Gold-Catalyzed Synthesis of Heterocycles from Alkynyl Ethers. Synthesis of Leucascandrolide A. Mechanistic Analysis of Oxidative C–H Cleavages using Inter- and Intramolecular Kinetic Isotope Effects.

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ABSTRACT

Gold-Catalyzed Synthesis of Heterocycles from Alkynyl Ethers.

Synthesis of Leucascandrolide A.

Mechanistic Analysis of Oxidative C–H Cleavages using Inter- and Intramolecular Kinetic Isotope Effects.

Hyung Hoon Jung, PhD

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Gold complexes catalyze the cyclyzation of homopropargylic ethers to prepare saturated hetercyclic ketones through a sequence of alkyne hydration, alkoxy elimination, and intramolecular conjugate addition of pendant oxygen or nitrogen nucleophiles. This reaction was used in an efficient total synthesis of the natural product andrachcinidine. Regioselective hydration of internal alkynes on propargylic ethers rather than homopropargylic ethers expanded the scope of products. Leucascandrolide A was synthesized through an Electron Transfer-Initiated Cyclization (ETIC) reaction as a key step. The reaction sequence also had highlights as stereoselective $BiBr_3$-mediated allylation, acetal formation as a fragment-coupling reaction, and a rhenium-mediated allylic alcohol transposition leading to stable macrolactol formation. Intra- and intermolecular kinetic isotope effects of oxidative carbon-hydrogen bond cleavage in DDQ-mediated cyclization reations were also explored. The carbon-hydrogen cleavage is rate determining and that a radical cation is most likely a key intermediate in the reaction mechanism.

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LIST OF ABBREVIATIONS

Ac = Acetyl
Acac = Acetylacetonate
Ar = Aryl
BINOL = 1,1'-Bi-2-naphthol
^{t}Boc = *tert*-Butoxycabonyl
Bn = Benzyl
Bu = Butyl
CAN = Ceric Ammonium Nitrate
Cbz = Carbobenzyloxy
CSA = Camphorsulfonic Acid
Cy = Cyclohexyl
DABCO = 1,4-Diazabicyclo[2.2.2]octane
dba = Dibenzylidene Acetone
DCC = Dicyclohexyl Carbodiimide
DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD = Diisopropyl Azadicarboxylate
DIBAL = Diisobutylaluminum Hydride
DMAP = 4-Dimethylaminopyridine
DMF = Dimethylformamide
DMP = Dess-Martin Periodinane
DMS = Dimethylsulfide
DMSO = Dimethylsulfoxide
DTBAD = Di-*tert*-butylazodicaboxlate
EDCl = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI = Electron Ionization
ESI = Electrospray Ionization
Et = Ethyl
ETIC = Electron Transfer-Initiated Cyclization
Fmoc = 9-Fluorenylmethyloxycarbonyl
Fur = Furyl
GC = Gas Chromatography
HMPA = Hexamethylphosphorictriamide
HRMS = High Resolution Mass Spectrometry
HOBt = Hydroxybenzotriazole
Ipc = Isopinocamphenyl
KHMDS = Potassium Hexamethyldisilazide
L.A. = Lewis Acid (generic)
LAH = Lithium Aluminium Hydride
LDA = Lithium Diisopropylamide
mCPBA = *meta*-Chloroperoxybenzoic acid
Me = Methyl
MOM = Methoxymethyl

MS = Molecular Sieves
NMO = *N*-Methylmorpholine-*N*-Oxide
NMR = Nuclear Magnetic Resonance
NOESY = Nuclear Overhauser Enhancement Spectroscopy
NR = No Reaction (generic)
Ns = Nitrobenzenesulfonyl
PCC = Pyridinium Chlorochromate
PDC = Pyridinium Dichromate
PG = Protecting Group (generic)
Ph = Phenyl
PMB = *para*-Methoxybenzyl
PMP = *para*-Methoxyphenyl
PPTS = Pyridinium *p*-Toluenesulfonate
Pr = Propyl
Py = Pyridyl
R = Alkyl Chain (generic)
RT = Room Temperature
Salen = *N*,*N'*-Ethylenebis(salicylimine)
TBAF = Tetra-*n*-butylamonium Fuoride
TBDPS = *tert*-Butyldiphenylsilyl
TBS = *tert*-Butyldimethylsilyl
TCC = *trans*-2-(*α*-Cumyl)cyclohexyl
Tf = Trifluoromethanesulfonyl
THF = Tetrahydrofuran
TIPS = Triisopropylsilyl
TMS = Trimethylsilyl
Ts = Toluenesulfonyl

PREFACE

For Hye Yong, Soomin, and Yoomin

1.0 Gold-Catalyzed Synthesis of Heterocycles from Alkynyl Ethers: Application to the Total Synthesis of Andrachcinidine

1.1 Introduction

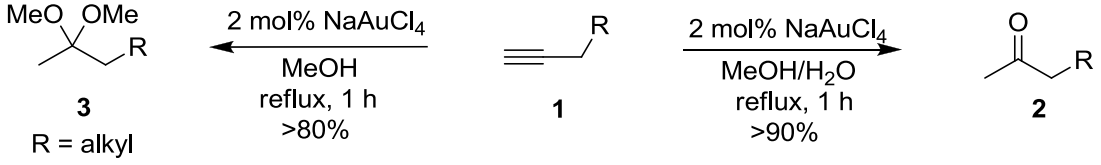
1.1.1 General

A wide range of naturally occurring and biologically active molecules contain saturated heterocycles as structural component. For example, tetrahydropyrans are present in several cytotoxins,[1] tetrahydrofuran subunits are located in the annonaceous acetogenins,[2] and larger oxygen-containing rings are components of the marine ladder toxins.[3] Particularly, substituted piperidine rings are common structural features in numerous alkaloids[4] and serve as attractive scaffoldings for medicinal agents because of their ability to be converted to derivatives such as sulfonamides and carbamates that project functional groups into various spatial arrangements for binding to biological targets. Consequently, the development of new and efficient preparation methods for saturated heterocycles with high chemo- and stereoselectivity continues to be an important objective in organic synthesis.

1.1.2 Gold catalysis in activation of alkynes and alkenes

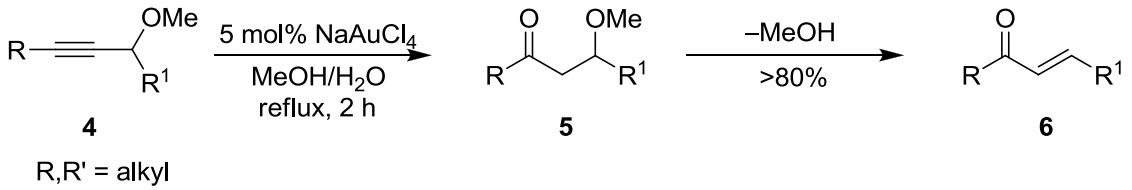
Alkene and alkyne activation by electrophilic transition metal catalysts is proving to be a successful strategy for achieving this objective, with gold reagents proving to be exceptionally effective and versatile. Gold catalysts complement classical transition metal catalysts, such as palladium and platinum, because of their opposite properties: gold compounds are easily reduced, and do not tend to undergo β-hydride elimination.[5]

In 1991, Utimoto and coworkers showed that $NaAuCl_4$ promoted the hydration of alkynes **1** to form ketones **2** in excellent yield in a methanol/water mixture at reflux; however, when pure methanol was used as the solvent, dimethylacetals **3** were isolated (Scheme 1).[6] Of note in this process is that hydration occurs with complete regiocontrol (Markovnikov's rule).



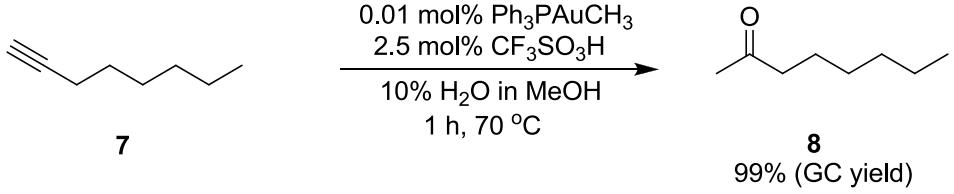
Scheme 1. Gold-catalyzed hydration of terminal alkyne.

Furthermore, they observed that the ether group directed the nucleophile to the remote carbon for propargylic ethers **4**, and consequently the β-alkoxy ketone **5** was formed. α,β-Unsaturated ketone **6** was obtained after the elimination of alcohol (Scheme 2).[7]



Scheme 2. Gold-catalyzed hydration of internal alkyne.

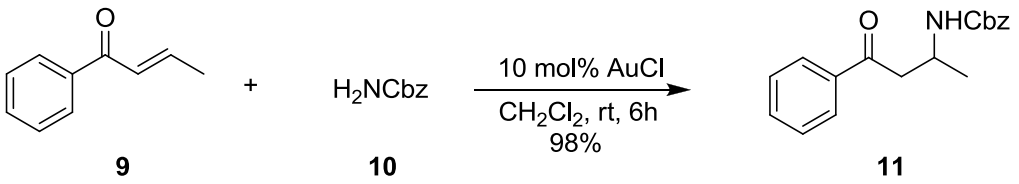
Cationic gold(I)-catalyzed alkyne hydration was reported by Tanaka and coworkers in 2002.[8] The cationic gold(I) complexes, first developed by Teles and coworkers,[9] can be generated *in situ* by protonation of Ph_3PAuCH_3 with a strong acid (e.g., H_2SO_4, CF_3SO_3H, CH_3SO_3H, $H_3PW_{12}O_{40}$, or HBF_4). Only 0.01 mol% of the gold catalyst, in the presence of CF_3SO_3H, was sufficient for alkyne hydration (Scheme 3). Control experiments showed that the reaction did not proceed in the absence of either the gold complex or Brønsted acids.



Scheme 3. Gold(I)-catalyzed hydration of alkyne.

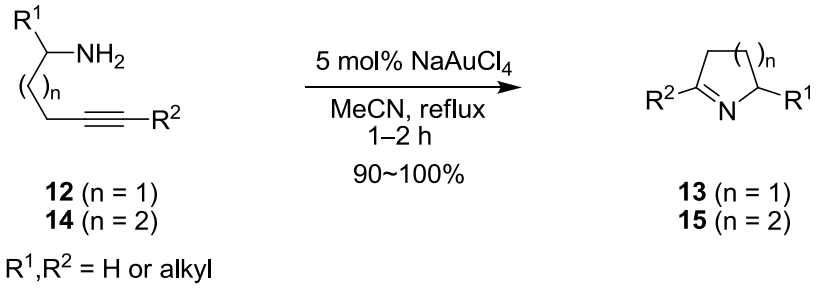
Kobayashi and coworkers surveyed the catalytic activity of various transition metal salts and reported that AuCl and $AuCl_3 \cdot 2H_2O$ were effective catalysts for the intermolecular addition of carbamates **10** to enone **9** at room temperature (Scheme 4).[10] On the other hand, the conventional oxophilic Lewis acids, such as $BF_3 \bullet OEt_2$, $AlCl_3$, $SnCl_4$, and $TiCl_4$.were found to be

less effective for this transformation.



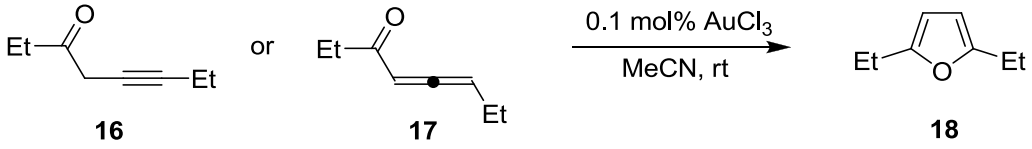
Scheme 4. Gold-catalyzed 1,4-addition.

Utimoto and co-workers also reported gold-catalyzed intramolecular hydroaminations. 2,3,4,5-Tetrahydropyridine **13** and dihydro-3*H*-pyrrole **15** can be obtained in two steps: the nucleophilic addition of the amino group to the alkyne followed by the tautomerization of the enamine intermediate to the imine product. In contrast to palladium-catalyzed reactions that proceed to give the expected products in moderate yields with the lack of regioselectivity,[11] $NaAuCl_4$ gave pyridines and pyrroles in quantitative yield within 1–2 hour(s) (Scheme 5).[12]



Scheme 5. Gold-catalyzed formation of C−N bond.

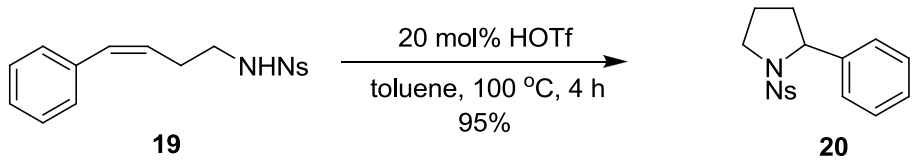
Hashmi and coworkers reported the cycloisomerization of propargyl ketones **16** and allenyl ketones **17** in presence of $AuCl_3$ to form furans **18** (Scheme 6).[13] This type of reaction had already been described as silver(I)-catalyzed process by Marshall and coworkers (typical reaction condition: 20% catalyst, reflux in acetone and a reaction time of several hours);[14] however, gold salts are significantly more active catalysts, which is confirmed by the observation that quantitative yields are obtained after a few minutes at room temperature and that only 0.1 mol% of catalyst is required.



Scheme 6. Gold-catalyzed formation of C−O Bond.

1.1.3 Controversy between Brønsted acid and transition metal catalysts

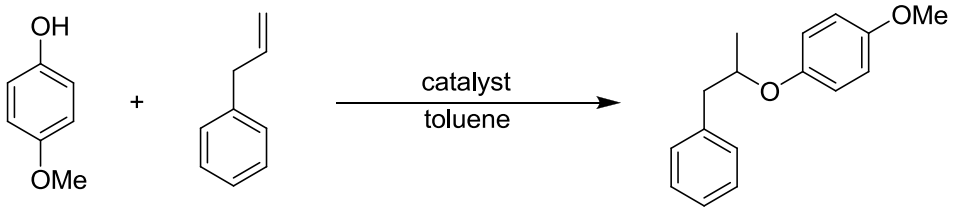
Brønsted acid catalysts are attractive as economical and environmentally benign reagents for many transformations. In 2002 a Brønsted acid-catalyzed intramolecular hydroamination was reported by Hartwig and coworkers.[15] In the course of their studies on the palladium-catalyzed cyclization of sulfonamides in the presence of trifluoromethanesulfonic acid (HOTf), they found the reactions occurred in the absence of palladium to give pyrrolidine **20** (Scheme 7). According to their mechanistic studies, the protonation of sulfonamide group was the first stage for cyclizations.



19 **20**

Scheme 7. Brønsted acid-catalyzed intramolecular hydroamination.

Four years later, He and co-workers also reported that Brønsted acids can efficiently catalyze the addition of nucleophiles (Scheme 8),[16] which were identical to those subjected to previous gold(I)-catalyzed addition reactions.[17] They proposed that the alkene was directly protonated by HOTf to form a carbocation which was subsequently trapped by nucleophiles. This statement might be controversial because Hartwig and co-workers observed no isomerization of the *Z*-olefin to *E*-olefin under their reaction condition (Scheme 7). Both groups had strong experimental results and observations to verify their hypotheses and the issue is still unresolved.



21 **22** **23**

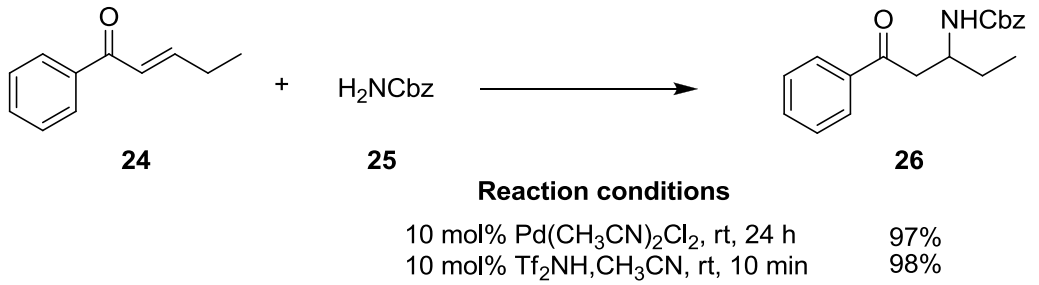
catalyst	temp	yield
5 mol% $Ph_3PAuOTf$	85	71%
2 mol% HOTf	RT	57%
5 mol% $Ph_3PAuOTf$*	RT	NR

*catalyst was pre-incubated at 85 °C in toluene overnight with or without **21**

Scheme 8. Intermolecular addition of nucleophile to alkene.

These groups also studied whether the gold-mediated reactions had been actually catalyzed by a Brønsted acid that was generated *in situ* from the reaction of gold with nucleophile. Pre-incubated $Ph_3PAuOTf$ that was prepared by heating overnight in toluene with or without **21**, could not promote the reaction at room temperature at which 2 mol% HOTf was sufficient to yield **23**. Based upon a series of control experiments, they postulated that Brønsted acids could not serve as the catalyst in gold-mediated reactions.

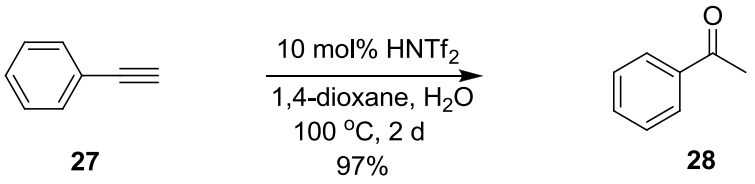
In 2001 Spencer and coworkers reported palladium-catalyzed aza-1,4-addition reaction with carbamate nucleophiles.[18] Later, they revealed that strong Brønsted acids, such as Tf_2NH, CF_3SO_3H, and HBF_4OMe_2, were also efficient to catalyze aza-, oxy-, and thio-1,4-addition reactions (Scheme 9),[19] though weaker acids, such as CH_3COOH, CF_3COOH, and HCl, did not promote 1,4-addition reactions.



Scheme 9. Palladium *vs* Brønsted acid-catalyzed 1,4-addition.

Although H_2SO_4-mediated alkyne hydration has been reported,[20] the need of a large excess of H_2SO_4 limits its synthetic utility. In 2000, Shirakawa and coworkers reported that 10 mol% of strong Brønsted acids such as Tf_2NH and TfOH promote the catalytic hydration of alkynes at 100 °C (Scheme 10).[21] However, aliphatic alkynes reacted less efficiently than aromatic

alkynes in the processes.



Scheme 10. Brønsted acid-catalyzed hydration of alkynes.

1.1.4 Summary

Recently numerous examples of the utility of gold as a catalyst for additions to alkynes, allenes, and alkenes have been reported. The clear picture emerging from those studies is that gold catalysts are soft Lewis acids that promote Markovnikov addition and the reactions can employ a range of oxygen and nitrogen nucleophiles. Although the exclusive or supporting role for Brønsted acids in some particular cases cannot be rigorously excluded, literature precedents show that gold-mediated conditions do not generate acids in sufficient concentration to promote reactions.

1.1.5 Goals and objectives

Selective manipulation of one functional group in the presence of other moieties with similar reactivity patterns is essential for the synthesis of structurally complex heterocycles. Gold

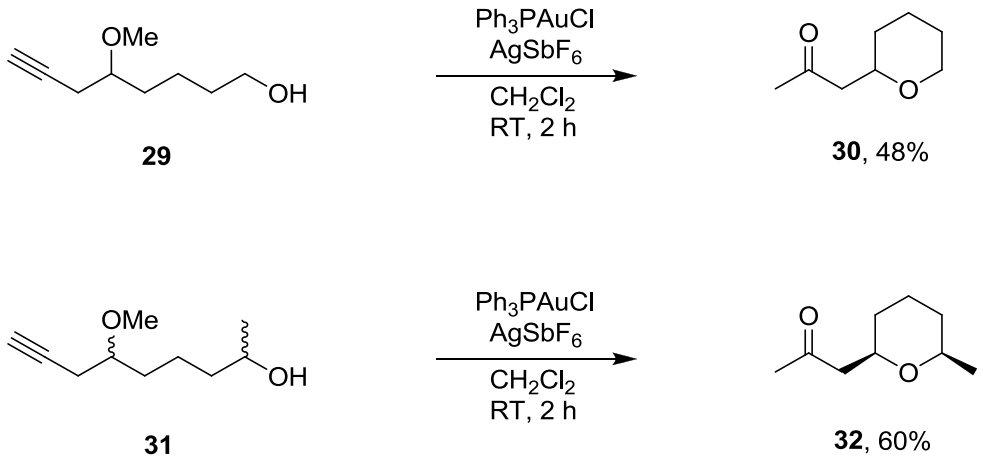
catalysts have been demonstrated to be extremely useful agents for generating electrophiles through their association with π–bonds, thereby selectively activating alkynes toward reactions with a remarkable range of nucleophiles.

Homopropargylic ethers were considered as intriguing substrates because of their ease of preparation, generally inert behavior toward nucleophiles, and wealth of potential reaction pathways upon treatment with gold catalysts. We chose to study the behavior of homopropargylic ethers that bear a distal nucleophilic group toward the objective of catalyzing cyclization reactions. Mechanistic details will be presented, as will its application as the key step in the enantioselective total synthesis of a monocyclic alkaloid.

1.2 Results and Discussion

1.2.1 Oxygen-containing heterocycle synthesis

Our initial studies showed that tetrahydropyran **30** was formed when homopropargylic ether **29** was subjected to 5 mol% of chloro(triphenylphosphine)gold(I) (Ph_3PAuCl) and 5 mol% of silver hexafluoroantimonate(V) ($AgSbF_6$) in unpurified CH_2Cl_2 under standard atmospheric conditions (Scheme 11). Similar treatment of ether **31**, prepared as a mixture of diastereomers, yielded **32** as a single diastereomer in 60% yield.



Scheme 11. Gold-mediated tetrahydropyran synthesis.

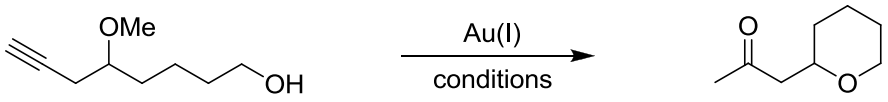
These results led us to explore the unique chemoselectivity of gold catalysis in the synthesis of polyfunctional molecules through a new, efficient, and mild approach to the preparation of oxygen-containing heterocyclic ketones.

1.2.1.1 Optimization of gold-mediated reaction

Our first consideration was to find the origin of additional oxygen because alkyne was converted to a ketone under the reaction conditions. However, continuous experimental observations with thin layer chromatography (TLC) analysis led us to anticipate that water, required for hydration, could be accessed from the adventitious moisture in atmosphere. Initial TLC analyses showed that the homopropargylic alcohols are inert in the presence of the catalyst. Surprisingly, frequent TLC analyses under an open atmosphere allowed for the introduction of a sufficient amount of water to complete the hydration reaction. Control experiments in the presence of molecular sieves (4 Å) confirmed that the reaction did not proceed in the absence of water.

Reproducible results were not observed for this reaction, however, possibly due to differences in atmospheric humidity.

In order to assure a sufficient source of water for the hydration, we found that the use of water-saturated CH_2Cl_2 (~60 mM), as the solvent, led to reproducible results for the reaction, giving clean and complete conversion in quantitative GC yield and 77% isolated yield of the semi-volatile product **30** (Table 1, entry 1). At lower temperatures, the gold did not promote the reaction (entry 2). Control reactions demonstrated that both gold and silver are essential for this process (see Table 1, entries 3 and 4).



29 **30**

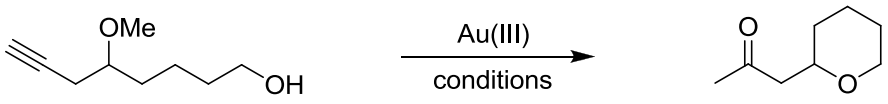
entry	**catalyst(s)**	**mol%**	**solvent**[a]	**temp** (°C)	**time** (h)	**GC yield**[b]
1	Ph_3PAuCl	5	CH_2Cl_2	35	24	100% (77%)[c]
	$AgSbF_6$	5				
2	Ph_3PAuCl	5		0	12	NR
	$AgSbF_6$	5				
3	Ph_3PAuCl	5		30	24	NR
4	$AgSbF_6$	5		30	24	NR

[a] Water-saturated solvent (~60 mM). [b] *p*-cymene was used as internal standard for GC yield. [c] number in parentheses is isolated yield.

Table 1. Optimizing reaction condition with Au(I).

Based upon the operational simplicity and reduced reaction cost, $NaAuCl_4$ was also employed as an alternative catalyst for these transformations. The reaction proceeded smoothly and reproducibly when **29** was exposed to $NaAuCl_4$ (5 mol%) in water-saturated CH_2Cl_2 (Table

2, entry 1). Adding a large quantity of catalyst (10 mol%) did not improve the product yield (entry 2) while loading each successive quantity of $NaAuCl_4$ (*ea.* 5 mol%) in two potions maintained the reactivity to provide a 96% GC yield and a 73% isolated yield (entry 3). Presumably $NaAuCl_4$ is converted to an inactive species over time.[22] Refluxing conditions in water-saturated dichloroethane were quite sluggish (entry 4). The use of water-saturated acetonitrile and aqueous THF (10:1 ratio (*v*/*v*) of THF/water) were not efficient with respect to catalytic activity, presumably due to the higher solubility of water in those solvents and/or the coordinating ability of heteroatom containing solvents, resulting in catalyst deactivation (entries 5 and 6).



29 **30**

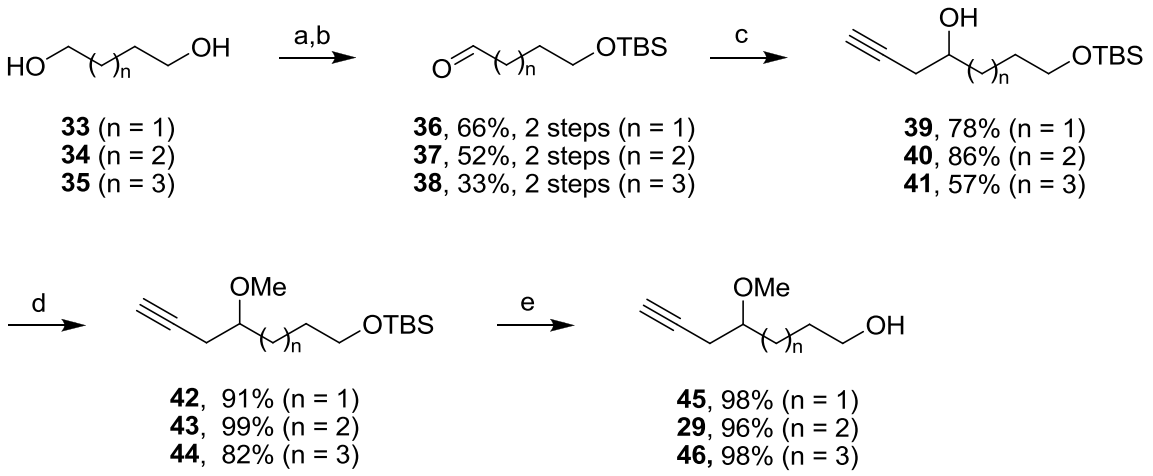
entry	**catalyst**	**mol%**	**solvent**[a]	**temp** (°C)	**time** (h)	**GC yield**[b]
1	$NaAuCl_4$	5	CH_2Cl_2	35	48	83%
2	$NaAuCl_4$	10	CH_2Cl_2	35	48	84%
3	$NaAuCl_4$	10[c]	CH_2Cl_2	35	48	96% (73%)[d]
4	$NaAuCl_4$	10[c]	$C_2H_4Cl_2$	85	48	39%
5	$NaAuCl_4$	10[c]	CH_3CN	35	48	NR
6	$NaAuCl_4$	10[c]	THF[e]	35	48	10%[f]

[a] Water-saturated solvent (~60 mM). [b] *p*-cymene was used as internal standard. [c] adding catalyst (5 mol%) two times at intervals of 12 hours. [d] number in parentheses is isolated yield(s). [e] 10:1 ratio (*v*/*v*) of THF/water. [f] isolated yield of hydrated product and 80% starting material recovered.

Table 2. Optimizing reaction conditions with Au(III).

1.2.1.2 Preparation of homopropargylic ethers

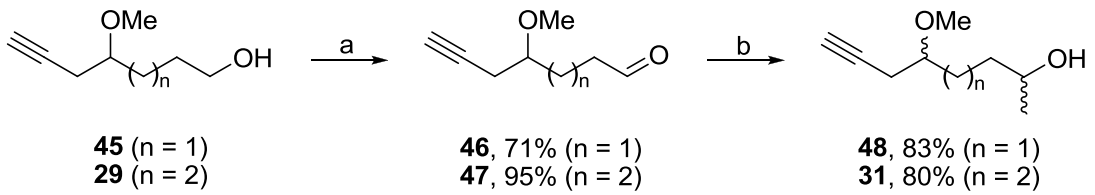
We prepared a range of substrates to study the mechanism and scope of the process. These substrates were designed to examine the facility of accessing multiple ring sizes, the capacity for diastereocontrol in the cyclization step, and the ability to conduct chemoselective cyclization reactions in the presence of other potentially reactive functional groups. Syntheses of substrates are shown in Scheme 12. Diol monosilylation[23] with TBSCl followed by Parikh-Doering oxidation[24] provided aldehyde **37** in 52% yield over 2 steps. Zinc-mediated Barbier-type propargyl addition under sonication[25] provided homopropargylic alcohol **36** in 86% yield. The formation of methyl ether **43** by the Williamson ether synthesis with sodium hydride and iodomethane followed by cleavage of the TBS ether with aqueous HCl in THF afforded **29** in 95% yield over 2 steps. Its lower and higher homologues **41** and **42** were also prepared in good yield under the identical reaction sequences described above.



Reagents and conditions: a) NaH, THF, then TBSCl, 0 °C to RT; b) SO_3•pyridine, Et_3N, DMSO, CH_2Cl_2, RT; c) propargyl bromide, Zn, 1,2-diiodoethane, THF, sonication; d) NaH, THF, then MeI, 0 °C to RT; e) HCl, H_2O, THF, RT.

Scheme 12. Preparation of homopropargylic ethers.

A mixture of diastereomeric methyl branched substrates **48** (n = 1) and **31** (n = 2) were prepared by the oxidation of alcohols **45** (n = 1) and **29** (n = 2) with pyridinium dichromate (PDC) and subsequent addition of methyl magnesium bromide (Scheme 13).



45 (n = 1)
29 (n = 2)

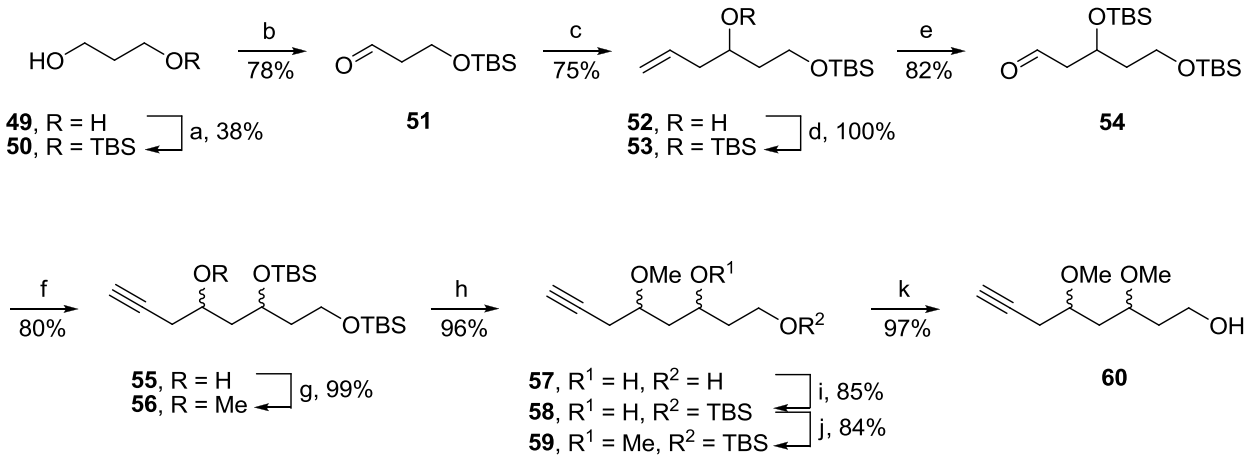
46, 71% (n = 1)
47, 95% (n = 2)

48, 83% (n = 1)
31, 80% (n = 2)

Reagents and conditions: a) PDC, CH_2Cl_2, RT; b) MeMgBr, THF, 0 °C.

Scheme 13. Preparation of branched homopropargylic ethers **48** and **31**.

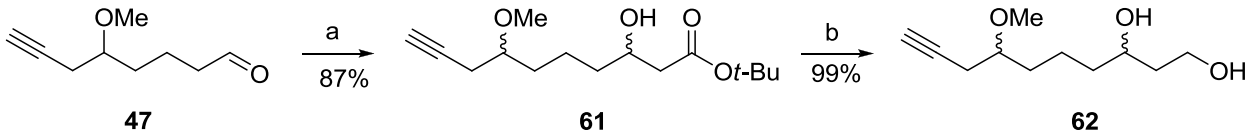
A methoxy-substituted substrate was prepared by the sequence in Scheme 14. Mono-protection[26] of **49** with TBSCl followed by Parikh-Doering oxidation[27] provided aldehyde **51** in 30% overall yield. Allylation of **51** with allylmagnesium bromide followed by TBS-protection gave homoallylic ether **53** in 75% overall yield. Oxidative cleavage by OsO_4−$NaIO_4$[26] followed by Barbier-type propargylation[28] and subsequent methyl ether formation yielded homopropargylic ether **56** in 65% yield over 3 steps. Hydroxy group manipulation gave branched homopropargylic ether **60** in 66% overall yield.



Reagents and conditions: a) NaH, THF, then TBSCl, 0 °C to RT; b) SO_3•pyridine, Et_3N, DMSO, CH_2Cl_2, RT; c) allylmagnesium bromide, THF, 0 °C to RT; d) NaH, THF, then TBSCl, 0 °C to RT; e) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1, *v*/*v*), RT; f) propargyl bromide, Zn, 1,2-diiodoethane, THF, sonication; g) NaH, THF, then MeI, 0 °C to RT; h) HCl, H_2O, THF, RT; i) TBSCl, Et_3N, DMAP, CH_2Cl_2, RT; j) 2,6-di-*tert*-butylpyridine, MeOTf, CH_2Cl_2, 0 °C to RT; k) HCl, H_2O, THF, RT.

Scheme 14. Preparation of branched homopropargylic ether **60**.

Aldol addition of the lithium enolate of *tert*-butylacetate to aldehyde **47** and subsequent reduction of *β*-hydroxy ester **61** with lithium aluminum hydride (LAH) provided diol **62** in 86% overall yield (Scheme 15).

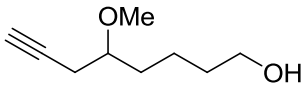
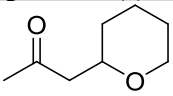
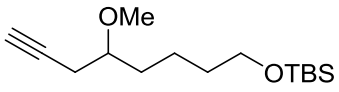
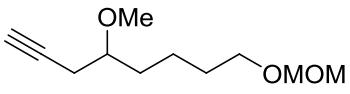


Reagents and conditions: a) *tert*-Butylacetate, LDA, THF, −78 °C; b) LAH, ether, −78 °C.

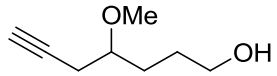
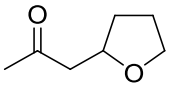
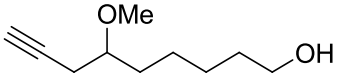
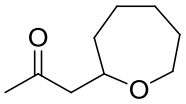
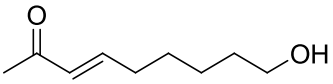
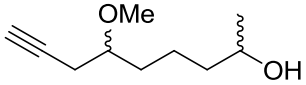
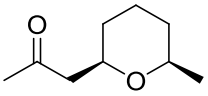
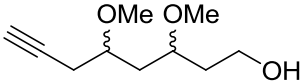
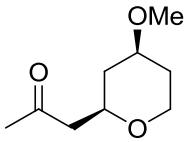
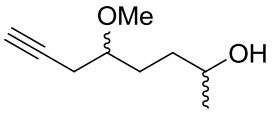
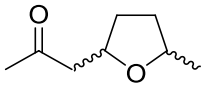
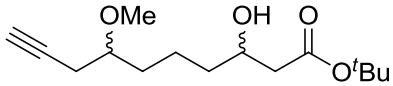
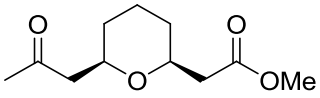
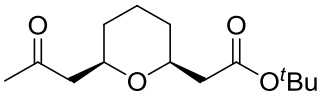
Scheme 15. Preparation of branched homopropargylic ether **62**.

1.2.1.3 Reaction scope and mechanism

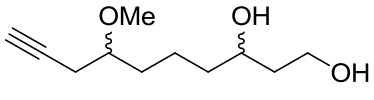
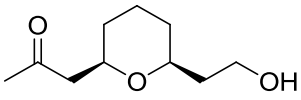
The scope and efficiency of the gold-mediated cyclization reaction are summarized in Table 3. Several aspects of this study are noteworthy. The overall transformations were, in general, quite efficient and proceeded in nearly quantitative yield. Although $NaAuCl_4$ was a suitable as a simpler and more economical catalyst for many reactions, the $Ph_3AuCl/AgSbF_6$ system produced a more active catalyst with respect to reaction time and product yield. Silyl- and MOM-protected nucleophilies **43** and **63** were sufficiently reactive to engage in this process (entries 2 and 3), alleviating the need for their cleavage prior to the cyclization reaction. Reactions, employing unprotected nucleophiles, produced methanol as the only side product. Tetrahydrofuran **64** was readily synthesized within 12 hours (entry 4). Substrates that yielded tetrahydrofuran products showed faster starting material consumption than substrates that yielded tetrahydropyran products. Intermediates along the reaction pathway did not accumulate to a significant extent except when **46** was subjected to the reaction condition to yield oxepane **65** and isolable α,β-unsaturated ketone **66** (entry 5).

entry	substrate	product(s)	time (h)	conditions[a]	yield(s)[b]
1	 **29**	 **30**	24 48	A B	100%[c] 96%[c]
2	 **43**	**30**	48	B	78%[c]
3	 **63**	**30**	72	B	66%[cd]

continued

4	 **45**	 **64**	12	B[e]	85%[c]
5	 **46**	 **65**	48	B	52%
		 **66**			10%
6	 **31**	 **32**	48	B	74%
7	 **60**	 **67**	6 72	A B	96% (2:1 *dr*)[g] 71%[f] (2:1 *dr*)[g]
8	 **48**	 **68**	6 6	A B[e]	96%[c] (55:45 *dr*)[g] 92%[c] (55:45 *dr*)[g]
9	 **61**	 **69**	6	A	60%
		 **70**			10%

continued

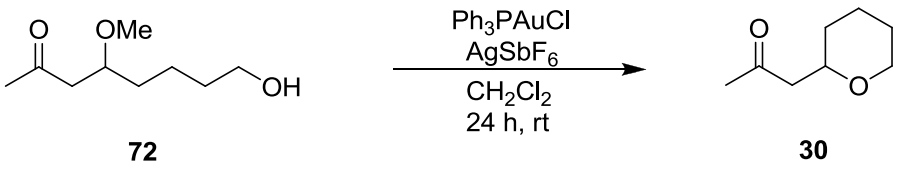
10	 **62**	 **71**	2 2	A B	97% 70%

[a] Condition A: substrate in water-saturated CH_2Cl_2 (~60 mM), Ph_3PAuCl (5 mol%), $AgSbF_6$ (5 mol%), 35 °C. condition B: substrate in water-saturated CH_2Cl_2 (~60 mM), $NaAuCl_4$ (2 × 5 mol%) at 12 h intervals, 35 °C. [b] yields are reported for isolated, purified products unless otherwise noted. [c] yield determined by GC. p-cymene was used as internal standard. [d] yield based upon 83% starting material consumption. [e] 5 mol% $NaAuCl_4$. [f] yield based upon 81% starting material consumption. [g] diastereomeric ratio determined by ^{1}H NMR.

Table 3. Reaction scope of oxygen-containing heterocycle syntheses.

Single diastereomers of the *cis*-2,6-disubstituted pyran products[27] were isolated in high yields from mixtures of diastereoisomers, suggesting that a planar intermediate forms during the reaction (entry 6). This outcome is consistent with the observation that *A*-values for substituents of tetrahydropyran at the 2- and 6-positions are higher than those at other positions due to shorter C−O bond lengths.[28] Treatment of **60** with both $Ph_3PAuCl/AgSbF_6$ and $NaAuCl_4$ catalysts yielded **67** in 96% and 71% yields respectively with a 2:1 dr (entry 7). Formation of tetrahydrofuran **68** shows very little conformational preference for the 2,5-*cis*-isomer relative to the 2,5-*trans*-isomer (entry 8). The reaction was tolerant of functional groups with ester, alkoxy, and hydroxyl groups providing to be compatible with the conditions, though methyl ester **69** was isolated as the major product, presumably due to methanolysis of the *tert*-butyl ester by the MeOH that is released in the reaction (entry 9). Diol **62** was also smoothly converted to pyran **71** without protecting the primary hydroxyl group, because 6-*exo* cyclizations are kinetically preferred over 8-*exo* cyclizations (entry 10).

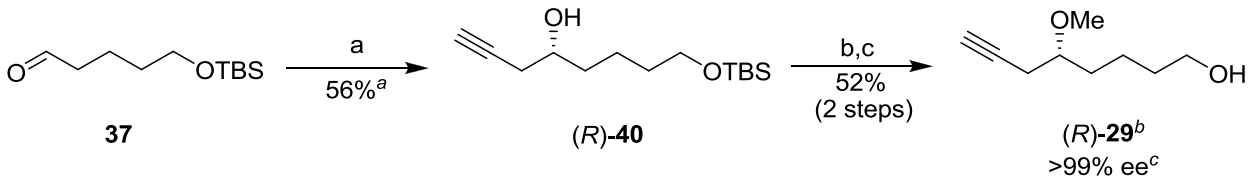
We were able to isolate a small amount of ketone **72** when reactions were stopped at partial conversion from **29**. Ketone **72** was re-subjected to the reaction condition, and cyclization was observed (Scheme 16).



72 **30**

Scheme 16. Cyclization of ketone intermediate.

The formation of tetrahydropyrans **32**, **69**, and **71** as single stereoisomers from diastereomeric mixtures of starting materials indicates that the stereogenic center, bearing the methoxy group, is lost or is subjected to stereochemical mutation during the course of the reaction. The possibility that the loss of stereogenicity is only relevant when secondary alcohols are used as nucleophiles was discounted by preparing **29** in enantiomerically enriched form through an asymmetric propargylation reaction in the presence of (*S*)-BINOL-Ti(IV) complex and trimethyl borate.[29] (Scheme 17).



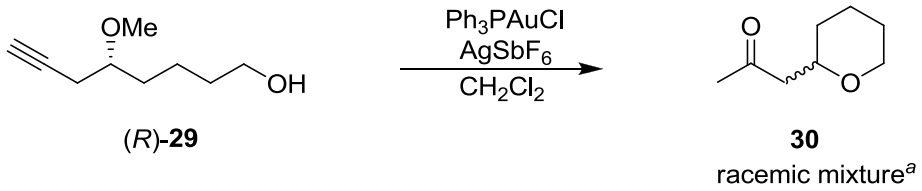
37 (*R*)-**40** (*R*)-**29**[b] >99% ee[c]

Reagents and conditions: a) (*S*)-BINOL, $Ti(O^iPr)_4$, $B(OMe)_3$, allenyltributyltin, 4 Å MS, CH_2Cl_2, 0 °C; b) NaH, THF, then MeI, RT; c) TBAF, THF, RT.

[a] yield based upon 64% starting material consumption. [b] $[\alpha]_D^{23}$ +3.4 (*c* 2.5, $CHCl_3$). [c] enatiomeric excess was determined by GC with a ChiraldexTM G-TA column.

Scheme 17. Preparation of enantiomerically enrich homopropargylic ether **29**.

When (*R*)-**29** was subjected to gold-catalyzed cyclization under standard atmospheric condition, a racemic mixture of **30** was formed, as determined by a GC experiment with a chiral stationary phase (Scheme 18).



(*R*)-**29** **30** racemic mixture[a]

[a] Racemic mixture was determined by chiral GC.

Scheme 18. Gold-mediated cyclization of enantiomerically enriched **30**.

When enone **66** was subjected to the reaction condition, oxepane **65** was formed. This indicates that enone intermediates are formed during the transformation. These experimental results, coupled with literature precedents, led us to propose the mechanism sequence shown in Figure 1. Ketone **72** is formed in the initial step through gold-mediated Markovnikov alkyne

hydration, followed by β-elimination of the methoxy group to yield enone **73**, and gold-mediated intramolecular conjugate addition of the nucleophilic hydroxyl group to provide **30**.

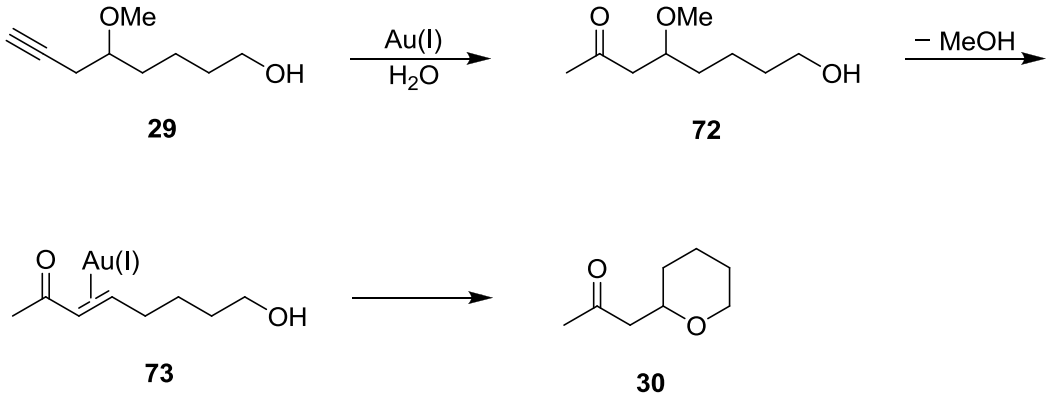
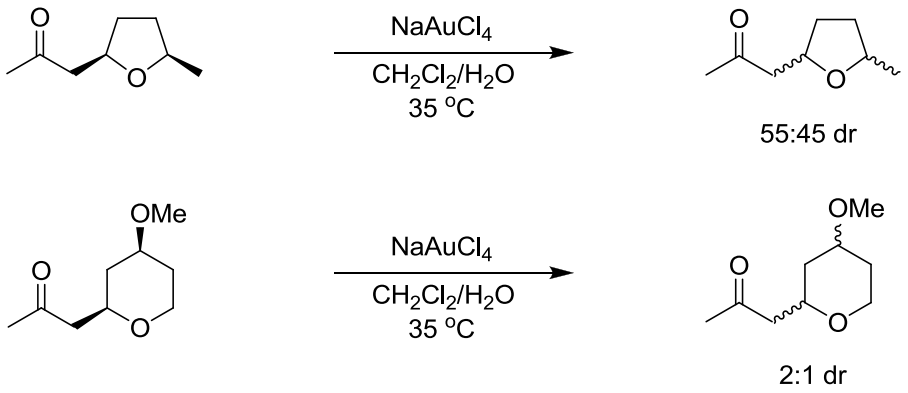


Figure 1. Proposed gold-mediated cyclization.

Several aspects of this mechanism merit further discussion. The initial alkyne hydration is well-precedented, though the elimination of the methoxy group has far less precedent. Utimoto and Fukuda observed the gold-mediated conversion of propargylic ethers to enones (see Scheme 2). However, the reaction proceeds through the formation of an enol intermediate that is adjacent to an alkoxy leaving group. The nucleophilic addition can simply be considered as the microscopic reverse of the elimination reaction. Several reports of gold-mediated additions of nucleophiles to alkenes have recently appeared in the literature, but these examples generally employ alkenes that are far more electron rich than the electron deficient intermediates that appear in this work. Trost, however, has postulated that ruthenium catalysts can promote tetrahydropyran formation through a similar mechanism[30] and Kobayashi has reported (see Scheme 6) carbamates undergo conjugate additions with α,β-unsaturated carbonyl compounds in the presence of gold catalysts. The failure of the enone to accumulate in most

cyclization reactions provides an evidence for gold-mediated cyclization reaction, since similar processes normally require somewhat forcing acid- or base-mediated conditions,[31] and indicates that gold-activated enones are quite reactive toward conjugate addition. The alternative possibility that the cyclization could be catalyzed by a phosphine-mediated alkoxide formation[32] can be discounted because of the ability of ligand-free $NaAuCl_4$ to promote the process. While a possible involvement of Brønsted acid in the alkyne hydration that could be generated from the reaction of water with the gold complex cannot be rigorously excluded, cyclization product, as well as any reaction intermediate, was not observed when substrate **29** was treated with a substoichiometric amount of HCl in the absence of gold catalysts. Neither Ph_3PAuCl nor $AgSbF_6$ alone promoted the cyclization from any of the proposed intermediates, though the combination promoted cyclizations of enone and *β*-methoxy ketone intermediates. This result indicates that gold catalysts are uniquely responsible for alkyne activation and that Brønsted acid, should it be a relevant catalyst, requires both catalysts to be generated.

The stereochemical outcomes in these reactions could arise from kinetic control or thermodynamic control because the products are *β*-alkoxy ketone that can undergoes elimination. To address whether stereochemical equilibration can occur during the course of the reaction, we subjected a single diastereomer of tetrahydrofuran **68** and tetrahydropyran **67** to the reaction conditions (Scheme 19). After several hours the equilibration was observed for both reactions to yield a mixture of diastereomers, which were identical to those that were observed in the previous cyclization reactions. These studies provide that stereochemical outcomes can be predicted based on thermodynamic grounds, with heightened *A*-values for substituents at the 2- and 6-positions of tetrahydropyrans[24] accounting for the exceptional diastereocontrol that is observed in their formation.



Scheme 19. Product equilibrium under cyclization condition.

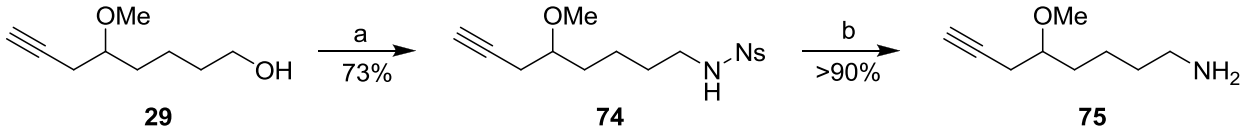
1.2.2 Nitrogen-containing heterocycle synthesis

Encouraged by the successful results from the gold-catalyzed synthesis of oxygen containing heterocycles, we next turned our attention to expanding the range of nucleophilic groups, as part of exploring the reaction scope upon the synthesis of nitrogen-containing heterocycles catalyzed by gold(I). Gold-catalyzed processes have been successfully accomplished using nitrogen nucleophiles[33] with the vast majority of reactions utilizing sulfonamides or carbamates instead of aliphatic amines. The objective of this study was to investigate the capacity of aliphatic amines, anilines, sulfonamides, and carbamates to serve as nucleophiles in this process and to assess the potential impact of the substituent on the nitrogen on the diastereoselectivity of the cyclization.

1.2.2.1 Preparation of substrate

A variety of substrates with different nucleophiles were prepared to evaluate the scope of the gold-catalyzed cyclizations. Sulfonamide **74** was prepared by Fukuyama-Mitsunobu procedure

whereby alcohol **29** was reacted with 2-nitrobenzenesulfonamide (*o*-$NsNH_2$) under di-*tert*-butylazodicaboxylate (DTBAD)−$PPyPh_2$ conditions[34] followed by adding HCl. Deprotection of the nosyl group[35] in **74** was achieved by the treatment with thiophenol and potassium carbonate in acetonitrile at room temperature to give amine **75** in over 90% yield (Scheme 20).

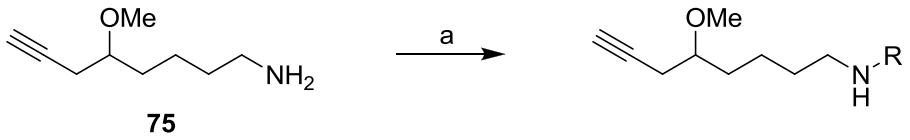


29 **74** **75**

Reagents and conditions: a) *o*-$NsNH_2$, Ph_2PyP, DTBAD, CH_2Cl_2, RT, then HCl; b) PhSH, $NaHCO_3$, CH_3CN, RT.

Scheme 20. Preparations of sulfonamide and amine.

Carbamates **76**−**79** were prepared in excellent yields with the appropriate acylating agents (Scheme 21).



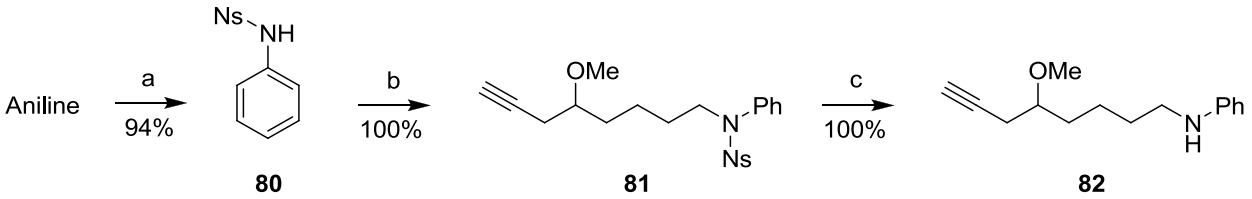
75

76, 87%: R = COOMe
77, 100%: Cbz
78, 85%: Fmoc
79, 68%: ^{t}Boc

Reagents and conditions: a) $NaHCO_3$, THF/H_2O (1:1), CH_3OCOCl (for **76**), CbzCl (for **77**), FmocCl (for **78**), $(^tBoc)_2O$ (for **79**), RT.

Scheme 21. Preparations of carbamates.

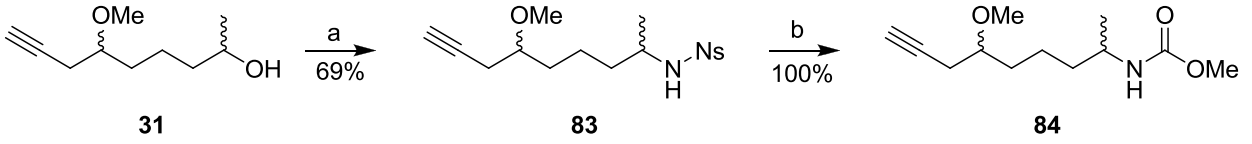
N-Phenyl 2-nitrobenzenesulfonamide **80**, readily prepared from *o*-NsCl and aniline in the presence of pyridine,[36] was alkylated efficiently under the Mitsunobu condition to give *N*,*N*-disubstituted 2-nitrobenzenesulfonamide **81** in quantitative yield. Facile nosyl deprotection of **96** was achieved by basic thiophenol in acetonitrile to provide aromatic amine **82** in quantitative yield (Scheme 22).



Reagents and conditions: a) *o*-NsCl, pyridine, CH_2Cl_2, RT; b) **29**, Ph_3P, DIPAD, CH_2Cl_2, RT, then H_3O^+; c) PhSH, $NaHCO_3$, CH_3CN, RT.

Scheme 22. Preparation of aromatic amine.

The treatment of **74** under Mitsunobu conditions gave branched sulfonamide **98** in 69% yield. Again, cleavage of nosyl group in **83** and *in situ* addition of methyl chloroformate gave branched carbamate **84** in quantitative yield (Scheme 23).

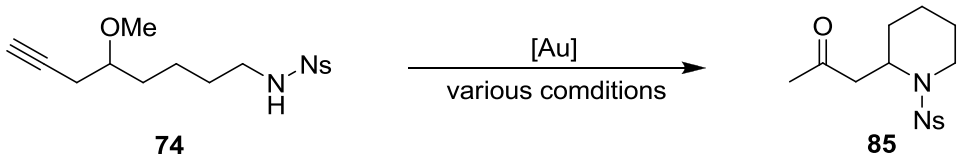


Reagents and conditions: a) *o*-$NsNH_2$, Ph_3P, DTBAD, CH_2Cl_2, RT; b) PhSH, $NaHCO_3$, CH_3CN, RT, then CH_3OCOCl, RT.

Scheme 23. Preparation of branched sulfonamide and carbamate.

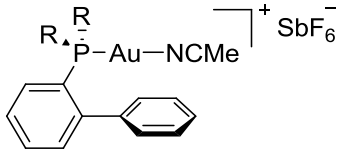
1.2.2.2 Optimazing reaction conditions and exploring reaction scope

Sulfonamide **74** was first subjected to gold-mediated reactions under the identical reaction conditions that have been highly effective in synthesizing pyrans. Unfortunately, the previous reaction conditions were not suitable for promoting complete conversion to piperidine **85** (entries 1 and 2 in Table 4). The reaction with unpurified CH_2Cl_2 gave **85** in moderate yield (entry 3). Echavarren and co-workers reported that biphenyl phosphine (Figure 2), as ligand for Au(I), achieved the higher reactivity in intramolecular [4+2] cyclization reactions.[37] Accordingly, cationic gold(I) complex **86** was prepared by known procedure,[38] and subjected to the cyclization reactions. The results showed that it was not efficient in our reaction system (entries 4−6). In the course of exploring better conditions, we discovered that changing the solvent from CH_2Cl_2 to water-saturated toluene and using a 1:2 ratio of Ph_3PAuCl to $AgSbF_6$ (procedure C) resulted in complete conversions and reduced reaction times. Notably, toluene can be used directly from the bottle with no loss of yield.



74 **85**

entry	catalyst(s)	mol%	solvent	temp (°C)	yield(s)[a]
1	Ph_3PAuCl	5	CH_2Cl_2[b]	35	<1%[c]
	$AgSbF_6$	5			
2	$NaAuCl_4$	5	CH_2Cl_2[b]		5%[d]
3	Ph_3PAuCl	5	CH_2Cl_2[e]		67%
	$AgSbF_6$	5			
4	**86**	5	CH_2Cl_2[e]	40	10%[f]
5	**86**	5	CH_2Cl_2[e]		34%
6	**86**	5	CH_2Cl_2[e]		43%
7	Ph_3PAuCl	5	toluene[e]		84%
	$AgSbF_6$	10			



86: R = ^{t}Bu

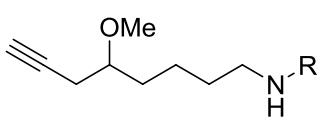
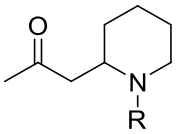
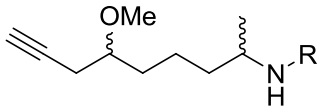
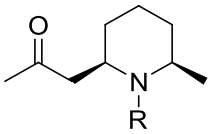
[a] Yields are reported for isolated, purified products unless otherwise noted. [b] water-saturated CH_2Cl_2, [c] 27% yield of hydrated product based upon 30% starting material consumption. [d] yield based upon 20% starting material consumption. [e] commercially available solvent was directly used without further purification. [f] 85% yield of hydrated product.

Figure 2

Table 4. Further optimization of reaction condition.

The results of exposing the nitrogen-containing substrates to these conditions are shown in Table 5. Methyl (**76**), benzyl (**77**), and fluorenyl methyl (**78**) carbamates smoothly underwent the transformation to give the corresponding piperidines in good to excellent yield (entries 2−4), though *tert*-butyl carbamate **79** did not yield any cyclization product (entry 5). This is most likely due to steric interactions in the cyclization transition state. Free amine **75** and aromatic amine **82** failed to react (entries 6 and 7), presumably as a result of higher basicity of free amine and aromatic amine, compared with sulfonamides and carbamates. Tanaka has

proposed[39] that amines react with gold catalysts, and the resulting species are less electrophilic than cationic Au(I) catalysts. Krause reported[40] that utilizing aliphatic amines in gold-catalyzed cyclization reactions results in substantially diminished rates when compared to the corresponding sulfonamides (5 d *vs* 1 h).

entry	substrate	product	time (h)	yield[b]
				
	R			
1	**74:** Ns	**85**	12	84%
2	**76:** CO_2Me	**87**	48	91%
3	**77:** Cbz	**88**	48	77%
4	**78:** Fmoc	**89**	48	84%
5	**79:** ^{t}Boc	-	-	NR
6	**75:** H	-	-	NR
7	**82:** Ph	-	-	NR
				
	R			
9	**83**: Ns	**90**	12	83% (92:8 *dr*)[c]
10	**84**: CO_2Me	**91**	48	84% (87:13 *dr*)[c]
11	**31**	**32**	1	78%

[a] Procedure C: substrate in water-saturated toluene (~25 mM), Ph_3PAuCl (5 mol%), $AgSbF_6$ (10 mol%), 40 °C. [b] yields are reported for isolated, purified products unless otherwise noted. [c] diastereomeric ratio determined by ^{1}H NMR.

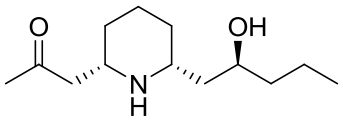
Table 5. Reaction scope of nitrogen-containing heterocycle syntheses.[a]

As observed in the oxygen-containing heterocycle syntheses, $AgSbF_6$ alone does not promote any of the steps in the sequence, suggesting that excess silver in these reactions simply promotes more efficient generation of the relevant cationic Au(I) catalyst. As shown in entry 11 (Table 5), exposing substrate **31** to procedure C led to complete conversion to oxygen-containing heterocycle **32** within 1 h rather than the 48 h that were required for the previous reactions (Table 2), highlighting the dramatic rate enhancement. Branched sulfonamides **83** and carbamates **84** react to form 2,6-disubstituted piperidines, with the *cis*-isomer being the dominant, though not exclusive, product in both cases.

Sulfonamide and carbamate groups have subtle structural differences. While the sulfonamide has an sp^3-hybridized nitrogen atom, the carbamate has an sp^2-hybridized nitrogen atom. We initially envisaged that these factors could impact the stereochemical outcome because allylic strain is expected in carbamates to change the thermodynamical equilibrium from the 2,6-*cis*-isomer to the 2,6-*trans*-isomer, and that accessing both stereochemical possibilities simply by changing group on the nitrogen atom would significantly enhance the utility of the method since both *cis*- and *trans*-isomers are present in numerous natural products. However, we observed 2,6-*cis*-isomer as major diastereoisomer from the reaction with carbamate **91** as well as sulfonamide **90** by analyzing a series of NMR data including 2D NOESY spectroscopy and 1D homonuclear decoupling experiments.

1.2.3 Total synthesis of (+)-andrachcinidine

Andrachcinidine is a piperidine-containing alkaloid isolated from the beetle *Andrachne aspera*[41] that has been implicated as a chemical defense agent (Figure 3).[42] We envisioned that preparing 2,6-*cis*-dialkylpiperidine rings of **92** through our gold-mediated cyclization reaction would provide an good example for demonstrating the capacity of the method as a key step in natural product total synthesis.



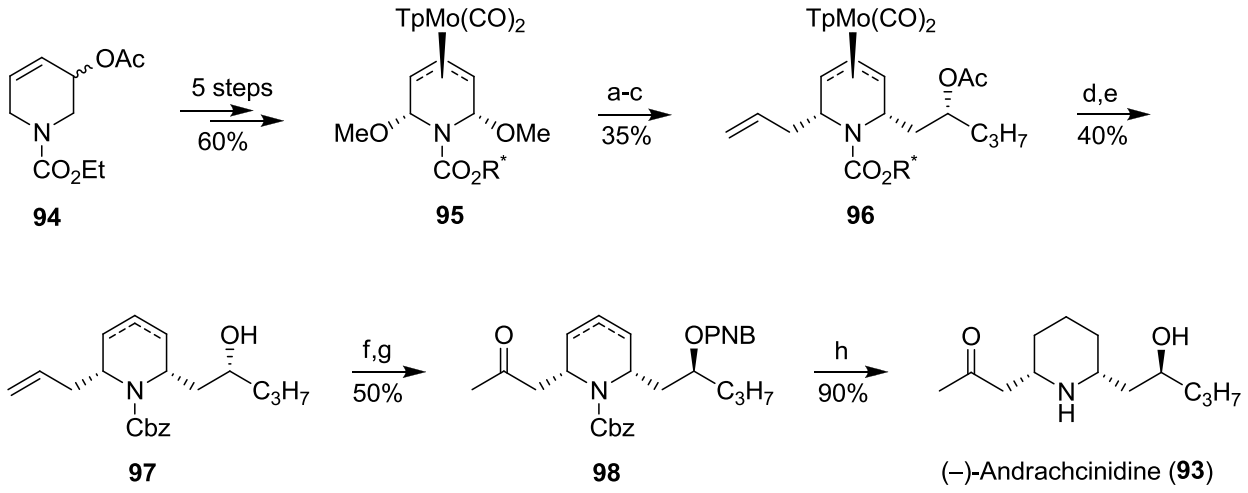
93

Figure 3. Andrachcinidine.

1.2.3.1 Precedent of andrachcinidine synthesis

Liebeskind and Shu reported the total synthesis of (–)-andrachcinidine based upon pseudo-desymmetrization (Scheme 24).[43] Chiral molybdenum complex **95** was prepared in 60% yield over five steps from racemic starting material **94**[44] which was also prepared over five steps from commercially available 1,2,3,6-tetrahydropyridine. The sequential functionalization of **95** was carried out by Lewis acid-mediated methoxy group abstractions and nucleophilic additions, followed by the selective reduction with K-Selectride® and acetylation to give **96** in 35% yield over 3 steps. The reductive demetalation by replacing CO with NO^+ followed by nucleophilic attack with $NaCNBH_3$ afforded a mixture of cyclohexene olefinic regioisomers. The (+)-TCC

auxiliary and acetate groups were cleaved, and the amine was reprotected with CbzCl to provide **97** in 40% over 2 steps. A Mitsunobu reaction, followed by a Wacker oxidation at the allyl side chain gave the isomeric mixture **98** in 50% yield over 2 steps. Finally, basic hydrolysis followed by hydrogenation provided (–)-**93** in 90% yield ($[\alpha]_D$ –20° (*c* 0.18 $CHCl_3$), *lit*. $[\alpha]_D$ –20° (*c* 1.6 $CHCl_3$)). The overall sequence was preceded in 13 steps in 3.8% yield from **94**.



R* = (+)-*trans*-2-(*α*-cumyl)cyclohexyl

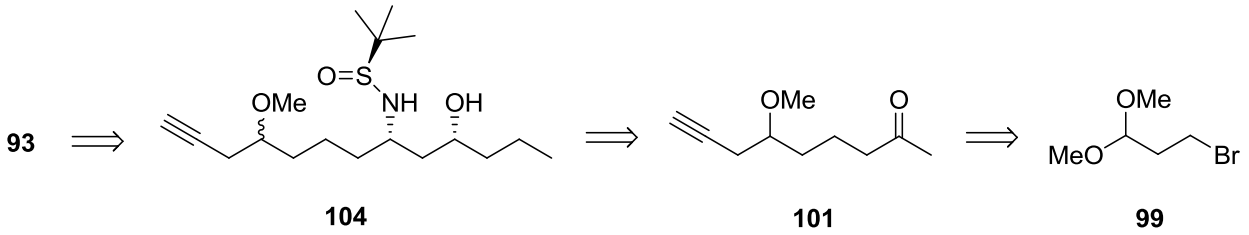
Reagents and conditions: a) Ph_3CPF_6 then allylmagnesium chloride; HBF_4 then CH_2=C(OLi)C_3H_7; b) K-Selectride®; c) Ac_2O, Et_3N, DMAP; d) $NOPF_6$ then $NaCNBH_3$; e) KOH/EtOH, seal tube (140 ℃), then CbzCl, NaOH; f) *p*-NO_2PhCO_2H, Ph_3P, DEAD; g) $PdCl_2$, CuCl, O_2, DMF/H_2O; h) KOH/MeOH then H_2, Pd/C, MeOH/EtOAc.

Scheme 24. Total synthesis of andrachcinidine by Liebeskind and Shu.

1.2.3.2 Restrosynthesis of (+)-andrachcinidine

Our retrosynthetic analysis of (+)-andrachcinidine (**102**) is shown in Scheme 25. The desired product could be accessed from **105**. A sulfonamide, instead of a sulfinamide, was chosen as

the distal nucleophile since we observed sulfinyl group cleavage and catalyst sequestration when sulfinyl substrates were subjected to the reaction conditions. Hydroxyl group protection would not be expected to be required due to the kinetic preference for 6-*exo* cyclizations over 8-*exo* cyclizations. Ellman's sulfinyl imine-based approach to amino alcohols **104** would be employed to set the absolute and relative stereochemical arrangements from ketone **101**. This ketone can be accessed readily from commercially available bromide **99**.

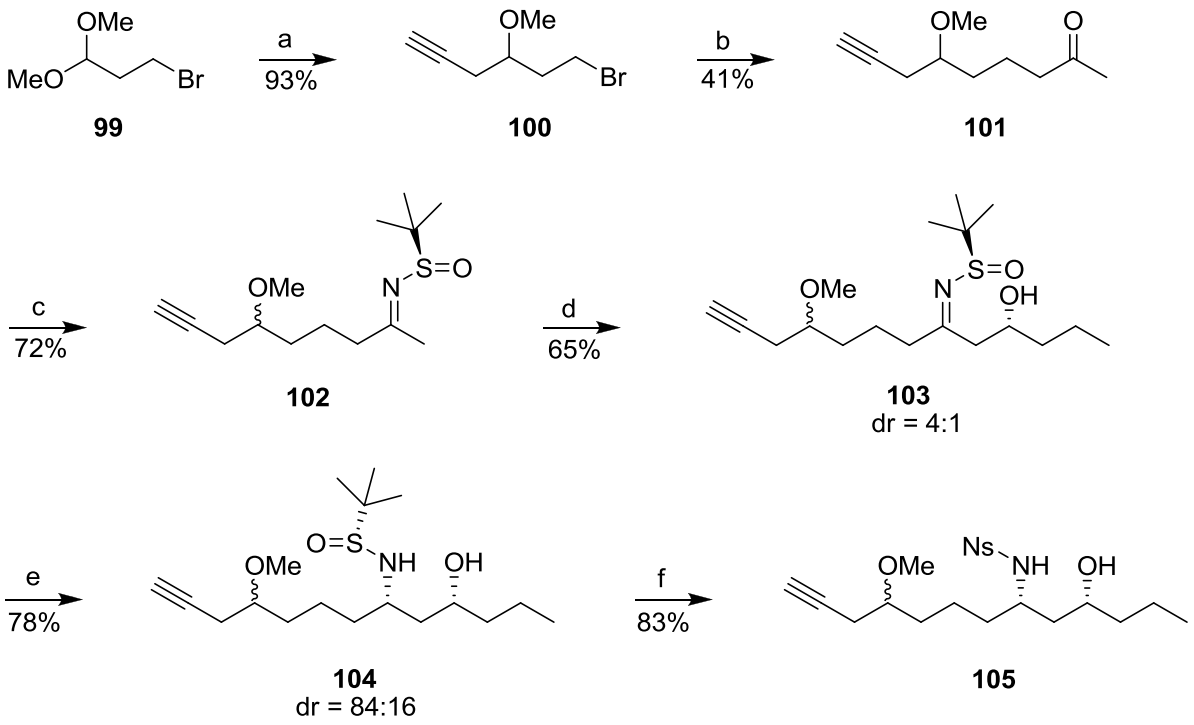


Scheme 25. Retrosynthetic analysis of andrachcinidine (**93**).

1.2.3.3 Total synthesis of (+)-andrachcinidine

The synthesis of andrachcinidine is shown in Scheme 26. Ionization of the commercially available 3-bromopropionaldehyde dimethyl acetal (**99**) with $TiCl_4$ at −78 °C and propargyl addition into the resulting oxocarbenium ion by allenyltributyltin[45] gave homopropargylic methyl ether **100** in 93% yield. The resulting homopropargylic ether was inert against the remaining reagents in the sequence, highlighting the utility of using this substrate as a ketone surrogate in multistep syntheses. Displacement of the bromide with the metalloenamine derived from the condensation of cyclohexylamine and acetone followed by acidic work-up,[46] provided ketone **101** in 41% yield. Condensation of (*R*)-*tert*-butanesulfinamide[47] with **101** in

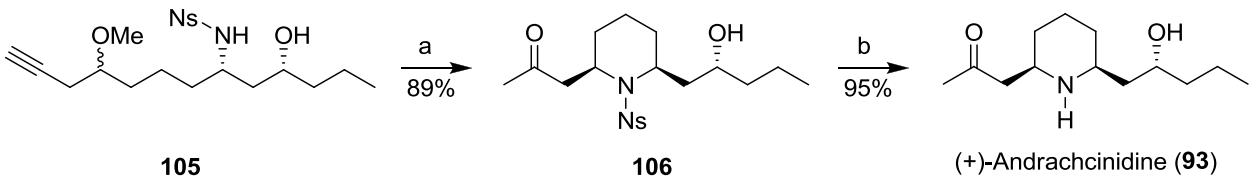
the presence of $Ti(OEt)_4$ at 70 °C afforded *N*-sulfinyl imine **102** in 72% yield. We selected this antipode of the auxiliary because it had previously been prepared in our group for a different purpose. While its use results in the synthesis of the enantiomer of the natural product, the antipodes of the sulfinamide are now equally accessible through an improved synthetic protocol. Thus this sequence can be applied to the synthesis of the correct enantiomer of the natural product. Again, the formation of the metalloenamine followed by addition of *n*-butyraldehyde with $MgBr_2$ at −78 °C provided an inseparable 4:1 diastereomeric mixture of *β*-hydroxy *N*-sulfinyl imine **103** in 65% yield.[48] Diastereoselective reduction of **103** with catecholborane[22] at −50 °C afforded a separable 84:16 diasteromeric mixture of amino alcohol **104** in 78% yield. The treatment of **104** with HCl for the removal of the sulfinyl group and the sequential formation of the nosyl group in basic condition provided the nosyl protected amino alcohol **105** in 83% yield in one-pot protocol. Mosher ester analysis showed the enantiomeric excess of **105** to be 94%. The high enantiomeric purity can be attributed to the sulfinyl auxiliary promoting good diastereocontrol in both the aldehyde addition and reduction steps.



Reagents and conditions: a) Allenyltributyltin, $TiCl_4$, CH_2Cl_2, −78 °C; b) acetone cyclohexylamine, LDA, THF, HMPA, −78 °C to RT, then H_3O^+; c) (*R*)-(+)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, 70 °C; d) LDA, THF, then $MgBr_2$, then *n*-butyraldehyde, −78 °C; e) catecholborane, THF, −50 °C; f) *i*. HCl, MeOH. *ii*. *o*-NsCl, $NaHCO_3$, H_2O/THF.

Scheme 26. Synthesis of homopropargylic ether amino alcohol **105**.

Exposing **105** to $Ph_3PAuCl/AgSbF_6$ system in water-saturated toluene at 40 °C afforded protected andrachcinidine (**106**) as single diastereomer in 89% yield. Finally, the removal of sulfonyl group with basic thiophenol yielded (+)-andrachcinidine in 95% yield. The spectroscopic data (^1H and ^{13}C NMR) of the synthetic product (+)-**93** are in excellent agreement with those of its enantiomers (–)-**93** reported in the literature ($[\alpha]_D^{23}$ +24 (*c* 0.39, $CHCl_3$)).



Reagents and conditions: a) PPh_3AuCl, $AgSbF_6$, water-saturated toluene, 40 °C; b) PhSH, $NaHCO_3$, CH_3CN, RT.

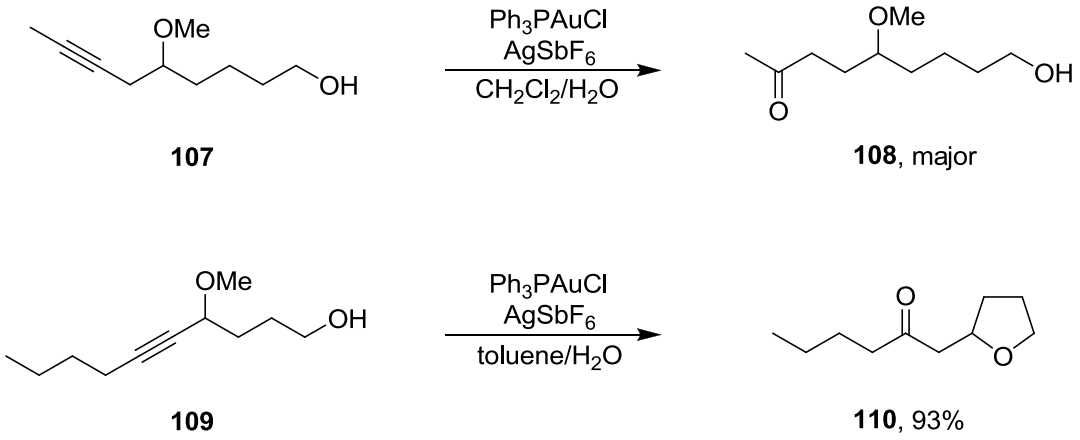
Scheme 27. Synthesis of (+)-andrachcinidine *via* gold-mediated cyclization.

Thus (+)-andrachcinidine can be prepared with excellent enantio- and diastereocontrol through a 8 steps sequence in 8% overall yield that was a substantial improvement over the 18 step sequence in the previously reported synthesis (Scheme 24).

1.2.4 Reaction with internal alkynes

Teminal alkynes have been subjected to the gold-mediated cyclization reaction and exhibit complete regioselectivity for the initial hydration reaction. Application of the internal alkynes to the mild gold-mediated cyclization conditions would immensely expand the scope of available products. Applying the standard reaction conditions to internal alkyne **107** (Scheme 28) provided a mixture of products with the major pathway being simple alkyne hydration in which water reacted at the distal carbon with respect to the methoxy group to yield ketone **108**. In an alternative approach, we exploited Utimoto's results[3] in which propargylic ethers undergo hydration at the distal carbon with respect to the alkoxy group, ultimately leading to the formation of enones (see Scheme 2). In efforts to be attentive to the presumed intermediacy of enones along our proposed mechanistic pathway, we have placed our focus on the cyclization of

propargylic ether **109**, and the results from exposing **109** to the standard cyclization protocol (procedure C) provided tetrahydrofuran **110** in 93% yield within 1 hour. This result clearly exhibits that internal alkynes can be used as substrates in this reaction. Additionally, the result indicates that any gold-mediated reaction that yields an α,β-unsaturated carbonyl group can potentially serve as an entry into heterocycle synthesis.[49]



Scheme 28. Cyclization with an internal alkyne substrate.

1.3 Conclusions

We have demonstrated that electrophilic gold catalysts mediate efficient oxygen- and nitrogen-heterocycle syntheses using homopropargylic ethers as latent electrophiles through a sequence of alkyne hydration, β-alkoxy group elimination, and conjugate addition. The process is experimentally simple and versatile, preceeds at ambient atmosphere, is tolerant of substrate functionality, and is viable with protected nucleophiles. In these reactions, hydroxyl, silyloxy, sulfonamide, and carbamate groups can play a role as nucleophiles in the cyclization event. Mechanistic investigations indicated that the reaction pathway proceeds through alkyne hydration, alkoxy group elimination to form an enone, and nucleophilic addition. Diastereoselectivity in these transformations can be predicted on the basis of product stability, and the reactions can be highly stereoselective when one diastereomer of the product is significantly more stable than the other because product stereoisomers interconvert under the reaction conditions. The method was applied to accomplish an efficient enantioselective synthesis of (+)-andrachcinidine that highlighted the capacity of the reaction to proceed without interference from a distal unprotected hydroxyl group. This result suggests that the formation of an electrophilic alkene could be led by gold-mediated protocols, which can be adapted to heterocycle synthesis.

1.4 Experimental

1.4.1 General

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively; or Bruker Avance 500 spectrometers at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.15 ppm. For ^{13}C NMR: $CDCl_3$ = 77.00 ppm, C_6D_6 = 128.00 ppm. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer. Analytical gas chromatography (GC) was performed using a Hewlett-Packard 6850 Series Gas Chromatograph fitted with a flame ionization detector. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was performed using ICN SiliTech 32–63 60 Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2) was distilled from CaH_2. Diethyl ether (Et_2O) and

tetrahydrofuran (THF) were dried by passing through aluminum drying column. Anhydrous methanol (MeOH), acetonitrile (CH_3CN) were purchased from Aldrich and used as is. All reactions were conducted under nitrogen atmosphere, unless otherwise specified. Water-saturated CH_2Cl_2 was prepared by shaking CH_2Cl_2 with H_2O in a separatory funnel and collecting the lower freaction. Water-saturated toluene was prepared by shaking toluene with H_2O in a separatoy funnel and colleting the top fraction.

1.4.2 Yield determination by gas chromatography

Three samples with different quantities of the pure pyran compound, which was confirmed to be pure by ^{1}H NMR, were diluted with CH_2Cl_2 to prepare 1.0 mL of sample solution. To each of three sample solutions was added 6.0 μL of *p*-cymene as internal standard. In order to generate a calibration curve for the quantification of the compound **30**, 2 μL portions of each sample solution was injected into the gas chromatograph. For reference, conditions of the gas chromatograph were shown in Table 6. From the GC data, the curves were constructed by plotting the ratio of the quantities of the compound **30** (x-axis) versus response ratio (y-axis), the area of the compound divided by the area of the internal standard. The linear calibration curve was shown in Figure 4, and the data for the compounds was displayed in Table 7. Regression analysis of the calibration curve yielded the following line equation 1:

$$y = 0.1134x - 0.037 \quad (1)$$

Where, y = the response ratio, x = the quantities of the compound **30**

Therefore, solving for x gave the following equation 2:

$$x = (y + 0.037) / 0.1134 \quad (2)$$

GC Column	HP19091Z-413E, 30 m × 0.32 mm × 0.25 μm
Front Detector Air Flow	450 mL/min
Front Detector H_2 Flow	40 mL/min
Front Inlet Total Flow	83 mL/min
Column Flow	1.6 mL/min
Oven Temperature	100 ℃
Front Detector Temperature	250 ℃
Front Inlet Temperature	200 ℃

Table 6. Gas chromatographic conditions.

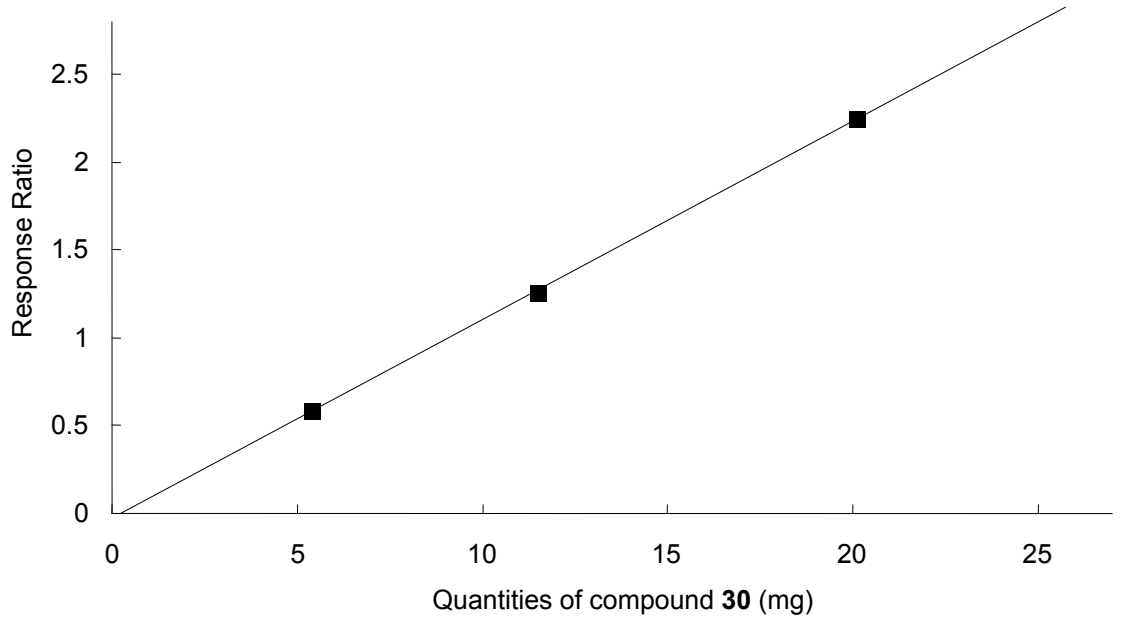


Figure 4. Calibration curve for compound.

	1st sample		2nd sample		3rd sample	
	Internal Standard	**30**	Internal Standard	**30**	Internal Standard	**30**
Molecular weight	134.22	142.19	134.22	142.19	134.22	142.19
Amount used	6.0 μL	5.4 mg	6.0 μL	11.5 mg	6.0 μL	20.1 mg
Retention time (min)	3.589	4.545	3.591	4.583	3.595	4.827
Peak Area	3822.9	2229.9	3981.9	4992.4	4107.1	9233.7
Response ratio	0.5833		1.2538		2.2482	

Table 7. Quantification of compound.

1.4.3 General cyclization procedures

Procedure A. In a 2 dram (8 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and water-saturated CH_2Cl_2 (~60 mM final concentration). To the stirred solution at room temperature were added 5 mol% of Ph_3PAuCl and 5 mol% of $AgSbF_6$. The white suspended mixture was stirred at 35 °C for given time. The completion of most reactions was checked by a thin layer chromatography at 12-hour intervals. In cases of the cyclization reactions to tetrahydrofurans, 6-hour intervals were suitable. The blackish reaction solution was dried over $MgSO_4$ and the crude contents of the vial in an ice bath were concentrated using a stream of N_2 gas. For volatile products yields were determined by GC with 6 μL of *p*-cymene as internal standard in accord with the procedure defined above.

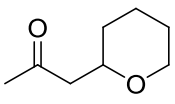
Procedure B. In a 2 dram (8 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and water-saturated CH_2Cl_2 (~60 mM final concentration). To the stirred solution at room temperature was added 5 mol% of $NaAuCl_4 \cdot 2H_2O$. The reaction

mixture was stirred at 35 °C for given time and, if necessary, additional 5 mol% of $NaAuCl_4 \bullet 2H_2O$ was added. The completion of most reactions was normally checked by a thin layer chromatography at 12-hour intervals. In cases of the cyclization reactions to tetrahydrofurans, 6-hour intervals were suitable. The dark yellowish reaction solution was dried over $MgSO_4$ and the crude contents of the vial in an ice bath were concentrated using a stream of N_2 gas. For volatile products yields were determined by GC with 6 μL of *p*-cymene as internal standard in accord with the procedure defined above.

Procedure C. In a 4 dram (16 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and bulk toluene or water-saturated toluene (~25 mM final concentration). To the stirred solution at room temperature were added 5 mol% of Ph_3PAuCl and 10 mol% of $AgSbF_6$. The white suspended mixture was stirred at 40 °C for given time. The completion of most reactions was normally checked by a thin layer chromatography at 12-hour intervals. The crude contents of the vial were directly subjected to chromatography on silica gel.

1.4.4 Oxygen-containing heterocycle compound

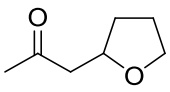
1-(Tetrahydropyran-2'-yl)propan-2-one (30)



General procedure A was followed with homopropargylic methyl ether **29** (31.3 mg, 0.20 mmol), Ph_3PAuCl (5.0 mg), and $AgSbF_6$ (3.4 mg) in water-saturated CH_2Cl_2 (4.0 mL) for 1 d to give pyran **30** (response ratio = 3.25, 29 mg, 0.20 mmol, 100% GC

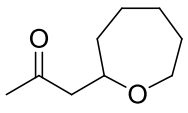
yield; 22 mg, 0.15 mmol, 77% isolated yield). General Procedure B was followed with **29** (30.8 mg, 0.20 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 4.0 mg) in water-saturated CH_2Cl_2 (4.0 mL) for 2 d to give **30** (response ratio = 2.86, 26 mg, 0.18 mmol, 91% GC yield; 21 mg, 0.14 mmol, 73% isolated yield). General procedure B was followed with homopropargylic methyl ether **29** (43.0 mg, 0.16 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 3.2 mg) in water-saturated CH_2Cl_2 (3.2 mL) for 2 d to give **30** (response ratio = 1.97, 18 mg, 0.12 mmol, 78% GC yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97−3.89 (m, 1H), 3.80−3.70 (m, 1H), 3.49−3.39 (m, 1H), 2.66 (dd, J = 15.6, 7.9 Hz, 1H), 2.41 (dd, J = 15.6, 4.8 Hz, 1H), 2.17 (s, 3H), 1.87−1.75 (m, 1H), 1.67−1.43 (m, 4H), 1.35−1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 74.1, 68.5, 50.4, 31.8, 30.9, 25.7, 23.3; IR (neat): 2636, 2848, 1713, 1440, 1377, 1357, 1090, 1047 cm^{-1}; HRMS (EI) m/z calcd. for $C_8H_{14}O_2$ $(M)^+$ 142.0994 found 142.0990. The spectroscopic data was consistent with the data reported in the literature.[50]

1-(Tetrahydrofuran-2'-yl)propan-2-one (64)

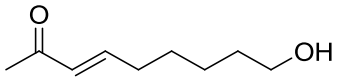


General procedure B was followed with homopropargylic methyl ether **45** (27.7 mg, 0.19 mmol) and $NaAuCl_4 \bullet 2H_2O$ (3.9 mg) in water-saturated CH_2Cl_2 (3.8 mL) for 12 h to give furan **64** (response ratio = 2.38, 21 mg, 0.17 mmol, 85% GC yield; 20 mg, 0.15 mmol, 79% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26−4.17 (m, 1H), 3.90−3.82 (m, 1H), 3.76−3.67 (m, 1H), 2.74 (dd, J = 15.9, 7.2 Hz, 1H), 2.55 (dd, J = 15.9, 5.6 Hz, 1H), 2.19 (s, 3H), 2.15−2.04 (m, 1H), 1.97−1.83 (m, 2H), 1.52−1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 75.0, 67.8, 49.6, 31.5, 30.6, 25.5; IR (neat): 2971, 2873, 1713, 1418, 1358, 1163, 1071 cm^{-1}; HRMS (EI) m/z calcd. for $C_7H_{12}O_2$ $(M)^+$ 128.0837 found 128.0839. The spectroscopic data was consistent with the data reported in the literature.[50]

1-(Oxepan-2'-yl)propan-2-one (65)

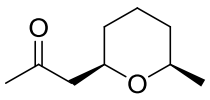


General procedure B was followed with homopropargylic methyl ether **46** (46.0 mg, 0.27 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 5.4 mg) in water-saturated CH_2Cl_2 (5.4 mL) for 2 d to give oxepane **65** (response ratio = 2.67, 24 mg, 0.15 mmol, 56% GC yield; 22 mg, 0.14 mmol, 52% isolated yield) and *α*,*β*-unsaturated ketone **66** (4.2 mg, 0.027 mmol, 10% isolated yield). For **65**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01−3.93 (m, 1H), 3.84−3.77 (m, 1H), 3.59−3.51 (m, 1H), 2.70 (dd, J = 15.6, 8.6 Hz, 1H), 2.38 (dd, J = 15.9, 4.4 Hz, 1H), 2.16 (s, 3H), 1.80−1.42 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.5, 75.8, 68.9, 50.6, 35.9, 30.9, 26.3, 25.9; IR (neat): 2928, 2858, 1716, 1445, 1358, 1115, 1098 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{16}O_2$ $(M)^+$ 156.1150 found 156.1154.



For **66**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (dt, J = 15.9, 6.9 Hz, 1H), 6.08 (dt, J = 15.9, 1.5 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 2.24 (s, 3H), 2.31−1.16 (m, 2H), 1.65−1.35 (m, 6H).

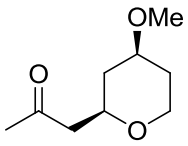
***cis*-1-(6'-Methyltetrahydro-*2H*-pyran-2'-yl)propan-2-one (32)**



General procedure B was followed with homopropargylic methyl ether **31**(44.0 mg, 0.26 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 5.2 mg) in water-saturated CH_2Cl_2 (5.2 mL) for 3 d to give pyran **32** (response ratio = 3.58, 32 mg, 0.20 mmol, 79% GC yield; 30 mg, 0.19 mmol, 74% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81−3.72 (m, 1H), 3.51−3.39 (m, 1H), 2.61 (dd, J = 15.5, 7.5 Hz, 1H), 2.42 (dd, J = 15.5, 5.2 Hz, 1H), 2.18 (s, 3H), 1.83−1.76 (m, 1H), 1.64−1.45 (m, 3H), 1.24−1.09 (m, 2H), 1.13 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 74.1, 74.0, 50.4, 32.9, 31.2, 31.0, 23.5, 22.1; IR (neat): 2970, 2933, 2860, 1715, 1371, 1356, 1074 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{16}O_2$ $(M)^+$

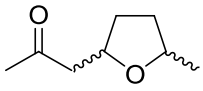
156.1150 found 156.1160. The spectroscopic data was consistent with the data reported in the literature.[31]

***cis*-1-(3'-Methoxytetrahydropyran-2'-yl)propan-2-one (67)**



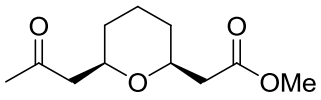
General procedure A was followed with homopropargylic methyl ether **60** (34.7 mg, 0.19 mmol), Ph_3PAuCl (4.7 mg), and $AgSbF_6$ (3.3 mg) in water-saturated CH_2Cl_2 (3.8 mL) for 6 h to give pyran **67** (31 mg, 0.18 mmol, 96% isolated yield). General procedure B was followed with **60** (39.7 mg, 0.21 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 4.2 mg) in water-saturated CH_2Cl_2 (4.2 mL) for 3 d to give **67** (21 mg, 0.12 mmol, 52% isolated yield) and **60** (8 mg, 19% recovered). ^{1}H NMR spectroscopic analysis of the crude products showed two diastereoisomers in the ratio of 2:1 by integration of the signals at δ_H = 2.40 (*cis*-isomer) and 2.37 (*trans*-isomer) respectively. For *cis*-**67**: ^{1}H NMR (300 MHz, C_6D_6): δ 3.72 (ddd, J = 11.7, 4.9, 1.8 Hz, 1H), 3.64−3.55 (m, 1H), 3.06 (s, 3H), 3.03 (dm, J = 11.7 Hz, 1H), 3.30−2.87 (m, 1H), 2.40 (dd, J = 15.9, 7.7 Hz, 1H), 1.93 (dd, J = 15.9, 4.8 Hz, 1H), 1.82 (dm, J = 12.3 Hz, 1H), 1.71 (s, 3H), 1.54 (dm, J = 12.5 Hz, 1H), 1.40−1.28 (m, 1H), 1.13−1.02 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 204.6, 76.4, 72.7, 65.9, 54.9, 49.6, 38.4, 32.5, 30.6; IR (neat): 2946, 2852, 1716, 1358, 1147, 1084 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{16}O_3$ $(M)^+$ 172.1099 found 172.1105. For *trans*-**67**: ^{1}H NMR (300 MHz, C_6D_6): δ 4.30−4.17 (m, 1H), 3.82−3.74 (m, 1H), 3.59−3.53 (m, 1H), 3.19 (m, 1H), 3.01 (s, 3H), 2.37 (dd, J = 15.3, 7.7 Hz, 1H), 1.99 (dd, J = 15.3, 5.2 Hz, 1H), 1.77 (s, 3H), 1.67 (dm, J = 11.1 Hz, 1H), 1.43−1.24 (m, 2H), 1.13-1.02 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 204.8, 72.8, 70.0, 62.9, 55.6, 50.1, 35.7, 30.3, 29.9.

***cis*- and *trans*-1-(6'-Methyltetrahydro-*2H*-furan-2'-yl)propan-2-one (68)**



General procedure A was followed with homopropargylic methyl ether **48** (27.2 mg, 0.17 mmol), Ph_3PAuCl (4.3 mg), and $AgSbF_6$ (3.0 mg) in water-saturated CH_2Cl_2 (3.4 mL) for 6 h to give furan **68** (response ratio = 2.65, 24 mg, 0.17 mmol, 96% GC yield; 18 mg, 0.13 mmol, 73% isolated yield). General procedure B was followed with **48** (27.7 mg, 0.18 mmol) and $NaAuCl_4 \bullet 2H_2O$ (3.6 mg) in water-saturated CH_2Cl_2 (3.6 mL) for 6 h to give **68** (response ratio = 2.60, 23 mg, 0.16 mmol, 92% GC yield; 18 mg, 0.13 mmol, 72% isolated yield). Gas chromatographic analysis of the crude product showed two diastereoisomers in the ratio of 55:45 by integration of the signals at t_R = 3.776 (*cis*-isomer) and 3.891 (*trans*-isomer). Data for *cis*-**68**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25−4.16 (m, 1H), 4.01−3.90 (m, 1H), 2.77 (dd, J = 15.9, 6.9 Hz, 1H), 2.56 (dd, J = 15.9, 6.0 Hz, 1H), 2.18 (s, 3H), 2.12−1.94 (m, 2H), 1.58−1.38 (m, 2H), 1.22 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 75.5, 75.1, 50.2, 32.7, 31.4, 30.7, 21.4; Data for *trans*-**68**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44−4.35 (m, 1H), 4.15−4.04 (m, 1H), 2.74 (dd, J = 15.7, 7.0 Hz, 1H), 2.52 (dd, J = 15.7, 5.9 Hz, 1H), 2.18 (s, 3H), 2.12−1.94 (m, 2H), 1.58−1.38 (m, 2H), 1.20 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.4, 74.8, 74.4, 50.0, 33.6, 32.4, 30.7, 21.2; Data for the mixture of isomers: IR (neat): 2964, 2927, 2871, 1716, 1457, 1375, 1358, 1085 cm^{-1}; HRMS (EI) m/z calcd. for $C_8H_{14}O_2$ $(M)^+$ 142.0994 found 142.0994.

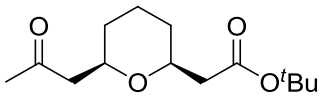
Methyl-2-(*cis*-6'-(2"-oxopropyl)tetrahydro-*2H*-pyran-2'-yl)acetate (69)



General procedure A was followed with homopropargylic methyl ether **61** (42.0 mg, 0.15 mmol), Ph_3PAuCl (3.7 mg), and $AgSbF_6$ (2.6 mg) in water-saturated CH_2Cl_2 (3.0 mL) for 12 h to give pyran **69** (20 mg, 0.09 mmol, 60%

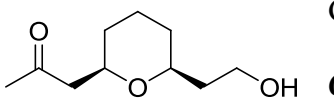
isolated yield) and pyran **70** (3.8 mg, 0.015 mmol, 10% isolated yield). For **69**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83−3.73 (m, 2H), 3.66 (s, 3H), 2.62 (dd, J = 15.2, 8.2 Hz, 1H), 2.49 (dd, J = 14.9, 8.1 Hz, 1H), 2.39 (dd, J = 15.2, 4.6 Hz, 1H), 2.28 (dd, J = 14.9, 5.2 Hz, 1H), 2.15 (s, 3H), 1.88−1.79 (m, 1H), 1.69−1.52 (m, 3H), 1.25 (s, -OH), 1.29−1.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.4, 171.6, 74.6, 74.5, 51.5, 50.3, 41.4, 31.0, 30.8, 30.6, 23.1; IR (neat): 2936, 2862, 1740, 1714, 1438, 1336, 1199, 1086, 1070, 1041, 1002 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{18}O_4$ $(M)^+$ 214.1205 found 214.1208.

tert-Butyl-2-(_cis_-6'-(2"-oxopropyl)tetrahydro-_2H_-pyran-2'-yl)acetate (70)



^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83−3.70 (m, 2H), 2.61 (dd, J = 15.1, 8.3 Hz, 1H), 2.37 (dd, J = 14.9, 8.0 Hz, 1H), 2.38 (dd, J = 15.1, 4.8 Hz, 1H), 2.27 (dd, J = 14.9, 5.2 Hz, 1H), 2.16 (s, 3H), 1.86−1.78 (m, 1H), 1.66−1.48 (m, 3H), 1.42 (s, 9H), 1.28−1.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.5, 170.5, 80.4, 74.8, 74.6, 50.3, 42.9, 31.1, 30.9, 30.7, 28.1, 23.2; IR (neat): 2934, 2862, 1730, 1368, 1164, 1087 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{21}O_4$ $(M-CH_3)^+$ 241.1440 found 241.1435.

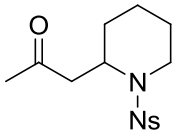
1-(_cis_-6'-(2"-Hydroxyethyl)tetrahydro-_2H_-pyran-2'-yl)propan-2-one (71)



General procedure A was followed with homopropargylic methyl ether **62** (49.9 mg, 0.25 mmol), Ph_3PAuCl (6.2 mg), and $AgSbF_6$ (4.3 mg) in water-saturated CH_2Cl_2 (5.0 mL) for 2 d to give pyran **71** (45 mg, 0.24 mmol, 97% isolated yield). General procedure B was followed with **62** (49.5 mg, 0.25 mmol) and $NaAuCl_4 \bullet 2H_2O$ (2 × 5.0 mg) in water-saturated CH_2Cl_2 (5.0 mL) for 2 d to give **71** (32 mg, 0.17 mmol, 70% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84−3.75 (m, 1H), 3.71 (t, J = 5.7 Hz, 2H),

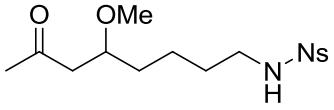
3.60−3.52 (m, 1H), 2.65 (s, OH), 2.64 (dd, J = 16.1, 8.0 Hz, 1H), 2.44 (dd, J = 16.1, 4.6 Hz, 1H), 2.14 (s, 3H), 1.84−1.76 (m, 1H), 1.70−1.45 (m, 3H), 1.33−1.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9, 78.0, 74.0, 61.0, 50.0, 38.1, 31.2, 30.1, 30.7, 23.2; IR (neat): 3457, 2936, 2861, 1713, 1446, 1439, 1358, 1076, 1042 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{18}O_4$ $(M-CH_3)^+$ 171.1021 found 171.1028.

1-(1-(2-Nitrophenylsulfonyl)piperidin-2-yl)propan-2-one (85)



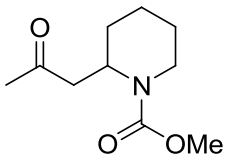
General procedure C was followed with homopropargylic methyl ether **74** (50.0 mg, 0.147 mmol), Ph_3PAuCl (3.8 mg, 7.7 μmol), and $AgSbF_6$ (5.2 mg, 15.1 μmol) in bulk toluene (6.0 mL) for 12 h to give piperidine **85** (40.5 mg, 0.124 mmol, 84% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (m, 1H), 7.67 (m, 3H), 4.46 (m, 1H), 3.78 (dm, J = 13.6 Hz, 1H), 3.00 (td, J = 13.6 Hz, 1H), 2.87 (dd, J = 16.7, 9.1 Hz, 1H), 2.70 (dd, J = 16.7, 4.3 Hz, 1H), 2.11 (s, 3H), 1.72−1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 147.7, 133.7, 133.4, 131.8, 131.2, 124.3, 49.2, 44.0, 41.8, 30.3, 28.1, 25.1, 18.3; IR (neat): 2944, 1716, 1544, 1342, 1372, 1160 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{14}H_{18}N_2O_5SNa$ $(M+Na)^+$ 349.0834 found 349.0811.

Hydrated intermediate from 74



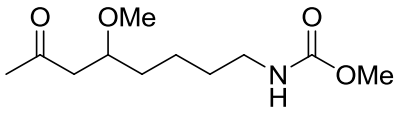
^{1}H NMR (300 MHz, C_6D_6): δ 7.81 (dd, J = 7.8, 1.3 Hz, 1H), 6.98 (dd, J = 7.8, 1.2 Hz, 1H), 6.70 (td, J = 7.8, 1.2 Hz, 1H), 6.56 (td, J = 7.8, 1.3 Hz, 1H), 5.16 (t, J = 5.9 Hz, 1H), 3.46 (p, J = 5.8 Hz, 1H), 3.04 (s, 3H), 2.73 (m, 2H), 2.29 (dd, J = 16.0, 6.9 Hz, 1H), 1.96 (dd, J = 16.0, 5.2 Hz, 1H), 1.74 (s, 3H), 1.19−1.01 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6): δ 205.9, 148.8, 134.7, 133.5, 132.3, 131.2, 125.3, 77.2, 57.0, 48.0, 44.0, 33.7, 31.0, 30.0, 22.4.

Methyl 2-(2-oxopropyl)piperidine-1-carboxylate (87)



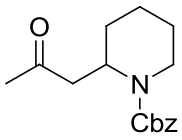
General procedure C was followed with homopropargylic methyl ether **76** (32.8 mg, 0.154 mmol), Ph_3PAuCl (4.0 mg, 8.1 μmol), and $AgSbF_6$ (5.3 mg, 15.4 μmol) in bulk toluene (6.0 mL) for 2 d to give piperidine **87** (27.8 mg, 0.140 mmol, 91% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (m, 1H), 4.00 (dm, J = 13.0 Hz, 1H), 3.67 (s, 3H), 2.82 (t, J = 13.0 Hz, 1H), 2.68 (m, 2H), 2.18 (s, 3H), 1.71−1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 156.0, 52.5, 47.5, 44.3, 39.7, 30.0, 28.3, 25.2, 18.8; IR (neat): 2940, 2862, 1696, 1447, 1407, 1264, 1169 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{17}NO_3$ $(M)^+$ 199.1208 found 199.1214.

Hydrated intermediate from 76



^{1}H NMR (300 MHz, $CDCl_3$): δ 4.67 (m, 1H), 3.68 (m, 1H), 3.66 (s, 3H), 3.31 (s, 3H), 3.17 (m, 2H), 2.69 (dd, J = 16.0, 7.1 Hz, 1H), 2.45 (dd, J = 16.0, 5.1 Hz, 1H), 2.18 (s, 3H), 1.55−1.29 (m, 6H).

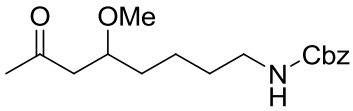
Benzyl 2-(2-oxopropyl)piperidine-1-carboxylate (88)



General procedure C was followed with homopropargylic methyl ether **77** (60.0 mg, 0.207 mmol), Ph_3PAuCl (5.2 mg, 10.5 μmol), and $AgSbF_6$ (7.2 mg, 20.9 μmol) in bulk toluene (8.5 mL) for 2 d to give piperidine **88** (44.2 mg, 0.161 mmol, 77% isolated yield) and hydrated product (13.1 mg, 0.043 mmol, 20% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H), 5.11 (s, 2H), 4.79 (m, 1H), 4.05 (dm, J = 12.6 Hz, 1H), 2.85 (t, J = 12.6 Hz, 1H), 2.70 (m, 2H), 2.13 (s, 3H), 1.68−1.38 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.7, 155.3, 136.8, 128.4, 127.9, 127.8, 67.1, 47.6, 44.3, 39.8, 30.0, 28.3, 25.2, 18.8; IR (neat): 2937, 1695, 1420, 1355, 1261, 1166 cm^{-1}; HRMS (EI) calcd. for $C_{13}H_{16}NO_2$ $(M-C_3H_5O)^+$ 218.1181

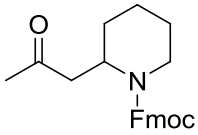
found 218.1182.

Hydrated intermediate from 77



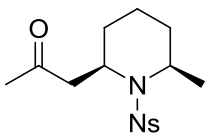
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.09 (m, 2H), 4.75 (m, 1H), 3.65 (m, 1H), 3.31 (s, 3H), 3.28 (m, 1H), 3.19 (q, J = 6.5 Hz, 2H), 2.68 (dd, J = 16.0, 7.1 Hz, 1H), 2.44 (dd, J = 16.0, 5.0 Hz, 1H), 2.17 (s, 3H), 1.63−1.29 (m, 6H).

(9H-Fluoren-9-yl)methyl 2-(2-oxopropyl)piperidine-1-carboxylate (89)



General procedure C was followed with homopropargylic methyl ether **78** (68.0 mg, 0.180 mmol), Ph_3PAuCl (4.5 mg, 9.1 μmol), and $AgSbF_6$ (6.2 mg, 18.0 μmol) in bulk toluene (7.0 mL) for 2 d to give piperidine **89** (55.0 mg, 0.151 mmol, 84% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 7.4 Hz, 2H), 7.58 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.31 (tt, J = 7.4, 1.1 Hz, 2H), 4.69 (m, 1H), 4.42 (m, 2H), 4.23 (t, J = 6.5 Hz, 1H), 3.98 (dm, J = 12.8 Hz, 1H), 2.81 (m, 1H), 2.68 (m, 1H), 2.55 (m, 1H), 2.10 (m, 3H), 1.69−1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 155.2, 144.1, 144.0, 141.4, 141.3, 127.6, 127.0, 124.9, 124.8, 119.9, 67.0, 47.4, 44.1, 39.8, 29.9, 28.0, 25.2, 18.8; IR (neat): 2939, 2861, 1694, 1450, 1422, 1354, 1261, 1166 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{23}H_{25}NO_3Na$ $(M+Na)^+$ 386.1732 found 386.1743.

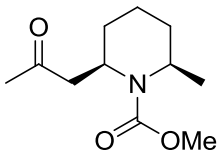
1-(*cis*-6'-methyl-1'-(2"-nitrophenylsulfonyl)piperidin-2'-yl)propan-2-one (90)



General procedure C was followed with homopropargylic methyl ether **83** (44.8 mg, 0.126 mmol), Ph_3PAuCl (3.2 mg, 6.4 μmol), and $AgSbF_6$ (4.4 mg, 12.8 μmol) in water-saturated toluene (5.0 mL) for 12 h to give piperidine **90** (35.9 mg, 0.106

mmol, 83% isolated yield). ^{1}H NMR spectroscopic analysis of the crude products showed two diastereoisomers in the ratio of 92:8 by integration of the signals at δ_H = 3.00 (*cis*-isomer) and 2.86 (*trans*-isomer) respectively. For *cis*-**90**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 1H), 7.67 (m, 3H), 4.30 (m, 1H), 4.24 (m, 1H), 2.98 (m, 2H), 2.18 (s, 3H), 1.69−1.43 (m, 6H), 1.37 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 147.8, 133.6, 133.3, 131.8, 131.3, 124.4, 49.0, 48.7, 47.9, 30.3, 29.5, 28.0, 22.0, 13.2. For *trans*-**90**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (m, 1H), 7.70 (m, 3H), 4.45 (m, 1H), 3.69 (m, 1H), 2.83 (m, 2H), 2.12 (s, 3H), 1.69−1.43 (m, 6H), 1.13 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6, 147.8, 133.6, 133.3, 132.9, 131.9, 124.3, 52.0, 51.5, 45.4, 32.4, 30.2, 28.8, 19.3, 18.6. For the mixture of isomers: IR (neat): 3096, 2943, 1716, 1544, 1373, 1337, 1170 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{17}N_2O_5S$ $(M-CH_3)^+$ 325.0858 found 325.0852.

***cis*-Methyl 2-methyl-6-(2-oxopropyl)piperidine-1-carboxylate (91)**

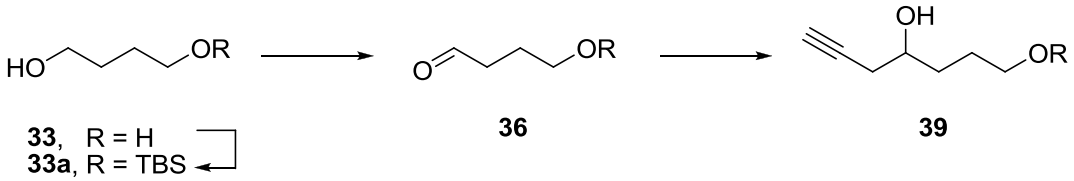


General procedure C was followed with homopropargylic methyl ether **84** (45.8 mg, 0.201 mmol), Ph_3PAuCl (5.0 mg, 10.1 μmol), and $AgSbF_6$ (7.0 mg, 20.4 μmol) in water-saturated toluene (8.0 mL) for 24 h to give piperidine **91** (36.0 mg, 0.169 mmol, 84% isolated yield). ^{1}H NMR spectroscopic analysis of the crude products showed two diastereoisomers in the ratio of 89:11 by integration of the signals at δ_H = 2.77 (*cis*-isomer) and 2.97 (*trans*-isomer) respectively. For *cis*-**91**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (m, 1H), 4.33 (m, 1H), 3.69 (s, 3H), 2.77 (dd, J = 15.5, 10.3 Hz, 1H), 2.57 (dd, J = 15.5, 3.4 Hz, 1H), 2.17 (s, 3H), 1.64−1.45 (m, 6H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 156.2, 52.5, 48.6, 46.3, 45.9, 30.0, 29.8, 27.9, 20.4, 13.6. For *trans*-**91**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (m, 1H), 4.11 (m, 1H), 3.66 (s, 3H), 2.97 (dd, J = 16.0,

4.9 Hz, 1H), 2.58 (m, 1H), 2.17 (s, 3H), 1.64−1.45 (m, 6H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 156.2, 52.1, 48.4, 47.9, 47.7, 30.0, 27.4, 26.0, 19.6, 14.8. For a mixture of isomers: IR (neat): 2929, 2855, 1695, 1443, 1362, 1096 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{19}NO_3$ $(M)^+$ 213.1365 found 213.1363.

1.4.5 Preparation of homopropargylic ethers

Preparation of 4-methoxyhept-6-yn-1-ol (45)



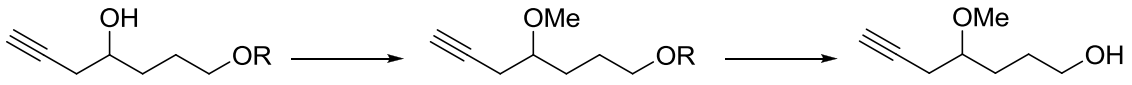
To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 905 mg, 22.64 mmol) in THF (60 mL) was added a solution of 1,4-butanediol (**33**) (2.06 g, 22.64 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 20 min at which time a large amount of an opaque white precipitate had formed. A solution of *tert*-butyldimethylsilyl chloride (4.25 mg, 27.35 mmol) in THF (20 mL) was then added. The resulting mixture was vigorously stirred for 24 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (4:1, Hexanes/EtOAc) to afford the desired *tert*-butyldimethylsilyloxy)butan-1-ol (**33a**) (2.83 g, 13.84 mmol, 61%) as a colorless oil. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 3.66 (m, 4H), 1.65 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[26]

To a solution of **33a** (2.82 g, 13.79 mmol) in CH_2Cl_2 (16 mL) were added DMSO (32 mL) and Et_3N (5.8 mL, 41.36 mmol) followed by the addition of sulfur trioxide pyridine complex (3.29 g, 20.68 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. EtOAc and water were added and the organic fraction was separated. The aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford 4-(*tert*-butyldimethylsilyloxy)butanal (**36**) (2.05 g, 10.13 mmol, 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (t, J = 1.7 Hz, 1H), 3.65 (t, J = 6.0 Hz, 2H), 2.50 (td, J = 7.1, 1.7 Hz, 2H), 1.86 (p, J = 6.5 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[51]

To a mixture of **36** (377 mg, 1.86 mmol) and dust zinc (609 mg, 9.31 mmol) in THF (30 mL) were added propargyl bromide (80wt% solution in toluene, 0.25 mL, 2.23 mmol) and 1,2-diiodoethane (525 mg, 1.86 mmol) at room temperature. The reaction mixture was sonicated for 10 h. After the sonication, the reaction solution was filtered through a silica gel plug and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue was purified by the flash chromatography on silica gel (10:1, hexanes/EtOAc) to afford 7-(*tert*-butyldimethylsilyloxy)hept-1-yn-4-ol (**39**) (350 mg, 1.44 mmol, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (m, 1H), 3.67 (m, 2H), 3.12 (bs, OH), 2.38 (dd, J = 6.0, 2.6 Hz, 2H), 2.02 (t, J = 2.6 Hz, 1H), 1.83−1.53 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.2, 70.4, 69.8, 63.4, 33.5, 29.0, 27.2, 25.9, 18.3, −4.8; IR (neat): 3400 (br),

3313, 2954, 2930, 2858, 2090, 1472, 1256, 1098 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{17}O_2Si$ $(M-C_4H_9)^+$ 185.0998 found 185.0994.



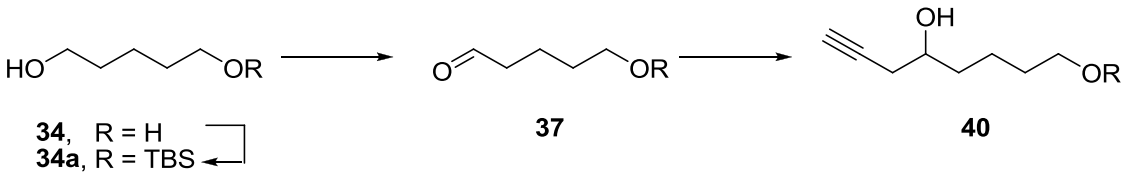
39, R = TBS **42** **45**

To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 243 mg, 6.08 mmol) in THF (20 mL) was added a solution of **39** (0.98 g, 4.05 mmol) in THF (30 mL) at room temperature. Methyl iodide (0.38 mL, 6.08 mmol) was added by a syringe. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (30:1, Hexanes/EtOAc) to afford *tert*-butyl(4-methoxyhept-6-ynyloxy)dimethylsilane (**42**) (950 mg, 3.70 mmol, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (m, 2H), 3.37 (s, 3H), 3.33 (p, J = 5.5 Hz, 1H), 2.40 (m, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.75−1.50 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 79.0, 69.8, 63.0, 56.9, 29.8, 28.4, 25.9, 23.1, 18.3, −5.3; IR (neat): 3314, 2954, 2930, 2858, 2825, 2100, 1472, 1361, 1100 cm^{-1}; HRMS (EI) m/z calcd. for $C_{10}H_{19}O_2Si$ $(M-C_4H_9)^+$ 199.1154 found 199.1161.

To a solution of **42** (902 mg, 3.51 mmol) in THF (25 mL) was added 10% aqueous HCl solution (5.0 mL) at room temperature. The reaction mixture was stirred for 24 h. The reaction was neutralized with sat. aqueous $NaHCO_3$ solution. The organic fraction was

separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2, hexanes/EtOAc) to afford 4-methoxyhept-6-yn-1-ol (**45**) (490 mg, 3.45 mmol, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (t, J = 6.0 Hz, 2H), 3.38 (s, 3H), 3.38−3.31 (m, 1H), 2.50−2.32 (m, 2H), 2.09 (s, OH), 1.99 (t, J = 2.7 Hz, 1H), 1.79−1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.8, 79.2, 70.0, 62.7, 56.9, 30.2, 28.5, 23.0; IR (neat): 3415 (br), 3294, 2936, 2873, 2829, 1456, 1360, 1097, 1067 cm^{-1}; HRMS (EI) m/z calcd. for $C_5H_{11}O_2$ $(M-C_3H_3)^+$ 103.0759 found 103.0757.

Preparation of 5-methoxyoct-7-yn-1-ol (29)



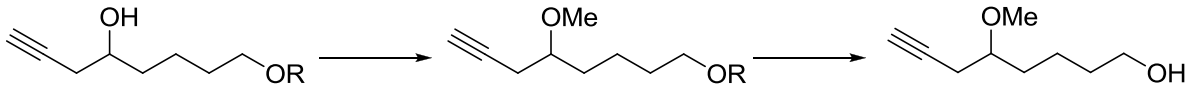
To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 4.51 g, 112.83 mmol) in THF (150 mL) was added a solution of 1,5-pentanediol (**34**) (12.24 g, 112.83 mmol) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 30 min at which time a large amount of an opaque white precipitate had formed. A solution of *tert*-butyldimethylsilyl chloride (17.53 g, 112.83 mmol) in THF (50 mL) was then added. The resulting mixture was vigorously stirred for 12 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide crude 5-(*tert*-butyldimethylsilyloxy)pentan-1-ol (**34a**) that was used for oxidation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (t, J = 6.4 Hz, 2H), 3.60 (t, J = 6.3 Hz, 2H), 1.78 (bs, OH), 1.54 (m, 4H), 1.37 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[26]

To a solution of crude **34a** (22.90 g, 104.84 mmol) in CH_2Cl_2 (100 mL) were added DMSO (150 mL) and Et_3N (29.5 mL, 209.68 mmol) followed by the addition of sulfur trioxide pyridine complex (16.70 g, 104.84 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. CH_2Cl_2 and water were added and the organic fraction was separated. The aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford 5-(*tert*-butyl dimethylsilyloxy)pentanal (**37**) (12.72 g, 58.78 mmol, 52% over 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (t, J = 1.7 Hz, 1H), 3.62 (t, J = 6.1 Hz, 2H), 2.45 (td, J = 7.2, 1.7 Hz, 1H), 2.37 (t, J = 7.3 Hz, 1H), 1.70 (m, 2H), 1.56 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[52]

To a mixture of **37** (12.72 g, 58.78 mmol) and dust zinc (19.22 mg, 293.90 mmol) in THF (250 mL) were added propargyl bromide (80 wt% solution in toluene, 9.8 mL, 88.17 mmol) and 1,2-diiodoethane (16.73 mg, 58.78 mmol) at room temperature. The reaction mixture was sonicated for 2 h. After the sonication, the reaction solution was filtered through a silica gel plug and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue was purified by the flash chromatography on silica gel (10:1, hexanes/EtOAc) to afford 8-(*tert*-butyldimethylsilyloxy)oct-1-yn-4-ol (**40**) (12.96 g, 50.55 mmol, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (p, J = 5.9 Hz, 1H), 3.61 (t, J = 6.1 Hz, 2H), 2.43 (ddd, J = 16.6, 4.8, 2.6 Hz, 1H), 2.31 (ddd, J = 16.6, 6.7, 2.6 Hz, 1H), 2.05 (t, J = 2.6 Hz,

1H), 1.96 (s, OH), 1.60−1.33 (m, 6H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.9, 70.7, 69.9, 63.0, 35.9, 32.6, 27.4, 26.0, 21.9, 18.3, −5.3; IR (neat): 3450, 3313, 2929, 2858, 2120, 1472, 1256, 1099, 1030 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{29}O_2Si$ $(M+H)^+$ 257.1937 found 257.1938.

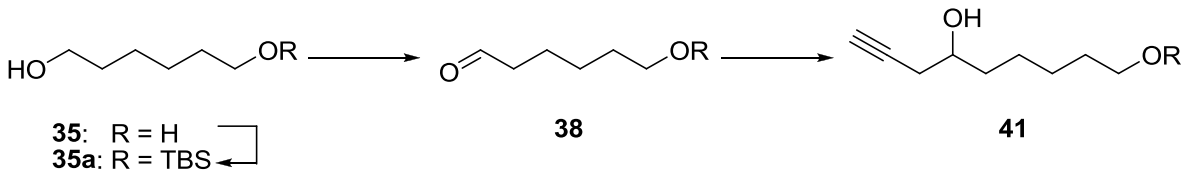


40, R = TBS **43** **29**

To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 572 mg, 14.25 mmol) in THF (30 mL) was added a solution of **40** (2.35 g, 9.18 mmol) in THF (20 mL) at room temperature. Methyl iodide (1.0 mL, 15.90 mmol) was added by a syringe. The reaction mixture was stirred at room temperature for 10 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (20:1, Hexanes/EtOAc) to afford *tert*-butyl-(5-methoxyoct-7-ynyloxy)dimethylsilane (**43**) (2.33 g, 9.09 mmol, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (t, J = 6.4 Hz, 2H), 3.38 (s, 3H), 3.30 (p, J = 6.2 Hz, 1H), 2.47−2.32 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.66−1.38 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.1, 79.2, 69.8, 63.1, 57.0, 33.4, 32.8, 26.0, 23.2, 21.6, 18.3, −5.3; IR (neat): 3314, 2930, 2858, 1472, 1361, 1255, 1103 cm^{-1}; HRMS (EI) m/z calcd. for $C_{12}H_{27}O_2Si$ $(M-C_3H_3)^+$ 231.1780 found 231.1786.

To a solution of **43** (896 mg, 3.49 mmol) in THF (15 mL) was added 10% aqueous HCl solution (10.0 mL) at room temperature. The reaction mixture was stirred for 2 h. The reaction was neutralized with sat. aqueous $NaHCO_3$ solution. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1, hexanes/EtOAc) to afford 5-methoxyoct-7-yn-1-ol (**29**) (524 mg, 3.35 mmol, 96%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (t, J = 6.3 Hz, 2H), 3.38 (s, 3H), 3.31 (p, J = 5.8 Hz, 1H), 2.48−2.32 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.69−1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.9, 79.1, 69.8, 62.5, 56.9, 33.2, 32.6, 23.0, 21.4; IR (neat): 3416 (br), 3296, 2938, 2865, 1459, 1359, 1100 cm^{-1}; HRMS (EI) m/z calcd. for $C_6H_{13}O_2$ $(M-C_3H_3)^+$ 117.0915 found 117.0914.

Preparation of 6-methoxynon-8-yn-1-ol (46)



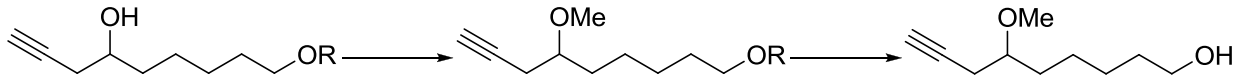
To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 502 mg, 12.55 mmol) in THF (50 mL) was added a solution of 1,6-hexanediol (**35**) (1.50 g, 12.55 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 20 min at which time a large amount of an opaque white precipitate had formed. A solution of *tert*-butyldimethylsilyl chloride (1.95 mg, 12.60 mmol) in THF (20 mL) was then added. The resulting mixture was vigorously stirred for 24 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with

EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (4:1, Hexanes/EtOAc) to afford 6-(*tert*-butyldimethylsilyloxy) hexan-1-ol (**35a**) (1.41 g, 6.07 mmol, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (t, J = 6.5 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 1.62-1.33 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[26]

To a solution of **35a** (1.40 g, 6.02 mmol) in CH_2Cl_2 (10 mL) were added DMSO (15 mL) and Et_3N (2.5 mL, 18.11 mmol) followed by the addition of sulfur trioxide pyridine complex (1.47 g, 9.04 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. EtOAc and water were added and the organic fraction was separated. The aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20:1 hexanes/EtOAc) to afford 6-(*tert*-butyldimethylsilyloxy) hexanal (**38**) (950 mg, 4.12 mmol, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (t, J = 1.8 Hz, 1H), 3.61 (t, J = 6.3 Hz, 2H), 2.43 (td, J = 7.3, 1.8 Hz, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.36 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[53]

To a mixture of **38** (178 mg, 0.773 mmol) and dust zinc (253 mg, 3.864 mmol) in THF (20 mL) were added propargyl bromide (80 wt% solution in toluene, 0.1 mL, 0.927 mmol) and 1,2-diiodoethane (218 mg, 0.773 mmol) at room temperature. The reaction mixture was sonicated for 10 h. After the sonication, the reaction solution was filtered through a silica gel plug and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue was purified by the flash chromatography on silica gel (10:1, hexanes/EtOAc) to

afford 9-(*tert*-butyldimethylsilyloxy)non-1-yn-4-ol (**41**) (120 mg, 0.444 mmol, 57%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (p, J = 5.9 Hz, 1H), 3.60 (t, J = 6.4 Hz, 2H), 2.44 (ddd, J = 16.6, 4.7, 2.6 Hz, 1H), 2.31 (ddd, J = 16.6, 6.7, 2.6 Hz, 1H), 2.05 (t, J = 2.6 Hz, 1H), 1.59−1.33 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.9, 70.8, 69.8, 63.1, 36.2, 32.7, 27.4, 26.0, 25.8, 25.4, 18.4, −5.3; IR (neat): 3400 (br), 3313, 2932, 2858, 2120, 1472, 1388, 1255, 1099 cm^{-1}; HRMS (EI) m/z calcd. for $C_{12}H_{27}O_2Si$ $(M-C_3H_3)^+$ 231.1780 found 231.1790.



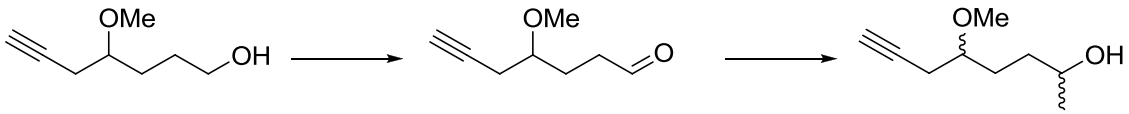
41: R = TBS **44** **46**

To a suspended mixture of sodium hydride (60% dispersion in mineral oil, 94 mg, 2.350 mmol) in THF (20 mL) was added a solution of **41** (318 mg, 1.175 mmol) in THF (10 mL) at room temperature. Methyl iodide (0.15 mL, 2.350 mmol) was added by a syringe. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (20:1, Hexanes/EtOAc) to afford *tert*-butyl(6-methoxynon-8-ynyloxy)dimethylsilane (**44**) (275 mg, 0.966 mmol, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, J = 6.4 Hz, 2H), 3.35 (s, 3H), 3.27 (p, J = 5.8 Hz, 1H), 2.36 (m, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.60−1.23 (m, 8H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 79.2, 69.7, 63.1, 56.9, 33.5, 32.7, 25.9, 25.8, 25.0, 23.1, 18.3, −5.3; IR (neat):

3314, 2931, 2858, 2825, 2100, 1472, 1360, 1255, 1101 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{29}O_2Si$ $(M-C_3H_3)^+$ 245.1937 found 245.1936.

To a solution of **44** (80 mg, 0.281 mmol) in THF (4 mL) was added 10% aqueous HCl solution (0.4 mL) at room temperature. The reaction mixture was stirred for 3 h. The reaction was neutralized with sat. aqueous $NaHCO_3$ solution. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1, hexanes/EtOAc) to afford 6-methoxynon-8-yn-1-ol (**46**) (47 mg, 0.277 mmol, 98%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (t, J = 6.5 Hz, 2H), 3.38 (s, 3H), 3.34−3.27 (m, 1H), 2.40 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.69−1.32 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 79.0, 69.9, 62.9, 57.0, 33.4, 32.6, 25.7, 25.0, 23.0; IR (neat): 3415 (br), 3298, 2935, 2861, 1462, 1359, 1089 cm^{-1}; HRMS (EI) m/z calcd. for $C_7H_{15}O_2$ $(M-C_3H_3)^+$ 131.1072 found 131.1071.

Preparation of 5-methoxyoct-7-yn-2-ol (48)



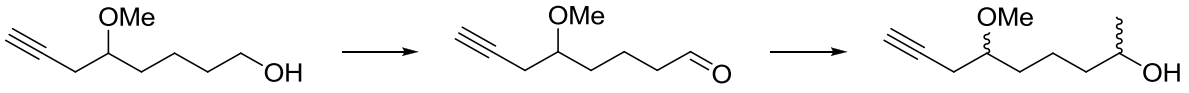
45 **46** **48**

To a suspended mixture of **45** (114 mg, 0.81 mmol) and 4Å powdered molecular sieves (100 mg) in CH_2Cl_2 (10 mL) was added pyridinium dichromate (619 mg, 1.61 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction solution was filtered through a silica gel plug and rinsed with CH_2Cl_2. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (10:1,

hexanes/EtOAc) to afford 4-methoxyhept-6-ynal (**46**) (80 mg, 0.57 mmol, 71%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (t, J = 1.7 Hz, 1H), 3.35 (s, 3H), 3.34 (m, 1H), 2.54 (td, J = 7.1, 1.7 Hz, 2H), 2.48 (ddd, J = 16.8, 4.6, 2.7 Hz, 1H), 2.32 (ddd, J = 16.8, 6.9, 2.7 Hz, 1H), 2.08−1.86 (m, 2H), 2.02 (t, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9, 80.3, 78.3, 70.4, 57.0, 39.8, 26.4, 23.0; IR (neat): 3287, 2933, 2829, 2730, 2118, 1720, 1441, 1359, 1192, 1115 cm^{-1}; HRMS (EI) m/z calcd. for $C_8H_{11}O_2$ $(M-H)^+$ 139.0759 found 139.0760.

To a cooled solution of **46** (25.0 mg, 0.178 mmol) in THF (5 mL) at 0 °C was added methylmagnesium bromide (3.0 M solution in ether, 0.12 mL, 0.357 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with diethyl ether. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and evaporated carefully in an ice bath. The crude residue was purified by flash chromatography on silica gel (1:1, pentane/diethyl ether) to afford volatile 5-methoxyoct-7-yn-2-ol (**48**) (23.0 mg, 0.147 mmol, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28 (h, J = 6.2 Hz, 1H), 3.37 (s, 3H), 3.40−3.30 (m, 1H), 2.49−2.31 (m, 2H), 2.15 (s, OH), 1.99 (m, 1H), 1.85−1.43 (m, 4H), 1.18 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.8, 79.4, 70.1, 70.0, 62.9, 67.7, 56.9, 35.0, 34.9, 30.0, 29.8, 23.4, 23.0; IR (neat): 3417 (br), 3299, 2931, 2828, 1457, 1373, 1090 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{15}O$ $(M-OH)^+$ 139.1123 found 139.1116.

Preparation of 6-methoxynon-8-yn-2-ol (31)



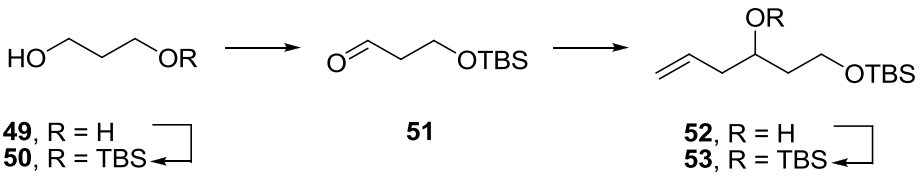
29 **47** **31**

To a suspended mixture of **29** (200 mg, 1.28 mmol) and 4Å powdered molecular sieves (50 mg)

in CH_2Cl_2 (5 mL) was added pyridinium dichromate (983 mg, 2.56 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction solution was filtered through a silica gel plug and rinsed with CH_2Cl_2. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (4:1, hexanes/EtOAc) to afford 5-methoxyoct-7-ynal (**47**) (188 mg, 1.22 mmol, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (t, J = 1.6 Hz, 1H), 3.38 (s, 3H), 3.32 (m, 1H), 2.48 (m, 2H), 2.40 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.86−1.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 80.7, 78.8, 70.1, 57.0, 43.7, 33.0, 22.9, 17.9; IR (neat): 3291, 2936, 1712, 1458, 1360, 1153, 1110 cm^{-1}.

To a cooled solution of **47** (130 mg, 0.843 mmol) in THF (10 mL) at 0 °C was added methylmagnesium bromide (3.0 M solution in ether, 0.42 mL, 1.264 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1, hexanes/EtOAc) to afford 6-methoxynon-8-yn-2-ol (**31**) (115 mg 0.675 mmol, 80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (h, J = 6.1 Hz, 1H), 3.38 (s, 3H), 3.31 (p, J = 6.3 Hz, 1H), 2.48−2.32 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.70−1.36 (m, 6H), 1.20 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 79.2, 79.1, 69.9, 67.8, 67.7, 56.9, 39.1, 33.4, 39.1, 33.4, 23.4, 23.1, 23.0, 21.4, 21.3, 21.4; IR (neat): 3417 (br), 3300, 2934, 2866, 2828, 1460, 1374, 1105 cm^{-1}; HRMS (EI) m/z calcd. for $C_7H_{15}O_2$ $(M-C_3H_3)^+$ 131.1072 found 131.1075.

Preparation of 3,5-dimethoxyoct-7-yn-1-ol (60)



To a stirred solution of NaH (1.00 g, 25.07 mmol) in THF (100 mL) was added a solution of 1,3-propanediol (**49**) (1.89 g, 24.41 mmol) in THF (25 mL) at room temperature. The reaction mixture was stirred for 30 min at which time a large amount of an opaque white precipitate had formed. A solution of TBDMSCl was then added. The resulting mixture was vigorously stirred for 24 h. The reaction was quenched by the addition of H_2O at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residues were purified by flash chromatography on silica gel (4:1 Hexanes/EtOAc) to afford the desired 3-(*tert*-butyldimethylsilyloxy)propan-1-ol (**50**) (1.76 g, 9.25 mmol, 38%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (m, 4H), 2.14 (bs, OH), 1.79 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[26]

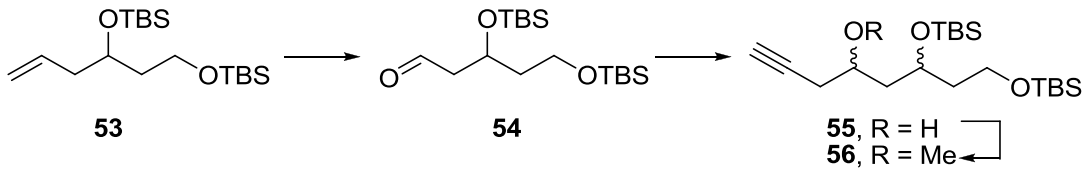
To a solution of **50** (1.64 g, 8.60 mmol) in CH_2Cl_2 (10 mL) were added DMSO (20 mL) and Et_3N (3.6 mL, 25.80 mmol) followed by the addition of SO_3•pyridine (2.09 g, 12.90 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6 h. Diethyl ether and water were added and the organic fraction was separated. The aqueous fraction was extracted with diethyl ether. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15:1 pentane/diethyl ether) to afford 3-(*tert*-butyldimethylsilyloxy)

propanal (**51**) (1.26 g, 6.67 mmol, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (t, J = 2.1 Hz, 1H), 3.98 (t, J = 6.0 Hz, 2H), 2.59 (td, J = 6.0, 2.1 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[54]

To a solution of **51** (1.21 g, 6.40 mmol) in THF (30 mL) at 0 °C was added 1.0 M solution of allylmagnesium bromide in diethyl ether (9.6 mL, 9.60 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (10:1 Hexanes/EtOAc) to afford 1-(*tert*-butyldimethylsilyloxy)hex-5-en-3-ol (**52**) (1.10 g, 4.79 mmol, 75%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.07 (m, 2H), 3.86 (m, 2H), 3.80 (m, 1H), 3.26 (bs, OH), 2.24 (m, 2H), 1.66 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[54]

To a solution of **52** (1.08 g, 4.70 mmol) in DMF (10 mL) was added a mixture of imidazole (0.5 g, 7.27 mmol) and TBDMSCl (1.10 g, 7.08 mmol) in DMF (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 7 h. EtOAc and water were added. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (40:1 hexanes/EtOAc) to afford 4,6-bis(*tert*-butyldimethylsilyloxy)hex-1-ene (**53**) (1.62 g, 4.70 mmol, 100%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.04 (m, 2H), 3.86 (p, J = 6.0 Hz, 1H), 3.66 (t, J = 6.9 Hz, 2H), 2.22 (m, 2H), 1.64 (m, 2H), 0.88

(s, 18H), 0.05 (s, 6H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[54]



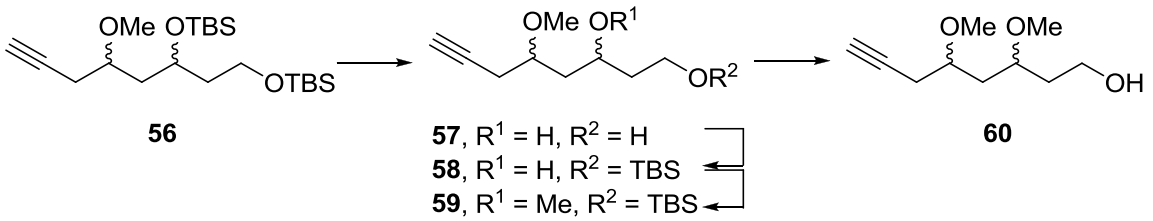
To a solution of **53** (1.65 g, 4.80 mmol) in 1,4-dioxane (35 mL) and water (12 mL) were added 2.6-lutidine (1.1 mL, 9.60 mmol), OsO_4 (24.4 mg, 0.096 mmol), and then $NaIO_4$ (4.15 g, 19.21 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, water and CH_2Cl_2 were added. The organic fraction was separated, and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (20:1, hexanes/EtOAc) to afford 3,5-bis(*tert*-butyldimethyl silyloxy)pentanal (**54**) (1.36 g, 3.92 mmol, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (m, 1H), 4.37 (p, J = 5.9 Hz, 1H), 3.68 (t, J = 6.1 Hz, 2H), 2.61 (ddd, J = 15.7, 5.2, 2.2 Hz, 1H), 2.52 (ddd, J = 15.7, 6.2, 2.9 Hz, 1H), 1.74 (m, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H). The spectroscopic data was consistent with the date reported in the literature.[54]

To a mixture of **54** (1.35 g, 3.89 mmol) and dust zinc (1.27 g, 19.43 mmol) in THF (30 mL) were added 80 wt% solution of propargyl bromide in toluene (0.52 mL, 4.66 mmol) and 1,2-diiodoethane (1.11 g, 3.89 mmol) at room temperature. The reaction mixture was sonicated for 10 h. After the sonication, the reaction solution was filtered through a silica gel pad and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue

was purified by the flash chromatography on silica gel (10:1, hexanes/EtOAc) to afford 6,8-bis(*tert*-butyldimethylsilyloxy)oct-1-yn-4-ol (**55**) (1.20 g, 3.10 mmol, 80%) as a colorless oil. ^{1}H NMR spectroscopic analysis of the substrate showed two diastereoisomers in the ratio of 1:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (m, 1/2H), 4.10 (m, 1H), 3.93 (1/2H), 3.65 (m, 2H), 2.37 (m, 2H), 2.02 (t, J = 2.5 Hz, 1H), 1.93−1.57 (m, 4H), 0.90 (s, 9/2H), 0.89 (s, 9/2H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H); IR (neat): 3458 (br), 3314, 2955, 2858, 2090, 1463, 1388, 1361, 1256, 1097 cm^{-1}; HRMS (EI) m/z calcd. for $C_{19}H_{39}O_3Si$ $(M-CH_3)^+$ 371.2438 found 371.2427.

To a suspended solution of sodium hydride (60% dispersion in mineral oil, 185.3 mg, 4.63 mmol) in THF (10 mL) was added a solution of **55** (1.19 g, 3.09 mmol) in THF (10 mL) followed by the addition of CH_3I (0.29 mL, 4.63 mmol) at room temperature. The reaction mixture was stirred at same temperature for 7 h. The reaction was quenched by adding water at 0 °C. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (20:1, hexanes/EtOAc) to afford 6,8-bis(*tert*-butyldimethylsilyloxy)-4-methoxyoct-1-yne (**56**) (1.24 g, 3.09 mmol, 99%) as a colorless oil. ^{1}H NMR spectroscopic analysis of the substrate showed two diastereoisomers in the ratio of 1:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (m, 1H), 3.67 (m, 2H), 3.45 (m, 1H), 3.36 (s, 3H), 2.41 (m, 2H), 1.98 (m, 1H), 1.79−1.66 (m, 4H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.8, 75.8, 70.1, 66.7, 59.5, 56.4, 42.3, 41.1, 25.9, 23.1, 18.2, 18.1, −4.2, −4.6, −5.3; For diastereoisomer: δ 81.0, 76.3, 69.9, 66.6, 59.8, 56.8, 41.5, 40.1, 25.9, 23.4, 18.7, 18.1, −4.4, −4.6, −5.3; IR (neat): 3315, 2929, 2886, 2857, 2100, 1472, 1388, 1255, 1102 cm^{-1}; HRMS (EI)

m/z calcd. for $C_{17}H_{35}O_3Si_2$ $(M-C_4H_9)^+$ 343.2125 found 343.2127.



To a solution of **56** (1.17 g, 2.93 mmol) in THF (30 mL) was added 10% aqueous HCl (3.2 mL) at room temperature. The reaction mixture was stirred for 12 h. The reaction was neutralized with sat. aqueous $NaHCO_3$ solution. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1, hexanes/EtOAc to EtOAc only) to afford 5-methoxyoct-7-yne-1,3-diol (**57**) (485 mg, 2.82 mmol, 96%) as a colorless oil. ^{1}H NMR spectroscopic analysis of the substrate showed two diastereoisomers in the ratio of 2:1 by integration of the signals at δ_H = 3.42 (major) and 3.43 (minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.16 (m, 1H), 3.87 (m, 2H), 3.69 (m, 1H), 3.42 (s, 3H), 2.91 (bs, 2OH), 2.48 (m, 2H), 2.01 (t, J = 2.7 Hz, 1H), 1.82 (m, 2H), 1.72 (m, 2H); For diastereoisomer: δ 4.10 (m, 1H), 3.83 (m, 2H), 3.61 (m, 1H), 3.43 (s, 3H), 2.91 (bs, 2OH), 2.43 (m, 2H), 2.03 (2.7 Hz, 1H), 1.83 (m, 2H), 1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.1, 77.1, 70.4, 68.9, 61.7, 57.2, 40.3, 38.7, 22.8; For diastereoisomer: δ 80.5, 77.1, 71.6, 70.7, 61.3, 56.7, 40.9, 38.7, 23.0; IR (neat): 3400, 3290, 2942, 2100, 1427, 1362, 1258, 1083 cm^{-1}; HRMS (EI) m/z calcd. for $C_9H_{17}O_3$ $(M+H)^+$ 173.1178 found 173.1181.

To a solution of **57** (297 mg, 1.72 mmol) in CH_2Cl_2 (10 mL) were added TBDMSCl (402 mg, 2.58 mmol), Et_3N (0.73 mL, 5.17 mmol), and DMAP (12.7 mg, 0.10 mmol) at room

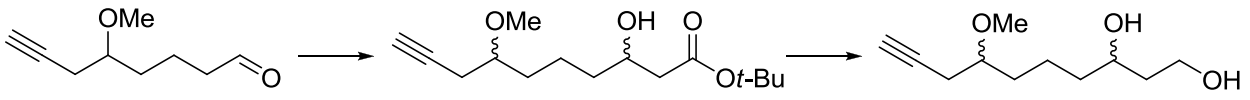
temperature. The resulting mixture was stirred at same temperature for 24 h. The reaction was quenched with sat. aqueous NH_4Cl solution. The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (10:1, hexanes/EtOAc) to afford 1-(*tert*-butyldimethylsilyloxy)-5-methoxyoct-7-yn-3-ol (**58**) (420 mg, 1.47 mmol, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10−3.93 (m, 1H), 3.90-3.76 (m, 2H), 3.68−3.53 (m, 1H), 2.46 (m, 2H), 1.99 (m, 1H), 1.81−1.60 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.3, 76.2, 70.1, 68.3, 62.4, 57.3, 41.7, 39.0, 25.9, 23.3, 18.1, −5.5; For diastereoisomer: δ 80.8, 80.5, 70.3, 69.2, 61.5, 56.7, 40.8, 39.3, 25.9, 22.9, 18.2, −5.5; IR (neat): 3501 (br), 3313, 2930, 2858, 2100, 1472, 1255, 1094 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{21}O_3Si$ $(M-C_4H_9)^+$ 229.1260 found 229.1262.

To a solution of **58** (239 mg, 0.83 mmol) in CH_2Cl_2 (0.4 mL) was added 2,6-di-*tert*-butylpyridine (0.29 mL, 1.25 mmol) at room temperature. The solution was cooled to 0 °C and then methyl trifluoromethanesulfonate (0.14 mL, 1.25 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with water. The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 times). The combined organic fraction was washed with sat. aqueous $NaHCO_3$ solution and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (10:1, hexanes/EtOAc) to afford *tert*-butyl(3,5-dimethoxyoct-7-ynyloxy)dimethylsilane (**59**) (210 mg, 0.70 mmol, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (m, 2H), 3.51 (m, 2H), 3.40 (s, 3H), 3.35 (s, 3H), 2.42 (m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.79−1.67 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); For

diastereoisomer: δ 3.71 (m, 2H), 3.49 (m, 2H), 3.37 (s, 3H), 3.32 (s, 3H), 2.44 (ABX system, m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.93−1.63 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.8, 76.1, 75.8, 70.1, 59.4, 57.1, 56.9, 39.7, 37.2, 25.9, 23.3, 18.2, −5.3; for diastereoisomer: δ 80.8, 76.1, 75.8, 70.1, 59.4, 56.9, 56.4, 37.4, 37.0, 23.2, 18.2, −5.3; IR (neat): 3313, 2930, 2857, 2824, 2121, 1472, 1387, 1255, 1109 cm^{-1}; HRMS (EI) m/z calcd. for $C_{12}H_{23}O_3Si$ $(M-C_4H_9)^+$ 243.1416 found 243.1416.

To a solution of **59** (150 mg, 0.50 mmol) in THF (5 mL) was added 10% aqueous HCl solution (0.7 mL) at room temperature. The reaction mixture was stirred for 12 h. The reaction was neutralized with sat. aqueous $NaHCO_3$ solution. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1, hexanes/EtOAc) to afford 3,5-dimethoxyoct-7-yn-1-ol (**60**) (90 mg, 0.48 mmol, 97%) as a colorless oil. ^{1}H NMR spectroscopic analysis of the substrate showed two diastereoisomers in the ratio of 2:1 by integration of the signals at δ_H = 3.40 (major) and 3.37 (minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86−3.70 (m, 2H), 3.69−3.56 (m, 1H), 3.55−3.40 (m, 1H), 3.40 (s, 3H, major), 3.39 (s, 3H, major), 3.37 (s, 3H, minor), 3.36 (s, 3H, minor), 2.44 (m, 2H), 2.02 (m, 1H), 1.99−1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.5 (minor), 80.4 (major), 78.1, 75.9, 70.3, 60.8 (minor), 60.2 (major), 57.0 (major), 56.9 (major), 56.8 (minor), 56.3 (minor), 39.1 (major), 36.9 (minor), 35.7 (major), 35.5 (minor), 23.2 (major), 23.1 (minor); IR (neat): 3418 (br), 3294, 2935, 2828, 1427, 1379, 1112 cm^{-1}; HRMS (EI) m/z calcd. for $C_{10}H_{18}O_3$ $(M)^+$ 186.1256 found 186.1257.

Preparation of 7-methoxydec-9-yne-1,3-diol (62)



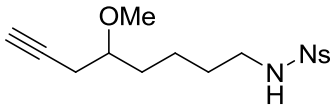
47 **61** **62**

To a cooled 1.0 M solution of LDA in THF (5.1 mL, 5.1 mmol) at −78 °C was added *tert*-butylacetate (0.64 mL, 4.67 mmol) dropwise over 2 min. The yellow mixture was stirred at −78 °C for 20 min at same temperature. A solution of **47** (360 mg, 2.33 mmol) in THF (7.0 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 20 min and allowed to warm to room temperature. The reaction mixture was then continued to stir for additional 2 h. The reaction was quenched by adding water at −78 °C and allowed to warm to room temperature. The organic fraction was separated and the aqueous fraction was extracted with EtOAc (2 times). The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography on silica gel (4:1, hexanes/EtOAc) to afford *tert*-butyl-3-hydroxy-7-methoxydec-9-ynoate (**61**) (550 mg, 2.03 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (m, 1H), 3.38 (s, 3H), 3.29 (m, 1H), 3.14 (s, OH), 2.48−2.28 (m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.71−1.35 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 81.2, 80.1, 79.2, 79.1, 69.9, 68.0, 67.9, 57.0, 42.3, 42.2, 36.4, 36.3, 33.5, 33.4, 28.1, 23.1, 21.3, 21.2; IR (neat): 3467 (br), 3297, 2978, 2933, 1726, 1368, 1151, 1113 cm^{-1}; HRMS (EI) m/z calcd. for $C_7H_{15}O_2$ (M−O*t*-Bu)$^+$ 197.1178 found 197.1183.

To a solution of **61** (300 mg, 1.11 mmol) in diethyl ether (10 mL) was added LAH (1.0 M solution in diethyl ether, 1.66 mL, 1.66 mmol) at 0 °C dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched by adding sat. aqueous sodium tartrate solution (10 mL) and then continued to stir for 30 min.

10% aqueous HCl solution (10 mL) was added and the resulting solution was stirred for additional 30 min. To the milky colored solution was added brine until reaction color became clear. The organic fraction was separated and the aqueous fraction was extracted with EtOAc (3 times). The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1, hexanes/EtOAc to EtOAc only) to afford 7-methoxydec-9-yne-1,3-diol (**62**) (220 mg, 1.10 mmol, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92−3.78 (m, 3H), 3.40-3.27 (m, 1H), 3.38 (s, 3H), 2.65 (brs, 2 × OH), 2.41 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.74−1.34 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.1, 79.2, 79.1, 71.9, 71.8, 69.9, 61.7, 57.0, 56.9, 38.3, 38.2, 37.7, 37.6, 33.4, 23.1, 23.0, 21.2, 21.1; IR (neat): 3415 (br), 3298, 2938, 1459, 1358, 1191, 1101 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{21}O_3$ $(M+H)^+$ 201.1491 found 201.1498.

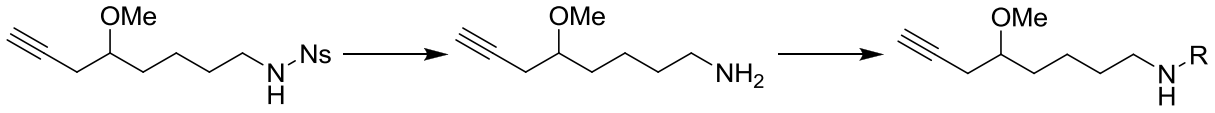
***N*-(5-Methoxyoct-7-ynyl)-2-nitrobenzenesulfonamide (74)**



To a solution of 2-nitrobenzenesulfonamide (3.59 g, 17.76 mmol), diphenyl-2-pyridylphophine (4.28 g, 17.76 mmol) and alcohol **29** (1.39 g, 8.88 mmol) in CH_2Cl_2 (120 mL) was added a solution of di-*tert*-butylazodicarboxylate (4.17 g, 17.76 mmol) in CH_2Cl_2 (30 mL) dropwise over 50 min at room temperature. The reaction mixture was stirred for 2 h at same temperature. HCl (4.0 M in 1,4-dioxane, 90.0 mL) was added, and the resulting mixture was continued to stir for additional 1 h. The solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 10% aqueous HCl solution (2 times). The organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford *N*-(5-methoxyoct-7-ynyl)-2-nitrobenzene

sulfonamide (**74**) (2.10 g, 6.17 mmol, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16−8.10 (m, 1H), 7.89−7.83 (m, 1H), 7.78−7.71 (m, 2H), 5.28 (t, J = 5.8 Hz, 1H), 3.34 (s, 3H), 3.29-3.21 (m, 1H), 3.11 (q, J = 6.6 Hz, 2H), 2.41 (ddd, J = 16.9, 4.7, 2.7 Hz, 1H), 2.32 (ddd, J = 16.9, 6.5, 2.7 Hz, 1H), 1.98 (t, J = 2.7 Hz, 1H), 1.61−1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 133.8, 133.5, 132.7, 131.0, 125.3, 80.8, 78.8, 70.0, 56.9, 43.7, 32.9, 29.6, 22.9, 22.2; IR (neat): 3293, 3069, 2938, 2866, 2120, 1593, 1539, 1441, 1362, 1165, 1124, 1101 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{15}H_{20}N_2O_5SNa$ $(M+Na)^+$ 363.0991 found 363.1004.

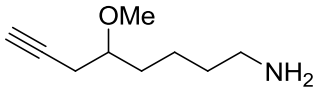
Preparation of carbamate substrates (76, 77, 78, and 79)



74 **75**

76, R = COOMe
77, R = Cbz
78, R = Fmoc
79, R = ^{t}Boc

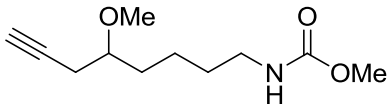
5-Methoxyoct-7-yn-1-amine (75)



To a solution of sulfonamide **74** (1.89 g, 5.54 mmol) in acetonitrile (50 mL) were added potassium carbonate (2.30 g, 16.63 mmol) and thiophenol (1.7 mL, 16.63 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 12 h. The yellowish mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (90:8:2, CH_2Cl_2/MeOH/Et_3N) to afford 5-methoxyoct-7-yn-1-amine (**75**) (750 mg, 4.83 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (bs, 2H), 3.37 (s, 3H), 3.30 (m, 1H), 2.78 (t, J = 7.1 Hz, 2H), 2.47−2.32 (m, 2H), 2.00 (t, J = 2.6 Hz, 1H), 1.67−1.32 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 79.1, 70.0, 57.0, 41.2, 33.2, 31.4, 23.1, 22.5; IR (neat): 3289, 2935, 1616, 1558, 1506, 1458, 1103 cm^{-1}; HRMA

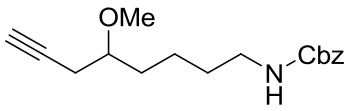
(EI) m/z, calcd. for $C_8H_{14}N$ $(M-OCH_3)^+$ 124.1126, found 124.1126.

Methyl 5-methoxyoct-7-ynylcarbamate (76)



To a solution of amine **75** (100 mg, 0.644 mmol) in THF/H_2O (10 mL, *v/v* 1:1) was added $NaHCO_3$ (81 mg, 0.966 mmol) at room temperature. The mixture was stirred at same temperature for 10 min, and methyl chloroformate (75 μL, 0.966 mmol) was then added. The resulting mixture was stirred for 30 min. The mixture was extracted with EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1, hexanes/EtOAc) to afford methyl 5-methoxyoct-7-ynylcarbamate (**76**) (120 mg, 0.563 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (bs, 1H), 3.65 (bs, 3H), 3.37 (s, 3H), 3.28 (m, 1H), 3.18 (m, 2H), 2.43 (ddd, J = 16.8, 4.9, 2.6 Hz, 1H), 2.36 (ddd, J = 16.8, 6.3, 2.6 Hz, 1H), 1.99 (t, J = 2.7 Hz, 1H), 1.69−1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 80.9, 79.0, 69.9, 57.0, 52.0, 41.0, 33.2, 30.0, 23.1, 22.4; IR (neat): 3335, 3308, 2933, 2864, 1712, 1532, 1460, 1251, 1103 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{11}H_{19}NO_3Na$ $(M+Na)^+$ 236.1263 found 236.1261.

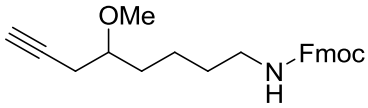
Benzyl 5-methoxyoct-7-ynylcarbamate (77)



To a solution of amine **75** (100 mg, 0.644 mmol) in THF/H_2O (10 mL, *v/v* 1:1) was added $NaHCO_3$ (81 mg, 0.966 mmol) at room temperature. The mixture was stirred at same temperature for 10 min, and benzyl chloroformate (140 μL, 0.966 mmol) was then added. The resulting mixture was stirred for 30 min. The milky suspended mixture was extracted with EtOAc. The organic fraction was

washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1, hexanes/EtOAc) to afford benzyl 5-methoxyoct-7-ynylcarbamate (**77**) (186 mg, 0.644 mmol, 100%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.12 (bs, 1H), 5.09 (s, 1H), 4.77 (bs, 1H), 3.36 (s, 3H), 3.29 (m, 1H), 3.20 (q, J = 6.5 Hz, 2H), 2.47−2.31 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.66−1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 136.7, 128.5, 128.0, 80.9, 79.0, 70.0, 66.6, 57.0, 41.0, 33.2, 30.0, 23.1, 22.4; IR (neat): 3335 (br), 3304, 2935, 1705, 1531, 1455, 1249, 1110 cm^{-1}; HRMS (EI) m/z calcd. for $C_{17}H_{23}NO_3$ $(M)^+$ 289.1678 found 289.1685.

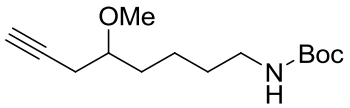
(9*H*-Fluoren-9-yl)methyl 5-methoxyoct-7-ynylcarbamate (78)



To a solution of amine (**75**) (241 mg, 1.552 mmol) in THF/H_2O (20 mL, *v/v* 1:1) was added $NaHCO_3$ (196 mg, 2.329 mmol) at room temperature. The mixture was stirred at same temperature for 10 min, and 9-fluoenylmethoxy carbonyl chloride (602 mg, 2.329 mmol) was then added. The resulting mixture was stirred for 1 h. The mixture was extracted with EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (4:1, hexanes/EtOAc) to afford (9*H*-fluoren-9-yl)methyl 5-methoxyoct-7-ynylcarbamate (**78**) (500 mg, 1.325 mmol, 85%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.4 Hz, 2H), 7.59 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.31 (td, J = 7.4, 1.1 Hz, 2H), 4.77 (bs, 1H), 4.40 (d, J = 6.8 Hz, 2H), 4.22 (t, J = 6.8 Hz, 1H), 3.38 (s, 3H), 3.32 (m, 1H), 3.21 (q, J = 6.6 Hz, 2H), 2.47−2.32 (m, 2H), 2.00 (t, J = 2.6 Hz, 1H), 1.68−1.32 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 144.0, 141.3, 127.6, 127.0, 125.0, 119.9, 80.9, 79.0, 70.0, 66.5, 57.0, 47.3, 40.9, 33.2, 29.9, 23.0, 22.4; IR (neat):

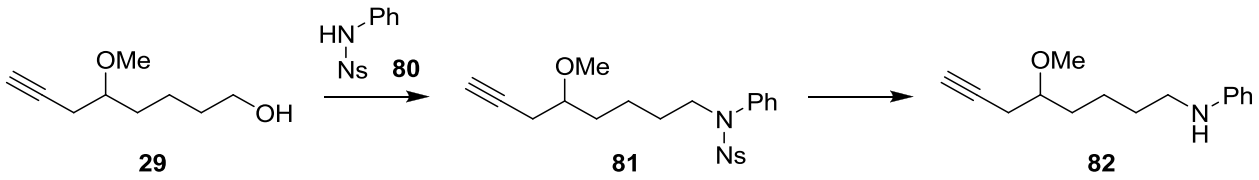
3334 (br), 3304, 2932, 2862, 1717, 1521, 1450, 1247, 1135, 1105 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{24}H_{27}NO_3Na$ $(M+Na)^+$ 400.1889 found 400.1866.

***tert*-Butyl 5-methoxyoct-7-ynylcarbamate (79)**

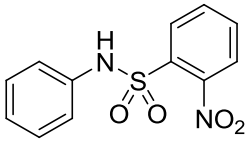


To a solution of amine **75** (160 mg, 1.031 mmol) in THF/H_2O (10 mL, *v/v* 1:1) was added $NaHCO_3$ (130 mg, 1.549 mmol) at room temperature. The mixture was stirred at same temperature for 10 min, and di-*tert*-butyl dicarbonate (273 mg, 1.237 mmol) was added. The resulting mixture was stirred for 12 h. The mixture was extracted with EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (4:1, hexanes/EtOAc) to afford *tert*-butyl 5-methoxyoct-7-ynylcarbamate (**79**) (180 mg, 0.705 mmol, 68%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 4.52 (bs, 1H), 3.37 (s, 3H), 3.29 (m, 1H), 3.11 (bm, 2H), 2.47−2.31 (m, 2H), 1.98 (t, J = 3.2 Hz, 1H), 1.64−1.30 (m, 6H), 1.43 (s, 9H); (300 MHz, C_6D_6): δ 4.02 (bs, 1H), 3.04 (s, 3H), 2.99 (m, 1H), 2.93 (m, 2H), 2.20 (ddd, J = 16.7, 4.9, 2.7 Hz, 1H), 2.09 (ddd, J = 16.7, 6.6, 2.7 Hz, 1H), 1.76 (t, J = 2.7 Hz, 1H), 1.46 (s, 9H), 1.42 (m, 1H), 1.24−1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 81.0, 79.1, 69.9, 57.0, 40.5, 33.2, 30.1, 28.4, 23.1, 22.5; (75 MHz, C_6D_6): δ 155.8, 81.5, 79.3, 78.4, 70.2, 56.7, 40.7, 33.6, 30.3, 28.6, 23.4, 22.6; IR (neat): 3399, 2982, 2934, 1742, 1515, 1447, 1373, 1242, 1047 cm^{-1}; HRMS (EI) m/z calcd. for $C_{10}H_{16}NO_3$ $(M-C_4H_9)^+$ 198.1130 found 198.1136.

Preparation of *N*-(5-methoxyoct-7-ynyl)benzenamine (82)



2-Nitro-*N*-phenylbenzenesulfonamide (80)



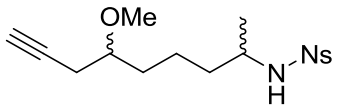
To a mixture of aniline (0.42 mL, 4.59 mmol) and 2-nitrobenzenesulfonyl chloride (525 mg, 2.30 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.56 mL, 6.89 mmol). The reaction mixture was stirred at room temperature for 3 h. 10% aqueous HCl solution was added until pH became approximately 1.0. The mixture was extracted with CH_2Cl_2 (2 times). The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:3, hexanes/CH_2Cl_2) to afford 2-nitro-*N*-phenylbenzene sulfonamide (**80**) (600 mg, 2.16 mmol, 94%) as a light yellowish solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.9, 1.2 Hz, 1H), 7.82 (dd, J= 7.8, 1.4 Hz, 1H), 7.69 (td, J = 7.7, 1.4 Hz, 1H), 7.57 (td, J = 7.7, 1.2 Hz, 1H), 7.29−7.15 (m, 5H). The spectroscopic data was consistent with the date reported in the literature.[55]

To a mixture of alcohol **29** (132 mg, 0.845 mmol), sulfonamide **80** (279 mg, 1.00 mmol), and triphenylphosphine (336 mg, 1.268 mmol) in CH_2Cl_2 (10 mL) was added di-*iso*-propylazo dicarboxylate (0.26 mL, 1.268 mmol) dropwise over 30 min. The reaction mixture was stirred at room temperature for 30 min. 10% aqueous HCl solution and CH_2Cl_2 were added and the organic fraction was separated. The aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel

(40:1, CH_2Cl_2/EtOAc) to afford *N*-(5-methoxyoct-7-ynyl)-2-nitro-*N*-phenylbenzenesulfonamide (**81**) (352 mg, 0.845 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 2H), 7.46 (m, 2H), 7.31 (m, 3H), 7.21 (m, 2H), 3.79 (t, J = 6.7 Hz, 2H), 3.34 (s, 3H), 3.26 (m, 1H), 2.45−2.30 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.67−1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 137.9, 133.4, 132.0, 131.8, 130.9, 129.4, 129.3, 128.4, 123.7, 80.9, 78.9, 69.9, 57.0, 52.0, 33.0, 28.6, 23.1, 22.0; IR (neat, cm^{-1}): 3294, 3094, 2937, 2865, 2118, 1593, 1544, 1372, 1164, 1127, 1103; HRMS (EI) m/z calcd. for $C_{21}H_{25}N_2O_5S$ $(M+H)^+$ 417.1484 found 417.1496.

To a solution of **81** (335 mg, 0.804 mmol) in acetonitrile (10 mL) were added potassium carbonate (333 mg, 2.413 mmol) and thiophenol (0.25 mL, 2.413 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 4 h. The yellowish mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (40:1, CH_2Cl_2/EtOAc) to afford *N*-(5-methoxyoct-7-ynyl)benzenamine (**82**) (186 mg, 0.804 mmol, 100%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (tm, J = 7.8 Hz, 2H), 6.69 (tm, J = 7.8 Hz, 1H), 6.60 (dm, J = 7.8 Hz, 2H), 3.62 (bs, 1H), 3.39 (s, 3H), 3.32 (m, 1H), 3.13 (t, J = 6.9 Hz, 2H), 2.49−2.34 (m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.73−1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 129.2, 117.1, 112.7, 80.9, 79.1, 70.0, 57.0, 43.8, 33.4, 29.5, 23.1, 22.9; IR (neat): 3400, 3292, 2935, 2861, 2118, 1603, 1507, 1320, 1101 cm^{-1}; HRMS (EI) m/z calcd. for $C_{15}H_{21}NO$ $(M)^+$ 231.1623 found 231.1619.

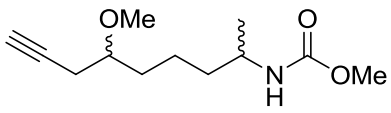
_N_-(6-Methoxynon-8-yn-2-yl)-2-nitrobenzenesulfonamide (83)



To a mixture of alcohol **31** (575 mg, 3.04 mmol), 2-nitrobenzenesulfonamide (1.23 g, 6.08 mmol), and triphenylphosphine (1.62 g, 6.08 mmol) in CH_2Cl_2 (70 mL) was added a solution of di-*iso*-

propylazodicarboxylate (1.31 g, 6.08 mmol) in CH_2Cl_2 (30 mL) dropwise over 1 h. The reaction mixture was stirred at room temperature for 8 h. Water and CH_2Cl_2 were added and the white solid was filtrated through a silica gel plug. The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (80:1, CH_2Cl_2/EtOAc) to afford *N*-(6-methoxynon-8-yn-2-yl)-2-nitrobenzenesulfonamide (**83**) (550 mg, 1.55 mmol, 51%) as a colorless oil. ^{1}H NMR spectroscopic analysis of the crude products showed two diastereoisomers in the ratio of 1:1 by integration of the signals at δ_H = 3.33 and 3.32 respectively. For a mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (m, 1H), 7.86 (m, 1H), 7.73 (m, 2H), 5.10 (m, 1H), 3.53 (m, 1H), 3.33 (s, 3/2H), 3.32 (s, 3/2H), 3.21 (m, 1H), 2.33 (m, 2H), 1.98 (m, 1H), 1.57−1.21 (m, 6H), 1.10 (d, J = 6.6 Hz, 3/2H), 1.09 (d, J = 6.6 Hz, 3/2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 135.2, 133.3, 132.8, 130.6, 125.4, (125.3 for diastereoisomer), 80.8, 78.9, 70.0, 57.0, 51.2, (51.1 for diastereoisomer), 37.4, 33.2, 23.0, 21.7, (21.6 for diastereoisomer), 21.4, (21.3 for diastereoisomer); IR (neat): 3293, 2118, 1540, 1418, 1361, 1166, 1123 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{19}N_2O_5S$ $(M-C_3H_3)^+$ 315.1015 found 315.1007.

Methyl 6-methoxynon-8-yn-2-ylcarbamate (84)

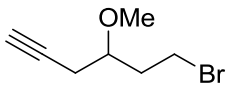


To a mixture of sulfonamide **83** (150 mg, 0.423 mmol) and potassium carbonate (230 mg, 1.664 mmol) in acetonitrile (10 mL) was added thiophenol (131 μL, 1.270 mmol). The reaction mixture was stirred at 40 °C for 2 h. After the denosylation was complete, to the yellowish solution was added methyl

chloroformate (200 μL, 2.539 mmol). The resulting mixture was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (4:1, hexanes/EtOAc) to afford methyl 6-methoxynon-8-yn-2-ylcarbamate (**84**) (96 mg, 0.423, 100%) as a colorless oil. ^{13}C NMR spectroscopic analysis of the crude products showed two diastereoisomers in the ratio of 1:1 by height of the signals at δ_c = 21.7 and 21.6 respectively. For a mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44 (m, 1H), 3.67 (m, 1H), 3.65 (s, 3H), 3.37 (s, 3H), 3.29 (p, J = 5.7 Hz, 1H), 2.40 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.68−1.30 (m, 6H), 1.13 (d, J = 6.5 Hz, 3H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 81.0, 79.1, 69.9, 57.0, 51.8, 47.1, 37.1, 33.4, 23.1, 21.7, (21.6 for diastereoisomer), 21.2; IR (neat): 3309, 2934, 2865, 2119, 1716, 1538, 1456, 1355, 1254, 1101 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{18}NO_3$ $(M-CH_3)^+$ 212.1287 found 212.1278.

1.4.6 Total synthesis of (+)-andrachcinidine

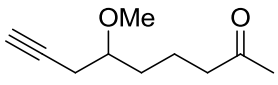
6-Bromo-4-methoxyhex-1-yne (99)



To a cooled solution of 3-bromopropionaldehyde dimethyl acetal (2.31 g, 11.36 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added allenyltributyltin(IV) (5.2 mL, 17.04 mmol), followed by the dropwise addition of 1.0 M solution of $TiCl_4$(IV) in CH_2Cl_2 (13.6 mL, 13.6 mmol). The dark brown mixture was stirred at −78 °C for 3 h. The reaction was quenched with sat. aqueous $NaHCO_3$ at −78 °C and then allowed to warm to room temperature. The reaction solution was poured into sat. aqueous $NaHCO_3$ solution. The crude

was extracted with EtOAc (2 times). The combined organic fraction was washed with brine (2 times), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (20:1, hexanes/EtOAc) to afford **99** (2.10 g, 10.54 mmol, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (m, 3H), 3.43 (s, 3H), 2.45 (dd, J = 5.4, 2.7 Hz, 2H), 2.14 (m, 2H), 2.03 (t, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.1, 76.8, 70.5, 57.4, 37.1, 29.8, 22.8; IR (neat): 3298, 2931, 2828, 2120, 1433, 1360, 1260, 1109 cm^{-1}; HRMS (EI) m/z calcd. for C_4H_9OBr $(M-C_3H_3)^+$ 151.9837 found 151.9824.

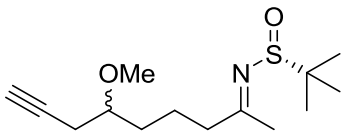
6-Methoxynon-8-yn-2-one (101)



To a cooled 1.0 M solution of LDA in THF (10 mL, 10.0 mmol) with HMPA (3.5 mL, 20.0 mmol) at −45 °C was added a cooled solution of cyclohexylimine (1.40 g, 10.1 mmol) in THF (5 mL) at −78 °C dropwise. The yellow mixture was stirred at −45 °C for 1.5 h. To a solution of metalloenamine was added a cooled solution of bromide **100** (1.58 g, 8.27 mmol) in THF (10 mL) at −78 °C dropwise. The resulting mixture was stirred at −45 °C for 2 h and allowed to warm to room temperature. The reaction mixture was then stirred at room temperature for 12 h. The reaction was quenched with water and acidified with 10% aqueous HCl solution at 0 °C (pH = 6). The organic fraction was separated and the aqueous fraction was extracted with EtOAc (2 times). The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography on silica gel (4:1, hexanes/EtOAc) to afford ketone **101** (573 mg, 3.41 mmol, 41%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.29 (m, 1H), 2.45 (t, J = 6.4 Hz, 2H), 2.39 (m, 2H), 2.12 (s,

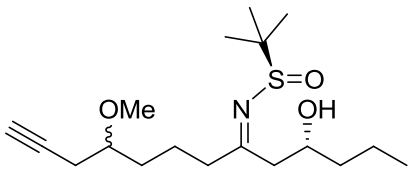
3H), 1.98 (t, J = 2.6 Hz, 1H), 1.73−1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6, 80.8, 79.0, 70.0, 57.0, 43.6, 33.0, 29.8, 23.0, 19.6; IR (neat): 3287, 2933, 2827, 2118, 1715, 1427, 1360, 1160, 1112 cm^{-1}; HRMS (EI) m/z calcd. for $C_7H_{13}O_2$ $(M-C_3H_3)^+$ 129.0915 found 129.0919.

(12*R*,*E*)-*N*-(6-Methoxynon-8-yn-2-ylidene)-2-methylpropane-2-sulfinamide (102)



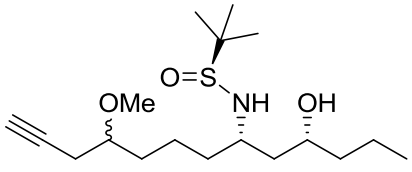
To a solution of ketone **101** (500 mg, 2.97 mmol) in THF (3 mL) was added $Ti(OEt)_4$ at room temperature, followed by adding a solution of (R)-(+)-2-methyl-2-propansulfamide (540 mg, 4.46 mmol) in THF (3 mL). The reaction mixture was stirred at 70 °C for 12 h. The reaction was cooled to 0 °C immediately and then poured into a brine solution with vigorously stirring. The resulting white suspended solution was filtered through a Celite pad and rinsed with EtOAc. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (10:1 to 4:1, hexanes/EtOAc with 5% Et_3N) to afford **102** (584 mg, 2.15 mmol, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.30 (m, 1H), 2.40 (m, 4H), 2.31 (s, 3H), 1.98 (t, J = 2.6 Hz, 1H), 1.67 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0, 80.8, 79.0, 70.0, 57.0, 56.2, 43.2, 33.0, 23.1, 22.9, 22.2, 21.3; IR (neat): 3469, 3294, 3235, 2928, 2826, 2118, 1624, 1475, 1362, 1189, 1112 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{26}NO_2S$ $(M+H)^+$ 272.1684 found 272.1685.

(*R*,*Z*)-*N*-((4*R*)-4-Hydroxy-10-methoxytridec-12-yn-6-ylidene)-2-methylpropane-2-sulfinamide (103)



To a cooled 1.0 M solution of LDA in THF (2.2 mL, 2.2 mmol) at −78 °C was added a cooled solution of **102** (502 mg, 1.85 mmol) in THF (8 mL). The mixture was stirred for 30 min and anhydrous $MgBr_2$ (670 mg, 3.70 mmol) was added with a portion. The mixture was stirred at −78 °C for 1 h. To the light yellowish metalloenamine solution was added *n*-butyraldehyde (0.25 mL, 2.77 mmol) dropwise. The reaction mixture was stirred at −78 °C for 24 h. After reaction was complete, a cooled 2.0 N AcOH in THF (10 mL) was added dropwise and the resulting mixture was then stirred at −78 °C for 20 min. Brine and sat. aqueous $NaHCO_3$ solution were added and reaction was allowed to warm to room temperature. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, concentrated under reduced pressure. The crude was purified with short silica gel chromatography (4:1 to 2:1, hexanes/EtOAc with 5% Et_3N) to afford **103** (410 mg, 1.19 mmol, 65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (d, J = 9.4 Hz, 1H), 3.77 (m, 1H), 3.38 (s, 3H), 3.31 (m, 1H), 3.11 (t, J = 11.4 Hz, 1H), 2.40 (m, 4H), 1.99 (t, J = 2.5 Hz, 1H), 1.71−1.33 (m, 8H), 1.26 (s, 9H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.8, 80.9, 79.2, 79.1, 70.0, 67.4, 57.7, 57.1, 45.2, 41.5, 40.9, 33.0, 22.5, 21.3, 18.8, 14.0.

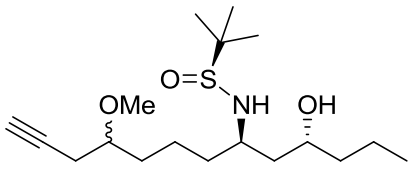
(*S*)-*N*-((4*R*,6*S*)-4-Hydroxy-10-methoxytridec-12-yn-6-yl)-2-methylpropane-2-sulfinamide (*syn*-104)



To a solution of **103** (404 mg, 1.18 mmol) in THF (8 mL) at −50 °C was added catecholborane (0.38 mL, 3.53 mmol) dropwise. The reaction mixture was stirred at same

temperature for 2 h. MeOH (10 mL) and sat. aqueous Na,K tartrate solution (10 mL) were added. The resulting mixture was continued to stir for an additional 20 min and allowed to warm to room temperature. The white solution was washed with brine and extracted with EtOAc. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was dried over $MgSO_4$, filtered, and concentrated. The crude was purified by flash chromatography on silica gel (1:1, hexanes/EtOAc to EtOAc only) to afford *syn*-**104** (258 mg, 0.75 mmol, 64%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (m, 1H), 3.72 (m, 1H), 3.36 (s, 3H), 3.30 (m, 2H), 2.90 (dd, J = 6.8, 2.9 Hz, 1H), 2.39 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.80 (m, 2H), 1.65-1.30 (m, 10H), 1.20 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.9, 79.0, 78.9 (for diastereoisomer), 71.5, 69.9, 57.0, 56.9, 56.8 (for diastereoisomer), 55.8, 43.1, 43.0 (for diastereoisomer), 40.9, 35.8, 35.7 (for diastereoisomer), 33.2, 23.0, 22.6, 21.6, 21.5, 18.5, 14.0; IR (neat): 3400 (br), 3311, 2932, 2870, 2119, 1645, 1457, 1364, 1106, 1043 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{18}H_{35}NO_3SNa$ $(M+Na)^+$ 368.2235 found 368.2217.

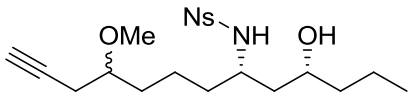
(*S*)-*N*-((4*R*,6*R*)-4-Hydroxy-10-methoxytridec-12-yn-6-yl)-2-methylpropane-2-sulfinamide (*anti*-114)



^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (m, 1H), 3.64 (m, 1H), 3.47 (m, 1H), 3.37 (s, 3H), 3.29 (m, 1H), 2.39 (ABX system, m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.76 (s, 1H), 1.64−1.27 (m, 12H), 1.23 (s, 9H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.9, 79.0, 69.9, 67.6, 57.0, 56.9 (for diastereoisomer), 55.8, 54.5, 54.4 (for diastereoisomer), 42.6, 40.0, 37.1, 33.3, 33.2 (for diastereoisomer), 23.1, 22.7, 21.7, 19.0, 14.1; IR (neat): 3400 (br), 3310, 2932, 2870, 2119, 1633, 1458, 1364, 1107, 1042 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{18}H_{35}NO_3SNa$ $(M+Na)^+$ 368.2235

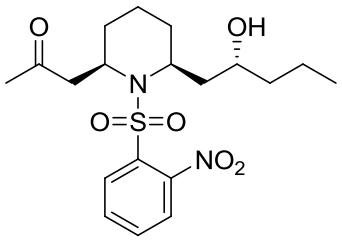
found 368.2235; $[\alpha]_D^{23}$ −29.0° (*c* 0.700, $CHCl_3$).

_N_-((4_R_,6_S_)-4-Hydroxy-10-methoxytridec-12-yn-6-yl)-2-nitrobenzenesulfonamide (105)



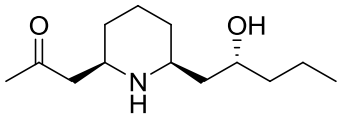
To a solution of *syn*-**104** (246 mg, 0.71 mmol) in CH_3OH (10 mL) was added 4.0 M HCl solution in 1,4-dioxane (0.36 mL, 1.42 mmol) at room temperature. The reaction mixture was stirred at same temperature for 1 h. After the desulfinylation was complete, excess HCl and solvents were evaporated under the reduced pressure. A mixture of THF/H_2O (*v*/*v* 1:1, 10 mL) was added, followed by the addition of $NaHCO_3$ (180 mg, 2.14 mmol) and 2-nitrobenzenesulfonyl chloride (181 mg, 0.85 mmol) at room temperature. The resulting mixture was stirred for 2 h. The crude was extracted with EtOAc (2 times). The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 to 1:1, hexanes/EtOAc) to afford **105** (252 mg, 0.59 mmol, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (m, 1H), 7.85 (m, 1H), 7.73 (m, 2H), 5.52 (d, J = 7.3 Hz, 1H), 3.64 (m, 2H), 3.31 (s, 3/2H), 3.29 (s, 3/2H), 3.17 (m, 1H), 2.29 (ABX system, m, 2H), 1.97 (m, 1H), 1.65−1.18 (m, 12 H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 135.0, 133.2, 132.7, 130.6, 125.2, 125.1 (for diastereoisomer), 80.8, 78.9, 78.8 (for diastereoisomer), 70.0, 69.3, 56.9, 53.6, 53.5 (for diastereoisomer), 42.6, 42.5 (for diastereoisomer), 40.1, 35.2, 33.2, 33.1 (for diastereoisomer), 23.0, 22.9 (for diastereoisomer), 18.5, 13.9; IR (neat): 3541, 3294, 3097, 2932, 2872, 2118, 1732, 1541, 1418, 1365, 1165 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{20}H_{30}N_2O_6SNa$ $(M+Na)^+$ 449.1722 found 449.1699; $[\alpha]_D^{23}$ +26.2° (*c* 0.480, $CHCl_3$).

1-((2*R*,6*S*)-6-((*R*)-2-Hydroxypentyl)-1-(2-nitrophenylsulfonyl)piperidin-2-yl)propan-2-one (106)



To a solution of **105** (70.0 mg, 0.164 mmol) in water saturated toluene (6.6 mL, 0.025 M) were added PPh_3AuCl (4.1 mg, 0.008 mmol) and $AgSbF_6$ (5.6 mg, 0.016 mmol). The reaction mixture was stirred at 40 °C for 24 h. The reaction solution was directly purified by chromatography on silica gel (10:1, CH_2Cl_2/EtOAc) to afford piperidine **106** (60.5 mg, 0.147 mmol, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (m, 1H), 7.68 (m, 3H), 4.43 (ddm, J = 9.8, 3.2 Hz, 1H), 4.25 (m, 1H), 3.59 (m, 1H), 3.01−2.85 (m, 2H), 2.98 (dd, J = 16.5, 3.4 Hz, 1H), 2.89 (dd, J = 16.5, 9.8 Hz, 1H), 2.20 (s, 3H), 1.89 (ddd, J = 13.8, 9.3, 3.2 Hz, 1H), 1.83 (ddd, J = 13.8, 9.6, 4.2 Hz, 1H), 1.69 (d, J = 6.9 Hz, OH), 1.65−1.34 (m, 10H), 0.95 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 147.7, 133.4, 131.9, 131.4, 124.5, 69.5, 50.1, 48.8, 48.1, 43.1, 40.5, 30.3, 27.7, 27.2, 18.8, 14.0, 13.3; IR (neat): 3400, 2955, 2871, 1714, 1544, 1373, 1340, 1168, 1136 cm^{-1}; HRMS (EI) m/z calcd. for $C_{16}H_{23}N_2O_5S$ $(M-C_3H_5O)^+$ 355.1337 found 355.1328 ; $[\alpha]_D^{23}$ −44.0° (*c* 0.425, $CHCl_3$).

(+)-Andrachcinidine (93)

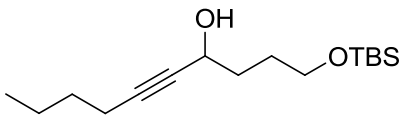


To a solution of **106** (50.0 mg, 0.121 mmol) in acetonitrile (3.0 mL) were added K_2CO_3 (83.7 mg, 0.606 mmol) and thiophenol (37 μL, 0.364 mmol). The yellowish reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc to 10:1, EtOAc/methanol with 5% Et_3N) to afford (+)-**93** (26.3 mg, 0.116 mmol, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (m, 1H), 2.97 (dtd, J = 11.2, 6.3, 2.7 Hz, 1H), 2.74 (tt, J = 10.3, 2.5 Hz, 1H), 2.49 (dd, J = 16.5, 6.7 Hz,

1H), 2.43 (dd, J = 16.5, 5.8 Hz, 1H), 2.11 (s, 3H), 1.82 (dm, J = 13.5 Hz, 1H), 1.66 (dm, J = 13.1 Hz, 1H), 1.62 (dm, J = 13.1 Hz, 1H), 1.52 (m, 1H), 1.49 (m, 1H), 1.40 (m, 2H), 1.32 (m, 2H), 1.21 (dt, J = 14.2, 10.2, 1H), 1.08−0.96 (m, 2H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 72.5, 58.2, 53.0, 50.5, 43.1, 40.4, 33.5, 32.5, 30.6, 24.5, 18.6, 14.1; IR (neat): 3299 (br), 2929, 2859, 1713, 1457, 1360, 1107 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{25}NO_2$ $(M)^+$ 227.1885 found 227.1882; $[\alpha]_D^{23}$ +24.1° (c 0.390, $CHCl_3$).

1.4.7 Preparation of internal alkyne and heterocycle compound

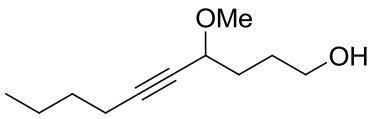
1-(*tert*-Butyldimethylsilyloxy)dec-5-yn-4-ol



To a cooled solution of 1-hexyne (243 mg, 2.96 mmol) in THF (10 mL) at −78 °C was added 1.6 M solution of *n*-BuLi in hexanes (1.85 mL, 2.96 mmol) dropwise. After the mixture was stirred at same temperature for 10 min, a solution of 4-(*tert*-butyldimethylsilyloxy)butanal[46] (500 mg, 2.47 mmol) in THF (5 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 0.5 h and quenched with water. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (1:10, EtOAc/hexanes) to afford 1-(*tert*-butyldimethylsilyloxy)dec-5-yn-4-ol (550 mg, 1.93 mmol, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.40 (m, 1H), 3.67 (m, 2H), 2.95 (d, J = 6.0 Hz, OH), 2.20 (td, J = 6.9, 1.8 Hz, 2H), 1.83−1.64 (m, 4H), 1.53−1.33 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.3, 81.2, 63.2, 64.4,

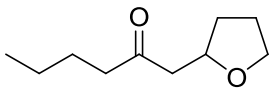
35.6, 30.8, 28.6, 25.9, 21.9, 18.4, 18.3, 13.6, −5.38; IR (neat) 3402 (br), 2956, 2930, 2858, 1472, 1255, 1103 cm^{-1}; HRMS (EI) m/z calcd. for $C_{16}H_{31}OSi$ (M−OH) 267.2144 found 267.2136.

4-Methoxydec-5-yn-1-ol (109)



To a solution of 1-(*tert*-butyldimethylsilyloxy)dec-5-yn-4-ol (400 mg, 1.40 mmol) in THF (15 mL) at room temperature was added NaH (60% dispersion in mineral oil, 84 mg, 2.11 mmol) with several portions, followed by addition of CH_3I (131 μL, 2.11 mmol). The reaction mixture was stirred for 2 h. 10% aqueous HCl solution (10 mL) was carefully added dropwise and the resulting mixture was stirred overnight. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (1:4, EtOAc/hexanes) to give **109** (257 mg, 1.39 mmol, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (m, 1H), 3.65 (app q, J = 5.5 Hz, 2H), 3.40 (s, 3H), 2.22 (td, J = 6.9, 1.8 Hz, 2H), 1.94 (m, OH), 1.78 (m, 4H), 1.54−1.37 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.9, 78.3, 71.3, 62.7, 56.2, 32.7, 30.8, 28.7, 21.9, 18.3, 13.6; IR (neat) 3403 (br), 2934, 2873, 2820, 2231, 1466, 1337, 1110 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{19}O$ (M−OH) 167.1436 found 167.1437.

1-(Tetrahydrofuran-2-yl)hexan-2-one (110)



General procedure C was followed with internal propargylic methyl ether **109** (39.4 mg, 0.214 mmol), Ph_3PAuCl (5.4 mg, 10.7 μmol), and $AgSbF_6$ (7.3 mg, 21.3 μmol) in water-saturated toluene (8.6 mL) for 0.5 h to give **110** (34 mg, 93%

isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (p, J = 6.7 Hz, 1H), 3.85 (m, 1H), 3.72 (m, 1H), 2.73 (dd, J = 15.6, 6.9 Hz, 1H), 2.51 (dd, J = 15.6, 6.0 Hz, 1H), 2.45 (t, J = 7.5 Hz, 2H), 2.10 (m, 1H), 1.88 (m, 2H), 1.55 (m, 2H), 1.48 (m, 1H), 1.29 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 75.1, 67.8, 48.6, 43.3, 31.5, 25.7, 25.6, 22.3, 13.8; IR (neat) 2958, 2872, 1712, 1465, 1380, 1040 cm^{-1}; HRMS (EI) m/z calcd. for $C_{10}H_{18}O_2$ (M^+) 170.1307 found 170.1305.

1.5 References

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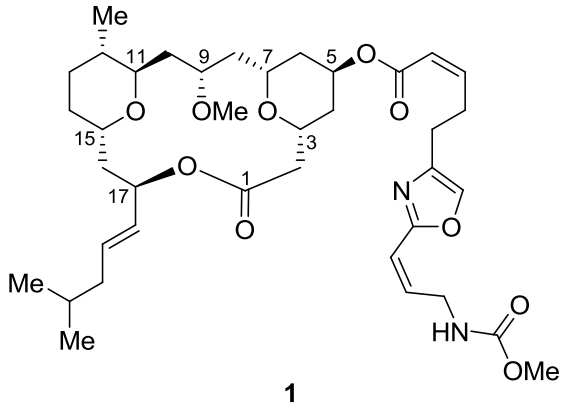
2.0 Synthesis of Leucascandrolide A

2.1 Introduction

2.1.1 Isolation

(+)-Leucascandrolide A[1] (**1**), a doubly oxygen-bridged macrolide, was isolated in 1996 from a calcareous sponge *Leucascandra caveolata* Borojevic and Klautau[2] by Pietra and co-workers (Figure 5).



1

Figure 5. Structure of leucascandrolide A (**1**).

The sponge was first collected along the Passe de Nakéty, on the eastern coast of New Caledonia in September 1989 (3 kg of fresh weight, 200 g of freeze-dried weight) and in July 1992 (40 g of freeze-dried weight). After extraction with CH_2Cl_2, flash chromatography and further purification by HPLC, 70 mg of pure leucascandrolide A were obtained. The sponge was regularly found at the same location where it had been first collected. However, in April 1995, only a few specimens could be found. Furthermore, samples collected in 1994 at the identical sampling location from the 1989 isolation did not contain any traces of **1**. Pietra and co-workers thus suspected that **1** could be biosynthesized from opportunistic microbes residing in dead portions of the sponges which has a limited life cycle of 2−3 years and displays a great sensitivity to ecological change.

2.1.2 Biological Activity

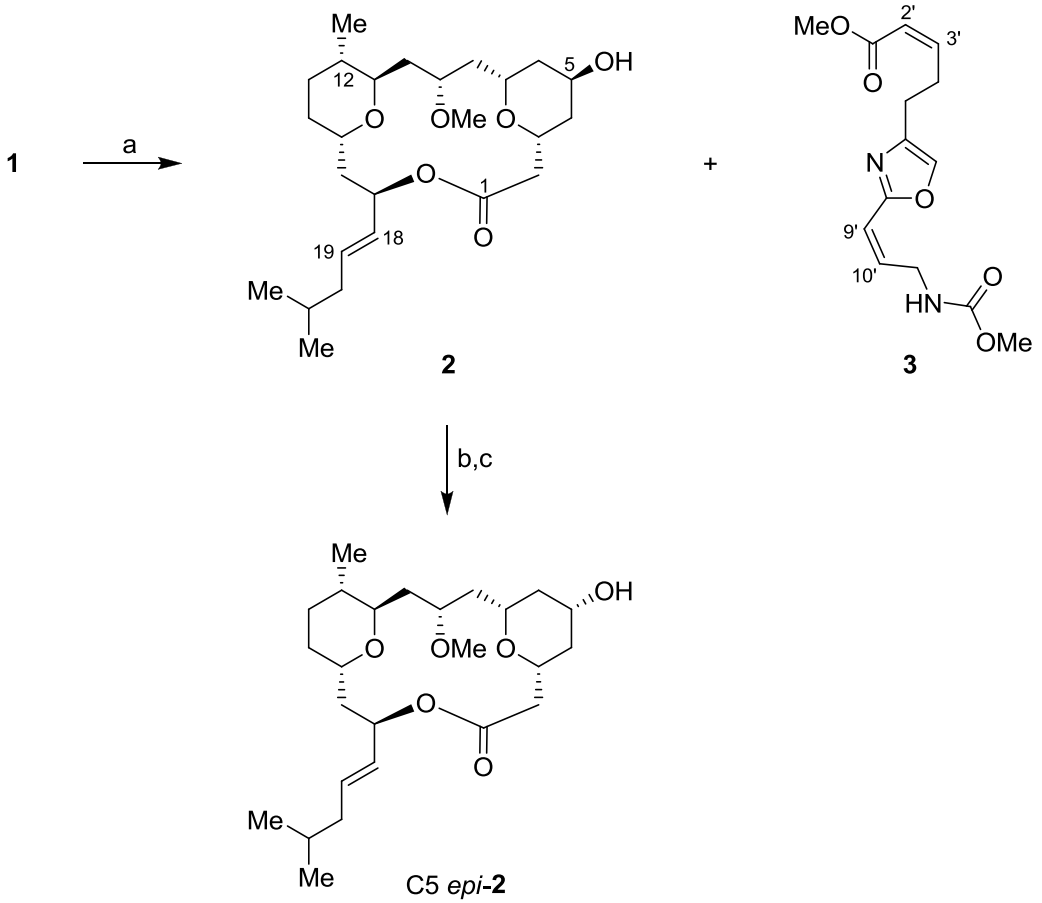
Leucascandrolide A (**1**) is not only the first powerfully potent bioactive metabolite isolated from a calcareous sponge, but also the first macrolide ever found in calcareas. Preliminary assays with the pure compound showed strong *in vitro* cytotoxic activity against KB tumor cell lines (IC_{50} 71 nM) and P338 murine leukemia cells (IC_{50} 356 nM). Strong inhibition was also found against the fungus *Candida albicans*, pathogenic yeast that causes oral candidiasis, which is a condition often observed in HIV infected patients and presages the progression to AIDS. Additional biological evaluations revealed that leucascandrolide A macrolide moiety **2** (see Scheme 29) is essential to the cytotoxic activity towards KB cells, with activity comparable to that of **1**, while the oxazole side chain **3** significantly contributes to the antifungal properties of the natural product. Recently, Kozmin and co-workers synthesized a racemic mixture of

leucascandrolide A (**1**), resolved both enantiomers[3] and performed bioassays on them.[4] However, they perceived that the naturally occurring (+)-**1** is only two- to three-fold more potent than the unnatural enantiomer (–)-**1** in a number of cancer cell lines and in *S. cerevisiae,* and thus proposed that the oxazole-containing side chain may be primarily responsible for the toxicity of leucascandrolide A.

2.1.3 Structure

The composition $C_{38}H_{56}N_2O_{10}$ was deduced from HR–EI–MS and ^{13}C NMR spectra and DEPT data, and structural details were assigned by HMQC, HMBC, DQ–COSY and ROESY experiments. To establish the absolute configuration, methanolysis of **1** with Na_2CO_3 in methanol proceeded to provide a macrolide alcohol **2** and oxazole-containing methyl ester **3** (Scheme 29). Converting alcohol **2** into its C5-epimer using a two-step reaction sequence: oxidation with PCC and subsequent reduction with $NaBH_4$ gave C5 *epi*-**2** with the hydroxyl group in equatorial position. Mosher–ester analysis[5] of C5 *epi*-**2** allowed for clear and unambiguous assignment of the (5*R*)-configuration in leucascandrolide A.

Leucascandrolide A displays several distinctive architectural features. The structure is characterized by extensive 1,3-dioxygenation, a single methyl branching (at C12), an (*E*)-olefinic bond (C18–C19) and a peculiar side chain bearing a 2,4-disubstituted oxazole and two (*Z*)-olefinic bonds (C2'–C3' and C9'–C10'). Its eighteen-membered macrolactone encompasses two trisubstituted tetrahydropyran rings whose endocyclic oxygens are directed towards the interior of the macrolide.



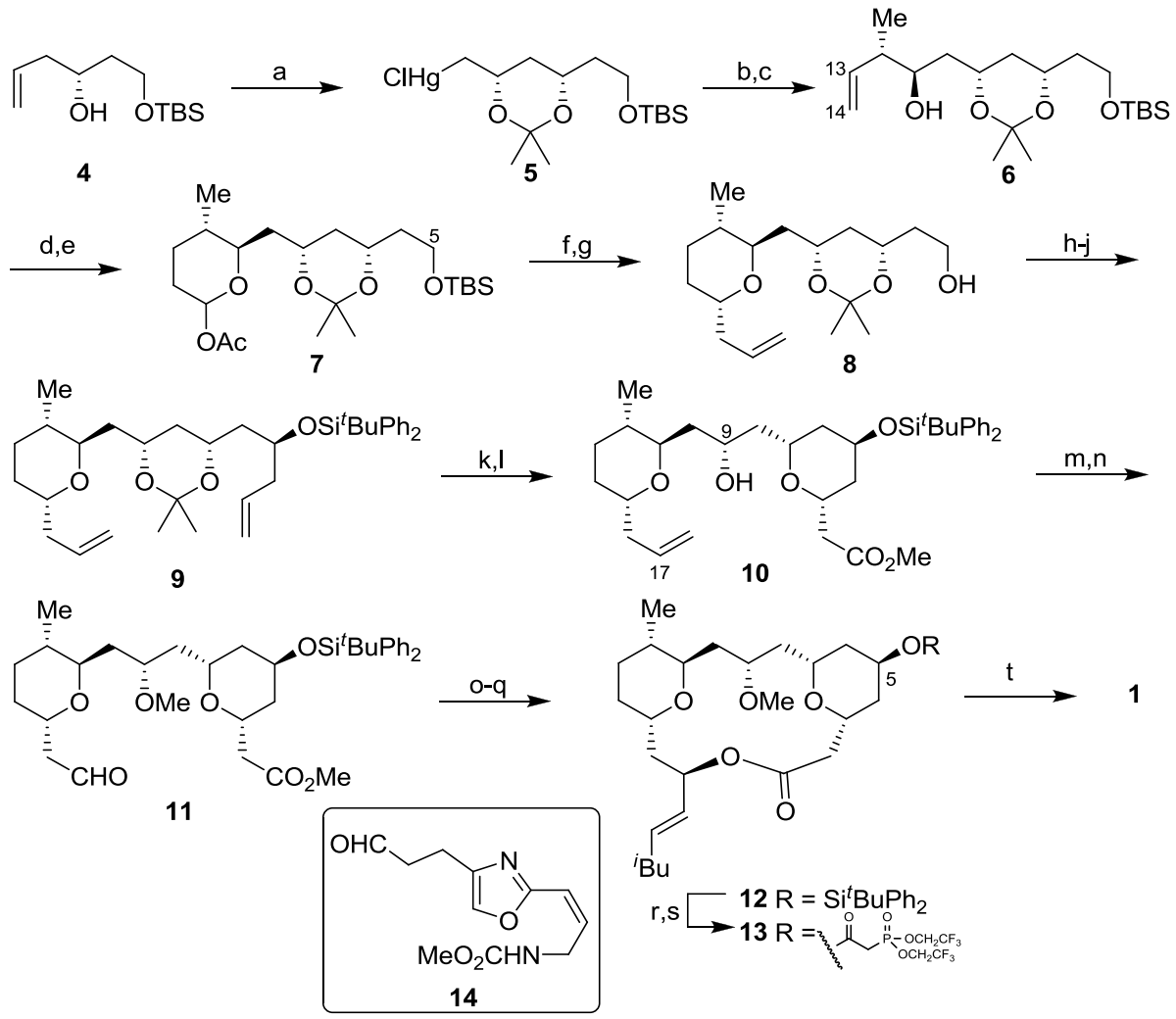
Reagents and conditions: a) Na_2CO_3, MeOH, 77%; b) PCC, CH_2Cl_2, 70%; c) $NaBH_4$, EtOH, 86%

Scheme 29. Methanolysis and epimerization on C5.

2.1.4 Previous Syntheses

The potent bioactivity, the lack of any reliable source from nature, and the unique structural features of leucascandrolide A sparked a tremendous response from the synthetic community.[6] The first total synthesis of leucascandrolide A was reported by Leighton and co-workers in

2000.[6(a)] Leighton's strategy towards **1** is highlighted by the successful reiterative application of metal-mediated carbonylation reactions. The synthesis began with the $Yb(OTf)_3$-catalyzed oxymercuration[7] with HgClOAc in acetone to produce the 1,3-*syn*-organomercury chloride **5** from the known homoallylic alcohol **4** (Scheme 30). A Rh(I)-catalyzed formylation[8] provided the aldehyde for the application of Brown's asymmetric crotylation. Regioselective hydroformylation of the C13–C14 olefin in **6** led to hemiacetals via internal cyclization. Transformation to tetrahydropyran was achieved via the Lewis acid-mediated addition of allyltrimethyl silane to acetals **7**. Deprotection and oxidation of the C5 alcohol, followed by an asymmetric allylation and then Semmelhack intramolecular alkoxy carbonylation[9] provided *cis*-tetrahydropyran **10** with >10:1 dr. Methylation of the C9 alcohol in **10** followed by oxidative cleavage of the C17 olefin provided aldehyde **11**. Addition of an organozinc reagent to **11** yielded allylic alcohol with a modest 3:1 dr. The seco-acid generated by hydrolysis of the methyl ester was subjected to Yamaguchi macrolactonization.[10] The C5 side chain was appended via sequential C5 esterification to phosphonate and the Still–Gennari modified Horner–Emmons *cis*-olefination with aldehyde **14** to complete the synthesis in 20 steps from **4**. Chemical synthesis of **1** also confirmed the relative and absolute stereochemistry reported by Pietra.

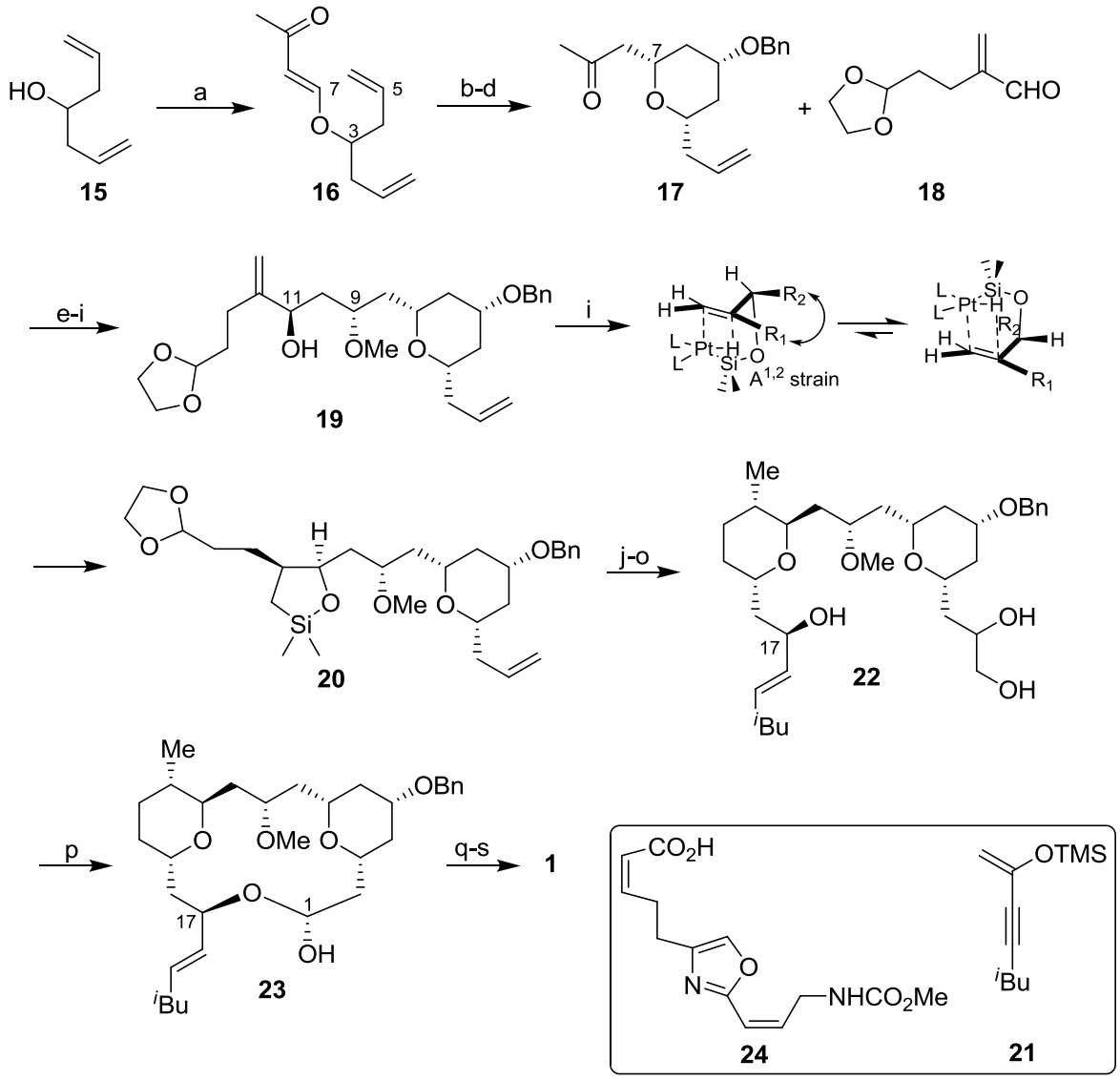


Reagents and conditions: a) HgClOAc, acetone, 5 mol% $Yb(OTf)_3$, 0 ºC to RT, 76%; b) 4 mol% $Rh(acac)(CO)_2$, 4 mol% P(O-*o*-*t*BuPh)$_3$, 50 mol% DABCO, 800 psi 1:1 CO/H_2, 50 ºC, 62%; c) (*E*)-crotyl-(–)-di-*iso*-pinocampheylborane, BF_3•OEt_2, –78 ºC; NaOH, H_2O_2, 67%; d) 2 mol% $Rh(acac)(CO)_2$, 8 mol% PPh_3, 400 psi 1:1 CO/H_2, 50 ºC, 89%; e) Ac_2O, DMAP, pyridine; f) H_2C=$CHCH_2SiMe_3$, $Ti(O\text{-}iPr)_2Cl_2$, –78 ºC; g) *n*-Bu_4NF, 64% over 3 steps; h) $(COCl)_2$, DMSO, Et_3N, –78 ºC to –40 ºC; i) allyl-(–)-diisopinocampheylborane, –78 ºC to RT; NaOH, H_2O_2, 75% over 2 steps; j) *tert*-$BuPh_2SiCl$, imidazole, 99%; k) AcOH, H_2O, 40 ºC, 98%; l) 10 mol% $PdCl_2$, 4 equiv $CuCl_2$, 1 atm CO, MeOH:PhCN (1:1), 75%; m) Me_3OBF_4, Proton Sponge®, 4 Å MS; n) O_3, –78 ºC; PPh_3, RT, 93%; o) 4-methyl-1-pentyne, Cy_2BH, Et_2Zn, *N*,*N*-dibutylamino-ethanol, then $Ti(O\text{-}iso\text{-}Pr)_4$, –40 ºC to –20 ºC, 60%, 3:1 *dr*; p) $KOSiMe_3$; q) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 76% over 2 steps; r) TBAF, 77%; s) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBt•$H_2O$; t) KHMDS, 18-crown-6, –78 ºC then **14**, –100 ºC, 7:1 ratio of olefin isomers, 55% over 2 steps.

Scheme 30. The Leighton synthesis of **1**.

Kozmin and co-workers reported an efficient stereocontrolled synthesis of racemic leucascandrolide A,[3,6(c),6(l), 11] featuring a substrate-directed relay of the stereochemical information via a series of highly diastereoselective transformations (Scheme 31). The synthesis began with intramolecular Prins cyclization of **16**, which was prepared by vinylogous transesterification of 4-methoxy-2-butenone with **15**. A C5 equatorial hydroxyl group in 2,6-*cis*-tetrahydropyrane ring, generated by subsequent basic hydrolysis of the trifluoroacetate, was protected as a benzyl ether. A boron-mediated aldol reaction of ketone **17** with aldehyde **18** furnished a *β*-hydroxy ketone as a single diastereomer through 1,5-*anti* stereoinduction.[12] A SmI_2-mediated reduction,[13] followed by methylation of C9 alcohol and reductive removal of the acetate led to key intermediate **19** for hydroxyl-directed hydrosilylation process.[14] Conversion to the C11 silyl ether using tetramethyldisilazane, followed by treatment with catalytic H_2PtCl_6 resulted in preferential formation of silacycle **20** with a dr of 87:13. The outcome of diastereoselectivity was explained by considering the minimization of unfavorable $A^{1,2}$ strain in the assumed stereochemistry-determining hydroplatination step. This is a distinctive stereoselective introduction of C12 methyl group while other groups employed asymmetric auxiliary-mediated enolate alkylation or crotylation. Protodesilylation of **20** was followed up by dioxolane removal, lactol acylation, and stereocontrolled C-glycosidation with silyl enol ether **21**. A diastereoselective reduction of the C17 ketone by L-Selectride® was followed by chemoselective dihydroxylation of the C1 terminal alkene and subsequent Red-Al® alkyne reduction to provide triol **22**. Triol **22** was subjected to oxidative cleavage of vicinal diol moiety. Unexpectedly, treatment with $Pb(OAc)_4$ afforded lactol **23** as a single diastereomer, presumably due to the spontaneous intramolecular macrolactolization process that results from the unusual thermodynamic stability of the macrocyle. PCC-mediated oxidation of the robust

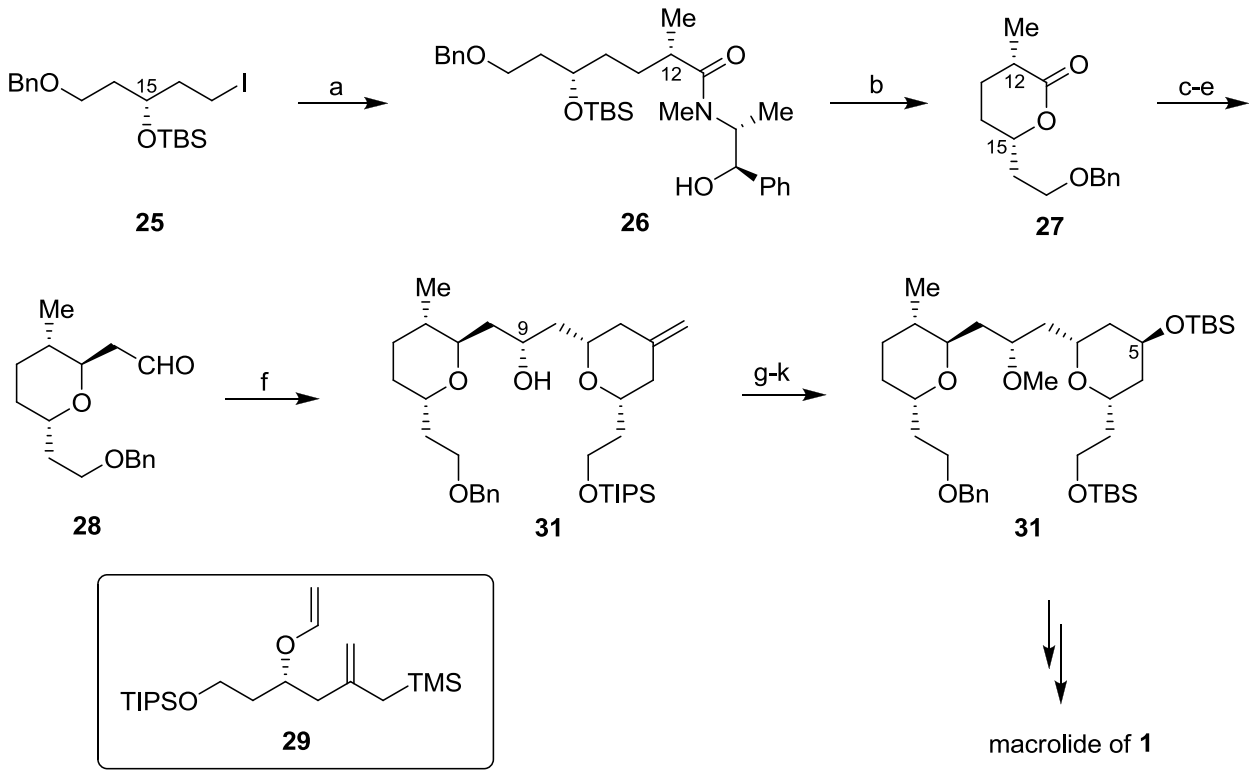
14-membered macrocycle afforded the macrolactone. Removal of the C5 benzyl ether set the stage for an efficient incorporation of the side chain **24** via Mitsunobu esterification. This final step concluded the racemic synthesis in 19 steps for the linear sequence from **15**.



Reagents and conditions: a) 4-methoxy-2-butenone, PPTS, 92%; b) CF_3CO_2H; c) LiOH, THF-H_2O, 77% over 2 steps; d) $BnO(NH)CCl_3$, cat. TfOH, 71%; e) Cy_2BCl, 0 ºC, then aldehyde at –78 ºC, 74%; f) SmI_2 (30 mol %), CH_3CHO, –10 ºC; g) MeOTf, 2,6-di-*tert*-butylpyridine, 71%; h) $LiAlH_4$, –78 ºC, 86%; i) $(Me_2HSi)_2NH$ then H_2PtCl_6, 50 ºC, *dr* 87:13; j) TBAF, 70 ºC, 54% over 2 steps; k) THF-H_2O, cat. H_2SO_4 then Ac_2O, pyridine, DMAP, 83%; l) $ZnCl_2$, **21**,–78 ºC to 0 ºC, 80%; m) L-Selectride®, –78 ºC, 3:1 *dr*, 91%; n) cat. OsO_4, NMO, *t*-BuOH-H_2O, 77%; o) Red-Al®, 20 ºC, 78%; p) $Pb(OAc)_4$, 0 ºC, filtered, concentrated, left standing for 18 h, single diastereomer of lactol, 92%; q) PCC,4 Å MS, 85%; r) DDQ, pH 7 buffer, 99%; s) **24**, DIAD, benzene, 78%.

Scheme 31. The Kozmin synthesis of **1**.

Rychnovsky chose a convergent assembly of the macrolide portion of **1** which utilized one pot Mukaiyama aldol-Prins cyclization cascade between **28** and **29** (Scheme 32),[6(b),6(n)] whereas Leighton and Kozmin constructed the molecule using consecutive cyclizations on a linear precursor. Myers' alkylation of iodide **25** with (–)-pseudoephedrine propionamide set the C12 methyl stereocenter of **26**. Treatment of **26** with acid yielded lactone **27** which was subsequently transformed to **28**. Coupling of aldehyde **28** and enol ether **29**, which was prepared in eight steps from 3-(tri-*iso*-propylsilyloxy)propanal, with $BF_3 \bullet Et_2O$ in the presence 2,6-di-*tert*-butylpyridine as a proton scavenger led to a simultaneous formation of **30** with moderate diastereoselectivity (5.5:1 ratio of C9 alcohols). The intermediate oxocarbenium ion was trapped internally with the allylsilane in a Prins-type reaction to form a *cis*-tetrahydropyran ring exclusively. A series of straightforward transformations which included a stereoselective reduction of the C5 ketone gave **31**.

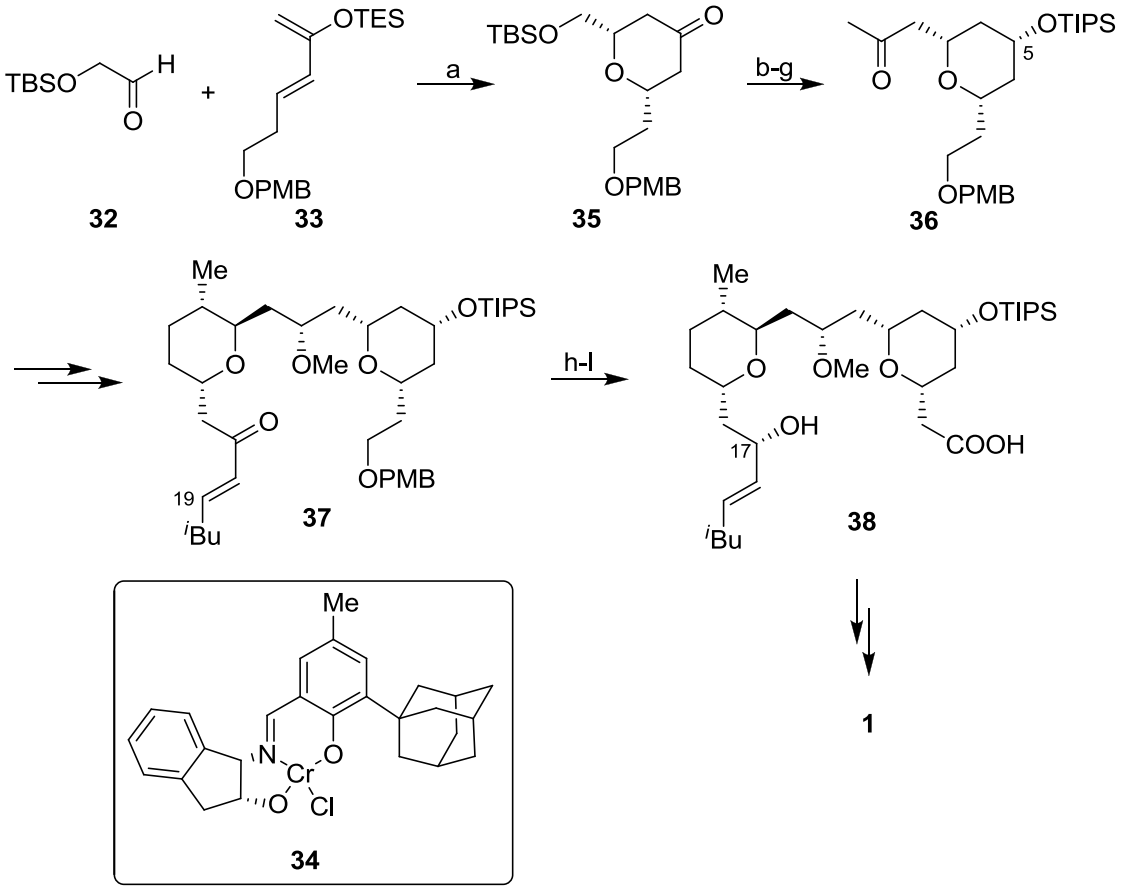


Reagents and conditions: a) LDA, (–)-pseudoephedrine propionamide, LiCl, then **25**, –78 ºC, 98%, 20:1 *dr*; b) 2N aq. H_2SO_4, 95 ºC, 77%; c) DIBAL, –78 ºC, then Ac_2O, DMAP, pyridine, 95%. d) allyltrimethylsilane, BF_3•OEt_2, –78 ºC, 97%, 20:1 *dr*; e) O_3, –78 ºC, then PPh_3, 95%; f) **29**, BF_3•OEt_2, 2,6-di-*tert*-butylpyridine, –78 ºC, 5.5:1 *dr* at C9; g) $MeO^+BF_4^-$, Proton Sponge®, 4 Å MS, 79% (single epimer) plus C9 epimer (15%). h) OsO_4, NMO, then $NaIO_4$, 80%; i) L-Selectride®, –90 to –60 ºC, 82% (single epimer) plus C5 epimer (10%); j) TBAF, 92%; j) TBSOTf, 2,6-lutidine, 89%.

Scheme 32. The Rychnovsky synthesis of the macrolide of **1**.

The Paterson approach[6(f),6(j)] to leucascandrolide A demonstrated the use of Jacobsen's asymmetric hetero Diels-Alder reaction with siloxydiene **33** and aldehyde **32**, generating 2,6-*cis*-tetrahydropyran-4-one **35** which upon reduction with sodium borohydride yielded the C5 equatorial alcohol (Scheme 33). Again, control of the C9 and C11 stereochemistry was possible with a boron-mediated aldol reaction through 1,5-*anti* stereoinduction. Instead of setting the requisite C17-(*R*) alcohol stereochemistry in the natural product, subjecting the ketone

37 to LiAlH(O*t*-Bu)$_3$ results in formation of the C17-(*S*) alcohol with superior stereocontrol (>32:1 *dr*). Later, Mitsunobu macrolactonization proceeded effectively set the C17-(*R*) configuration via inversion.



Reagents and conditions: a) 10 mol% **34**, 4 Å MS, acidified $CHCl_3$, >20:1 *dr*, >98% ee, 80%; b) $NaBH_4$, 13:1 *dr*, 99%; c) TIPSOTf, lutidine, –78 °C; d) CSA, 2:1 MeOH/CH_2Cl_2, 82% over 2 steps; e) Tf_2O, pyridine, –10 °C; f) LDA, TMSCCH, HMPA, –78 to 20 °C; K_2CO_3, MeOH, 84% over 2 steps; g) cat. $Hg(OAc)_2$, PPTS, wet THF, 40 °C, 86%; h) LiAlH(O*t*-Bu)$_3$, –78 to 10 °C, 32:1 *dr*, 76%; i) Ac_2O, pyridine, DMAP; j) DDQ, 10:1 CH_2Cl_2/pH 7 buffer; k) TEMPO, $PhI(OAc)_2$, $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*-BuOH, 0 to 20 °C; l) K_2CO_3, MeOH, 70% over 4 steps.

Scheme 33. The Paterson synthesis of **1**.

2.1.5 Electron-Transfer-Initiated Cyclization (ETIC)

Our group has developed the electron transfer initiated cyclization (ETIC) reaction.[16] The proposed mechanism for the ETIC reaction (Figure 6) involves coordination of Ce(IV) to the dimethyl-*p*-methoxy benzyl arene, followed by an inner-sphere electron transfer to give Ce(III) and a radical cation of the substrate. The radical cation can undergo mesolytic cleavage to produce a radical and a cation. The resulting oxocarbenium ion is then trapped by the pendant enol acetate nucleophile to yield the desired 4-tetrahydropyranone. Furthermore, 6-*endo*-cyclizations to proceed through chairlike transition states provide excellent levels of stereocontrol in the synthesis of *syn*-2,6-dialkyl tetrahydropyran-4-ones which are useful building blocks in natural product synthesis.

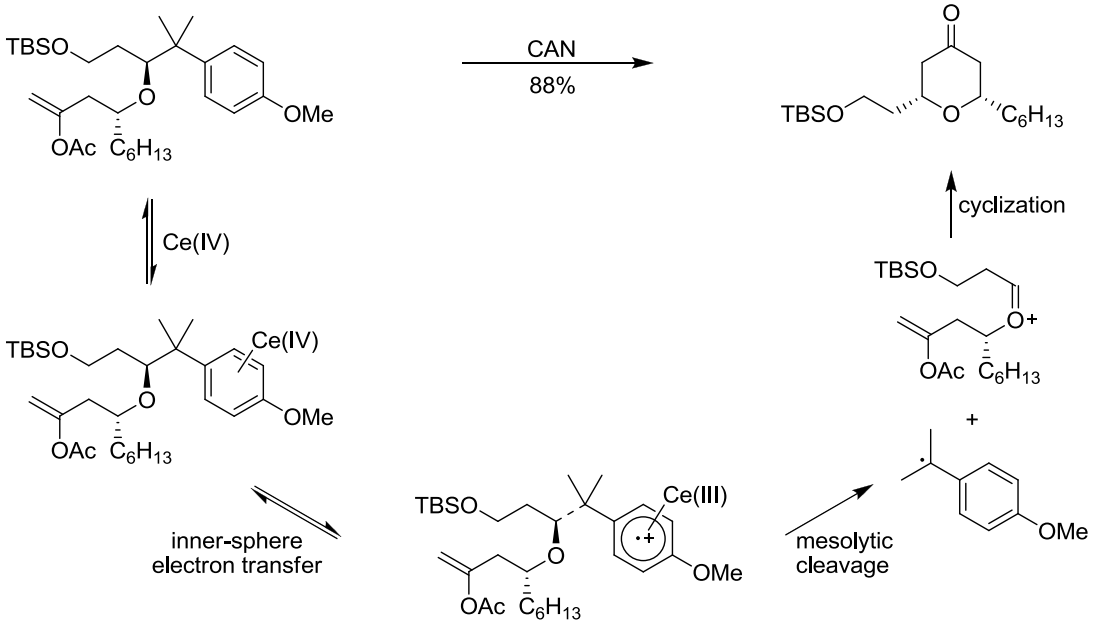


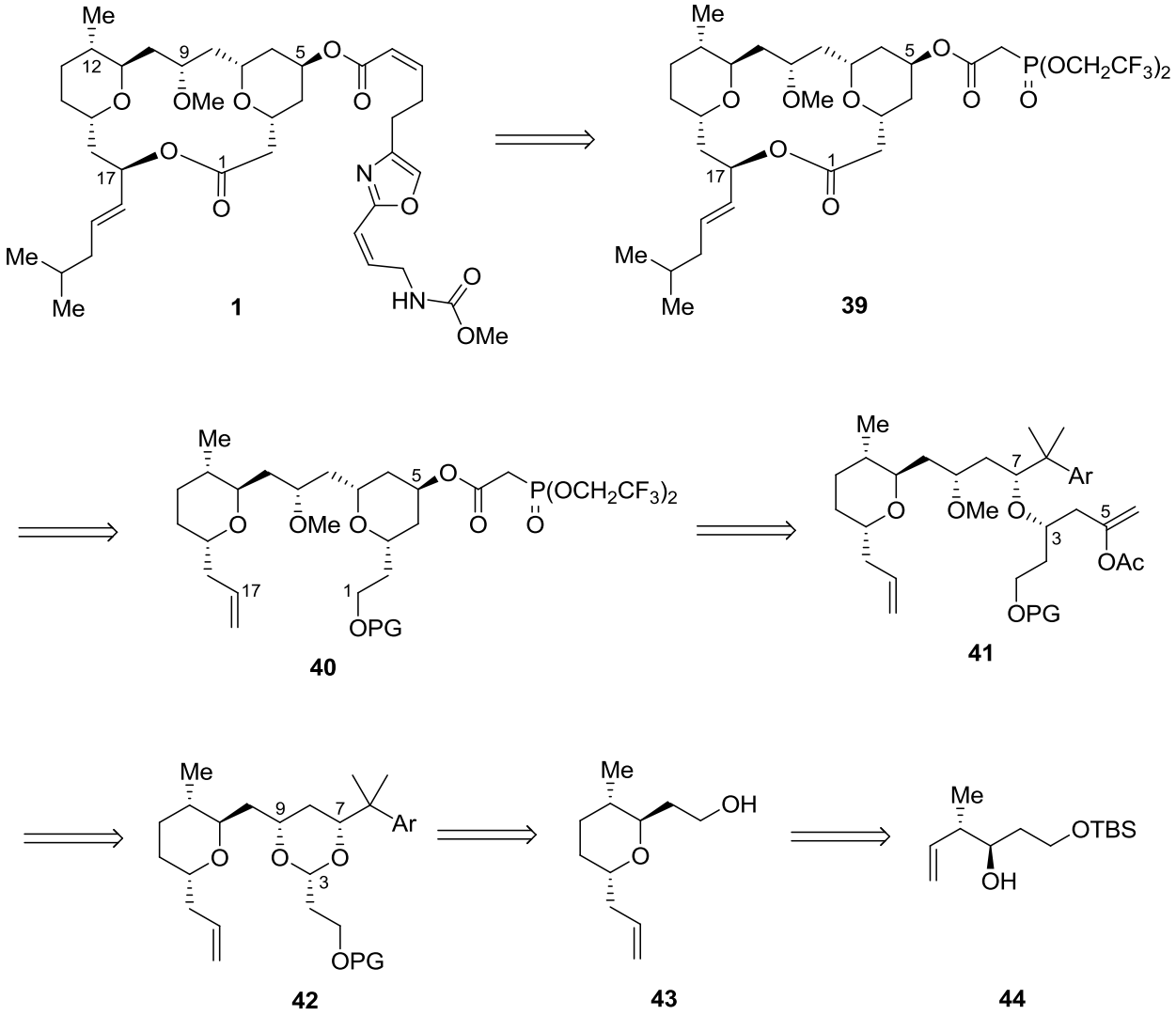
Figure 6. Proposed ETIC reaction pathway.

2.1.6 Retrosynthesis

The synthesis of leucascandrolide A (**1**) became the focus of our study since 2,6-*cis*-dialkyltetrahydropyran-4-one, relevant to the C3–C7 portion of **1**, could be prepared through efficient oxidative cleavage reactions of homobenzylic ethers.[15] The initial effort to synthesize **1** by Dr. Seiders,[19] who was a previous group member, proved that application of diastereoselective electron-transfer-initiated cyclization (ETIC) method[16] for natural product synthesis was feasible. Moreover, the exhibited sequence was designed to minimize the use of protecting groups and reagent-based stereoinduction resulting in an efficient approach with respect to linear and overall step counts.

Our retrosynthetic analysis of **1** is outlined in Scheme 34. Phosphonate **39**, which had been converted into the natural product in one step by Leighton and co-workers,[6(a)] was chosen for our synthetic target molecule. The macrocyclization reaction, planned by lactolization of *ω*-hydroxyl aldehyde, was believed to be facilitated by the presence of both tetrahydropyran rings because of reduced degrees of freedom as compared to a linear substrate and unusual thermodynamic stability of the macrocyle, proposed by Kozmin and co-workers.[6(l)] Unraveling of requisite C17 allylic alcohol could be achieved by cross-metathesis reaction. 2,6-*cis*-Dialkyltetrahypropyran in **40** would be accessed through the single-electron oxidation, fragmentation, and cyclization of **41**. Enol acetate **41** could be obtained from the metal-mediated addition of acetic acid to homopropargylic ether, which was generated by a diastereoselective opening of a cyclic acetal **42**. The challenging disconnection of ether between C3 and C7 on **41** could be solved by nucleophilic opening of acetal **42**. While tetrahydropyran **43** could be prepared from alcohol **44** by various ways, we envisioned

hydroformylation as an efficient route to meet the goals. Alcohol **44** could be readily prepared in high enantiomeric purity through a reported three-step sequence[17] from a commercially available 1,3-propanediol that utilizes a Brown crotylation reaction[18] to establish relative and absolute stereochemical control.

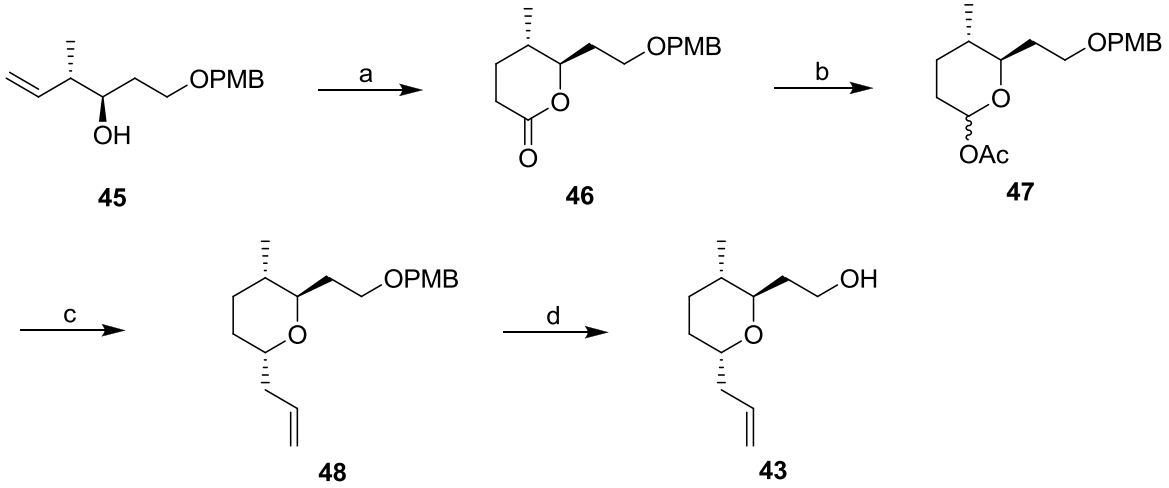


Ar = *p*-methoxyphenyl

Scheme 34. Retrosynthetic analysis of leucascandrolide A (**1**).

2.2 Results and Discussion

The synthesis of leucascandrolide A commenced with the preparation of 2,6-*trans*-disubstituted tetrahydropyran **43** (Scheme 35). Our initial synthetic effort[19] clearly showed that **43** can be prepared through a highly diastereoselective four step sequence from the known enantiomerically enriched alcohol. Accordingly, alcohol **45**[17] was subjected to the ruthenium catalyzed hydroesterification/lactonization protocol developed in our labs,[20] to afford lactone **46** in 78% yield. Conversion to acyl lactol **47** was carried out by one pot reduction/acylation protocol.[21] Subsequent treatment of **47** with BF_3•OEt_2 in the presence of allyltrimethylsilane gave 2,6-*trans*-tetrahydropyran **48** as a single diastereomer in 90% yield over two steps. The *p*-methoxybenzyl ether was oxidatively removed using DDQ to give alcohol **43**.



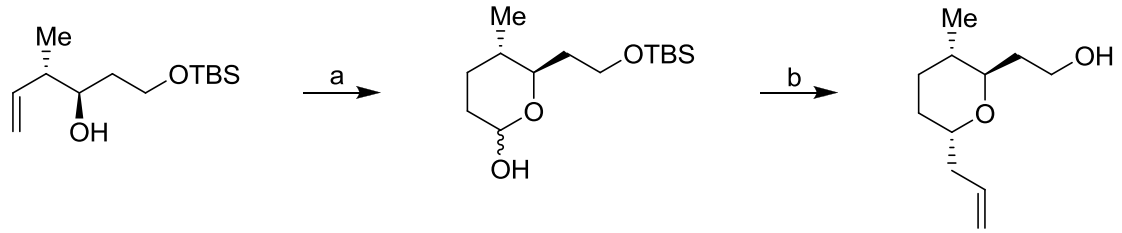
45 **46** **47** **48** **43**

Reagents and conditions: a) i. 5 mol% $Ru_3(CO)_{12}$, 2-pyridylmethyl formate, 15 mol% NMO, 110 °C; ii. HOAc/THF/H_2O (1:2:1), 85 °C, 78%; b) i. DIBAL, CH_2Cl_2, –78 °C; ii. pyridine, DMAP, Ac_2O, CH_2Cl_2, –78 to –35 °C; c) BF_3•OEt_2, allyltrimethylsilane, CH_2Cl_2, –78 °C, 90% over two steps; d) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 98%.

Scheme 35. Tetrahydropyran synthesis.

While our initially developed protocol provided 2,6-*trans*-tetrahydropyran **43** in excellent overall yields, we re-deigned an alternative complement pathway to avoid harsh reaction conditions and the use of cryogenic conditions. To access a tetrahydropyran group in a single step from **44**[17] (Scheme 36), we employed Briet and co-workers' hydroformylation [22] (step (a) in Scheme 36) for this transformation. This extraordinarily facile procedure, shown in Figure 7 (H_2 and CO can be introduced individually through separate balloons, making the need to purchase syngas unnecessary), provided lactol **49** in 90% yield. Exposing **49** to allyl trimethylsilane and $BiBr_3$[23] at room temperature yielded tetrahydropyranyl alcohol **43** as a single stereoisomer in nearly quantitative yield within 20 minutes.

Figure 7. Hydroformylation.



44 **49** **43**

Reagents and conditions: a) H_2, CO, 5 mol% $Rh(acac)(CO)_2$, 25 mol% 6-diphenylphosphino-2-pyridone (6-DPPon), THF, 1 atm, RT, 90%; b) allyl trimethylsilane, 50 mol% $BiBr_3$, CH_3CN, RT, 99%.

Scheme 36. Revised tetrahydropyran synthesis.

The reaction proceeded through the instantaneous formation of an isolable bridged bicyclic acetal **50**, arising from the intramolecular addition of the silyloxy group into the intermediate oxocarbenium ion and subsequent desilylation, followed by a second ionization that allowed for allyl group incorporation. Subjecting the isolated acetal **50** to identical reaction conditions also gave **43** as a single diastereomer. The high stereoselectivity of the C-glycosidation reaction results from axial attack of the energetically favorable conformation in which both alkyl groups occupy pseudo-equatorial positions.[24] Axial addition of the nucleophile to the ring flip conformation is highly disfavored due to the *syn*-pentane interaction developed in the transition state and two pseudo-axial substituents (Figure 8). These conditions promote direct nucleophilic substitutions of lactols and avoid cryogenic conditions without sacrificing efficiency or stereocontrol. It is also noteworthy that new pathway obviates an additional manipulation of protecting groups.

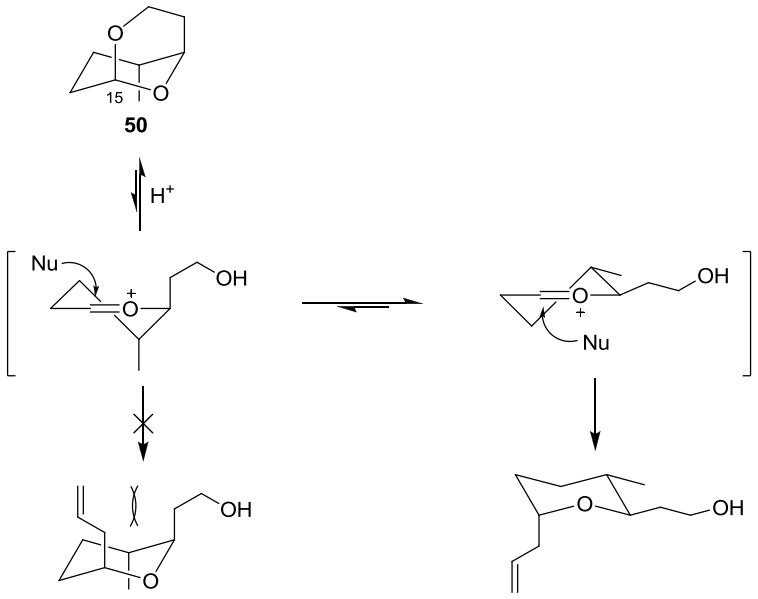
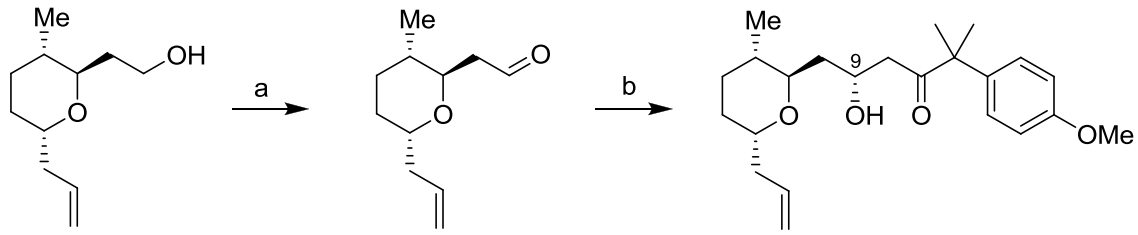
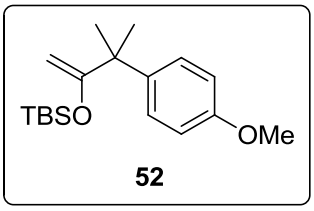


Figure 8. Mechanism for the stereocontrol in the C-glycosidation reaction.

The introduction of electroauxiliary for the key ETIC reaction (Scheme 37) proceeded through a sequence of alcohol oxidation with the Dess-Martin periodinane and subsequent BF_3•OEt_2-mediated Mukaiyama aldol addition[25] of enolsilane **52**[26] to provide *β*–hydroxyketone **53** as an inseparable 4.5:1 mixture of diastereomers, as determined by ^{1}H NMR spectroscopy. Diastereomers could be separated by chromatography at a later stage. Higher diastereocontrol (7.8:1) was observed when the solvent was changed from CH_2Cl_2 to toluene, but the overall yield was reduced (50%). The use of $TiCl_4$ or $TiCl_2(O\text{-}i\text{-}Pr)_2$ as a chelating Lewis acid could not enhance the stereoselectivity.





entry	Lewis acid	solvent	yield	dr
1	BF_3·OEt	CH_2Cl_2	78%	4.5:1
2	BF_3·OEt	toluene	50%	7.8:1
3	$TiCl_4$	CH_2Cl_2	67%	3:2
4	$TiCl_2(O\text{-}i\text{-}Pr)_2$	toluene	NR	

Reagents and conditions: a) Dess–Martin periodinane, pyridine, CH_2Cl_2; b) **52**, BF_3•OEt_2, CH_2Cl_2, –78 °C, 78% over two steps, 4.5:1 *dr*.

Scheme 37. Formation of *β*–hydroxy ketone **53**.

The BF_3•OEt_2-mediated Mukaiyama aldol reaction with *α*-unsubstituted *β*-alkoxy aldehydes affords good levels of 1,3-*anti* induction in the absence of internal aldehyde chelation.

Evans' polar model[19] provides the explanation of stereoselectivity in this transformation, in which the level of 1,3-induction is primarily dependent on minimization of internal electrostatic and steric repulsion between the aldehyde carbonyl moiety and the *β*-substituents resulting in placing the largest alkyl group perpendicular to the aldehyde's *π*-system. The alkyl group then blocks one face of the aldehyde from nucleophilic attack, and the nucleophile attacks from the opposite face (Figure 9). The solvent effects are consistent with the fact that 1,3-induction is based on electrostatic interactions that are enhanced in nonpolar media.

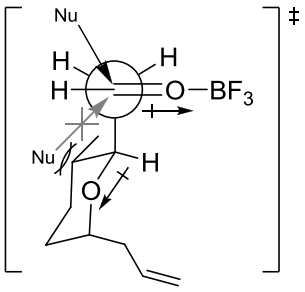
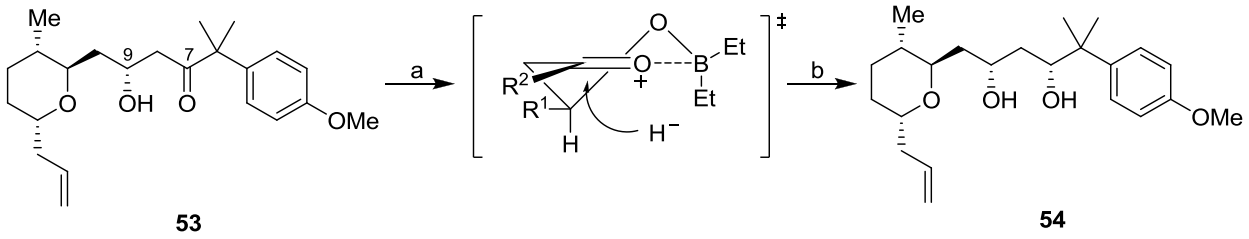


Figure 9. Proposed transition state for the Mukaiyama aldol reaction.

Highly selective *syn*-reduction with $NaBH_4$ and Et_2BOMe[27] gave diol **54**, which could be isolated in 76% yield as a single stereoisomer (Scheme 38). It is worth noting that establishing C7 stereocenter is required for introducing subsequent stereocenters on the molecule, even though it is later sacrificed during the ETIC reaction. The observed selectivity can be rationalized by chelation-controlled 1,3-induction with energetically more favorable half-chair conformation where R^1 and R^2, as the large substituents, occupy pseudo-equatorial positions. Intermolecular hydride delivery occurs axially to give the *syn*-diol as the preferred product.

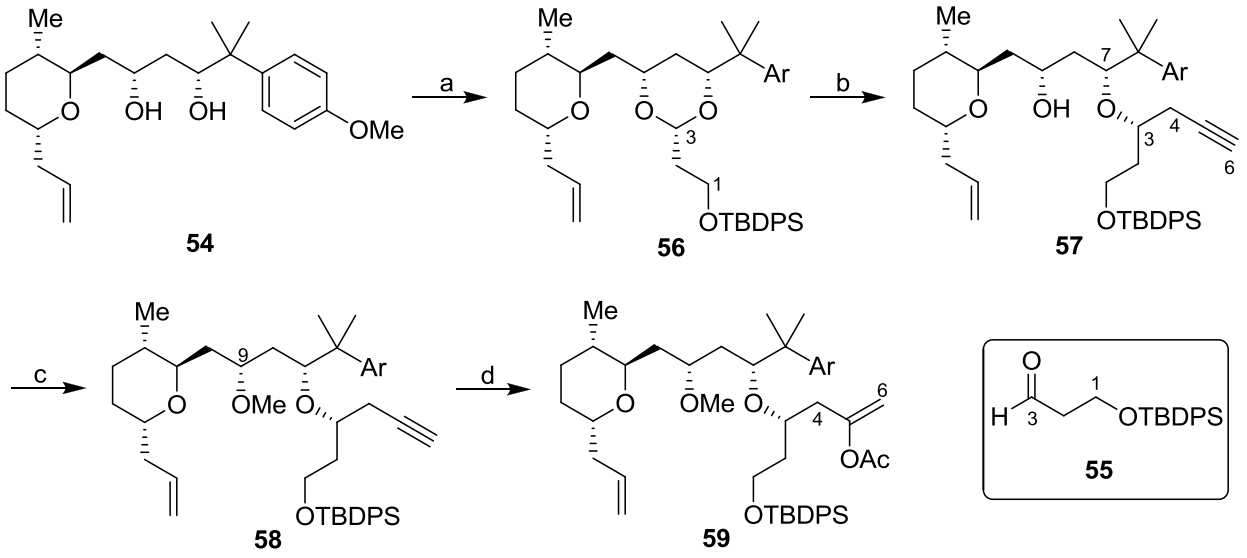


53 54

Reagents and conditions: a) Et_2BOMe, 10:1 MeOH/THF, –78 °C; b) $NaBH_4$, –78 °C, then H_2O_2, 0 °C to RT, 76%.

Scheme 38. Conversion of *β*-hydroxy ketone to *syn*-diol.

The preparation of substrate for ETIC reaction was shown in Scheme 39. To establish C1–C3 fragment, Noyori's acetalization protocol[28] was carried out through the formation of the bis(trimethylsilyl) ether of **54** and subsequent addition of known aldehyde **55**[29] with catalytic TMSOTf[30] to yield **56** in 87% yield. The C4–C6 subunit was then incorporated by a Lewis acid-mediated acetal opening[31] in the presence of allenyltributyltin, thereby completing the construction of the requisite ether linkage between C3 and C7 on **57** for the oxidative cyclization reaction. Maintaining the reaction temperature to –78 °C was required to avoid an intramolecular Friedel-Crafts reaction by the arene. The hindered hydroxyl group on **57** was transformed to methyl ether **58** in 87% yield upon treatment with MeOTf and 2,6-di-*tert*-butylpyridine.[32] The synthesis of cyclization precursor **59** was completed by ruthenium-mediated Markovnikov addition of acetic acid across the alkyne.[33]



Reagents and conditions: a) i. TMSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C; ii. **55**, 10 mol% TMSOTf, CH_2Cl_2, –78 to –45 °C, 87%; b) allenyltributyltin, 3:1 $TiCl_4$/Ti(O*i*-Pr)$_4$, CH_2Cl_2, –78 °C, 89%; c) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to RT, 87%; d) 2 mol% [Ru(*p*-cymene)Cl_2]$_2$, 4 mol% (2-furyl)$_3$P, HOAc, Na_2CO_3, toluene, 80 °C, 72%.

Scheme 39. Synthesis of ETIC substrate.

Regioselective formation of the C9 hydroxyl group in this reaction results from Lewis acid chelation between C9 and C11 oxygen atoms, while coordinating to the C7 oxygen atom by Lewis acid is expected to develop the sterically disfavorable interaction with germinal methyl groups on the electroauxiliary (Figure 10). Furthermore, tight ion-pair between oxocarbenium ion and oxyanion bound with titanium that keeps the stereochemical conformation results in shielding *Si*-face from nucleophilic additions.

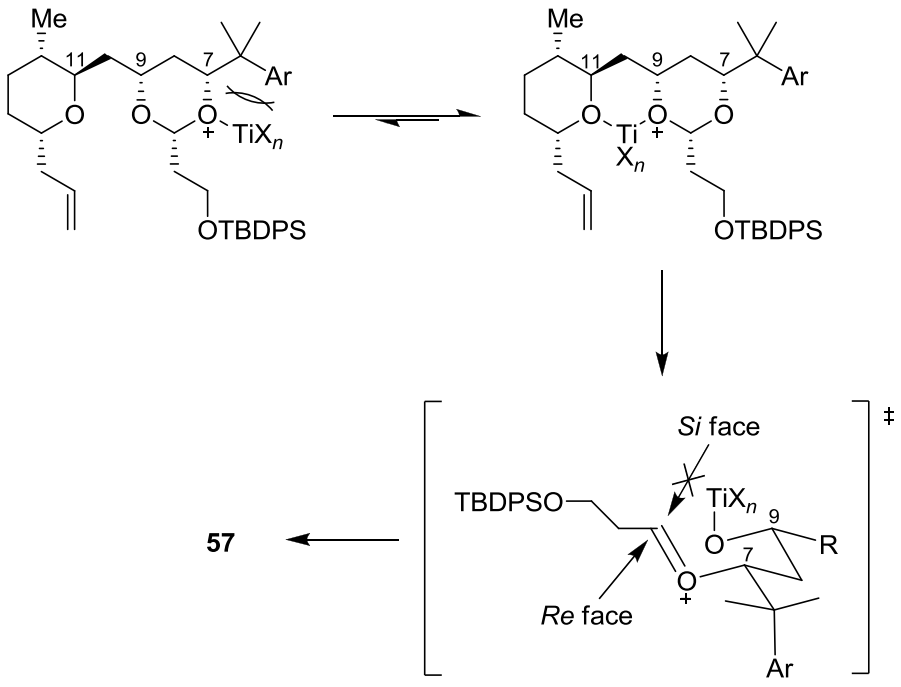
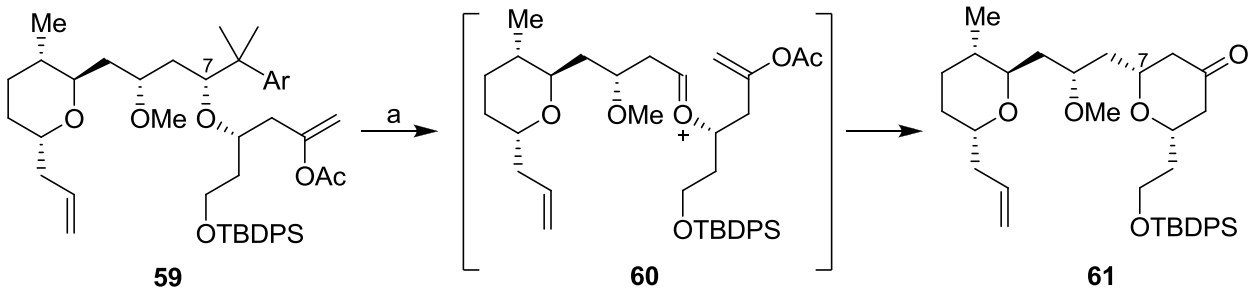


Figure 10. Transition state of diastereoselective Lewis acid-mediated acetal ring opening.

The key transformation in the synthesis of leucascandrolide A to form C3–C7 *syn*-2,6-tetrahydropyran ring involved the ETIC reaction. Treating **59** with ceric ammonium nitrate (CAN) at room temperature provided **61** in 68% yield as a single stereoisomer[34] (Scheme 40). This reaction proceeded through oxidative cleavage of the benzylic carbon–carbon bond to form oxocarbenium ion **60**, with the excellent diastereoselectivity arising from the much-precedented chair transition state for *endo*-cyclizations of this type.

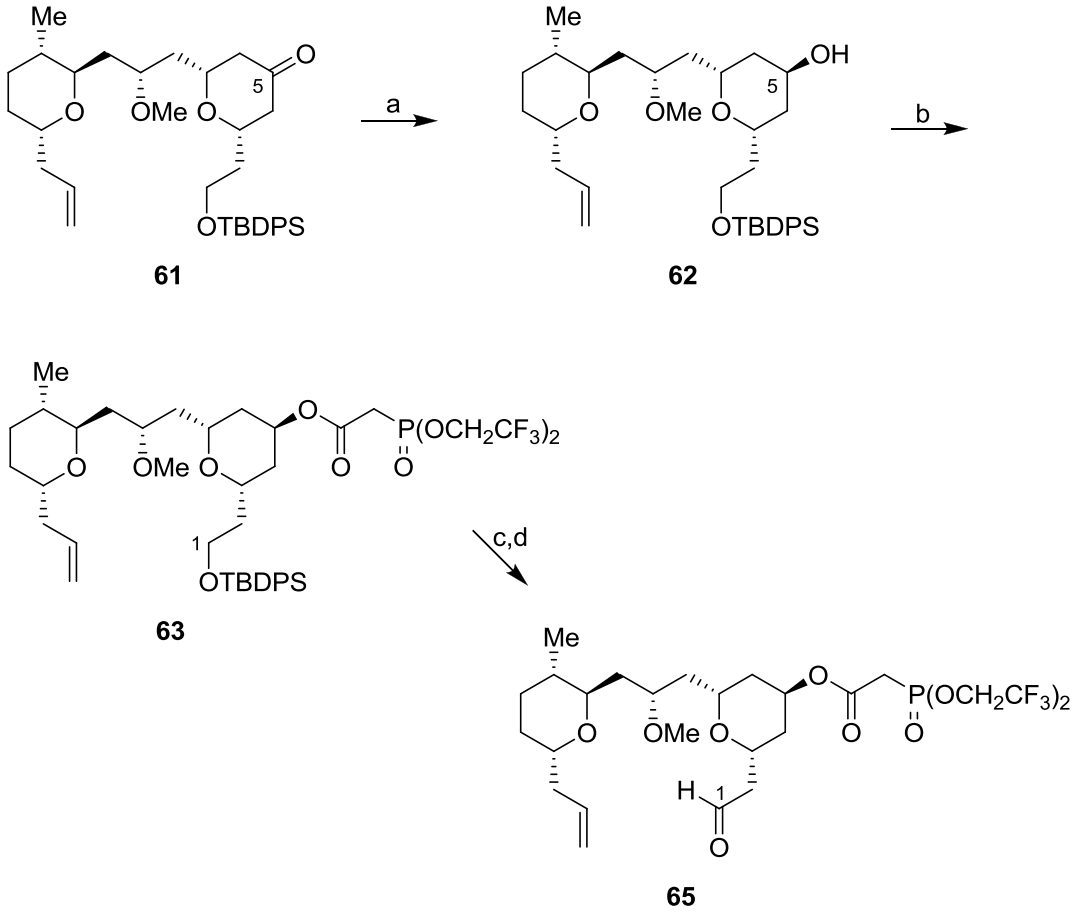


Reagents and conditions: a) Ceric ammonium nitrate (CAN), 4 Å MS, $NaHCO_3$, 1,2-dichloroethane, CH_3CN, RT, 68%.

Scheme 40. ETIC reaction.

With the two tetrahydropyran rings in place, we turned our attention to completing the synthesis of the macrocycle (Scheme 41). The need for reducing the C5 ketone on **61** was apparent. Although both diastereomers of the C5 alcohol had been successfully converted into the natural product, we made a decision to proceed through the axial alcohol. Therefore, ketone **61** was reduced with L-Selectride®[35] to provide **62** in 76% yield along with 8% of the equatorial alcohol. Instead of capping the resulting alcohol with a protecting group we converted **62** into phosphonoacetate **63** using $(CF_3CH_2O)_2P(O)CH_2CO_2H$ and EDC.[36] While the phosphonate group could be ultimately used for the construction of the C5 side chain through a Still–Gennari olefination,[37] the presence of this electrophilic group required us to complete the synthesis under very mild conditions. Removal of the TBDPS group by exposure to hydrochloric acid in methanol at room temperature readily furnished alcohol **64** in quantitative yield which was subsequently subjected to oxidation with Dess-Martin periodinane[38] to provide aldehyde **65** in 95% yield. Notably, we observed that attempts to conduct the silyl group cleavage reaction with fluoride sources, such as TBAF and HF·pyridine, promoted the cleavage of one

trifluoroethoxy group from the phophonate.

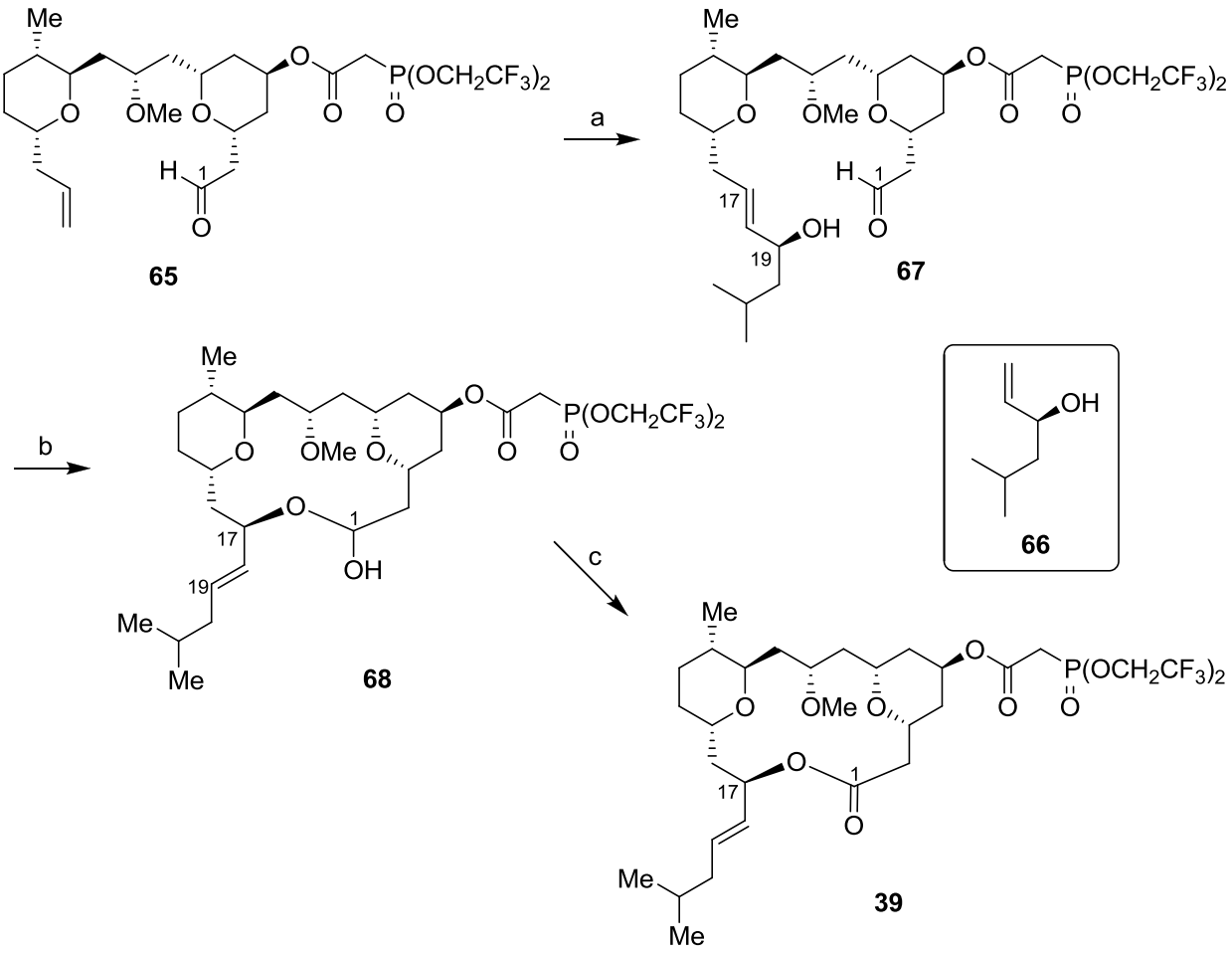


Reagents and conditions: a) L-Selectride®, THF, –90 °C, 76%; b) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDC, HOBt, CH_2Cl_2, RT, 92%; c) HCl, MeOH, RT, 98%; d) Dess–Martin periodinane, CH_2Cl_2, RT, 95%.

Scheme 41. Formation of phosphonate **65**.

Completion of our synthesis was shown in Scheme 42. A cross-metathesis reaction[39] between **65** and **66** using the Hoveyda–Grubbs catalyst[40] and quick purification by a flash chromatography provided *trans*-allylic alcohol **67**. Enatiomerically enriched **66** was prepared by means of the addition of vinylmagnesium bromide to isovaleraldehyde and subsequent

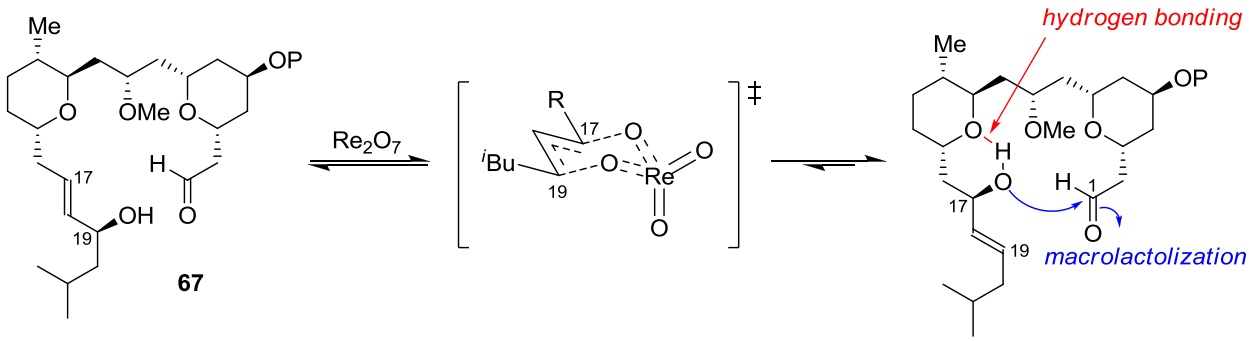
Sharpless kinetic resolution of the resulting racemic allylic alcohol.[41] Adding 1,4-benzoquinone to this reaction resulted to be useful for inhibiting ketone formation through olefin migration.[42]



Reagents and conditions: a) **66**, 20 mol% Hoveyda–Grubbs catalyst, 40 mol% 1,4-benzoquinone, CH_2Cl_2, reflux, 70%; b) Re_2O_7, Et_2O, 69%; c) PCC, CH_2Cl_2, 81%.

Scheme 42. Completion of the synthesis.

At this stage, allylic alcohol transposition was required prior to macrolide formation. While **67** and the product of its transposition are both secondary allylic alcohols, we postulated that the desired transposed hydroxyl group on C17 would be formed preferentially under equilibrating conditions through a chair-like transition state. A bias of this equilibrium was assumed to be caused by the capacity for the transposed hydroxy group to engage in hydrogen bonding with oxygen on the tetrahydropyranyl ring and its potential to add into the pendent C1 carbonyl group by considering the unusual thermodynamic stability of leucascandrolide A macrolactol (Scheme 43).[11]



Scheme 43. Proposed bias of equilibrium.

Thus we exposed **67** to Re_2O_7 in Et_2O[43] at room temperature to promote suprafacial migration. Indeed, lactol **68** was directly formed in 69% yield through the transposition of the allylic hydroxyl group. Notably, we observed that subjecting the C19-epimer of **67**, prepared through the cross metathesis of **65** with the enantiomer of **67**, to the transposition conditions also provided **68** in 49% yield. This result suggests that epimerization can occur during the transposition and that resolving **59** prior to metathesis is not necessary. While the mechanism for the epimerization has yet to be determined, we speculate that the transposition is rapid and

reversible, and that rearrangement occasionally proceeds through a boat-like rather than a chair-like transition state. Oxidizing **68** with PCC completed the synthesis of leucascandrolide macrolactone **39**. Since **37** has been converted in one step into leucascandrolide A by the Leighton group (see Scheme 30), this completes a formal synthesis. Cleaving the phosphonoacetate group (Na_2CO_3, MeOH) provided a C5 alcohol that is spectroscopically identical to material[44] that was derived from cleaving the ester side chain from **1**, thereby confirming the structural assignment.

2.3 Conclusion

We have developed a highly efficient and concise formal synthesis of leucascandrolide A through a sequence in which our ETIC method was employed for the stereoselective formation of a key 2,6-*cis*-tetrahydropyran ring from an advanced intermediate. Thus, our efforts established the utility of the method in the framework of complex molecule construction. Additionally, we make significant progresses through (*i*) the minimization of protecting group manipulations (only two steps in the longest linear sequence were solely devoted to functional group protection or deprotection), (*ii*) the use of $BiBr_3$ in a mild and efficient lactol functionalization, (*iii*) the extensive use of substrate-derived stereocontrol, and (*iv*) the utilization of macrolactol formation as a thermodynamic driving force for allylic alcohol transposition. The sequence proceeds in 17 linear steps from the known alcohol **44** (19 steps from commercially available material) and in 4.5% yield, making this route quite competitive with the most efficient enantioselective routes to leucascandrolide A.

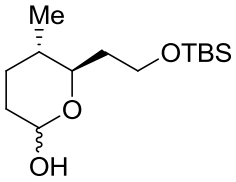
2.4 Experimental

General

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively; or Bruker Avance 500 spectrometers at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.15 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, C_6D_6 = 128.0, TMS = 0.00. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was performed using ICN SiliTech 32–63 60 Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2) was distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried

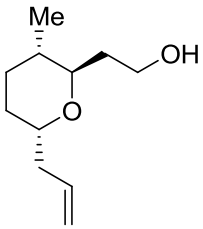
by passing through aluminum drying column. Anhydrous methanol (CH_3OH), and acetonitrile (CH_3CN) were purchased from Aldrich and used as is. All reactions were conducted under nitrogen atmosphere, unless otherwise specified.

(5*R*,6*S*)-6-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-ol (49)



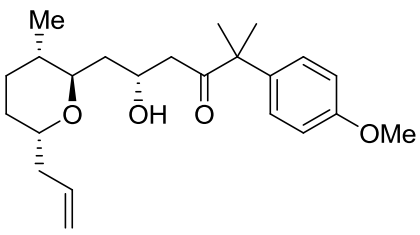
In a two neck round-bottom flask connected to a three way adapter were placed $Rh(acac)(CO)_2$ (42.2 mg, 0.164 mmol), 6-diphenylphosphanyl-2-pyridone (6-DPPon) (228.5 mg, 0.818 mmol), and THF (5 mL). After stirring at room temperature for 10 min under an atmosphere of Ar gas, a solution of **44** (800 mg, 3.273 mmol) in THF (2.0 mL) was added. A CO balloon and a H_2 balloon were individually fitted into the three way adapter. The reaction mixture was saturated with a mixture of CO and H_2 gases applying three cycles of careful evacuation and refilling with a mixture of gases. The brown mixture was vigorously stirred at room temperature for 3 days. Then solvent was removed under a reduced pressure. The crude was purified by flash column chromatography on silica gel (1:10 to 1:4, EtOAc/Hexanes) to afford **49** (808.5 mg, 2.946 mmol, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (dd, J = 4.8, 2.7 Hz, 0.5H), 4.67 (ddd, J = 9.3, 5.7, 2.1 Hz, 0.5H), 3.78–3.67 (m, 2.5H), 3.20 (td, J = 9.6, 2.4 Hz, 0.5H), 2.79 (m, 0.5H), 2.33 (m, 0.5H), 1.93–1.23 (m, 7H), 0.89 (s, 9H), 0.86 (d, J = 6.3 Hz, 1.5H), 0.83 (d, J = 6.3 Hz, 1.5H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.3, 91.4, 78.2, 71.3, 59.8, 59.4, 36.2, 36.1, 35.0, 34.4, 33.3, 31.6, 30.2, 26.3, 26.0, 18.3, 18.1, 17.2, –5.22, –5.24, –5.27, –5.32; IR (neat): 3402 (br), 2954, 2929, 2857, 1472, 1462, 1256, 1087 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{29}O_2Si$ $(M–OH)^+$ 257.1937 found 257.1945; $[\alpha]_D^{23}$ −56.17 (*c* 1.54, $CHCl_3$).

2-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (43)



To a solution of **49** (3.0 g, 10.93 mmol) in acetonitrile (50 mL) was added allyltrimethylsilane (8.68 mL, 54.62 mmol). After stirring at room temperature for 5 min, bismuth(III) bromide (2.45 g, 5.45 mmol) was added with a portion. The clear yellow mixture was stirred at room temperature for 20 min. Aqueous saturated $NaHCO_3$ solution (20 mL) was then added. The resulting solution was stirred at same temperature for additional 20 min. With EtOAc, the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1:4 to 1:2, EtOAc/hexanes) gave **43** (2.0 g, 10.85 mmol, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (m, 1H), 5.10 (m, 2H), 3.96 (m, 1H), 3.73 (m, 2H), 3.45 (td, J = 9.0, 3.0 Hz, 1H), 2.95 (m, OH), 2.60 (m, 1H), 2.17 (m, 1H), 1.85−1.32 (m, 7H), 0.87 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.3, 116.8, 76.4, 71.6, 61.6, 35.7, 34.8, 34.7, 27.7, 26.9, 18.0; IR (neat): 3421 (br), 3075, 2930, 2873, 1459, 1439, 1379, 1355, 1236, 1053 cm^{-1}; HRMS (EI) m/z calcd. for $C_{11}H_{21}O_2$ $(M+H)^+$ 185.1541 found 185.1537; $[\alpha]_D^{23}$ −45.65 (*c* 1.64, $CHCl_3$).

(*S*)-6-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-one (53)

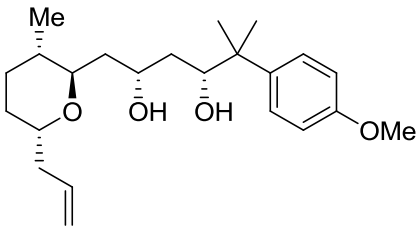


To a solution of **43** (413 mg, 2.24 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.73 mL, 9.02 mmol) followed by the addition of Dess-Martin periodinane (1.90 g, 4.48 mmol) at

0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction was quenched with a mixture of aqueous saturated $Na_2S_2O_3$ solution and aqueous saturated $NaHCO_3$ solution (*v*/*v* 1:5, 20 mL). The resulting milky solution was then stirred vigorously until the solution became clear (*ca*. 30 min). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with aqueous saturated NH_4Cl solution and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the resulting residue was dissolved in CH_2Cl_2. To a cooled solution of the crude aldehyde in CH_2Cl_2 at –78 °C was added freshly distilled $BF_3{\cdot}OEt_2$ (0.43 mL, 3.39 mmol) dropwise followed by the addition of enolsilane **52** (1.18 g, 4.46 mmol) dropwise. The reaction mixture was then stirred at –78 °C for 2 h and quenched with aqueous saturated NH_4Cl. The resulting mixture was warmed to room temperature. The mixture was then poured into water. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 times). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography on silica gel (1:4, EtOAc/hexanes) to provide ketone **53** (658 mg, 1.76 mmol, 78% over two steps) as an inseparable 4.5:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (dm, J = 9.0 Hz, 2H), 6.86 (dm, J = 9.0, 2H), 5.76 (m, 1H), 5.05 (m, 2H), 4.17 (m, 1H), 3.83 (m, 1H), 3.79 (s, 3H), 3.39 (td, J = 8.6, 2.7 Hz, 1H), 2.45 (m, 1H), 2.40 (m, 2H), 2.13 (m, 1H), 1.69 (m, 1H), 1.60−1.25 (m, 6H), 1.48 (s, 3H), 1.43 (s, 3H), 0.83 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.7, 158.5, 135.6, 127.2, 116.5, 114.1, 72.7, 71.7, 65.0, 55.2, 51.5, 44.3, 38.7, 35.6, 34.5, 27.6, 26.9, 25.4, 24.8, 18.0; ^{13}C NMR (75 MHz, C_6D_6): δ 212.7, 159.0, 136.22, 136.19, 127.5, 116.4, 114.4, 73.0, 71.6, 65.4, 54.7, 51.7, 45.0, 39.5, 36.1, 34.7, 27.9, 27.2, 25.6, 24.9,

18.1; IR (neat): 3489 (br), 2932, 1702, 1513, 1463, 1253, 1035 cm^{-1}; HRMS (EI) m/z calcd. for $C_{23}H_{34}O_4$ $(M)^+$ 374.2457 found 374.2445.

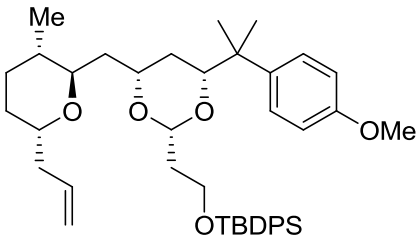
(2*R*,4*S*)-1-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-5-(4-methoxyphenyl)-5-methylhexane-2,4-diol (54)



To a solution of **53** (1.65 g, 4.40 mmol) in THF/CH_3OH (*v*/*v* 10:1, 55 mL) at –78 °C was added Et_2BOMe (0.87 mL, 6.62 mmol) dropwise. The clear solution was stirred at same temperature for 1 h and $NaBH_4$ (501 mg, 13.24 mmol) was then added with several portions. The reaction mixture was stirred at –78 °C for 1 h and poured into an ice-cooled pH 7 buffer solution (100 mL) with caution (bubbling and eruption). After stirring at 0 °C for 30 min, hydrogen peroxide (wt. 30% solution in water, 10 mL) was added dropwise. The resulting mixture was vigorously stirred at room temperature overnight (*ca.* 10 h). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with water, aqueous saturated Na_2SO_3 solution and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography (1:4, EtOAc/hexanes) to afford **54** (1.27 g, 3.37 mmol, 76%) as a single stereoisomer. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0, 2H), 5.81 (m, 1H), 5.09 (m, 2H), 3.97 (m, 2H), 3.87 (m, 1H), 3.78 (s, 3H), 3.75 (s, OH), 3.60 (s, OH), 3.40 (td, J = 8.7, 3.0 Hz, 1H), 2.57 (m, 1H), 2.13 (m, 1H), 1.78 (m, 1H), 1.66−1.30 (m, 8H), 1.31 (s, 3H), 1.29 (s, 3H), 0.81 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 139.4, 136.0, 127.5, 116.8, 113.4, 80.2, 72.3, 71.9, 70.0, 55.2, 41.6, 39.9, 37.3, 35.2, 35.0, 27.9, 27.0, 25.2, 23.1, 17.9; IR (neat): 3444 (br), 3074, 2931, 1641, 1611, 1513, 1251,

1185 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{23}H_{36}O_4Na$ $(M+Na)^+$ 399.2511 found 399.2530; $[\alpha]_D^{23}$ −33.15 (*c* 1.49, $CHCl_3$).

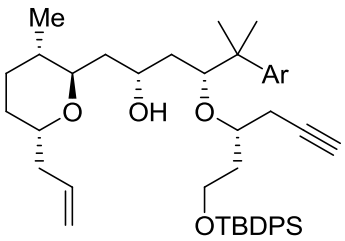
(2-((2*S*,4*S*,6*S*)-4-(((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)methyl)-6-(2-(4-methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (56)



To a cooled solution of diol **54** (1.32 g, 3.50 mmol) in CH_2Cl_2 (35 mL) at –78 °C was added 2,6-lutidine (1.63 mL, 14.00 mmol) followed by the dropwise addition of TMSOTf (1.59 mL, 8.76 mmol). The reaction mixture was stirred at –78 °C for 2 h and poured into water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with HCl (wt. 10% solution in water), water and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the resulting residue was dissolved in CH_2Cl_2 (20 mL) and cooled down to –78 °C. Aldehyde **55** (1.31 g, 4.21 mmol) was added followed by the addition of TMSOTf (64 μL, 0.35 mmol). The reaction mixture was then slowly warmed to –45 °C and stirred for 2 h. The reaction was quenched with pyridine (43 μL, 0.52 mmol) and poured into water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography (1:20, EtOAc/hexanes) to afford **56** (2.05 g, 3.05 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.40 (m, 6H), 7.23 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0, 2H), 5.72 (m, 1H), 5.01 (m, 2H), 4.69 (dd, J = 6.6, 4.2 Hz, 1H), 3.85−3.65 (m, 4H), 3.77 (s, 3H), 3.52 (m, 1H), 3.42 (app t, J = 8.2 Hz, 1H), 2.49 (m, 1H), 2.08−1.82 (m,

3H), 1.73−1.55 (m, 3H), 1.46 (m, 1H), 1.34−1.27 (m, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.07 (m, 2H), 1.05 (s, 9H), 0.84 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 138.7, 135.54, 135.52, 135.47, 134.02, 133.99, 129.5, 127.7, 127.6, 116.4, 113.1, 99.1, 83.8, 72.9, 71.6, 71.2, 59.9, 55.1, 40.5, 39.6, 38.1, 35.9, 34.7, 32.2, 27.9, 27.1, 26.9, 26.1, 22.8, 19.2, 18.1; IR (neat): 3071, 2930, 1641, 1612, 1513, 1361, 1251, 1185 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{42}H_{58}O_5SiNa$ $(M+Na)^+$ 693.3951 found 693.3951; $[\alpha]_D^{23}$ −24.56 (c 1.71, $CHCl_3$).

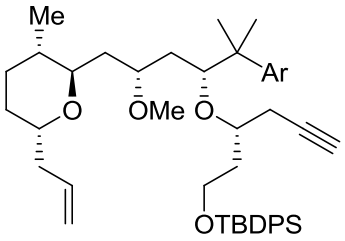
(2*S*,4*S*)-1-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-4-((*S*)-1-(*tert*-butyldiphenyl-silyloxy)hex-5-yn-3-yloxy)-5-(4-methoxyphenyl)-5-methylhexan-2-ol (57)



To a cooled solution of acetal **56** (200 mg, 0.298 mmol) and allenyltributyltin (294 mg, 0.894 mmol) in CH_2Cl_2 (3 mL) at –78 °C was added a freshly prepared a mixture of $TiCl_4$ (286 μL, 2.61 mmol) and Ti(O-*i*-Pr)$_4$ (0.262 μL, 0.89 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at same temperature for 1 h and quenched with CH_3OH. The resulting mixture was poured into aqueous saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with water and KF (wt. 10% solution in water), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was then purified *via* flash column chromatography (1:20 to 1:10, EtOAc/hexanes) to give **57** (188 mg, 0.265 mmol, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.40 (m, 6H), 7.27 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0, 2H), 5.74 (m, 1H), 5.02 (m, 2H), 3.83−3.72 (m, 3H), 3.75 (s, 3H), 3.68 (m, 2H), 3.33 (m, 2H), 3.17 (d, J = 3.0 Hz, OH), 2.45 (m, 1H), 2.39 (ddd, J = 16.5, 5.7, 3.0 Hz, 1H), 2.29 (ddd, J = 16.5, 3.6, 3.0 Hz, 1H), 2.07 (m, 1H), 1.96 (t, J = 2.6 Hz, 1H), 1.91 (app q, J =

6.3 Hz, 2H), 1.67 (m, 1H), 1.57−1.23 (m, 8H), 1.33 (s, 3H), 1.26 (s, 3H), 1.04 (s, 9H), 0.72 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 139.7, 135.8, 135.6, 135.5, 133.9, 129.5, 127.7, 127.63, 127.61, 116.4, 113.2, 81.7, 81.5, 72.8, 71.8, 71.6, 70.1, 66.7, 60.6, 55.1, 42.2, 39.6, 39.5, 36.3, 35.4, 34.1, 27.8, 27.0, 26.9, 26.7, 23.2, 22.9, 19.2, 18.0; IR (neat): 3497 (br), 3309, 3071, 3031, 2118, 1611, 1513, 1428, 1251, 1098 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{45}H_{62}O_5SiNa$ $(M+Na)^+$ 733.4264 found 733.4268.

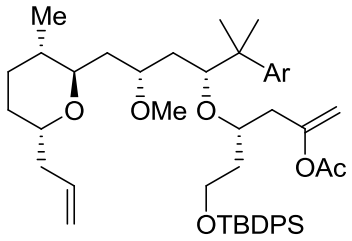
((*S*)-3-((3*S*,5*S*)-6-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-5-methoxy-2-(4-methoxyphenyl)-2-methylhexan-3-yloxy)hex-5-ynyloxy)(*tert*-butyl)diphenylsilane (58)



To a solution of alcohol **57** (369 mg, 0.519 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added 2,6-di-*tert*-butylpyridine (459, 2.076 mmol) followed by the addition of MeOTf (176 μL, 1.557 mmol). The reaction was then slowly warmed to room temperature and stirred for 24 h. The reaction was quenched with aqueous saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (1:20 to 1:10, EtOAc/hexanes) afforded **58** (329 mg, 0.454 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.38 (m, 6H), 7.26 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0, 2H), 5.72 (m, 1H), 5.01 (m, 2H), 3.78 (m, 3H), 3.76 (s, 3H), 3.67 (m, 1H), 3.41 (app t, J = 4.6 Hz, 1H), 3.24 (m, 1H), 3.16 (s, 3H), 2.94 (m, 1H), 2.41−2.27 (m, 3H), 2.17 (m, 1H), 1.95 (t, J = 2.6 Hz, 1H), 1.92 (m, 2H), 1.60−1.15 (m, 9H), 1.31 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H), 0.82 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 139.6, 135.7, 135.6, 135.5, 134.0, 129.5, 127.9,

127.6, 116.3, 113.1, 81.9, 80.3, 72.8, 71.8, 70.9, 69.8, 60.9, 57.2, 55.1, 42.3, 38.5, 37.8, 37.2, 36.9, 34.0, 27.1, 26.9, 26.7, 26.5, 23.1, 23.0, 19.2, 18.2; IR (neat): 3497 (br), 3309, 3071, 2930, 2119, 1611, 1513, 1428, 1251, 1111 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{46}H_{64}O_5SiNa$ $(M+Na)^+$ 747.4421 found 747.4431.

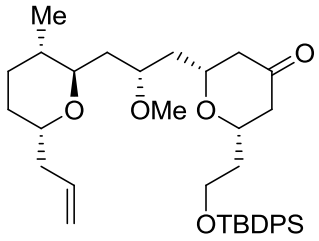
(*R*)-4-((3*S*,5*S*)-6-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-5-methoxy-2-(4-methoxyphenyl)-2-methylhexan-3-yloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-1-en-2-yl acetate (59)



To a solution of alkyne (316 mg, 0.435 mmol) in toluene (10 mL) was added Na_2CO_3 (7.0 mg, 0.066 mmol) followed by the addition of acetic acid (50 μL, 0.871 mmol) under an atmosphere of Ar gas. The mixture was stirred at room temperature for 10 min, and [Ru(*p*-cymene)Cl_2]$_2$ (5.3 mg, 8.7 μmol), tri(2-furyl)phosphine (4.0 mg, 17.4 μmol). The brown reaction mixture was stirred at 80 °C for 36 h. The color of reaction was slowly changed to green over 6 h. The mixture was cooled to room temperature and the solvent was then removed under reduced pressure. The resulting residue was purified *via* flash column chromatography (1:20 to 1:10, EtOAc/hexanes) to give **59** (245 mg, 0.312 mmol, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.37 (m, 6H), 7.25 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7, 2H), 5.71 (m, 1H), 5.01 (m, 2H), 4.78 (s, 1H), 4.73 (s, 1H), 3.77 (m, 3H), 3.76 (s, 3H), 3.67 (m, 1H), 3.39 (app t, J = 4.6 Hz, 1H), 3.22 (m, 1H), 3.15 (s, 3H), 2.90 (m, 1H), 2.55 (dd, J = 14.7, 4.2 Hz, 1H), 2.33 (m, 1H), 2.23−2.05 (m, 2H), 2.11 (s, 3H), 1.90−1.71 (m, 2H), 1.60−1.15 (m, 9H), 1.28 (s, 3H), 1.24 (s, 3H), 1.05 (s, 9H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 157.6, 153.7, 139.7, 135.7, 135.6, 135.5, 134.0, 129.50, 129.48, 127.9, 127.6,

116.3, 113.1, 103.51, 80.0, 76.4, 72.6, 71.0, 60.8, 57.2, 55.1, 42.3, 38.7, 37.9, 37.7, 37.1, 36.7, 34.2, 27.0, 26.9, 26.7, 26.6, 23.0, 21.1, 19.2, 18.2; IR (neat): 3071, 2931, 2858, 1757, 1665, 1513, 1428, 1368, 1200, 1109 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{48}H_{68}O_7SiNa$ $(M+Na)^+$ 807.4632 found 807.4608; $[\alpha]_D^{23}$ −2.82 (*c* 1.42, $CHCl_3$).

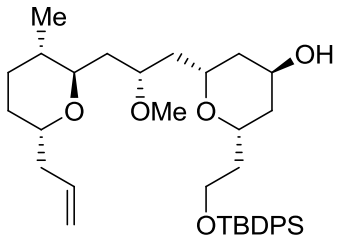
(2*S*,6*R*)-2-((*R*)-3-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methoxyprop-yl)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-tetrahydropyran-4-one (61)



To a solution of enol acetate **59** (236 mg, 0.301 mmol) in 1,2-dichloroethane (6 mL) was added $NaHCO_3$ (472 mg) and 4 Å molecular sieves (472 mg). After stirring at room temperature for 20 min, a dark orange colored solution of ceric ammonium nitrate (CAN) (659 mg, 1.202 mmol) in acetonitrile (1 mL) was added dropwise. The dull green colored reaction mixture was stirred at room temperature for an additional 2 h. The resulting mixture was filtered through a small silica plug and washed with EtOAc. The filtrate was then concentrated under reduced pressure and the residue was purified *via* flash column chromatography (1:10 to 1:4, EtOAc/hexanes) to provide **61** (121 mg, 0.204 mmol, 68%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (app d, J = 7.2 Hz, 4H), 7.40 (m, 6H), 5.78 (m, 1H), 5.05 (m, 2H), 3.87−3.68 (m, 5H), 3.56−3.44 (m, 2H), 3.30 (s, 3H), 2.48−2.34 (m, 3H), 2.30−2.16 (m, 3H), 1.98−1.84 (m, 2H), 1.81−1.44 (m, 7H), 1.40−1.23 (m, 2H), 1.03 (s, 9H), 0.89 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.4, 135.6, 135.5, 133.7, 133.6, 129.63, 129.62, 127.7, 116.4, 74.3, 73.91, 73.87, 72.6, 71.2, 60.1, 56.8, 48.1, 47.8, 40.6, 39.3, 38.6, 36.8, 34.2, 27.3, 26.8, 26.6, 19.1, 18.3; IR (neat): 3071, 2929, 2857, 1720, 1460, 1427, 1147, 1109, 1090 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{36}H_{52}O_5SiNa$ $(M+Na)^+$ 615.3482 found 615.3455;

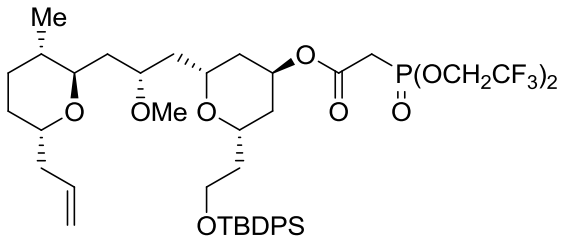
$[\alpha]_D^{23}$ −22.25° (*c* 2.00, $CHCl_3$).

(2*R*,4*R*,6*R*)-2-((*R*)-3-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methoxypropyl)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-tetrahydro-2*H*-pyran-4-ol (62)



To a cooled solution of ketone **61** (349 mg, 0.589 mmol) in THF (30 mL) at –90 °C was slowly added L-Selectride® (1.0 M solution in THF, 0.88 mL, 0.88 mmol) over 5 min. The reaction mixture was stirred at same temperature for 1 h and quenched with aqueous saturated potassium sodium tartrate solution (30 mL). The solution was allowed to warm to room temperature. Diethyl ether (30 mL) was added and the resulting mixture was vigorously stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 times). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography on silica gel (1:2, EtOAc/hexanes) to afford **62** (266 mg, 0.447 mmol, 76%) and the epimer (30 mg, 0.050 mmol, 8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.38 (m, 6H), 5.79 (m, 1H), 5.04 (m, 2H), 4.20 (m, 1H), 3.95−3.81 (m, 2H), 3.79 (t, J = 6.6 Hz, 2H), 3.74 (m, 1H), 3.52 (m, 2H), 3.30 (s, 3H), 2.40 (m, 1H), 2.21 (m, 1H), 1.86−1.25 (m, 15H), 1.05 (s, 9H), 0.91 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 135.5, 134.1, 134.0, 129.5, 127.6, 116.3, 74.4, 72.7, 70.8, 68.6, 68.4, 64.8, 60.8, 56.8, 40.4, 39.3, 39.0, 38.7, 38.5, 37.2, 33.9, 27.1, 26.9, 26.5, 19.2, 18.4; IR (neat): 3436 (br), 3071, 2931, 2858, 1460, 1428, 1109 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{36}H_{54}O_5SiNa$ $(M+Na)^+$ 617.3638 found 617.3591; $[\alpha]_D^{23}$ −25.80° (*c* 2.05, $CHCl_3$).

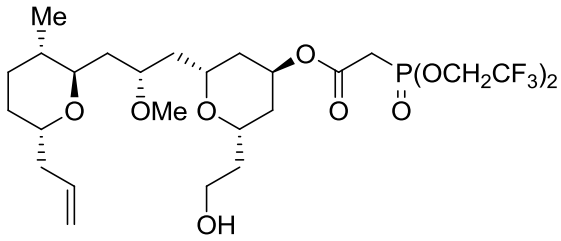
(2*S*,4*R*,6*R*)-2-((*R*)-3-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methoxypropyl)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)tetrahydro-2*H*-pyran-4-yl 2-((bis(2,2,2-trifluoroethoxy))-phosphoryl)acetate (63)



To a mixture of alcohol **62** (80.1 mg, 0.135 mmol) and bis-(2,2,2-trifluoroethyl)phosphonoacetic acid[45] (81.8 mg, 0.269 mmol) in CH_2Cl_2 (10 mL) were added HOBt•H_2O (9.1 mg, 0.067 mmol) and then EDC•HCl (51.6 mg, 0.269 mmol). The reaction mixture was stirred at room temperature for 1.5 h and quenched with aqueous saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography on silica gel (1:3, EtOAc/hexanes) to afford **63** (109.1 mg, 0.124 mmol, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.39 (m, 6H), 5.77 (m, 1H), 5.24 (m, 1H), 5.04 (m, 2H), 4.47 (qd, $^3J(^1H,^{19}F)$ = 8.1 Hz, $^3J(^1H,^{31}P)$ = 3.6 Hz, 2H), 4.44 (qd, $^3J(^1H,^{19}F)$ = 8.1 Hz, $^3J(^1H,^{31}P)$ = 3.6 Hz, 2H), 3.77 (m, 5H), 3.49 (m, 2H), 3.27 (s, 3H), 3.15 (d, $^2J(^1H,^{31}P)$ = 21.0 Hz, 1H), 3.14 (d, $^2J(^1H,^{31}P)$ = 21.0 Hz, 1H), 2.40 (m, 1H), 2.21 (m, 1H), 1.85−1.44 (m, 13H), 1.29 (m, 2H), 1.03 (s, 9H), 0.88 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (d, $^2J(^{13}C,^{31}P)$ = 4 Hz), 135.7, 135.5, 133.94, 133.89, 129.6, 127.6, 122.5 (q, $^1J(^{13}C,^{19}F)$ = 274 Hz), 122.4 (q, $^1J(^{13}C,^{19}F)$ = 274 Hz), 116.3, 74.4, 72.5, 71.0, 70.8, 69.2, 68.9, 62.6 (qm, $^2J(^{13}C,^{19}F)$ = 37 Hz), 62.5 (qm, $^2J(^{13}C,^{19}F)$ = 37 Hz), 60.6, 56.7, 40.1, 39.0, 38.5, 36.9, 35.7, 35.3, 34.2 (d, $^1J(^{13}C,^{31}P)$ = 143 Hz), 34.1, 27.2, 26.8, 26.6, 19.2, 18.3; IR (neat): 3072, 2931, 2858, 1737, 1460, 1427, 1299, 1269, 1175, 1101 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{42}H_{59}O_9F_6SiPNa$ $(M+Na)^+$ 903.3468 found 903.3495; $[\alpha]_D^{23}$

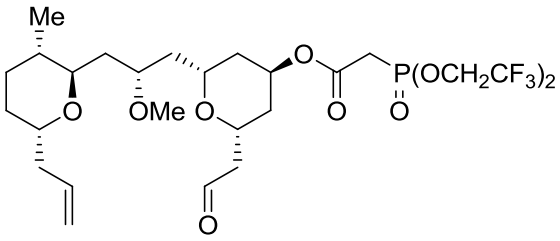
−16.95° (*c* 2.56, $CHCl_3$).

(2*S*,4*R*,6*R*)-2-((*R*)-3-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methoxypropyl)-6-(2-hydroxyethyl)-tetrahydro-2*H*-pyran-4-yl 2-((bis(2,2,2-trifluoroethoxy))phospho-ryl)acetate (64)



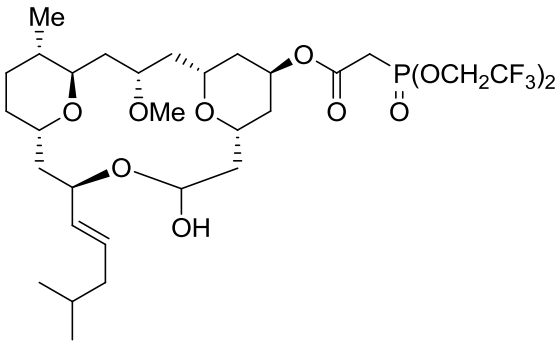
A solution of **63** (107.7 mg, 0.122 mmol) in 3% HCl in CH_3OH (10 mL) was stirred at room temperature for 2 h. The reaction was quenched with aqueous saturated $NaHCO_3$. After adding EtOAc, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified *via* flash chromatography on silica gel (1:1, EtOAc/hexanes) to give alcohol **64** (76.6 mg, 0.119 mmol, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.25 (m, 1H), 5.07 (m, 2H), 4.48 (q, $^3J(^1H,^{19}F)$ = 8.1 Hz, 2H), 4.45 (q, $^3J(^1H,^{19}F)$ = 8.1 Hz, 2H), 3.96−3.79 (m, 3H), 3.73−3.60 (m, 3H), 3.48 (app t, *J* = 8.1 Hz, 1H), 3.35 (br s, OH), 3.32 (s, 3H), 3.19 (d, $^2J(^1H,^{31}P)$ = 21.3 Hz, 2H), 2.56 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H), 1.81−1.47 (m, 11H), 1.34 (m, 3H), 0.88 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (d, $^2J(^{13}C,^{31}P)$ = 5 Hz), 135.6, 122.4 (q, $^1J(^{13}C,^{19}F)$ = 275 Hz), 122.3 (q, $^1J(^{13}C,^{19}F)$ = 275 Hz), 116.5, 74.2, 72.1, 71.9, 70.6, 70.1, 69.6, 62.6 (qm, $^2J(^{13}C,^{19}F)$ = 37 Hz), 62.5 (qm, $^2J(^{13}C,^{19}F)$ = 37 Hz), 58.6, 56.6, 38.9, 37.9, 37.5, 35.8, 35.6, 35.4, 35.1, 34.4 (d, $^1J(^{13}C,^{31}P)$ = 143 Hz), 27.8, 27.1, 18.2; IR (neat): 3467 (br), 2927, 2858, 1737, 1459, 1269, 1174, 1073 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{26}H_{41}O_9F_6PNa$ $(M+Na)^+$ 665.2290 found 665.2281; $[\alpha]_D^{23}$ −25.29° (*c* 1.70, $CHCl_3$).

(2*S*,4*S*,6*S*)-2-((*R*)-3-((2*S*,3*R*,6*R*)-6-Allyl-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methoxypropyl)-6-(2-oxoethyl)-tetrahydro-2*H*-pyran-4-yl 2-((bis(2,2,2-trifluoroethoxy))phosphoryl)acetate (65)



To a solution of alcohol **64** (100 mg, 0.156 mmol) in CH_2Cl_2 was added pyridine (50 μL, 0.622 mmol) followed by the addition of Dess-Martin periodinane (132 mg, 0.311 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was filtered through a short silica plug and washed with EtOAc. The filtrate was concentrated. The crude was purified *via* flash column chromatography on silica gel (1:1, EtOAc/hexanes) to afford **65** (95 mg, 0.148 mmol, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (dd, J = 1.8, 2.7 Hz, 1H), 5.81 (m, 1H), 5.27 (m, 1H), 5.06 (m, 2H), 4.50 (qd, $^3J(^1H,^{19}F)$ = 8.1 Hz, $^3J(^1H,^{31}P)$ = 1.2 Hz, 2H), 4.47 (qd, $^3J(^1H,^{19}F)$ = 8.1 Hz, $^3J(^1H,^{31}P)$ = 1.2 Hz, 2H), 4.22 (m, 1H), 3.82 (m, 2H), 3.51 (m, 2H), 3.29 (s, 3H), 3.20 (d, $^2J(^1H,^{31}P)$ = 21.3 Hz, 2H), 2.55 (ddd, J = 16.2, 8.4, 2.7 Hz, 1H), 2.51−2.41 (m, 1H), 2.39 (ddd, J = 16.2, 4.5, 1.8 Hz, 1H), 2.28−2.17 (m, 1H), 1.87−1.47 (m, 11H), 1.35 (m, 2H), 0.93 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 163.8 (d, $^2J(^{13}C,^{31}P)$ = 5 Hz), 135.7, 122.4 (q, $^1J(^{13}C,^{19}F)$ = 276 Hz), 122.3 (q, $^1J(^{13}C,^{19}F)$ = 276 Hz), 116.3, 74.3, 72.5, 71.2, 70.1, 69.2, 67.6, 62.6 (qd, $^2J(^{13}C,^{19}F)$ = 37 Hz, $^2J(^{13}C,^{31}P)$ = 2 Hz), 62.5 (qd, $^2J(^{13}C,^{19}F)$ = 37 Hz, $^2J(^{13}C,^{31}P)$ = 2 Hz), 56.6, 49.3, 39.6, 38.5, 36.7, 35.4, 34.9, 34.4 (d, $^1J(^{13}C,^{31}P)$ = 142 Hz), 34.3, 27.4, 26.7, 18.3; IR (neat): 2928, 2876, 1731, 1420, 1299, 1270, 1174, 1074 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{26}H_{39}O_9F_6PNa$ $(M+Na)^+$ 663.2134 found 663.2106; $[\alpha]_D^{23}$ −25.12° (*c* 1.60, $CHCl_3$).

Macrocyclic lactol (68)

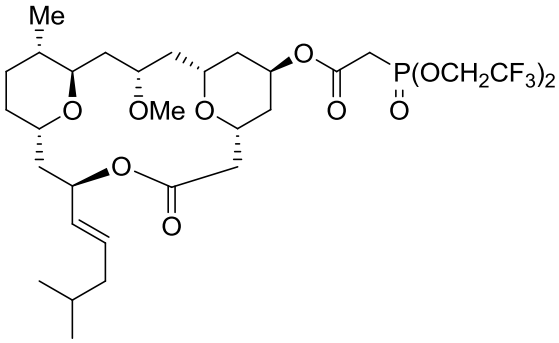


To a solution of alkene **65** (20.0 mg, 31.2 μmol) and (*S*)-5-methylhex-1-en-3-ol[46] (17.8 mg, 155.9 μmol) in CH_2Cl_2 (3 mL) was added Hoveyda-Grubbs (2nd generation) (3.9 mg, 6.2 μmol) followed by the addition of 1,4-benzoquinone (1.3 mg, 12.5 μmol). The flask was fitted with a condenser and refluxed at 45 °C for 6 h under an atmosphere of N_2 gas. The greenish crude was then concentrated under reduced pressure and purified by flash chromatography on silica gel (1:1 to 2:1, EtOAc/hexanes) to give **67** (15.9 mg, 21.9 μmol, 70%) as a colorless oil that was allowed to use directly for the next reaction of rhenium-catalyzed 1,3-isomerization by ^{1}H NMR analysis.

To a solution of allyl alcohol **67** (14.5 mg, 19.9 μmol) in diethyl ether (2 mL) was added Re_2O_7 (0.9 mg, 1.9 μmol). The reaction mixture was stirred at room temperature for 2.5 h and then concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography on silica gel (1:2 to 1:1, EtOAc/hexanes) to give **68** (10.0 mg, 13.8 μmol, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (dt, J = 15.3, 7.2 Hz, 1H), 5.26 (m, 1H), 5.10 (dd, J = 15.3, 8.7 Hz, 1H), 4.92 (dm, J = 10.2 Hz, 1H), 4.70 (m, 1H), 4.47 (q, $^3J(^1H,^{19}F)$ = 8.1 Hz, 2H), 4.44 (q, $^3J(^1H,^{19}F)$ = 8.1 Hz, 2H), 4.25 (m, 1H), 3.94 (dm, J = 11.4 Hz, 1H), 3.83 (m, 1H), 3.74 (tm, J = 11.7 Hz, 1H), 3.65 (tm, J = 11.7 Hz, 1H), 3.37 (s, 3H), 3.22 (d, $^2J(^1H,^{31}P)$ = 21.0 Hz, 1H), 3.21 (d, $^2J(^1H,^{31}P)$ = 21.0 Hz, 1H), 2.55 (ddm, J = 14.1, 12.6 Hz, 1H), 2.02−1.36 (m, 18H), 1.19 (d, J = 7.2 Hz, 3H), 1.05 (ddd, J = 14.1, 11.0, 2.1 Hz, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8 (d, $^2J(^{13}C,^{31}P)$ = 5 Hz), 134.1, 130.7, 122.4 (q, $^1J(^{13}C,^{19}F)$ = 276 Hz), 122.3 (q, $^1J(^{13}C,^{19}F)$ = 276 Hz), 90.94, 74.0, 73.8, 71.4,

70.7, 70.3, 68.8, 63.1, 62.6 (qd, $^{2}J(^{13}C,^{19}F)$ = 37 Hz, $^{2}J(^{13}C,^{31}P)$ = 2 Hz), 62.5 (qd, $^{2}J(^{13}C,^{19}F)$ = 37 Hz, $^{2}J(^{13}C,^{31}P)$ = 2 Hz), 57.1, 44.2, 41.7, 39.8, 38.7, 35.8, 35.6, 35.5, 34.4 (d, $^{1}J(^{13}C,^{31}P)$ = 142 Hz), 31.2, 28.1, 27.3, 24.2, 22.3, 22.2, 18.4; IR (neat): 3487 (br), 2927, 1740, 1457, 1271, 1173, 1097, 1075 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{31}H_{49}O_{10}F_6PNa$ $(M+Na)^+$ 749.2865 found 749.2833; $[\alpha]_D^{23}$ −39.30° (*c* 1.20, $CHCl_3$).

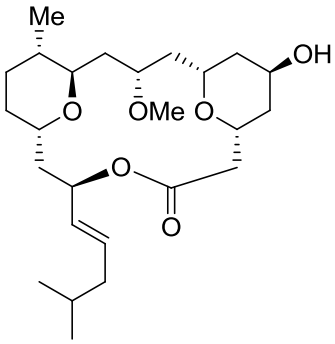
Macrocyclic lactone (39)



To a solution of lactol **68** (8.2 mg, 11.3 μmol) in CH_2Cl_2 (3 mL) was added 4 Å molecular sieves (8.2 mg). After gently stirring for 10 min, pyridinium chlorochromate (PCC) (4.9 mg, 22.6 μmol) was added with a portion. The resulting mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography on silica gel (1:10 to 1:4, EtOAc/hexanes) to provide **39** (6.6 mg, 9.1 μmol, 81%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (m, 1H), 5.37 (m, 1H), 5.36 (m, 1H), 5.27 (m, 1H), 4.46 (m, 4H), 4.01 (tm, *J* = 11.5 Hz, 1H), 3.89 (dm, *J* = 11.5 Hz, 1H), 3.61 (tm, *J* = 11.5 Hz, 2H), 3.53 (tm, *J* = 11.0 Hz, 1H), 3.35 (s, 3H), 3.23 (d, $^{2}J(^{1}H,^{31}P)$ = 21.0 Hz, 1H), 3.22 (d, $^{2}J(^{1}H,^{31}P)$ = 21.0 Hz, 1H), 2.52 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.45 (m, 1H), 2.31 (dd, *J* = 13.0, 12.0 Hz, 1H), 2.01−1.84 (m, 4H), 1.76−1.65 (m, 2H), 1.63−1.49 (m, 7H), 1.42 (dm, *J* = 13.0 Hz, 1H), 1.32 (dm, *J* = 13.0 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.01 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 163.7 (d, $^{2}J(^{13}C,^{31}P)$ = 5 Hz), 132.4, 130.1, 122.4 (q, $^{1}J(^{13}C,^{19}F)$ = 276 Hz), 122.3 (q, $^{1}J(^{13}C,^{19}F)$ = 276 Hz), 73.7, 73.3, 70.9, 70.4, 69.7, 69.3, 63.0, 62.6 (m), 62.5 (m), 57.3, 43.2, 42.8,

41.6, 39.1, 35.5, 35.2, 35.1, 34.4 (d, $^{1}J(^{13}C,^{31}P)$ = 142 Hz), 31.0, 28.1, 27.2, 24.0, 22.2, 18.3; IR (neat): 2927, 1739, 1459, 1271, 1171, 1073 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{31}H_{47}O_{10}F_6PNa$ $(M+Na)^+$ 747.2709 found 747.2685; $[\alpha]_D^{23}$ −40.30° (*c* 0.67, $CHCl_3$).

Validation of stereochemistry for macrocyclic lactone (39)



To a solution of macrocyclic lactone **39** (3.5 mg, 4.8 μmol) in CH_3OH (1 mL) was added K_2CO_3 (0.1 mg, 0.7 μmol). The reaction mixture was stirred at room temperature for 20 min and concentrated under reduced pressure. The crude was purified *via* flash column chromatography on silica gel (1:1 to 2:1, EtOAc/hexanes) to afford the desired product (1.8 mg, 4.1 μmol, 85%) which provided to be identical with spectroscopic data reported by Crimmins and Siliphaivanh.[44]

2.5 References

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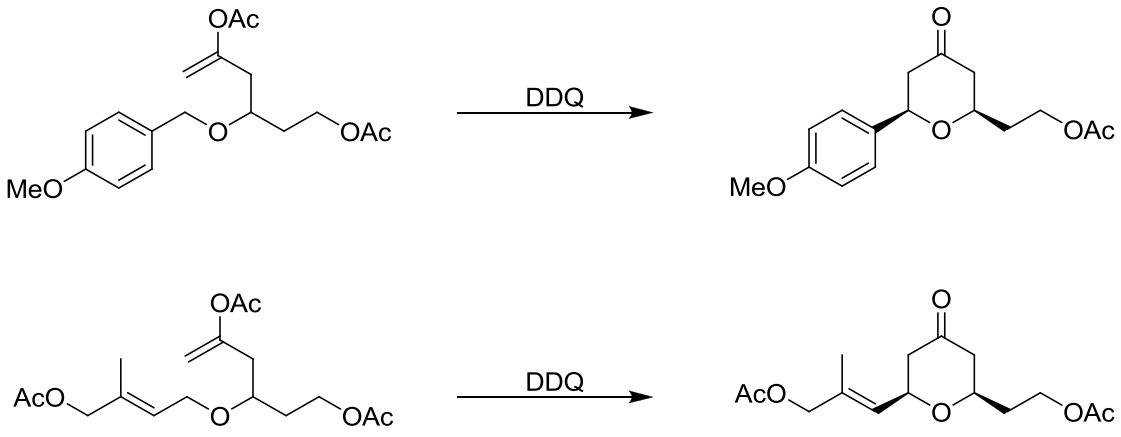
3.0 Mechanistic Analysis of Oxidative C–H Cleavages using Inter- and Intramolecular Kinetic Isotope Effects.[1]

3.1 Introduction

Oxygen-containing heterocycles are present in numerous biologically active compounds, making these structures the focus of intensive reaction development studies.[2] These units are often prepared through variations in the Prins reaction, in which ring formation occurs via intramolecular additions of carbon nucleophiles to oxocarbenium ions.[3] These processes often require the use of strongly acidic conditions to initiate ionization, thereby limiting functional group compatibility. In an effort to enhance functional group tolerance, Floreancig group has developed a DDQ-mediated synthesis of tetrahydropyranone (Scheme 44).[4] The cyclization reactions can be initiated by forming oxocarbenium ions through DDQ-mediated oxidative carbon–hydrogen bond activation from benzylic and allylic ethers. The development of this promising method would be facilitated by a greater understanding of the mechanistic nuances of the individual steps of the process. We have initiated studies that are directed toward elucidating the details of the carbon–hydrogen bond activation step. In this chapter we detail our findings from inter- and intramolecular kinetic isotope effect studies and present evidence for the formation of a radical cation intermediate prior to hydrogen atom abstraction en route to the oxocarbenium ion intermediate.



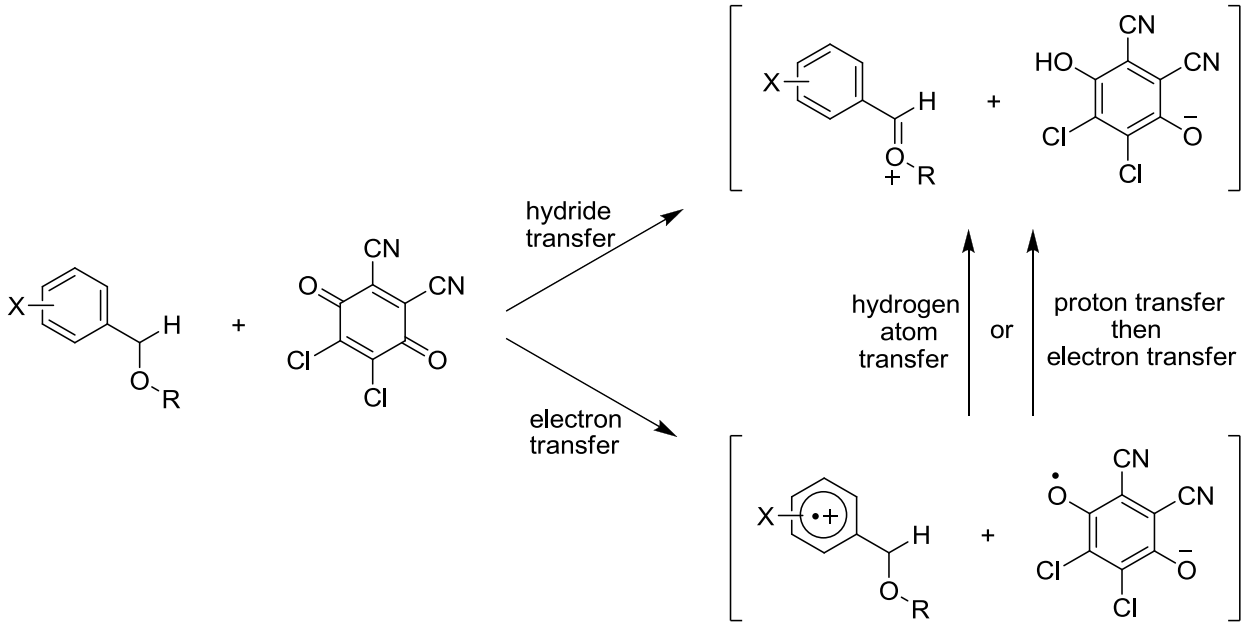
Scheme 44. Cyclization reactions through oxidative carbon–hydrogen bond activation.

3.2 Results and Discussion

3.2.1 Background

Three mechanisms have been postulated for the generation of stabilized carbocations through DDQ-mediated oxidation (Scheme 45). The most direct pathway proceeds through a one-step hydride transfer to DDQ.[5] The other two pathways proceed through an initial electron transfer to form the radical cation of the substrate and the radical anion of DDQ. The oxocarbenium ion can then be accessed through hydrogen atom abstraction or proton abstraction followed by a second electron transfer. Bordwell and Zhang postulated[6] that proton transfer should be

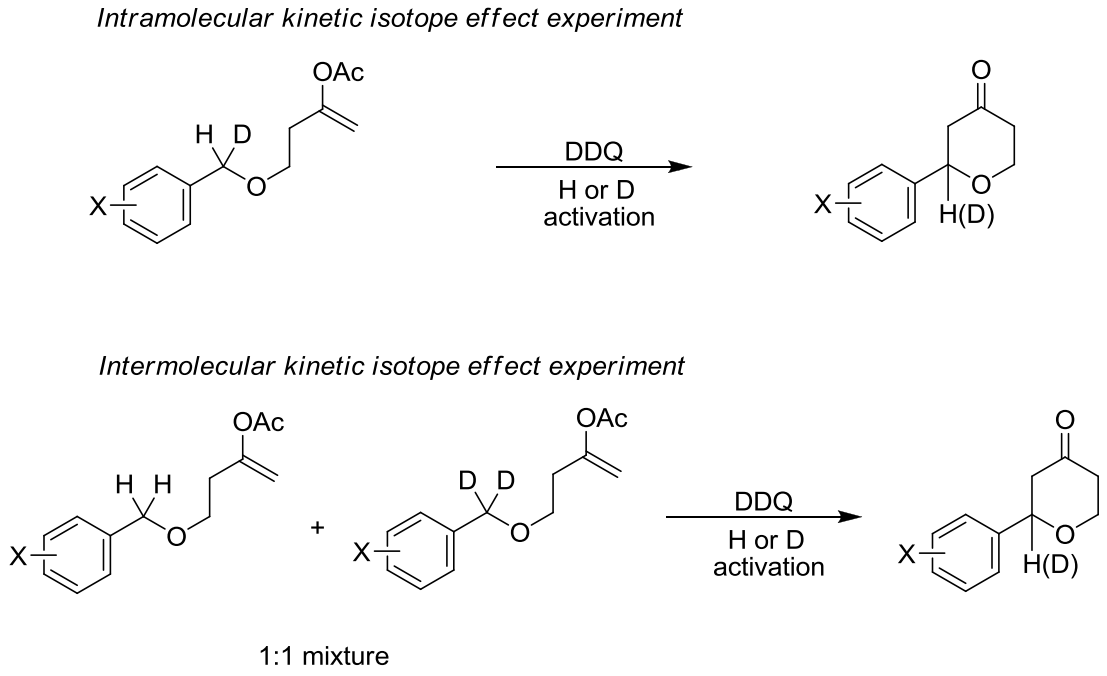
favored over hydrogen atom transfer for radical cations in solution based on the highly favorable proton solvation energy, though this analysis does not discuss the role that a quinone radical anion would play in partitioning the pathways. Baciocchi and co-workers provided solvent-dependent spectroscopic evidence[7] for both hydrogen atom transfer and proton transfer in photoinitiated oxidations of diarylmethanes by tetrachloroquinone.



Scheme 45. Possible mechanisms of oxidative carbocation formation.

We initiated a series of inter- and intramolecular kinetic isotope effect studies on several benzylic and allylic ether substrates (Scheme 46) to study the mechanism of carbocation formation in these reactions. Intramolecular kinetic effects are used to determine the preference for cleaving a C–H bond when a C–D bond is present in the same methylene group. Intermolecular kinetic isotope effects measure the rate difference between substrates that contain

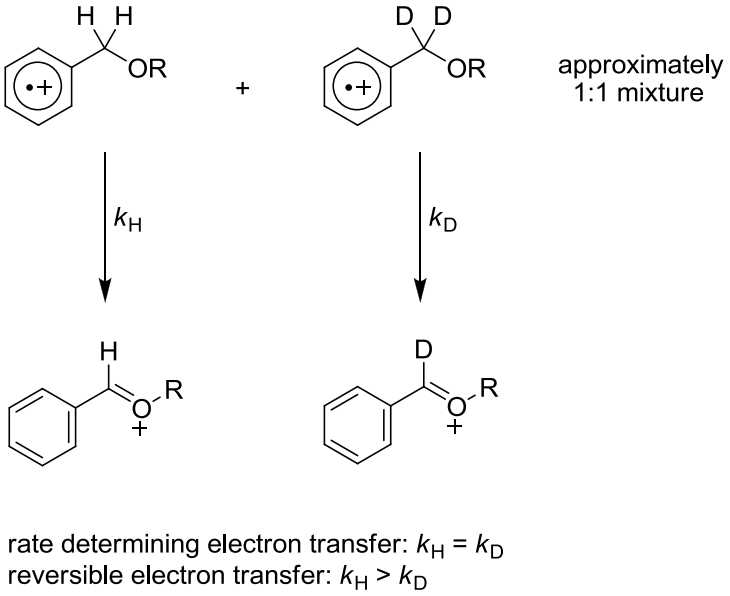
a reactive CH_2 group relative to substrates that contain a CD_2 group at the corresponding position.



Scheme 46. Intra- and intermolecular kinetic isotope effects.

Comparisons of intermolecular and intramolecular kinetic isotope effects have been used to provide evidence for the formation of a reactive intermediate as a rate determining step prior to bond cleavage.[8] In this study, rate determining electron transfer would not necessarily diminish the kinetic isotope effect in the intramolecular experiments because the C–H and C–D bond strengths would be still different in a putative radical cation intermediate. Isotope effects would significantly lessen if electron transfer were rate determining in the intermolecular experiments, however (Scheme 47). The radical cations from the H_2 and D_2 substrates are expected to form in approximately identical concentrations because of their similar oxidation

potentials, and the rate of bond cleavage would not be isotope dependent because this step would have a lower energetic barrier than return electron transfer. Intermolecular kinetic isotope effects would be approximately equal to intramolecular kinetic isotope effects if electron transfer was not rate determining since equilibration of the radical cations would occur prior to bond cleavage.

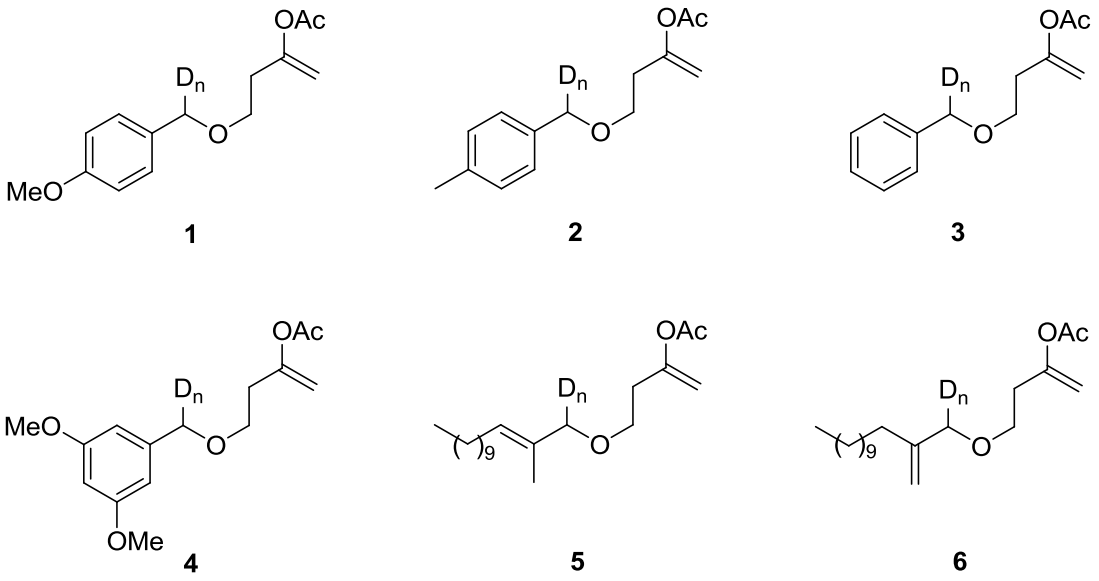


Scheme 47. Relative rate constants for intermolecular KIE studies.

3.2.2 Substrate design and synthesis

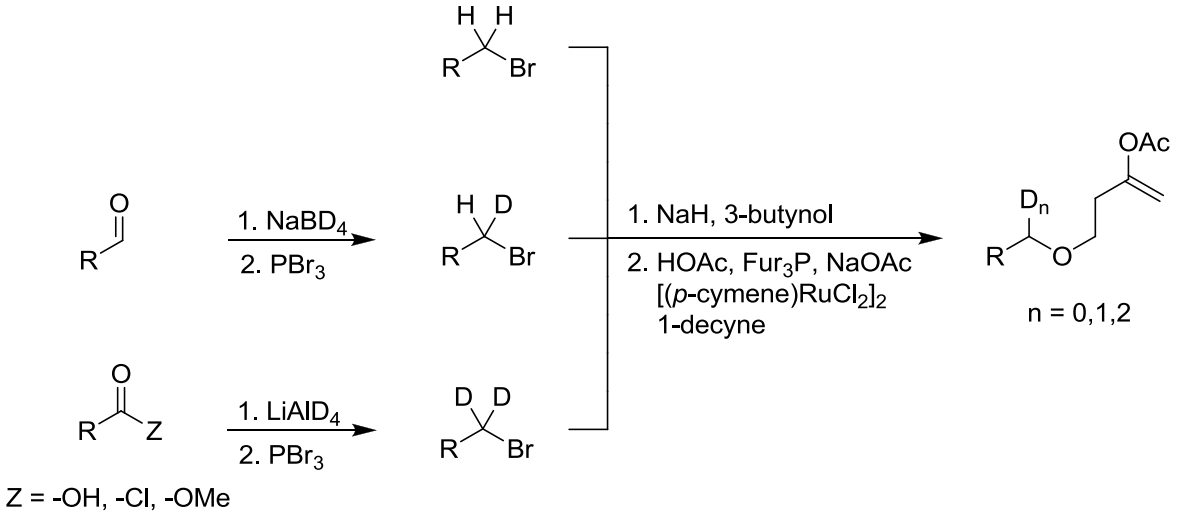
The substrates in this study were selected to cover a wide range of reactivities in the oxidative cyclization reactions (Scheme 48).[4a] We prepared benzylic ethers that undergo oxidative cyclization quickly (*p*-methoxybenzyl ether **1**), moderately quickly (*p*-methylbenzyl ether **2**), and

slowly (benzyl ether **3**), with reactivity paralleling the ease of substrate oxidation. We also prepared ether **4** in which the cyclization proceeds at a moderate rate despite the low substrate oxidation potential. Highly reactive allylic ether **5** and relatively unreactive allylic ether **6** were also prepared. While our prior work utilized substrates that contain branched ethers, we employed unbranched ether groups to circumvent the possibility of a kinetic resolution in the carbon–hydrogen bond activation step.



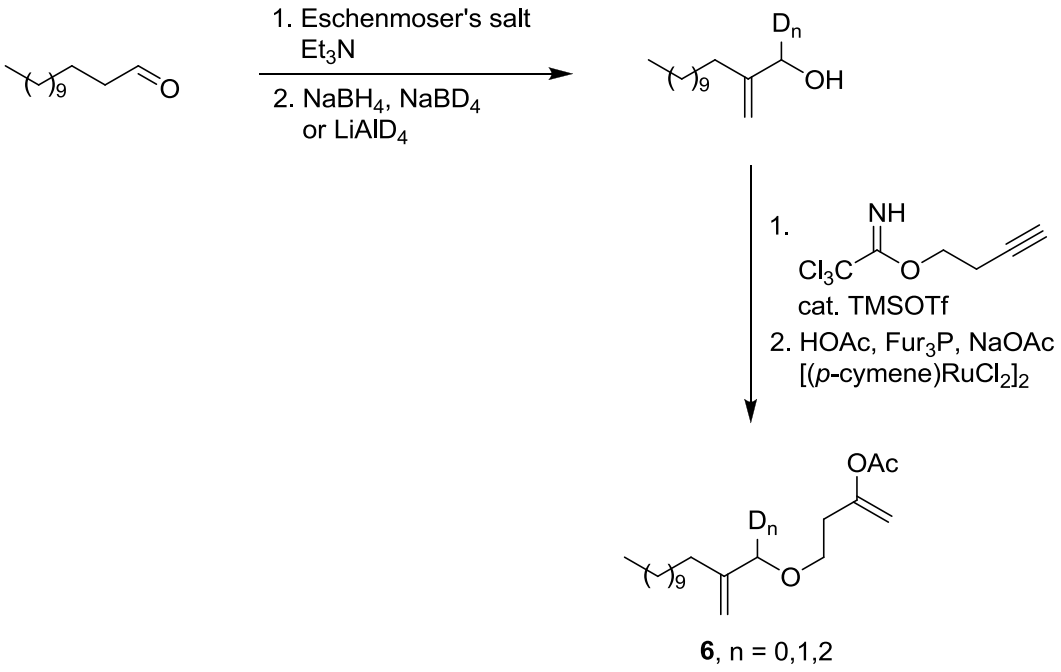
Scheme 48. Cyclization substrates, n=0–2.

Compounds **1**–**5** were prepared (Scheme 49) through reductions, brominations, standard Williamson ether syntheses between the non-, mono-, and dideuterated benzylic or allylic bromides, and the sodium alkoxide of 3-butyn-1-ol followed by ruthenium catalyzed enol acetate formation.[9] Tri-substituted allylic alcohol for compound **5** was prepared by cross-metathesis reaction between 1-dodecene and methacrolein using Grubbs catalyst (2nd generation).



Scheme 49. Preparation of cyclization substrates **1**–**5**.

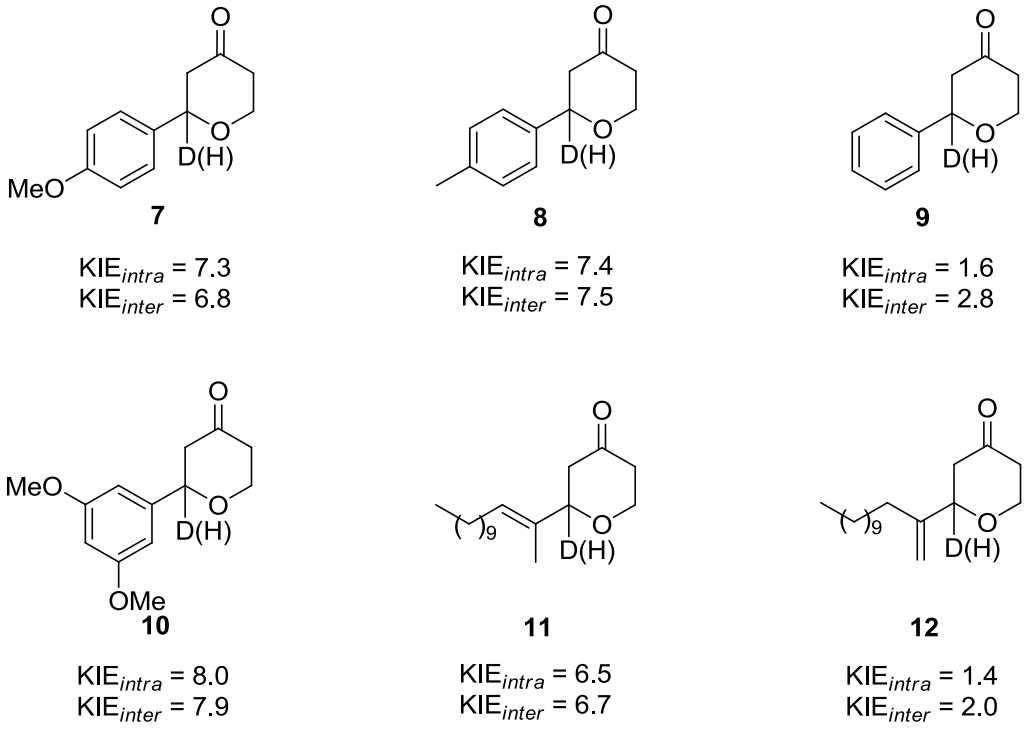
Preparation of compound **6** was started from the reaction with Eschenmoser's salt to provide a methylene group in the α-position of the aldehyde (Scheme 50). In order to avoid the possibility of label scrambling through an S_N2' reaction, Lewis acid-mediated reaction between the allylic alcohol and the trichloroacetimidate of butynol was accomplished.



Scheme 50. Preparation of cyclization substrates **6**.

3.2.3 Isotope effect determination

Intramolecular kinetic isotope effect studies were conducted by exposing monodeuterated substrates to DDQ and 2,6-dichloropyridine, while intermolecular kinetic isotope effect studies were conducted by exposing 1:1 mixtures of non-deuterated and dideuterated substrates to the reaction conditions. The reactions were taken to approximately 10% conversion to avoid interpretation errors that could arise from product oxidation in the intramolecular series and from selective starting material depletion in the intermolecular series. Kinetic isotope effects were determined by comparing the intensities of ^{1}H NMR (500 MHz) signals from the benzylic or allylic hydrogens in the products to reference signals.



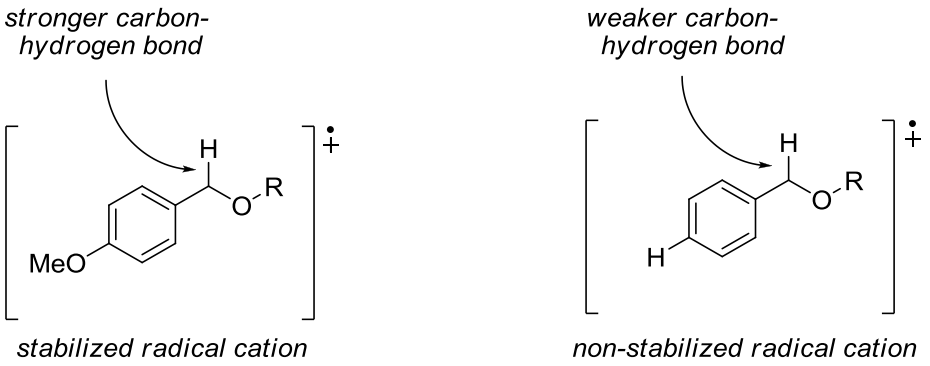
Scheme 51. Cyclization products and intra- and intermolecular kinetic isotope effects.

The products of the oxidative cyclizations (**7**–**12**) and values for intra- and intermolecular kinetic isotope effects are shown in Scheme 51. The magnitudes of the kinetic isotope effects were largest with the more reactive substrates **1**, **2**, **4**, and **5**. Intra- and intermolecular effects were reasonably consistent for each substrate.

3.2.4 Discussion

Several aspects of these data merit further comment. All substrates showed a kinetic isotope effect, indicating that carbon–hydrogen bond cleavage is involved in the rate determining step.

The similar values between the intra- and intermolecular KIE's in all examples confirm that reactive intermediate formation prior to carbon–hydrogen cleavage is not the rate determining step. The magnitudes of the values for rapidly reacting substrates **1**, **2**, **4**, and **5** are at or above the theoretically maximum value of 6.5 for primary KIE's at room temperature. Secondary KIE's are also possible for these reactions since bond cleavage results in a change of hybridization at the benzylic or allylic position. Secondary KIE values would be >1 when D is retained after cleavage and <1 when H is retained, indicating that primary and secondary effects are synergistic for intramolecular experiments and are antagonistic for intermolecular experiments. The generally close agreement between the intra- and intermolecular KIE values indicates that secondary KIE's are minimal and do not contribute to the large observed values. The largest KIE values are consistent with a modest contribution from tunneling in the transition states. The magnitude of the KIE values correlates to substrate reactivity, with compounds that react quickly showing large effects and compounds that react slowly showing small effects. This indicates that bond cleavage is more difficult for substrates that react most quickly, in contrast to the result that would be expected for a one-step hydride transfer process. The result is consistent, however, with an electron transfer mechanism. Substrates with lower oxidation potentials, upon single electron oxidation, will form less reactive radical cations than substrates with high oxidation potentials (Figure 11). This phenomenon can be explained by Eq. 3,[10] in which BDE(RC) is the bond dissociation energy of the cleaving bond in the radical cation, BDE(S) is the bond dissociation energy of this bond in the neutral substrate, E_{pa}(S) is the oxidation potential of the substrate, and $E_{pa}(E^{\bullet})$ is the oxidation potential of the radical from the fragment that becomes the carbocation in the cleavage step. Thus lowering the oxidation potential of the substrate[11] by appending electron donating groups increases the bond



$$BDE(RC) = BDE(S) - E_{pa}(S) + E_{pa}(E') \qquad (1)$$

Figure 11. Bond strength as a function of radical cation stability.

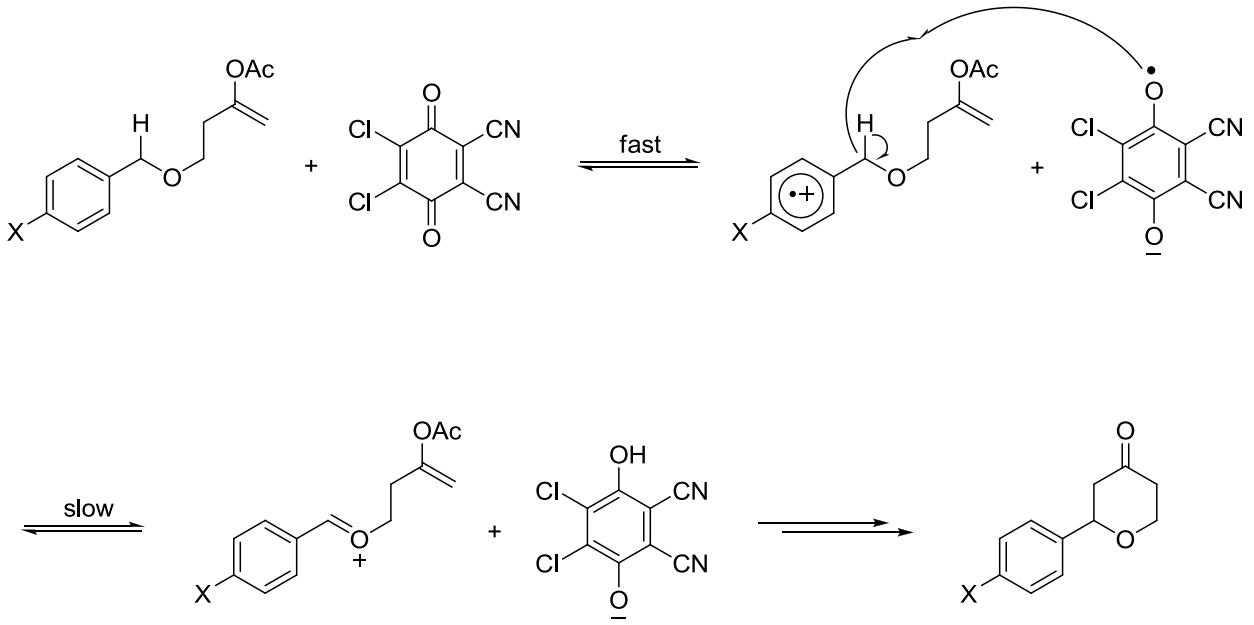
dissociation energy of the scissile carbon–hydrogen bond. While these results strongly suggest the presence of an intermediate radical ion pair, a concern for the electron transfer mechanism lies in the considerably disfavorable thermodynamics of electron transfer between the substrates in this study and DDQ. Kochi, however, has reported[12] that rates for electron transfer and carbon–hydrogen bond cleavage for quinone/arene mixtures are substantially faster than predicted values based on Rehm–Weller considerations,[13] particularly for endergonic transformations, due to the formation of an encounter complex that promotes inner sphere electron transfer.

The high rates of reactions for compounds that have low oxidation potentials appear to contrast the high KIE values for these substrates. These observations can be reconciled by considering the rate equation for cation formation that would arise from the proposed mechanism in Scheme 52. In this relationship (Eq. 2) the rate of cation formation depends on the rate

constant for hydrogen atom transfer k, the concentration of the radical cation [RC], and the concentration of the DDQ radical anion [RA]. While the values of k are expected to be smaller for substrates with low oxidation potentials than for substrates with high oxidation potentials, the concentrations of the radical cations and the radical anions would be higher. The higher concentrations for these species overwhelm the smaller values of k and lead to faster reactions.

$$\text{Rate} = k[\text{RC}][\text{RA}] \qquad (2)$$

While these data provide compelling evidence for an electron transfer pathway, determining whether the bond cleavage results from hydrogen atom abstraction to form the cation directly or from deprotonation, with carbocation formation arising from subsequent radical oxidation, remains a difficult issue to resolve. Baciocchi's studies[7] of diarylmethane oxidation by tetrachloroquinone are instructive in this regard. This work showed that hydrogen atom abstraction should be favored on thermodynamic grounds, but that the pathway could be perturbed by solvent polarity. Polar solvents promote direct hydrogen atom transfer while non-polar solvents promote deprotonation through destabilizing the negative charge on the quinone radical anion. According to Eq. 1 our substrates should be more prone to undergo direct cation formation than those in the Baciocchi study because alkoxy groups lower the oxidation potential of alkyl radicals more than aryl groups.[14] Moreover, the negative charge of the radical anion of DDQ will be stabilized by the cyano groups to a greater degree than the corresponding charge in the radical anion of tetrachloroquinone, thereby lessening its capacity for deprotonation. Thus we postulate that these reactions proceed through hydrogen atom abstraction to form the oxocarbenium ions directly, as shown in Scheme 52.



Scheme 52. Proposed reaction mechanism.

3.3 Summary

We have shown that cyclization reactions that proceed through oxidative carbon–hydrogen bond activation exhibit moderate to large k_H/k_D kinetic isotope effects. This result is consistent with bond cleavage occurring in the rate determining step. The magnitudes of the effects were consistent when determined by intra- and intermolecular processes, confirming that the formation of a reactive intermediate prior to bond cleavage is not rate determining. KIE values

were largest for substrates that have low oxidation potentials and react quickly. This behavior suggests the intermediacy of radical cation intermediates in which the bond dissociation energies for allylic and benzylic carbon–hydrogen bonds are highest when substrate oxidation potentials are low. The higher reaction rates for substrates that form stable radical cations with stronger carbon–hydrogen bonds must be attributed to the higher concentrations of reactive intermediates. Literature analogy indicates that these reactions most likely proceed through hydrogen atom abstraction from the radical cation to form oxocarbenium ions directly.

3.4 Experimental

3.4.1 General

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300 MHz and 75 MHz, respectively, or at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (d) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Methylene chloride was distilled under N_2 from CaH_2. 1,2-Dichloroethane was dried over 4 Å molecular sieves. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32–63 60 Å silica gel. Sodium borodeuteride and lithium aluminum deuteride were purchase from Sigma–Aldrich. Reagent grade ethyl acetate, diethyl ether, pentane, and hexanes (commercial mixture) were purchased from EM Science and used as purchased for chromatography. All reactions

were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

3.4.2 Method for determining intramolecular kinetic isotope effects

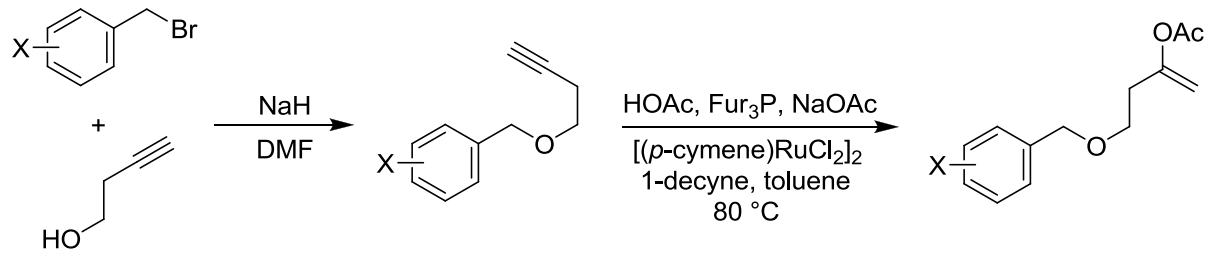
To a 0.1 M solution of the ether substrate-d_1 (1.0 equiv) and 2,6-dichloropyridine (0.2 equiv) in anhydrous 1,2-dichloroethane was added powdered 4 Å molecular sieves (2 mass equiv). In the case of the allylic ether substrate, $LiClO_4$ (0.1 equiv) was added. The mixture was stirred at room temperature for 15 min, and then DDQ (0.1 equiv) was added in one portion. The resulting reaction mixture was stirred at room temperature for 24 h. The crude solution was directly purified by flash chromatography, and a mixture of non- (d_0) and monodeuterated (d_1) products was separated from the starting substrate. The product ratio of d_1 to d_0 was calculated by acquiring a ^{1}H NMR spectrum (500 MHz, pulse delay time = 10 s) and comparing the intensities of the signals from the benzylic or allylic hydrogen to a signal from a hydrogen that was unaffected by the reaction.

3.4.3 Method for determining intermolecular kinetic isotope effects

To a 0.1 M solution of the ether substrate-d_0 (0.5 equiv) and ether substrate-d_2 (0.5 equiv) and 2,6-dichloropyridine (0.2 equiv) in anhydrous 1,2-dichloroethane was added powdered 4 Å molecular sieves (2 mass equiv). In the case of the allylic ether substrates, $LiClO_4$ (0.1 equiv) was added. The mixture was stirred at room temperature for 15 min, and then DDQ (0.1 equiv)

was added in one portion. The resulting reaction mixture was stirred at room temperature for 24 h. The crude solution was directly purified by flash chromatography, and a mixture of non- (d_0) and monodeuterated (d_1) products was separated from the starting substrate. The product ratio of d_1 to d_0 was calculated by acquiring a ^{1}H NMR spectrum (500 MHz, pulse delay time = 10 s) and comparing the intensities of the signals from the benzylic or allylic hydrogen to a signal from a hydrogen that was unaffected by the reaction.

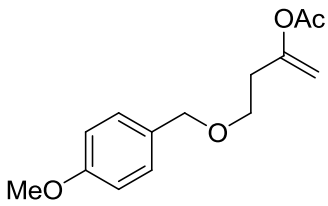
3.4.4 General method for preparing benzylic ether substrates (d_0)



To a solution of benzylic bromide (1.0 equiv) and 3-butyn-1-ol (1.2 equiv) in DMF was added sodium hydride (60% dispersion in mineral oil, 1.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for approximately 2–3 h and quenched with water at 0 °C. The organic fraction was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was filtrated through a short pad of silica gel with EtOAc/hexanes (1:4) as the eluent to afford the homoproparylic benzylic ether (d_0) as a colorless oil (>90% yield).

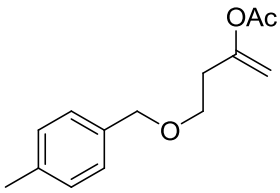
To a mixture of [Ru(*p*-cymene)Cl_2]$_2$ (0.01 equiv), tri(2-furyl)phosphine (0.02 equiv), Na_2CO_3 (0.5 equiv) and 1-decyne (0.3 equiv) in toluene was added acetic acid (5.0 equiv). The brown mixture was stirred at 80 °C until the reaction color was changed to green (ca. 2–4 h) and cooled to room temperature. A solution of homopropargylic ether (d_0) (1.0 equiv) in toluene was added. The resulting mixture was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified via flash column chromatography to afford the benzylic substrates-d_0 as a colorless oil (>70% yield).

4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1-d_0)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.80 (s, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.57 (t, J = 6.5 Hz, 2H), 2.53 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 159.2, 153.5, 130.3, 129.3, 113.8, 102.8, 72.6, 66.7, 55.3, 33.9, 21.0; IR (neat): 3003, 2936, 2862, 1754, 1667, 1612, 1513, 1369, 1249, 1215,1181,1098, 1032, 822 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{14}H_{18}O_4$ $(M)^+$ 250.1205, found 250.1192.

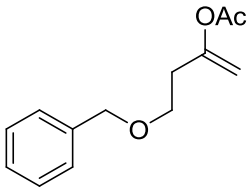
4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2-d_0)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.80 (s, 2H), 4.48 (s, 2H), 3.58 (t, J = 6.5 Hz, 2H), 2.54 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.5, 137.3, 135.1, 129.0, 127.8, 102.7, 72.8, 66.9, 33.9, 21.1, 21.0; IR (neat): 3021, 2923, 2862, 1755, 1667, 1368, 1214,1183,1100, 1020, 881, 804 cm^{-1}; HRMS (EI) *m*/*z* calcd. for

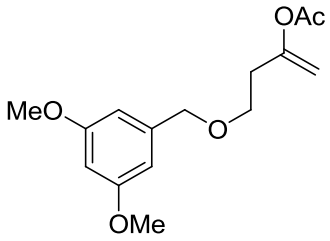
$C_{14}H_{18}O_3$ $(M)^+$ 234.1256, found 234.1261.

4-(Benzyloxy)but-1-en-2-yl acetate (3-d_0)



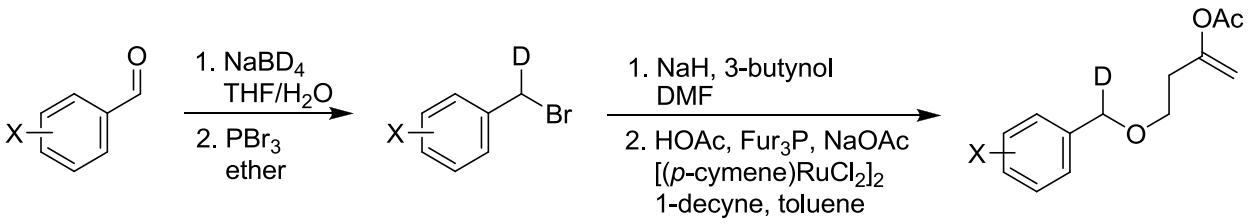
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (sm, 4H), 7.28 (m, 1H), 4.81 (s, 2H), 4.52 (s, 2H), 3.60 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.4, 138.2, 128.4, 127.7, 127.6, 102.9, 73.0, 67.0, 33.9, 21.0; IR (neat): 3031, 2862, 1755, 1667, 1369, 1214, 1184, 1103, 1020, 739 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{16}O_3Na$ $(M+Na)^+$ 243.0997, found 243.1127.

4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4-d_0)



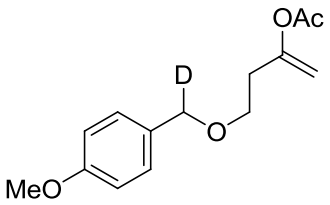
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.81 (sm, 2H), 4.47 (s, 2H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 160.9, 153.4, 140.6, 105.3, 102.9, 99.6, 72.9, 67.0, 55.3, 33.9, 21.0; IR (neat): 2939, 2841, 1754, 1598, 1463, 1367, 1206, 1156, 1106, 835 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{15}H_{20}O_5Na$ $(M+Na)^+$ 303.1208, found 303.1182.

3.4.5 General method for preparing benzylic ether substrates (d_1)



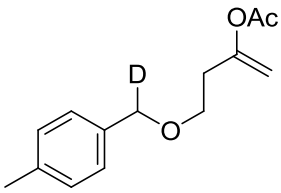
To a solution of benzaldehyde (1.0 equiv) in THF was added $NaBD_4$ (1.0 equiv) with one portion at 0 °C, followed by addition of water (several drops). The reaction mixture was stirred at room temperature for approximately 1–3 h and quenched with water at 0 °C. The resulting mixture was stirred at room temperature overnight and extracted with ether or EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was dissolved in diethyl ether, followed by addition of phosphorous tribromide (0.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for approximately 2–3 h and quenched with caution by adding aqueous saturated $NaHCO_3$ solution dropwise. The organic fraction was separated and the aqueous layer was extracted with ether. The combined organic fraction was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was directly subjected to next general procedures, described above in preparation of benzylic ether substrates-d_0.

4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1-d_1)



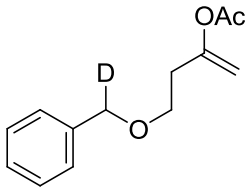
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (dm, J = 8.5 Hz, 2H), 6.88 (dm, J = 8.5 Hz, 2H), 4.80 (s, 2H), 4.43 (s, 1H), 3.80 (s, 3H), 3.56 (t, J = 6.5 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 159.2, 153.5, 130.3, 129.3, 113.8, 102.7, 72.2 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 22 Hz), 66.7, 55.3, 33.9, 21.0; IR (neat): 3002, 2932, 2862, 2120, 1755, 1667, 1612, 1513, 1370, 1247, 1183, 1101, 1032, 881, 822 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{14}H_{17}DO_4Na$ $(M+Na)^+$ 274.1166, found 274.1167.

4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2-d_1)



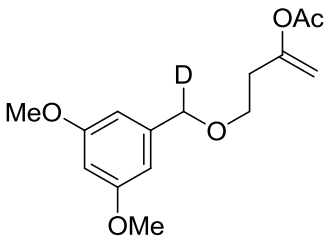
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.80 (sm, 2H), 4.46 (s, 1H), 3.57 (t, J = 6.5 Hz, 2H), 2.53 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 153.5, 137.3, 135.1, 129.0, 127.8, 102.7, 72.5 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 22 Hz), 66.9, 34.0, 21.1, 21.0; IR (neat): 3022, 2923, 2865, 2121, 1756, 1667, 1370, 1185,1104, 1020, 881, 794 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{17}DO_3$ $(M)^+$ 235.1319, found 235.1323.

4-(Benzyloxy)but-1-en-2-yl acetate (3-d_1)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (sm, 4H), 7.28 (m, 1H), 4.81 (sm, 2H), 4.50 (s, 1H), 3.59 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 153.5, 138.2, 128.4, 127.7, 127.6, 102.8, 72.6 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 22 Hz), 67.0, 34.0, 21.0; IR (neat): 3062, 3029, 2865, 2120, 1755, 1667, 1369, 1215, 1184, 1107, 1021, 880, 727 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{15}D_1O_3$ $(M)^+$ 221.1162, found 221.1169.

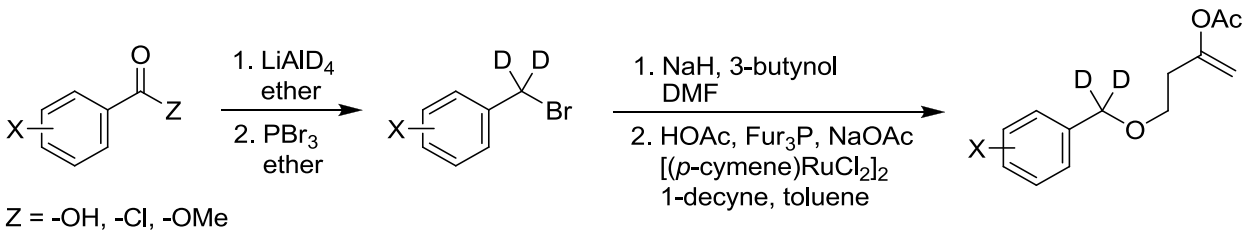
4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4-d_1)



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.81 (sm, 2H), 4.44 (s, 1H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 160.9, 153.4, 140.6, 105.3, 102.9, 99.7, 72.6 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 22 Hz), 66.9, 55.3, 33.9, 21.0; IR (neat): 3001, 2940, 2868, 2840, 2121, 1754, 1667, 1598, 1462, 1350, 1206, 1155, 1109, 1063, 1021, 883, 833 cm^{-1}; HRMS (EI) m/z calcd. for

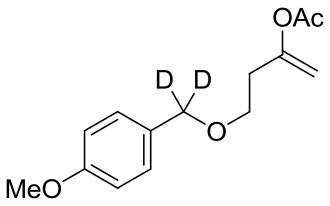
$C_{15}H_{19}DO_5Na$ $(M)^+$ 281.1373, found 281.1363.

3.4.6 General method for preparing benzylic ether substrates (d_2)



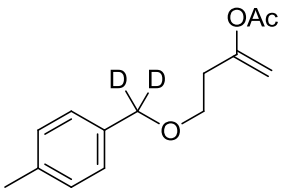
To a solution of benzoic acid (1.0 equiv) in diethyl ether was added $LiAlD_4$ (1.0 equiv) with several portions at 0 °C. The reaction mixture was stirred at same temperature for approximately 1–2 h and then at room temperature overnight. The reaction was quenched with D_2O at 0 °C. Water (H_2O) and EtOAc or ether were added. Organic fraction was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was dissolved in diethyl ether, followed by addition of phosphorous tribromide (0.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for approximately 2–3 h and quenched with caution by adding aqueous saturated $NaHCO_3$ solution dropwise. The organic fraction was separated and the aqueous layer was extracted with ether. The combined organic fraction was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was directly subjected to next general procedure, described above in preparation of benzylic ether substrates-d_0.

4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1-d_2)



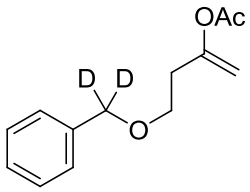
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (dm, J = 8.5 Hz, 2H), 6.88 (dm, J = 8.5 Hz, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 3.56 (t, J = 6.5 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 159.2, 153.5, 130.1, 129.3, 113.8, 102.8, 66.6, 55.3, 33.9, 21.0; IR (neat): 3003, 2957, 2862, 2165, 2061, 1754, 1667, 1612, 1513, 1370, 1255, 1183, 1104, 1030, 879, 801 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{14}H_{16}D_2O_4Na$ $(M+Na)^+$ 275.1228, found 275.1271.

4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2-d_2)



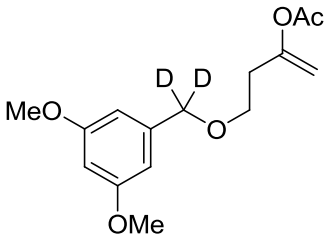
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.81 (s, 2H), 3.57 (t, J = 6.5 Hz, 2H), 2.53 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 153.5, 137.3, 135.0, 129.0, 127.8, 102.7, 66.8, 34.0, 21.1, 21.0; IR (neat): 3022, 2923, 2863, 2167, 2064, 1755, 1667, 1370, 1216, 1186,1107, 1020, 880, 780 cm^{-1}; HRMS (EI) m/z calcd. for $C_{14}H_{16}D_2O_3$ $(M)^+$ 236.1381, found 236.1377.

4-(Benzyloxy)but-1-en-2-yl acetate (3-d_2)



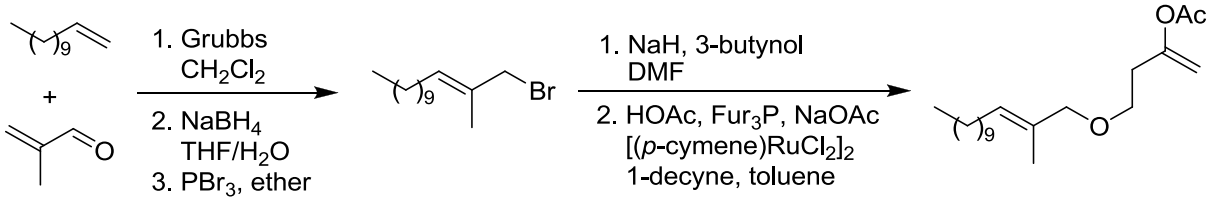
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (sm, 4H), 7.28 (m, 1H), 4.81 (sm, 2H), 3.59 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.4, 138.0, 128.4, 127.7, 127.6, 102.9, 66.9, 33.9, 21.0; IR (neat): 3028, 2863, 2168, 2063, 1755, 1667, 1370, 1217, 1185, 1111, 1021, 882, 721 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{13}H_{14}D_2O_3Na$ $(M+Na)^+$ 245.1123, found 245.1348.

4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4-d_2)



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.82 (sm, 2H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 160.8, 153.4, 140.5, 105.3, 102.9, 99.6, 66.8, 55.3, 33.9, 21.0; IR (neat): 3001, 2941, 2864, 2840, 2170, 2068, 1753, 1598, 1428, 1369, 1156, 1112, 1063, 882, 831 cm^{-1}; HRMS (EI) m/z calcd. for $C_{15}H_{18}D_2O_5Na$ $(M)^+$ 282.1436, found 282.1432.

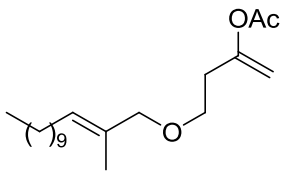
3.4.7 Preparation of 1,1,2-trisubstituted allylic ether substrates (d_0)



A mixture of 1-dodecene (2.0 g, 12 mmol), methacrolein (2.0 mL, 24 mmol) and Grubbs (2nd generation) (101 mg, 10 μmol) in CH_2Cl_2 (35 mL) was refluxed at 50 °C for 12 h. The mixture was filtrated through a short pad of silica gel and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude was purified via flash column chromatography to afford (*E*)-2-methyltridec-2-enal as a colorless oil (2.0 g, 9.5 mmol, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 (s, 1H), 6.48 (t, J = 7.5 Hz, 1H), 2.33 (q, J = 7.5 Hz, 2H), 1.73 (s, 3H), 1.49 (p, J = 7.5 Hz, 2H), 1.35–1.21 (brs, 14H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 155.0, 139.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.28, 29.0, 28.4, 22.6, 14.0, 9.1.

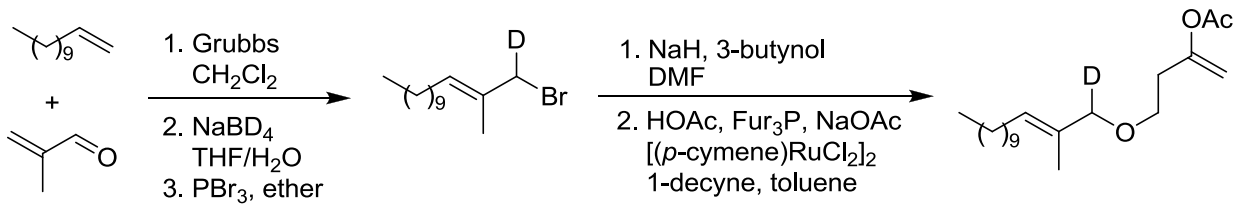
To a solution of aldehyde (1.0 g, 4.7 mmol) in THF (20 mL) was added $NaBH_4$ (0.18 g, 4.7 mmol) with one portion at 0 °C, followed by addition of water (1 mL). The reaction mixture was stirred at room temperature for 3 h and quenched with water at 0 °C. The resulting mixture was stirred at room temperature overnight and extracted with EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in diethyl ether (40 mL), followed by addition of phosphorous tribromide (0.22 mL, 2.4 mmol) at room temperature. The reaction mixture was stirred for 2 h and quenched with caution by adding aqueous saturated $NaHCO_3$ solution dropwise. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was directly subjected to next general procedure, described in preparation of benzylic ether substrates-d_0.

(*E*)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate(5-d_0)



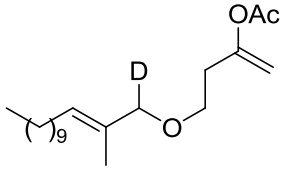
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (t, J = 7.0 Hz, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 3.83 (s, 2H), 3.46 (t, J = 7.0 Hz, 2H), 2.48 (t, J = 7.0 Hz, 2H), 2.11 (s, 3H), 2.00 (q, J = 7.0 Hz, 2H), 1.61 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 153.6, 131.8, 128.6, 102.5, 77.0, 66.3, 33.9, 31.8, 29.6, 29.5, 29.4, 29.30, 29.27, 27.6, 22.6, 20.9, 14.0, 13.7; IR (neat): 2924, 2854, 1760, 1667, 1464, 1369, 1213, 1185, 1093, 1019, 871 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{36}O_3$ $(M)^+$ 324.2664, found 324.2673.

3.4.8 Preparation of 1,1,2-trisubstituted allylic ether substrates (d_1)



To a solution of (*E*)-2-methyltridec-2-enal (0.7 g, 3.3 mmol) in THF (15 mL) was added $NaBD_4$ (0.14 g, 3.3 mmol) with one portion at 0 °C, followed by addition of water (1 mL). The reaction mixture was stirred at room temperature for 3 h and quenched with water at 0 °C. The resulting mixture was stirred at room temperature overnight and extracted with EtOAc. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was dissolved in diethyl ether (30 mL), followed by addition of phosphorous tribromide (0.16 mmol, 1.7 mmol) at room temperature. The reaction mixture was stirred for 2 h and quenched with caution by adding aqueous saturated $NaHCO_3$ solution dropwise. The organic fraction was separated and the aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was directly subjected to next general procedure described above in preparation of benzylic ether substrates-d_0.

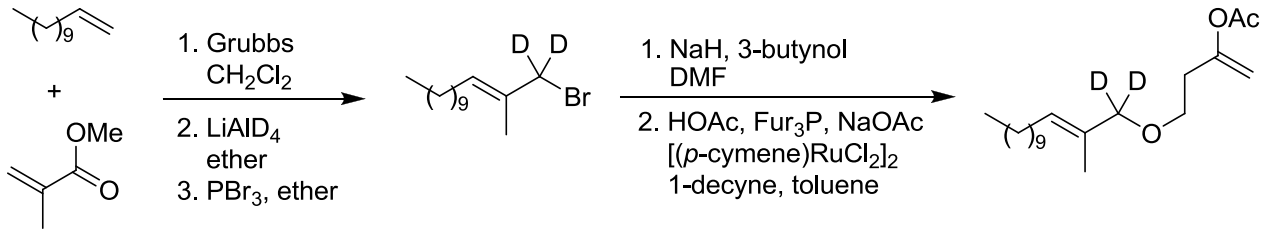
(*E*)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate (5-d_1)



^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39 (t, J = 7.0 Hz, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 3.82 (s, 1H), 3.47 (t, J = 7.0 Hz, 2H), 2.50 (t, J = 7.0 Hz,

2H), 2.13 (s, 3H), 2.02 (q, J = 7.0 Hz, 2H), 1.63 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.7, 131.8, 128.7, 102.6, 76.7 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 21 Hz), 66.3, 34.0, 31.9, 29.6, 29.54, 29.50, 29.4, 29.3, 27.7, 22.7, 21.0, 14.1, 13.8; IR (neat): 2924, 2855, 2130, 1759, 1668, 1464, 1369, 1215, 1186, 1102, 1020, 873 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{35}DO_3$ $(M)^+$ 325.2727, found 325.2719.

3.4.9 Preparation of 1,1,2-trisubstituted allylic ether substrates (d_2)

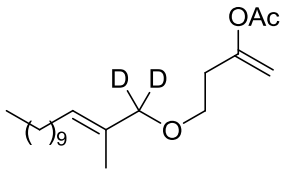


A mixture of 1-dodecene (1.32 mL, 5.6 mmol), methyl methacrylate (1.2 mL, 11 mmol) and Grubbs (2nd generation) (48 mg, 50 μmol) in CH_2Cl_2 (20 mL) was refluxed at 50 °C for 2 days. The mixture was concentrated under reduced pressure. The residue was purified via flash column chromatography to afford (*E*)-methyl 2-methyltridec-2-enoate as a colorless oil (1.33 g, 5.5 mmol, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (t, J = 7.5 Hz, 1H), 3.73 (s, 3H), 2.16 (q, J = 7.5 Hz, 2H), 1.82 (s, 3H), 1.48–1.38 (m, 2H), 1.38–1.21 (brs, 14H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 142.8, 127.3, 51.6, 31.9, 29.6, 29.5, 29.44, 29.36, 29.3, 28.7, 28.6, 22.7, 14.1, 12.3.

To a solution of ester (700 mg, 2.9 mmol) in diethyl ether (15 mL) was added $LiAlD_4$ (122 mg, 2.9 mmol) with several portions at 0 °C. The reaction mixture was stirred at same

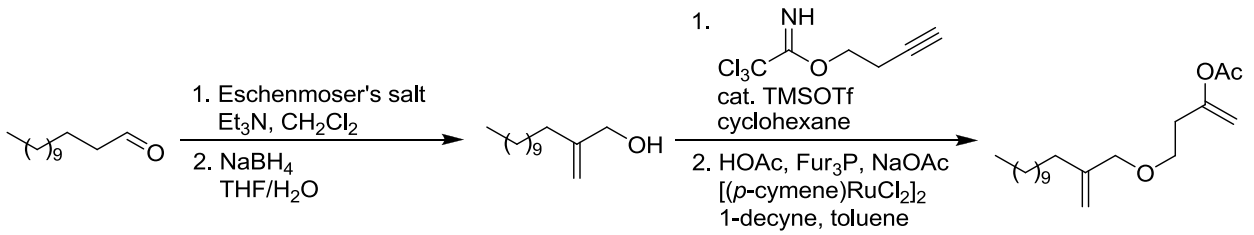
temperature for 2 h and then at room temperature overnight. The reaction was quenched with D_2O at 0 °C. Water (H_2O) and EtOAc were added and the organic fraction was separated. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in diethyl ether (30 mL), followed by addition of phosphorous tribromide (0.14 mL, 1.45 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and quenched with caution by adding aqueous saturated $NaHCO_3$ solution dropwise. The organic fraction was separated and the aqueous fraction was extracted with ether. The combined organic fraction was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was directly subjected to next general procedure, describe above in preparation of benzylic ether substrates-d_0.

(*E*)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate (5-d_2)



^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39 (t, J = 7.0 Hz, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 3.47 (t, J = 7.0 Hz, 2H), 2.50 (t, J = 7.0 Hz, 2H), 2.13 (s, 3H), 2.02 (q, J = 7.0 Hz, 2H), 1.63 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 153.7, 131.8, 128.8, 102.6, 66.2, 34.0, 31.9, 29.6, 29.54, 29.50, 29.4, 29.3, 27.7, 22.7, 21.0, 14.1, 13.7; IR (neat): 2925, 2854, 2166, 2061, 1760, 1667, 1464, 1370, 1215, 1186, 1106, 1020, 876 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{34}D_2O_3$ $(M)^+$ 326.2790, found 326.2785.

3.4.10 Preparation of 1,1-disubstituted allylic ether substrates (d_0)



To a solution of tridecanal (1.5 g, 7.6 mmol) and triethylamine (3.2 mL, 23 mmol) in CH_2Cl_2 (70 mL) was added *N*,*N*-dimethylmethyleneiminium iodide (2.8 g, 15 mmol) at room temperature. The yellow reaction mixture was stirred at same temperature overnight and quenched with aqueous saturated $NaHCO_3$ solution. The organic fraction was separated and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via flash chromatography on silica gel (1:20, EtOAc/hexanes) to afford methylenealdehyde (0.95 g, 4.5 mmol, 60% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (s, 1H), 6.24 (s, 1H), 5.98 (s, 1H), 2.23 (t, J = 7.5 Hz, 2H), 1.44 (q, J = 7.5 Hz, 2H), 1.34–1.22 (brs, 16H), 0.88 (t, J = 7.0 Hz, 3H).

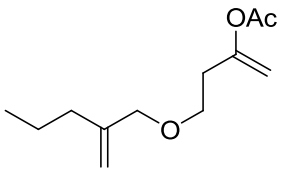
To a mixture of methylenealdehyde (300 mg, 1.4 mmol) in THF (10 mL) was added $NaBH_4$ (54 mg, 1.4 mmol) with several portions at room temperature, followed by addition of H_2O (1 mL). The reaction mixture was stirred at same temperature overnight. Water and EtOAc were added and the organic fraction was separated. The aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried, filtered and concentrated under reduced pressure. The crude was purified via flash chromatography on silica gel (1:10, EtOAc/hexanes) to give alcohol (273 mg, 1.3 mmol, 90% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (s, 1H), 4.87 (s, 1H), 4.08 (s, 2H), 2.05 (t, J = 7.6 Hz, 2H), 1.49–1.35 (m, 2H), 1.35–1.22 (m, 16), 0.88 (t, J = 7.0 Hz, 3H).

To a solution of alcohol (269 mg, 1.3 mmol) and imidate (448 mg, 2.1 mmol) in cyclohexane (15 mL) was added TMSOTf (25 μL, 0.14 mmol) at room temperature. The reaction mixture was stirred at same temperature for 2 h for which the clear reaction mixture was become milky. The solvent was evaporated under reduced pressure and the residue was directly purified via flash chromatography on silica gel (1:20, EtOAc/hexanes) to give alkyne (285 mg, 1.1 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (s, 1H), 4.90 (s, 1H), 3.95 (s, 2H), 3.53 (t, J = 7.0 Hz, 2H), 2.48 (td, J = 7.0, 2.4 Hz, 2H), 2.04 (t, J = 7.2 Hz, 2H), 1.98 (t, J = 2.4 Hz, 1H), 1.48–1.38 (m, 2H), 1.34–1.20 (brs, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 111.4, 81.4, 73.9, 69.2, 67.9, 33.0, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 19.8, 14.1.

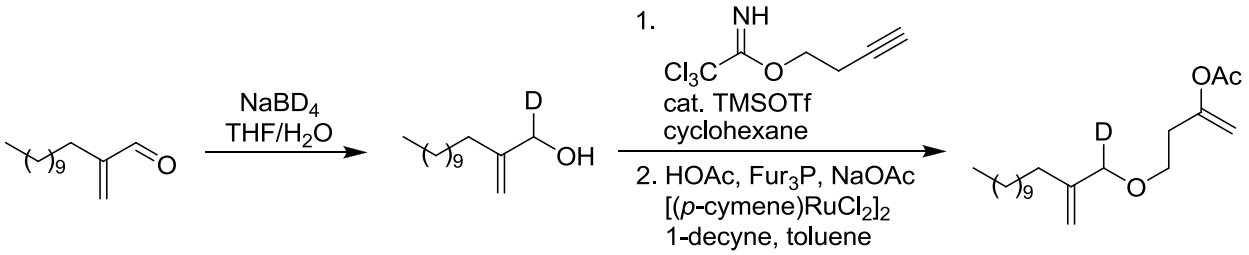
To a mixture of [Ru(*p*-cymene)Cl_2]$_2$ (5.5 mg, 9.0 μmol), tri(2-furyl)phosphine (4.2 mg, 18 μmol), Na_2CO_3 (68.5 mg, 0.45 mmol) and 1-decyne (49 μL, 0.27 mmol) in toluene (10 mL) was added acetic acid (0.26 mL, 4.5 mmol). The brown mixture was stirred at 80 °C until the reaction color was changed to green (approximately 3–4 h) and cooled to room temperature. A solution of alkyne (240 mg, 0.91 mmol) in toluene (2 mL) was added. The resulting mixture was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified via flash column chromatography (1:20, EtOAc/hexanes) to afford enolacetate (233 mg, 0.72 mmol, 79% yield) as a colorless oil.

4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (6-d_0)



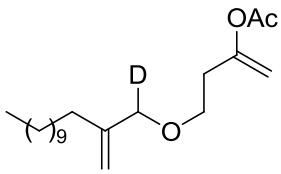
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.79 (sm, 1H), 3.90 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.13 (s, 3H), 2.03 (t, J = 7.5 Hz, 2H), 1.43 (p, J = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.5, 146.3, 111.1, 102.8, 73.9, 66.9, 34.0, 33.1 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2060, 1760, 1667, 1464, 1369, 1213, 1185, 1103, 1019, 900 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{34}D_2O_3$ $(M)^+$ 324.2664, found 324.2665.

3.4.11 Preparation of 1,1-disubstituted allylic ether substrates (d_1)



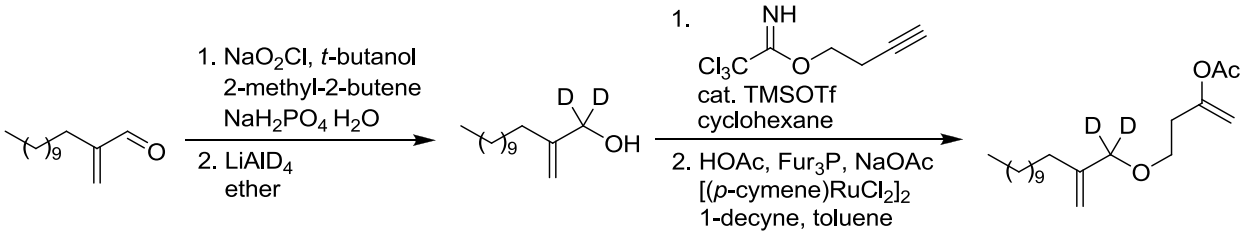
To a mixture of methylenealdehyde (300 mg, 1.4 mmol) in THF (10 mL) was added $NaBD_4$ (54 mg, 1.4 mmol) with several portions at room temperature, followed by addition of H_2O (1 mL). The reaction mixture was stirred at same temperature overnight. Water and EtOAc were added and the organic fraction was separated. The aqueous fraction was extracted with EtOAc. The combined organic fraction was washed with brine, dried, filtered and concentrated under reduced pressure. Without further purification, the crude material was followed to next general procedures, described above in preparation of (**6**-d_0).

4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (6-d_1)



^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.79 (sm, 1H), 3.88 (s, 1H), 3.52 (t, J = 6.5 Hz, 2H), 2.51 (t, J = 6.5 Hz, 2H), 2.14 (s, 3H), 2.03 (t, J = 7.5 Hz, 2H), 1.43 (p, J = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.5, 146.2, 111.2, 102.8, 73.5 (t, 1:1:1, $^2J(^{13}C, ^2H)$ = 21 Hz), 66.8, 33.9, 33.1 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2135, 1759, 1667, 1464, 1370, 1215, 1186, 1107, 1020, 898 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{35}DO_3$ $(M)^+$ 325.2727, found 325.2738.

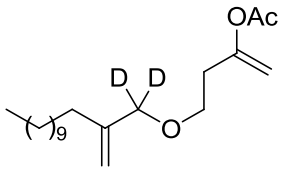
3.4.12 Preparation of 1,1-disubstituted allylic ether substrates (d_2)



To a solution of methylenealdehyde (174 mg, 0.83 mmol) in *tert*-butanol (10 mL) was added 2-methyl-2-butene at room temperature. A solution of sodium chlorite (1.35 g, 15 mmol) and sodium phosphate monobasic monohydrate (1.08 g, 7.8 mmol) in water (8.5 mL) was added. The reaction mixture was stirred at same temperature for 3 h. The slightly lime green solution was diluted with water and EtOAc. The organic fraction was separated and the aqueous fraction was extracted with EtOAc (2 times). The combined organic fraction was washed with water, 10% aqueous solution of citric acid and brine, dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The crude material was dissolved in ether. $LiAlD_4$ (52 mg, 1.24 mmol) was added with several potions at 0 °C. The resulting mixture was stirred at same temperature for 2 h and then at room temperature overnight. The reaction was quenched with D_2O at 0 °C. Water (H_2O) and EtOAc were added and the organic fraction was separated. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, the crude was followed to next general procedures, described above in preparation of (**6**-d_0).

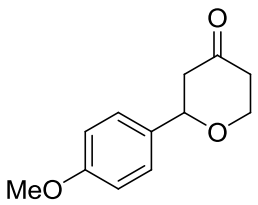
4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (d_2).



^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.79 (sm, 1H), 3.52 (t, J = 6.5 Hz, 2H), 2.51 (t, J = 6.5 Hz, 2H), 2.13 (s, 3H), 2.03 (t, J = 7.5 Hz, 2H), 1.43 (p, J = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 153.6, 146.2, 111.3, 102.8, 66.8, 34.0, 33.1 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2170, 2065, 1758, 1668, 1464, 1370, 1216, 1186, 1109, 1020, 875 cm^{-1}; HRMS (EI) m/z calcd. for $C_{20}H_{34}D_2O_3$ $(M)^+$ 326.2790, found 326.2785.

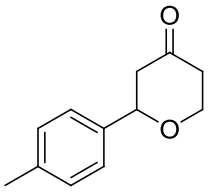
3.4.13 Products of the oxidative cyclization

2-(4-Methoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one (7)



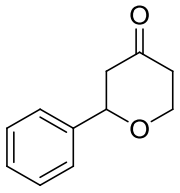
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 4.60 (dd, J = 10.5, 3.5 Hz, 1H), 4.40 (ddd, J = 11.5, 7.5, 1.5 Hz, 1H), 3.83 (td, J = 11.5, 2.5 Hz, 1H), 3.81 (s, 3H), 2.75–2.68 (m, 2H), 2.65–2.59 (m, 1H), 2.42 (dm, J = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 159.5, 132.7, 127.1, 114.0, 79.5, 66.6, 55.3, 49.8, 42.2; IR (neat): 2964, 2935, 2839, 1718, 1613, 1514, 1369, 1249, 1032, 831 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{12}H_{14}O_3$ $(M)^+$ 206.0943, found 206.0940.

2-*p*-Tolyldihydro-2*H*-pyran-4(3*H*)-one (8)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.61 (dd, J = 9.0, 5.5 Hz, 1H), 4.42 (ddd, J = 11.5, 7.5, 1.5 Hz, 1H), 3.83 (td, J = 11.5, 3.0 Hz, 1H), 2.72 (ddd, J = 14.5, 9.5, 7.5 Hz, 1H), 2.64 (m, 2H), 2.43 (dm, J = 14.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 137.9, 137.7, 129.3, 125.7, 79.8, 66.7, 49.9, 42.2, 21.1; IR (neat): 2965, 2922, 2855, 1720, 1516, 1370, 1315, 1247, 1167, 1073, 805 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{12}H_{14}O_2$ $(M)^+$ 190.0994, found 190.0986.

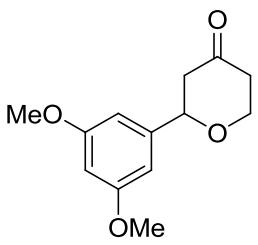
2-Phenyldihydro-2*H*-pyran-4(3*H*)-one (9)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (brs, 4H), 7.35–7.31 (m, 1H), 4.65 (dd, J = 9.0, 5.5 Hz, 1H), 4.44 (ddd, J = 11.0, 7.5, 1.5 Hz, 1H), 3.85 (td, J = 11.0, 2.5 Hz, 1H), 2.72 (ddd, J = 14.5, 12.5, 7.5 Hz, 1H), 2.65 (m, 2H), 2.43 (dm, J = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 140.6, 128.7, 128.2, 125.7, 79.8, 66.8, 50.0, 42.2; IR

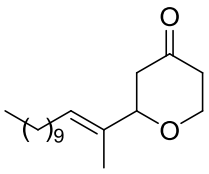
(neat): 3032, 2968, 2924, 2857, 1720, 1415, 1370, 1247, 1152, 1075, 756 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{11}H_{12}O_2$ $(M)^+$ 176.0837, found 176.0841.

2-(3,5-Dimethoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one (10)



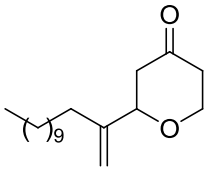
^1H NMR (500 MHz, $CDCl_3$): δ 6.52 (d, J = 2.5 Hz, 2H), 6.41 (t, J = 2.5 Hz, 1H), 4.58 (dd, J = 10.0, 4.0 Hz, 1H), 4.43 (ddd, J = 12.0, 7.5, 2.0 Hz, 1H), 3.82 (m, 1H), 3.80 (s, 6H), 2.71 (ddd, J = 14.5, 12.5, 7.5 Hz, 1H), 2.63 (m, 2H), 2.42 (dm, J = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 161.0, 143.0, 103.5, 100.0, 79.7, 66.7, 55.3, 49.9, 42.1; IR (neat): 2963, 2843, 1717, 1598, 1462, 1430, 1367, 1204, 1155 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{13}H_{16}O_4$ $(M)^+$ 236.1048, found 236.1058.

(*E*)-2-(Tridec-2-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (11)



^1H NMR (500 MHz, $CDCl_3$): δ 5.46 (td, J = 7.0, 1.5 Hz, 1H), 4.29 (ddd, J = 11.5, 7.5, 2.0 Hz, 1H), 3.97 (dd, J = 11.0, 2.5 Hz, 1H), 3.70 (td, J = 11.5, 3.0 Hz, 1H), 2.60 (ddd, J = 14.5, 12.0, 7.5 Hz, 1H), 2.53 (dm, J = 14.5 Hz, 1H), 2.38 (ddm, J = 14.5, 2.5 Hz, 1H), 2.34 (dm, J = 14.5 Hz, 1H), 2.03 (td, J = 7.0, 4.0 Hz, 1H), 2.02 (td, J = 7.0, 3.0 Hz, 1H), 1.68 (s, 3H), 1.38–1.30 (m, 2H), 1.30–1.22 (m, 14 H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 133.5, 128.3, 82.9, 66.1, 47.1, 42.2, 31.9, 29.6, 29.5, 29.3, 27.6, 22.7, 14.1, 12.1; IR (neat): 2924, 2854, 1721, 1465, 1371, 1246, 1155, 1078 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{18}H_{32}O_2$ $(M)^+$ 280.2402, found 280.2411.

2-(Tridec-1-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (12)



^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (s, 1H), 4.95 (s, 1H), 4.30 (dm, J = 11.5 Hz, 1H), 4.05 (dd, J = 9.5, 4.0 Hz, 1H), 3.71 (td, J = 11.5, 3.0 Hz, 1H), 2.61 (ddd, J = 14.5, 11.5, 7.0 Hz, 1H), 2.52–2.46 (m, 2H), 2.37 (dm, J = 14.5 Hz, 1H), 2.15–2.07 (m, 1H), 2.07–2.00 (m, 1H), 1.50–1.41 (m, 2H), 1.34–1.18 (m, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9, 148.3, 110.8, 80.0, 66.2, 47.2, 42.2, 32.1, 31.9, 29.65, 29.62, 29.59, 29.5, 29.4, 29.3, 27.8, 22.7, 14.1; IR (neat): 2925, 2853, 1722, 1465, 1248, 1154, 1088 cm^{-1}; HRMS (EI) m/z calcd. for $C_{18}H_{32}O_2$ $(M)^+$ 280.2402, found 280.2403.

3.5 References

[1] Reproduced from *Tetrahedron* **2009**, *65*, 10830−10836. All work in this manuscript was conducted by Hyung Hoon Jung.

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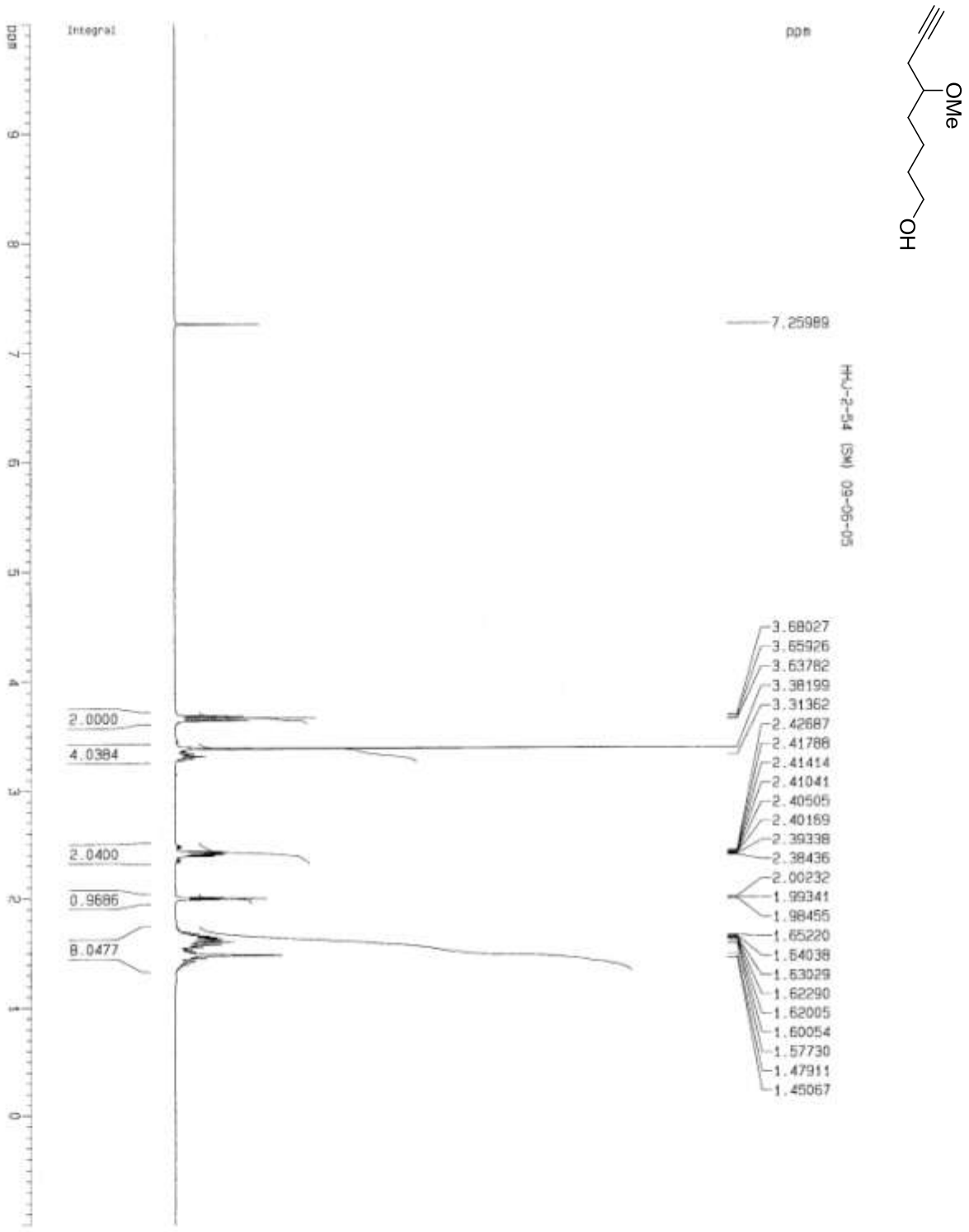
APPENDIX A

Gold-Catalyzed Synthesis of Heterocycles from Alkynyl Ethers: Application to the Total Synthesis of Andrachcinidine (Supporting Information ^{1}H and ^{13}C NMR Spectra)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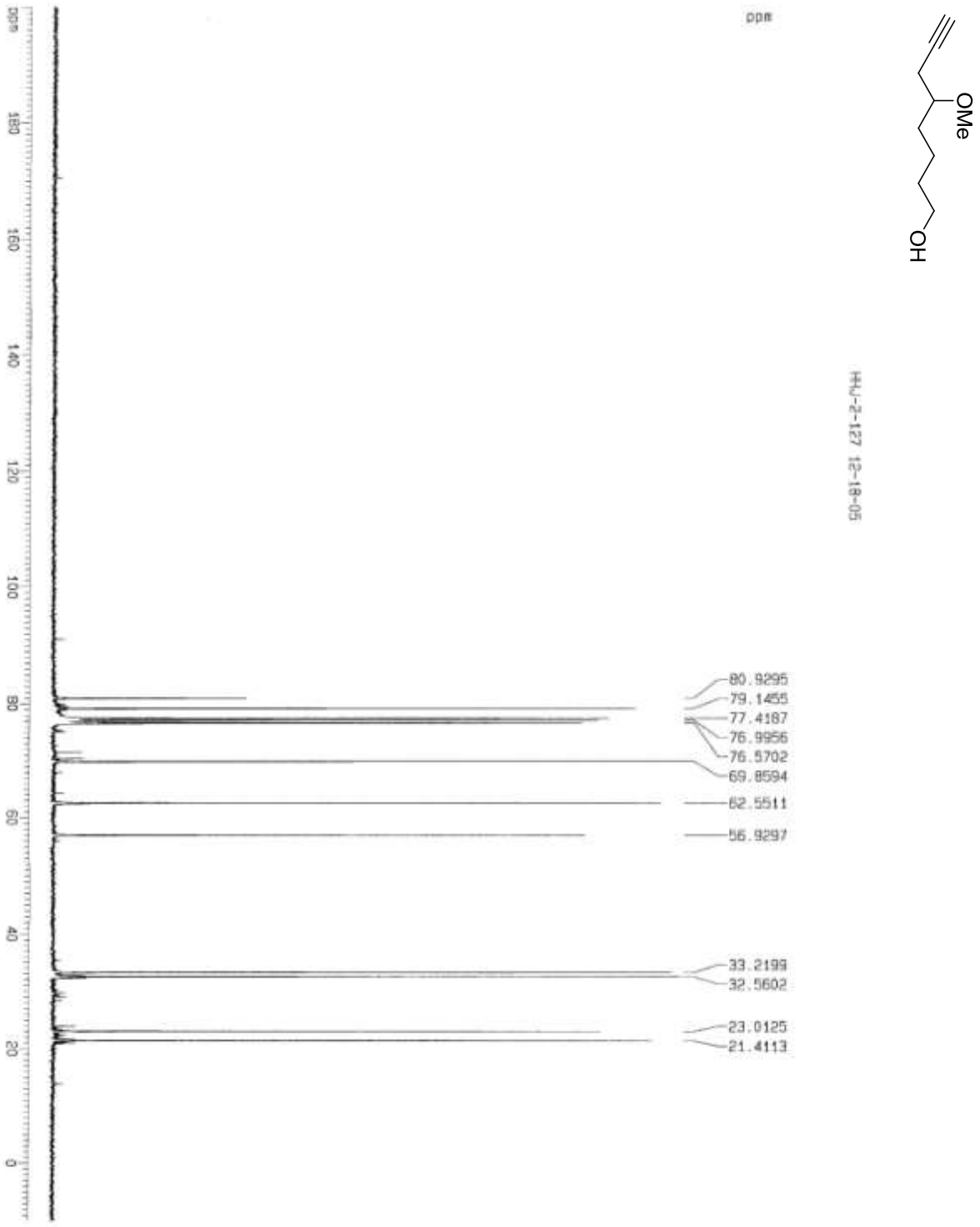
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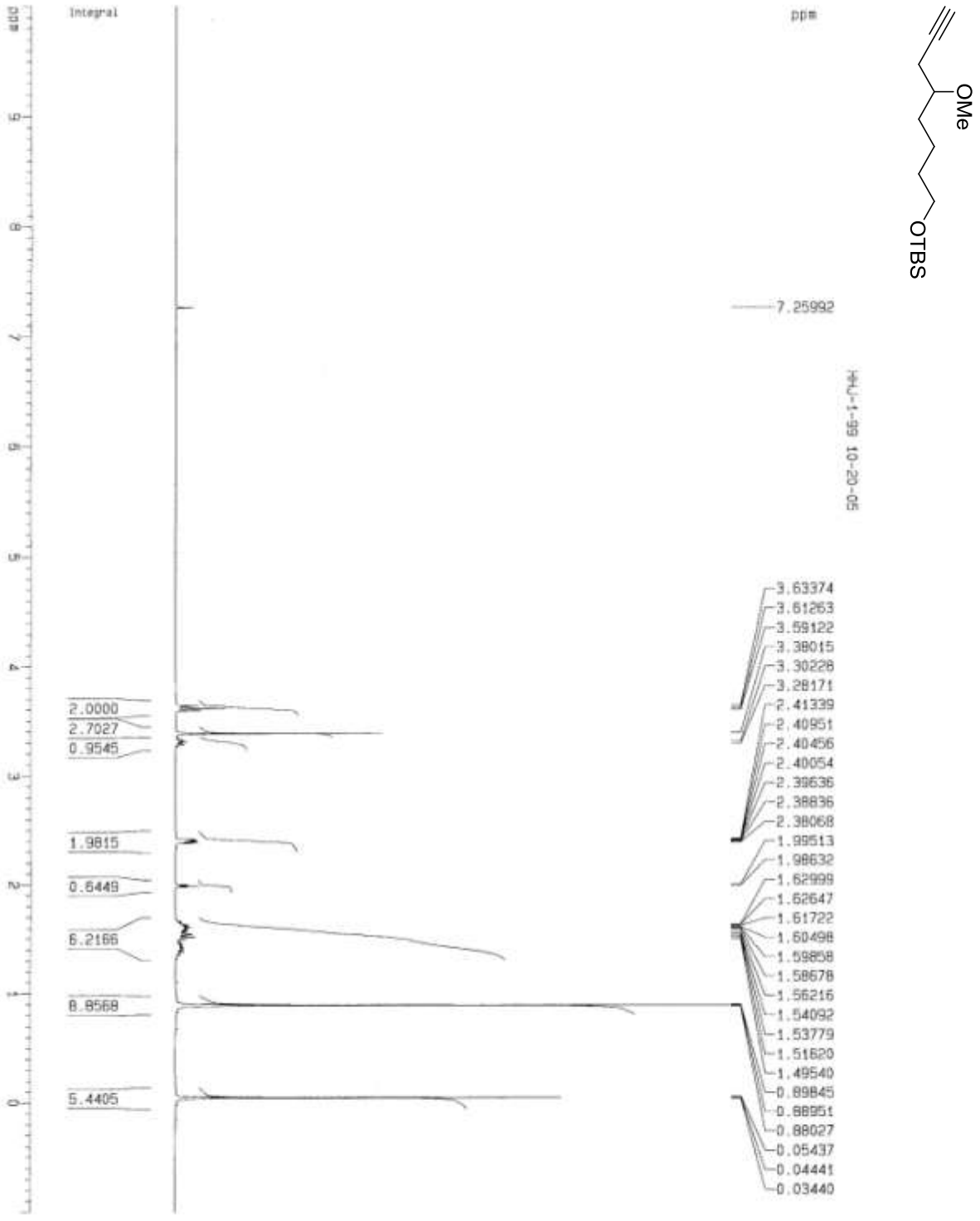
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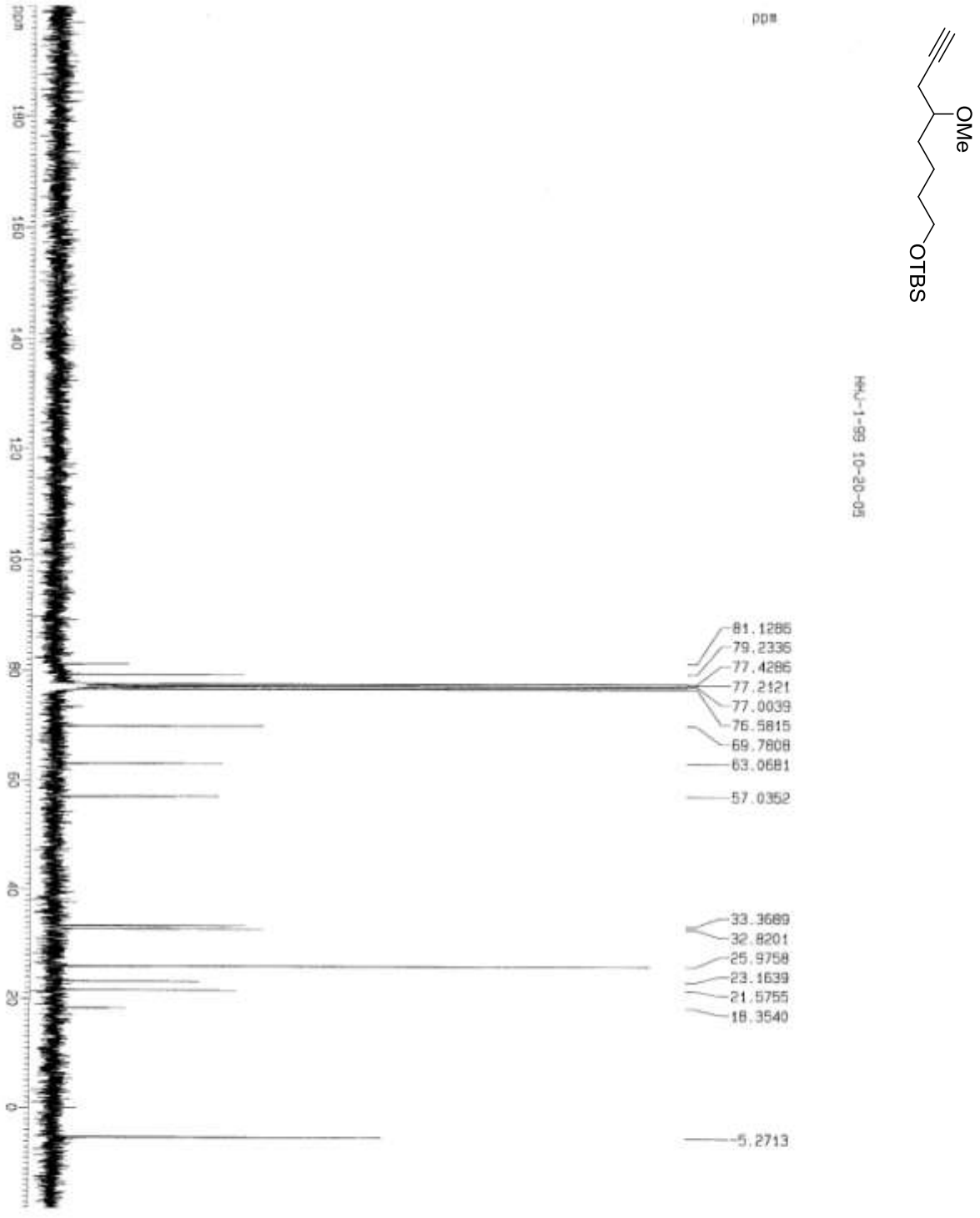
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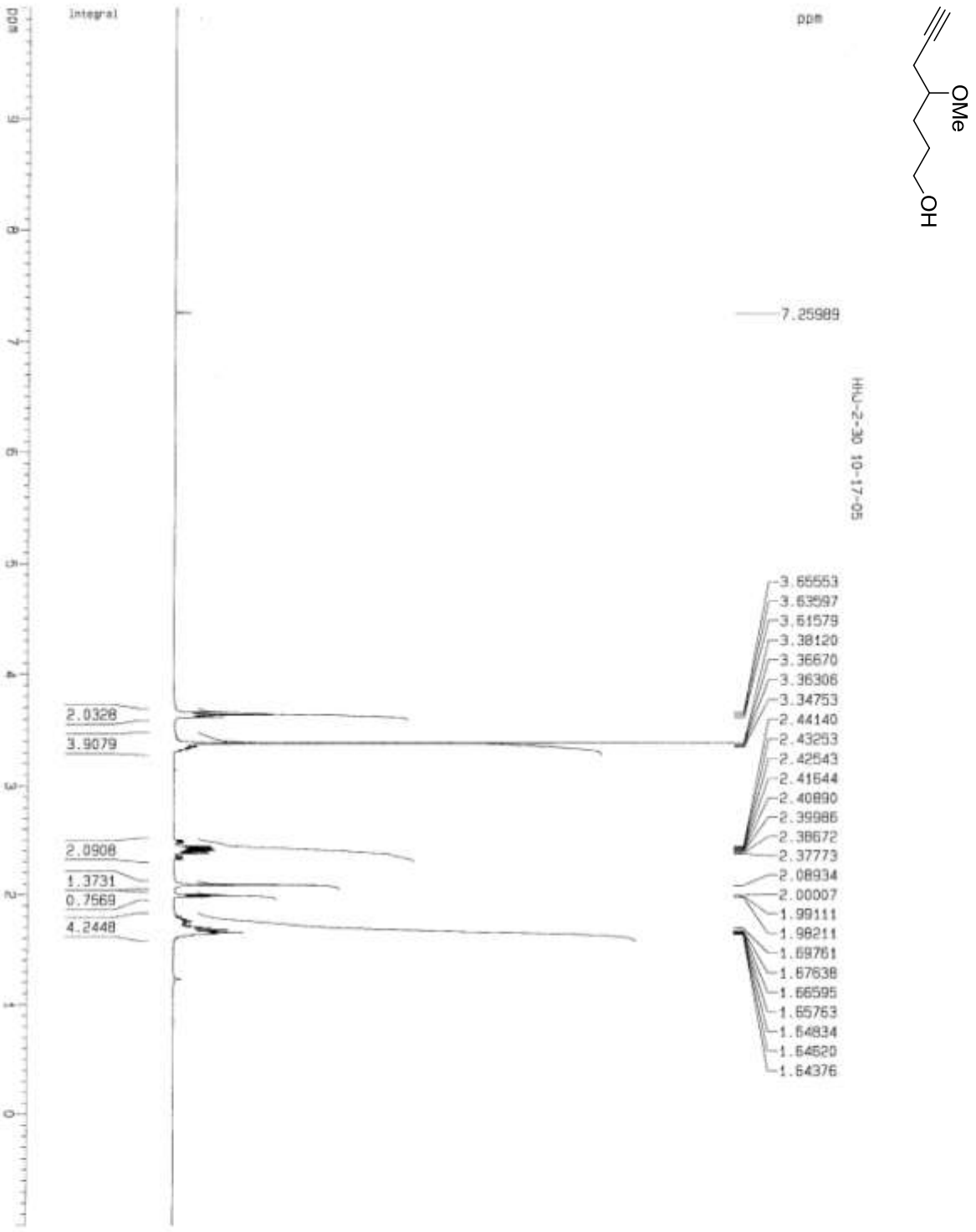
OTBS
HHJ-1-98 10-20-05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ppm
OMe
OH
7.25989
HHJ-2-30 10-17-05
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3.61579
3.38120
3.36670
3.36306
3.34753
2.44140
2.43253
2.42543
2.41644
2.40890
2.39986
2.38672
2.37773
2.08934
2.00007
1.99111
1.98211
1.69761
1.67638
1.66595
1.65763
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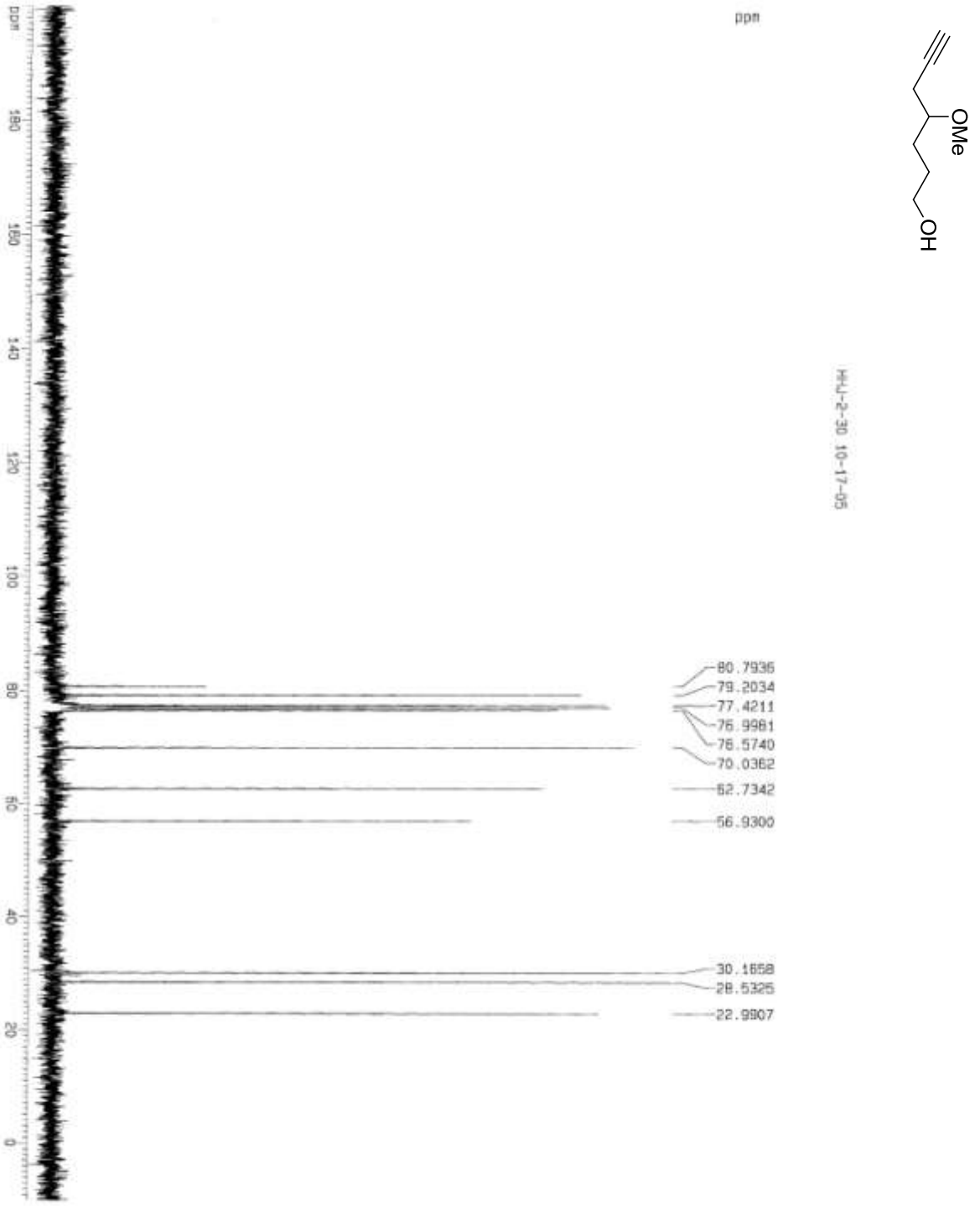
1.64520
1.64376
2.0328
3.9079
2.0908
1.3731
0.7569
4.2448


ppm
ppm
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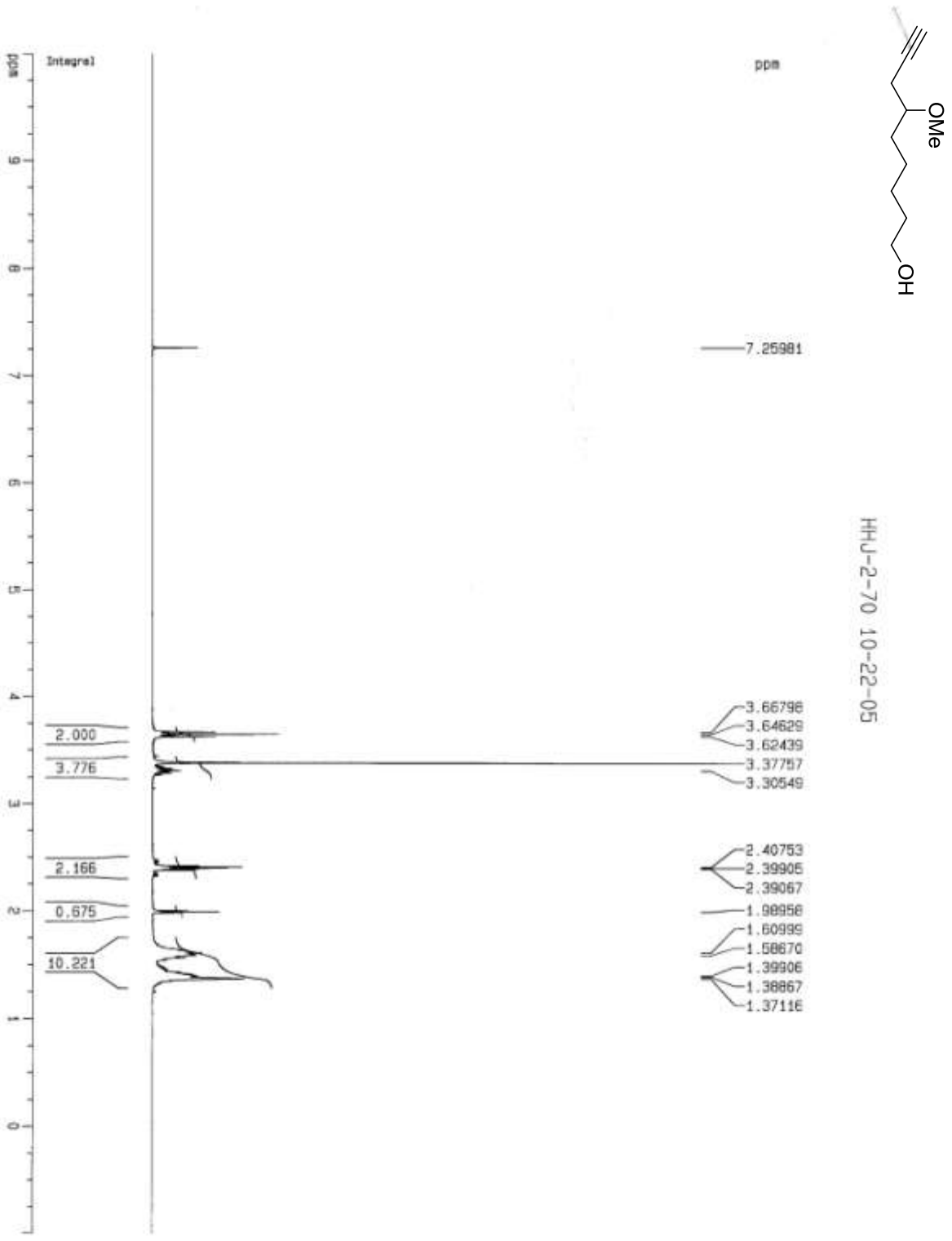
180
160
140
120
100
80
60
40
20
0
80.7936
79.2034
77.4211
76.9981
76.5740
70.0362
62.7342
56.9300
30.1658
28.5325
22.9907
OMe
OH
HHJ-2-30 10-17-05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3.62439
3.37757
3.30549
2.40753
2.39905
2.39067
1.98958
1.60999
1.58670
1.39906
1.38867
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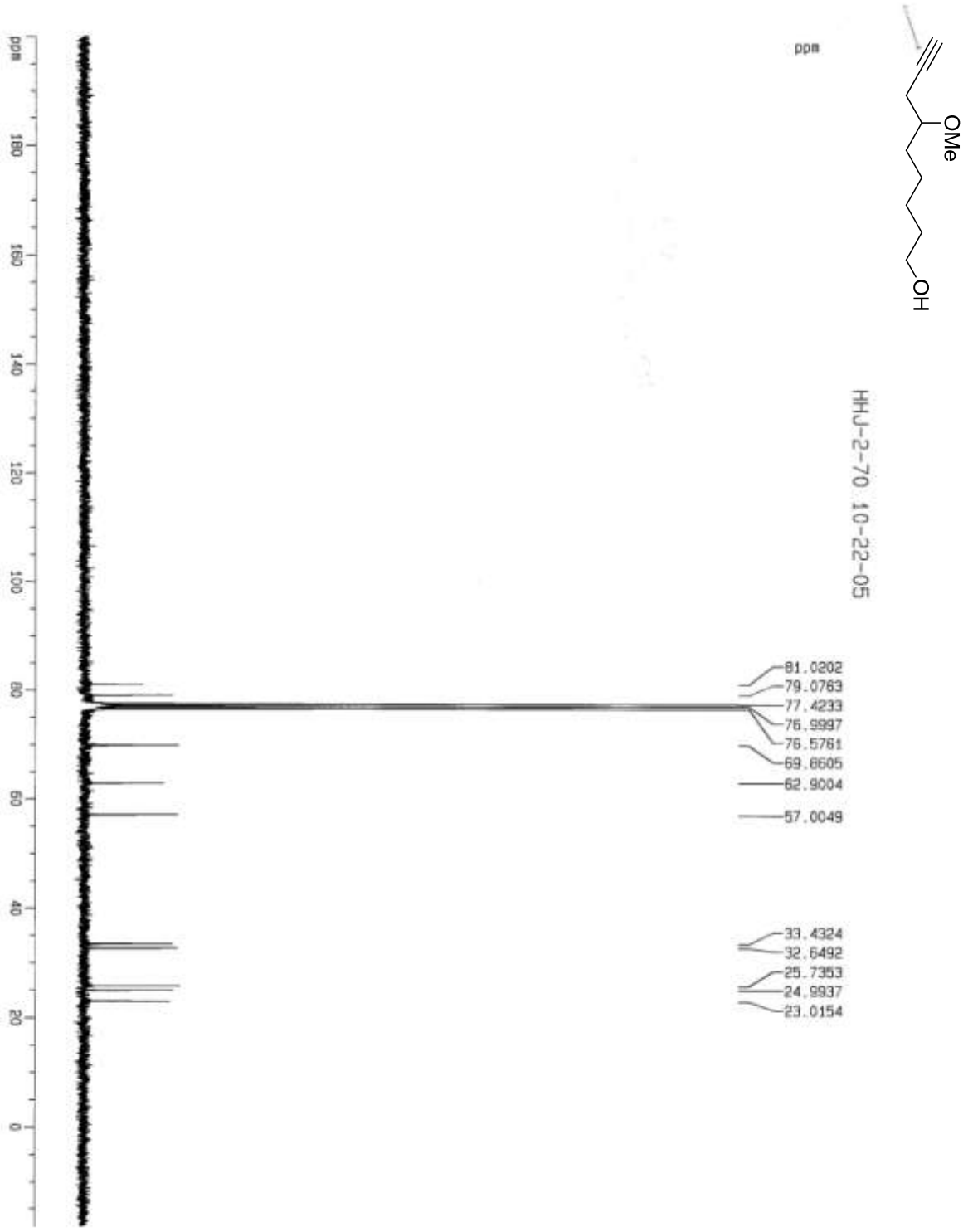
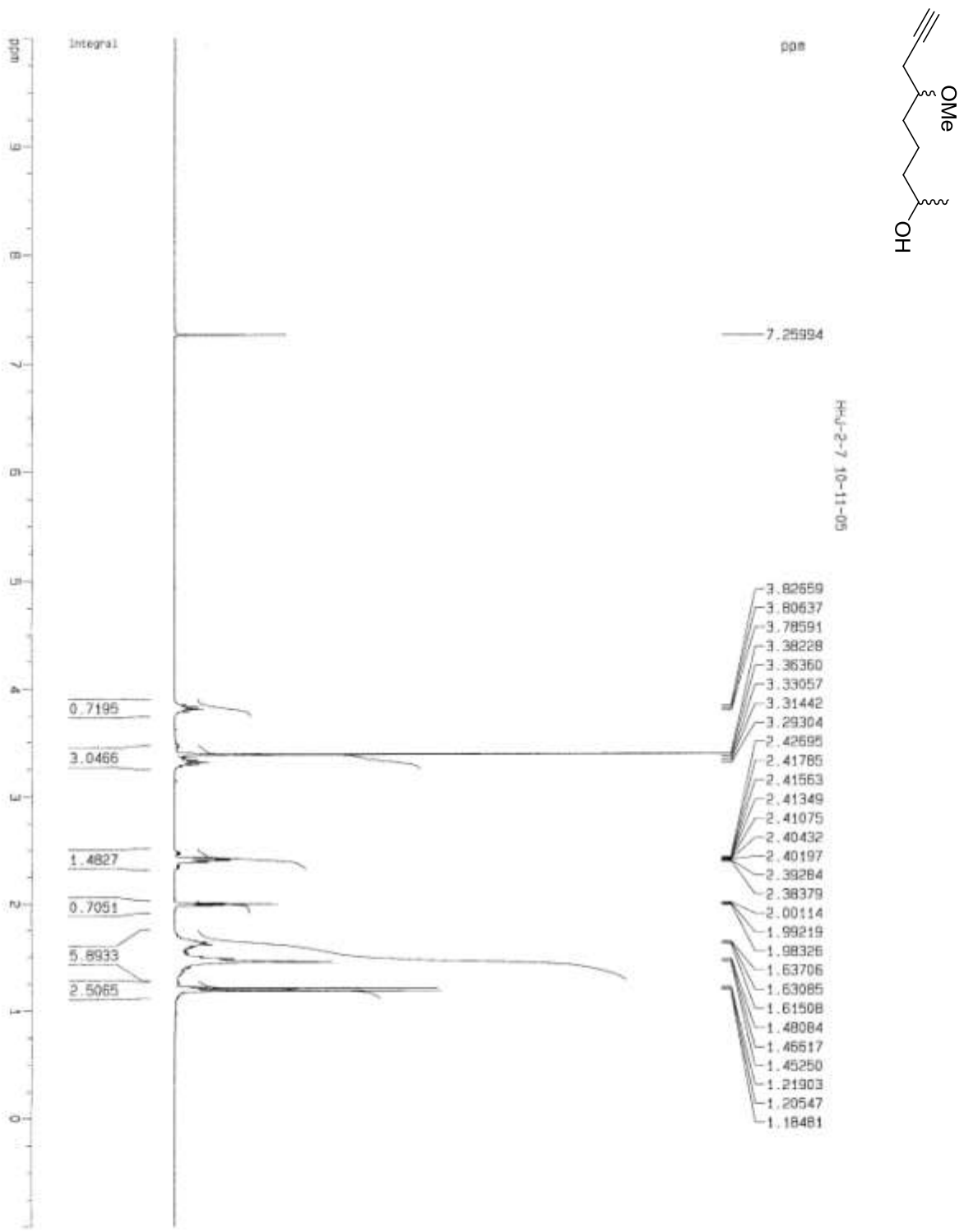
2.000
3.776
2.166
0.675
10.221
OMe
OH
HHJ-2-70 10-22-05


OMe
OH
ppm
HHJ-2-70 10-22-05
81.0202
79.0763
77.4233
76.9997
76.5761
69.8605
62.9004
57.0049
33.4324
32.6492
25.7353
24.9937
23.0154
ppm
180
160
140
120
100
80
60
40
20
0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OH
Integral
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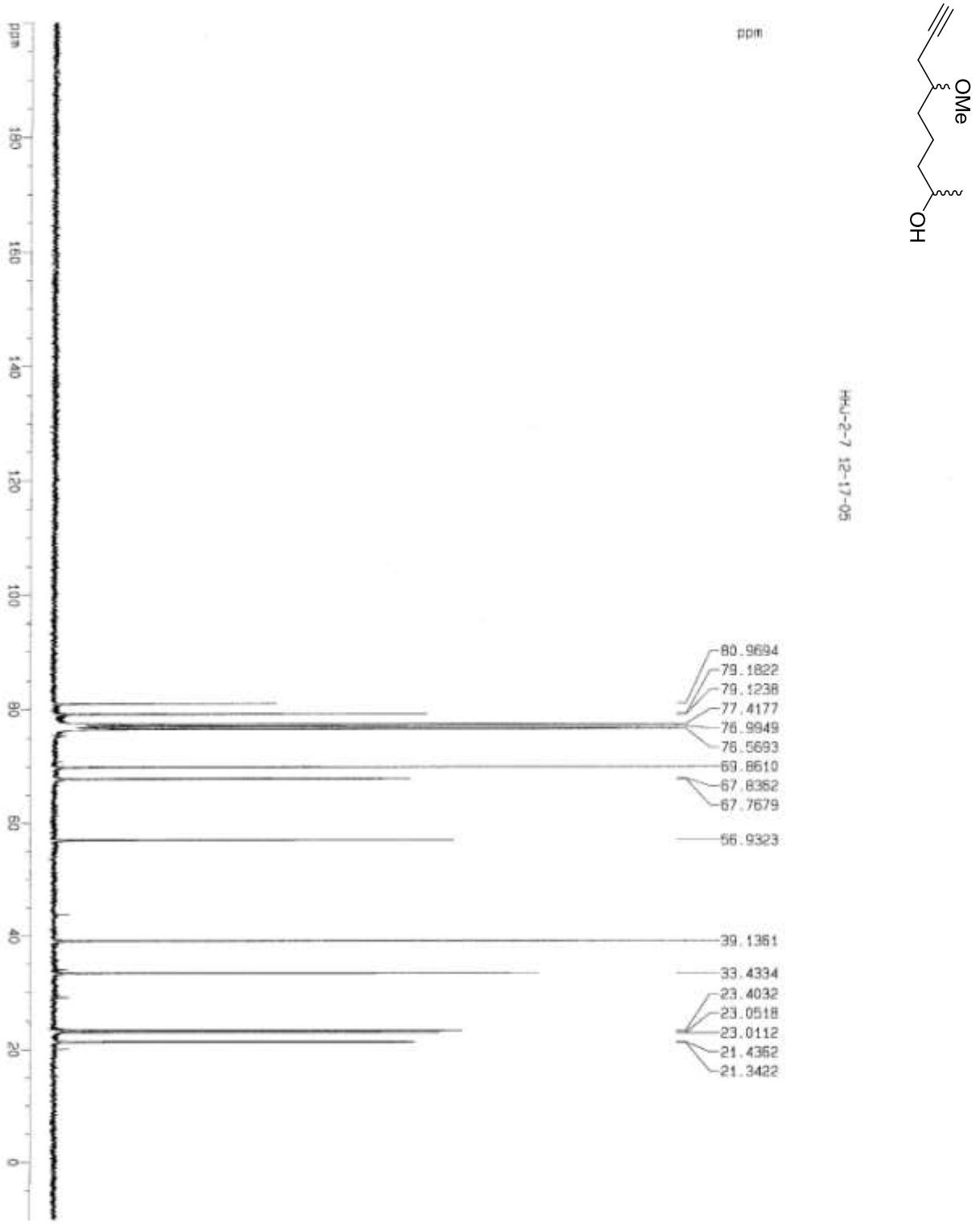
3.38228
3.36360
3.33057
3.31442
3.29304
2.42695
2.41785
2.41563
2.41349
2.41075
2.40432
2.40197
2.39284
2.38379
2.00114
1.99219
1.98326
1.63706
1.63085
1.61508
1.48084
1.46517
1.45250
1.21903
1.20547
1.18481
0.7195
3.0466
1.4827
0.7051
5.8933
2.5065
HH-J-2-7 10-11-05


OMe
OH
ppm
HH-2-7 12-17-05
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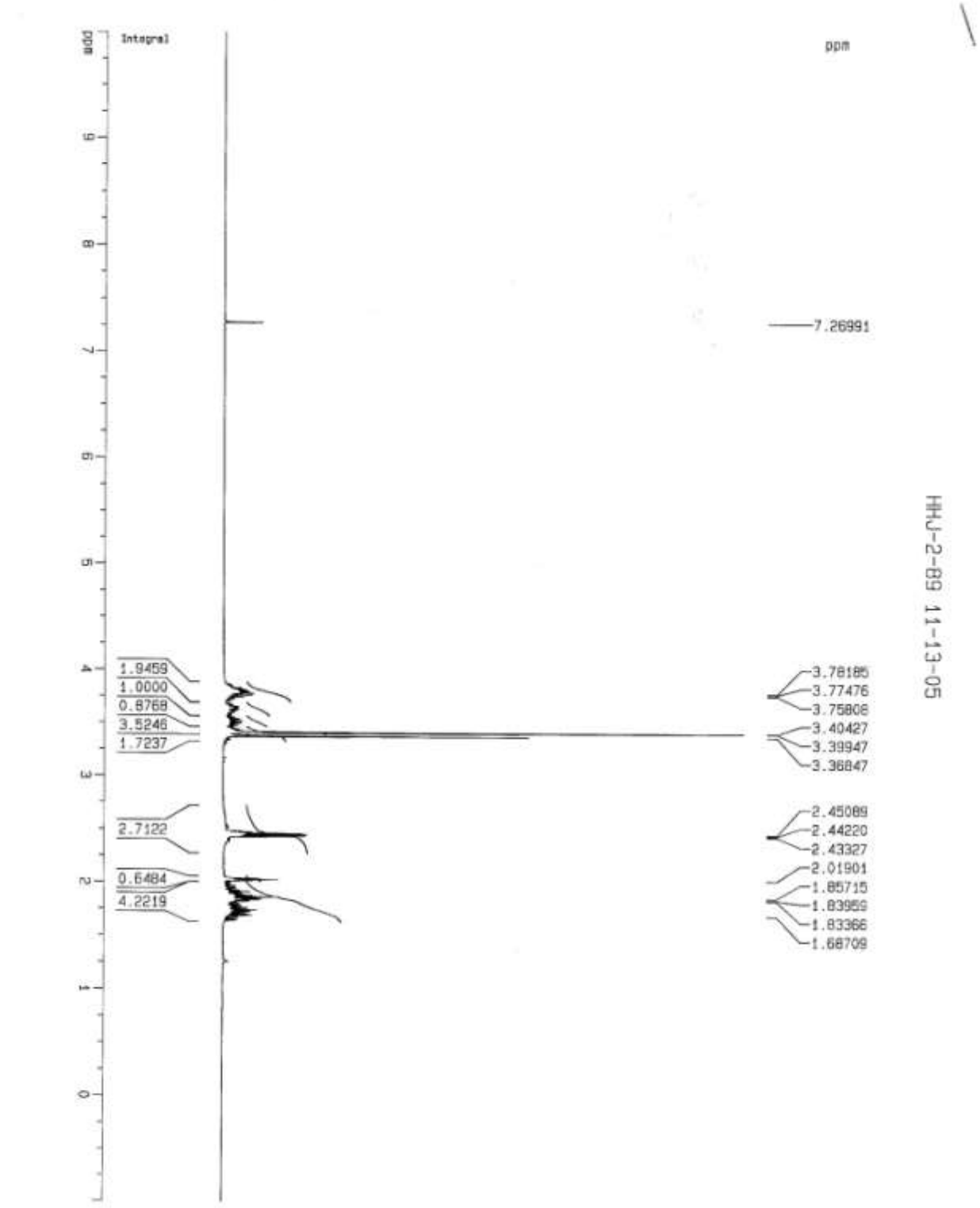
79.1822
79.1238
77.4177
76.9949
76.5693
69.8610
67.8362
67.7679
56.9323
39.1361
33.4334
23.4032
23.0518
23.0112
21.4362
21.3422


Integral
ppm
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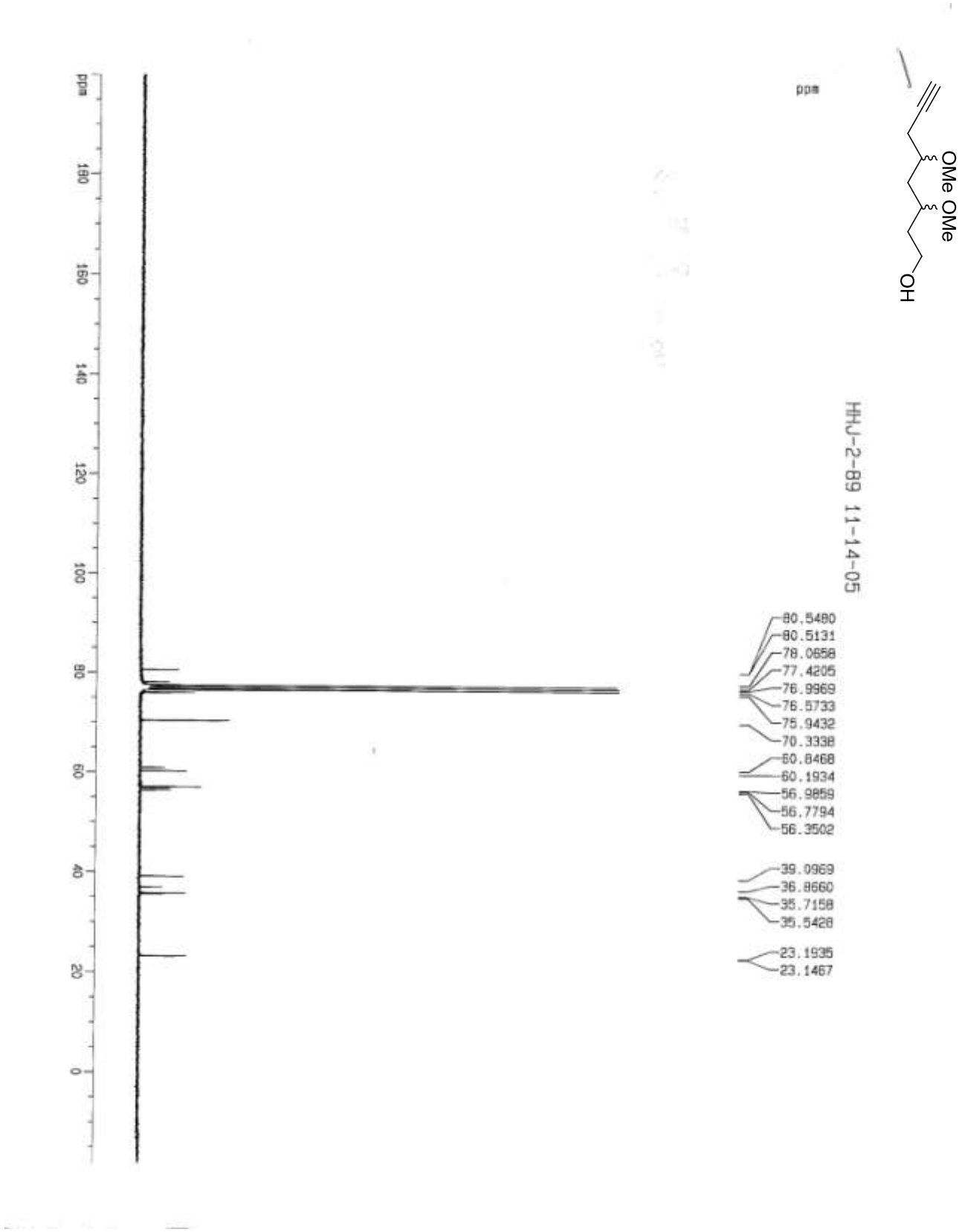
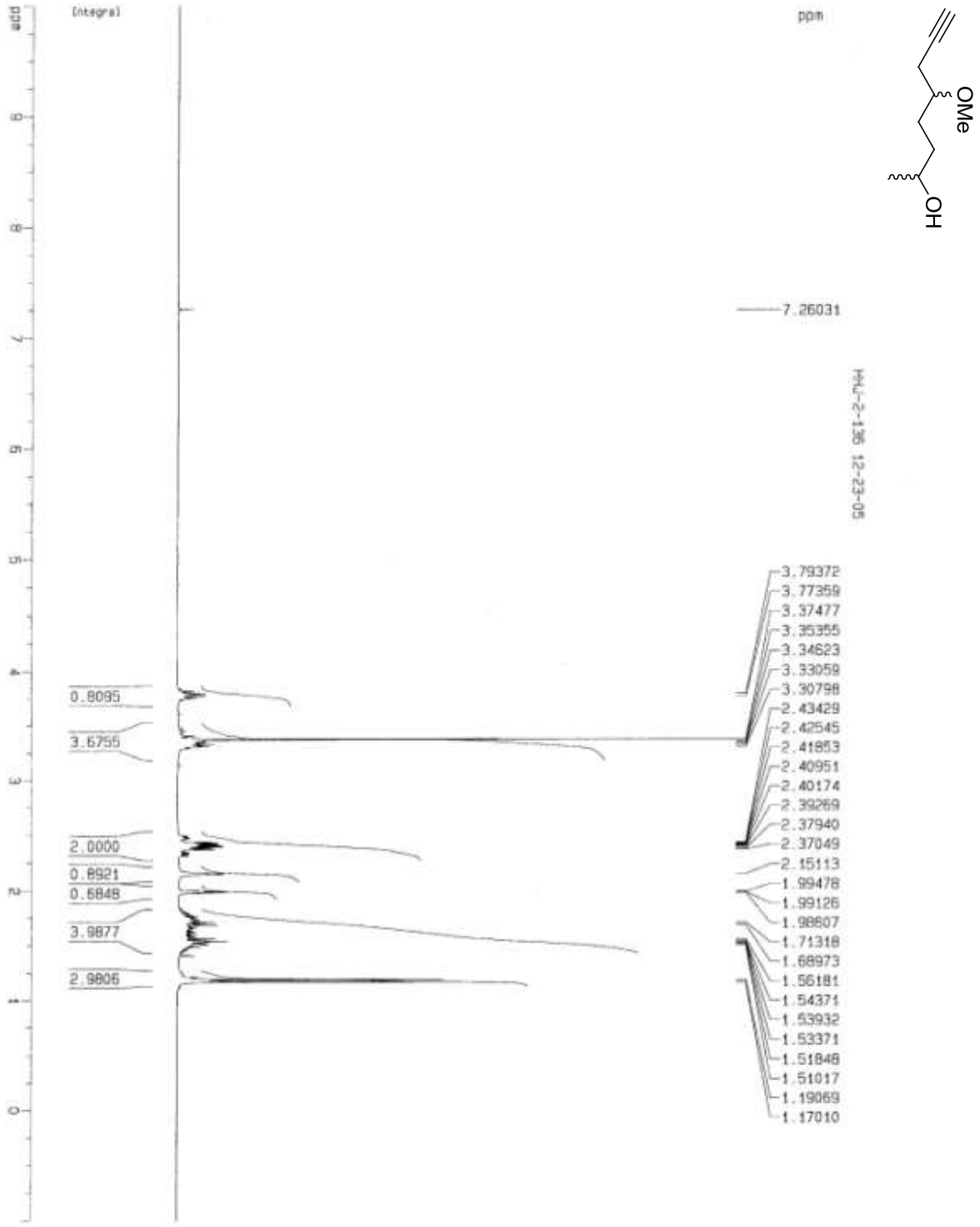
1.0000
0.8768
3.5246
1.7237
2.7122
0.6484
4.2219
3.78185
3.77476
3.75808
3.40427
3.39947
3.36847
2.45089
2.44220
2.43327
2.01901
1.85715
1.83959
1.83366
1.68709
HHJ-2-89 11-13-05


OMe OMe
OH
ppm
HHJ-2-89 11-14-05
80.5480
80.5131
78.0658
77.4205
76.9969
76.5733
75.9432
70.3338
60.8468
60.1934
56.9859
56.7794
56.3502
39.0969
36.8660
35.7158
35.5428
23.1935
23.1467
ppm
180
160
140
120
100
80
60
40
20
0


Integral
ppm
OMe
OH
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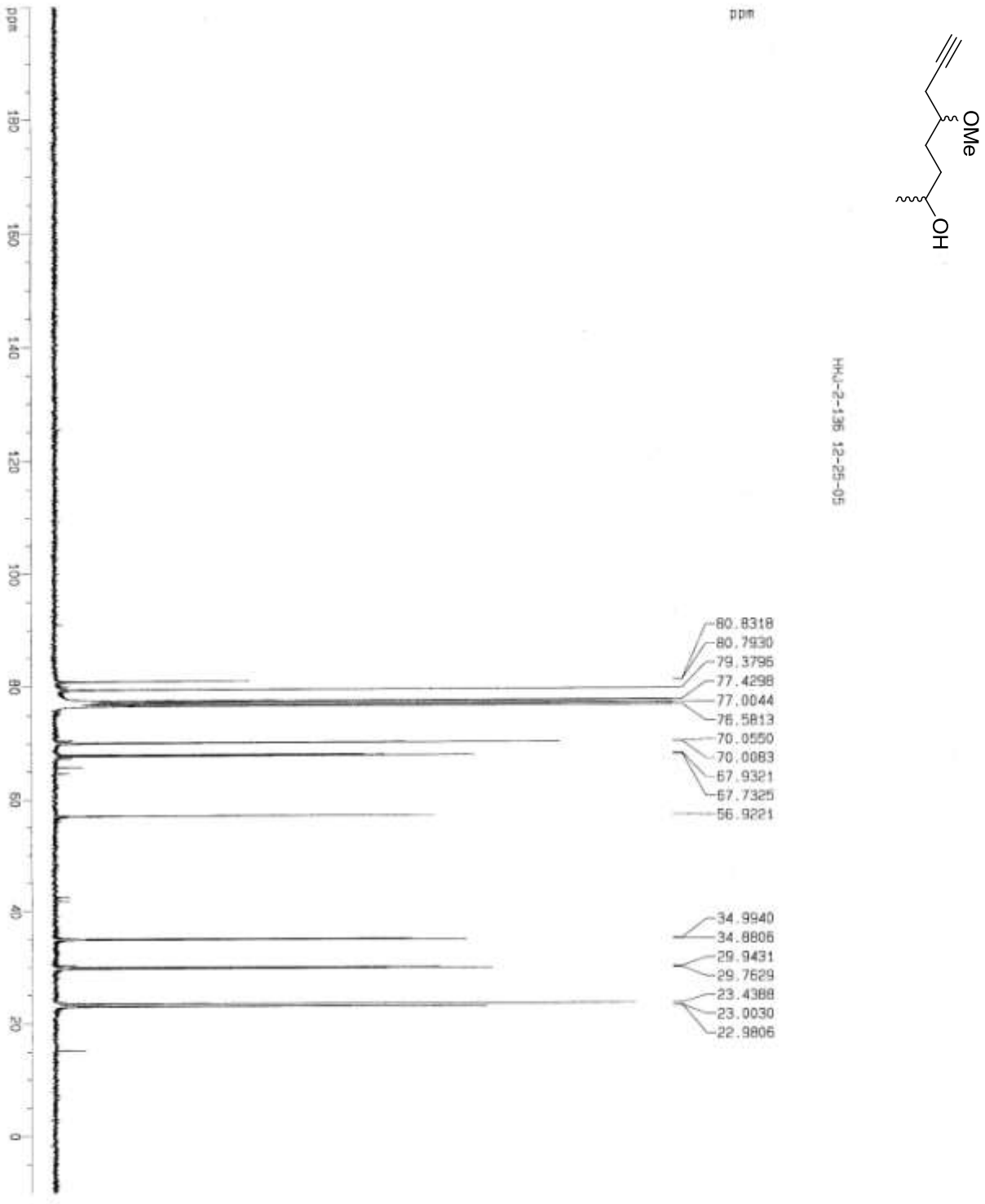
3.77359
3.37477
3.35355
3.34623
3.33059
3.30798
2.43429
2.42545
2.41853
2.40951
2.40174
2.39269
2.37940
2.37049
2.15113
1.99478
1.99126
1.98807
1.71318
1.68973
1.56181
1.54371
1.53932
1.53371
1.51848
1.51017
1.19069
1.17010
0.8095
3.6755
2.0000
0.8921
0.6848
3.9877
2.9805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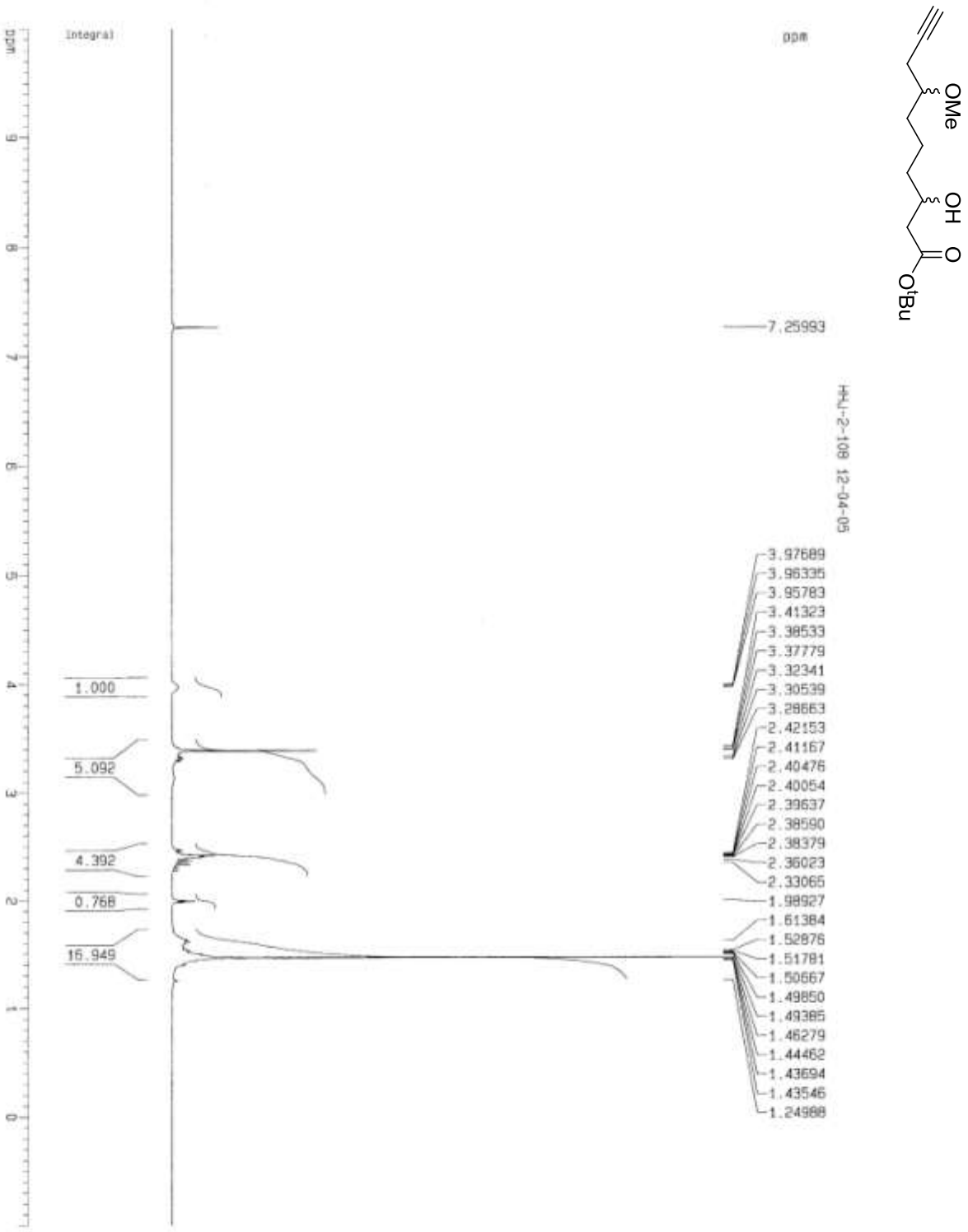
ppm
180
160
140
120
100
80
60
40
20
0
80.8318
80.7930
79.3796
77.4298
77.0044
76.5813
70.0550
70.0083
67.9321
67.7325
56.9221
34.9940
34.8806
29.9431
29.7629
23.4388
23.0030
22.9806
OMe
OH
HHJ-2-136 12-25-05


OMe
OH
O
OtBu
integral
ppm
HHJ-2-108 12-04-05
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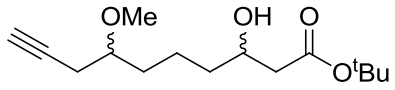
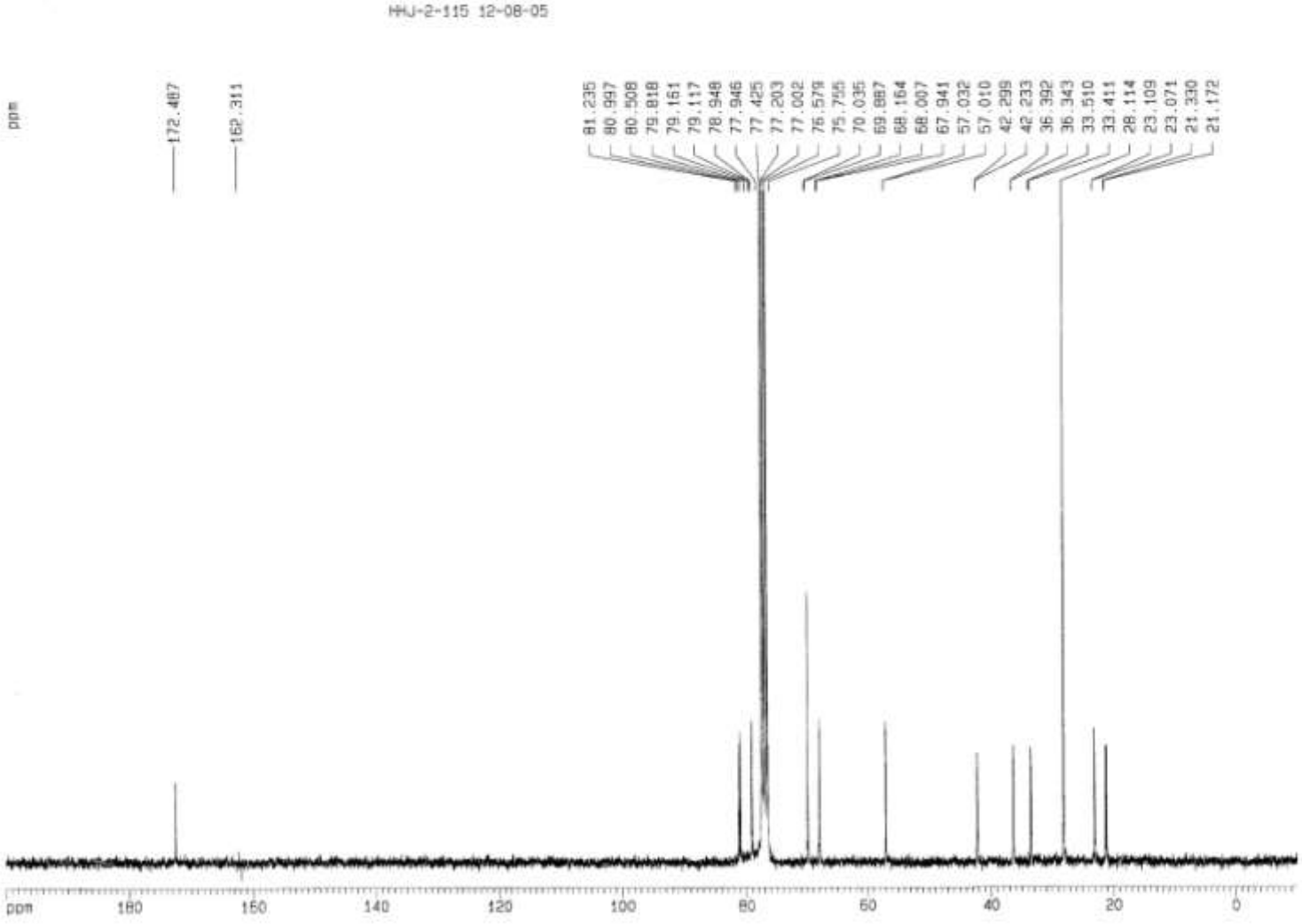
3.96335
3.95783
3.41323
3.38533
3.37779
3.32341
3.30539
3.28663
2.42153
2.41167
2.40476
2.40054
2.39637
2.38590
2.38379
2.36023
2.33065
1.98927
1.61384
1.52876
1.51781
1.50667
1.49850
1.49385
1.46279
1.44462
1.43694
1.43546
1.24988
1.000
5.092
4.392
0.768
16.949


OMe
OH
O
O^{t}Bu


HHJ-2-115 12-08-05
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80.997
80.508
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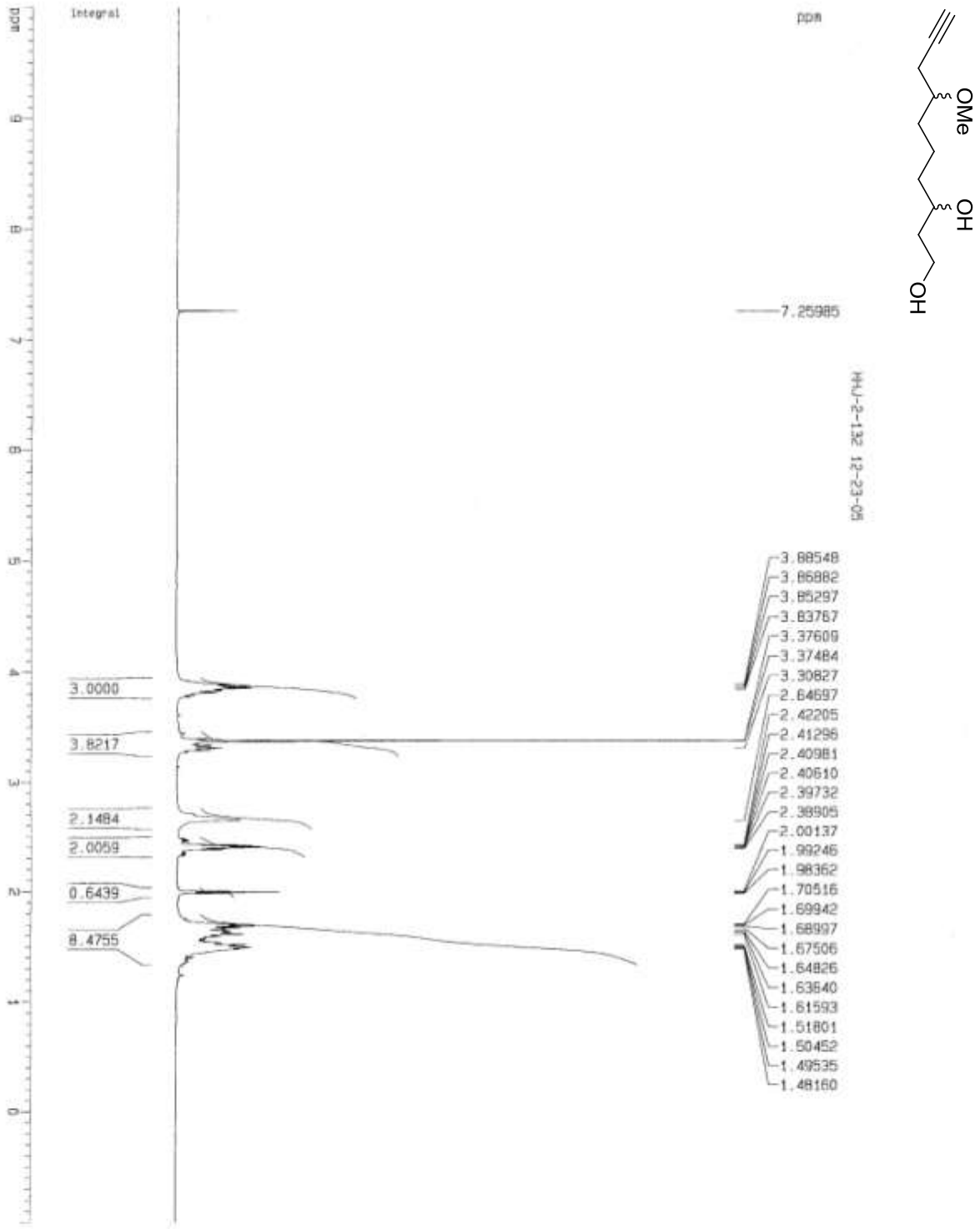
79.161
79.117
78.948
77.946
77.425
77.203
77.002
76.579
75.755
70.035
69.887
68.164
68.007
67.941
57.032
57.010
42.299
42.233
36.392
36.343
33.510
33.411
28.114
23.109
23.071
21.330
21.172
ppm
180
160
140
120
100
80
60
40
20
0


Integral
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3.85297
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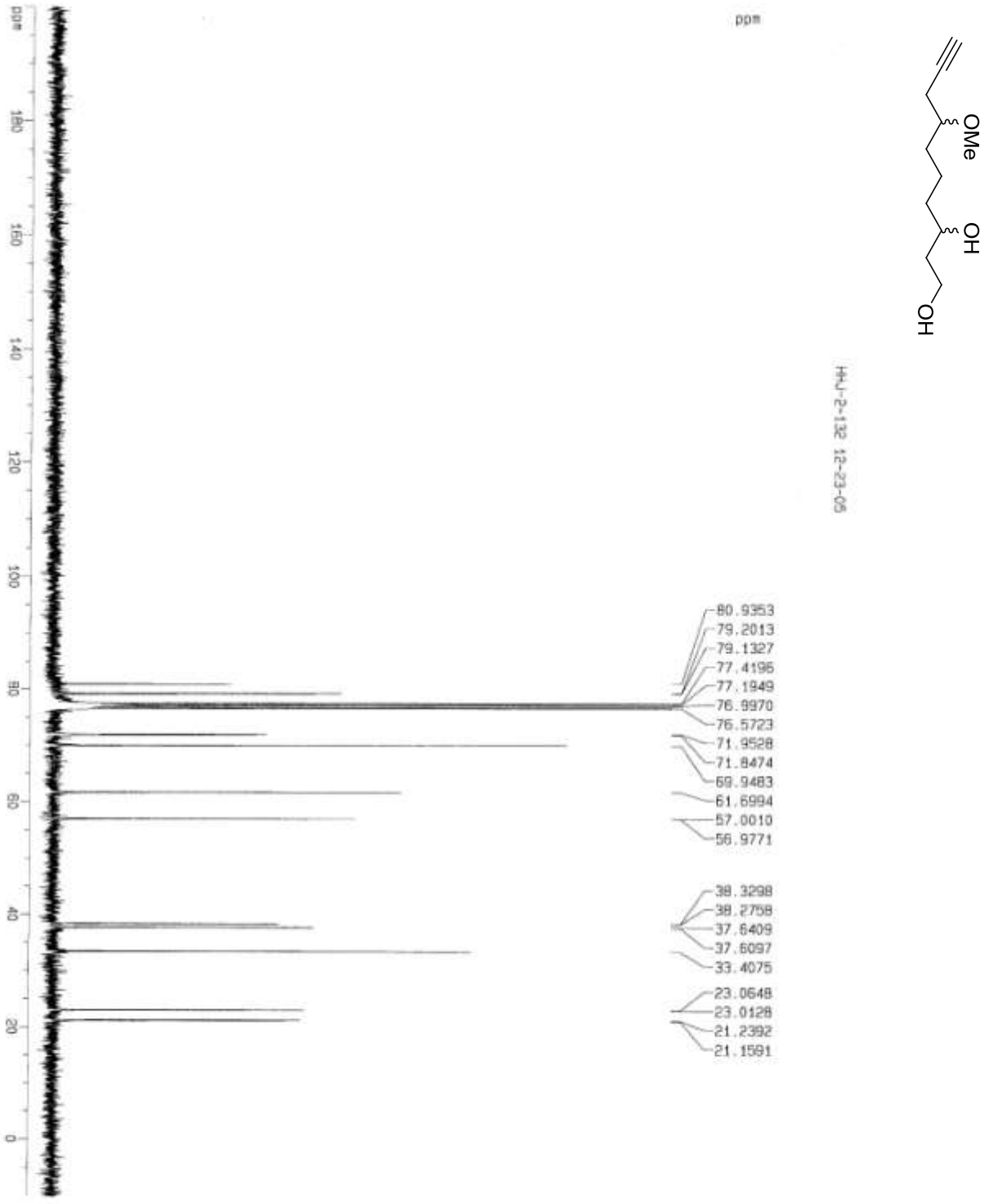
3.37609
3.37484
3.30827
2.64697
2.42205
2.41296
2.40981
2.40610
2.39732
2.38905
2.00137
1.99246
1.98362
1.70516
1.69942
1.68997
1.67506
1.64826
1.63640
1.61593
1.51801
1.50452
1.49535
1.48160
3.0000
3.8217
2.1484
2.0059
0.6439
8.4755
HHJ-2-132 12-23-05
OMe
OH
OH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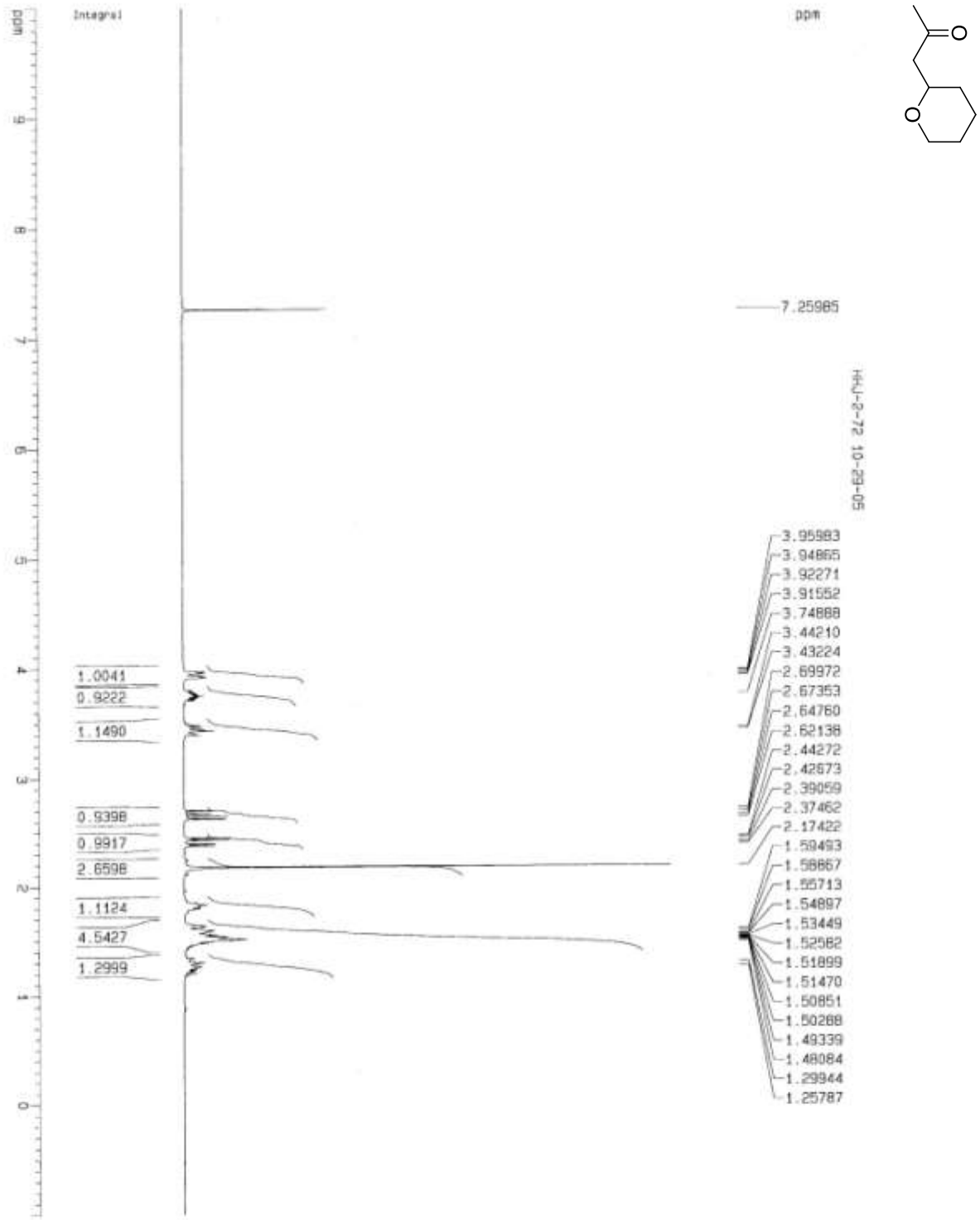
180
160
140
120
100
80
60
40
20
0
80.9353
79.2013
79.1327
77.4196
77.1949
76.9970
76.5723
71.9528
71.8474
69.9483
61.6994
57.0010
56.9771
38.3298
38.2758
37.6409
37.6097
33.4075
23.0648
23.0128
21.2392
21.1591
OMe
OH
OH
HHJ-2-132 12-23-05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HHJ-2-72 10-29-05
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3.91552
3.74888
3.44210
3.43224
2.69972
2.67353
2.64760
2.62138
2.44272
2.42673
2.39059
2.37462
2.17422
1.59493
1.58867
1.55713
1.54897
1.53449
1.52582
1.51899
1.51470
1.50851
1.50288
1.49339
1.48084
1.29944
1.25787
1.0041
0.9222
1.1490
0.9398
0.9917
2.6598
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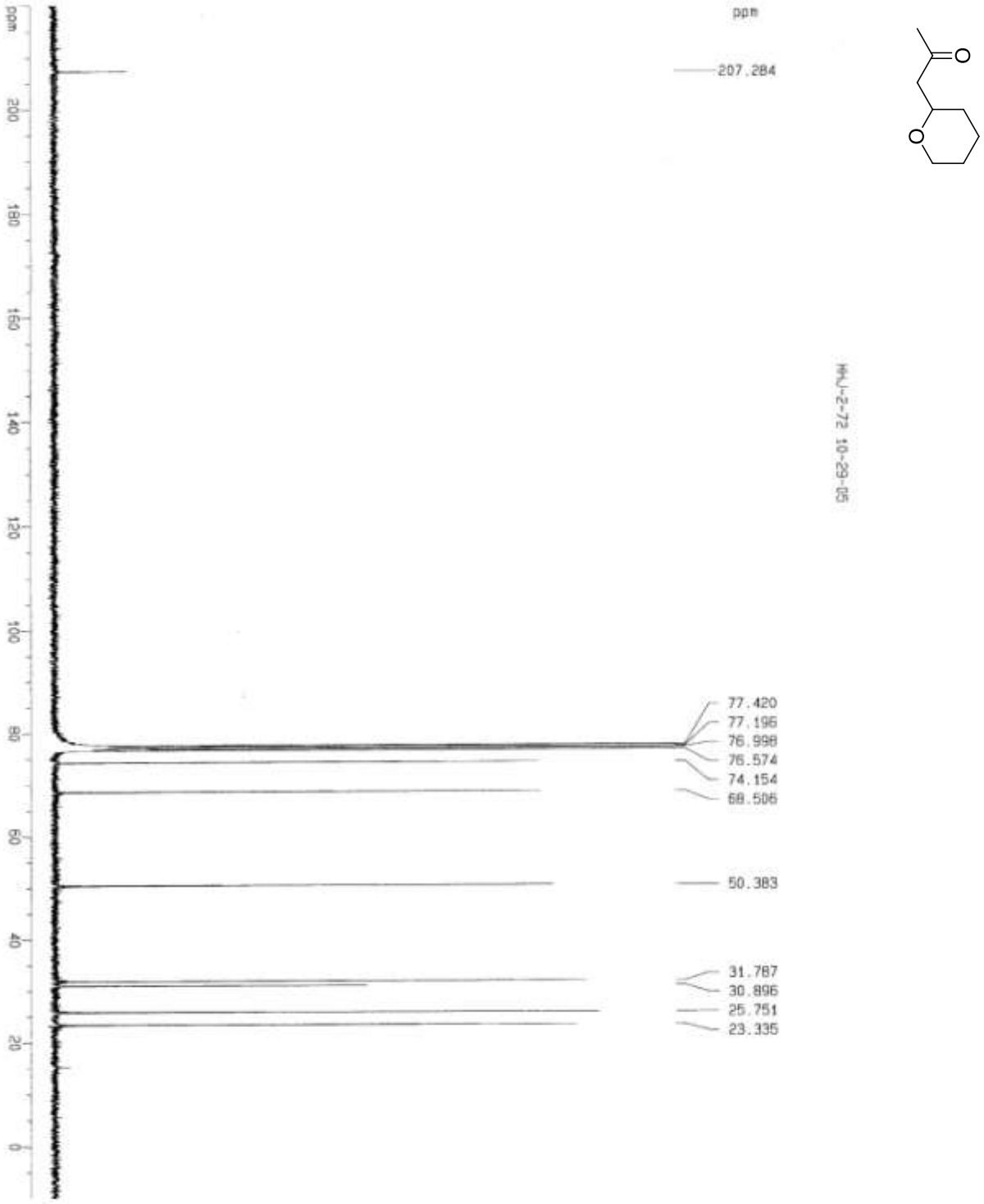
4.5427
1.2999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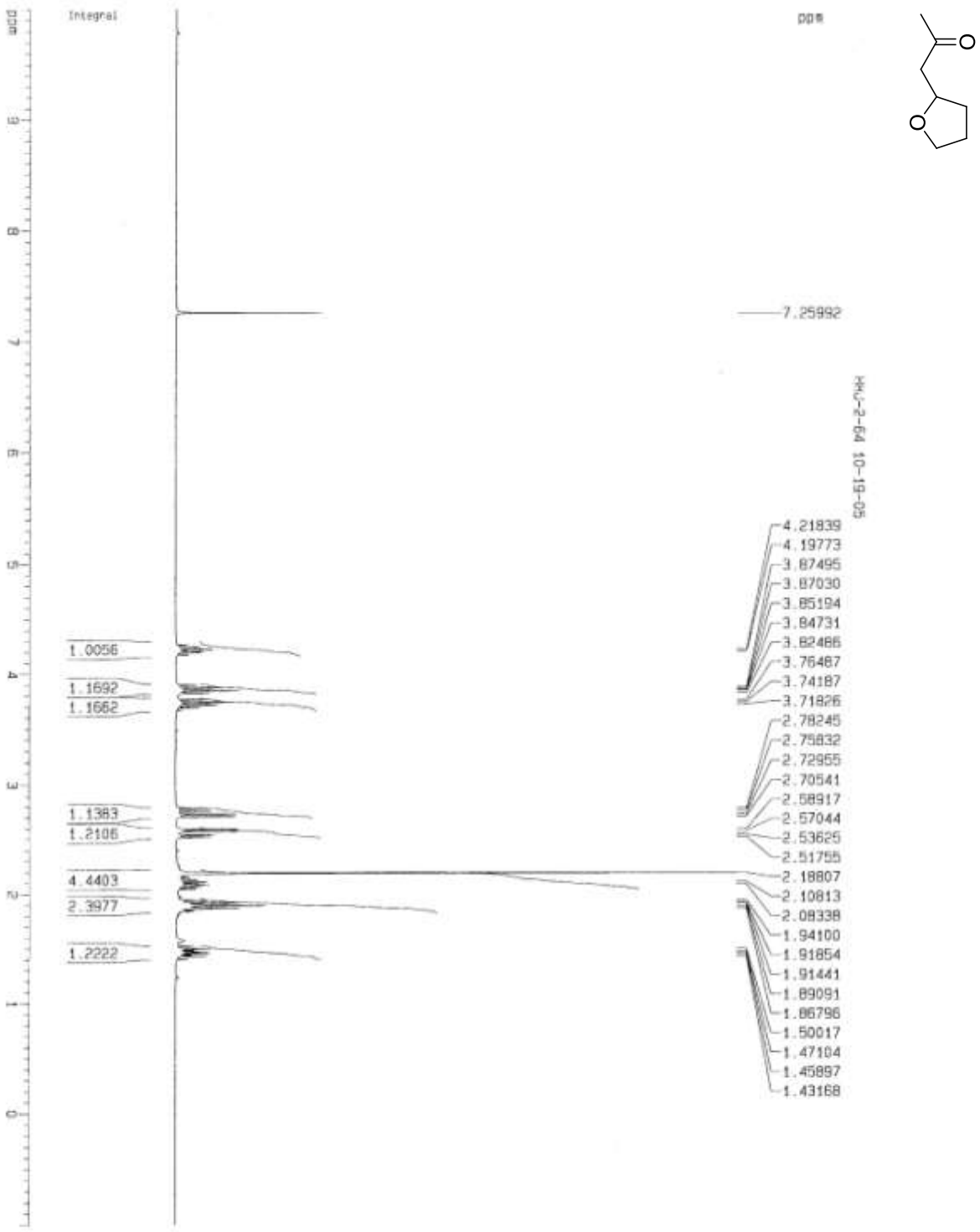
76.574
74.154
68.506
50.383
31.787
30.896
25.751
23.335
HHJ-2-72 10-29-05


Integral
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3.87495
3.87030
3.85194
3.84731
3.82486
3.76487
3.74187
3.71826
2.78245
2.75832
2.72955
2.70541
2.58917
2.57044
2.53625
2.51755
2.18807
2.10813
2.08338
1.94100
1.91854
1.91441
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1.86796
1.50017
1.47104
1.45897
1.43168
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1.1662
1.1383
1.2106
4.4403
2.3977
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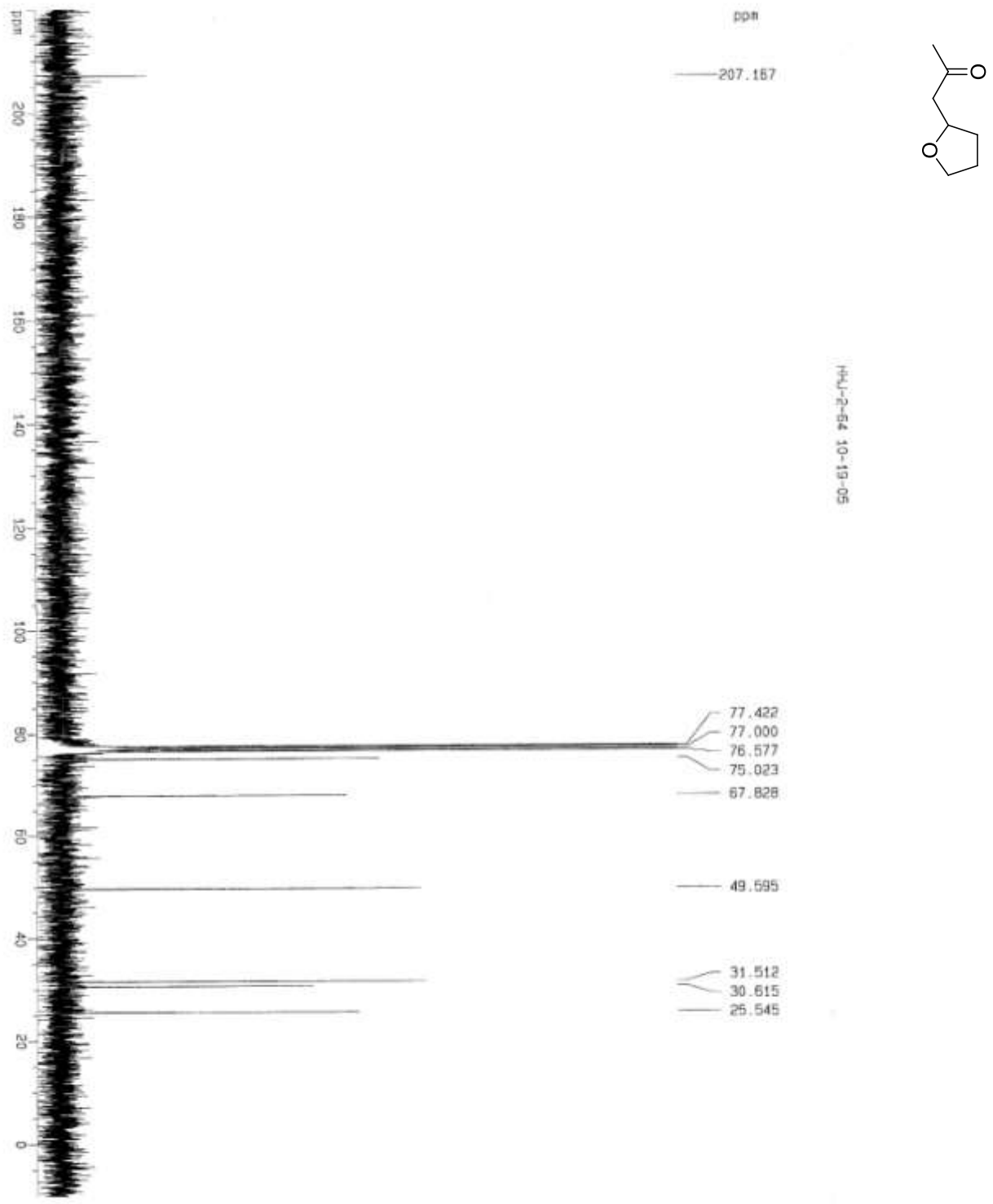
HHV-2-64 10-19-05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76.577
75.023
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49.595
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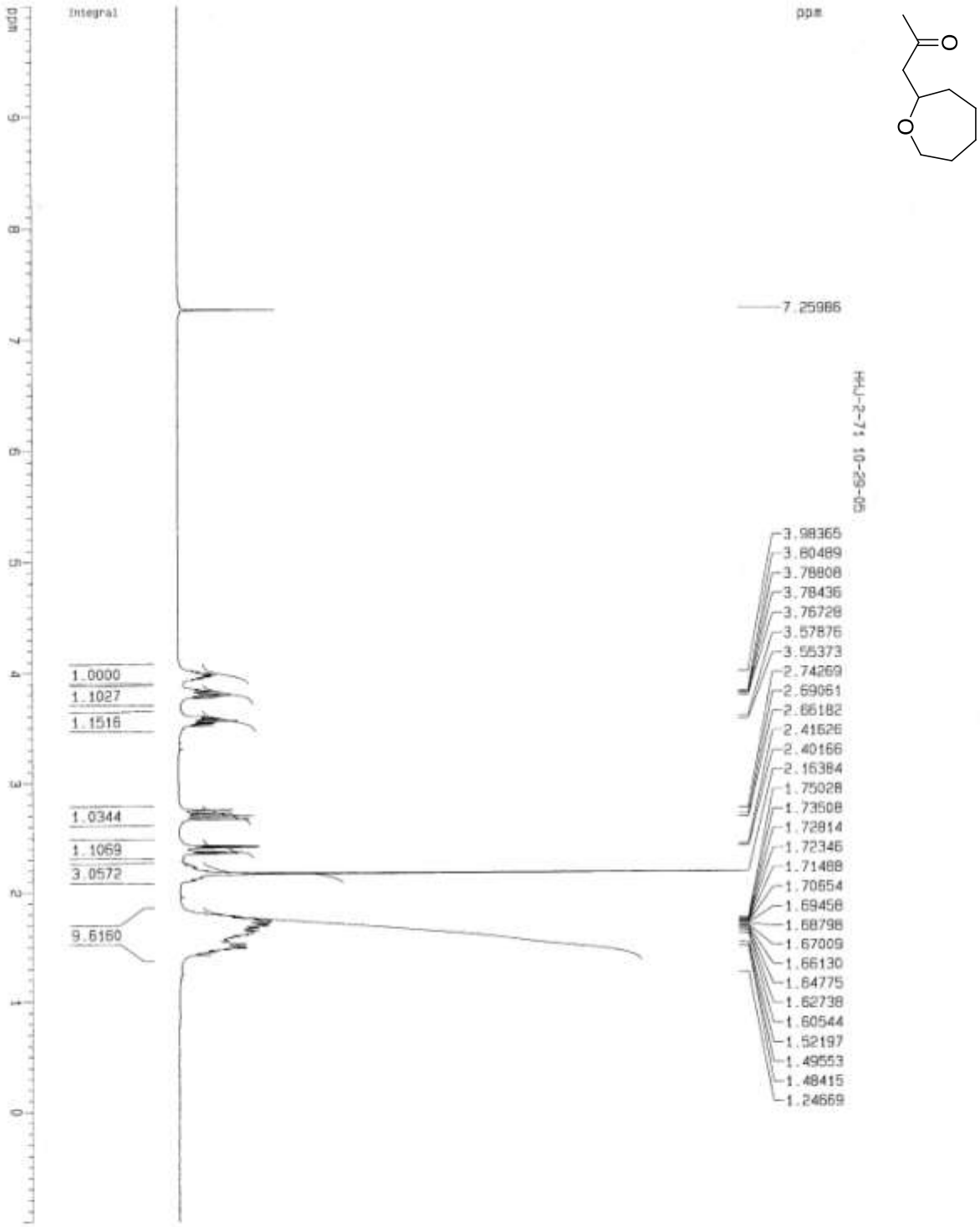
30.615
25.545
HHJ-2-64 10-19-05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HHJ-2-71 10-29-05
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3.78436
3.76728
3.57876
3.55373
2.74269
2.59061
2.56182
2.41626
2.40166
2.16384
1.75028
1.73508
1.72814
1.72346
1.71488
1.70654
1.69458
1.68798
1.67009
1.66130
1.64775
1.62738
1.60544
1.52197
1.49553
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1.24669
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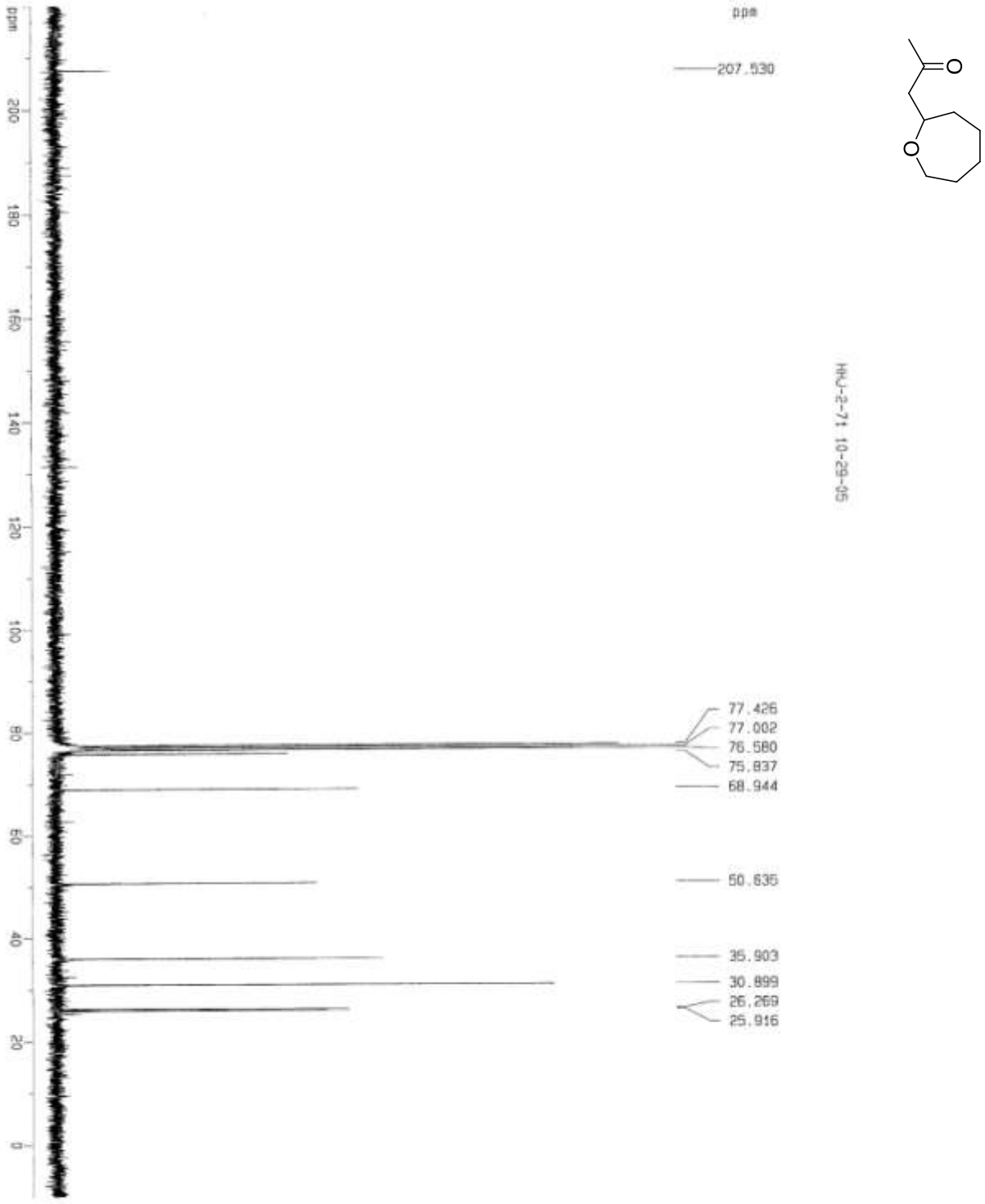
1.1027
1.1516
1.0344
1.1069
3.0572
9.6160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76.580
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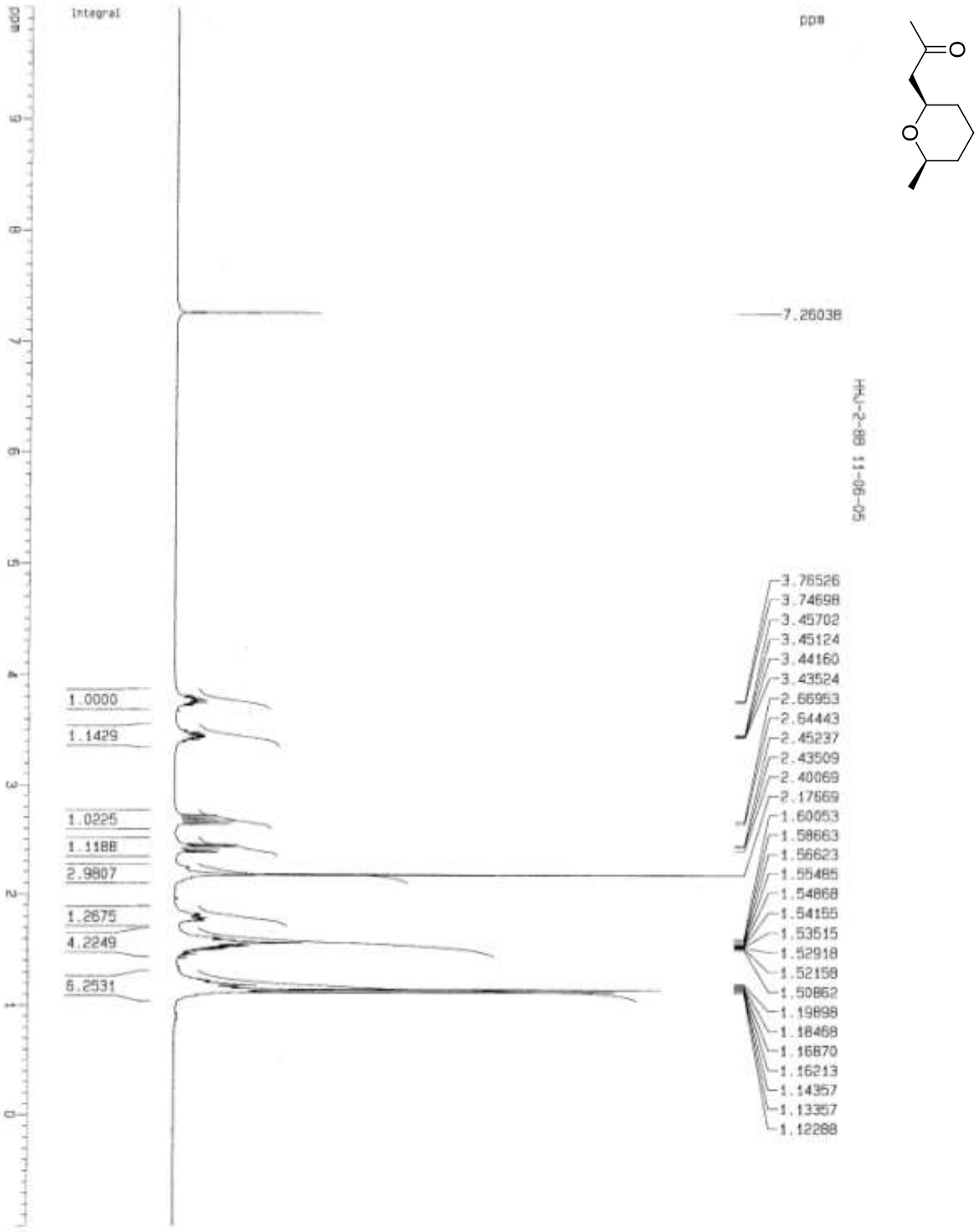
35.903
30.899
26.269
25.916
HHJ-2-71 10-29-05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3.44160
3.43524
2.66963
2.64443
2.45237
2.43509
2.40069
2.17669
1.60053
1.58663
1.56623
1.55485
1.54868
1.54155
1.53515
1.52918
1.52158
1.50862
1.19898
1.18468
1.16870
1.16213
1.14357
1.13357
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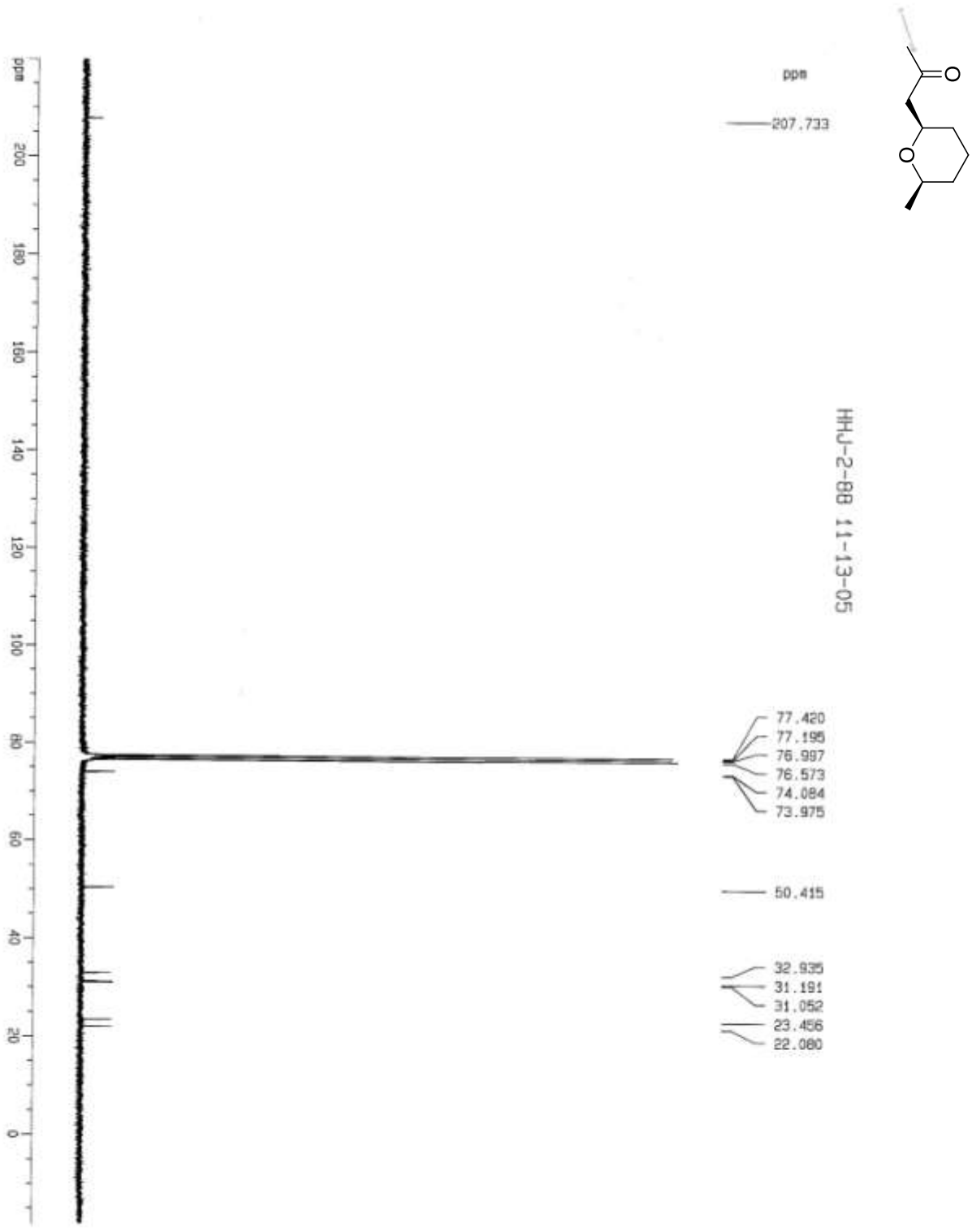
1.0000
1.1429
1.0225
1.1188
2.9807
1.2675
4.2249
6.2531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76.997
76.573
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73.975
50.415
32.935
31.191
31.052
23.456
22.080
HHJ-2-88 11-13-05
ppm
200
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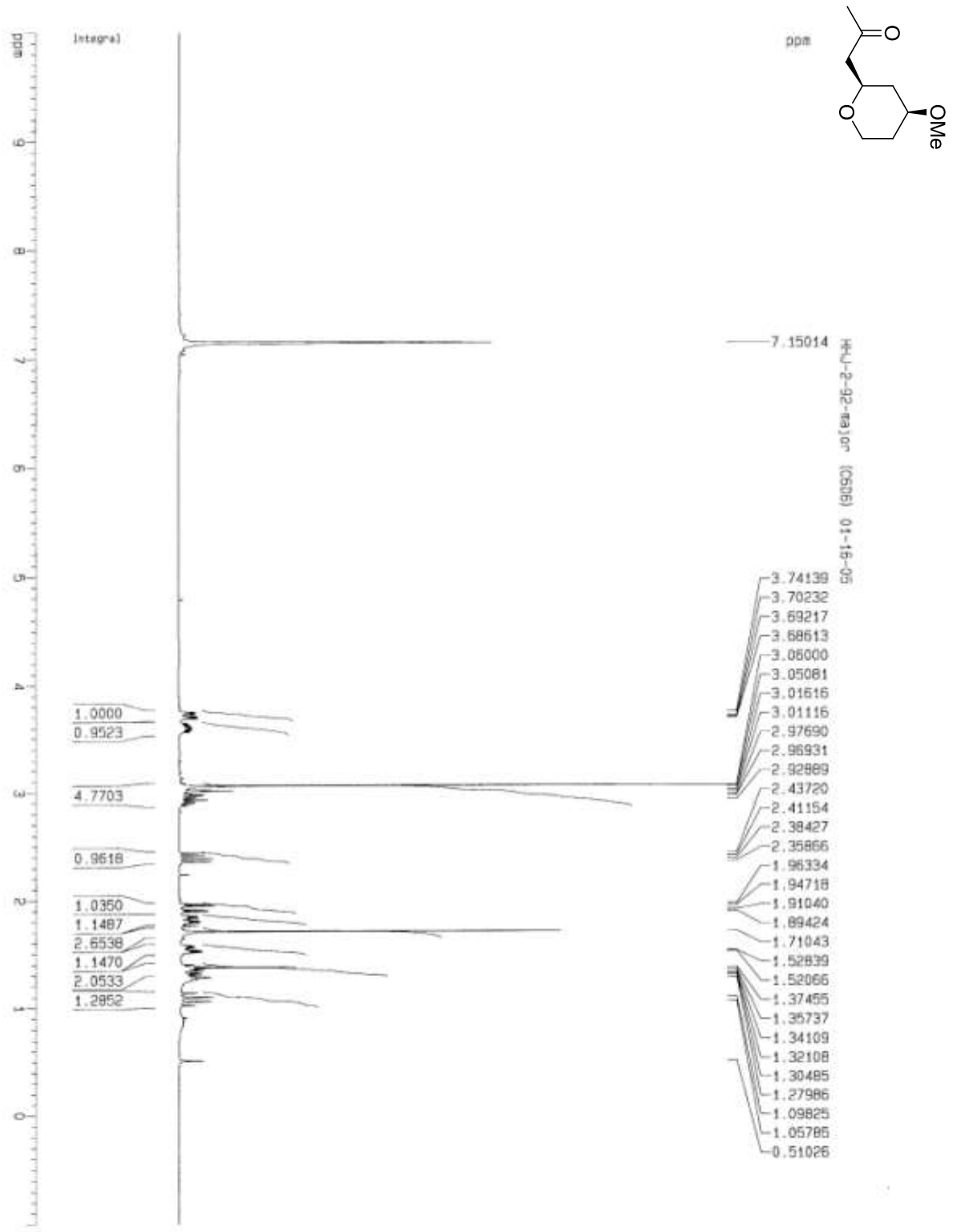
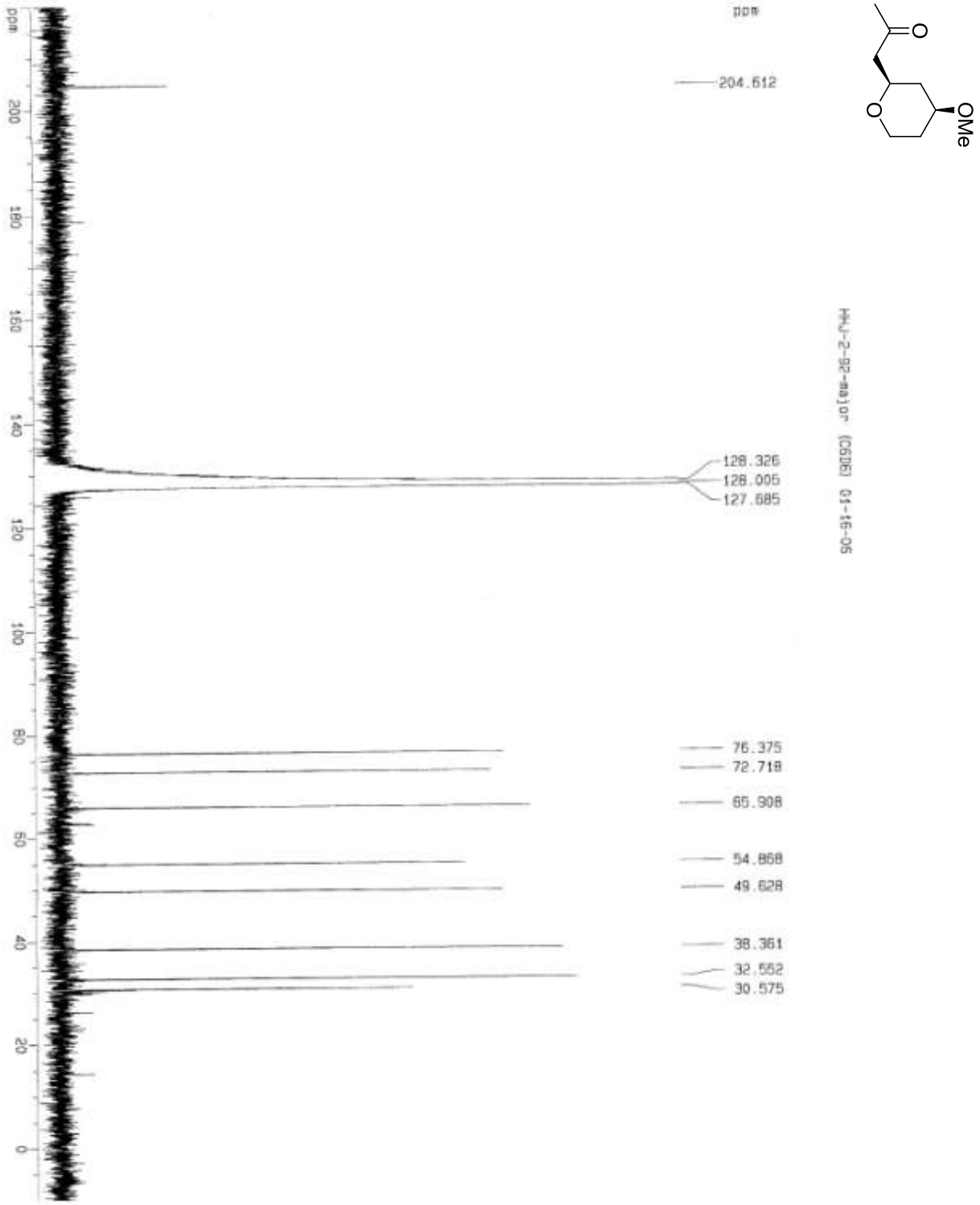
160
140
120
100
80
60
40
20
0


ppm
Integral
7.15014
3.74139
3.70232
3.69217
3.68613
3.06000
3.05081
3.01616
3.01116
2.97690
2.96931
2.92889
2.43720
2.41154
2.38427
2.35866
1.96334
1.94718
1.91040
1.89424
1.71043
1.52839
1.52066
1.37455
1.35737
1.34109
1.32108
1.30485
1.27986
1.09825
1.05785
0.51026
1.0000
0.9523
4.7703
0.9618
1.0350
1.1487
2.6538
1.1470
2.0533
1.2952
OMe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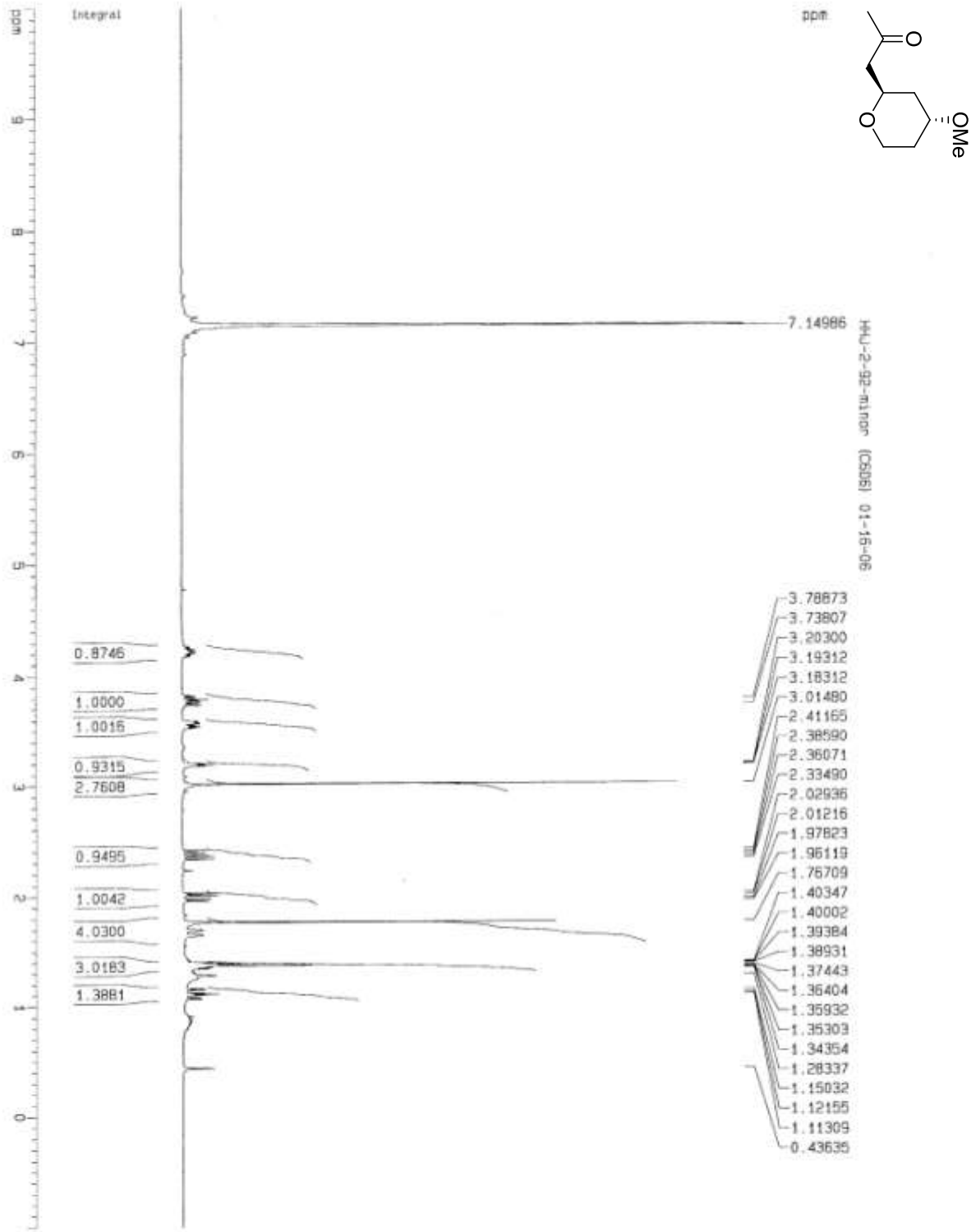
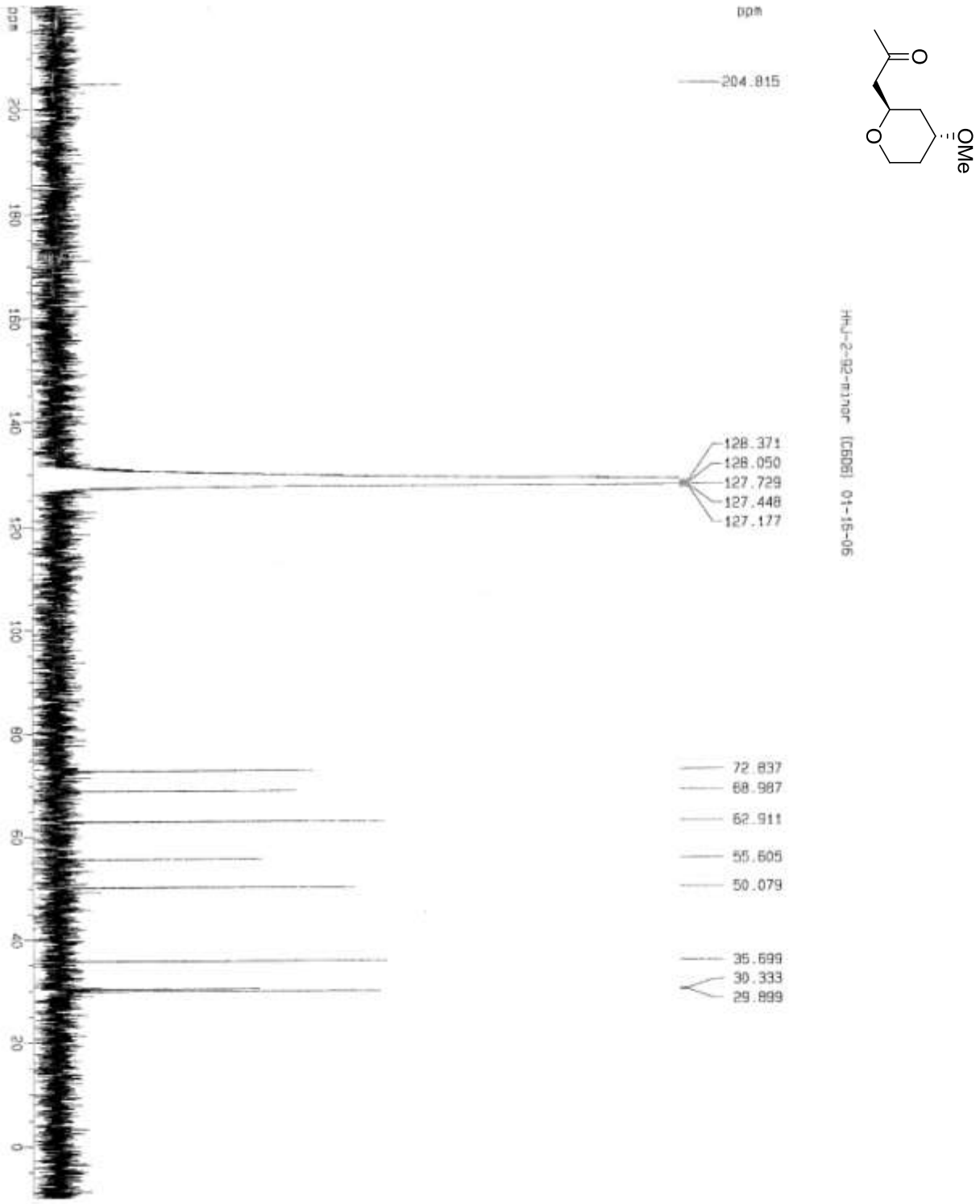
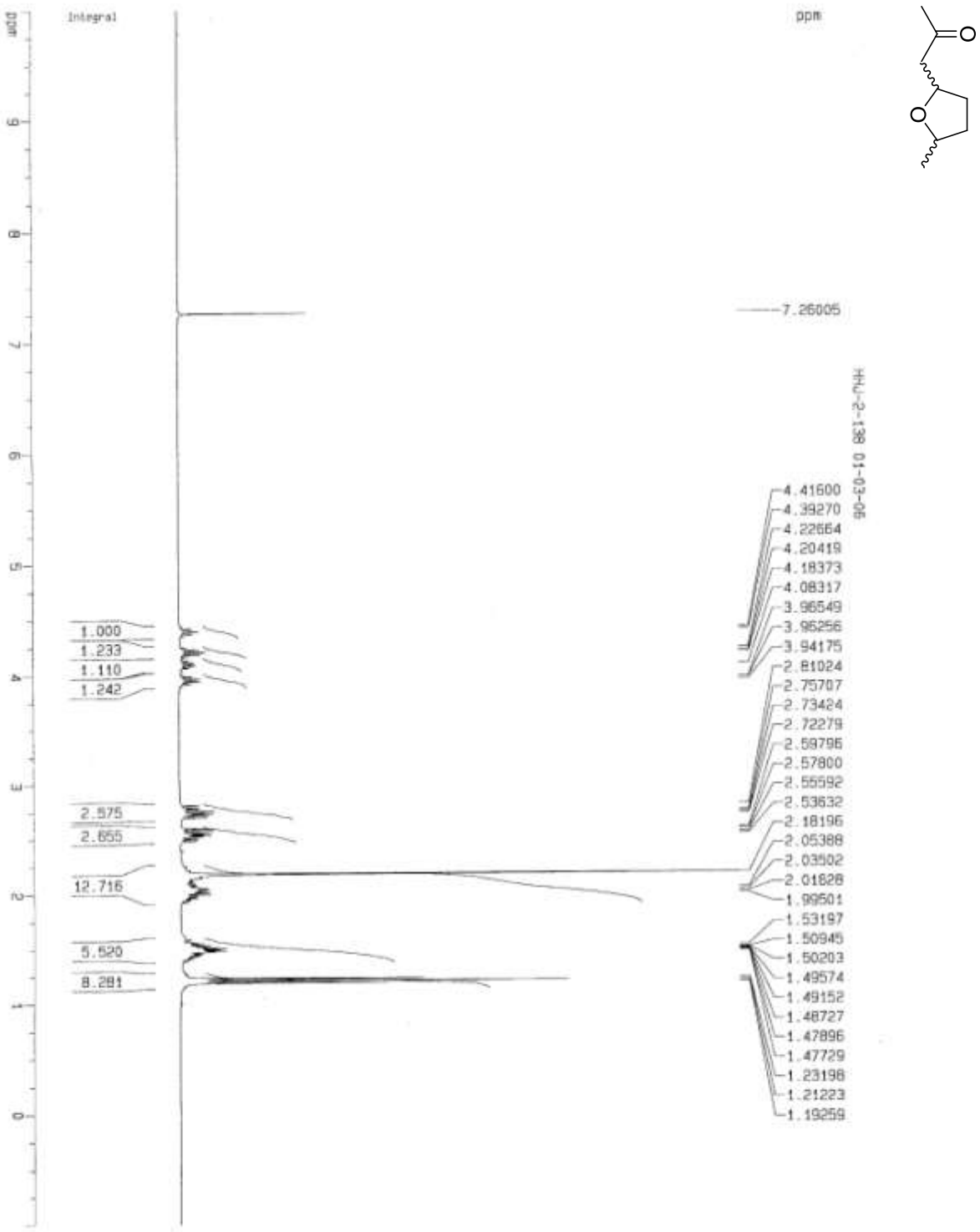
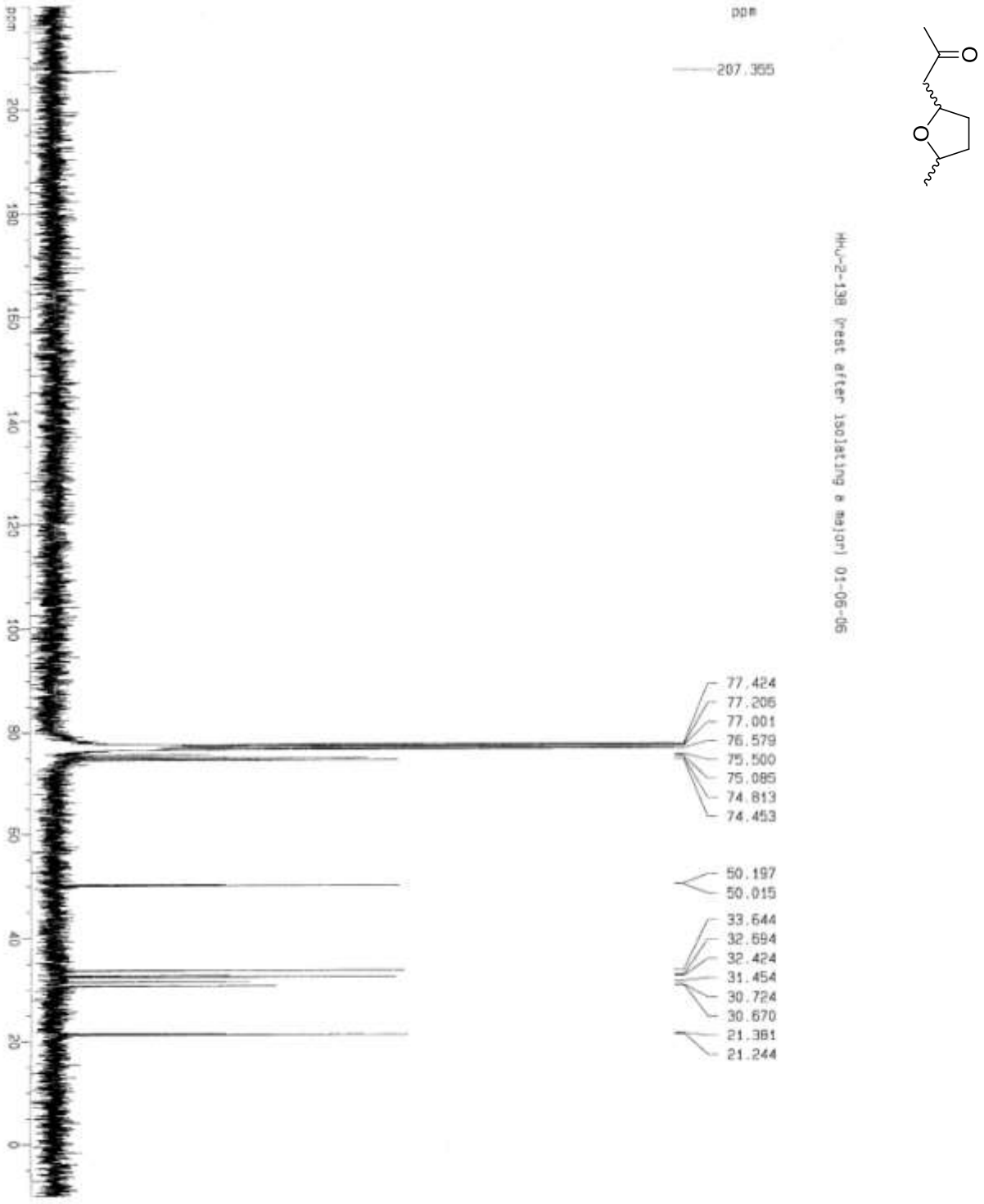
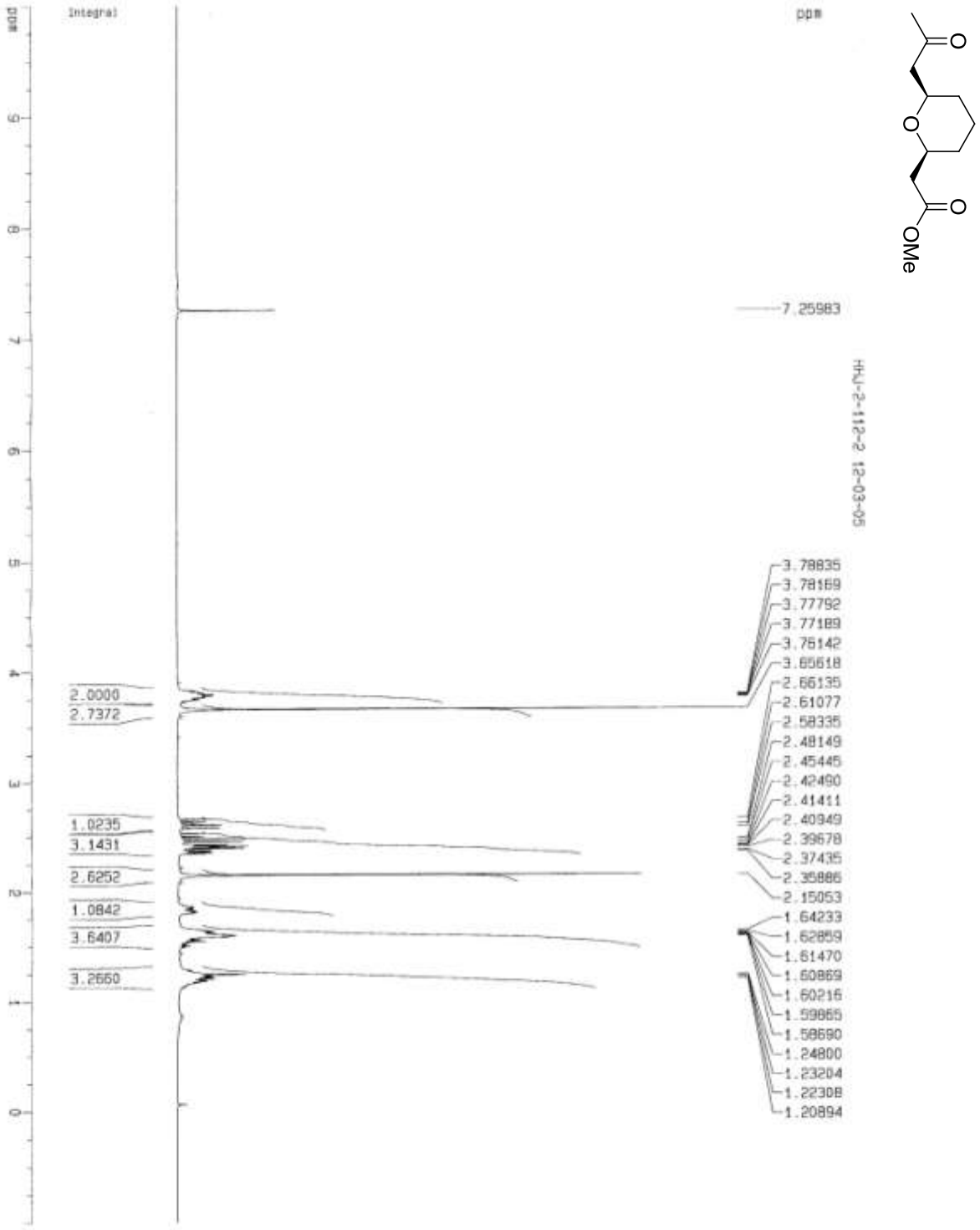
128.005
127.685
76.375
72.718
65.908
54.868
49.628
38.361
32.552
30.575
HHJ-2-92-major (C606) 01-16-05
OMe
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0

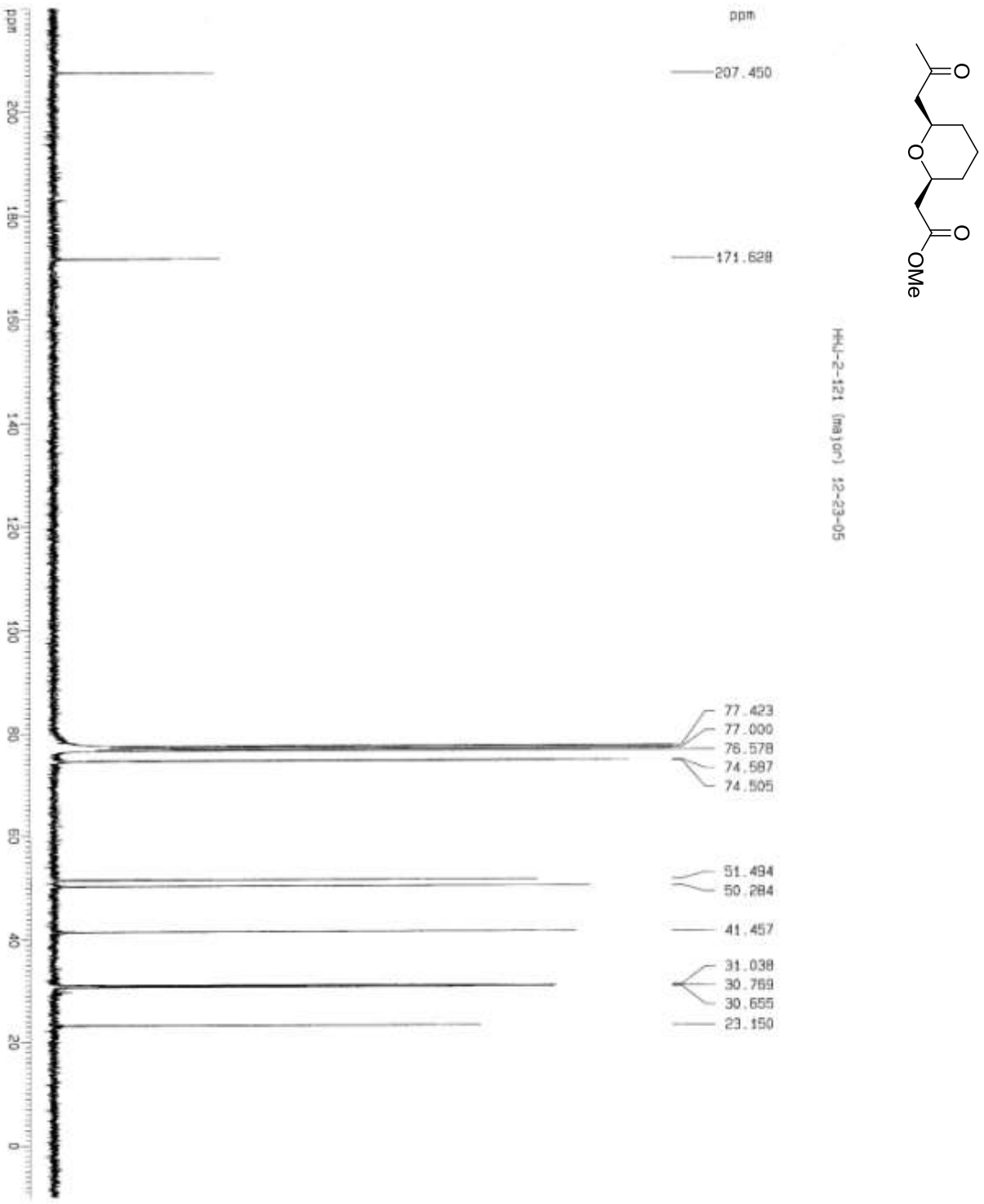

Integral
ppm
7.14986
HHJ-2-92-minor (C5D6) 01-16-06
3.78873
3.73807
3.20300
3.19312
3.18312
3.01480
2.41165
2.38590
2.36071
2.33490
2.02936
2.01216
1.97823
1.96119
1.76709
1.40347
1.40002
1.39384
1.38931
1.37443
1.36404
1.35932
1.35303
1.34354
1.28337
1.15032
1.12155
1.11309
0.43635
0.8746
1.0000
1.0016
0.9315
2.7608
0.9495
1.0042
4.0300
3.0183
1.3881
OMe

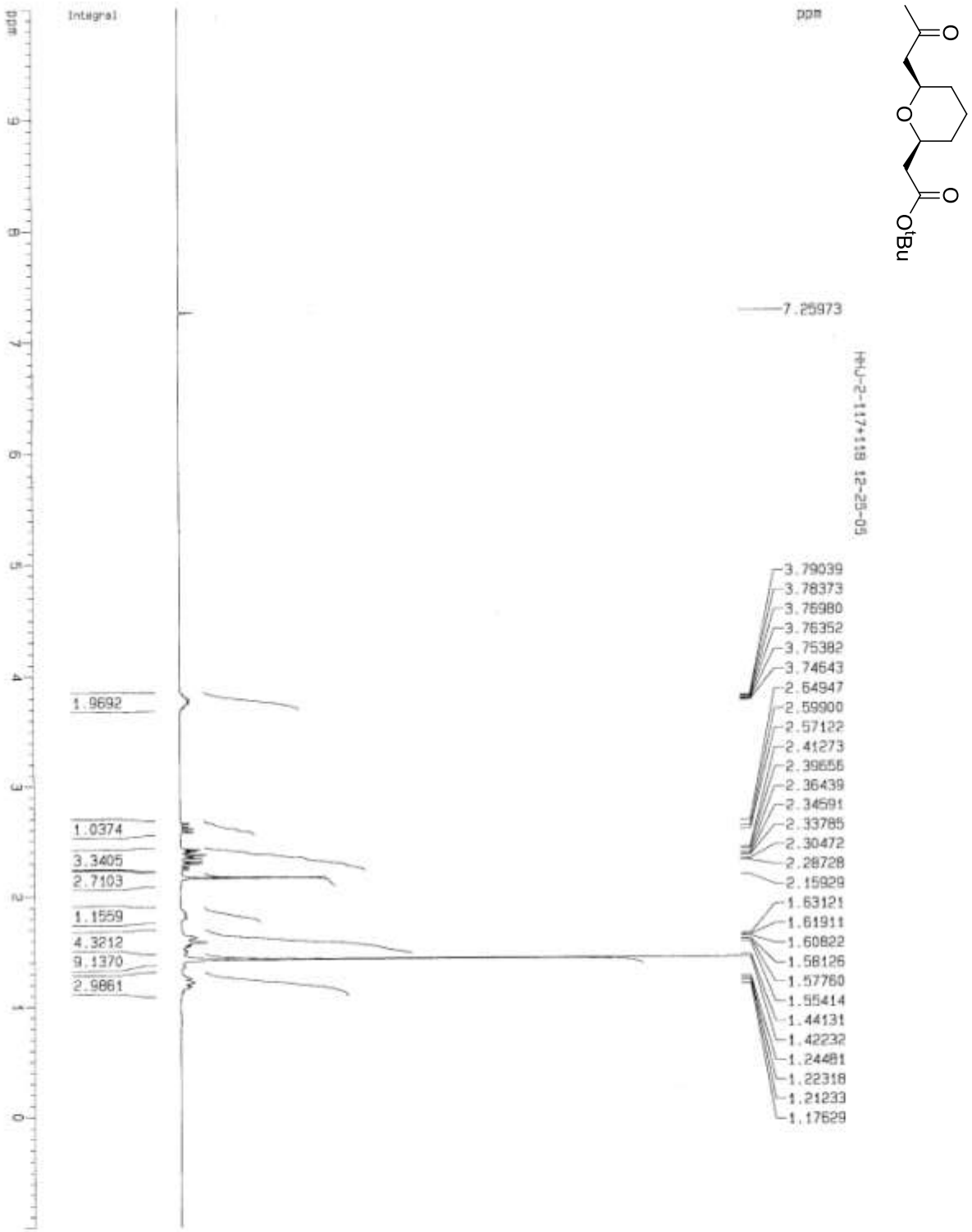

ppm
204.815
128.371
128.050
127.729
127.448
127.177
72.837
68.987
62.911
55.605
50.079
35.699
30.333
29.899
OMe
HHJ-2-92-minor [C6D6] 01-15-06

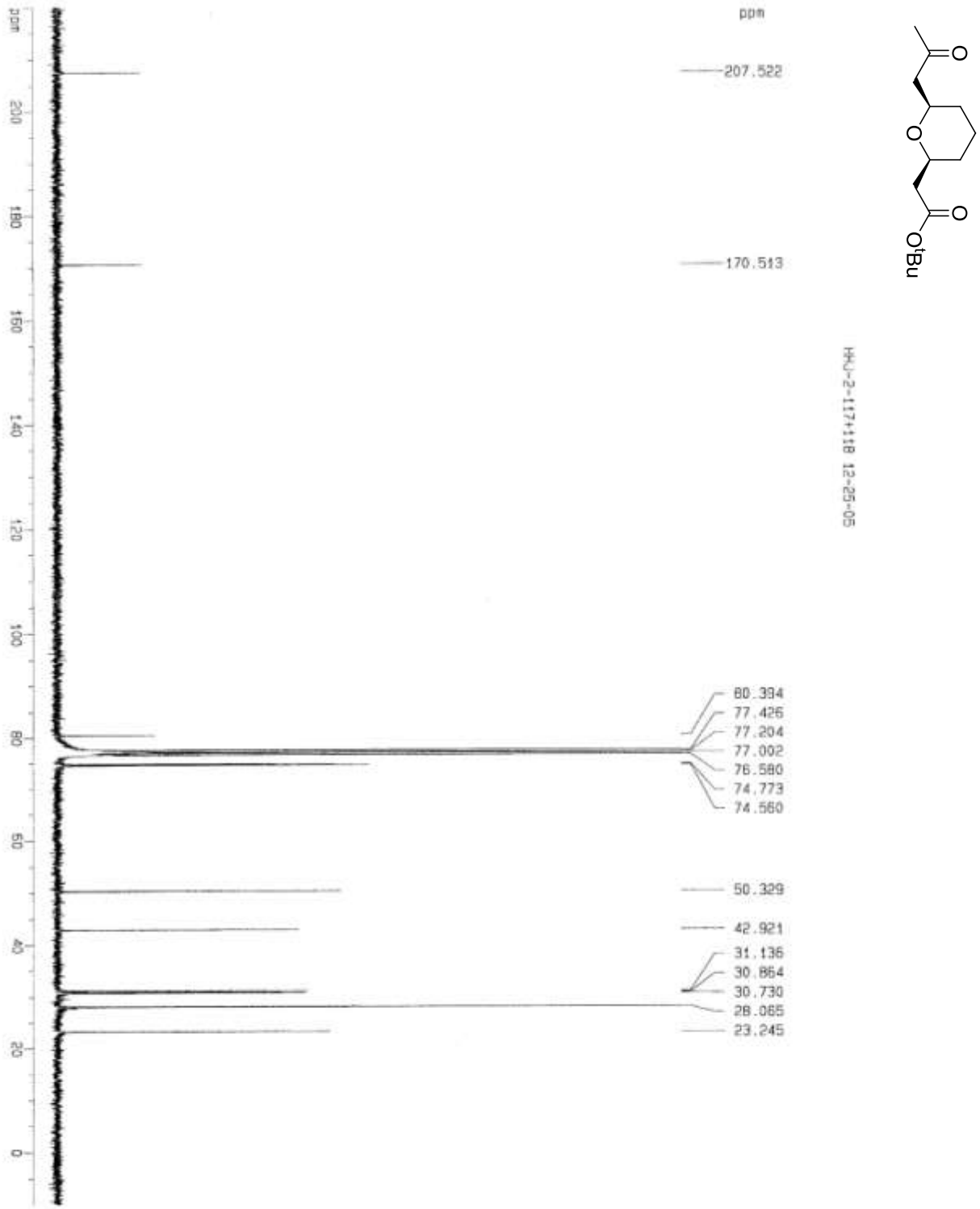

Integral
ppm
7.26005
HHJ-2-138 01-03-06
4.41600
4.39270
4.22664
4.20419
4.18373
4.08317
3.96549
3.96256
3.94175
2.81024
2.75707
2.73424
2.72279
2.59796
2.57800
2.55592
2.53632
2.18196
2.05388
2.03502
2.01828
1.99501
1.53197
1.50945
1.50203
1.49574
1.49152
1.48727
1.47896
1.47729
1.23198
1.21223
1.19259
1.000
1.233
1.110
1.242
2.575
2.655
12.716
5.520
8.281

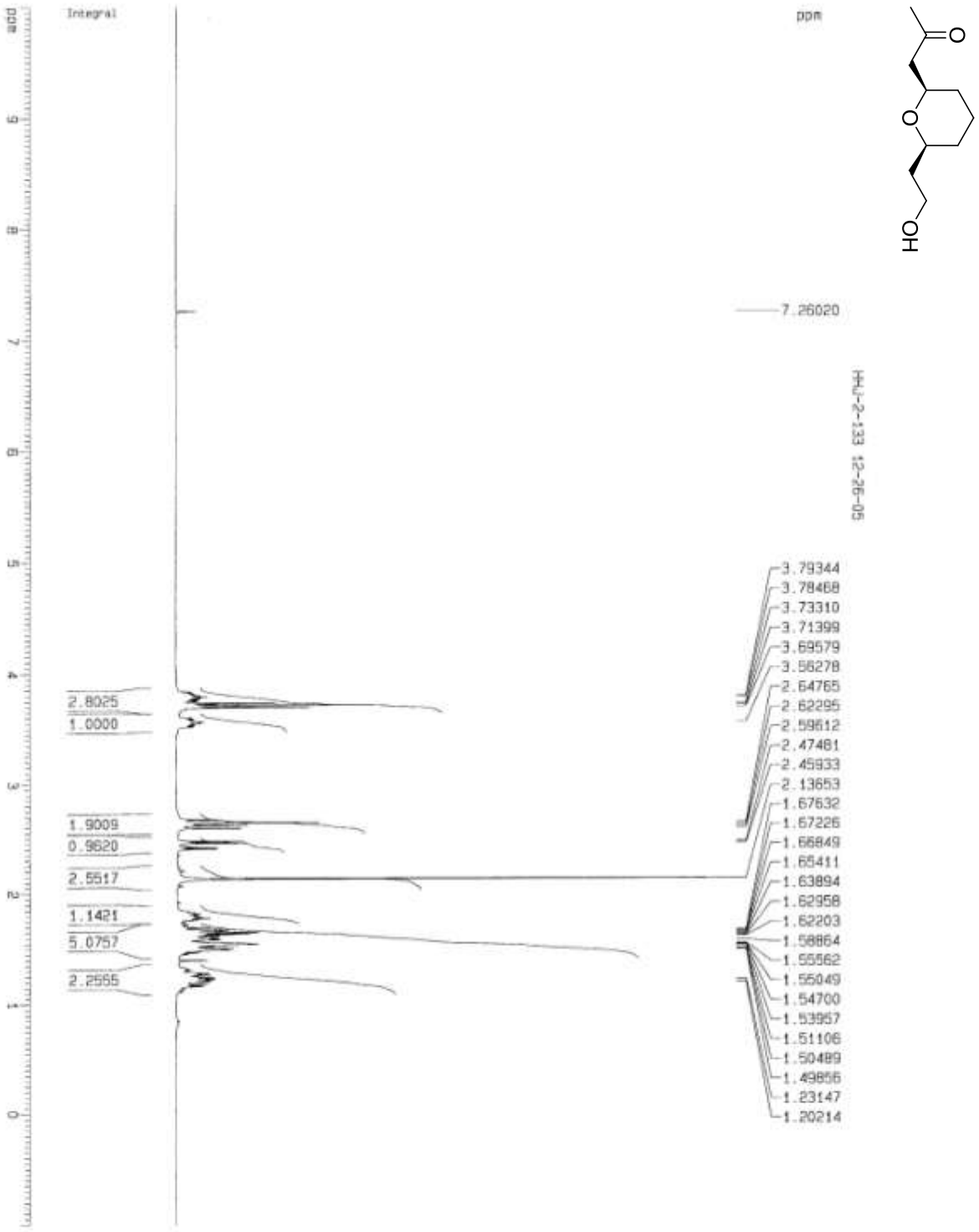

ppm
207.365
77.424
77.206
77.001
76.579
75.500
75.085
74.813
74.453
50.197
50.015
33.644
32.694
32.424
31.454
30.724
30.670
21.381
21.244
HHu-2-138 (rest after isolating a major) 01-06-06

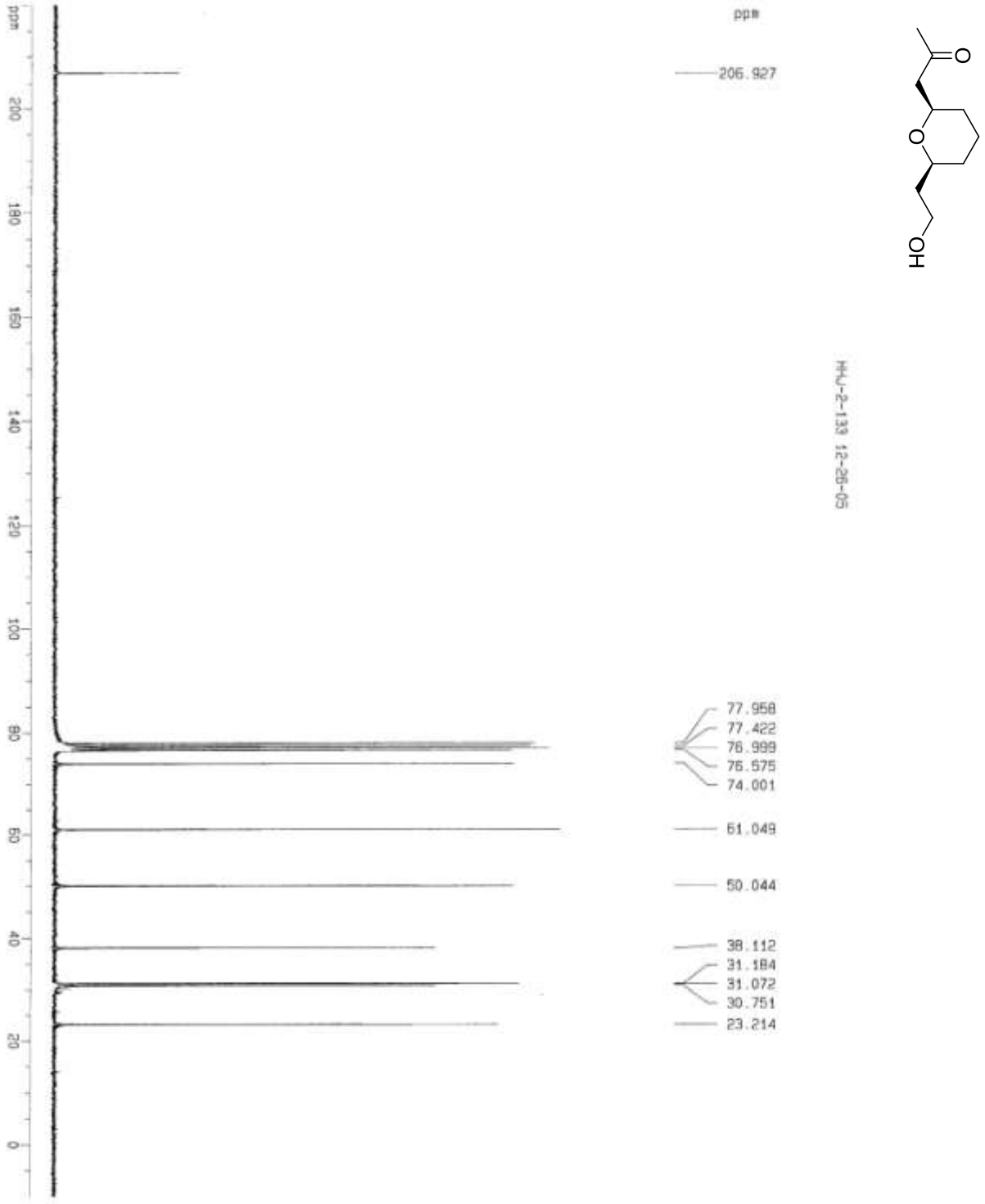

Integral
ppm
7.25983
HHJ-2-112-2 12-03-05
3.78835
3.78169
3.77792
3.77189
3.76142
3.65618
2.66135
2.61077
2.58335
2.48149
2.45445
2.42490
2.41411
2.40949
2.39678
2.37435
2.35886
2.15053
1.64233
1.62859
1.61470
1.60869
1.60216
1.59865
1.58690
1.24800
1.23204
1.22308
1.20894
2.0000
2.7372
1.0235
3.1431
2.6252
1.0842
3.6407
3.2650
O
O
O
OMe

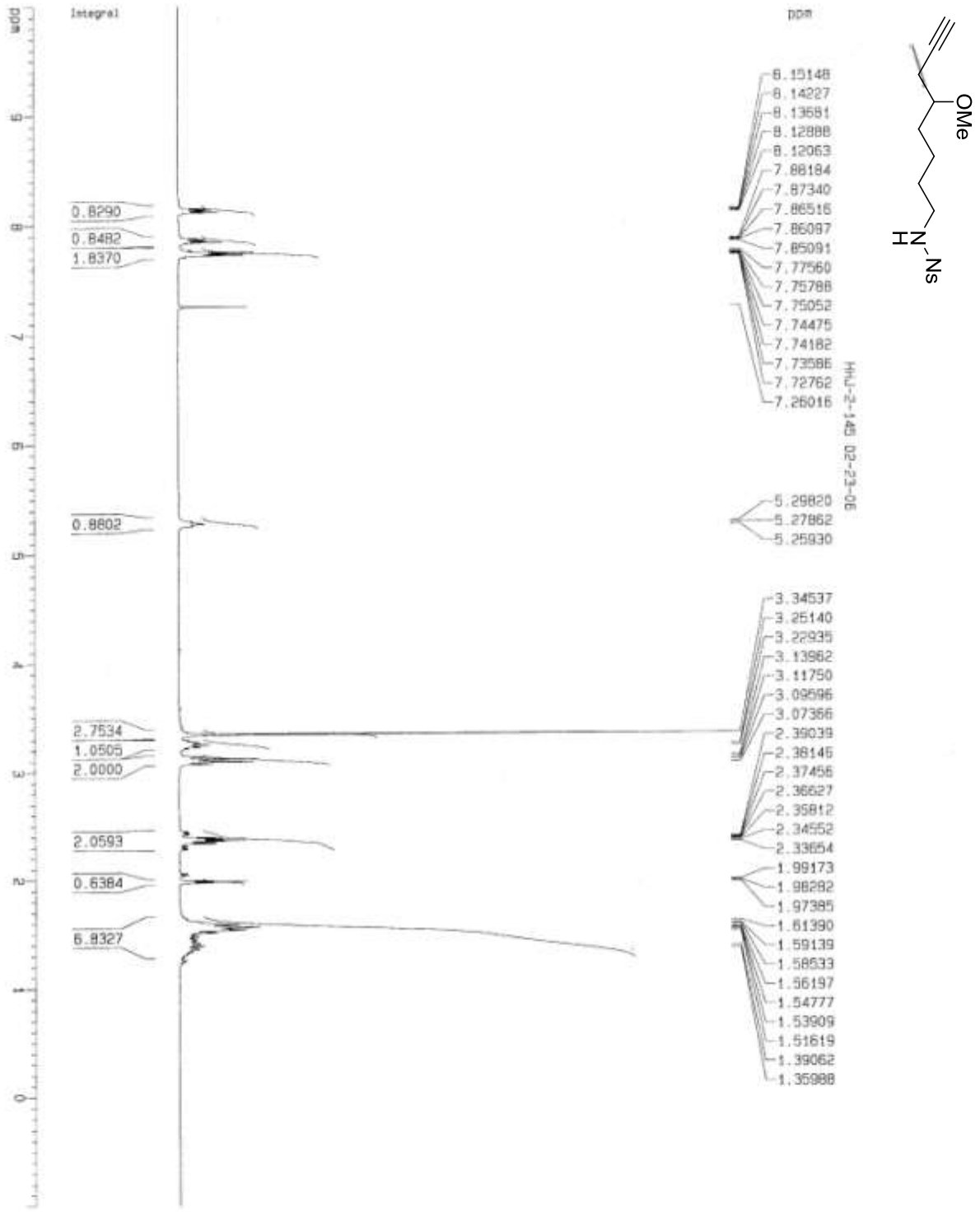

ppm
207.450
171.628
77.423
77.000
76.578
74.587
74.505
51.494
50.284
41.457
31.038
30.769
30.655
23.150
HHJ-2-121 (major) 12-23-05
OMe

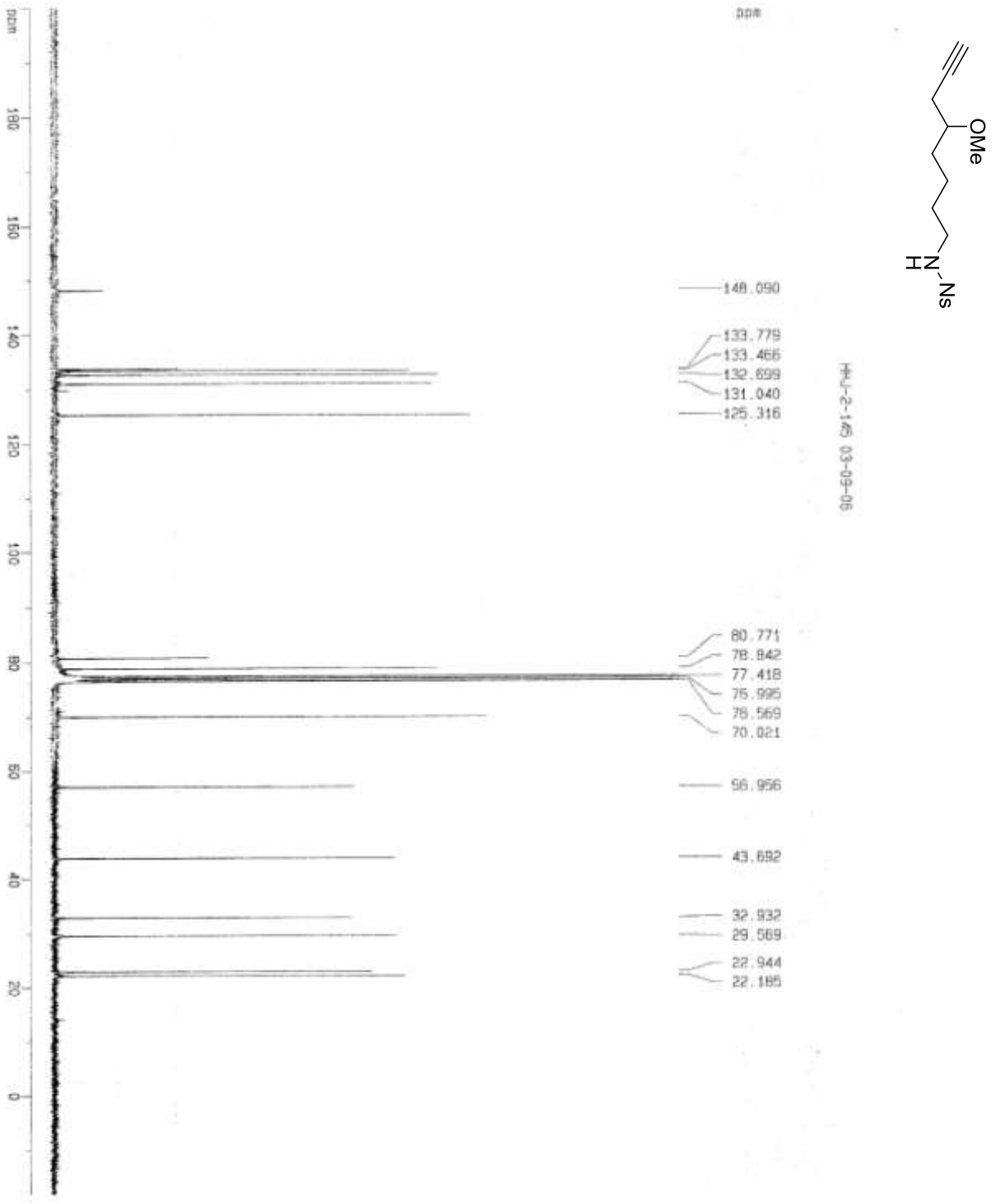

Integral
ppm
7.25973
HHJ-2-117+118 12-25-05
3.79039
3.78373
3.76980
3.76352
3.75382
3.74643
2.64947
2.59900
2.57122
2.41273
2.39656
2.36439
2.34591
2.33785
2.30472
2.28728
2.15929
1.63121
1.61911
1.60822
1.58126
1.57760
1.55414
1.44131
1.42232
1.24481
1.22318
1.21233
1.17629
1.9892
1.0374
3.3405
2.7103
1.1559
4.3212
9.1370
2.9861
OtBu

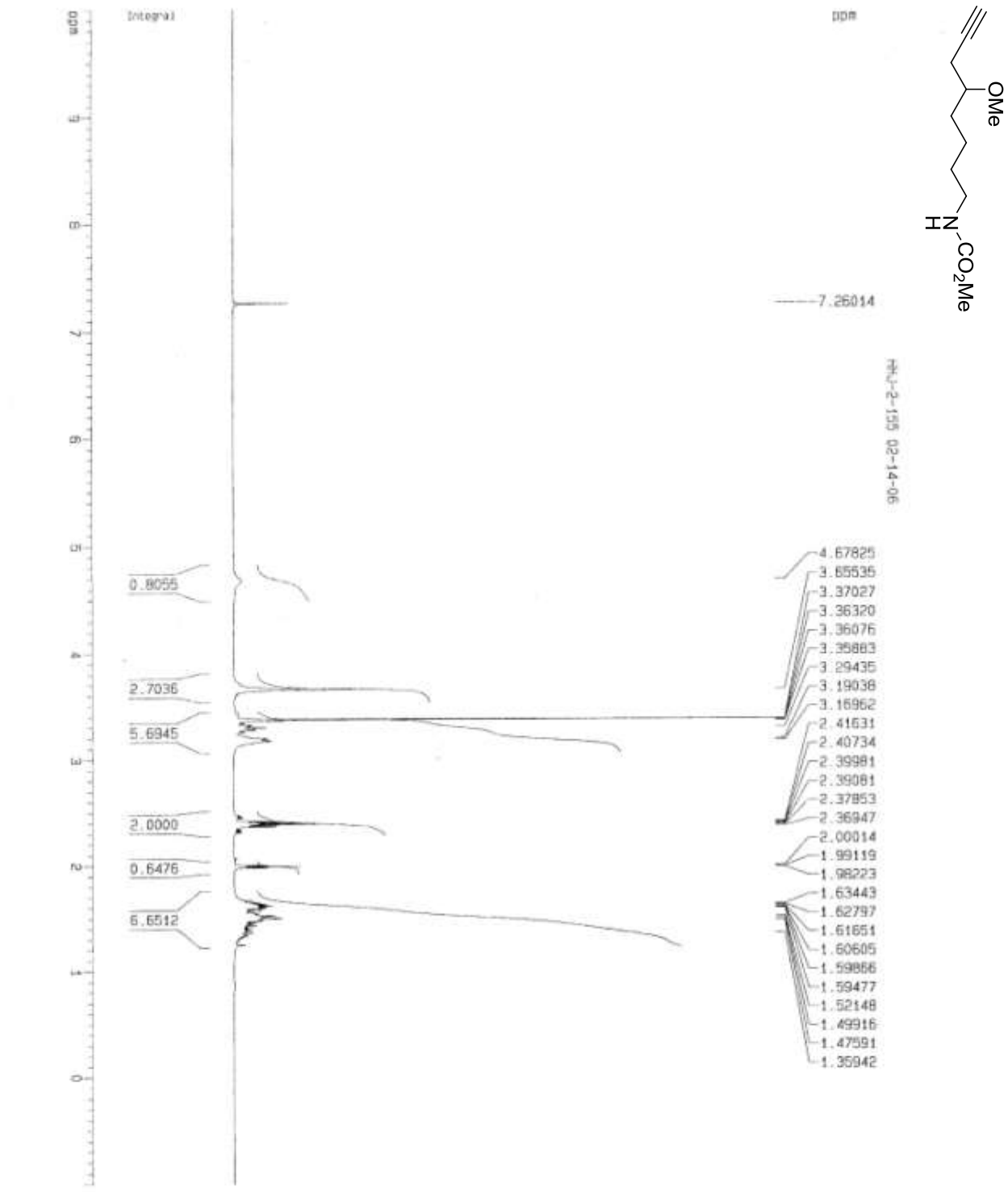

ppm
207.522
170.513
80.394
77.426
77.204
77.002
76.580
74.773
74.560
50.329
42.921
31.136
30.864
30.730
28.065
23.245
HHJ-2-117-11B 12-25-05
O
O
O
O
tBu

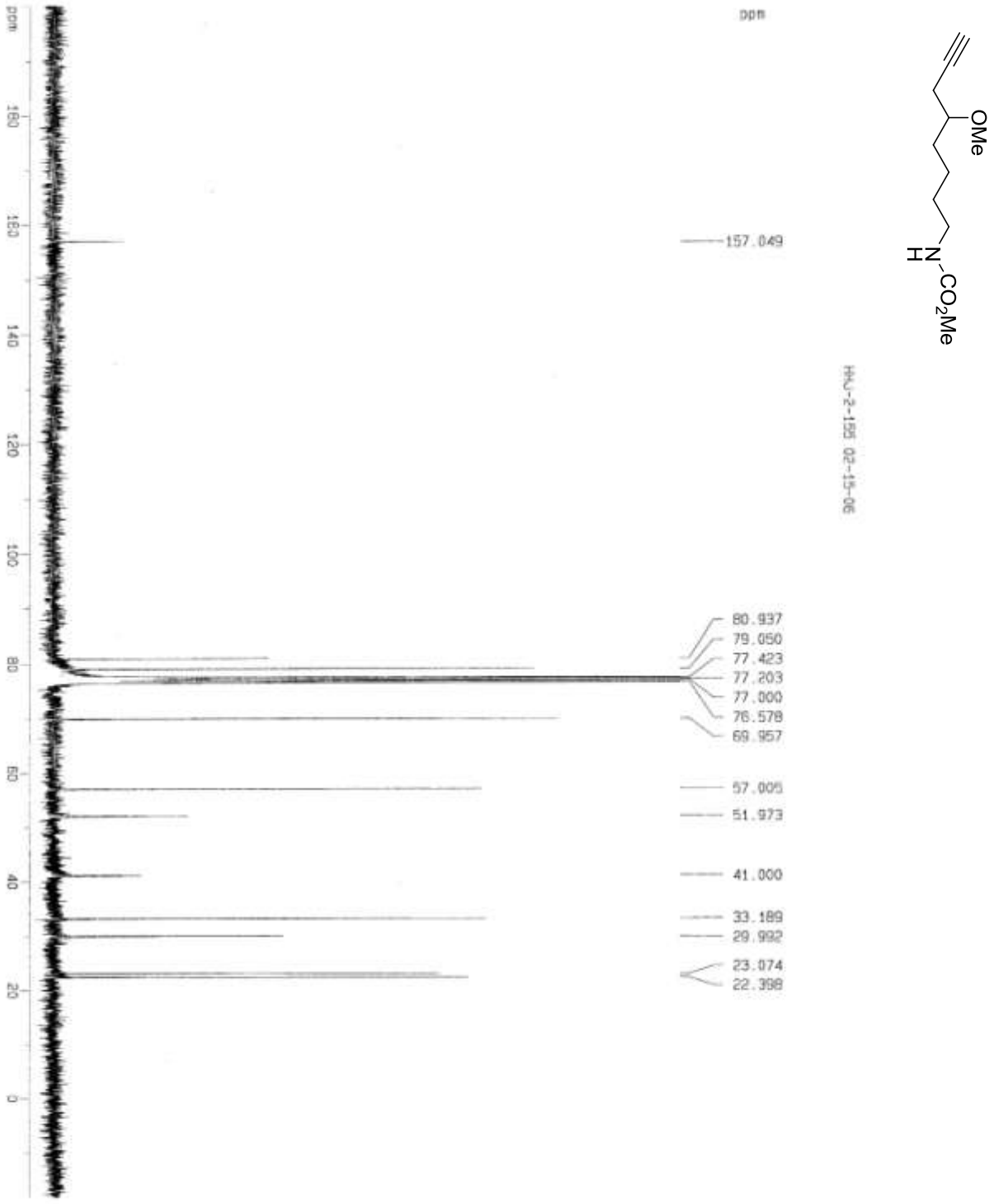

Integral
ppm
7.26020
HHJ-2-133 12-26-05
3.79344
3.78468
3.73310
3.71399
3.69579
3.56278
2.64765
2.62295
2.59612
2.47481
2.45933
2.13653
1.67632
1.67226
1.66849
1.65411
1.63894
1.62958
1.62203
1.58864
1.55562
1.55049
1.54700
1.53957
1.51106
1.50489
1.49856
1.23147
1.20214
2.8025
1.0000
1.9009
0.9620
2.5517
1.1421
5.0757
2.2555
O
O
OH

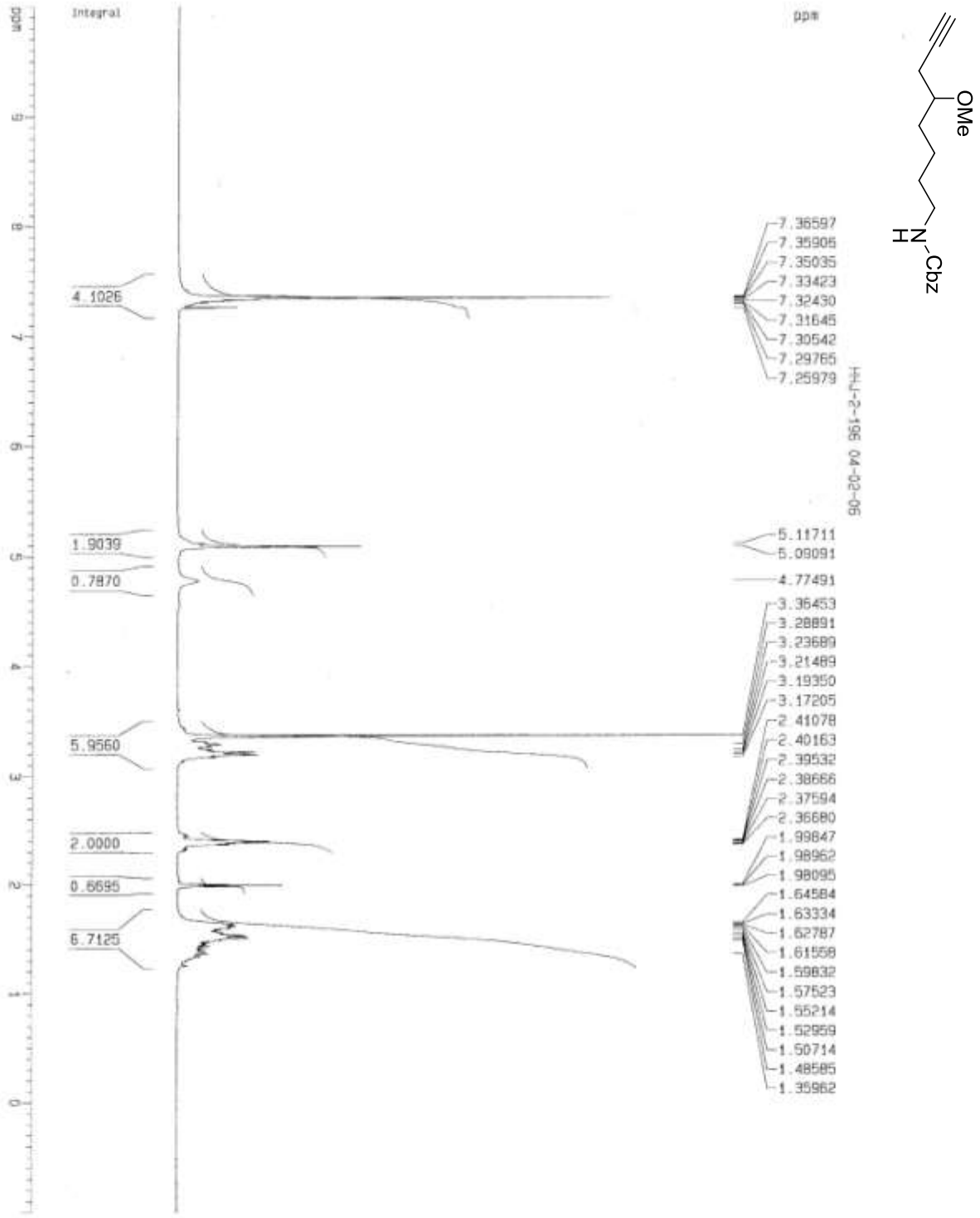

ppm
206.927
77.958
77.422
76.999
76.575
74.001
61.049
50.044
38.112
31.184
31.072
30.751
23.214
HHJ-2-133 12-26-05
O
O
HO

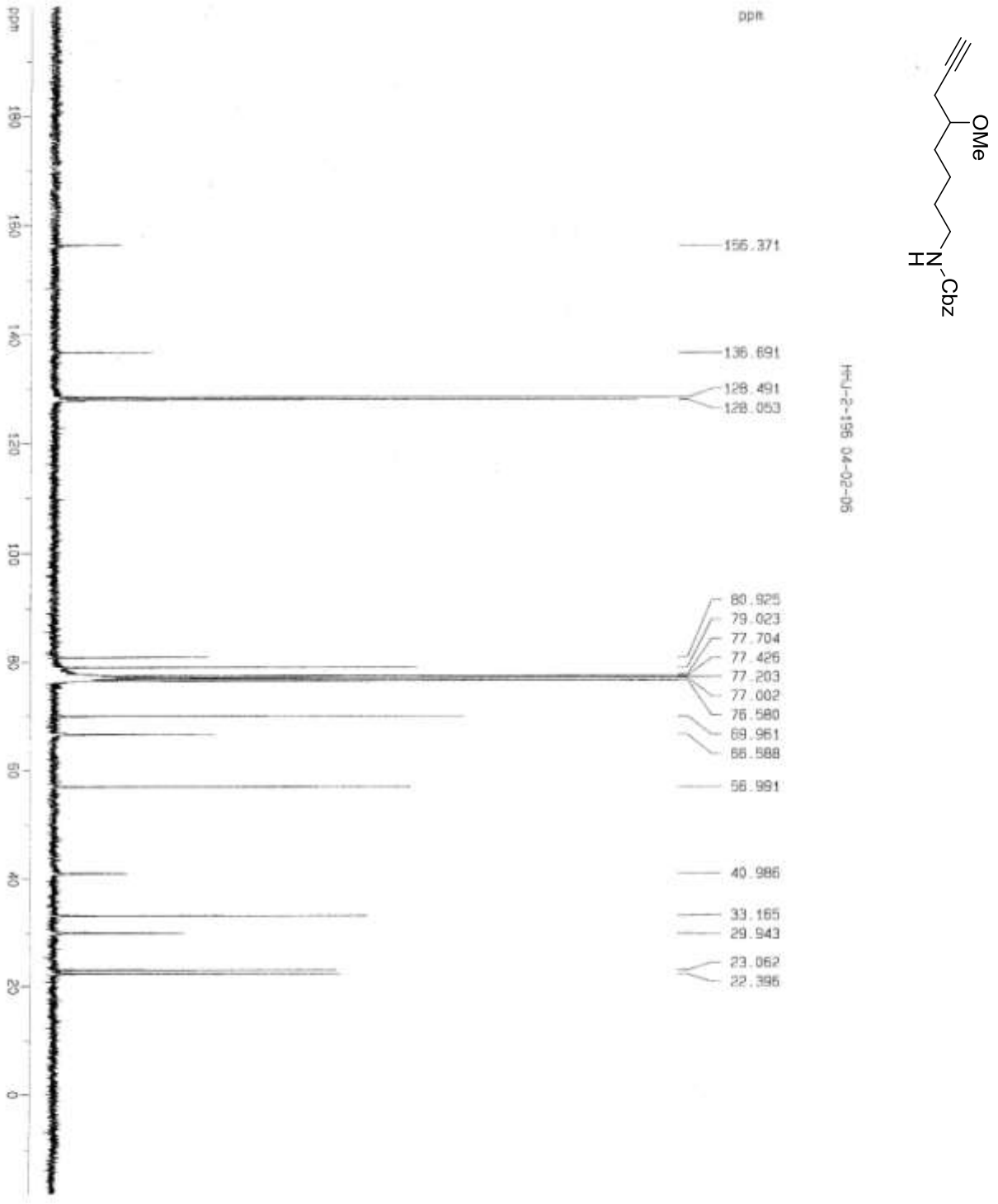

Integral
ppm
0.8290
0.8482
1.8370
0.8802
2.7534
1.0505
2.0000
2.0593
0.6384
6.8327
8.15148
8.14227
8.13681
8.12888
8.12063
7.88184
7.87340
7.86516
7.86087
7.85091
7.77560
7.75788
7.75052
7.74475
7.74182
7.73586
7.72762
7.26016
5.29820
5.27862
5.25930
3.34537
3.26140
3.22935
3.13962
3.11750
3.09596
3.07366
2.39039
2.38146
2.37456
2.36627
2.35812
2.34552
2.33654
1.99173
1.98282
1.97385
1.61390
1.59139
1.58533
1.56197
1.54777
1.53909
1.51619
1.39062
1.35988
HHJ-2-148 D2-23-06
OMe
H
N
Ns

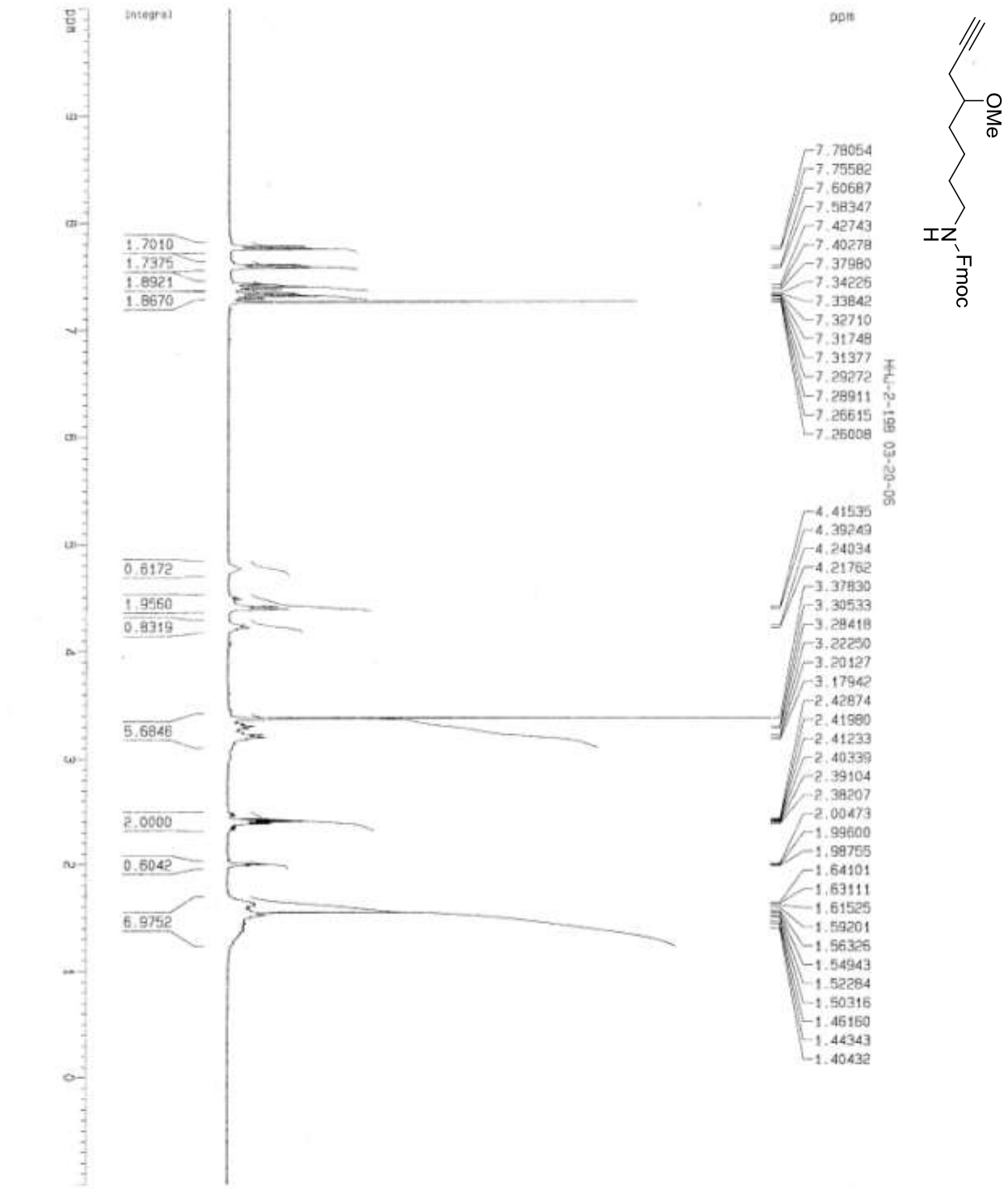

OMe
N
H
Ns
ppm
148.090
133.779
133.466
132.699
131.040
125.316
80.771
78.842
77.418
76.995
76.569
70.021
56.956
43.692
32.932
29.569
22.944
22.185
HE-2-149 03-09-06

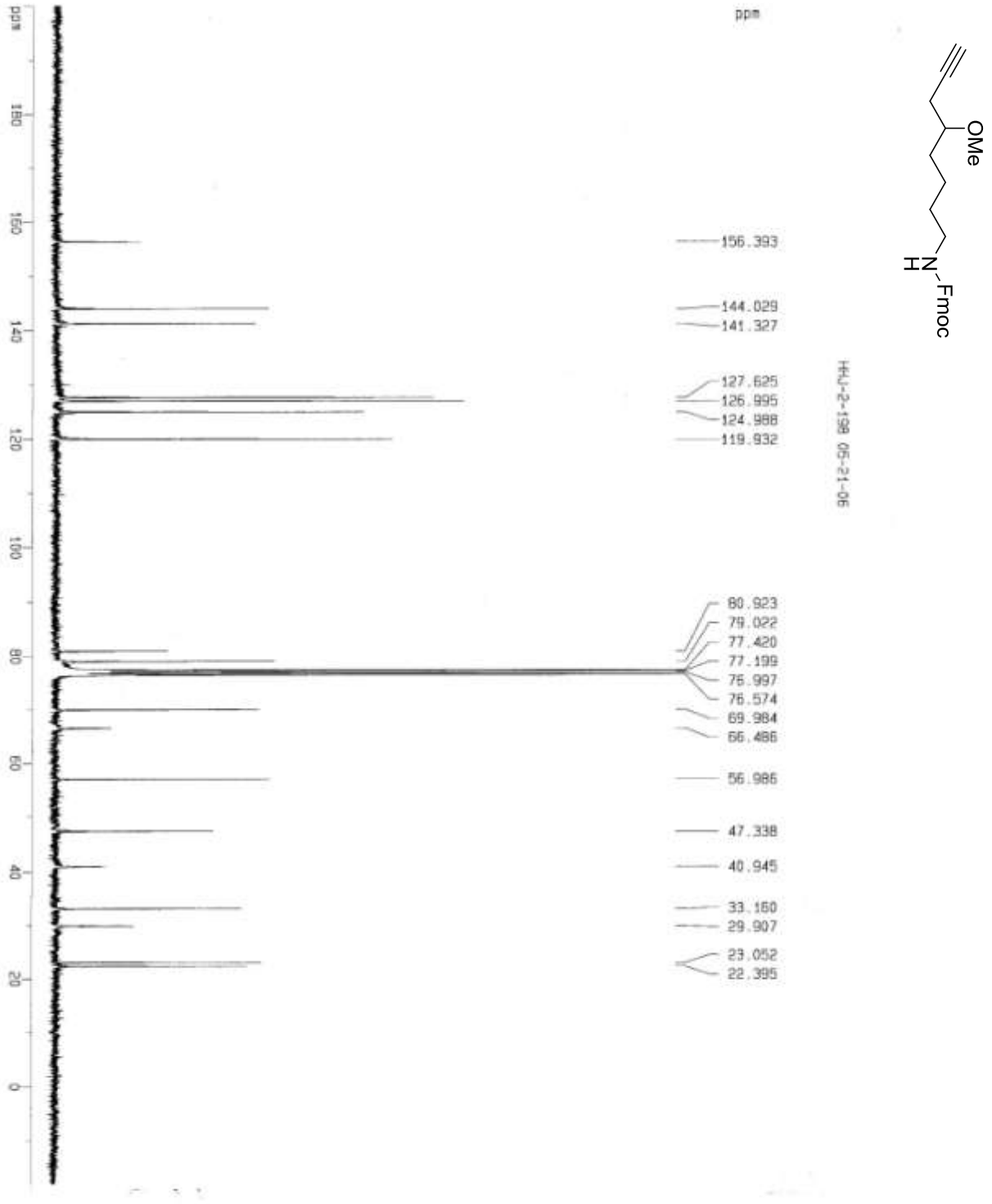

Integral
ppm
7.26014
4.67825
3.65535
3.37027
3.36320
3.36076
3.35883
3.29435
3.19038
3.16962
2.41631
2.40734
2.39981
2.39081
2.37853
2.36947
2.00014
1.99119
1.98223
1.63443
1.62797
1.61651
1.60605
1.59866
1.59477
1.52148
1.49916
1.47591
1.35942
0.8055
2.7036
5.6945
2.0000
0.6476
6.6512
HNJ-2-155 02-14-06
OMe
N
H
CO2Me

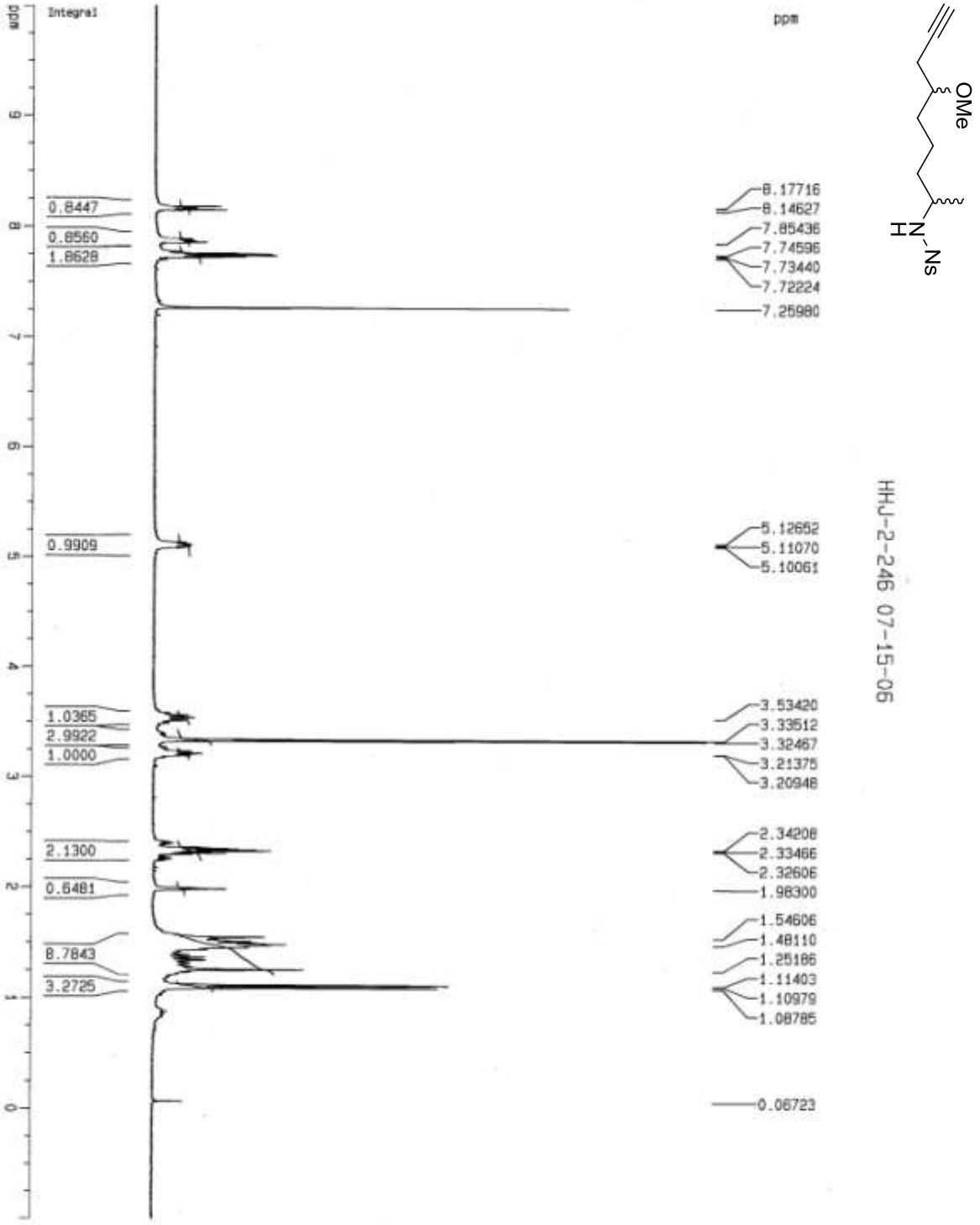

ppm
180
160
140
120
100
80
60
40
20
0
157.049
80.937
79.050
77.423
77.203
77.000
76.578
69.957
57.005
51.973
41.000
33.189
29.992
23.074
22.398
OMe
N
H
CO2Me
HAU-2-155 02-15-06

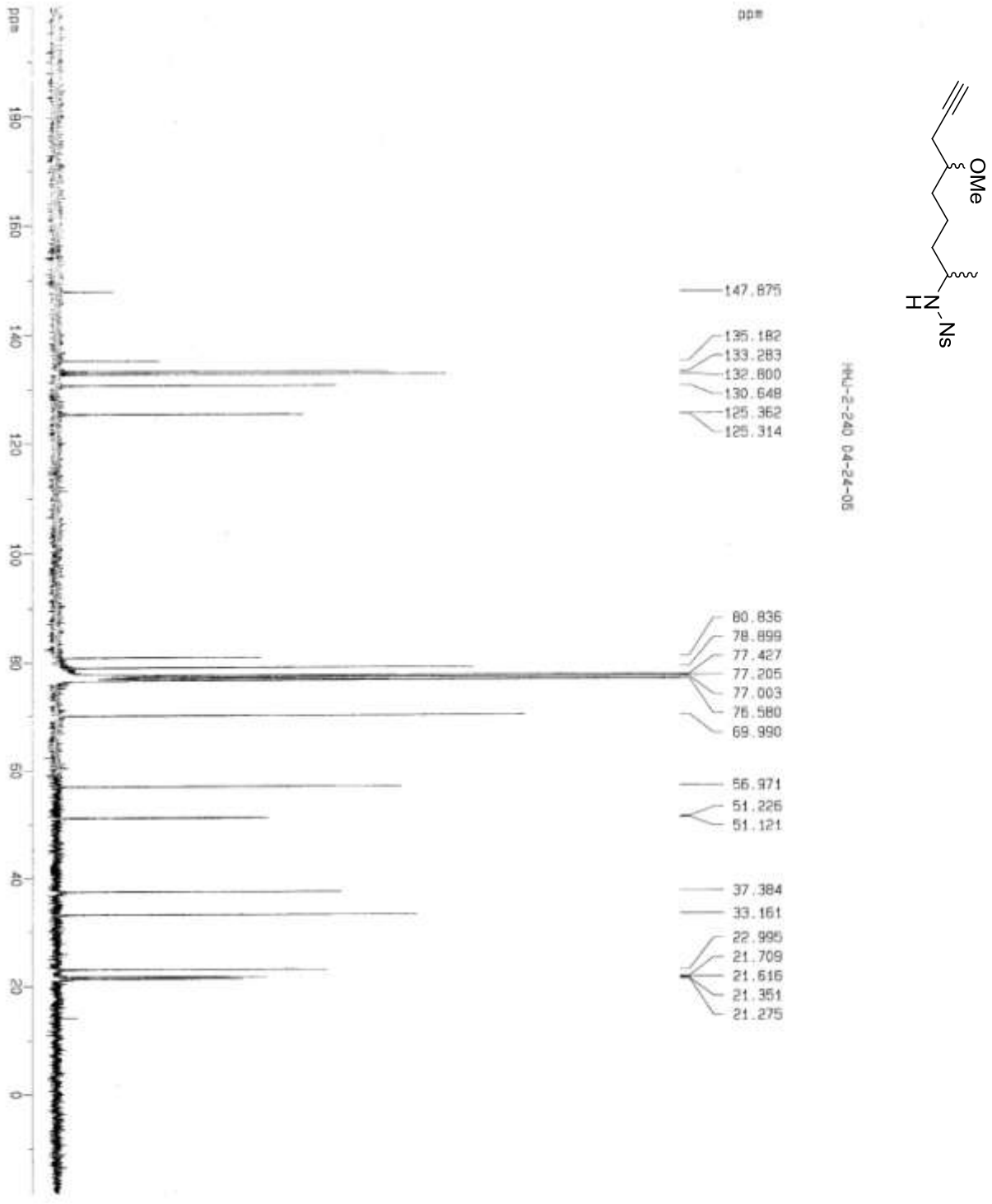

Integral
ppm
4.1026
1.9039
0.7870
5.9560
2.0000
0.6695
6.7125
7.36597
7.35905
7.35035
7.33423
7.32430
7.31645
7.30542
7.29765
7.25979
5.11711
5.09091
4.77491
3.36453
3.28891
3.23689
3.21489
3.19350
3.17205
2.41078
2.40163
2.39532
2.38666
2.37594
2.36680
1.99847
1.98962
1.98095
1.64584
1.63334
1.62787
1.61558
1.59832
1.57523
1.55214
1.52959
1.50714
1.48585
1.35962
HH-2-196 04-20-06
OMe
H
N
Cbz

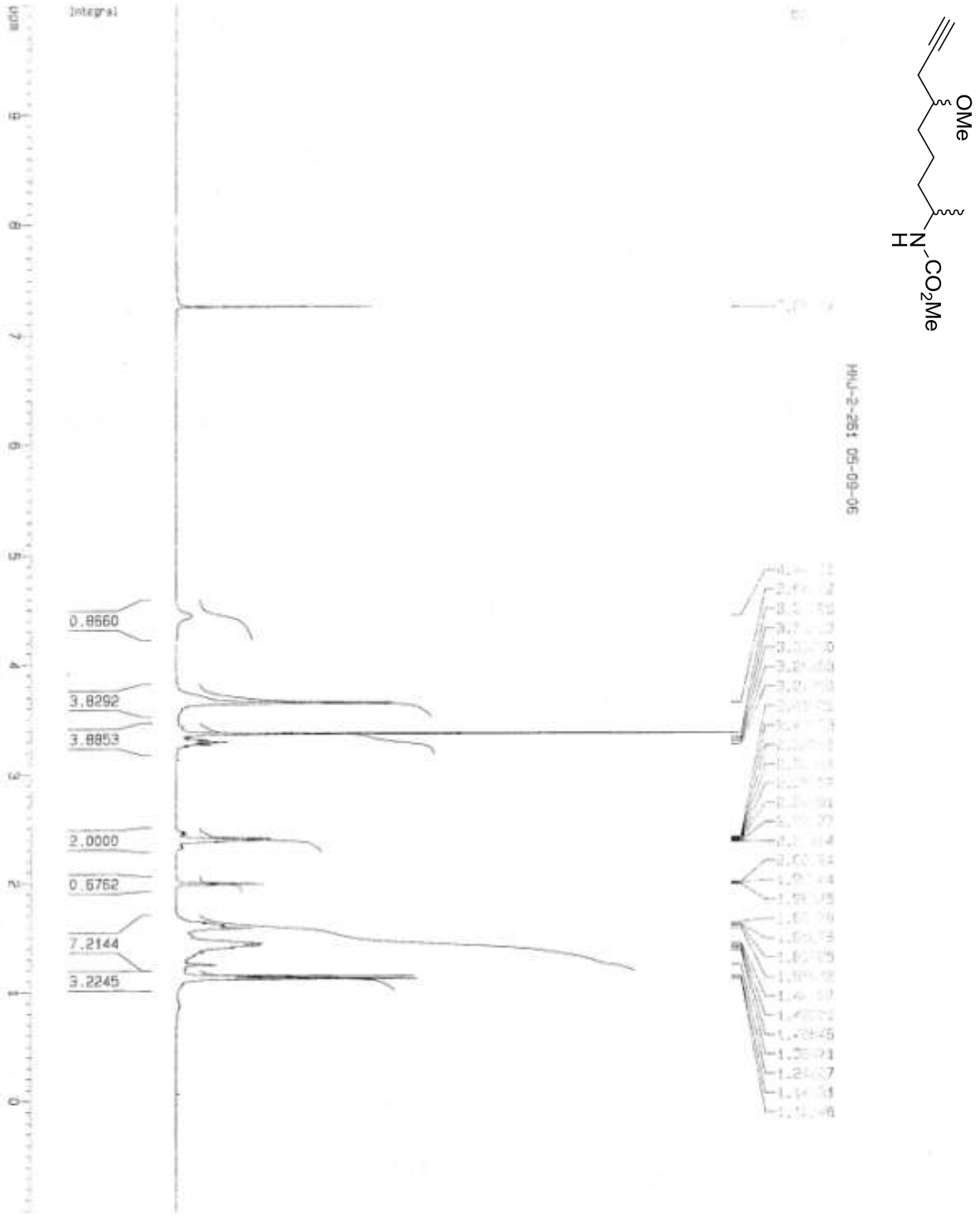

ppm
180
160
140
120
100
80
60
40
20
0
156.371
136.691
128.491
128.053
80.925
79.023
77.704
77.426
77.203
77.002
76.580
69.961
66.588
56.991
40.986
33.165
29.943
23.062
22.396
OMe
N
H
Cbz
HHJ-2-156 04-02-06

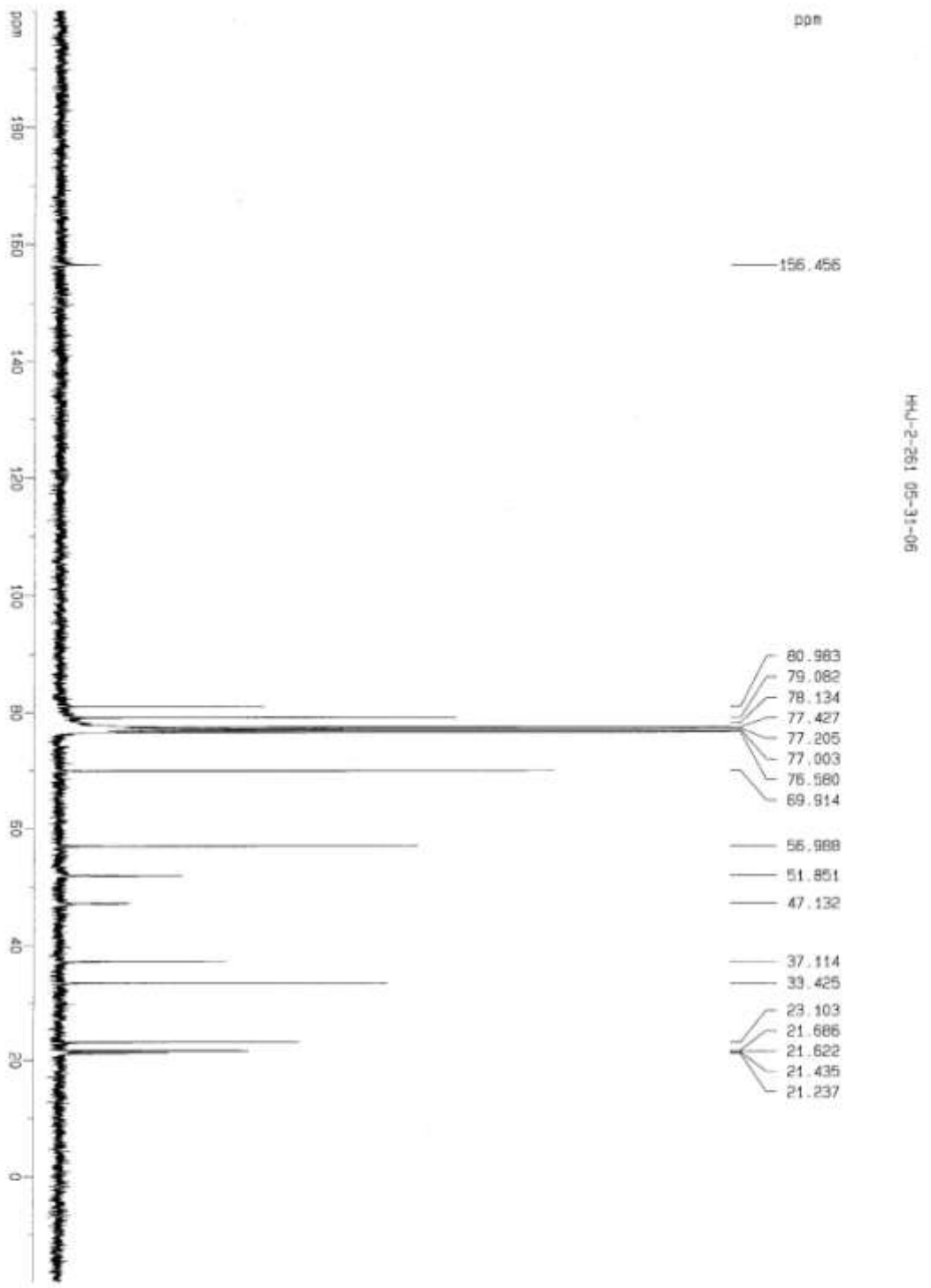

integral
ppm
1.7010
1.7375
1.8921
1.8670
0.6172
1.9560
0.8319
5.6846
2.0000
0.6042
6.9752
7.78054
7.75582
7.60687
7.58347
7.42743
7.40278
7.37980
7.34225
7.33842
7.32710
7.31748
7.31377
7.29272
7.28911
7.26615
7.26008
4.41535
4.39249
4.24034
4.21762
3.37830
3.30533
3.28418
3.22250
3.20127
3.17942
2.42874
2.41980
2.41233
2.40339
2.39104
2.38207
2.00473
1.99600
1.98755
1.64101
1.63111
1.61525
1.59201
1.56326
1.54943
1.52284
1.50316
1.46160
1.44343
1.40432
HH-2-199 03-20-06
OMe
N
H
Fmoc

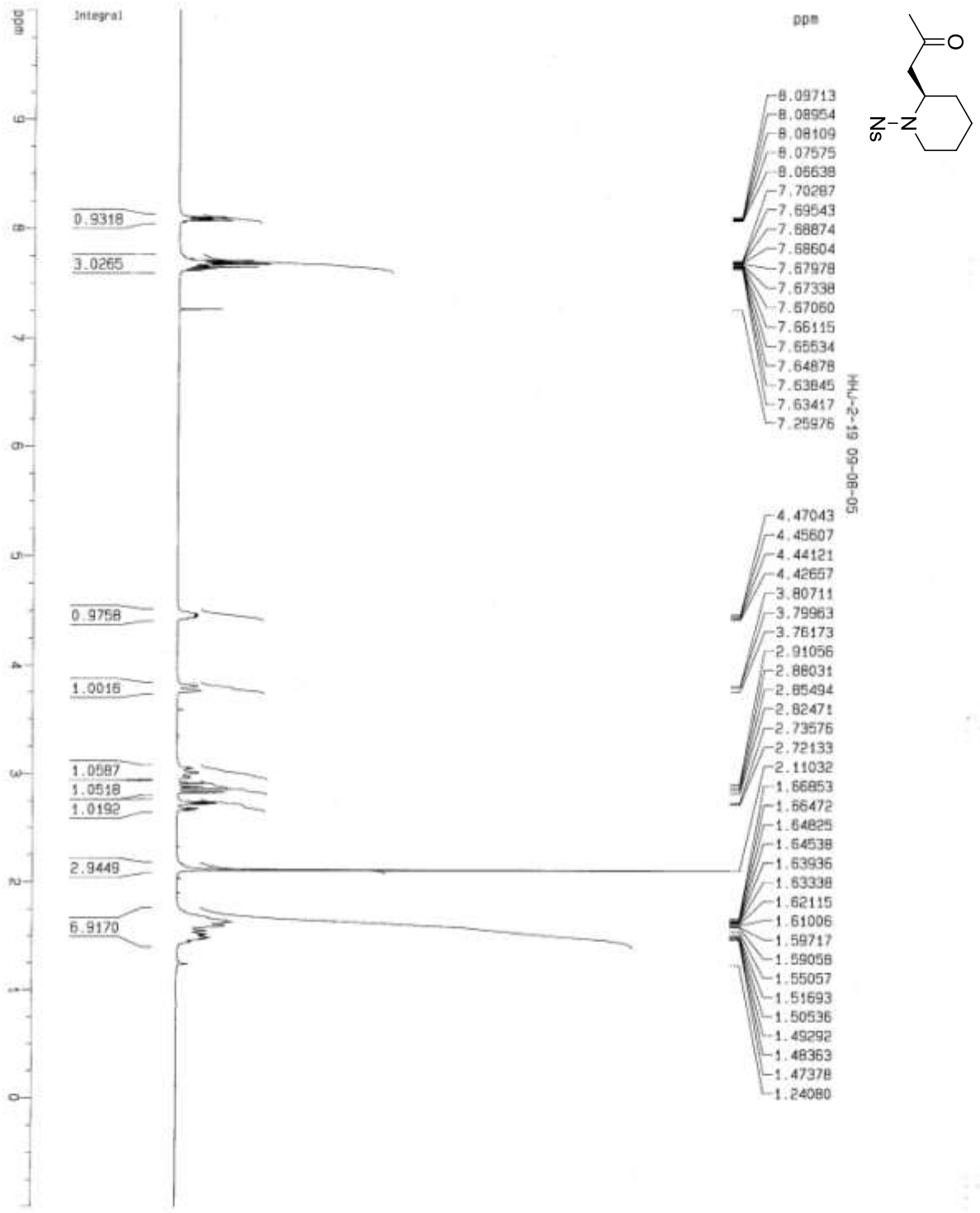

ppm
156.393
144.029
141.327
127.625
126.995
124.988
119.932
80.923
79.022
77.420
77.199
76.997
76.574
69.984
66.486
56.986
47.338
40.945
33.160
29.907
23.052
22.395
HHJ-2-198 05-21-06
OMe
N
H
Fmoc

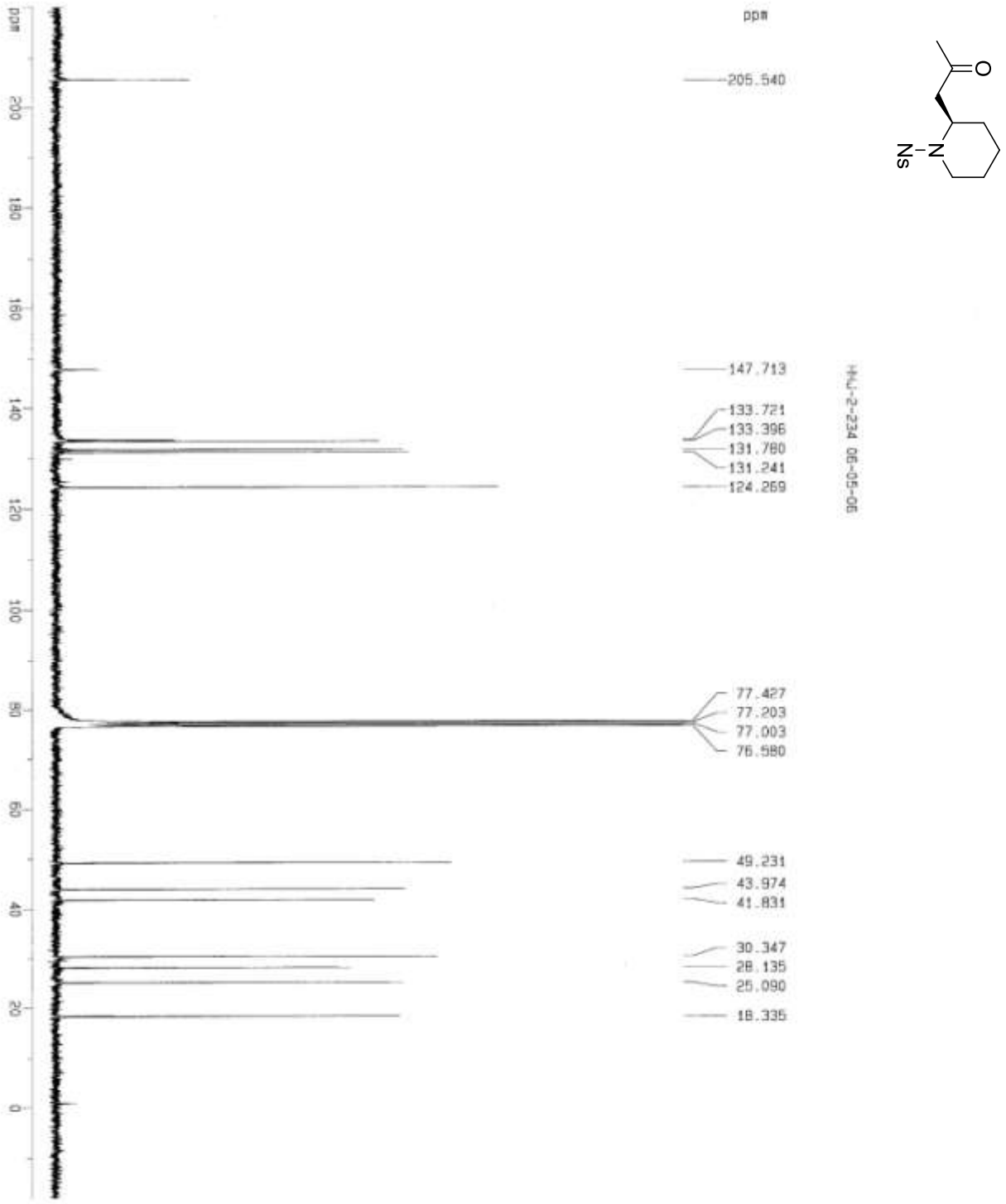

Integral
ppm
0.8447
0.8560
1.8628
0.9909
1.0365
2.9922
1.0000
2.1300
0.6481
8.7843
3.2725
8.17716
8.14627
7.85436
7.74596
7.73440
7.72224
7.25980
5.12652
5.11070
5.10061
3.53420
3.33512
3.32467
3.21375
3.20948
2.34208
2.33466
2.32606
1.98300
1.54606
1.48110
1.25186
1.11403
1.10979
1.08785
0.06723
OMe
N
H
Ns
HHJ-2-246 07-15-06

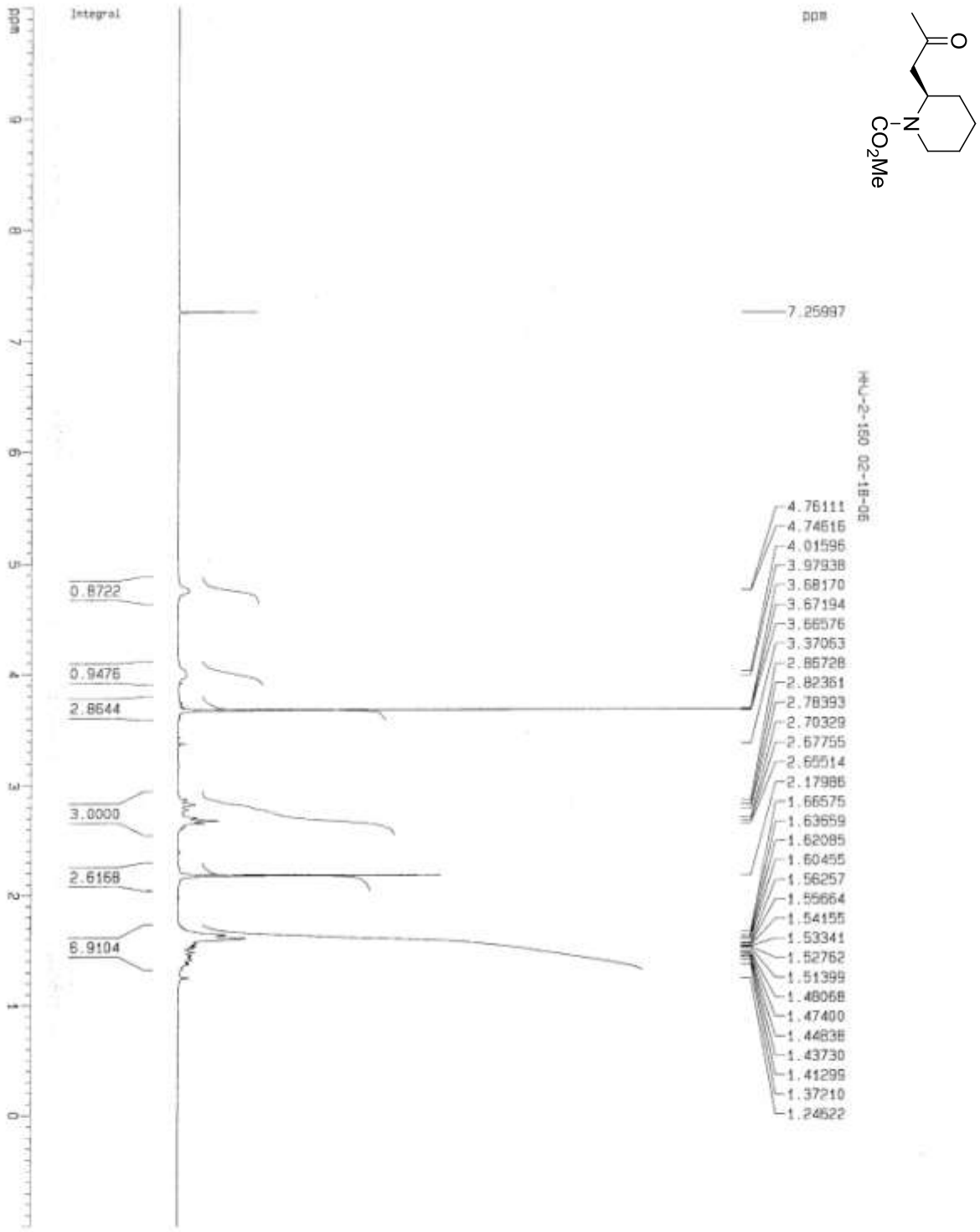

ppm
190
160
140
120
100
80
60
40
20
0
147.875
135.182
133.283
132.600
130.648
125.362
125.314
80.836
78.899
77.427
77.205
77.003
76.580
69.990
56.971
51.226
51.121
37.384
33.161
22.995
21.709
21.616
21.351
21.275
OMe
N
H
Ns
HHJ-2-240 04-24-06

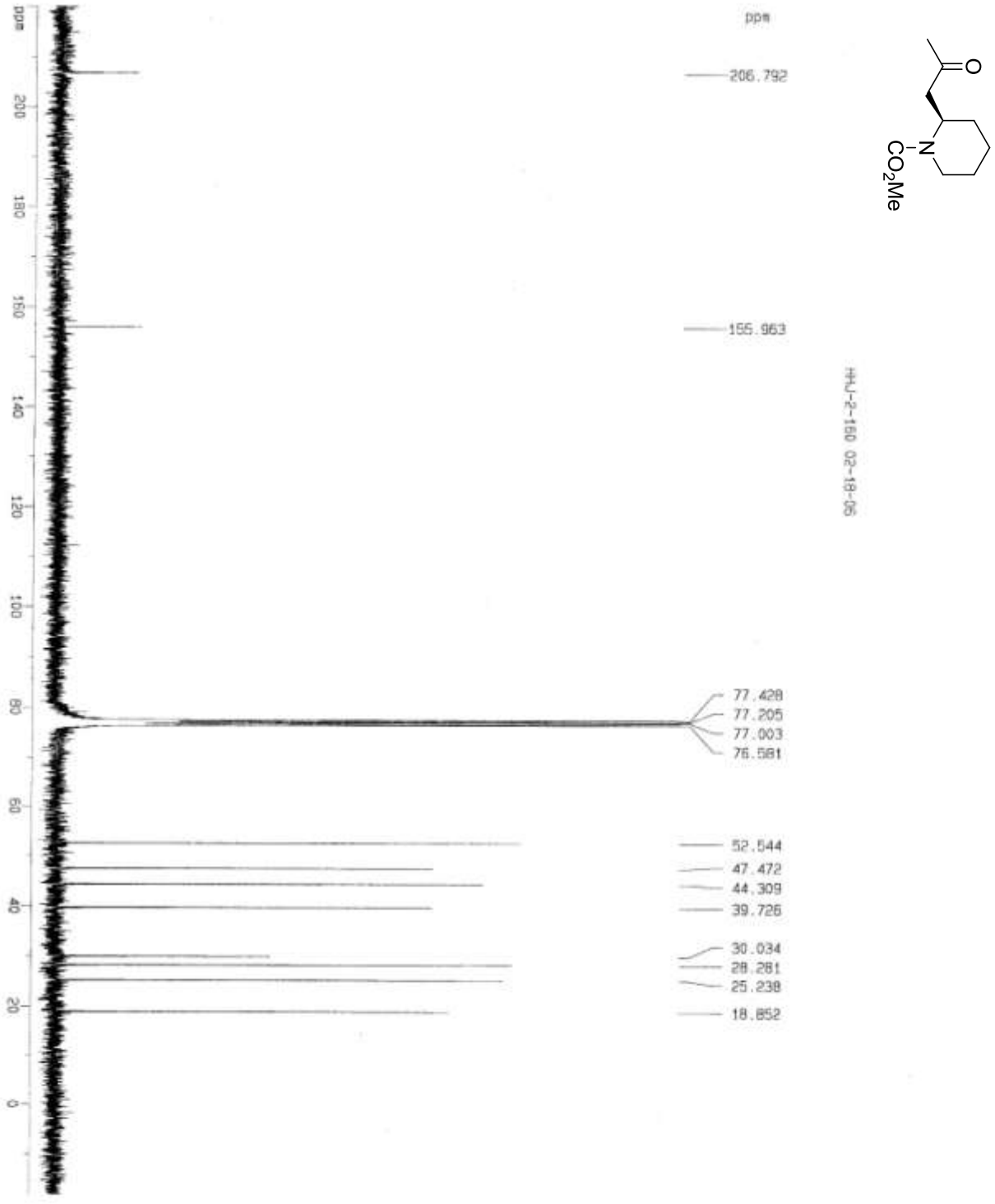

Integral
0.8660
3.8292
3.8853
2.0000
0.6762
7.2144
3.2245
HHJ-2-261 05-09-06
OMe
N
H
CO2Me

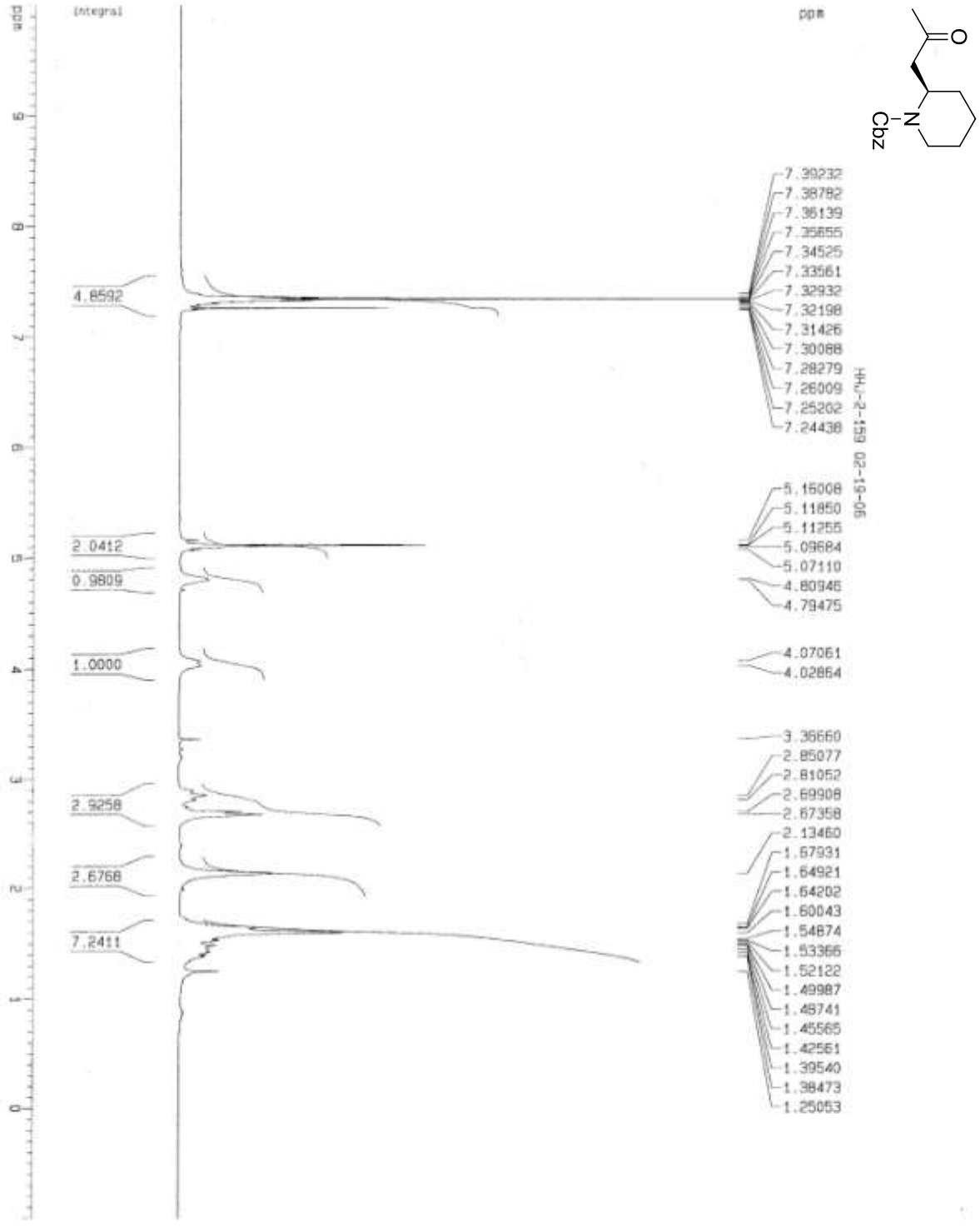

ppm
200
180
160
140
120
100
80
60
40
20
0
156.456
80.983
79.082
78.134
77.427
77.205
77.003
76.580
69.914
56.988
51.851
47.132
37.114
33.425
23.103
21.686
21.622
21.435
21.237
HHJ-2-261 05-31-06
OMe
N
H
CO2Me

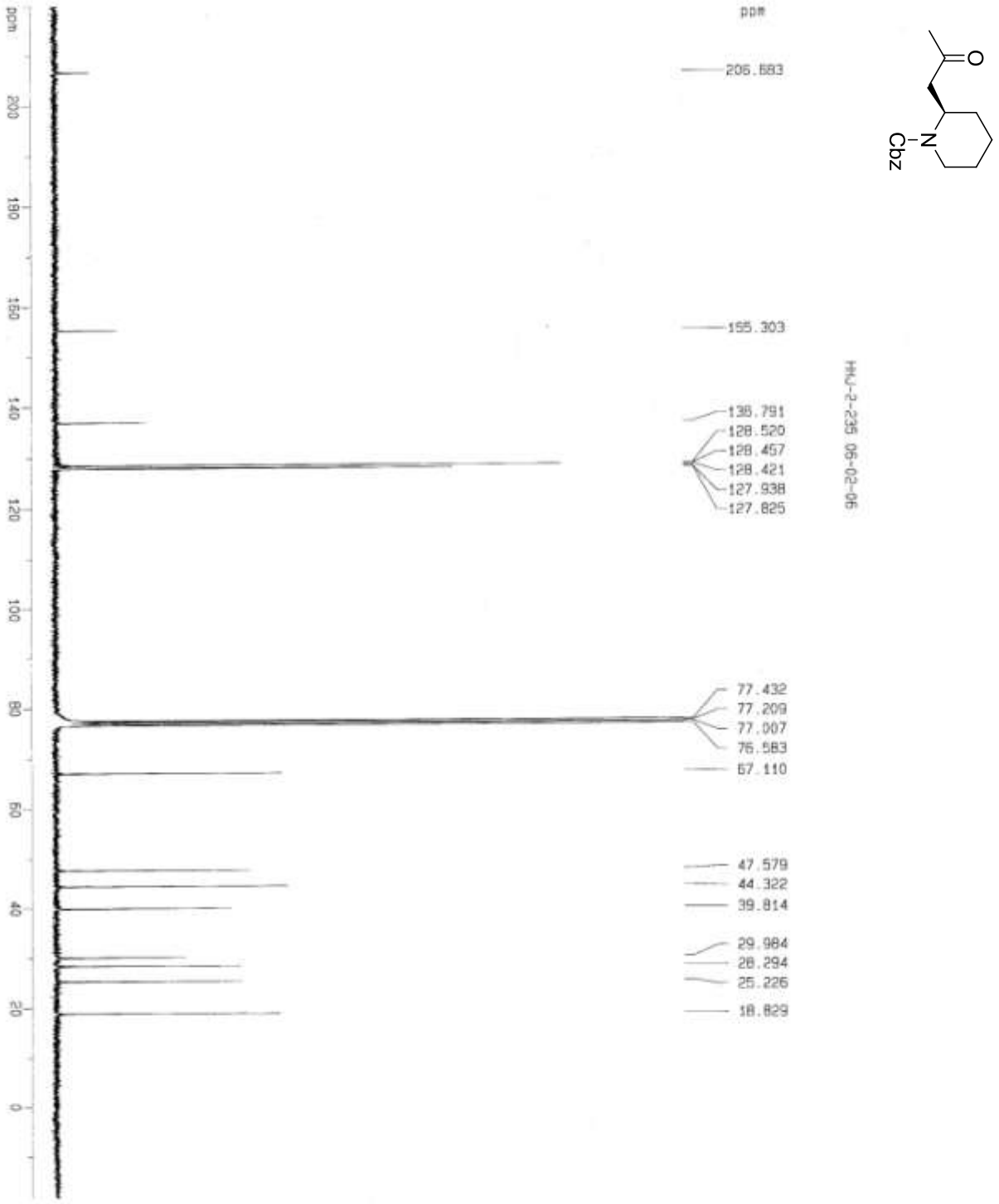

Integral
ppm
0.9318
3.0265
0.9758
1.0016
1.0587
1.0518
1.0192
2.9449
6.9170
8.09713
8.08954
8.08109
8.07575
8.05638
7.70287
7.69543
7.68874
7.68604
7.67978
7.67338
7.67060
7.66115
7.65534
7.64878
7.63845
7.63417
7.25976
4.47043
4.45607
4.44121
4.42657
3.80711
3.79983
3.76173
2.91056
2.88031
2.85494
2.82471
2.73576
2.72133
2.11032
1.66853
1.66472
1.64825
1.64538
1.63936
1.63338
1.62115
1.61006
1.59717
1.59058
1.55057
1.51693
1.50536
1.49292
1.48363
1.47378
1.24080
HH-2-19 09-08-05
O
N
N
Ns

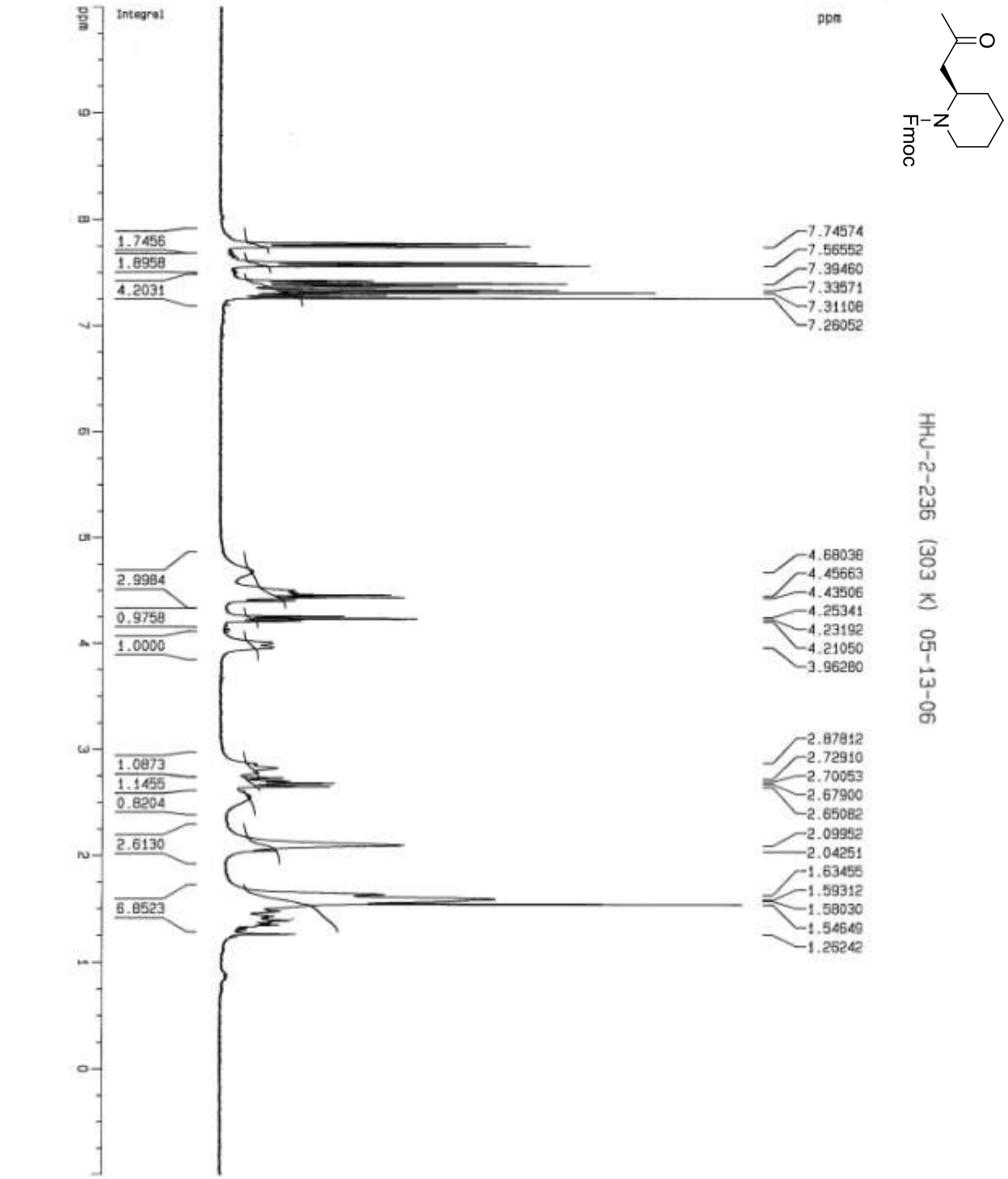

ppm
205.540
147.713
133.721
133.396
131.780
131.241
124.269
77.427
77.203
77.003
76.580
49.231
43.974
41.831
30.347
28.135
25.090
18.335
HNJ-2-234 06-05-06
ppm
200
180
160
140
120
100
80
60
40
20
0
O
N
Ns

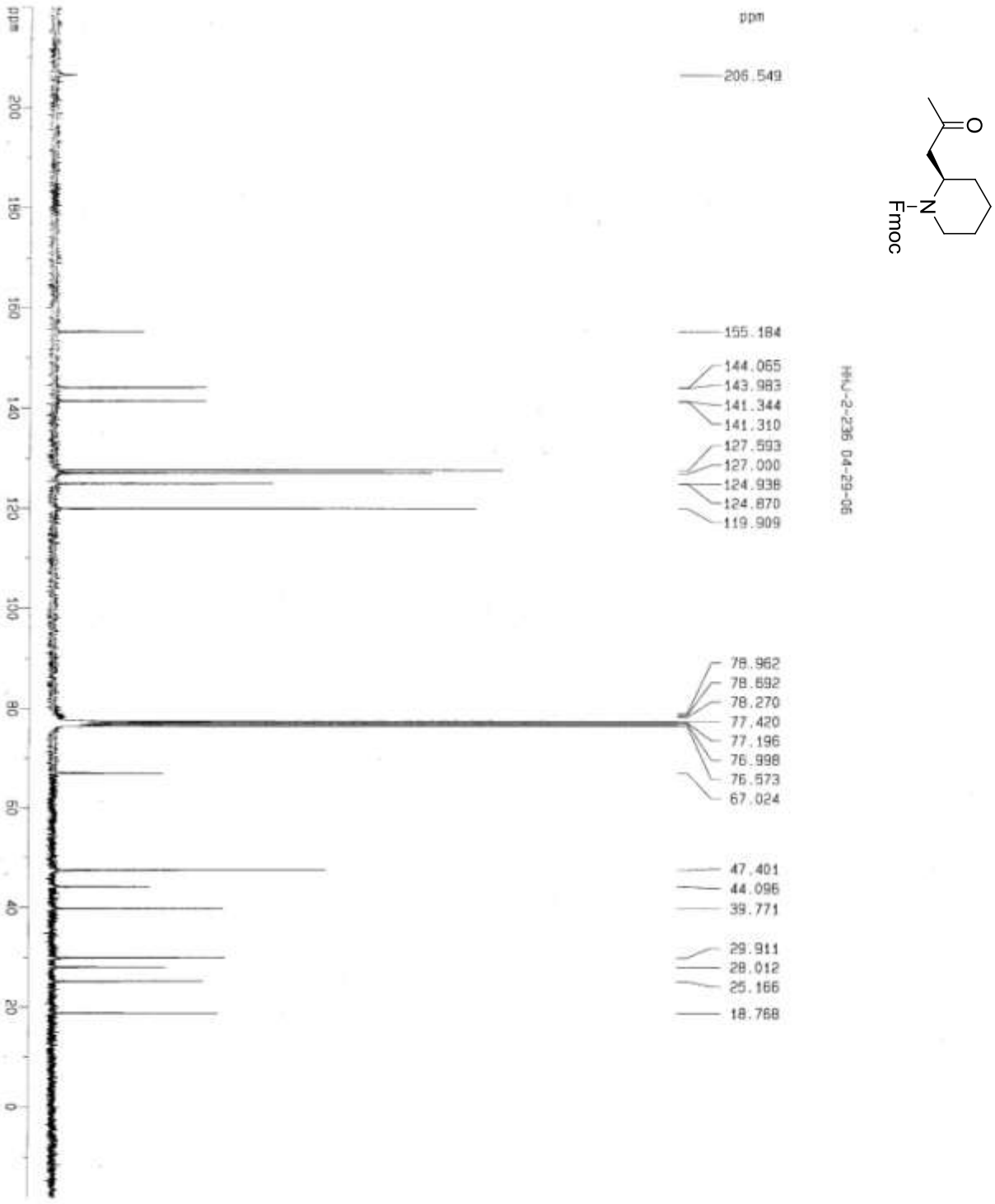

Integral
ppm
7.25997
4.76111
4.74616
4.01596
3.97938
3.68170
3.67194
3.66576
3.37063
2.86728
2.82361
2.78393
2.70329
2.67755
2.66514
2.17986
1.66575
1.63659
1.62085
1.60455
1.56257
1.55664
1.54155
1.53341
1.52762
1.51399
1.48068
1.47400
1.44838
1.43730
1.41299
1.37210
1.24622
0.8722
0.9476
2.8644
3.0000
2.6158
6.9104
HH-2-150 02-18-06
O
N
CO2Me

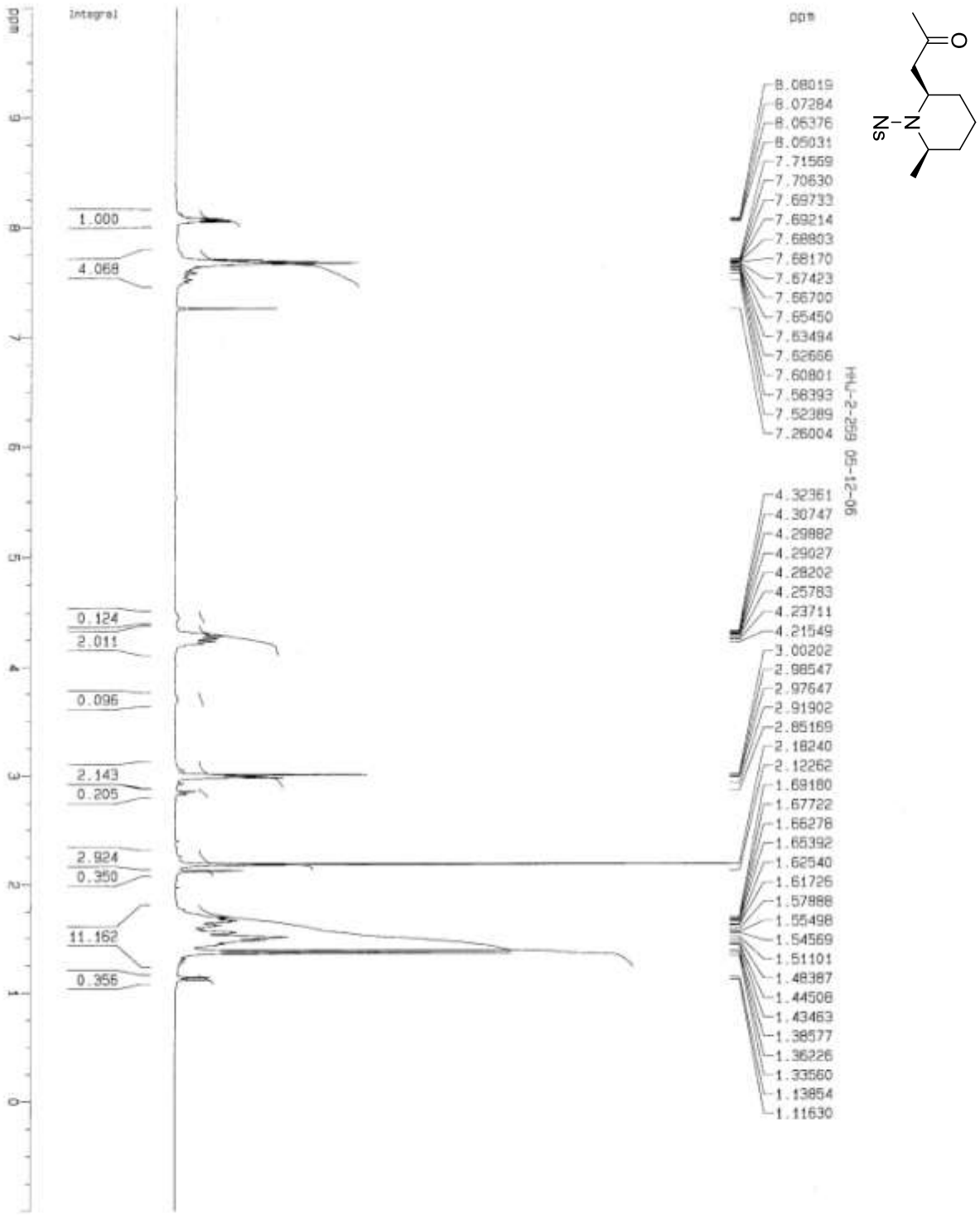

ppm
206.792
155.963
77.428
77.205
77.003
76.581
52.544
47.472
44.309
39.726
30.034
28.281
25.238
18.852
HHJ-2-160 02-18-05
O
N
CO2Me

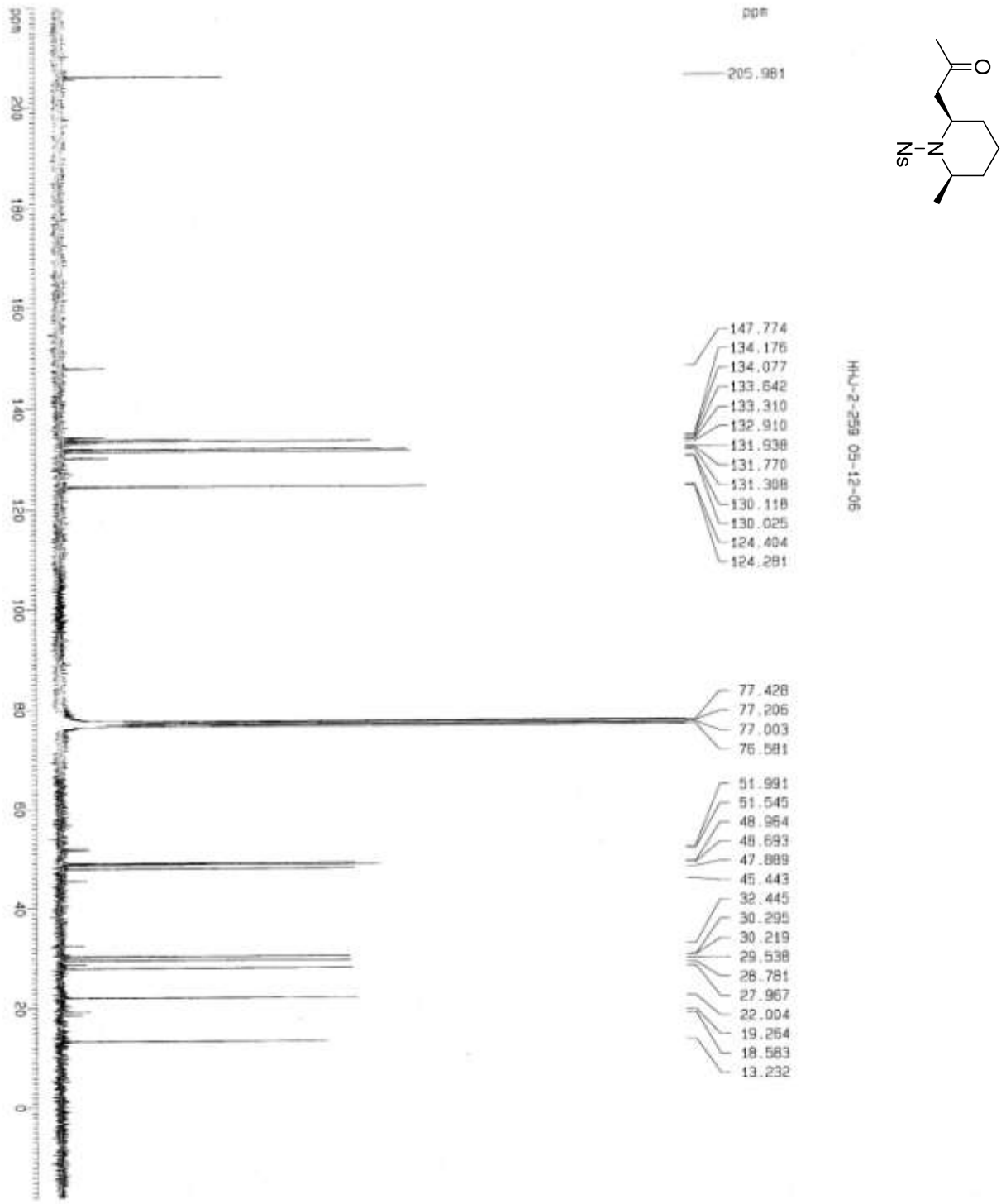

Integral
ppm
4.8592
2.0412
0.9809
1.0000
2.9258
2.6768
7.2411
7.39232
7.38782
7.36139
7.35655
7.34525
7.33561
7.32932
7.32198
7.31426
7.30088
7.28279
7.26009
7.25202
7.24438
5.15008
5.11850
5.11255
5.09684
5.07110
4.80946
4.79475
4.07061
4.02864
3.36660
2.85077
2.81052
2.69908
2.67358
2.13460
1.67931
1.64921
1.64202
1.60043
1.54874
1.53366
1.52122
1.49987
1.48741
1.45565
1.42561
1.39540
1.38473
1.25053
HHJ-2-159 02-19-06
O
N
Cbz

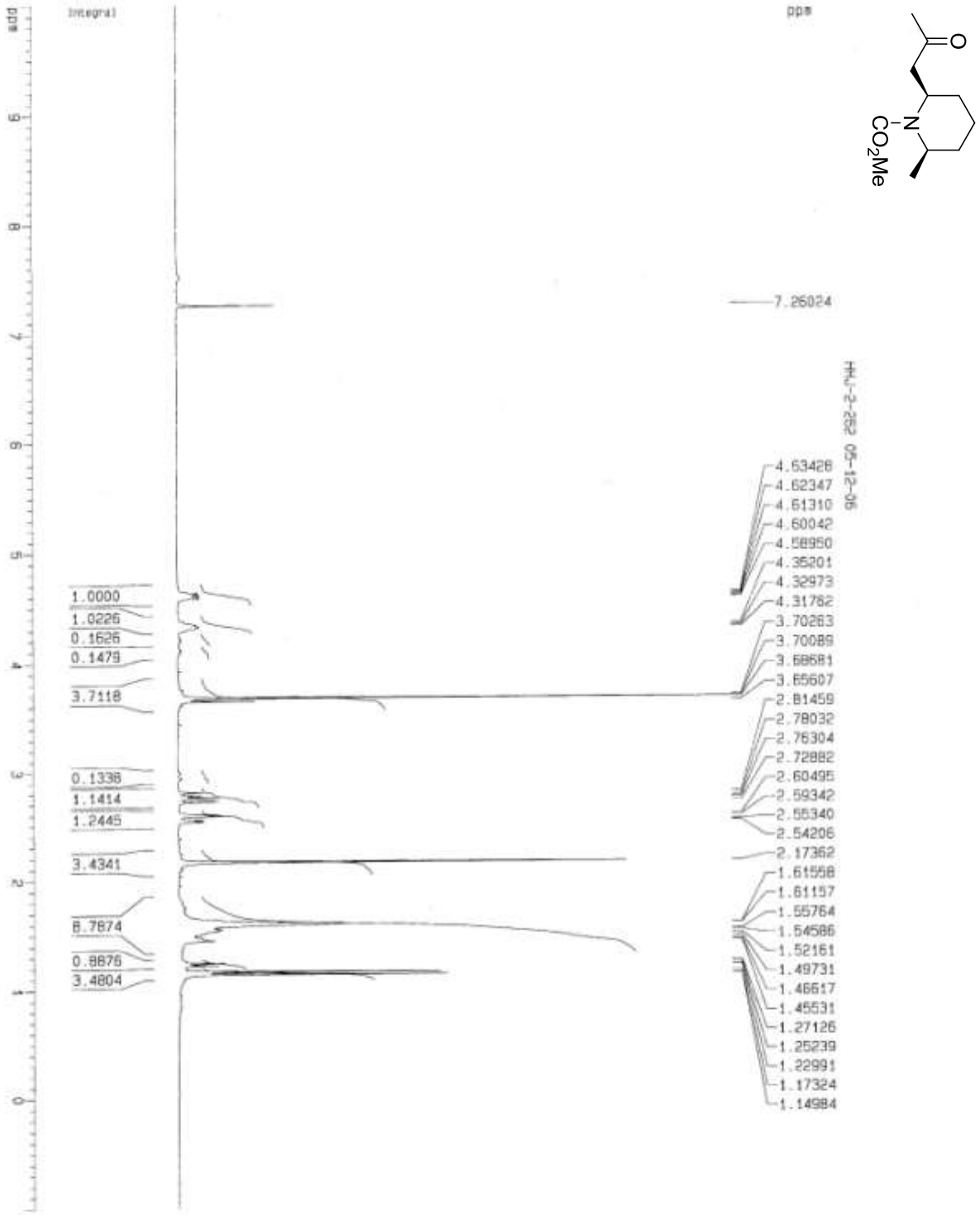

ppm
206.683
155.303
136.791
128.520
128.457
128.421
127.938
127.825
77.432
77.209
77.007
76.583
67.110
47.579
44.322
39.814
29.984
28.294
25.226
18.829
HHJ-2-235 06-02-06
O
N
Cbz

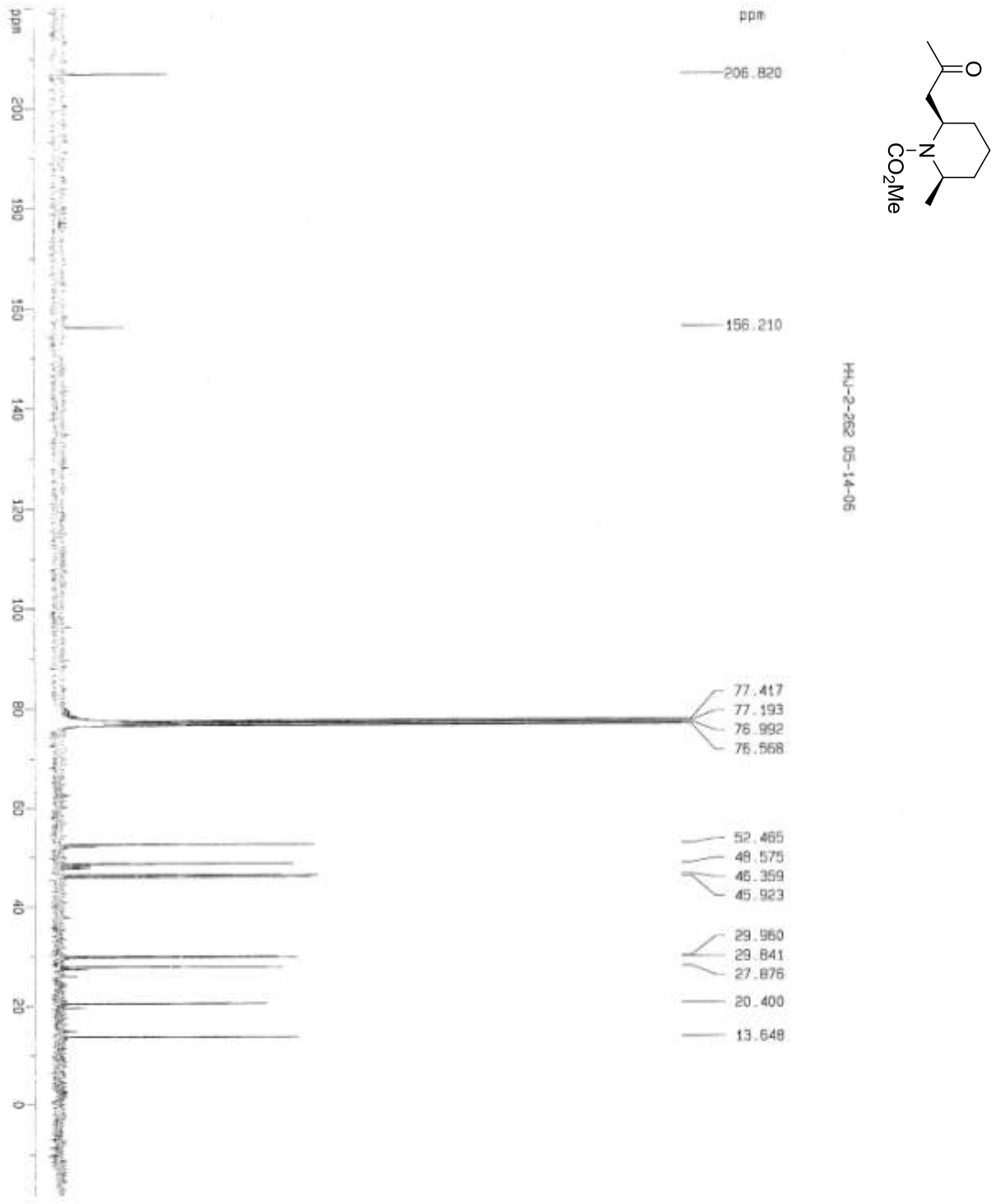

Integral
ppm
1.7456
1.8958
4.2031
2.9984
0.9758
1.0000
1.0873
1.1455
0.8204
2.6130
6.8523
7.74574
7.56552
7.39460
7.33571
7.31108
7.26052
4.68038
4.45663
4.43506
4.25341
4.23192
4.21050
3.96280
2.87812
2.72910
2.70053
2.67900
2.65082
2.09952
2.04251
1.63455
1.59312
1.58030
1.54649
1.26242
HHJ-2-236 (303 K) 05-13-06
Fmoc
N
O

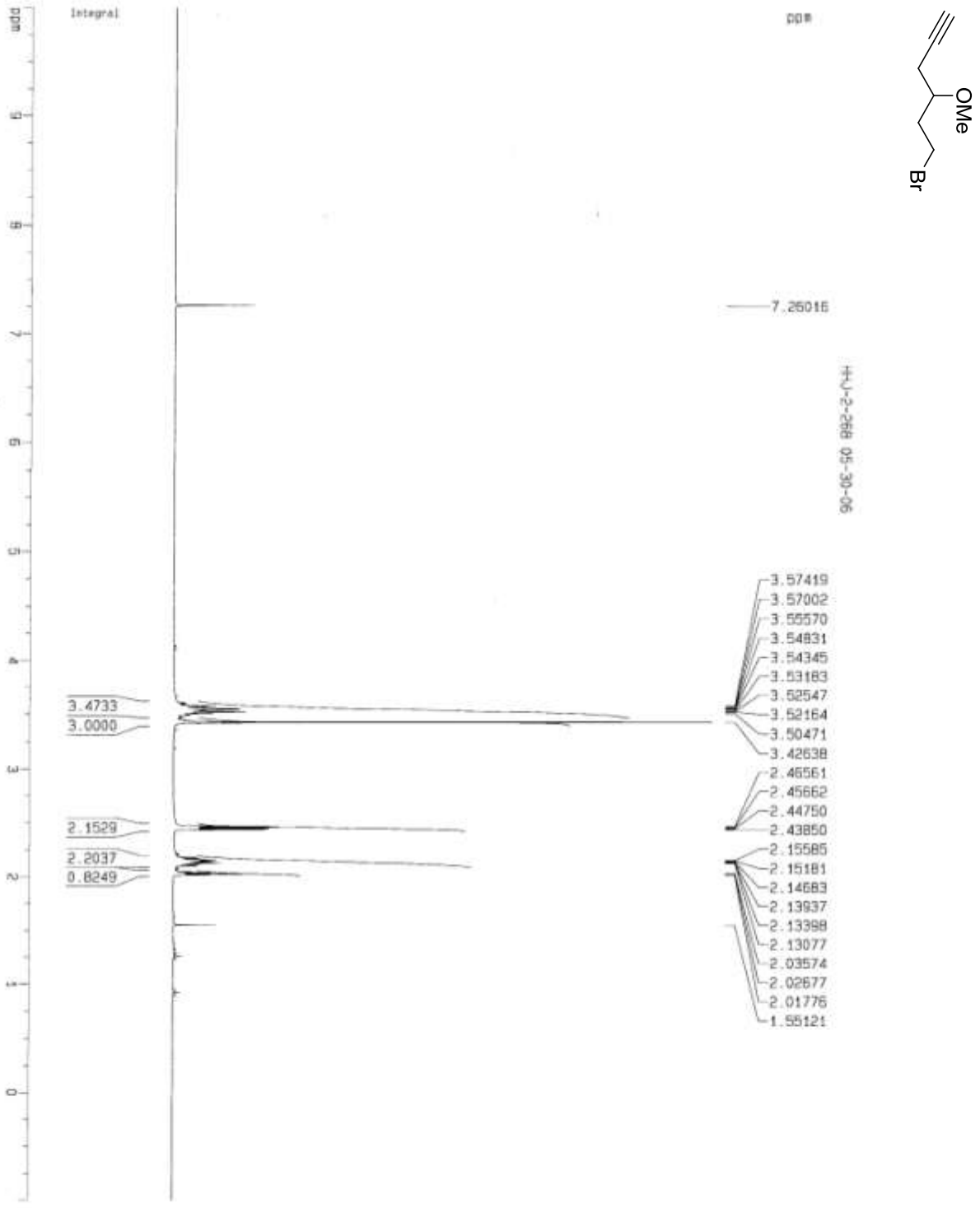

ppm
206.549
155.184
144.065
143.983
141.344
141.310
127.593
127.000
124.938
124.870
119.909
78.962
78.692
78.270
77.420
77.196
76.998
76.573
67.024
47.401
44.096
39.771
29.911
28.012
25.166
18.768
HHJ-2-236 04-29-06
O
N
Fmoc

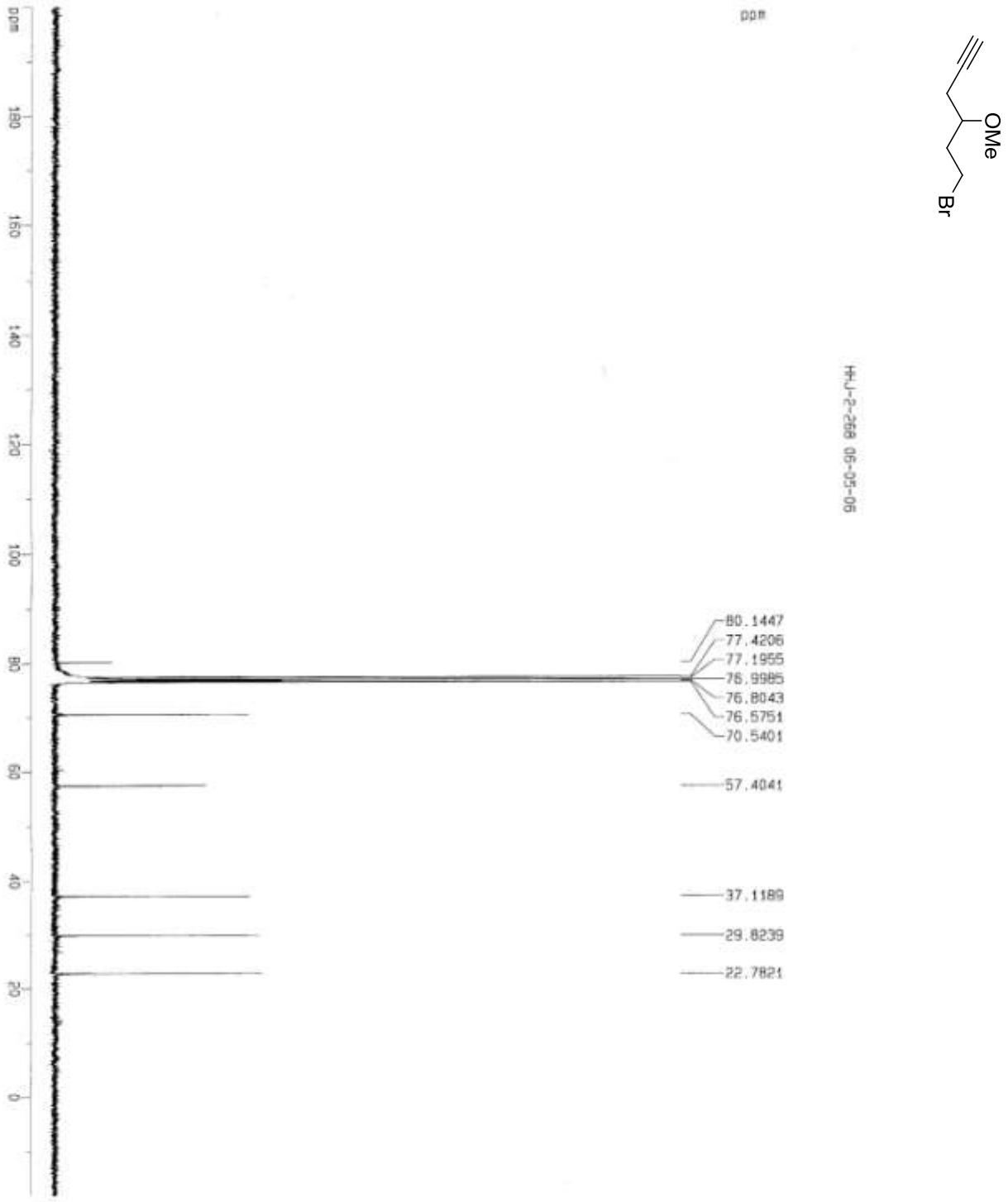

ppm
Integral
1.000
4.068
0.124
2.011
0.096
2.143
0.205
2.924
0.350
11.162
0.356
8.08019
8.07284
8.06376
8.05031
7.71569
7.70630
7.69733
7.69214
7.68803
7.68170
7.67423
7.66700
7.65450
7.63494
7.62656
7.60801
7.58393
7.52389
7.26004
4.32361
4.30747
4.29882
4.29027
4.28202
4.25783
4.23711
4.21549
3.00202
2.98547
2.97647
2.91902
2.85169
2.18240
2.12262
1.69180
1.67722
1.66278
1.65392
1.62540
1.61726
1.57888
1.55498
1.54569
1.51101
1.48387
1.44508
1.43463
1.38577
1.36226
1.33560
1.13854
1.11630
HHL-2-259 05-12-06
O
N
N
Ns

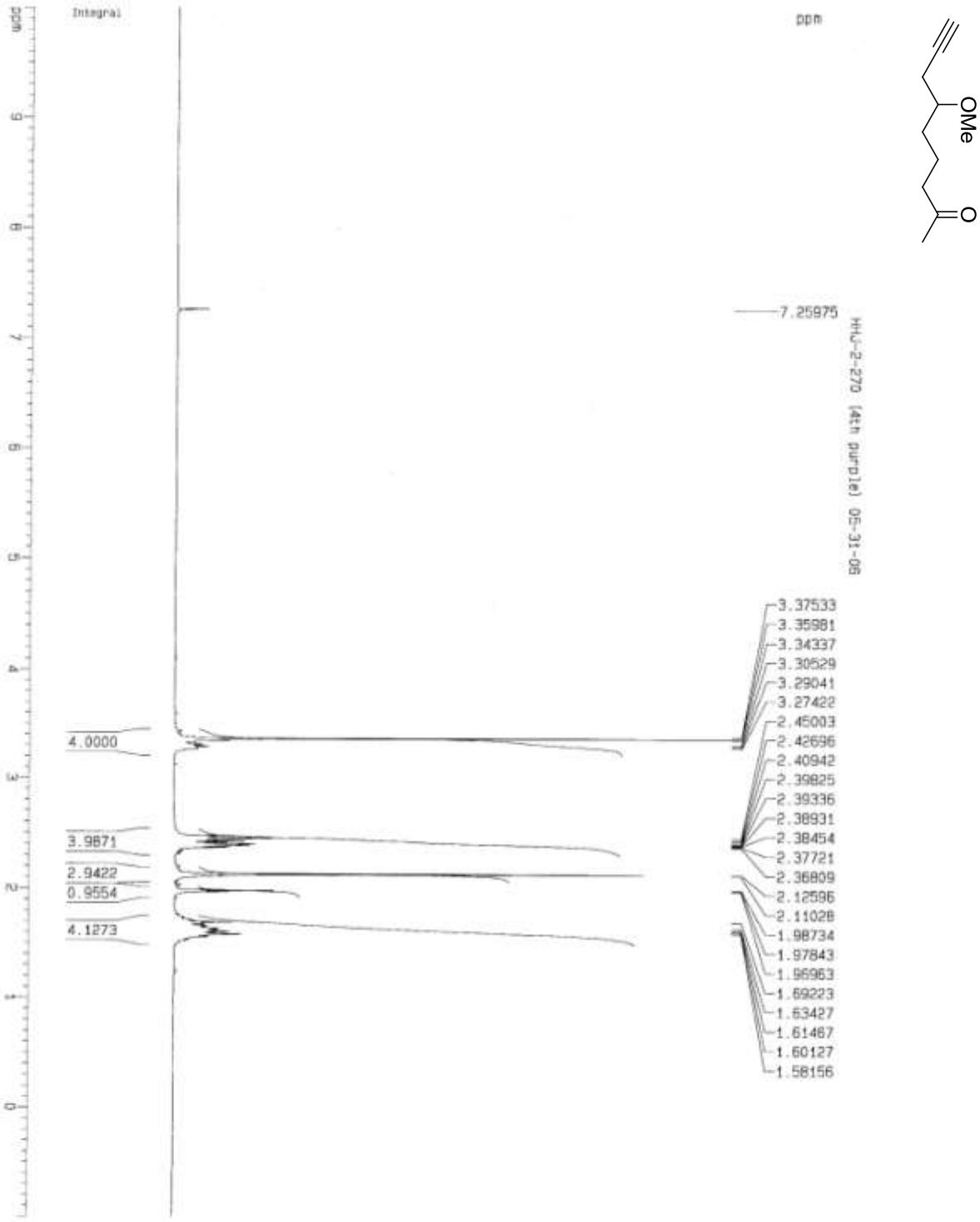

ppm
205.981
147.774
134.176
134.077
133.642
133.310
132.910
131.938
131.770
131.398
130.118
130.025
124.404
124.281
77.428
77.206
77.003
76.581
51.991
51.545
48.964
48.693
47.889
45.443
32.445
30.295
30.219
29.538
28.781
27.967
22.004
19.264
18.583
13.232
HHJ-2-259 05-12-06
Ns
N
O

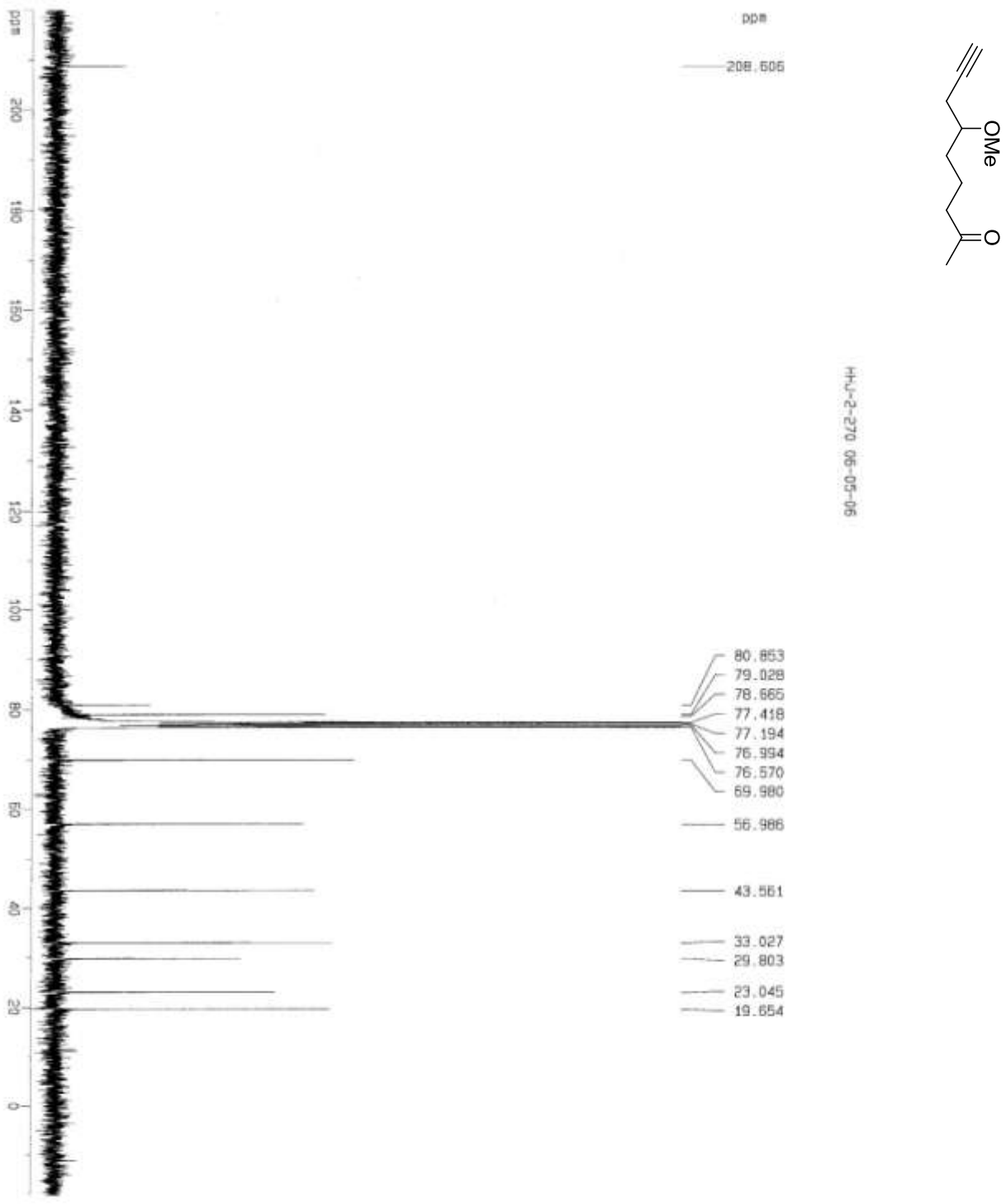

Integral
ppm
7.26024
4.63428
4.62347
4.61310
4.60042
4.58950
4.35201
4.32973
4.31762
3.70263
3.70089
3.68681
3.65607
2.81459
2.78032
2.76304
2.72882
2.60495
2.59342
2.55340
2.54206
2.17362
1.61558
1.61157
1.55764
1.54586
1.52161
1.49731
1.46617
1.45531
1.27126
1.25239
1.22991
1.17324
1.14984
1.0000
1.0226
0.1626
0.1479
3.7118
0.1338
1.1414
1.2445
3.4341
8.7874
0.8876
3.4804
HH-2-282 05-12-06
O
N
CO2Me

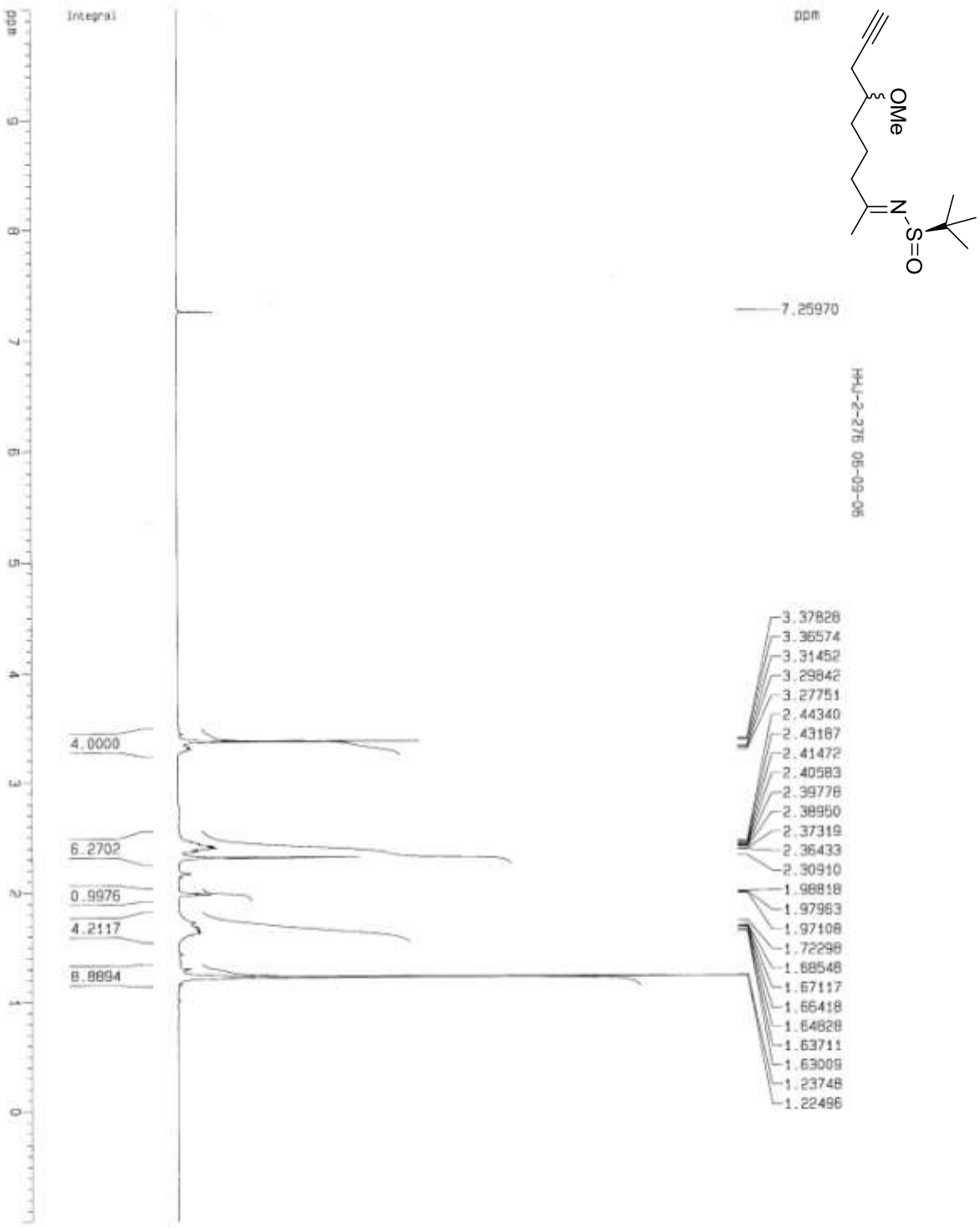

ppm
206.820
156.210
77.417
77.193
76.992
76.568
52.465
48.575
46.359
45.923
29.960
29.841
27.876
20.400
13.648
HHJ-2-262 05-14-06
O
N
CO2Me

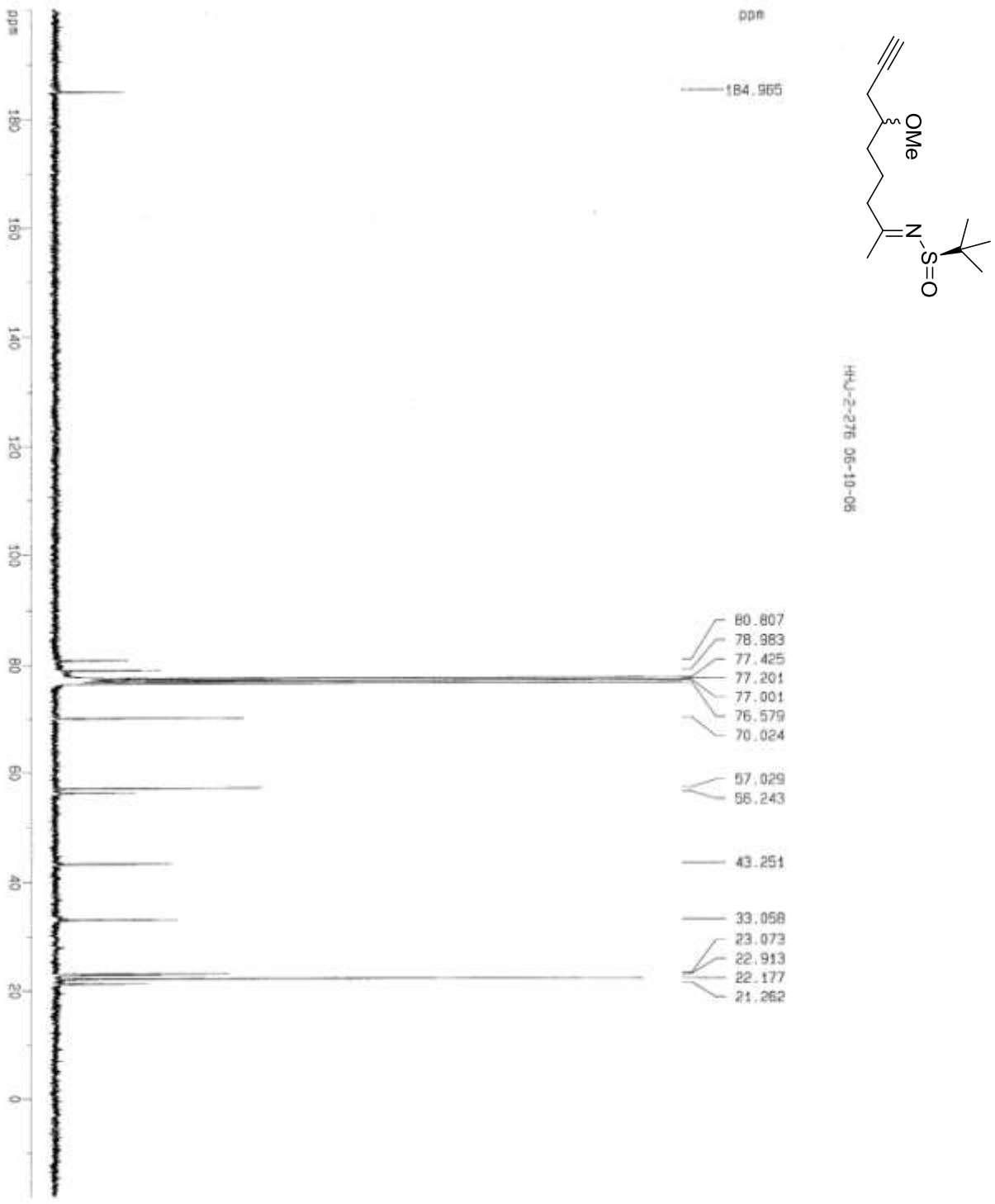

Integral
ppm
7.26016
HHJ-2-268 05-30-06
3.57419
3.57002
3.55570
3.54831
3.54345
3.53183
3.52547
3.52164
3.50471
3.42638
2.46561
2.45662
2.44750
2.43850
2.15585
2.15181
2.14683
2.13937
2.13398
2.13077
2.03574
2.02677
2.01776
1.55121
3.4733
3.0000
2.1529
2.2037
0.8249
OMe
Br

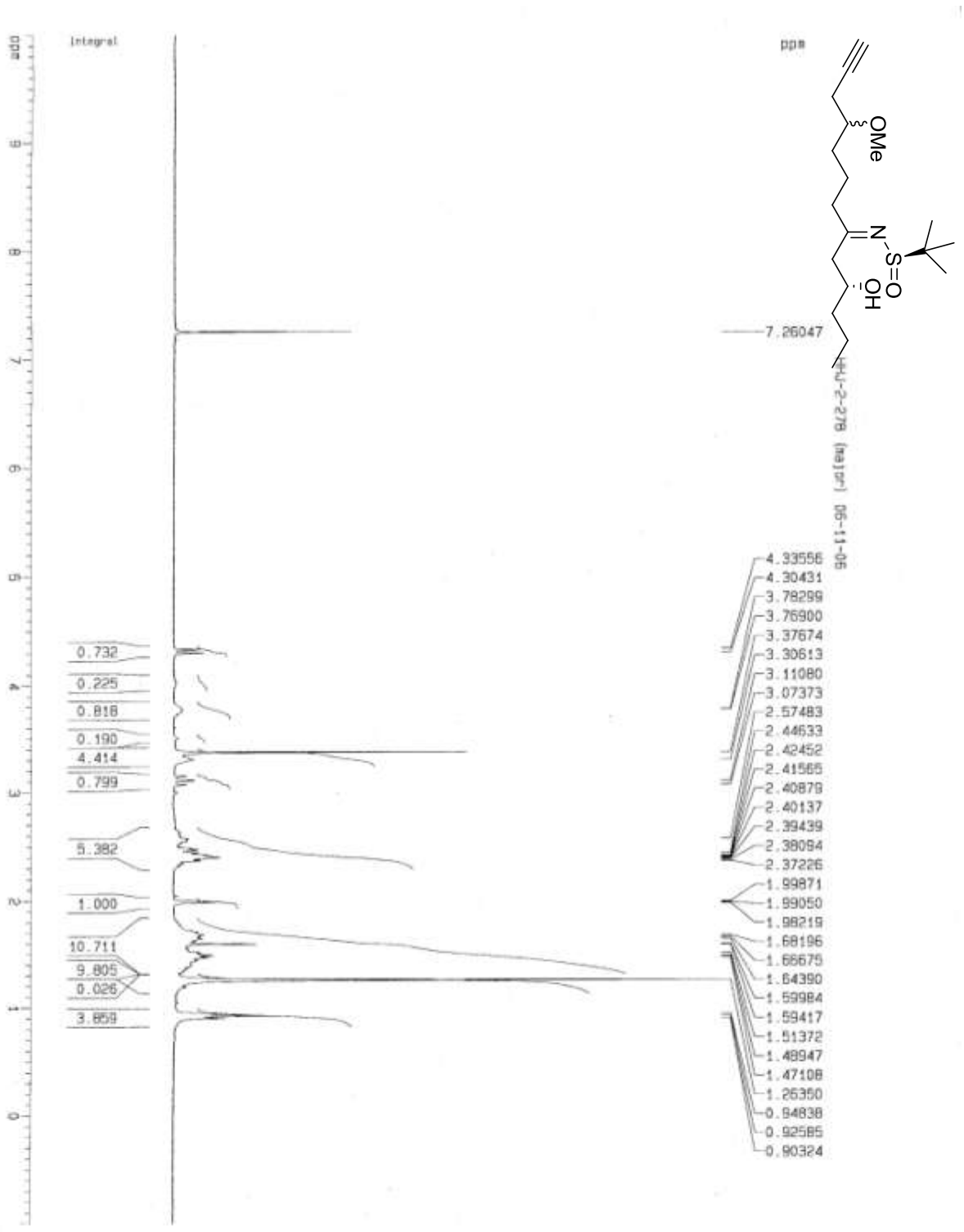

ppm
ppm
200
180
160
140
120
100
80
60
40
20
0
80.1447
77.4206
77.1955
76.9985
76.8043
76.5751
70.5401
57.4041
37.1189
29.8239
22.7821
HHJ-2-268 06-05-06
OMe
Br

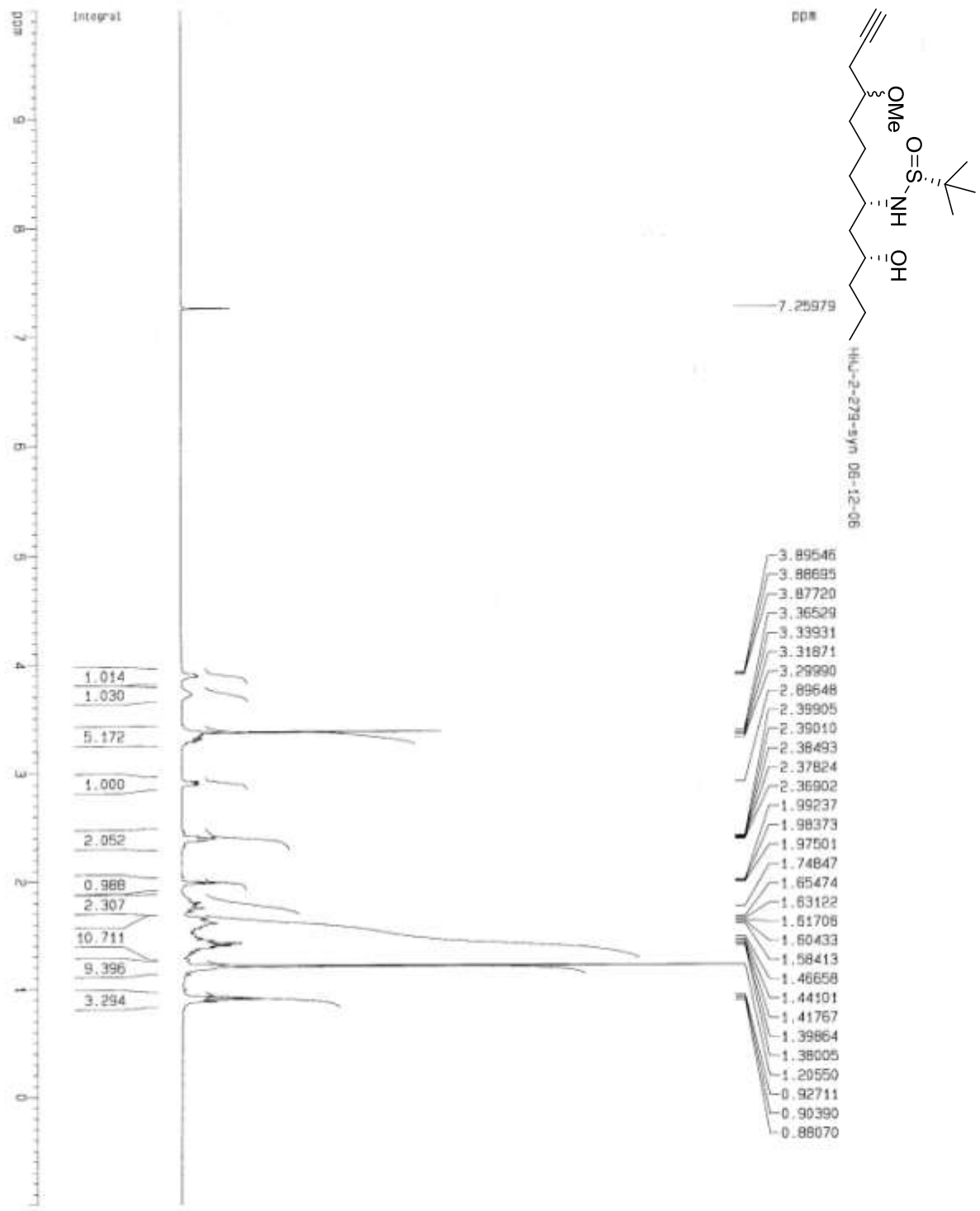

Integral
ppm
7.25975
HHJ-2-270 (4th purple) 05-31-06
3.37533
3.35981
3.34337
3.30529
3.29041
3.27422
2.45003
2.42696
2.40942
2.39825
2.39336
2.38931
2.38454
2.37721
2.36809
2.12596
2.11028
1.98734
1.97843
1.96963
1.69223
1.63427
1.61467
1.60127
1.58156
4.0000
3.9871
2.9422
0.9554
4.1273
OMe
O

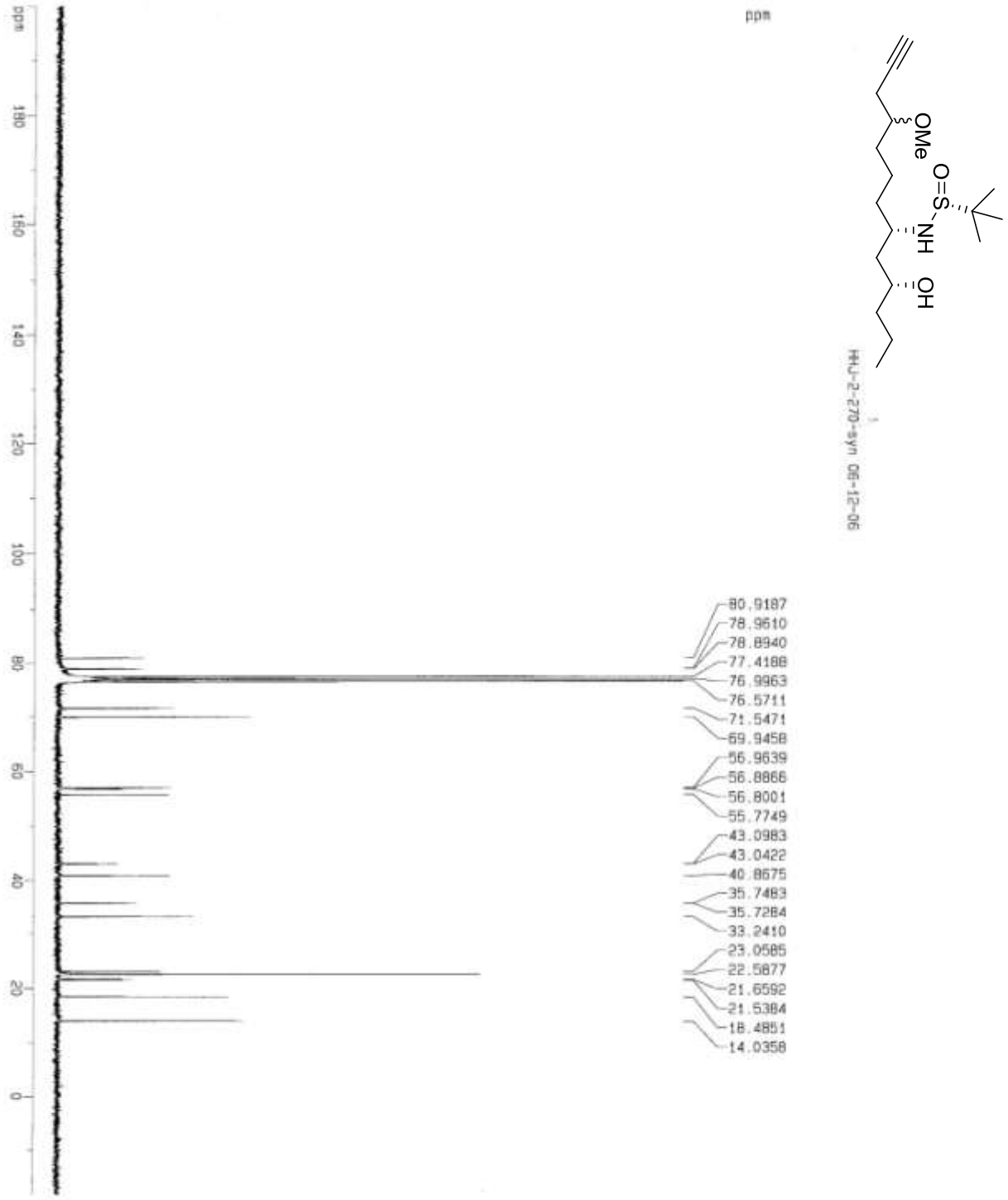

ppm
208.606
80.853
79.028
78.665
77.418
77.194
76.994
76.570
69.980
56.986
43.561
33.027
29.803
23.045
19.654
OMe
O
HH-2-270 06-05-06

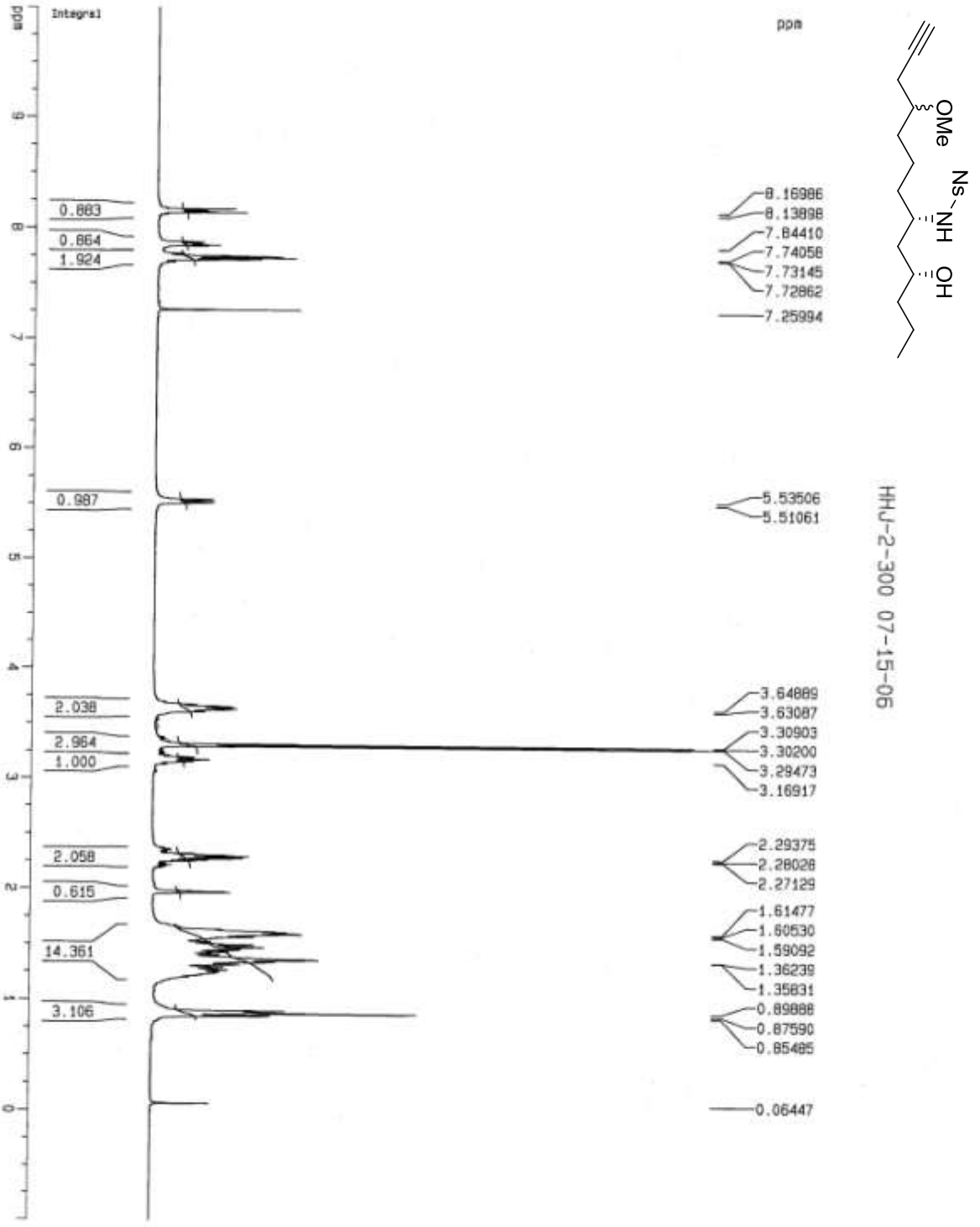

Integral
ppm
OMe
N
S=O
7.25970
HHJ-2-276 06-09-06
3.37828
3.36574
3.31452
3.29842
3.27751
2.44340
2.43187
2.41472
2.40583
2.39778
2.38950
2.37319
2.36433
2.30910
1.98818
1.97963
1.97108
1.72298
1.68548
1.67117
1.66418
1.64828
1.63711
1.63009
1.23748
1.22496
4.0000
6.2702
0.9976
4.2117
8.8894

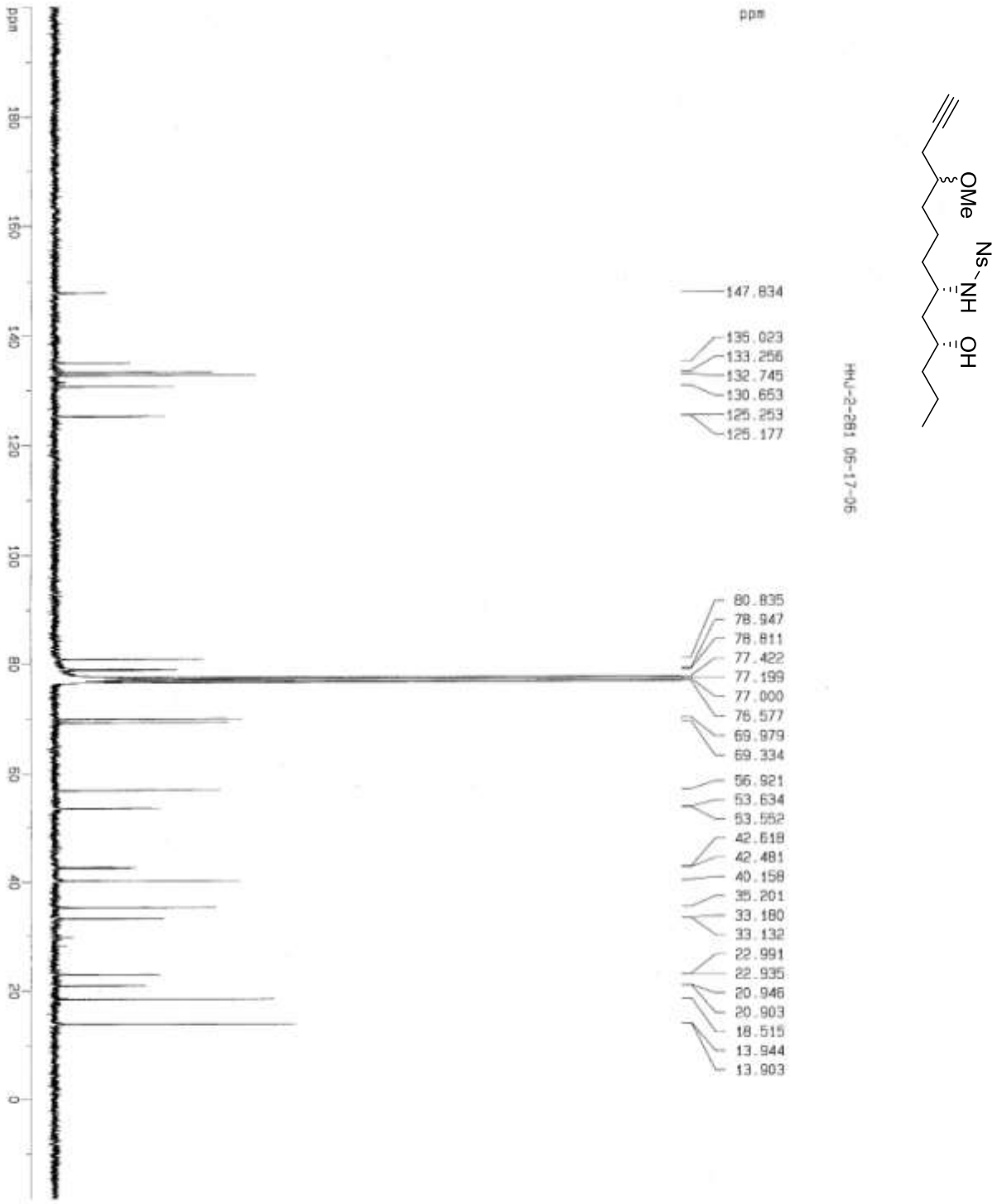

ppm
184.965
80.807
78.983
77.425
77.201
77.001
76.579
70.024
57.029
56.243
43.251
33.058
23.073
22.913
22.177
21.262
OMe
N
S=O
HHJ-2-276 06-10-06


Integral
ppm
OMe
N
S=O
OH
7.26047
HH-2-278 (major) 06-11-05
4.33556
4.30431
3.78299
3.76900
3.37674
3.30613
3.11080
3.07373
2.57483
2.44633
2.42452
2.41565
2.40879
2.40137
2.39439
2.38094
2.37226
1.99871
1.99050
1.98219
1.68196
1.66675
1.64390
1.59984
1.59417
1.51372
1.48947
1.47108
1.26350
0.94838
0.92585
0.90324
0.732
0.225
0.818
0.190
4.414
0.799
5.382
1.000
10.711
9.805
0.026
3.859


Integral
ppm
OMe
O=S
NH
OH
7.25979
HHJ-2-279-syn 06-12-06
3.89546
3.88695
3.87720
3.36529
3.33931
3.31871
3.29990
2.89648
2.39905
2.39010
2.38493
2.37824
2.36902
1.99237
1.98373
1.97501
1.74847
1.65474
1.63122
1.61706
1.60433
1.58413
1.46658
1.44101
1.41767
1.39864
1.38005
1.20550
0.92711
0.90390
0.88070
1.014
1.030
5.172
1.000
2.052
0.988
2.307
10.711
9.396
3.294


ppm
180
160
140
120
100
80
60
40
20
0
80.9187
78.9610
78.8940
77.4188
76.9963
76.5711
71.5471
69.9458
56.9639
56.8866
56.8001
55.7749
43.0983
43.0422
40.8675
35.7483
35.7284
33.2410
23.0585
22.5877
21.6592
21.5384
18.4851
14.0358
OMe
O=S
NH
OH
HHJ-2-270-syn 06-12-06


Integral
ppm
0.883
0.864
1.924
0.987
2.038
2.964
1.000
2.058
0.615
14.361
3.106
8.16986
8.13898
7.84410
7.74058
7.73145
7.72862
7.25994
5.53506
5.51061
3.64889
3.63087
3.30903
3.30200
3.29473
3.16917
2.29375
2.28028
2.27129
1.61477
1.60530
1.59092
1.36239
1.35831
0.89888
0.87590
0.85485
0.06447
OMe
Ns
NH
OH
HHJ-2-300 07-15-06


ppm
180
160
140
120
100
80
60
40
20
0
147.834
135.023
133.256
132.745
130.653
125.253
125.177
80.835
78.947
78.811
77.422
77.199
77.000
76.577
69.979
69.334
56.921
53.634
53.552
42.618
42.481
40.158
35.201
33.180
33.132
22.991
22.935
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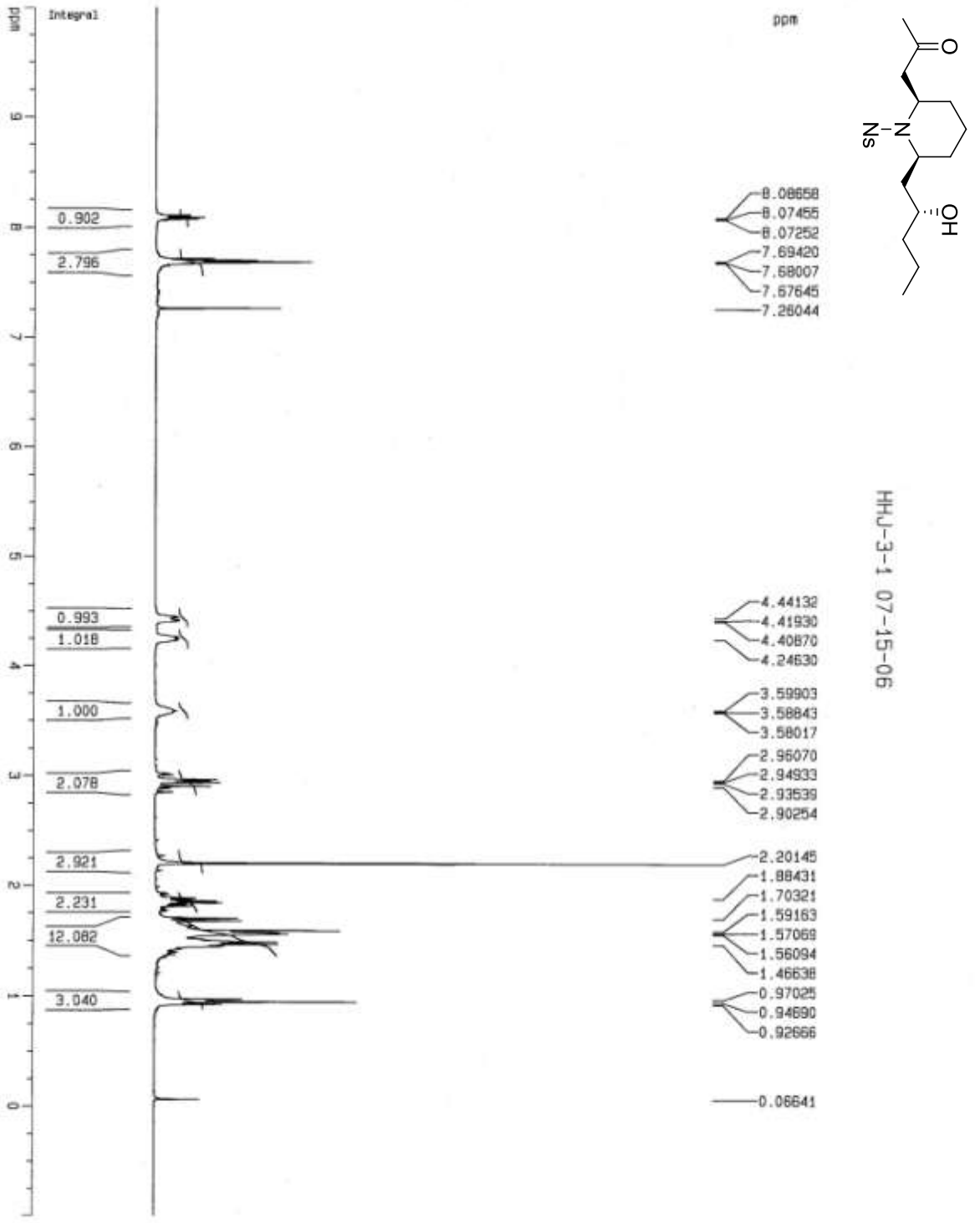
20.903
18.515
13.944
13.903
HHJ-2-281 06-17-06
OMe
Ns
NH
OH


Integral
ppm
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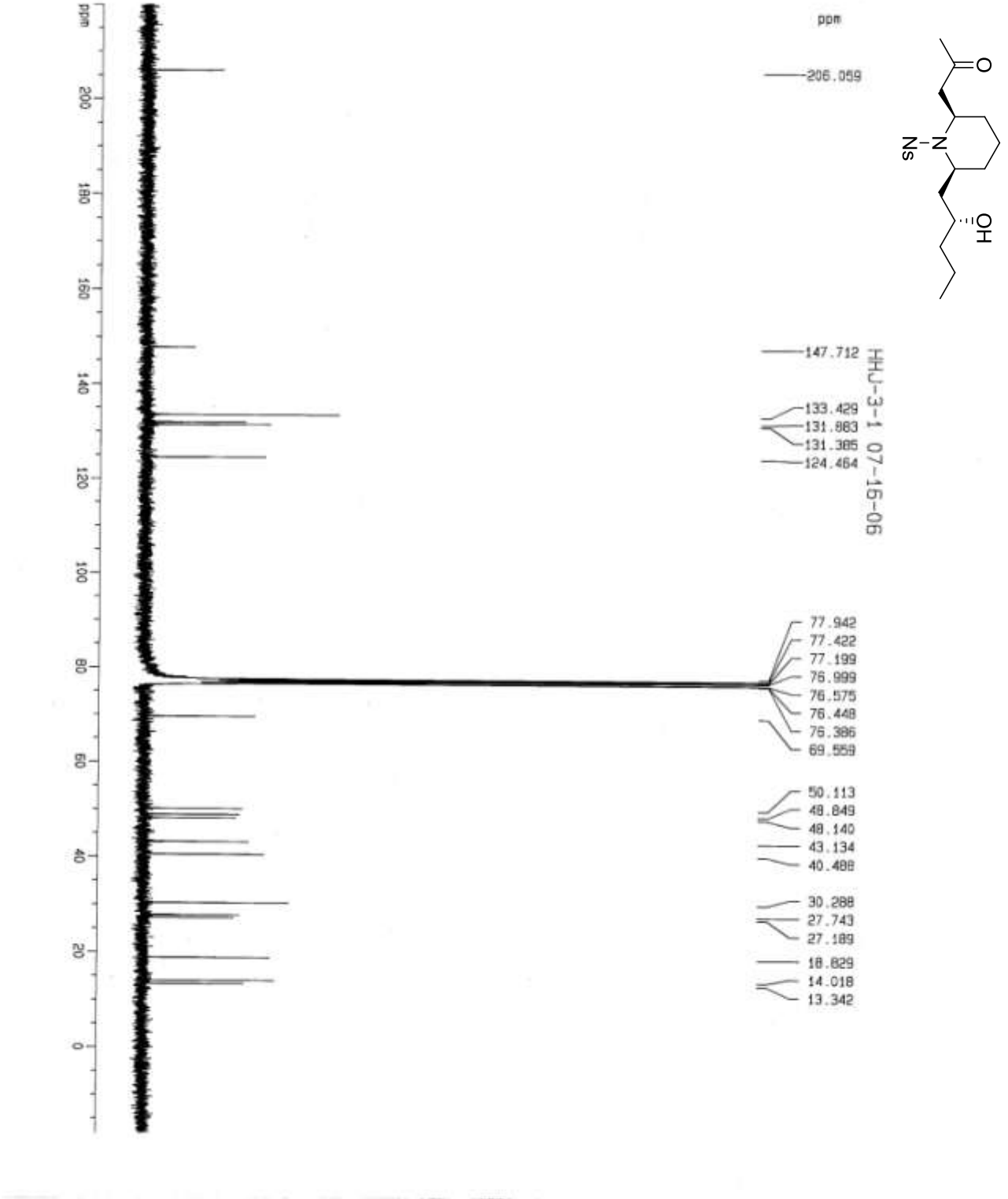
0.993
1.018
1.000
2.078
2.921
2.231
12.082
3.040
8.08658
8.07455
8.07252
7.69420
7.68007
7.67645
7.26044
4.44132
4.41930
4.40870
4.24630
3.59903
3.58843
3.58017
2.96070
2.94933
2.93539
2.90254
2.20145
1.88431
1.70321
1.59163
1.57069
1.56094
1.46638
0.97025
0.94690
0.92666
0.06641
HHJ-3-1 07-15-06
O
N
Ns
OH


ppm
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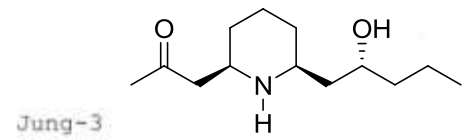
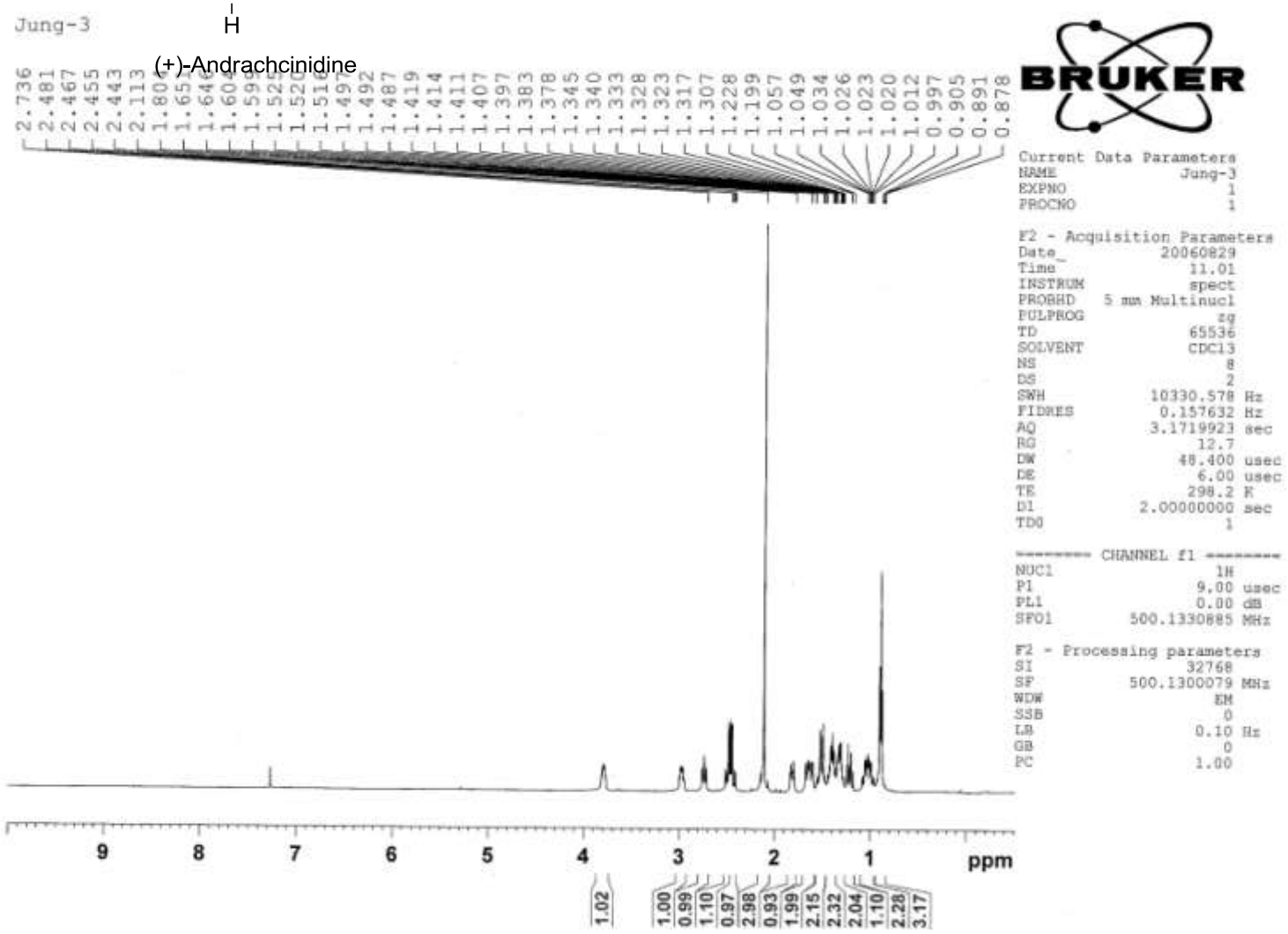
131.883
131.385
124.464
77.942
77.422
77.199
76.999
76.575
76.448
76.386
69.559
50.113
48.849
48.140
43.134
40.488
30.288
27.743
27.189
18.629
14.018
13.342
HHJ-3-1 07-15-06
O
N
N
Ns
OH



Jung-3

(+)-Andrachcinidine



BRUKER

```
Current Data Parameters
NAME                  Jung-3
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20060829
Time                  11.01
INSTRUM               spect
PROBHD   5 mm Multinucl
PULPROG                zg
TD                     65536
SOLVENT                CDCl3
NS                         8
DS                         2
SWH               10330.578 Hz
FIDRES            0.157632 Hz
AQ                3.1719923 sec
RG                      12.7
DW                   48.400 usec
DE                    6.00 usec
TE                   298.2 K
D1                2.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1           500.1330885 MHz

F2 - Processing parameters
SI                     32768
SF             500.1300079 MHz
WDW                       EM
SSB                        0
LB                     0.10 Hz
GB                         0
PC                      1.00
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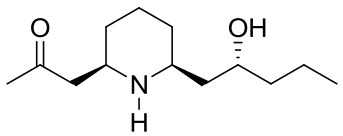
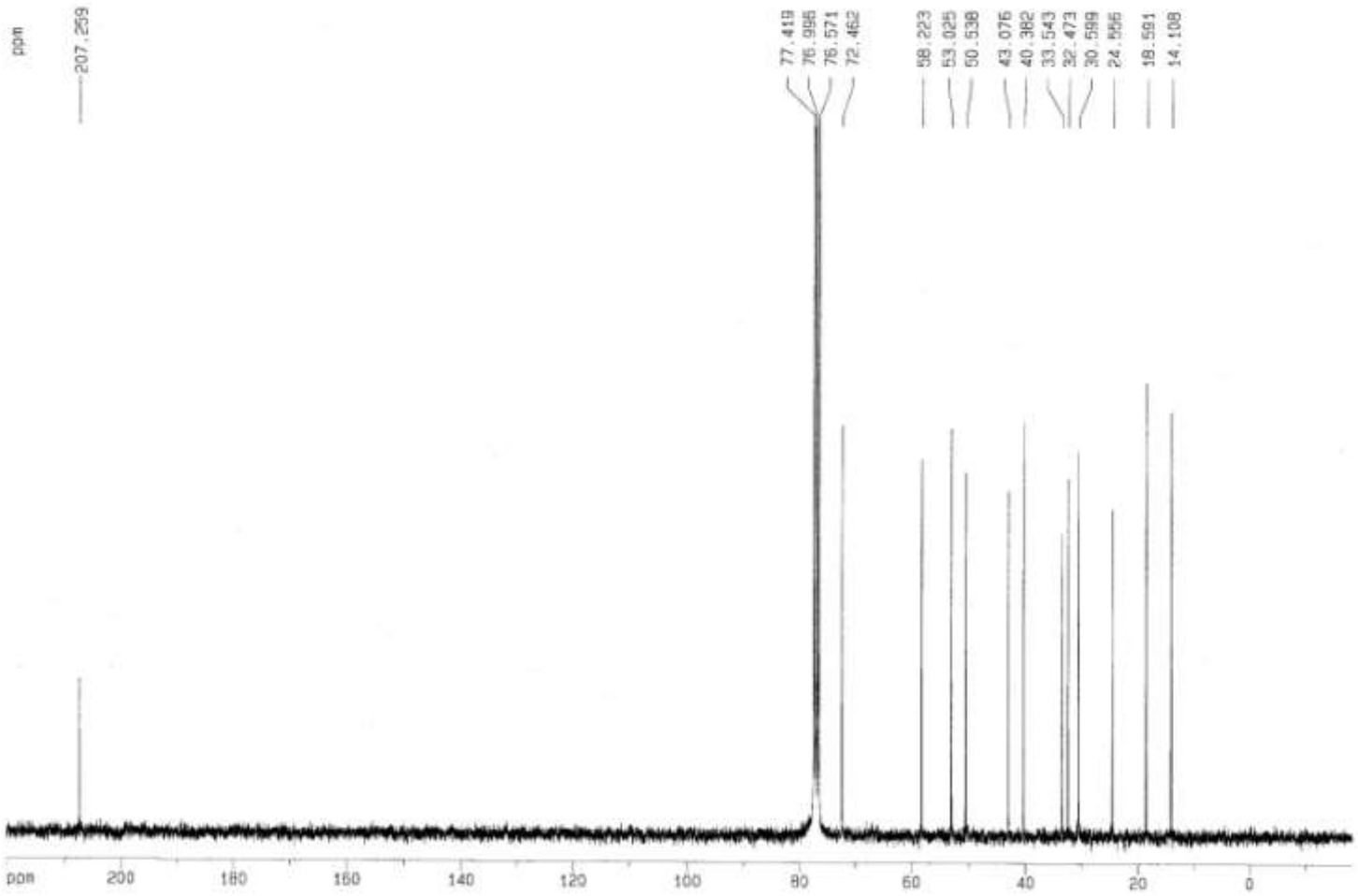
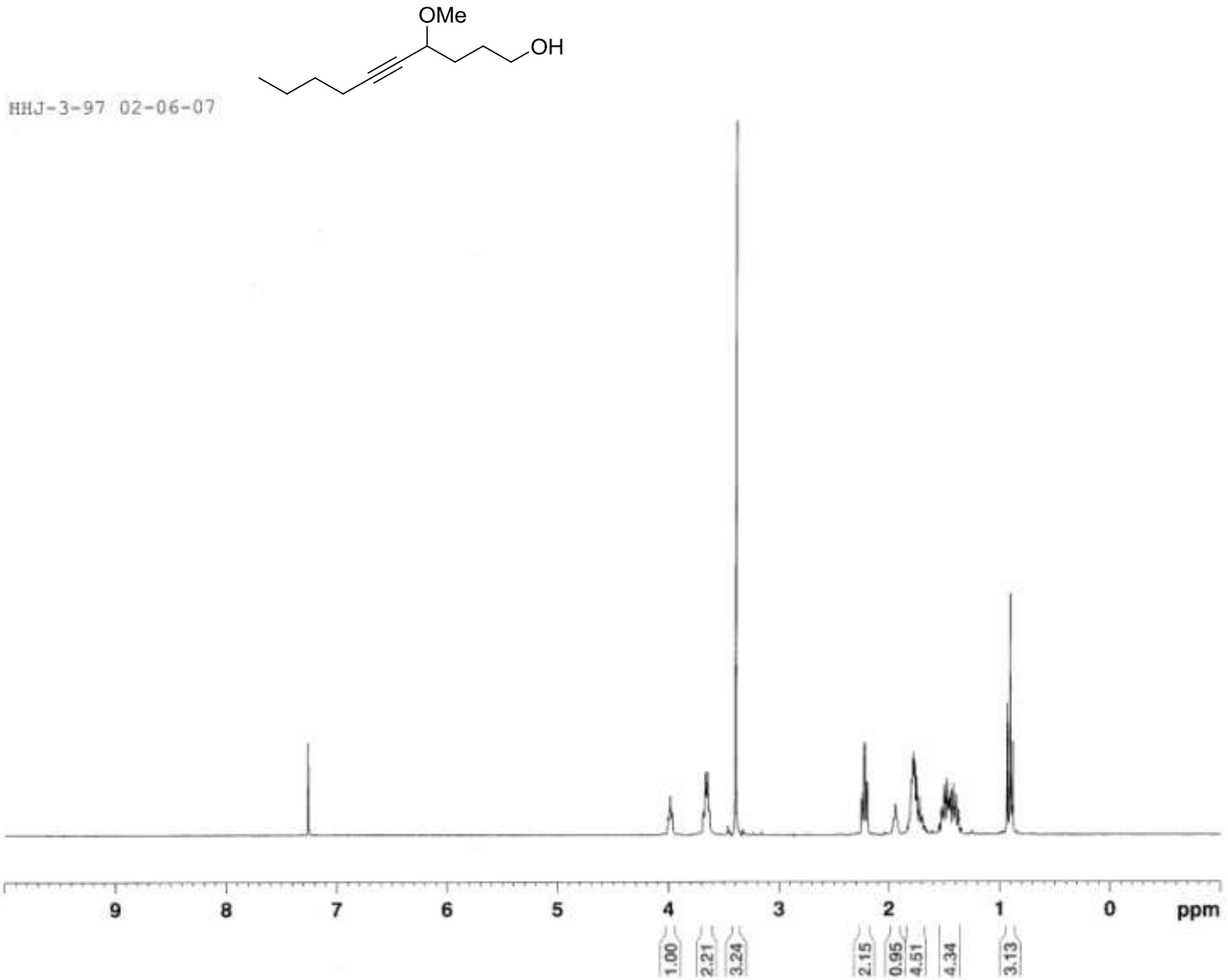
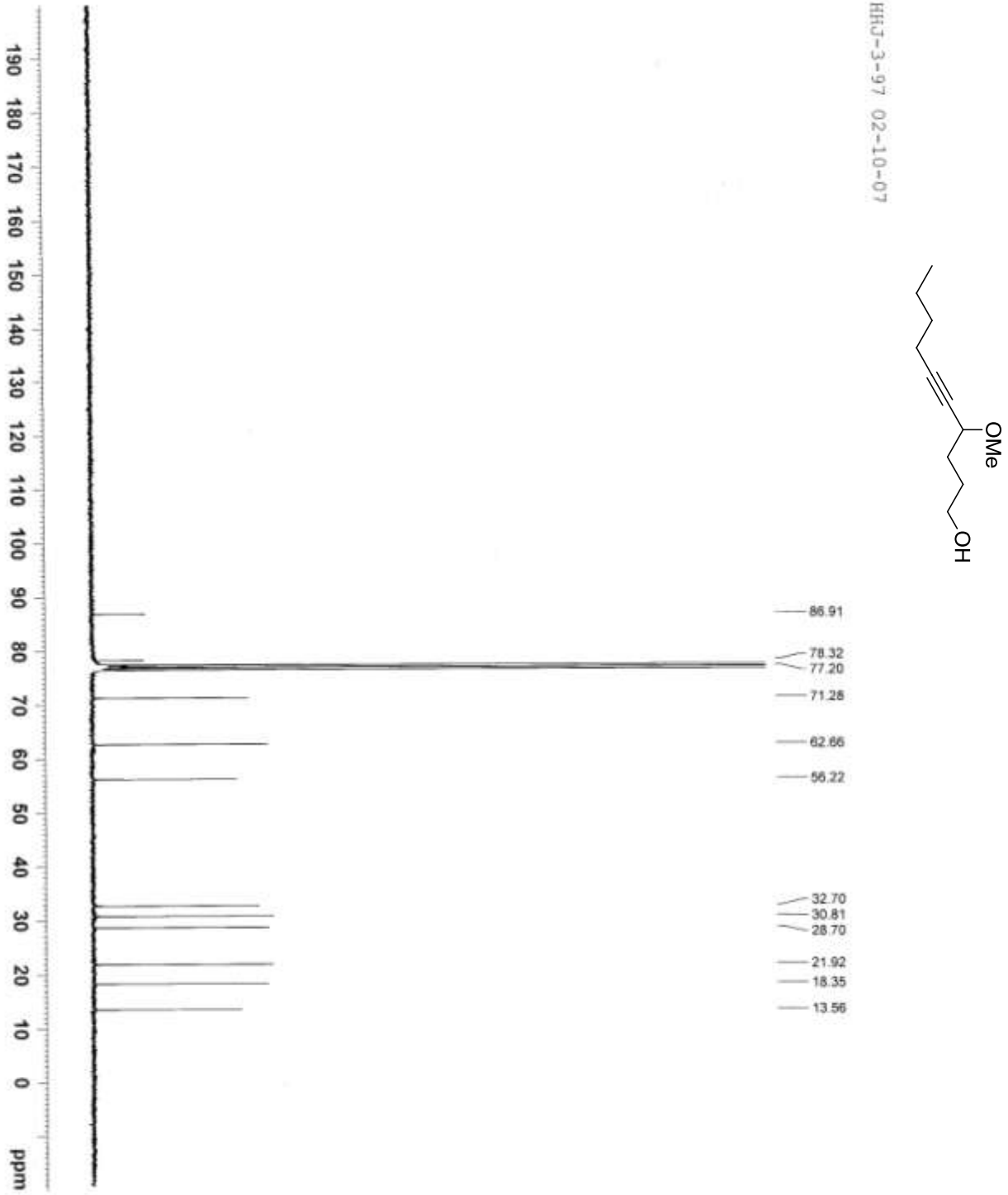
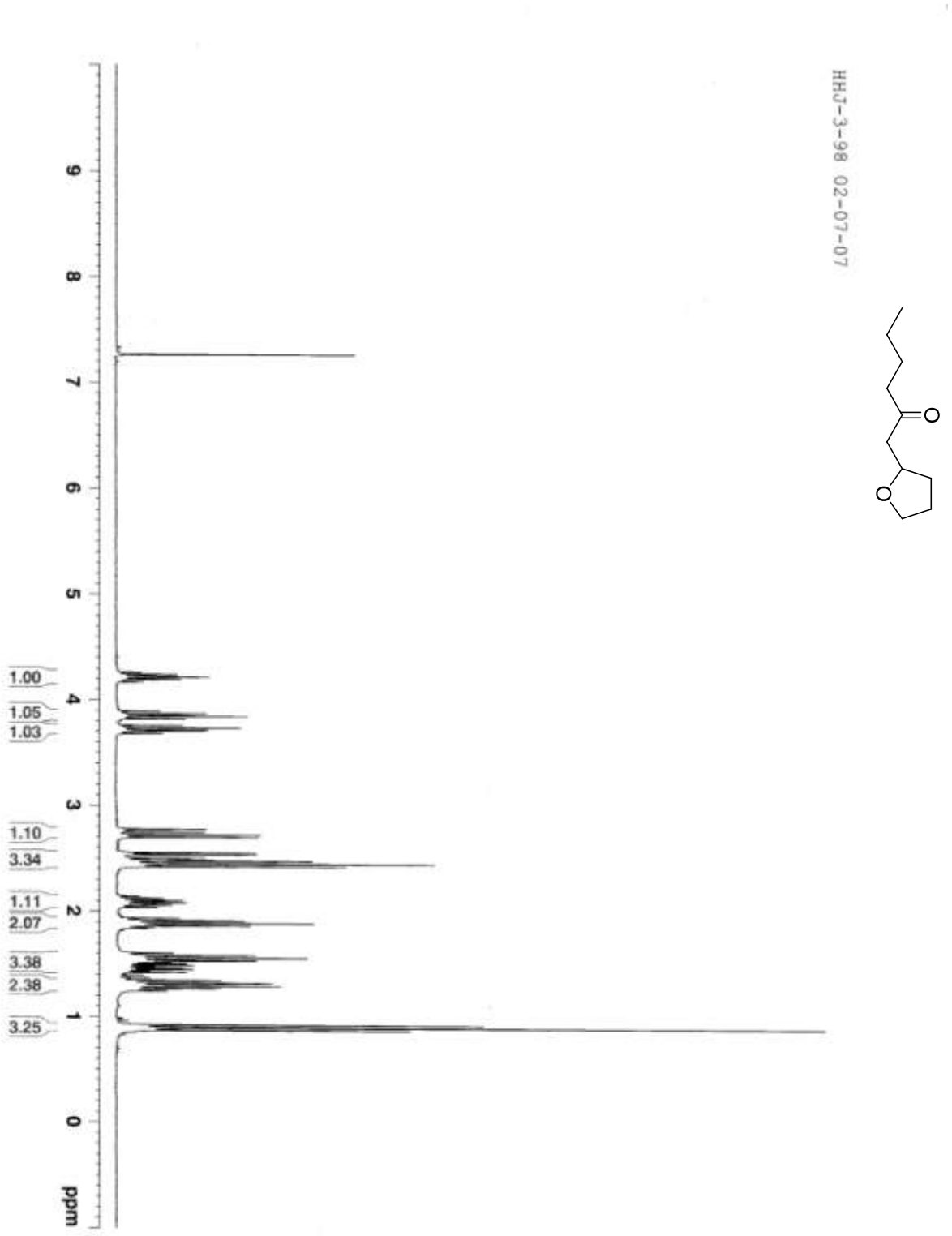


(+)-Andrachcinidine HHJ-2-283 06-15-06




OMe
OH
HHJ-3-97 02-06-07
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.21
3.24
2.15
0.95
4.51
4.34
3.13


HHJ-3-97 02-10-07
OMe
OH
86.91
78.32
77.20
71.28
62.66
56.22
32.70
30.81
28.70
21.92
18.35
13.56
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HHJ-3-98 02-07-07
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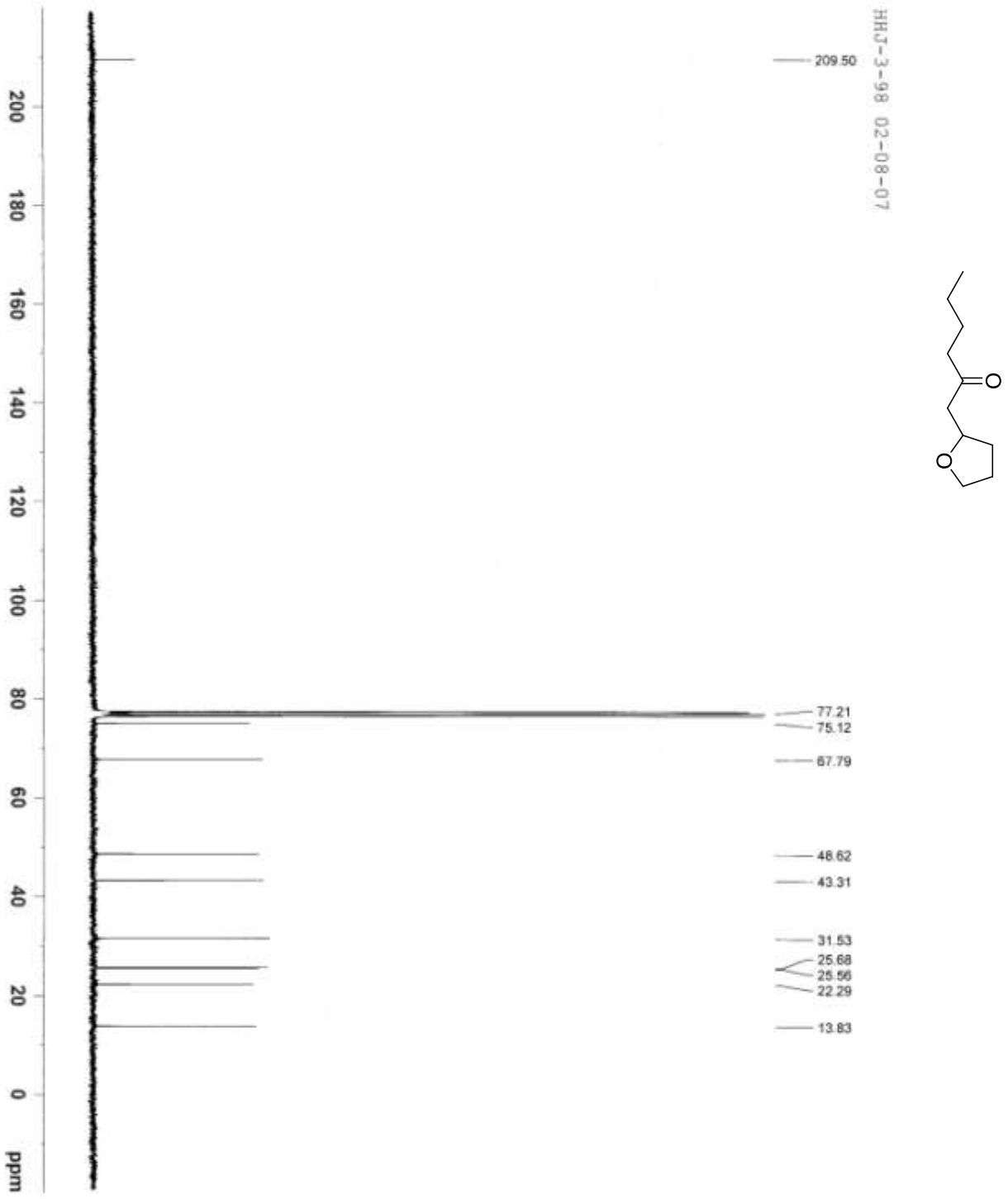
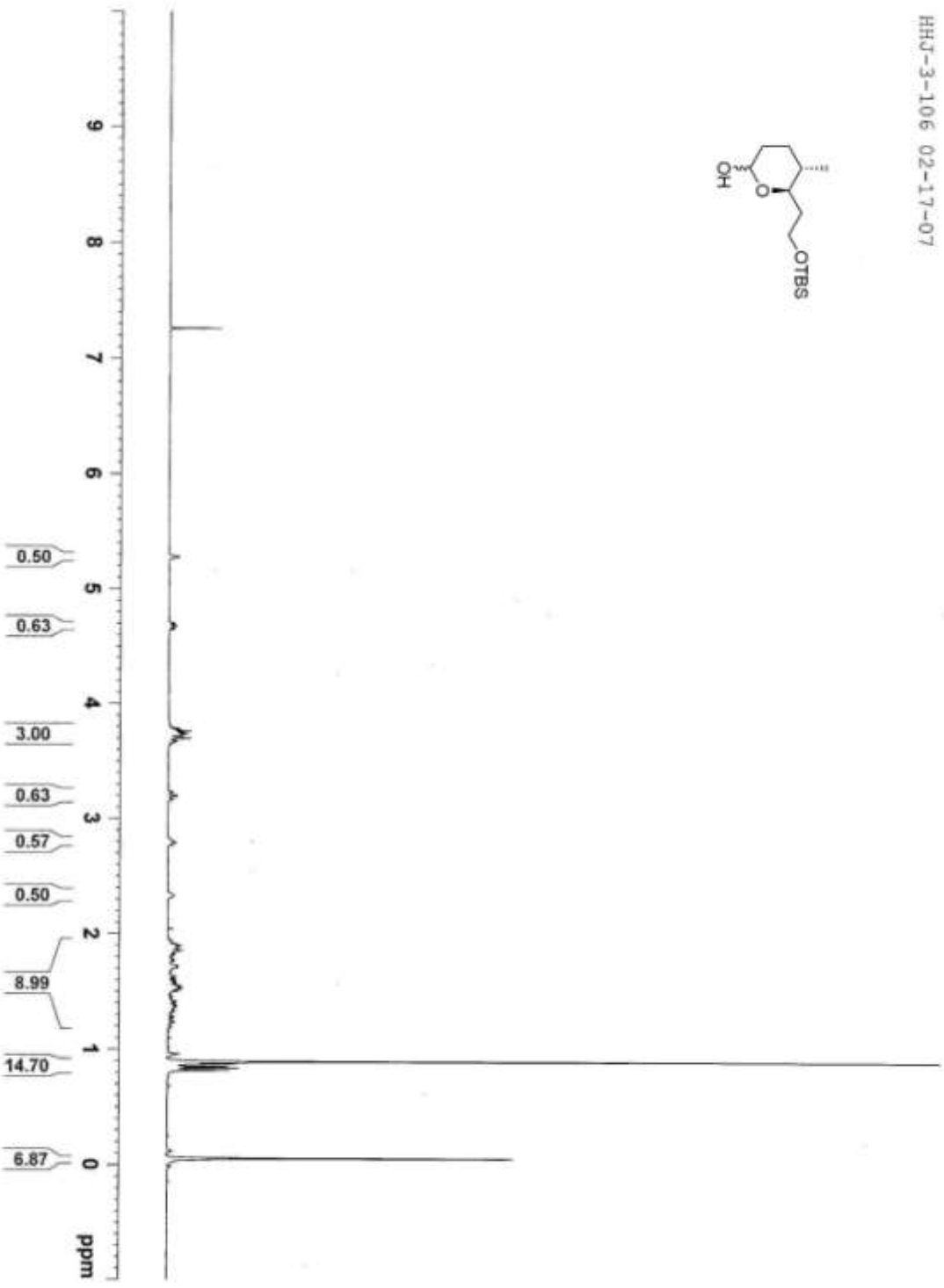
1.05
1.03
1.10
3.34
1.11
2.07
3.38
2.38
3.25
ppm

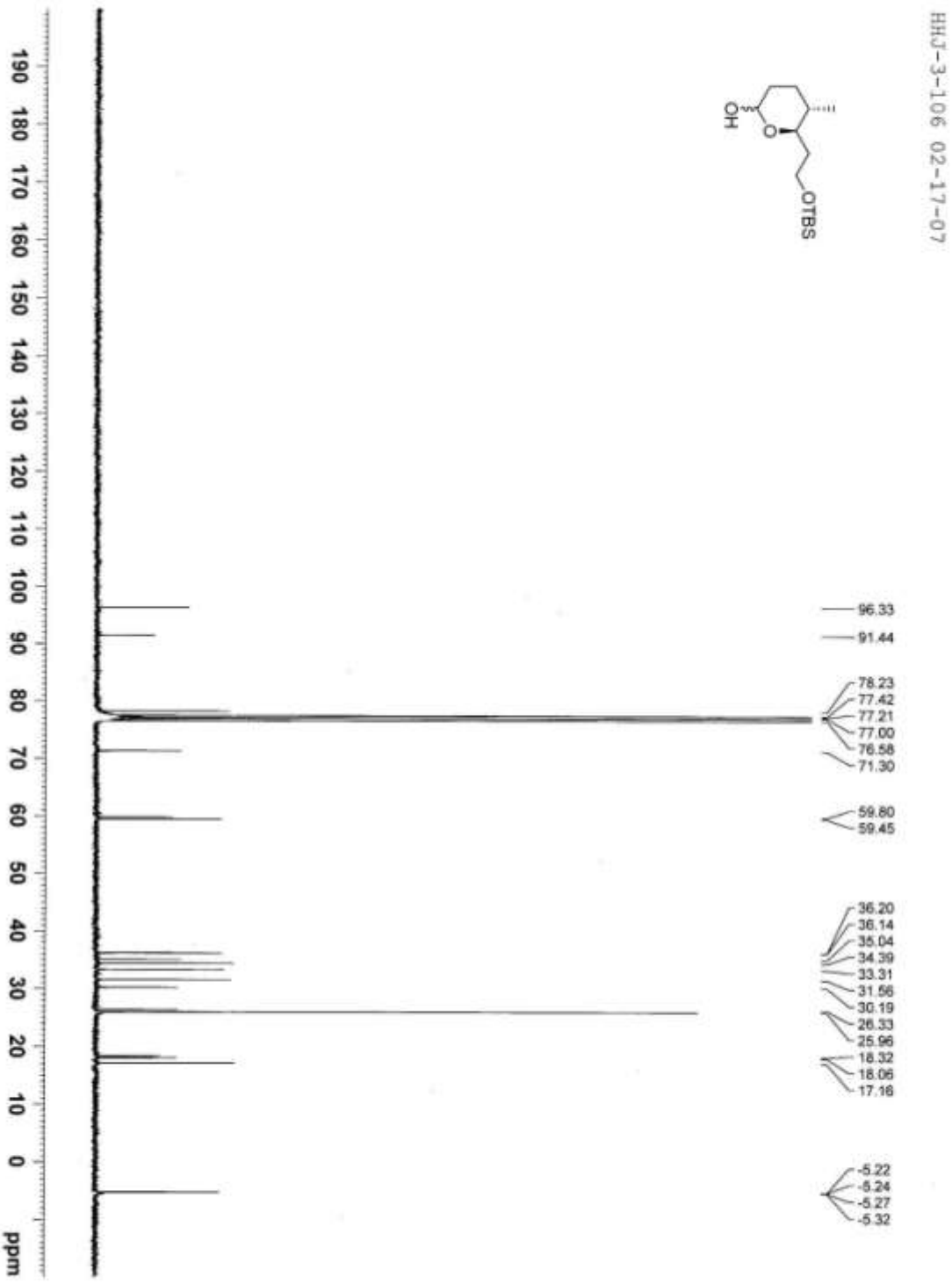

HHJ-3-98 02-08-07
209.50
77.21
75.12
67.79
48.62
43.31
31.53
25.68
25.56
22.29
13.83
200
180
160
140
120
100
80
60
40
20
0
ppm

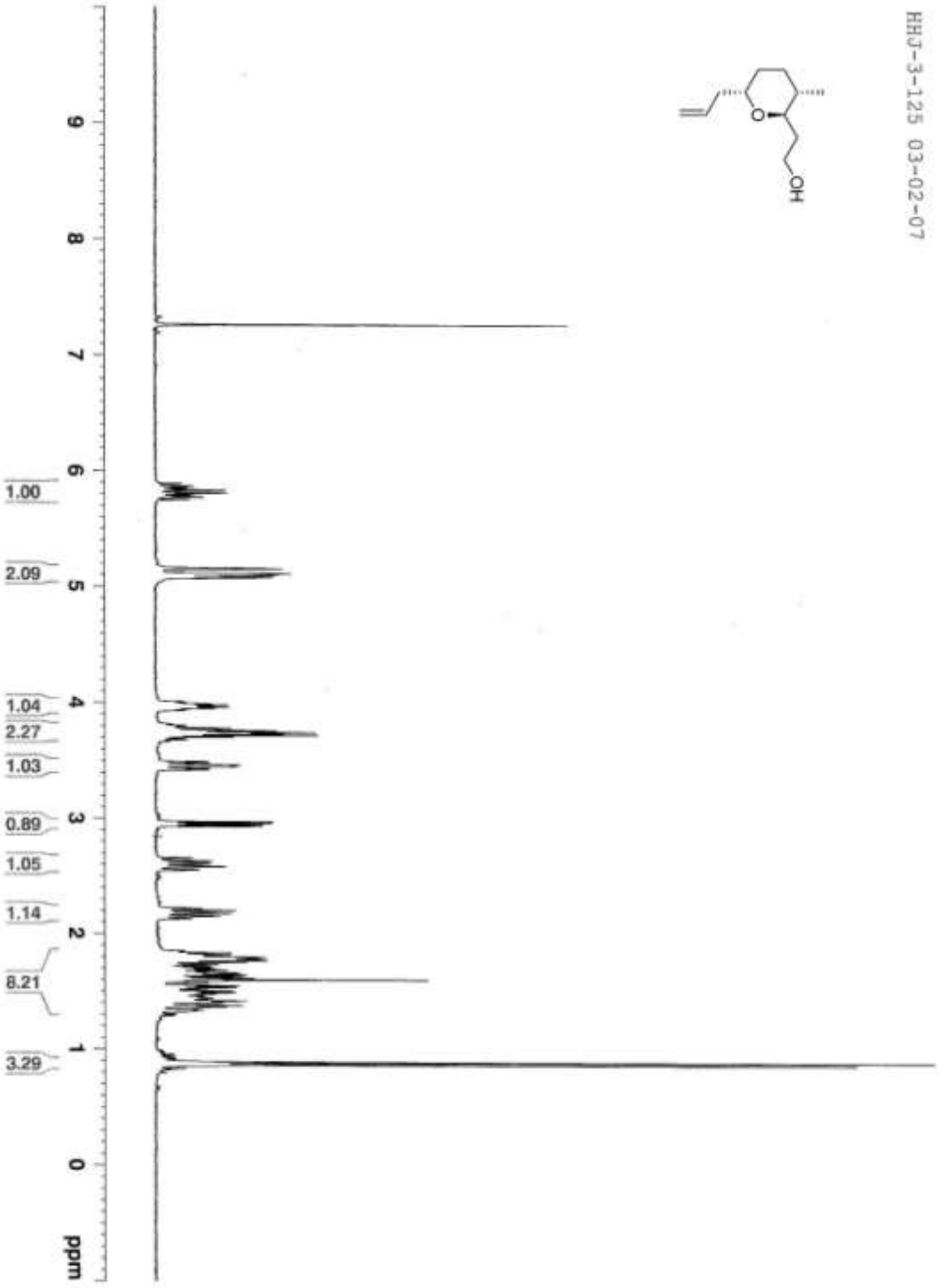
APPENDIX B

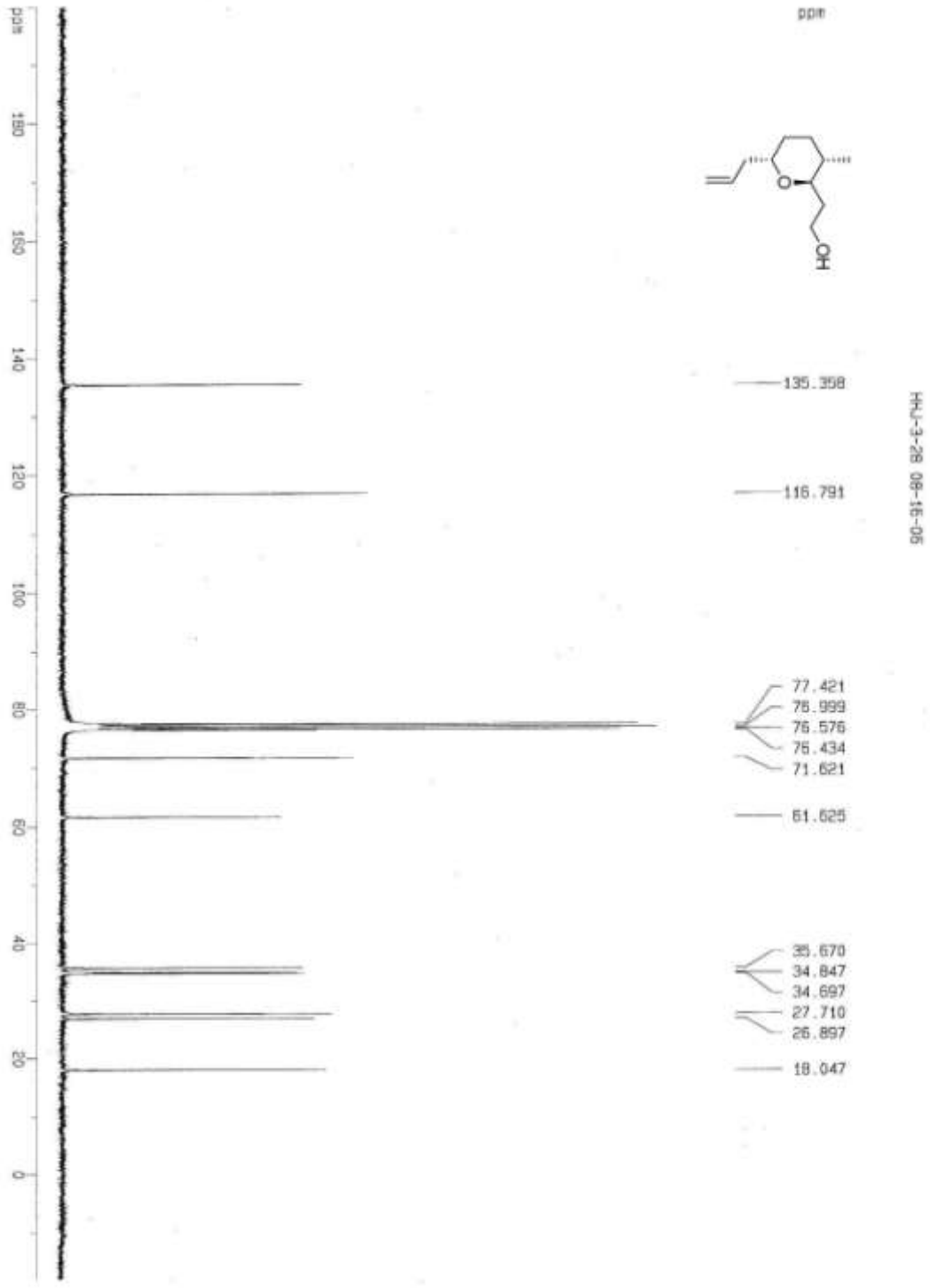
Synthesis of Leucascandrolide A

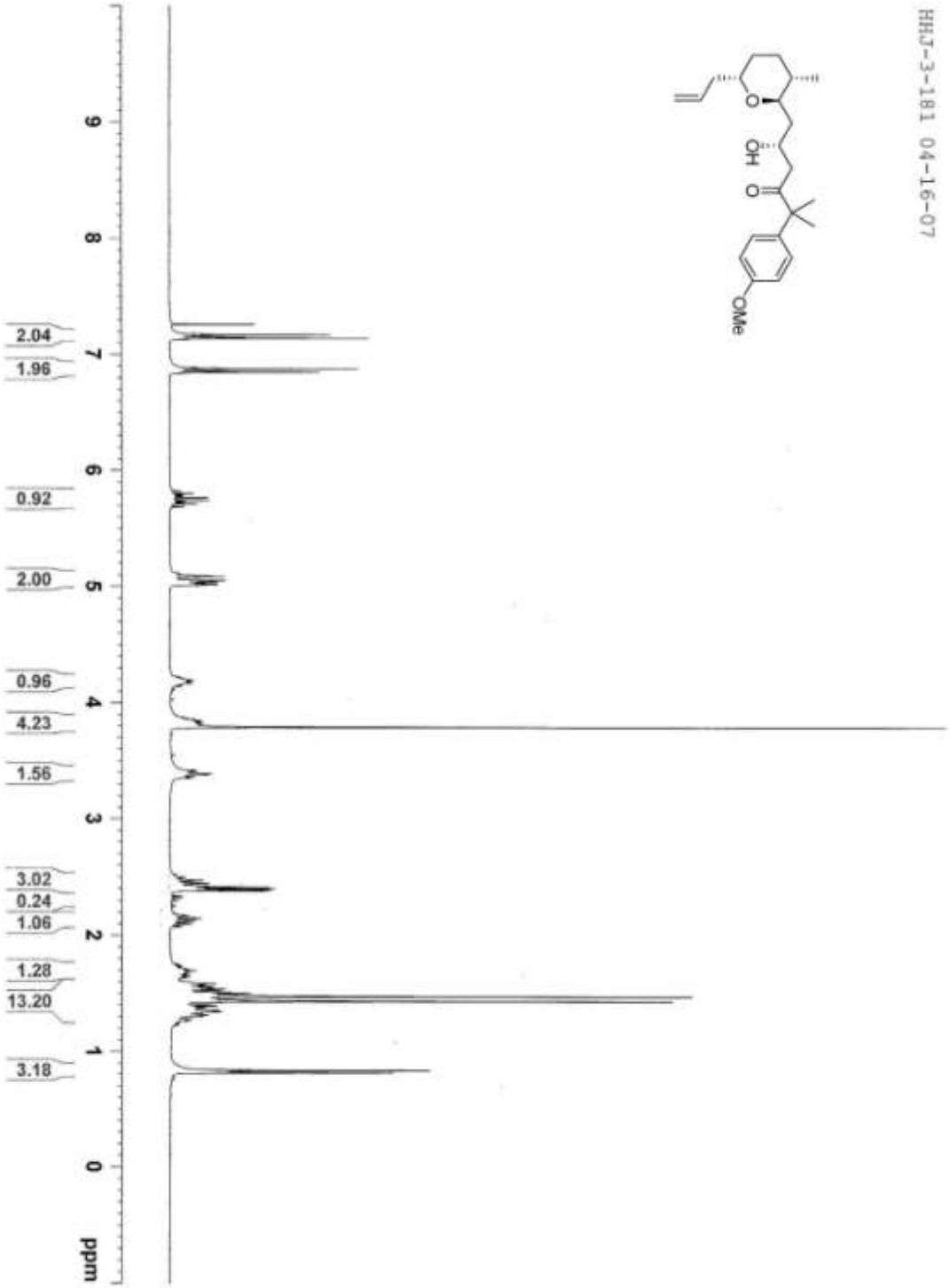
(Supporting Information ^{1}H and ^{13}C NMR Spectra)

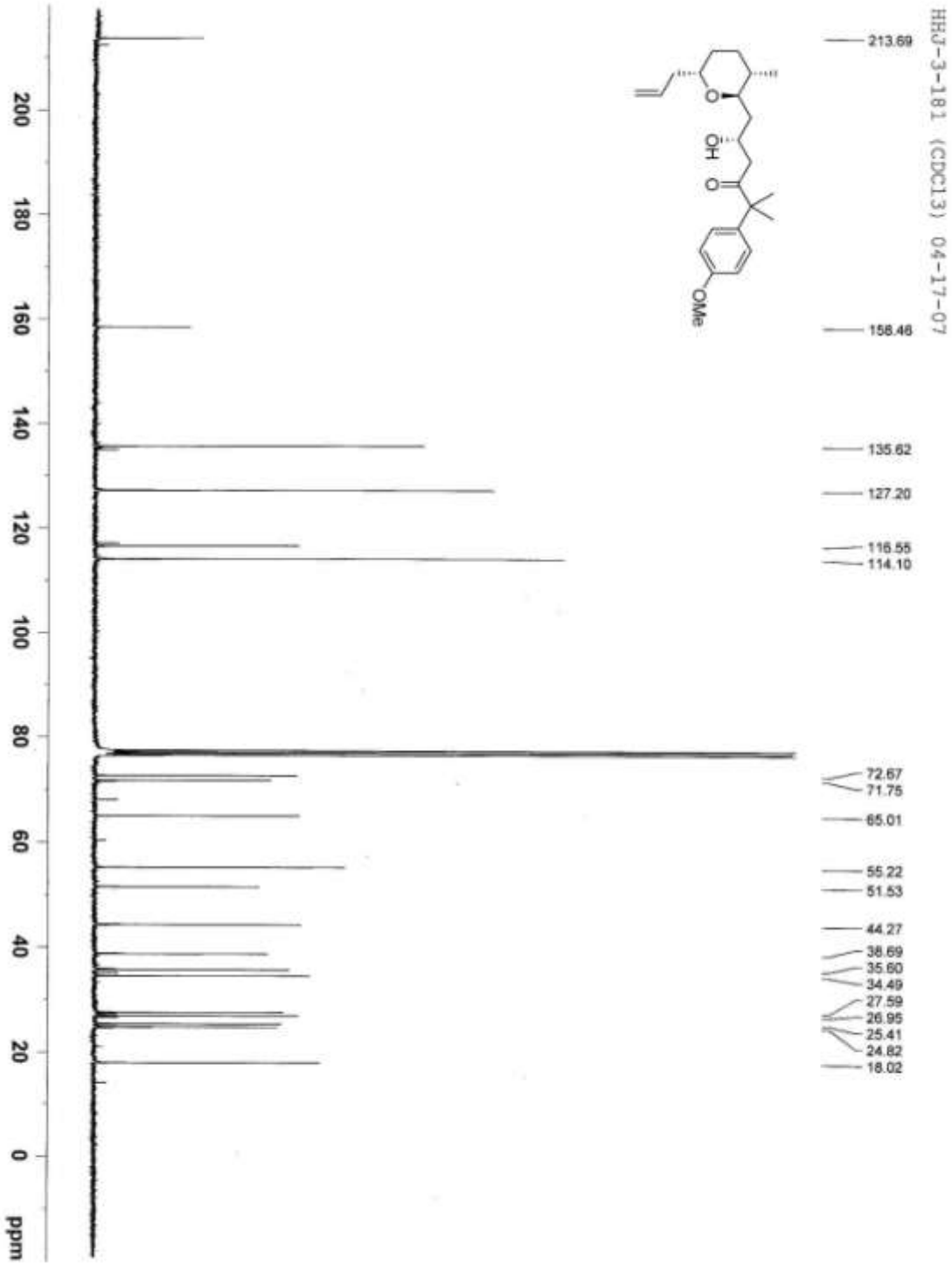

HHJ-3-106 02-17-07
OH
O
OTBS
0.50
0.63
3.00
0.63
0.57
0.50
8.99
14.70
6.87
9
8
7
6
5
4
3
2
1
0
ppm

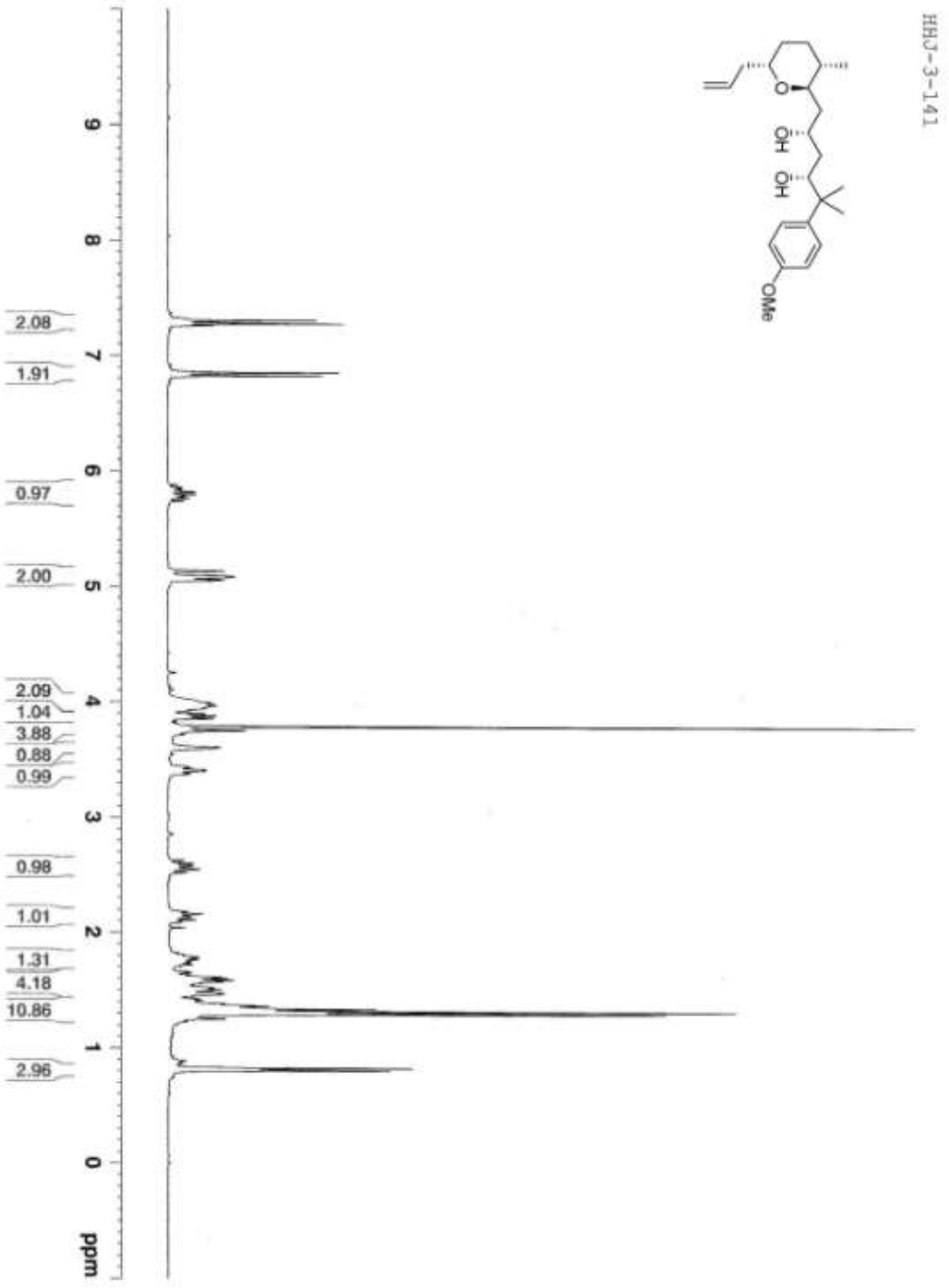

HHJ-3-106 02-17-07
OH
O
OTBS
96.33
91.44
78.23
77.42
77.21
77.00
76.58
71.30
59.80
59.45
36.20
36.14
35.04
34.39
33.31
31.56
30.19
26.33
25.96
18.32
18.06
17.16
-5.22
-5.24
-5.27
-5.32
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

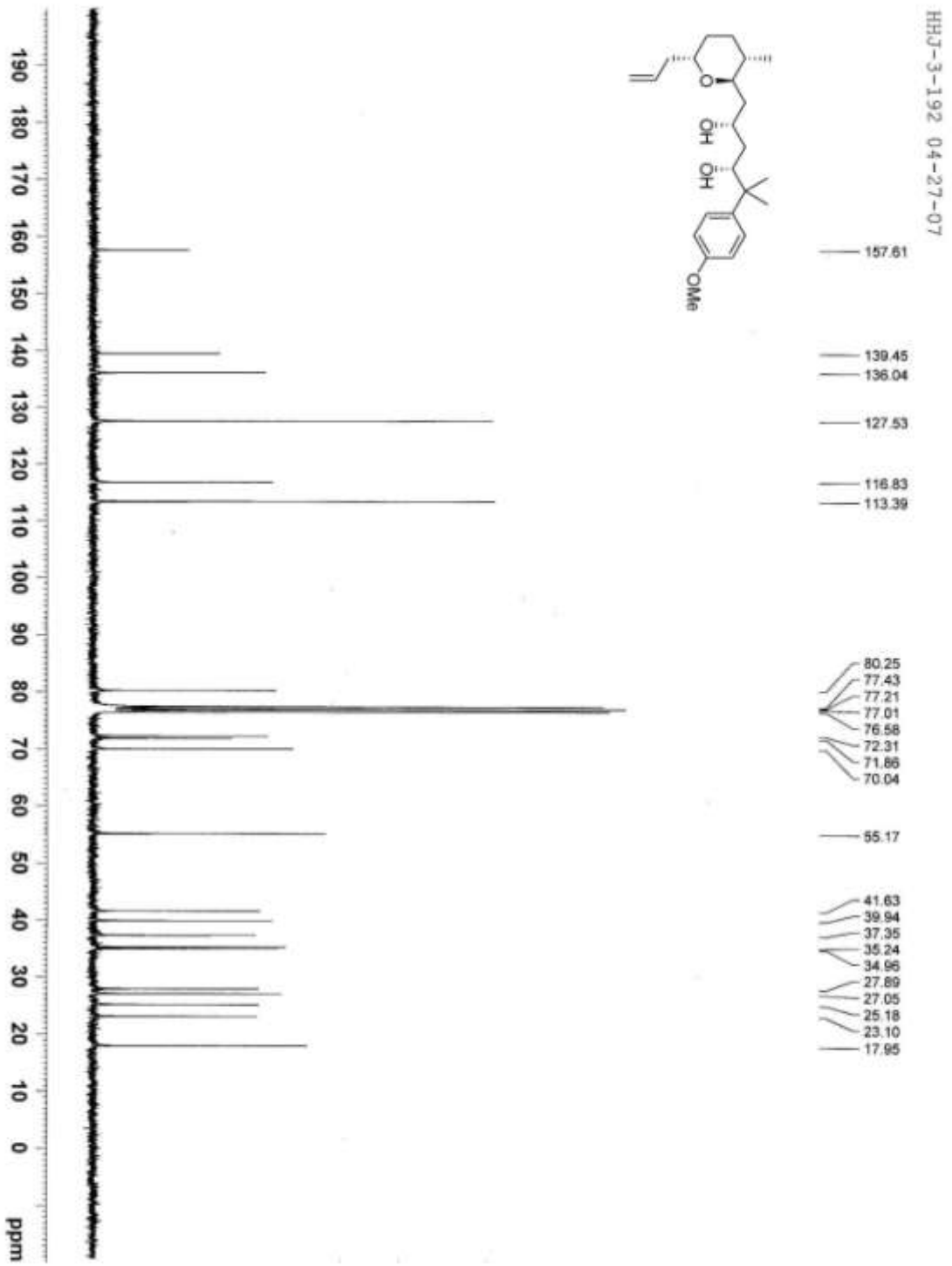

HHJ-3-125 03-02-07
OH
1.00
2.09
1.04
2.27
1.03
0.89
1.05
1.14
8.21
3.29
ppm


ppm
180
160
140
120
100
80
60
40
20
0
135.358
116.791
77.421
76.999
76.576
75.434
71.621
61.625
35.670
34.847
34.697
27.710
26.897
18.047
OH
HHJ-3-28 08-16-06


HHJ-3-181 04-16-07
OMe
OH
O
O
2.04
1.96
0.92
2.00
0.96
4.23
1.56
3.02
0.24
1.06
1.28
13.20
3.18
ppm


HHJ-3-181 (CDCl3) 04-17-07
213.69
158.46
135.62
127.20
116.55
114.10
72.67
71.75
65.01
55.22
51.53
44.27
38.69
35.60
34.49
27.59
26.95
25.41
24.82
18.02
OH
O
OMe
200
180
160
140
120
100
80
60
40
20
0
ppm


HHJ-3-141
OH
OH
OMe
2.08
1.91
0.97
2.00
2.09
1.04
3.88
0.88
0.99
0.98
1.01
1.31
4.18
10.86
2.96
9
8
7
6
5
4
3
2
1
0
ppm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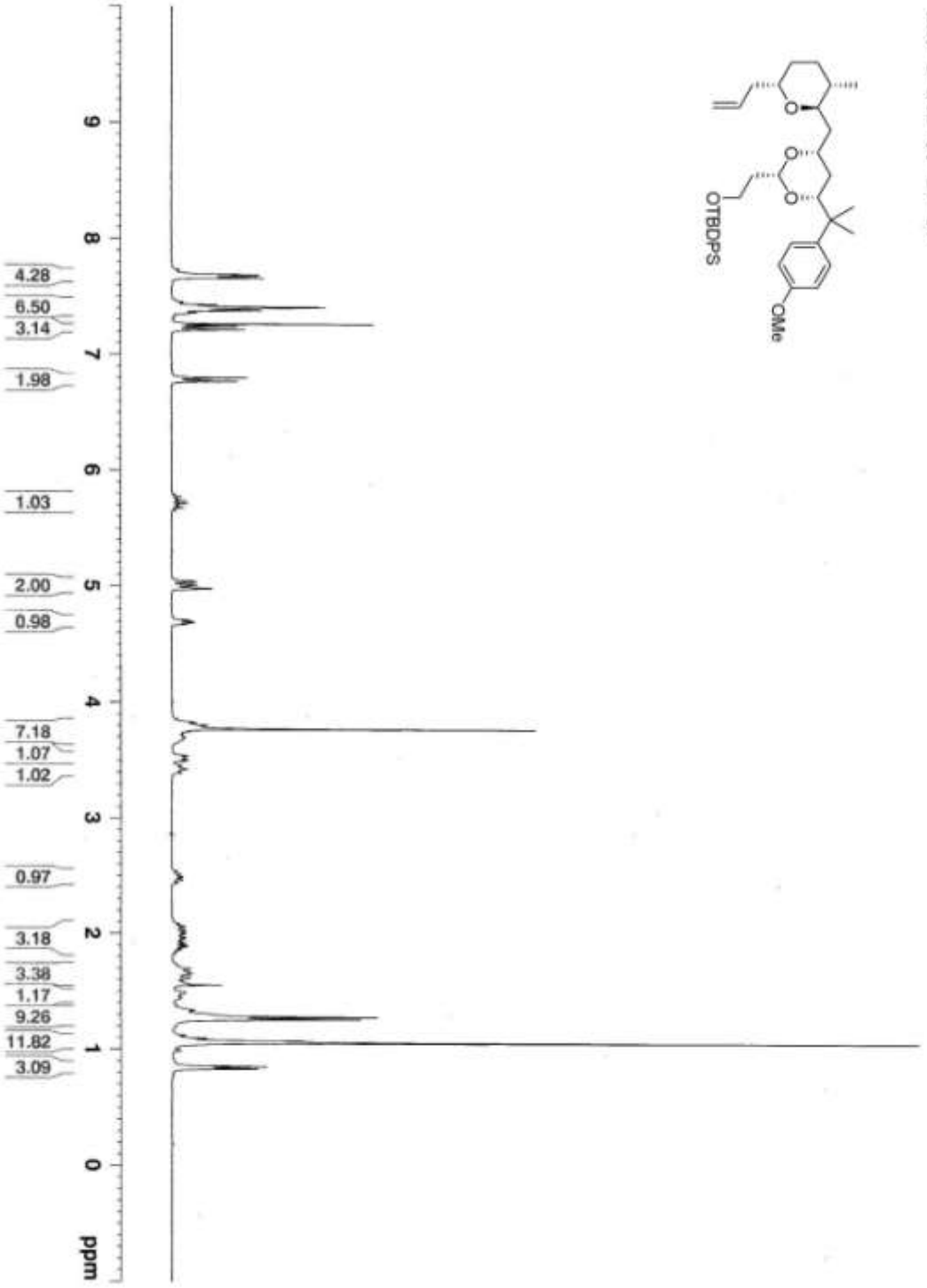
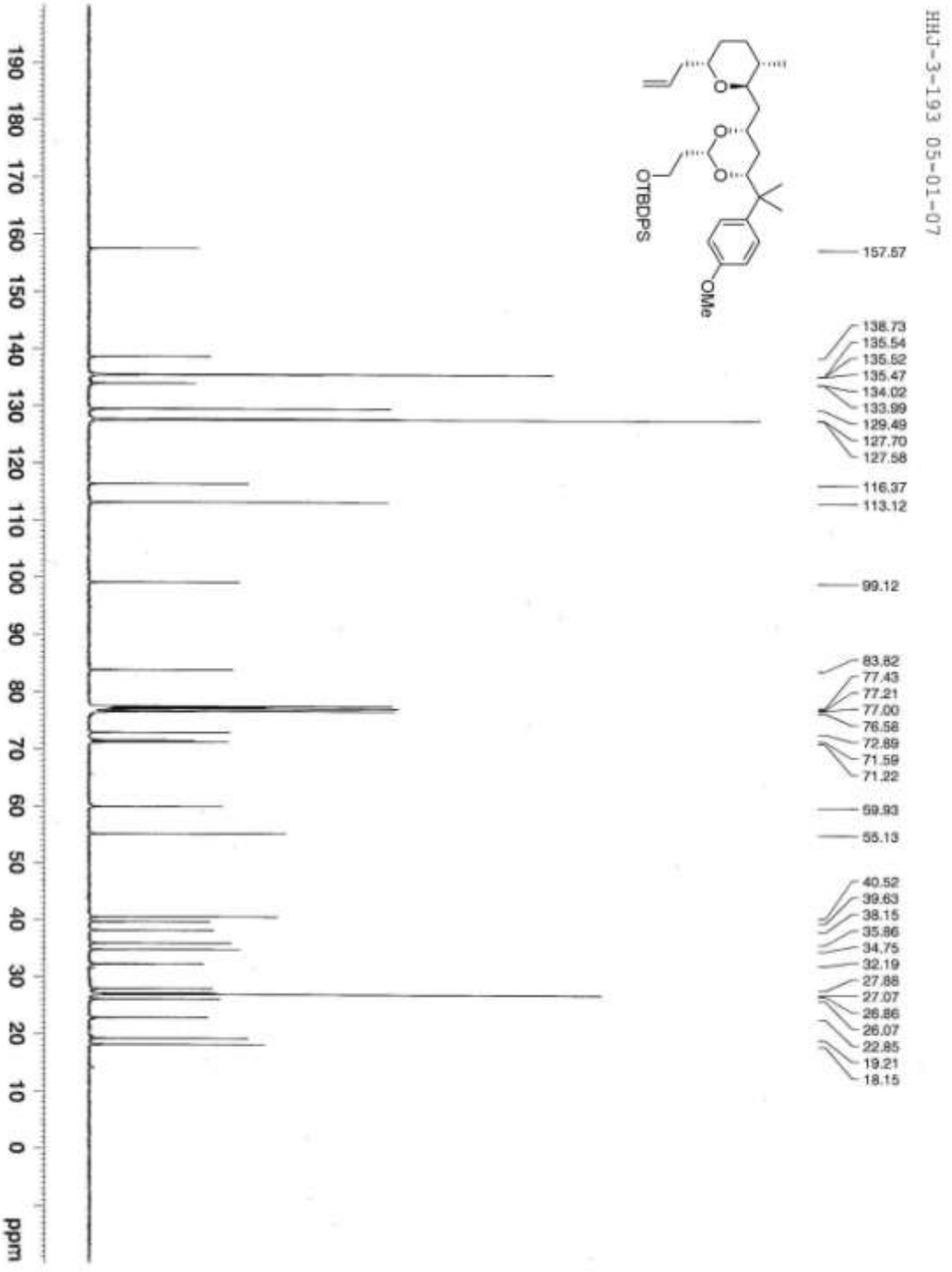
OH
OH
OMe
157.61
139.45
136.04
127.53
116.83
113.39
80.25
77.43
77.21
77.01
76.58
72.31
71.86
70.04
55.17
41.63
39.94
37.35
35.24
34.96
27.89
27.05
25.18
23.10
17.95
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HHJ-3-141 03-17-07
OTBDPS
OMe
4.28
6.50
3.14
1.98
1.03
2.00
0.98
7.18
1.07
1.02
0.97
3.18
3.38
1.17
9.26
11.82
3.09
9
8
7
6
5
4
3
2
1
0
ppm


HHJ-3-193 05-01-07
OTBDPS
OMe
157.57
138.73
135.54
135.52
135.47
134.02
133.99
129.49
127.70
127.58
116.37
113.12
99.12
83.82
77.43
77.21
77.00
76.58
72.89
71.59
71.22
59.93
55.13
40.52
39.63
38.15
35.86
34.75
32.19
27.88
27.07
26.86
26.07
22.85
19.21
18.15
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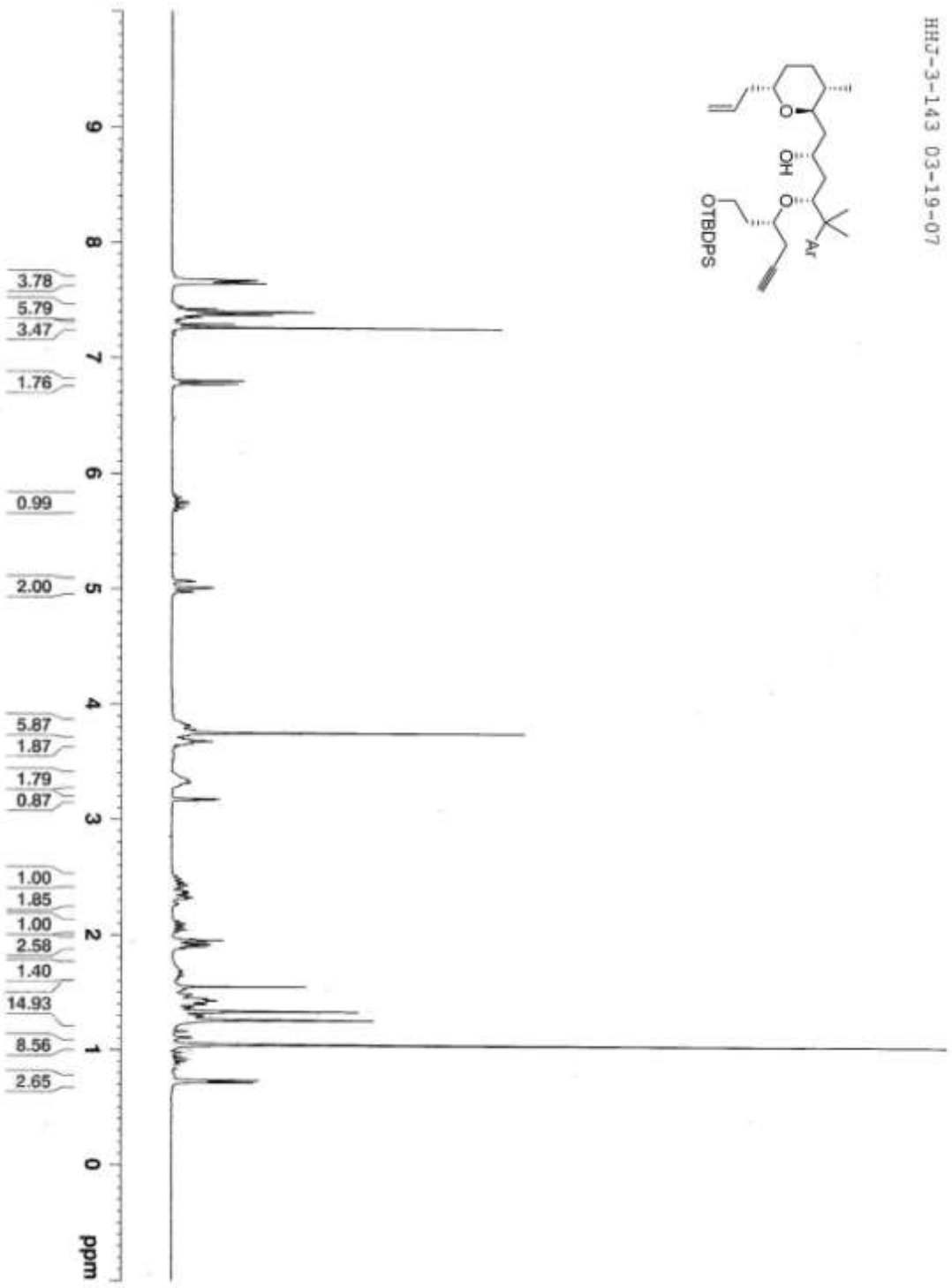
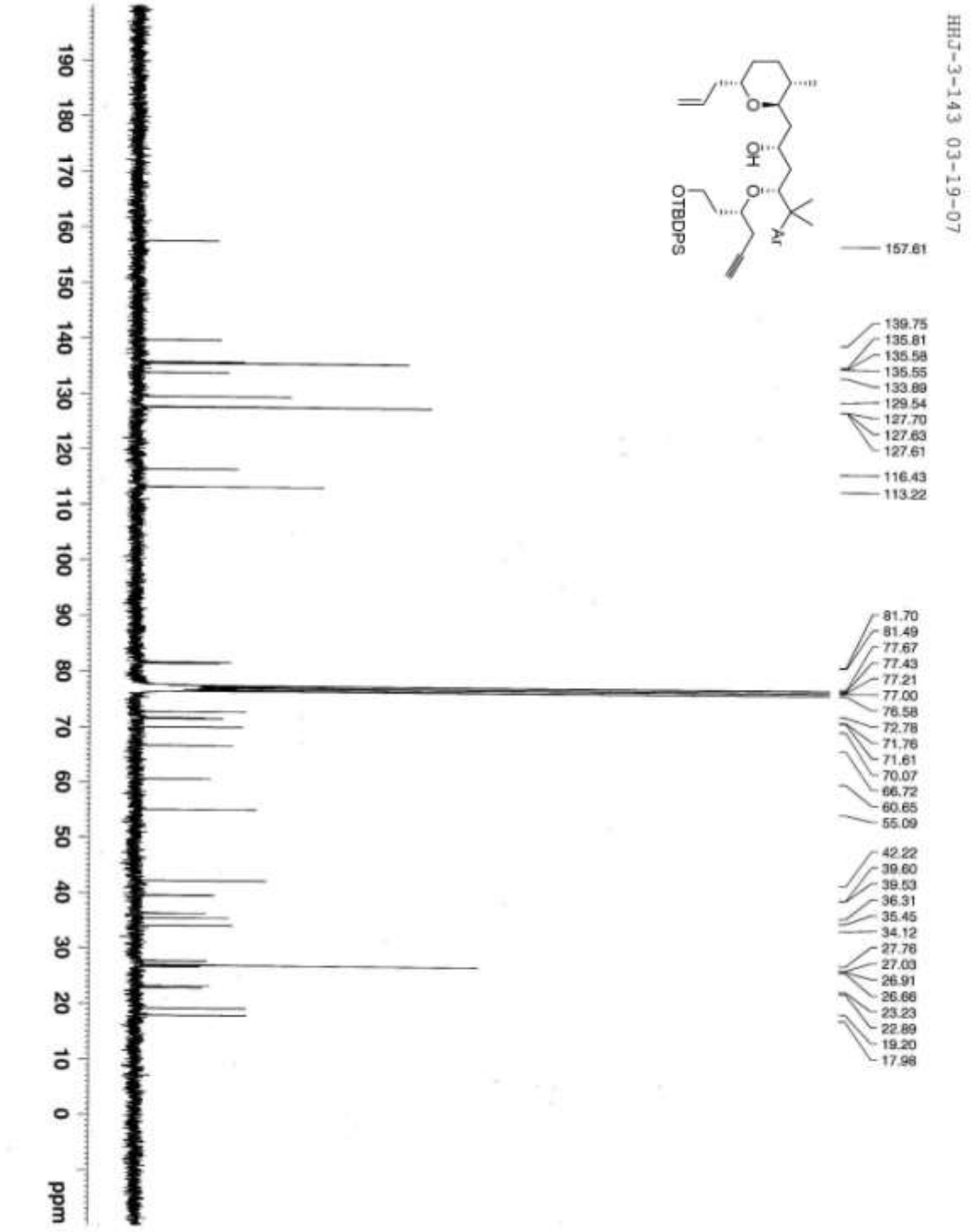

HHJ-3-143 03-19-07
OH
O
Ar
OTBDPS
3.78
5.79
3.47
1.76
0.99
2.00
5.87
1.87
1.79
0.87
1.00
1.85
1.00
2.58
1.40
14.93
8.56
2.65
9
8
7
6
5
4
3
2
1
0
ppm


HHJ-3-143 03-19-07
OTBDPS
OH
Ar
157.61
139.75
135.81
135.58
135.55
133.89
129.54
127.70
127.63
127.61
116.43
113.22
81.70
81.49
77.67
77.43
77.21
77.00
76.58
72.78
71.76
71.61
70.07
66.72
60.65
55.09
42.22
39.60
39.53
36.31
35.45
34.12
27.76
27.03
26.91
26.66
23.23
22.89
19.20
17.98
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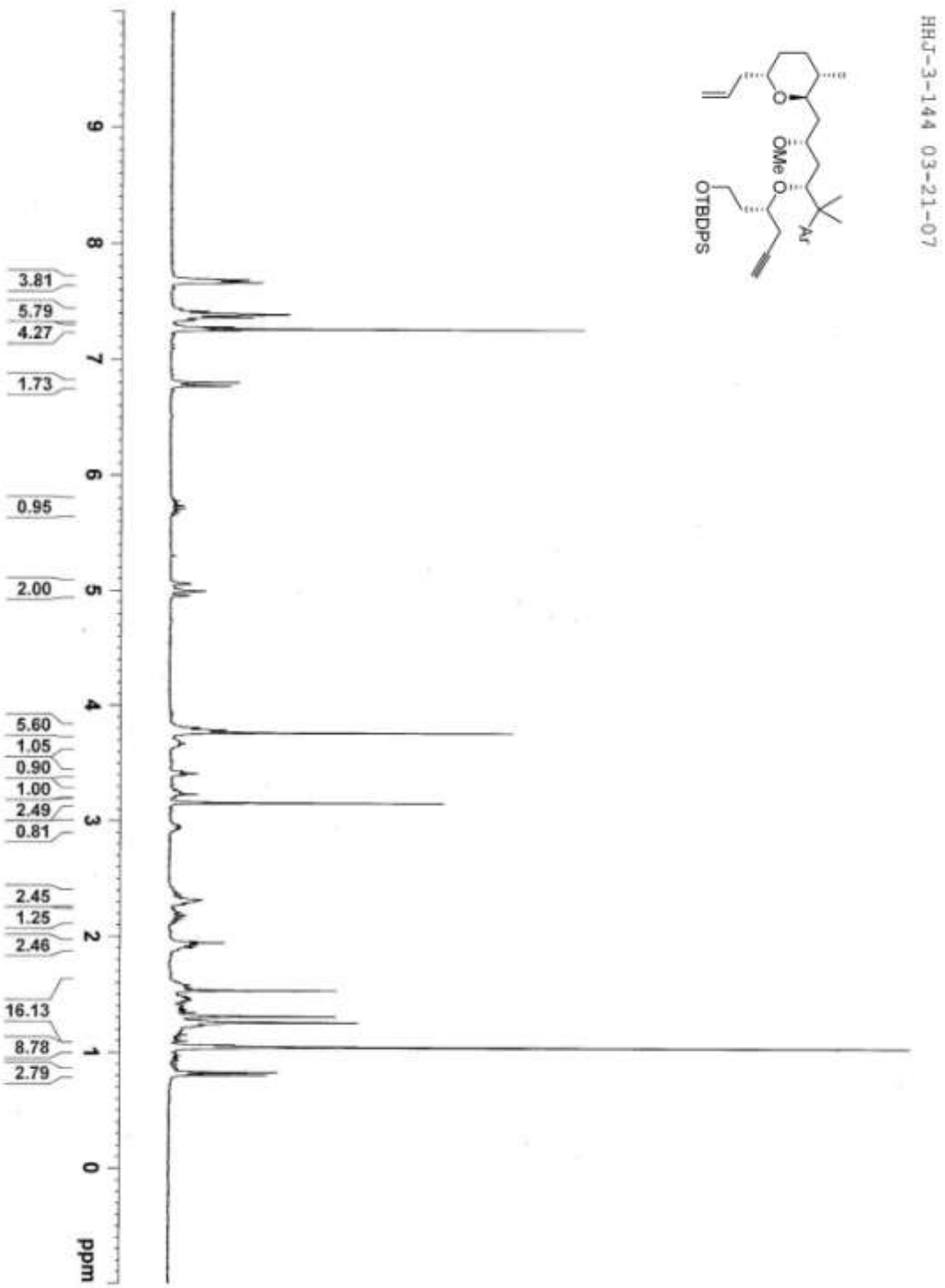
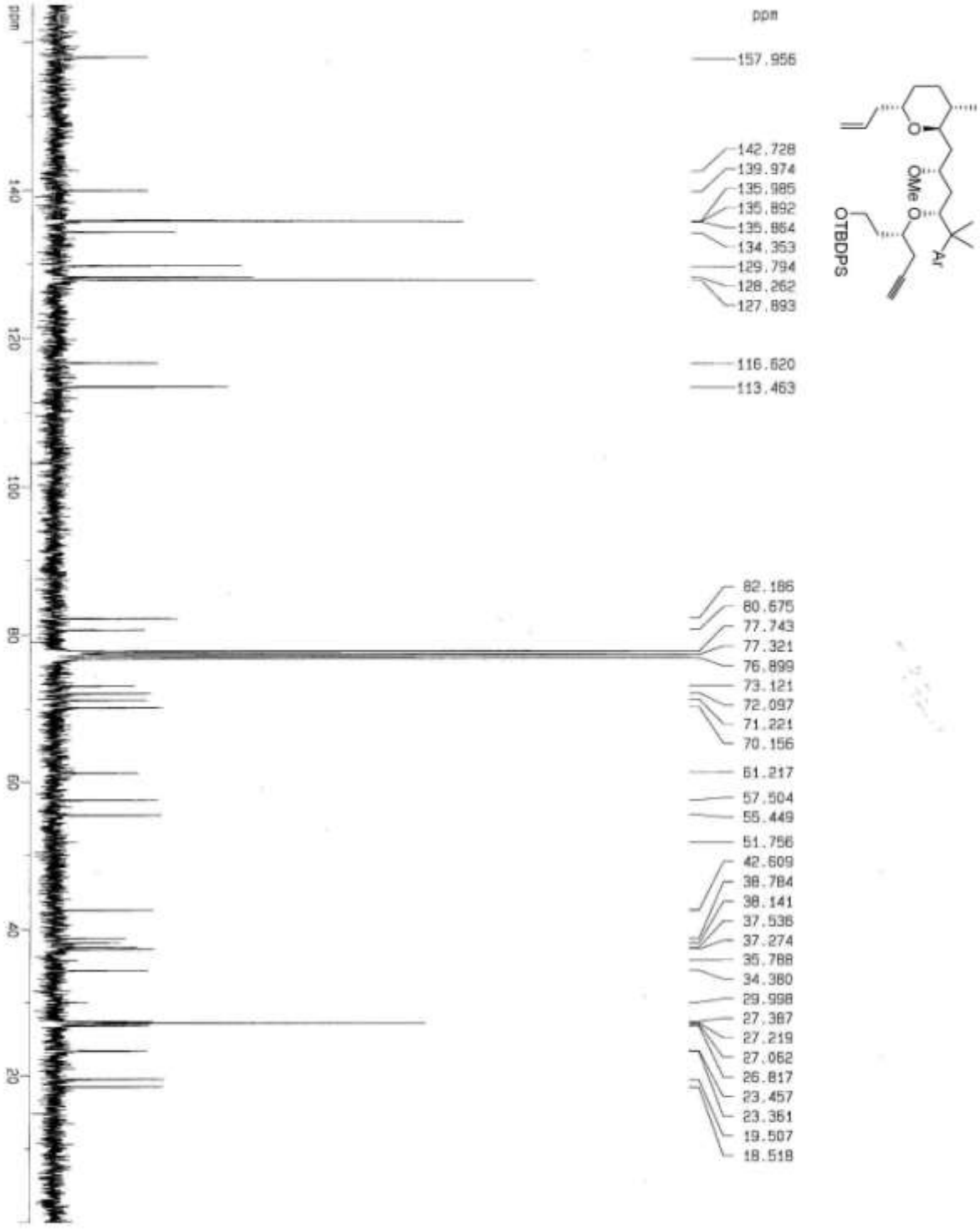

HHJ-3-144 03-21-07
OMe
OTBDPS
Ar
3.81
5.79
4.27
1.73
0.95
2.00
5.60
1.05
0.90
1.00
2.49
0.81
2.45
1.25
2.46
16.13
8.78
2.79
9
8
7
6
5
4
3
2
1
0
ppm


ppm
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139.974
135.985
135.892
135.864
134.353
129.794
128.262
127.893
116.620
113.463
82.186
80.675
77.743
77.321
76.899
73.121
72.097
71.221
70.156
61.217
57.504
55.449
51.756
42.609
38.784
38.141
37.538
37.274
35.788
34.380
29.998
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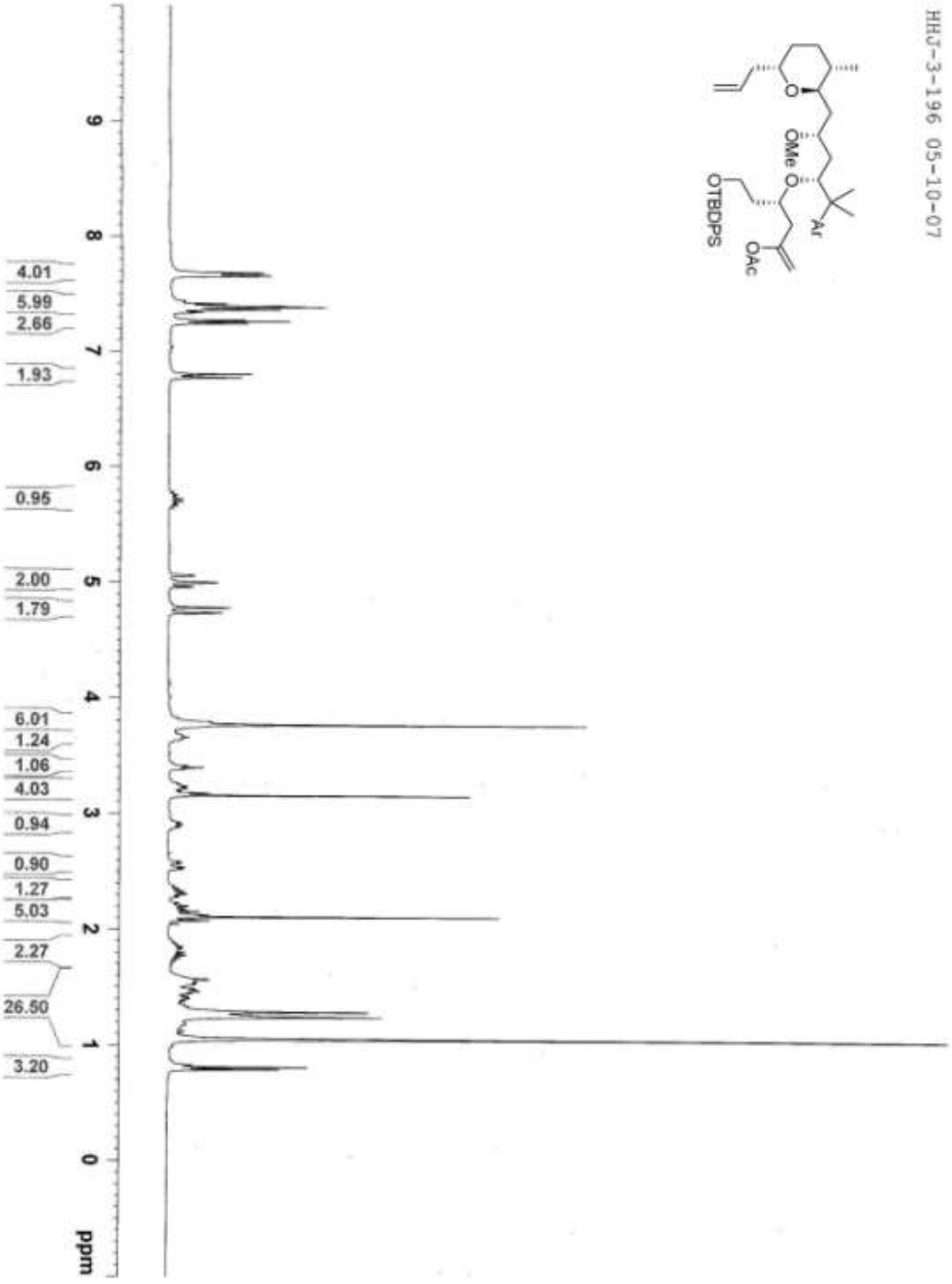
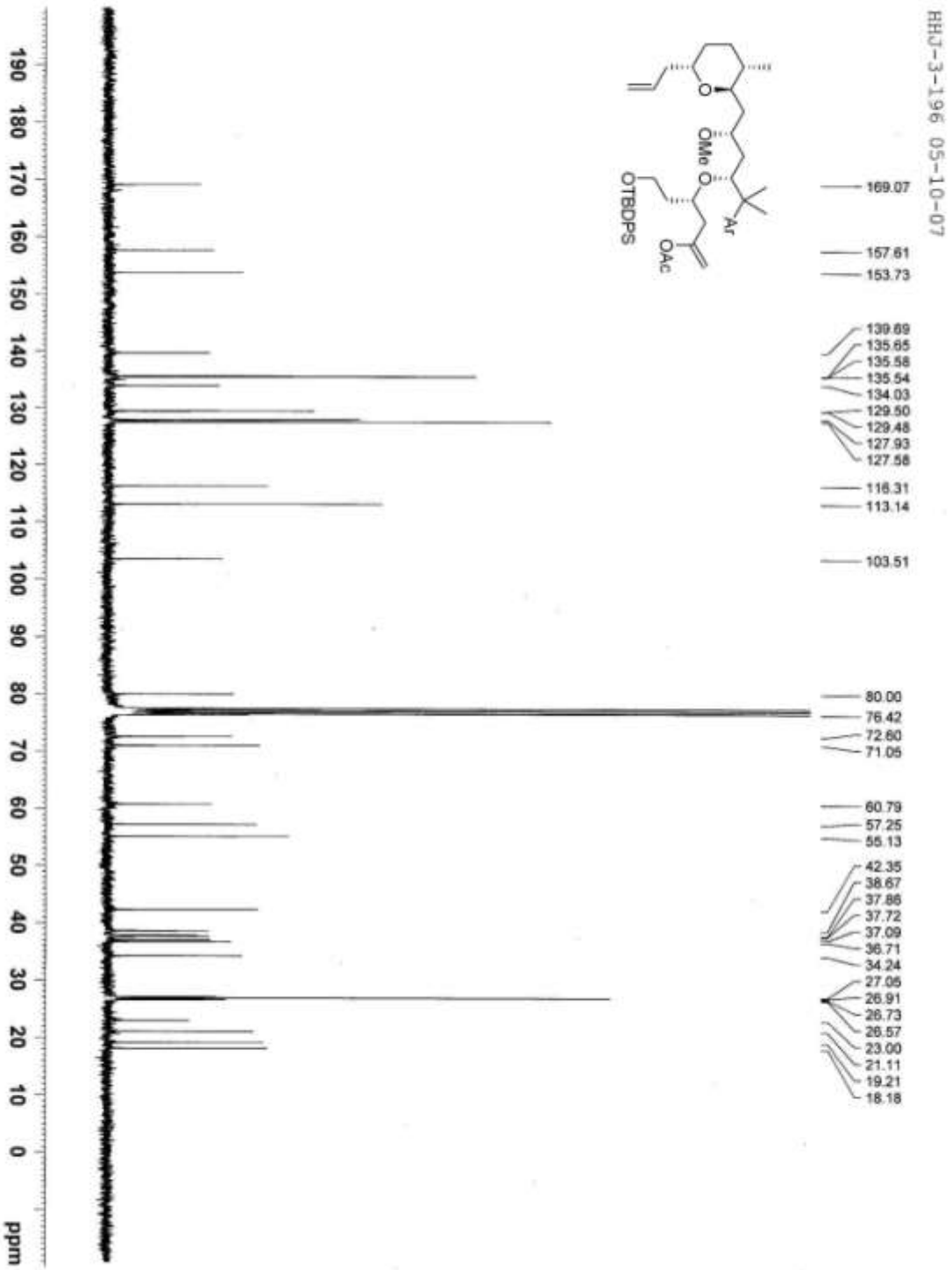
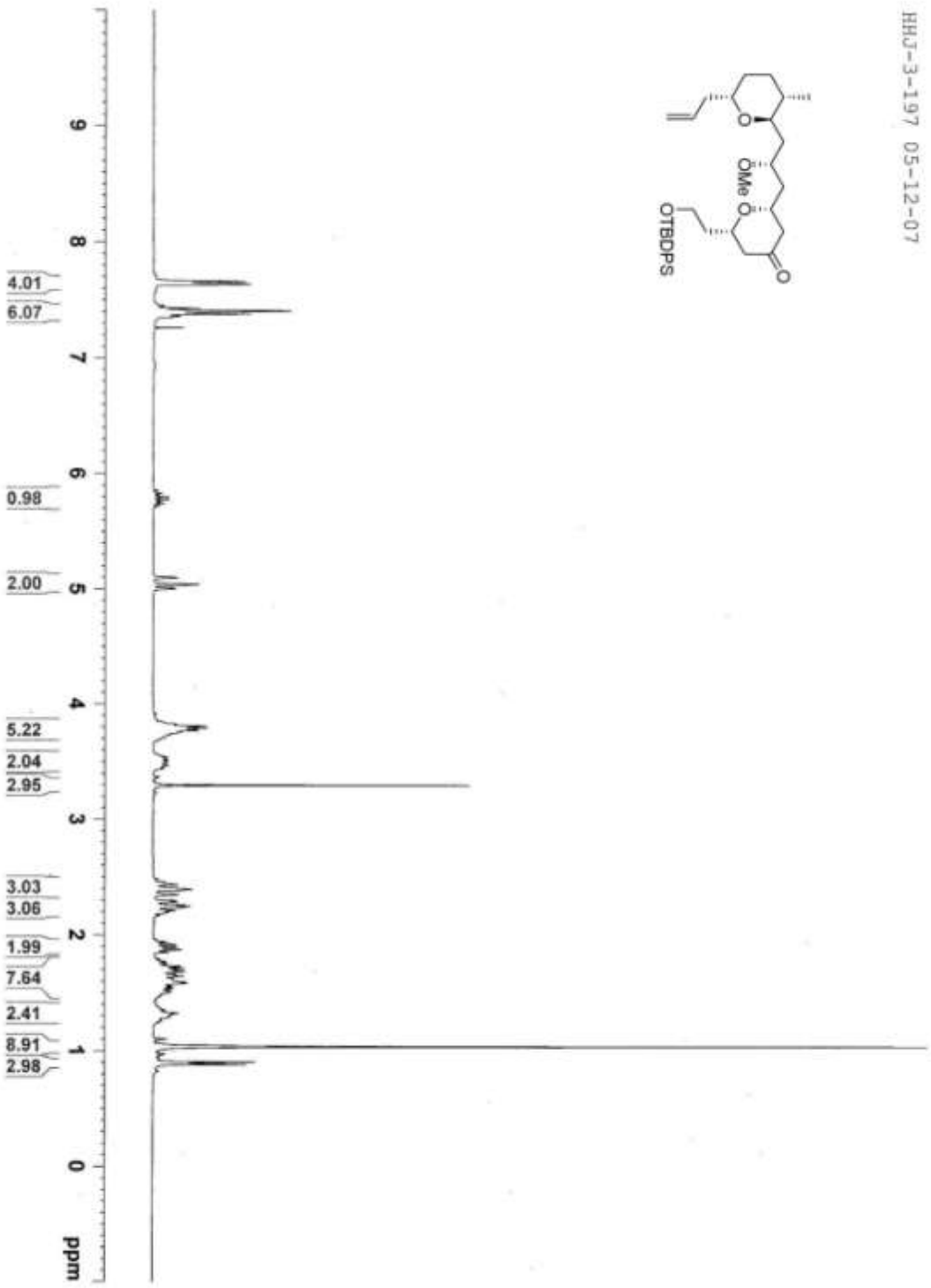
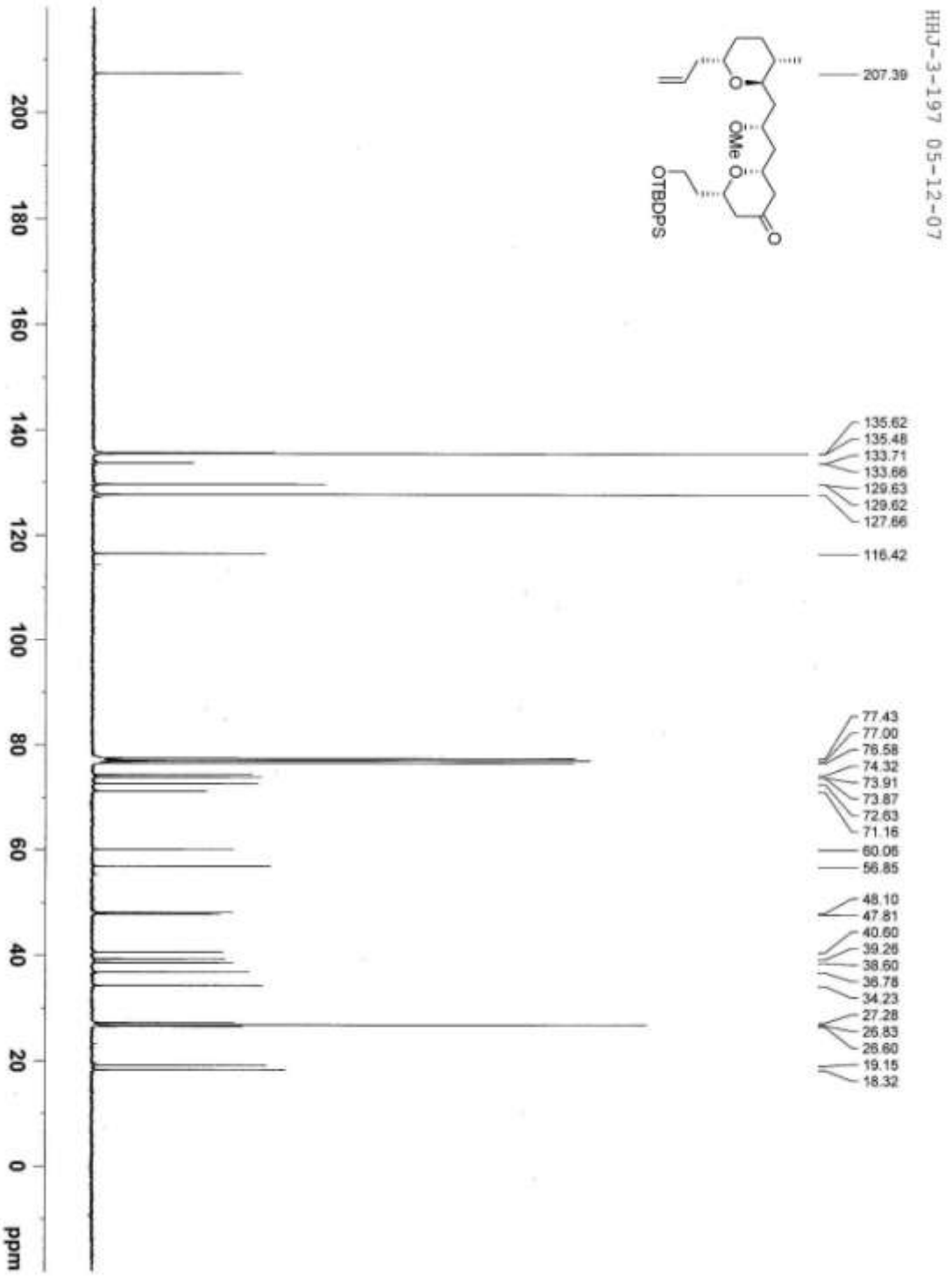
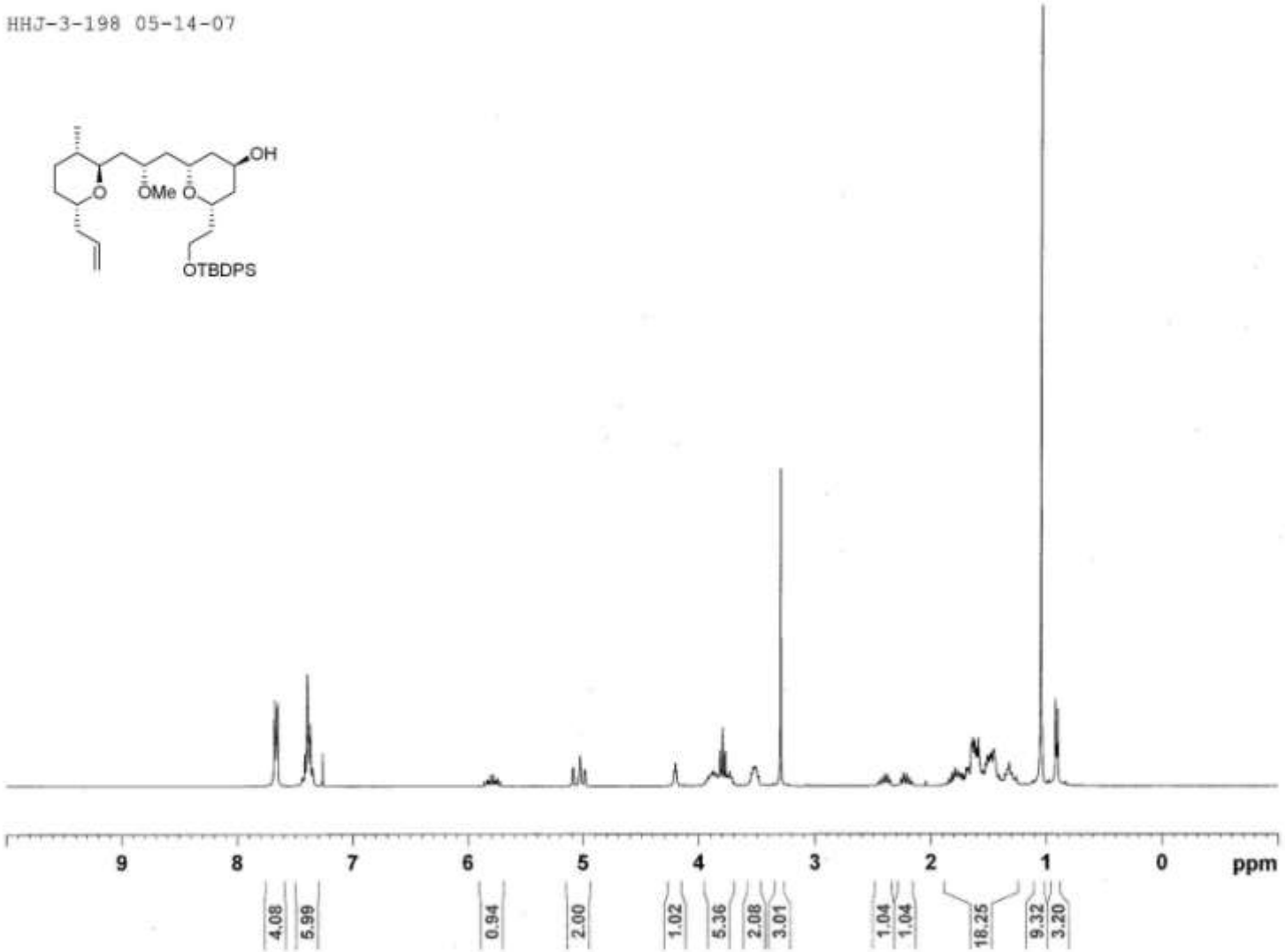
27.219
27.062
26.817
23.457
23.351
19.507
18.518
OTBDPS
OMe
Ar

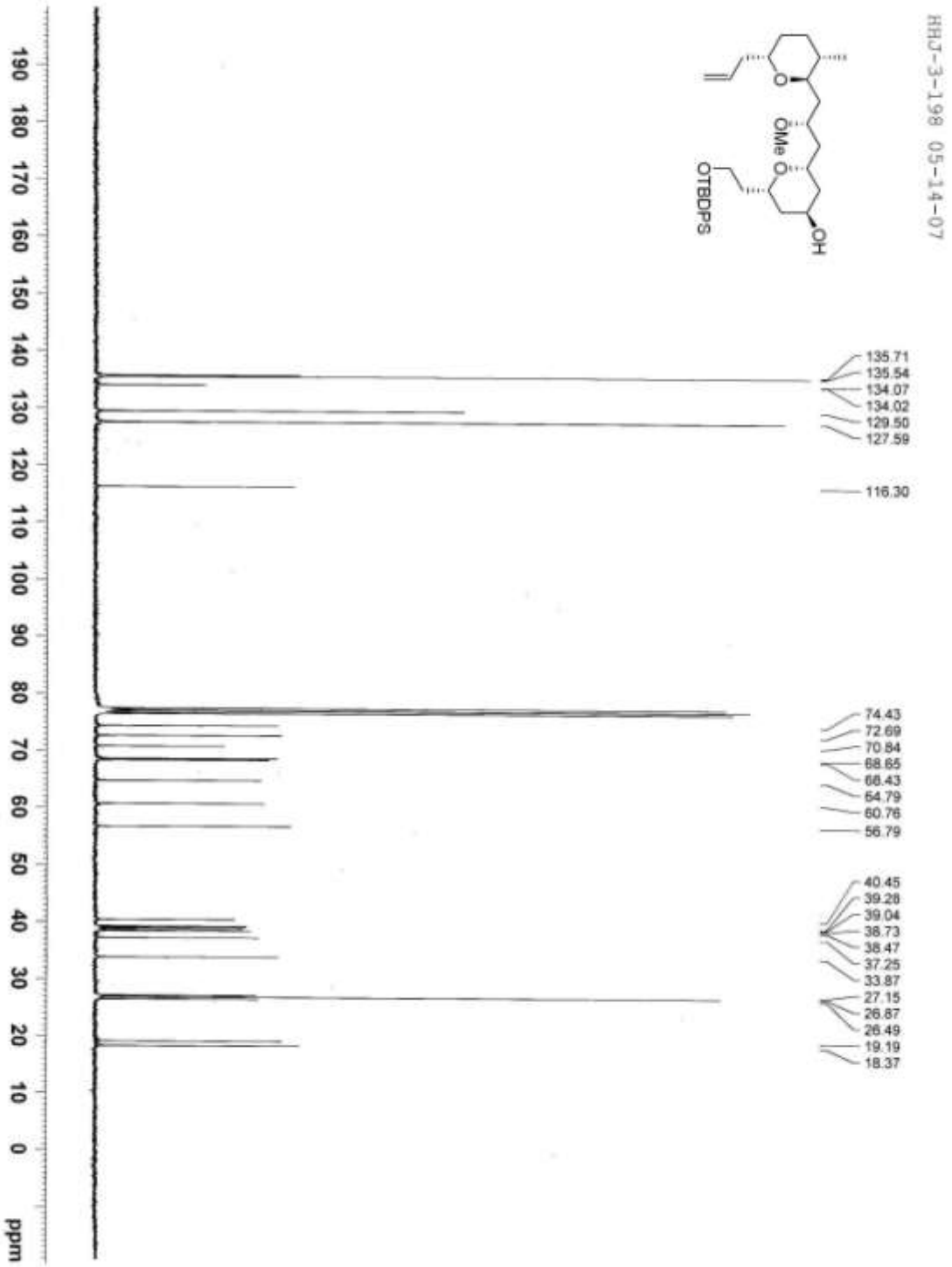

HHJ-3-196 05-10-07
OTBDPS
OMe
OAc
Ar
4.01
5.99
2.66
1.93
0.95
2.00
1.79
6.01
1.24
1.06
4.03
0.94
0.90
1.27
5.03
2.27
26.50
3.20
ppm

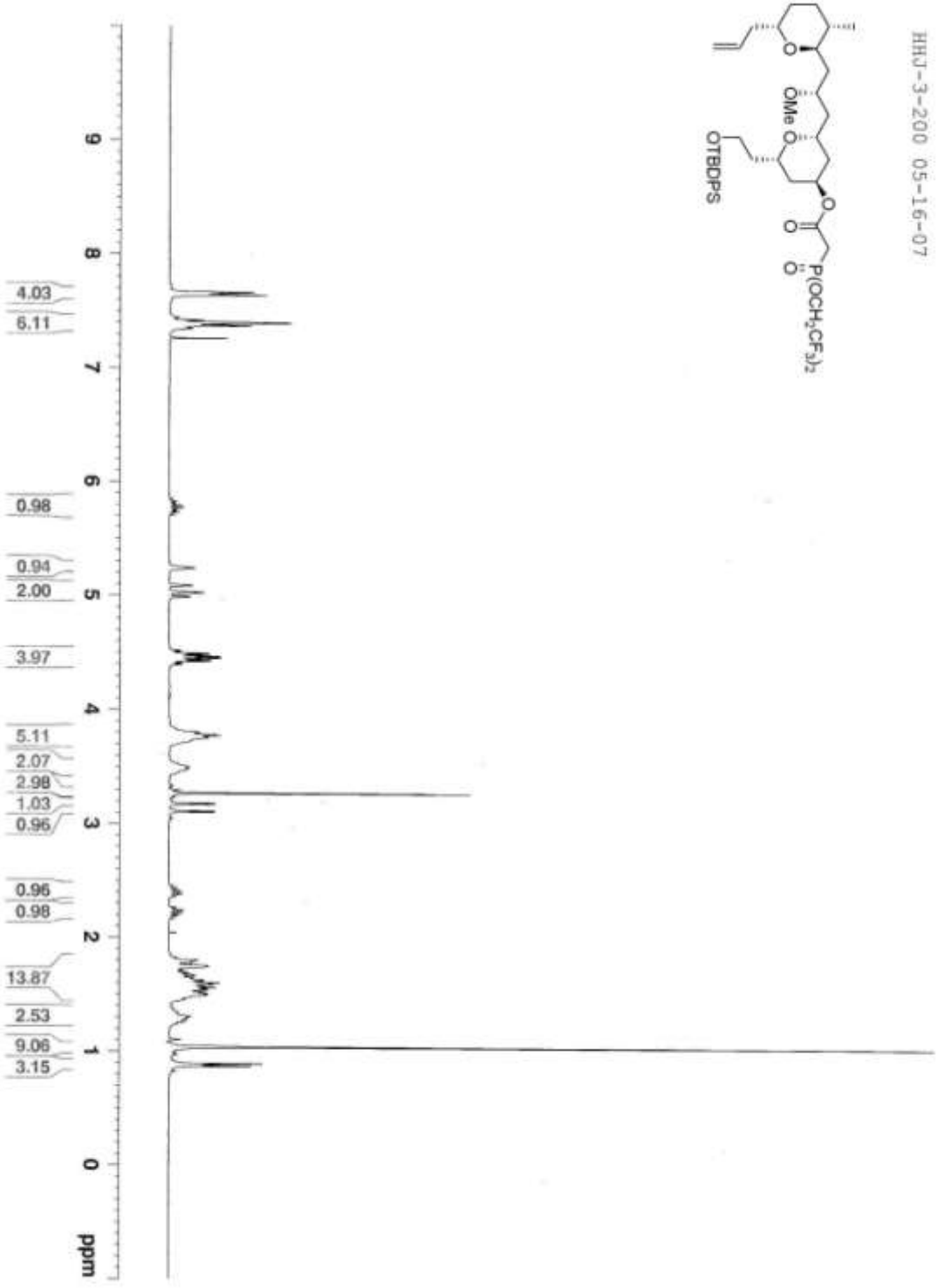

HHJ-3-196 05-10-07
OTBDPS
OAc
OMe
Ar
169.07
157.61
153.73
139.69
135.65
135.58
135.54
134.03
129.50
129.48
127.93
127.58
118.31
113.14
103.51
80.00
76.42
72.60
71.05
60.79
57.25
55.13
42.35
38.67
37.86
37.72
37.09
36.71
34.24
27.05
26.91
26.73
26.57
23.00
21.11
19.21
18.18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

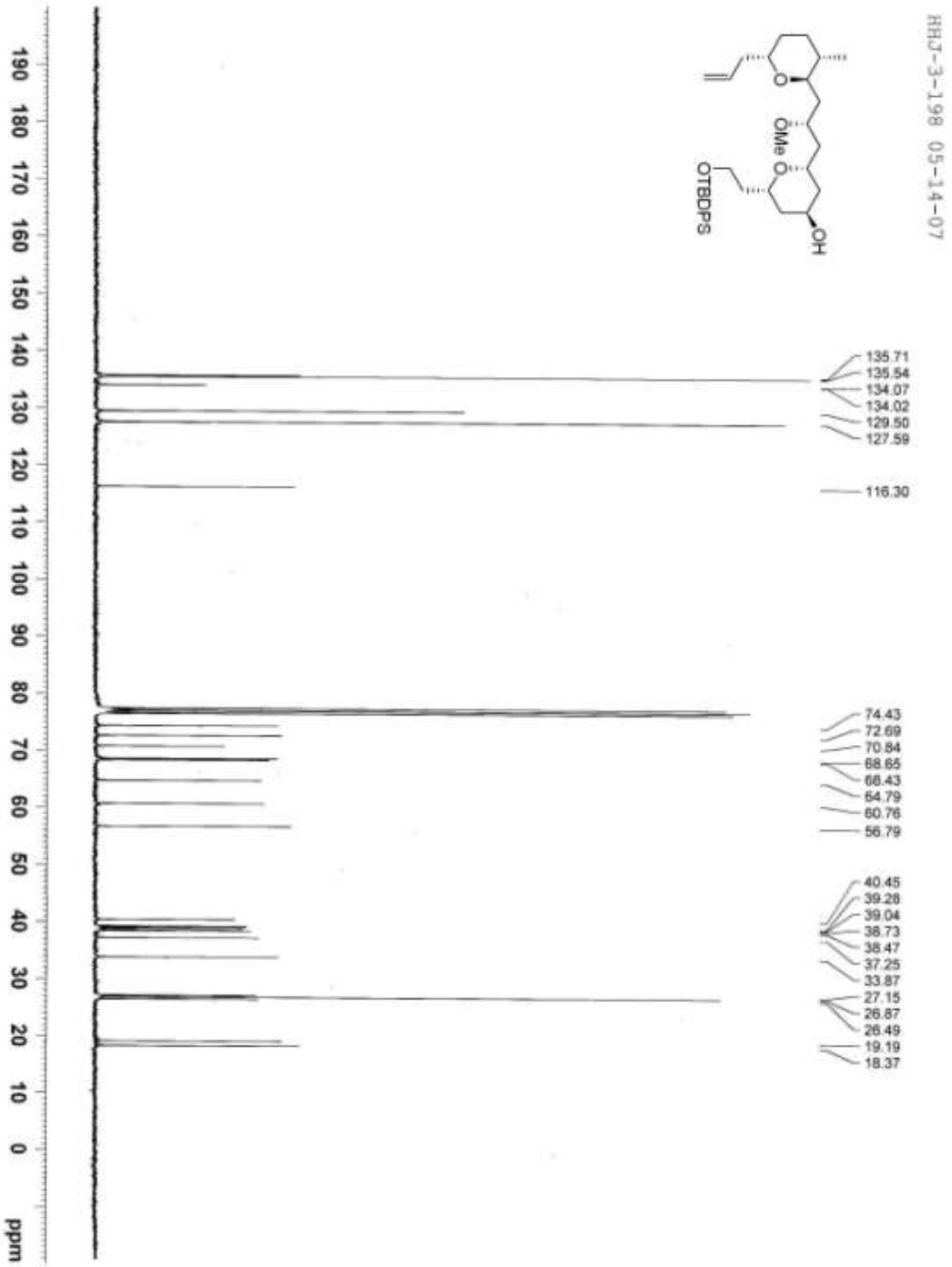

HHJ-3-197 05-12-07
OMe
OTBDPS
4.01
6.07
0.98
2.00
5.22
2.04
2.95
3.03
3.06
1.99
7.64
2.41
8.91
2.98
ppm

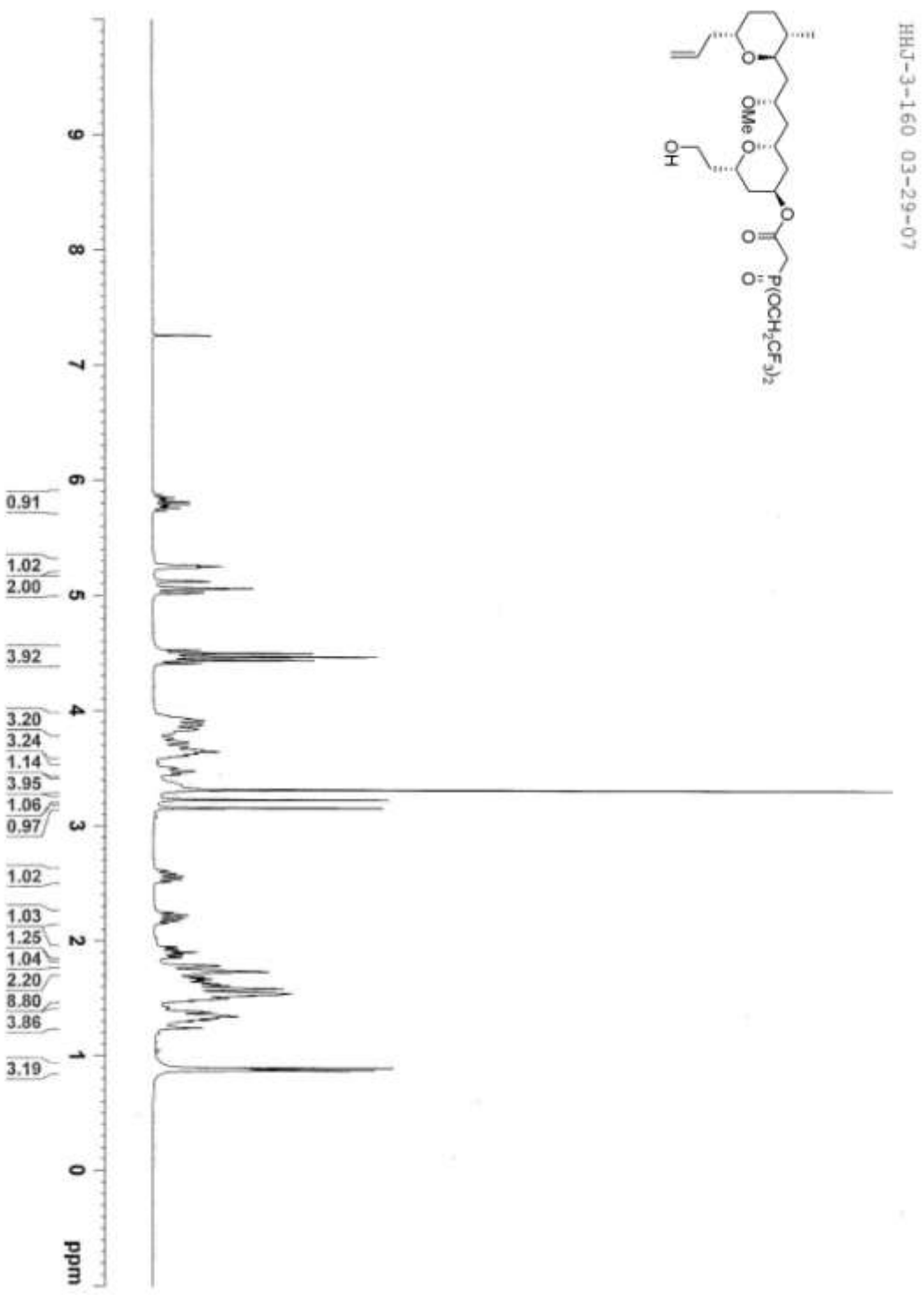

HHJ-3-197 05-12-07
OTBDPS
OMe
O
O
207.39
135.62
135.48
133.71
133.66
129.63
129.62
127.66
116.42
77.43
77.00
76.58
74.32
73.91
73.87
72.63
71.16
60.06
56.85
48.10
47.81
40.60
39.26
38.60
36.78
34.23
27.28
26.83
26.60
19.15
18.32
200
180
160
140
120
100
80
60
40
20
0
ppm

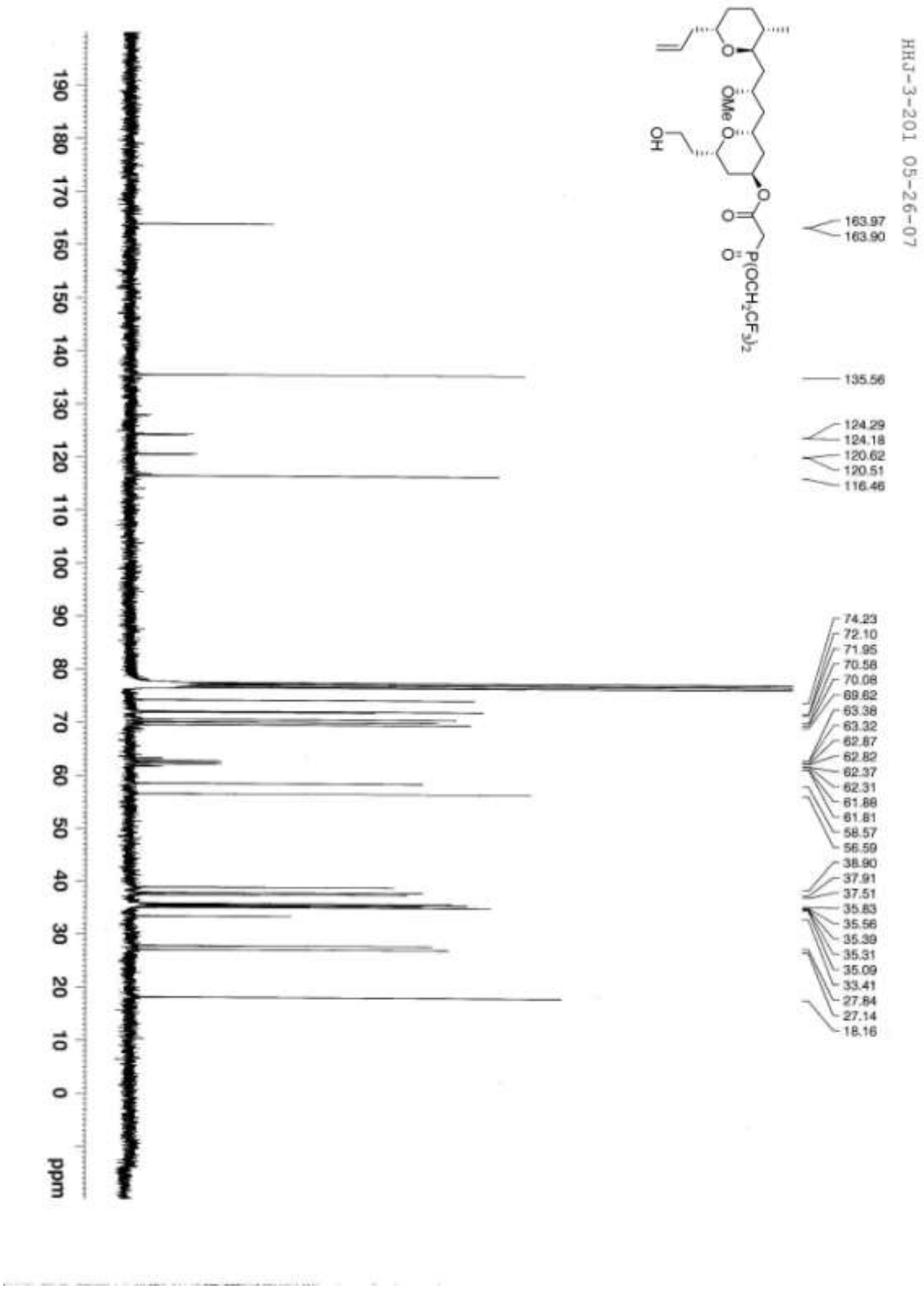

HHJ-3-198 05-14-07
OH
OMe
O
O
OTBDPS
9
8
7
6
5
4
3
2
1
0
ppm
4.08
5.99
0.94
2.00
1.02
5.36
2.08
3.01
1.04
1.04
18.25
9.32
3.20

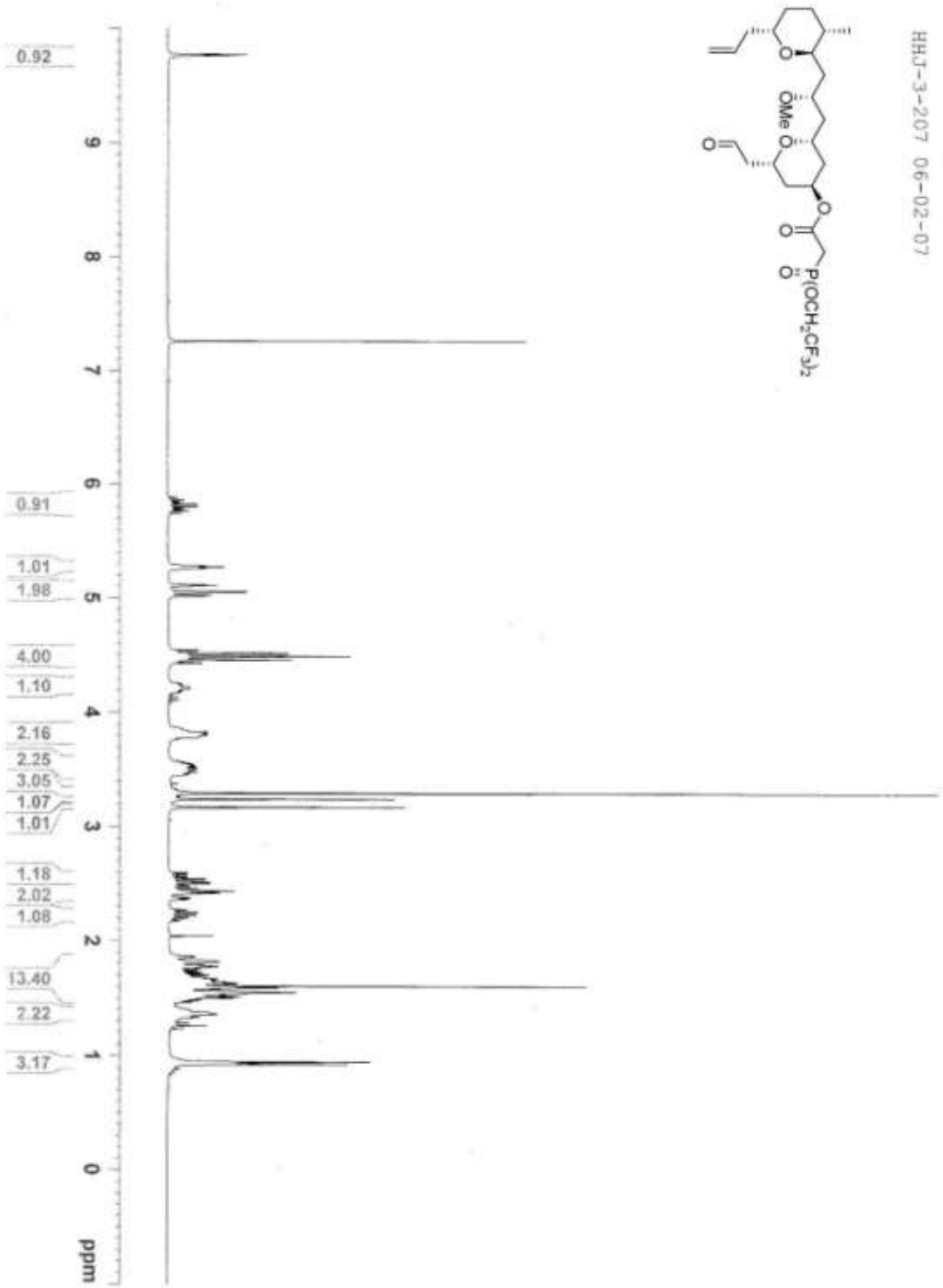

HHJ-3-198 05-14-07
OTBDPS
OMe
OH
135.71
135.54
134.07
134.02
129.50
127.59
116.30
74.43
72.69
70.84
68.65
66.43
64.79
60.76
56.79
40.45
39.28
39.04
38.73
38.47
37.25
33.87
27.15
26.87
26.49
19.19
18.37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

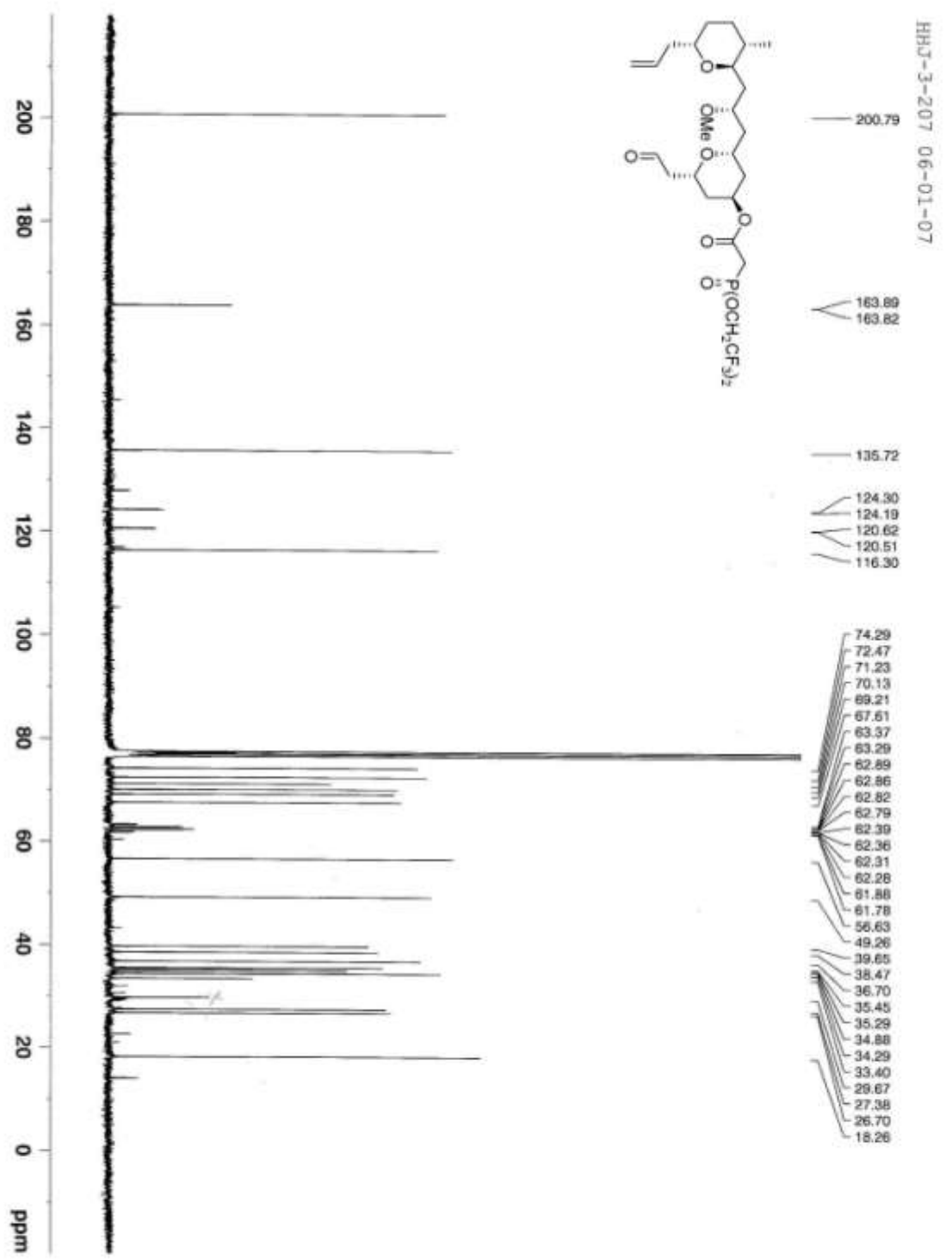

HHJ-3-200 05-16-07
OMe
OTBDPS
P(OCH2CF3)2
4.03
6.11
0.98
0.94
2.00
3.97
5.11
2.07
2.98
1.03
0.96
0.96
0.98
13.87
2.53
9.06
3.15
ppm

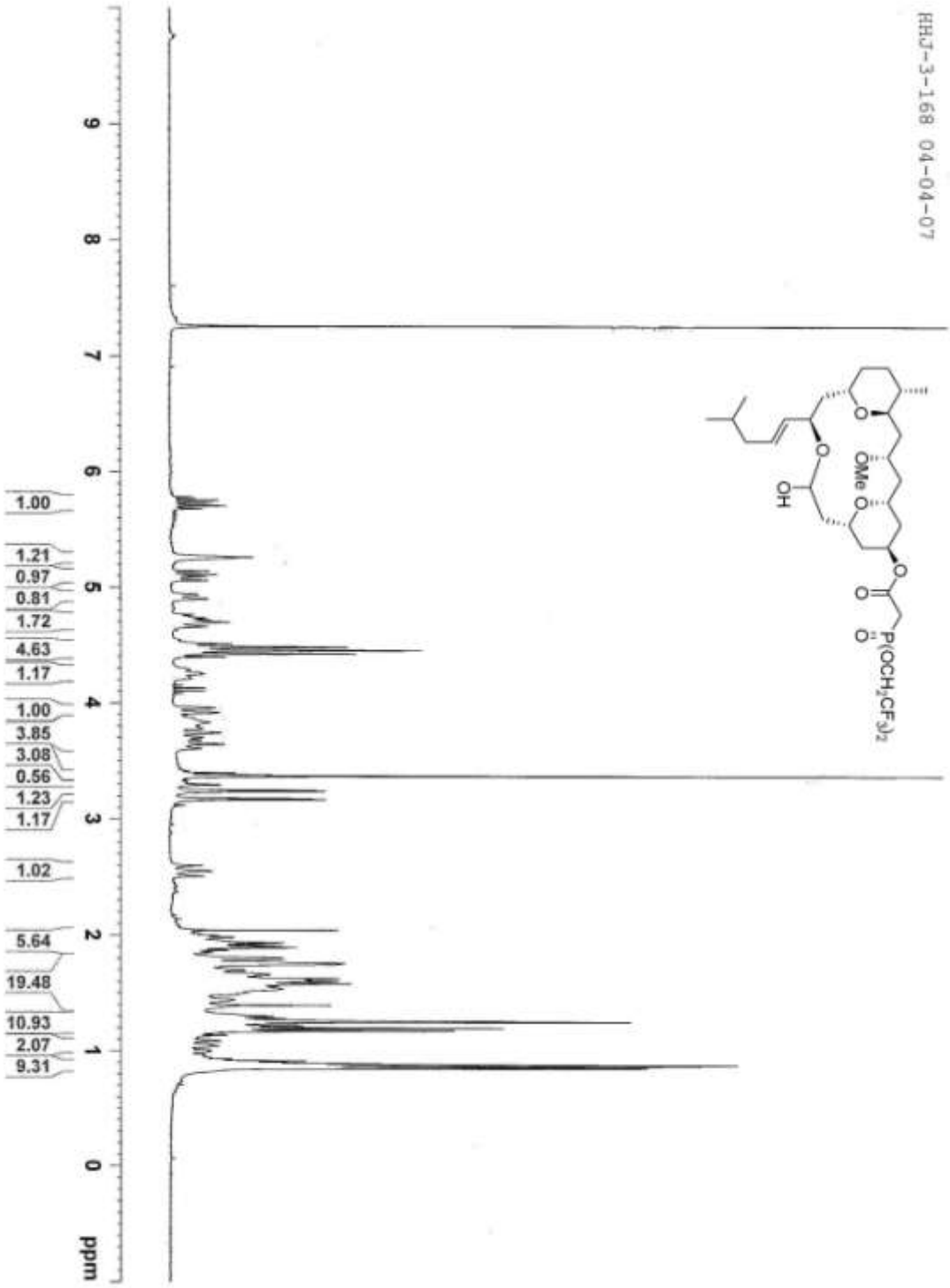

HHJ-3-198 05-14-07
OTBDPS
OMe
OH
135.71
135.54
134.07
134.02
129.50
127.59
116.30
74.43
72.69
70.84
68.65
66.43
64.79
60.76
56.79
40.45
39.28
39.04
38.73
38.47
37.25
33.87
27.15
26.87
26.49
19.19
18.37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

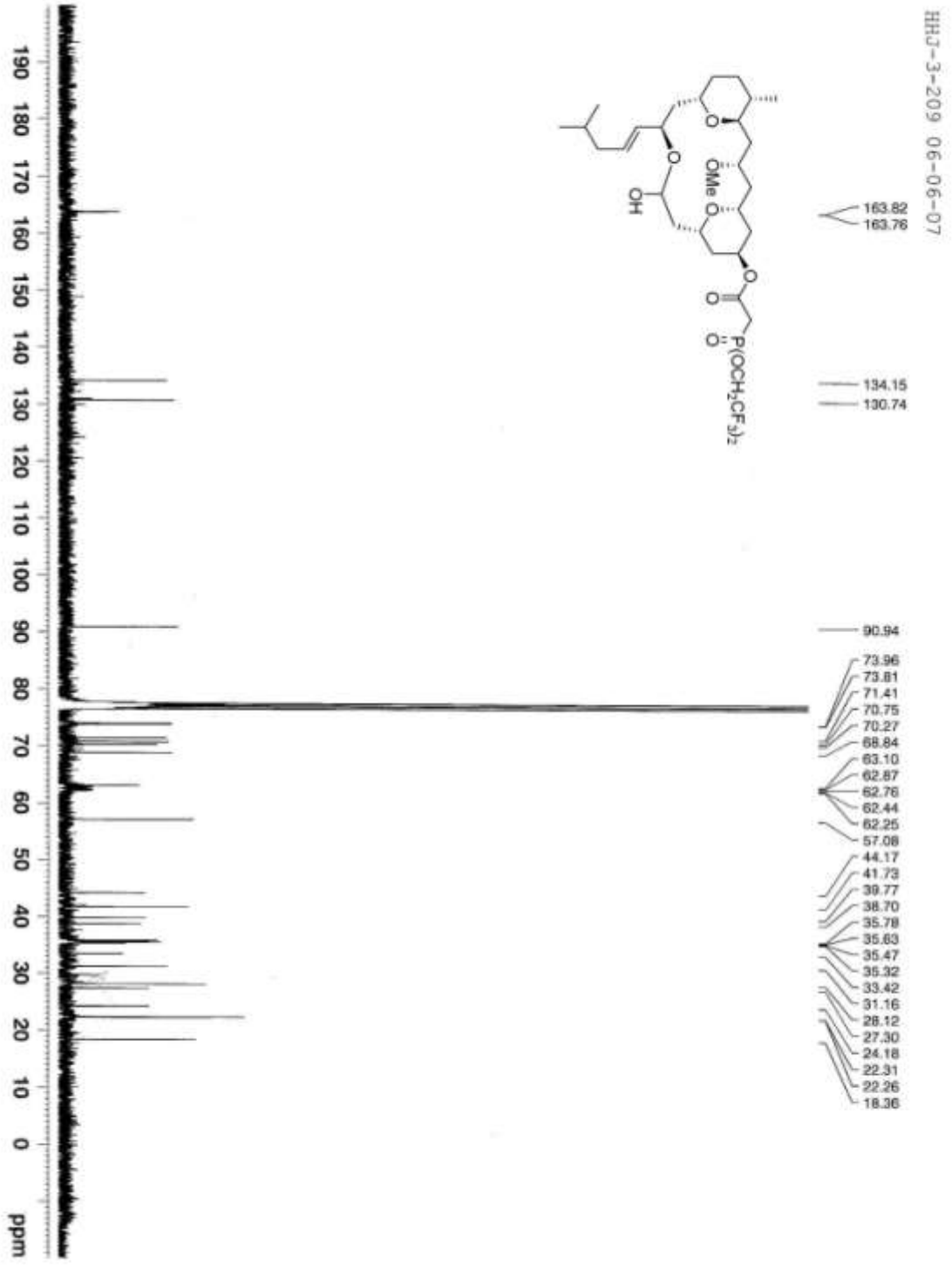

HHJ-3-160 03-29-07
OMe
OH
P(OCH2CF3)2
0.91
1.02
2.00
3.92
3.20
3.24
1.14
3.95
1.06
0.97
1.02
1.03
1.25
1.04
2.20
8.80
3.86
3.19
ppm

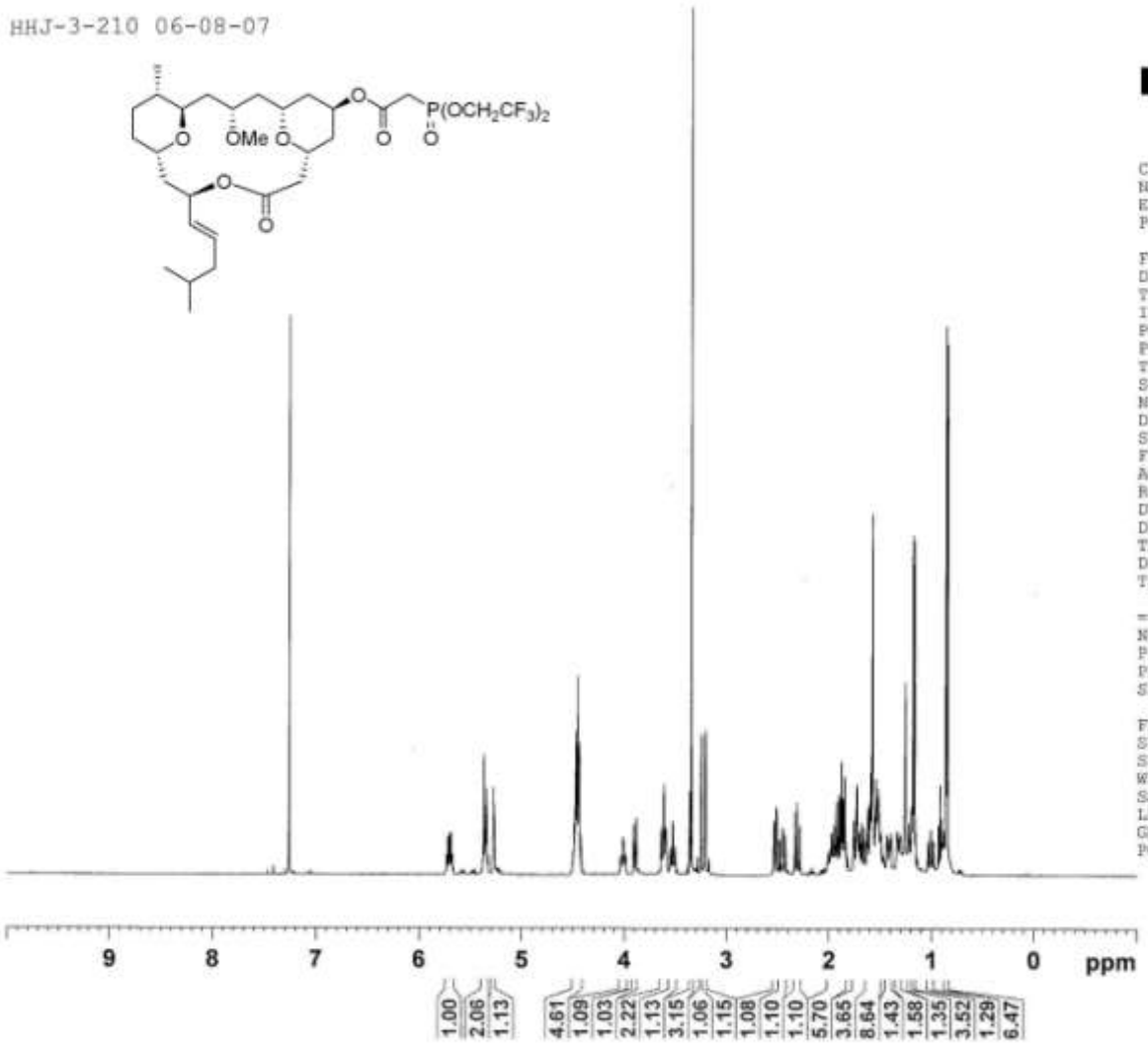

HHJ-3-201 05-26-07
OMe
OH
P(OCH2CF3)2
163.97
163.90
135.56
124.29
124.18
120.62
120.51
116.46
74.23
72.10
71.95
70.56
70.08
69.62
63.38
63.32
62.87
62.82
62.37
62.31
61.88
61.81
58.57
56.59
38.90
37.91
37.51
35.83
35.56
35.39
35.31
35.09
33.41
27.84
27.14
18.16
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HHJ-3-207 06-02-07
OMe
P(OCH2CF3)2
0.92
0.91
1.01
1.98
4.00
1.10
2.16
2.25
3.05
1.07
1.01
1.18
2.02
1.08
13.40
2.22
3.17
ppm


HHJ-3-207 06-01-07
OMe
P(OCH2CF3)2
200.79
163.89
163.82
135.72
124.30
124.19
120.62
120.51
116.30
74.29
72.47
71.23
70.13
69.21
67.61
63.37
63.29
62.89
62.86
62.82
62.79
62.39
62.36
62.31
62.28
61.88
61.78
56.63
49.26
39.65
38.47
36.70
35.45
35.29
34.88
34.29
33.40
29.67
27.38
26.70
18.26
200
180
160
140
120
100
80
60
40
20
0
ppm


HHJ-3-168 04-04-07
OMe
OH
P(OCH2CF3)2
1.00
1.21
0.97
0.81
1.72
4.63
1.17
1.00
3.85
3.08
0.56
1.23
1.17
1.02
5.64
19.48
10.93
2.07
9.31
ppm


HHJ-3-209 06-06-07
OMe
OH
P(OCH2CF3)2
163.82
163.76
134.15
130.74
90.94
73.96
73.81
71.41
70.75
70.27
68.84
63.10
62.87
62.76
62.44
62.25
57.08
44.17
41.73
39.77
38.70
35.78
35.63
35.47
35.32
33.42
31.16
28.12
27.30
24.18
22.31
22.26
18.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



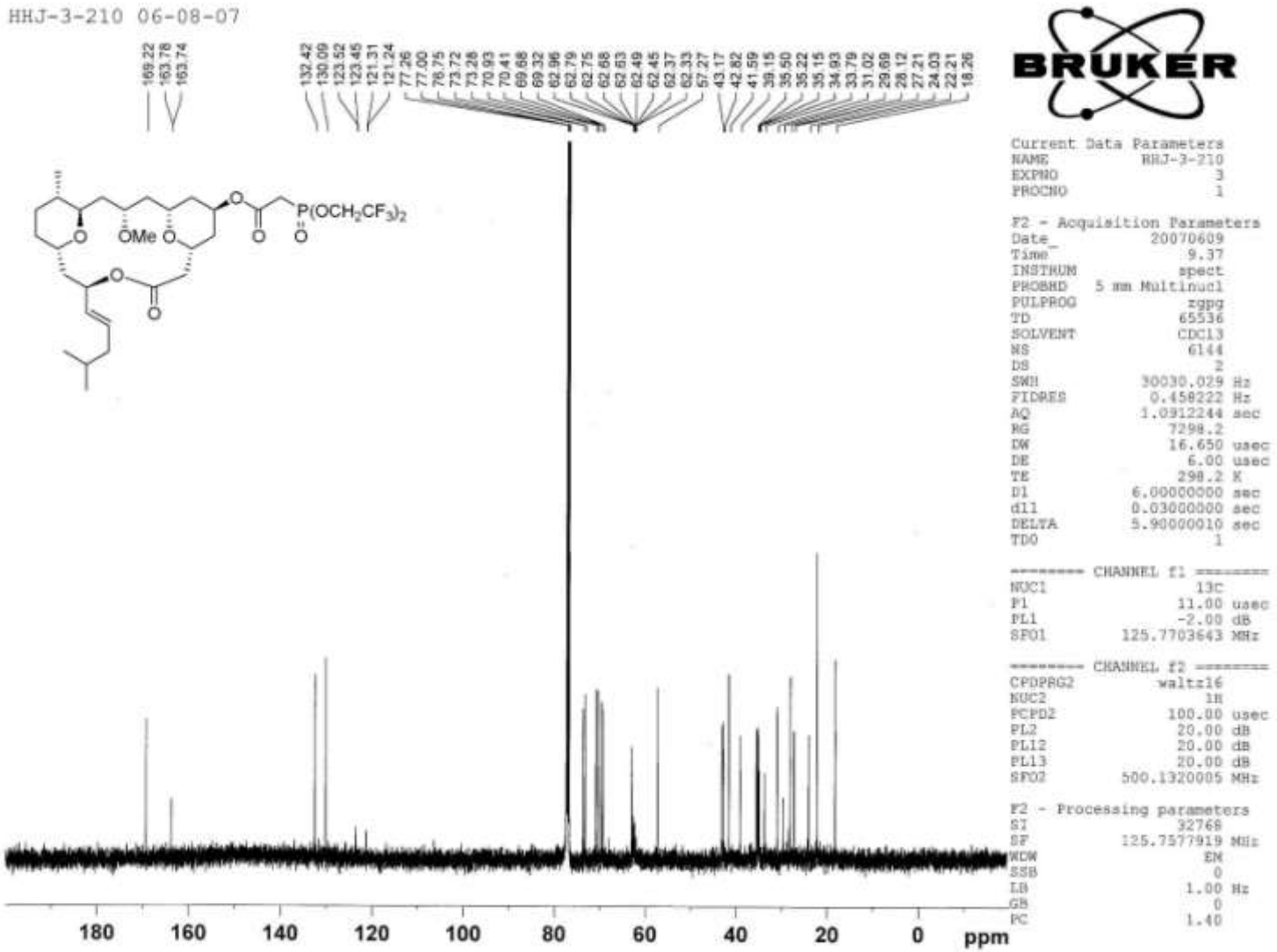
BRUKER

Current Data Parameters
NAME HHJ-3-210
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070608
Time 21.21
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 80.6
DW 48.400 usec
DE 6.00 usec
TE 298.2 K
D1 6.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300135 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00



BRUKER

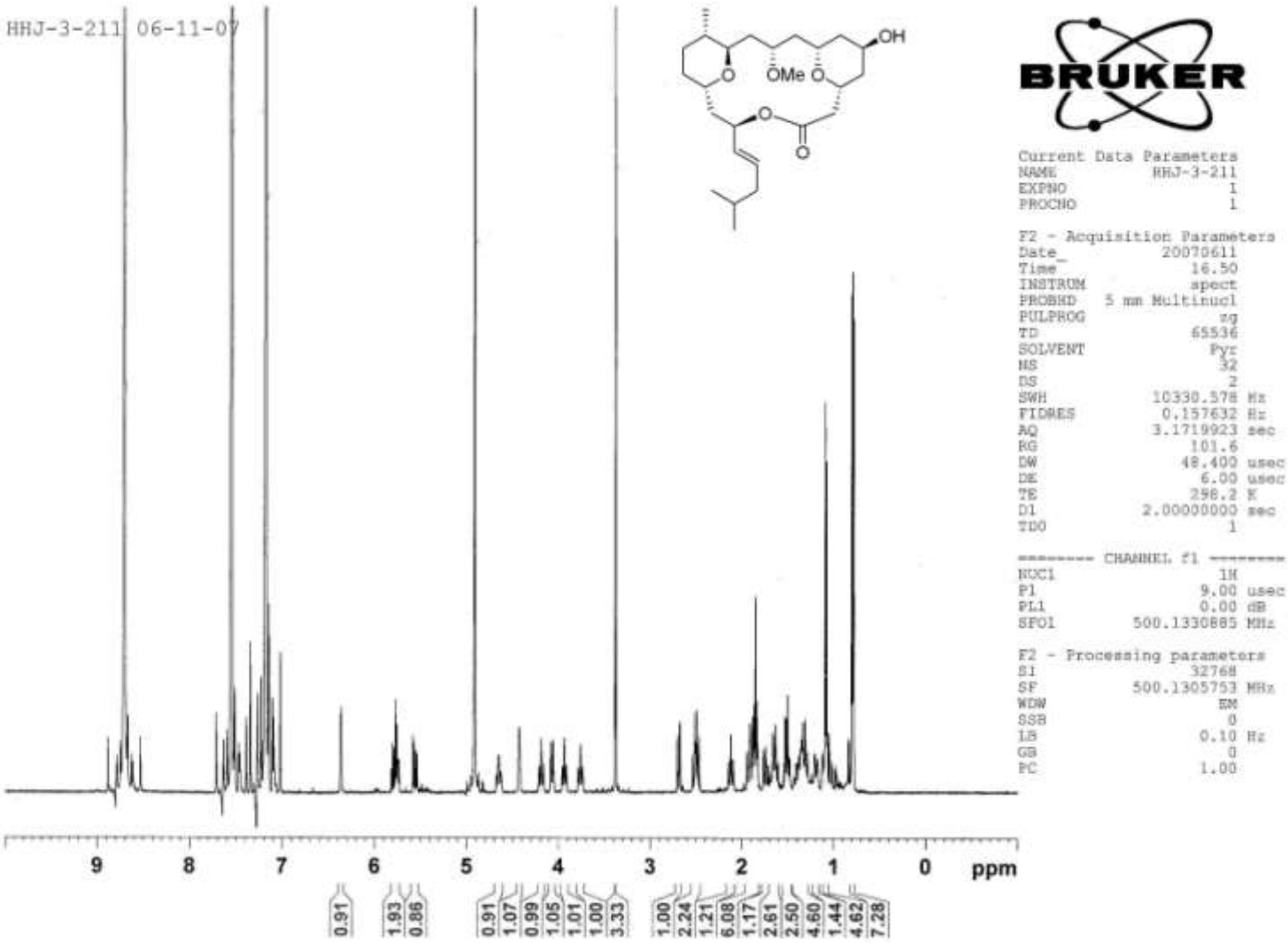
Current Data Parameters
NAME HHJ-3-210
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070609
Time 9.37
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 6144
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 7298.2
DW 16.650 usec
DE 6.00 usec
TE 298.2 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13c
P1 11.00 usec
PL1 -2.00 dB
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 20.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 500.1320005 MHz

F2 - Processing parameters
SI 32768
SF 125.7577919 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

Current Data Parameters
NAME HHJ-3-211
EXPNO 1
PROCNO 1

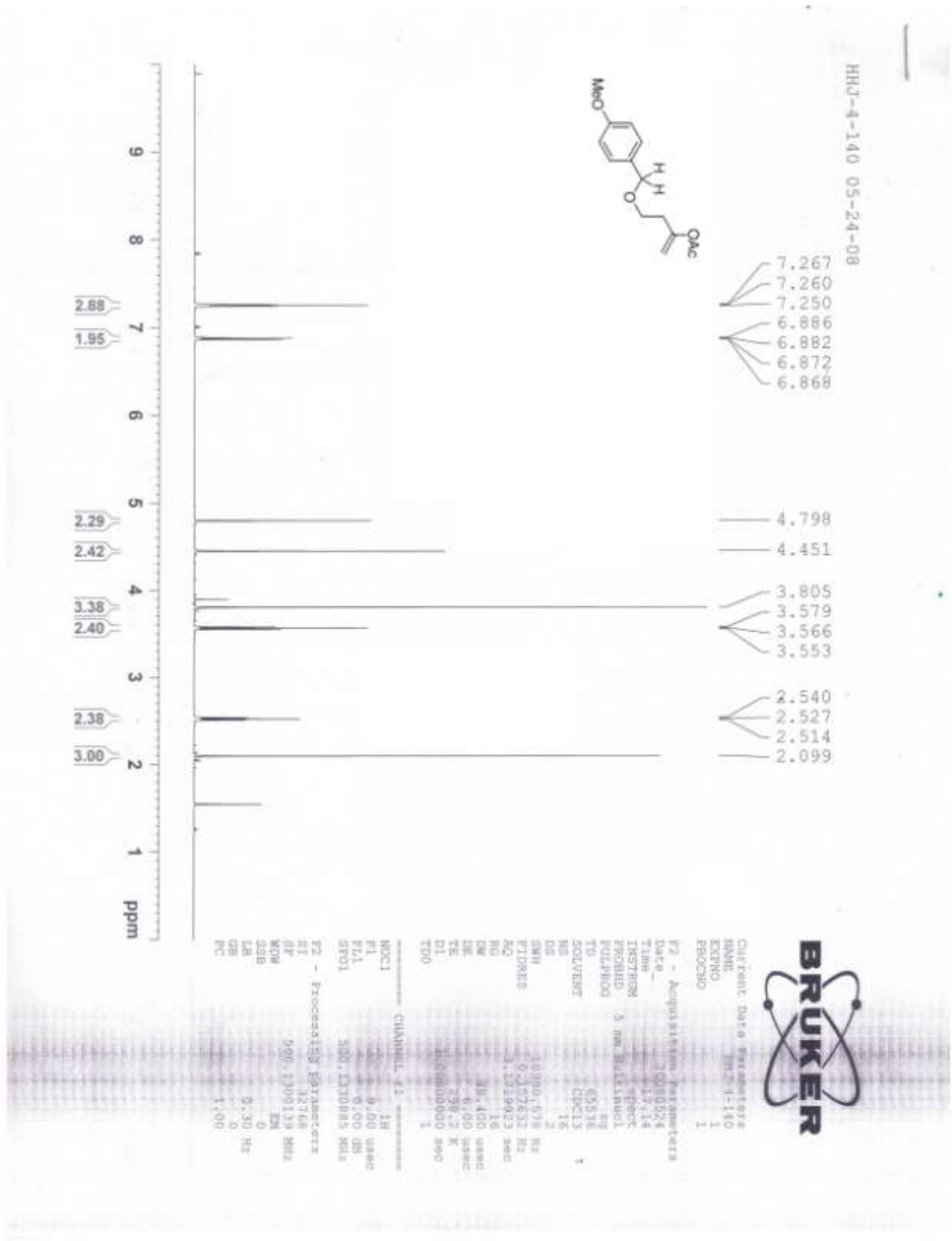
F2 - Acquisition Parameters
Date_ 20070611
Time 16.50
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT Pyr
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 101.6
DW 48.400 usec
DE 6.00 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1

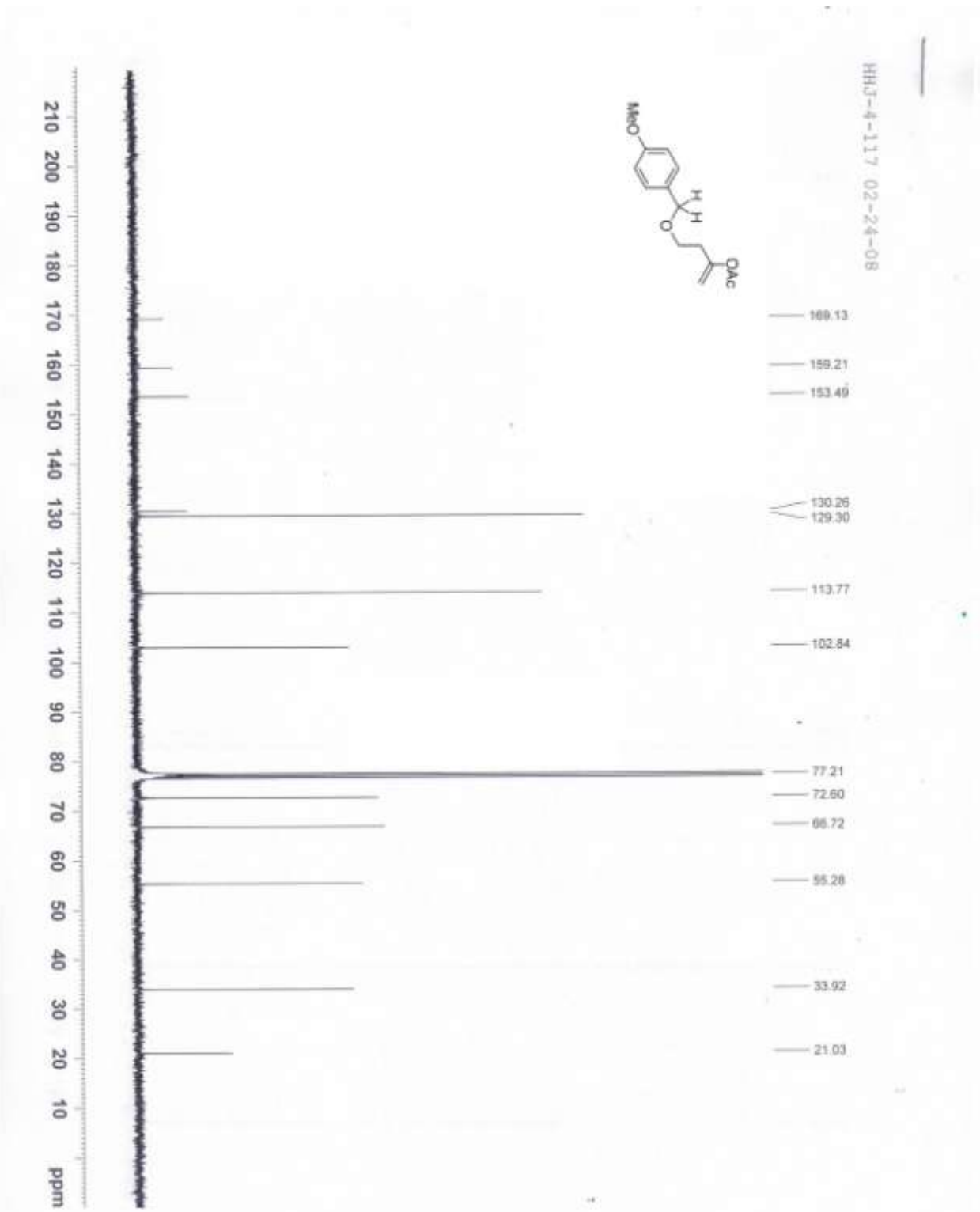
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz

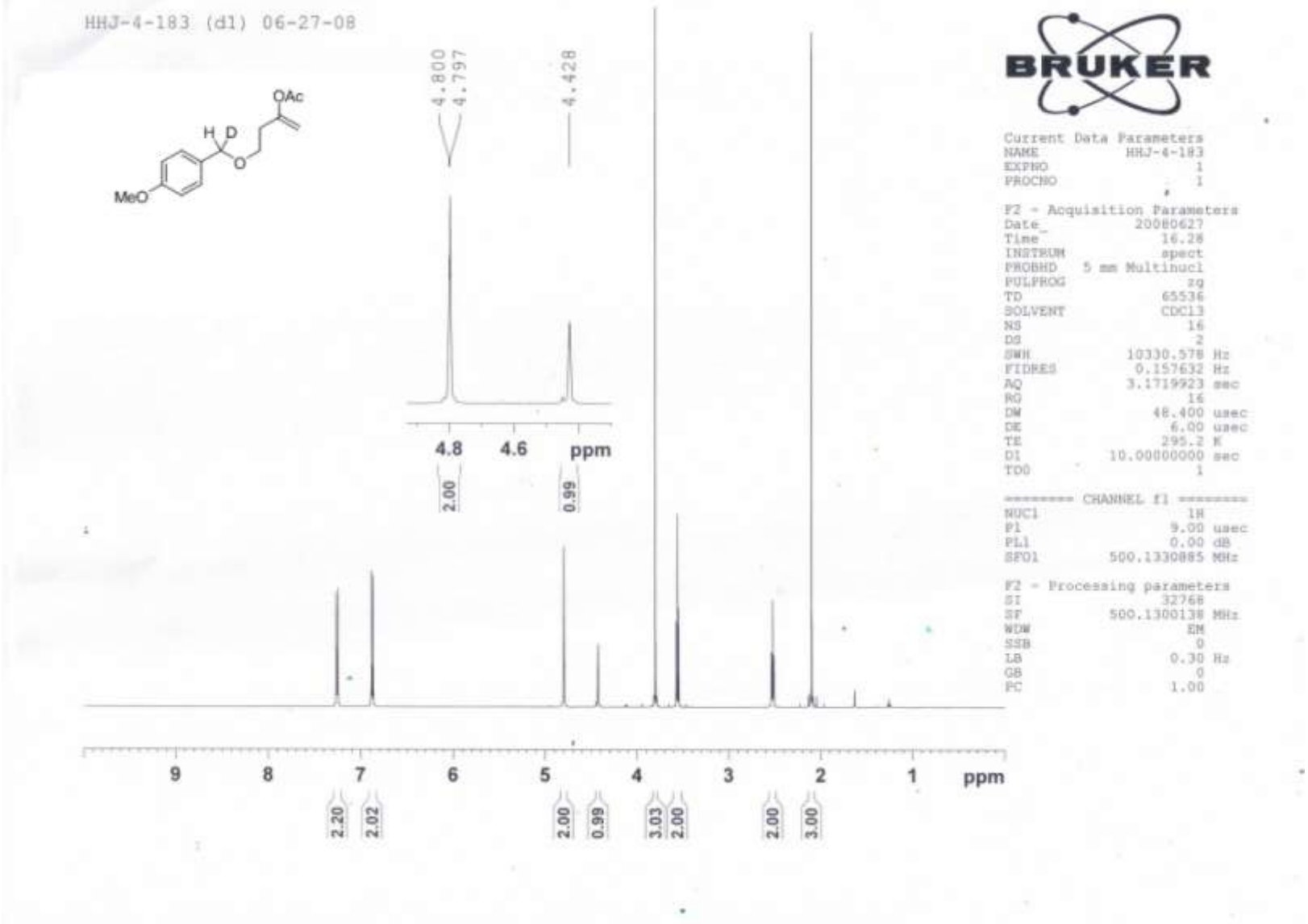
F2 - Processing parameters
SI 32768
SF 500.1305753 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

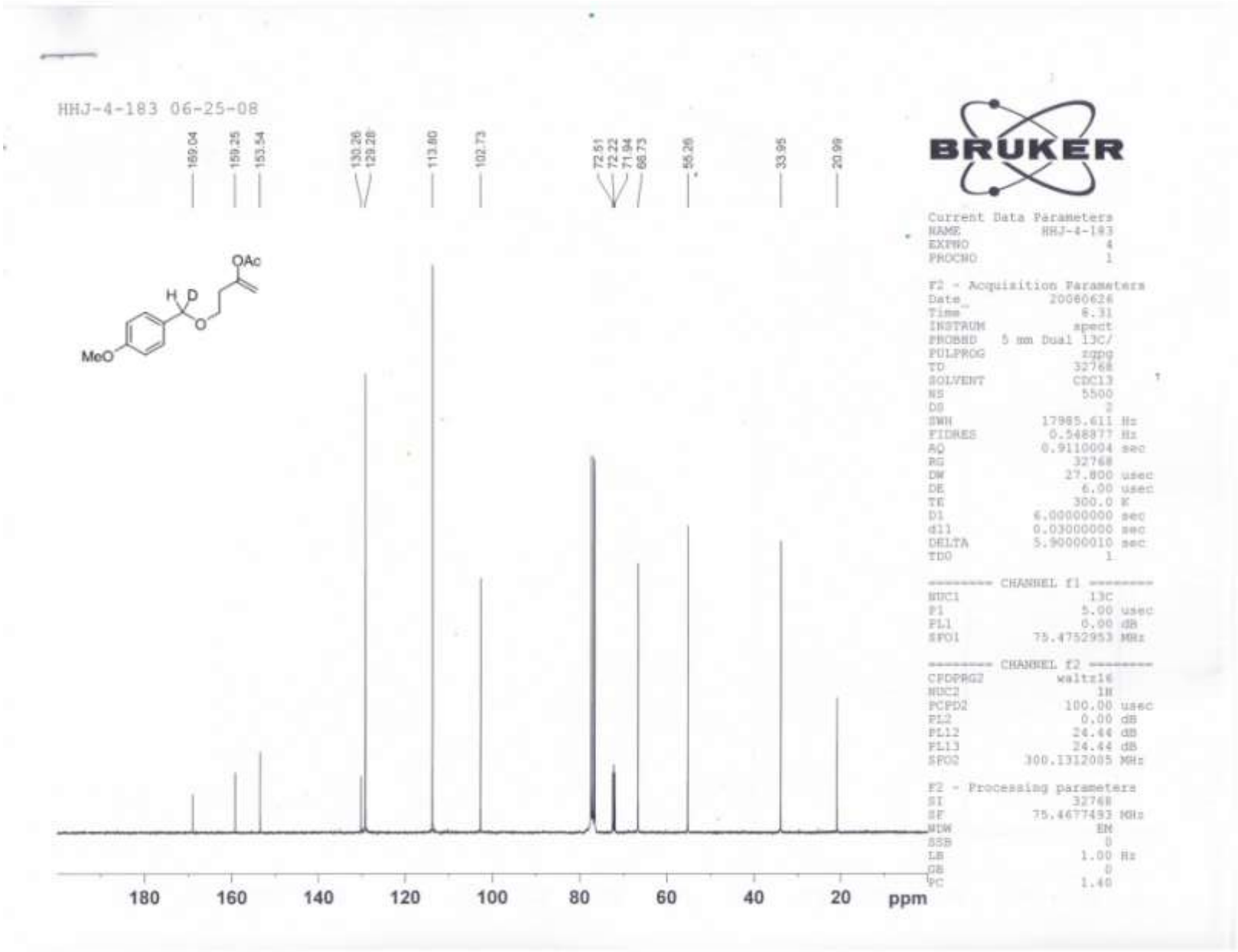
APPENDIX C

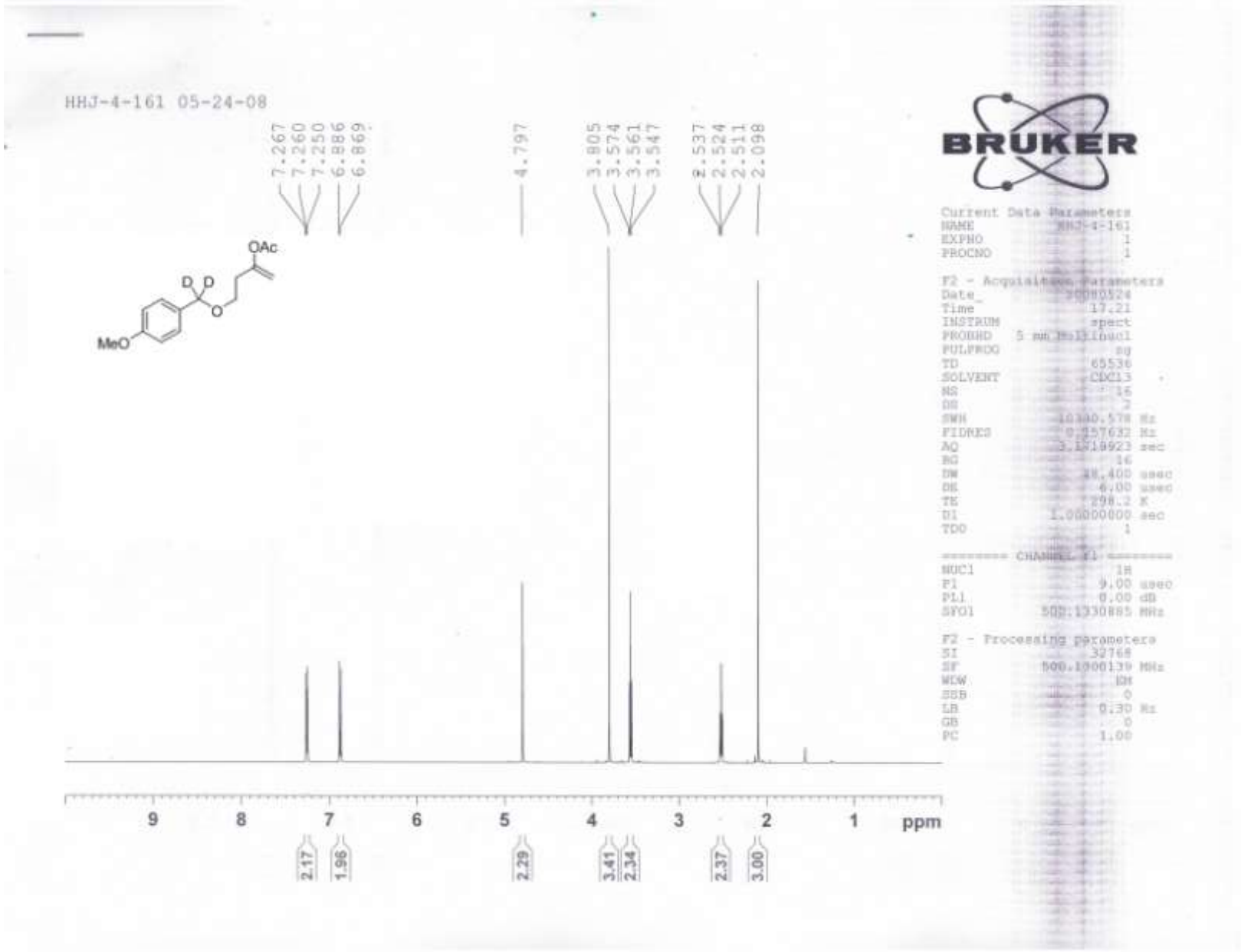
Mechanistic Analysis of Oxidative C–H Cleavages using Inter- and Intramolecular Kinetic Isotope Effects. (Supporting Information ^{1}H and ^{13}C NMR Spectra)

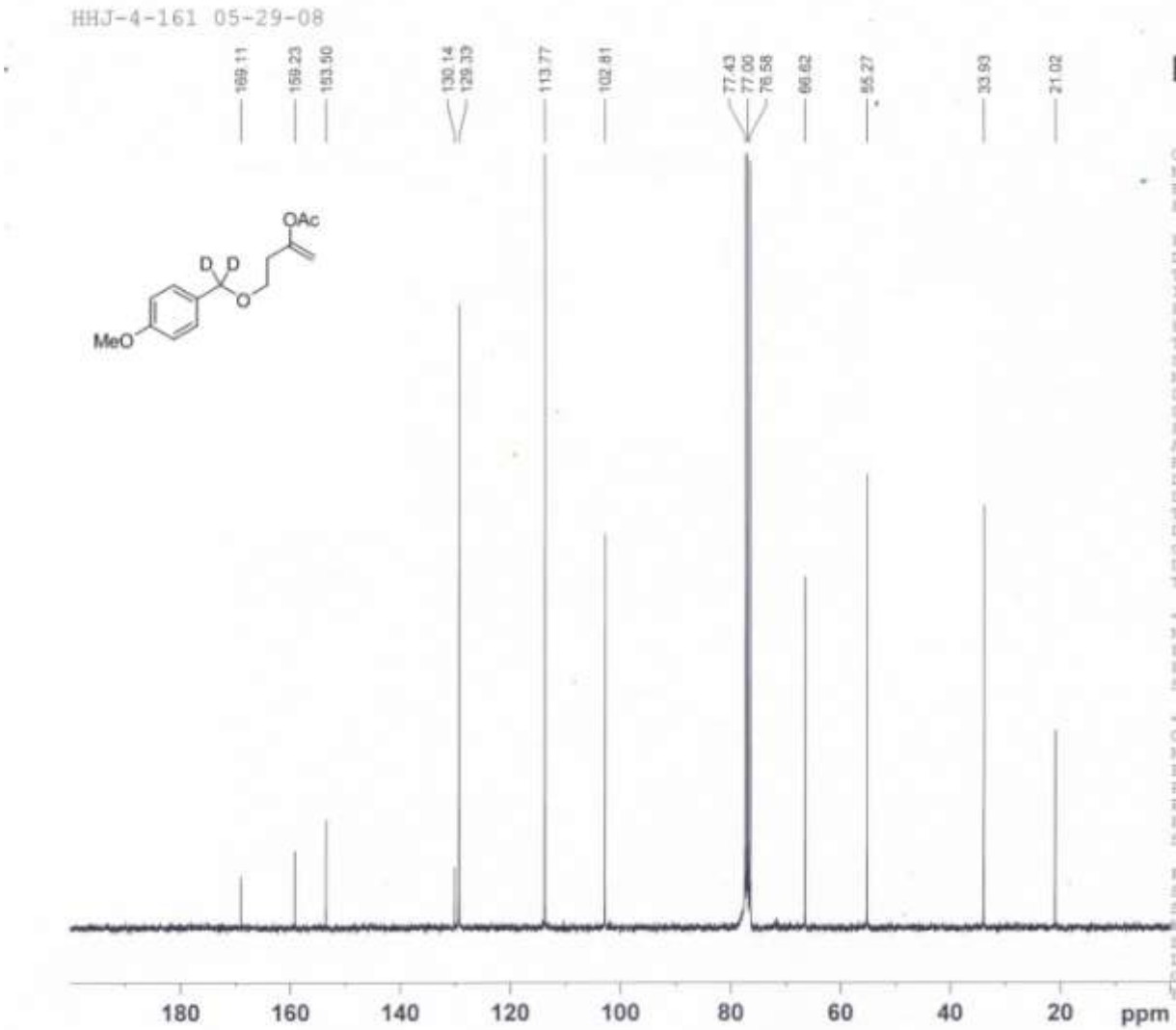

HHJ-4-140 05-24-08
MeO
OAc
7.267
7.260
7.250
6.886
6.882
6.872
6.868
4.798
4.451
3.805
3.579
3.566
3.553
2.540
2.527
2.514
2.099
2.88
1.95
2.29
2.42
3.38
2.40
2.38
3.00
ppm


HHJ-4-117 02-24-08
MeO
OAc
169.13
159.21
153.49
130.26
129.30
113.77
102.84
77.21
72.60
66.72
55.28
33.92
21.03
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HHJ-4-183 (d1) 06-27-08
OAc
H D
O
MeO
4.800
4.797
4.428
4.8
4.6
ppm
2.00
0.99
9
8
7
6
5
4
3
2
1
ppm
2.20
2.02
2.00
0.99
3.03
2.00
2.00
3.00
BRUKER
Current Data Parameters
NAME HHJ-6-183
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080627
Time 16.28
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300138 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


HHJ-4-183 06-25-08
169.04
159.25
153.54
130.26
129.28
113.80
102.73
72.51
72.22
71.94
68.73
55.26
33.95
20.99
OAc
H D
O
MeO
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-183
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060626
Time 6.31
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5500
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677493 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-161 05-24-08
7.267
7.260
7.250
6.886
6.869
4.797
3.805
3.574
3.561
3.547
2.537
2.524
2.511
2.098
OAc
D
D
O
MeO
9
8
7
6
5
4
3
2
1
ppm
2.17
1.96
2.29
3.41
2.34
2.37
3.00
BRUKER
Current Data Parameters
NAME HHJ-4-161
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080524
Time 17.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1718923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300139 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

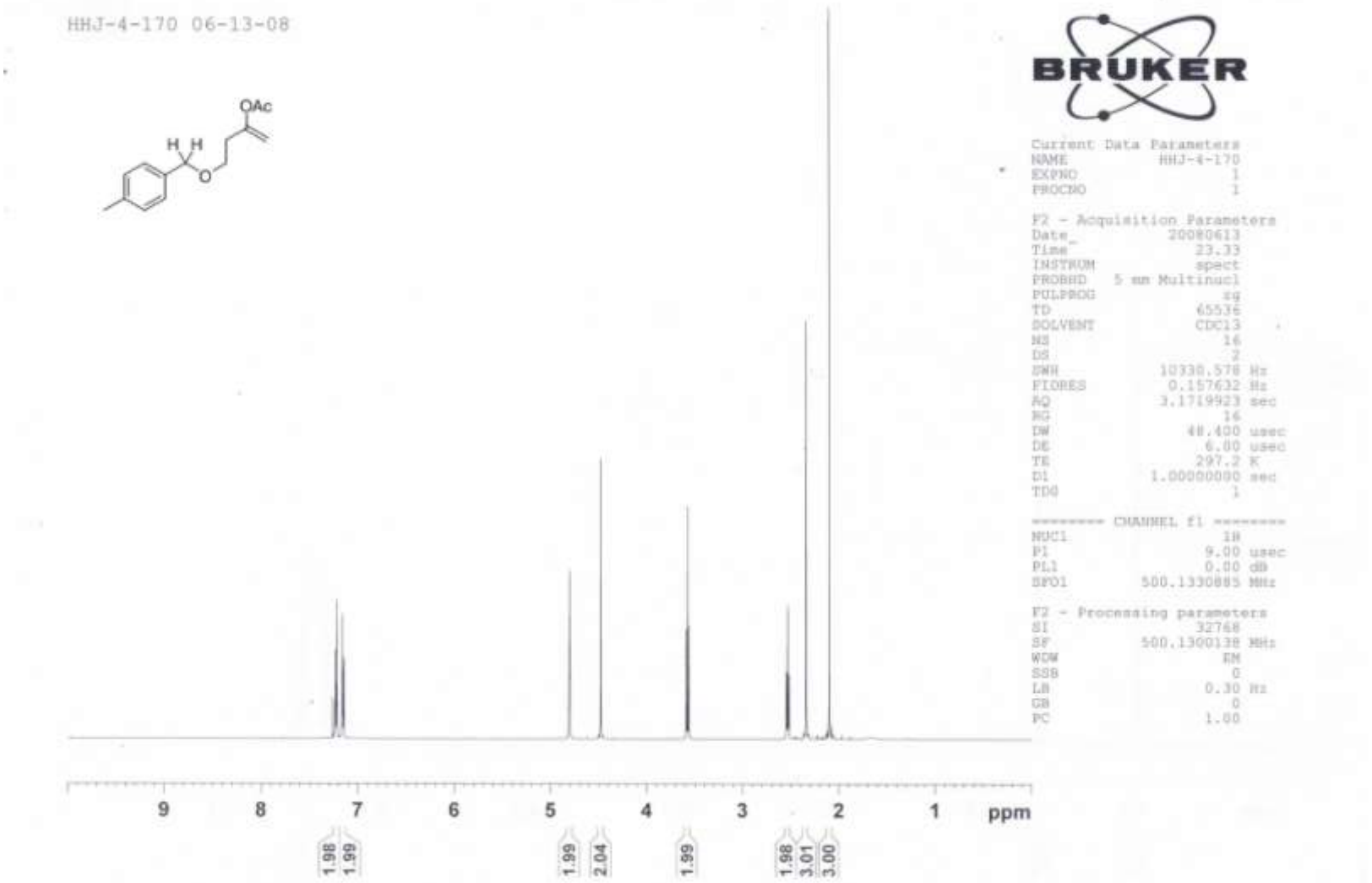
```
Current Data Parameters
NAME                  HHJ-4-161
EXPNO                         4
PROCNO                        1

F2 - Acquisition Parameters
Date_              20080530
Time                      7.53
INSTRUN                 spect
PROBHD    5 mm Dual 13C/
PULPROG                 zgpg
TD                       32768
SOLVENT                  CDCl3
NS                        5500
DS                           2
SWH                17985.611 Hz
FIDRES              0.548877 Hz
AQ                  0.9110004 sec
RG                       32768
DW                    27.800 usec
DE                     6.00 usec
TE                     300.0 K
D1                6.00000000 sec
d11               0.03000000 sec
DELTA             5.90000010 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       13C
P1                        5.00 usec
PL1                       0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   100.00 usec
PL2                       0.00 dB
PL12                     24.44 dB
PL13                     24.44 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                 75.4677499 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```



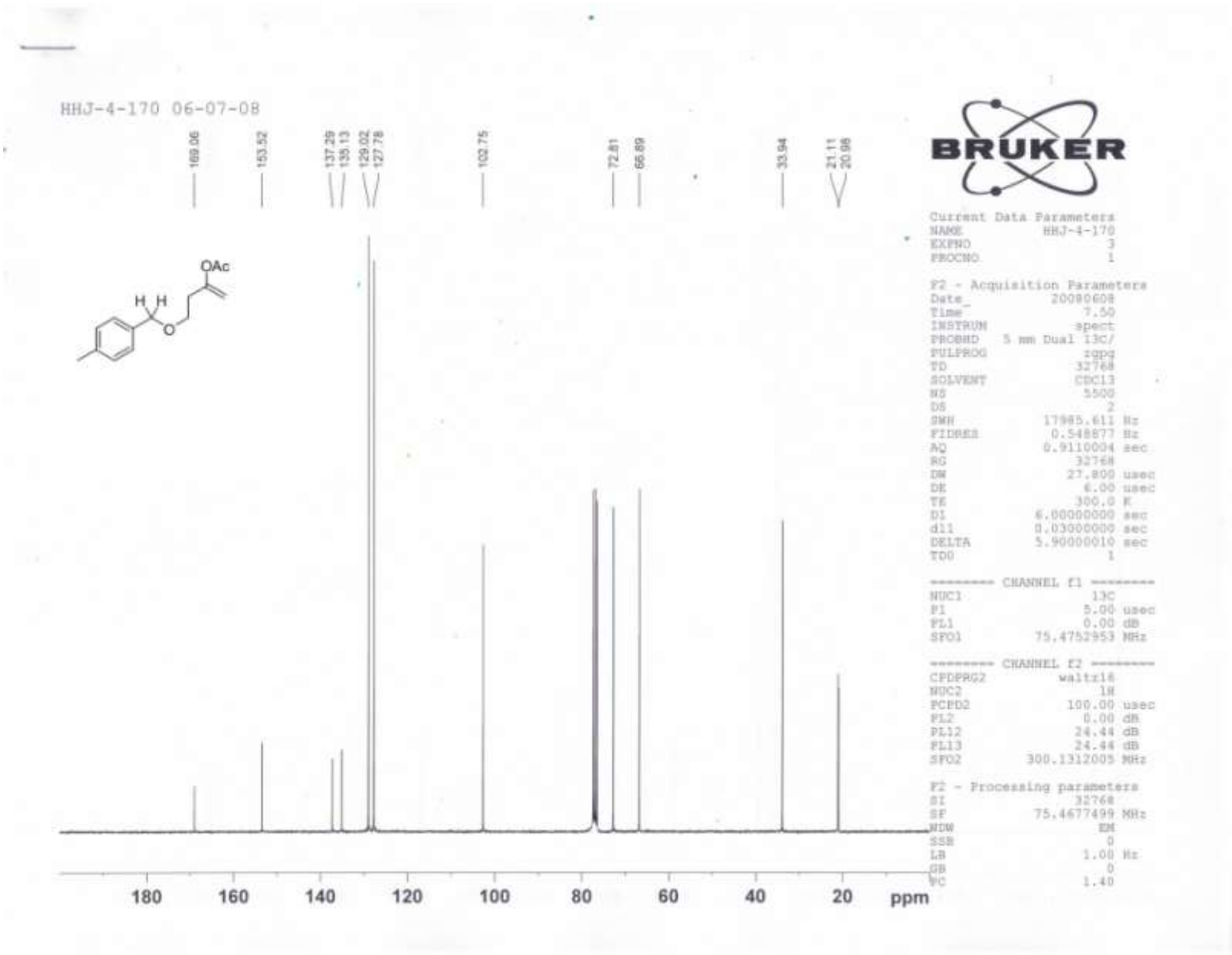
BRUKER

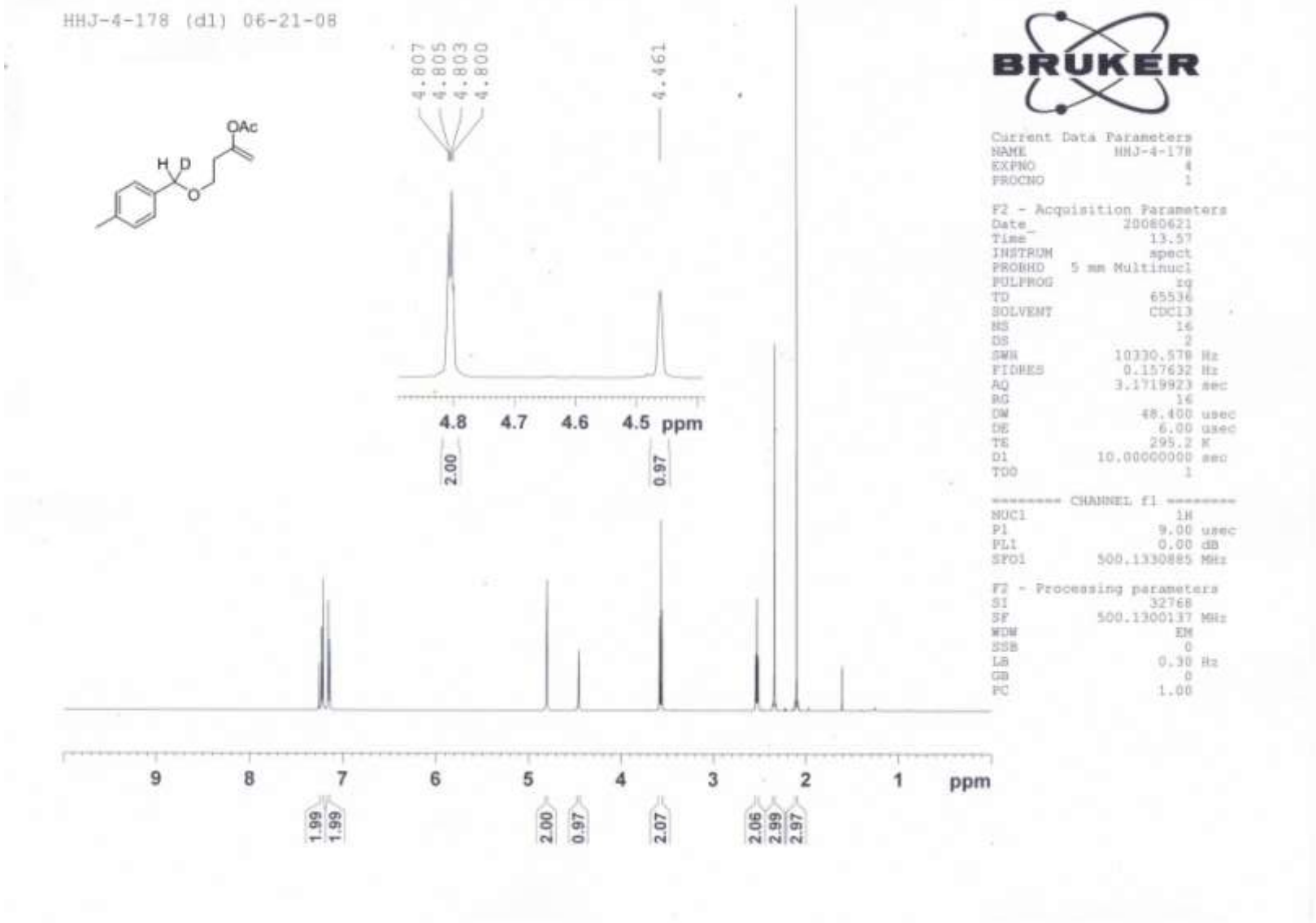
```
Current Data Parameters
NAME                  HHJ-4-170
EXPNO                         1
PROCNO                        1

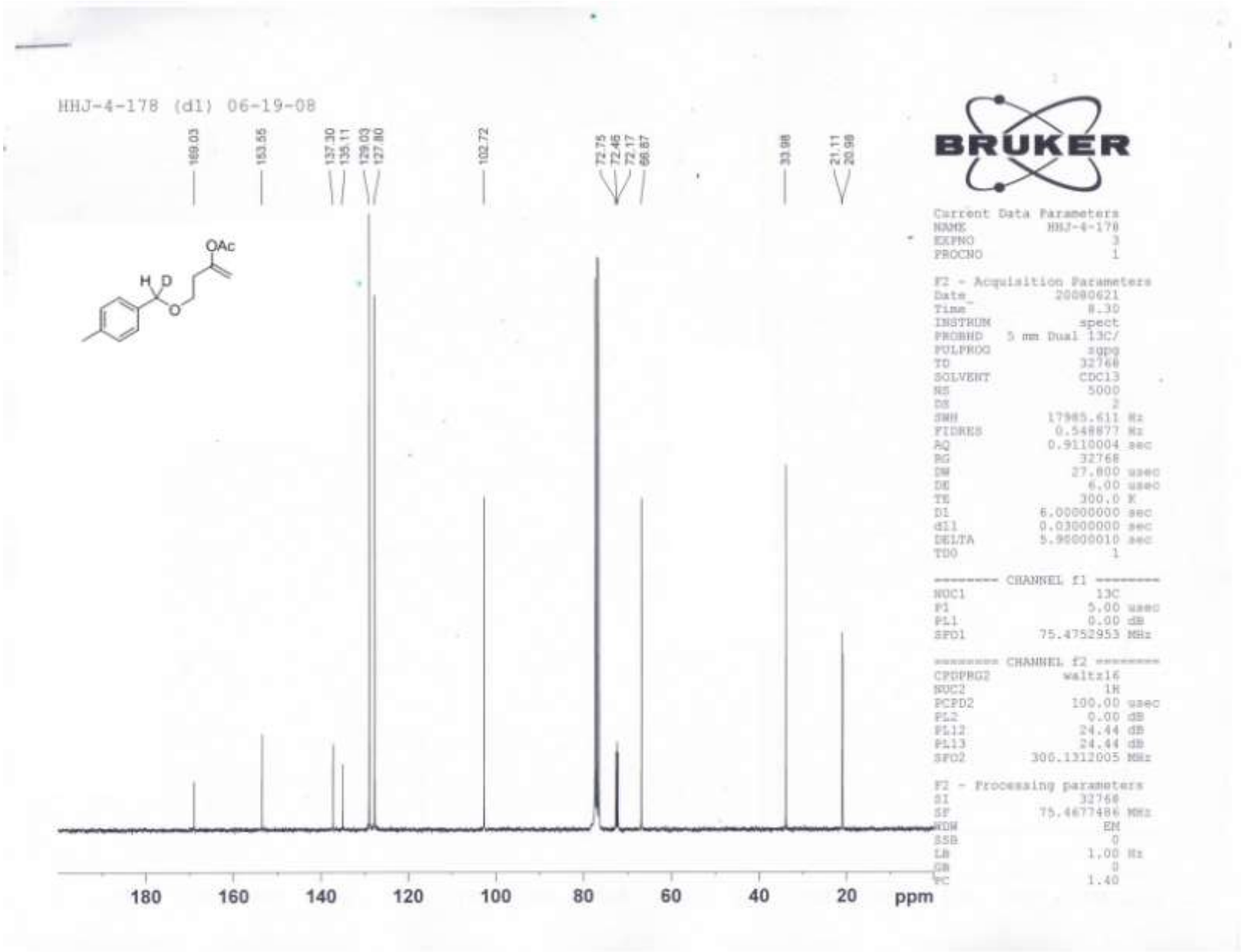
F2 - Acquisition Parameters
Date_              20080613
Time                      23.33
INSTRUM                   spect
PROBHD    5 mm Multinucl
PULPROG                     zg
TD                         65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                   10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719923 sec
RG                           16
DW                       48.400 usec
DE                        6.00 usec
TE                       297.2 K
D1                    1.00000000 sec
TD0                           1

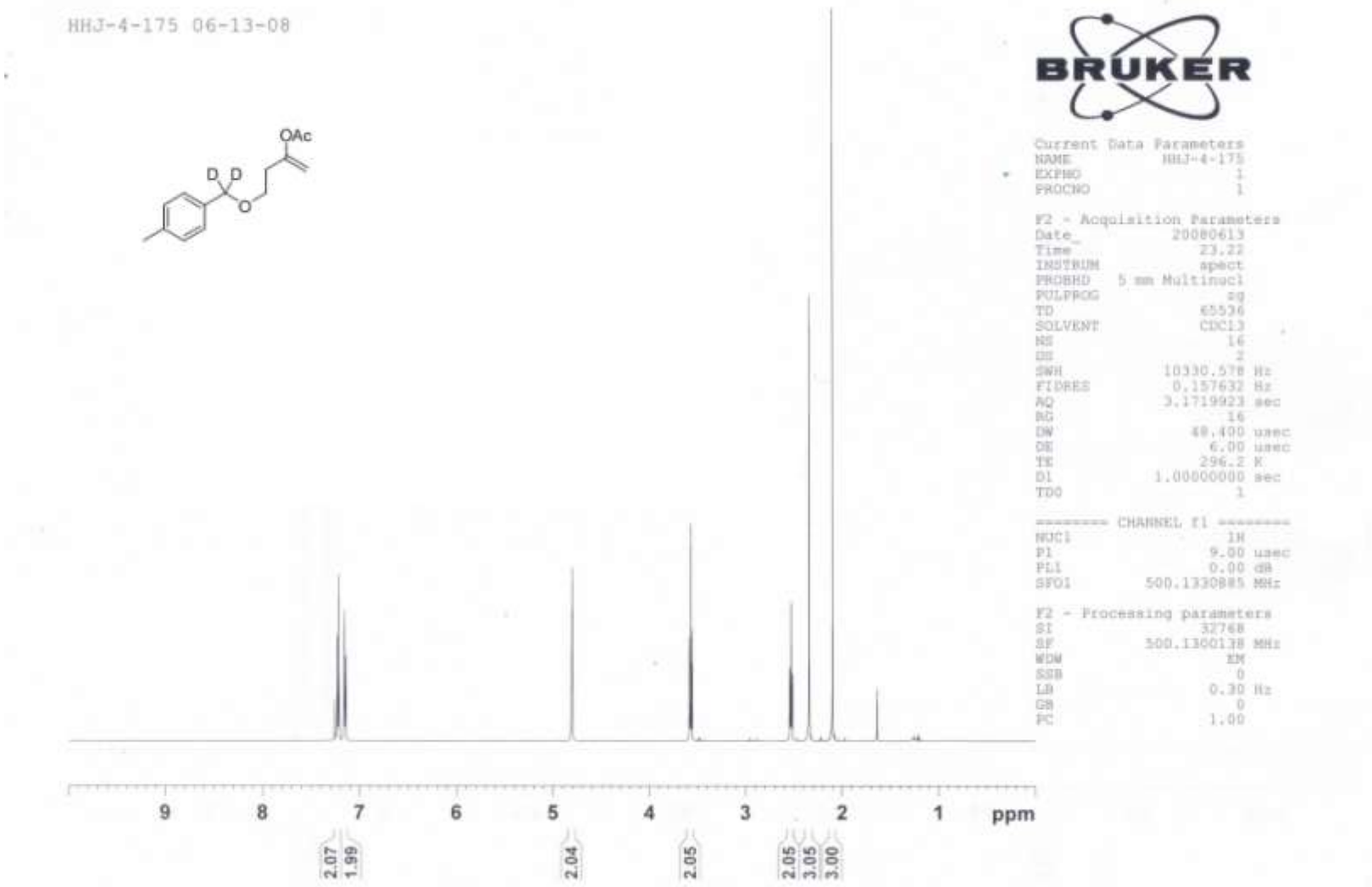
======== CHANNEL f1 ========
NUC1                         1H
P1                        9.00 usec
PL1                       0.00 dB
SFO1               500.1330885 MHz

F2 - Processing parameters
SI                        32768
SF                 500.1300138 MHz
WDW                          EM
SSB                           0
LB                        0.30 Hz
GB                            0
PC                        1.00
```


HHJ-4-170 06-07-08
169.06
153.52
137.29
135.13
129.02
127.78
102.75
72.81
66.89
33.94
21.11
20.98
OAc
H H
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-170
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080608
Time 7.50
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5500
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677499 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-178 (d1) 06-21-08
OAc
H D
O
4.807
4.805
4.803
4.800
4.461
4.8
4.7
4.6
4.5 ppm
2.00
0.97
9
8
7
6
5
4
3
2
1
ppm
1.99
1.99
2.00
0.97
2.07
2.06
2.99
2.97
BRUKER
Current Data Parameters
NAME HHJ-4-178
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080621
Time 13.57
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300137 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


HHJ-4-178 (d1) 06-19-08
169.03
153.55
137.30
135.11
129.03
127.80
102.72
72.75
72.46
72.17
66.87
33.98
21.11
20.98
OAc
H D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-178
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080621
Time 8.30
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.96000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677486 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



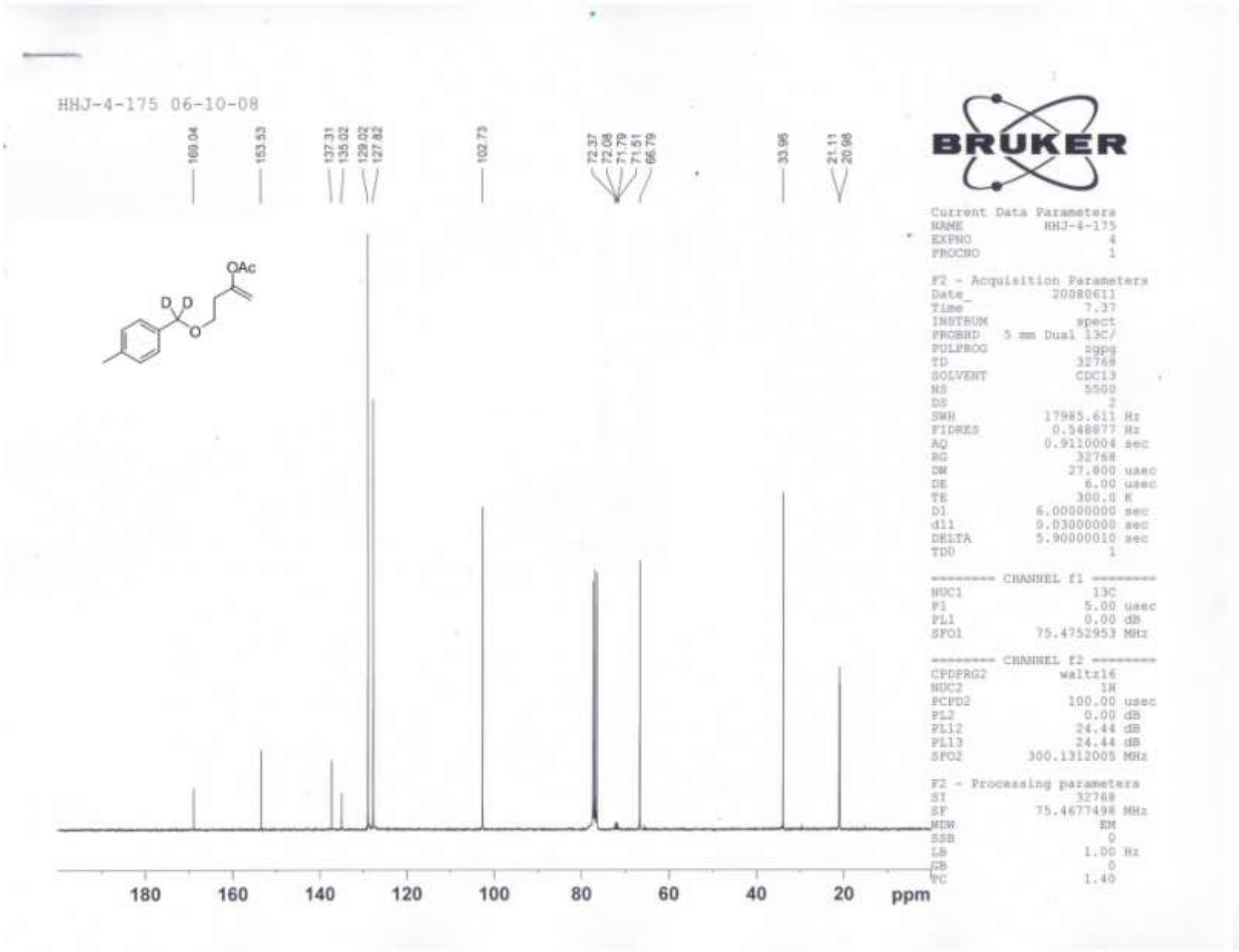
BRUKER

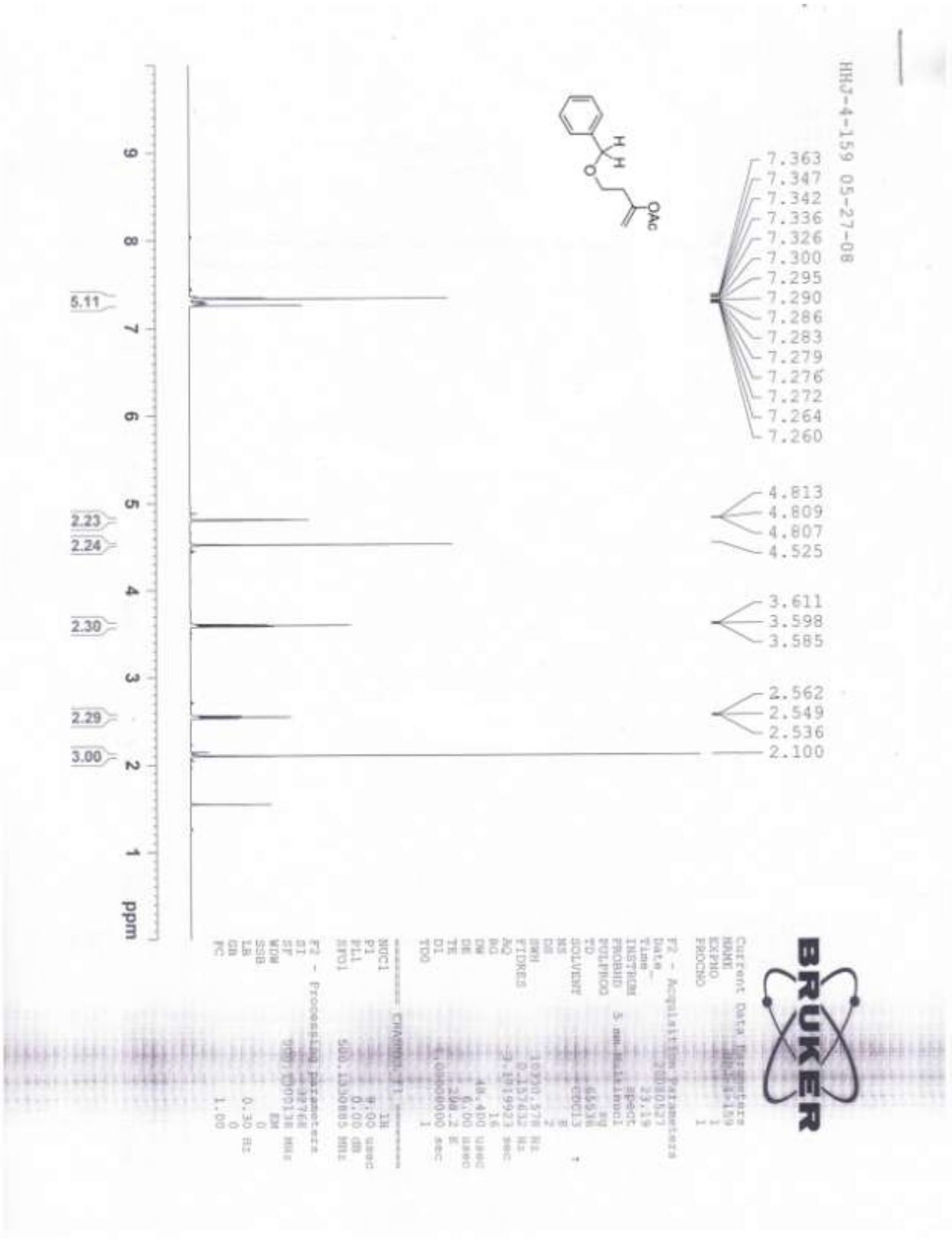
```
Current Data Parameters
NAME                  HHJ-4-175
EXPNO                         1
PROCNO                        1

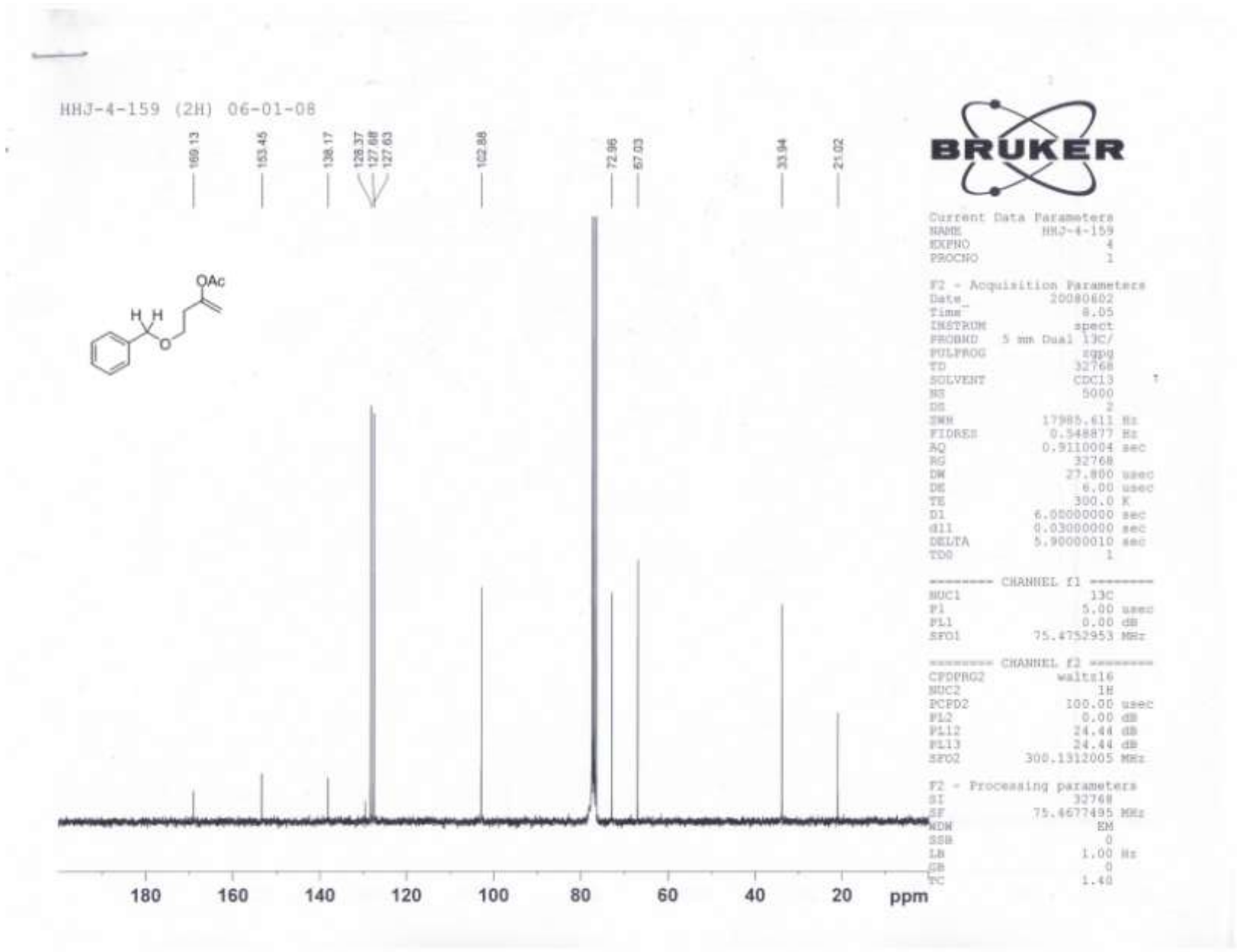
F2 - Acquisition Parameters
Date_              20080613
Time                   23.22
INSTRUM                apect
PROBHD   5 mm Multinucl
PULPROG                   zg
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                 3.1719923 sec
RG                        16
DW                   48.400 usec
DE                    6.00 usec
TE                   296.2 K
D1                1.00000000 sec
TD0                        1

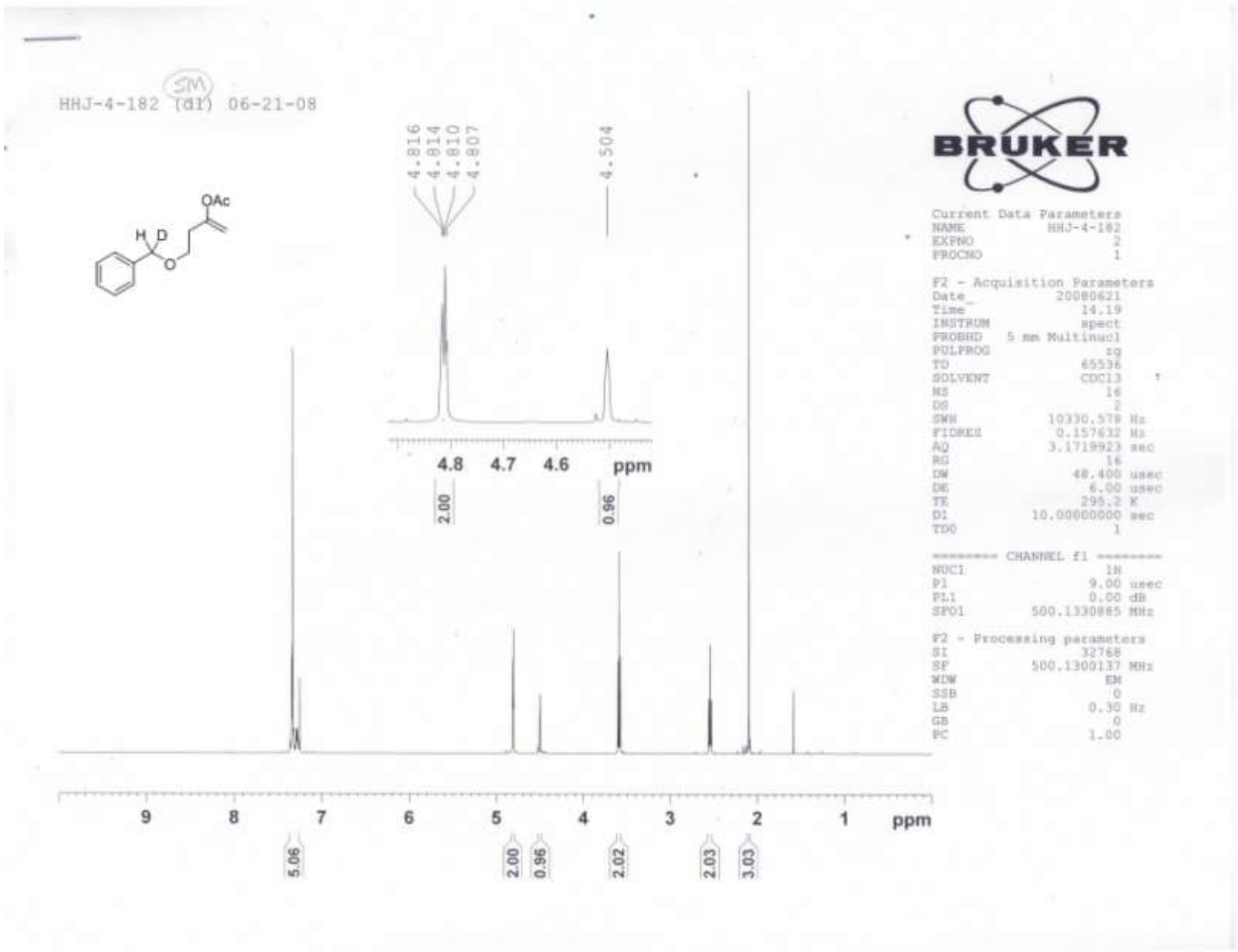
======== CHANNEL f1 ========
NUC1                      1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           500.1330885 MHz

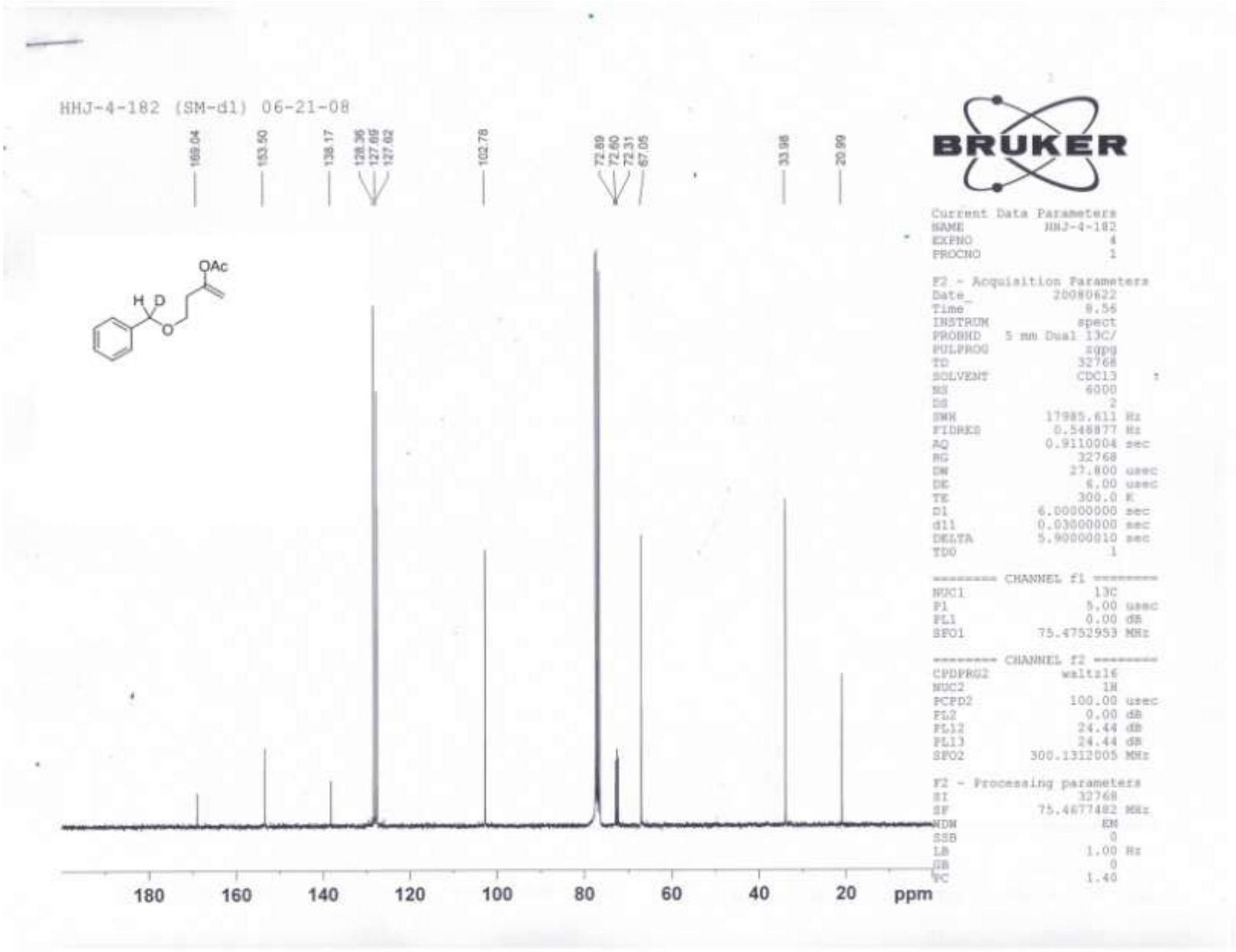
F2 - Processing parameters
SI                        32768
SF              500.1300138 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                     1.00
```

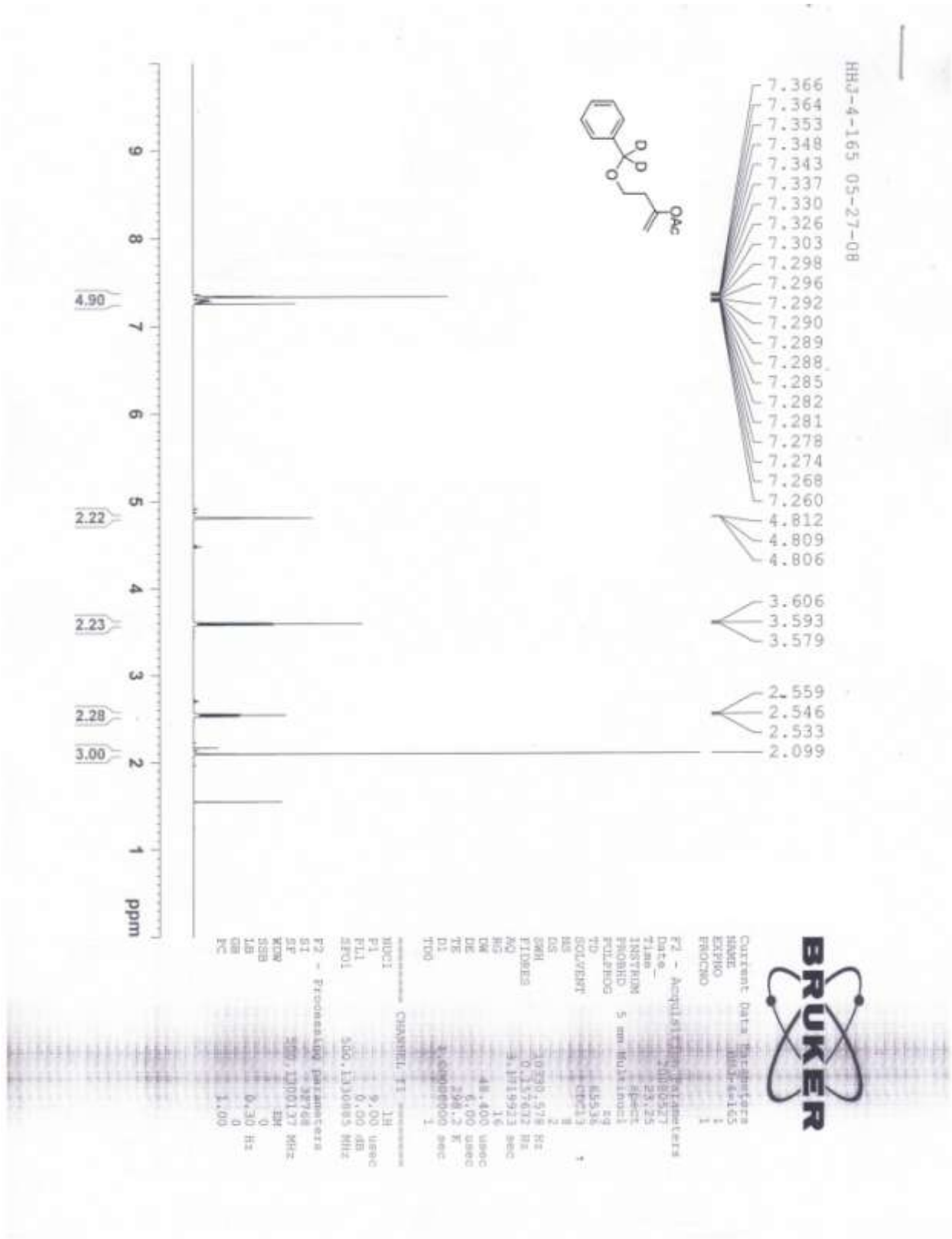

HHJ-4-175 06-10-08
169.04
153.53
137.31
135.02
129.02
127.82
102.73
72.37
72.08
71.79
71.51
66.79
33.96
21.11
20.98
OAc
D
D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-175
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080611
Time 7.37
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5500
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677498 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

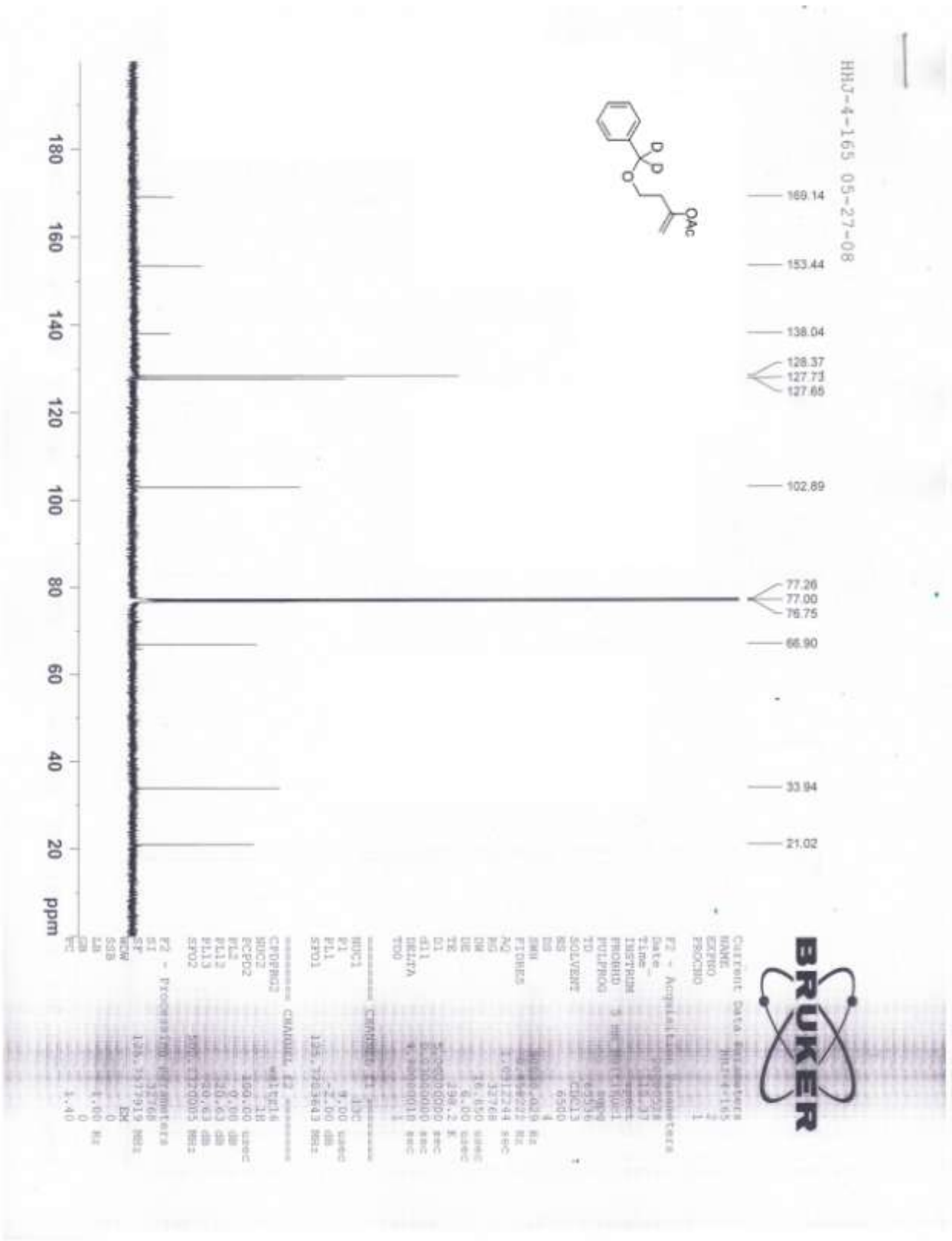

HHJ-4-159 05-27-08
7.363
7.347
7.342
7.336
7.326
7.300
7.295
7.290
7.286
7.283
7.279
7.276
7.272
7.264
7.260
4.813
4.809
4.807
4.525
3.611
3.598
3.585
2.562
2.549
2.536
2.100
OAc
5.11
2.23
2.24
2.30
2.29
3.00
ppm
BRUKER

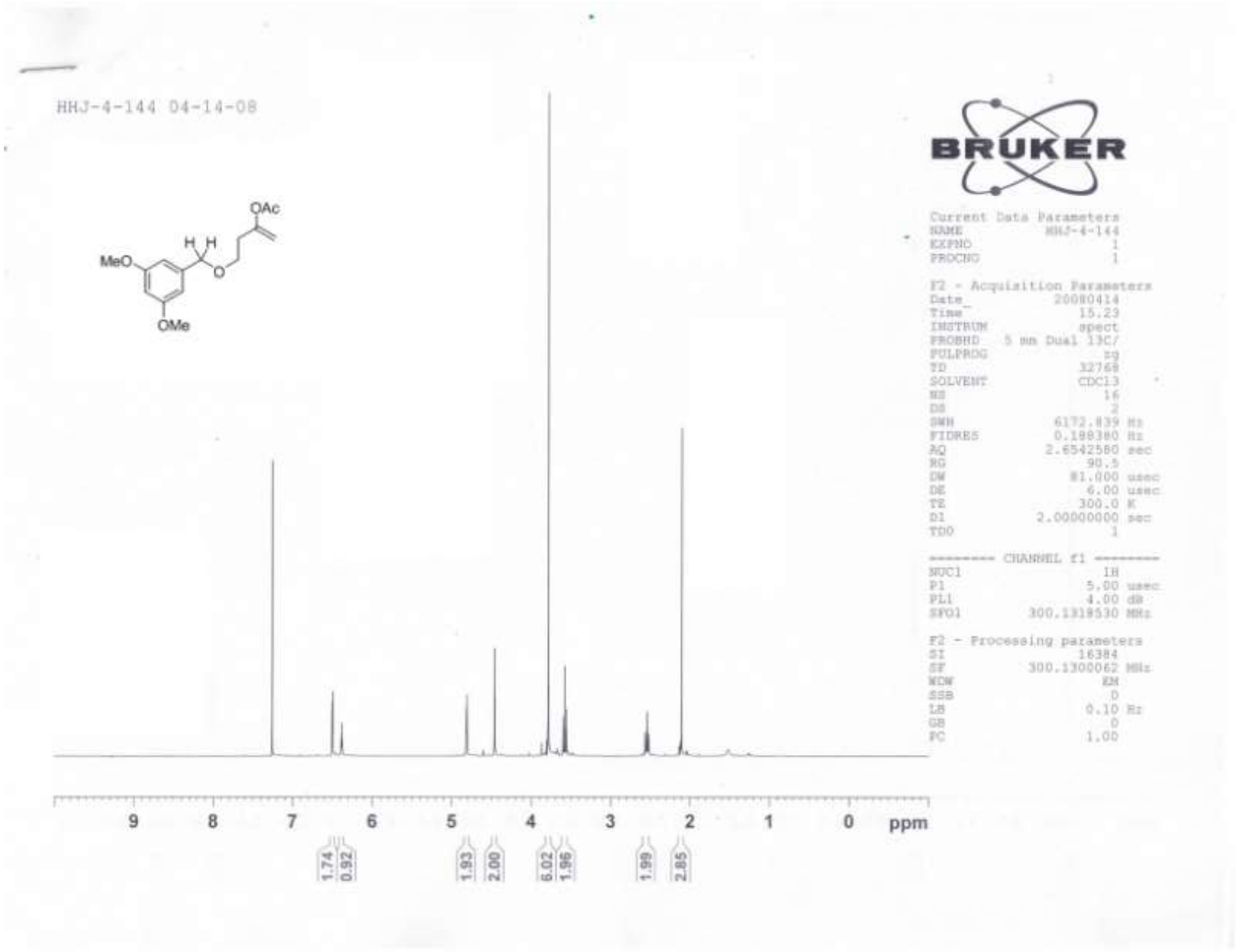

HHJ-4-159 (2H) 06-01-08
169.13
153.45
138.17
128.37
127.68
127.63
102.88
72.96
67.03
33.94
21.02
OAc
H H
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-159
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080602
Time_ 8.05
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677495 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

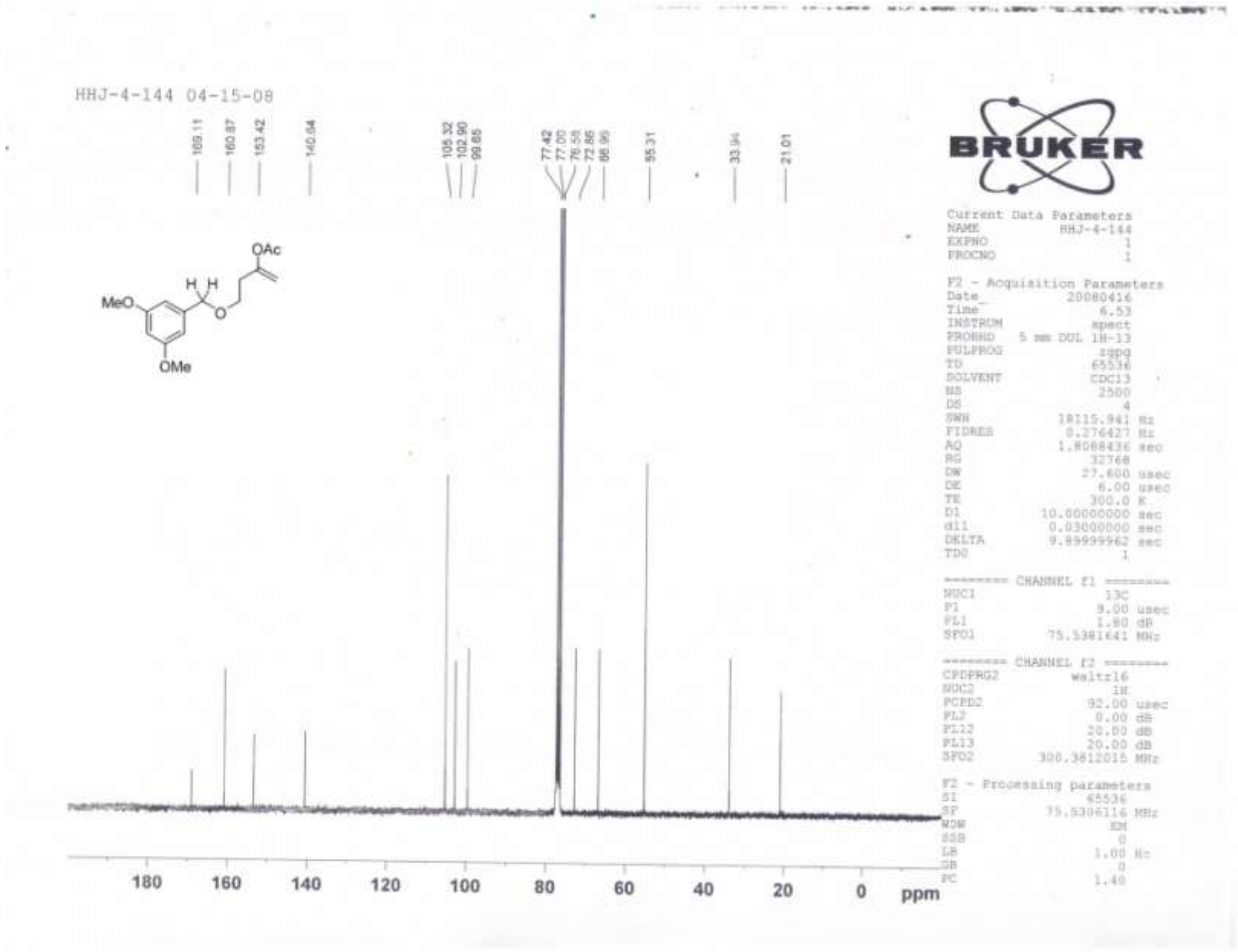

HHJ-4-182 (d1) 06-21-08
SM
OAc
H D
O
4.816
4.814
4.810
4.807
4.504
4.8
4.7
4.6
ppm
2.00
0.96
BRUKER
Current Data Parameters
NAME HHJ-4-102
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080621
Time 14.19
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330865 MHz
F2 - Processing parameters
SI 32768
SF 500.1300137 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
5.06
2.00
0.96
2.02
2.03
3.03

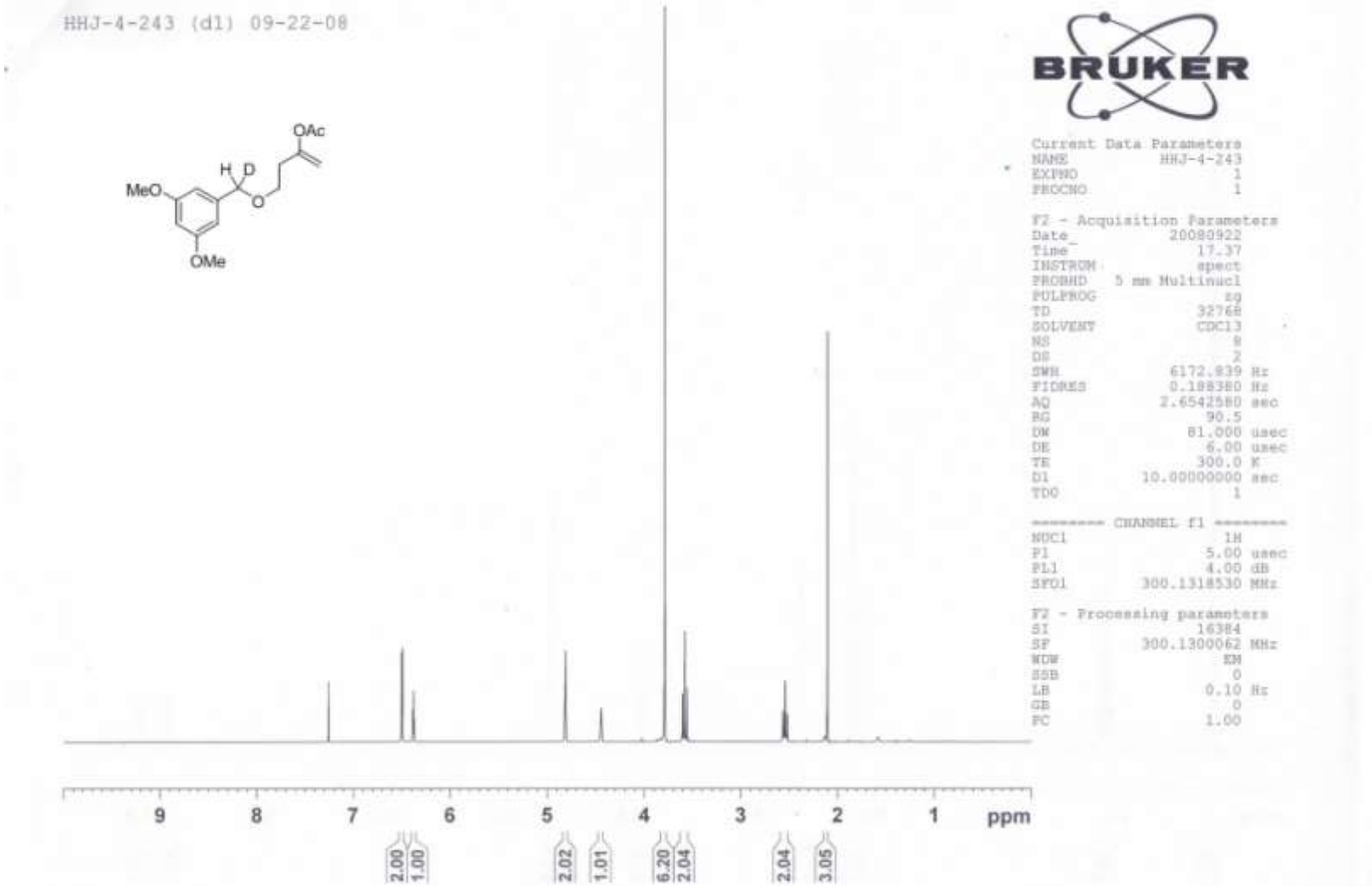

HHJ-4-182 (SM-d1) 06-21-08
169.04
153.50
138.17
128.36
127.69
127.62
102.78
72.89
72.60
72.31
67.05
33.98
20.99
OAc
H D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-182
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080622
Time 8.56
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 6000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677482 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

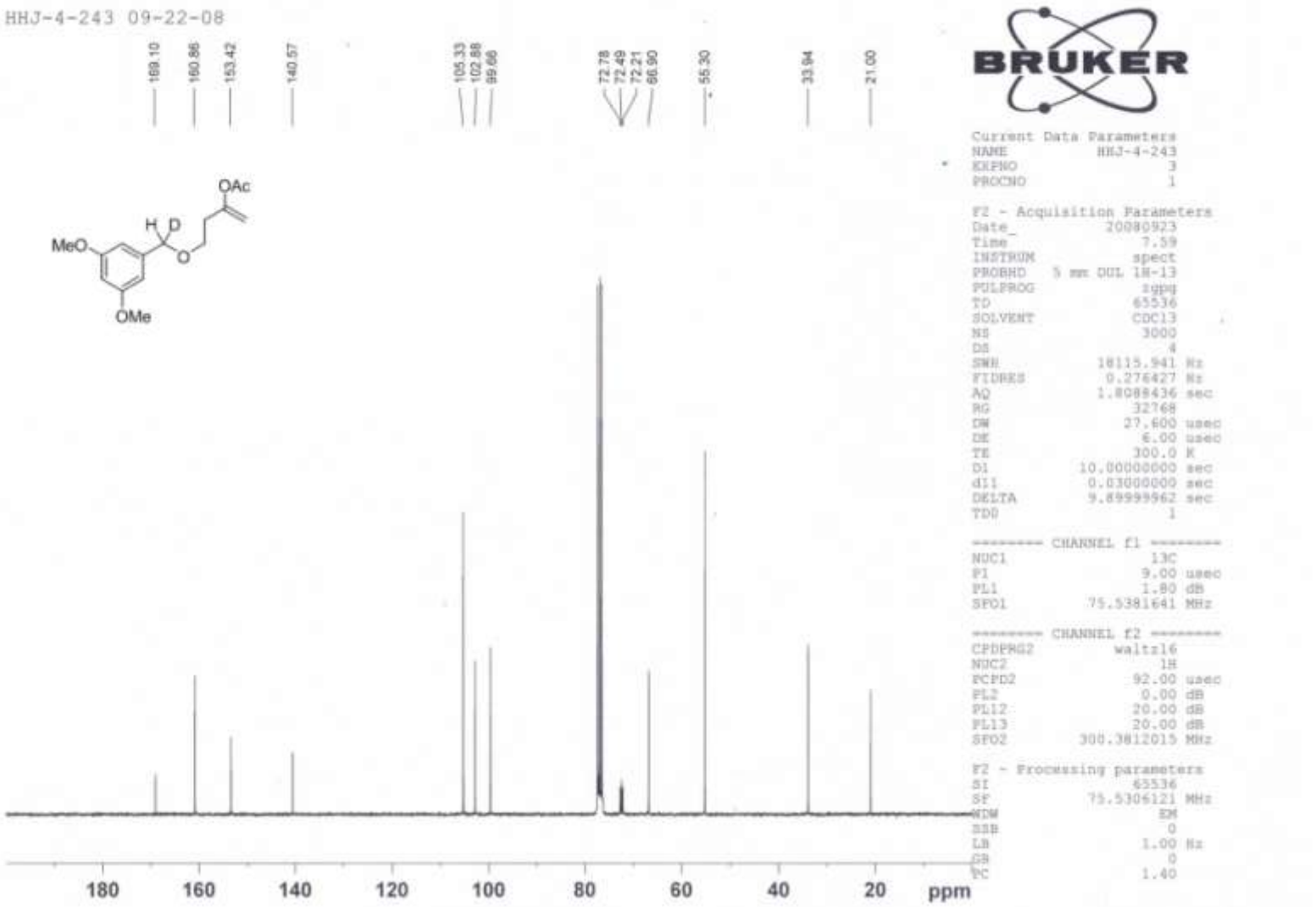

HHJ-4-165 05-27-08
7.366
7.364
7.353
7.348
7.343
7.337
7.330
7.326
7.303
7.298
7.296
7.292
7.290
7.289
7.288
7.285
7.282
7.281
7.278
7.274
7.268
7.260
4.812
4.809
4.806
3.606
3.593
3.579
2.559
2.546
2.533
2.099
4.90
2.22
2.23
2.28
3.00
ppm
BRUKER

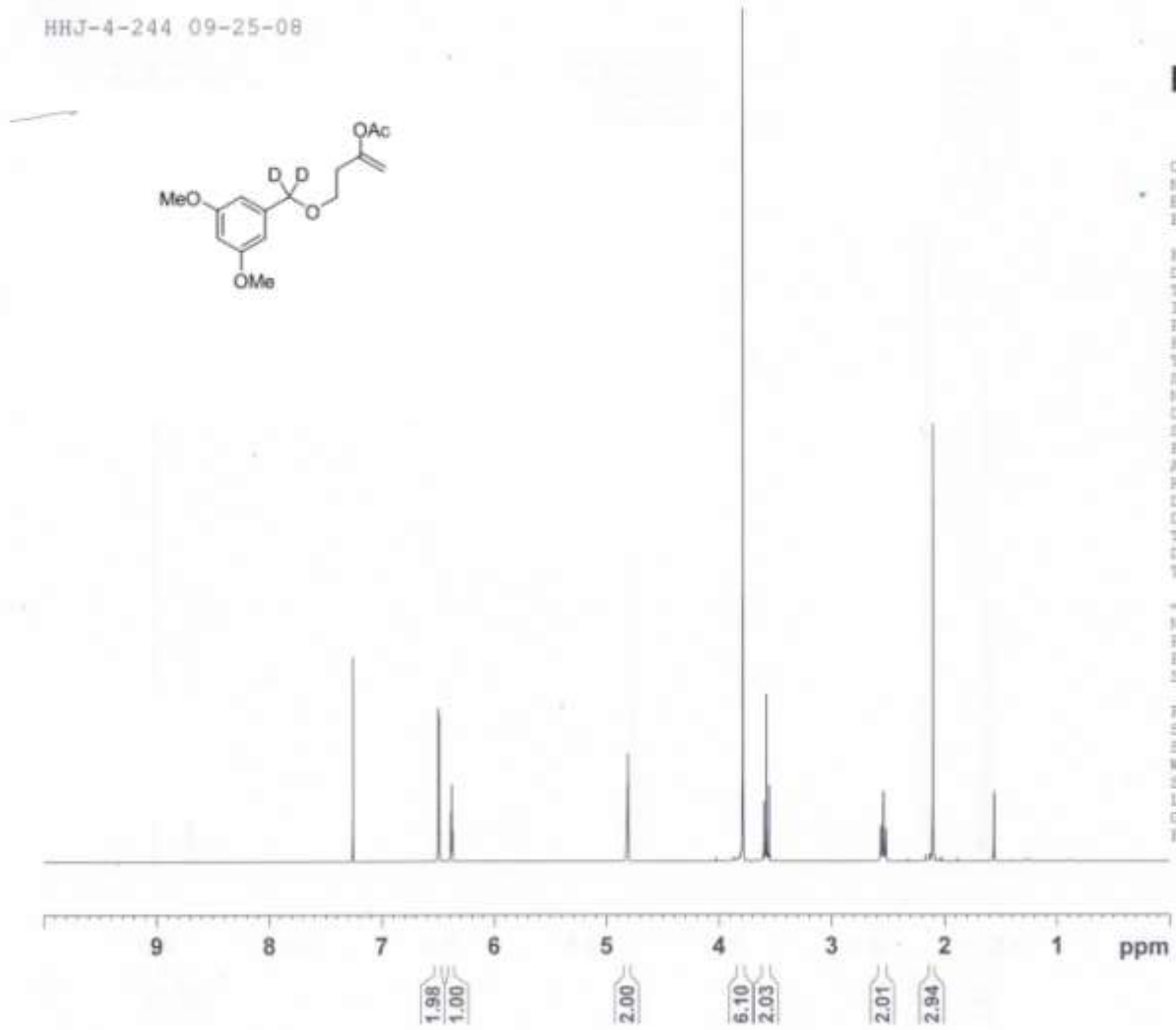

HHJ-4-165 05-27-08
169.14
153.44
138.04
128.37
127.73
127.65
102.89
77.26
77.00
76.75
66.90
33.94
21.02
180
160
140
120
100
80
60
40
20
ppm
D
D
O
OAc


HHJ-4-144 04-14-08
OAc
H H
MeO
O
OMe
BRUKER
Current Data Parameters
NAME HHJ-4-144
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080414
Time 15.29
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
0
ppm
1.74
0.92
1.93
2.00
6.02
1.96
1.99
2.85


HHJ-4-144 04-15-08
169.11
160.87
153.42
140.64
105.32
102.90
99.65
77.42
77.00
76.58
72.86
66.99
55.31
33.96
21.01
OAc
H H
MeO
O
OMe
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-144
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080416
Time 6.53
INSTRUM spect
PROBHD 5 mm DUL 1H-13
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8068436 sec
RG 32768
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.89999962 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 1.80 dB
SFO1 75.5381641 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 92.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 300.3812015 MHz
F2 - Processing parameters
SI 65536
SF 75.5306116 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-243 (d1) 09-22-08
OAc
H D
MeO
O
OMe
BRUKER
Current Data Parameters
NAME HHJ-4-243
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080922
Time 17.37
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
2.00
1.00
2.02
1.01
6.20
2.04
2.04
3.05


HHJ-4-243 09-22-08
169.10
160.86
153.42
140.57
105.33
102.88
99.66
72.78
72.49
72.21
66.90
55.30
33.94
21.00
OAc
H D
MeO
O
OMe
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-243
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080923
Time 7.59
INSTRUM spect
PROBHD 5 mm DUL 1H-13
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 3000
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 32768
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.89999962 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 1.80 dB
SFO1 75.5381641 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 92.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 300.3812015 MHz
F2 - Processing parameters
SI 65536
SF 75.5306121 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



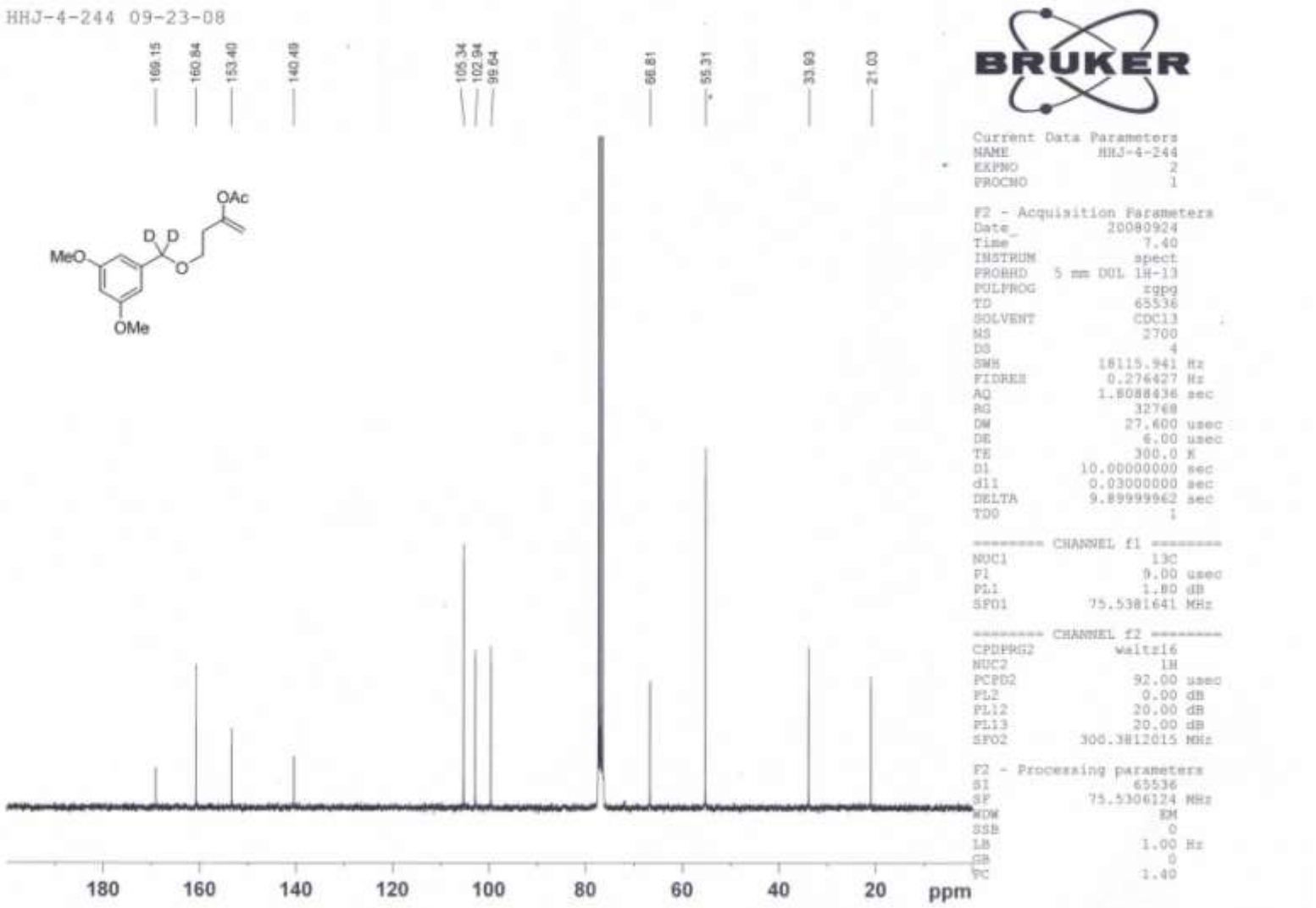
BRUKER

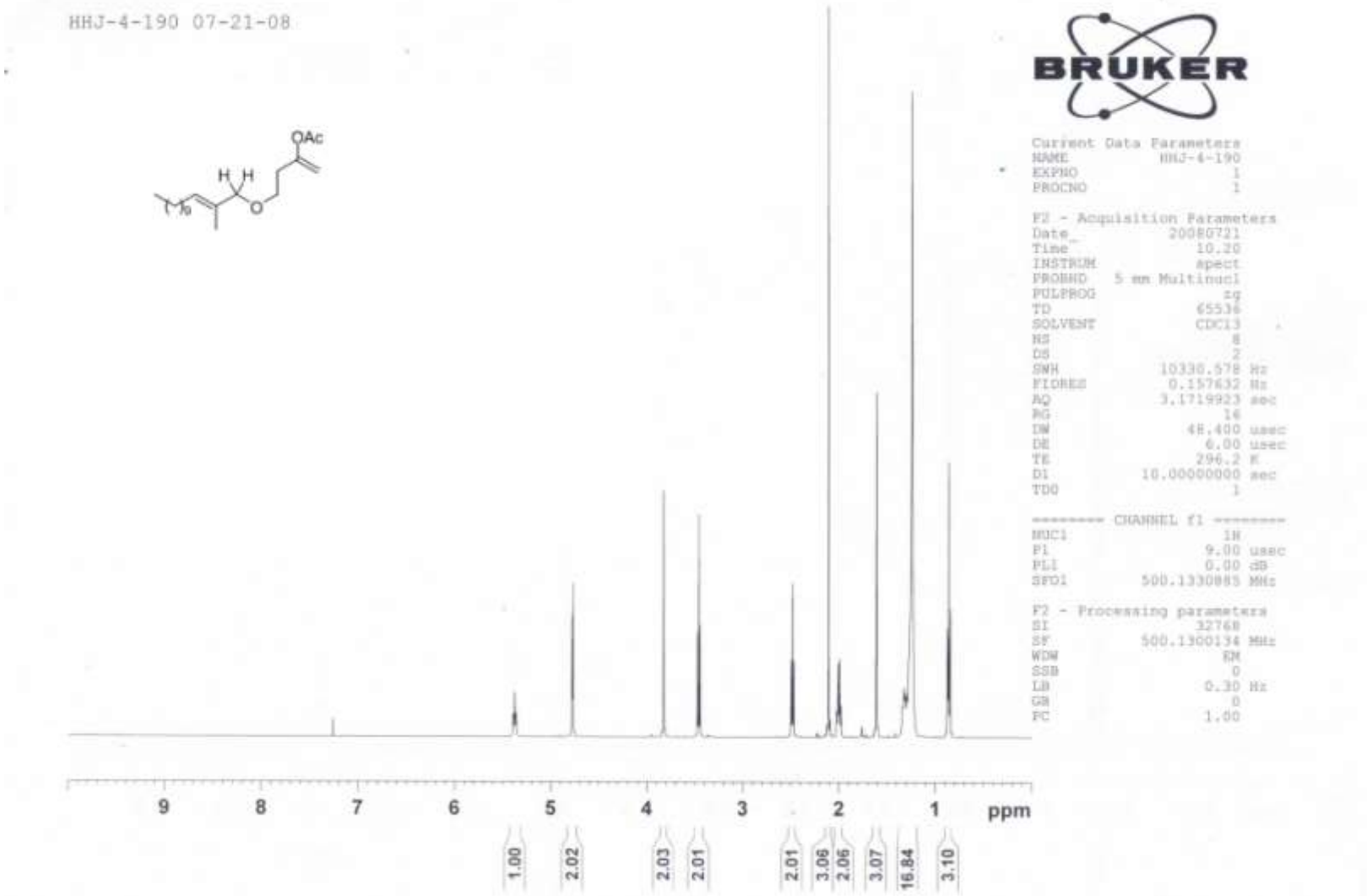
```
Current Data Parameters
NAME                  HHJ-4-244
EXPNO                         1
PROCNO                        1

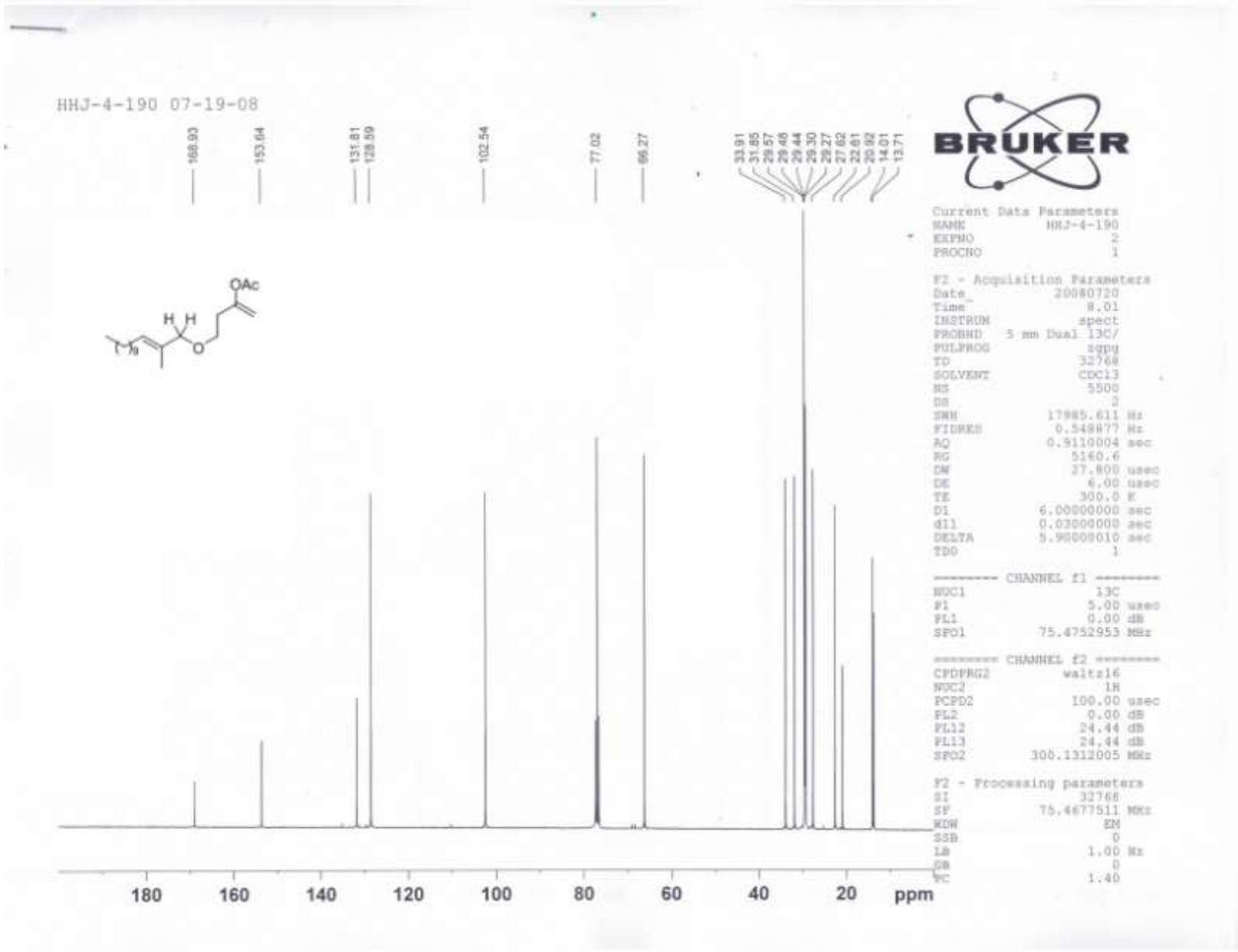
F2 - Acquisition Parameters
Date_              20080925
Time                     11.04
INSTRUM                  spect
PROBHD    5 mm Multinucl
PULPROG                     zg
TD                       32768
SOLVENT                  CDCl3
NS                           8
DS                           2
SWH                 6172.839 Hz
FIDRES              0.188380 Hz
AQ                  2.6542580 sec
RG                        90.5
DW                    81.000 usec
DE                     6.00 usec
TE                     300.0 K
D1                10.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                     5.00 usec
PL1                    4.00 dB
SFO1              300.1318530 MHz

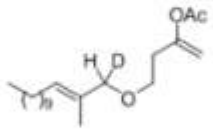
F2 - Processing parameters
SI                       16384
SF                300.1300062 MHz
WDW                         EM
SSB                          0
LB                     0.10 Hz
GB                           0
PC                        1.00
```


HHJ-4-244 09-23-08
169.15
160.84
153.40
140.49
105.34
102.94
99.64
66.81
55.31
33.93
21.03
OAc
D D
MeO
O
OMe
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-244
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080924
Time 7.40
INSTRUM spect
PROBHD 5 mm DUL 1H-13
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 2700
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 32768
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.89999962 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 1.80 dB
SFO1 75.5381641 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 92.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 300.3812015 MHz
F2 - Processing parameters
SI 65536
SF 75.5306124 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-190 07-21-08
OAc
H H
O
BRUKER
Current Data Parameters
NAME HHJ-4-190
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080721
Time 10.20
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 296.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300134 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
2.02
2.03
2.01
2.01
3.06
2.06
3.07
16.84
3.10


HHJ-4-190 07-19-08
168.93
153.64
131.81
128.59
102.54
77.02
66.27
33.91
31.85
29.57
29.46
29.44
29.30
29.27
27.62
22.61
20.92
14.01
13.71
OAc
H H
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-190
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080720
Time 8.01
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG sgpg
TD 32768
SOLVENT CDCl3
NS 5500
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 5160.6
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.98000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677511 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

HHJ-4-191 07-11-08



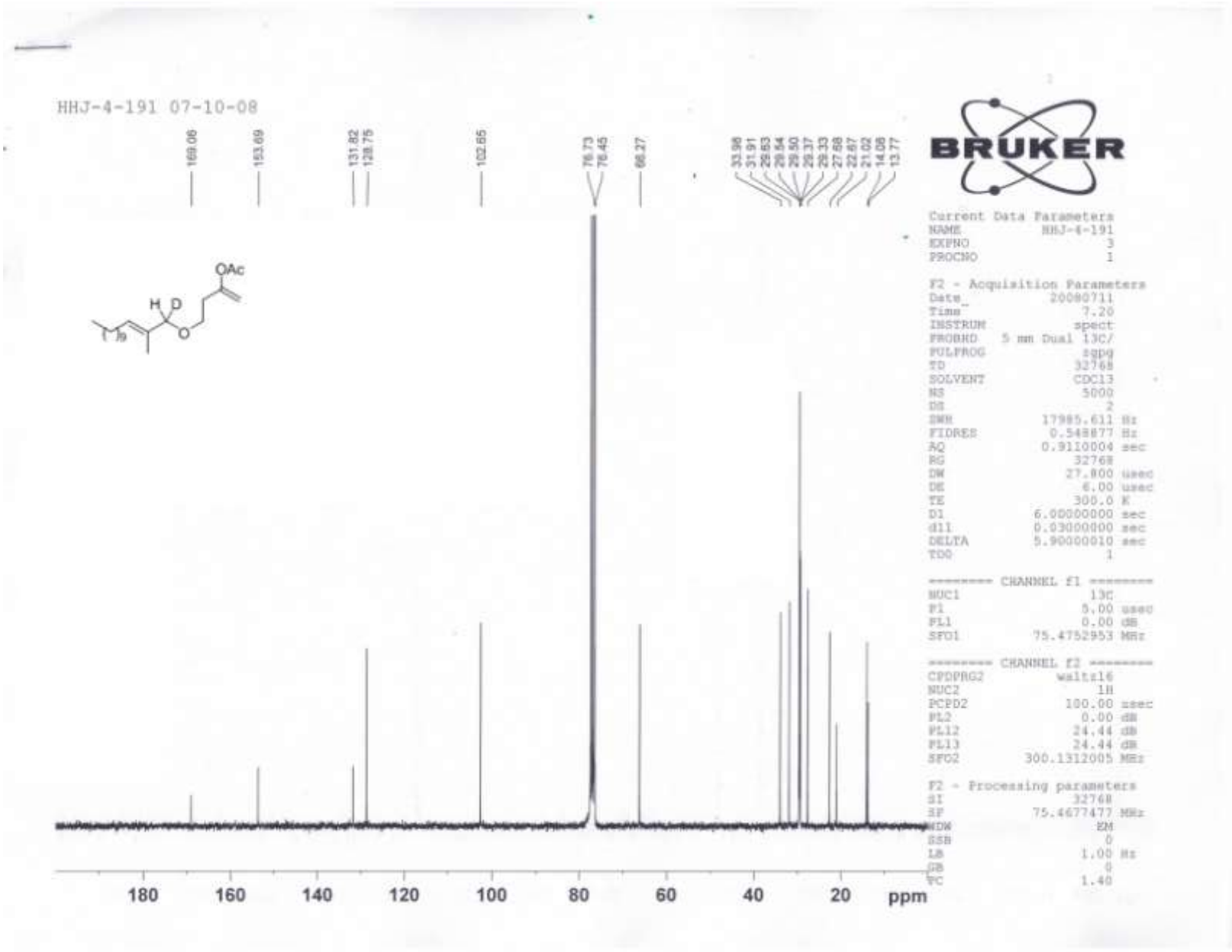
BRUKER

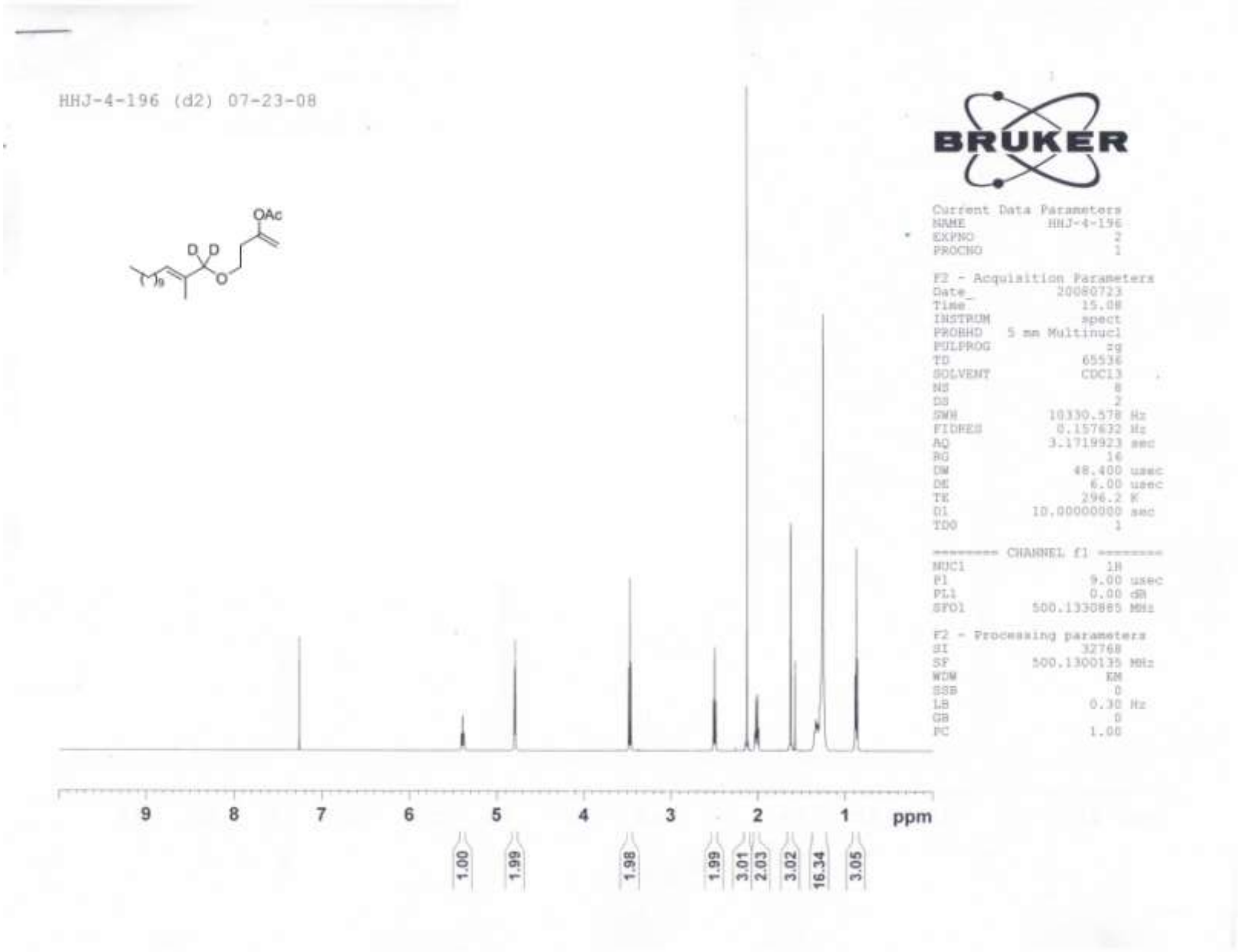
```
Current Data Parameters
NAME                  HHJ-4-191
EXPNO                         1
PROCNO                        1

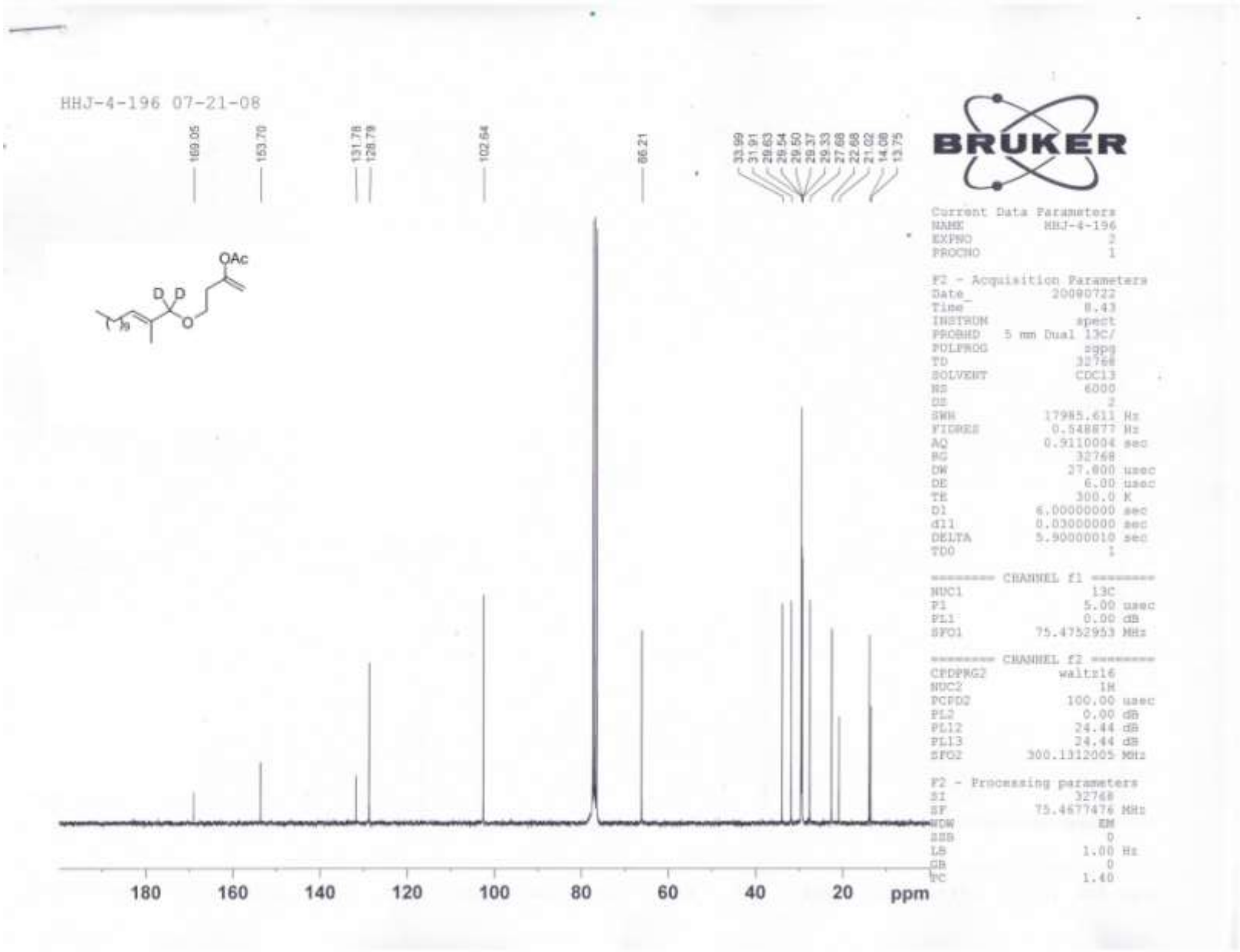
F2 - Acquisition Parameters
Date_              20080711
Time                      13.39
INSTRUM                   spect
PROBHD    5 mm Multinucl
PULPROG                      zg
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                  10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719923 sec
RG                           16
DW                       48.400 usec
DE                        6.00 usec
TE                       296.2 K
D1                 10.00000000 sec
TD0                           1

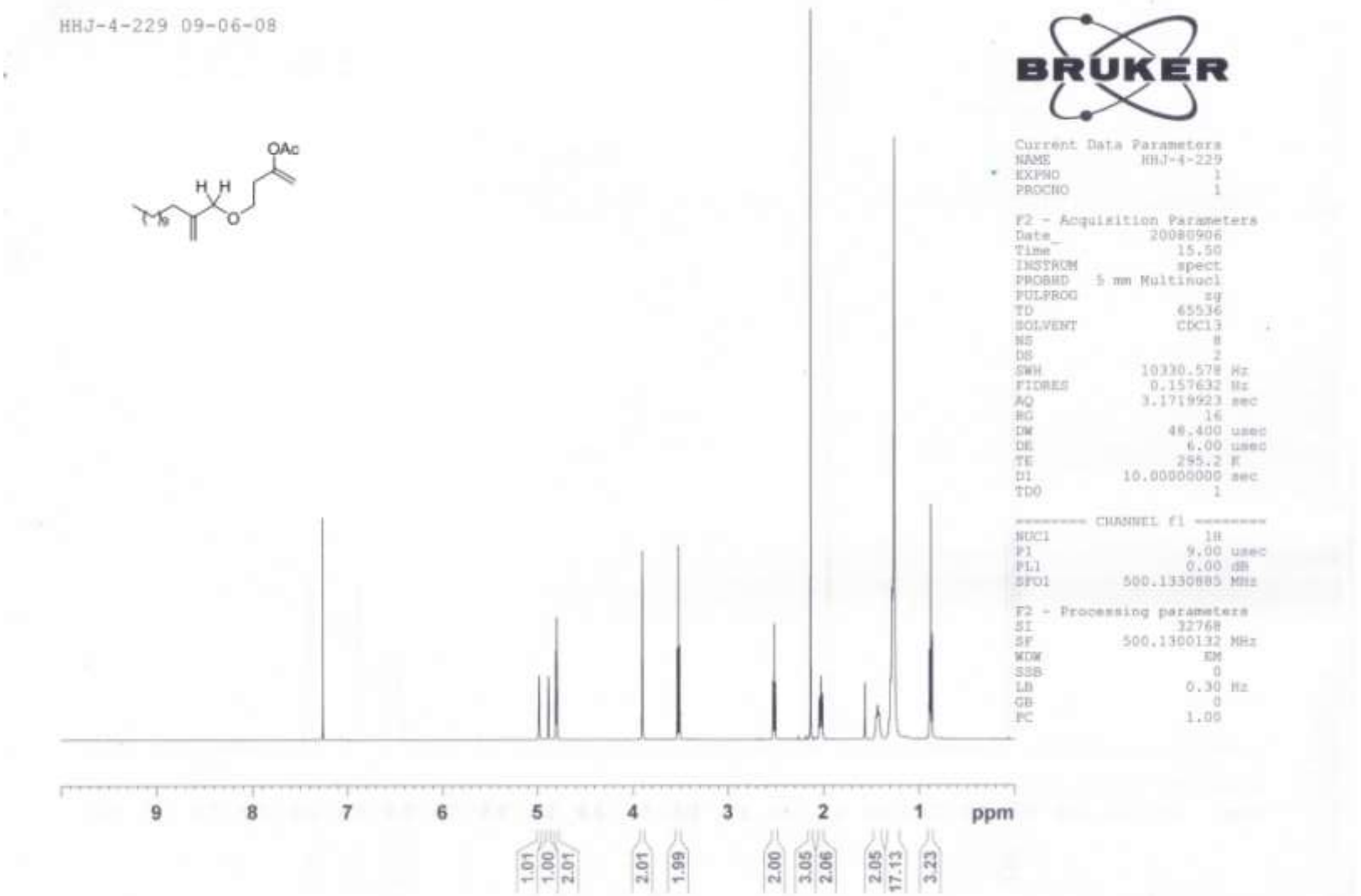
======== CHANNEL f1 ========
NUC1                         1H
P1                        9.00 usec
PL1                       0.00 dB
SFO1               500.1330885 MHz

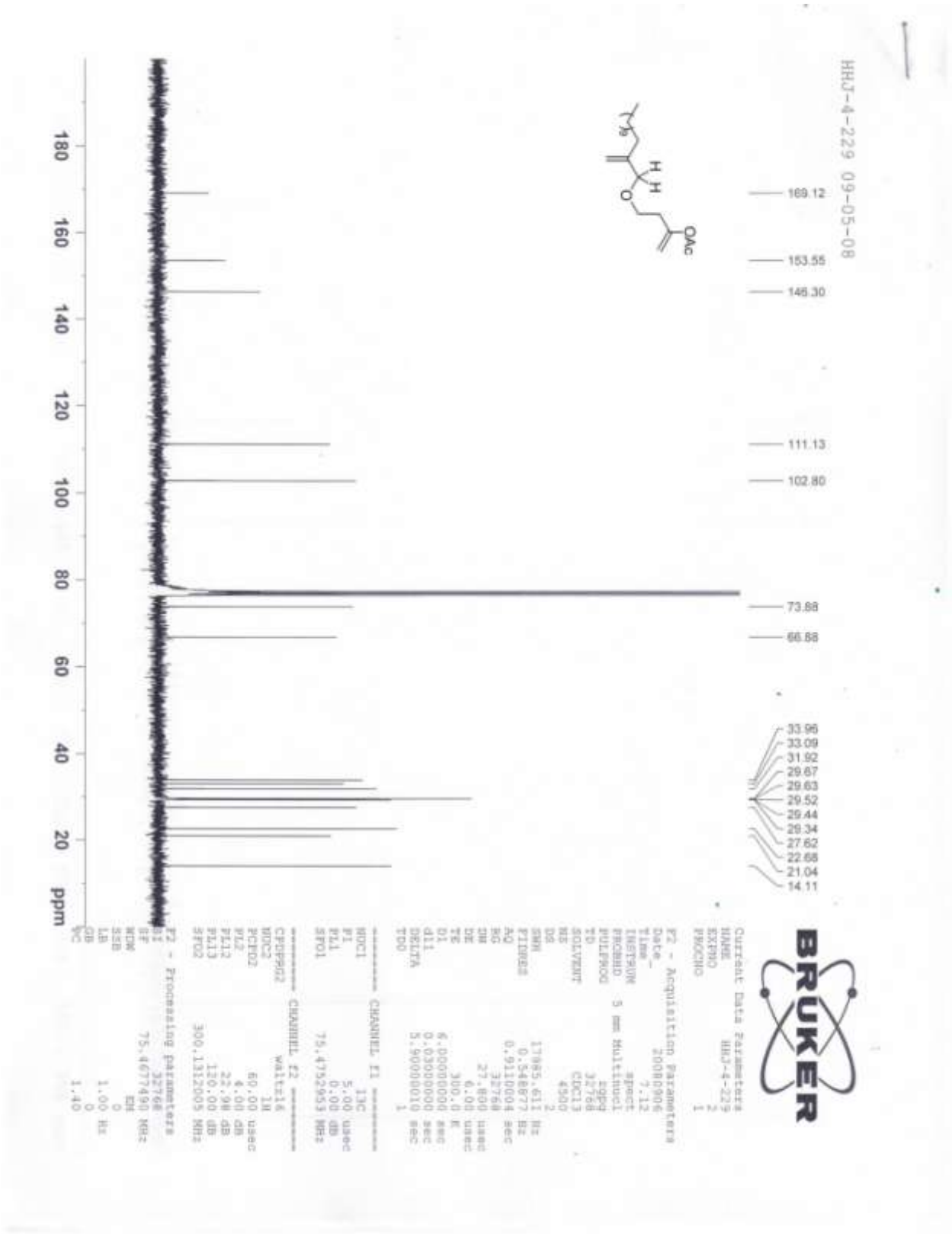
F2 - Processing parameters
SI                        32768
SF                 500.1300135 MHz
WDW                          EM
SSB                           0
LB                        0.30 Hz
GB                            0
PC                        1.00
```

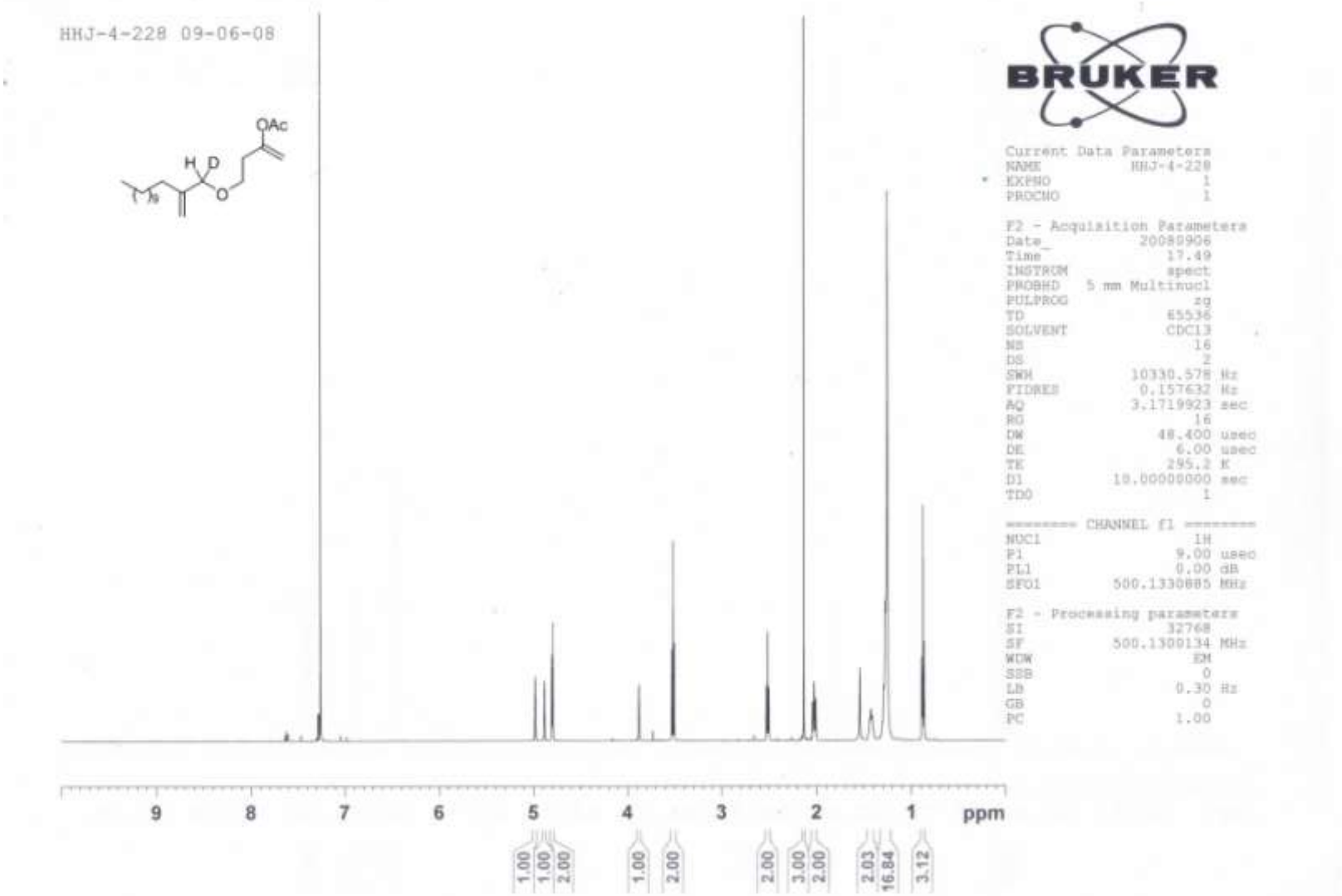

HHJ-4-191 07-10-08
169.06
153.69
131.82
128.75
102.65
76.73
76.45
66.27
33.98
31.91
29.63
29.54
29.50
29.37
29.33
27.68
22.67
21.02
14.08
13.77
OAc
H
D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-191
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080711
Time 7.20
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG sgpg
TD 32768
SOLVENT CDCl3
NS 5000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677477 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

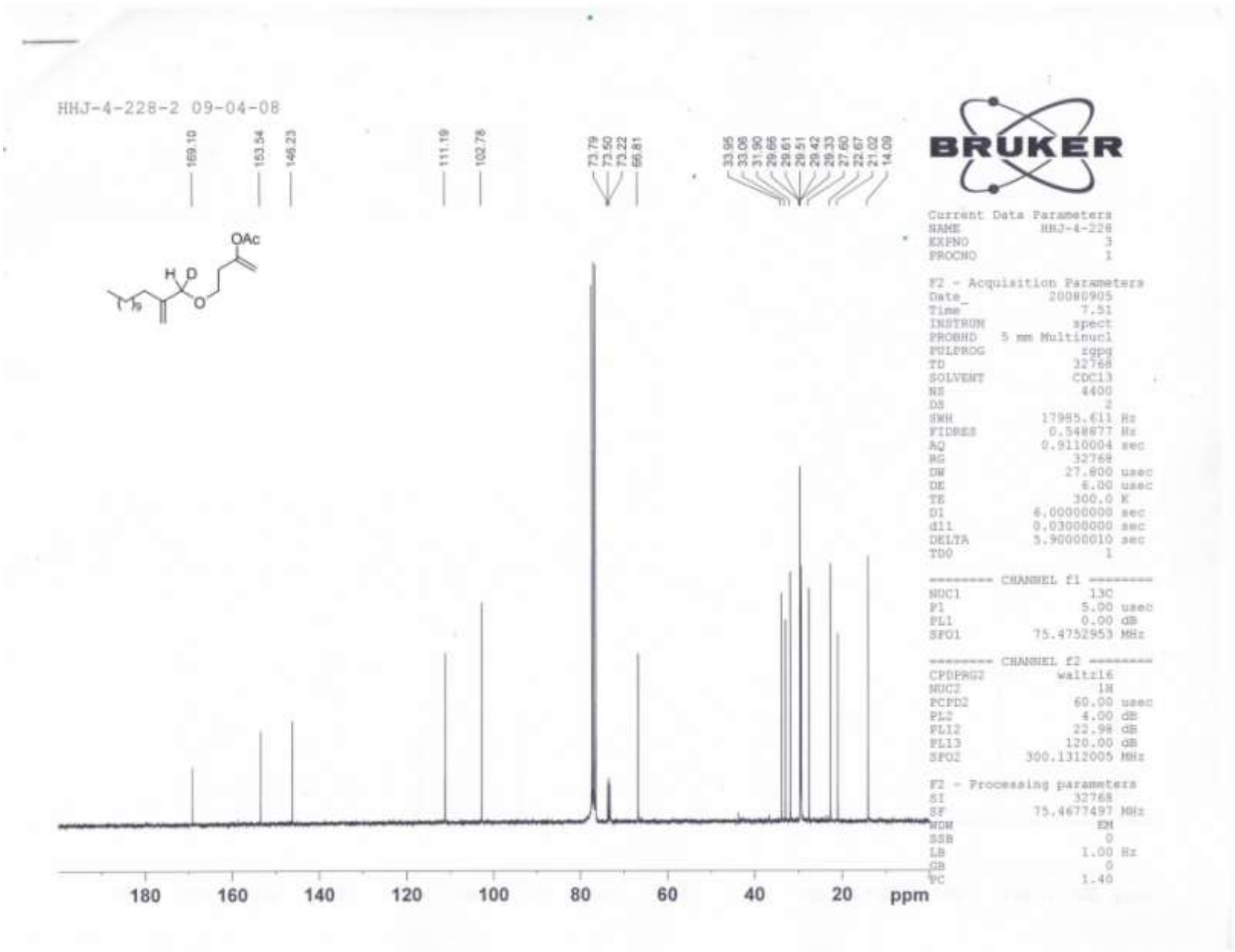

HHJ-4-196 (d2) 07-23-08
OAc
D D
O
BRUKER
Current Data Parameters
NAME HHJ-4-196
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080723
Time 15.08
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 296.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330865 MHz
F2 - Processing parameters
SI 32768
SF 500.1300135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
1.99
1.98
1.99
3.01
2.03
3.02
16.34
3.05

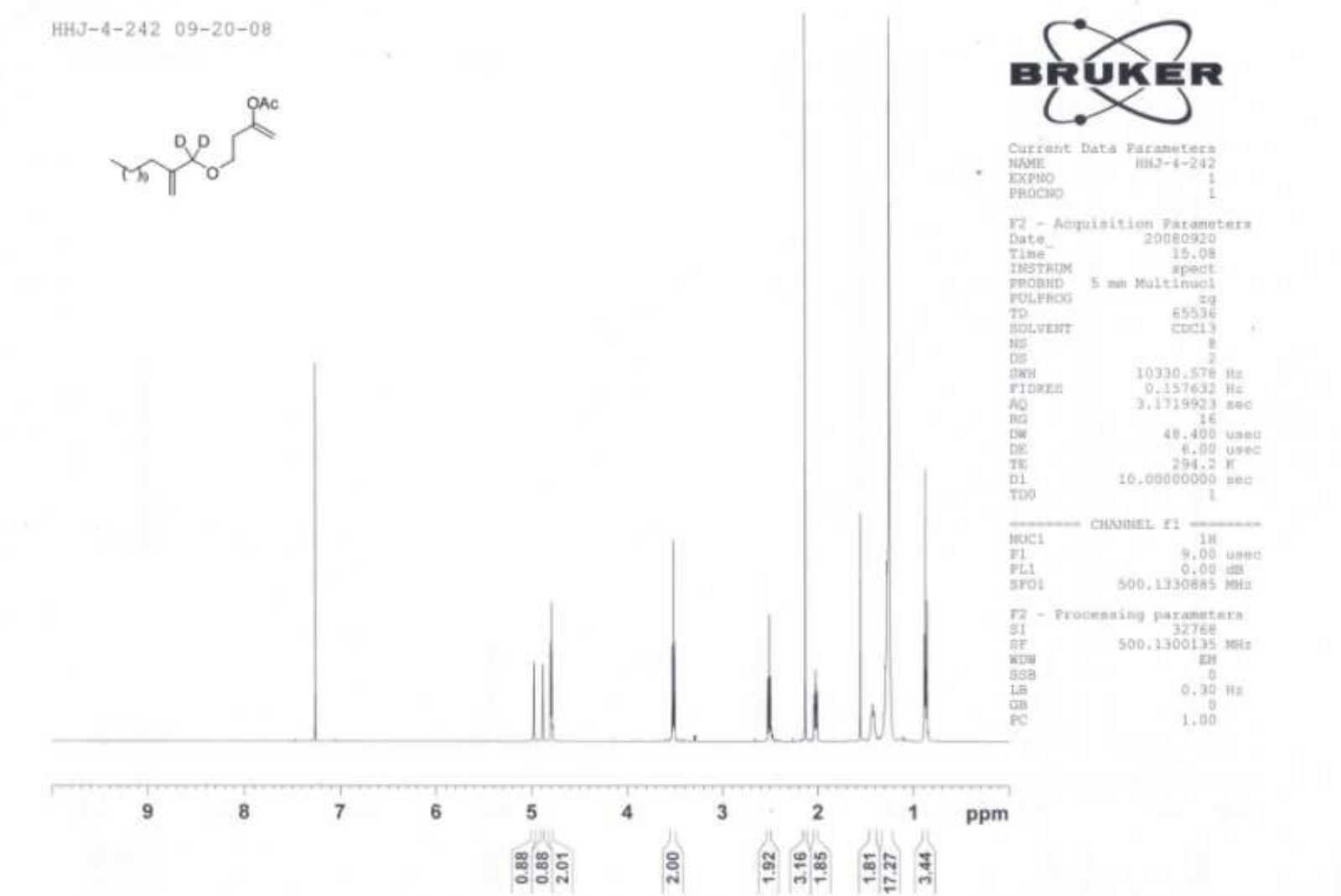

HHJ-4-196 07-21-08
169.05
153.70
131.78
128.79
102.84
86.21
33.99
31.91
29.63
29.54
29.50
29.37
29.33
27.68
22.68
21.02
14.08
13.75
OAc
D D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-196
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080722
Time 8.43
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 6000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677476 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-229 09-06-08
OAc
H H
O
BRUKER
Current Data Parameters
NAME HHJ-4-229
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080906
Time 15.50
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300132 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.01
1.00
2.01
2.01
1.99
2.00
3.05
2.06
2.05
17.13
3.23


HHJ-4-229 09-05-08
OAc
169.12
153.55
146.30
111.13
102.80
73.88
66.88
33.96
33.09
31.92
29.67
29.63
29.52
29.44
29.34
27.62
22.68
21.04
14.11
BRUKER
180
160
140
120
100
80
60
40
20
ppm


HHJ-4-228 09-06-08
OAc
H
D
O
BRUKER
Current Data Parameters
NAME HHJ-4-228
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080906
Time 17.49
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300134 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
2.00
1.00
2.00
2.00
3.00
2.00
2.03
16.84
3.12


HHJ-4-228-2 09-04-08
169.10
153.54
145.23
111.19
102.78
73.79
73.50
73.22
66.81
33.95
33.08
31.90
29.65
29.61
29.51
29.42
29.33
27.60
22.67
21.02
14.09
OAc
H
D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-228
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080905
Time 7.51
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 4400
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 60.00 usec
PL2 4.00 dB
PL12 22.98 dB
PL13 120.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677497 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



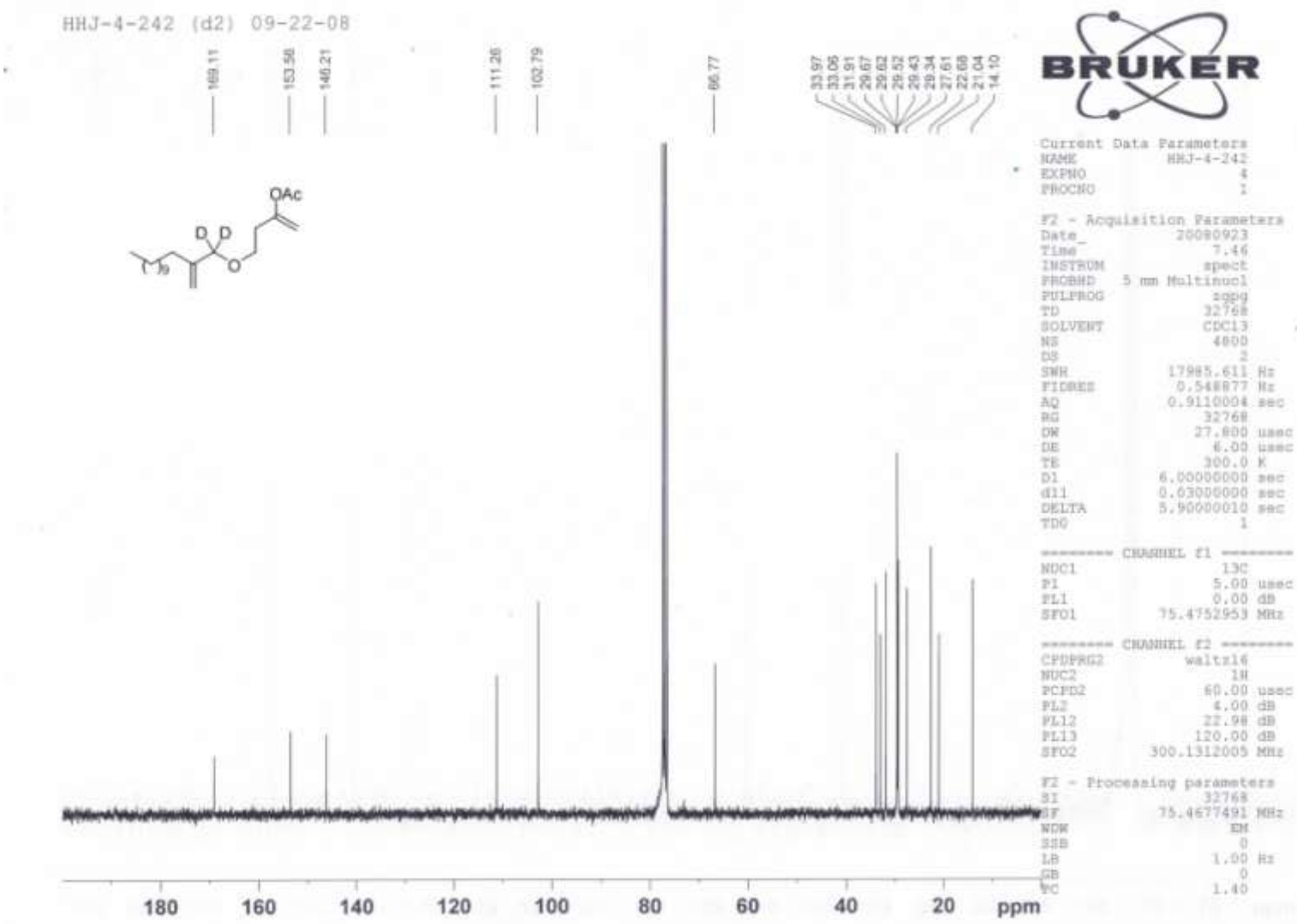
BRUKER

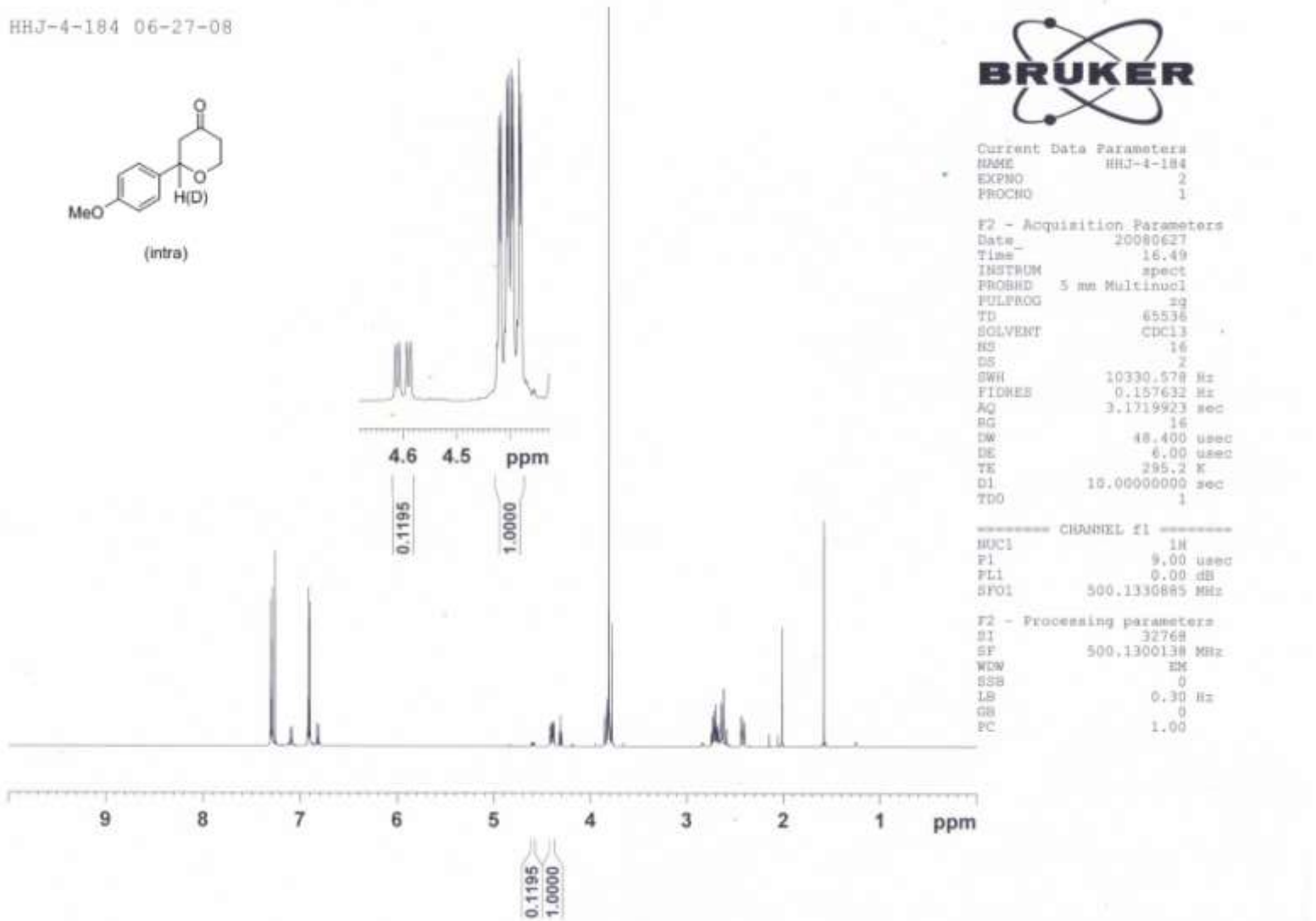
```
Current Data Parameters
NAME                  HHJ-4-242
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20080920
Time                    15.08
INSTRUM                 spect
PROBHD    5 mm Multinucl
PULPROG                   zg
TD                     65536
SOLVENT                CDCl3
NS                            8
DS                            2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                 3.1719923 sec
RG                           16
DW                   48.400 usec
DE                    6.00 usec
TE                   294.2 K
D1               10.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        9.00 usec
PL1                       0.00 dB
SFO1            500.1330885 MHz

F2 - Processing parameters
SI                        32768
SF              500.1300135 MHz
WDW                          EM
SSB                           0
LB                        0.30 Hz
GB                            0
PC                        1.00
```


HHJ-4-242 (d2) 09-22-08
169.11
153.56
146.21
111.26
102.79
86.77
33.97
33.06
31.91
29.67
29.62
29.52
29.43
29.34
27.61
22.68
21.04
14.10
OAc
D D
O
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-242
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080923
Time 7.46
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 4800
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 60.00 usec
PL2 4.00 dB
PL12 22.98 dB
PL13 120.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677491 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



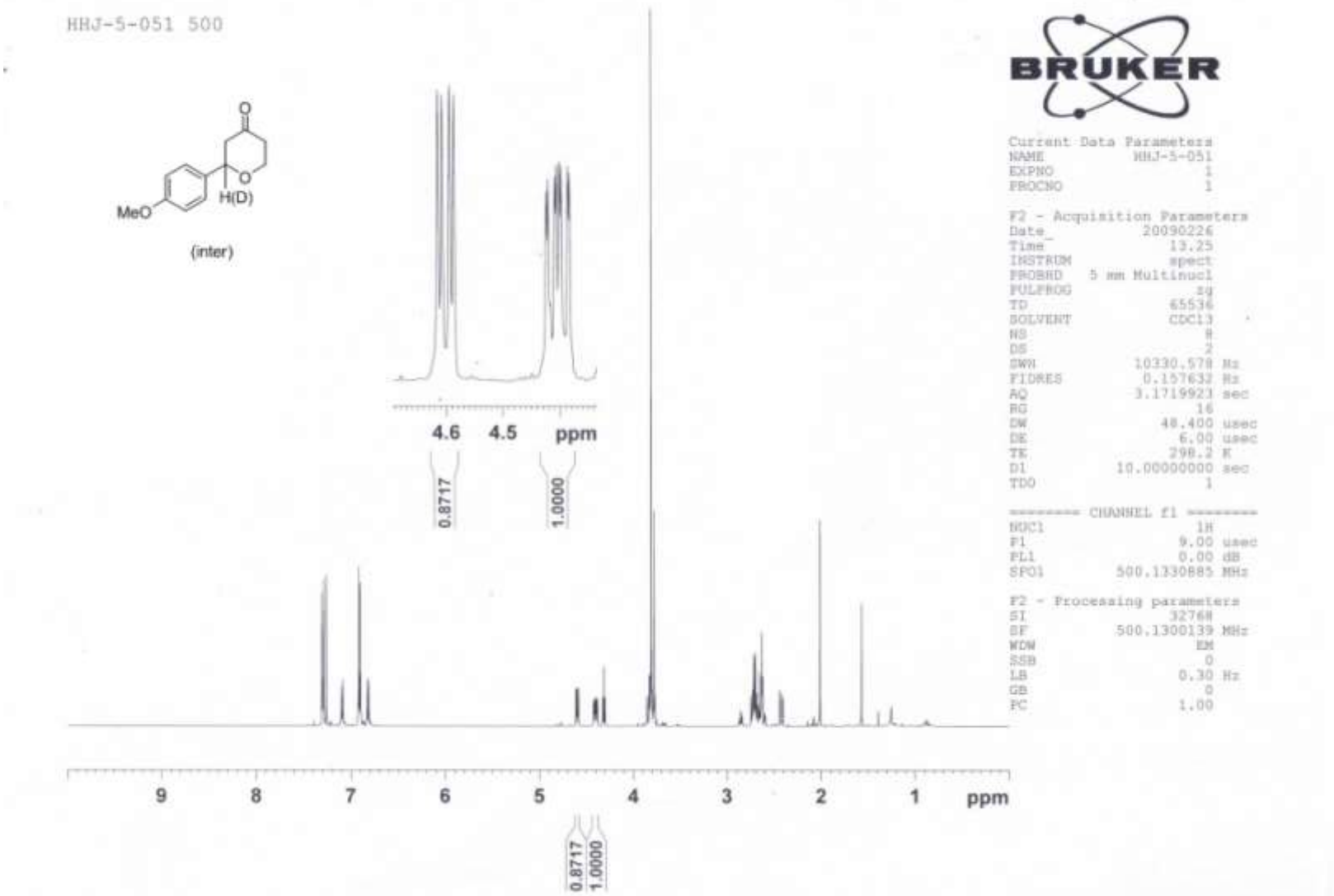
BRUKER

```
Current Data Parameters
NAME                  HHJ-4-184
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_              20080627
Time                    16.49
INSTRUM                 spect
PROBHD    5 mm Multinucl
PULPROG                    zg
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                10330.578 Hz
FIDRES              0.157632 Hz
AQ                  3.1719923 sec
RG                         16
DW                    48.400 usec
DE                     6.00 usec
TE                    295.2 K
D1                 10.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.00 usec
PL1                     0.00 dB
SFO1              500.1330885 MHz

F2 - Processing parameters
SI                      32768
SF                500.1300138 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```



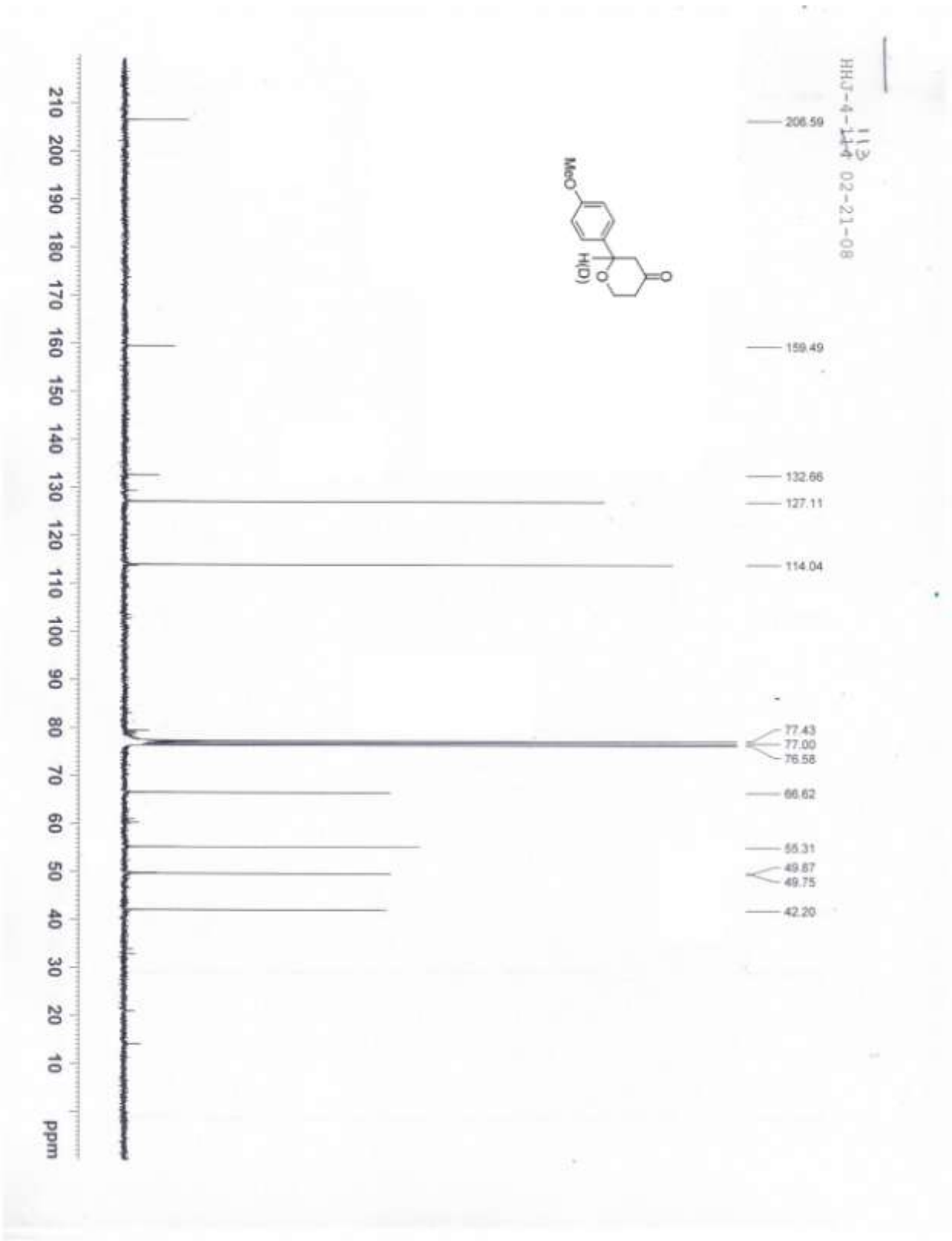
BRUKER

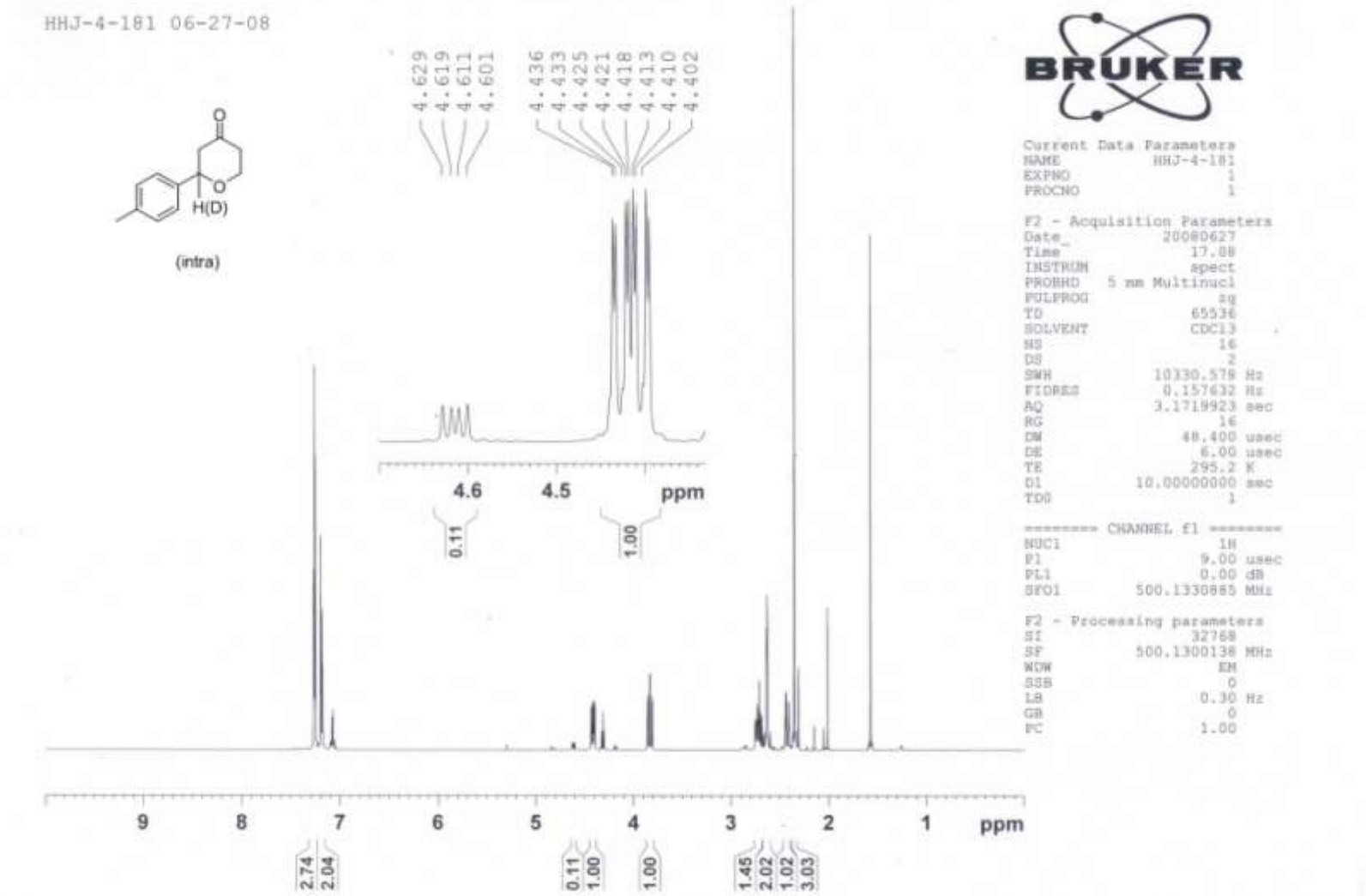
```
Current Data Parameters
NAME                  HHJ-5-051
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20090226
Time                    13.25
INSTRUM                 spect
PROBHD     5 mm Multinucl
PULPROG                    zg
TD                      65536
SOLVENT                 CDCl3
NS                          8
DS                          2
SWH                10330.578 Hz
FIDRES              0.157632 Hz
AQ                  3.1719923 sec
RG                         16
DW                    48.400 usec
DE                     6.00 usec
TE                    298.2 K
D1                10.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.00 usec
PL1                     0.00 dB
SFO1              500.1330885 MHz

F2 - Processing parameters
SI                      32768
SF                500.1300139 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```


113
HHJ-4-114 02-21-08
MeO
H(D)
O
O
206.59
159.49
132.66
127.11
114.04
77.43
77.00
76.58
66.62
55.31
49.87
49.75
42.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



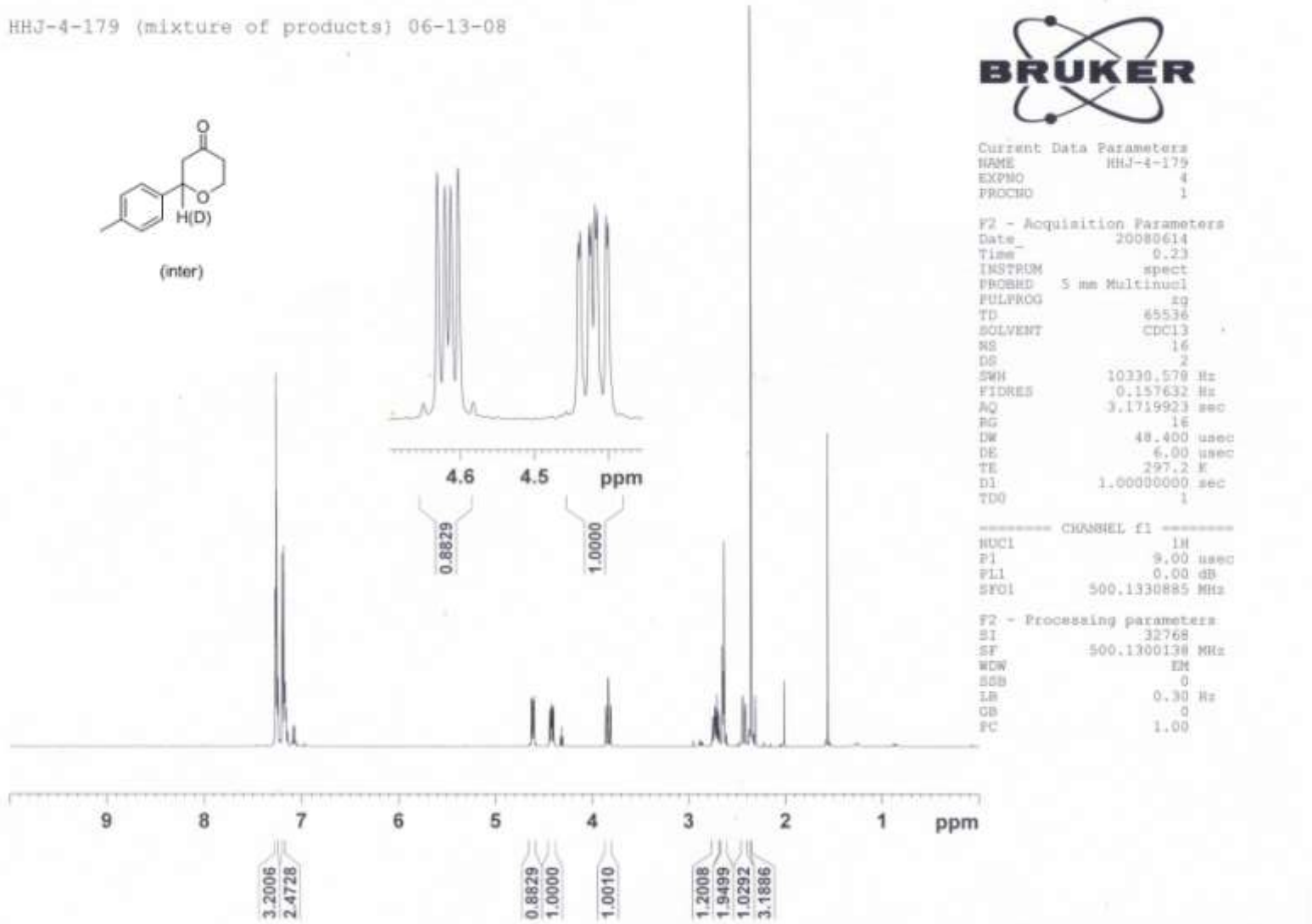
BRUKER

```
Current Data Parameters
NAME                 HHJ-4-181
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20080627
Time                   17.08
INSTRUM                apect
PROBHD    5 mm Multinucl
PULPROG                   zg
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                10330.579 Hz
FIDRES              0.157632 Hz
AQ                  3.1719923 sec
RG                        16
DW                    48.400 usec
DE                     6.00 usec
TE                    295.2 K
D1                 10.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1              500.1330885 MHz

F2 - Processing parameters
SI                     32768
SF                500.1300138 MHz
WDW                       EM
SSB                        0
LB                     0.30 Hz
GB                         0
PC                      1.00
```



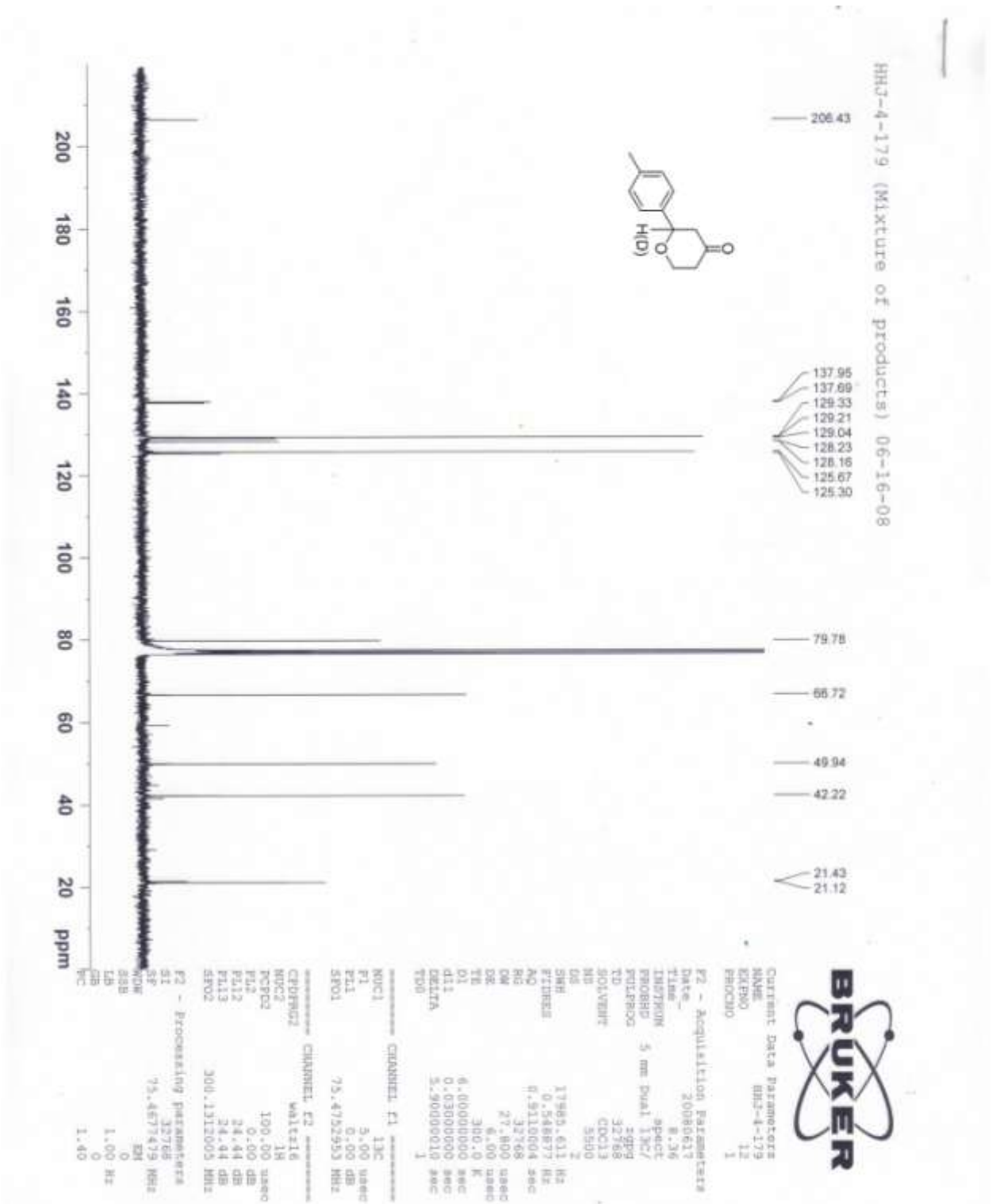
BRUKER

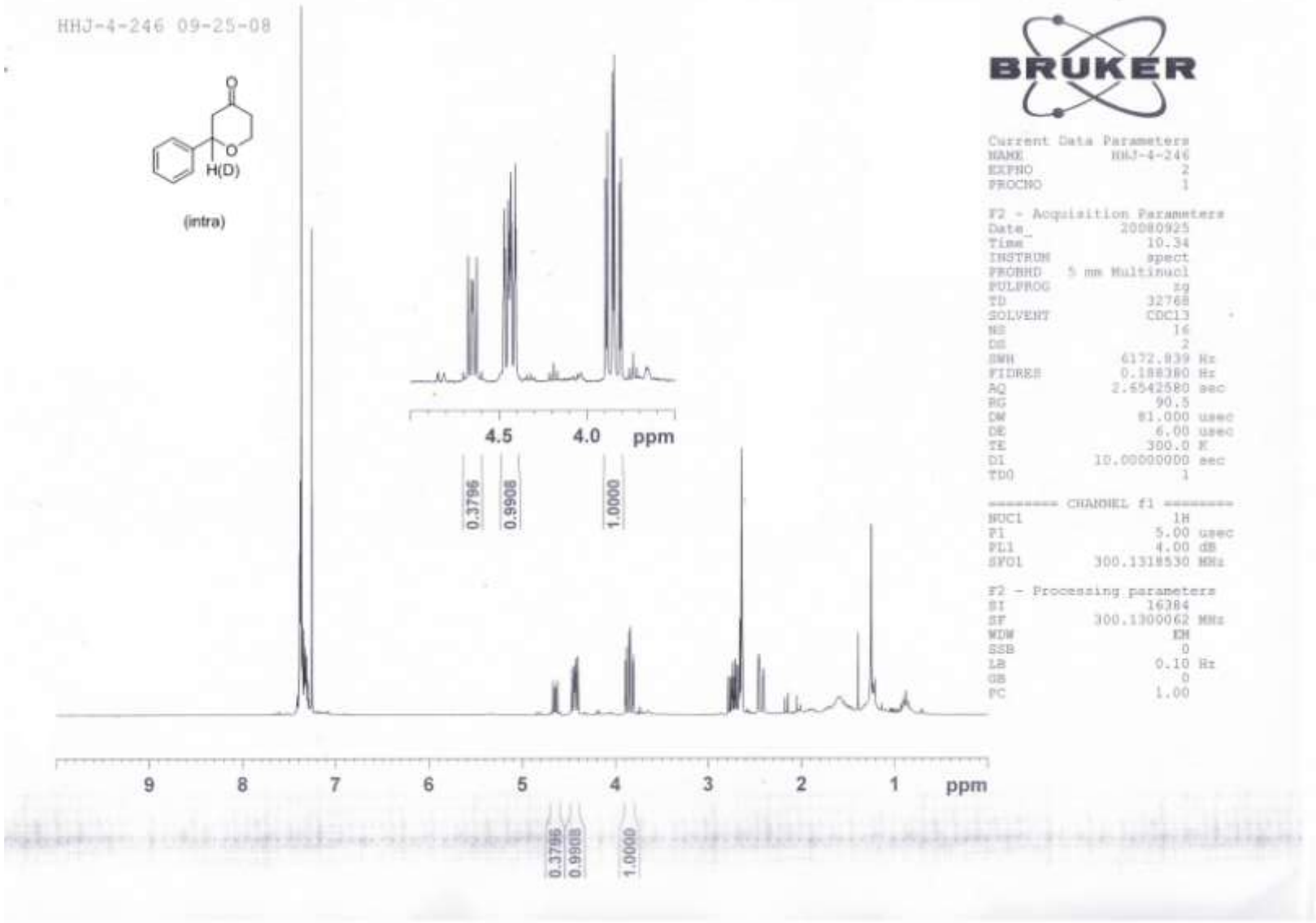
```
Current Data Parameters
NAME                  HHJ-4-179
EXPNO                         4
PROCNO                        1

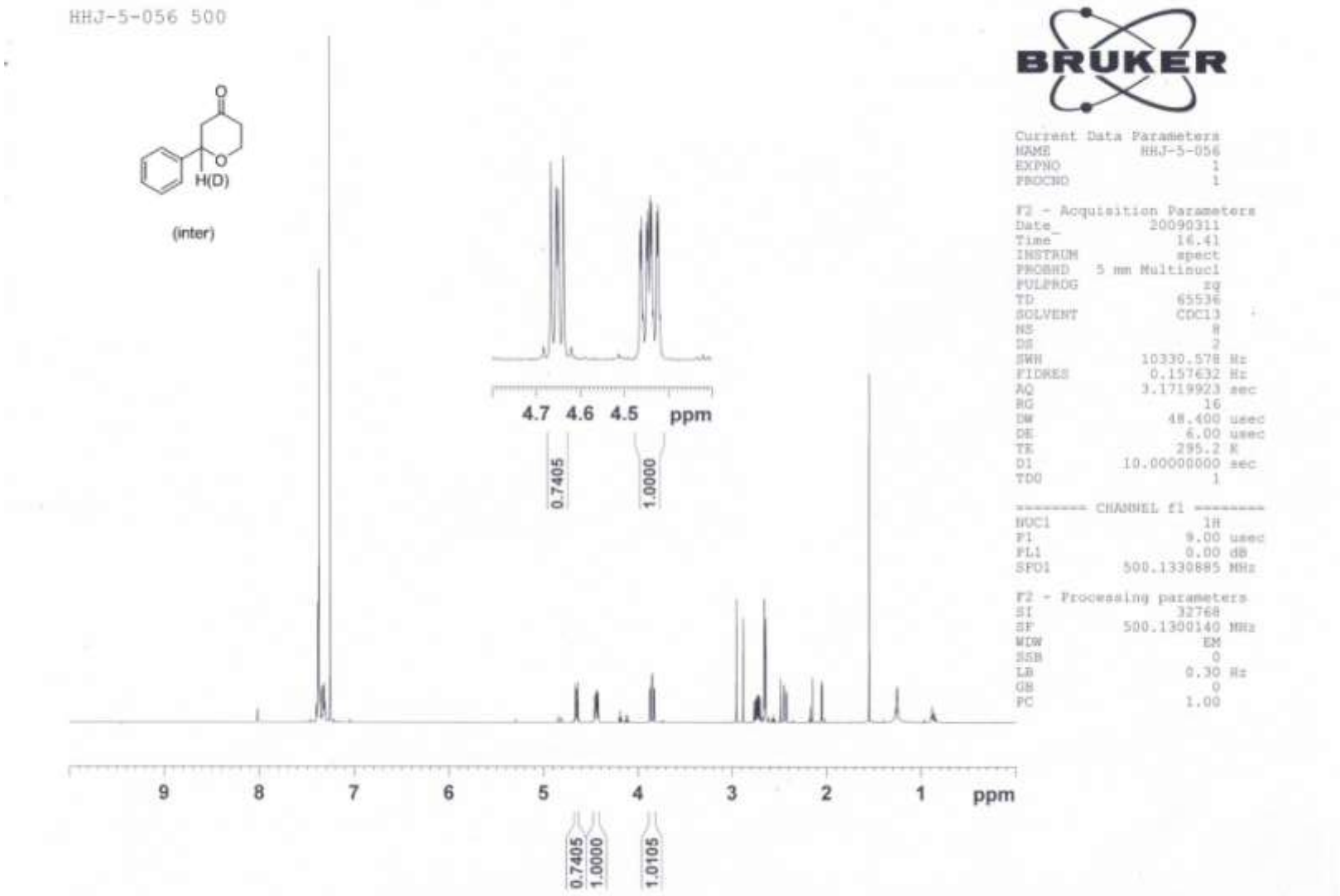
F2 - Acquisition Parameters
Date_              20080614
Time                      0.23
INSTRUM                  spect
PROBHD    5 mm Multinucl
PULPROG                     zg
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                  10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719923 sec
RG                          16
DW                     48.400 usec
DE                      6.00 usec
TE                       297.2 K
D1                 1.00000000 sec
TD0                          1

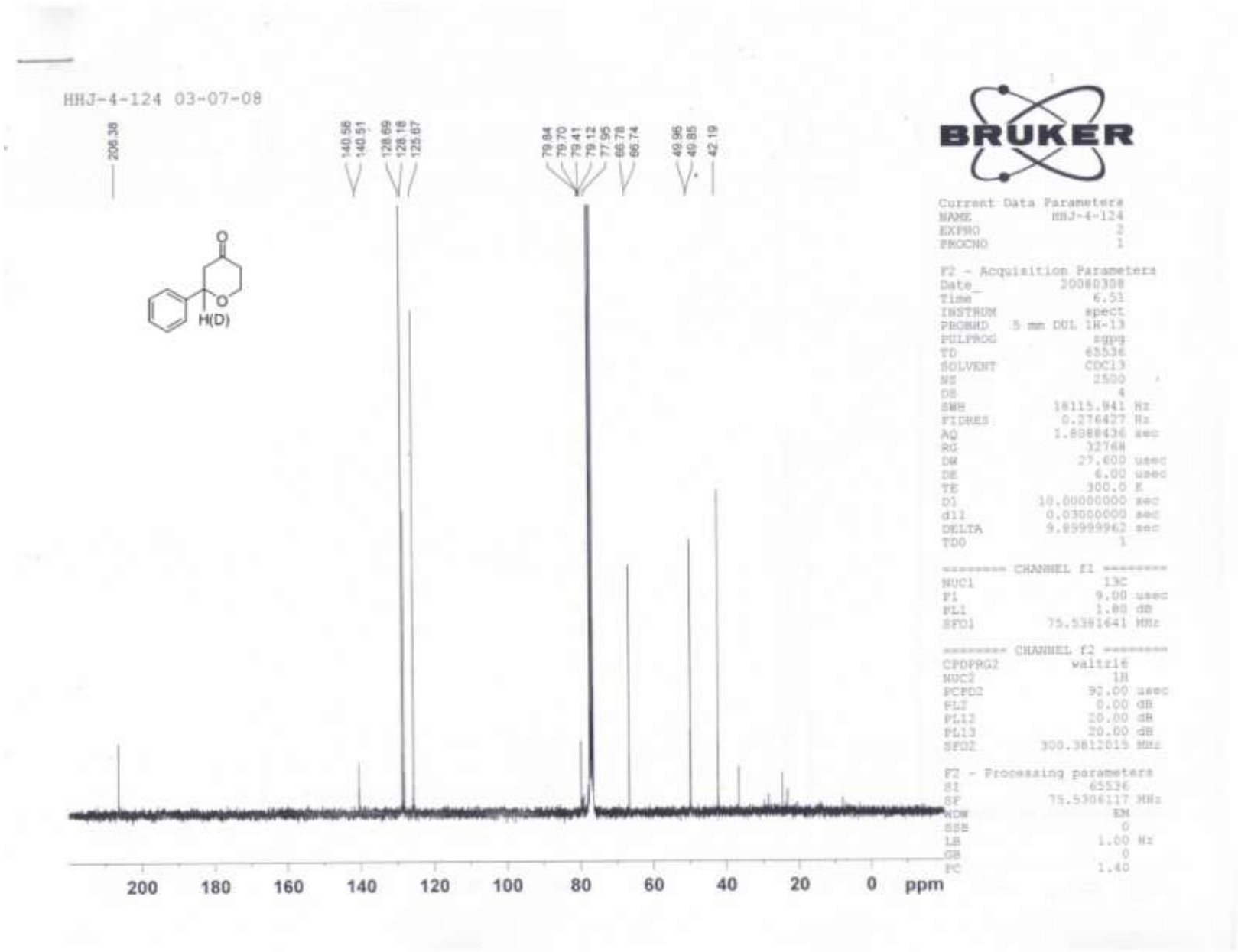
======== CHANNEL f1 ========
NUC1                        1H
P1                       9.00 usec
PL1                      0.00 dB
SFO1          500.1330885 MHz

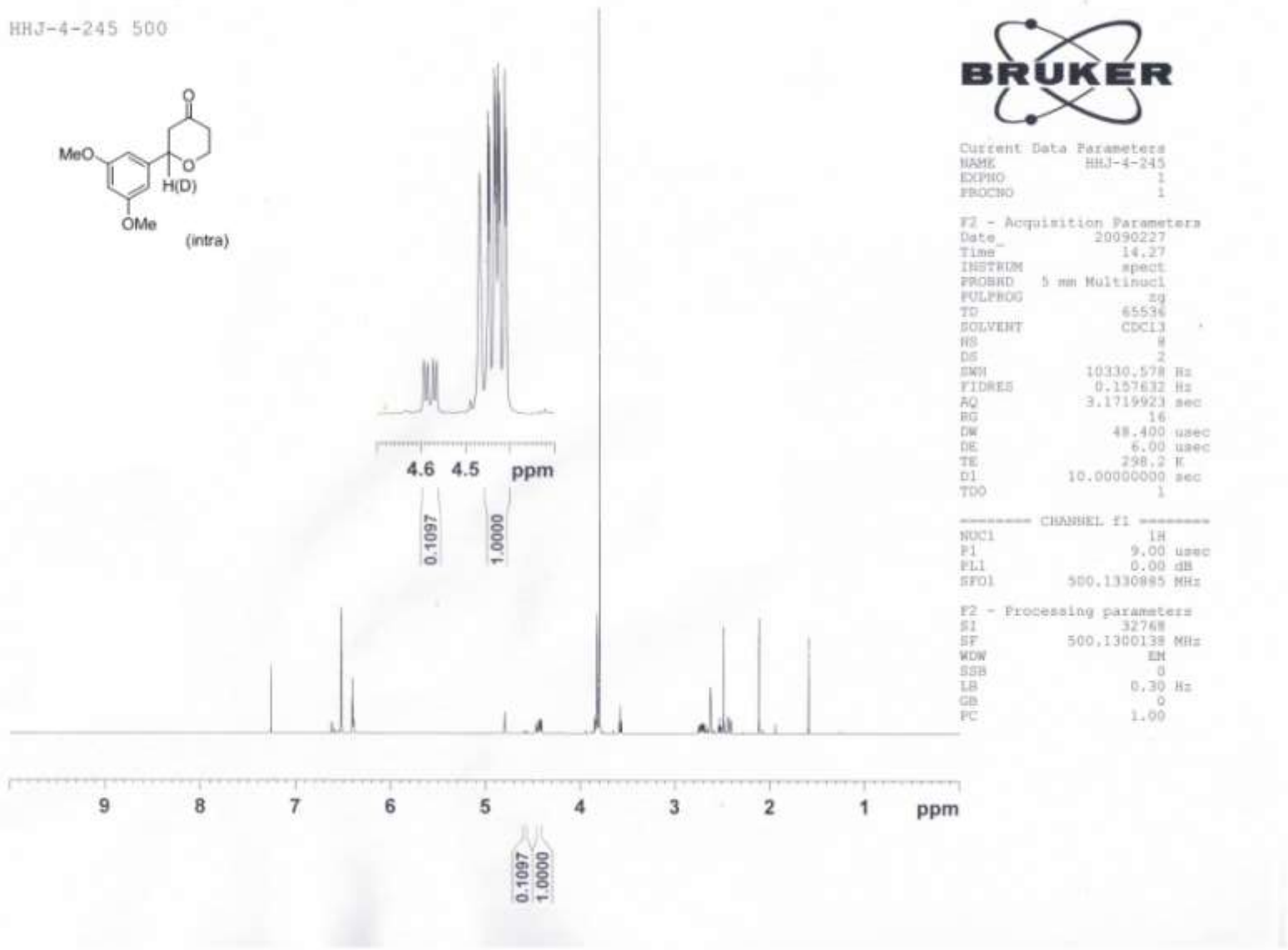
F2 - Processing parameters
SI                       32768
SF                500.1300138 MHz
WDW                         EM
SSB                          0
LB                       0.30 Hz
GB                           0
PC                        1.00
```

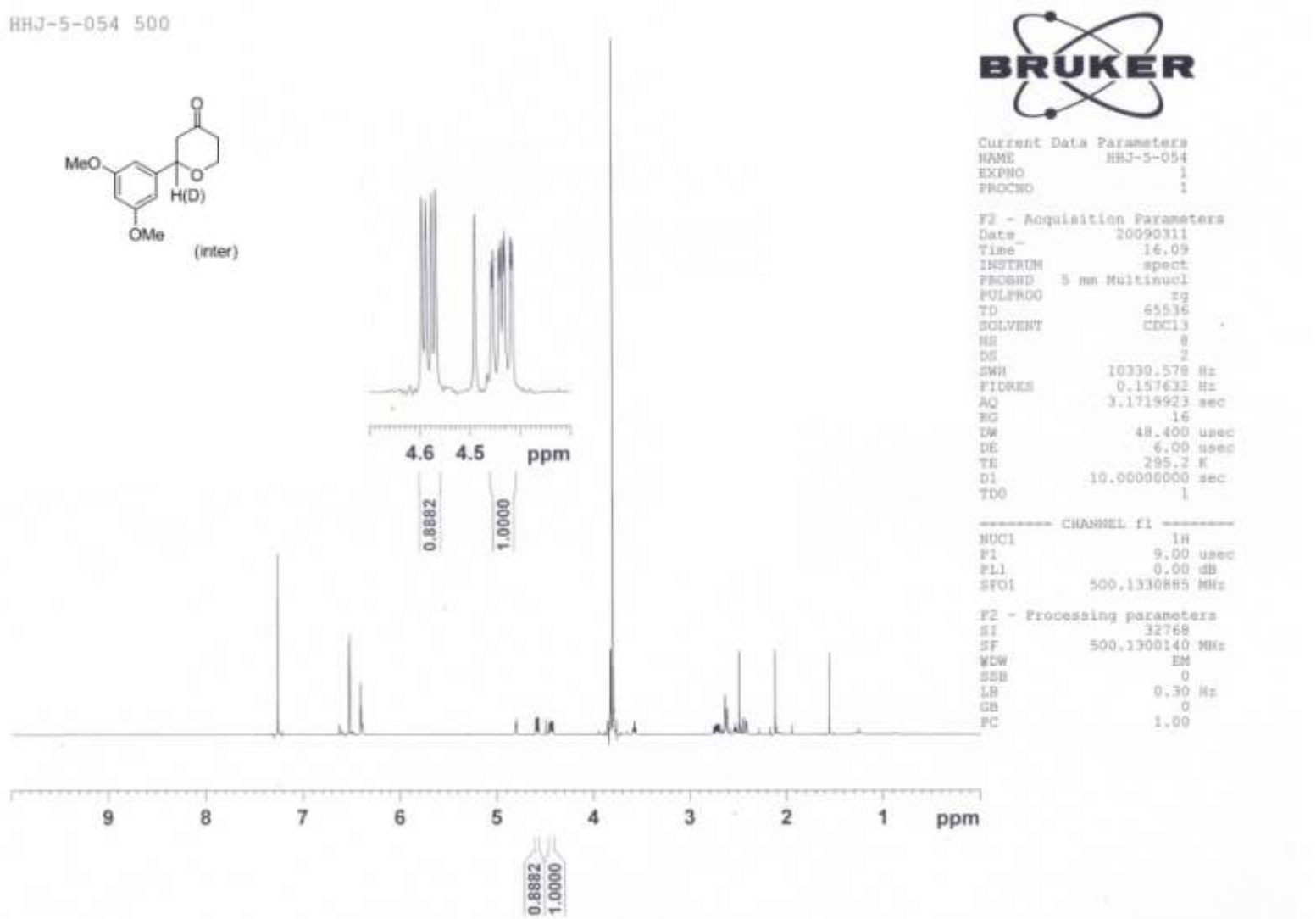

HHJ-4-179 (Mixture of products) 06-16-08
206.43
137.95
137.69
129.33
129.21
129.04
128.23
128.16
125.67
125.30
79.78
66.72
49.94
42.22
21.43
21.12
H(D)
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-179
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080617
Time 8.36
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5500
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677479 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-246 09-25-08
O
O
H(D)
(intra)
4.5
4.0
ppm
0.3796
0.9908
1.0000
9
8
7
6
5
4
3
2
1
ppm
0.3796
0.9908
1.0000
BRUKER
Current Data Parameters
NAME HHJ-4-246
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080925
Time 10.34
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00


HHJ-5-056 500
O
O
H(D)
(inter)
4.7 4.6 4.5 ppm
0.7405
1.0000
9 8 7 6 5 4 3 2 1 ppm
0.7405
1.0000
1.0105
BRUKER
Current Data Parameters
NAME HHJ-5-056
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090311
Time 16.41
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300140 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


HHJ-4-124 03-07-08
206.38
140.56
140.51
128.69
128.18
125.67
79.84
79.70
79.41
79.12
77.95
66.78
66.74
49.96
49.85
42.19
H(D)
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-124
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080308
Time 6.51
INSTRUM spect
PROBHD 5 mm DUL 1H-13
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 32768
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.85999962 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 1.00 dB
SFO1 75.5381641 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 92.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 300.3812015 MHz
F2 - Processing parameters
SI 65536
SF 75.5306117 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-245 500
MeO
O
H(D)
OMe
(intra)
4.6 4.5 ppm
0.1097
1.0000
9 8 7 6 5 4 3 2 1 ppm
0.1097
1.0000
BRUKER
Current Data Parameters
NAME HHJ-4-245
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090227
Time 14.27
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 298.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300139 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



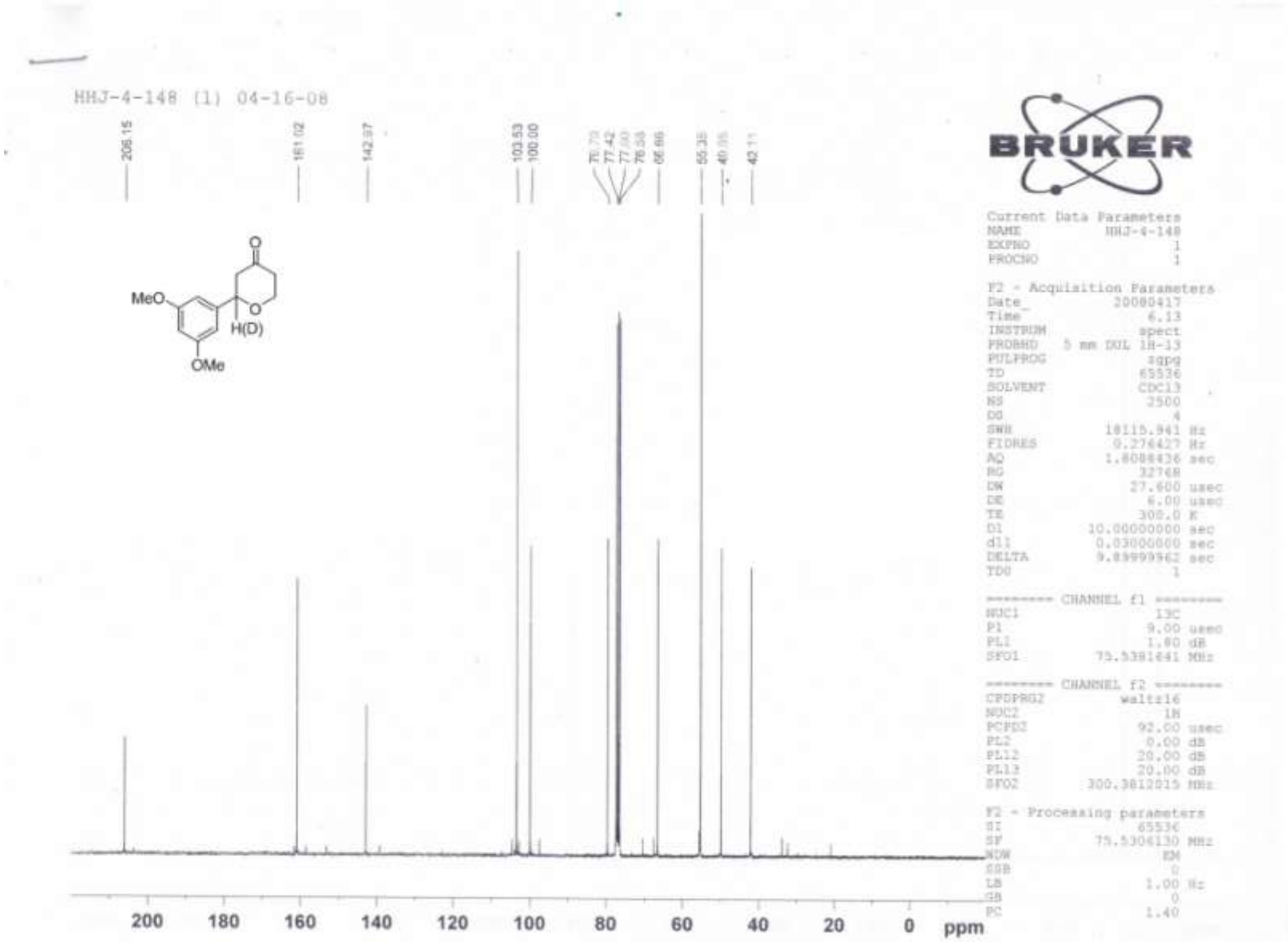
BRUKER

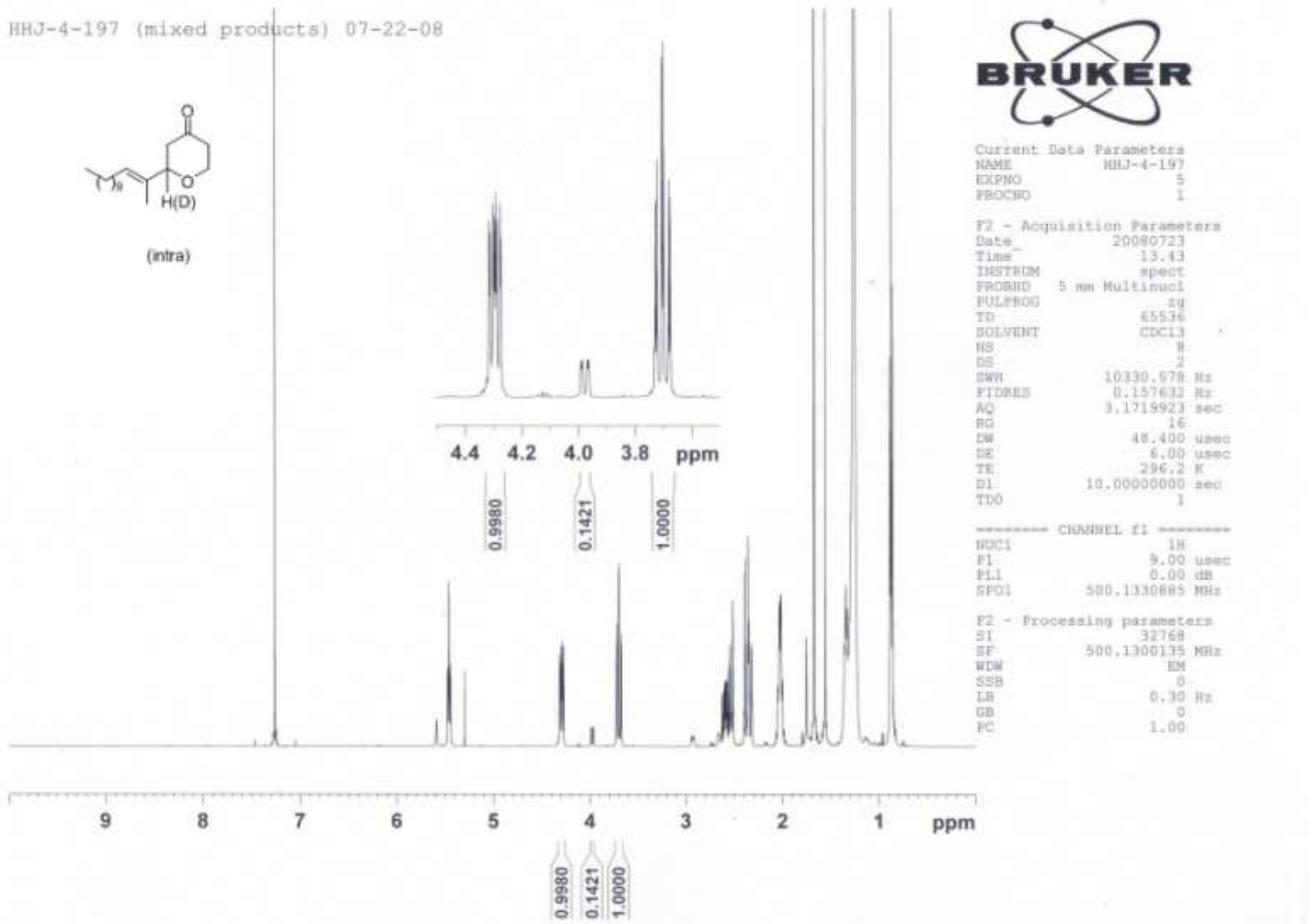
```
Current Data Parameters
NAME                  HHJ-5-054
EXPNO                         1
PROCNO                        1

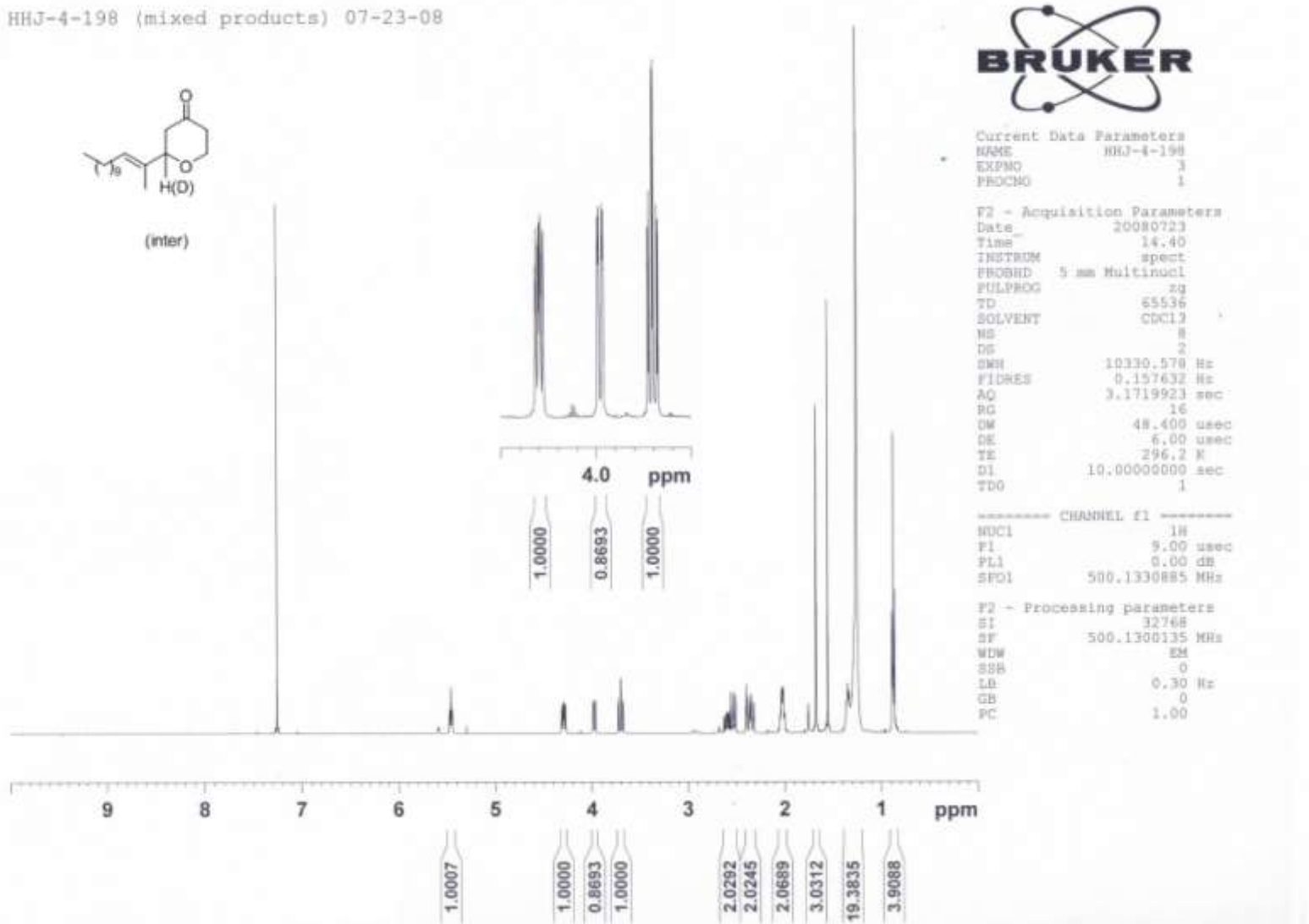
F2 - Acquisition Parameters
Date_                  20090311
Time                      16.09
INSTRUM                   spect
PROBHD     5 mm Multinucl
PULPROG                     zg
TD                       65536
SOLVENT                  CDCl3
NS                           8
DS                           2
SWH                  10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719923 sec
RG                           16
DW                       48.400 usec
DE                        6.00 usec
TE                       295.2 K
D1                 10.00000000 sec
TD0                          1

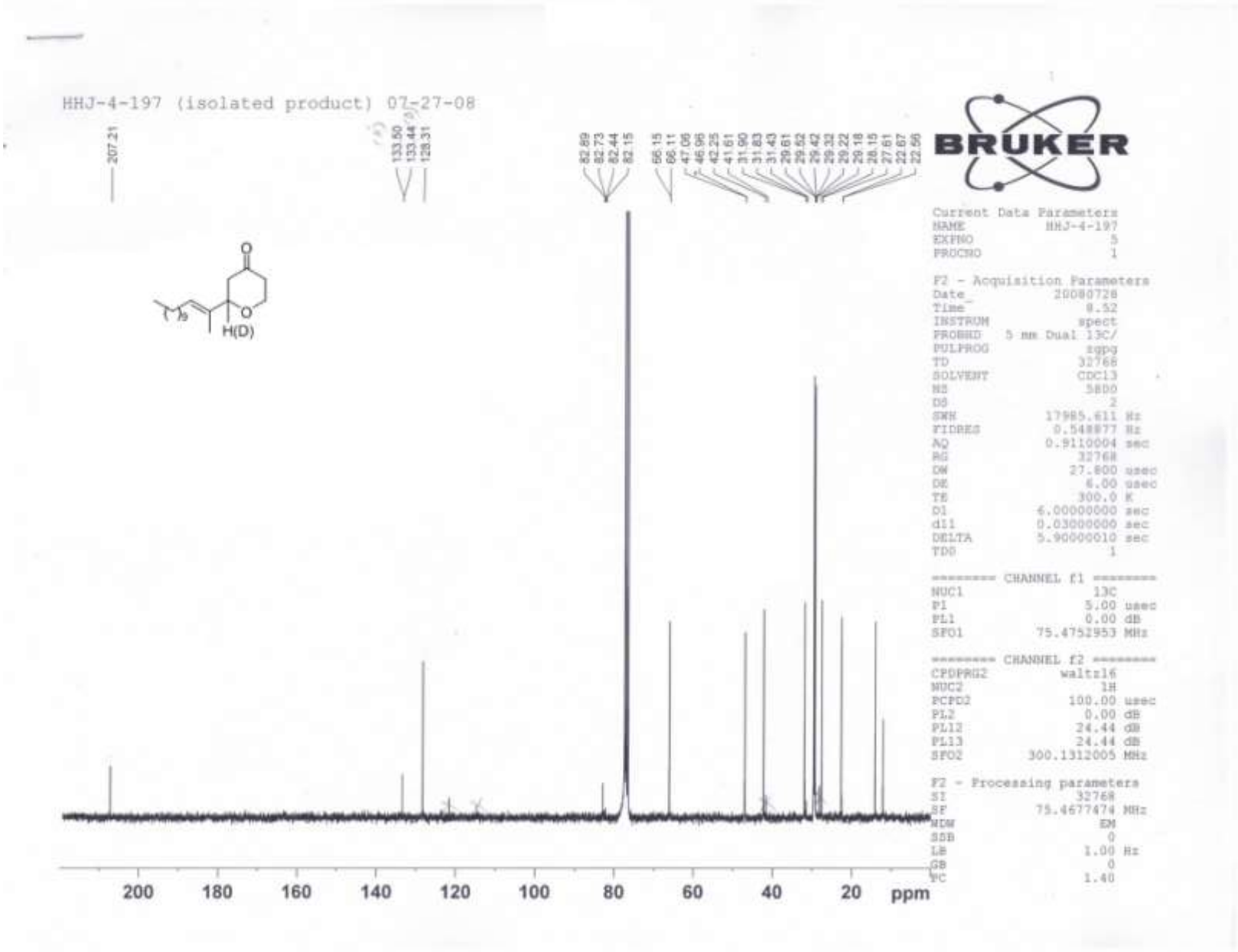
======== CHANNEL f1 ========
NUC1                        1H
P1                        9.00 usec
PL1                       0.00 dB
SFO1               500.1330885 MHz

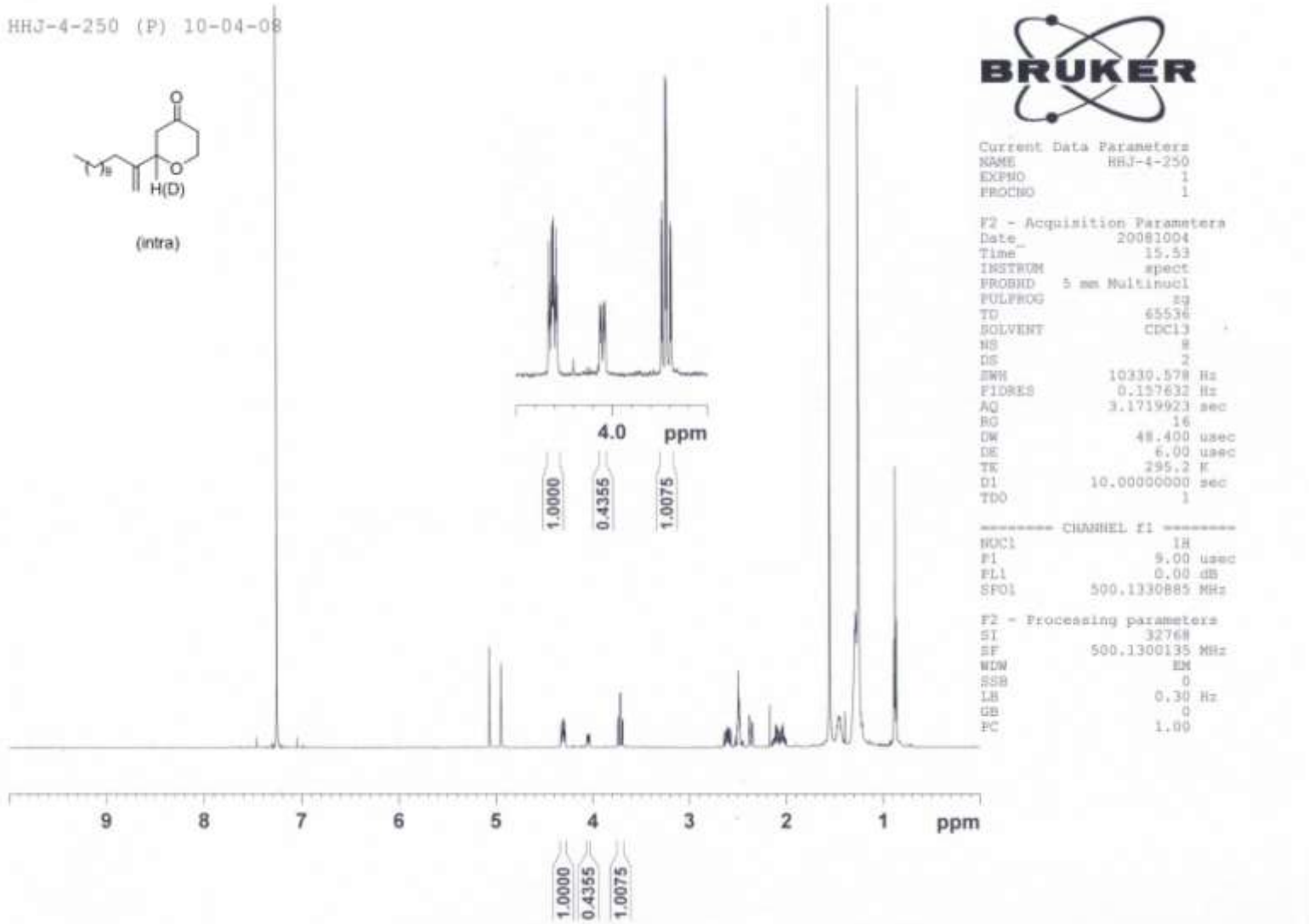
F2 - Processing parameters
SI                       32768
SF                 500.1300140 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
```


HHJ-4-148 (1) 04-16-08
206.15
161.02
142.97
103.53
100.00
77.42
55.36
42.11
MeO
H(D)
OMe
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-148
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080417
Time 6.13
INSTRUM spect
PROBHD 5 mm DUL 13C-13
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 32768
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.89999962 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 1.00 dB
SFO1 75.5381641 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 92.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 300.3812015 MHz
F2 - Processing parameters
SI 65536
SF 75.5306130 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


HHJ-4-197 (mixed products) 07-22-08
H(D)
(intra)
4.4
4.2
4.0
3.8
ppm
0.9980
0.1421
1.0000
9
8
7
6
5
4
3
2
1
ppm
0.9980
0.1421
1.0000
BRUKER
Current Data Parameters
NAME HHJ-4-197
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080723
Time 13.43
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 296.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


HHJ-4-198 (mixed products) 07-23-08
H(D)
(inter)
4.0 ppm
1.0000
0.8693
1.0000
9 8 7 6 5 4 3 2 1 ppm
1.0007
1.0000
0.8693
1.0000
2.0292
2.0245
2.0689
3.0312
19.3835
3.9088
BRUKER
Current Data Parameters
NAME HHJ-4-198
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080723
Time 14.40
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 296.2 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


HHJ-4-197 (isolated product) 07-27-08
207.21
133.50
133.44
128.31
82.89
82.73
82.44
82.15
66.15
66.11
47.06
46.96
42.25
41.61
31.90
31.83
31.43
29.61
29.52
29.42
29.33
29.22
29.18
28.15
27.61
22.67
22.56
O
O
H(D)
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-4-197
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080728
Time 8.52
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5800
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677474 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



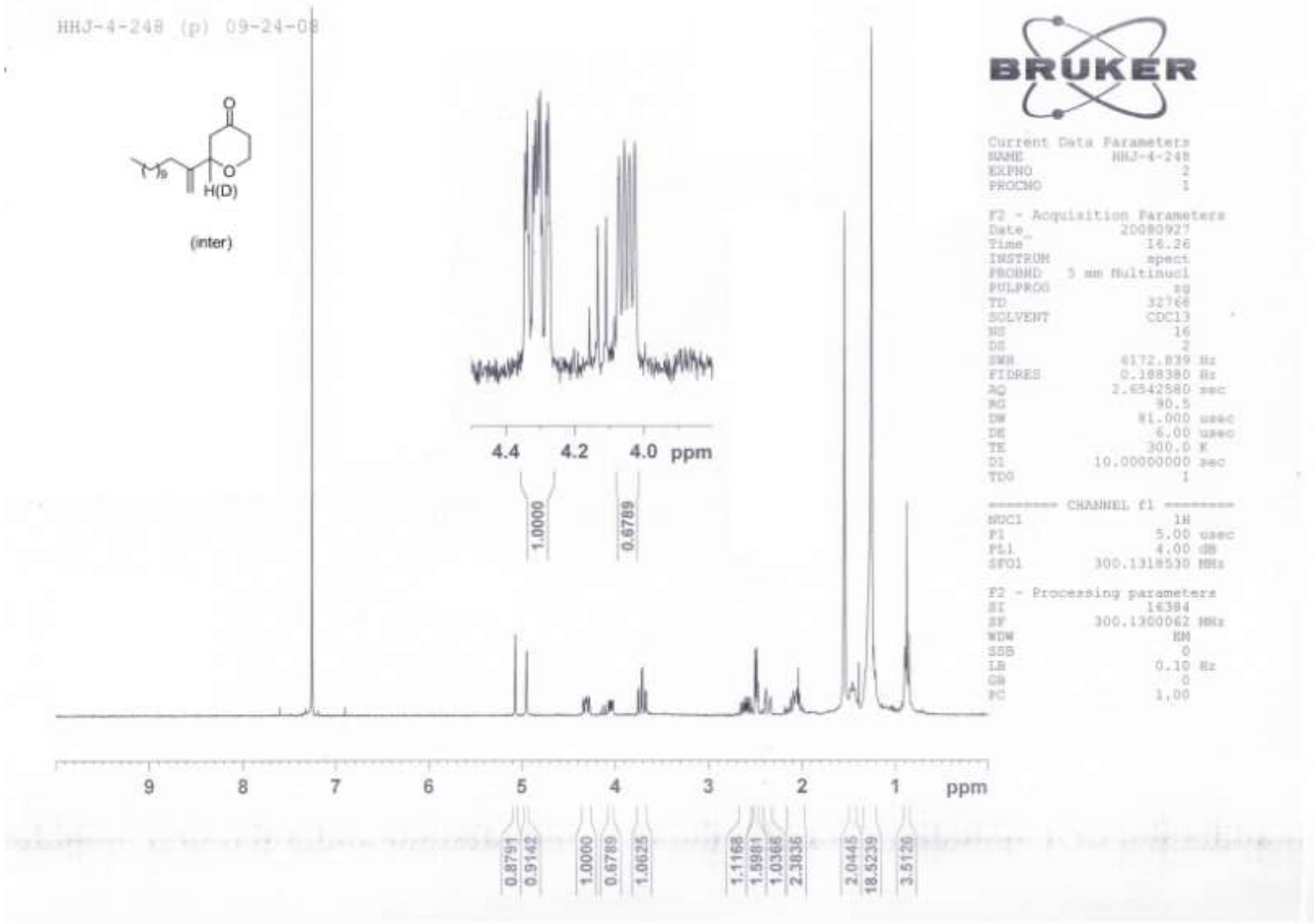
BRUKER

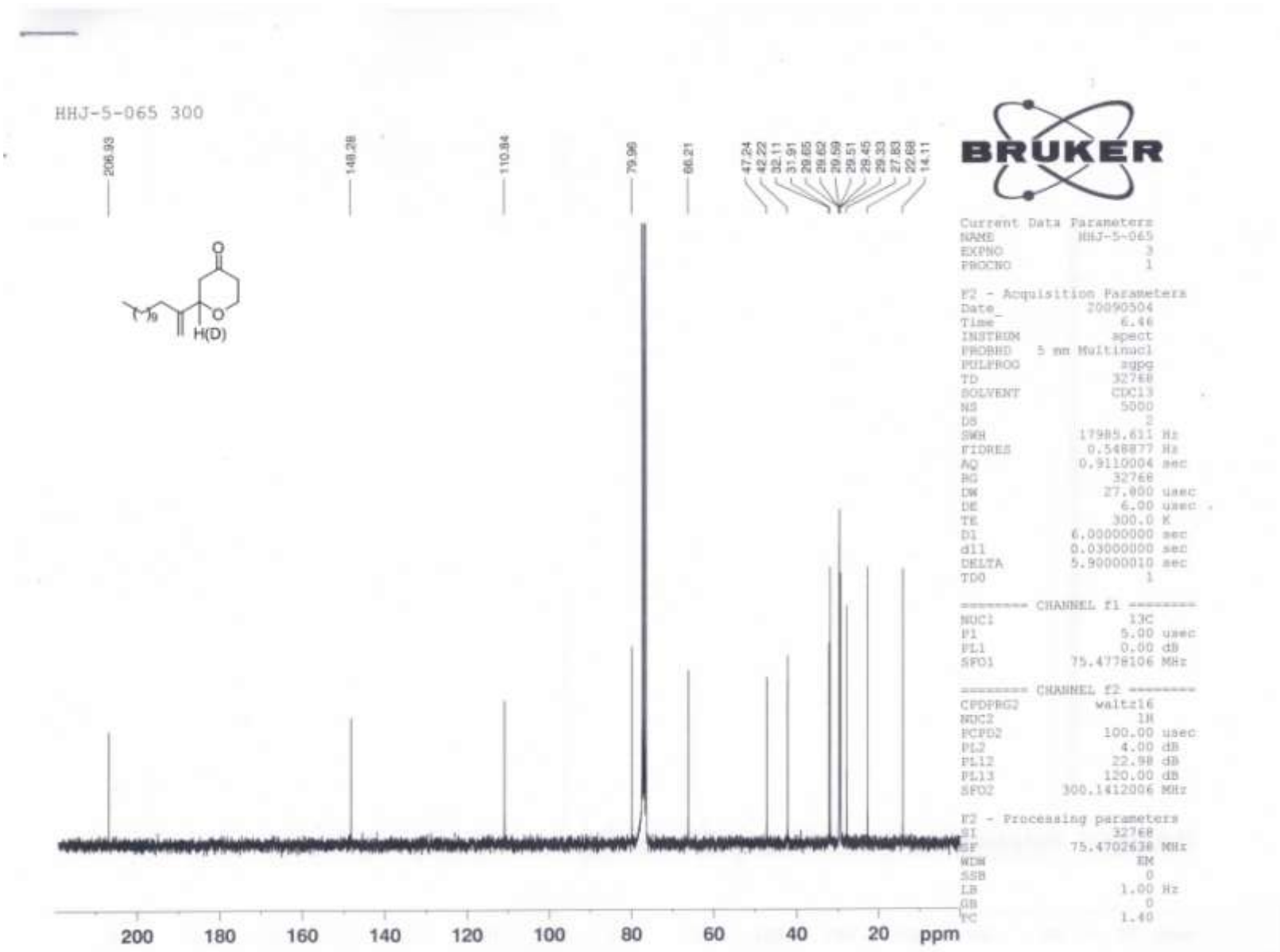
```
Current Data Parameters
NAME                 HHJ-4-250
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20081004
Time                    15.53
INSTRUM                 spect
PROBHD     5 mm Multinucl
PULPROG                 zg
TD                      65536
SOLVENT                 CDCl3
NS                          8
DS                          2
SWH                 10330.578 Hz
FIDRES              0.157632 Hz
AQ                  3.1719923 sec
RG                         16
DW                     48.400 usec
DE                      6.00 usec
TE                     295.2 K
D1                 10.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.00 usec
PL1                     0.00 dB
SFO1               500.1330885 MHz

F2 - Processing parameters
SI                      32768
SF                 500.1300135 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```


HHJ-4-248 (p) 09-24-08
O
O
H(D)
(inter)
4.4
4.2
4.0 ppm
1.0000
0.6789
9
8
7
6
5
4
3
2
1
ppm
0.8791
0.9142
1.0000
0.6789
1.0625
1.1168
1.5981
1.0366
2.3836
2.0445
18.5239
3.5126
BRUKER
Current Data Parameters
NAME HHJ-4-248
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080927
Time 16.26
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 32766
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00


HHJ-5-065 300
206.93
148.28
110.84
79.96
66.21
47.24
42.22
32.11
31.91
29.65
29.62
29.59
29.51
29.45
29.33
27.83
22.68
14.11
H(D)
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME HHJ-5-065
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090504
Time 6.46
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 5000
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 6.00000000 sec
d11 0.03000000 sec
DELTA 5.90000010 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4778106 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 4.00 dB
PL12 22.98 dB
PL13 120.00 dB
SFO2 300.1412006 MHz
F2 - Processing parameters
SI 32768
SF 75.4702638 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40