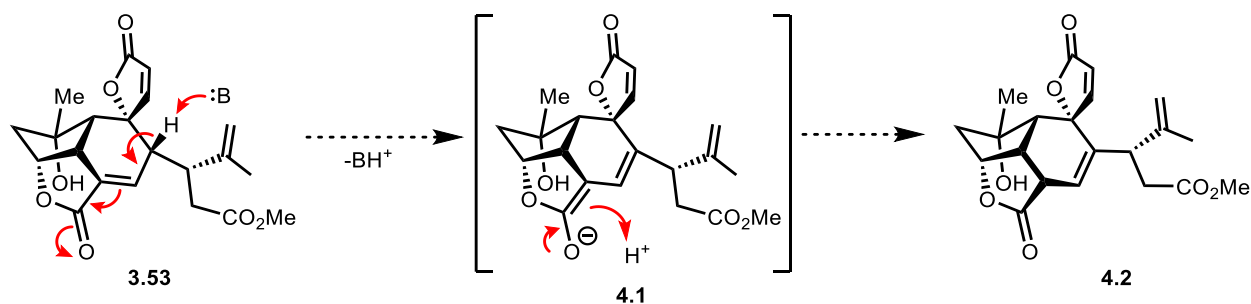


Figure 4.1. Visualisation of H₁₄’s $\sigma_{(C-H)}$ versus the enone system’ plane.

The measured angle of 107.68° versus the plane of the π system of the conjugated alkene gave hope that this proton would be acidic enough to be deprotonated and form the corresponding dienolate. With these two theoretical factors well aligned with the desired goals, **3.53** would be exposed to a plethora of bases in hopes of deprotonating γ proton H₁₄ of the σ - β unsaturated lactone. Doing so would generate dienolate **4.1** (Scheme 4.2), which theoretically was believed to only be able to reprotonate in α to the carbonyl due to a misalignment of the dienolate imparted by ring strain, and on the convex face only, finally affording **4.2**. This theoretically could be accomplished using thermodynamic bases, like DBU for example.

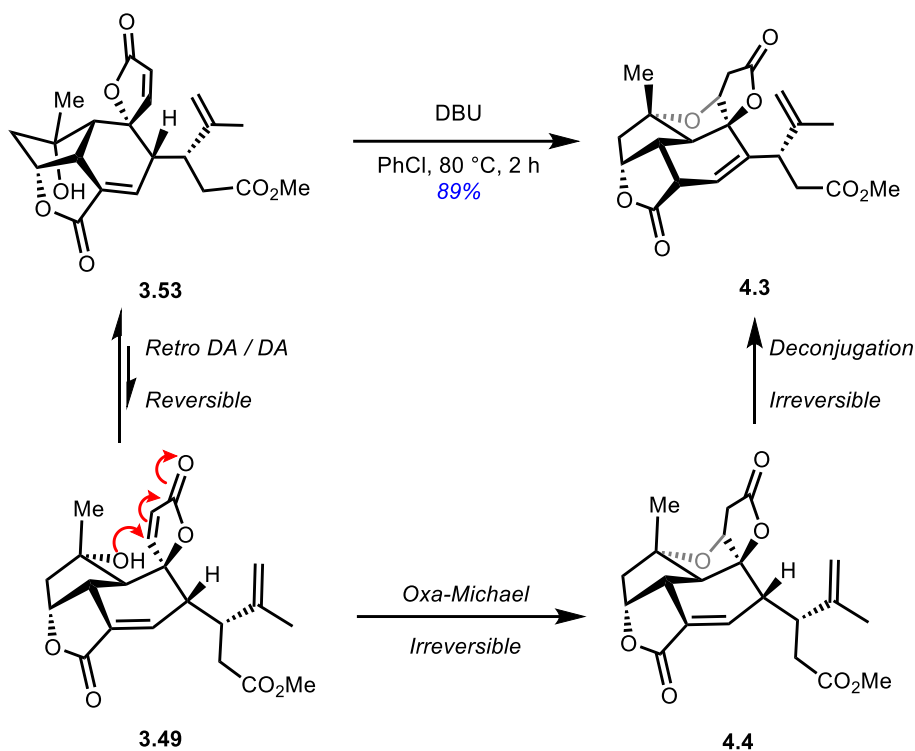


Scheme 4.2. Desired reaction mechanism of **3.53** towards **4.2**.

4.2 – Deconjugation of the Δ^{12-13} alkene.

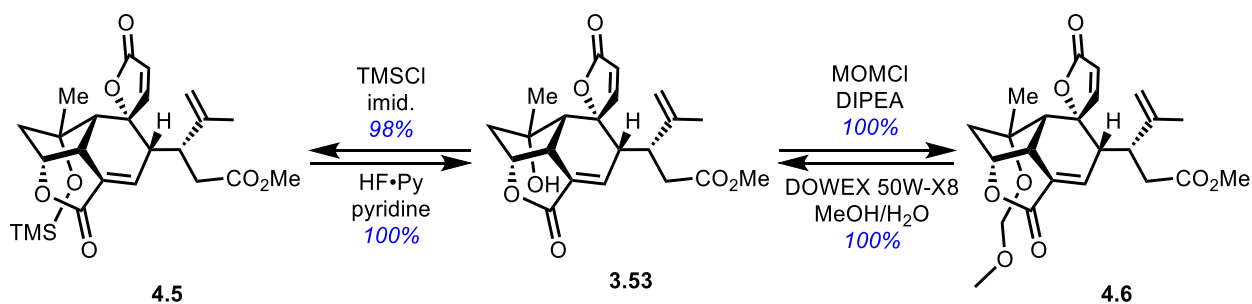
4.2.1 – Base-mediated alkene deconjugation.

The core of the natural product **3.53**, which was available in gram quantities at that point, was subjected to DBU, as it seemed the most potent base for the deconjugation of these fused unsaturated [4.3.0.2_{1,8}] lactones. As such, **3.53** was first exposed to DBU in chlorobenzene at 80°C (Scheme 4.3), and doing so yielded only *endo* adduct **4.3** in high yield (89%), being highlighted by a high $^3J_{\text{HH}}$ coupling between H₇-H₁₁ of > 12 Hz (similar to what was previously observed in scheme 3.14 A). The obtention of this product was rationalized by the concluding that the *endo* adduct **3.49** and the *exo* adduct **4.4** could exist in equilibrium in solution, though **3.49** was heavily disfavored. When the latter was formed, it could engage in an oxa-Michael reaction with the π system of the spirolactone due to favorable alignment, affording **4.4**, creating a thermodynamic sink and a pooling all of **3.53** towards *endo* adducts. Then, the deconjugation previously observed could afford **4.3**. From this experiment, it was concluded that the C₈ tertiary alcohol needed to be protected to 1) disfavor the reversibility of the Diels-Alder reaction and 2) disable the irreversible oxa-Michael reactivity observed from **3.49** to **4.4**.



Scheme 4.3. Proposed mechanism for the formation of **4.3**.

To remedy this problem, the alcohol in **3.53** was protected. A wise choice of protection would be key here, as it could have an impact on the conformation of the tetracyclic substrate, and further chemistry. The ease of deprotection would also play a key role in the choice of protection of **3.53** (Scheme 4.4). As such, the TMS group and the MOM group was chosen, as a TMS could be removed orthogonally on the substrate, and tertiary MOM groups have been shown to be easily added¹ and removed² in the late stages of the total synthesis of natural products. The tetracyclic structure **3.53** was then protected as its TMS analog **4.5** in almost quantitative yield using TMSCl and imidazole, which could be removed quantitatively using HF•pyridine in pyridine

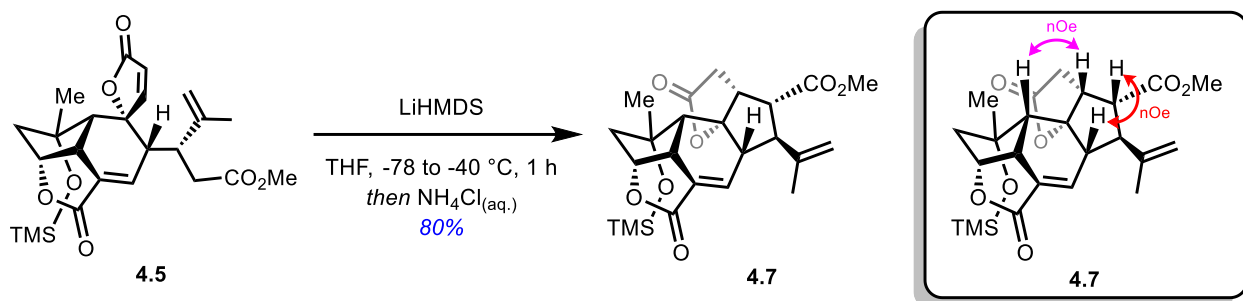


Scheme 4.4. Protection group strategy of **3.53**.

as the solvent. In an analogous manner, the MOM-protected analog **4.6** was produced by exposing **3.53** to MOMBr and Hünig's base in quantitative yield, as well as removed also quantitatively using ion exchange resin DOWEX 50W-X8 in boiling MeOH/H₂O overnight. It is worthy of noting that the quantitative yields observed in these transformations are a testament to the robustness of this substrate, a fact that would pose a problem during further derivatization to the natural product.

After accessing these C₈-protected variants, **4.5** and **4.6** were treated with DBU in polar and non-polar solvents at various temperatures but unfortunately only returned the starting material. Perhaps thinking that DBU's bulkiness caused inaccessibility to H₁₄ due to steric hinderance, reactions using more nimble bases with a similar pK_b were attempted, such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,1,3,3-tetramethylguanidine (TMG) but to avail. Strategies to increase the basicity of these, such as using MeCN as a solvent (pK_a increase of 2 units to DBU)³ also failed. The only observed transformation of **4.5** was after its treatment with DBU in toluene at elevated temperatures (> 120 °C) for prolonged periods of time, which returned a product that was proposed to be the nucleophilic addition of DBU onto the southwestern lactone to generate a zwitterionic species by ¹H NMR (*not shown*). This substance was sensitive to SFC and could not be fully characterized and thus, remains a hypothesis. Other methods to acidify H₁₄ such as soft enolization⁴ by using alkali salts failed to yield any deconjugated product.

Following this roadblock, the use of stronger bases would be necessary. We were fully aware that using strong, kinetic bases at cryogenic temperatures risked the enolization of the methyl ester-containing sidechain, leading to unproductive reaction pathways, but a step-up in base strength was required. Thus, **4.5** was exposed to LiHMDS at -78°C and warmed to -40 °C (Scheme 4.5) and the Michael adduct **4.7** was obtained in high yield. This product was not expected, as it was believed that there would be a high entropy cost to any intramolecular Michael addition to the spirolactone moiety due to the creation of a 5th ring, but obtaining **4.7** proved otherwise. While the treatment of **4.5** using these conditions did not give the desired deconjugation product, it has proven to be a valuable lesson : the spirolactone's C₅ carbon seemed to be highly electrophilic in an intramolecular reaction. This proposed hypothesis that will be thoroughly tested later in this thesis, as the internal delivery of an oxygen atom was pondered and would be explored after scoping out the alkene isomerization chemistry.

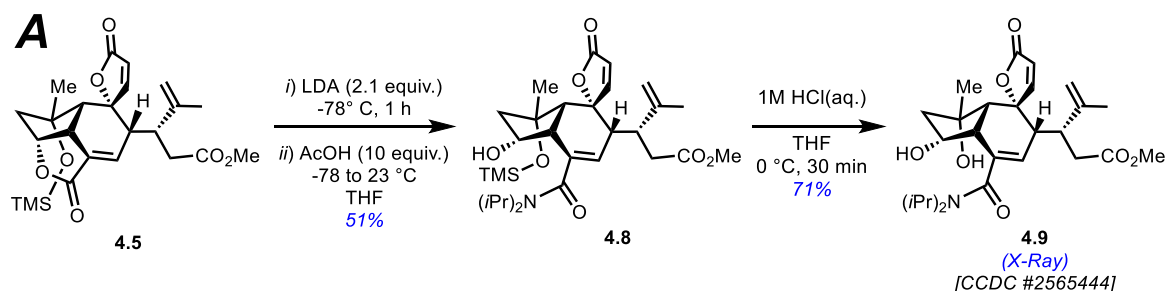


Scheme 4.5. Formation of the intramolecular Michael addition product **4.7**.

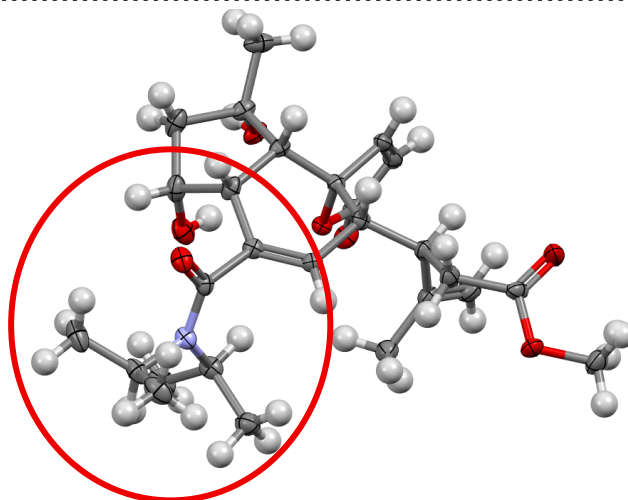
The same conjugate addition products were observed when using **4.6** as a substrate, different alkali salts of the base (NaHMDS, KHMDS) or different *tert*-butoxides ($\text{KO}-t\text{Bu}$, $\text{NaO}-t\text{Bu}$). Interestingly, the only diastereoisomer observed in all cases came from the *Si* face, as predicted in section 2.2, and was assigned by nOe interactions between $\text{H}_2 / \text{H}_{14}$ (*red*) and H_5 / H_7 (*pink*) by 2D NMR.

Furthermore, other strong bases, such as LDA, were tested to effect the desired reaction. LDA is a strong non-nucleophilic base and was thought to be competent to accomplish the desired alkene deconjugation. As such, **4.5** was treated with LDA at cryogenic temperatures and quenched with AcOH. The result of this reaction was surprising : only the diisopropylamine addition product **4.8** was observed (Scheme 4.6, A). LDA is known to be non-nucleophilic, but it is believed that the strain imparted by the Δ^{12-13} alkene makes the southwestern lactone more reactive than in traditional α - β unsaturated lactone systems, yielding a product that could offer a better alignment of the $\pi_{(\text{C-O})}$ with the alkene in the ring-opened form. This structure was initially ambiguous by NMR, and as such, attempts to crystallize this amide were undertaken. The amide **4.8** itself was not crystalline, and removing the TMS group would make it more polar, thus hopefully more crystalline. In that manner, the TMS group was ablated using aqueous HCl and **4.9** was obtained in 71% yield. Surprisingly, **4.9** was crystalline and did not require further chemical derivatization, and so, crystals could be grown from slow evaporation from a $\text{CH}_2\text{Cl}_2/\text{C}_6\text{H}_6$ mixture. A SCXRD analysis of the crystals of **4.9** revealed its X-Ray structure as a C_6H_6 co-crystal (Scheme 4.6, B), which was uploaded to the CCDC with the deposition number #2565444.

Again, faced with a non-productive reaction, more conditions were tested using **4.5** and **4.6** as substrates. A total of over 40 attempts using other organic (MeONa , MeOLi , EtONa) and inorganic (K_2CO_3 , KHCO_3) bases in polar aprotic solvent (DMF, MeCN, THF, DCM, DCE) failed



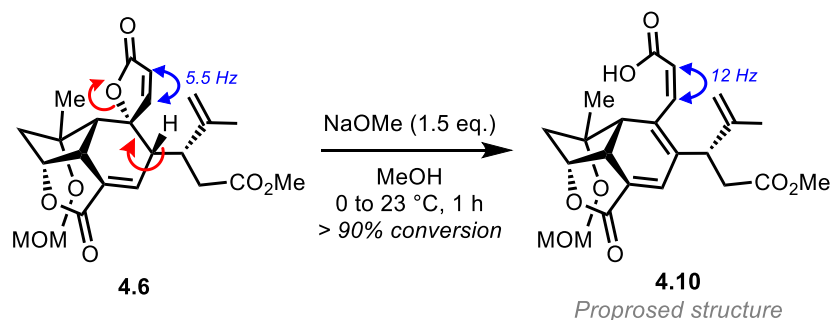
B



Scheme 4.6. (A) Synthesis of amide **4.8** and (B) ORTEP diagram of amide **4.9** at 50% probability thermal ellipsoids.¹

to give rise to any transformations in most cases. The use of alkoxides (MeONa NaOH, KOH) in polar protic solvent (H₂O/THF, MeOH, *i*-PrOH) either completely degraded the product through presumable hydrolysis of the other ester functionalities or gave very polar products that were not stable on silica. One such product is carboxylic acid **4.10**, which could not be fully characterized due to its instability on silica gel and was observed in high conversions when **4.6** was treated with stoichiometric amounts of NaOMe in MeOH. In that case, H₁₄ would be the sole acidic proton that gets eliminated, since α to that position is a good leaving group (*i.e.* an acetate group). The characteristic alkene protons in **3.53** (and its congeners **4.5** & **4.6**) couple with a ³J_{HH} of 5.5 Hz in all cases, and it was observed by ¹H NMR that these protons now shift to a ³J_{HH} of 12 Hz, a value in line with the presence of linear *Z* alkenes, in which case the structure of **4.10** was proposed (Scheme 4.7).

¹ C₆H₆ co-crystal was omitted for clarity.



Scheme 4.7. Proposed mechanism for the formation of putative carboxylic acid **4.10**.

4.2.2 – Alkene deconjugation attempts by changing the spacial disposition of γ -proton H_{14} .

Faced with the reality that this alkene isomerization would not be as easy as observed in the *endo* cycloadducts previously observed, other unorthodox strategies were explored. One such strategy was changing the spacial disposition of H_{14} , which could be accomplished by changing the geometry of the precursor diene responsible for the stereochemical outcome at C_{14} (14-*epi*-**3.53**, Figure 4.2). Perhaps in that case, the new disposition of H_{14} would be favor its deprotonation

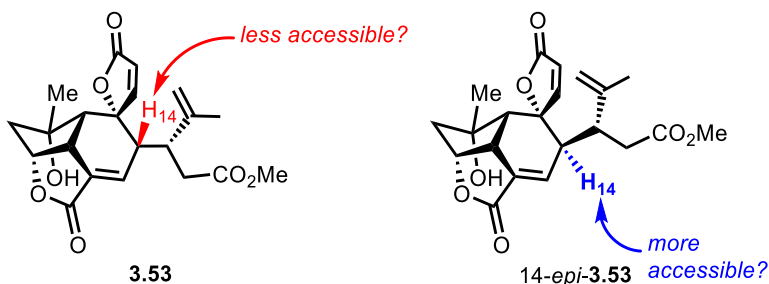
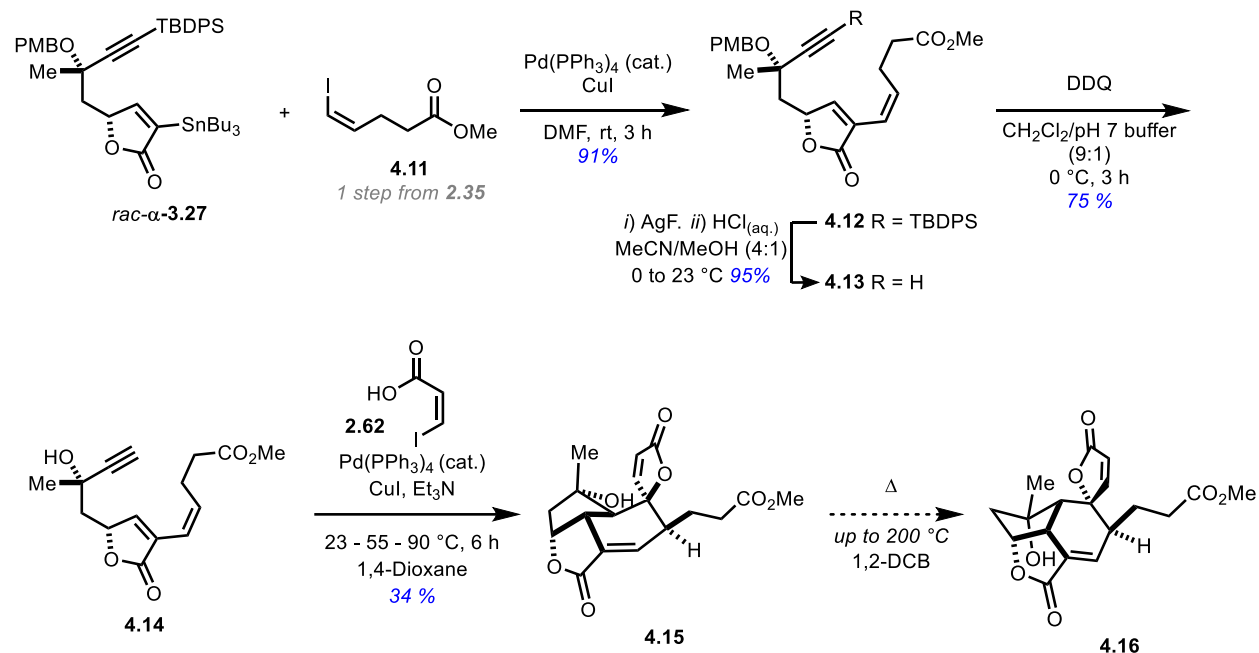


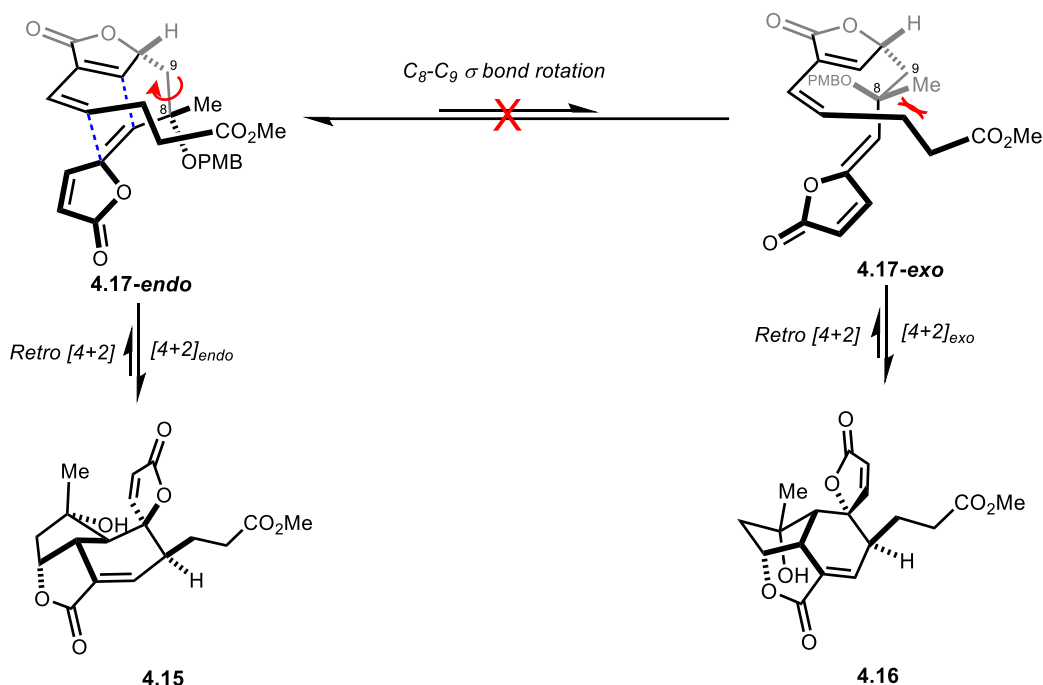
Figure 4.2. Proposed structure change and accessibility to H_{14} of **3.53**.

changing its chemical environment, though now this proton had its $\sigma(C-H)$ not as well aligned with the π system of the alkene, it was a strategy deemed to be worth attempting in the lab. To explore this hypothesis, the geometry of the diene participating in the Diels-Alder reaction would need to be modified. As such, a model system was quickly put in place from the chemistry previously developed in this research (Scheme 4.8). To synthesize 14-*epi*-**3.53**, **4.11** was synthesized in 1 step from alkyne **2.35** using conditions reported on a similar substrate.⁵ This *Z*-iodoalkene was then cross-coupled with *rac*-**α**-**3.27** using the previously used conditions to afford diene **4.12** in 91% yield, which was then stripped of the TBDPS group using AgF to afford **4.13** in 95% yield. Then, DDQ was employed to remove the PMB protecting group to afford **4.14** in 75% yield. By doing



Scheme 4.8. Attempts at synthesizing a model system of 14-*epi*-3.53.

so, it was hoped that the reaction cascade could still be achieved to afford the *exo* adduct, and as such, **4.14** was exposed to **2.62** using the previously developed cascade reaction condition. Using this system, it was observed that only the *endo* adduct **4.15** was obtained, in lower yield. Perhaps this substrate needed more thermal energy to cross energy of activation of the retro [4+2]_{endo} / [4+2]_{exo}. Thus, the latter was heated in 1,2-dichlorobenzene (1,2-DCB) at temperature step gradients of 100 °C, 150 °C and 200 °C for 2 hours each, trying to observe any change by ¹H NMR between the experiments. Unfortunately, **4.15** did not react when it was heated up to 150 °C, and decomposed to more than four observable products when heated to 200 °C. The incapability of the system to convert **4.15** towards **4.16** could perhaps be explained by a three-dimensional analysis of the Diels-Alder reaction adducts (Scheme 4.9). Adduct **4.15**, when heated, could give rise to its *endo* retro [4+2] diene-dienophile pair **4.17-endo**. The side-chain ester is now geometrically much closer to the native substrate, and the required C₈-C₉ σ bond rotation presumably would require a much higher energy of activation to overcome the steric clash imparted by the substrate. Thus, at these temperatures, it is presumed that the *exo* diene-dienophile **4.17-exo** cannot be accessed, and even if *exo* adduct **4.16** would be thermodynamically favored, it could not be accessed using this system. With only the *endo* adduct being accessible using *Z*-iodoalkene **4.14**, this pathway was not given any more attention and other ideas to effect the alkene isomerisation were explored.

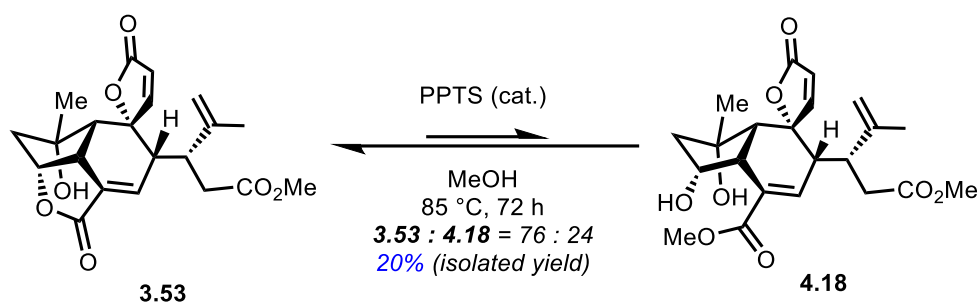


Scheme 4.9. Spatial considerations of the desired retro[4+2]_{endo} / [4+2]_{exo} reaction of **4.15**.

4.2.3 – Alkene deconjugation attempts through a ring-opened lactone moiety.

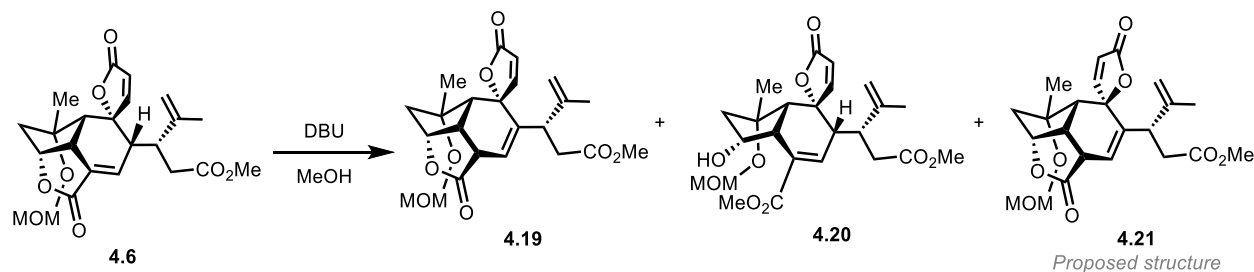
Derivation of tetracyclic substrate **3.53** was thought to be required to enable the penultimate alkene isomerisation reaction. One such idea was to “open” the southwestern lactone moiety into its ester-diol through a transesterification. It was believed that an ester would allowed alignment of the π system better than the closed lactone form, and thus, enable transformations such as deconjugation and/or conjugate chemistry, and as such, protocols to esterify the lactone were explored. It was previously mentioned in this chapter that **3.53**, or its derivatives, were susceptible to decomposition or could be over-saponified when subjected to basic conditions in protic solvents. Thus, ester hydrolysis conditions in acidic media were explored (Scheme 4.10). Very rapidly, it was observed that this operation could be completed by heating **3.53** in boiling methanol using pyridinium *p*-toluenesulfonate (PPTS) as a catalyst to afford **3.53** and methyl ester **4.18** in a 74:26 ratio (¹H NMR) and in 20% isolated yield. The same ratio was observed after running this reaction for 7 days, which suggested **3.53** and **4.18** reached a thermodynamic equilibrium and indeed, by re-entering **4.18** in the same reaction conditions, the same ~3:1 ratio of **3.53** : **4.18** was observed. Interestingly, the same product distribution could be observed using MOM-protected substrate **4.6**,

which presumably undergoes a rapid MOM deprotection, and reaches the identical equilibrium between **3.53** and **4.18**.



Scheme 4.10. Translactonisation of **3.53** to methyl ester **4.18**.

To obtain a higher throughput of methyl ester **4.18**, its more favorable generation was thought to be possible by running the reaction using catalytic amounts of methoxide in methanol. Indeed, by adding a catalytic amount of DBU in MeOH, it was thought that creating a minute amount of alkoxide *in situ* to act as a nucleophile could selectively open up the more reactive ester (as seen with LDA). As such, **4.6** was treated with a catalytic amount of DBU in MeOH. When **4.6** and 20 mol% DBU were heated to 70 °C in MeOH, **4.19** could be observed and isolated for the first time! This product was produced along with methyl ester **4.20** and the proposed structure **4.21**, presumably produced through the intermediacy of carboxylic acid **4.10** proposed earlier. Since this reaction provided the first traces of **4.19**, an optimisation was completed (Table 4.1). Bringing the temperature up to 90 °C at 10 mol% and 50 mol% DBU (entries 2 & 3) slightly bumped up the yield to 32%. Bringing the DBU quantities up to quasi stoichiometric amounts (80 mol%, entry 4) produced mostly side products. Running this reaction over longer periods of time (5 d) at higher temperatures (120 °C, entry 5) afforded the best conversion yet and produced **4.19** as the major product, for the first time, in 55% yield. Using 50 mol% DBU (entry 6) produced similar results. As the reaction time became a limiting factor for throughput, a microwave (μ W) reactor was used to speed up this reaction. In entries 7 and 8, the reaction time was drastically lowered by running the reaction at 140 °C in the reactor, offering similar yields and quasi-complete conversion. Bringing the temperature up to 150 °C completely degraded any substrate or products (entry 9), and so, a hard ceiling of 140 °C was kept. To play it safe when scaling up, the next reactions were run at a maximum of 130 °C, and doing so on a slightly larger scale (22 mg, entry 10) fully converted **4.6** and gave **4.19** in 55% yield. Scaling up even more (125 mg, entry 11) gave

Table 4.1. Deconjugation of **4.6** using the DBU/MeOH system,

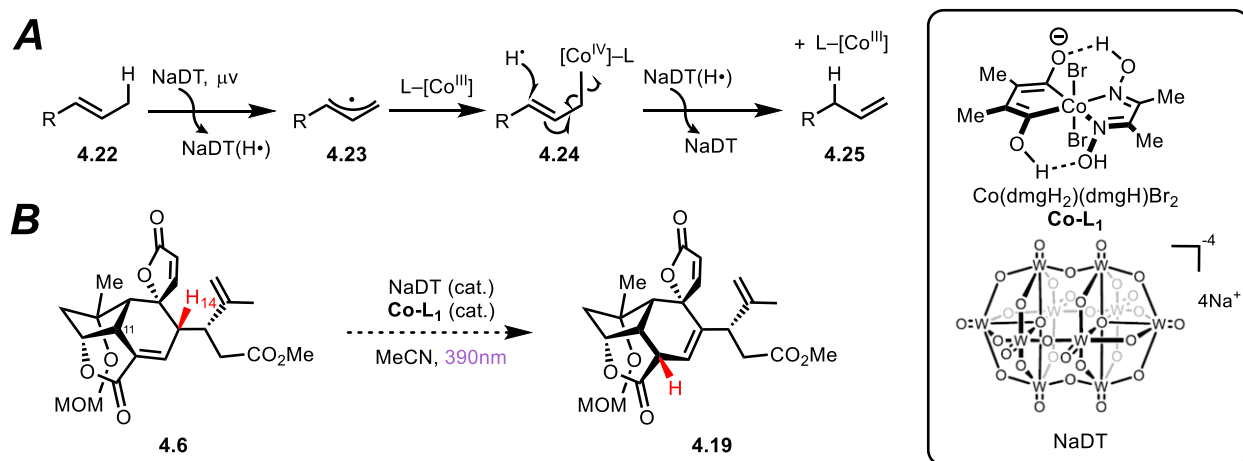
Entry ^a	Conditions	Conversion ^b	Ratio 4.19 : 4.20 : 4.21 ^b
1	DBU (20 mol%), 70 °C, 40 h	54%	15 : 43 : 33
2	DBU (10 mol%), 90 °C, 5 d	57%	20 : 47 : 33
3	DBU (50 mol%), 90 °C, 40 h	78 %	32 : 18 : 52
4 ^c	DBU (80 mol%), 90 °C, 40 h	100 %	05 : 08 : 00
5	DBU (10 mol%), 120 °C, 5 d	100 %	56 : 00 : 44
6	DBU (50 mol%), 120 °C, 5 d	100 %	50 : 00 : 50
7	DBU (10 mol%), 140 °C, 3 h (μW)	70 %	39 : 14 : 47
8	DBU (10 mol%), 140 °C, 7 h (μW)	84 %	46 : 00 : 54
9 ^c	DBU (10 mol%), 150 °C, 3 h (μW)	100%	00 : 00 : 00
10^d	DBU (10 mol%), 130 °C, 8 h (μW)	100 %	55 : 00 : 45
11 ^c	DBU (10 mol%), 130 °C, 8 h (μW)	100 %	49: 00 : 51

^aRan on 5mg (0.012 mmol) scale. ^bDetermined by ¹H NMR analysis of the reaction crude. ^cDecomposition observed. ^d22 mg scale (29% isolated yield). ^e125 mg scale (13% isolated yield).

rise to **4.19** and **4.21** in a quasi-equipolar ratio (49:51). Interestingly, even as ¹H NMR confirmed an acceptable presence of **4.19** in the reaction mixture, only very low amounts of product could be isolated, which can perhaps be explained due to the instability of **4.19** on silica gel. Another practical problem was the hard SFC purification of these three products : all products and byproducts had near-identical polarity on silica gel, and purification was laborious and never offered a perfect separation, as the only eluent system that did not trail or crash the products was MeOH/CH₂Cl₂. With this result in hand, other systems were explored, as perhaps they might offer a cleaner practical access to **4.19**.

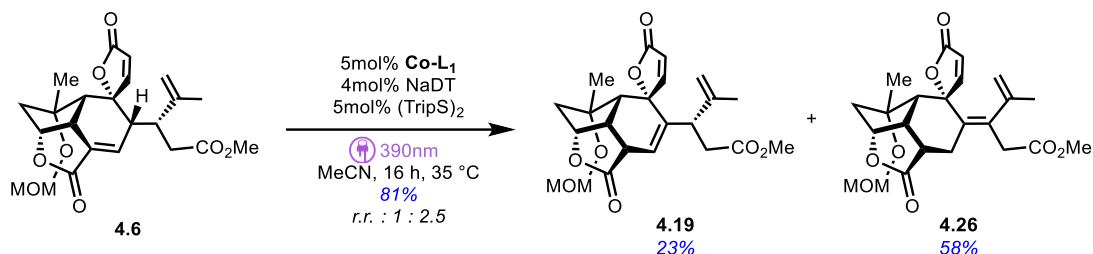
4.2.4 – Alkene deconjugation using photochemistry and the total synthesis of (+)-anhydrohavellockate.

While the previous efforts were underway, a conversation with a colleague revealed that using newly developed radical chemistry might be the way to effectively shift the alkene from Δ^{12-13} to Δ^{13-14} . Chemistry developed by the Wendlandt research group studied the *contra*-thermodynamic positional isomerisation of alkenes using a dual cobalt/sodium decatungstate (NaDT) catalytic system under photochemical conditions.⁶ This methodology describes the isomerisation of unactivated alkenes, but also the isomerisation of enones away from conjugation, which was highly promising as a methodology offered an answer to the deconjugation of **3.53**. The mechanism of this transformation (Scheme 4.11, A) is proposed to undergo through the abstraction of allylic hydrogen of **4.22** to generate an allylic radical **4.23**, which undergoes capture using a Co^{III} metal species at the least hindered position, affording allylcobalt species **4.24**. This species is proposed to undergo a regiospecific bimolecular homolytic substitution ($\text{S}_{\text{H}}2'$) using hydrogen radical ($\text{H}^\bullet$) to afford a formally isomerized product **4.25**. This methodology, if no compatibility problems would be posed by our substrate, would be ideal, as the only other alkene moiety was terminal and the spirolactone's π system does not possess a γ hydrogen atom, and as such, H_{14} was thought to be the sole reaction site (Scheme 4.11, B). The allylic hydrogen H_{11} was not initially a cause for concern, as it was thought that shifting the alkene at that position would generate a highly strained tetrasubstituted alkene. In this methodology, $(\text{TripS})_2$ is used as a hydrogen atom transfer



Scheme 4.11. (A) Mechanism of the NaDT/Co catalyzed alkene isomerization and (B) application to this synthesis.

(HAT) agent and is not always required, as per the report. As such, both NaDT and Co(dmgh)(dmgh₂)Br₂ (**Co-L₁**) were synthesized in-house and the photocatalyzed isomerisation was attempted on **4.5** but gave only full decomposition of the substrate. When attempted on **4.6** however, isomerisation products **4.19** and **4.26** could be observed in 81% yield of combined isomers (Scheme 4.12). These two regioisomers very were hard to purify by preparative TLC, even many elutions of a preparative TLC plate, and as such, they would be carried forward as a mixture.



Scheme 4.12. Photochemical $\Delta^{12-13} - \Delta^{13-14}$ alkene isomerization of **4.6**.

After observing reactivity by using **Co-L₁**, a short literature survey highlighted research by the Leonori group, who measured the reduction potential of the cobalt-ligand complexes during these reactions and the latter had an effect on the ratio of products observed in halogen-atom transfer chemistry.⁷ As such, a variety of ligands were synthesized⁷ and applied in the photochemical deconjugation chemistry of **4.6** (Figure 4.3).

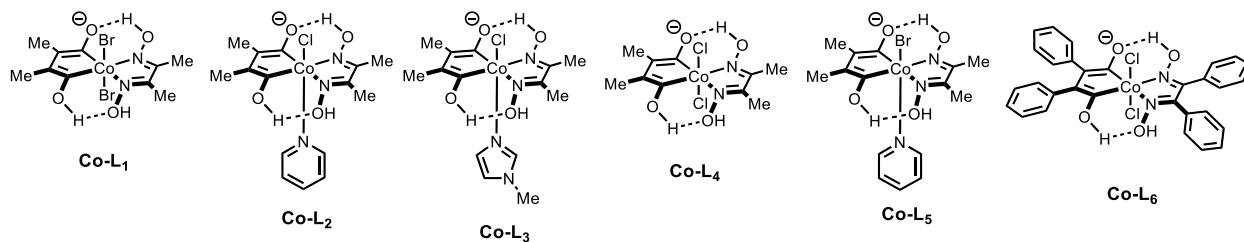


Figure 4.3. Synthesized ligands used in the photochemical deconjugation reaction of **4.6**.

The major byproduct of this reaction, **4.26**, was thought to arise from the uncontrolled over-isomerisation of **4.6**, contained a doubly allylic proton at C₁, which was thought to have a then lower bond dissociation energy (BDE), which could re-engage in the mechanism proposed above. This parasitic pathway would need to be controlled should this chemistry be used further, as it ablates the stereochemical information at C₁ and is a chemical dead-end. To obtain a better yield of **4.19**, an optimization of this chemistry was completed (Table 4.2).

Table 4.2. Optimisation of the photochemical isomerisation of **4.26**.

Entry ^a	Deviation from std. conditions	Isolated yield (Σ of isomers)	Ratio 4.19 : 4.26 ^b
1	None	81 %	1 : 2.5
2	Co-L₂ instead of Co-L₁	<i>N/A</i>	Complex mixture ^c
3	Co-L₃ instead of Co-L₁	<i>N/A</i>	Complex mixture ^c
4	Co-L₄ instead of Co-L₁	<i>N/A</i>	Complex mixture ^c
5	Co-L₅ instead of Co-L₁	71 %	1 : 2.6
6	Co-L₆ instead of Co-L₁	78 %	Complex mixture ^c
7	No (TripS) ₂	70 %	1 : 2.9
8	TBADT instead of NaDT	85 %	1 : 3.9
9 ^d	1% Co-L₁	15 %	1 : 1
10	20% Co-L₁	70 %	1.3 : 1
11	30% Co-L₁ , 60 ° C	84%	1.4 : 1
12	40% Co-L₁, 60 °C	96 %	1.6 : 1
13 ^e	40% Co-L ₁ , 60 °C	46 %	1.3 : 1

^aRan on 5mg (0.012 mmol) scale. ^bDetermined by ¹H NMR analysis of the isolated, inseparable products. ^cOver 4 products observed by ¹H NMR of reaction crude. ^dIncomplete (40%) conversion. ^e50mg scale.

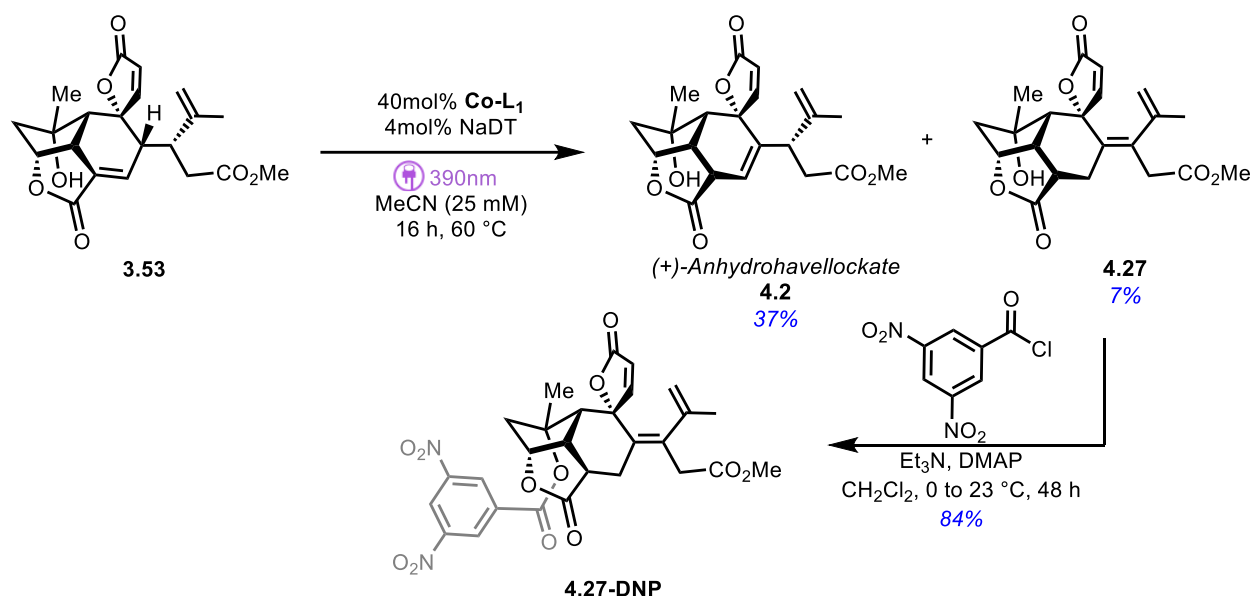
To try to optimize the ratio between **4.19** and **4.26**, the first deviation from the initial conditions found was the nature of the cobalt-ligand **Co-L₁**. The first three metal-ligand complexes to get tested in this reaction, **Co-L₂**, **Co-L₃** and **Co-L₄** (entries 2–4) returned over 4 different products as a complex, inseparable mixture, and were not studied further. However, using **Co-L₅** (entry 5) afforded a similar ratio of **4.19** & **4.26** in a slightly lower yield than the initial conditions. Using **Co-L₆** (entry 6) returned a complex mixture of products, same as entries 2–4. As varying the ligand did not impact the reaction much, an optimization study was completed, and individual reagents were taken out one by one. Entry 7 is such an attempt, where the HAT agent (TripS)₂ was removed, the reaction also proceeded in similar yield and ratio, continuing on what the authors addressed in their initial report : “*For many substrates, the addition of (TripS)₂ was found to be unnecessary, in which case this additive could be omitted without negative impact on the reaction outcome*”.⁶ Removing either **Co-L₁** or NaDT failed to yield any desired products in the reaction (*not shown*). Switching the homemade NaDT for the commercially available tetrabutylammonium

decatungstate (TBADT) worsened the ratio of **4.19** : **4.26** in a nearly identical overall isolated yield (entry 8). The biggest breakthrough was then the amount of **Co-L1** participating in the reaction was changed. By lowering the amount of **Co-L1** in solution to 1 mol% (entry 9), an incomplete conversion was observed after 16 h. However, 20 mol% **Co-L1** (entry 10) afforded the first favorable ratio of **4.19** : **4.26** in 70% total yield. Bringing this **Co-L1** loading to 30% or 40% (entries 11-12) at higher temperatures² gave better yields, and the best performing conditions were found in entry 12 of this table, with an isolated yield for **4.16** of 59%, as an inseparable mixture with **4.26**.

A now efficient pathway to **4.19** was developed. Upon scale up to 50 mg (entry 13), however, the yield plummeted and a lower ratio of 1.3 : 1 of **4.19** : **4.26** was observed. This conclusion was made over several attempts to scale up this chemistry. It is also important to note that this reaction was hardly scalable above 10 mg, and was hardly reproducible in most cases, as the maximal allowed scale to afford a somewhat reproducible yield for this reaction was 10 mg. Weighing the reagents on this scale also required milligram or sub milligram quantities, and as such, scale precision and user error gave high variations in yield from experiment to experiment when these 10 mg reactions were run in parallel. This synthetic methodology, although new at the time, paved an access to **4.19** that was reproducible on < 10 mg scale, although it could not be separated from **4.26** on larger scales, where preparative TLC purifications would be impractical. AgNO₃-impregnated silica gel also failed to properly separate the mixture of isomers **4.19** and **4.26**.

In parallel, a similar optimisation (*not shown*) was completed on **3.53**, as free alcohols have shown that did not impact the photochemical isomerisation in the initial report.⁶ After 30 deviations of the standard conditions that have been tested with similar to the ones seen in table 4.2, the best yield observed for **4.2** (anhydrohavellockate) was 37% along with 7% for **4.27** (Scheme 4.13). The application of this chemistry on the protecting group-free substrate also suffered from scalability problems, reactions with over 10 mg gave overall lower yields but had the distinct advantage that **4.2** and **4.27** were now separable by SFC. This application was not tolerant of (TripS)₂, where its use decomposed the starting material. Multiple attempts failed to yield crystals suitable for XRD. The derivatization of **4.27** to its dinitrobenzoate derivative **4.27-DNP** also suffered the same fate.

² These two experiments were run in parallel, and the cooling fans were not turned on due to forgetfulness on a late evening and serendipitously gave a better yield of **4.19**.



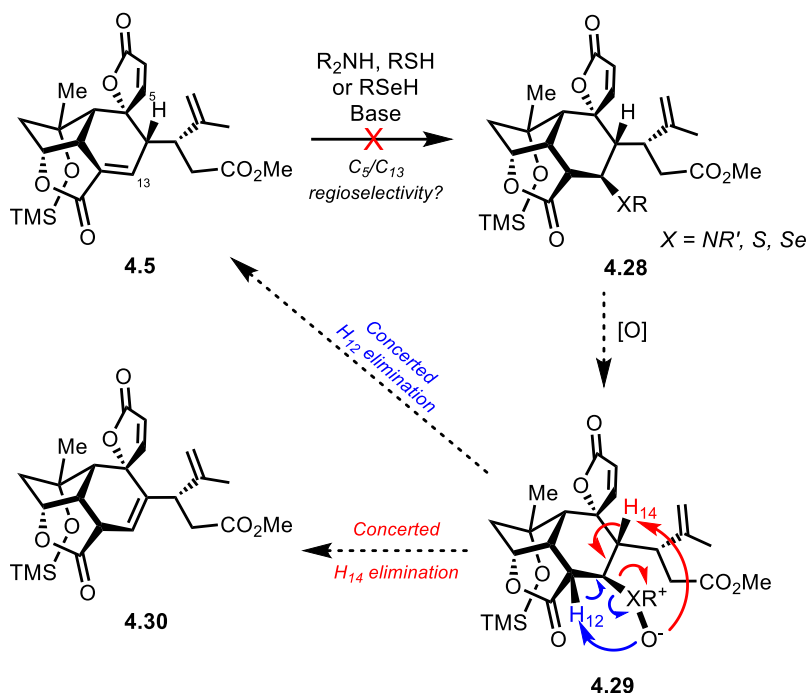
Scheme 4.13. Total synthesis of (+)-anhydrohavellockate (4.2).

4.2.5 – Deconjugation through a Grieco or Cope elimination.

As other nucleophiles failed to undergo the desired conjugate addition, more simple nucleophiles capable of Michael addition were studied. Indeed, it was thought that the conjugate addition of nucleophiles capable of being oxidized to their oxides could then be used to undergo a concerted Grieco⁸ (for sulfur and selenium) or Cope⁹ (for nitrogen) eliminations (Scheme 4.14). In this methodology, a C₅ conjugate addition was unwanted, but if the addition could be completed selectively at C₁₃, the addition on 4.5 would be stereoselective and from the convex β face, affording adduct 4.28. The oxidation of this heteroatom to its oxide could provide 4.29, which itself had access to two protons, H₄ and H₁₂. A concerted elimination (*in red*) of H₁₄ would give the wanted regioisomer 4.30. If 4.29 could be accessed, H₁₂ could also be eliminated (*in blue*) as it is also on the same face of the oxide, in agreement with concerted elimination requirements, and would regenerate 4.5. The pathway back to 4.5 was anticipated to happen in higher proportions, as H₁₂ is more acidic and thus possesses a weaker bond, promoting a lower energy pathway.

In agreement with this proposition, 4.5 was exposed to thiols, selenols and amines bearing alkyl or aryl substituents in presence of bases. Unfortunately, no conjugate addition products were ever observed after two dozen attempts, even at high temperatures and with 10 equivalents of thiol/amines/selenols were used. These negative results strongly reinforced the fact that these two

enones systems do not behave like traditional Michael addition systems. To complement the now developed pathways to **4.19**, other chemistry was explored. The same conclusion was reached when **4.6** was used, as no addition products were ever observed at either C₅ or C₁₃. Again, this substrate proved how difficult it would be to functionalize in late-stages. Still, now equipped with less-than-ideal conditions to afford the alkene-shifted substrate, the search for a more efficient pathway to **4.19** or **4.30** were stopped and the last transformation was attempted.



Scheme 4.14. Failed Michael addition towards a Grieco or Cope elimination.

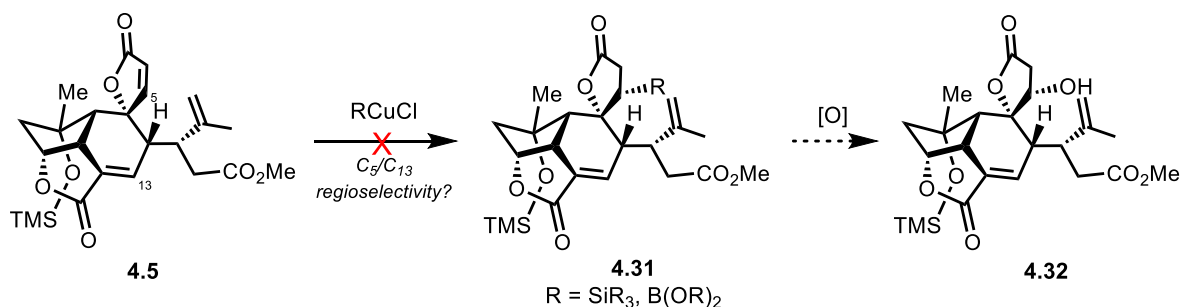
4.3 – Introduction of the oxygen atom at the C₅ position.

4.3.1 – Conjugate additions.

With a synthetic access to **4.19**, even though it could not be separated from the byproduct **4.26**, the installation of the oxygen at C₅, could finally be studied. In the initial retrosynthetic analysis (Scheme 2.2), this operation was planned to be completed through a conjugate addition of a silicon or boron cuprate reagent to **4.5** to give **4.31**, that could be chemically transformed into **4.32** using oxidative conditions such as the Tamao-Fleming oxidation (Scheme 4.15). This chemistry was tested on the conjugated substrate **4.5**, as it was less precious and available in larger quantities, and was thought to mimic the reactivity of **4.19** as their chemical composition is nearly

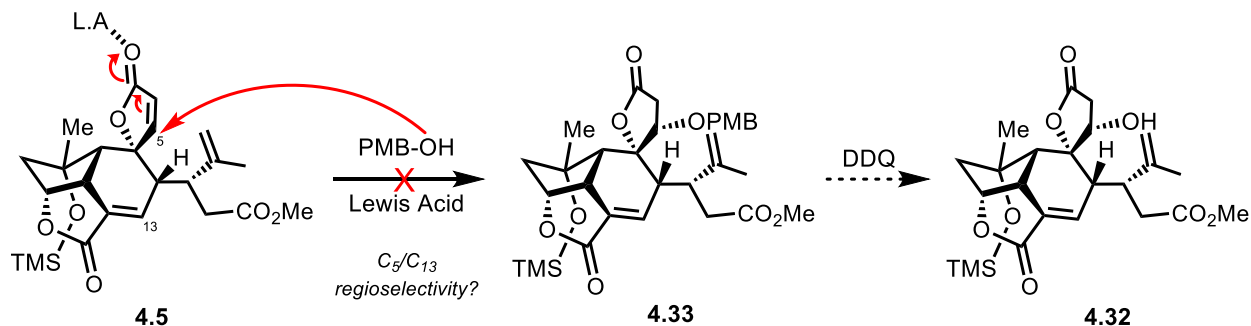
identical, though a small conformation change existed between the two, which could slightly affect their reactivity.

The difficulty in derivatizing the tetracyclic structure was confirmed when attempts at affecting a conjugate addition of boron cuprate reagents to **4.5** using either phosphine^{10–13} or *N*-heterocyclic carbene (NHC) ligands¹⁴ also failed to yield any conversion of the starting material. The same conclusions were drawn using OMOM protected **4.6** or using the unprotected precursor **3.53** as a substrate.



Scheme 4.15. Attempted oxidation of C₅ through conjugate addition & oxidation.

These conjugated π systems are also known to be electrophilic towards alcohols themselves, often through carbonyl activation using Lewis acids. Another strategy to introduce the oxygen atom at C₅ was through the addition of an alcohol nucleophile & removal of its carbon backbone after the addition. Addition of benzyl alcohol or 4-methoxybenzyl alcohol to **4.5** could give rise to **4.33**, then the benzyl group could either be removed through oxidative or dealkylative means to afford **4.32** (Scheme 4.16). This strategy, though straightforward, risked to transesterify of the many ester moieties found on this molecule, but was still attempted. Many protocols descri-

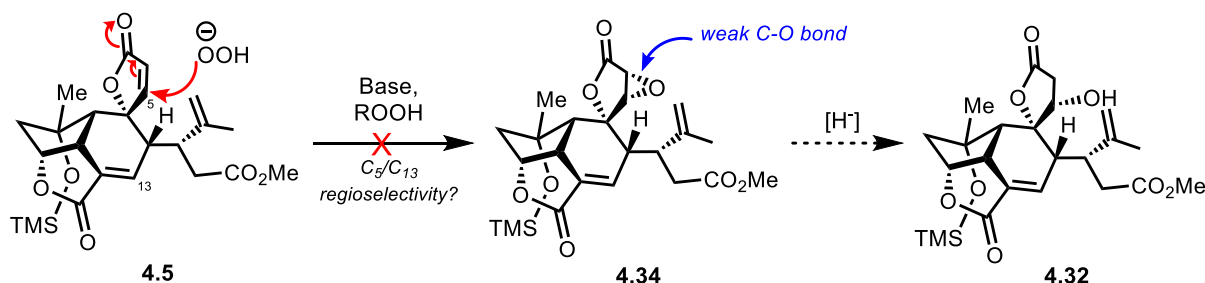


Scheme 4.16. Planned nucleophilic addition of PMB alcohol & oxidative cleavage to give **4.32**.

bed this reaction in the literature, using PMB alcohol as a nucleophile, either with¹⁵ or without¹⁶ Lewis acid activation of the carbonyl. All of the known base-catalyzed^{17–19} or acid-based²⁰ protocols of an oxa-Michael addition of PMB alcohol failed to transform **4.5** (or its MOM protected congener **4.6**) into β -alkoxy species **4.33**. These constant roadblocks were telling us that the spirolactone α,β -unsaturated system was highly unreactive and a clever solution was needed.

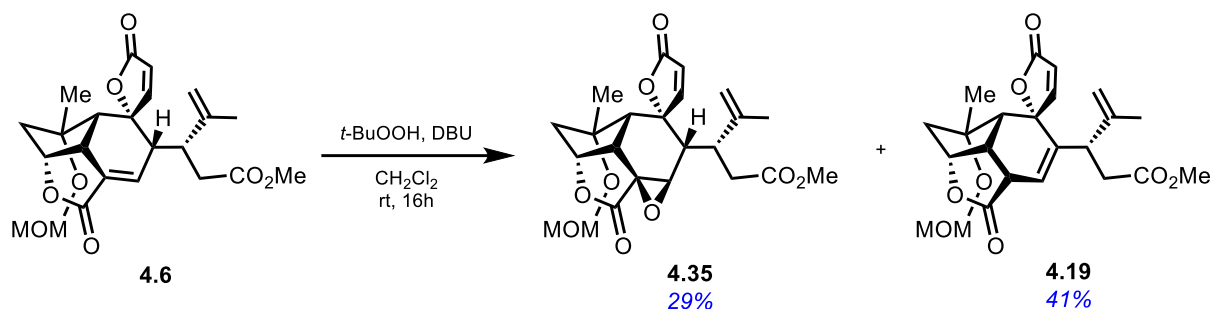
4.3.2 – Nucleophilic Weitz-Scheffer epoxidation.

Another access to C₅-oxidized substrates was thought to happen using a nucleophilic Weitz-Scheffer epoxidation.²¹ Exposing **4.5** to these reaction conditions could afford epoxide **4.34**, which would be followed by a reduction at α to afford β -hydroxy **4.32**. α - β Epoxycarbonyl species can undergo preferential reductive cleavage of the α -C-O bond because the adjacent carbonyl can better stabilize radical or anionic intermediates formed during the bond cleavage event, resulting in high site selectivity and affording β -hydroxycarbonyl species (Scheme 4.17)^{22–24}.



Scheme 4.17. Planned oxidation of C₅ through nucleophilic epoxidation / reduction.

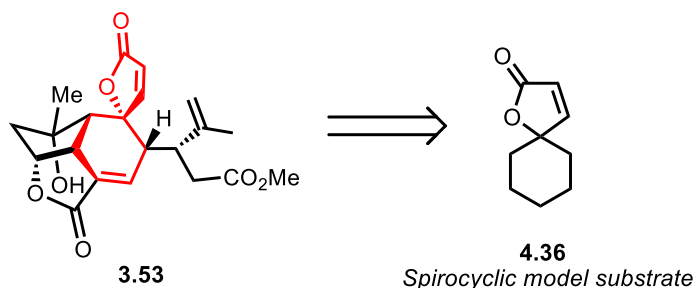
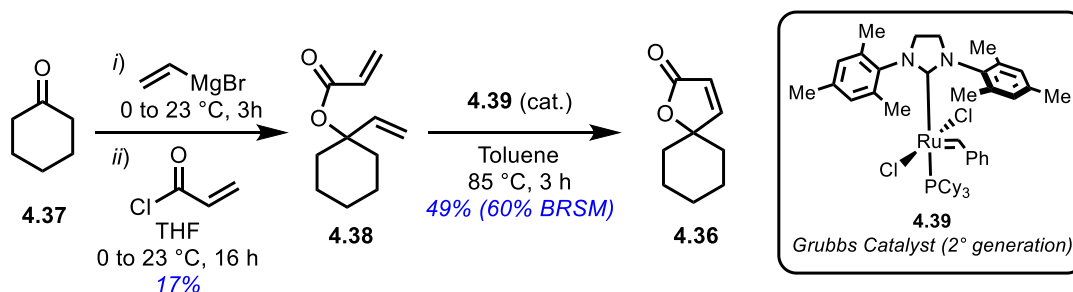
As such, multiple attempts at epoxidation were first probed using multiple different oxygen peroxides and bases used for this reaction. Unfortunately, over 30 attempts of these conditions on **4.5** (or its MOM protected congener **4.6**) failed to yield epoxide **3.34** through different combinations of known conditions used in natural product synthesis^{25–33} and mix-matched conditions using NaOCl, H₂O₂, *t*-BuOOH, CumylOOH or TrtOOH as oxygen sources and pyridine, TBAOH, Triton B (Me₃BnN⁺OH⁻), DBU or NaOH as bases. These reaction conditions returned either only the starting material or degraded the substrate when alkali protic conditions were used. Interestingly, a single condition using **4.6** was able to give any epoxidation product, which happened at C₁₂-C₁₃ by using *t*BuOOH and DBU. These conditions not only afforded epoxide **4.35** in 29% but also returned deconjugated product **4.19** as the major product in 41% yield (scheme **4.18**).



Scheme 4.18. Synthesis of epoxide **4.35** & unexpected obtention of **4.19**.

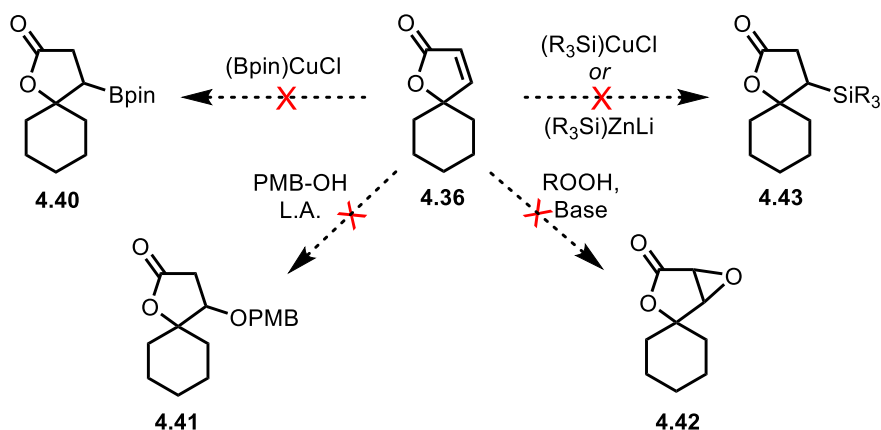
4.4 – Synthesis of a model system.

While these efforts at effectively derivatizing **3.53** and its C₈-protected variants were undergoing were consuming large quantities of the late-stage materials, and a constant batch-up was almost always running in the background while frontline material was used. While faced with this roadblock, where **3.53** was found to be mostly unreactive and to preserve late-stage material, the synthesis of a model system representing the C and D cycle of the natural product was undertaken. This model system would allow to test the reactivity of this spiro lactone system towards the C₅-oxidation of **3.53** and remove any chemical moieties and excessive steric bulk found on **3.53** in order to better test the feasibility of these oxidation reactions. The spirocyclic lactone **4.36** (Scheme 4.19, A) was thus targeted. This chemical entity was made much simpler and could be accessed in a handful of chemical transformations (Scheme 4.19, B). First, cyclohexanone **4.37** was treated with vinylmagnesium bromide, and after being formed, the corresponding alkoxide was treated with acryloyl chloride overnight to afford **4.38** in 17%. The low yield observed for this product can be explained by expedient two bond-forming reactions being done in the same pot. Since throughput was emphasized, yield wasn't the focus, and the latter could be ran on large scale using readily available and low-costing reagents. This substrate was then engaged in an RCM reaction using catalyst **4.39** to afford enone **4.36** in 49% yield. As an access to model system for **3.53** was now available, it was exploited to try to affect all the transformations seen in chapter 4 so far (Scheme 4.20). Also, since **4.36** was available in 2 steps (instead of 11 steps for **4.5**), reactions could be ran on larger scales, making reagent preparation more practical than when reactions needed to be ran on μmol scale. Alas, even with a much smaller substrate where general steric hinderance was lowered or the other functional groups

A**B**

Scheme 4.19. Identification (A) and synthesis (B) of a model system of **3.53**.

were ablated, no productive reactivity was observed in the conjugate boron addition (towards **4.40**), conjugate alcohol addition (towards **4.41**), Weitz-Scheffer epoxidation (towards **4.42**) or silyl cuprate/zincate³⁴ addition (towards **4.43**). In light of these results, it is easy to observe that this α,β unsaturated system is very inert, and that a late-stage introduction of a nucleophile at this position would be arduous, so other strategies would be needed to accomplish this reaction.

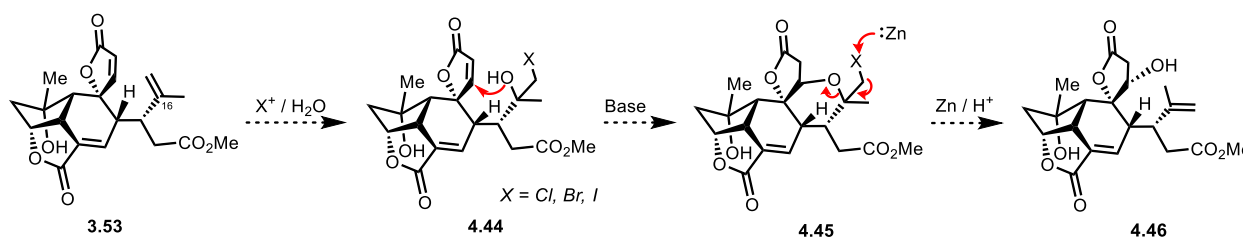


Scheme 4.20. Failed oxygen installation on α,β -unsaturated spiro lactone **4.36**.

4.5 – Intramolecular assistance in the functionalization at C₅.

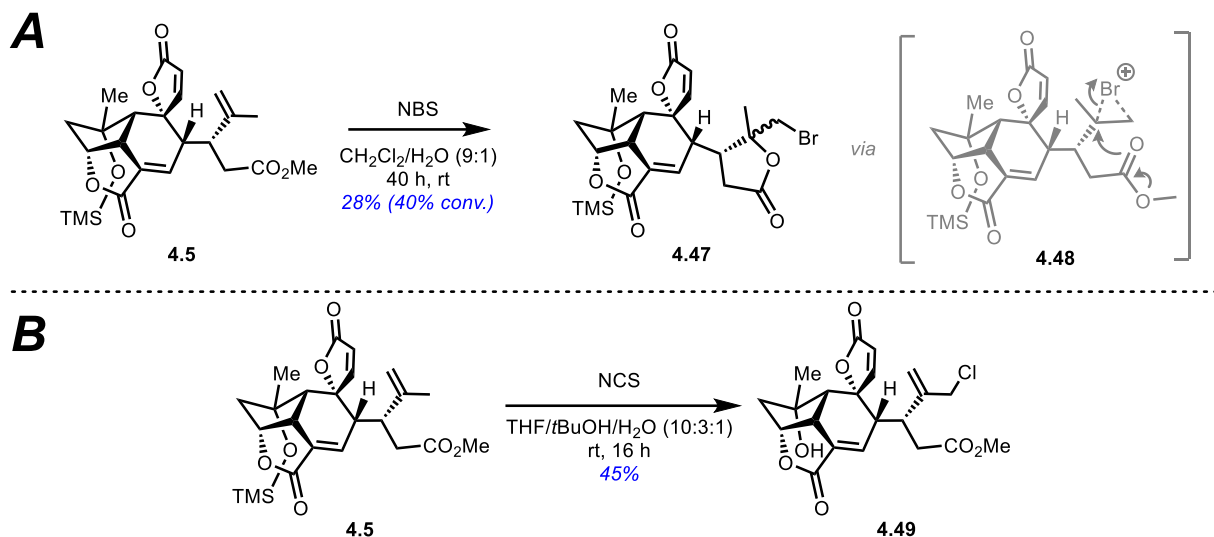
Earlier, in the attempts at deconjugation, it was observed that C₅ indeed acted as an electrophile, but only in intramolecular additions (Schemes 4.3 and 4.5). Taking this into consideration, it was considered that installing an oxygen at this position could be completed through an intramolecular delivery. Fortunately, the *iso*-propenyl moiety on the eastern ester sidechain possessed a reactive site that would be able to provide reactivity to first install this oxygen atom. This moiety would need to be functionalized twice, as only adding a single oxygen atom that would undergo the conjugate addition would leave no possibility to regenerate the alkene functional group after the fact.

This strategy would rely on the derivatization of **3.53** by exposing it latter to a halogen source in aqueous media to afford halohydrin **4.44** (Scheme 4.21). This regioselective reaction would install the oxygen at C₁₆ and also generate a C-X bond that would be prime to undergo elimination. This halohydrin could then putatively engage in a base-mediated oxa-Michael addition to afford ether **4.45**. The treatment of the latter with Zn/AcOH could then break the ether bond and regenerate the alkene moiety and give **4.46**. This strategy was used multiple times in the context of total synthesis of natural products and would be viable in these efforts.^{35–40}



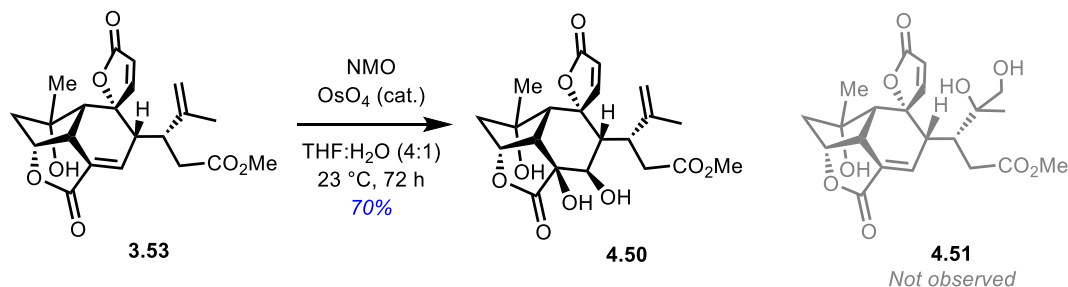
Scheme 4.21. Proposed intramolecular installation of the C₅ oxygen via halohydrins.

As such, **4.5** was exposed to *N*-bromosuccinimide (NBS) in H₂O-saturated CH₂Cl₂ or THF (Scheme 4.22, A). Surprisingly, the desired halohydrin **4.44** could not be observed, as only the lactone **4.47** was recovered in 28% yield after 40% conversion. This product is proposed to be formed by the intramolecular trapping of bromonium **4.48** by the appendant ester, affording a formally demethylated product and a new lactone moiety. The attempts at synthesizing the chlorohydrin derivative using *N*-chlorosuccinimide (NCS) were also met with failure, as treatment in similar conditions only afforded α -chlorinated alkene **4.49** in 45% from **4.5**. (Scheme 4.22, B)



Scheme 4.22. Attempts at obtaining bromohydrin (A) and chlorohydrin (B) derivatives of **4.5**.

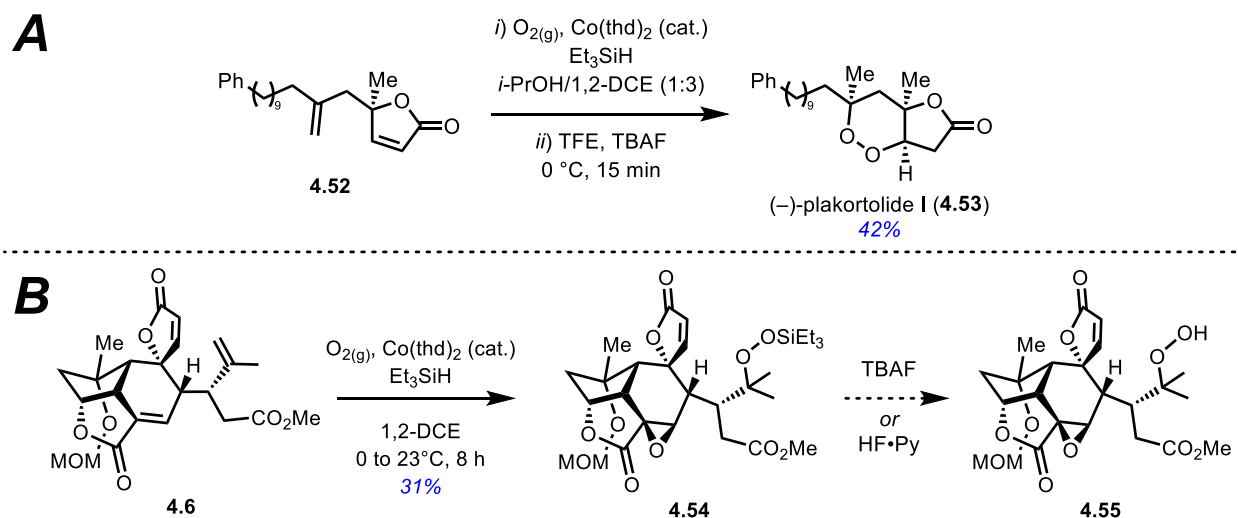
As an access to the halohydrin **4.44** failed, other difunctionalization of **3.53**'s Δ^{15-16} alkene was attempted in the form of a dihydroxylation (Scheme 4.23). This reaction would also install two reactive sites, one of which could be used in the nucleophilic attack, and the other for the elimination. As such, **3.53** was exposed to asymmetric dihydroxylation mix (AD-mix)³ α or β but failed to yield any products. Then, Ley oxidation conditions using catalytic OsO₄ and *N*-methylmorpholine *N*-oxide (NMO) was able to deliver a dihydroxylation product in high yield (Scheme 4.23). After a thorough 2D NMR analysis, it was revealed that the alkene that had reacted, surprisingly, was the Δ^{12-13} alkene, leaving the Δ^{15-16} alkene untouched and failing to deliver the desired diol **4.51**. This was highly surprising, but at the same time, not so much, as Δ^{12-13} continuously failed to behave as an enone, and this example clearly showed how reactive it was towards electrophiles, perhaps due to the strain energy of the ABC tricyclic system found in **3.53**.



Scheme 4.23. Obtained and anticipated dihydroxylation products of **3.53**.

³ Commercially available mixtures of reagents used for the Sharpless asymmetric dihydroxylation reaction.

Also, in the same line of ideas, the Δ^{15-16} alkene could be used as an anchor to install a peroxide moiety to effect an intramolecular oxa-Michael addition. A very similar strategy was used in the total synthesis of endoperoxide-containing plakortolide natural products by the Christmann group. In the last step of their synthesis, a Markovnikov hydroperoxidation of alkene **4.52** afforded the corresponding peroxide, which after *in situ* desilylation, underwent an oxa-Michael reaction to furnish the natural product plakortolide I (**4.53**) in 42% (Scheme 4.24, A). This protocol could be applied to this synthetic challenge, if a formation of a 7-member endoperoxide would be entropically favored. The breaking of this weak endoperoxide O-O bond would then have stereoselectively installed the oxygen at C₅, while leaving a tertiary alcohol that could eliminate



Scheme 4.24. (A) Endoperoxide formation via oxa-Michael addition in the synthesis of (–)-plakortolide I **4.53** and (B) application to this synthesis.

to regenerate the Δ^{15-16} alkene. As such, the reported conditions were attempted on substrate **4.6**, which returned epoxyperoxide **4.54** in 31% yield (Scheme 4.24, B). Surprisingly, the Δ^{12-13} alkene also reacted to afford the corresponding epoxide. Submitting this substrate to fluorine sources (TBAF, HF·Py) failed to afford free peroxide **4.55** or any detectable oxa-Michael reaction products. Perhaps, more experimentations to generate a free peroxide, without the use of Et₃SiH would be the key to attempting the desired oxa-Michael reaction. The 7-*endo*-dig cyclization of a peroxide onto an enone acceptor is widely reported and was used extensively in the synthesis of derivatives of artemisinin.^{41–45}

4.6 – Conclusion.

Several late-stage transformations were attempted on the tetracyclic structure **3.53**, which had all the carbon atoms installed stereoselectively. Ultimately, a direct access to anhydrohavellockate (**4.2**) was developed through studying multiple strategies to accomplish the Δ^{12-13} to Δ^{13-14} alkene shift, but suffered scalability or purification issues, making its practical access difficult. Accompanied by these efforts were multiple attempts and strategies for the stereospecific installation of the last remaining oxygen atom at C₅, all of which failed. Several fascinating challenges were faced during the endgame of this synthesis, mostly brought forward by the bulky substrate, the presence of multiple competing functional groups and the low reactivity of the spirocyclic α - β unsaturated lactone moiety.

This synthetic endeavor has brought forward multiple new concepts, such as the development of a 5-in-1 reaction cascade to access the core of the natural product. Such reactivity had never been observed, to the best of our knowledge, and will contribute as a great foundation for the total synthesis of multiple natural products of the cembranoid and norcembranoid family.

When a synthetic route is planned on paper, it hardly goes according to plan, and it is up to the chemist to adapt to the conclusions of his experimentations. In this case, a lot was learned, and completing the total synthesis of (+)-havellockate (**1.17**) was the initial goal, which seemed like looking up at a mountain at the time. After years of carving this chemistry, it is important to reflect on the progress made, the science developed and the lessons were learned. We are confident that havellockate, and multiple other natural products of this family, will succumb to total synthesis in the future using this chemistry. While this monograph does not describe the completion of this natural product, the sum of achievements herein laid a very strong groundwork required for its completion in a very efficient and scalable manner.

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CONTRIBUTIONS TO KNOWLEDGE

1. A spectacular reaction cascade consisting of a Sonogashira cross-coupling / 5-*exo-dig* cyclization / Inverse demand Diels-Alder reaction cascade was discovered. This reaction was observed when the monocyclic substrate **2.62** and iodoacrylic acid **2.63** reacted together to serendipitously yield the tetracyclic core of havellockate **2.65** in racemic form.
2. A convergent enantioselective synthesis of the cascade precursor **α -3.28** enabled the study of this cascade, revealing that the protection group strategy enabled a precise stereo control of the critical Diels-Alder reaction. It was discovered that the PMB protected substrate **α -3.28** lead only to the *endo* adduct, while the unprotected substrate **3.54** lead to the *endo* adduct followed by a thermal isomerisation to the *exo* adduct. This reagent-controlled cascade enables the divergent synthesis of the polycyclic core of multiple other *Cembranoid* natural products such as mandapamate, plumarellide and confertdiolate.

An optimised synthetic pathway enabled a gram-scale synthesis of the tetracyclic core of (+)-havellockate **3.53** in 10 steps and 3.7% overall yield in the longest linear sequence from TMS acetylene and could deliver **3.53** on gram scale.

3. Multiple protocols were studied for the selective Δ^{12-13} to Δ^{13-14} alkene migration, ultimately settling on photochemical conditions that delivered (+)-anhydrohavellockate **4.2**. Multiple hundreds of attempts at hydration of the C₅ position of **4.2** to obtain the natural product (+)-havellockate were unsuccessful.

CONTRIBUTORS

DFT calculations to understand the fundamental states of molecules involved in this project were graciously completed by Lucas Facurri Villela and Joshua Tapp. The talented undergraduate students Awa Ndiaye, Ève Bergeron and Eleni Karaiskos worked on the development of side-routes that were ultimately not included in this thesis. Elliott Jackson was a skillful summer student that helped the development a protecting group-free strategy, as seen in section **3.3.4**.

CHAPTER 5

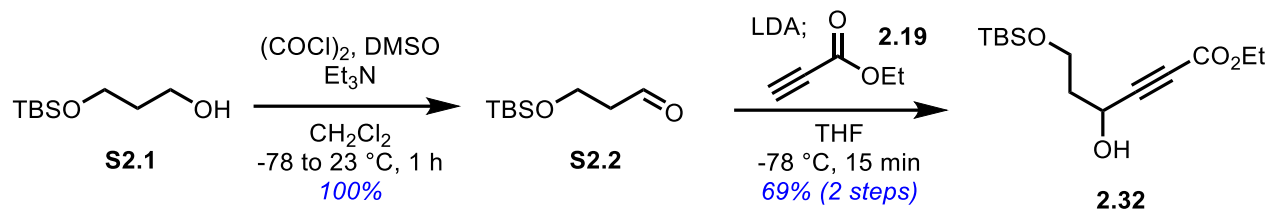
Experimental section

General information

All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Diisopropylamine (DIPA) was distilled over CaH_2 and stored over flame dried 3 Å molecular sieves (1-2 mm beads) under argon atmosphere. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene and methanol (MeOH) were prepared by storing over flame dried 3 Å molecular sieves (1-2mm beads) under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates (SiliaPlate TLC Plates, Aluminium-Backed, Silica, 200 μm , F254) were viewed under UV light and stained with potassium permanganate or *p*-anisalehyde staining solution. Silica flash chromatography was carried out with silica gel 60 (230-400 mesh, Silicycle Inc.). Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker Avance 300 MHz, Bruker Avance II 400 MHz, and Bruker Avance III 600 MHz spectrometers. NMR samples were dissolved in deuterated chloroform (CDCl_3) or benzene (C_6D_6) and chemical shifts are reported in ppm referenced to the solvent residual peak (Chloroform: 7.26 ppm; Benzene: 7.16 ppm). Data are reported as follows: chemical shift, multiplicity, coupling, integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 75 MHz, 101 MHz or 151 MHz. Chemical shifts are reported in ppm referenced to the solvent residual peak (Chloroform: 77.16 ppm; Benzene: 128.06 ppm). IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond attenuated total reflectance (ATR) module. HRMS were obtained on a Kratos Analytical Concept-Magnetic Sector Electron Impact Mass Spectrometer instrument and Micromass Q-TOF I – TOF Electrospray Ionisation mass spectrometer (University of Ottawa Mass Spectrometry Centre). Melting points were determined with a Gallenkamp Melting Point Apparatus. Optical rotations were measured using an Anton Paar MCP500 polarimeter using $\lambda=589$ nm emission light at 24 °C in a 0.1 dm path length cell.

NOTE : ^{13}C NMR spectra taken on the Bruker Avance III 600 MHz spectrometer often displayed an artifact peak at 105 ppm, which can be attributed to impurity in the spectrometer probe or hardware defect and could not be removed. The artifact was identified in all spectra recorded on this instrument.

Ethyl 6-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyhex-2-ynoate (**2.32**).



OTBS alcohol **S2.1** was prepared according to a known procedure in 100% yield in 1 step from propane-1,3-diol **2.31**.¹ A 500 mL round bottom flask was charged with a stir bar, oxalyl chloride (2.48 mL, 28.9 mmol, 1.10 eq.), dry CH₂Cl₂ (130 mL). This solution was cooled to -78 °C under Ar_(g) before DMSO (4.10 mL, 57.8 mmol, 2.20 eq.) was added dropwise over 5 min. The solution was stirred at -78 °C for 10 min. A solution of alcohol **S2.1** (5.0 g, 26.3 mmol, 1.00 eq.) in CH₂Cl₂ (20 mL) was then added dropwise, and the reaction was stirred at -78 °C for 1 h. Triethylamine (18.3 mL, 131 mmol, 5.0 eq.) was then added dropwise over 10 min, and the reaction mixture was maintained at -78 °C for 10 min before being warmed to room temperature over 1 h. The resulting thick slurry stirred vigorously for 30 min at room temperature. The reaction was then quenched with water (150 mL), and the phases were separated. The organic layer was washed sequentially with 1M HCl (150 mL), satd. NaHCO_{3(aq.)} (150 mL), brine (150 mL) and dried over Na₂SO₄. The solvent was removed via rotary evaporation, yielding the crude aldehyde **S2.2** (5.0 g, 100%) as an amber oil (>95% purity, ¹H NMR) which was used directly in the next reaction without purification.

A 250mL round bottom flask containing a stir bar torched under vacuum for 5 minutes, cycled between vacuum/Ar_(g) (3x) then cooled back to room temperature. A mixture of freshly distilled diisopropylamine (4.13 mL, 29.2 mmol, 1.20 eq.) and anhydrous THF (50 mL, 0.5 M) was cooled to -78 °C before *n*-BuLi (10.7 mL, 26.8 mmol, 1.1 eq., 2.5 M in hexane) was added dropwise. A solution of ethyl propiolate **2.19** (2.70 mL, 25.6 mmol, 1.05 eq.) in THF (10 mL) was added dropwise and stirred 30 min at this temperature. A solution of crude aldehyde **S2.2** (5.0 g, 26.3 mmol, 1.00 eq) in THF (10 mL) was added dropwise and the mixture was stirred 15 min at this temperature. The reaction was subsequently quenched with satd. NH₄Cl_(aq.) (70 mL) then stirred while warming to room temperature. The organic phase collected and the aqueous phase extracted with Et₂O (3 x 60 mL), the combined organic phases were combined, washed with brine (50 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. Purification by silica flash chromatography (15% EtOAc:Hexanes) afforded title compound **2.32** (5.02 g, 69%, 2 steps).

TLC R_f 0.55 (20% EtOAc:Hexanes) [KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 4.74 (q, *J* = 5.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.06 (ddd, *J* = 10.4, 8.7, 3.5 Hz, 1H), 3.86 (ddd, *J* = 10.4, 5.5, 4.2 Hz, 1H), 3.69 (d, *J* = 6.5 Hz, 1H), 2.09 (ddt, *J* = 14.4, 8.5, 4.1 Hz, 1H), 1.90 (dddd, *J* = 14.4, 6.5, 5.4, 3.4 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.10 (d, *J* = 4.7 Hz, 6H).

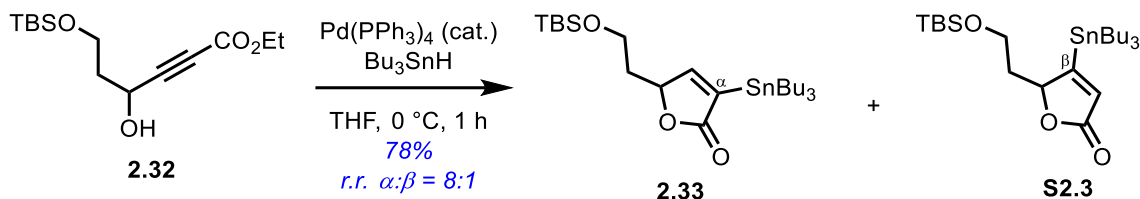
¹³C NMR (101 MHz, CDCl₃) δ 153.6, 87.3, 62.2, 61.9, 61.1, 37.6, 25.9, 18.3, 14.1, -5.4, -5.5

HRMS-ESI (*m/z*) calcd. for C₁₄H₂₆O₄Si : 309.1498 [M+Na]⁺, found 309.1493 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2934, 2855, 2237, 1710, 1472, 1363, 1239, 1093.

Physical State Yellow oil.

5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(tributylstannyl)furan-2(5H)-one (**2.33**).



In a 100 mL round bottom flask containing a stirbar was added **2.32** (5.02 g, 17.5 mmol, 1.0 eq.) dissolved in anhydrous THF (35 mL, 0.5 M) was sparged for 10 min with $\text{Ar}_{(\text{g})}$. $\text{Pd(PPh}_3)_4$ (1.01 g, 0.88 mmol, 0.05 eq.) was then added portionwise over 5 minutes. The subsequent mixture was stirred 10 min before Bu_3SnH (4.82 mL, 17.9 mmol, 1.02 eq.) was added drop wise over 20 minutes. The resulting mixture was stirred 1 h at room temperature. The reaction solution was then concentrated *in vacuo* and the resulting crude mixture was purified by silica flash chromatography (5 to 7% EtOAc:Hex, 1% Et_3N) to yield title compound **2.33** (7.29 g, 78%) and β -Sn regioisomer **S2.3** (0.84 g, 9%)

Rf 0.4 (5% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 1.4$ Hz, 1H), 5.13 (ddd, $J = 8.2, 5.1, 1.5$ Hz, 1H), 3.85 – 3.73 (m, 2H), 1.91 (ddt, $J = 14.0, 8.6, 5.5$ Hz, 1H), 1.75 (ddt, $J = 14.0, 8.6, 4.5$ Hz, 1H), 1.58 – 1.41 (m, 6H), 1.38 – 1.25 (m, 6H), 1.18 – 0.96 (m, 6H), 0.94 – 0.85 (m, 18H), 0.07 (d, $J = 2.9$ Hz, 6H).

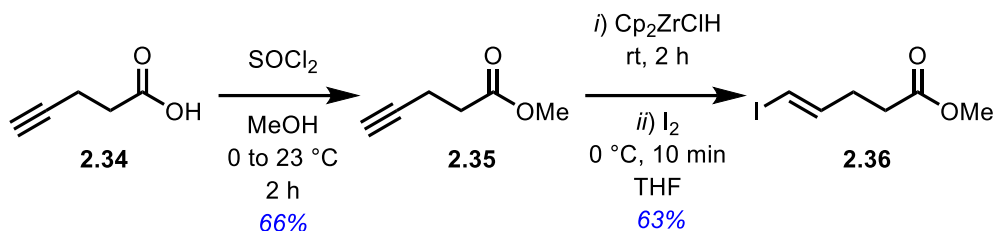
^{13}C NMR (101 MHz, CDCl_3) δ 178.1, 166.4, 134.7, 82.9, 59.4, 37.2, 29.1, 27.3, 26.1, 18.4, 13.8, 9.8, -5.3.

HRMS-EI (m/z) Calcd. for $\text{C}_{24}\text{H}_{48}\text{O}_3\text{SiSn}$ [M^+] 532.2395, found 532.2399 [M^+].

FTIR-ATR (thin film) ν [cm^{-1}] 2920, 2853, 1734, 1462, 1251, 1091.

Physical State Colorless oil.

Methyl (*E*)-5-iodopent-4-enoate (**2.36**).



Ester **2.35** was prepared from a known protocol in 66% yield in 1 step from pent-4-ynoic acid **2.34**.² This protocol is adapted from a procedure by Baran *et al.*³ A 250 mL round bottom flask containing a stir bar was oven-dried overnight and transferred in a glovebox, where Schwartz' reagent (7.59 g, 29.4 mmol, 1.10 eq.). The flask was taken out of the GB and sealed with a sceptor, then THF (60 mL, 0.45 M) was added. The thick white suspension was cooled to 0 °C before a solution of **2.35** (3.0 g, 26.8 mmol, 1.0 eq.) in THF (13 mL) was added dropwise. This mixture was then warmed to 23 °C and stirred 30 min (*NOTE : mixture turns from opaque to translucent*). This mixture was then cooled back to 0 °C before iodine (8.15 g, 32.1 mmol, 1.20 eq.) was added portion wise over 5 min. This reaction was stirred 10 min at 0 °C then quenched by transferring the contents of the flask into a separatory funnel containing ice-cold 1 M $\text{HCl}_{(\text{aq})}$ (100 mL). The purple organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were collected, washed with 10% $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq})}$ (40 mL), water (2 × 40 mL), brine (40 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by silica flash chromatography (10% EtOAc:Hexanes) afforded title compound **2.36** (4.05 g, 63%).

NOTE : This reaction was protected from light at all time since the zirconocene intermediate is light sensitive.

Rf 0.45 (10% EtOAc:Hexanes) [UV / KMnO_4]

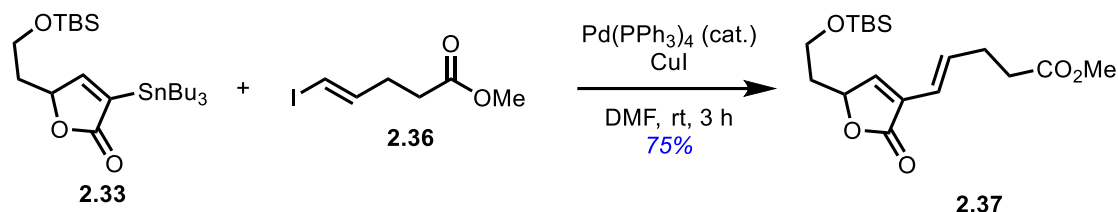
^1H NMR (400 MHz, CDCl_3) δ 6.52 (dt, J = 13.9, 6.8 Hz, 1H), 6.11 (dt, J = 14.5, 1.3 Hz, 1H), 3.68 (s, 4H), 2.71 – 2.16 (m, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.88, 144.25, 76.38, 51.89, 32.77, 31.25

Physical State Light yellow oil.

Analytical data match previously reported values.⁴

Methyl (E)-5-(5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**2.37**).



Under inert atmosphere, a conical 100 mL flask was charged with **2.33** (7.29 g, 13.7 mmol, 1.0 eq.) and anhydrous DMF (65 mL). This solution was sparged with Ar_(g) for 10 min before it was transferred via canula to a 250 mL round bottom flask containing a stirbar and a previously Ar_(g)-sparged solution of **2.36** (3.95 g, 16.5 mmol, 1.2 eq.) in anhydrous DMF (65 mL). Pd(PPh₃)₄ (792 mg, 0.69 mmol, 0.05 eq.) was then added and stirred 10 min, before CuI (3.13 g, 16.5 mmol, 1.2 eq.) was then added, and the resulting suspension was stirred vigorously for 3 h at room temperature. This mixture was then transferred to a 500 mL Erlenmeyer flask containing satd. NH₄Cl_(aq.) (150 mL) and stirred vigorously for 10 minutes. The resulting suspension was filtered on a hardpacked celite pad and washed with Et₂O (2 x 50 mL). The filtrate was transferred to an extraction funnel, organic phase was collected and aqueous phase was extracted with Et₂O (5x50 ml), the organic phases were combined, washed with brine (100 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc:Hexanes) afforded title compound **2.37** (3.63 g, 75%).

Rf 0.45 (20% EtOAc:Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, *J* = 1.9 Hz, 1H), 6.77 (dt, *J* = 16.0, 6.3 Hz, 1H), 6.15 (d, *J* = 15.8 Hz, 1H), 5.11 (t, *J* = 6.7 Hz, 1H), 3.85 – 3.71 (m, 2H), 3.68 (s, 3H), 2.60 – 2.37 (m, 4H), 1.96 – 1.72 (m, 1H), 1.83 – 1.76 (m, 1H), 0.89 (s, 9H), 0.06 (d, *J* = 4.6 Hz, 6H).

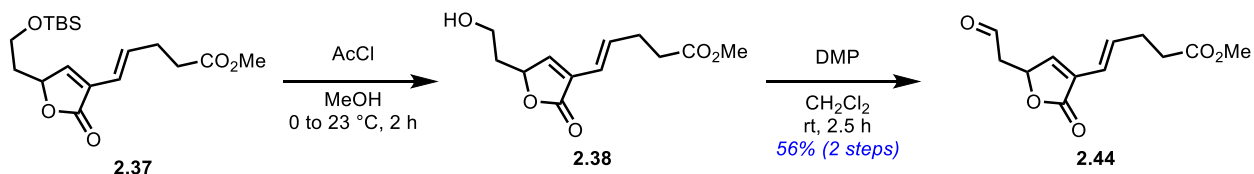
¹³C NMR (101 MHz, CDCl₃) δ 173.3, 172.1, 147.9, 135.8, 128.8, 119.8, 78.4, 58.9, 51.8, 36.9, 33.2, 28.6, 26.0, 18.4, -5.3, -5.2.

HRMS-EI (*m/z*) calcd for C₁₈H₃₀O₅Si : 355.1896 [M+H]⁺, found 355.1933 [M+H]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2956, 2925, 2857, 1751, 1734, 1436, 1253, 1160.

Physical State Orange oil (*solidifies when stored at -20 °C*)

Methyl (*E*)-5-(2-oxo-5-(2-oxoethyl)-2,5-dihydrofuran-3-yl)pent-4-enoate (**2.44**).



A 100 mL round bottom flask containing a stirbar was charged with **2.37** (1.57 g, 4.43 mmol, 1.0 eq.) and anhydrous MeOH (30 mL). This mixture was cooled to 0 °C before acetyl chloride (38 μ L, 0.53 mmol, 0.12 eq.) was dropwise over 3 minutes. This reaction was then warmed to room temperature and stirred 2 h. Satd. NaHCO_{3(aq.)} (1.5 mL) was then added and the mixture was concentrated *in vacuo* to approximately 25% of the original volume. Then, it was transferred to an extraction funnel containing DI water (75 mL). The aqueous phase was extracted with AcOEt (4 x 25 mL). The organic layers were combined washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo* to yield the crude intermediate alcohol **2.38** as a dark yellow oil, which was then co-evaporated with CH₂Cl₂ (10 mL).

The crude alcohol **2.38** was dissolved in CH₂Cl₂ (45 mL) and Dess-Martin Periodinane (2.82 g, 6.64 mmol, 1.5 eq.) was added in a single addition. This mixture was stirred at room temperature for 2.5 h, which was then quenched by adding satd. NaHCO_{3(aq.)} (8 mL), satd. 10% Na₂S₂O_{3(aq.)} (8 mL) and DI water (8 mL) and was stirred vigorously for 25 min. The mixture was then transferred to an extraction funnel containing DI water (50 mL) and the organic layer was collected. The aqueous layer was extracted with CH₂Cl₂ (3x 30 mL), the organic layers were combined, washed with brine, dried by Na₂SO₄, concentrated *in vacuo*. Purification by silica flash chromatography (60% to 70% EtOAc :Hexanes) afforded title compound **2.44** (575 mg, 54%).

NOTE : Addition of AcCl to MeOH is very exothermic and produces pops&bangs when added quickly. Use cold MeOH and very slow addition of AcCl.

Rf 0.40 (60% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 9.81 (s, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 6.81 (dt, *J* = 16.0, 6.4 Hz, 1H), 6.15 (d, *J* = 15.9 Hz, 1H), 5.38 (td, *J* = 7.2, 1.8 Hz, 1H), 3.68 (s, 3H), 3.03 (dd, *J* = 17.5, 7.3 Hz, 1H), 2.74 (dd, *J* = 17.5, 7.3 Hz, 1H), 2.56 – 2.42 (m, 4H).

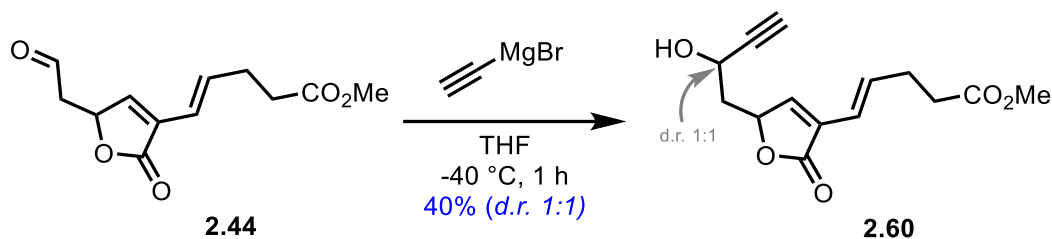
¹³C NMR (101 MHz, CDCl₃) δ 197.7, 173.2, 171.2, 145.6, 136.9, 129.9, 119.4, 75.3, 51.9, 46.9, 33.1, 28.6.

HRMS-ESI (*m/z*) calcd for C₁₂H₁₄O₅ : 261.0739 [M+Na]⁺, found 261.0725 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2954, 2937, 1718, 1700, 1688, 1435, 1372, 1239, 1166, 1098.

Physical State Light orange oil.

Methyl (*E*)-5-(5-(2-hydroxybut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**2.60**).



A 25 mL round bottom flask containing a stir bar and **2.44** (418 mg, 1.76 mmol, 1.0 eq.) was cycled between vacuum/ $\text{Ar}_{(\text{g})}$ (3x) and anhydrous THF (7 mL) was added. This mixture was cooled to $-40\text{ }^\circ\text{C}$ before a solution of ethynylmagnesium bromide (4.56 mL, 2.28 mmol, 1.3 eq., 0.5 M in THF) was added dropwise. This reaction was stirred 1 h at this temperature before TLC then indicated full consumption of the starting material. The reaction was quenched by addition of satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (6 mL) and the mixture was warmed back to room temperature over 30 minutes. The mixture transferred into an extraction funnel containing water (20 mL) and aqueous phase extracted with EtOAc (5x 20 mL). The combined organic extracts were washed with brine (10 mL), dried on Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (60% EtOAc:Hexanes) afforded title compound **2.60** (187 mg, 40%) as an inseparable 1:1 mixture of the two diastereoisomers.

Rf 0.55 (60% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.17 (dd, $J = 20.1, 1.9$ Hz, 1H), 6.80 (dt, $J = 15.9, 6.4$ Hz, 1H), 6.16 (d, $J = 15.6$ Hz, 1H), 5.27 – 5.23 (m, 0.5H), 5.20 – 5.15 (m, 0.5H), 4.71–4.64 (m, 1H), 3.68 (s, 3H), 2.58 (d, $J = 2.1$ Hz, 0.5H), 2.54 (d, $J = 2.2$ Hz, 0.5H), 2.52 – 2.44 (m, 4H), 2.11 – 2.07 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 146.7, 146.6, 136.5, 136.4, 129.2, 119.6, 119.5, 83.2, 77.9, 74.9, 74.3, 59.6, 59.1, 51.8, 41.3, 41.1, 33.2, 28.6.

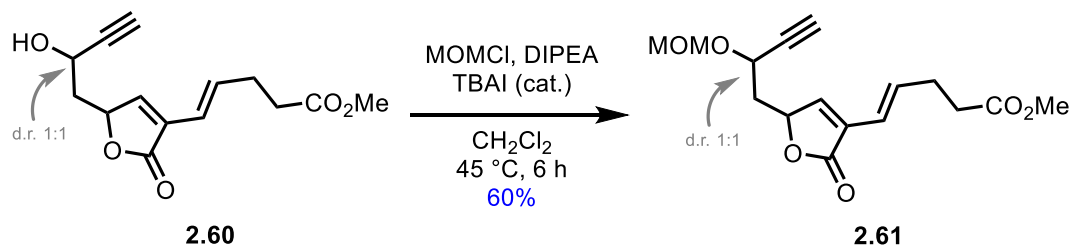
HRMS-ESI (m/z) calcd for $\text{C}_{14}\text{H}_{16}\text{O}_5$: 287.0895 $[\text{M}+\text{Na}]^+$, found 287.0891 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3262, 2952, 2918, 2364, 1719, 1706, 1375, 1163, 1033.

Physical State Colorless oil

NOTE : Individual NMR peaks that split due to the presence of diastereoisomers were underlined for clearer interpretation.

Methyl (E)-5-(5-(2-(methoxymethoxy)but-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**2.61**).



A 20 mL pressure flask was charged with a stir bar, **2.60** (150 mg, 568 μmol , 1.0 eq.), Hünig's base (395 μL , 2.27 mmol, 4.0 eq.), tetrabutylammonium iodide (21 mg, 57 μmol , 0.1 eq.) and anhydrous CH_2Cl_2 (2.8 mL). The headspace of the flask was flushed with Ar(g) for 2 minutes before a solution of chloromethyl methyl ether (129 μL , 1.70 mmol, 3.0 eq.) in CH_2Cl_2 (1 mL) was added dropwise. The flask was then capped and heated to 45 $^\circ\text{C}$ for 3 hours. After 3 hours, a second addition of a solution of chloromethyl methyl ether (129 μL , 1.70 mmol, 3.0 eq.) in CH_2Cl_2 (1 mL) was added to the flask and further stirred 3 h at 45 $^\circ\text{C}$. After a total of 6 h, the mixture was cooled down to room temperature, diluted with CH_2Cl_2 (15 mL) transferred to an extraction funnel containing water (15 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 , and then concentrated *in vacuo*. Purification by silica flash chromatography (40 % EtOAc:Hexanes) afforded title compound **2.61** (105 mg, 60 %) as an inseparable 1:1 mixture of the two diastereoisomers.

Rf 0.6 (50% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.17 (dd, $J = 20.1, 1.9$ Hz, 1H), 6.79 (dt, $J = 15.9, 6.4$ Hz, 1H), 6.15 (ddd, $J = 15.8, 1.4, 0.7$ Hz, 1H), 5.20 (q, $J = 7.6$ Hz, 1H), 4.95 (dd, $J = 18.8, 6.8$ Hz, 1H), 4.62 (dd, $J = 18.8, 6.8$ Hz, 1H), 4.63–4.55 (m, 1H), 3.68 (s, 3H), 3.38 (d, $J = 18.7$ Hz, 3H), 2.50 (dd, $J = 15.9, 2.1$ Hz, 1H), 2.52 – 2.45 (m, 4H), 2.21 – 1.92 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 171.7, 171.6, 146.9, 146.6, 136.4, 136.3, 129.4, 129.1, 119.7, 119.6, 94.4, 94.3, 81.4, 80.8, 77.8, 77.1 (Overlap), 75.6, 74.7, 62.7, 61.8, 56.2, 56.1, 51.8, 40.1, 39.4, 33.2, 28.6.

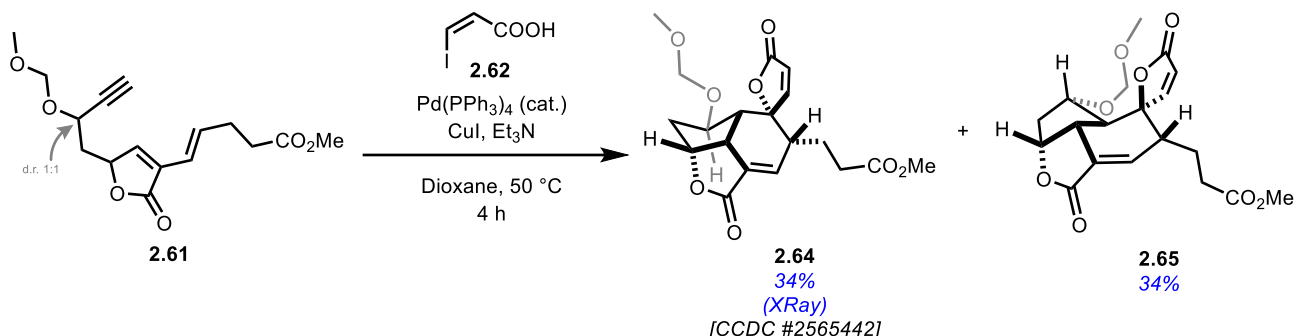
HRMS-ESI (m/z) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_6$: 331.1158 $[\text{M}+\text{Na}]^+$, found 331. 1165 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3274, 2952, 2163, 1722, 1700, 1436, 1148, 1097.

Physical State Light yellow oil.

NOTE : Individual NMR peaks that split due to the presence of diastereoisomers were underlined for clearer interpretation.

methyl 3-((2R,2a'R,2a1'R,4'R,4a'R,6'R)-4'-(methoxymethoxy)-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)propanoate (**2.64**) and methyl 3-((2S,2a1'R,4'R,5a'S,6'S, 7a'R)-6'-(methoxymethoxy)-2',5-dioxo-2a1',4',5a',6',7',7a'-hexahydro-2'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan] -4'-yl)propanoate (**2.65**)



To an oven-dried 10 mL Schlenk flask was added a stir bar and **2.61** (27 mg, 87.6 μmol , 1.0 eq.). Anhydrous dioxane (0.9 mL, 0.1 M) was then added, and this solution was degassed by the freeze-pump-thaw method (3 cycles, 5min per operation) and backflow of $\text{Ar}_{(\text{g})}$ after the last cycle. $\text{Pd(PPh}_3)_4$ (3.5 mg, 3.1 μmol , 0.035 eq.), CuI (1.2 mg, 6.1 μmol , 0.07 eq.) and freshly crystallized (*Z*)-3-iodoacrylic acid **2.62** (23.6 mg, 119 μmol , 1.4 eq.) were weighted in a glove box. The solids were placed inside a vial which was taken out of the glovebox and added quickly to the Schlenk flask while under a continuous stream of $\text{Ar}_{(\text{g})}$. Freshly distilled Et_3N (49 μL , 350 μmol , 4.0 eq.) was then added and the mixture was sealed. This mixture was heated to 50 $^\circ\text{C}$ and stirred for 4 h under $\text{Ar}_{(\text{g})}$ atmosphere, at which point TLC analysis shows full consumption of the starting material. The mixture was cooled to room temperature and washed with 10% $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and extracted with EtOAc (4 x 10 mL). The organic layers were combined, washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. This crude mixture was passed through a short silica plug eluted with 1% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to afford a 1:1 mixture of **2.64** and **2.65**, which was purified by preparative TLC (70% EtOAc :Hexanes, 20 cm x 20 cm aluminium backed TLC plate) to afford the title compounds **2.64** (11.3 mg, 34%) and **2.65** (11.3 mg, 34%) After being left in a freezer at -20°C for multiple months, **2.64** slowly crystallized, crystals were obtained and SCXRD analysis confirmed its structure. The crystal structure was uploaded to the CCDC with the deposition number #2565442.

For **2.64**

Rf (0.4 in 80% EtOAc :Hexanes) [UV / KMnO_4]

^1H NMR (500 MHz, CDCl_3) δ 7.46 (d, J = 5.6 Hz, H_Q), 6.76 (t, J = 3.7 Hz, H_P), 6.24 (d, J = 5.6 Hz, H_O), 5.21 (dt, J = 8.4, 6.8 Hz, H_N), 4.49 (dd, J = 14.8, 7.0 Hz, 2H_M), 3.70 (q, J = 3.9 Hz, H_L), 3.67 (s, 3H_K), 3.47 – 3.42 (m, H_J), 3.28 (s, 3H_I), 2.84 (dd, J = 9.7, 2.2 Hz, H_H), 2.55 (dt, J = 17.0, 5.6 Hz, H_G), 2.48 (dq, J = 11.5, 3.3 Hz, H_F), 2.40 (ddd, J = 17.1, 9.5, 6.2 Hz, H_E), 2.23 (ddd, J = 14.2, 6.8, 3.9 Hz, H_D), 1.88 (ddd, J = 14.1, 6.9, 5.0 Hz, H_C), 1.77 (dddd, J = 13.9, 9.6, 6.4, 3.4 Hz, H_B), 1.63-1.55 (m, H_A).

^{13}C NMR (126 MHz, CDCl_3) δ 173.2, 171.6, 168.4, 158.3(C_Q), 138.1(C_P), 132.7, 122.6(C_O), 95.9(C_M), 91.4, 81.6(C_N), 78.5(C_L), 55.7(C_I), 52.0(C_K), 50.6(C_H), 43.1(C_F), 42.0(C_J), 39.7($\text{C}_{\text{C,D}}$), 30.9($\text{C}_{\text{E,G}}$), 22.3 ($\text{C}_{\text{A,B}}$).

HRMS-ESI (m/z) calcd for $\text{C}_{19}\text{H}_{22}\text{O}_8$: 401.1212 [$\text{M}+\text{Na}$] $^+$, found 401.1195 [$\text{M}+\text{Na}$] $^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2944, 1718, 1708, 1683, 1436, 1193, 1162, 1098.

Physical State White needles

For **2.65**

Rf (0.7 in 80% EtOAc :Hexanes) [UV / KMnO_4]

^1H NMR (500 MHz, CDCl_3) δ 7.20 (d, J = 5.7 Hz, H_Q), 6.54 (dd, J = 3.9, 2.5 Hz, H_P), 6.19 (d, J = 5.6 Hz, H_O), 4.86 (td, J = 7.5, 4.1 Hz, H_N), 4.44 (dd, J = 20.0, 6.8 Hz, 2H_M), 4.05 (ddd, J = 10.9, 8.8, 6.4 Hz, H_L), 3.68 (s, 3H_K), 3.25 (s, 3H_I), 3.02 (ddt, J = 11.7, 7.3, 2.1 Hz, H_J), 2.96-2.91 (m, H_H), 2.93 (ddd, J = 14.3, 7.7, 6.4 Hz, H_G), 2.48 (ddd, J = 15.1, 9.7, 5.4 Hz, H_F), 2.36 (ddd, J = 16.2, 9.2, 6.6 Hz, H_E), 1.92 (ddd, J = 14.5, 8.9, 4.2 Hz, H_D), 1.82 (dddt, J = 13.9, 9.7, 6.7, 4.5 Hz, H_C), 1.69 (dddd, J = 14.1, 12.1, 9.4, 5.3 Hz, H_B), 1.54 (dd, J = 12.1, 10.9 Hz, H_A).

^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 171.7, 167.5, 158.2(C_Q), 141.5, 136.7(C_P), 121.8(C_O), 96.2(C_M), 87.2, 75.8(C_N), 75.1(C_L), 60.3(C_A), 55.9(C_J), 52.1(C_K), 50.4(C_G), 44.2(C_I), 42.1($\text{C}_{D,H}$), 32.8 ($\text{C}_{E,F}$), 24.8 ($\text{C}_{B,C}$).

HRMS-ESI (m/z) calcd for $\text{C}_{19}\text{H}_{22}\text{O}_8$: 401.1212 $[\text{M}+\text{Na}]^+$, found 401.1190 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2951, 1750, 1735, 1646, 1436, 1173, 1106, 1044.

Physical State Amorphous white solid.

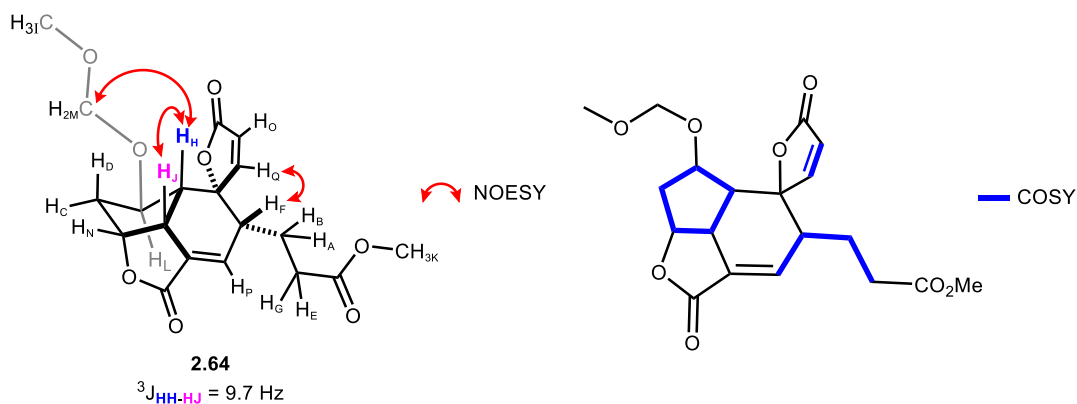


Figure 5.1. Selected $^3J_{\text{HH}}$, COSY and nOe correlations in **2.64**.

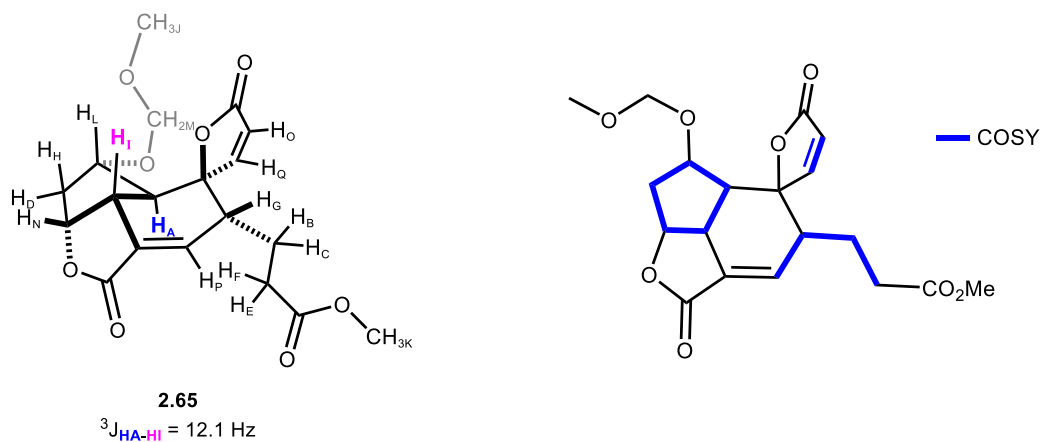


Figure 5.2. Selected $^3J_{\text{HH}}$ and COSY correlations in **2.65**.

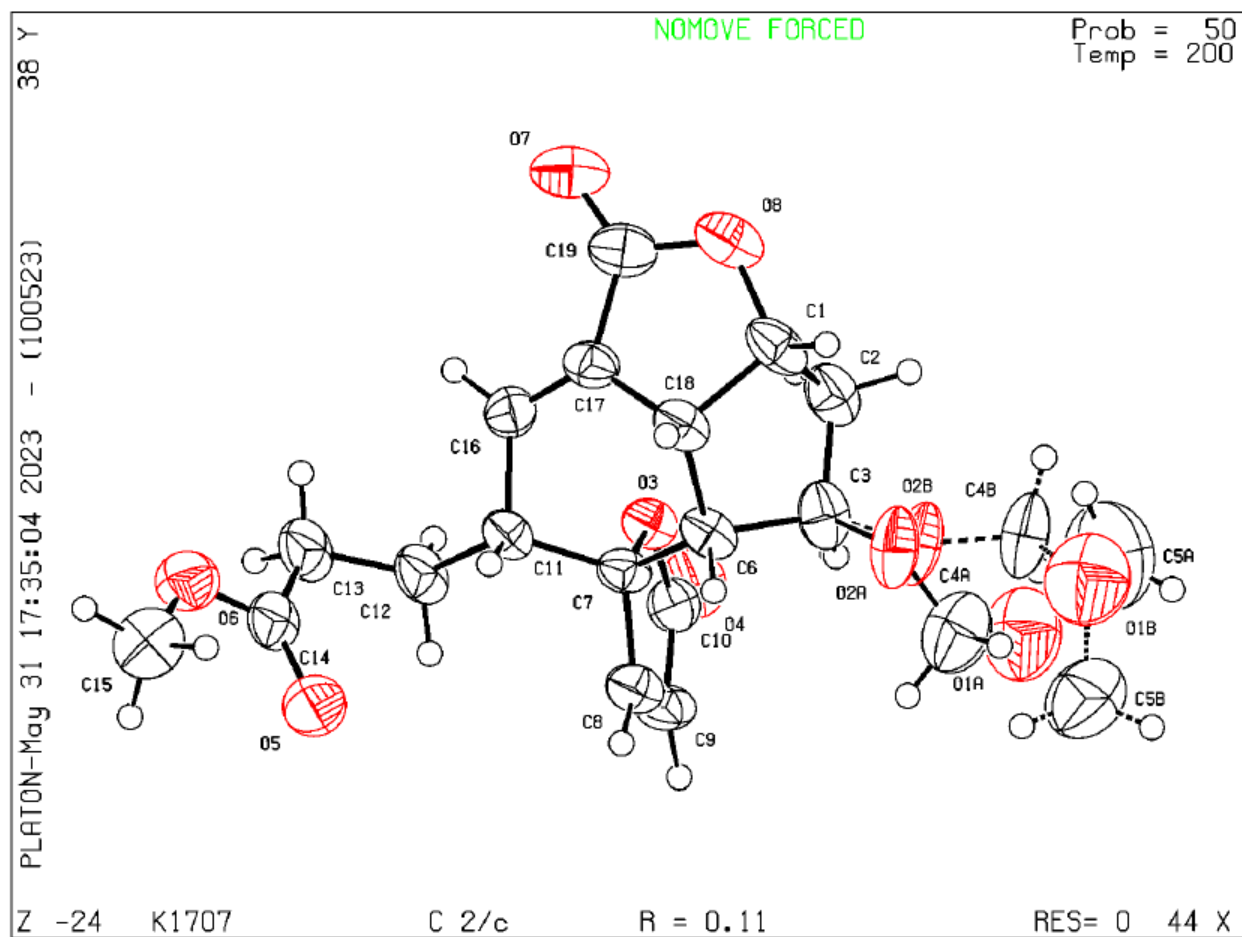
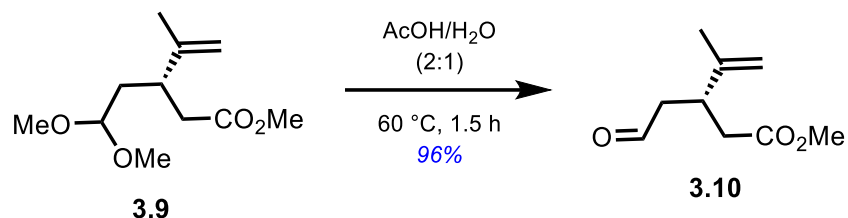


Figure 5.3. CHECKCIF file of 2.64.

Methyl (S)-4-methyl-3-(2-oxoethyl)pent-4-enoate (**3.10**)



A 500 mL round bottom flask containing a magnetic stir bar was charged with acetal **3.9** (21.6 g, 99.7 mmol, 1.00 eq.) (4 steps from (+)-Carvone)⁵ followed by addition of an AcOH/H₂O mixture (2:1, 250 mL, 0.4 M). This mixture was stirred at 60°C for 1.5 h after which TLC showed full consumption of the starting material. The mixture was cooled to room temperature, poured into a 2 L extraction funnel containing water (750 ml) and extracted with dichloromethane (3 x 200 ml). The combined organic extracts were washed with water (300 mL), satd. NaHCO_{3(aq.)} (100 mL) and brine (50 mL), dried with Na₂SO₄ and concentrated *in vacuo* to yield title compound **3.10** (16.2 g, 96%). A ¹H NMR analysis of the crude showed high purity (>95%) and the aldehyde was carried in the next step without further purification.

TLC R_f 0.55 (20% EtOAc/Hexanes) [KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 9.61 (t, *J* = 2.1 Hz, 1H), 4.76 (p, *J* = 1.4 Hz, 1H), 4.74 (dt, *J* = 1.4, 0.8 Hz, 1H), 3.59 (s, 3H), 3.09 (p, *J* = 7.2 Hz, 1H), 2.48 (dd, *J* = 7.2, 2.1 Hz, 2H), 2.42 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.35 (dd, *J* = 15.3, 7.5 Hz, 1H), 1.66 (dd, *J* = 1.4, 0.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 201.1, 172.2, 145.2, 112.4, 51.6, 46.7, 38.2, 37.5, 19.8.

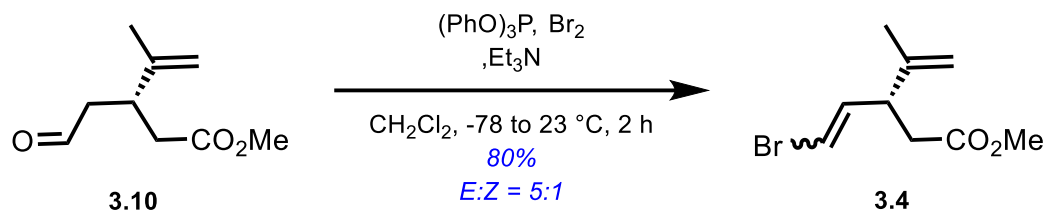
HRMS-ESI (*m/z*) calcd. for C₉H₁₄O₃ : 193.0841 [M+Na]⁺, found 193.0834 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2952, 1736, 1721, 1436, 1157.

[α]_D²⁴ +5.3 ° (c = 2.00, CHCl₃)

Physical State Light yellow oil.

(E)-Methyl (R)-5-bromo-3-(prop-1-en-2-yl)pent-4-enoate (**3.4**)



A 250 mL round bottom flask containing a magnetic stir bar was charged with triphenyl phosphite (9.69 g, 31.3 mmol, 1.40 eq.) and anhydrous CH_2Cl_2 (90 mL) and then cooled to -78 °C. Br_2 (1.38 mL, 26.8 mmol, 1.20 eq.) and Et_3N (7.47 mL, 53.6 mmol, 2.40 eq.) were added dropwise sequentially. When the foggy vapor disappeared from the head space (approx. 10 min), a solution of aldehyde **3.10** (3.80 g, 22.3 mmol, 1.00 eq.) in CH_2Cl_2 (10 mL) was added dropwise. The reaction was warmed to room temperature over 2 hours. The reaction was then quenched by direct addition onto a silica pad. The substrate was passed through and washed with 20% EtOAc/Hexanes. The solution was concentrated *in vacuo*. Purification by silica flash chromatography (2% Et_2O / Hexanes) to afford title compound **3.4** (4.18 g, 80%) as an inseparable mixture of 5:1 $E:Z$ geometrical isomers.

NOTE : For simplification purposes, only the major E isomer was characterized by NMR.

TLC R_f 0.30 (5% Et_2O / Hexanes) [KMnO_4]

^1H NMR for *E*-**3.4** : (300 MHz, CDCl_3) δ 6.16 (d, $J = 13.6$ Hz, 1H), 6.08 (dd, $J = 13.6, 7.5$ Hz, 1H), 4.85 (p, $J = 1.4$ Hz, 1H), 4.79 (q, $J = 0.9$ Hz, 1H), 3.67 (s, 3H), 3.30 – 3.17 (m, 1H), 2.62 – 2.48 (m, 2H), 1.72 (dd, $J = 1.4, 0.9$ Hz, 3H).

^{13}C NMR for *E*-**3.4** : (101 MHz, CDCl_3) δ 172.1, 143.2, 114.7, 51.9, 48.1, 43.4, 42.8, 38.3, 18.6.

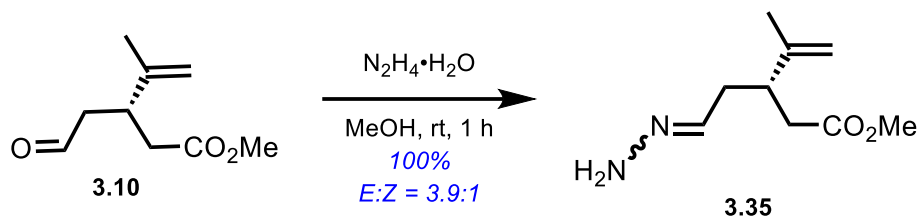
HRMS-ESI Multiple *EI/ESI* mass spectrometry analyses failed to identify m/z fragments belonging to the product.

FTIR-ATR (thin film) ν [cm^{-1}] 2952, 2851, 1733, 1435, 1259, 1161.

$[\alpha]_D^{24}$ -35.0° ($c = 0.50$, CHCl_3)

Physical State Light yellow oil

Methyl (S,E)-3-(2-hydrazineylideneethyl)-4-methylpent-4-enoate (**3.35**)



A 250 mL round bottom flask containing a stir bar was charged with MeOH (65 mL) and hydrazine hydrate (1.49 mL, 31.0 mmol, 1.10 eq.). This mixture was stirred vigorously and a solution of aldehyde **3.10** (4.80 g, 28.2 mmol, 1.00 eq.) in MeOH (65 mL) in an addition funnel was added dropwise over 15 minutes. This solution was further stirred 1 h at room temperature until TLC analysis showed full consumption of the starting material. The reaction flask was then concentrated *in vacuo*. The crude reaction mixture was then co-evaporated with C₆H₆ (5 x 20 mL) to yield title compound **3.35** (5.22 g, 100%) in an inconsequential 3.9:1 E/Z mixture as observed by NMR, and showed >95% purity without further purification.

NOTE : The hydrazones could not be purified by silica chromatography. Spectroscopic data (NMR) was reported only for the E isomer for clarity purposes. The hydrazones were obtained as a thick sirup after co-evaporations and solidified upon storing at -20 °C. Engaging the solid in the next reaction was operationally difficult as they are mostly insoluble, and as such, they should be used directly in the next reaction while as the thick sirup, which is soluble in most organic solvents.

TLC R_f 0.1 (20% EtOAc/Hexanes) [KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 6.98 (t, *J* = 5.7 Hz, 1H), 5.12 (br s, *NH*), 4.78 (d, *J* = 1.4 Hz, 2H), 3.63 (s, 3H), 2.81 – 2.74 (m, 1H), 2.41 (d, *J* = 7.5 Hz, 2H), 2.34 – 2.22 (m, 2H), 1.69 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.7, 145.7, 144.2, 112.2, 51.6, 41.5, 38.2, 35.7, 19.4.

HRMS-ESI (*m/z*) calcd. for C₉H₁₆O₂N₂ : 207.1109 [M+Na]⁺, found 207.1155 [M+Na]⁺.

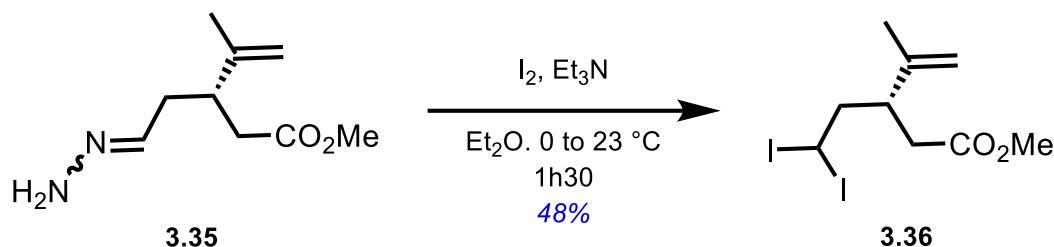
FTIR-ATR (thin film) ν [cm⁻¹] 3385, 3251, 2952, 2924, 1736, 1643, 1438, 1162.

[α]_D²⁴ -15.6 ° (c = 1.00, CHCl₃)

Physical State White waxy solid

Melting Point 70 – 72 °C

Methyl (R)-3-(2,2-diiodoethyl)-4-methylpent-4-enoate (**3.36**)



NOTE : Shield from light at all times.

A 250 mL round bottom flask containing a stir bar was charged with **3.35** (2.32 g, 12.6 mmol, 1.00 eq.), anhydrous Et₂O (85 mL) and Et₃N (10.5 mL, 75.4 mmol, 6.00 eq.). The mixture was cooled to 0 °C using an ice bath before an addition funnel containing a solution of I₂ (4.78 g, 18.8 mmol, 1.50 eq.) in Et₂O (50 mL) was added dropwise over 30 minutes. The ice bath was then taken out and the mixture was stirred an additional 1 h at room temperature. Satd. Na₂S₂O_{3(aq.)} (60 mL) was then added and stirred for 5 minutes. The mixture was added to an extraction funnel and the organic layer was collected. The aqueous layer was extracted with Et₂O (3x 40 mL). The organic layers were combined, dried with MgSO₄ and concentrated *in vacuo*. The resulting oily crude was passed through a silica plug (20% EtOAc:Hexanes) and concentrated *in vacuo* to yield crude title compound **3.36** (2.47 g, 48%), which contained minute amount of Et₃N.

*NOTE : The yields for this experiment ranged from 35-48% depending on the scale. Gem-diiodoester **3.36** was found to be unstable when stored under Ar_(g) at -20 °C overnight. A ¹H NMR analysis of the crude mixture after silica plug showed presence of the desired diiodomethyne ¹H and ¹³C peaks. The NMR tube turns pink when exposed to ambient light for ~1 h.*

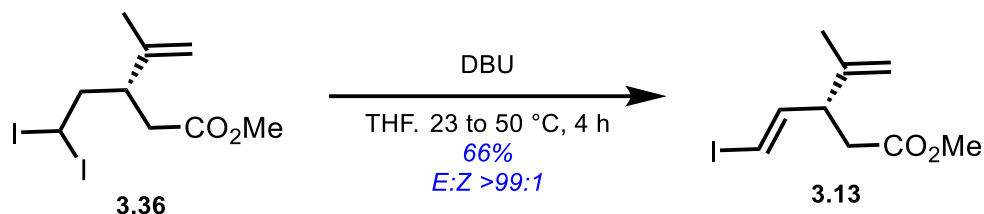
TLC R_f 0.75 (20% EtOAc/Hexanes) [KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 4.92 (s, 1H), 4.91 – 4.89 (m, 1H), 4.80 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.68 (s, 3H), 2.73 (dtd, *J* = 9.7, 7.5, 4.7 Hz, 1H), 2.59 – 2.31 (m, 4H), 1.67 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 172.1, 142.9, 114.8, 51.9, 50.9, 45.4, 37.7, 18.3, -29.9.

Physical State Yellow to light orange oil.

Methyl (R,E)-5-iodo-3-(prop-1-en-2-yl)pent-4-enoate (**3.13**)



A 100 mL round bottom flask containing a stir bar was charged with **3.36** (2.47 g, 6.06 mmol, 1.00 eq.) and THF (20 mL). DBU (3.62 mL, 24.2 mmol, 4.00 eq.) was then injected (*NOTE : reaction mixture turns a deep purple*). The reaction headspace was displaced with Ar(g) and a water bath was added. The mixture was heated to 50 °C for 4 hours, after which it was cooled to room temperature and concentrated *in vacuo* (rotavap bath < 25°C). Purification by silica flash chromatography (0% to 5% EtOAc / Hexanes) afforded title compound **3.13** (1.23 g, 66%) as a single E geometrical isomer.

NOTE : 3.13 was found to be stable up to >3 months when stored at -20 °C. HRMS analysis was attempted thrice and showed at best a ΔDA of 0.0065 between calculated and observed.

TLC R_f 0.45 (10% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 6.43 (dd, J = 14.5, 8.1 Hz, 1H), 6.16 (dd, J = 14.5, 1.0 Hz, 1H), 4.88 – 4.83 (m, 1H), 4.79 (s, 1H), 3.67 (s, 3H), 3.23 (q, J = 8.1 Hz, 1H), 2.54 (dd, J = 15.2, 7.2 Hz, 1H), 2.48 (dd, J = 15.2, 8.1 Hz, 1H), 1.71 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.1, 146.3, 144.3, 112.1, 76.8, 51.9, 49.6, 37.4, 20.8.

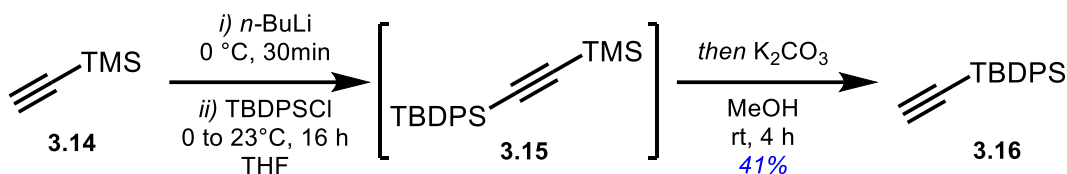
HRMS-ESI (m/z) calcd. for C₉H₁₃O₂I : 302.9858 [M+Na]⁺, found 303.0508 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2924, 2854, 1751, 1513, 1248, 1172.

$[\alpha]_D^{24}$ -45.1 ° (c = 1.00, CHCl₃)

Physical State Light yellow oil

Tert-butyl(ethynyl)diphenylsilane (**3.16**)



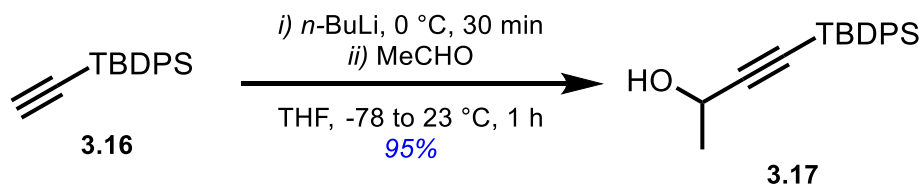
A 2 L round bottom flask containing a magnetic stir bar was flame-dried under vacuum then cycled between Vacuum/Ar_(g) (3x). Anhydrous THF (420 mL, 0.6 M) was added, followed by addition of TMS Acetylene (35.6 mL, 250 mmol, 1.00 eq.). The resulting solution was cooled to 0 °C. A *n*-BuLi solution (2.5M in hexanes, 100 mL, 250 mmol, 1.00 eq.) was transferred by canulation directly from its reagent bottle in a dropwise manner over 15-20 min. The resulting solution was stirred an additional 30 min at this temperature before TBDPSCl (68.7 g, 250 mmol, 1.00 eq.) in THF (40 mL) as added dropwise over 15-20 minutes by canulation. This mixture was stirred an additional 1 h at 0 °C before the ice bath was removed and the mixture was stirred 16 h at room temperature to generate intermediate **3.15**. Then, anhydrous MeOH (210 mL) and K₂CO₃ (69.1 g, 500 mmol, 2.00 eq.) were added sequentially, and the resulting heterogenous solution stirred vigorously for 4 h at room temperature. The reaction was subsequently quenched with satd. NH₄Cl_(aq.) (150mL) and stirred 30 min. At this point, the heterogenous mixture was filtered through cotton and concentrated to *ca.* 15% of its original volume. The resulting suspension was then partitioned between EtOAc (500 mL) and H₂O (500 mL) and stirred 15 min. This biphasic mixture was transferred to an extraction funnel containing H₂O (500 mL), the organic phase collected and aqueous phase was extracted with EtOAc (3x 300 mL). The organic layers were combined, washed with brine (100 mL), dried on Na₂SO₄ and concentrated *in vacuo*. The resulting solid was dissolved in a minimal amount of CH₂Cl₂ and adsorbed on Celite™. Purification by silica flash chromatography (100% Hexanes) afforded the title compound **3.16** (27.0 g, 41%). The spectroscopic values of this compound matched the values reported in the literature.⁶

TLC R_f 0.45 (100% Hexanes) [UV / KMnO₄]

¹H NMR (300 MHz, CDCl₃) δ 7.83 – 7.77 (m, 4H), 7.45 – 7.33 (m, 6H), 2.71 (s, 1H), 1.11 (s, 9H).

Physical State White solid.

4-(*tert*-Butyldiphenylsilyl)but-3-yn-2-ol (**3.17**).



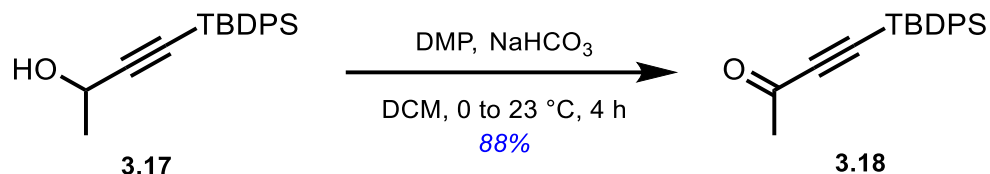
A 250 mL round bottom flask containing a magnetic stir bar and **3.16** (5.53 g, 20.9 mmol, 1.00 eq.) was cycled between Vacuum/ $\text{Ar}_{(\text{g})}$ (3x) before anhydrous THF (60 mL) was added. This solution was cooled to 0 °C before *n*-BuLi (2.5M in Hexanes, 8.4 mL, 20.9 mmol, 1.00 eq) was injected dropwise. The reaction mixture was allowed to stir at 0 °C for 30 min (*solution becomes dark orange*). The reaction vessel was then cooled to -78 °C before a solution of acetaldehyde (1.52 mL, 27.2 mmol, 1.30 eq.) in THF (20 mL) was added dropwise. When the addition was complete, the cooling bath was removed and the mixture was allowed to slowly warm to room temperature over 60 minutes. Satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (40 mL) was added and the mixture transferred to a separatory funnel. The organic phase was collected and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (25 mL), dried on Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/Hexanes) afforded title compound **3.17** (6.11 g, 95%). The spectroscopic values of this compound matched the values reported in the literature.⁶

TLC R_f 0.35 (10% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.72 (m, 4H), 7.50 – 7.36 (m, 6H), 2.47 (s, 3H), 1.13 (s, 9H).

Physical State Pale yellow oil

4-(*tert*-butyldiphenylsilyl)but-3-yn-2-one (**3.18**).



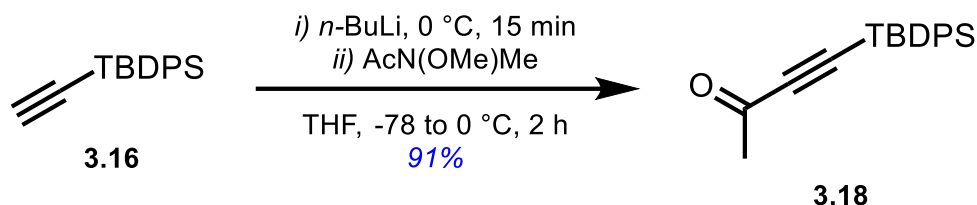
A 100 mL round bottom flask containing a stir bar was charged with **3.17** (5.34 g, 17.3 mmol, 1.00 eq.) and CH_2Cl_2 (40 mL). This solution was cooled to 0 °C before NaHCO_3 (4.36 g, 51.9 mmol, 3.00 eq.) and Dess-Martin Periodane (8.81 g, 20.8 mmol, 1.20 eq.) were then added in a single portion. The cooling bath was removed and the suspension was stirred at room temperature for 4 h. Satd. $\text{Na}_2\text{S}_2\text{O}_3(\text{aq.})$ (30 mL) and satd. $\text{NaHCO}_3(\text{aq.})$ (30 mL) were then carefully added (*NOTE : vigorous gas evolution!*). This biphasic mixture was stirred vigorously for 20 min before it was transferred to an extraction funnel. The organic phase was collected and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was coevaporated with hexanes (2 x 50 mL) to ensure full removal of the polar solvents. Purification by flash column chromatography (0%, 2.5%, 5% EtOAc:Hexanes) yielded a thick colorless oil, which was left in the freezer overnight to solidify into a white solid. This solid was broken up and crushed to a fine powder using a mortar & pestil and left 24 h on high vacuum to afford title compound **3.18** (4.69 g, 88%). The spectroscopic values of this compound matched the values reported in the literature.⁶

TLC R_f 0.50 (5% Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.78-7.73 (m, 4H), 7.47 – 7.37 (m, 6H), 2.46 (s, 3H), 1.13 (s, 9H).

Physical State : Thick colorless sirup (*solidifies to a white solid upon cooling at -20 °C overnight*).

4-(*tert*-butyldiphenylsilyl)but-3-yn-2-one (**3.18**).



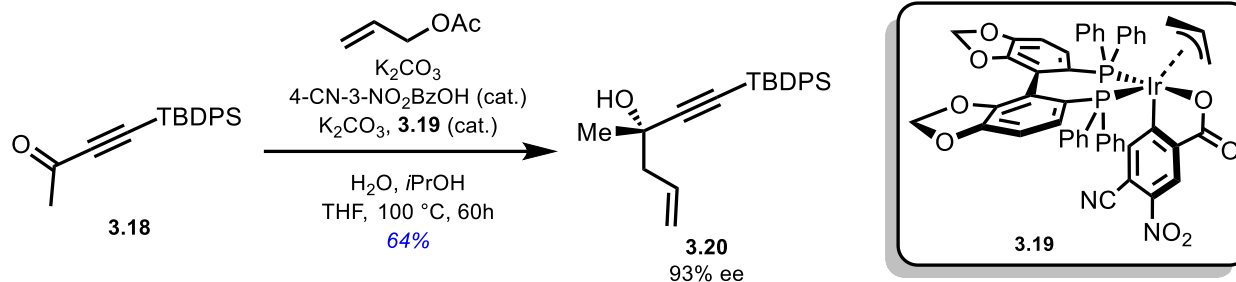
A 2-neck, 2 L round bottom flask containing a magnetic stir bar was flame-dried under vacuum then cycled between vacuum/ $\text{Ar}_{(\text{g})}$ (3x). Under an $\text{Ar}_{(\text{g})}$ stream, the flask was charged with **3.16** (27.0 g, 102 mmol, 1.00 eq.). Anhydrous THF (500 mL, 0.2 M) was added and the solution was cooled to 0 °C before a solution of *n*-BuLi (2.5M in hexanes, 44.9 mL, 112 mmol, 1.10 eq.) was added dropwise over 15 minutes. This mixture was stirred an additional 15 minutes at this temperature before the solution was cooled to -78 °C and N-Methoxy-N-methylacetamide (12.6 g, 13.0 mL, 122 mmol, 1.20 eq.) was added dropwise over 15 minutes. The reaction was stirred 30 min at -78 °C before the cooling bath was changed for an ice bath and this mixture was stirred an additional 2 hour at this temperature. The reaction was quenched half saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (400 mL) and stirred an additional 15 minutes while warming to room temperature. The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organic layers were combined, washed with and brine (100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude mixture was coevaporated with hexanes (2 x 200 mL) to ensure full removal of the polar solvents. Purification by flash column chromatography (0%, 2.5%, 5% EtOAc:Hexanes) yielded a thick colorless oil, which was left in the freezer overnight to solidify into a white solid. This solid was broken up and crushed to a fine powder using a mortar & pestil and left 24 h on high vacuum to afford title compound **3.18** (28.5 g, 91%). The spectroscopic values of this compound matched the values reported in the literature.⁶

TLC R_f 0.50 (5% Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.78-7.73 (m, 4H), 7.47 – 7.37 (m, 6H), 2.46 (s, 3H), 1.13 (s, 9H).

Physical State : Thick colorless sirup (solidifies to a white solid upon cooling at -20 °C overnight).

(*S*)-1-(*tert*-butyldiphenylsilyl)-3-methylhex-5-en-1-yn-3-ol (**3.20**).



This protocol is adapted from Krische *et al.* with minimal modifications.⁶ A 75 mL pressure tube equipped with a magnetic stir bar was charged with **3.18** (6.50 g, 21.2 mmol, 1.00 eq.), K₂CO₃ (1.46 g, 10.6 mmol, 0.50 eq.), Ir catalyst **3.19**⁷ (1.09 g, 1.06 mmol, 0.05 eq.), and 4-cyano-3-nitro-benzoic acid (407 mg, 2.12 mmol, 0.10 eq.). To the solids was added anhydrous THF (21 mL, 1.0 M), *i*-PrOH (1.95 mL, 25.5 mmol, 1.20 eq.), allyl acetate (4.58 mL, 42.4 mmol, 2.00 eq.) and H₂O (383 μ L, 21.2 mmol, 1.00 eq.). The headspace of the reaction vessel was displaced by Ar(g) for 5 minutes and it was sealed tightly. This heterogenous mixture was stirred vigorously at 100 °C for 60 h. The mixture was then cooled to ambient temperature, and CH₂Cl₂ (40 mL) was added. The suspension was filtered on a Celite™ pad with and washed with copious amounts of CH₂Cl₂. The filtrate was concentrated *in vacuo* and was purified by silica flash chromatography (5-10% EtOAc:Hexanes) to afford title compound **3.20** (4.74 g, 64%). The enantiomeric excess was determined to be 93% by HPLC analysis of the dinitrobenzoate ester derivative (*vide infra*).

TLC R_f 0.35 (10% EtOAc:Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.78 (m, 4H), 7.46 – 7.35 (m, 6H), 6.09 (dddd, *J* = 17.0, 10.8, 8.0, 6.7 Hz, 1H), 5.32 – 5.22 (m, 2H), 2.63 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.51 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.37 (br s, OH), 1.64 (s, 3H), 1.11 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 135.7, 133.3, 133.2, 129.7, 127.9, 119.9, 113.5, 83.1, 67.7, 48.4, 29.5, 27.2, 18.6.

HRMS-ESI (*m/z*) calcd. for C₂₃H₂₈OSi : 371.1795 [M+Na]⁺, found 371.1807 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 3416, 3071, 2929, 2857, 2166, 1428, 1110.

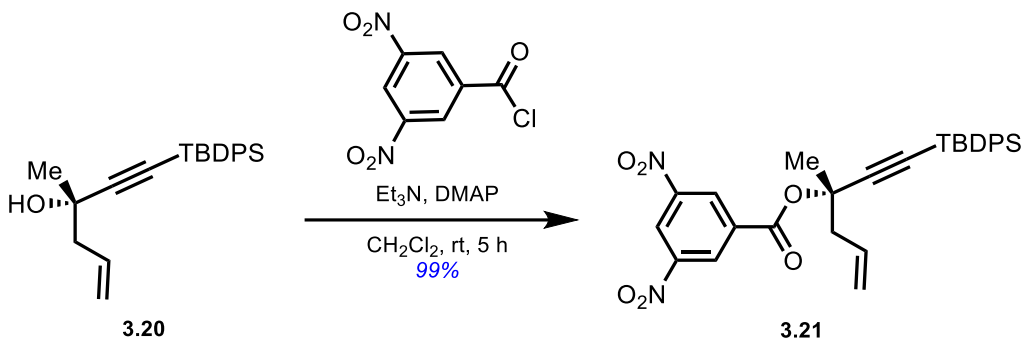
$[\alpha]_D^{24}$ -14.7 ° (c=2.0, CHCl₃) (litt. $[\alpha]_D^{20}$ = -19.6 °, c=1.0, CHCl₃)⁶

Physical State Pale yellow oil.

Synthesis of rac-3.20

A 100 mL round bottom flask containing a magnetic stir bar and ketone **3.18** (3.09 g, 10.1 mmol, 1.00 eq.) was cycled between vacuum/Ar(g) (3x). Anhydrous THF (33 mL, 0.3M) was added. The flask was cooled to -78 °C. After stirring for 10 min at -78 °C, a solution of allylmagnesium bromide (1 M in Et₂O, 13.1 mL, 13.1 mmol, 1.30 eq.) was added dropwise to the reaction mixture over 5 minutes. The cryogenic bath was removed and the reaction was stirred 2 h while warming to room temperature. Satd. NH₄Cl(aq.) was then added carefully and stirred another 5 minutes. The mixture was transferred to an extraction funnel. The organic layer was collected and the aqueous layer was extracted with Et₂O (3 x 50 mL). The organic phases were combined, washed with brine (25 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude mixture was flushed through a short silica plug using 20% EtOAc:Hexanes as an eluent to furnish *rac*-**3.20** (3.40 g, 97%) in high purity (>95%) and was used in the next reaction without further purification.

(*S*)-1-(*tert*-butyldiphenylsilyl)-3-methylhex-5-en-1-yn-3-yl 3,5-dinitrobenzoate (**3.21**).



A 5 mL round bottom flask was charged with a magnetic stir bar, **3.20** (13.0 mg, 0.037 mmol, 1.0 eq.) and CH₂Cl₂ (0.5 mL, 75 mM). To this flask was sequentially added Et₃N (16μL, 112 μmol, 3.0 eq.) and 3,5-dinitrobenzoyl chloride (17.2 mg, 74.6 μmmol, 2.0 eq.). DMAP (5.5 mg, 44.8 μmol, 1.20 eq.) was then added, which turned the solution from colorless to a bright red. The reaction mixture was stirred at room temperature for 5 h, at which point TLC analysis showed full consumption of the starting material. The reaction was quenched by addition of satd. NaHCO₃ (aq.) (2 mL) and the mixture was transferred to an extraction funnel, where it was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic phases were dried with MgSO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (10% EtOAc/Hexanes) afforded title compound **3.21** (20.1 mg, 99%). A chiral HPLC analysis revealed that alcohol 3.21 was present in 93% enantiomeric excess.

TLC R_f 0.50 (10% EtOAc:Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 9.22 (t, *J* = 2.1 Hz, 1H), 9.14 (d, *J* = 2.1 Hz, 2H), 8.15 – 7.73 (m, 4H), 7.56 – 7.33 (m, 6H), 6.04 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.42 – 5.21 (m, 2H), 3.03 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.95 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.98 (s, 3H), 1.09 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 160.5, 148.8, 135.7, 134.9, 132.9, 131.7, 129.8, 129.6, 127.9, 122.4, 120.4, 107.6, 87.7, 77.8, 45.8, 27.1, 26.6, 18.8.

HRMS-ESI (m/z) calcd. for $C_{30}H_{30}N_2O_6Si$: 565.1771 $[M+Na]^+$, found 565.1771 $[M+Na]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3101, 2929, 2857, 2156, 1738, 1545, 1343, 1279, 1110.

$$[\alpha]_D^{24} -4.4^\circ (c = 1.00, \text{CHCl}_3)$$

Physical State Yellow viscous oil

Datafile: C:\Chem32\1\Data\Roxanne\06042025_LC_IB_CN_Alc-Rac_02.D

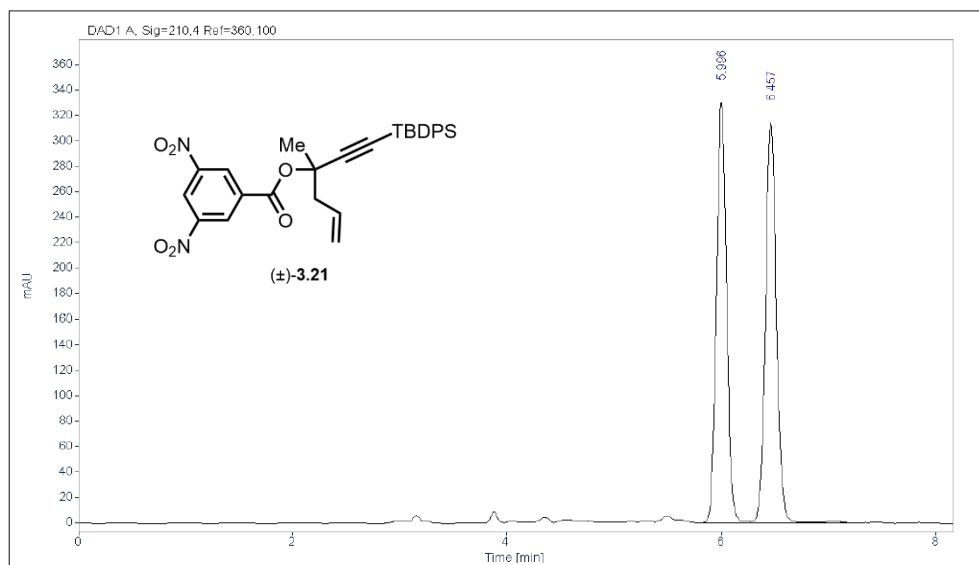
LibID: N/R

Sample Name [Location]: [3]

CCRI HTE Lab [LC/MS]

Acq. Method; Acq. Date - [DA]: RC_April2025_ChiralScreening.M (6/4/2025 3:10:18 PM) - [RC_TD_09122023.M]

Sample Info: 99.0:1.0 Hexane:IPA, 15 degC, 1.0 mL/min, 10 uL injection



Signal: DAD1 A, Sig=210.4 Ref=360.100

RT [min]	Compound Name	Area	Height	Area%	RespFactor	Amount (ng/ul)
5.996		2168.334	330.555	49.0		0.000
6.457		2259.020	314.064	51.0		0.000

Figure 5.4. Chiral HPLC chromatogram of (±)-3.21.

Datafile: C:\Chem32\1\Data\Roxanne\06042025_LC_IB_CN_Alc-En_02b.D

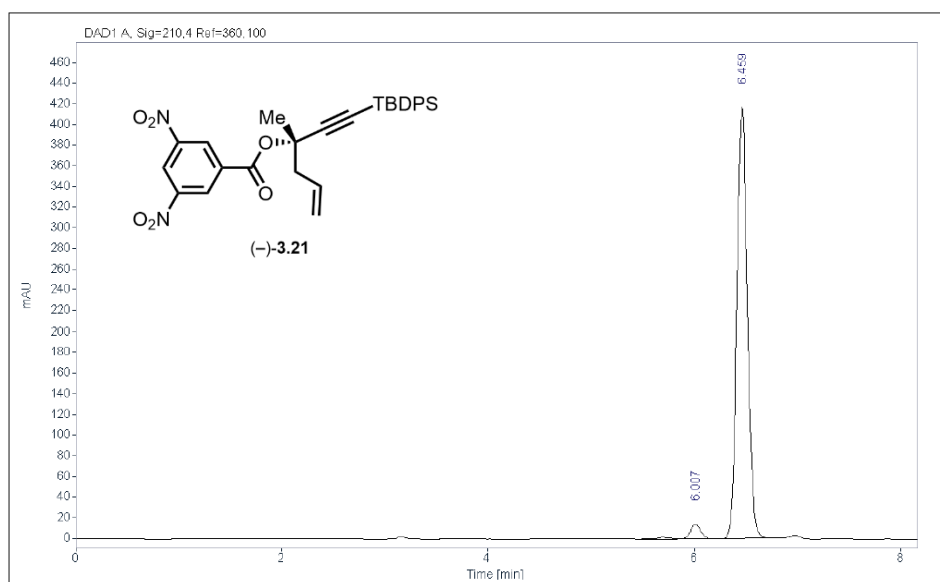
LibID: N/R

Sample Name [Location]: [2]

CCRI HTE Lab [LC/MS]

Acq. Method; Acq. Date - [DA]: RC_April2025_ChiralScreening.M (6/4/2025 3:50:57 PM) - [RC_TD_09122023.M]

Sample Info: 99.0:1.0 Hexane:IPA, 15 degC, 1.0 mL/min, 10 uL injection

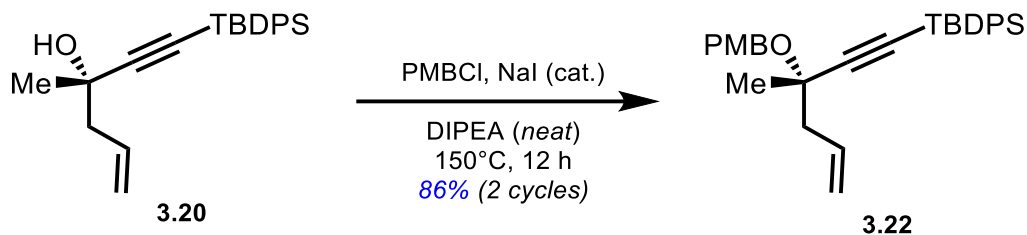


Signal: DAD1 A, Sig=210.4 Ref=360.100

RT [min]	Compound Name	Area	Height	Area%	RespFactor	Amount (ng/ul)
6.007		111.896	14.043	3.6		0.000
6.459		2959.420	416.882	96.4		0.000

Figure 5.5. Chiral HPLC chromatogram of (–)-3.21.

(*S*)-*tert*-butyl(3-((4-methoxybenzyl)oxy)-3-methylhex-5-en-1-yn-1-yl)diphenylsilane (**3.22**).



A 75 mL pressure flask was charged with a magnetic stir bar, **3.20** (8.78 g, 25.2 mmol, 1.00 eq.), PMBCl (5.78 mL, 42.8 mmol, 1.70 eq.), DIPEA (7.90 mL, 45.3 mmol, 1.80 eq.) and NaI (378 mg, 2.52 mmol, 0.10 eq.). The headspace of the tube was flushed with Ar_(g), capped tightly and stirred at 150 °C for 12 h. The reaction was then cooled to room temperature and the mixture solidified. This solid was taken in a minimal amount of CH₂Cl₂ (*ca.* 10 mL) and purified by silica flash chromatography (2.5 to 5% Et₂O/Hexanes) to afford title compound **3.22** (8.72 g, 74%). Along with recovered starting material. The recovered starting material was run again in the same reactions condition to yield an additional 1.42 g (12%), for a total of 10.1 g (86%).

NOTE : This reaction is higher yielding (>90%) when ran on <1 mmol scale but suffers scalability issues when ran on >10 mmol scale, and usually required a second cycle to convert the recovered starting material.

TLC R_f 0.45 (10% Et₂O:Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.78 (m, 4H), 7.48 – 7.34 (m, 6H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.03 (dddd, *J* = 17.1, 10.2, 7.4, 6.8 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.75 (d, *J* = 10.5 Hz, 1H), 4.69 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 2.70 (ddt, *J* = 13.8, 6.9, 1.3 Hz, 1H), 2.61 (ddt, *J* = 13.8, 7.4, 1.2 Hz, 1H), 1.61 (s, 3H), 1.11 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 159.4, 135.9, 133.8, 133.5, 129.9, 129.7, 128.1, 118.8, 114.1, 111.7, 85.9, 77.6, 74.1, 66.8, 55.6, 46.4, 27.4, 26.7, 18.9.

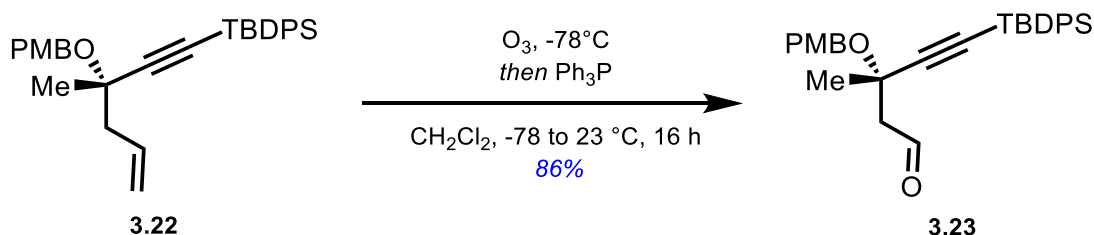
HRMS-ESI (*m/z*) calcd. for C₃₁H₃₆O₂Si : 491.2382 [M+Na]⁺, found 491.2419 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 3071, 2930, 2857, 2166, 1513, 1247, 1109.

[α]_D²⁴ +19.3 ° (c = 2.00, CHCl₃)

Physical State Pale yellow oil

(*S*)-5-(*tert*-butyldiphenylsilyl)-3-((4-methoxybenzyl)oxy)-3-methylpent-4-ynal (**3.23**).



To a 250 mL round bottom flask containing a stir bar was added **3.23** (10.1 g, 21.6 mmol, 1.00 eq.) and CH_2Cl_2 (145 mL) was added. This mixture was cooled to -78°C before ozone was bubbled in the solution through a gas dispersion tube until TLC (PA stain) confirmed the full consumption of the starting material (approx. 2 h). $\text{Ar}_{(\text{g})}$ was then bubbled through the reaction mixture for 10 min, and triphenylphosphine (11.3 g, 43.1 mmol, 2.00 eq.) was added in a single addition. The reaction mixture was allowed to slowly warm to room temperature over a period of 12 h. The crude mixture was then concentrated *in vacuo* and the resulting viscous oil was purified by silica flash chromatography (7.5 to 10% EtOAc/Hexanes) to afford title compound **3.23** (8.76 g, 86%).

NOTE: Conversion of the alkene into the molozonide must be followed using PA stain, as it has the same R_f and staining color as the starting material when revealed using UV pr KMnO_4 . On small scale (ca. 1 mmol), only 10-15 min of $\text{O}_{3(\text{g})}$ bubbling is required.

TLC R_f 0.40 (10% EtOAc:Hexanes) [UV / KMnO_4 / UV]

^1H NMR (400 MHz, CDCl_3) δ 10.02 (t, $J = 2.8$ Hz, 1H), 7.80 – 7.74 (m, 4H), 7.51 – 7.34 (m, 6H), 7.27 (d, $J = 9.1$ Hz, 2H, overlap with CHCl_3 signal), 6.87 (d, $J = 8.7$ Hz, 2H), 4.82 (d, $J = 10.4$ Hz, 1H), 4.66 (d, $J = 10.4$ Hz, 1H), 3.81 (s, 3H), 2.86 (dd, $J = 15.6, 2.9$ Hz, 1H), 2.81 (dd, $J = 15.6, 2.7$ Hz, 1H), 1.73 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 200.9, 159.4, 135.6, 132.8, 130.3, 129.9, 129.5, 128.0, 113.9, 109.3, 88.1, 71.4, 66.8, 55.4, 54.5, 27.2, 27.1, 18.7.

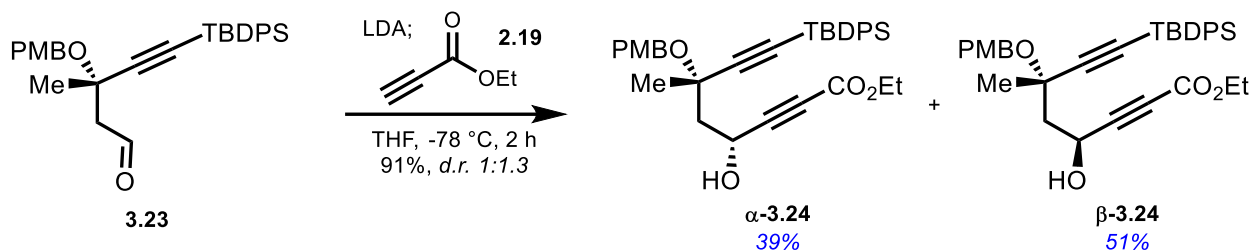
HRMS-ESI (m/z) calcd. for $\text{C}_{30}\text{H}_{34}\text{O}_3\text{Si}$: 493.2175 $[\text{M}+\text{Na}]^+$, found 493.2228 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3069, 2929, 2857, 2172, 1726, 1514, 1248, 1110.

$[\alpha]_D^{24} +13.2^\circ$ ($c = 0.50$, CHCl_3)

Physical State Colorless oil

Ethyl (4R,6S)-8-(*tert*-butyldiphenylsilyl)-4-hydroxy-6-((4-methoxybenzyl)oxy)-6-methylocta-2,7-diynoate (**α -3.24**) and Ethyl (4S,6S)-8-(*tert*-butyldiphenylsilyl)-4-hydroxy-6-((4-methoxybenzyl)oxy)-6-methylocta-2,7-diynoate (**β -3.24**).



A 250 mL round bottom flask containing a magnetic stir bar was flame-dried under vacuum then cycled between vacuum/ $\text{Ar}_{(\text{g})}$ (3x). Diisopropylamine (3.68 mL, 26.1 mmol, 1.35 eq.) and anhydrous THF (43 mL) were added. This mixture was cooled to -78°C before a *n*-BuLi solution (2.5M in hexanes, 9.66 mL, 24.1 mmol, 1.25 eq.) was added. This mixture was stirred for 5 minutes at -78°C before a solution of ethyl propiolate **2.19** (2.37 g, 24.1 mmol, 1.25 eq.) in THF (12 mL) was added dropwise. After stirring this solution for 30 min, a solution of **3.23** (9.09 g, 19.3 mmol, 1.00 eq.) in THF (10 mL + 2 x 1 mL washes) was added dropwise. This solution was stirred at -78°C for 2 h at this temperature. The reaction was then quenched with satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (100 mL) and the mixture was allowed to warm to room temperature over 30 minutes. The mixture was transferred to an extraction funnel where organic phase collected. The aqueous phase extracted with Et_2O (3 x 50 mL), the combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4 , filtrated and concentrated *in vacuo*. Purification by silica flash chromatography (0.5% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ until **α -3.24** fully eluted, then 3% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) afforded title compounds **α -3.24** (5.39 g, 39%) and **β -3.24** (7.05 g, 51%).

For **α -3.24**:

TLC R_f 0.40 (2% $\text{EtOAc}:\text{CH}_2\text{Cl}_2$) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.78 – 7.73 (m, 4H), 7.54 – 7.32 (m, 6H), 7.25 (d, J = 8.0 Hz, 2H, *overlap with* CHCl_3), 6.86 (d, J = 8.5 Hz, 2H), 5.02 – 4.96 (m, 1H), 4.80 (d, J = 10.3 Hz, 1H), 4.61 (d, J = 10.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.40 (d, J = 2.8 Hz, *OH*), 2.55 (dd, J = 14.7, 9.4 Hz, 1H), 2.30 (dd, J = 14.7, 2.6 Hz, 1H), 1.72 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.5, 153.5, 135.6, 132.8, 130.0, 129.9, 129.6, 128.0, 114.1, 109.9, 87.8, 87.1, 76.5, 73.2, 66.9, 62.2, 59.5, 55.5, 47.9, 27.2, 26.2, 18.7, 14.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{40}\text{O}_5\text{Si}$: 591.2543 $[\text{M}+\text{Na}]^+$, found 591.2523 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3483, 2929, 2856, 2237, 2170, 1715, 1704, 1513, 1245.

$[\alpha]_D^{24} +23.0^{\circ}$ (c = 0.50, CHCl_3)

Physical State Light yellow oil

For **β -3.24**:

TLC R_f 0.50 (2% $\text{EtOAc}:\text{CH}_2\text{Cl}_2$) [KMnO_4 / UV]

^1H NMR (600 MHz, CDCl_3) δ 7.80 – 7.75 (m, 4H), 7.40 (dtd, J = 14.1, 7.1, 2.1 Hz, 6H), 7.22 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.24 (d, J = 9.9 Hz, 1H), 4.81 (d, J = 10.1 Hz, 1H), 4.55 (d, J = 10.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.97 (br s, *OH*), 3.79 (s, 3H), 2.38 (dd, J = 14.6, 10.0 Hz, 1H), 2.29 – 2.23 (m, 1H), 1.69 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.6, 153.5, 135.6, 132.7, 129.9, 129.7, 129.6, 128.1, 114.2, 108.5, 88.6, 87.1, 76.1, 75.5, 66.9, 62.2, 60.9, 55.4, 48.6, 27.2, 26.9, 18.7, 14.1.

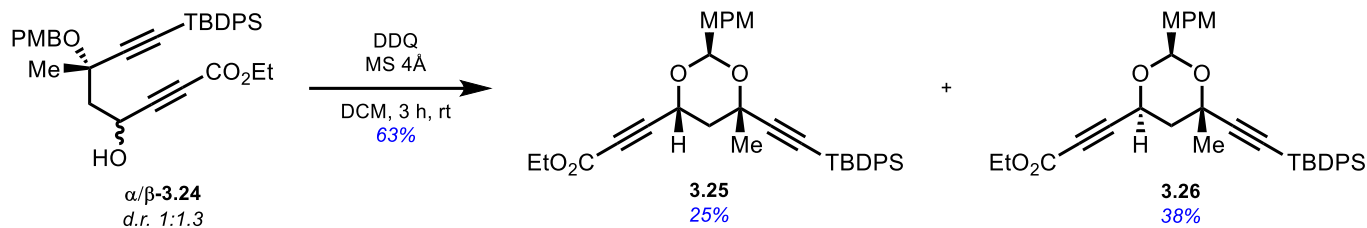
HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{40}\text{O}_5\text{Si}$: 591.2543 $[\text{M}+\text{Na}]^+$, 591.2525 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3484, 2930, 2857, 2246, 2165, 1719, 1709, 1513, 1243, 1109.

$[\alpha]_D^{24} +77.0^{\circ}$ (c = 0.50, CHCl_3)

Physical State Light yellow oil

Ethyl 3-((2R,4R,6S)-6-((*tert*-butyldiphenylsilyl)ethynyl)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)propionate (**3.25**) and Ethyl 3-((2R,4S,6S)-6-((*tert*-butyldiphenylsilyl)ethynyl)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)propionate (**3.26**).



A flame-dried 5 mL round bottom flask was charged with a stir bar, the 1:1.3 diastereomeric mixture of propargylic alcohols **α -3.24** and **β -3.24** (25.8 mg, 45.5 μ mol, 1.00 eq.) and anhydrous CH_2Cl_2 (0.5 mL, 45 mM) was added, followed by addition of 4Å powdered molecular sieves (51.6 mg). This mixture was cooled to 0°C before DDQ (20.6 mg, 90.7 μ mol, 2.00 eq.) was added in a single portion. A sceptor was added to the flask and the ice bath was taken off. The dark green reaction mixture was stirred at room temperature for 3 hours, after which TLC analysis showed full consumption of the starting material. The reaction mixture was filtered through a Celite™ pad and eluted with EtOAc (~10 mL). The filtrate was transferred to an extraction funnel and washed with satd. $\text{NaHCO}_3(\text{aq.})$ (5 mL). The organic layer was collected and the aqueous layer extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried by Na_2SO_4 and concentrated *in vacuo*. The crude mixture (*deep red color*) was passed through a short silica pad using CHCl_3 (~10 mL) to remove the DDQ-derived impurities. The colorless filtrate was concentrated *in vacuo*. A ^1H NMR analysis of the crude mixture revealed a 1:1.5 mixture of acetals. Purification by Preparative TLC (20% EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compounds **3.25** (6.4 mg, 25%) and **3.26** (9.8 mg, 38%)

For **3.25**

TLC R_f 0.50 (20% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.87 – 7.78 (m, 4H), 7.45 (d, J = 8.8 Hz, 2H), 7.42 – 7.34 (m, 6H), 6.92 (d, J = 8.5 Hz, 2H), 6.52 (s, 1H), 5.23 (d, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.78 (q, J = 7.2 Hz, 2H), 2.34 (dd, J = 13.8, 7.0 Hz, 1H), 2.20 (d, J = 13.7 Hz, 1H), 1.73 (s, 3H), 1.10 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 160.3, 152.9, 135.7, 135.6, 133.2, 133.1, 130.3, 129.6, 129.6, 127.9, 127.9, 127.8, 113.9, 110.2, 94.1, 87.5, 84.9, 79.5, 69.3, 62.9, 61.9, 55.5, 38.1, 31.8, 27.2, 18.8, 13.7.

HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{38}\text{O}_5\text{Si}$: 589.2386 $[\text{M}+\text{Na}]^+$, found 589.2379 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3070, 2929, 2857, 2237, 1711, 1702, 1517, 1246, 1128.

$[\alpha]_D^{24}$ -7.0° (c = 0.50, CHCl_3)

Physical State Yellow oil

For **3.26**

TLC R_f 0.60 (20% EtOAc:Hexanes) [KMnO_4 / UV]

^1H NMR (600 MHz, CDCl_3) δ 7.80 – 7.75 (m, 4H), 7.47 – 7.36 (m, 8H), 6.90 (d, J = 8.7 Hz, 2H), 6.09 (s, 1H), 5.13 (dd, J = 11.4, 2.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.81 (d, J = 3.7 Hz, 3H), 2.18 (dd, J = 13.2, 11.4 Hz, 1H), 2.13 (dd, J = 13.2, 2.9 Hz, 1H), 1.72 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 160.5, 153.2, 135.6, 132.8, 132.7, 129.9, 128.1, 127.9, 113.9, 108.6, 97.7, 88.6, 84.0, 70.9, 64.6, 62.4, 55.5, 42.1, 29.6, 27.2, 18.7, 14.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{38}\text{O}_5\text{Si}$: 589.2386 $[\text{M}+\text{Na}]^+$, found 589.2356 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2932, 2856, 2246, 1715, 1517, 1250.

$[\alpha]_D^{24}$ +5.0° (c = 1.00, CHCl_3)

Physical State Yellow oil

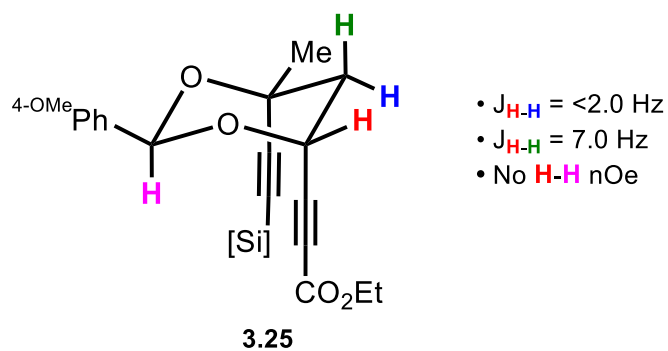


Figure 5.6. Structural analysis of acetal **3.25** and assignment of the configuration of propargylic alcohols α -**3.24**.

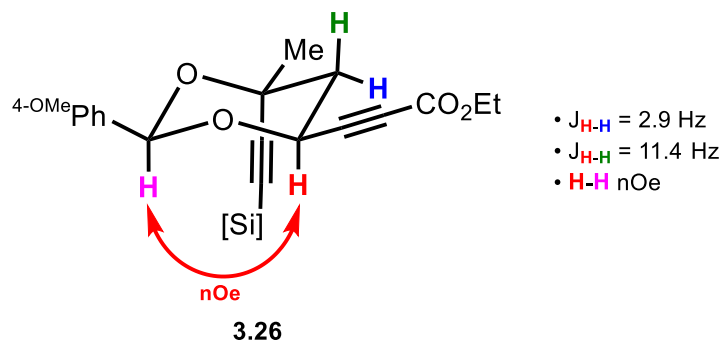
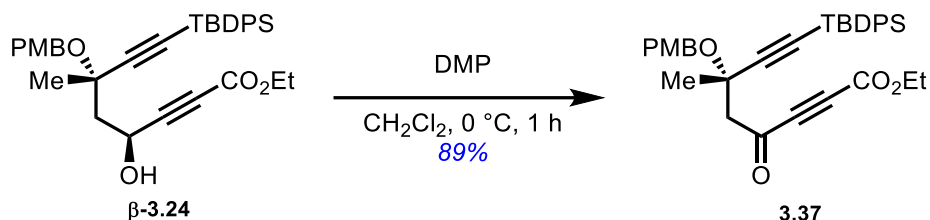


Figure 5.7. Structural analysis of acetal **3.26** and assignment of the configuration of propargylic alcohol β -**3.24**.

Ethyl (S)-8-(*tert*-butyldiphenylsilyl)-6-((4-methoxybenzyl)oxy)-6-methyl-4-oxoocta-2,7-diynoate (**3.37**).



A 500 mL round bottom flask containing a stir bar was charged with **$\beta\text{-3.24}$** (7.05 g, 12.4 mmol, 1.0 eq.) and CH_2Cl_2 (125 mL) was added. This mixture was cooled to 0 °C before Dess–Martin Periodinane (7.89 g, 18.6 mmol, 1.50 eq.) was added portion wise over 5 minutes. The reaction was stirred at 0 °C for 1 h at this temperature after which TLC showed full consumption of starting material. Satd. $\text{Na}_2\text{S}_2\text{O}_3(\text{aq.})$ (60 mL) and satd. $\text{NaHCO}_3(\text{aq.})$ (60 mL) were carefully added (*NOTE : vigorous gas generation*) and the mixture was stirred vigorously for 20 min while warming to room temperature. The mixture was transferred to an extraction funnel and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 75 mL). The organic phases were combined and washed with water (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (15% EtOAc/Hexanes) yielded title compound **3.37** (6.27 g, 89%).

TLC R_f 0.45 (40% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.79 (dt, $J = 7.9, 1.9$ Hz, 4H), 7.44 – 7.34 (m, 6H), 7.30 (d, $J = 8.7$ Hz, 2H), 6.90 – 6.82 (d, $J = 8.7$ Hz, 2H), 4.80 (d, $J = 10.3$ Hz, 1H), 4.68 (d, $J = 10.3$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 3.21 (s, 2H), 1.76 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 182.1, 159.3, 152.3, 135.7, 132.9, 130.3, 129.8, 129.6, 127.9, 113.9, 108.8, 87.9, 81.6, 79.0, 71.9, 66.9, 62.9, 55.5, 55.4, 27.2, 27.2, 18.7, 14.0.

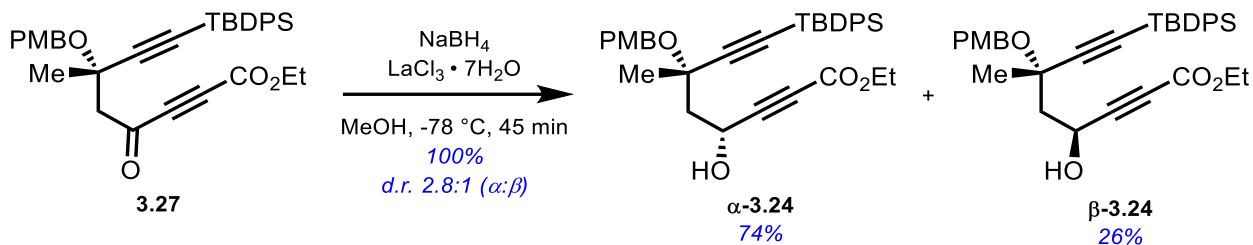
HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{38}\text{O}_5\text{Si}$: 589.2386 $[\text{M}+\text{Na}]^+$, found 589.2383 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2929, 2858, 2172, 1718, 1676, 1513, 1242, 1109, 1030.

$[\alpha]_D^{24}$ +21.7 ° ($c = 1.00$, CHCl_3)

Physical State Viscous light-yellow oil

Ethyl (4R,6S)-8-(*tert*-butyldiphenylsilyl)-4-hydroxy-6-((4-methoxybenzyl)oxy)-6-methylocta-2,7-diynoate (**α -3.24**) and Ethyl (4S,6S)-8-(*tert*-butyldiphenylsilyl)-4-hydroxy-6-((4-methoxybenzyl)oxy)-6-methylocta-2,7-diynoate (**β -3.24**)



A 1 L round bottom flask containing a stir bar was charged with **3.27** (6.27 g, 11.1 mmol, 1.00 eq.) and anhydrous MeOH (111 mL, 0.1 M). This mixture was cooled to -78 °C before $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ (6.16 g, 16.6 mmol, 1.50 eq.) was added. This mixture was stirred 10 minutes at this temperature before NaBH_4 (627 mg, 16.6 mmol, 1.5 eq.) was added portionwise over 5 minutes. The reaction mixture was stirred at -78 °C for 45 minutes at which point TLC monitoring showed full consumption of the starting material. Satd. $\text{NaHCO}_3(\text{aq})$ (150 mL) was carefully added (*NOTE: Vigorous gas generation!*). The suspension was then stirred vigorously while warming to room temperature. The resulting thick white suspension was then concentrated *in vacuo* to remove all the volatiles. The resulting solid was partitioned between H_2O (300 mL) and EtOAc (150 mL) and stirred vigorously for 30 minutes. The mixture was transferred to an extraction funnel containing brine (200 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield title compounds **α -3.24** and **β -3.24** (6.27 g, 100%) in a 2.8:1 mixture in high purity (>98%) as observed by ^1H NMR. Purification by silica flash chromatography (0.5% EtOAc/ CH_2Cl_2 until **α -3.24** fully eluted, then 3% EtOAc/ CH_2Cl_2) afforded title compounds **α -3.24** (4.63 g, 74%) and **β -3.24** (1.64 g, 26%).

For **α -3.24**:

TLC R_f 0.40 (2% EtOAc: CH_2Cl_2) [KMnO_4 / UV]

^1H NMR (600 MHz, CDCl_3) δ 7.78 – 7.73 (m, 4H), 7.54 – 7.32 (m, 6H), 7.25 (d, J = 8.0 Hz, 2H, *overlap with CHCl_3*), 6.86 (d, J = 8.5 Hz, 2H), 5.02 – 4.96 (m, 1H), 4.80 (d, J = 10.3 Hz, 1H), 4.61 (d, J = 10.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.40 (d, J = 2.8 Hz, OH), 2.55 (dd, J = 14.7, 9.4 Hz, 1H), 2.30 (dd, J = 14.7, 2.6 Hz, 1H), 1.72 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.5, 153.5, 135.6, 132.8, 130.0, 129.9, 129.6, 128.0, 114.1, 109.9, 87.8, 87.1, 76.5, 73.2, 66.9, 62.2, 59.5, 55.5, 47.9, 27.2, 26.2, 18.7, 14.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{40}\text{O}_5\text{Si}$: 591.2543 [$\text{M}+\text{Na}$] $^+$, found 591.2523 [$\text{M}+\text{Na}$] $^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3483, 2929, 2856, 2237, 1715, 1704, 1513, 1245, 1109

$[\alpha]_D^{24} +23.0^\circ$ (c = 0.50, CHCl_3)

Physical State Light yellow oil

For **β -3.24**:

TLC R_f 0.50 (2% EtOAc: CH_2Cl_2) [KMnO_4 / UV]

^1H NMR (600 MHz, CDCl_3) δ 7.80 – 7.75 (m, 4H), 7.40 (dtd, J = 14.1, 7.1, 2.1 Hz, 6H), 7.22 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.24 (d, J = 9.9 Hz, 1H), 4.81 (d, J = 10.1 Hz, 1H), 4.55 (d, J = 10.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.97 (br s, OH), 3.79 (s, 3H), 2.38 (dd, J = 14.6, 10.0 Hz, 1H), 2.29 – 2.23 (m, 1H), 1.69 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.6, 153.5, 135.6, 132.7, 129.9, 129.7, 129.6, 128.1, 114.2, 108.5, 88.6, 87.1, 76.1, 75.5, 66.9, 62.2, 60.9, 55.4, 48.6, 27.2, 26.9, 18.7, 14.1.

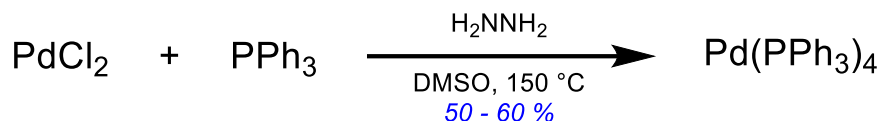
HRMS-ESI (m/z) calcd. for $\text{C}_{35}\text{H}_{40}\text{O}_5\text{Si}$: 591.2543 [$\text{M}+\text{Na}$] $^+$, 591.2525 [$\text{M}+\text{Na}$] $^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3484, 2930, 2857, 2246, 1719, 1709, 1513, 1243, 1109

$[\alpha]_D^{24} +77.0^\circ$ (c = 0.50, CHCl_3)

Physical State Light yellow oil

Tetrakis(triphenylphosphine)palladium(0)



Protocol adapted from *Coulson et al.*⁸ A 50 mL Schlenk flask containing a stir bar was capped with a new sceptor, flame-dried under vacuum and backfilled with Ar_(g) (3 cycles). The sceptor was removed and under positive pressure of Ar_(g), PdCl₂ (356 mg, 2.00 mmol, 1.00 eq.) and PPh₃ (2.62 g, 10.0 mmol, 5.0 eq.) were added. The sceptor was reattached and the flask was once again cycled between vacuum and Ar_(g) (3 cycles). DMSO (25 mL) was sparged Ar_(g) for 15 minutes and transferred to the Schlenk flask. The mixture was plunged into a wax bath that was preheated to 160 °C. This mixture was stirred vigorously until all the contents were dissolved. When the solution became homogenous, hydrazine hydrate (388 µL, 8.00 mmol, 4.00 eq.) was injected rapidly, the mixture was taken out of the wax bath and stirring turned off. The solution was allowed to cool and within minutes, crystals of Pd(PPh₃)₄ can be seen crystallizing out of solution. When the mixture had reached room temperature and under a positive pressure of Ar_(g), the stir bar was removed and the sceptor was swapped with a sceptor containing a Schlenk filtration apparatus (long needle head wrapped with filter paper tied by copper wire, see figure 5.8). The DMSO was filtered out by connecting the Schlenk filtration apparatus to another Schlenk flask under vacuum. The remaining light orange solid was washed with EtOH (2 x 10 mL) and Et₂O (2 x 10 mL). Under positive Ar_(g) pressure, the Schlenk filtration apparatus was removed and a new sceptor was attached. The content of the Schlenk flask was dried under high vacuum overnight and subsequently backfilled with Ar_(g). The flask was transferred to a glovebox where the freshly synthesized light yellow Pd(PPh₃)₄ was stored and ready for use.

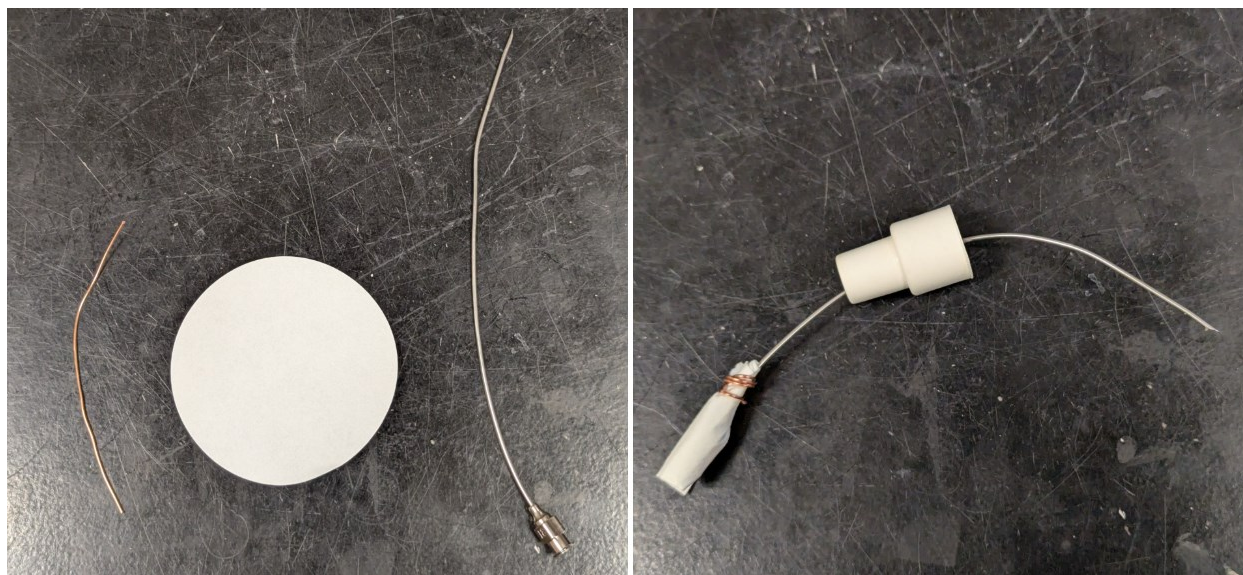
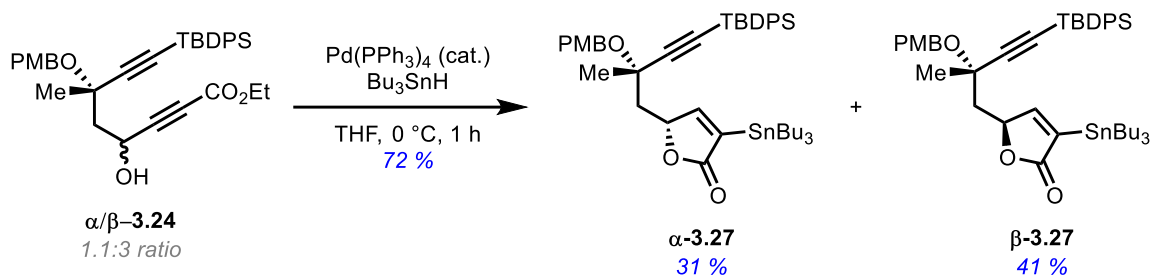


Figure 5.8. Schlenk filtration apparatus.

(R)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-3-(tributylstannyl)furan-2(5H)-one (**α** -3.27) and (S)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-3-(tributylstannyl)furan-2(5H)-one (**β** -3.27)



A two-neck 100 mL round bottom flask containing a magnetic stir bar and a 1:1.3 mixture of propargylic alcohols **α/β** -3.24 (2.66 g, 4.68 mmol, 1.00 eq.) was cycled between vacuum/ $\text{Ar}_{(\text{g})}$ (3x). Anhydrous THF (26 mL) was added and the mixture was cooled to 0 °C. $\text{Pd}(\text{PPh}_3)_4$ (270 mg, 0.234 mmol, 0.05 eq.) was then added portionwise (5x equal portions over 10 minutes). After stirring an additional 10 min, Bu_3SnH (1.29 mL, 4.78 mmol, 1.08 eq.) was then added dropwise over 5 minutes and the resulting mixture was stirred at 0 °C for 1 h, at which point TLC monitoring showed full consumption of the starting material. At this point, silica gel (SiO_2 , *ca.* 5 g) was added to the reaction mixture and the solvent was removed *in vacuo*. The crude mixture was directly purified by dry loading silica flash chromatography (60 % CH_2Cl_2 /Hexanes until **α** -3.27 fully eluted, then 100% CH_2Cl_2) to afford title compounds **α** -3.27 (1.05 g, 28%) and **β** -3.27 (1.49 g, 39%).

For **α** -3.27

TLC R_f 0.40 (70% CH_2Cl_2 /Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, J = 7.6 Hz, 4H), 7.59 (s, 1H), 7.44 – 7.34 (m, 6H), 7.26 (d, J = 8.5 Hz, 2H overlap with CHCl_3), 6.86 (d, J = 8.5 Hz, 2H), 5.44 (t, J = 6.2 Hz, 1H), 4.80 (d, J = 10.2 Hz, 1H), 4.58 (d, J = 10.2 Hz, 1H), 3.80 (s, 3H), 2.32 (dd, J = 13.9, 5.5 Hz, 1H), 2.06 (dd, J = 13.9, 7.8 Hz, 1H), 1.71 (s, 3H), 1.52 – 1.39 (m, 6H), 1.27 (h, J = 7.3 Hz, 6H), 1.11 (s, 9H), 1.05 – 0.97 (m, 6H), 0.86 (t, J = 7.3 Hz, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 177.9, 167.3, 159.4, 135.6, 133.9, 132.9, 130.5, 129.9, 129.6, 128.0, 113.9, 109.7, 87.7, 83.1, 72.9, 66.7, 55.4, 46.1, 29.0, 27.3, 27.2, 27.1, 18.7, 13.8, 9.8.

HRMS-ESI (m/z) calcd. for $\text{C}_{45}\text{H}_{62}\text{O}_4\text{SiSn}$: 837.3337 $[\text{M}+\text{Na}]^+$, found 837.3345 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2955, 2926, 2856, 2359, 1743, 1514, 1248, 1104, 1020.

$[\alpha]_D^{24}$ -7.8 ° (c = 0.50, CHCl_3)

Physical State Viscous light-yellow oil

For **β** -3.27

TLC R_f 0.25 (70% CH_2Cl_2 /Hexanes) [KMnO_4 / UV]

^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, J = 6.9 Hz, 4H), 7.53 (d, J = 1.4 Hz, 1H), 7.45 – 7.32 (m, 6H), 7.28 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.34 (t, J = 5.6 Hz, 1H), 4.75 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 10.5 Hz, 1H), 3.80 (s, 3H), 2.34 (dd, J = 14.7, 5.2 Hz, 1H), 2.17 (dd, J = 14.6, 7.1 Hz, 1H), 1.77 (s, 3H), 1.54 – 1.35 (m, 6H), 1.27 (dq, J = 14.5, 7.3 Hz, 6H), 1.09 (s, 9H), 1.05 – 0.98 (m, 6H), 0.87 (t, J = 7.3 Hz, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 177.9, 166.3, 159.3, 135.6, 134.9, 133.0, 130.7, 129.8, 129.5, 127.9, 113.9, 111.1, 86.2, 81.52, 72.2, 66.7, 55.4, 45.4, 29.0, 27.3, 27.2, 26.4, 18.7, 13.8, 9.8.

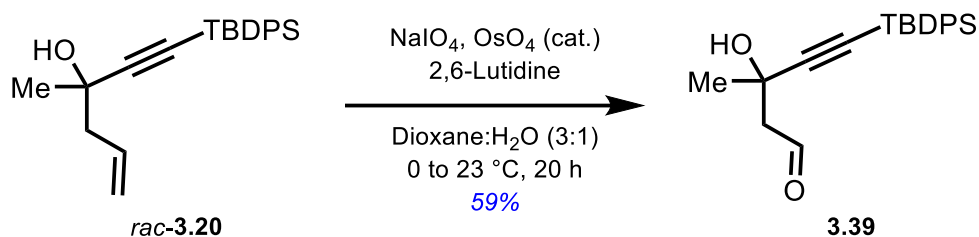
HRMS-ESI (m/z) calcd. for $\text{C}_{45}\text{H}_{62}\text{O}_4\text{SiSn}$: 837.3337 $[\text{M}+\text{Na}]^+$, found 837.3326 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2957, 2928, 2852, 2361, 1743, 1513, 1249, 1109, 1027.

$[\alpha]_D^{24}$ 42.4 ° (c = 0.25, CHCl_3)

Physical State Viscous dark orange oil

5-(*tert*-Butyldiphenylsilyl)-3-hydroxy-3-methylpent-4-ynal (**3.39**).



To a 25 mL round bottom flask was added a magnetic stir bar, *rac*-**3.20** (590 mg, 1.69 mmol, 1.00 eq.) and 1,4-dioxane/water (3:1, 8 mL, 0.21 M). This mixture was cooled to 0 °C before 2,6-lutidine (392 μ L, 3.36 mmol, 2.00 eq.), NaIO₄ (1.45 g, 6.77 mmol, 4.00 eq.) and a solution of OsO₄ (4% in H₂O, 323 μ L, 51 μ mol, 0.03 eq.) were sequentially added. The ice bath was then removed and the reaction was allowed to warm to room temperature. After 20 h, TLC analysis revealed full consumption of the starting material. Water (10 mL) was added and the mixture was transferred to an extraction funnel and was extracted with CH₂Cl₂ (3x 5 mL). The organic layers were combined, washed with brine (5 mL), dried by Na₂SO₄ and concentrated *in vacuo*. The compound was semi-purified by passing the crude through a short silica plug (*ca.* 3 cm) eluting with 20% EtOAc:Hexanes to yield the title compound **3.39** (351 mg, 59%).

NOTE : This aldehyde is not stable on silica and showed significant amount of decomposition when purified by a longer SFC. A ¹H NMR analysis of one fraction obtained during purification is furnished. This aldehyde was carried through the next step without further purification.

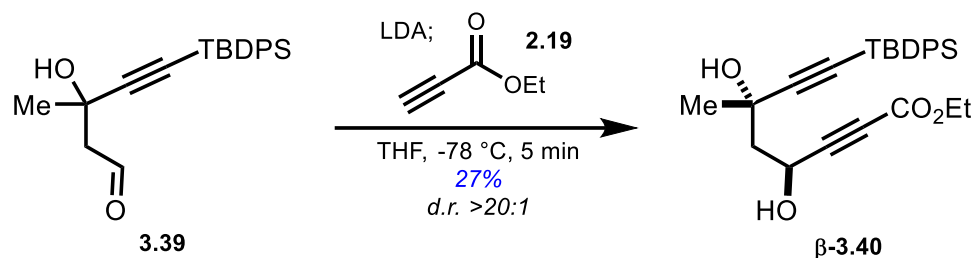
TLC R_f 0.25 (20% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 9.97 (t, *J* = 1.7 Hz, 1H), 7.81 – 7.67 (m, 4H), 7.45 – 7.29 (m, 6H), 3.12 (br s, *OH*), 2.95 (dd, *J* = 16.7, 1.8 Hz, 1H), 2.81 (dd, *J* = 16.7, 1.7 Hz, 1H), 1.68 (s, 3H), 1.08 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 201.1, 135.5, 132.8, 129.7, 127.8, 111.7, 84.4, 65.6, 55.3, 30.3, 27.0, 18.6.

Physical State Yellow oil

Ethyl (4S,6S)-8-(*tert*-butyldiphenylsilyl)-4,6-dihydroxy-6-methylocta-2,7-diyneate (**β -3.40**).



A 5 mL round bottom flask containing a stirbar flask was torched under vacuum and cycled between vacuum and Ar_(g) (3 x 5min/cycle) before diisopropylamine (73 μ L, 0.519 mmol, 5.20 eq.) and anhydrous THF (0.5 mL) were added. This mixture was cooled to -78°C before *n*-BuLi (2.5 M in hexanes, 204 μ L, 0.509 mmol, 5.10 eq.) was added. Then, a solution of **2.19** (56 μ L, 0.529 mmol, 5.30 eq.) in THF (0.5 mL) was added dropwise, and, 30 min later, a solution of **3.39** (35 mg, 0.100 mmol, 1.00 eq.) in THF (0.5 mL) was added dropwise. The solution was stirred at -78°C for 5 min at this temperature before the reaction was quenched with satd. NH₄Cl_(aq.), (3 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (3 mL) and dried over Na₂SO₄, filtrated and concentrated in vacuo. A purification by a short silica plug (50% Et₂O/Hexanes) afforded title compound **β -3.40** (11.9 mg, 27%) as the sole diastereoisomer.

NOTE : This reaction could be ran using LiHMDS as a base with a higher yield of 72% in a 1:4.6 d.r. α : β -3.40
Diols α -3.40 & β -3.40 were found to be unstable on silica and purification by SFC significantly degraded the material. A ¹H NMR analysis of the reaction crudes determined the diastereomeric ratio. The diastereoisomers were identified vide infra by turning them into their corresponding carbonates.

For **β -3.40**

TLC R_f 0.45 (33% Et₂O/Hexanes) [UV / KMnO₄]

¹H NMR (300 MHz, CDCl₃) δ 7.77 – 7.71 (m, 4H), 7.43 – 7.34 (m, 6H), 5.00 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.44 (dd, *J* = 14.5, 9.0 Hz, 1H), 2.24 (dd, *J* = 14.5, 3.8 Hz, 1H), 1.70 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H).

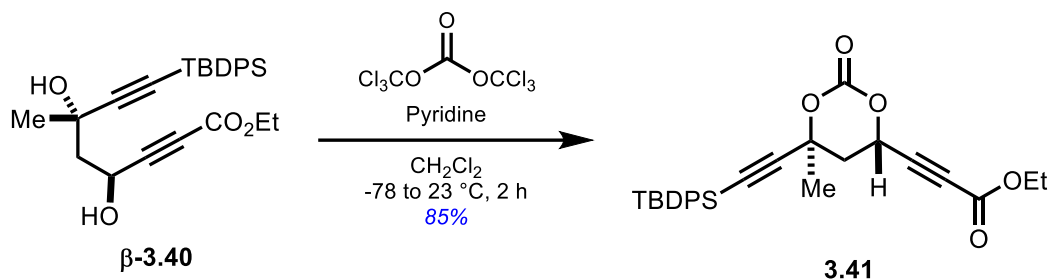
For **α -3.40**

TLC R_f 0.45 (33% Et₂O/Hexanes) [UV / KMnO₄]

¹H NMR (300 MHz, CDCl₃) δ 7.77 – 7.71 (m, 4H), 7.43 – 7.34 (m, 6H), 5.15 (dd, *J* = 8.9, 1.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.27 (dd, *J* = 14.6, 10.9 Hz, 1H), 2.14 (dd, *J* = 14.5, 2.3 Hz, 1H), 1.64 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 2H), 1.05 (s, 9H).

Physical State Orange oil

Ethyl 3-((4*S*,6*S*)-6-((*tert*-butyldiphenylsilyl)ethynyl)-6-methyl-2-oxo-1,3-dioxan-4-yl)propiolate (**3.41**).



To a 5 mL round bottom flask was added a magnetic stir bar, **β-3.40** (11.9 mg, 26.7 μ mol, 1.00 eq.) and CH_2Cl_2 (0.5 mL). Pyridine (22 μ L, 268 μ mol, 10.0 eq.) was added and the resulting mixture was cooled to -78°C . A solution of triphosgene (16.3 mg, 54.8 μ mol, 2.05 eq.) in CH_2Cl_2 (0.5 mL) was added dropwise and the mixture was stirred for 1 h at this temperature before the mixture was warmed to room temperature and allowed to stir for another hour. At this point, TLC analysis indicated full consumption of the starting material. Satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (3 mL) was added and the mixture was stirred vigorously for 10 min. The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by Preparative TLC (25% EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **3.41** (10.8 mg, 85%).

TLC R_f 0.55 (25% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.72 – 7.65 (m, 4H), 7.49 – 7.34 (m, 6H), 5.67 (ddd, J = 12.1, 3.8, 2.2 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.55 (dd, J = 14.2, 3.9 Hz, 1H), 2.34 (dd, J = 14.2, 12.1 Hz, 1H), 1.85 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.5, 146.0, 135.5, 131.9, 131.8, 130.2, 128.2, 104.9, 90.4, 79.7, 79.5, 75.3, 66.6, 62.9, 39.1, 28.7, 27.1, 18.7, 14.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_5\text{Si}$: 497.1760 $[\text{M}+\text{Na}]^+$, found 497.1754 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2936, 2858, 2168, 1775, 1717, 1262, 1233, 1111.

Physical State Colorless oil

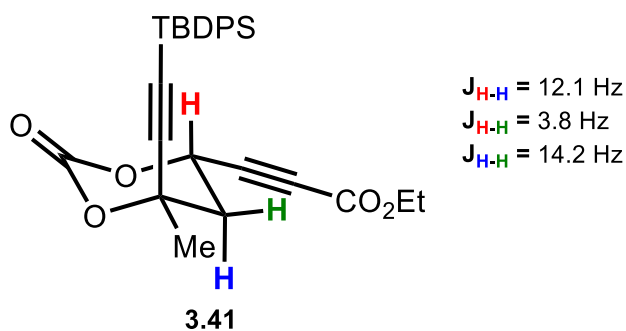
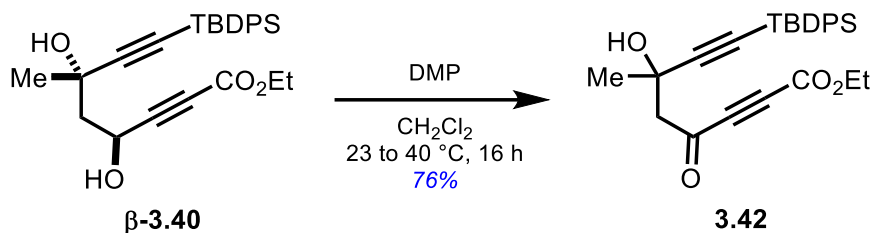


Figure 5.9. Structural analysis of carbonate **3.41** and determination of the relative configuration of diol **β-3.40**.

Ethyl 8-(*tert*-butyldiphenylsilyl)-6-hydroxy-6-methyl-4-oxoocta-2,7-diynoate (**3.42**).



A 25 mL pressure vial containing a stir bar was charged with **$\beta\text{-3.40}$** (312 mg, 695 μmol , 1.00 eq.) and CH_2Cl_2 (10 mL). Dess-Martin Periodane (619 mg, 1.46 mmol, 2.10 eq.) was then added portion wise over 10 minutes. The headspace was displaced with $\text{Ar}_{(\text{g})}$ for 60 seconds, sealed, lowered in an oil bath and subsequently heated to 40 $^\circ\text{C}$ for 16 h. The reaction mixture was then cooled to room temperature before satd. $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq.})}$ (3 mL) and satd. $\text{NaHCO}_3_{(\text{aq.})}$ (3 mL) were added. This mixture was stirred vigorously for 30 minutes before it was transferred to an extraction funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (20% CH_2Cl_2 /Toluene) afforded the title compound **3.42** (235 mg, 76%).

NOTE : Compound 3.42 is not stable over prolonged periods of time and showed decomposition when stored at -20 $^\circ\text{C}$ after 3 days and must be used immediately after it is synthesized. This experiment was conducted by Elliot Jackson.

TLC R_f 0.20 (20% CH_2Cl_2 /Toluene) [UV / KMnO_4]

^1H NMR (300 MHz, CDCl_3) δ 7.75 (dq, J = 8.4, 2.9 Hz, 4H), 7.38 (ddd, J = 6.1, 3.3, 1.8 Hz, 6H), 4.29 (q, J = 7.1 Hz, 2H), 3.61 (br s, OH), 3.30 (d, J = 17.3 Hz, 1H), 3.05 (d, J = 17.3 Hz, 1H), 1.66 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 197.9, 164.9, 154.5, 135.6, 132.4, 129.9, 127.9, 108.3, 94.1, 88.2, 78.7, 60.6, 48.6, 29.9, 28.7, 27.1, 18.7, 14.4.

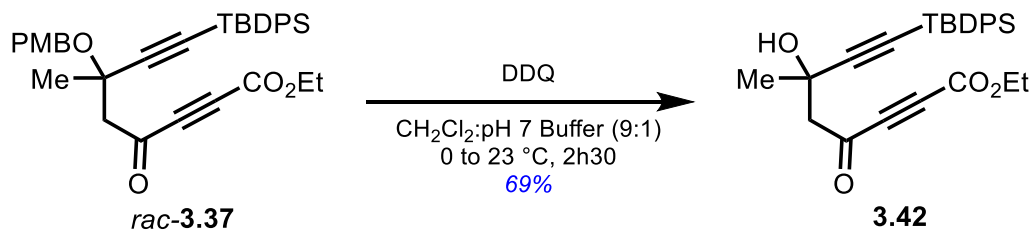
HRMS-ESI (m/z) calcd. for $\text{C}_{27}\text{H}_{30}\text{O}_4\text{Si}$: 447.1992 $[\text{M}+\text{H}]^+$, found 447.1986 $[\text{M}+\text{H}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3487, 2956, 2930, 2857, 2177, 1718, 1685, 1243, 1222, 1110.

Physical State White waxy solid

Melting Point *ca.* 10 – 15 $^\circ\text{C}$

Ethyl 8-(*tert*-butyldiphenylsilyl)-6-hydroxy-6-methyl-4-oxoocta-2,7-diynoate (**3.42**).



To a 5 mL round bottom flask containing a magnetic stir bar and *rac*-**3.37** (48.0 mg, 84.7 μmol , 1.00 eq.) was added CH_2Cl_2 (1.80 mL) and pH 7 phosphate buffer (0.2 mL). This mixture was cooled to 0 °C before DDQ (38.4 mg, 169 μmol , 2.00 eq.) was added in 4 equal portions over *ca.* 30 minutes. The mixture was then warmed to room temperature and stirred vigorously an additional 2 h after which TLC analysis indicated full consumption of the starting material. Satd. $\text{NaHCO}_3(\text{aq.})$ (2 mL) and stirred vigorously for 10 min. The organic layer was then removed from the reaction flask by using a Pasteur pipette and the aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (20% CH_2Cl_2 /Toluene) afforded title compound **3.42** (26.0 mg, 69%).

NOTE : Compound **3.42** is not stable over prolonged periods of time and showed decomposition when stored at -20 °C after 3 days and must be used immediately after it is synthesized.

TLC R_f 0.20 (20% CH_2Cl_2 /Toluene) [UV / KMnO_4]

^1H NMR (300 MHz, CDCl_3) δ 7.77 (dq, J = 8.4, 2.9 Hz, 4H), 7.40 (ddd, J = 6.1, 3.3, 1.8 Hz, 6H), 4.31 (q, J = 7.1 Hz, 2H), 3.63 (br s, OH), 3.32 (d, J = 17.3 Hz, 1H), 3.07 (d, J = 17.3 Hz, 1H), 1.68 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 197.9, 164.9, 154.5, 135.6, 132.4, 129.9, 127.9, 108.3, 94.1, 88.2, 78.7, 60.6, 48.6, 29.9, 28.7, 27.1, 18.7, 14.4.

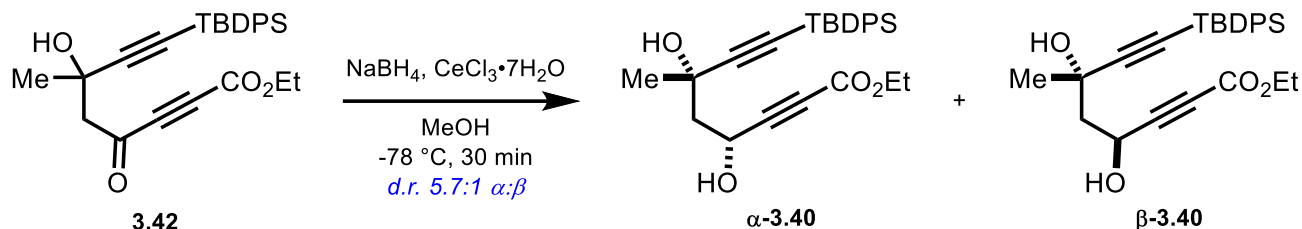
HRMS-ESI (m/z) calcd. for $\text{C}_{27}\text{H}_{30}\text{O}_4\text{Si}$: 447.1992 $[\text{M}+\text{H}]^+$, found 447.1986 $[\text{M}+\text{H}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3487, 2956, 2930, 2857, 2177, 1718, 1685, 1243, 1222, 1110.

Physical State White waxy solid

Melting Point *ca.* 10 – 15 °C

Ethyl (4R,6S)-8-(*tert*-butyldiphenylsilyl)-4,6-dihydroxy-6-methylocta-2,7-diynoate (**α -3.40**) and ethyl (4S,6S)-8-(*tert*-butyldiphenylsilyl)-4,6-dihydroxy-6-methylocta-2,7-diynoate (**β -3.40**).



A 4 mL vial containing a magnetic stir bar was charged with **3.42** (26.0 mg, 58.2 μmol , 1.00 eq.) and MeOH (0.6 mL). This solution was cooled to $-78\text{ }^\circ\text{C}$ (*NOTE : precipitation observed.*) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (32.5 mg, 87.3 μmol , 1.50 eq.) was added. This mixture was stirred 15 minutes at this temperature before NaBH_4 (4.4 mg, 116 μmol , 2.00 eq.) was added in a single addition and the mixture was stirred at $-78\text{ }^\circ\text{C}$. After 30 minutes, TLC analysis showed full consumption of the starting material. Satd. $\text{NaHCO}_3(\text{aq.})$ (1.5 mL) was added dropwise and the mixture warmed to room temperature, where it was extracted with Et_2O (3 x 2 mL). The organic layers were concentrated *in vacuo* and the resulting mixture was washed with H_2O (2 mL) and extracted again using EtOAc (3x 2 mL). The combined organic layers were dried using Na_2SO_4 and concentrated *in vacuo*. A ^1H NMR analysis of the crude mixture showed a diastereomeric ratio of 5.7:1 of title compounds **α -3.40** and **β -3.40**.

Diols α -3.40 and β -3.40. were found to be unstable on silica and purification significantly degraded the material. A ^1H NMR analysis of the reaction crudes determined the diastereomeric ratio. The diastereoisomers were identified vide infra by turning them into their corresponding carbonates and were carried to the next reaction without further purification.

For **β -3.40**

TLC R_f 0.45 (33% Et_2O /Hexanes) [UV / KMnO_4]

^1H NMR (300 MHz, CDCl_3) δ 7.77 – 7.71 (m, 4H), 7.43 – 7.34 (m, 6H), 5.00 (dd, $J = 9.0, 3.8\text{ Hz}$, 1H), 4.21 (q, $J = 7.1\text{ Hz}$, 2H), 2.44 (dd, $J = 14.5, 9.0\text{ Hz}$, 1H), 2.24 (dd, $J = 14.5, 3.8\text{ Hz}$, 1H), 1.70 (s, 3H), 1.29 (t, $J = 7.1\text{ Hz}$, 3H), 1.08 (s, 9H).

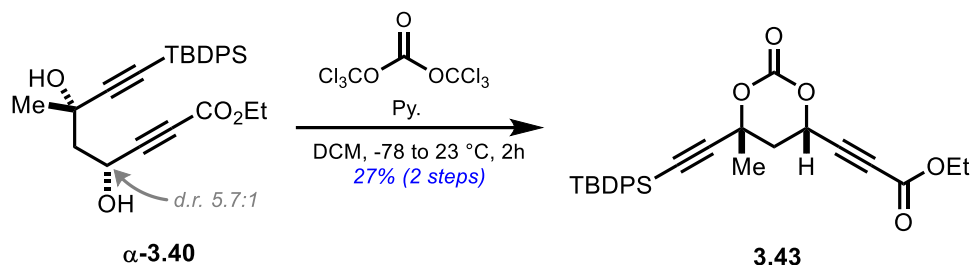
For **α -3.40**

TLC R_f 0.45 (33% Et_2O /Hexanes) [UV / KMnO_4]

^1H NMR (300 MHz, CDCl_3) δ 7.77 – 7.71 (m, 4H), 7.43 – 7.34 (m, 6H), 5.15 (dd, $J = 8.9, 1.1\text{ Hz}$, 1H), 4.22 (q, $J = 7.1\text{ Hz}$, 2H), 2.27 (dd, $J = 14.6, 10.9\text{ Hz}$, 1H), 2.14 (dd, $J = 14.5, 2.3\text{ Hz}$, 1H), 1.64 (s, 3H), 1.28 (t, $J = 7.1\text{ Hz}$, 2H), 1.05 (s, 9H).

Physical State Orange oil

Ethyl 3-((4S,6R)-6-((*tert*-butyldiphenylsilyl)ethynyl)-6-methyl-2-oxo-1,3-dioxan-4-yl)propionate (**3.43**).



To a 5 mL round bottom flask was added a magnetic stir bar, crude **α -3.40** (*d.r.* 5.7:1 *syn/anti*, crude from ketone **3.42** reduction) (< 26 mg, <58.2 μ mol, 1.00 eq.) and CH_2Cl_2 (0.5 mL). Pyridine (47 μ L, 580 μ mol, 10.0 eq.) was added and the resulting mixture was cooled to -78°C . A solution of triphosgene (35.3 mg, 54.8 μ mol, 2.05 eq.) in CH_2Cl_2 (0.5 mL) was added dropwise. This mixture was stirred for 1 h at this temperature before the cooling bath was taken away and slowly warmed to room temperature for 1 h. At this point, TLC analysis indicated full consumption of the starting material. Satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (3 mL) was added and the mixture was stirred vigorously for 10 min. The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by Preparative TLC (30% EtOAc/Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **3.43** (7.3 mg, 27% over 2 steps).

TLC R_f 0.50 (30% EtOAc/Hexanes) [KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.73 (dq, $J = 6.7, 1.5$ Hz, 4H), 7.43 – 7.36 (m, 6H), 5.39 (dd, $J = 8.3, 5.2$ Hz, 1H), 4.09 (dd, $J = 11.7, 7.1$ Hz, 2H), 2.74 (dd, $J = 14.4, 8.3$ Hz, 1H), 2.55 (dd, $J = 14.5, 5.2$ Hz, 1H), 1.87 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 152.4, 146.3, 135.6, 135.6, 135.6, 132.2, 132.1, 129.9, 128.1, 127.9, 105.9, 89.5, 80.1, 79.6, 75.1, 65.1, 62.7, 38.1, 28.6, 27.2, 27.1, 18.7, 13.9.

HRMS-ESI (m/z) calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_5\text{Si}$: 497.1760 $[\text{M}+\text{Na}]^+$, found 497.1734 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2929, 2847, 2252, 1765, 1714, 1257, 1229, 1110, 700

Physical State Light yellow oil

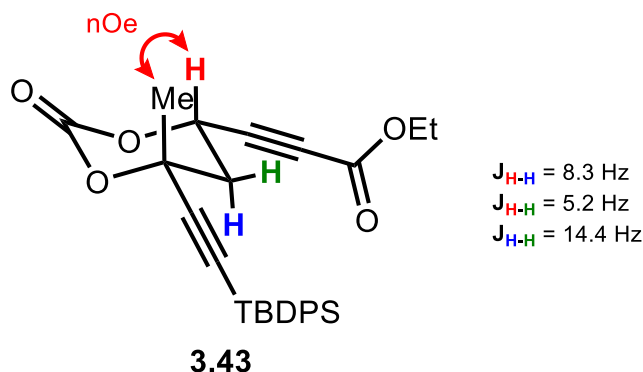
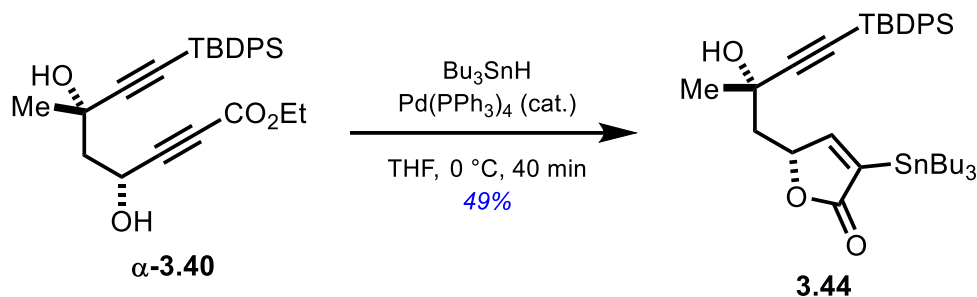


Figure 5.10. Structural analysis of carbonate **3.43** and determination of the relative configuration of diol **α -3.40**.

(*R*)-5-((*R*)-4-(*tert*-butyldiphenylsilyl)-2-hydroxy-2-methylbut-3-yn-1-yl)-3-(tributylstannyl)furan-2(5H)-one (**3.44**)



A 5 mL round bottom flask containing a magnetic stir bar was charged with **α -3.40** (25.3 mg, 56.4 μ mol, 1.00 eq.) and THF (0.8 mL) was added. This mixture was cooled to 0 °C before Pd(PPh₃)₄ (3.3 mg, 2.8 μ mol, 0.05 eq.) was added. (*NOTE : Mixture turns to a dark orange color*). After 10 min at this temperature, Bu₃SnH (17 μ L, 62.0 μ mol, 1.10 eq.) was added over 2 minutes and the resulting mixture was kept at 0 °C. After 40 min, TLC analysis showed full consumption of the starting material, at which point silica gel (*ca.* 100 mg) was then added and the reaction mixture was concentrated *in vacuo* until dry. Purification by silica flash chromatography (5% EtOAc/Hexanes) afforded title compound **3.44** (19.0 mg, 49%)

TLC R_f 0.55 (10% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.81 – 7.76 (m, 4H), 7.68 (d, *J* = 1.4 Hz, 1H), 7.47 – 7.37 (m, 6H), 5.42 (td, *J* = 6.6, 1.4 Hz, 1H), 2.22 (br s, *OH* – *Overlap*) 2.21 (dd, *J* = 14.2, 6.8 Hz, 1H – *Overlap*), 2.08 (dd, *J* = 14.1, 6.5 Hz, 1H), 1.76 (s, 3H), 1.59 – 1.49 (m, 6H), 1.34 (h, *J* = 7.3 Hz, 6H), 1.18 – 1.04 (m, 15H), 0.91 (t, *J* = 7.3 Hz, 9H).

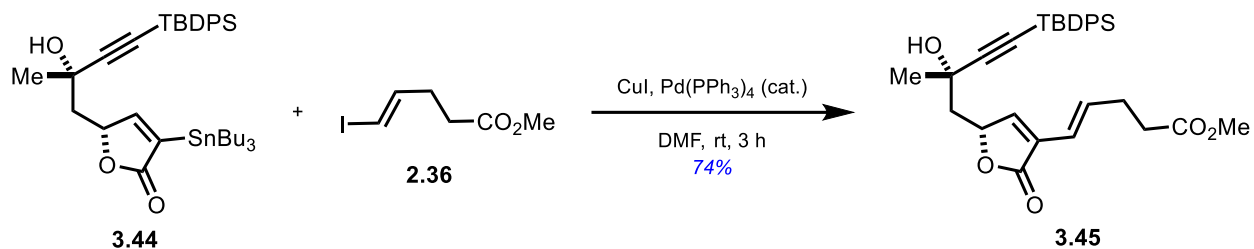
¹³C NMR (151 MHz, CDCl₃) δ 177.8, 166.5, 135.7, 135.6, 134.6, 132.9, 129.8, 127.9, 112.1, 85.1, 82.8, 67.6, 46.6, 31.4, 29.1, 27.3, 27.2, 18.7, 13.8, 9.9.

HRMS-ESI (*m/z*) calcd. for C₃₇H₅₄O₃SiSn : 717.2762 [M+Na]⁺, found 717.2814 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 3446, 2956, 2928, 2857, 2178, 1743, 1720, 1428, 1147, 1110.

Physical State Yellow oil

Methyl (R,E)-5-((R)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-hydroxy-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**3.45**).



A 5 mL Schlenk flask containing a magnetic stir bar was flame-dried and transferred into a glovebox where $\text{Pd(PPh}_3)_4$ (2.8 mg, 2.45 μmol , 0.10 eq.) was added. The flask was fitted with a septa, taken out of the GB then fitted with an $\text{Ar}_{(\text{g})}$ balloon. On the side, a solution of **2.36** (8.2 mg, 34.3 μmol , 1.40 eq.) in anhydrous DMF (0.5 mL) was injected into the Schlenk flask. This was stirred 5 minutes before a solution of **3.44** (17 mg, 24.5 μmol , 1.00 eq.) in anhydrous DMF (0.5 mL) was added to the Schlenk flask. When the additions were complete, the septa of the Schlenk flask was quickly removed and under the steam of $\text{Ar}_{(\text{g})}$, CuI (6.5 mg, 34.3 μmol , 1.40 eq) was quickly added and the septa was reattached to the Schlenk flask. This mixture was stirred for 3 h at room temperature. Satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (3 mL) was then added and the suspension stirred vigorously for 30 minutes before it was filtrated on a short Celite™ pad, which was washed with EtOAc (*ca.* 10 mL). The filtrate was transferred to an extraction funnel containing H_2O (5 mL). The organic layer was collected and aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried by Na_2SO_4 and concentrated *in vacuo*. Purification by Preparative TLC (30% EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **3.45** (10.1 mg, 74%).

NOTE : DMF was sparged with $\text{Ar}_{(\text{g})}$ for 30 minutes before use. This experiment was conducted by Elliot Jackson.

TLC R_f 0.50 (30% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.77 – 7.74 (m, 4H), 7.45 – 7.36 (m, 6H), 7.34 (d, J = 1.7 Hz, 1H), 6.77 (dt, J = 15.8, 6.4 Hz, 1H), 6.13 (d, J = 15.9 Hz, 1H), 5.36 (t, J = 6.6 Hz, 1H), 3.69 (s, 3H), 2.53 – 2.41 (m, 4H), 2.27 (dd, J = 14.0, 6.1 Hz, 1H), 2.15 (br s, OH), 2.04 (dd, J = 14.0, 7.3 Hz, 1H), 1.73 (s, 3H), 1.09 (s, 9H).

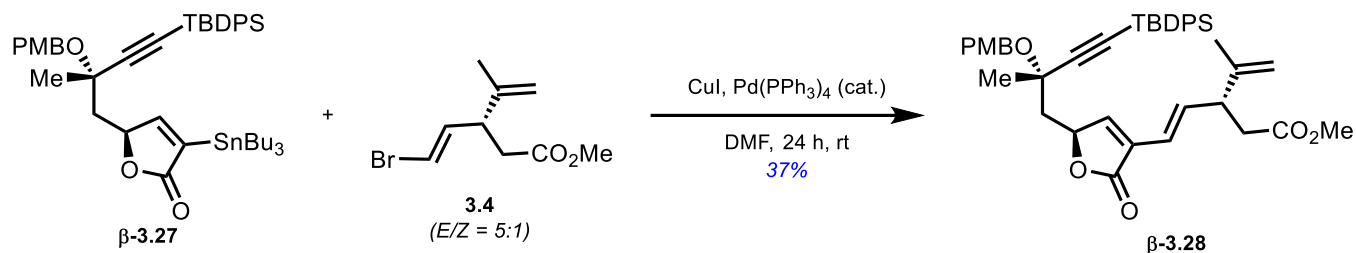
^{13}C NMR (151 MHz, CDCl_3) δ 173.3, 171.8, 148.2, 136.0, 135.6, 135.6, 132.8, 132.8, 129.9, 128.7, 128.0, 119.7, 111.7, 85.5, 78.7, 67.3, 51.8, 46.3, 33.2, 31.7, 28.6, 27.2, 18.7.

HRMS-ESI (m/z) calcd. for $\text{C}_{31}\text{H}_{36}\text{O}_5\text{Si}$: 539.2230 $[\text{M}+\text{Na}]^+$, found 539.2239 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3457, 2956, 2929, 2857, 2173, 1760, 1739, 1429, 1110.

Physical State Yellow oil

Methyl (R,E)-5-((S)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**β -3.28**).



A 50 mL Schlenk flask containing a magnetic stir bar was flame-dried and transferred into a glovebox where Pd(PPh₃)₄ (119 mg, 103 μ mol, 0.10 eq.) was added. The flask was fitted with a septa, taken out of the GB then fitted with an Ar(g) balloon. On the side, a solution of **3.4** (*E/Z* ratio of 5:1, 478 mg, 2.05 mmol, 2.00 eq.) in anhydrous DMF (5 mL) was sparged Ar(g) (5 min) and transferred via canula to the Schlenk flask. This was stirred 5 minutes before a solution of **β -3.27** (835 mg, 1.03 mmol, 1.00 eq.) in anhydrous DMF (5 mL) was sparged with Ar(g) (5 min) and also transferred via canula to the Schlenk flask. When the transfer was complete, the septa of the Schlenk flask was removed and under the steam of Ar(g), CuI (293 mg, 1.54 mmol, 1.50 eq.) was quickly added and the septa was reattached to the Schlenk flask. This mixture was stirred for 24 h at room temperature, after which TLC analysis showed full consumption of **β -3.27**. Satd. NH₄Cl(aq.) (10 mL) was then added and the suspension stirred vigorously for 30 minutes before it was filtrated on a short Celite™ pad, which was washed with EtOAc (~30 mL). The filtrate was transferred to an extraction funnel containing H₂O (30 mL). The organic layer was collected and aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (0% to 20% EtOAc:Hexanes) afforded the title compound **β -3.28** (259 mg, 37%).

TLC R_f 0.30 (20% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.80 – 7.73 (m, 4H), 7.44 – 7.36 (m, 6H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.62 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.98 (d, *J* = 15.9 Hz, 1H), 5.33 – 5.27 (m, 1H), 4.81 (s, 1H), 4.77 (s, 1H – *Overlap*), 4.76 (d, *J* = 10.3 Hz, 1H – *Overlap*), 4.65 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.25 (q, *J* = 7.7 Hz, 1H), 2.56 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.48 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.34 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.23 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.74 (s, 3H), 1.68 (s, 3H), 1.10 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 172.4, 171.7, 159.4, 148.5, 145.2, 137.9, 135.6, 132.9, 132.8, 130.5, 129.9, 129.5, 128.7, 128.0, 119.3, 114.0, 111.9, 110.8, 87.0, 71.9, 66.7, 55.5, 51.8, 46.9, 45.7, 37.8, 27.2, 26.9, 20.8, 18.7.

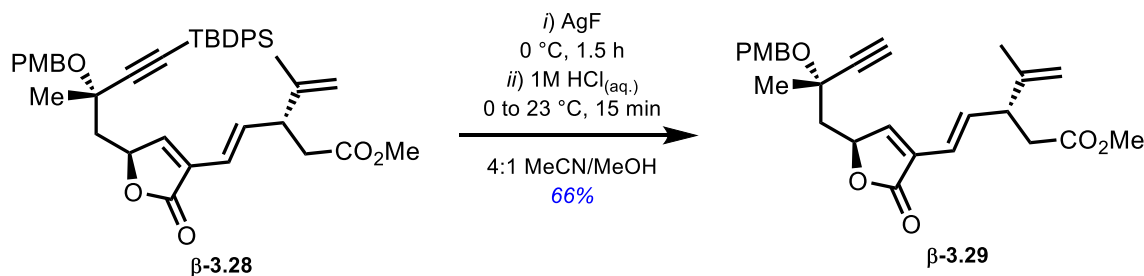
HRMS-ESI (*m/z*) calcd. for C₄₂H₄₈O₆Si : 699.3118 [M+Na]⁺, found 699.3112 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2952, 2927, 2857, 2167, 1760, 1736, 1515, 1248, 1111.

$[\alpha]_D^{24}$ 46.4 ° (*c* = 0.25, CHCl₃)

Physical State Light yellow oil

Methyl (R,E)-5-((S)-5-((S)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**β -3.29**).



A 5 mL round bottom flask was charged with a magnetic stir bar, **β -3.28** (83 mg, 123 μ mol, 1.00 eq.) and 4:1 anhydrous ACN/anhydrous MeOH (1.2 mL, 0.1 M). This mixture was cooled to 0 °C before AgF (23.3 mg, 184 μ mol, 1.50 eq.) was added in a single portion. The reaction mixture was warmed to room temperature. After 1 h 30 at this temperature, TLC analysis indicated full consumption of the starting material. The mixture was cooled back to 0 °C before 1 M HCl_(aq.) (245 μ L, 245 μ mol, 2.00 eq.) was added. The mixture was warmed to room temperature over 10 minutes after which H₂O (3 mL) was added. The mixture was transferred to an extraction funnel and extracted with EtOAc (3 $\times$ 2 mL). The organic layers were combined, washed with brine (3 mL), dried with Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (25% EtOAc:Hexanes) afforded title compound **β -3.29** (35.5 mg, 66%).

*NOTE : This reaction must be run in the dark since the Ag-acetylide intermediate is light-sensitive. Dienyne **β -3.29** is not stable when left in solvent for prolonged amounts of time (gives rise to cycloadduct **3.30**) and must be consumed immediately after it is synthesized.*

TLC R_f 0.35 (25% EtOAc:Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.28 (d, J = 1.4 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H – *Overlap with CHCl₃*), 6.89 (d, J = 8.5 Hz, 2H), 6.69 (dd, J = 15.9, 8.0 Hz, 1H), 6.14 (d, J = 15.9 Hz, 1H), 5.27 – 5.22 (m, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 4.62 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.31 (q, J = 7.7 Hz, 1H), 2.61 (dd, J = 15.2, 8.3 Hz, 1H – *Overlap*), 2.60 (s, 1H – *Overlap*), 2.54 (dd, J = 15.2, 7.9 Hz, 1H), 2.22 (dd, J = 14.4, 6.3 Hz, 1H), 2.16 (dd, J = 14.5, 6.3 Hz, 1H), 1.73 (s, 3H), 1.63 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.5, 171.7, 159.4, 148.4, 145.3, 137.9, 130.5, 129.4, 128.7, 119.5, 114.0, 111.9, 84.6, 74.8, 71.2, 66.4, 55.5, 51.8, 46.9, 45.4, 37.9, 26.7, 20.8.

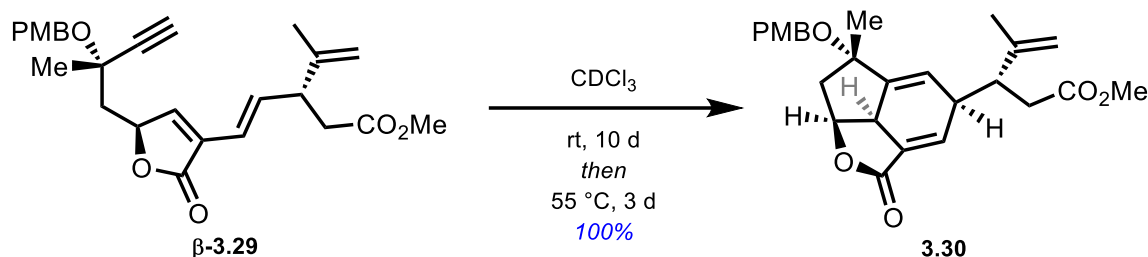
HRMS-ESI (m/z) calcd. for C₂₆H₃₀O₆ : 461.1940 [M+Na]⁺, found 461.1942 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2952, 2925, 2853, 2156, 1751, 1734, 1515, 1247, 1032

[α]_D²⁴ +27.0 ° (c = 0.3, CHCl₃)

Physical State Light yellow oil

Methyl (R)-3-((2a1S,4R,6S,7aS)-6-((4-methoxybenzyl)oxy)-6-methyl-2-oxo-2,2a1,4,6,7,7a-hexahydroindeno[1,7-bc]furan-4-yl)-4-methylpent-4-enoate (**3.30**).



A sample of dienyne **β-3.29** (6.0 mg, 13.7 μmol, 1.00 eq.) was left in CDCl₃ (0.65 mL) in an NMR tube for 10 d at room temperature. After 10 d at room temperature, ¹H NMR analysis taken to verify its stability showed a 50% conversion to a new product which turned out to be cycloadduct **3.30** when left standing. This tube was then placed in a water bath at 55 °C for 3 d before a ¹H NMR analysis showed full conversion of the starting material. The sample was concentrated *in vacuo* to afford title compound **3.30** (6.0 mg, 100%).

TLC R_f 0.30 (25% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.97 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.86 – 5.83 (m, 1H), 5.29 (dt, *J* = 8.9, 7.2 Hz, 1H), 4.99 (p, *J* = 1.4 Hz, 1H), 4.90 (dt, *J* = 1.5, 0.8 Hz, 1H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.36 (ddt, *J* = 12.5, 9.1, 3.2 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.70 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.58 (dd, *J* = 15.5, 9.6 Hz, 1H), 2.48 (dd, *J* = 15.5, 4.3 Hz, 1H), 1.79 (s, 3H), 1.52 – 1.46 (m, 1H), 1.45 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.6, 168.4, 159.3, 148.7, 144.2, 140.7, 134.6, 130.9, 129.1, 125.8, 114.3, 113.9, 85.5, 79.2, 66.0, 55.5, 51.9, 48.9, 47.4, 45.1, 42.9, 35.8, 20.8, 18.5.

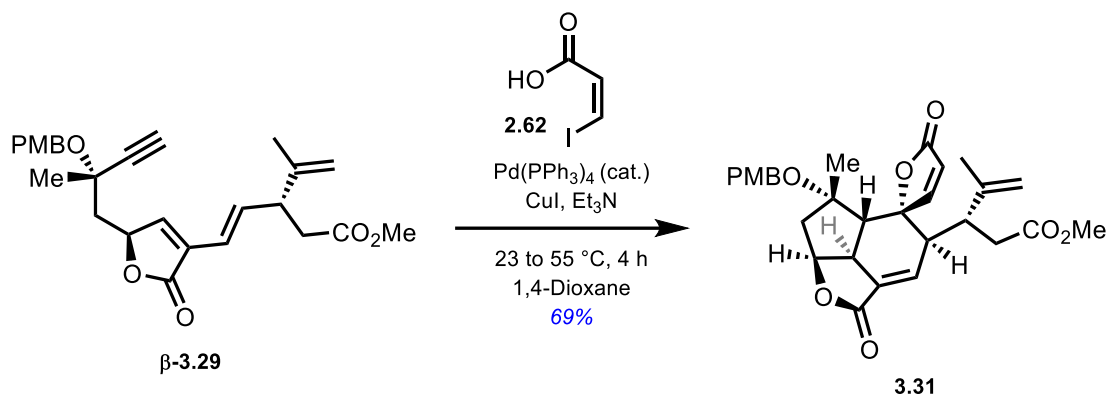
HRMS-ESI (*m/z*) calcd. for C₂₆H₃₀O₆ : 461.1940 [M+Na]⁺, found 461.1912 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2929, 2863, 1763, 1739, 1514, 1435, 1298, 1246

[α]_D²⁴ +52.5 ° (c = 0.20, CHCl₃)

Physical State Light yellow oil

Methyl (R)-3-((2R,2a'S,2a1'S,4'S,4a'R,6'R)-4'-((4-methoxybenzyl)oxy)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.31**).



A 10 mL Schlenk was loaded with a magnetic stir bar, flame-dried then transferred to a glovebox. This flask was charged with Pd(PPh₃)₄ (7.0 mg, 6.0 μ mol, 0.13 eq.), CuI (8.9 mg, 46.5 μ mol, 1.00 eq.) and (Z)-iodoacrylic acid **2.62** (30.4 mg, 154 μ mol, 3.30 eq.). The flask was capped with a septa, taken out of the GB and an Ar(g) balloon was connected to the flask. A solution of dienyne **β -3.29** (20.4 mg, 46.5 μ mol, 1.00 eq.) in dioxane (*previously freeze-pump-thawed*, 0.4 mL + 2 x 0.2 mL washes) was injected. This solution was stirred and was followed by the quick addition of a solution of Et₃N (39 μ L, 279 μ mol, 6.00 eq.) in dioxane (0.2 mL). This mixture was stirred 5 min at room temperature dilute green color was observed, which quickly faded. This mixture was heated to 55 °C and stirred for 4 h under Ar(g). The mixture was then cooled to room temperature and 10% NH₄Cl(aq.) was added and stirred 10 min. The suspension was transferred to an extraction funnel and extracted with EtOAc (4 x 10 mL). The organic layers were combined, washed with sat. NaHCO₃ (3 x 5 mL), brine (10 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (40% EtOAc:Hexanes) afforded title compound **3.31** (16.3 mg, 69%).

TLC R_f 0.35 (50% EtOAc:Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, C₆D₆) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.36 (dd, *J* = 4.1, 2.7 Hz, 1H), 6.22 (d, *J* = 5.6 Hz, 1H), 5.68 (d, *J* = 5.6 Hz, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 4.30 (td, *J* = 7.6, 4.7 Hz, 1H), 4.07 (d, *J* = 11.1 Hz, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 3.02 (ddt, *J* = 12.1, 7.8, 2.3 Hz, 1H), 2.88 (td, *J* = 4.2, 1.7 Hz, 1H), 2.61 (dt, *J* = 10.7, 3.5 Hz, 1H), 2.37 (dd, *J* = 15.9, 10.9 Hz, 1H), 2.30 (ddd, *J* = 14.8, 7.4, 1.1 Hz, 1H), 1.83 (dd, *J* = 15.8, 3.2 Hz, 1H), 1.56 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.25 (dd, *J* = 14.9, 4.7 Hz, 1H), 0.67 (s, 3H), 0.39 (d, *J* = 12.0 Hz, 1H).

¹³C NMR (151 MHz, C₆D₆) δ 171.5, 170.5, 167.6, 159.7, 155.7, 145.2, 142.7, 132.4, 131.2, 128.7, 123.8, 114.2, 112.9, 87.8, 84.7, 77.1, 64.8, 63.3, 54.8, 53.1, 51.4, 46.5, 46.4, 40.9, 35.9, 21.0, 20.6.

HRMS-ESI (*m/z*) calcd. for C₂₉H₃₂O₈ : 531.1995 [M+Na]⁺, found 531.1995 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2925, 2854, 1751, 1513, 1247, 1172, 1009.

$[\alpha]_D^{24}$ +23.8 ° (*c* = 0.50, CHCl₃)

Physical State White solid

Melting Point 107 – 109 °C

Chemical reaction scheme showing the conversion of compound **3.31** to compound **3.32**.

Reaction conditions: DBU, DCM, rt, 30 min, 99% yield.

TLC R_f 0.65 (60% EtOAc:Hexanes) [KMnO_4]

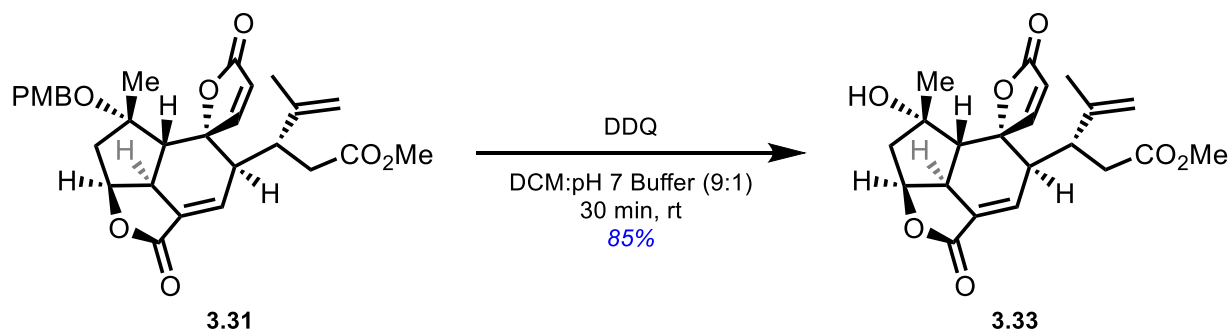
¹³C NMR (101 MHz, C₆D₆) δ 174.0, 172.0, 170.8, 159.6, 154.9, 144.2, 140.5, 131.2, 128.6, 123.9, 123.5, 114.2, 113.6, 87.3, 84.9, 78.9, 64.1, 54.8, 53.2, 51.5, 46.1, 43.1, 42.9, 42.1, 37.9, 22.3, 18.5.

FTIR-ATR (thin film) ν [cm⁻¹] 2924, 2852, 1758, 1743, 1513, 1246, 1146, 1080.

Physical State Amorphous white solid

Melting point 91 – 93 °C

Methyl (R)-3-((2R,2a'S,2a1'S,4'S,4a'R,6'R)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.33**).



To a 5 mL round bottom flask containing a magnetic stir bar and **3.31** (5.0 mg, 9.8 μmol , 1.00 eq.) was added CH_2Cl_2 (180 μL) and pH 7 phosphate buffer (20 μL). DDQ (4.5 mg, 19.7 μmol , 2.00 eq.) was then added in a single addition. The mixture was stirred vigorously at room temperature for 30 min after which TLC analysis indicated full consumption of the starting material. Satd. $\text{NaHCO}_3(\text{aq.})$ (1 mL) and stirred vigorously for 10 min. After which, the organic layer was extracted by use of a Pasteur pipette and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (60 to 80% EtOAc:Hexanes) afforded title compound **3.33** (3.5 mg, 92%).

TLC R_f 0.30 (60% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 6.24 (dd, $J = 4.7, 2.5$ Hz, 1H), 5.88 (d, $J = 5.7$ Hz, 1H), 5.52 (d, $J = 5.7$ Hz, 1H), 4.72 (s, 1H), 4.62 (s, 1H), 4.48 (td, $J = 7.4, 3.9$ Hz, 1H), 3.30 (s, 3H), 2.91 – 2.82 (m, 1H), 2.68 (t, $J = 5.3$ Hz, 1H), 2.50 (ddd, $J = 9.9, 6.0, 3.5$ Hz, 1H), 2.26 (dd, $J = 15.7, 10.5$ Hz, 1H), 2.11 (dd, $J = 14.5, 7.5$ Hz, 1H), 1.87 (br s, OH), 1.84 (dd, $J = 15.7, 3.5$ Hz, 1H), 1.57 (s, 3H), 1.48 – 1.44 (m, 1H), 0.67 (s, 3H), 0.34 (d, $J = 11.9$ Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 171.4, 170.3, 167.3, 156.4, 144.6, 143.0, 131.9, 122.9, 113.8, 88.6, 79.8, 77.2, 61.4, 52.4, 51.5, 51.4, 47.1, 40.9, 36.7, 25.0, 19.9.

HRMS-ESI (m/z) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: 411.1420 $[\text{M}+\text{Na}]^+$, found 411.1402 $[\text{M}+\text{Na}]^+$.

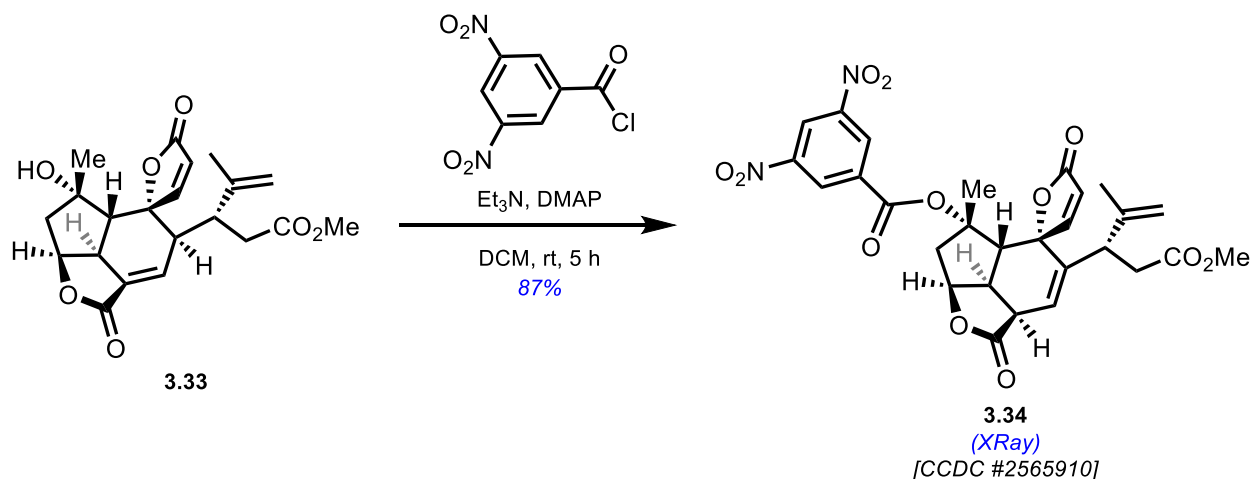
FTIR-ATR (thin film) ν [cm^{-1}] 3486, 2956, 2924, 2854, 1749, 1737, 1456, 1170, 1011.

$[\alpha]_D^{24}$ -75.0 $^\circ$ ($c = 0.02$, CHCl_3)

Physical State White solid

Melting Point > 190 $^\circ\text{C}$ (Decomposition)

(2S,2a'S,2a1'S,4'S,4a'R,7a'R)-6'-((S)-5-methoxy-2-methyl-5-oxopent-1-en-3-yl)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-4'-yl 3,5-dinitrobenzoate (**3.34**)



To a 5 mL round bottom flask containing a stir bar and **3.33** (12.0 mg, 30.9 μmol , 1.00 eq.) was added anhydrous CH_2Cl_2 (0.3 mL, 0.1 M). To this mixture was added Et_3N (13 μL , 92.7 μmol , 3.00 eq.) and 3,5-dinitrobenzoyl chloride (14.2 mg, 61.8 μmol , 2.00 eq.). DMAP (4.5 mg, 37.1 μmol , 1.20 eq.) was added (*NOTE : solution turns bright red*) and the reaction mixture was stirred at room temperature for 3 h. After this time, a second addition of Et_3N , 3,5-dinitrobenzoyl chloride and DMAP was completed in the same original amounts. After another 2 h (5 h total reaction time), TLC analysis showed full consumption of the starting material. The reaction was quenched with satd. $\text{NaHCO}_3(\text{aq.})$ (2 mL) and the mixture was extracted with CH_2Cl_2 (3 x 3 mL). The organic phases were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by Preparative TLC (50%EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **3.34** (17.4 mg, 97%). Slow evaporation of a solution of **3.34** dissolved in 1:1 EtOAc:Hexanes (*ca.* 0.5 mL) afforded crystals suitable for single crystal X-Ray diffraction. The crystal structure was uploaded to the CCDC with the deposition number #2565910.

TLC R_f 0.75 (50% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 8.87 (d, $J = 2.1$ Hz, 2H), 8.43 (t, $J = 2.1$ Hz, 1H), 6.84 (d, $J = 5.7$ Hz, 1H), 5.75 (d, $J = 5.4$ Hz, 1H), 5.47 (d, $J = 5.7$ Hz, 1H), 4.74 – 4.71 (m, 1H), 4.59 (s, 1H), 4.14 – 4.07 (m, 1H), 3.44 (s, 3H), 3.11 (dd, $J = 9.4, 6.5$ Hz, 1H), 3.03 (ddd, $J = 12.6, 6.7, 5.6$ Hz, 1H), 2.89 (dd, $J = 17.0, 6.8$ Hz, 1H), 2.82 – 2.76 (m, 1H), 2.45 (dd, $J = 15.8, 9.5$ Hz, 1H), 2.17 (dd, $J = 15.8, 6.5$ Hz, 1H), 1.74 (dd, $J = 16.9, 1.4$ Hz, 1H), 1.53 – 1.49 (m, 1H), 1.46 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 173.2, 171.9, 170.4, 161.6, 155.5, 148.5, 143.8, 139.8, 133.1, 129.2, 128.6, 123.5, 123.4, 122.5, 114.0, 91.0, 86.8, 78.0, 53.3, 51.6, 46.2, 44.8, 43.0, 42.3, 37.8, 30.2, 23.2, 18.2.

HRMS-ESI (m/z) calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_{12}$: 605.1383 $[\text{M}+\text{Na}]^+$, found 605.1359 $[\text{M}+\text{Na}]^+$.

Physical State White needles

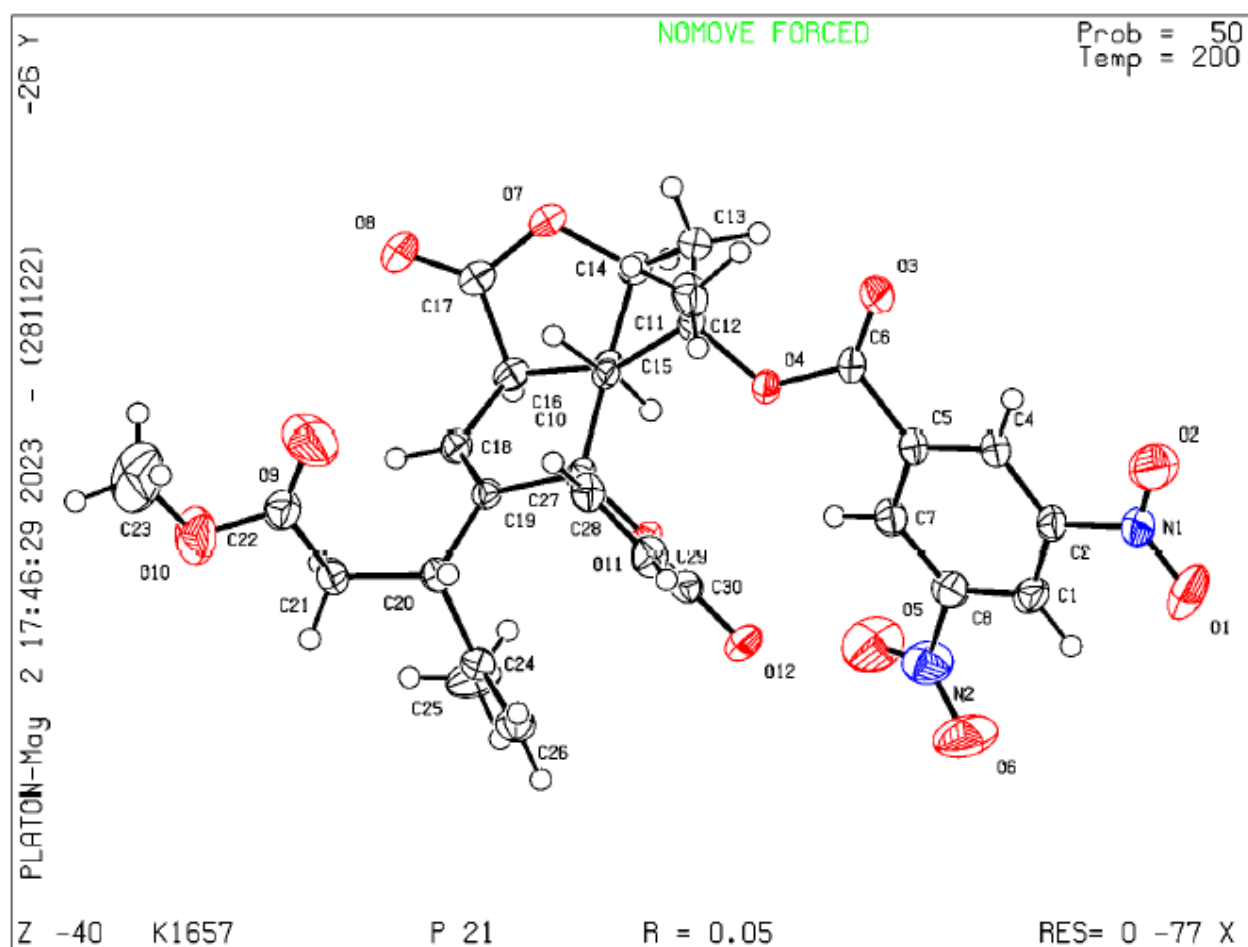
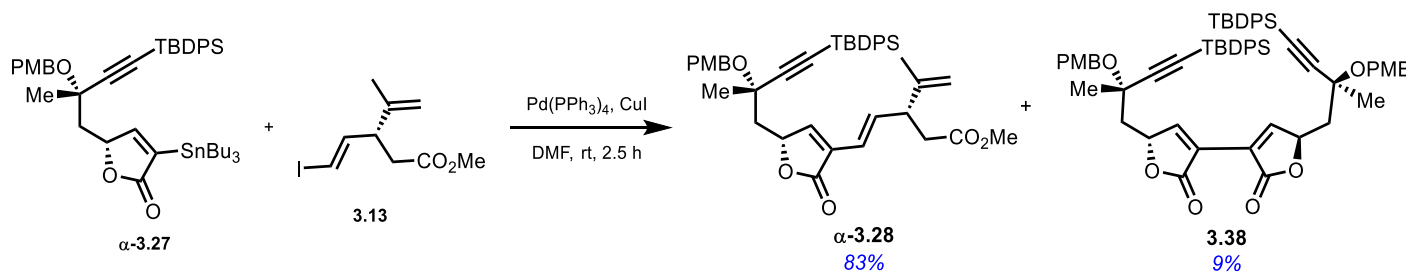


Figure 5.11. CHECKCIF file of 3.34.

Methyl (R,E)-5-((R)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**α -3.28**) and (5R,5'R)-5,5'-bis((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-[3,3'-bifuran]-2,2'-(5H,5'H)-dione (**3.38**).



An oven-dried 200 mL Schlenk flask containing a stir bar was transferred to a glovebox and charged with $\text{Pd(PPh}_3)_4$ (466 mg, 0.404 mmol, 0.05 eq.). The flask was stoppered with a septa, taken out of GB and fitted with an $\text{Ar}_{(\text{g})}$ balloon. A solution of **3.13** (3.17 g, 11.3 mmol, 1.40 eq) in anhydrous DMF (40 mL) was freeze-pump-thawed (5 min / operation, 3 cycles) and transferred by canula to the Schlenk flask. This mixture was stirred 10 minutes at room temperature before a solution of **α -3.27** (6.59 g, 8.07 mmol, 1.00 eq.) in anhydrous DMF (40 mL) previously freeze-pump-thawed (5 min / operation, 3 cycles) was also transferred by canula to the Schlenk flask. The septa was removed and under a positive $\text{Ar}_{(\text{g})}$ stream, glovebox-kept CuI (2.15 g, 11.3 mmol, 1.40 eq.) was then added in a single portion and the septa was quickly re-fitted. This mixture, which slowly turned from light yellow to dark orange, was stirred at room temperature for 2.5 hours after which TLC analysis showed full consumption of the starting material. Satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (100 mL) was added and stirred vigorously for 10 minutes, after which the mixture was transferred to an extraction funnel containing additional $\text{NH}_4\text{Cl}_{(\text{aq})}$ (100 mL). The organic phase was collected and the aqueous phase extracted with EtOAc (5 x 75 mL). The organic phases were combined, washed thoroughly with brine (3x 50 mL), dried by Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (15% EtOAc/Hexanes) afforded 5.29 g of an inseparable mixture of title products **α -3.28** (4.55 g, 83%) and **3.38** (736 mg, 9%), as calculated by ^1H NMR of the purified sample. An analytical sample of both products was obtained for characterization by preparative TLC purification of this sample (20 % EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate, eluted twice).

NOTE : DMF was sparged with $\text{Ar}_{(\text{g})}$ for 30 minutes. Degassing using Freeze-Pump-Thaw technique was found to lead to significantly more oxidative homodimerization product **3.38** (up to 35%).

For **α -3.28**

TLC R_f 0.55 (20% EtOAc:Hexanes) [UV / KMnO_4]

^1H NMR ^1H NMR (600 MHz, CDCl_3) δ 7.78 (ddd, J = 8.0, 3.3, 1.4 Hz, 4H), 7.42 – 7.36 (m, 6H), 7.26 (d, J = 8.6 Hz, 2H – Overlaps CHCl_3 peak), 7.23 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.62 (dd, J = 15.9, 8.2 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 5.43 – 5.35 (m, 1H), 4.84 – 4.81 (m, 1H), 4.79 (dd, J = 5.9, 4.3 Hz, 2H), 4.58 (d, J = 10.2 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.27 (q, J = 7.8 Hz, 1H), 2.58 (dd, J = 15.3, 7.4 Hz, 1H), 2.50 (dd, J = 15.3, 7.8 Hz, 1H), 2.36 (dd, J = 13.9, 5.2 Hz, 1H), 2.07 (dd, J = 13.9, 8.2 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.5, 171.8, 159.4, 149.4, 145.4, 137.8, 135.6, 132.9, 132.8, 130.4, 129.9, 129.7, 128.1, 128.1, 119.5, 114.0, 111.8, 109.4, 88.0, 78.8, 72.8, 66.8, 55.4, 51.8, 46.9, 45.9, 37.9, 27.2, 27.1, 20.8, 18.7.

HRMS-ESI (m/z) calcd. for $\text{C}_{42}\text{H}_{48}\text{O}_6\text{Si}$: 699.3118 $[\text{M}+\text{Na}]^+$, found 699.3104 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2950, 2929, 2857, 2165, 1761, 1738, 1514, 1428, 1247, 1109

$[\alpha]_D^{24}$ -28.8 $^\circ$ (c = 0.50, CHCl_3)

Physical State Light yellow oil

For **3.38**

TLC R_f 0.57 (20% EtOAc:Hexanes) [UV / KMnO_4]

¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 1.2 Hz, 2H), 7.80 – 7.78 (m, 8H), 7.44 – 7.36 (m, 12H), 7.30 (d, *J* = 8.6 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 5.54 (t, *J* = 6.4 Hz, 2H), 4.81 (d, *J* = 10.3 Hz, 2H), 4.61 (d, *J* = 10.4 Hz, 2H), 3.79 (s, 6H), 2.31 (dd, *J* = 14.1, 6.2 Hz, 2H), 2.19 (dd, *J* = 14.1, 6.9 Hz, 2H), 1.72 (s, 6H), 1.12 (s, 18H).

¹³C NMR (101 MHz, CDCl₃) δ 171.1, 159.4, 153.3, 135.6, 132.9, 132.9, 130.3, 129.9, 129.6, 128.0, 121.2, 114.1, 109.3, 88.2, 79.9, 72.7, 66.9, 55.5, 45.6, 27.2, 18.7.

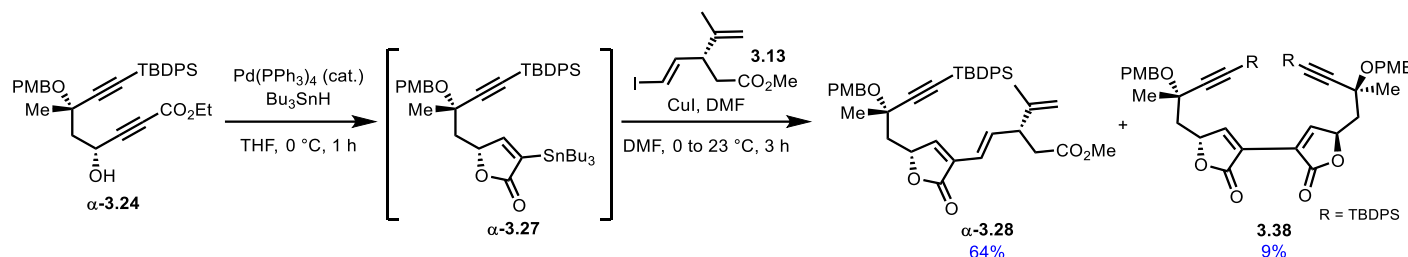
HRMS-ESI (*m/z*) calcd. for C₆₆H₇₀O₈Si₂ : 1069.4507 [M+Na]⁺, found 1069.4521 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2954, 2928, 2857, 2160, 1762, 1515, 1248, 1109.

[α]_D²⁴ -8.2 ° (c = 0.5, CHCl₃)

Physical State Light yellow oil

Methyl (R,E)-5-((R)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**α -3.28**) and (5R,5'R)-5,5'-bis((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-[3,3'-bifuran]-2,2'(5H,5'H)-dione (**3.38**).



An oven-dried 200ml Schlenk containing a magnetic stir bar was loaded in a glovebox and charged with $\text{Pd}(\text{PPh}_3)_4$ (760 mg, 658 mmol, 0.05 eq.). The flask was capped with a rubber sceptor and was taken out of the glovebox and an $\text{Ar}_{(\text{g})}$ balloon was attached. THF (20 mL) was added and flask was cooled to 0 °C. A solution of **α -3.24** (7.49 g, 13.2 mmol, 1.00 eq.) in THF (40 mL + 2x 5 mL washes) previously cooled to 0 °C in THF was cannulated over 5 minutes. After stirring 10 min at this temperature, a solution of Bu_3SnH (3.72 mL, 4.03 g, 13.8 mmol, 1.05 eq.) in THF (5 mL + 2x 2.5 mL washes) was cannulated dropwise. This mixture was stirred 45 min at 0 °C before the starting material was fully transformed to intermediate **α -3.27**. Then, a solution of **3.13** (5.16 g, 18.4 mmol, 1.40 eq.) in DMF (70 mL + 2x 5 mL washes) was cannulated in the Schlenk flask. The sceptor was removed under an $\text{Ar}_{(\text{g})}$ stream before CuI (3.51 g, 18.4 mmol, 1.40 eq.) was quickly added all at once. The sceptor was reattached and reaction was allowed to stir at room temperature for 3 h. The mixture was added to satd. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (200 mL) and stirred vigorously for 1 h. The organic phase was collected and the aqueous phase was extracted with EtOAc (5 x 75 mL). The organic layers were combined and washed thoroughly with brine (2x 50 mL), dried on Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (10% – 15% EtOAc /Hexanes) afforded 6.93 g of an inseparable mixture of title compounds **α -3.28** (5.70 g, 64%) and **3.38** (1.23 g, 9%), as calculated by ^1H NMR of the purified sample

NOTE : DMF and THF were both sparged with $\text{Ar}_{(\text{g})}$ for 30 minutes. Degassing the solvents using Freeze-Pump-Thaw techniques lead to significantly more oxidative homodimerization product **3.38** (up to 35%).

For **α -3.28**

TLC R_f 0.55 (20% EtOAc :Hexanes) [$\text{UV} / \text{KMnO}_4$]

^1H NMR ^1H NMR (600 MHz, CDCl_3) δ 7.78 (ddd, J = 8.0, 3.3, 1.4 Hz, 4H), 7.42 – 7.36 (m, 6H), 7.26 (d, J = 8.6 Hz, 2H – Overlaps CHCl_3 peak), 7.23 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.62 (dd, J = 15.9, 8.2 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 5.43 – 5.35 (m, 1H), 4.84 – 4.81 (m, 1H), 4.79 (dd, J = 5.9, 4.3 Hz, 2H), 4.58 (d, J = 10.2 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.27 (q, J = 7.8 Hz, 1H), 2.58 (dd, J = 15.3, 7.4 Hz, 1H), 2.50 (dd, J = 15.3, 7.8 Hz, 1H), 2.36 (dd, J = 13.9, 5.2 Hz, 1H), 2.07 (dd, J = 13.9, 8.2 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.5, 171.8, 159.4, 149.4, 145.4, 137.8, 135.6, 132.9, 132.8, 130.4, 129.9, 129.7, 128.1, 128.1, 119.5, 114.0, 111.8, 109.4, 88.0, 78.8, 72.8, 66.8, 55.4, 51.8, 46.9, 45.9, 37.9, 27.2, 27.1, 20.8, 18.7.

HRMS-ESI (m/z) calcd. for $\text{C}_{42}\text{H}_{48}\text{O}_6\text{Si}$: 699.3118 $[\text{M}+\text{Na}]^+$, found 699.3104 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2950, 2929, 2857, 2165, 1761, 1738, 1514, 1428, 1247, 1109

$[\alpha]_D^{24}$ -28.8 ° (c = 0.50, CHCl_3)

Physical State Light yellow oil

For **3.38**

TLC R_f 0.57 (20% EtOAc :Hexanes) [KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, J = 1.2 Hz, 2H), 7.74 – 7.68 (m, 8H), 7.37 – 7.28 (m, 12H), 7.23 (d, J = 8.6 Hz, 4H), 6.81 (d, J = 8.6 Hz, 4H), 5.47 (t, J = 6.4 Hz, 2H), 4.74 (d, J = 10.3 Hz, 2H), 4.54 (d, J = 10.4 Hz, 2H), 3.71 (s, 6H), 2.24 (dd, J = 14.1, 6.2 Hz, 2H), 2.12 (dd, J = 14.1, 6.9 Hz, 2H), 1.64 (s, 6H), 1.04 (s, 18H).

^{13}C NMR (101 MHz, CDCl_3) δ 171.1, 159.4, 153.3, 135.6, 132.9, 132.9, 130.3, 129.9, 129.6, 128.0, 121.2, 114.1, 109.3, 88.2, 79.9, 72.7, 66.9, 55.5, 45.6, 27.2, 18.7.

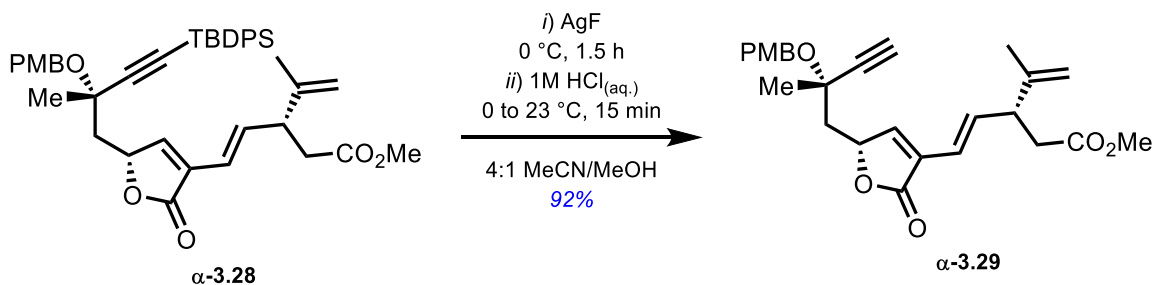
HRMS-ESI (m/z) calcd. for $\text{C}_{66}\text{H}_{70}\text{O}_8\text{Si}_2$: 1069.4507 $[\text{M}+\text{Na}]^+$, found 1069.4521 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm⁻¹] 2954, 2928, 2857, 2160, 1762, 1515, 1248, 1109.

$[\alpha]_D^{24}$ -8.2 ° (c = 0.5, CHCl₃)

Physical State Light yellow oil

Methyl (R,E)-5-((R)-5-((S)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**α -3.29**).



A 250 mL round bottom flask containing a magnetic stir bar was charged with **α -3.28** (5.29, 7.80 mmol, 1.00 eq – as a 9.6:1 mixture with homodimer **3.38**), anhydrous MeOH (16mL) and anhydrous MeCN (64 mL). The mixture was cooled to 0 °C and wrapped with aluminum foil. AgF (1.49 g, 11.7 mmol, 1.50 eq.) was then added in a single portion. The ice bath was taken away and the mixture was allowed to stir at room temperature for 1.5 h. The resulting mixture was cooled back to 0 °C before 1 M HCl_(aq.) (15.6 mL, 15.6 mmol, 2.00 eq.) was added dropwise, and the resulting suspension stirred to room temperature for 15 minutes. This mixture was then added to an extraction funnel containing water (300 mL) and the aqueous layer extracted with CH₂Cl₂ (4 x 75 mL). The organic layers were combined, washed with brine (50 mL), dried by Na₂SO₄, filtered on a Celite™ pad and concentrated *in vacuo*. Purification by silica flash chromatography (20% EtOAc/Hexanes) afforded title compound **α -3.29** (2.84 g, 92%).

NOTES : The reaction mixture must be shielded from light as the intermediate silver(I) acetylide is photolabile. The terminal alkyne is thermally sensitive and prone to undergo early [4+2] reaction. Thus, rotavap baths were kept < 25 °C and the product was used directly after it was synthesized.

TLC R_f 0.40 (40% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 8.1 Hz, 2H – Overlap with CHCl₃ peak), 7.21 (d, *J* = 1.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.61 (dd, *J* = 15.9, 8.1 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.34 – 5.29 (m, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.67 (d, *J* = 10.3 Hz, 1H), 4.49 (d, *J* = 10.3 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.27 (q, *J* = 7.8 Hz, 1H), 2.66 (s, 1H), 2.58 (dd, *J* = 15.2, 7.4 Hz, 1H), 2.51 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.24 (dd, *J* = 13.9, 5.3 Hz, 1H), 1.99 (dd, *J* = 13.9, 8.0 Hz, 1H), 1.71 (s, 3H), 1.59 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.5, 171.8, 159.4, 149.5, 145.4, 137.7, 130.4, 129.6, 128.1, 119.5, 114.0, 111.8, 83.4, 78.7, 75.6, 72.0, 66.5, 55.4, 51.8, 46.9, 45.8, 37.9, 26.9, 20.8.

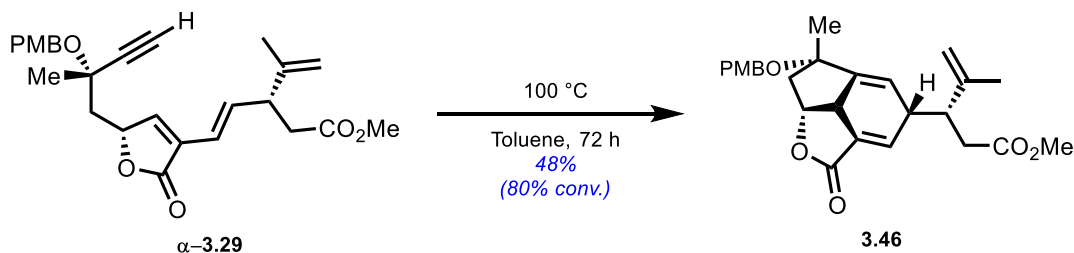
HRMS-ESI (*m/z*) calcd. for C₂₆H₃₀O₆ : 461.1940 [M+Na]⁺, found 461.1916 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 3269, 2925, 2863, 2113, 1752, 1735, 1245, 1107, 1024.

$[\alpha]_D^{24}$ -86.1 ° (*c* = 1.00, CHCl₃)

Physical State Light yellow oil

Methyl (R)-3-((2a1R,4S,6S,7aR)-6-((4-methoxybenzyl)oxy)-6-methyl-2-oxo-2,2a1,4,6,7,7a-hexahydroindeno[1,7-bc]furan-4-yl)-4-methylpent-4-enoate (**3.46**).



A 8 mL pressure tube was charged with a micro stir bar and **α -3.29** (9.2 mg, 0.021 mmol, 1.00 eq.) and anhydrous toluene (1 mL). The headspace of the vial was filled with Ar_(g), the vial was capped tightly and the mixture was stirred at 100 °C for 72 h. The mixture was then cooled down to room temperature and solvent removed *in vacuo*. A ¹H NMR analysis showed 80% conversion of the starting material into cycloadduct **3.46**. Removal of the toluene *in vacuo* yielded a light yellow solid. Purification by preparative thin layer chromatography (33% EtOAc:Hexanes) afforded title compound **3.46** (4.4 mg, 48%).

TLC R_f 0.50 (33% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.23 (d, *J* = 8.7 Hz, 2H), 7.09 (dd, *J* = 3.3, 2.1 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.73 (dd, *J* = 2.5, 1.5 Hz, 1H), 5.12 – 5.05 (m, 1H), 4.96 – 4.93 (m, 1H), 4.83 (s, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.34 (tt, *J* = 9.8, 3.1 Hz, 1H), 2.97 (td, *J* = 9.0, 5.1 Hz, 1H), 2.92 – 2.86 (m, 1H), 2.59 – 2.48 (m, 2H), 2.44 (dd, *J* = 12.8, 7.2 Hz, 1H), 1.89 (dd, *J* = 12.8, 7.5 Hz, 1H), 1.72 (s, 3H), 1.47 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.5, 168.2, 159.2, 148.9, 144.1, 142.9, 133.4, 130.8, 128.7, 120.8, 114.9, 114.0, 84.8, 76.7, 65.7, 55.4, 51.9, 45.5, 45.5, 44.5, 43.6, 36.6, 25.6, 20.2.

HRMS-ESI (*m/z*) calcd. for C₂₆H₃₀O₆ : 461.1940 [M+Na]⁺, found 461.1938 [M+Na]⁺.

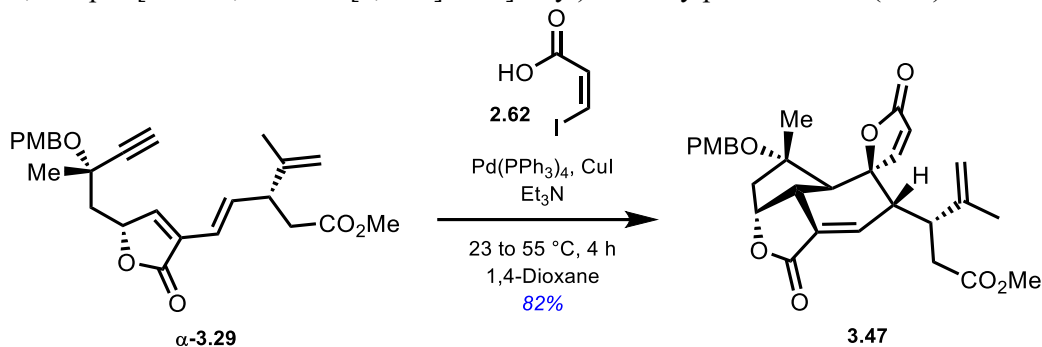
FTIR-ATR (thin film) ν [cm⁻¹] 2956, 2923, 2858, 1762, 1735, 1514, 1247, 1166, 1031.

[α]_D²⁴ +39.2 ° (c = 0.25, CHCl₃)

Physical State White solid

Melting Point 112-114 °C

Methyl (R)-3-((2S,2a'R,2a1'R,4'S,4a'S,6'S)-4'-((4-methoxybenzyl)oxy)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.47**).



An oven dried 10 mL Schlenk flask was charged with a stir bar and transferred to a glovebox where Pd(PPh₃)₄ (13.9 mg, 0.012 mmol, 0.13 eq.), CuI (17.6 mg, 0.092 mmol) and (Z)-iodoacrylic acid **2.62** (60.3 mg, 0.305 mmol, 3.30 eq.) were added. A septa was connected and an Ar_(g) balloon was connected to the flask. Dioxane (1.0 mL) was added, followed by a solution of **α-3.29** (40.5 mg, 0.092 mmol, 1.00 eq.) in dioxane (1.0 mL). Then, a solution of Et₃N (77 μL, 0.554 mmol, 6.00 eq.) in Dioxane (0.5 mL) was injected dropwise. The mixture was stirred 10 minutes at 23°C before it was plunged in an oil bath set at 55 °C for 4 h. *NOTE : 5 min after Et₃N addition, a dilute green color was observed.* The mixture was then cooled to room temperature and a solution of 10% NH₄Cl_(aq.) was added. The suspension was extracted with EtOAc (4x 10 mL). The combined organic layers were washed with satd. NaHCO_{3(aq.)} (3x 5 mL), brine (5 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (40% EtOAc/Hexanes) afforded title compound **3.47** (38.7 mg, 82%).

TLC R_f 0.45 (40% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, C₆D₆) δ 7.00 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 5.7 Hz, 1H), 6.54 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.64 (d, *J* = 5.7 Hz, 1H), 4.58 (s, 1H), 4.56 (s, 1H), 4.09 (td, *J* = 7.8, 5.0 Hz, 1H), 4.04 (d, *J* = 10.5 Hz, 1H), 3.75 (d, *J* = 10.5 Hz, 1H), 3.34 (s, 3H), 3.27 (s, 3H), 2.84 (ddd, *J* = 8.3, 3.9, 1.9 Hz, 1H), 2.58 (td, *J* = 8.3, 6.0 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.21 – 2.11 (m, 2H), 1.87 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.76 (dd, *J* = 13.6, 5.1 Hz, 1H), 1.31 (s, 3H), 1.20 (d, *J* = 12.5 Hz, 1H), 0.97 (s, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 171.2, 171.0, 167.3, 159.7, 158.5, 144.6, 140.8, 134.8, 131.0, 128.9, 121.2, 115.6, 114.1, 88.1, 83.6, 75.3, 66.0, 62.8, 54.9, 52.1, 51.3, 48.9, 43.3, 43.2, 37.4, 20.1, 19.6.

HRMS-ESI (*m/z*) calcd. for C₂₉H₃₂O₈ : 531.1995 [M+Na]⁺, found 531.1998 [M+Na]⁺.

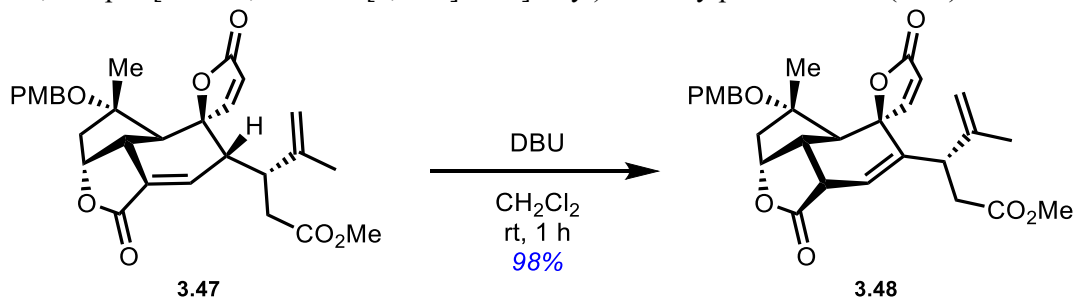
FTIR-ATR (thin film) ν [cm⁻¹] 2926, 2856, 1763, 1750, 1515, 1250, 1197.

[α]_D²⁴ +174 ° (c = 0.50, CHCl₃)

Physical State White solid

Melting point 147-149 °C

Methyl (S)-3-((2R,2a'S,2a1'R,5a'S,6'S,7a'R)-6'-((4-methoxybenzyl)oxy)-6'-methyl-2',5-dioxo-2a',2a1',5a',6',7',7a'-hexahydro-2'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-4'-yl)-4-methylpent-4-enoate (**3.48**).



A 2 mL vial containing a magnetic stir bar was charged with **3.47** (5.3 mg, 10.4 μmol , 1.00 eq.) and anhydrous CH_2Cl_2 (0.5 mL). This mixture was stirred and DBU (4.6 μL , 31.2 μmol , 3.00 eq.) was added. This mixture was stirred for 1 h min at room temperature at which point TLC analysis showed full consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude mixture was passed through a short silica pad in a Pasteur piette, eluting with 100% EtOAc (~10 mL). The filtrate was concentrated *in vacuo* to yield title compound **3.48** (23.2 mg, 98%) in very high purity (> 98% by ^1H NMR) and did not require further purification.

TLC R_f 0.65 (60% EtOAc:Hexanes)

^1H NMR (600 MHz, CDCl_3) δ 7.36 (d, $J = 5.7$ Hz, 1H), 7.14 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.13 (d, $J = 5.7$ Hz, 1H), 6.01 (d, $J = 5.5$ Hz, 1H), 4.92 – 4.88 (m, 1H), 4.88 (s, 1H), 4.71 (s, 1H), 4.42 (d, $J = 10.5$ Hz, 1H), 4.20 (d, $J = 10.5$ Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.57 (t, $J = 6.2$ Hz, 1H), 3.16 – 3.05 (m, 1H), 2.95 – 2.88 (m, 1H), 2.57 (dd, $J = 15.2$, 6.9 Hz, 1H), 2.48 (dd, $J = 15.2$, 9.0 Hz, 1H), 2.41 (d, $J = 13.8$ Hz, 1H), 2.31 (d, $J = 13.6$ Hz, 1H), 2.26 (dd, $J = 15.1$, 6.5 Hz, 1H), 1.63 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 174.3, 172.3, 171.5, 159.3, 158.3, 143.9, 140.5, 130.5, 129.0, 123.9, 120.9, 115.3, 114.0, 87.2, 84.2, 78.8, 66.3, 55.4, 52.3, 51.9, 45.8, 43.6, 43.3, 39.6, 38.9, 20.8, 20.5.

HRMS-ESI (m/z) calcd. for $\text{C}_{29}\text{H}_{32}\text{O}_8$: 531.1995 $[\text{M}+\text{Na}]^+$, found 531.1992 $[\text{M}+\text{Na}]^+$.

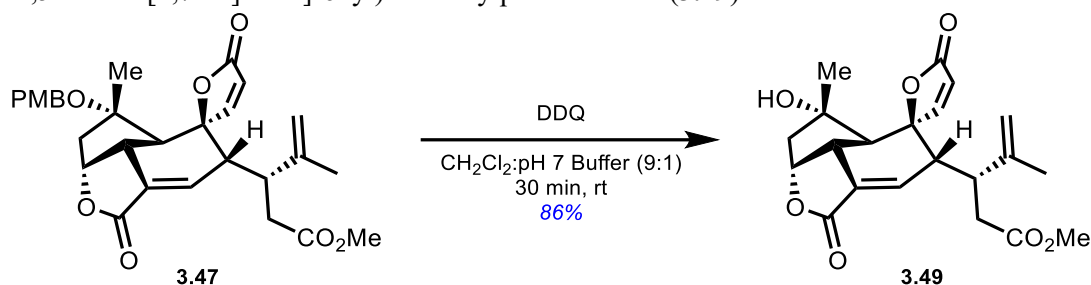
FTIR-ATR (thin film) ν [cm^{-1}] 2952, 2923, 2854, 1753, 1743, 1514, 1248, 1142.

$[\alpha]_D^{24} +218^\circ$ ($c=0.5$, CHCl_3)

Physical State White solid

Melting point > 190 $^\circ\text{C}$ (Decomposition).

Methyl (R)-3-((2S,2a'R,2a1'R,4'S,4a'S,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.49**).



A 2 mL vial containing a stir bar was charged with **3.47** (9.70 mg, 0.019 mmol, 1.00 eq.), anhydrous CH_2Cl_2 (450 μL) and pH 7 phosphate buffer (50 μL). The suspension was vigorously stirred before DDQ (8.9 mg, 0.038 mmol, 2.00 eq.) was added at once. The mixture was stirred vigorously for 30min then quenched with satd. $\text{NaHCO}_3(\text{aq.})$ (1 mL). The mixture was then extracted with CH_2Cl_2 (3x 2 mL) and the combined organic layers were washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. Purification by preparative thin layer chromatography (60% EtOAc/Hexanes) afforded title compound **3.49** (6.4 mg, 86%)

TLC R_f 0.30 (60% EtOAc/Hexanes) [UV (*weak*) / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.54 (d, $J = 5.6$ Hz, 1H), 6.77 (dd, $J = 3.7, 2.6$ Hz, 1H), 6.19 (d, $J = 5.6$ Hz, 1H), 4.96 (s, 1H), 4.90 (td, $J = 7.8, 5.2$ Hz, 1H), 4.76 (d, $J = 1.0$ Hz, 1H), 3.64 (s, 3H), 3.22 (ddt, $J = 12.6, 8.0, 2.4$ Hz, 1H), 3.16 (ddd, $J = 7.5, 3.7, 2.1$ Hz, 1H), 2.83 – 2.70 (m, 1H), 2.52 (dd, $J = 15.4, 8.2$ Hz, 1H), 2.48 (dd, $J = 14.2, 7.8$ Hz, 1H), 2.35 (dd, $J = 15.4, 6.3$ Hz, 1H), 2.15 (dd, $J = 14.1, 5.0$ Hz, 1H), 1.68 (d, $J = 0.8$ Hz, 3H), 1.63 (d, $J = 12.4$ Hz, 1H), 1.30 (d, $J = 1.0$ Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.6, 171.5, 167.9, 158.7, 144.2, 139.9, 135.6, 121.6, 116.2, 88.9, 79.7, 75.6, 63.0, 52.7, 52.1, 44.0, 42.9, 37.7, 29.9, 24.4, 20.9.

HRMS-ESI (m/z) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: 411.1420 $[\text{M}+\text{Na}]^+$, found 411.1409 $[\text{M}+\text{Na}]^+$.

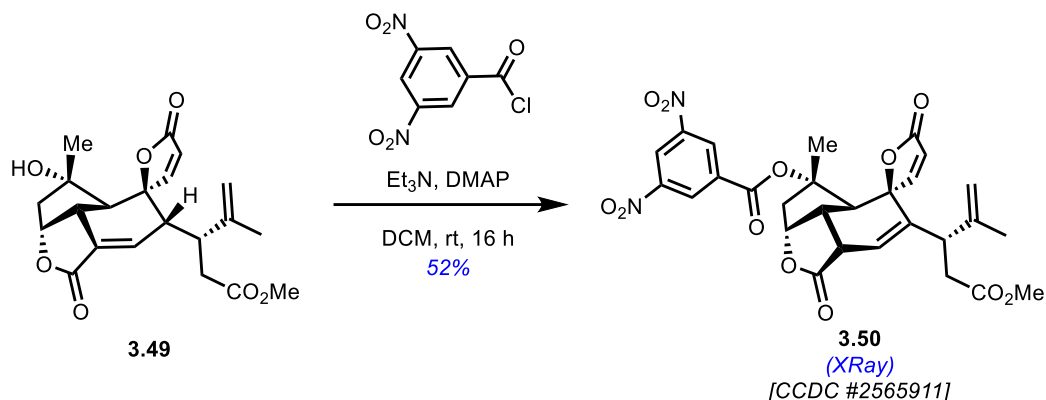
FTIR-ATR (thin film) ν [cm^{-1}] 3500, 2921, 2853, 1736, 1719, 1457, 1194, 1169.

$[\alpha]_D^{24} +66.0^\circ$ ($c = 0.03$, CHCl_3)

Physical State White solid

Melting Point 168 – 170 $^\circ\text{C}$

(2R,2a'R,2a1'R,4'S,4a'S,7a'S)-6'-((S)-5-Methoxy-2-methyl-5-oxopent-1-en-3-yl)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-4'-yl 3,5-dinitrobenzoate (**3.50**).



A 2 mL vial containing a micro stir bar was charged with **3.49** (6.4 mg, 0.016 mmol, 1.00 eq.) and anhydrous CH_2Cl_2 (0.4 mL), followed by the addition of Et_3N (14 μL , 0.099 mmol, 6.00 eq.) and 3,5-dinitrobenzoyl chloride (15.2 mg, 0.066 mmol, 4.00 eq.). Then, DMAP (4.0 mg, 0.033 mmol, 2.00 eq.) was added. The headspace of the vial was displaced with $\text{Ar}_{(\text{g})}$ and a cap screwed tightly. This reaction was allowed to stir overnight at room temperature. *NOTE : a dark red color is observed upon addition of DMAP.* The reaction was then quenched with satd. $\text{NaHCO}_3(\text{aq.})$ (2 mL). The organic layer was pipetted out of the mixture and the aqueous phase was extracting with CH_2Cl_2 (3 x 3 mL). The combined organic phases were washed with Na_2SO_4 and concentrated *in vacuo*. Purification by preparative thin layer chromatography (50% EtOAc/Hexanes) afforded title compound **3.50** (5.0 mg, 52%) as an amorphous white solid. Crystals suitable for X-ray diffraction were obtained by slow evaporation of a solution in EtOAc/Hexanes. The crystal structure was uploaded to the CCDC with the deposition number #2565911.

NOTE : Crystals of 3.50 diffracted poorly, and a checkcif file was not included in the report by the crystallographer. Thus, this SCXRD analysis cannot be considered worthy for publication, but confirm the connectivity in this case.

TLC R_f 0.55 (50% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, C_6D_6) δ 8.55 (t, $J = 2.1$ Hz, 1H), 8.37 (d, $J = 2.1$ Hz, 2H), 7.38 (d, $J = 5.7$ Hz, 1H), 6.03 (d, $J = 5.7$ Hz, 1H), 5.95 (d, $J = 5.6$ Hz, 1H), 4.85 (s, 1H), 4.76 (s, 1H), 3.90 (q, $J = 7.1$ Hz, 2H), 3.49 (s, 3H), 3.02 (t, $J = 7.9$ Hz, 1H), 2.82 (t, $J = 5.7$ Hz, 1H), 2.46 (dd, $J = 15.9, 6.8$ Hz, 1H), 2.35 (d, $J = 3.7$ Hz, 1H), 2.33 (d, $J = 1.8$ Hz, 1H), 2.24 – 2.14 (m, 2H), 1.50 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ 172.9, 170.9, 170.8, 160.7, 156.3, 148.3, 144.6, 139.6, 133.4, 125.2, 122.6, 121.9, 114.7, 89.1, 86.1, 77.3, 51.6, 46.5, 44.2, 42.7, 39.0, 38.4, 31.9, 23.1, 20.6, 20.4, 14.4, 14.2.

HRMS-ESI (m/z) calcd. for $\text{C}_{28}\text{H}_{26}\text{O}_2\text{N}_2$: 583.1564 $[\text{M}+\text{H}]^+$, found 583.1558 $[\text{M}+\text{H}]^+$.

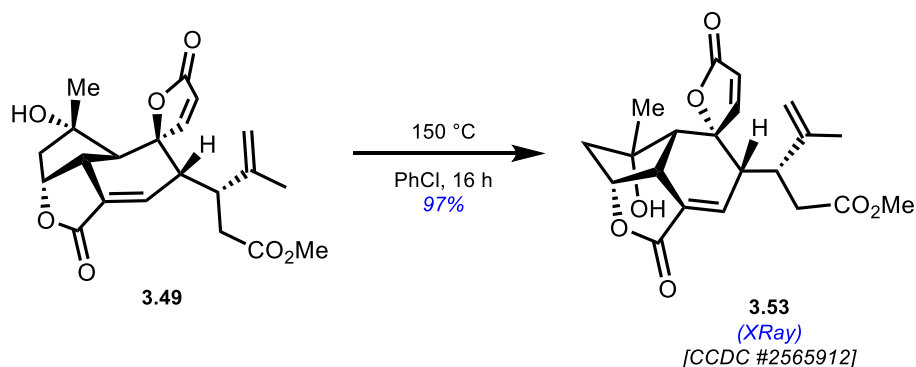
FTIR-ATR (thin film) ν [cm^{-1}] 2959, 2924, 2854, 1772, 1759, 1734, 1544, 1346, 1282, 1144.

$[\alpha]_D^{24} +160.8^\circ$ ($c = 0.40$, CHCl_3)

Physical State Colorless needles

Melting Point 117-119 $^\circ\text{C}$

Methyl (R)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.53**).



A 8 mL reaction tube was charged with a micro stir bar and **3.49** (10.2 mg, 0.026 mmol, 1.00 eq.) then PhCl (1.0 mL) was added. The headspace of the reaction tube was displaced with Ar_(g) and screwed tightly. The tube was then placed in a wax bath and heated to 150 °C for 16 h, after which the reaction mixture was then cooled to room temperature and the solvent was removed with a gentle stream of air. The remaining solid was dissolved in CH₂Cl₂ (2 mL) and passed through a short silica plug using 5% MeOH/CH₂Cl₂ to elute. This mixture was then concentrated *in vacuo* to afford title compound **3.53** (9.9 mg, 97%) as a white solid in high purity (>98% by ¹H NMR). A recrystallization of the solid from EtOAc afforded crystals suitable for X-ray crystallography. The crystal structure was uploaded to the CCDC with the deposition number #2565912.

TLC R_f 0.60 (5% MeOH/CH₂Cl₂) [UV (*weak*) / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 5.6 Hz, 1H), 6.94 (dd, *J* = 4.8, 3.5 Hz, 1H), 6.19 (d, *J* = 5.6 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.63 (s, 3H), 3.35 – 3.28 (m, 1H), 2.87 – 2.80 (m, 1H), 2.77 (d, *J* = 2.7 Hz, 1H), 2.60 (d, *J* = 9.0 Hz, 1H), 2.57 (td, *J* = 5.3, 1.7 Hz, 1H), 2.50 (dd, *J* = 7.2, 3.3 Hz, 2H), 2.29 (d, *J* = 14.9 Hz, 1H), 1.82 (ddd, *J* = 14.9, 6.6, 2.7 Hz, 1H), 1.74 (s, 3H), 1.16 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.1, 171.1, 168.7, 159.5, 143.9, 135.9, 132.0, 120.9, 116.4, 93.1, 81.5, 80.3, 54.5, 51.9, 48.6, 47.7, 44.8, 41.1, 39.0, 26.9, 19.9.

HRMS-ESI (*m/z*) calcd. for C₂₁H₂₄O₇ : 411.1420 [M+Na]⁺, found 411.1392 [M+Na]⁺.

FTIR-ATR (neat) ν [cm⁻¹] 3567, 2971, 2925, 1772, 1747, 1436, 1206.

[α]_D²⁴ +25.6 ° (c = 0.50, CHCl₃)

Physical State Light beige solid (after SFC) or colorless needles (after recrystallization)

Melting point 236 – 238 °C

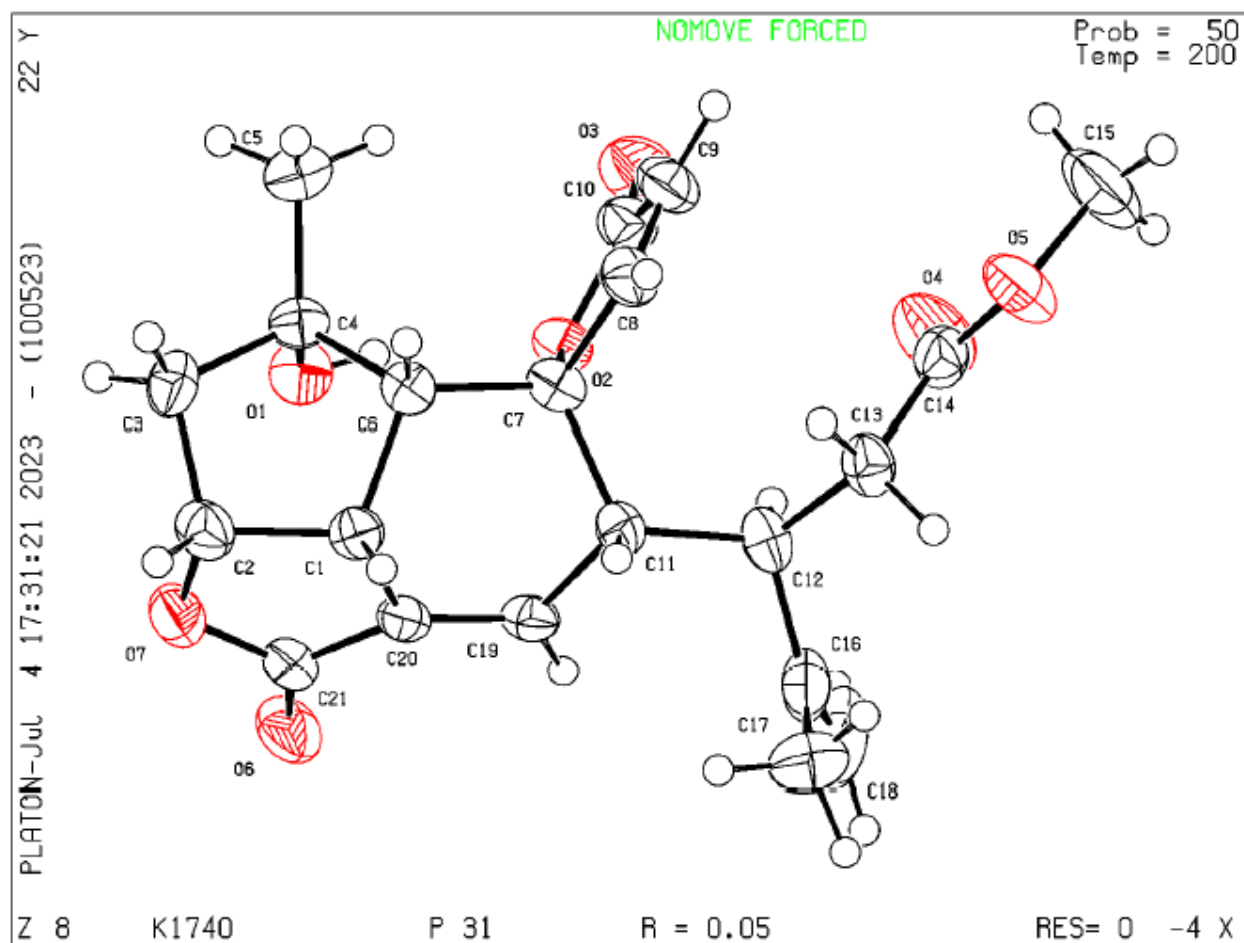
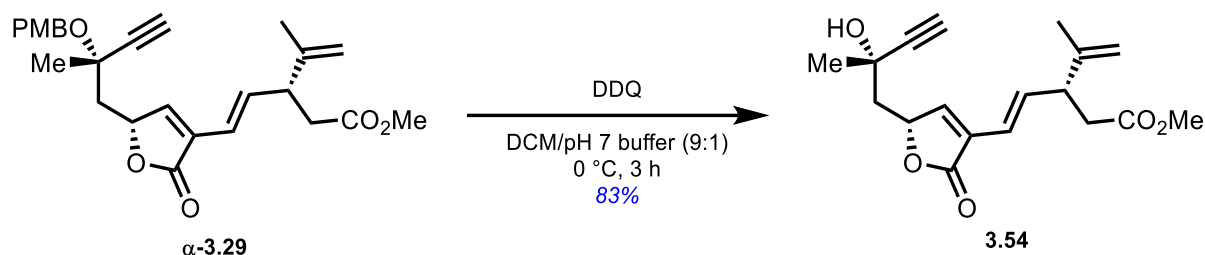


Figure 5.12. CHECKCIF file of 3.53.

Methyl (R,E)-5-((R)-5-((S)-2-hydroxy-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-3-(prop-1-en-2-yl)pent-4-enoate (**3.54**).



To a 250 mL round bottom flask containing a magnetic stir bar and **α -3.29** (2.16 g, 4.93 mmol, 1.00 eq.) was added CH_2Cl_2 (90 mL) and pH 7 phosphate buffer (10 mL). This mixture was stirred vigorously and cooled to 0 °C before DDQ (1.11 g, 4.93 mmol, 1.00 eq.) was added in small portions over 10 minutes. After 1 h at this temperature, equal portions of DDQ (0.20 eq.) were added periodically every 15 minutes until TLC showed full consumption of the starting material, for a total of 8 times over 2 hours (Total DDQ = 2.8 eq.). Then, satd. $\text{NaHCO}_3(\text{aq.})$ (100 mL) was added and stirred vigorously for 10 min while warming to room temperature. The mixture was transferred to an extraction funnel containing water (200 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3x 75 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (30 to 40% EtOAc/Hexanes) afforded title compound **3.54** (1.30 g, 83%).

NOTES : Alkyne **3.54** is thermally unstable and prone to undergo early [4+2]. The rotavap baths must be kept under 25 °C to prevent early cycloaddition. The substrate was stable at -20 °C for 24 h but showed instability when kept for prolonged periods of time (>7 days). Slow and careful addition of DDQ is required to suppress oxidative side-reactions during the PMB removal.

TLC R_f 0.40 (40% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, J = 1.8 Hz, 1H), 6.71 (dd, J = 15.9, 8.1 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.29 (t, J = 5.9 Hz, 1H), 4.85 – 4.83 (m, 1H), 4.81 (s, 1H), 3.65 (s, 3H), 3.31 (q, J = 7.8 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.58 (s, 1H), 2.15 (dd, J = 14.0, 6.2 Hz, 1H), 1.95 (dd, J = 14.0, 7.2 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.5, 171.6, 148.8, 145.3, 138.1, 128.5, 119.4, 111.9, 85.9, 78.6, 73.4, 66.7, 51.8, 46.9, 46.1, 37.9, 31.5, 20.8.

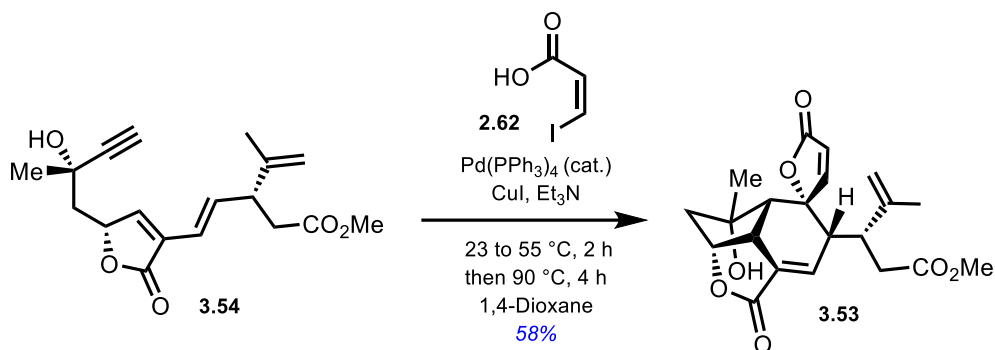
HRMS-ESI (m/z) calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_5$: 319.1545 $[\text{M}+\text{H}]^+$, found 319.1546 $[\text{M}+\text{H}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3450, 2925, 2855, 2359, 1754, 1737, 1435, 1105.

$[\alpha]_D^{24}$ -25.6 ° (c = 0.25, CHCl_3)

Physical State Yellow oil

Methyl (R)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.53**).



An oven-dried 200 mL Schlenk flask loaded with a magnetic stir bar was transferred to a glovebox. This flask was charged with Pd(PPh₃)₄ (530 mg, 0.46 mmol, 0.10 eq.), CuI (875 mg, 4.59 mmol, 1.00 eq.) and (Z)-iodoacrylic acid **2.62** (3.00 g, 15.2 mmol, 3.30 eq.). The flask was capped with a septa, taken out of the GB and an Ar_(g) balloon was connected to the flask. 1,4-Dioxane (41 mL) was added before a solution of **3.54** (1.46 g, 4.59 mmol, 1.00 eq.) in dioxane (20 mL + 2 x 5 mL wash) was transferred to the Schlenk flask by cannulation. This solution was stirred before a solution of Et₃N (2.88 mL, 20.7 mmol, 4.5 eq.) in dioxane (10 mL + 2x 2.5 mL wash) was added. This mixture was stirred 10 min at room temperature before it was placed in an oil bath and heated to 55 °C. After 2 h at this temperature, the oil bath temperature was raised to 90 °C and further stirred 4 hours at this temperature. The mixture was then cooled to room temperature before satd. NH₄Cl_(aq.) (85 mL) was added. After stirring vigorously for 15 minutes, the resulting suspension was transferred to an extraction funnel and extracted with EtOAc (5 x 50 mL). The organic layers were combined, washed with sat. NaHCO₃ (2 x 20 mL), brine (50 mL), dried by Na₂SO₄ and concentrated *in vacuo* to around 100 mL before a stir bar and anhydrous MgCl₂ (3.06 g, 32.2 mmol, 7.00 eq.) were added. The resulting suspension was stirred vigorously for 60 h.⁹ The TPPO•MgCl₂ crystals were filtered on a Celite™ pad and the filtrate was concentrated *in vacuo*. Purification by silica flash chromatography (20 - 40% Acetone/Toluene) afforded title compound **3.53** (1.04 g, 58%) as a light beige solid. A recrystallization of the solid from EtOAc afforded crystals suitable for X-ray crystallography.

NOTE : Dioxane was degassed by sparging Ar_(g) for 30 minutes before use. MgCl₂ treatment is required as TPPO tends to stick to substrate and could not be removed by chromatography.⁹

TLC R_f 0.60 (5% MeOH/CH₂Cl₂) [UV (*weak*) / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 5.6 Hz, 1H), 6.94 (dd, *J* = 4.8, 3.5 Hz, 1H), 6.19 (d, *J* = 5.6 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.63 (s, 3H), 3.35 – 3.28 (m, 1H), 2.87 – 2.80 (m, 1H), 2.77 (d, *J* = 2.7 Hz, 1H), 2.60 (d, *J* = 9.0 Hz, 1H), 2.57 (td, *J* = 5.3, 1.7 Hz, 1H), 2.50 (dd, *J* = 7.2, 3.3 Hz, 2H), 2.29 (d, *J* = 14.9 Hz, 1H), 1.82 (ddd, *J* = 14.9, 6.6, 2.7 Hz, 1H), 1.74 (s, 3H), 1.16 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.1, 171.1, 168.7, 159.5, 143.9, 135.9, 132.0, 120.9, 116.4, 93.1, 81.5, 80.3, 54.5, 51.9, 48.6, 47.7, 44.8, 41.1, 39.0, 26.9, 19.9.

HRMS-ESI (*m/z*) calcd. for C₂₁H₂₄O₇ : 411.1420 [M+Na]⁺, found 411.1392 [M+Na]⁺.

FTIR-ATR (neat) ν [cm⁻¹] 3567, 2971, 2925, 1772, 1747, 1436, 1206.

[α]_D²⁴ +25.6 ° (c = 0.50, CHCl₃)

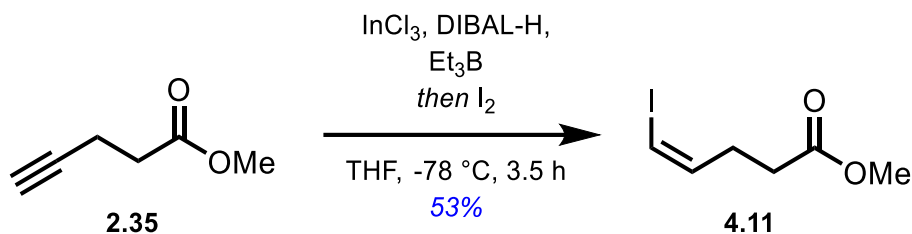
Physical State Light beige solid (after SFC) or colorless needles (after recrystallization)

Melting Point 236 – 238 °C



Figure 5.13. Pictures of the large-scale crystal crop from the recrystallisation of **3.53**.

Methyl (Z)-5-iodopent-4-enoate (**4.11**)



A 50 mL round bottom flask containing a stir bar and anhydrous InCl_3 (1.06 g, 4.82 mmol, 1.35 eq.) was heated under vacuum for 5 min using a heat gun. THF (13 mL) was added and the solution was cooled to -78°C . DIBAL-H (1.23 M in hexanes, 3.77 mL, 4.64 mmol, 1.30 eq.) was added dropwise and the mixture was stirred 30 min at this temperature. Then, a solution of **2.35** (400 mg, 3.57 mmol, 1.00 eq.) in THF (4 mL) and a solution of triethylborane (1.0M in hexanes, 0.71 mL, 0.71 mmol, 0.20 eq.) were injected sequentially, and the resulting mixture was stirred 2.5 h at this temperature, after which iodine (5.43 g, 21.4 mmol, 6.00 eq.) was added. After being stirred for 30 min at -78°C , the reaction mixture was poured into an Erlenmeyer containing satd. $\text{NaHCO}_3(\text{aq.})$ (40 mL). Satd. $\text{Na}_2\text{S}_2\text{O}_3(\text{aq.})$ was added until solution turned colorless (approx. 10 mL). The mixture was transferred to an extraction funnel and extracted with hexanes (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (2.5% EtOAc/Hexanes) afforded the title compound **4.11** (450 mg, 53%).

NOTE : HRMS analysis was attempted thrice and showed at best a ΔDA of 0.0041 between calculated and observed

TLC R_f 0.55 (10% EtOAc/Hexanes) [KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 6.31 – 6.17 (m, 2H), 3.69 (s, 3H), 2.49 – 2.37 (m, 4H).

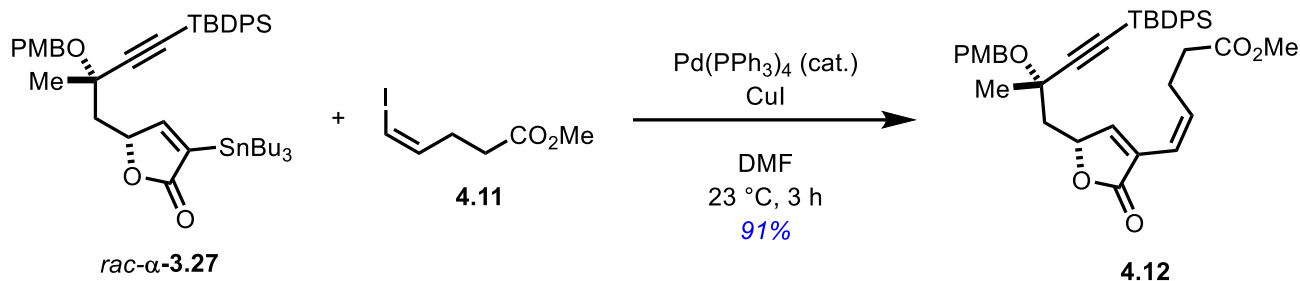
^{13}C NMR ^{13}C NMR (101 MHz, CDCl_3) δ 173.1, 139.3, 83.9, 51.9, 32.4, 30.3.

HRMS-ESI (m/z) calcd. for $\text{C}_6\text{H}_9\text{O}_2\text{I}$: 240.9725 [$\text{M}+\text{H}$] $^+$, found 241.0138 [$\text{M}+\text{H}$] $^+$.

FTIR-ATR (neat) ν [cm^{-1}] 2952, 2843, 1732, 1435, 1194, 1149.

Physical State Colorless oil

Methyl (Z)-5-((R)-5-((S)-4-(*tert*-butyldiphenylsilyl)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**4.12**)



A 10 mL Schlenk flask containing a magnetic stir bar was flame-dried and transferred into a glovebox where Pd(PPh₃)₄ (15.7 mg, 0.014 mmol, 0.05 eq.) was added. The flask was fitted with a septa, taken out of the GB then fitted with an Ar(g) balloon. On the side, a solution of **4.11** (58.7 mg, 0.244 mmol, 0.90 eq.) in anhydrous DMF (2 mL) was sparged with Ar(g) for 5 min injected into the Schlenk flask. This was stirred 5 minutes before a solution of *rac*- α -**3.27** (221 mg, 0.272 mmol, 1.00 eq.) in anhydrous DMF (2 mL) was sparged with Ar(g) for 5 min and injected into the Schlenk flask. When the transfer was complete, the septa of the Schlenk flask was removed and under the stream of Ar(g), CuI (72.4 mg, 0.380 mmol, 1.40 eq.) was quickly added and the septa was reattached to the Schlenk flask. This mixture was stirred for 3 h at room temperature, after which TLC analysis showed full consumption of *rac*- α -**3.27**. Satd. NH₄Cl(aq.) (5 mL) was then added and the suspension stirred vigorously for 30 minutes before it was transferred to an extraction funnel containing additional satd. NH₄Cl(aq.) (10 mL) and then extracted with EtOAc (5 x 15 mL). The combined organic phases were washed with brine (2 x 15 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (15% to 20% EtOAc:Hexanes) afforded title compound **4.12** (142 mg, 91%).

TLC R_f 0.30 (EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.82 – 7.76 (m, 4H), 7.43 – 7.36 (m, 7H – *Overlap of aromatic and β -H*), 7.27 (d, *J* = 6.6 Hz, 2H – *Overlap with CHCl₃ peak*), 6.86 (d, *J* = 8.6 Hz, 2H), 6.05 (d, *J* = 11.5 Hz, 1H), 5.78 (dt, *J* = 12.2, 6.3 Hz, 1H), 5.51 – 5.45 (m, 1H), 4.80 (d, *J* = 10.0 Hz, 1H), 4.57 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.42 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.29 (dd, *J* = 15.9, 6.0 Hz, 4H), 2.09 (dd, *J* = 13.9, 8.5 Hz, 1H), 1.72 (s, 3H), 1.12 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 173.2, 173.1, 159.4, 150.7, 136.9, 135.6, 132.9, 132.9, 130.4, 129.9, 129.9, 128.1, 127.4, 117.9, 114.0, 109.4, 88.1, 79.6, 72.8, 66.8, 55.4, 51.8, 46.1, 33.2, 29.8, 27.3, 27.1, 24.8, 18.7.

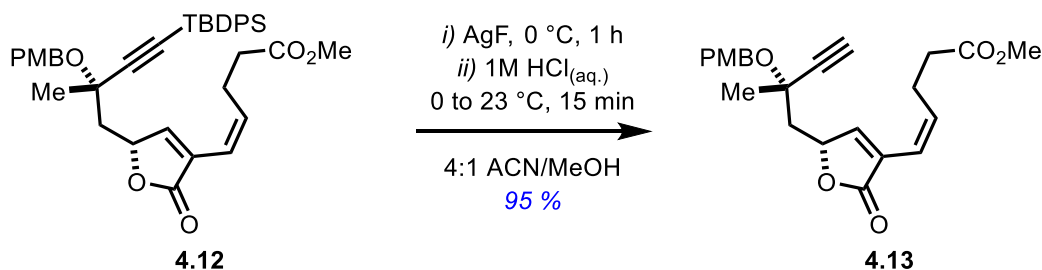
HRMS-ESI (*m/z*) calcd. for C₃₉H₄₄O₆Si : 659.2805 [M+Na]⁺, found 659.2802 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2953, 2927, 2856, 2361, 1762, 1740, 1515, 1250, 1110.

Physical State White waxy solid

Melting point >180 °C (*decomp.*)

Methyl (Z)-5-((R)-5-((S)-2-((4-methoxybenzyl)oxy)-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**4.13**).



A 10 mL round bottom flask containing a magnetic stir bar was charged with **4.12** (142 mg, 0.223 mmol, 1.00 eq), anhydrous MeOH (0.5 mL) and anhydrous MeCN (2.0 mL). The mixture was cooled to 0 °C and wrapped with aluminum foil. AgF (42.4 mg, 0.334 mmol, 2.00 eq.) was then added in a single portion. The ice bath was taken away and the mixture was allowed to stir at room temperature for 1 h. The resulting mixture was cooled back to 0 °C before 1M HCl_(aq.) (446 µL, 0.446 mmol, 2.00 eq.) was added dropwise, and the resulting suspension stirred to room temperature for 15 minutes. This mixture was then added to an extraction funnel containing water (10 mL) and the aqueous layer extracted with CH₂Cl₂ (4 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried by Na₂SO₄, filtered on Celite™ pad and concentrated *in vacuo*. Purification by silica flash chromatography (25% EtOAc/Hexanes) afforded title compound **4.13** (84.2 mg, 95%).

TLC R_f 0.20 (25% EtOAc/Hexanes) [UV / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.09 – 6.00 (m, 1H), 5.78 (dt, *J* = 11.6, 6.7 Hz, 1H), 5.44 – 5.36 (m, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 4.48 (d, *J* = 10.1 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.69 (s, 1H), 2.38 – 2.22 (m, 5H), 2.01 (dd, *J* = 13.8, 8.5 Hz, 1H), 1.61 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.2, 173.1, 159.4, 150.7, 136.9, 130.4, 129.8, 127.3, 117.9, 113.9, 83.5, 79.4, 75.7, 71.9, 66.5, 55.4, 51.8, 45.9, 33.2, 26.9, 24.8.

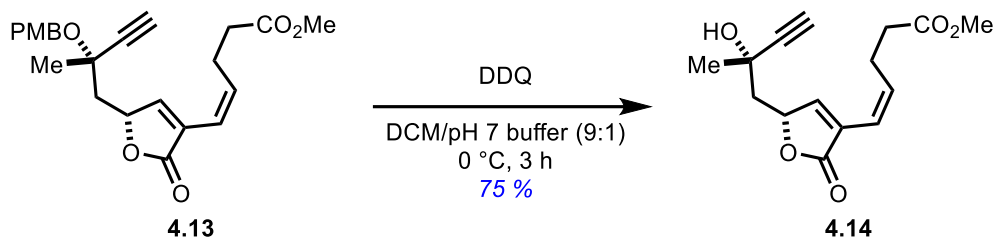
HRMS-ESI (*m/z*) calcd. for C₂₃H₂₆O₆ : 421.1627 [M+Na]⁺, found 421.1629 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 2953, 2923, 2855, 2103, 1755, 1735, 1514, 1246, 1028.

Physical State White waxy solid

Melting Point 76 – 78 °C

Methyl (Z)-5-((R)-5-((S)-2-hydroxy-2-methylbut-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)pent-4-enoate (**4.14**)



To a 10 mL round bottom flask containing a magnetic stir bar and **4.13** (74.3 mg, 0.186 mmol, 1.00 eq.) was added CH_2Cl_2 (4.5 mL) and pH 7 phosphate buffer (0.5 mL). This mixture was stirred vigorously and cooled to $0\text{ }^{\circ}\text{C}$ before DDQ (42.3 mg, 0.186 mmol, 1.00 eq.) was added in small portions over 10 minutes. After 1 h at this temperature, DDQ (1.0 eq.) was added every hour until TLC analysis showed full consumption of starting material, for a total of 3.0 eq. DDQ added over 3 hours. Then, satd. $\text{NaHCO}_3(\text{aq.})$ (5 mL) was added and stirred vigorously for 10 min while warming to room temperature. The mixture was transferred to an extraction funnel containing water (10 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (35% EtOAc/Hexanes) afforded title compound **4.14** (38.7 mg, 75%).

TLC R_f 0.40 (40% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 7.55 (s, 1H), 6.16 – 6.07 (m, 1H), 5.87 (dt, $J = 11.6, 7.0$ Hz, 1H), 5.38 (t, $J = 6.8$ Hz, 1H), 3.69 (s, 3H), 2.62 – 2.56 (m, 2H – *Overlap*), 2.61 (s, 1H – *Overlap*), 2.53 – 2.44 (m, 2H), 2.22 (dd, $J = 14.0, 6.2$ Hz, 1H), 2.01 (dd, $J = 14.0, 7.2$ Hz, 1H), 1.64 (s, 3H), 1.58 (br s, *OH*).

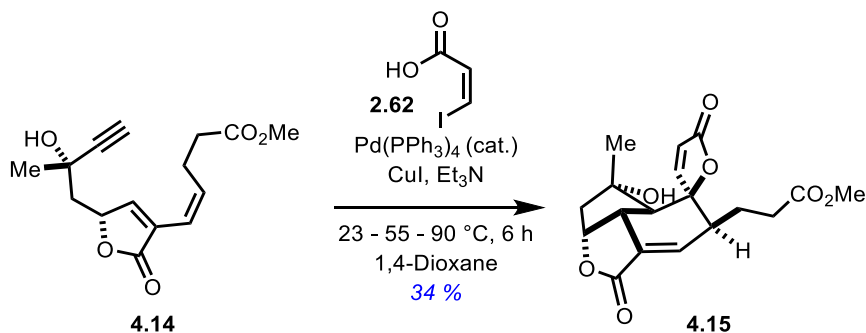
^{13}C NMR (101 MHz, CDCl_3) δ 173.4, 172.9, 150.0, 136.9, 127.8, 118.2, 86.0, 79.2, 73.5, 66.6, 51.9, 46.4, 33.4, 31.5, 25.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: 301.1052 $[\text{M}+\text{Na}]^+$, found 301.1053 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3445, 2954, 2923, 2858, 2149, 1734, 1441, 1374, 1204.

Physical State Light yellow oil

Methyl 3-((2S,2a1'R,4'S,5a'S,6'S,7a'R)-6'-hydroxy-6'-methyl-2',5'-dioxo-2a1',4',5a',6',7',7a'-hexahydro-2'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-4'-yl)propanoate (**4.15**)



An oven dried 10 mL Schlenk flask was charged with a stir bar and transferred to a glovebox where Pd(PPh₃)₄ (10.3 mg, 8.88 μmol, 0.13 eq.), CuI (13.0 mg, 0.068 mmol) and (Z)-iodoacrylic acid **2.62** (44.6 mg, 0.225 mmol, 3.30 eq.) were added. A septa was connected and an Ar(g) balloon was connected to the flask. Dioxane (1.0 mL) was added, followed by a solution of **4.14** (19.0 mg, 0.068 mmol, 1.00 eq.) in dioxane (1.0 mL). Then, a solution of Et₃N (43 μL, 0.307 mmol, 4.50 eq.) in Dioxane (0.5 mL) was injected dropwise (*NOTE : 5 min after Et₃N was added, a dilute green color was observed*). The mixture was stirred 10 minutes at 23 °C before it was plunged in an oil bath set at 55 °C for 2 h. The temperature was then ramped up to 90 °C and the mixture stirred an additional 4 h. The mixture was then cooled to room temperature and a solution of satd. NH₄Cl_(aq.) (5 mL) was added. The suspension was extracted with EtOAc (4x 10 mL). The combined organic layers were washed with satd. NaHCO_{3(aq.)} (3x 5 mL), brine (5 mL), dried by Na₂SO₄ and concentrated *in vacuo*. Purification by silica flash chromatography (25 to 35% Acetone/Toluene) afforded title compound **4.15** (8.0 mg, 34%).

TLC R_f 0.30 (25% Acetone/Toluene) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.47 (d, *J* = 5.6 Hz, 1H), 6.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 6.24 (d, *J* = 5.6 Hz, 1H), 4.84 (td, *J* = 7.9, 5.8 Hz, 1H), 3.67 (s, 3H), 3.38 (ddt, *J* = 12.8, 8.6, 2.3 Hz, 1H), 3.06 (dtd, *J* = 10.1, 5.2, 2.0 Hz, 1H), 2.51 (ddd, *J* = 16.6, 7.4, 5.5 Hz, 1H), 2.44 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.37 (ddd, *J* = 16.4, 8.5, 7.3 Hz, 1H), 2.09 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.94 (d, *J* = 12.4 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.73 – 1.64 (m, 1H), 1.59 (br s, OH) 1.19 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 173.1, 171.8, 168.5, 157.9, 137.5, 135.2, 121.9, 87.8, 79.6, 75.4, 62.3, 52.2, 51.9, 48.1, 40.6, 31.5, 23.4, 22.1.

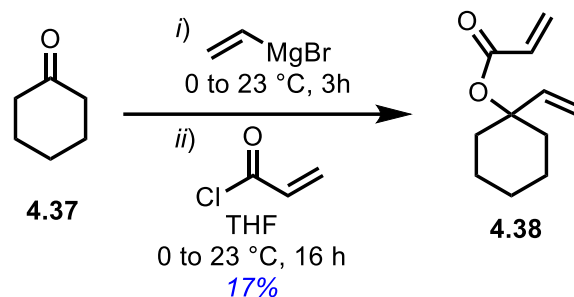
HRMS-ESI (*m/z*) calcd. for C₁₈H₂₀O₇ : 371.1107 [M+Na]⁺, found 371.1100 [M+Na]⁺.

FTIR-ATR (thin film) ν [cm⁻¹] 3479, 2954, 2923, 2853, 1750, 1729, 1457, 1378, 1176.

Physical State Crystalline white solid

Melting Point 134 – 136 °C

1-Vinylcyclohexyl acrylate (**4.38**).



A 100 mL round bottom flask containing a magnetic stir bar was charged with **4.37** (1.49 g, 15.2 mmol, 1.00 eq.) and THF (12 mL) was added. The mixture was cooled to 0 °C before a solution of vinylmagnesium bromide (0.7M in THF, 26.1 mL, 18.3 mmol 1.20 eq.) was added dropwise over 5 minutes. This mixture was allowed to warm up to temperature and stirred for 3 h before it was cooled back to 0 °C to add acryloyl chloride (3.70 mL, 45.7 mmol, 3.00 eq.) dropwise. The ice bath was taken out and the mixture was stirred at room temperature for 16 h. Satd. $\text{NH}_4\text{Cl}_{(\text{aq.})}$ (20 mL) was added, the mixture was transferred to an extraction funnel and the organic layer was collected. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organic layers were combined and washed with brine (15 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by silica flash chromatography (2% EtOAc / Hexanes) to afford title compound **4.38** (893 mg, 17%). The spectroscopic values of this compound matched the values reported in the literature.¹⁰

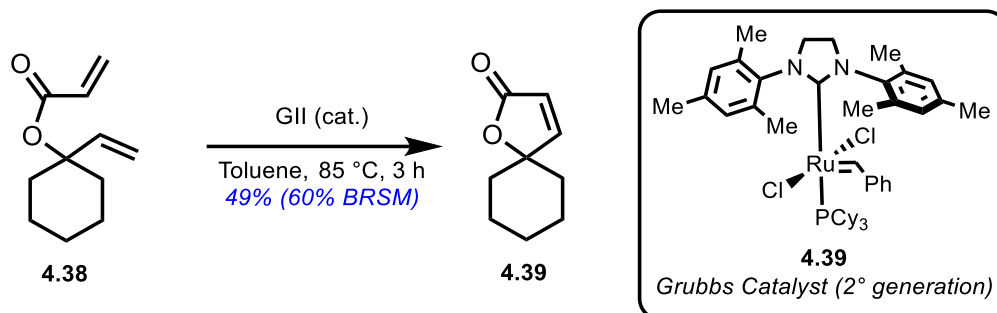
TLC R_f 0.70 (10% EtOAc:Hexanes) [KMnO_4]

^1H NMR (400 MHz, CDCl_3) δ 6.28 (d, J = 17.0 Hz, 1H), 6.14 – 5.95 (m, 2H), 5.69 (d, J = 10.3 Hz, 1H), 5.09 (t, J = 14.2 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.70 – 1.49 (m, 7H), 1.31 – 1.22 (m, 1H).

^{13}C NMR ^{13}C NMR (101 MHz, CDCl_3) δ 165.1, 141.9, 130.1, 129.9, 113.8, 82.2, 35.0, 25.5, 21.9.

Physical State Colorless oil

1-Oxaspiro[4.5]dec-3-en-2-one (**4.36**).



A 500 mL round bottom flask containing a magnetic stir bar was charged with **4.38** (893 mg, 4.95 mmol, 1.00 eq.) and toluene (250 mL, 20 mM). This mixture was sparged by Ar_(g) for 30 minutes, Grubbs' catalyst second generation **4.39** (105 mg, 0.12 mmol, 0.025 eq.) was then added and the resulting mixture was heated to 85 °C. After 3 h at this temperature, the solvent was removed *in vacuo* and the mixture was passed through an activated basic alumina plug flushing with CH₂Cl₂ (ca. 20 mL). The filtrate was concentrated *in vacuo* and purified by silica flash chromatography (20% EtOAc/Hexanes) to afford title compound **4.39** (372 mg, 49%) and recovered starting material (153 mg). The spectroscopic values of this compound matched the values reported in the literature.¹⁰

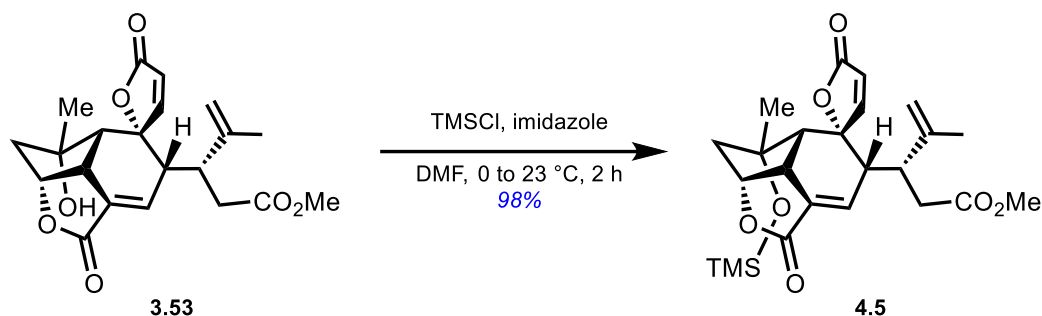
TLC R_f 0.45 (30% EtOAc/Hexanes) [UV (*weak*) / KMnO₄]

¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 5.7 Hz, 1H), 6.00 (d, *J* = 5.7 Hz, 1H), 1.76 (ddt, *J* = 14.9, 6.9, 4.6 Hz, 2H), 1.71 – 1.59 (m, 7H), 1.39 (ddt, *J* = 16.9, 10.2, 5.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 172.7, 160.7, 120.3, 88.7, 34.8, 24.8, 22.6.

Physical State Yellow oil

Methyl (R)-4-methyl-3-((2R,2a'R,2a1'R,4'S,4a'S,6'S)-4'-methyl-1',5-dioxo-4'-((trimethylsilyl)oxy)-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)pent-4-enoate (**4.5**)



A 10 mL round bottom flask containing a stir bar was charged with **3.53** (44.4 mg, 114 μmol , 1.00 eq.), imidazole (23.3 mg, 343 μmol , 3.00 eq) and DMF (1.5 mL). The mixture was cooled to 0 $^\circ\text{C}$ before freshly distilled TMSCl (43.5 μL , 343 μmol , 3.00 eq.) was injected dropwise. The mixture was warmed to room temperature slowly over 2 hours, at which point TLC analysis showed full consumption of the starting material. Brine (3 mL) was added and the suspension transferred to an extraction funnel and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried by Na_2SO_4 and concentrated *in vacuo*. Purification by silica flash chromatography (80% – 100% EtOAc/Hexanes) afforded title compound **4.5** (51.7 mg, 98%).

TLC R_f 0.50 (80% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 7.07 – 7.06 (m, 1H), 6.44 (d, J = 5.6 Hz, 1H), 5.58 (d, J = 5.6 Hz, 1H), 4.70 – 4.67 (m, 1H), 4.58 – 4.54 (m, 1H), 4.23 (dt, J = 8.3, 6.6 Hz, 1H), 3.29 (s, 3H), 2.68 (q, J = 7.1 Hz, 1H), 2.33 (tt, J = 9.1, 3.2 Hz, 1H), 2.20 (dd, J = 15.7, 7.6 Hz, 1H), 2.14 (dd, J = 15.7, 6.8 Hz, 1H), 2.04 (ddd, J = 5.8, 4.6, 2.8 Hz, 1H), 1.97 (dd, J = 12.7, 6.7 Hz, 1H), 1.54 (s, 3H), 1.48 (d, J = 9.6 Hz, 1H), 1.38 (dd, J = 12.7, 6.6 Hz, 1H), 0.77 (s, 3H), 0.11 (s, 9H).

^{13}C NMR (151 MHz, C_6D_6) δ 171.9, 171.8, 168.2, 156.5, 144.1, 135.2, 133.1, 122.7, 116.3, 91.7, 82.3, 78.2, 53.1, 51.2, 47.3, 46.4, 42.3, 41.5, 38.8, 29.8, 19.7, 2.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{24}\text{H}_{32}\text{O}_7\text{Si}$: 483.1815 $[\text{M}+\text{Na}]^+$, found 483.1821 $[\text{M}+\text{Na}]^+$.

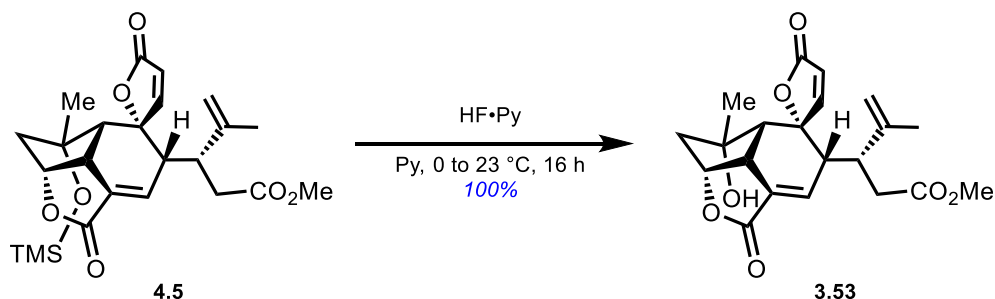
FTIR-ATR (thin film) ν [cm^{-1}] 2955, 2923, 2853, 1747, 1736, 1250, 1205, 1168, 1026.

$[\alpha]_D^{24}$ -7.2 $^\circ$ (c = 0.25, CHCl_3)

Physical State White solid

Melting Point 198 – 200 $^\circ\text{C}$

Methyl (R)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.53**).



A 4 mL vial containing a magnetic stir bar was charged with **4.5** (5.1 mg, 11.1 μmol , 1.00 eq.) and pyridine (0.4 mL). The mixture was cooled to 0 $^\circ\text{C}$ before 70% HF·Pyridine (5 drops, ~ 0.1 mL) were added dropwise from a Pasteur pipette. The reaction was allowed to stir back to room temperature overnight, after which TLC analysis showed full consumption of the starting material. Satd. $\text{NaHCO}_3(\text{aq.})$ (2 mL) was slowly added (*NOTE : Vigorous $\text{CO}_2(\text{g})$ generation!*) and the mixture was extracted with EtOAc (4 x 3 mL). The combined organic layers were washed with brine (3 mL), dried by Na_2SO_4 and concentrated *in vacuo* to give title compound **3.53** (4.3 mg, 100%) in very high purity (>99%, NMR) and required no further purification.

NOTE : This experiment needs to be conducted in disposable borosilicate glass vials as to not permanently damage glass round bottom flasks. HF·Pyridine is extremely toxic/corrosive and proper PPE must be used.

TLC R_f 0.60 (5% MeOH/ CH_2Cl_2) [UV (*weak*) / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.60 (d, $J = 5.6$ Hz, 1H), 6.94 (dd, $J = 4.8, 3.5$ Hz, 1H), 6.19 (d, $J = 5.6$ Hz, 1H), 5.07 (t, $J = 7.0$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.63 (s, 3H), 3.35 – 3.28 (m, 1H), 2.87 – 2.80 (m, 1H), 2.77 (d, $J = 2.7$ Hz, 1H), 2.60 (d, $J = 9.0$ Hz, 1H), 2.57 (td, $J = 5.3, 1.7$ Hz, 1H), 2.50 (dd, $J = 7.2, 3.3$ Hz, 2H), 2.29 (d, $J = 14.9$ Hz, 1H), 1.82 (ddd, $J = 14.9, 6.6, 2.7$ Hz, 1H), 1.74 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.1, 171.1, 168.7, 159.5, 143.9, 135.9, 132.0, 120.9, 116.4, 93.1, 81.5, 80.3, 54.5, 51.9, 48.6, 47.7, 44.8, 41.1, 39.0, 26.9, 19.9.

HRMS-ESI (m/z) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: 411.1420 $[\text{M}+\text{Na}]^+$, found 411.1392 $[\text{M}+\text{Na}]^+$.

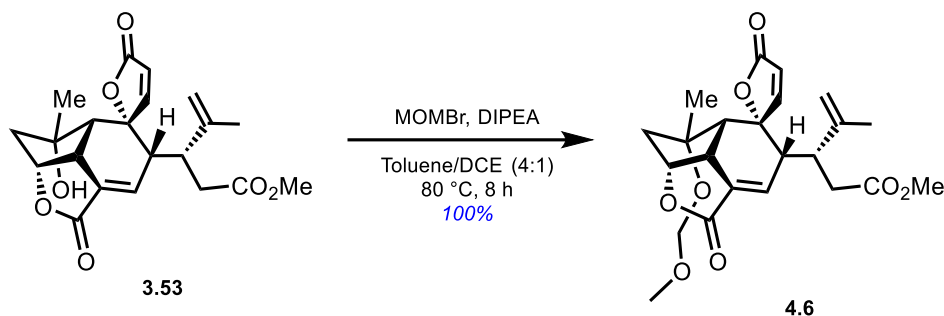
FTIR-ATR (neat) ν [cm^{-1}] 3567, 2971, 2925, 1772, 1747, 1436, 1206.

$[\alpha]_D^{24} +25.6^\circ$ ($c = 0.50$, CHCl_3)

Physical State Light beige solid (after SFC) or colorless needles (after recrystallization)

Melting Point 236 – 238 $^\circ\text{C}$

Methyl (R)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-(methoxymethoxy)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**4.6**).



A 50 mL pressure flask was charged with a stir bar and **3.53** (99.6 mg, 256 μmol , 1.00 eq.). Anhydrous toluene (4 mL) and anhydrous 1,2-DCE (1 mL) were added. The headspace was displaced with Ar(g) for 30 seconds before DIPEA (223 μL , 1.28 mmol, 5.00 eq.) was injected, followed by dropwise addition of MOMBr (technical grade 85%, 104 μL , 1.28 mmol, 5.00 eq.). The pressure flask was then sealed tightly and the mixture was ramped up to 80°C using an oil bath. After 8 h at this temperature, the mixture was cooled to room temperature and quenched with satd. $\text{NaHCO}_3(\text{aq.})$ (20 mL). The resulting suspension was transferred to an extraction funnel and extracted with CH_2Cl_2 (3x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated *in vacuo*. Purification by silica flash chromatography (40 - 60 - 80 - 100% Acetone/Hexanes) afforded title compound **4.6** (111 mg, 100%)

TLC R_f 0.55 (50% Acetone/Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.40 (d, $J = 5.6$ Hz, 1H), 7.06 (t, $J = 4.1$ Hz, 1H), 6.11 (d, $J = 5.6$ Hz, 1H), 4.91 (td, $J = 8.3, 6.8$ Hz, 1H), 4.87 – 4.84 (m, 1H), 4.71 (s, 1H), 4.55 (d, $J = 7.7$ Hz, 1H), 4.46 (d, $J = 7.7$ Hz, 1H), 3.63 (s, 3H), 3.37 (tt, $J = 9.4, 3.3$ Hz, 1H), 3.27 (s, 3H), 2.74 (q, $J = 6.9$ Hz, 1H), 2.56 – 2.54 (m, 1H), 2.53 – 2.50 (m, 1H), 2.49 (dd, $J = 7.2, 3.6$ Hz, 2H), 2.26 (dd, $J = 12.6, 6.6$ Hz, 1H), 2.12 (dd, $J = 12.6, 8.1$ Hz, 1H), 1.71 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 172.1, 168.8, 156.9, 143.3, 137.4, 131.6, 123.1, 116.9, 92.6, 92.1, 84.8, 78.7, 55.9, 53.0, 51.9, 47.1, 43.1, 41.9, 41.4, 38.8, 27.1, 19.9.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_8$: 455.1682 $[\text{M}+\text{Na}]^+$, found 455.1663 $[\text{M}+\text{Na}]^+$.

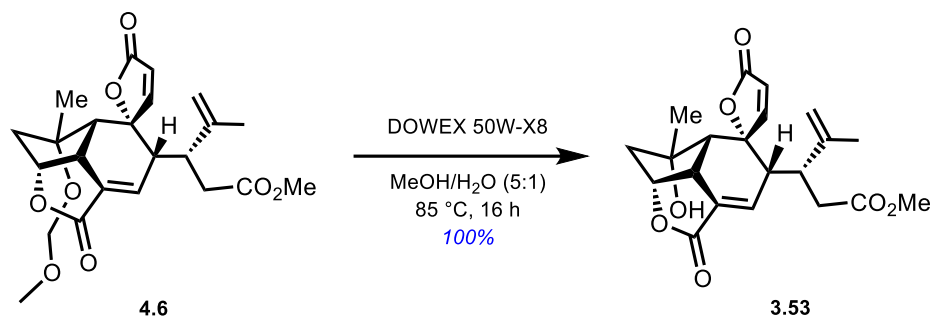
FTIR-ATR (thin film) ν [cm^{-1}] 2938, 2875, 1748, 1736, 1436, 1202, 1017.

$[\alpha]_D^{24}$ -22.0 $^{\circ}$ ($c = 0.40$, CHCl_3)

Physical State White solid

Melting Point 200 – 202 $^{\circ}\text{C}$

Methyl (R)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**3.53**).



To a 8 mL quartz flask containing a magnetic stir bar was added **4.6** (7.5 mg, 17.3 μ mol, 1.00 eq.) and previously treated DOWEX® 50WX8 resin (7.5 mg). A 5:1 MeOH:H₂O mixture (0.8 mL) was added and the flask was sealed tightly and heated to 85 °C for 16 h using an oil bath. After cooling down to room temperature, the crude mixture was passed through a Celite™ pad and washed with methanol (*ca.* 5 mL). The filtrate was concentrated *in vacuo* and water was removed azeotropically by coevaporation with toluene (5 x 5 mL) to give title compound **3.53** (6.7 mg, 100%) in very high purity (>99%, NMR) and required no further purification.

Pretreatment of resin : Purchased commercial resin (Dowex® 50WX8 hydrogen form 200-400 mesh) was used after successive washing with : DI H₂O – 2M NaOH – DI H₂O – 2M HCl and DI H₂O on a glass fritted filter until a pH=7 was obtained.

TLC R_f 0.60 (5% MeOH/CH₂Cl₂) [UV (*weak*) / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 5.6 Hz, 1H), 6.94 (dd, *J* = 4.8, 3.5 Hz, 1H), 6.19 (d, *J* = 5.6 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.63 (s, 3H), 3.35 – 3.28 (m, 1H), 2.87 – 2.80 (m, 1H), 2.77 (d, *J* = 2.7 Hz, 1H), 2.60 (d, *J* = 9.0 Hz, 1H), 2.57 (td, *J* = 5.3, 1.7 Hz, 1H), 2.50 (dd, *J* = 7.2, 3.3 Hz, 2H), 2.29 (d, *J* = 14.9 Hz, 1H), 1.82 (ddd, *J* = 14.9, 6.6, 2.7 Hz, 1H), 1.74 (s, 3H), 1.16 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.1, 171.1, 168.7, 159.5, 143.9, 135.9, 132.0, 120.9, 116.4, 93.1, 81.5, 80.3, 54.5, 51.9, 48.6, 47.7, 44.8, 41.1, 39.0, 26.9, 19.9.

HRMS-ESI (*m/z*) calcd. for C₂₁H₂₄O₇ : 411.1420 [M+Na]⁺, found 411.1392 [M+Na]⁺.

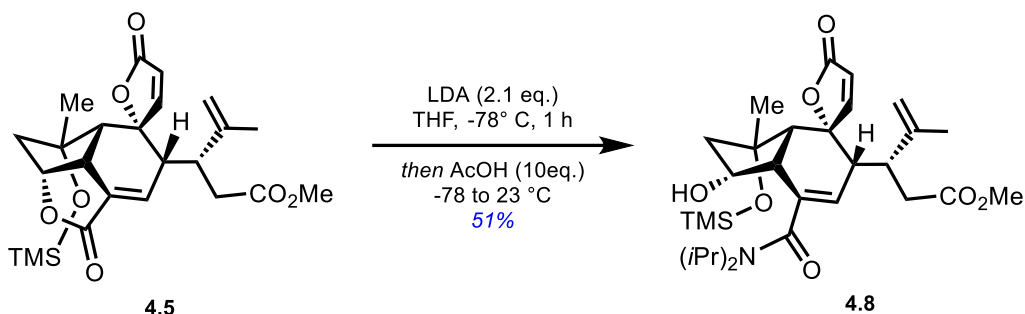
FTIR-ATR (neat) ν [cm⁻¹] 3567, 2971, 2925, 1772, 1747, 1436, 1206.

$[\alpha]_D^{24}$ +25.6 ° (*c* = 0.50, CHCl₃)

Physical State Light beige solid (after SFC) or colorless needles (after recrystallization)

Melting Point 236 – 238 °C

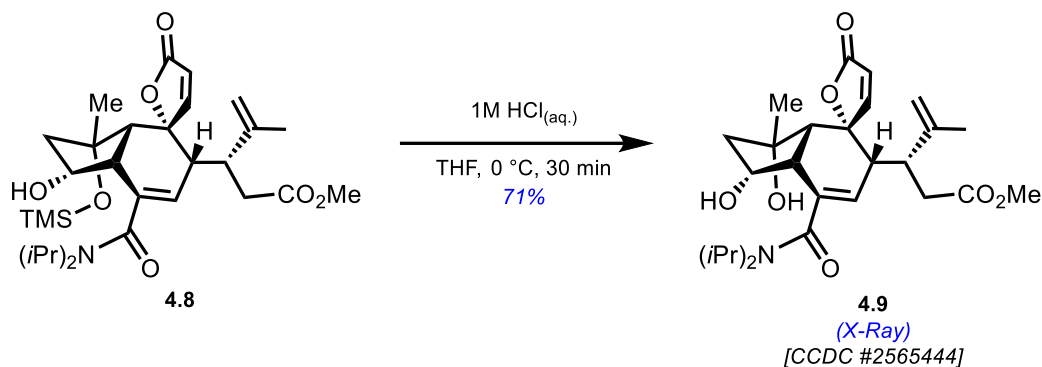
Methyl (R)-3-((1'R,2R,3'S,3a'S,5'S,7a'R)-7'-(diisopropylcarbamoyl)-1'-hydroxy-3'-methyl-5-oxo-3'-((trimethylsilyl)oxy)-1',2',3',3a',5',7a'-hexahydro-5H-spiro[furan-2,4'-inden]-5'-yl)-4-methylpent-4-enoate (**4.8**).



A 50 mL round bottom flask was charged with a stir bar and **4.5** (98.8 mg, 215 μmol , 1.00 eq.). The flask was cycled between Vacuum and $\text{Ar}_{(\text{g})}$ (3x 5min / each) before anhydrous THF (9.0 mL) was added. This solution was cooled to -78°C . before LDA (0.65M in THF, 693 μL , 450 μmol , 2.10 eq.) was added dropwise over 10 minutes (*NOTE: A faint yellow color is observed after addition*). The mixture was Stirred 50 more minutes at this temperature before AcOH (1M in THF, 2.14 mL, 2.14 mmol, 10.0 eq.) was injected dropwise over 5 minutes. This mixture was then stirred 5 min at -78°C before the cold bath was removed and the flask was allowed to warm to room temperature. Satd. $\text{NaHCO}_{3(\text{aq.})}$ (15 mL) was added and stirred vigorously 5 minutes and the mixture was transferred to an extraction funnel. The organic phase was collected and the aqueous phase extracted with EtOAc (3x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. A short silica plug using 100% EtOAc to elute afforded crude title compound **4.8** (61.5 mg, 51%) as a white solid. This amide was used directly in the next reaction without further purification.

Preparation of LDA solution : A 5 mL round bottom flask containing a stir bar was flame-dried and cycled 3 times between vacuum and $\text{Ar}_{(\text{g})}$. Anhydrous THF (5.0 mL) and freshly distilled diisopropylamine (0.77 mL) were then added. This solution was cooled to -78°C before nBuLi (2.5M in hexanes, 2.0 mL) was added dropwise over 5 minutes. This was stirred 5 minutes at this temperature before warming to room temperature. This protocol generated a 0.65 M solution of LDA in THF.

Methyl (R)-3-((1'R,2R,3'S,3a'R,5'S,7a'R)-7'-(diisopropylcarbamoyl)-1',3'-dihydroxy-3'-methyl-5-oxo-1',2',3',3a',5',7a'-hexahydro-5H-spiro[furan-2,4'-inden]-5'-yl)-4-methylpent-4-enoate (**4.9**).



A 8 mL vial containing a stir bar was charged with **4.8** (20.4 mg, 36.3 μmol , 1.00 eq.) and THF (1.5 mL). This mixture was cooled to 0 $^{\circ}\text{C}$ before 1M $\text{HCl}_{(\text{aq.})}$ (150 μL , 150 μmol , 4.13 eq.) was added slowly. After 30 min at this temperature, a TLC analysis showed the full consumption of the starting material. Then, satd. $\text{NaHCO}_{3(\text{aq.})}$ (2 mL) was added and the mixture was warmed up to room temperature over 10 minutes. The organic layer was collected and the aqueous layer was extracted with EtOAc (4 x 2 mL), the organic layers were combined, washed with brine (5 mL), dried by Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (100% EtOAc, 20 cm x 20 cm aluminium backed TLC plate, two elutions) afforded title compound **4.9** (12.7 mg, 71%). A slow evaporation of a solution of **4.9** in a 1:1 mixture of $\text{CH}_2\text{Cl}_2/\text{C}_6\text{H}_6$ afforded crystals suitable for SCXRD analysis and gave a crystal structure as a co-crystal with C_6H_6 . The crystal structure was uploaded to the CCDC with the deposition number #2565444.

NOTE : **4.9** was not soluble in C_6D_6 and hardly soluble in CDCl_3 and thus, signals in NMR appear broadened.

TLC R_f 0.35 (3% MeOH/ CH_2Cl_2) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.34 – 7.28 (m, 1H), 6.05 (d, J = 5.5 Hz, 1H), 5.68 (s, 1H), 4.69 (s, 1H), 4.55 (s, 1H), 4.20 (s, 1H), 3.54 (s, 3H), 3.35 (s, 1H), 2.70 (s, 1H), 2.53 (s, 1H), 2.46 – 2.29 (m, 3H), 1.83 (d, J = 13.2 Hz, 1H), 1.60 (s, 3H), 1.36 (br s, 5H), 1.22 (s, 3H), 1.16 (br s, 3H), 1.08 (br s, 6H), 1.01 (br s, 2H), 0.89 – 0.77 (m, 1H).

^{13}C NMR ^{13}C NMR (151 MHz, CDCl_3) δ 172.8, 172.4, 143.9, 128.1, 127.9, 127.8, 115.8, 88.6, 81.6, 74.0, 59.7, 53.6, 51.9, 51.1, 46.2, 44.7, 42.7, 38.4, 38.3, 31.4, 29.9, 22.8, 21.6, 20.8, 20.5, 20.1, 14.3.

HRMS-ESI (m/z) calcd. for $\text{C}_{27}\text{H}_{39}\text{NO}_7$: 490.2805 $[\text{M}+\text{H}]^+$, found 490.2815 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3498, 3311, 2955, 2926, 2895, 1769, 1749, 1734, 1594, 1446.

$[\alpha]_D^{24} +1.5^{\circ}$ (c = 0.40, CHCl_3)

Physical State Colorless needles

Melting Point 97 – 99 $^{\circ}\text{C}$

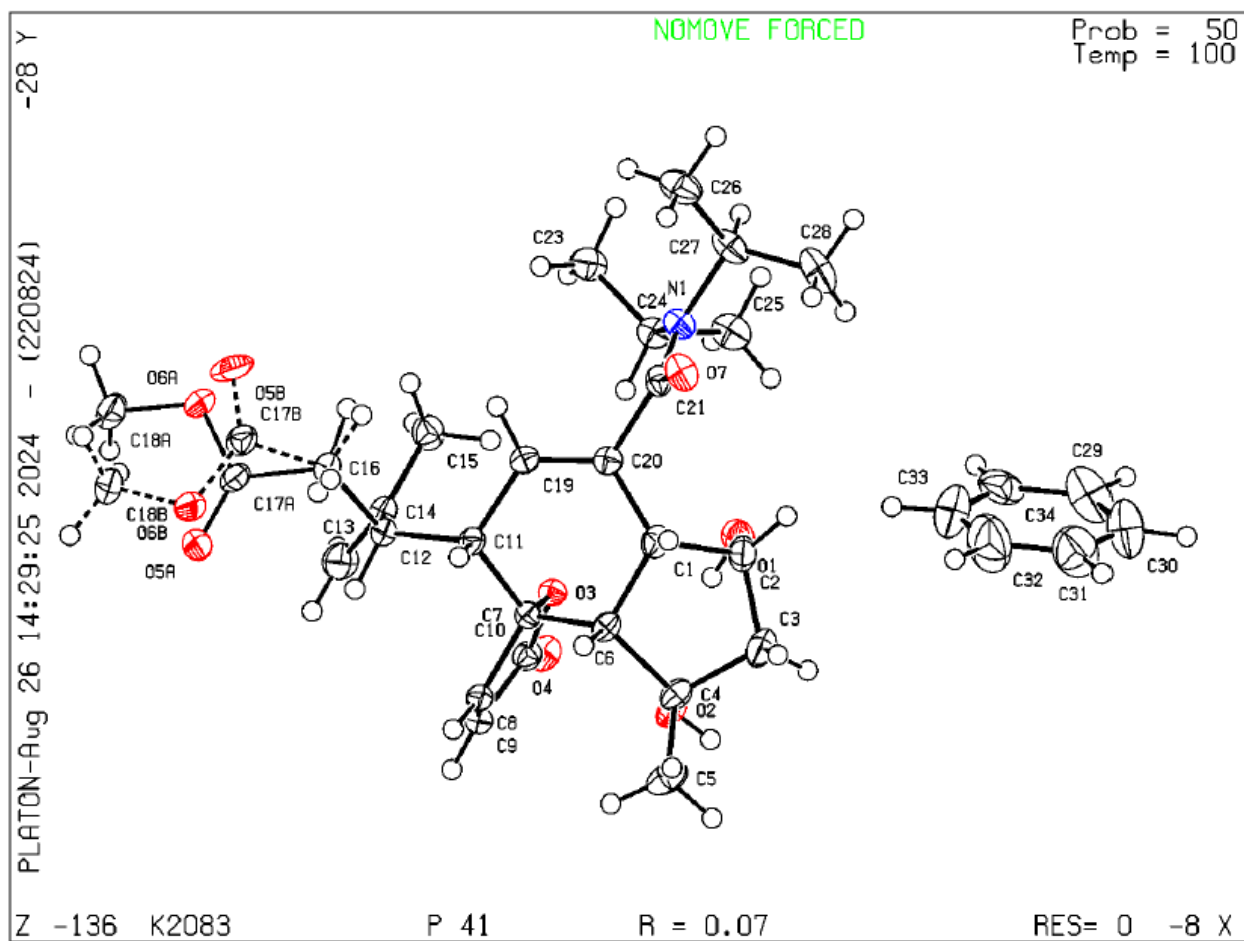
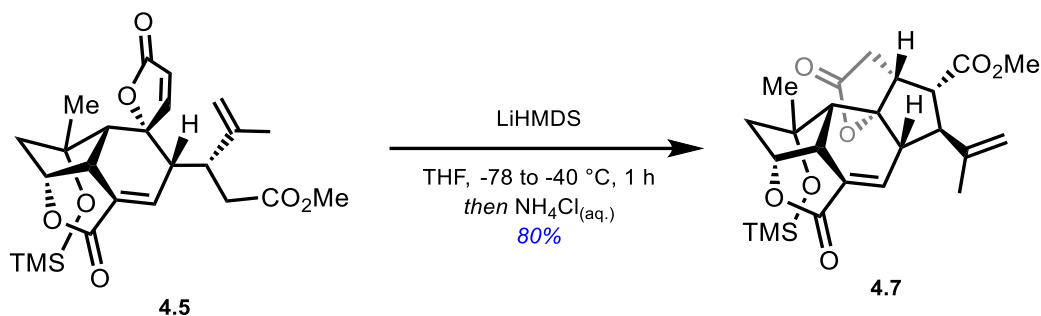


Figure 5.14. Checkcif file of 4.9.

Methyl (4R,5S,8aR,10R,10bR)-10-methyl-2,7-dioxo-5-(prop-1-en-2-yl)-10-((trimethylsilyl)oxy)-3,3a,4,5,5a,6a1,8a,9,10,10a-decahydro-2H,7H-as-indaceno[8b,1-b:6,5-b'c']difuran-4-carboxylate (**4.7**).



A 2 mL vial containing a magnetic stir bar was charged with **4.5** (4.4 mg, 9.55 μ mol, 1.00 eq.). The flask was then cycled between vacuum/ $\text{Ar}_{(\text{g})}$ (3 cycles) before THF (0.5 mL) was added. This solution was cooled to -78°C before LiHMDS (1M in THF, 24 μ L, 23.9 μ mol, 2.50 eq.) was added dropwise over 5 minutes. The mixture was warmed to 40°C and kept at this temperature for 1 h, at which point, satd. $\text{NH}_4\text{Cl}_{(\text{aq.})}$ (0.2 mL) was added and the resulting suspension was warmed back to room temperature. Brine (1 mL) was added, the organic layer collected and the aqueous phase extracted with EtOAc (3 x 1 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (75% EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded title compound **4.7** (3.5 mg, 80%).

TLC R_f 0.80 (75% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 6.87 (t, $J = 3.9$ Hz, 1H), 4.79 – 4.75 (m, 1H), 4.68 (s, 1H), 4.16 (td, $J = 9.4, 6.7$ Hz, 1H), 3.22 (s, 3H), 2.85 (dd, $J = 18.2, 10.5$ Hz, 1H), 2.82 – 2.75 (m, 2H – *Overlap*), 2.58 (ddd, $J = 10.7, 8.6, 2.1$ Hz, 1H), 2.48 (tt, $J = 9.6, 3.3$ Hz, 1H), 2.35 (dd, $J = 18.2, 2.2$ Hz, 1H), 2.12 – 2.07 (m, 1H), 1.67 (dd, $J = 11.4, 7.1$ Hz, 1H), 1.65 – 1.61 (m, 1H), 1.50 (d, $J = 10.0$ Hz, 1H), 1.44 (s, 3H), 0.79 (s, 3H), 0.06 (s, 9H).

^{13}C NMR (151 MHz, C_6D_6) δ 174.5, 171.1, 167.8, 141.4, 136.5, 133.3, 114.4, 95.2, 81.6, 77.2, 57.8, 54.1, 53.4, 51.4, 45.7, 43.6, 42.9, 32.9, 31.7, 30.2, 19.9, 2.5

HRMS-ESI (m/z) calcd. for $\text{C}_{24}\text{H}_{32}\text{O}_7\text{Si}$: 483.1815 $[\text{M}+\text{Na}]^+$, found 483.1849 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2953, 2923, 2852, 2362, 1776, 1749, 1739, 1215.

$[\alpha]_D^{24}$ -8.8° ($c = 0.25$, CHCl_3)

Physical State White solid

Melting Point $> 260^\circ\text{C}$ (*Decomp.*)

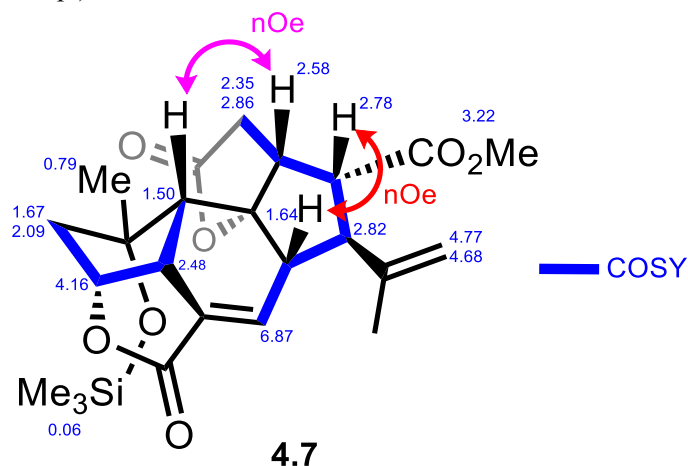
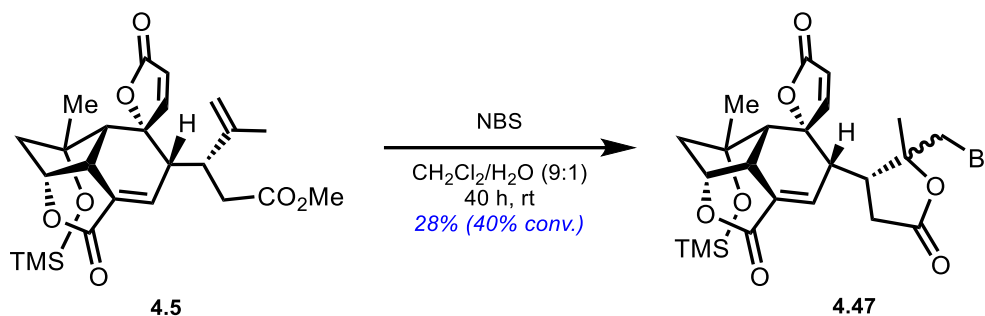


Figure 5.15. ^1H NMR assignment, COSY and selected NOESY correlations for **4.7**.

(2R,2a'R,2a1'R,4'S,4a'S,6'S)-6'-((R)-2-(bromomethyl)-2-methyl-5-oxotetrahydrofuran-3-yl)-4'-methyl-4'-((trimethylsilyl)oxy)-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-1',5-dione (**4.47**).



A 4 mL vial containing a magnetic stir bar was charged with **4.5** (5.9 mg, 12.8 μ mol, 1.00 eq.), followed by the addition of CH_2Cl_2 (450 μ L) and H_2O (50 μ L). The reaction mixture was stirred vigorously for 5 minutes before freshly recrystallized *N*-bromosuccinimide (4.6 mg, 25.6 μ mol, 2.00 eq.) was added. After stirring 16 h at room temperature, TLC analysis revealed that the starting material wasn't fully consumed. Then, CH_2Cl_2 (300 μ L), H_2O (50 μ L) and *N*-bromosuccinimide (4.6 mg, 25.6 μ mol, 2.00 eq.) were added and stirred at room temperature for another 24 h at room temperature. At that point, half satd. $\text{Na}_2\text{S}_2\text{O}_3(\text{aq.})$ (2 mL) was added and stirred 10 minutes, before the vial was extracted with EtOAc (3 x 2 mL). Combined organic layers were dried by Na_2SO_4 and concentrated *in vacuo*. A ^1H NMR analysis of the crude reaction mixture showed 40% conversion. Purification by preparative TLC (90% EtOAc:Hexanes, 20 cm x 20 cm aluminium backed TLC plate) afforded title compound **4.47** (1.9 mg, 28%)

NOTE : This reaction was shielded from light at all times by wrapping the reaction vial with $\text{Al}(\text{s})$ paper.

TLC R_f 0.25 (90% EtOAc/Hexanes) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.38 (d, $J = 5.5$ Hz, 1H), 6.64 (t, $J = 4.0$ Hz, 1H), 6.16 (d, $J = 5.5$ Hz, 1H), 4.95 (dt, $J = 8.3, 6.7$ Hz, 1H), 3.84 (d, $J = 12.2$ Hz, 1H), 3.63 (d, $J = 12.3$ Hz, 1H), 3.41 (tt, $J = 8.9, 3.1$ Hz, 1H), 2.98 – 2.90 (m, 1H), 2.78 – 2.63 (m, 1H), 2.49 (d, $J = 9.4$ Hz, 1H), 2.41 (ddd, $J = 10.9, 4.6, 2.3$ Hz, 1H), 2.24 (dd, $J = 17.3, 11.4$ Hz, 1H), 2.15 – 2.02 (m, 2H), 1.44 (s, 3H), 1.29 (s, 3H), 0.08 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.2, 171.7, 168.4, 158.9, 134.8, 134.2, 122.5, 92.6, 85.9, 82.5, 78.9, 53.7, 49.4, 46.4, 42.7, 40.2, 38.4, 37.6, 30.4, 21.3, 2.1.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{29}\text{BrO}_7\text{Si}$: 547.0764 $[\text{M}+\text{Na}]^+$, found 547.0747 $[\text{M}+\text{Na}]^+$.

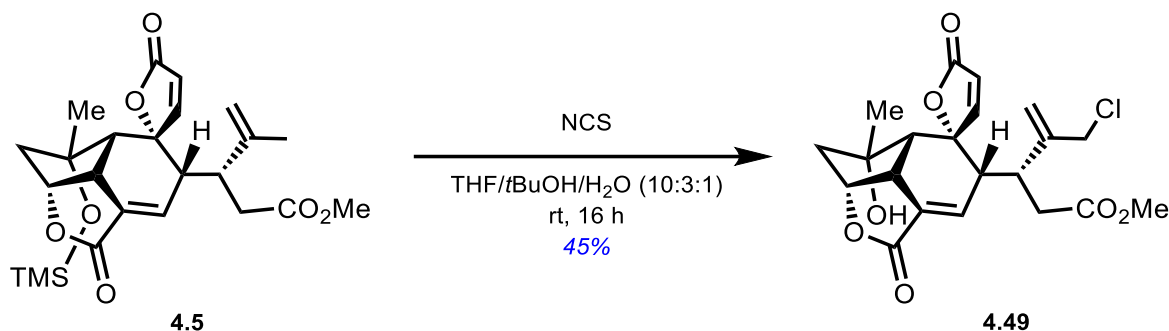
FTIR-ATR (thin film) ν [cm^{-1}] 2961, 2926, 2853, 2362, 1750, 1733, 1250, 1196, 1017.

$[\alpha]_D^{24}$ -24.6 $^\circ$ ($c = 0.50$, CHCl_3)

Physical State White solid

Melting Point 154 – 156 $^\circ\text{C}$

Methyl (R)-4-(chloromethyl)-3-((2R,2a'R,2a1'R,4'S,4a'R,6'S)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)pent-4-enoate (**4.49**).



A 4 mL vial containing a magnetic stir bar was charged with **4.5** (6.6 mg, 14.3 μmol , 1.00 eq.), THF (500 μL), *t*BuOH (150 μL) and H₂O (50 μL). The reaction mixture was stirred vigorously for 5 minutes before *N*-chlorosuccinimide (3.8 mg, 28.7 μmol , 2.00 eq.) was added. After stirring 16 h at room temperature, TLC analysis showed full consumption of the starting material. At that point, satd. Na₂S₂O_{3(aq.)} (1 mL) and brine (1 mL) were added and stirred 10 minutes, before the vial was extracted with EtOAc (4 x 2 mL). Combined organic layers were dried by Na₂SO₄ and concentrated *in vacuo*. Purification by preparative TLC (100% EtOAc, 20 cm x 20 cm aluminium backed TLC plate) afforded title compound **4.49** (2.7 mg, 45%)

NOTE : This reaction was shielded from light at all times by wrapping the reaction vial with Al_(s) paper.

TLC R_f 0.20 (100% EtOAc) [UV / KMnO₄]

¹H NMR (600 MHz, CDCl₃) δ 7.68 (d, *J* = 5.5 Hz, 1H), 6.97 (dd, *J* = 5.3, 2.3 Hz, 1H), 6.22 (d, *J* = 5.4 Hz, 1H), 5.38 (s, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.06 (s, 1H), 4.11 (dd, *J* = 11.9, 7.2 Hz, 2H), 3.66 (s, 3H), 3.37 – 3.30 (m, 1H), 2.99 (q, *J* = 6.7 Hz, 1H), 2.79 – 2.74 (m, 1H), 2.69 (d, *J* = 7.3 Hz, 2H), 2.64 (br s, OH), 2.60 (d, *J* = 8.8 Hz, 1H), 2.30 (d, *J* = 14.9 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.17 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.3, 171.1, 168.5, 160.5, 144.3, 136.3, 131.5, 120.9, 120.6, 93.0, 81.6, 80.2, 54.3, 52.1, 48.7, 47.7, 47.4, 44.9, 39.8, 37.5, 26.9.

HRMS-ESI (*m/z*) calcd. for C₂₁H₂₃O₇Cl : 423.1211 [M+H]⁺, found 423.1212 [M+H]⁺.

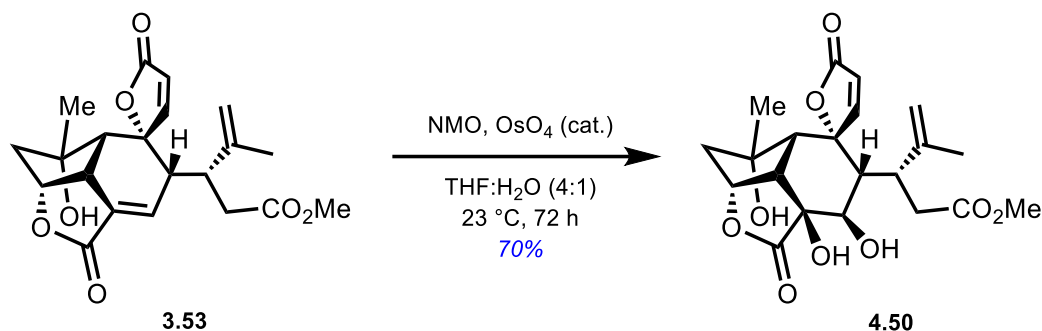
FTIR-ATR (thin film) ν [cm⁻¹] 3565, 2953, 2924, 2855, 1750, 1736, 1213, 1176.

[α]_D²⁴ -14.0 ° (c = 0.05, CHCl₃)

Physical State White solid

Melting Point 188 – 190 °C

Methyl (R)-4-methyl-3-((2R,2a'R,2a1'S,4'S,4a'R,6'R,7'R,7a'S)-4',7',7a'-trihydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6',7',7a'-octahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)pent-4-enoate (**4.50**).



A 4 mL vial containing a magnetic stir bar was charged with **3.53** (5.0 mg, 12.6 μmol , 1.00 eq.) and a mixture of THF:H₂O (4:1, 0.5 mL). Then, NMO (50% W/W solution in H₂O, 10.6 μL , 45.1 μmol , 3.50 eq.) and OsO₄ (4% W/W solution in water, 10.6 μL , 1.7 μmol , 0.13 eq.) were added sequentially, and the resulting mixture was stoppered and stirred at room temperature. After 72 h, TLC analysis showed full consumption of the starting material. Brine (2 mL) was added and the mixture was extracted with EtOAc (5 x 2 mL). The organic layers were combined, washed with brine (3 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by preparative TLC (5% MeOH:CH₂Cl₂, 20 cm x 20 cm aluminium backed TLC plate) afforded title compound **4.50** (3.8 mg, 70%).

NOTE : Multiple attempts at recrystallization of the diol (slow evaporation from : C₆H₆, EtOAc/MeOH, CH₂Cl₂/Hexanes, EtOAc) failed to generate crystals suitable for SCXRD.

TLC R_f 0.40 (3% MeOH / CH₂Cl₂) [KMnO₄]

¹H NMR (600 MHz, C₆D₆) δ 6.55 (d, *J* = 5.5 Hz, 1H), 5.35 (d, *J* = 5.5 Hz, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.46 – 4.41 (m, 1H), 4.37 (br s, OH), 3.82 (br s, OH), 3.41 (s, 3H), 3.26 (dq, *J* = 10.0, 5.0 Hz, 1H), 2.91 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.84 (br s, OH), 2.81 (dd, *J* = 16.7, 9.6 Hz, 1H), 2.50 (dd, *J* = 10.4, 7.6 Hz, 1H), 2.24 (dd, *J* = 11.8, 3.3 Hz, 1H), 1.89 (d, *J* = 15.0 Hz, 1H), 1.72 (s, 3H), 1.21 (d, *J* = 10.5 Hz, 1H), 0.98 (s, 3H), 0.81 (dd, *J* = 14.9, 6.1 Hz, 1H).

¹³C NMR (151 MHz, C₆D₆) δ 178.8, 173.5, 171.8, 160.8, 145.5, 119.0, 114.1, 90.3, 80.9, 80.8, 75.3, 67.8, 51.2, 50.5, 47.3, 47.1, 42.2, 40.9, 36.6, 26.3, 22.2.

HRMS-ESI (*m/z*) calcd. for C₂₁H₂₆O₉ : 445.1475 [M+Na]⁺, found 445.1502 [M+Na]⁺.

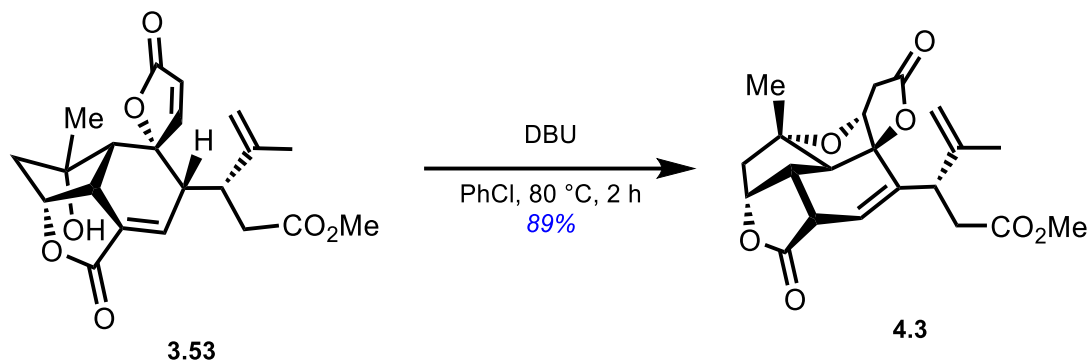
FTIR-ATR (thin film) ν [cm⁻¹] 3481, 2952, 2923, 2853, 1761, 1739, 1459, 1378, 1222.

$[\alpha]_D^{24}$ 11.6 ° (*c* = 0.25, CHCl₃)

Physical State White amorphous solid

Melting Point > 124 °C (*Decomp.*)

Pentacyclic structure **4.3**.



A 4 mL vial was charged with a magnetic stir bar and **3.53** (5.3 mg, 13.6 μmol , 1.00 eq.). Chlorobenzene (0.4 mL) was then added, followed by DBU (8.1 μL , 54.6 μmol , 4.00 eq.) and the resulting mixture was placed in an oil bath and heated to 80 $^\circ\text{C}$. After 1h30 at this temperature, a TLC analysis showed full consumption of the starting material. At this point, the mixture was cooled to room temperature and the chlorobenzene was removed by blowing a gentle stream of compressed air in the vial to yield a dark yellow oil. Purification by silica flash chromatography in a Pasteur pipette (90% EtOAc/Hexanes) afforded pentacycle **4.3** (4.7 mg, 89%) as a white solid.

TLC R_f 0.50 (90% EtOAc/Hexanes) [KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 5.66 (d, J = 8.2 Hz, 1H), 4.93 (s, 1H), 4.68 – 4.66 (m, 1H), 4.14 (d, J = 6.0 Hz, 1H), 3.98 (t, J = 5.6 Hz, 1H), 3.65 (t, J = 7.7 Hz, 1H), 3.34 (s, 3H), 2.85 – 2.80 (m, 1H), 2.47 (dd, J = 15.3, 7.8 Hz, 1H), 2.43 – 2.35 (m, 2H – *Overlap*), 2.31 – 2.21 (m, 3H – *Overlap*), 2.03 (ddd, J = 12.3, 9.5, 6.0 Hz, 1H), 1.43 (s, 3H), 1.12 (s, 3H), 0.98 (dd, J = 15.5, 5.2 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 175.0, 174.6, 171.2, 144.6, 142.2, 121.4, 114.5, 95.6, 95.5, 85.8, 83.8, 59.4, 51.3, 45.3, 43.3, 41.9, 40.9, 39.0, 38.8, 27.1, 20.3.

HRMS-ESI (m/z) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: 411.1420 $[\text{M}+\text{Na}]^+$, found 411.1400 $[\text{M}+\text{Na}]^+$.

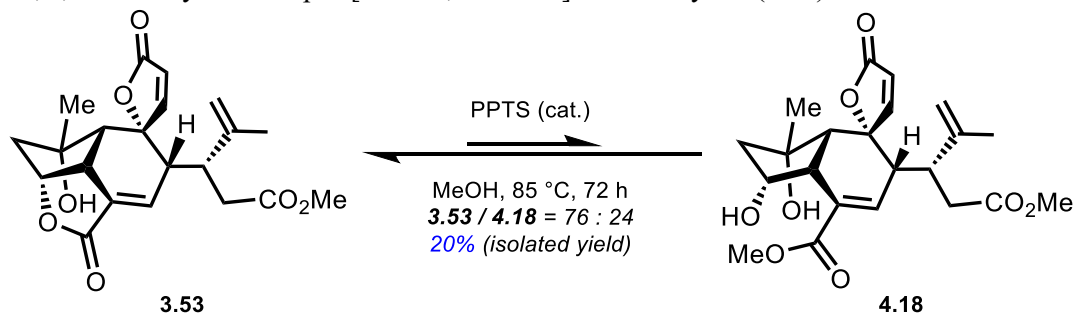
FTIR-ATR (thin film) ν [cm^{-1}] 2953, 2922, 2853, 1784, 1765, 1755, 1457, 1158.

$[\alpha]_D^{24}$ +31.0 $^\circ$ (c = 0.50, CHCl_3)

Physical State White solid

Melting Point > 140 $^\circ\text{C}$ (*Decomp.*)

Methyl (1'R,2R,3'S,3a'R,5'S,7a'R)-1',3'-dihydroxy-5'-((R)-5-methoxy-2-methyl-5-oxopent-1-en-3-yl)-3'-methyl-5-oxo-1',2',3',3a',5',7a'-hexahydro-5H-spiro[furan-2,4'-indene]-7'-carboxylate (**4.18**).



A 8 mL pressure vial containing a magnetic stir bar was charged with **3.53** (5.0 mg, 12.9 μmol , 1.00 eq.) and pyridinium *p*-toluenesulfonate (1.3 mg, 5.1 μmol , 0.40 eq.). Anhydrous MeOH (1.0 mL) was then added and the vial was screwed tightly. This mixture was heated in an oil bath at 85 $^\circ\text{C}$ for 72 h, after which it was cooled to room temperature. Brine (3 mL) was added and the mixture was extracted with EtOAc (5 x 2 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. A ^1H NMR analysis of the crude revealed a 76:24 ratio between **3.53** and **4.18** with no other products detected. Purification by preparative TLC (2% MeOH: CH_2Cl_2 , 20 cm x 20 cm aluminium backed TLC plate) afforded title compound **4.18** (1.1 mg, 20%).

NOTE : **4.18** can also be obtained by using **4.6** as the starting material, where rapid MOM deprotection rapidly occurs followed by equilibration observed in this experiment. Diester **4.18** was reengaged in the same reaction conditions to afford a 75:25 ratio of **3.53** : **4.18**, showing the equilibrium of the two in solution.

TLC R_f 0.20 (2% MeOH/ CH_2Cl_2) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.47 (d, $J = 5.7$ Hz, 1H), 7.10 (t, $J = 2.5$ Hz, 1H), 6.12 (d, $J = 5.7$ Hz, 1H), 4.76 (s, 1H), 4.68 (td, $J = 5.2, 2.1$ Hz, 1H), 4.62 (s, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.14 (ddt, $J = 10.8, 5.6, 3.0$ Hz, 1H), 2.95 (td, $J = 7.3, 4.7$ Hz, 1H), 2.73 (dt, $J = 5.2, 3.1$ Hz, 1H), 2.59 (dd, $J = 15.8, 7.4$ Hz, 1H), 2.52 (dd, $J = 15.8, 7.3$ Hz, 1H), 2.38 (d, $J = 10.5$ Hz, 1H), 1.99 (dd, $J = 14.2, 5.3$ Hz, 1H), 1.89 (dd, $J = 14.2, 2.2$ Hz, 1H), 1.70 (s, 3H), 1.58 (br s, OH), 1.35 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.6, 172.2, 166.8, 156.8, 144.0, 138.8, 130.1, 123.2, 115.8, 88.4, 80.6, 73.3, 52.3, 52.0, 51.9, 50.3, 45.5, 45.3, 42.6, 38.2, 30.5, 20.0.

HRMS-ESI (m/z) calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_8$: 443.1682 $[\text{M}+\text{Na}]^+$, found 443.1697 $[\text{M}+\text{Na}]^+$.

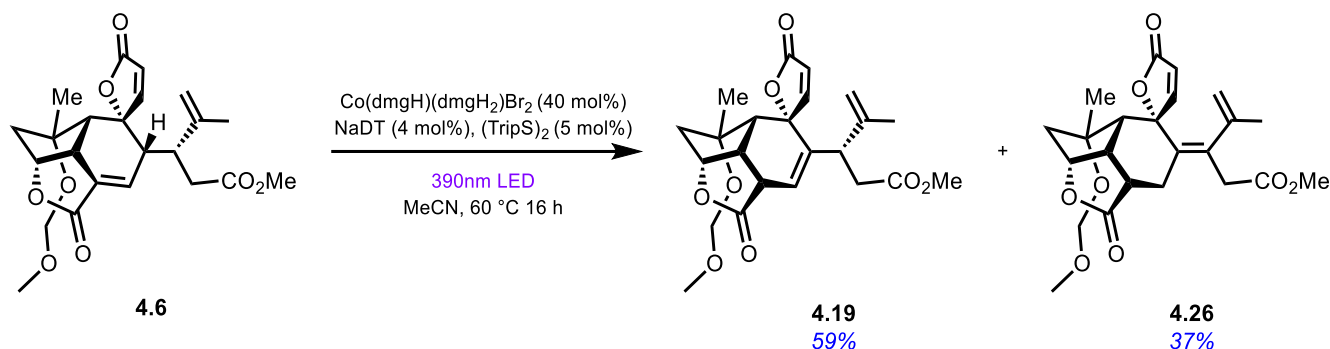
FTIR-ATR (thin film) ν [cm^{-1}] 3487, 2956, 2922, 2854, 1740, 1718, 1436, 1268, 1206.

$[\alpha]_D^{24}$ -1.4 $^\circ$ ($c = 0.50$, CHCl_3)

Physical State White solid

Melting Point > 102 $^\circ\text{C}$ (Decomp.)

Methyl (3S)-3-((2S,2a'R,2a1'R,4'S,4a'R)-4'-(methoxymethoxy)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**4.19**) and Methyl (Z)-3-((2S,2a'R,2a1'R,4'S,4a'R)-4'-(methoxymethoxy)-4'-methyl-1',5-dioxo-2a',3',4',4a',7',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'(2a'H)-ylidene)-4-methylpent-4-enoate (**4.26**).



A 8 mL screw-top Pyrex tube (12 mm diameter) containing a magnetic stir bar was placed in an oven overnight to dry, then cooled to room temperature under $\text{Ar}_{(\text{g})}$. To the reaction tube was added **4.6** (11.4 mg, 26.4 μmol , 1.00 eq.), NaDT (2.8 mg, 1.1 μmol , 0.04 eq.), $\text{Co(dmgh)(dmgh}_2\text{)Br}_2$ (4.7 mg, 1.1 μmol , 0.40 eq.) and $(\text{TripS})_2$ (0.6 mg, 1.3 μmol , 0.05 eq.). Anhydrous MeCN (1.0 mL) was added and the resulting suspension was sparged vigorously by $\text{Ar}_{(\text{g})}$ for 5 minutes. The tube was capped tightly, sealed with electrical tape and then irradiated using a 390 nm blue UV light (Kessil® PR160L-390nm, 2 cm distance) with no fan ventilation (*ca.* 60 °C core temperature) for 16 h. The reaction was then taken out of the reactor and cooled to room temperature, where half satd. brine (2 mL) was added and further stirred 10 min. The resulting suspension was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried by Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (3% MeOH: CH_2Cl_2 , 20 cm x 20 cm aluminium backed TLC plate, three elutions) afforded title compounds **4.19** (6.7 mg, 59%) and **4.26** (4.2 mg, 37%).

For **4.19**

TLC R_f 0.85 (4% MeOH/ CH_2Cl_2) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 6.48 (d, J = 5.4 Hz, 1H), 5.85 (d, J = 4.2 Hz, 1H), 5.68 (d, J = 5.4 Hz, 1H), 5.05 (s, 1H), 4.78 (s, 1H), 4.62 (d, J = 7.8 Hz, 1H), 4.50 (d, J = 7.8 Hz, 1H), 4.19 – 4.13 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 3.01 (t, J = 7.9 Hz, 1H), 2.60 (dd, J = 11.6, 4.1 Hz, 1H), 2.46 – 2.40 (m, 2H), 2.25 (d, J = 15.5 Hz, 1H), 2.23 – 2.17 (m, 1H), 1.64 (s, 3H), 1.28 (s, 3H), 0.91 (d, J = 9.5 Hz, 1H), 0.74 (dd, J = 15.5, 5.9 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 174.3, 171.9, 171.7, 159.2, 144.3, 135.3, 122.1, 119.2, 113.2, 92.3, 88.3, 85.6, 80.4, 56.3, 53.0, 51.0, 43.8, 42.3, 39.3, 39.2, 38.1, 23.6, 20.8.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_8$: 455.1682 $[\text{M}+\text{Na}]^+$, found 455.1684 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2956, 2926, 2855, 1758, 1735, 1182, 1027.

$[\alpha]_D^{24}$ +139 ° (c = 0.25, CHCl_3)

Physical State White solid

Melting Point 137 – 139 °C

For **4.26**

TLC R_f 0.90 (4% MeOH/ CH_2Cl_2) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 6.61 (d, J = 5.7 Hz, 1H), 5.66 (d, J = 5.7 Hz, 1H), 4.68 (s, 1H), 4.50 (s, 1H), 4.35 – 4.31 (m, 1H), 4.30 (d, J = 7.6 Hz, 1H), 4.15 (d, J = 7.6 Hz, 1H), 3.30 (s, 3H), 3.02 (s, 3H), 2.58 (td, J = 7.3, 4.8 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.25 – 2.20 (m, 1H), 2.16 (dd, J = 9.8, 7.4 Hz, 2H), 2.02 (s, 1H), 1.93 (dd, J = 11.3, 6.8 Hz, 1H), 1.82 (dt, J = 10.5, 4.9 Hz, 1H), 1.50 – 1.46 (m, 1H – *Overlap*), 1.49 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 172.2, 171.8, 171.7, 165.7, 155.2, 143.8, 128.6, 123.6, 115.9, 91.5, 88.2, 86.9, 79.0, 55.6, 51.2, 50.5, 44.4, 43.6, 42.5, 37.9, 28.9, 23.1, 21.6.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_8$: 455.1682 $[\text{M}+\text{Na}]^+$, found 455.1699 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm⁻¹] 2954, 2925, 2854, 1751, 1745, 1166, 1025.

$[\alpha]_D^{24}$ -3.0 ° (c = 0.1, CHCl₃)

Physical State White solid

Melting Point 152 – 154 °C

The reactions were conducted in 8 mL oven-dried screw-top Pyrex tube (12 mm diameter) for all the optimization reactions, placed on a stir plate and fixed on a position relative to the light sources (1–2 cm). The 40W Blue LED lamps were purchased from Kessil (Kessil® PR160L-390nm) and two lamps were used. A fan was placed overhead to keep the area cooled to ambient temperature (*ca.* 30 °C) or at higher temperatures (*ca.* 60 °C) when the fans were turned off. This Kessil light set up was used for reaction optimization of the deconjugation of **4.6** and **3.53**.

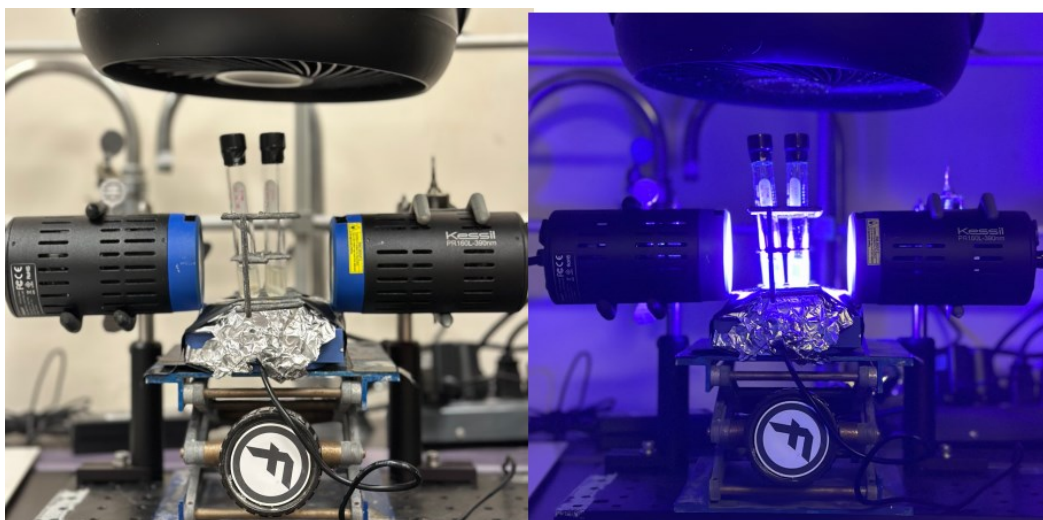
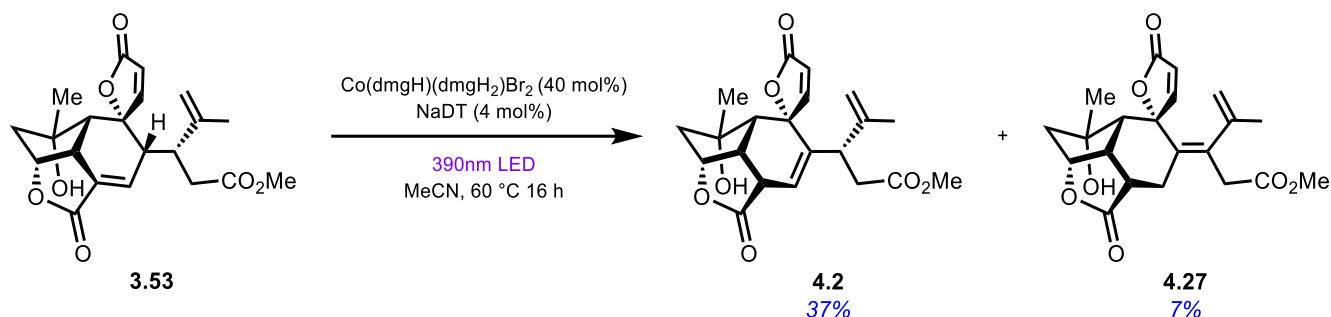


Figure 5.16. Photocatalytic reaction setup for alkene isomerization chemistry.

Methyl (3S)-3-((2S,2a'R,2a1'R,4'S,4a'R)-4'-hydroxy-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**4.2**) and methyl (Z)-3-((2S,2a'R,2a1'R,4'S,4a'R)-4'-hydroxy-4'-methyl-1',5-dioxo-2a1',3',4',4a',7',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'(2a'H)-ylidene)-4-methylpent-4-enoate (**4.27**).



A 8 mL screw-top Pyrex tube (12 mm diameter) containing a magnetic stir bar was placed in an oven overnight to dry, then cooled to room temperature under $\text{Ar}_{(\text{g})}$. To the reaction tube was added **3.53** (10.0 mg, 25.7 μmol , 1.00 eq.), NaDT (2.5 mg, 1.00 μmol , 0.04 eq.) and $\text{Co(dmgh)(dmgh}_2\text{)Br}_2$ (4.6 mg, 10.3 μmol , 0.40 eq.). Anhydrous MeCN (1.0 mL) was added and the resulting suspension was sparged vigorously by $\text{Ar}_{(\text{g})}$ for 5 minutes. The tube was capped tightly, sealed with electrical tape and then irradiated using a 390 nm blue UV light (Kessil® PR160L-390nm, 2 cm distance) with no fan ventilation (*ca.* 60 °C core temperature) for 16 h. The reaction was then taken out of the reactor and cooled to room temperature, where half satd. brine (2 mL) was added and further stirred 10 min. The resulting suspension was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried by Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (3% MeOH: CH_2Cl_2 , 20 cm x 20 cm aluminium backed TLC plate) afforded title compounds **4.2** (3.7 mg, 37%) and **4.27** (0.7 mg, 7%).

NOTE : Multiple attempts are slow crystallization of either **4.2** or **4.27** by slow evaporation from CHCl_3 , EtOAc, C_6H_6 or solvent diffusion failed to yield crystals suitable for SCXRD.

For **4.2**

TLC R_f 0.40 (3% MeOH/ CH_2Cl_2) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 6.46 (d, J = 5.4 Hz, 1H), 5.97 (d, J = 3.9 Hz, 1H), 5.65 (d, J = 5.4 Hz, 1H), 4.96 (s, 1H), 4.71 (s *app. t*, 1H), 4.21 (dd, J = 7.7, 6.2 Hz, 1H), 3.27 (s, 3H), 2.79 (dd, J = 10.9, 5.1 Hz, 1H), 2.66 (ddd, J = 11.9, 3.9, 1.2 Hz, 1H), 2.46 (dd, J = 16.4, 10.9 Hz, 1H), 2.24 – 2.20 (m, 1H – *overlap*), 2.20 (dd, J = 16.4, 5.1 Hz, 1H – *overlap*), 1.89 (d, J = 14.9 Hz, 1H), 1.65 (d, J = 2.2 Hz, 1H), 1.61 (s, 3H), 1.16 (s, 3H), 0.92 (d, J = 9.3 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 174.2, 171.9, 171.6, 158.6, 146.9, 134.1, 123.7, 119.1, 112.9, 88.4, 80.9, 80.6, 51.5, 51.1, 47.8, 42.0, 39.7, 39.2, 37.9, 28.0, 21.8.

HRMS-ESI (m/z) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: 411.1420 $[\text{M}+\text{Na}]^+$, found 411.1446 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 3489, 2954, 2924, 2855, 1761, 1735, 1457, 1378, 1181.

$[\alpha]_D^{24}$ +89.0 ° (c = 0.10, CHCl_3)

Physical State Amorphous white solid

Melting Point 173 – 175 °C

For 4.27

TLC R_f 0.20 (3% MeOH/CH₂Cl₂) [UV / KMnO₄]

¹H NMR ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 5.7 Hz, 1H), 6.18 (d, J = 5.7 Hz, 1H), 4.98 (ddd, J = 9.5, 6.1, 2.1 Hz, 1H), 4.88 (s, 1H), 4.67 (s, 1H), 3.65 (s, 3H), 2.90 – 2.84 (m, 1H), 2.73 – 2.63 (m, 1H), 2.56 – 2.45 (m, 4H), 2.38 – 2.30 (m, 2H), 1.72 (s, 3H), 1.68 (d, J = 10.4 Hz, 1H), 1.45 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 172.5, 172.5, 172.4, 166.8, 156.2, 143.2, 127.9, 124.0, 116.5, 89.2, 83.6, 78.7, 51.9, 49.3, 47.6, 43.9, 42.3, 38.1, 33.2, 22.8, 21.5.

HRMS-ESI (m/z) calcd. for C₂₁H₂₄O₇ : 411.1420 [M+Na]⁺, found 411.1453 [M+Na]⁺.

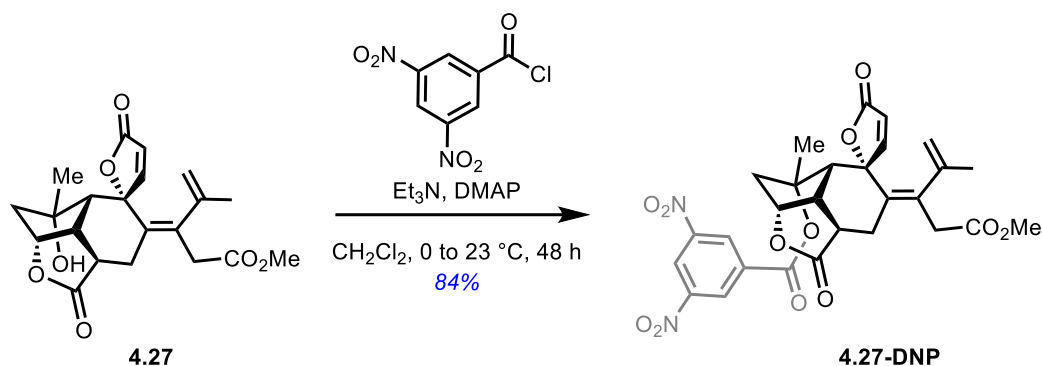
FTIR-ATR (thin film) ν [cm⁻¹] 3484, 2952, 2928, 2855, 1736, 1734, 1210, 1166.

$[\alpha]_D^{24}$ +7.0 ° (c = 0.1, CHCl₃)

Physical State Amorphous white solid

Melting Point 193 – 195 °C

(2S,2a'R,2a1'R,4'S,4a'R,7a'R,Z)-6'-(5-methoxy-2-methyl-5-oxopent-1-en-3-ylidene)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',6',7',7a'-octahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-4'-yl 3,5-dinitrobenzoate (**4.27-DNP**)



A 1 mL reaction flask containing a magnetic stir bar was charged with **4.27** (3.0 mg, 7.7 μ mol, 1.00 eq.) and CH_2Cl_2 (0.5 mL). This solution was cooled to 0 °C before Et_3NE (5.4 μ L, 38.6 μ mol, 5.00 eq.), 3,5-dinitrobenzoyl chloride (3.6 mg, 15.4 μ mol, 2.00 eq.) and DMAP (1.4 mg, 11.6 μ mol, 1.50 eq.) were added. (*NOTE: Solutions turns light red upon DMAP addition*). The ice bath was then removed and the mixture was allowed to stir to room temperature. After 24 h, TLC analysis showed approx. 50% conversion of the starting material. Then, Et_3N (5.4 μ L, 38.6 μ mol, 5.00 eq.), 3,5-dinitrobenzoyl chloride (3.6 mg, 15.4 μ mol, 2.00 eq.) and DMAP (1.4 mg, 11.6 μ mol, 1.50 eq.) were added to the mixture and further stirred 24 h at room temperature. The mixture was then filtered through a short silica plug and flushed with EtOAc (ca. 5 mL) and the filtrate concentrated *in vacuo*. Purification by preparative TLC (100% EtOAc , 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **4.27-DNP** (3.8 mg, 84%).

NOTE: Multiple attempts at recrystallization of 4.27-DNP (slow evaporation from : EtOAc /Hexanes – vapor diffusion from CHCl_3 & Pentanes, CHCl_3 & Cyclopentane, 1:1 Et_2O /Benzene & Pentane) failed to generate crystals suitable for SCXRD.

TLC R_f 0.80 (100% EtOAc) [UV / KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 9.23 (t, J = 2.1 Hz, 1H), 8.90 (d, J = 2.1 Hz, 2H), 7.81 (d, J = 5.6 Hz, 1H), 6.16 (d, J = 5.6 Hz, 1H), 5.16 – 5.10 (m, 1H), 4.86 (s, 1H), 4.64 (s, 1H), 3.67 (s, 3H), 3.40 (s, 1H), 3.24 (dd, J = 11.5, 6.8 Hz, 1H), 2.69 (td, J = 7.3, 4.3 Hz, 1H), 2.58 – 2.52 (m, 2H), 2.49 (dd, J = 9.8, 7.4 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.85 (s, 3H), 1.69 (s, 3H), 0.88 (dd, J = 7.1, 1.5 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.4, 171.7, 171.2, 163.9, 162.1, 157.4, 148.7, 142.8, 133.9, 129.7, 129.5, 123.2, 122.9, 117.0, 91.8, 89.0, 78.8, 52.1, 51.4, 44.4, 43.9, 42.4, 37.8, 28.6, 22.7, 21.6.

HRMS-ESI (m/z) calcd. for $\text{C}_{28}\text{H}_{26}\text{O}_{12}\text{N}_2$: 605.1383 $[\text{M}+\text{Na}]^+$, found 605.1404 $[\text{M}+\text{Na}]^+$.

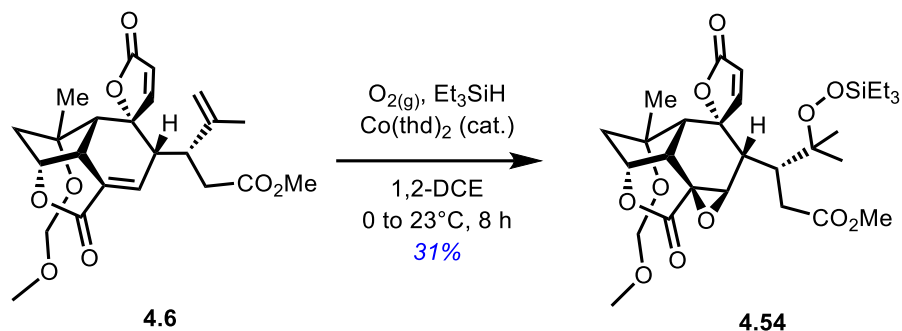
FTIR-ATR (thin film) ν [cm^{-1}] 3103, 2955, 2923, 2854, 1760, 1735, 1545, 1346, 1161.

$[\alpha]_D^{24}$ -29.6 ° (c = 0.25, CHCl_3)

Physical State White solid

Melting Point > 105 °C (*Decomp.*)

Methyl (R)-3-((1a'S,1a1'S,2R,3a'R,5'S,5a'R,7'R,7a'R)-5'-(methoxymethoxy)-5'-methyl-2',5-dioxo-1a1',3a',5',5a',7',7a'-hexahydro-2'H,4'H,5H-spiro[furan-2,6'-oxireno[2',3':6,7]indeno[1,7-bc]furan]-7'-yl)-4-methyl-4-((triethylsilyl)peroxy)pentanoate (**4.54**)



A flame-dried 8 mL UV tube containing a stirbar was charged with **4.6** (5.4 mg, 12.5 μmol , 1.00 eq), $\text{Co}(\text{thd})_2$ (1.6 mg, 3.7 μmol , 0.30 eq.) and 1,2-DCE (1.0 mL). This solution was cooled to 0°C and sparged with $\text{O}_{2(g)}$ for 5 minutes before Et_3SiH (4.8 μL , 30.0 μmol , 2.40 eq.) was injected. The ice bath was removed and the reaction was allowed to warm to room temperature under $\text{O}_{2(g)}$ atmosphere. After 8 h, a TLC analysis showed full consumption of the starting material. The solvent was then removed *in vacuo* and dried under high vacuum. Purification by preparative TLC (100% EtOAc, 20 cm x 20 cm aluminium backed TLC plate) afforded the title compound **4.54** (2.3 mg, 31%).

TLC R_f 0.80 (100% EtOAc) [KMnO_4]

^1H NMR (600 MHz, CDCl_3) δ 7.56 (d, $J = 5.4$ Hz, 1H), 5.98 (d, $J = 5.4$ Hz, 1H), 5.03 (d, $J = 11.5$ Hz, 1H), 4.95 (dd, $J = 7.4, 5.8$ Hz, 1H), 4.74 – 4.67 (m, 2H), 3.65 (s, 3H), 3.49 (s, 3H), 3.48 – 3.44 (m, 1H), 2.54 (t, $J = 11.1$ Hz, 1H), 2.43 (d, $J = 15.3$ Hz, 1H), 2.35 – 2.25 (m, 3H), 2.11 (dd, $J = 17.1, 2.6$ Hz, 1H), 1.56 (dd, $J = 15.3, 5.8$ Hz, 1H Overlap with HDO peak), 1.33 (s, 3H), 1.29 (s, 3H), 1.09 (s, 3H), 0.98 (t, $J = 8.0$ Hz, 9H), 0.71 (qd, $J = 7.8, 5.0$ Hz, 6H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.8, 172.2, 161.6, 119.3, 91.7, 87.8, 86.2, 85.3, 81.0, 80.6, 56.6, 52.2, 51.8, 45.4, 43.7, 40.1, 37.8, 36.8, 24.9, 21.6, 20.1, 6.8, 3.9.

HRMS-ESI Multiple ESI mass spectrometry analyses failed to identify m/z fragment belonging to the product.

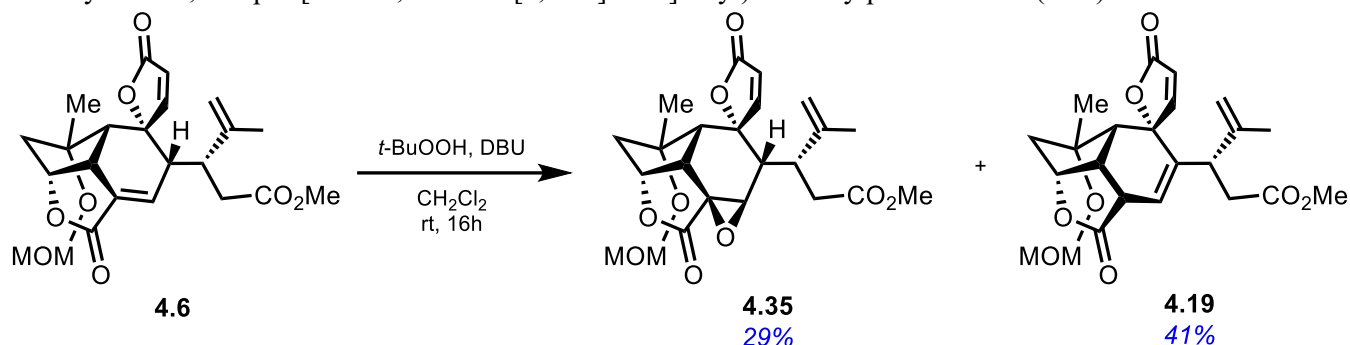
FTIR-ATR (thin film) ν [cm^{-1}] 2953, 2878, 1763, 1739, 1240, 1207, 1022.

$[\alpha]_D^{24} +211^\circ$ ($c = 0.1$, CHCl_3)

Physical State White solid

Melting point $86 - 88^\circ\text{C}$

Methyl (R)-3-((1a'S,1a1'S,2R,3a'R,5'S,5a'R,7'R,7a'R)-5'-(methoxymethoxy)-5'-methyl-2',5-dioxo-1a1',3a',5',5a',7',7a'-hexahydro-2'H,4'H,5H-spiro[furan-2,6'-oxireno[2',3':6,7]indeno[1,7-bc]furan]-7'-yl)-4-methylpent-4-enoate (**4.35**) and methyl (3S)-3-((2S,2a'R,2a1'R,4'S,4a'R)-4'-(methoxymethoxy)-4'-methyl-1',5-dioxo-2a',2a1',3',4',4a',7a'-hexahydro-1'H,5H-spiro[furan-2,5'-indeno[1,7-bc]furan]-6'-yl)-4-methylpent-4-enoate (**4.19**).



A 2 mL vial containing a stir bar was charged with **4.6** (7.0 mg, 16.2 μmol , 1.00 eq.) and CH_2Cl_2 (0.5 mL). Then, *t*-BuOOH (5.5 M in decane, 17.7 μL , 97.1 μmol , 6.00 eq.) and DBU (9.7 μL , 64.7 μmol , 4.00 eq.) added successively. This mixture was stirred at room temperature for 16 h, after which a satd. $\text{FeSO}_4(\text{aq.})$ solution (2 mL) was added and stirred vigorously for 15 minutes. This mixture was extracted with CH_2Cl_2 (4 x 2 mL), the combined organic layers were dried by Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (100% EtOAc, 20 x 20 cm aluminium backed TLC plate) afforded the title compound **4.35** (2.1 mg, 29%) and **4.19** (2.9 mg, 41%).

For 4.35

TLC R_f 0.50 (100% EtOAc) [UV / KMnO_4]

^1H NMR (^1H NMR (600 MHz, CDCl_3) δ 7.41 (d, J = 5.6 Hz, 1H), 6.10 (d, J = 5.6 Hz, 1H), 5.07 (dt, J = 9.2, 7.2 Hz, 1H), 4.94 (s, 1H), 4.81 (s, 1H), 4.62 (d, J = 7.6 Hz, 1H), 4.50 (d, J = 7.6 Hz, 1H), 3.64 (s, 3H – *Overlap*), 3.63 (s, 1H – *Overlap*), 3.30 (s, 3H), 3.17 (t, J = 9.4 Hz, 1H), 2.70 (q, J = 7.4 Hz, 1H), 2.49 (d, J = 6.8 Hz, 2H), 2.41 (dd, J = 13.1, 7.1 Hz, 1H), 2.36 – 2.30 (m, 2H), 1.77 (s, 3H), 1.68 (dd, J = 8.2, 4.5 Hz, 1H), 1.33 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 172.5, 172.3, 171.9, 158.0, 143.1, 121.5, 117.3, 91.9, 90.4, 84.6, 78.6, 59.2, 57.4, 56.2, 53.3, 51.9, 48.1, 43.1, 41.7, 38.9, 37.9, 26.2, 19.7.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_9$: 471.1631 $[\text{M}+\text{Na}]^+$, found 471.1630 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2952, 2924, 2857, 1774, 1751, 1736, 1252, 1146, 1025.

$[\alpha]_D^{24}$ -6.0 $^\circ$ (c = 0.1, CHCl_3)

Physical State White solid

Melting Point 179 – 181 $^\circ\text{C}$

For 4.19

TLC R_f 0.40 (100% EtOAc) [UV / KMnO_4]

^1H NMR (600 MHz, C_6D_6) δ 6.48 (d, J = 5.4 Hz, 1H), 5.85 (d, J = 4.2 Hz, 1H), 5.68 (d, J = 5.4 Hz, 1H), 5.05 (s, 1H), 4.78 (s, 1H), 4.62 (d, J = 7.8 Hz, 1H), 4.50 (d, J = 7.8 Hz, 1H), 4.19 – 4.13 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 3.01 (t, J = 7.9 Hz, 1H), 2.60 (dd, J = 11.6, 4.1 Hz, 1H), 2.46 – 2.40 (m, 2H), 2.25 (d, J = 15.5 Hz, 1H), 2.23 – 2.17 (m, 1H), 1.64 (s, 3H), 1.28 (s, 3H), 0.91 (d, J = 9.5 Hz, 1H), 0.74 (dd, J = 15.5, 5.9 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 174.3, 171.9, 171.7, 159.2, 144.3, 135.3, 122.1, 119.2, 113.2, 92.3, 88.3, 85.6, 80.4, 56.3, 53.0, 51.0, 43.8, 42.3, 39.3, 39.2, 38.1, 23.6, 20.8.

HRMS-ESI (m/z) calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_8$: 455.1682 $[\text{M}+\text{Na}]^+$, found 455.1684 $[\text{M}+\text{Na}]^+$.

FTIR-ATR (thin film) ν [cm^{-1}] 2956, 2926, 2855, 1758, 1735, 1182, 1027.

$[\alpha]_D^{24}$ +139 $^\circ$ (c = 0.25, CHCl_3)

Physical State White solid

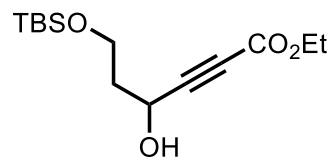
Melting Point 137 – 139 $^\circ\text{C}$

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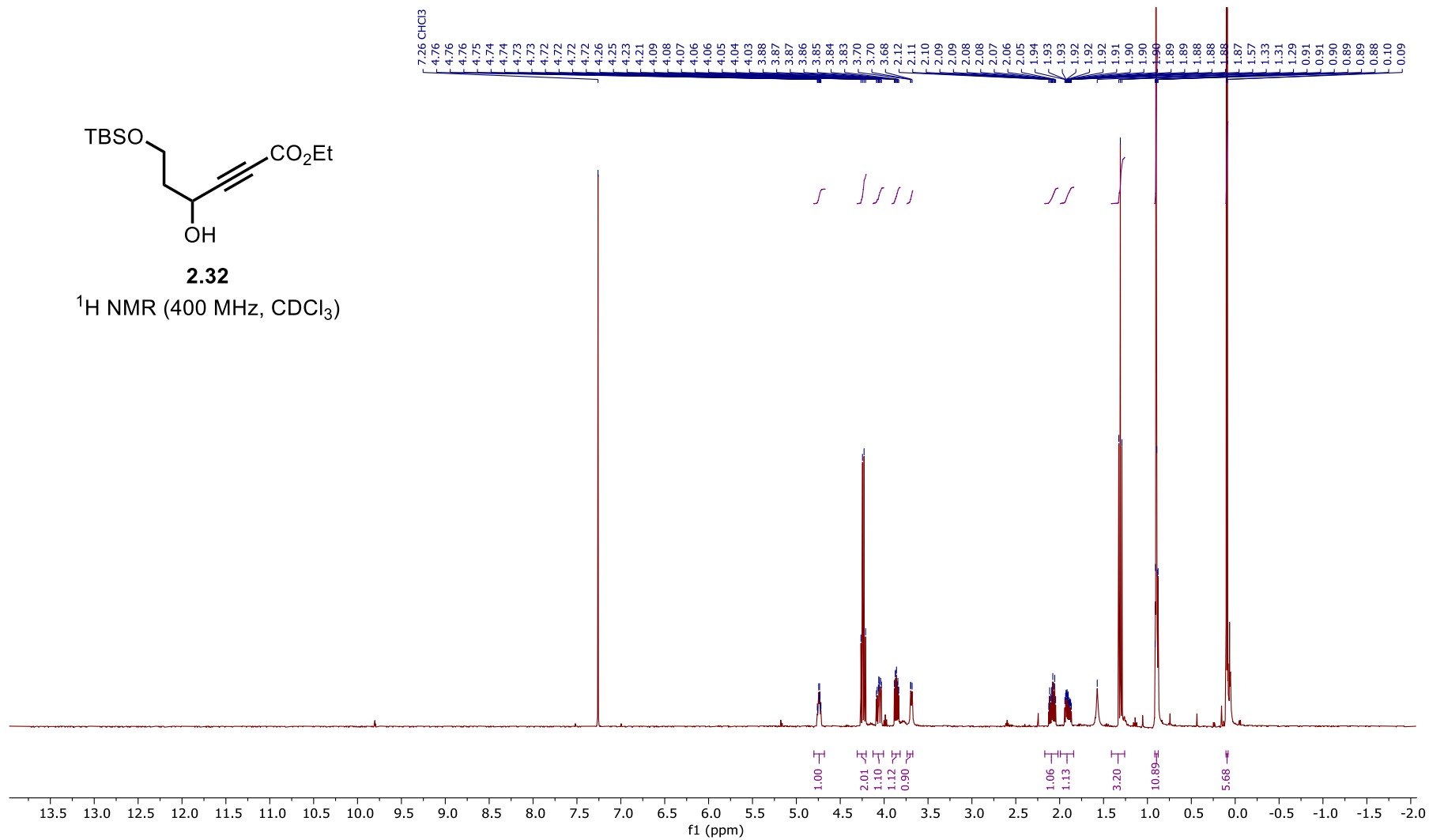
CHAPTER 6

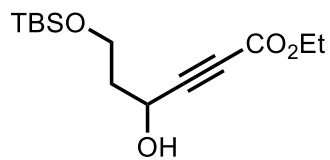
NMR Spectra



2.32

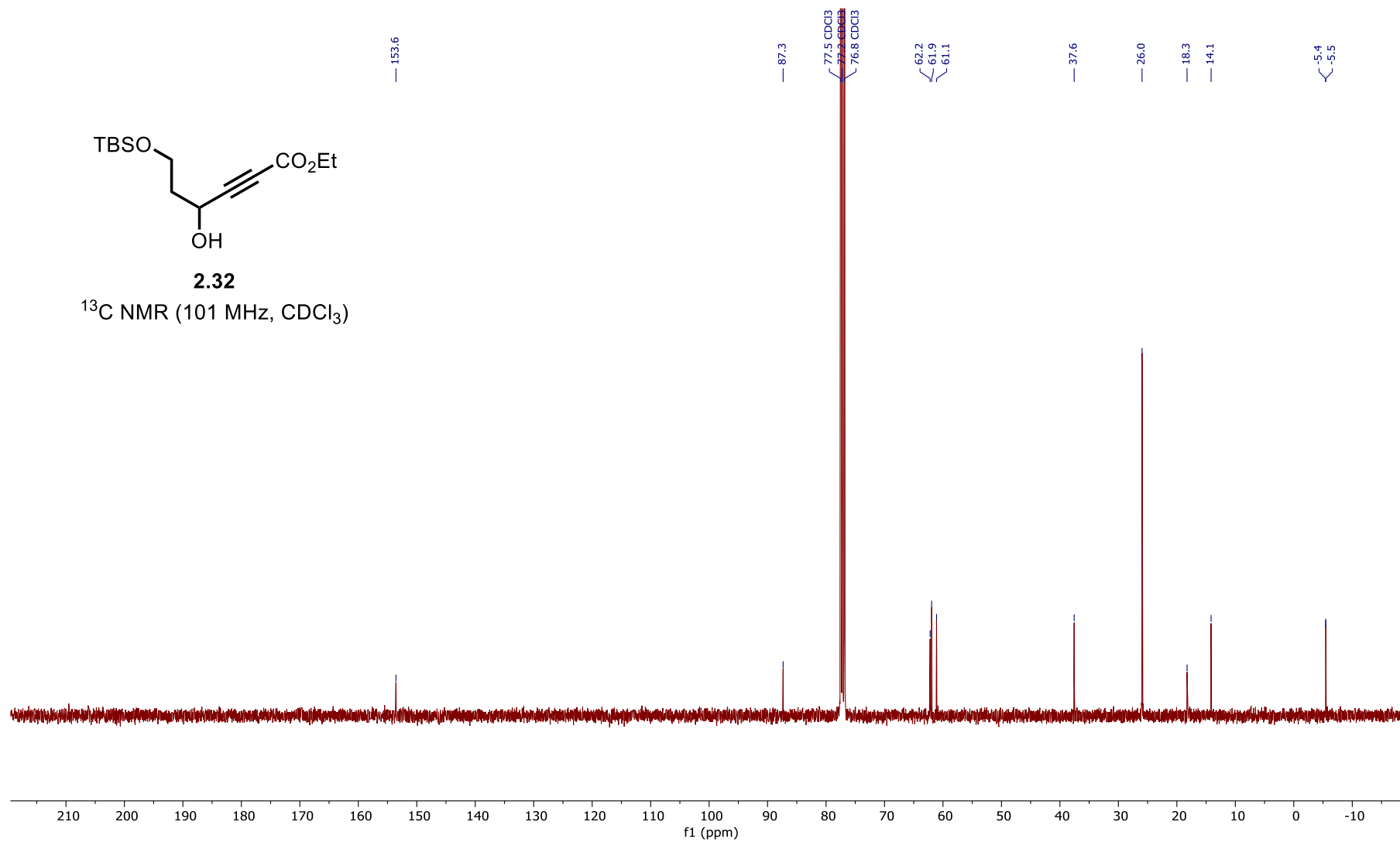
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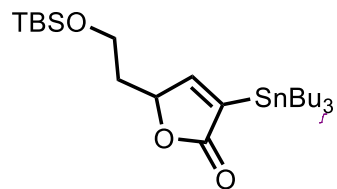




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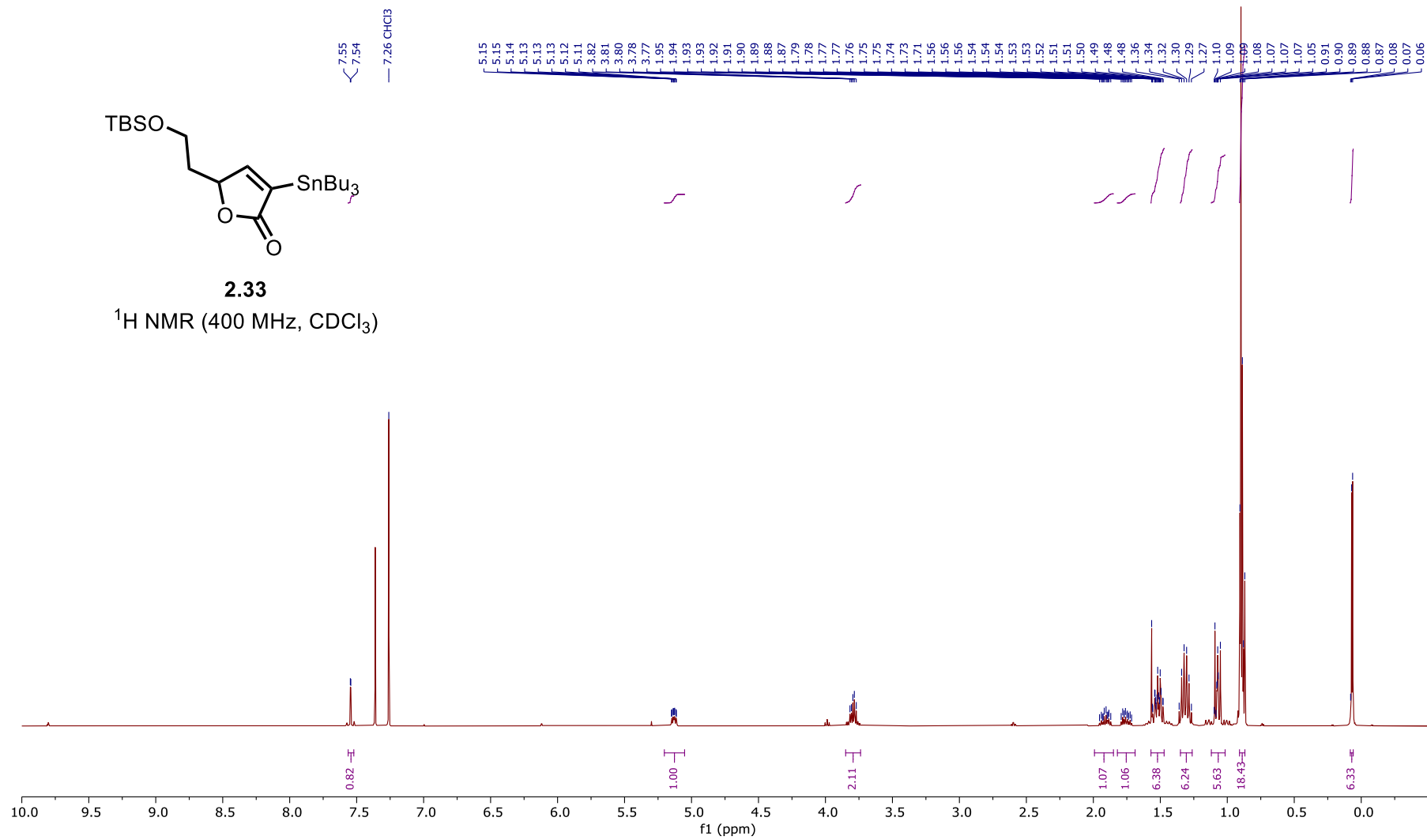
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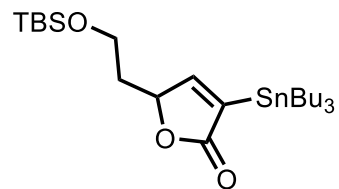




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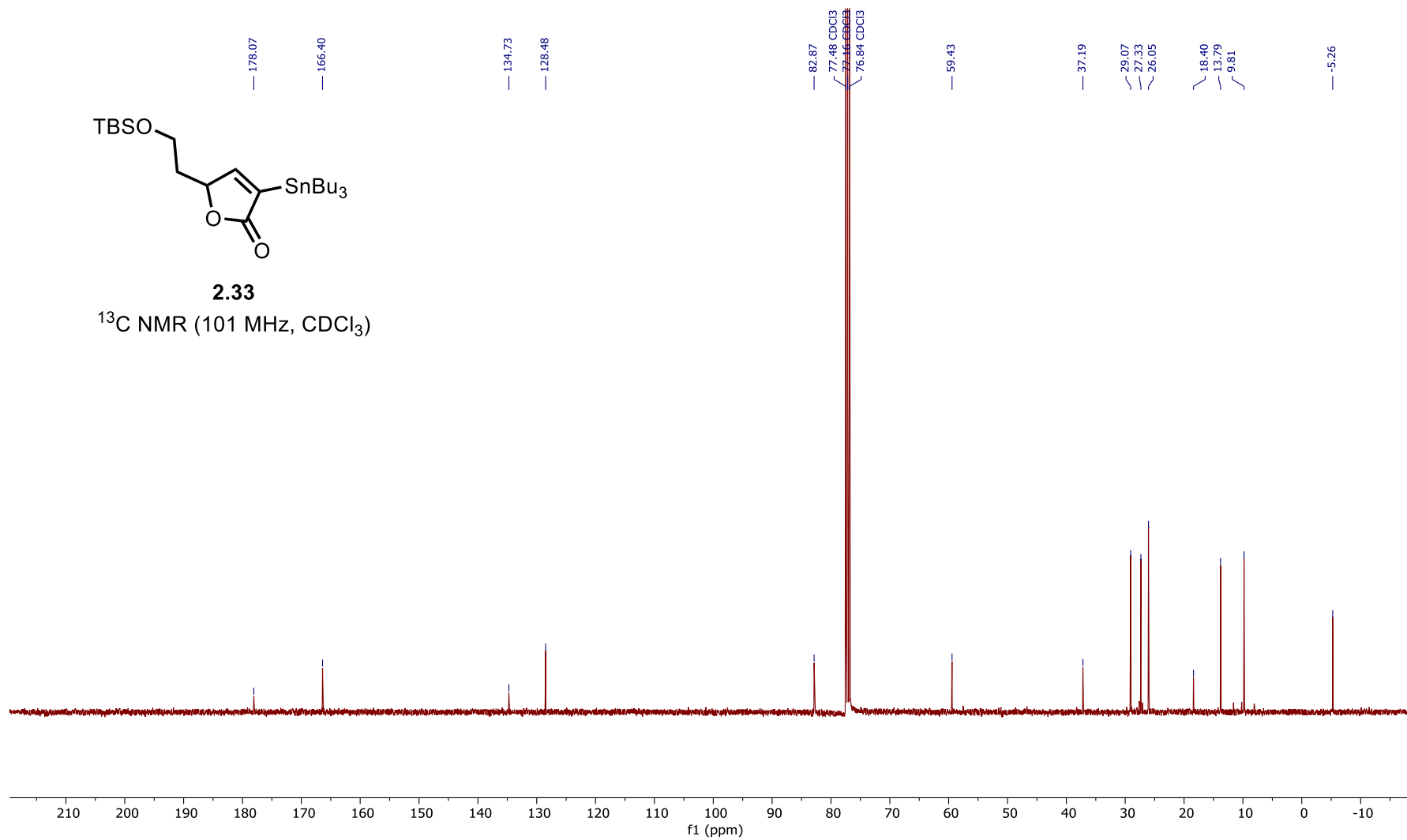
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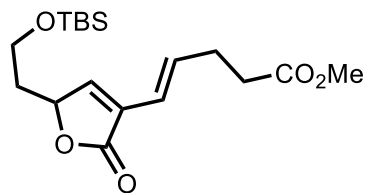




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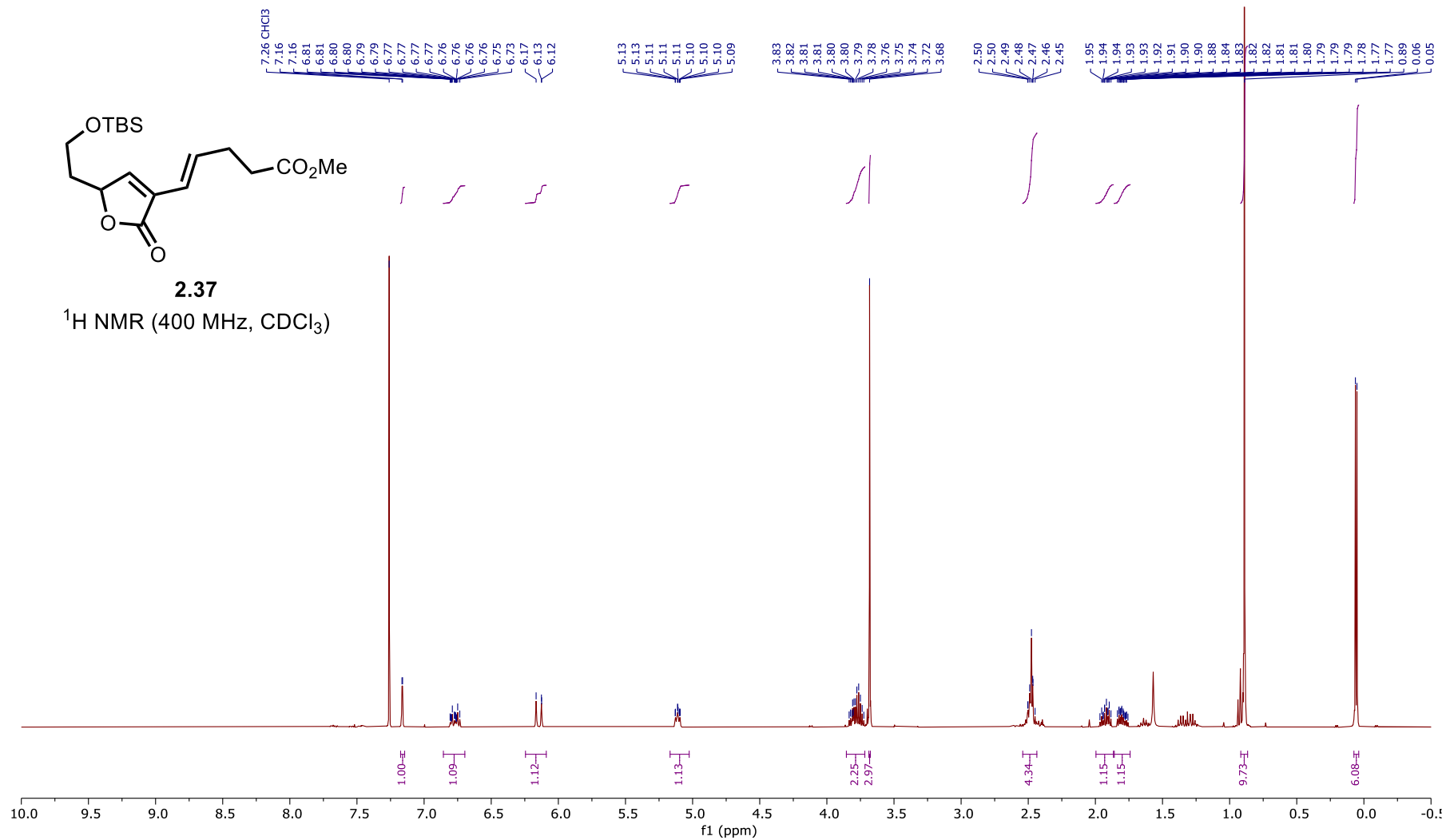
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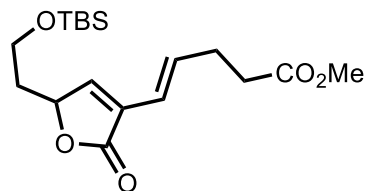




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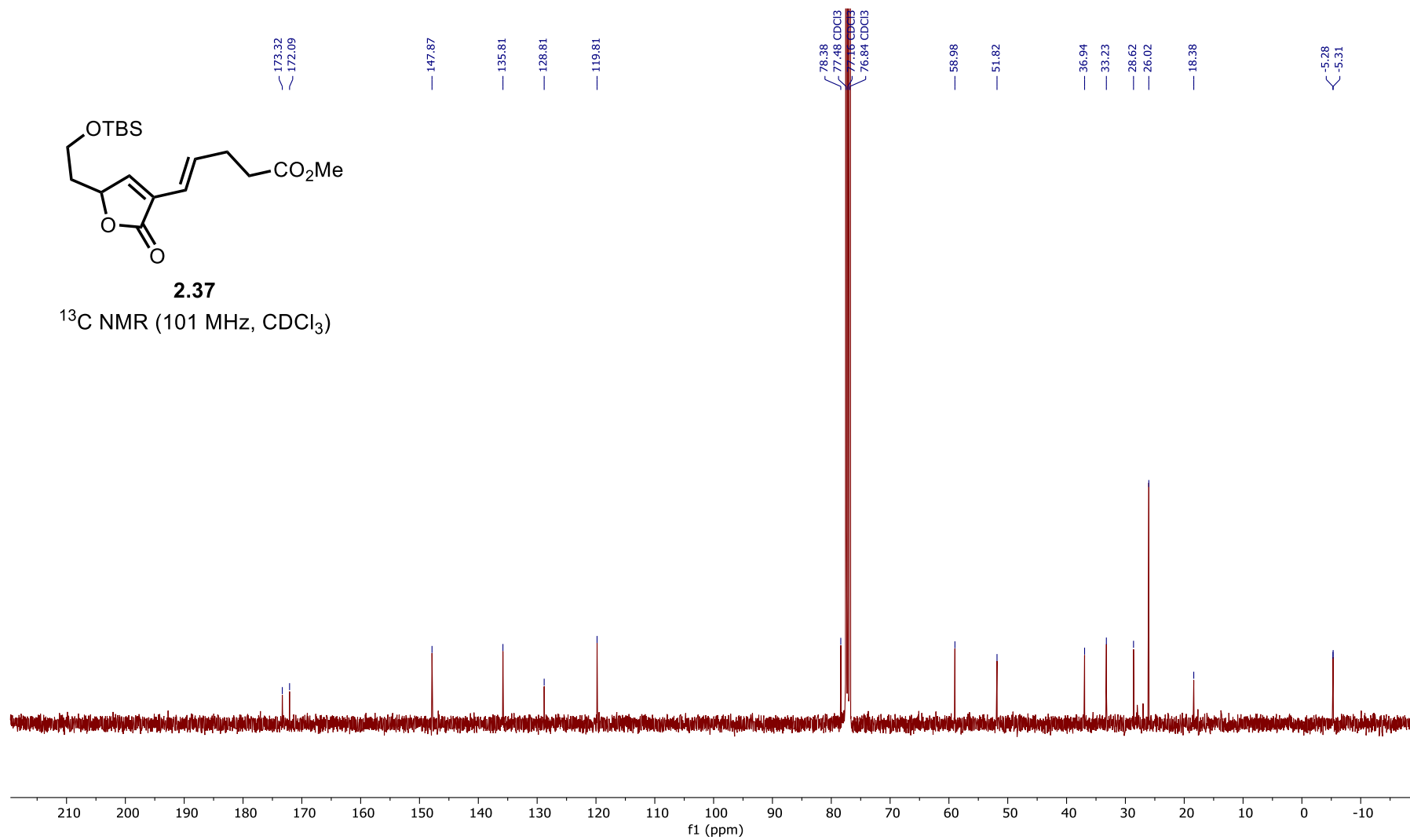
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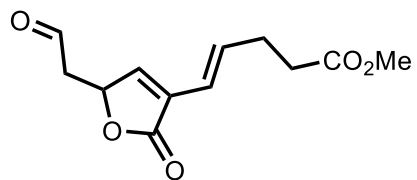




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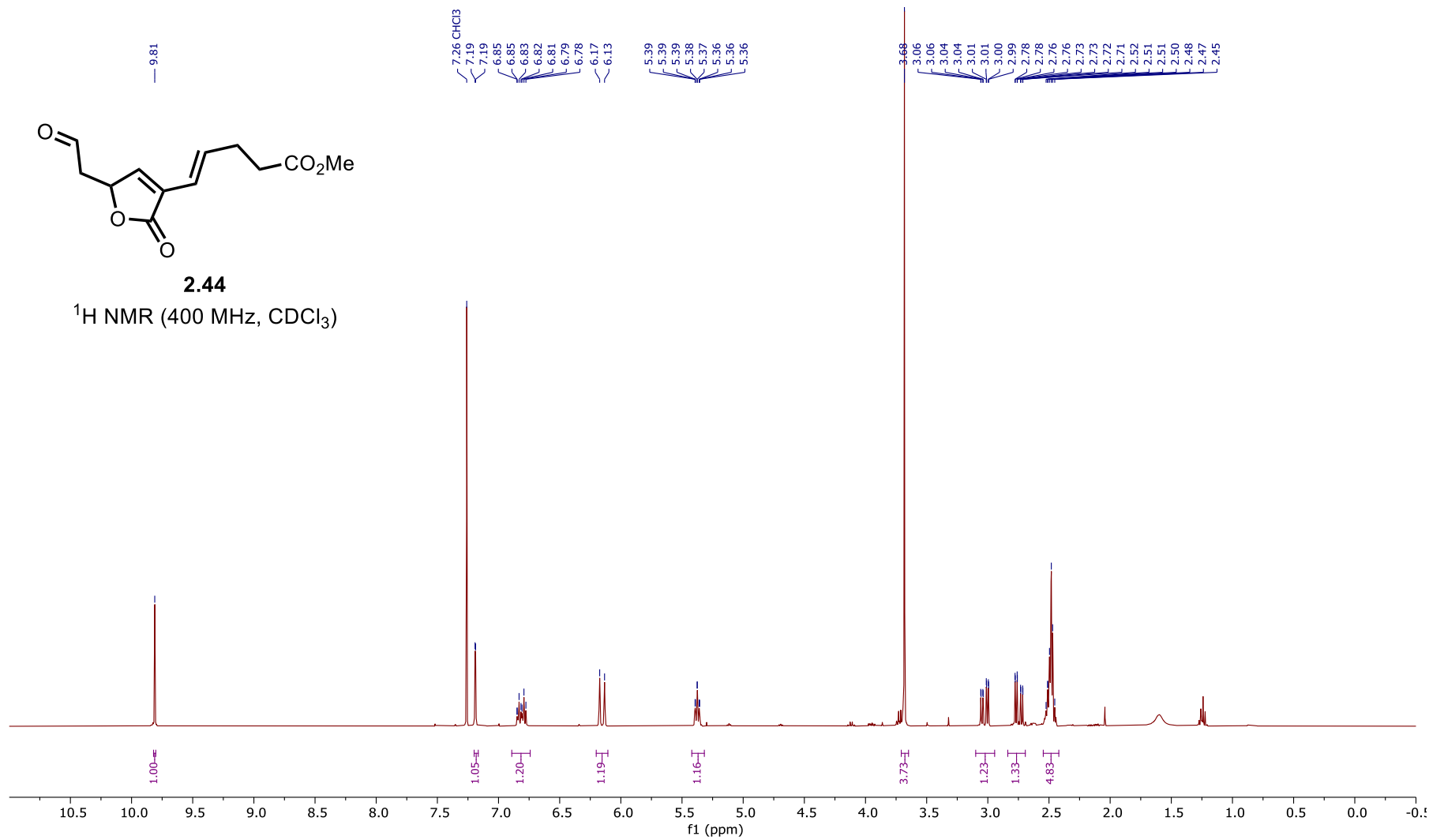
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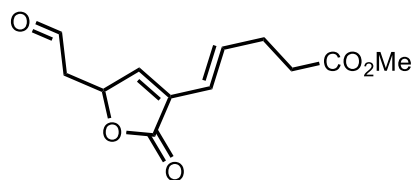




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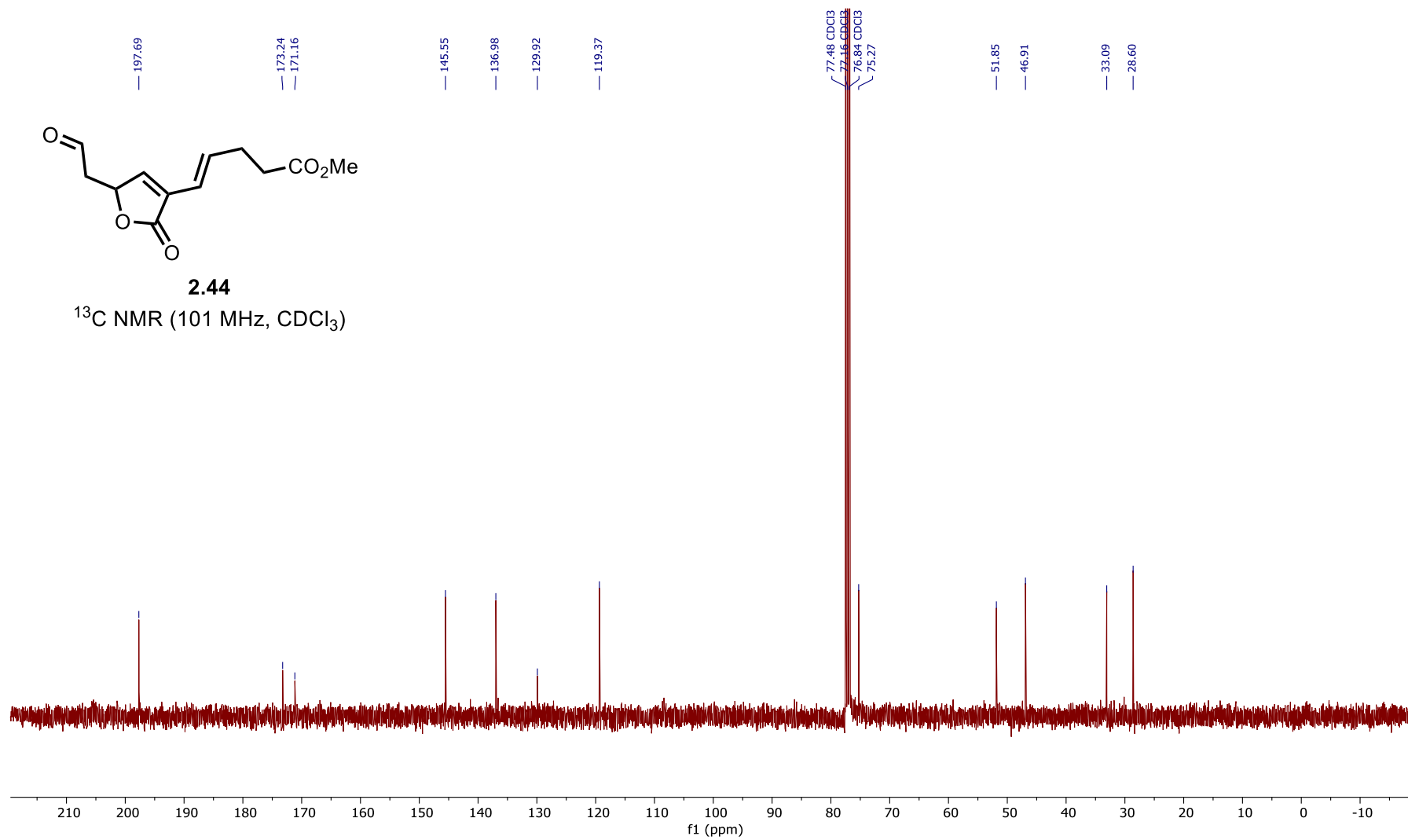
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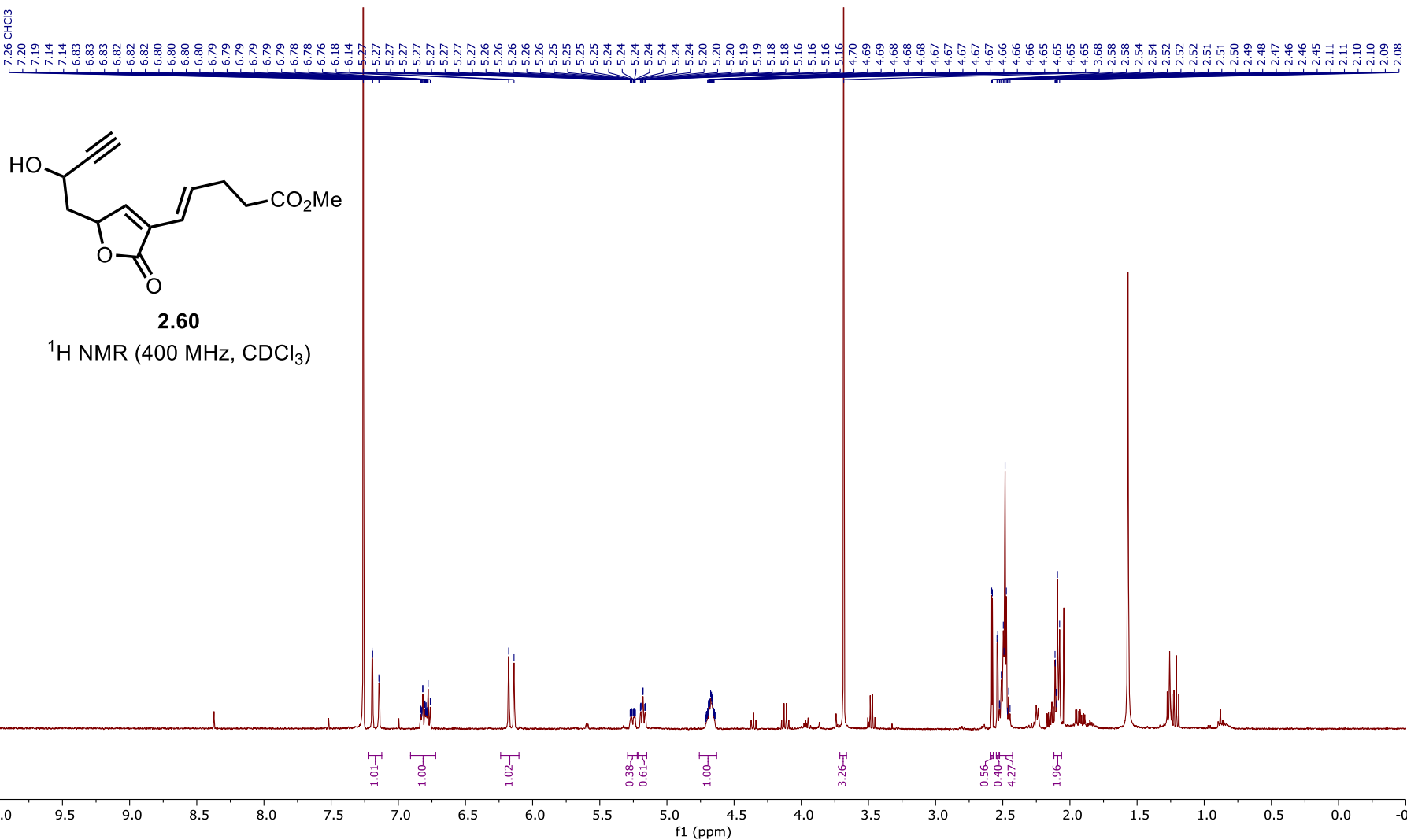


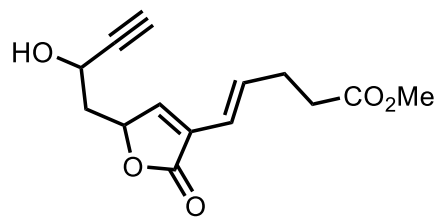


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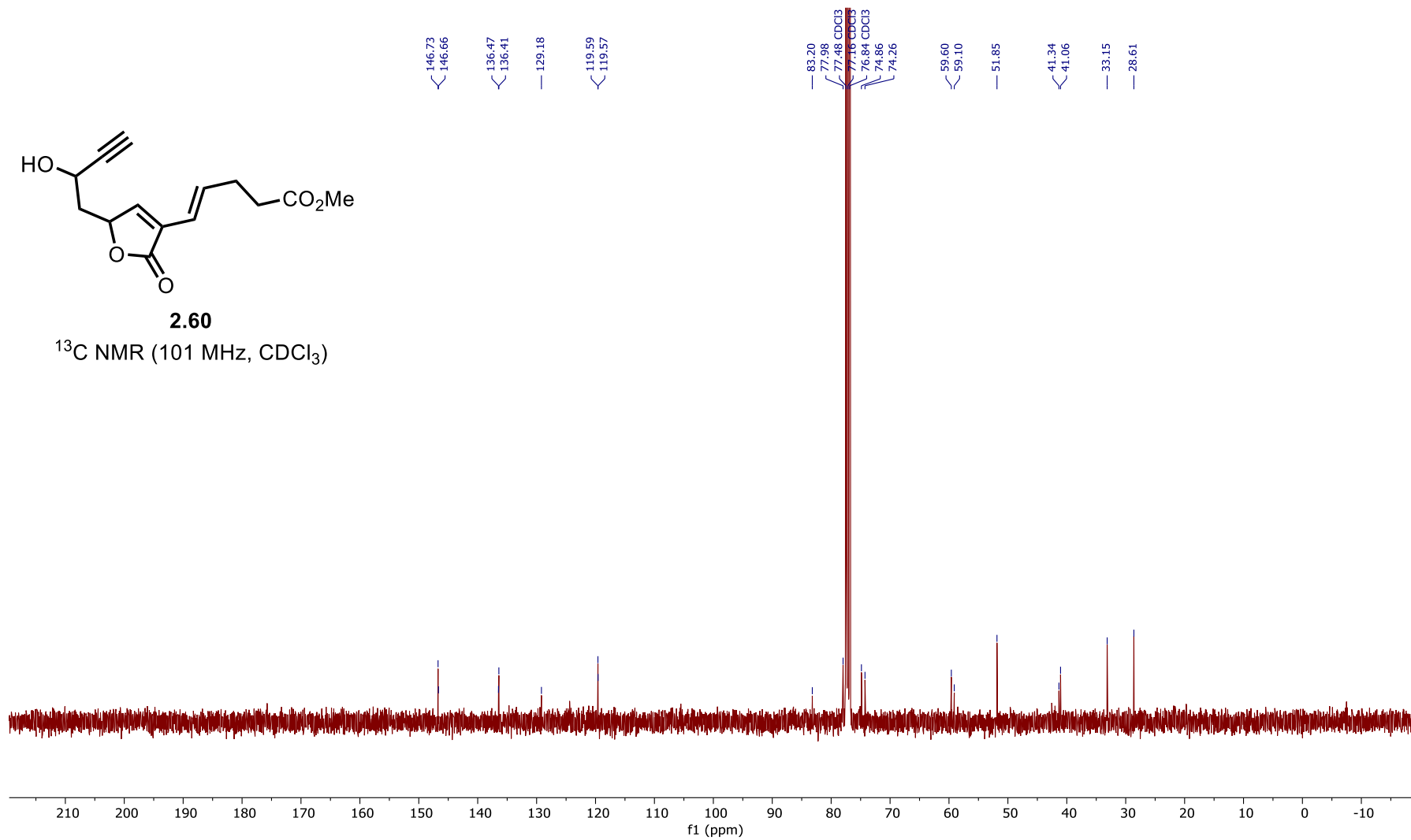


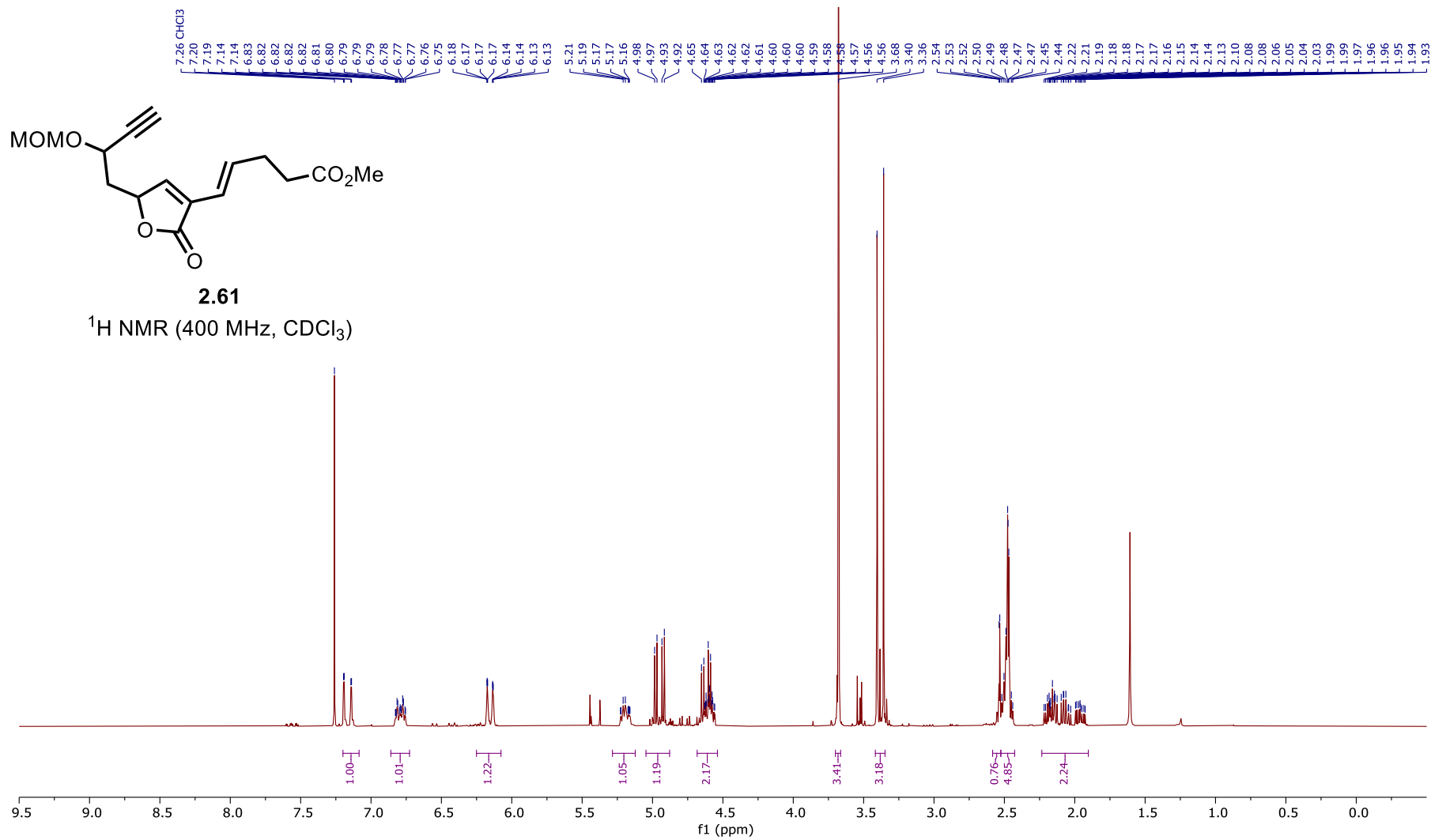


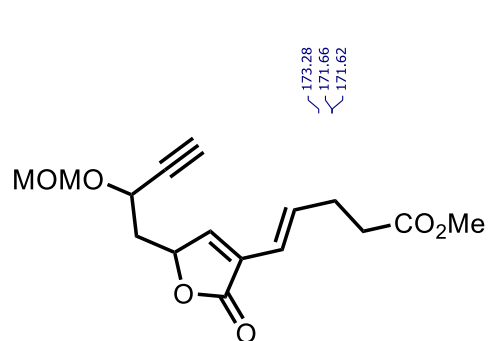


2.60

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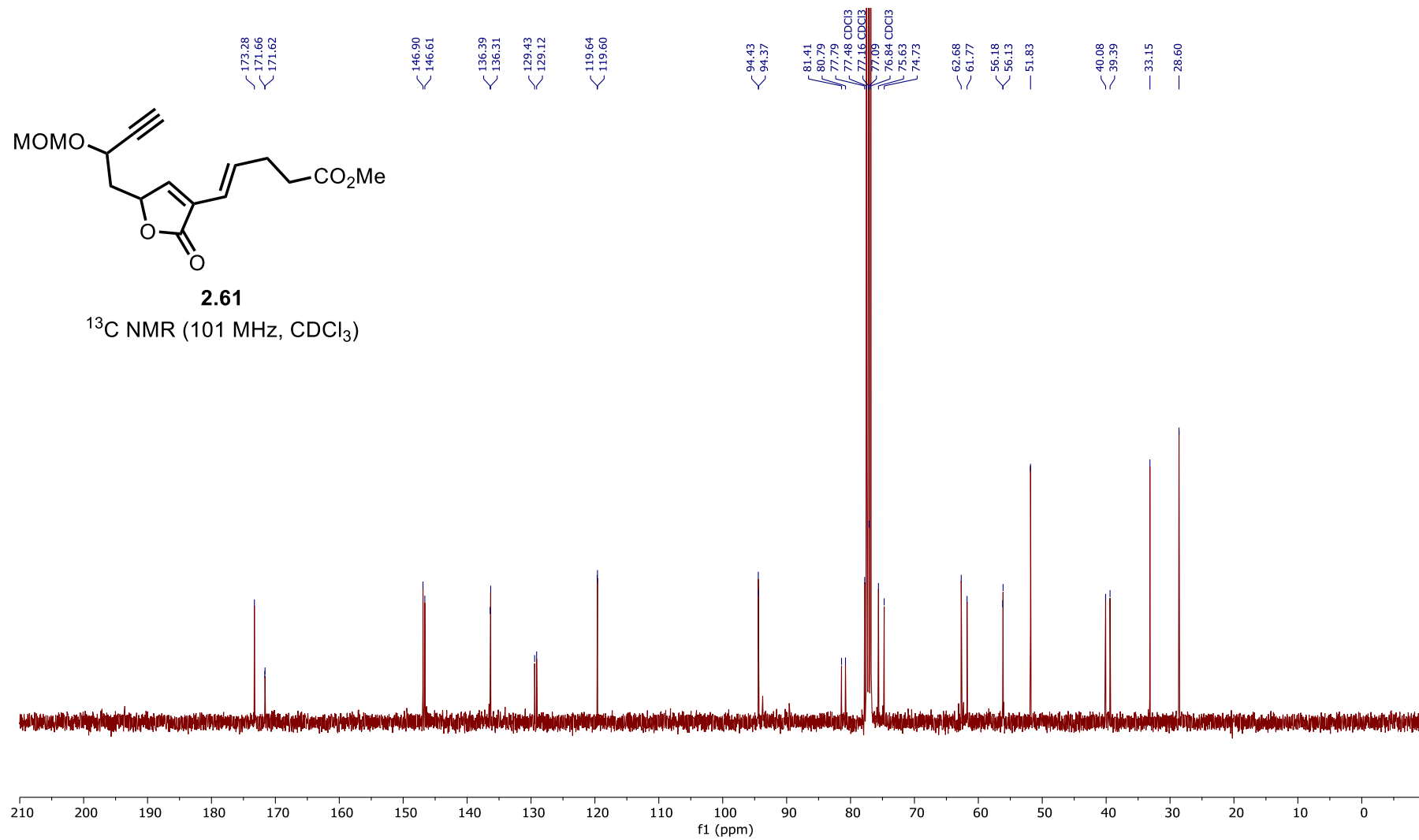


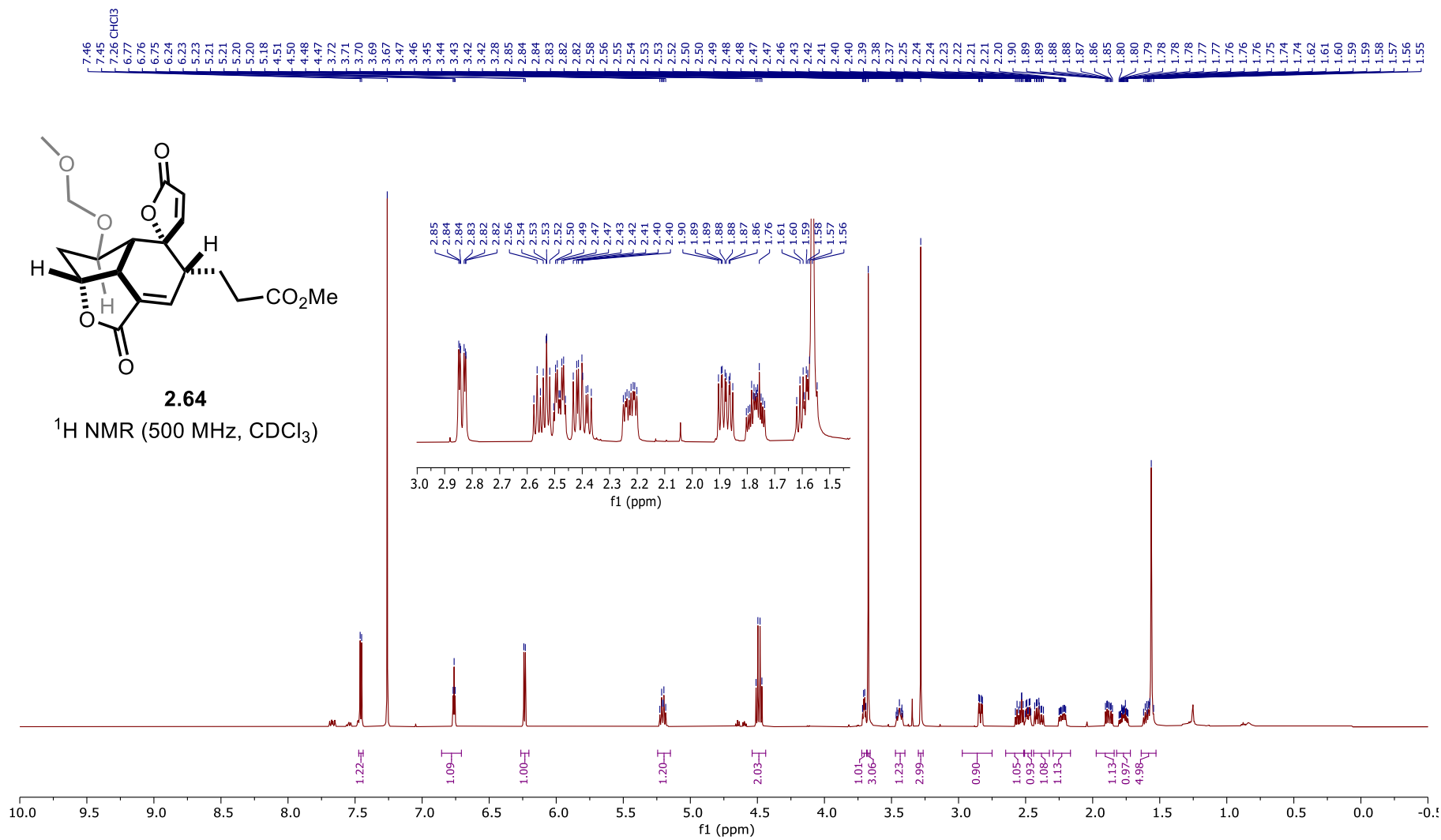


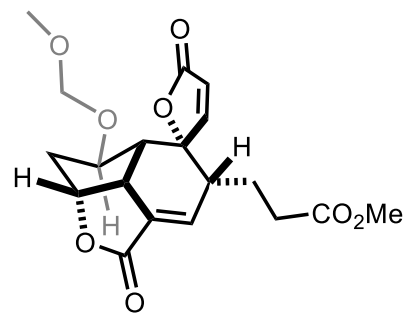


2.61

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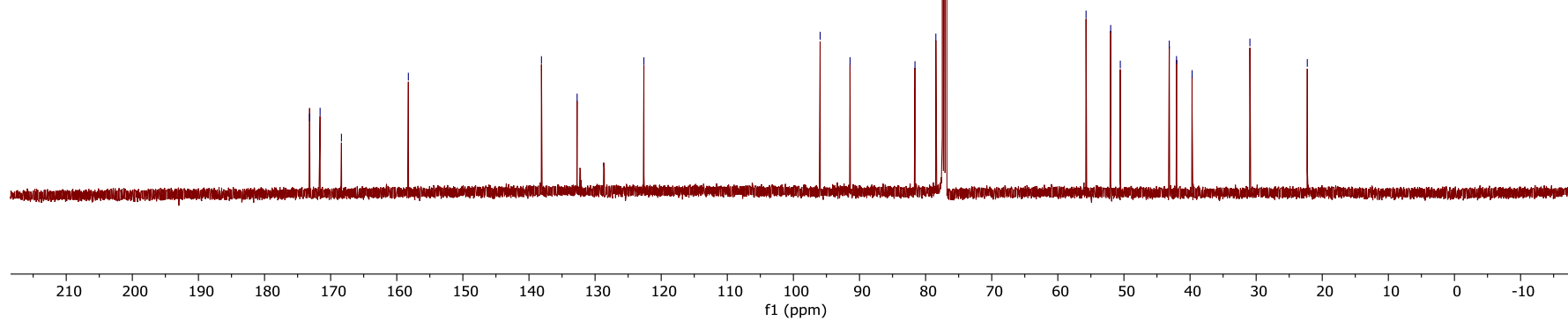


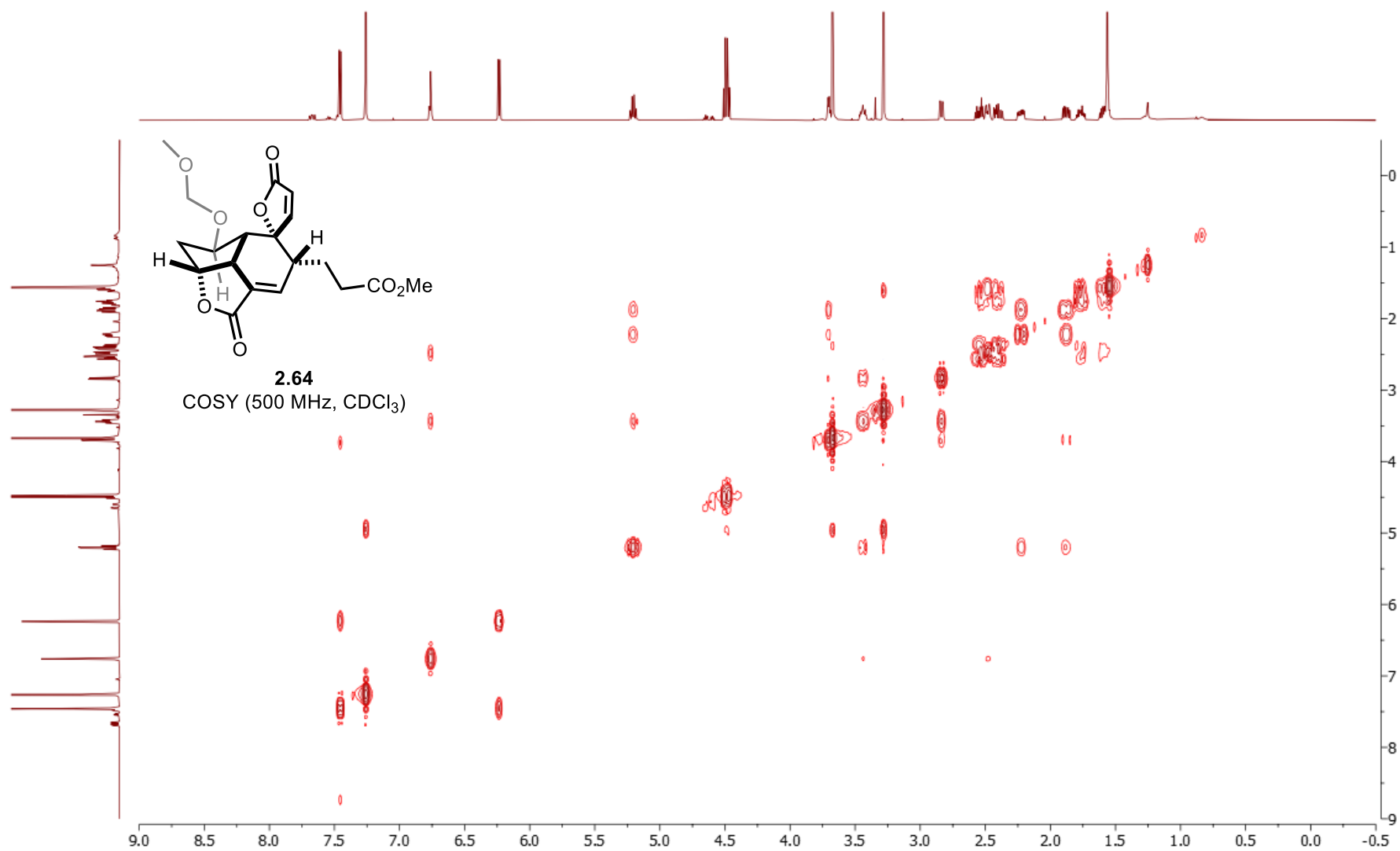


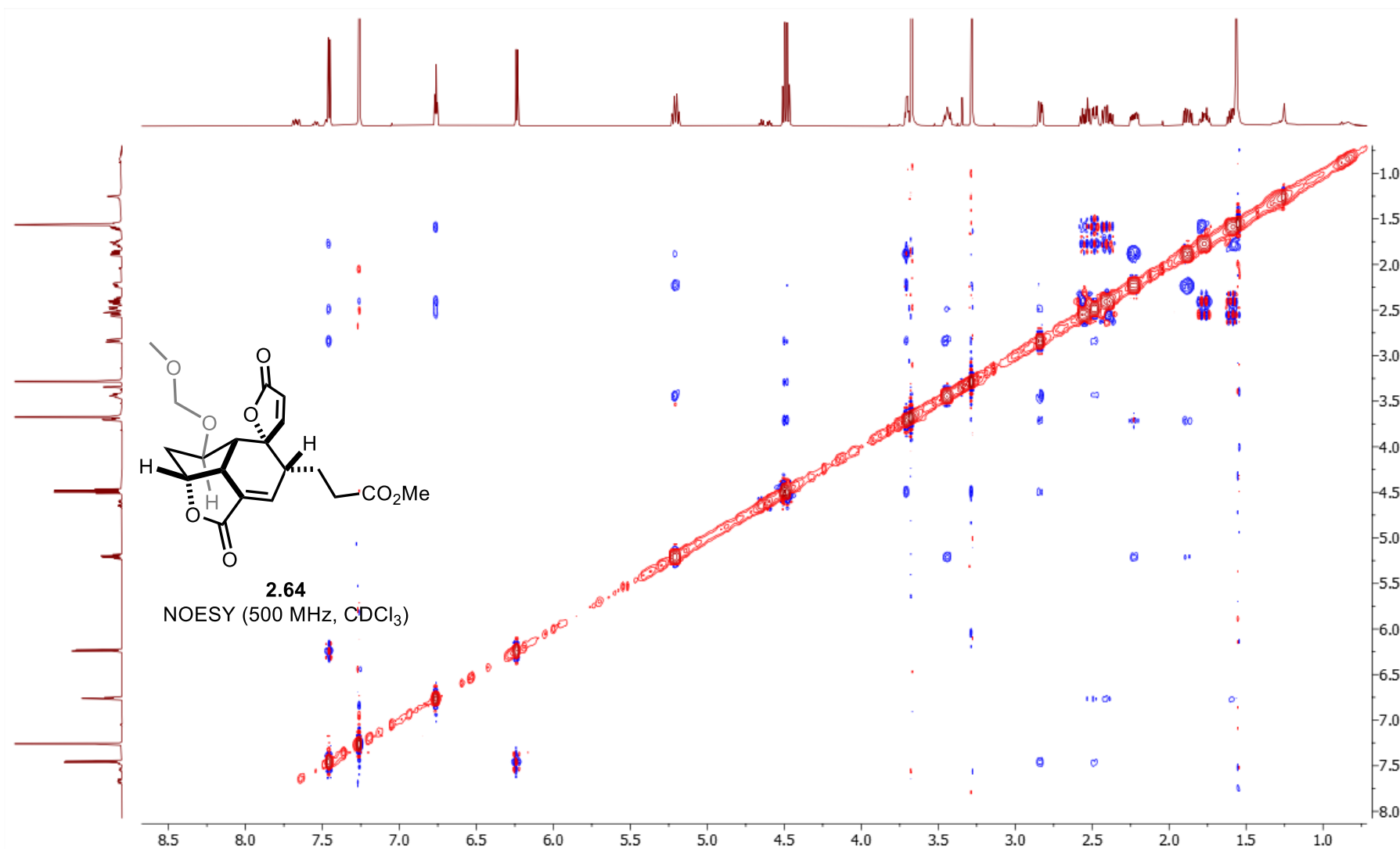


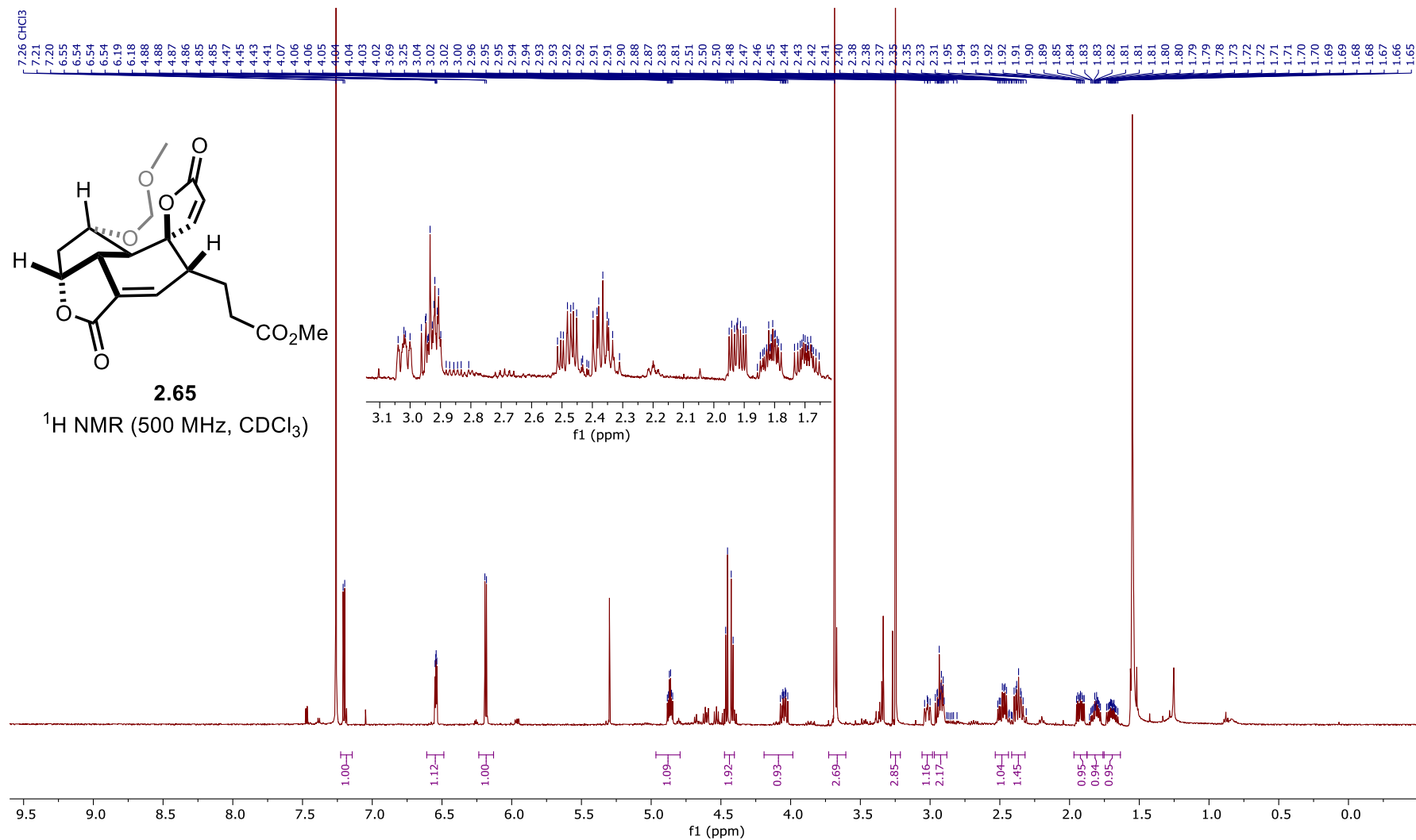
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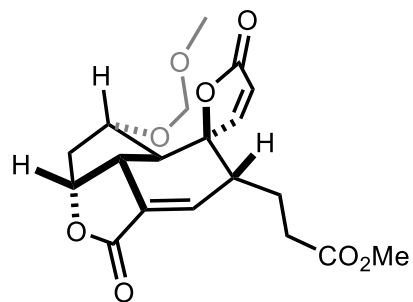
¹³C NMR (126 MHz, CDCl₃)





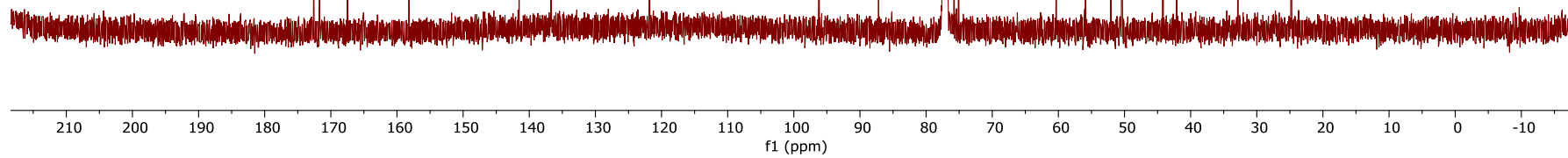


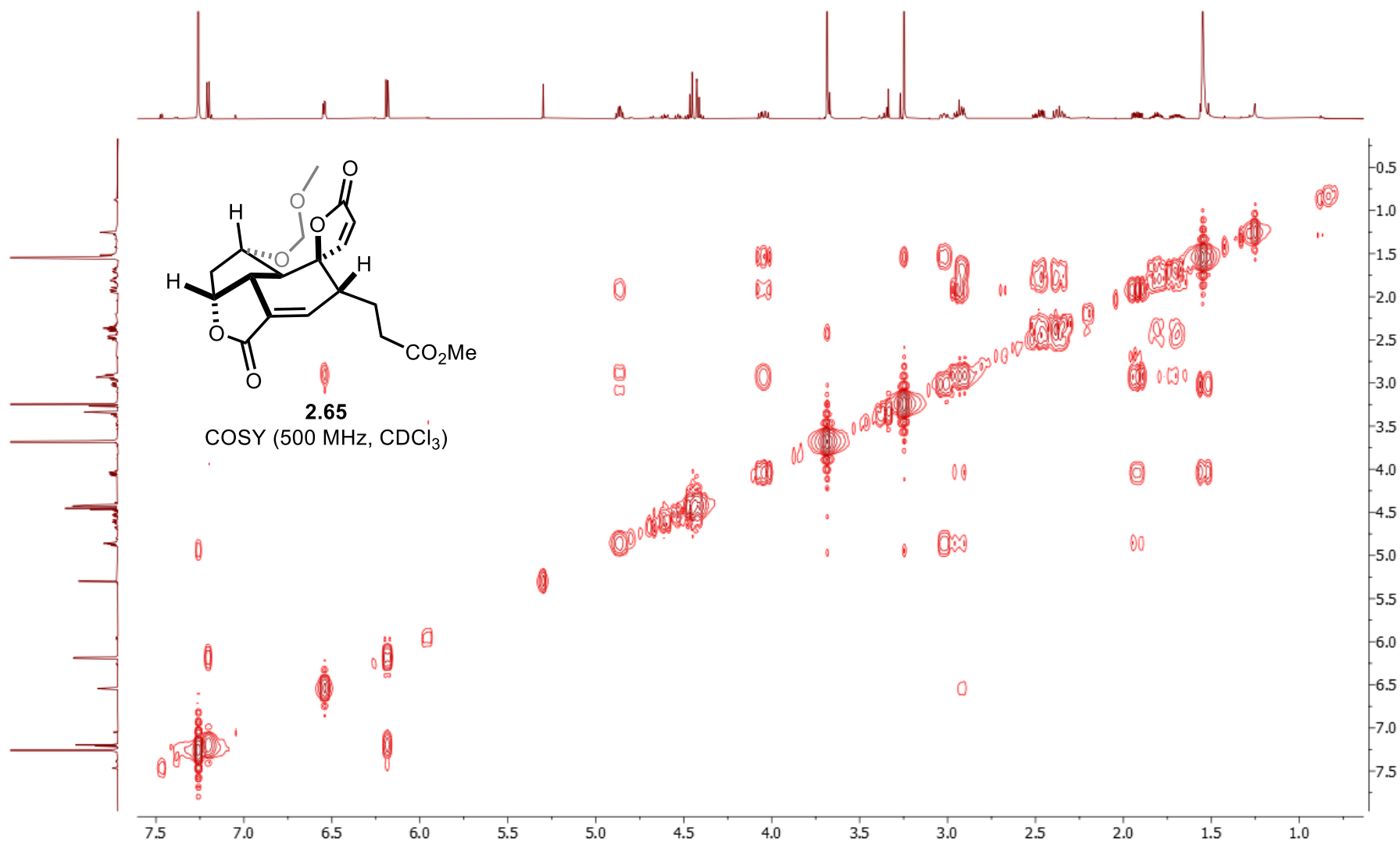


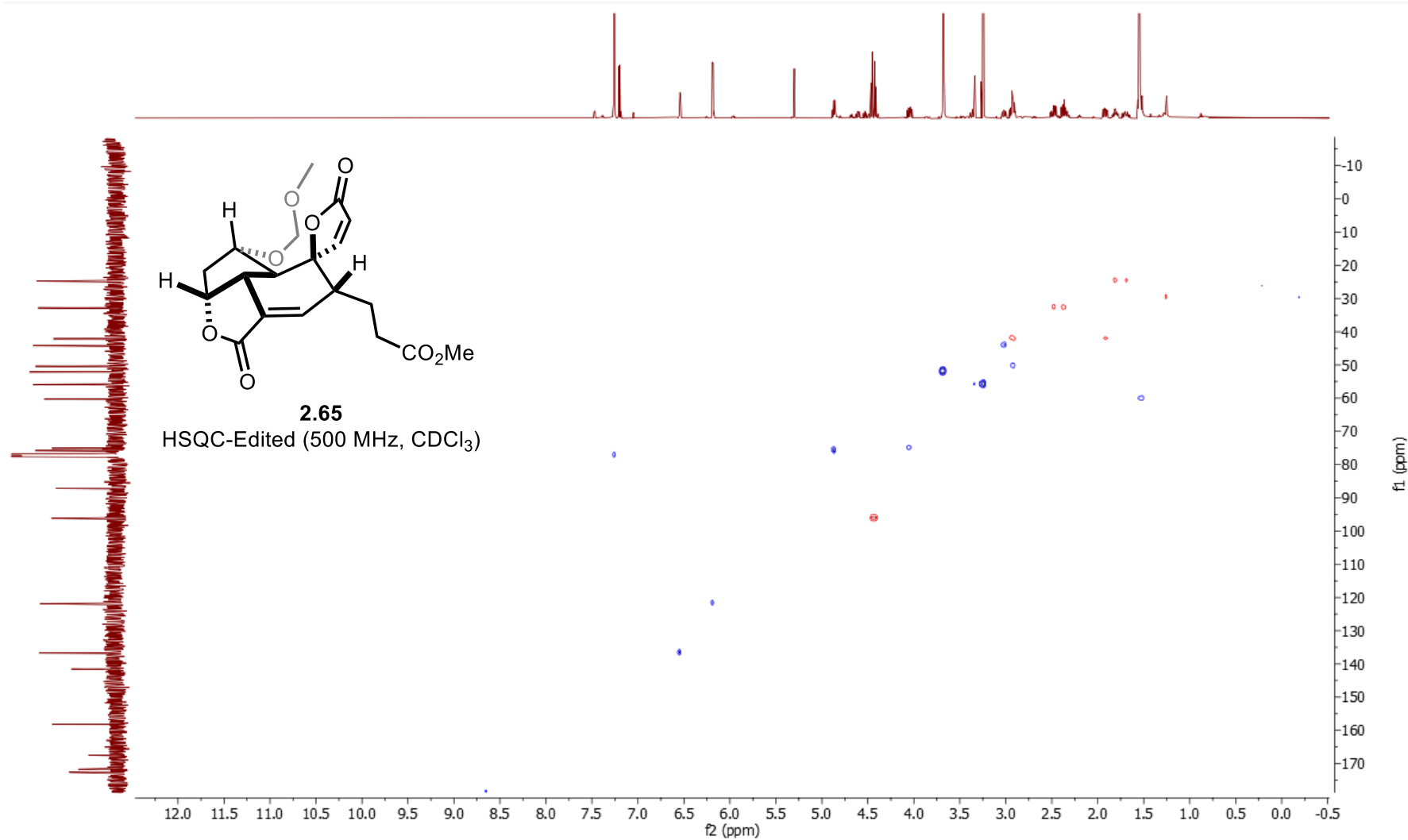


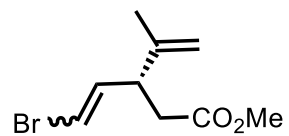
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^{13}C NMR (126 MHz, CDCl_3)



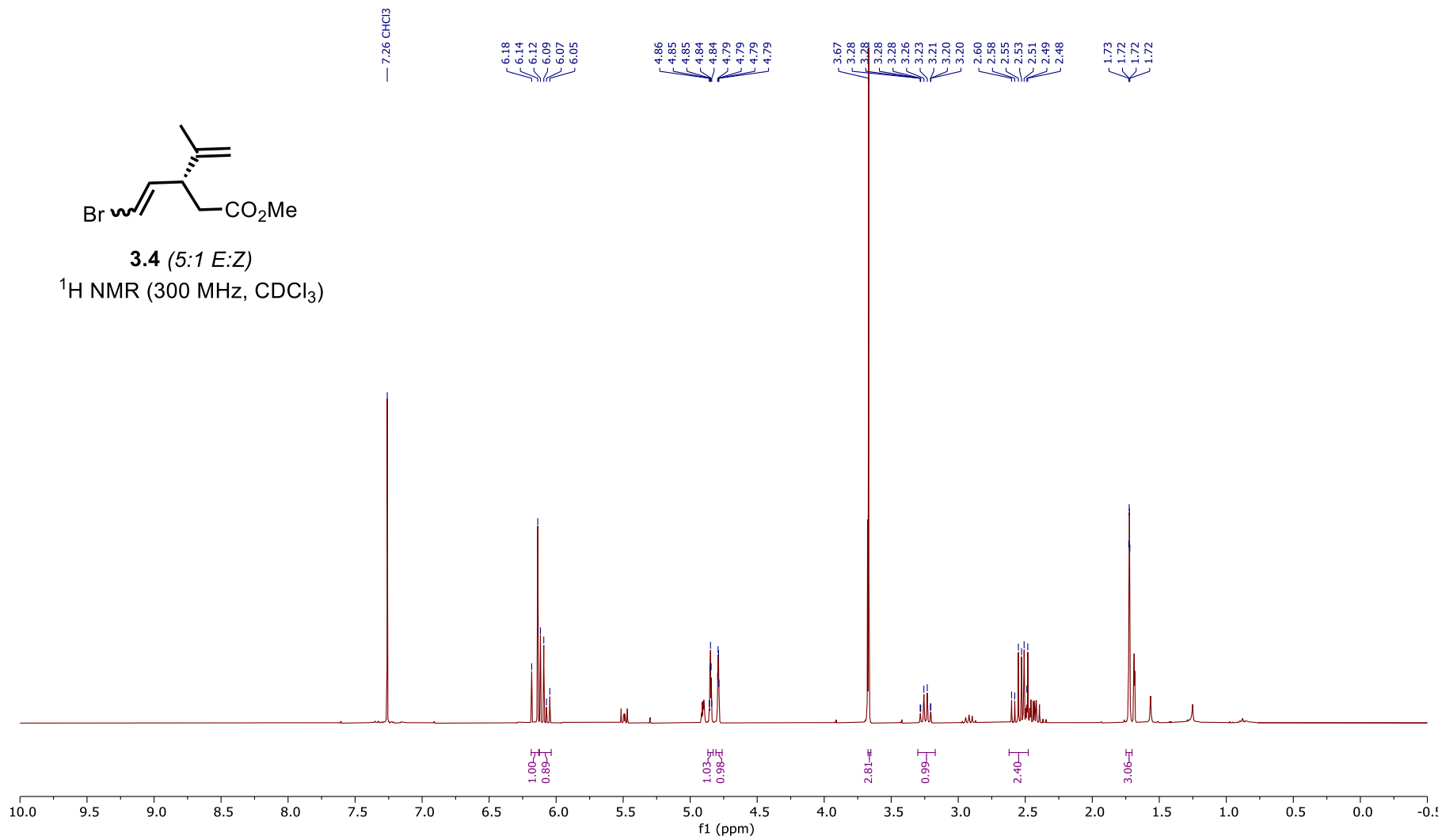


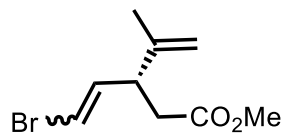




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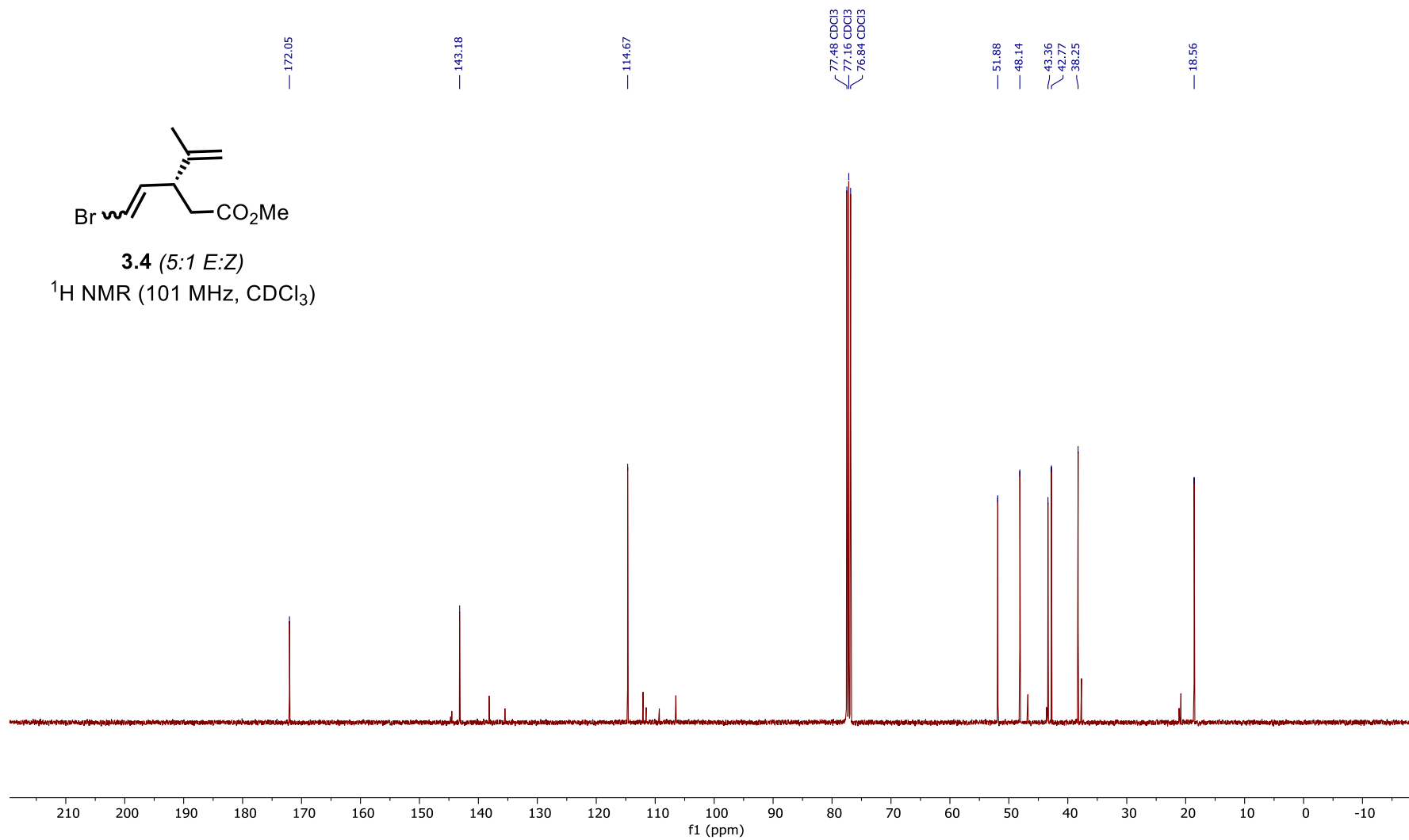
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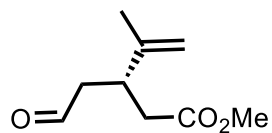




3.4 (5:1 E:Z)

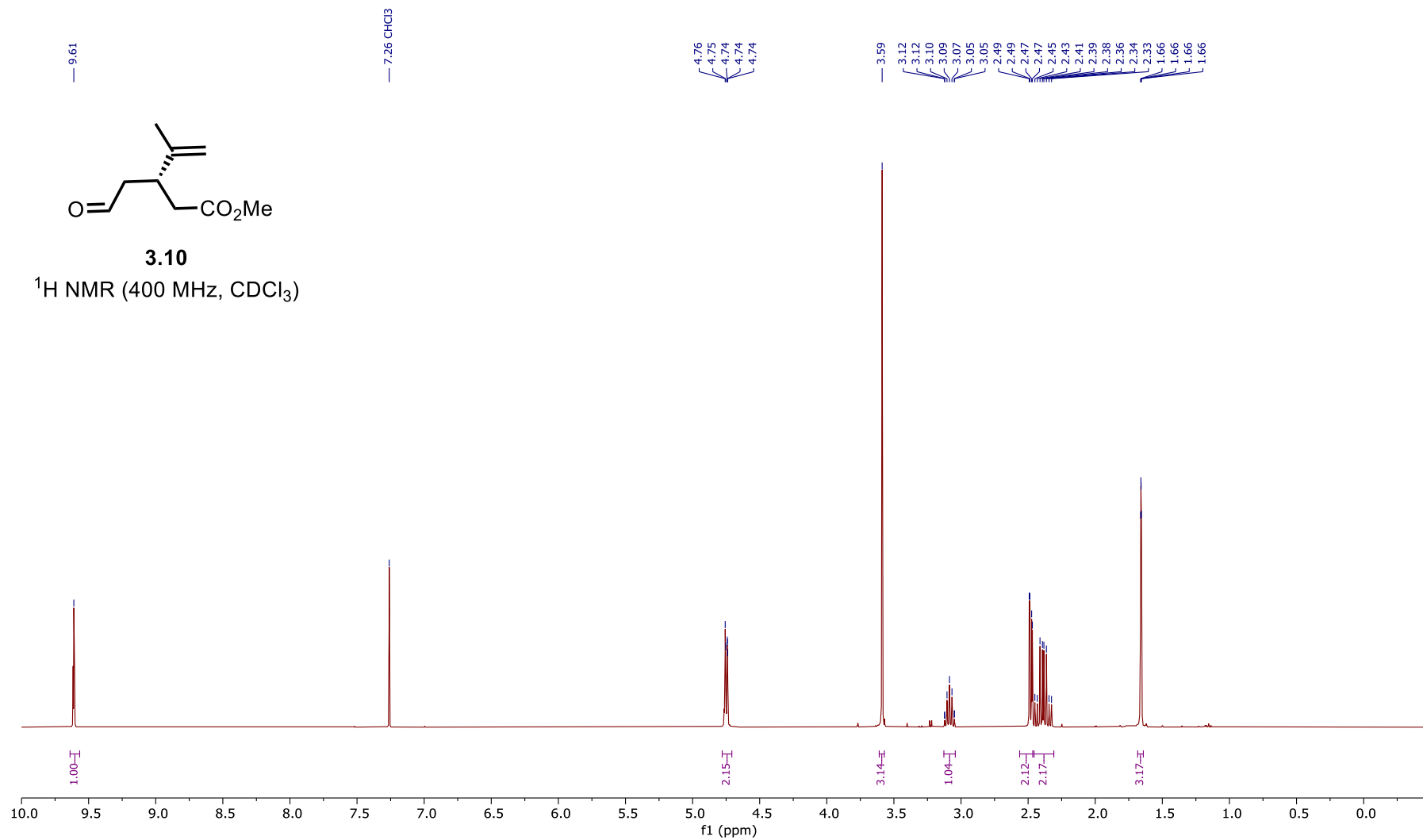
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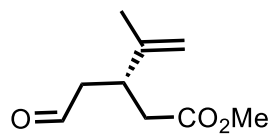




3.10

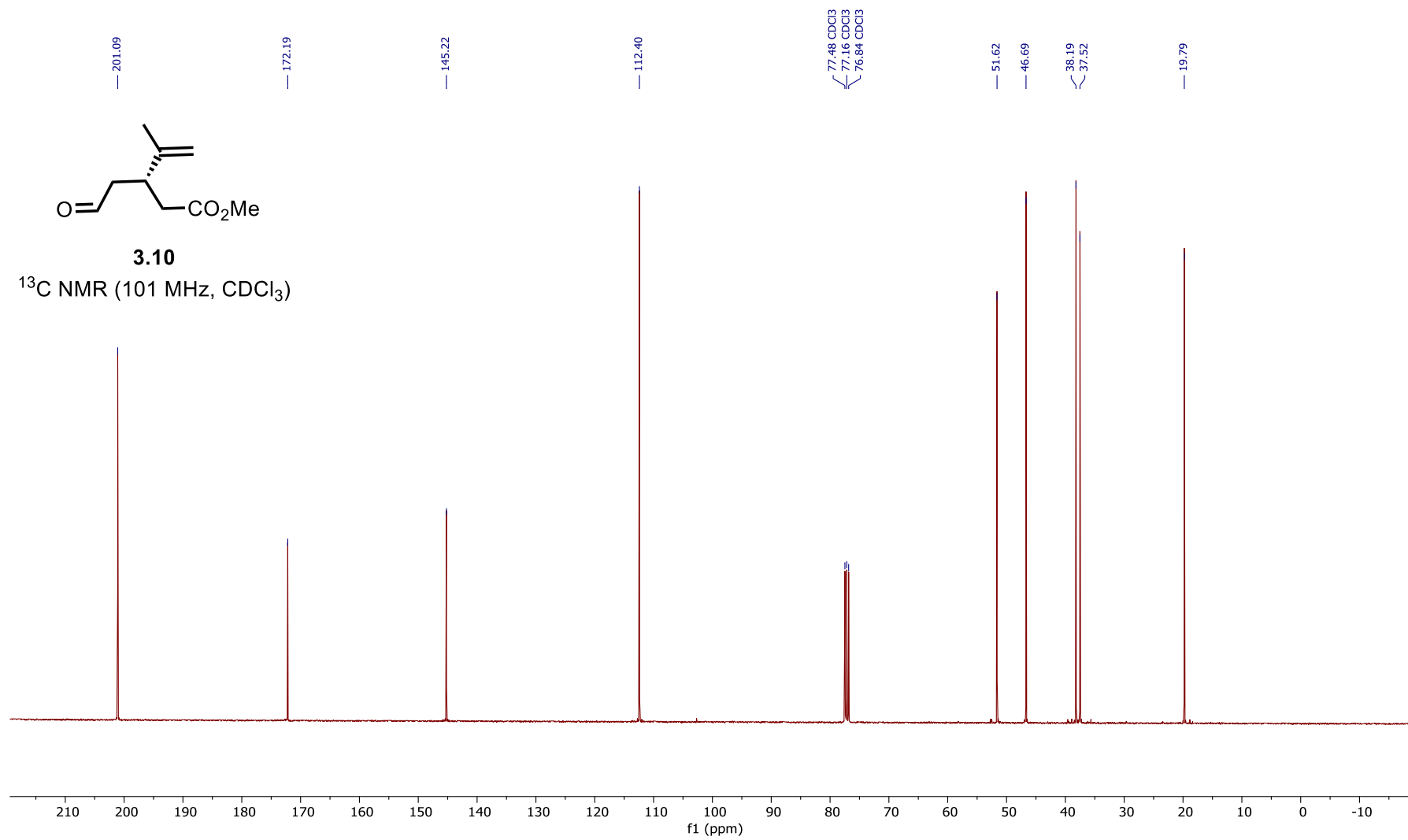
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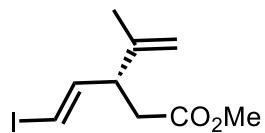




3.10

^{13}C NMR (101 MHz, CDCl_3)





3.13

¹H NMR (600 MHz, CDCl₃)

7.26 CHCl₃

6.44
6.43
6.42
6.41
6.17
6.15

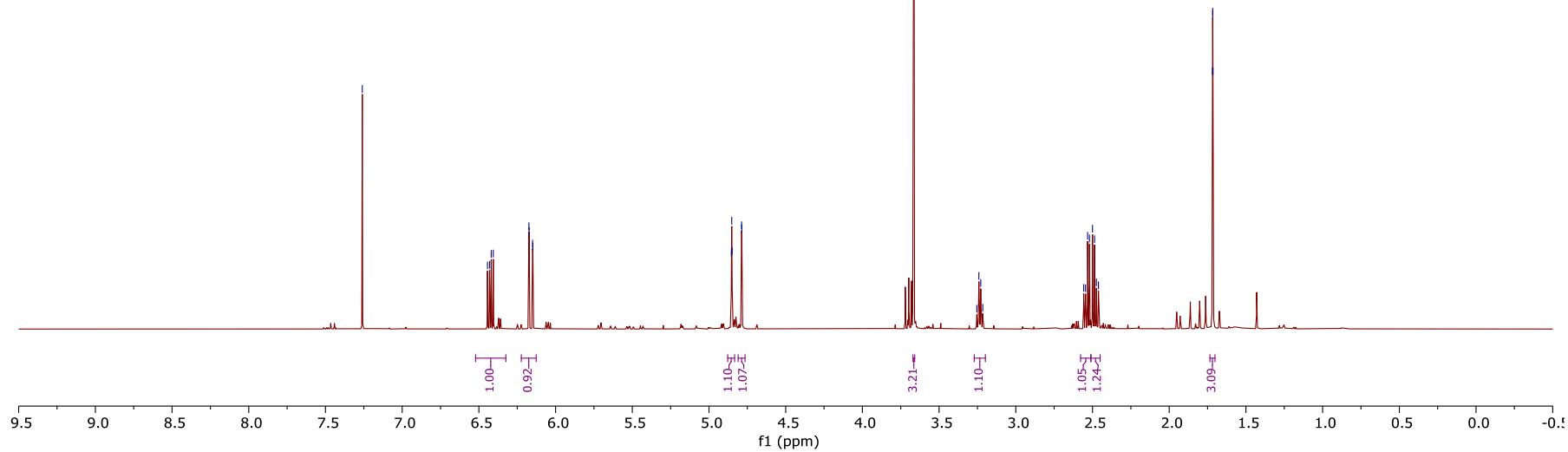
4.85
4.85
4.85
4.79

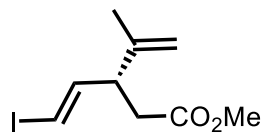
3.62

3.25
3.24
3.23
3.22

2.56
2.55
2.53
2.52
2.50
2.49
2.47
2.46

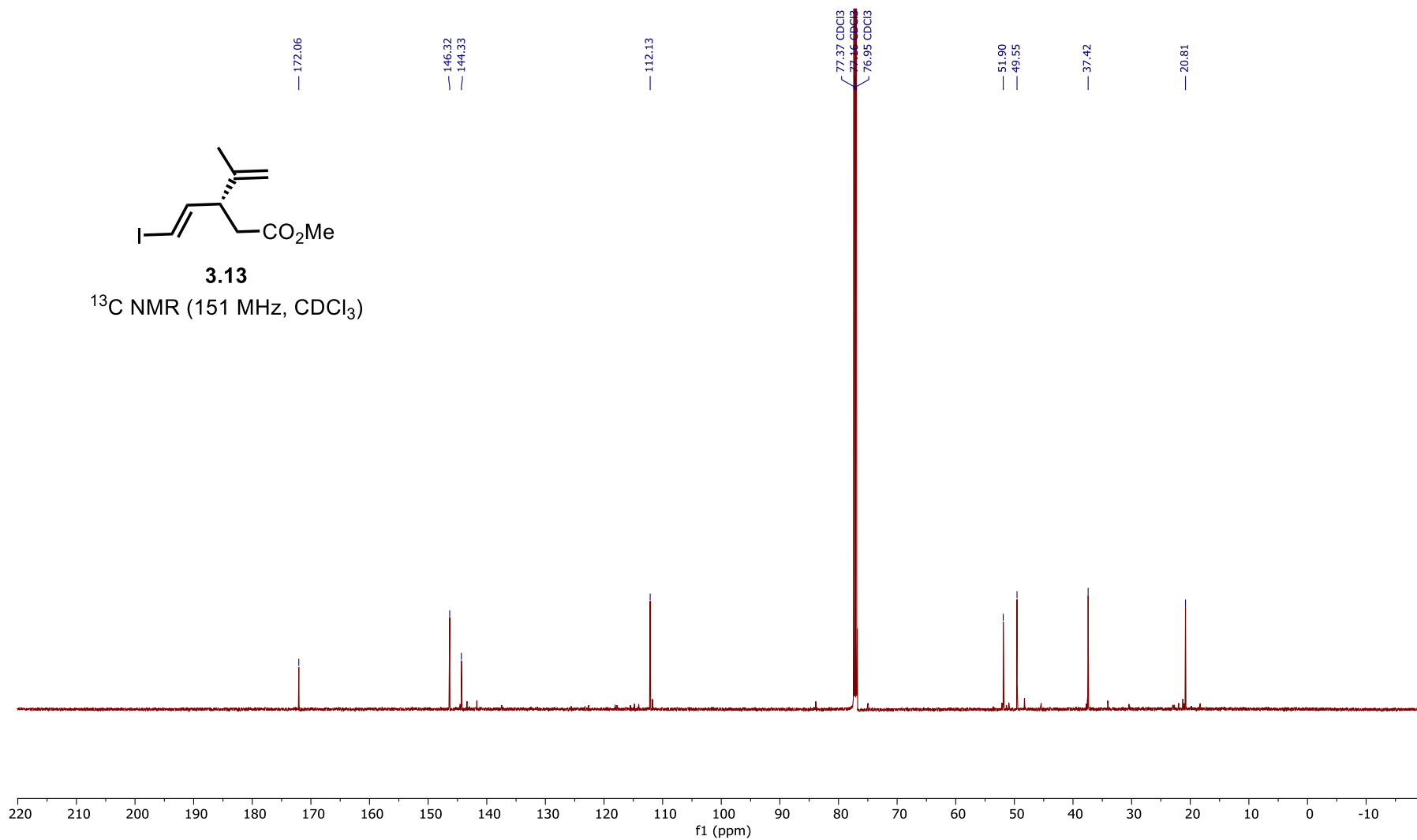
1.72
1.72
1.72
1.71

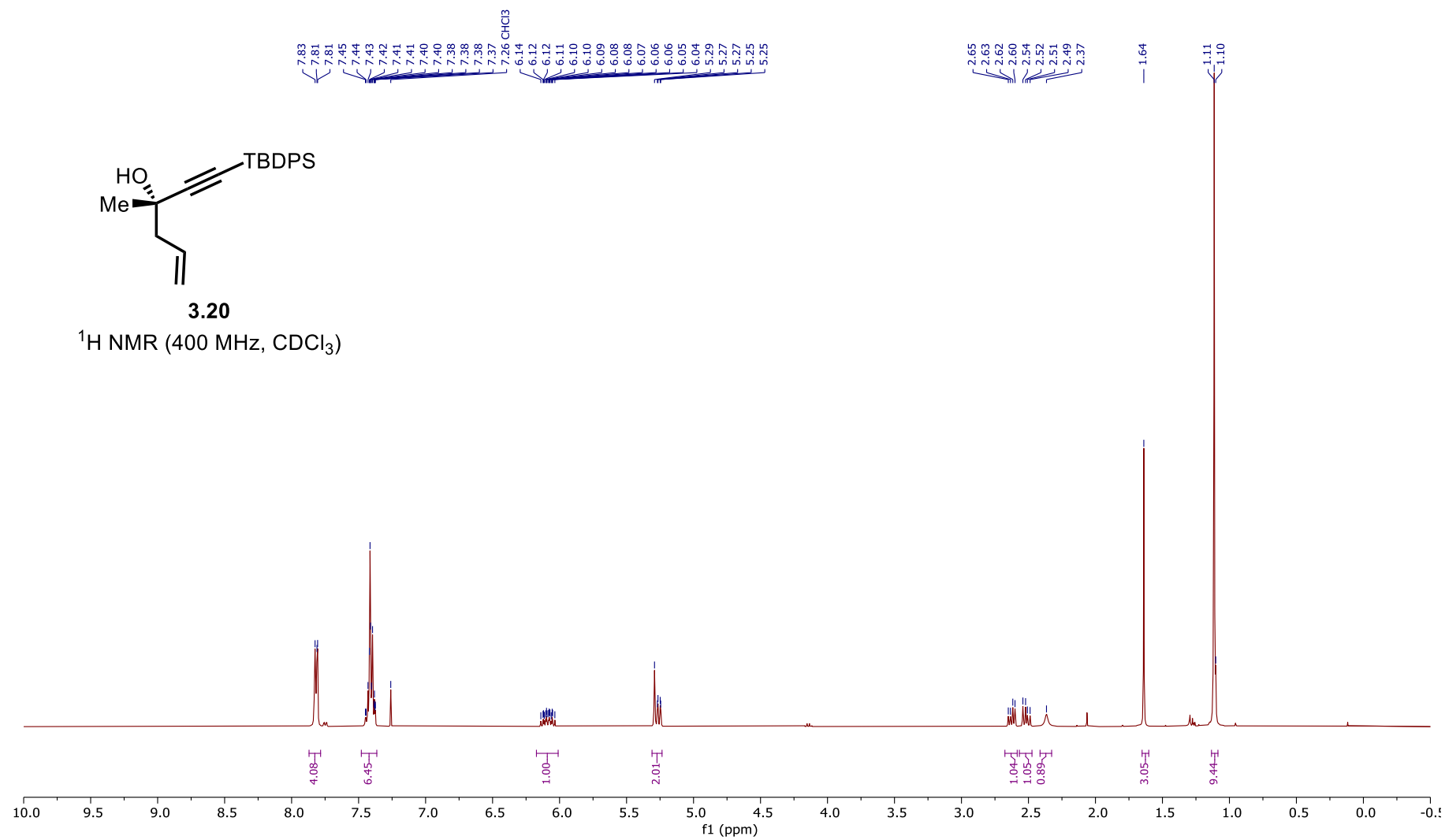


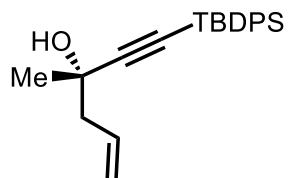


3.13

^{13}C NMR (151 MHz, CDCl_3)

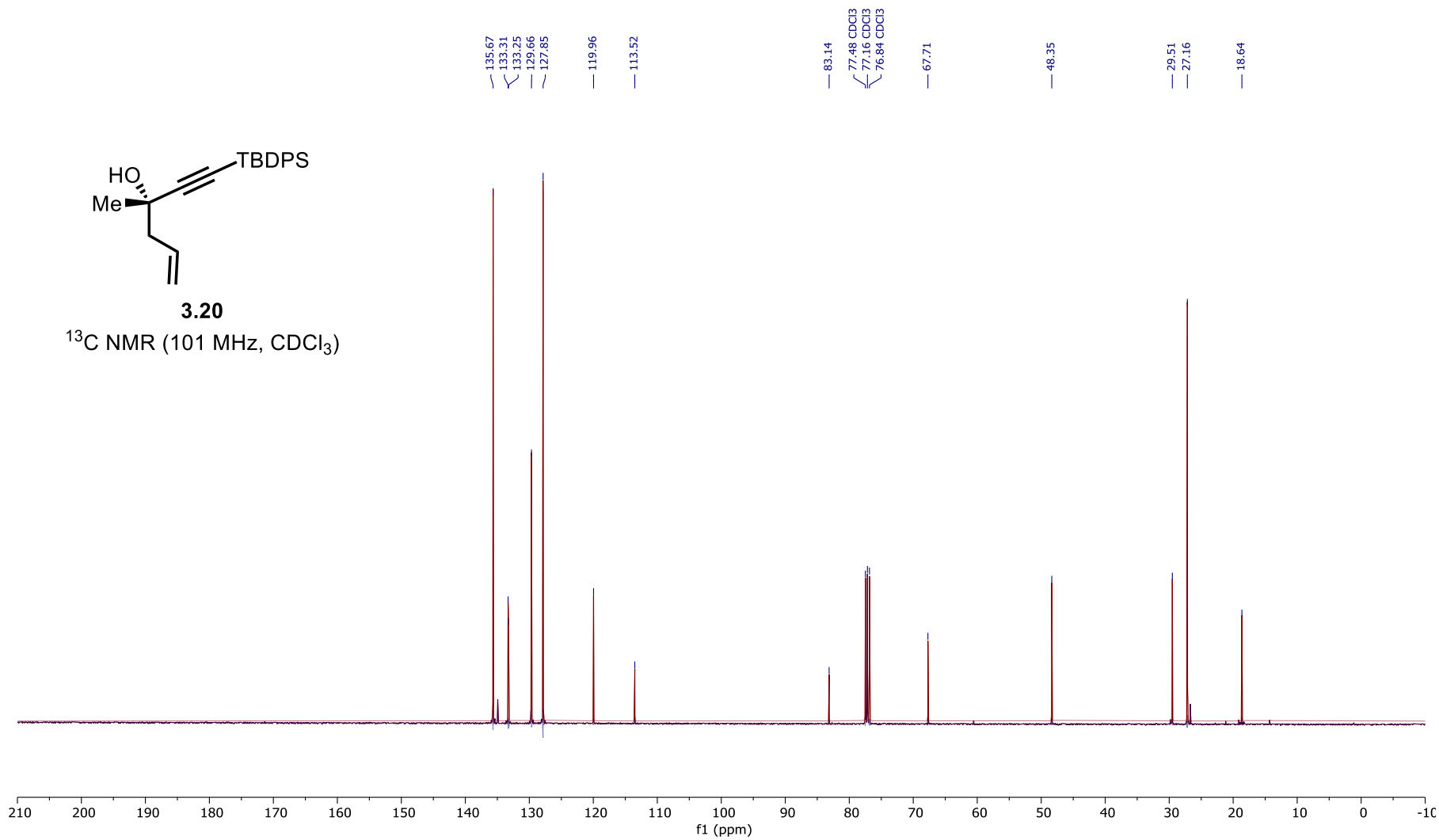


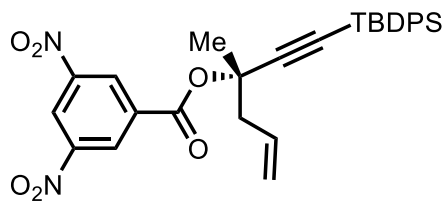




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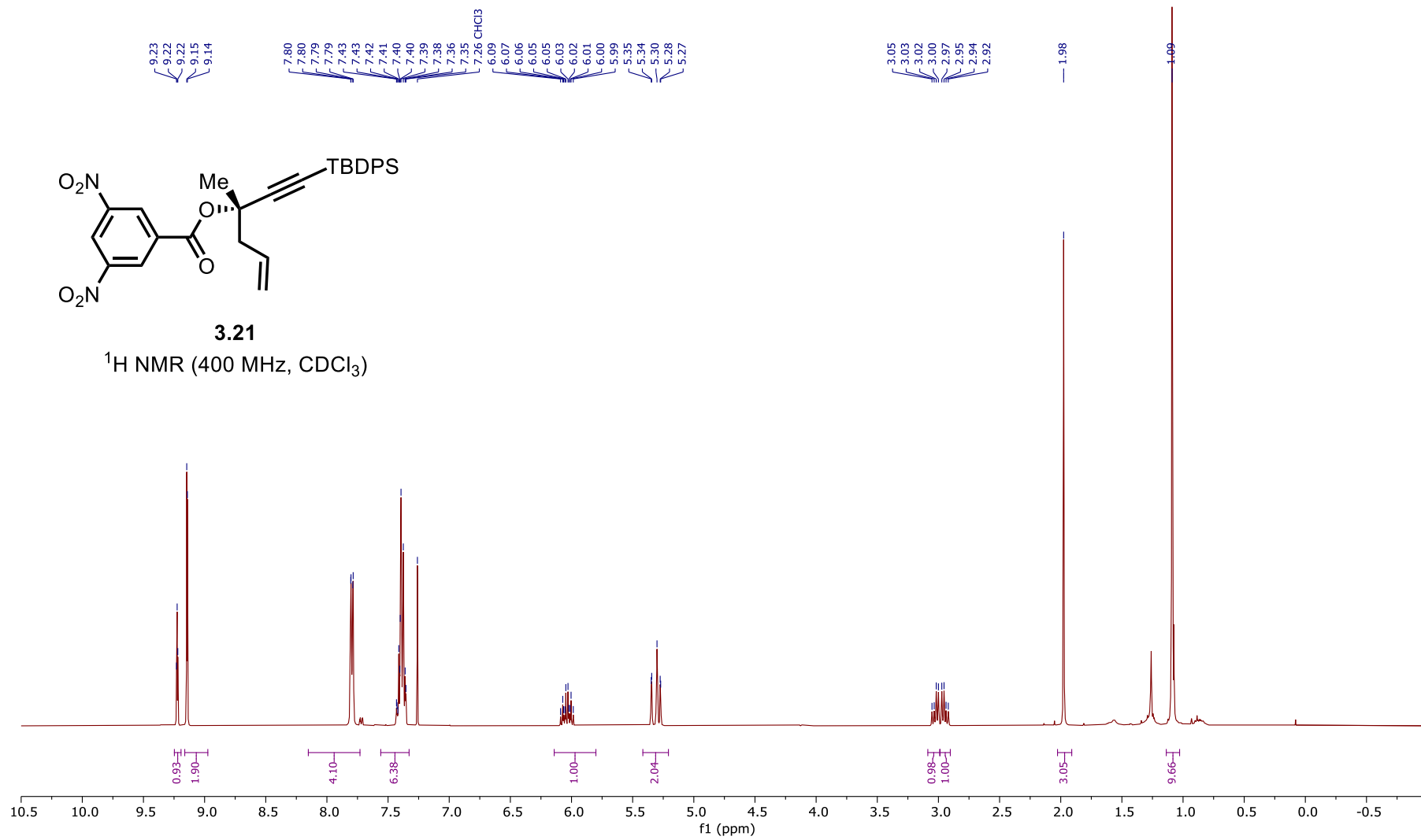
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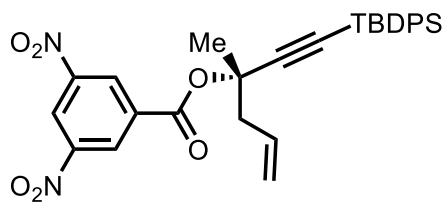




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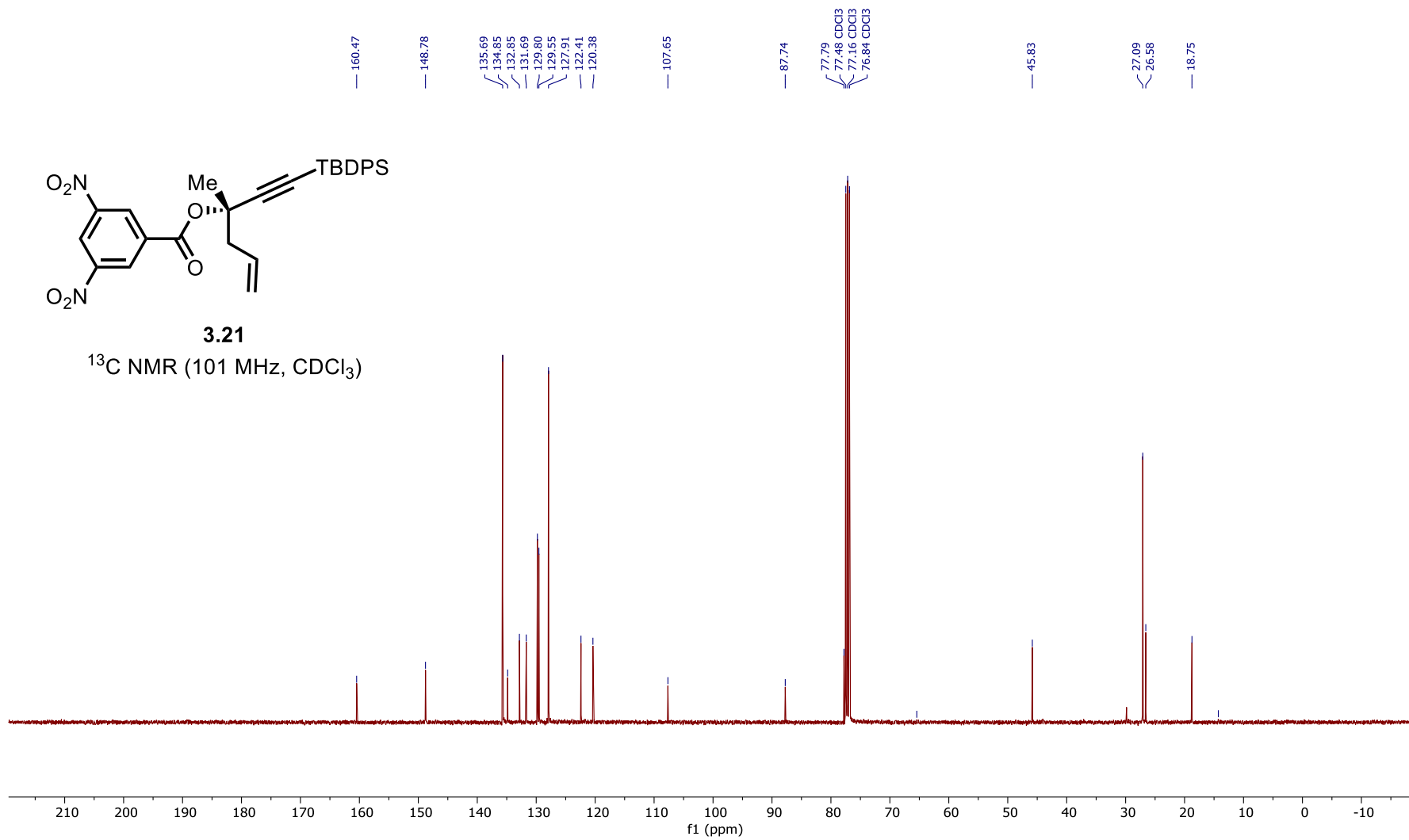
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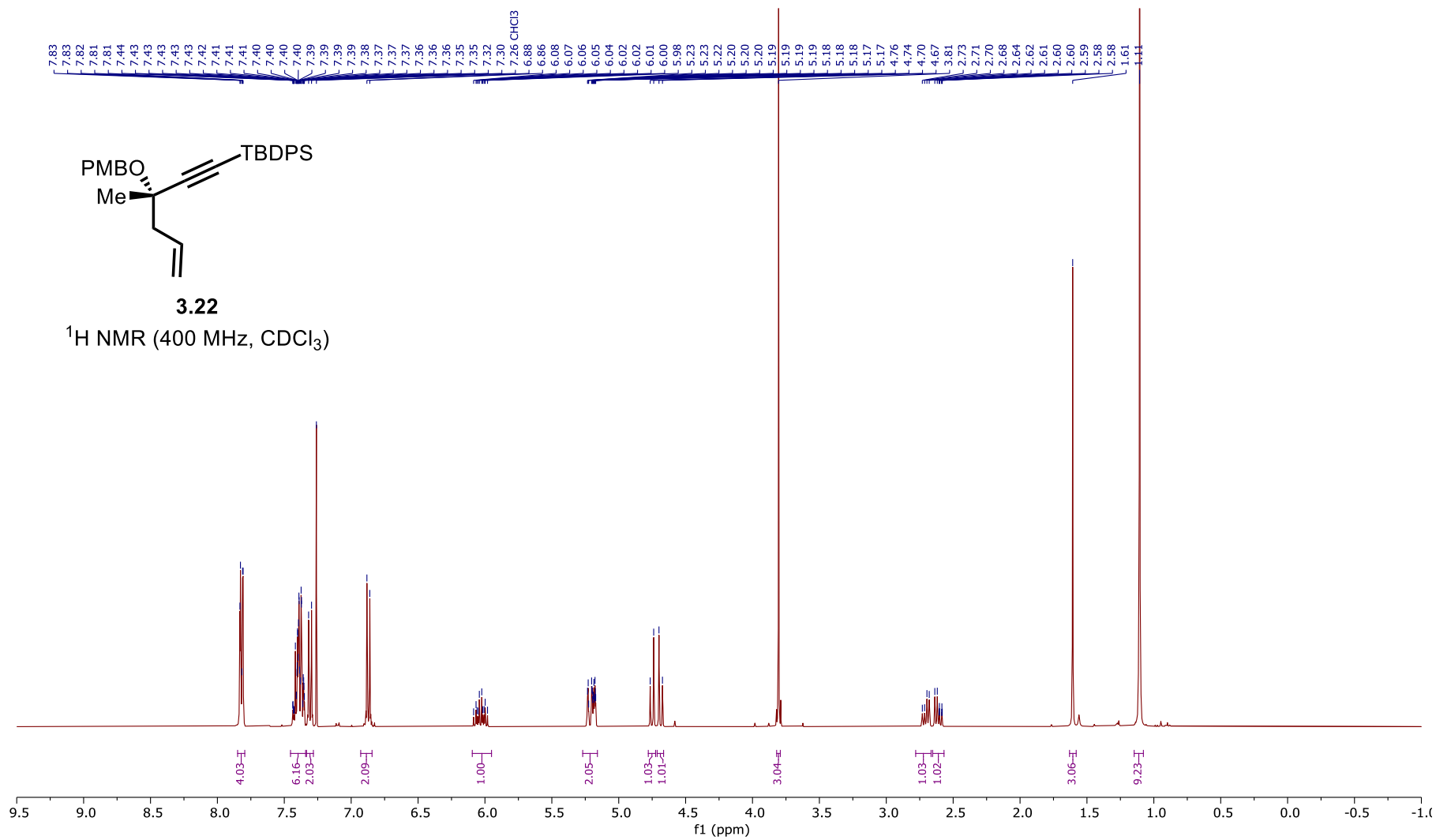


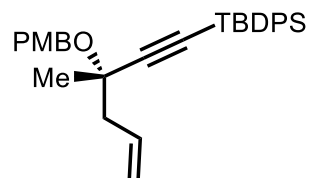


3.21

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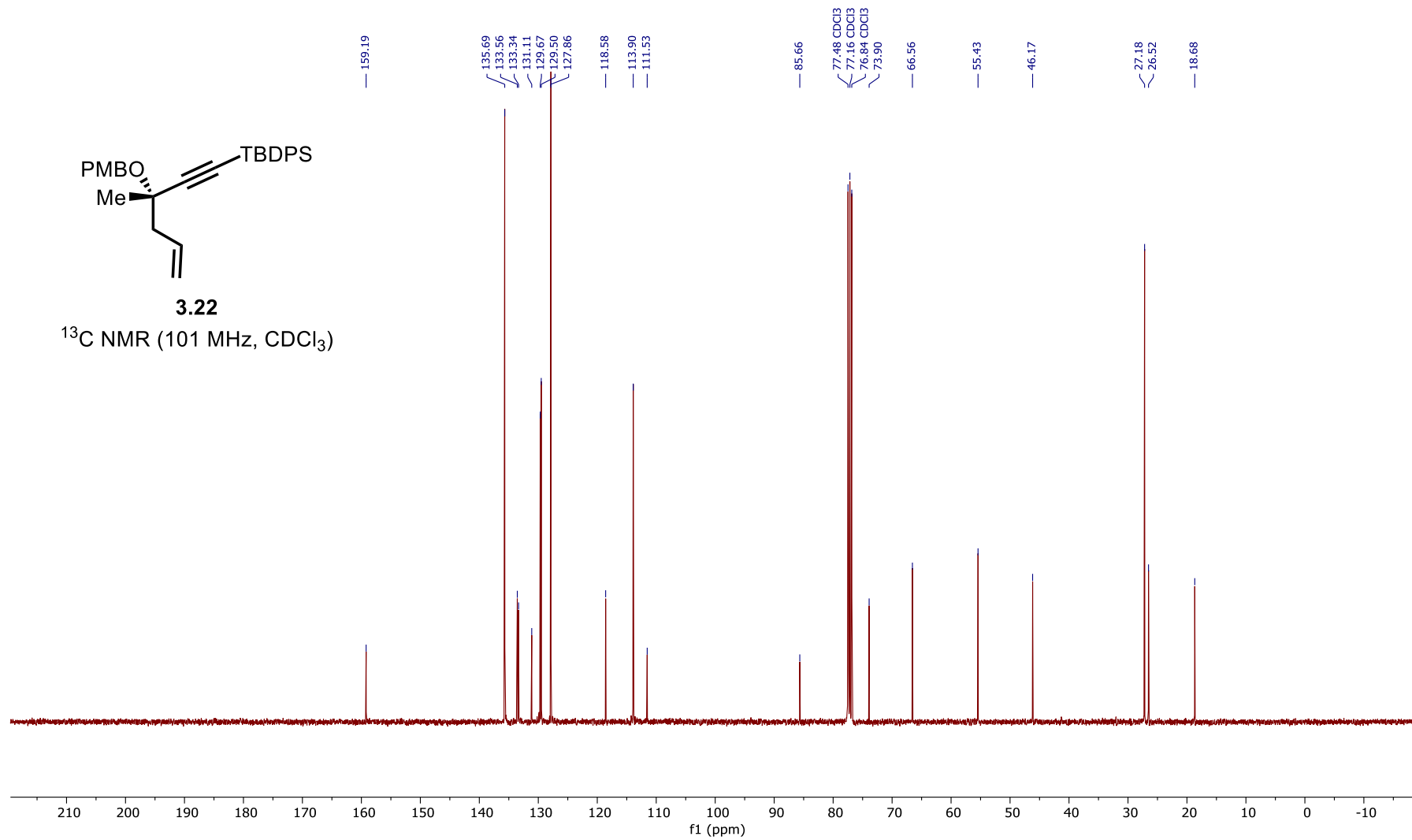


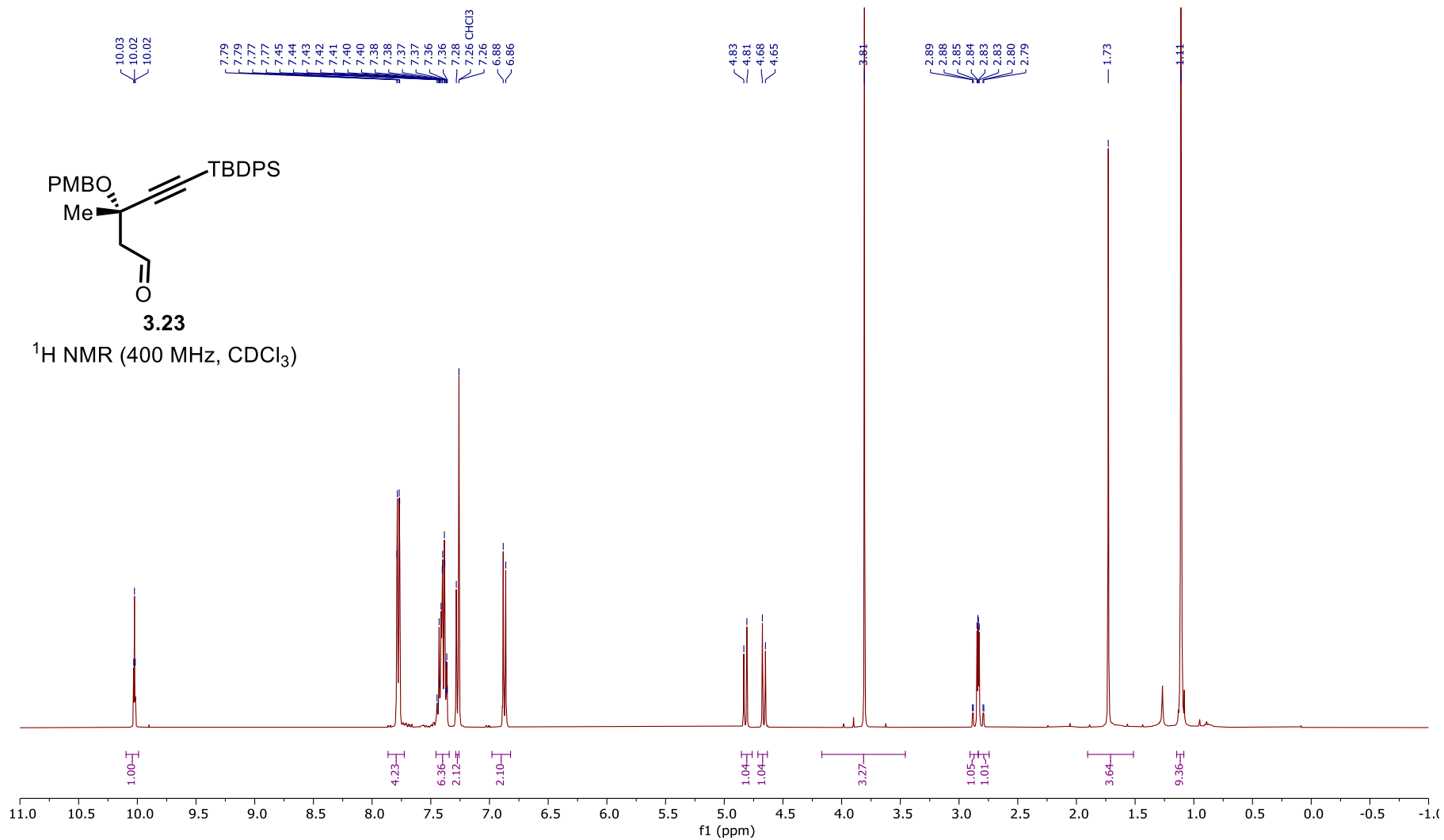


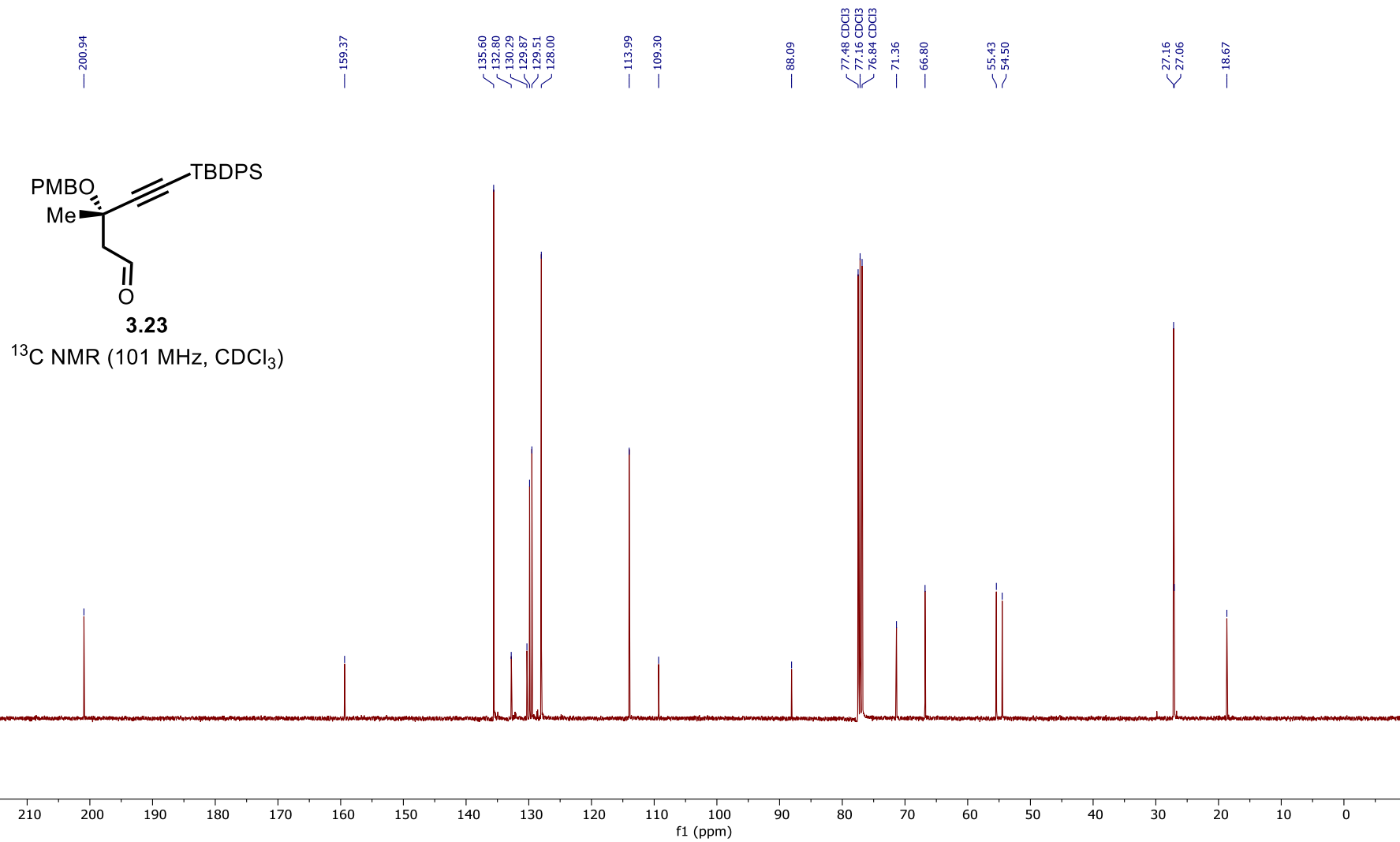


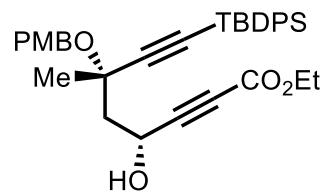
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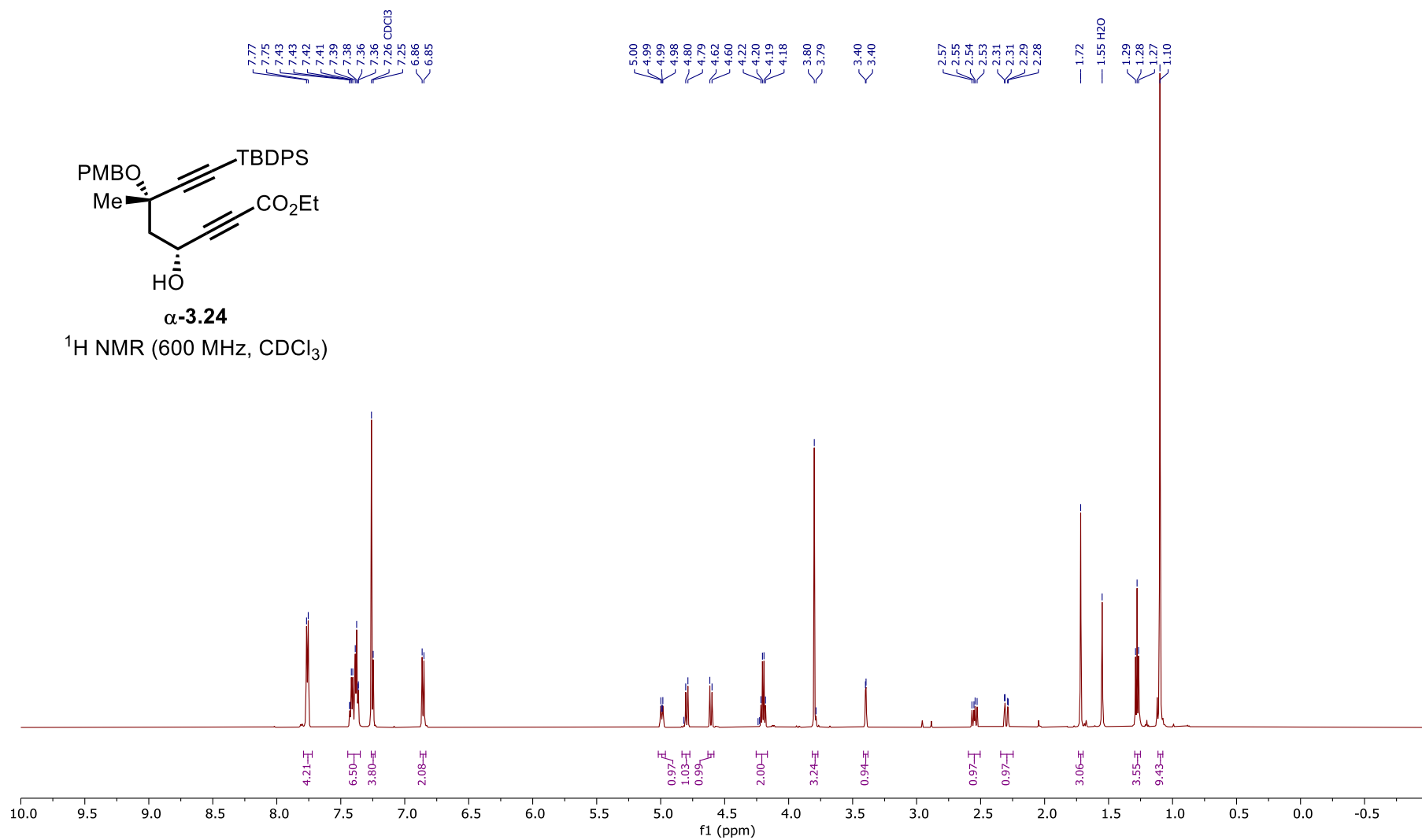


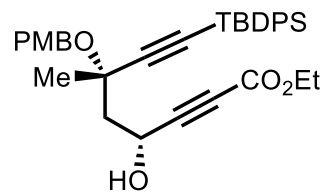




α-3.24

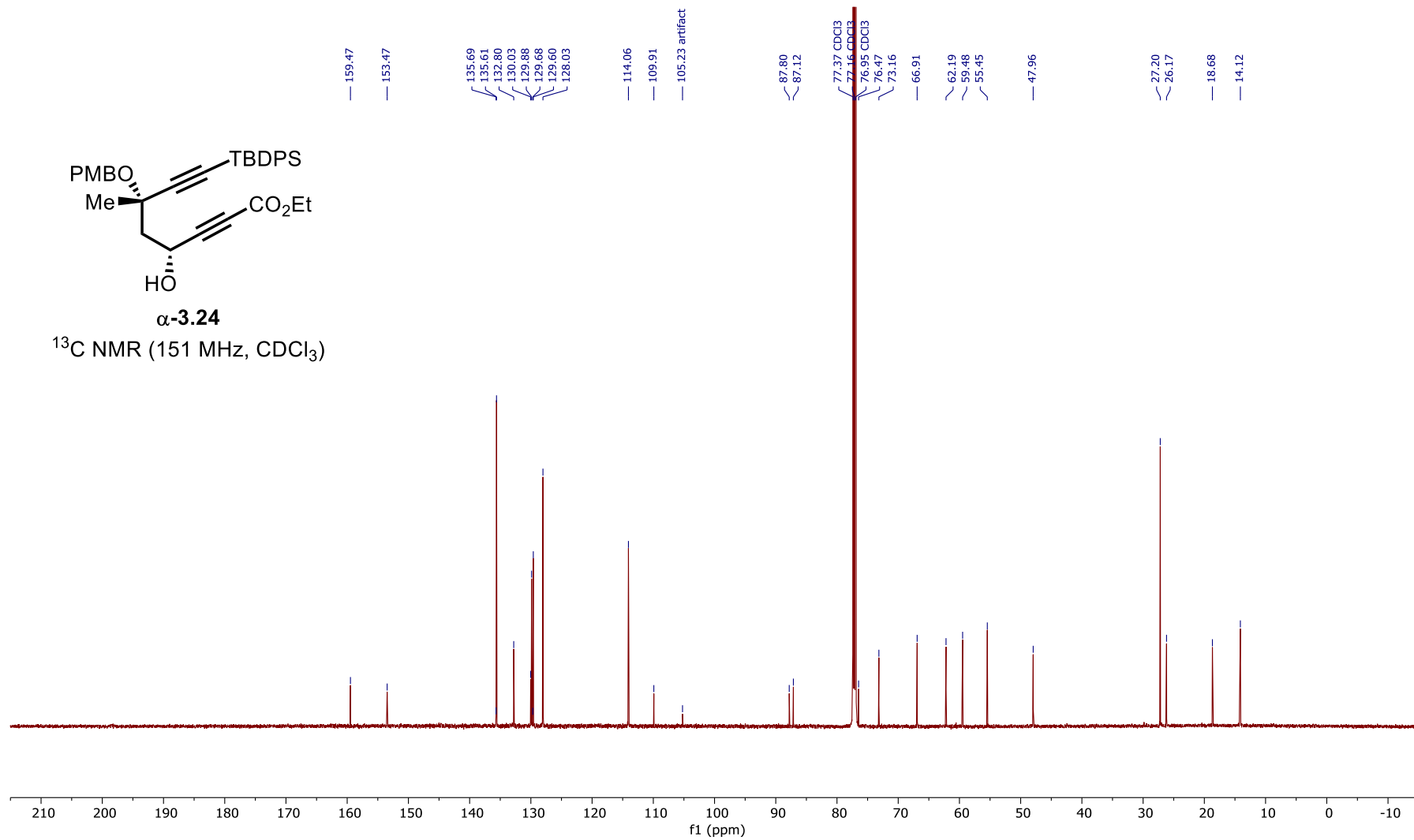
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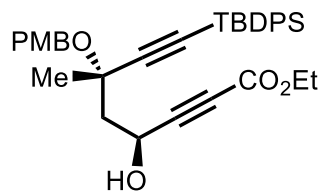




α-3.24

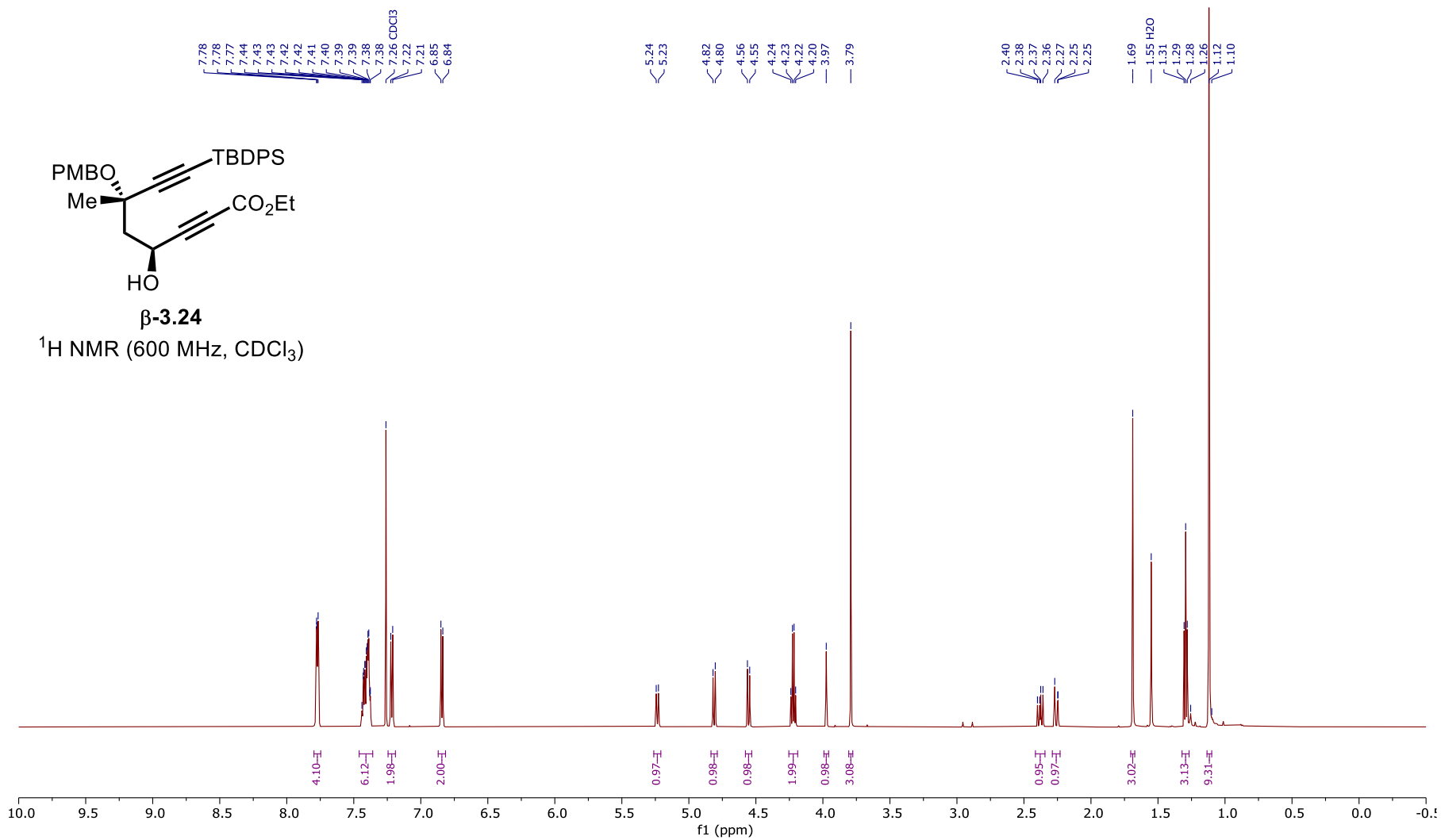
^{13}C NMR (151 MHz, CDCl_3)

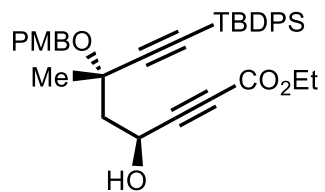




β -3.24

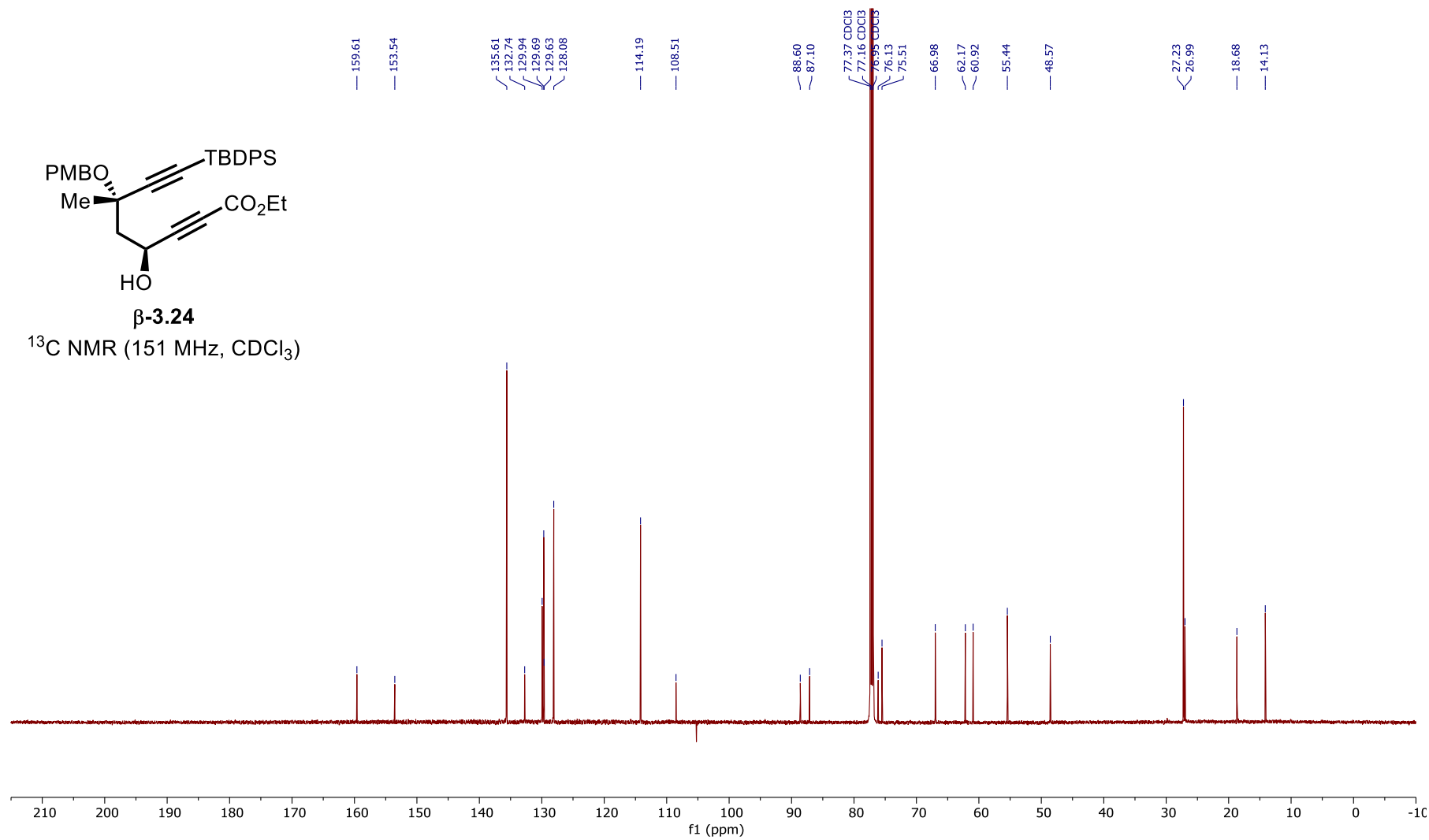
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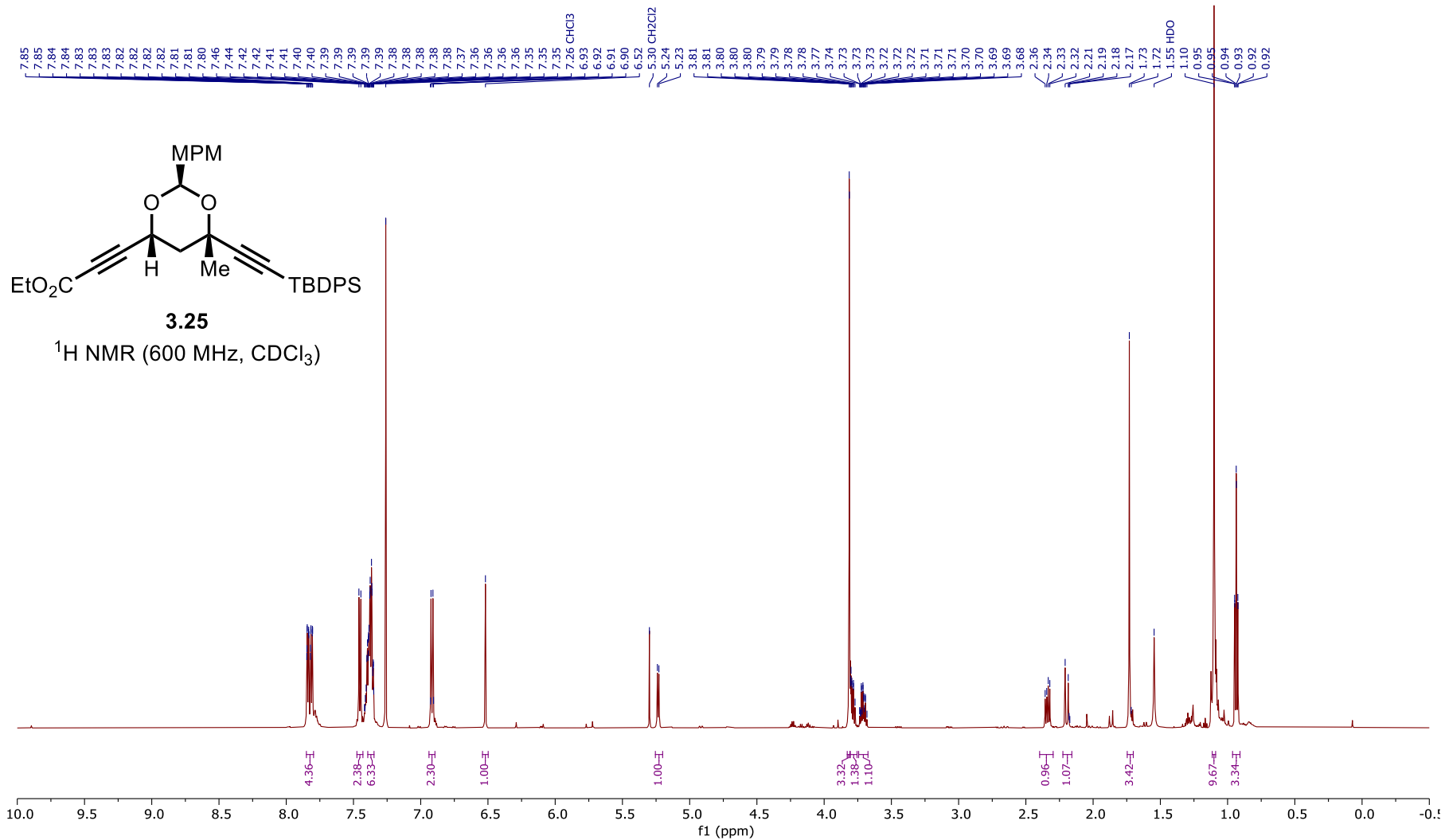


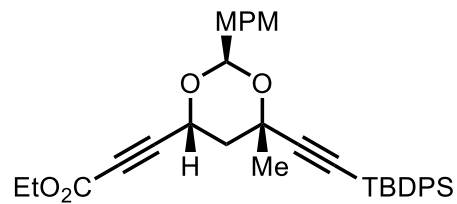


β -3.24

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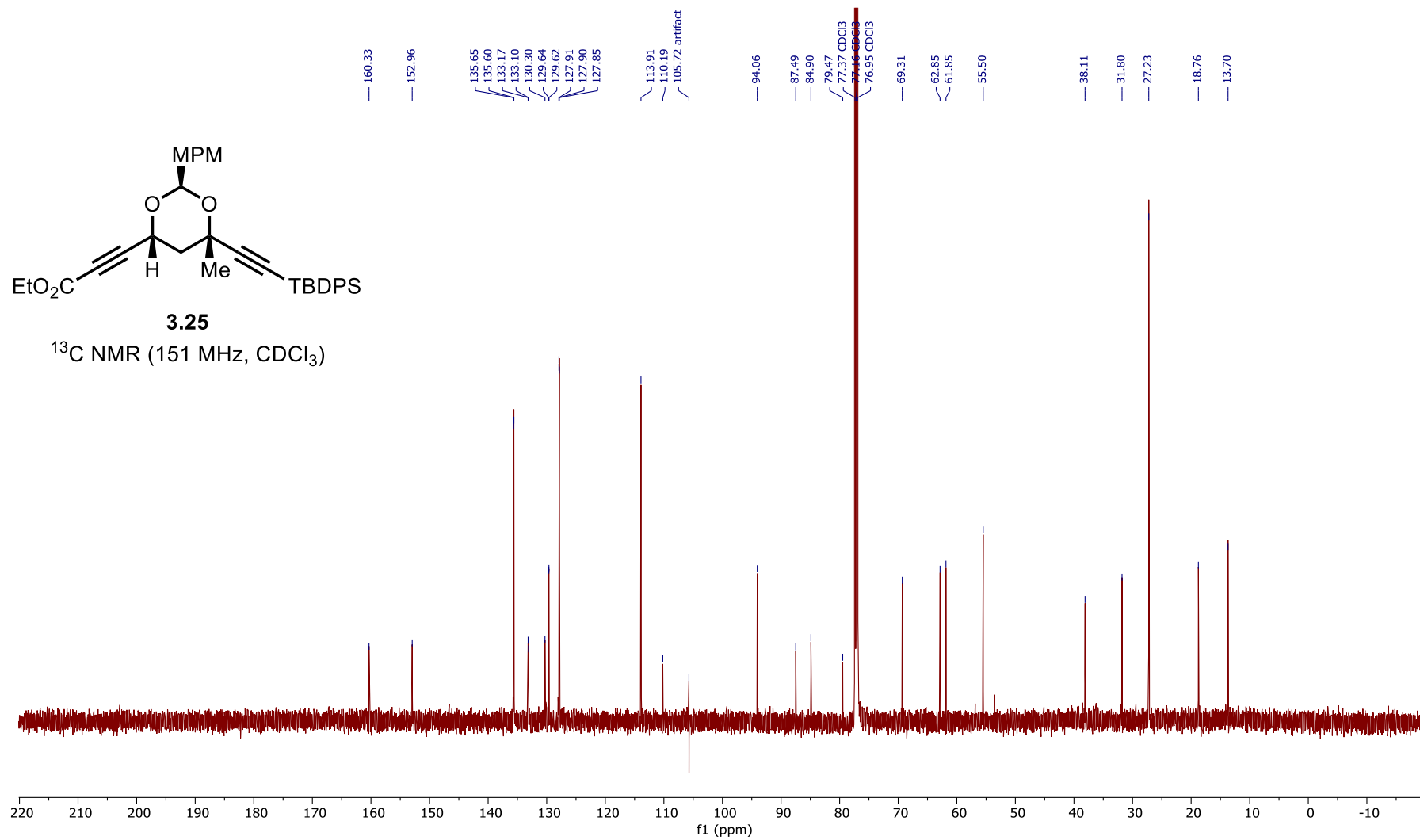


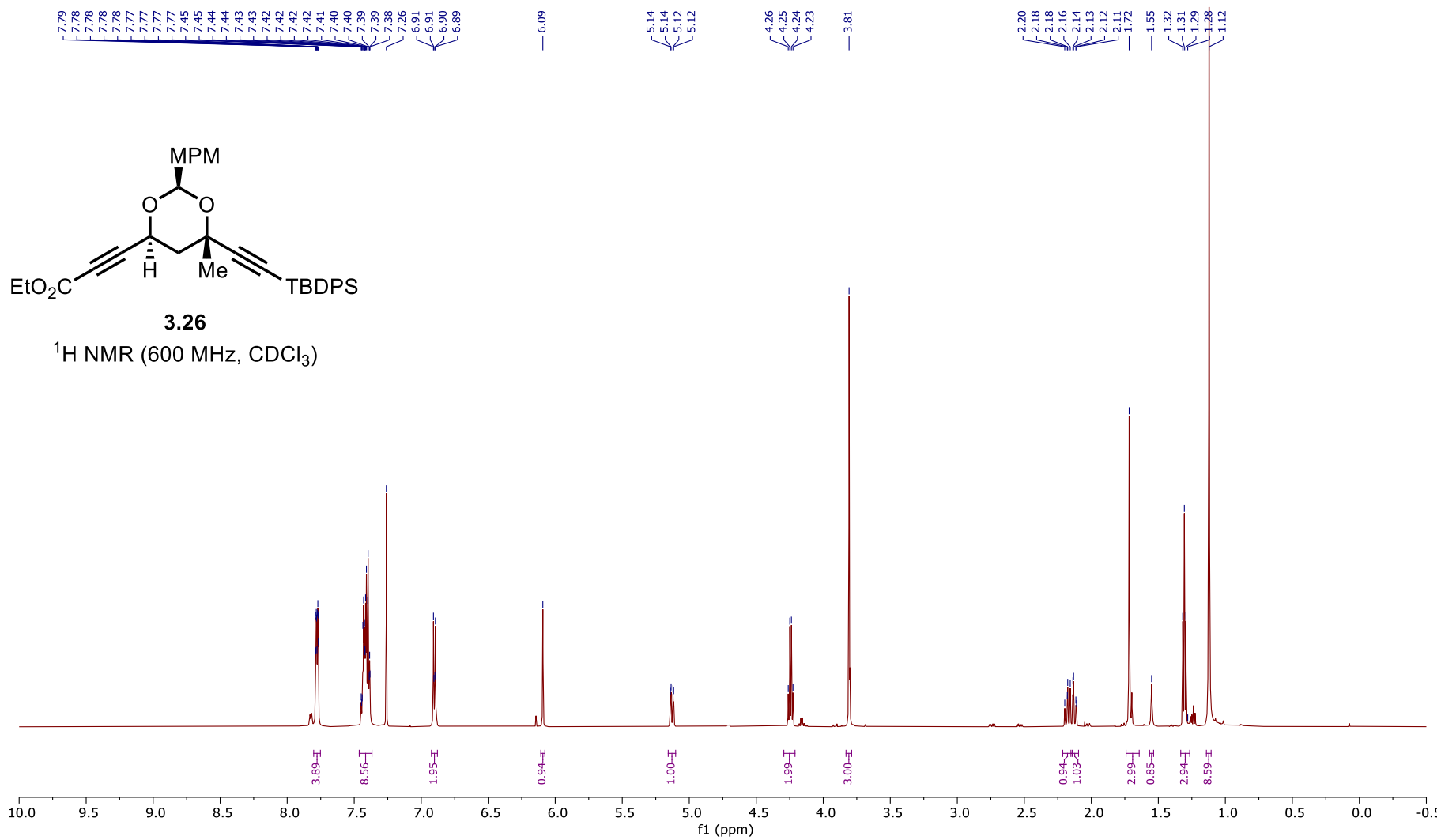


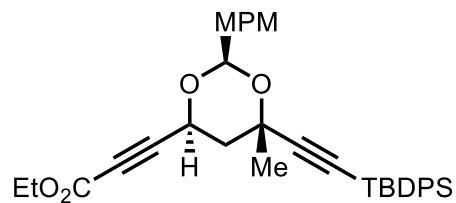


3.25

¹³C NMR (151 MHz, CDCl₃)

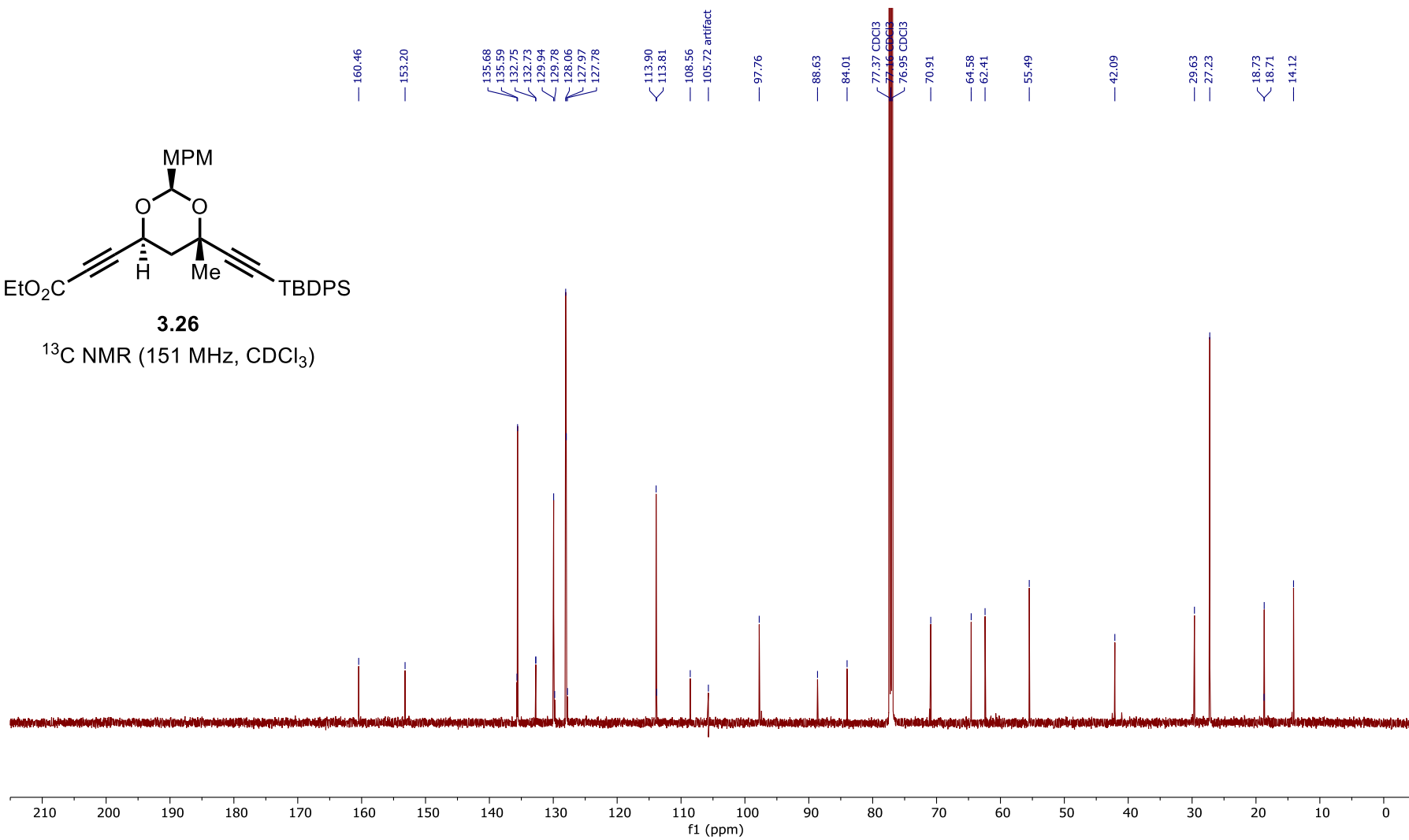


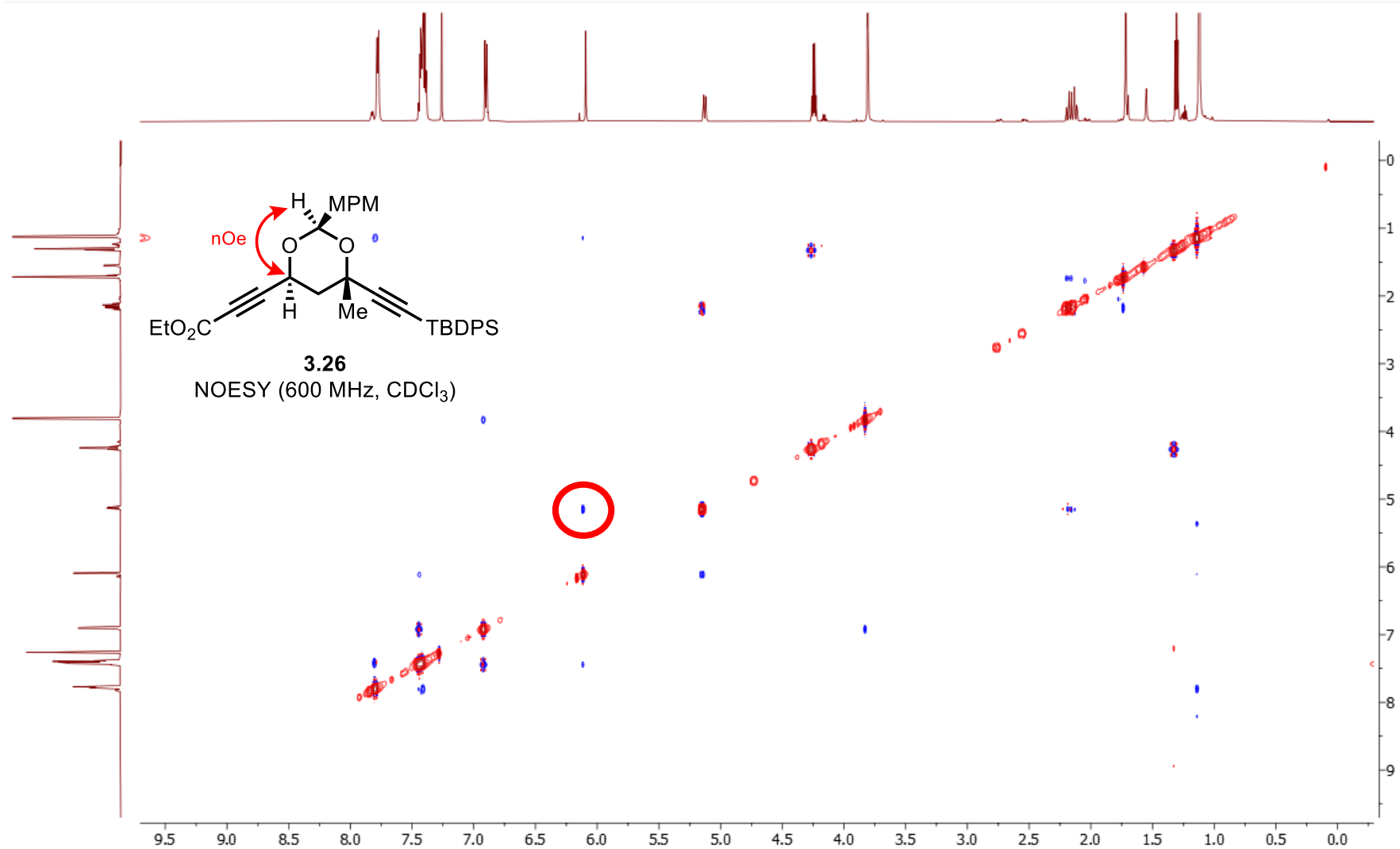


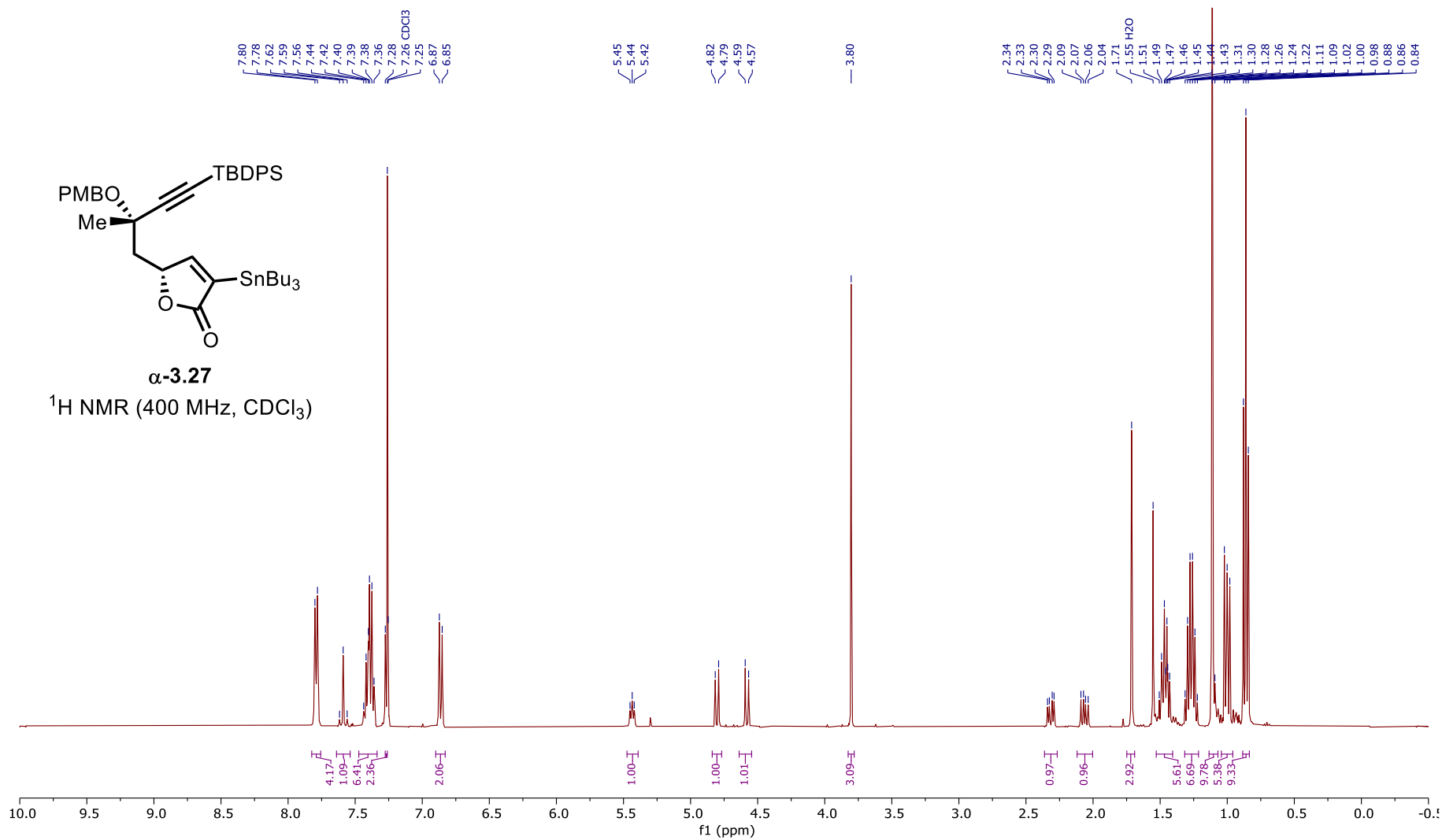


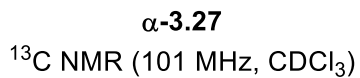
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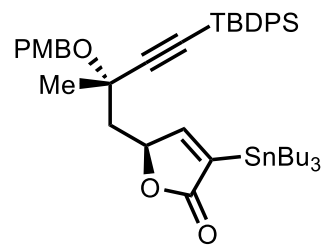
¹³C NMR (151 MHz, CDCl₃)





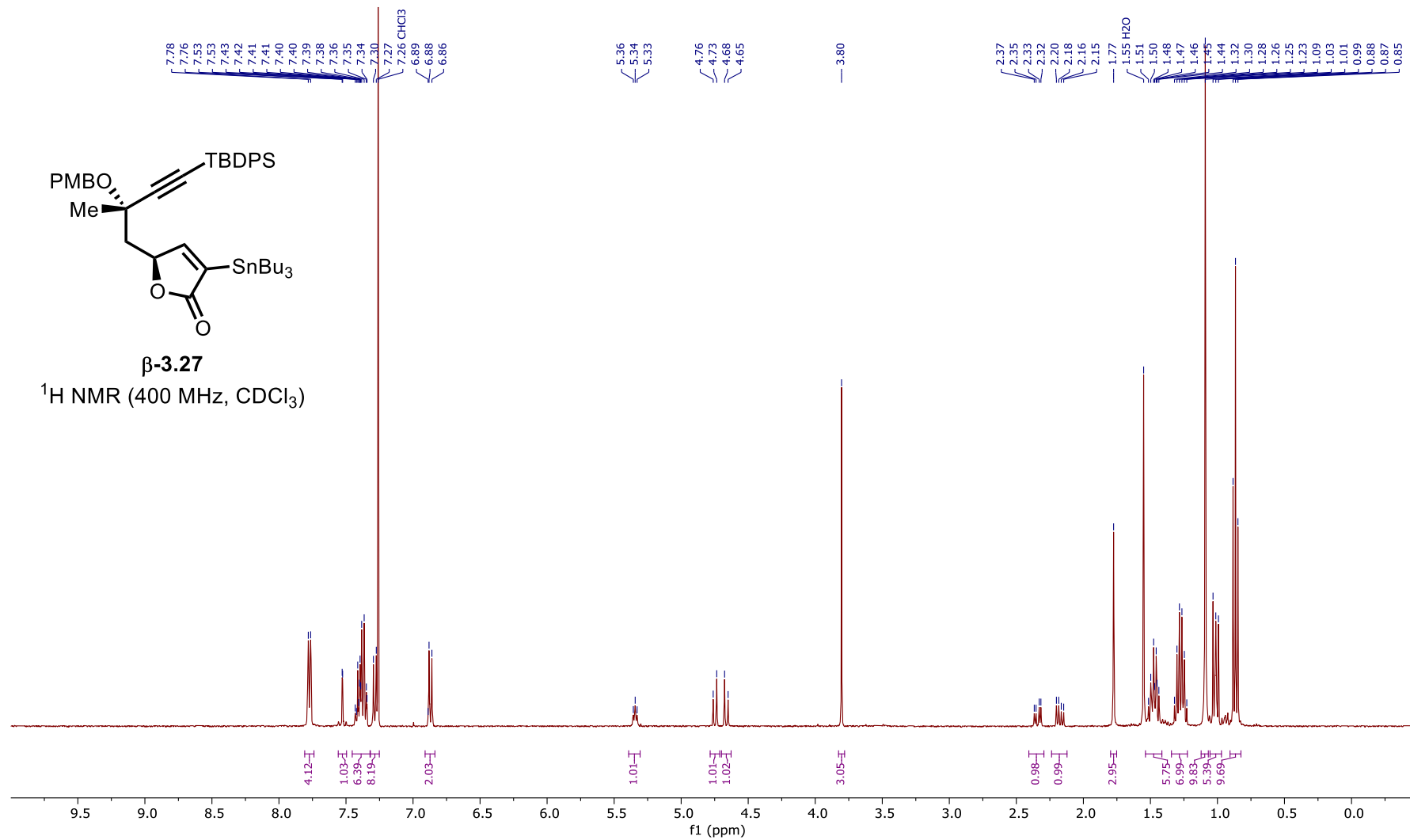


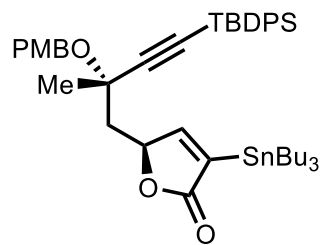




β -3.27

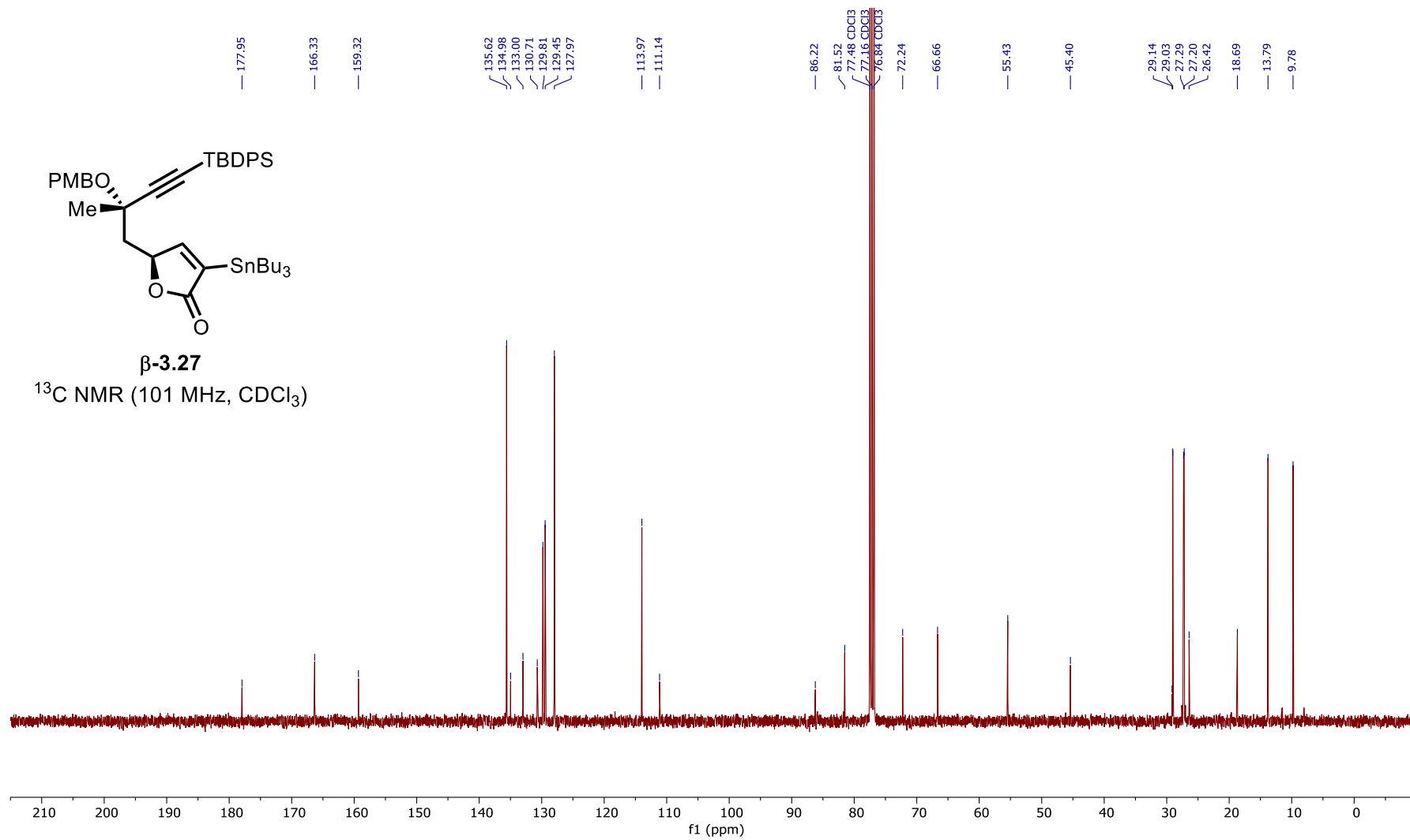
^1H NMR (400 MHz, CDCl_3)

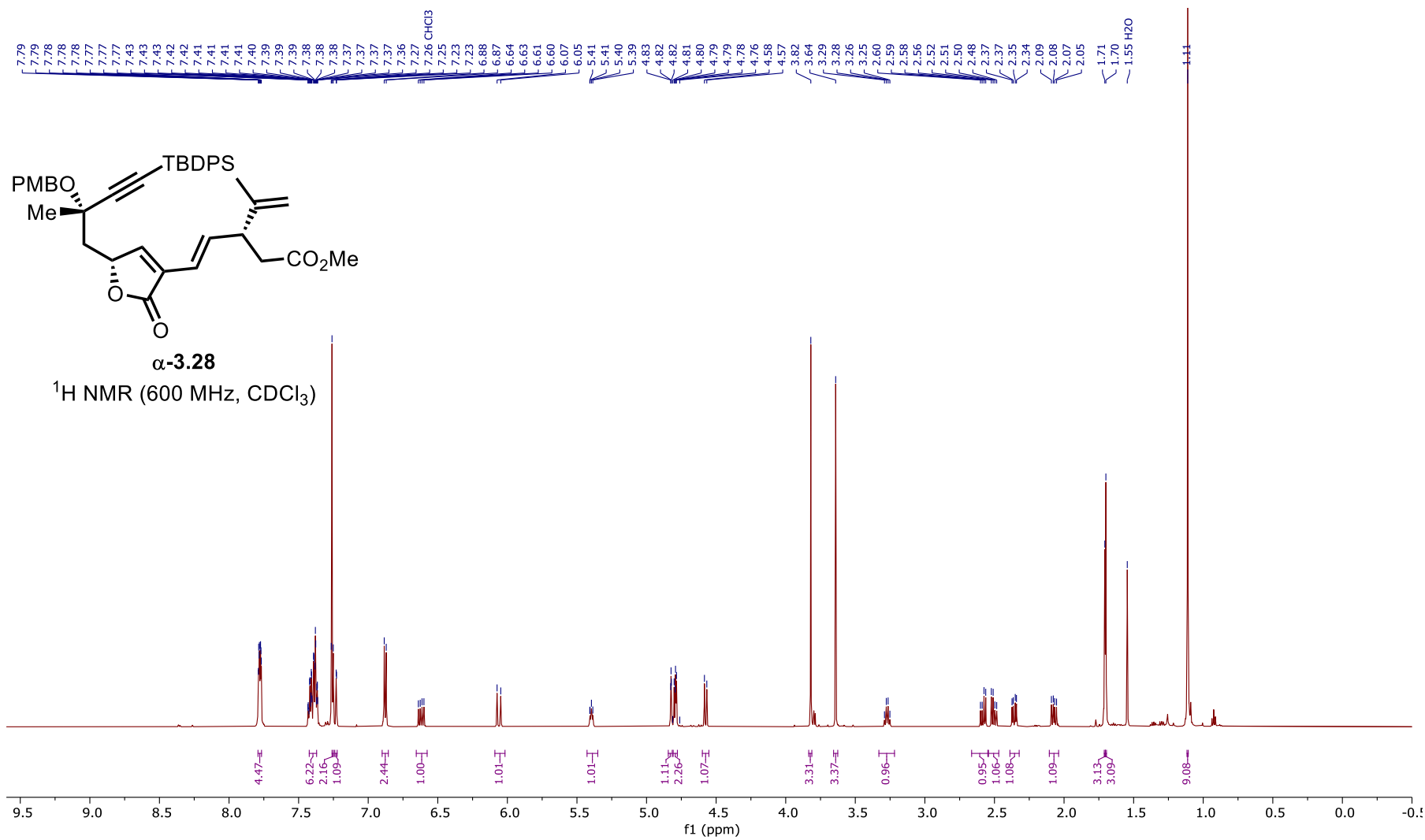


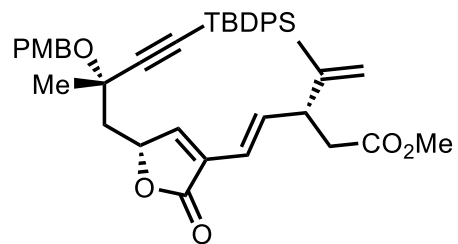


β -3.27

^{13}C NMR (101 MHz, CDCl_3)

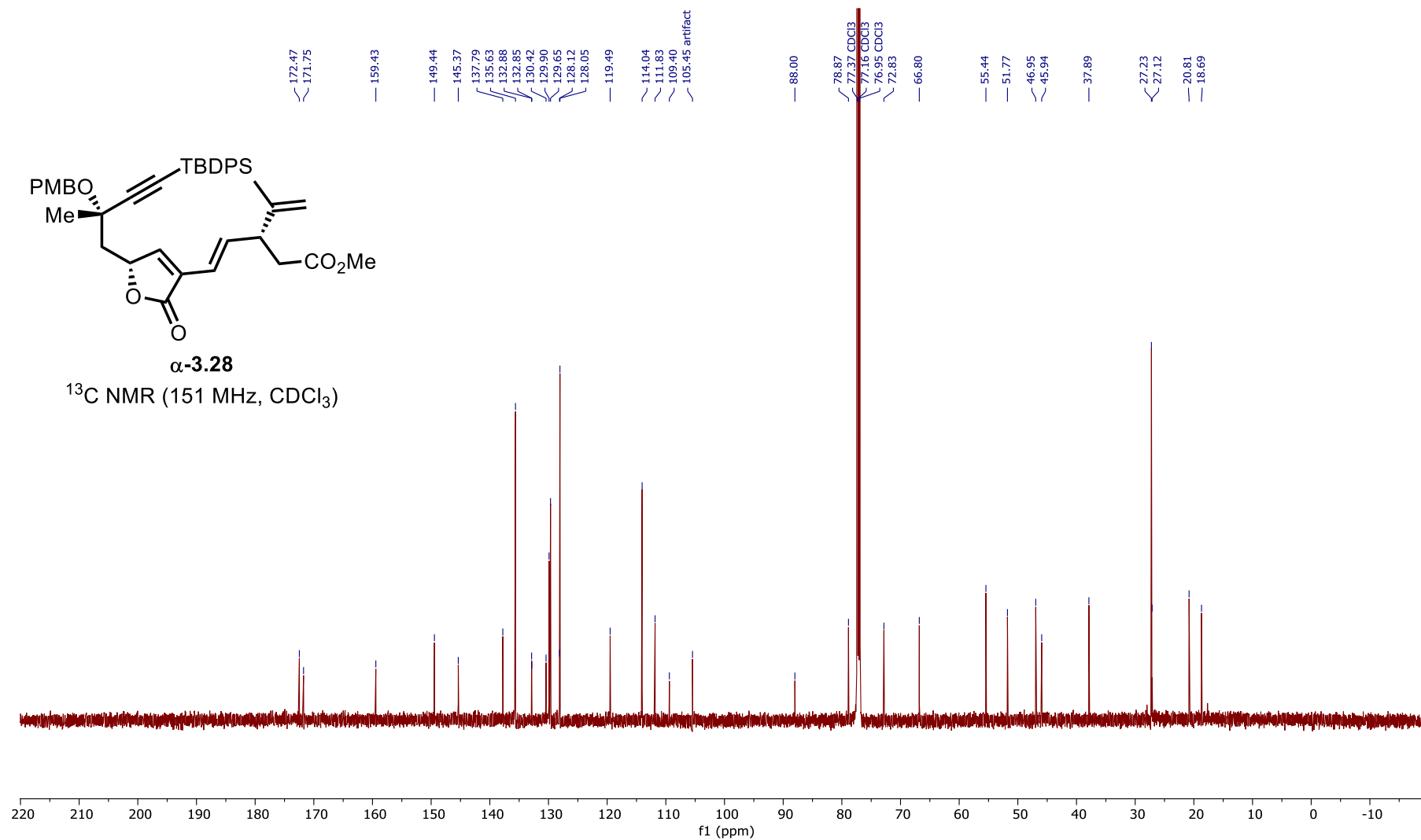


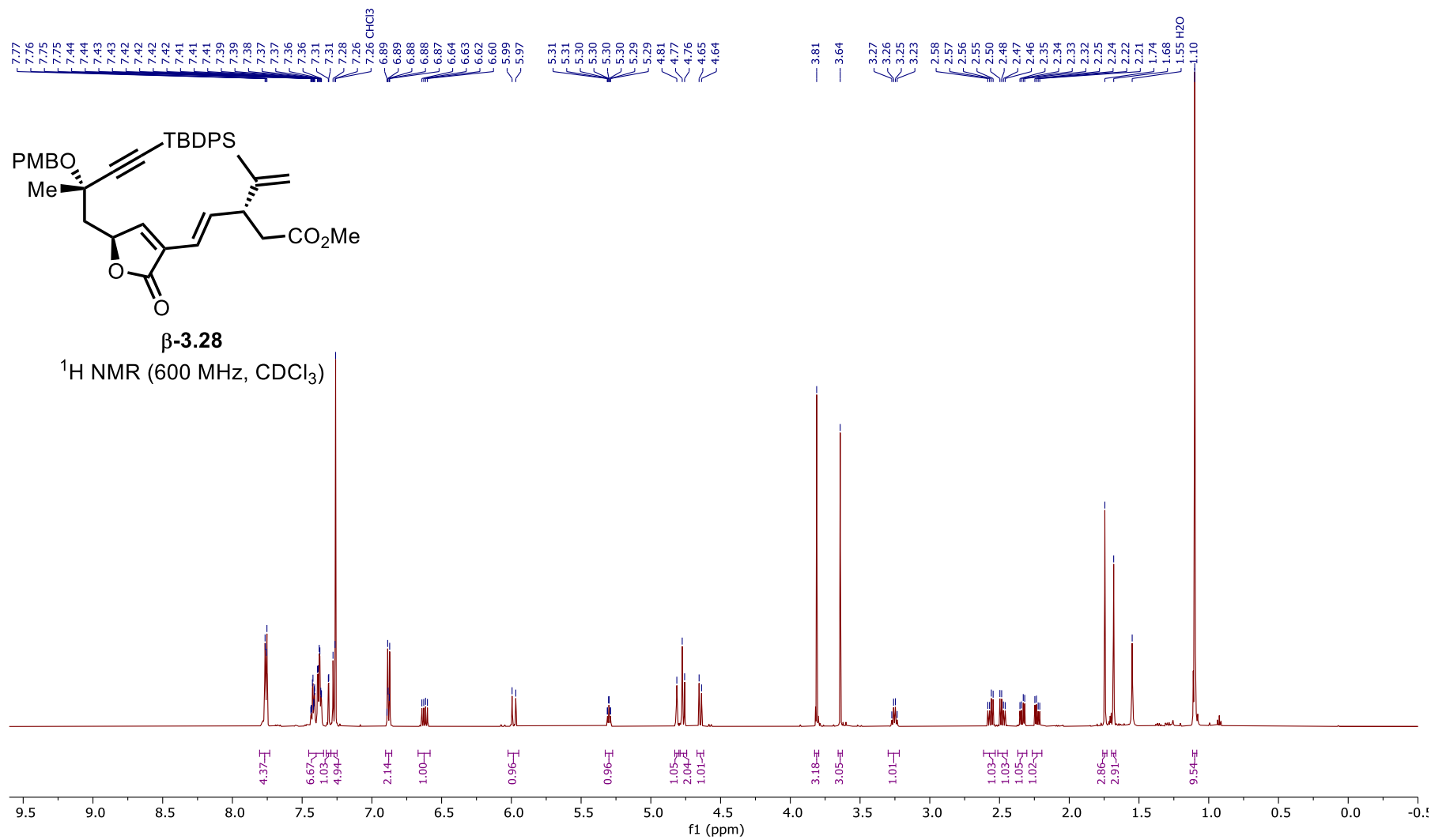


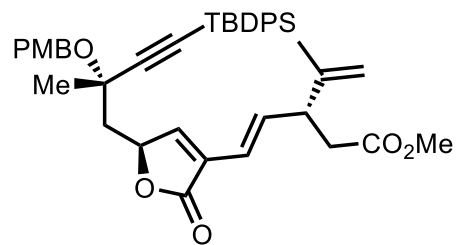


α -3.28

^{13}C NMR (151 MHz, CDCl_3)

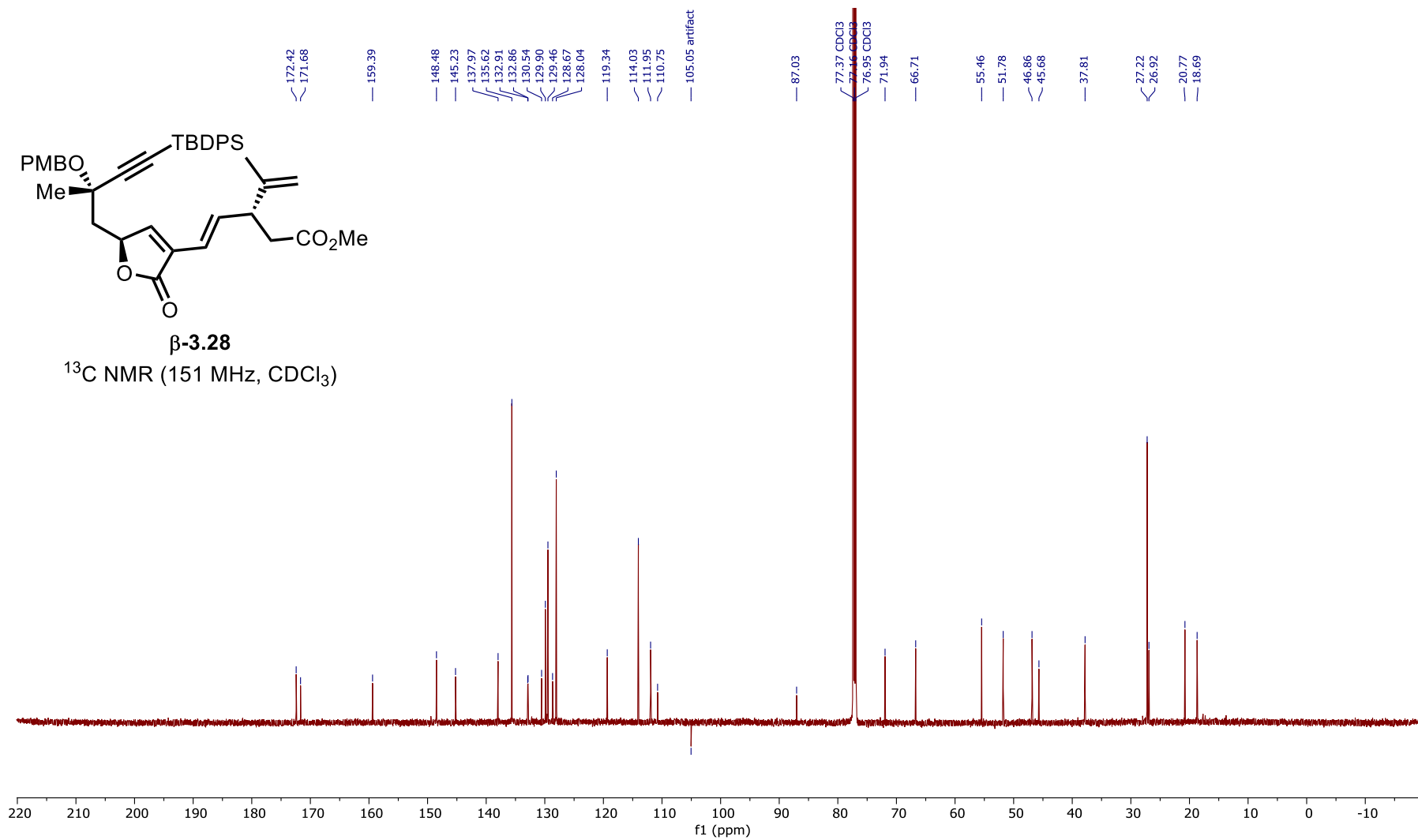


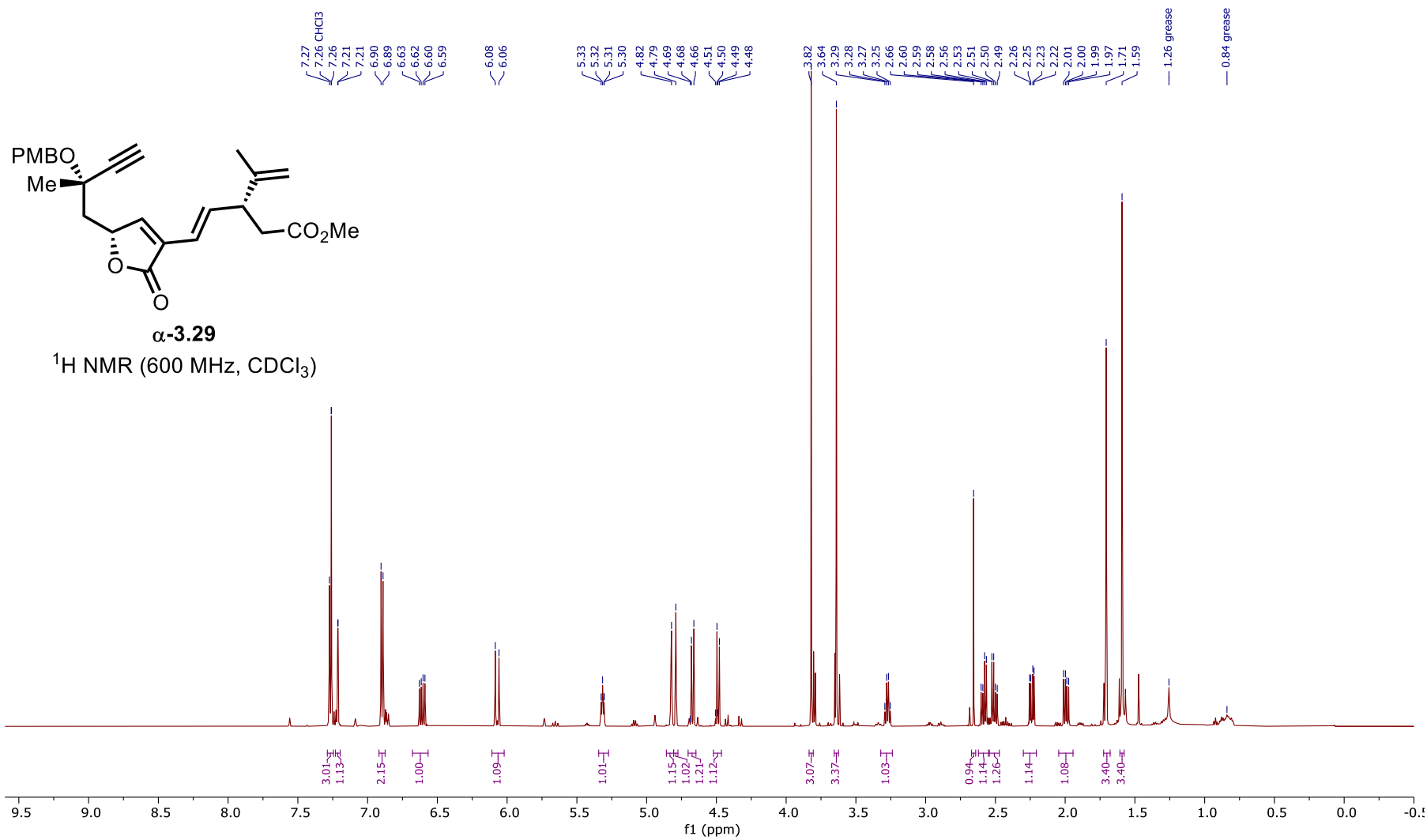


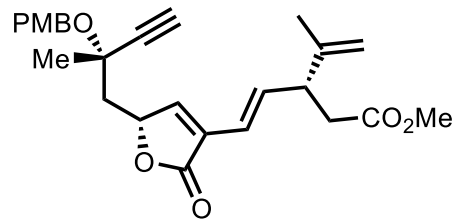


β -3.28

^{13}C NMR (151 MHz, CDCl_3)

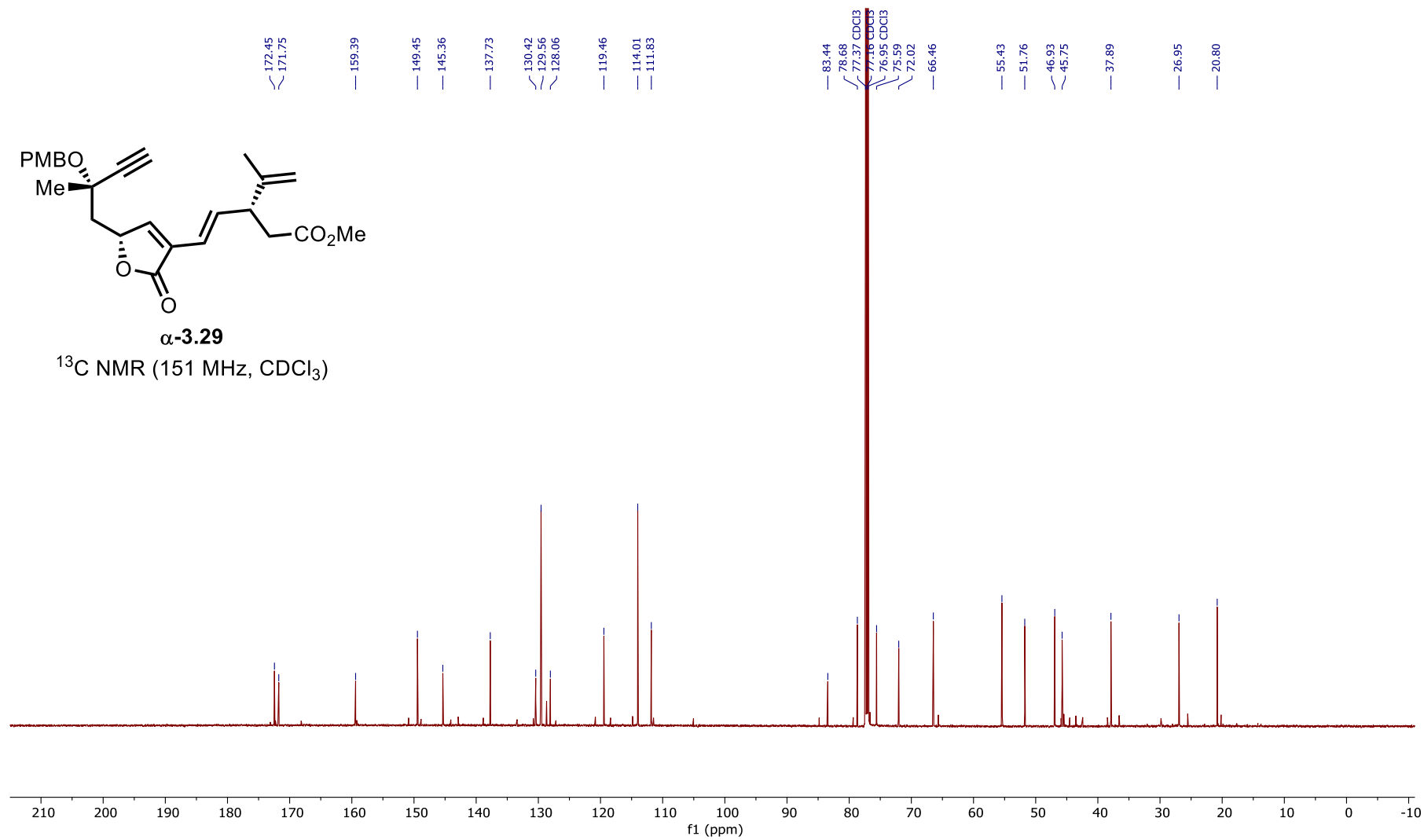


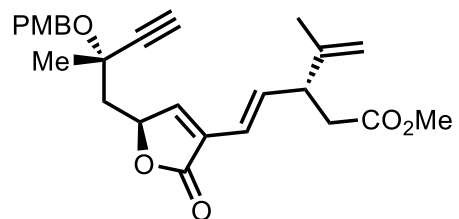




α-3.29

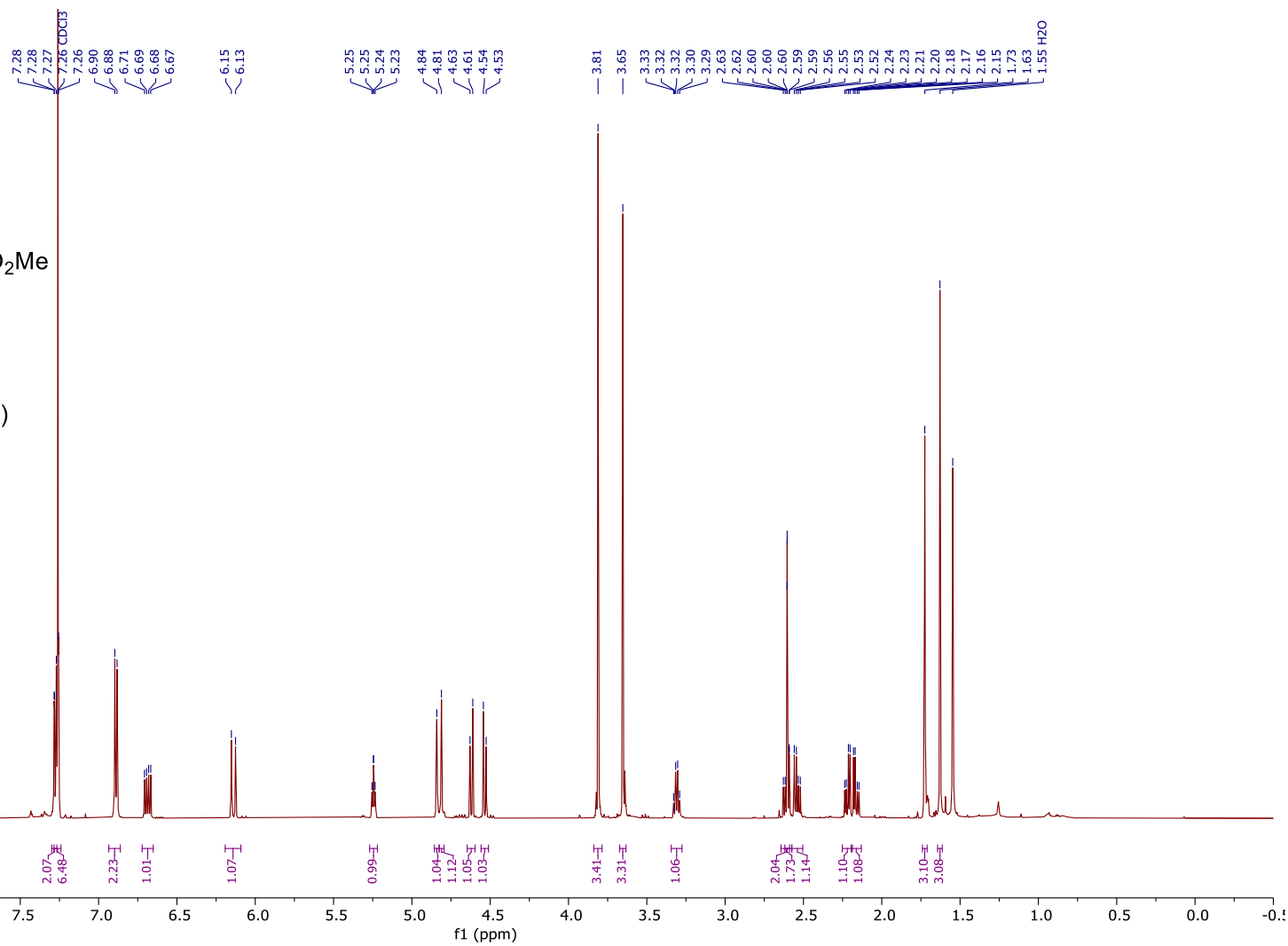
^{13}C NMR (151 MHz, CDCl_3)

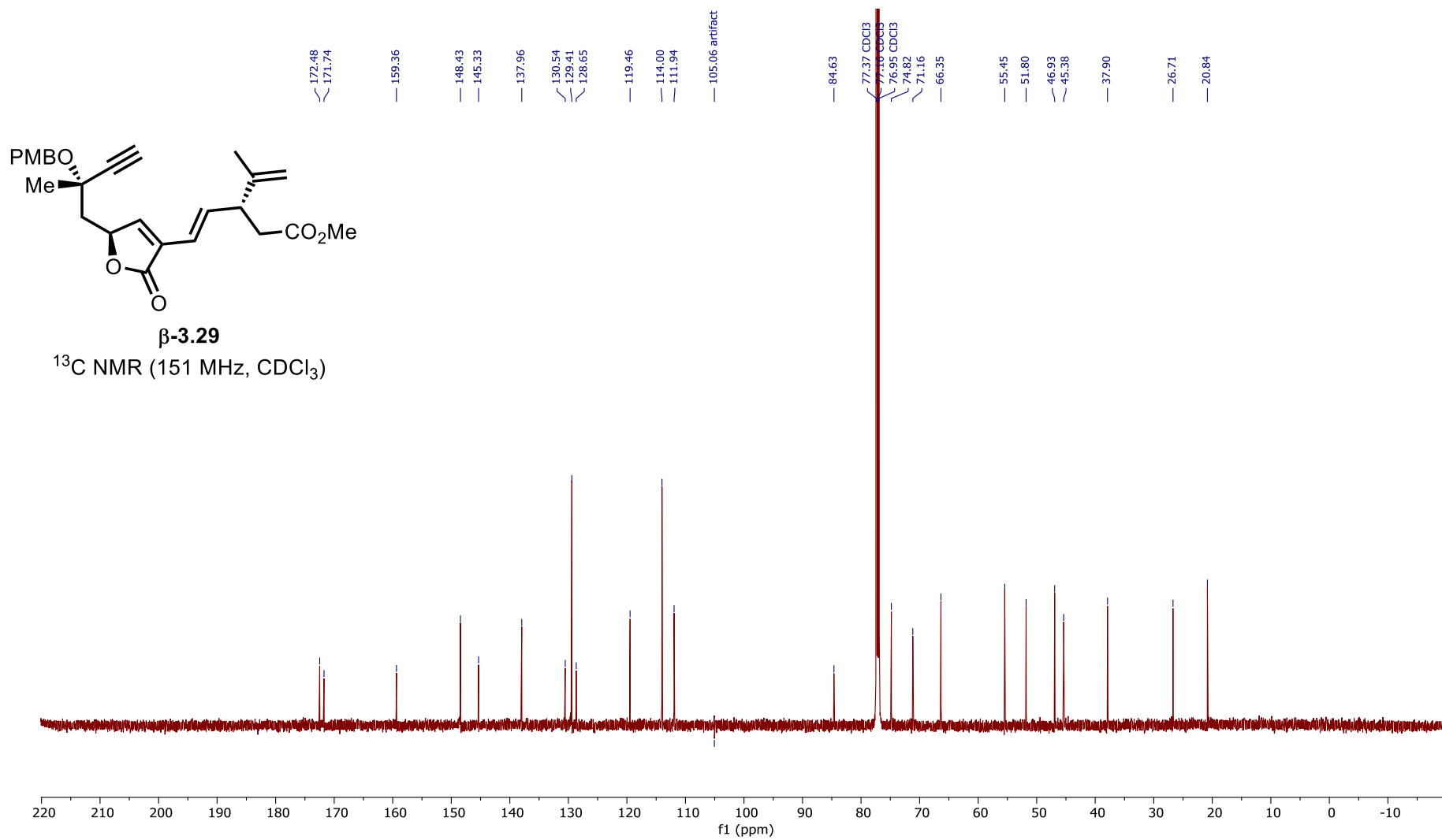


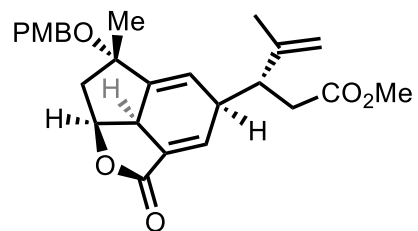


β -3.29

^1H NMR (600 MHz, CDCl_3)

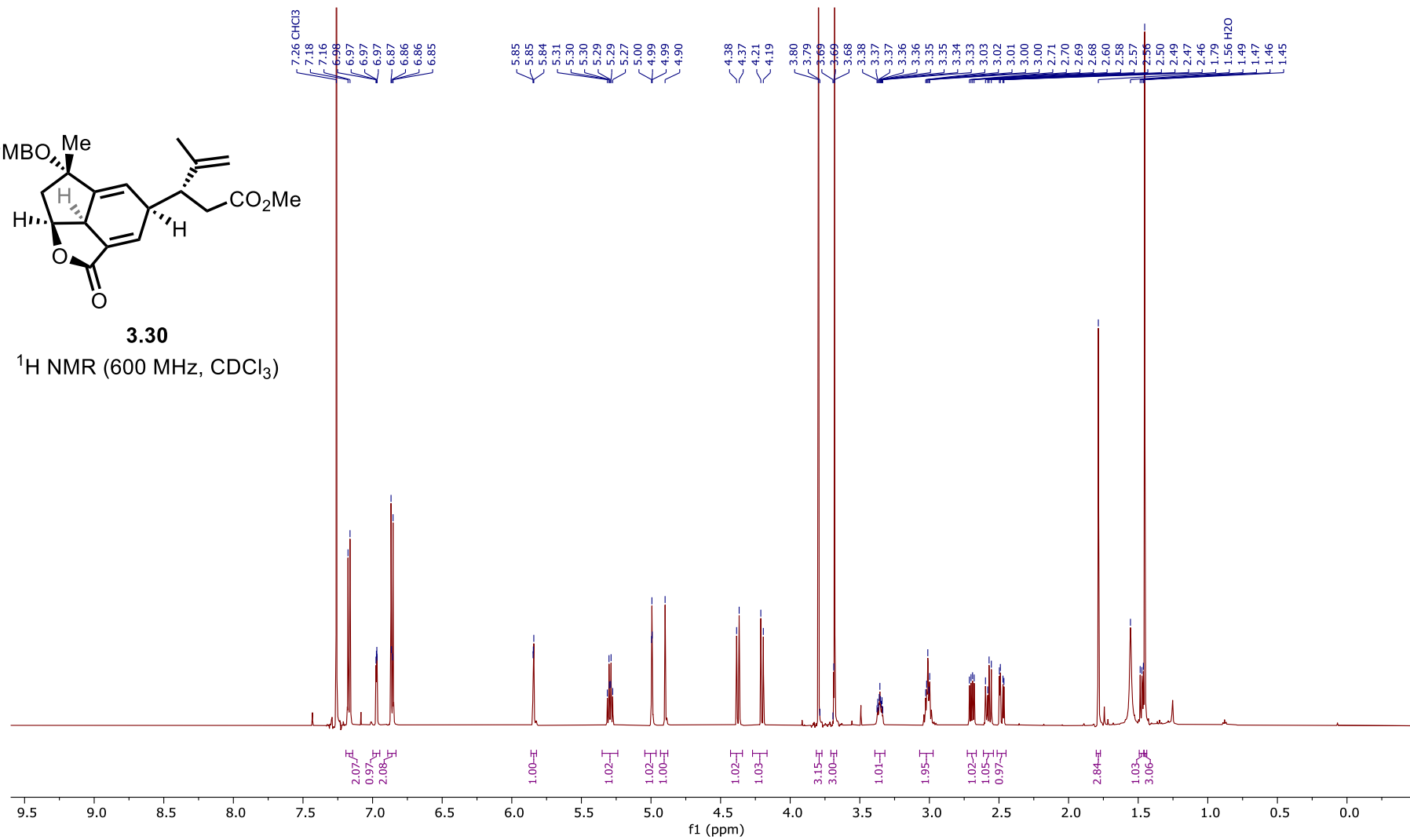


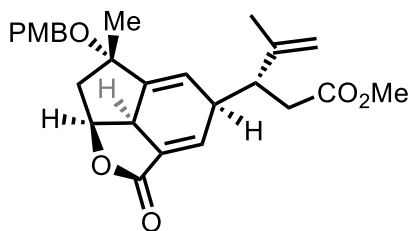




3.30

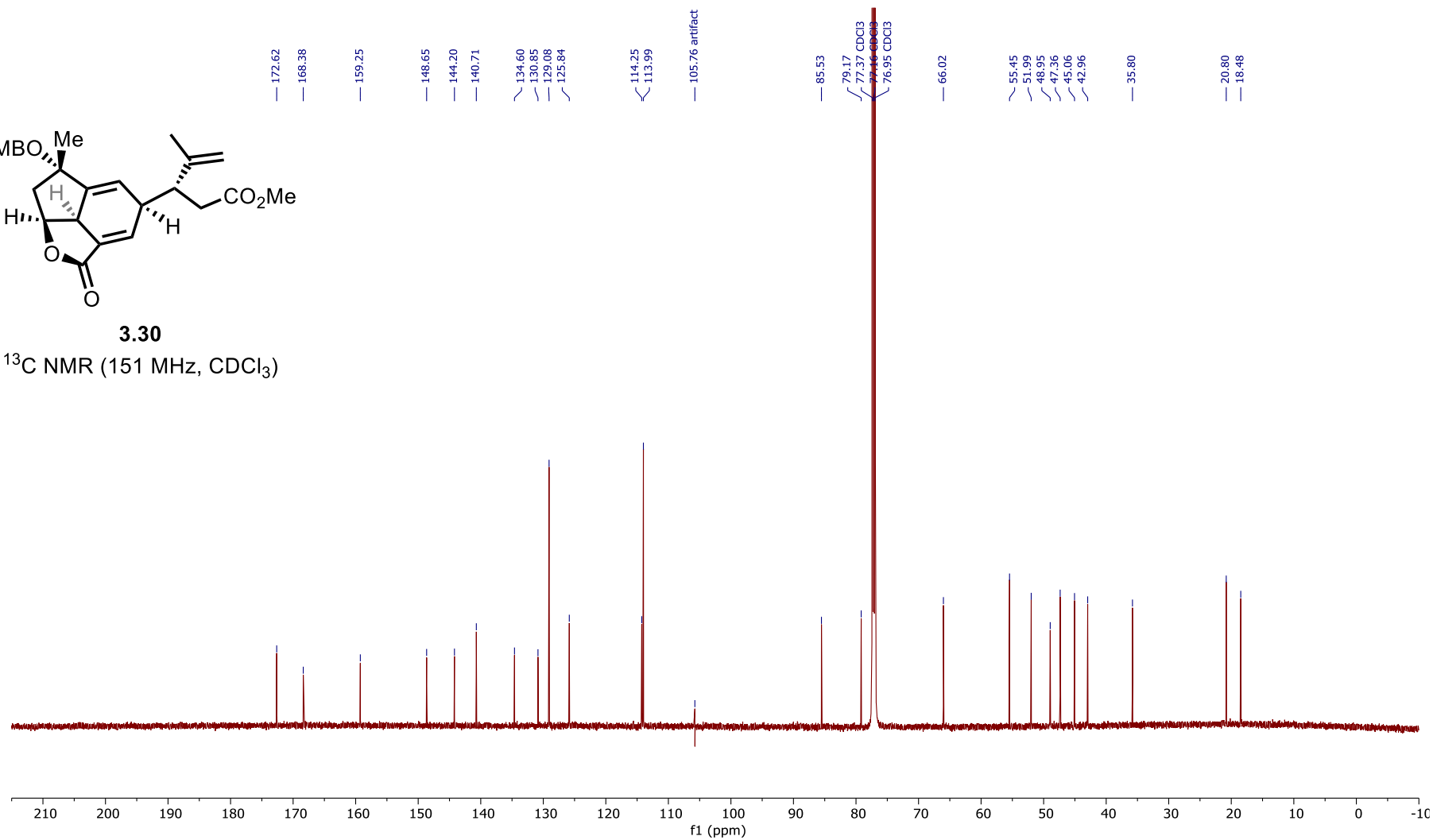
^1H NMR (600 MHz, CDCl_3)

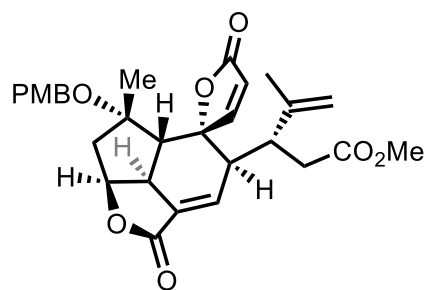




3.30

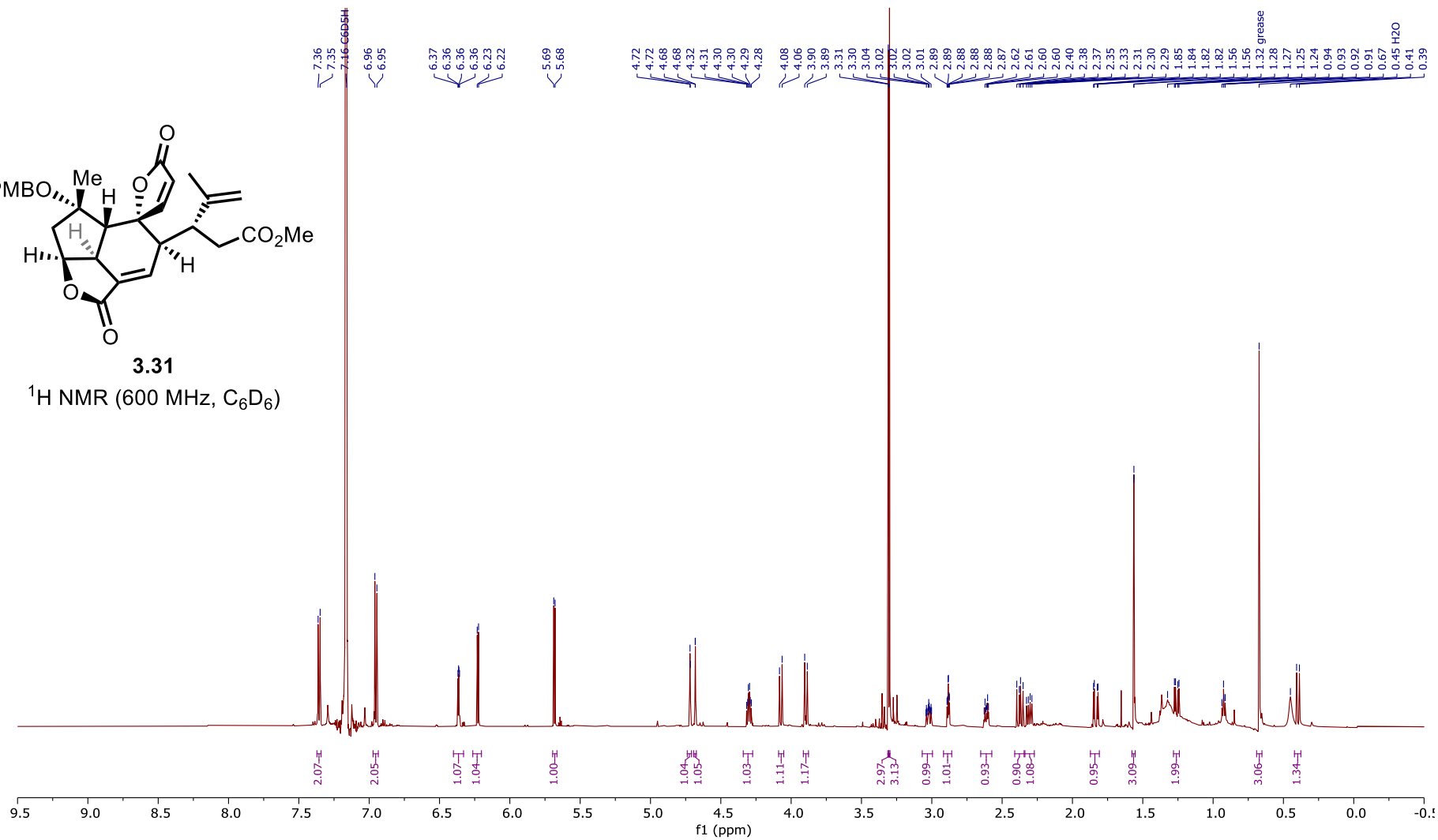
^{13}C NMR (151 MHz, CDCl_3)

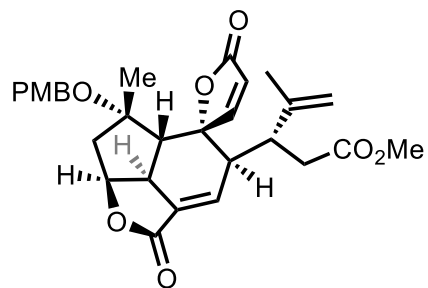




3.31

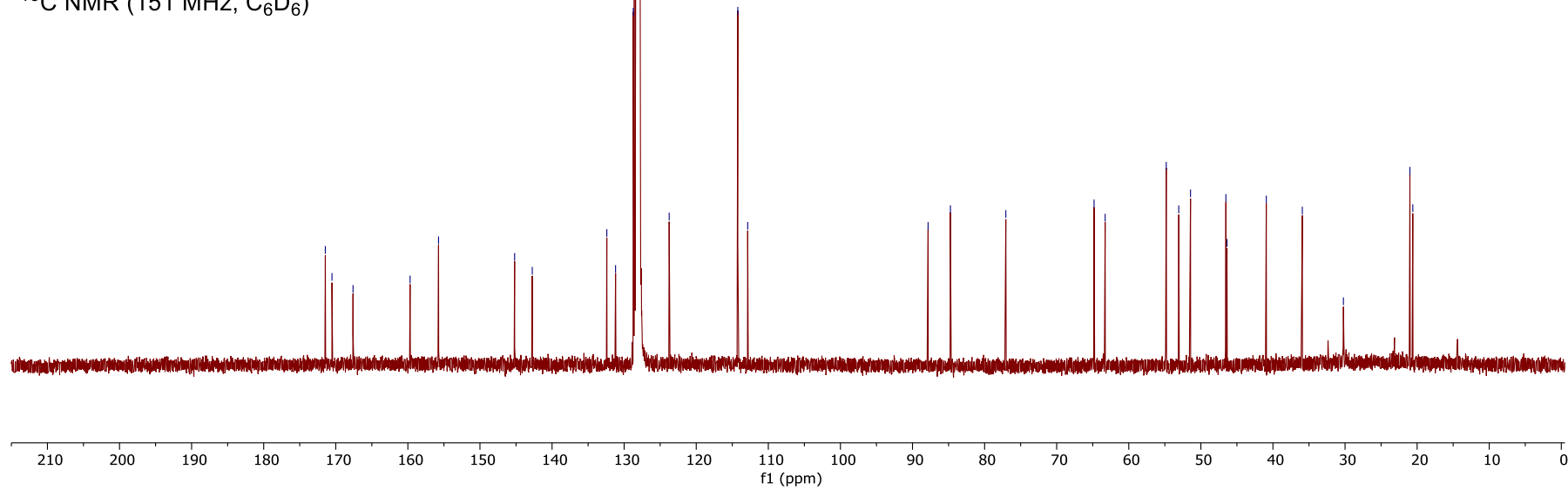
^1H NMR (600 MHz, C_6D_6)

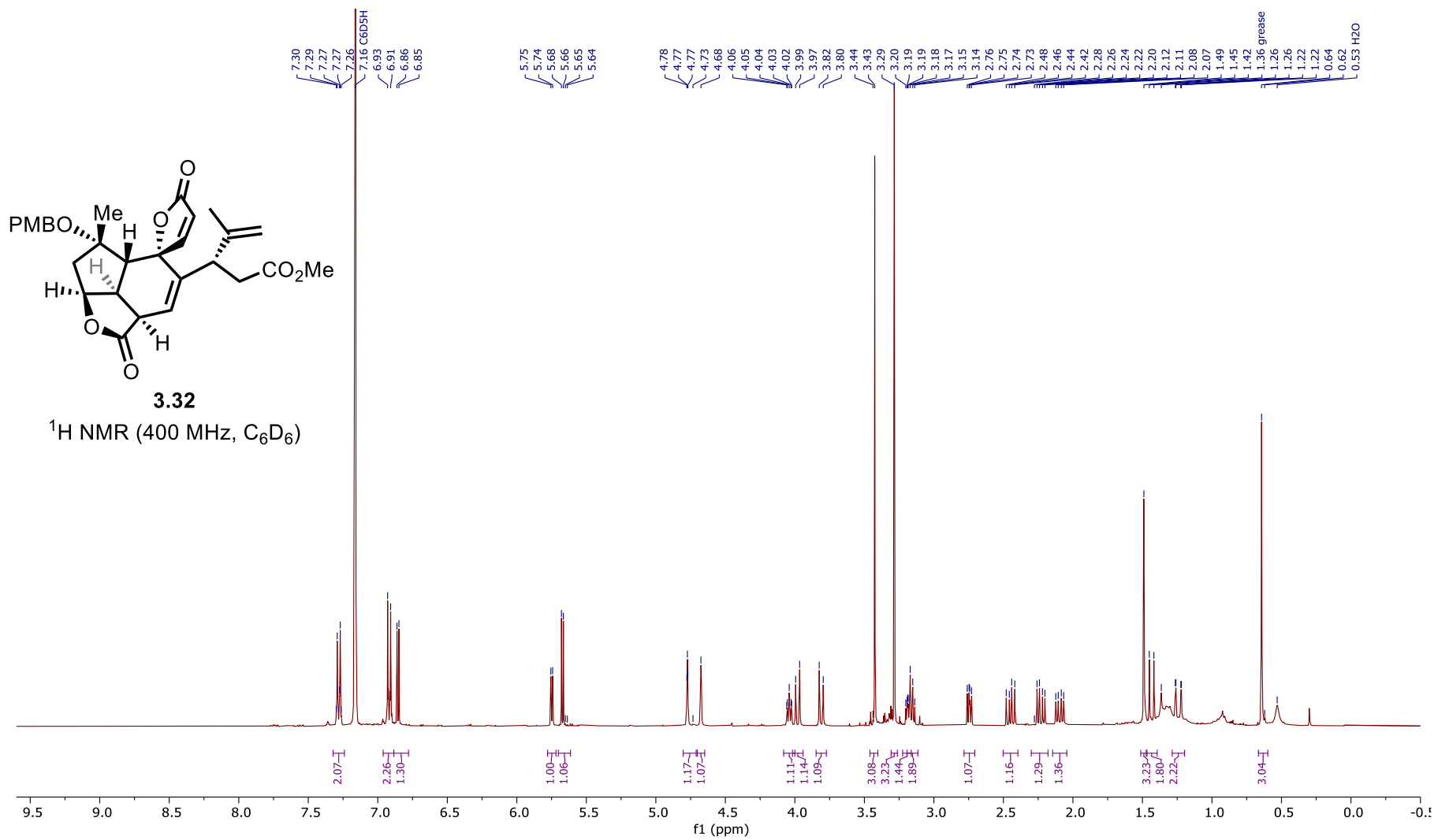


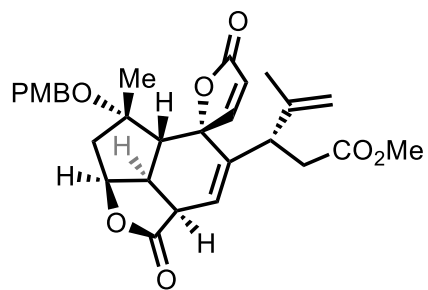


3.31

¹³C NMR (151 MHz, C₆D₆)

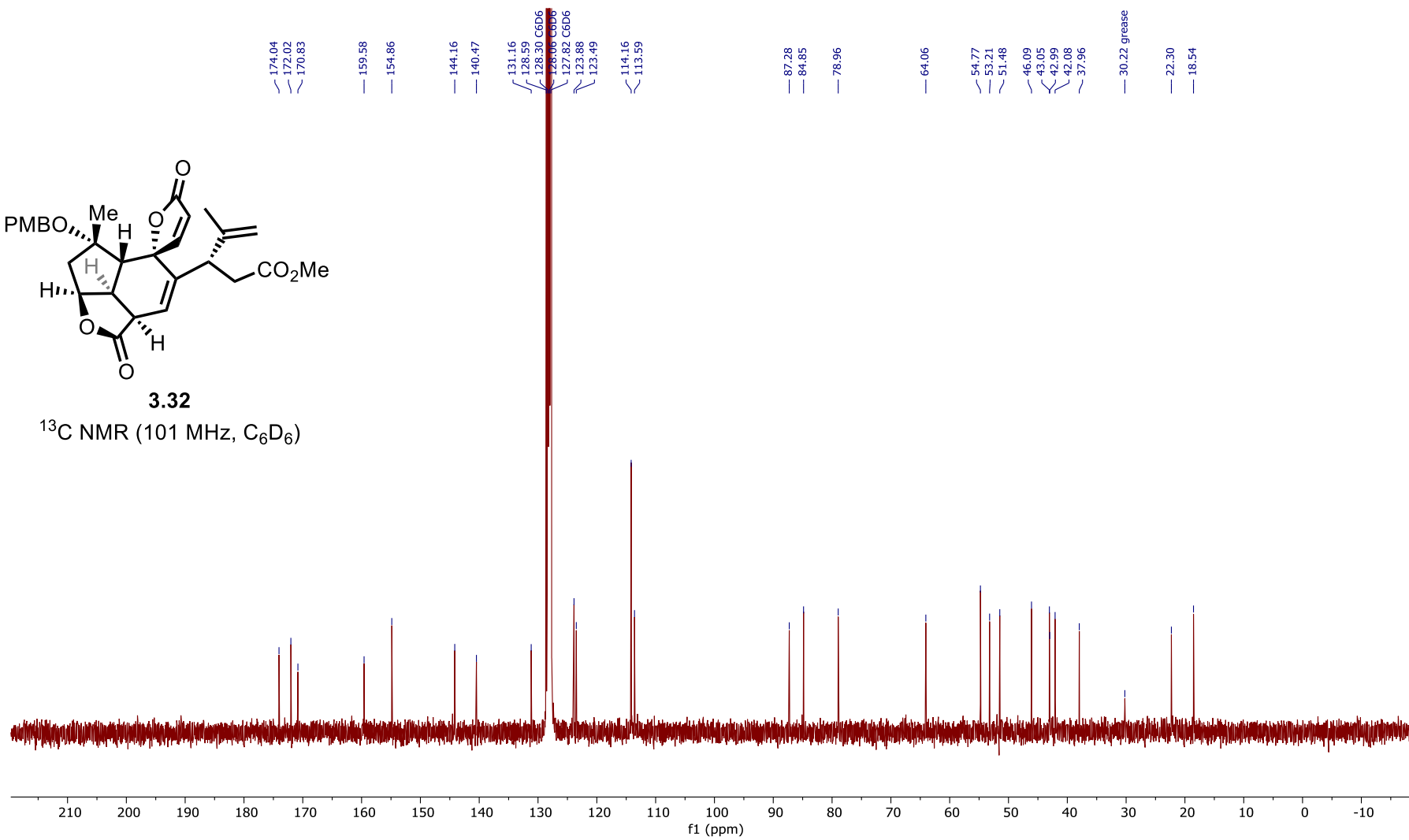


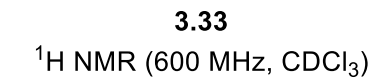


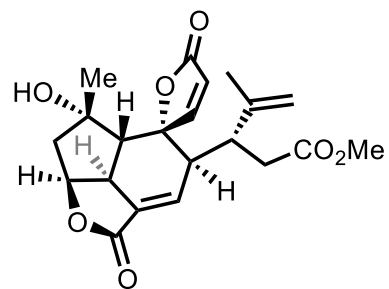


3.32

^{13}C NMR (101 MHz, C_6D_6)

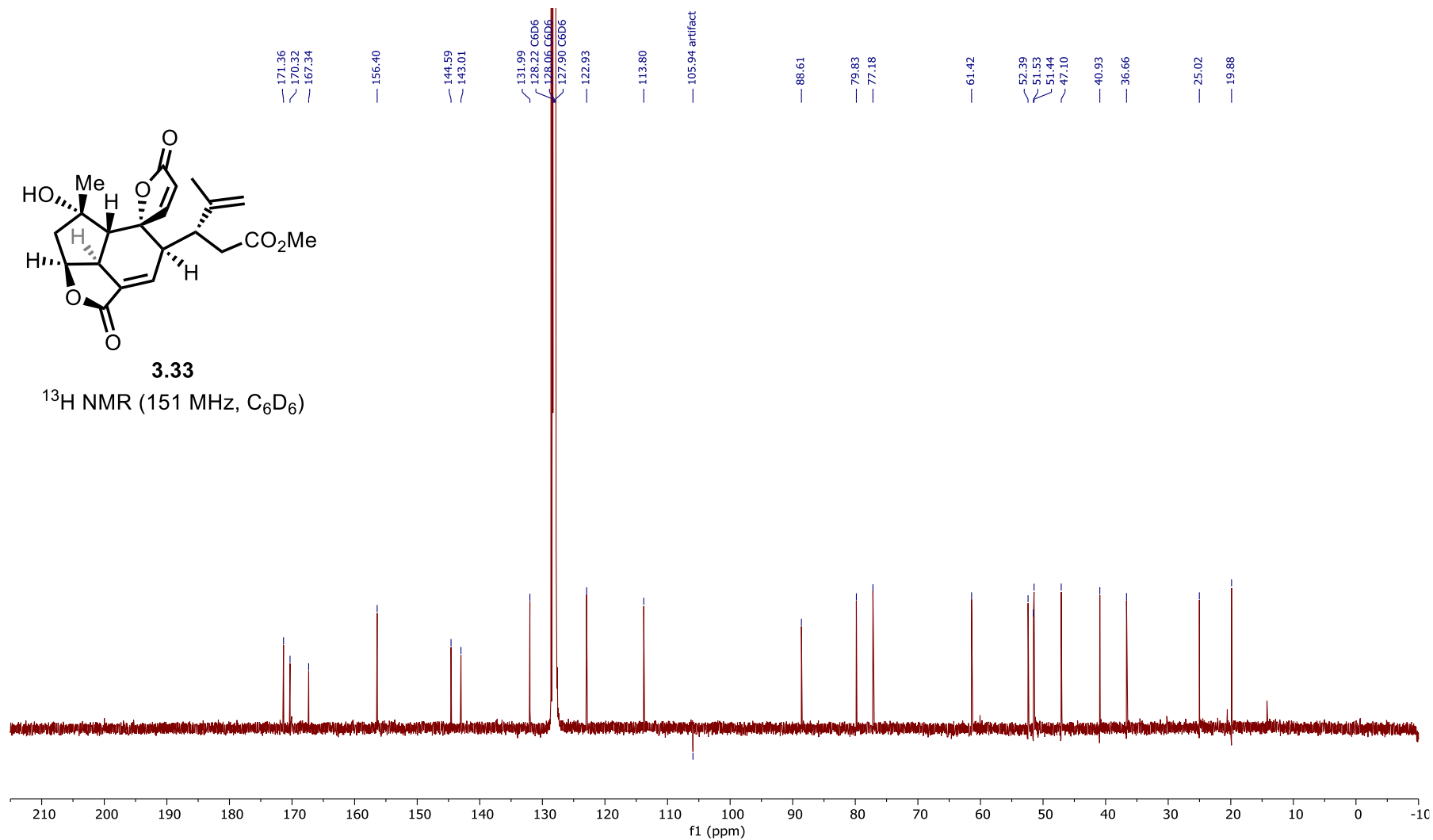


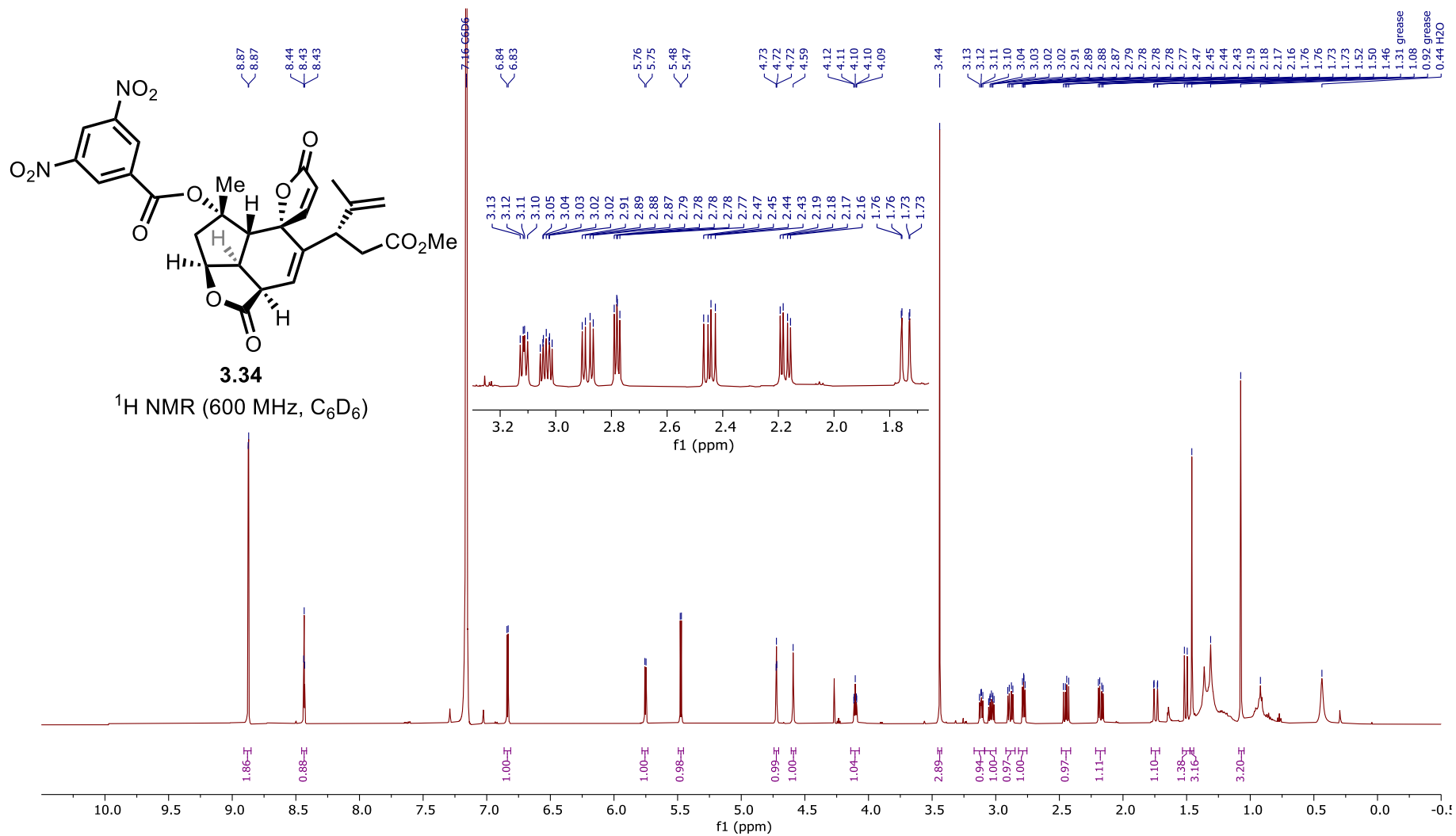


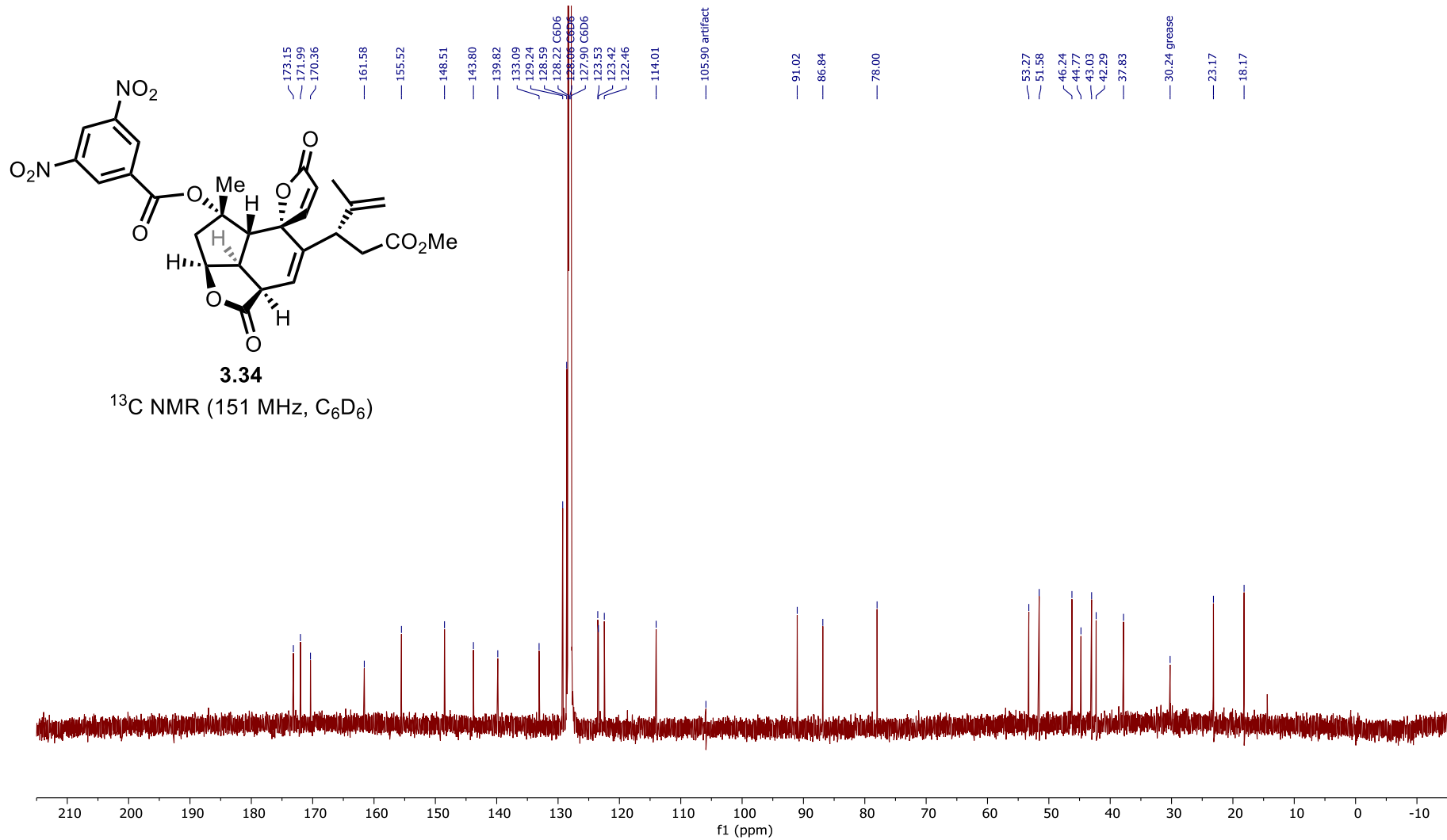


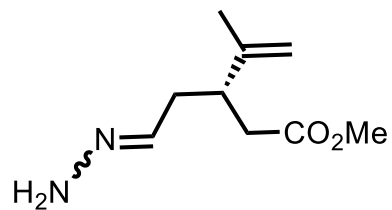
3.33

¹³H NMR (151 MHz, C₆D₆)





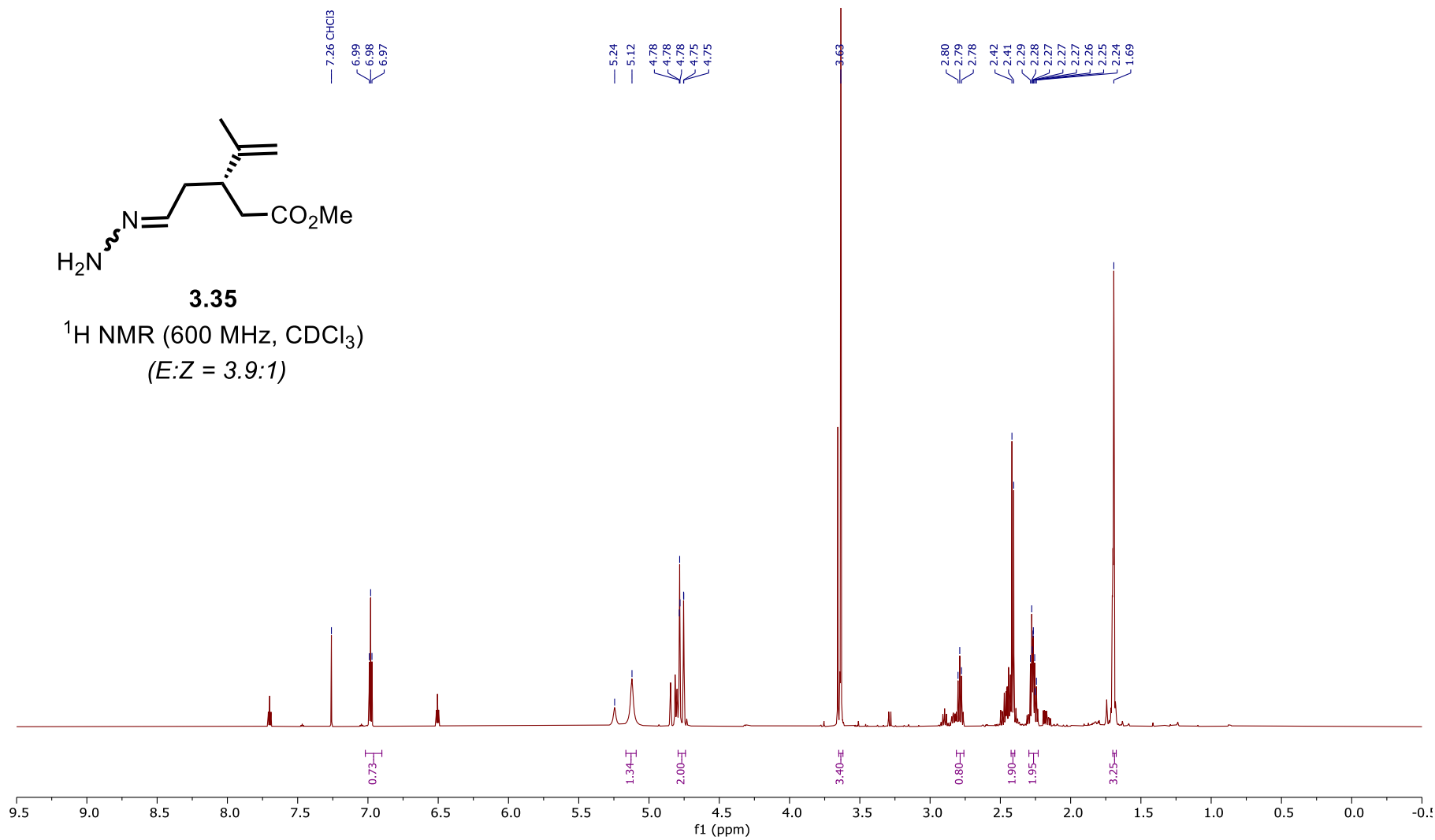


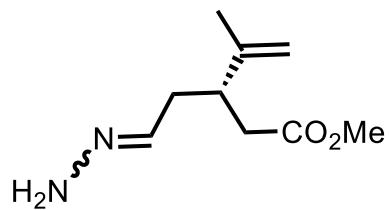


3.35

^1H NMR (600 MHz, CDCl_3)

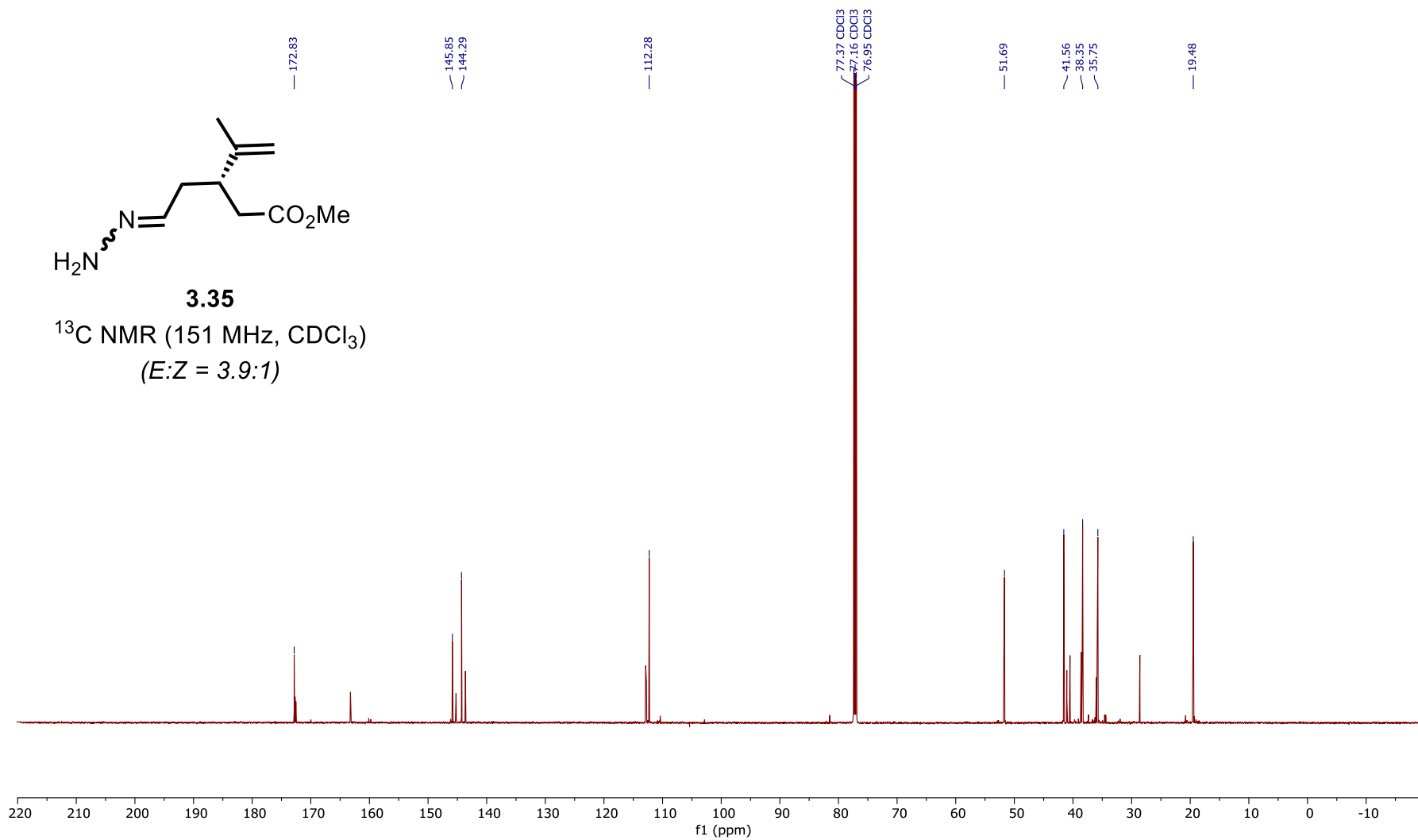
(*E:Z* = 3.9:1)

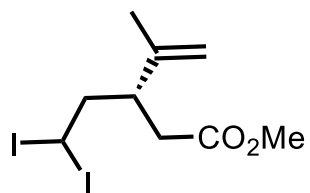




3.35

¹³C NMR (151 MHz, CDCl₃)
(*E:Z* = 3.9:1)

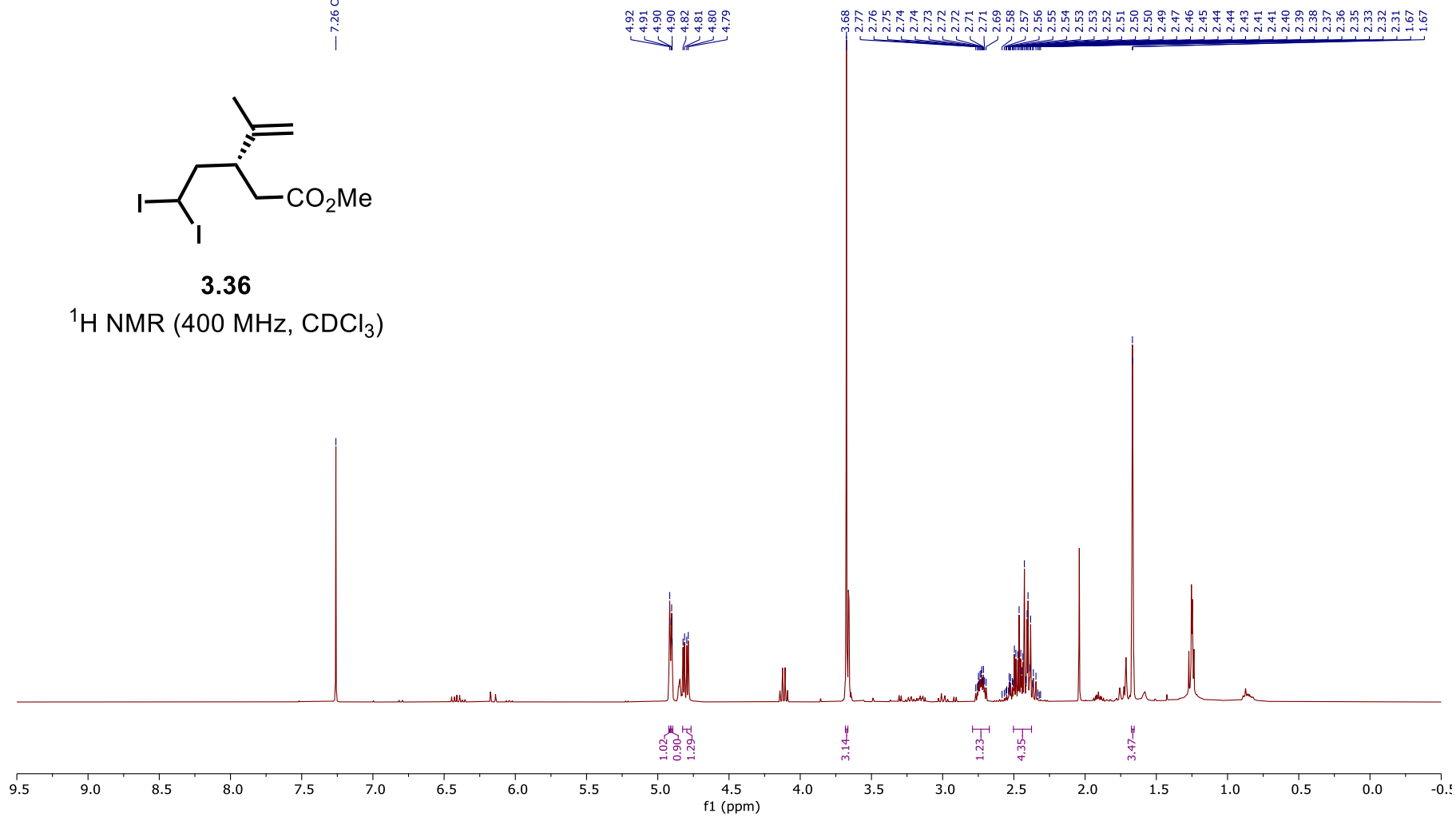


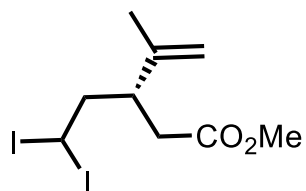


3.36

¹H NMR (400 MHz, CDCl₃)

— 7.26 CHCl₃





3.36

^{13}C NMR (101 MHz, CDCl_3)

172.07

142.91

114.82

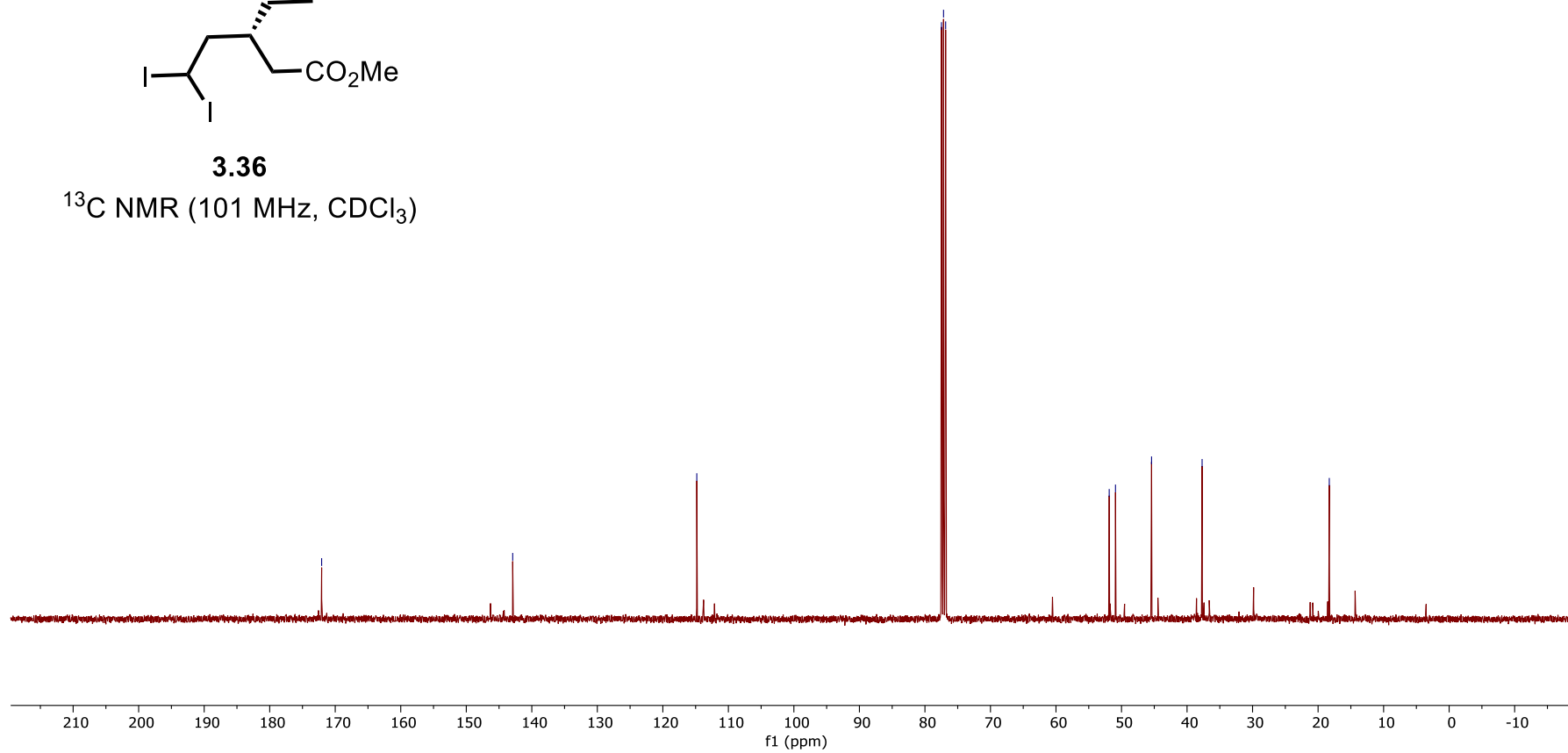
77.48 CDCl_3
77.16 CDCl_3
76.84 CDCl_3

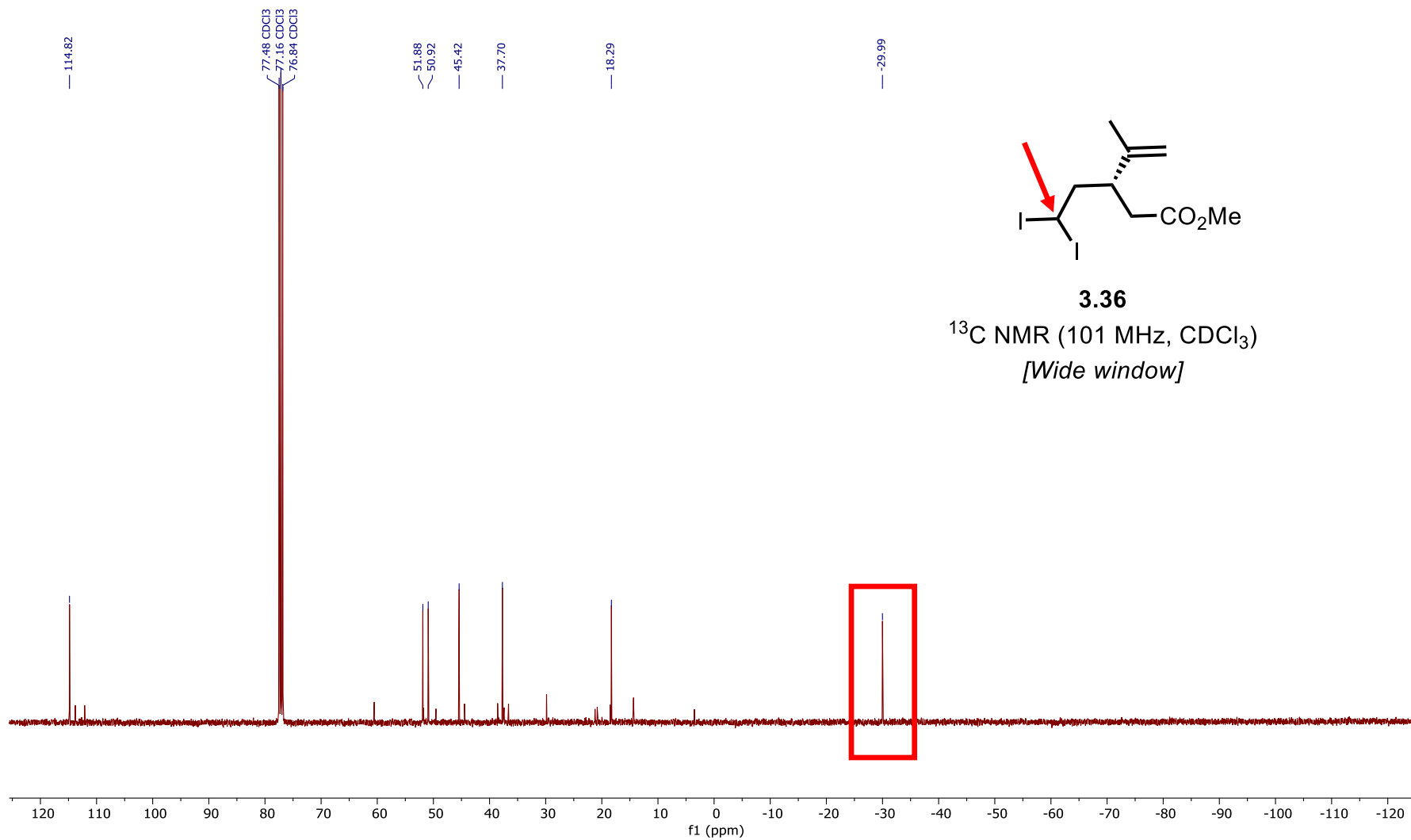
51.88
50.92

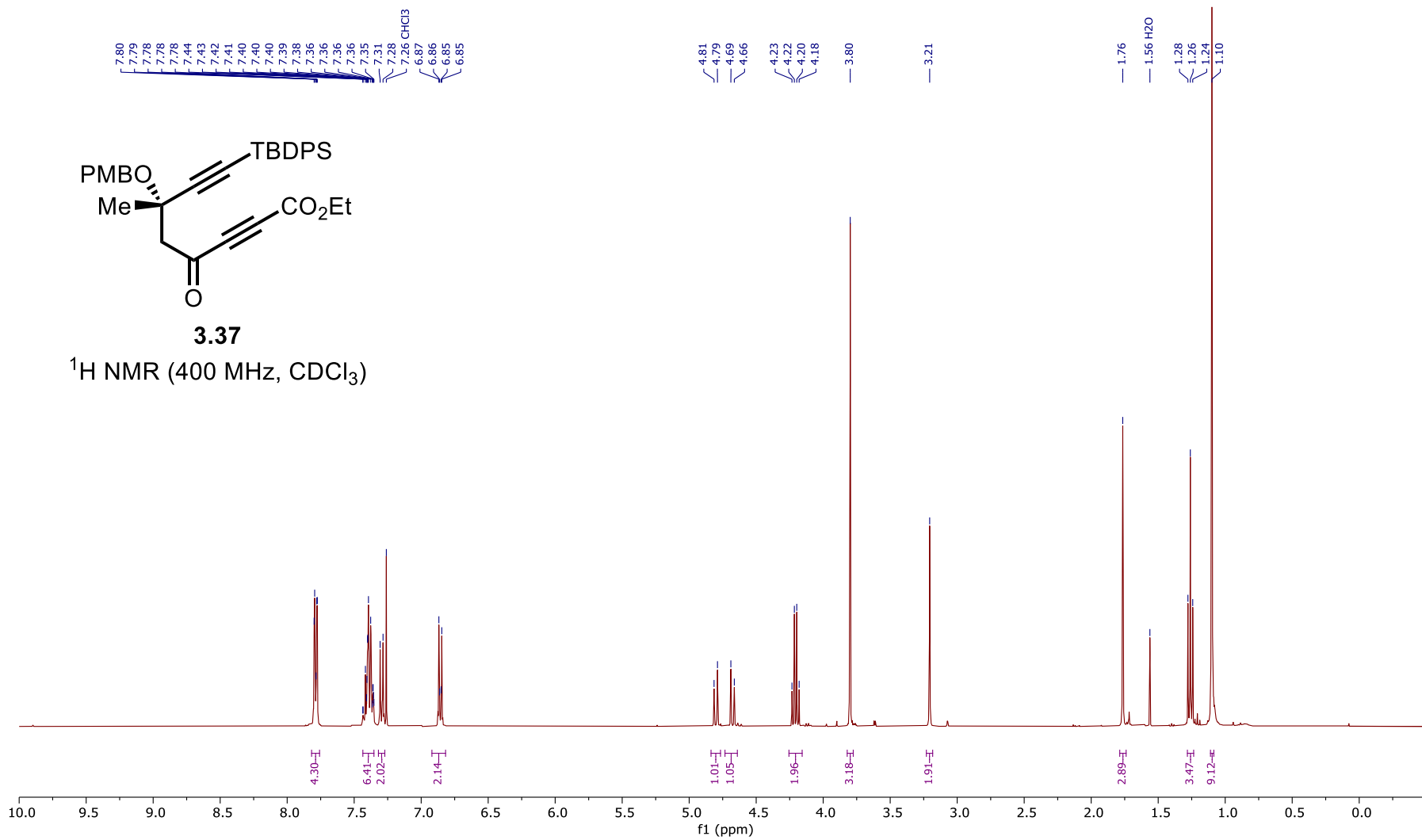
45.41

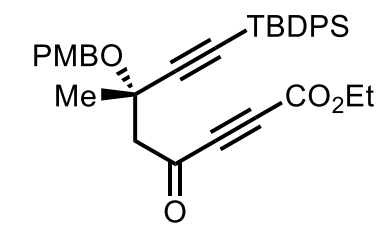
37.70

18.29



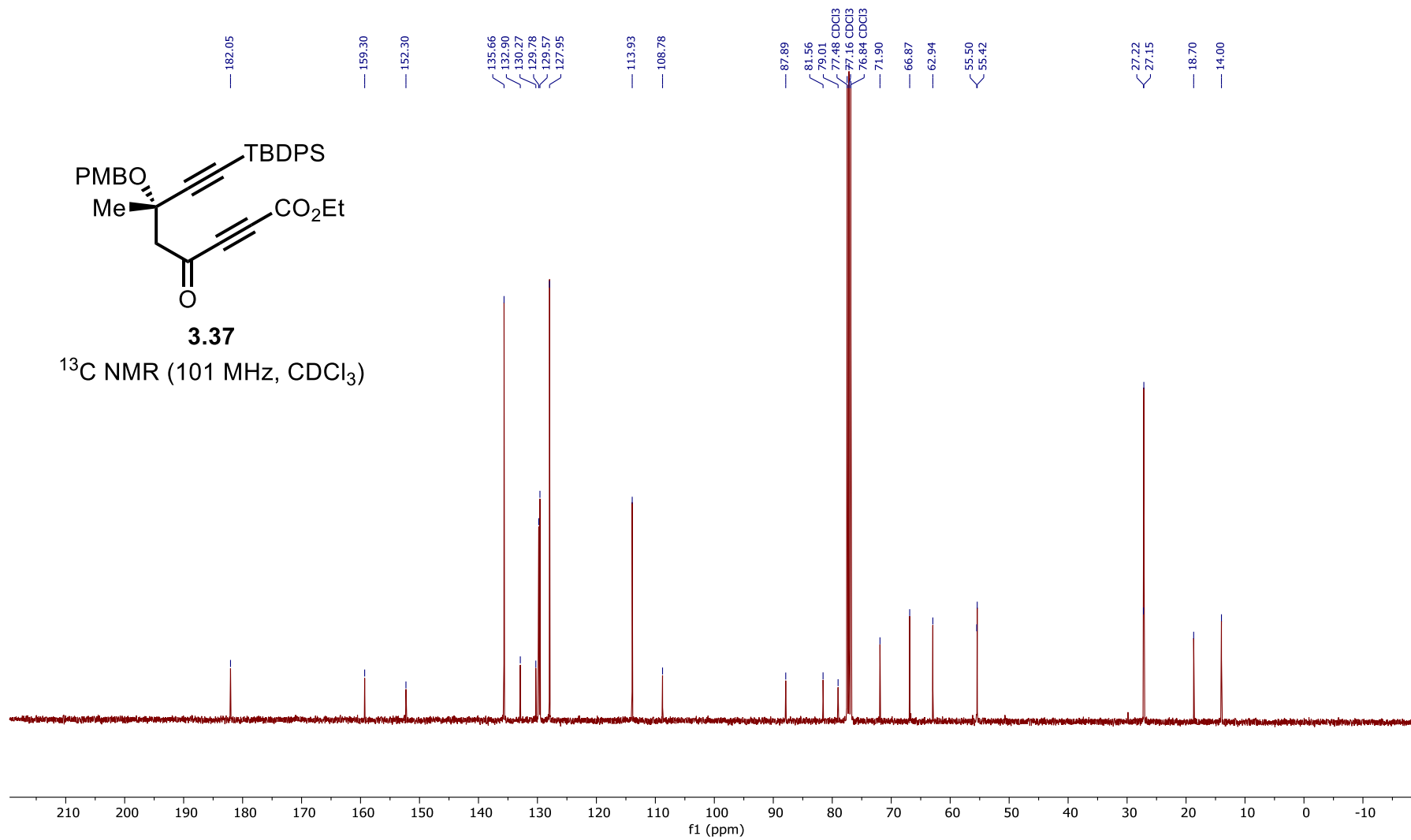


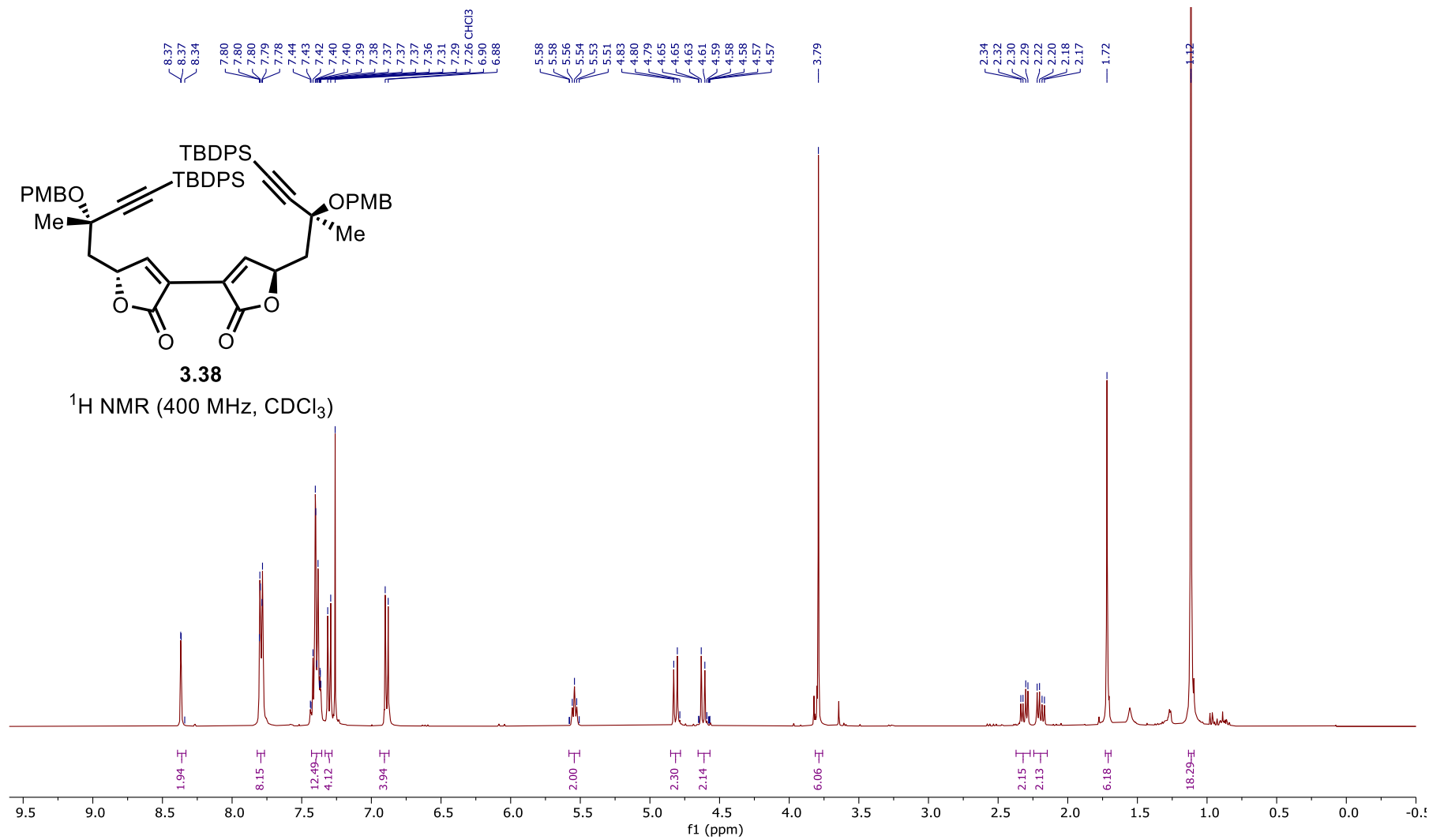


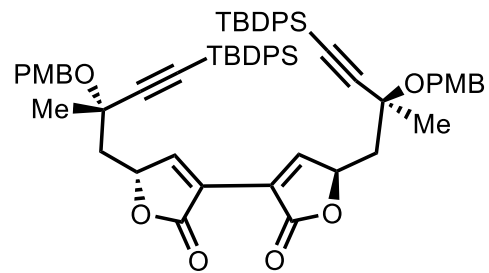


3.37

^{13}C NMR (101 MHz, CDCl_3)

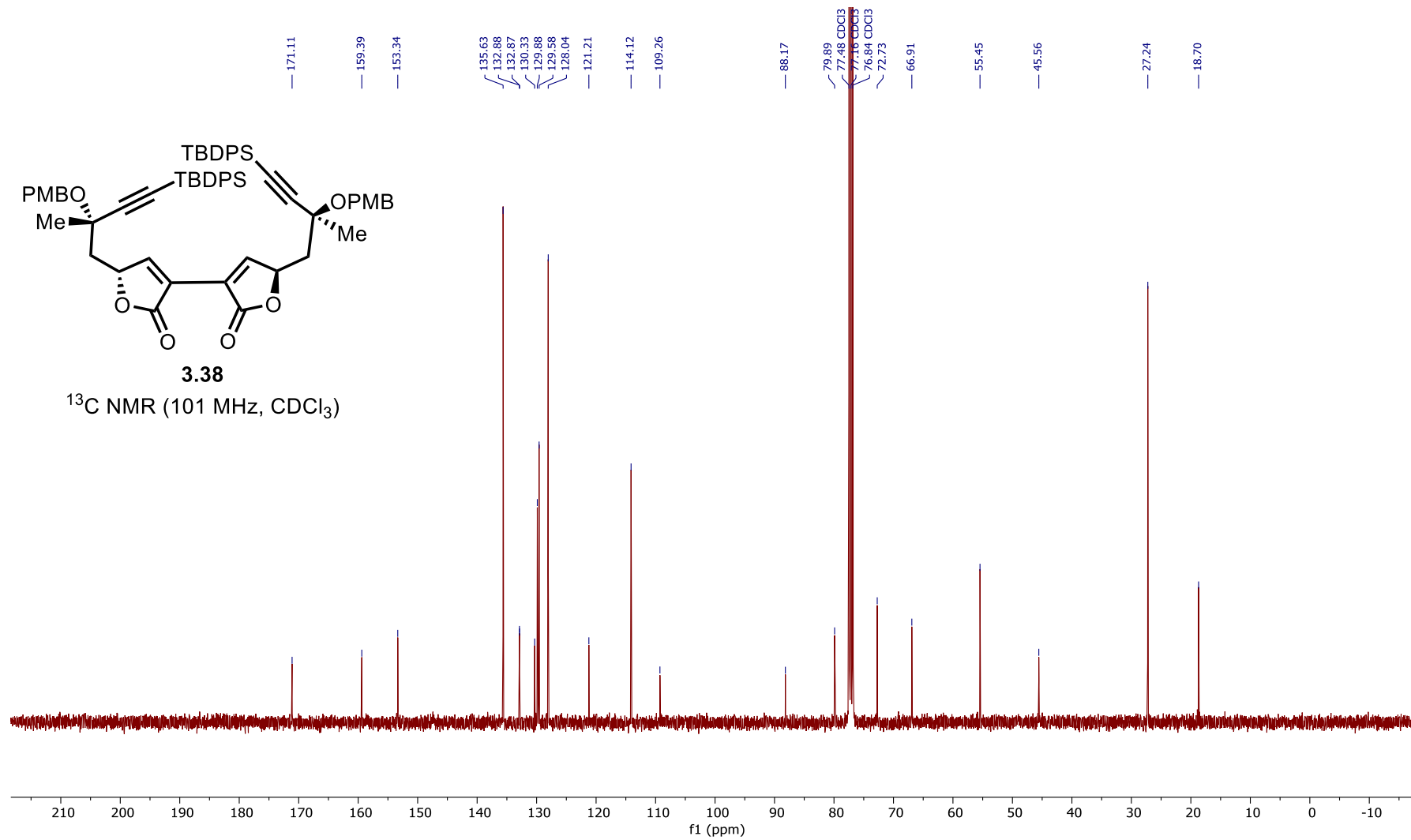


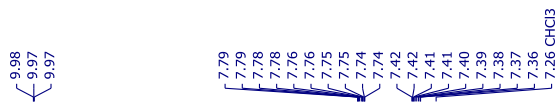


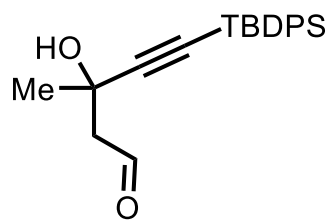


3.38

^{13}C NMR (101 MHz, CDCl_3)

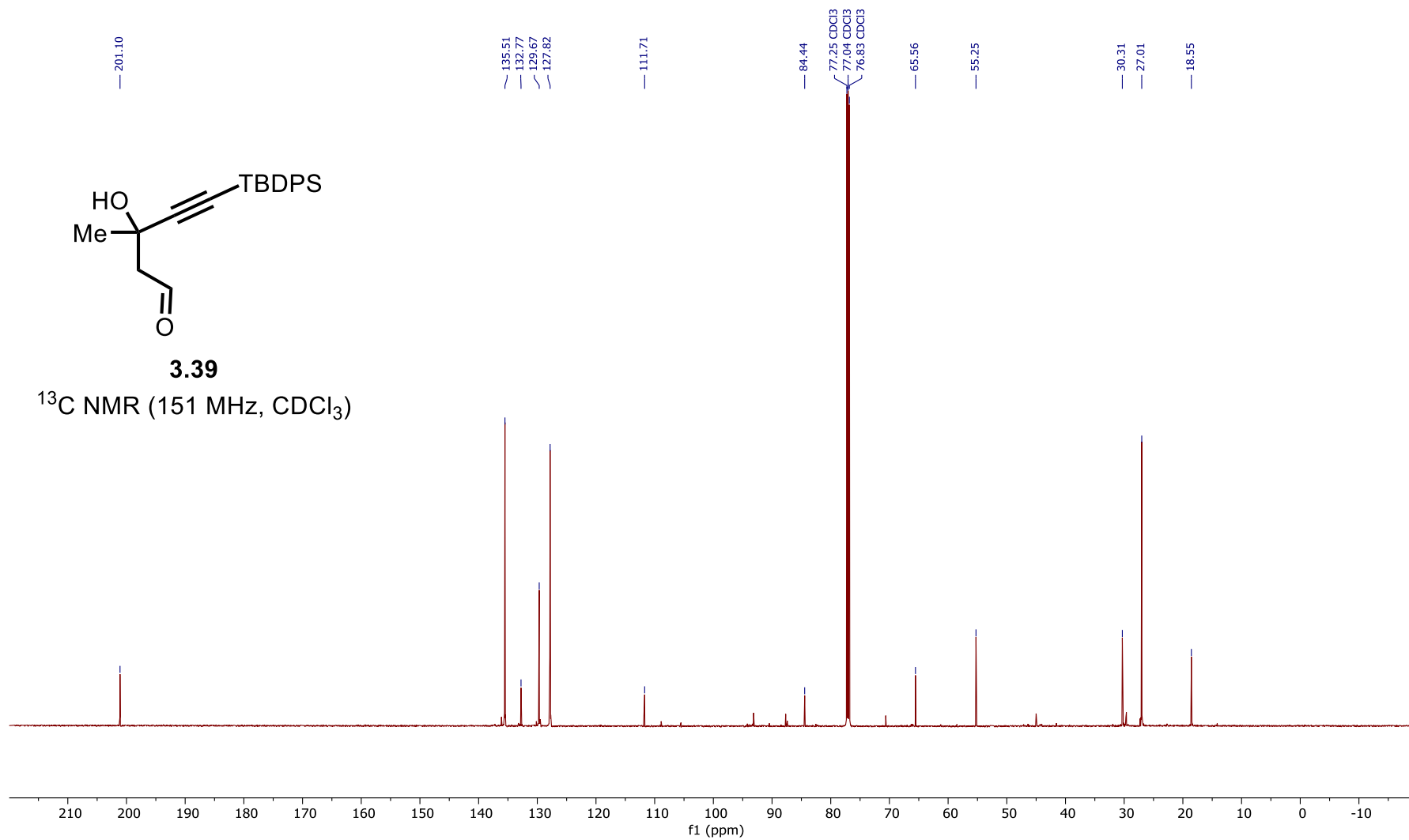


¹H NMR (600 MHz, CDCl₃)

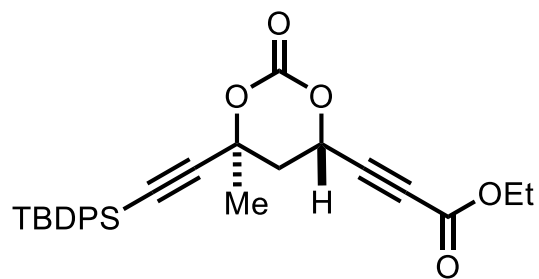


3.39

^{13}C NMR (151 MHz, CDCl_3)

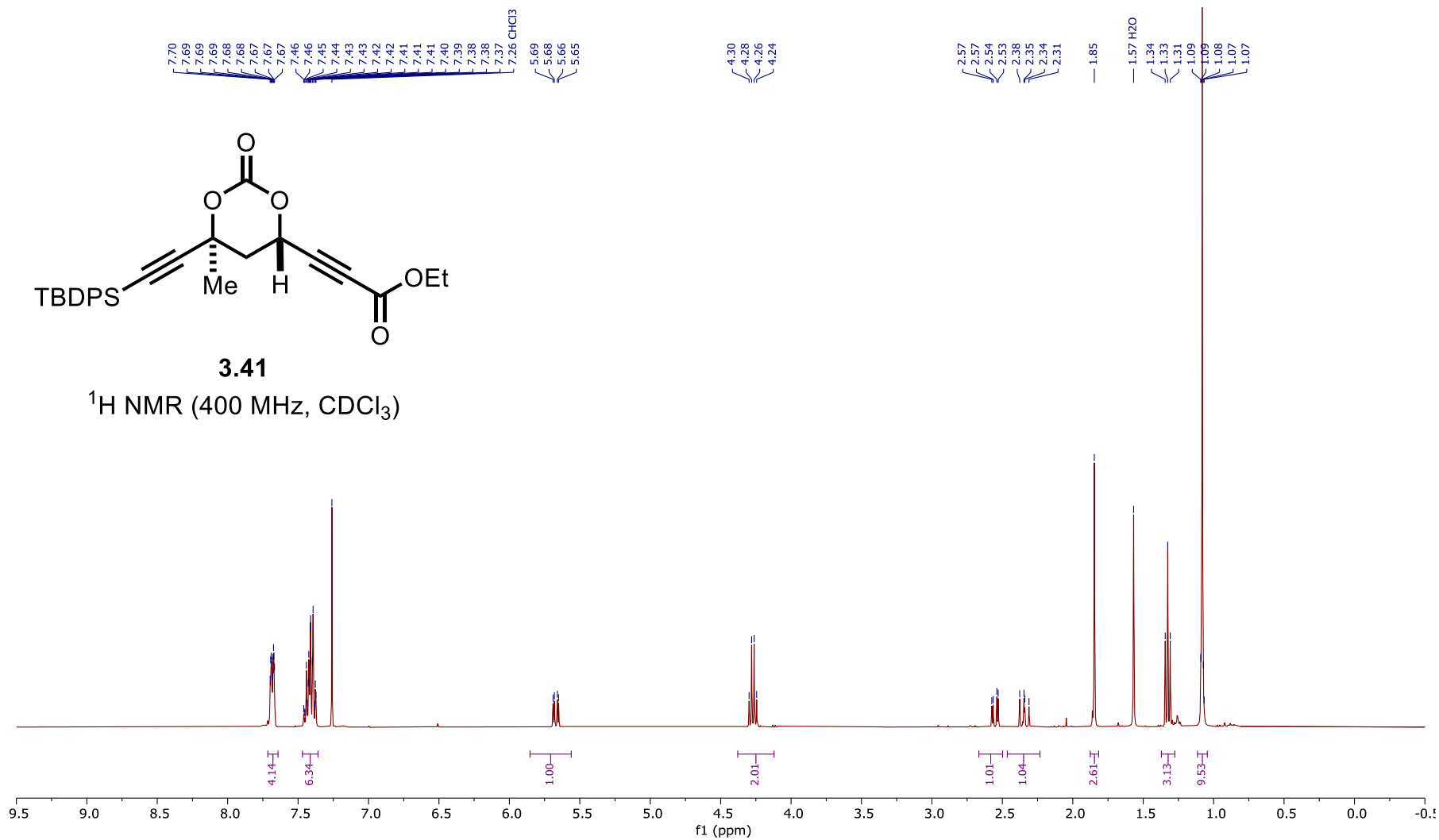


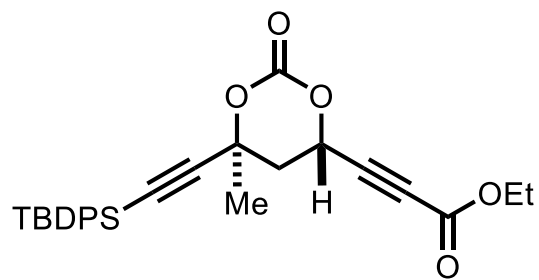




3.41

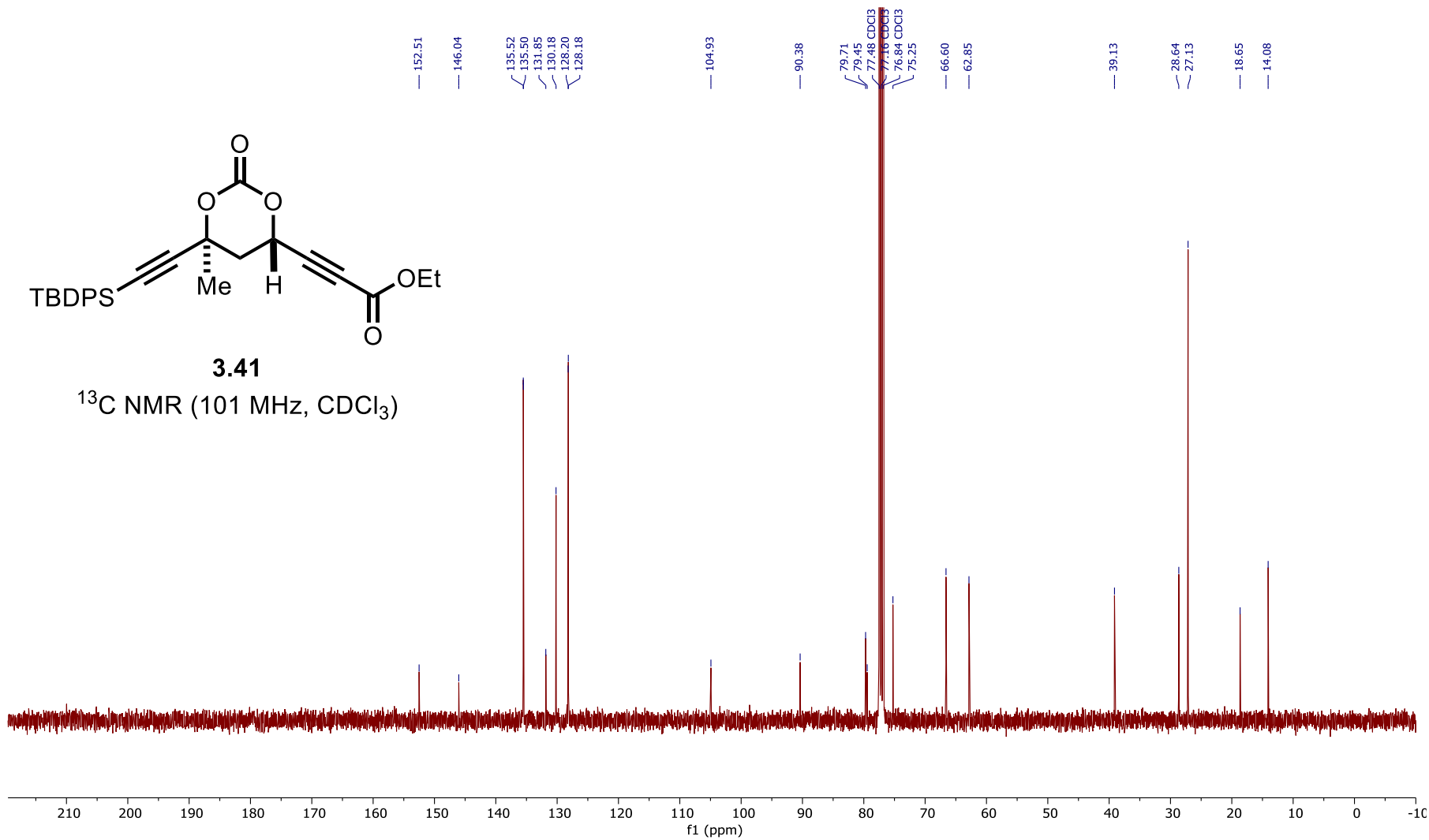
^1H NMR (400 MHz, CDCl_3)

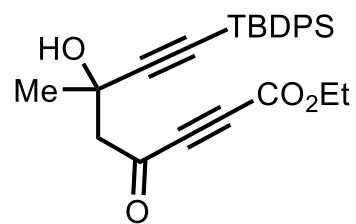




3.41

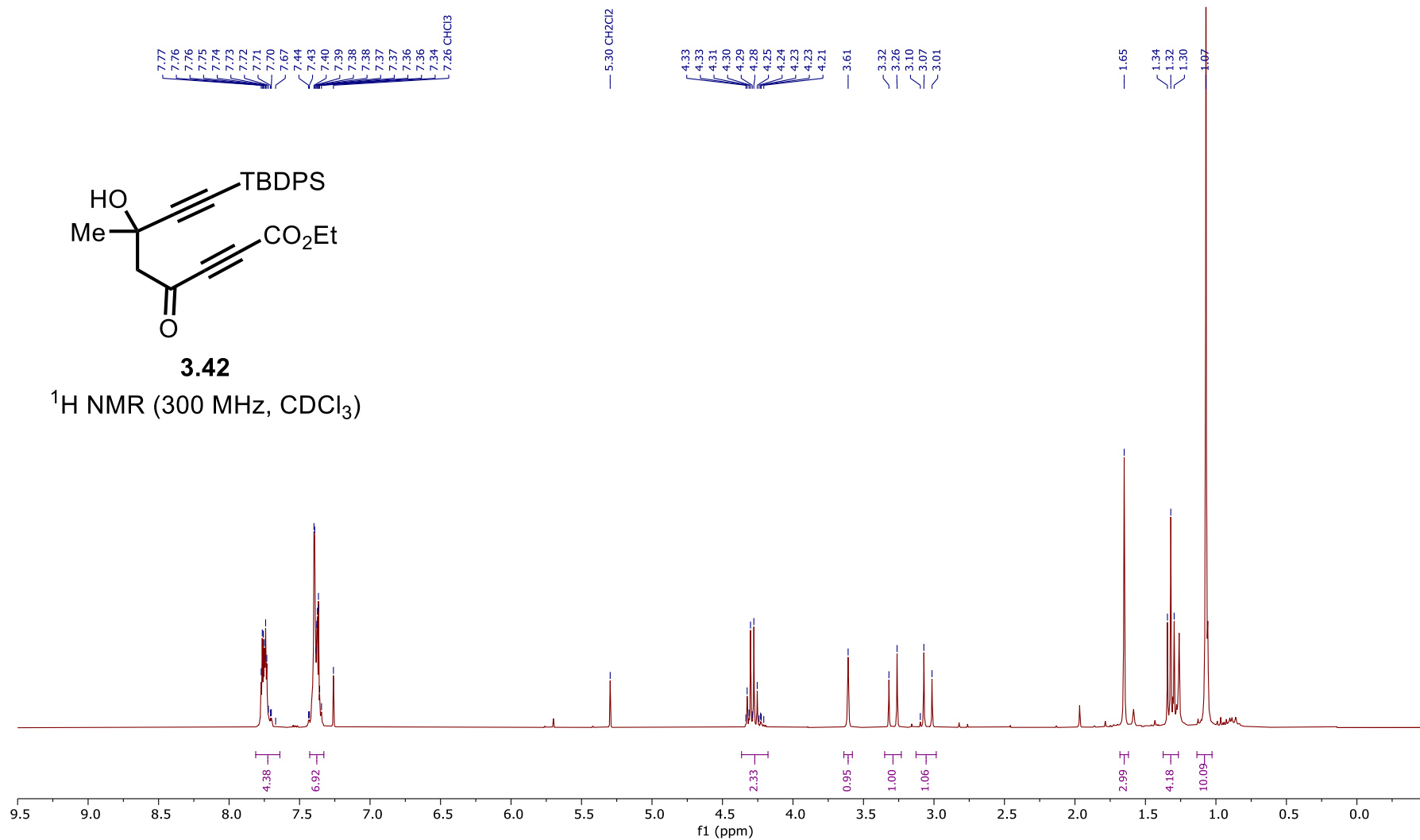
^{13}C NMR (101 MHz, CDCl_3)

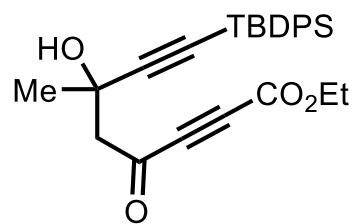




3.42

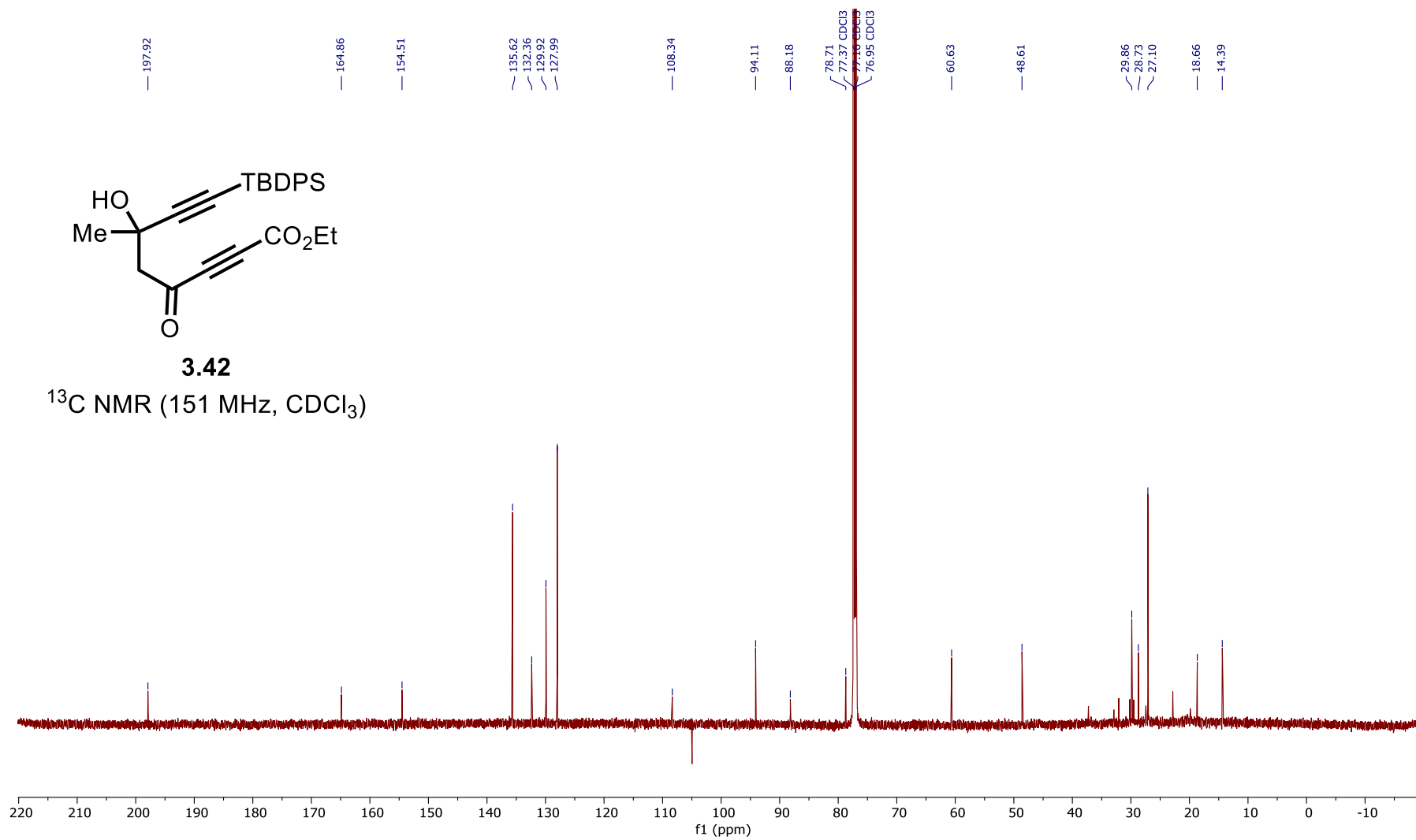
¹H NMR (300 MHz, CDCl₃)

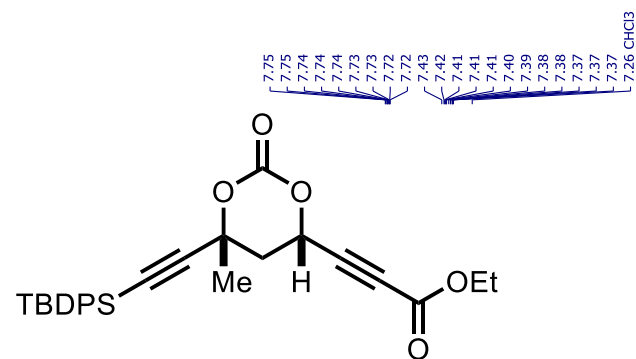




3.42

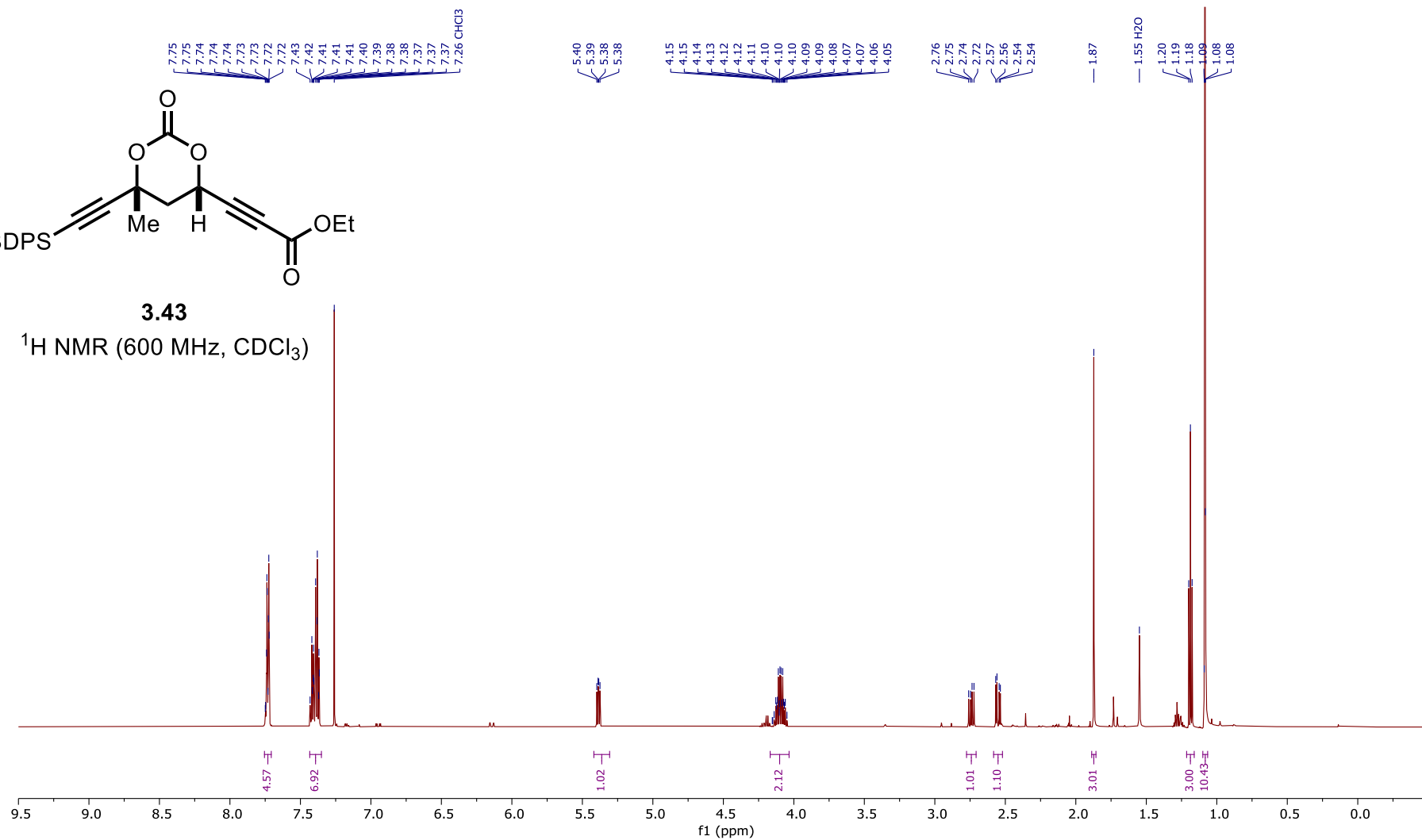
^{13}C NMR (151 MHz, CDCl_3)

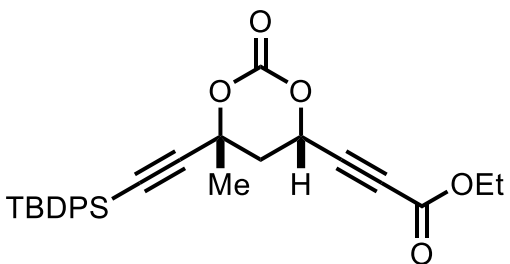




3.43

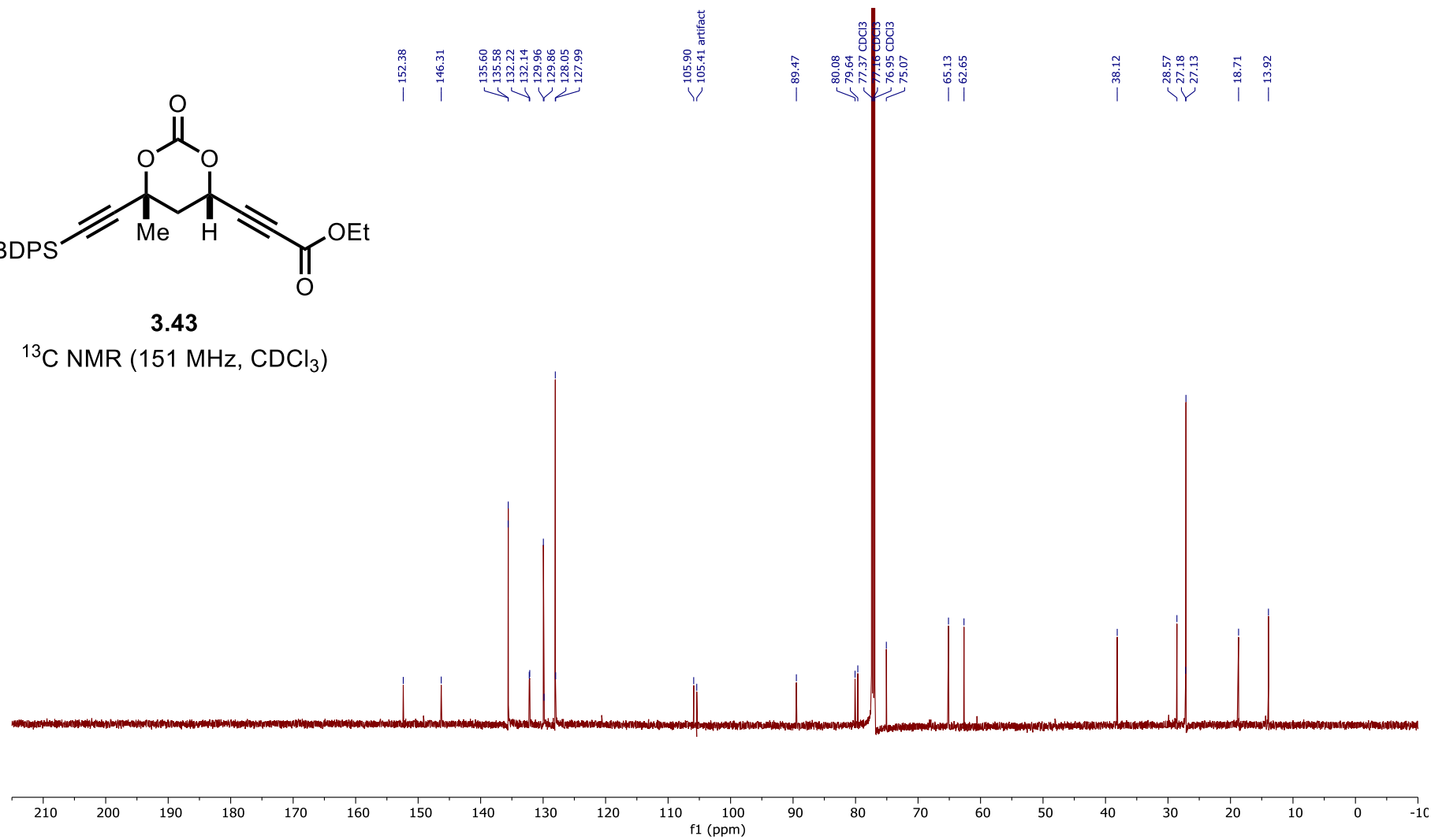
^1H NMR (600 MHz, CDCl_3)

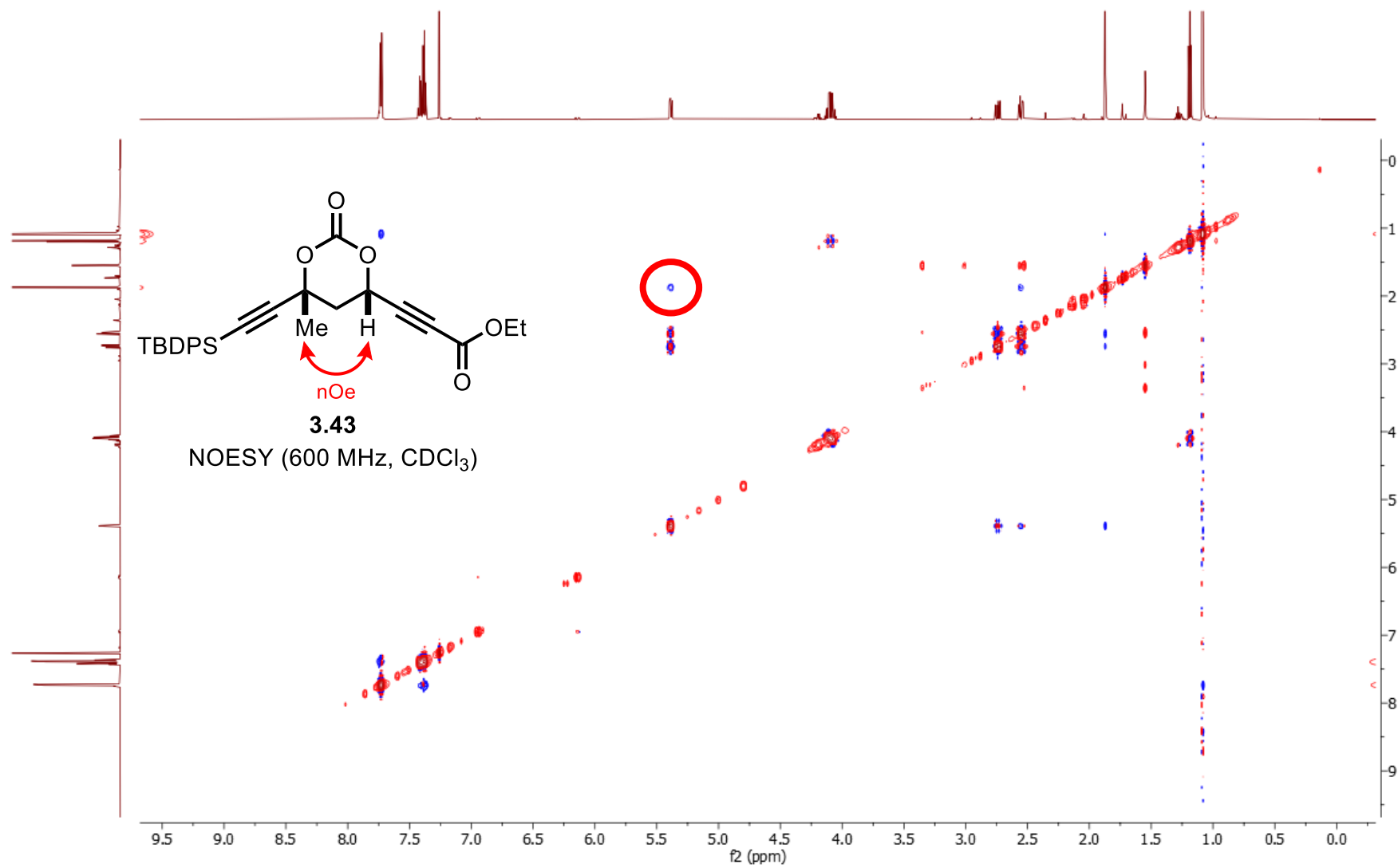


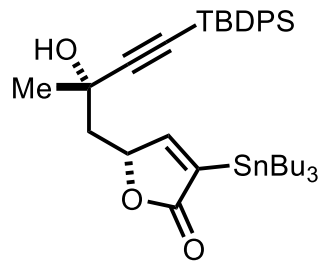


3.43

^{13}C NMR (151 MHz, CDCl_3)

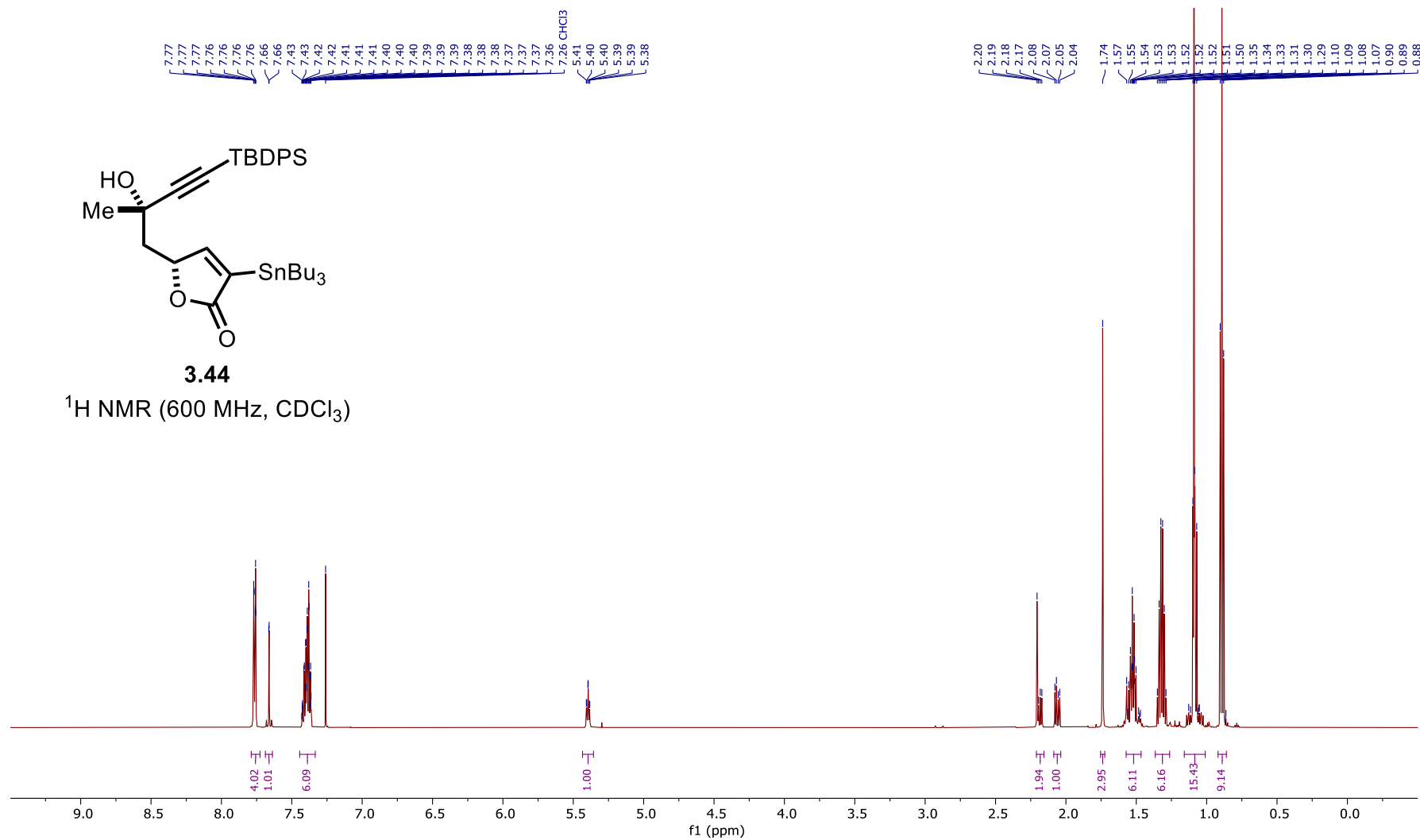


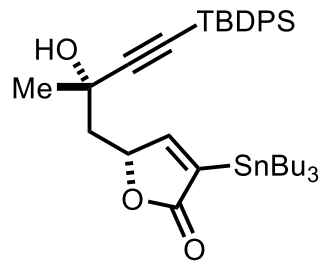




3.44

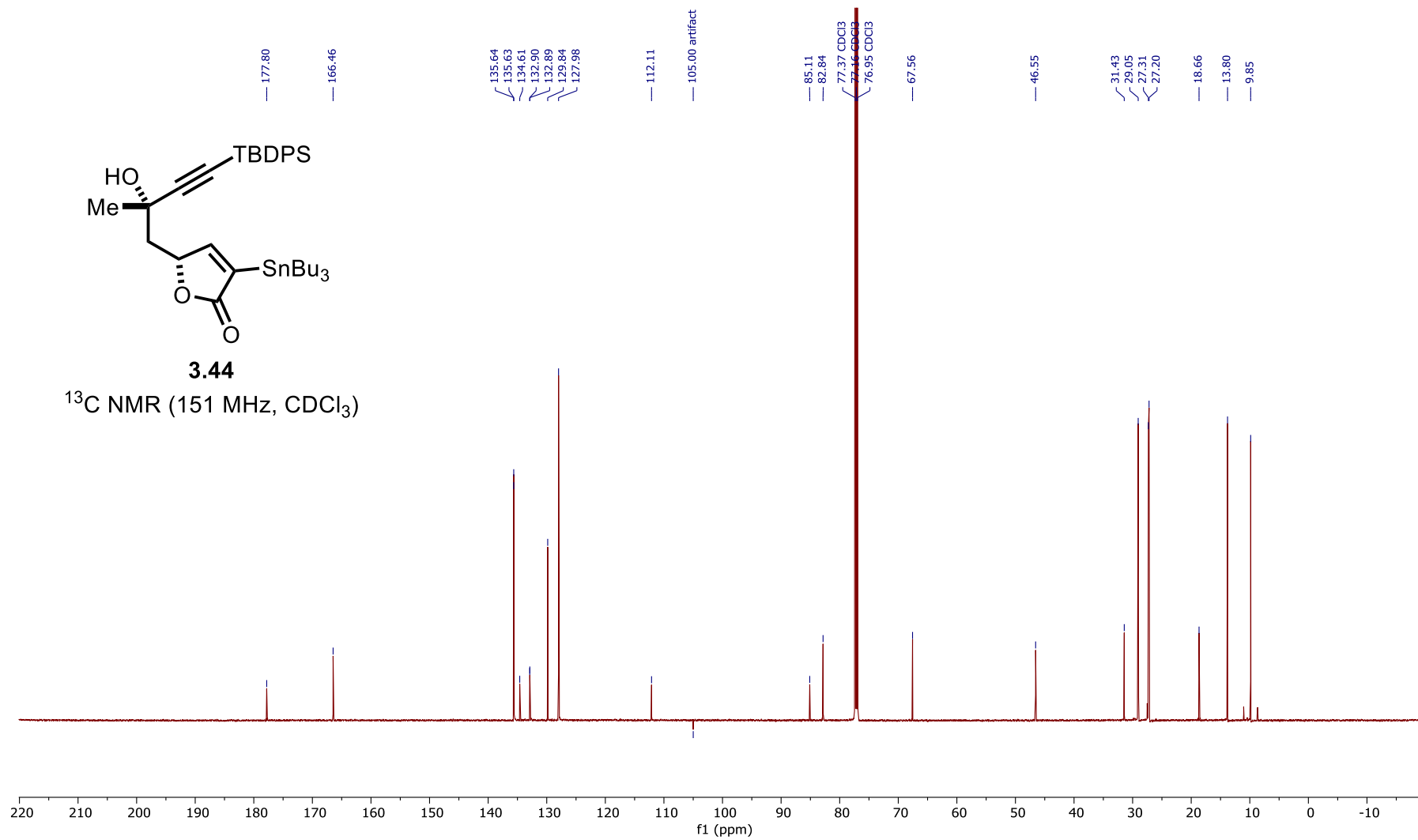
^1H NMR (600 MHz, CDCl_3)

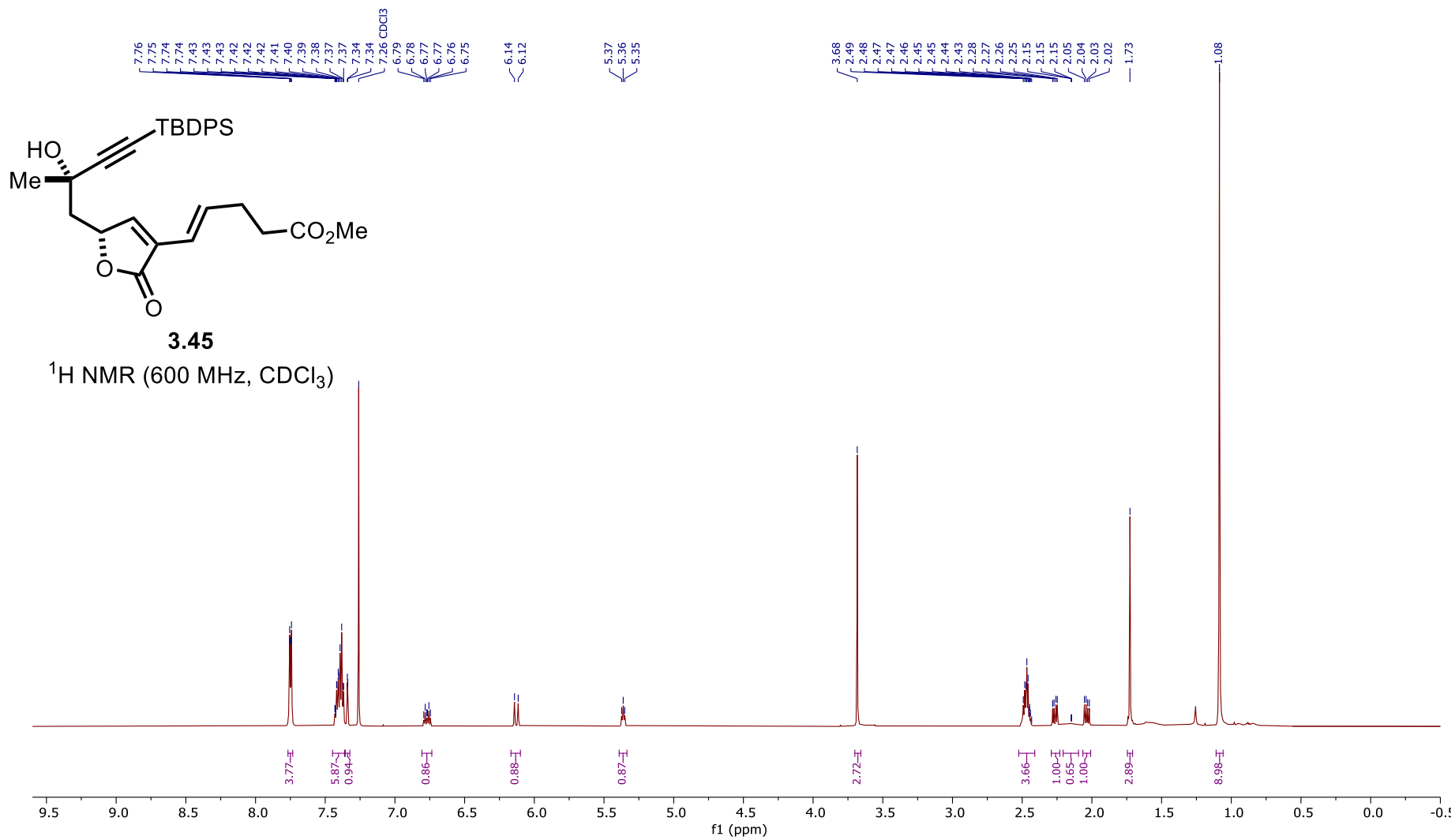


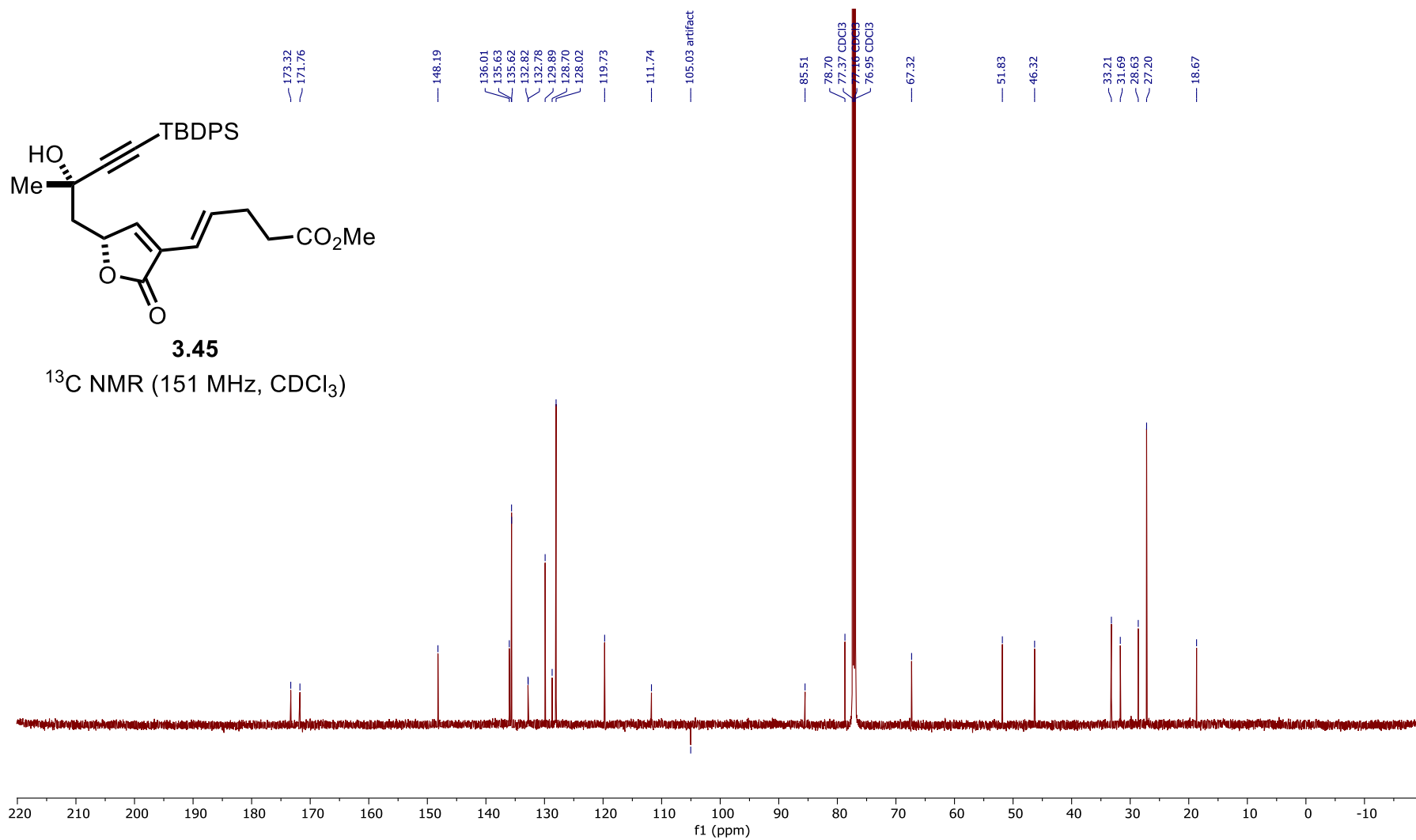


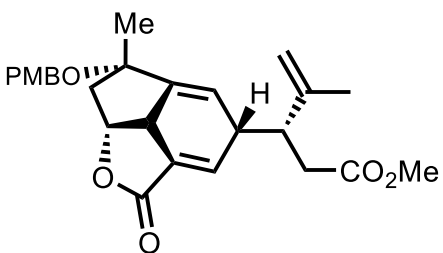
3.44

^{13}C NMR (151 MHz, CDCl_3)



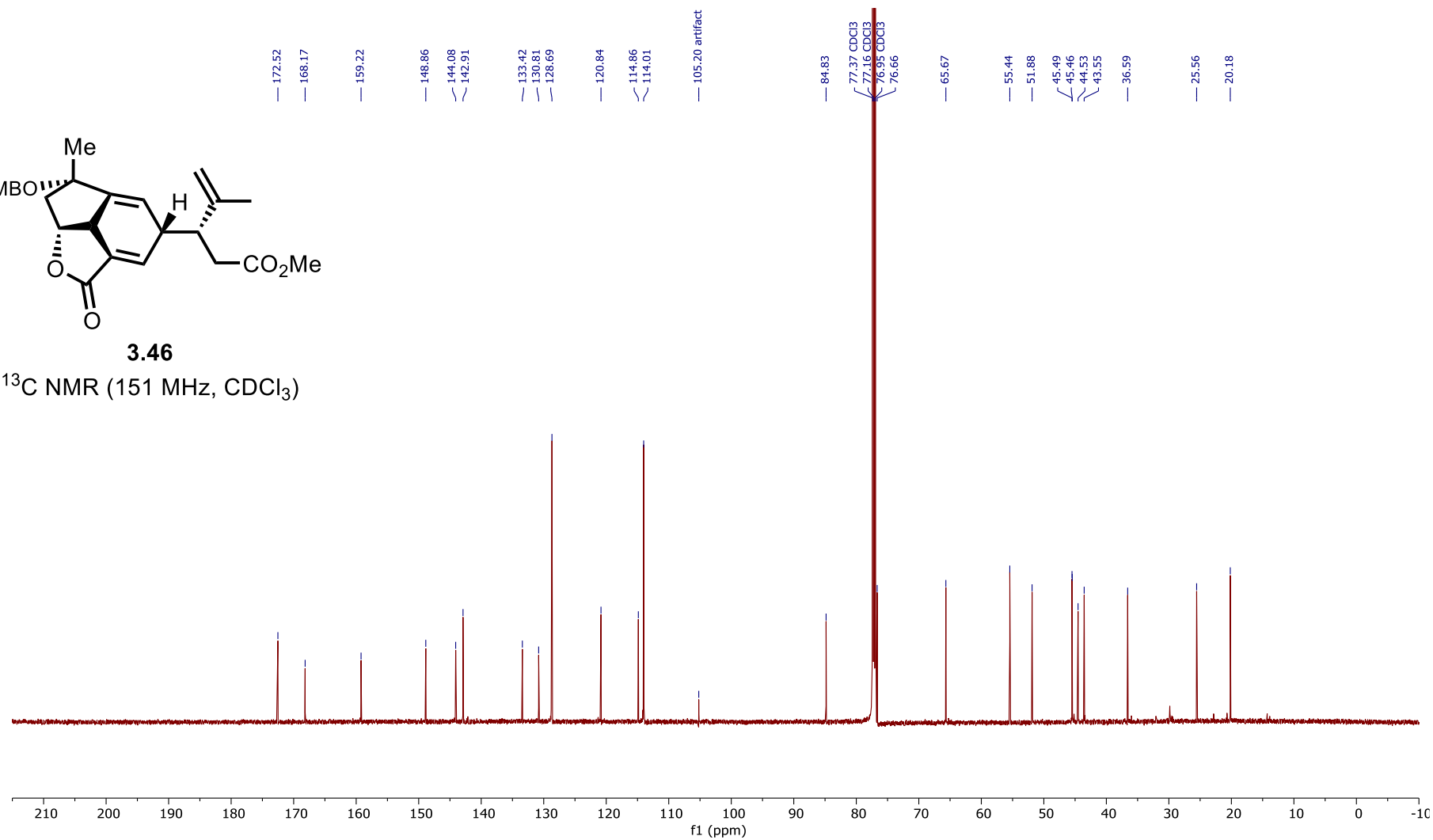


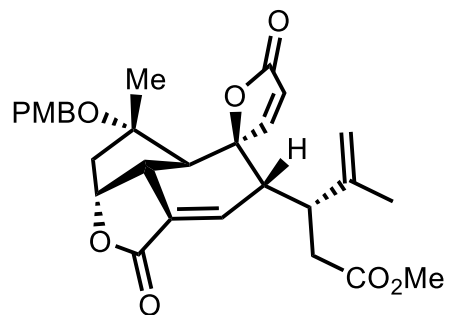




3.46

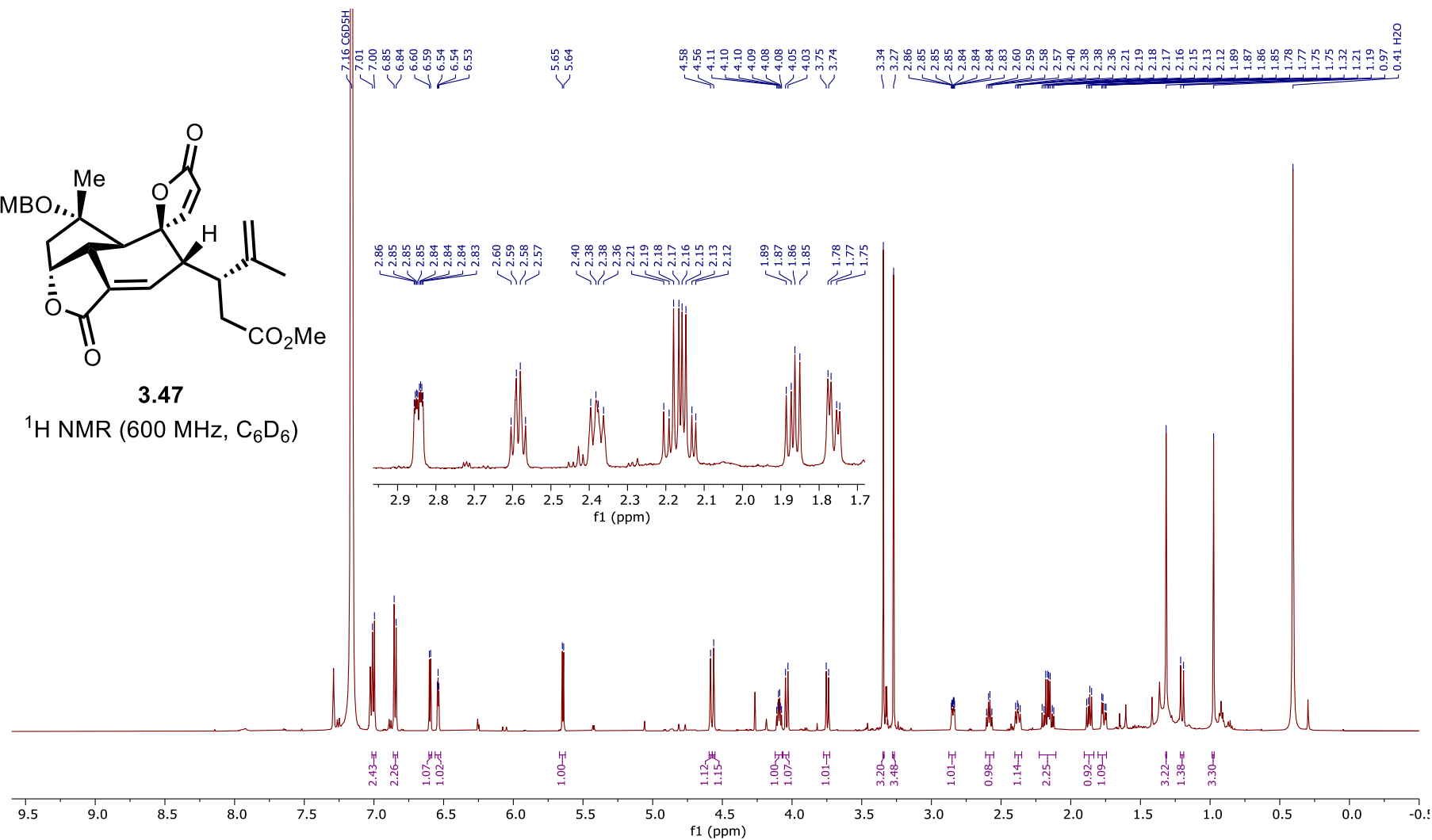
^{13}C NMR (151 MHz, CDCl_3)

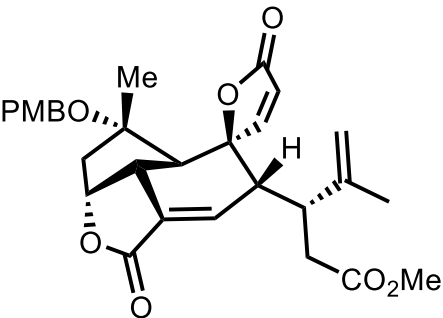




3.47

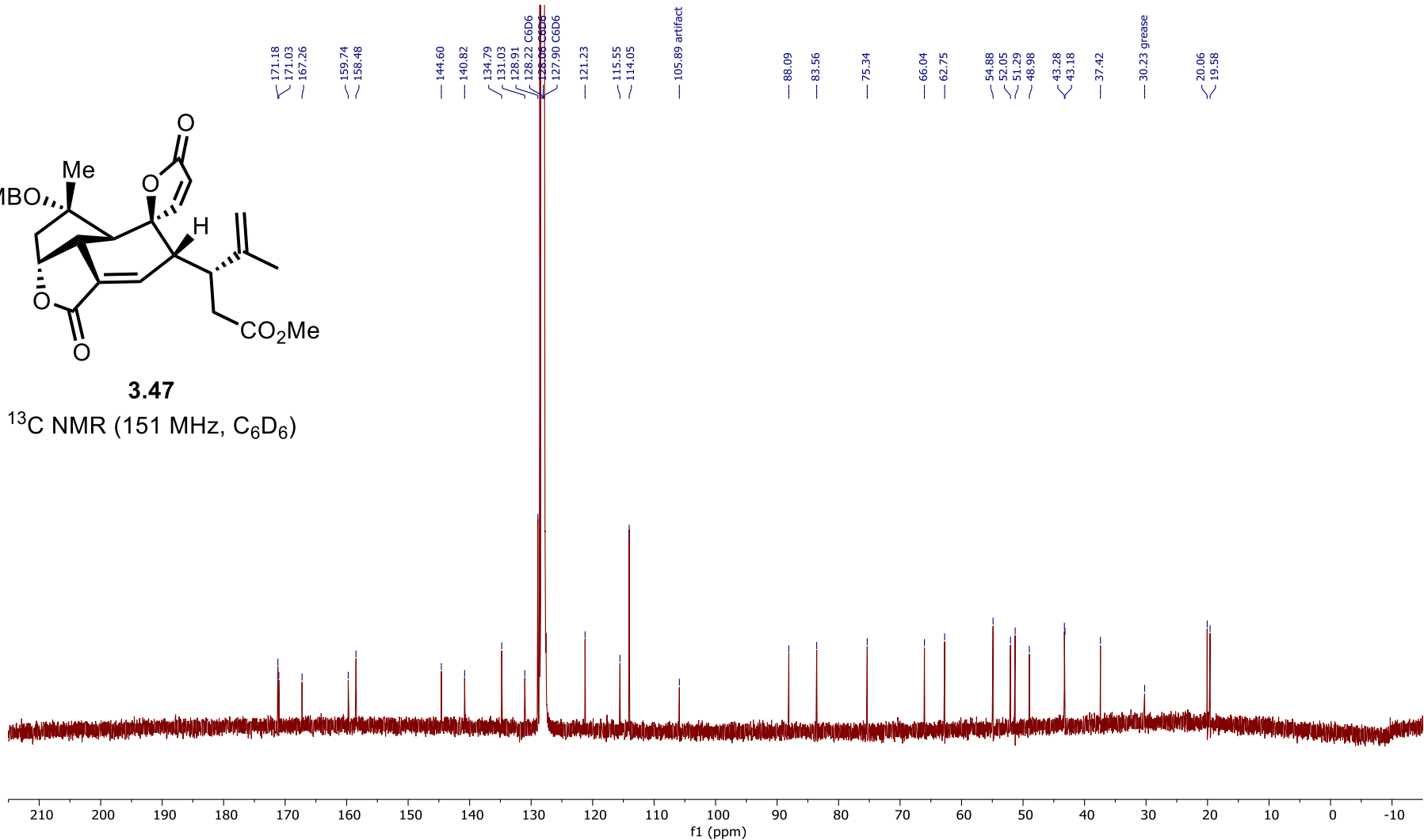
¹H NMR (600 MHz, C₆D₆)

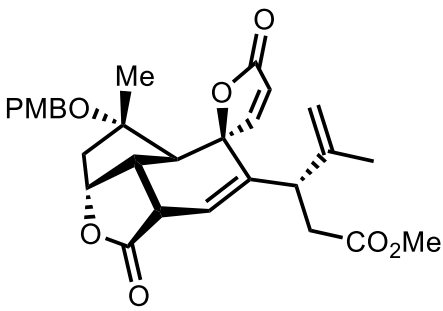




3.47

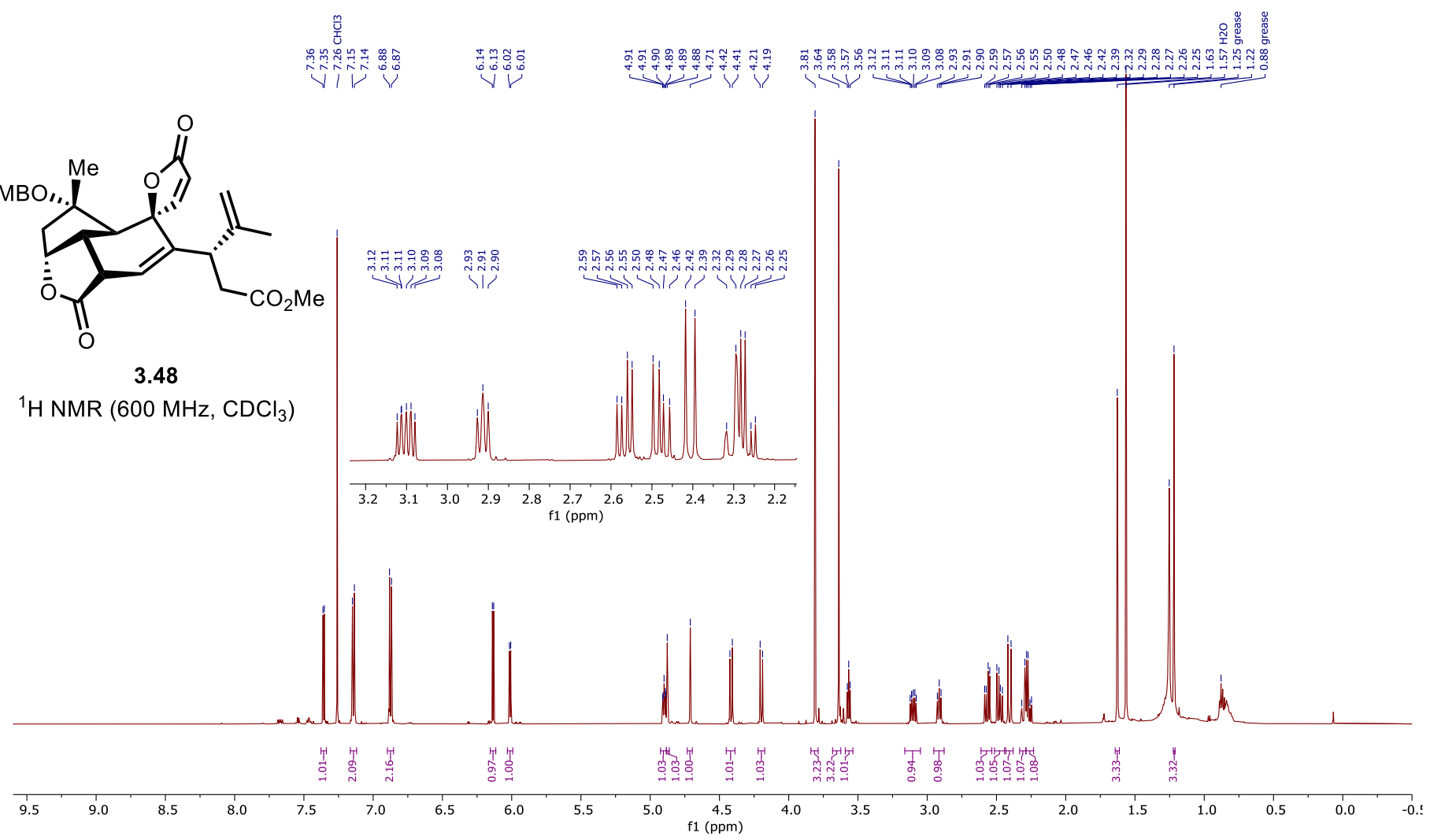
¹³C NMR (151 MHz, C₆D₆)

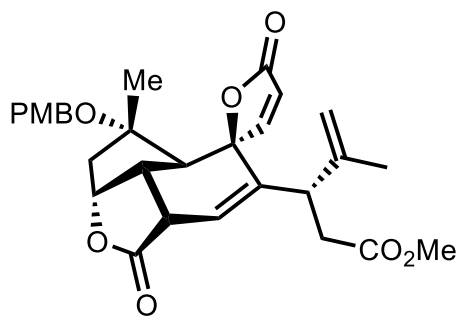




3.48

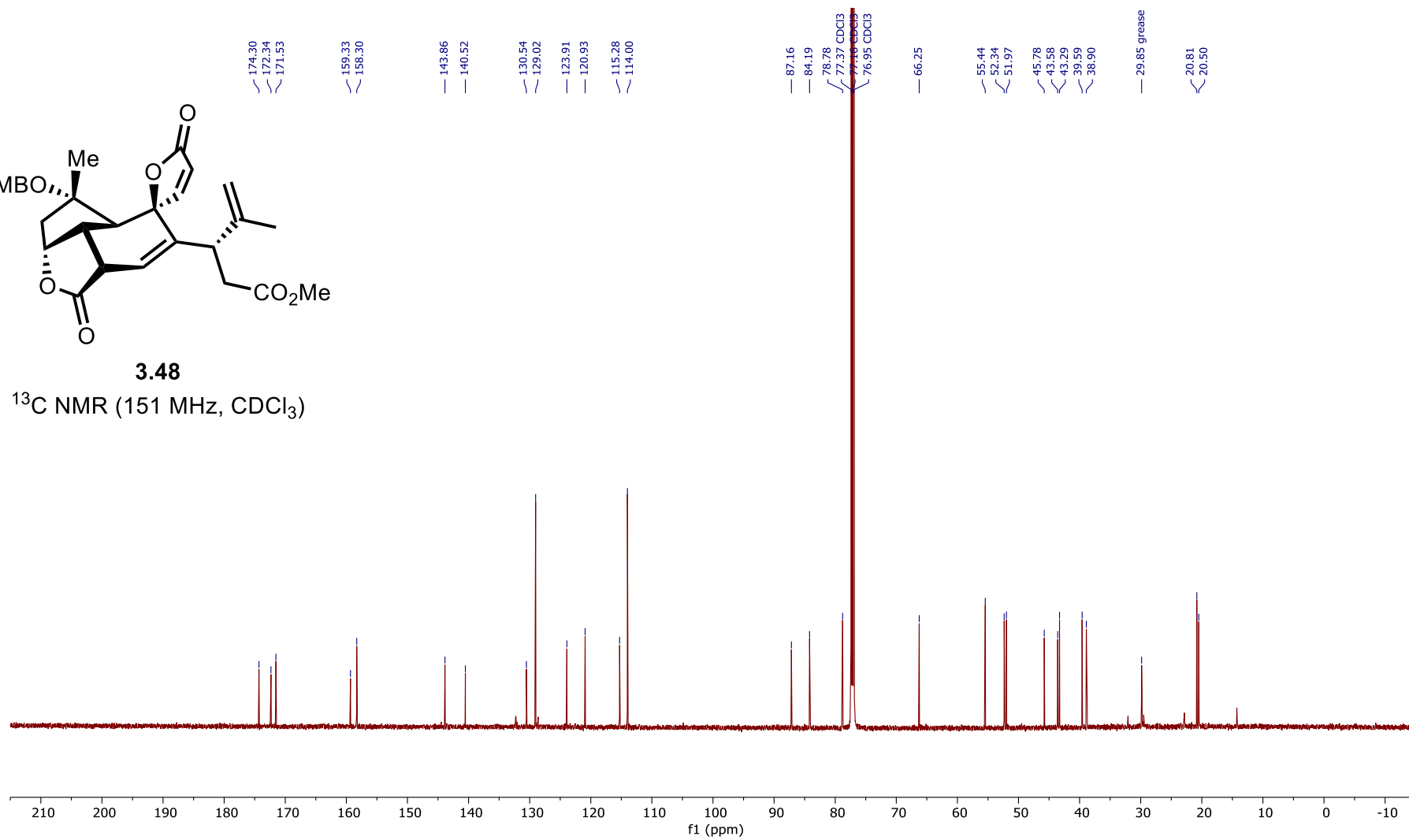
^1H NMR (600 MHz, CDCl_3)

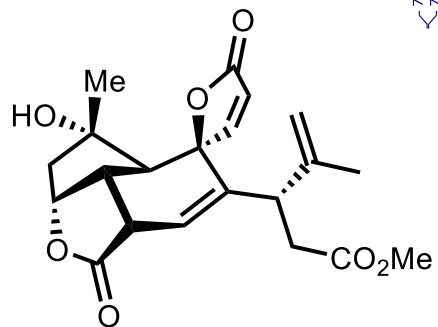




3.48

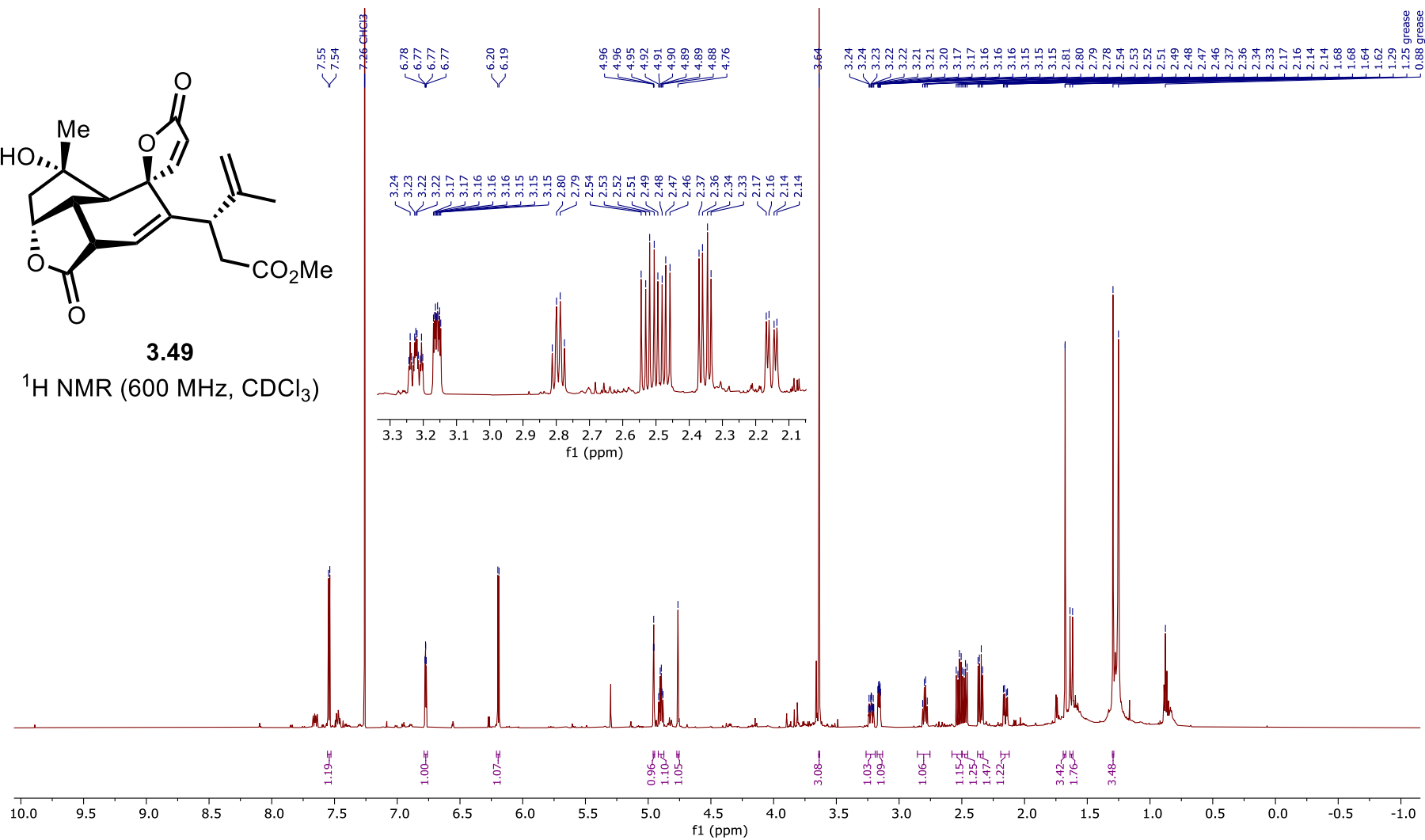
^{13}C NMR (151 MHz, CDCl_3)

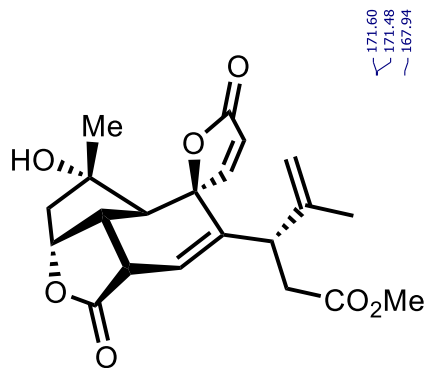




3.49

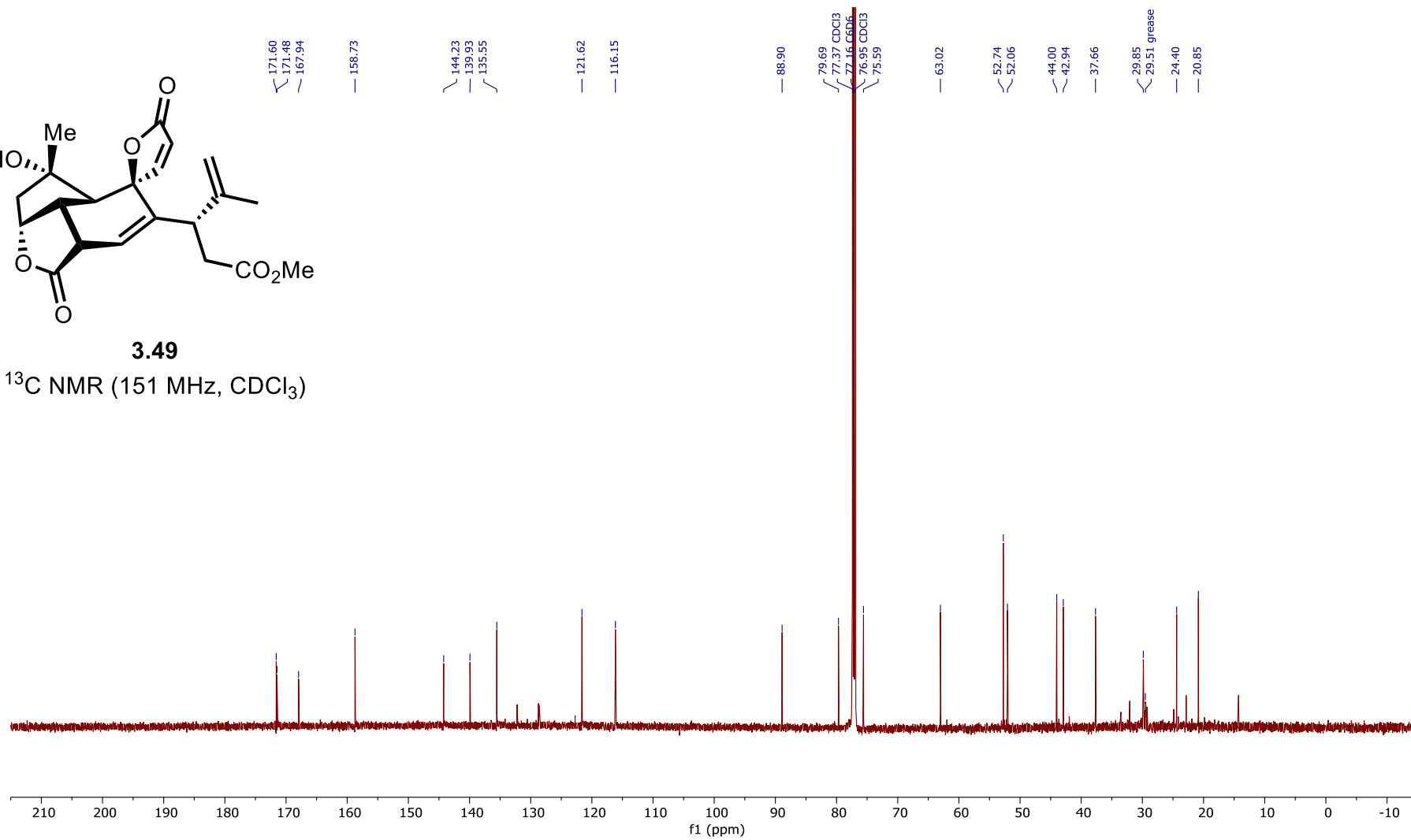
^1H NMR (600 MHz, CDCl_3)

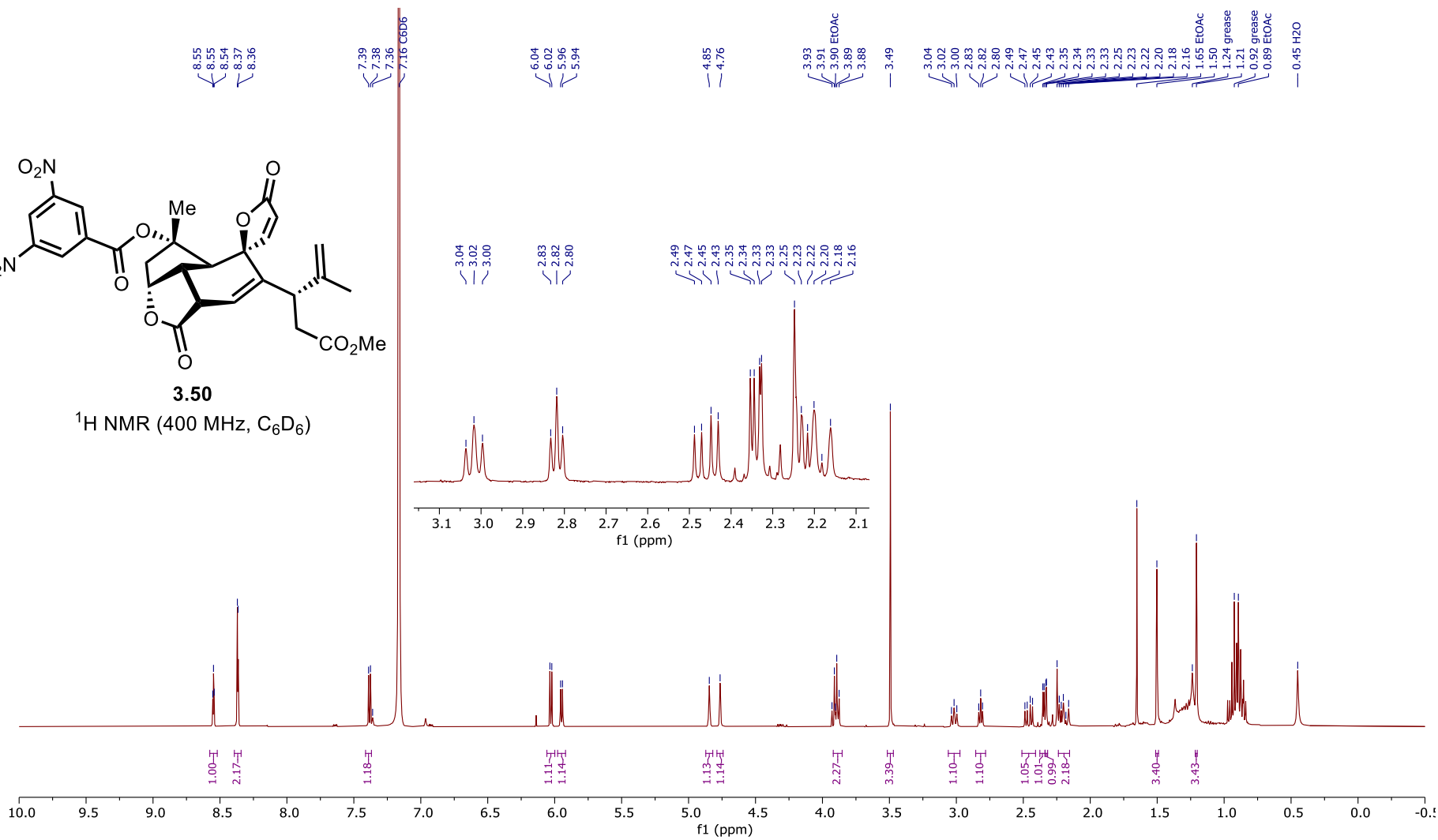


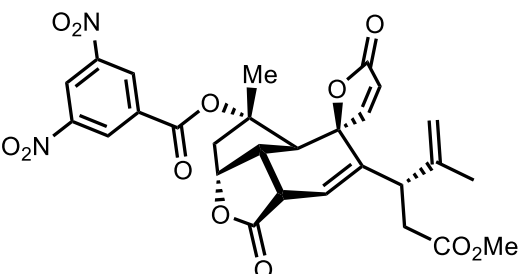


3.49

¹³C NMR (151 MHz, CDCl₃)

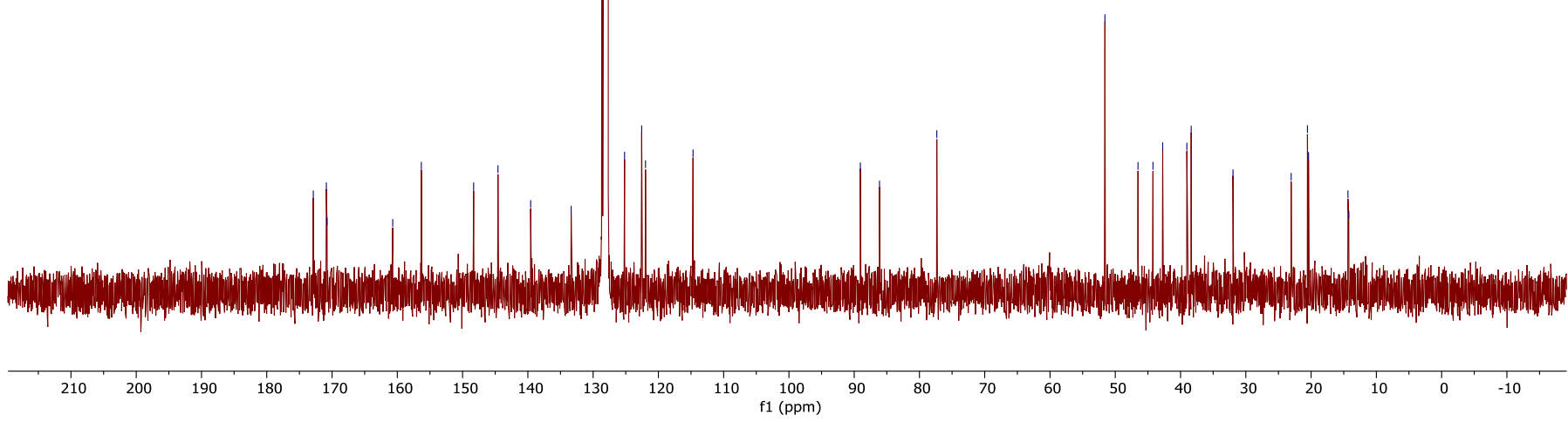


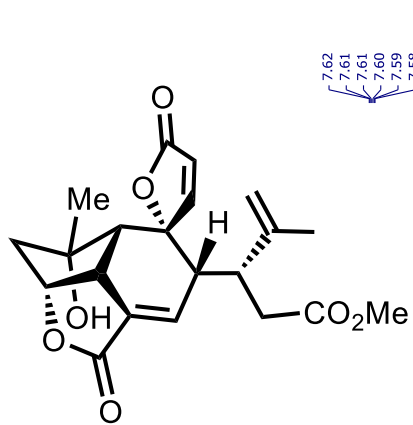




3.50

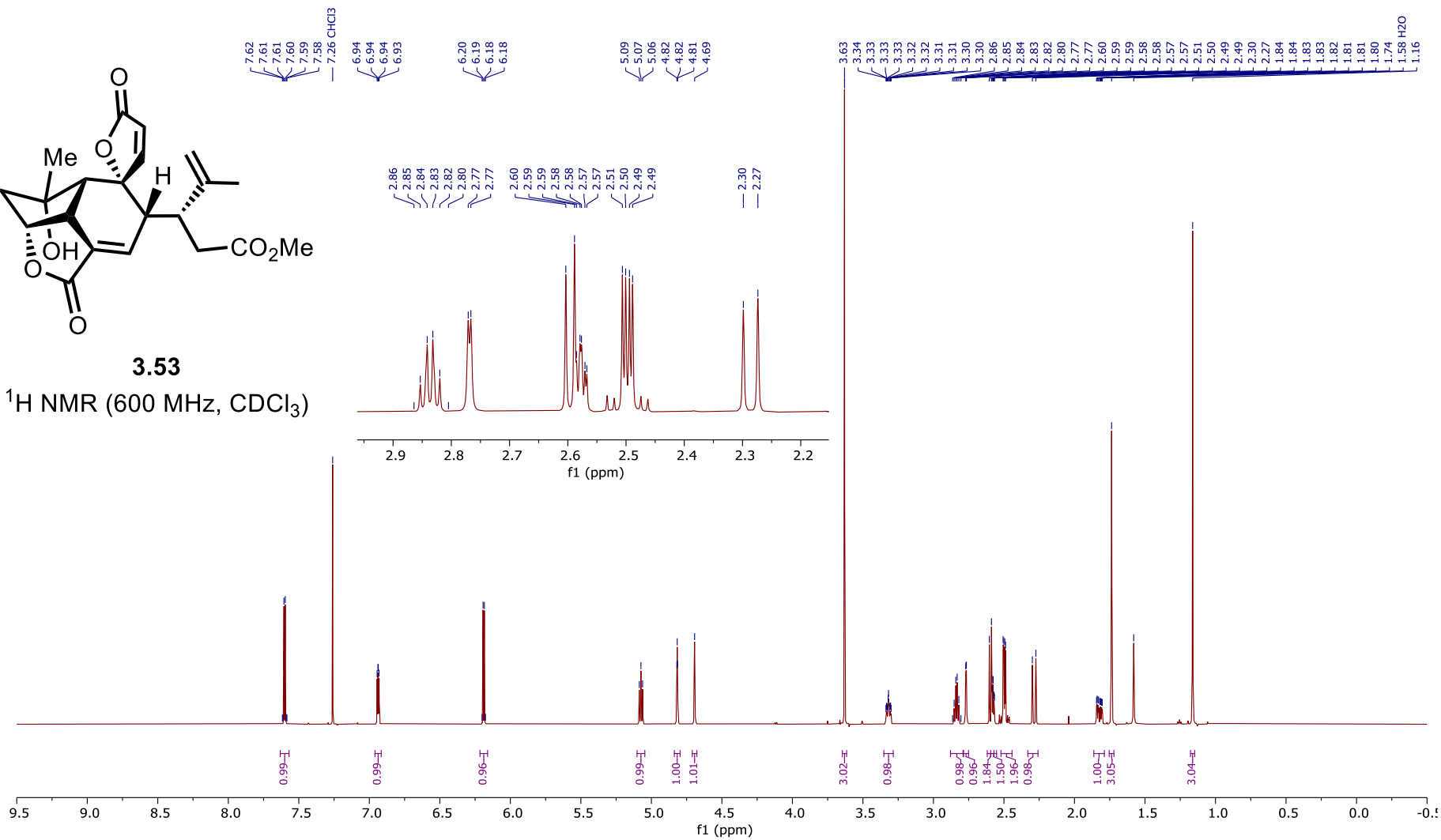
¹H NMR (101 MHz, C₆D₆)

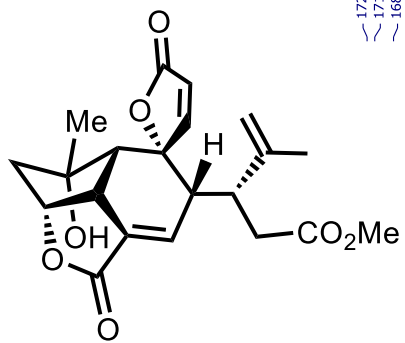




3.53

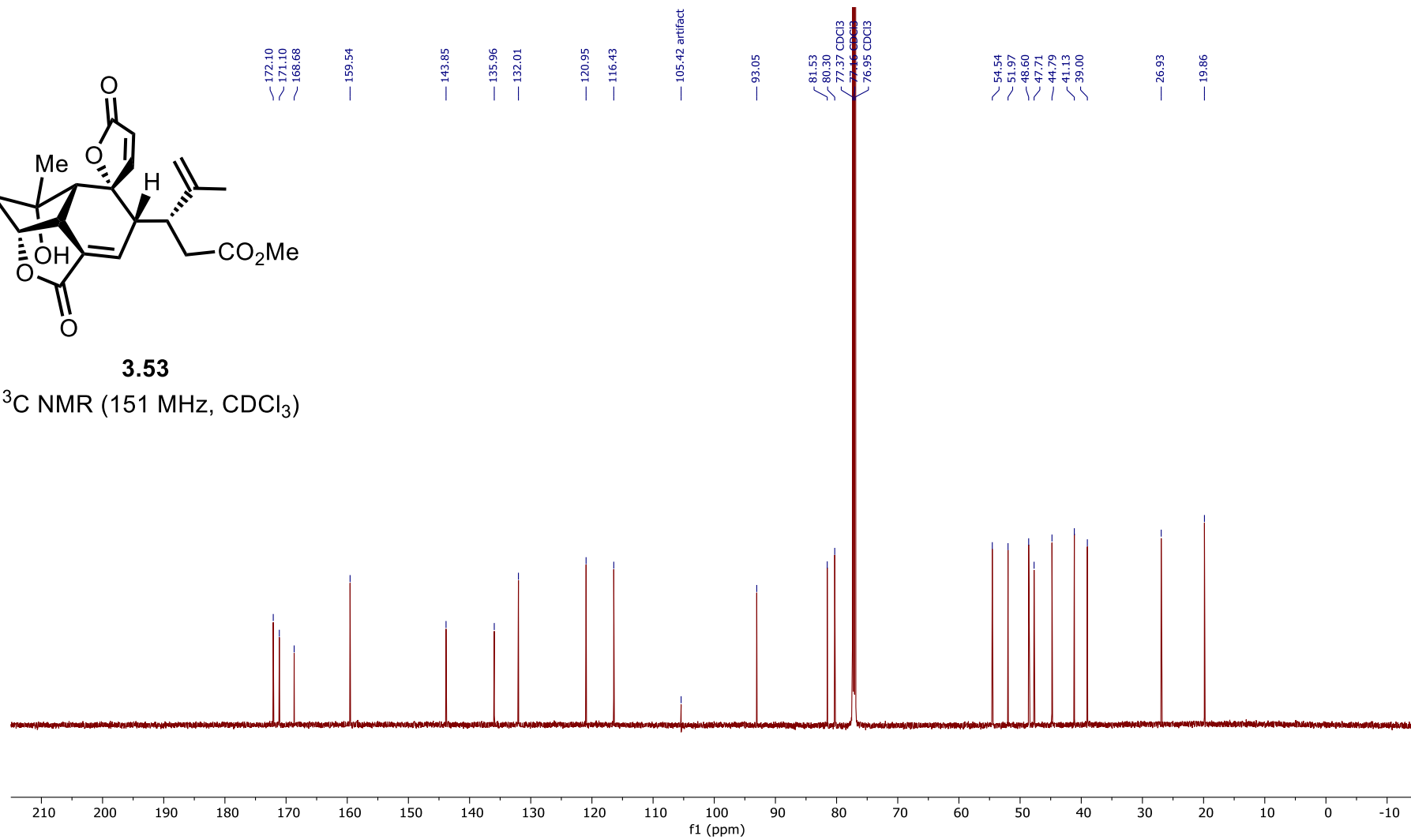
^1H NMR (600 MHz, CDCl_3)

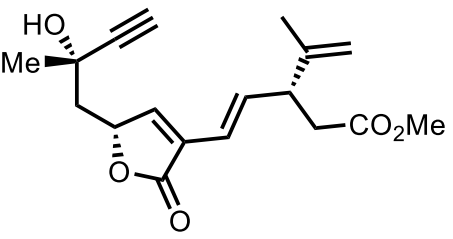




3.53

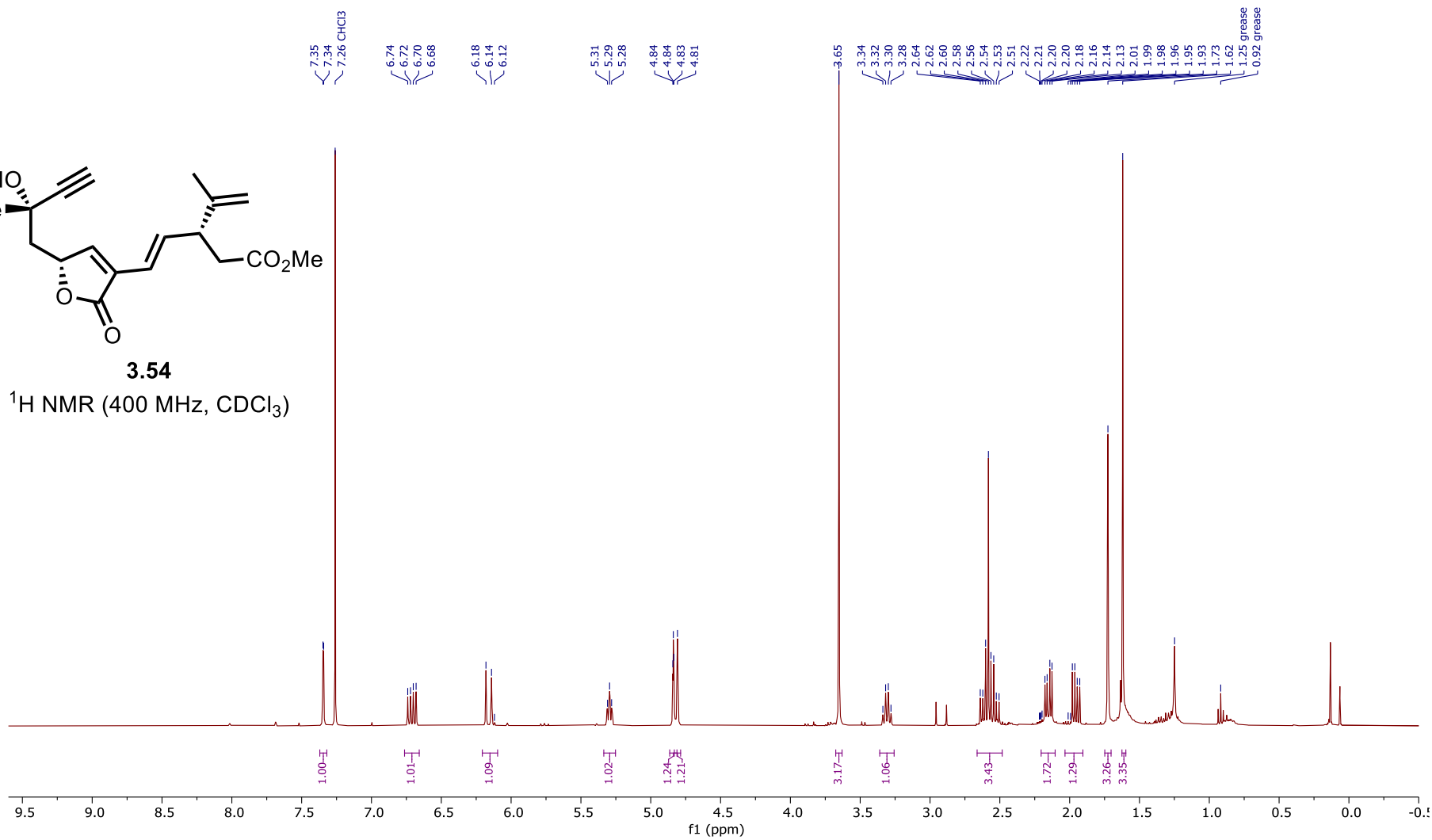
¹³C NMR (151 MHz, CDCl₃)

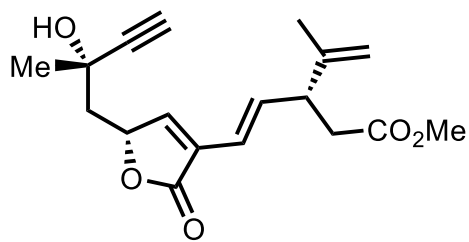




3.54

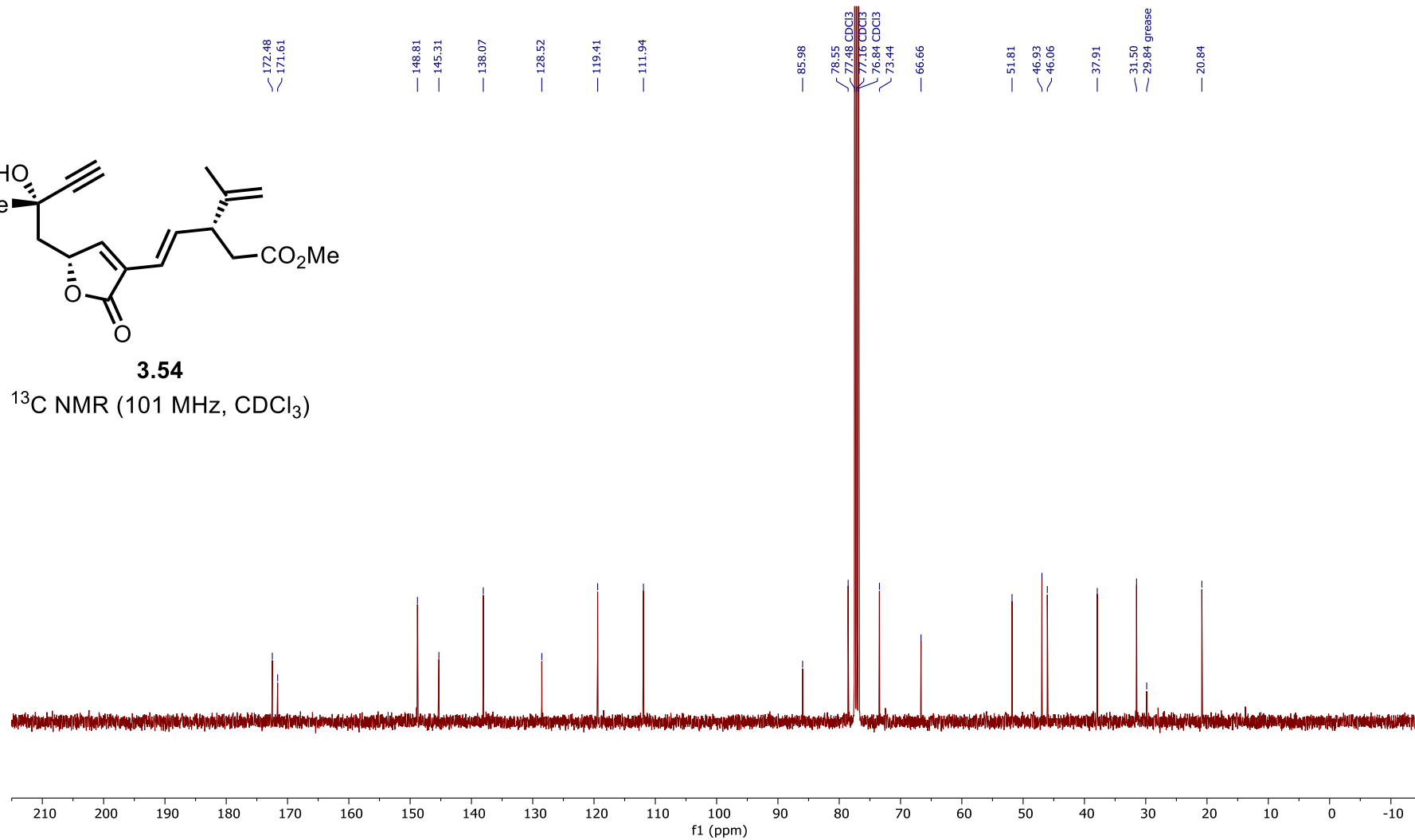
¹H NMR (400 MHz, CDCl₃)

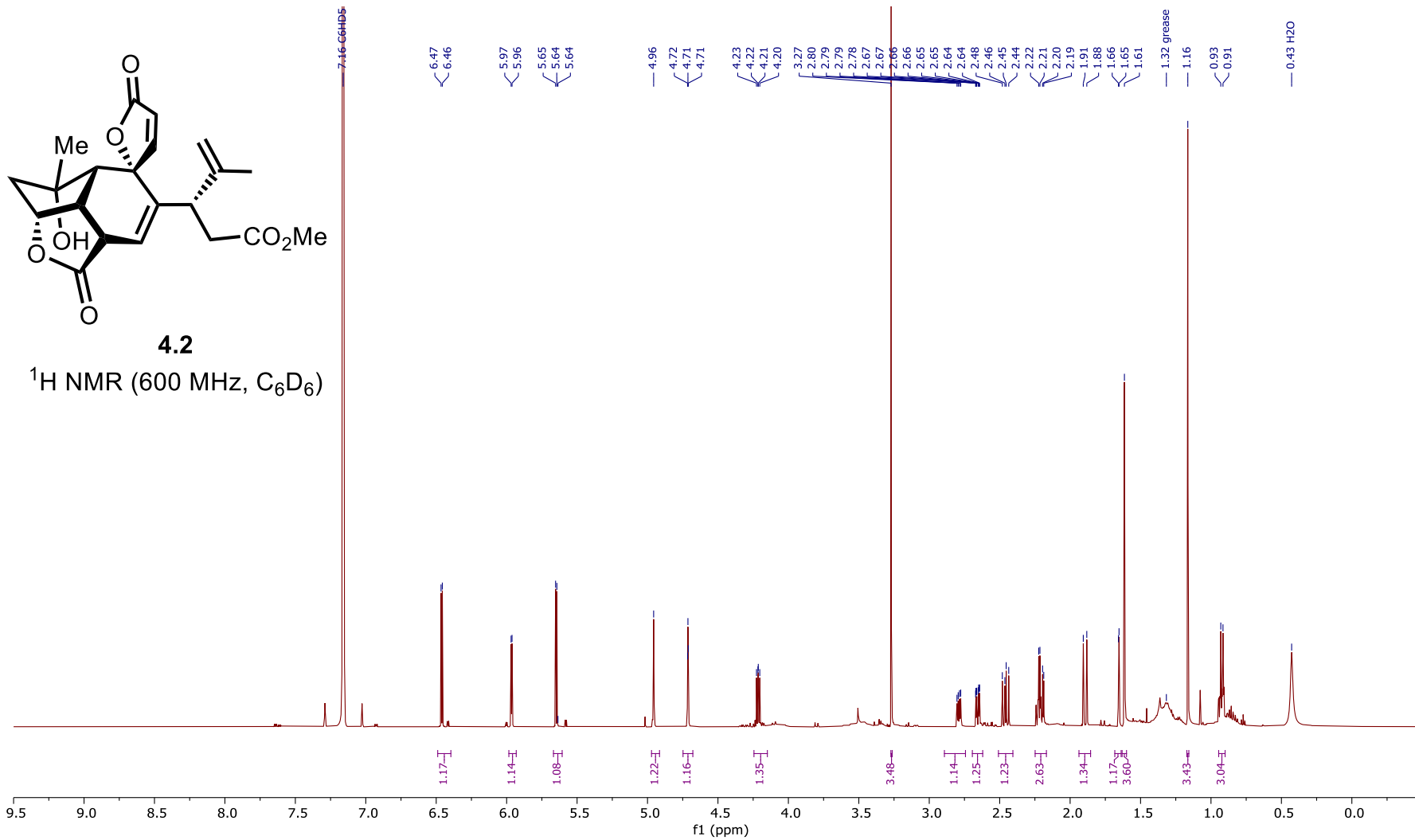


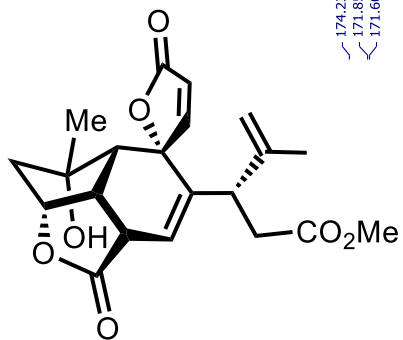


3.54

^{13}C NMR (101 MHz, CDCl_3)

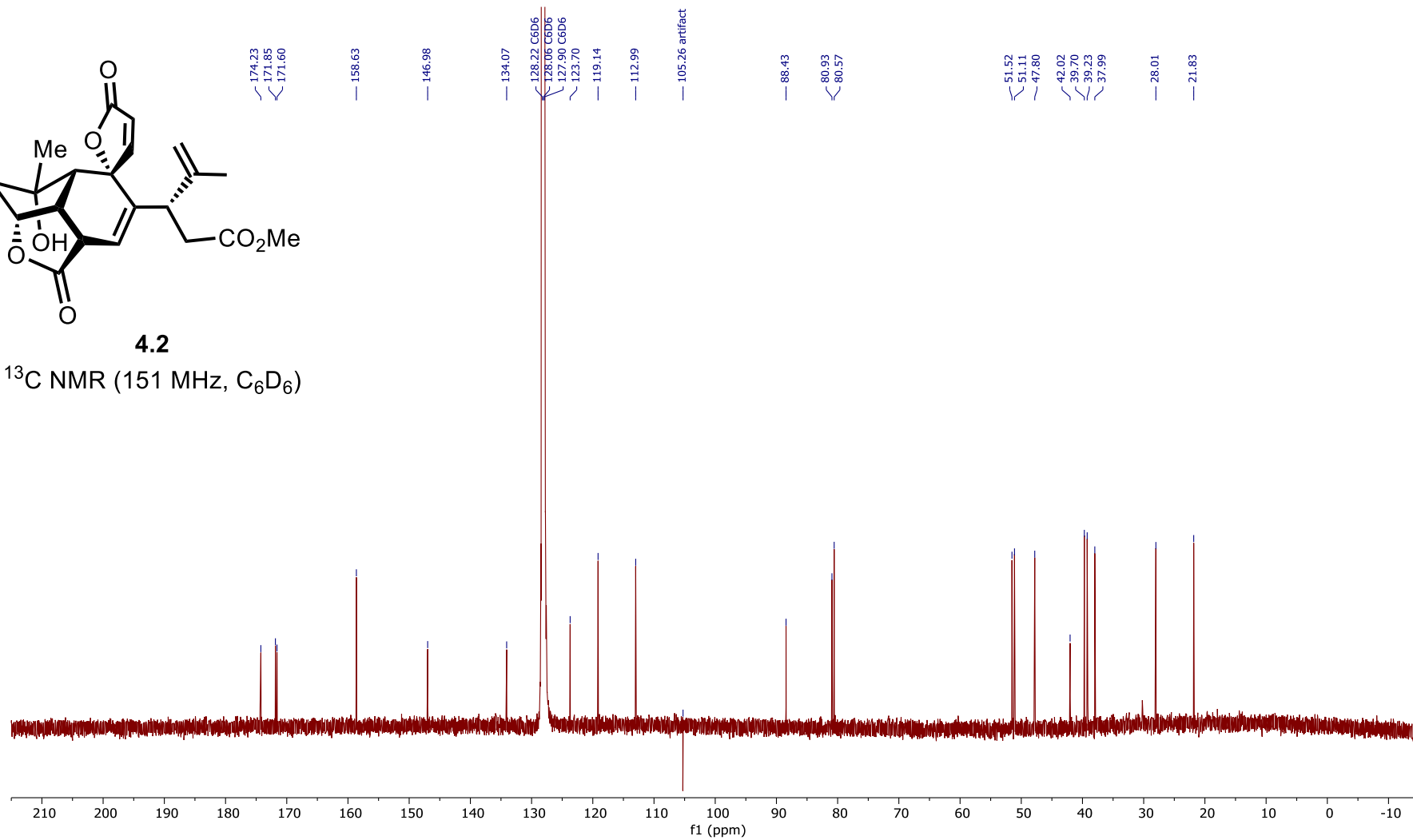


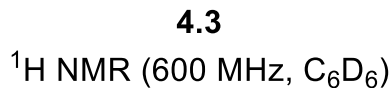


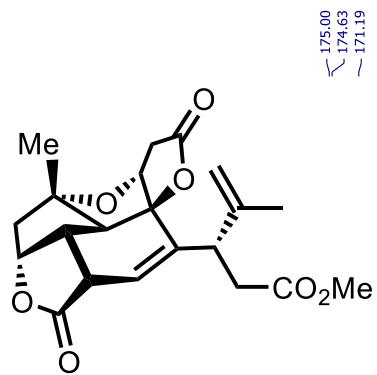


4.2

¹³C NMR (151 MHz, C₆D₆)

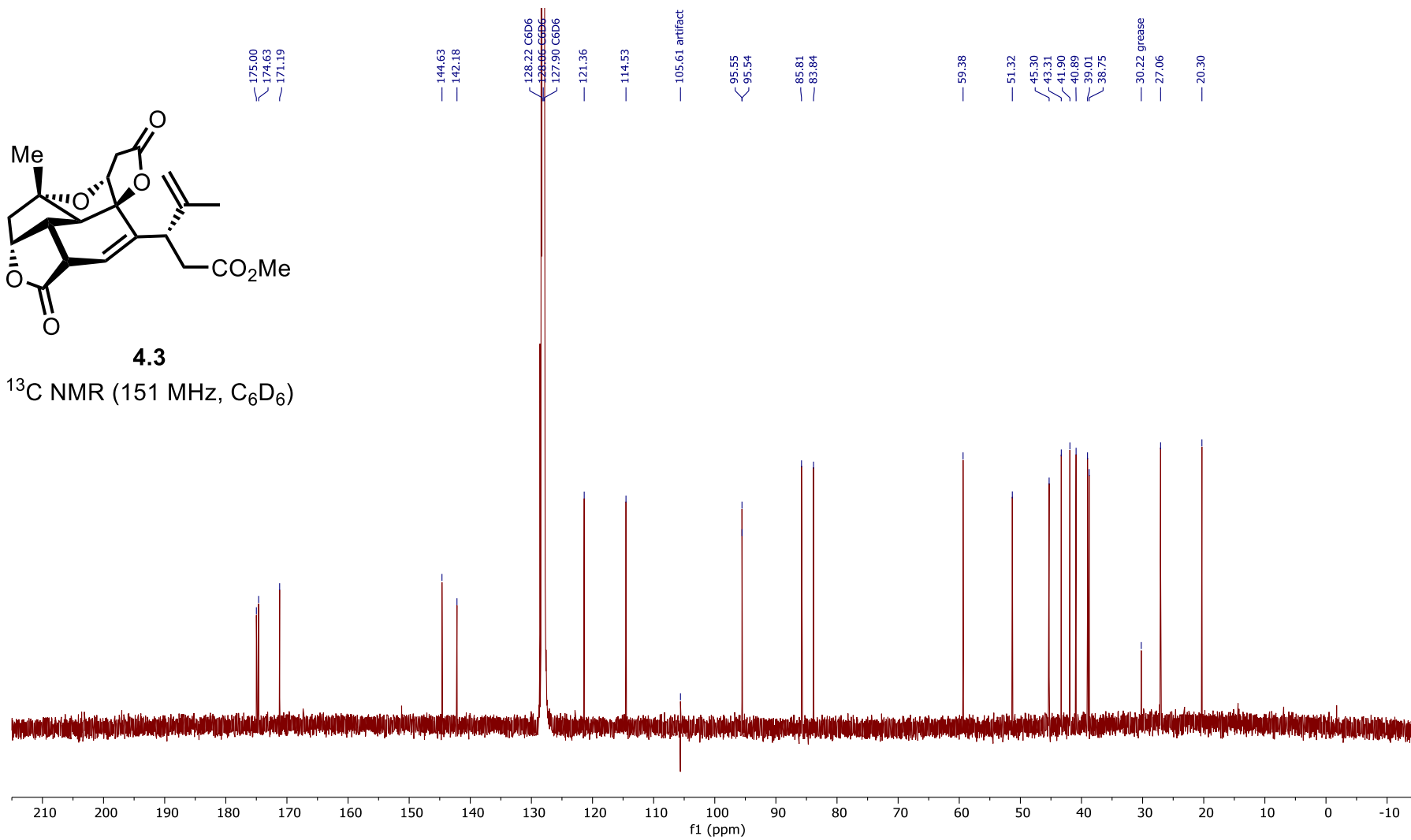


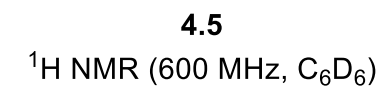


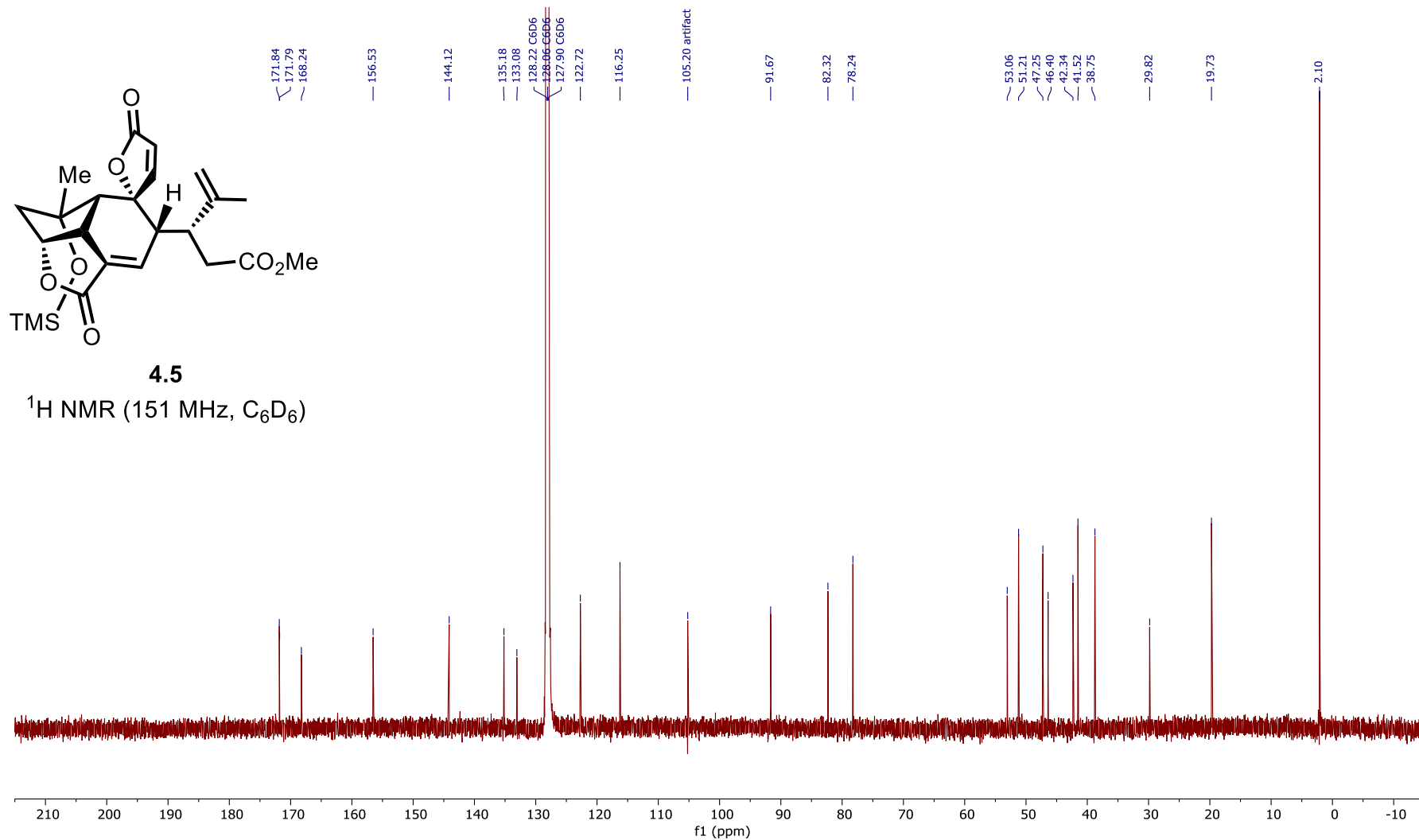


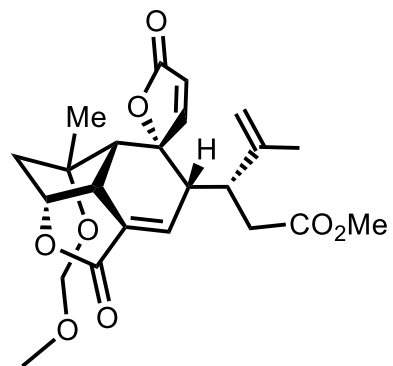
4.3

¹³C NMR (151 MHz, C₆D₆)



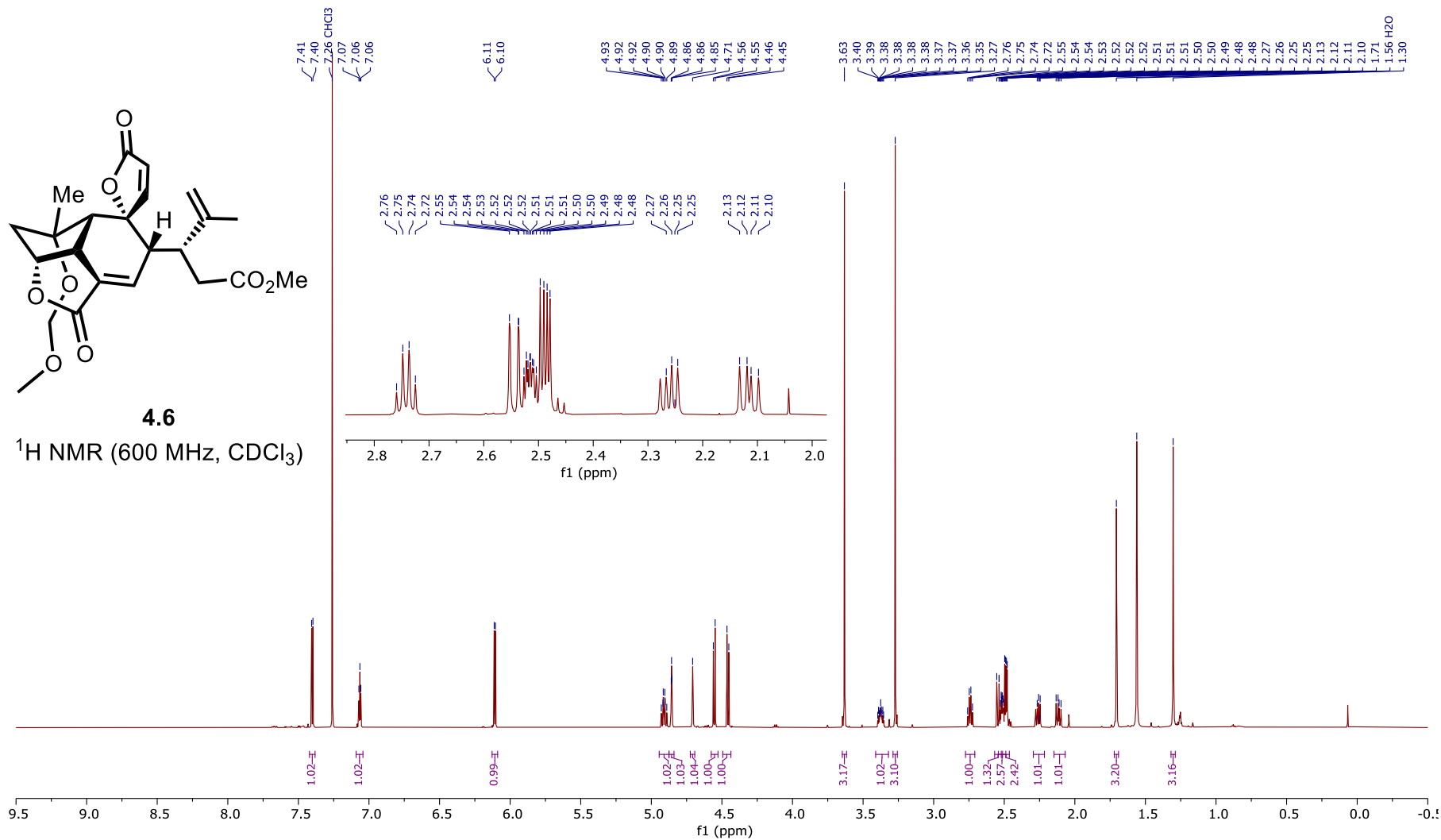


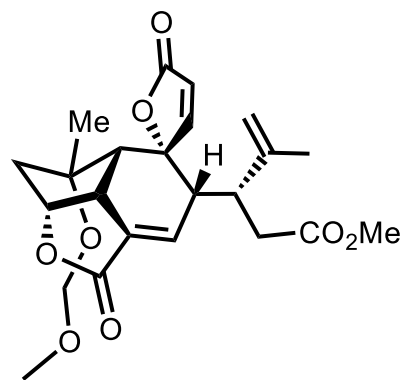




4.6

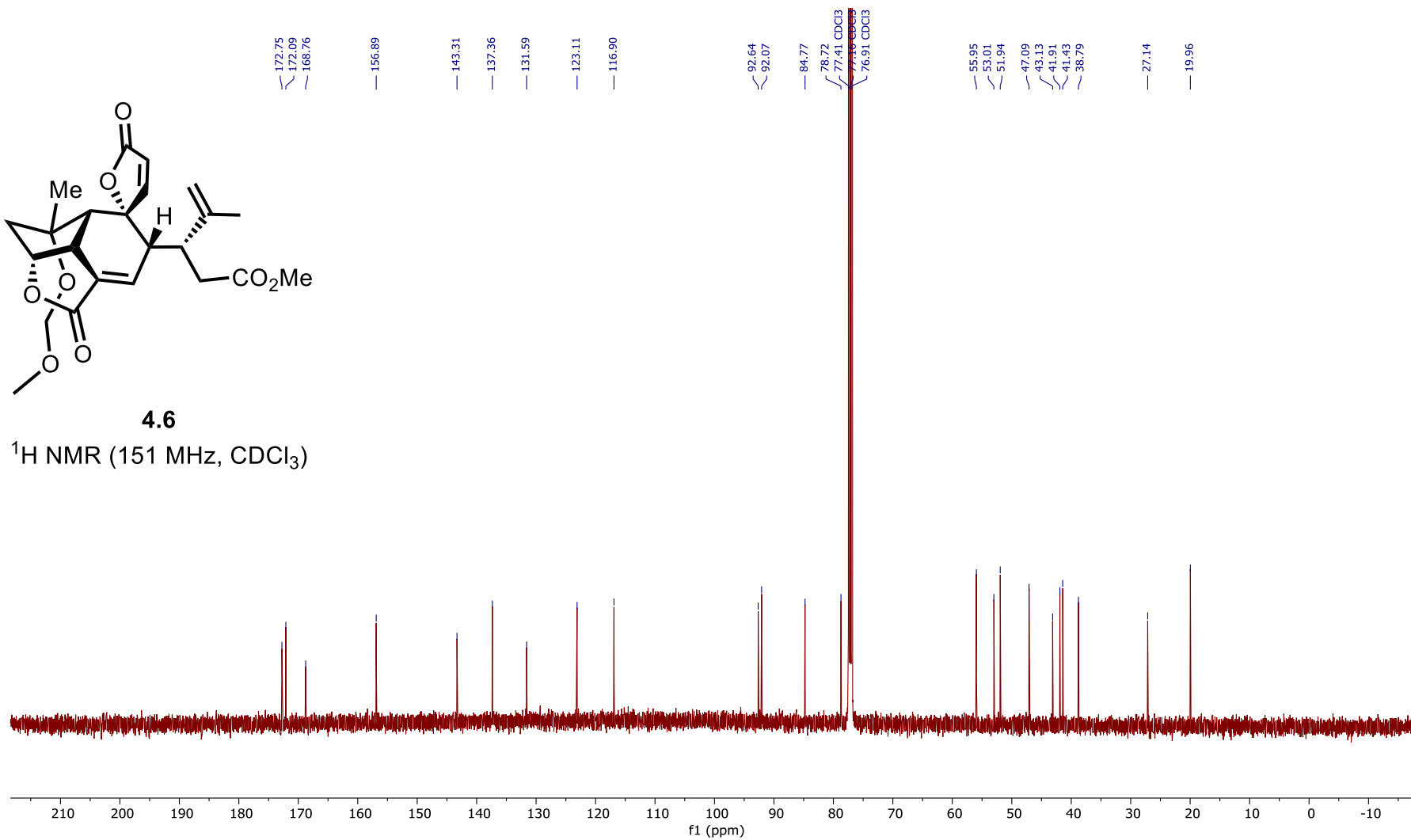
^1H NMR (600 MHz, CDCl_3)

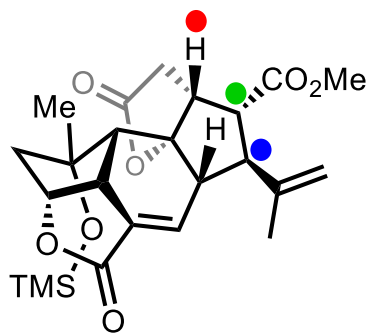




4.6

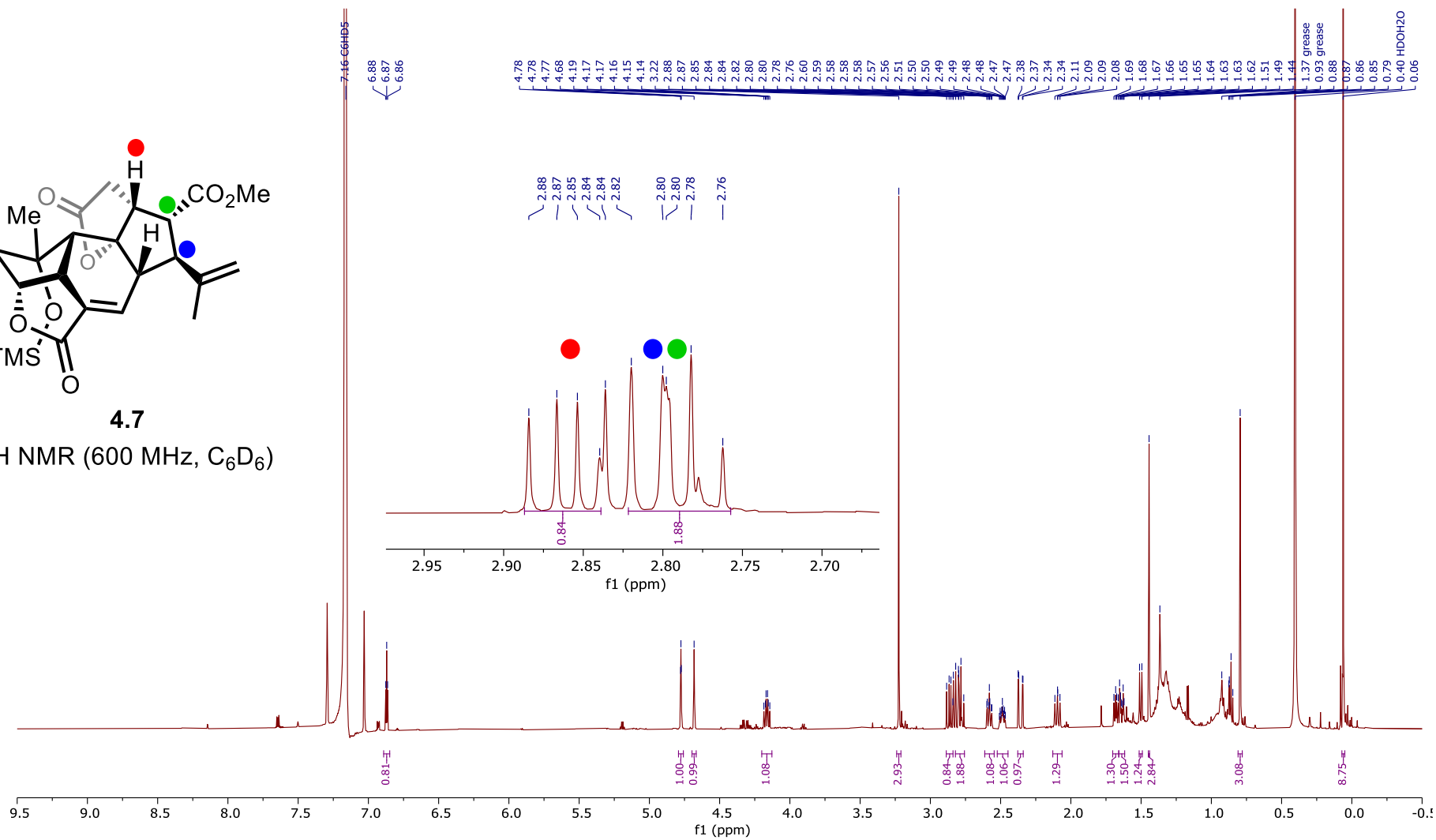
^1H NMR (151 MHz, CDCl_3)

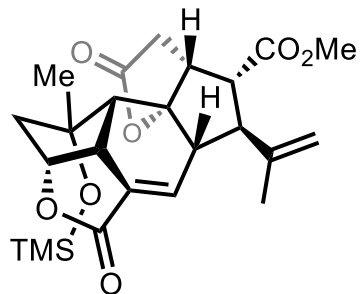




4.7

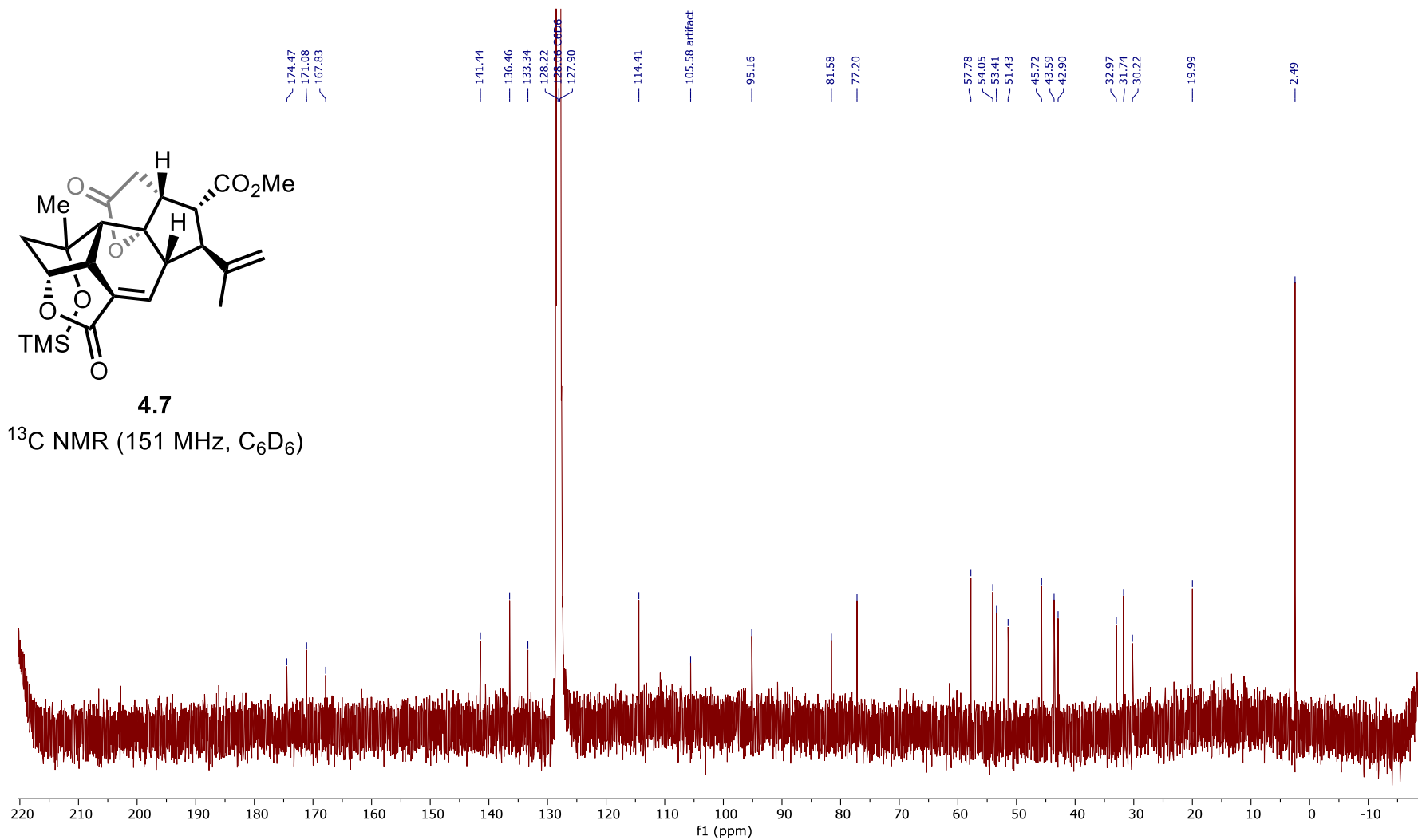
^1H NMR (600 MHz, C_6D_6)

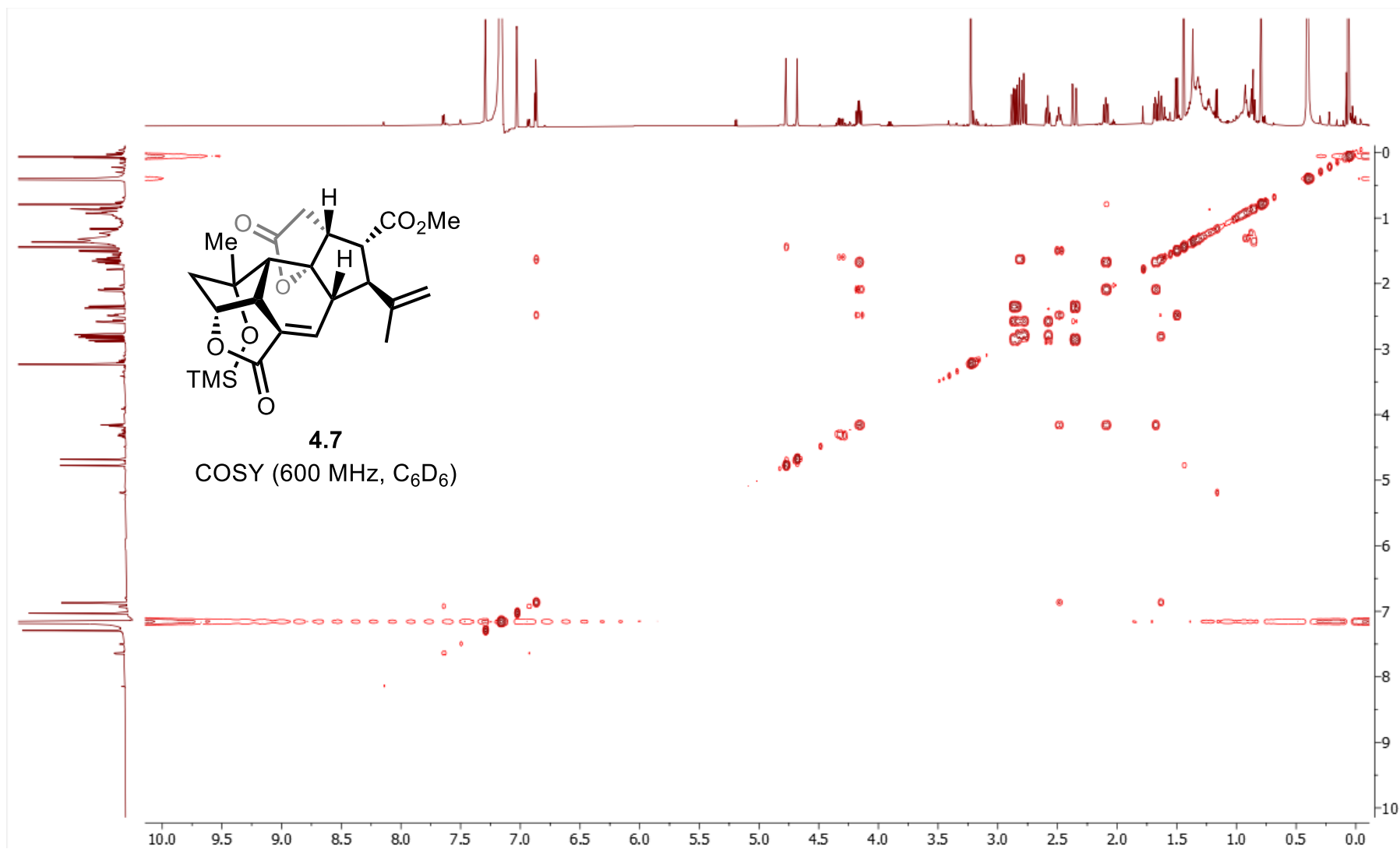


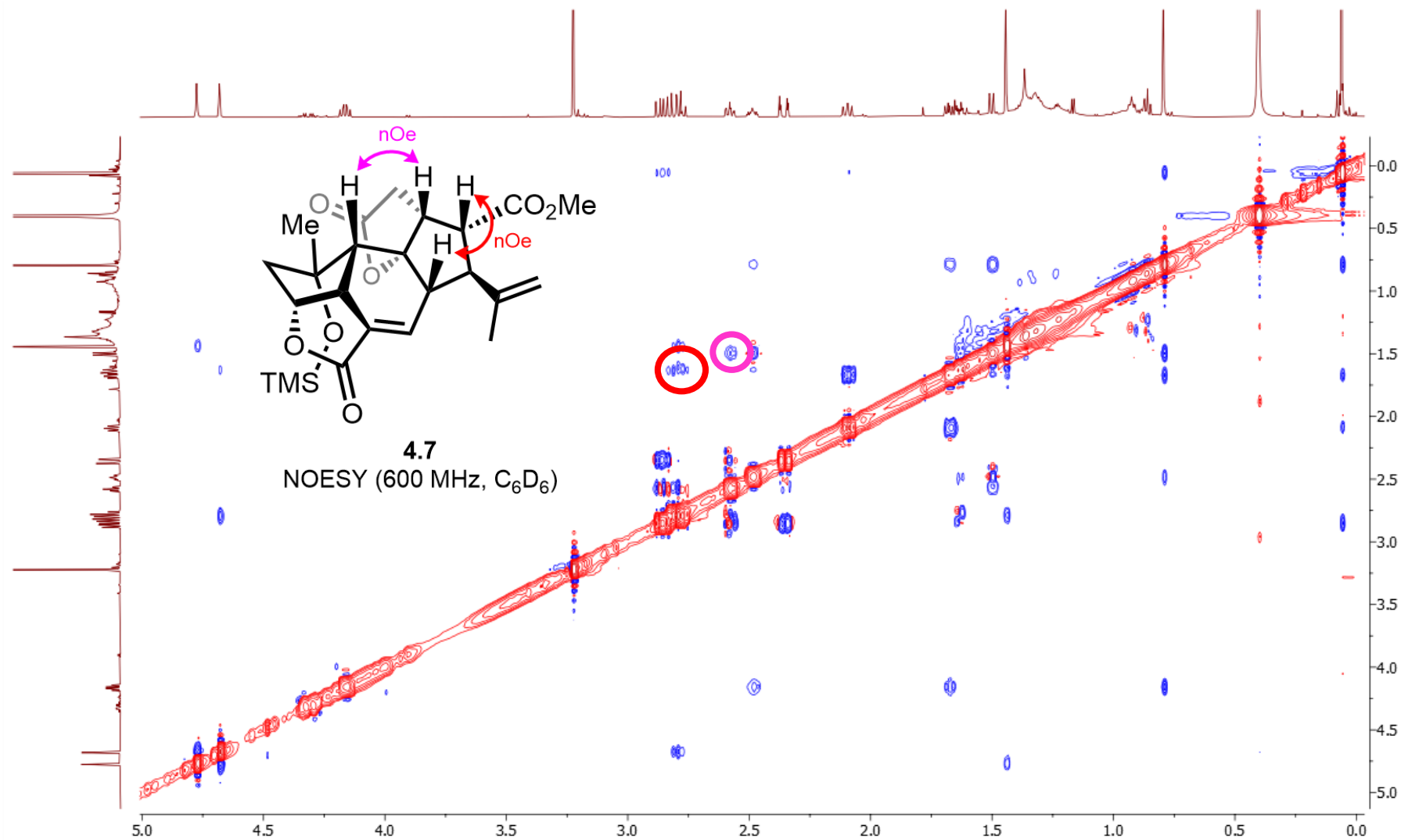


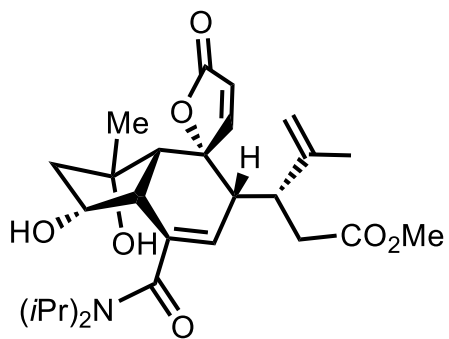
4.7

¹³C NMR (151 MHz, C₆D₆)



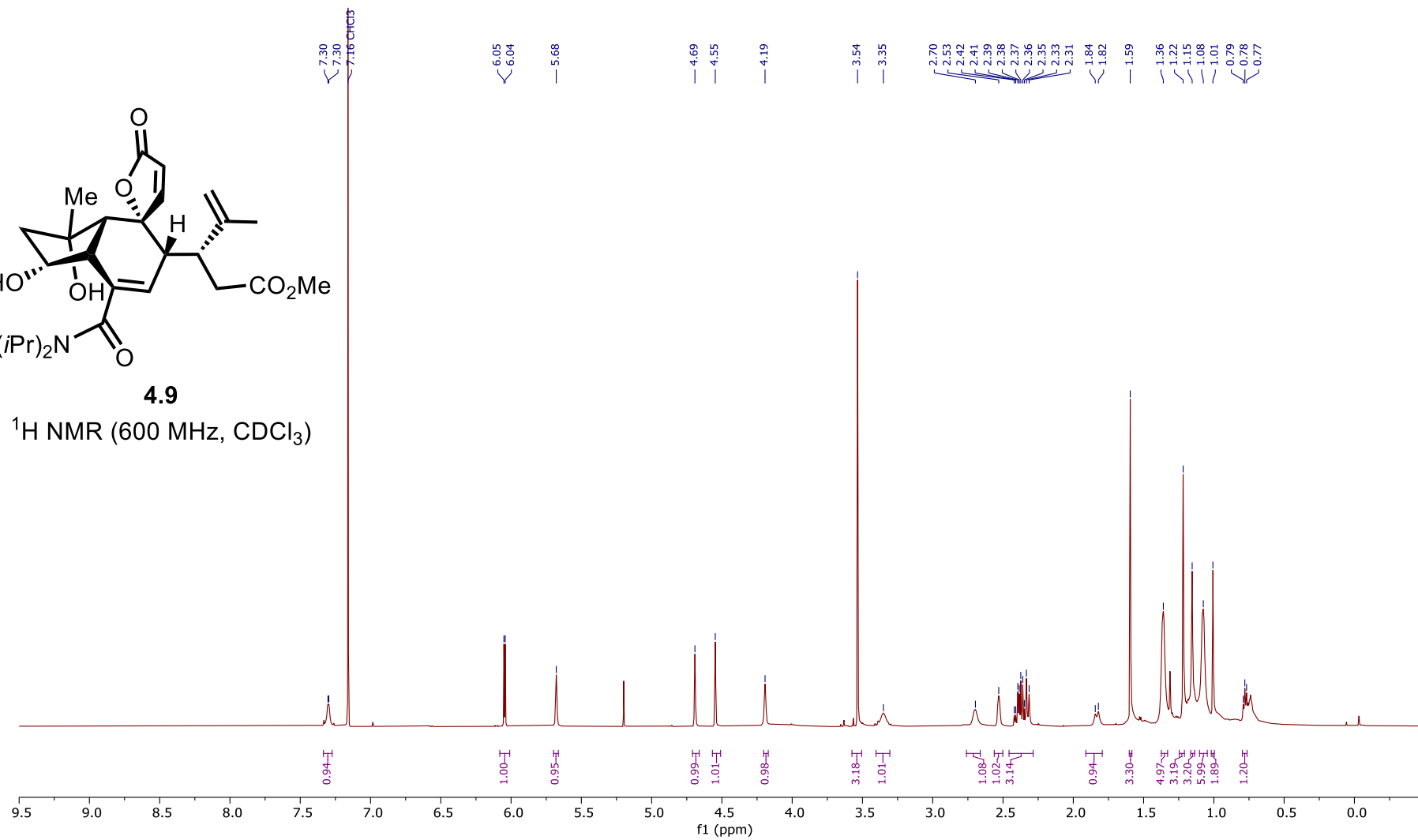


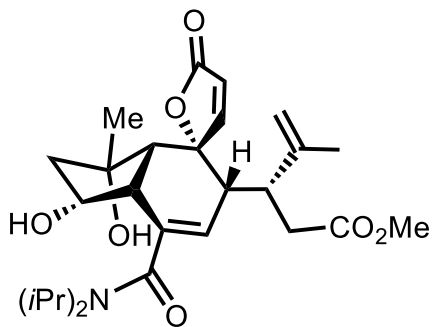




4.9

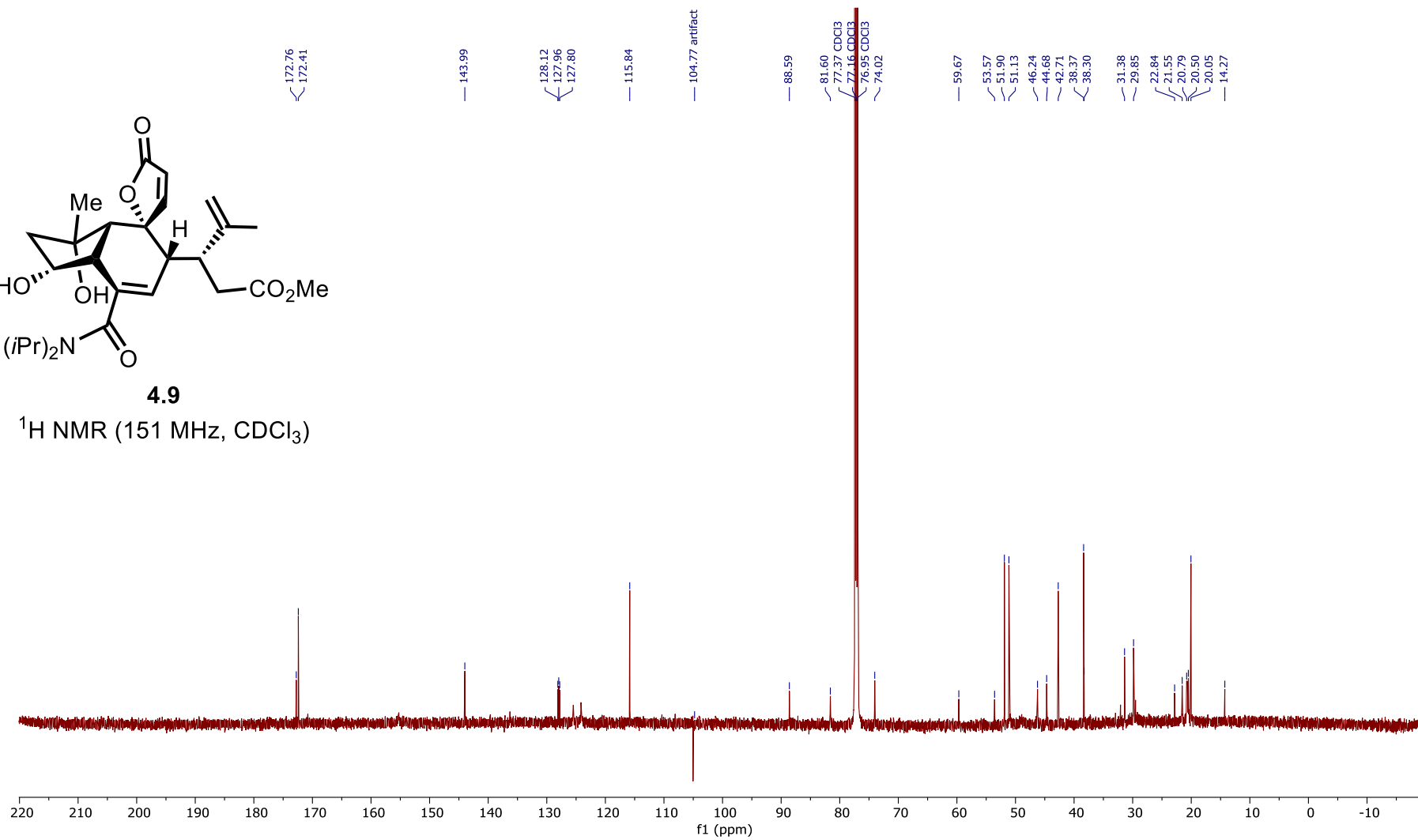
1H NMR (600 MHz, $CDCl_3$)

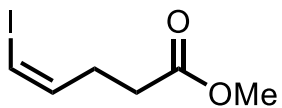




4.9

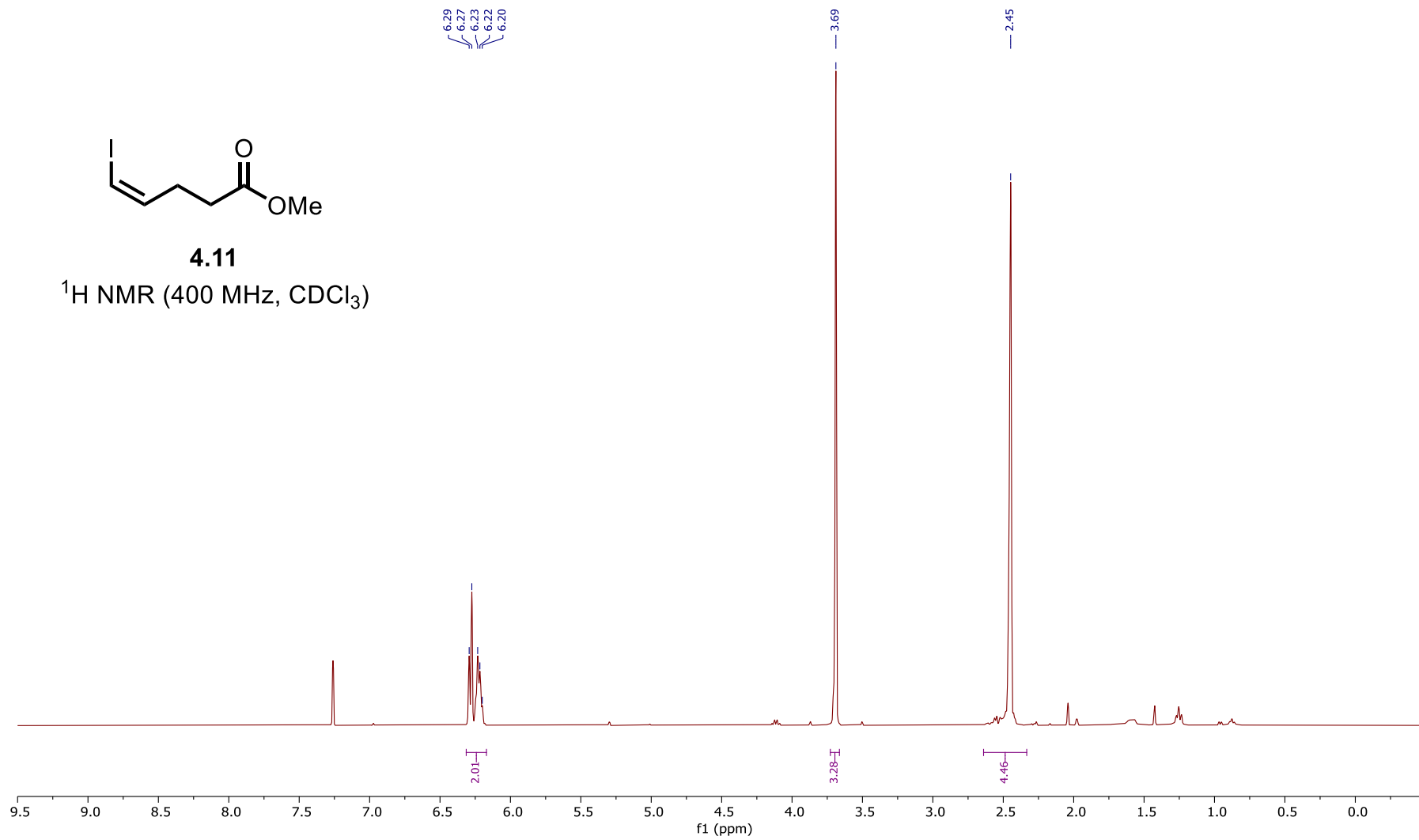
^1H NMR (151 MHz, CDCl_3)

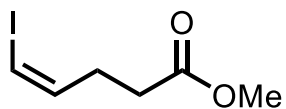




4.11

^1H NMR (400 MHz, CDCl_3)





4.11

^{13}C NMR (101 MHz, CDCl_3)

— 173.11

— 139.31

— 83.97

(77.48 CDCl_3

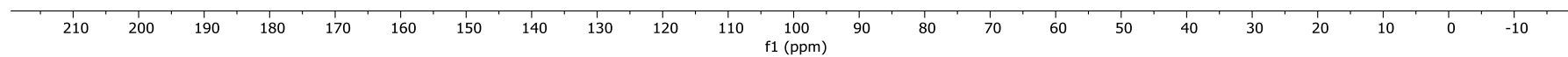
77.16 CDCl_3

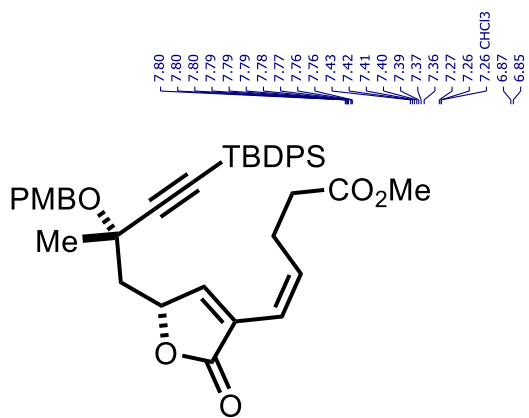
76.84 CDCl_3

— 51.87

— 32.38

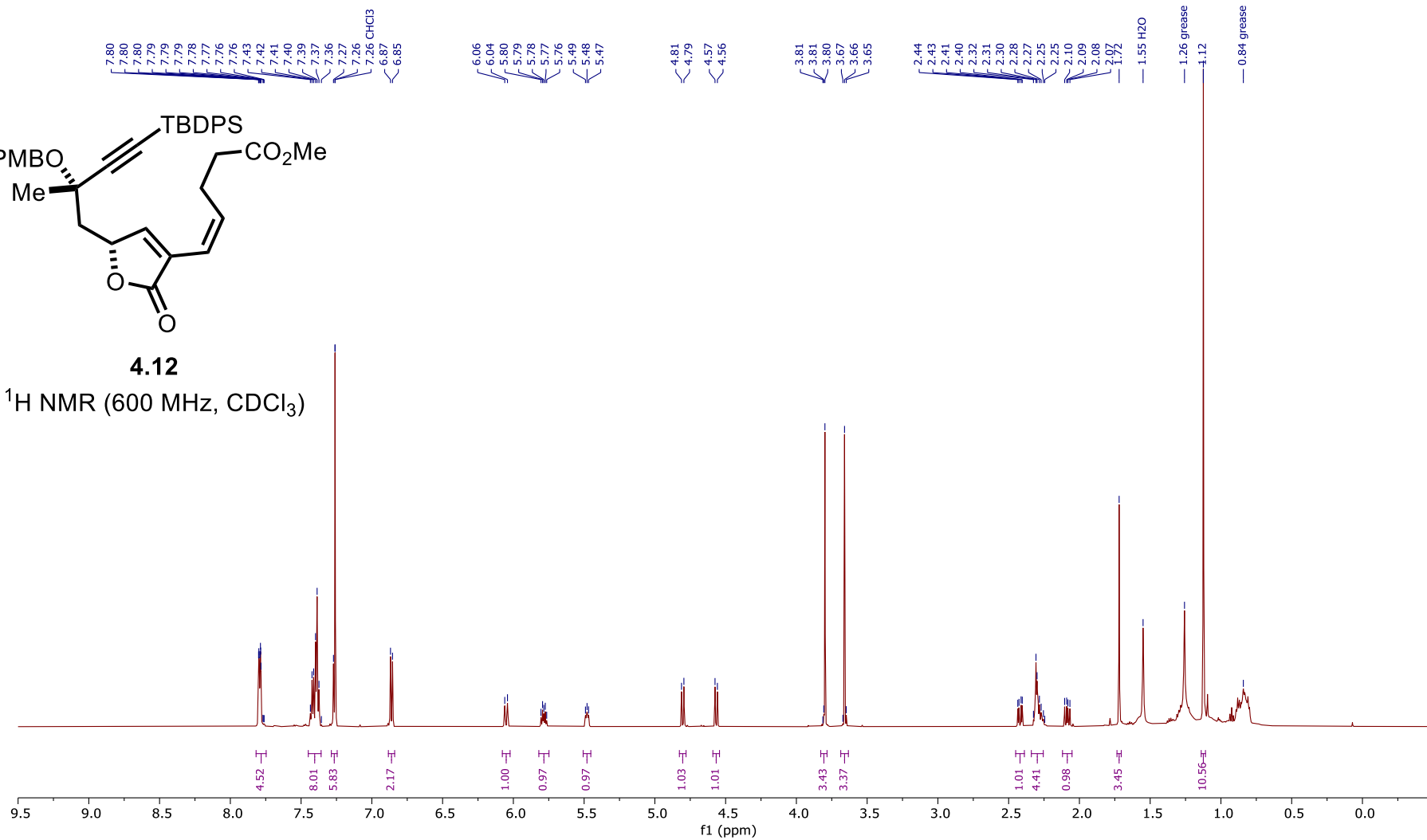
— 30.30

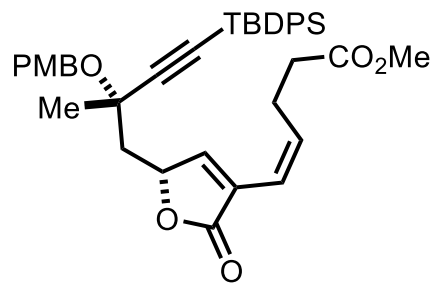




4.12

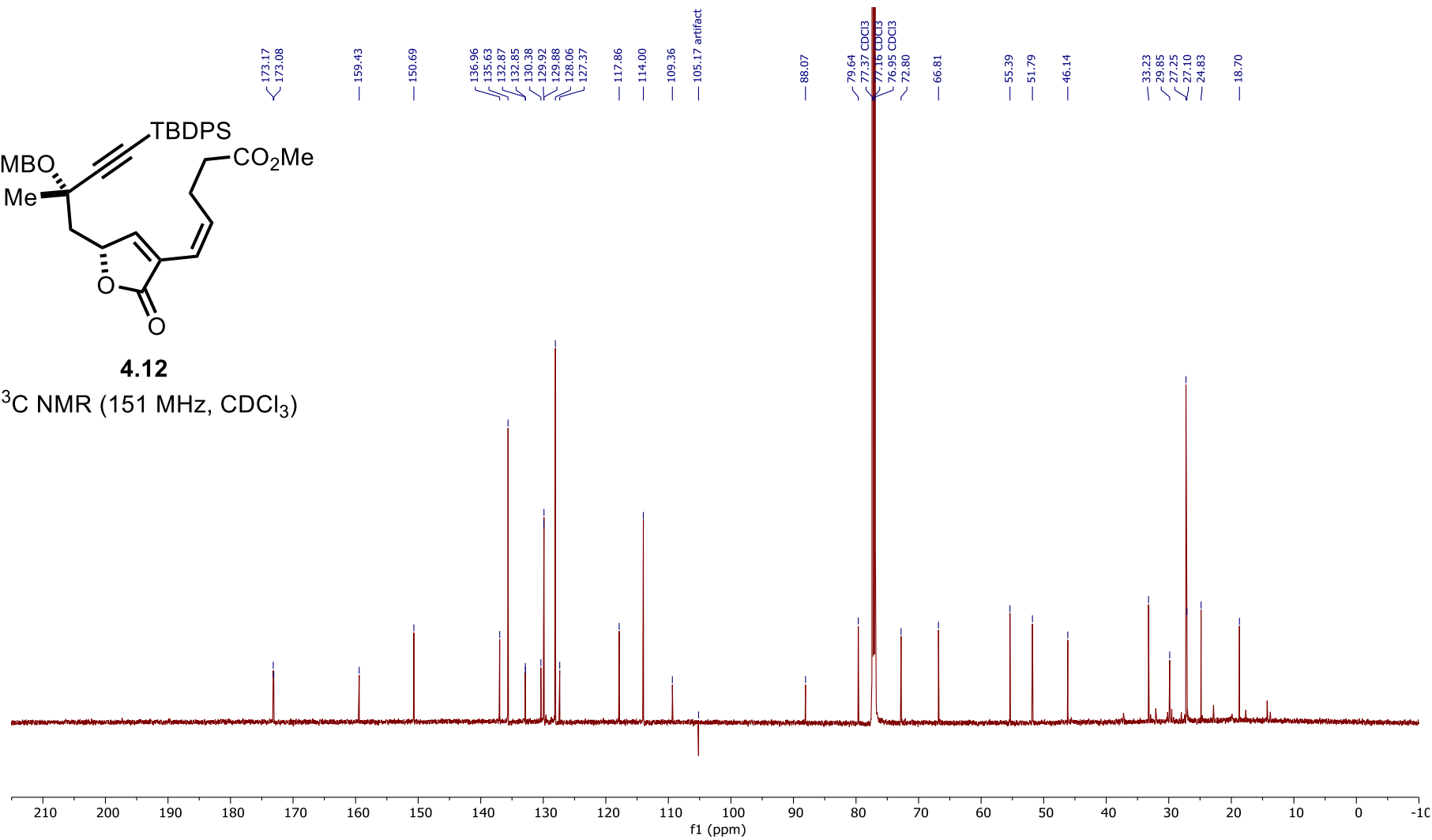
¹H NMR (600 MHz, CDCl₃)

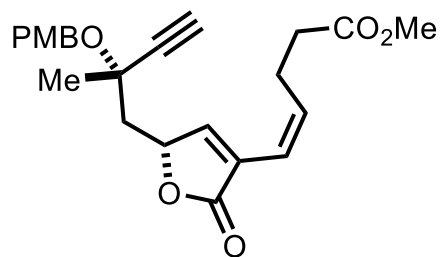




4.12

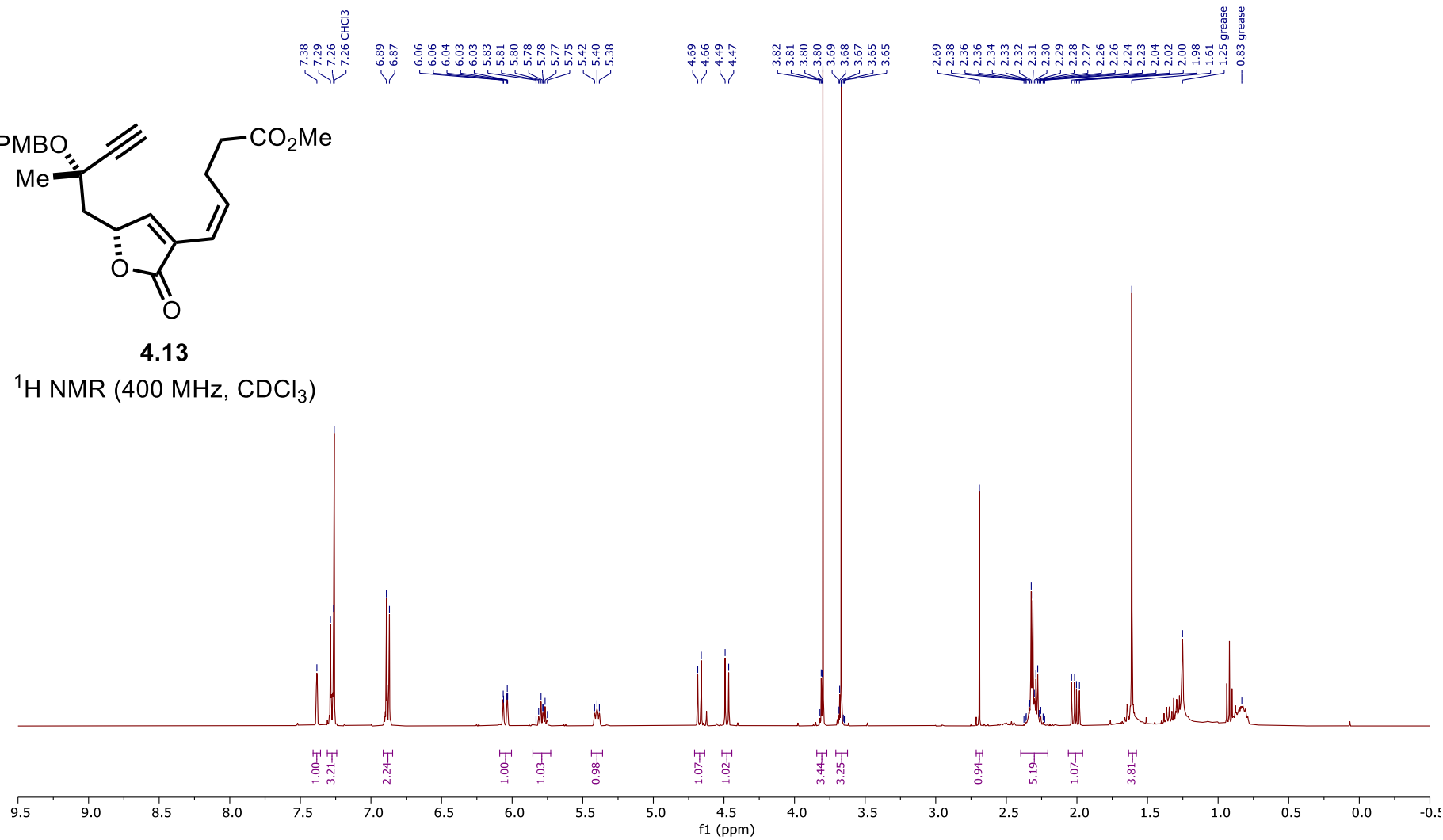
^{13}C NMR (151 MHz, CDCl_3)

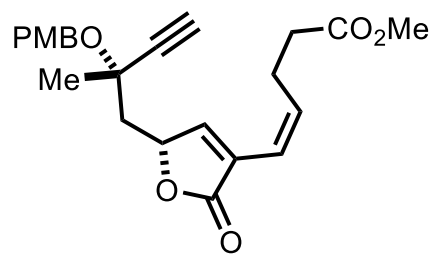




4.13

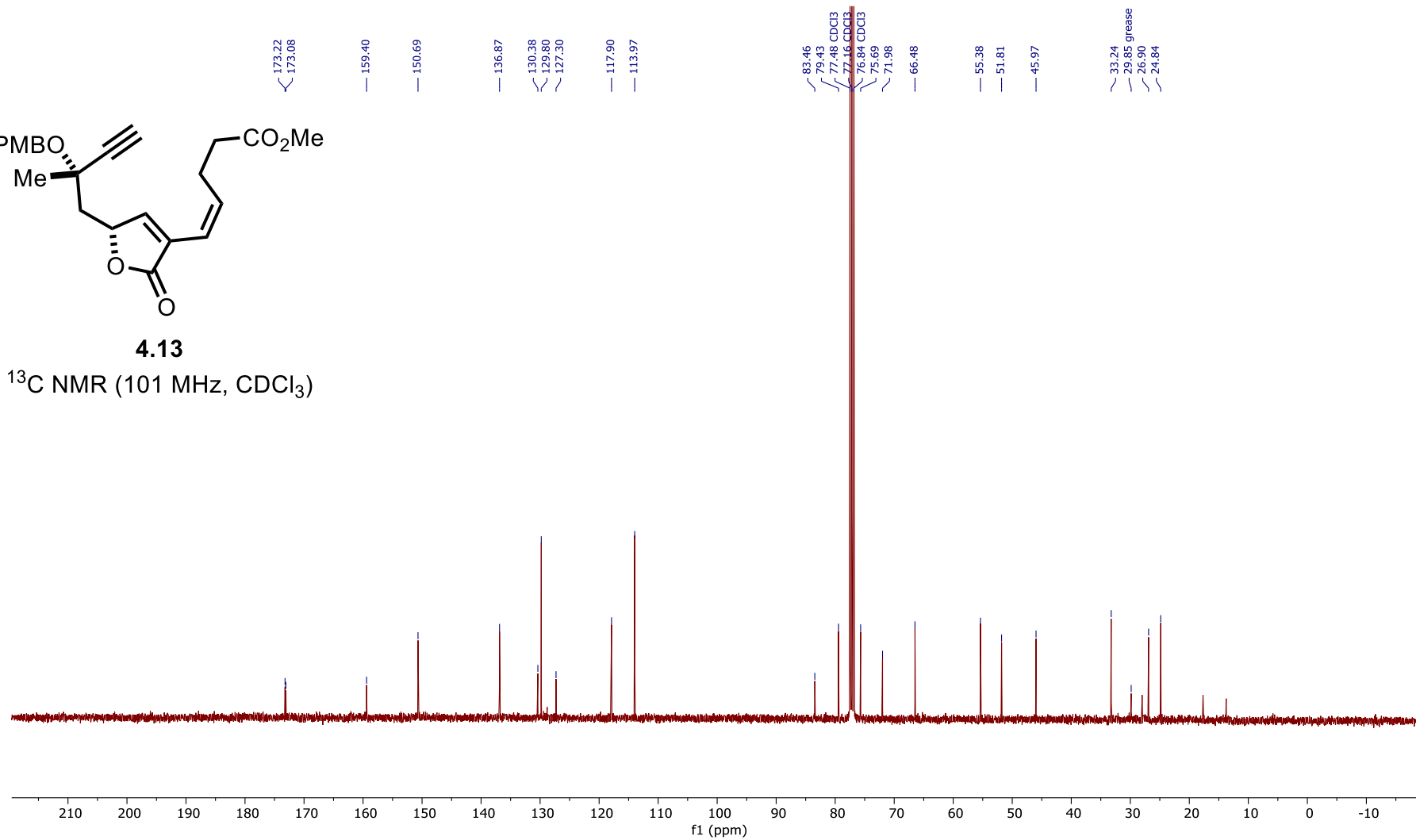
¹H NMR (400 MHz, CDCl₃)

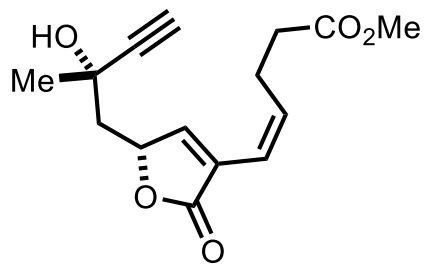




4.13

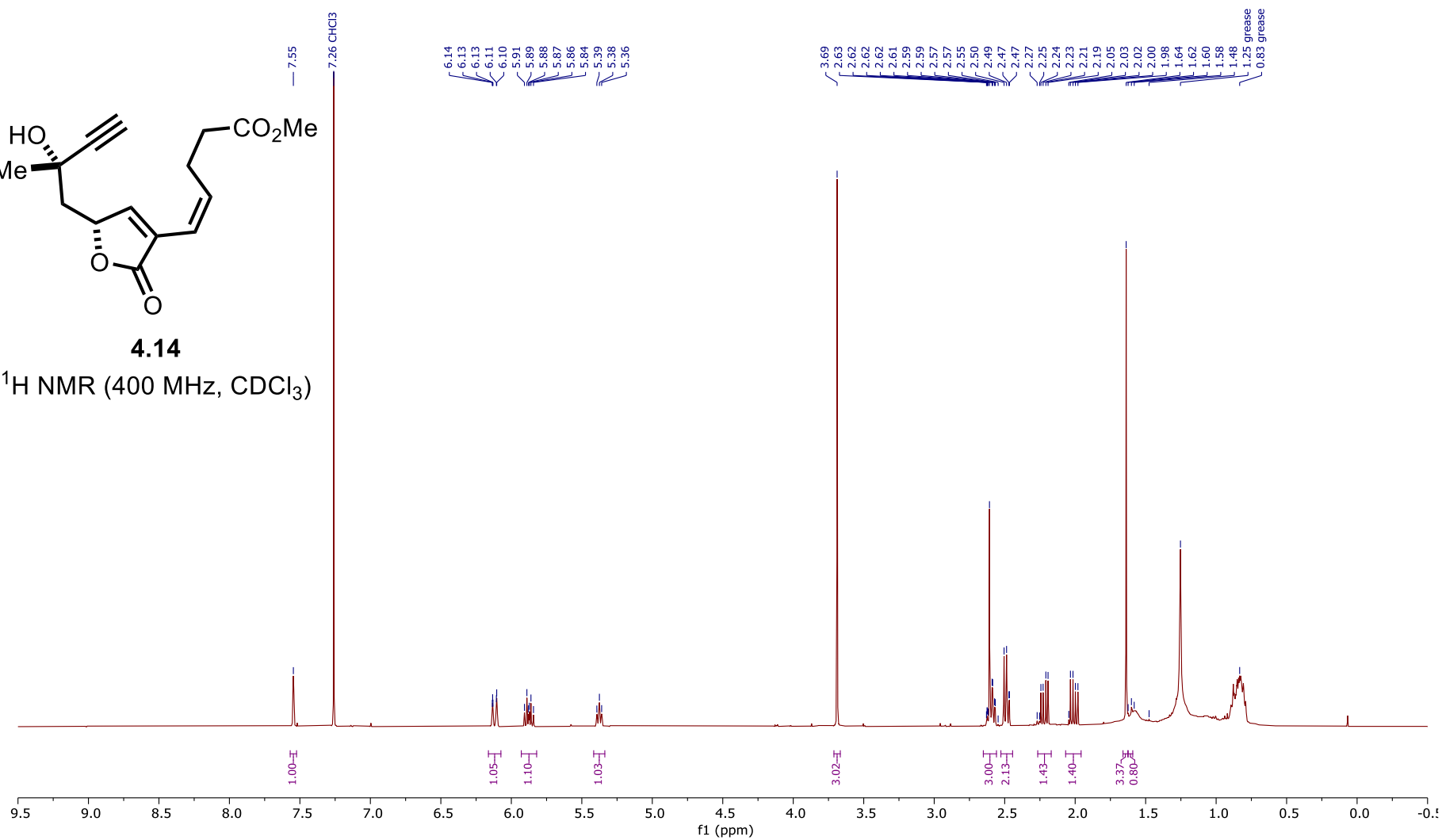
^{13}C NMR (101 MHz, CDCl_3)

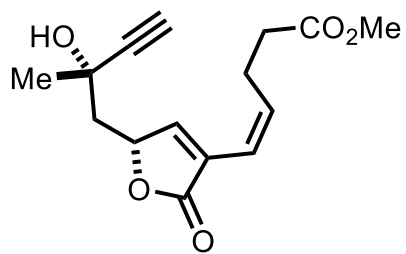




4.14

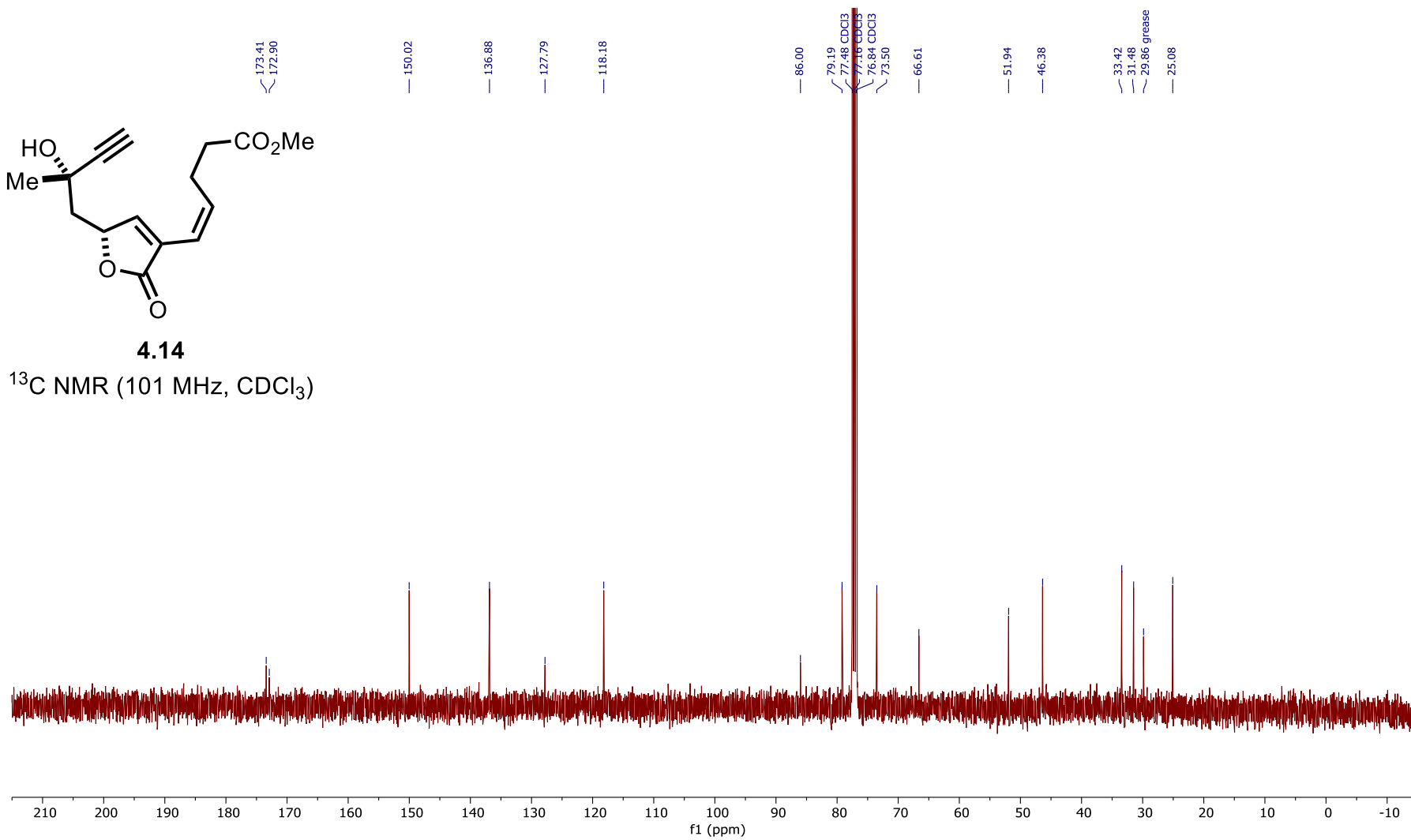
^1H NMR (400 MHz, CDCl_3)

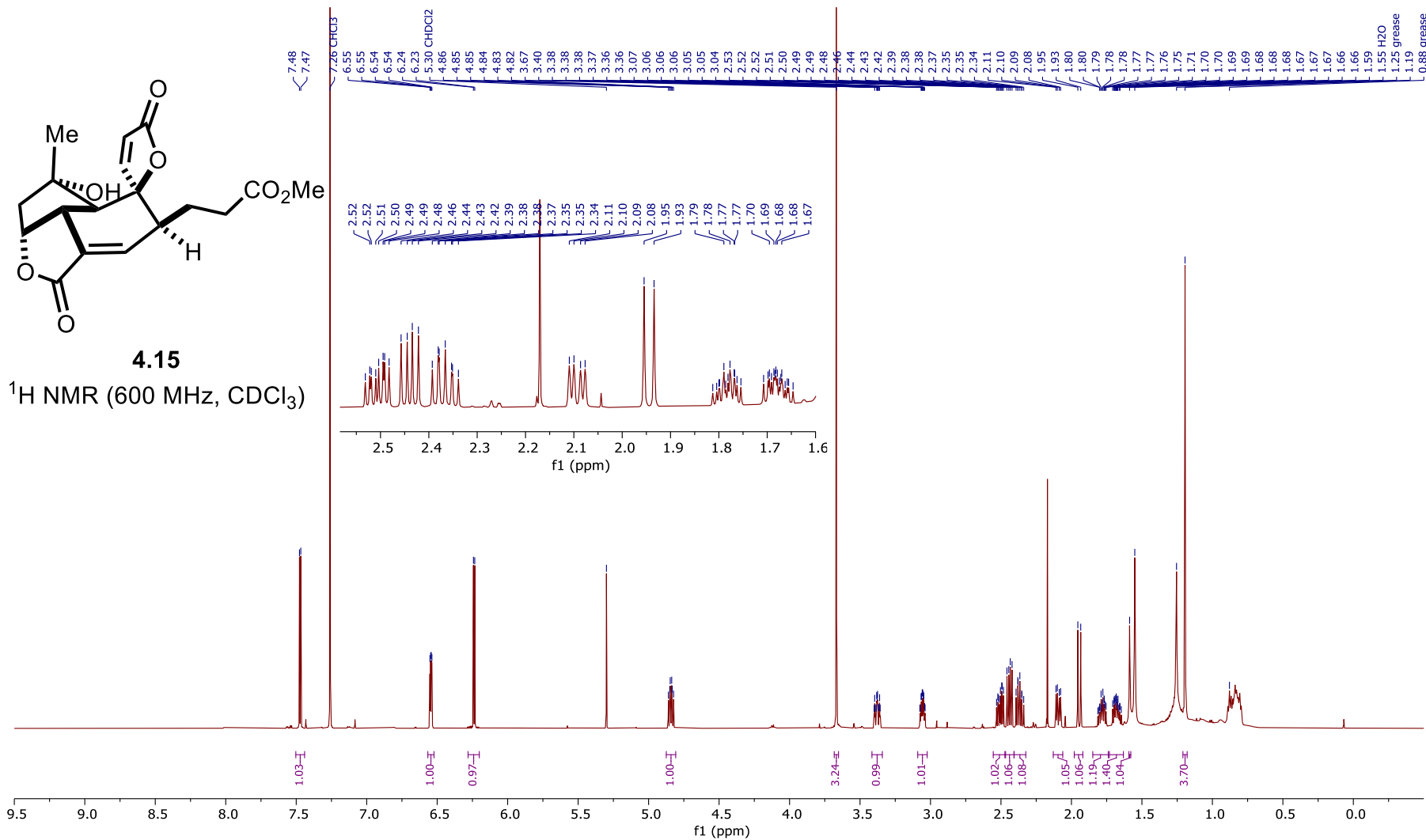


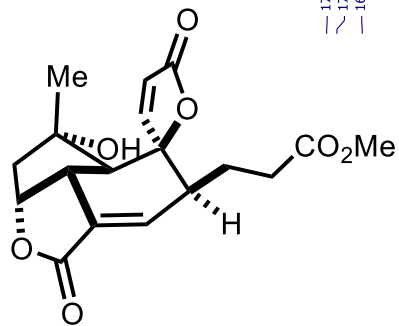


4.14

^{13}C NMR (101 MHz, CDCl_3)

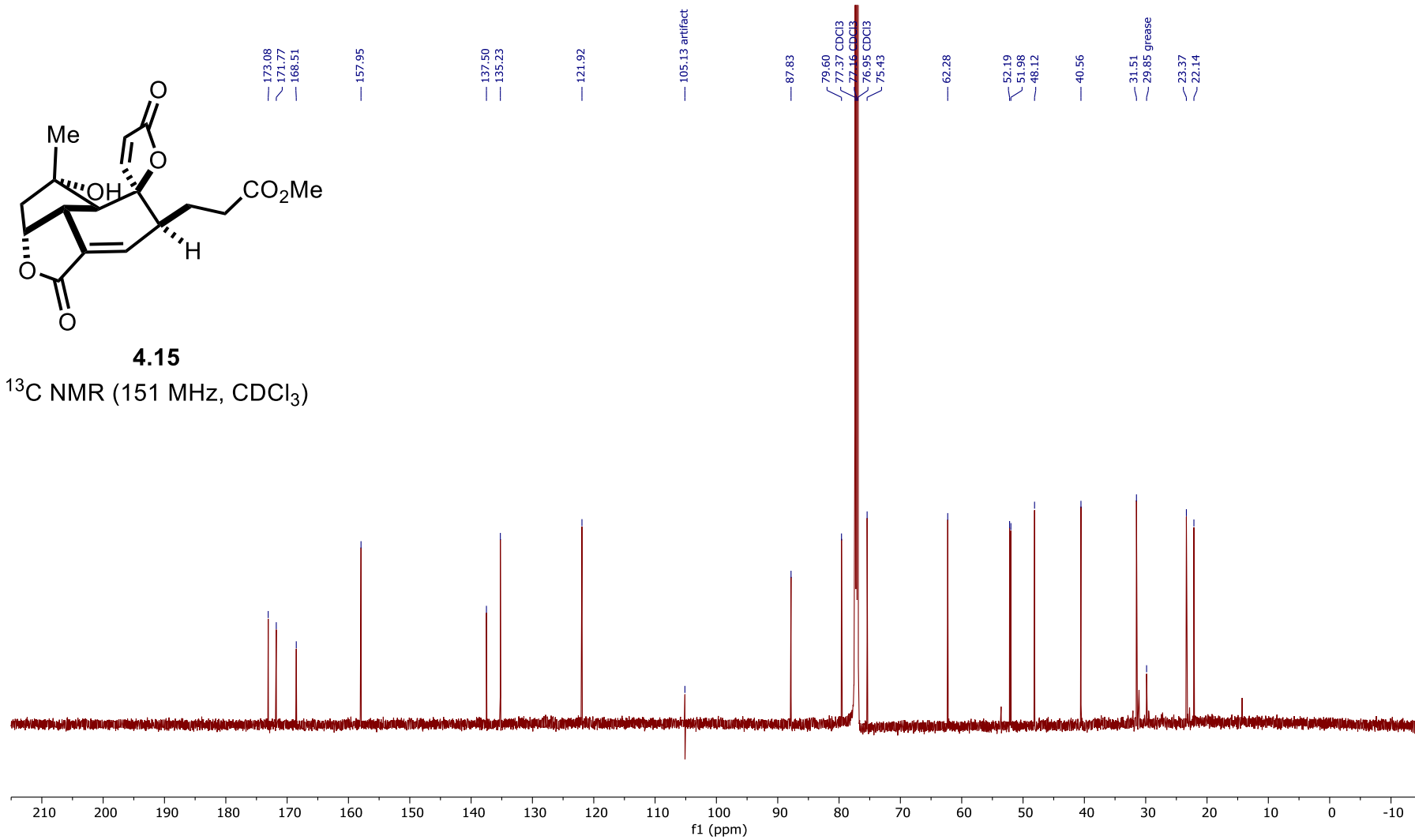


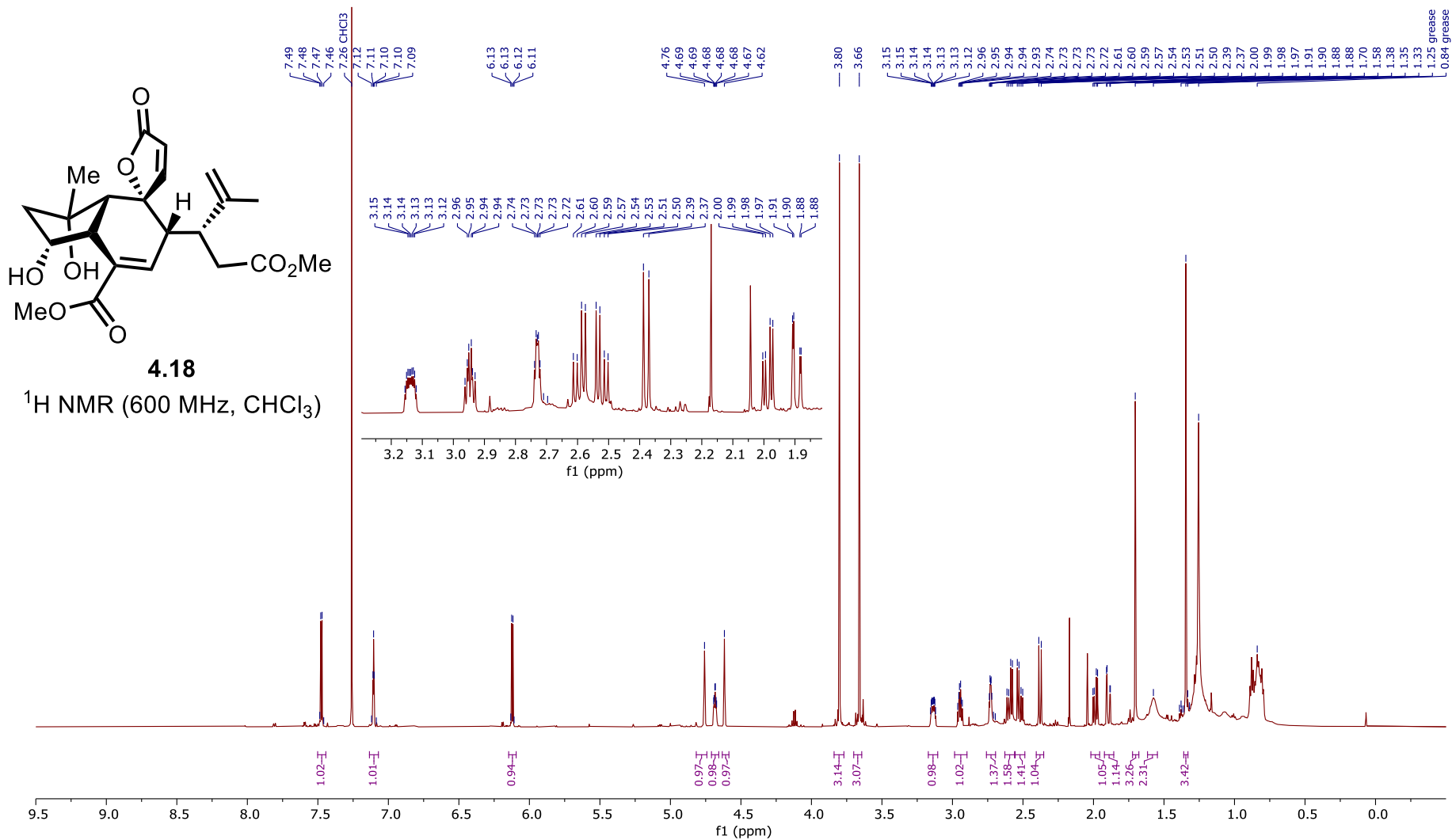


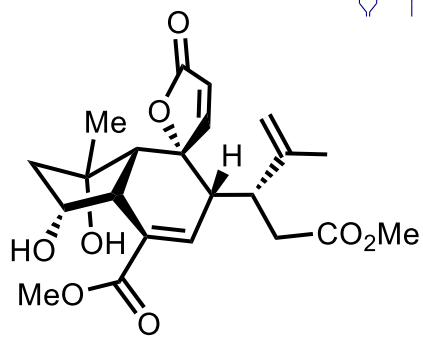


4.15

¹³C NMR (151 MHz, CDCl₃)

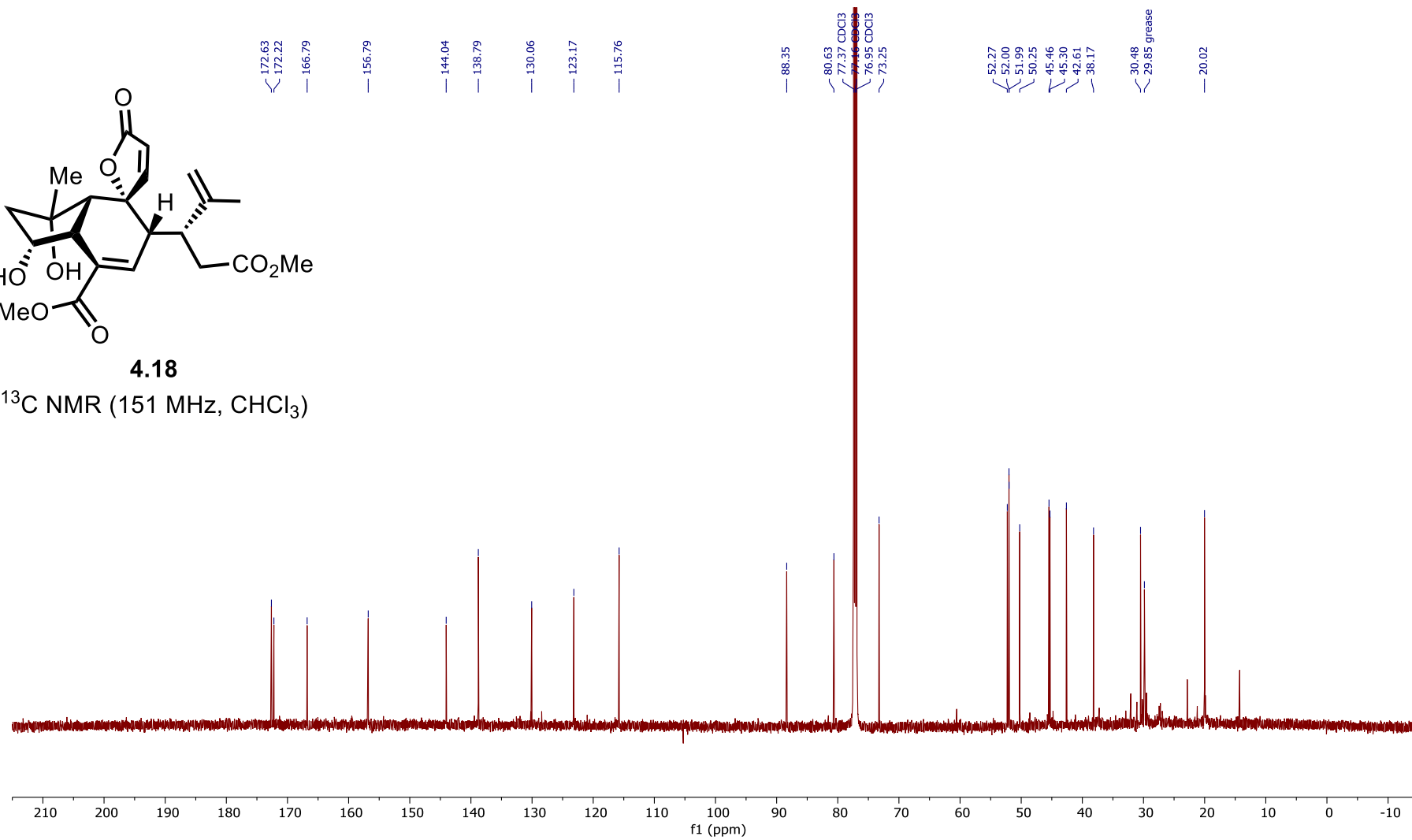


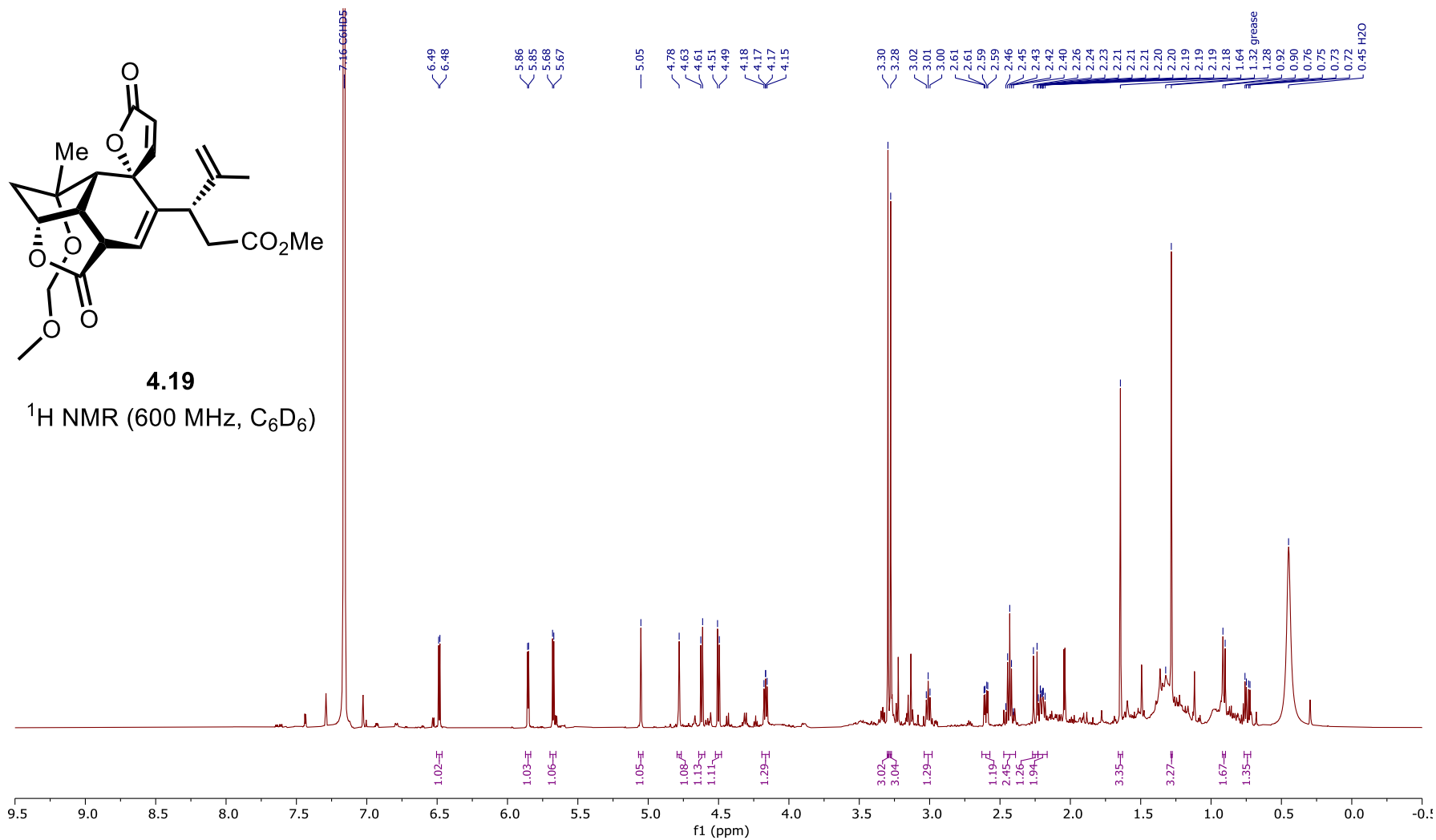


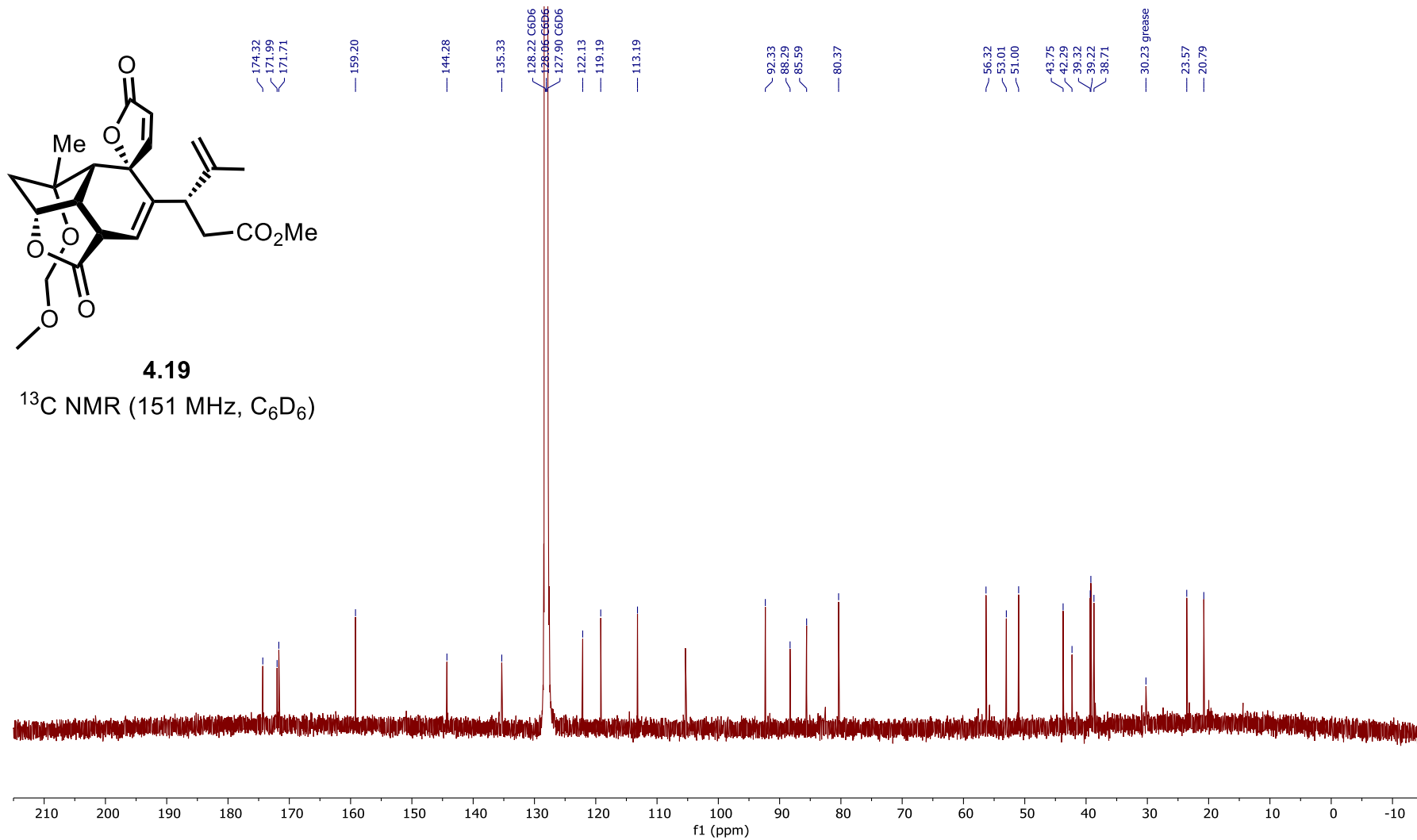


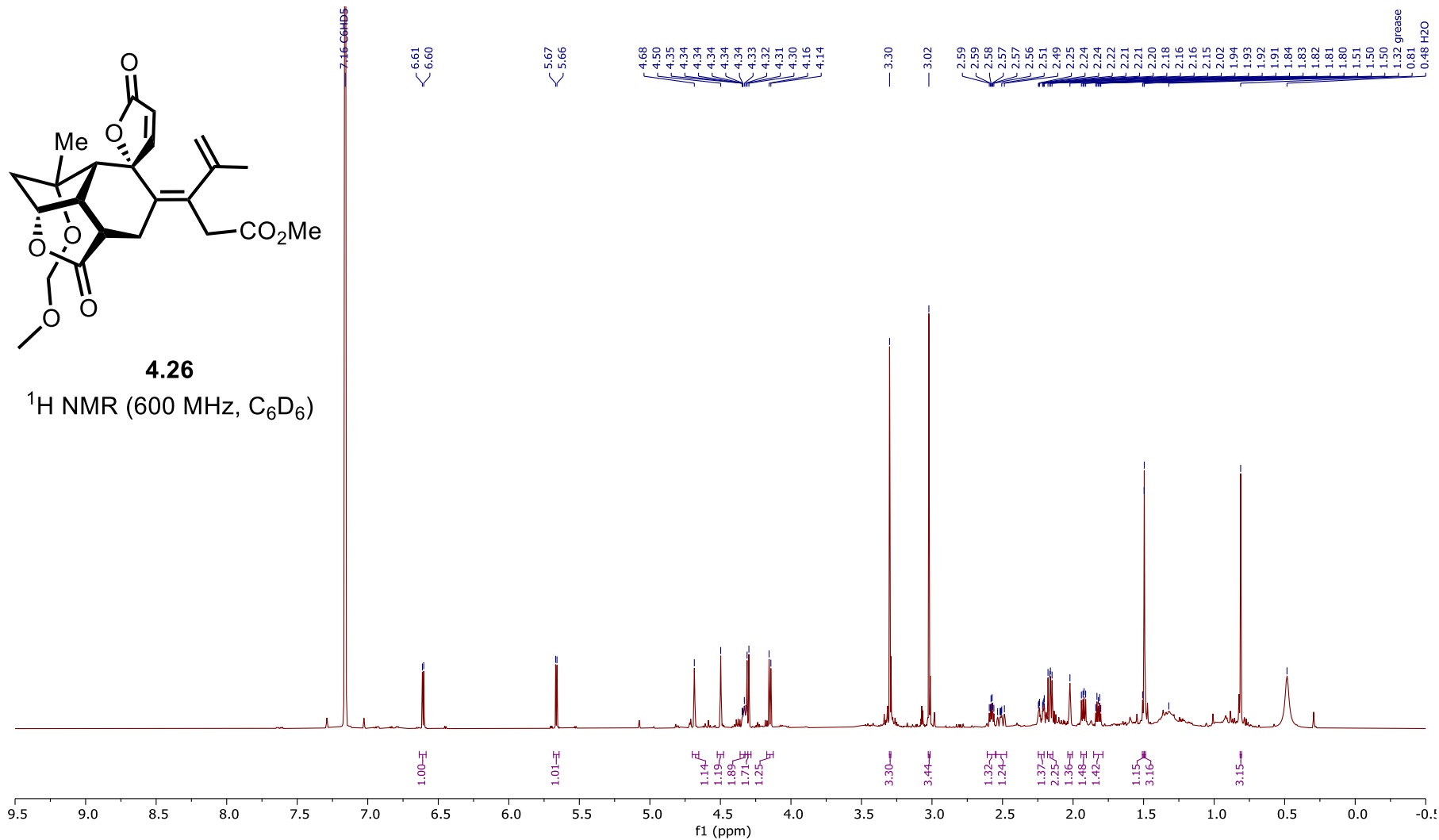
4.18

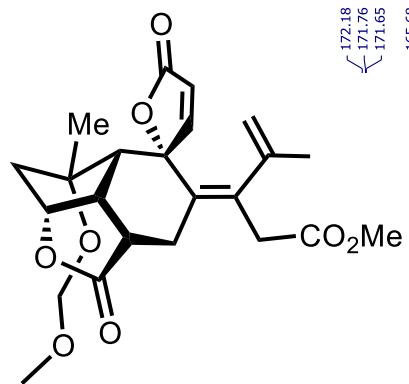
^{13}C NMR (151 MHz, CHCl_3)





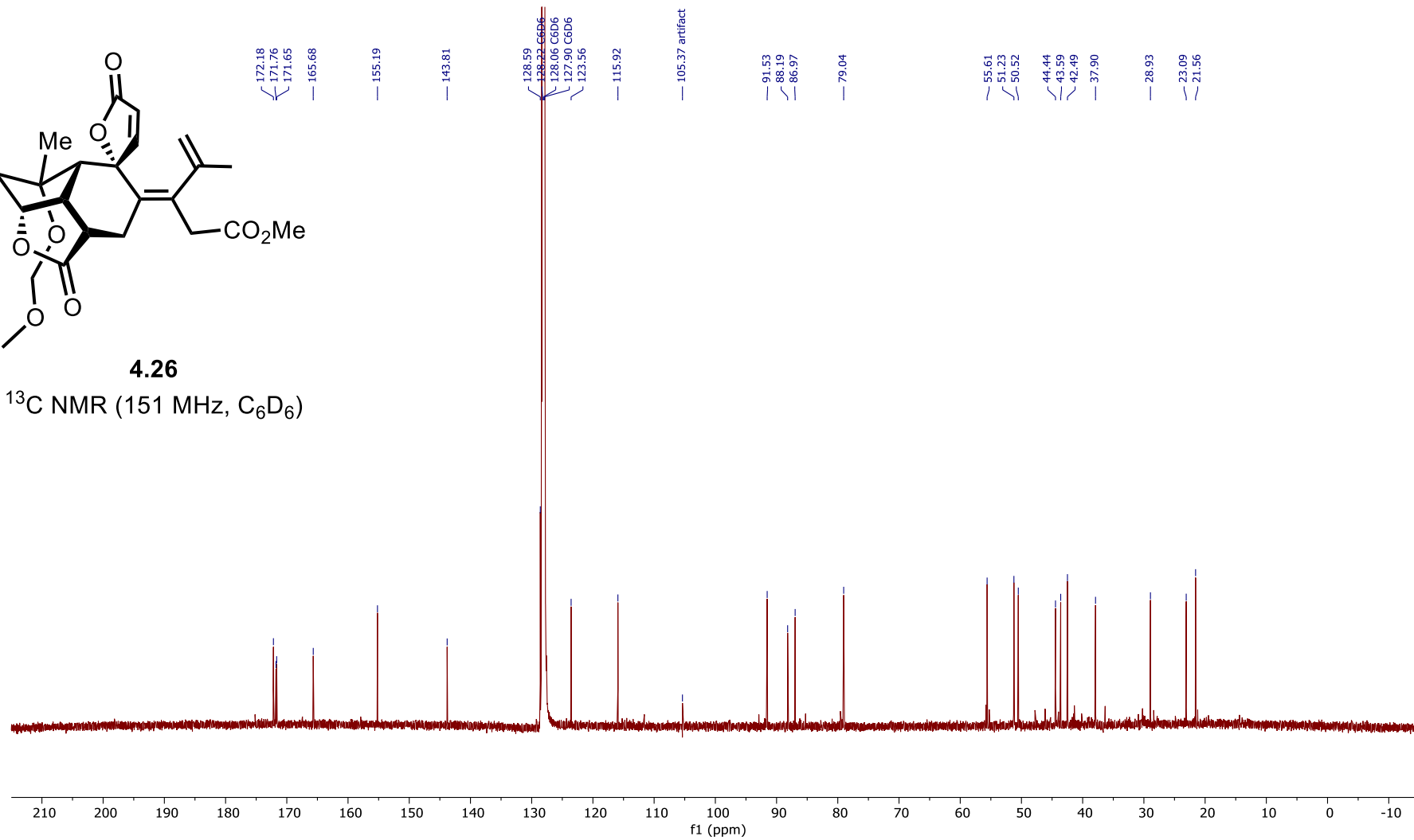


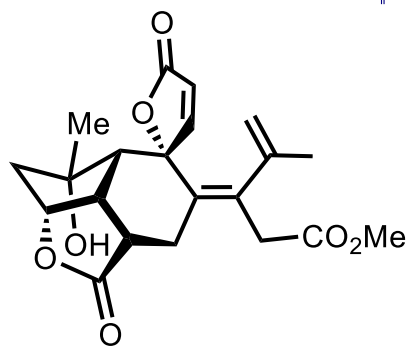




4.26

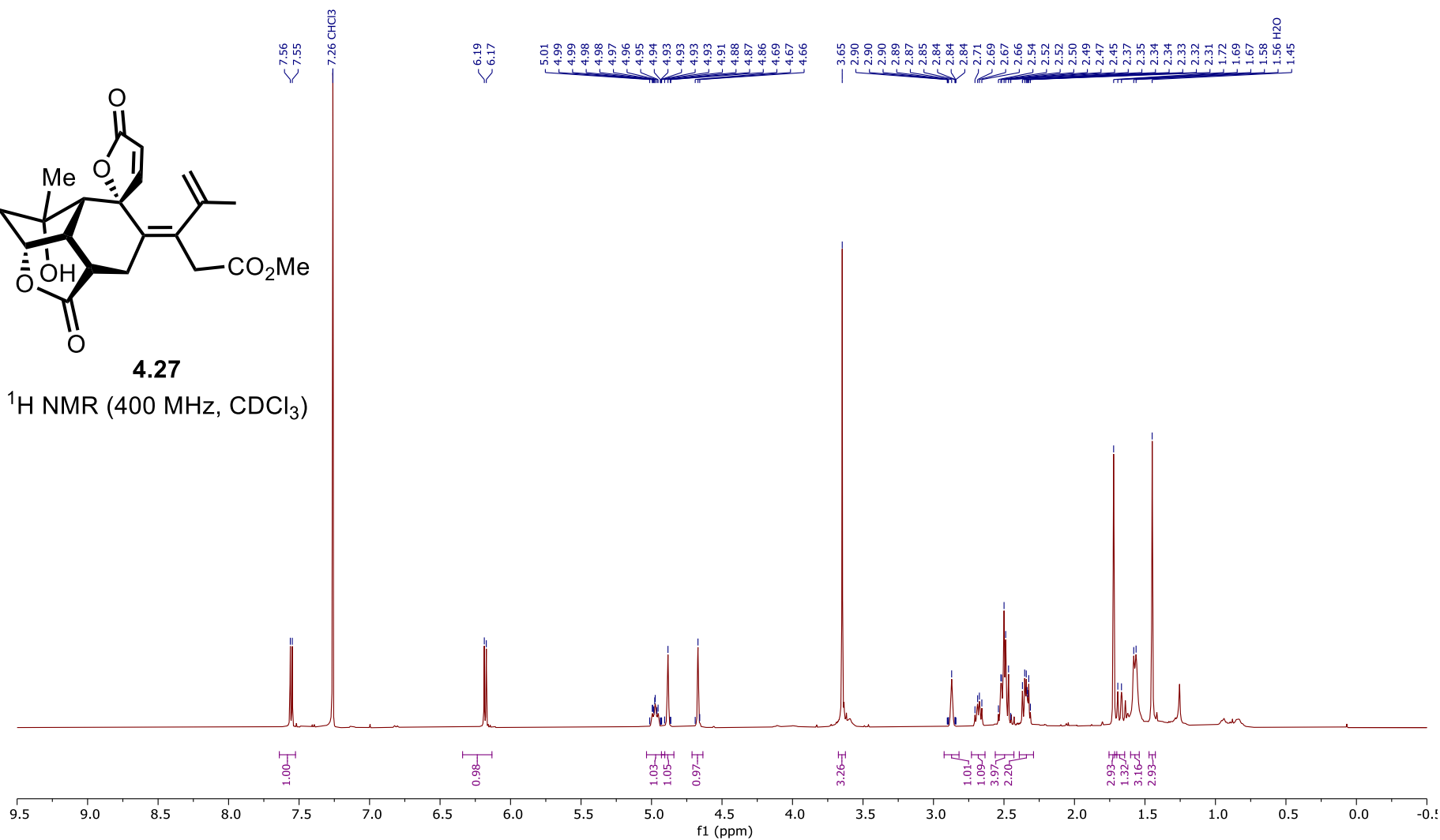
¹³C NMR (151 MHz, C₆D₆)

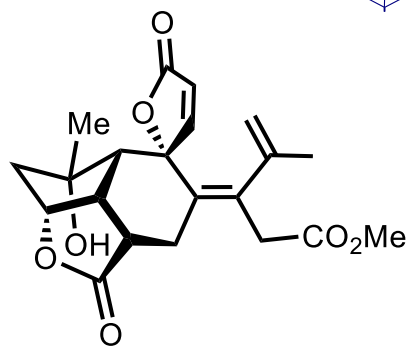




4.27

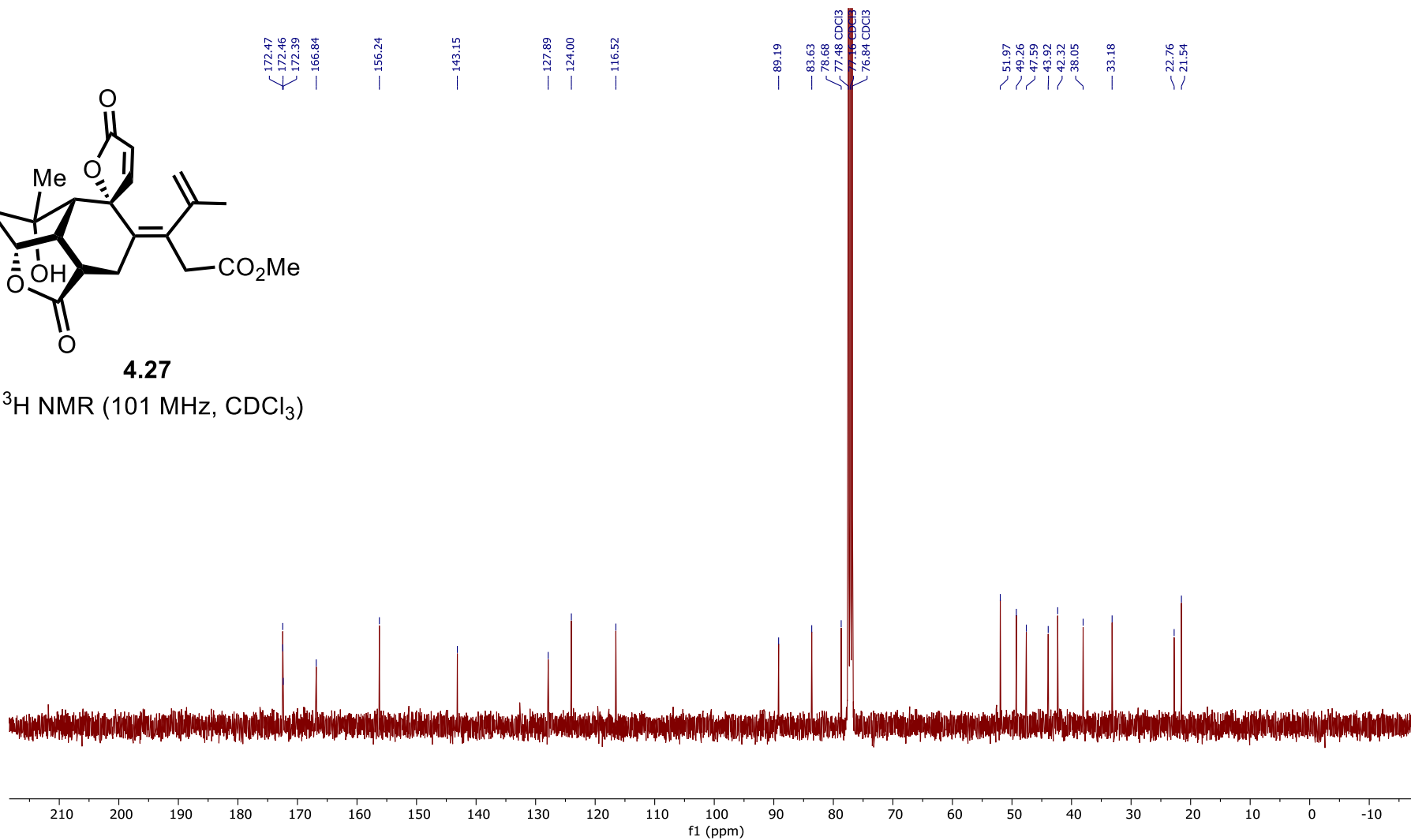
^1H NMR (400 MHz, CDCl_3)

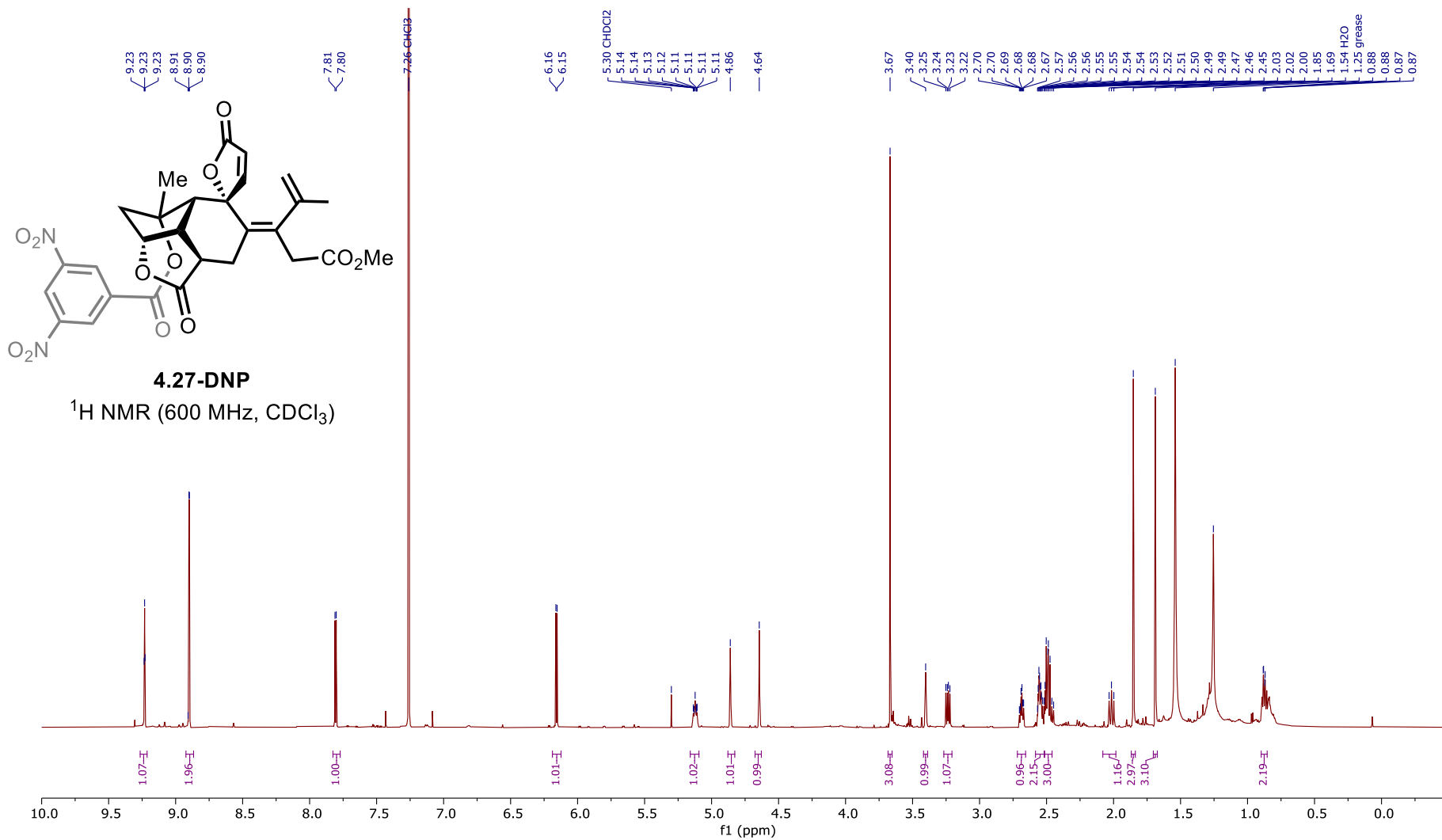


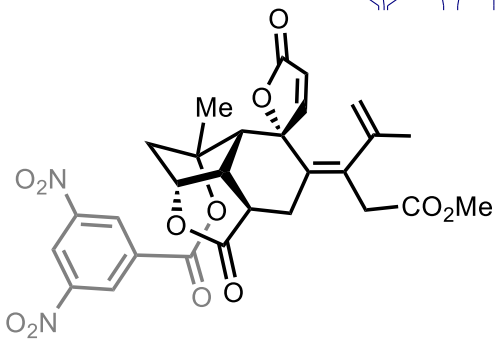


4.27

¹³H NMR (101 MHz, CDCl₃)

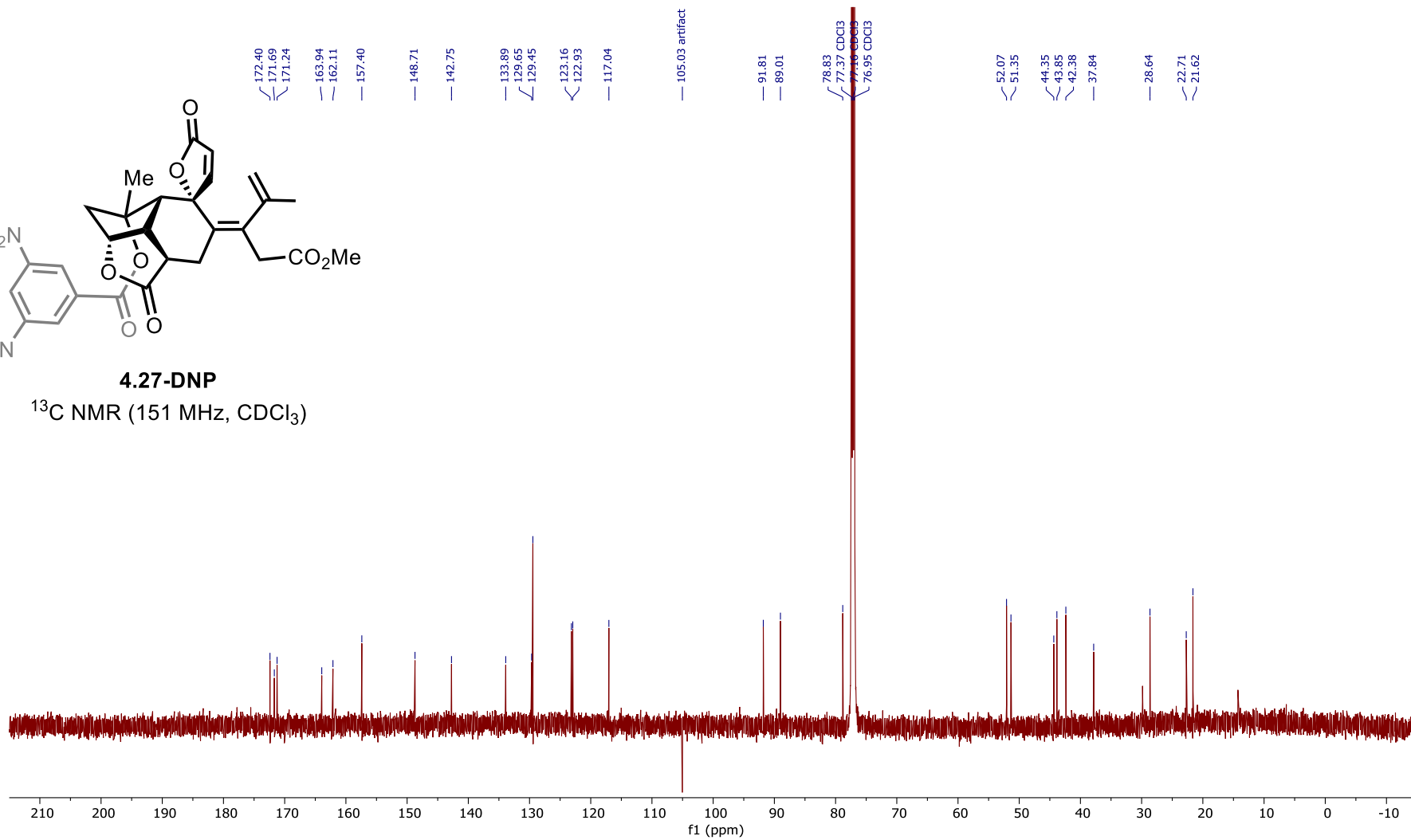


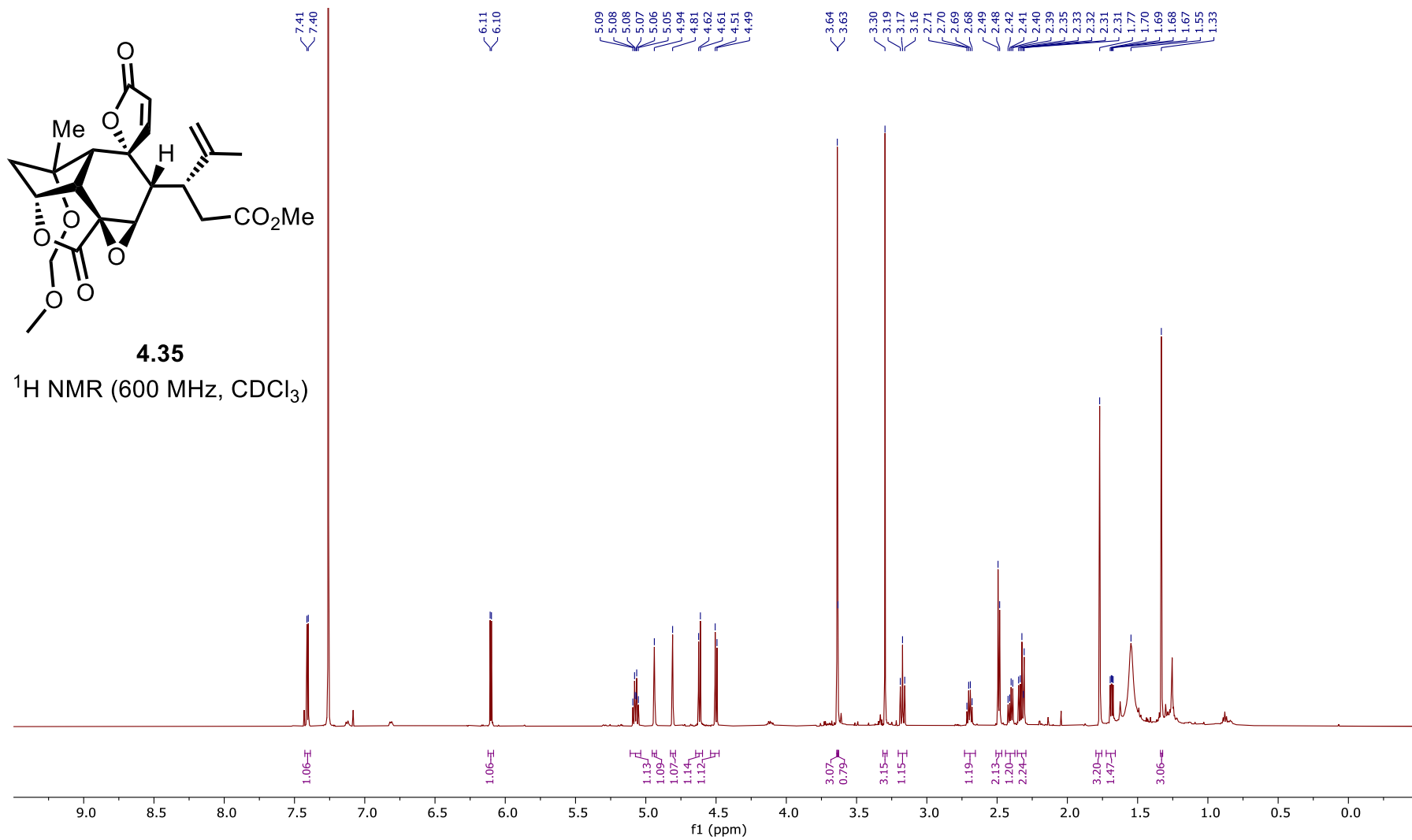


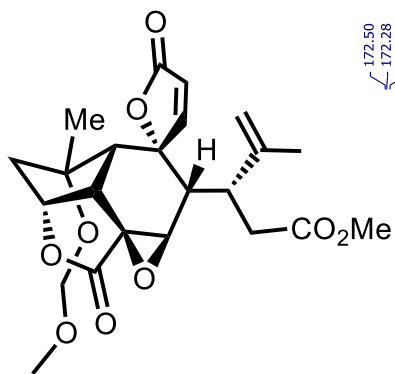


4.27-DNP

^{13}C NMR (151 MHz, CDCl_3)

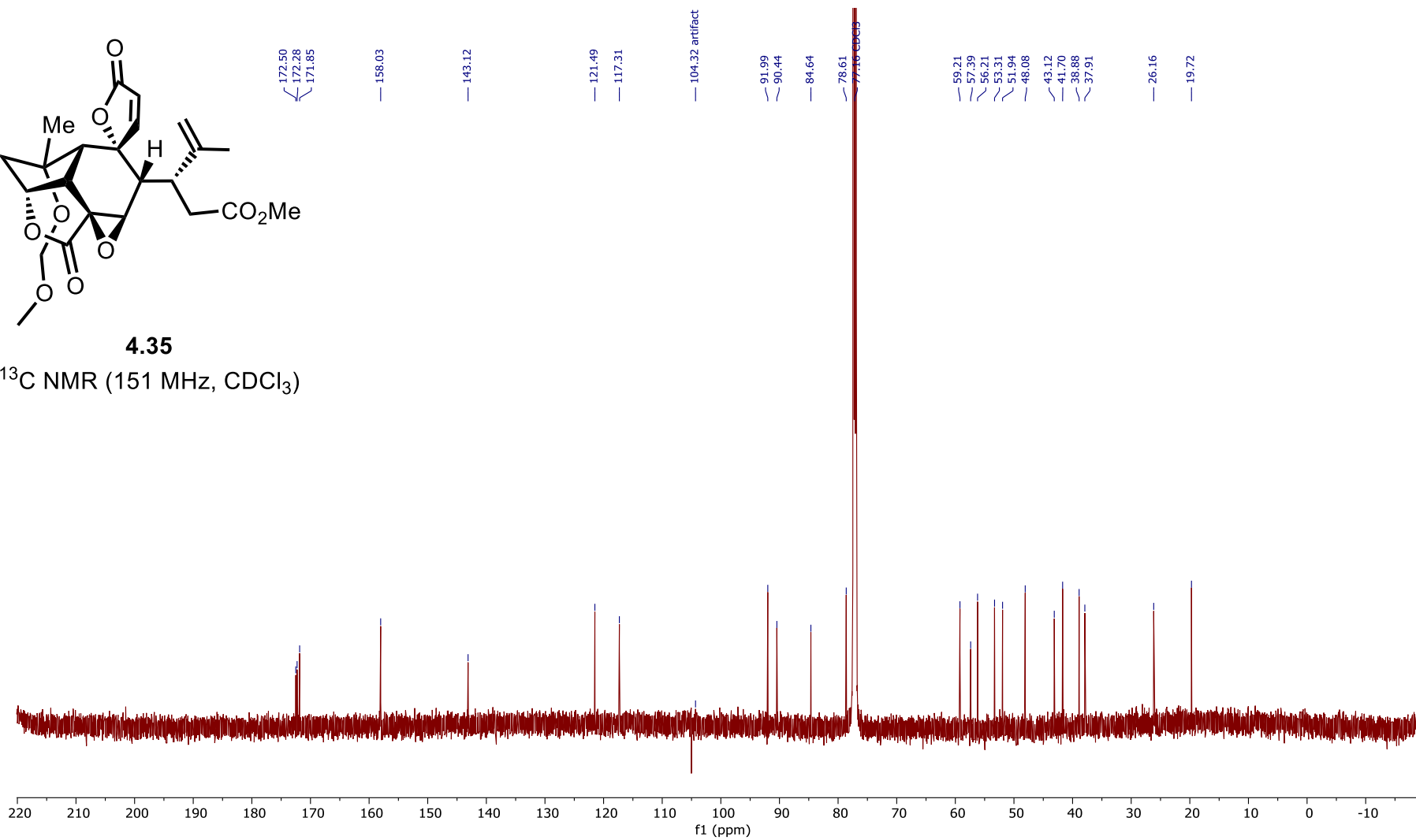


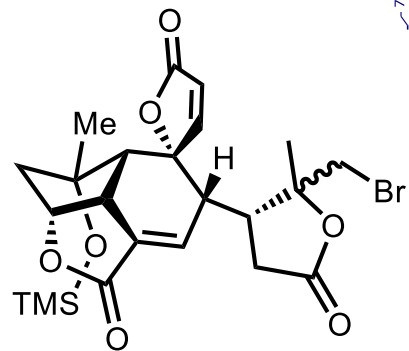




4.35

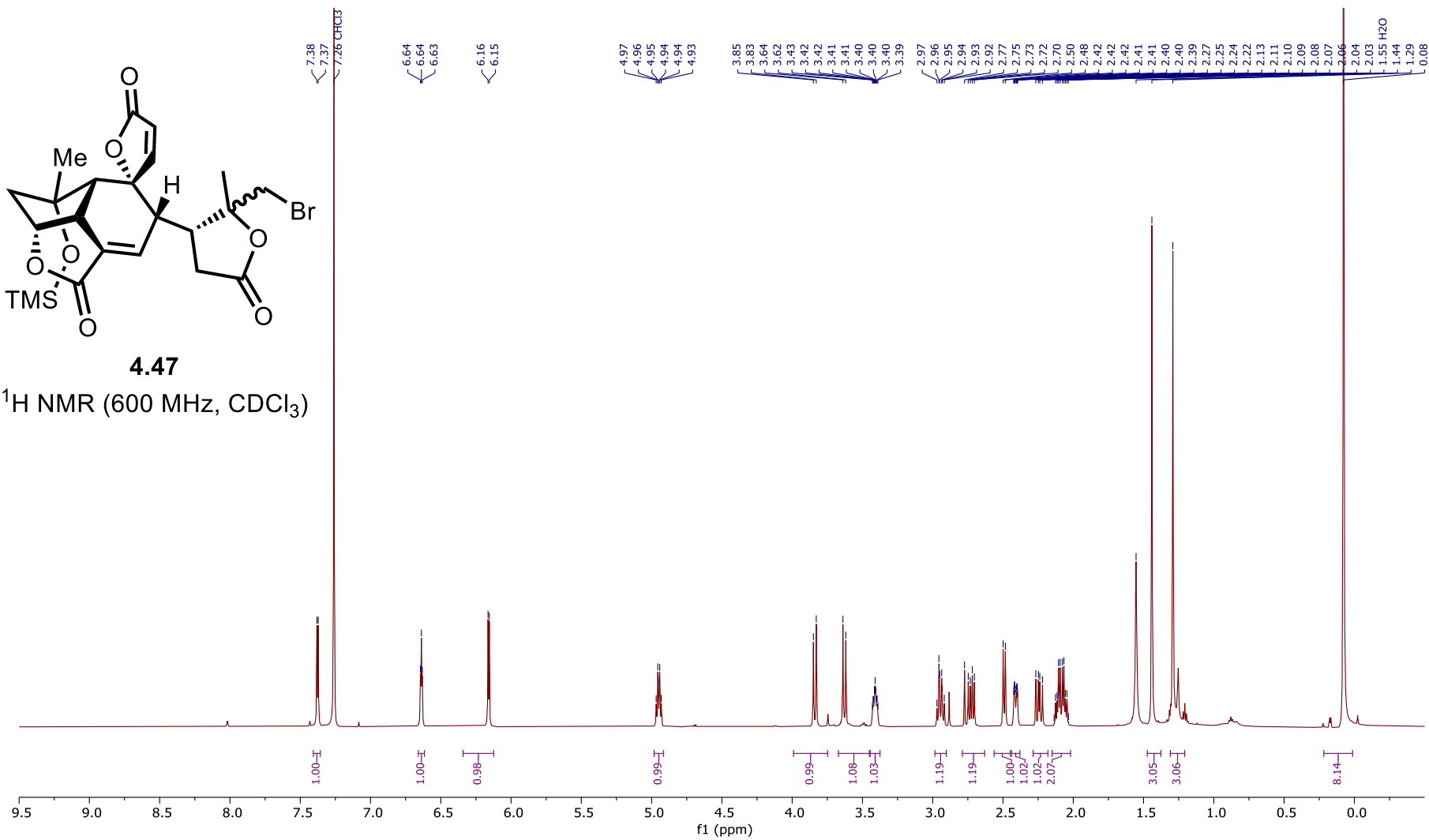
¹³C NMR (151 MHz, CDCl₃)

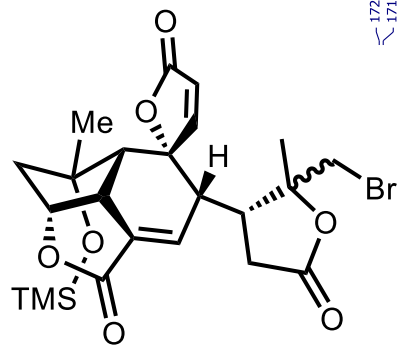




4.47

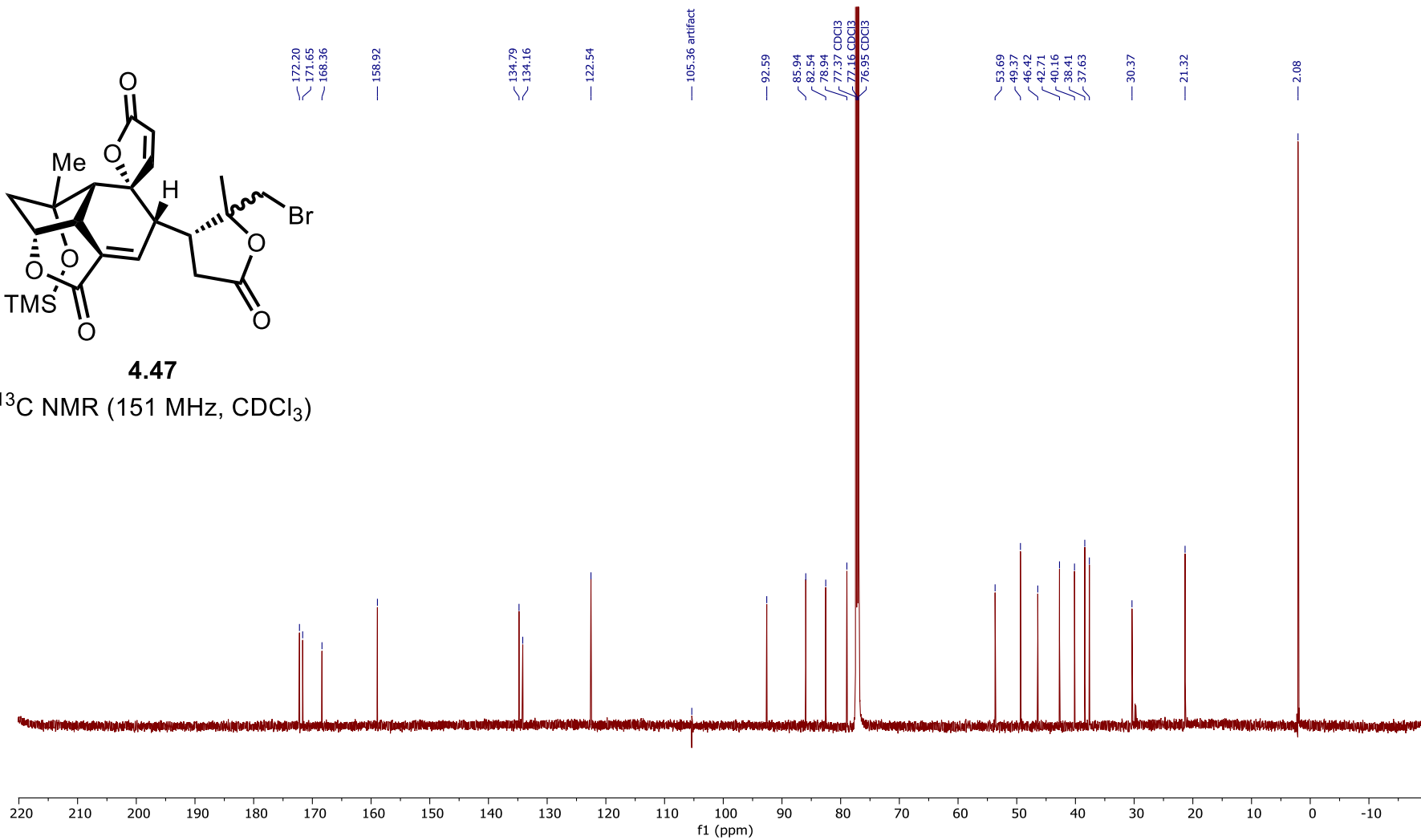
^1H NMR (600 MHz, CDCl_3)

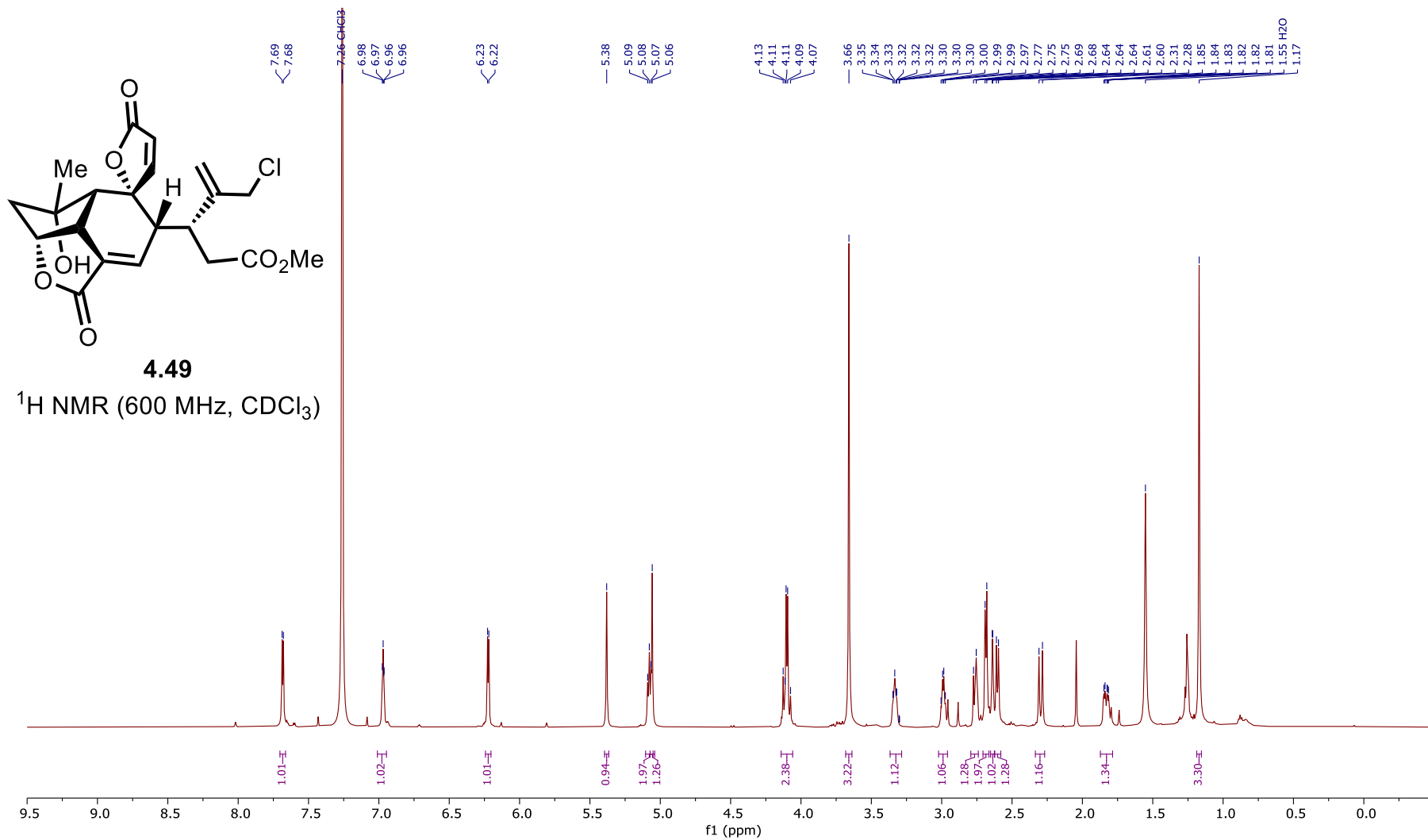


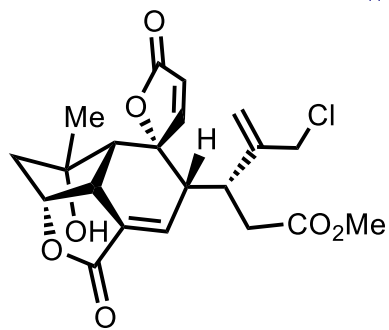


4.47

^{13}C NMR (151 MHz, CDCl_3)

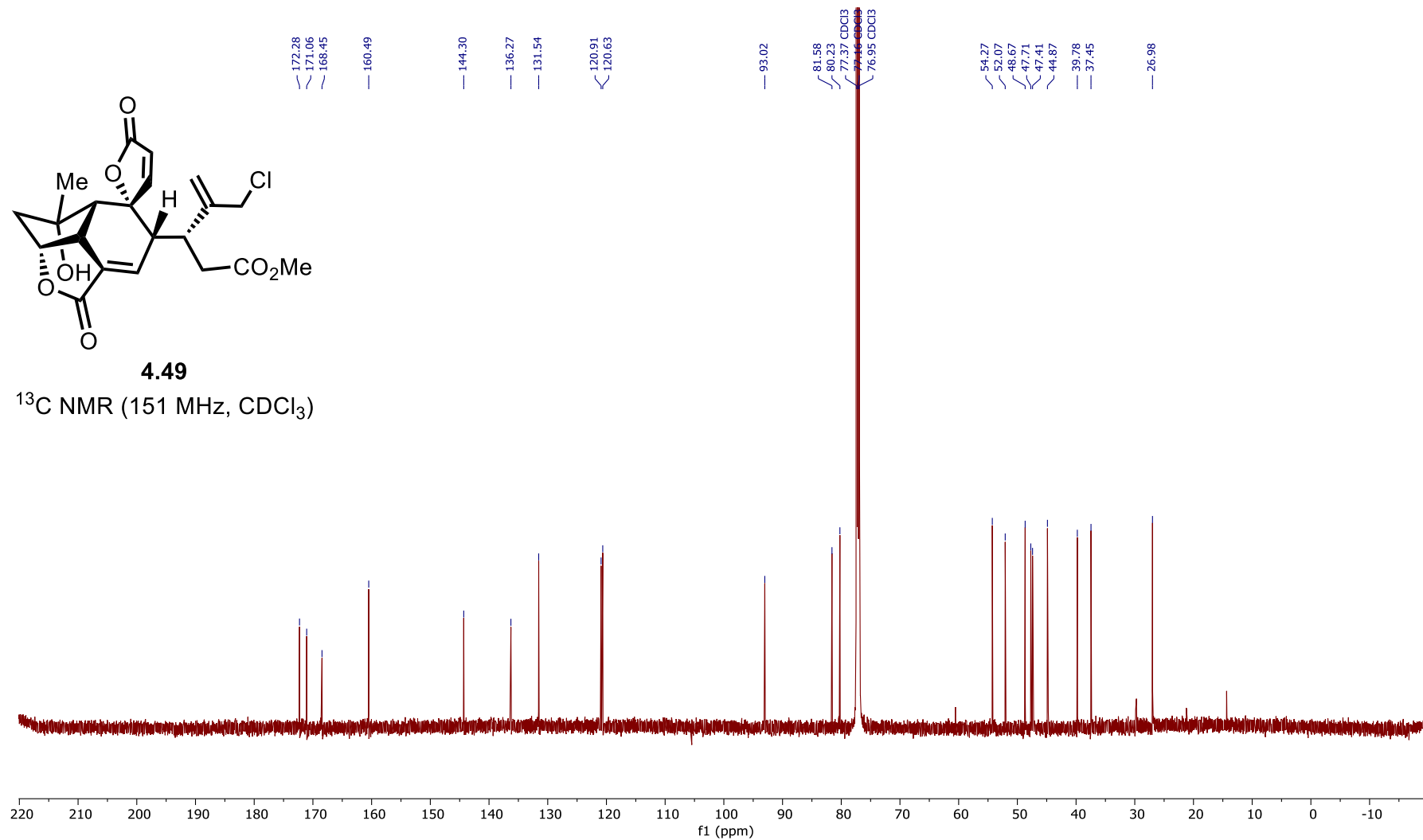


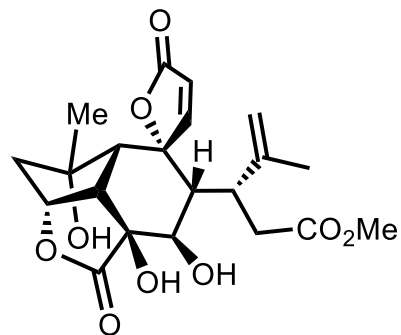




4.49

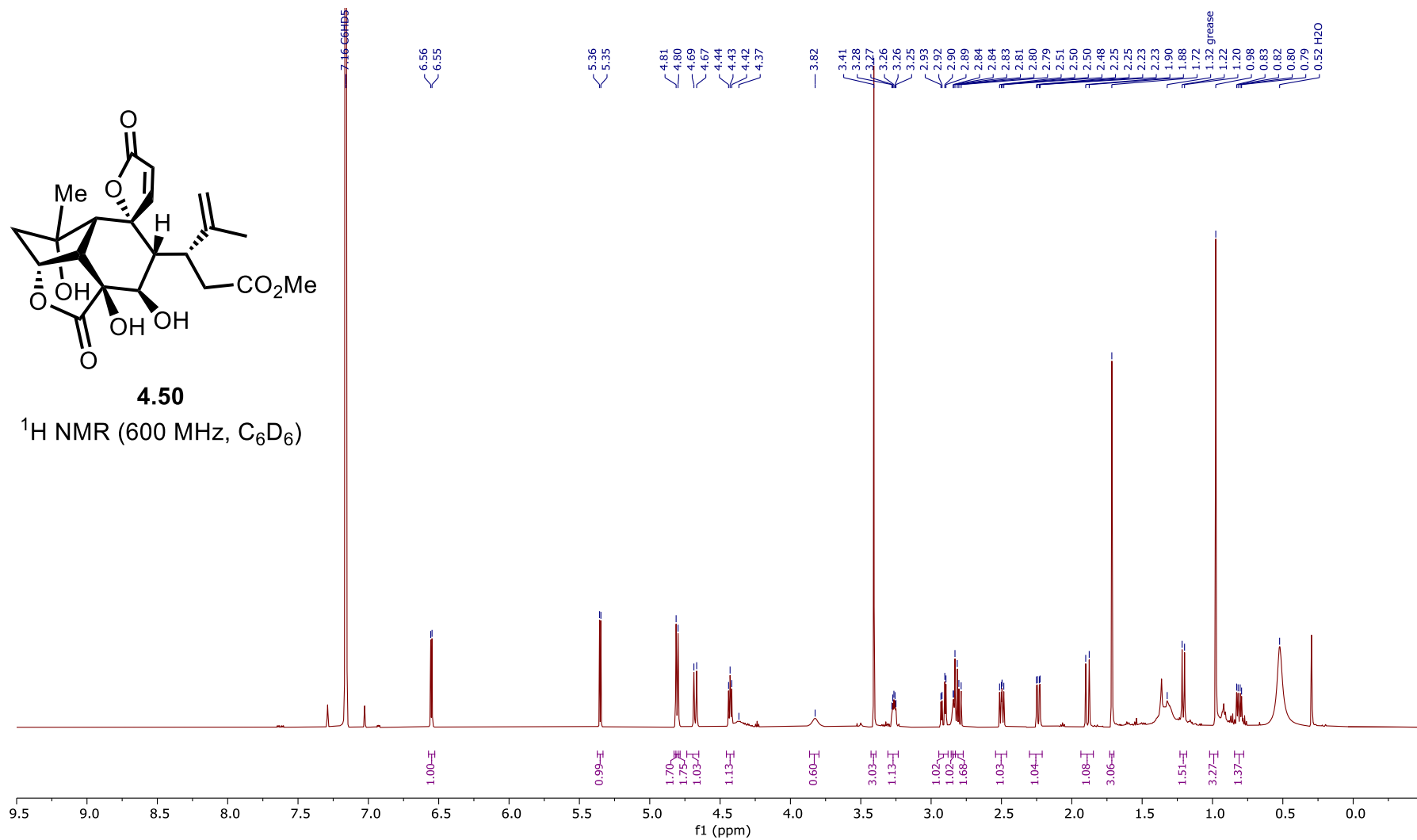
¹³C NMR (151 MHz, CDCl₃)

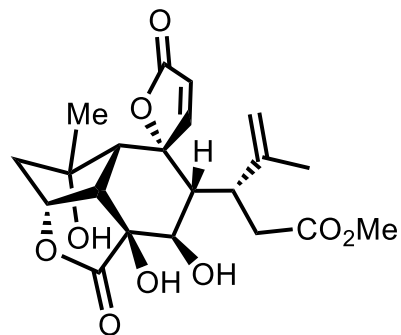




4.50

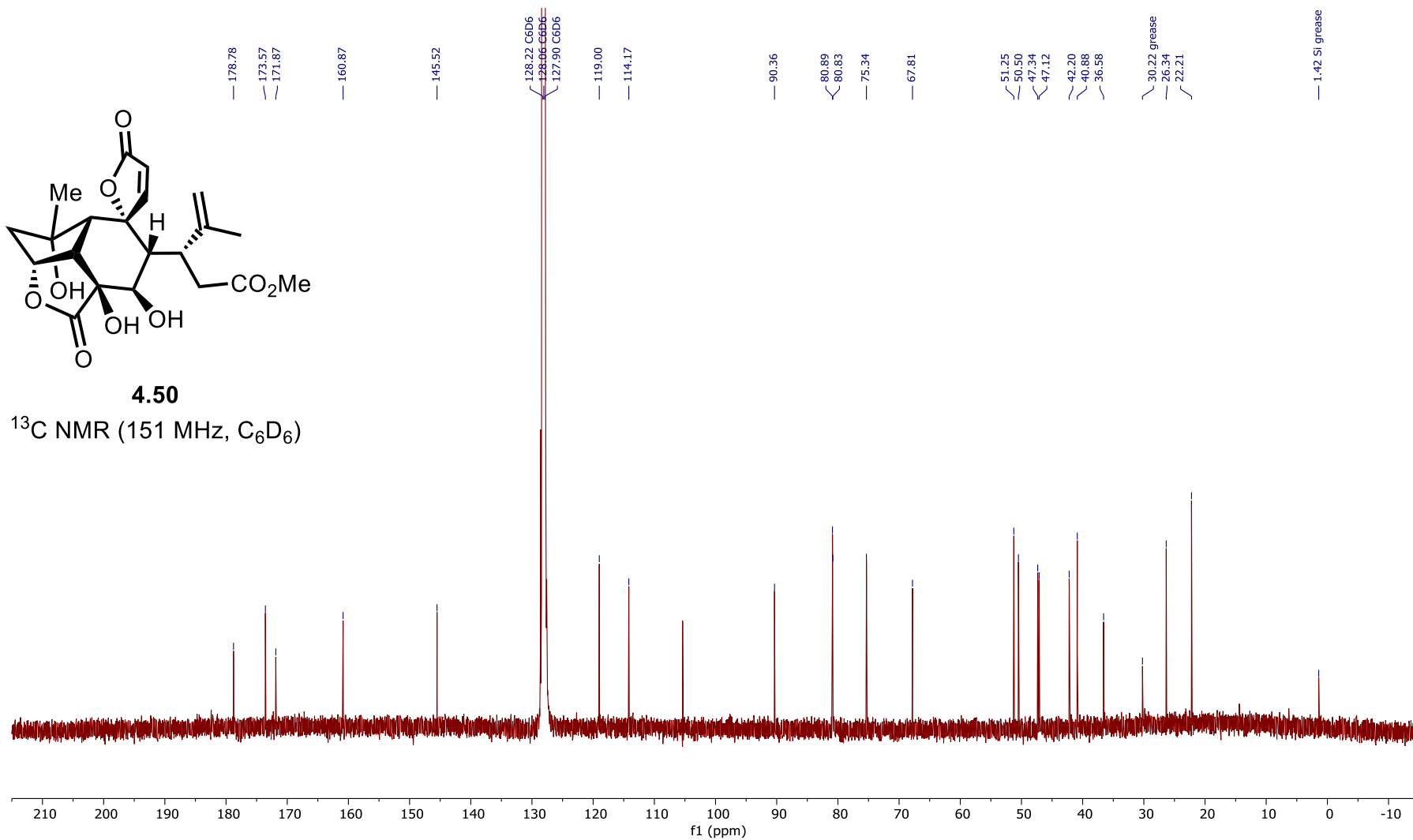
^1H NMR (600 MHz, C_6D_6)

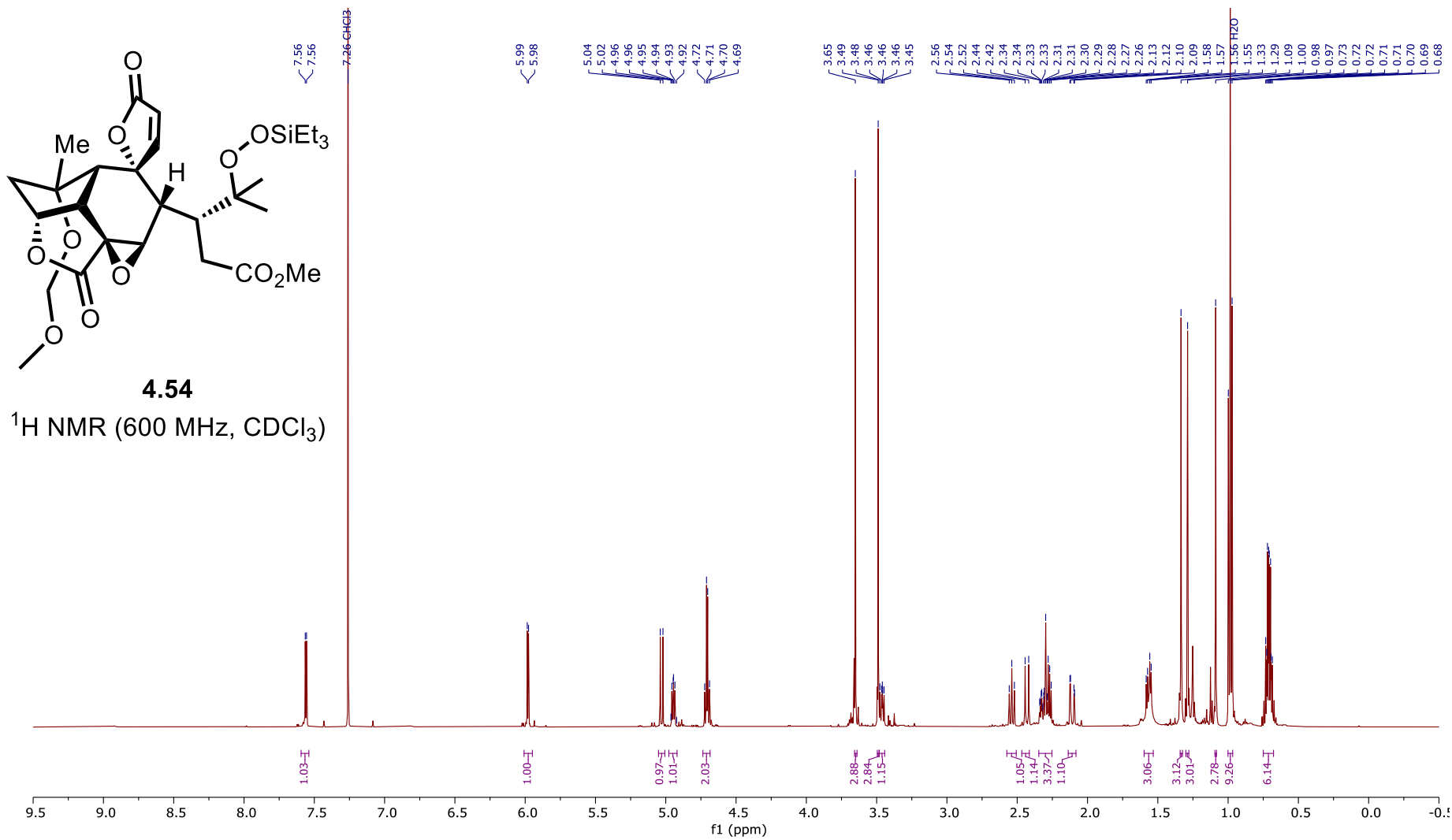


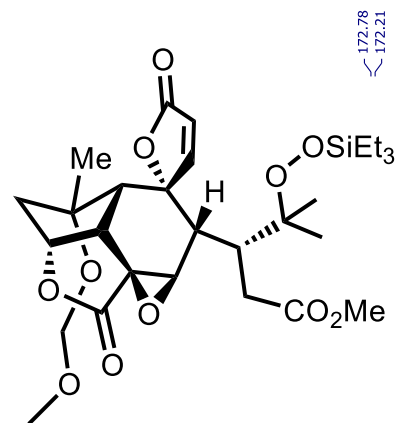


4.50

¹³C NMR (151 MHz, C₆D₆)







4.54

^{13}C NMR (151 MHz, CDCl_3)

