Stony Brook University

Part I. Studies of Stereoselective C-H Amination

Part II. Synthetic Studies of Edaxadiene

Part III. Studies towards the Synthesis of Alchivemycin A

Part IV. The Formal Synthesis of (-)-Englerin A by RRCM and Etherification

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Abstract of the Dissertation

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Part I. Various polysaccharides and glycosidic antibiotics including anthracycline and vancomycin have been widely used to treat cancer or infection. Amino sugars are often found in their structures and play an important role in biological activities. C-H amination is one of valuable methods to streamline the synthesis of C-N bond. Regio-, stereoselective C-H amination has been studied to produce useful amino sugars from glycals and alkynol carbamates.

Part II. Edaxadiene was considered as a new diterpene that had biological activities to inhibit the infection process of Mycobacterium tuberculosis. We describe a design to access a bicyclic backbone, which is the core structure of this compound by an intramolecular Diels-Alder (IMDA) reaction.

Part III. Progress toward the synthesis of a key moiety of alchivemycin A, which was isolated from a plant-derived actinomycete Streptomyces sp and displayed selective and potent antibiotic activity against Micrococcus luteus, has been focused on the construction of a bicyclic structure by the IMDA reaction.

Part IV. (–)-Englerin A is a natural product from *phyllathus engleri*, a plant common in east Africa. It showed an interesting biological activity in its ability to inhibit the growth of kidney cancer cell lines in the NCI-60 screen. The useful bioactivity and unique structure of (–)-englerin A have inspired many scientists to develop synthetic approaches to understand the structure-activity relationship (SAR). We reported the formal synthesis of (–)-englerin A and established an efficient synthetic route by a relay ring closing metathesis (RRCM) reaction and etherification. This study includes the efficient opening of the epoxide ring of a β-substituted α-epoxy alcohol under the lithium acetylide reagent, the relay ene-yne-ene metathesis method for the preparation of a diene that is disubstituted on both ends, and the transannular stereo- and regio-specific oxymercuration of the C-6, C-7 olefin in the guaiane ring system.

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List of Abbreviations

α	alpha
β	beta
±	Racemate
Ac	Acetyl
AcCN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AE	Asymmetric epoxidation
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
br	Broad
CDI	1,1'-Carbonyldiimidazole
CSA	10-Camphorsulfonic acid
Conc. HCl	Concentrated hydrochloric acid
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DIPET	Diisopropyl tartrate
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Gram
h	Hour(s)
HMPA	Hexamethylphosphoramide
Hz	Hertz
$I(Collins)_2PF_6$	Bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate
IC_{50}	Concentration for 50 % inhibition
IMDA	Intramolecular Diels-Alder reaction
*i*Pr	Isopropyl
IR	Infrared spectroscopy
J	First order coupling constant (NMR)

LAH	Lithium aluminum hydride
m	Multiplet
mCPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute(s)
mL	Milliliter
mmol	Millimole
mol	Mole
mp	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
MTPA-Cl	α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride
m/z	Mass-charge ratio
NaHMDS	Sodium 1,1,1,3,3,3-hexamethyldisilazide
NBS	N-Bromosuccinimide
NIS	N-iodosuccinimide
NMR	Nuclear magnetic resonance
9-OMe-9-BBN	9-OMe-9-borobicyclo[3,3,1]nonane
PCC	Pyridinium chlorochromate

PDC	Pyridinium dichromate
Ph	Phenyl
ppm	Parts per million
Py	Pyridine
q	Quartet
R_f	Retention factor
$Rh_2(esp)_4$	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
RRCM	Relay ring closing metathesis
rt	Room temperature
s	Singlet
SAR	Structure-activity relationship
Sat.	Saturated
t	Time, or triplet (NMR)
TBAF	Tetra-N-butylammonium fluoride
TBHP	tert-Butyl hydroperoxide
TBS	tert-Butyldimethylsilyl
$TcesNH_2$	2,2,2-Trichloroethoxysulfonamide
TADA	Transannular Diels-Alder reaction
Tf	Trifluoromethane sulfonate
THF	Tetradydrofuran
TLC	Thin layer chromatography

TMS	Trimethylsilyl
Ts	Para-Toluenesulfonyl (tosyl)
UV	Ultraviolet

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see their growth and give my deep love. Now, they are not young girls but ladies. It is my great pleasure to hear that they still remember me.

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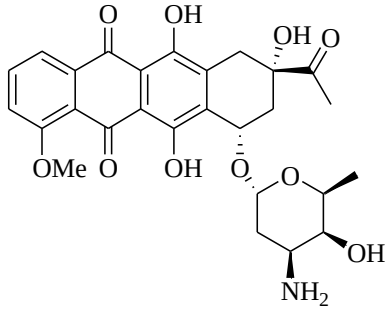
Part I.

Studies of Stereoselective C-H Amination

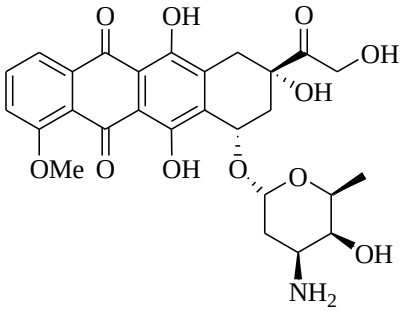
1.1. Introduction

1.1.1. 3-Amino hexoses

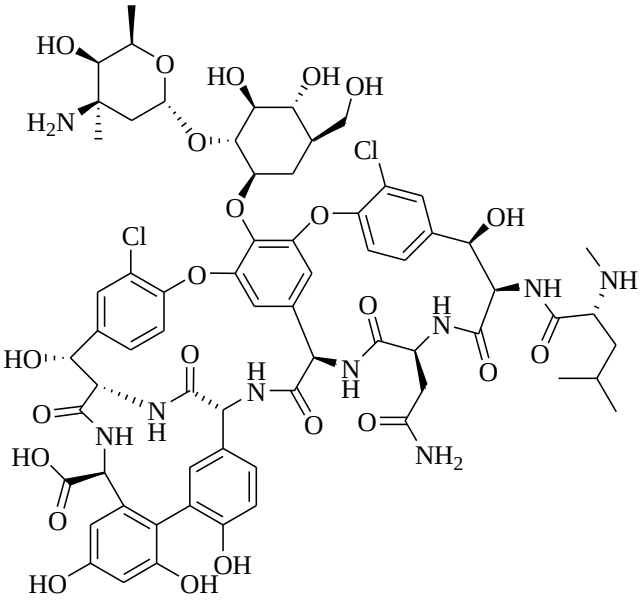
Various polysaccharide and glycosidic antibiotics have been widely used to treat cancer or bacterial infection. These antibiotics including daunorubicin (**1**), doxorubicin (**2**), and vancomycin (**3**) contain amino sugars, 2,3,6-trideoxy-3-aminohexoses (Figure 1), which play an important role in their biological activities.[1]



Daunorubicin (**1**)



Doxorubicin (**2**)



Vancomycin (**3**)

Figure 1. Examples of glycosidic and polysaccharide antibiotics

These amino hexoses were generally isolated through hydrolysis of the parent antibiotics and some amino hexoses are not naturally found in nature, but had been obtained as minor products in other synthetic studies. Among them, are the simple amino hexoses represented in Figure 2.[1]

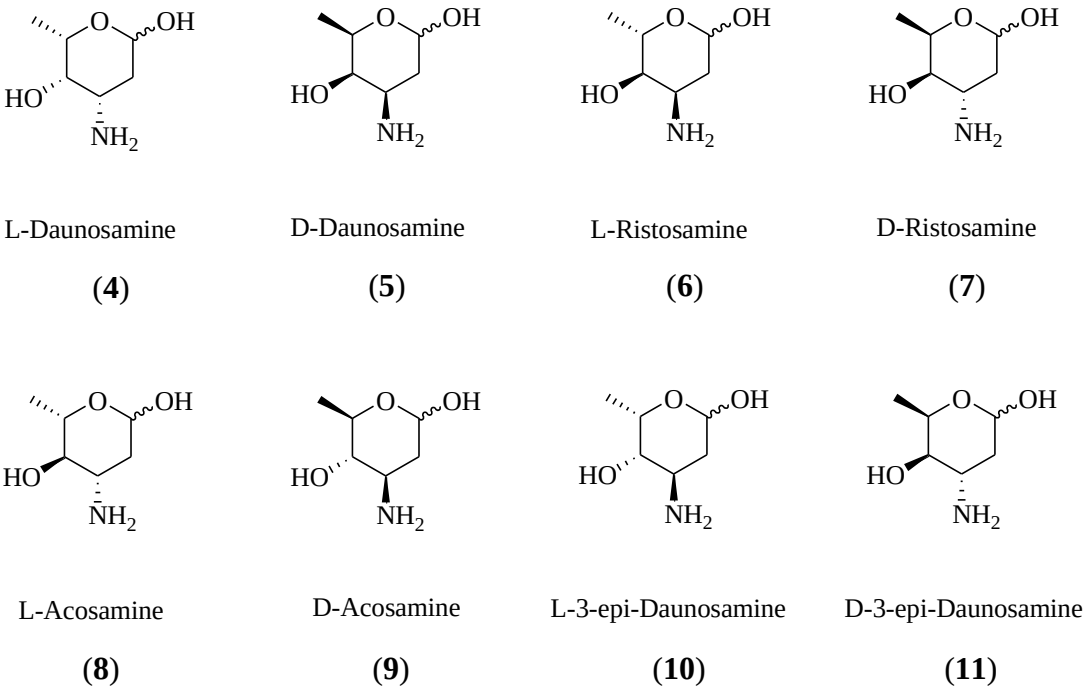
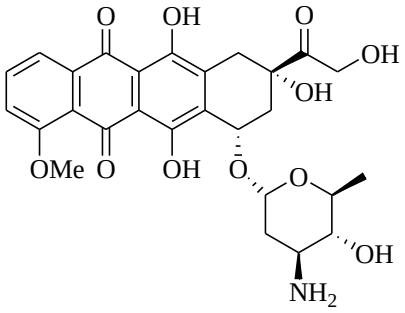


Figure 2. Examples of representative simple amino hexoses

Like daunorubicin (**1**) and doxorubicin (**2**), epirubicin (**12**), one of the more famous anthracycline drugs has been used against various cancers such as breast tumor, ovarian tumor, and lung tumor.[2] Epirubicin (**12**) is a synthetic analogues of doxorubicin (**2**), but it contains 2,3,6-trideoxy-3-aminohexose called L-acosamine (**8**), which was first isolated from the antibiotic actinoidin by Lomakina and co-workers.[1] It (**12)** has almost the same structure as doxorubicin (**2**), but shows fewer side effects while having similar antitumor activity.[3] The only difference between epirubicin (**12**) and doxorubicin (**2**) is aminohexose that the former has namely L-acosamine (**8**) rather than L-daunosamine (**4**).



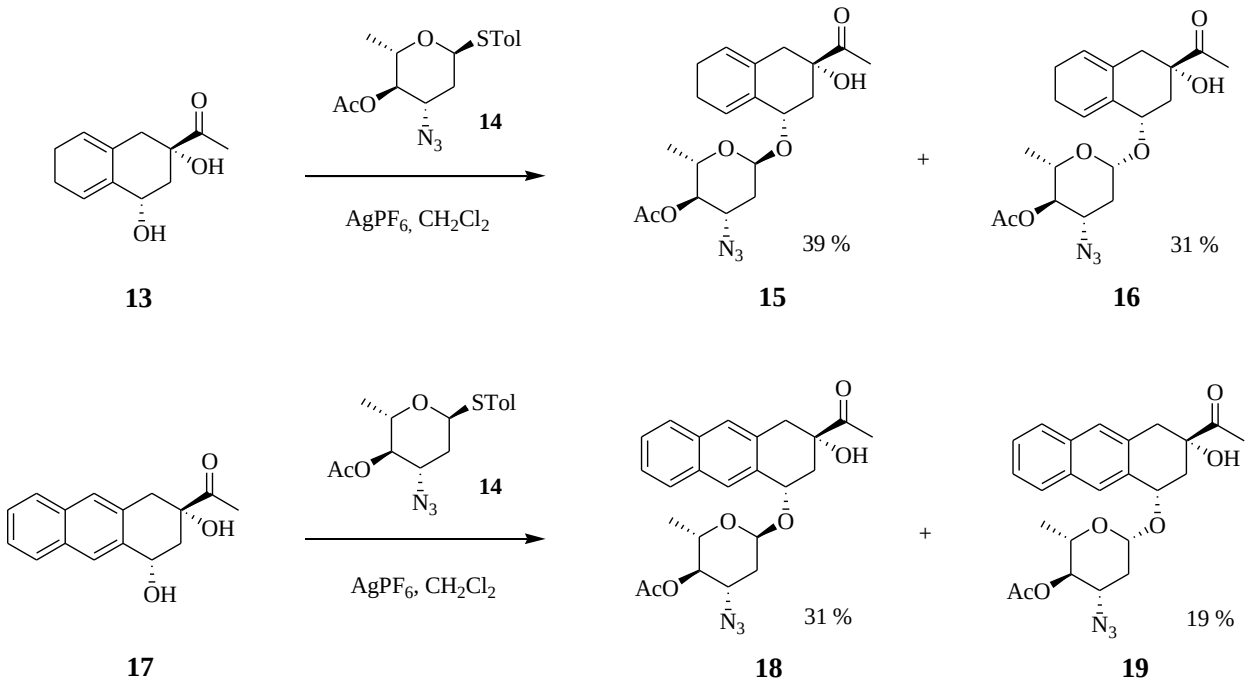
Epirubicin (**12**)

Figure 3. The structure of epirubicin (**12**)

Therefore, L-acosamine (**8**) is very important moiety in its relationship to the impressive biological activity of epirubicin (**12**). Some amino sugars such as L-acosamine (**8**) and L-3-epi-daunosamine (**10**) (Figure 2) have the anti-configuration between the amine and hydroxyl groups and **10** does not occur naturally. Many synthetic analogues of anthracycline have been synthesized in an attempt to reduce cytotoxicity or enhance antitumor activity, but there are not many examples where this has been successful.[3-4] Thus, it would be valuable to investigate efficient and simple methods to produce precursors of L-acosamine (**8**) or other amino sugar analogues. These glycoside precursors can yield amino sugars moieties by glycosylation.[4d,4f,4k,4m]

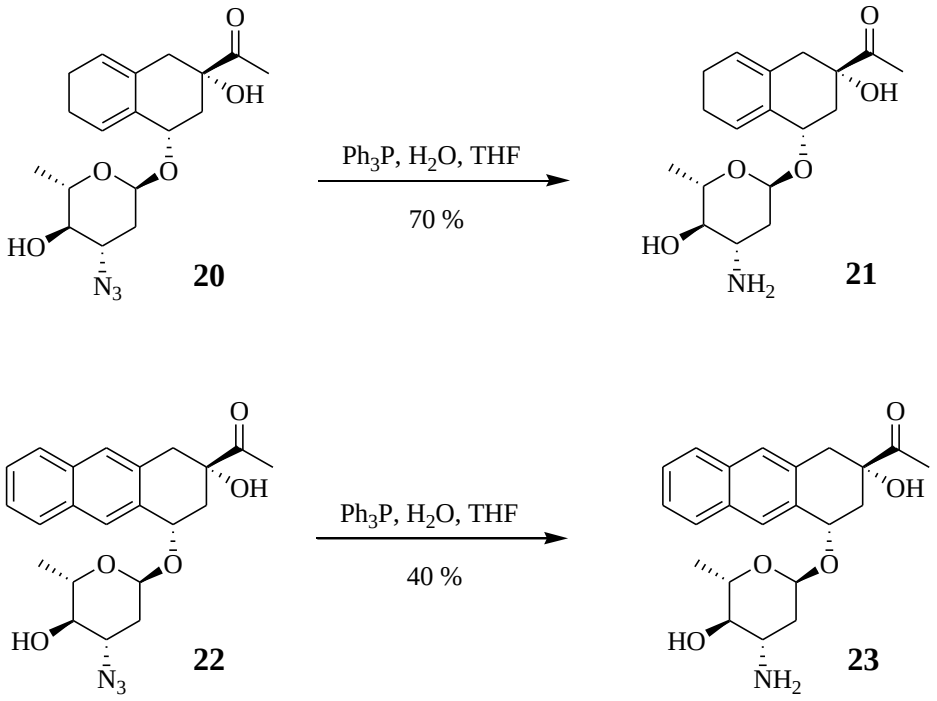
1.1.2. Glycosylation

To introduce the amino sugar moiety, several glycosidic bond formations have been developed to provide glycosides from derivatives of 3-aminohexoses (Figure 2). For example, Lowary et al.[4f] introduced daunorubicin (**1**) analogues **15**, **16**, **18**, and **19**, which have azido sugars, by glycosylation in 2007 (Scheme 1).



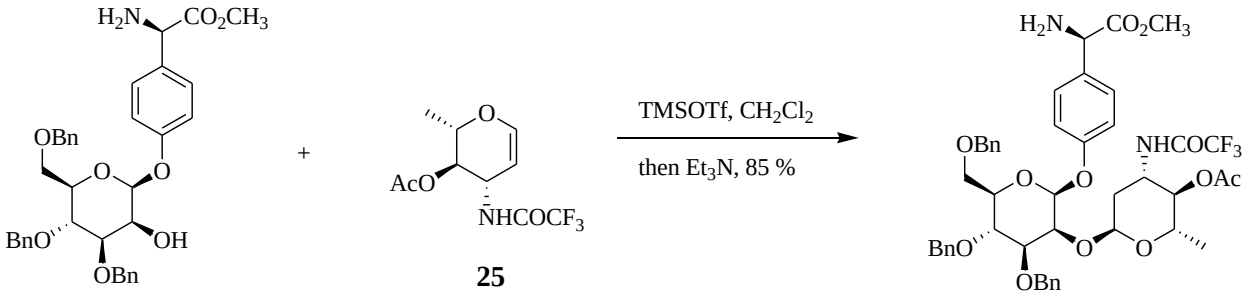
Scheme 1. Syntheses of daunorubicin (**1**) analogues, which have azido sugars by glycosylation

After removal of acetate groups, the azido sugars **20** and **22** were transformed to give the L-acosamine moiety (**8**) in daunorubicin (**1**) analogues **21** and **23** by Staudinger reduction (Scheme 2).



Scheme 2. Syntheses of daunorubicin (**1**) analogues **21** and **23** by the Lowary et al.[4f]

In addition, 3-amino glycals can be valuable glycoside precursors to introduce amino sugars. They also produced a mixture of glycosides, but sometimes, only the α-glycoside was obtained from glycals. Monneret et al.[5] demonstrated an example to show usefulness of 3-amino glycal **25** in 1998 (Scheme 3).

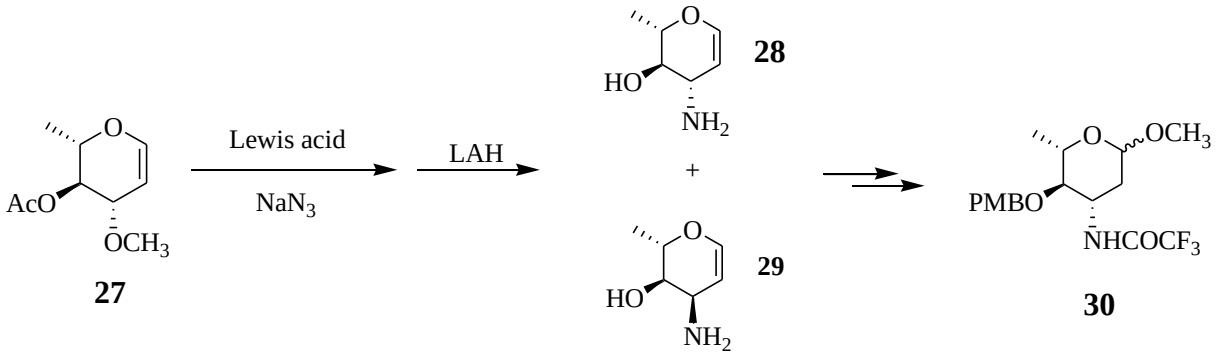


Scheme 3. Synthesis of α-glycoside from 3-amino glycal **25** by Monneret et al.[5]

Those examples show the usefulness of derivatives of 3-aminohexoses to obtain glycosides.

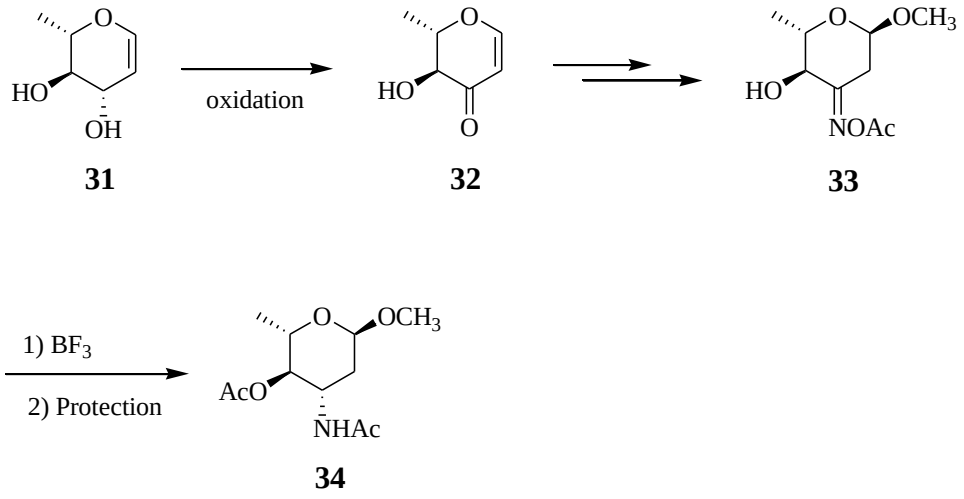
1.1.3. **Previous synthetic approaches to precursors of L-acosamine (8)**

Originally, these promising intermediates, related to L-acosamine (**8**) and 3-amino glycals, were prepared from carbohydrates, especially L-rhamnal in 1980.[1,4g] For example, the Boivin group in 1980 reported the preparation of protected L-acosamine derivative **30,** from the protected L-rhamnal derivative **27** by acid catalyzed azide addition (Scheme 4).[4g]



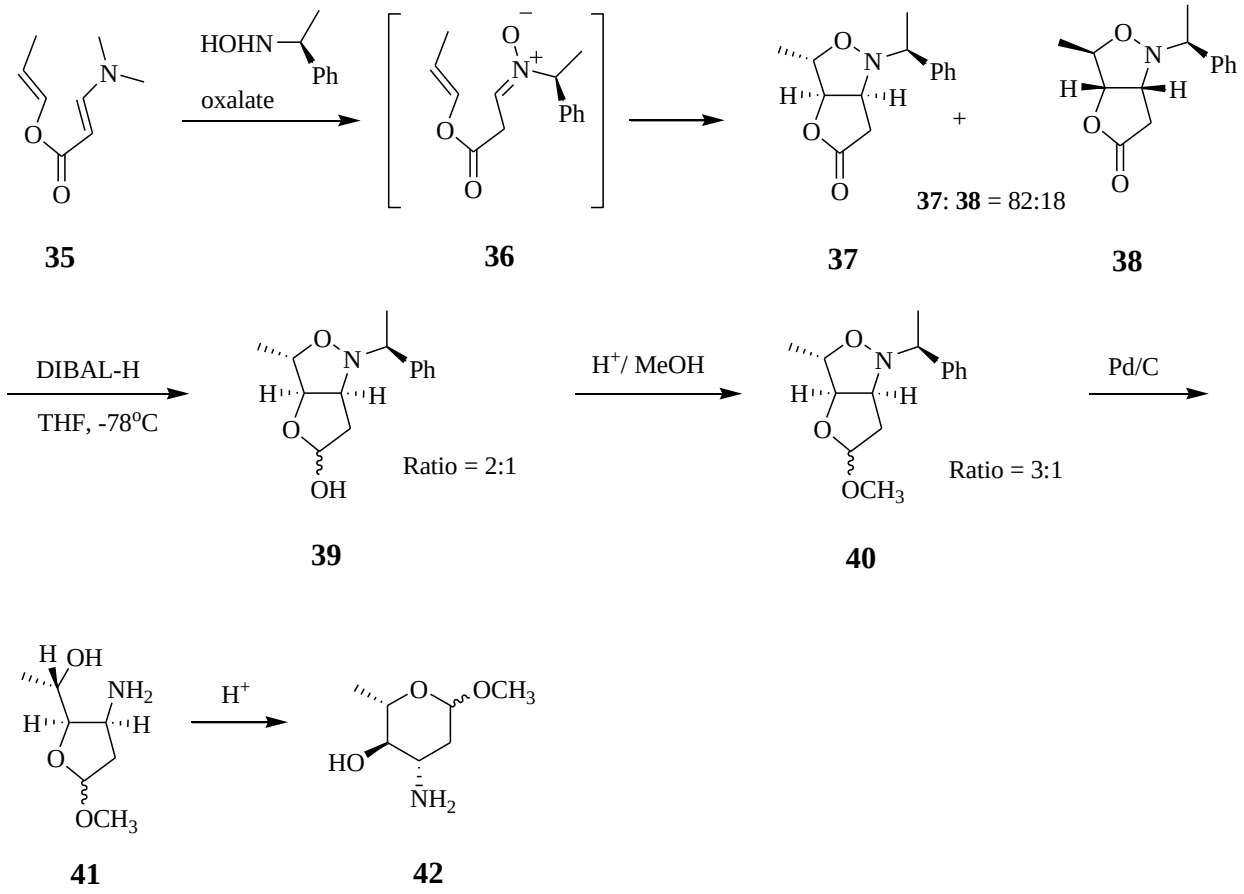
Scheme 4. Synthesis of protected L-acosamine derivative **30** by Boivin et al.[4g]

Pelyvas et al.[4h] also reported another procedure to prepare L-acosamine derivative **34** by selective oxidation with Fetizon's reagent (Ag_2CO_3 precipitated on Celite) from L-rhamnal (**31**) in 1980 (Scheme 5).



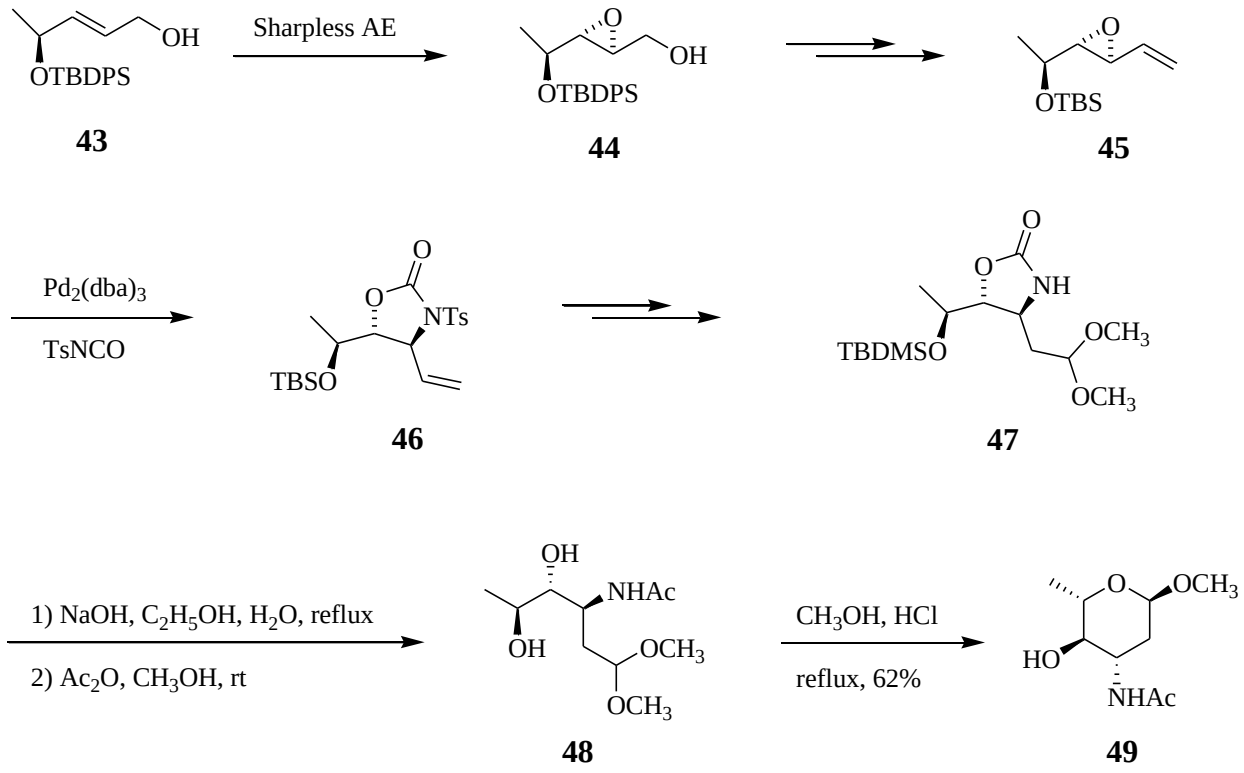
Scheme 5. Synthesis of protected L-acosamine derivative **34** by Pelyvas et al.[4h]

Several strategies have been tried to synthesize derivatives of L-acosamine (**8**) from non-carbohydrates. Firstly, Wovkulich et al.[4i] introduced a asymmetric synthesis of L-acosamine derivatives **42** by an enantioselective intramolecular [3+2] cycloaddition of a chiral nitrone in 1981 (Scheme 6).



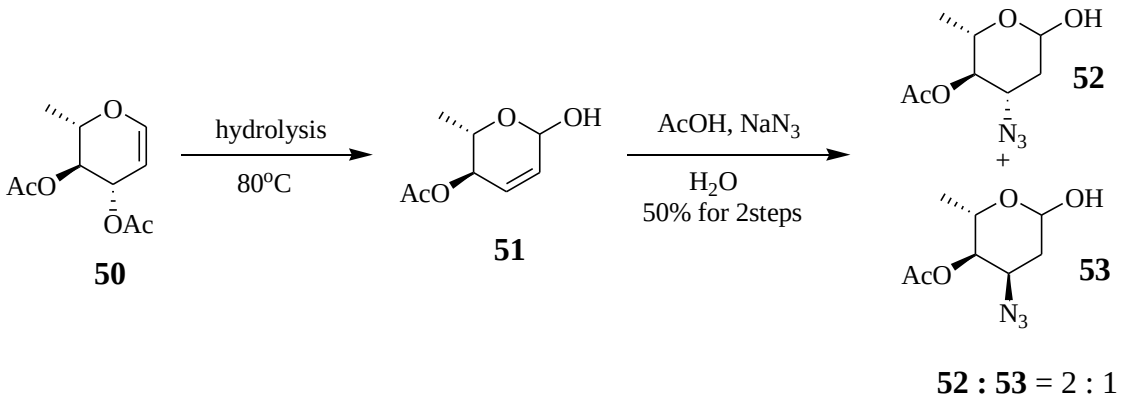
Scheme 6. Asymmetric synthesis of L-acosamine derivative **42** from non-carbohydrate **35**

On the other hand, Trost et al.[4j] also synthesized the chiral L-acosamine derivative **49** from 2-oxazolidone **46**, which was prepared from the optically pure vinyl epoxide **45** obtained via a palladium-mediated vicinal hydroxyamination in 1987 (Scheme 7).



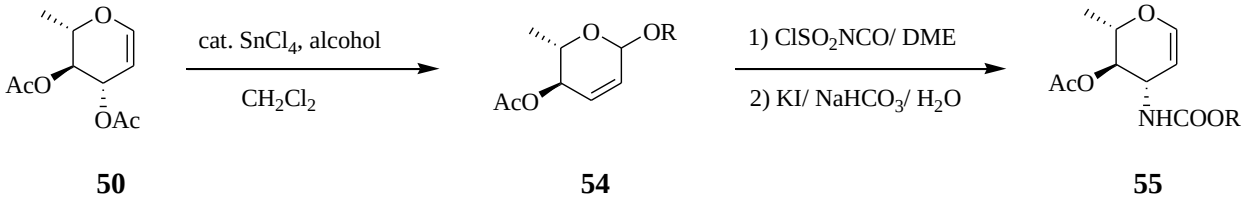
Scheme 7. Synthesis of L-acosamine derivatives **49** by Trost et al.[4j]

The Fiebig group in 2000 developed a strategy, by which they convert L-rhamnal diacetate (**50**) to a precursor of L-acosamine derivative **52**.[4l] They used hydrolysis to obtain alcohol **51** from **50** and sodium azide as a nitrogen source to introduce the amine moiety of **52**. The stereoselectivity of addition of azide was only moderate (**52** / **53** = 2 / 1) (Scheme 8).



Scheme 8. Synthesis of a precursor of L-acosamine derivative **52** by Fiebig et al.[4l]

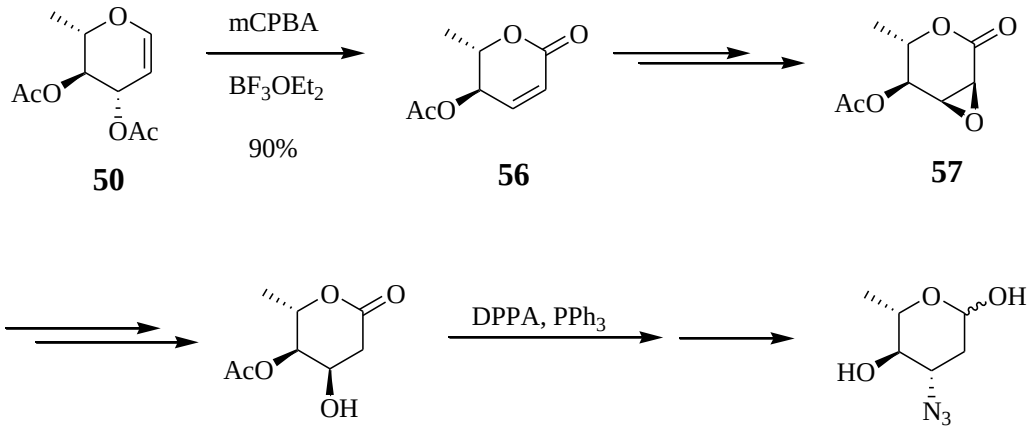
The Pucko group in 2006 demonstrated the synthesis of protected L-acosamine glycal **55**.[4n,6] Isocyanate was used to convert **54** to a chlorosulfonyl compound, which is an valuable intermediate for the synthesis of L-acosamine glycal **55** (Scheme 9).



50 **54** **55**

Scheme 9. Synthesis of protected L-acosamine glycal **55** by the Pucko group

Zhang and co-workers in 2007 developed a different approach, which uses a α,β-unsaturated lactone **56** as a key intermediate.[3] It was prepared by a reaction with $BF_3.OEt_2$ and mCPBA from L-rhamnal diacetate (**50**). The treatment with diphenylphosphoryl azide (DPPA) produced azido sugar **59** that is one of precursors to prepare L-acosamine (**8**) (Scheme 10).

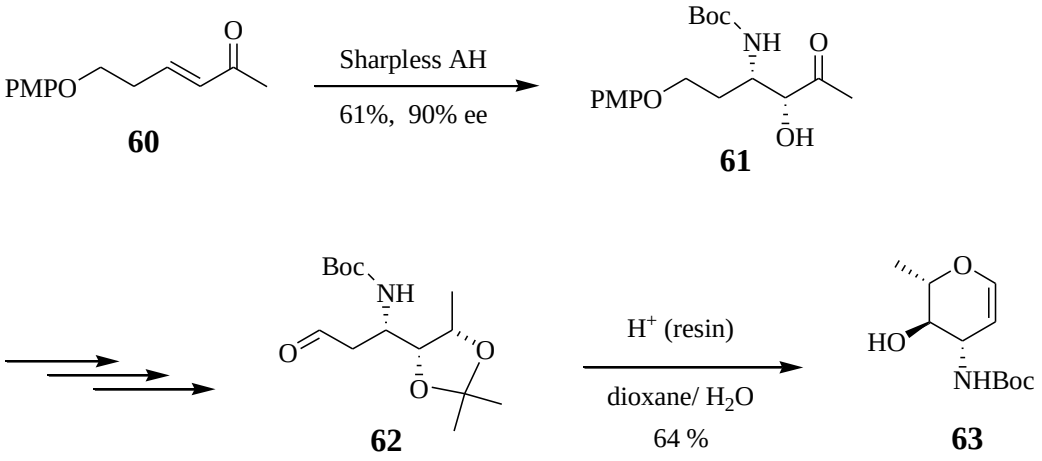


50 **56** **57**

58 **59**

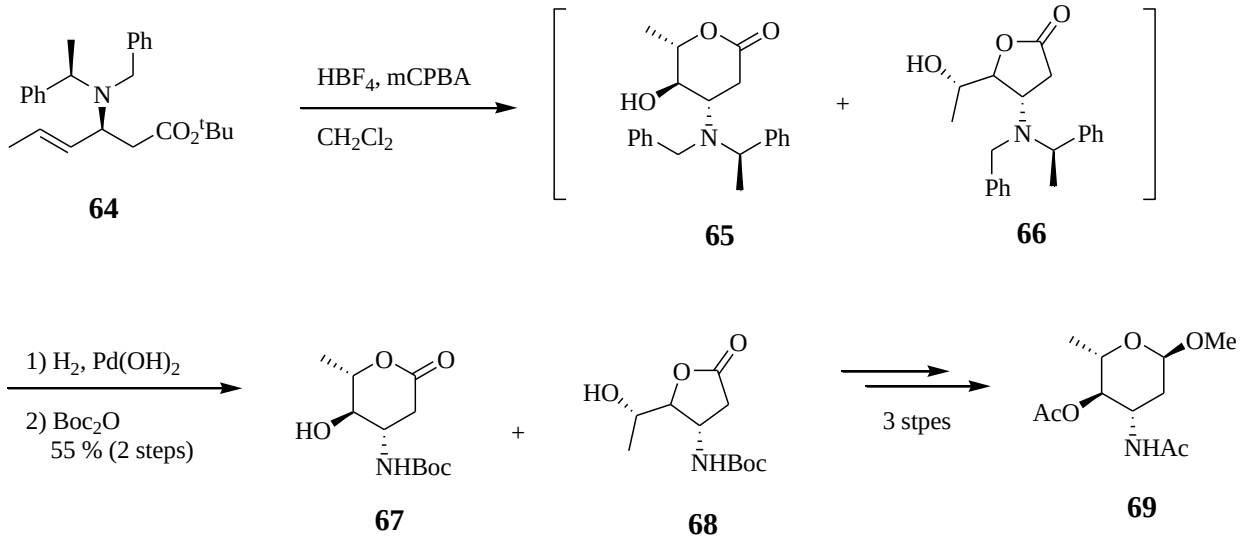
Scheme 10. Synthesis of L-acosamine derivative **59** by Zhang et al.[3]

In 2007, McLeod and co-workers reported a synthesis of protected L-acosamine glycal **63** from a non-carbohydrate **60** via asymmetric aminohydroxylation (Scheme 11).[4o]



Scheme 11. Synthesis of L-acosamine glycal **63** by the McLeod group

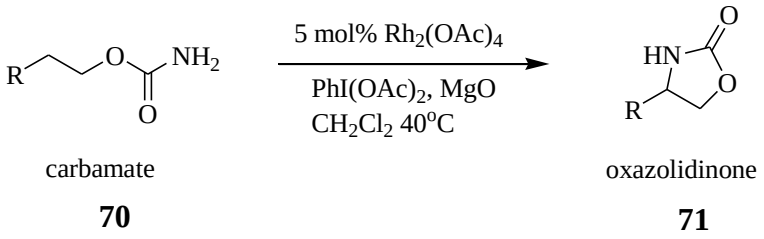
Finally, Bagal et al.[4p] reported an asymmetric synthesis of a derivative of L-acosamine **8** and the β-amino ester **64** was converted to the lactone **67** that was subjected to a reduction with DIBAL-H to produce **69** (Scheme 12).



Scheme 12. Synthesis of L-acosamine derivative **69** by Bagal et al.[4p]

1.1.4. Previous syntheses of 3-amino sugar intermediate by C-H amination

Recently, intramolecular amination of C-H bond, especially Du Bois reaction[7] (Scheme 13), has been ultimately developed ranging from catalysts to reagents to synthesize nitrogen-containing molecules and amine-derived natural products.[8]

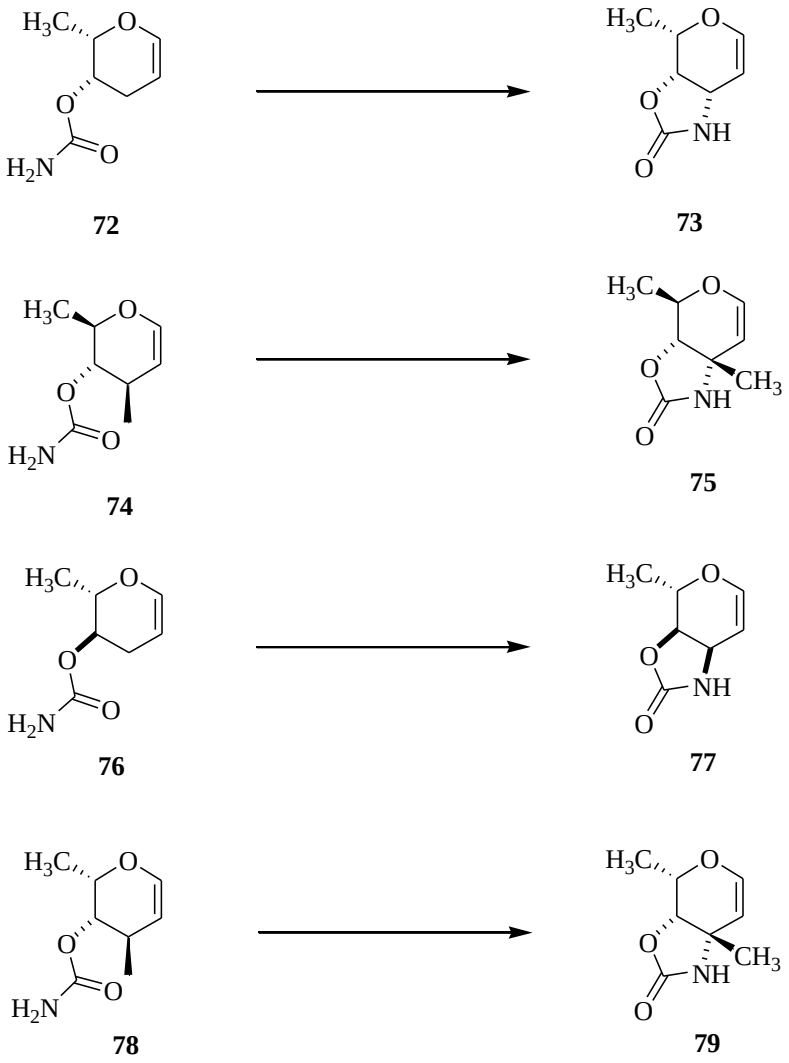


carbamate **70**

oxazolidinone **71**

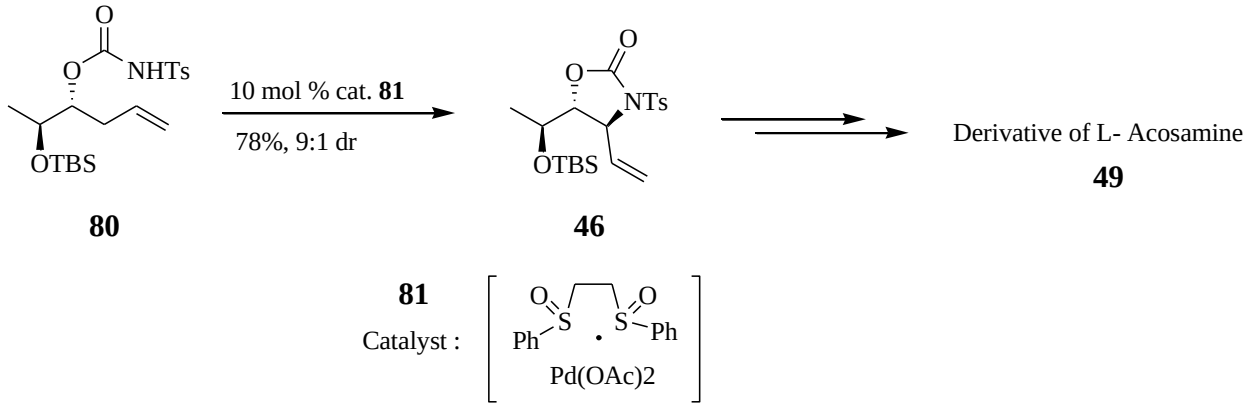
Scheme 13. The intramolecular C-H amination by the Du Bois group

In 2003 and 2005, the Parker group[9] demonstrated that the intramolecular C-H amination using the Du Bois reaction, can be applied to produce valuable 3-amino glycals derivatives such as L-daunosamine (**73**), D-saccharosamine (**75**), L-ristosamine (**77**), and L-vancosamine (**79**) from glycals **72**, **74**, **76**, and **78** with high stereoselectivity (Scheme 14).



Scheme 14. Synthesized protected 3-amino glycals by the Du Bois reaction[7]

The white group also reported new allylic C-H amination and the preparation of a key intermediate, which allowed Trost and co-workers [4j] (Scheme 7) to synthesize L-acosamine **8**. The oxazolidinone **46** was prepared from carbamate **80** via allylic C-H amination with a palladium catalyst **81** (Scheme 15).[10-11]



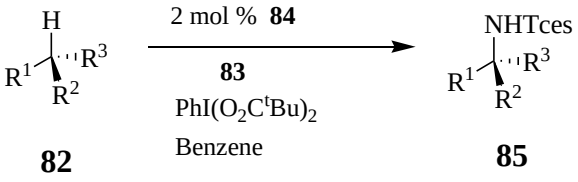
Scheme 15. Synthesis of the oxazolidinone via allylic C-H amination

These examples prove usefulness of C-H amination methods to provide various amino sugars. Thus, studies of stereoselectivity of C-H amination of appropriate substituents would be valuable to develop application of amino sugars syntheses.

1.1.5. A new investigation of the intermolecular C-H amination of glycals

As we discussed, previously the Parker group demonstrated that the regiospecific C-H insertions of glycals (see Scheme 14) and allylic positions are preferred other sites.[9] However, the intramolecular C-H amination on a cyclic system cannot be applied to the preparation of 3,4-trans-3-aminoglycals from deoxy glycals because it produces cis-addition products. Therefore, the intramolecular C-H amination cannot give L-acosamine glycal **92** and 3-epi-daunosamine **94** (see Scheme 17).

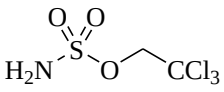
In 2007, Du Bois et al.[12] also introduced the intermolecular C-H amination (Scheme 16) and some of the examples showed stereoselective insertions of C-H bond (Table 1).



82 **85**

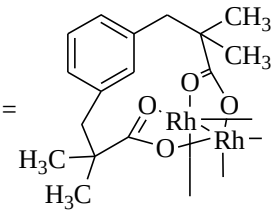
83

$TcesNH_2$ =



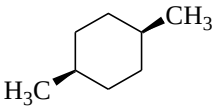
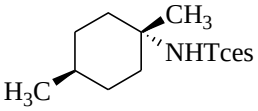
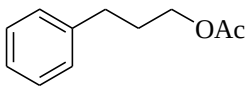
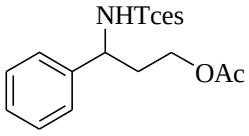
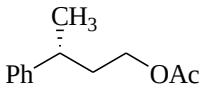
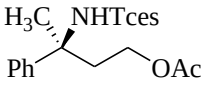
84

$Rh_2(esp)_2$ =



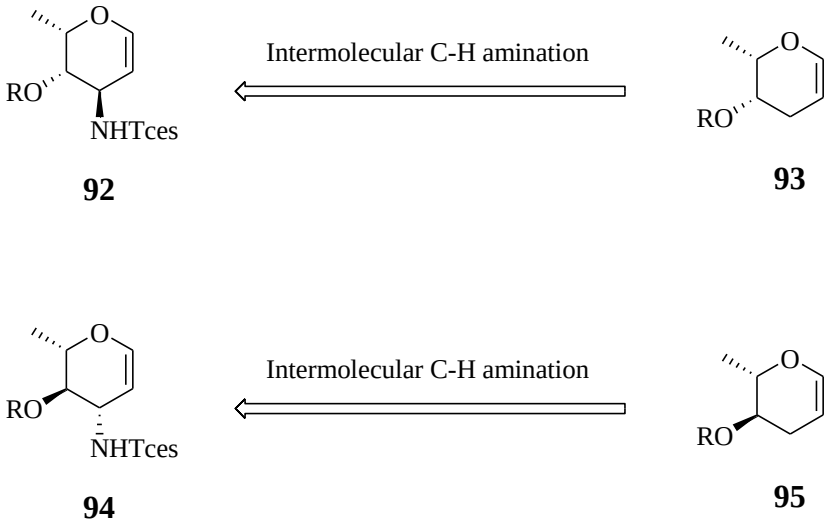
Scheme 16. The intermolecular C-H amination developed by Du Bois et al.[12]

Table 1. Examples for a stereoselective intermolecular amination by the Du Bois group

Substrate	Product	Yield (%)
 **86**	 **87**	46
 **88**	 **89**	74
 **90**	 **91**	10

Thus, we wanted to build a new efficient way to synthesize them from glycals via the intermolecular C-H amination. Due to steric hindrance, we expected that stereoselectivity would

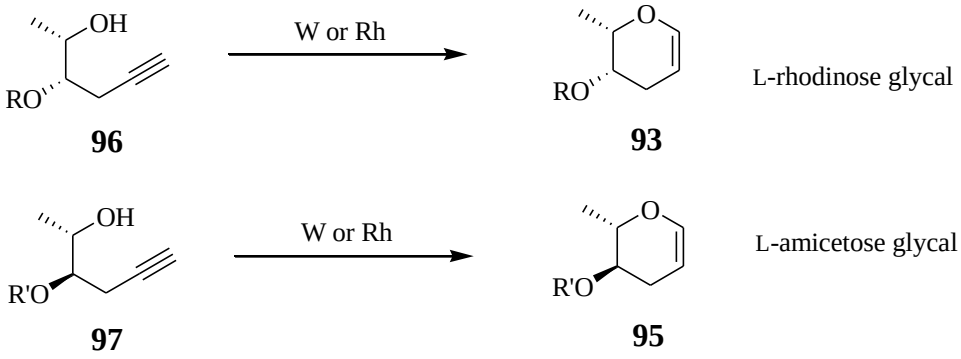
be controlled by the intermolecular C-H amination to provide useful other 3-amino sugars including L-rhodinose glycal (**92**) and L-amicetose glycal (**94**) if allylic positions were more reactive than other sites. (Scheme 17).



92 **93** **94** **95**

Scheme 17. Retrosynthetic analyses for syntheses of 3-amino glycals **93** and **95**

To investigate them, we needed to prepare glycals **93** and **95** as precursors. There are few methods for the preparation of L-rhodinose glycal (**93**) and L-amicetose glycal (**95**). Efficient methods has been developed by McDonald et al.[13] in 1998 and Trost et al.[14] in 2002 (Scheme 18).

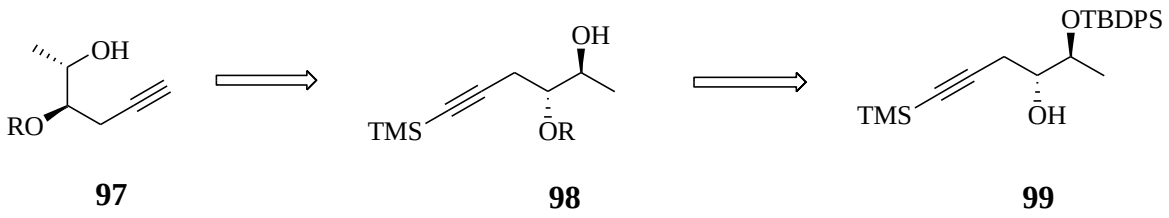


96 **93** **97** **95**

Scheme 18. Syntheses of glycals **93** and **95** by the McDonald group and the Trost group

Both methods can produce two glycals **93** and **95** by tungsten[13] or rhodium[14]-catalyzed cycloisomerization, but precursors **96** and **97** are not prepared by asymmetric syntheses.[13-14]

When the Parker group synthesized L-ristosamine (**77**), **99** was prepared by asymmetric synthesis (see scheme 21).[9a] We believe that the intermediate **97** could be obtained after protection and deprotection of the alcohol **99**. (Scheme 19)



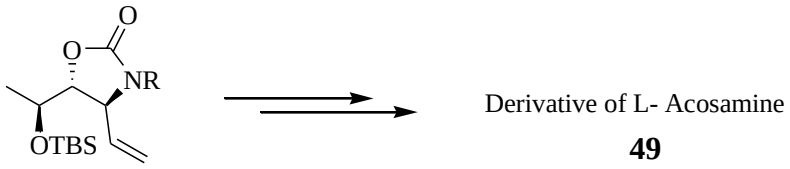
97 **98** **99**

Scheme 19. Retrosynthetic analysis of alkynol **99**

In progress of synthesis of the alkynol **97**, asymmetric procedure was reported by Schmidt and co-worker.[15] L-Rhodinose glycal (**93**) and L-amicetose glycal (**95**) were prepared from the ethyl lactate (**107**) via a ring closing metathesis isomerization. These new methods seem to be efficient and useful, so we adopted their procedures and prepared L-rhodinose glycal (**93**). Finally, the intermolecular C-H amination was applied to know the stereoselective C-H insertion of a glycal.

1.1.6. A new investigation of the intramolecular C-H amination of alkynol carbamates

As we discussed, Trost and White groups showed preparations of the oxazolidinone **46** as the key intermediate to synthesize L-acosamine (**8**) from the epoxide **45** and the carbamate **80** (Scheme 20).

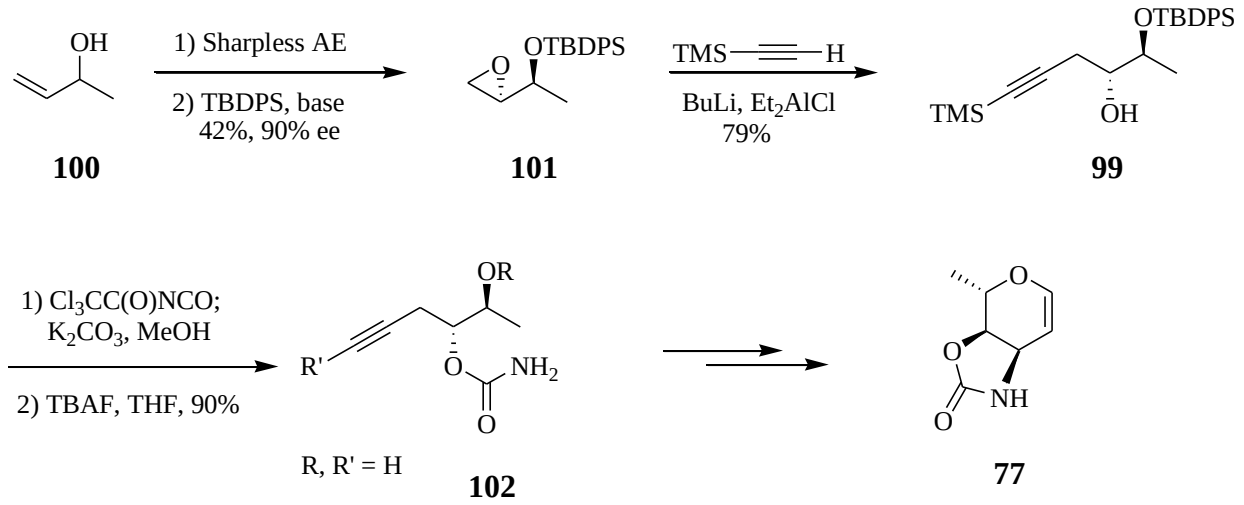


46 (R=Ts) **49**

Scheme 20. The key precursor **46** of L-acosamine derivative **49**

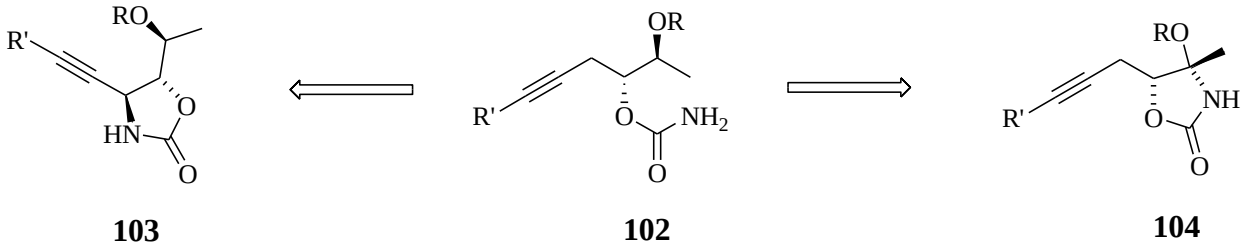
We focused on another possibility to access the intermediate oxazolidinone **46** from an alkyne **102** (see Scheme 23) by the intramolecular C-H amination (Du Bois reaction).

When the Parker group disclosed a preparation of L-ristosamine glycal (**77**), they also developed a procedure to provide a carbamate **102** (Scheme 21)[9a], but the regioselectivity of C-H amination of the alkynol carbamate **102** was not explored.



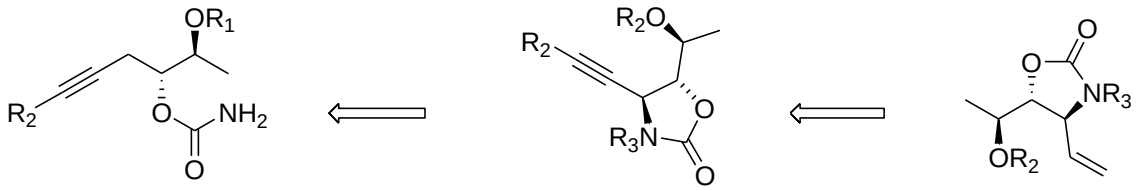
Scheme 21. Asymmetric synthesis of the carbamate **102** by the Parker group

At that time, there was no example to expect results from C-H amination, but we could expect two possible products (Scheme **22**).



Scheme 22. Expected products from C-H amination of alkynol carbamates

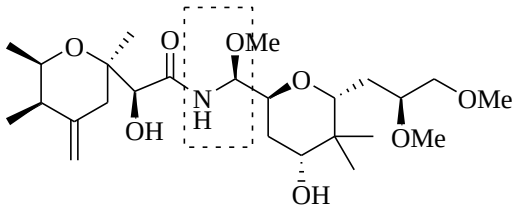
When it provides the insertion of a nitrene into a propargylic C-H bond, we expected that a precursor of oxazolidinone **103** might be produced from the carbamate **102**, which will subjected to a reduction of alkyne **103** to provide a valuable intermediate **46**[4j] for L-Acosamine (**8**) (Scheme 23). The stereoselectivity could be controlled by cis-addition of the intramolecular C-H amination.



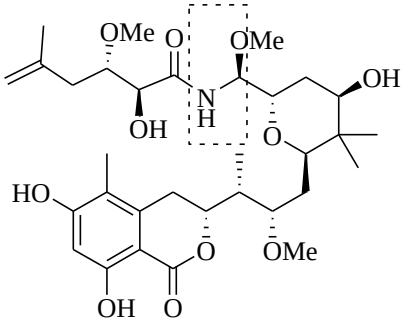
102 **103** **46**

Scheme 23. Retrosynthetic analysis of the oxazolidinone **46** by the Du Bois reaction

In addition, another expected product **104** was an aminal structure, which has amine and alcohol functional group on the same carbon atom. A wide variety of natural products, which show incredible bioactivities for cancer cells, have aminal structures as a key moiety such as pederin (**105**) and psymberin (**106**). Preparing the aminal moiety and control of its stereochemistry are the central problems in their syntheses.[16] If we would control the stereoselectivity of aminal structures, it could be a new strategy to produce valuable natural compounds (Figure 4).



Pederin (**105**)



(+)-Psymberin (**106**)

Figure 4. Natural products, which have aminal structures

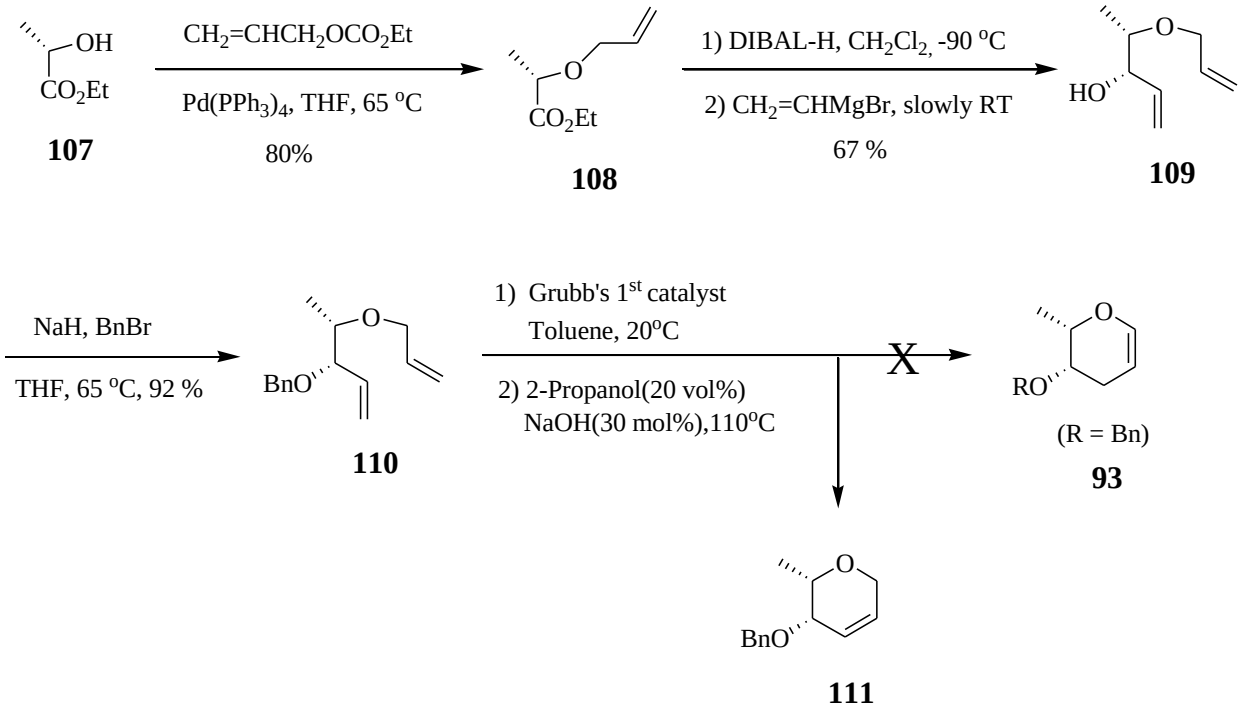
Thus, we have investigated reactivity and selectivity of alkynol carbamates of intramolecular C-H amination.

1.2. Result and discussion

1.2.1. Intermolecular C-H amination of L-rhodinose glycals (93)

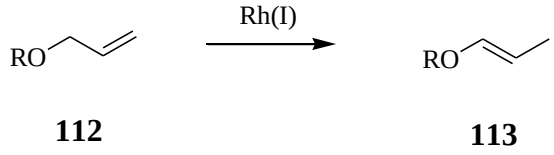
1.2.1.1. Synthesis of L-rhodinose glycals (93)

To investigate the stereoselectivity of the intermolecular C-H amination of L-rhodinose glycal (**93**) and L-amicetose glycal (**95**), we decided to follow procedures developed by Schmidt group[15]. They produced **93** and **95** from ethyl lactate (**107**) via the RCM-isomerization. The first step was a synthesis of allyl ethyl lactate **108**[17] from the ethyl lactate (**107**) via a palladium-catalyzed O-allylation with allyl ethyl carbonate. Reduction of the allyl ethyl lactate **108**, and then addition of vinyl magnesium bromide produced alcohol **109**. Benzyl protection of the alcohol **109** afforded benzyl ether **110**. However, we were not able to prepare L-rhodinose glycal (**93**) from **110** through the RCM-isomerization. Instead of **93**, a dihydropyran **111** was obtained. We also used other reagents such as NaH and $NaBH_4$ instead of NaOH for the RCM-isomerization[18], but all reactions produced the only dihydropyran **111** (Scheme 24).



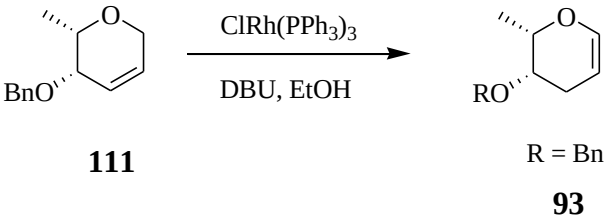
Scheme 24. Preparation of the dihydopyran **111** from the ethyl lactate **107**

In 1973, Corey group reported the isomerization of allyl ether that Wilkinson's catalyst, $RhC1(PPh_3)_3$, can catalyze isomerization of allyl ether **112** to 1-propenyl ether **113** (Scheme 25).[19]



Scheme 25. Isomerization of allyl ether with Rh catalyst

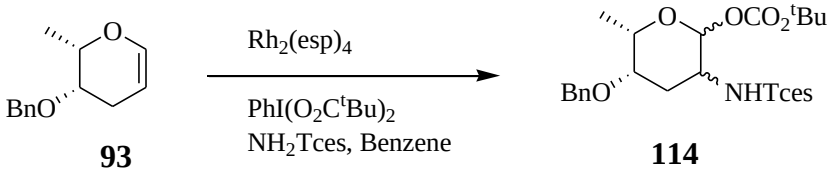
Thus, the dihydropyran **111** was treated with Wilkinson's catalyst and finally we could obtain the protected L-rhodinose glycal **93** (Scheme 26).[19-20]



Scheme 26. Synthesis of the protected L-rhodinose glycal **93** by isomerization with Rh catalyst

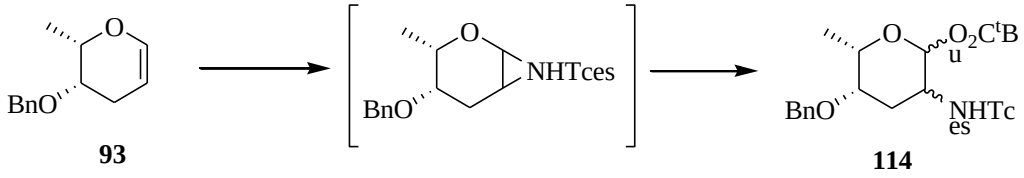
1.2.1.2. Intermolecular C-H amination of L-rhodinose glycal (93)

After preparing C-H amination reagents such as $TcesNH_2$ **83**, $PhI(O_2C^tBu)_2$, and $Rh_2(esp)_2$ **84**, we investigated the selectivity of the intermolecular C-H amination[12] of the protected L-rhodinose glycal **93** to know if L-epi-daunosamine glycal (**92**) could be produced from the protected L-rhodinose glycal **93**. However, we found that the product was not the 3-amino glycal **92** but the 2-aminosugar **114** (Scheme 27).



Scheme 27. Synthesis of 2-aminosugar **114** from the protected L-rhodinose glycal **93**

On the basis of a reference[21], we believe that a rhodium nitrene insertion prefers forming an aziridine ring with a double bond of **93** to C-H amination of C3-H bond of **93**, and 2-aminosugar **114** was produced via an aziridine ring opening by ($-^tBuCO_2$) generated from a reagent, $PhI(CO_2^tBu)_2$ (Scheme 28).



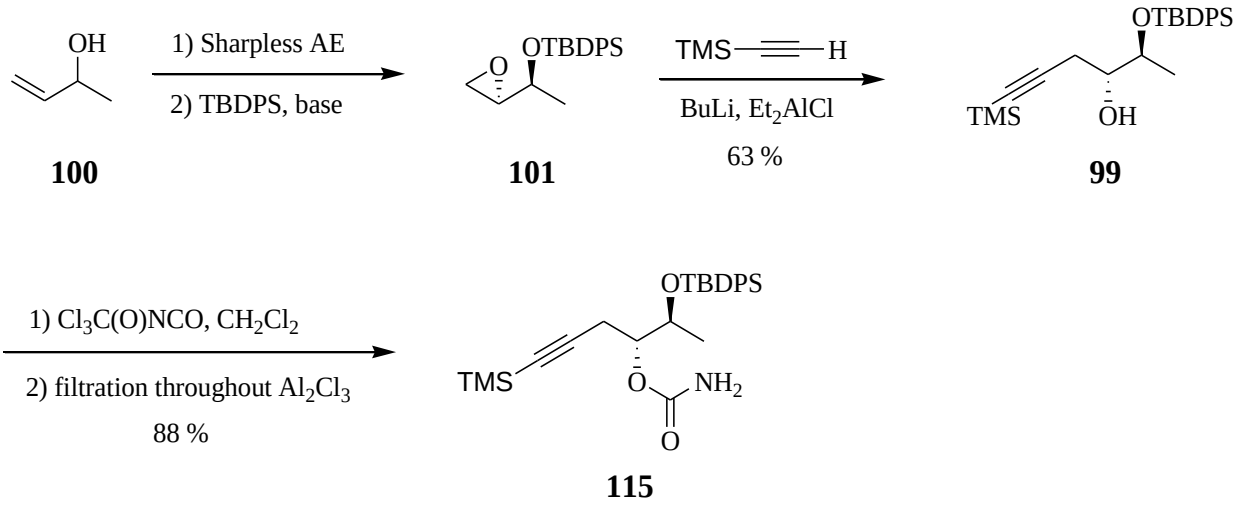
Scheme 28. Formation of 2-aminosugar **114** via aziridine ring opening

So far, there are not so many examples[22] to prepare 2-amino glycosides. Our approach would be good access to introduce 2-amino sugar moiety for natural products analogues.

1.2.2. Intermolecular C-H amination of alkynol carbamates

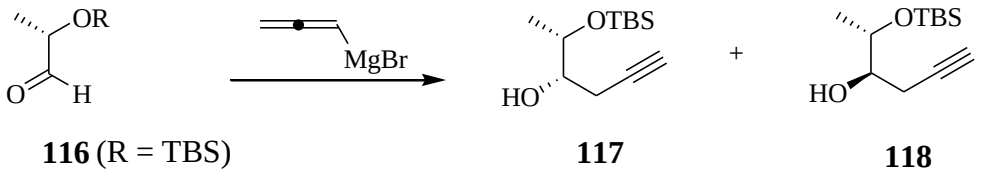
1.2.2.1. Preparation of alkynol carbamates

First of all, the alkynol carbamate **115** was prepared from 3-buten-2-ol (**100**) using the procedure developed by the Parker group.[9a] The epoxide was produced from 3-butene-2-ol (**100**) by Sharpless asymmetric epoxidation and the epoxy alcohol was protected by TBDPS to provide **101**. The treatment of the epoxide **101** with acetylide in the presence of Lewis acid (Et_2AlCl) gave alkynol **99** that was converted to the alkynol carbamate **115** (Scheme 29).



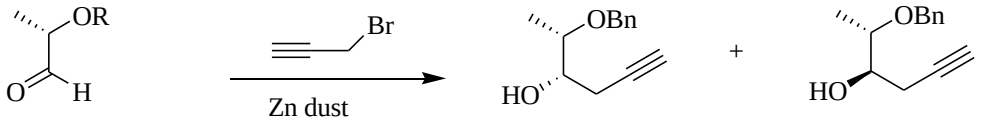
Scheme 29. Asymmetry synthesis of the alkynol carbamate **115**

In addition, we also applied another synthetic way to easily prepare alkynol carbamates, two diastereomers **122** and **123**. The McDonald group reported that a treatment of aldehyde **116** (R = TBS) with allenylmagnesium bromide could give a partially separable mixture of TBS-protected alkynols **117** and **118**, but it is not convenient to make allenylmagnesium bromide (Scheme 30).[13]



Scheme 30. Synthesis of alkynols **117** and **118** with allenylmagnesium bromide

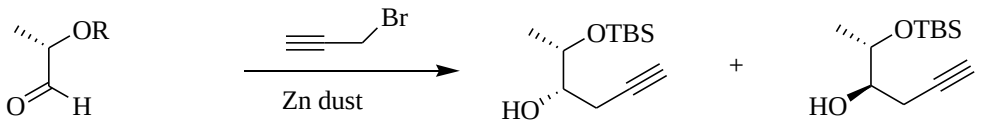
Wu et al.[23] also introduced a synthesis of Bn-protected alkynols **119** and **120** from the aldehyde **116** (R = Bn) by a propargylation with Zn-dust and propargyl bromide, which is an effective and convenient method, but they gave an inseparable mixture (Scheme 31).



116 (R = Bn) **119** **120**

Scheme 31. Synthesis of alkynols **119** and **120** with Zn-dust and propargyl bromide

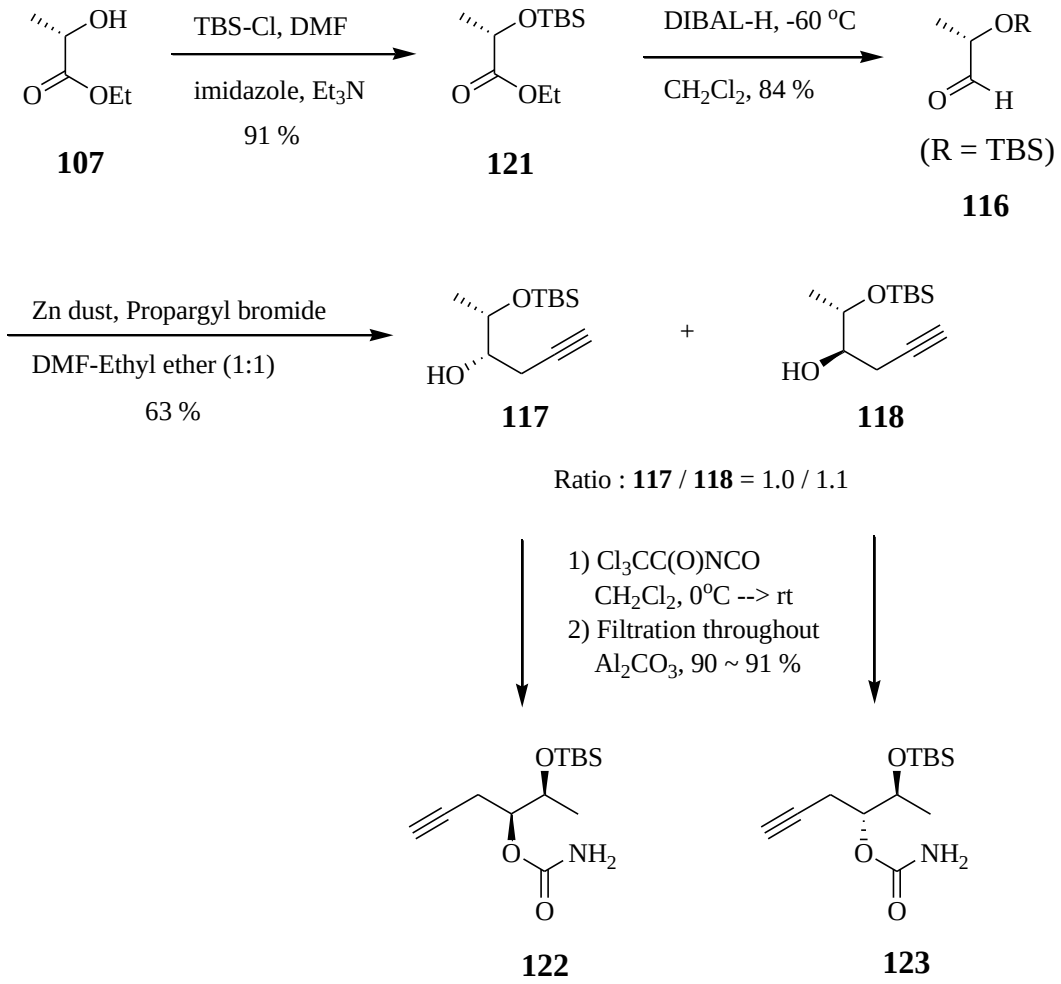
Therefore, we decided to apply allylation with Zn-dust and propargyl bromide to produce carbamates **117** and **118** from aldehyde (R = TBS) **116** that can be separable by silica gel chromatography (Scheme 32).



116 (R = TBS) **117** **118**

Scheme 32. Synthesis of alkynols **117** and **118** with Zn-dust and propargyl bromide

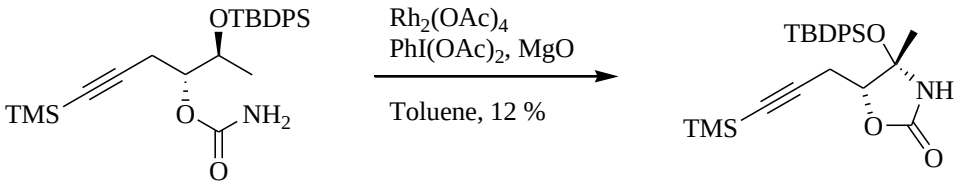
(-)-Ethyl lactate (**107**) was simply converted to TBS-protected ethyl lactate **121**. The DIBAL-H reduction of TBS-protected ethyl lactate **121** gave an aldehyde **116**.[24] The treatment of the aldehyde **116** with Zn dust and propargyl bromide provided alkynols as two diastereomers **117** and **118** that were partially separated by silica gel chromatography. Finally, an addition of isocyanate to each alkynol **117** and **118** followed by filtration throughout Al_2CO_3[25] resulted in two diastereomers, carbamates **122** and **123** (Scheme 33).



Scheme 33. Preparation of two alkynol carbamates diastereomers **122** and **123**

1.2.2.2. C-H amination of alkynol carbamates

We had been investigating the C-H amination of carbamate **115** under the Du Bois reaction condition[7]. After several experiments, although this reaction just gave small amount of a product **124** (12 %), it showed that the carbamate **115** had reactivity for C-H amination and the product is the aminal **124** (Scheme 34) (Table 2).



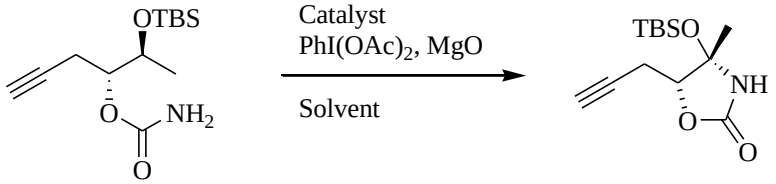
115 **124**

Scheme 34. Synthesis of aminal **124** from carbamate **115**

Table 2. Results of C-H amination of alkynol carbamate **115**

Catalyst (% mol)		$PhI(OAc)_2$ (eq.)	MgO (eq.)	Temp. (°C)	Solvent	Result
$Rh_2(OAc)_4$	5%	1.4	2.3	40	CH_2Cl_2	no rxn
$Rh_2(OAc)_4$	10%	1.4	2.3	40	CH_2Cl_2	no rxn
$Rh_2(OAc)_4$	20%	1.4	2.4	40	CH_2Cl_2	no rxn
$Rh_2(OAc)_4$	20% X 2	1.4 X 2	2.4 X 2	90	Toluene	Y = 12 %

After we obtained a small amount of product, we prepared two carbamate diastereomers **122** and **123** and another catalyst, $Rh_2(tpa)_4$, to examined the regio and stereoselectivity of C-H amination for carbamates. Firstly, the carbamate **123** that has the same stereo configuration as the carbamate **115** was examined and it gave us only aminal structure **125** like **124** in 52 % yield. The $Rh_2(tpa)_4$ catalyst[7,26] is more efficient and powerful than the $Rh_2(OAc)_4$ for the carbamate **123** in C-H amination reaction. The relative stereochemistry of the aminal **125** was assigned on the basis of nuclear Overhauser effects (Scheme 35) (Table 3).



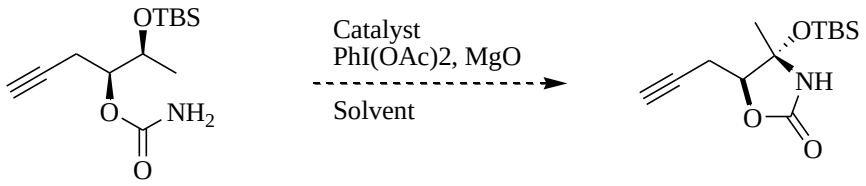
123 **125**

Scheme 35. Synthesis of aminal **125** from carbamate **123**

Table 3. Results of C-H amination of alkynol carbamate **123**

Catalyst (% mol)		$PhI(OAc)_2$ (eq.)	MgO (eq.)	Temp. (℃)	Solvent	Result
$Rh_2(OAc)_4$	20%	1.4	2.4	50	benzene	conversion 50%
$Rh_2(OAc)_4$	20%	1.4	2.4	90	toluene	no product and no **123**
$Rh_2(tpa)_4$	20%	1.4	2.4	50	benzene	Y = 40 %, no starting
$Rh_2(tpa)_4$	3%	1.4	2.4	50	benzene	Y = 52 %, 19% starting (**123**) recovered

On the other hand, another diastereomer **122** did not give any product, although several reaction conditions including different catalysts were tried (Scheme 36) (Table 4).



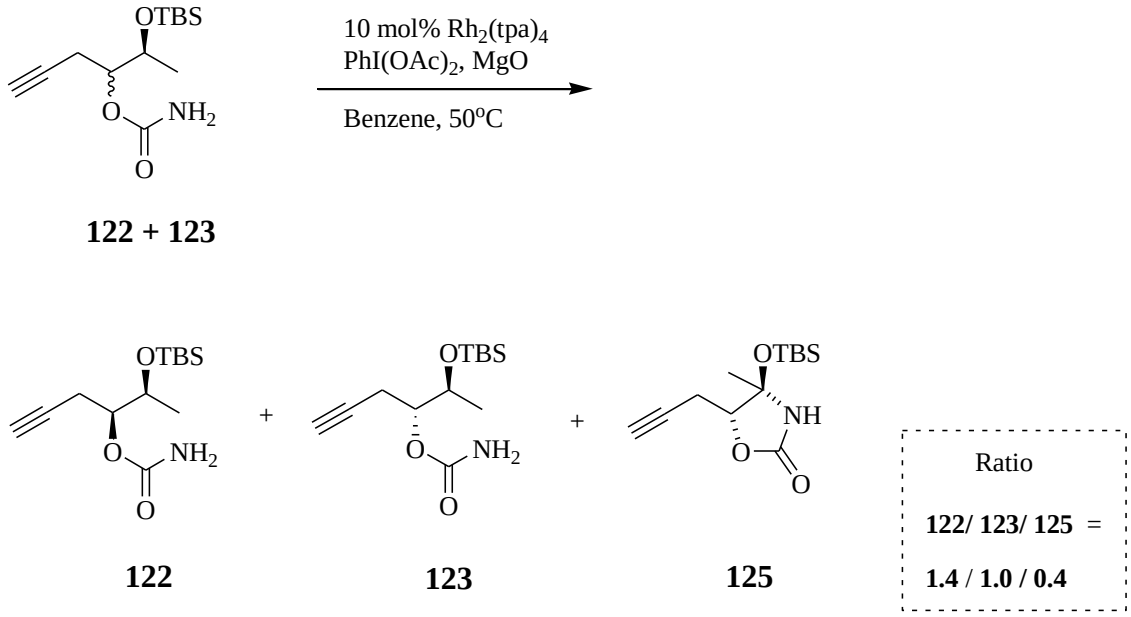
122 (not detected) **126**

Scheme 36. C-H amination of carbamate **122**

Table 4. Results of C-H amination of alkynol carbamate **122**

Catalyst (% mol)		$PhI(OAc)_2$ (eq.)	MgO (eq.)	Temp. (℃)	Solvent	Result
$Rh_2(OAc)_4$	20%	1.4	2.4	40	CH_2Cl_2	no rxn
$Rh_2(OAc)_4$	20%	1.4	2.4	80	benzene	no rxn
$Rh_2(tpa)_4$	4%	1.4	2.0	40	benzene	96 % **122** recovered
$Rh_2(tpa)_4$	10%	1.8	2.4	50	benzene	no rxn
$Rh_2(tpa)_4$	40%	1.8	3.0	40	benzene	no **122** and no product
$Rh_2(tpa)_4$	20%	3.5	6.0	50	benzene	no **122** and no product

Under the same reaction condition, the anti-alkynol carbamate **123** just gave aminal product **125**, but the syn-alkynol **122** was not reactive and did not give products. To confirm previous results for selective amination, a mixture of **122** and **123** (1:1 ratio) was examined under the Du Bois reaction and this experiment gave us more a reliable result that the anti-alkynol carbamate **123** could just do C-H insertion and the syn-alkynol carbamate **122** did not give any C-H insertion product on based of NMR analysis (Scheme 37).



Scheme 37. C-H amination of a mixture of diastereomers of **122** and **123**

1.3. Conclusion

In conclusion, in attempting to examine the stereoselectivity of intermolecular C-H amination for L-rhodinose glycal (**93**), we discovered that the 2-amino sugar **114** was produced from the glycal **93** in 57 % yield. This experimental result clearly shows that the intermolecular C-H amination of glycals prefer 2-amino sugars to 3-amino sugars. We can explain that the intermolecular C-H amination by the formation of an aziridine ring intermediate instead of nitrene C-H insertion and thereafter aziridine ring opening would provide the 2-amino sugar **93**.

In addition, we had investigated and discovered that the intramolecular C-H amination of anti-alkynol carbamates **115** and **123** give aminal structures **124** and **125** with high regio-, and stereoselectivity, but the isomeric syn-alkynol carbamates **122** do not provide any product. Experimental result also showed that the $Rh_2(tpa)_4$ catalyst is more reactive than the $Rh_2(OAc)_4$ for the C-H amination of alkynol carbamates. Further studies of the C-H amination of alkynol carbamates are needed to allow the syntheses of aminal subunits in valuable natural compounds.

1.4. Reference

(1) Hauser, F. M.; Ellenberger, S. R.: Syntheses of 2,3,6-trideoxy-3-amino- and 2,3,6-trideoxy-3-nitrohexoses, *Chem. Rev.* **1986**, *86*, 35.

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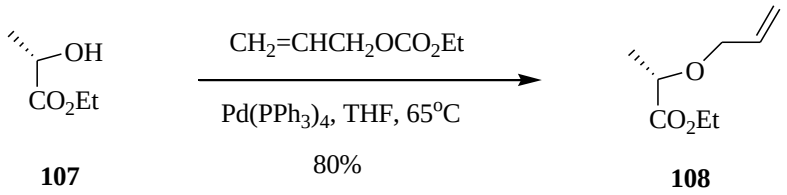
1.5. Experimental section

General Information

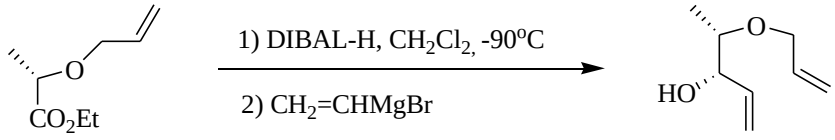
All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å , 230-400 mesh, surface area 500-600 m^2/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), a Varian Inova-500 (500 MHz for ^1H and 125 MHz for ^{13}C), Bruker-400 (400 MHz for ^1H and 100 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C, or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

1.5.1. Experimental Procedure for intermolecular C-H amination of glycals



107 **108**

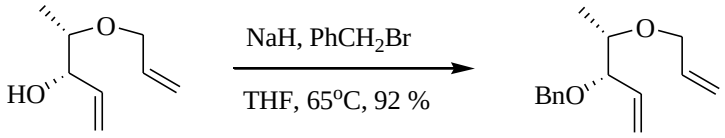
Ally ethyl lactate 108.[17] To solution of ethyl lactate (**107**) (0.590 g, 5.00 mmol) in THF (5 mL) was added a solution of ally ethyl carbonate (1.30 g, 10.0 mmol) and $Pd(PPh_3)_4$ (0.144 g, 0.125 mmol) in THF (5 mL) via a cannula. The mixture was stirred and heated to reflux for 5 h. The reaction was allowed to cool to ambient temperature and then filtered through a short pad of silica followed by washing with ethyl ether. After evaporation, the crude product was purified on silica gel chromatography (elution with petroleum ether / EtOAc = 9 : 1) to give allyl ethyl lactate **108** (0.63 g, 80 %) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, 1H, *J* = 17.2, 10.4, 6.0, 5.5 Hz), 5.26 (ddd, 1H, *J* = 16.9, 3.4, 1.5 Hz), 5.16 (ddt, *J* = 10.4, 1.4 Hz, 1H), 4.18 (dq, *J* = 7.2 Hz, 2H), 4.11 (ddt, *J* = 12.5, 5.5, 1.4 Hz, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 3.91 (ddt, *J* = 12.5 Hz, 6.0Hz, 1.4Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). Spectroscopic properties were in agreement with literature values.[17]



108 **109**

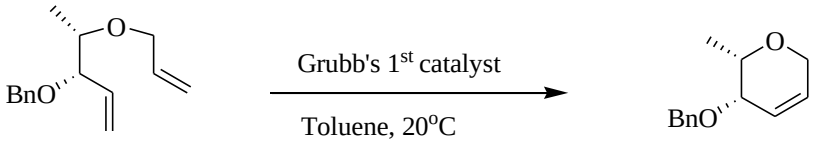
Alcohol 109.[15,27] A solution DIBAL-H (1.0 M in hexane, 1.23 mL, 1.23 mmol) was added at - 90 °C to a solution of lactate **108** (0.142 mg, 0.900 mmol) in CH_2Cl_2 (5 ml). After stirring at this temperature for 30 min, TLC (EtOAc : hexanes = 1 : 20) indicated complete consumption of the starting material. Vinyl magnesium bromide (0.7 M solution in THF, 2.51 mL, 1.76 mmol) was then added via syringe and the mixture was allowed to warm to ambient temperature. It was then poured onto water and diethyl ether, and the precipitate was dissolved with a saturated solution

of K tartrate. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried with $MgSO_4$. After evaporation, the crude product was purified on silica gel chromatography (elution with EtOAc : hexane = 1 : 20) to give alcohol **109** (85 mg, 67 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (dddd, *J* = 17.3, 10.5, 5.5, 5.5 Hz, 1H) 5.79 (ddd, *J* = 17.3, 10.5, 6.5 Hz, 1H), 5.34 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.25 (dm, *J* = 17.3 Hz, 1H), 5.19 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1H), 5.15 (dm, *J* = 10.5 Hz, 1H), 4.12 (dddd, *J* = 12.8, 5.5, 1.3, 1.3 Hz, 1H), 3.93 (dddd, *J* = 12.8, 5.5, 1.3, 1.3 Hz, 1H), 3.89 (dd, *J* = 7.0, 6.5 Hz, 1H), 3.32 (dq, *J* = 7.0, 6.3 Hz, 1H), 2.80 (br s, 1H), 1.11 (d, *J* = 6.3 Hz, 1H). Spectroscopic properties were in agreement with literature values.[16,28]



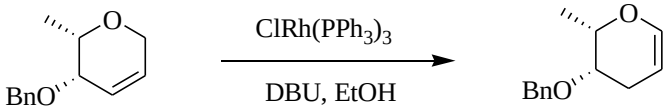
109 **110**

Benzyl protected benzyl ether 110.[15] NaH (60 % dispersion in mineral oil, 3.0 mg, 0.08 mmol) was added to a solution of **109** (9.0 mg, 0.06 mmol) in THF (2.5 mL) and the mixture was heated to reflux for 30 min. Benzyl bromide (13.2 mg, 0.077 mmol) was added, and the mixture was heated to reflux for 30 min again. NaH (60 % dispersion in mineral oil, 3.0 mg, 0.08 mmol) was 2 times more added until TLC (EtOAc : hexane = 1 : 7) indicated complete consumption of the starting material. After evaporation, the crude product was purified on silica gel chromatography (elution with EtOAc : hexane = 1: 20) to afford benzyl ether **110** (13.5 mg, 92 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 - 7.25 (m, 5H), 5.93 (dddd, *J* = 17.0, 10.5, 5.7, 5.4 Hz, 1H), 5.82 (ddd, *J* = 17.2, 10.2, 7.5 Hz, 1H), 5.36 - 5.24 (m, 3H), 5.16 (dm, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.10 - 4.07 (dt, *J* = 2.4, 2H), 3.83 - 3.78 (m, 1H), 3.58 (dq, J = 6.2, 6.2 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H). Spectroscopic properties were in agreement with literature values.[15]



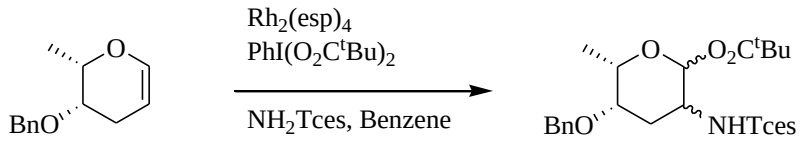
110 **111**

3,6-Dihydropyran 111.[15] Grubb's 1st generation catalyst (2.3 mg, 5.0 mol %) was added to a solution of ether **110** (13 mg, 0.056 mmol) in toluene (1.5 mL). The solution was stirred at ambient temperature, until the starting material was fully consumed as indicated by TLC and all volatiles were evaporated. The residue was purified by silica gel column chromatography (elution with EtOAc : hexanes = 1 : 20) to give colorless oil **111** (6.0 mg, 53 %). ^{1}H NMR (400 MHz) δ 7.34 - 7.25 (m, 5H), 5.98 (m, 2H), 4.60 (dd, *J* = 12.0 Hz, 2H), 4.18 (m, 2H), 3.67 (m, 1H), 3.63 (m, 1H), 1.35 (d, *J* = 2.4 Hz, 3H).



111 **93**

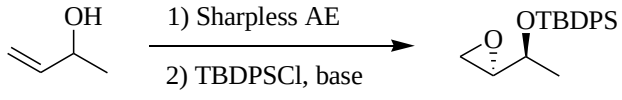
L-Rhodinose glycal (93). To a solution of dihydropyran **111** (6.0 mg, 29 μmol) in absolute EtOH (3 mL) was added $RhCl(PPh_3)_3$ (5.4 mg, 5.9 μmol) and DBU (1.1 μL, 7.4 μmol).[20,28-29] The mixture was heated to 70 °. After 16 h, the reaction temperature was increased to 85 °C. The catalyst (5.4 mg, 5.9 μmol) and DBU (7 μL) were added more and stirred for 2.5 h at the same temperature. After evaporation, the residue was purified by silica gel column chromatography (elution with EtOAc : hexanes = 1 : 20) to give colorless oil **93** (5.0 mg, 83 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 6.31 (m, 1H), 4.66 (d, *J* = 12.2 Hz,1H), 4.61 (m, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.13 (dq, *J* = 2.7 Hz, 1H), 3.67 (dt, *J* = 2.7, 5.7 Hz, 1H), 2.27 - 2.11 (m, 2H), 1.28 (d, *J* = 6.5 Hz, 3H). Spectroscopic properties were in agreement with literature values.[16,28]



93 **114**

2-Amino sugar 114. To a solution of glycal **93** (14.3 mg, 0.070 mmol) in benzene (0.8 mL) was added $Rh_2(esp)_4$ **84** (4.0 mg, 0.005 mmol) and NH_2Tces **83** (10.2 mg, 0.070 mmol) under argon and then a solution of $PhI(O_2C^tBu)_2$ (56.9 mg, 0.140 mmol) in benzene (0.5 mL) was added dropwise for 3 h with a syringe pump. The reaction mixture was stirred for 3 hr and sat. thiourea solution was added. The mixture was separated, extracted with CH_2Cl_2 (3 times), and dried over anhydrous $MgSO_4$. The combined organic extract was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 20) to give white solid **114** (21 mg, 57 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 - 7. 30 (m, 5H), 6.19 (d, *J* = 3.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.62 (s, 2H), 4.56 (d, *J* = 9.9 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.25 - 4.15 (m, 1H), 3.90 (qd, *J* = 6.6, 1.2 Hz, 1H), 3.49 (s, 1H), 2.50 (dt, *J* = 14.4, 0.9 Hz, 1H), 1.82 (td, *J* = 12.9, 2.1 Hz, 1H), 1.25 (s, 9H), 1.21 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 137.8, 128.7, 128.2, 93.5, 91.0, 78.5, 76.9, 73.7, 71.6, 68.7, 48.5, 39.6, 29.6, 27.3, 16.7.

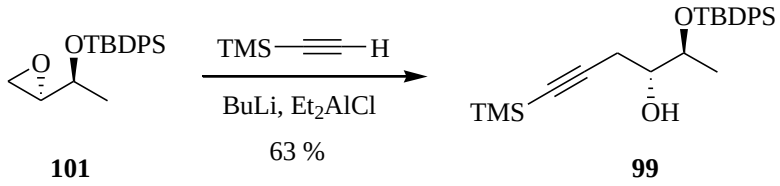
1.5.2. Experimental Procedure for intramolecular of C-H amination of alkynol carbamates



100 **101**

Epoxide 101[9a] Powdered 3Å molecular sieves (500 mg) were placed in a flask and heated at 300 ℃ under reduced pressure (ca. 0.5 mmHg) for 3 h. To the cooled flask, maintained under argon, were added CH_2Cl_2 (100 mL), 3-butene-2-ol (**100**) (2.0 mL, 23 mmol), and L-(+)-DIPT

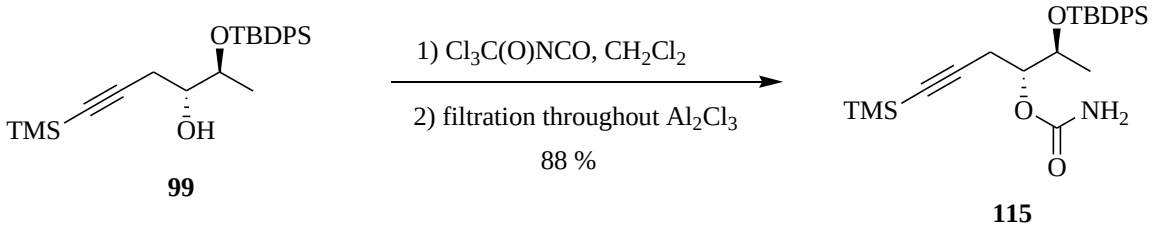
(730 μL, 3.5 mmol). The stirred mixture was cooled to -20 ℃ and treated with Ti(O-*i*-Pr)$_4$ (680 μL, 2.3 mmol). After 30 min, TBHP in decane (6.0 M, 1.73 mL, 10 mmol), dried with activated 3Å molecular sieves prior to use, was added dropwise. The reaction mixture was stirred at -20 ℃ for 21 h and then diluted with CH_2Cl_2 (50 mL). To the stirred mixture at -20 ℃ were added imidazole (4.7 g, 69 mmol), and TBDPS-Cl (9.0 mL, 35 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was slowly warmed to rt and stirred for 12 h. Then 10 % saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was filtered through a short Celite column and concentrated. The residue was extracted with hexane (2 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : hexanes = 1 : 150) on silica gel, that had been treated with Et_3N (0.1 mL per 100 mL gel) in hexane before use, to afford epoxide **101** (2.7 g, 38 % for two steps, theoretical yield: 45 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.40 (m,6H), 3.59 (m, 1H), 2.86 (m, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 1.20 (d, *J* = 5.9 Hz, 3H), 1.06 (s, 9H). Spectroscopic properties were in agreement with literature values.[9a]



101 **99**

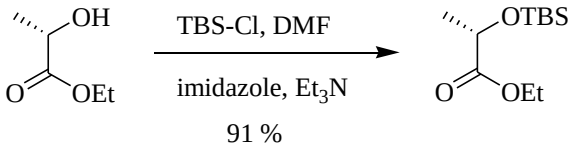
Alkynol 99.[9a] To the solution of trimethylsilyl acetylene (1.83 mL, 12.9 mmol) in toluene (13 mL) was added n-BuLi in hexane (1.6 M, 8.09 mL, 13 mmol) and the mixture was stirred at - 35 ℃. After 15 min, the white suspension was warmed to 0 ℃ and Et_2AlCl in toluene (1.8 M, 7.19 mL, 13 mmol) was added. The mixture was vigorously stirred at 0 ℃ for 1 h and epoxide **101** (2.11 g, 6.47 mmol) in toluene (9 mL) was added via cannula. The mixture was slowly warmed to 10 ℃ and stirred for 12 h. Then, it was quenched with saturated aqueous NH_4Cl (4 mL) and water (10 mL). The organic layer was separated and the aqueous phase was extracted with ether (5 × 5 mL). The combined organic solution was dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography on silica gel (elution with EtOAc : hexanes = 1 : 60) to provide alcohol **99** (2.2 g, 63 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.41 (m, 6H), 3.98 (dd, *J* = 4.4, 1H), 3.74 (dt, *J* = 6.8, 4.4, 1H), 2.48 (dd, *J* = 17.0, 6.8 Hz, 1H), 2.36 (dd, *J*

= 16.8, 6.8 Hz, 1H), 1.04 (s, 9H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.07 (s, 9H). Spectroscopic properties were in agreement with literature values.[9a]



99 **115**

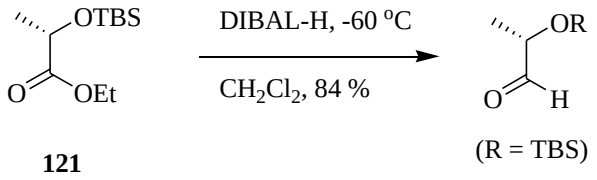
Carbamate 115. To a solution of alcohol **99** (56.8 mg, 0.134 mmol) in CH_2Cl_2 was added isocyanate (20.5 μL, 0.167 mmol)[9a] dropwise at 0 ^oC under argon. The mixture was slowly warned to rt, and stirred at rt for 1 hr. The mixture was filtered throughout Al_2O_3 with CH_2Cl_2 and then concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (elution with EtOAc : n-hexane = 1 : 50) to afford carbamate **115** (55 mg, 88 %) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.45 (m, 6H), 7.65 - 7.71 (m, 4H), 4.76 - 4.81 (m, 1H), 4.44 (br, 2H), 4.10 - 4.07 (m, 1H), 2.76 - 2.58 (m, 2H), 1.06 (s, 9H), 1.02 (d, J = 6.4 Hz, 3H), 0.12 (s, 9H).; IR (neat) ν_{max} 3501, 3341, 2958, 2929, 2179, 1728, 1590, 1427, 1389, 1250, 1112 cm^{-1}. Spectroscopic properties were in agreement with literature values.[9a]



107 **121**

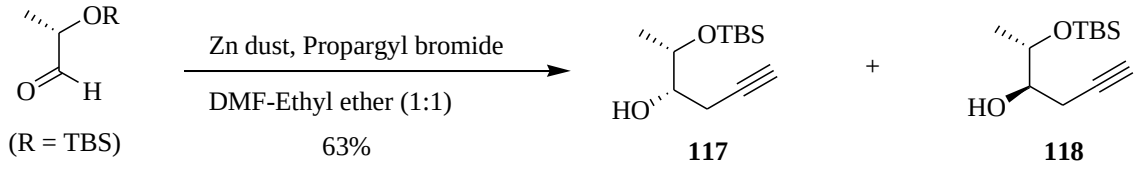
TBS - protected ethyl lactate 121.[24] To a solution of ethyl lactate **107** (0.50 g, 3.2 mmol) in THF (5 ml) was added Et_3N (0.83 g, 8.2 mmol), DMAP (37 mg , 0.30 mmol) and TBS-Cl (0.63 g, 4.3 mmol) under argon, and the mixture was stirred at rt for 20 hr. The mixture was concentrated under reduced pressure. Ethyl ether was added, and salts were removed by filtration. The filtrate was washed with 15 % acetic acid, water, Saturated aq. $NaHCO_3$, and water and then dried over $MgSO_4$. The combined mixture was concentrated under reduced pressure to give the crude product **121** (744 mg, 91.0 %). ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 6.9 Hz, 1H),

4.23 - 4.10 (m, 2H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.26 (t, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 8.7 Hz, 6H) Spectroscopic properties were in agreement with literature values.[29]



121 (R = TBS) **116**

Aldehyde 116.[29,24] To a solution of TBS-protected ethyl ester **121** (500 mg, 2.15 mmol) in CH_2Cl_2 (10 mL)was cooled to -55 °C ~ -65 °C , and then DIBAL-H (2.9 mL, 2.88 mmol, 1.3 ~ 1.5 M solution in CH_2Cl_2) was added dropwise for 20 min. The mixture was stirred at - 60 ℃ for 20 min, and then H_2O was added dropwise. The mixture was filtered to remove white solid, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with CH_2Cl_2 : hexane = 1 : 1) to afford aldehyde **116** (0.34 mg, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, *J* = 0.9 Hz, 1H), 4.09 (qd, *J* = 1.2, 6.9 Hz, 1H), 1.28 (d, *J* = 3.3 Hz, 3H), 0.92 (s, 9H), 0.10 (d, *J* = 3.9 Hz, 6H). Spectroscopic properties were in agreement with literature values.[29]



(R = TBS) **116** **117** **118**

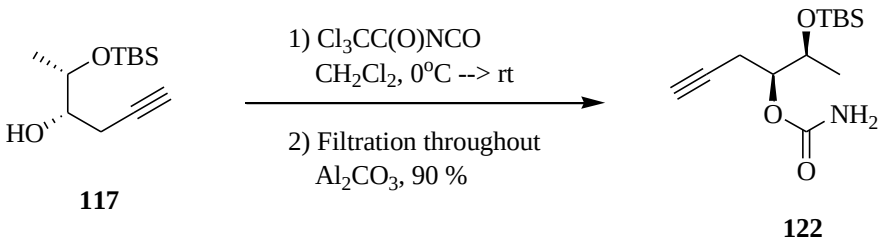
Alkynol 117 and 118. To a solution of aldehyde **116** (0.46 mg, 1.97 mmol) in a mixed solvent (8 mL, DMF and ethyl ether = 1:1) was added activated Zn dust (0.387 mg, 5.92 mmol) and propargyl bromide (0.59 mg, 3.95 mmol)[23] and the reaction was stirred at rt for 14 hr. The reaction mixture was filtered to remove Zn dust and saturated aq. NH_4Cl solution was added. The organic phase was separated and the aqueous layer was extracted with ehtyl ether (5 mL X 2). The combined organic layers were washed with brine and dried over anhydrous MgSO4. The

crude oil was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with pentene : ethyl ether = 100 : 1 and then 20 : 1) to afford **117** (90.9 mg, 20 %), **118** (51 mg, 11 %), and the mixture of **117** and **118** (142 mg, 32 %).

Akynol **117**[13]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (dq, *J* = 3.3, 6.3 Hz, 1H), 3.50 (m, 1H), 2.40 (dd, *J* = 2.7, 6.5 Hz, 2H), 2.02 (t, *J* = 2.4, 1H), 1.2 (d, *J* = 6.3, 3H), 0.90 (s, 9H), 0.11 (s, 6H).

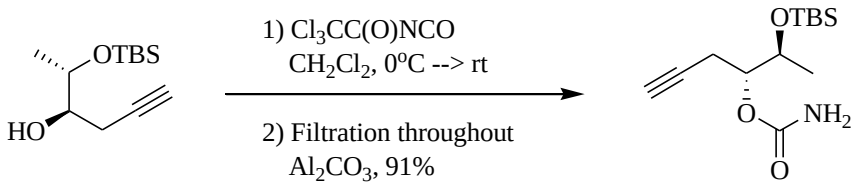
Alkynol **118**[13]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (m, 1H), 3.65 (m, 1H), 2.41 (m, 2H), 2.27 (br, 1H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

Spectroscopic properties were in agreement with literature values.[13]



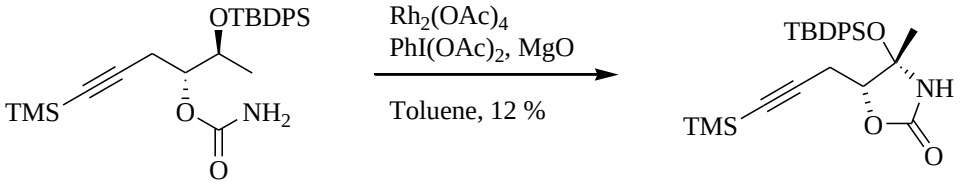
117 **122**

Carbamate 122. To a solution of alcohol **117** (77 mg, 0.34 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 ℃ and added isocyanate (69 mg, 0.37 mmol) dropwise.[9a] The reaction was slowly warmed to rt and stirred for 1 hr. The reaction mixture was filtered throughout Al_2O_3[25] and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : n-hexane = 1 : 20) to afford **122** (82 mg, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 - 4.70 (m, 3H), 4.12 (q, *J* = 7.2 Hz, 1H), 2.51 (dddd, *J* = 24.9, 16.8, 5.7, 2.7 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.15 (d, *J* = 6.3, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 3.0, 6H).; IR (neat) ν_{max} 3482, 3313, 2928, 2857, 1725, 1599, 1389, 1257, 1109 cm^{-1}.



118 **123**

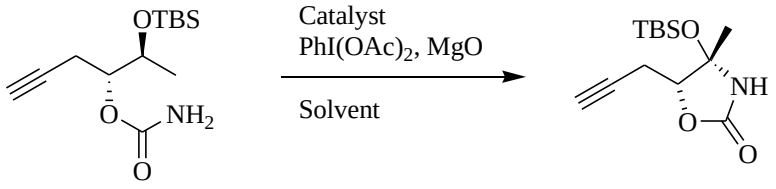
Carbamate 123. To a solution of alcohol **118** (50.5 mg, 0.221 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 ^oC and added isocyanate dropwise (45.8 mg, 0.243 mmol).[9a] The reaction was slowly warmed to rt and stirred for 1 hr. The reaction mixture was filtered throughout Al_2O_3[25] and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : n-hexane = 1 : 20) to afford **123** (55 mg, 91 %). ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (br, 1H), 4.65 (q, *J* = 5.4, 1H), 4.00 (app. quintet, *J* = 6.3 Hz, 2H), 2.63 - 2.48 (m, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 3.0 Hz, 6H).; IR (neat) ν_{max} 3314, 2925, 2853, 1724, 1463, 1379, 1259, 1074 cm^{-1}.



115 **124**

Oxazolidinone 124. To a dried vial were added the carbamate **115** (8.0 mg, 0.017 mmol), toluene (3 ml), MgO (3 mg, 0.074 mmol), $PhI(OAc)_2$ (7.7 mg, 0.025 mmol), and $Rh_2(OAc)_4$ (1.5 mg, 0.0034 mmol).[7] The mixture was stirred at 90 ^oC for 36 hr, and then cooled to rt. MgO (3.0 mg, 0.074 mmol), $PhI(OAc)_2$ (7.7 mg, 0.025 mmol), and $Rh_2(OAc)_4$ (1.5 mg, 0.0034 mmol) were additionally added. The mixture was stirred at 90 ^oC for 18 hr again. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to afford oxazolidinone **124** (1.0 mg, 12 %). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.50 - 7.39 (m, 6H), 4.81 (s, 1H), 4.35 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.06 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.90 (dd, *J* = 15.0, 3.0 Hz, 1H), 1.51 (s, 3H), 1.07 (s, 9H), 0.20 (s, 9H); IR (neat) ν_{max} 3274, 3071, 2960, 2926, 2181, 1775 cm^{-1}.

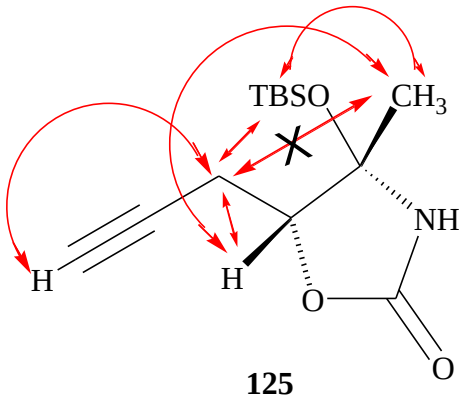
Representative procedure for intramolecular C-H amination



123 **125**

Oxazolidinone 125. To a solution of carbamate **123** (55.0 mg, 0.203 mmol) in benzene (1 mL) were added $Rh_2(tpa)_4$ (8.2 mg, 0.007 mmol), $PhI(OAc)_4$ (99.6 mg, 0.309 mmol), and MgO (21.3 mg, 0.528 mmol) and then stirred at 50 ℃ for 3hr. The mixture was cooled to rt and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to afford **125** (23 mg, 52 %) and recovered starting material **123** (10 mg, 19 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (br, 1H), 4.34 (dd, *J* = 8.0, 4.0, 1H), 2.75 - 2.63 (m, 2H), 2.15 (t, *J* = 2.7 Hz, 1H), 1.62 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 86.2, 84.6, 78.8, 70.62, 27.3, 25.5, 18.9, 18.0, -3.6. IR (neat) 3312, 2929, 1767.; IR (neat) ν_{max} 3313, 2926, 2854, 1762, 1724, 1587, 1462, 1260, 1037 cm^{-1}.

Difference NOE for compound **125**.



125

Inverted peak (ppm)	Enhanced peaks (ppm)
CH (4.34)	CH_2 (2.75 - 2.63), CH_3 (1.62)
CH_2 (2.70)	CH (4.34), CH (2.15), C_4H_9 (0.90)
CH_3 (1.62)	CH (4.34), C_4H_9 (0.90), CH_3 (0.17), CH_3 (0.16)

Part II.

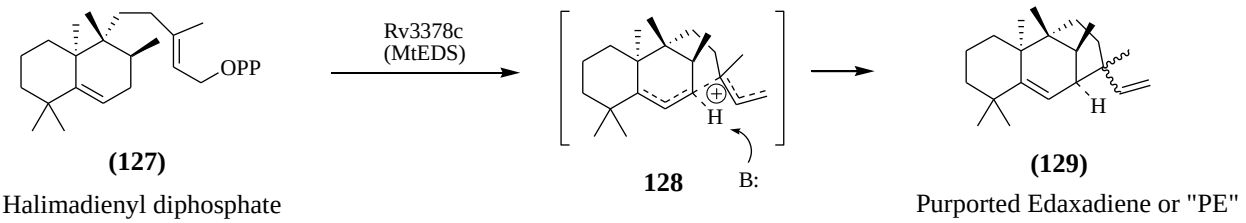
Synthetic Studies of Edaxadiene (129)

2.1. Introduction

2.1.1. Background

Tuberculosis (TB) is an infectious disease and an incredibly serious problem around the world. It is caused by mycobacteria, mainly Mycobacterium tuberculosis. This tuberculosis is a pathogenic bacteria species, and more than one-third of global population has been infected.[1] In 2009, Mann and co-workers reported that they found a new bioactive diterpene **129**, which inhibits endosomal progression to suppress phagosome maturation in the infection process of Mycobacterium tuberculosis.[2] Subverting phagosomal processing allows the bacterium to enter and reside in its host cell macrophage. Mycobacterium tuberculosis also prevents phagosomal maturation, and an enzyme encoded by Rv3377c plays an important role for Mycobacterium tuberculosis to enter into macrophage at initial stage.

The Rv3378c enzyme produces halimadienyl diphosphate (**127**). Mann and co-workers expected that an enzyme encoded by Rv3378c could give a further product from halimadienyl diphosphate (**127**). Finally, they got a single diterpene **129** (Scheme 38).



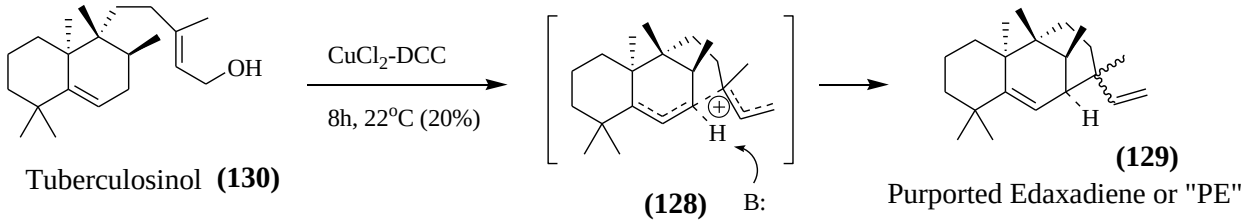
(127)
Halimadienyl diphosphate

128

(129)
Purported Edaxadiene or "PE"

Scheme 38. Catalyzed cyclization of **127** to **129** by Rv3378c/MtEDS and proposed a mechanism **128**

However, it is difficult to do a large scale incubation of Rv3378c encoded enzyme because this enzyme is unstable. Therefore, they developed the biomimetic synthesis of "PE" (**129)** from tuberculosinol (**130**) (Scheme 39).



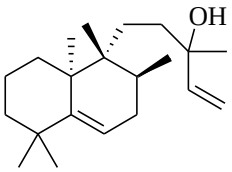
Tuberculosinol **(130)** **(128)** **(129)**

Purported Edaxadiene or "PE"

Scheme 39. Corresponding biomimetic synthesis of "PE" (**129**) from tuberculosinol (**130**)

After characterization of the structure of "PE" (**129**), they proposed the structure and named it edaxadiene (**129**).

Later, Maugel and Mann et al.[3] questioned the structure of "PE" (**129**), so they synthesized another possible structure, nosyberkol (isotuberculosinol) (**131**) and elucidated that the diterpene is not "PE" (**129**), but nosyberkol (isotuberculosinol) (**131**), which was isolated by Kashman et al.[4] in 2004 from the Nosy be Islands sponge Raspailia sp. (Figure 5).

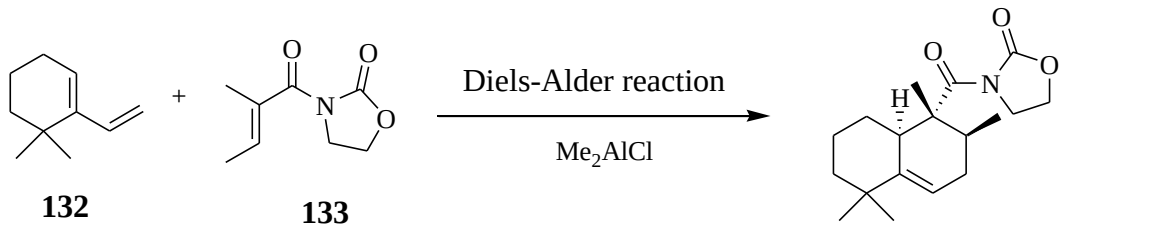


Nosyberkol (**131)**

Figure 5. Revised structure **131** of the diterpene **129**

2.1.2. Synthetic approaches to nosyberkol (131) and "PE" (129)

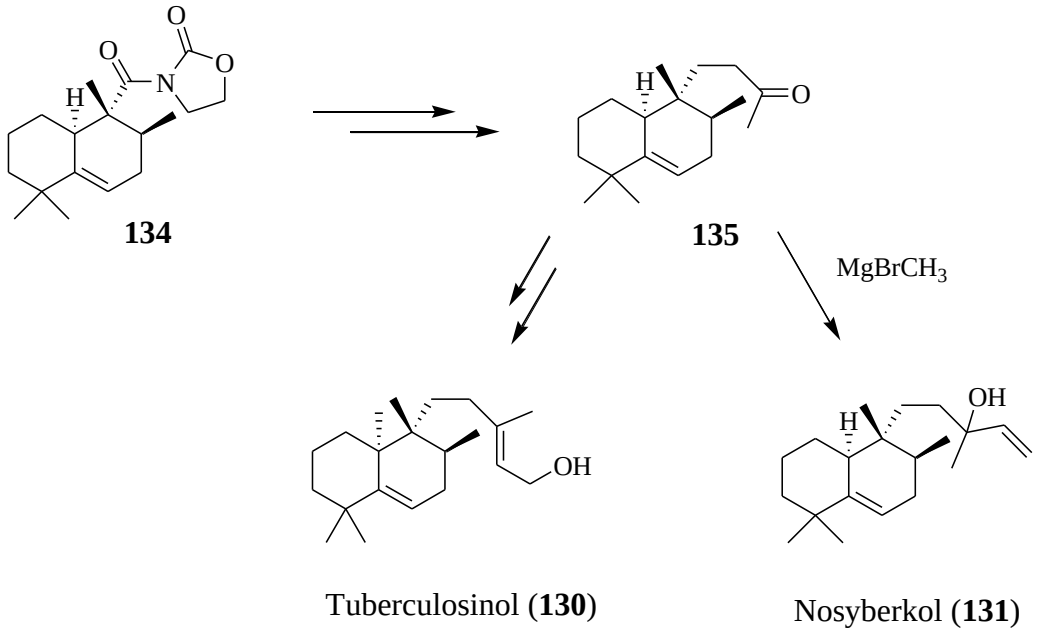
In 2010, (±)-nosyberkol (**131**) was synthesized by Maugel et al.[3a] to compare the spectra data of the diterpene **129** they isolated to nosyberkol (**131**) (Scheme 36). A bicyclic structure **134** was prepared by an intermolecular Diels-Alder reaction (Scheme 40).



132 **133** **134** (dr = 10 : 1)

Scheme 40. Construction of a backbone **134** of (±)-nosyberkol (**131**) by Maugel et al.[3a]

From a bicyclic compound **134**, they demonstrated syntheses of tuberculosinol (**130**) and (±)-nosyberkol (**131**) (Scheme 41).

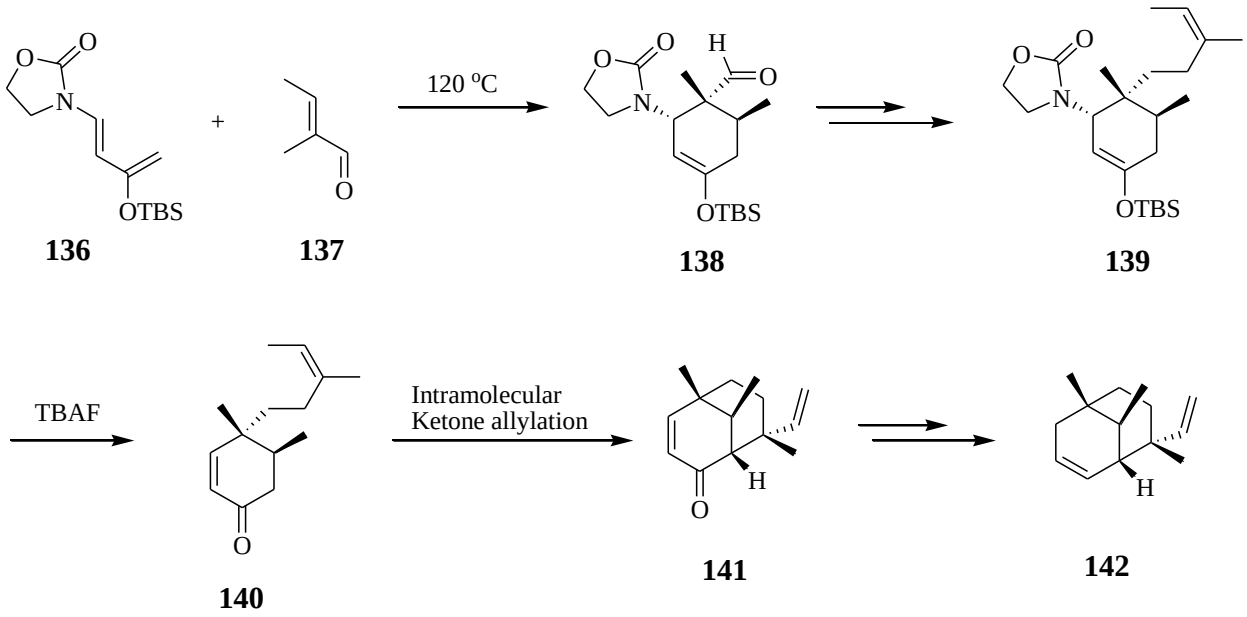


134 **135** Tuberculosinol (**130**) Nosyberkol (**131**)

Scheme 41. Syntheses of tuberculosinol (**130**) and (±)-nosyberkol (**131**) by Maugel et al.[3a]

In 2010, Sorensen group displayed a synthesis of the [3.3.1] bicyclic core **142** of "PE" (**129**) by an intramolecular ketone allylation.[5] A Diels-Alder reaction in thermal condition with a modified Rawal diene **136** and tiglaldehyde **137** provided silyl enol ether **138**, which was subjected to methylation and Suzuki-Miyaura coupling to give a right linear piece of alkene chain **139**. After TBS-deprotection, the oxazolidinone was removed to afford α,β-unsaturated ketone **140**, which was treated with Mn and Cu in AcOH-benzene to produce bicycles **141**. After

a reduction and dehydration, they showed the synthesis of bicyclic core **142** by an intramolecular ketone allylation (Scheme 42).



136 **137** **138** **139** **140** **141** **142**

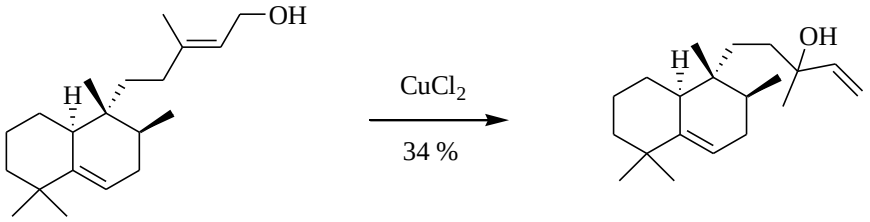
Scheme 42. Synthesis of the [3.3.1] bicyclic core **142** of "PE" (**129**) by Sorensen group

In the progress of their research, Maugel et al.[3] revised the structure of **129**, so Sorensen group changed the target compound "PE" (**129**) to tuberculosinol (**130**) and (±)-nosyberkol (**131**) and also confirmed the structure of **129**. A Diels-Alder reaction in thermal condition produced inseparable products **144** in favor of a desired major product (Scheme 43).

132 **143** **144** (endo : exo = 1 : 2)

Scheme 43. Construction of a backbone **144** of (±)-nosyberkol (**131**) by Sorensen group

In addition, they demonstrated biomimetic conversion of tuberculosinol (**130**) into nosyberkol (**131**) (See Scheme 38). They found that this reaction is a Lewis acid-mediated allylic transposition[6] and the treatment of tuberculosinol (**130**) with $CuCl_2$ produced nosyberkol (**131**) in 34 % yield (Scheme 44).



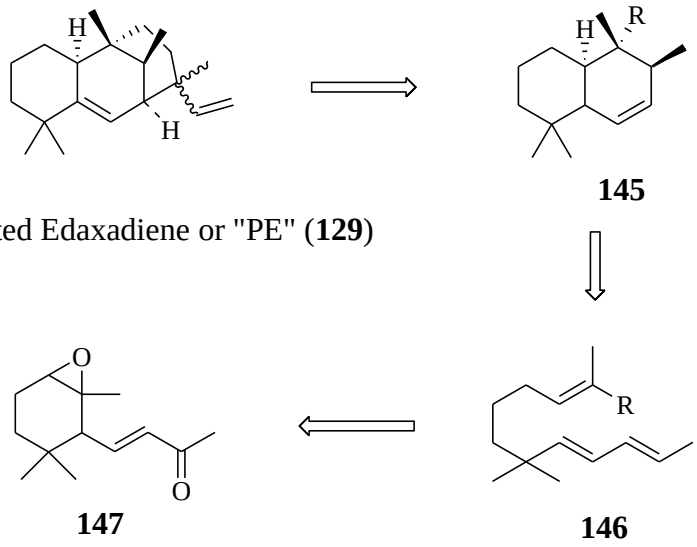
Tuberculosinol **(130)** Nosyberkol **(131)**

Scheme 44. Syntheses of nosyberkol (**131**) from tuberculosinol (**130**) by Sorensen group

When we started a synthesis of "PE" (**129)**, we focused on the preparation of a bicyclic core by an intramolecular Diels-Alder reaction, but in the progress of our research, we found that the diterpene **(129)** is nosyberkol (**131**). Therefore, we also changed a target compound "PE" (**129**) to nosyberkol (**131**) and examined a procedure to convert tuberculosinol (**130**) to **131**.

2.1.3. A new synthetic approach to a key core of "PE" (129)

We envisioned that the bicyclic core **145**, of "PE" (**129**) could be prepared by the intramolecular Diels-Alder (IMDA) reaction [7] of triene **146**. This was an attractive approach because a powerful fragmentation approach provided **146** from a commercially available epoxide **147** (Scheme 45).



Purported Edaxadiene or "PE" (**129**)

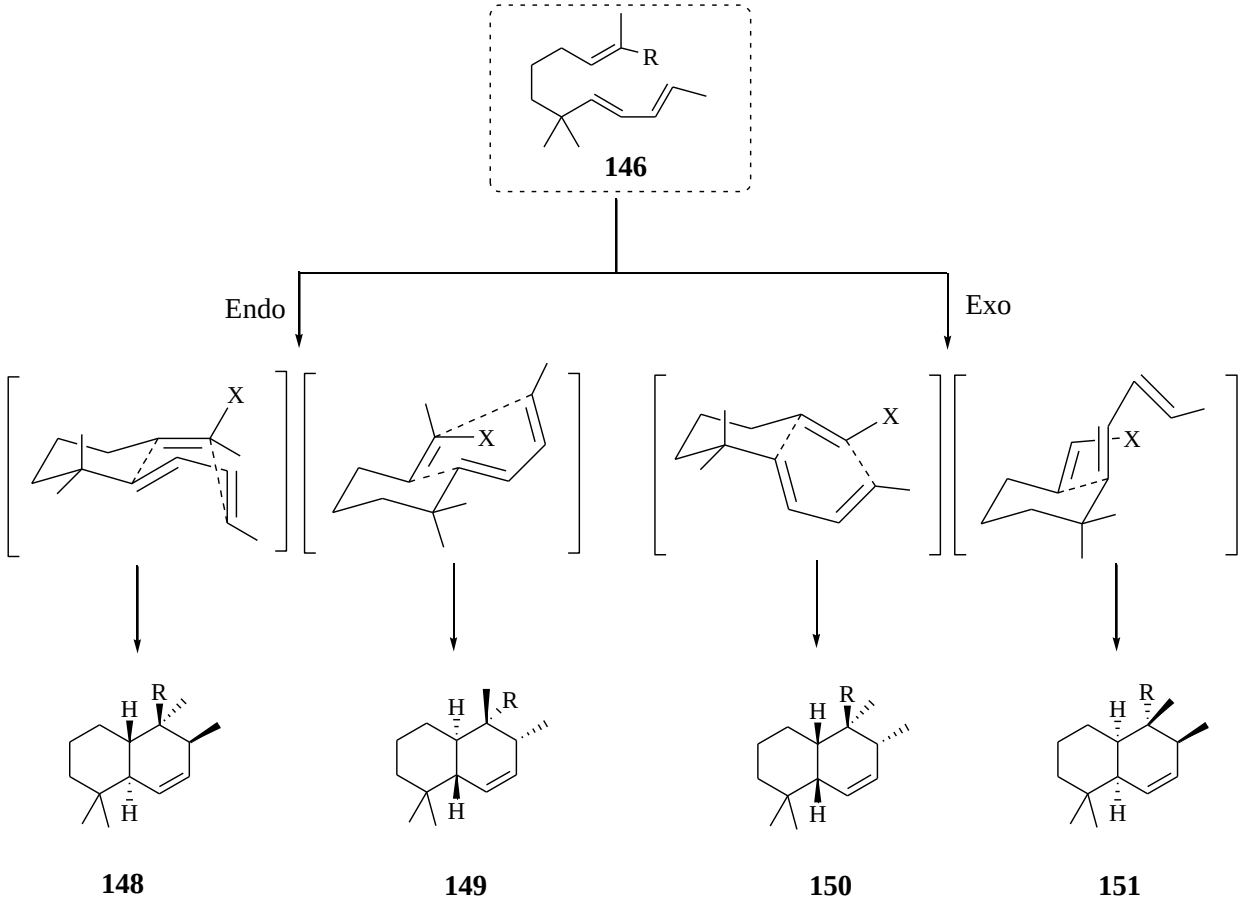
145

147

146

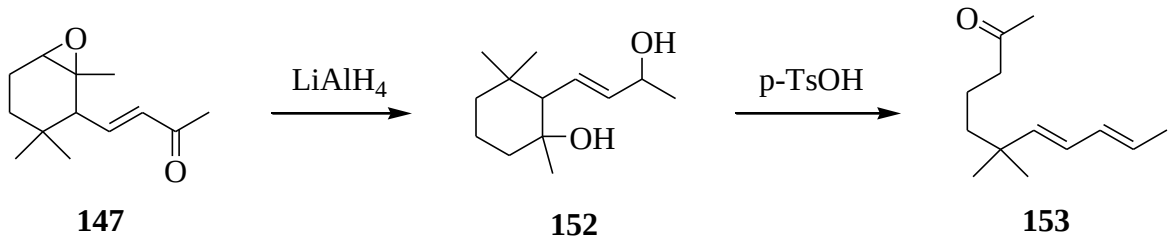
Scheme 45. Retrosynthetic analysis of “PE” (**129**)

The intramolecular Diels-Alder reaction (IMDA)[7] could have 4 possible transition states to produce a diastereomers mixture. Desired products **150** and **151** would be produced throughout endo-transition state as an isomeric mixture in thermal condition (Scheme 46).



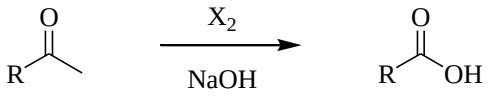
Scheme 46. Proposed transition states of the intramolecular Diels-Alder reaction

Based on our expectation, we designed a retrosynthetic approach to access a precursor of an IMDA. We focused on synthesis of methyl ketone **153** reported by Skorianetz et al.[8] It was simply prepared from an epoxide, 4-(1,3,3-trimethylbicyclo[4.1.0]hept-2-yl)-3-Buten-2-one **147**, a commercially available material by two steps (Scheme 47).



Scheme 47. Preparation the methyl ketone **153** from the epoxide **147** by Skorianetz et al.[8]

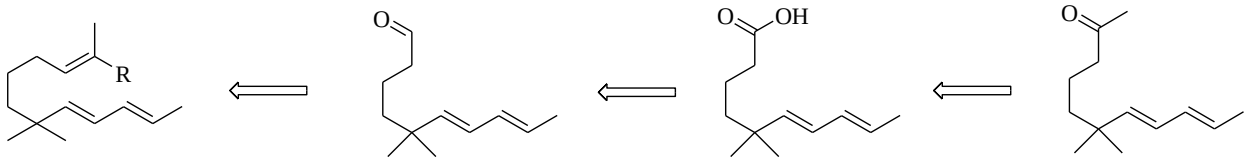
In addition, the haloform reaction has been widely used to convert ketones **154** to carboxylic acids **155** (Scheme 48).[9a]



154 **155** X = halogen

Scheme 48. Conversion ketones **154** to carboxylic acids **155** by haloform reaction

Therefore, we believed that haloform reaction would give us carboxylic acid **157** from methyl ketone **153**. Reduction of carboxylic acid **157** followed by oxidation could produce aldehyde **156**, which would be subjected to Wittig reaction to prepare a precursor **146** for an IMDA reaction (Scheme 49).



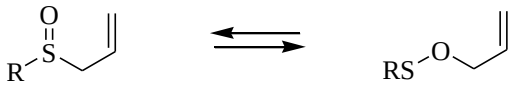
146 **156** **157** **153**

Scheme 49. Retrosynthetic analysis of a precursor **146**

Furthermore, after we proved the usefulness of our simple procedure, introducing a chiral auxiliary to a precursor for an IMDA would control stereoselectivity to provide a desired product **151**. Based on our retrosynthetic analysis, we started the synthetic approach of "PE" (**129**).

2.1.4. A new approach for the preparation of nosyberkol (131) from tuberculosinol (130)

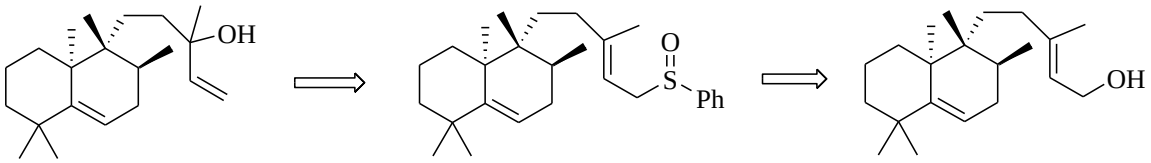
In the progress of our research, it was elucidated that the diterpene **129** isolated by Mann et al. is nosyberkol (**131**). Therefore, we examined a synthetic route to obtain nosyberkol (**131**) from tuberculosinol (**130**) because we also wanted to confirm the structure of "PE" (**129**) by the synthesis of nosyberkol (**131**) from tuberculosinol (**130**) using a promising synthetic method for 1,3-transposition of primary allylic alcohols. There are some methods to convert primary allylic alcohols to vinyl tertiary alcohols.[10] Especially, we focused on sulfoxide-sulfenate ester rearrangement (Scheme 50).[11]



158 **159**

Scheme 50. Sulfoxide-sulfenate ester rearrangement

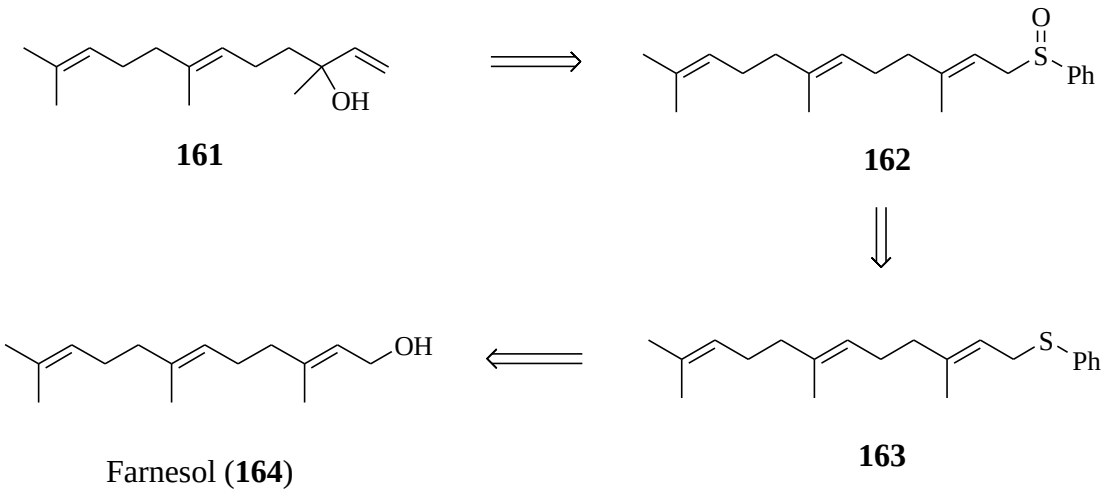
Thus, we envisioned another promising method to nosyberkol (**131**) from tuberculosinol (**130**) by sulfoxide-sulfenate ester rearrangement (Scheme 51).



Nosyberkol (**131**) **160** Tuberculosinol (**130**)

Scheme 51. Retrosynthetic approaches of nosyberkol (**131**) from tuberculosinol (**130**)

We used a model compound, farnesol (**164**), and explored synthetic methods with this rearrangement to obtain a vinyl tertiary alcohol **161** (Scheme 52).



161 **162** **163**

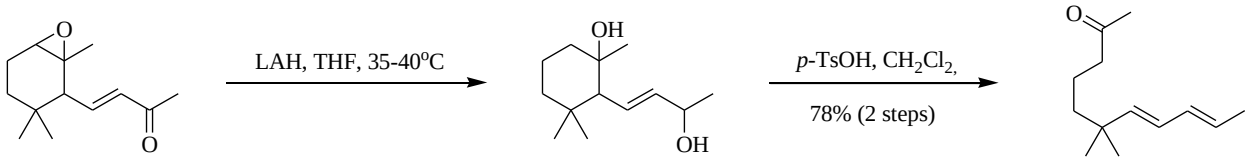
Farnesol (**164**)

Scheme 52. Retrosynthetic analysis of a tertiary alcohol **161** from farnesol **(164)**

2.2. Result and Discussion

2.2.1. Studies of synthesis of "PE" (129)

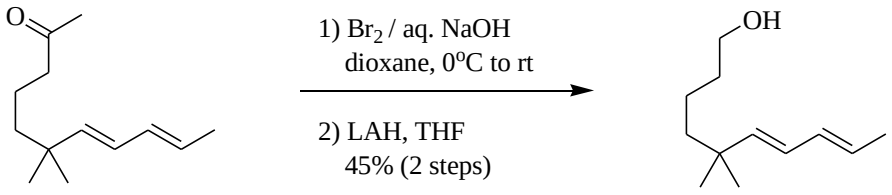
As we envisioned retrosynthetic analysis of "PE" (**129**), the mixtures of diastereomers **152** were obtained from the epoxide **147** by reduction with $LiAlH_4$. After dehydration, the mixture **155** gave the methyl ketone **153** as one product in 78 % for 2 steps (Scheme 53).[8,12]



147 **152** **153**

Scheme 53. Preparation of the methyl ketone **153** from the epoxide **147**

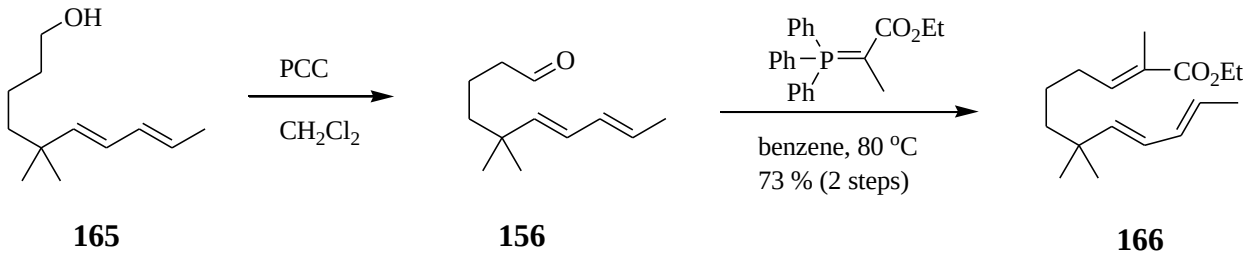
To convert the methyl ketone **153** to a carboxylic acid, the haloform reaction [9a] was examined to give a product. When it was treated with bromine, a desired product was obtained. The crude acid was directly used to the next step, reduction with $LiAlH_4$, to produce an alcohol **165** in 45 % for 2 steps (Scheme 54).



153 **165**

Scheme 54. Preparation of the alcohol **165** from the methyl ketone **153**

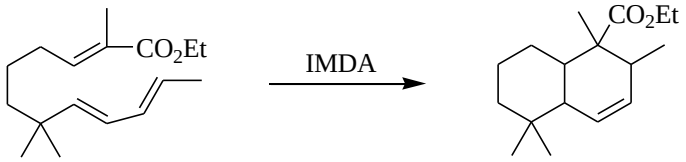
The treatment of the alcohol **165** with PCC afforded an aldehyde **156**, which was subjected to Wittig reaction to provide an ester **166**, a precursor of the IMDA reaction (Scheme 55).



165 **156** **166**

Scheme 55. Preparation of the triene **166** from the alcohol **165**

Finally, in thermal condition, the IMDA reaction was applied to the ester **166** to produce a bicyclic core and we believed that products **167** were an inseparable mixture of diastereomers (Scheme 56).

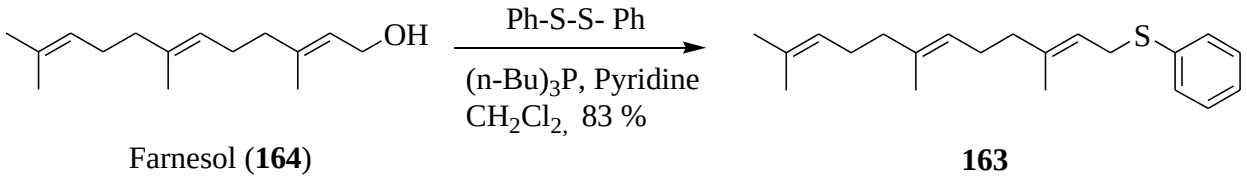


166 **167**

Scheme 56. Preparation of the bicyclic compounds **167** from the triene **166**

2.2.2. Studies of synthesis of nosyberkol (131) from tuberculosinol (130)

A sulfide **163** was synthesized from an allylic alcohol **164**, farnesol, which is a commercially available compound. Farnesol (**164**) was treated with diphenyl sulfide[13], tributyl phosphine, and pyridine to provide a sulfide **163** (Scheme 57). Other phosphine reagents were explored, but tributyl phosphine gave high conversion (Table 5).



Farnesol (**164**) **163**

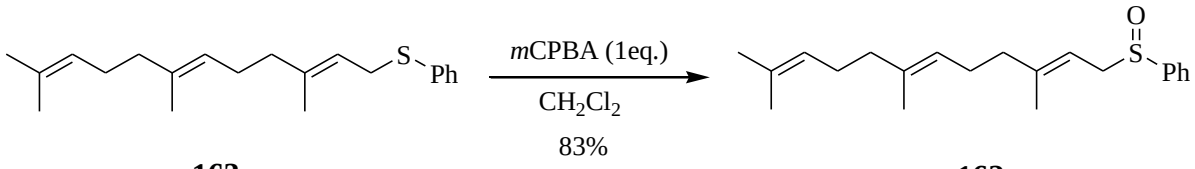
Scheme 57. Synthesis of the sulfide **163** from the farnesol (**164**)

Table 5. Results of synthesis of the sulfide **163**

Phosphine reagent	Solvent	Temperature	Result
Triphenyl phosphine	CH_2Cl_2	RT	No rxn
Triphenyl phosphine	CH_2Cl_2	Reflux	No rxn
Tris(dimethylamino)phosphine	CH_2Cl_2	RT	Conversion 23%
Tris(dimethylamino)phosphine	$C_2H_4Cl_2$	reflux	Conversion 35%
Tributyl phosphine	CH_2Cl_2	RT	Conversion ~ 100% Y = 83%

RT = room temperature

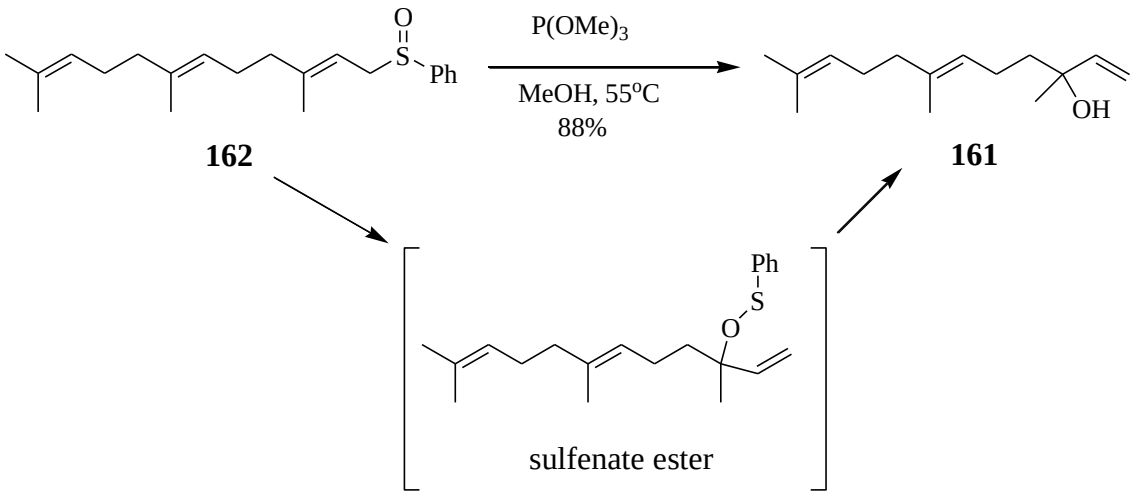
In addition, a treatment of the sulfide **163** with mCPBA provided a sulfoxide **162** (scheme 58).[14]



163 **162**

Scheme 58. Preparation of the sulfoxide **162** from the sulfide **163**

Finally, a vinyl tertiary alcohol **161** was produced from the sulfoxide **162** by sulfoxide-sulfenate ester rearrangement[11a,b] and sulfenate cleavage. $P(OMe)_3$ was used as thiophile[15] (Scheme 59). The tertiary alcohol **161** was successfully synthesized from the model compound, farnesol (**164**).



Scheme 59. Synthesis of the vinyl tertiary alcohol **161** from the sulfoxide **162**

We obtained a vinyl tertiary alcohol **161** in 61 % yield for 3 steps and proved sulfoxide-sulfenate ester rearrangement is a mild reaction to provide vinyl tertiary alcohols from allylic alcohols. However, the progress of their research, Sorensen group also proved the structure of "PE" (**129**), so we did not try to synthesize nosyberkol (isotuberculosinol) (**131**) from tuberculosinol (**130**)

2.3. Conclusion

In conclusion, a bicyclic structure **167**, which would be a key structure of natural products, was simply constructed from epoxide **147**, a commercially available material, by seven steps. Our procedure would be applied to syntheses of other natural products. In addition, we also demonstrated that the vinyl tertiary alcohol **161** can prepared from the farnesol (**164**) via the sulfoxide-sulfenate ester rearrangement and total yields for 3 steps were 61 %. Nosyberkol (**131**) could be prepared from tuberculosinol (**130**) by our developed process.

2.4. Reference

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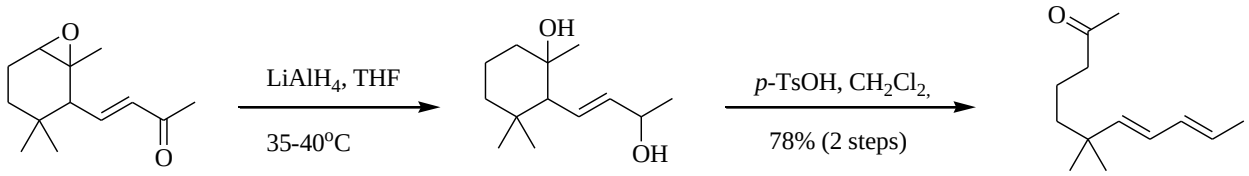
2.5. Experimental Section

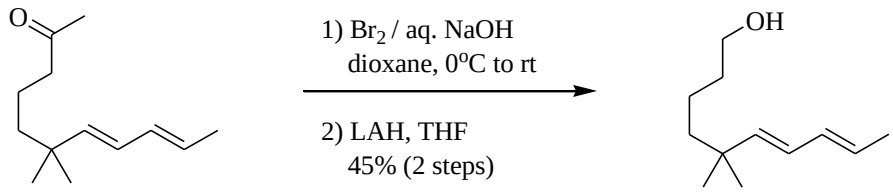
General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å , 230-400 mesh, surface area 500-600 m^2/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), a Varian Inova-500 (500 MHz for ^1H and 125 MHz for ^{13}C), Bruker-400 (400 MHz for ^1H and 100 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C, or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.



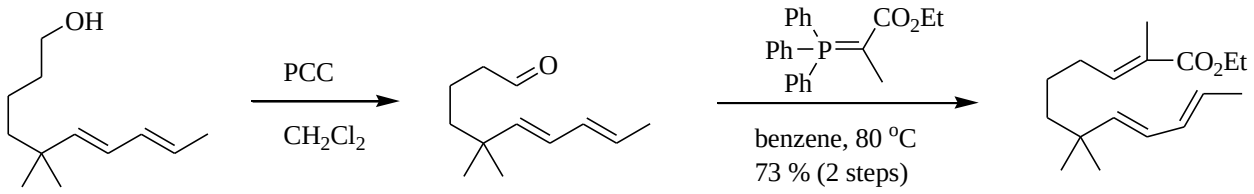
147 **152** **153**

Methyl ketone 153. To a stirred solution of $LiAlH_4$ (LAH) (155 mg, 155 mmol) in THF (10 mL) was added dropwise epoxide **147** (300 mg, 1.44 mmol) solution in THF (5 mL). The reaction mixture was heated to 35 ^oC for 6.5 h and cooled to rt. To a reaction mixture was added dropwise EtOAc under an ice bath and then ice water was added. Volatile organic mixture was evaporated and EtOAc (20 mL) was added again. After separation of the organic layer, the aqueous phase was extracted with EtOAc (15 mL X 2). The combined organic layer was washed with aq. NaCl and dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 20 to 1 : 1) to provide a mixture of diastereomers **152**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.51 (m, 1H), 4.35 (quint, J = 6.0, 1H), 1,74 (m, 2H), 1.57 – 1.34 (m, 7H), 1.53 (d, J = 10.2, 1H), 1.46 (m, 1H), 1.29 (d, J = 6.3, 3H), 1.08 (m, 3H), 1.00 (m, 3H), 0.79 (m, 3H); IR (neat) 3386, 2928, 1458 cm^{-1}. Without a further purification, it was directly used to the next step. To a stirred solution of mixture products **152** in CH_2Cl_2 (15 mL) was added p-TsOH (30 mg) and stirred at rt for 19 h. The reaction mixture was washed with brine and extracted with CH_2Cl_2 (10 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to afford methyl ketone **153** (197 mg, 78 % for 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 – 6.06 (m, 2H), 5.55 – 5.66 (m, 1H), 5.49 (d, J = 15.0 Hz, 1H), 2.37 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 1.73 (dd, J = 6.9, 1.5 Hz, 3H), 1.54 – 1.43 (m, 2H), 1.27 – 1.21 (m, 2H), 0.99 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 141.6, 132.1, 127.2, 126.7, 44.6, 42.8, 36.0, 30.1, 27.4, 19.4, 18.3.



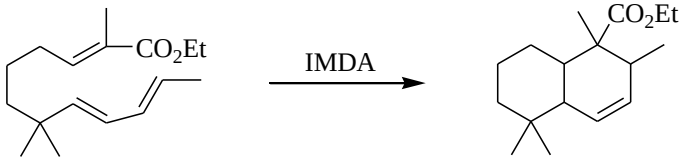
153 **165**

Alcohol 165. To a stirred solution of NaOH (265 mg, 6.60 mmol) in H_2O (2.2 mL) was cooled to 0 ^oC and bromine (0.086 mL, 1.7 mmol) was added dropwise for 5 min. The reaction mixture was stirred for 7 min and dioxane (1.5 mL) was added dropwise for 5 min. Then, to a reaction mixture were added dropwise the solution of methyl ketone **153** in dioxane (2.5 mL) and H_2O (0.7 mL) at 0 ^oC. The reaction solution was slowly warmed to rt over 3 h and stirred at rt for 2 h. Na_2SO_3 (63 mg, 0.50 mmol) and H_2O (0.06 mL) were added and then the resulting mixture was immersed in a pre-heated oil bath 90 ^oC for 15 min and cooled to rt. After evaporation, the residue was washed with Et_2O (10 mL) and 25 % H_2SO_4 was added and extracted with Et_2O (20 mL X 2). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a product, crude carboxylic acid, (106 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 – 6.03 (m, 2H), 5.58 (m, 1H), 5.46 (d, J = 15.6, 1H), 2.28 (t, J = 7.6 Hz, 2H), 1.71 (dd, J = 6.8, 1.2 Hz, 3H), 1.71 – 1.49 (m, 2H), 1.31 – 1.28 (m, 2H), 0.98 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 141.4, 132.2, 127.3, 126.8, 42.7, 36.0, 34.9, 27.3, 20.3, 18.2.; IR (neat) 2500 - 3700, 2960, 1713 cm^{-1}. To a stirred solution of $LiAlH_4$ (131 mg, 3.45 mmol) was added dropwise the carboxylic acid (106 mg) solution in THF (10 mL) for 10 min and stirred at rt for 4 h. H_2O (1 mL) was added dropwise very carefully and then aq. 10 % NaOH was added. The resulting mixture was filtered throughout Celite and rinsed with E_2O, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20 to 7 : 1) to afford alcohol **165** (44 mg, 45 % for 2 steps) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 – 5.97 (m, 1H), 5.89 (m, 1H), 3.63 (t, J = 6.6 Hz, 2H), 1.73 (dd, J = 6.9, 1.5 Hz, 3H), 1.55 - 1.49 (m, 2H), 1.33 – 1.22 (m, 2H), 0.99 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ142.0, 132.2, 127.1, 126.5, 63.2, 43.3, 36.1, 33.7, 27.4, 21.1, 18.2.; IR (neat) 3364, 2933 cm^{-1}.



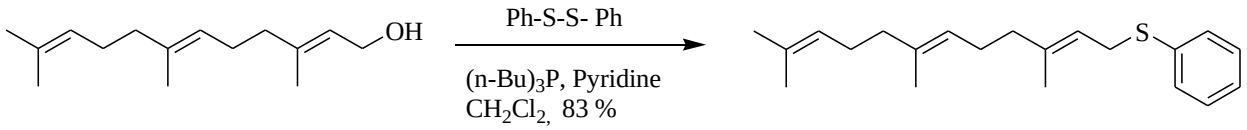
165 **156** **166**

Ester 166. To a stirred solution of alcohol **165** (81.6 mg, 0.447 mmol) in CH_2Cl_2 (6.5 mL) was added PCC (Pyridinium chlorochromate) reagent (156 mg, 1.79 mmol) and stirred at rt. After 5 h, the reaction mixture was concentrated under reduced pressure and ethyl ether was added. The resulting mixture was filtered throughout Celite and concentrated under reduced pressure again. Then the residue was purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to give crude aldehyde **156**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, J = 1.6 Hz, 1H), 6.01 – 5.85 (m, 2H), 5.56 (m, 1H), 5.44 (d, J = 15.2 Hz, 1H), 2.33 (td, J = 7.2, 1.6 Hz, 2H), 1.69 (dd, J = 6.8, 1.2 Hz, 3H), 1.55 – 1.47 (m, 2H), 1.28 – 1.22 (m, 2H), 0.97 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 132.1, 127.4, 127.0, 44.7, 42.8, 36.1, 29.9, 27.3, 17.7; IR (neat) 2959, 1727 cm^{-1}. To a stirred solution of crude aldehyde **156** in benzene (9 mL) was added triphenyl phosphorane (162 mg, 0.468 mmol). The reaction mixture was heated and stirred at 80 °C. After 9 h, the resulting mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 100 to 1 : 50) to provide ester **166** (86 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (tq, J = 1.2, 7.2, 1H), 6.07 - 5.86 (m, 2H), 5.60 (m, 1H), 5.45 (d, J = 15.2, 1H), 4.14 (q, J = 7.2, 2H), 2.08 (q, J = 6.8, 2H), 1.78 (s, 3H), 1.70 (dd, J = 6.4, 0.8, 3H), 1.35 - 1.24 (m, 7H), 0.95 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 142.0, 141.5, 131.9, 127.7,126.9, 126.4, 60.3, 42.9, 35.8, 29.3, 27.2, 23.8, 18.0, 14.5, 12.5; IR (neat) 2959, 1712 cm^{-1}.



166 **167**

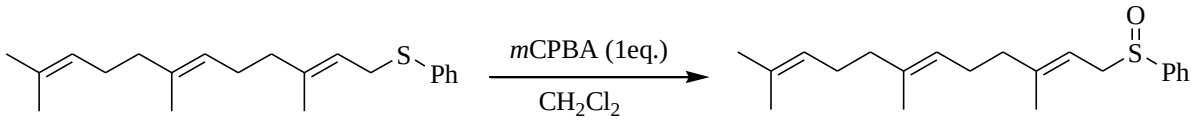
Bicyclic compounds 167. The solution of ester **166** (15.4 mg, 0.0582 mmol) in toluene (6.0 mL) was heated to 160 ^{o}C. After 24 h, the reaction solution was concentrated under reduced pressure and purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 100) to give crude esters. This crude was purified again by Plate TLC to provide diastereomer mixtures **167** (7 mg, 46 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.64 – 5.57 (m, 2H), 4.21 – 4.03 (m, 2H), 2.91 – 2.89 (m, 0.5H), 2.30 (dt, J = 12.6 Hz, 0.5 H), 2.02 (m, 0.5H), 1.89 (td, J = 10.8, 2.4, 0.5H, 1.71 – 1.67 (m, 1H), 1.58 – 1.48 (m, 4H), 1.43 – 1.35 (m, 1H), 1.27 – 1.23 (m, 3H), 1.22 (s, 3H), 1.18 – 1.14 (m, 3H), 1.01 – 0.99 (m, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.86 (d, J = 6.6 Hz, 1H), 0.81 (s, 1H); IR (neat) 2961, 1729 cm^{-1}.



Farnesol (**164**) **163**

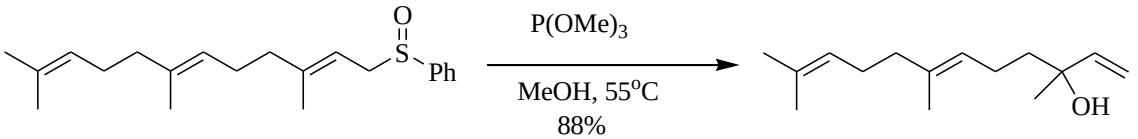
Sulfide 163. To a stirred solution of farnesol (**164**) (18.6 mg, 0.0840 mmol) in CH_2Cl_2 (1 mL) were added phenyl sulfide (55.3 mg, 0.251 mmol) and pyridine (33.0 mg, 0.418 mmol). The mixture was cooled to 0℃ and tributyl phosphine (63 μL, 0.251 mmol) was added dropwise. The reaction mixture was slowly warmed to rt and stirred for 14 hr. $NaBH_4$ (14.5 mg, 0.251 mmol) was added and stirred for 1 hr. Then, 10% NaOH solution was added and the mixture was separated. After extraction with CH_2Cl_2 (2 times), the combined organic extract was treated with 25 % H_2SO_4 and $NaHCO_3$. The mixture was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by Plate TLC (elution with EtOAc : n-hexane = 1 : 4) to afford sulfide **163** (22 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.14 ~ 7.36 (m, 5H), 5.31 (m, 1H), 5.09 (m, 2H), 3.55 (d, J = 7.5 Hz, 2H), 2.02 (m, 8H), 1.68 (d, J = 1.2 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 9H).



163 **162**

Sulfoxide 163. mCPBA (4.2mg, 0.019 mmol) was added to a solution of sulfide **163** (6.0 mg, 0.019 mmol) in CH_2Cl_2 (0.8 mL). The reaction mixture was stirred under argon for 1 hr, and H_2O was added. The organic phase was separated and extracted with CH_2Cl_2 (2 times). The combined organic extract was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (elution with EtOAc : hexane = 1 : 20) to afford **162** (5.2 mg, 83 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 ~ 7.63 (m, 2H), 7.48 ~ 7.50 (m, 3H), 5.06 (m, 3H), 3.59 (qd, J = 16.5, 8.1 Hz, 2H), 2.08 (m, 8H), 1.67 (d, J = 1.2 Hz, 3H), 1.59 (d, J = 1.5 Hz, 6H), 1.42 (d, J = 1.5 Hz, 3H).



162 **161**

Vinyl tertiary alcohol 161. To a solution of sulfoxide **162** (2.0 mg, 0.0061 mmol) in MeOH (1.0 mL) was added $P(OMe)_3$ (11.0 mg, 0.089 mmol). The mixture was stirred at 55 ℃ for 12 hr under argon. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (elution with EtOAc : hexane = 1 : 4) to afford vinyl tertiary alcohol **161** (1.2 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (dd, J = 10.2 Hz, 1H), 5.22 (d, J = 11.4 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 5.07 (m, J = 2.7 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 6H), 1.28 (s, 3H); IR (neat) 3416, 2969, 2926, 1450, 1375, 1109 cm^{-1}.

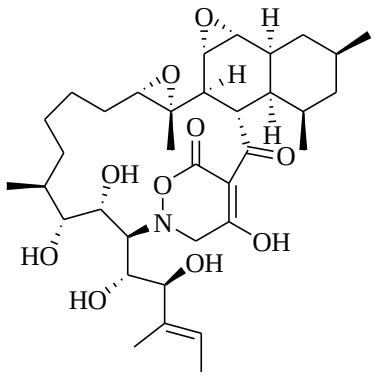
Part III.

Studies Towards the Synthesis of Alchivemycin A (168)

3.1. Introduction

3.1.1. Background

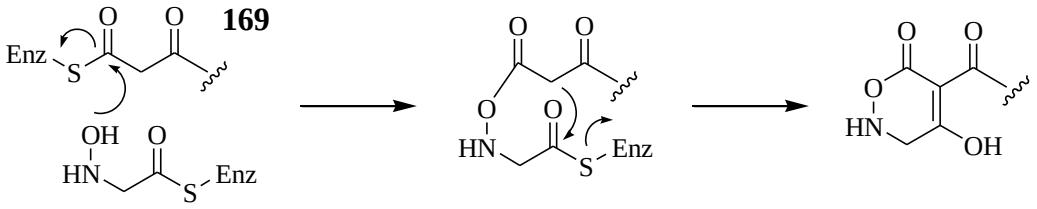
Alchivemycin A (**168**), a bioactive polycyclic polyketide, was discovered from the culture extract of a *Streptomyces* strain from a leaf of a Chinese chive by Furuma et al[1] in 2010. Strain TP-A0867 produced was cultured in A-11 M medium 30 ^{o}C for 6 days and was extracted with 1-butanol to produce Alchivemycin A (**168**) (Figure 6). It showed not only a selective antimicrobial activity for *Micrococcus luteus* in MIC value of 50 nM, but also bioactivity for a murine colon carcinoma with an IC_{50} of 0.34 µM without cytotoxic effects.



Alchivemycin A (**168**)

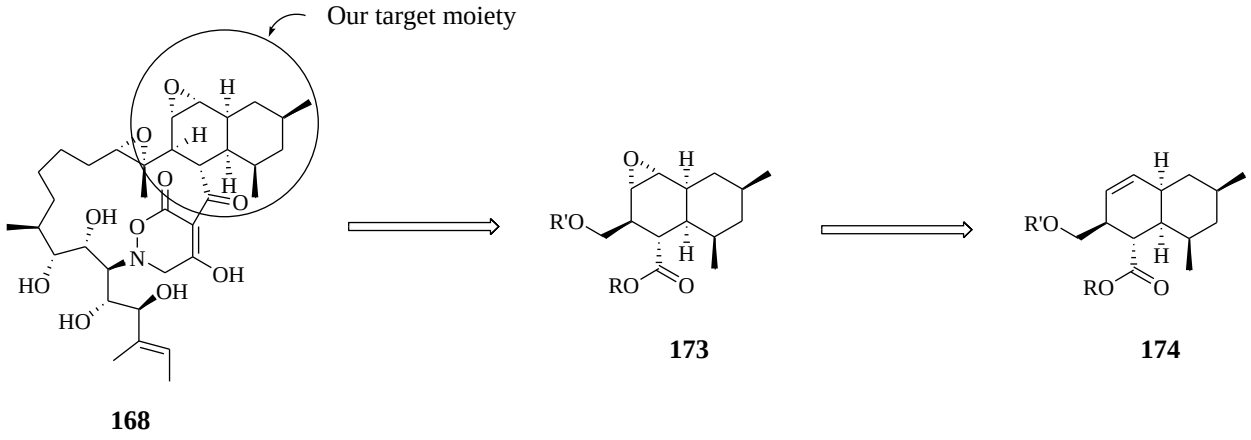
Figure 6. The structure of Alchivemycin A (**168**)

A structure of Alchivemycin A (**168**) was determined and showed a highly interesting core and a 2H-tetrahydro-4,6-dioxo-1,2-oxazine ring **172**. Furuma and co-workers also suggested a possible biogenesis of that oxazine ring (scheme 60).



Scheme 60. A possible biogenesis of oxazine ring **172** proposed by the Furuma group

We focused on a bicyclic structure that would be a good starting point to construct alchivemycin A (**168**) and could be prepared by a Diels-Alder reaction, especially an intramolecular Diels-Alder (IMDA) reaction[2] or a transannular Diels-Alder (TADA) reaction[3] (Scheme 61). Generally, expectations with transition state conformations predicted products and transition state conformations would be controlled by reaction conditions and an appropriate design of precursors.

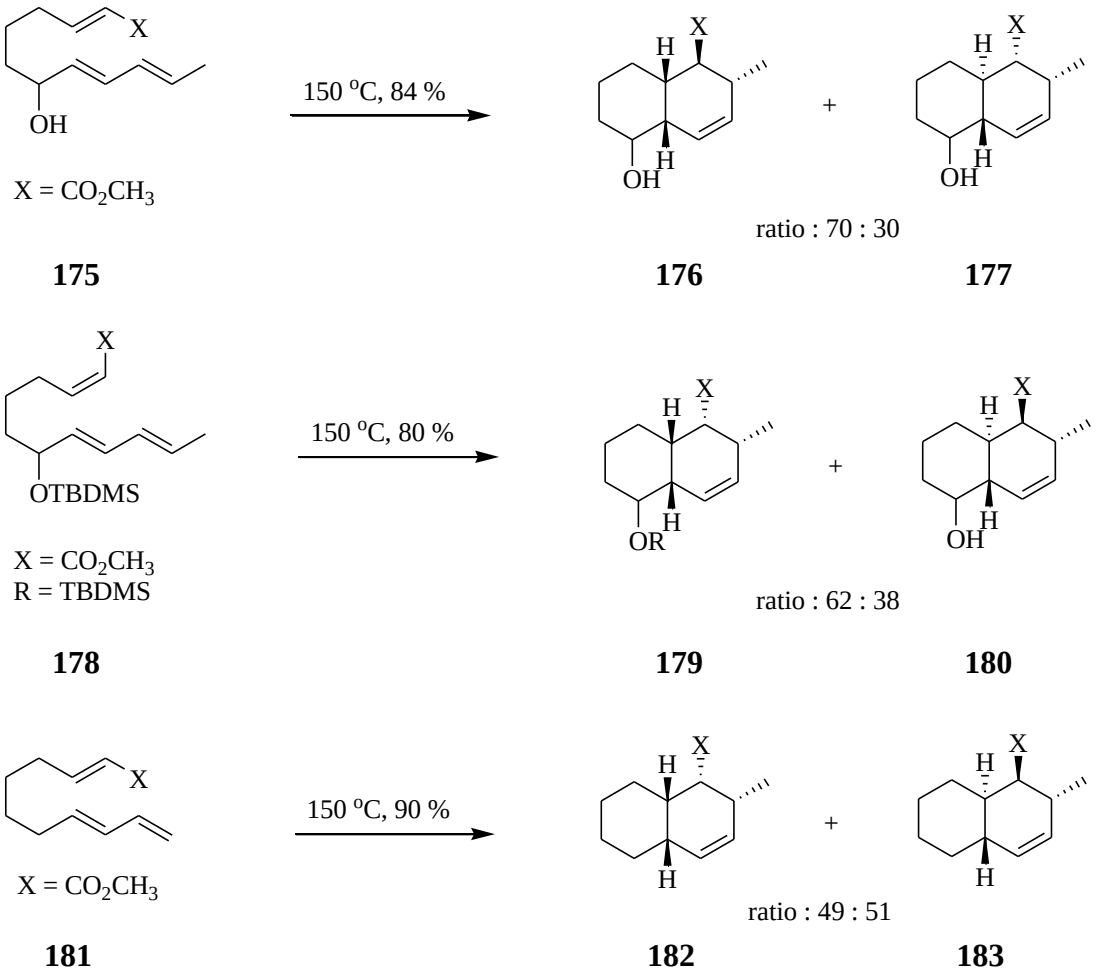


Scheme 61. Retrosynthetic analysis of alchivemycin A (**168**)

3.1.2. Stereochemistry of the intramolecular and transannular Diels-Alder reaction

The intramolecular Diels-Alder (IMDA) reactions have produced a wide variety of bicyclic cores of many natural products and demonstrated valuable IMDA applications. In spite of a large number of examples of these reactions, the control of stereoselectivity of IMDA reactions has been not fully understood and it is still very important to discover the origin of

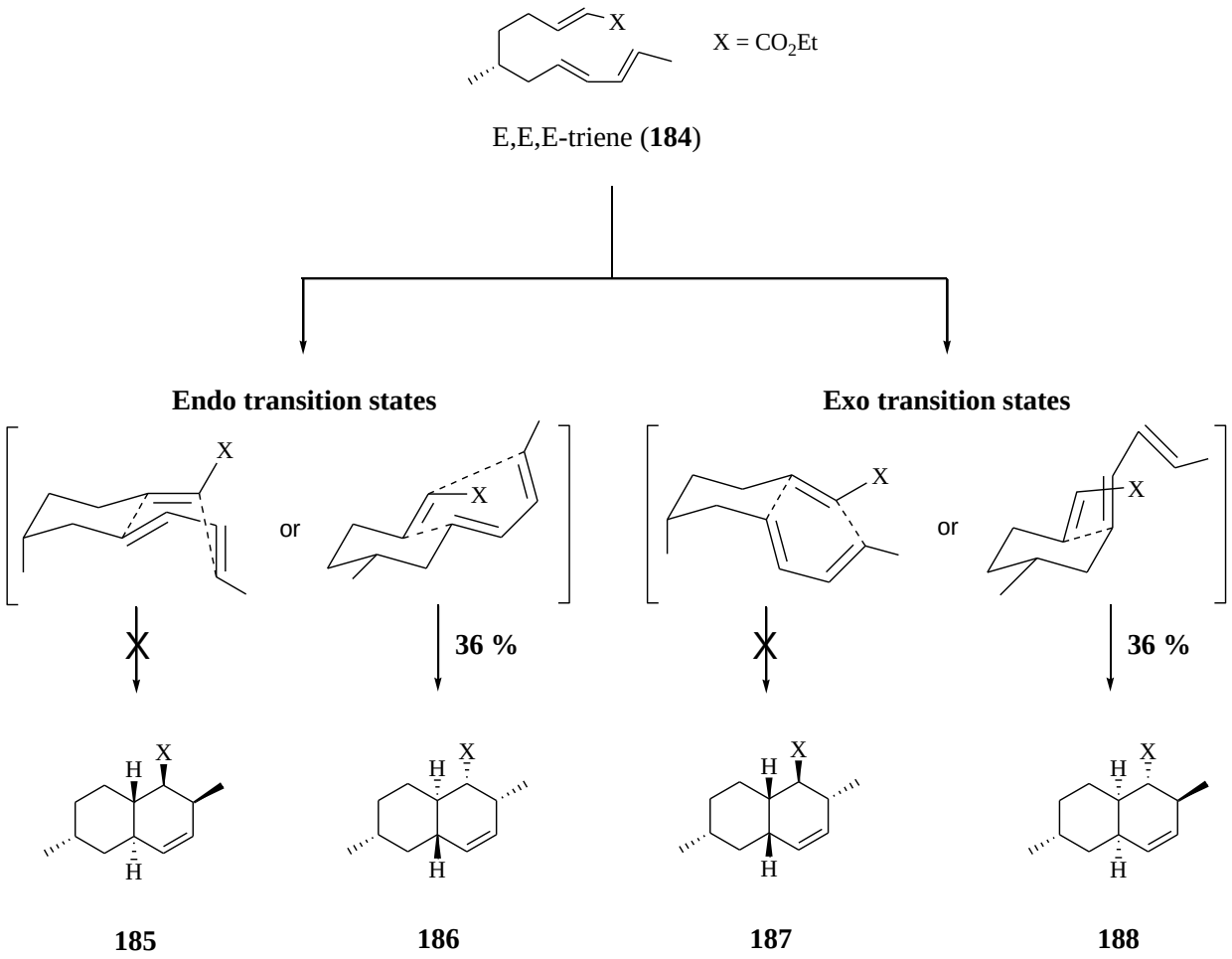
stereoselectivity.[2,4] In principal, IMDA reactions would have 2 transition states of endo and exo to generate trans-fused or cis-fused products. Thermal cyclization could provide cis-fused products by exo-mode cyclization or a mixture of trans and cis-fused rings. For example, Roush and co-worker in 1981 displayed some examples.[5] In thermal condition, products depend on precursors of IMDA reactions, but cis-fused products can be generated as one of major products (Scheme 62).



Scheme 62. Intramolecular Diels-Alder reactions by the Roush group

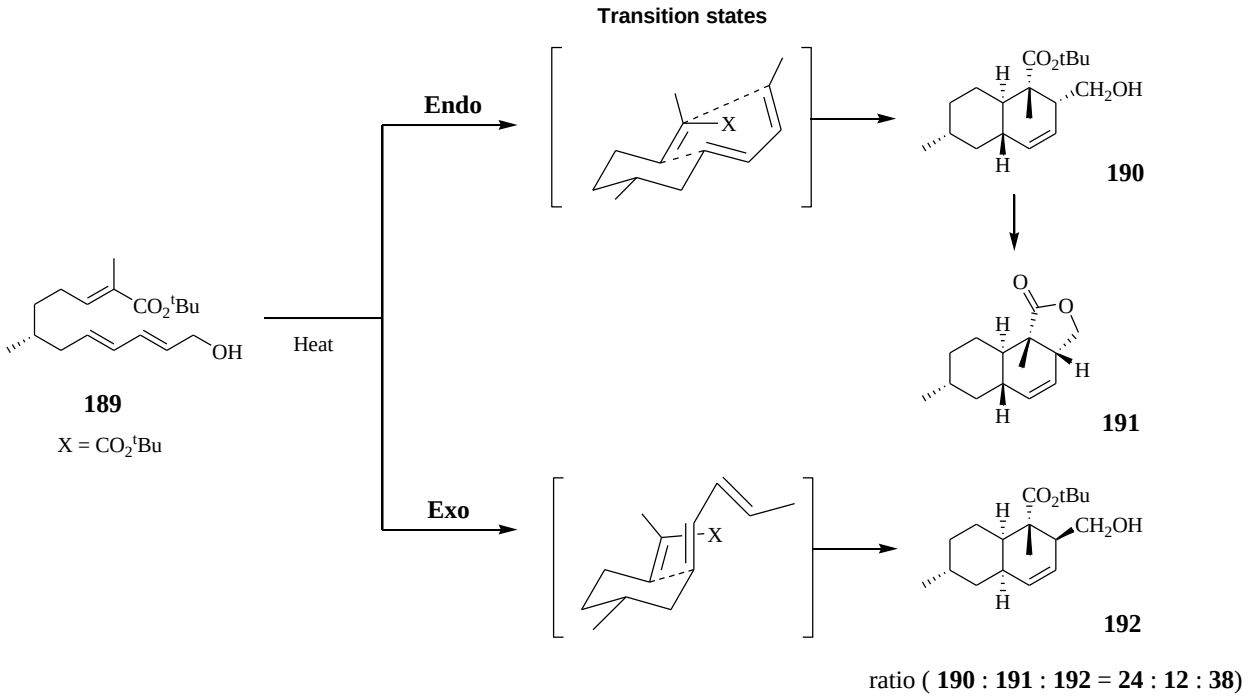
The Vederas group reported bicyclic structure syntheses by IMDA reactions in 1996.[4a] The IMDA reaction can have endo and exo transition states and each provides two diastereomers in which methyl the group is pseudoaxial and pseudoequatorial at C-6. Both thermal and Lewis

acid ($EtAlCl_2$)[6] catalyzed conditions were applied to a triene **184**. Thermal condition gave two products (**186** and **188)** from endo and exo transition states and the Lewis acid condition produced the endo product **186** selectively. None of the reactions showed any product from transition states in which the methyl at C-6 is pseudoaxial. Therefore, comparing endo and exo transition states of triene (**184**) can sometimes allow us to predict products from IMDA reactions (Scheme 63).

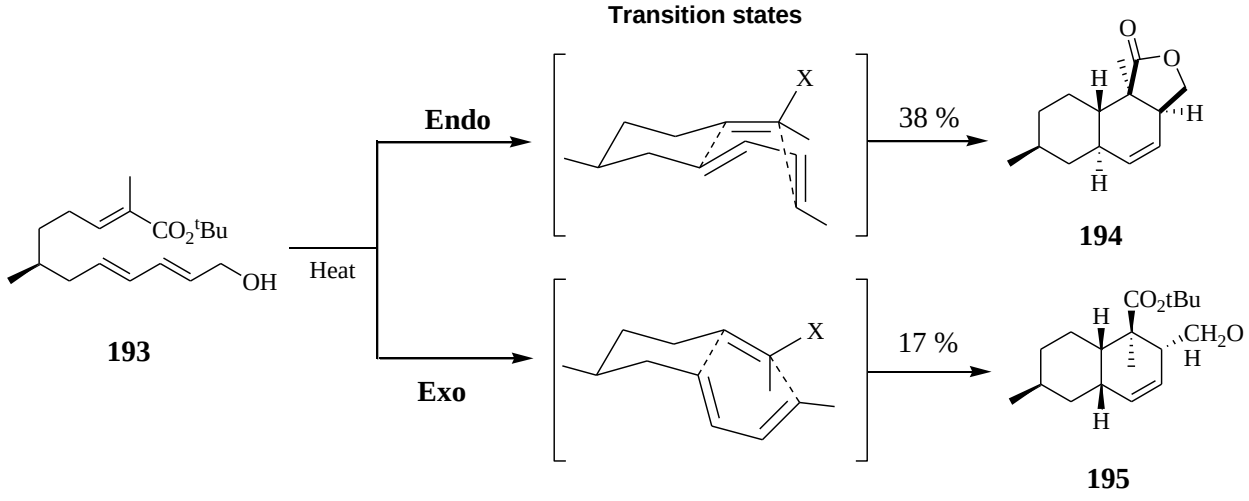


Scheme 63. Endo and exo products **186** and **188** from IMDA reactions

The Shing group also reported the synthesis of (-)-oblongolide by the IMDA reaction.[7] They also showed similar results for stereoselectivity controlled by a methyl group at C-6 (Schemes 64 and 65)



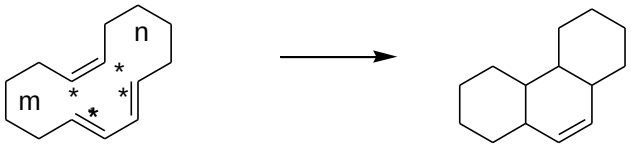
Scheme 64. Bicyclic compounds from the IMDA reaction in the thermal condition by the Shing group



Scheme 65. Bicyclic compounds from the IMDA reaction in the thermal condition by the Shing group

Based on their results, methyl group at C6 would play an important role to control stereoselectivity of bicyclic structures from IMDA reactions.

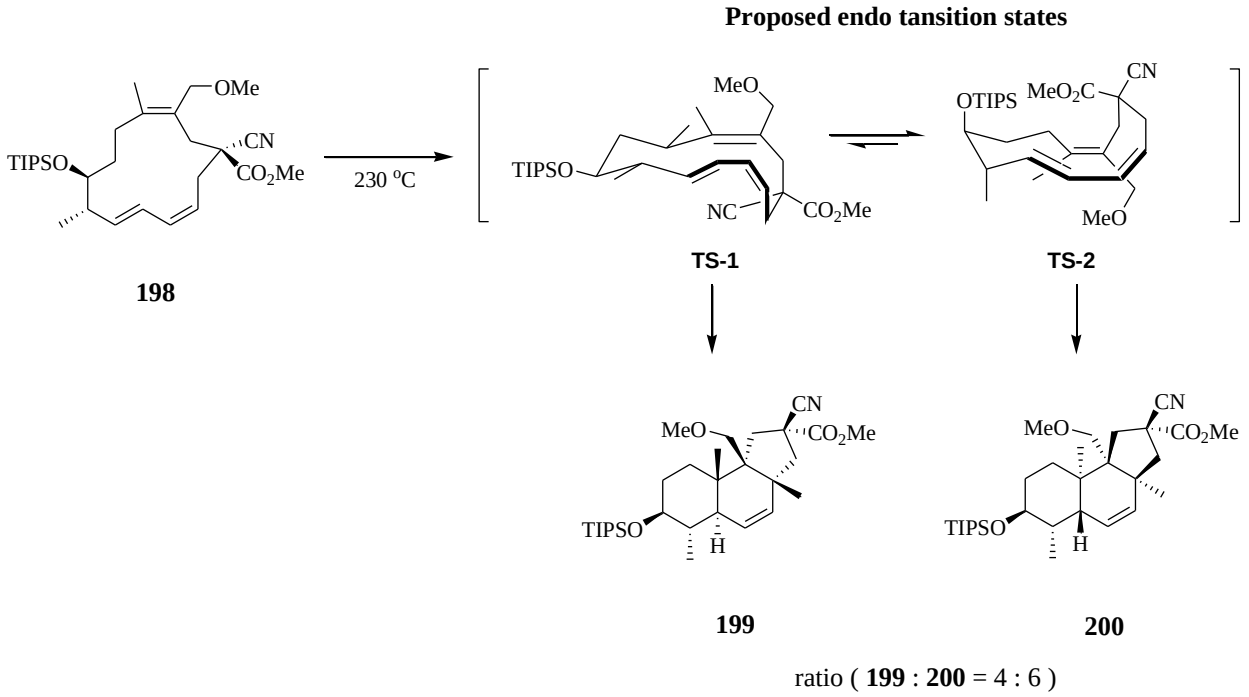
In addition, there are other examples of controlling endo and exo transition states to obtain desired products by the transannular Diels-Alder (TADA) reaction.[3,8] TADA reactions can produce a tricycle **197** from a macrocycle **196**. The stereochemistry of the tricycles can be predicted and controlled by geometry of double bonds and substituents of macrocycles (Scheme 66).



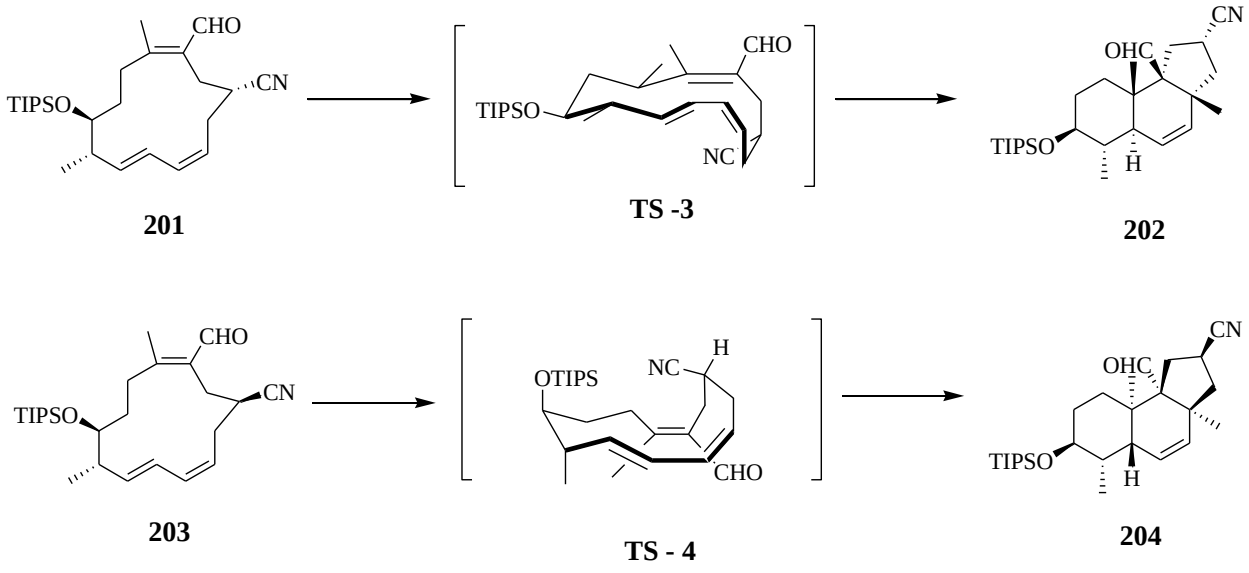
Trienes (**196**) **197**

Scheme 66. Transannular Diels-Alder reaction (TADA)

The Toró group investigated a stereocontrol of TADA reactions and showed syntheses of bicyclic cores.[9] In macrocylces, both exo transition states are sterically prohibited and only endo transition conformations can be applied to provide products. As expected, two endo products (**199** and **200**) from **198** were isolated, but the major product was **200** (Scheme 67). The endo product **204** was produced from **203** (Scheme 68). The results were a little surprising because the -OTBS at C3 and the methyl group at C4 of **198** and **204** would be axial in a transition state **TS-2** and **TS-4** to product **200** and **204**. This experiment demonstrated that the steric effects of the substituent -OTBS and methyl groups are not enough to control a stereoselectivity of products and they suggested -COOMe group and -CN group would prefer to be inside of boat - like conformation.

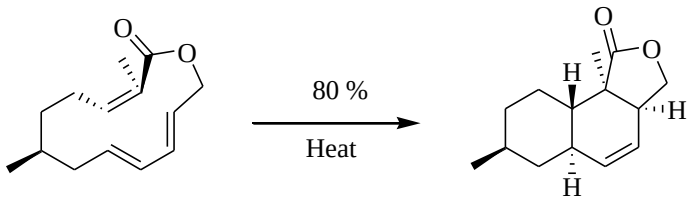


Scheme 67. Bicyclic cores **199** and **200** produced by the TADA reaction in thermal condition by the Toró group



Scheme 68. Bicyclic cores **202** and **204** produced by TADA reactions with Et_2AlCl by the Toró group

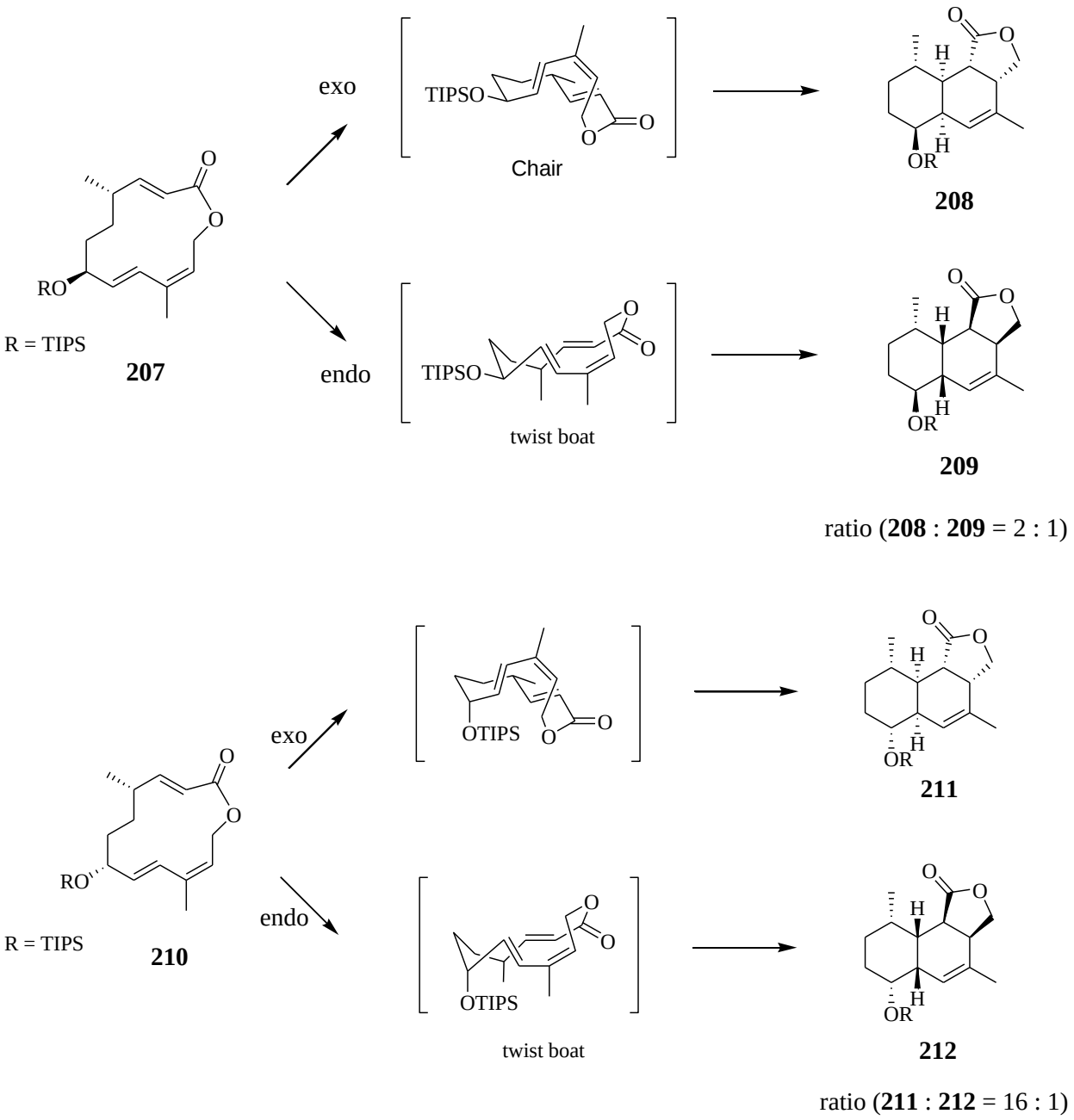
The Shing group displayed usefulness of TADA reactions in the synthesis of (-)-oblongolide from (E,E,E)-macrocycle (**205**) in 1995.[7b] This triene gave the only bicyclic core **206** from the macrocycle (**205**) by endo-mode cyclization (Scheme 69).



(E,E,E) - triene (**205**) **206**

Scheme 69. A synthesis of a backbone of (-)-oblongolide from a (E,E,E)-macrocycle (**205**) by a TADA reactions

The Nakada group demonstrated a synthesis of (+)-phomopsidin from (E,Z,E)-trienes **207** and **210** by the TADA reaction (Scheme 70).[10] The only difference between **207** and **210** is the stereochemistry of the OTIPS groups. The major products were **209** and **211** in spite of axial hydroxyl and methyl groups in transition states.

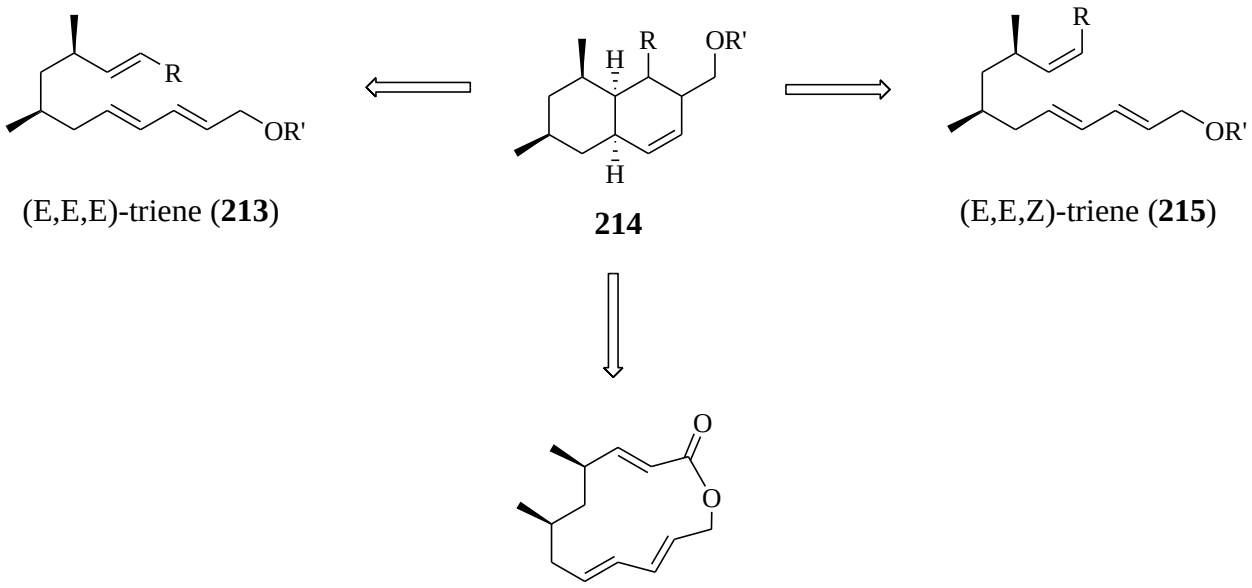


Scheme 70. Bicyclic cores and proposed transition states by the TADA reaction by the Nakada group

These syntheses clearly demonstrate that the bicyclic cores of natural products can be constructed by Diels-Alder reactions and that stereoselectivity would be determined by various factors including the preference for an equatorial position of substituents and the geometry of double bonds of macrocycles.

3.1.3. A new synthetic approach to a key core of alchivemycin A (168)

In intramolecular Diels-Alder (IMDA) reactions, trans-fused products have been produced predominately in many cases, but cis-fused products can be obtained from proper precursors in thermal reaction conditions. To construct a key moiety of Alchivemycin A (**168**), we also need to prepare cis-fused rings and control transition states to prohibit trans-fused products, so three trienes (**213**, **215**, and **216**) were designed to investigate possible precursors and reaction conditions to produce a moiety of Alchivemycin A (**168**) by IMDA or TADA reactions (Scheme 71).

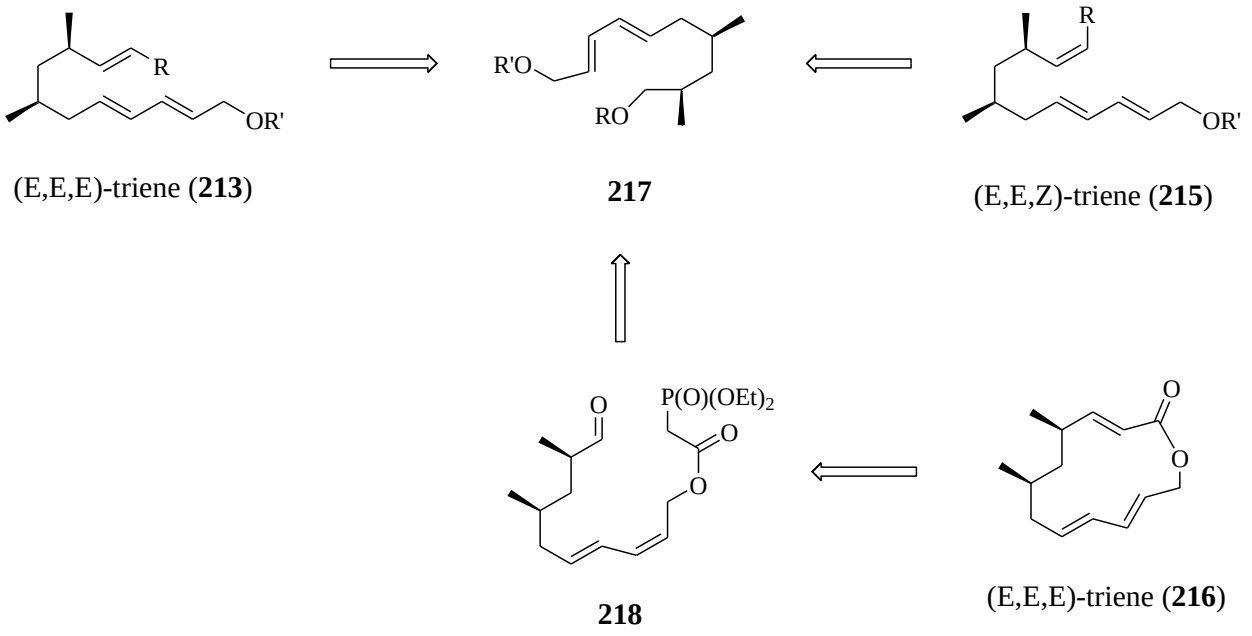


(E,E,E)-triene (**213**) **214** (E,E,Z)-triene (**215**)

(E,E,E)-triene (**216**)

Scheme 71. Designed precursors to investigate IMDA and TADA reactions

In addition, dienes **217** can be common precurors to prepare three trienes (**213**, **215**, and **216**) (Scheme 72).

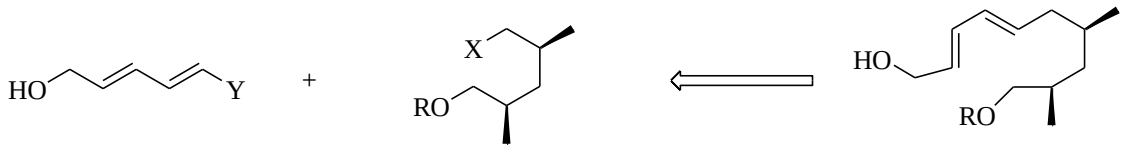


(E,E,E)-triene (**213**) **217** (E,E,Z)-triene (**215**)

218 (E,E,E)-triene (**216**)

Scheme 72. Retrosynthetic analyses of trienes (**213**, **215**, and **216**)

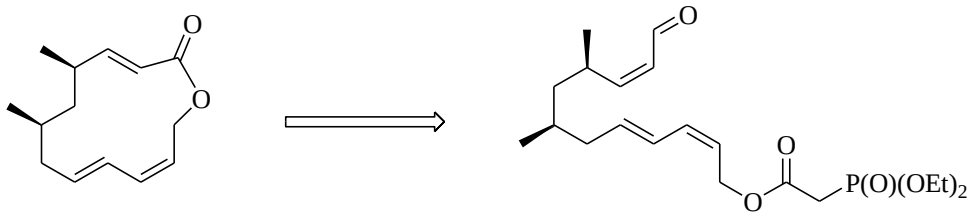
We believed that dienes **217** can be prepared by cross coupling reactions[11] (e.g. Negishi and Suzuki - Miyaura coupling reactions) from known compounds **219**[12] and **220**[13] (Scheme 73).



219 **220** **217**

Scheme 73. Retrosynthetic analysis of the diene **213**

Further, after investigation of three trienes (**213**, **215**, and **216**), the next triene will be other macrolactons like a (E,Z,E)-triene **221** (Scheme 74).



(E,Z,E)-triene (**221**) **222**

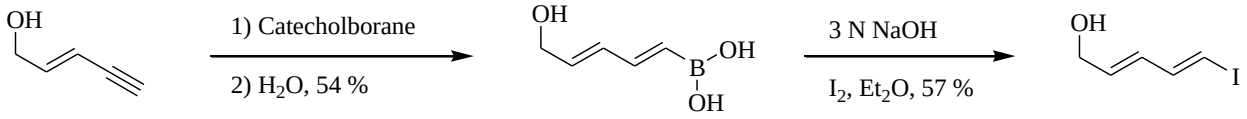
Scheme 74. The Structure of the (E,Z,E)-triene (**221**)

3.2. Result and Discussion

3.2.1. Synthetic approach to precursors of IMDA and TADA reactions

To efficiently investigate precursors to prepare a target structure **214** by the IMDA reaction, the (E,E,E)-triene **213**, the (E,E,Z)-triene **215**, and the macrolactone **216** were prepared as racemic mixtures.

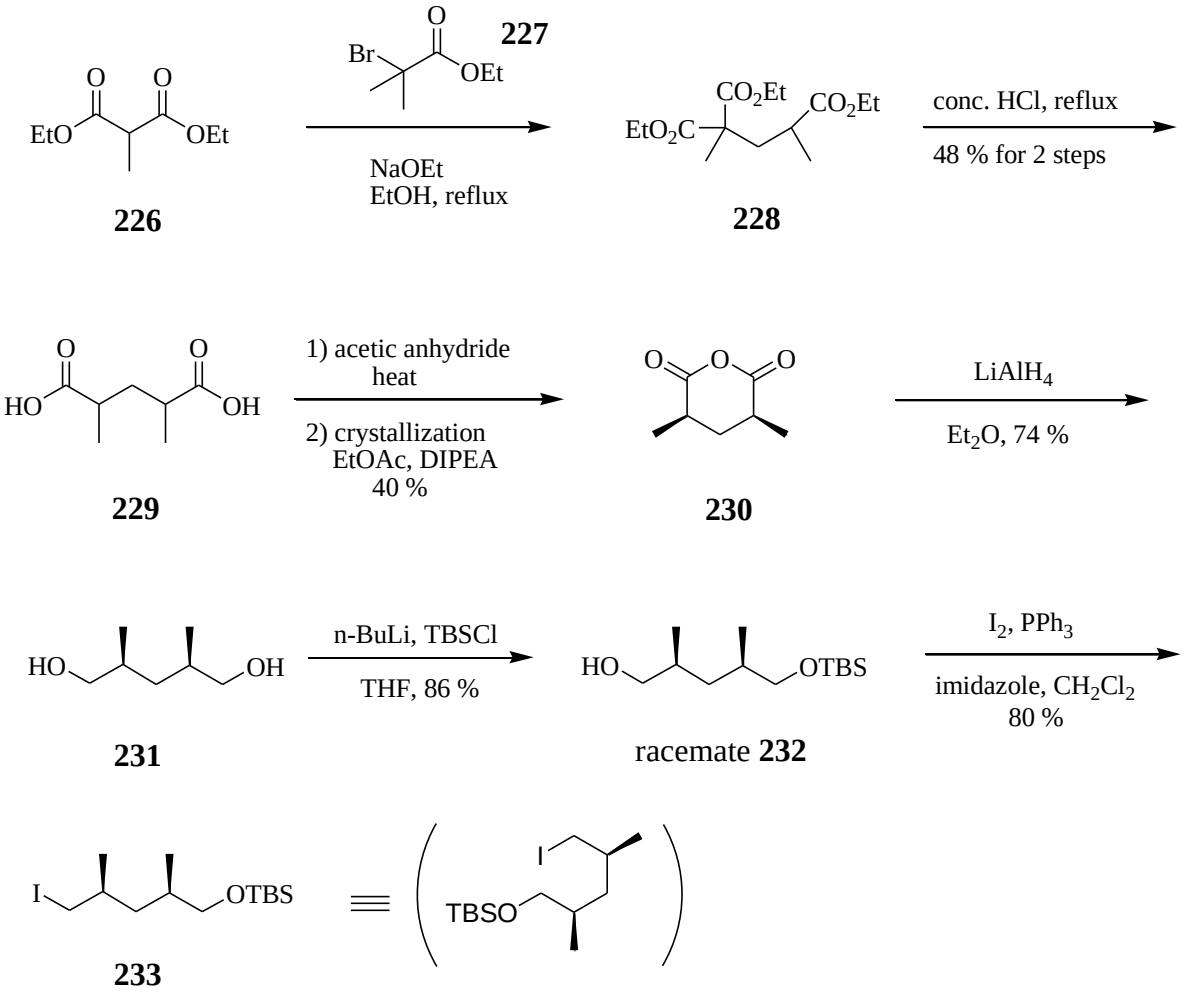
The left and the right pieces were prepared by known procedures. First, an iododiene **225** was synthesized by the literature method.[12-13] Alkyne **223** was treated with catecholborane and water to generate boronic acid **224**. The treatment of **224** with I_2 and NaOH solution produced the iodo alcohol **225** as a left piece (Scheme 75).



223 **224** **225**

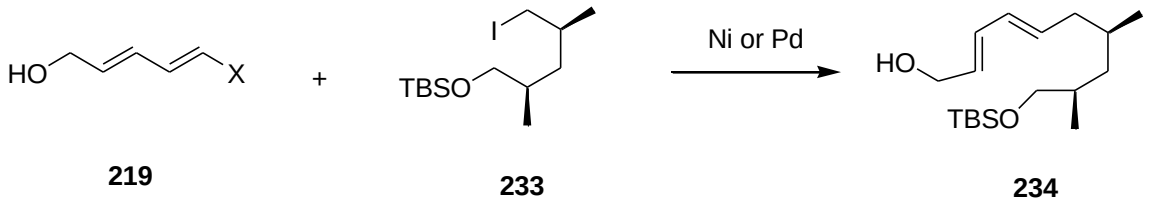
Scheme 75. Preparation of the iododiene **225**

Next, we synthesized an iodide **233**. A diester **226** was treated with a bromoester **227** to produce a triester **228**, which was subject to hydrolysis with acid and lactonization with acetic anhydride to give an anhydride mixture. It was treated with DIPEA in EtOAc and recrystallized at -20 ^{o}C to generate a meso compound **230** as a white solid.[14,15] Reduction with lithium aluminium hydride provided diol **231** [16]. Finally, the selective protection of the diol **231** with TBSCl gave the racemate **232** at low temperature[17], which was subjected to Appel type reaction to afford the corresponding right piece **233**[18]. Herein, if we use an enzyme and vinyl acetate, it will provide an acetate protected alcohol from the diol **231** as an enantiomer (Scheme 76).[16,19]



Scheme 76. Preparation of the iodo alkane **233**

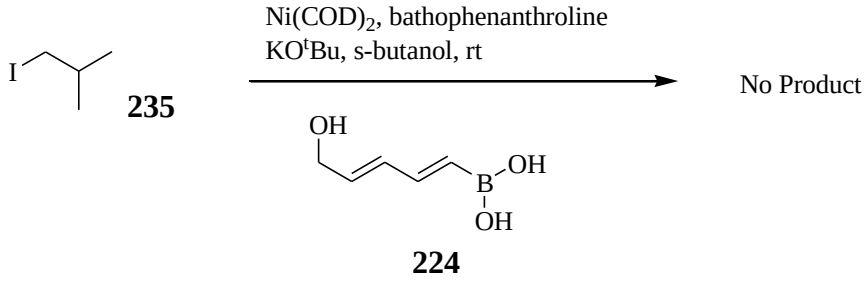
After preparing precursors (**224**, **225** and **233**), we examined the Negishi and Suzuki - Miyaura coupling reactions to obtain a common precursor **234** (Scheme 77).



Scheme 77. Preparation of the common precursor **234**

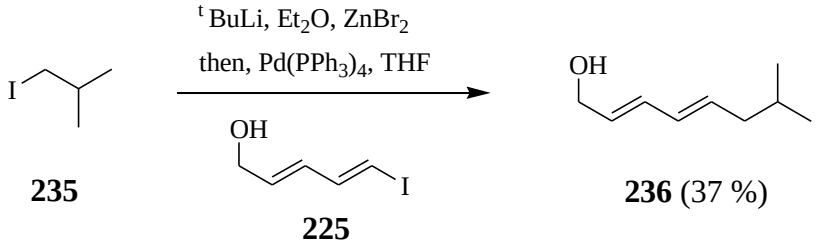
There are a few examples to show sp^3 - sp^2 cross couping reactions, so we decided to do model tests with a commercially available iodo alkane **235** instead of the right piece iodide **233** because left pieces **224** and **225** are easily prepared by one or two steps, but the right piece **233** demands six steps.

Firstly, Suzuki-Miyaura coupling reaction with $Ni(COD)_2$ catalyst developed by the Fu group[20] was tested with **235**, but in spite of several trials, we did not isolate any product from this reaction conditions (Scheme 78).



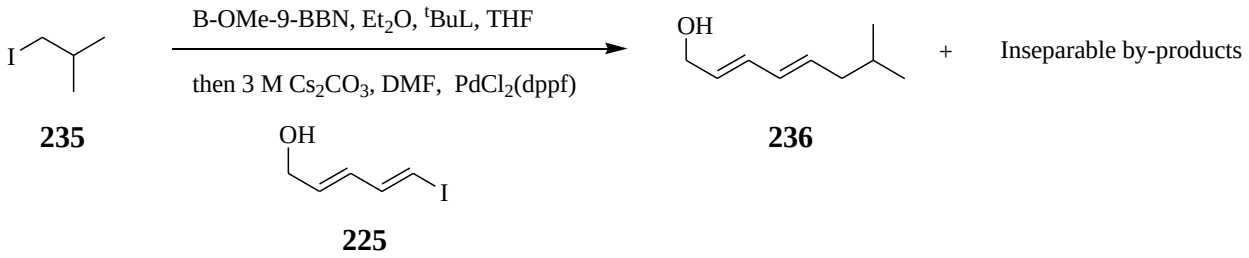
Scheme 78. The model test by Suzuki coupling reaction with $Ni(COD)_2$ catalyst

Next, Negishi coupling[21] was applied and we could isolate a desire product **236** in 37 % yield (Scheme 79). However, it demanded the excess amount of the iodo alkane **235** (more than 2 equivalent of dienol **225)** to produce **236** and the isolated yield was not high.



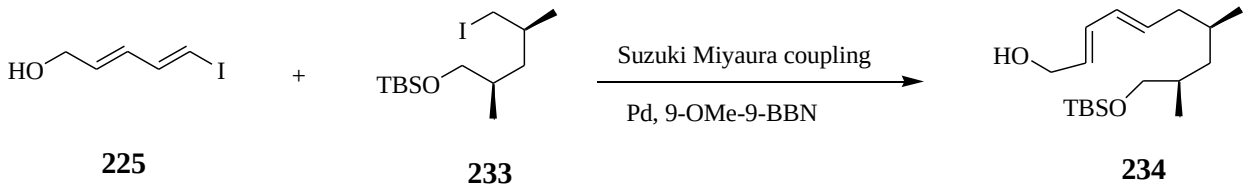
Scheme 79. The model test by Neghishi coupling reaction

Finally, diene **236** was also produced by Suzuki-Miyaura coupling reaction[22] with 9-OMe-9-BBN. However, inseparable by-products were generated (Scheme 80).



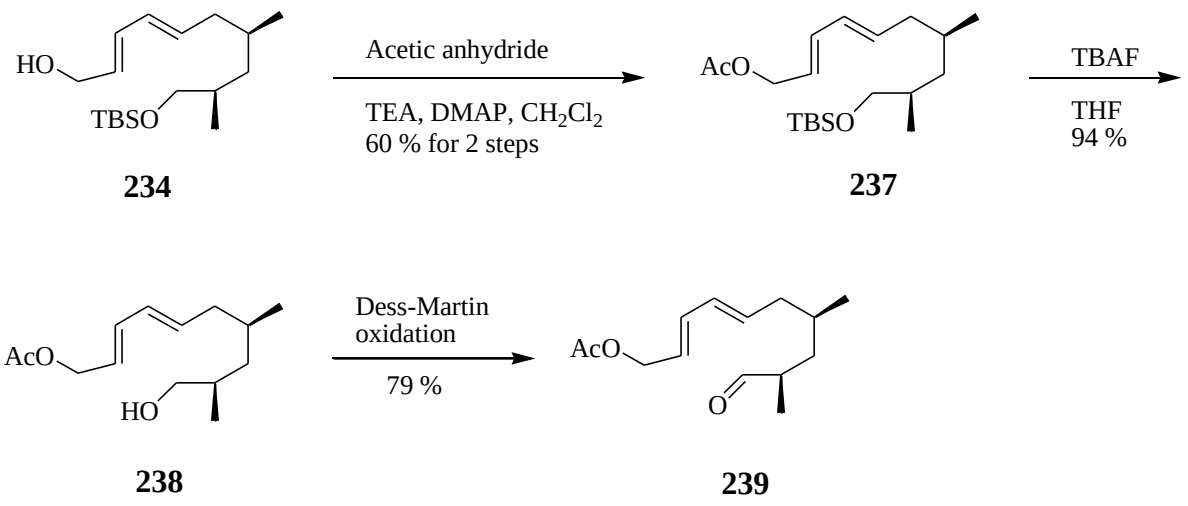
Scheme 80. The model test by Suzuki-Miyaura coupling reaction using 9-OMe-9-BBN

Although the product **236** included inseparable unknown products, this reaction gives more advantages that the excess amount of the iodo alkane **235** can be used and the reaction condition is mild (9-BBN complex with **235** is not sensitive for moisture). Therefore, this reaction condition was applied to our real substituents **225** and **233**. It gave us **234** and concomitant impurities (Scheme 81).



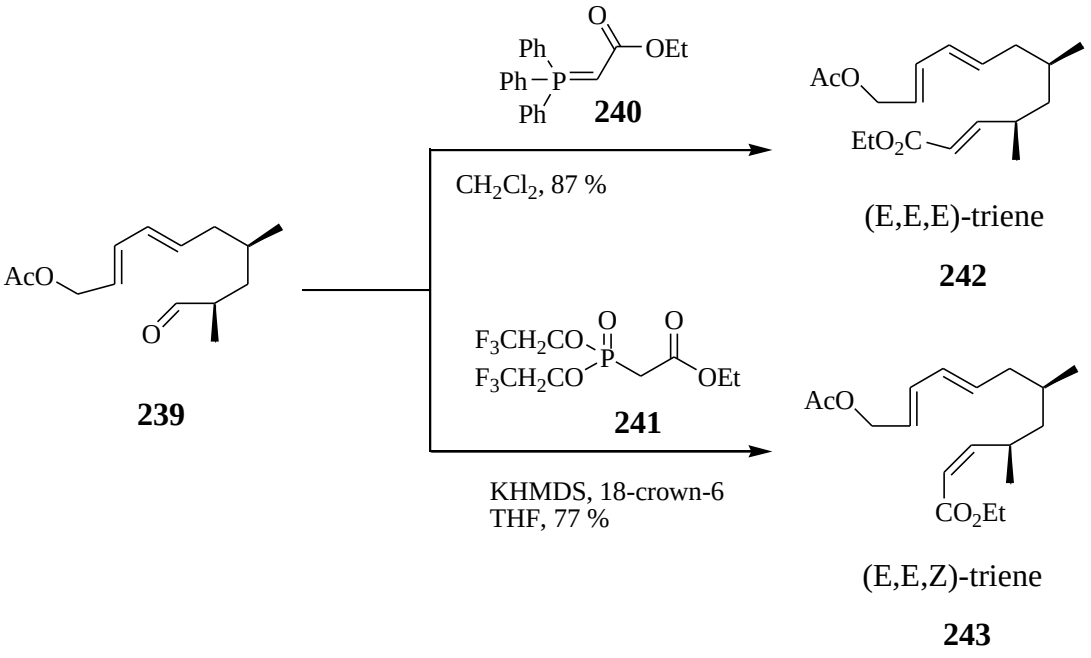
Scheme 81. Preparation of **234** by Suzuki-Miyaura coupling reaction using 9-OMe-9-BBN

After the alcohol protection of **234** with acetate, we could remove almost all of impurities from coupling reactions. After deprotection of TBS group, we prepared an alcohol **238**, which was subjected to Dess-Martin oxidation to give the aldehyde **239** (Scheme 82).



Scheme 82. Preparation of the aldehyde **239**

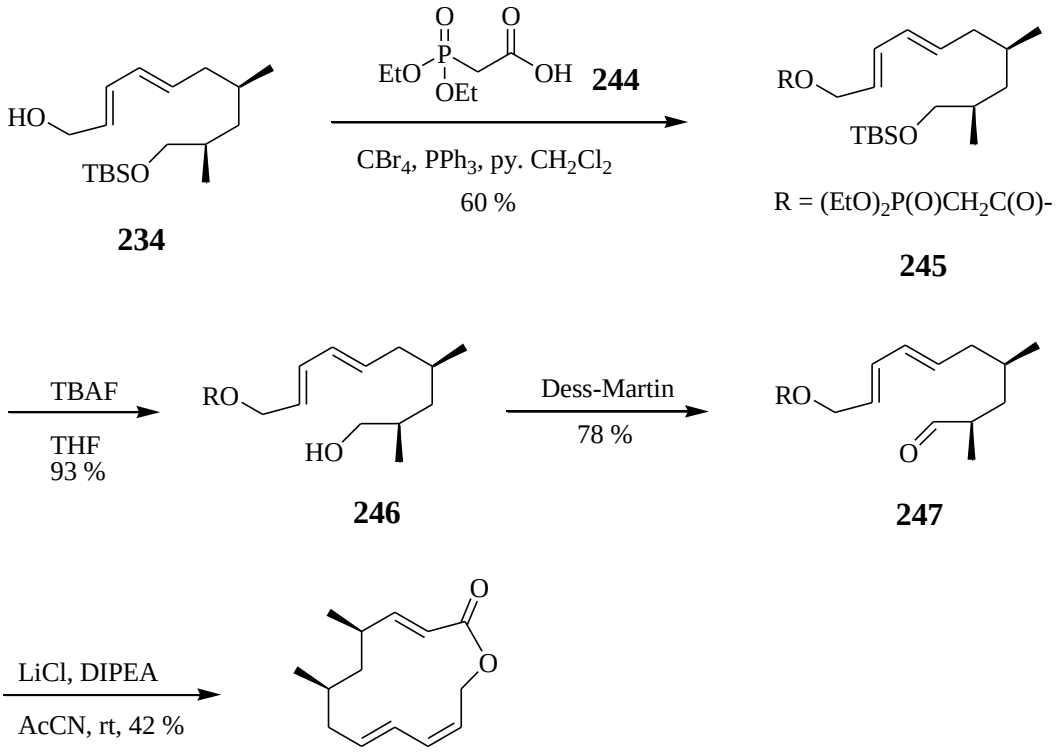
From the aldehyde **239**, the (E,E,E)-triene **242** and the (E,E,Z)-triene **243**, two precursors of IMDA reactions, were synthesized by Wittig reaction and the Still-Gennari olefination (Scheme 83).



Scheme 83. Preparation of the (E,E,E)-triene **242** and the (E,E,Z)-triene **243**

On the other hand, the macrocyclic lactone (**216**) was generated by an intramolecular Horner-Wadsworth-Emmons reaction. Suzuki-Miyaura coupling gave the same alcohol **234**, followed by

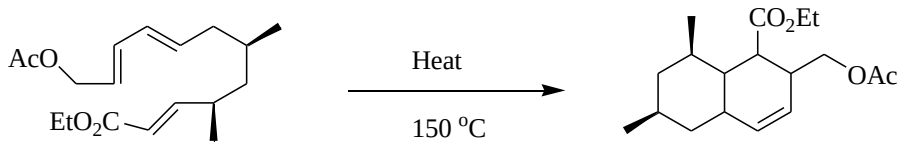
treatment with diethylphosphonoacetic acid[10a] **244** to produce the phosphorane **245**. Deprotection of TBS group followed by Dess-Martin oxidation gave an aldehyde **247**, which was subjected to Horner-Wadsworth-Emmons reaction to provide a macrocyclic lactone (**216**) (Scheme 84).



Scheme 84. Preparation of the macrolactone **216**

3.2.2. Investigation of an intramolecular Diels-Alder (IMDA) reactions

From the (E,E,E)-triene **242**, the IMDA reaction gave us an inseparable mixture of two diastereomers **248** under thermal conditions (Scheme 85). After the IMDA reaction, we isolated one spot on TLC by a silica gel column chromatography, but the ^{1}H NMR spectrum showed two strong methyl peaks of acetate groups, so we believed that it was a mixture **248** of diastereomers.



(E,E,E)-triene

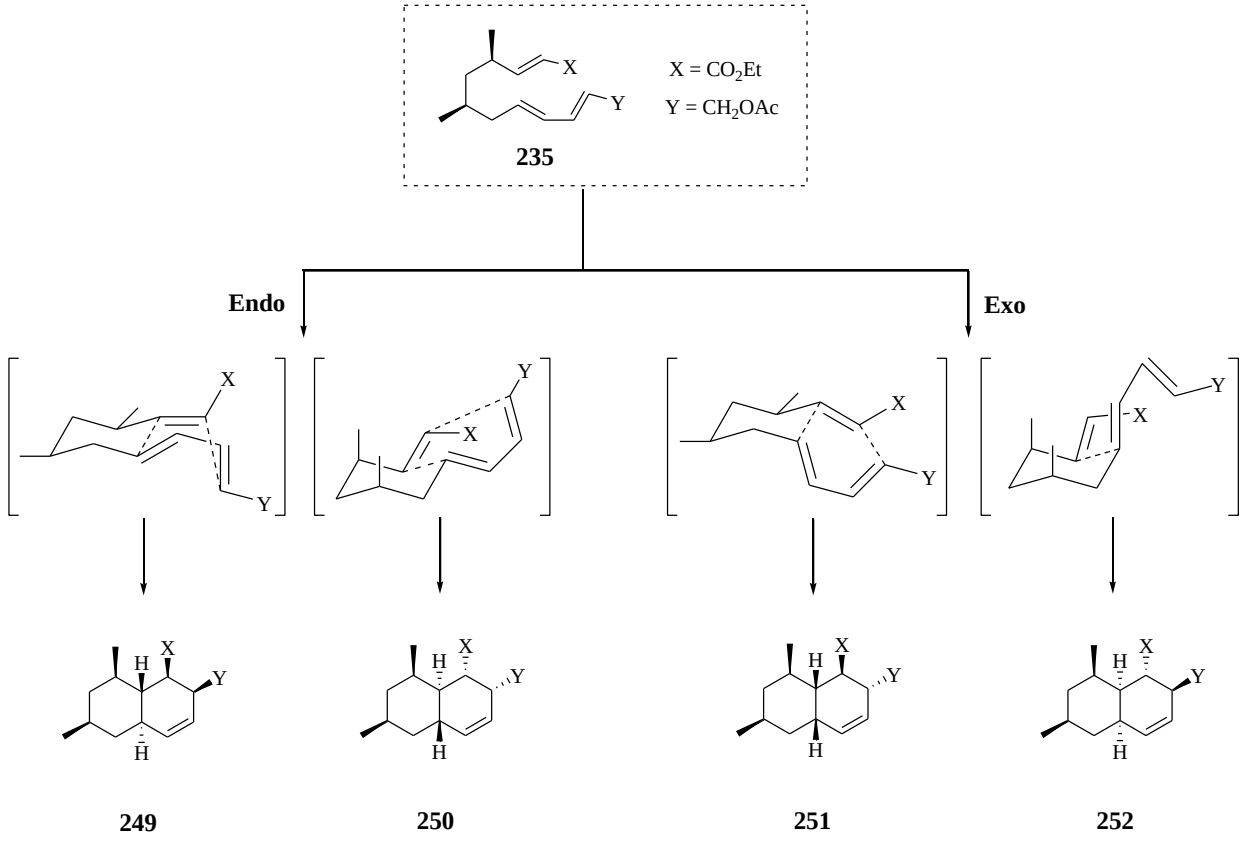
242

Mixture of 2 diastereomers

248

Scheme 85. Two diastereomers produced by the IMDA reaction

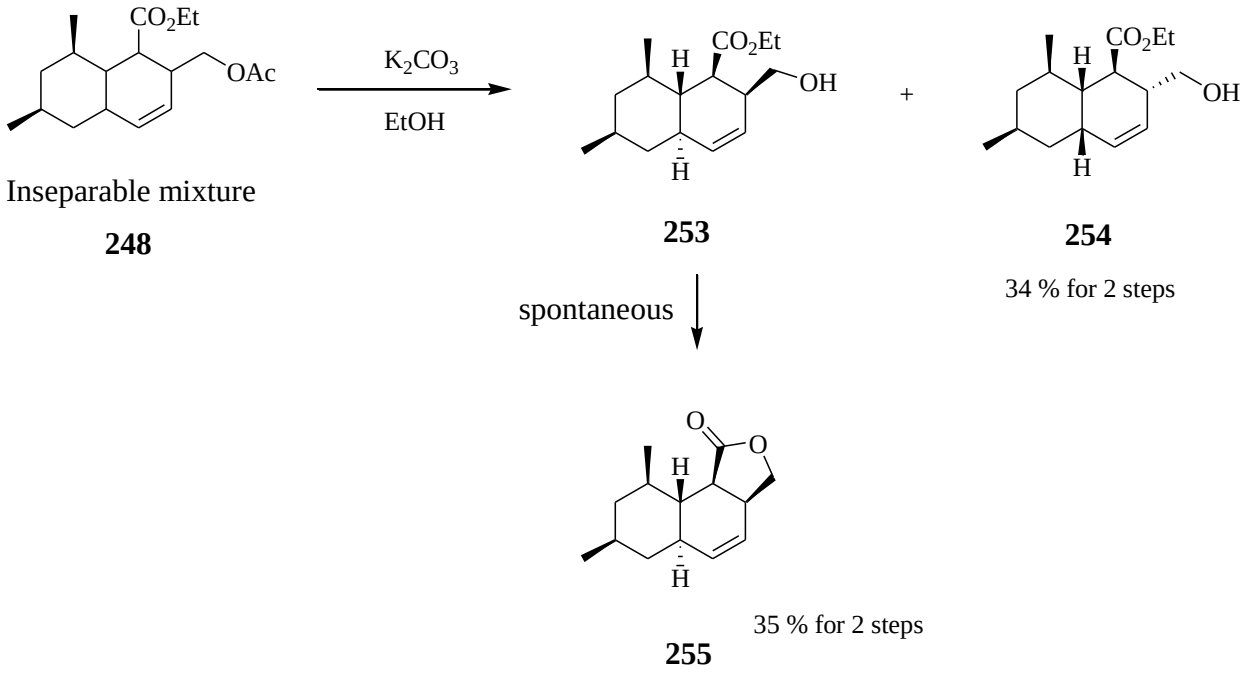
From the IMDA reaction of (E,E,E)-triene **242**, we expected 4 possible diastereomers (Scheme 86).



Scheme 86. Proposed transition states and products of the IMDA reaction from the (E,E,E)-triene **242**

We had tried to separate the mixture **248** to identify each diastereomer. After deprotection of the alcohols, we could separate two products from the mixture **248**. One of products was a lactone **255** and we believe that after hydrolysis, an alcohol **253** spontaneously underwent the

lactonization reaction[7b] to provide **255**. 1D NOE and COSY spectrum data explained the relative stereochemistry of the lactone **255**, so we believe that **255** is a trans-fused bicyclic product from the endo chair transition state, which is also energetically favored. The stereochemical assignment of another product was established by ^{1}H, ^{13}C, COSY, NOESY, and HMQC and we confirmed that it was the cis-fused product **254** from an exo chair transition state. Therefore, we could confirm that the mixture **248** gave two products (**249** and **251**) and we elucidated the relative stereochemistry of these compounds (Scheme 87). The preferred equatorial position of both methyl groups would be a key factor to control a stereoselectivity of **253** and **254**.



Inseparable mixture

248

253

254

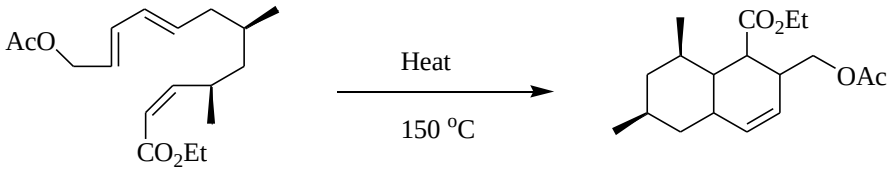
34 % for 2 steps

35 % for 2 steps

255

Scheme 87. The lactone **255** and the alcohol **254** separated by deprotection of acetate of **248**

The (E,E,Z)-triene (**243**) was also subjected to thermal conditions and it appeared to give only one product **256** because a methyl group of acetate showed one peak in the ^{1}H NMR spectrum data (Scheme 88).



(E,E,Z)-triene

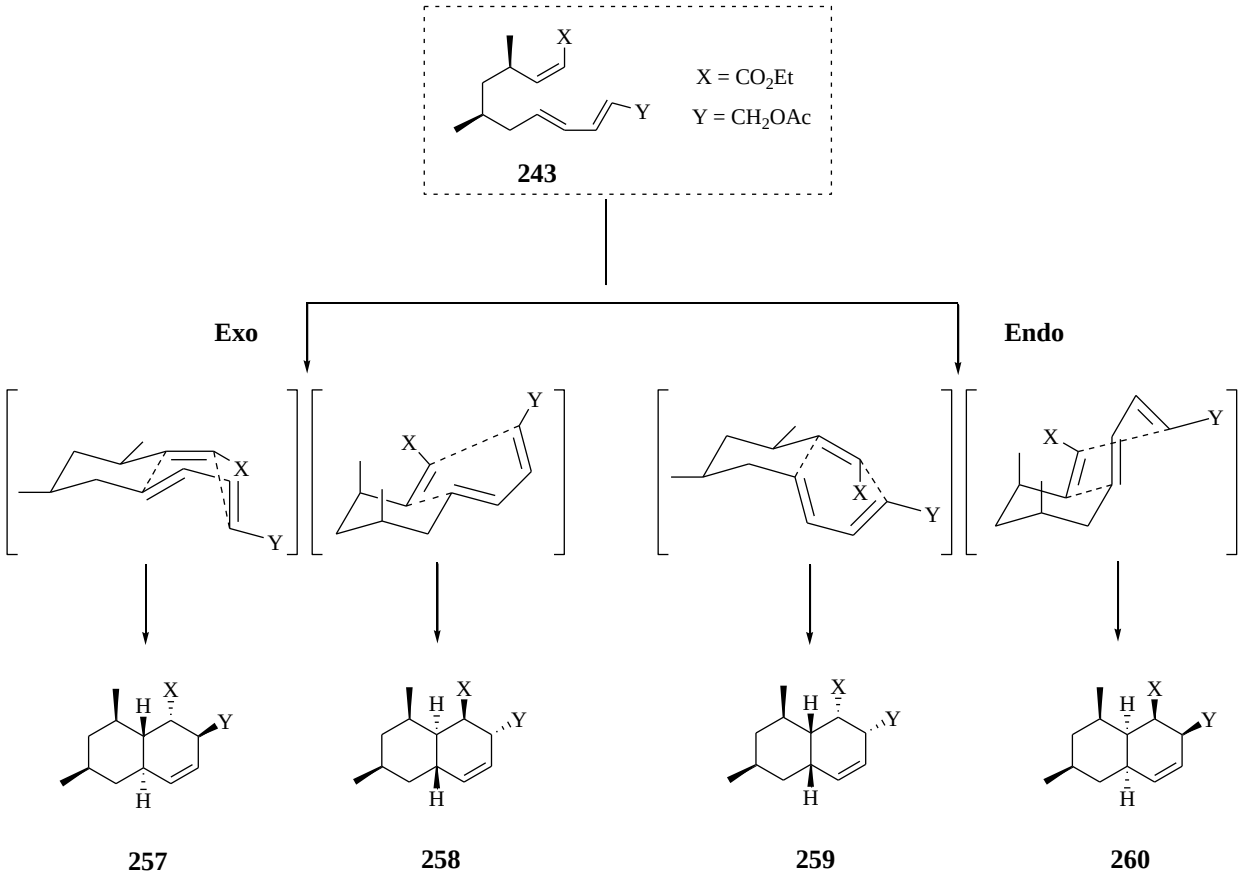
243

One product

256

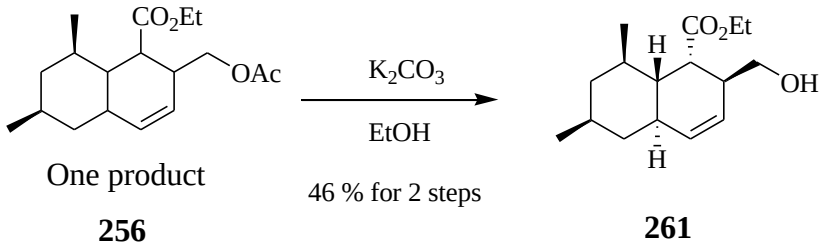
Scheme 88. Bicyclic core **243** from the (E,E,Z)-triene **256** by the IMDA reaction

From the IMDA reaction of (E,E,Z)-triene **236**, we also expected four possible diastereomers (Scheme 89)



Scheme 89. Proposed transition states and products of the IMDA reaction from the (E,E,Z)-triene (**243**)

The product **256** had few impurities. We removed the acetate group and obtained one product **261** (Scheme 90). Its structure was assigned by ^{1}H, COSY, and 1D NOE. This product **261** would be a trans-fused ring produced from **257** (See Scheme 89) through the endo transition state because of the preferred equatorial position of both methyl groups and steric hindrance between the methyl group at C8 and -CH_2OAc.



One product

256

261

Scheme 90. The alcohol **261** by separated by deprotection of acetate of **256**

3.3. Conclusion

In conclusion, the valuable intermediate **234** was efficiently prepared by the Suzuki-Miyaura coupling reaction. From **234**, two model compounds **242** and **243** were successfully synthesized and examined to give bicyclic cores by the intramolecular Diels-Alder reactions. The (E,E,E)-triene **242** produced the inseparable mixture but after deprotection of alcohols, we could isolate products **254** and **255**. From these compounds, we could assign relative stereochemistry to the cycloaddition products. In addition, only one diastereomer **256** was synthesized from the (E,E,Z)-triene **243** and we also confirmed a stereochemistry of **243** after deprotection of an acetate group. Although the stereochemistry of the bicyclic cores was consistent with expectations, none had the relative stereochemistry required for alchivemycin A (**168**). We began the preparation of the macrolactone **216** and it will be examined soon. Control the stereochemistry of bicyclic cores of alchivemycin A (**168**) will be supported by future experiments.

3.4. Reference

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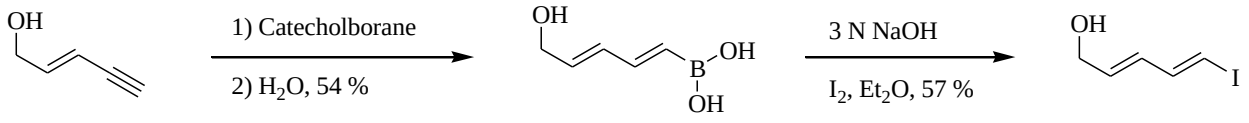
3.5. Experimental section

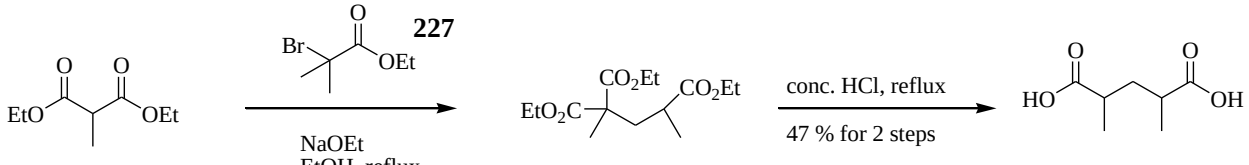
General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å , 230-400 mesh, surface area 500-600 m^2/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), a Varian Inova-500 (500 MHz for ^1H and 125 MHz for ^{13}C), Bruker-400 (400 MHz for ^1H and 100 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C, or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.



223 **224** **225**

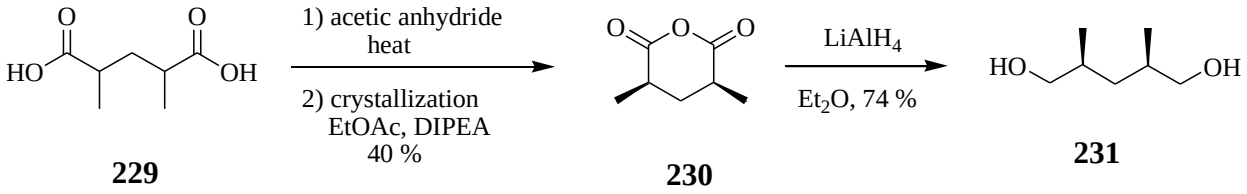
Boronic acid 225.[12-13] To the alcohol **223** (484 mg, 5.89 mmol) was added catecholborane (1.484 g, 12.37 mmol) at 0 °C under argon, allowing release for hydrogen. The reaction mixture was stirred for 2 h. It was stored at - 20 ~ 25 °C for 16 h. The cold water (12 mL) was added and stirred for 4.5 h. The resulting solution was saturated with NaCl and extracted with EtOAc (10 mL X 5). The combined organic solution was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 1 to CH_2Cl_2 : MeOH = 95 : 5) to produce **224** (408 g, 54 %). To a stirred solution of **224** (408 mg, 3.19 mmol) in ethyl ether (10 mL) was added 3N NaOH at 0 ° and then I_2 (891 mg, 3.52 mmo) solution in ethyl ether (10 mL). The reaction mixture was slowly warmed to rt and stirred for 1 h and quenched by addition of saturated aq. $Na_2S_2O_3$ solution. The aqueous layer was extracted with (6 mL X 3) and the combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 3) to give **225** (381 mg, 57 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 10.5, 1H), 6.36 (dd, *J* = 14.4, 0.6 Hz, 1H), 6.20 (dd, *J* = 15.3, 10.5 Hz, 1H), 5.86 (dt, *J* = 14.4, 5.4 Hz, 1H), 4.17 (t, *J* = 4.8 Hz, 2H). Spectroscopic properties were in agreement with literature values.[18]



226 **228** **229**

Diacid 229.[14,15] To ethanol (28 mL) was added Na (1.055 g, 44.89 mmol) and the resulting solution was heated to reflux. Malonate **226** (7.959 g, 45.23 mmol) was bromide **227** (9.121 g, 46.7 mmol) were added and stirred at 90 °C (an oil bath temperature). After 5 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. Ethyl ether (25 mL) and water

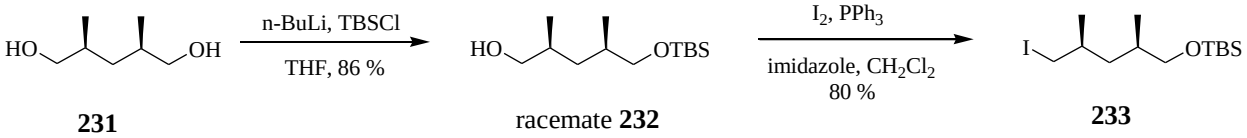
(4 mL) were added and the aqueous layer was extracted with ethyl ether (15 mL X 3). The combined organic layer was dried over MgSO4 and concentrated under reduced pressure to give a crude product the triester **228** (11.09 g). Conc. HCl was added to **228** (11.09 g) and stirred at 100 ^{o}C for 8 h and stored at -25 ^{o}C for 1 day. A white solid was filtered and dissolved in ethyl ether. The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the white solid **229** (3.07 g). The filtrate was extracted with ethyl ether and the combined organic layer was concentrated under educed pressure. Hexane was added and stored at -25 ^{o}C for 1 day. A white solid was filtered and followed the same procedure above to give the **229** (0.397 g) as white solid. The white solids **229** were combined (3.46 g, 48 % for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (sext, *J* = 6.9 Hz, 1H), 2.54 (m, 1H), 1.97 (dd, *J* = 5.7, 6.3 Hz, 1H), 1.21 (d, *J* = 5.7 Hz, 3H) 1.20 (d, *J* = 6.0 Hz, 3H). Spectroscopic properties were in agreement with literature values. [14-15]



229 **230** **231**

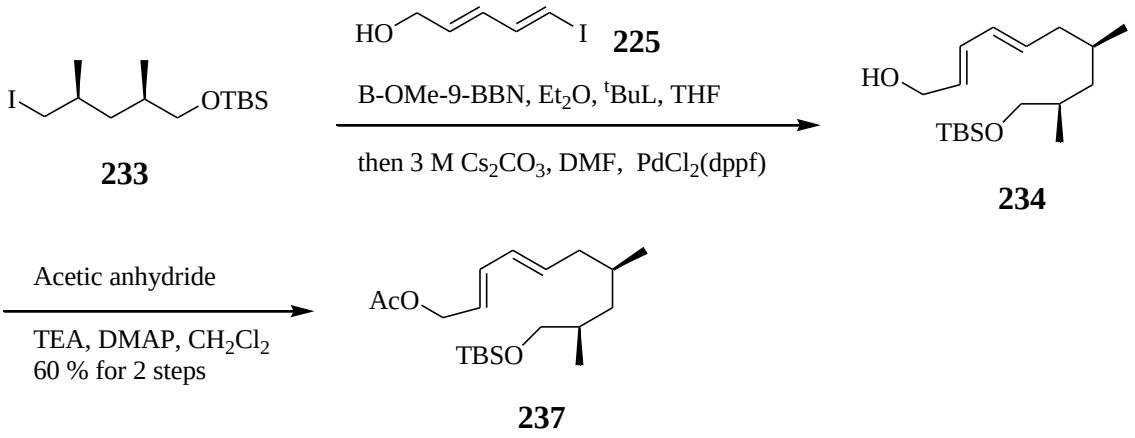
Diol 231.[14,15-16] A stirred solution of diacid **229** (3.39 g, 21.16 mmol) in acetic anhydride (10 mL) was heated to 115 ^{o}C (an oil bath temperature). After 24 h, the reaction mixture was cooled to rt and then acetic acid and acetic anhydride were distilled to give a white solid (2.6 g). EtOAc (3.1 mL) and DIPEA (0.6 mL) were added and stirred at rt for 14 h. The mixture was cooled to -30 ^{o}C for 1 day. The white solid was filtered and washed wit EtOAc (pre-cooled to -30 ^{o}C). The white solid **230** (580 mg) was obtained. The filtrate was concentrated under reduced pressure. The residue was added EtOAc and recrystallized again to produce **230** (610 mg). The filtrate was reused to obtain **230**. Crystallized white solid **230** (1.19 g, 40 %) from1st and 2nd recrystallization. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 - 2.63 (m, 2H), 2.06 (dt, *J* = 13.6, 5.3 Hz, 1H), 1.69 - 1.58 (m, 1H), 1.37 (dd, *J* = 6.9, 0.5 Hz, 6H). To stirred solution of **230** (658 mg, 4.63 mmol) in Et_2O was added $LiAlH_4$ (351 mg, 9.25 mmol) and stirred for 1 h at rt. To the resulting mixture was added Et_2O (15 mL) and water (3 mL) carefully and then 10 % NaOH (1.2 mL). The mixture was filtered through Celite and Et_2O was added. The organic layer was concentrated under reduced

pressure to give a crude product **231** (454 mg, 74 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.45 - 5.39 (m, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.98 (d, *J* = 1.4 Hz, 1H), 4.85 (s, 1H), 4.07 - 3.94 (m, 6H), 2.70 (dd, *J* = 11.6, 3.1 Hz, 1H), 2.46 - 2.24 (m, 3H), 2.11 (ddd, *J* = 34.8, 14.4, 9.8 Hz, 2H), 1.92 (dtd, *J* = 13.0, 6.9, 3.4 Hz, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.17 - 1.04 (m, 13H), 0.14 (s, 9H). Spectroscopic properties were in agreement with literature values.[14]



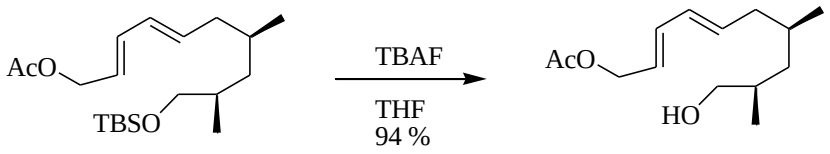
231 racemate **232** **233**

Iodide 233. To a stirred solution of diol **231**(267 mg, 2.017 mmol) in THF (4 mL) was added n-BuLi (1.34 mL, 2.14 mmol, 1.6 M in hexane) dropwise at - 78 ^{o}C and stirred for 30 min. TBS-Cl solution in THF (2 mL) was added dropwise at -78 ^{o}C for 40 min and stirred for 4 h at -78 ^{o}C and stored at - 30 ^{o}C for 14h. It was quenched with saturated aq. NH_4Cl (2.5 mL) and Ethyl ether (5 mL) were added. The aqueous layer was extracted with ethyl ether (1 mL X 3). The combined organic phase was washed with brine and water and dried over $MgSO_4$. After concentration, the crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide **232**[17] (427 mg, 86 %) and the recovered starting **231** (38 mg, 14 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 -3.32 (m, 4H), 2.01 (s, 1H), 1.69 (quint, *J* = 5.6 Hz, 2H), 1.41 (quint, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 - 0.87 (m, 13H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.3, 68.0, 37.3, 33.2, 33.2, 25.9, 18.3, 17.8, 17.7, -5.4. To a stirred solution of iodine (520.6 mg, 2.051 mmol) in CH_2Cl_2 (10 mL) were added imidazole (151.3 mg, 2.222 mmol) and PPh_3 (538 mg, 2.051 mmol) at 0 ^{o}C under argon. The reaction mixture was stirred for 10 min, and then the solution of **232** (419.3 mg, 1.701 mmol) in CH_2Cl_2 (4 mL) was added and the syringe was rinsed with CH_2Cl_2 (1 mL). The resulting mixture was warmed to rt and stirred for 2 h. It was concentrated under reduced pressure and purified with silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to give a iodo alkane **233**[18] (489 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.35 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.26 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.10 (dd, *J* = 6.9, 6.0 Hz, 1H), 1.75 - 1.15 (m, 3H), 1.06 - 0.79 (m, 16H), 0.893 (s, 6H). Spectroscopic properties were in agreement with literature values.[17-18]



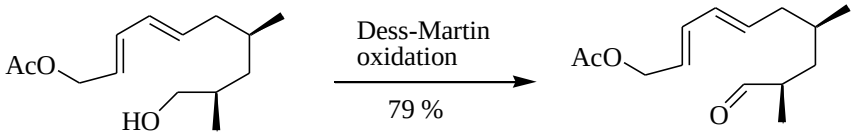
Diene 237. To a stirred solution of **233** (16.2 mg, 0.0455 mmol) was Et_2O (0.6 mL) was added B-OMe-9-BBN (0.21 mL, 0.21 mmoL) at -78 ^oC under argon and stirred for 10 min. t-BuLi (0.13 mL, 0.21 mmol, 1.6 M pentane) was added and stirring for 15 min at -78 ^oC. THF (0.9 mL) was added dropwise and stirring for 20 min. The resulting mixture was slowly warmed to rt and stirred for 2.5 h. To the solution were added 3 M $CsCO_3$ (0.05 mL, 0.16 mmol), $PdCl_2(dppf)Cl_2$ (3.7 mg, 0.0046 mmol), diene **225** (13.4 mg, 0.0636 mmol) solution in DMF (0.9 mL), and $AsPh_3$ (2.1 mg, 0.0068 mmol) for 36 h. It was quenched with saturated aq. NaCl (1.0 mL) and Et_2O (3 mL) was added. The resulting mixture was extracted with Et_2O (3 mL X 3) and the combined organic phase was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide the crude **234** (25.3 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 15, 10.5 Hz, 1H), 6.03 (dd, *J* = 15, 10.5 Hz, 1H), 5.71 (m, 2H), 4.17 (m, 2H), 3.43 (dd, *J* = 9.5, 5 Hz, 1H), 3.32 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.11 (m, 1H), 1.87 (m, 1H), 1.58 - 1.72 (m, 2H), 1.34 (quint, *J* = 6.5 Hz, 1H), 1.26 (m, 2H), 0.89 (s, 9H), 0.88 (m, 6H), 0.03 (s, 6H).; IR (neat) ν_{max} 3377.1, 2925.3, 2858.7 cm^{-1}. To a stirred solution of **234** (25.3 mg) in CH_2Cl_2 was added Et_3N (10.6 mg, 0.105 mmol), DMAP (1.0 mg, 0.008 mmol), and acetic anhydride (9.1 mg, 0.089 mmol) and stirred for 14 h at rt. It was quenched with saturated aq. $NaHCO_3$ and water was added. The resulting mixture was extracted with CH_2Cl_2 (3 mL X 2) and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide the pure **237** (10 mg, 60 % for 2 steps). ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.02 (dd, *J* = 15.0, 10.0 Hz, 1H), 5.61 - 5.75 (m,

2H), 4.57 (d, *J* = 5.0 Hz, 2H), 3.43 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.32 (dd, *J* = 9.7, 6.5 Hz, 1H), 2.15 - 2.03 (m, 4H), 1.87 (dt, *J* = 14.5, 7.6 Hz, 1H), 1.73 - 1.55 (m, 3H), 1.34 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.25 (s, 1H), 0.95 - 0.91 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 5.0 Hz, 6H), 0.03 (s, 6H).; IR (neat) ν_{max} 2956, 2928, 2856, 1744 cm^{-1}.



237 **238**

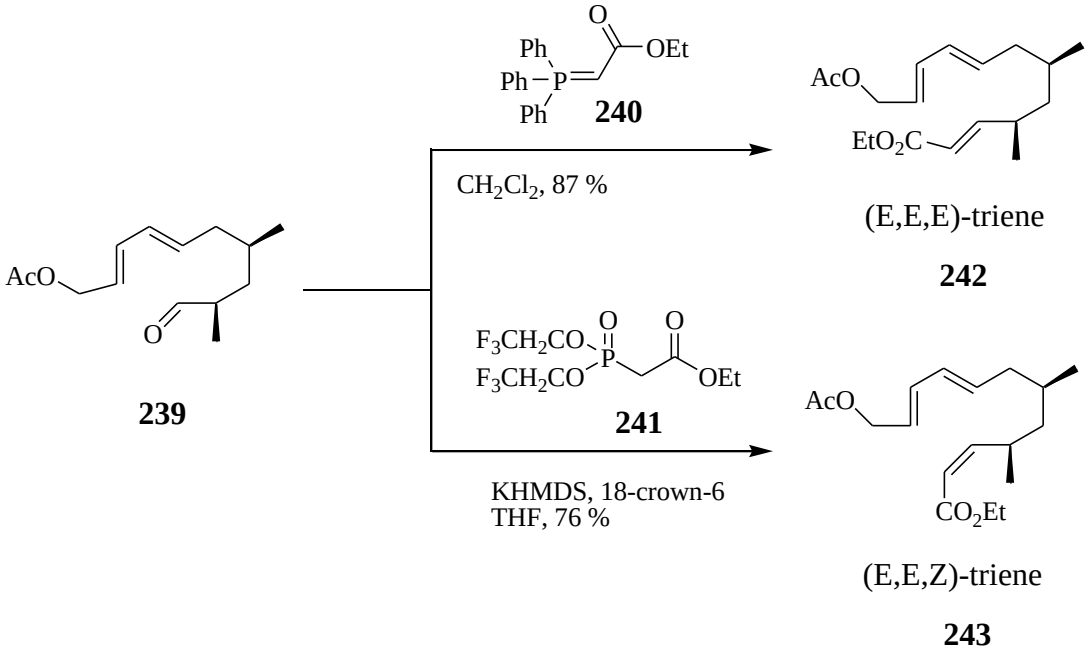
Alcohol 238. To a stirred solution of **237** (10 mg, 0.027 mmol) in THF (1.0 mL) was added TBAF (0.05 mL, 0.05 mmol, 1.0 M in THF). The reaction mixture was stirred for 3 h at rt and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide **238** (6.4 mg, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 - 6.24 (m, 1H), 6.05 - 6.00 (m, 1H), 5.74 - 5.61 (m, 2H), 4.57 (d, *J* = 6.5 Hz, 2H), 3.51 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.38 (dd, *J* = 10.5, 7.0 Hz, 1H), 2.15 - 2.10 (m, 1H), 2.06 (s, 3H), 1.89 (quint, *J* = 7.0 Hz, 1H), 1.71 (sext, *J* = 6.5 Hz, 1H), 1.66 - 1.59 (m, 1H), 1.37 - 1.28 (m, 2H), 0.99 - 0.94 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H).



238 **239**

Aldehyde 239. To a stirred solution of **239** (6.4 mg, 0.027 mmol) in CH_2Cl_2 (4.0 mL) was added Dess-Martin periodinane (18.2 mg, 0.042 mmol). The reaction mixture was stirred for 14 h at rt and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide **239** (5.1 mg, 79 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (d, *J* = 2.5 Hz, 1H), 6.26 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.04

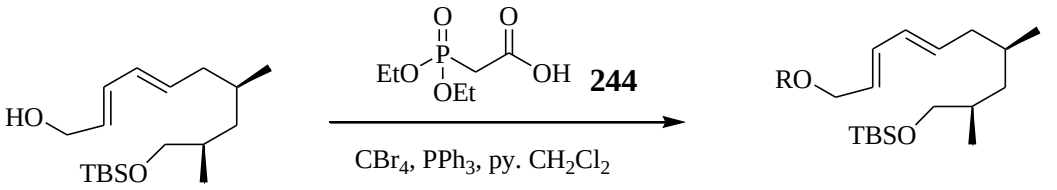
(dd, *J* = 15.0, 10.0 Hz, 1H), 5.72 - 5.63 (m, 2H), 4.58 (d, *J* = 6.0 Hz, 2H), 2.41 - 2.48, (m, 1H), 2.13 - 2.08 (m, 1H), 2.07 (s, 3H), 2.02 - 1.92 (m, 1H), 1.77 - 1.71 (m, 1H), 1.65 - 1.59 (m, 1H), 1.21 - 1.11 (m, 1H), 1.09 (d, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H).



(E,E,E)-triene 242. To a stirred solution of aldehyde **239** (10.9 mg, 0.046 mmol) in CH_2Cl_2 (3.3 mL) was added **240** (71.8 mg, 0.206 mmol). The reaction mixture was stirred for 17 h and **240** (14.6 mg, 0.0419 mmol) was added more. After 3 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide **242** (12.2 mg, 87 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 15.7, 8.5 Hz, 1H), 6.34 - 6.18 (m, 1H), 6.09 - 5.94 (m, 1H), 5.86 - 5.56 (m, 3H), 4.57 (dd, *J* = 6.7, 1.2 Hz, 2H), 4.25 - 4.10 (m, 2H), 2.49 - 2.33 (m, 1H), 2.14 - 1.84 (m, 6H), 1.61 (d, *J* = 3.0 Hz, 1H), 1.53 - 0.97 (m, 11H), 0.97 - 0.79 (m, 4H). IR (neat) ν_{max} 2960, 2915, 1741, 1719 cm^{-1}.

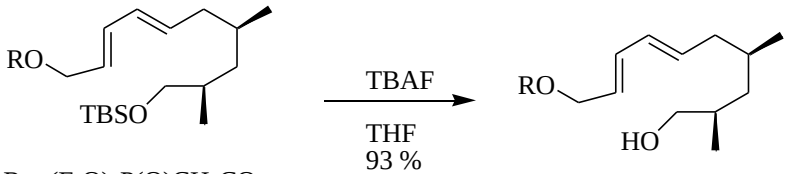
(E,E,Z)-triene 243. To a stirred solution of **241** (27.2 mg, 0.0794 mmol) in THF (1 mL) was added 18-crown-6 (24.5 mg, 0.0926 mmol) and cooled at 0 ^{o}C. To the reaction mixture was added dropwise KHMDS (0.08 mL, 0.08 mmol, 1 M in THF) and stirred at 0 ^{o}C. The mixture was cooled to -78 ^{o}C and aldehyde **239** (6.3 mg, 0.026 mmol) solution in THF (1 mL) was added dropwise and the syringe was rinsed with THF (0.05 mL). The resulting mixture was stirred for 1

h at -78 ^{o}C and stored at -25 ^{o}C for 15 h. It was quenched with saturated aq. NH_4Cl (0.5 mL) and EtOAc (3 mL) was added. The aqueous phase was extracted with EtOAc (3 mL X 2). The combined organic mixture was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide **242** (6.2 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 15.6, 10.1 Hz, 1H), 6.10 - 5.84 (m, 2H), 5.82 - 5.58 (m, 3H), 4.57 (d, *J* = 6.6 Hz, 2H), 4.16 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.65 (tt, *J* = 10.5, 5.3 Hz, 1H), 2.06 (d, *J* = 1.3 Hz, 4H), 1.94 (dq, *J* = 14.1, 6.7 Hz, 1H), 1.57 (d, *J* = 1.3 Hz, 1H), 1.44 (tq, *J* = 13.4, 7.4 Hz, 1H), 1.35 - 1.19 (m, 4H), 1.19 - 0.82 (m, 7H).



233 **245**

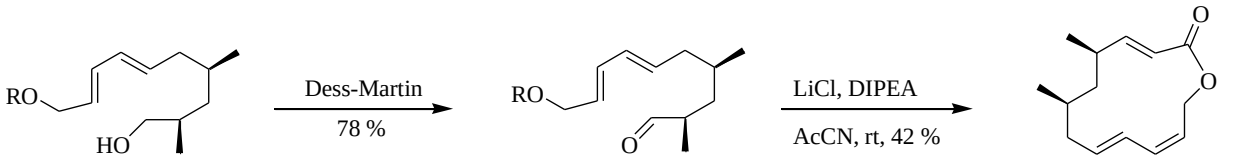
Phosphorane 245. To a stirred solution of the crude alcohol **233** (28.0 mg, 0.090 mmol) in CH_2Cl_2 were added pyridine (14.2 mg, 0.179 mmol), CBr_4 (44.6 mg, 0.134 mmol), PPh_3 (32.9 mg, 0.125 mmol), and acid **244** (21.0 mg, 0.108 mmol). The mixture was stirred for 18 h and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7 to 1 : 2) to provide **245** (17.5 mg, 60 %, b.r.s.m) and recovered **233** (9.4 mg). δ 6.27 (dd, *J* = 15.3, 10.4 Hz, 1H), 6.01 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.76 - 5.58 (m, 2H), 4.64 (d, *J* = 6.7 Hz, 2H), 4.16 (m, 4H), 3.42 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.33 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.00 (d, *J* = 24, 2H), 2.13 - 2.07 (m, 1H), 1.90 - 1.83 (m, 1H), 1.70 - 1.57 (m, 3H), 1.34 (m, 7H), 0.90 (s, 9H), 0.87 (d, *J* = 1.6 Hz, 3H), 0.86 (d, *J* = 2.0 Hz, 3H), 0.2 (s, 6H). IR (neat) ν_{max} 3419, 2956, 1738, 1443 cm^{-1}.



R = $(EtO)_2P(O)CH_2CO_2$-

245 **246**

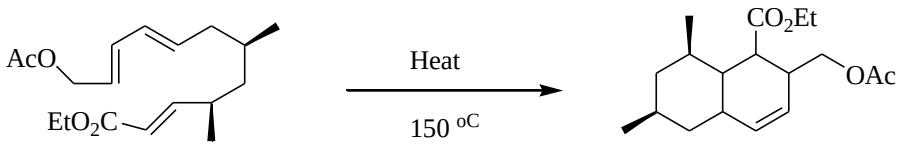
Alcohol 246. To a stirred solution of **245** (17.4 mg, 0.0355 mmol) in THF (1.5 mL) was added TBAF (0.09 mL, 0.09 mmol, 1.0 M in THF). The reaction mixture was stirred for 15 h at rt and it was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 2 to 1 : 1) to provide **246** (7.1 mg, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.02 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.68 (ddt, *J* = 34.8, 14.7, 7.0 Hz, 2H), 4.65 (d, *J* = 6.7 Hz, 2H), 4.17 (quint, *J* = 7.3 Hz, 4H), 3.53 - 3.37 (m, 2H), 2.98 (d, *J* = 21.6, 2H), 2.16 - 2.09 (m, 1H), 1.89 (dt, *J* = 14.6, 7.7 Hz, 1H), 1.79 - 1.61(m, 2H), 1.43 (s, 3H), 1.34 (t, J = 7.2 Hz, 6H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).



246 **247** Macrolactone **(216)**

Aldehyde 216. To a stirred solution of **246** (5.3 mg, 0.014 mmol) in CH_2Cl_2 (2.0 mL) was added Dess-Martin periodinane (9.0 mg, 0.021 mmol). The reaction mixture was stirred for 5 h at rt and it was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 1) to provide **247** (4.1 mg, 78 %). To a stirred solution of **247** (4.1 mg, 0.011 mmol) in CH_3CN (10.0 mL) was added LiCl (10.0 mg, 0.229 mmol) and DIPEA (28.3 mg, 0.219 mmol). The reaction mixture was stirred. After 3 days, it was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford **216** (1.0 mg, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (ddd, *J* = 15.8, 8.6, 1.8 Hz, 1H), 6.25 (t, *J* = 12.9 Hz,

1H), 6.09 - 5.98 (m, 1H), 5.81 - 5.63 (m, 3H), 4.72 (dd, *J* = 13.5, 6.1 Hz, 1H), 4.61 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.42 (s, 1H), 1.97 (q, *J* = 8.0 Hz, 1H), 1.43 (m, 2H), 1.15 - 0.97 (m, 4H), 0.91 (dd, *J* = 19.6, 6.3 Hz, 3H).



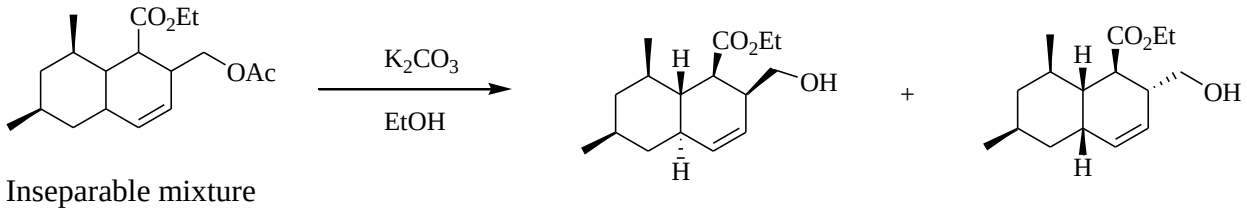
(E,E,E)-triene

242

Mixture of 2 diastereomers

248

Diastereomer mixture 248. The solution of **242** (11.5 mg, 0.037 mmol) in toluene (3.7 mL) was heated to 150 ^{o}C for 20 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to afford the mixture **248** (8.4 mg, 73 %).



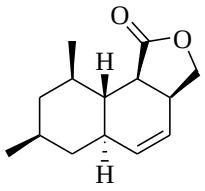
Inseparable mixture

248

253

254

spontaneous



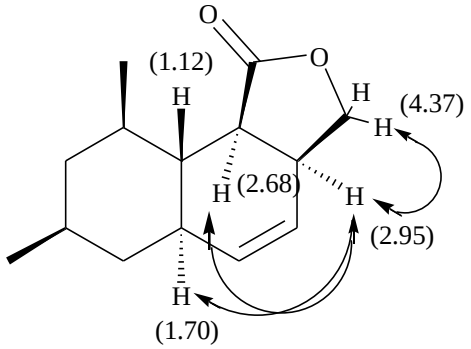
255

Lactone 255 and alcohol 254. To a stirred solution of the mixture of **248** (8.4 mg, 0.027 mmol) in absolute EtOH (1.5 mL) was added K_2CO_3 (2.5 mg, 0.018 mmol). The reaction mixture was stirred for 11 h. It was quenched with saturated aq. NH_4Cl and Et_2O was added. The mixture was concentrated under reduced pressure. To residue was added CH_2Cl_2 and water. The organic layer was separated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford the mixture **255** (2.9 mg, 35 % for 2 steps) and **254** (3.4 mg, 34 %).

255 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dt, *J* = 9.3, 3.0 Hz, 1H), 5.64 (dt, *J* = 9.3, 2.8 Hz, 1H), 4.41 - 4.21 (m, 2H), 2.96 (ddt, *J* = 8.4, 5.8, 2.8 Hz, 1H), 2.72 - 2.62 (m, 1H), 1.94 - 1.84 (m, 1H), 1.78 - 1.64 (m, 2H), 1.55 (s, 5H), 1.41 (tdd, *J* = 12.8, 6.2, 4.2 Hz, 1H), 1.32 - 0.68 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 139.1, 127.7, 71.6, 46.0, 44.9, 43.8, 40.8, 39.6, 38.4, 36.76, 32.2, 22.3, 20.1.; IR (neat) ν_{max} 2915, 1765, 1456 cm^{-1}.

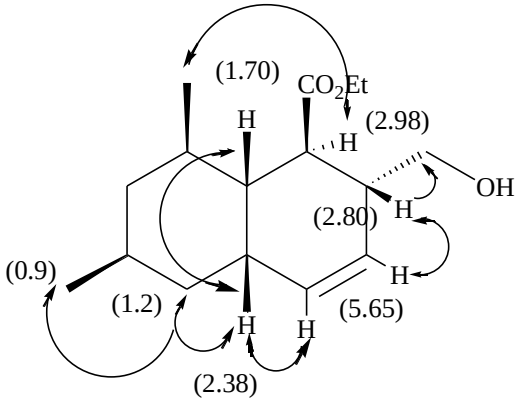
254 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 - 5.53 (m, 2H), 4.15 (qd, *J* = 7.1, 4.7 Hz, 2H), 3.69 (dd, *J* = 10.5, 6.4 Hz, 1H), 3.50 (t, *J* = 9.7 Hz, 1H), 2.98 (t, *J* = 2.4 Hz, 1H), 2.77 (ddt, *J* = 9.0, 6.1, 2.8 Hz, 1H), 2.39 (s, 1H), 1.70 (td, *J* = 13.3, 12.7, 6.5 Hz, 2H), 1.63 - 1.46 (m, 6H), 1.33 - 1.12 (m, 5H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.69 (q, *J* = 11.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 133.1, 125.4, 65.4, 60.5, 44.4, 42.9, 41.2, 40.0, 38.7, 32.6, 30.1, 27.8, 22.5 , 20.2, 14.2.

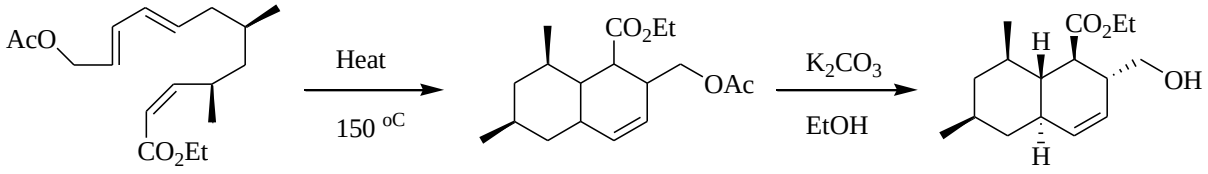
Difference NOE chart for compound **255**



Inverted peak	Enhanced peaks
2.68 ppm	2.95 ppm, 1.08 ppm
2.95 ppm	5.66 ppm, 4.38 ppm, 1.70 ppm
4.37 ppm	2.68 ppm

Difference NOESY chart for compound **254**





(E,E,Z)-triene **243**

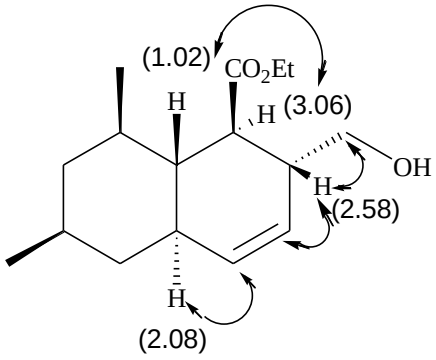
One product **256**

261

Diene 261. The solution of **243** (5.0 mg, 0.016 mmol) in toluene (3 mL) was heated to 150 ^{o}C for 21 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to afford the impure **248** (3.5 mg). Without further purification, it was used to the next reaction. To a stirred solution of the mixture of **248** (3.5 mg) in absolute EtOH (2.5 mL) was added K_2CO_3 (2.0 mg, 0.014 mmol). The reaction mixture was stirred for 11 h. It was quenched with saturated aq. NH_4Cl and Et_2O was added. The mixture was concentrated under reduced pressure. To

residue was added CH_2Cl_2 and water. The organic layer was separated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford **261** (2.0 mg, 46 % for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 - 5.63 (d, *J* = 10.0 Hz, 1H), 5.53 - 5.49 (dt, *J* = 10.0, 3.0 Hz, 1H), 4.22 - 4.02 (m, 2H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.46 (t, *J* = 9.6 Hz, 1H), 3.06 (d, *J* = 3.9 Hz, 1H), 2.58 (s, 1H), 2.08 (t, *J* = 12.0 Hz, 1H), 1.75 (ddt, *J* = 23.4, 13.2, 3.0 Hz, 2H), 1.47 (d, *J* = 33.5 Hz, 13H), 1.33 - 1.13 (m, 4H), 1.04 - 0.82 (m, 8H), 0.79 - 0.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 135.3, 123.6, 65.6, 60.0, 45.3, 44.4, 41.9, 41.3, 41.0, 36.7, 33.7, 32.2, 30.3, 22.4, 19.4, 14.3.

Difference NOE chart for compound **255**



Inverted peak	Enhanced peaks
2.58 ppm	5.55 ppm, 3.69 ppm, 3.66 ppm
3.06 ppm	1.02 ppm
2.08 ppm	5.65 ppm, 1.55 ppm

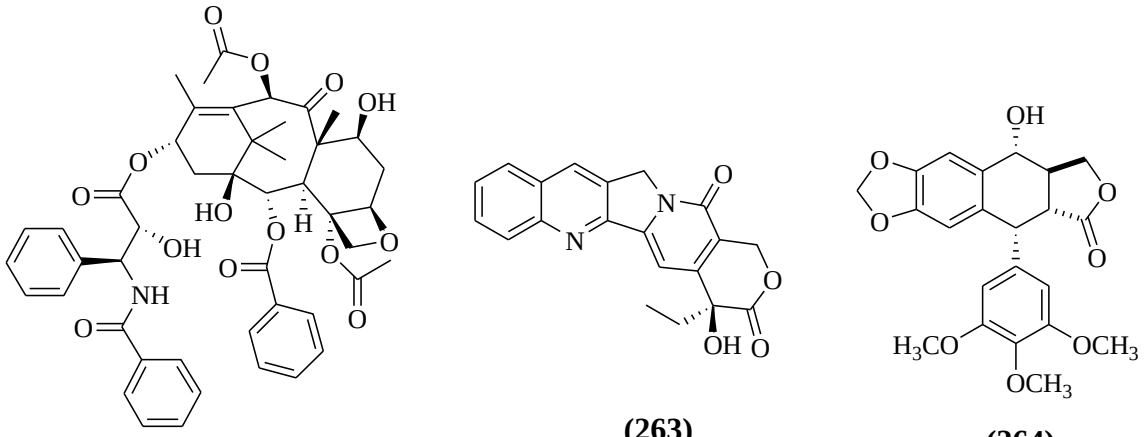
Part IV.

The Formal Synthesis of (-)-Englerin A (267) by RRCM and Etherification

4.1. Introduction

4.1.1. Background

Nature is a major source for useful medical products. Many natural products have been isolated from various natural sources ranging from plants to marine sponges; some have been developed as valuable drugs such as aspirin, penicillin and taxol (**262**) to treat a wide spectrum of human diseases. Throughout the ages, plants, in particular, have been major natural sources for important drugs. For example, the record for Egyptian medicine, which was written in "Ebers Papyrus", shows that the Egyptians used more than 700 drugs from natural sources, mostly plant origins, to treat many diseases around 1500 BCE. Until now a number of natural products from plants have been used without modification.[1] Although the number of natural compounds isolated from medical plants have been rapidly decreasing since early 1981's, they have played a pivotal role in the development of valuable drugs such as taxol (**262**), camptothecin (**263**), and podophyllotoxin (**264**) (Figure 7).[2]



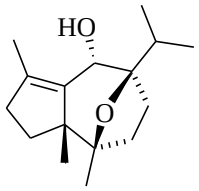
(262)
Taxol

(263)
Camptothecin

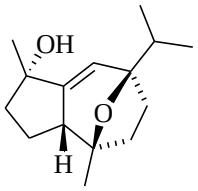
(264)
Podophyllotoxin

Figure 7. Valuable drugs from plant origin sources

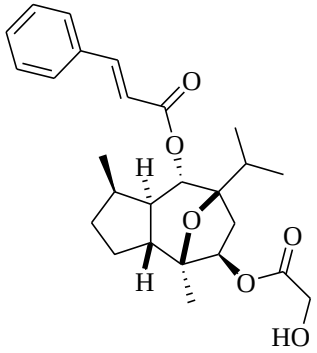
Recently, new guaiane sesquiterpenes such as (+)-oriental F (**265**)[3], (±)-pubinernoid B (**266**)[4], (-)-englerin A (**267**)[5] and (-)-englerin B (**268**)[5] were reported (Figure 8).



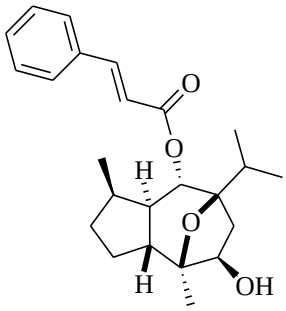
(+)-Orientalol F (**265**)



Pubinernoid B (**266**)



(-)-Englerin A (**267**)



(-)-Englerin B (**268**)

Figure 8. Guaiane sesquiterpenes

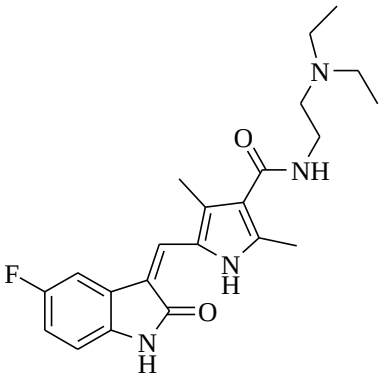
Among them, (-)-englerin A (**267**) and B (**268**) were firstly isolated from root and stem bark of *phyllanthus engleri* that is a very popular plant in East Africa, particularly Tanzania and Zimbabwe by the Beutler group in 2008.[5] Extraction yields from the plant, *phyllanthus engleri* are not high; the yields were 0.24% (2.4 g/kg) from root bark and 0.12% (1.2 g/kg) from stem bark. (-)-Englerin A (**267**) displayed excellent biological activities to inhibit the growth of kidney cancer cell lines. The Beutler group also demonstrated their structures and relative stereo configurations of (-)-englerin A (**267**) and B (**268**). They have tricyclic cores, which have also oxa-cyclic substructures and show interesting structure-activity relationship (SAR). Englerin A (**267**) and B (**268**) have almost the same structure except a substituent at C9 position (Figure 8), but Englerin B (**268**) showed low activity and selectivity for renal cancer cells. In 2009, Christmann and co-workers synthesized unnatural (+)-englerin A and confirmed an absolute

stereochemistry of (-)-englerin A (**267**).[6] Various research groups have also reported efficient strategies to provide (-)-englerin A (**267**) and its analogues.[7]

Our research group has been also interested in this unique structure and excellent bioactivity and it allowed us to invent a new process to obtain the key core structure of (-)-englerin A (**267**). We have believed that it would contribute to study preliminary structure-activity relationship (SAR) and launch a new kidney cancer drug.

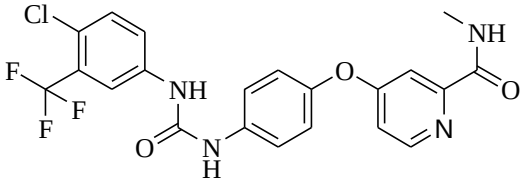
4.1.2. Biological activities of (-)-englerin A (267) and analogues of (-)-englerin A (267)

The biological activity and selectivity of (-)-englerin A (**267**) has attracted many scientists because the medical treatment of renal cancer is very difficult and challenging task and there are no satisfactory medicines. Although there are some medicines such as bevacizumab (**269**), sunitinib[8] (**270**), and sorafenib (**271**)[9] (Figure 9) to treat renal cancers, they have serious side effects or no medicinal effects.[5]



Sunitinib

(**270**)



Sorafenib

(**271**)

Figure 9. Drugs for kidney cancers

The Beutler group reported biological tests of (-)-englerin A (**267**) that showed high selective and potent for kidney cancer cell line panel at concentrations under 20 nM (Table 6).

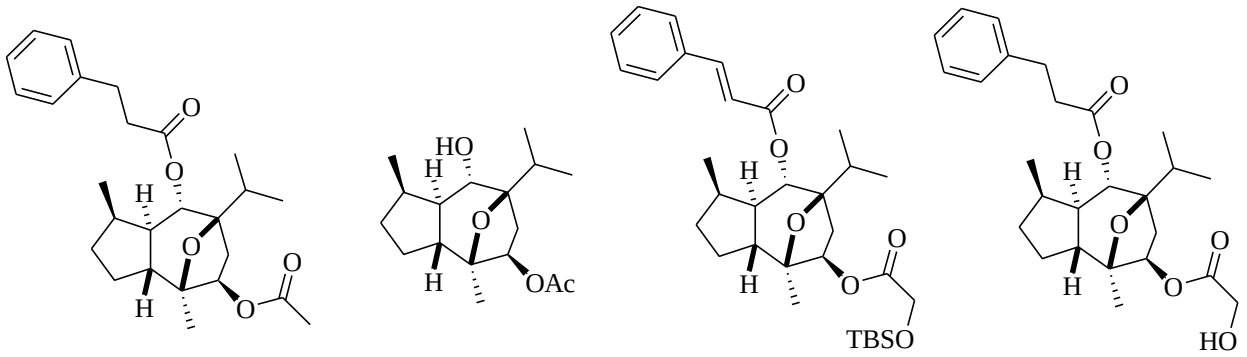
Table 6. Renal Cancer Cell Growth Inhibition Data of (-)-englerin A (**267**)

Renal cell line	(-)-Englerin A (**267**)	Taxol (**262**)
786-0	< 0.01	0.034
A498	< 0.01	0.10
ACHN	< 0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	< 0.01	0.45

(Mean GI_{50} in μM)

In addition, (-)-englerin A (**267**) and B (**268**) displayed impressive structure-activity relationship (SAR). Therefore exploring the SAR will be helpful to find and develop a new kidney cancer drug. Many research groups have prepared various analogues of (-)-englerin A (**267**) and tried to elucidate SAR.

Nicolaou and co-workers in 2010 reported biological studies for (±)-englerin A (**272**) and (±)-analogues against cancer cell lines including breast (MCF-7), lung (NCI-H460), and renal (ACHN, A498, and UO31).[10] (±)-Englerin A (**272**) displayed high potency and selectivity toward renal cancer cells. (±)-Englerin B (**273**), (±)-englerin B acetate (**274**), and (±)-analogues showed no or little activities (Figure 10) (Table 7).



274 **275** **276** **277**

Figure 10. Structures of (±)-englerin B acetate (**274**), hydroxy acetate (**275**), TBS-ether (**276**), and hydrogenated englerin A (**277**)

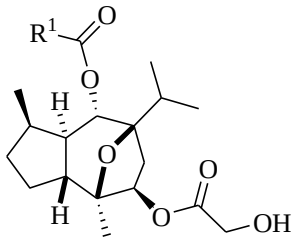
Table 7. Cytotoxicity of (±)-Englerin A (**272**) and Englerin A analogues

Compound	MCF-7	NCI-H460	ACHN	A498	UO31
Doxorubicin	0.066 ± 0.004	0.010 ± 0.000	0.072 ± 0.006	0.243 ± 0.062	0.693 ± 0.221
Taxol	0.007 ± 0.001	0.006 ± 0.001	0.076 ± 0.008	0.078 ± 0.006	0.721 ± 0.146
(±)-Englerin A (**272**)	> 10	> 10	0.113 ± 0.071	0.045 ± 0.004	0.037 ± 0.005
(±)-Englerin B (**273**)	> 10	> 10	> 10	> 10	> 10
(±)-Englerin B acetate (**274**)	> 10	> 10	> 10	6.341 ± 0.229	9.275 ± 0.013
Hydroxy acetate (**275**)	> 10	> 10	> 10	> 10	> 10
TBS-ether (**276**)	> 10	> 10	> 10	> 10	> 10
Hydrogenated englerin A (**277**)	> 10	> 10	0.745 ± 0.166	0.287 ± 0.139	0.359 ± 0.006

(GI_{50} values in μM)

Christmann and co-workers had prepared (-)-englerin A (**267**) and 32 analogues to test cytotoxicity with A498 kidney cancer cell lines to extend SAR study to find new potential compounds.[11] First, they changed cinnamoyl ester of (-)-englerin A (**267**) and found 3 analogues (**279**, **280**, and **285**) that are twice as potent as (-)-englerin A (**267**) (Figure 11) (Table 8). They

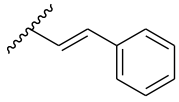
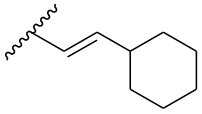
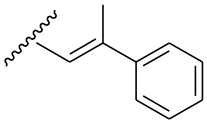
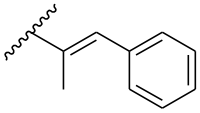
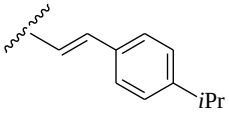
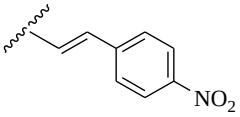
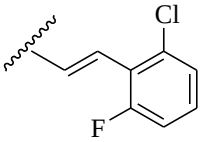
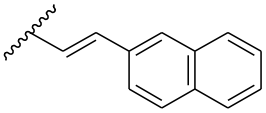
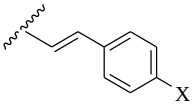
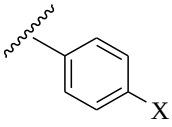
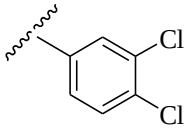
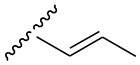
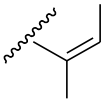
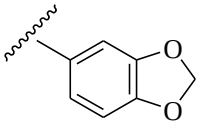
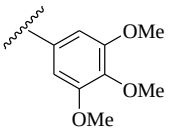
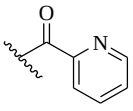
proved that cinnamoyl ester of (-)-englerin A (**267**) can be replaced and changed to improve activities.



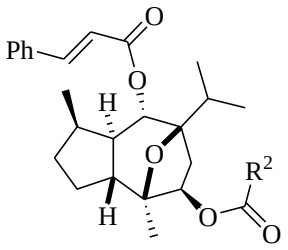
278

Figure 11. Structure of (-)-Englerin A analogues (**278**)

Table 8. The cytotoxicity of 32 englerin A analogues (**278**) was tested with the A498 by the Christmann group

<table>
<tr><th colspan="6">R^1 (IC_{50} value)</th></tr>
<tr><td> 
(-)-englerin A (267)
(45 nM)</td><td> 
279 (25 nM)</td><td> 
280 (26 nM)</td><td colspan="2"> 
281 (> 10 µM)</td></tr>
<tr><td> 
282 (> 10 µM)</td><td> 
283 (> 10 µM)</td><td> 
284 (92 nM)</td><td colspan="2"> 
285 (24 nM)</td></tr>
<tr><td rowspan="2"> 
286
X = Cl (4.59 µM)
X = Br (> 10 µM)
X = F (0.72 µM)</td><td rowspan="2"> 
287
X = H (> 10 µM)
X = Cl (1.48 µM)
X = F (> 10 µM)
X = NO_2 (1.84 µM)</td><td> 
288 (0.28 µM)</td><td> 
289 (> 10 µM)</td><td> 
290
(> 10 µM)</td></tr>
<tr><td> 
291 (4.88 µM)</td><td> 
292 (> 10 µM)</td><td> 
293
(> 10 µM)</td></tr>
</table>

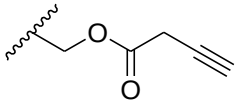
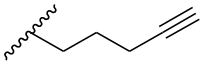
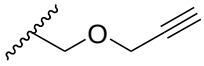
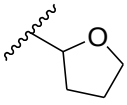
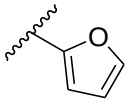
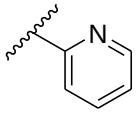
Secondly, the glycolate ester was replaced. The resulting analogues (**294**) gave extremely decreased activities (Figure 12) (Table 9). They showed that the glycolate ester part is very sensitive for a modification.



294

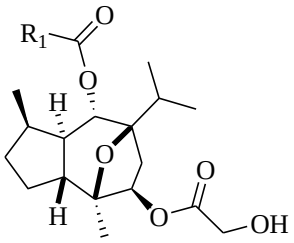
Figure 12. Structure of (-)-Englerin A analogues (**294)**

Table 9. The cytotoxicity of 32 englerin A analogues (**294**) was tested with the A498 by Christmann group

R^2 (IC_{50} value)		
 **295** (0.23 µM)	 **296** (4.61 µM)	 **297** (1.54 µM)
 **298** (5.23 µM)	 **299** (> 10 µM)	 **300** (> 10 µM)
- CH_2OMe **301** (0.65 µM)	- CH_2NHCH_3 **302** (5.04 µM)	- $CH_2N(Boc)Me$ **303** (> 10 µM)

Thirdly, replacing the isopropyl group with methyl and ethyl groups dramatically decreases biological activities. Therefore, this part is also important to obtain high activity.

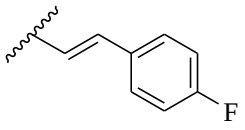
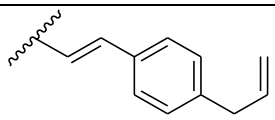
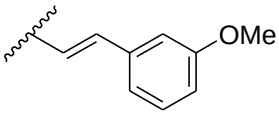
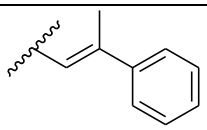
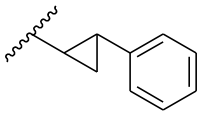
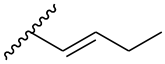
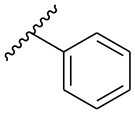
The Chan group in 2011 also introduced biological evaluation of (±)-englerin analogues.[12] They changed the cinnamoyl ester of (±)-englerin A (**272**). Analogues (**305**) and (**309**) showed similar or slightly improved activities (Figure 13) (Table 10).



304

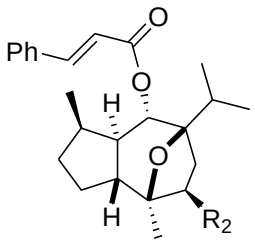
Figure 13. Structure of (±)-englerin analogues **304**

Table 10. The cytotoxicity of englerin A (**272**) analogues by the Chans group

R_1	UO31	A498	R_1	UO31	A498
(±)-englerin A (**272**)	0.037	0.045	 **305**	0.040	0.032
 **306**	0.150	0.340	 **307**	0.071	0.060
 **308**	0.014	0.086	 **309**	0.007	0.049
 **310**	> 10	> 10	 **311**	8.6	> 10

(GI_{50} values in μM)

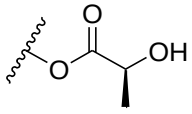
They also replaced the glycolate . However, two analogues **313** and **314** gave no activities (Figure 14) (Table 11). Although these analogues did not give significant improvement of activities, they showed a role of structure of (±)-englerin A (**272**).



312

Figure 14. Structure of (±)-Englerin A analogues (**312**)

Table 11. The cytotoxicity of englerin A analogues (**312**) by the Chan group

R_2	UO31	A498	R_2	UO31	A498
- $CH_2OC(O)CH_2OH$ **313**	> 10	> 10	- CO_2H **314**	> 10	> 10
- $C(O)OCH_2CH_2OH$ **315**	0.035	0.048	 **316**	0.047	0.020

(GI_{50} values in µM)

Theodorakis and co-workers finally reported SAR of truncated englerins (Figure 15).[13] Truncated englerin **317** and **319** compounds did not give any activity in A498 cancer cell, so they suggested that a five membered ring of englerin A (**267**) is essential to inhibit a growth of renal cancer cells. Antiproliferative activity of (-)-englerin A (**267**) and truncated englerin analogues in CEM T- cell acute lymphoblastic leukemia cells was also evaluated. (-)-Englerin A (**267**) and **320** that have additional rings showed no or little cytotoxicity in 20 µM, but **321** and **322** analogues, which have single ring gave high cytotoxicity against leukemia cells in low concentration (GI_{50} = 1-3 µM). They explained a role of structures of (-)-englerin A (**267**) (Figure 15).

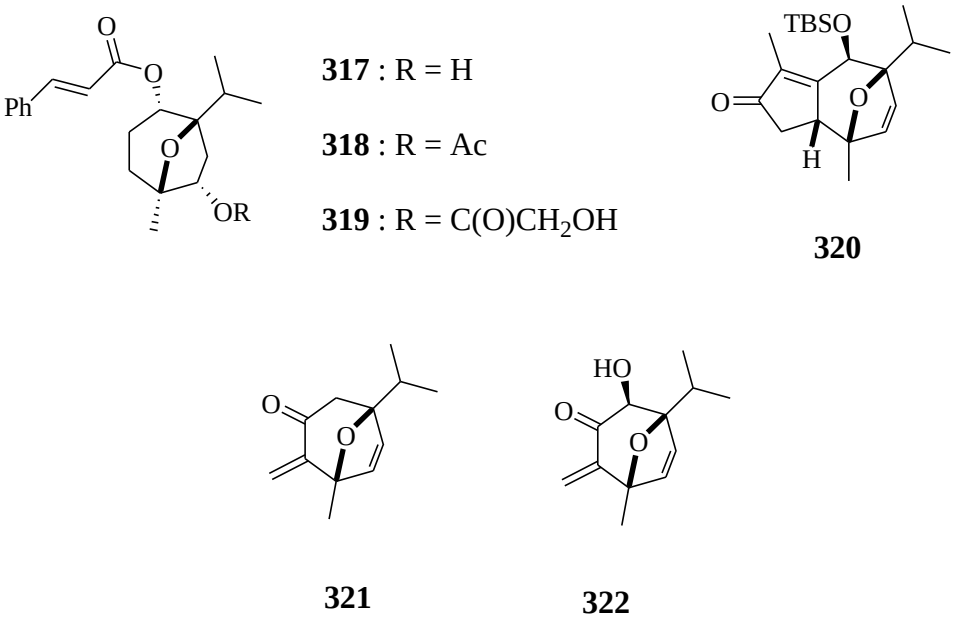
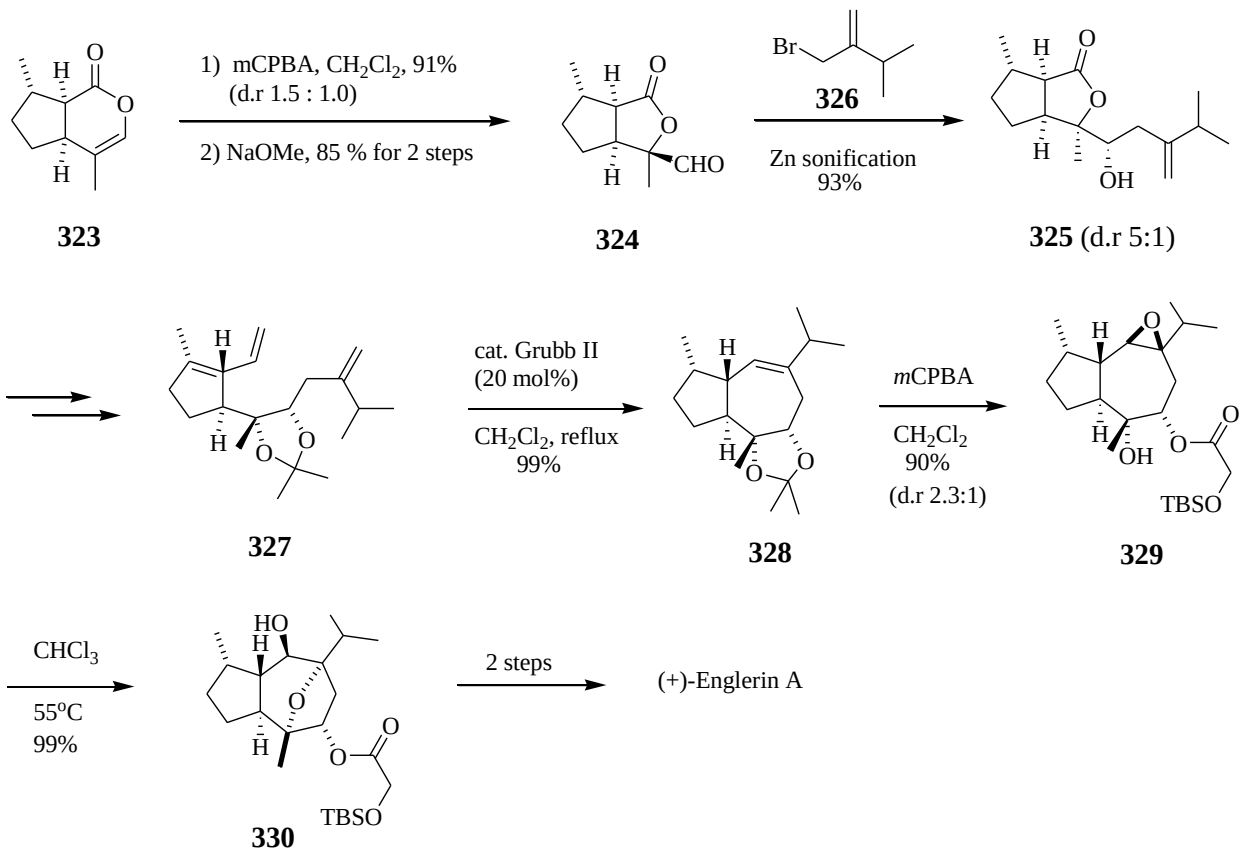


Figure 15. Structures of truncated englerins prepared by the Theodorakis group

4.1.3. Previous synthetic approaches to englerin A

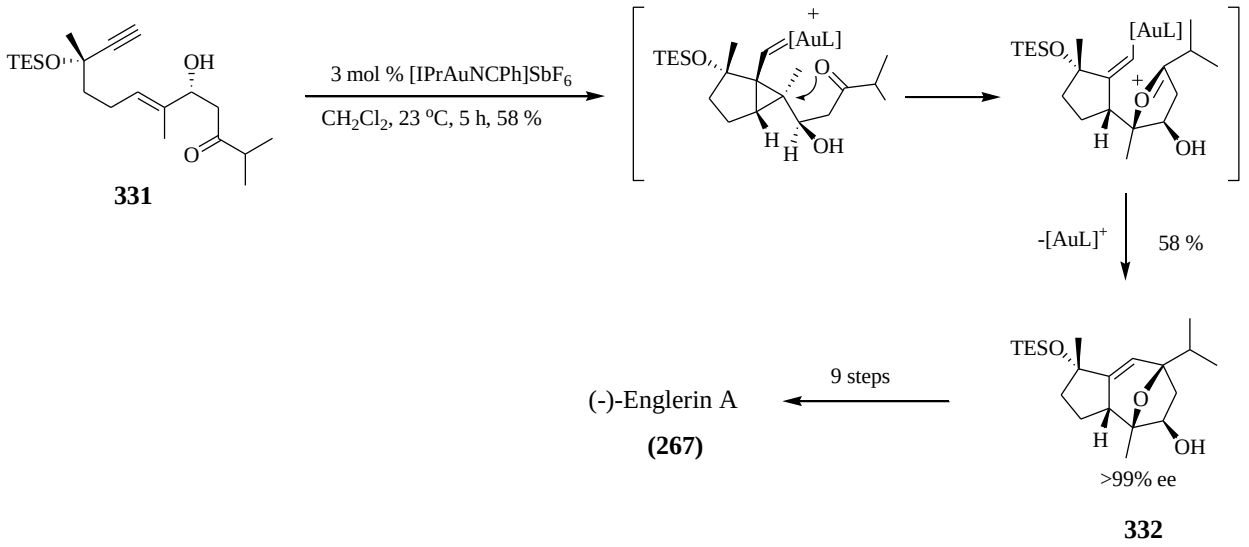
The Beutler group in 2008 reported the natural product, (-)-englerin A (**267**) and demonstrated the relative stereochemistry of this compound. The absolute configuration of (-)-englerin A (**267**) was established by Christmann and co-workers in 2009. They introduced the first synthetic route for (+)-englerin A from (+)-*cis,trans*-neopetalactone **323** using key strategies such as an epoxylactone rearrangement, a stereoselective Barbier addition, and a ring-closing metathesis (RCM) reaction (Scheme 91).[6] In addition, they demonstrated that (-)-englerin A (**267**) can be synthesized from (-)-*cis,trans*-neopetalactone (see Scheme 101) by the same strategies in 2011.[11]



Scheme 91. The total synthesis of (+)-Englerin A

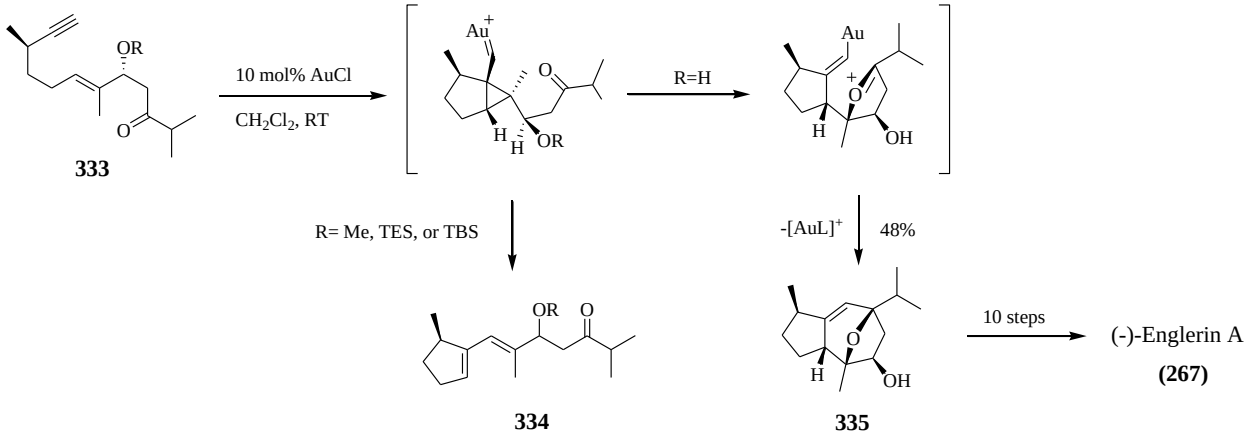
After the Christmann group identified the absolute configuration of (-)-englerin A (**267**), the research groups of Ma and Echavarren reported the total synthesis of (-)-englerin (**267**) by a gold-catalyzed cyclization in 2010.

Echavarren *et al.*[14] generated a tricyclic alcohol **332** from a protected ketone **331** by the gold-catalyzed cyclization (Scheme 92).



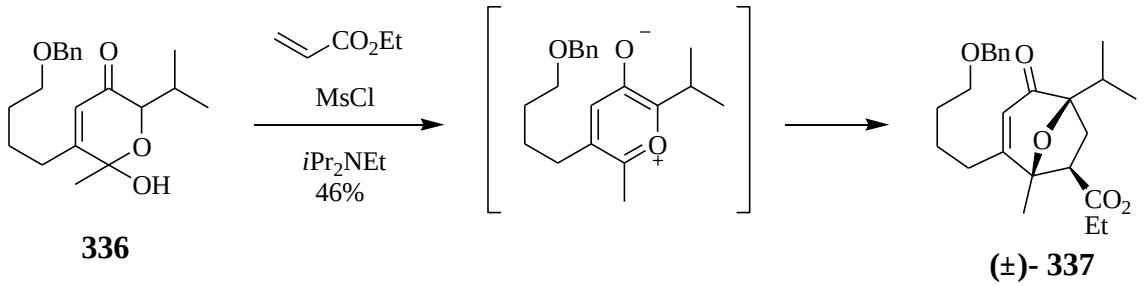
Scheme 92. The mechanism of the backbone synthesis of (-)-Englerin A (**267**) by the Echavarren group

Ma *et al*.[15] also showed the synthesis of (-)-englerin A (**267**) from an unprotected alcohol **333** by the Au-catalyzed cyclization. The tricyclic alcohol **335**, the backbone of (-)-englerin A (**267**), was constructed from the free alcohol **333** (Scheme 93).



Scheme 93. The mechanism of the backbone synthesis of (-)-Englerin A (**267**) by the Ma group

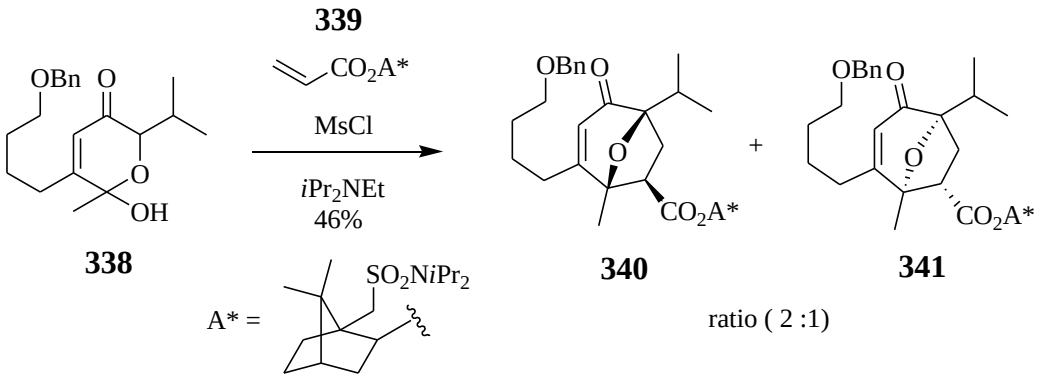
Nicolaou and co-workers introduced a [5+2] cycloaddition for the construction of a seven-membered ring (**337)** in 2010 (Scheme 94).[10]



336 **(±)- 337**

Scheme 94. The construction of the 7-memebred ring (**337)** by Nicolaou and co-workers

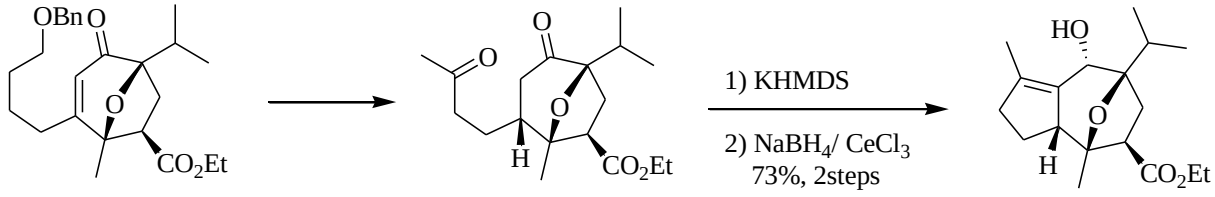
In addition, they showed stereoselective [5+2] cycloaddition using the chiral auxiliary **339** to obtain the optically pure **340** (Scheme 95).



338 **340** **341**

Scheme 95. Stereoselective [5+2] cycloaddition using the chiral auxiliary **339** by Nicolaou and co-workers

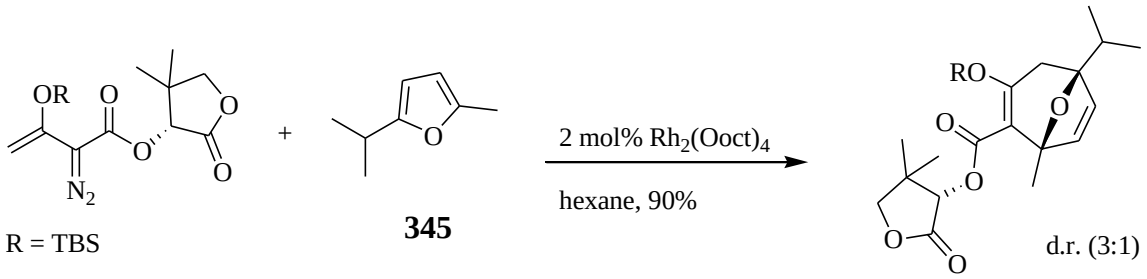
The oxatricyclic structure **343** was formed by the aldol condensation followed by reduction (Scheme 96).



(±)- 337 **342** **343**

Scheme 96. The synthesis of the oxatricyclic structure **343** by Nicolaou and co-workers

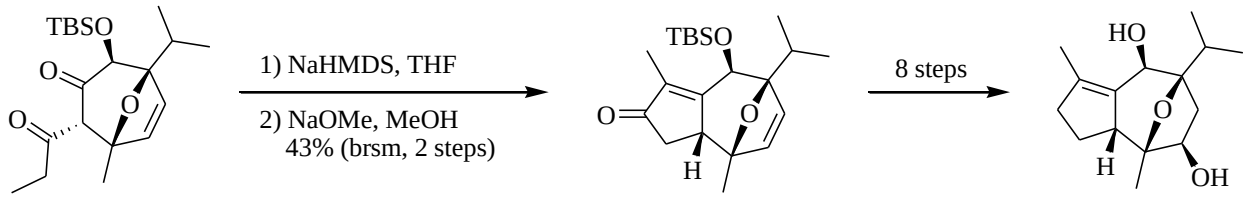
The Theodorakis group reported a formal synthesis of (-)-englerin A (**267**).[16] They used the [4+3] cycloaddition for construction of the 7-membered oxabicycle **346** (Scheme 97) and the aldol condensation to generate the tricyclic core **349** (Scheme 98). The origin of diastereoselectivity of [4+3] cycloaddition was controlled by an interaction between the carbonyl group of the auxiliary of **344** and rhodium carbenoid generated from diazo compound of **344**.



344 **345** **346**

Scheme 97. The synthesis of the oxabicycle **346** by the Theodorakis group

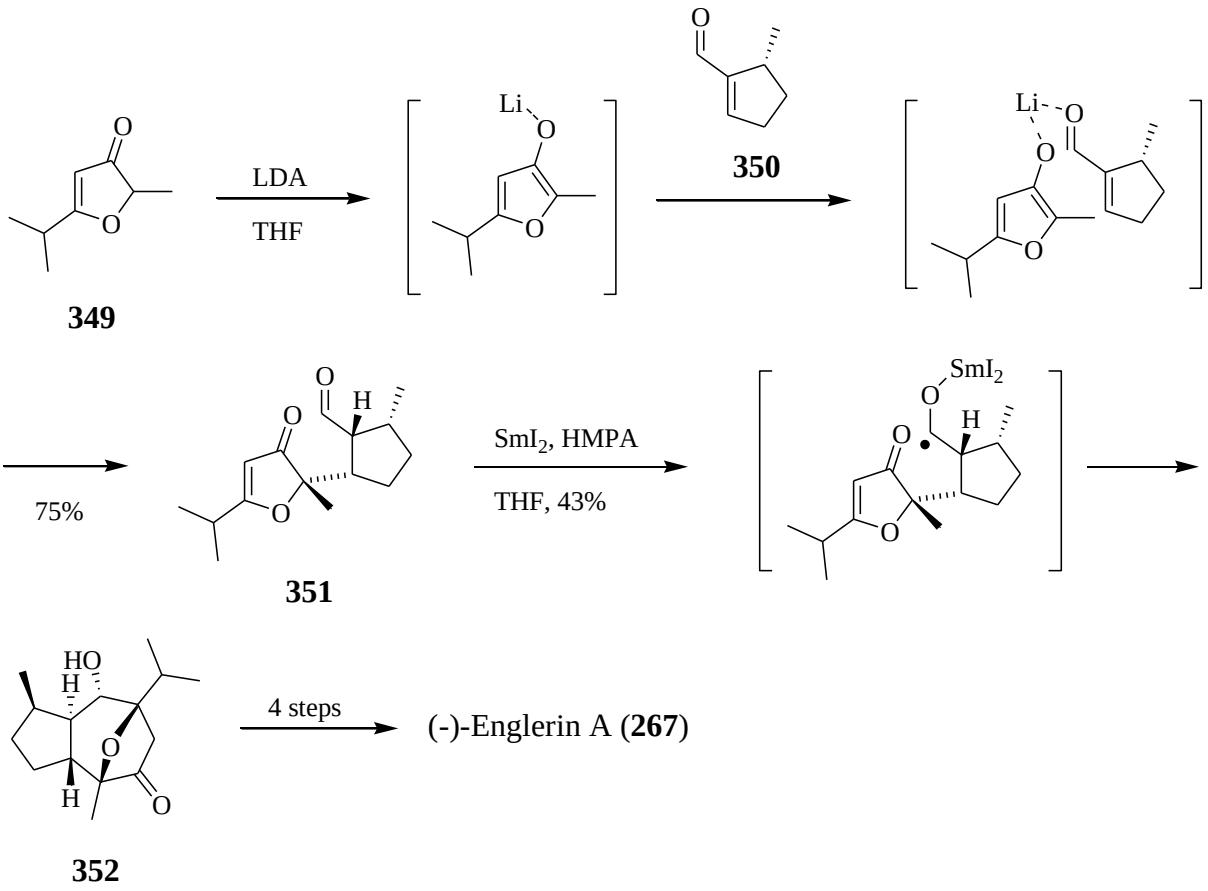
The adol condensation provided the tricyclic intermediate **348** from a diketone **347**. After 8 steps, **348** was converted to the known compound **349** reported by Ma *et al*.[15](Scheme 98).



347 **348** **349**

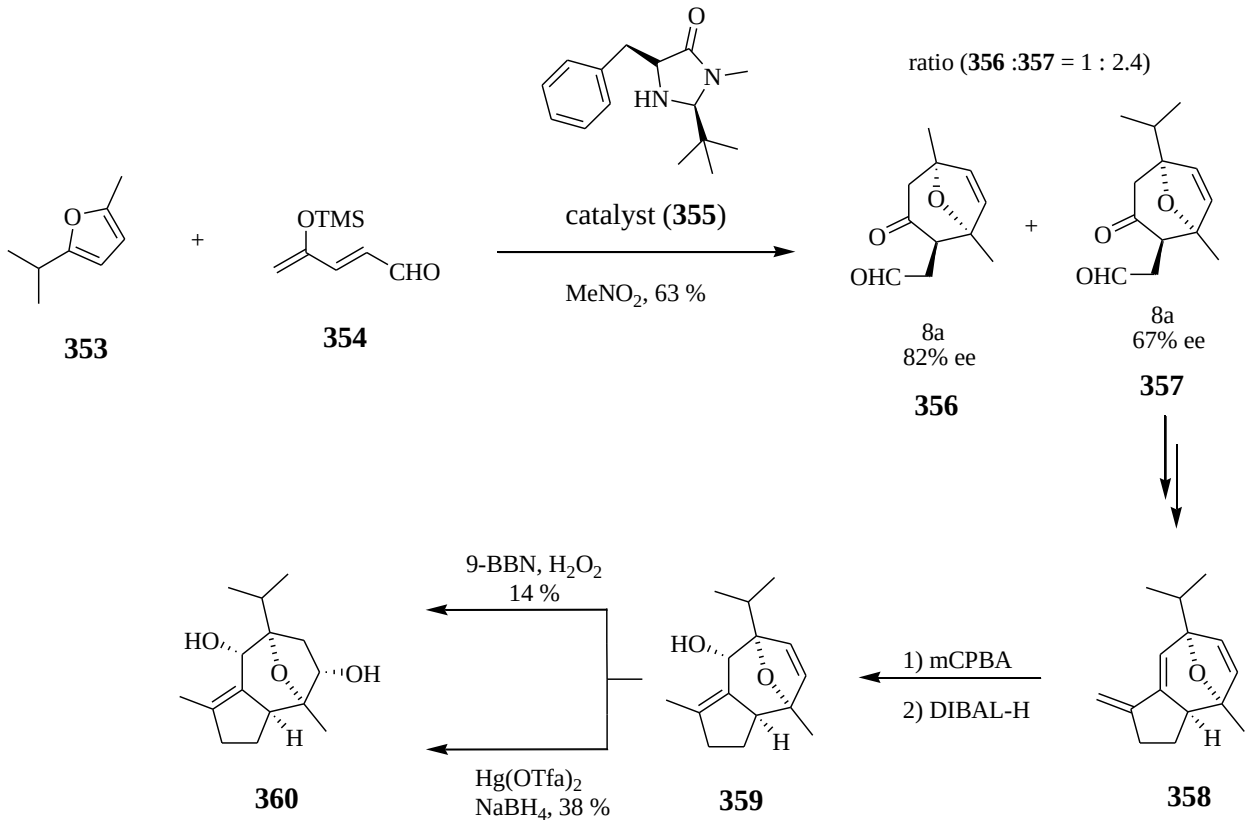
Scheme 98. The synthesis of the oxatricyclic structure **349** by the Theodorakis group

The Chain group in 2011 displayed the most efficient synthesis.[17] A 5-membered ring **351** was prepared from lithium enolates by Michael addition and 7-membered oxatricyclic core **352** was constructed through a reductive carbonyl-alkene cyclization. 3-Furanone **349** was treated with LDA to produce lithium enolate that was subjected to Michael addition with an aldehyde **350** to give inseparable 5-membered rings in favor of a desired product **351** in d.r. 2:1. A reductive carbonyl-alkene cyclization with SmI_2 gave the valuable ketone **352** that is a known compound synthesized by the Ma group.[15] It is very a concise synthetic strategy to furnish (-)-englerin A (**267**) (Scheme 99).



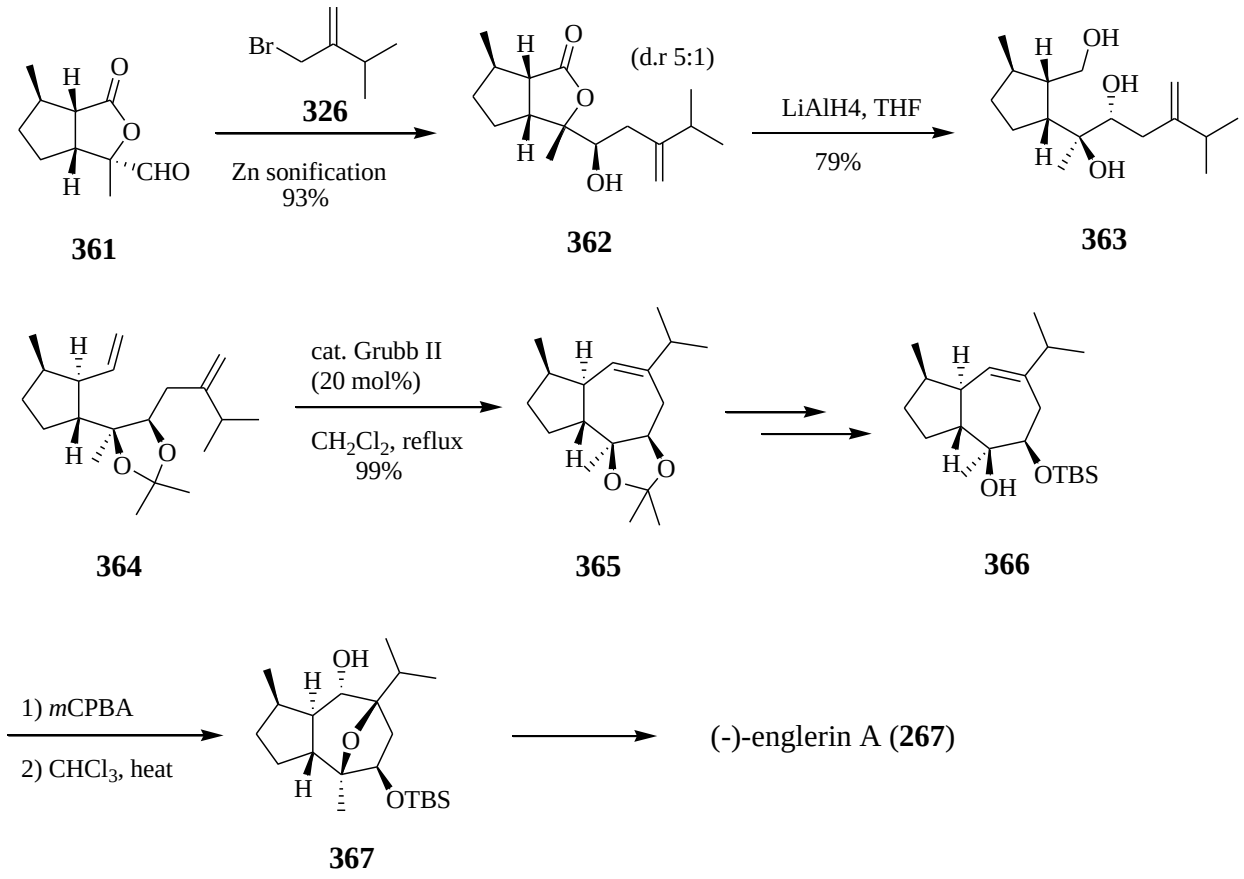
Scheme 99. The synthesis of (-)-englerin A (**267**) by the Chain group

Lin and co-workers showed a formal synthesis of (+)-englerin A by organocatalytic [4+3]-cycloaddition (Scheme 100).[18]



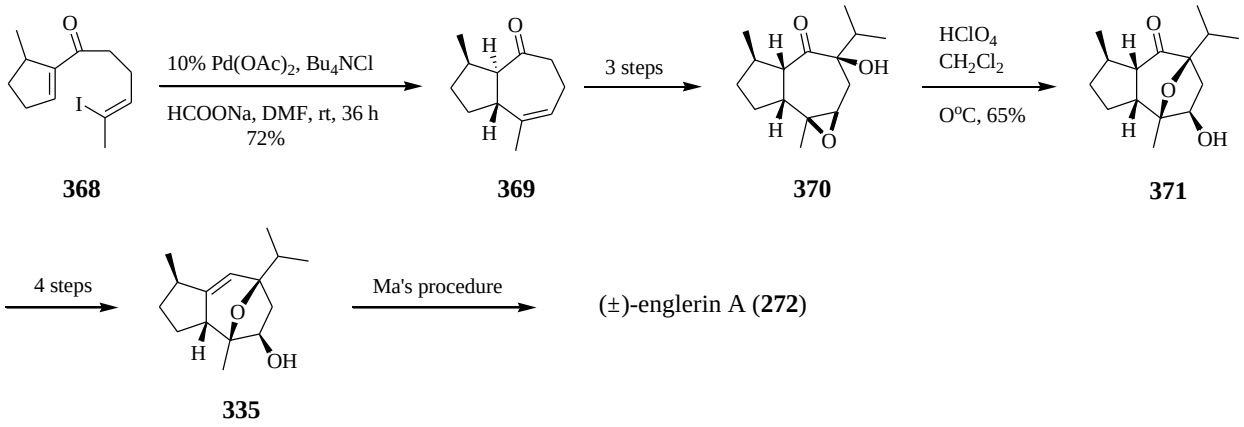
Scheme 100. Preparation of oxabicycle by organocatalytic [4+3]-cycloaddition by the Lin group

The Christmann group in 2011 used the same strategy, which was used to synthesize (+)-englerin A, to prepare (-)-englerin A (**267**) (Scheme 101).[11]



Scheme 101. The total synthesis of (-)-englerin A (**267**) by the Christmann group

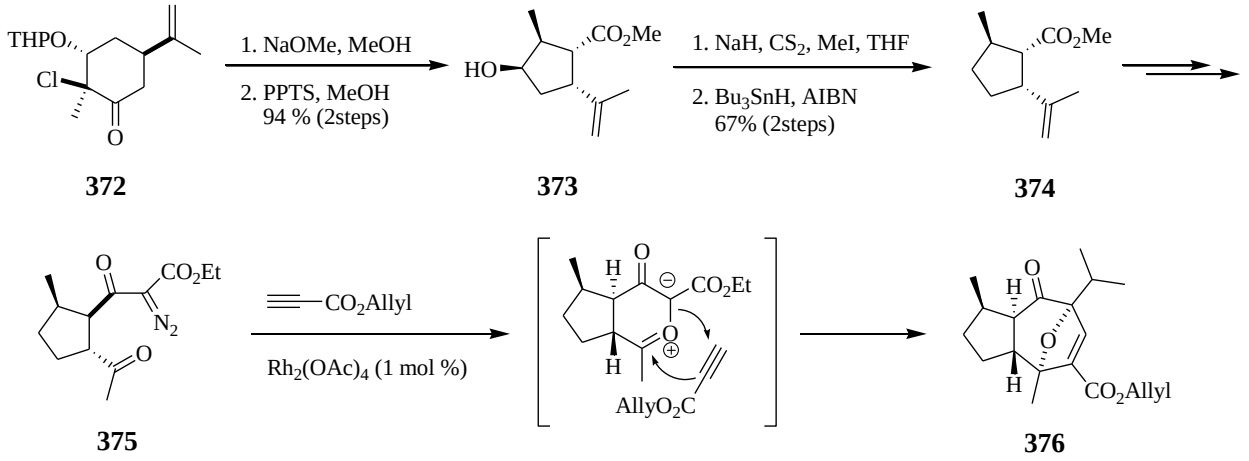
Recently, Cook and co-worker reported a reductive-Heck approach to key cores of (±)-englerin A (**272**). A hydroazulene ring **369** was constructed by the Heck reaction. They showed a preparation of a known alcohol **335** reported by the Ma group (Scheme 102).[19]



Scheme 102. The formal synthesis of (±)-englerin A (**272**) by the Cook group

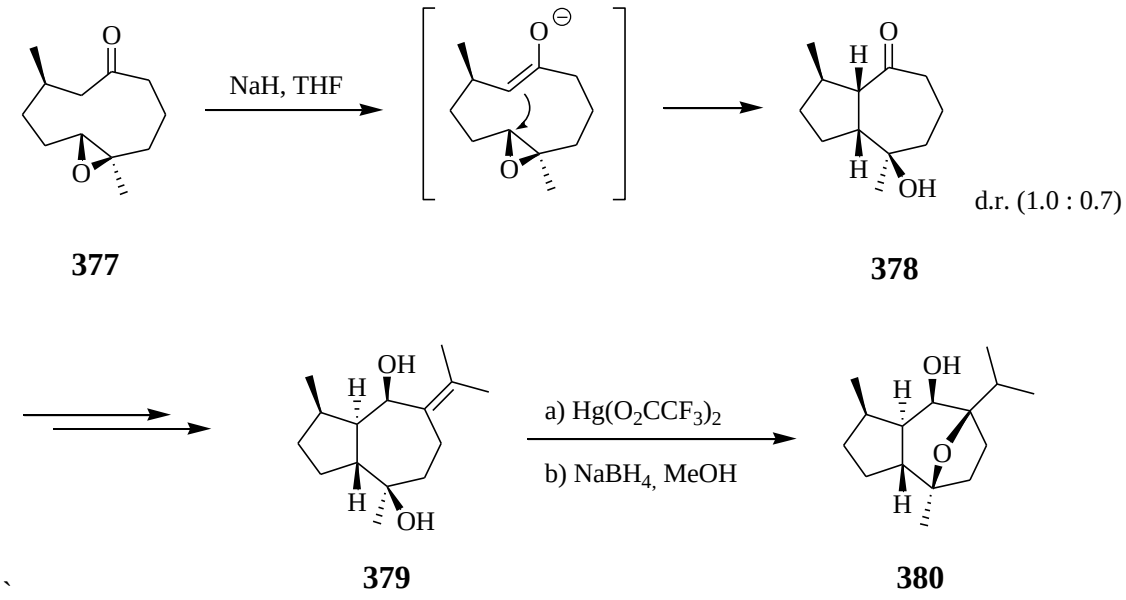
4.1.4. Previous syntheses of guaiane cores of englerins

The Maier group used carbonyl ylide-alkyne 1,3-dipolar cycloaddition to generate a oxo-bridged guaiane **376**.[20] A 5-membered ring **374** was prepared from **372** by Favorskii rearrangement and Barton-McCombie protocol. They utilized carbonyl ylide-alkyne 1,3-dipolar cycloaddition to build a 7-membered ring **376** from diazoketone **375** (Scheme 103).



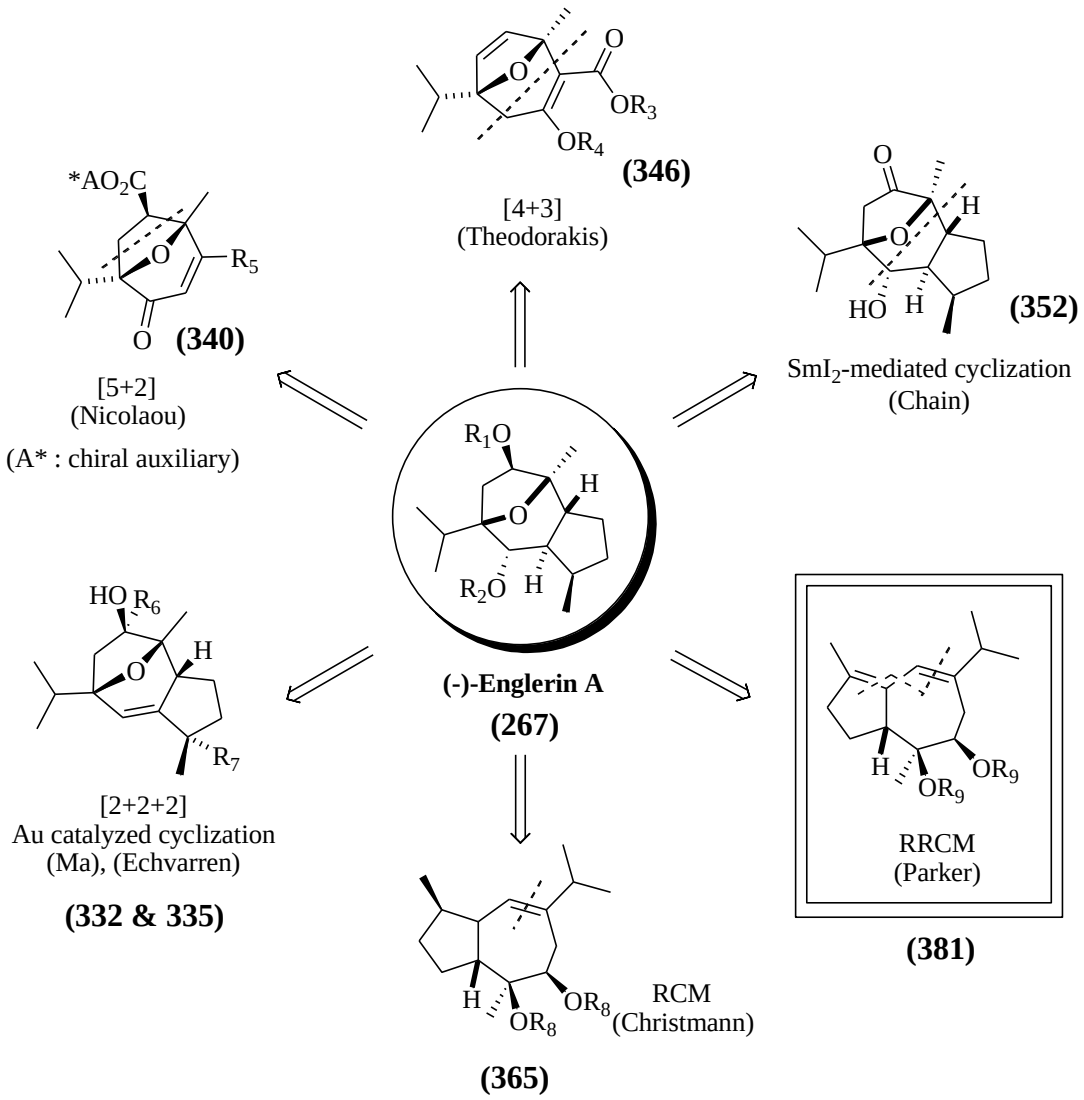
Scheme 103. Preparation of a oxo-bridged guaiane structure **376**

The synthesis of analogue, (-)-9-deoxy-englerin A (**380**) was reported by the same group (Scheme 104).[21] They used intramolecular epoxide opening of a ketone enolate for the construction of a bicyclic ketone **378**. Oxymercuration of **379** followed by reduction gave the oxygen-bridged structure **380**.



Scheme 104. Preparation of a bicyclic ketone **380**

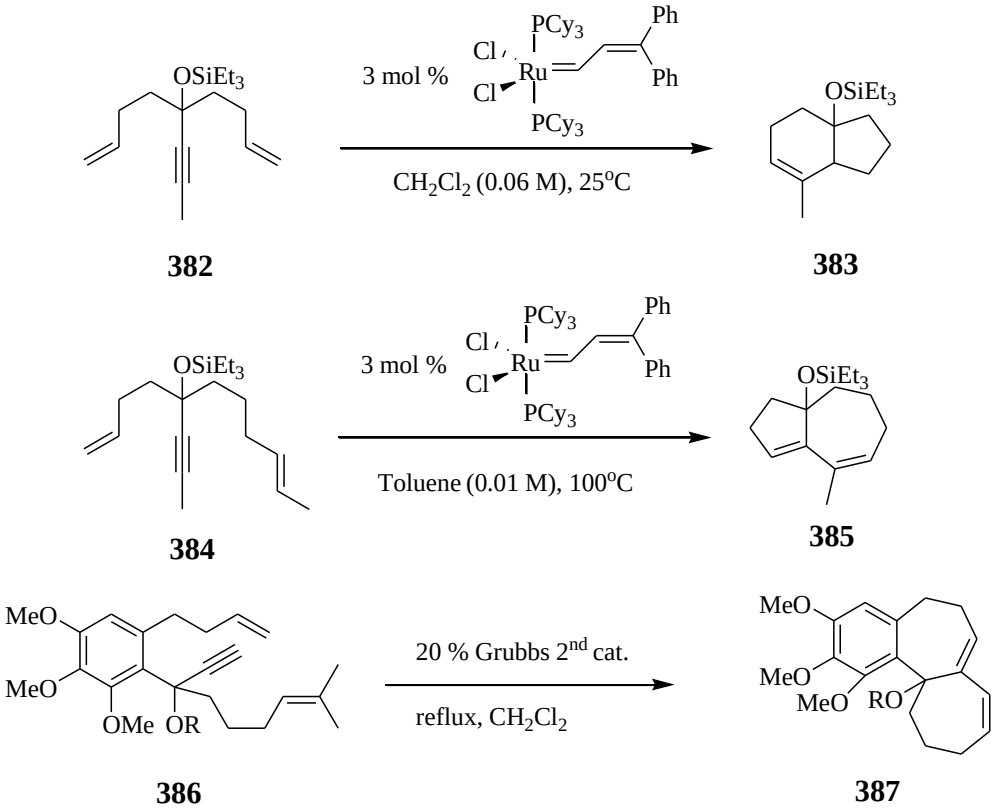
As we discussed, there have been a lot of synthetic approaches to prepare englerin A and because of selective and potential biological activities of (-)-englerin A (**267**) for renal cancer cells and studies for SAR to disclose new potential compounds from (-)-englerin A (**267**). Herein, we describe a new strategy for a formal synthesis of (-)-englerin A (**267**) by a relay ring closing metathesis (RRCM) reaction and transannular etherification.[22] Now, asymmetric syntheses of (-)-englerin A (**267**) can be summarized[23] as follows (Scheme 105).



Scheme 105. Asymmetric syntheses of (-)-englerin A (**267**)

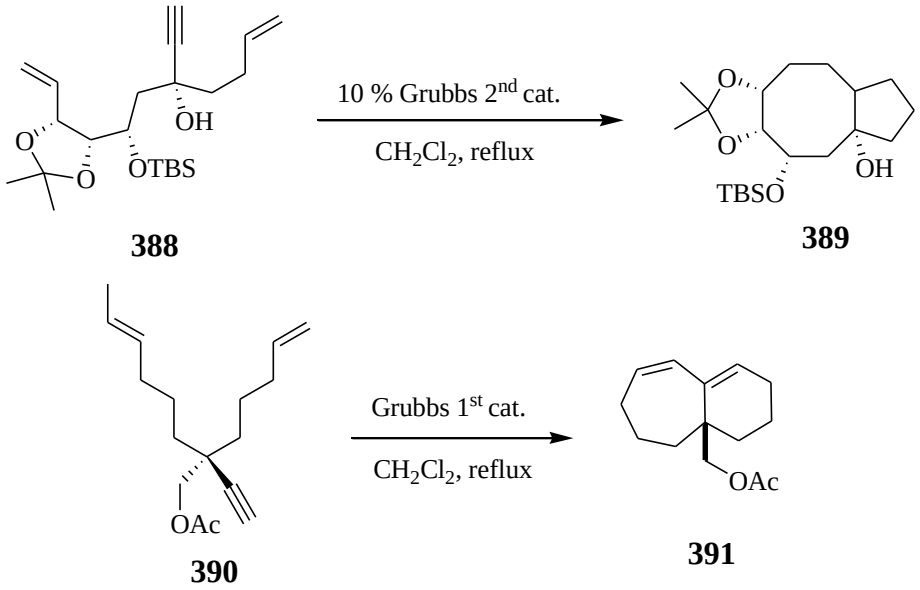
4.1.5. A new approach to a key core of (-)-englerin (267) A by RRCM and transannular etherification

A cascade metathesis has been investigated for some time and it is well known to produce easily various bicyclic dienes (Scheme 106).[24]



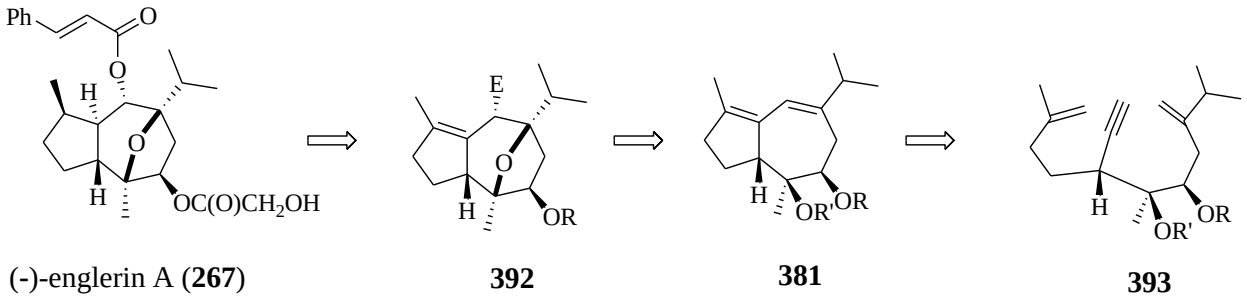
Scheme 106. Preparation of various bicyclic dienes by a cascade metathesis

There are also some examples of dienyne metathesis from optically pure dienyne (Scheme 107).[25]



Scheme 107. Examples of dienyne metathesis from optically active dienyne

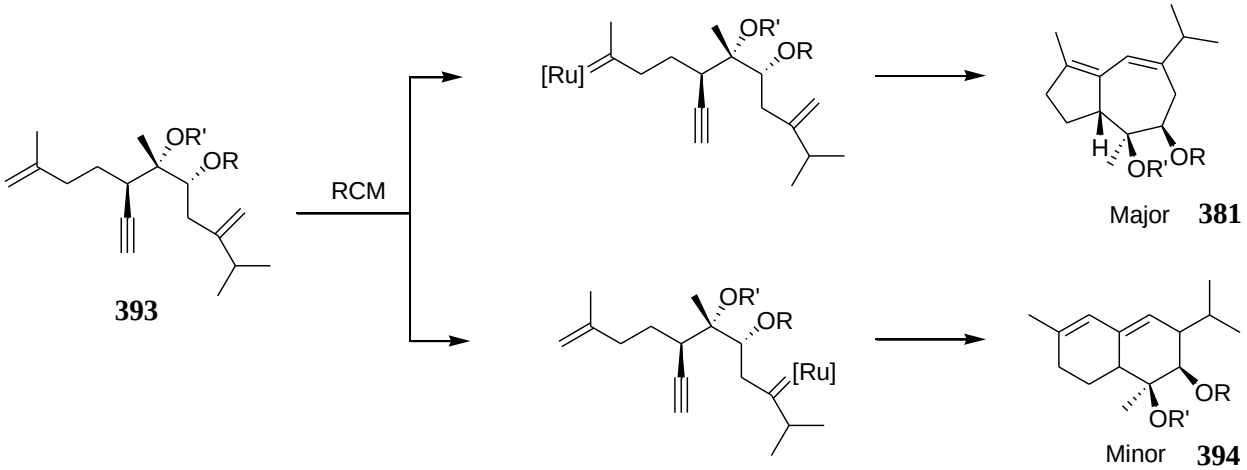
Therefore, we believed that optically active hydroazulene **381** can be prepared by ene-yne-ene metathesis and an important structure to synthesize (-)-englerin A (**267**). In addition, based on our analysis, transannular etherification was expected to produce an oxa-bicyclic structure **392** from a hydroazulene **381**, which can be probably converted to the key intermediates to synthesize (-)-englerin A (**267**) (Scheme 108).



(-)-englerin A (**267**) **392** **381** **393**

Scheme 108. Retrosynthetic analysis of (-)-englerin A (**267**) by RCM and transannular etherification

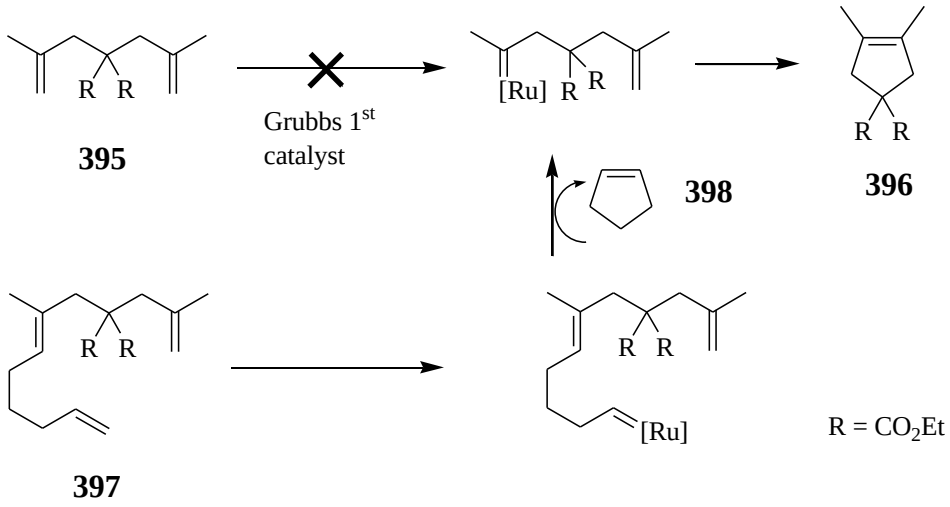
First, we designed an acetylene diol precursor **393** to obtain the hydroazulene **381** by the cascade metathesis and found two problems. A desired diene **381** would be a major product because a less hindered site might be more reactive with a catalyst, but it has a possibility to have another diene **394** (Scheme 109).



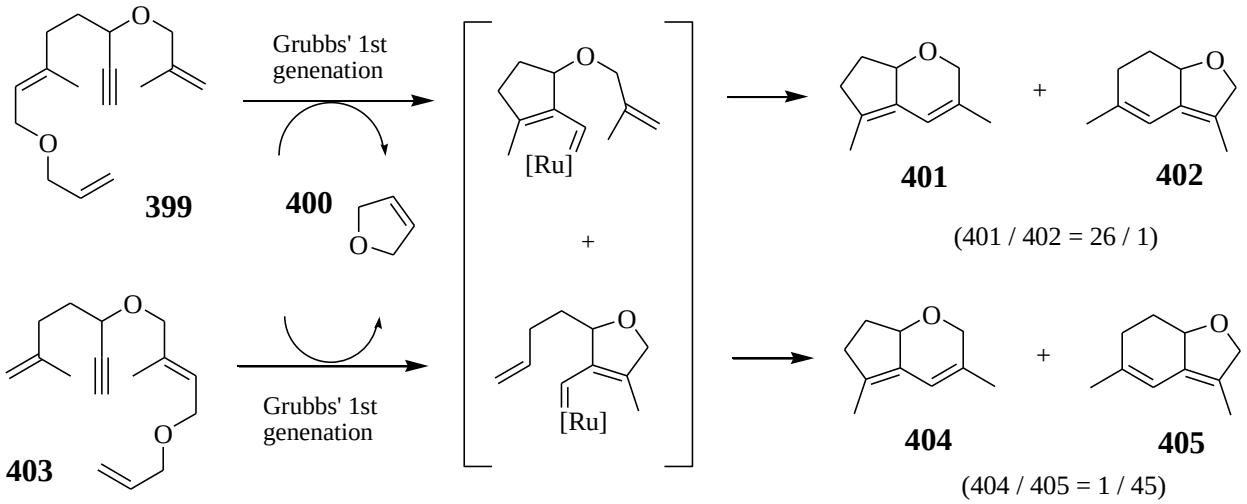
393

Scheme 109. Possible two diene products from a ring closing metathesis (RCM) reaction

In addition, it cannot be easy to initiate a ring closing metathesis because geminally substituted terminal alkenes are unreactive with a relay ring closing (RCM) catalysts. Therefore, to give more promising results, we decided to introduce a relay metathesis step to give high reactivity and regio selectivity of ene-yne-ene metathesis. Hoye and co-workers developed relay metathesis to resolve reactivity (Scheme 110) and selectivity (Scheme 111) problems of terminal alkenes **395** that are geminally substituted.[26]

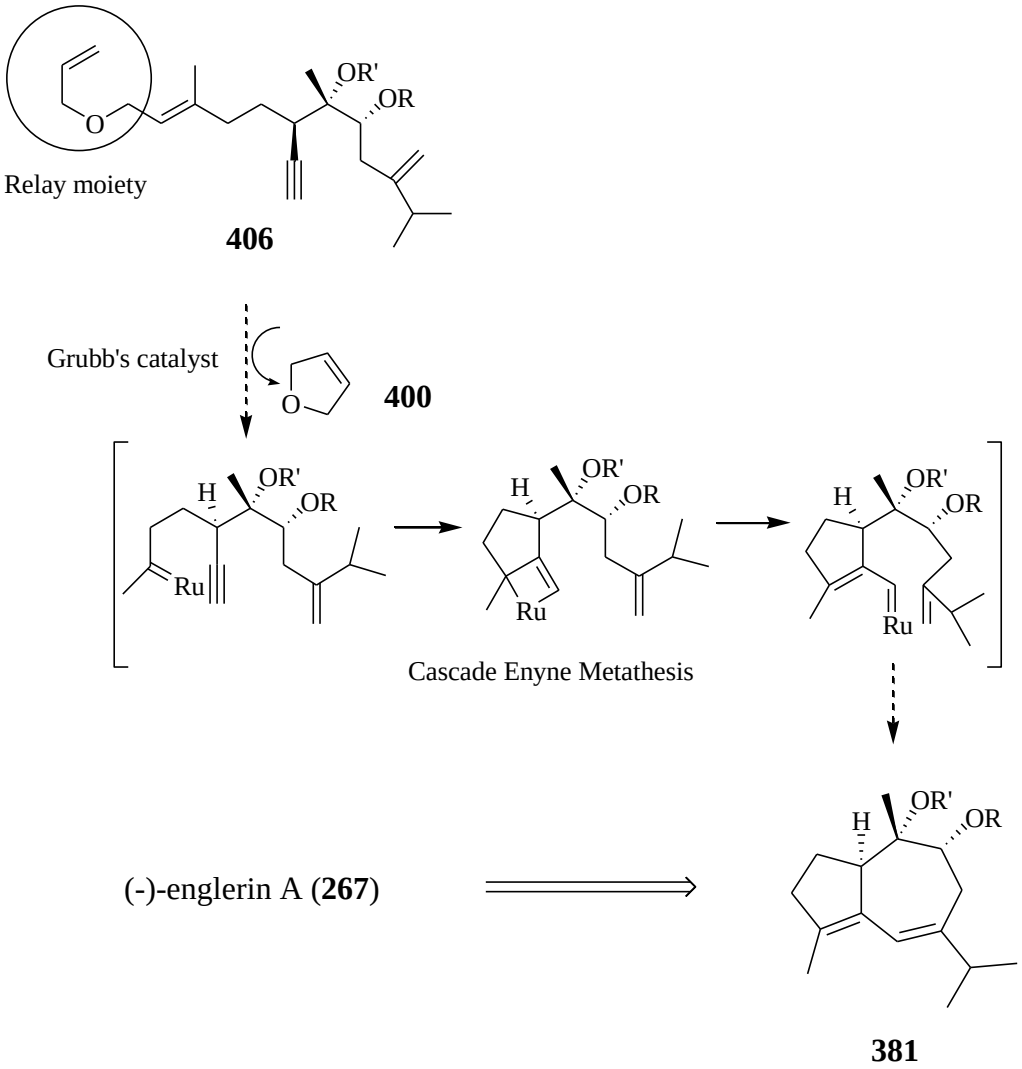


Scheme 110. The relay ring closing metathesis reaction for unreactive geminally substituted alkenes



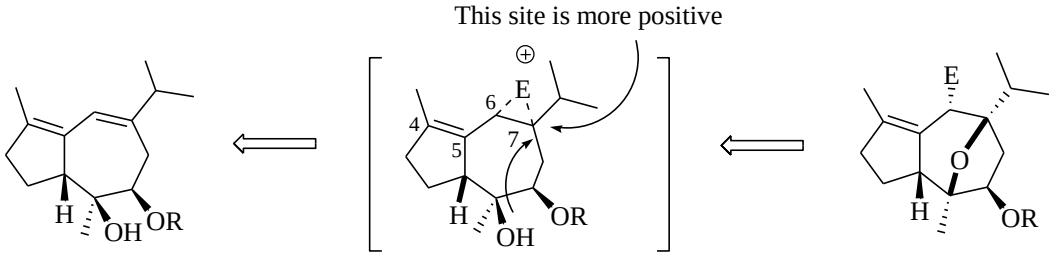
Scheme 111. Regioselectivity of the relay ring closing metathesis

Therefore, it is prudent to initiate site-specific ruthenium carbine to produce a desired diene **381**, so we decided to use the relay ring closing metathesis (RRCM) to construct hydroazulene **381** (Scheme 112).



Scheme 112. The Synthesis of the hydroazulene **381** by the RRCM reaction

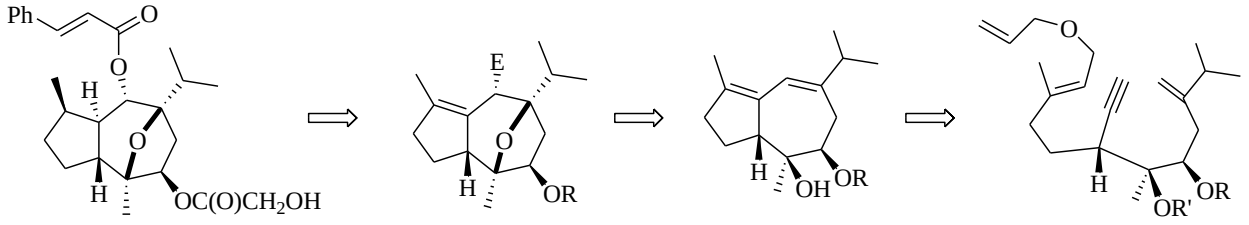
After a construction of **381**, we postulated that the oxa-bicyclic structure **392** would be approached by transannular etherification. Hydroxyl nucleophile would not only attack C-7 because this site is more positive than C-6, but also approach from front side of C-7 of unstrained conformations because backside attack would not be possible due to a ring strain (Scheme 113).



381 **392**

Scheme 113. Oxa-bicyclic structure **392** from the hydroazulene **381** by transannular etherification

Thus, the final retrosynthetic analysis of (-)-englerin (**267**) is as follows (Scheme 114).

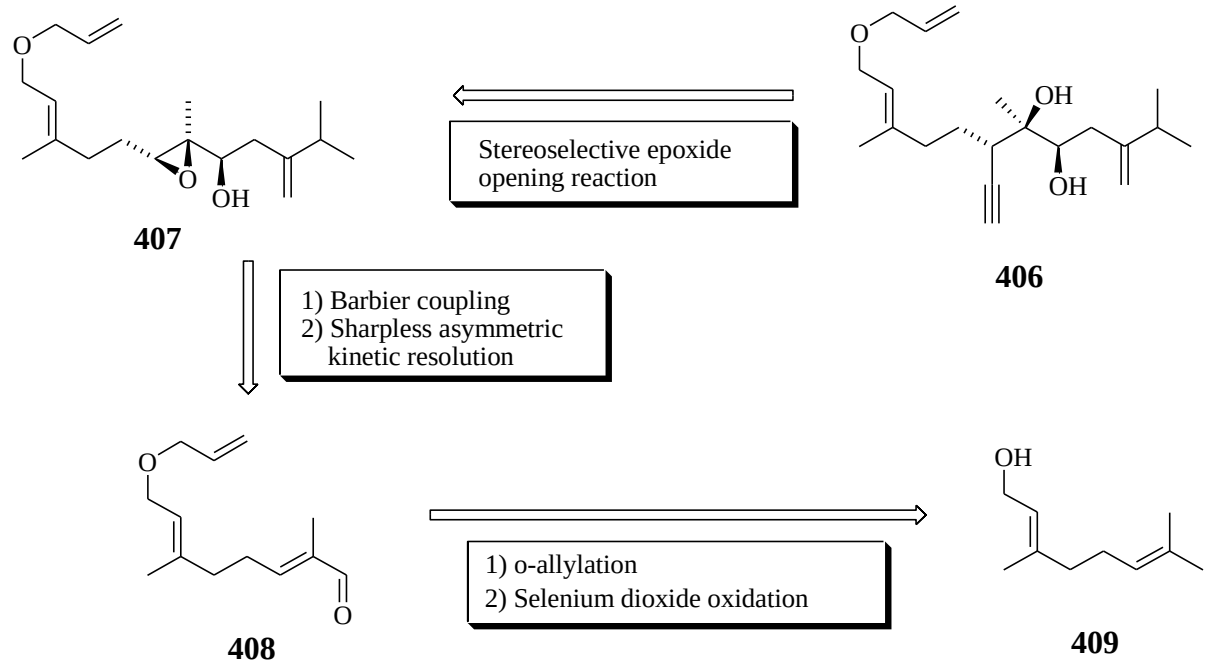


(-)-englerin A (**267**) **392** **381** **406**

Scheme 114. Retrosynthetic analysis of (-)-englerin A (**267**) by RRCM reaction and transannular etherification

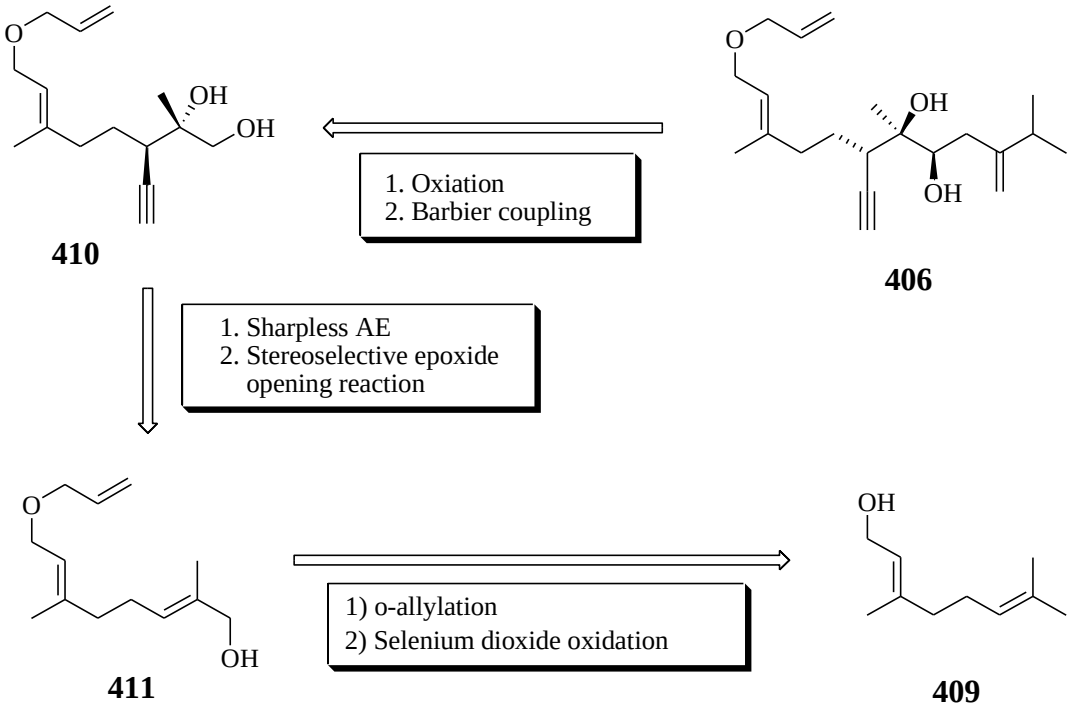
Based on our expectation, we designed two retrosynthetic strategies to access the diol **406** to prepare the hydroazulene **381**.

The first retrosynthetic plan of **406** is to use Sharpless asymmetric kinetic resolution[27] to control stereoselectivity of the hydroazulene **381** (Scheme115). An aldehyde **408** can be prepared from Geraniol **409**, a commercially available starting material, by selenium oxidation. Optically pure epoxy alcohol **407** would be obtained by Sharpless asymmetric kinetic resolution from a secondary allylic alcohol made by a Barbier addition based. Although the maximum yield would be 50 % from epoxidation, another diastereomer recovered from Sharpless epoxidation might be easily separable and reused by oxidation and stereoselective reduction. Finally, the target precursor of RRCM, diol **406**, would be prepared by stereo-, regio selective epoxide opening reaction because generally less hinder site of epoxide has more reactive in nucleophilic addition reaction.



Scheme 115. The first retrosynthetic plan to prepare diol **406**

The second retrosynthetic plan of **406** is to use Sharpless asymmetric epoxidation to introduce stereoselectivity of hydroazulene **381** (Scheme 116). Our second retrosynthetic scheme would be alternative to produce the same intermediate, the diol **406**. Herein, stereoselectivity of an epoxy alcohol could be controlled by Sharpless epoxidation and epoxide opening could provide **410**. Oxidation and a Barbier coupling reaction would produce the mixture of diastereomers **406**, but a desired diastereomer could be produced as a major product through non-chelation transition state.



Scheme 116. The second retrosynthetic plan to prepare diol **406**

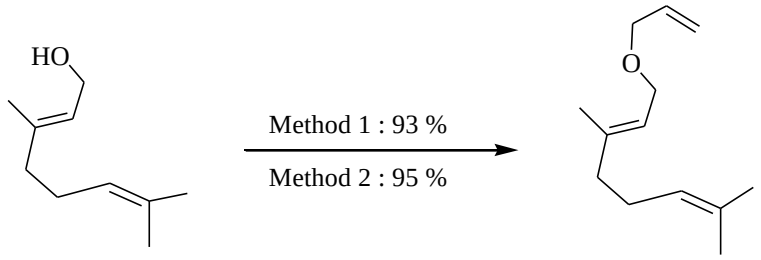
Based on our synthetic analysis of (-)-englerin A (**267**), we decided to apply the first strategies (Scheme 115) to produce acetylene diol **406**, but we found that epoxide opening of **407** did not give desired product **406**. Therefore, we have prepared three model compounds, epoxy alcohols, and investigated epoxide opening reactions. After examination, the second method (Scheme 116) was applied to obtain the hydroazulene **381** and we proved that **381** can be converted to the key structure **392** of (-)-englerin A (**267**) by transannular etherification.

4.2. Result and discussion

4.2.1. Investigation of preparation of diol acetylene (406)

4.2.1.1. The first-generation approach (Scheme 115)

To investigate a relay ring closing metathesis (RRCM) reaction to construct the hydroazulene **381**, we needed to prepare the diol **406** with a desired stereochemistry (See Scheme 112). First, allyl ether **412** was synthesized from a geraniol **409** to give a moiety of the relay ring closing metathesis by two methods (Scheme 117). Both methods gave us high yields; the 2nd method is more convenient for a large scale experiment, so we decided to use the 2nd method.



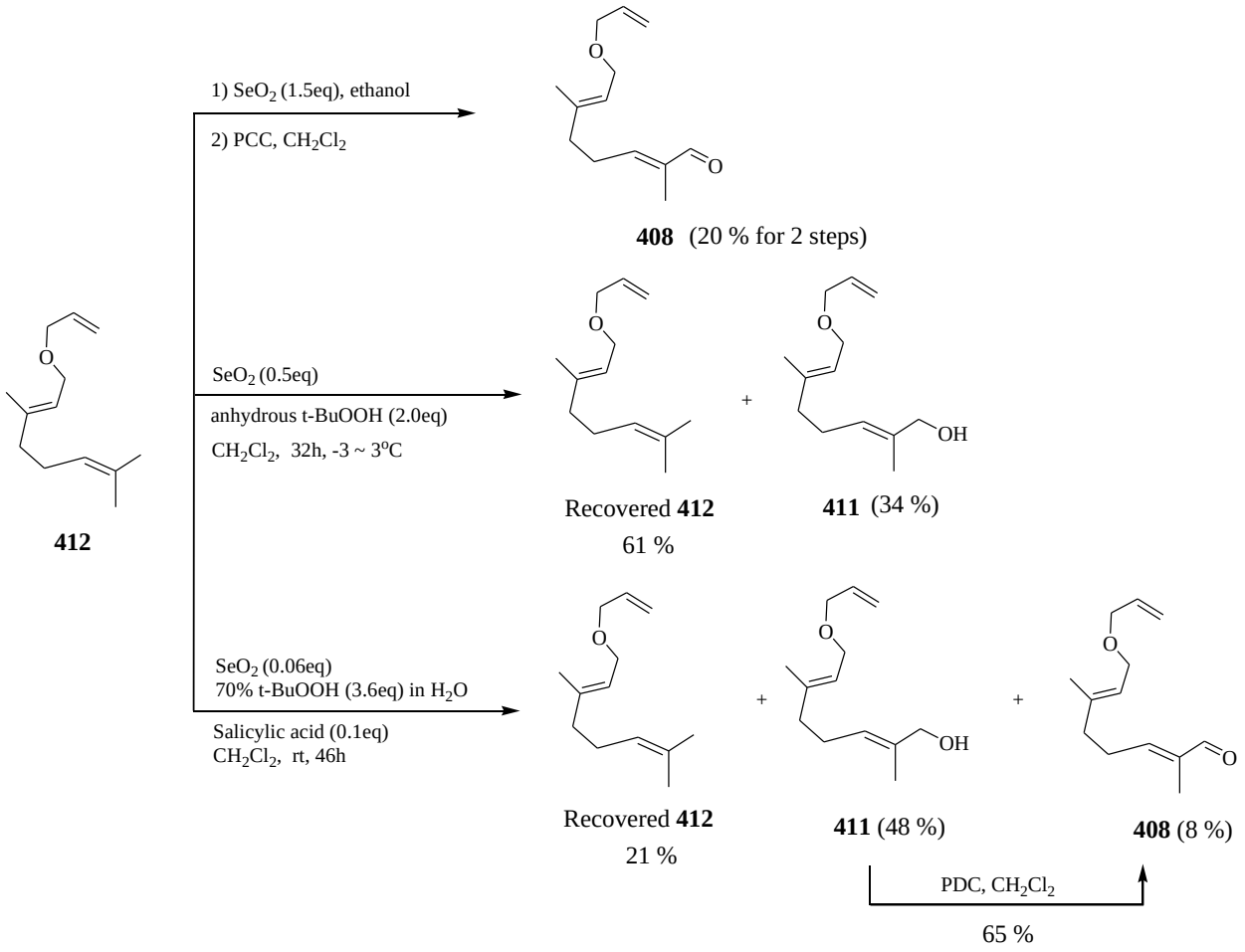
409 **412**

1st Method : allyl bromide, KOH, TBAI, no solvent, rt (Lit. Y = 91%) [28]

2nd Method : allyl bromide, NaH, THF

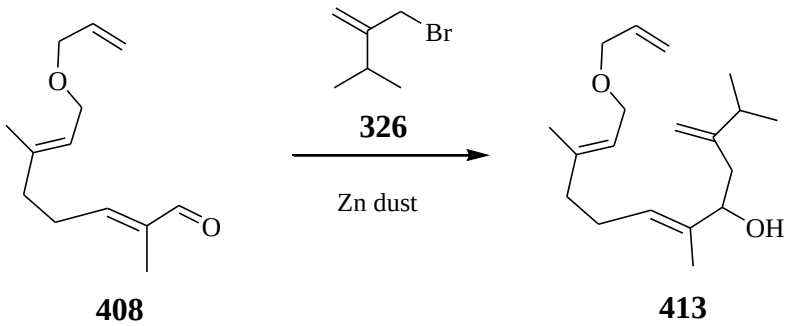
Scheme 117. Preparation of allyl ether **412**

After o-allylation of a geraniol **409**, we have explored SeO_2 oxidation to provide the aldehyde **408** from allyl ether **412**. After several examinations[29], we decided to use catalytic SeO_2 oxidation method[29b] to produce an alcohol **411** and the aldehyde **408** because other reaction conditions showed low conversion or low yield. PDC oxidation was applied to convert the alcohol **411** to the aldehyde **408** in 65 % yield (Scheme 118).



Scheme 118. SeO_2 oxidation to prepare alcohol **411** and aldehyde **408**

The aldehyde **408** was treated with 2-bromo-methyl-3-methyl-1-butene (**326**) to afford an alcohol **413** by a Barbier addition. We tested reaction conditions and found that when 3 equivalent of allyl bromide **326** was used in a solvent mixture[30] of THF and saturated aq. NH_4Cl, the yield of **413** was increased to 95 % (Scheme 119) (Table 12).



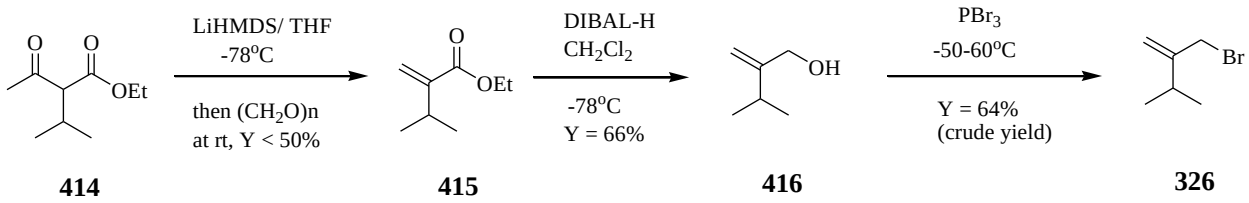
Scheme 119. Preparation of the alcohol **413** by a Barbier addition

Table 12. Results of synthesis of the alcohol **413** by a Barbier addition

Activated Zn (eq.)	Bromide **326** (eq.)	Solvent (v/v)	Result
3	2	THF	No reaction
3	2	THF / NH_4Cl (sat.) = 2/1	Y = 85 - 90 %
3	3	THF / NH_4Cl (sat.) = 2/1	Y > 95 %

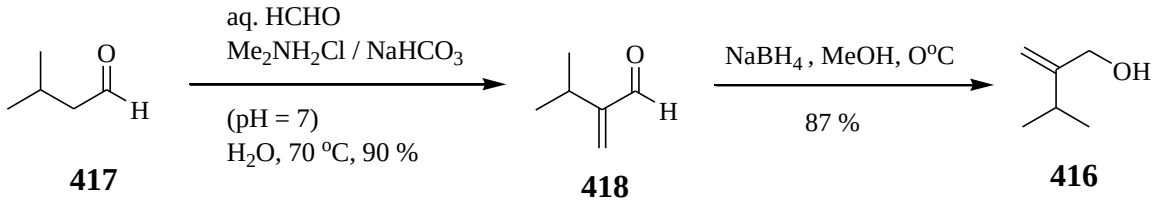
(v/v = volume / volume)

In addition, the bromide **326** was prepared from an alcohol **416** by a literature method.[31] Firstly, the alcohol **416** was prepared from an ester **415** by a literature method[32], but a synthesis of **416** was not easy to obtain enough the bromide **326** because of a low yield and by-products in a large scale (Scheme 120).



Scheme 120. Preparation of bromide **326** by literature methods

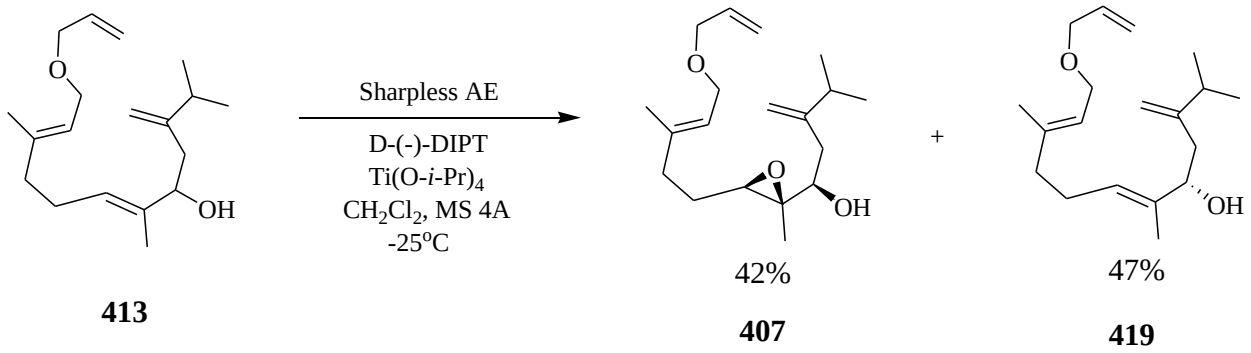
Thus, another route was developed to provide the alcohol **416**. An aldehyde **418** was prepared from a literature method[33] and a simple reduction of **418** with $NaBH_4$ gave us the alcohol **416**, which is a precursor to make the bromide **326** (Scheme 121).



Scheme 121. Preparation the alcohol **416** from the aldehyde **417**

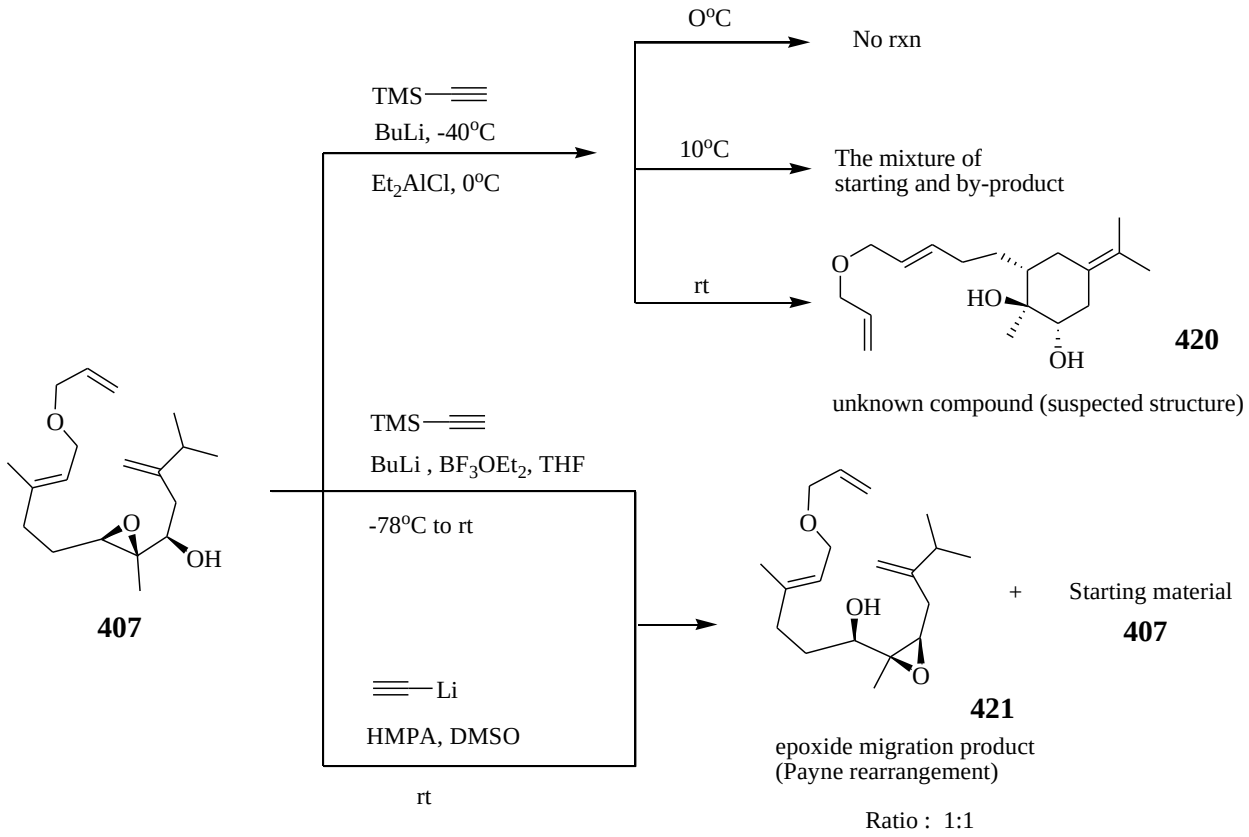
Sharpless kinetic resolution[27] was used to give a chiral epoxide **407** from the secondary alcohol **413**. Epoxidation of one of isomers would be faster and give an optically pure epoxy alcohol **407**. The epoxy alcohol **407** was obtained in 42 % yield and **419** was recovered in 47%

yield. We did not identify an enantiomeric excess of **407** because it would be ease to confirm an absolute stereochemistry of **407** after an epoxide opening reaction (Scheme 122).



Scheme 122. Preparation the epoxy alcohol **407** from the secondary alcohol **413**

After obtaining the epoxy alcohol **407**, representative methods had been tested to open an epoxide ring of **407** to provide a chirality of alcohol position and desired stereochemistry of alkyne of **406** (see Scheme 115). However, acetylene did not attack the epoxide ring of **407** to produce the acetylene diol **406**. When the epoxy alcohol **407** was treated with TMS-acetylene and Et_2AlCl[34], it gave an unknown product **420**. The ^1H NMR spectrum of **420** did not show proton peaks from a double bond of isobutene structure of **407**. It might be possible that a double bond of isobutene of **407** would attack the epoxide ring to afford a cyclized product **420**. In addition, when **407** was treated with TMS-acetylene and BF_3OEt_2[35] or Li-acetylene diamine complex[34b,36], Payne rearrangements was occurred to produce a mixture of **407** and **421** that were an inseparable mixture and ratio (1:1) was determined by the ^1H NMR spectrum (Scheme 123).



Scheme 123. Epoxide opening reactions from the epoxy alcohol **407**

Representative procedures to open epoxides did not give us the desired product **406** and there are few references to open an acetylide opening of a 2-alkyl-2,3-epoxy alcohol and their examples are not exactly match with our epoxy alcohol **407**.[37] Therefore, more experiments was required to find efficient methods to provide the desired acetylene diol **406** and we started to investigate epoxide opening reactions with model compounds.

4.3.1.2. Model test of epoxide ring opening

We synthesized six model compounds that are free or Bn-protected epoxy alcohols (Figure 16).

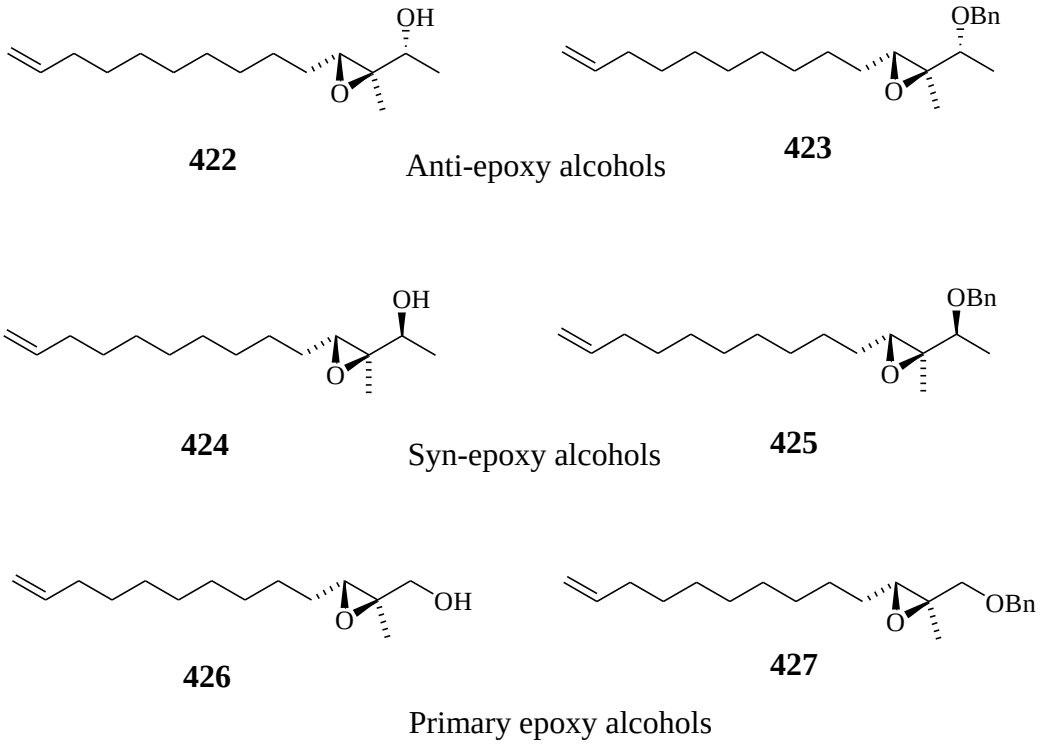
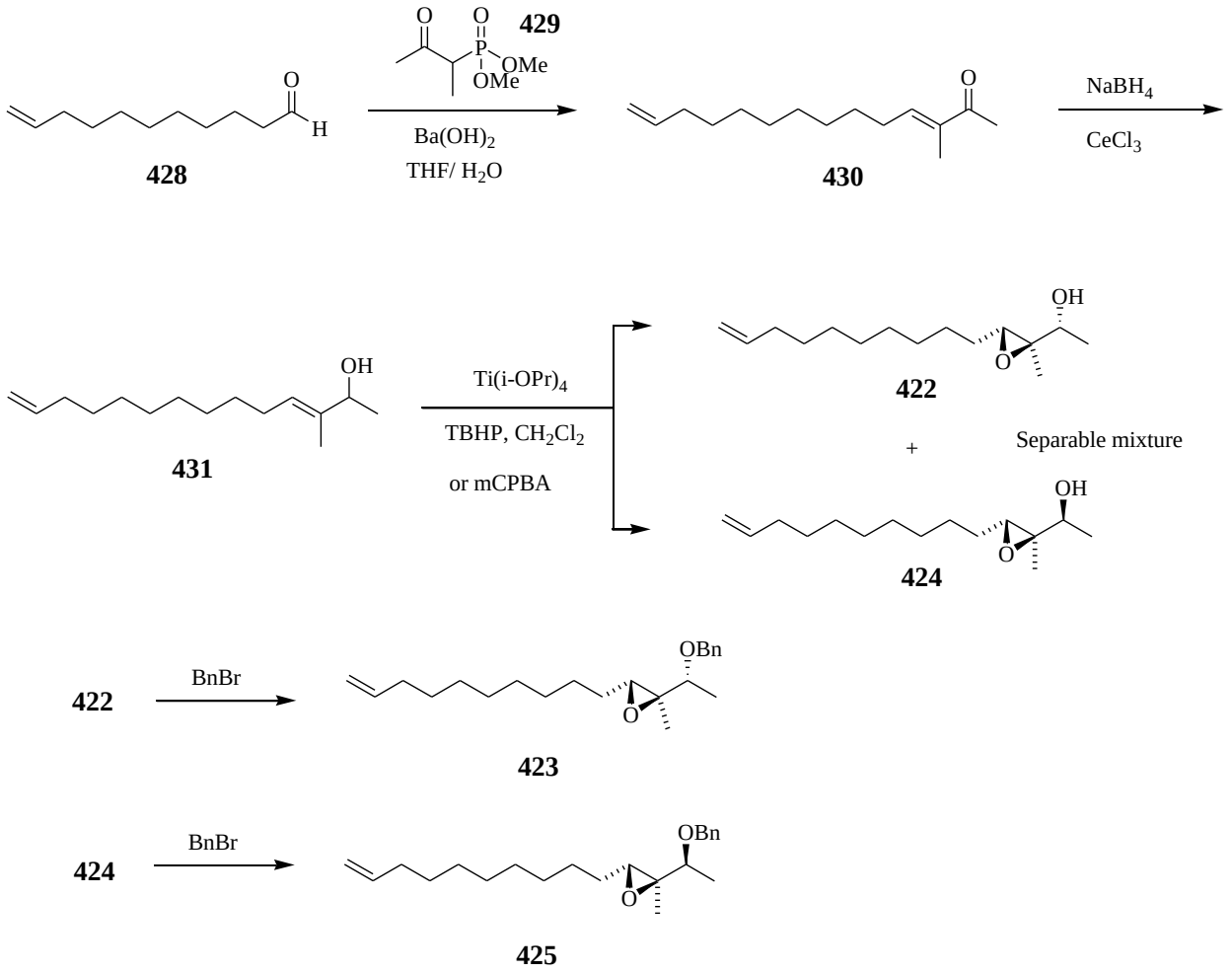


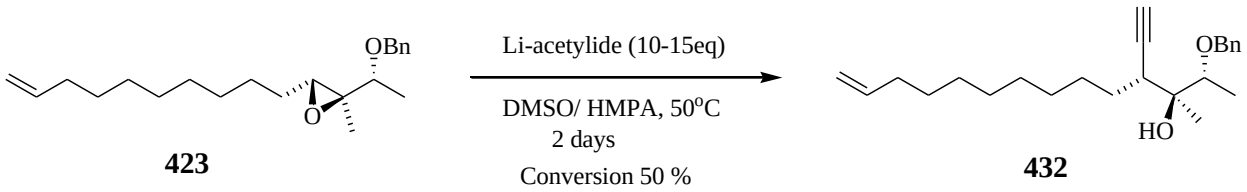
Figure 16. Structures of six model compounds

Firstly, secondary epoxide alcohols (**422**, **423**, **424**, and **425**) were prepared from 10-undecenal (**428**) by general methods. Horner–Wadsworth–Emmons reaction gave a α,β-unsaturated ketone **430** and a reduction of **430** with $NaBH_4$ produced an allylic alcohol **431** that was subjected to epoxidation with Ti(*i*-OPr)$_4$ to give anti- and syn-epoxy alcohols **422** and **424** in a ratio (2 : 1 or 1 : 2). Relative configuration of epoxy alcohols **422** and **424** was not determined by other experiments, but the major product would be the anti-epoxy alcohol **422** based on references[38], which showed that Ti(*i*-OPr)$_4$ catalyst can produce anti-epoxy alcohols as a major product and most of all anti-epoxy alcohols gave proton peaks of epoxide in down field of ^{1}H NMR more than syn- epoxy alcohols. When the alcohol **431** was treated with mCPBA, it gave a 1:1 mixture of syn- and anti-epoxy alcohols **422** and **424**. After separation, we also prepared benzyl protected alcohols **423** and **425** from two isomers **422** and **424** (Scheme 124).



Scheme 124. Preparation of secondary epoxy alcohols as model compounds

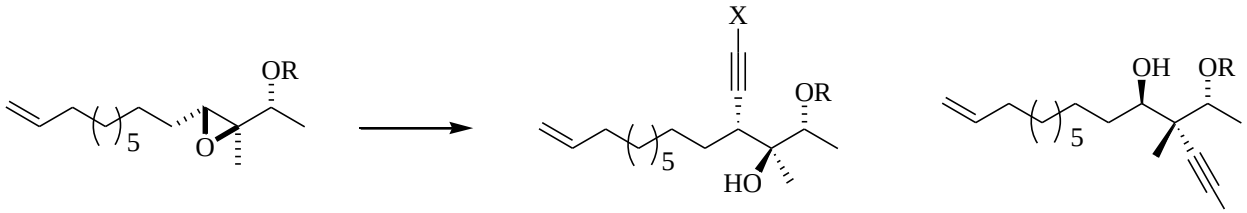
After preparation of four epoxy alcohols, we tested the anti-epoxy alcohol **422**, which has the same relative configuration as the epoxy alcohol **407** (Scheme 123), with Et_2AlCl or Li-acetylene diamine complex to open an epoxide ring, but we could not get acetylene diols (**433** or **434**). Bn-protected the anti-epoxy alcohols **423** had been also investigated to explore epoxide opening reactions with various Lewis acids (Et_2AlCl, Me_2AlCl[39], BF_3OEt_2, and $AlMe_3$[40]) and Li-acetylene diamine complex. We realized that Li-acetylene diamine complex can give the acetylene 1,2-diol **432** from the protected epoxy alcohol **423** when a reaction temperature was increased at 50 ^oC, but the reaction conversion was 50 % (Scheme 125). When we increased a reaction temperature to 70 ^oC, the conversion was increased to 85-90%, but an unknown by-product was formed (Table 13).



423 **432**

Scheme 125. Preparation of acetylene diol **432** with Li-acetylene diamine complex from **423**

The experiment results were summarized as follows (Scheme 126) (table 13).



422 and **423** 2, 3 - diol 2, 4 - diol

433 **434**

Scheme 126. Epoxide opening reactions from anti-epoxy alcohols **422** and **423**

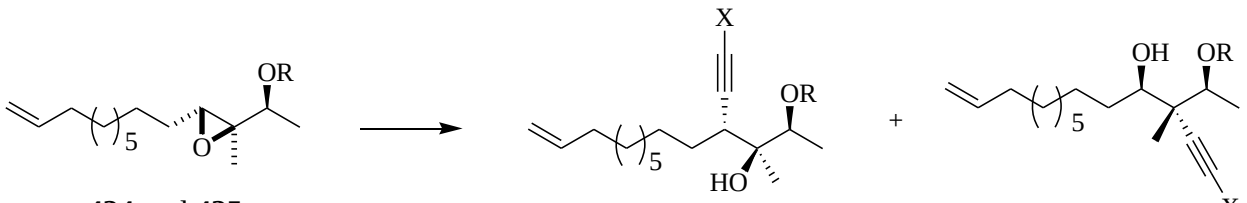
Table 13. Results of epoxide opening reactions from anti-epoxy alcohols **422** and **423**

R	X	Reaction condition	Result
H	H	Li-acetylide (10 eq.), DMSO / HMPA, rt, 2 days	No reaction
H	TMS	TMS-acetylene (3.8 eq.), n-BuLi (3.8 eq.), Et_2AlCl(3.8 eq.), rt	No reaction
Bn	H	Li-acetylide (10-15 eq.), DMSO / HMPA, rt, 1 day	No reaction
Bn	H	Li-acetylide (10-15 eq.), DMSO / HMPA, 50 °C, 1–3 days	Conversion 50 % Ratio (**423** : **433** = 1 : 1)
Bn	H	Li-acetylide (10-15 eq.), DMSO, 50 °C, 1 day	No reaction
Bn	H	Li-acetylide (10-1 5eq), DMSO / HMPA, 70°C, 1-3 days	**423 (**10–15% left) Major by-product formed
Bn	TMS	TMS-acetylene (3 eq.), n-BuLi (3 eq.), Et_2AlCl (3 eq.), Cat. $NiCl_2$, 35 °C	Some unknown spots, but almost **423** left

Bn	TMS	TMS-acetylene (32 eq.), n-BuLi (32 eq.), Et_2AlCl (32 eq.), rt, 4 days	Ratio (**433** : **434** = 1 / 1) **423** (20 - 30% left)
Bn	TMS	TMS-acetylene (2 eq), n-BuLi (2 eq), Me_3Al (1.9 eq),4.5 hr, rt	No reaction
Bn	TMS	TMS-acetylene (3 eq), n-BuLi (3 eq), Me_2AlCl (2.9 eq),14 hr, rt	No reaction
Bn	TMS	TMS-acetylene (5 eq), BF_3OEt_2 (2.2 eq), BuLi (4.6 eq), rt, 24 hr	No reaction
Bn	TMS	TMS-acetylene (5 eq), BF_3OEt_2 (2.2 eq), BuLi (4.6 eq), THF, 60 ^oC , 44 hr	Starting and messy unknown products

However, syn-epoxy alcohols **424** and **425** displayed different reactivity and results. It gave us an acetylene 2,3-diol **435** as major product in 42 % yield and an acetylene 2,4-diol **436** as a by-product in 10 - 15 % yield when it was treated with Et_2AlCl and TMS-acetylene. Li-acetylene diamine complex can also open a ring of the protected syn-epoxy alcohol **425** to give **435** even at a room temperature, although the conversion was 15-20 %. When a reaction temperature was increased to 50 ^oC, the conversion was 50 % after 3 days. Therefore, both epoxy alcohols **424** and **425** produced acetylene diols **435** by different methods.

The experiment results were summarized as follows (Scheme 127) (Table 14).



424 and **425**

2, 3 - diol

435

2, 4 - diol

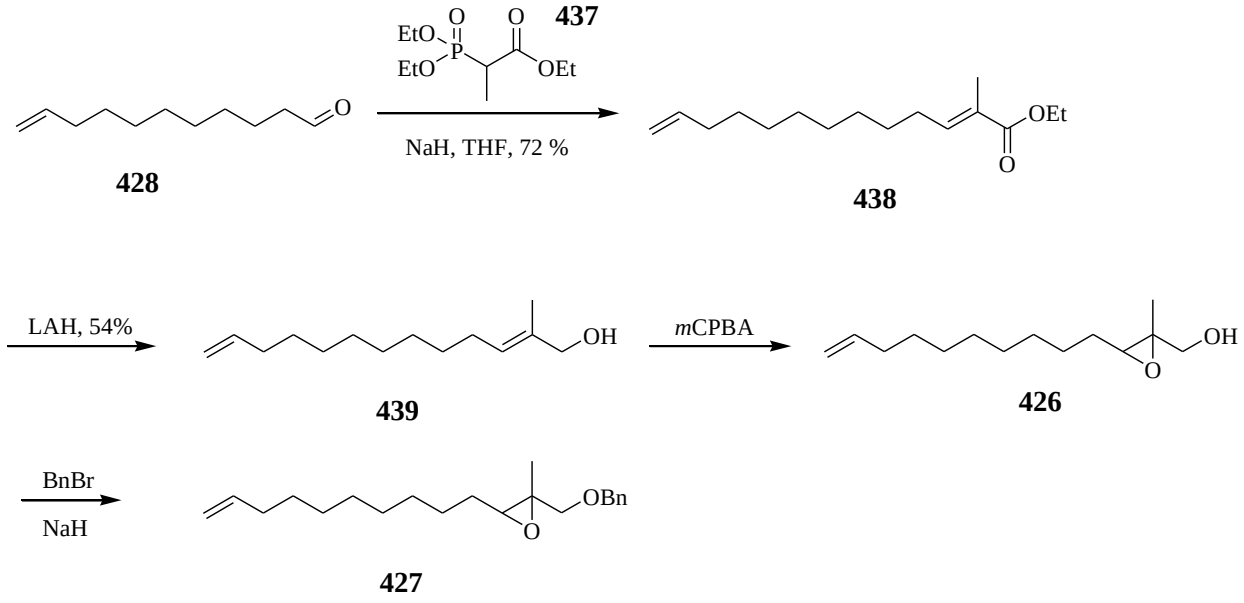
436

Scheme 127. Epoxide opening reactions from syn-epoxy alcohols **424** and **425**

Table 14. Results of epoxide opening reactions from syn-epoxy alcohols **424** and **425**

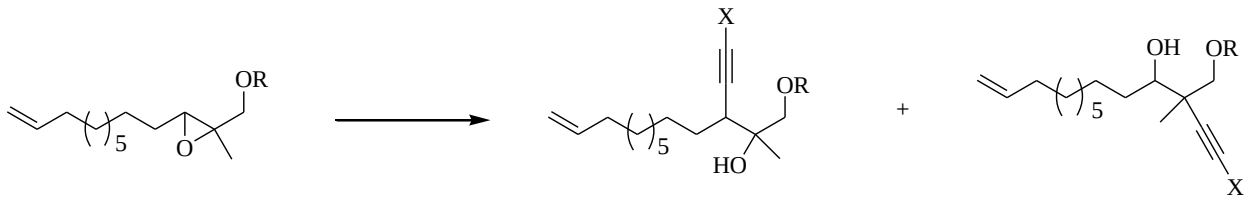
R	X	Reaction condition	Result
H	H	Li-acetylide, (10 eq.), DMSO / HMPA, rt, 2 days	No reaction
H	TMS	TMS-acetylene (3.8 eq.), n-BuLi (3.8 eq.), Et_3Al (3.8 eq.), rt	**435** (yield : 42 %) **436** (yield : 5-10%)
Bn	H	Li-acetylide, (15 eq.), DMSO / HMPA, rt, 3 days	Ratio :(**425** : **435** = 7 : 3)
Bn	H	Li-acetylide, (2 eq.), DMSO / HMPA, rt, 3 days	Almost starting **427** left
Bn	H	Li-acetylide, (10 eq.), DMSO/ HMPA, 50 ^oC, 3 days	Ratio (**425** : **435** = 1 : 1)
Bn	TMS	TMS-acetylene(5eq.), BF_3OEt_2 (2.2eq.), BuLi (4.6eq.), THF, 60 ^oC , 44 hr	**425** and messy unknown products

On the other hand, the primary epoxy alcohols **426** and **427** were synthesized from the 10-undecenal (**428**) to explore another possible access to have the acetylene 2,3-diols **440** (Scheme 129). The 10-undecenal (**428**) was treated with phosphonopropionate **437** to furnish a α, β-unsaturated ester **438**. The reduction of **438** followed by epoxidation with mCPBA provided the epoxy alcohol **426**. Benzyl protection of **426** afforded the Bn-protected epoxy alcohol **427** (Scheme 128).



Scheme 128. Preparation of primary epoxy alcohols **426** and **427** as model compounds

This epoxy alcohol **426** was treated with Et_2AlCl and it provided the acetylene 2,3-diols **440** as a major product, but the protected alcohol **427** did not give the desired product **440**. Therefore, we decided to use the second strategy (see Scheme 112) to prepare acetylene diol **406** from the primary epoxy alcohol **411** because a protection free procedure is better to save synthetic steps. The experiment results were summarized as follows (Scheme 129) (Table 15).



426 and **427** 2, 3 - diol **440** 2, 4 - diol **441**

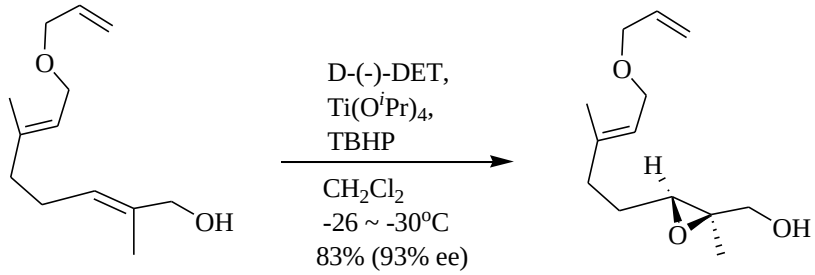
Scheme 129. Epoxide opening reaction from primary epoxy alcohols **426** and **427**

Table 15. Results of epoxide opening reactions from primary epoxy alcohols **426** and **427**

R	X	Reaction condition	Result
H	TMS	TMS-acetylene (4.3eq), n-BuLi (3.0eq), Et_2Al Cl(3.0eq), rt	Yield 55 % Ratio (**440** : **441** = 5 : 1)
Bn	H	Li-acetylide (10-15 eq), DMSO / HMPA, rt, 24 hr	No reaction
Bn	H	Li-acetylide (10-15 eq), DMSO / HMPA, 50 ^oC, 1-3 days	No reaction
Bn	TMS	TMS-acetylene (5 eq), BF_3OEt_2 (2.2 eq), BuLi (4.6 eq), THF, rt, 48 hr	Almost starting
Bn	TMS	TMS-acetylene (5 eq), BF_3OEt_2 (2.2 eq), BuLi (4.6 eq), THF, 60 ^oC , 44 hr	Starting and messy Unknown products

4.2.1.3. The second - generation approach (Scheme 116)

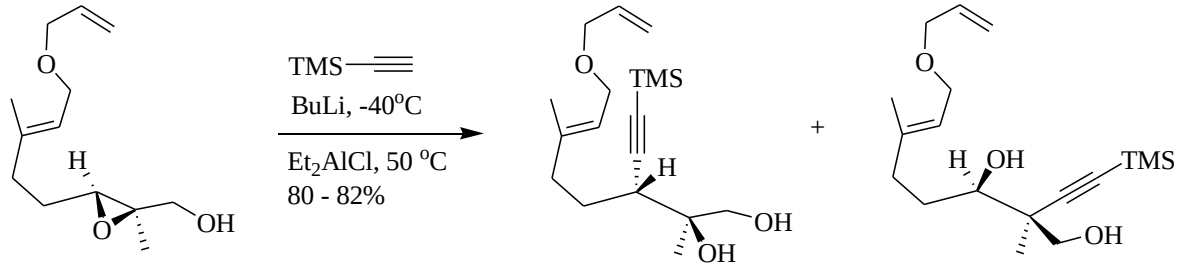
To introduce chirality of the primary epoxy alcohol **442**, we used Sharpless epoxidation[41] (Scheme 130) and enantiomeric excess was determined by ^1H NMR of its Mosher esters.



411 **442**

Scheme 130. Preparation the epoxy alcohol **442** from the allylic alcohol **411**

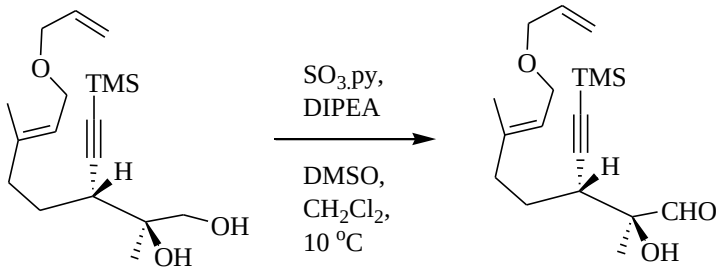
The epoxide **442** was treated with Et_2AlCl and TMS-acetylene gave a 2,3-diol product **443** as a major product (ratio 1.4 : 1.0). To prohibit a formation of 2,4-diol **444**, we had tried to change reaction conditions and found high reaction temperature can depress 2,4-diol formation to give more of the 2,3-diol **443**. When a reaction temperature was 50 ^oC, it afforded a mixture of the 2,3-diol **443** and the 2,4-diol **444** as a moderate ratio (1.5 ~ 3.0 : 1.0) in 80 % yield (Scheme 131).



442 2, 3 - diol **443** 2, 4 - diol **444**

Scheme 131. Preparation of 2,3-diol **443** with Et_2AlCl and TMS-acetylene

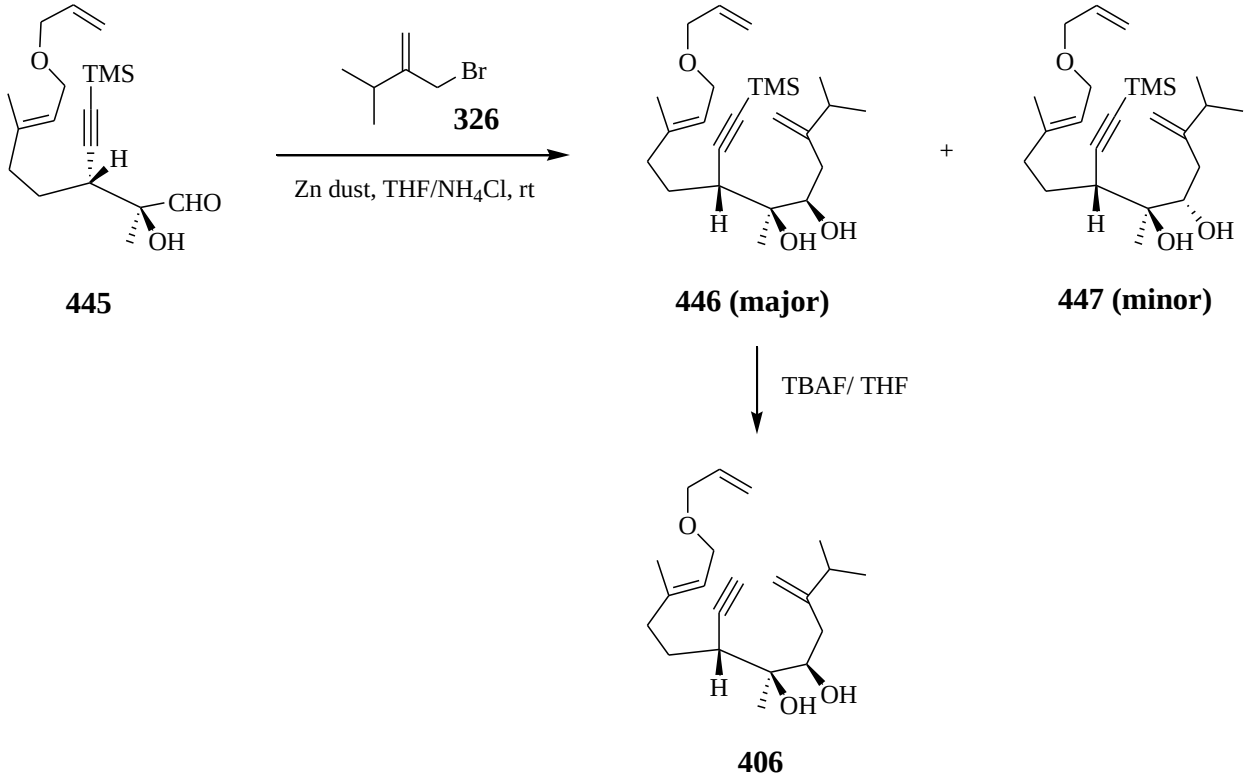
The separation of two isomers **443** and **444** was difficult, but **444** can be removed by silica gel column chromatography to give **443**, which has adequate purity for the next step. The oxidation of alcohol **443** with SO_3·Py complex and triethyl amine[42] gave an aldehyde **445** in 51 % yield. We tried to use the Swern oxidation to improve a yield of **445**, but the yield was 61 % yield. Finally, Parikh-Doering oxidation with diisopropyl ethyl amine (DIPEA) provided the best yield in 67 % yield (Scheme 132).



443 **445**

Scheme 132. Preparation of the aldehyde **445** by Parikh-Doering oxidation

The Barbier addition produced a TMS-acetylene diol **446** and **447** from the aldehyde **445** in 93 % yield. Later, the major compound was assigned structure **446**. The separation of two diastereomers **446** and **447** is not easy, but we could obtain some pure **446** and **447** by silica gel column chromatography. TMS deprotection of **446** gave the diol **406** to make a diene **381** in 94 - 98 %. (Scheme 133).



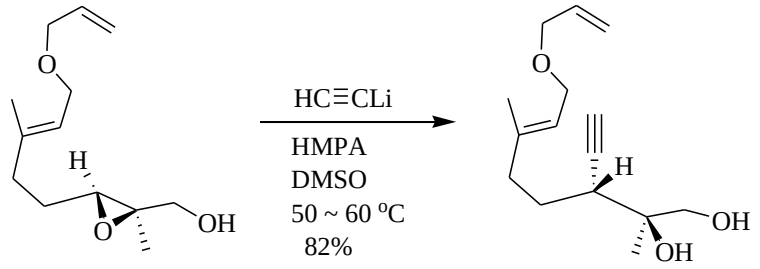
445 **446 (major)** **447 (minor)**

406

Scheme 133. Preparation of the diol **406** by the Barbier addition and TMS-deprotection

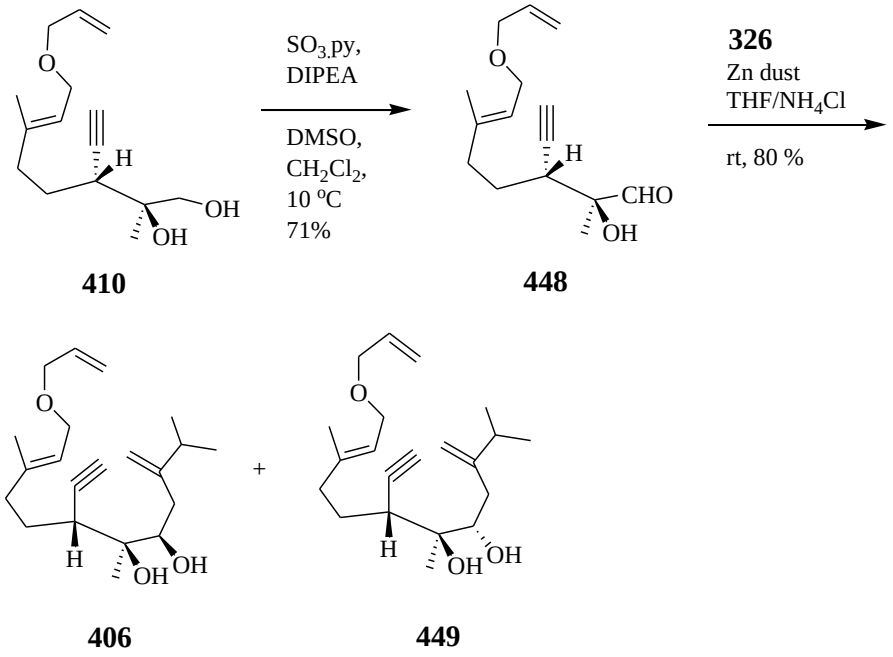
The best reaction condition was found that a crude aldehyde **445** without column purification was directly subject to a Barbier addition to afford the TMS-acetylene diols (ratio **446**: **447** = 2: 1) in 70 % for 2 steps.

In addition, we finally found another good procedure to open the epoxy alcohol **442** with high regio-selectivity. Li-acetylene diamine complex in DMSO and HMPA directly produced the only desired product **410** in 82 % at 50 - 60 ^{o}C (Scheme 134).



Scheme 134. Preparation of the diol **410** with Li-acetylene diamine complex

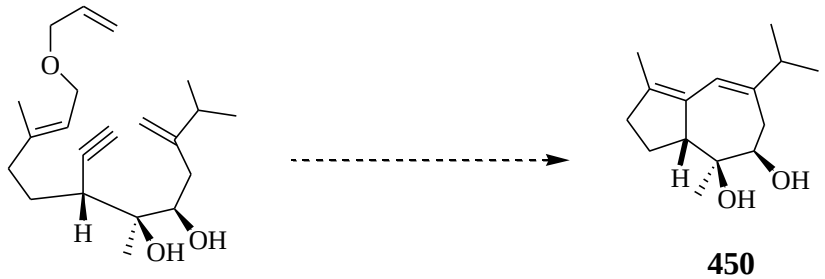
The acetylene diol **406** was produced from **410** by Parikh-Doering oxidation with diisopropyl ethyl amine (DIPEA) and the Barbier addition (ratio **406**: **449** = 1.8: 1.0) (Scheme 135).



Scheme 135. Preparation of the diol **406** with Li-acetylene diamine complex

4.2.2. Investigation of RRCM and preparation of TBS-protected diol (466)

After successfully preparing the acetylene diols, a major diastereomer of diol **406** was tested to construct a guaiane structure **450** by the ring closing metathesis (RRCM) reactions. However, we could not obtain any product or just recover the starting material **406** under various reaction conditions such as a high temperature like 110 ℃ and high loading catalysts (20 - 30 %). (Scheme 136) (Table 16).



406 **450**

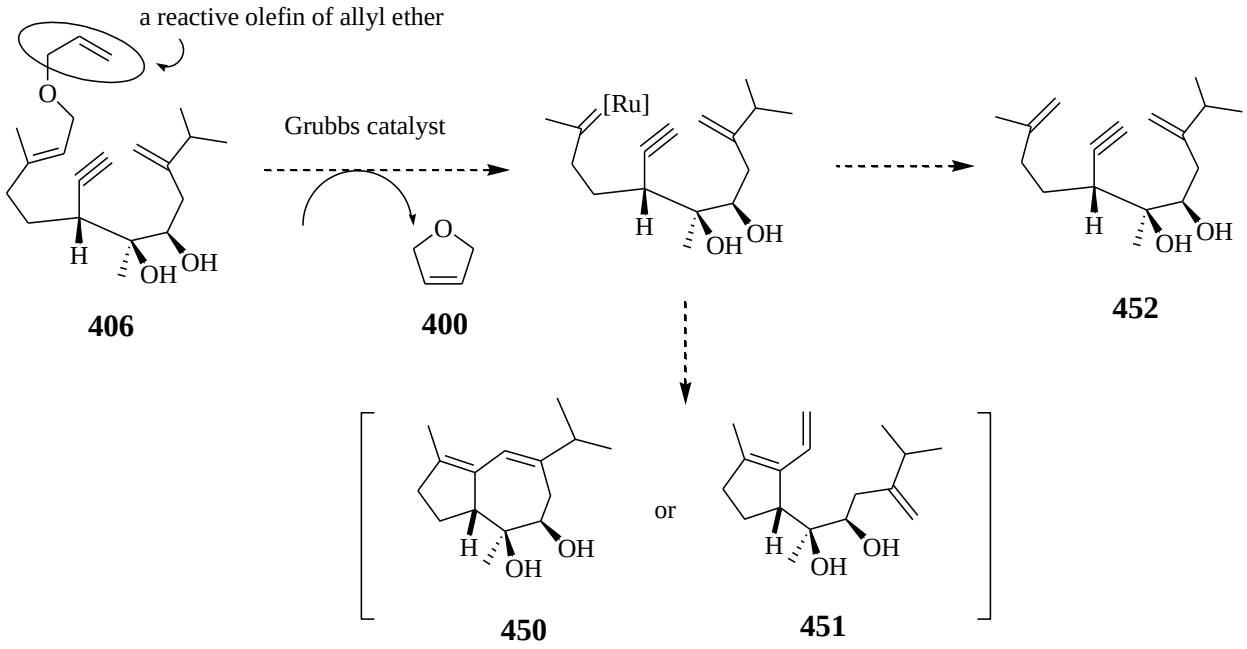
Scheme 136. Construct a guaiane structure **406** by the closing metathesis (RRCM) reactions

Table 16. Results of the RRCM reaction of **406**

Catalyst	Mole % of catalyst	Solvent	Temperature (^oC)	Time (h)	Concentration (M)	Result	comment
G II	8.5	CH_2Cl_2	Reflux	16	0.005	No rxn	starting recovered
G II	30	Toluene	95-100	5	0.005	Decomposed	
G I	20	Toluene	50	20	0.01	Decomposed	

G I : Grubbs 1st catalyst , G II : Grubbs 2nd catalyst

We focused one result that the starting material **406** was just recovered when **406** was treated with 8.5 mol% of Grubbs 2nd catalyst in CH_2Cl_2 at reflux. It was very interesting because the Grubbs 2nd catalyst did not give any expected product (Scheme 137). The 2,5-dihydrofuran **400** has low boiling point, so it is not possible to detect **400**, but a by-product **452** of RRCM reaction could be produced when Grubbs 2nd catalyst have a chance to react with the allyl ether moiety of **406**.



Scheme 137. Expected products by ring closing metathesis (RRCM) reactions

One of possible reasons would be deactivation of catalysts by a formation of a chelate between the diol of **406** and catalysts. We tested to use $Ti(O^{i}Pr)_4$ reagent[43] because this reagent can inhibit a formation of a chelate between catalysts and functional groups. However, we could not obtain products (Table 13).

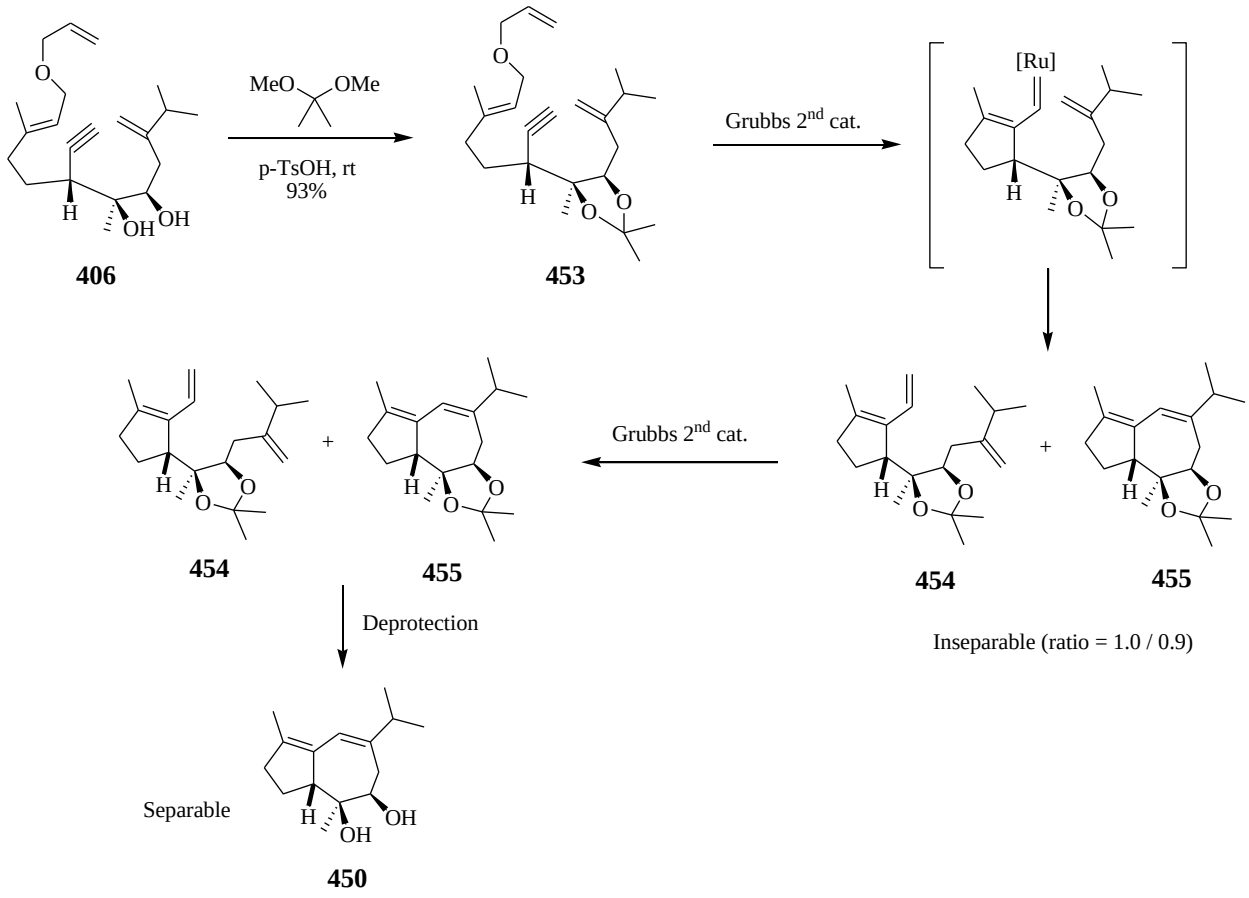
Table 13. Results of RRCM of **406** with $Ti(O^{i}Pr)_4$

Catalyst	Mole % of catalyst	Solvent	Temperature (^{o}C)	Time (h)	$Ti(O$*i*$Pr)_4$ (eq.)	Result
GI	30	CH_2Cl_2	Reflux	14	10	Starting & messy
GI	30	Toluene	Reflux	14	2	Decomposed

G I : Grubbs 1st catalyst

The next possibility would be conformation problems and conformational constraints could improve RCM.[44] To remove all possible problems, the diol **406** was protected as the acetonide **453** which provided metathesis products **454** and **455**. After a protection, the RRCM reaction produced an unknown product, which was isolated by silica gel column chromatography, and it showed one spot on TLC. In ^{1}H NMR spectrum, it displayed many peaks from 5-7 ppm and the integration of each peak indicated around one proton. These peaks probably come from protons of double bonds. We suspected that it can be a mixture of a diene **455** and a 5-memebered ring

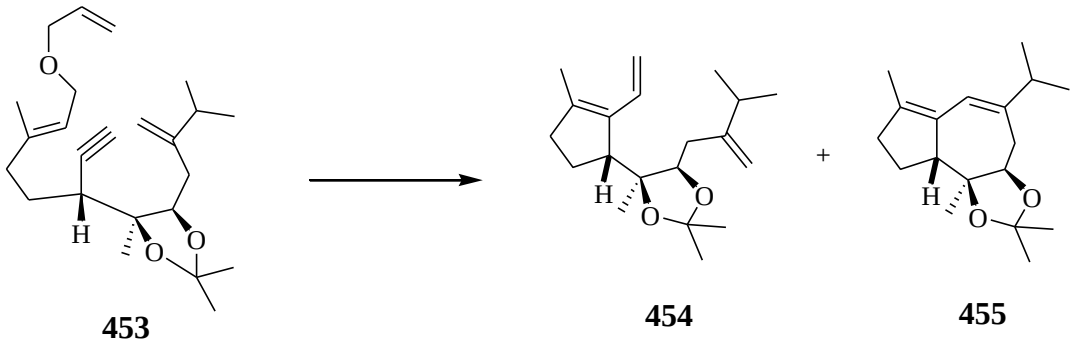
454, so it was treated with Grubbs 2nd catalyst again in the same reaction condition. After 20 h, some peaks became smaller and other peaks became bigger in the ^{1}H NMR spectrum, so we proved that it was an inseparable mixture. After deprotection of the mixture of **454** and **455**, we could isolate the hydroazulene **450**. The relative stereo configuration of **450** was determined on the basis of nuclear Overhauser effects and we confirmed that the diene **450** was a desired diene for the synthesis of (-)-Englerin A (**267**). Therefore, we proved that the hydroazulene **450** can be constructed by the RRCM reaction (Scheme 138).



Scheme 138. Preparation of the hydroazulene **450** by the RRCM reaction

Many reaction conditions had been examined to find the best condition. Grubbs 1st and 2nd catalysts and Hoveyda-Grubbs 2nd catalyst had been used to improve a conversion from the 5-membered ring **454** to the diene **455**. Grubbs 1st catalyst gave less unknown by-products and was similar conversion to Grubbs 2nd catalyst. Hoveyda-Grubbs 2nd catalyst did give lower

conversion than Gruubs 2nd catalyst. In addition, long reaction time and high loading catalysts gave more unknown by-products (Scheme 135). However, all reactions did not give 100 % conversion from **454** to **455**.



453 **454** **455**

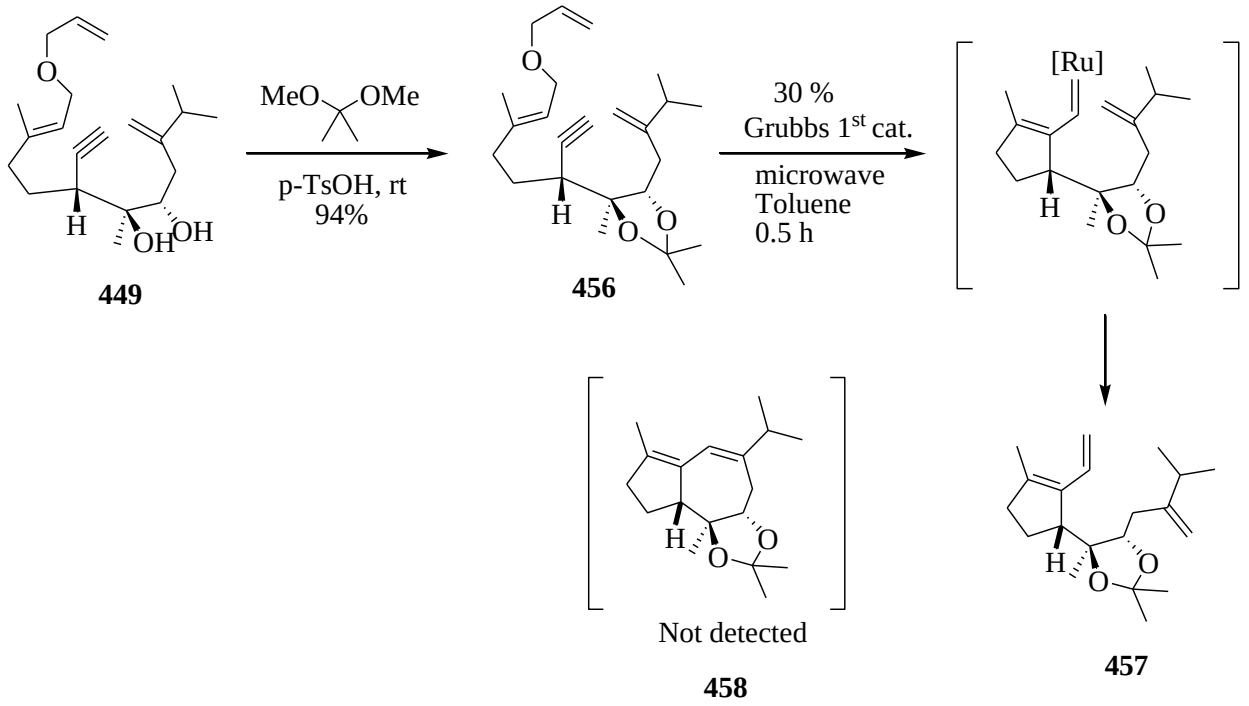
Scheme 139. Preparation of the hydroazulene **455** from **453** by the RRCM reaction

Table 17. Results of synthesis of the hydroazulene **455** by the RRCM reaction

Catalyst	Mole % of catalyst	Solvent	Temp. (^{o}C)	Time (h)	Concentration (M)	Crude NMR ratio (**454** / **455**)	comment
G II	10	CH_2Cl_2	Reflux	20	0.01	1.5 /1.0	
G II	20	CH_2Cl_2	Reflux	19	0.01	0.9 / 1.0	
G II	30	Toluene	60 – 70	60	0.005	0.4 / 1.0	
G II	35	Toluene	Reflux	14	0.005	0.3 / 1.0	
G I	30	Toluene	80	24	0.005	0.4 -0.5 / 1.0	
G I	30	Toluene	140	0.5	0.01	0.3 / 1.0	microwave
G I	35	Toluene	Reflux	13	0.005	0.4 / 1.0	
HG II	20	CH_2Cl_2	Reflux	36	0.005	0.8 / 1.0	

* G I : Grubbs 1st catalyst, G II : Grubbs 2nd catalyst, HG II : Hoveyda-Grubbs 2nd catalyst

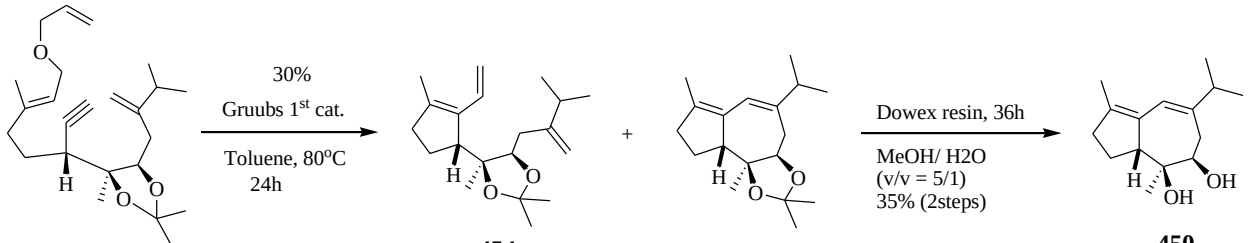
On the other hand, an acetonide **456** from the minor diastereomer diol **449** did produce not any diene **458**, but a 5-memebred ring **457** by theRRCM reaction when **456** was treated with Grubbs 1st catalyst (Scheme 140).



449 **456** **458** **457**

Scheme 140. RRCM of the acetonide **456** from the diastereomer diol **449**

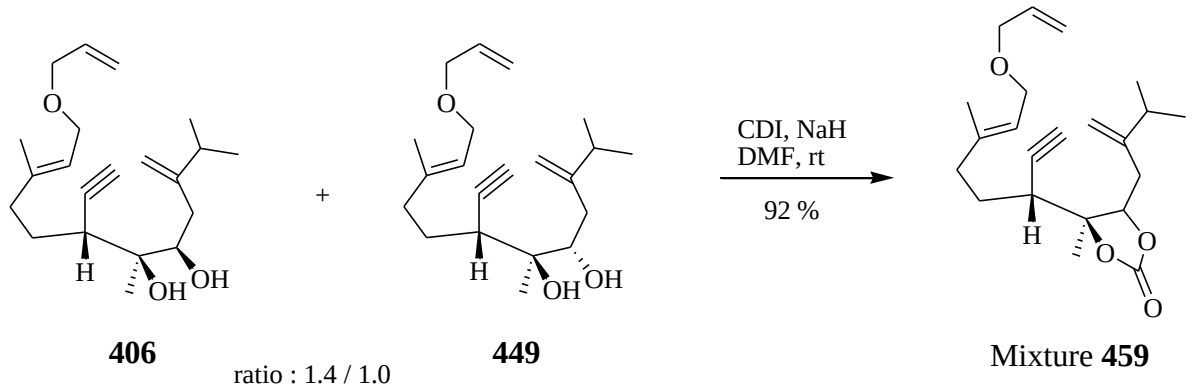
Based on our experiments, we decided a reaction condition, 30 % Grubbs 1st catalyst in toluene at 80 ^{o}C for 24 h because it gave fewer by-products. The RRCM reaction provided the inseparable mixture of **454** and **455**. After deprotection, we isolated the diene **450** in 35 % yield for 2 steps and the deprotection yield was moderate (~ 75%) from **455**. We also tried to obtain the 5-membered ring **451** (see Scheme 137) from deprotection of **454** to reuse **451**, but we could not separate **451** because the hydrolysis of the mixture of **454** and **455** gave messy products (Scheme 141).



453 **454** **455** Inseparable **450**

Scheme 141. Synthesis of the hydroazulene **450** from the acetonide **453**

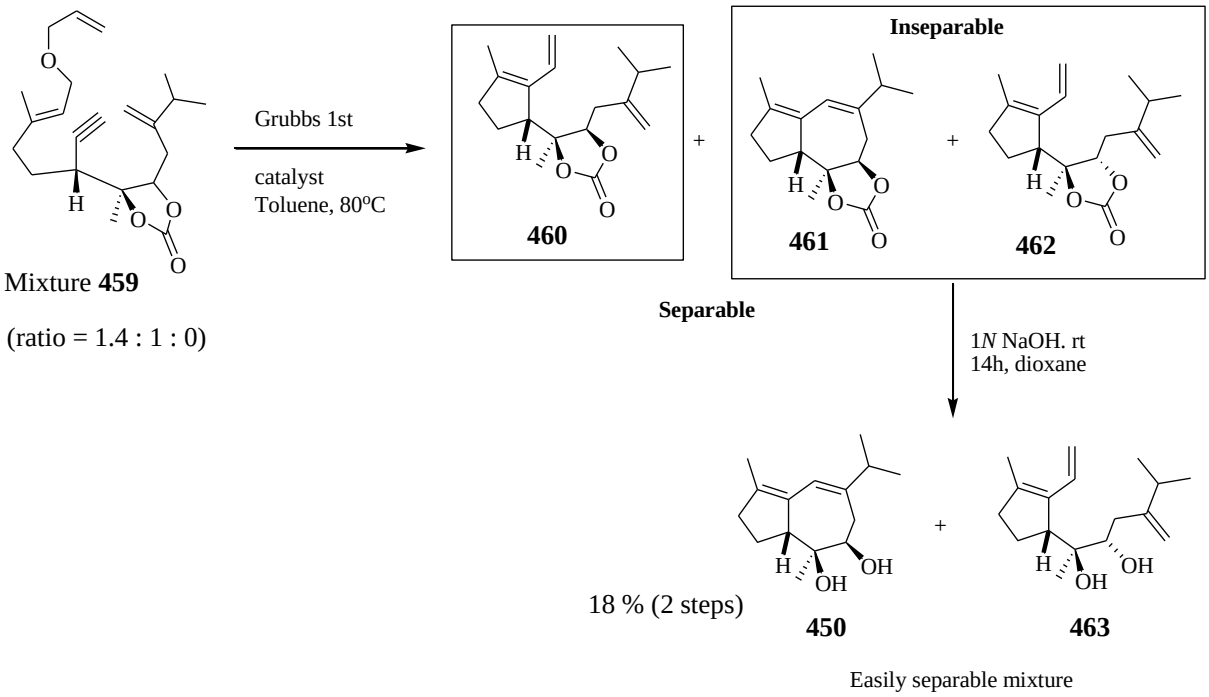
Therefore, we decided to use carbonate protecting groups to protect the diol **406** that can be easily removed in a mild condition. We used the mixture of diastereomers (**406** and **449**) and obtained carbonates **459** in 83 % when it was treated with CDI (1,1'-carbonyldiimidazole) in THF at reflux or toluene at 80 ^{o}C, but the yield of **459** was increased to 92 % when it was treated with CDI and NaH in DMF at rt (Scheme 142).



406 ratio : 1.4 / 1.0 **449** Mixture **459**

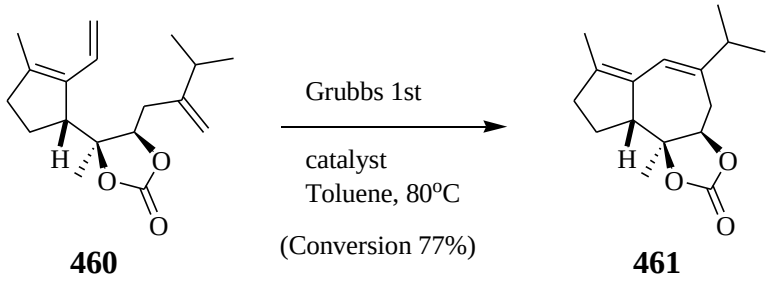
Scheme 142. Synthesis of carbamates mixture **459** from the mixture of **406** and **449**

Carbonates **459** were tested under the same reaction condition (30% Grubbs 1st catalyst, toluene, 80 ^{o}C). The result was little disappointing because the conversion from the 5-membered ring **460** to the diene **461** was 50 %. However, surprisingly, we can separate the 5-membered ring **460** by silica gel column chromatography. After the deprotection of carbonates, the hydroazulene **450** and a five-membered ring **463** were easily isolated by silica gel column chromatography. Deprotection of carbonate groups was very simple and clean to produce the hydroazulene **450** (Scheme 143).



Scheme 143. Synthesis of the hydroazulene **450** from carbonates mixture **459**

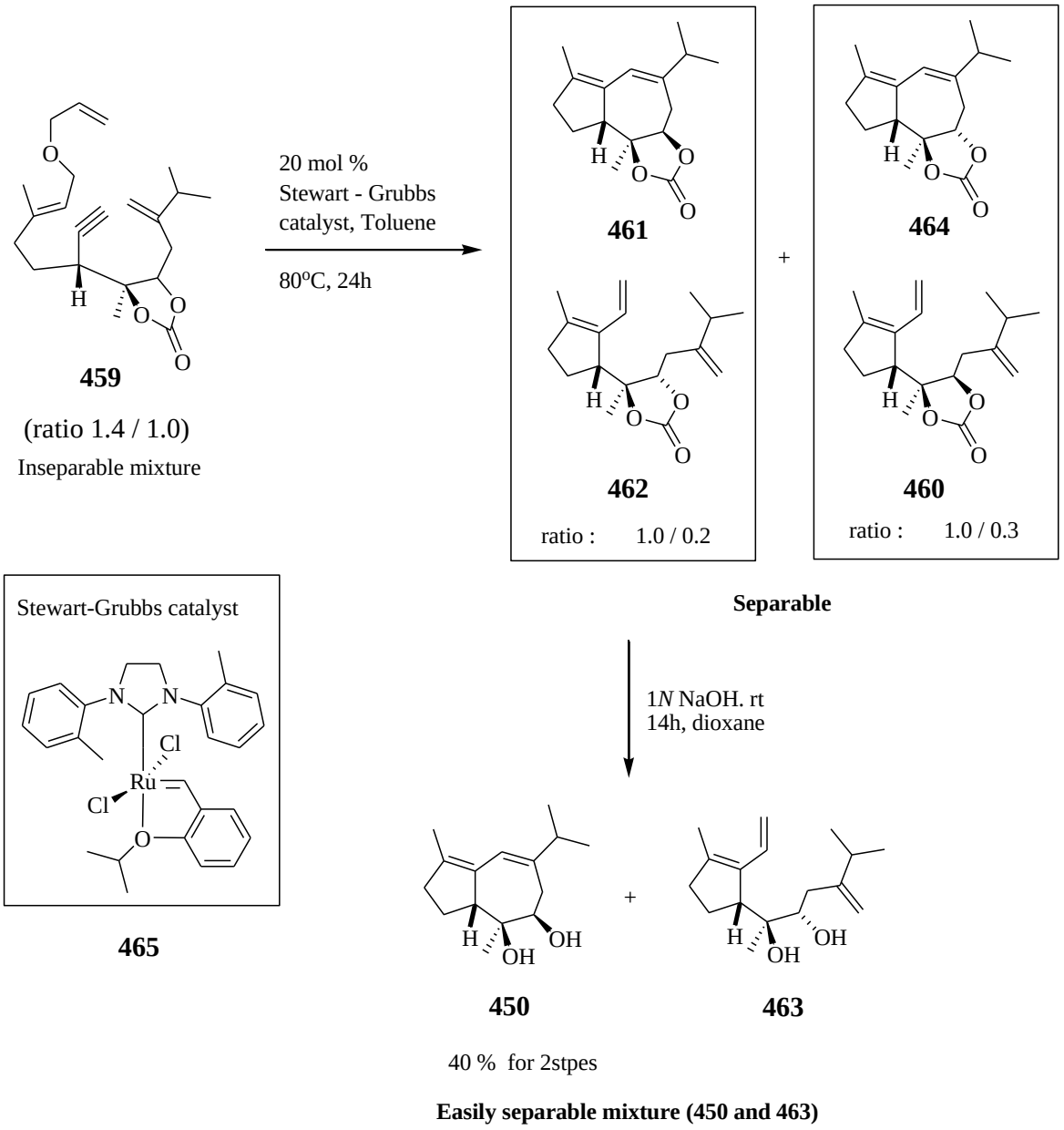
Although the carbonate **459** gave the lower yield of **450** (18 % for 2 steps) and the low conversion (~ 50 % from **460** to **461**), deprotection and isolation procedures were more efficient and easier than acetonide experiments. In addition, the isolated 5-membered ring **460** was reused to provide diene **461**. It was treated with Grubbs 1st catalyst again and showed 77 % conversion to afford **461** (Scheme 144).



Scheme 144. Synthesis of the hydroazulene **461** from carbonates mixture **460**

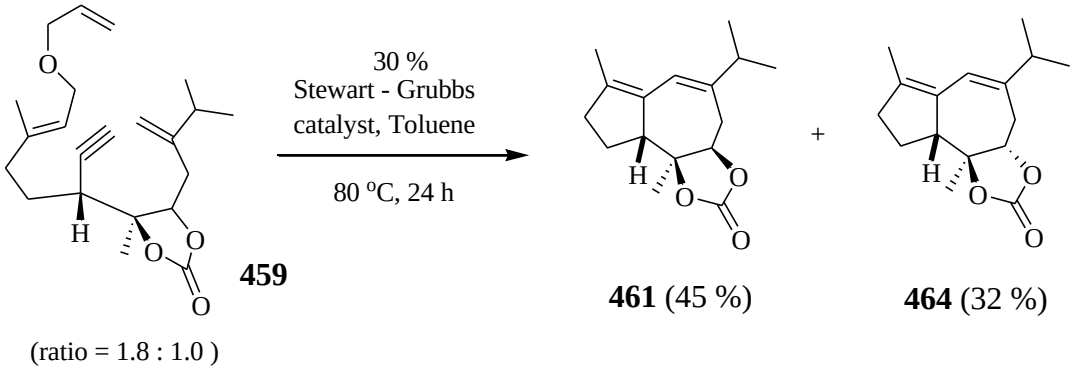
Therefore, we decided to use the carbonate protection and to continue to try to find more a reactive catalyst to give quantitative conversion from this carbonates **459**

One of more reactive RCM catalysts, Stewart-Grubbs catalyst (**465**) [45], was tested for RRCM. When **459** was treated with 20 % Stewart-Grubbs catalyst **465**, it provided two dienes (**460** and **463**) and two 5-memebred rings (**461** and **459**) from both of stereoisomers **458**. Each product could be isolated after deprotection of carbonates (Scheme 145).



Scheme 145. Synthesis of the hydroazulene **450** from carbonates mixture **459** with Stewart-Grubbs catalyst **465**

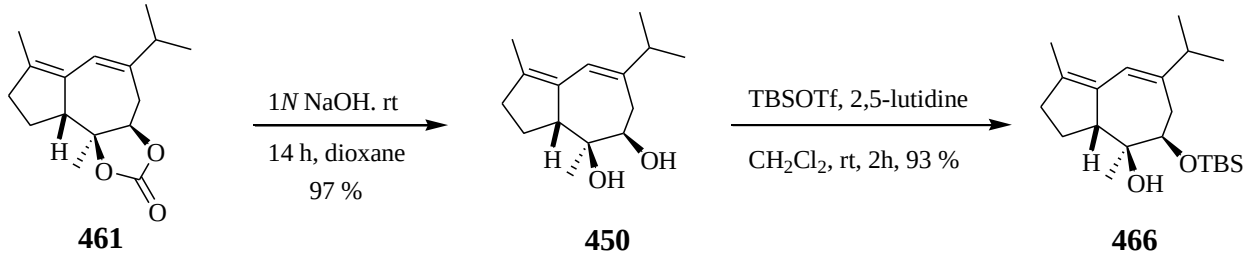
Therefore, we found that both dienes **461** and **464** can be produced by Stewart-Grubbs catalyst **465** and the carbonates **459** can also give a high conversion and yields. Finally, when we used 30 % Stewart-Grubbs catalyst **464**, it gave a quantitative conversion from carbonates **459** to dienes **461** and **464**. The relative stereochemistry of both dienes **461** and **464** were assigned on the basis of nuclear Overhauser effects (Scheme 146).



Scheme 146. Synthesis of the dienes **461** and **464** from carbonates **459** with 30 % Stewart-Grubbs catalyst **465**

This result gave us strong points that we do not have to isolate diastereomer diols **406** and **449** after the Barbier addition (see Scheme 133) because they were easily isolated after the RRCM reaction. The epimer diene **464** could be used to develop new structures or changed to the desired hydroazulene **450** by general methods after deprotection of carbonate groups.

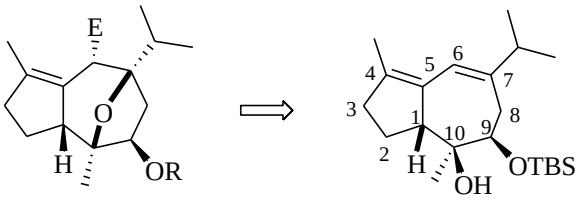
The desired diene **461** was easily hydrolyzed by a treatment of base, NaOH in dioxane and gave the hydroazulene **450** in 97 % yield. The secondary alcohol of the hydroazulene **450** was protected with TBS group to afforded TBS–protected diene **466** in 93 % yield (Scheme 147).



Scheme 147. Synthesis of TBS–protected diene **466** from **461**

4.2.3. Investigation of transannular etherification and the synthesis of an oxa-bicyclic structure (469)

After preparing the TBS-protected diene **466**, we have developed procedures to provide the oxa-bicyclic structure **392** that is an important intermediate for the synthesis of (-)-englerin A (**267**) (Scheme 148).



392 **466**

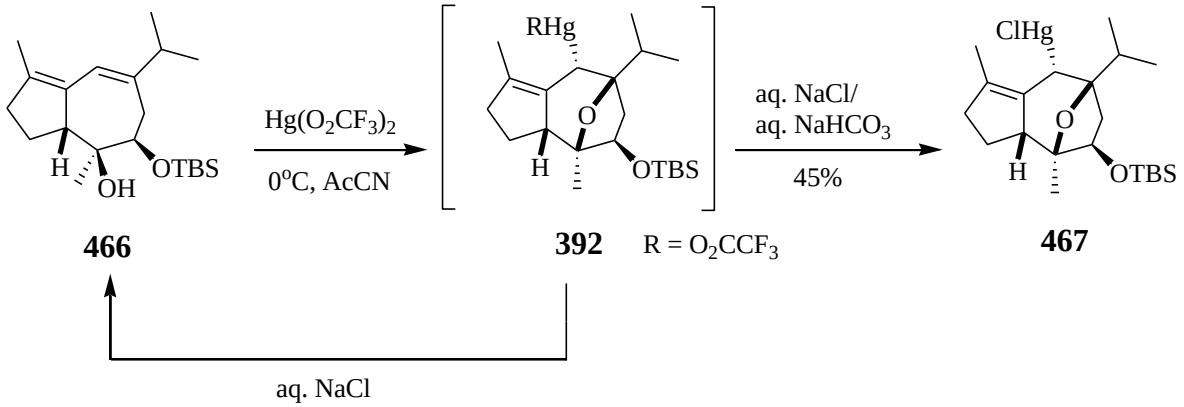
Scheme 148. Synthesis of **392** by transannular etherification

Various methods have been tested to initiate a transannular cyclization that would affect conversion of **466** to **392**. An epoxidation with mCPBA provided a product in which the olefinic proton was retained. Treatments of **466** with I_2[46], NIS[25a,47], NBS[48], $PhI(O_2CCF_3)_2$[49], and $(Coll)_2IPF_6$[50] did not provide the oxa-bicyclic compound **392** (Table 18). After several experiments, we realized that oxymercuration of **466** with $Hg(O_2CCF_3)_2$[51] affords a transannular cyclized product **392**.

Table 18. Results of synthesis of the oxa-bicyclic compound **392** by transannular etherification

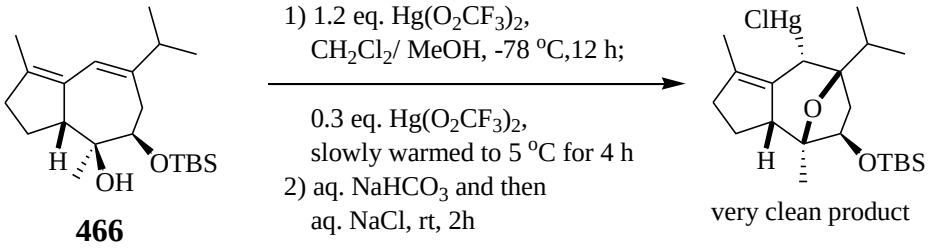
Reagent	Reaction condition	Result
$PhI(O_2CCF_3)_2$	2.4 eq., CH_2Cl_2, rt, 4 h	TLC (no spots), Crude NMR (showed peaks from reagents)
	1.0 eq., CH_2Cl_2, rt, 4 -20 h	TLC (no spots), crude NMR (showed **466** peaks and some small peaks)
	1.2 eq., CH_2Cl_2, rt, 18 h	TLC (**466** spot), crude NMR (showed **466** and some small peaks)
NIS	K_2CO_3 (5.5 eq.), CH_2Cl_2, rt, 38 h	TLC (messy, **466** spot), crude NMR (showed **466** and some very small peaks)
	CSA (1.0 eq.), 2,4,6-collidine (1.0 eq.), rt, 20 h	TLC (messy,**466** spot), crude NMR showed **466** and some very small peaks)
	AcCN, rt, 5 h	TBS deprotected **466** (= **450**)
I_2	KI, K_2CO_3, THF, rt , 5 h	**466** was recovered
	KI, K_2CO_3, THF, 50 ^oC, 10 h	**466** was recovered.
	$NaHCO_3$, AcCN, rt , 12 h	Messy unknown products
$I(Collidine)_2PF_6$	1.6 eq., CH_2Cl_2, rt, 21 h 35^oC, 20 h	**466** was recovered
	1.6 eq., CH_2Cl_2, 35 ^oC , 20 h	**466** was recovered
	10 eq., $ClCH_2CH_2Cl$ 50 ^{o} C, 3.5 h	**465** was recovered
	10 eq., $ClCH_2CH_2Cl$ 60-64 ^oC, 15 h	TLC (**466** spot), Crude NMR (**466** and showed some small peaks).
	2 eq., toluene, 100 ^oC	**466** was recovered
NBS (4.5 eq.)	4A MS, CH_2Cl_2, rt, 1 h	Messy unknown products
$Hg(O_2CF_3)_2$	AcCN, O ^oC	**392** (R = HgCl) , yield = 45 %
	CH_2Cl_2/ MeOH (cat.), -78 ^oC (12 h) over 0 ^oC (5 ^oC)	**392** (R = HgCl), a very clean product

Oxymercuration gave expected regio- and stereoselective addition of C6-C7 olefin and the hydroxyl group at C10 exactly attached to C7 position in Hg complex with the diene **466**, so it provided the only product **467**. This result showed that the hydroxyl nucleophile effects ring opening by attack at C-7 and a backside attack is not allowed (Scheme 149).



Scheme 149. Synthesis of the alkyl Hg compound **467** by transannular etherification

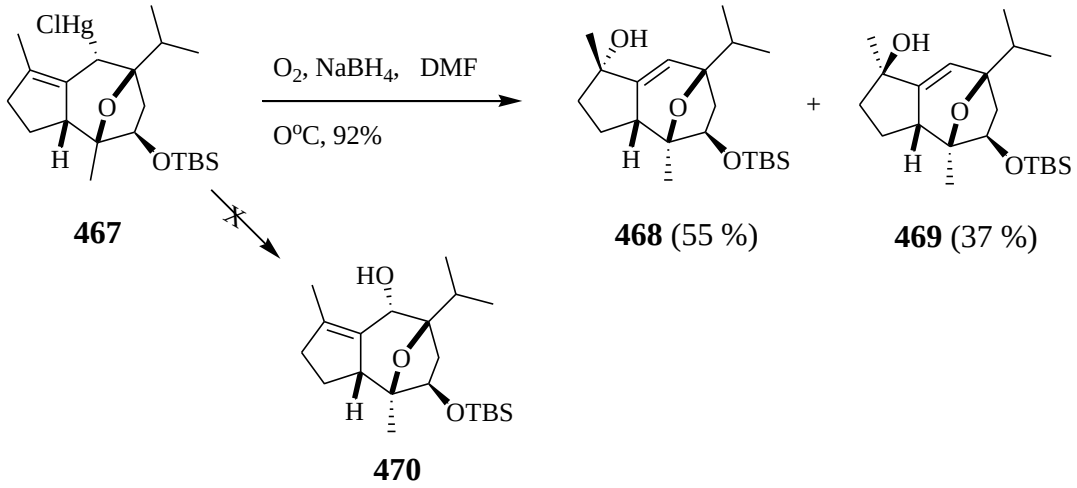
After the construction of the alkyl $Hg(O_2CCF_3)$ intermediate **392** in situ condition, we found that saturated aq. NaCl solution was doing rapid reversion to the starting material **466** and it would be because of aq. CF_3COOH generated by aq. NaCl solution.[51a] Therefore, a chloromercurial compound **467** was produced by the treatment with saturated aq. NaCl solution after neutralizing the acid with saturated aq. $NaHCO_3$ solution. This chloromercurial compound **467** was very stable, so we isolated **467** by silica gel column chromatography and identified **467** by ^1H NMR spectrum. This spectrum showed that a proton peak from double bond of C6 and C7 had disappeared and a new peak had appeared; therefore we proved the highly regio, stereoselective etherification from the diene **466**. To improve yields and reduce by-products, we tried to optimize reaction conditions. The reaction temperature was cooling down to 0 ^oC and it gave 45 % yield and showed fewer by-products on TLC. Therefore, we believed that low temperature can depress the formation of by-products and decided to use CH_2Cl_2 / MeOH solvents system at low temperature (-78 ^oC). After 12 h, the reaction showed the only product, but **466** was still left on TLC, so 0.3 eq. $Hg(O_2CCF_3)_2$ was added more and slowly warmed to 5 ^oC over 4 h, and then starting completely disappeared. Finally, we obtained a very clean a crude product (TLC showed the only product) (Scheme 150). For the next reaction, the purification of chloromercurial was not necessary, so it was directly used without purification.



466 **467**

Scheme 150. Synthesis of the alkyl Hg compound **467** at low temperature

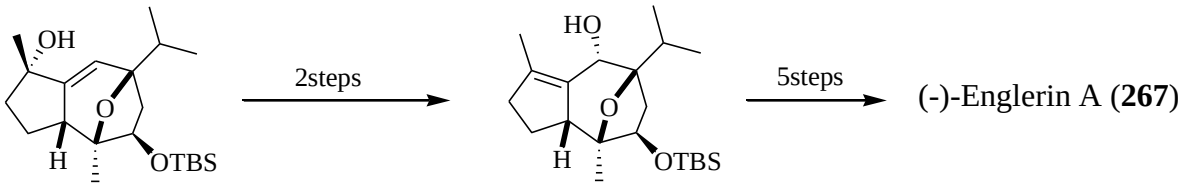
The second, we desired to convert the chloromercurial **467** to the alcohol **470**. Until now, there are two methods to do oxidative demercuration. One is to use O_2 and another is to use O_2 and TEMPO.[52] Both methods are radical reactions. We expected they could produce the secondary alcohol **470** directly from chloromercurial **467**. However, after several tries, we found that radical generated from oxygen was trapped at the tertiary position and produced tertiary alcohols. Both methods gave us the same products, but O_2 and TEMPO provided a low yield. The chloromercurial **467** was treated with $NaBH_4$ and O_2 in DMF to produce a mixture of stereoisomeric tertiary alcohols **468** and **469** (Scheme 151).



467 **468** (55 %) **469** (37 %) **470**

Scheme 151. Synthesis of tertiary alcohols **468** and **469** by oxidative demercuration

Although we would have preferred to obtain the known alcohol **470** directly, the alcohol **468** has been produced by oxidative demercuration through the radical intermediate. However, the major product **468** is also the valuable known alcohol, which has been converted to (-)-englerin A (**267**) in seven steps[14] (by way of alcohol **470**). Therefore, access to alcohol **468** completes a formal synthesis of (–)-englerin A (**267**) (Scheme 152).



468 **470**

Scheme 152. The synthesis of (-)-englerin A (**267**) from the alcohol **468**

4.3. Conclusion

In conclusion, we illustrated the efficient stratiges to approach the key core of (-)-englerin A (**267**). First of all, we introduced the epoxide opening reaction to access the acetylene diol **406** from alkyl-2,3-epoxide derivatives with lithium acetylide condition. In addition, the optically pure hydroazulene **450**, which has disubstituted olefins both side, was synthesized by the relay ene-yne-ene metathesis reaction. The carbamate from the sterically hindered diol **449** was also converted to the hydroazulene **464** by Stewart-Grubbs catalyst. Furthermore, we demonstrated that the oxa-bicyclic structure **468** can be constructed by transannular etherification with $Hg(O_2CCF_3)_2$ and oxidative demercuration. It also proved that ionic transannular oxymercuration of **466** gave the regio specific halomercurial **467**.

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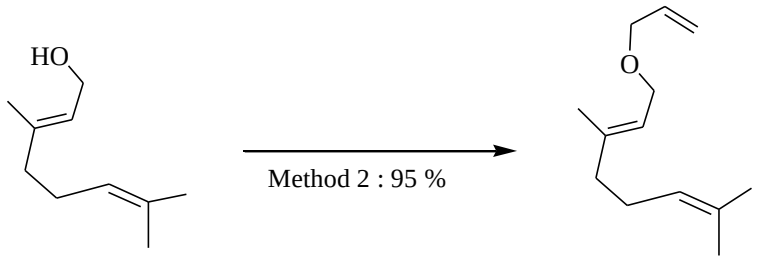
4.5. Experimental Section

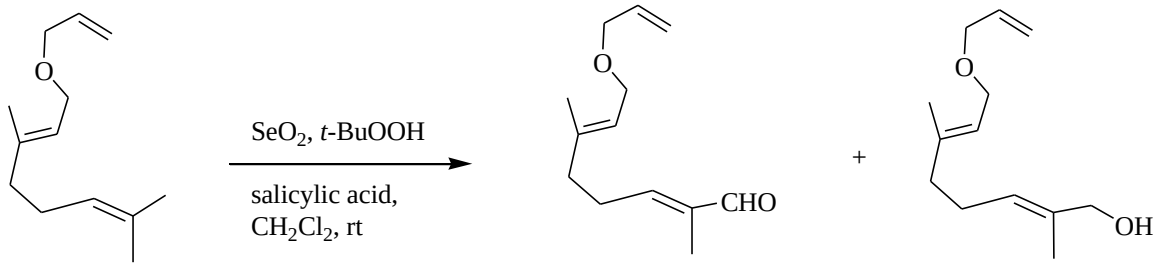
General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å , 230-400 mesh, surface area 500-600 m^2/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), a Varian Inova-500 (500 MHz for ^1H and 125 MHz for ^{13}C), Bruker-400 (400 MHz for ^1H and 100 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C, or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.



409 **412**

Ether 412. To a stirred solution of geraniol (**409**, 5.00 g, 32.4 mmol) in THF (50 mL) were added allyl bromide (4.71 g, 38.9 mmol) and slowly NaH (1.43 g, 60 %, 35.7 mmol) under argon. The reaction mixture achieved a gentle reflux and then it was allowed to cool down to room temperature. After stirring for 14 h, the mixture was filtered through Celite to remove a solid and the filter cake was washed with THF. The resulting solution was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with hexane) to give allyl ether **412** (5.98 g, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 5.35 (tdd, *J* = 6.9, 2.4, 1.2 Hz, 1H), 5.27 (ddt, *J* = 17.4, 1.7 Hz, 1H), 5.17 (dm, *J* = 10.2 Hz, 1H), 5.09 (m, 1H), 3.99 (dd, *J* = 6.9, 0.9 Hz, 2H), 3.96 (dt, *J* = 5.7, 1.4 Hz, 2H), 1.98 – 2.15 (m, 4H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.66 (m, 3H), 1.60 (d, *J* = 0.3 Hz, 3 H). The ^{1}H NMR data were consistent with the reported values.[28]



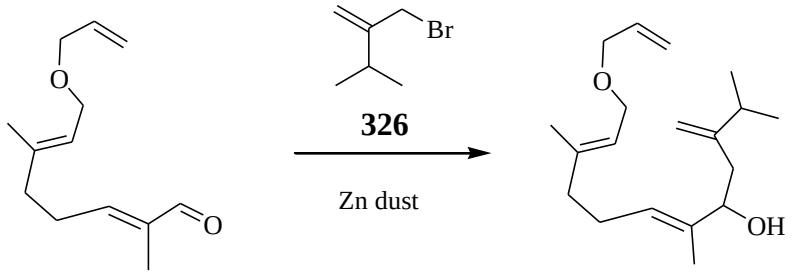
412 **408** **411**

Aldehyde 408 and alcohol 411. To a stirred solution of SeO_2 (2.3 mg, 0.62 mmol) in CH_2Cl_2 (3 mL) were added salicylic acid (14.2 mg, 0.10 mmol), *t*-BuOOH (477 mg, 70 % in H_2O, 3.71 mmol), and ether **412** (200 mg, 1.03 mmol) under Ar. The mixture was stirred for 46 h. Then volatile compounds were removed under reduced pressure and the residue was diluted with Et_2O (10 mL). The organic solution was washed with 10 % NaOH (5 mL X 3) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by silica gel

column chromatography (elution with EtOAc : Hexane = 1:20 to 1:2) to give alcohol **411** (104.4 mg, 48 %) as an oil, the corresponding aldehyde **408** (17.4 mg, 8 %), and recovered **412** (42.3 mg, 21 %).

Alcohol 411: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.37 (quintet d, *J* = 6.6, 1.2 Hz, 1H), 5.26 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.97 (m, 6H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.07 (t, *J* = 7.8 Hz, 2H), 1.66 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 16.4, 25.7, 39.1, 66.5, 69.0, 71.0, 117.0, 121.1, 125.6, 135.0, 135.1, 139.7.; IR (neat) ν_{max} 3397, 2918, 2857, 1670, 1647, 1448, 1383 cm^{-1}. HRMS[ES+] calcd for $C_{13}H_{22}O_2$ [M + Na]$^{+}$ 233. 1517, found 233.1523. .

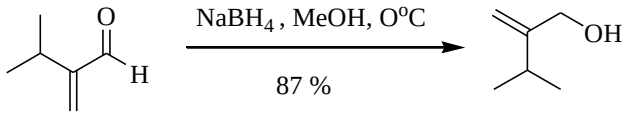
Aldehyde 408 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34(s, 1H), 6.43 (tdd, *J* = 7.5, 2.7, 1.2 Hz, 1H), 5.88 (ddt, *J* = 17.4, 10.5, 5.7 Hz, 1H), 5.37 (tdd, *J* = 6.6, 2.7, 1.2 Hz, 1H), 5.23 (ddt, *J* = 17.4, 1.5 Hz, 1H), 5.16 (m, 0.5H), 5.12 (m, 0.5H), 3.95 (dd, *J* = 6.9, 0.9 Hz, 2H), 3.93 (ddd, *J* = 6.0, 1.5 Hz, 2H), 2.46 (m, 2H), 2.19 (t, 2H), 1.70 (dt, *J* = 2.1, 0.9 Hz, 3H), 1.66 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 16.3, 26.9, 37.7, 66.3, 71.0, 117.0, 121.9, 134.7, 138.3, 139.4, 153.7, 195.1. IR (neat) ν_{max} 2924, 2853, 2711, 1687, 1645, 1447, 1360 cm^{-1}.



408 **413**

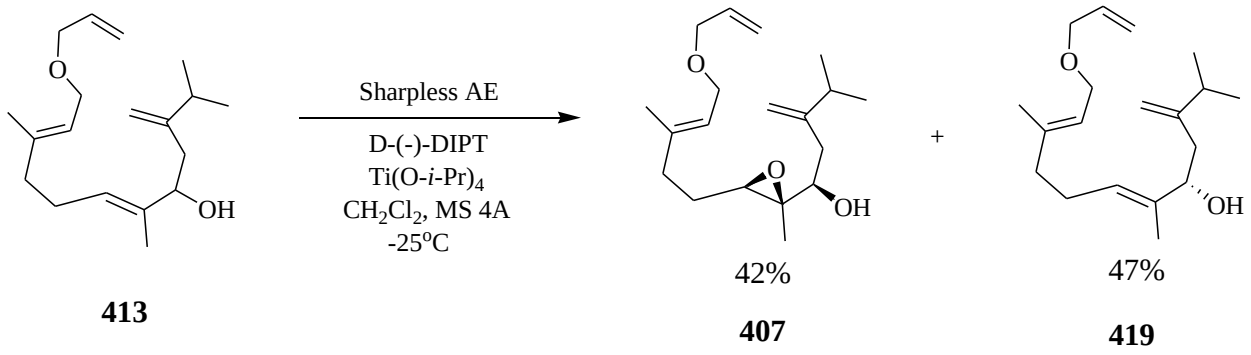
Alcohol 413. To a stirred solution of **408** (781 mg, 2.70 mmol) in THF (7 mL) and saturated aq. NH_4Cl (3.5 mL) were added Zn dust (530 mg, 8.10 mmol) and bromide **326** (880 mg, 5.40 mmol). After 16 h, to the reaction mixture were added Zn dust (176 mg, 2.70 mml) and bromide **326** (440 mg, 2.70 mml) and stirred for 5 h. To the resulting mixture were added Et_2O (5 mL) and water (3 mL) and the aqueous layer was extracted with Et_2O (20 mL X 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (elution with EtOAc : Hexane = 1:20 to 1:2) to provide alcohol **413** (750 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 - 5.85 (m, 1H), 5.45 – 5.30 (m, 2H), 5.26 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.16 (ddt, *J* = 10.2, 1.8, 1.2 Hz, 1H), 4.88 (t, *J* = 1.2 Hz, 1H), 4.80 (d, *J* = 1.2 Hz, 1H), 4.09 (q, *J* = 4.5 Hz, 1H), 3.98 - 3.94 (m, 4H), 2.32 - 2.03 (m, 7H), 1.88 (s, 1H), 1.63 (dm, *J* = 11.1 Hz, 6H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 152.6, 139.7, 136.9, 134.9, 125.6, 120.9, 117.0, 110.0, 74.9, 71.0, 66.0, 41.3, 39.0, 33.2, 25.7, 21.6, 16.4, 11.6.; IR (neat) ν_{max} 3445, 2961, 2928, 2870, 1668, 1641, 1449, 1380 cm^{-1}. HRMS[ES+] calcd for $C_{19}H_{32}O_2$ $[M + Na]^+$ 315.2296, found 315.2300.



418 **416**

Alcohol 416. To a stirred solution of aldehyde **418**[33] (3.04 g, 30.1 mmol) in MeOH (50 mL) was added $NaBH_4$ (1.17 g, 30.1 mmol) at 0 ^{o}C. After stirring at room temperature for 1 h, the reaction was quenched with saturated NH_4Cl (8 mL). The resulting mixture was diluted with H_2O (12 mL) and Et_2O (20 mL) then filtered through Celite to remove the white solids. Volatile organic solvent was carefully removed under reduced pressure (note the volatility of the product) and the residue was extracted with CH_2Cl_2 (15 mL X 4). The combined organic solution was concentrated and purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 9) to provide **416** (2.51 g, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.82 (m, 1H), 4.05 (s, 2H), 2.43 (br s, 1H), 2.26 (sept, *J* = 6.8 Hz, 1H), 1.01 (s, 3H), 1.00 (s, 3H). ^{1}H NMR data were consistent with the reported values.[32] 2-Bromo-methyl-3-methyl-1-butene (**326**) was prepared from this alcohol according to Barton et al.[31]



413

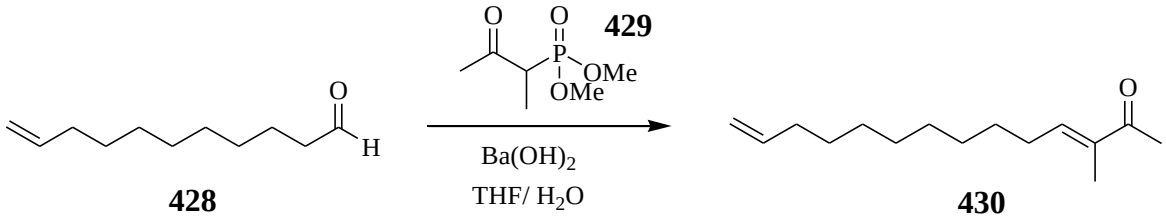
42%

407

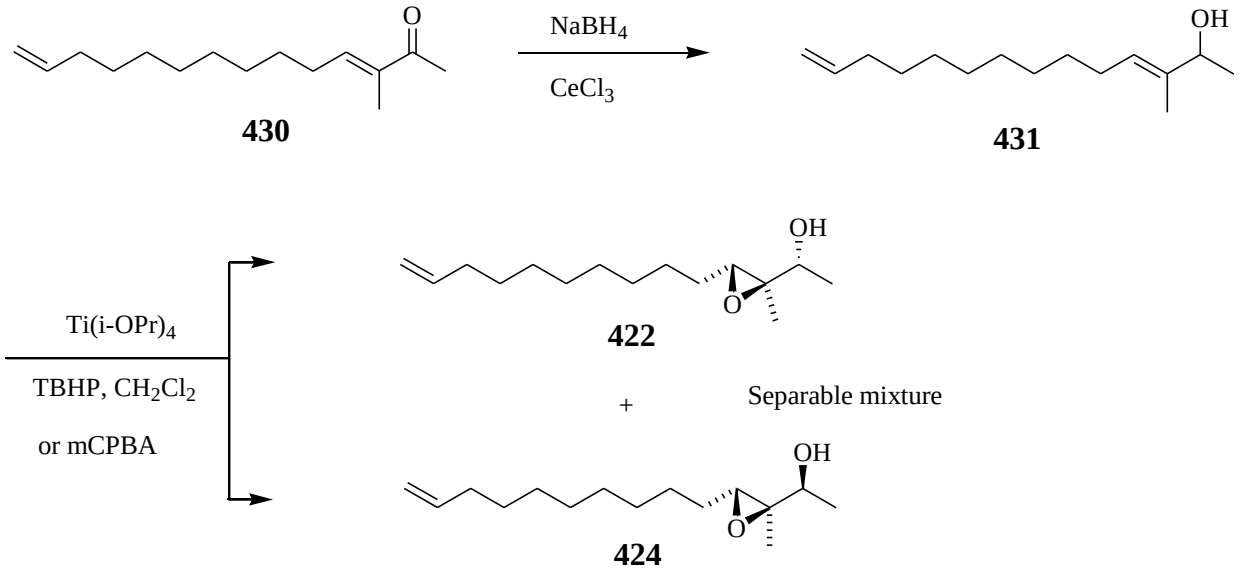
47%

419

Epoxide 407. To a stirred suspension of activated 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (45 mL) were added alcohol **413** (845 mg, 2.90 mmol) and D-(-)-DIPT (104 mg, 0.435 mmol) under Ar. The resulting mixture was stirred and cooled to - 20 ^oC. The solution of $Ti(O^iPr)_4$ (82.4 mg, 0.290 mmol) in CH_2Cl_2 (1 mL) was added dropwise and stirred at -20 ^oC for 30 min. TBHP (0.34 mL, 1.88 mmol, 5.5 M in decane with molecular sieves) was added dropwise and the resulting mixture was cooled to -25 ^oC for 20 h. It was warmed to 0 ^oC and water (1 mL) was added and then warmed to room temperature. Aqueous NaOH solution 30 % saturated NaCl (0.2 mL) was added and the resulting mixture was stirred vigorously for 30 min. The resulting mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2. The combined organic solution was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20 to 1 : 10) to afford epoxide **407** (379 mg, 42 %) as colorless oil and recovered **419** (402 mg, 47 %). **Epoxide 407 :** ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz,$CDCl_3$) δ 5.91 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1H), 5.41 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.31 - 5.12 (m, 2H), 4.86 (dt, *J* = 17.5, 1.3 Hz, 2H), 4.01 - 3.92 (m, 4H), 3.59 (ddd, *J* = 9.6, 2.9, 1.3 Hz, 1H), 2.95 (t, *J* = 6.3 Hz, 1H), 2.42 - 2.03 (m, 6H), 1.80 - 1.62 (m, 5H), 1.28 (s, 3H), 1.04 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 138.9, 134.8, 121.6, 117.0, 109.3, 72.0, 71.1, 66.4, 62.4, 60.3, 38.2, 36.1, 33.2, 26.2, 21.9, 21.5, 16.4, 13.6.; IR (neat) ν_{max} 3462, 3081, 2961, 2870, 1643, 1460, 1382 cm^{-1}. HRMS[ES+] calcd for $C_{19}H_{32}O_3$ $[M + Na]^+$ 331.2249, found.331.2246.



Methyl Ketone 430. To a stirred solution of a phosphonate **429** (1.155 g, 6.412 mmol) in THF (35 ml) was added $Ba(OH)_2$ (5.000 g, 29.14 mmol) and 10-undecenal (**428**) (1.116 g, 5.829 mmol). The reaction mixture was stirred for 5 min and hold for 16 h. To the resulting mixture was added saturated aq. $NaHCO_3$ and CH_2Cl_2, and then filtered. The aqueous later was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to give a product **430** (1.1 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* = 7.2 Hz, 1H), 5.86 - 5.76 (m, 1H), 5.01 - 4.91 (m, 1H), 2.30 (s, 3H), 2.22 (q, *J* = 7.3 Hz, 2H), 2.01 - 2.06 (m, 1H), 1.76 (s, 3H), 1.48 - 1.30 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 144.0, 139.1, 137.6, 114.1, 33.8, 29.4, 29.3, 29.1, 29.0, 28.9, 28.6, 25.4, 11.1.; IR (neat) ν_{max} 2926, 1670 cm^{-1}. HRMS[ES+] calcd for $C_{15}H_{26}O$ $[M + H]^+$ 223.2062, found 223.2062.



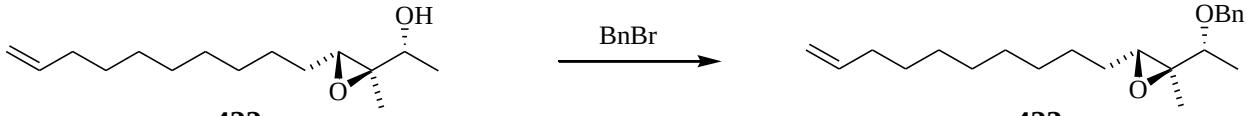
Alcohol 431. To a stirred solution of the methyl ketone **430** (1.05 g, 5.38 mmol) in MeOH (20 mL) was added $CeCl3_7 \cdot H_2O$ (2.05 g, 5.38 mmol). The reaction mixture was cooled to 0 ^oC and $NaBH_4$ (204 mg, 5.38 mmol) was added and stirred for 1 h at 0 ^oC. The resulting mixture was quenched with saturated aq. NH_4Cl (5 mL) and concentrated under reduced pressure. The residue was extracted with Et_2O (15 mL X 3). The combined organic layer was washed with brine, and dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1 : 10) to give alcohol **431** (945 mg, 95 %). ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 - 5.75 (m, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 5.03 - 4.89 (m, 3H), 4.25 - 4.16 (m, 1H), 2.08 - 1.96 (m, 4H), 1.62 (s, 3H), 1.35 - 1.23 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.3, 125.4, 114.0, 73.5, 33.8, 29.5, 29.5, 29.4, 29.3, 29.1, 28.9, 27.5, 21.6, 11.4.; IR (neat) ν_{max} 3343, 2925 cm^{-1}. HRMS[EI] calcd for $C_{15}H_{26}O$ $[M]^+$ 224.21402, found 224.21353.

Epoxy alcohols 422 and 424 (model compounds). To a stirred suspension of activated 4 Å molecular sieves (0.4 g) in CH_2Cl_2 (34 mL) were added alcohol **431** (0.975 g, 4.97 mmol) and cooled at - 20 ^oC. Ti reagent was added and the reaction mixture was stirred for 0.5 h. TBHP (2.2 mL, 0.993 mmol, 5.5 M) was added and the resulting mixture was stirred for 5 h at -20 ^oC. The mixture was quenched with water and warmed to rt. The mixture was filtered and extracted with CH_2Cl_2. The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1: 4) to

afford the anti-epoxy alcohol **422** (690 mg, 58 % : the fast moving isomer) and **424** (315 mg, 31 % : the slow moving isomer).

Anti - epoxy alcohol 422: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 - 5.73 (m, 1H), 5.05 – 4.86 (m, 2H), 3.77 (q, *J* = 6.3, 1H), 3.02 (t, *J* = 6.0 Hz, 1H), 2.23 (s, 1H), 2.10 - 1.96 (m, 2H), 1.62 - 1.25 (m, 17H), 1.20 (d, *J* = 6.3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 68.5, 63.6, 59.0, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.1, 26.4, 18.4, 14.3.; IR (neat) ν_{max} 3450, 2926, 2855 cm^{-1}. HRMS[EI] calcd for $C_{15}H_{28}O_2$ $[M]^+$ 241.21676, found 241.21609.

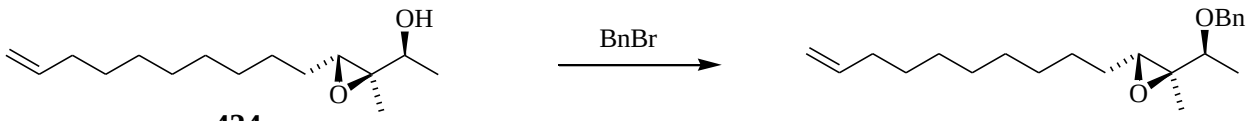
Syn- epoxy alcohol 424: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 - 5.78 (m, 1H), 4.98 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.95 (m, 1H), 3.47 - 3.41 (m, 1H), 2.88 (t, *J* = 6.0 Hz, 1H), 2.12 (d, *J* = 4.8 Hz, 1H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.61 - 1.27 (m, 17H), 1.22 (d, *J* = 9.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 72.3, 63.9, 61.8, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.1, 26.4, 18.7, 11.3.; IR (neat) ν_{max} 3418, 2926, 2856 cm^{-1}. HRMS[ES+] calcd for $C_{15}H_{28}O_2$ $[M + Na]^+$ 263.1996, found 263.1987.



422 **423**

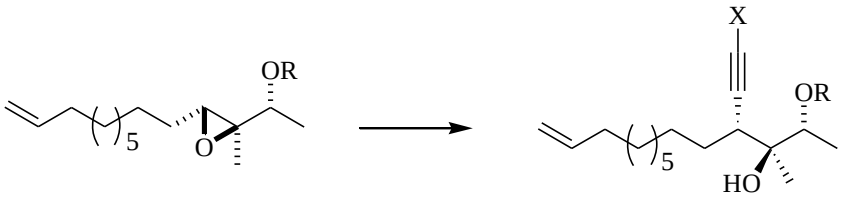
Bn-protected alcohol 423. To a stirred solution of epoxide **422** (457 mg, 2.02 mmol) in THF (9 mL) was added BnBr (414 mg, 2.43 mmol) and NaH (96.9 mg, 2.42 mmol, 60 %). The reaction mixture was stirred for 21 h. The resulting mixture was quenched with water (1 mL) and Et_2O (3 mL) was added. After separation, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 10 : 100 to 1: 20) to afford epoxide **423** (442 mg, 91 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 - 7.25 (m, 5H), 5.85 - 5.78 (m, 1H), 4.99 (dd, *J* = 17.4, 1.8 Hz, 1H), 4.94 - 4.92 (m, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 3.13 (q, *J* = 6.4 Hz, 1H), 2.82 (t, *J* = 6.0 Hz, 1H), 2.05 (m, 2H), 1.58 - 1.27 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.5, 128.3, 127.5, 127.4, 114.1, 79.0, 71.1, 64.0, 61.0, 33.7, 29.4, 29.3, 29.1, 28.9, 28.4, 26.4, 16.4, 11.4.; IR (neat) ν_{max}

3065, 3030, 2976, 2926, 2855 cm^{-1}. HRMS[ES+] calcd for $C_{22}H_{34}O_2$ $[M + Na]^+$ 353.2457, found 353.2449.



424 **245**

Bn-protected alcohol 425. To a stirred solution of epoxide **424** (74.9 mg, 0.312 mmol) in THF (1 mL) was added BnBr (63.9 mg, 0.374 mmol) and NaH (17.4 mg, 0.436 mmol, 60 %). The reaction mixture was stirred for 14 h. The resulting mixture was quenched with water (0.3 mL) and added Et_2O (3 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to afford epoxide **425** (89 mg, 91 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.23 (m, 5H), 5.86 - 5.76 (m, 1H), 4.99 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.95 - 4.92 (m, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 3.15 (q, *J* = 6.6 Hz, 1H), 2.61 (m, 1H), 2.04 (m, 2H), 1.68 - 1.30 (m, 17H), 1.20 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.7, 128.3, 127.6, 127.4, 114.1, 80.2, 71.1, 63.2, 59.0, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.0, 26.4, 17.9, 11.0; IR (neat) ν_{max} 3064, 3031, 2976, 2925, 2854 cm^{-1}. HRMS[ES+] calcd for $C_{22}H_{34}O_2$ $[M + Na]^+$ 353.2457, found 353.2463.

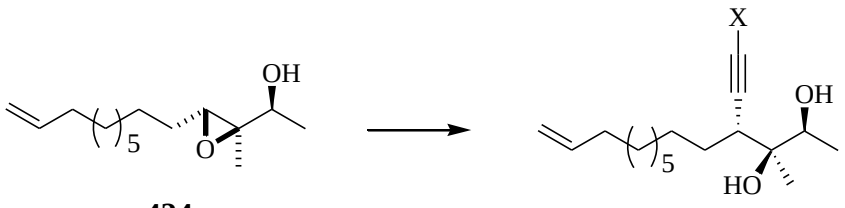


423 (R = Bn) 2, 3 - diol

433 (R = Bn, X = H)

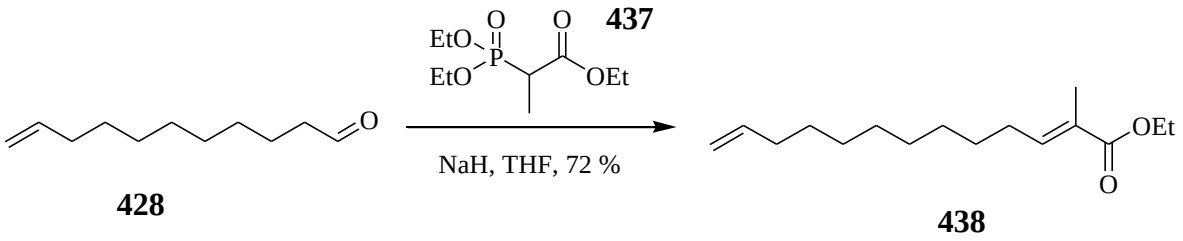
Diol 433: To a stirred solution of epoxide **423** (31.5 mg, 0.10 mmol) in DMSO (0.35 mL) were added HMPA (0.35 mL) and Li-acetylene diamine complex (153 mg, 1.66 mmol). The reaction

mixture was stirred at 50 ^{o}C for 24 h. To the mixture were added saturated aq. NH_4Cl (1 mL) and H_2O (1 mL), and saturated aq. LiCl (1 mL). After separation, the organic layer was concentrated under reduced pressure and purified by a silica gel column chromatography to provide **433** (2.4 mg, 7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.31 (m, 5H), 5.74 - 5.88 (m, 1H), 5.03 - 4.90 (m, 3H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 3.66 (q, *J* = 6.3 Hz, 1H), 3.48 (q, *J* = 3.51 - 3.44 (m, 1H), 2.07 (d, *J* = 2.4 H, 1H), 1.30 - 1.25 (m, 19). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 128.4, 127.8, 127.7, 114.1, 85.1, 79.1, 75.4, 71.5, 71.2, 39.1, 33.8, 29.7, 29.5, 29.4, 29.1, 28.9, 28.6, 28.1, 20.6, 12.8.; IR (neat) ν_{max} 3307, 2926, 2854 cm^{-1}. HRMS[ES+] calcd for $C_{24}H_{36}O_2$ $[M + Na]^+$ 379.2613, found 379.2615.



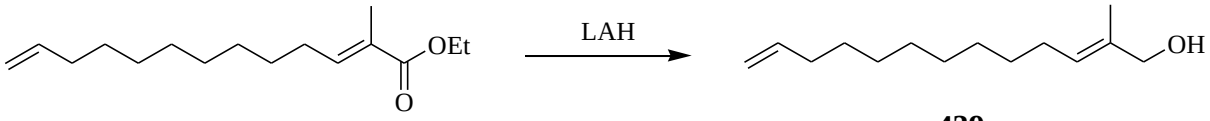
424 X = TMS **435**

Diol 435 (X = TMS): To a stirred solution of TMS-acetylene (0.15 mL, 1.1 mmol) was added n-BuLi (0.43 mL, 0.696 mmol, 1.6 M) dropwise at - 15 ^{o}C and stirred for 30 min at the same temperature. Et_2AlCl (0.43 mL, 0.70 mmol) was added dropwise. The reaction mixture was warmed to O ^{o}C and stirred for 1.5 h at the same temperature. The epoxy alcohol **424** was added, and the resulting mixture was warmed to rt and stirred for 12 h. The reaction mixture was quenched with saturated aq. NH_4Cl solution and Et_2O was added. After separation, the organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 7) to afford diol **435** (26 mg, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 - 5.76 (m, 1H), 5.01 - 4.91 (m, 2H), 4.03 (d, *J* = 5.5 Hz, 1H), 2.58 (d, *J* = 9.9 Hz, 2H), 2.22 (s, 1H), 2.08 (s, 1H), 2.04 (q, *J* = 6.9 Hz, 2H), 1.43 - 1.36 (m, 14H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.14 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 107.8, 88.5, 75.6, 70.9, 41.5, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.7, 28.1, 19.4, 17.0, 0.07.; IR (neat) ν_{max} 3392, 2923, 2852, 2161 cm^{-1}. HRMS[ES+] calcd for $C_{20}H_{38}O_2Si$ $[M + H]^+$ 339.2719, found 339.2722.



428 **438**

Ester 438. To a stirred solution of phosphonate **437** (4.72 g, 19.7 mmol) in THF (25 ml) was added NaH (0.984 mg, 24.6 mmol) at 0 ^{o}C and slowly warmed. The reaction mixture was stirred for 1 h at rt and cooled to 0 ^{o}C. 10-undecenal (**428**) (3.15 g, 16.45 mmol) was added and then the resulting mixture was warmed to rt. After 20 h, the mixture was quenched with water. After separation, the aqueous layer was extracted with Et_2O (20 mL X 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1: 4) to afford ester **438** (3.24 g, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (t, *J* = 7.5 Hz, 1H), 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.97 - 4.87 (m, 2H), 4.18 - 4.12 (q, *J* = 7.1 Hz, 2H), 2.13 (q, *J* = 7.4 Hz, 2H), 2.00 (q, *J* = 6.9 Hz, 2H), 1.79 (s, 3H), 1.42 - 1.24 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 142.2, 138.9, 127.6, 114.0, 60.2, 33.7, 29.3, 29.2, 29.0, 28.8, 28.6, 28.5, 14.2, 12.2.; IR (neat) ν_{max} 2928, 1714 cm^{-1}. HRMS[ES+] calcd for $C_{16}H_{28}O_2$ $[M + H]^+$ 253.2168, found 253.2170.



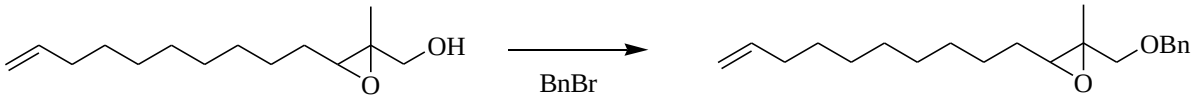
438 **439**

Alcohol 439. To a solution of the ester **438** (2.04 g, 8.09 mmol) in THF (95 mL) was added LAH (very slowly) (321 mg, 8.45 mmol) and stirred at rt. After 24 h, it was quenched with water (15 mL) and extracted with Et_2O (20 mL X 3). The combined organic mixture was concentrated reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to give alcohol **439** (941 mg, 55 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 - 5.76 (m, 1H), 5.41 (td, *J* = 7.2, 1.2, 1H), 4.99 (ddd, *J* = 17.2, 3.6, 1.6, 1H), 4.93 (dm, *J* = 10.2, 1H), 4.00 (s, 2H), 2.03 (quint, *J* = 7.1, 4H), 1.66 (s, 3H), 1.39 - 1.28 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$)

139.2, 134.5, 126.7, 114.1, 69.1, 33.8, 29.49, 29.48, 29.4, 29.3, 29.1, 28.9, 27.6, 13.6.; IR (neat) ν_{max} 3328, 2924, 2854. HRMS[EI] calcd for $C_{14}H_{26}O$ [M]$^+$ 210.19837, found 210.19865.

439 **426**

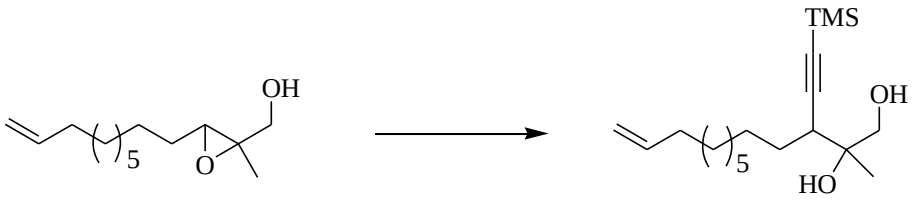
Epoxide 426. To the alcohol **439** (225 mg, 1.07 mmol) solution in CH_2Cl_2 (3 ml) was added mCPBA (251 mg, 1.12 mmol, max 77%) at 0 ^oC and stirred for 1 h. 10 % KOH solution was added and extracted with CH_2Cl_2 (5 ml X 2) and dried over $MgSO_4$ and concentrated under reduced pressure. After silica gel column chromatography, 211 mg epoxide **426** was obtained in 88 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 - 5.75 (m, 1H), 4.98 (ddd, *J* = 17.1, 3.6, 1.6 Hz, 1H), (dm, *J* = 10.2 Hz, 1H), 3.67 (dd, *J* = 12.2, 3.7 Hz, 1H), 3.56 (dd, *J* = 12.2, 8.1 Hz, 1H), 3.02 (m, 1H), 2.03 (q, *J* = 6.8 Hz, 2H), 1.71 (s, 1H), 1.58 - 1.27 (m, 17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 114.0, 65.5, 60.9, 60.3, 33.7, 29.3, 29.2, 29.0, 28.8, 28.1, 26.3, 14.1. ; IR (neat) ν_{max} 3418, 3077, 2924 cm^{-1}.



426 **427**

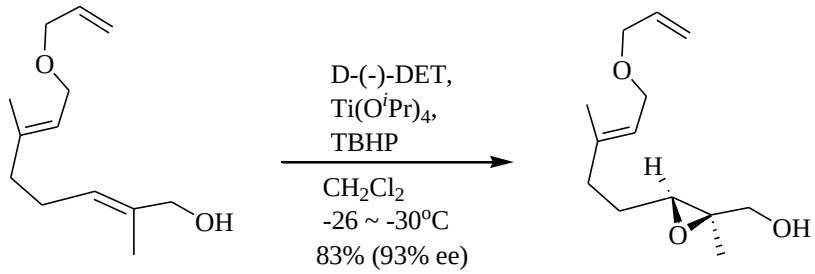
Bn-protected alcohol 427. To a stirred solution of epoxide **426** (183 mg, 0.809 mmol) in THF (3 mL) was added BnBr (168 mg, 0.971 mmol) and NaH (38.9 mg, 0.971 mmol, 60 %). The reaction mixture was stirred for 21 h and it was quenched with water (1 mL) and Et_2O was added. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1: 20) to afford the Bn-protected epoxy alcohol **427** (249 mg, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 - 7.23 (m, 5H), 5.88 - 5.75 (m, 1H), 5.03 - 4.91 (m, 2H), 4.59 (d, *J* = 12.3 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 3.50 (d, *J* = 10.9 Hz, 1H), 3.44 (d, *J* = 10.9 Hz, 1H), 2.87 - 2.84 (m, 1H), 1.59 - 1.30 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.1, 128.3, 127.7, 114.1, 74.9, 73.1, 61.1, 59.7, 33.8, 29.5, 29.4,

29.3, 29.1, 28.9, 28.2, 26.5, 14.5.; IR (neat) ν_{max} 3065, 3031, 2926, 2854 cm^{-1}. HRMS[ES+] calcd for $C_{21}H_{32}O_2$ $[M + Na]^+$ 339.2300, found 339.2305.



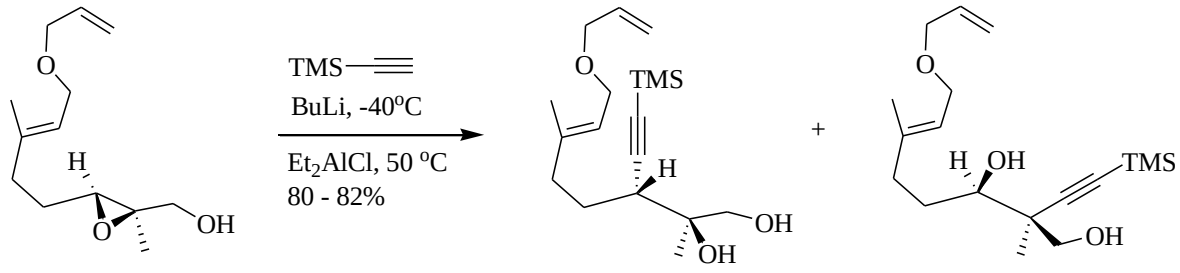
426 2, 3 - diol **440**

Diol 440 : To a stirred solution of TMS-acetylene (0.15 mL, 1.1 mmol) was added n-BuLi (0.44 mL, 0.70 mmol, 1.6 M) dropwise at - 30 ^oC and stirred for 30 min at the same temperature. The resulting mixture was warmed to 0 ^oC and added Et_2AlCl (0.70 mL, 0.70 mmol, 1.0 M) dropwise and stirred for 1.5 h at 0 ^oC. The epoxy alcohol **426** (53 mg, 0.23 mmol) was added and the mixture was warmed to rt and stirred for 17 h. The reaction mixture was quenched with saturated aq. NH_4Cl (1 mL) and Et_2O (2 mL) were added. After separation, the aqueous layer was extracted with Et_2O (3 mL X 4). The combined organic layer was concentrated under reduced pressure and purified by a silica gel column chromatography (eluent with EtOAc : hexane = 1 : 7) to afford diol **440** (41 mg, 55 %). ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.92 (d, *J* = 9.5 Hz, 1H), 3.78 (d, *J* = 11.0, 1H), 3.48 (d, *J* = 11.0, 1H), 2.53 - 2.50 (m, 1H), 2.06 - 2.01 (m, 2H), 2.26 (br s, 1H), 2.13 (br, 1H), 1.71 - 1.60 (m, 1H), 1.37 - 1.29 (m, 13H), 1.19 (s, 3H), 0.14 (s, 9H). NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 107.2, 88.3, 74.0, 68.8, 41.2, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.6, 28.1, 20.2, - 0.05.; IR (neat) ν_{max} 3343, 2921, 2850, 2159 cm^{-1}. HRMS[ES+] calcd for $C_{19}H_{36}O_2Si$ $[M + H]^+$ 325.2563, found 325.2568.



411 **442**

Epoxy Alcohol 442. Regio- and stereoselective epoxidation was accomplished by the catalytic procedure of Sharpless. To a stirred suspension of activated 4 Å molecular sieves (1.6 g) in CH_2Cl_2 (124 mL) under argon were added alcohol **411** (2.59 g, 12.3 mmol) and D-(-)-DET (381 mg, 1.85 mmol). The resulting mixture was stirred and cooled to - 20 ^oC. A solution of Ti(O^{i}Pr)$_4$ (350 mg, 1.23 mmol) in CH_2Cl_2 (2 mL) was added dropwise and stirred at -20 ^oC for 30 min. Then TBHP (4.50 mL, 24.7 mmol, 5.5 M in decane with molecular sieves) was added dropwise and the resulting mixture was cooled to -26 to -30 ^oC. After 2.5 h, it was warmed to 0 ^oC, water (7 mL) was added, and the solution was allowed to warm to room temperature. A 30% NaOH solution saturated with solid NaCl was prepared. Of this, 1.4 mL was added to the reaction mixture. Vigorous stirring was continued for 30 min. Then the reaction mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2. The combined organic solution was concentrated under reduced pressure and subjected to silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4 to 1 : 1) to afford epoxide **442** (2.42 g, 83 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.69 (s, 3H), 1.79 – 1.65 (m, 2H), 1.84 (d, *J* = 5.0 Hz, 1H), 2.20 (m, 1H), 3.03 (t, *J* = 6.5 Hz, 1H), 3.60 (dd, *J* = 12.3, 8.3 Hz, 1H), 3.61 (dd, *J* = 12.5, 4.3 Hz, 1H), 3.98 (t, 4H), 5.18 (d, *J* = 10.5 Hz, 1H), 5.27 (d, *J* = 17.5 Hz, 1H), 5.41 (t, *J* = 6.5 Hz, 1H), 5.92 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 16.3, 26.3, 36.1, 60.0, 60.9, 65.6, 66.4, 71.1, 117.0, 121.5, 134.8, 138.9.; IR (neat) ν_{max} 3441, 2925, 2857, 1741, 1670, 1647, 1449, 1384 cm^{-1}. HRMS[ES+] calcd for $C_{13}H_{22}O_3$ [M + Na]$^+$ 249.1467, found 249.1456. The enantiomeric excess was determined to be 93 % ee by comparison of the ^{1}H NMR of the (*S*)-MTPA and the (*R*)-MTPA ester.



442 2, 3 - diol **443** 2, 4 - diol **444**

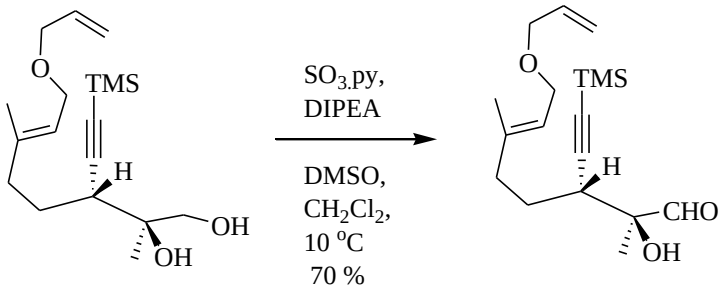
Diols 443 and 444. To a solution of TMS-acetylene (1.33 mL, 9.31 mmol) in toluene (12 mL) was added n-BuLi (2.8 mL, 6.98 mmol, 2.5 M) for 3 min at - 60 °C. The reaction mixture was warmed to °C. Et_2AlCl (7.0 mL, 6.98 mmol, 1.0 M) was added dropwise for 20 min and the resulting mixture was stirred for 1h at 0 °C and an ice bath was removed. The solution of epoxide **442** (535 g, 2.27 mmol) in toluene (7 mL) was added and the mixture was directly immersed a pre-heated (50 - 60 °C) oil bath. The reaction mixture was stirred overnight. The mixture was quenched with saturated aq. NH_4Cl and water. Et_2O was added and the aqueous layer was extracted with Et_2O (15 mL X 3 times). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue (a ratio of **443** : **444** = 3.5 : 1.0) was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 4) to give **443** (484 mg, a ratio of **443** : **444** = 2.6 : 1.0, 66 %) and **443** (118 mg, a ratio of **443** : **444** = 1 : 1, 16 %).

Slow moving isomer 443: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 - 5.88 (m, 1H), 5.41 (td, *J* = 6.8, 1.2 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.02 – 3.95 (m, 4H), 3.77 (d, *J* = 11.2 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.50 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.36 - 2.30 (m, 3H), 2.12 - 2.04 (m, 1H), 1.84 (dddd, *J* = 12.8, 10.1, 7.2, 3.3 Hz, 1H), 1.68 (s, 3H), 1.52 - 1.43 (m, 1H), 1.18 (s, 3H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 135.0, 121.3, 117.2, 107.0, 88.4, 74.0, 71.1, 68.9, 66.5, 40.2, 37.8, 26.7, 19.9, 16.5, 0.04.; IR (neat) ν_{max} 3408, 2958, 2167 cm^{-1}. HRMS[ES+] calcd for $C_{18}H_{32}O_3Si$ $[M + Na]^+$ 347.2018, found 347.2015.

Fast moving isomer 444: HRMS[ES+] calcd for $C_{18}H_{32}O_3Si$ $[M + H]^+$ 325.2199, found 325.2198.

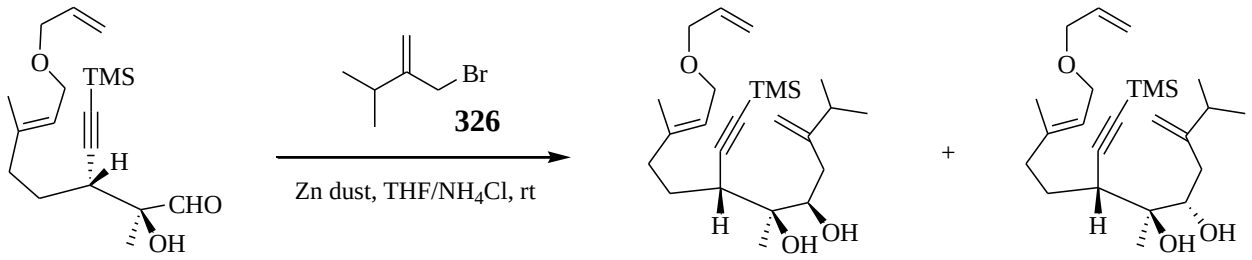
Mixture of isomer 443 and 444 (ratio = 1 : 1) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 - 5.88 (m, 1H), 5.45 - 5.40 (m, 1H), 5.27 (dd, *J* = 17.2, 0.6 Hz, 1H), 5.18 (d, *J* = 10.4, 1H), 4.06 – 3.97 (m,

4H), 3.78 (d, *J* = 11.0 Hz, 0.5H), 3.69 (dd, *J* = 10.4, 1.4 Hz, 0.5H), 3.64 (d, *J* = 10.8 Hz, 0.5H), 3.55 (d, *J* = 10.8 Hz, 0.5H), 3.47 (d, *J* = 11.0, 0.5H), 2.50 (dd, *J* = 11.7, 3.2 Hz, 0.5 H), 2.36 - 2.26 (m, 2H), 2.19 - 2.04 (m, 2H), 1.97- 1.80 (m, 2H), 1.68 (s, 3H), 1.19 (s, 1.5H), 1.13 (s, 1.5H), 1.56 - 1.44 (m, 1H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 139.7, 135.0, 134.9, 121.4, 121.3, 117.1, 108.9, 106.9, 88.6, 88.5, 77.2, 74.6, 74.0, 71.1, 68.8, 68.7, 66.5, 66.4, 43.3, 40.4, 37.8, 36.5, 30.0, 26.8, 20.0, 17.2, 16.5, 16.3, 0.10, 0.05. IR (neat) ν_{max} 3404, 2958, 2166, 1249 cm^{-1}.



443 **445**

Aldehyde 445. To a solution of **443** (660 g, 2.04 mmol, a ratio of **443** : **444** = 2.6 : 1.0) in CH_2Cl_2 was added DIPEA (1.368 g, 10.58 mmol) and DMSO (1.670 g, 21.37 mmol) and cooled to 0 °C. SO_3Py complex (992 mg, 6.107 mmol) was added and stirred for 30 min at 0 °C. The reaction mixture was warmed to 10 °C and stirred for 4 h. 1N HCl was added to adjust pH 3 ~ 4. After separation, CH_2Cl_2 (5 mL) was added and washed with $NaHCO_3$ (sat.) and brine. It was dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde **445** (908 g) was directly used in a Barbier addition. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 0.7 Hz, 1H), 5.92 (ddt, *J* = 16.9, 10.3, 5.6 Hz, 1H), 5.39 (t, *J* = 6.4 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dd, *J* = 10.4, 0.8, 1H), 3.97 (t, *J* = 7.2 Hz, 4H), 3.16 (br s, 1H), 2.47 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.34 - 2.28 (m, 1H), 2.12 - 2.04 (m, 1H), 1.73 -1.58 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 0.16 (d, *J* = 0.8 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 135.0, 121.4, 121.5, 117.3, 107.2, 88.6, 74.2, 71.2, 69.0, 66.7, 66.6, 40.4, 37.9, 26.9, 20.1, 20.0, 16.6, 16.5, 0.2.; IR (neat) ν_{max} 3422, 2959, 2169, 1734, 1251 cm^{-1}.



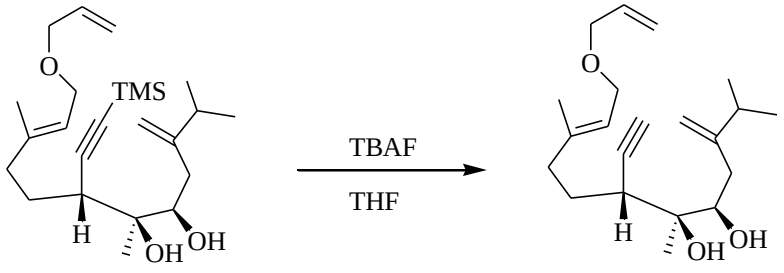
445 **446 (major)** **447 (minor)**

Diols 446 and 447. To a solution of aldehyde **445** (908 g) in THF (18 mL) were added saturated aq. NH_4Cl (9 mL), bromide **326** (896 mg, 5.49 mmol), and Zn dust (599 mg). The resulting mixture was stirred for 20 h. If **445** is left, Zn dust and bromide will be added more (the conversion should be checked by proton NMR because TLC does not show clearly a progress of the reaction). The reaction mixture was extracted with Et_2O (10 mL X 3 times) and filtered throughout Celite to remove Zinc dust. The organic layer was washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure. The residue (a ratio of **446** : **447** = 2 : 1) was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 9) to provide **446** (165 mg, 28 % for 2 steps based on **443**), and **447** (132 mg, 22 % for 2 steps based on **443**), and the mixture of **446** and **447** (121 mg, 20 % for 2 steps based on **443**).

Slower moving isomer (major 446): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 - 5.86 (m, 1H), 5.44 - 5.40 (m, 1H), 5.28 (dq, *J* = 17.4, 1.5 Hz, 1H), 5.18 (dm, *J* = 10.2 Hz, 1H), 4.83 (s, 1H), 4.04 - 3.93 (m, 4H), 3.78 (d, *J* = 10.8 Hz, 1H), 2.60 (d, *J* = 13.6 Hz, 1H), 2.46 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.42 – 2.21 (m, 3H), 2.18 – 2.00 (m, 3H), 1.99 – 1.86 (m, 1H), 1.69 (s, 3H), 1.57 - 1.49 (m, 1H), 1.31 (s, 3H), 1.11 - 1.09 (d, *J* = 4.5 Hz, 3H), 1.07 (d, *J* = 4.5 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 140.0, 135.0, 116.9, 110.8, 106.7, 88.2, 76.7, 74.8, 72.1, 71.0, 66.5, 39.6, 37.8, 36.3, 32.9, 27.1, 22.4, 21.5, 20.7, 16.5, 0.04.

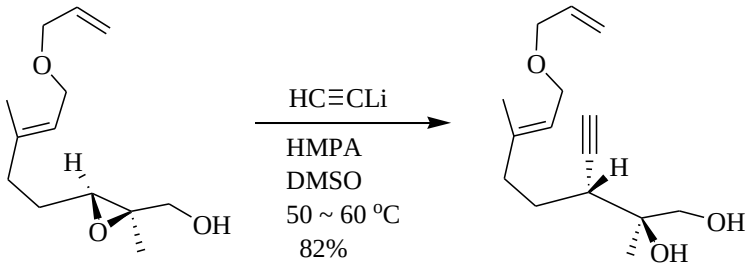
Faster moving isomer (minor 447): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 - 5.90 (m, 1H), 5.42 (t, *J* = 6.5 Hz, 1H), 5.28 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.98 (s, 1H), 4.85 (s, 1H), 4.04 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.01 - 3.96 (m, 4H), 2.70 (dd, *J* = 11.5, 3.0 Hz, 1H), 2.42 (d, *J* = 13.5 Hz, 1H), 2.38 - 2.31 (m, 1H), 2.28 (quint, *J* = 7.0 Hz, 1H), 2.14 (dd, *J* = 11.0 Hz, 1H), 2.11 - 2.05 (m, 1H), 1.96 - 1.90 (m, 1H), 1.68 (s, 3H), 1.55- 1.47 (m, 1H), 1.15 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

153.0, 139.9, 135.0, 121.2, 116.9, 110.6, 108.0, 87.7, 75.3, 71.2, 70.9, 66.5, 40.8, 38.1, 36.4, 33.4, 26.7, 22.1, 21.5, 17.8, 16.4, 0.04.; IR (neat) ν_{max} 3397, 3082, 2963, 2164, 1640, 1452, 1250 cm^{-1}.



446 (major) **406**

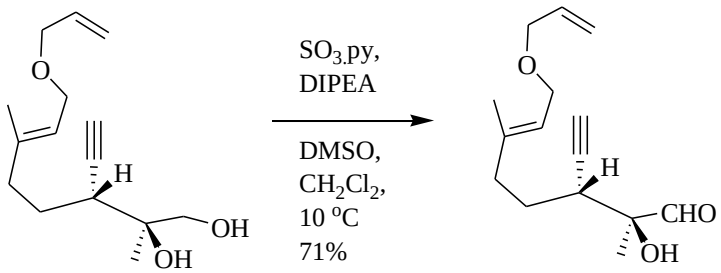
406 : To a stirred solution of **446** (165 mg, 0.405 mmol) in THF (12 mL) was added TBAF (0.47 mL, 0.461 mmol, 1.0 M). The reaction mixture was stirred for 5 h and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 4) to provide **446** (138 mg, 99 %). The ^{1}H NMR data were consistent with the reported values of the same product, which was synthesized from **448**.



442 **410**

Diol 410. To a stirred solution of epoxide **442** (933 mg, 3.95 mmol) in DMSO (13 mL) and HMPA (13 mL) under argon was added Li-acetylide·ethylenediamine complex (2.02 g, 19.8 mmol, 90 %) at room temperature. The mixture was warmed to 55 ^oC and stirred for 3.5 h. The reaction mixture was carefully quenched with saturated aq. NH_4Cl (3 mL) at 0 ^oC and the resulting mixture was diluted with Et_2O (45 mL). Then saturated aq. LiCl was added very carefully. The resulting mixture was separated and the aqueous solution was extracted with Et_2O (20 mL X 5). The combined organic solution was dried over $MgSO_4$, decolorized with activated

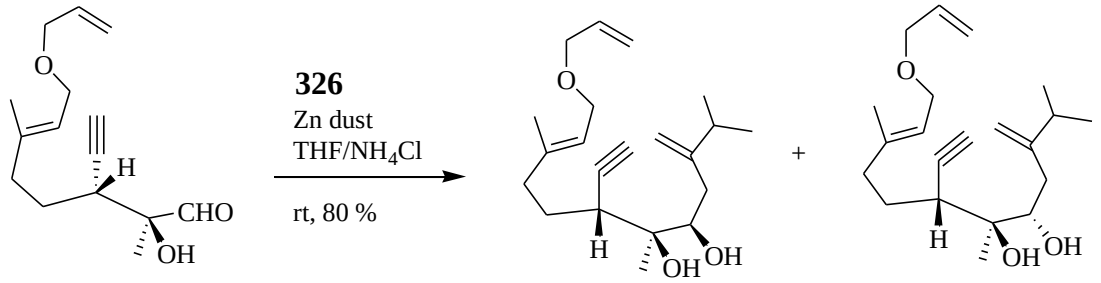
charcoal, and concentrated under reduced pressure. Silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 1) provided diol **410** (814 mg, 82 %) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.43 (m, 1H), 1.61 (s, 3H), 1.84 (m, 1H), 2.03 (m, 1H), 2.07 (d, *J* = 2.8 Hz, 1H), 2.28 (m, 1H), 2.43 (dt, *J* = 11.6, 2.6 Hz, 1H), 3.05 (br, 1H), 3.40 (d, *J* = 11.2 Hz, 1H), 3.70 (d, *J* = 11.2 Hz, 1H), 3.92 (m, 4H), 5.12 (dd, *J* = 10.4, 4.0 Hz, 1H), 5.21 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.35 (td, *J* = 7.2, 1.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 19.3, 26.3, 37.5, 38.3, 66.3, 68.4, 70.8, 71.4, 73.9, 84.5, 117.0, 120.9, 134.6, 139.6.; IR (neat) ν_{max} 3418, 3080, 2935, 2110, 1668, 1646, 1455, 1381 cm^{-1}. HRMS[ES+] calcd for $C_{15}H_{24}O_3$ $[M + Na]^+$ 275.1623, found 275.1615.



410 **448**

Aldehyde 448. Oxidation was performed by the Parikh-Doering method. To a stirred solution of diol **410** (200 mg, 0.793 mmol) in CH_2Cl_2 (5.5 mL) were added DMSO (495 mg, 6.34 mmol) and *N*,*N*-diisopropylamine (DIPEA) (410 mg, 3.17 mmol). Then the reaction mixture was cooled to 0 °C under argon. The SO_3·Py complex (322 mg, 1.98 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. Then it was warmed to 10 °C andstirred for 2 h. Additional DMSO (0.14 mL, 1.97 mmol), DIPEA (0.10 mL, 0.57 mmol), and SO_3·Py complex (130 mg, 98%, 0.80 mmol) were added and stirring was continued for 1h. The reaction mixture was quenched with 1*N* HCl (3 mL) and extracted with CH_2Cl_2 (5 mL X 2). The combined organic solution was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford aldehyde **448** as a colorless oil (142 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.59 (s, 3H), 1.61 (m, 1H), 2.01 - 2.10 (m, 1H), 2.18 (d, *J* = 2.4 Hz, 1H), 2.24 - 2.31 (m, 1H), 2.46 (ddd, *J* = 10.4, 4.4, 2.4 Hz, 1H), 3.35 (br, 1H), 3.91 (m, 4H), 5.12 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.21 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.34 (td, *J* = 6.4, 0.8 Hz,

1H), 5.86 (m, 1H), 9.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 19.6, 26.8, 36.9, 38.4, 66.2, 70.8, 73.2, 78.0, 81.9, 116.8, 121.7, 134.8, 138.6, 203.3.; IR (neat) ν_{max} 3430, 3295, 3080, 2935, 2859, 1732, 1669, 1646, 1452, 1349 cm^{-1}. HRMS[ES+] calcd for $C_{15}H_{22}O_3$ $[M + H]^+$ 251.1647, found 251.1657.



448 **406** **449**

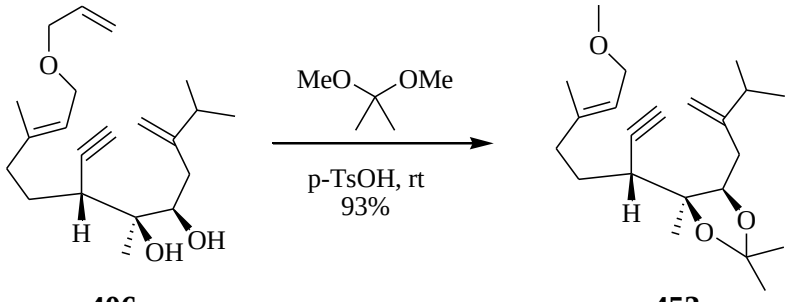
Diols 406 and 449. The allylation procedure of Luche et al. was used. To a stirred solution of aldehyde **448** (374 mg, 1.43 mmol) in THF (10 mL) and saturated aq. NH_4Cl (5 mL) were added 2-bromo-methyl-3-methyl-1-butene (**326**) (1.07 g, 6.57 mmol) and activated Zn dust (683 mg, 10.5 mmol). The reaction mixture was stirred for 12 h under argon and diluted with Et_2O (10 mL). The resulting mixture was filtered through Celite and the filter cake was washed with Et_2O. After separation of the layers, the aqueous phase was extracted with Et_2O (10 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford a mixture of **5a** and **13a** (398 mg, 80 %, d.r. **5a** : **13a** = 1.8 : 1.0).

A sample of the mixture was subjected to additional chromatography and spectroscopic data were obtained for each isomer.

Slower moving isomer, later shown to be 406 (colorless oil) : ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.32 (s, 3H), 1.57 (m, 1H), 1.69 (s, 3H), 1.97 (m, 1H), 2.02 (m, 1H), 2.07 – 2.14 (m, 3H), 2.29 (m, 1H), 2.37 (m, 1H), 2.47 (dt, *J* = 11.5, 2.6 Hz, 1H), 2.58 (d, *J* = 13.5 Hz, 1H), 3.79 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.98 (dd, *J* = 11.5, 6.0 Hz, 4H), 4.84 (s, 1H), 4.98 (s,1H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.27 (dd, *J* = 15.5, 1.5, 1H), 5.43 (td, *J* = 5.5, 1.0 Hz, 1H), 5.89 – 5.97 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 20.7, 21.4, 22.2, 26.9,

33.0, 36.2, 37.7, 38.4, 66.5, 70.9, 71.8, 71.9, 74.7, 84.2, 110.8, 116.9, 121.3, 135.0, 139.7, 153.2.; IR (neat) ν_{max} 3454, 3307, 3081, 2962, 2871, 1640, 1455, 1379 cm^{-1}. HRMS[ES+] calcd for $C_{21}H_{34}O_3$ $[M + Na]^+$ 357.2406, found 357.2398.

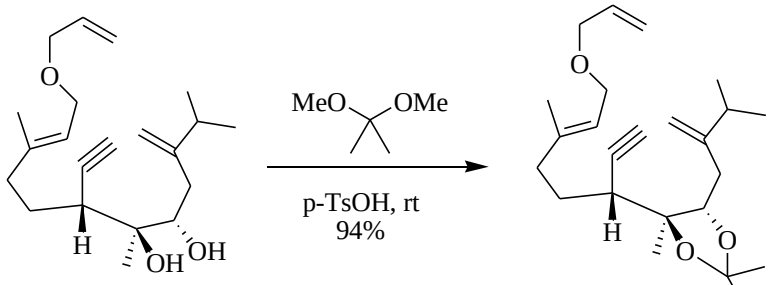
Faster moving isomer, later shown to be 449 (white solid) : ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.16 (s, 3H), 1.53 (m, 1H), 1.68 (s, 3H), 1.96 (m, 1H), 2.05 – 2.11 (m, 1H), 2.11 (d, *J* = 2.4 Hz, 1H), 2.13 – 2.19 (m, 1H), 2.18 (d, *J* = 2.0 Hz, 1H), 2.25 (s, 1H), 2.25 – 2.30 (m, 1H), 2.33 – 2.40 (m, 1H), 2.41 (d, *J* = 14.0 Hz, 1H), 2.71 (dt, *J* = 11.6, 2.8 Hz, 1H), 3.96 (dt, *J* = 6.0, 1.2 Hz, 2H), 3.99 – 4.02 (m, 3H), 4.85 (s, 1H), 4.99 (s, 1H), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.27 (dq, *J* = 17.6, 1.6 Hz, 1H), 5.42 (td, *J* = 6.8, 0.8 Hz, 1H), 5.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 17.6, 21.5, 22.2, 26.7, 33.3, 36.4, 37.9, 39.5, 66.5, 70.8, 70.9, 71.3, 75.2, 85.3, 110.6, 116.9, 121.3, 135.0, 139.8, 153.0.; IR (neat) ν_{max} 3382, 3304, 3229, 2961, 2916, 2850, 1643, 1455, 1391 cm^{-1}. HRMS[ES+] calcd for $C_{21}H_{34}O_3$ $[M + Na]^+$ 357.2406, found 357.2401. mp = 53 - 55 ^oC.



406 **453**

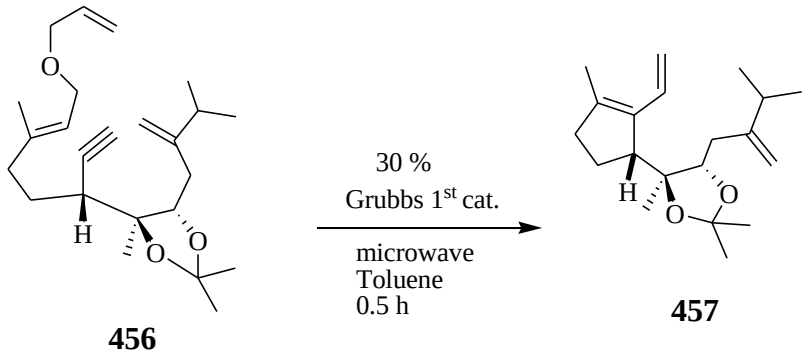
Acetonide 453: To a stirred solution of diol **406** (200 mg, 0.602 mmol) in CH_2Cl_2 (6.0 mL) were added 2,2-dimethyloxypropane (0.15 mL, 1.2 mmol) and *p*-TsOH (11.5 mg, 0.0602 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was quenched with saturated aq. $NaHCO_3$ to adjust pH 7. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL X 2). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide **453** (196 mg, 93 %). ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 - 5.85 (m, 1H), 5.41 (td, *J* = 6.8, 0.8 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.2, 1H), 4.85 (d, *J* = 3.6, 2H), 3.98 - 3.93 (m, 5H), 2.62 (d, *J* = 15.6 Hz, 1H), 2.49 (dt, *J* = 11.6, 2.4 Hz, 1H), 2.38

- 2.26 (m, 3H), 2,13 (d, *J* = 2.4 Hz, 1H), 2.08 - 2.00 (m, 2H), 1.66 (s, 3H), 1.34 (s, 6H), 1.33 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 139.4, 134.9, 121.4, 116.8, 107.7, 106.8, 85.3, 83.1, 82.5, 72.2, 70.8, 66.5, 37.3, 35.8, 33.9, 33.8, 28.2, 27.4, 26.5, 21.7, 21.6, 19.9, 16.5.; IR (neat) ν_{max} 3308, 3081, 2982, 2935, 2871, 1645, 1378 cm^{-1}.



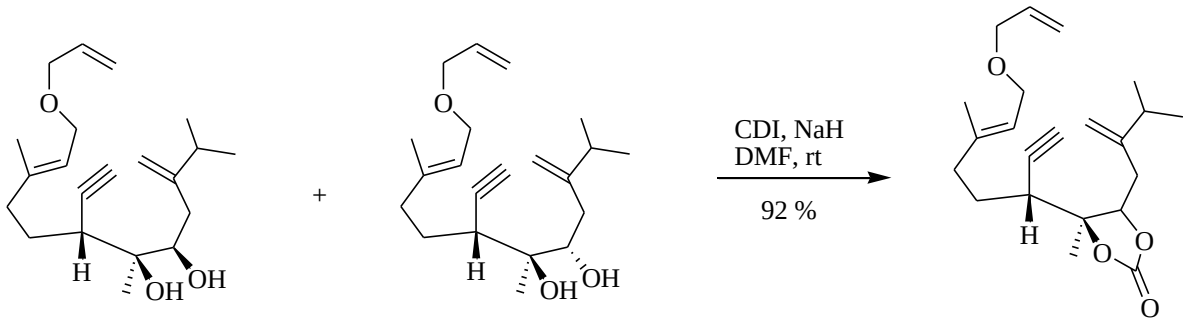
449 **456**

Acetonide 456: To a stirred solution of diol **449** (24.4 mg, 0.071 mmol) in CH_2Cl_2 (3.5 mL) were added 2,2-dimethyloxypropane (14.7 mg, 0.14 mmol) and *p*-TsOH (1.4 mg, 0.007 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was quenched with saturated aq. $NaHCO_3$ to adjust pH 7. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL X 2). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide **453** (25 mg, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 - 5.86 (m, 1H), 5.43 (td, *J* = 6.9, 1.2 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.18 (dm, *J* = 10.5, 1H), 4.90 (d, *J* = 1.5 Hz, 1H), 4.86 (s, 1H), 2.02 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.01 - 3.95 (m, 4H), 2.61 (d, *J* = 15.9 Hz, 1H), 2.38 (dt, *J* = 11.4, 2.7 Hz, 1H), 2.33 - 2.20 (m, 3H), 2.12 (d, *J* = 2.7 Hz, 1H), 2.16 - 2.10 (m, 1H), 1.99 - 1.93 (m, 1H), 1.68 (s, 3H), 1.56 - 1.53 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.06 (d, *J* = 2.1 Hz, 3H), 1.04 (d, *J* = 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 139.3, 135.0, 121.5, 116.9, 106.7, 84.1, 82.5, 81.9, 72.1, 71.0, 66.5, 41.5, 37.3, 35.6, 33.7, 28.6, 27.8, 26.6, 21.8, 21.7, 17.4, 16.4.



456 **457**

Five membered ring 437 : To a solution of 456 (18.8 mg, 0.0521 mmol) was added Grubb's 1st catalyst (12.9 mg, 0.0156 mmol). The reaction mixture was heated by a microwave (setting temp. 150 ^{o}C, W = 100). The temperature of the microwave was increased to 115 ^{o}C for 10 min and to 139 ^{o}C for 30 min. The resulting mixture was cooled to 65 ^{o}C for 20 min. The mixture was concentrated under reduced pressure. The residue was purified by PTLC (eluent with EtOAc : hex = 20 : 1) to provide **457** (6.4 mg, 40 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.54 (dd, J = 17.4, 11.4 Hz, 1H), 5.09 (d, J = 17.4 Hz, 1H), 5.05 (d, J = 11.2, 1H), 4.87 (d, J = 7.1 Hz, 2H), 4.11 (t, J = 5.8, 1H), 3.03 (d, J = 8.8 Hz, 1H), 2.53 - 2.47 (m, 1H), 2.25 (quint, J = 6.6 Hz, 1H), 2.16 - 2.12 (m, 3H), 2.08 - 2.05 (m, 1H), 1.95 - 1.89 (m, 1H), 1.81 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.06 (s, 3H), 1.03 (d, *J* = 7.2 , 6H).

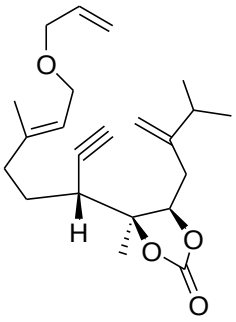


406 ratio : 1.8 / 1.0 **449** Mixture **459**

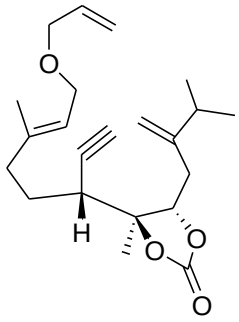
Carbonates 5b+13b. To a stirred solution of the mixture of **5a** and **13a** (177 mg, 0.528 mmol) in DMF (1.7 mL) under argon was added NaH (44.3 mg, 60%, 1.11 mmol). The reaction mixture was stirred for 15 min and then 1,1'-carbonyldiimidazole (CDI) (530 mg, 3.17 mmol) was added slowly. The resulting mixture was stirred at room temperature for 4 h. Et_2O and saturated aq. NH_4Cl were added and the resulting mixture was stirred for 10 min. After separation of the two

layers, the organic solution was washed with water (1.5 mL X 3) and brine and then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to provide a mixture of carbonates **5b** and **13b** (175 mg, 92 %) as a colorless oil. Without further purification, the mixture of carbonate **5b** and **13b** was directly used for the next step.

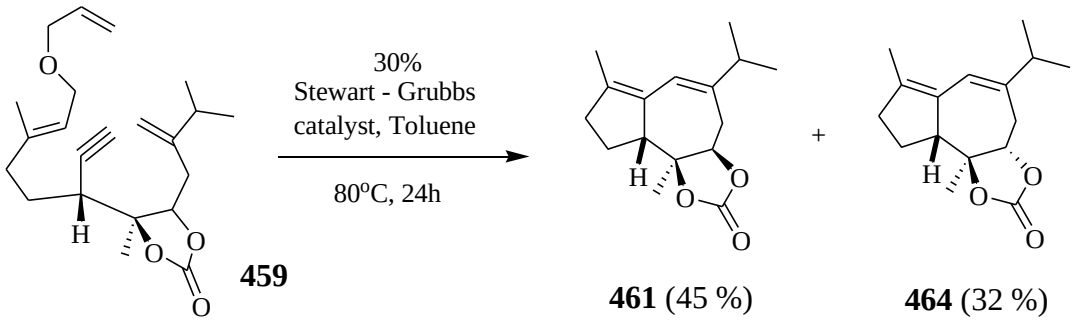
For the purpose of characterization, each carbonate isomer was prepared from the corresponding diol (see above).



Major product : ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, J = 6.6 Hz, 6H), 1.56 (s, 3H), 1.65 (m, 1H), 1.66 (s, 3H), 1.87 – 1.94 (m, 1H), 2.11 (m, 1H), 2.24 – 2.37 (m, 4H), 2.69 (d, *J* = 11.4 Hz, 1H), 2.81 (d, *J* = 15.0 Hz, 1H), 3.97 (dd, *J* = 12.6, 6.0 Hz, 4H), 4.46 (d, *J* = 12.0, 1H), 4.85 (s, 1H), 4.93 (s, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.28 (d, *J* = 18.0 Hz, 1H), 5.41 (t, *J* = 6.6 Hz, 1H), 5.87 – 5.94 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 20.5, 21.4, 21.6, 27.4, 33.5, 33.7, 35.3, 36.9, 66.3, 71.0, 73.5, 81.9, 84.9, 85.7, 110.6, 116.9, 122.2, 134.8, 138.4, 149.5, 153.4.; IR (neat) ν_{max} 3288, 3083, 2964, 2872, 1808, 1646, 1455, 1384 cm^{-1}. HRMS[ES+] calcd for $C_{22}H_{32}O_4$ [M + Na]$^+$ 383.2198, found 383.2199



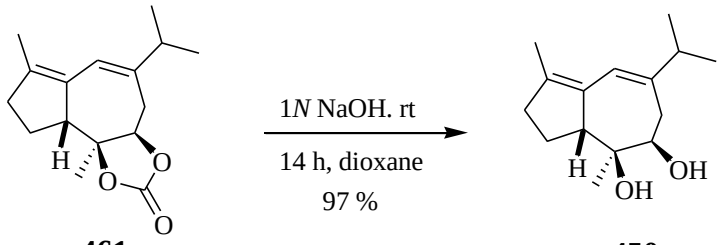
Minor product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 4.8 Hz, 3H), 1.06 (d, *J* = 4.8 Hz, 3H), 1.43 (s, 3H), 1.59 (m, 1H), 1.67 (s, 3H), 1.86 – 1.94 (m, 1H), 2.12 (m, 1H), 2.22 (d, *J* = 2.4 Hz, 1H), 2.26 – 2.38 (m, 2H), 2.40 (d, *J* = 10.4 Hz, 1H), 2.51 (d, *J* = 15.2 Hz, 1H), 2.65 (dt, *J* = 8.8, 2.4 Hz, 1H), 3.98 (m, 4H), 4.64 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.90 (s, 1H), 4.94 (s, 1H), 5.18 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.28 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.42 (t, *J* = 6.4 Hz, 1H), 5.88 – 5.98 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 16.3, 21.5, 21.6, 27.0, 33.5, 35.4, 36.9, 41.3, 66.5, 71.1, 73.5, 81.2, 83.8, 85.8, 110.5, 117.0, 122.4, 134.9, 138.2, 149.9, 153.2.; IR (neat) ν_{max} 3288, 2962, 2871, 1805, 1646, 1455, 1385 cm^{-1}. HRMS[ES+] calcd for $C_{22}H_{32}O_4$ [M + Na]$^+$ 383.2198, found 383.2194.



Bicyclic dienes 461 and 464. To a stirred solution of the mixture of carbonates **459** (31.7 mg, 0.088 mmol) in toluene (8.8 mL) under Argon was added 30 mol % Stewart -Grubbs catalyst (15.0 mg, 0.026 mmol). The resulting mixture was stirred at 80 ^{o}C for 24 h. After cooling down to room temperature, the reaction mixture was concentrated. The residue was subjected to silica gel flash column chromatography (elution with EtOAc : hexane = 1 : 4) to give diene **461** (10.3 mg, 45 %) as an oil and diene **464** (7.4 mg, 32 %) as an oil.

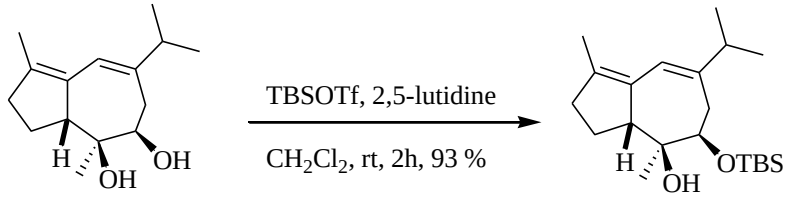
461 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3.2 Hz, 1H), 1.35 (d, *J* = 3.6 Hz, 3H), 1.33 (s, 3H), 1.74 (s, 3H), 1.89 – 1.95 (m, 1H), 1.99 – 2.07 (m, 1H), 2.31 (dd, *J* = 14.8, 4.0 Hz, 1H), 2.35 – 2.37 (m, 3H), 2.97 (t, *J* = 12.8 Hz, 1H), 3.64 (d, *J* = 8.0 Hz, 1H), 4.27 (dd, *J* = 12.2, 3.8 Hz, 1H), 6.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.9, 20.9, 21.2, 23.3, 30.2, 37.5, 37.8, 50.8, 84.6, 87.1, 120.1, 131.2, 139.3, 139.6, 153.9.; IR (neat) ν_{max} 2960, 2927, 1805, 1466, 1383 cm^{-1}. HRMS[ES+] calcd for $C_{16}H_{22}O_3$ $[M + Na]^+$ 285.1467, found 285.1462.

464 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.6 Hz, 6H), 1.17 (s, 3H), 1.73 – 1.78 (m, 1H), 1.77 (s, 3H), 2.03 (m, 1H), 2.38 (sext, 4H), 2.67 (dd, *J* = 17.2, 4.4 Hz, 1H), 3.03 (m, 1H), 4.42 (dd, *J* = 12.0, 4.4 Hz, 1H), 6.19 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.5, 21.5, 22.1, 23.8, 28.4, 37.7, 39.0, 54.9, 84.9, 87.5, 118.5, 129.4, 137.1, 142.6, 154.9.; IR (neat) ν_{max} 2961, 2930, 1809, 1462, 1382 cm^{-1}. HRMS[ES+] calcd for $C_{16}H_{22}O_3$ $[M + Na]^+$ 285.1467, found 285.1470.



461 **450**

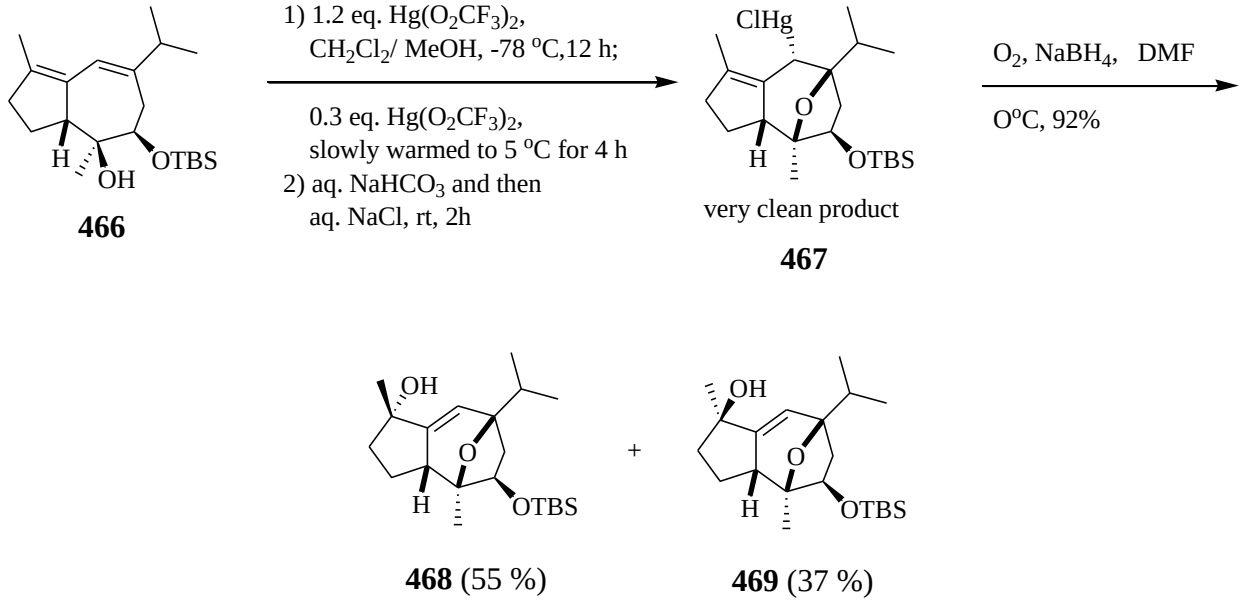
Diol 450. To a stirred solution of carbonate **461** (67.2 mg, 0.256 mmol) in dioxane (3.2 mL) was added 1*N* NaOH (0.7 mL) and the resulting mixture was stirred for 14 h at room temperature. The reaction was quenched with saturated aq. NH_4Cl and the resulting mixture was diluted with Et_2O. After separation of layers, the aqueous layer was extracted with Et_2O (5 mL X 2) and the combined organic solution was washed with brine and water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to provide diol **450** (58.7 mg, 97 %) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.04 (s, 3H), 1.13 (s, 3H), 1.73 (s, 3H), 1.90 – 2.02 (m, 2H), 2.06 (dd, *J* = 16.8, 1.2 Hz, 1H), 2.14 (s, 1H), 2.20 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.33 (quint, *J* = 6.6 Hz, 1H), 2.41 (quint, *J* = 8.4 Hz, 1H), 2.56 (br, 1H), 2.73 (dd, *J* = 16.2, 10.2 Hz, 1H), 3.04 (d, *J* = 9.0 Hz, 1H), 3.45 (d, *J* = 9.0 Hz, 1H), 6.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.7, 21.1, 21.5, 24.3, 34.4, 37.6, 37.8, 53.7, 76.8, 77.2, 119.0, 132.7, 137.2, 144.6.; IR (neat) ν_{max} 3396, 2959, 2924, 1714, 1557, 1463, 1379 cm^{-1}. HRMS[ES+] calcd for $C_{15}H_{24}O_2$ $[M + Na]^+$ 259.1674, found 259.1685.



450 **466**

Cyclization Substrate 466. To a stirred solution of diol **450** (R = H) (8.5 mg, 36 µmol) in CH_2Cl_2 (2.0 mL) under argon was added 2,6-lutidine (9.2 mg, 86 µmol). Then TBSOTf (11.4 mg, 43.0 µmol) was added dropwise and the resulting mixture was stirred for 2 h, quenched with water, and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (1 mL X 3) and

the combined organic solution was dried over $MgSO_4$, concentrated under reduced pressure, and subjected to silica gel flash column chromatography (elution with EtOAc : hexane = 1 : 20). Alcohol **466** (11.7 mg, 93 %) was isolated as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.03 (dd, *J* = 6.8, 1.6 Hz, 6H), 1.04 (s, 3H), 1.74 (s, 3H), 1.81 (dd, *J* = 20.8, 1.6 Hz, 1H), 1.90 – 1.98 (m, 1H), 2.02 – 2.07 (m, 1H), 2.17 (dd, *J* = 16.7, 9.6 Hz, 1H), 2.31 (quint, *J* = 6.8 Hz, 1H), 2.37 – 2.46 (m, 1H), 2.89 (dd, *J* = 16.8, 9.6, 1H), 3.03 (d, *J* = 4.8 Hz, 1H), 3.11 (s, 1H), 3.43 (dd, *J* = 10.8, 1.6 Hz, 1H), 6.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -3.8, 14.3, 18.0, 21.2, 21.5, 21.9, 24.7, 25.9, 34.3, 37.8, 37.9, 53.1, 76.0, 78.8, 119.1, 133.1, 136.8, 145.2. IR (neat) ν_{max} 3544, 2956, 2930, 2857, 1651, 1472, 1361 cm^{-1}. HRMS[ES+] calcd for $C_{21}H_{38}O_2Si$ $[M + Na]^+$ 373.2539, found 373.2535.



466 **467**

468 (55 %) **469** (37 %)

Alcohols 468 and 469. Oxymercuration was carried out according to a hybrid procedure derived from related literature.[9] To a stirred solution of alcohol **466** (16.0 mg, 45.6 µmol) in CH_2Cl_2 (2 mL) under argon was added MeOH (5.0 mg) at room temperature. The reaction mixture was cooled to -78 °C, $Hg(O_2CCF_3)_2$ (23.8 mg, 54.8 µmol) was added, and stirring was continued for 24 h. Then additional $Hg(O_2CCF_3)_2$ (5.9 mg, 14 µmol) was added and the reaction mixture was

[9] (a) Broka, C. A.; Lim, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876. (b) Kang, S.H.; Kim, M.; Kang, S. Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 6177 (c) Ushakov, D. B.; Navickas, V.; Ströbele, M.; Maichle-Mössmer, C.; Sasse, F.; Maier, M.E. *Org. Lett.* **2011**, *13*, 2090.

slowly warmed to 5 ^{o}C over 3.5 h. The reaction was quenched with saturated aq. $NaHCO_3$ (2 mL) and then saturated aq. NaCl (2 mL). The resulting mixture was stirred at room temperature for 2 h, and then extracted with Et_2O (5 mL X 3). The ether solution was washed with brine and then with water, dried over $MgSO_4$, and concentrated under reduced pressure to provide an organomercurial intermediate **467**. Without further purification, the crude product was directly used for the next step. **467** : ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.30 (s, 3H), 0.88 (s, 9H), 1.2 (d, *J* = 6.0 Hz, 1H), 1.45 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 1H), 1.26 – 1.34 (m, 1H),1.81 – 1.96 (m, 4H), 2.00 (s, 3H), 2.31 – 2.40 (m, 2H), 2.71 (m, 1H), 2.93 (s, 1H), 3.99 (dd, *J* = 7.2, 3.0 Hz, 1H).

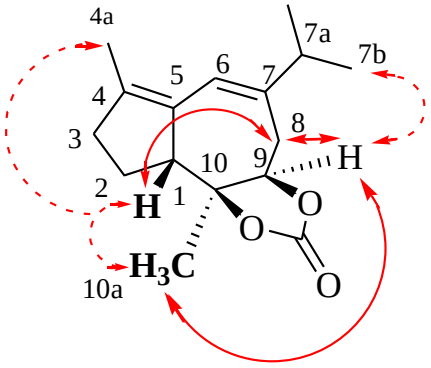
Oxidative demercuration was accomplished according to Hill and Whitesides. A stream of oxygen gas was bubbled into a solution of $NaBH_4$ (9.5 mg, 0.11 mmol) in DMF (3.5 mL) at 0^{o}C for 30 min. To the resulting mixture was added dropwise a solution of the alkylmercurial **467** in DMF (0.7 mL) by syringe pump at 0 ^{o}C for 1h. During this time, oxygen bubbling was continued. The syringe was filled with DMF (0.2 mL) and this wash was added dropwise (oxygen bubbling continued). When addition was complete, the resulting mixture was warmed slowly to room temperature over 2.5 h (oxygen bubbling continued). The reaction mixture was quenched with 1*N* HCl, diluted with Et_2O (15 mL), and filtered through Celite. Water and Et_2O were added to the filtrate and the layers were separated. The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel Flash column chromatography (elution with EtOAc : hexane = 1 : 3) to afford the known **468** (9.2 mg, 55 % for 2 steps) as an oil and its isomer **469** (6.2 mg, 37 % for 2 steps), also as an oil.

Compound **468** : ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.88 (s, 9H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 1.39 – 1.41 (m, 1H), 1.56 – 1.58 (m, 2H), 1.73 – 1.78 (m, 3H), 1.91 (hept, *J* = 6.6 Hz, 1H), 2.30 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.70 (m, 1H), 4.13 (t, *J* = 6.0, 1H), 5.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.5, 17.8, 17.7, 18.0, 20.7, 23.5, 25.8, 28.0, 34.1, 41.0, 50.2, 51.0, 73.4, 77.4, 83.3, 85.1, 119.3, 148.9.; IR (neat) ν_{max} 3419, 2959, 2929, 2857, 1472, 1386 cm^{-1}. ^{1}H NMR and ^{13}C NMR data were consistent with the reported values.[14]

Compound **469** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s,3H), 0.88 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.17 – 1.24 (m, 1H), 1.26 (s, 3H), 1.37 (s, 3H), 1.60 (m, 1H), 1.70 (m, 1H), 1.84 – 1.97 (m, 1H), 2.26 (dd, *J* = 11.2, 7.2, 1H), 3.07 (td, *J* = 9.2, 2.4 Hz,

1H), 4.01 (m, 1H), 5.65 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) -5.0, -4.5, 17.7, 17.8, 18.0, 20.7, 22.9, 25.5, 25.8, 34.0, 40.8, 49.5, 50.8, 73.4, 77.1, 83.1, 85.2, 120.0, 146.7.; IR (neat) ν_{max} 3373, 2959, 2930, 2857, 1463, 1386 cm^{-1}.

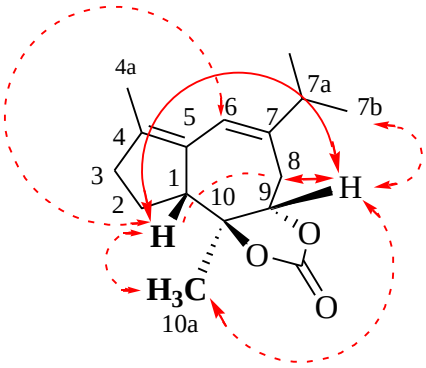
Difference NOE for compound **461**



Difference NOE chart for compound **461**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH_3 (10a, 1.33)	CH_2 (2, 1.89 – 1.95), CH_2 (2.35 – 2.37), CH (9, 4.27)
CH (1, 3.64)	CH_3 (10a, 1.33), CH_3 (4a, 1.74), CH_2 (1.89 – 1.95), CH_2 (2, 1.99 – 2.07), CH_2 (2.35 – 2.37), CH_2 (8, 2.97)
CH (9, 4.27)	CH3 (7b, 1.04), CH_3 (10a, 1.33), CH_2 (2.31), CH_2 (8, 2.97)

Difference NOE for compound **464**



Difference NOE chart for compound **464**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH (10a, 1.17)	CH_2 (2, 1.73 – 1.78), CH_2 (2, 2.03), CH_2 (2.38), CH (1, 3.03), CH (9, 4.42), CH (6, 6.19)
CH (1, 3.03)	CH (10a, 1.17), CH_2 (1.73 – 1.78), CH_2 (2.38), CH_2 (2, 2.03), CH (9, 4.42), CH (6, 6.19)
CH (9, 4.42)	CH3 (7b, 1.04), CH (10a, 1.17), CH_2 (2.38), CH_2 (8, 2.67), CH (1, 3.03), CH (6, 6.19)

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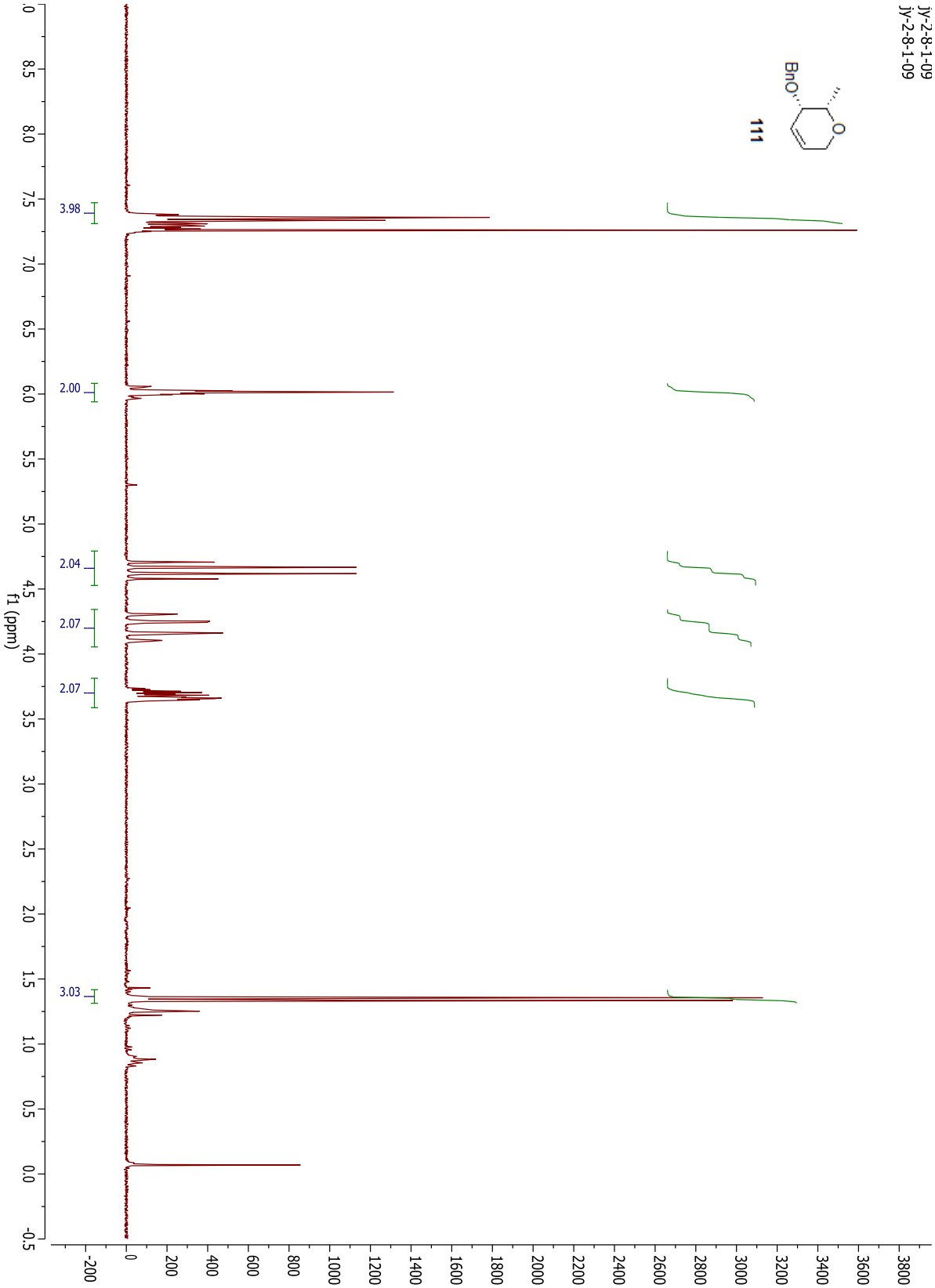
Appendix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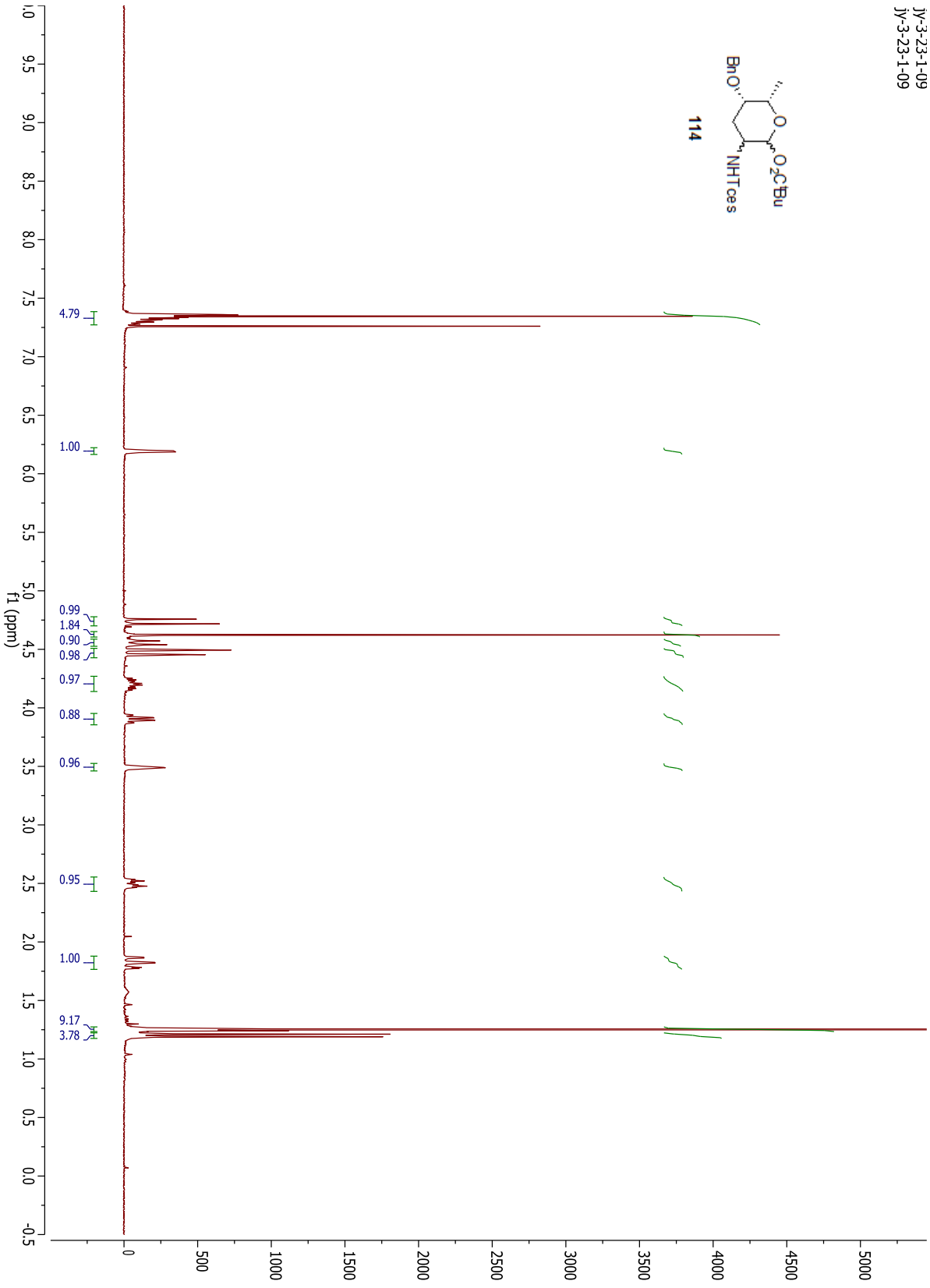
2.00
2.04
2.07
2.07
3.03
f1 (ppm)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O2CtBu
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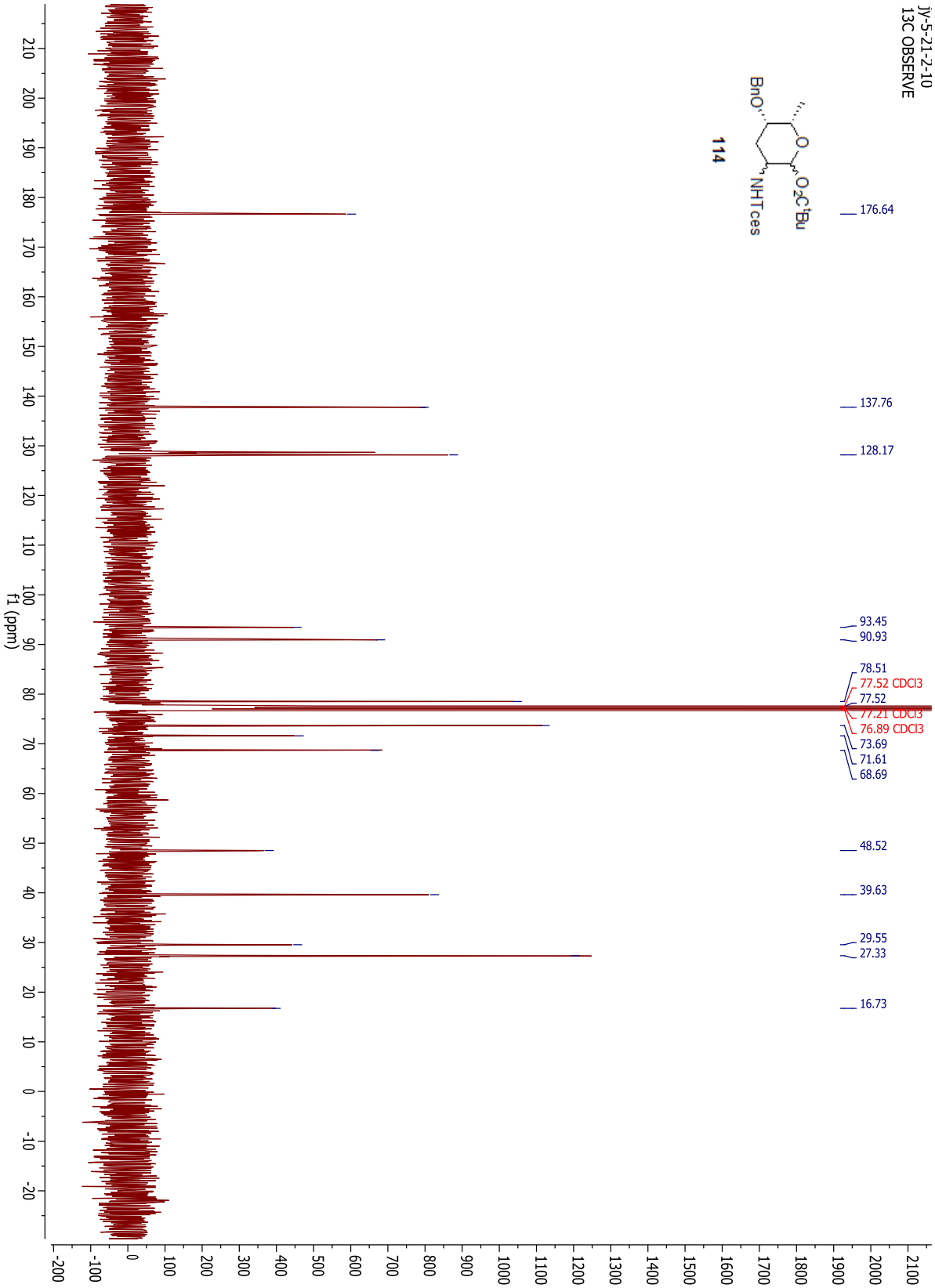
0.98
0.97
0.88
0.96
0.95
1.00
9.17
3.78
f1 (ppm)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137.76
128.17
93.45
90.93
78.51
77.52 CDCl3
77.52
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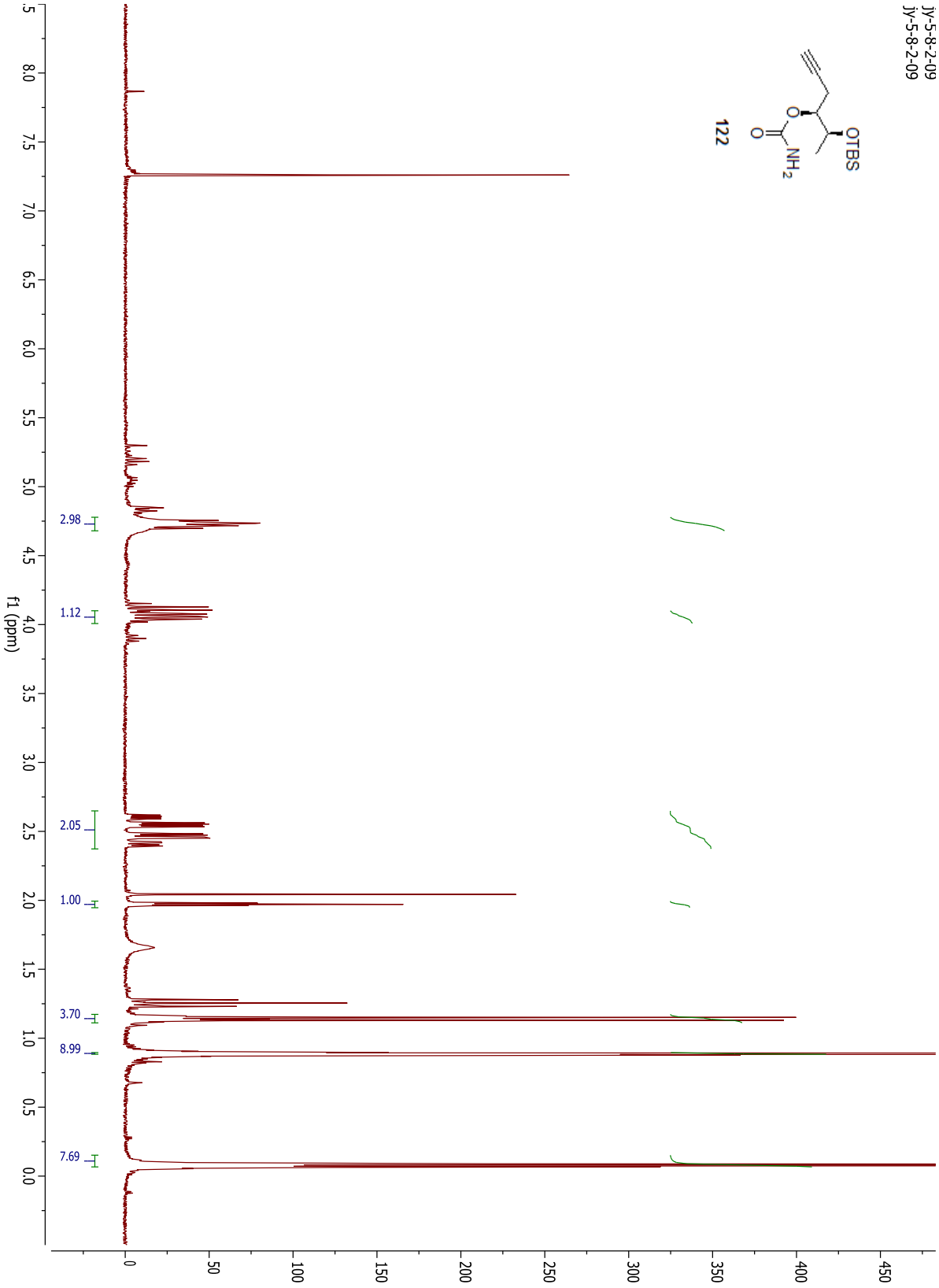
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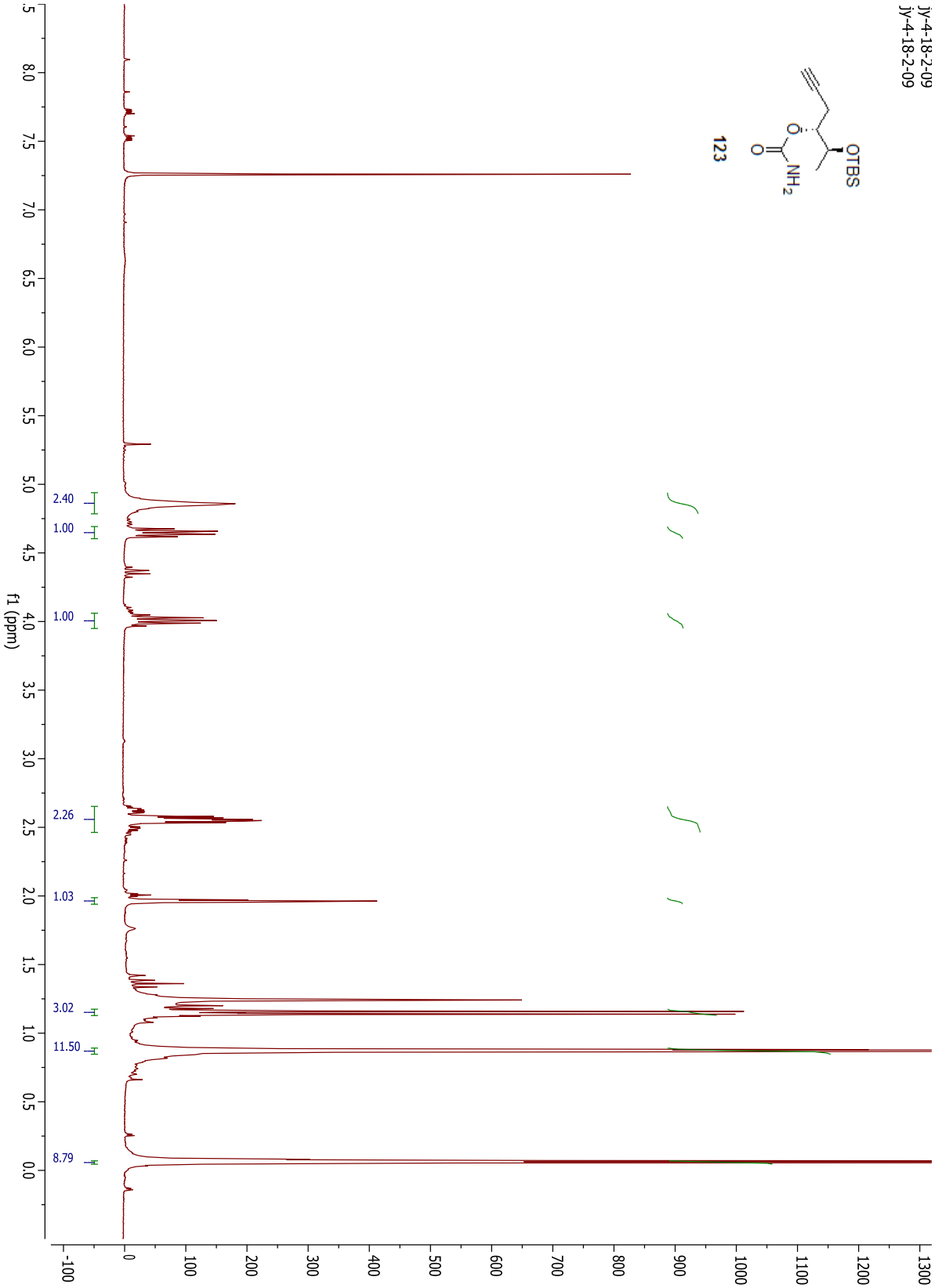
2.05
1.00
3.70
8.99
7.69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1.03
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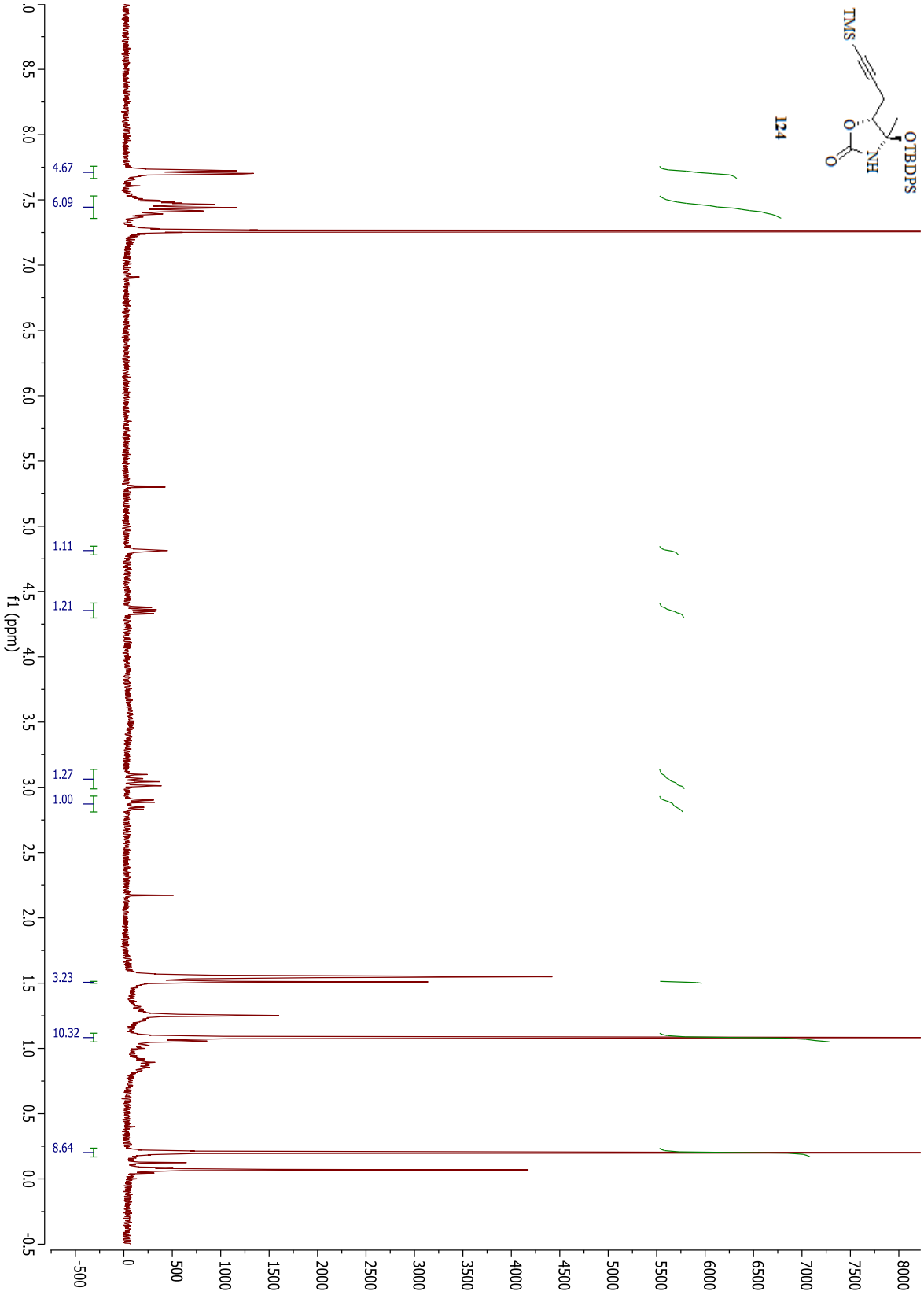
8.79
f1 (ppm)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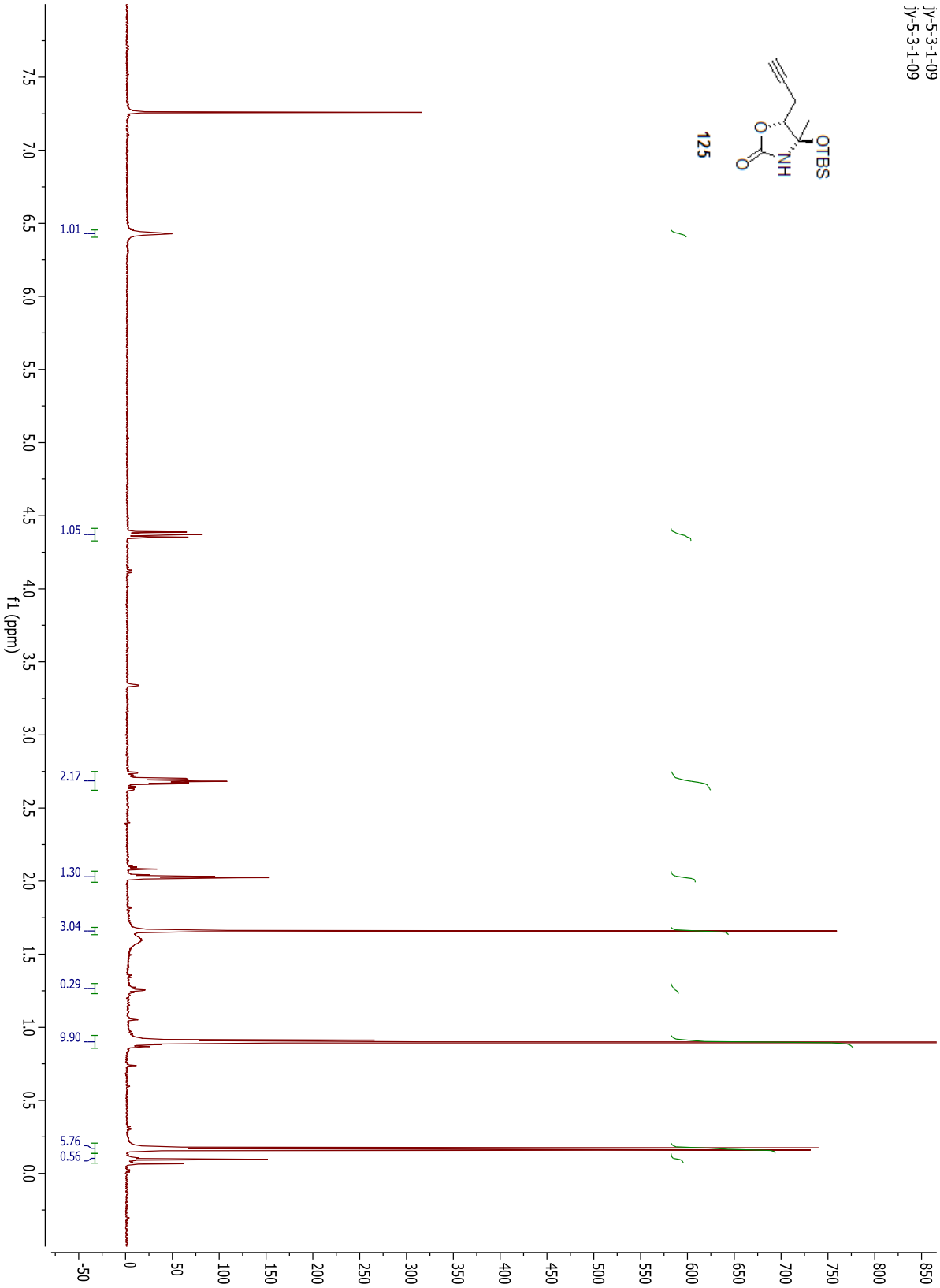
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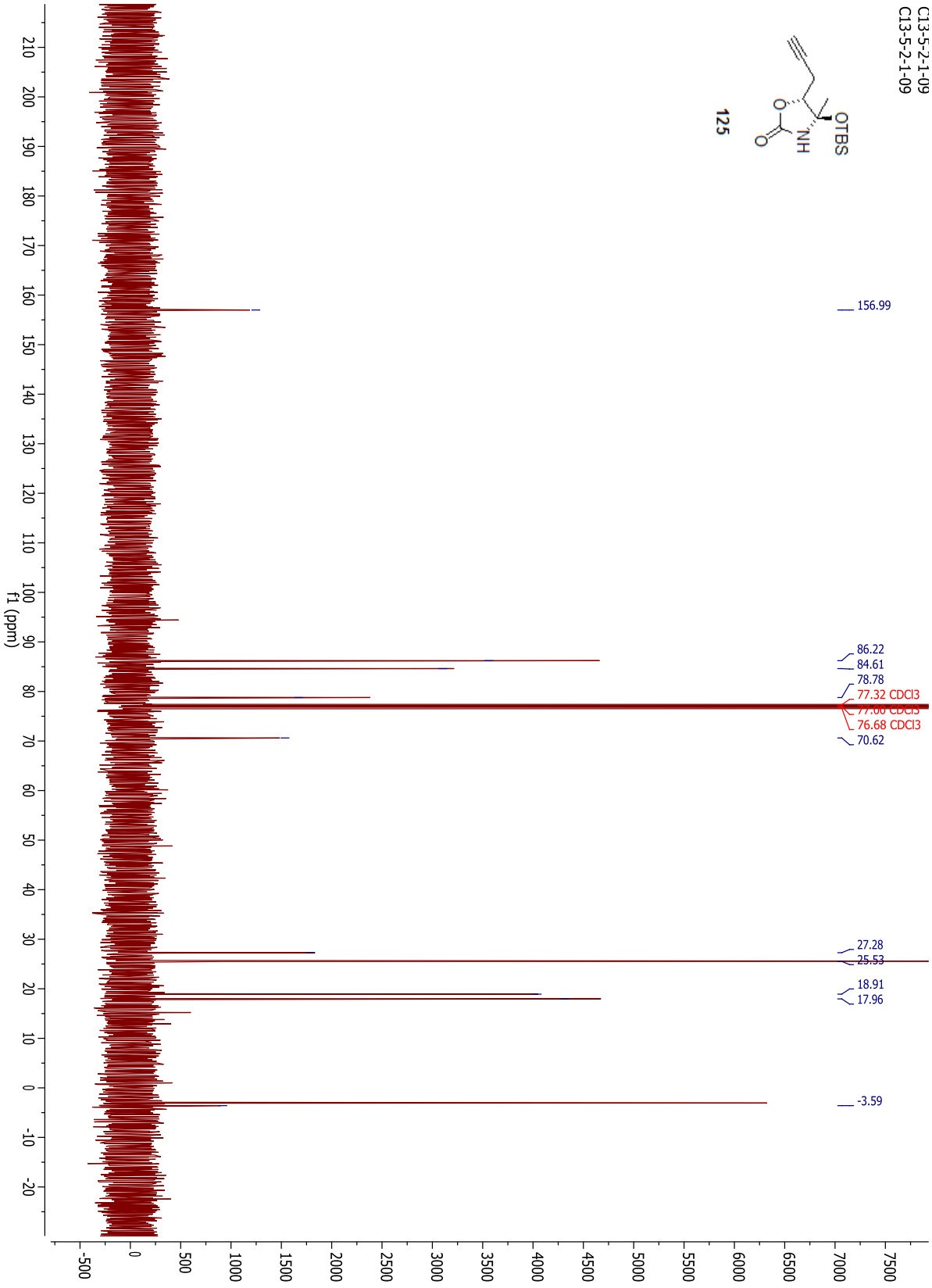
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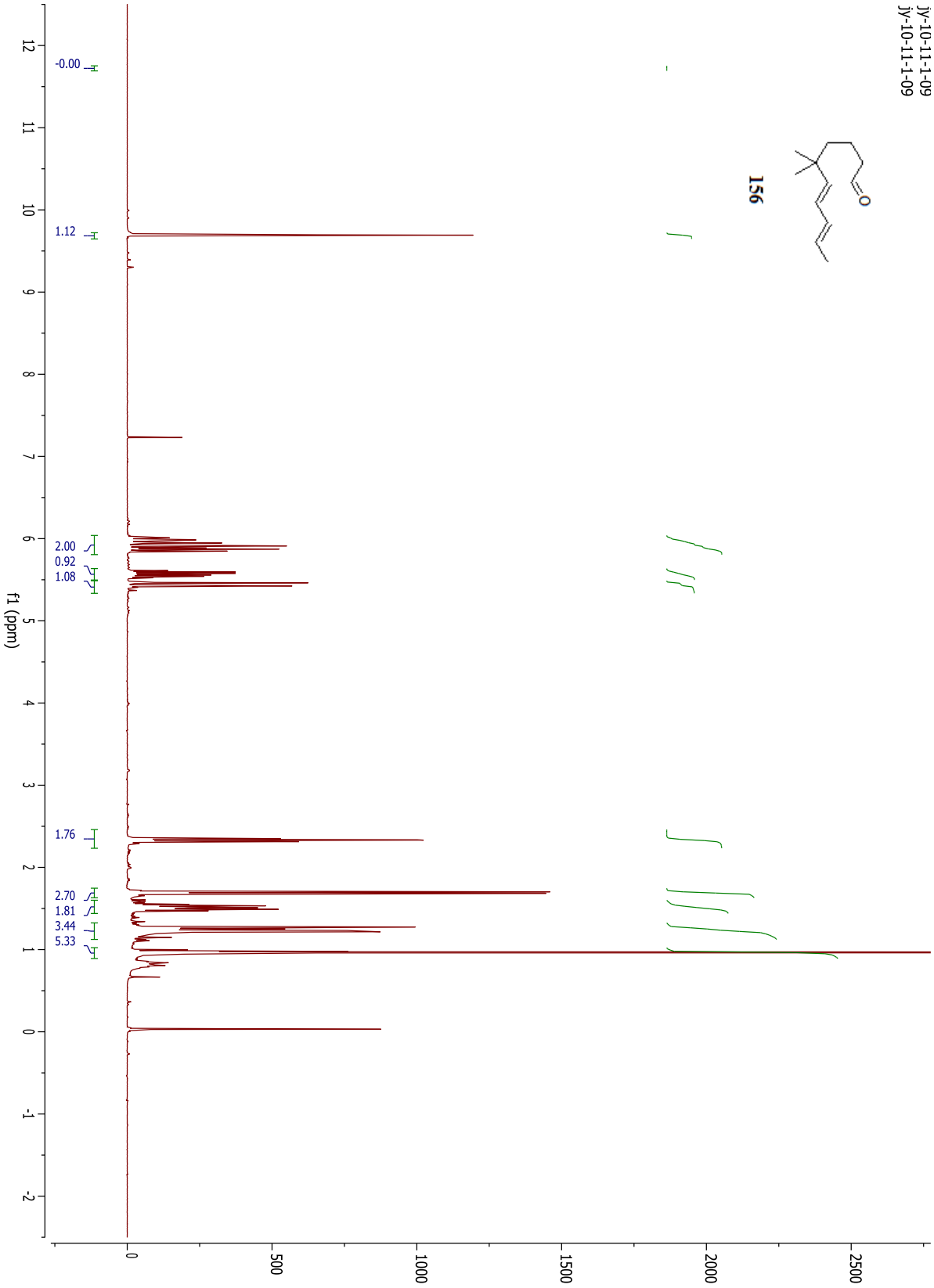
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2.70
1.81
3.44
5.33
f1 (ppm)
12
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10
9
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7
6
5
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3
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0
-1
-2
0
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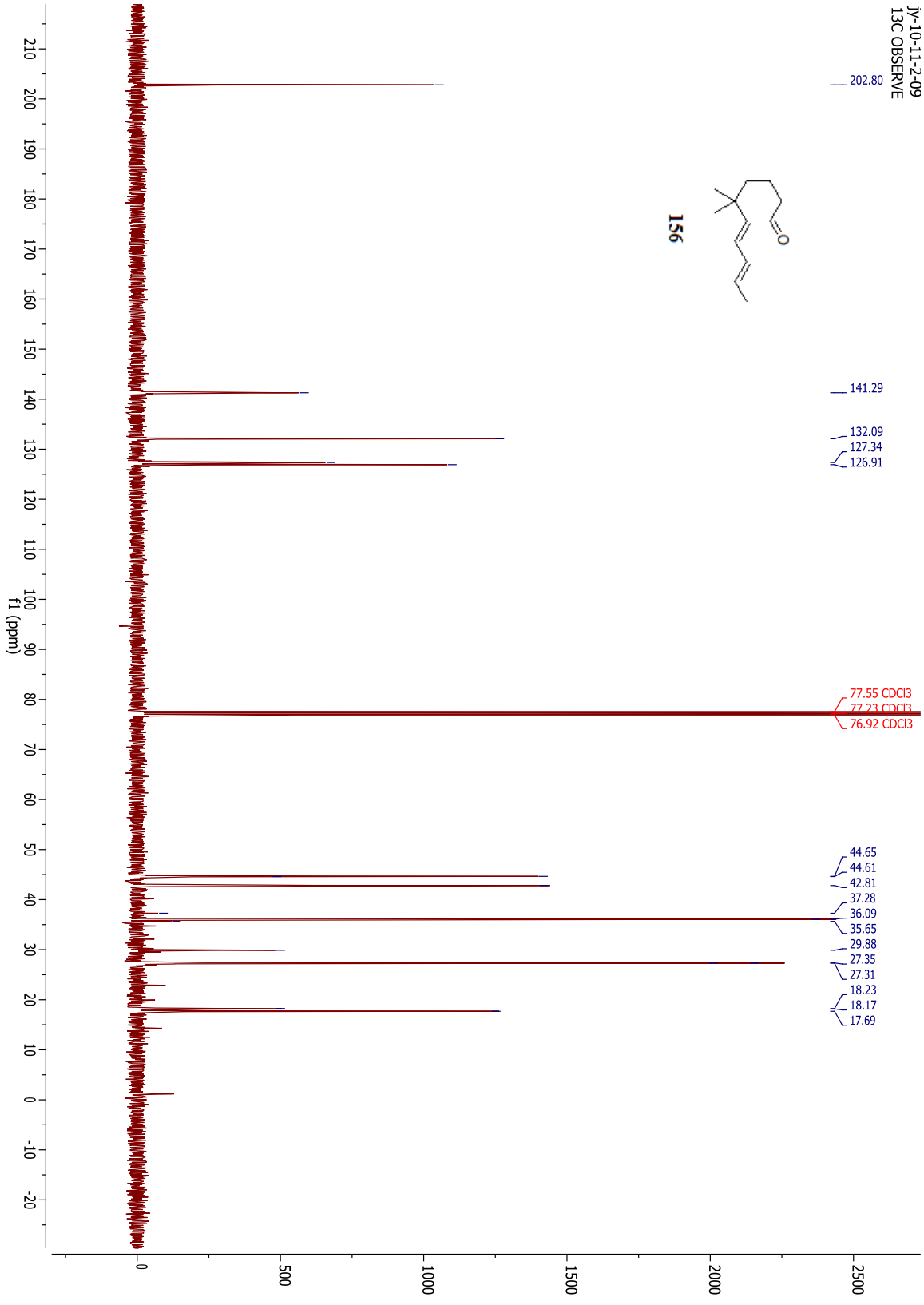
1000
1500
2000
2500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77.23 CDCl3
76.92 CDCl3
44.65
44.61
42.81
37.28
36.09
35.65
29.88
27.35
27.31
18.23
18.17
17.69
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
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1000
1500
2000
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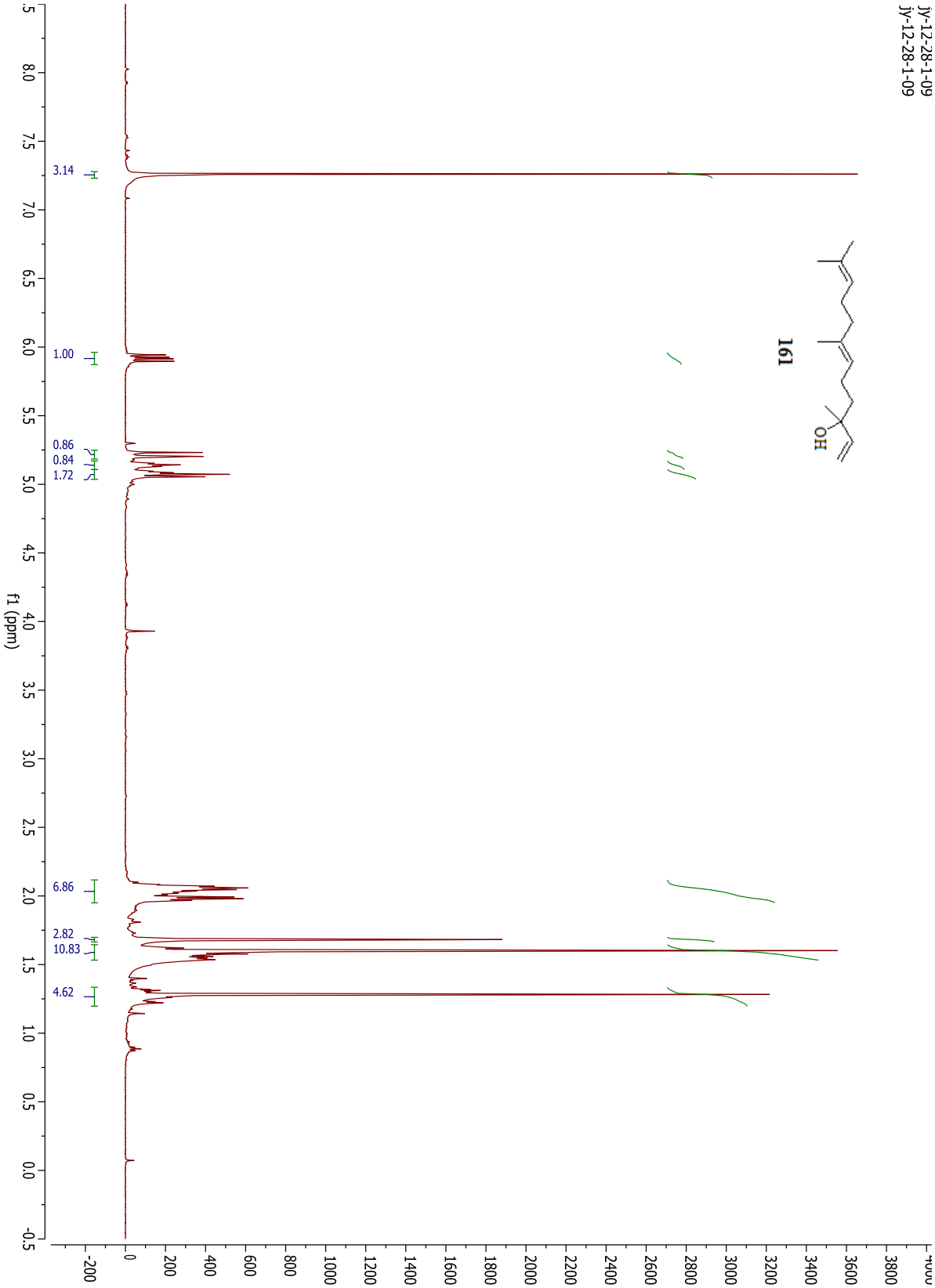
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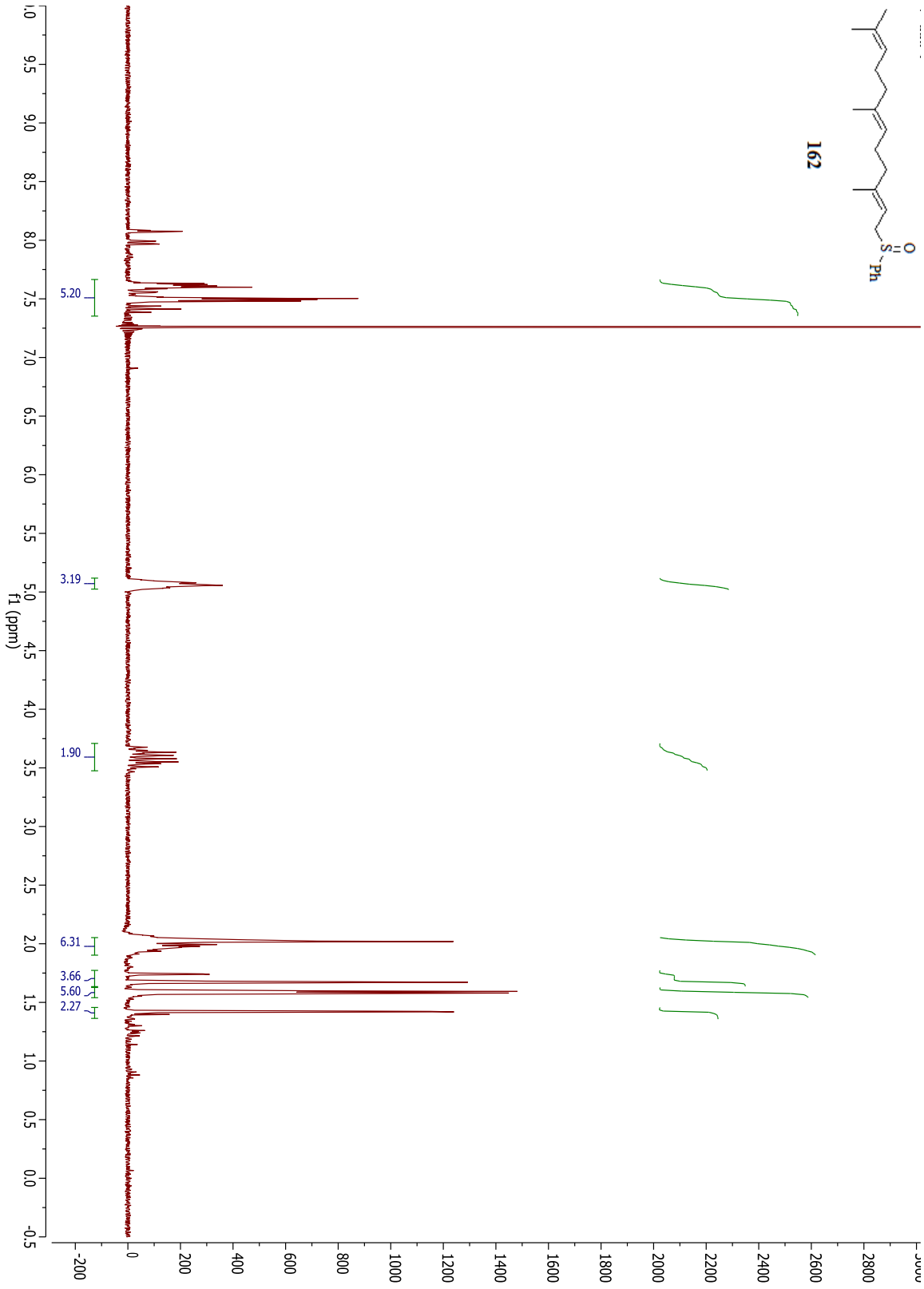
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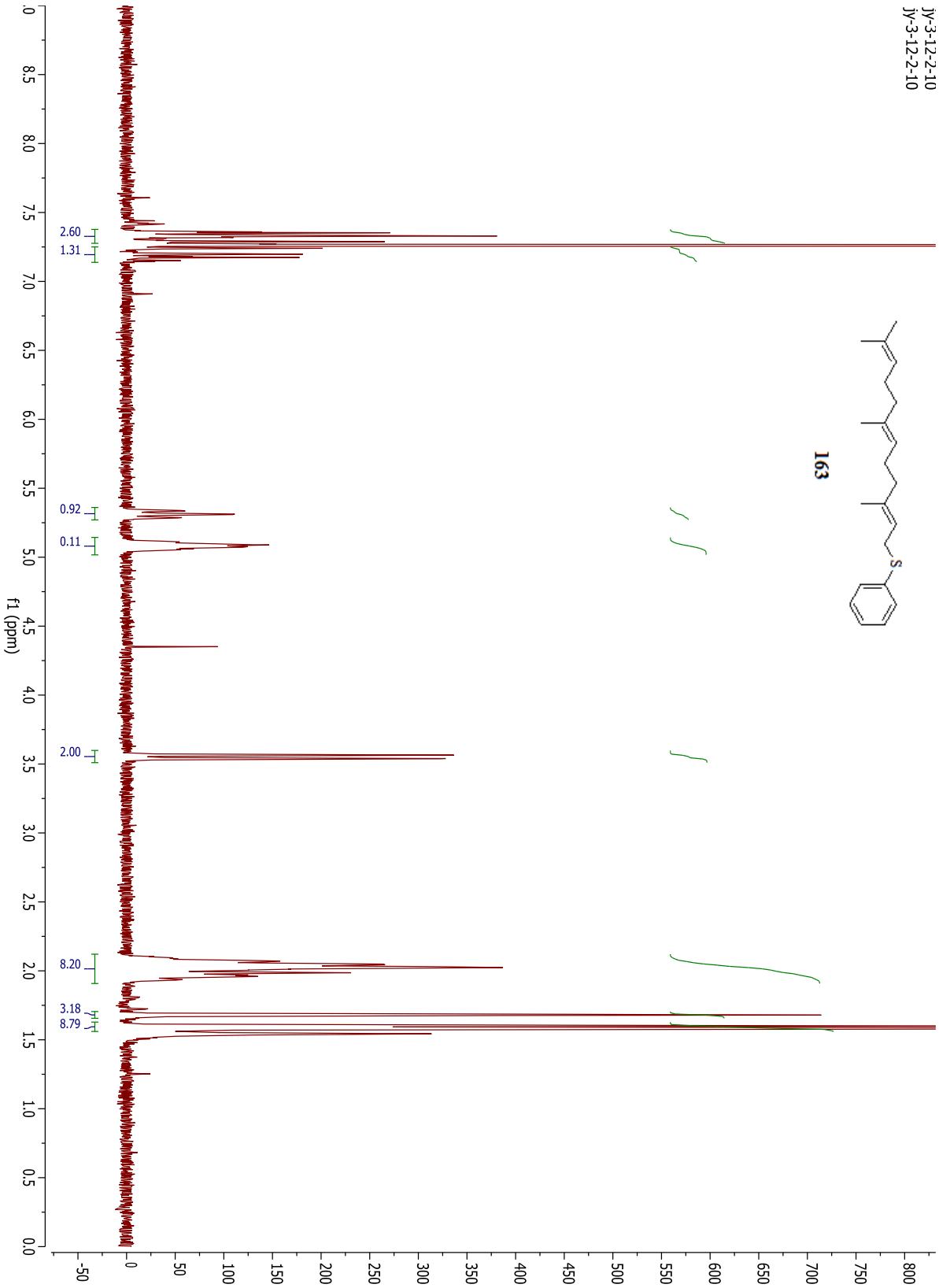
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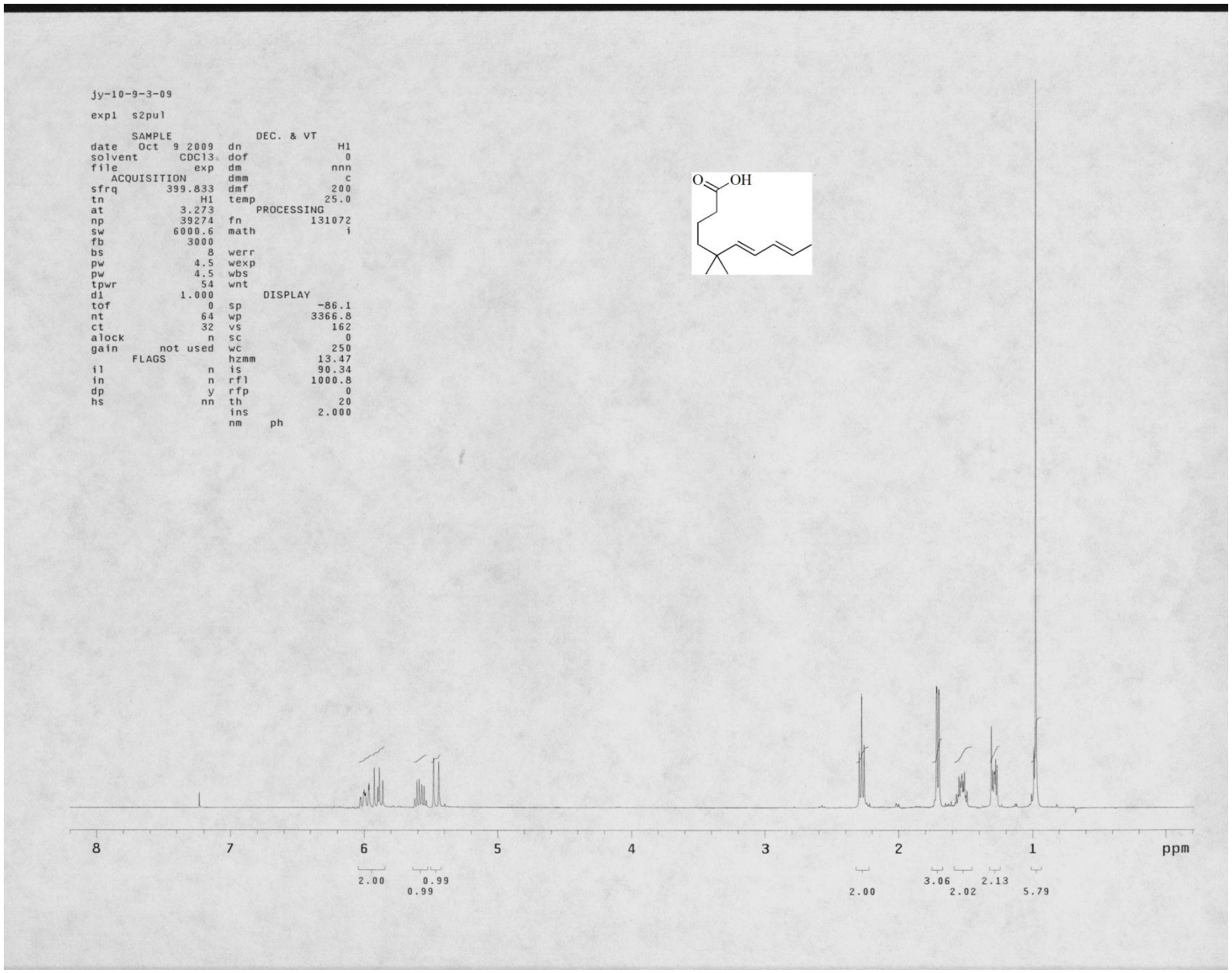
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gain not used
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dof 0
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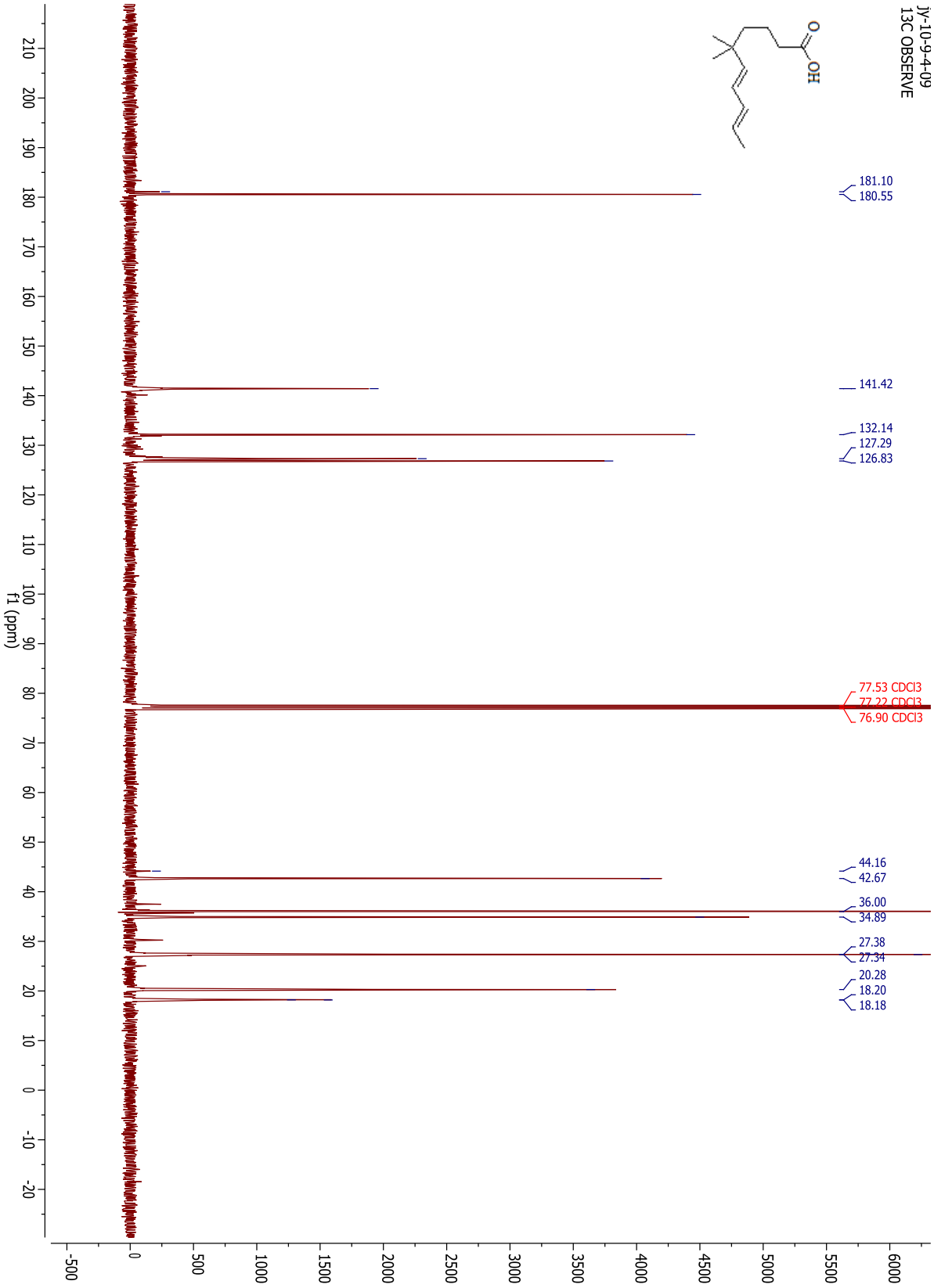
5.79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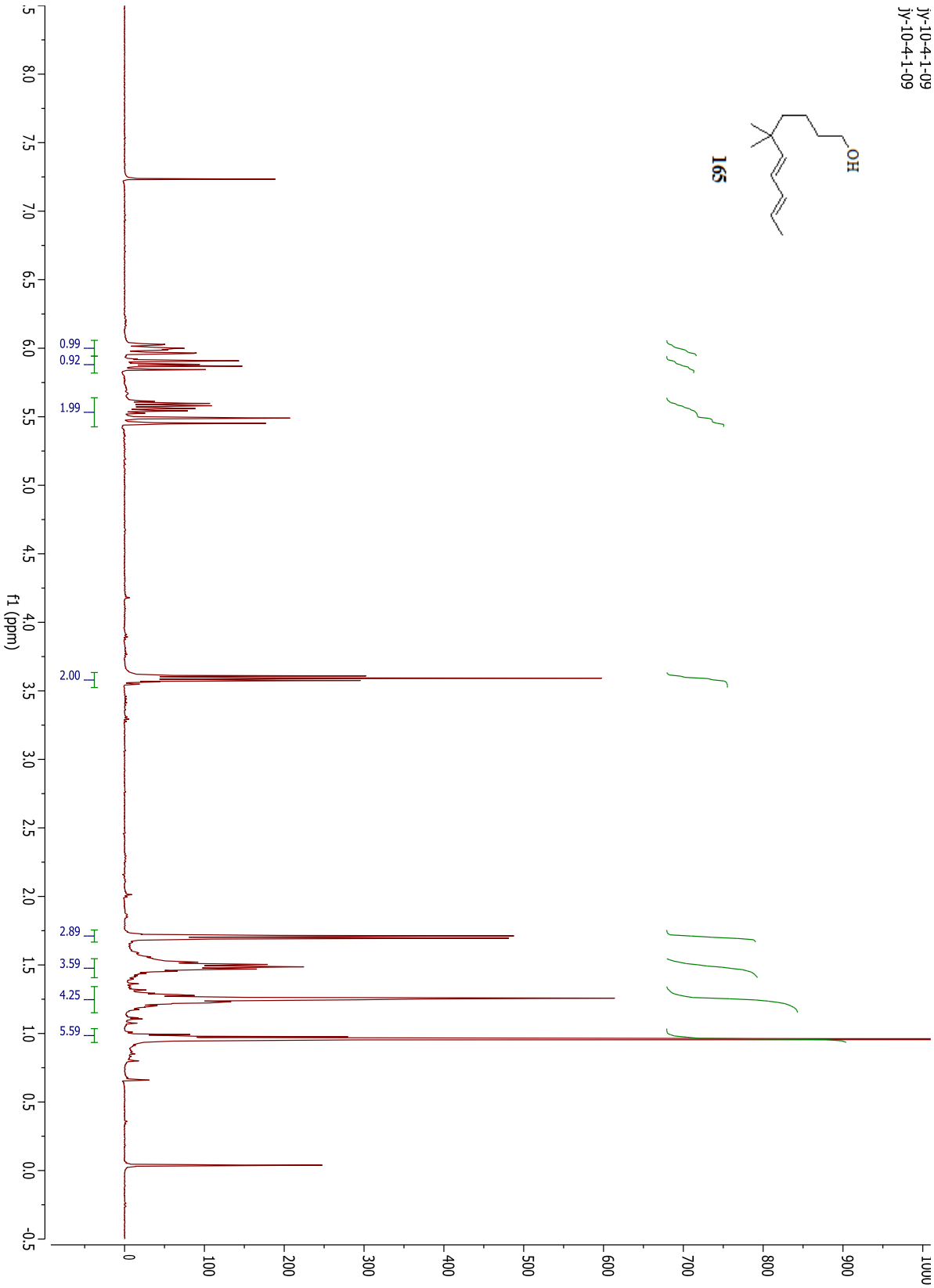
f1 (ppm)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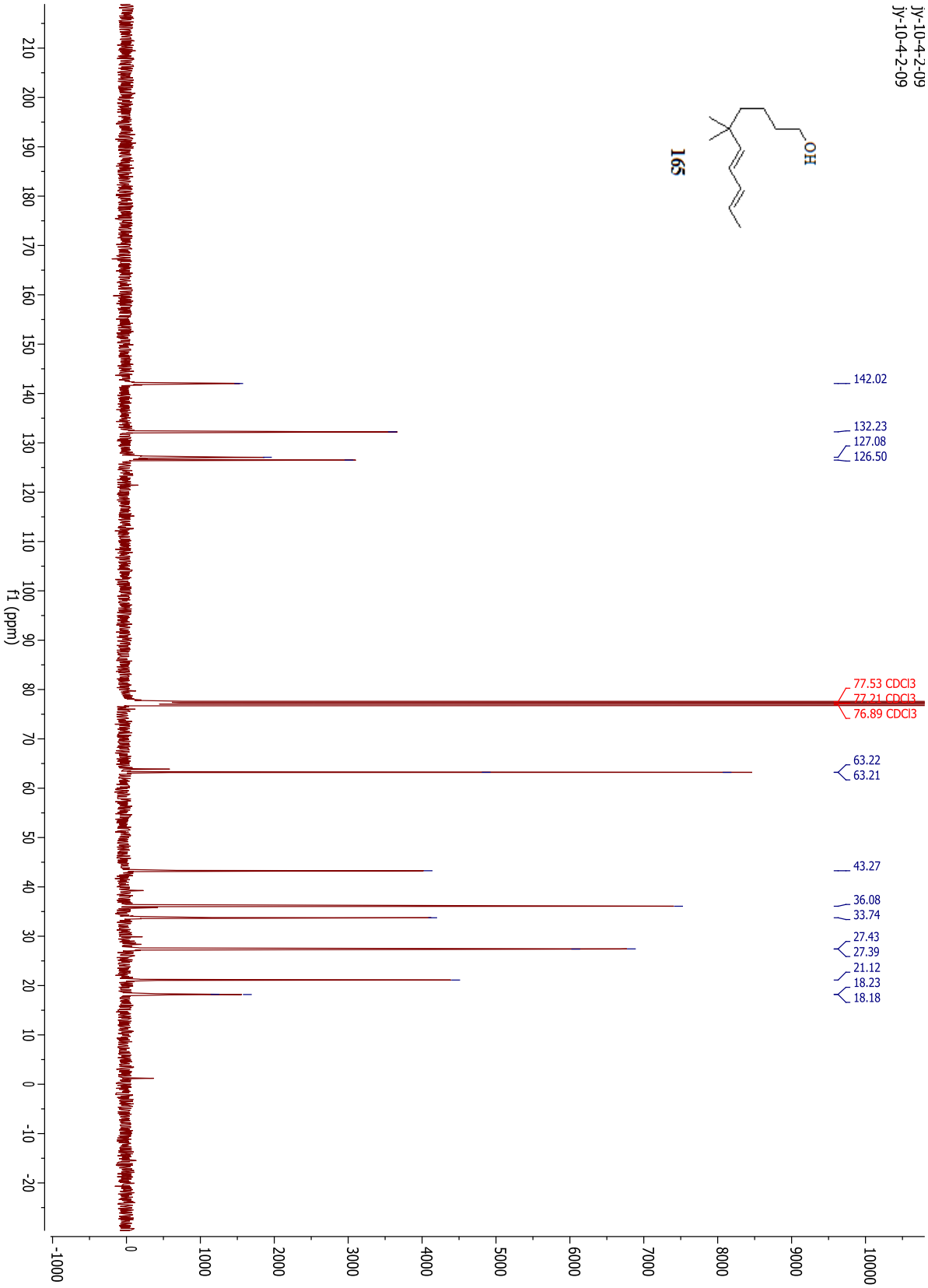
f1 (ppm)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27.43
27.39
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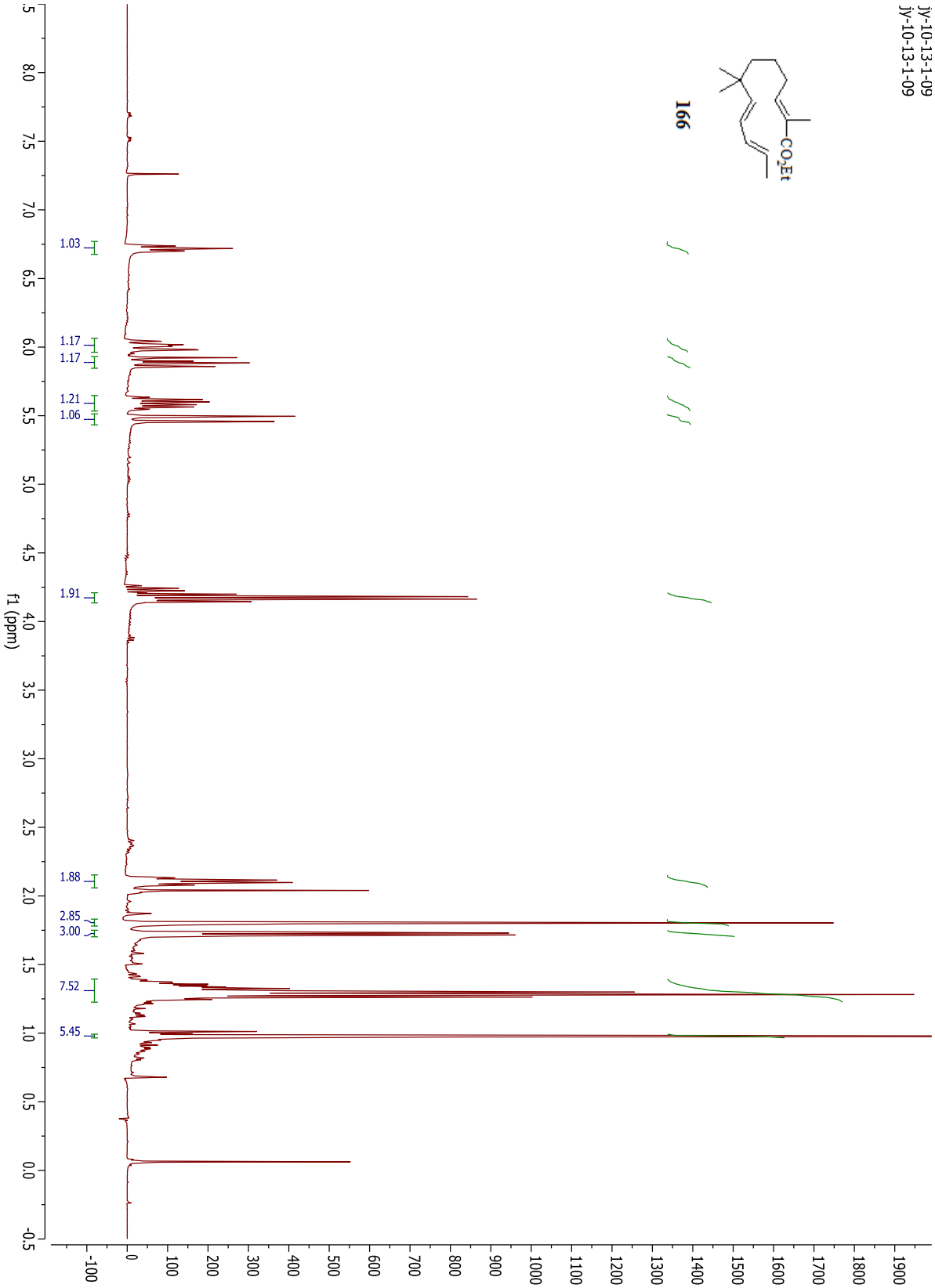
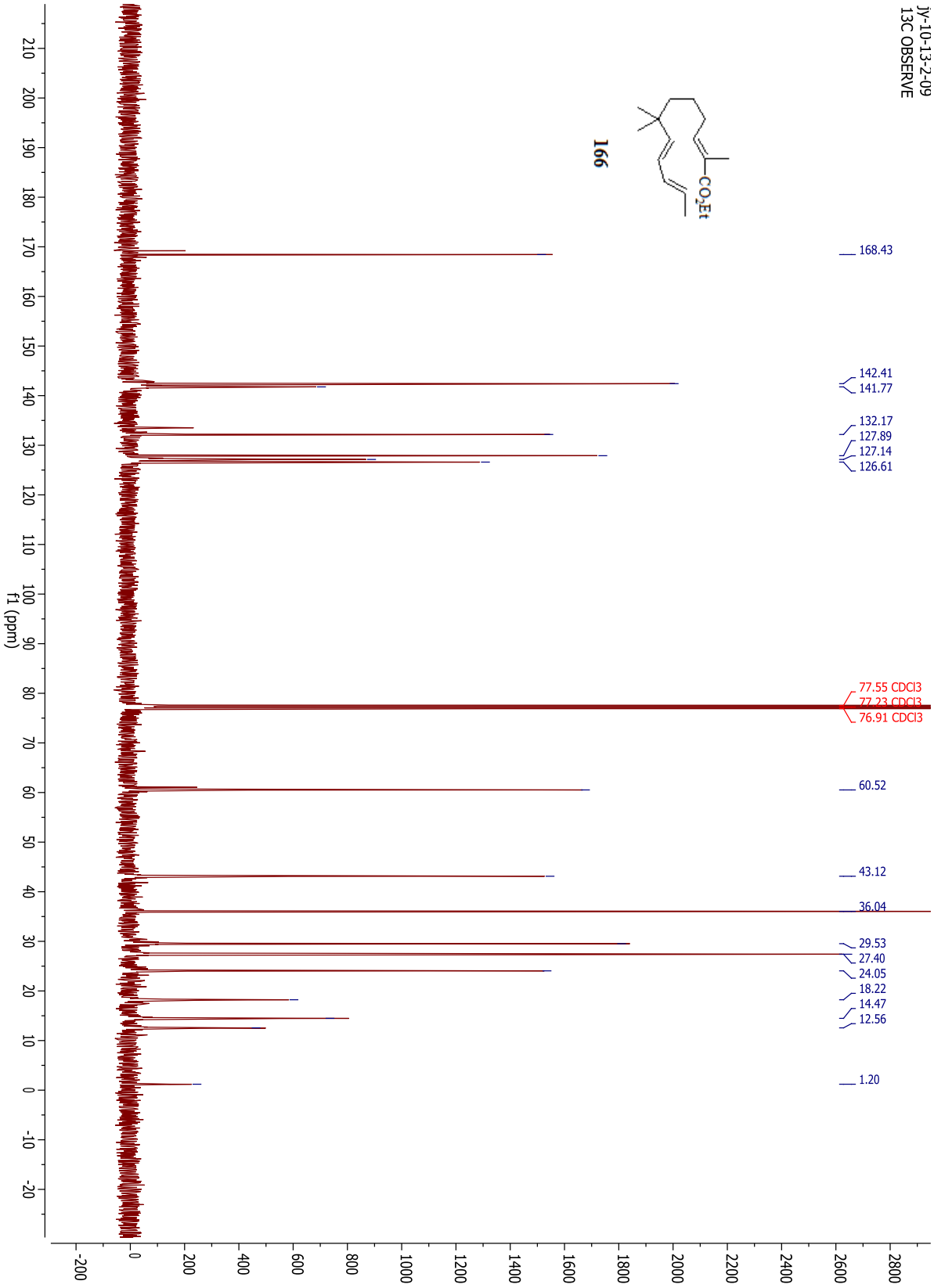
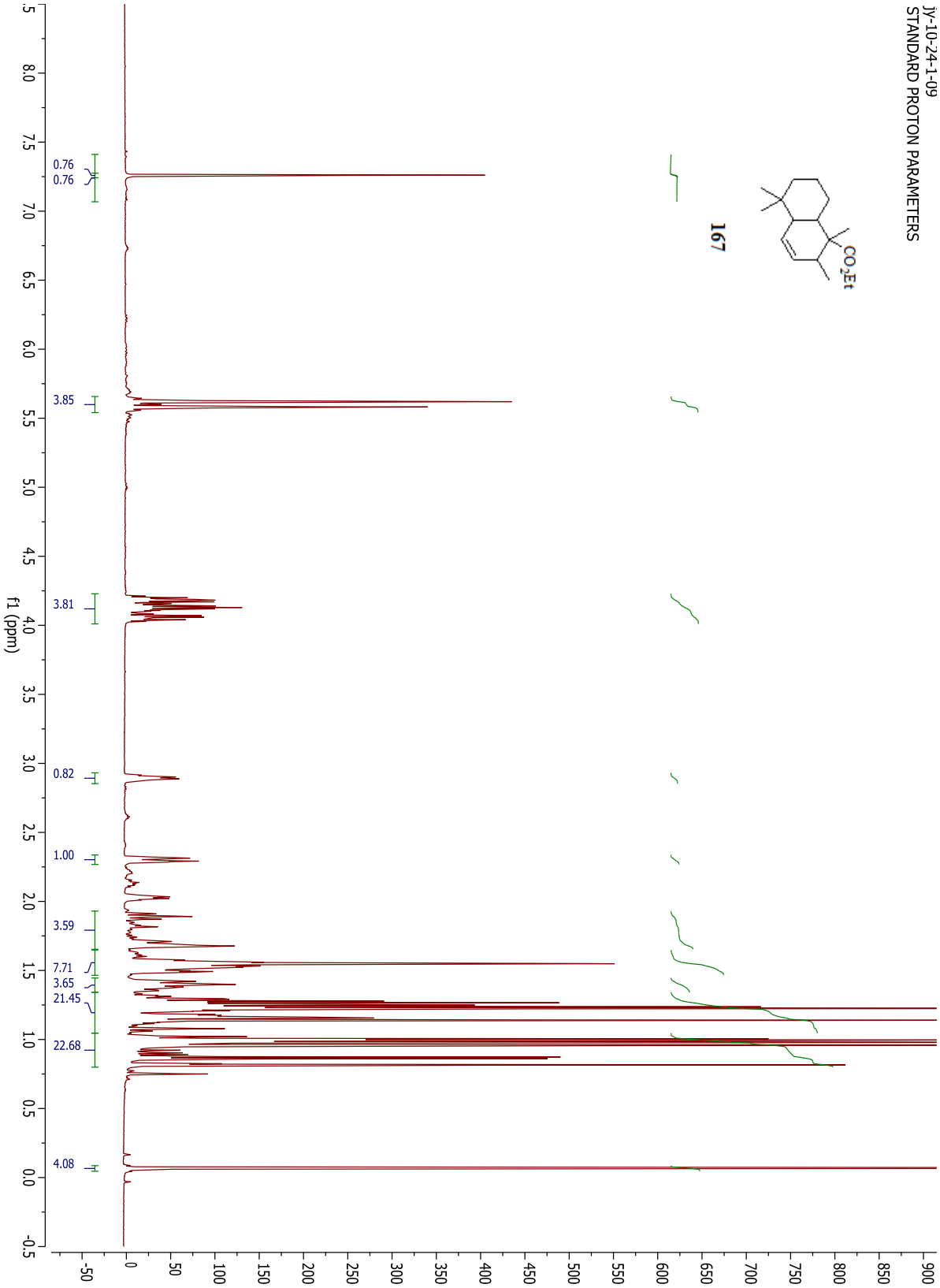
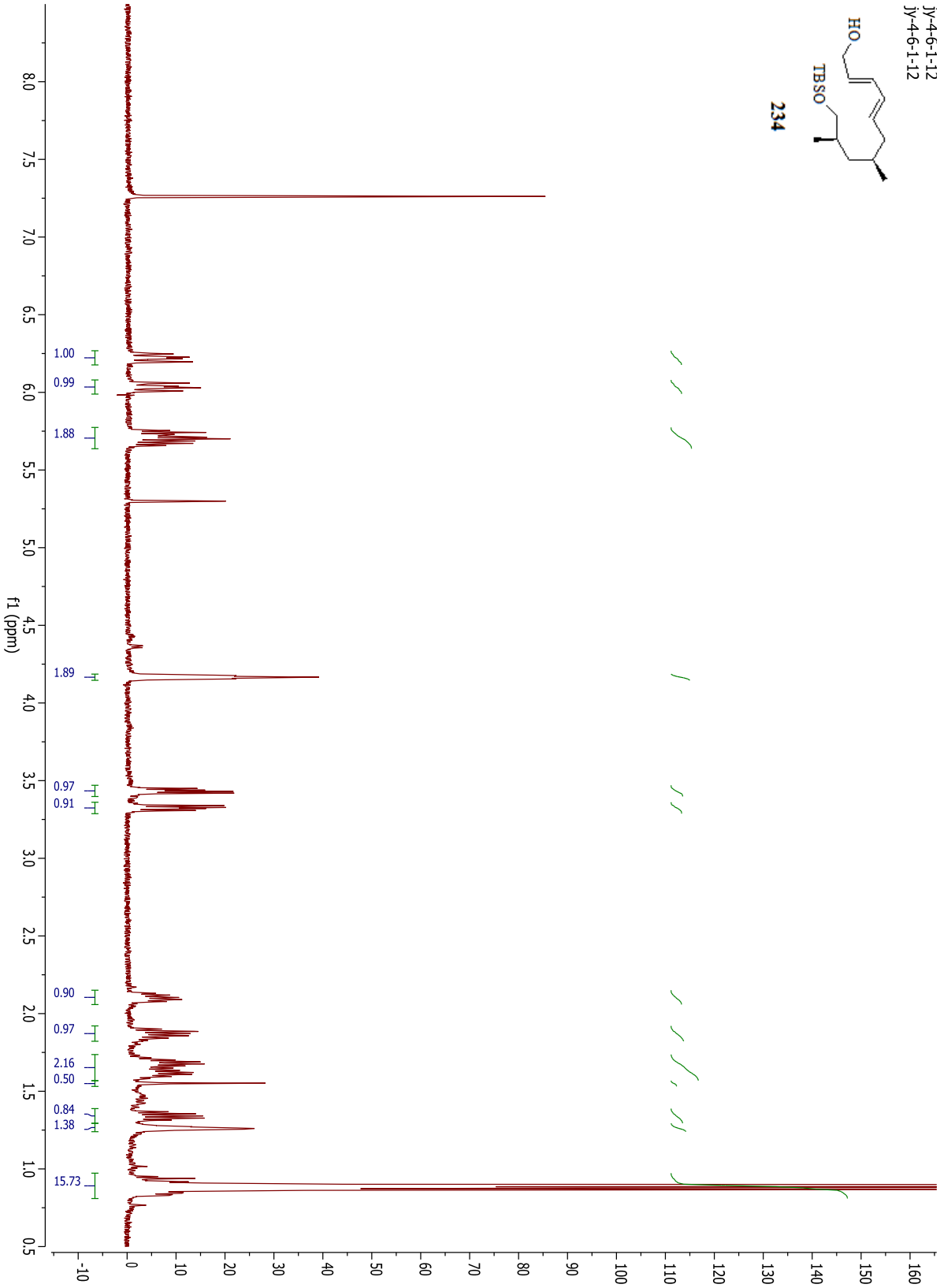
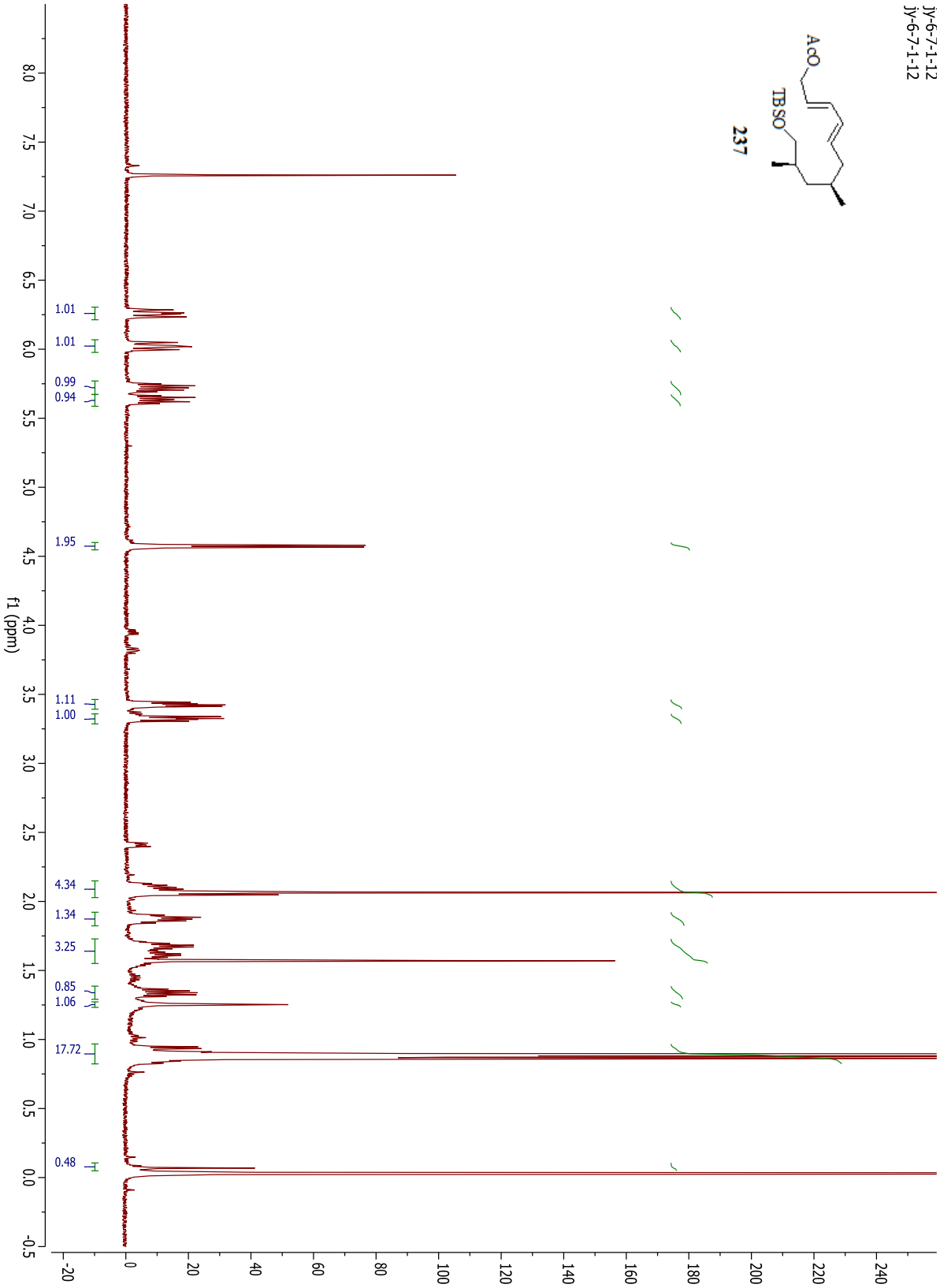
18.23
18.18
f1 (ppm)


jy-10-13-1-09
jy-10-13-1-09
166
CO2Et
1.03
1.17
1.17
1.21
1.06
1.91
1.88
2.85
3.00
7.52
5.45
f1 (ppm)

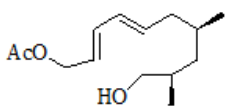

JY-10-13-2-09
13C OBSERVE
166
CO2Et
168.43
142.41
141.77
132.17
127.89
127.14
126.61
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
60.52
43.12
36.04
29.53
27.40
24.05
18.22
14.47
12.56
1.20
f1 (ppm)


jy-10-24-1-09
STANDARD PROTON PARAMETERS
167
CO2Et
f1 (ppm)
0.76
0.76
3.85
3.81
0.82
1.00
3.59
7.71
3.65
21.45
22.68
4.08

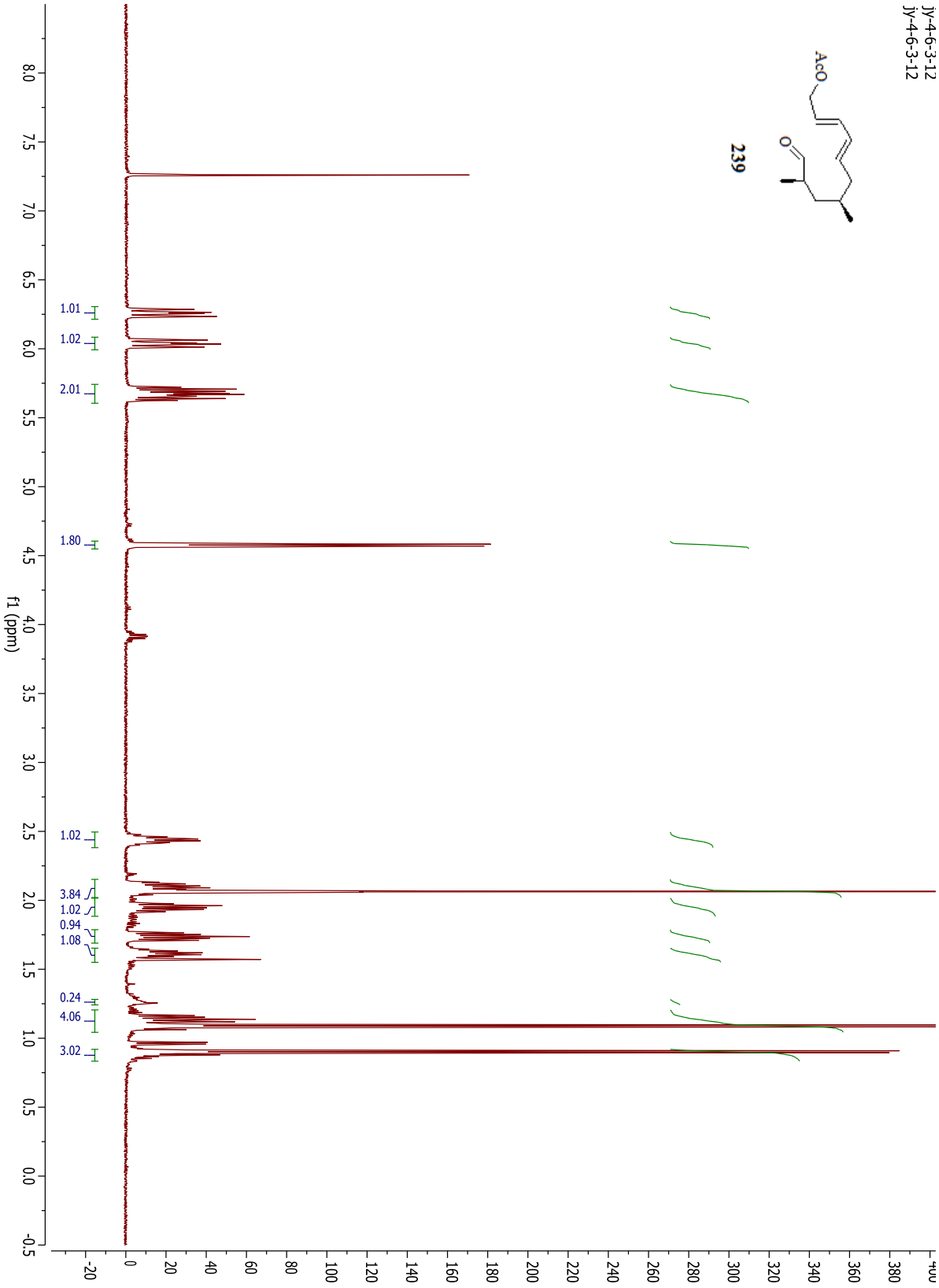

jy-4-6-1-12
jy-4-6-1-12
HO
TBSO
234
f1 (ppm)
1.00
0.99
1.88
1.89
0.97
0.91
0.90
0.97
2.16
0.50
0.84
1.38
15.73

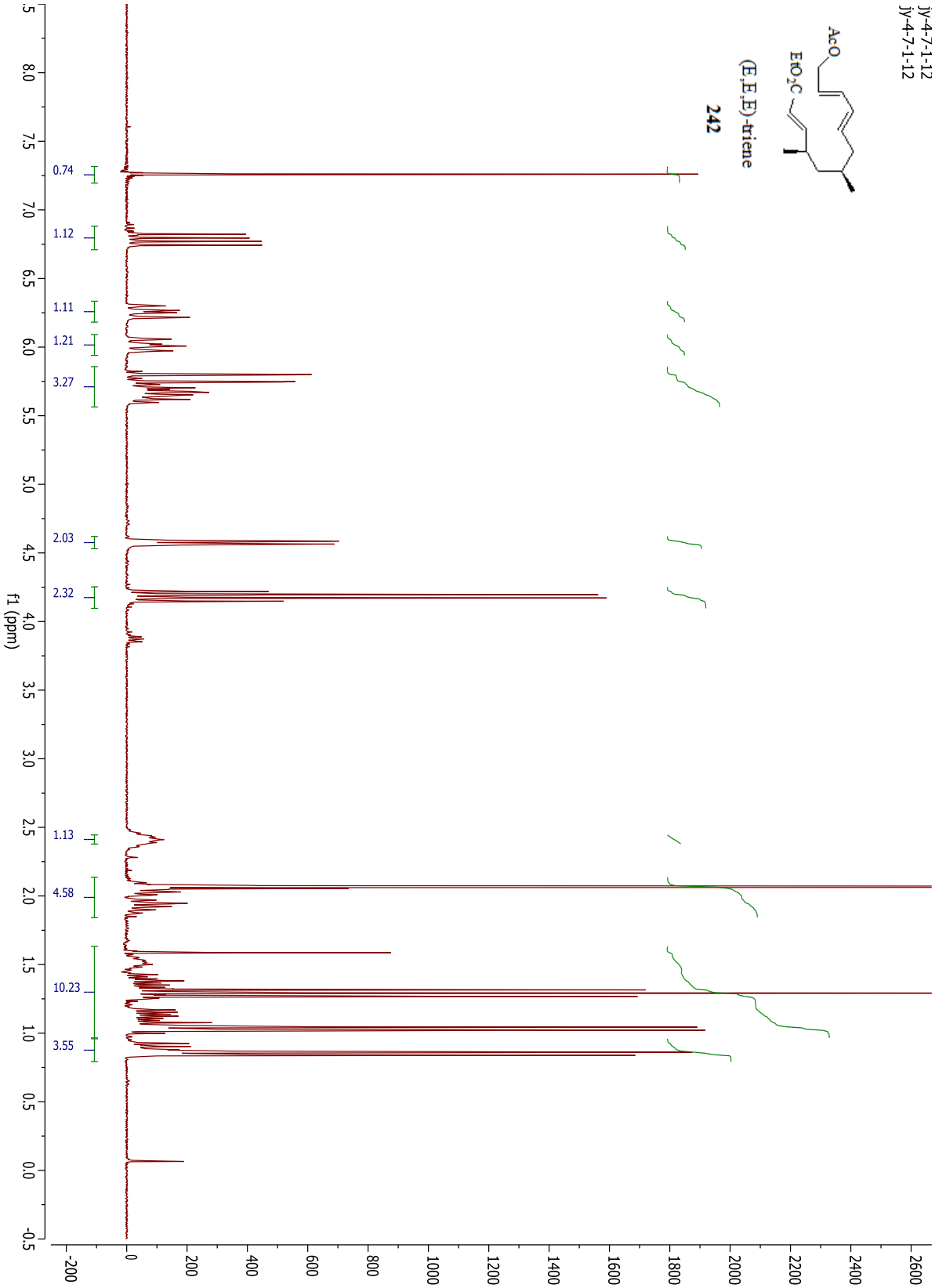

jy-6-7-1-12
jy-6-7-1-12
AcO
TBSO
237
f1 (ppm)
1.01
1.01
0.99
0.94
1.95
1.11
1.00
4.34
1.34
3.25
0.85
1.06
17.72
0.48

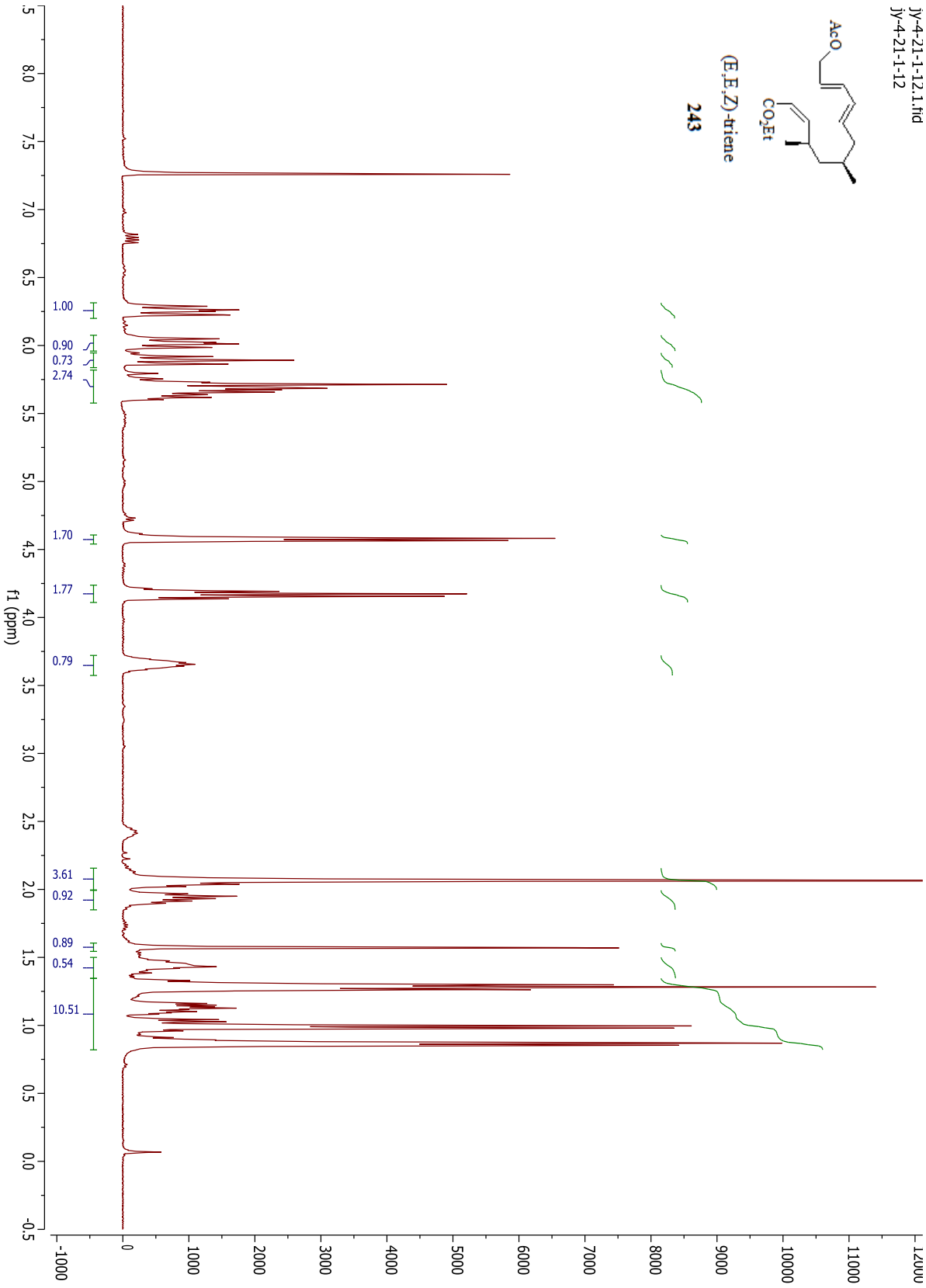
jy-4-13-1-12
jy-4-13-1-12

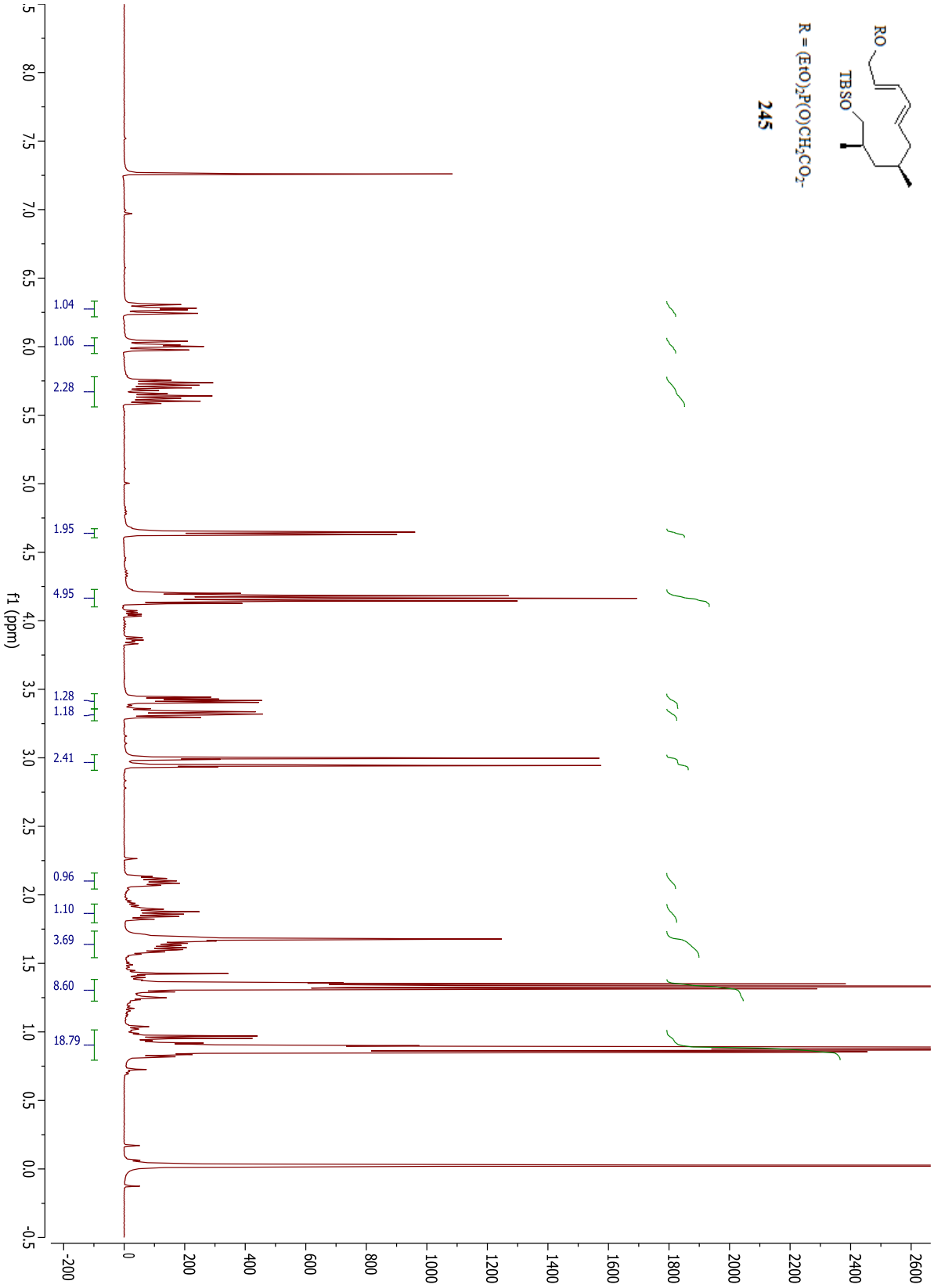


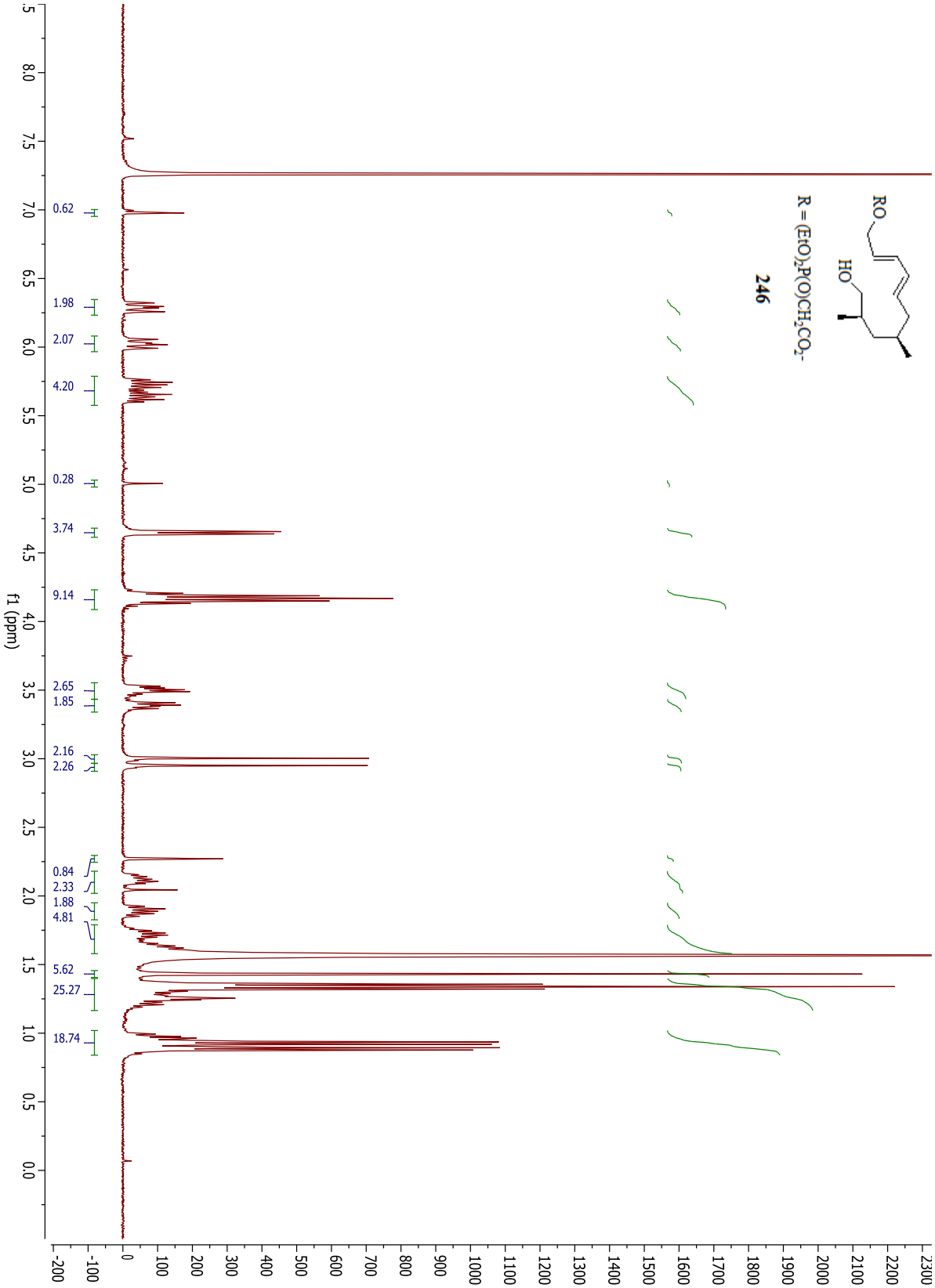
238

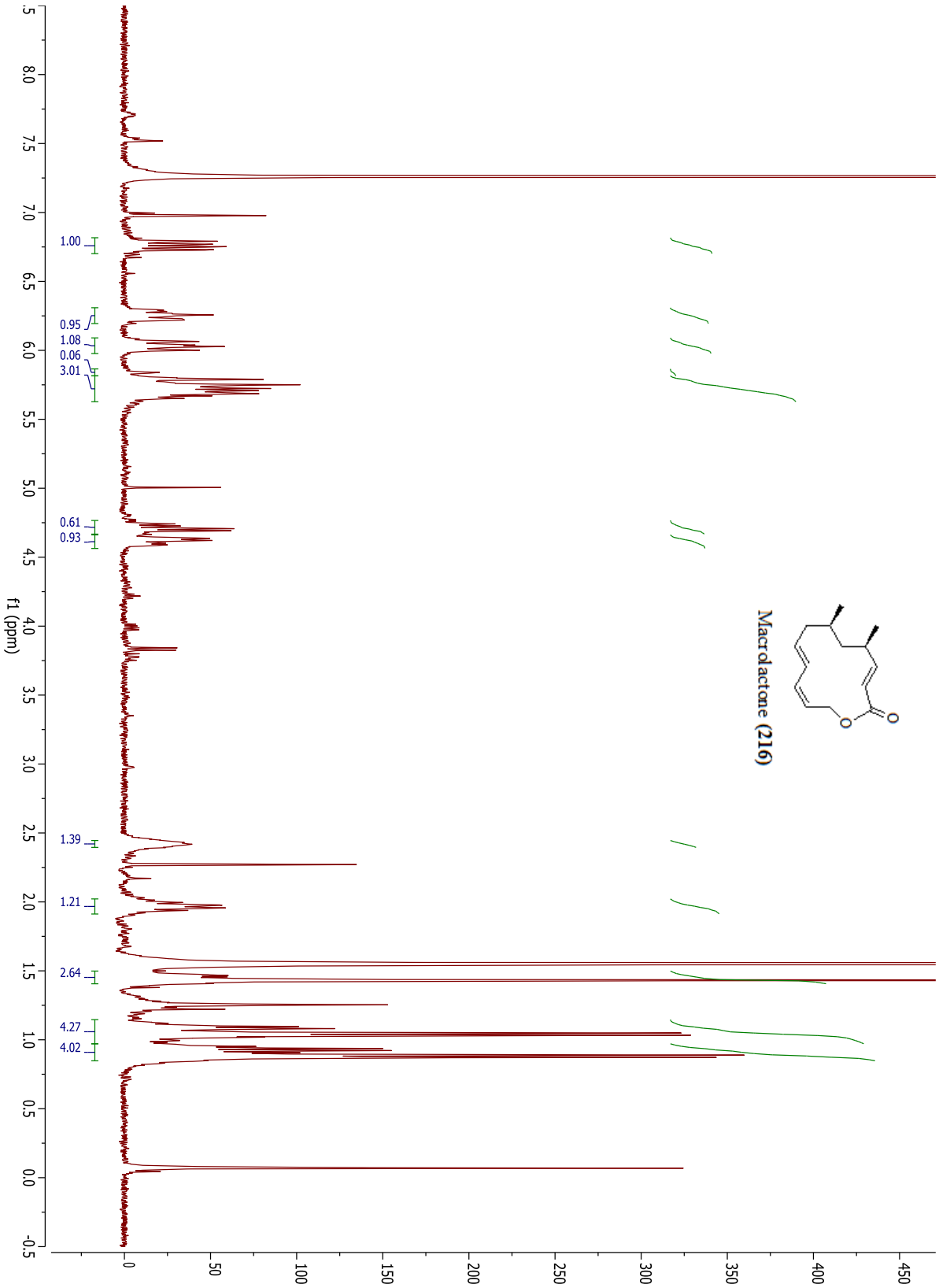

jy-4-6-3-12
jy-4-6-3-12
AcO
O
239
1.01
1.02
2.01
1.80
1.02
3.84
1.02
0.94
1.08
0.24
4.06
3.02
f1 (ppm)

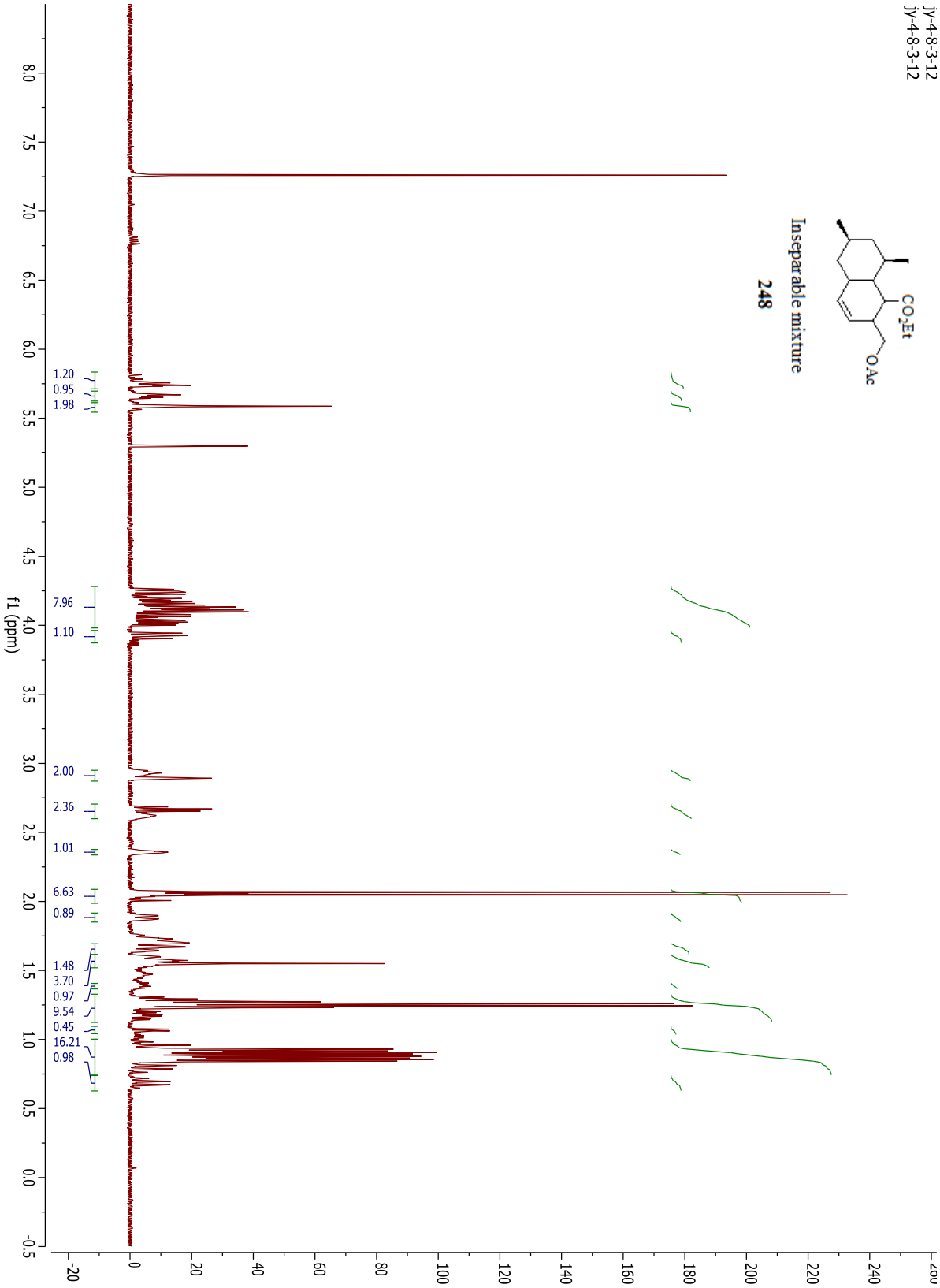

jy-4-7-1-12
jy-4-7-1-12
AcO
EtO2C
(E,E,E)-triene
242
0.74
1.12
1.11
1.21
3.27
2.03
2.32
1.13
4.58
10.23
3.55
f1 (ppm)

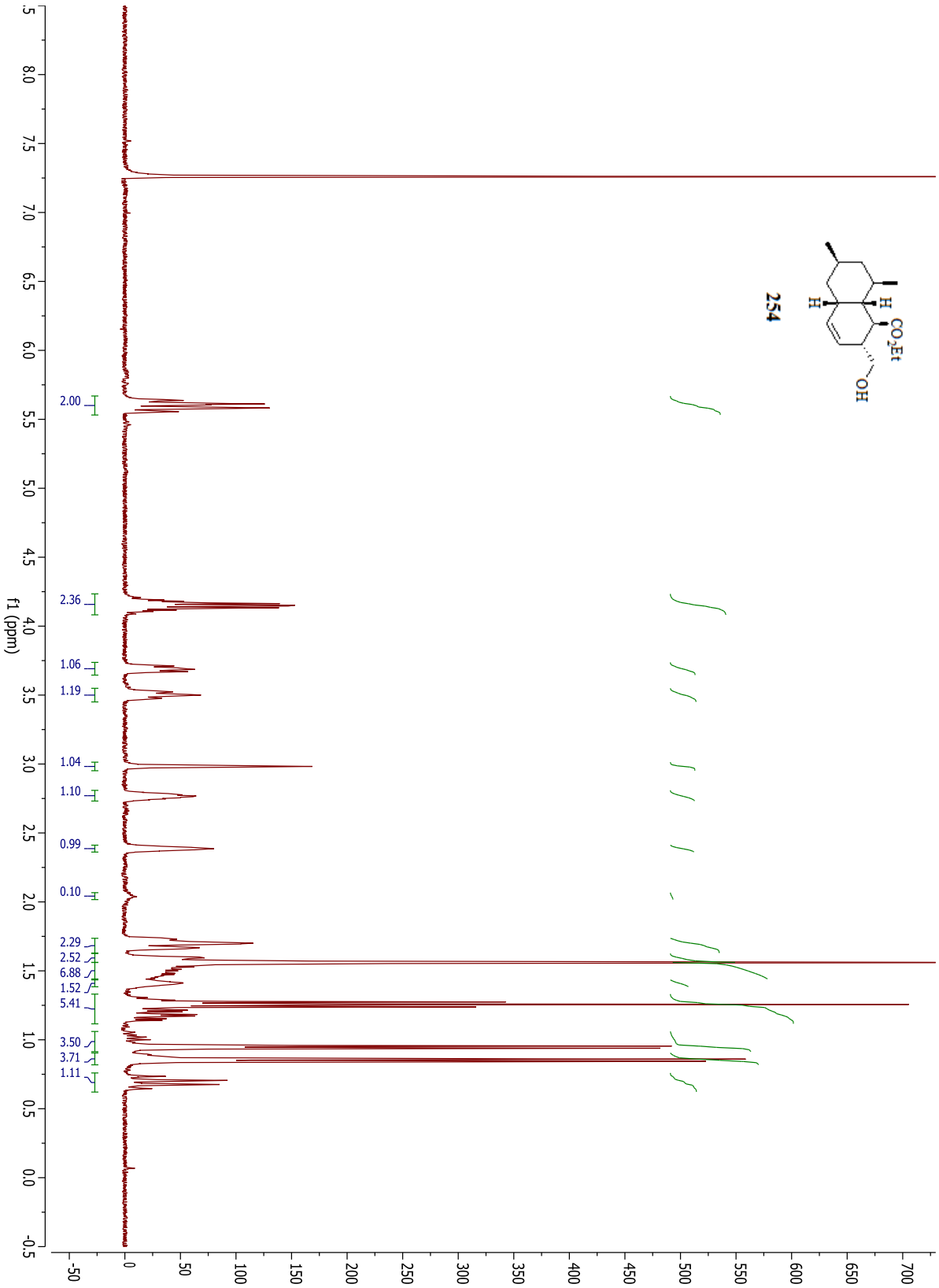

jy-4-21-1-12.1.fid
jy-4-21-1-12
AcO
CO2Et
(E,E,Z)-triene
243
1.00
0.90
0.73
2.74
1.70
1.77
0.79
3.61
0.92
0.89
0.54
10.51
f1 (ppm)

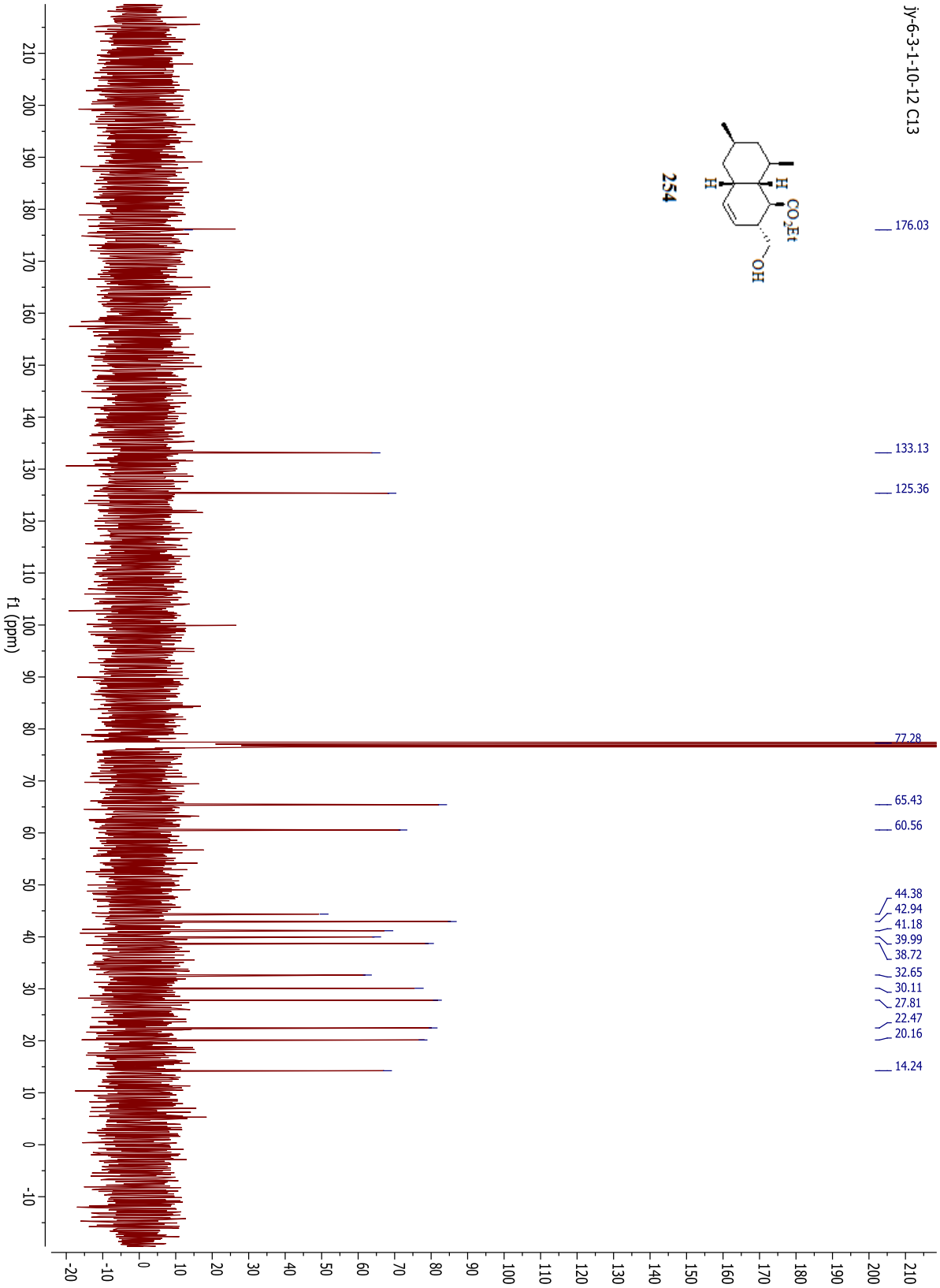

RO
TBSO
R = (EtO)2P(O)CH2CO2-
245
1.04
1.06
2.28
1.95
4.95
1.28
1.18
2.41
0.96
1.10
3.69
8.60
18.79
f1 (ppm)

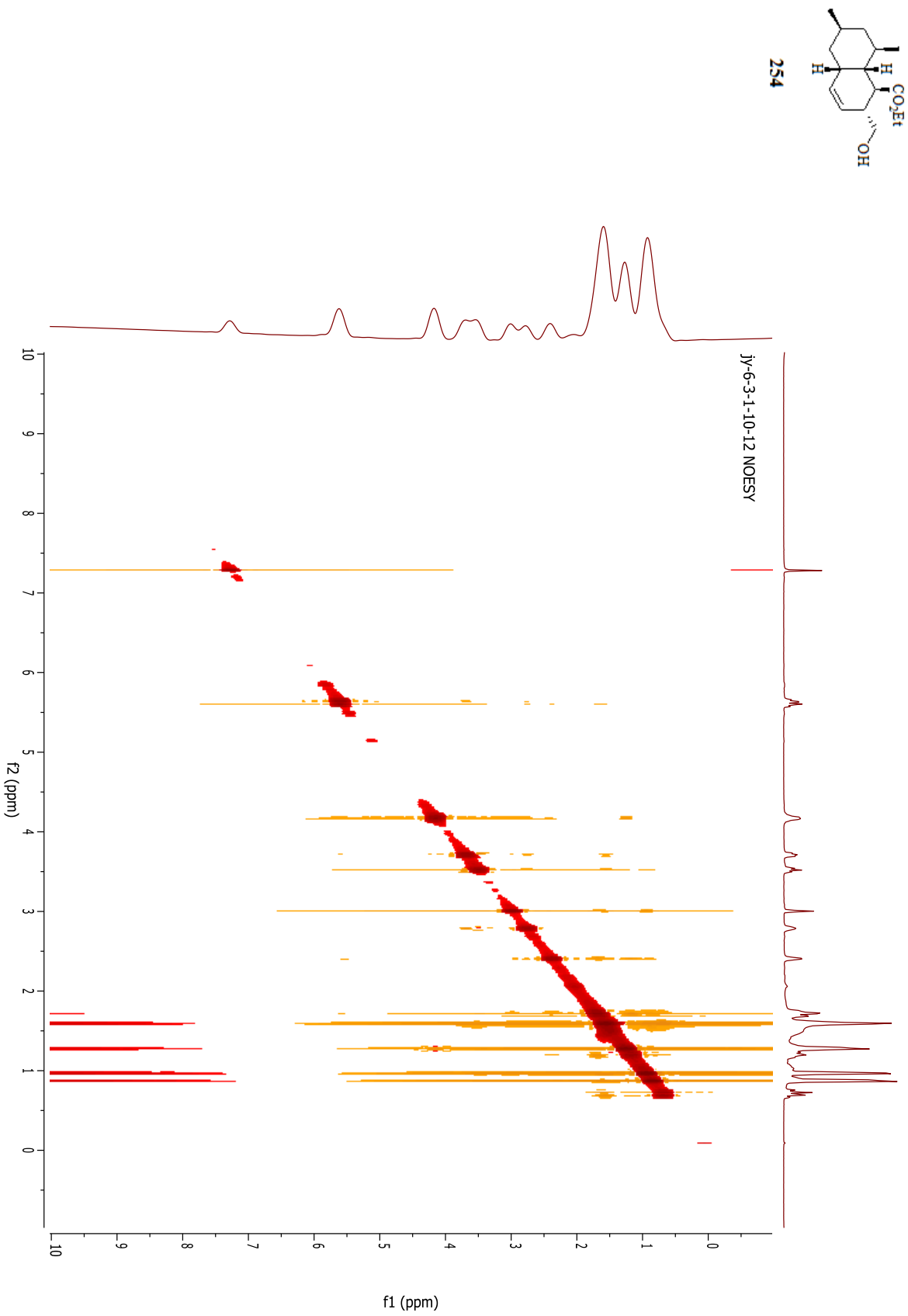

RO
HO
R = (EtO)2P(O)CH2CO2-
246
f1 (ppm)
0.62
1.98
2.07
4.20
0.28
3.74
9.14
2.65
1.85
2.16
2.26
0.84
2.33
1.88
4.81
5.62
25.27
18.74

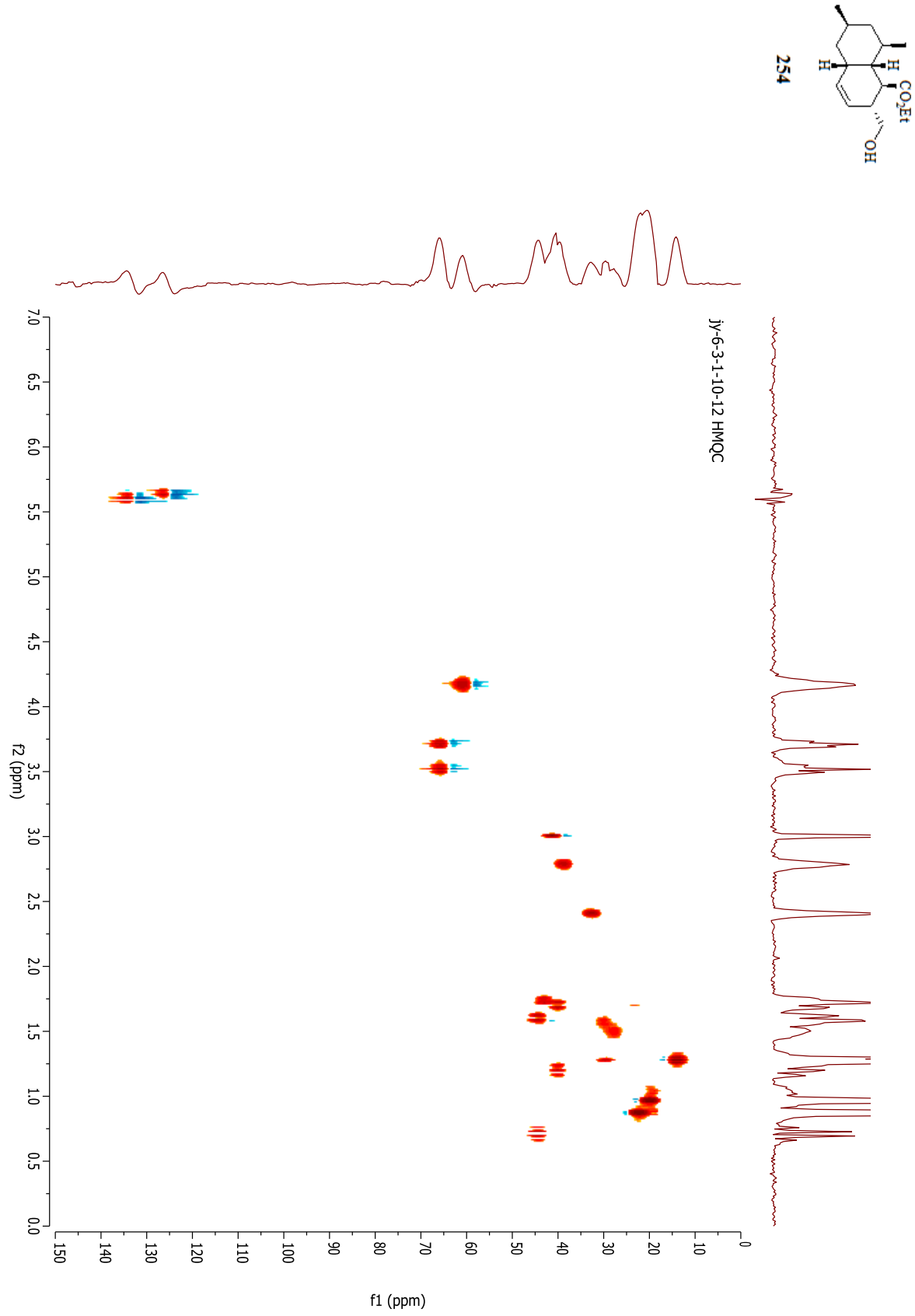

Macrolactone (216)
f1 (ppm)
1.00
0.95
1.08
0.06
3.01
0.61
0.93
1.39
1.21
2.64
4.27
4.02

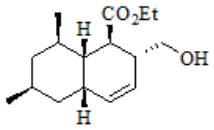

Jy-4-8-3-12
Jy-4-8-3-12
CO2Et
OAc
Inseparable mixture
248
1.20
0.95
1.98
7.96
1.10
2.00
2.36
1.01
6.63
0.89
1.48
3.70
0.97
9.54
0.45
16.21
0.98
f1 (ppm)


254
CO2Et
OH
H
H
2.00
2.36
1.06
1.19
1.04
1.10
0.99
0.10
2.29
2.52
6.88
1.52
5.41
3.50
3.71
1.11
f1 (ppm)

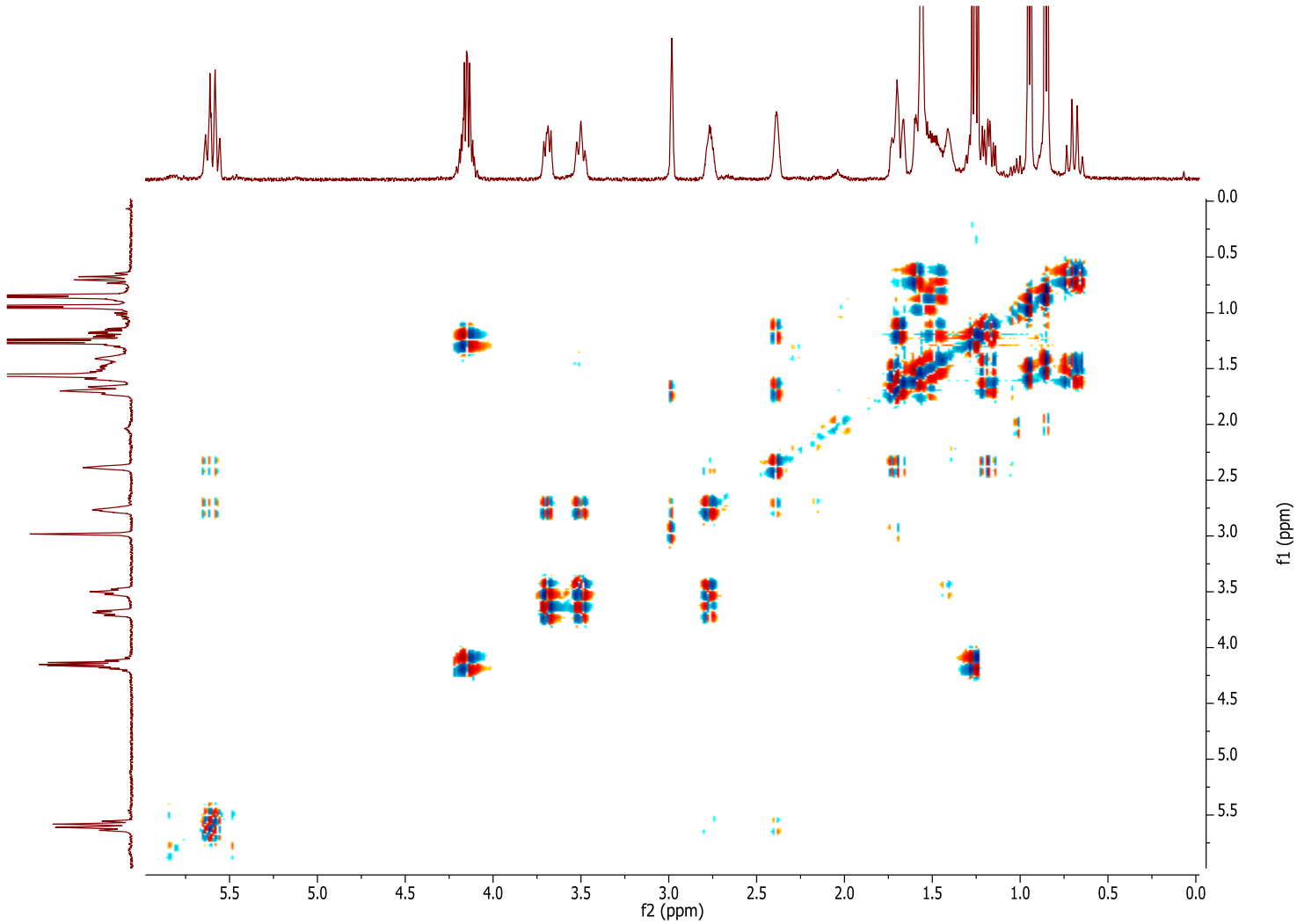

jy-6-3-1-10-12 C13
254
176.03
133.13
125.36
77.28
65.43
60.56
44.38
42.94
41.18
39.99
38.72
32.65
30.11
27.81
22.47
20.16
14.24
f1 (ppm)

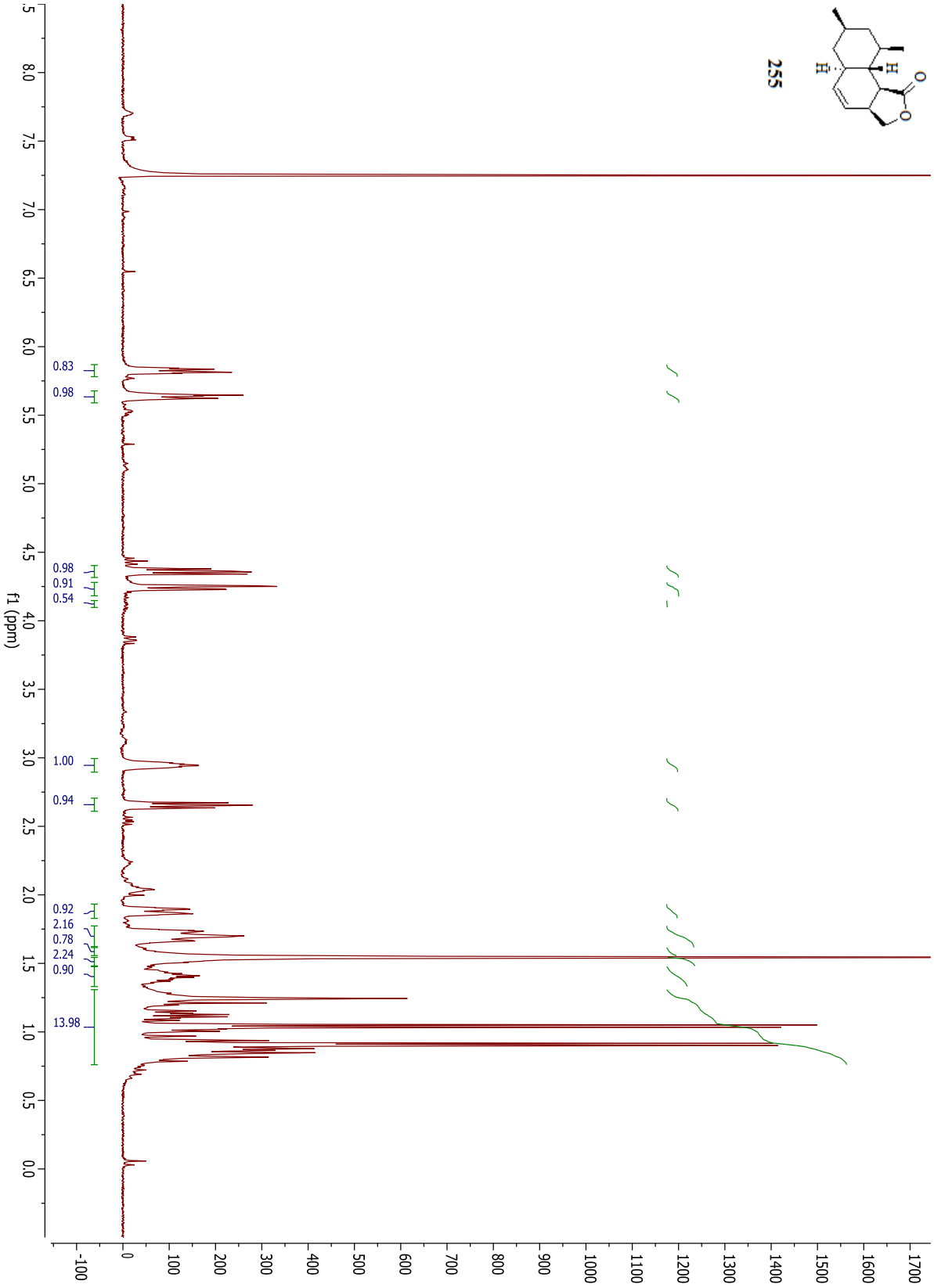

254
jy-6-3-1-10-12 NOESY
f2 (ppm)
f1 (ppm)

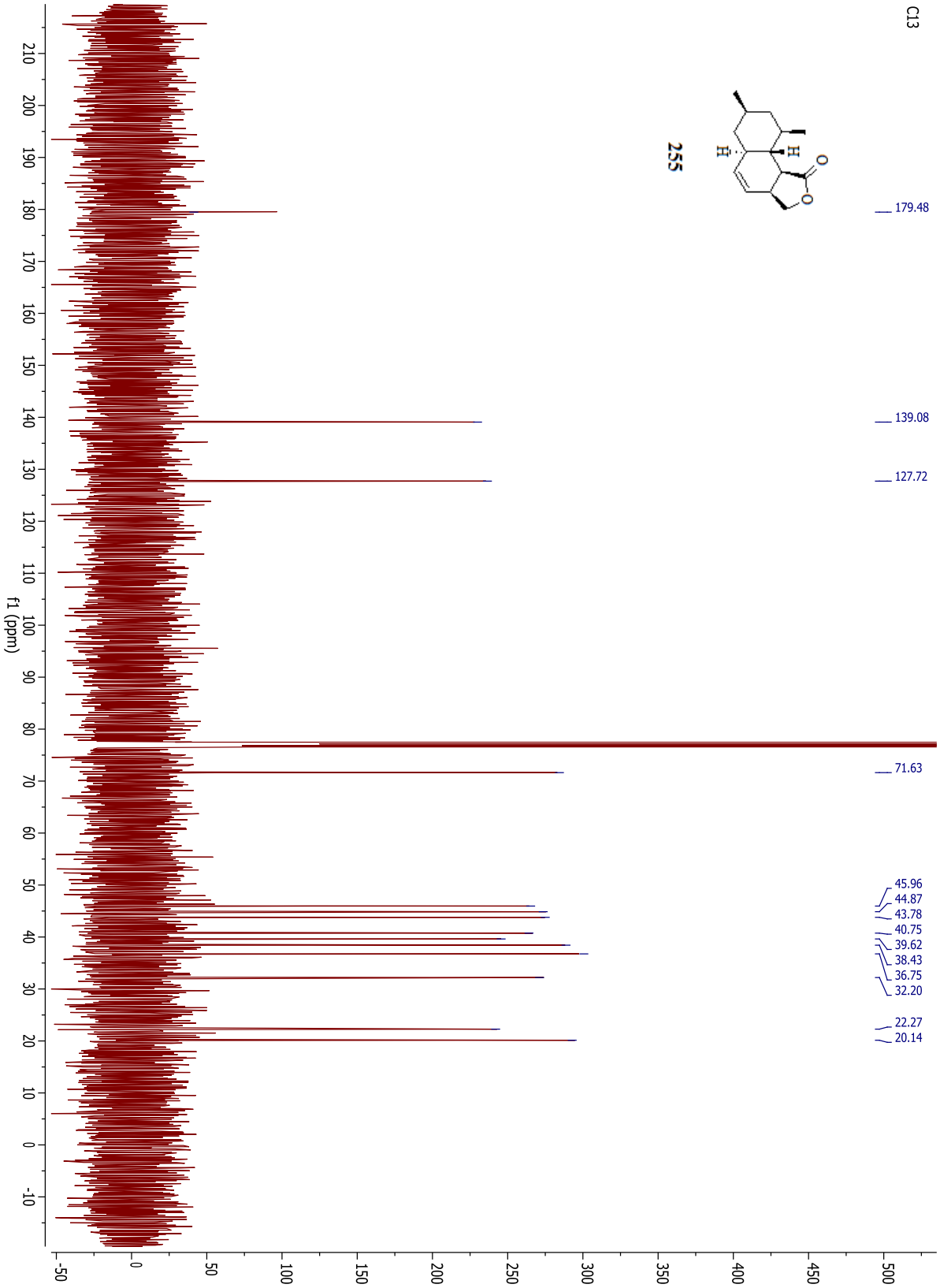

254
H
H
CO2Et
OH
jy-6-3-1-10-12 HMQC
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


CO2Et
H
OH
H

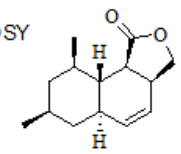
254 (COSY)


0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

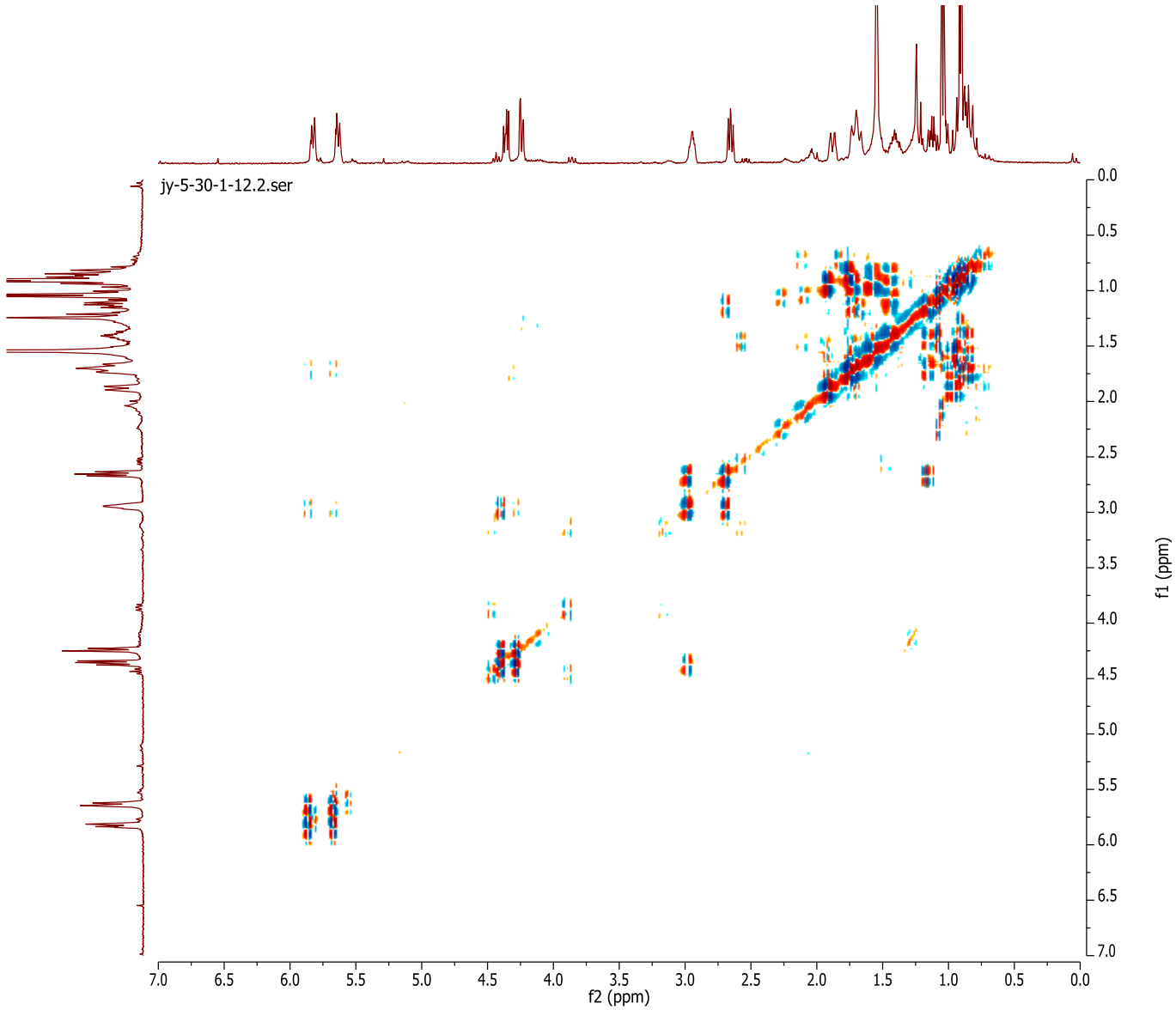

255
0.83
0.98
0.98
0.91
0.54
1.00
0.94
0.92
2.16
0.78
2.24
0.90
13.98
f1 (ppm)

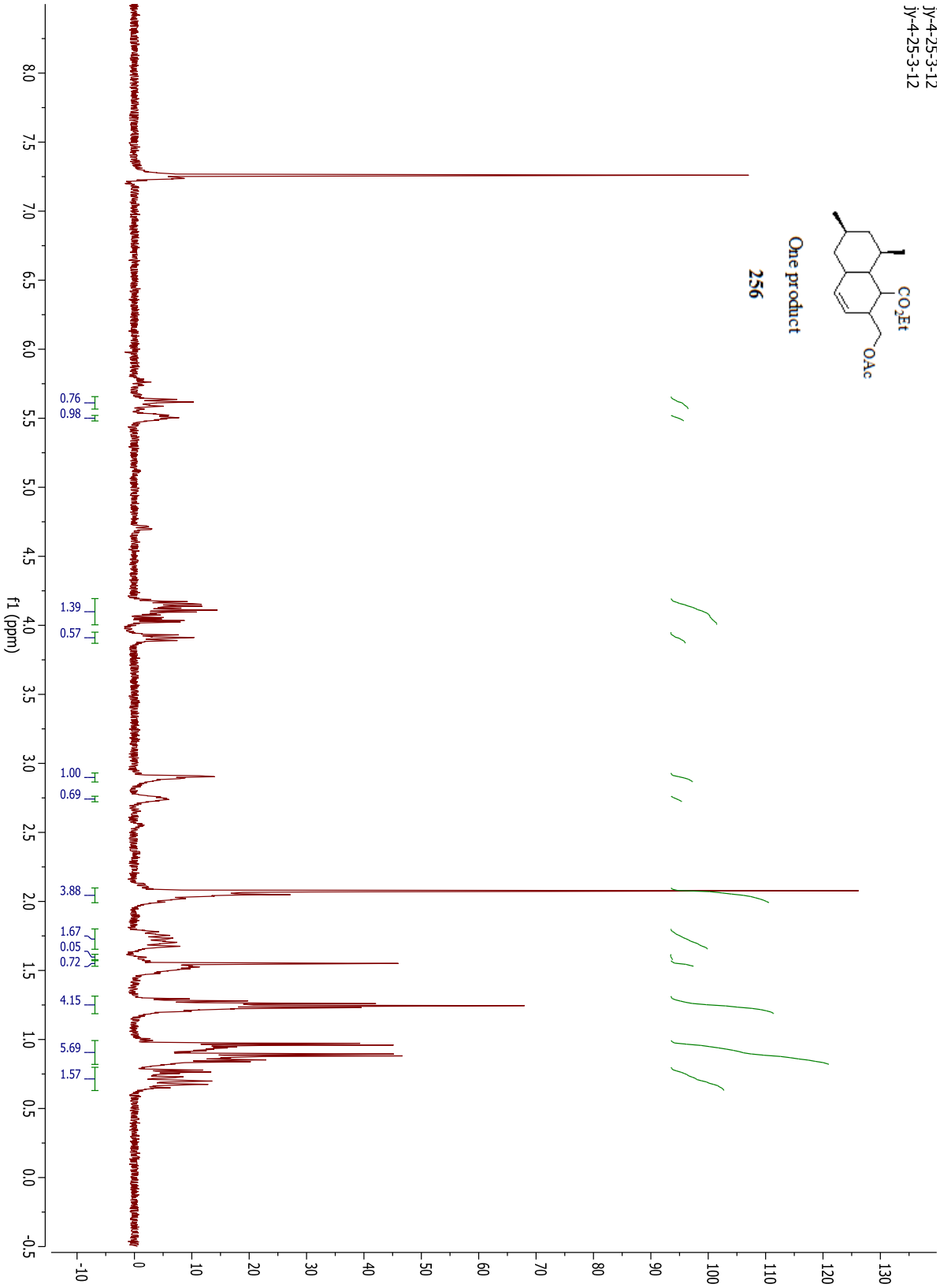

C13
255
179.48
139.08
127.72
71.63
45.96
44.87
43.78
40.75
39.62
38.43
36.75
32.20
22.27
20.14
f1 (ppm)

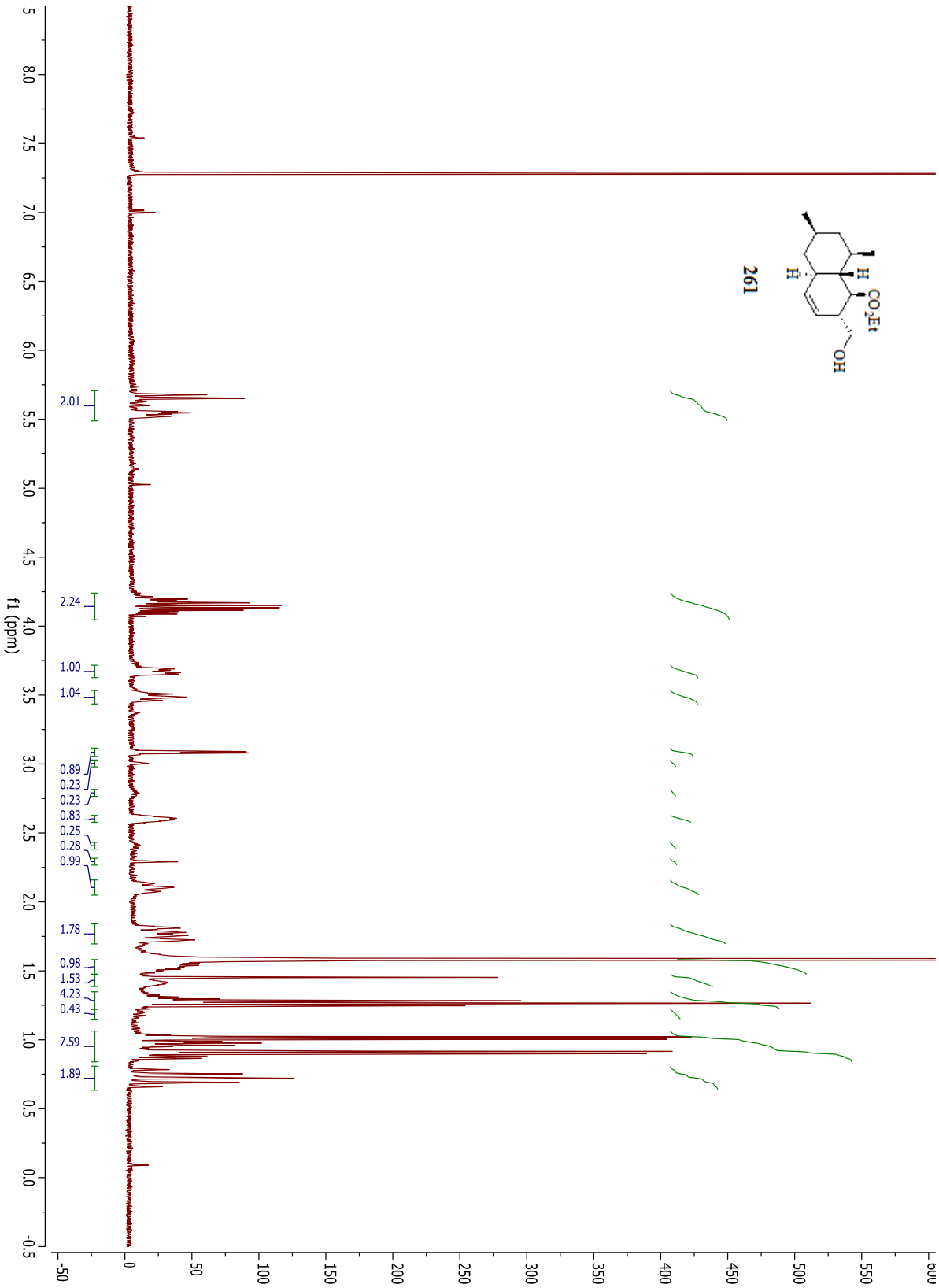
COSY

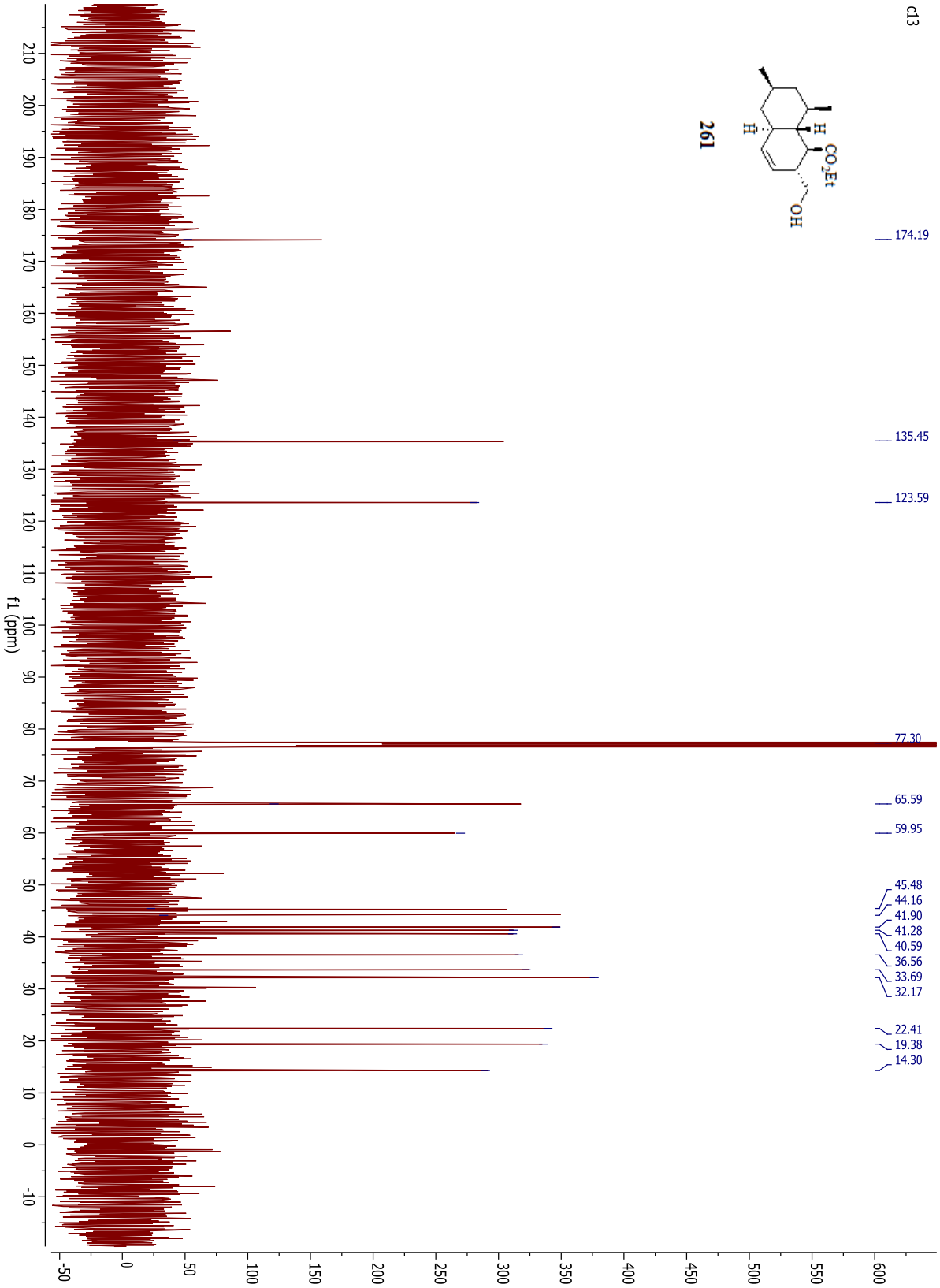


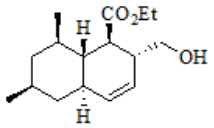
255


jy-5-30-1-12.2.ser
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

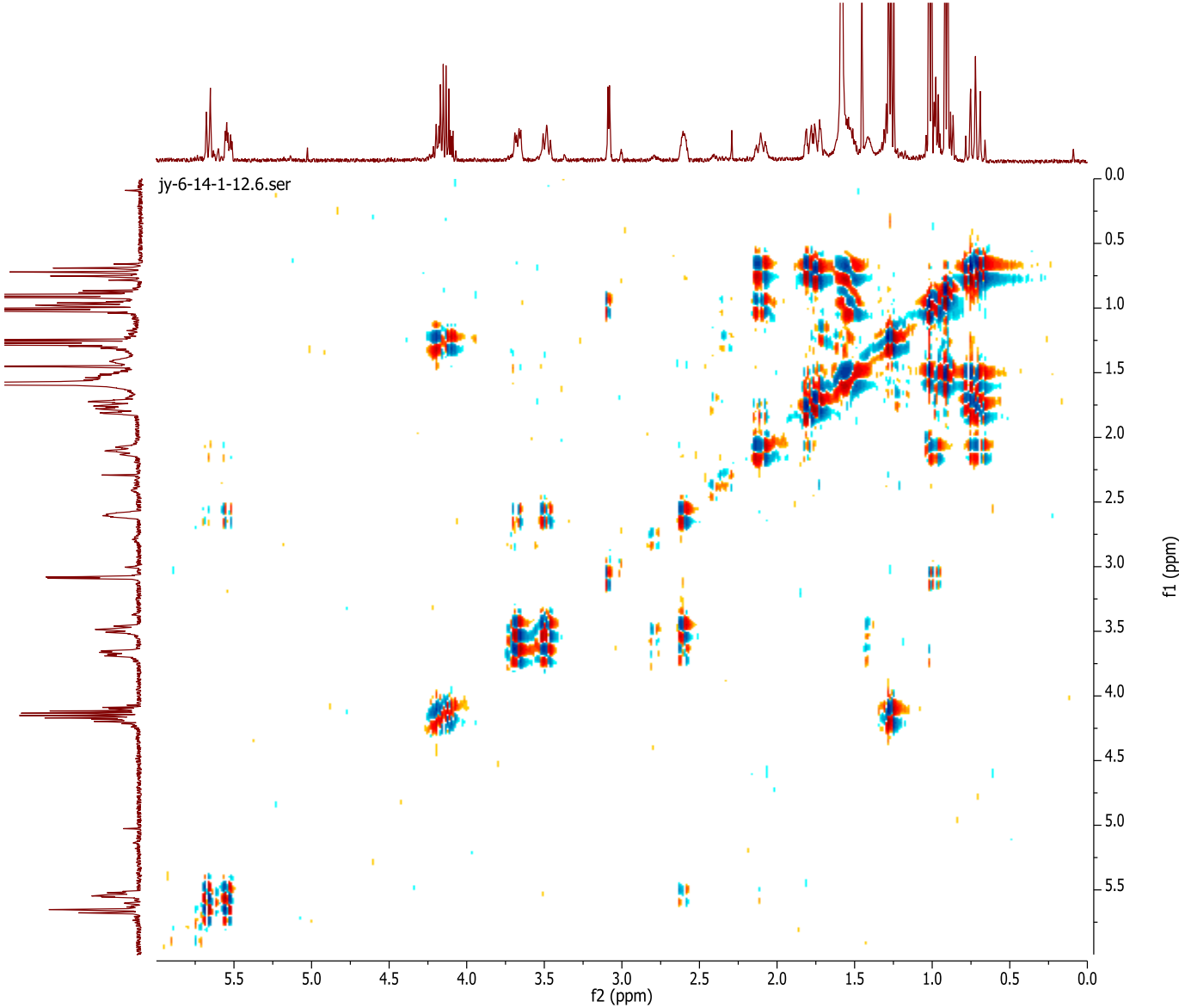

jy-4-25-3-12
jy-4-25-3-12
CO2Et
OAc
One product
256
0.76
0.98
1.39
0.57
1.00
0.69
3.88
1.67
0.05
0.72
4.15
5.69
1.57
f1 (ppm)

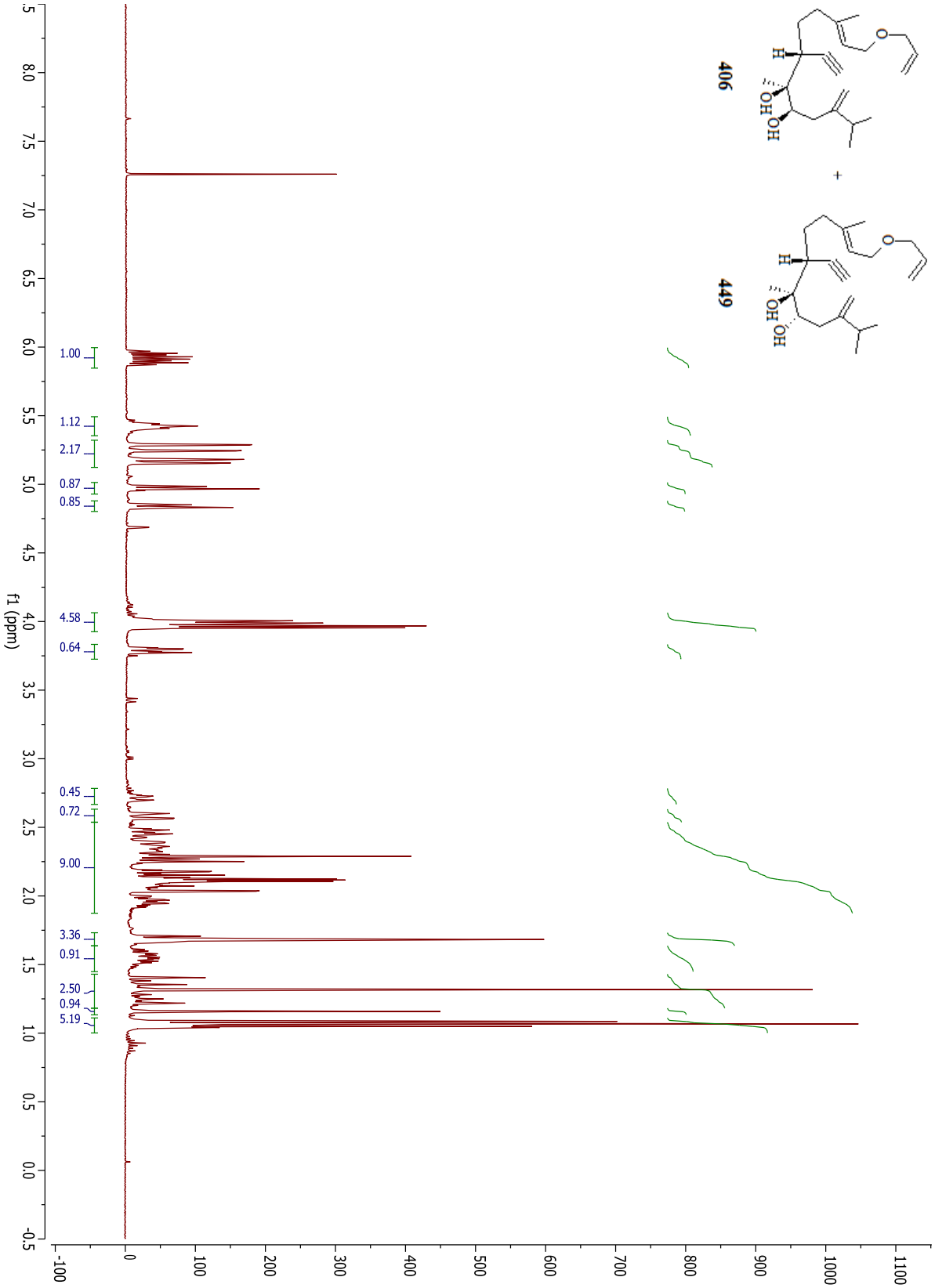

261
CO2Et
H
H
OH
2.01
2.24
1.00
1.04
0.89
0.23
0.23
0.83
0.25
0.28
0.99
1.78
0.98
1.53
4.23
0.43
7.59
1.89
f1 (ppm)

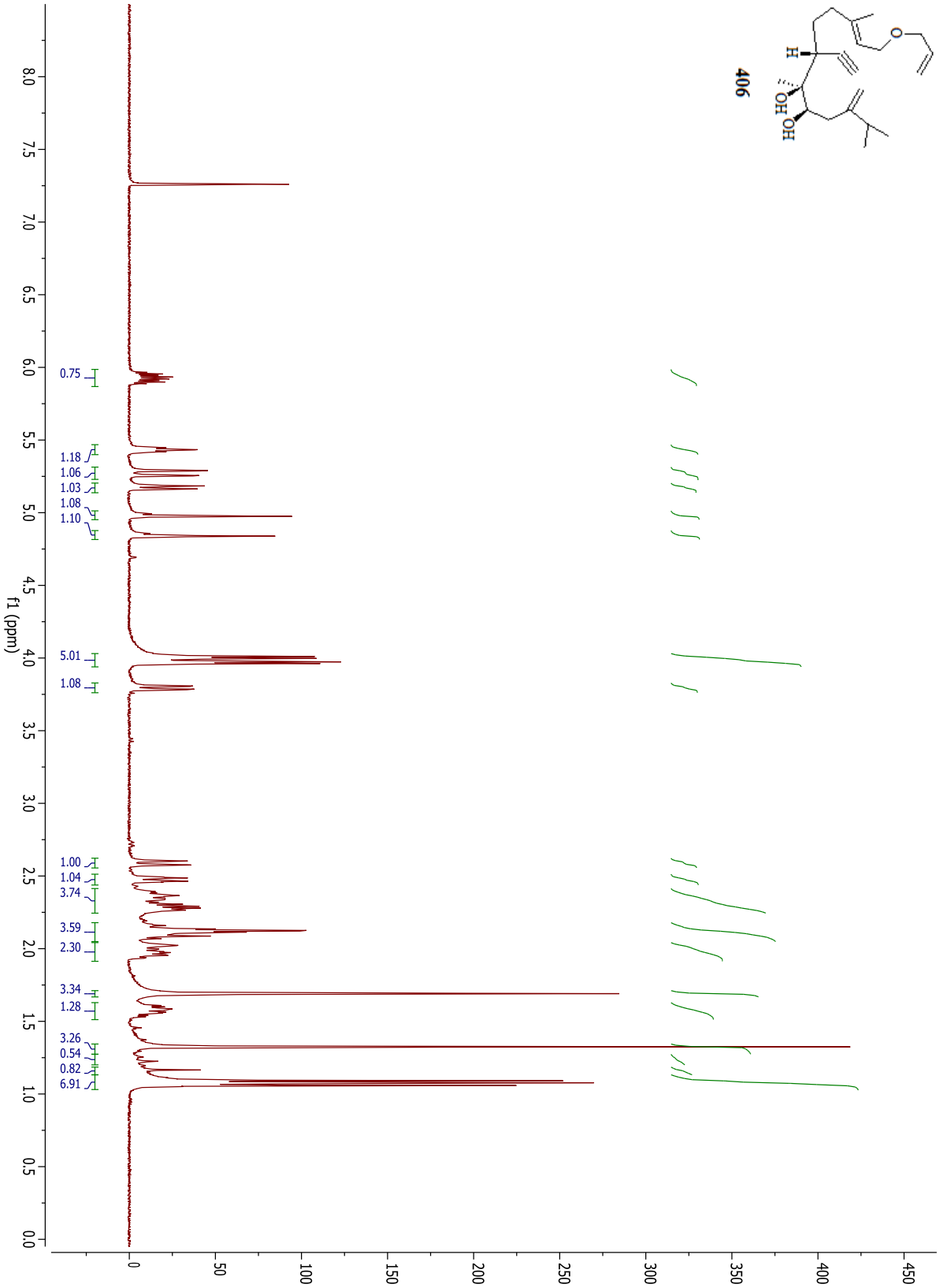

c13
261
H
H
CO2Et
OH
174.19
135.45
123.59
77.30
65.59
59.95
45.48
44.16
41.90
41.28
40.59
36.56
33.69
32.17
22.41
19.38
14.30
f1 (ppm)

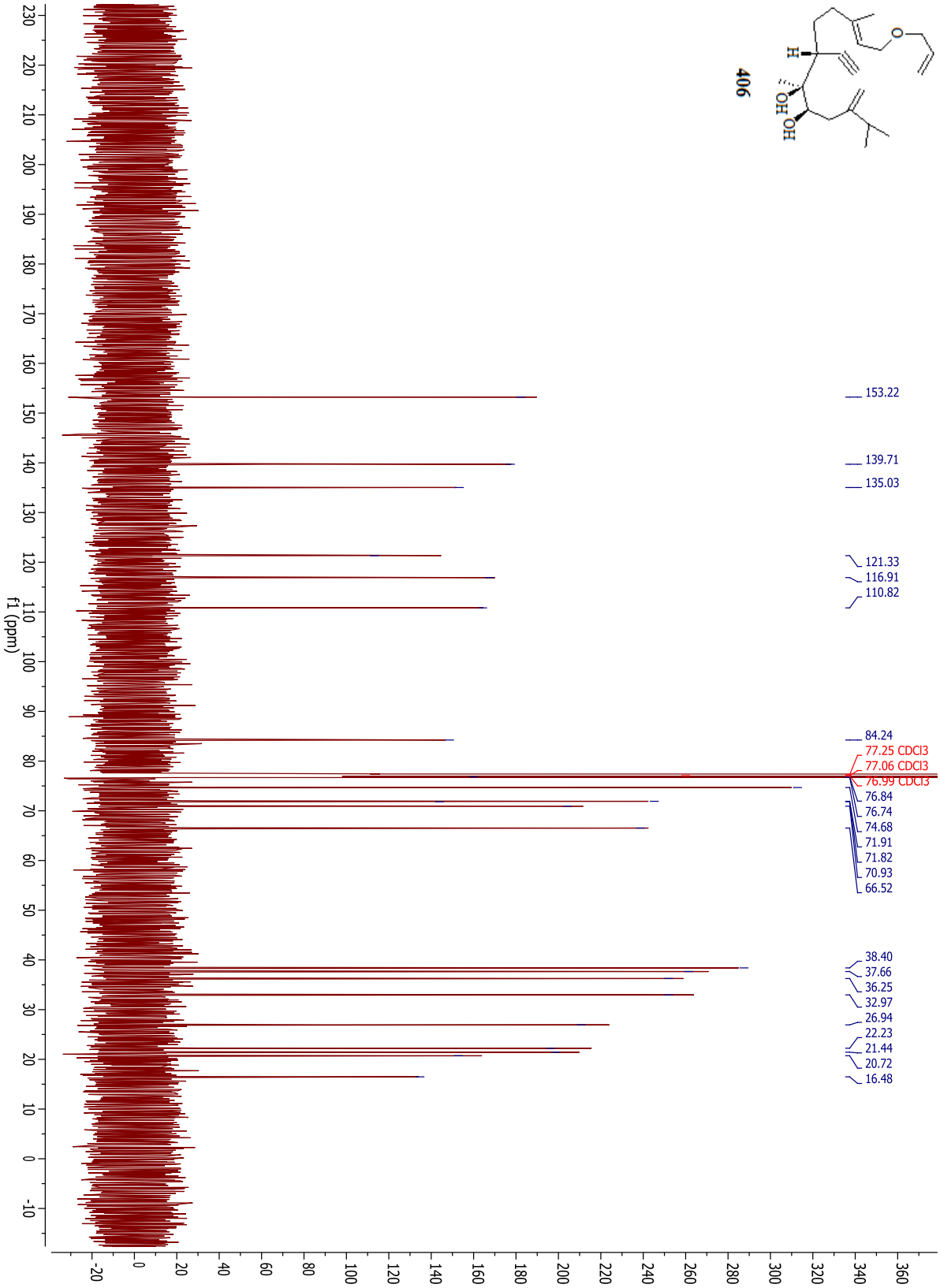

H
CO2Et
OH
H

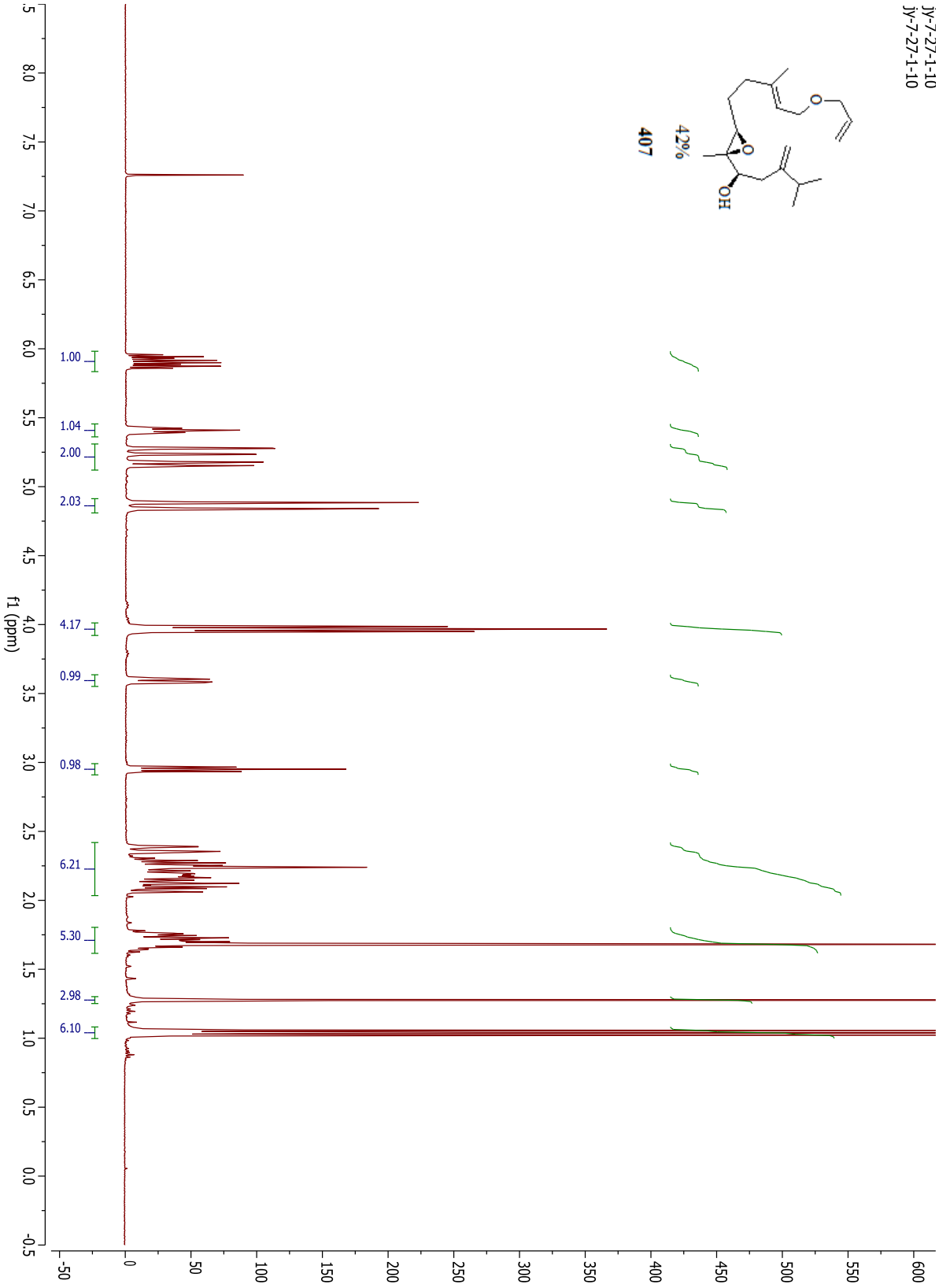
261 (COSY)

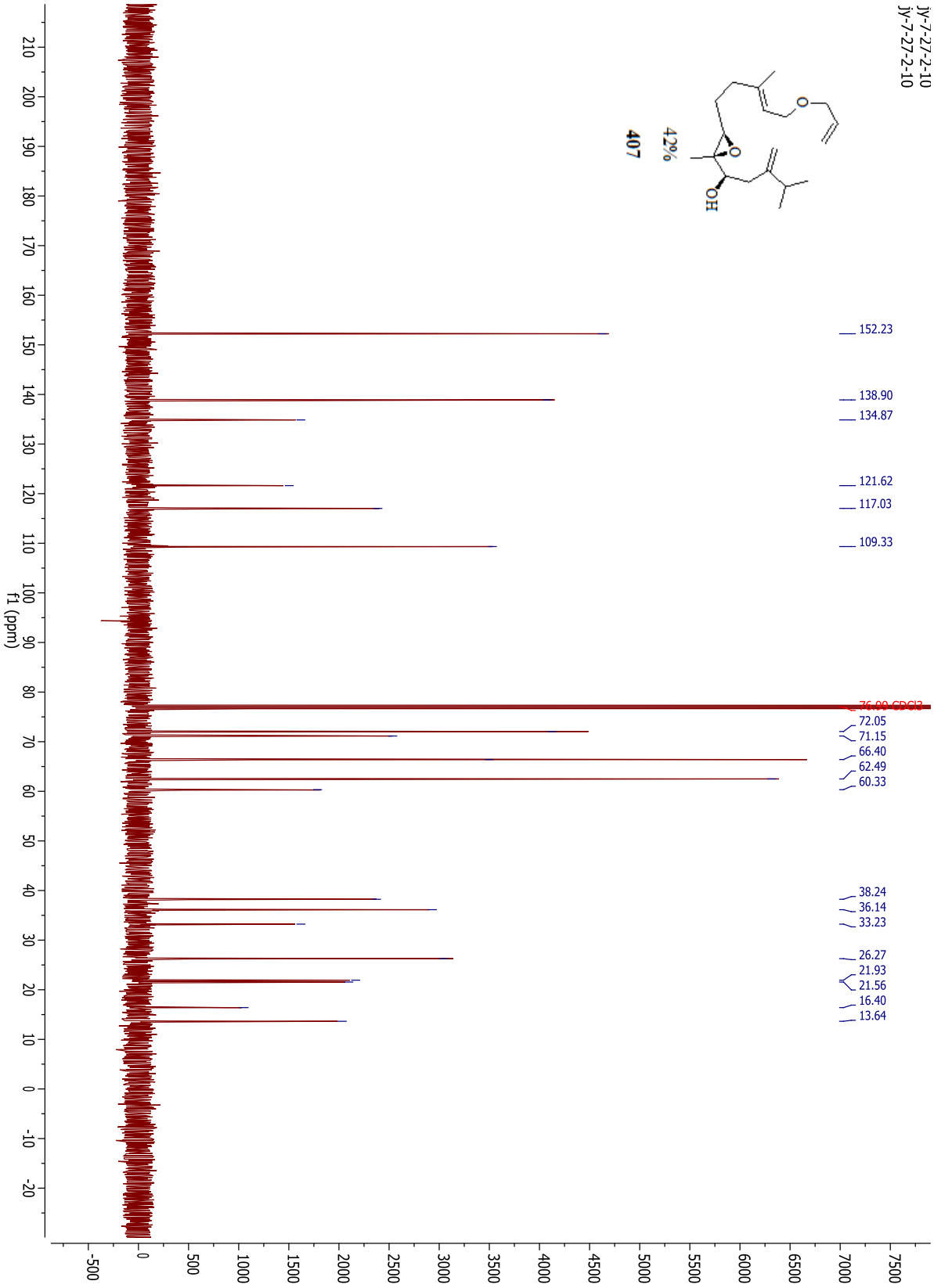

jy-6-14-1-12.6.ser
f2 (ppm)
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

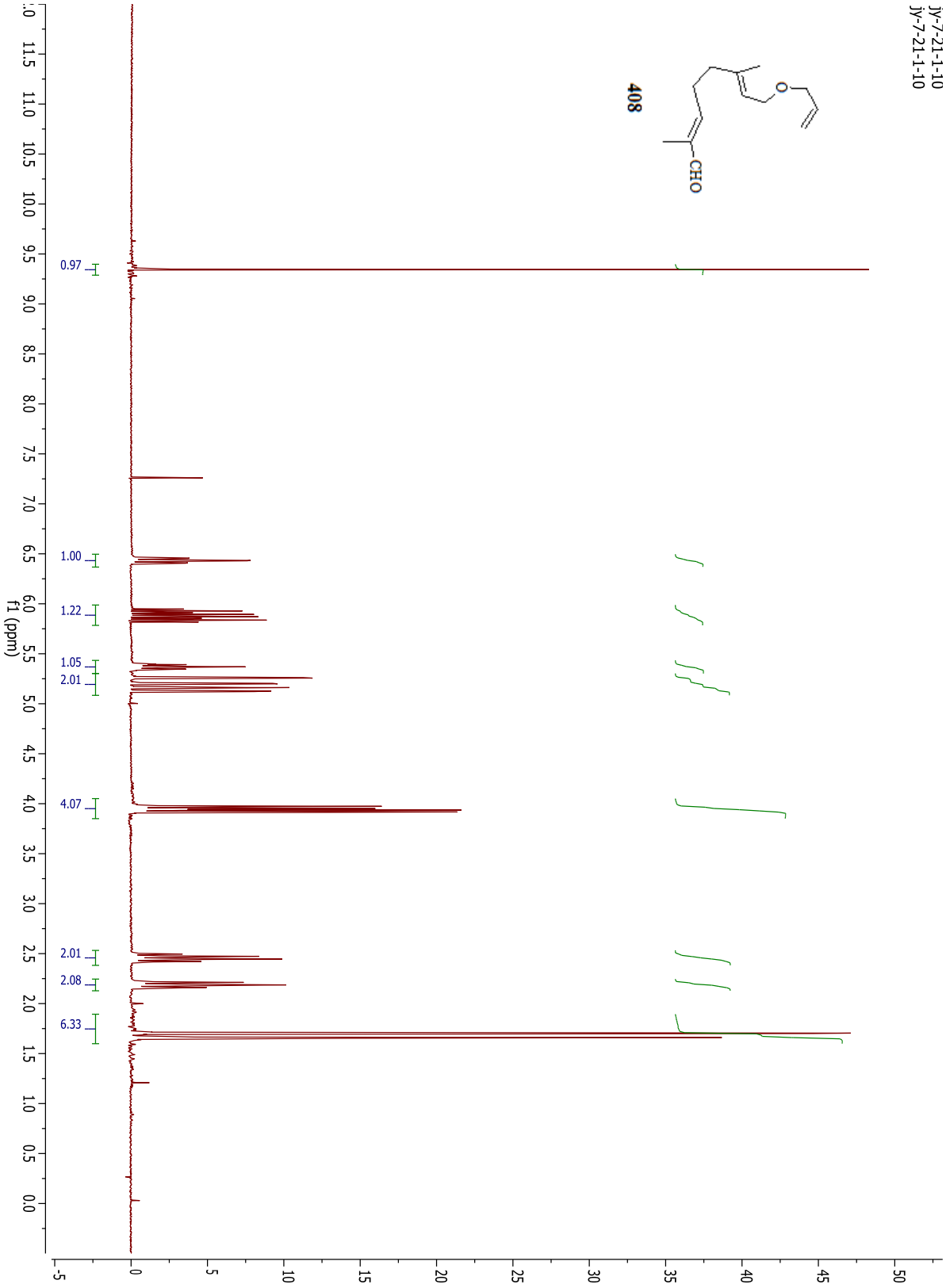

406
449
1.00
1.12
2.17
0.87
0.85
4.58
0.64
0.45
0.72
9.00
3.36
0.91
2.50
0.94
5.19
f1 (ppm)

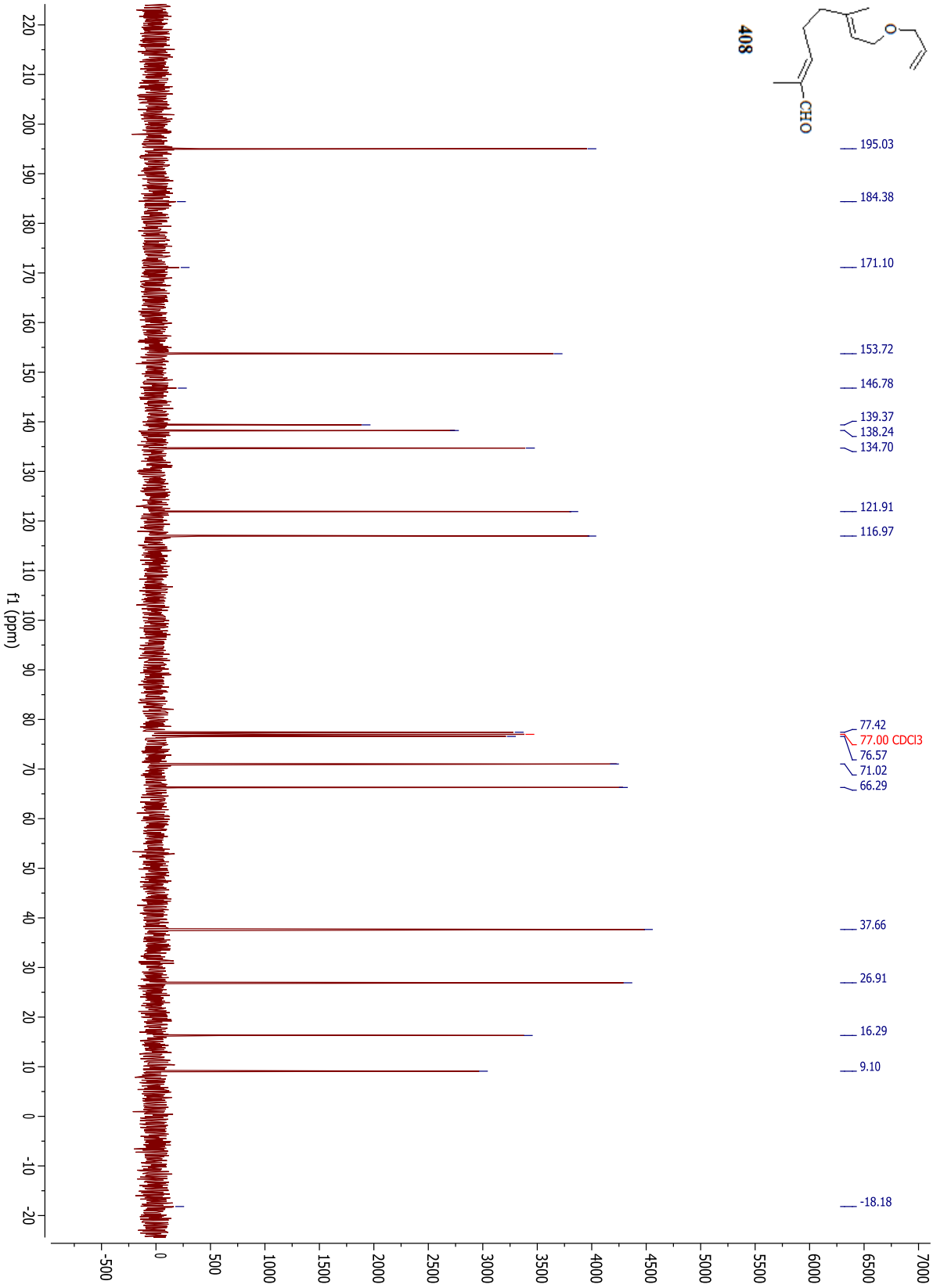

406
H
OH
OH
O
f1 (ppm)
0.75
1.18
1.06
1.03
1.08
1.10
5.01
1.08
1.00
1.04
3.74
3.59
2.30
3.34
1.28
3.26
0.54
0.82
6.91

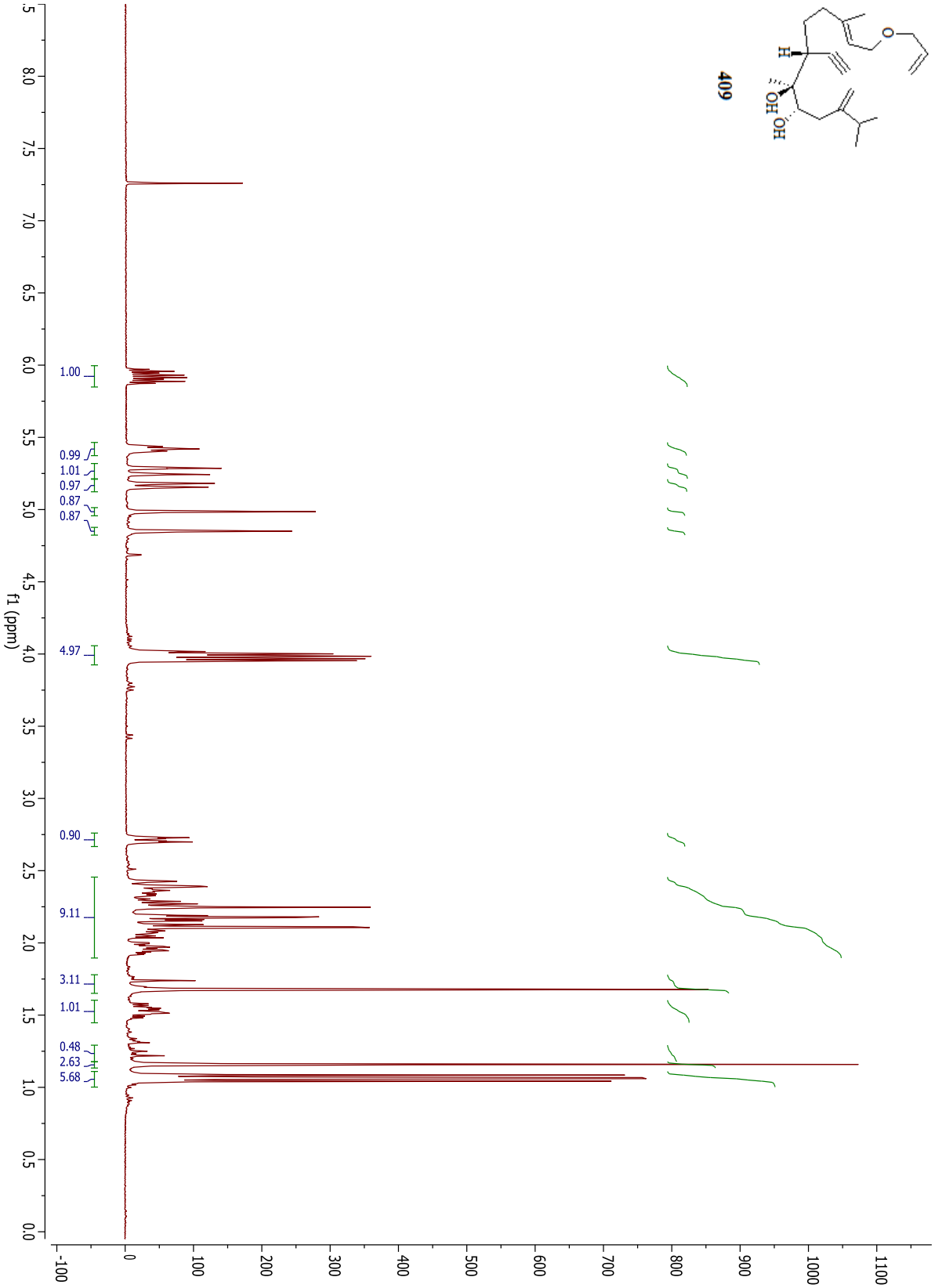

406
153.22
139.71
135.03
121.33
116.91
110.82
84.24
77.25 CDCl3
77.06 CDCl3
76.99 CDCl3
76.84
76.74
74.68
71.91
71.82
70.93
66.52
38.40
37.66
36.25
32.97
26.94
22.23
21.44
20.72
16.48
f1 (ppm)

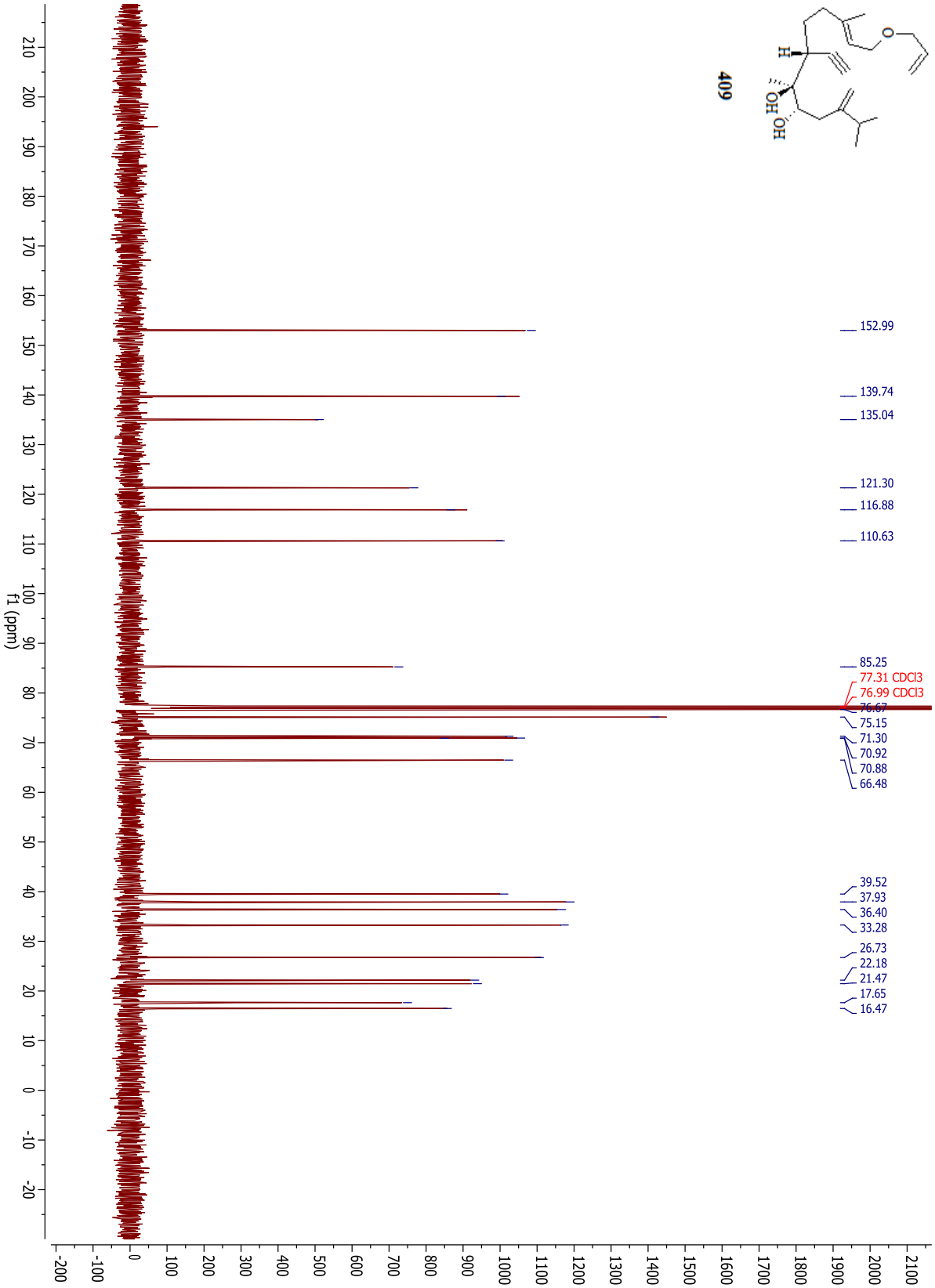

jy-7-27-1-10
jy-7-27-1-10
407
42%
O
OH
O
f1 (ppm)
1.00
1.04
2.00
2.03
4.17
0.99
0.98
6.21
5.30
2.98
6.10

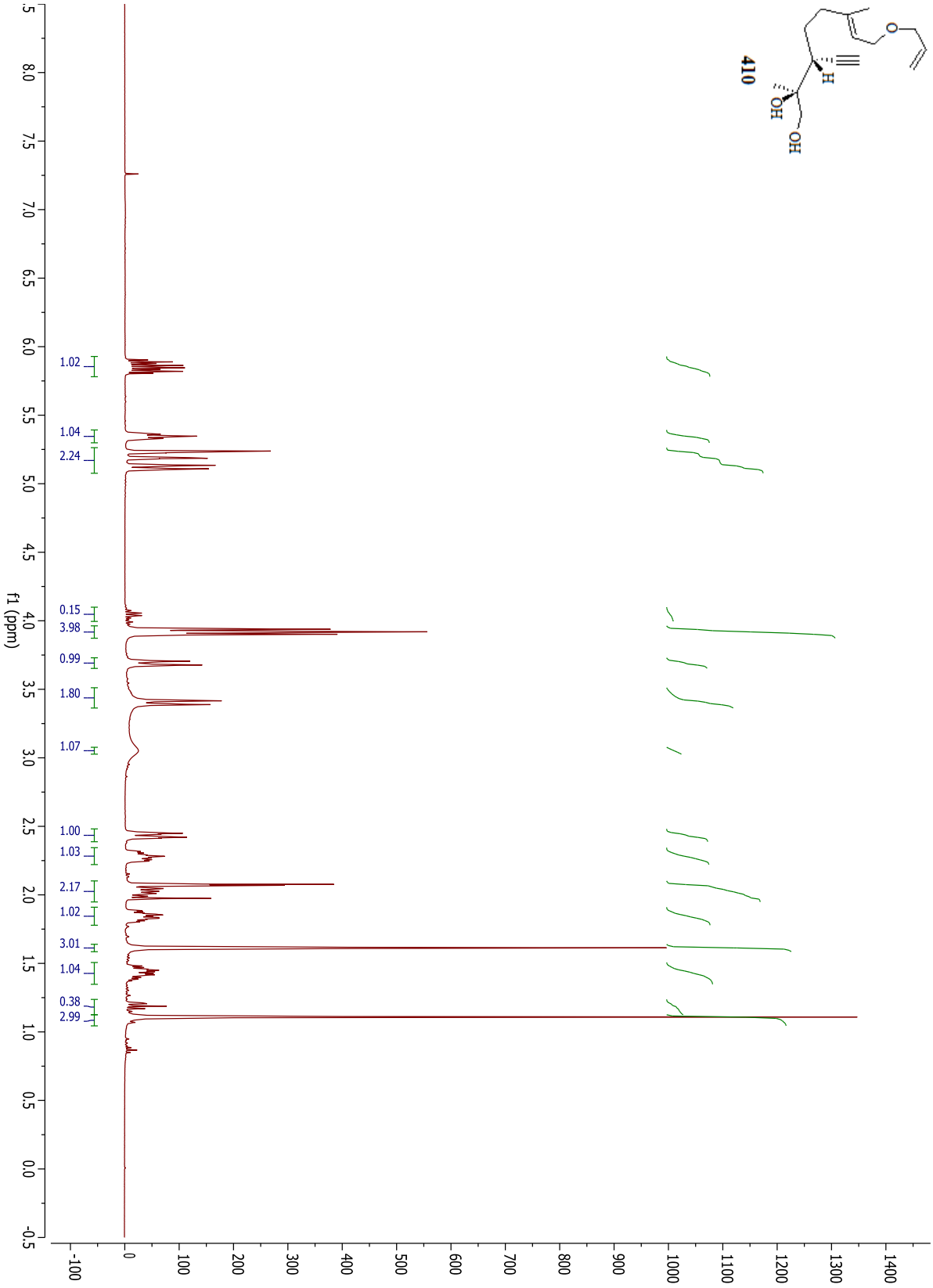

jy-7-27-2-10
jy-7-27-2-10
407
42%
OH
152.23
138.90
134.87
121.62
117.03
109.33
76.99 CDCl3
72.05
71.15
66.40
62.49
60.33
38.24
36.14
33.23
26.27
21.93
21.56
16.40
13.64
f1 (ppm)

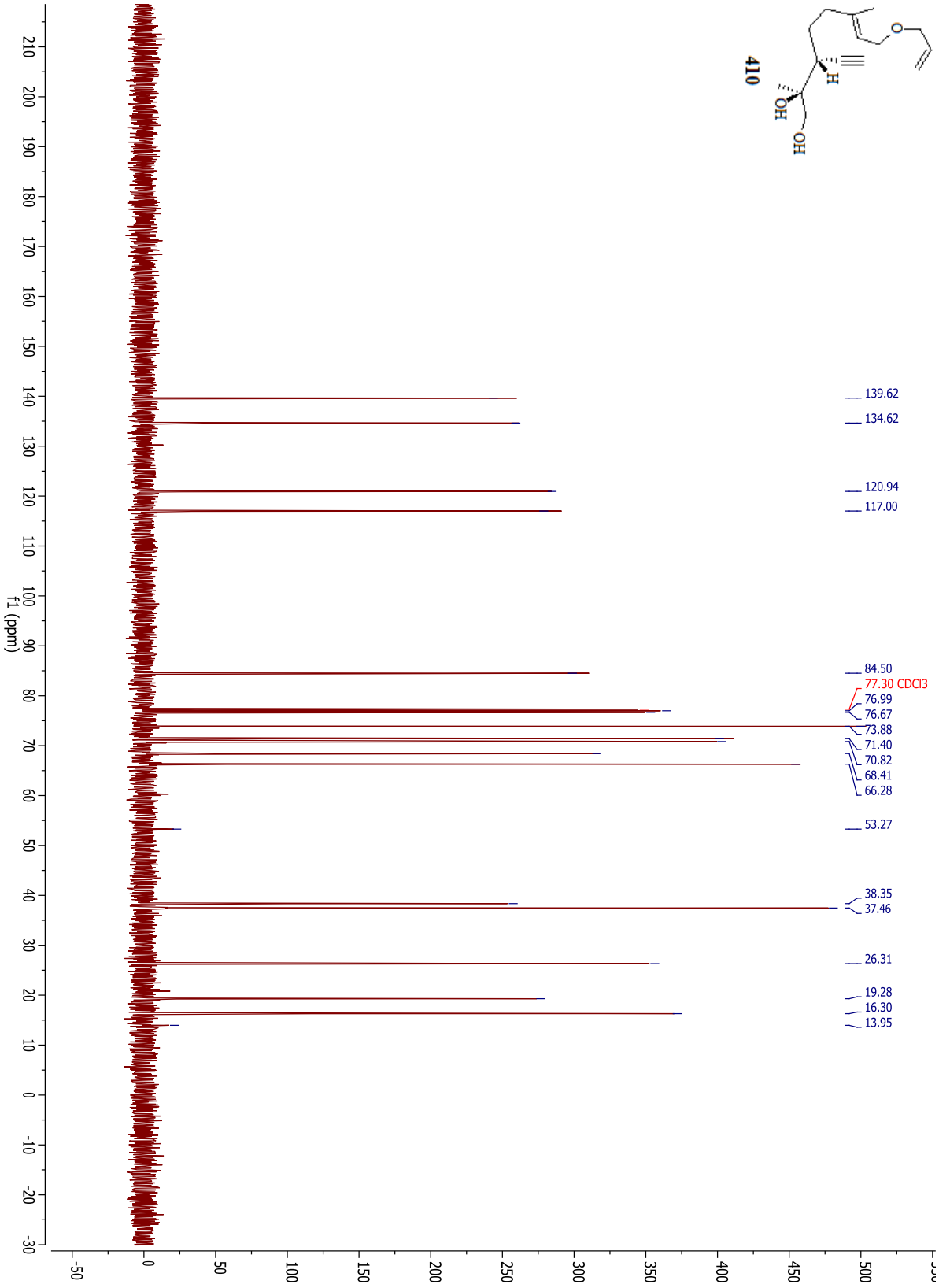

jy-7-21-1-10
jy-7-21-1-10
408
CHO
O
0.97
1.00
1.22
1.05
2.01
4.07
2.01
2.08
6.33
f1 (ppm)

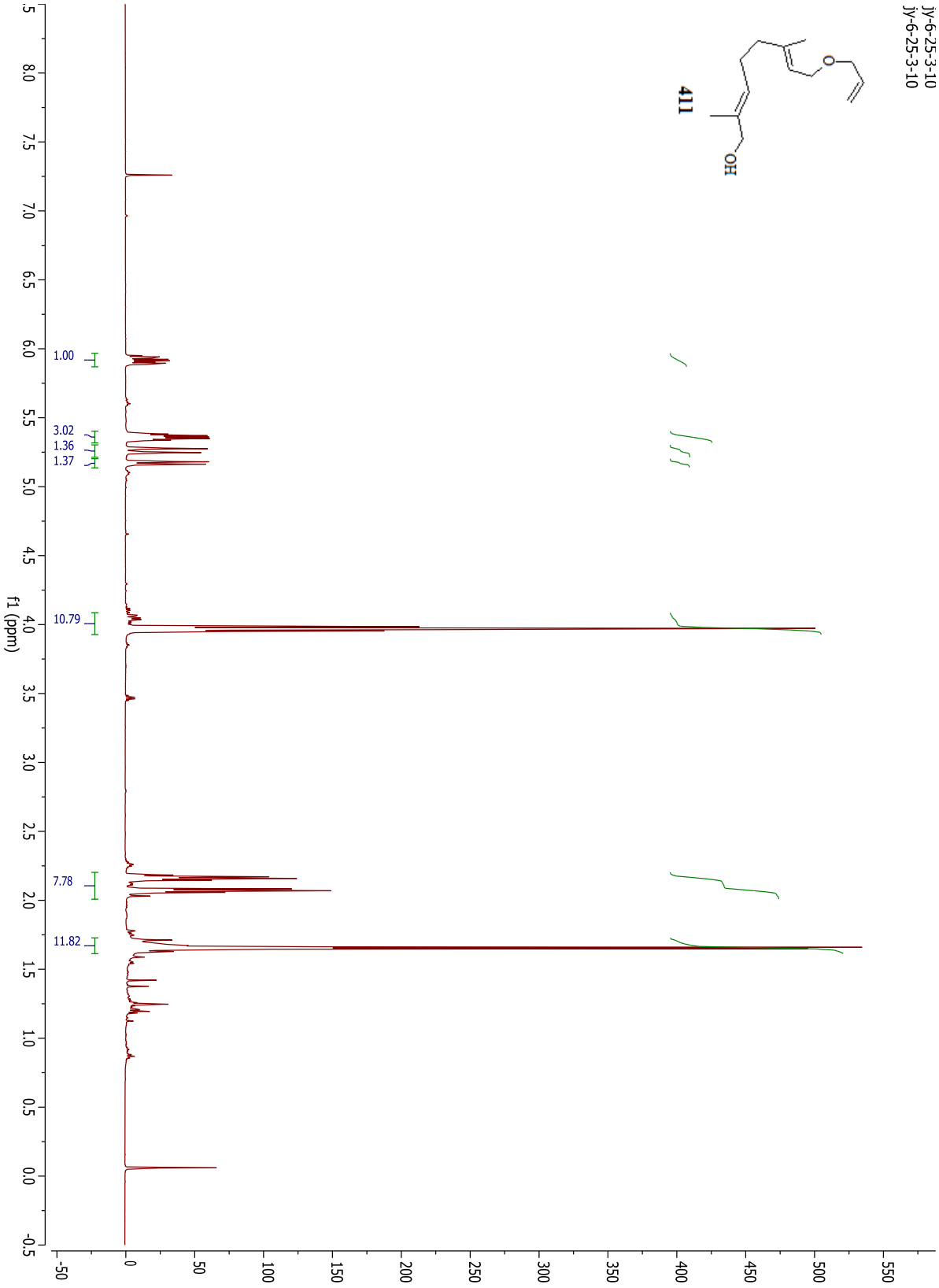

408
CHO
O
195.03
184.38
171.10
153.72
146.78
139.37
138.24
134.70
121.91
116.97
77.42
77.00 CDCl3
76.57
71.02
66.29
37.66
26.91
16.29
9.10
-18.18
f1 (ppm)

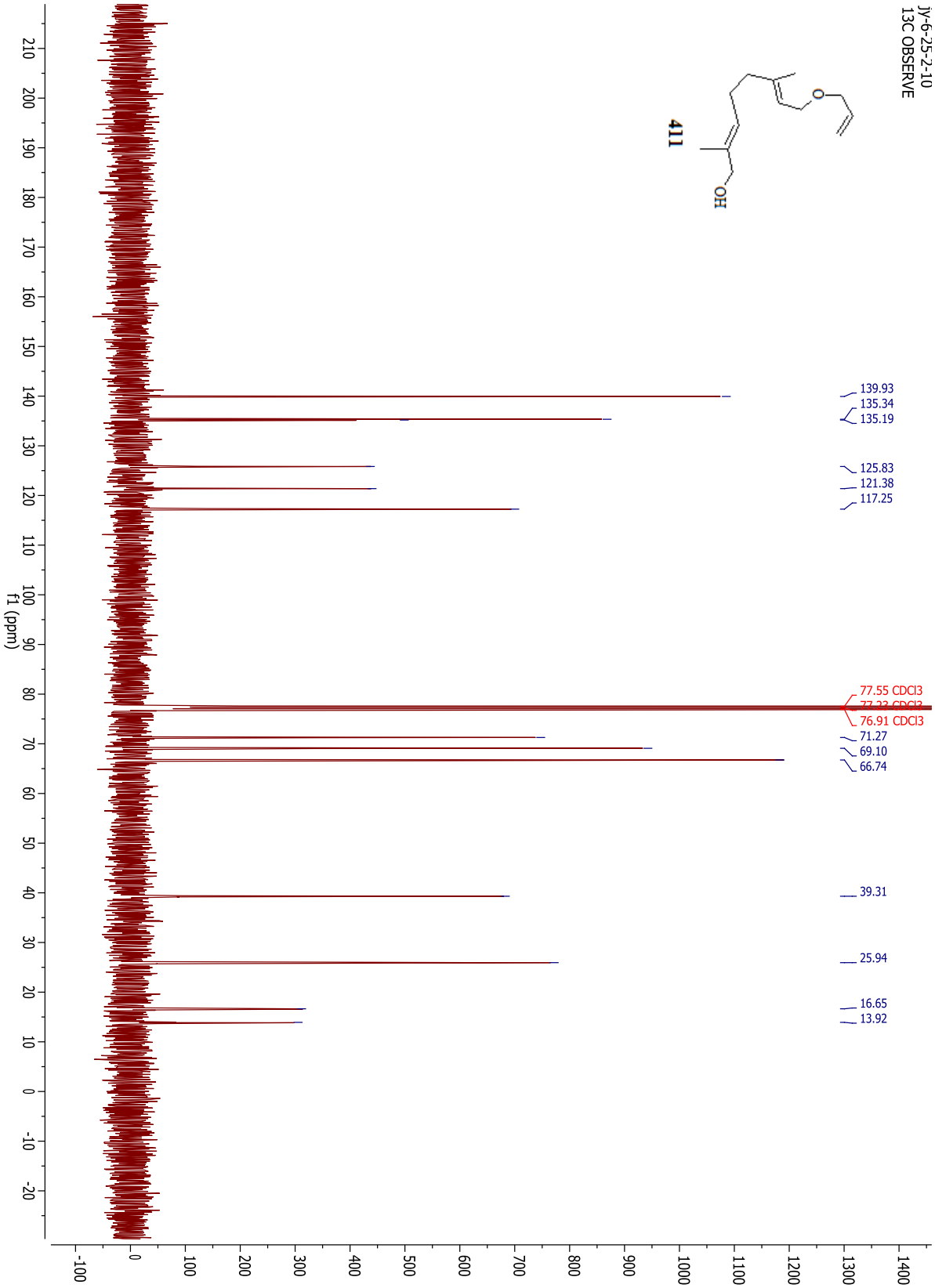

409
HO
HO
H
O
f1 (ppm)
1.00
0.99
1.01
0.97
0.87
0.87
4.97
0.90
9.11
3.11
1.01
0.48
2.63
5.68

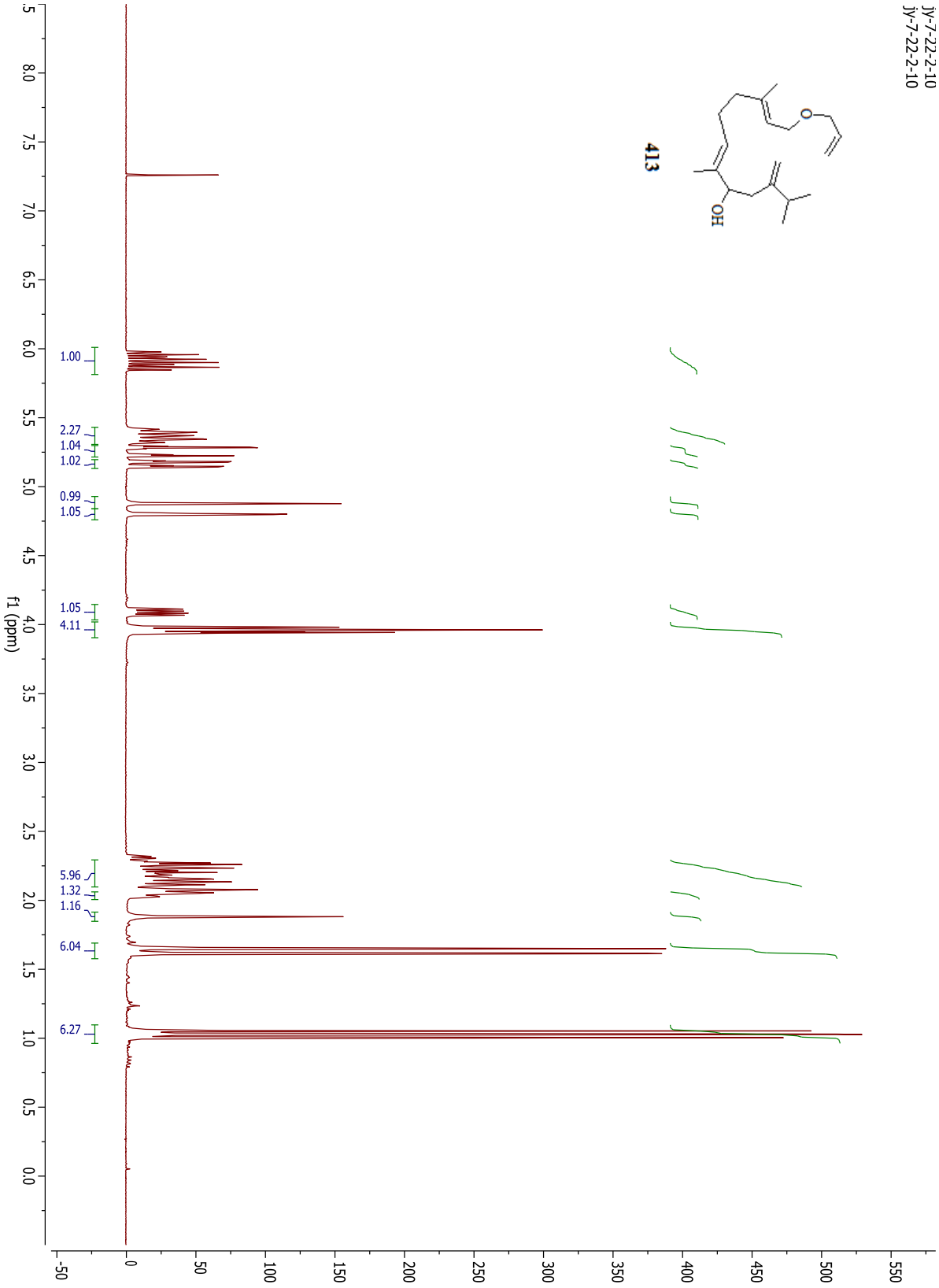

409
HO
HO
H
O
f1 (ppm)
152.99
139.74
135.04
121.30
116.88
110.63
85.25
77.31 CDCl3
76.99 CDCl3
76.67
75.15
71.30
70.92
70.88
66.48
39.52
37.93
36.40
33.28
26.73
22.18
21.47
17.65
16.47

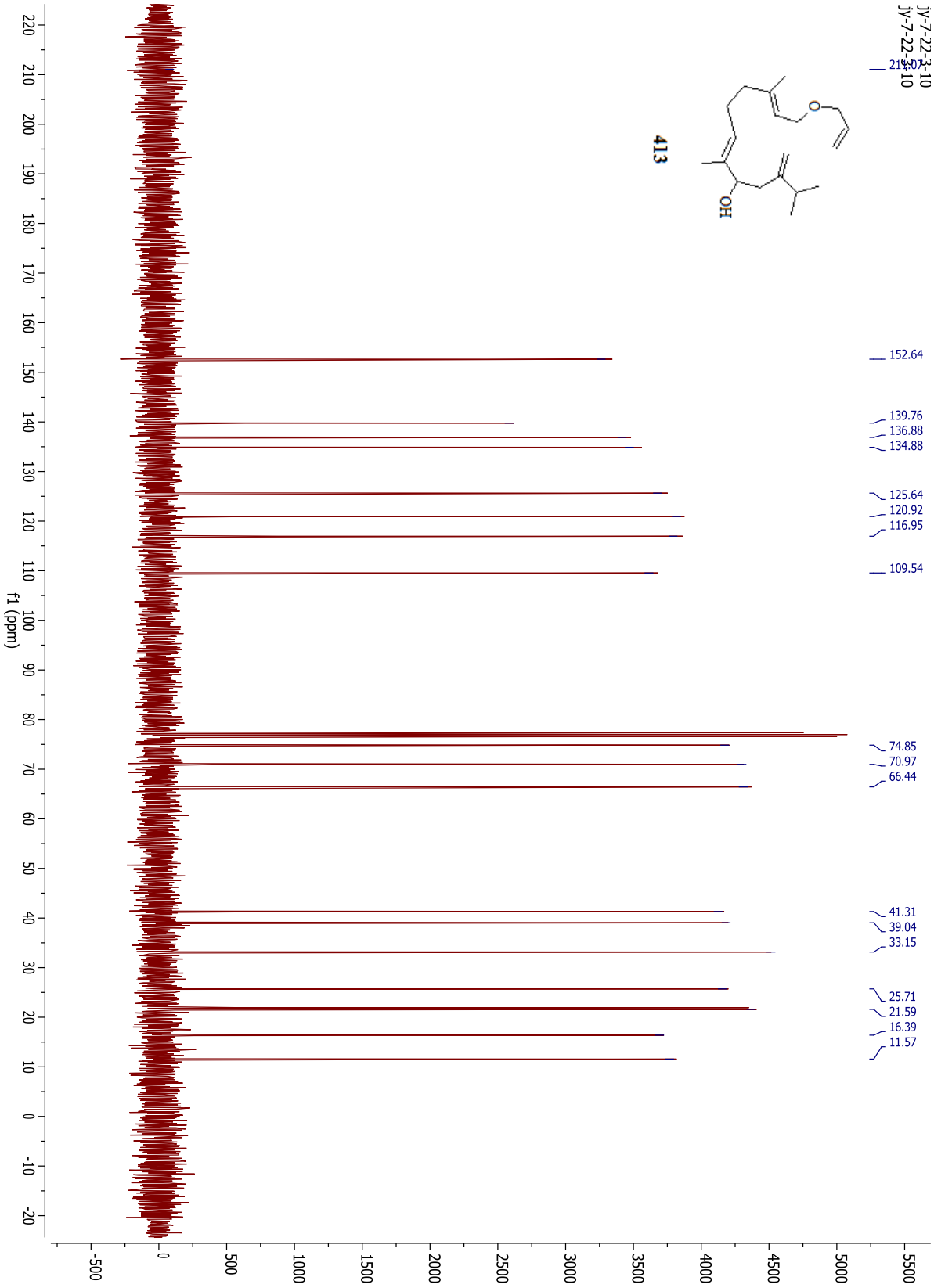

410
OH
OH
H
O
f1 (ppm)
1.02
1.04
2.24
0.15
3.98
0.99
1.80
1.07
1.00
1.03
2.17
1.02
3.01
1.04
0.38
2.99

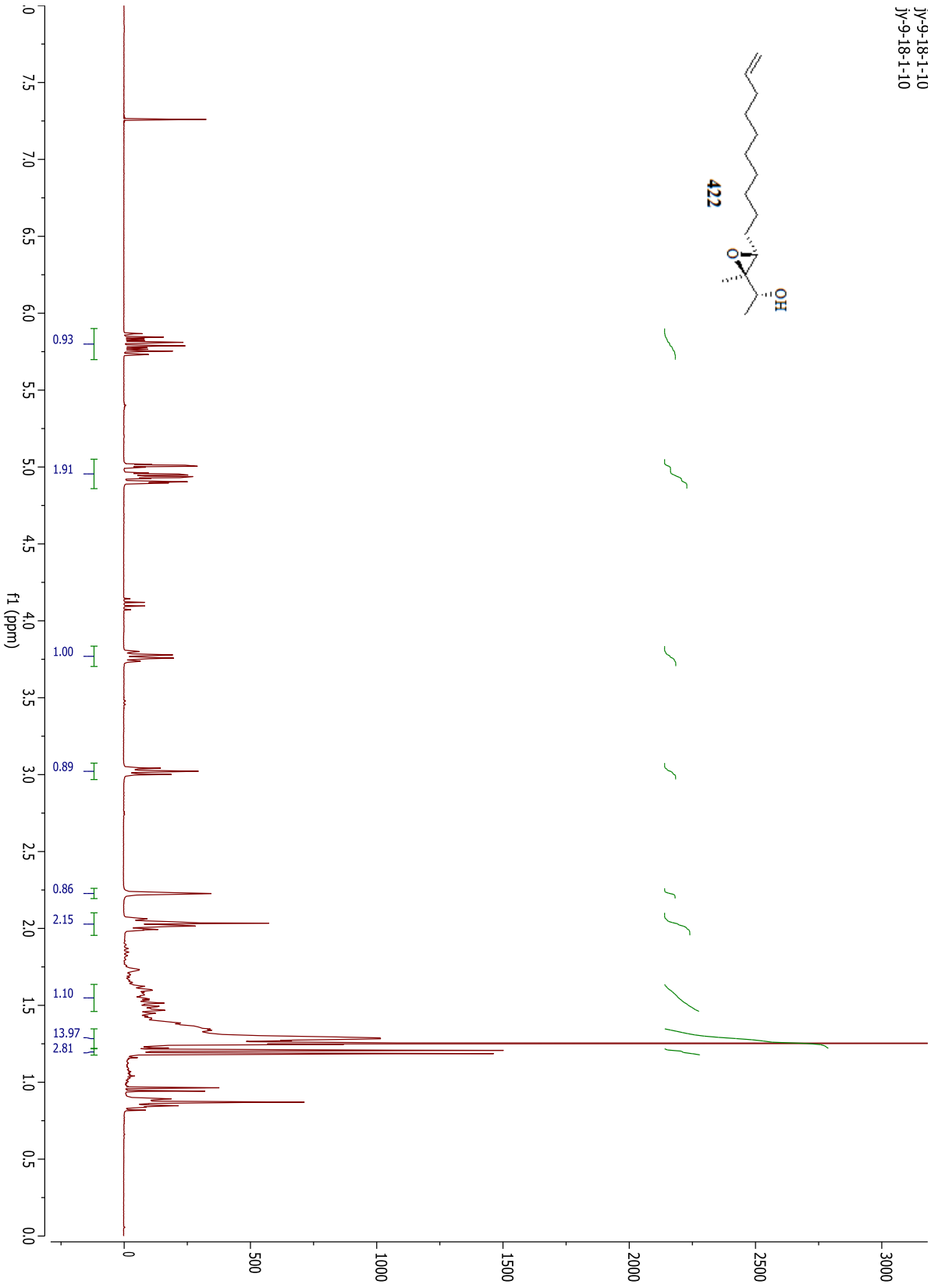

410
OH
OH
H
O
f1 (ppm)
139.62
134.62
120.94
117.00
84.50
77.30 CDCl3
76.99
76.67
73.88
71.40
70.82
68.41
66.28
53.27
38.35
37.46
26.31
19.28
16.30
13.95

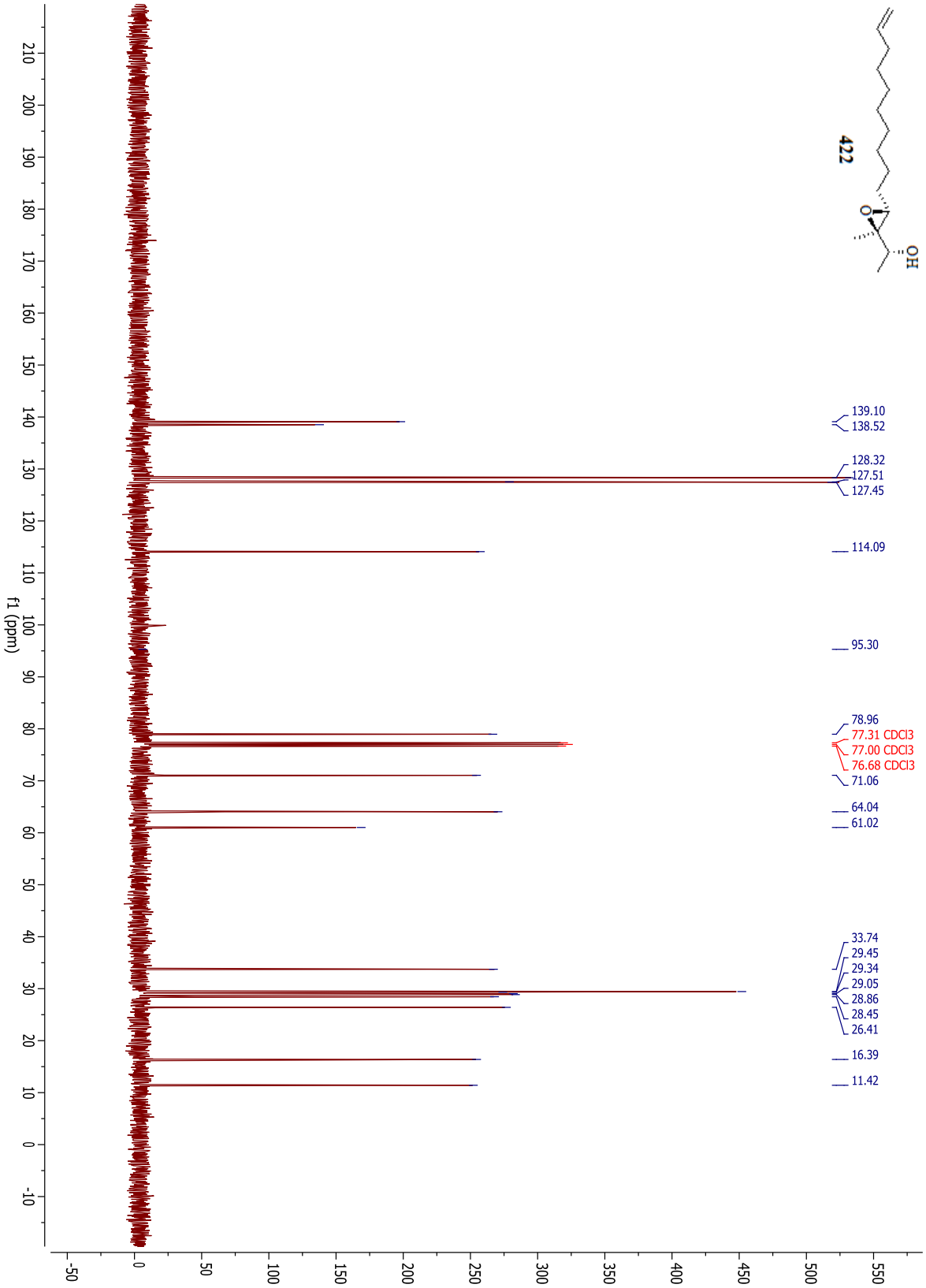

jy-6-25-3-10
jy-6-25-3-10
411
OH
O
1.00
3.02
1.36
1.37
10.79
7.78
11.82
f1 (ppm)

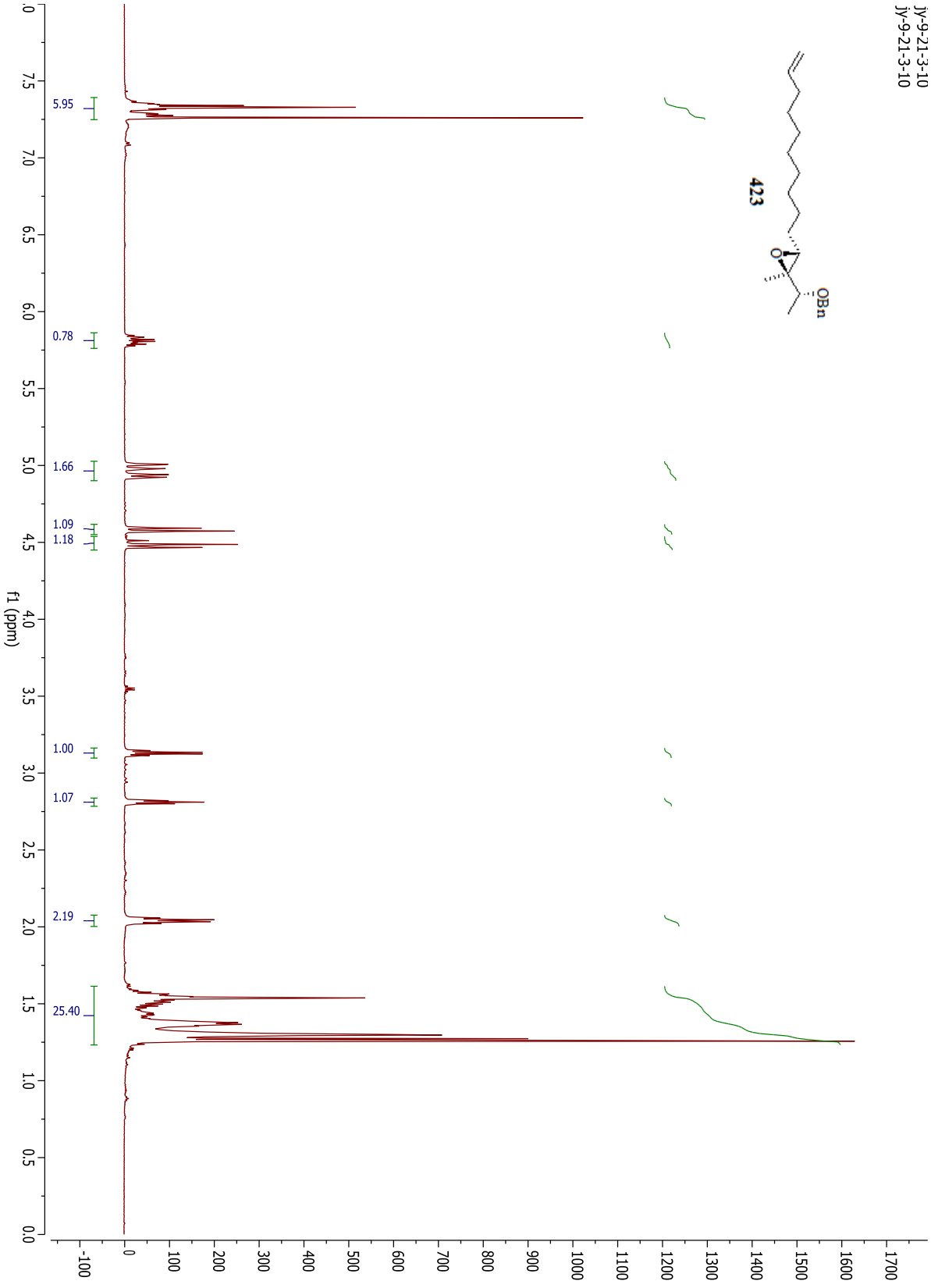

Jy-6-25-2-10
13C OBSERVE
411
OH
O
139.93
135.34
135.19
125.83
121.38
117.25
77.55 CDCl3
76.91 CDCl3
71.27
69.10
66.74
39.31
25.94
16.65
13.92
f1 (ppm)

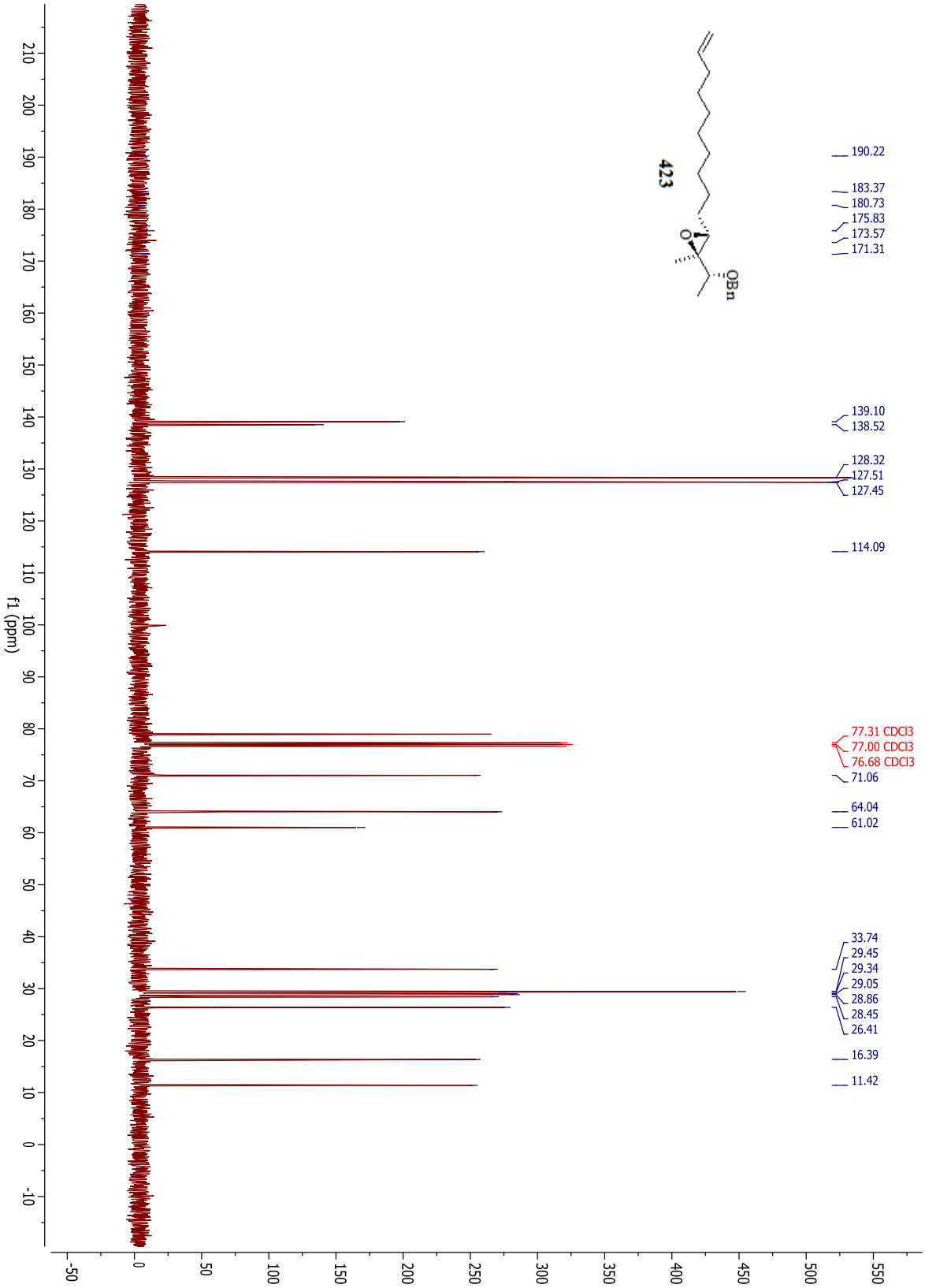

jy-7-22-2-10
jy-7-22-2-10
413
OH
O
1.00
2.27
1.04
1.02
0.99
1.05
1.05
4.11
5.96
1.32
1.16
6.04
6.27
f1 (ppm)

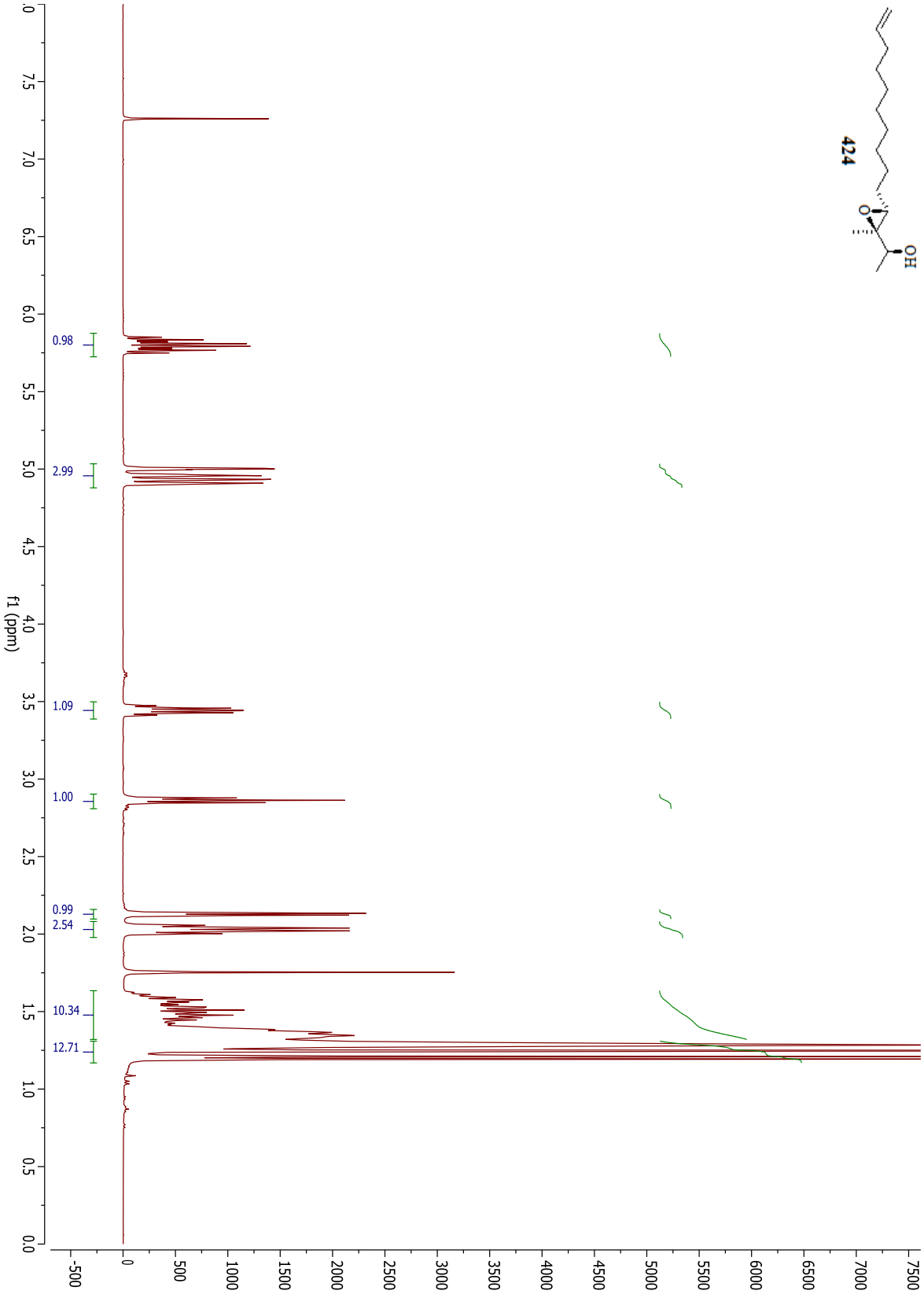

413
OH
O
jy-7-22-3-10
jy-7-22-3-10
219.07
152.64
139.76
136.88
134.88
125.64
120.92
116.95
109.54
74.85
70.97
66.44
41.31
39.04
33.15
25.71
21.59
16.39
11.57
f1 (ppm)

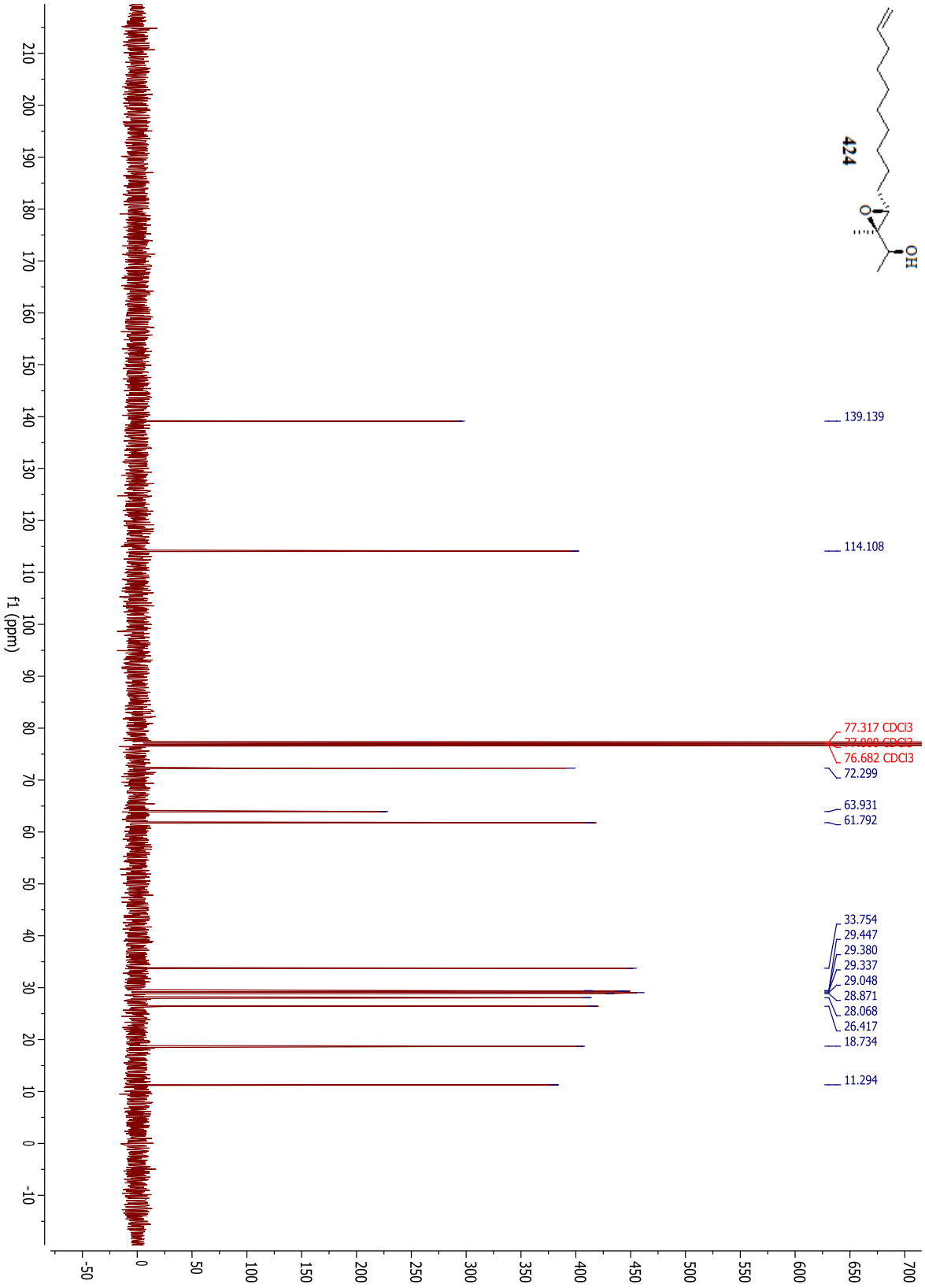

jy-9-18-1-10
jy-9-18-1-10
422
OH
O
f1 (ppm)
0.93
1.91
1.00
0.89
0.86
2.15
1.10
13.97
2.81

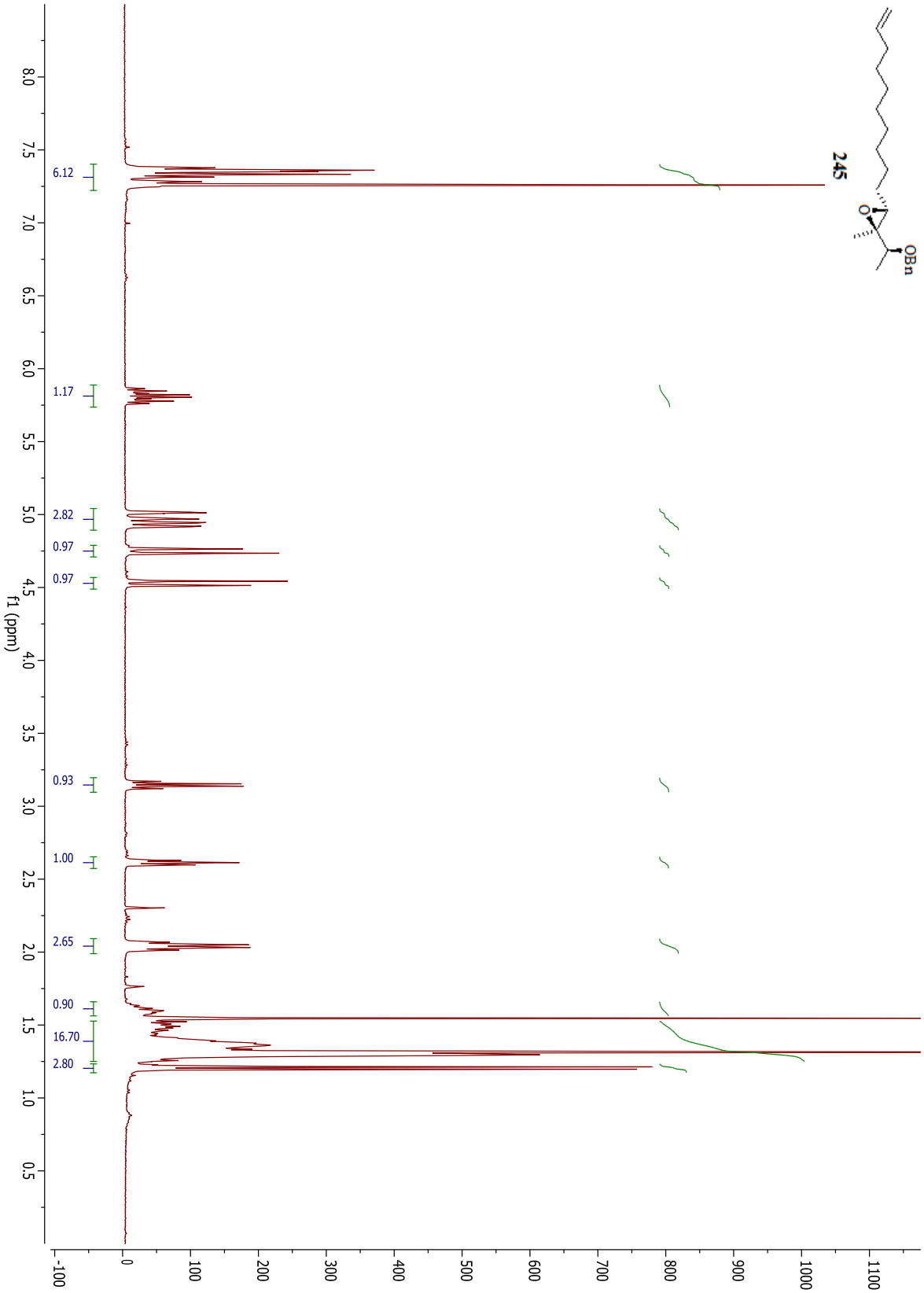

422
O
OH
139.10
138.52
128.32
127.51
127.45
114.09
95.30
78.96
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
71.06
64.04
61.02
33.74
29.45
29.34
29.05
28.86
28.45
26.41
16.39
11.42
f1 (ppm)

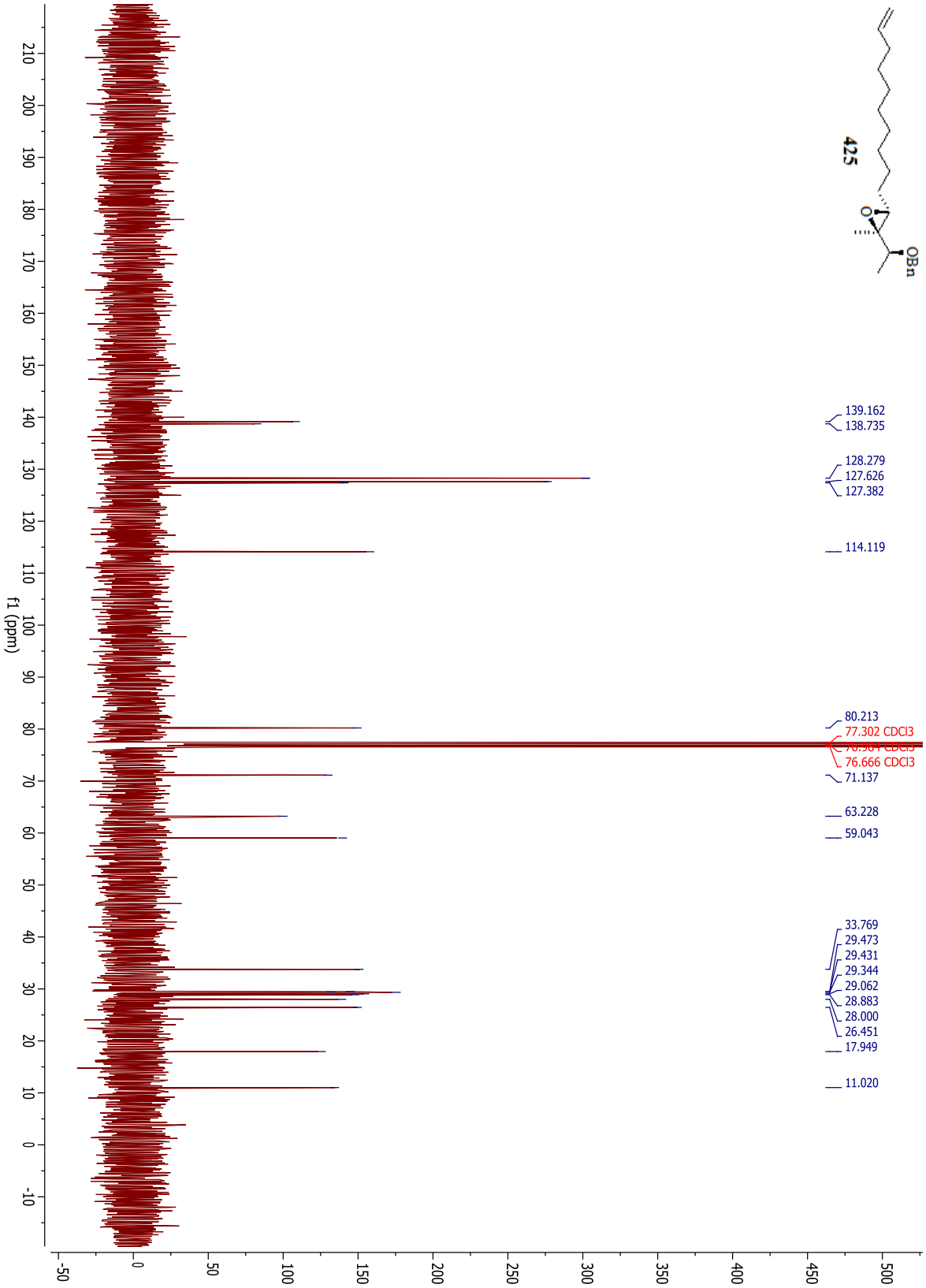

jy-9-21-3-10
jy-9-21-3-10
423
OBn
5.95
0.78
1.66
1.09
1.18
1.00
1.07
2.19
25.40
f1 (ppm)

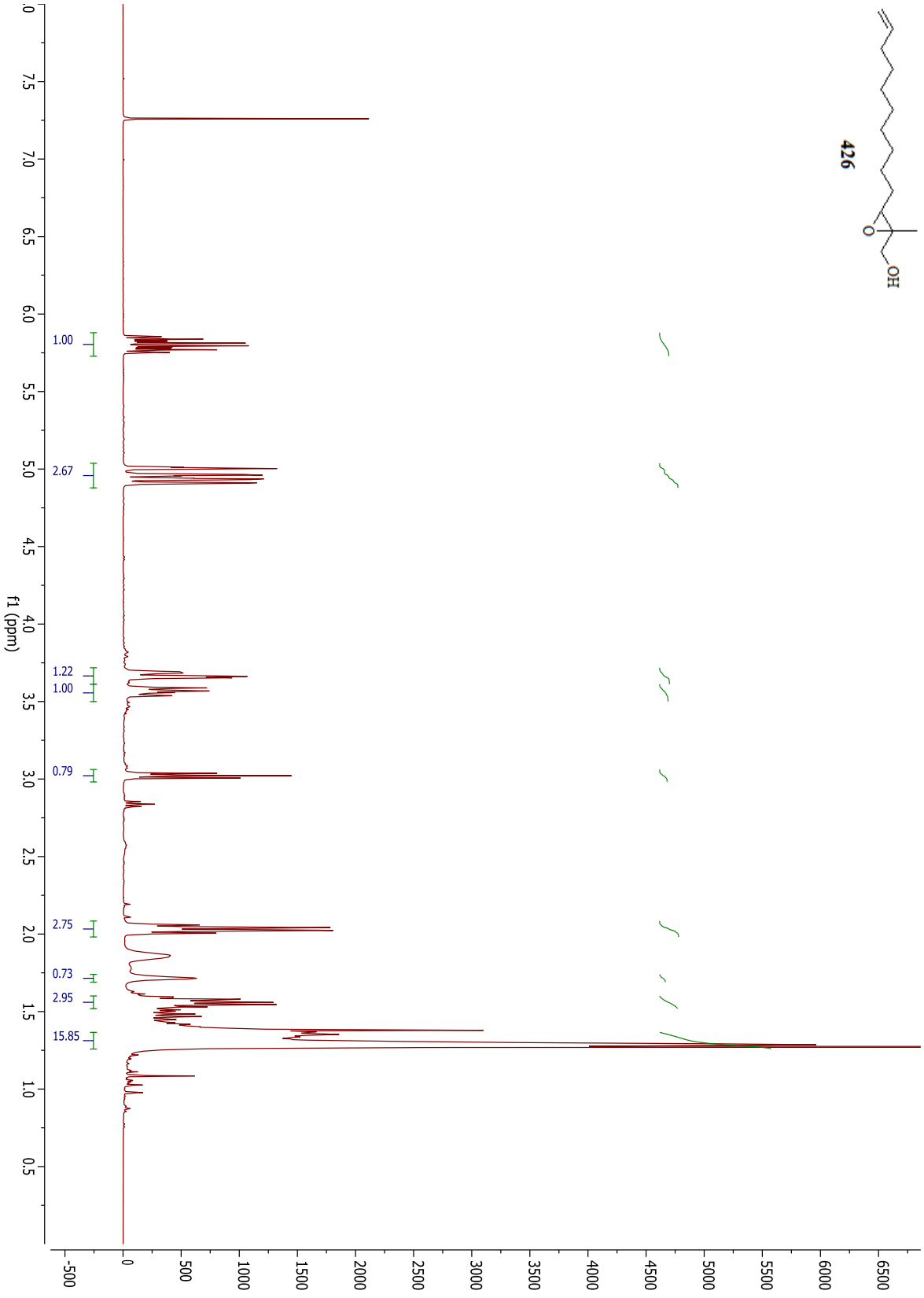

423
OBn
O
190.22
183.37
180.73
175.83
173.57
171.31
139.10
138.52
128.32
127.51
127.45
114.09
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
71.06
64.04
61.02
33.74
29.45
29.34
29.05
28.86
28.45
26.41
16.39
11.42
f1 (ppm)

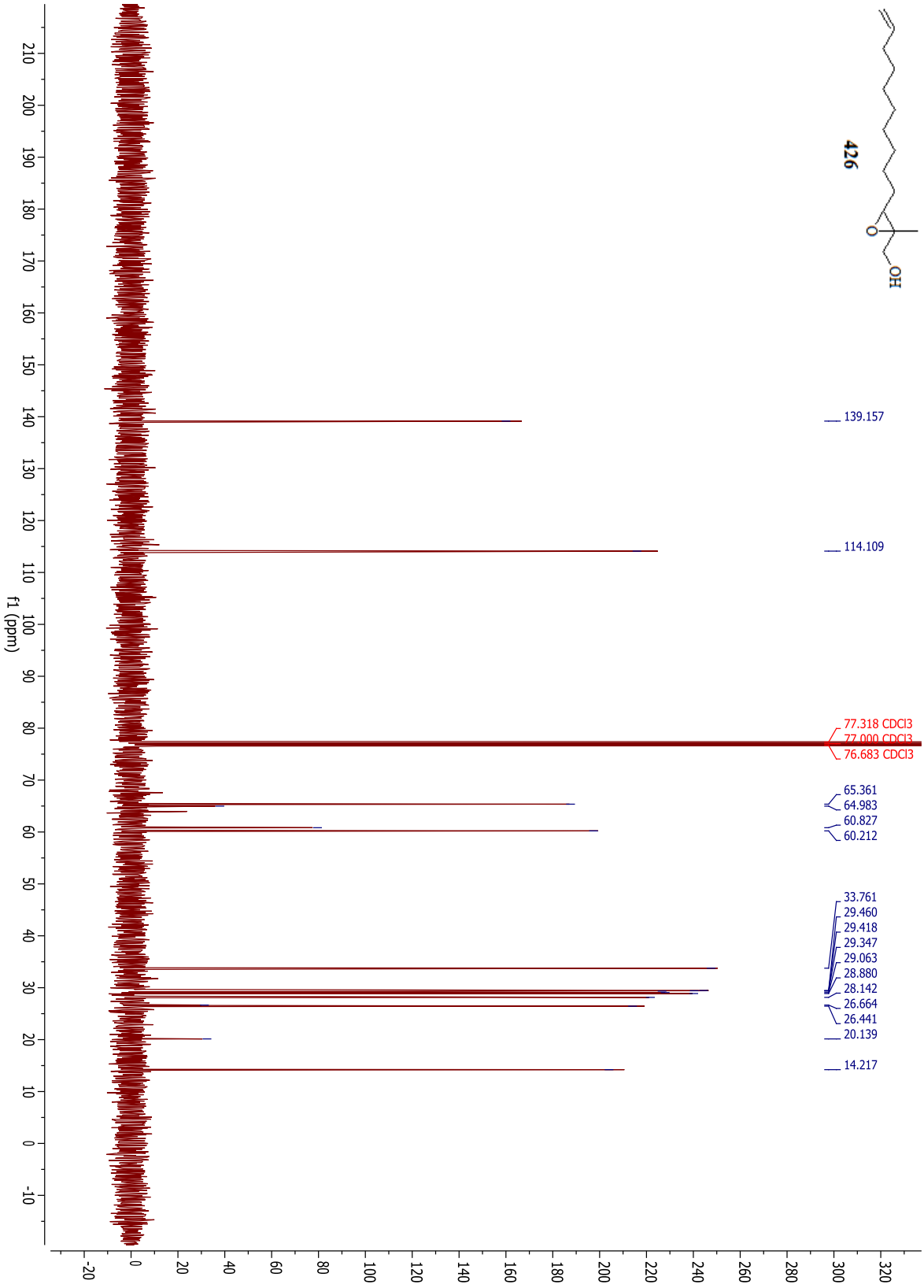

424
OH
O
0.98
2.99
1.09
1.00
0.99
2.54
10.34
12.71
f1 (ppm)

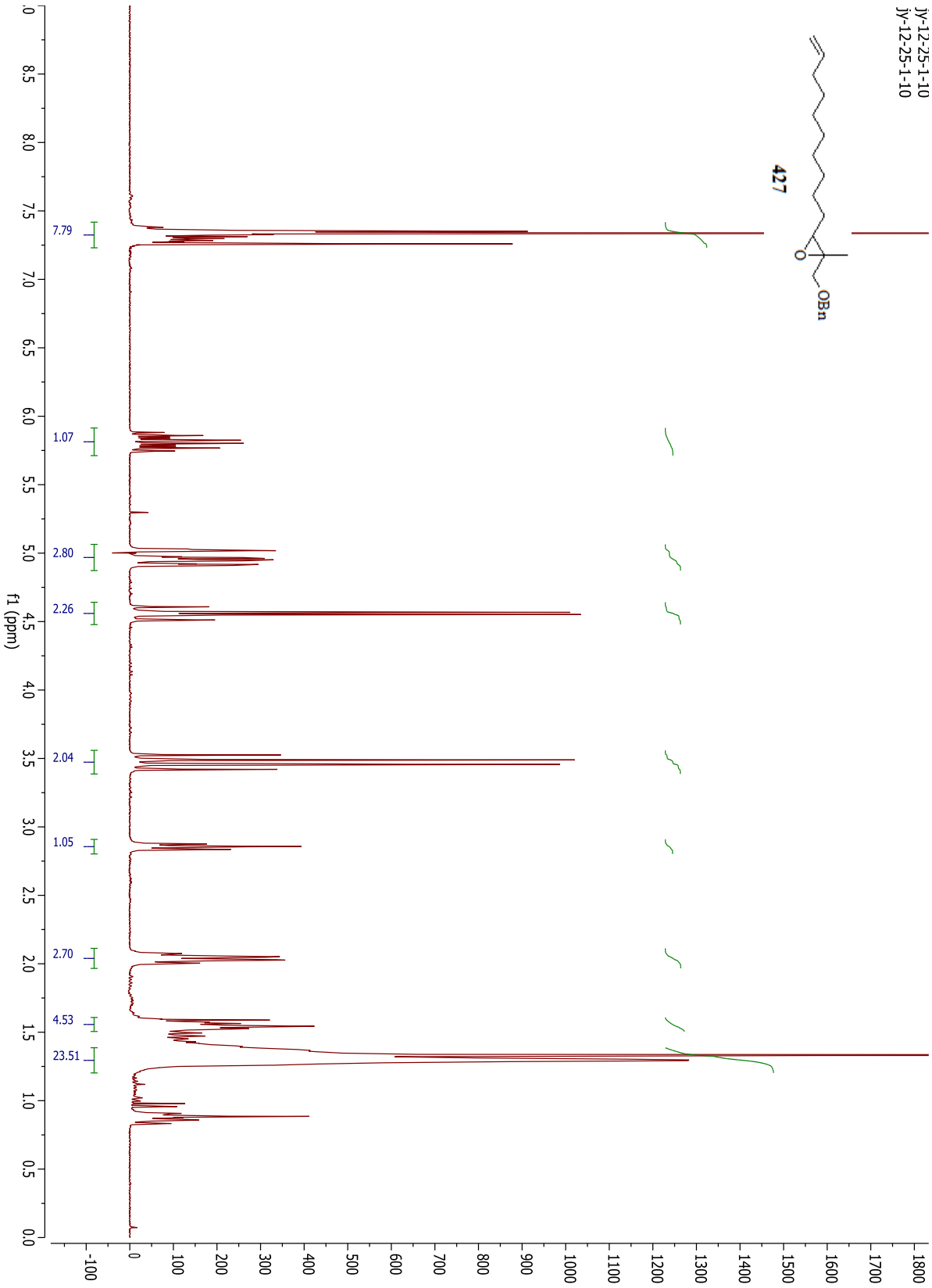

424
O
OH
f1 (ppm)
139.139
114.108
77.317 CDCl3
77.000 CDCl3
76.682 CDCl3
72.299
63.931
61.792
33.754
29.447
29.380
29.337
29.048
28.871
28.068
26.417
18.734
11.294

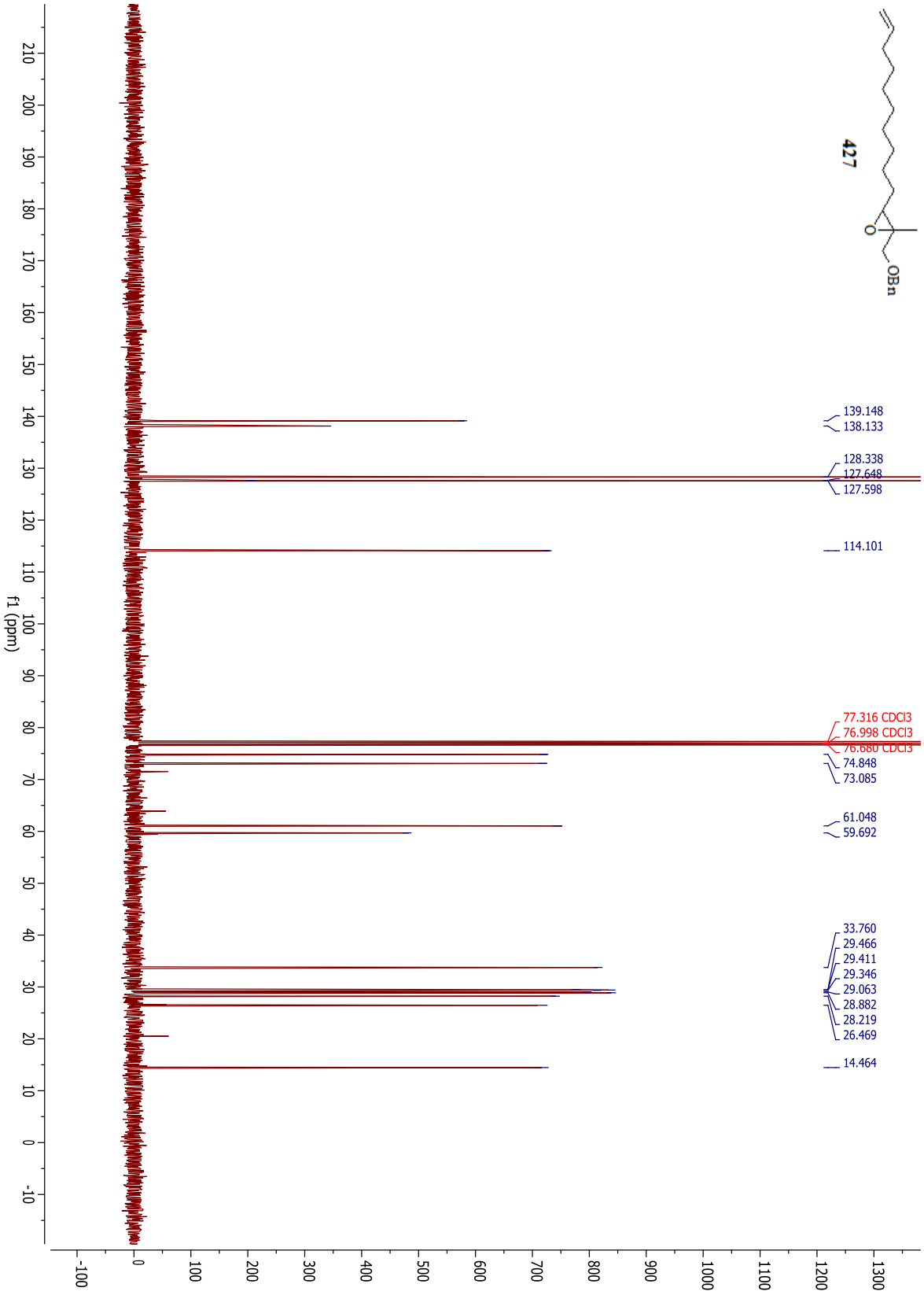

245
OBn
6.12
1.17
2.82
0.97
0.97
0.93
1.00
2.65
0.90
16.70
2.80
f1 (ppm)

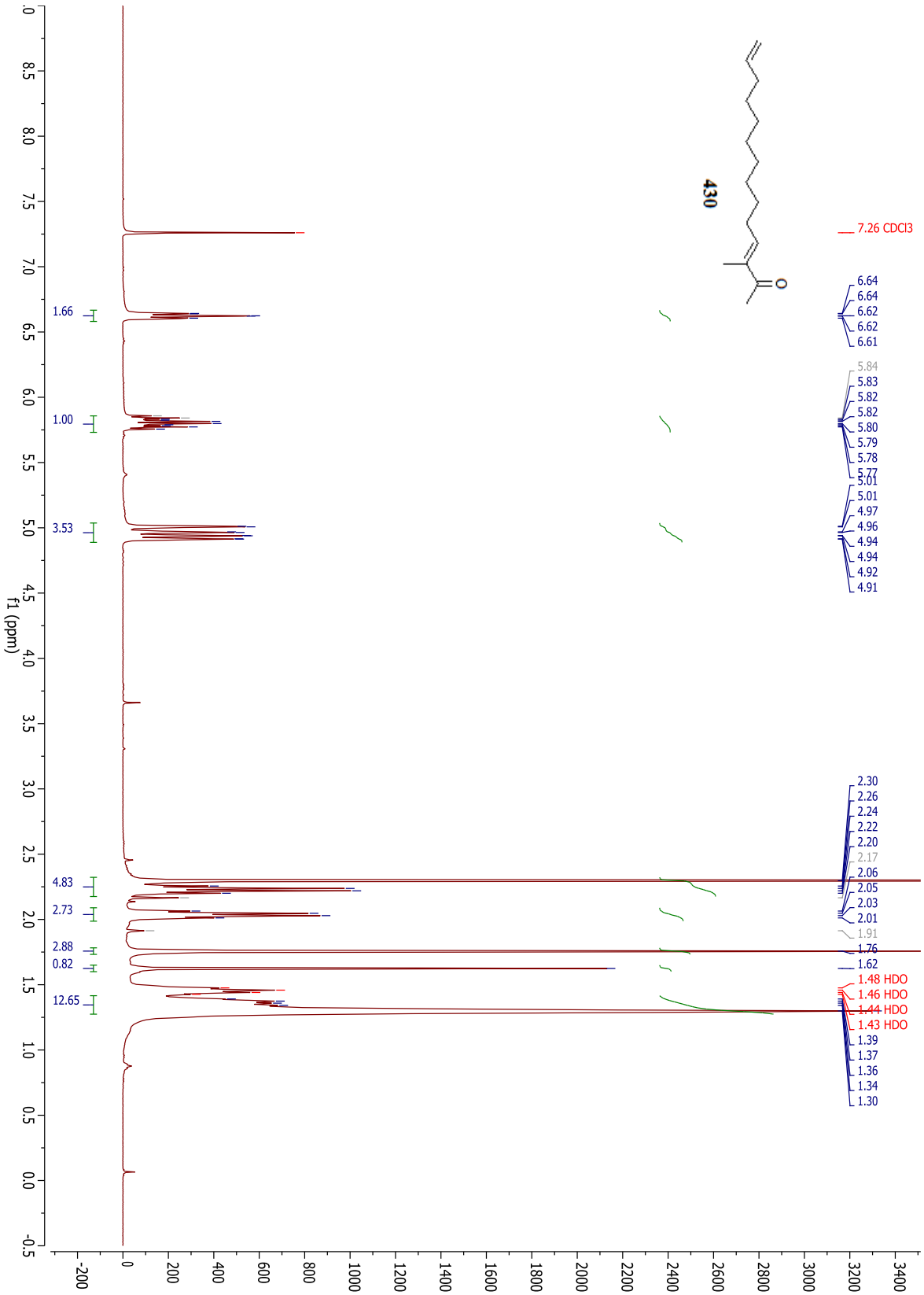

425
OBn
O
f1 (ppm)
139.162
138.735
128.279
127.626
127.382
114.119
80.213
77.302 CDCl3
76.666 CDCl3
71.137
63.228
59.043
33.769
29.473
29.431
29.344
29.062
28.883
28.000
26.451
17.949
11.020

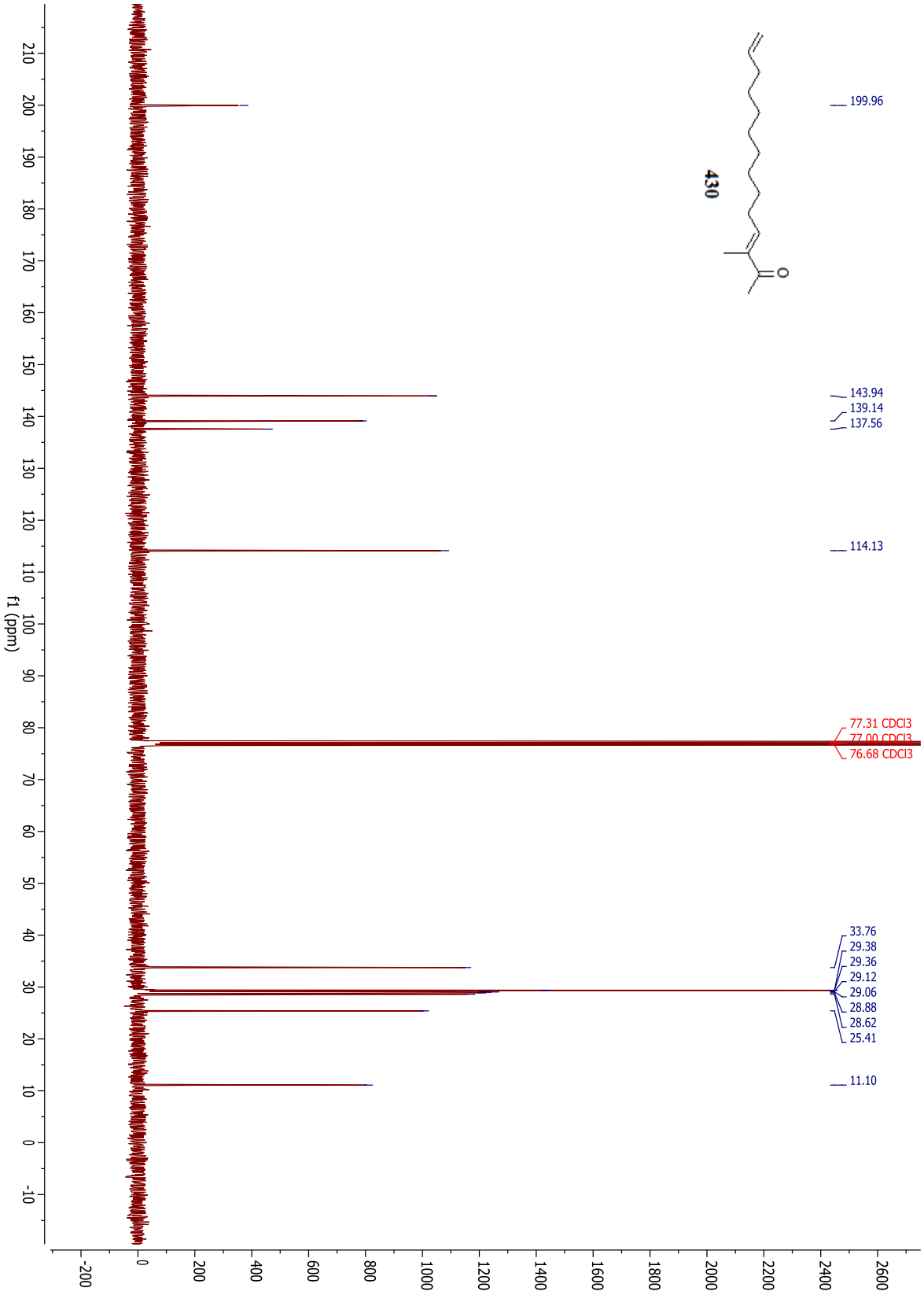

426
O
OH
1.00
2.67
1.22
1.00
0.79
2.75
0.73
2.95
15.85
f1 (ppm)

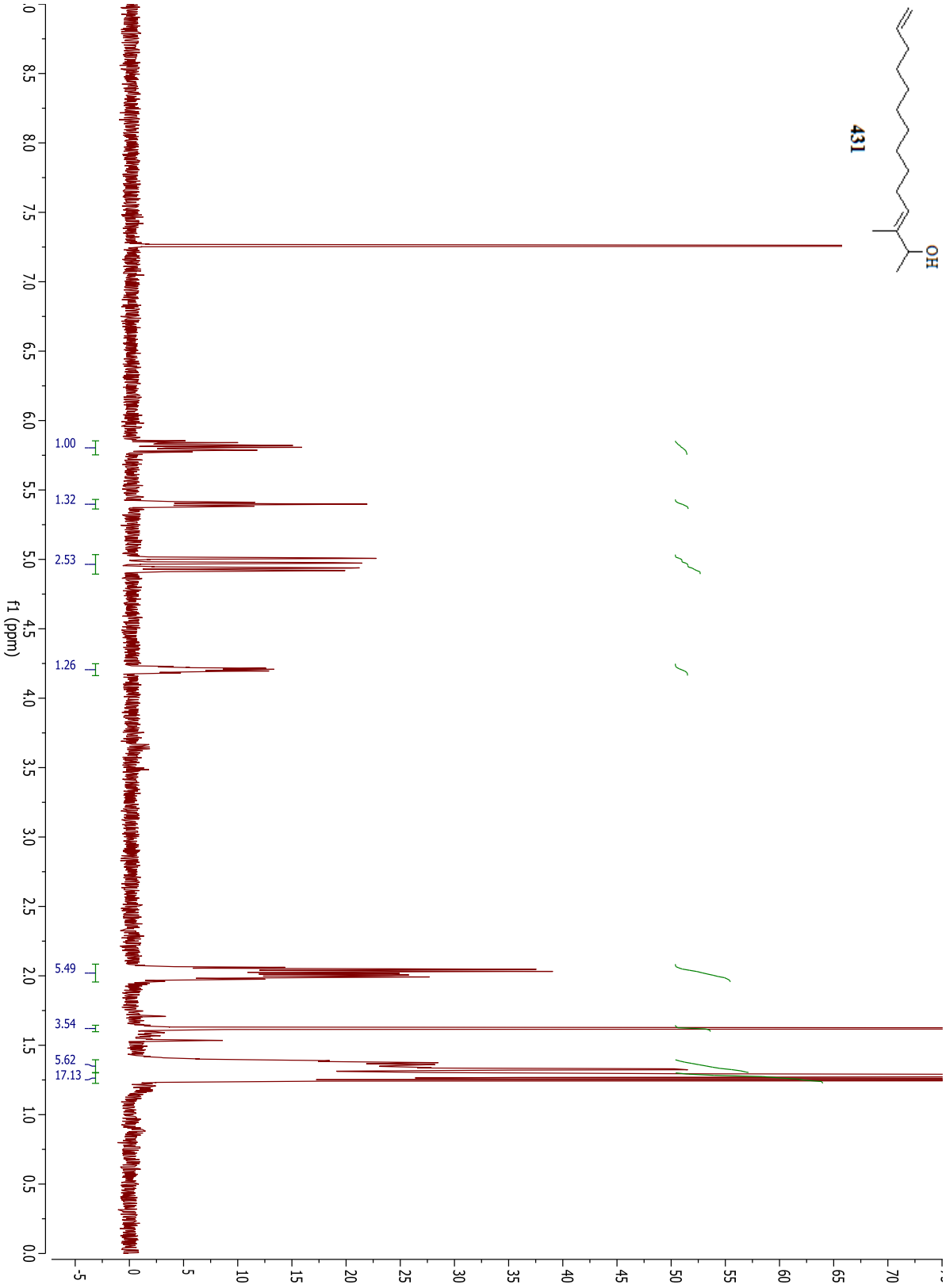

426
O
OH
f1 (ppm)
139.157
114.109
77.318 CDCl3
77.000 CDCl3
76.683 CDCl3
65.361
64.983
60.827
60.212
33.761
29.460
29.418
29.347
29.063
28.880
28.142
26.664
26.441
20.139
14.217

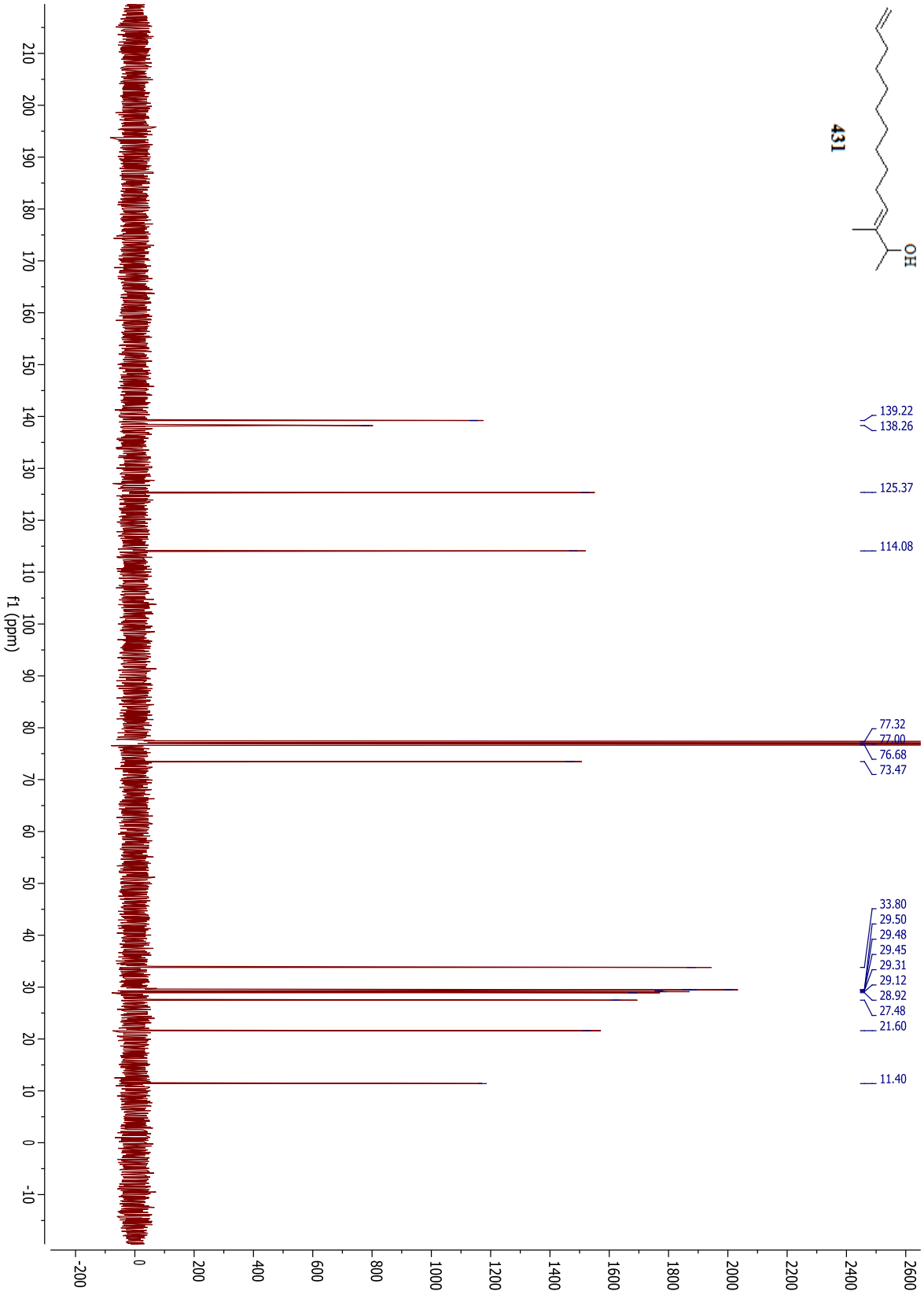

jy-12-25-1-10
jy-12-25-1-10
427
OBn
7.79
1.07
2.80
2.26
2.04
1.05
2.70
4.53
23.51
f1 (ppm)

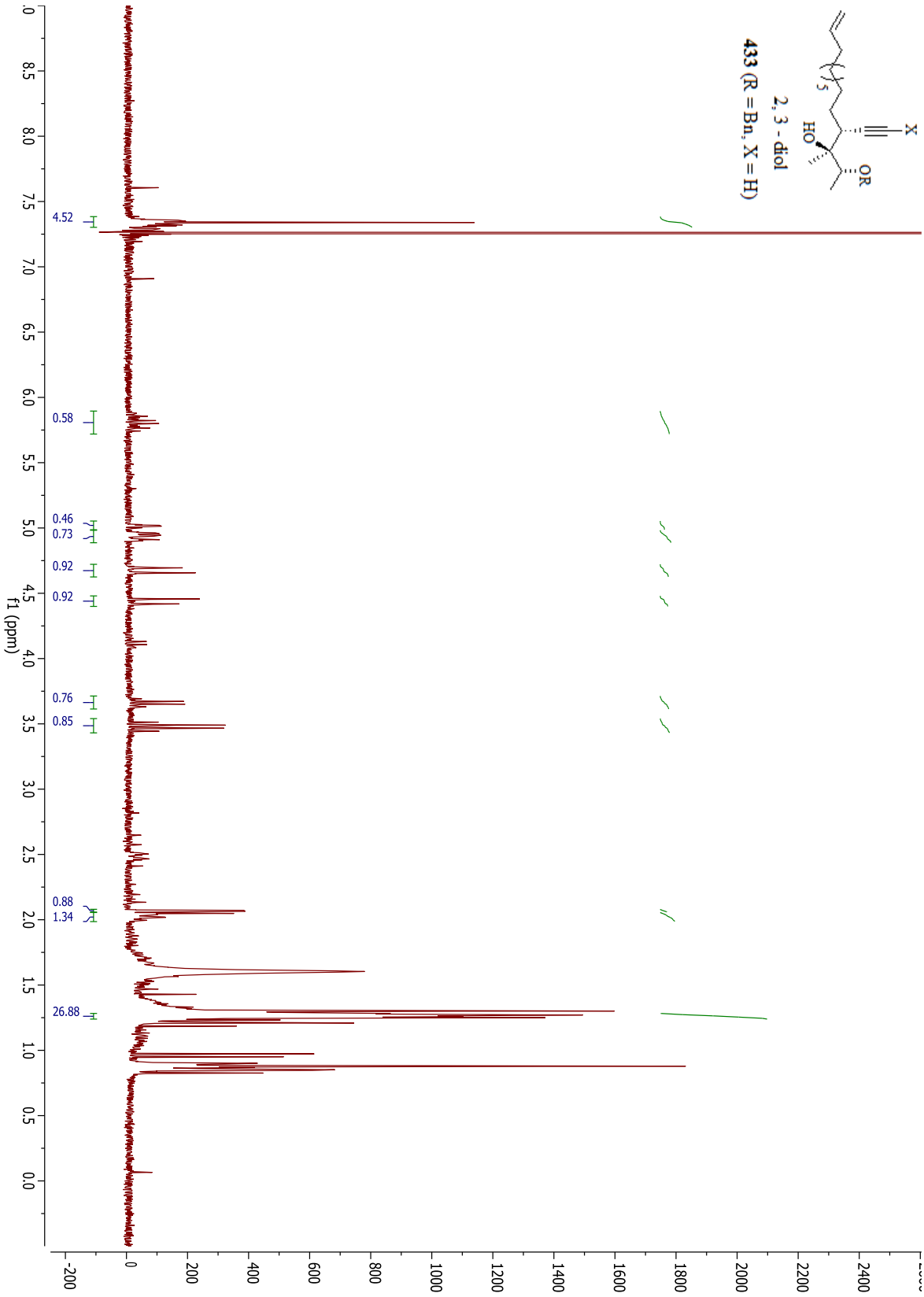

427
OBn
O
139.148
138.133
128.338
127.648
127.598
114.101
77.316 CDCl3
76.998 CDCl3
76.680 CDCl3
74.848
73.085
61.048
59.692
33.760
29.466
29.411
29.346
29.063
28.882
28.219
26.469
14.464
f1 (ppm)

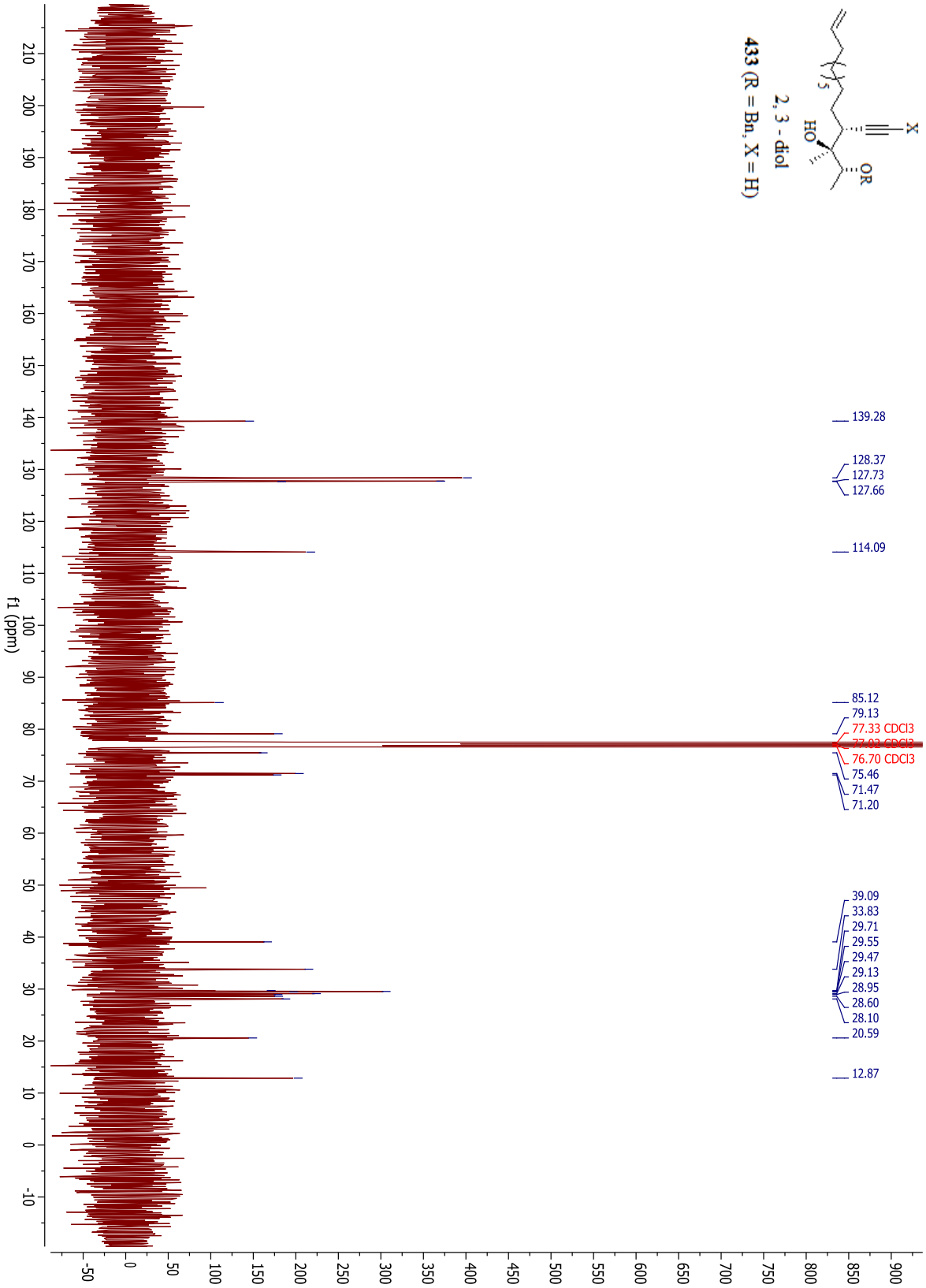

430
7.26 CDCl3
6.64
6.64
6.62
6.62
6.61
5.84
5.83
5.82
5.82
5.80
5.79
5.78
5.77
5.01
5.01
4.97
4.96
4.94
4.94
4.92
4.91
2.30
2.26
2.24
2.22
2.20
2.17
2.06
2.05
2.03
2.01
1.91
1.76
1.62
1.48 HDO
1.46 HDO
1.44 HDO
1.43 HDO
1.39
1.37
1.36
1.34
1.30
1.66
1.00
3.53
4.83
2.73
2.88
0.82
12.65
f1 (ppm)

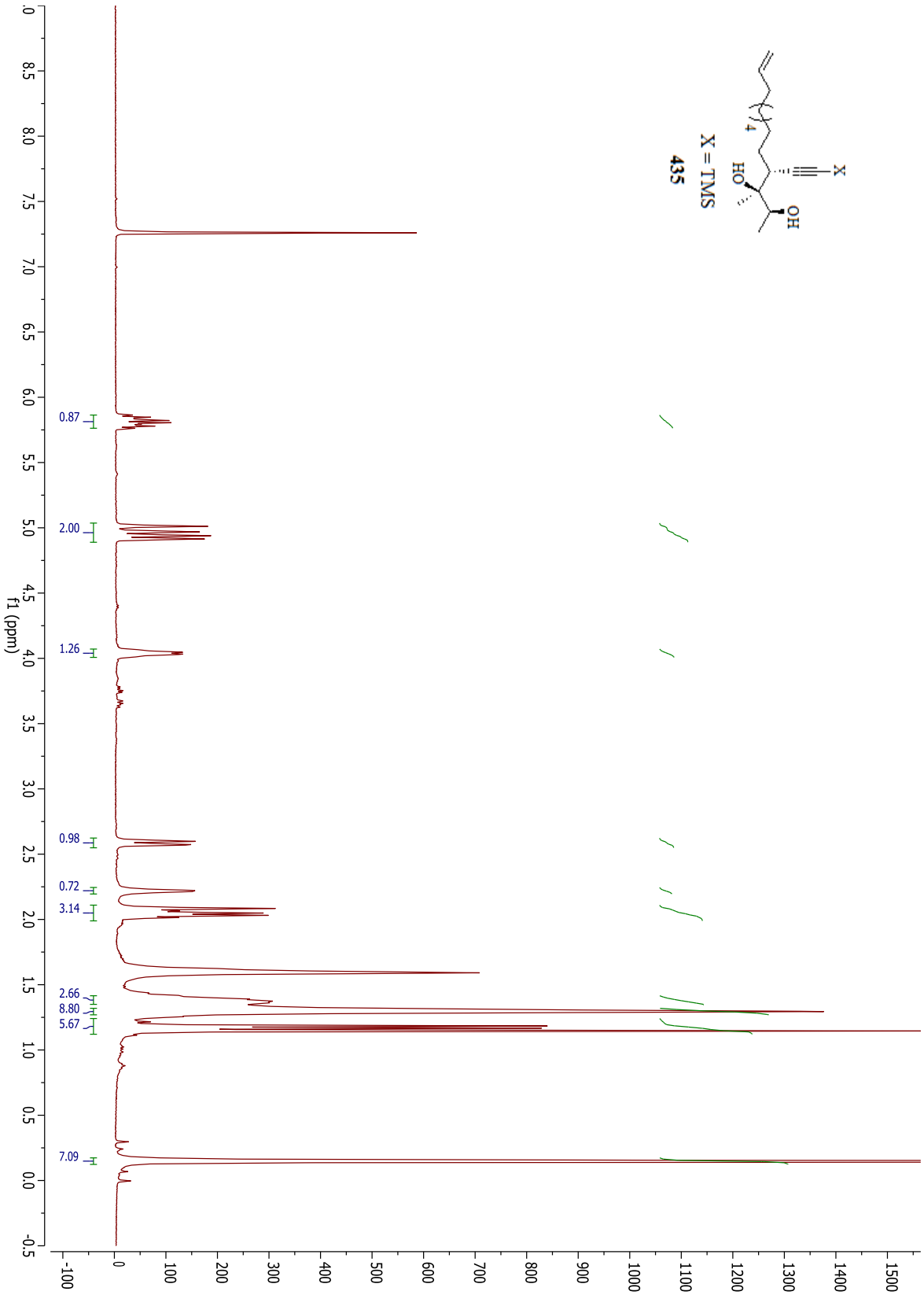

430
O
199.96
143.94
139.14
137.56
114.13
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
33.76
29.38
29.36
29.12
29.06
28.88
28.62
25.41
11.10
f1 (ppm)

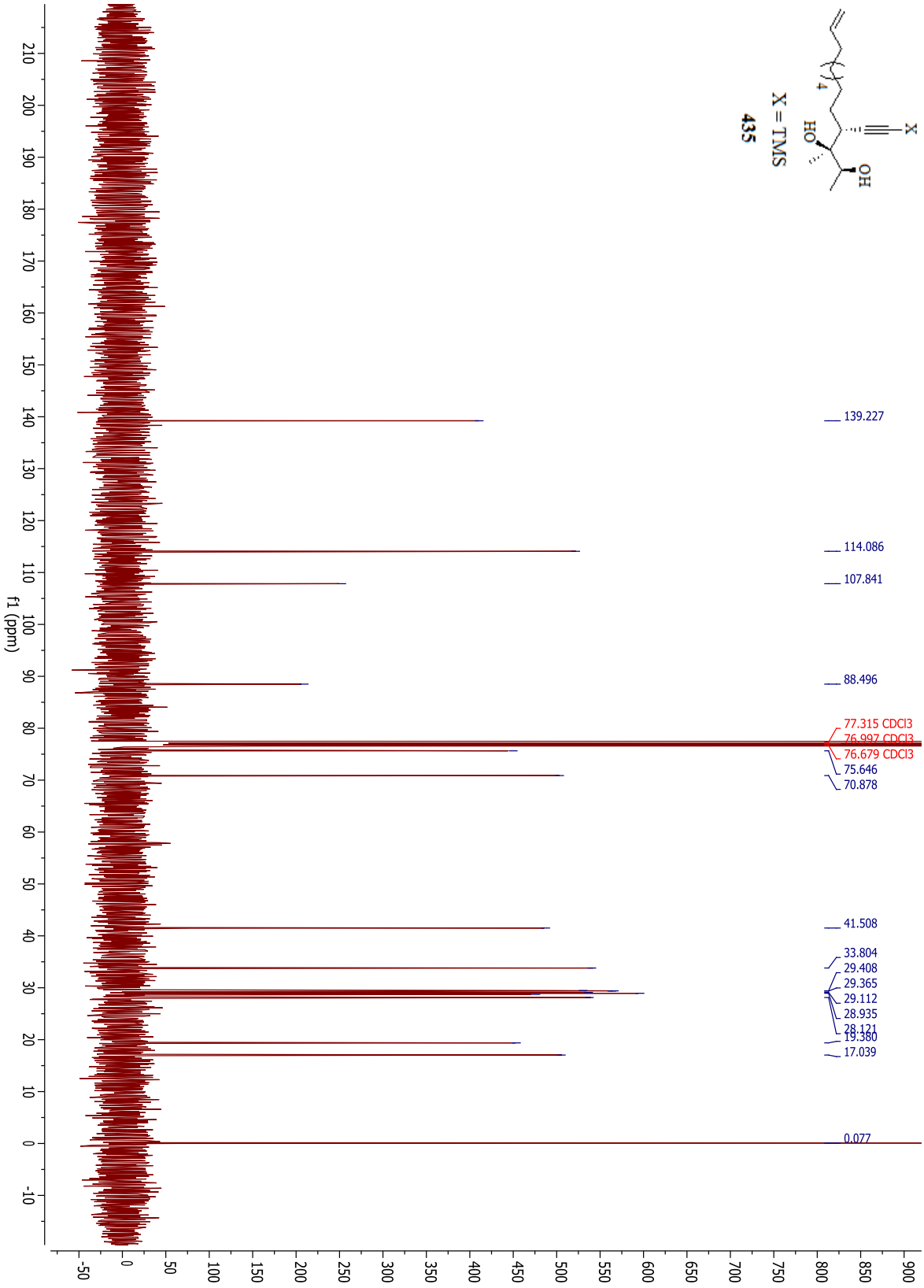

431
OH
f1 (ppm)
1.00
1.32
2.53
1.26
5.49
3.54
5.62
17.13

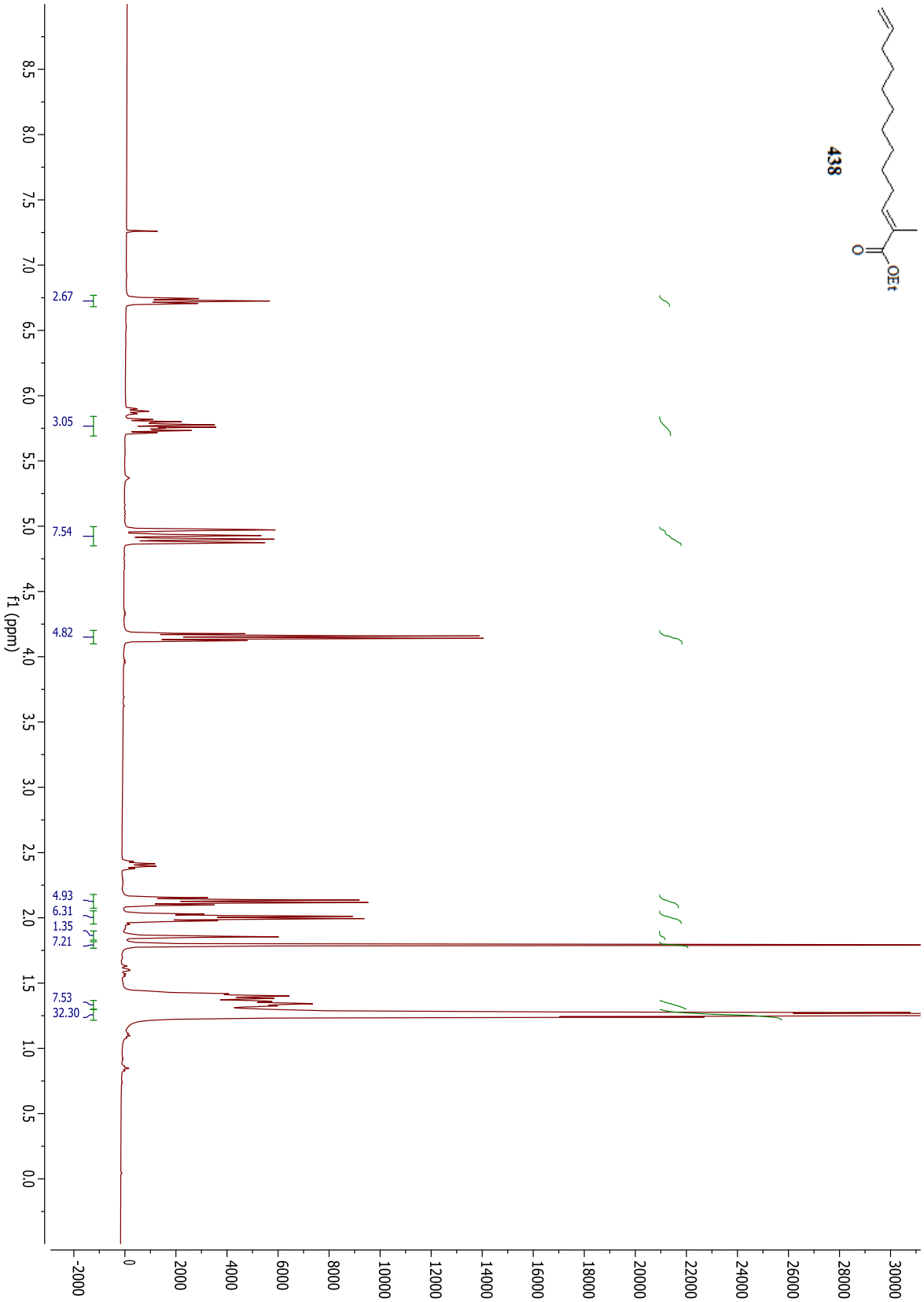

431
OH
139.22
138.26
125.37
114.08
77.32
77.00
76.68
73.47
33.80
29.50
29.48
29.45
29.31
29.12
28.92
27.48
21.60
11.40
f1 (ppm)

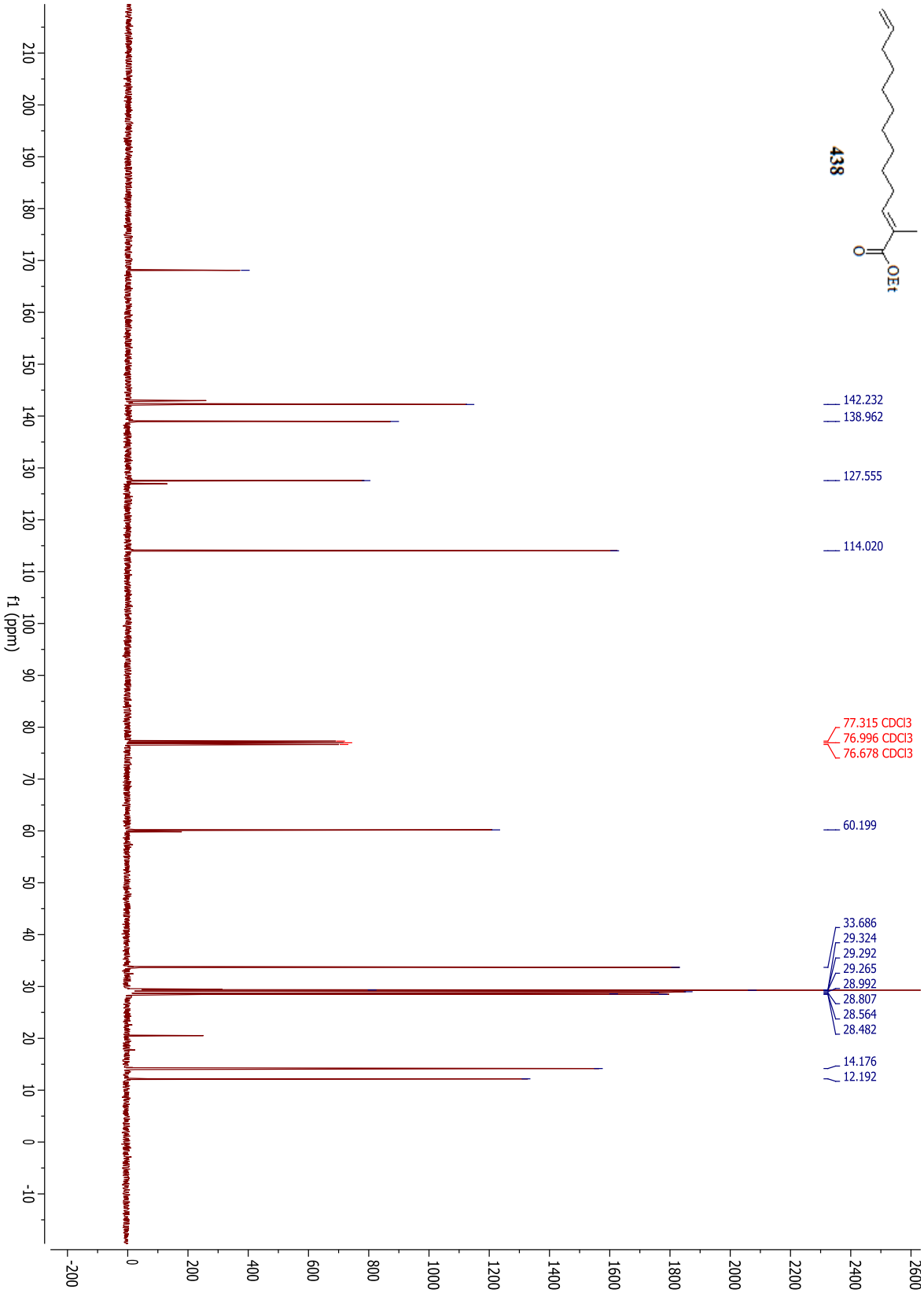

X
OR
HO
5
2, 3 - diol
433 (R = Bn, X = H)
4.52
0.58
0.46
0.73
0.92
0.92
0.76
0.85
0.88
1.34
26.88
f1 (ppm)

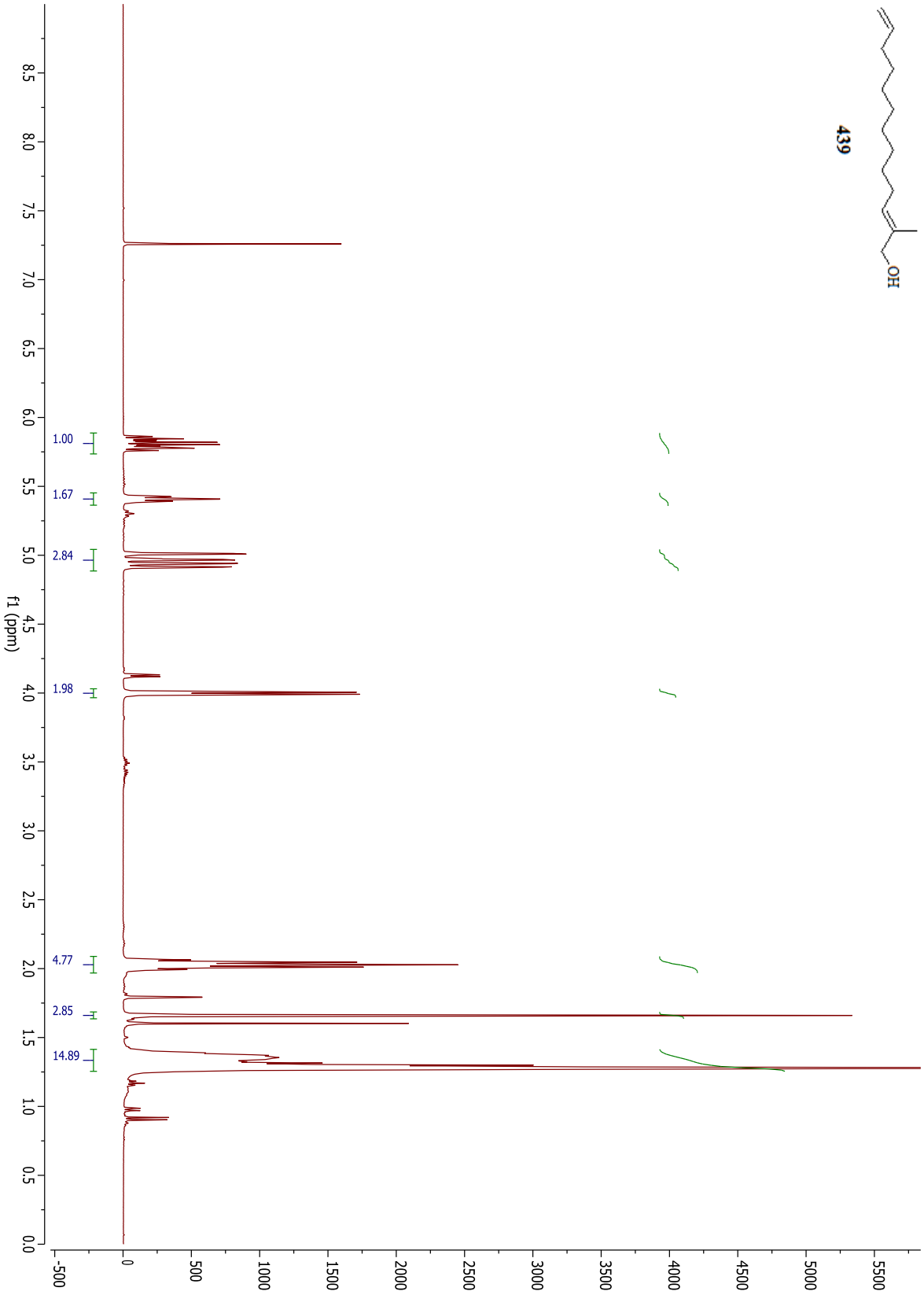

433 (R = Bn, X = H)
2, 3 - diol
HO
OR
X
f1 (ppm)
139.28
128.37
127.73
127.66
114.09
85.12
79.13
77.33 CDCl3
76.70 CDCl3
75.46
71.47
71.20
39.09
33.83
29.71
29.55
29.47
29.13
28.95
28.60
28.10
20.59
12.87

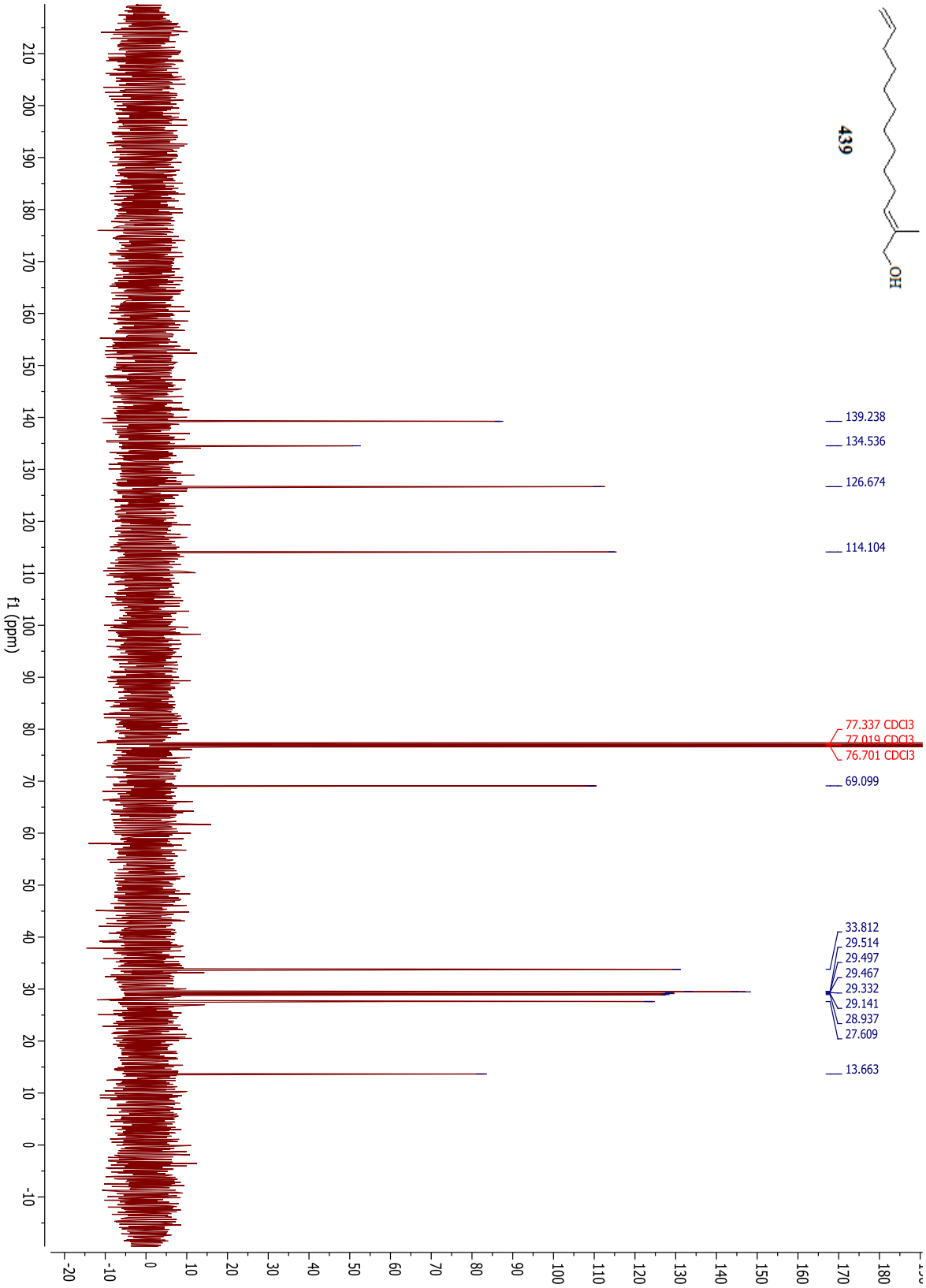

X = TMS
435
X
OH
HO
4
f1 (ppm)
0.87
2.00
1.26
0.98
0.72
3.14
2.66
8.80
5.67
7.09

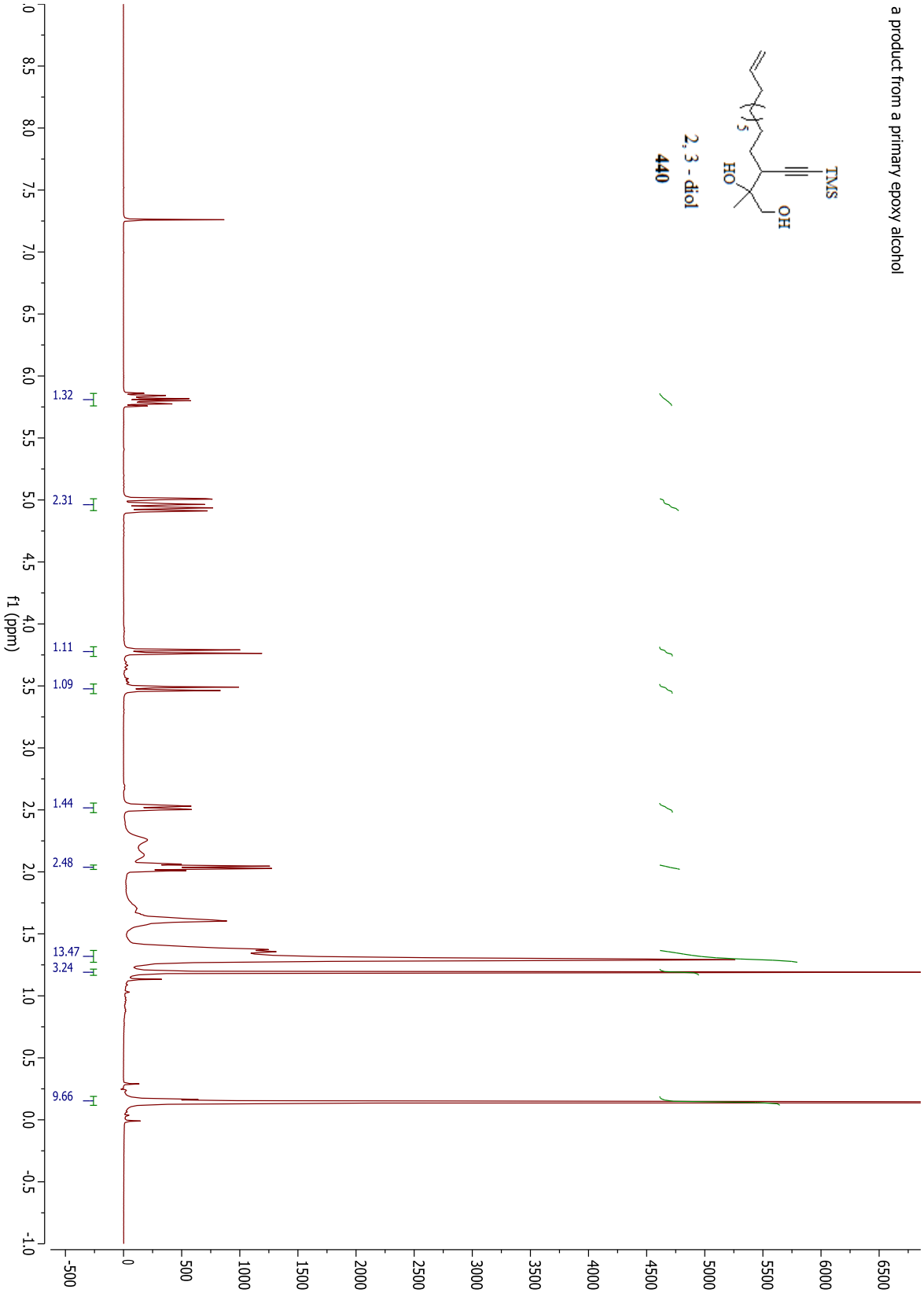

X = TMS
435
HO
OH
X
4
f1 (ppm)
139.227
114.086
107.841
88.496
77.315 CDCl3
76.997 CDCl3
76.679 CDCl3
75.646
70.878
41.508
33.804
29.408
29.365
29.112
28.935
28.121
19.380
17.039
0.077

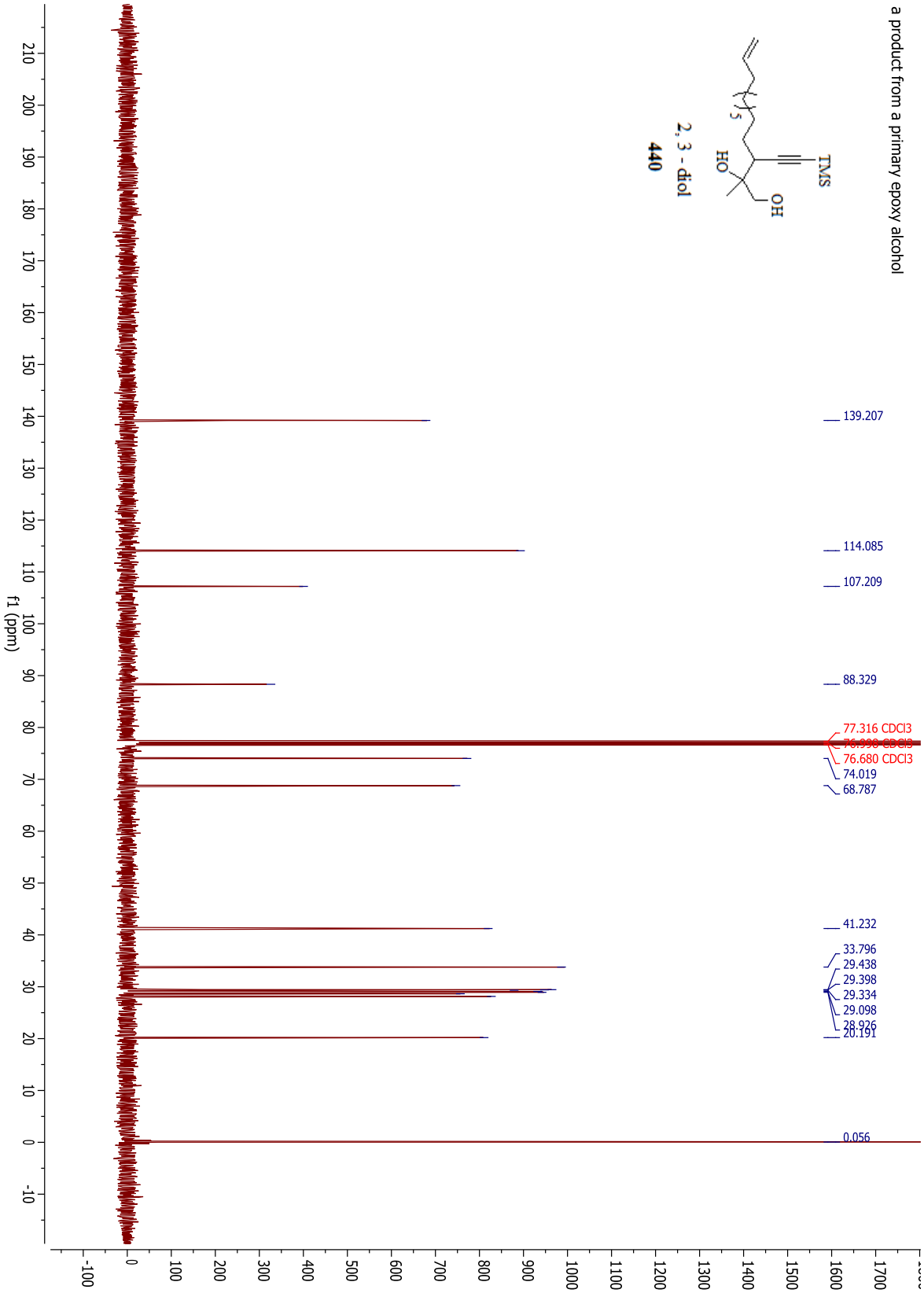

438
OEt
O
f1 (ppm)
2.67
3.05
7.54
4.82
4.93
6.31
1.35
7.21
7.53
32.30

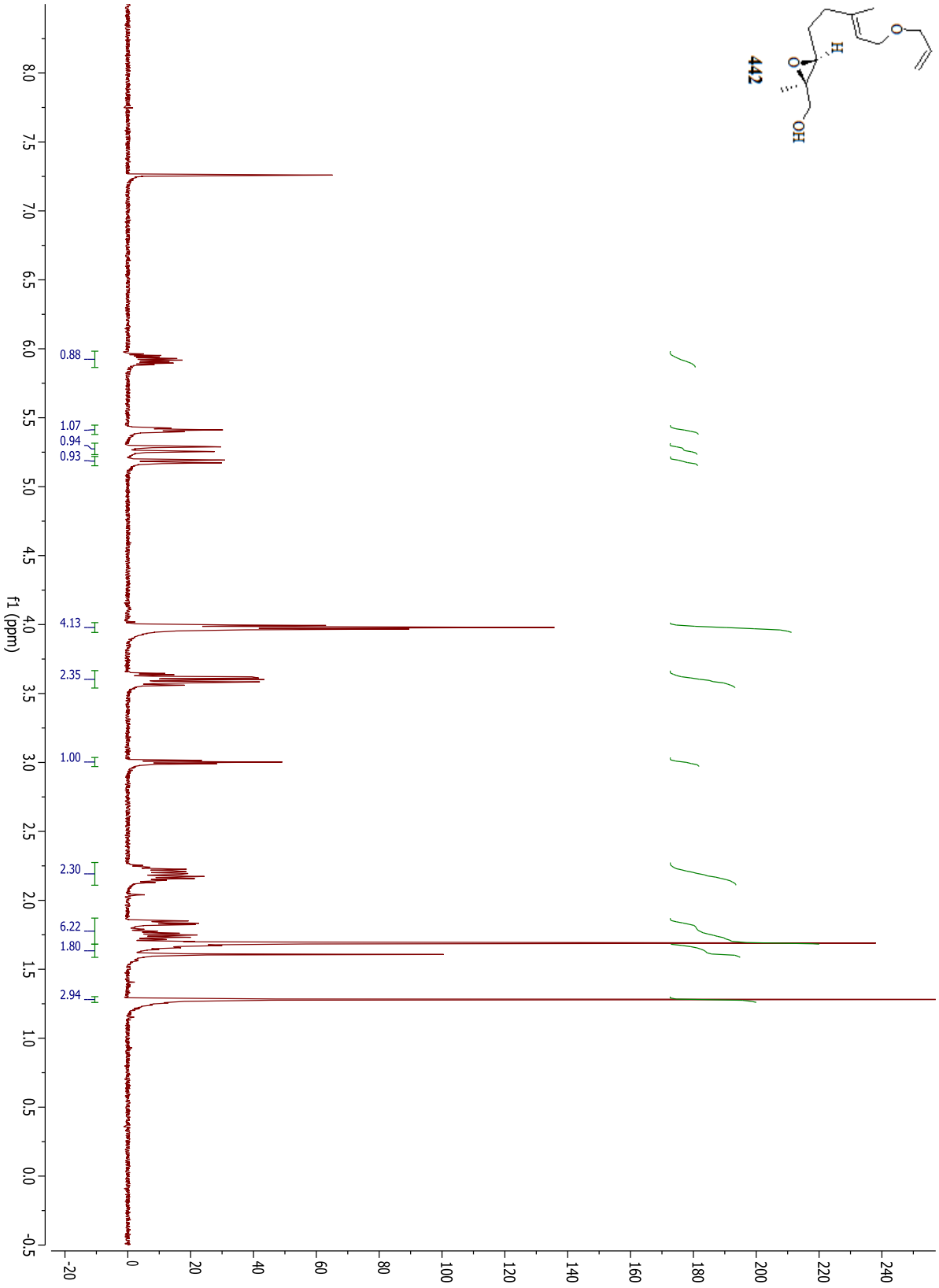

438
O
OEt
142.232
138.962
127.555
114.020
77.315 CDCl3
76.996 CDCl3
76.678 CDCl3
60.199
33.686
29.324
29.292
29.265
28.992
28.807
28.564
28.482
14.176
12.192
f1 (ppm)

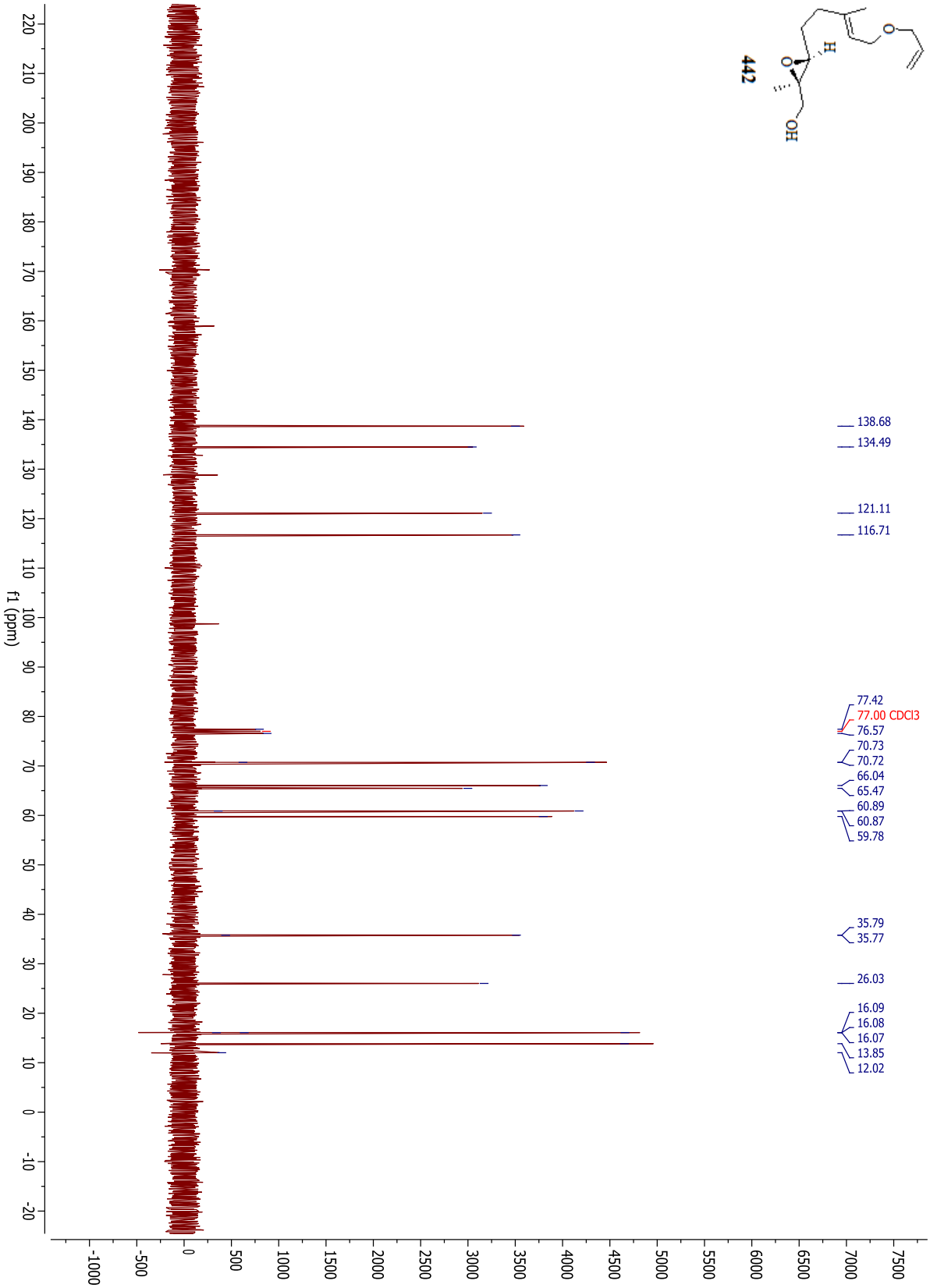

439
OH
1.00
1.67
2.84
1.98
4.77
2.85
14.89
f1 (ppm)

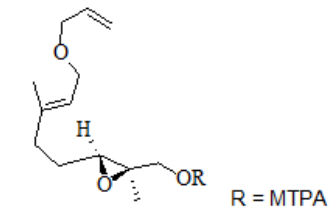

439
OH
f1 (ppm)
139.238
134.536
126.674
114.104
77.337 CDCl3
77.019 CDCl3
76.701 CDCl3
69.099
33.812
29.514
29.497
29.467
29.332
29.141
28.937
27.609
13.663


a product from a primary epoxy alcohol
2, 3 - diol
440
TMS
OH
HO
f1 (ppm)
1.32
2.31
1.11
1.09
1.44
2.48
13.47
3.24
9.66


a product from a primary epoxy alcohol
2, 3 - diol
440
TMS
OH
HO
f1 (ppm)
139.207
114.085
107.209
88.329
77.316 CDCl3
76.998 CDCl3
76.680 CDCl3
74.019
68.787
41.232
33.796
29.438
29.398
29.334
29.098
28.926
20.191
0.056

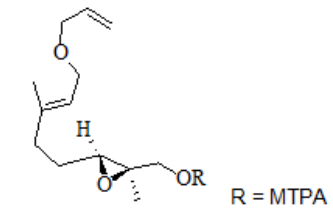

442
OH
O
H
O
0.88
1.07
0.94
0.93
4.13
2.35
1.00
2.30
6.22
1.80
2.94
f1 (ppm)


442
OH
O
H
O
f1 (ppm)
138.68
134.49
121.11
116.71
77.42
77.00 CDCl3
76.57
70.73
70.72
66.04
65.47
60.89
60.87
59.78
35.79
35.77
26.03
16.09
16.08
16.07
13.85
12.02



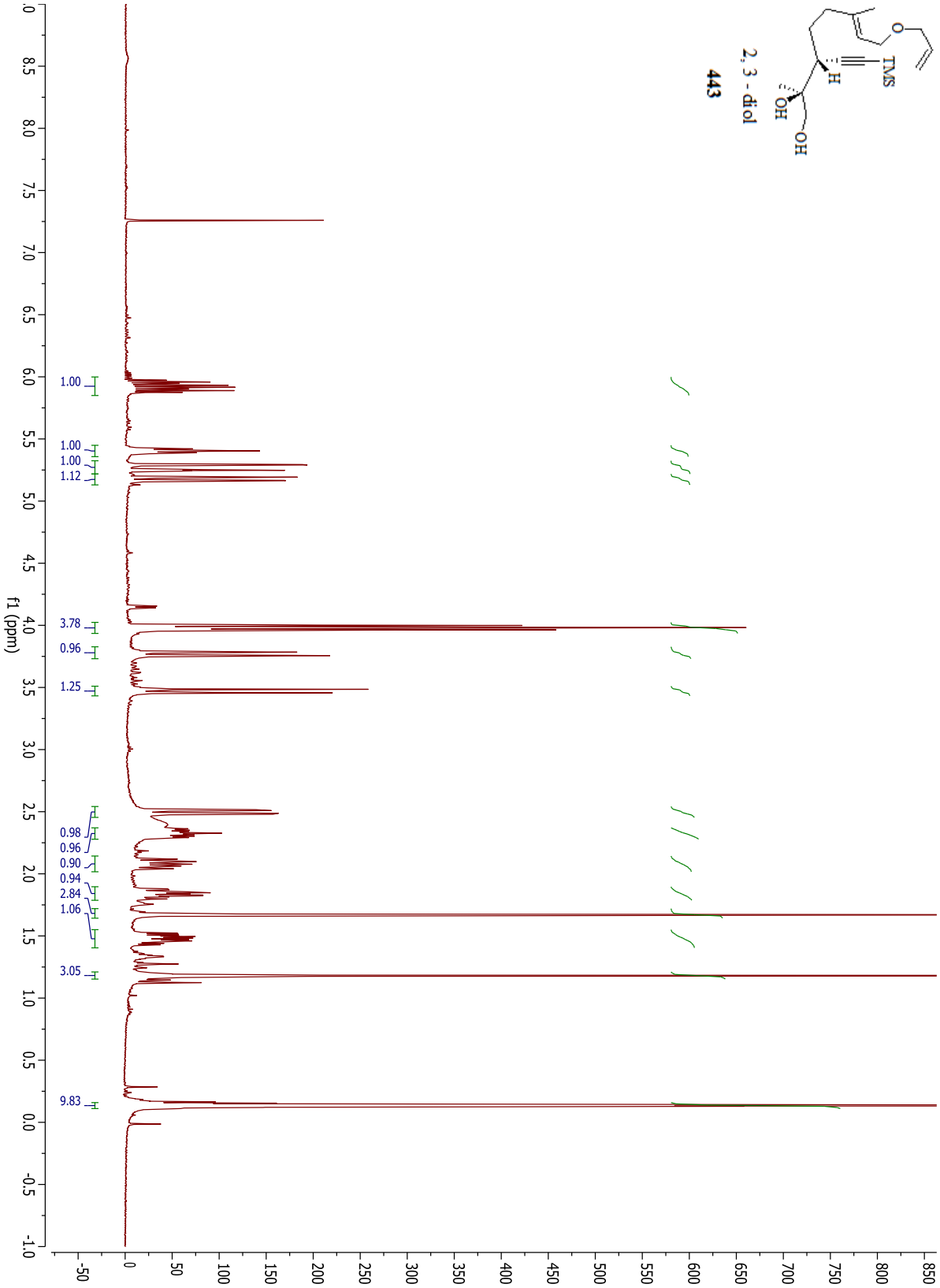
R = MTPA

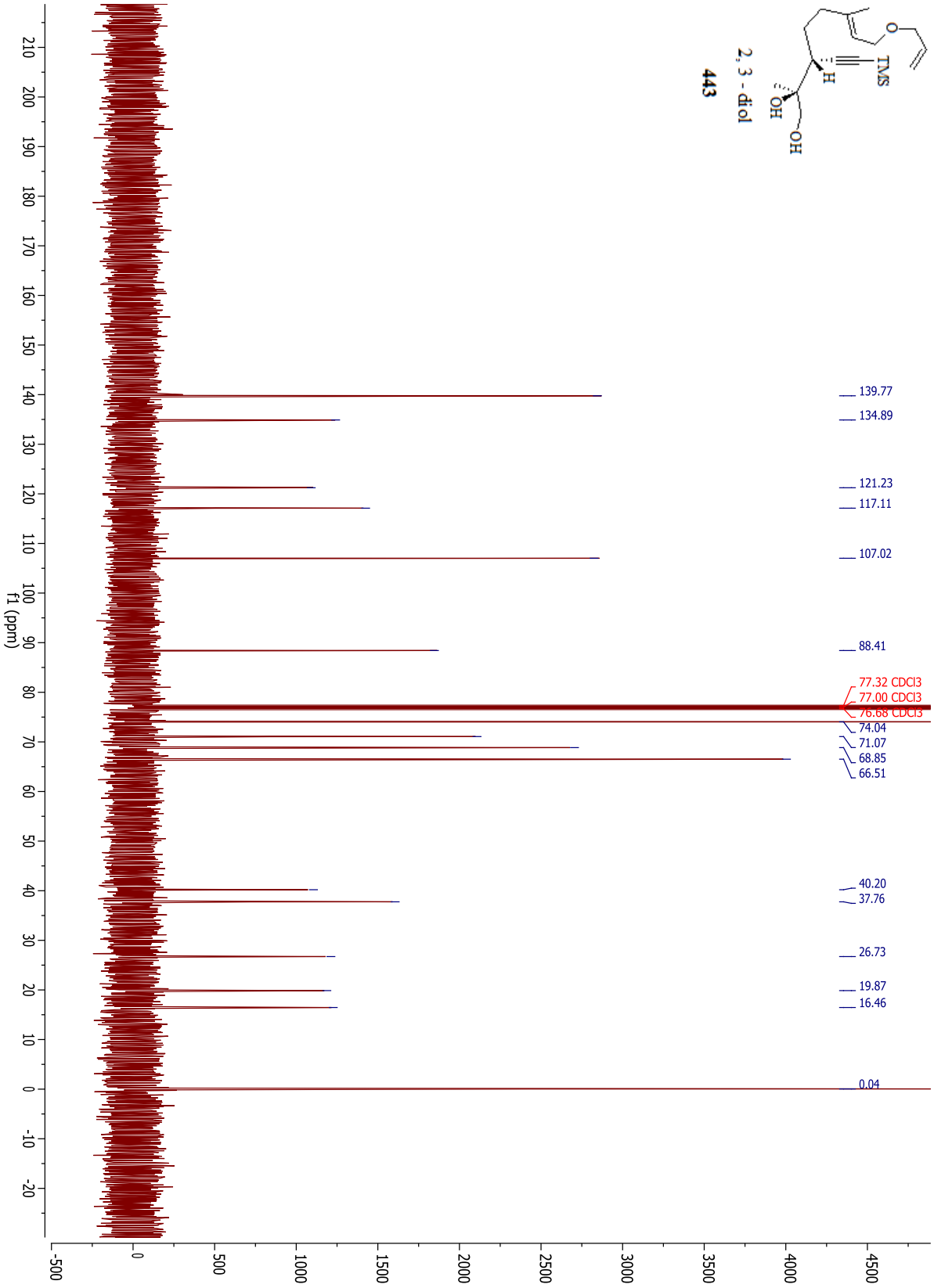
(R)-MTPA ester of 442

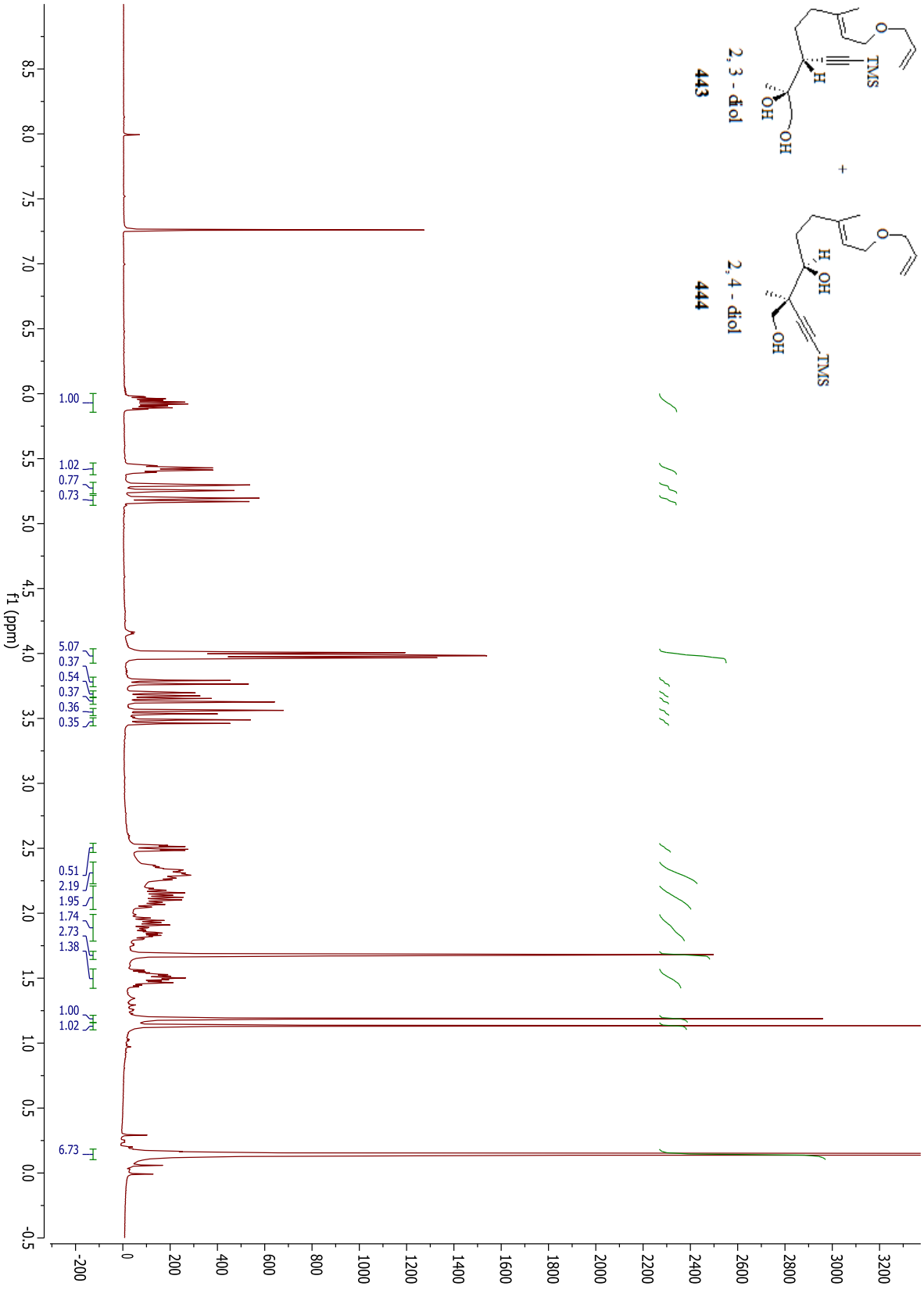


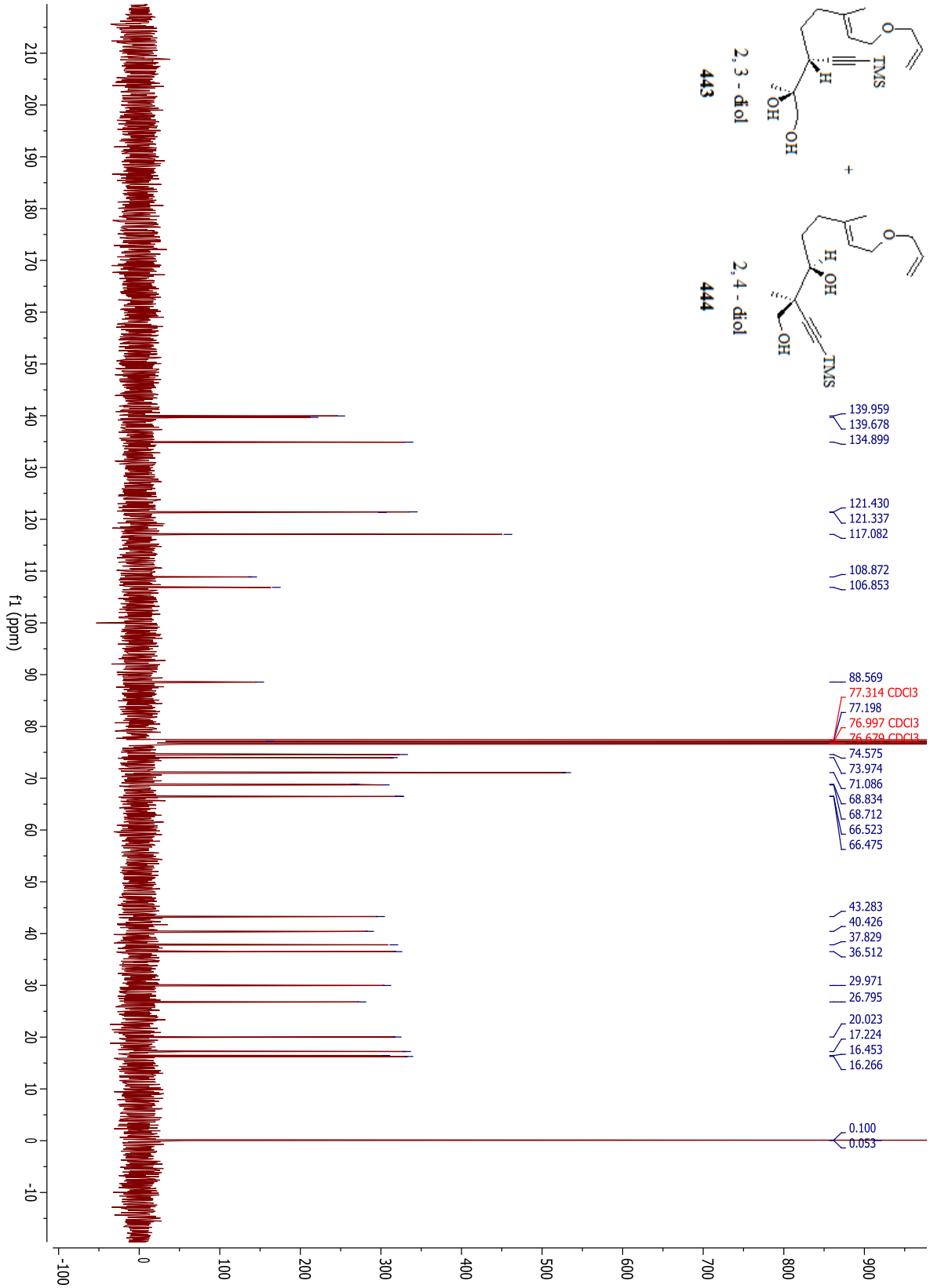
R = MTPA

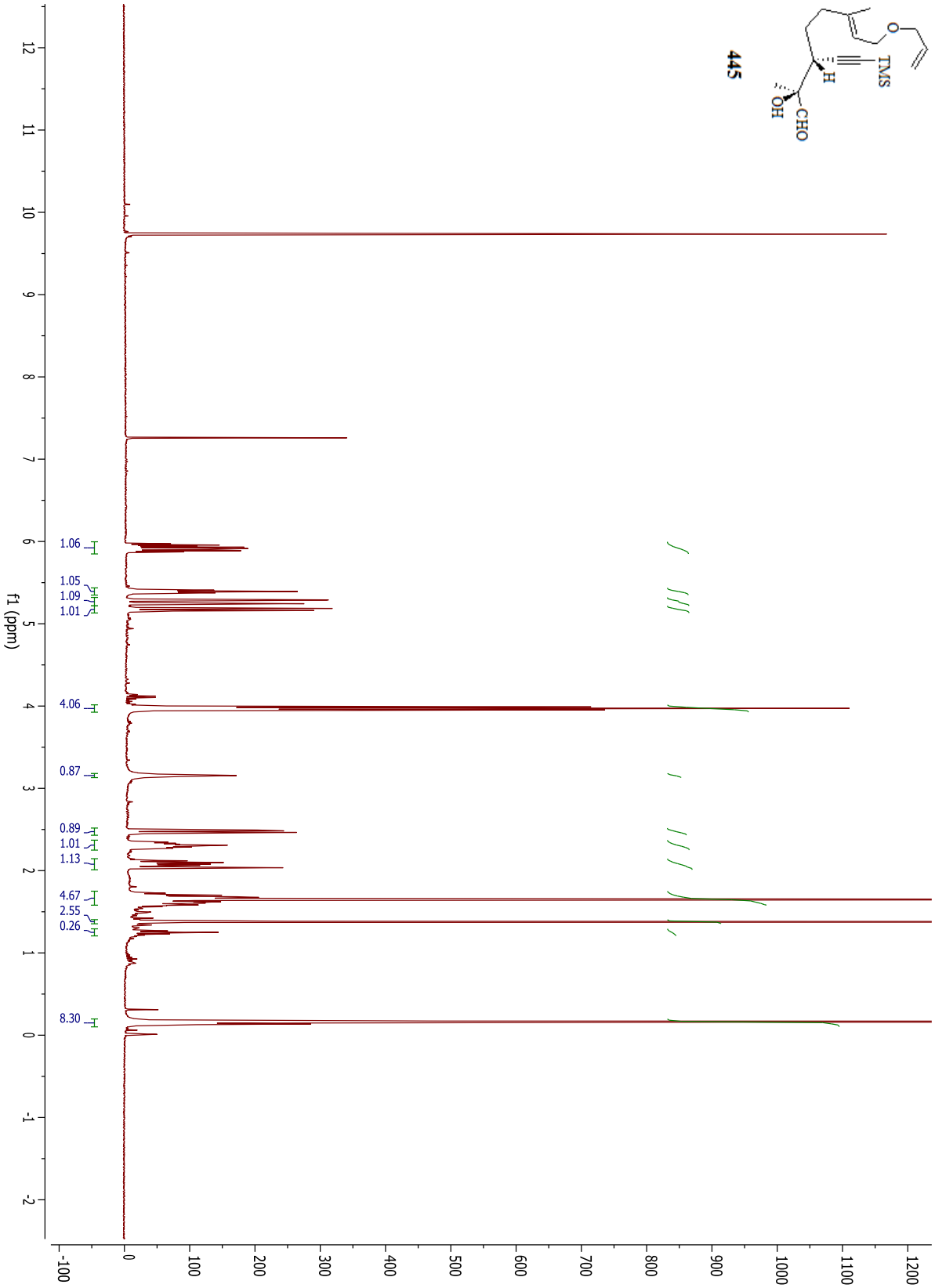
(S)-MTPA ester of 442

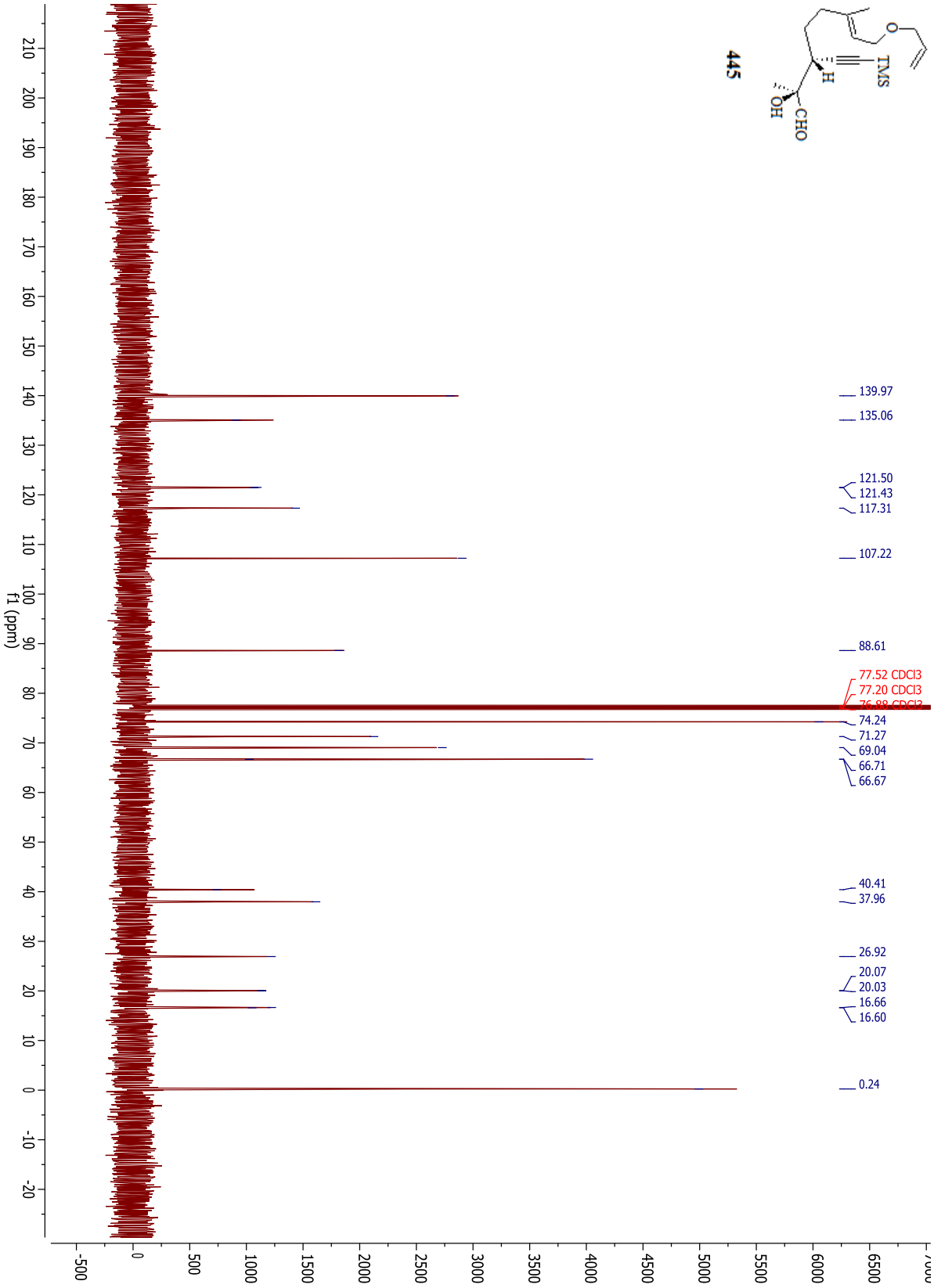

2, 3 - diol
443
TMS
H
OH
OH
O
f1 (ppm)
1.00
1.00
1.00
1.12
3.78
0.96
1.25
0.98
0.96
0.90
0.94
2.84
1.06
3.05
9.83

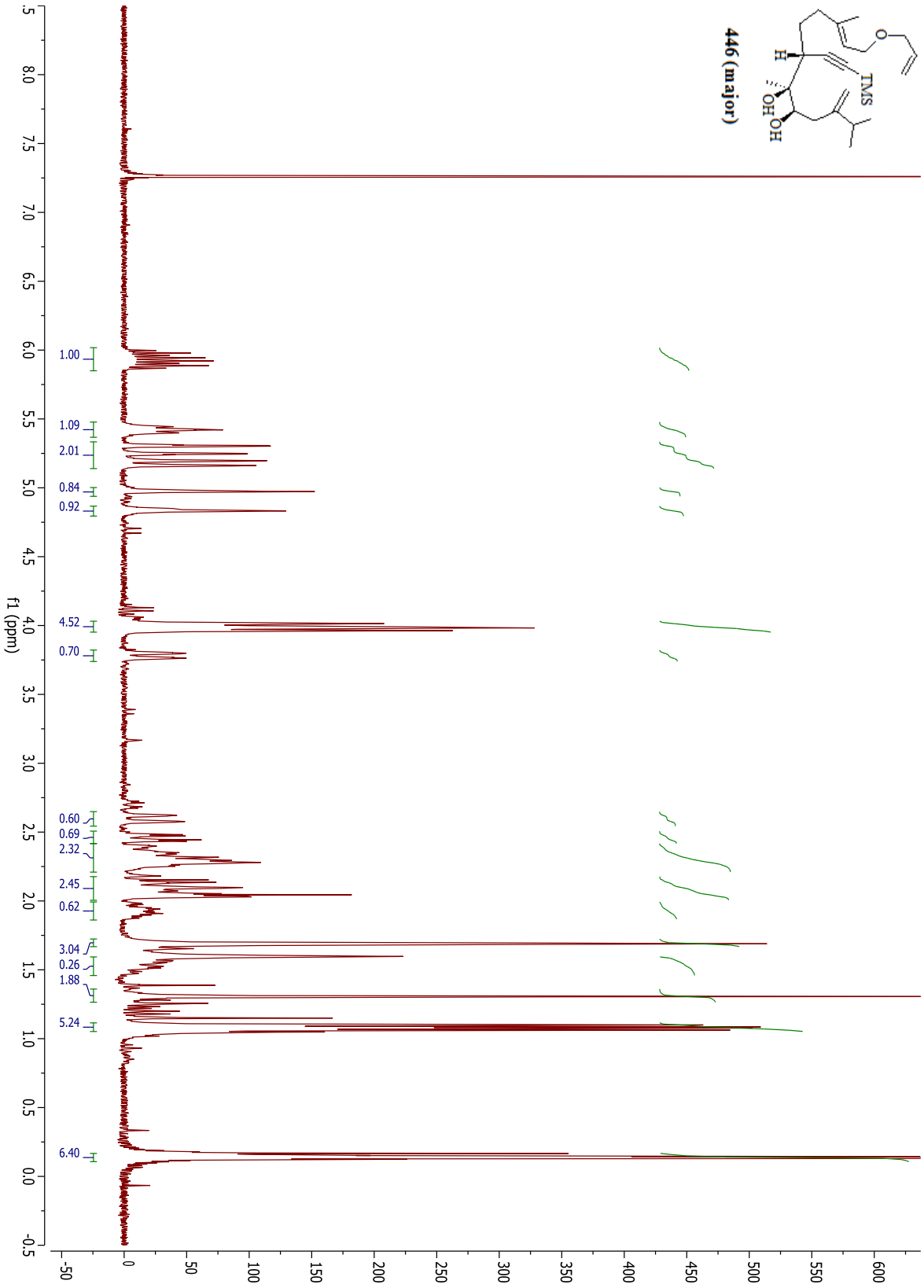

443
2, 3 - diol
TMS
OH
OH
f1 (ppm)
139.77
134.89
121.23
117.11
107.02
88.41
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
74.04
71.07
68.85
66.51
40.20
37.76
26.73
19.87
16.46
0.04

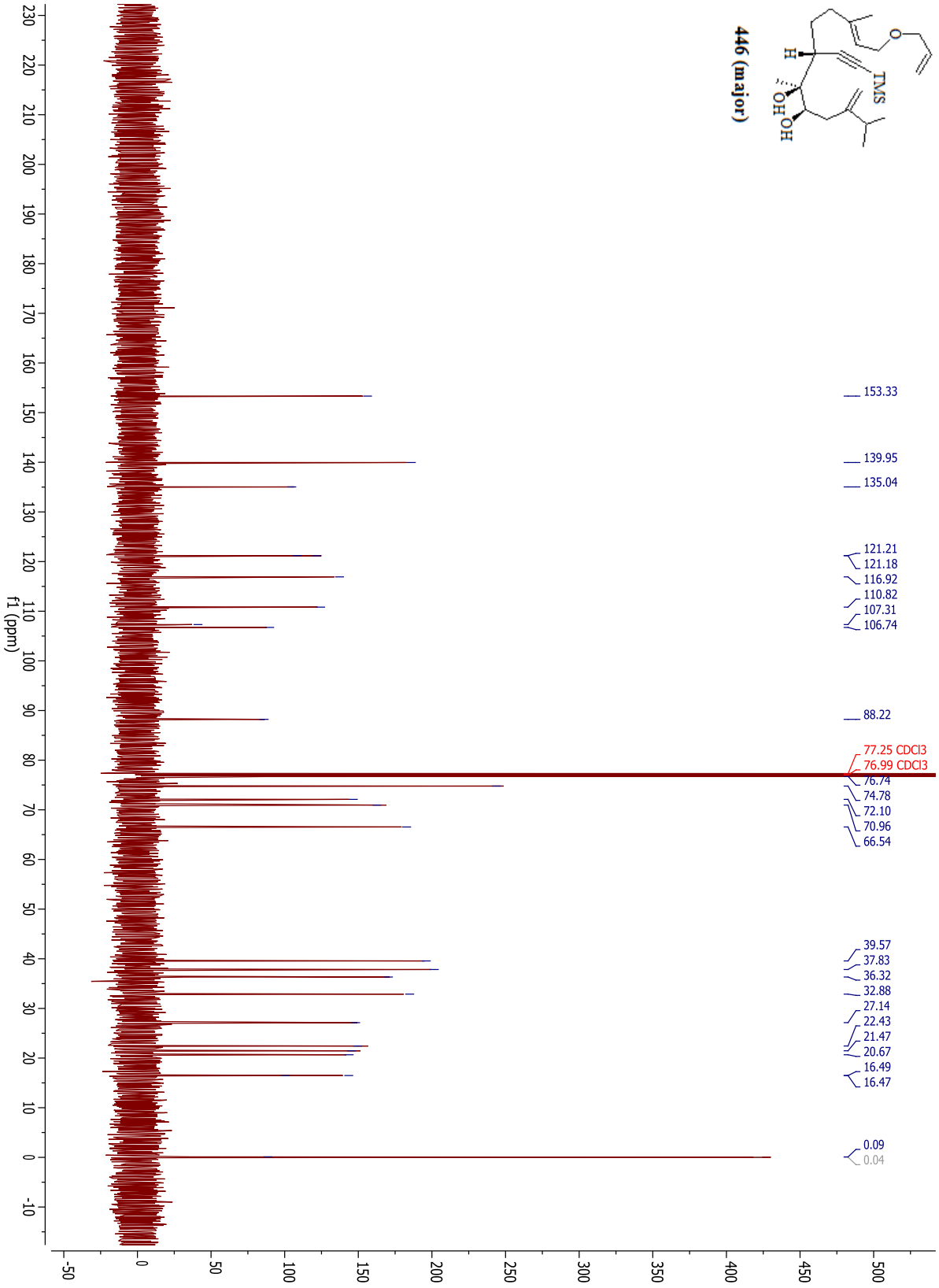

TMS
H
OH
OH
2, 3 - diol
443
+
H
OH
OH
TMS
2, 4 - diol
444
f1 (ppm)
1.00
1.02
0.77
0.73
5.07
0.37
0.54
0.37
0.36
0.35
0.51
2.19
1.95
1.74
2.73
1.38
1.00
1.02
6.73

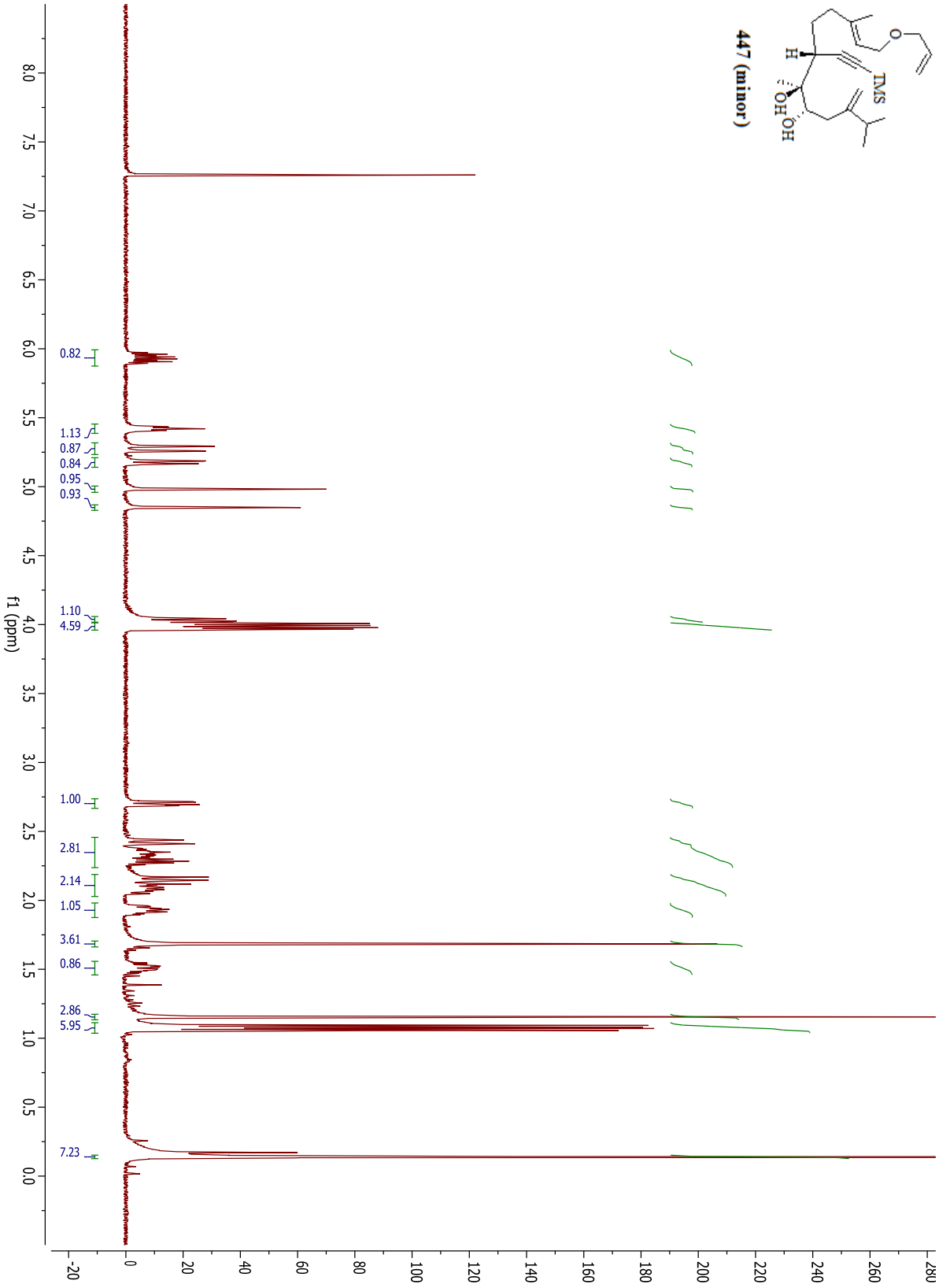

443
2, 3 - diol
444
2, 4 - diol
TMS
OH
H
O
+
139.959
139.678
134.899
121.430
121.337
117.082
108.872
106.853
88.569
77.314 CDCl3
77.198
76.997 CDCl3
74.575
73.974
71.086
68.834
68.712
66.523
66.475
43.283
40.426
37.829
36.512
29.971
26.795
20.023
17.224
16.453
16.266
0.100
0.053
f1 (ppm)

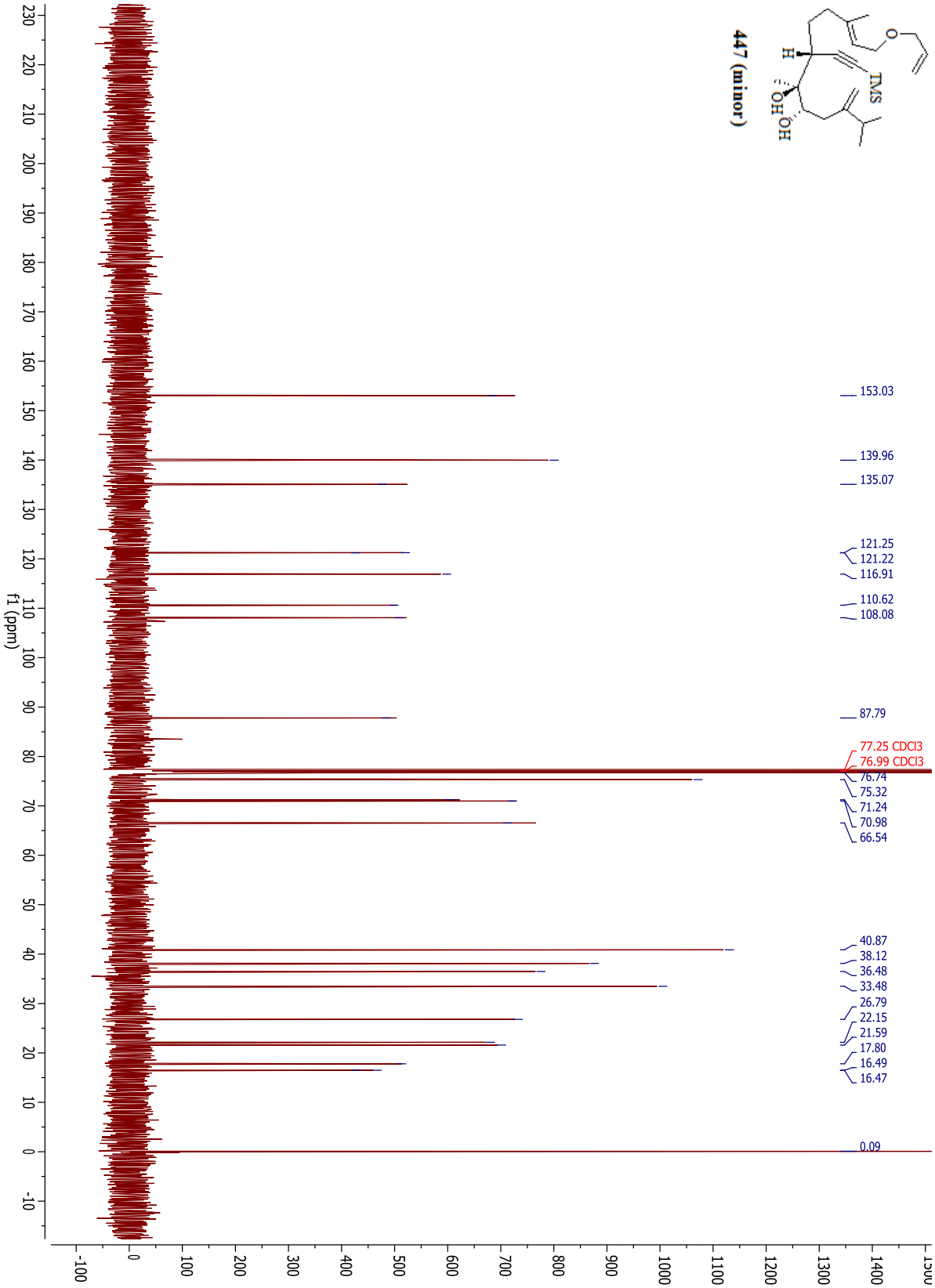

445
TMS
H
OH
CHO
f1 (ppm)
1.06
1.05
1.09
1.01
4.06
0.87
0.89
1.01
1.13
4.67
2.55
0.26
8.30

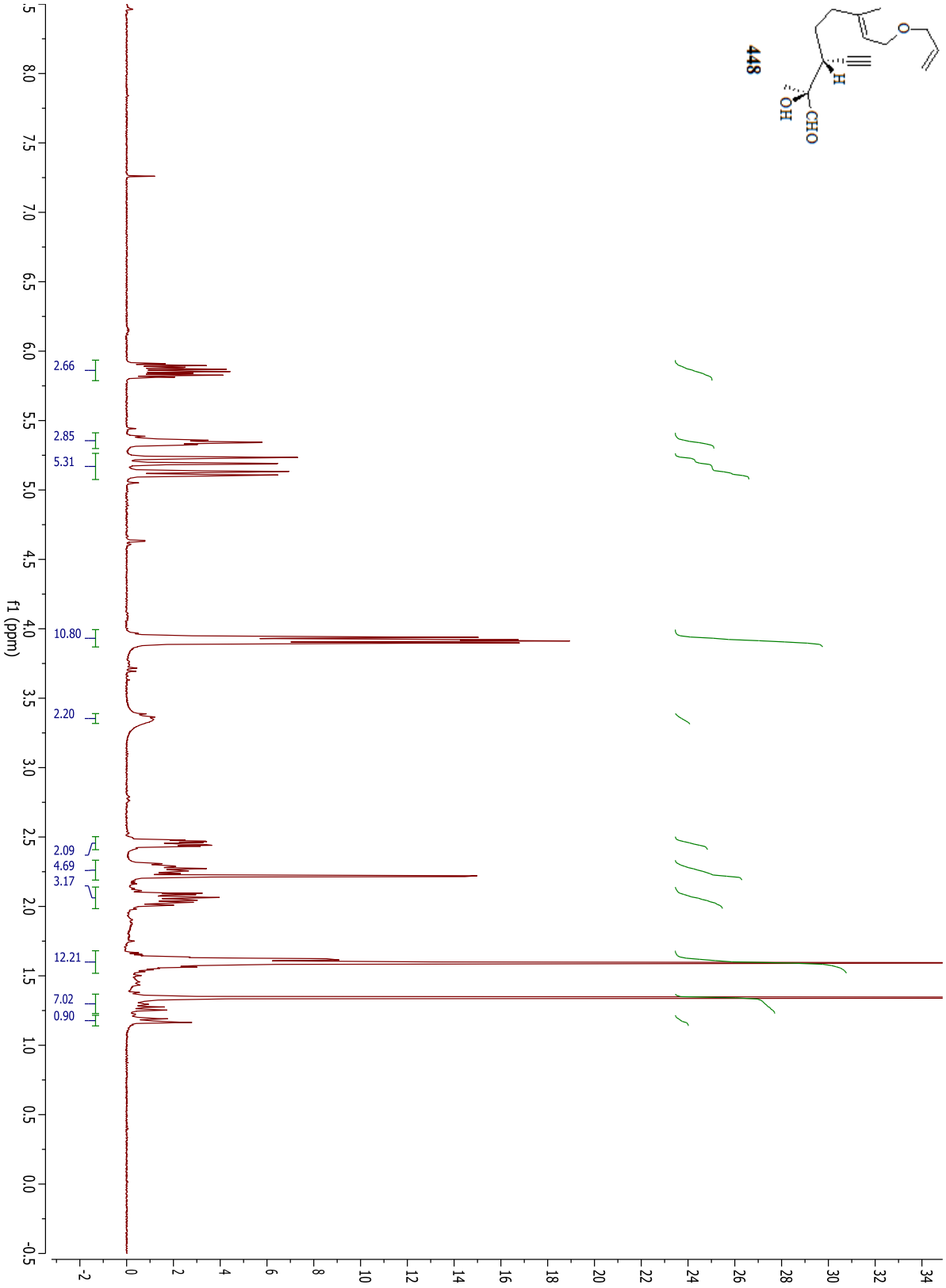

445
TMS
H
OH
CHO
O
f1 (ppm)
139.97
135.06
121.50
121.43
117.31
107.22
88.61
77.52 CDCl3
77.20 CDCl3
74.24
71.27
69.04
66.71
66.67
40.41
37.96
26.92
20.07
20.03
16.66
16.60
0.24

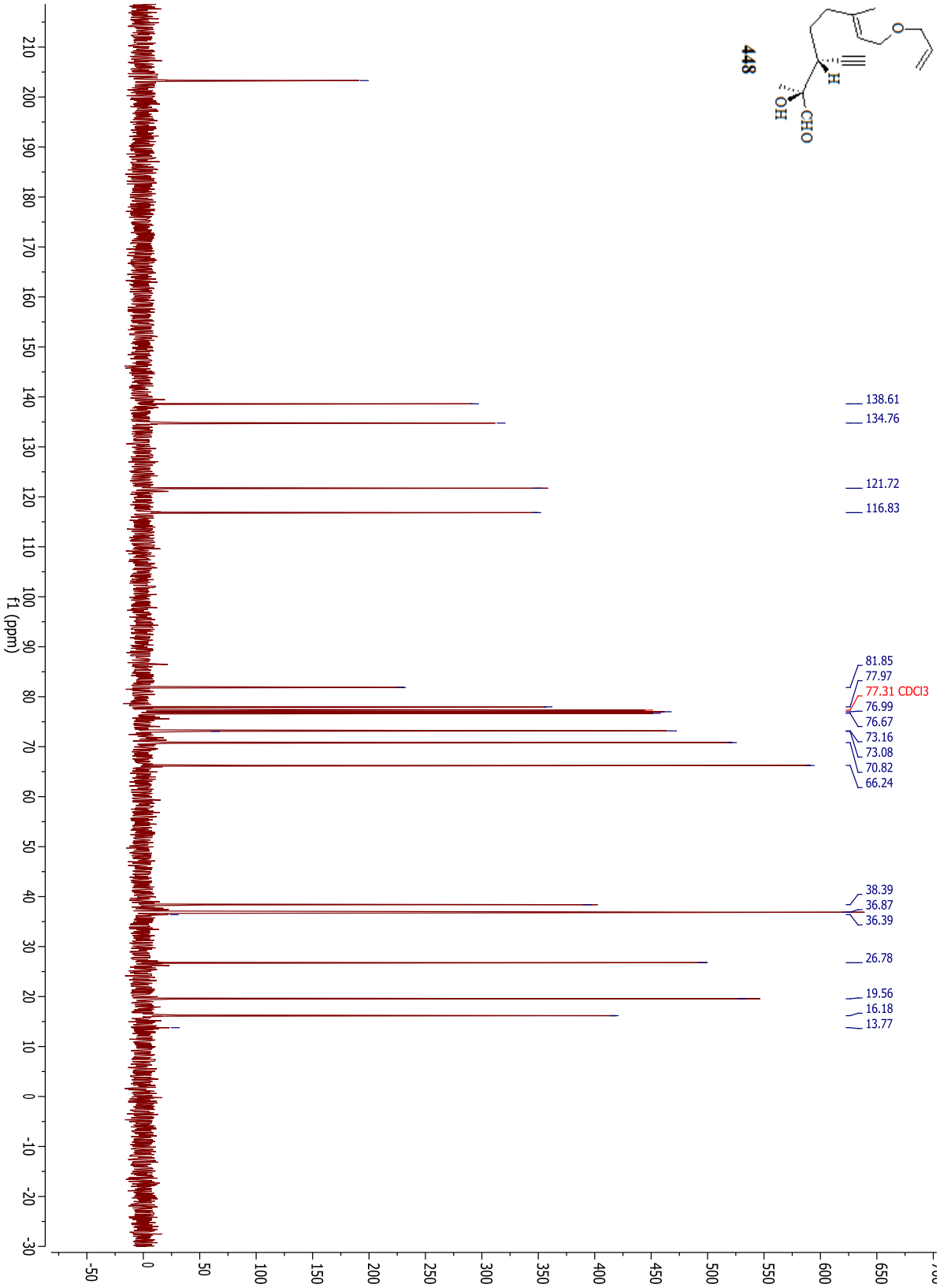

446 (major)
TMS
OH
OH
H
O
f1 (ppm)
1.00
1.09
2.01
0.84
0.92
4.52
0.70
0.60
0.69
2.32
2.45
0.62
3.04
0.26
1.88
5.24
6.40


446 (major)
H
OH
OH
TMS
O
153.33
139.95
135.04
121.21
121.18
116.92
110.82
107.31
106.74
88.22
77.25 CDCl3
76.99 CDCl3
76.74
74.78
72.10
70.96
66.54
39.57
37.83
36.32
32.88
27.14
22.43
21.47
20.67
16.49
16.47
0.09
0.04
f1 (ppm)


447 (minor)
TMS
H
OH
OH
O
f1 (ppm)
0.82
1.13
0.87
0.84
0.95
0.93
1.10
4.59
1.00
2.81
2.14
1.05
3.61
0.86
2.86
5.95
7.23

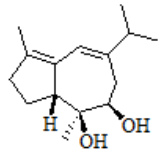

447 (minor)
TMS
H
OH
OH
O
f1 (ppm)
153.03
139.96
135.07
121.25
121.22
116.91
110.62
108.08
87.79
77.25 CDCl3
76.99 CDCl3
76.74
75.32
71.24
70.98
66.54
40.87
38.12
36.48
33.48
26.79
22.15
21.59
17.80
16.49
16.47
0.09


448
OH
H
CHO
O
f1 (ppm)
2.66
2.85
5.31
10.80
2.20
2.09
4.69
3.17
12.21
7.02
0.90

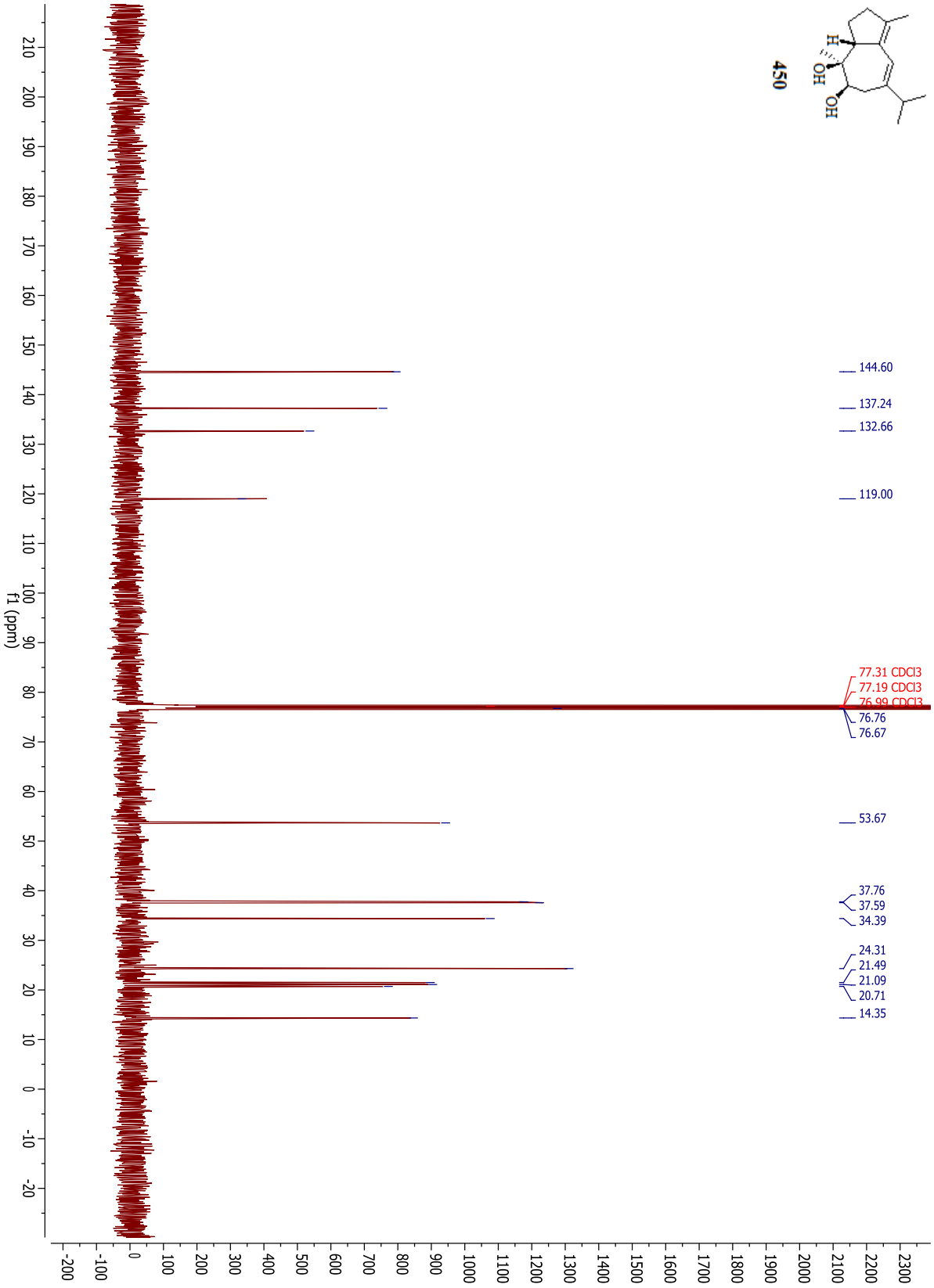

448
OH
CHO
H
O
138.61
134.76
121.72
116.83
81.85
77.97
77.31 CDCl3
76.99
76.67
73.16
73.08
70.82
66.24
38.39
36.87
36.39
26.78
19.56
16.18
13.77
f1 (ppm)

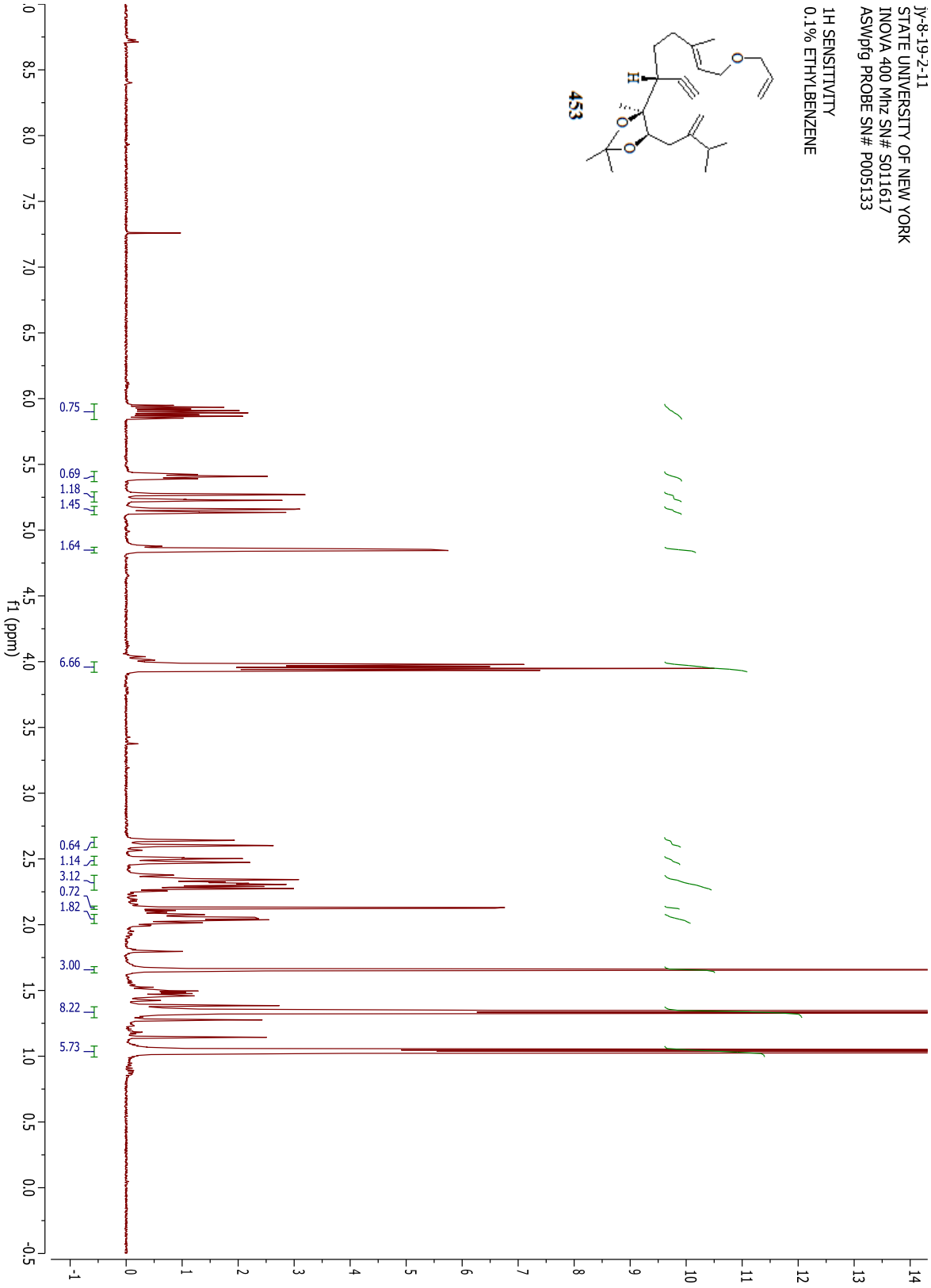
jy-9-26-3-11
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133

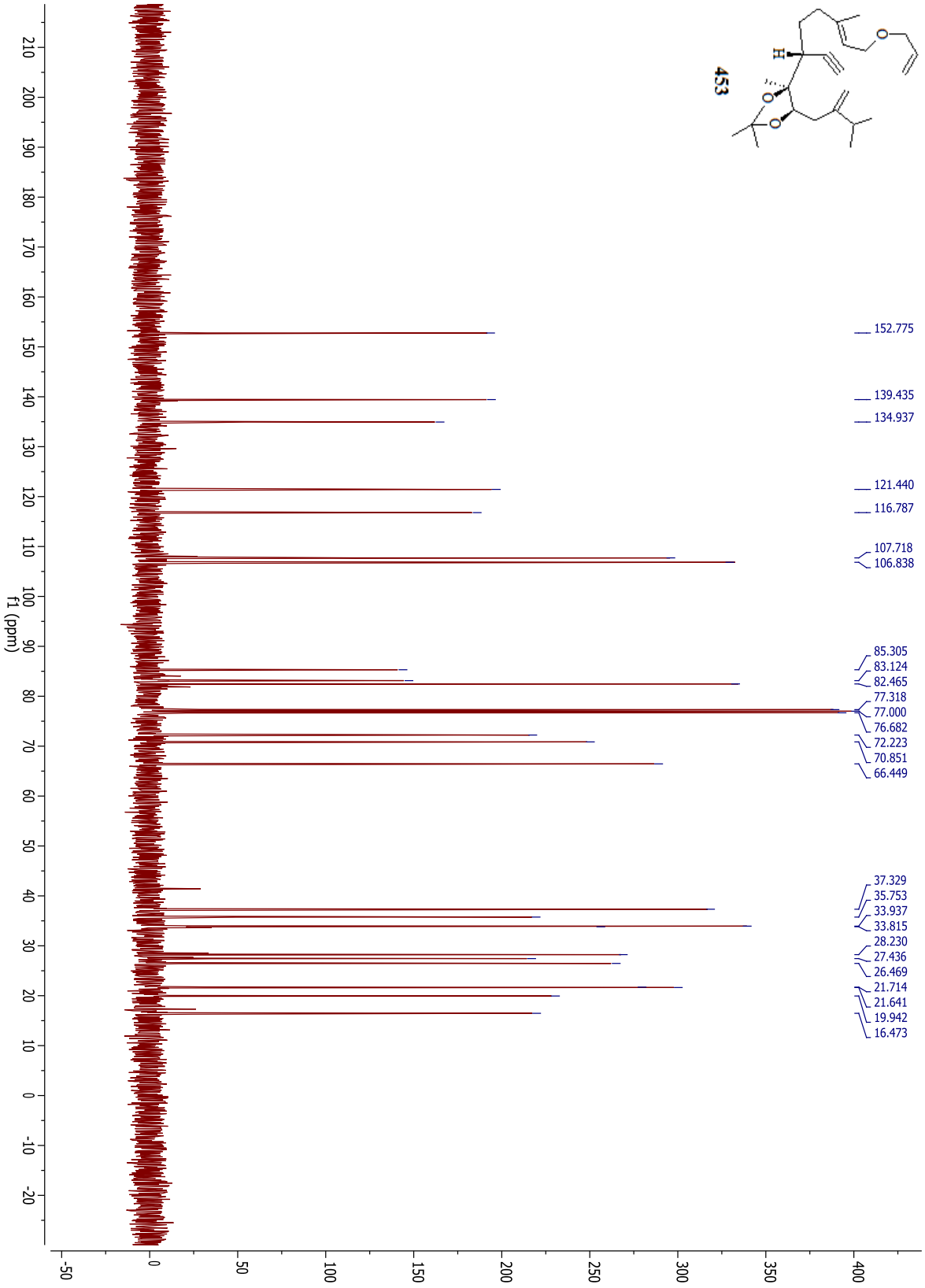
1H SENSITIVITY
0.1% ETHYLBENZENE

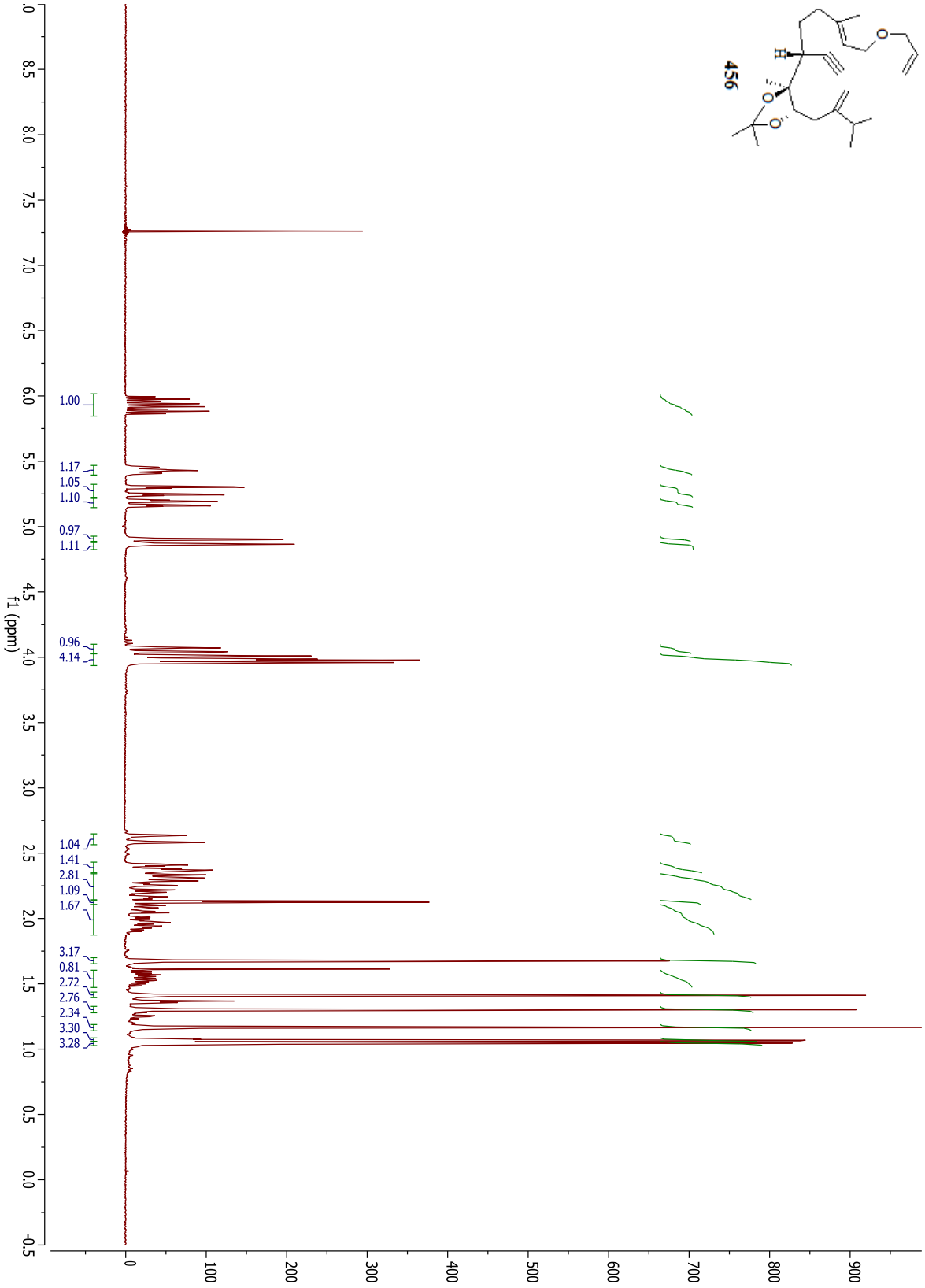


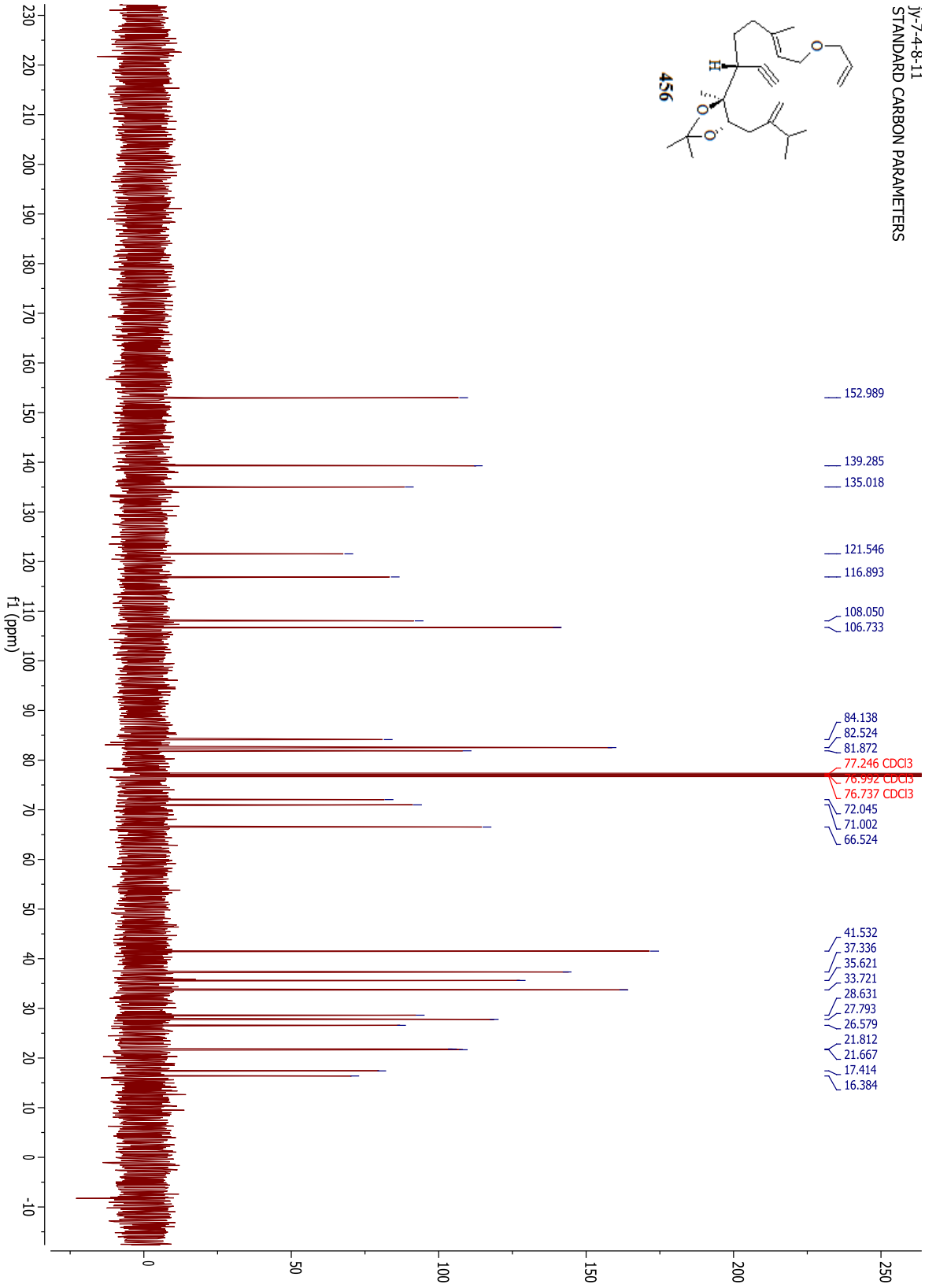
450

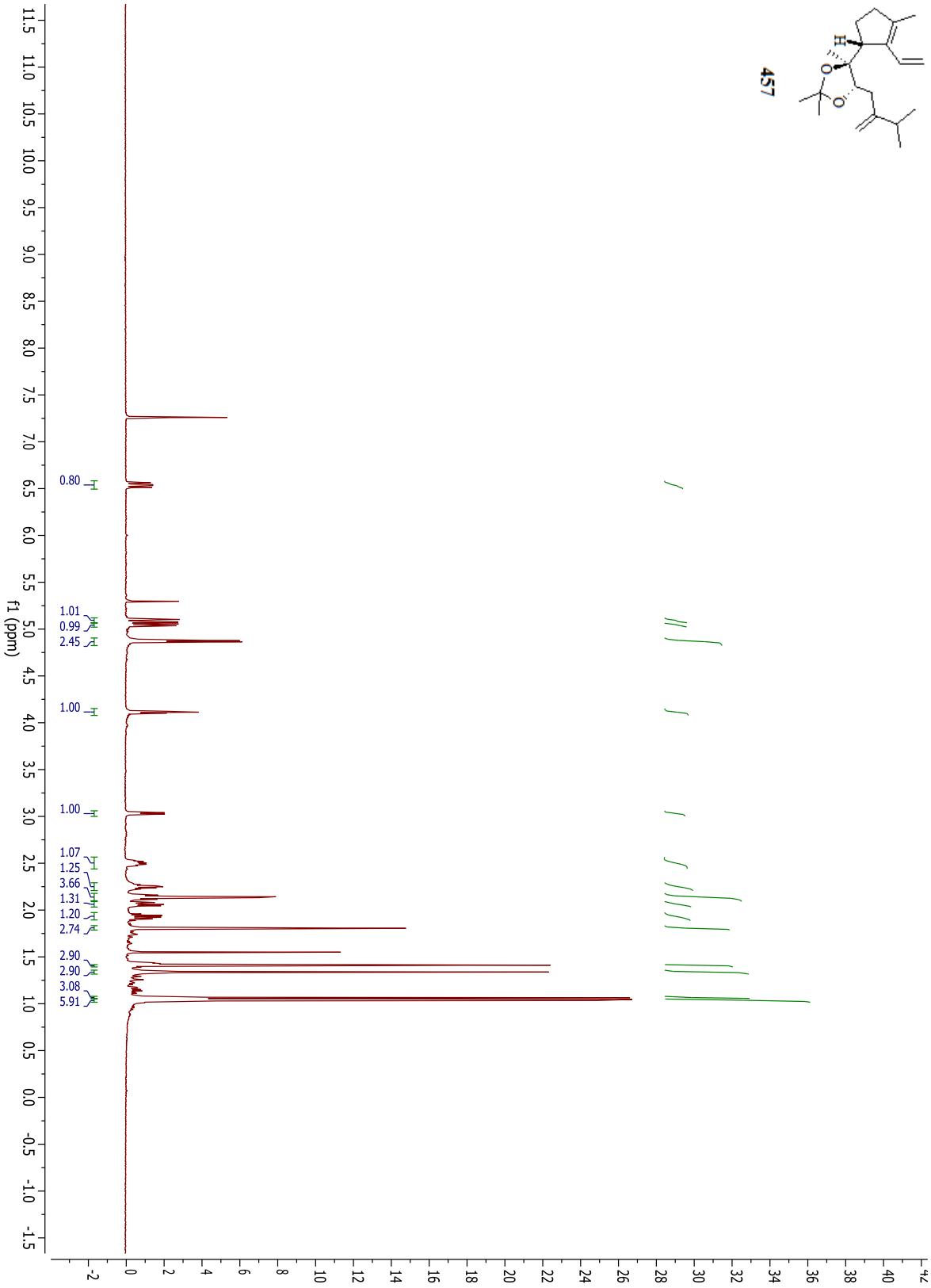

450
144.60
137.24
132.66
119.00
77.31 CDCl3
77.19 CDCl3
76.99 CDCl3
76.76
76.67
53.67
37.76
37.59
34.39
24.31
21.49
21.09
20.71
14.35
f1 (ppm)

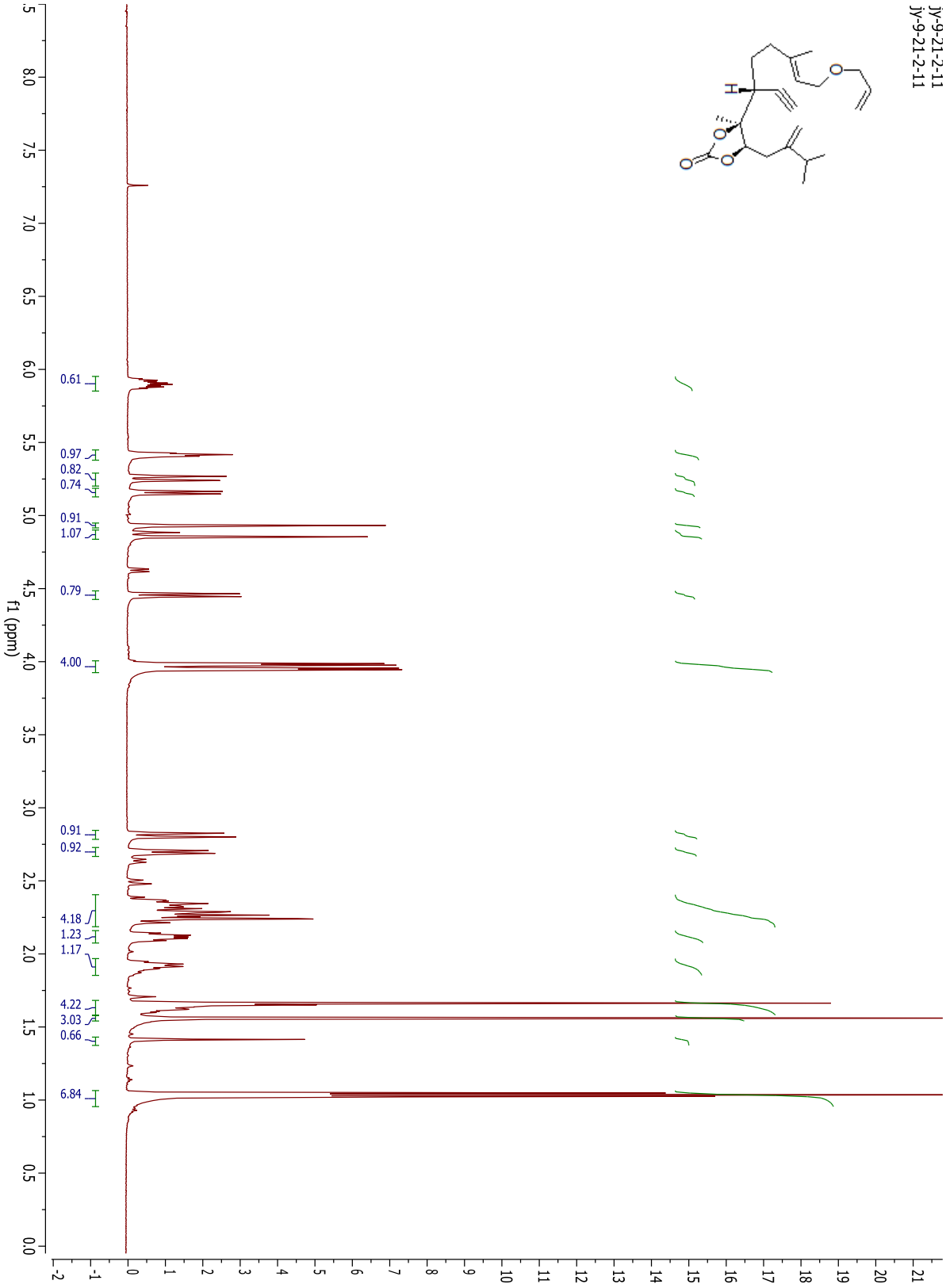

jy-8-19-2-11
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
453
0.75
0.69
1.18
1.45
1.64
6.66
0.64
1.14
3.12
0.72
1.82
3.00
8.22
5.73
f1 (ppm)

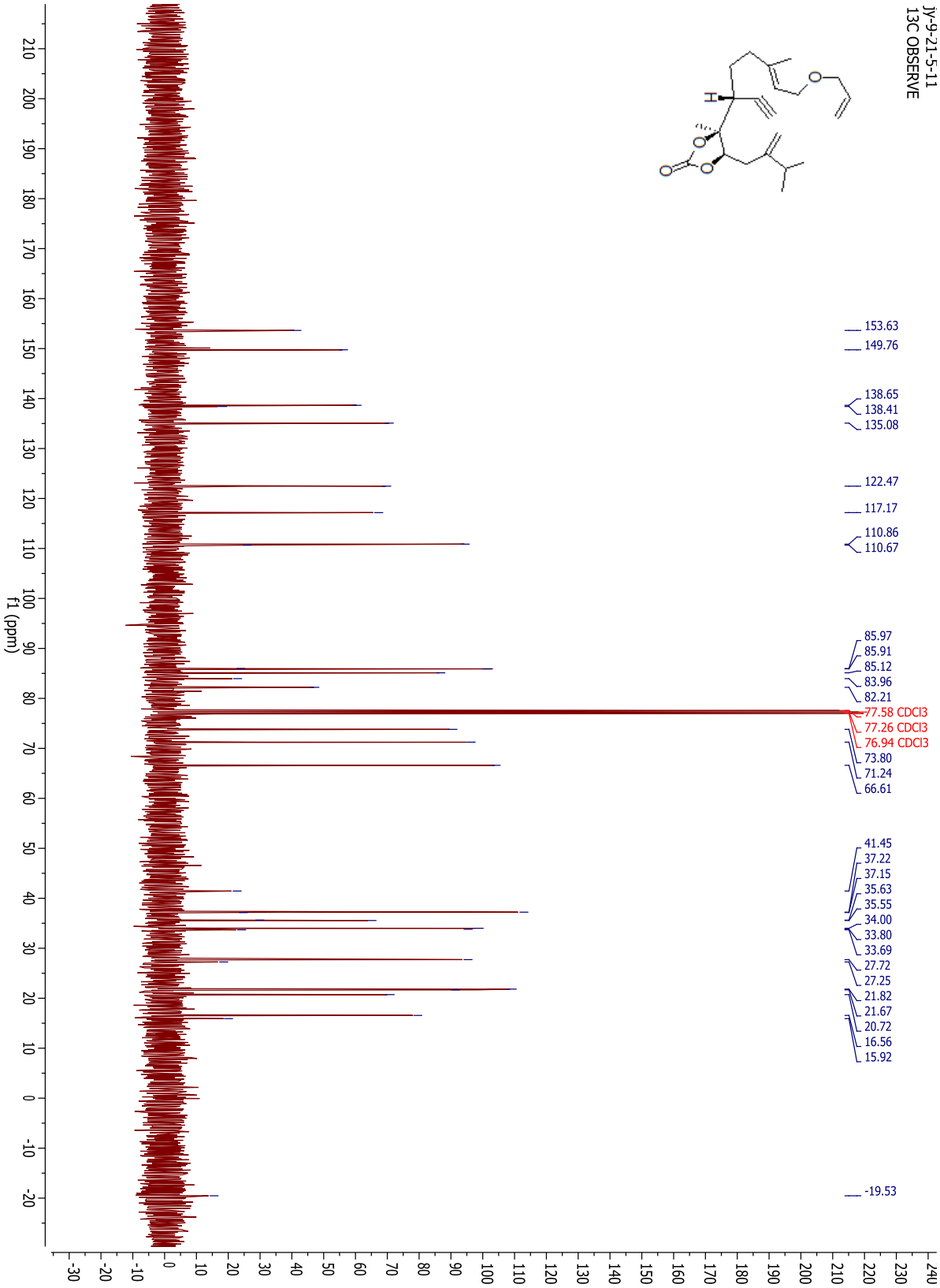

453
152.775
139.435
134.937
121.440
116.787
107.718
106.838
85.305
83.124
82.465
77.318
77.000
76.682
72.223
70.851
66.449
37.329
35.753
33.937
33.815
28.230
27.436
26.469
21.714
21.641
19.942
16.473
f1 (ppm)

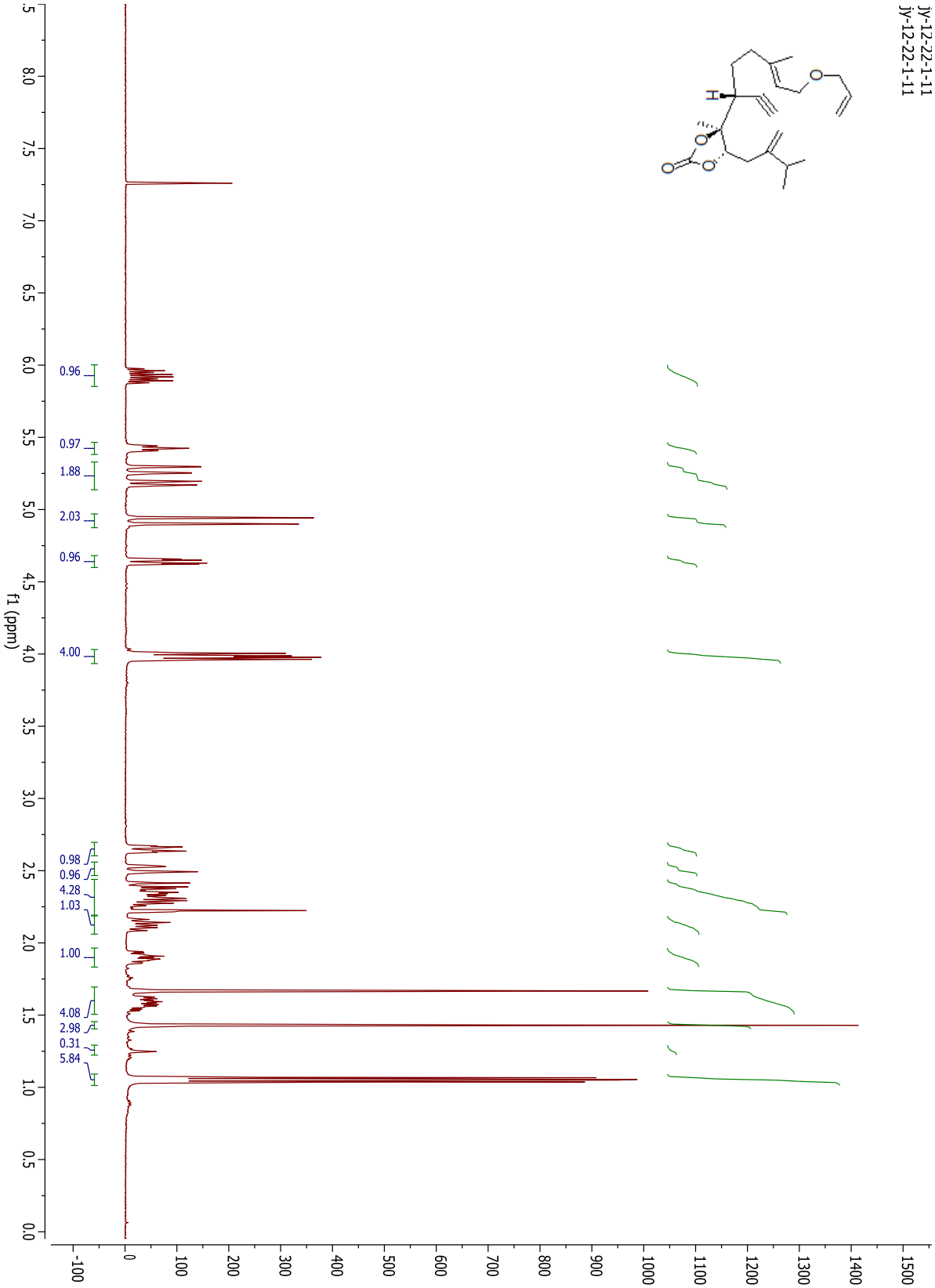

456
f1 (ppm)
1.00
1.17
1.05
1.10
0.97
1.11
0.96
4.14
1.04
1.41
2.81
1.09
1.67
3.17
0.81
2.72
2.76
2.34
3.30
3.28

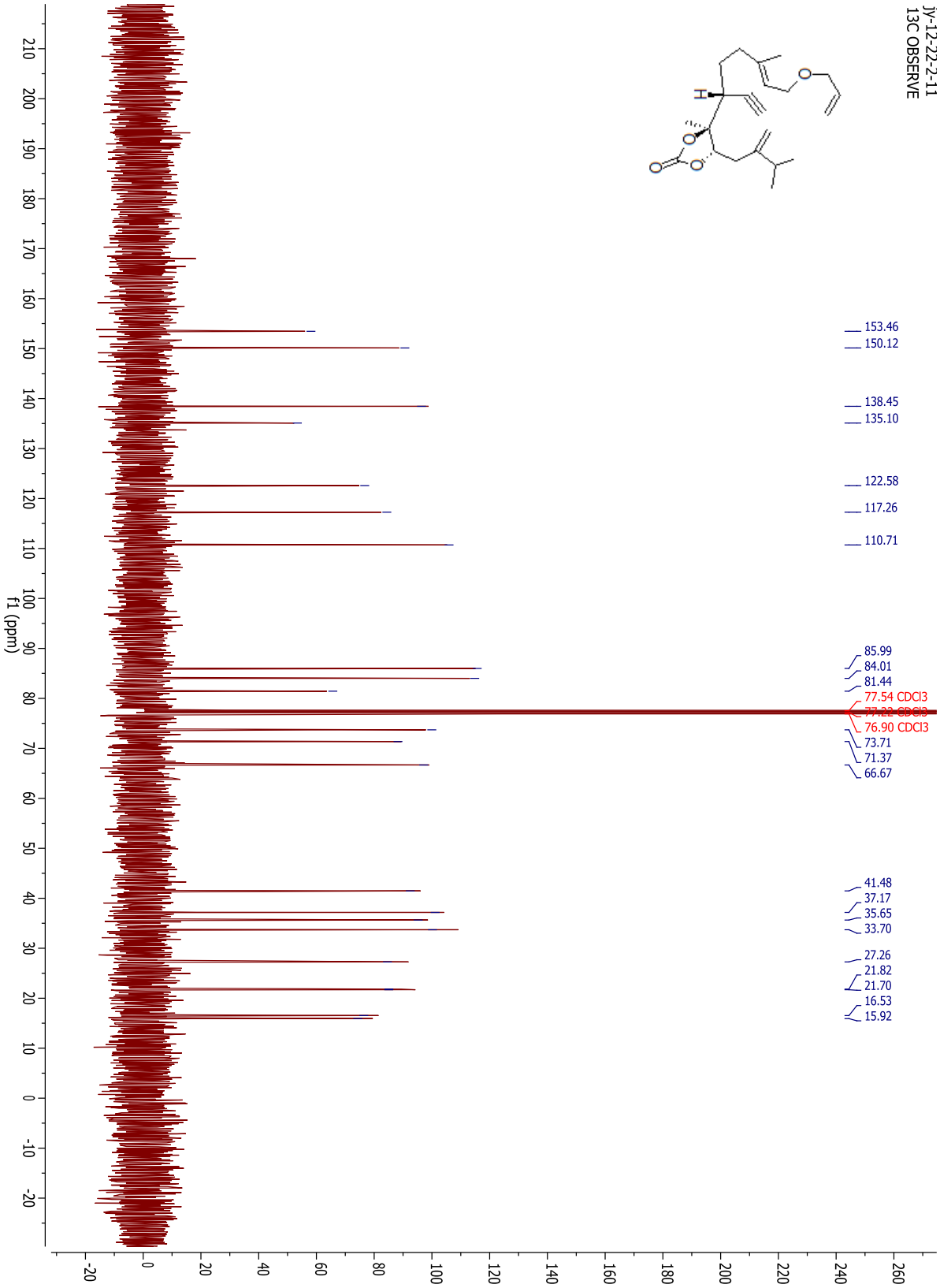

jy-7-4-8-11
STANDARD CARBON PARAMETERS
456
152.989
139.285
135.018
121.546
116.893
108.050
106.733
84.138
82.524
81.872
77.246 CDCl3
76.992 CDCl3
76.737 CDCl3
72.045
71.002
66.524
41.532
37.336
35.621
33.721
28.631
27.793
26.579
21.812
21.667
17.414
16.384
f1 (ppm)

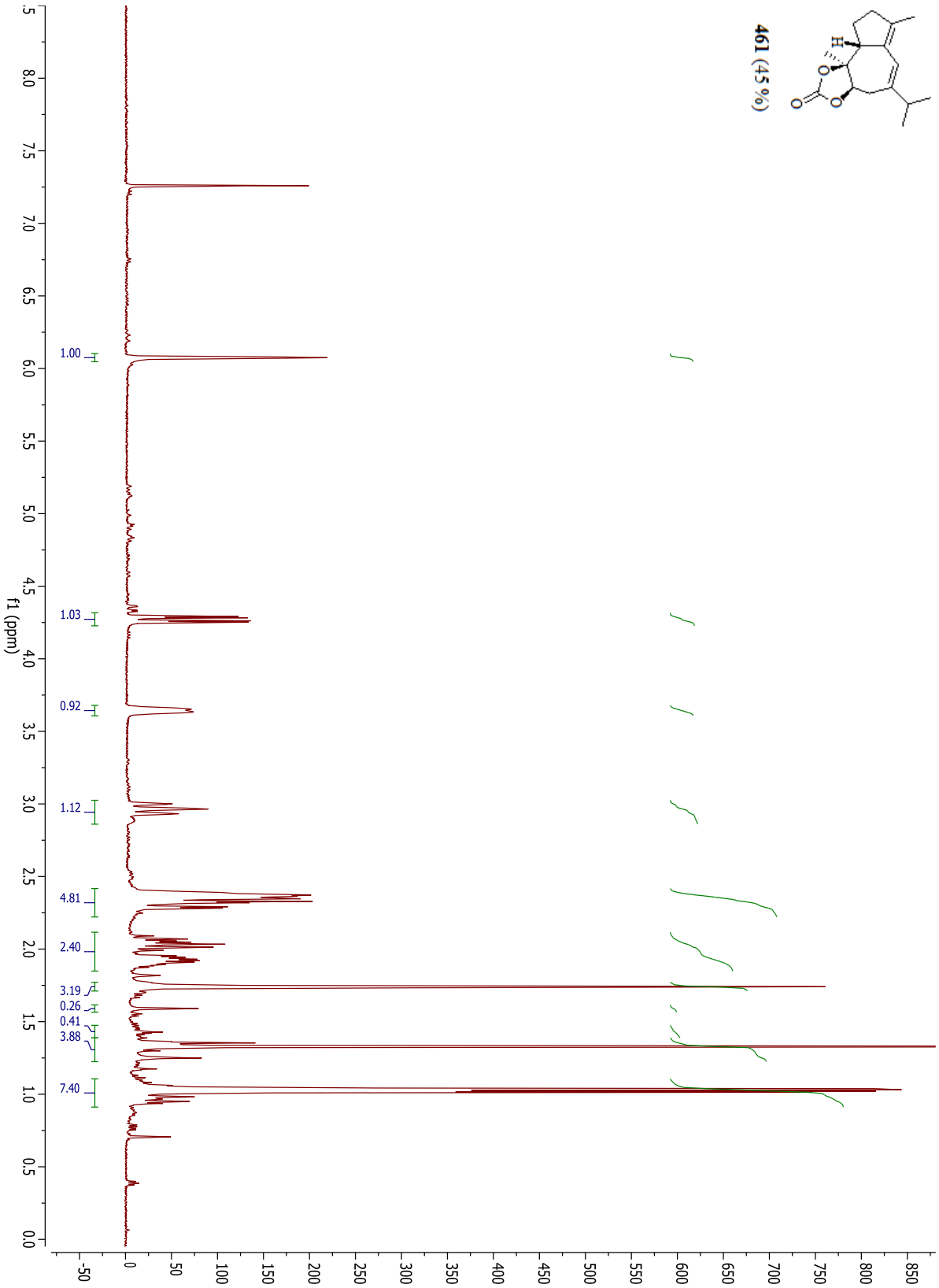

457
f1 (ppm)
0.80
1.01
0.99
2.45
1.00
1.00
1.07
1.25
3.66
1.31
1.20
2.74
2.90
2.90
3.08
5.91

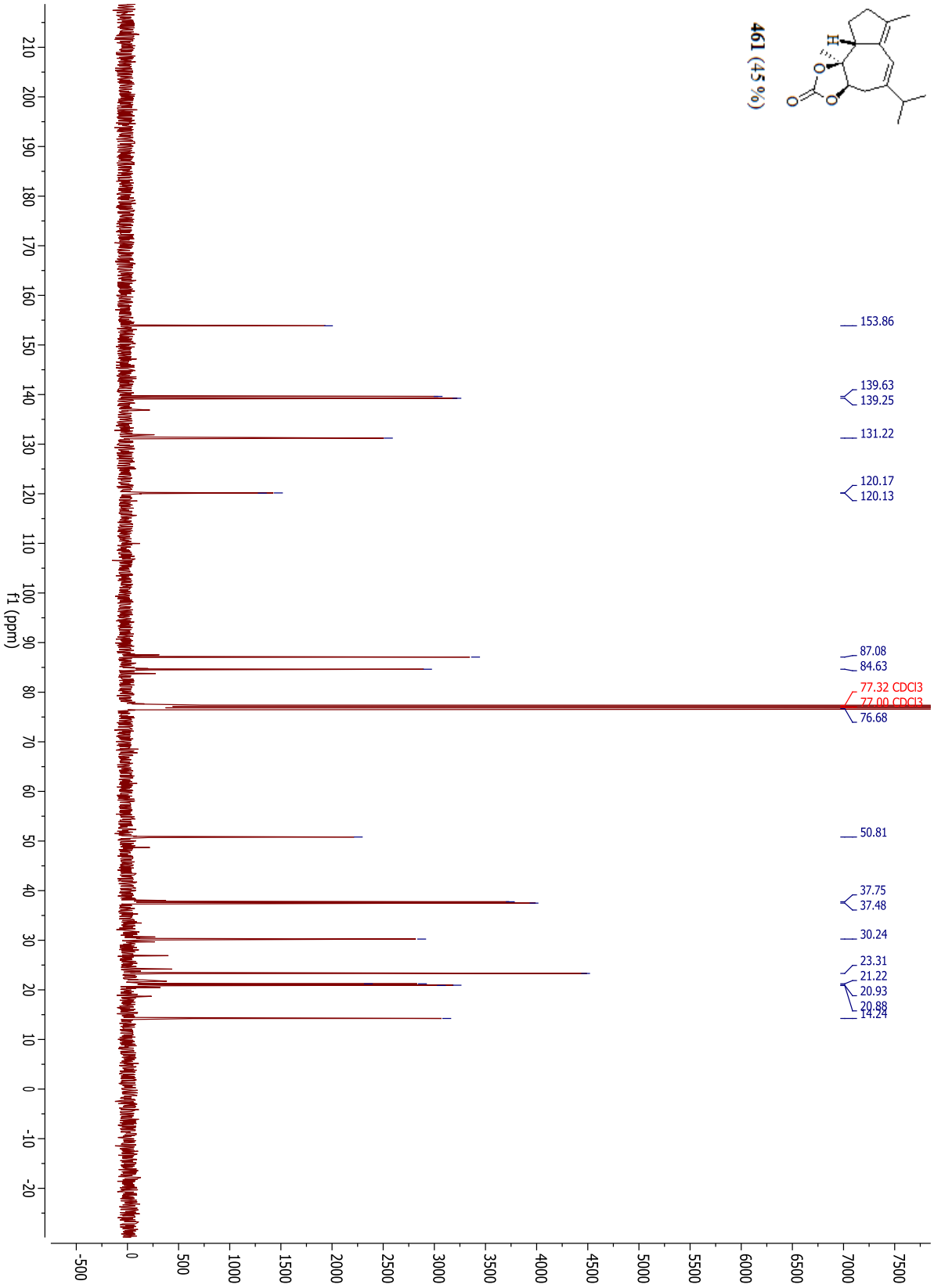

jy-9-21-2-11
jy-9-21-2-11
f1 (ppm)
0.61
0.97
0.82
0.74
0.91
1.07
0.79
4.00
0.91
0.92
4.18
1.23
1.17
4.22
3.03
0.66
6.84

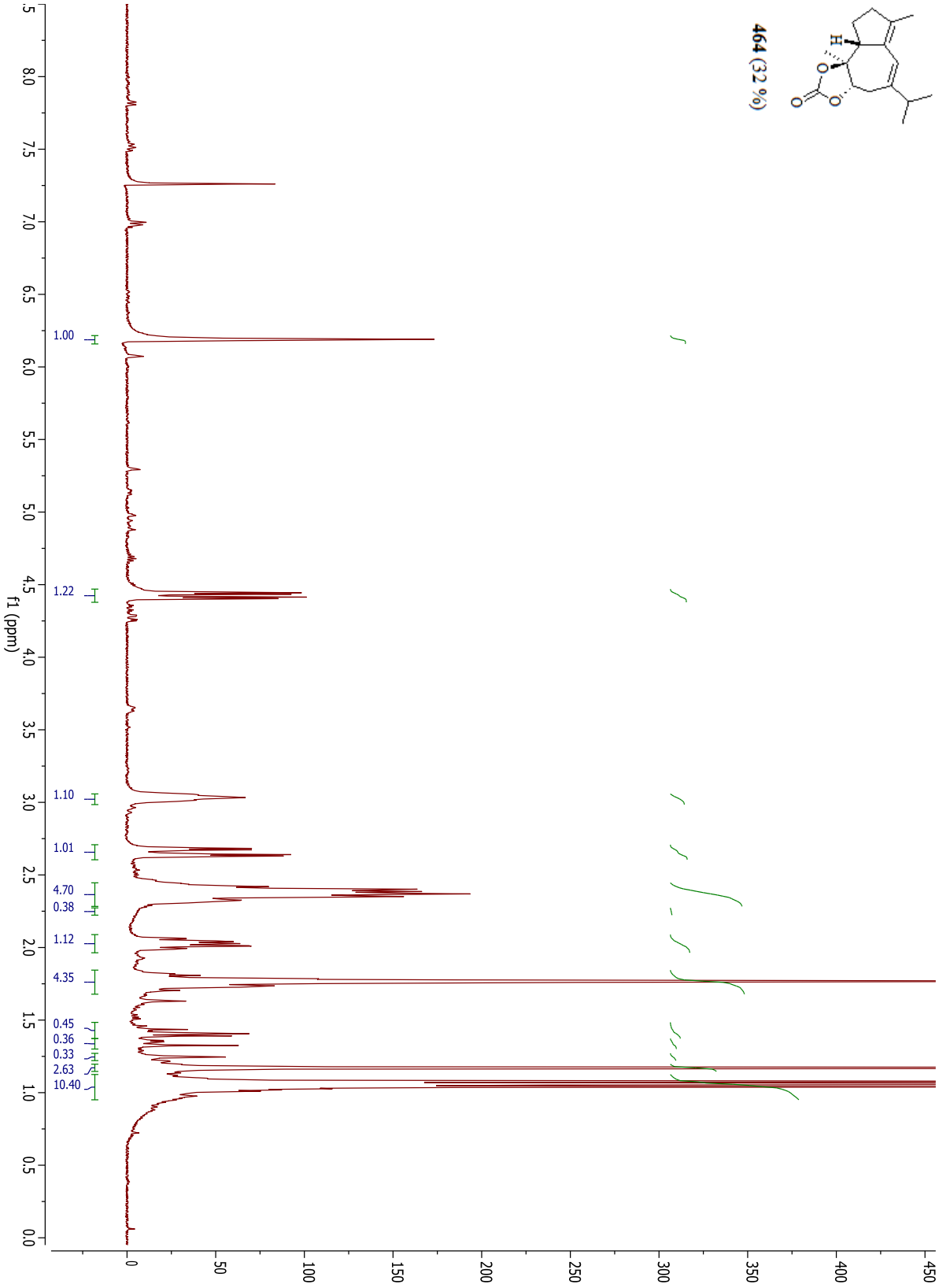

jy-9-21-5-11
13C OBSERVE
f1 (ppm)
153.63
149.76
138.65
138.41
135.08
122.47
117.17
110.86
110.67
85.97
85.91
85.12
83.96
82.21
77.58 CDCl3
77.26 CDCl3
76.94 CDCl3
73.80
71.24
66.61
41.45
37.22
37.15
35.63
35.55
34.00
33.80
33.69
27.72
27.25
21.82
21.67
20.72
16.56
15.92
-19.53

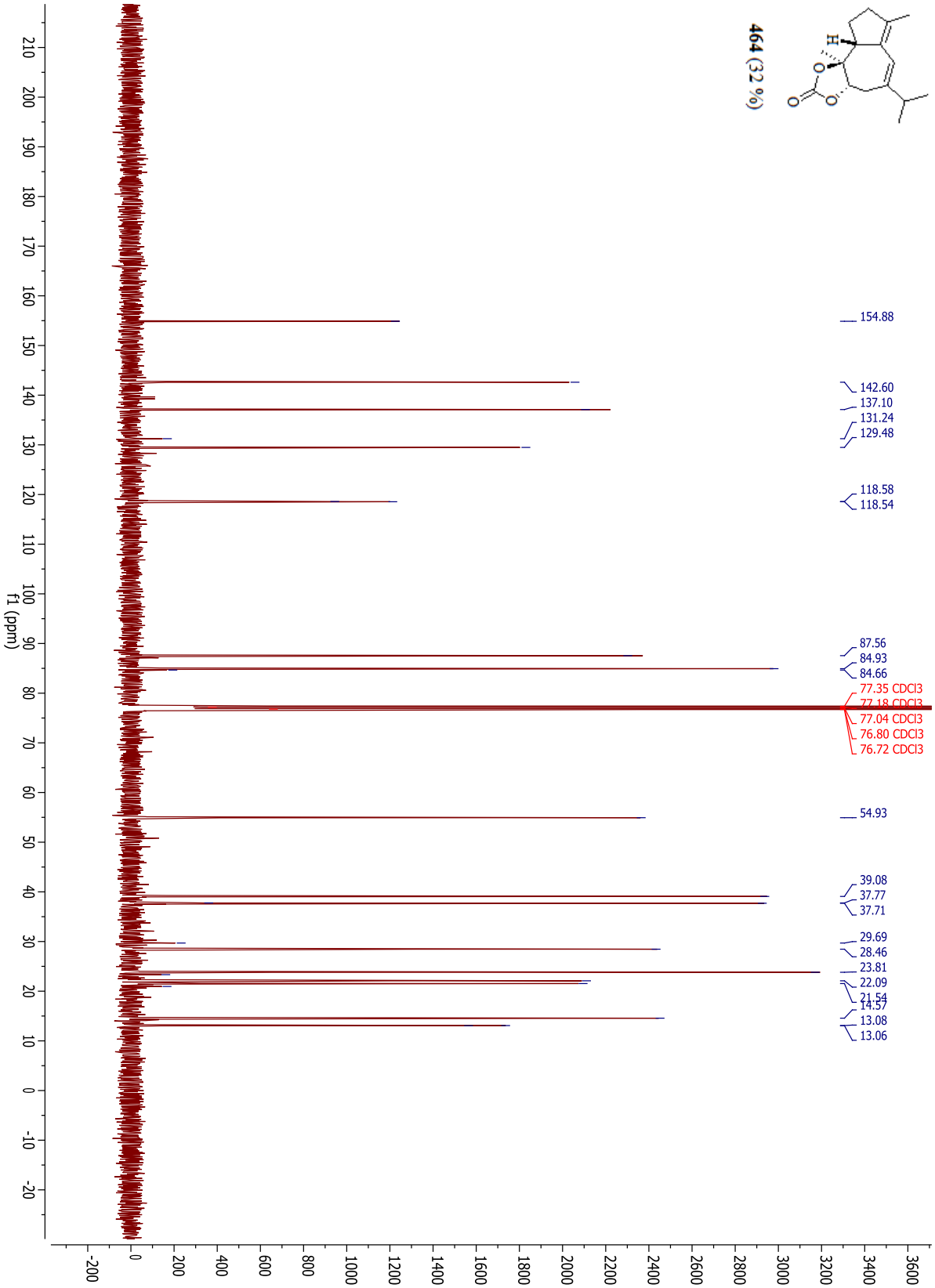

jy-12-22-1-11
jy-12-22-1-11
f1 (ppm)
0.96
0.97
1.88
2.03
0.96
4.00
0.98
0.96
4.28
1.03
1.00
4.08
2.98
0.31
5.84

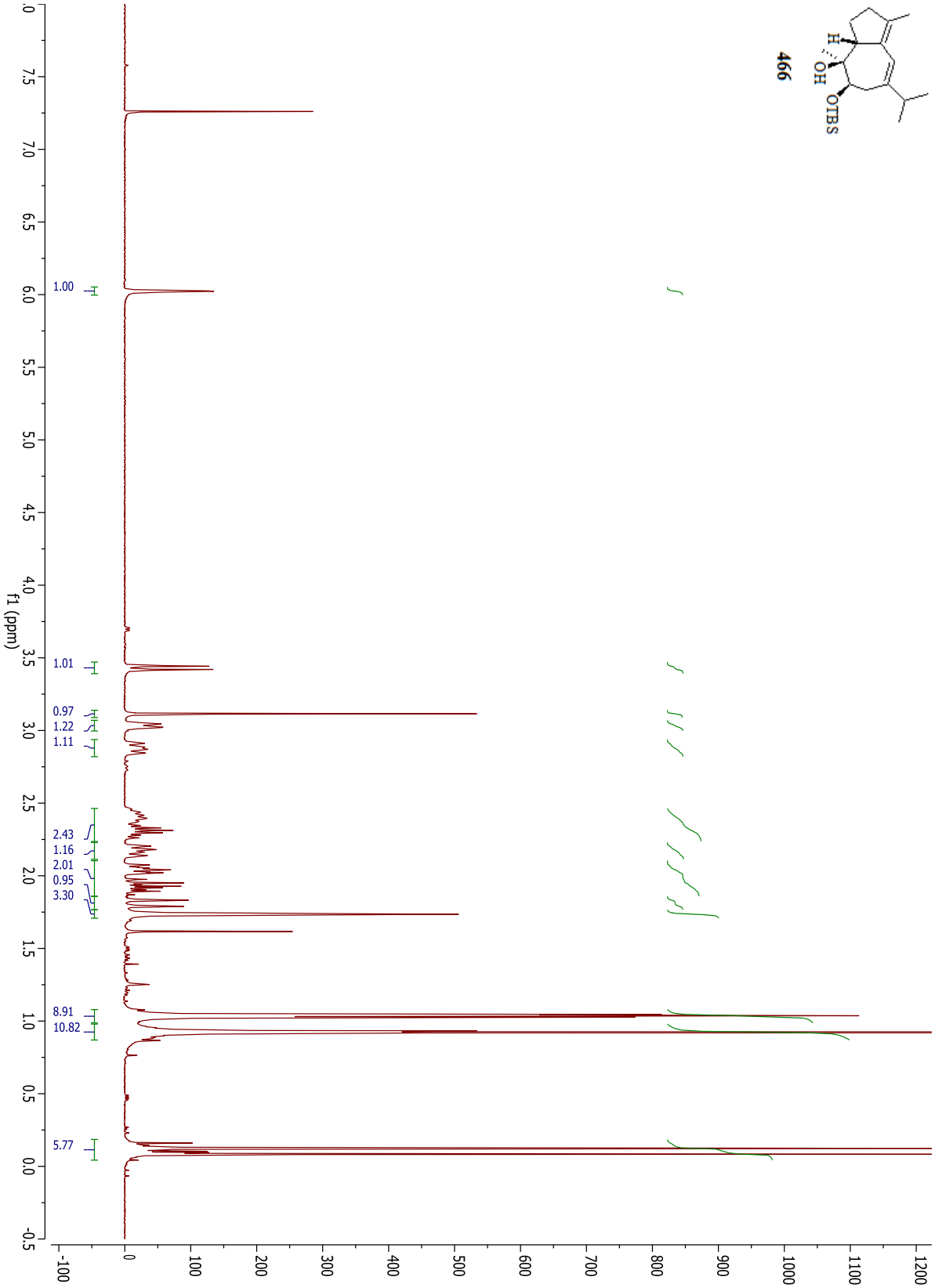

jy-12-22-2-11
13C OBSERVE
f1 (ppm)
153.46
150.12
138.45
135.10
122.58
117.26
110.71
85.99
84.01
81.44
77.54 CDCl3
77.22 CDCl3
76.90 CDCl3
73.71
71.37
66.67
41.48
37.17
35.65
33.70
27.26
21.82
21.70
16.53
15.92

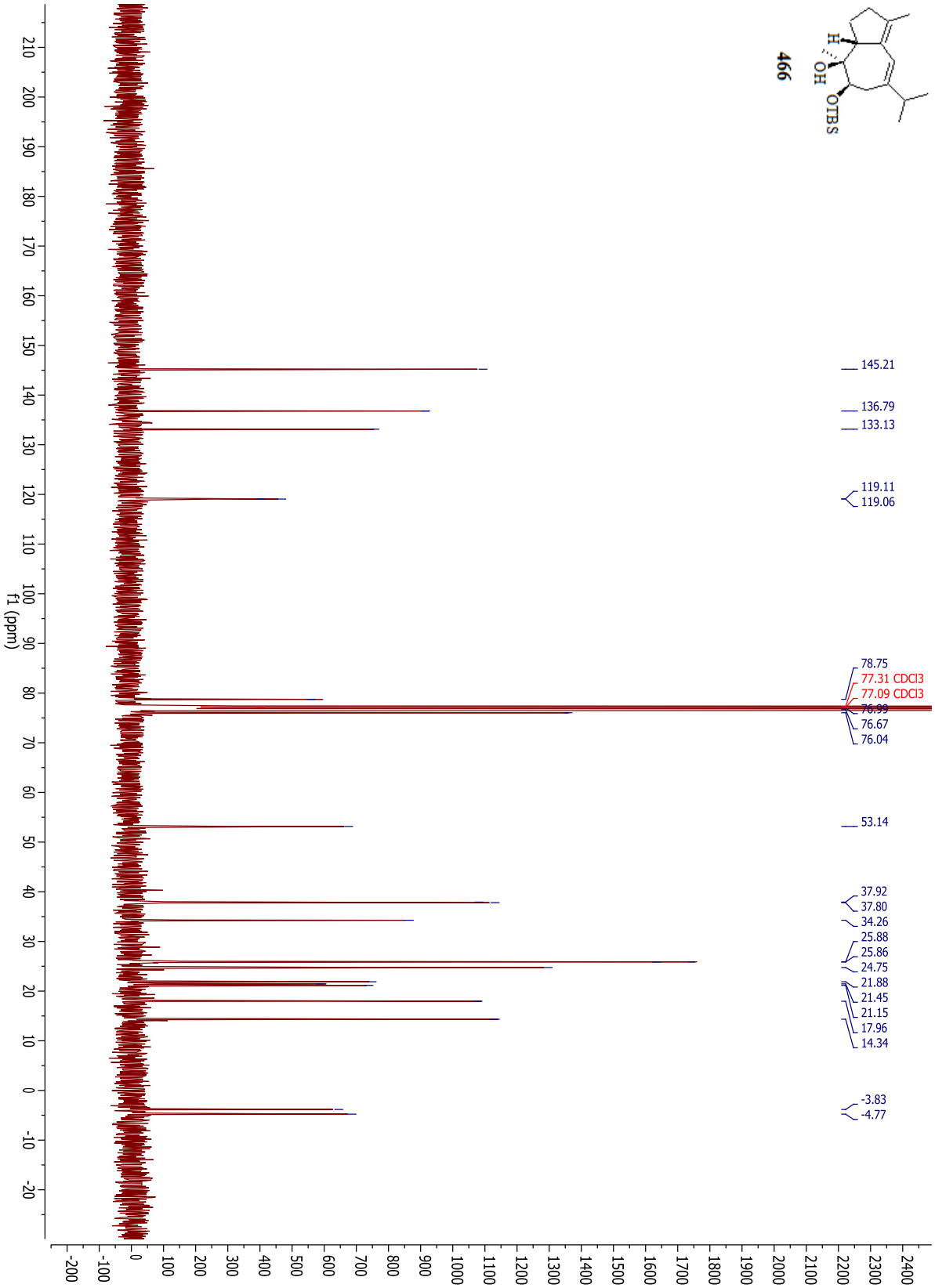

461 (45 %)
f1 (ppm)
1.00
1.03
0.92
1.12
4.81
2.40
3.19
0.26
0.41
3.88
7.40

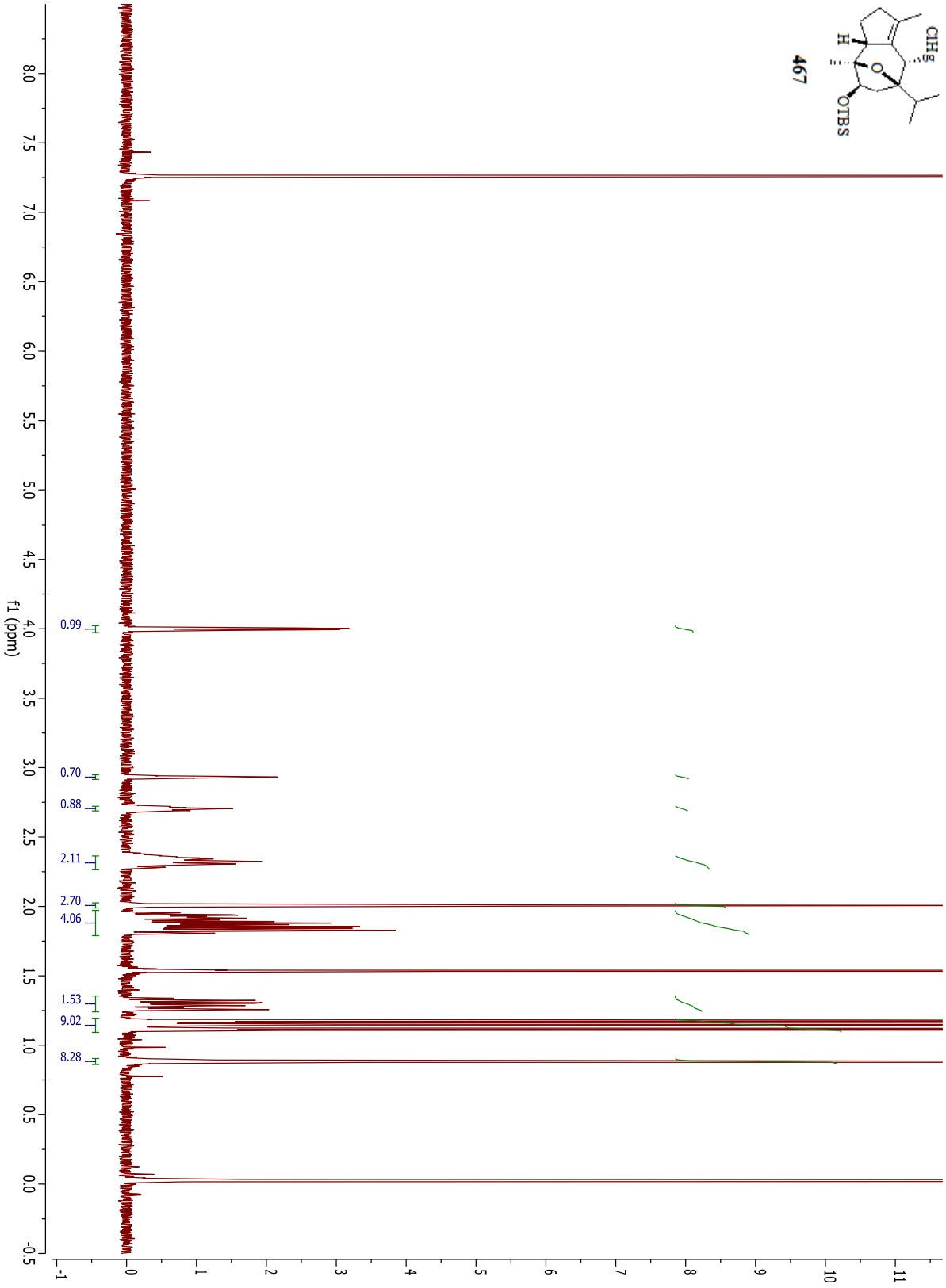

461 (45 %)
H
O
O
O
153.86
139.63
139.25
131.22
120.17
120.13
87.08
84.63
77.32 CDCl3
77.00 CDCl3
76.68
50.81
37.75
37.48
30.24
23.31
21.22
20.93
20.88
14.24
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-500
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
6000
6500
7000
7500

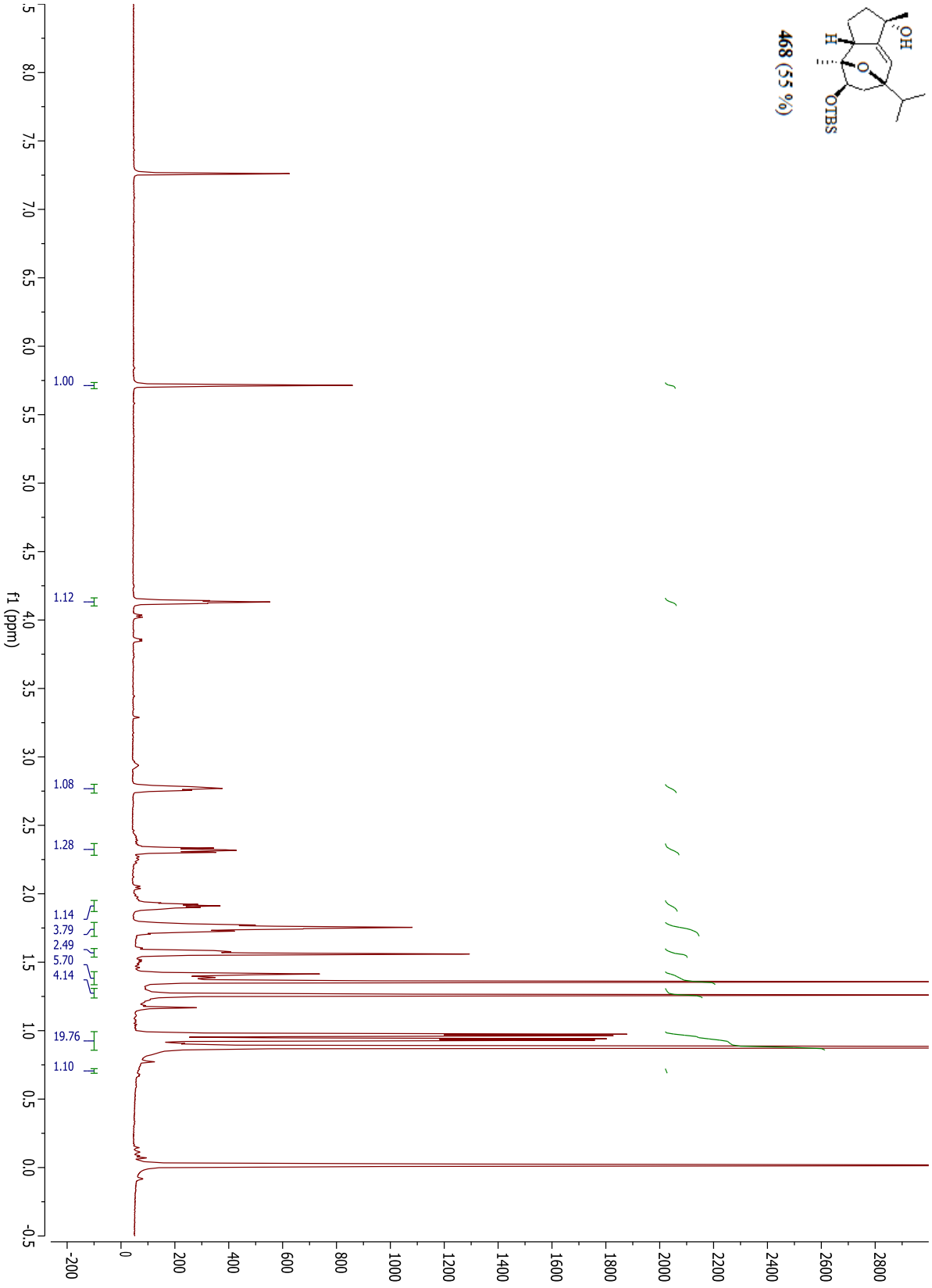

464 (32 %)
f1 (ppm)
1.00
1.22
1.10
1.01
4.70
0.38
1.12
4.35
0.45
0.36
0.33
2.63
10.40

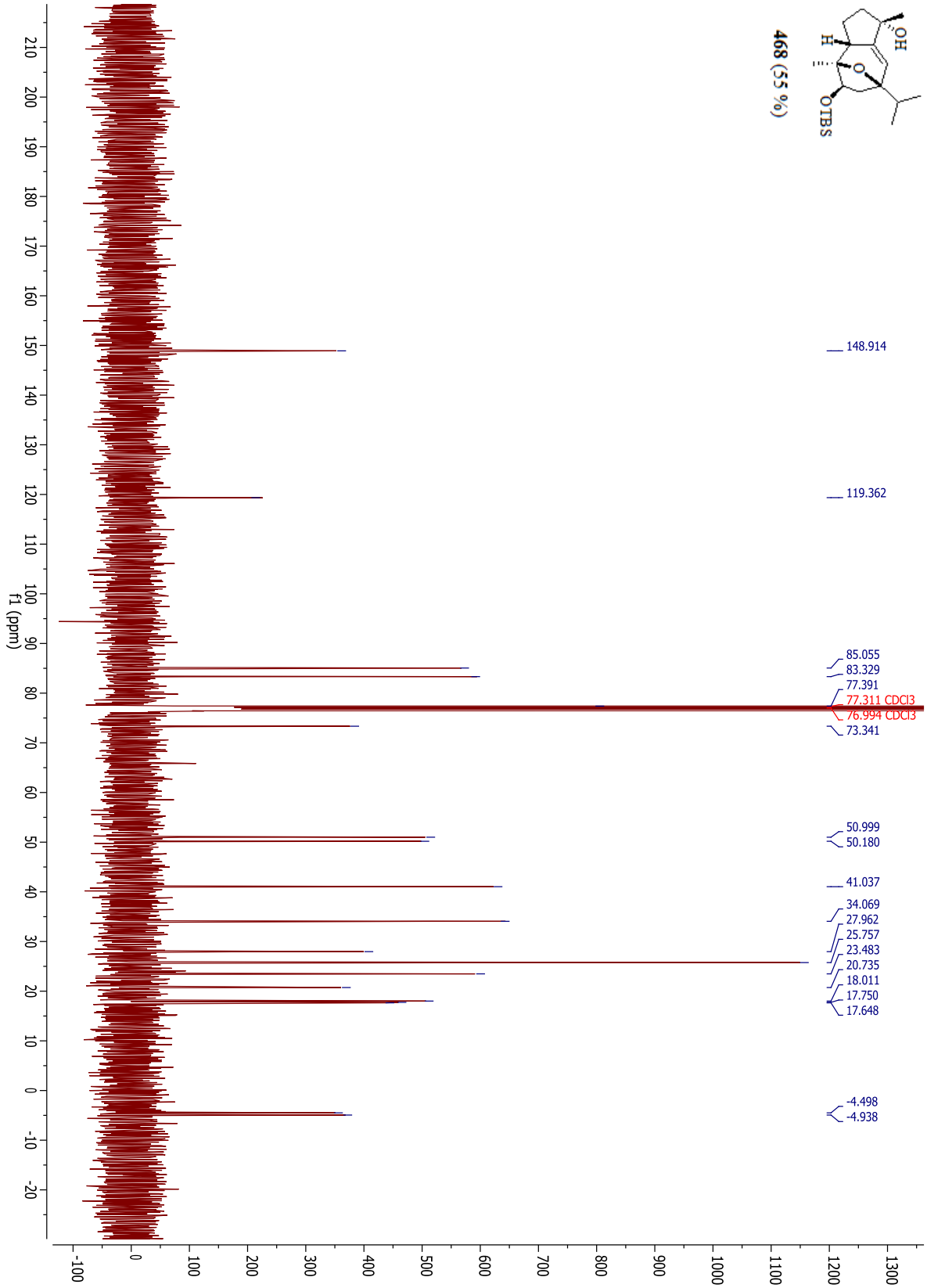

464 (32 %)
f1 (ppm)
154.88
142.60
137.10
131.24
129.48
118.58
118.54
87.56
84.93
84.66
77.35 CDCl3
77.18 CDCl3
77.04 CDCl3
76.80 CDCl3
76.72 CDCl3
54.93
39.08
37.77
37.71
29.69
28.46
23.81
22.09
21.54
14.57
13.08
13.06

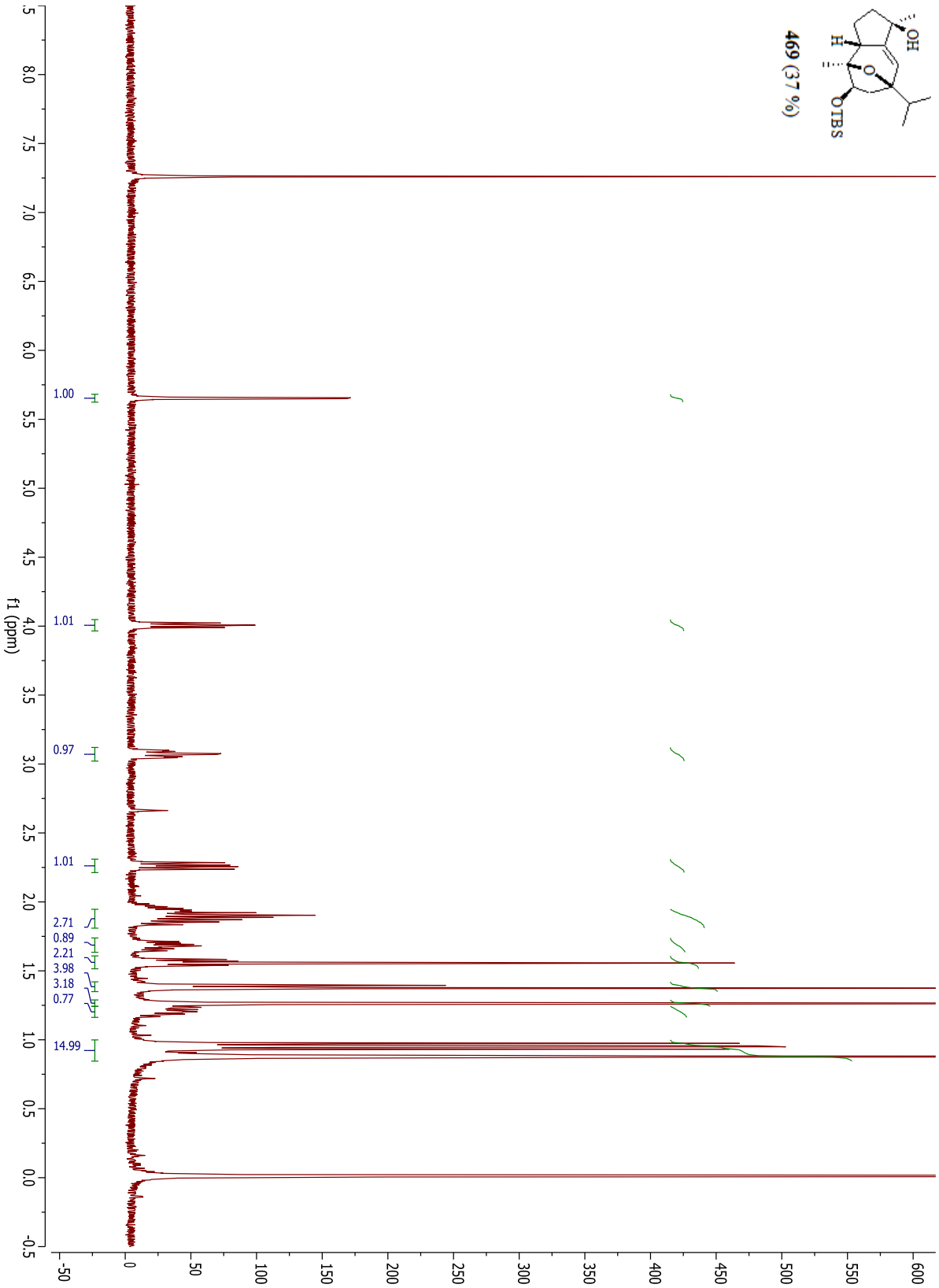

466
H
OH
OTBS
f1 (ppm)
1.00
1.01
0.97
1.22
1.11
2.43
1.16
2.01
0.95
3.30
8.91
10.82
5.77

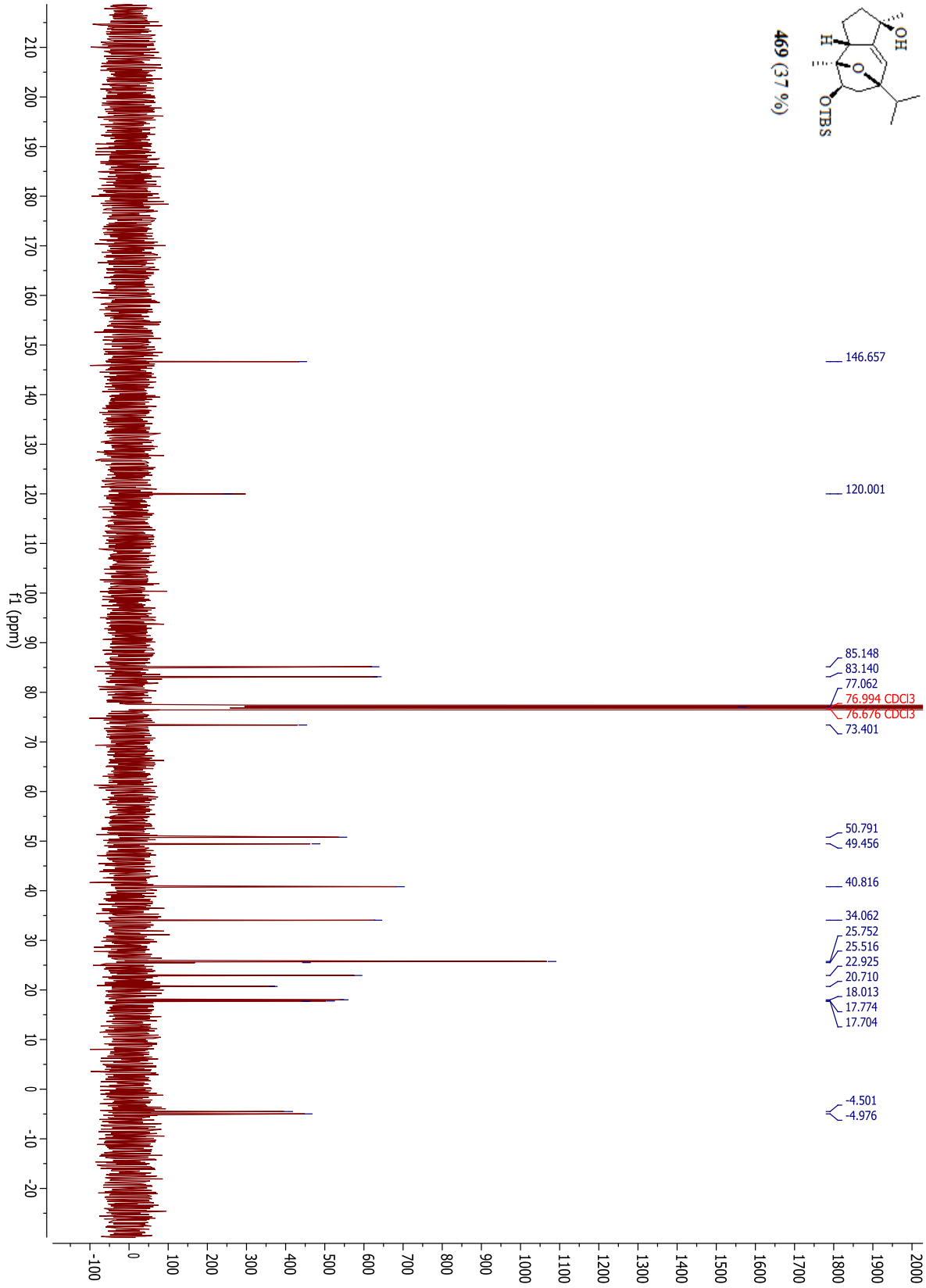

466
H
OH
OTBS
145.21
136.79
133.13
119.11
119.06
78.75
77.31 CDCl3
77.09 CDCl3
76.99
76.67
76.04
53.14
37.92
37.80
34.26
25.88
25.86
24.75
21.88
21.45
21.15
17.96
14.34
-3.83
-4.77
f1 (ppm)


467
ClHg
H
O
OTBS
f1 (ppm)
0.99
0.70
0.88
2.11
2.70
4.06
1.53
9.02
8.28


OH
H
O
OTBS
468 (55 %)
f1 (ppm)
1.00
1.12
1.08
1.28
1.14
3.79
2.49
5.70
4.14
19.76
1.10


468 (55 %)
OH
H
O
OTBS
f1 (ppm)
148.914
119.362
85.055
83.329
77.391
77.311 CDCl3
76.994 CDCl3
73.341
50.999
50.180
41.037
34.069
27.962
25.757
23.483
20.735
18.011
17.750
17.648
-4.498
-4.938


469 (37 %)
OH
H
O
OTBS
f1 (ppm)
1.00
1.01
0.97
1.01
2.71
0.89
2.21
3.98
3.18
0.77
14.99


469 (37 %)
OH
H
O
OTBS
f1 (ppm)
146.657
120.001
85.148
83.140
77.062
76.994 CDCl3
76.676 CDCl3
73.401
50.791
49.456
40.816
34.062
25.752
25.516
22.925
20.710
18.013
17.774
17.704
-4.501
-4.976