SYNTHETIC EFFORTS TOWARD THE NATURAL PRODUCTS

(–)-VERRUCAROL AND PSIGUADIAL A

&

ANILINE *N*-OXIDE FUNCTIONALIZATION

by

Michael Francis Wisthoff

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry and Biochemistry

Fall 2017

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Å	Ångström
Ac	acetyl
Ac_2O	acetic anhydride
Anis.	*p*-anisaldehyde
app	apparent
aq	aqueous
ATP	attached proton test
br	broadened
Bu	butyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
°C	degrees Celsius
^{13}C	carbon-13 nuclear magnetic resonance
Calcd.	calculated
CAM	ceric ammonium molybdate
cat.	catalytic
CD	circular dichroism
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CI	chemical ionization
cm^{-1}	reciprocal centimeters
COSY	homonuclear correlation spectroscopy

CPD	composite pulse decoupling
δ	chemical shift (parts per million)
2D	two dimensional
3D	three dimensional
d	doublet
dd	doublet of doublets
dd	doublet of doublet of doublets
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	*Ger.*, entgegen
Ed.	editor
ed.	edition
EDCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EI	electron impact
equiv.	equivalent(s)
ES	electrospray ionization

Et	ethyl
Et_2O	diethyl ether
ether	diethyl ether
EtOAc	ethyl acetate
^{19}F	fluorine-19 nuclear magnetic resonance
FD	field desorption
g	gram(s)
^{1}H	proton nuclear magnetic resonance
h	hour(s)
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple-bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single-quantum correlation spectroscopy
hν	photoirradiation
Hz	hertz
IC_{50}	half maximal inhibitory concentration
IR	infrared
i-Pr	isopropyl
J	coupling constant x
L	liter(s)

LAH	lithium aluminum hydride
LC	liquid chromatography
LDA	lithium diisopropylamine
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet; or milli (10-3); or meter
M	molar (mol L^{-1}); or metal
M^+	molecular ion (positive)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mm	Hg millimeters of mercury
mL	milliliter(s)
mmol	millimole(s)
mol	mole
MOM	methoxymethyl
mp	melting point
µL	microliter(s)
MS	mass spectrometry; or molecular sieves
m/z	mass to charge ratio
N	normal (concentration)

N.A.	not available
NaOMe	sodium methoxide
n-BuLi	*n*-butyllithium
Et_3N	triethylamine
NHC	*N*-heterocyclic carbene
nm	nanometer(s)
nM	nanomolar
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
N. R.	no reaction
nOe	nuclear Overhauser effect
Nu	nucleophile
OAc	acetoxy
o-QM	*ortho*-quinone methide
ORTEP	Oak Ridge thermal ellipsoid plot
p	*para*
p	page
p-TSA	*para*-toluenesulfonic acid monohydrate
Ph	phenyl
PMP	*para*-methoxy phenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr.	pyridine

q	quartet
quant.	quantitative
R	rectus
red.	reduction
R_f	retention factor
RT	room temperature
s	second(s); in NMR: singlet
S	sinister
satd.	saturated
$Sc(OTf)_3$	scandium(III) trifluoromethanesulfonate
t	triplet xii
t	tertiary
t-Am	*tert*-amyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
t-BuOH	*tert*-butyl alcohol
t-BuOOH	*tert*-butyl hydroperoxide
td	triplet of doublets
TEA	triethylamine
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
$TiCl_4$	titanium(IV) chloride
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UPLC	ultra-performance liquid chromatography
UV	ultraviolet
wt. %	weight percent
Z	*Ger.*, zusammen

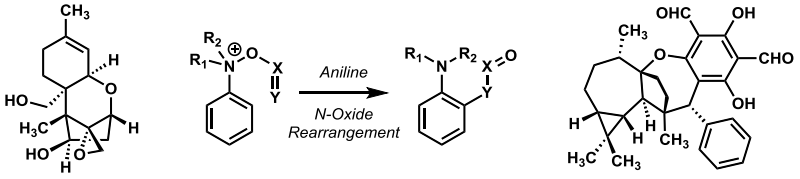
ABSTRACT

The first project involves our efforts toward the core structure of the macrocyclic trichothecene (–)-verrucarol (**3**). We developed a short synthetic concept for the enantioselective synthesis of the natural product. The key step is an asymmetric intramolecular Mizoroki-Heck reaction. In order to evaluate the key step, we synthesized several substrates and screened various reaction conditions.

The second project involves the discovery of a method for the functionalization of aniline-*N*-oxides. Discovery of the method took place while searching for a general method for the generation of aza-*ortho*-xylylenes *in situ*. We found the reaction to be quite general, allowing us to access aminophenols, aminoarylsulfonates, alkylated anilines, and aminoanilines in 29−95% yield in a single laboratory operation from easily isolable, bench-stable *N*,*N*-dialkylaniline *N*-oxides.

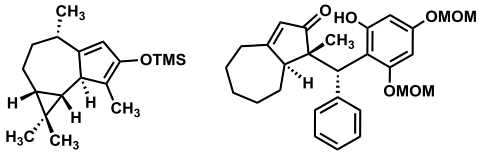
The final project involves our efforts toward the total synthesis of the meroterpenoid psiguadial A (**190**). The key step is an enolate–*ortho*-quinone methide (*o*-QM) reaction followed by an oxa-Michael addition to form the seven-member heterocyclic ring. The first generation synthesis toward the terpene derived silyl enol ether (**225**) was investigated. In an effort to better understand and optimize the two key steps in the synthesis, a model system of psiguadial A (**190**) was developed. We successfully synthesized the product of the enolate–*o*-QM reaction, that is, the keto phenol (**254A**). Evaluation of the oxa-Michael reaction, did not return the desired products. Several synthetic strategies were developed and implemented, but did not lead to the seven-member heterocyclic ring. Current efforts involve the synthesis of

intermediates of form the seven-member heterocycle to form the via copper-catalyzed C-O coupling. A second generation of the silyl enol ether (**225**) is also being investigated and addresses the major problems of the first generation's synthetic challenges.



(–)-Verrucarol (**3**)

Psiguadial A (**190**)



225

254A

Chapter 1

EFFORTS TOWARD A TOTAL SYNTHESIS OF (–)-VERRUCAROL

1.1 Introduction to Macrocyclic Trichothecenes and (–)-Verrucarol

The trichothecenes are a collection of over 180 sesquiterpenes containing a shared tricyclic core structure (**1**, ABC ring system, **Figure 1.1**). Two subclasses exist within the trichothecenes, the verrucaroids (**5**, C27 compounds) and the roridoids (**4**, C29 compounds), each of which are decorated with macrocyclic esters linking C4 and C15 of the ABC ring system. The tricyclic core structure and the macrocyclic esters contain varying degrees of oxygenation.[1]

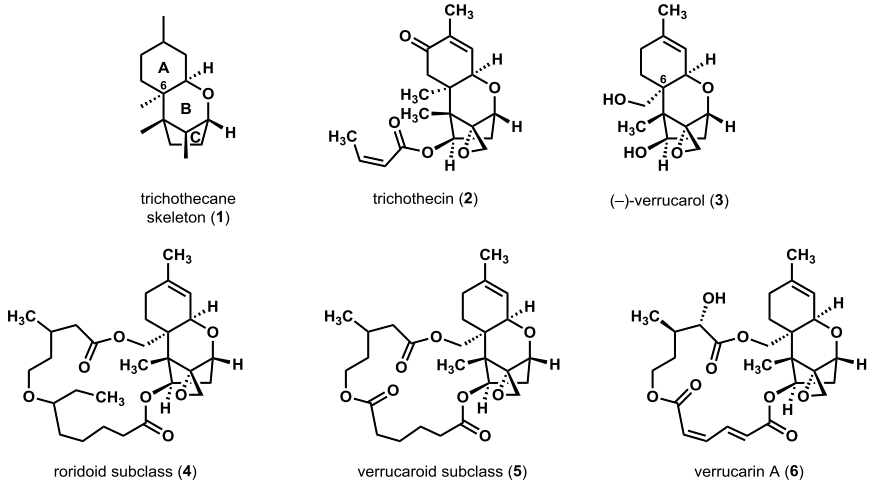


Figure 1.1 Trichothecene Natural Products

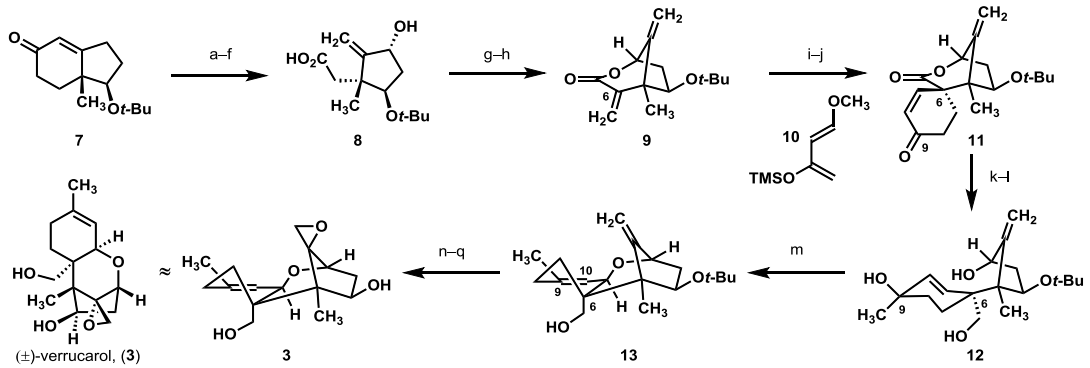
In 1948, Freeman and Morrison isolated the first trichothecene, trichothecin (**2**), from the fungus *Trichothecium roseum*.[2] Following this initial discovery, numerous unique trichothecenes have been isolated from plant and fungal sources. For example, in the early 1960's Tamm and Gutzwiller isolated the macrocyclic trichothecene verrucarin A from extracts of the fungus *Myrothecium verrucaria*. They then found that when verrucarin A (**6**) was subjected to basic hydrolysis conditions the tricyclic core (–)-verrucarol (**3**) could be isolated and its structure fully elucidated.[3]

The biological activity of the trichothecenes interested both chemists and biologists in understanding this group of sesquiterpenes natural products. The fungal sources of the trichothecenes (genera *Fusarium, Myrothecium, Trichothecium,* and *Trichoderma)* are parasitic on cereal grains and are thus commonly encountered as food contaminants. The trichothecenes bearing a macrocyclic ester functionality (e.g., verrucarin A) are the most toxic in the class. The lethal dose is relatively high for oral toxicity and higher when injected (LD_{50} mg/kg for mice, rat, and rabbits, respectively, 1.5, 0.87, 0.54). This toxicity has led to a myriad of studies examining their biological activity including potent antiproliferative, antiviral, antimalarial, antifungal, and insecticidal activities.[4]

The trichothecenes have received attention from nine different synthetic organic chemistry research groups over the past 40 years. Within this considerable amount of chemical literature, four distinct syntheses of verrucarol have been completed, three racemic and one enantioselective. The syntheses described to date range from 17 to 43 individual steps.[5] Central to these classical syntheses lies the problem of establishing the key C6 all-carbon quaternary center ring junction and the stereochemistry of this critical structural feature.

1.2 Prior Syntheses of (–)-Verrucarol

The first completed synthesis was reported by Schlessinger and Nugent in 1982 (**Figure 1.2**).[5f] The biomimetically inspired racemic synthesis began with the ketone **7** undergoing an *m*-CPBA mediated oxidation, then ozonolysis with loss of two carbon atoms, and another oxidation to furnish the keto acid **8**. Wittig conditions converted the ketone to an exocyclic olefin, and selenium dioxide oxidation yielded the allylic alcohol which was immediately converted to the corresponding lactone. Finally, deprotonation and trapping with monomeric formaldehyde made the α-methylene lactone **9**. The key C6 all-carbon quaternary center ring junction and the stereochemistry at this center was constructed via a Diels–Alder [4+2] cycloaddition reaction between 1-methyloxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene, **10**) and the methylene lactone **9** to give the enone **11**. The remainder of the synthesis consisted of installation of a methyl group at C9, reduction of the lactone to the triol **12** with lithium aluminum hydride. The triol **12** was then converted to **13** via an acid-mediated allylic substitution. Due to the concomitant oxidation between the trisubstituted olefin and the exocyclic olefin, additional steps were required to install the epoxide present in the natural product. These steps required masking the 9,10-trisubstituted olefin, cleavage of the *tert*-butyl protecting group, and then stereospecific epoxidation of the exocyclic olefin. Finally, unmasking of the 9,10-trisubstituted olefin produced racemic verrucarol in 17 linear steps and 3.4% overall yield.

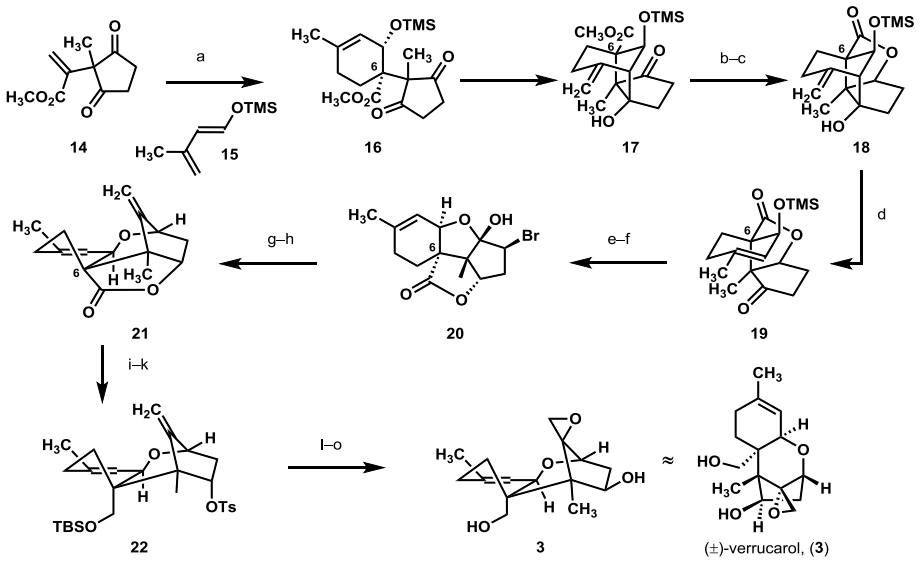


(a) LDA, THF, −78 °C, then TMSCl, Et_3N, THF, 0 °C. (b) *m*-CPBA, $NaHCO_3$, hexane, *t*-BuOH, 0 °C. (c) O_3, MeOH, −78 °C. (d) $NaIO_4$, CrO_3, AcOH, H_2O, 22 °C. (e) $(Ph)_3PCH_3Br$, NaO*t*-Am, $PhCH_3$, 110 °C. (f) SeO_2, *t*-BuOOH, CH_2Cl_2, 22 °C, 53% over 5 steps. (g) *p*-TSA, CH_2Cl_2, 22 °C 55%. (h) LDA, THF, −78 °C, then CH_2O THF, 22 °C, 62%. (i) **10**, methylene blue, $PhCH_3$, 140 °C. (j) Amberlite IR-120, CH_2Cl_2, 22 °C, 76% over 2 steps. (k) MeLi, THF, −78 °C, 93%. (l) LAH, DME, reflux. (m) *p*-TSA, CH_2Cl_2, 22 °C, 73% over 2 steps. (n) NBS, acetone, 22 °C. (o) $TiCl_4$, CH_2Cl_2, 0 °C, 85% over 2 steps. (p) *m*-CPBA, CH_2Cl_2, 22 °C, 70%. (q) Na^0, $EtNH_2$, THF, 0 °C, 62%.

Figure 1.2 Schlessinger's Total Synthesis of (±)-Verrucarol

In the same year, Trost and McDougal presented a total synthesis of racemic verrucarol starting with the prochiral **14** produced in four steps from 2-methyl-1,3-cyclopentanedione (**Figure 1.3**).[5a,g,j] The dienophile **14** and 1-(trimethylsilyloxy)-3-methyl-1,3-butadiene (**15**), underwent a Diels–Alder [4+2] cycloaddition reaction producing **16** and forming the key C6 all-carbon quaternary center ring junction. The product **16** left a carbonyl in the correct position to undergo an ene reaction generating **17**. Reduction and lactonization produced **18** and thermolysis resulted in a further retro-ene to give the polycyclic ketone **19**. Formation of the final ring came first with introducing a leaving group α to the ketone in **19**, then production of a hemiketal under thermodynamic conditions, **20**. Treatment of the hemiketal **20** with fluoride induced a skeletal rearrangement and then a Wittig reaction installed the exocyclic olefin seen in **21**. Finally, reduction of the lactone, chemoselective silylation generated

22 while inversion of the secondary alcohol and a directed epoxidation lead to the racemic verrucarol in 18 linear steps and 2% overall yield.

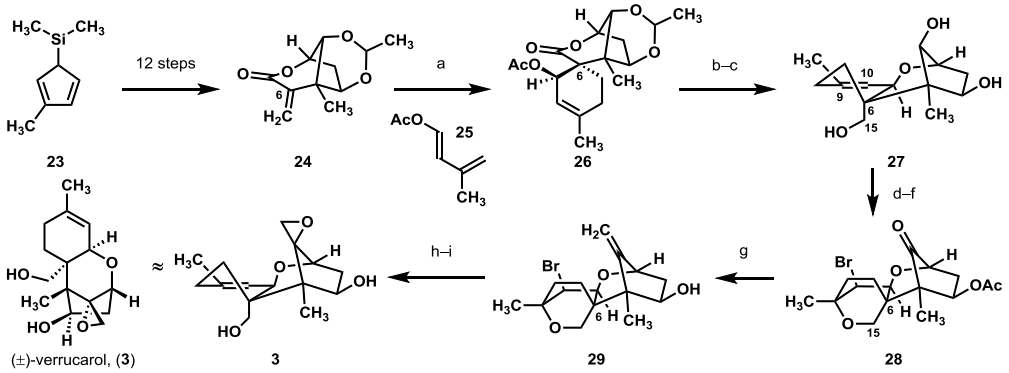


(a) **15**, mesitylene, 155 °C, 63%. (b) $NaBH_4$, MeOH, 92%. (c) $CrO_3 \cdot 2pyr$, CH_2Cl_2, 92%. (d) hot tube, 16 cm, 470 °C, 89%. (e) Lithium tetramethylpiperidide, THF, 0 °C, then TMSCl, 0 °C, then Br_2·dioxane, CH_2Cl_2, pyridine, –78 °C. (f) TFA in ethylene dichloride, H_2O, 32 to 45 to 55 °C. (g) (n-Bu)$_4$NF, THF, 70% over 3 steps. (h) Ph_3PCH_2, LiBr, THF, 60 °C, 95%. (i) DIBALH, $PhCH_3$, 95%. (j) TBSCl, DMAP, CH_2Cl_2, 0 °C, 82%. (k) TsCl pyridine, 34 °C, 79%. (l) $CsO_2CCH_2CH_3$, 1,3-dimethyl-2-imidazolidinone, 150 °C, then TBSCl, imidazole, DMF. (m) K_2CO_3, wet MeOH, 31% over 2 steps. (n) $Mo(CO)_6$, t-BuOOH, PhH, 63 °C, 85%. (o) (n-Bu)$_4$NF, THF, 91%.

Figure 1.3 Trost's Total Synthesis of (±)-Verrucarol

In 1983, Roush and D'Ambra concluded a series of manuscripts describing a racemic synthesis of verrucarol beginning with the protected α-methylene lactone **24** produced in 12 steps from (methylcyclopentadienyl)trimethyl silane (**23**) (**Figure 1.4**).[5b,e,h] A Diels–Alder [4+2] cycloaddition reaction between the α-methylene lactone **24** and 3-methyl-1-acetoxybuadiene **25** produced the spiroannulation product **26** and established the key C6 all-carbon quaternary center ring junction. Reduction

with LAH produced a triol which was then treated with PPTS affecting an acid catalyzed S_N' cyclization to form the triol **27**, constituting the tricyclic skeleton of verrucarol. To complete the sequence, the diol was mono acylated, the secondary alcohol was oxidized, and necessary protection/masking of the C15 hydroxyl groups and the 9,10- trisubstituted olefin with NBS produced the bromo ether **28**. A Wittig reaction installed the exocyclic olefin and cleaved the acetate protecting group to produced **29**. Epoxidation and cleavage of the bromo ether afforded racemic verrucarol in 21 linear steps.

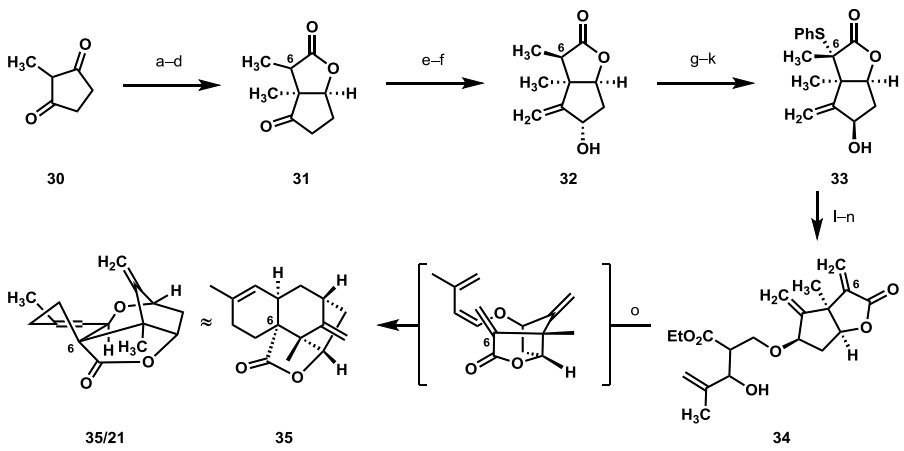


(a) **25**, $PhCH_3$, BHT, 140 °C, 57%. (b) LAH, DME, reflux. (c) PPTS, PhH, reflux. 65% over 2 steps. (d) NBS, CH_3CN. (e) Ac_2O, pyridine. 30% over two steps. (f) CrO_3, H_2SO_4, acetone, 88%. (g) Ph_3PCH_2, THF, 60 °C, 60%. (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 95%. (i) Zn-Ag, THF, EtOH, reflux, 82%.

Figure 1.4 Roush's Total Synthesis of (±)-Verrucarol

In 1988, Koreeda et. al. reported a formal synthesis toward verrucarol (**Figure 1.5**).[5k] In four steps, 2-methyl-1,3-cyclopentanedione (**30**) was converted to the keto lactone **31**. A Witting reaction to **31** and allylic oxidation yielding the single diastereomer **32**. Necessary inversion of the allylic alcohol and masking of the

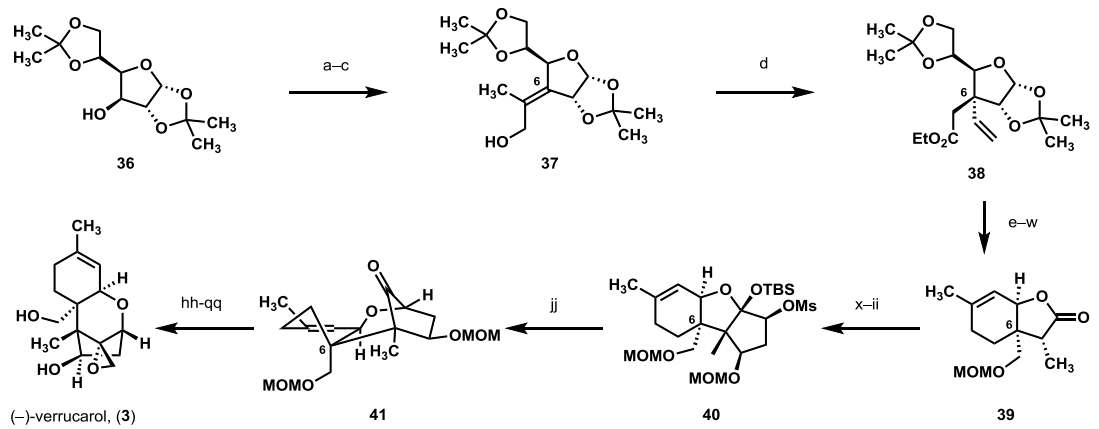
forthcoming dienophile by enolate formation and sulfenylation generated **33**. Installation of the Z-dienol ether function furnished the penultimate synthetic intermediate **34**. The key C6 all-carbon quaternary center ring junction was generated via an intramolecular Diels–Alder reaction under the action of neutral alumina for the formation of the A/B ring system in **35**. Koreeda described **35** as synthetically identical intermediate to Trost's intermediate **21** (**Figure 1.3**). Thus, the Koreeda group generated the advanced intermediate **35** over 17 linear steps in 16.6% overall yield and based on this report, a theoretical racemic synthesis of verrucarol would be possible in 24 steps.



(a) crotyl alcohol, *p*-TSA, $PhCH_3$, reflux, 95%. (b) $KMn0_4$, CH_2Cl_2, H_20, AcOH, 0 °C. (c) CH_2N_2, Et_2O, 77% over two steps. (d) $LiAl(O\textit{t}\text{-}Bu)_3H$, THF, –78 to 20 °C, 95%. (e) Ph_3PCH_3Br, KO*t*-Bu, *t*-BuOH, THF, 93%. (f) SeO_2, *t*-BuOOH, dichloroethane, reflux 75%. (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 98%. (h) LDA, THF, –78 °C, then Ph_2S_2, HMPA THF, 20 °C, 95%. (i) $(n\text{-}Bu)_4NF$, THF, 90%. (j) Ph_3P, DEAD, $PhCO_2H$, THF, 91%. (k) K_2CO_3, CH_3OH, H_2O, 95%. (l) TlOEt, PhH, then $BrCH_2CO_2Et$, CH_3CN, 95%. (m) LDA, THF, , –78 °C, then methacrolein, –78 °C, 80%. (n) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, then $CaCO_3$, CCl_4, reflux, 75%. (o) neutral alumina, hexane, ethyl acetate, 83%.

Figure 1.5 Koreeda's Formal Synthesis of (±)-Verrucarol

The first enantioselective total synthesis of verrucarol was reported by Tadano and coworkers in 1997 (**Figure 1.6**).[5m,n] The sequence began with a three step sequence in which D-glucose (**36**) was transformed into the allylic alcohol **37**. At this point, the key C6 all-carbon quaternary center ring junction and the associated stereochemistry required for the trichothecane skeleton was produced via a Johnson *ortho*–ester Claisen rearrangement.[6] The product of this acid-mediated rearrangement reaction between **37** and triethyl orthoacetate gave the tetrahydrofuran intermediate **38**. Continuing the sequence, the enantiomerically pure α-methylated bicyclic γ lactone **39** was generated in 19 linear steps. The mesylate **40** was fashioned in 12 more steps before it was subjected to fluoride. The spontaneous ring expansion of the mesylate **40** to give **41** was similar to the ring expansion executed with Trost's bromide **20** (**Figure 1.3**). Finally, the synthesis of (–)-verrucarol (**3**) was completed in 10 more operations for a total of 43 steps.



(a) PCC, CH_2Cl_2. (b) Ph_3PCHCO_2Et, PhH, 80 °C, 60% over two steps. (c) DIBALH, 86%. (d) $CH_3C(OEt)_3$, $EtCO_2H$, 135 °C, 64%. (e) LAH, THF, 0 °C, quant. (f) Ph_3P, DEAD, MeI, THF,0 °C, 90%. (g) NaH, $CH_2(CO_2CH_3)_2$, THF, 0 °. (h) 60% aq. AcOH, 99%. (i) $NaIO_4$, MeOH. (j) $NaOCH_3$, MeOH, 94% over two steps. (k) Ac_2O, pyr. 92%. (l) O_3, MeOH, CH_2Cl_2, –78 °C, then $NaBH_4$, 98%. (m) DMSO, H_2O, NaCl, 160 °C, 47%. (n) MOMCl, *i*-Pr_2NEt, 83%. (o) DIBALH, CH_2Cl_2, –78 °C, quant. (p) Ph_3P, CCl_4, PhH, reflux, 88%. (q) *n*-Bu_3SnH, AIBN, $PhCH_3$, reflux, quant. (r) 60% aq. TFA, 0 °C, 63%. (s) *p*-TSA, MeOH, 60%. (t) NaH, imidazole, THF, then CS_2, then MeI, 96%. (u) *n*-Bu_3SnH, AIBN, $PhCH_3$, reflux, 90%. (v) Jones reagent, acetone, 0 °C, 76%. (w) LDA, MeI, THF, –78 °C, 96%. (x) LDA, 4-*O*-(*t*-butyldiphenylsilyloxy)butanal, THF, $PhCH_3$, –78 °C, 50%. (y) (*n*-Bu)$_4$NF, THF. (z) PivCl, pyr. (aa) MOMCl, *i*-Pr_2NEt, $CHCl_3$, reflux. (bb) $NaOCH_3$, MeOH, 58% over four steps. (cc) Jone's reagent, acetone, 0 °C. (dd) CH_2N_2, Et_2O, $CHCl_3$, 0 °C, 72% over two steps. (ee) KHMDS, THF, –78 °C, 82%. (ff) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 75%. (gg) 4 M KOH, MeOH, 80 °C, 81%. (hh) WSC, DMAP, *N*-hydroxpyridine-2-thione, *t*-BuSH, O_2, CH_2Cl_2, 84%. (ii) MsCl, pyr. 99%. (jj) (*n*-Bu)$_4$NF, THF, 98%. (kk) Ph_3PCH_2, THF, 60 °C, 73%. (ll) TMSBr, 4Å MS, CH_2Cl_2, –30 °C, 78%. (mm) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 40%. (nn) NBS, acetone, 0 °C, 94%. (oo) (*n*-Bu)$_4$NF, THF, 96%. (pp) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 91%. (qq) Zn-Ag, THF, EtOH, reflux, 81%.

Figure 1.6 Tadano's Total Synthesis of (–)-Verrucarol

1.3 Retrosynthetic Analysis of (–)-Verrucarol

We believe the central challenge and the key to efficiently constructing the trichothecene core structure (and thus (–)-verrucarol (**3**)) is establishing the key C6 all-carbon quaternary center ring junction. In order to produce a short synthetic sequence, we envisioned this all-carbon quaternary center arising from **47** via an asymmetric intramolecular Heck reaction to give the lactone **46** (**Figure 1.7**). Tackling this major obstacle at the outset of the synthetic sequence addresses the crux of the trichothecene

problem as described in the context of previous syntheses. After the key step, we envision opening of the lactone to give **45**. This intermediate would then be subjected to a diastereoselective allylation at the aldehyde function to produce **44**. Finally, the core of the trichothecene skeleton would be completed via an intramolecular S_N' cyclization of an allylic silane to aldehyde to **43**. The well-precedented epoxidation of the exocyclic olefin **42** would produce the title natural product in as few as 16 linear steps.

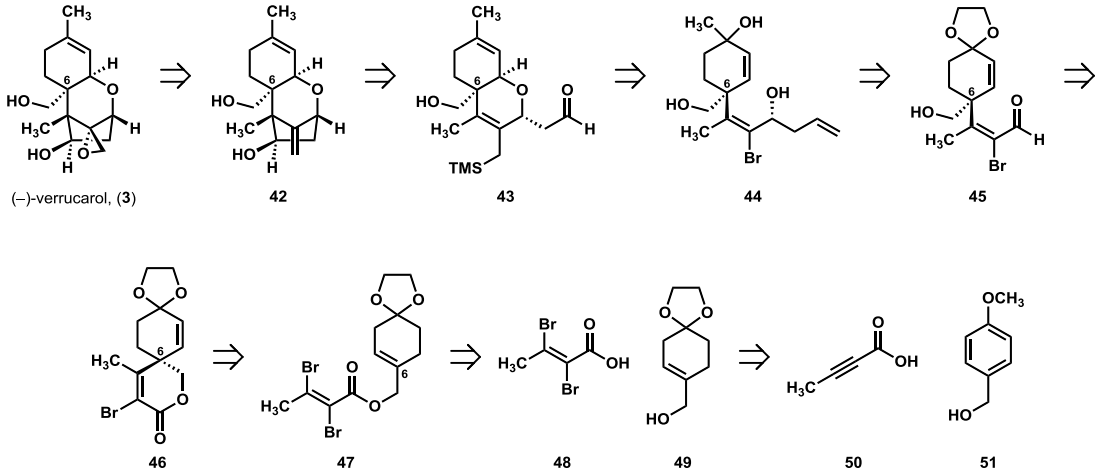


Figure 1.7 Retrosynthetic Analysis of (–)-Verrucarol

1.3.1 Asymmetric Intramolecular Heck Reactions in Synthesis

The low-valent palladium-mediated cross coupling reaction joining an olefin and an aryl or a vinyl halide was first described over 40 years ago in independent studies by Mizoroki and Heck.[7,8] In 1989, Shibasaki and Overman disclosed the first examples of an asymmetric intramolecular Heck reaction.[9] Shibasaki and his group

demonstrated the first enantioselective construction of a tertiary stereocenter (**52**) via an intramolecular Heck cyclization (**Figure 1.8**).

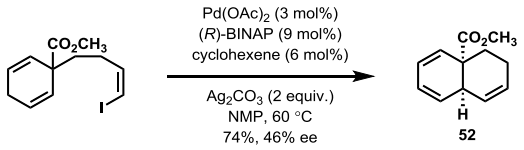


Figure 1.8 Shibasaki's Intramolecular Heck Cyclization

Meanwhile, Overman reported the first direct formation of a quaternary carbon stereocenter (**53**) (**Figure 1.9**), a milestone for the catalytic construction of quaternary carbon stereogenic centers.

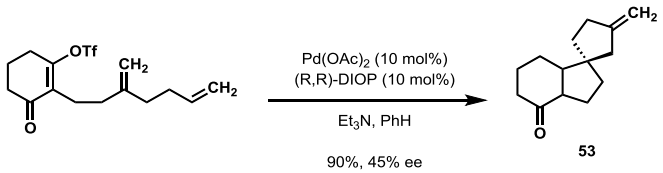


Figure 1.9 Overman's Intramolecular Heck Cyclization

In 1990, Overman demonstrated the power of the palladium-mediated quaternary carbon formation (**54** → **55**) in the total synthesis of the natural products (±)-tazettine (**56**) and (±)-6a-epipretazettine (**57**) (**Figure 1.10**).[10]

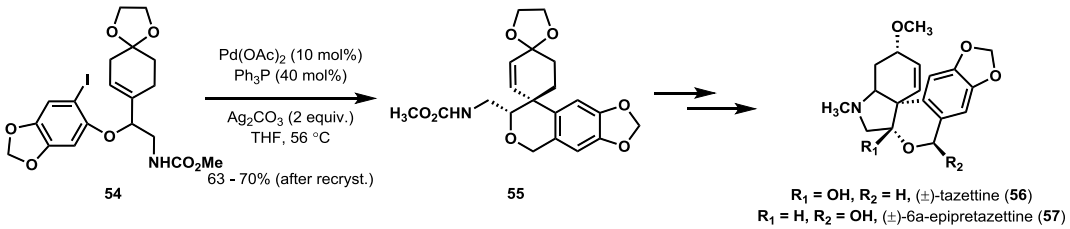


Figure 1.10 Intramolecular Heck Cyclization for Natural Product Synthesis

In 1998, Overman and coworkers released a series of publications that explored the effects of chiral diphosphine ligands, methods of catalyst generation, reaction solvent and HX scavenger for the formation of enantioenriched asymmetric Heck cyclizations products similar to the ester **59** and the lactam **61** (**Figure 1.11**).[11] They found that by varying the HX scavenger (silver salt or tertiary amine), both enantiomers could be accessed by means of the same chiral diphosphine ligand.

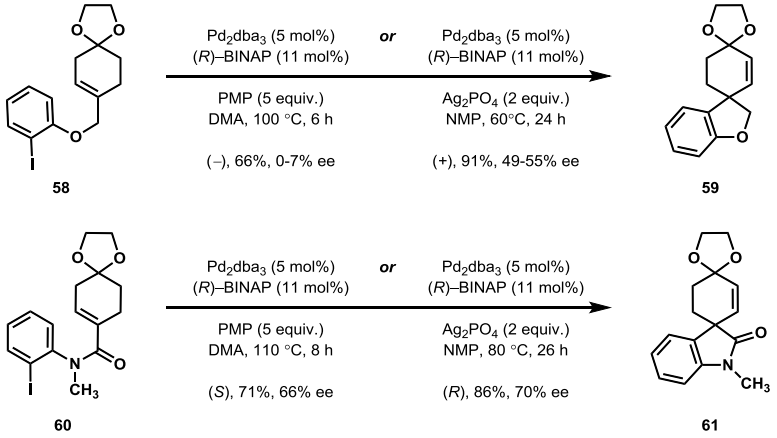


Figure 1.11 Examples of Heck Reactions to Form Spirocycles

Most recently in the total synthesis of (±)-galanthamine, Guillou has shown that a ligandless system can decrease the time required to produce quaternary carbons through Heck cyclizations from 72 hours to 5 hours (**62** → **63**) (**Figure 1.12**).[12]

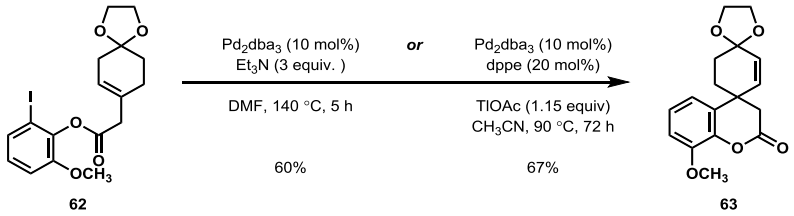


Figure 1.12 Example of Ligandless Heck Reaction to Form Spirocycles

Our target Heck cyclization substrate contains the same alkene insertion partner as much of the prototypical Heck platforms (e.g., **Figure 1.11** and **1.12**), and if successful, would represent the first example of a Heck reaction employing a β-halo enone as the oxidative addition partner (**64** + **65** → **66**) (**Figure 1.13**).[11c]

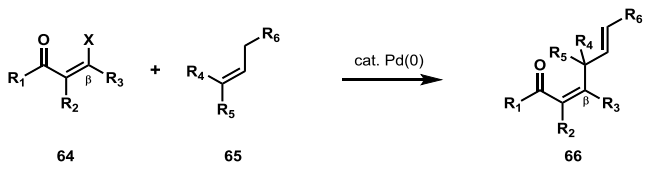


Figure 1.13 General Heck Reaction Partners

1.3.1.1 Mechanism of Intramolecular Heck Reaction

The sequence of events within the Heck reaction and the exact mechanistic details can vary with the catalyst, substrate, additives, and other reaction conditions. The possible mechanisms of the Heck reaction have been extensively discussed and

are the subject of ongoing investigations.[13] Intramolecular Heck reactions typically invoke one of two mechanisms: the "neutral pathway" or the "cationic pathway". In the " neutral pathway", the active palladium catalyst complex features two phosphine ligands and engages the carbon-halogen bond in an oxidative addition process (**Figure 1.14**). The oxidative addition is often the rate-determining step, and is governed by the identity of the halogen, where X = I > Br > > Cl. This trend parallels bond dissociation energies for carbon-halogen bonds (H_3C–X where X = I, Br, Cl, and F; BDE (kcal/mol) = 57, 70, 83, and 110, respectively).[14] Loss of a phosphine ligand allows coordination and *syn* insertion of the olefin. The resulting σ-bonding allylpalladium intermediate undergoes *syn* β-hydride elimination, resulting in the newly coupled olefin and a hydrido palladium complex. A stoichiometric amount of base turns over the active palladium catalyst.

In the "cationic pathway", perfluorosulfonated olefins (X = Tf or Nf) take the place of the halogen (**Figure 1.14**). The oxidative addition process with the active palladium catalyst results in a cationic intermediate. No loss of phosphine ligand is observed and coordination followed by *syn* insertion takes place, as seen in the "neutral pathway". The resulting σ-bonding allylpalladium intermediate undergoes *syn* β-hydride elimination, resulting in the newly coupled olefin and a hydrido palladium complex. A stoichiometric amount of base turns over the active palladium catalyst.

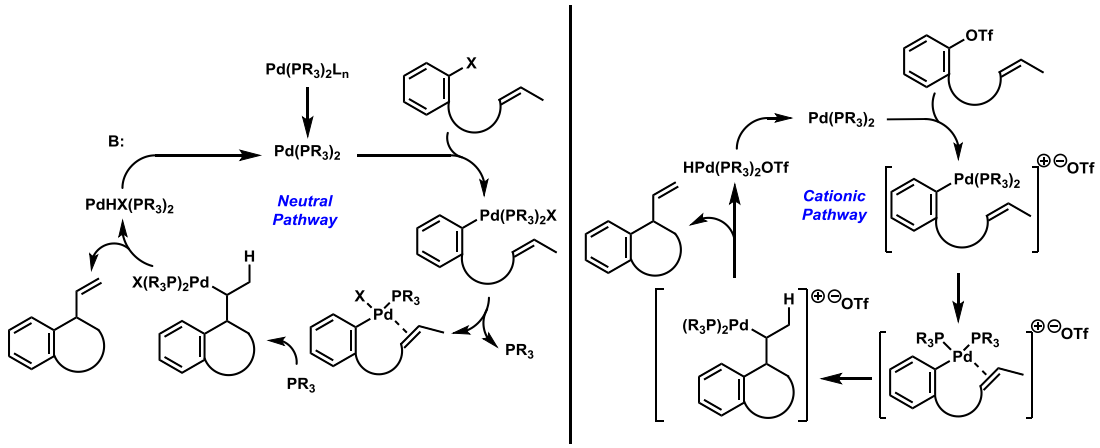


Figure 1.14 Neutral and Cationic Mechanisms of Heck Reaction

1.4 Preliminary Investigations and Synthesis of Dibromo Ester 47

Progress toward the natural product began with the synthesis of the key Heck cyclization substrate dibromo **47** (**Figure 1.15**), which we approached with a high degree of confidence given its similarity to the substrates in the seminal work in asymmetric Heck-type chemistry. Standard Birch reduction of commercially available anisyl alcohol (**51**) yielded the allylic alcohol **67** and protection of the ketone function as the corresponding ketal with ethylene glycol in the presence of boron trifluoride ethyl etherate provided the allylic alcohol **49**.[15]

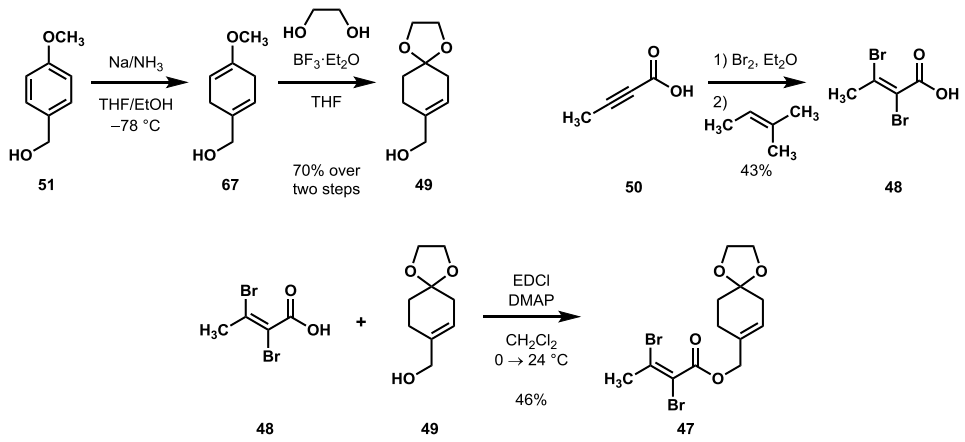


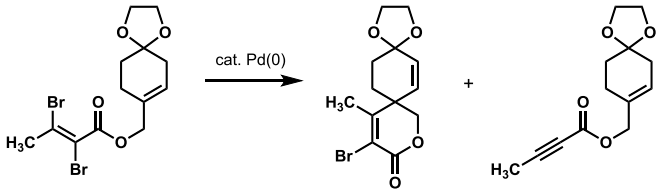
Figure 1.15 Synthesis of Dibromo Ester **47**

For the preparation of the acid **48**, 2-butynoic acid (**50**) and bromine were combined at 0 °C and then excess bromine was quenched by the addition of 2-methyl-2-butene (**Figure 1.15**). Standard methods for the preparation of the acid **48** call for quenching with an aqueous sodium metabisulfite solution.[16] The procedure, while successful, was amended due to the difficulty of removing the resulting sulfur byproducts and the detrimental effects of sulfur in forthcoming organometallic reactions.[17] With the acid **48** and the allylic alcohol **49** in hand, the esterification was achieved with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) activation and catalytic 4-dimethylaminopyridine (DMAP) to yield **47**. At this point, investigations into the key intramolecular asymmetric Heck cyclization (**47** → **46**) took place.

1.4.1 Screening Conditions for Heck Reaction on Dibromo Ester 47

A variety of conditions were screened on the dibromo ester **47** due to their previously reported success with other similar substrates reported in the literature.

Table 1.1 Screening Conditions for Heck Reaction on Dibromo Ester **47**

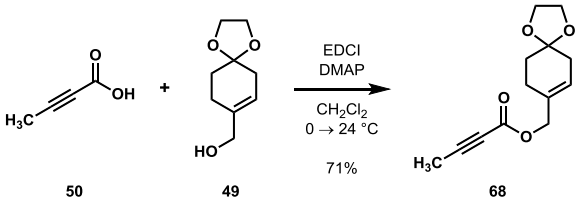


47 46 68

#	Catalyst	Catalyst Loading	Ligand	HX scavenger	Solvent	Recovered
1[a]	Pd_2dba_3	5 mol%	Ph_3P	Ag_2CO_3	CH_3CN	**47** and **68**
2[b]	Pd_2dba_3	5 mol%	Ph_3P	Ag_2CO_3	THF	**47** and **68**
3[a]	Pd_2dba_3	5 mol%	Ph_3P	K_2CO_3	CH_3CN	**47** and **68**
4[a]	Pd_2dba_3	10 mol%	-	Et_3N	DMF	**68**
5[a,c]	$Pd(dppf)Cl_2$	20 mol%	-	Et_3N	THF	N. R.
6[a,d]	(*i*-Pr)$Pd(Cl_2)(Et_3N)$ (**69**)	5 mol%	-	K_2CO_3	DMF	**68**

[a] Conditions: 2.0 equiv. of HX scavenger, 0.06 M substrate, 80 °C, 22h. [b] 60 °C, 22h. [c] Catalyst reduced with 2.0 equiv. of CuI before addition of substrate. [d] 2.0 equiv. of $(n\text{-Bu})_4NBr$ added.

Similar conditions reported by Overman for the synthesis of quaternary carbon centers of spirocylic products were used in runs 1-3 (**Table 1.1**). Under these conditions the cyclization of the dibromo **47** proved to be unsuccessful giving the elimination product alkyne **68**. The alkyne product we recovered from the runs was confirmed via NMR and TLC to the independently prepared sample of the ester alkyne **68** (**Figure 1.16**).



50 49 68

Figure 1.16 Synthesis of Ester Alkyne **68**

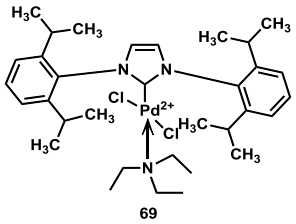
The exact conditions for cyclization reported by Guillou employed in the total synthesis of (–)-galothamine were investigated in run 4. In these ligandless conditions, Guillou employs only triethylamine and Pd_2dba_3 in DMF to complete the reaction. In our hands, these conditions again gave only the elimination product **68**.

Investigations with Pd(dppf)Cl_2 (1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride) were conducted in run 5. It is known that dppf and its analogues are excellent ligands for Heck reactions due to their air stability and regioselective olefin insertion by virtue of their chelate effect. [18] When employed, these bidentate phosphine precatalyst must first be reduced, in this case with 2.0 equivalents of CuI, then our substrate was added. Our use of the dppf ligand system returned only the starting material dibromo **47**.

Investigations with a *N*-heterocyclic carbene (NHC) ligand system were employed in run 6. Heterocyclic carbene ligands have gained notice in catalytic organometallic carbon-carbon coupling reactions because of their ability to be tuned both with respect to sterics and electronics.[19] NHC catalysts are known to be great σ-electron donors and weak π-electron acceptors. This ability allows for the catalyst to oxidatively add to bonds that are historically difficult to activate, such as carbon-chlorine bonds. The sterics of NHC's can also be tuned for preferred stereochemical outcomes dependent on the geometry of the substrate.

The NHC precatalyst used, (*i*-Pr)Pd(Cl_2)(Et_3N) (**69**), (**Figure 1.17**), was donated by Dr. Oscar Navarro at the University of Sussex, Brighton, UK. Navarro's protocol for using NHC catalysts called for the use of phase transfer catalysts in phosphine-free Heck cyclizations commonly referred to as Jeffery conditions.[20] Using the exact Jeffery conditions that the Navarro group employs for intermolecular Heck

reactions between aryl chlorides and an olefin again gave only the elimination product **68**.



69

Figure 1.17 *N*-Heterocyclic Carbene Precatalyst (*i*-Pr)Pd(Cl_2)(Et_3N)

1.5 Synthesis and Investigations of Monobromo Ester 72

After many attempts to affect a Heck reaction with the dibromo ester **47**, it was clear that elimination was kinetically competitive with the intended cyclization. In order to prevent elimination of the *anti* dibromide, a new strategy was developed. We hypothesized that replacing one bromide with a proton, the monobromo ester **72**, might render the elimination kinetically slower and/or less likely to occur.

The synthesis of the monobromo ester **72** began by means of the regio- and stereospecific hydrohalogenation reaction of 2-butynoic acid (**50**) with lithium bromide and acetic acid at reflux for 24 hours to produce the monobromo acid **71** (**Figure 1.18**).[21] Coupling the acid **71** with the neopentylglycol protected allylic alcohol **70** via EDCI activation produced the monobromo ester **72** in good yield. Switching the protecting group of the Birch reduction product **60** produced a solid material, rather than an oil, making material handling far more convenient.

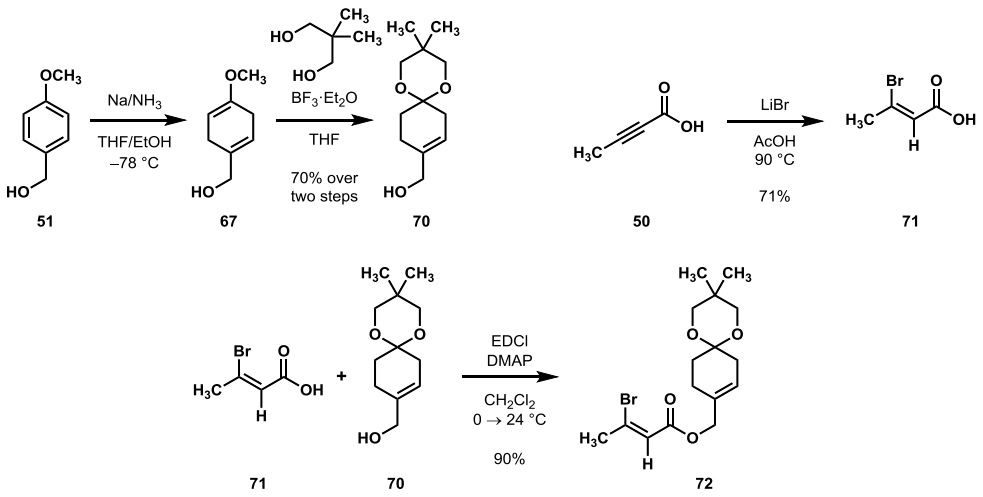
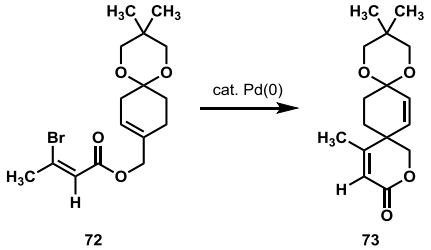


Figure 1.18 Synthesis of Monobromo Ester **72**

Table 1.2 Screening Conditions for Heck Reaction on Monobromo Ester **72**



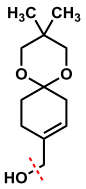
72 73

#	Catalyst	Catalyst Loading (mol%)	Ligand	Time (h)	HX scavenger	Solvent	Heck Product
1[a]	Pd_2dba_3	5	Ph_3P	20	Ag_2CO_3	THF	**72** and **74** (25%)
2[a]	Pd_2dba_3	5	Ph_3P	19	Ag_2CO_3	CH_3CN	**72** and **74**
3[a]	Pd_2dba_3	5	Ph_3P polymer	24	Ag_2CO_3	THF	N.R.
4[b]	Pd_2dba_3	5	Ph_3P	22	Ag_2CO_3	THF	**72** and **74**
5[c]	$Pd(Ph_3P)_4$	20	-	5	Ag_2CO_3	CH_3CN	**72** and **74**
6[a]	Pd_2dba_3	5	Ph_3As	24	NMI	CH_3CN	N.R.
7[d]	Pd_2dba_3	10	-	15	Et_3N	DMF	**68** like and **74**
8[d]	Pd_2dba_3	10	-	15	Et_3N	CH_3CN	N.R.
9[d]	Pd_2dba_3	10	-	15	Et_3N	THF	N.R.
10[d]	Pd_2dba_3	10	-	15	Et_3N	$PhCH_3$	N.R.
11[d]	Pd_2dba_3	10	-	15	Et_3N	NMP	N.R.
12[e,f]	$Pd(dppf)Cl_2$	20	-	48	Et_3N	THF	**72**
13[e,g]	$Pd(dppf)Cl_2$	20	-	24	Et_3N	THF	**72**
14[a,f]	$Pd(OAc)_2$	20	Ph_3P polymer	68	Ag_2CO_3	$PhCH_3$	**72**
15[a,h]	(*i*-Pr) $Pd(Cl_2)(Et_3N)$ (**69**)	5	-	46	K_2CO_3	DMF	**70**

[a] Conditions: 2.0 equiv. of HX scavenger, 0.1 M substrate, reflux. [b] 2.0 equiv. of HX scavenger, 0.05 M substrate, reflux. [c] 2.0 equiv. of HX scavenger, 0.1 M substrate, reflux, 24h. [d] 3.0 equiv. of HX scavenger, 0.01 M substrate, 80 °C (THF 60°C). [e] Catalyst reduced with CuI before addition of substrate, 2.0 equiv. of HX scavenger, reflux. [f] 0.01 M substrate. [g] 0.001 M substrate. [h] 2.0 equiv. of (*n*-Bu)$_4$NBr added.

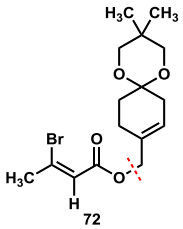
Investigations to induce a Heck reaction of the monobromo ester **72** to produce the desired spirocycle **73** were extensive. Application of Overman's amended protocol (**Table 1.2**, runs 1 and 2) provided a possible Heck cyclization product. NMR spectra (^{1}H and ^{13}C) of this new product were encouraging, however, with careful inspection of peak integration, something was awry. In the proton NMR, all peaks were accounted for, yet the integration for the olefinic protons in the desired product **73** was not consistent with the structure (3H expected, 2H observed). Carbon NMR had a twinning effect associated with all of the peaks, which excited us, because we thought we had an equilibrating mixture of conformers.

Further investigation with low resolution mass spectrometry analysis of the unknown Heck cyclization product along with interpretation of starting materials mass spectra provided the ultimate answer (**Figure 1.19**). Beginning with the allylic alcohol **70**, this compound was calculated to have an exact molecular mass of 212.14 m/z [M] and we observed a mass of 213.13 m/z $[M + H]^{+}$. We also observed a mass of 195.13 m/z $[M + H - H_2O]^{+}$; this was due to the loss of hydroxide.



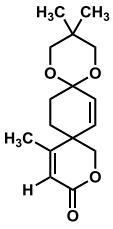
70

Exact Mass $[M]^{+}$: 212.14 m/z
Observed Collected $[M+H]^{+}$: 213.13 m/z
Observed Collected $[M+H-H_2O]^{+}$: 195.13 m/z



72

Exact Mass $[M]^{+}$: 358.08 m/z and 360.08 m/z
Observed Mass $[M+H]^{+}$: 359.08 m/z and 361.08 m/z
Observed Mass $[M-C_4H_4BrO_2]^{+}$: 195.13 m/z



73

Exact Mass $[M]^{+}$: 278.15 m/z
Observed Mass $[M+H_2O]^{+}$: 576.35 m/z
Observed Mass $[M+Na]^{+}$: 581.31 m/z

Figure 1.19 LRMS Analysis of Allylic Alcohol **70**, Monobromo Ester **72**, and Cyclization Product **73**

We expected the monobromo **72** to have two peaks of nearly equal counts with exact masses of 358.08 m/z and 360.08 m/z [M] (two bromine isotopes, ^{79}Br and ^{81}Br 51 and 49% natural abundance, respectively).[22] We observed small amounts of the expected exact masses and with the natural bromine isotopic distribution (**Figure 1.19**). These masses were 359.08 m/z and 361.08 m/z $[M + H]^+$. Along with the molecular mass, we observed a mass for the cleavage of the ester, 195.13 m/z $[M - C_4H_4BrO_2]^+$. This fragmentation pattern was consistent with the allylic alcohol **70**'s loss of hydroxide.

Continuing with our analysis, we calculated the exact mass of our desired Heck cyclization product **73** to be 278.15 m/z [M] (**Figure 1.19**). We did not observe this mass even after multiple trials. Instead, we observed masses of 576.35 m/z $[M + H_2O]^+$ and 581.31 m/z $[M + Na]^+$ (**74**) (**Figure 1.20**).

We performed a standard reduction (Pd/C, H_2) of this unknown Heck cyclization product and observed masses of 584.41 m/z $[M + H_2O]^+$and 1155.76 m/z $[2M + Na]^+$ (**75**) (**Figure 1.20**).

Rationalizing these data, we assigned a structure to our product as **74**, the dimerization of product of monobromo **73**. The dimer **74** would have an expected mass of 558.32 m/z [M] and 581.31 m/z $[M + Na]^+$. Reduction of the dimer **74** yielded the fully saturated product **75** which contained eight more hydrogen atoms that it's starting material (**Figure 1.20**). This reduced dimer was expected to have a mass of 566.38 m/z [M] and 1155.75 m/z $[2M + Na]^+$.

Revisiting the NMR data, it is clear why there are not three protons in the olefinic region. Mechanistically, it is reasonable to conclude that that the catalyst is

competent, undergoing oxidative addition to the C_{sp2}-Br bond, but not undergoing any π-coordination and subsequent insertion event on to the allylic olefin.

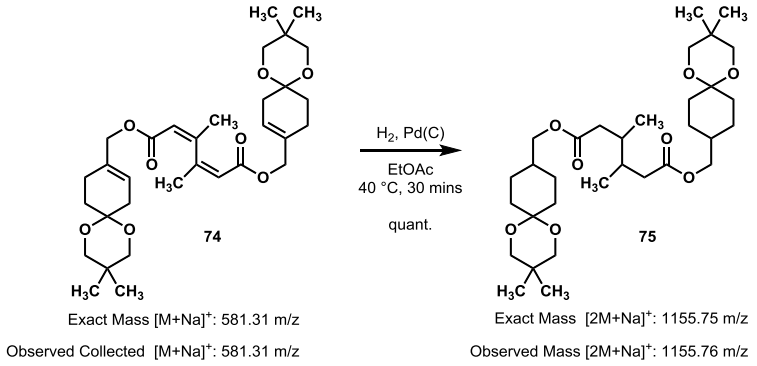


Figure 1.20 Dimerization Products **74** and **75**

Substrate **72** was subjected to other Heck catalysts. Many of the conditions screened produced the known dimer **74**, elimination products similar to **68**, or returned starting material unchanged. Concentrations were varied (runs 4, 12, 13) with the belief that dilution would lead to less dimerization. Unfortunately, reactions run at high dilution also gave **74**.

1.6 Synthesis and Investigation of Analogues in Heck Cyclization Reaction

A series of analogues were synthesized and tested with standard Heck conditions. The first and second sets of analogues replaced the ester linkage with an ether and contain the mono- or dibromo functionalities. The third set of analogues sought to change the identity of the oxidation addition partner to a more reactive species. The fourth set contains the ester functionality, but does not contain the conjugation seen in similar substrates. The fifth set of analogues were created to understand whether π-coordination of the olefin to the catalyst was possible under the

most ideal conditions. The sixth set was created to rule out the involvement of other functional groups interfering during the course of the reaction. Finally a seventh set was synthesized as an experimental control.

1.6.1 Synthesis and Investigations of Dibromo Ether 79

Esters typically exhibit an s-*trans* conformation rather than an s-*cis* configuration due to stereoelectronic effects associated with oxygen lone pairs and the adjacent C–O sigma and pi antibonding orbitals.[23] Esters typically have a slightly restricted rotation about the C–O bond linkage as a consequence, and therefore conformational flexibility of the overall structure may be impacted.

Based on the products alkyne **68** and dimer **74** from previous attempted Heck reactions, as well as the accepted mechanisms of the Heck reaction, we believed that oxidative addition step was occurring. Unfortunately, the π-coordination of the olefin to the catalyst was presumably hindered in some way, precluding a Heck-type insertion. We reasoned that removing the carbonyl function (ester) within the substrate would in turn increase structural flexibility and thus allow the necessary reorganization of catalyst and olefin for coordination. Thus, a series of ethers bearing mono- and dibromo functions were created.

The synthesis of the ether **79** began with bromination of 2-butynol (**76**) producing the dibromo ether **77** in good yield (**Figure 1.21**).[24] The allylic alcohol **70** was converted to the corresponding mesylate, which was then substituted with lithium bromide to yield the allylic bromide **78**. This product proved to be somewhat unstable and required immediate coupling with the dibromo ether **79** via a Williamson ether synthesis.[25] Unfortunately and unsurprisingly, subjecting the dibromo ether **79** to standard Heck conditions produced the elimination product **80**.

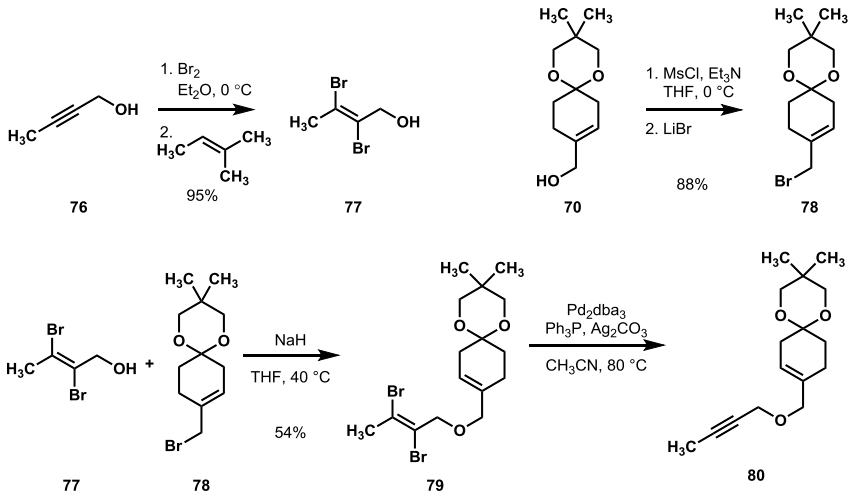


Figure 1.21 Synthesis and Screening of Dibromo Ether **82**

1.6.2 Synthesis and Investigations of Monobromo Ether 83

We hoped to address the ester conformational issues and stop unwanted elimination with the second set of analogues. The synthesis of the monobromo ether **83** began with the previously synthesized mono bromo acid **71**; this species was converted to the methyl ester **81** and then reduced to the allylic alcohol **82** in two steps (**Figure 1.22**). Williamson ether synthesis between the allylic bromide **78** and allylic alcohol **82** produced the monobromo ether **83**. This product was again subjected to standard Heck reaction conditions and what was recovered was the known allylic alcohol **70**. Interpretation of these results lead us to conclude that oxidative addition was occurring within substrate **83**, resulting in some kind of π-allyl palladium complex which fragmented and produced the recovered allylic alcohol **70**.

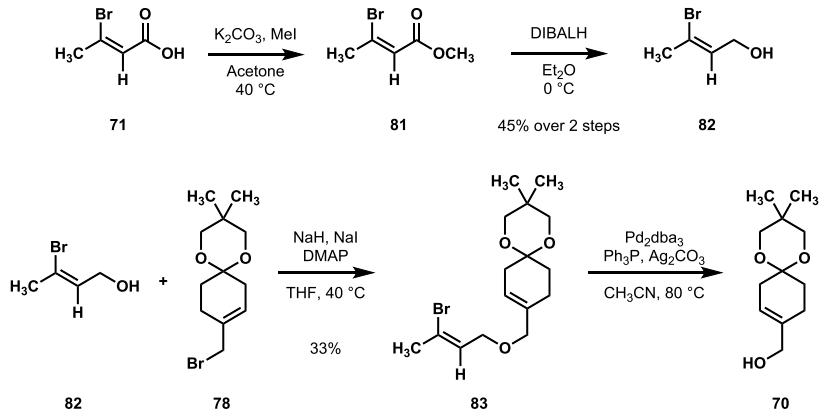


Figure 1.22 Synthesis and Screening of Monobromo Ether **83**

1.6.3 Synthesis and Investigations of Triflates 89, 93, and Iodides 96, 98, 101

A third sequence was developed with the intent to invert the electronics of the substrates by exchanging the carbonyl and allylic alcohol portions of the molecule (**70** → **88**). Additionally, we reasoned that a more reactive oxidation addition substrate may facilitate more efficient cyclization reactions.

The synthesis of triflate **89** began with triflation of ethyl acetoacetate (**84**) yielding **85** utilizing an unusual biphasic system consisting of aqueous lithium hydroxide and trifluoromethanesulfonic anhydride in hexane; these conditions were described specifically to generate the desired *Z*-alkene isomer (**Figure 1.23**).[26] Reduction of the ester **85** with diisobutylaluminum hydride generated the allylic alcohol **86** in good yield.

In order to generate a carbonyl-containing fragment from the previously synthesized allylic alcohol **70**, we employed a copper (I)/TEMPO-catalyzed aerobic alcohol oxidation to cleanly generate the aldehyde **87** in high yield.[27] Aldehyde **87** was further oxidized to the acid **88** via the Pinnick protocol.[28] The key cyclization substrate **89** was generated by a straightforward EDCI-mediated coupling reaction of

88 and **86**. Exhaustive reaction screening with the Heck substrate **89** produced only the reduced product **90** (one example shown in **Figure 1.23**).

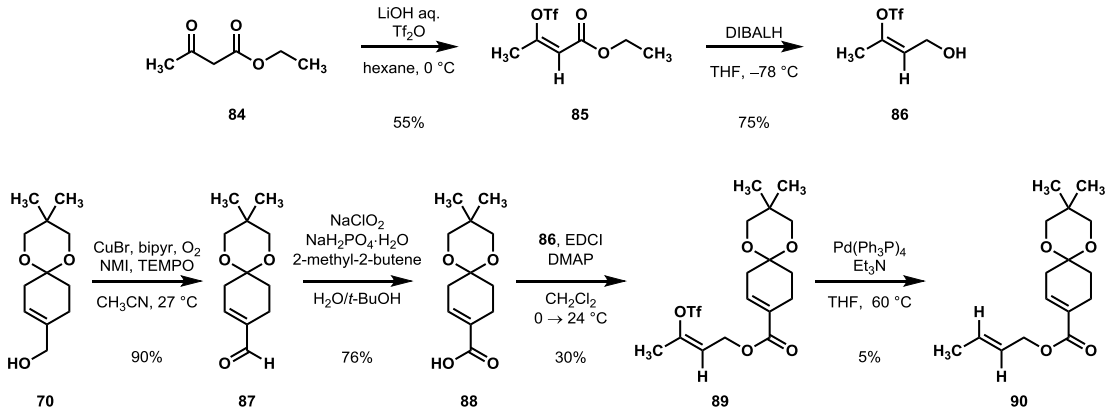


Figure 1.23 Synthesis and Screening of Ester Triflate **89**

The synthesis of the triflate **93** began by joining 2-methyl-3-oxobutanoic acid (**91**) and the allylic alcohol **70** by an EDCI-mediated coupling reaction (**Figure 1.24**). Aqueous conditions were avoided in the subsequent triflation reaction in order to generate the desired *Z*-alkene isomer while preserving the ester function. The *Z*-enolate was formed selectively by stirring the ester with sodium hydride in a mixture of toluene and THF, which was then trapped with trifluoromethanesulfonic anhydride to give the triflate **93**. Exhaustive reaction screening with the triflate **93** routinely produced a mixture of the *Z* and *E* reduction product isomers **94** (one example shown in **Figure 1.24**).

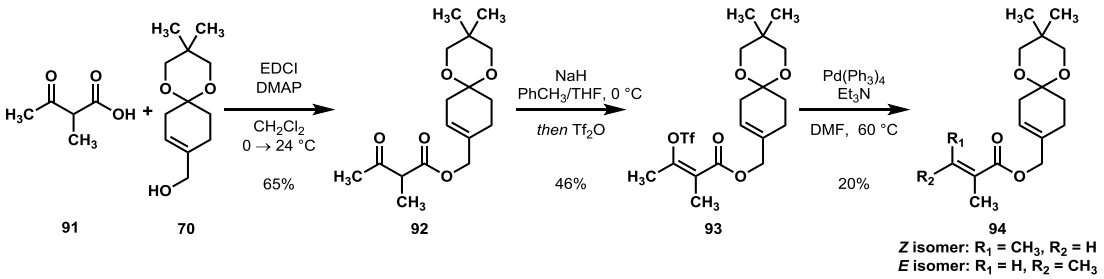


Figure 1.24 Synthesis and Screening of Ester Triflate **93**

A series of iodide substrates were synthesized and tested for possible Heck cyclization. Analogous to the monobromo ester **72**, monoiodo ester **96** was synthesized and tested in the Heck cyclization reactions. The sequence began by treating 2-butynoic acid (**50**) with sodium iodide in hot acetic acid to produce the monoiodo acid **95** (**Figure 1.25**). This product was coupled with the allylic alcohol **70** under EDCI coupling conditions to afford the monoiodo ester **96**. Similar to the monobromo **72**, subjecting the monoiodo **96** to standard Heck conditions produced the previously identified dimer product **74** (**Figure 1.20**).

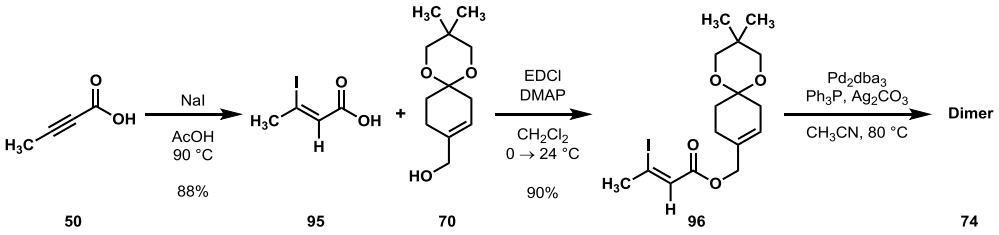


Figure 1.25 Synthesis and Screening of Monoiodo Ester **96**

To test **98** in the Heck reaction, the previously synthesized monoiodo acid **95** was reduced directly to the allylic alcohol with DIBALH to make the allylic alcohol

97 in low yield (**Figure 1.26**). Bringing together the allylic alcohol **97** and acid **88** with EDCI coupling produced the monoiodo ester **98** again in low yield. All attempts at cyclization with this substrate returned no discernable products.

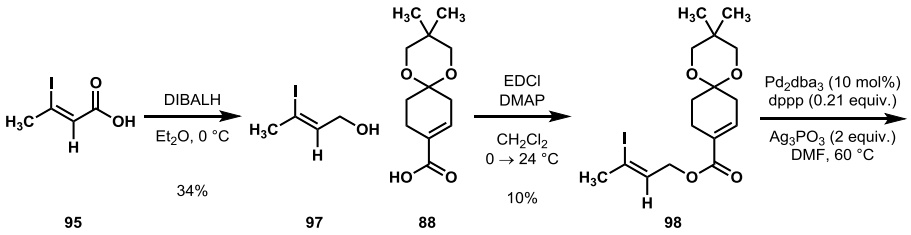


Figure 1.26 Synthesis and Screening of Iodo Ester **98**

The final iodo analog tested was **101**. This sequence began by treating but-3-yn-1-ol (**99**) with sodium iodide and trimethylchlorosilane to produce the homoallylic alcohol **100** (**Figure 1.27**). This product was subjected to EDCI coupling conditions with the acid **88** to produce the iodo ester **101** in high yield. Applying a number of conditions toward the desired Heck cyclization, we observed only the dimer product **102**.

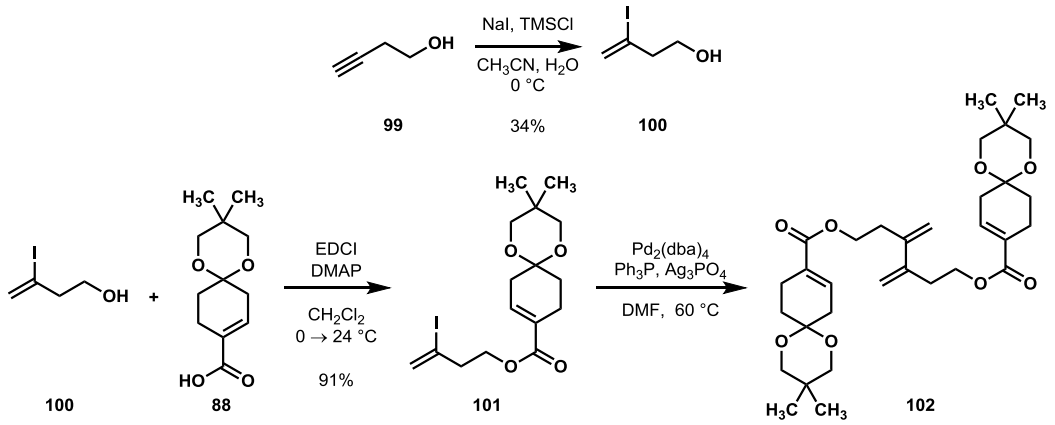


Figure 1.27 Synthesis of and Screening Iodo Ester **101**

1.6.4 Efforts Toward the Synthesis of Bromo Ester 106

The fourth set of analogues contained the ester functionality but not the conjugation seen in similar substrates. Synthesis toward the monobromo ester **106** began with oxidation of butynol (**99**) with Jones reagent to provide the acid **103** (**Figure 1.28**). This product was then isomerized with base to the allene **104**. Hydrohalogenation of **104** with lithium bromide and hot acetic acid produced bromide **105**. The next steps coupling the allylic alcohol **70** and monobromo acid **105** proved to be a challenge. Standard coupling with EDCI and catalytic DMAP provided the chloro ester **107** in 19% yield and an equal amount of the allene ester **108**. Presumably under the conditions of EDCI coupling, the targeted bromo ester **106** undergoes elimination of HBr to give the allene ester **108**, which then presumably undergoes a conjugate addition by chloride ion (we presume form the EDCI reagent). Exchanging DCC for EDCI as the coupling reagent provided the allene ester **108** as the sole product, supporting our hypothesis. Efforts to generate the desired monobromo ester **106** from the allene ester **108** via lithium bromide and hot acetic

acid only afforded the ketone **109**. The bromo ester **106** was not completed, and therefore was not screened in the Heck cyclization reaction.

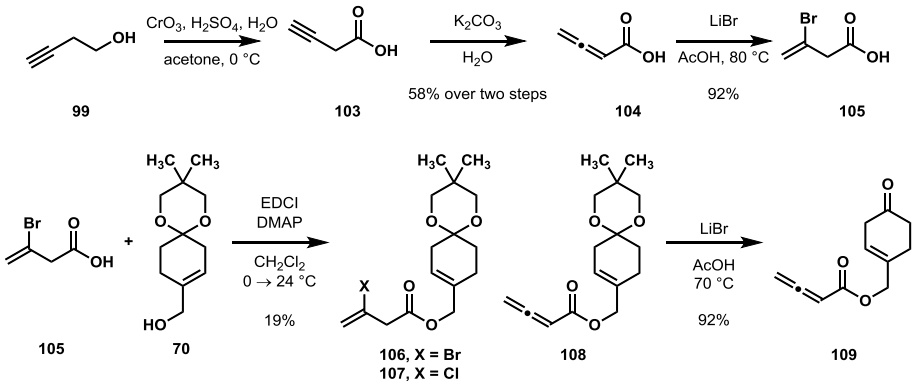


Figure 1.28 Efforts Toward the Synthesis of Bromo Ester **106**

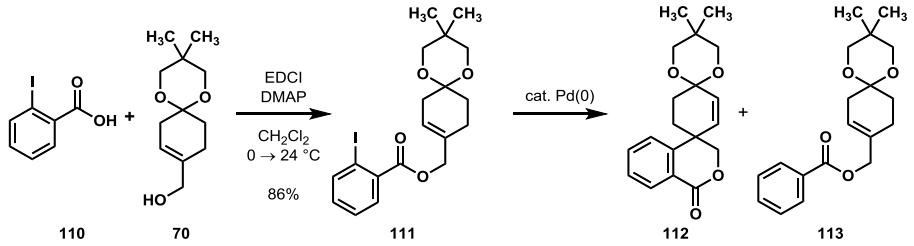
1.6.5 Synthesis and Investigations of Iodide 111 and Triflate 115

The fifth set of analogues, the iodide **111** and triflate **115**, were synthesized to test if Heck cyclization with these substrates would occur if the problem of beta elimination was precluded. Returning to the mechanism of the Heck reaction, we have evidence of oxidative addition to our substrates, but no evidence of π-coordination of the olefin to the catalyst followed by *syn*-addition. We wanted to test the hypothesis that after the oxidative addition in our reaction, would we find evidence of coordination then possible *syn*-addition with a substrate that cannot undergo beta elimination.

Synthesis of these model analogues began with 2-iodobenzoic acid (**110**) and allylic alcohol **70** coupling via together with EDCI and catalytic DMAP provided ester **111** (**Table 1.3**). This substrate was subjected to multiple reaction conditions, and no

Heck cyclization product **112** was detected, however, under one set of conditions we did isolate the reduced product **113** (**Table 1.3**, run 2).

Table 1.3 Synthesis and Screening Iodo Ester **111**



#	Catalyst	Catalyst Loading	Ligand	HX scavenger	Solvent	Heck Product
1[a]	Pd_2dba_3	5 mol%	Ph_3P	Ag_2CO_3	CH_3CN	N. R.
2[b]	Pd_2dba_3	5 mol%	Ph_3P	Ag_2CO_3	THF	**113**
3[a]	Pd_2dba_3	5 mol%	Ph_3P	K_2CO_3	CH_3CN	N. R.
4[a]	Pd_2dba_3	10 mol%	-	Et_3N	DMF	N. R.
5[a,c]	$Pd(dppf)Cl_2$	20 mol%	-	Et_3N	THF	N. R.
6[a,d]	(*i*-Pr)$Pd(Cl_2)(Et_3N)$ (**69**)	5 mol%	-	K_2CO_3	DMF	N. R.

[a] Conditions: 2.0 equiv. of HX scavenger, 0.05 M substrate, 80 °C, 44 h. [b] 60°C, 22h. [c] Catalyst reduced with CuI before addition of substrate. [d] 2.0 equiv. of $(n\text{-Bu})_4NBr$ added.

We synthesized the triflate **115** by coupling salicylic acid (**110**) and allylic alcohol **70** via standard EDCI coupling to form the ester **114** in low yield (**Figure 1.29**). The ester **114** was treated with trifluoromethanesulfonic anhydride to give the triflate **115** which was then screened for possible Heck cyclization. No discernable products were detected.

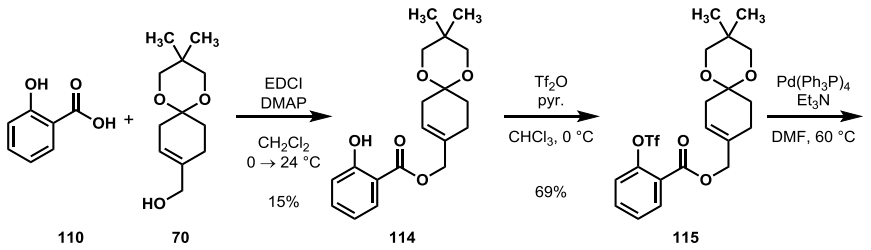


Figure 1.29 Synthesis and Screening of Triflate Ester **115**

1.6.6 Synthesis and Investigations of Monobromo Esters 116 and 120

The sixth set of analogues was created to address the possible complication imparted by the cyclic acetal protecting group. Removing the acetal function and otherwise masking the ketone functionality would modify the conformational flexibility of the A ring. Our hope was that this change would more easily allow for the necessary rearrangement of the molecule to form the desired carbon-carbon bond.

To test the ester **116**, we simply coupled the monobromo **71** and allylic alcohol **60** with using EDCI and catalytic DMAP (**Figure 1.30**). Exhaustive reaction screening with the ester **116** provided no discernable products.

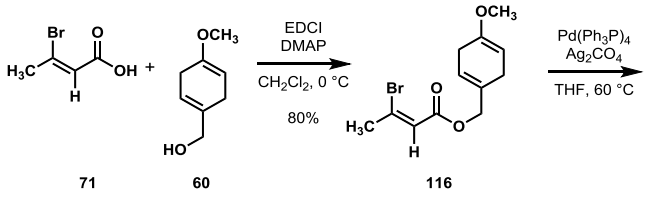


Figure 1.30 Synthesis of Monobromo Ester **116**

To test the Heck cyclization on a substrate without the spirocycle protecting group as well as a substrate that had a lower energy barrier for ring flips, the synthesis

of the monobromo ester **120** was developed. Our efforts toward testing the monobromo ester **120** in the Heck cyclization began with cyclohexanone (**117**) subjected to lithium hydroxide and bromoform to provide the acid **118** (**Figure 1.31**), and then reduced with lithium aluminum hydride to give the allylic alcohols **119A** and **119B** as an inseparable mixture. The monobromo **71** and allylic alcohol **119A** and **119B** was coupled with EDCI and catalytic DMAP to yield the monobromo esters **120A** and **120B**. Testing the ester **120A** with standard Heck conditions for possible cyclization products provided no discernable products.

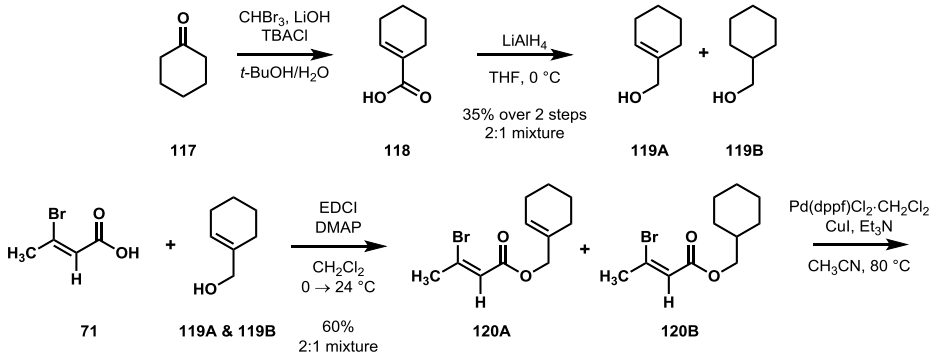


Figure 1.31 Synthesis of Monobromo Ester **120A**

1.6.7 Synthesis and Investigations of Amide 123

Finally a seventh set was synthesized as an experimental control. We wanted to test whether our procedure, lab technique, and reagents were sufficient and could affect any Heck cyclization. Thus we synthesized and tested a substrate similar to Overman's spirocycles (**60** → **61**) (**Figure 1.11**).

The sequence to synthesize the amide **123** began with generating *in situ* the acyl chloride of the acid **88** with thionyl chloride and then the addition of 2-

bromoaniline (**121**) to provide the amide **122** (**Figure 1.32**). Deprotonation of the amide **122** with sodium hydride followed by methylation with methyl iodide gave the amide **123**. The amide **123** was subjected to Overman's exact conditions for the intramolecular Heck cyclization to form spirocycles, in our hands, provided 10% of the intended product, the lactam **124**.

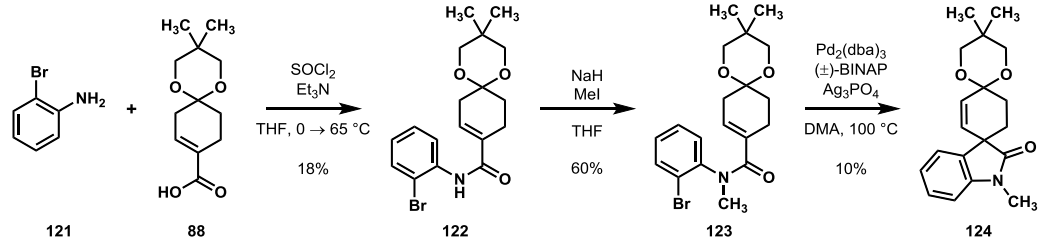


Figure 1.32 Synthesis of Amide **123** and Lactam **124**

1.6.8 High Throughput Screening of Dibromo Ester 47

Most recently, we have sought to develop reaction conditions to affect the desired intramolecular Heck cyclization reaction by making use of high-throughput screening methods[29] and our original dibromo ester **47** substrate (**Figure 1.33**). High-throughput screening generally describes an automated process that can be used to quickly assay the biochemical activity of a large number of drug-like compounds, search for a desired physical attribute of a set of molecules or materials, and/or rapidly screen reaction conditions for a desired process. For example, we are making use of high-throughput screening to examine a large number different catalyst, ligand, base, and solvent combinations in short order to develop reaction conditions that will affect the desired Heck-type cyclization.

Initial tests involved screening the dibromo ester **47** with the same palladium source and HX scavenger, tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct and trimethylamine, respectively. Reaction screening was conducted with four solvents, (toluene, DMF, trifluorotoluene, and dioxane), and a small library of monodentate phosphine ligands (23 ligands, including Buchwald-type phosphines) for a total count of 96 distinct reaction conditions.[30] All reactions were conducted outside of the glovebox at 80 °C for 24h. After heating, 1,3,5-trimethyoxy benzene in acetonitrile was added as an internal standard, and the reactions were analyzed via UPLC-MS searching for a mass of 314 m/z (the mass of the cyclization product lactone **46**). Thus far, no desired product has been detected.

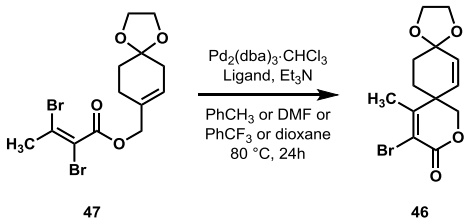


Figure 1.33 High Throughput Screening of Dibromo Ester **47**

1.7 Summary

In summary, the core structure of macrocyclic trichothecene natural products such as (–)-verrucarol (**3**) has been synthesized in several distinct sequences. We have developed a short synthetic concept toward the enantioselective synthesis of (–)-verrucarol (**3**). The key step is an asymmetric intramolecular Mizoroki-Heck reaction. Several substrates and reaction conditions have been screened in order to evaluate the key step.

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EXPERIMENTAL PROCEDURE

General Information: All reactions were performed in single-neck oven- or flame-dried round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 10 Torr (diaphragm vacuum pump) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 5–20 μm, Silicycle) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), ethanolic phosphomolybdic acid solution (PMA), acidic ethanolic p-anisaldehyde solution (Anis.), or aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (215 °C, 10–15 s). Flash chromatography was performed as described by Still et al.[1], employing silica gel (60-Å pore size, 40–63 μm, standard grade, Silicycle) or basic alumina (60-Å pore size, 50–200 μm, Brockmann I, Sorbent Technologies or Acros Organics).

Materials: Commercial reagents and solvents were used as received with the following exceptions. Triethylamine, dichloromethane, ethyl ether, dimethylsulfoxide, tetrahydrofuran, hexane, toluene, and benzene were purified by the method of

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Pangborn, et. al.[2] *N*,*N*-dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure (0.1 Torr) and stored under argon. Iodomethane was filtered through a column of basic alumina, neat, immediately prior to use. Where noted, solvents were deoxygenated before use by bubbling with argon for 15 minutes.

Instrumentation: Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Mercury Plus 300 MHz/75 MHz or Varian Unity INOVA 500 MHz/125 MHz NMR spectrometers at 23 °C. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Varian Mercury Plus 282 MHz spectrometer at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, CD_2HOD: δ 3.31, CD_3SOCD_2H: δ 2.50, C_6D_5H: δ 7.16). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3OD: δ 49.00, CD_3SOCD_3: δ 39.52, C_6D_6: δ 128.00). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1 FT-IR spectrophotometer referenced to a polystyrene standard and data are represented as frequency of absorption (cm^{-1}). Accurate mass measurements were obtained on a Waters LCT premier (ESI source,

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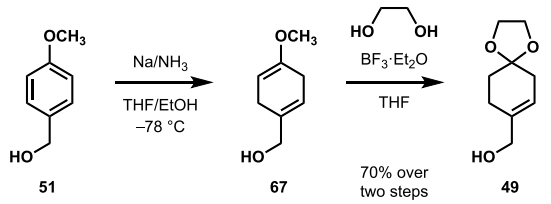
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

flow injection analysis) or a Waters GCT premier (GC-MS fitted with an EI or CI source) at the Mass Spectrometry Facility at the University of California at Irvine.



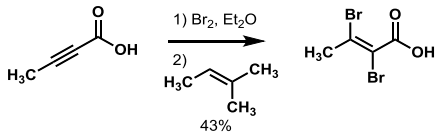
Allylic Alcohol **49**:

Sodium (6.00 g, 270 mmol, 3.7 equiv.) was added slowly over 30 min to a cooled (−78 °C) three-neck round-bottom flask fitted with a cold finger (cooled to −78 °C) containing a mixture of the anisyl alcohol **51** (10.0g, 72.0 mmol, 1.0 equiv.), THF (27 mL), anhydrous ethanol (90 mL), and ammonia (135 mL). After stirring for 40 min at −78 °C, solid ammonium chloride (14 g) was added and the reaction mixture was allowed to slowly warm to room temperature over 2 h (Caution! Gas evolution!). Water (50 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the allylic alcohol **67** (8.98 g) as a clear yellow oil which was used without further purification.

Boron trifluoride diethyl etherate (2.00 mL, 12.0 mmol, 0.20 equiv.) was added to a to a cooled (0 °C) mixture of the allylic alcohol **67** (8.98 g, 64.0 mmol, 1.0 equiv.) and ethylene glycol (14.4 mL, 256 mmol, 4.0 equiv.) in THF (20 mL, 3.2 M). Once the reaction was judged complete via TLC, the reaction was slowly quenched with saturated aqueous sodium bicarbonate (50 mL). The resulting biphasic mixture was extracted with dichloromethane (3 x 20 mL) and the combined extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30% ethyl

acetate–hexane) to provide the allylic alcohol **49** (8.61g, 70% over two steps) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	5.61 (ddt, J_1 = 5.2, J_2 = 3.7, J_3 = 1.5 Hz, 1H), 4.04 (s, 2H), 3.99 (s, 4H), 2.33 – 2.20 (m, 4H), 1.80 (tt, J = 6.7, 0.9 Hz, 2H), 1.48 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	137.4, 120.0, 108.2, 66.8, 64.6, 35.5, 31.0, 24.9.
TLC (50% EtOAc–Hex), R_f:	Alcohol **49**: 0.22 (CAM, Anis.).



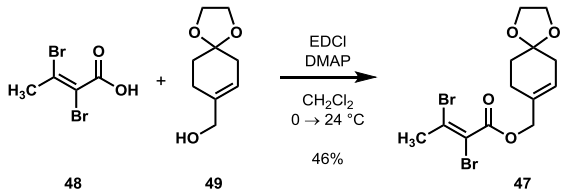
Dibromo Acid **48**:

Bromine (2.00 mL, 39 mmol, 2.0 equiv.) was added dropwise to a cooled (–8 °C) solution of 2-butynoic acid **50** (1.45 g, 17.0 mmol, 1.0 equiv.) in diethyl ether (20 mL) and then stirred at that temperature for 15 min whereupon 2-methyl-2-butene (5.0 mL) was added. The red-orange reaction mixture was warmed to 23 °C and 0.01M aqueous hydrochloric acid solution (20 mL) was added and the resultant biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The resulting yellow/orange solid was recrystallized from dichloromethane to afford the dibromo acid **48** (1.80 g, 43%) as a pale yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 11.90 (s, 1H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.7, 126.0, 107.2, 30.0.

TLC (20% EtOAc–Hex), R_f: Dibromo Acid **48**: 0.23 ($KMnO_4$).



48 49 47

Dibromo Ester **47**:

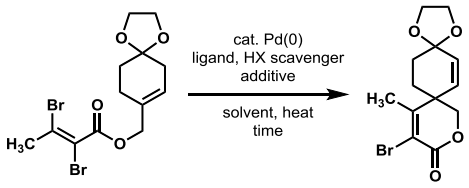
A solution of the dibromo acid **48** (576 mg, 2.30 mmol, 2.0 equiv.) in dichloromethane (3 mL) was added to a cooled (0 °C) solution of the allylic alcohol **49** (200 mg, 12.0 mmol, 1.0 equiv.), EDCI (563 mg, 2.90 mmol, 2.5 equiv.), and DMAP (43.0 mg, 0.350 mmol, 0.30 equiv.) in dichloromethane (10 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (15 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the dibromo ester **47** (213 mg, 46%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.76 (s, 1H), 4.65 (s, 2H), 3.99 (s, 4H), 2.50 (s, 3H), 2.32 (m, 4H), 1.81 (t, J_1 = 6.4 Hz, 2H).

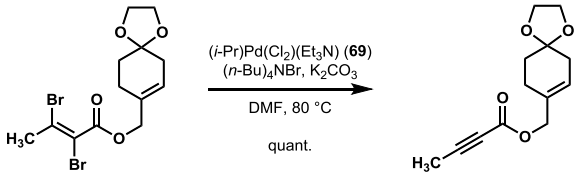
^{13}C NMR (100 MHz, $CDCl_3$), δ: 163.6, 131.8, 124.9, 122.3, 107.8, 107.7, 69.8, 64.6, 35.7, 30.9, 28.7, 25.3.

TLC (50% EtOAc–Hex), R_f: Dibromo Ester **47**: 0.80 (CAM).

General Procedure for the Heck Cyclization Reaction



To a dry, argon filled round-bottom flask, a mixture of ligand, proton scavenger, palladium source, and solvent was stirred at room temperature for 0.5-1 h, and then a solution of starting material in a small amount of solvent was added. After heating for an amount of time, the reaction was diluted with diethyl ether and saturated aqueous sodium bicarbonate solution. The resulting biphasic mixture was extracted with additional diethyl ether. The combined organic extracts were washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography to provide the product.



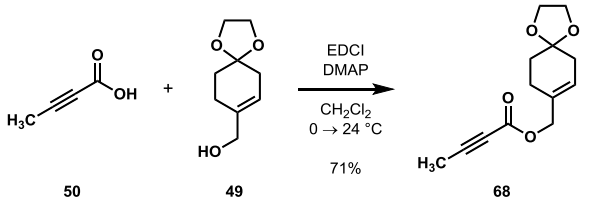
47 68

Alkyne Ester **68**:

The NHC precalalyst (*i*-Pr)Pd(Cl_2)(Et_3N) (**69**, 2.20 mg, 0.00330 mmol, 0.050 equiv.), (*n*-Bu)$_4$NBr (33.1 mg, 0.103 mmol, 1.5 equiv.), potassium carbonate (18.9 mg, 0.137 mmol, 2.0 equiv.), and *N*,*N*- dimethylformamide (0.8 mL) were added to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon the dibromo ester **47** (27.0 mg, 0.0682 mmol, 1.0 equiv.) in *N*,*N*-dimethylformamide (0.2 mL) was added. The mixture was degassed, and heated to 80 °C for 24 h. The resultant mixture was cooled to room temperature and was directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the alkyne ester **68** (17.0 mg, quant.) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.66 (s, 1H), 4.53 (s,2), 3.95 (s, 4H), 2.41 – 2.16 (m, 4H), 1.95 (s, 3H), 1.77 (t, J_1 = 6.5 Hz, 2H).

TLC (50% EtOAc–Hex), R_f: Alkyne Ester **68**: 0.78 (CAM).

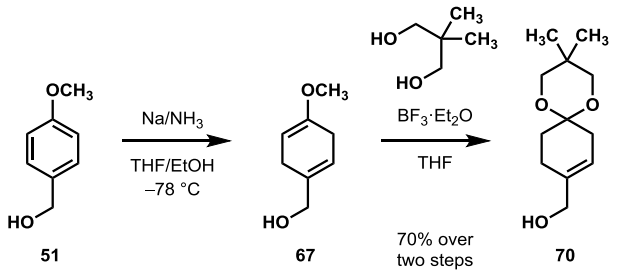


Alkyne Ester **68**:

A solution of the 2-butynoic acid **50** (82.0 mg, 0.980 mmol, 2.0 equiv.) in dichloromethane (2 mL) was added to a cooled (0 °C) solution of the allylic alcohol **49** (83.0 mg, 0.490 mmol, 1.0 equiv.), EDCI (280 mg, 1.50 mmol, 3.0 equiv.), and DMAP (20.0 mg, 0.160 mmol, 0.30 equiv.) in dichloromethane (15 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 50 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the alkyne ester **68** (83.0 mg, 71%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.66 (s, 1H), 4.53 (s,2), 3.95 (s, 4H), 2.41 – 2.16 (m, 4H), 1.95 (s, 3H), 1.77 (t, J_1 = 6.5 Hz, 2H).

TLC (50% EtOAc–Hex), R_f: Alkyne Ester **68**: 0.78 (CAM).



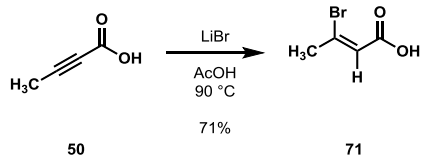
Allylic Alcohol **70**:

Sodium (3.50 g, 152 mmol, 3.5 equiv.) was added slowly over 30 min to a cooled (–78 °C) three-neck round-bottom flask fitted with cold finger (cooled to –78 °C) containing a mixture of anisyl alcohol **51** (6.00 g, 43.0 mmol, 1.0 equiv.), THF (16 mL), anhydrous ethanol (55 mL), and ammonia (82 mL). After stirring for 1 h at –78 °C, solid ammonium chloride (8 g) was added and the reaction mixture was allowed to slowly warm to room temperature over 2 h. (Caution! Gas evolution!). Water (50 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the allylic alcohol **67** (6.40 g) as a clear yellow oil which was used without further purification.

Boron trifluoride diethyl etherate (600 μL, 4.80 mmol, 0.15 equiv.) was added to a to a cooled (0 °C) mixture of the allylic alcohol **67** (3.00 g, 21.0 mmol, 1.0 equiv.) and neopentylglycol (3.50 g, 34.0 mmol, 1.6 equiv.) in THF (17 mL). Once the reaction was judged complete via TLC, the reaction was slowly quenched with saturated aqueous sodium bicarbonate (30 mL). The resulting biphasic mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30%

ethyl acetate–hexane) to provide the allylic alcohol **70** (3.66 g, 80%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	5.53 (s, 1H), 3.99 (s, 2H), 3.75 – 3.27 (m, 4H)., 2.38 (s, 2H), 2.16 – 2.09 (m, 2H), 2.06 – 1.94 (m, 2H), 1.03 (s, 3H), 0.90 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$), δ:	137.3, 119.3, 97.4, 70.4, 66.8, 34.9, 30.4, 27.1, 23.9, 22.9, 22.6.
LRMS $(ES)^+$:	Calcd. for $C_{12}H_{20}O_3H$ $[M + H]^+$: 213.15. Found: 213.13.
TLC (50% EtOAc–Hex), R_f:	Allylic Alcohol **70**: 0.50 (CAM).



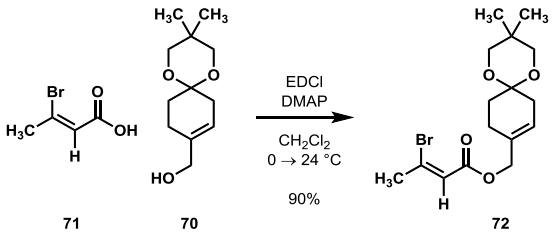
50 **71**

Monobromo Acid **71**:

2-Butynoic acid **50** (400 mg, 4.70 mmol, 1.0 equiv.), lithium bromide (410 mg, 4.80 mmol, 1.1 equiv.), and glacial acetic acid (5 mL) were added sequentially to a flask fitted with a reflux condenser, and then the mixture was heated to 90 °C for 24 h. The resultant mixture was cooled to room temperature and then as much acetic acid was removed by rotary evaporation as was possible. The residue was placed on silica gel and purified by flash column chromatography (50% ethyl acetate–hexane) to provide the monobromo acid **71** (356 mg, 71%) as a pale yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.35 (d, J_1 = 1.2 Hz, 1H), 2.51 (d, J_1 = 1.2 Hz, 3H).

TLC (80% EtOAc–Hex), R_f: Monobromo Acid **71**: 0.64 ($KMnO_4$).



71 70 72

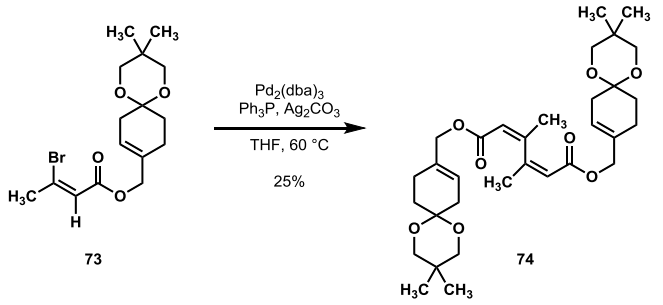
Monobromo Ester **72**.

A solution of the monobromo acid **71** (186 mg, 1.13 mmol, 1.2 equiv.) dissolved in dichloromethane (2.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **70** (200 mg, 0.942 mmol, 1.0 equiv.), EDCI (253 mg, 1.32 mmol, 1.4 equiv.), and DMAP (20.0 mg, 0.160 mmol, 0.14 equiv.) in dichloromethane (30 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 48 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the monobromo ester **72** (300 mg, 90%) as a clear, pale yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.20 (2, 1H), 5.50 (s, 1H), 4.41 (s, 2H), 3.58 – 3.25 (m, 4H), 2.34 (s, 3H), 2.27 (s, 2H), 2.05 – 1.96 (m, 2H), 1.96 – 1.73 (m, 2H), 0.90 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 164.1, 137.0, 132.4, 123.1, 120.0, 97.1, 70.4, 67.9, 34.8, 31.2, 30.4, 27.2, 24.3, 22.9, 22.6.

LRMS $(ES)^+$:	Calcd. for $C_{16}H_{23}BrO_4H_2O$ $[M + H]^+$: 359.09. Found: 259.08.
TLC (30% EtOAc–Hex), R_f:	Monobromo Ester **72**: 0.66 (CAM).



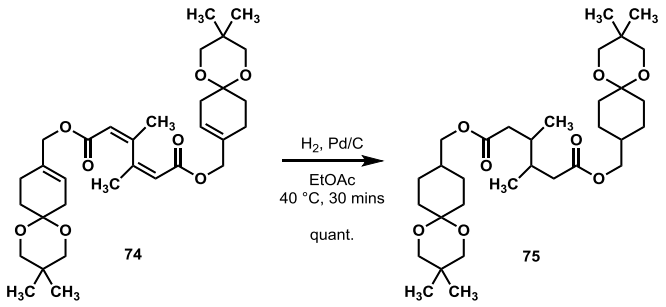
Dimer **74**:

Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 25.0 mg, 0.0273 mmol, 0.050 equiv.), triphenylphosphine (70.0 mg, 0.267 mmol, 0.45 equiv.), silver carbonate (300 mg, 1.09 mmol, 1.9 equiv.), and THF (4.0 mL) were added sequentially to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon the dibromo ester **47** (205 mg, 0.571 mmol, 1.0 equiv.) in THF (2.0 mL) was added. The mixture was degassed, and heated to 60 °C for 20 h. The resultant mixture was cooled to room temperature, concentrated, and residue was directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the dimer **74** (79.0 mg, 25%) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.74 – 5.49 (m, 4H), 4.57 – 4.36 (m, 4H), 3.67 – 3.40 (m, 8H), 2.42 – 2.37 (m, 4H), 2.22 (s, 3H), 2.15 – 2.07 (m, 4H), 2.03 – 1.94 (m, 7H), 1.03 (s, 6H), 0.92 (d, J_1 = 2.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$), δ: 167.9, 166.0, 164.9, 163.6, 160.3, 158.8, 157.9, 132.6, 132.4, 122.8, 122.7, 122.4, 116.3, 115.1, 108.1, 96.9, 96.9, 70.3, 67.6, 67.4, 67.2, 34.7,

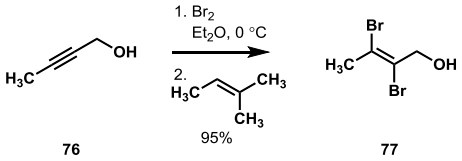
	34.7, 34.6, 30.2, 27.1, 27.0, 26.9, 24.6, 24.2, 24.1, 24.1, 22.7, 22.5, 21.7, 20.9, 17.9.
LRMS $(ES)^+$:	Calcd. for $C_{32}H_{46}O_8Na$ $[M + Na]^+$: 581.31. Found: 581.31.
TLC (30% EtOAc–Hex), R_f:	Dimer **74**: 0.54 (CAM).



Saturated Dimer **75**:

A balloon filled with hydrogen gas was bubbled into a solution of the unsaturated dimer **74** (26.6 mg, 0.0480 mmol, 1.0 equiv.), 5% palladium on carbon (40.0 mg, 0.20 equiv.), in ethyl acetate (5.0 mL). The mixture was heated to 40 °C for 30 min. The resultant mixture was cooled to room temperature, filtered with a pad of celite, and the pad was washed with ethyl acetate (10 mL). The filtrate was concentered and the residue was purified by flash chromatography (20% ethyl acetate–hexane) to provide the saturated dimer **75** (27.0 mg, quant.) as a clear, colorless oil.

LRMS $(ES)^+$: Calcd. for $C_{64}H_{108}O_{16}Na$ $[2M + Na]^+$: 1155.75.
Found: 1155.76.



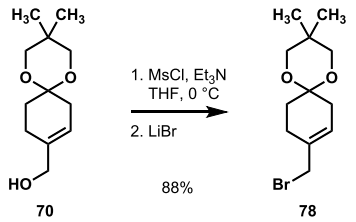
76 77

Dibromo Alcohol **77**:

Bromine (2.50 mL, 49.0 mmol, 1.2 equiv.) was added dropwise to a cooled (0 °C) solution of butyn-1-ol **76** (3.00 mL, 40.0 mmol, 1.0 equiv.) in diethyl ether (20 mL) and then stirred at that temperature for 1 h whereupon 2-methyl-2-butene (1.5 mL) was added. The red-orange mixture was warmed to room temperature. The resultant mixture was concentrated and the residue was purified by flash chromatography (20% ethyl acetate–hexane) to provide the dibromo alcohol **77** (9.00 g, 95%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.45 (s, 2H), 3.27 (br, 1H), 2.39 (s, 3H).

TLC (30% EtOAc–Hex), R_f: Dibromo Alcohol **77**: 0.74 ($KMnO_4$).

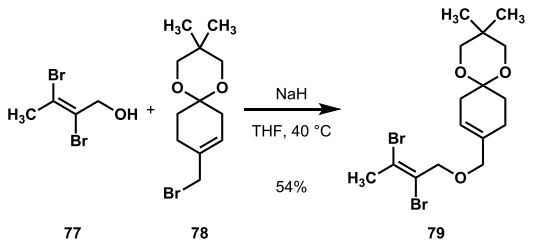


Allylic Bromide **78**:

Methanesulfonyl chloride (164 μL, 2.10 mmol, 1.5 equiv.) was added dropwise to cooled (0 °C) solution of the allylic alcohol **70** (300 mg, 1.40 mmol, 1.0 equiv.), and triethylamine (394 μL, 2.80 mmol, 2.0 equiv.) in THF (6 mL, 0.2 M) stirred for 1 h whereupon a solution of anhydrous lithium bromide (365 mg, 4.20 mmol, 3.0 equiv.) in THF (2.0 mL) was added. The resultant mixture was warmed to 23 °C and stirred for 4 h. The resultant mixture was diluted with water (5.0 mL) and the resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the allylic bromide **78** (345 mg, 88%) as a clear, colorless oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.70 (s, 1H), 3.93 (s, 2H), 3.69 – 3.40 (m, 5H), 2.38 (s, 2H), 2.30 – 2.20 (m, 2H), 2.00 (t, J_1 = 6.5 Hz, 3H), 1.02 (s, 3H), 0.90 (s, 3H).

TLC (50% EtOAc–Hex), R_f: Allylic Bromide **78**: 0.74 (CAM).

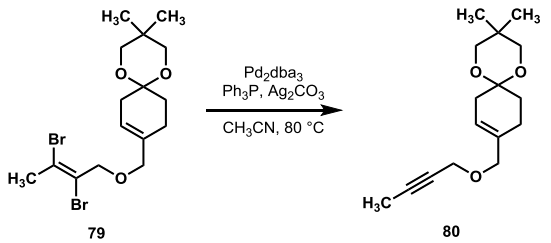


77 78 79

Dibromo Ether **79**:

Clean, dry sodium hydride (20.4 mg, 0.850 mmol, 1.4 equiv.) was added to a solution of the allylic alcohol **77** (166 mg, 0.720 mmol, 1.2 equiv.) in THF (6.0 mL) and stirred at 23 °C for 1 h whereupon the allylic bromide **78** (167 mg, 0.600 mmol, 1.0 equiv.) in THF (2 mL) was added. The mixture was heated to 40 °C for 15 h. The resultant mixture was diluted with a slow addition of water (5.0 mL) and diethyl ether (5 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the dibromo ether **79** (140 mg, 54%) as a clear, yellow oil.

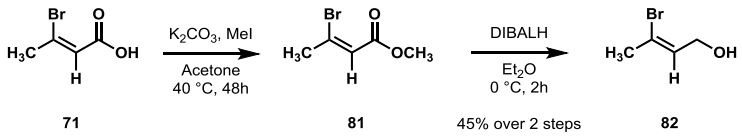
^{1}H NMR (300 MHz, $CDCl_3$), δ:	5.57 (s, 1H), 4.33 (s, 2H), 3.88 (s, 2H), 3.62 – 3.42 (m, 4H), 2.46 (s, 3H), 2.38 (s, 2H), 2.21–2.13 (m, 2H), 2.02 – 1.95 (m, 2H), 1.02 (s, 3H), 0.91 (s, 3H).
TLC (20% EtOAc–Hex), R_f:	Dibromo Ether **79**: 0.6 ($KMnO_4$).



Alkyne Ether **80**:

Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 3.50 mg, 0.00383 mmol, 0.050 equiv.), triphenylphosphine (8.50 mg, 0.0323 mmol, 0.42 equiv.), silver carbonate (45.0 mg, 0.164 mmol, 2.1 equiv.), and acetonitrile (1.0 mL) were added to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon the dibromo ether **79** (33.0 mg, 0.0778 mmol, 1.0 equiv.) in acetonitrile (0.5 mL) was added. The mixture was degassed and heated to 80 °C for 24 h. The resultant mixture was cooled to room temperature and was directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the alkyne ether **80** as a clear, colorless oil.

TLC (30% EtOAc–Hex), R_f: Alkyne Ether **80**: 0.71 (CAM).

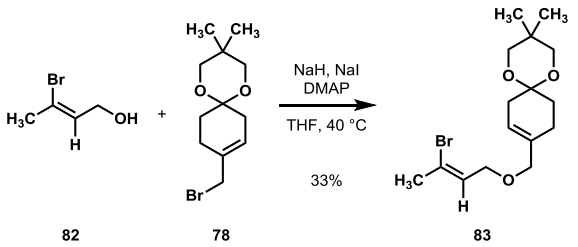


Monobromo Alcohol **82**:

Methyl iodide (1.50 mL, 24.0 mmol, 2.0 equiv.) was added to a solution of the monobromo acid **71** (2.00 g, 12.0 mmol, 1.0 equiv.), and potassium carbonate (1.85 g, 14.0 mmol, 1.1 equiv.) in acetone (15 mL) and the mixture was heated to 40 °C for 48 h. The resultant mixture was diluted with water (10 mL) and diethyl ether (20 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the monobromo ester **81** (3.05 g) as a clear yellow oil which was used without further purification.

Diisobutylaluminum hydride (0.30 M in heptane, 80.0 mL, 240 mmol, 1.5 equiv.) was added slowly to a cooled (0 °C) solution of the monobromo ester **81** (3.05 g, 17.0 mmol, 1.0 equiv.) in diethyl ether (100 mL) and stirred at that temperature for 2 h. The resultant mixture was carefully diluted with saturated aqueous potassium sodium tartrate solution (50 mL), warmed to room temperature, and stirred for 1 h. The resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% diethyl ether–pentane) to provide the monobromo alcohol **82** (0.800 mg, 45% over two steps) as a clear, colorless oil.

TLC (20% EtOAc–Hex), R_f: Monobromo Alcohol **82**: 0.17 (KMnO4).

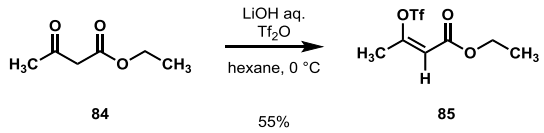


82 78 83

Monobromo Ether **83**:

Clean, dry sodium hydride (165 mg, 6.80 mmol, 6.0 equiv.) was added to a solution of the monobromo alcohol **82** (323 mg, 2.10 mmol, 1.9 equiv.) in THF (30 mL) and stirred for 2 h whereupon a solution of the allylic bromide **78** (313 mg, 1.10 mmol, 1.0 equiv.) in THF (2.0 mL), DMAP (10.0 mg, 0.0820 mmol, 0.080 equiv.), and sodium iodide (20.0 mg, 0.130 mmol, 0.12 equiv.) were added sequentially. The mixture was heated to 40 °C for 15 h. The resultant mixture was diluted with a slow addition of water (5.0 mL) and diethyl ether (5 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL) and the combined extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the monobromo ester **83** (250 mg, 30%) as a clear, colorless oil.

TLC (20% EtOAc–Hex), R_f: Ether **83**: 0.57 (CAM).



Triflate Ester **85**:

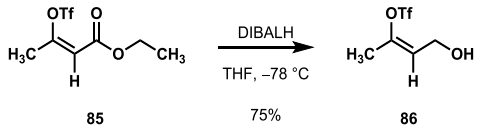
A saturated aqueous lithium hydroxide solution (12 mL) was added to a cooled (0 °C) solution of ethyl acetoacetate **84** (1.40 g, 11.0 mmol, 1.0 equiv.) in hexane (30 mL), and stirred for 10 min whereupon trifluoromethanesulfonic anhydride (4.50 mL, 27.0 mmol, 2.5 equiv.) was added dropwise. The resultant mixture was stirred for 10 min at 0 °C. When the reaction was judge complete via TLC, the mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL) and the combined extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the triflate ester **85** (1.50 g, 55%) as a clear, colorless oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.75 (dq, J_1 = 2.2, J_2 = 1.1 Hz, 1H), 4.23 (q, J_1 = 7.1 Hz, 2H), 2.15 (d, J_1 = 1.1 Hz, 3H), 1.29 (t, J_1 = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 162.4, 155.2, 112.9, 61.3, 21.0, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.7.

TLC (20% EtOAc–Hex), R_f: Triflate Ether **85**: 0.59 (CAM).



85 86

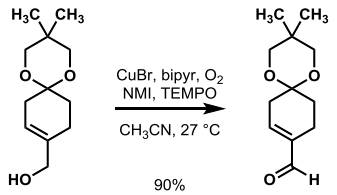
Triflate Alcohol **86**:

Diisobutylaluminum hydride (0.90 M in heptane, 16.0 mL, 18.0 mmol, 2.5 equiv.) was added slowly to a cooled (–78 °C) solution of the triflate ester **85** (1.50 g, 5.70 mmol, 1.0 equiv.) in THF (15 mL) and stirred at that temperature for 1 h. The resultant mixture was carefully diluted with saturated aqueous potassium sodium tartrate solution (30 mL), warmed to room temperature, and stirred for 1 h. The resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the triflate alcohol **86** (0.955 g, 75%) as a clear, colorless oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.54 (t, *J* = 6.9 Hz, 1H), 4.49 – 4.16 (m, 2H), 2.10 (s, 3H).

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.5.

TLC (20% EtOAc–Hex), R_f: Triflate Alcohol **86**: 0.22 ($KMnO_4$).



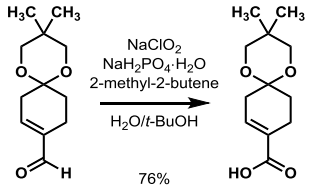
70 87

Aldehyde **87**:

To a solution of the allylic alcohol **70** (300 mg, 1.40 mmol, 1.0 equiv.) in acetonitrile (7.0 mL, 0.2 M) was added sequentially copper bromide (16.2 mg, 0.11 mmol, 0.080 equiv.), bipyridine (17.6 mg, 0.110 mmol, 0.080 equiv.), *N*-methyl imidazole (9.00 μL, 0.220 mmol, 0.16 equiv.), and TEMPO (17.6 mg, 0.110 mmol, 0.080 equiv.). Once combined, air was bubbled into the dark red mixture. The mixture was monitored via TLC until no starting material remained (the mixture changed in color to green-blue). The resultant mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the aldehyde **87** (267 mg, 90%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.41 (s, 1Hz, 1H), 6.64 – 6.57 (m, 1H), 3.64 – 3.36 (m, 1H), 2.62 (s, 2H), 2.27 (dt, J_1 = 4.5, 2.1 Hz, 2H), 2.02 – 1.95 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	193.2, 146.9, 140.8, 97.0, 70.4, 36.8, 30.2, 25.8, 22.9, 22.4, 19.5.
TLC (20% EtOAc–Hex), R_f:	Aldehyde **87**: 0.40 (CAM).



87 **88**

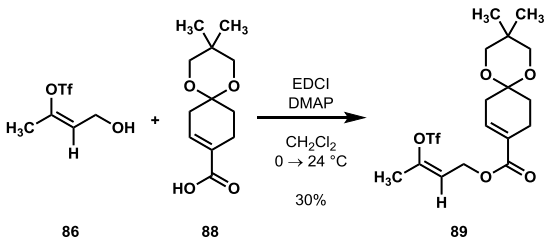
Acid **88**:

A solution of sodium chlorite (274 mg, 3.00 mmol, 1.2 equiv.) and sodium phosphate monobasic monohydrate (600 mg, 4.40 mmol, 1.8 equiv.) in water (5.0 mL) was slowly added to a solution of the aldehyde **87** (526 mg, 2.50 mmol, 1.0 equiv.) and 2,3-dimethyl-2-butene (3.0 mL) in *tert*-butyl alcohol (16 mL). The mixture was stirred at 23 °C for 24 h. The resultant mixture was concentrated to provide an aqueous solution. The aqueous solution was basified to pH 14 with 6 M aqueous sodium hydroxide solution and washed with hexane (2 x 10 mL). The aqueous solution was acidified to pH 1 with 6 N aqueous hydrochloride solution and then extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the acid **88** (430 mg, 76%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.00 – 6.92 (m, 1H), 3.65 – 3.40 (m, 4H), 2.56 (s, 2H), 2.43 – 2.34 (m, 2H), 2.09 – 1.95 (m, 2H), 1.05 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 172.1, 138.7, 129.4, 96.6, 70.5, 35.9, 30.3, 26.9, 22.9, 22.6, 22.3.

TLC (20% EtOAc–Hex), R_f: Acid **88**: 0.30 ($KMnO_4$).



86 88 89

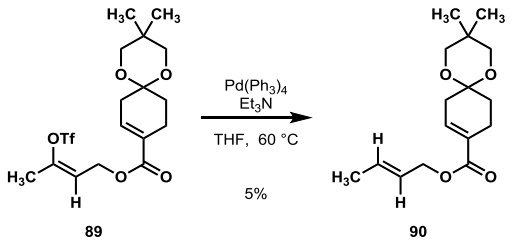
Triflate Ester **89**:

A solution of the acid **88** (350 mg, 1.50 mmol, 0.90 equiv.) in dichloromethane (4.0 mL) was added to a cooled (0 °C) solution of the triflate alcohol **86** (378 mg, 1.70 mmol, 1.0 equiv.), EDCI (500 mg, 2.60 mmol, 1.5 equiv.), and DMAP (25.0 mg, 0.20 mmol, 0.10 equiv.) in dichloromethane (20 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the triflate ester **89** (210 mg, 31%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.99 – 6.76 (m, 1H), 5.50 (td, J_1 = 6.9, 1.2 Hz, 1H), 4.72 (dd, J_1 = 6.9, 1.2 Hz, 2H), 3.71 – 3.37 (m, 4H), 2.58 – 2.51 (m, 2H), 2.44 – 2.35 (m, 2H), 2.12 (s, 3H), 2.00 (t, J_1 = 6.5 Hz, 2H), 1.05 (s, 3H), 0.91 (s, 3H).

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.4.

TLC (20% EtOAc–Hex), R_f: Triflate Ether **89**: 0.72 (CAM).



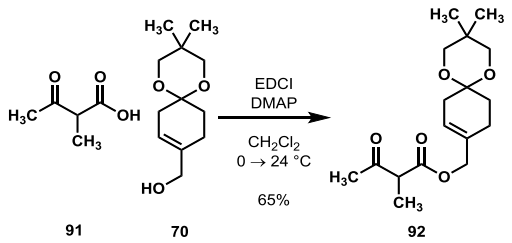
Ester **90**:

Tetrakis(triphenylphosphine)palladium(0) (16.1 mg, 0.0139 mmol, 0.20 equiv.), triethylamine (19.5 μL, 0.140 mmol, 2.0 equiv.), and THF (3.1 mL) were added sequentially to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon the triflate ether **89** (30.0 mg, 0.0700 mmol, 1.0 equiv.) in acetonitrile (1.0 mL) was added. The mixture was degassed and heated to 60 °C for 14 h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the ester **90** (1.00 mg, 5%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.83 – 6.77 (m, 1H), 6.46 – 6.25 (m, 1H), 5.59 (td, J_1 = 7.0, J_2 = 1.6 Hz, 1H), 4.48 (d, J_1 = 7.0 Hz, 2H), 3.63 – 3.42 (m, 4H), 2.54 – 2.49 (m, 2H), 2.43 – 2.35 (m, 2H), 1.99 (t, J_1 = 6.5 Hz, 2H), 1.88 (d, J_1 = 1.3, 3H), 1.04 (s, 3H), 0.91 (s, 3H).

HRMS $(CI)^+$: Calcd. for $C_{16}H_{24}O_4H$ $[M + H]^+$: 281.1753. Found: 281.1752.

TLC (20% EtOAc–Hex), R_f: Ester **90**: 0.73 (CAM).



91 **70** **92**

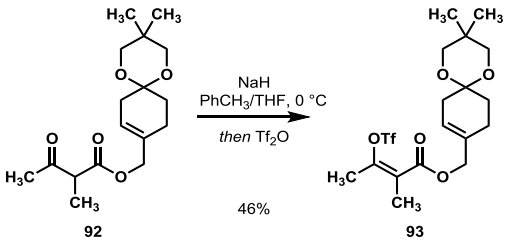
Ester **92**:

A solution of 2-methyl-3-oxobutanoic acid **91** (205 mg, 2.00 mmol, 1.0 equiv.) in dichloromethane (2.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **70** (639 mg, 3.01 mmol, 1.5 equiv.), EDCI (769 mg, 4.01 mmol, 2.0 equiv.), and DMAP (76.0 mg, 0.623 mmol, 0.2.0 equiv.) in dichloromethane (20 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the ester **92** (400 mg, 65%) as a colorless crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.55 (s, 1H), 4.48 (s, 2H), 3.58 – 3.35 (m, 5H), 2.39 – 2.27 (m, 2H), 2.18 (s, 3H), 2.09 – 2.00 (m, 2H), 1.99 – 1.85 (m, 2H), 1.31 –1.25 (m, 3H), 0.97 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 203.5, 170.3, 132.0, 123.1, 96.8, 70.3, 68.6, 53.6, 34.7, 30.2, 28.5, 27.0, 24.1, 22.8, 22.5, 12.8.

TLC (20% EtOAc–Hex), R_f: Ester **92**: 0.3 (CAM).



Triflate Ester **93**:

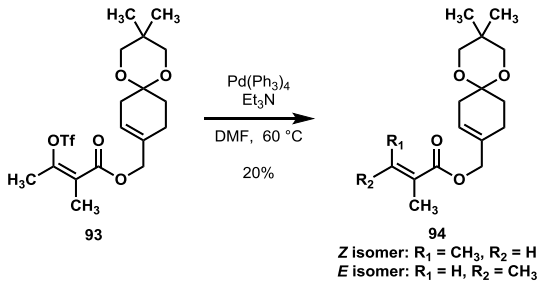
Clean, dry sodium hydride (28.0 mg, 1.16 mmol, 1.8 equiv.) was added to a cooled (0 °C) solution of the ester **92** (200 mg, 0.645 mmol, 1.0 equiv.) in toluene (2.0 mL) and THF (2.0 mL) and stirred for 1h whereupon trifluoromethanesulfonic anhydride (0.163 mL, 0.968 mmol, 1.5 equiv.) was added. The mixture was stirred at 0 °C for 1 h. The resultant mixture was carefully diluted with water (2.0 mL) and ethyl acetate (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the triflate ester **93** (143 mg, 46%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.60 (s, 1H), 4.57 (s, 2H), 3.62 – 3.38 (m, 4H), 2.37 (s, 2H), 2.12 – 2.08 (m, 5H), 2.00 – 1.91 (m, 5H), 1.00 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.1, 147.8, 131.9, 123.4, 121.8, 96.9, 70.3, 68.8, 34.8, 30.3, 27.0, 24.2, 22.8, 22.5, 17.7, 15.3.

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.7

TLC (20% EtOAc–Hex), R_f: Triflate Ester **93**: 0.33 ($KMnO_4$).



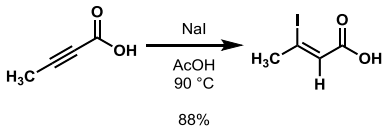
Triflate Ester **93**:

Tetrakis(triphenylphosphine)palladium(0) (45.0 mg, 0.0390 mmol, 0.20 equiv.), triethylamine (55.0 μL, 0.395 mmol, 2.0 equiv.), and *N*,*N*-dimethylformamide (1.5 mL) were added sequentially to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon the triflate ester **93** (88.0 mg, 0.199 mmol, 1.0 equiv.) in *N*,*N*-dimethylformamide (1.0 mL) was added. The mixture was degassed, and heated to 60 °C for 24 h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide a mixture of inseparable Z/E isomers of the ester **94** (11.0 mg, 20%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, mixture of Z/E isomers), δ: 6.97 (dq, J_1 = 3.8, J_2 = 1.9 Hz, 1H), 5.87 (dd, J_1 = 17.4, J_2 = 10.7 Hz, 1H), 5.69 – 5.50 (m, 2H), 4.58 – 4.35 (m, 4H), 3.65 – 3.40 (m, 8H), 2.39 (d, J_1 = 3.8 Hz, 5H), 2.32 (q, J_1 = 4.8 Hz, 3H), 2.16 – 2.03 (m, 6H), 1.98 (q, J_1 = 6.9 Hz, 5H), 1.03 (s, 6H), 0.92 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 174.2, 166.7, 139.6, 137.2, 132.8, 132.4, 129.6, 122.3, 121.9, 115.4, 97.1, 70.4, 68.2, 67.7, 47.5,

	34.9, 34.7, 32.3, 30.4, 29.7, 27.3, 27.1, 24.3, 24.2, 22.9, 22.7, 21.9.
TLC (20% EtOAc–Hex), R_f:	Ester **94**: 0.24 (CAM).



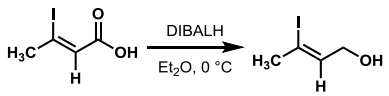
50 **95**

Iodo Acid **95**:

2-Butynoic acid **50** (500 mg, 5.95 mmol, 1.0 equiv.), sodium iodide (1.07 g, 7.13 mmol, 1.2 equiv.), and glacial acetic acid (5 mL) were added sequentially to a flask fitted with a reflux condenser, and heated to 90 °C for 24 h. The resultant mixture was cooled to room temperature and then as much acetic acid was removed by rotary evaporation as was possible. The residue was placed on silica gel and purified by flash column chromatography (50% ethyl acetate–hexane) to provide the iodo acid **95** (1.16 g, 88%) as an off-white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.41 (s, 1H), 6.62 – 5.98 (m, 1H), 2.76 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Iodo Acid **95**: 0.38 ($KMnO_4$).



34%

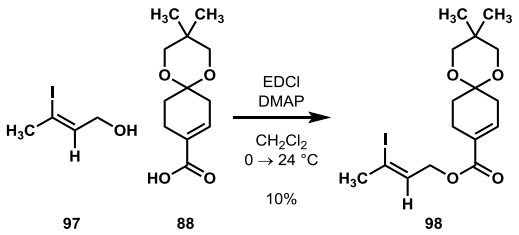
95 **97**

Allylic Alcohol **97**:

Diisobutylaluminum hydride (12.0 mL, 5.81 mmol, 1.5 equiv.) was slowly added to a cooled (0 °C) solution of the iodo acid **95** (1.12 g, 3.88 mmol, 1.0 equiv.) in diethyl ether (20 mL) and stirred for 1 h. The resultant mixture was carefully diluted with saturated aqueous potassium sodium tartrate solution (30 mL) and stirred for 1 h. The resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the allylic alcohol **97** (353 mg, 34%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.78 (t, J_1 = 6.0, Hz, 1H), 4.29 – 3.98 (m, 2H), 2.54 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Allylic Alcohol **97**: 0.62 ($KMnO_4$).



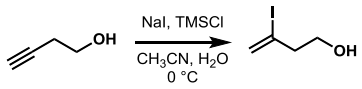
97 88 98

Iodo Ester **98**:

A solution of the acid **88** (268 mg, 1.18 mmol, 1.0 equiv.) in dichloromethane (2.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **97** (353 mg, 1.78 mmol, 1.5 equiv.), EDCI (389 mg, 2.03 mmol, 2.0 equiv.), and DMAP (30.0 mg, 0.246 mmol, 0.20 equiv.) in dichloromethane (15 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the iodo ester **98** (43.0 mg, 10%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.84 (dq, J_1 = 3.9, J_2 = 1.9 Hz, 1H), 5.75 (tt, J_1 = 5.0, J_2 = 4.4, J_3 = 1.6 Hz, 1H), 4.63 (d, J_1 = 6.1, Hz, 2H), 3.80 – 3.26 (m, 4H), 2.55 – 2.50 (m, 5H), 2.44 – 2.36 (m, 2H), 2.00 (t, J_1 = 6.5 Hz, 2H), 1.04 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	166.6, 136.5, 130.3, 129.7, 104.2, 96.6, 70.5, 68.8, 35.8, 33.9, 30.3, 26.8, 22.9, 22.7, 22.6.
TLC (20% EtOAc–Hex), R_f:	Iodo Ester **98**: 0.48 (CAM).



99 34% **100**

Homoallylic Alcohol **100**:

Followed literature procedure for the monoallylic alcohol[3]:

Trimethylchlorosilane (2.16 mL, 17.0 mmol, 2.0 equiv.) as added to a solution of sodium iodide (2.54 g, 17.0 mmol, 2.0 equiv.) in acetonitrile (15 mL) and water (0.15 mL) and stirred for 15 min whereupon but-3-yn-1-ol **99** (0.640 mL, 8.47 mmol, 1.0 equiv.) was slowly added and stirred for 1 h. The resultant mixture was diluted with water (15 mL) and diethyl ether (15 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the homoallylic alcohol **100** (571 mg, 34%) as a pale yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.13 – 5.96 (m, 1H), 5.73 (dd, J_1 = 1.5, J_2 = 1.0 Hz, 1H), 3.71 – 3.55 (m, 2H), 3.32 (s, 1H), 2.53 (tt, J_1 = 6.0, J_2 = 1.0 Hz, 2H).

TLC (20% EtOAc–Hex), R_f: Homoallylic Alcohol **100**: 0.36 ($KMnO_4$).

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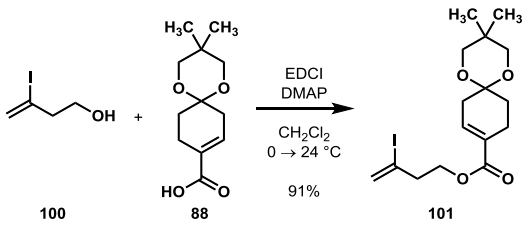
3. Brooks, J. L.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 16551.

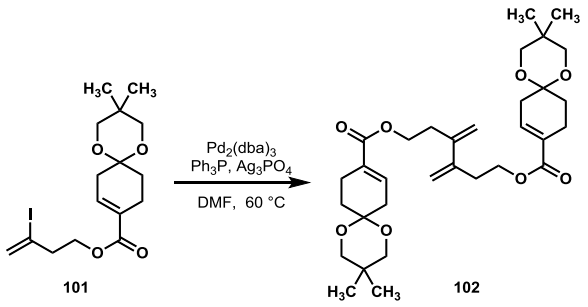


Iodo Ester **101**:

A solution of the acid **88** (264 mg, 1.17 mmol, 1.0 equiv.) in dichloromethane (2.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **100** (571 mg, 2.88 mmol, 2.5 equiv.), EDCI (690 mg, 3.60 mmol, 3.0 equiv.), and DMAP (58.0 mg, 0.475 mmol, 0.41 equiv.) in dichloromethane (15 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the iodo ester **101** (436 mg, 91%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.74 – 6.70 (m, 1H), 6.03 (d, J_1 = 1.5 Hz, 1H), 5.88 – 5.56 (m, 1H), 4.14 (t, J_1 = 6.3 Hz, 2H), 3.62 – 3.26 (m, 4H), 2.70 – 2.58 (m, 2H), 2.45 – 2.40 (m, 2H), 2.33 – 2.25 (m, 2H), 1.90 (t, J_1 = 6.5 Hz, 3H), 0.95 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	166.6, 136.3, 129.8, 128.5, 128.1, 105.9, 96.6, 70.5, 62.7, 44.5, 35.8, 30.3, 26.8, 22.9, 22.7, 22.6.
TLC (20% EtOAc–Hex), R_f:	Iodo Ester **101**: 0.37 (CAM).



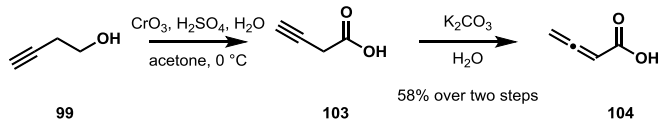
Dimer **102**:

Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 6.76 mg, 0.00732 mmol, 0.010 equiv.), triphenylphosphine (7.90 mg. 0.0301 mmol, 0.41 equiv.), silver phosphate (61.7 mg, 0.148 mmol, 2.0 equiv.), and *N*,*N*-dimethylacetamide (2.0 mL) were added sequentially to a round–bottom flask, the solution was degassed, and stirred for 20 min whereupon a solution of the iodo ester **101** (30.0 mg, 0.0740 mmol, 1.0 equiv.) in *N*,*N*-dimethylacetamide (1.0 mL) was added. The mixture was degassed and heated to 60 °C for 40 h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the dimer **102** as a colorless crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.81 (dt, J_1 = 4.1, J_2 = 2.3 Hz, 2H), 5.23 (s, 2H), 5.07 (s, 2H), 4.35 – 3.90 (m, 4H), 3.70 – 3.36 (m, 8H), 2.61 (t, J_1 = 7.1 Hz, 4H), 2.52 (dd, J_1 = 4.2, J_2 = 2.3 Hz, 4H), 2.38 (tt, J_1 = 4.2, J_2 = 2.1 Hz, 4H), 1.99 (t, J_1 = 6.5 Hz, 4H), 1.04 (s, 6H), 0.91 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 166.8, 142.7, 136.0, 130.0, 114.6, 96.7, 70.5, 63.4, 35.8, 33.4, 30.3, 26.9, 22.9, 22.7, 22.6.

TLC (20% EtOAc–Hex), R_f: Dimer **102**: 0.32 (CAM).



Allene **104**:

Jones reagent (CrO_3 in H_2SO_4, 1.36 M, 21.0 mL, 29.0 mmol, 2.0 equiv.) was slowly added to a cooled (0 °C) solution of 2,3-butnyol **99** (1.02 g, 14.3 mmol, 1.0 equiv.) in acetone (50 mL) until the mixture maintained a yellow-orange color. The mixture was stirred for an additional 10 min then carefully quenched with isopropanol (10 mL). The resultant mixture was diluted with water (20 mL) and diethyl ether (10 mL) The resulting biphasic mixture was extracted with diethyl ether (5 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered, the filtrate was concentrated to provide the acid **103** as a colorless crystalline solid which was used without further purification.

A solution of aqueous potassium carbonate (0.724 M, 20.0 mL) was added to the acid **103** and stirred at 23 °C for 20 h. The resultant mixture was acidified to pH 1 with 3 N aqueous hydrogen chloride solution and the resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered, the filtrate was concentrated to provide the allene **104** (712 mg, 58% over two steps) as a colorless crystalline solid which was used without further purification.

Acid **103**:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.37 (d, J_1 = 2.7 Hz, 2H), 2.24 (t, J_1 = 2.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.3, 74.9, 72.5, 25.7.

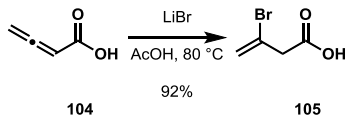
TLC (20% EtOAc–Hex), R_f: Acid **103**: 0.0.40 ($KMnO_4$).

Allene **104**:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.74 – 5.59 (m, 1H), 5.29 (d, J_1 = 6.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 217.1, 87.8, 79.8.

TLC (20% EtOAc–Hex), R_f: Allene **104**: 0.40 ($KMnO_4$).



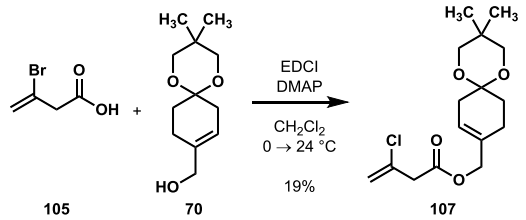
104 105

Bromo Acid **105**:

The allene **104** (200 mg, 2.38 mmol, 1.0 equiv.), lithium bromide (300 mg, 3.49 mmol, 1.5 equiv.), and glacial acetic acid (7.0 mL) were added sequentially to a flask fitted with a reflux condenser, and heated to 80 °C for 9 h. The resultant mixture was cooled to room temperature and as much of the acetic acid was removed by rotary evaporation as was possible. The residue was placed on silica gel and purified by flash column chromatography (50% ethyl acetate–hexane) to provide the bromo acid **105** (364 mg, 92%) as an off-white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.71 (dt, J_1 = 2.0, J_2 = 1.0 Hz, 1H), 5.57 (dd, J_1 = 2.0, J_2 = 0.5 Hz, 1H), 3.45 (d, J_1 = 1.0 Hz, 2H).

TLC (40% EtOAc–Hex), R_f: Bromo Acid **105**: 0.25 ($KMnO_4$).

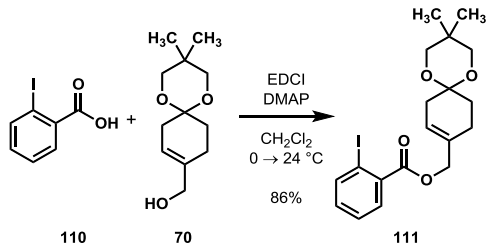


Chloro Ester **107**:

A solution of the bromo acid **105** (274 mg, 1.66 mmol, 1.0 equiv.) in dichloromethane (5.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **70** (423 mg, 2.00 mmol, 1.2 equiv.), EDCI (447 mg, 2.33 mmol, 1.4 equiv.), and DMAP (60.0 mg, 0.492 mmol, 0.30 equiv.) in dichloromethane (15 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 5 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the chloro ester **107** (119 mg, 19%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.60 (s, 1H), 5.42 – 5.29 (m, 1H), 4.51 (s, 2H), 3.70 – 3.39 (m, 4H), 3.35 (s, 2H), 2.37 (s, 2H), 2.15 – 2.04 (m, 2H), 2.00 – 1.92 (m, 2H), 1.00 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δ:	168.6, 134.3, 132.1, 131.7, 123.8, 123.0, 116.7, 96.9, 96.9, 70.3, 69.0, 68.5, 44.7, 34.8, 34.7, 30.3, 27.1, 27.0, 24.1, 24.1, 22.8, 22.5.
TLC (20% EtOAc–Hex), R_f:	Chloro Ester **107**: 0.28 (CAM).

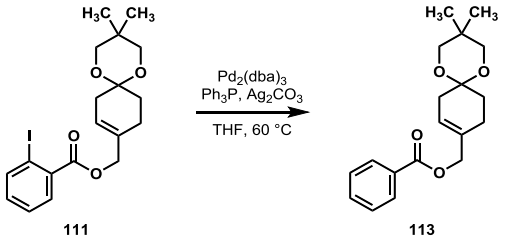


Iodo Ester **111**:

2-Iodobenzoic acid **110** (643 mg, 2.59 mmol, 1.0 equiv.) in dichloromethane (5.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **70** (825 mg, 3.89 mmol, 1.5 equiv.), EDCI (847 mg, 4.42 mmol, 1.1 equiv.), and DMAP (34.8 mg, 0.285 mmol, 0.11 equiv.) in dichloromethane (10 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the iodo ester **111** (994 mg, 92%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.98 (dt, J_1 = 7.9, J_2 = 1.0 Hz, 1H), 7.80 (dd, J_1 = 7.8, J_2 = 1.8 Hz, 1H), 7.40 (td, J_1 = 7.6, J_2 = 1.0 Hz, 1H), 7.22 – 7.09 (m, 1H), 5.72 (dq, J_1 = 2.9, J_2 = 1.5 Hz, 1H), 4.74 (s, 2H), 3.82 – 3.27 (m, 5H), 2.63 – 2.34 (m, 3H), 2.23 (s, 2H), 2.15 – 1.86 (m, 3H), 1.04 (s, 3H), 0.93 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Iodo Ester **111**: 0.0.68 (CAM).

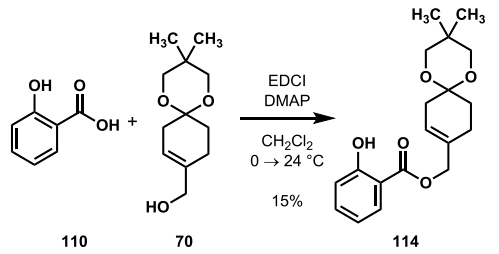


Ester **113**:

Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 3.10 mg, 0.00339 mmol, 0.050 equiv.), triphenylphosphine (2.30 mg. 0.00878 mmol, 0.41 equiv.), silver carbonate (36.9 mg, 0.134 mmol, 2.0 equiv.), and THF (0.8 mL) were added sequentially to a round-bottom flask, the solution was degassed, and stirred for 20 min whereupon a solution of the iodo ester **111** (30.0 mg, 0.0678 mmol, 1.0 equiv.) in THF (0.5 mL) was added. The mixture was degassed and heated to 60 °C for 22 h. the resultant mixture was cooled to room temperature and directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the ester **113** as a colorless crystalline solid

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (dt, J_1 = 8.2, J_2 = 1.1 Hz, 2H), 7.65 – 7.50 (m, 1H), 7.50 – 7.39 (m, 2H), 5.69 (s, 1H), 4.73 (s, 2H), 3.65 – 3.44 (m, 4H), 2.44 (s, 2H), 2.20 (d, J_1 = 6.9 Hz, 2H), 2.03 (t, J_1 = 6.4 Hz, 2H), 1.04 (s, 3H), 0.93 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Ester **113**: 0.41(CAM).



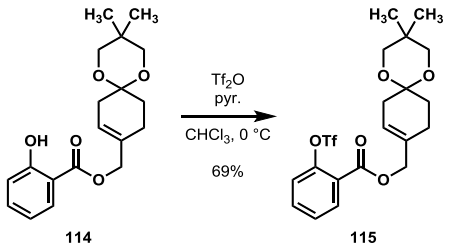
110 70 114

Phenol Ester **114**:

A solution of salicylic acid **110** (260 mg, 1.88 mmol, 1.0 equiv.) in dichloromethane (4.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **70** (500 mg, 2.36 mmol, 1.3 equiv.), EDCI (539 mg, 2.81 mmol, 1.5 equiv.), and DMAP (34.0 mg, 0.279 mmol, 0.15 equiv.) in dichloromethane (10 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the phenol ester **114** (88.0 mg, 15%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 10.77 (d, J_1 = 1.0 Hz, 1H), 7.85 (dt, J_1 = 8.0, J_2 = 1.3 Hz, 1H), 7.44 (dddd, J_1 = 8.3, J_2 = 7.2, J_3 = 1.8, J_4 = 0.9 Hz, 1H), 6.97 (dd, J_1 = 8.4, J_2 = 1.1 Hz, 1H), 6.87 (ddt, J_1 = 8.2, J_2 = 7.2, J_3 = 1.1 Hz, 1H), 5.70 (s, 1H), 4.92 – 4.56 (m, 2H), 3.89 – 3.37 (m, 4H), 2.48 – 2.40 (m, 2H), 2.25 – 2.15

	(m, 2H), 2.09 – 1.99 (m, 2H), 1.04 (s, 3H), 0.93 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	170.0, 161.8, 135.8, 132.1, 130.1, 123.2, 119.2, 117.7, 112.6, 97.0, 70.4, 68.5, 34.8, 30.4, 27.2, 24.3, 22.9, 22.6.
TLC (20% EtOAc–Hex), R_f:	Phenol Ester **114**: 0.45 (CAM).



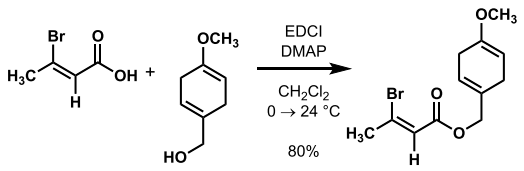
114 115

Triflate Ester **115**:

Trifluoromethanesulfonic anhydride (0.053 mL, 0.315 mmol, 1.2 equiv.) was added dropwise to a cooled (0 °C) solution of the phenol ester **114** (88.0 mg, 0.265 mmol, 1.0 equiv.) and pyridine (0.042 mL, 0.521 mmol, 2.0 equiv.) in dichloromethane (1.0 mL) and stirred at 0 °C for 4 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (1.0 mL) and diluted with diethyl ether (5 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the triflate ester **115** (85.0 mg, 69%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.07 (dd, J_1 = 7.8, J_2 = 1.8 Hz, 1H), 7.68 – 7.56 (m, 1H), 7.46 (td, J_1 = 7.6, J_2 = 1.2 Hz, 1H), 7.30 (d, J_1 = 8.2 Hz, 1H), 5.70 (s, 1H), 4.81 – 4.73 (m, 2H), 3.66 – 3.42 (m, 4H), 2.47 – 2.36 (m, 2H), 2.26 – 2.12 (m, 2H), 2.01 (t, J_1 = 6.4 Hz, 2H), 1.03 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	163.6, 148.5, 134.3, 132.7, 132.0, 128.5, 124.8, 123.8, 122.8, 116.7, 97.0, 70.4, 69.3, 34.9, 30.3, 27.1, 24.3, 22.9, 22.6.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–73.3.
TLC (20% EtOAc–Hex), R_f:	Triflate Ester **115**: 0.45 (CAM).



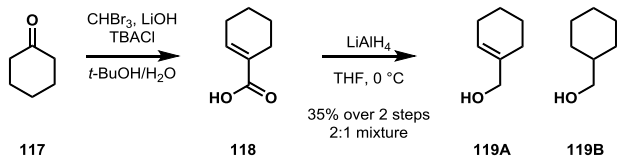
71 60 116

Monobromo Ester **116**:

A solution of the monobromo acid **71** (217 mg, 1.32 mmol, 1.1 equiv.) in dichloromethane (5.0 mL) was added to a cooled (0 °C) solution of the allylic alcohol **60** (170 mg, 1.21 mmol, 1.0 equiv.), EDCI (239 mg, 1.25 mmol, 1.0 equiv.), and DMAP (23.0 mg, 0.189 mmol, 0.16 equiv.) in dichloromethane (10 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the monobromo ester **116** (282 mg, 80%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.36 – 6.22 (m, 1H), 5.82 – 5.55 (m, 1H), 4.66 – 4.62 (m, 1H), 4.59 (s, 3H), 3.55 (s, 4H), 3.06 – 2.63 (m, 4H), 2.47 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Monobromo Ester **116**: 0.80 (CAM).



Allylic Alcohols **119A** and **119B**:

Followed literature procedure for acid **118**[4]:

Bromoform (3.67 mL, 42.4 mol, 4.0 equiv.) was slowly added to a cooled (0 °C) solution of cyclohexanone **117** (1.00 g, 10.5 mmol, 1.0 equiv.), *n*-tetrabutylammonium chloride (282 mg, 1.01 mmol, 0.10 equiv.), and lithium hydroxide monohydride (8.82 g, 210 mol, 20 equiv.) in *t*-BuOH/water (5:1 ratio, 48 mL total) and stirred for 24 h. The resultant mixture was slowly diluted until the pH was 1 with 3 N aqueous hydrogen chloride solution. The resulting biphasic mixture was extracted with toluene (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the acid **118** (1.13 g) as a clear, colorless oil which was used without further purification.

A solution of the acid **118** (1.13 g, 8.97 mol, 1.0 equiv.) in THF (10 mL) was slowly added to a cooled (0 °C) solution of lithium aluminum hydride (1.71 g, 45.1 mol, 5.0 equiv.) in THF (20 mL) and stirred for 3 h while warming to 23 °C. The resultant mixture was carefully quenched with saturated aqueous ammonium chloride solution (5.0 mL), then diluted with additional water (20 mL) and ethyl acetate (20 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL).

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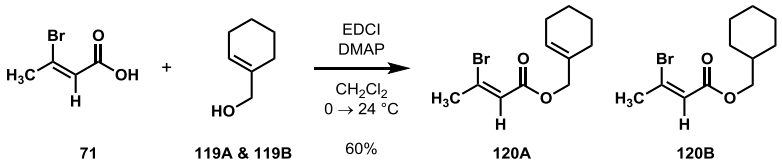
4. Vitnik, V. D.; Ivanovic, M. D.; Vitnik, Z. J.; Dordevic, J. B.; Zizak, Z. S.; Juranic, Z. D.; Juranic, I. O. *Synth. Commun*. **2009**, *39*, 1457.

The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide an inseparable mixture of the allylic alcohols **119A** and **119B** (405 mg, 35%, 2:1 mixture) as a clear, colorless oil.

Allylic alcohols **119A** and **119B** were isolated as a mixture of reduction products; pound denotes **119A** and **119B** mixture of peaks, and asterisk denotes **119B** peaks alone.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	5.66 (s, 1H), 3.96 (s, 2H), 3.41* (d, J_1 = 6.6 Hz, 1H), 1.99$^{\#}$ (s, 4H), 1.86 – 1.45$^{\#}$ (m, 8H), 1.38 – 1.05$^{\#}$ (m, 2H), 0.93* (t, J_1 = 11.8 Hz, 1H).
TLC (30% EtOAc–Hex), R_f:	Allylic Alcohols **119A** and **119B**: 0.40 ($KMnO_4$).



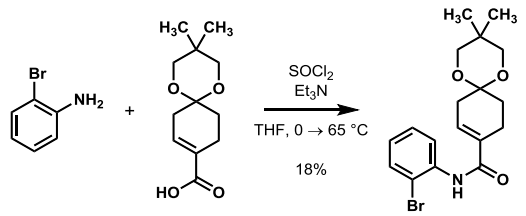
Monobromo Esters **120A** and **120B 93**:

A solution of the monobromo acid **71** (392 mg, 2.39 mmol, 1.0 equiv.) in dichloromethane (5.0 mL) was added to a cooled (0 °C) solution of the allylic alcohols **119A** and **119B** (400 mg, 1.5 equiv.), EDCI (801 mg, 4.18 mmol, 1.1 equiv.), and DMAP (30.0 mg, 0.246 mmol, 0.10 equiv.) in dichloromethane (20 mL). After 30 min, the reaction was removed from the ice bath and stirred at 24 °C for 24 h. The resultant mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide an inseparable mixture of the monobromo esters **120A** and **120B** (368 mg, 60%) as a clear, colorless oil.

Monobromo esters **120A** and **120B** were isolated as a mixture; pound denotes **120A** and **120B** mixture of peaks, and asterisk denotes **120b** peaks alone.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.31$^{\#}$ (s, 2H), 5.77* (s, 1H), 4.52 (s, 2H), 3.96* (d, J_1 = 6.5 Hz, 1H), 2.46$^{\#}$ (s, 5H), 2.13 – 1.95$^{\#}$ (m, 4H), 1.83 – 1.48$^{\#}$ (m, 8H), 1.36 – 1.12* (m, 2H), 1.00* (t, J_1 = 11.4 Hz, 1H).

TLC (30% EtOAc–Hex), R_f: Monobromo Ester **120A** and **120B**: 0.81 (CAM).



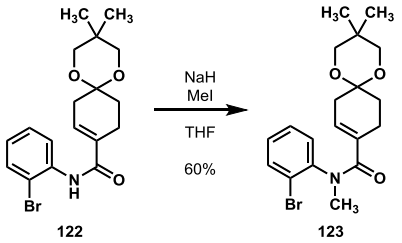
121 88 122

Amide **122**:

Sodium hydride (50% suspension in oil, 86.0 mg, 1.79 mmol, 1.1 equiv.) was added to a cooled (0 °C) solution of the acid **88** (430 mg, 1.90 mmol, 1.0 equiv.) in THF (2.5 mL) and stirred at 0 °C for 1 h whereupon thionyl chloride (0.152 mL, 2.09 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred at 0 °C for 1 h whereupon a solution of 2-bromoaniline **121** (0.226 mL, 2.00 mmol, 1.0 equiv.) and triethylamine (0.278 mL, 2.00 mmol, 1.1 equiv.) in THF (3.0 mL) was added. The mixture was heated to reflux for 4 h. The resultant mixture was cooled to room temperature and diluted with water (5.0 mL) and diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the amide **122** (130.0 mg, 18%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.37 (dd, J_1 = 8.3, J_2 = 1.5 Hz, 1H), 7.99 (s, 1H), 7.47 (dd, J_1 = 8.0, J_2 = 1.4 Hz, 1H), 7.25 (ddd, J_1 = 8.6, J_2 = 7.5, J_3 = 1.5 Hz, 1H), 6.90 (ddd, J_1 = 8.2, J_2 = 7.3, J_3 = 1.5 Hz, 1H), 6.82 – 6.43 (m, 1H), 3.78 – 3.30 (m, 4H), 2.51 (ddt, J_1 = 18.0, J_2

	= 6.4, J_3 = 2.1 Hz, 4H), 2.03 (t, J_1 = 6.4 Hz, 2H), 1.00 (s, 3H), 0.89 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	171.0, 165.3, 135.8, 133.2, 132.1, 131.5, 128.4, 124.9, 121.7, 113.6, 96.4, 70.3, 60.3, 35.2, 30.2, 27.1, 22.7, 22.7, 22.4, 21.0, 14.2.
TLC (20% EtOAc–Hex), R_f:	Amide **122**: 0.37 (CAM).



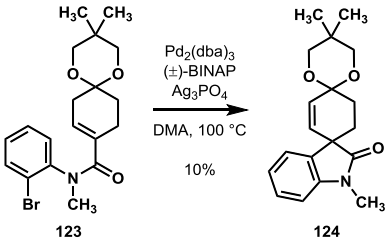
122 123

Amide **123**:

Sodium hydride (50% suspension in oil, 24.0 mg, 0.500 mmol, 1.5 equiv.) was added to a solution of the amide **122** (130 mg, 0.342 mmol, 1.0 equiv.) in THF (5.0 mL) and stirred for 10 min whereupon methyl iodide (0.053 mL, 0.851 mmol, 2.5 equiv.) was added. The mixture was stirred for 2 h. The resultant mixture was slowly diluted with water (3.0 mL) and diethyl ether (5.0 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the amide **123** (80.0 mg, 60%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.57 (dd, J_1 = 8.2, J_2 = 1.5 Hz, 1H), 7.26 (td, J_1 = 7.5, J_2 = 1.5 Hz, 1H), 7.12 (ddd, J_1 = 8.1, J_2 = 6.3, J_3 = 1.8 Hz, 2H), 5.66 (bs, 1H), 3.33 (td, J_1 = 18.3, J_2 = 15.6, J_3 = 7.2 Hz, 4H), 3.20 (s, 3H), 2.20 – 2.09 (s, 4H), 1.84 – 1.66 (s, 2H), 0.86 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	171.7, 133.7, 133.7, 129.9, 128.9, 128.4, 122.7, 96.3, 70.1, 36.6, 33.6, 30.1, 28.0, 24.3, 22.7, 22.7.
TLC (20% EtOAc–Hex), R_f:	Amide **123**: 0.10 (CAM).



Lactam **124**:

Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 9.28 mg, 0.0101 mmol, 0.050 equiv.), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((±)-BINAP, 14.7 mg, 0.0222 mmol, 0.11 equiv.), silver phosphate (169 mg, 0.404 mmol, 2.0 equiv.), and *N*,*N*-dimethylacetamide (1.0 mL) were added sequentially to a round-bottom flask, the solution was degassed, and stirred for 20 min. The solution changed in color during this time: cloudy yellow to cloudy red. After 20 min, a solution of the amide **123** (80.0 mg, 0.203 mmol, 1.0 equiv.) in *N*,*N*-dimethylacetamide (1.0 mL) was added, the mixture was degassed, and heated to 100 °C for 24 h. During the course of the reaction the color of the reaction changed; cloudy red to black. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (20% ethyl acetate–hexane) to provide the lactam **124** (6.00 mg, 10%) as a colorless crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.34 – 7.13 (m, 4H), 7.04 (td, J_1 = 7.5, J_2 = 1.0 Hz, 1H), 6.84 (d, J_1 = 7.9 Hz, 1H), 6.48 (d, J_1 = 10.2 Hz, 1H), 5.45 (d, J_1 = 10.2 Hz, 1H), 3.84 – 3.51 (m, 4H), 3.21 (s, 3H), 2.61 – 2.38 (m, 1H), 2.30 – 2.10 (m, 2H), 2.04 – 1.88 (m, 1H), 1.07 (s, 3H), 0.98 (s, 3H).

HRMS $(ES)^+$:	Calcd. for $C_{19}H_{23}NO_3Na$ $[M + Na]^+$: 336.1576. Found: 336.1570.
TLC (20% EtOAc–Hex), R_f:	Lactam 1**24**: 0.27 (CAM).

Chapter 2

ANILINE *N*-OXIDE FUNCTIONALIZATION

2.1 Discovery of the Rearrangements

The synthesis of nitrogen-containing natural products and synthetic derivatives lead to the development of a general method to functionalize anilines. Several natural product total synthesis projects in the Chain laboratory make use of an enolate–*ortho*-quinone methide (*o*-QM) coupling reaction. The scope of the enolate–*ortho*-quinone methide reaction has been described in detail (**Figure 2.1**).[1] In this single pot reaction, a mixture of the silyl enol ether **125** and silyl-protected phenolic benzyl halide **126** reveal the enolates **127** and *ortho*-quinone methides **128**, respectively, upon treatment with anhydrous fluoride. The enolate then adds to the *ortho*-quinone methides in a Michael addition to give the ketophenoxide **129**, thus restoring aromaticity.

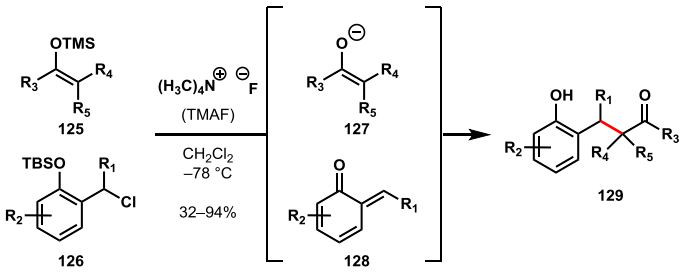


Figure 2.1 Enolate–*ortho*-Quinone Methide Reaction

The Chain laboratory is interested in the synthesis of nitrogen-containing natural products and synthetic derivatives and thus we require convenient access to anilines, aminophenols, and other substituted aromatic amines. We were interested in generating an enolate–aza-ortho-xylylene (AOX) coupling reaction analogous to our enolate-OQM reaction in order to gain access to nitrogen containing derivatives. Investigations to access AOX intermediates like **131** began with the direct adaptation of our OQM protocols; treatment of the silylated aniline **130** with anhydrous fluoride (**Figure 2.2**) was expected to expel a benzylic leaving group and generate the aza-ortho-xylylene in situ. Treatment of **130** with fluoride at –78 °C indeed cleaved the TBS from the aniline, but expulsion of the benzylic leaving group was not achieved until the reaction mixture was heated beyond temperatures compatible with enolate nucleophiles; the desilylation of the aniline analog was expected to be slower than the corresponding phenol due to the increased basicity of the substrate, however the rate of benzylic group expulsion was not expected to be significantly different.

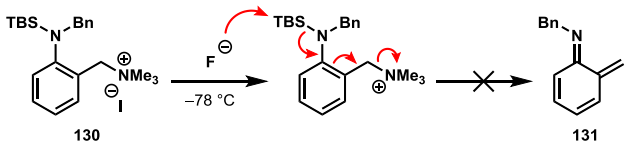


Figure 2.2 Attempted Fluoride-Generated Aza-*ortho*-Xylylene

Undismayed, alternative methods for the generation of aza-*ortho*-xylylenes suggested that more forcing conditions may be required in contrast to the facile production of OQMs. A report by Shudo et. al. employing *N*,*N*-dimethylaniline-*N*-oxides **123** and strong acid in benzene gave *ortho*- and *para*-arylation products, **135**

and **136** respectively (**Figure 2.3**).[2] The report suggests that the products are formed through doubly cationic intermediates, **133** and **134**. When *N*,*N*,4-trimethylaniline-*N*-oxide **137** is subjected to the same reaction conditions, a cohort of products (**143**, **144**, **145**, and **146**) are made presumably through doubly cationic intermediates, **139** and **140** (**Figure 2.4**).

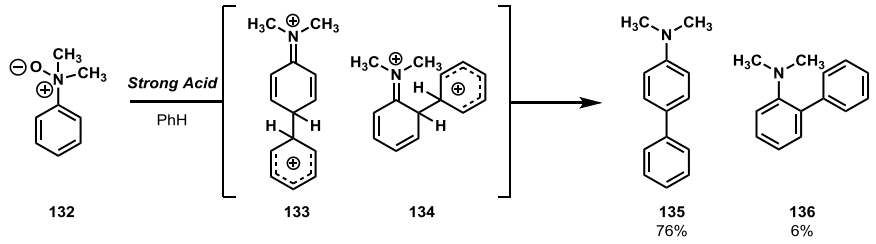


Figure 2.3 Arylation of *N*,*N*-Dimethylaniline *N*-Oxides

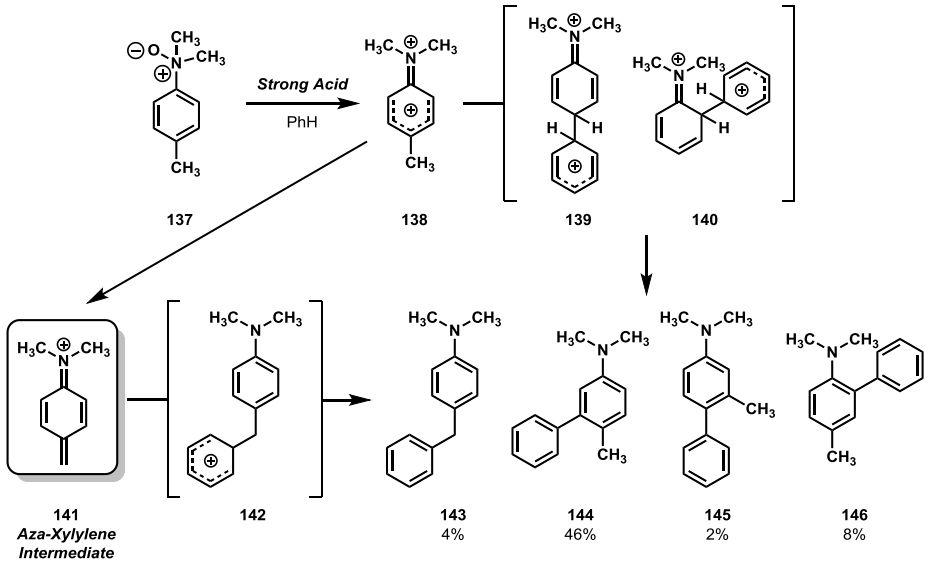


Figure 2.4 Arylation of *N*,*N*,4-Trimethylaniline *N*-Oxide

The presence of the minor product **143** suggests the possibility that an aza-*ortho*-xylylene intermediate like **141** (**138** → **141**) was generated and intercepted by benzene solvent. This electrophilic aromatic substitution reaction suggested that an aza-*ortho*-xylylene could be generated by activation and expulsion of a suitable group from nitrogen (such as an ester), and that this electrophile is highly reactive. To further support the possibility of the aza-*ortho*-xylylene intermediate like **141**, the simple aniline *N*-oxide **132** was treated with trifluoroacetic anhydride in benzene and the arylated aniline **147** was detected (**Figure 2.5**).

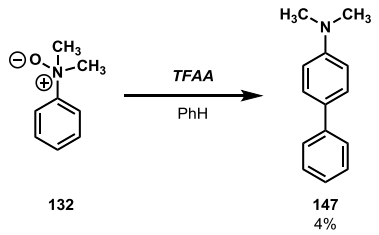


Figure 2.5 Arylation of *N*,*N*-Dimethylaniline *N*-Oxide with Trifluoroacetic Anhydride

We therefore reasoned that trifluoroacetic anhydride (among other appropriate activating agents) might allow us to access aza-*ortho*-xylylenes by reversing the flow of electrons (**Figure 2.6**) relative to the OQM generation strategy. A silyl group located on the benzyl carbon (**148**), combined with an appropriate leaving group at nitrogen, might generate aza-*ortho*-xylylenes **149** in a controlled fashion upon exposure to fluoride.

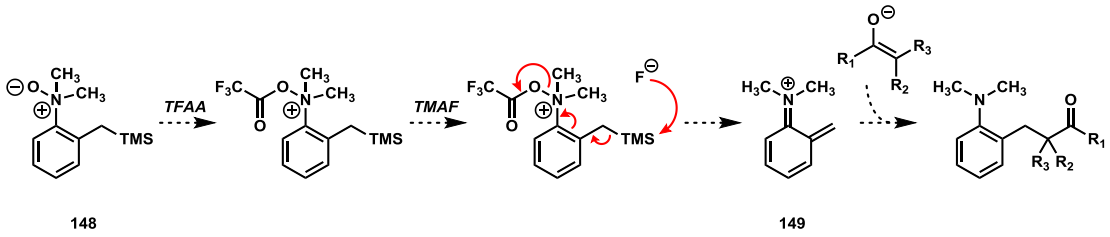


Figure 2.6 Activation of *N*,*N*-Dimethylaniline *N*-Oxide with Trifluoroacetic Anhydride

To test our hypothesis, the synthesis of the appropriate test substrates began with *ortho*-lithiation of the corresponding *N*,*N*-dimethyl-*ortho*-toluidine **150** and silylation of the anion with a chlorosilane, followed by oxidation of the benzyl silanes with *m*-CPBA to give the aniline *N*-oxides **151** and **152** (**Figure 2.7**).

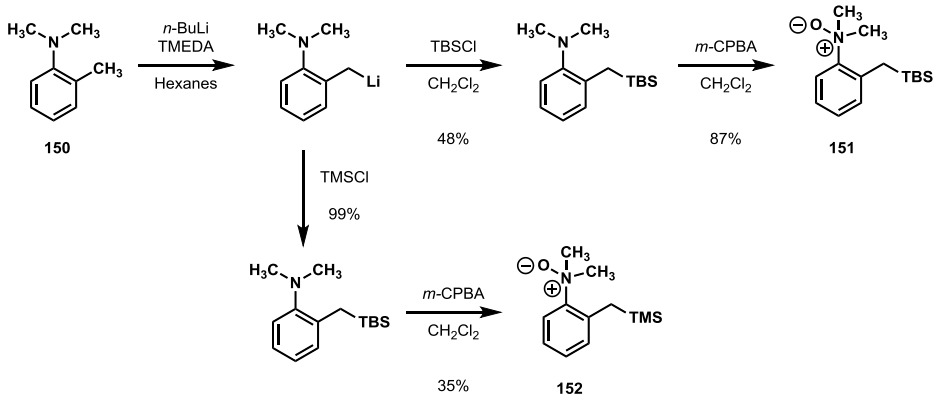


Figure 2.7 Synthesis of *N*-Oxides **151**and **152**

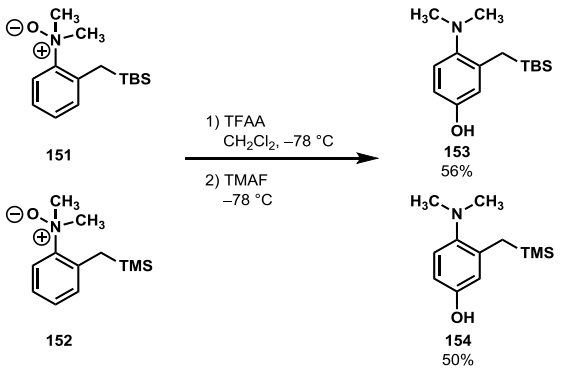


Figure 2.8 Unexpected Hydroxylation

To probe the possible generation and capture of the aza-*ortho*-xylylene intermediate, we treated **151** and **152** with trifluoroacetic anhydride, followed by a TMS enol ether and a fluoride source (**Figure 2.8**). Thin-layer chromatography indicated the clean formation of a single new product; the predicted aza-*ortho*-xylylene alkylation product was not detected, and instead the phenols **153** and **154** were isolated in 56% and 50% yield, respectively. Moreover, these products were also generated efficiently in the absence of enol nucleophiles, provided a base was present. Intrigued by this result, we sought to shed light on the mechanism of this transformation and expand the reaction scope.

2.2 Metal-Free Functionalization of *N,N*-Dialkylanilines

The reaction we uncovered caused excitement for several reasons. Engaging anilines at nitrogen and executing a group transfer from nitrogen to carbon is an attractive method for the controlled functionalization of electron-rich aromatic rings, which are otherwise more problematic to manipulate.[3] The aniline and aminophenol substructures are embedded in many synthetic building blocks, ligands and other catalyst frameworks, as well as myriad biologically-active compounds.[4] Efficient

access to these structures is of value to chemists in many fields, yet methods that allow selective and controlled elaboration of anilines remain rare.

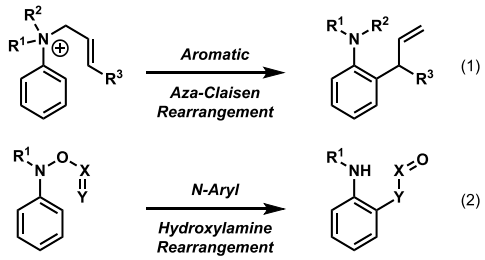


Figure 2.9 Aromatic Rearrangements Featuring *N* ⟶ *C* Group Transfer

The all-carbon aza-Claisen rearrangement of alkylated anilines is an inefficient process and does not provide a synthetically useful means of aromatic functionalization **(Figure 2.9,** eq. 1).[5] The introduction of weak, excisable *N*–*O* bonds into the operative bond network affords the opportunity to exploit this important scaffold for complexity generating reactions.[6] The rearrangement of various acylated *N*-aryl-hydroxylamines in this pursuit to give protected hydroxyanilines has a long history dating to the mid 1950's, and -various pericyclic, ion-pair, and radical-type mechanisms have been examined (**Figure 2.9**, eq. 2).[6,7] A small number of carbon–carbon bond formations utilizing these substrates have also been described over the same time period, but substrate scope is generally limited to migrating groups that can support an anion.[8] A recent series of investigations greatly expanded the landscape of carbon–heteroatom bond formations in *N*-aryl-hydroxylamine rearrangements, allowing access to hydroxy- and aminoanilines, as well as cyclized products.[9] These transformations are described as concerted [3,3]-sigmatropic rearrangements, and in most cases require prolonged exposure to elevated temperature, microwave heating, or

other harsh reaction conditions. Most of these transformations are efficient but require judicious choice of nitrogen-protective groups and can also be sensitive to the electronic nature of the aromatic ring.

Similar transformations in this context were probed briefly in the past, and in these early mechanistic studies, reaction yields varied widely (6–90%) with side products attributed to the multiple mechanistic pathways that are available (concerted rearrangements, ion-pair, and radical pathways).[10] To our knowledge, there are only two prior examples of carbon–carbon bond formations in this context, the reaction of *N*,*N*-dimethylaniline-*N*-oxide with diketene and acetylene dicarboxylates.[11] In that work, spectroscopic data supported mechanisms in which *O*-acylation/alkylation events are followed by fragmentations into radical pairs, which recombined to give the alkylated products. The alkylated products were accompanied by several side products and thus other mechanistic possibilities could not be excluded. The transformation of *N*,*N*-dialkylaniline-*N*-oxides into oxygenated anilines was explored in the classical Boyland-Sims oxidation,[12] with several mechanistic inquiries described in the literature.[13] Methods for the direct amination of anilines are exceptionally rare.[9]

2.3 Results and Scope

We produced C–O, C–C, and C–N bond formations to anilines under exceptionally mild reaction conditions facilitated by an increase in oxidation level from aniline to aniline-*N*-oxide. Aniline-*N*-oxides are conveniently generated from the corresponding anilines, easily isolated and handled, and are generally bench stable.[14] Following an *O*-acylation event, group transfer from nitrogen to carbon excises the weak *N*–*O* bond and gives an iminium ion, and after loss of a proton,

aromaticity and electron density at nitrogen are restored. These bond formations proceed in seconds to minutes at low temperature.

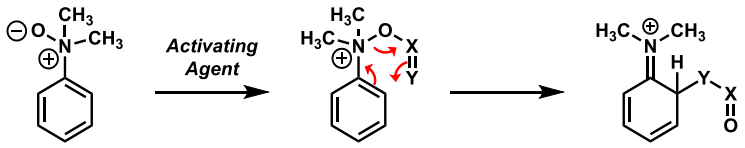


Figure 2.10 Rearrangements of Activated Aniline *N*-Oxides

2.3.1 Hydroxylation of *N*,*N*-Dialkylaniline *N*-Oxides

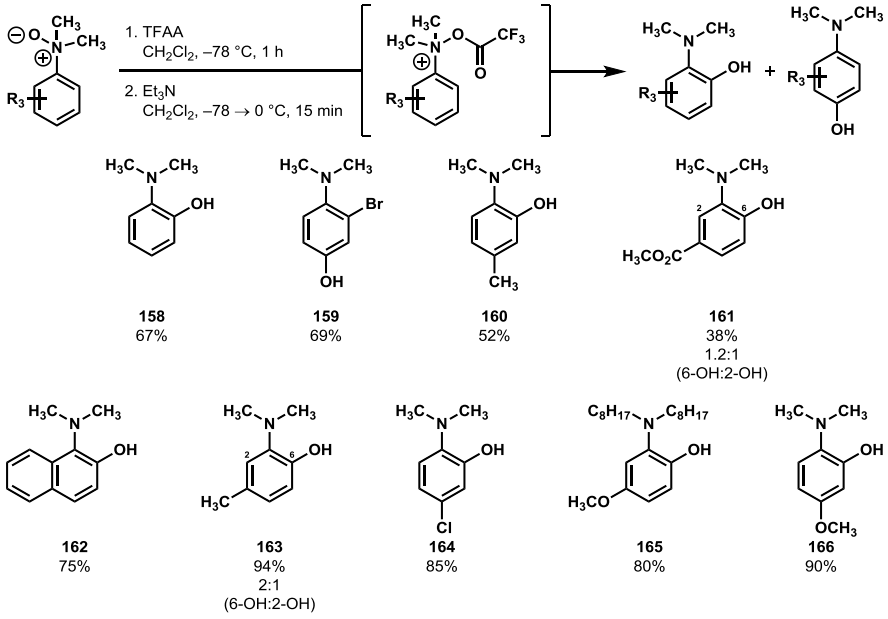


Figure 2.11 Hydroxylation of *N*,*N*-Dialkylaniline *N*-Oxides

We achieved efficient access to a variety of aminophenols by sequential treatment of *N*,*N*-dialkylaniline-*N*-oxides with trifluoroacetic anhydride and triethylamine in dichloromethane at –78 °C (**Figure 2.11**). The intermediate

trifluoroacetate esters are hydrolyzed on workup to give the phenols directly in 52–94% yield. These conditions strongly favor *ortho* functionalization, with the exception that substrates bearing a single *ortho* substituent favor the 4-hydroxy-*N*,*N*-dialkylaniline product (e.g., **Figure 2.11**, product **159**). As in prior investigations, mechanistic possibilities include concerted [3,3]-sigmatropic rearrangements, ion-pair, and radical pathways. In any case, we were not surprised to observe that substrates with no open *ortho* or *para* positions (i.e. 2,4,6- trimethyl-*N*,*N*-dimethylaniline) give no hydroxylated product. Substrates bearing *meta* substitution give mixtures of *ortho* hydroxylation products, favoring the less sterically encumbered product (1.2–2:1). The reaction functions well with both electron-donating and -withdrawing substituents with two notable exceptions, substrates bearing *ortho* methyl or *para* carbonyl substituents. In the case of *ortho* methyl substitution, the acylation event is followed by nonspecific decomposition via what appears to be a deprotonation that gives an aza-xylylene, much as we had originally desired.[15] In the case of *para* carbonyl substitution, the acylation event is followed by deprotonation of the *N*-methyl to give an iminium ion that hydrolyzes on workup to result in the corresponding *N*-methylaniline product.[16]

2.3.2 Trifluoromethanesulfonylation and *p*-Toluenesulfonylation of *N*,*N*-Dialkylaniline *N*-Oxides

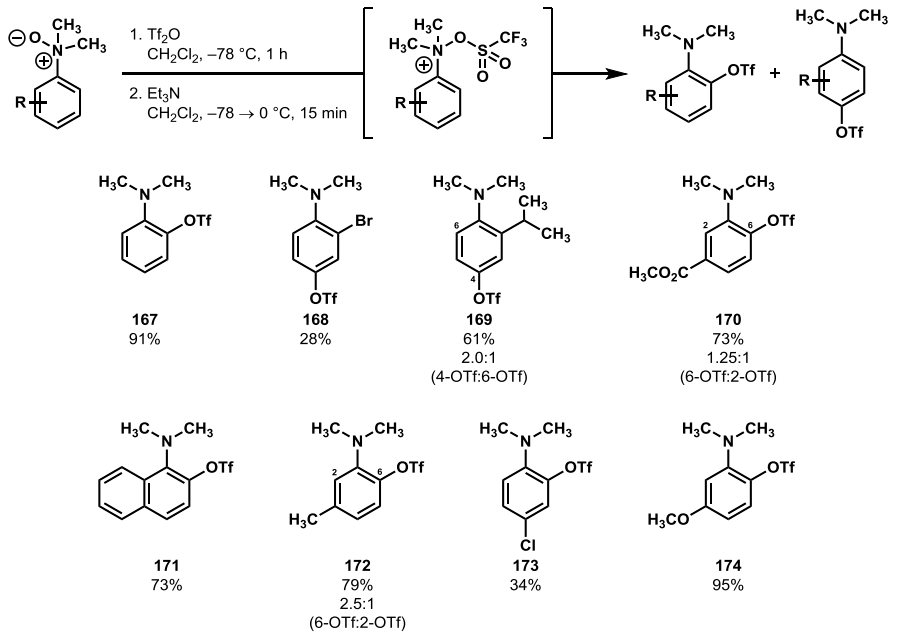


Figure 2.12 Trifluoromethanesulfonylation of *N*,*N*-Dialkylaniline *N*-Oxides

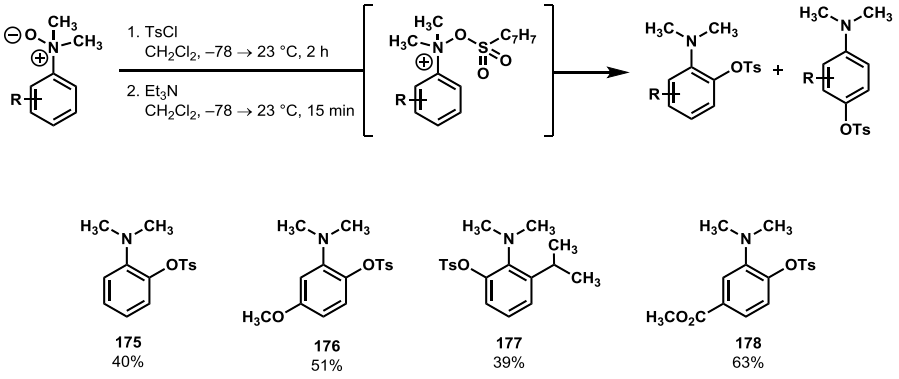


Figure 2.13 *p*-Toluenesulfonylation of *N*,*N*-Dialkylaniline *N*-Oxides

Trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) and *p*-toluenesulfonyl chloride (tosyl chloride) also serve as viable acylation/oxygenation

agents (**Figures 2.12 and 2.13**).[8] Sequential treatment of *N*,*N*-dialkylaniline-*N*-oxides with triflic anhydride or tosyl chloride and triethylamine in cold dichloromethane gives a variety of aryl sulfonates in moderate to excellent yields. As above, we observed the same regiochemical preferences for functionalization and the same liabilities with respect to methyl and carbonyl substitution. Additionally, the sulfonylated aniline-*N*-oxides are more vulnerable to the unproductive elimination reaction pathway that gives rise to *N*-methylanilines. This reaction pathway dominates in substrates bearing strong electron donors at the *para* position (e.g. *N*,*N*-dimethyl-*p*-anisidine), but strong electron donors are tolerated at the *meta* position (e.g. *N*,*N*-dimethyl-*m*-anisidine gives products **174** and **176** in 95% and 51% yield, respectively).

2.3.3 Alkylation of *N*,*N*-Dialkylaniline *N*-Oxides with Ethyl Malonyl Chloride

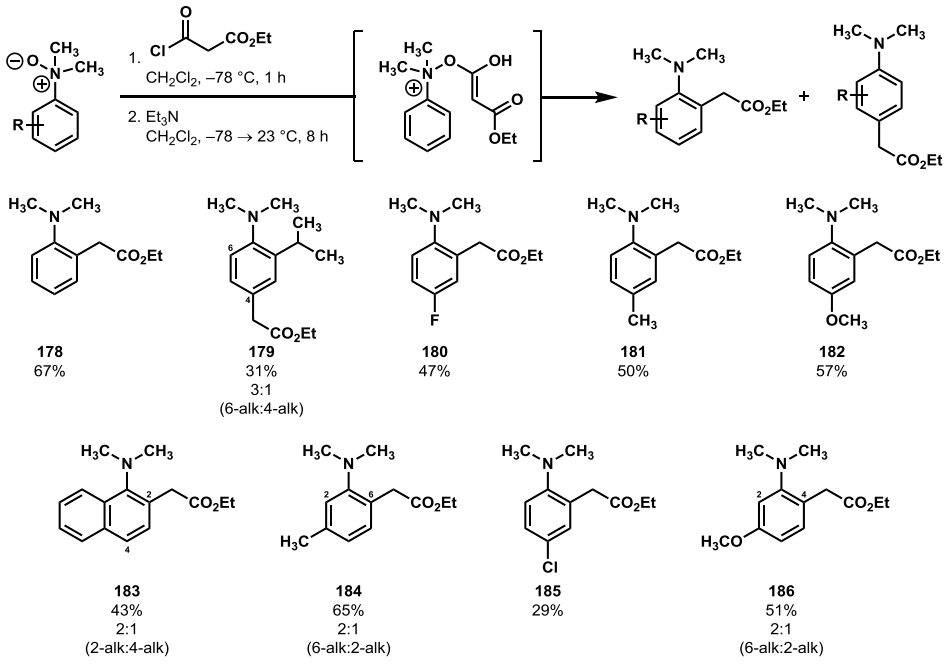


Figure 2.14 Alkylation of *N*,*N*-Dialkylaniline *N*-Oxides with Ethyl Malonyl Chloride

Importantly, the elevated reactivity of *N*,*N*-dialkylaniline-*N*-oxides allows facile carbon–carbon bond formation under exceptionally mild reaction conditions: *O*-acylation events that give C–C π-systems in their wake result in efficient and clean *N* → *C* group transfer, and following rearrangement, a decarboxylation gives the final alkylated products. Ethyl malonyl chloride,[17] a substrate that will present a π-system by virtue of its existence predominantly as an enol tautomer, functions successfully in this context (**Figure 2.14**). We have noted the same regiochemical preferences as in the above carbon–heteroatom bond formations, and the same liability with respect to demethylation to give *N*-methylanilines. Moreover, the carbon–carbon bond formation event appears to be quite facile, occurring at low temperature in a matter of

minutes; the slowest event of the reaction sequence appears to be the decarboxylation. The reaction functions well for both electron-donating and -withdrawing substituents and *C*-alkylated products are obtained cleanly in 29–67% yield.

2.3.4 Amination of *N*,*N*-Dimethylaniline *N*-Oxide

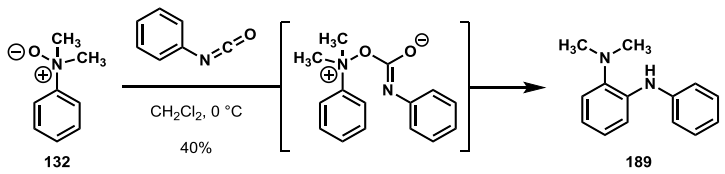


Figure 2.15 Amination of *N*,*N*-Dimethylaniline *N*-Oxide

We were also able to execute other assorted group transfers (**Figure 2.15**). We formed a new C–N bond using *N*,*N*-dialkylaniline-*N*-oxide **132** and phenylisocyanate as a nitrogen source, which to our knowledge, is only the second example of the introduction of a new C–N bond on an aromatic ring utilizing an aniline-*N*-oxide.[12b,18]

2.4 Summary

In summary, while researching a general method for the aza-*ortho*-xylylenes *in situ* for the analogous enolate–*o*-QM reaction we discovered a method for the functionalization of aniline-*N*-oxides. We have discovered the reaction to be quite general, allowing us to access aminophenols, aminoarylsulfonates, alkylated anilines, and aminoanilines in 29−95% yield in a single laboratory operation from easily isolable, bench-stable *N*,*N*-dialkylaniline *N*-oxides. By increasing the oxidation level from aniline to aniline-*N*-oxide and excision of the weak N–O bond we introduced C–O, C–C, and C–N bond formations to anilines under exceptionally mild reaction

conditions. The elevated reactivity of *N*,*N*-dialkylaniline *N*-oxides facilitates clean, efficient, controlled, and scalable introduction of carbon−heteroatom and carbon−carbon bonds onto the aromatic ring in the absence of metals, Lewis acids, or other exotic reagents. Our future efforts are directed toward unraveling the mechanistic details of these reactions, expanding the scope of new bond forming reactions of aniline-*N*-oxides, and the application of these methods to natural product synthesis.

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18. The aniline-*N*-oxides can act as a Lewis base catalyst in a dimerization of the isocyanate but this reaction can be suppressed by the slow addition of the isocyanate to the aniline-*N*-oxide. The dimerization of isocyanates to give carbodiimides has been reported for other Lewis base catalysts such as phosphines and phosphine oxides. For examples, see: (a) Monagle, J. J.; Campbell, T. W.; McShane, Jr.; H. F. *J. Am. Chem. Soc.* **1962**, *84*, 4288. (b) Blair, J. S.; Smith, G. E. P. *J. Am. Chem. Soc.* **1934**, *56*, 907. (c) Raiford, L. C.; Freyermuth, H. B. *J. Org. Chem.* **1943**, *8*, 230. (d) Campbell, T. W.; Monagle, J. J. *J. Am. Chem. Soc.* **1962**, *84*, 3673.

EXPERIMENTAL PROCEDURE

General Information: All reactions were performed in single-neck oven- or flame-dried round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 10 Torr (diaphragm vacuum pump) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 5–20 μm, Silicycle) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), ethanolic phosphomolybdic acid solution (PMA), acidic ethanolic p-anisaldehyde solution (Anis.), or aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (215 °C, 10–15 s). Flash chromatography was performed as described by Still et al.[1], employing silica gel (60-Å pore size, 40–63 μm, standard grade, Silicycle) or basic alumina (60-Å pore size, 50–200 μm, Brockmann I, Sorbent Technologies or Acros Organics).

Materials: Commercial reagents and solvents were used as received with the following exceptions. Triethylamine, dichloromethane, ethyl ether, dimethylsulfoxide, tetrahydrofuran, hexane, toluene, and benzene were purified by the

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method of Pangborn, et. al.[2] *N*,*N*-dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure (0.1 Torr) and stored under argon. Iodomethane was filtered through a column of basic alumina, neat, immediately prior to use. Where noted, solvents were deoxygenated before use by bubbling with argon for 15 minutes.

Instrumentation: Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Mercury Plus 300 MHz/75 MHz or Varian Unity INOVA 500 MHz/125 MHz NMR spectrometers at 23 °C. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Varian Mercury Plus 282 MHz spectrometer at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, CD_2HOD: δ 3.31, CD_3SOCD_2H: δ 2.50, C_6D_5H: δ 7.16). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3OD: δ 49.00, CD_3SOCD_3: δ 39.52, C_6D_6: δ 128.00). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1 FT-IR spectrophotometer referenced to a polystyrene standard and data are represented as frequency of absorption (cm^{-1}). Accurate mass measurements were obtained on a

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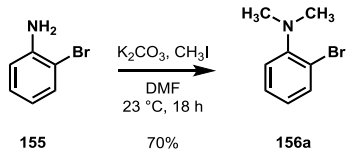
Waters LCT premier (ESI source, flow injection analysis) or a Waters GCT premier (GC-MS fitted with an EI or CI source) at the Mass Spectrometry Facility at the University of California at Irvine

General Procedure for the Synthesis of N,N-Dimethylanilines



2-Bromo-*N*,*N*-dimethylaniline **156a**[3]:

Iodomethane (3.97 mL, 63.8 mmol, 2.2 equiv.) was added dropwise to a stirred suspension of 2-bromoaniline **155** (5.00 g, 29.1 mmol, 1.0 equiv.) and potassium carbonate (12.0 g, 86.8 mmol, 3.0 equiv.) in *N*,*N*-dimethylformamide (100 mL). The reaction mixture was stirred at 23 °C for 18 h, then was filtered and diluted with water (100 mL). The resultant solution was extracted diethyl ether (3 × 50 mL) and the combined organic extracts were washed with water (3 × 30 mL) and then with saturated aqueous sodium chloride solution (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and the dried solution was concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate–hexane) to afford the 2-bromo-*N*,*N*-dimethylaniline **156a** (4.08 g, 70%) as a clear, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.55 (m, 1H), 7.26 (m, 1H), 7.09 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 6.89 (m, 1H), 2.80 (s, 6H).
TLC (5% EtOAc–Hex), R_f:	2-Bromo-*N*,*N*-dimethylaniline **156a**: 0.42 (UV, $KMnO_4$).

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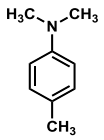


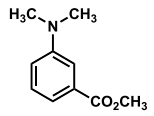
156b

4-Methyl-*N*,*N*-dimethylaniline **156b**[4]:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.07 (m, 2H), 6.70 (m, 2H), 2.91 (s, 6H), 2.27 (s, 3H).

TLC (5% EtOAc–Hex), R_f: 4-Methyl-*N*,*N*-dimethylaniline **156b**: 0.34 (UV, $KMnO_4$).

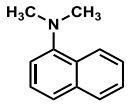
4. Lundgren, R.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. Eur. J.*, **2010**, *16*, 1983.



156c

Methyl 3-(*N*,*N*-dimethylamino)benzoate **156c**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.41 – 7.35 (m, 2H), 7.28 (t, J_1 = 7.9 Hz, 1H), 6.90 (m,1H), 3.90 (s, 3H), 3.00 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	167.9, 150.6, 130.9, 129.1, 117.6, 116.8, 113.3, 52.2, 40.7.
FTIR (NaCl, thin film), cm^{-1}:	2950, 2808, 1724, 1603, 1438, 1354, 1113, 1008, 784.
HRMS $(ES)^+$:	Calcd. for $C_{10}H_{13}NO_2Na$ $[M + Na]^+$: 202.0844. Found: 202.0840.
TLC (5% EtOAc–Hex), R_f:	Methyl 3-(*N*,*N*-dimethylamino)benzoate **156c**: 0.20 (UV, $KMnO_4$).

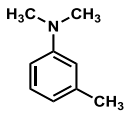


156d

1-(*N*,*N*-Dimethylamino)naphthalene **156d**[5]:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	8.24 (m, 1H), 7.83 (m, 1H), 7.57 – 7.43 (m, 3H), 7.40 (m, 1H), 7.08 (m, 1H), 2.91 (s, 6H).
FTIR (NaCl, thin film), cm^{-1}:	3047, 2939, 2785, 1575, 1395, 1305, 773.
HRMS $(EI)^+$:	Calcd. for $C_{12}H_{13}N$ $[M^{\bullet}]^+$: 171.1048. Found: 171.1040.
TLC (5% EtOAc–Hex), R_f:	1-(*N*,*N*-Dimethylamino)naphthalene **156d**: 0.41 (UV, $KMnO_4$).

5. Shohji, N.; Kawaji, T.; Okamoto, S. *Org. Lett.*, **2011**, *13*, 2626.



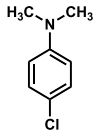
156e

3-Methyl-*N*,*N*-dimethylaniline **156e**[6]:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.16 (m, 1H), 6.59 (m, 3H), 2.95 (s, 6H), 2.34 (s, 3H).

TLC (5% EtOAc–Hex), R_f: 3-Methyl-*N*,*N*-dimethylaniline **156e**: 0.41 (UV, $KMnO_4$).

6. Dichiarante, V.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **2010**, *75*, 2171.

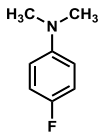


156f

4-Chloro-*N*,*N*-dimethylaniline **156f**[7]:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.18 (d, J_1 = 9.0 Hz, 2H), 6.63 (d, J_1 = 9.0 Hz, 2H), 2.93 (s, 6H).
TLC (5% EtOAc–Hex), R_f:	4-Chloro-*N*,*N*-dimethylaniline **156f**: 0.37 (UV, $KMnO_4$).

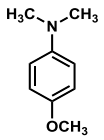
7. Huang, L.; Niu, T.; Wu, J.; Zhang, Y. *J. Org. Chem.*, **2011**, *76*, 1739.



156g

4-Fluoro-*N*,*N*-dimethylaniline **156g**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	6.97 (m, 2H), 6.68 (m, 2H), 2.91 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	155.7 (d, J_1 = 235.1 Hz), 147.6, 115.4 (d, J_1 = 21.8 Hz), 114.0 (d, J_1 = 7.3 Hz), 41.5.
FTIR (NaCl, thin film), cm^{-1}:	2886, 1848, 1526, 1448, 1225, 814.
HRMS $(EI)^+$:	Calcd. for $C_8H_{10}FN$ $[M^{\bullet}]^+$:139.0797. Found: 139.0800.
TLC (5% EtOAc–Hex), R_f:	4-Fluoro-*N*,*N*-dimethylaniline **156g**: 0.37 (UV, $KMnO_4$).



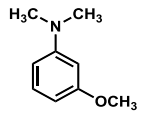
156h

4-Methoxy-*N*,*N*-dimethylaniline **156h**[8]:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.88 – 6.72 (m, 4H), 3.78 (s, 3H), 2.87 (s, 6H).

TLC (5% EtOAc–Hex), R_f: 4-Methoxy-*N*,*N*-dimethylaniline **156h**: 0.16 (UV, $KMnO_4$).

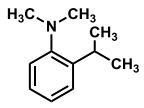
8. Lee, B.; Biscoe, M.; Buchwald, S. *Tetrahedron Lett.* **2009**, *50*, 3672.



156i

3-Methoxy-*N*,*N*-dimethylaniline **156i**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.17 (m, 1H), 6.39 (m, 1H), 6.35 – 6.27 (m, 2H), 3.81 (s, 3H), 2.95 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	160.8, 152.1, 129.8, 105.9, 101.5, 99.2, 55.2, 40.7.
HRMS $(ES)^+$:	Calcd. for $C_9H_{14}NO$ $[M + H]^+$: 152.1075. Found: 152.1075.
TLC (5% EtOAc–Hex), R_f:	3-Methoxy-*N*,*N*-dimethylaniline **156i**: 0.26 (UV, $KMnO_4$).

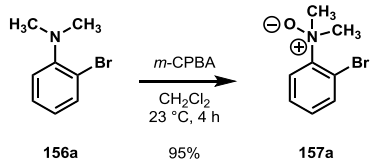


156j

2-*iso*-Propyl-*N*,*N*-dimethylaniline **156j**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.28 (m, 1H), 7.10 (m, 3H), 3.55 (hept, J_1 = 6.8 Hz, 1H), 2.67 (s, 6H), 1.24 (d, J_1 = 0.7 Hz, 3H), 1.22 (d, J_1 = 0.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	152.0, 144.3, 126.6, 126.3, 124.0, 119.7, 46.0, 26.8, 24.3.
FTIR (NaCl, thin film), cm^{-1}:	2964, 2824, 1490, 1448, 946, 764.
HRMS $(ES)^+$:	Calcd. for $C_{11}H_{17}NH$ $[M + H]^+$: 164.1439. Found: 164.1433.
TLC (5% EtOAc–Hex), R_f:	2-*iso*-Propyl-*N*,*N*-dimethylaniline **156j**: 0.68 (UV, $KMnO_4$).

General Procedure for the Synthesis of N,N-Dimethylaniline-N-Oxides



156a 95% **157a**

2-Bromo-*N*,*N*-dimethylaniline-*N*-oxide **157a**:

A solution of the 2-bromo-*N*,*N*-dimethylaniline **156a** (4.08 g, 20.4 mmol, 1.0 equiv.) in dichloromethane (50 mL) was transferred via cannula to a stirred solution of 3-chloroperbenzoic acid (70% w/w, 5.03 g, 20.4 mmol, 1.0 equiv.) in dichloromethane (50 mL). The resultant mixture was stirred for at 23 °C for 4 then was loaded directly onto a basic alumina column and eluted with 25% methanol–chloroform. The combined filtrates were concentrated to afford the 2-bromo-*N*,*N*-dimethylaniline-*N*-oxide **157a** (4.19 g, 95% yield) as an orange-yellow crystalline solid.

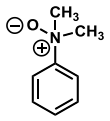
^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.14 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H), 7.62 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.48 (ddd, J_1 = 8.6 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 7.29–7.18 (m, 1H), 3.80 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$), δ: 152.6, 135.4, 131.1, 129.2, 125.8, 112.7, 60.9, 50.7.

FTIR (NaCl, thin film), cm^{-1}: 3100, 1644, 1451, 1436.

HRMS $(EI)^{+}$: Calcd. for $C_8H_{10}BrNO$ $[M^{\bullet}]^{+}$: 214.9945.

	Found: 214.9955.
TLC (2-15% EtOAc–Hex), R_f:	2-Bromo-*N*,*N*-dimethylaniline-*N*-oxide **157a**: 0.0 (UV, $KMnO_4$).



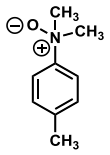
132

<u>*N*,*N*-Dimethylaniline-*N*-oxide **132**[9]:</u>

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.98 (m, 2H), 7.53–7.42 (m, 3H), 3.59 (s, 6H).

TLC (2-15% EtOAc–Hex), R_f: *N*,*N*-Dimethylaniline-*N*-oxide **132**: 0.0 (UV, $KMnO_4$).

9. Imada, Y.; Iida, H.; Ono, S.; Murahashi, S. *J. Am. Chem. Soc*. **2003**, *125*, 2868.



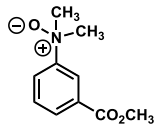
157b

4-Methyl-*N*,*N*-dimethylaniline-*N*-oxide **157b**[10]:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.81 (m, 2H), 7.25 (m, 2H), 3.55 (s, 6H), 2.37 (s, 3H).

TLC (2-15% EtOAc–Hex), R_f: 4-Methyl-*N*,*N*-dimethylaniline-*N*-oxide **157b**: 0.0 (UV, $KMnO_4$).

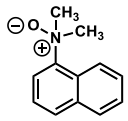
10. Chen, F.; Qiu, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron*, **2004**, *60*, 10449.



157c

Methyl 3-(*N*,*N*-dimethylamino)benzoate-*N*-oxide **157c**:

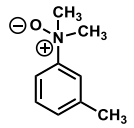
^{1}H NMR (300 MHz, $CDCl_3$), δ:	8.49 – 8.37 (m, 2H), 8.07 (m, 1H), 7.57 (m, 1H), 3.93 (s, 3H), 3.60 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	166.0, 155.0, 131.2, 130.2, 129.8 125.2, 120.9, 63.6, 52.7.
FTIR (NaCl, thin film), cm^{-1}:	3103, 2952, 1671, 1441, 1344, 1292, 1243, 1209.
HRMS $(ES)^{+}$:	Calcd. for $C_{10}H_{13}rNO_3Na$ $[M + Na]^{+}$: 218.0793. Found: 218.0788.
TLC (2-15% EtOAc–Hex), R_f:	Methyl 3-(*N*,*N*-dimethylamino)benzoate-*N*-oxide **157c**: 0.0 (UV, $KMnO_4$).



157d

1-(*N*,*N*-Dimethylamino)naphthalene-*N*-oxide **157d**:

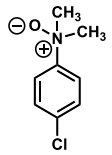
^{1}H NMR (300 MHz, $CDCl_3$), δ:	9.08 (m, 1H), 8.31 (m, 1H), 7.92 (m, 2H), 7.69 – 7.52 (m, 2H), 7.49 (m, 1H), 3.91 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	135.8, 131.0, 129.6, 127.1, 126.2, 125.8, 125.4, 124.5, 118.4, 62.7.
FTIR (NaCl, thin film), cm^{-1}:	3325, 3057, 2360, 2313, 1506.
HRMS $(EI)^{+}$:	Calcd. for $C_{12}H_{13}NO$ $[M^{\bullet}]^{+}$: 187.0997. Found: 187.0995.
TLC (2-15% EtOAc–Hex), R_f:	1-(*N*,*N*-Dimethylamino)naphthalene-*N*-oxide **157d**: 0.0 (UV, $KMnO_4$).



157e

3-Methyl-*N*,*N*-dimethylaniline-*N*-oxide **157e**:

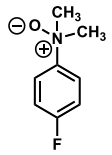
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.86 (s, 1H), 7.60 (m, 1H), 7.30 (m, 1H), 7.17 (m, 1H), 3.54 (s, 6H), 2.39 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	139.8, 129.7, 129.0, 120.8, 116.7, 110.1, 63.3, 21.7.
FTIR (NaCl, thin film), cm^{-1}:	2935, 2856, 2353, 1550, 1264, 1218, 1008, 987, 748.
HRMS $(ES)^{+}$:	Calcd. for $C_9H_{13}NONa$ $[M + Na]^{+}$: 174.0895. Found: 174.0894.
TLC (2-15% EtOAc–Hex), R_f:	3-Methyl-*N*,*N*-dimethylaniline-*N*-oxide **157e**: 0.0 (UV, $KMnO_4$).



157f

4-Chloro-*N*,*N*-dimethylaniline-*N*-oxide **157f**:

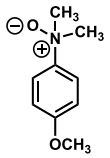
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.93 (m, 2H), 7.43 (m, 2H), 3.57 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	153.2, 135.1, 129.3, 121.8, 63.6.
FTIR (NaCl, thin film), cm^{-1}:	3340, 1661, 1485, 1459.
HRMS $(EI)^{+}$:	Calcd. for $C_8H_{10}ClNO$ $[M^{\bullet}]^{+}$: 171.0451. Found: 171.0449.
TLC (2-15% EtOAc–Hex), R_f:	4-Chloro-*N*,*N*-dimethylaniline-*N*-oxide **157f**: 0.0 (UV, $KMnO_4$).



157g

4-Fluoro-*N*,*N*-dimethylaniline-*N*-oxide **157g**:

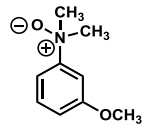
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.88 (m, 2H), 7.12 – 6.89 (m, 2H), 3.47 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	162.2 (d, J_1 = 248.9 Hz), 150.3, 122.1 (d, J_1 = 8.5 Hz), 115.8 (d, J_1 = 22.9 Hz), 63.5.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	−112.9.
FTIR (NaCl, thin film), cm^{-1}:	1647, 1600, 1501, 562.
HRMS $(ES)^+$:	Calcd. for $C_8H_{10}FNONa$ $[M + Na]^+$: 178.0644. Found: 178.0637.
TLC (2-15% EtOAc–Hex), R_f:	4-Fluoro-*N*,*N*-dimethylaniline-*N*-oxide **157g**: 0.0 (UV, $KMnO_4$).



126h

4-Methoxy-*N*,*N*-dimethylaniline-*N*-oxide **157h**:

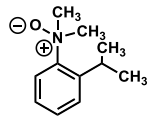
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.93 – 7.79 (m, 2H), 6.99 – 6.86 (m, 2H), 3.83 (s, 3H), 3.56 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	159.7, 147.5, 121.3, 114.1, 63.7, 55.8.
FTIR (NaCl, thin film), cm^{-1}:	2958, 2842, 1593, 1505.
HRMS $(EI)^{+}$:	Calcd. for $C_9H_{13}NO_2$ $[M^{\bullet}]^{+}$: 167.0946. Found: 167.0942.
TLC (2-15% EtOAc–Hex), R_f:	4-Methoxy-*N*,*N*-dimethylaniline-*N*-oxide **157h**: 0.0 (UV, $KMnO_4$)



157i

3-Methoxy-*N*,*N*-dimethylaniline-*N*-oxide **157i**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.71 (m, 1H), 7.25 – 7.10 (m, 2H), 6.80 (m, 1H), 3.74 (s, 3H), 3.44 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	160.2, 155.7, 129.5, 114.9, 111.2, 106.1, 63.2, 55.6.
FTIR (NaCl, thin film), cm^{-1}:	3044, 2940, 2410, 1610, 1484, 1259, 1036.
HRMS $(ES)^{+}$:	Calcd. for $C_9H_{13}NO_2Na$ $[M + Na]^{+}$: 190.0844. Found: 190.0836.
TLC (2-15% EtOAc–Hex), R_f:	3-Methoxy-*N*,*N*-dimethylaniline-*N*-oxide **157i**: 0.0 (UV, $KMnO_4$).

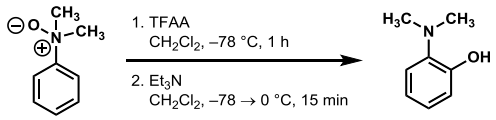


157j

2-*iso*-Propyl-*N*,*N*-dimethylaniline-*N*-oxide **157j**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	8.19 (m, 1H), 7.43 (m, 1H), 7.35 (m, 1H), 7.32 – 7.21 (m, 1H), 4.11 (hept, J_1 = 6.8 Hz, 1H), 3.68 (s, 6H), 1.35 (d, J = 0.8 Hz, 3H), 1.32 (d, J_1 = 0.8 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	41.9, 129.5, 129.3, 126.5, 120.2, 62.8, 29.6, 24.4.
FTIR (NaCl, thin film), cm^{-1}:	3052, 2986, 2357, 1422, 1265, 896, 738.
HRMS $(ES)^+$:	Calcd. for $C_{11}H_{17}NOH$ $[M + H]^+$: 180.1388. Found: 180.1379.
TLC (2-15% EtOAc–Hex), R_f:	2-*iso*-Propyl-*N*,*N*-dimethylaniline-*N*-oxide **157j**: 0.0 (UV, $KMnO_4$).

General Procedure for the Synthesis of Hydroxylated N,N-Dimethylanilines (1 mmol scale)



132 158

2-Hydroxy-*N*,*N*-dimethylaniline **158**:

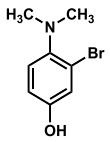
A stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (0.137 g, 1.00 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (10 mL) was cooled to –78 °C whereupon trifluoroacetic anhydride (0.155 mL, 1.10 mmol, 1.1 equiv.) was added dropwise via syringe. The resultant solution was stirred for 1 h whereupon triethylamine (0.276 mL, 2.00 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was quenched by the addition of three drops of acetic acid. The resultant mixture was warmed to 23 °C, then was concentrated. Purification of the residue by flash column chromatography (gradient elution 1 → 5% ethyl acetate–hexane) afforded the 2-hydroxy-*N*,*N*-dimethylaniline **158** (0.0916 g, 67%) as a pale yellow oil.

General procedure for the Synthesis of Hydroxylated N,N-Dimethylanilines (10 mmol scale)

A stirred solution of *N*,*N*-dimethylaniline-*N*-oxide **132** (1.37 g, 10.0 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (100 mL) was cooled to –78 °C whereupon trifluoroacetic anhydride (1.55 mL, 11.0 mmol, 1.1 equiv.) was added dropwise via syringe (addition time approximately 2 min). The resultant solution was stirred for 1 h whereupon triethylamine (2.76 mL, 20.0 mmol,

2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was warmed to 0 °C for 45 min before being quenched by the addition of water (1.0 mL) and silica gel (4.0 g). The resultant mixture was concentrated to a volume of 20 mL, then was diluted with hexane (20 mL). The resultant mixture was filtered through a 1" by 1" plug of silica gel topped with 0.5 cm of anhydrous sodium sulfate. The plug was further eluted with 10% ethyl acetate–hexane (100 mL). The filtrate was concentrated to afford 2-hydroxy-*N*,*N*-dimethylaniline **158** (0.880 g, 64%) as an orange oil which slowly solidified.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.67 (s, 1H), 7.18 (dd, J_1 = 7.9, J_2 = 1.5 Hz, 1H), 7.13 – 7.02 (m, 1H), 6.96 (dd, J_1 = 8.1, J_2 = 1.5 Hz, 1H), 6.92 – 6.80 (m, 1H), 2.69 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	151.5, 140.1, 126.4, 120.8, 120.1, 114.6, 45.2.
FTIR (NaCl, thin film), cm^{-1}:	3325, 2945, 2888, 2789, 2358, 1741, 1589.
HRMS $(ES)^+$:	Calcd. for $C_8H_{12}NO$ $[M + H]^+$: 138.0919. Found: 138.0920.
TLC (10% EtOAc–Hex), R_f:	2-Hydroxy-*N*,*N*-dimethylaniline **158**: 0.26 (UV, $KMnO_4$).

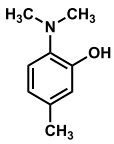


159

69%

3-Bromo-4-(*N*,*N*-dimethylamino)phenol **159**:

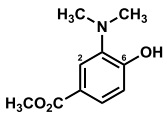
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.09 (dd, J_1 = 2.0, J_2 = 0.5 Hz, 1H), 7.01 (s, 1H), 6.99 (dd, J_1 = 2.1, J_2 = 0.6 Hz, 1H), 2.62 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	152.6, 139.9, 123.1, 122.3, 118.8, 117.6, 45.2.
FTIR (NaCl, thin film), cm^{-1}:	3262, 2938, 2873, 1573, 1446.
HRMS (TOF MS CI)$^-$:	Calcd. for C_8H_9BrNO $[M - H]^-$: 213.9868. Found: 213.9861.
TLC (2-15% EtOAc–Hex), R_f:	3-Bromo-4-(*N*,*N*-dimethylamino)phenol **159**: 0.32 (UV, $KMnO_4$).



160
52%

2-(*N*,*N*-Dimethylamino)-5-methylphenol **160**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.09 (d, J_1 = 8.0 Hz, 1H), 6.814 (s, 1H), 6.71 (d, J_1 = 8.0 Hz, 1H), 2.66 (s, 6H), 2.32 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	151.3, 138.0, 136.1, 120.6, 120.5, 114.7, 45.4, 21.3.
FTIR (NaCl, thin film), cm^{-1}:	3085, 2961, 2797, 2658, 1615, 1447.
HRMS $(ES)^+$:	Calcd. for $C_9H_{13}NOH$ $[M + H]^+$: 152.1075. Found: 152.1075.
TLC (20% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-5-methylphenol **160**: 0.58 (UV, $KMnO_4$).



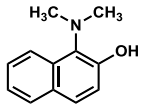
161
38%
1.2:1
(6-OH:2-OH)

Methyl 3-(dimethylamino)-4-hydroxybenzoate **161**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.87 (d, J_1 = 2.0 Hz, 1H), 7.78 (dd, J_1 = 8.4, J_2 = 2.0 Hz, 1H), 6.94 (d, J_1 = 8.4 Hz, 1H), 3.87 (s, 3H), 2.66 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	167.0, 156.0, 140.5, 128.6, 123.0, 122.2, 113.9, 52.0, 45.2.
FTIR (NaCl, thin film), cm^{-1}:	3336, 2984, 2951, 2834, 1713, 1594.
HRMS $(ES)^+$:	Calcd. for $C_{10}H_{13}NO_3H$ $[M + H]^+$: 196.0974. Found: 196.0970.
TLC (10% EtOAc–Hex), R_f:	Methyl 3-(dimethylamino)-4-hydroxybenzoate **161**: 0.37 (UV, $KMnO_4$).

Methyl 3-(dimethylamino)-2-hydroxybenzoate **161**:

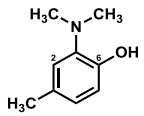
^{1}H NMR (500 MHz, $CDCl_3$), δ:	11.35 (s, 1H), 7.47 (dd, J_1 = 8.0, J_2 = 1.6 Hz, 1H), 7.07 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 2H), 6.81 (t, J_1 = 7.9 Hz, 1H), 3.93 (s, 3H), 2.82 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	171.5, 155.4, 142.2, 123.5, 122.5, 118.8, 112.3, 52.4, 43.1.
FTIR (NaCl, thin film), cm^{-1}:	3103, 3081, 2952, 2832, 2784, 1671, 1441.
HRMS $(ES)^+$:	Calcd. for $C_{10}H_{13}NO_3Na$ $[M + Na]^+$: 218.0793. Found: 218.0795.
TLC (10% EtOAc–Hex), R_f:	Methyl 3-(dimethylamino)-2-hydroxybenzoate **161**: 0.16 (UV, $KMnO_4$).



162
75%

1-(*N*,*N*-Dimethylamino)naphthalen-2-ol **162**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	8.11 (s, 1H), 7.90 (d, J_1 = 8.4 Hz, 1H), 7.82 (d, J_1 = 8.6 Hz, 1H), 7.65 (d, $J=1$ = 9.0 Hz, 1H), 7.47 (t, J_1 = 7.0 Hz, 2H), 7.29 (m, 2H), 3.059 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	151.8, 131.7, 129.8, 129.6, 128.2, 126.0, 122.5, 122.0, 116.1, 44.0.
FTIR (NaCl, thin film), cm^{-1}:	3275, 2973, 2936, 2873, 1623, 1598, 1519, 1206.
HRMS $(ES)^+$:	Calcd. for $C_{12}H_{13}NOH$ $[M + H]^+$: 188.1075. Found: 188.1071.
TLC (20% EtOAc–Hex), R_f:	1-(*N*,*N*-Dimethylamino)naphthalen-2-ol **162**: 0.72 (UV, $KMnO_4$).

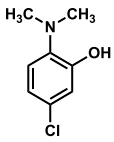


163
94%
2:1
(6-OH:2-OH)

2-(*N*,*N*-Dimethylamino)-4-methylphenol **163**:

Isolated as a mixture of regioisomers, asterisk denotes minor peaks.

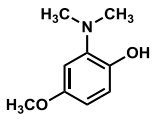
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.48* (s, 1H), 7.08* (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 7.04 (s, 1H), 6.98* (d, J_1 = 7.5 Hz, 1H), 6.91 (s, 2H), 6.82* (t, J_1 = 7.7 Hz, 1H), 2.73 (s, 6H), 2.69* (s, 3H), 2.34* (s, 3H), 2.32 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	149.8, 149.0, 139.9, 139.4, 129.3, 127.5, 126.7, 123.5, 121.2, 119.2, 118.0, 114.2, 45.3, 45.1, 20.8, 15.9.
FTIR (NaCl, thin film), cm^{-1}:	3383, 2944, 2831, 2789, 1474.
HRMS $(ES)^+$:	Calcd. for $C_9H_{13}NOH$ $[M + H]^+$: 152.1075. Found: 152.1073.
TLC (20% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-4-methylphenol **163**: 0.30 (UV, $KMnO_4$).



164
85%

5-Chloro-2-(*N*,*N*-dimethylamino)phenol **164**:

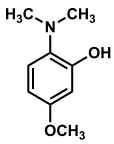
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.07 (d, J_1 = 8.5 Hz, 1H), 6.94 (s, 1H), 6.824 (d, J_1 = 8.5 Hz, 1H), 2.62 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	152.3, 139.4, 131.1, 121.8, 120.1, 114.7, 45.2.
FTIR (NaCl, thin film), cm^{-1}:	2999, 2879, 2840, 1509, 1464.
HRMS $(EI)^+$:	Calcd. for $C_8H_{10}ClNO$ $[M^{\bullet}]^+$: 171.0451. Found: 171.0452.
TLC (10% EtOAc–Hex), R_f:	5-Chloro-2-(*N*,*N*-dimethylamino)phenol **164**: 0.26 (UV, $KMnO_4$).



165
75%

2-*iso*-Propyl-*N*,*N*-dimethylaniline-*N*-oxide **165**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	6.85 (d, J_1 = 8.4 Hz, 1H), 6.74 (d, J_1 = 3.0 Hz, 1H), 6.60 (dd, J_1 = 8.7 J_2 = 3.0 Hz, 1H), 3.75 (s, 3H), 2.64 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	153.3, 145.4, 141.2, 114.2, 110.2, 107.6, 55.9, 45.1.
FTIR (NaCl, thin film), cm^{-1}:	3369, 2945, 2833, 1761, 1611, 1505, 1456.
HRMS $(ES)^+$:	Calcd. for $C_9H_{13}NO_2H$ $[M + H]^+$: 168.1024. Found: 168.1026.
TLC (10% EtOAc–Hex), R_f:	2-*iso*-Propyl-*N*,*N*-dimethylaniline-*N*-oxide **165**: 0.21 (UV, $KMnO_4$).

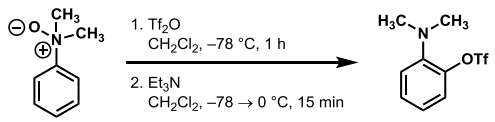


166
90%

2-(*N*,*N*-Dimethylamino)-5-methoxyphenol **166**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.09 (d, J_1 = 8.5 Hz, 1H), 6.53 (d, J_1 = 2.5 Hz, 1H), 6.41 (dd, J_1 = 8.5, J_2 = 2.5 Hz, 1H), 3.76 (s, 3H), 2.61 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	158.0, 152.5, 133.6, 121.4, 105.2, 105.2, 99.8, 55.3, 45.6.
FTIR (NaCl, thin film), cm^{-1}:	3362, 2947, 2867, 2833, 1623, 1509, 1507.
HRMS $(EI)^+$:	Calcd. for $C_9H_{13}NO_2$ $[M^{\bullet}]^+$: 167.0946. Found: 167.0942.
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-5-methoxyphenol **166**: 0.32 (UV, $KMnO_4$).

General Procedure for the Synthesis of Sulfonylated N,N-Dimethylanilines (1.0 mmol scale)



132 **167**

2-(*N*,*N*-Dimethylamino)phenyl trifluoromethanesulfonate **167**:

A stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (0.137 g, 1.00 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (10 mL) was cooled to –78 °C whereupon trifluoroacetic anhydride (0.155 mL, 1.10 mmol, 1.1 equiv.) was added dropwise via syringe. The resultant solution was stirred for 1 h whereupon triethylamine (0.276 mL, 2.00 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was quenched by the addition of three drops of acetic acid. The resultant mixture was warmed to 23 °C, then was concentrated. Purification of the residue by flash column chromatography (gradient elution 1 → 5% ethyl acetate–hexane) afforded the 2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **167** (0.0916 g, 67%) as a pale yellow oil.

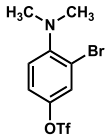
General Procedure for the Synthesis of Sulfonylated N,N-Dimethylanilines (10 mmol scale)

A stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (1.37 g, 10.0 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (100 mL) was cooled to –78 °C whereupon trifluoroacetic anhydride (1.55 mL, 11.0 mmol, 1.1 equiv.) was added dropwise via syringe (addition time approximately 2 min). The resultant solution was stirred for 1 h whereupon triethylamine (2.76 mL, 20.0 mmol,

2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was warmed to 0 °C for 45 min before being quenched by the addition of water (1.0 mL) and silica gel (4.0 g). The resultant mixture was concentrated to a volume of 20 mL, then was diluted with hexane (20 mL). The resultant mixture was filtered through a 1" by 1" plug of silica gel topped with 0.5 cm of anhydrous sodium sulfate. The plug was further eluted with 10% ethyl acetate–hexane (100 mL). The filtrate was concentrated to give 2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **167** (0.880 g, 64%) as an orange oil which slowly solidified.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.34 – 7.25 (m, 1H), 7.17 (dd, J_1 = 8.1, J_2 = 1.5 Hz, 1H), 7.11 (dd, J_1 = 8.1, J_2 = 1.6 Hz, 1H), 7.00 (ddd, J_1 = 8.0, J_2 = 7.3, J_3 = 1.7 Hz, 1H), 2.81 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	146.7, 143.4, 129.0, 122.5, 122.3, 120.5, 118.7 (q, J_1 = 318 Hz), 43.1.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–74.7.
FTIR (NaCl, thin film), cm^{-1}:	2954, 2841, 2792, 1609, 1499.
HRMS $(ES)^+$:	Calcd. for $C_9H_{10}F_3NO_3S$ $[M + H]^+$: 270.0412. Found: 270.0407.

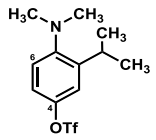
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)phenyl trifluoromethanesulfonate **167**: 0.68 (UV, $KMnO_4$).



168
28%

3-Bromo-4-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **168**:

^{1}H NMR (300 MHz, $CDCl_{3)}$, δ:	7.48 (d, J_1 = 2.9 Hz, 1H), 7.19 (dd, J_1 = 8.9, J_2 = 2.8 Hz, 1H), 7.08 (d, J_1 = 8.9 Hz, 1H), 2.81 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	152.3, 143.9, 127.0, 121.0, 120.9, 119.0, 118.8 (q, J_1 = 318 Hz), 44.1.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–72.7.
FTIR (NaCl, thin film), cm^{-1}:	2951, 2839, 2790, 1490, 1425.
HRMS $(ES)^+$:	Calcd. for $C_9H_9BrF_3NO_3SH$ $[M + H]^+$: 347.9517. Found: 347.9510.
TLC (20% EtOAc–Hex), R_f:	3-Bromo-4-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **168**: 0.59 (UV, $KMnO_4$).



169
61%
2.0:1
(4-OTf:6-OTf)

3-Isopropyl-4-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate *para*-**169**:

^{1}H NMR (300 MHz, $CDCl_{3)}$, δ: 7.14 – 7.08 (m, 2H), 7.03 (dd, J_1 = 8.8 Hz, 3.0 Hz, 1H), 3.52 (hept, J_1 = 6.8 Hz, 1H), 2.68 (s, 6H), 1.21 (d, J_1 = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 152.0, 146.9, 146.0, 121.2, 119.5, 119.0 (q, J_1 = 319 Hz), 118.9, 45.7, 27.2, 24.0.

^{19}F NMR (282 MHz, $CDCl_3$), δ: –72.9.

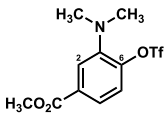
FTIR (NaCl, thin film), cm^{-1}: 2967, 2870, 2830, 1602, 1492, 1423.

HRMS $(EI)^+$: Calcd. for $C_{12}H_{16}F_3NO_3S$ $[M^{\bullet}]^+$: 311.0803. Found: 311.0794.

TLC (20% EtOAc/Hex), R_f: 3-Isopropyl-4-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate *para*-**169**: 0.72 (UV, $KMnO_4$).

3-Isopropyl-2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate *ortho*-**169**:

^{1}H NMR (300 MHz, $CDCl_{3)}$, δ:	7.13 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 1H), 7.05 (t, J_1 = 7.9 Hz, 1H), 6.91 (dd, J_1 = 8.0, J_2 = 1.7 Hz, 1H), 3.21 (hept, J_1 = 6.9 Hz, 1H), 2.73 (d, J_1 = 0.5 Hz, 6H), 1.13 (d, J_1 = 6.9 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	151.2, 148.8, 142.7, 126.7, 126.4, 118.6 (q, J_1 = 319 Hz), 118.5, 43.5, 28.4, 24.2.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–75.0.
FTIR (NaCl, thin film), cm^{-1}:	2969, 2871, 2797, 1454, 1417.
HRMS $(EI)^+$:	Calcd. for $C_{12}H_{16}F_3NO_3S$ $[M^{\bullet}]^+$: 311.0803. Found: 311.0799.
TLC (20% EtOAc–Hex), R_f:	3-Isopropyl-2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate *ortho*-**169**: 0.81 (UV, $KMnO_4$).



170
73%
1.25:1
(6-OTf:2-OTf)

Methyl 3-(*N*,*N*-dimethylamino)-4-(trifluoromethanesulfonate)benzoate **170**:

^{1}H NMR (300 MHz, $CDCl_{3)}$, δ: 7.76 (d, J_1 = 2.0 Hz, 1H), 7.67 (ddd, J_1 = 8.4, J_2 = 2.1, J_3 = 1.1 Hz, 1H), 7.28 – 7.16 (m, 1H), 3.92 (d, J_1 = 1.1 Hz, 3H), 2.83 (d, J_1 = 1.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$), δ: 166.1, 146.7, 146.1, 130.8, 123.8, 122.5, 121.8, 118.8 (q, J_1 = 320 Hz), 52.6, 43.1.

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.5.

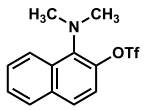
FTIR (NaCl, thin film), cm^{-1}: 2956, 2845, 2796, 1730, 1499, 1424.

HRMS $(ES)^+$: Calcd. for $C_{11}H_{12}F_3NO_5SNa$ $[M + Na]^+$: 350.0286. Found: 350.0281.

TLC (10% EtOAc–Hex), R_f: Methyl 3-(*N*,*N*-dimethylamino)-4-(trifluoromethanesulfonate)benzoate **170**: 0.81 (UV, $KMnO_4$).

Methyl 3-(*N*,*N*-dimethylamino)-2-(trifluoromethanesulfonate)benzoate **170**:

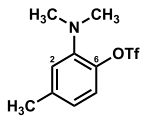
^{1}H NMR (500 MHz, $CDCl_{3)}$, δ:	7.59 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1H), 7.38 – 7.27 (m, 2H), 3.93 (s, 3H), 2.78 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	165.0, 147.6, 142.3, 128.3, 125.5, 125.3, 124.9, 118.8 (q, J_1 = 319 Hz), 52.8, 43.4.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–74.9.
FTIR (NaCl, thin film), cm^{-1}:	2957, 2876, 2844, 1735, 1421.
HRMS $(ES)^+$:	Calcd. for $C_{11}H_{12}F_3NO_5SNa$ $[M + Na]^+$: 350.0286. Found: 350.0287.
TLC (10% EtOAc–Hex), R_f:	Methyl 3-(*N*,*N*-dimethylamino)-2-(trifluoromethanesulfonate)benzoate **170**: 0.55 (UV, $KMnO_4$).



171
73%

1-(*N*,*N*-Dimethylamino)naphthalene-2-trifluoromethanesulfonate **171**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	8.29 (dd, J_1 = 8.1, J_2 =1.9 Hz, 1H), 8.11 – 8.03 (d, 1H), 7.67 – 7.57 (m, 2H), 7.38 (dd, J_1 = 8.5 Hz, J_2 = 1.9 Hz, 1H), 7.00 (d, J_1 = 8.4 Hz, 1H), 2.92 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	151.5, 141.1, 129.9, 127.7, 127.6, 126.5, 124.9, 121.3, 118.9 (q, J_1 = 320 Hz), 117.9, 112.8, 45.2.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–73.8.
FTIR (NaCl, thin film), cm^{-1}:	2984, 2945, 2835, 2790, 1599, 1575, 1419, 600.
HRMS $(ES)^+$:	Calcd. for $C_{14}H_{12}F_3NO_3SH$ $[M + H]^+$: 320.0568. Found: 320.0575.
TLC (20% EtOAc–Hex), R_f:	1-(*N*,*N*-Dimethylamino)naphthalene-2-trifluoromethanesulfonate **171**: 0.73 (UV, $KMnO_4$).



172
79%
2.5:1
(6-OTf:2-OTf)

2-(*N*,*N*-Dimethylamino)-4-methylphenyl trifluoromethanesulfonate **172**:

Isolated as a mixture of regioisomers, asterisk denotes minor peaks.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.20* (t, J_1 = 7.8 Hz, 1H), 7.08 (d, J_1 = 8.2 Hz, 1H), 7.06 – 7.03* (m, 1H), 6.96* (ddd, J_1 = 7.6, J_2 = 1.7, J_3 = 0.8 Hz, 1H), 6.93 (d, J_1 = 2.2 Hz, 1H), 6.85–6.78 (m, 1H), 2.81 (s, 6H), 2.74* (s, 6H), 2.37 (d, J_1 = 3.7 Hz, 3H), 2.37* (d, J_1 = 3.7 Hz, 3H).

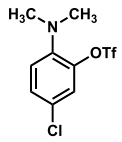
^{13}C NMR (125 MHz, $CDCl_3$), δ: 146.9, 146.2, 143.7, 141.4, 139.2, 131.1, 129.0, 128.1, 126.0, 123.0, 122.7, 121.9, 121.0, 120.2, 120.1, 118.8, 117.8, 117.6, 117.6, 114.5, 113.6, 110.5, 110.1, 43.4, 43.1, 21.3, 16.3.

^{19}F NMR (282 MHz, $CDCl_3$), δ: –74.6, –74.7.

FTIR (NaCl, thin film), cm^{-1}: 2952, 2876, 2839, 2791, 1607, 1501.

HRMS $(ES)^+$: Calcd. for $C_{10}H_{12}F_3NO_3SH$ $[M + H]^+$: 284.0568. Found: 284.0559.

TLC (20% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-4-methylphenyl trifluoromethanesulfonate **172**: 0.73 (UV, $KMnO_4$).

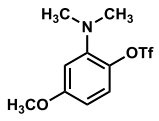


173

34%

5-Chloro-2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **173**:

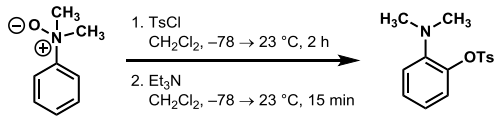
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.25 (dd, J_1 = 8.7, J_2 = 2.4 Hz, 1H), 7.16 (d, J_1 = 2.4 Hz, 1H), 7.02 (d, J_1 = 8.7 Hz, 1H), 2.78 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	145.6, 143.0, 129.1, 127.0, 122.8, 121.2, 118.8 (q, J = 318 Hz), 43.1.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–74.9.
FTIR (NaCl, thin film), cm^{-1}:	2956, 2844, 2794, 1497, 1424.
HRMS $(EI)^+$:	Calcd. for $C_9H_9ClF_3NO_3S$ $[M^{\bullet}]^+$: 302.9943. Found: 302.9938.
TLC (10% EtOAc–Hex), R_f:	5-Chloro-2-(*N*,*N*-dimethylamino)phenyl trifluoromethanesulfonate **173**: 0.73 (UV, $KMnO_4$).



174
95%

2-(*N*,*N*-Dimethylamino)-4-methoxyphenyl trifluoromethanesulfonate **174**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.08 (d, J_1 = 8.9 Hz, 1H), 6.59 (d, J_1 = 2.9 Hz, 1H), 6.47 (dd, J_1 = 8.9, J_2 = 2.9 Hz, 1H), 3.80 (s, 3H), 2.79 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	159.7, 147.6, 137.0, 122.9, 118.8 (q, J_1 = 320 Hz), 106.6, 105.9, 55.7, 43.0.
^{19}F NMR (282 MHz, $CDCl_3$), δ:	–74.5.
FTIR (NaCl, thin film), cm^{-1}:	2951, 2841, 2795, 1615, 1504, 1418.
HRMS $(ES)^+$:	Calcd. for $C_{10}H_{12}F_3NO_3SH$ $[M + H]^+$: 300.0517. Found: 300.0522.
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-4-methoxyphenyl trifluoromethanesulfonate **174**: 0.59 (UV, $KMnO_4$).



132 **175**

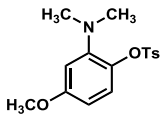
2-(*N*,*N*-Dimethylamino)phenyl (4-methylbenzene)sulfonate **175**:

A solution of *p*-toluenesulfonyl chloride (220 mg, 1.15 mmol, 1.2 equiv.) in dichloromethane (4 mL) was added dropwise to a stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (137 mg, 1.00 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (10 mL) at –78 °C. The resultant mixture was warmed to 23 °C and was stirred at that temperature for 2 h before being cooled to –78 °C. Triethylamine (0.276 mL, 2.00 mmol, 2.0 equiv.) was added dropwise via syringe and the resultant mixture was warmed to 23 °C, stirred for 15 min, then was diluted with hexane (10 mL). The resultant mixture was filtered through a plug of silica gel (hexane) and concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate–hexane) afforded 2-(*N*,*N*-dimethylamino)phenyl (4-methylbenzene)sulfonate **175** (0.111 g, 38%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.69 (d, J_1 = 8.1 Hz, 5H), 7.28 – 7.18 (m, 3H), 7.17 – 7.07 (m, 1H), 6.95–6.81 (m, 1H), 6.78 (dd, J_1 = 8.1, J_2 = 1.6 Hz, 1H), 2.52 (s, 6H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 145.8, 144.9, 141.9, 133.5, 129.1, 128.7, 127.8, 124.4, 121.1, 118.9, 42.5, 21.8.

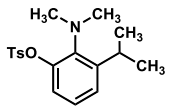
FTIR (NaCl, thin film), cm^{-1}:	2944, 2837, 2788, 1600, 1499, 1370.
HRMS $(ES)^+$:	Calcd. for $C_{15}H_{17}NO_3SNa$ $[M + Na]^+$: 300.0517. Found: 300.0522.
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)phenyl (4-methylbenzene)sulfonate **175**: 0.48 (UV, $KMnO_4$).



176
51%

2-(*N*,*N*-Dimethylamino)-4-methoxyphenyl (4-methylbenzene)sulfonate **176**:

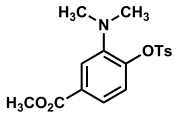
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.64 (d, J_1 = 8.3 Hz, 2H), 7.21 (d, J_1 = 8.0 Hz, 2H), 7.09 (d, J_1 = 8.8 Hz, 1H), 6.35 (dd, J_1 = 8.8, J_2 = 2.9 Hz, 1H), 6.25 (d, J_1 = 2.9 Hz, 1H), 3.72 (s, 3H), 2.46 (s, 6H), 2.39 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	158.7, 146.6, 144.8, 135.4, 133.3, 129.0, 128.5, 124.8, 105.1, 104.4, 55.4, 42.1, 21.6.
FTIR (NaCl, thin film), cm^{-1}:	2943, 2838, 2790, 1600, 1505, 1366.
HRMS $(ES)^+$:	Calcd. for $C_{16}H_{19}NO_4SNa$ $[M + Na]^+$: 344.0933. Found: 344.0923.
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-4-methoxyphenyl (4-methylbenzene)sulfonate **176**: 0.33 (UV, $KMnO_4$).



177
39%

2-(*N*,*N*-Dimethylamino)-3-isopropylphenyl (4-methylbenzene)sulfonate **177**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.87 (d, J_1 =8.4 Hz, 2H), 7.38 (d, J_1 = 8.4 Hz, 2H), 7.15 (dd, J_1 = 7.9, J_2 = 1.7 Hz, 1H), 7.02 (t, J_1 = 7.9 Hz, 1H), 6.89 (dd, J_1 = 8.1, J_2 = 1.6 Hz, 1H), 3.48 (hept, J_1 = 7.0 Hz, 1H), 2.75 (s, 6H), 2.48 (s, 3H), 1.20 (d, J_1 = 7.0 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	150.1, 148.5, 145.2, 142.8, 134.4, 129.9, 128.3, 125.3, 124.7, 119.2, 43.9, 27.9, 24.0, 21.8.
FTIR (NaCl, thin film), cm^{-1}:	2964, 2927, 2360, 2331,1455, 1373.
HRMS $(ES)^+$:	Calcd. for $C_{18}H_{23}NO_3SNa$ $[M + Na]^+$: 356.1296. Found: 356.1294.
TLC (10% EtOAc–Hex), R_f:	2-(*N*,*N*-Dimethylamino)-3-isopropylphenyl (4-methylbenzene)sulfonate **177**: 0.67 (UV, $KMnO_4$).

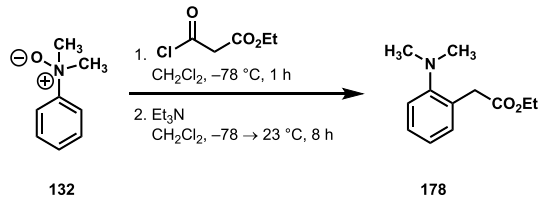


178
63%

Methyl 3-(*N*,*N*-dimethylamino)-4-(*p*-toluenesulfonate)benzoate **178**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.67 (dd, J_1 = 8.4, J_2 = 1.6 Hz, 2H), 7.53 (dd, J_1 = 8.4, J_2 = 2.1 Hz, 1H), 7.44 (d, J_1 = 2.0 Hz, 1H), 7.29 – 7.20 (m, 3H), 3.89 (s, 3H), 2.56 (s, 6H), 2.41 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	166.6, 145.7, 145.3, 145.0, 133.2, 129.4, 129.3, 128.6, 124.3, 122.4, 120.2, 52.4, 42.4, 21.8.
FTIR (NaCl, thin film), cm^{-1}:	2951, 2842, 1723, 1596, 1501, 1375.
HRMS $(ES)^+$:	Calcd. for $C_{17}H_{19}NO_3SNa$ $[M + Na]^+$: 372.0882. Found: 372.0884.
TLC (10% EtOAc–Hex), R_f:	Methyl 3-(*N*,*N*-dimethylamino)-4-(*p*-toluenesulfonate)benzoate **178**: 0.30 (UV, $KMnO_4$).

General procedure for the Synthesis of Alkylated N,N-Dimethylanilines (1.0 mmol scale)



132 178

Ethyl [2-(*N*,*N*-dimethylamino)phenyl]acetate **178**:

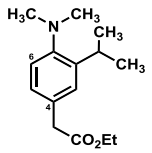
A stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (0.137 g, 1.00 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (20 mL) was cooled to –78 °C whereupon ethyl malonyl chloride (0.140 mL, 1.10 mmol, 1.1 equiv.) was added dropwise via syringe. The resultant solution was stirred for 1 h whereupon triethylamine (0.237 mL, 1.10 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was warmed to 23 °C, stirred at that temperature for 8 h, then was concentrated. Purification of the residue by flash column chromatography (gradient elution 1 → 2% ethyl acetate–hexane) afforded the ethyl [2-(*N*,*N*-dimethylamino)phenyl]acetate **178** (0.136 g, 67%) as a pale yellow oil.

General procedure for the Synthesis of Alkylated N,N-Dimethylanilines (10 mmol scale)

A stirred solution of the *N*,*N*-dimethylaniline-*N*-oxide **132** (1.37 g, 10.0 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (200 mL) was cooled to –78 °C whereupon ethyl malonyl chloride (1.40 mL, 11.0 mmol, 1.1 equiv.) was added dropwise via syringe (addition time approximately 2 min). The resultant solution was stirred for 1 h whereupon triethylamine (2.37 mL, 20.0 mmol,

2.0 equiv.) was added. The reaction mixture was stirred for 15 min, then was warmed to 23 °C, stirred at that temperature for 8 h, then was concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate–hexane) afforded the ethyl [2-(*N*,*N*-dimethylamino)phenyl]acetate **178** (1.13 g, 55%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.25–7.20 (m, 2H), 7.18–7.11 (m, 1H), 7.05 (td, J_1 = 7.4, J_2 = 1.4 Hz, 1H), 4.16 (q, J_1 = 7.2, 2H), 3.73 (s, 2H), 2.64 (s, 6H), 1.25 (t, J_1 = 7.1 Hz, 4H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	172.6, 153.2, 131.0, 130.5, 128.1, 123.9, 120.3, 60.7, 45.1, 37.3, 14.4.
FTIR (NaCl, thin film), cm^{-1}:	2980, 2939, 2877, 2785, 1735, 1495.
HRMS $(ES)^+$:	Calcd. for $C_{12}H_{17}NO_2Na$ $[M + Na]^+$: 230.1157. Found: 230.1152.
TLC (10% EtOAc–Hex), R_f:	Ethyl [2-(*N*,*N*-dimethylamino)phenyl]acetate **178**: 0.48 (UV, $KMnO_4$).



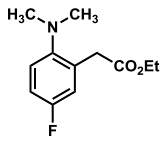
179
31%
3:1
(6-alk:4-alk)

Ethyl [4-(*N*,*N*-dimethylamino)-3-isopropylphenyl]acetate *para*-**179**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.15 (d, J_1 = 1.4 Hz, 1H), 7.06 (d, J_1 = 1.3 Hz, 2H), 4.15 (q, J_1 = 7.1 Hz, 2H), 3.56 (s, 2H), 3.50 (hept, J_1 = 6.9 Hz, 1H), 2.66 (s, 6H), 1.31 – 1.17 (m, 9H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	171.9, 150.7, 144.1, 129.3, 127.4, 126.9, 119.7, 60.7, 45.8, 41.0, 26.6, 24.1, 14.2.
FTIR (NaCl, thin film), cm^{-1}:	2963, 2935, 2868, 1735, 1501.
HRMS $(ES)^+$:	Calcd. for $C_{15}H_{23}NO_2Na$ $[M + Na]^+$: 272.1627. Found: 272.1620.
TLC (10% EtOAc–Hex), R_f:	Ethyl [4-(*N*,*N*-dimethylamino)-3-isopropylphenyl]acetate *para*-**179**: 0.57 (UV, $KMnO_4$).

Ethyl [2-(*N*,*N*-dimethylamino)-3-isopropylphenyl]acetate *ortho*-**179**:

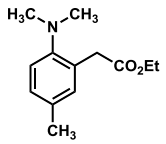
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.17 (d, J_1 = 7.5 Hz, 1H), 7.12 (t, J_1 = 7.5 Hz, 1H), 7.05 (d, J_1 = 7.5 Hz, 1H), 4.17 (q, J_1 = 7.0 Hz, 2H), 3.61 (s, 2H), 3.18 (m, 1H), 2.76 (s, 6H), 1.27 – 1.21 (m, 9H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	172.1, 150.9, 144.3, 129.5, 127.6, 127.1, 119.8, 60.9, 46.0, 41.2, 26.8, 24.3, 14.4.
FTIR (NaCl, thin film), cm^{-1}:	2963, 2868, 2784, 1735, 1447.
HRMS $(ES)^+$:	Calcd. for $C_{15}H_{23}NO_2Na$ $[M + Na]^+$: 272.1627. Found: 272.1621.
TLC (10% EtOAc–Hex), R_f:	Ethyl [2-(*N*,*N*-dimethylamino)-3-isopropylphenyl]acetate *ortho*-**179**: 0.61 (UV, $KMnO_4$).



180
47%

Ethyl (2-(*N*,*N*-dimethylamino)-5-fluorophenyl)acetate **180**:

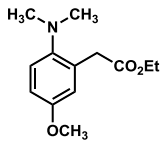
^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.12 (dd, J_1 = 8.8, J_2 = 5.2 Hz, 1H), 7.00 – 6.87 (m, 2H), 4.17 (q, J_1 = 7.0 Hz, 2H), 3.71 (s, 2H), 2.60 (s, 6H), 1.26 (t, J_1 = 7.1, 3H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	172.0, 159.3 (d, J_1 = 242 Hz), 149.3, 132.8, 121.9 (d, J_1 = 7.6 Hz), 117.4 (d, J_1 = 22.1 Hz), 114.6 (d, J_1 = 22.1 Hz), 60.9, 45.4, 37.1, 14.4.
^{19}F NMR (470 MHz, $CDCl_3$), δ:	–118.3.
FTIR (NaCl, thin film), cm^{-1}:	2982, 2940, 2828, 1735, 1499.
HRMS $(EI)^+$:	Calcd. for $C_{12}H_{16}FNO_2$ $[M^{\bullet}]^+$: 225.1165. Found: 225.1168.
TLC (10% EtOAc–Hex), R_f:	Ethyl (2-(*N*,*N*-dimethylamino)-5-fluorophenyl)acetate **180**: 0.48 (UV, $KMnO_4$).



181
50%

Ethyl (2-(*N*,*N*-dimethylamino)-5-methylphenyl)acetate **181**:

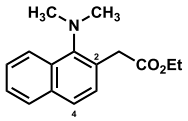
^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.07 (s, 3H), 4.18 (dd, J_1 = 7.1, J_2 = 0.6 Hz, 2H), 3.71 (s, 2H), 2.62 (d, J_1 = 0.6 Hz, 6H), 2.30 (s, 3H), 1.50 – 1.07 (m, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	172.7, 150.7, 133.4, 131.5, 130.4, 128.7, 120.2, 60.6, 45.2, 37.2, 20.9, 14.4.
FTIR (NaCl, thin film), cm^{-1}:	2979, 2930, 2858, 1735, 1503, 1454.
HRMS $(ES)^+$:	Calcd. for $C_{13}H_{19}NO_2Na$ $[M + Na]^+$: 244.1313. Found: 244.1311.
TLC (20% EtOAc–Hex), R_f:	Ethyl (2-(*N*,*N*-dimethylamino)-5-methylphenyl)acetate **181**: 0.66 (UV, $KMnO_4$).



182
57%

Ethyl (2-(*N*,*N*-dimethylamino)-5-methoxyphenyl)acetate **182**:

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.12 (d, J_1 = 8.5 Hz, 1H), 6.80 (m, 2H), 4.17 (q, J_1 = 7 Hz, 2H), 3.76 (s, 3H), 3.71 (s, 2H), 2.59 (s, 6H), 1.26 (t, J_1 = 7.1, 3H).
^{13}C NMR (125 MHz, $CDCl_3$), δ:	172.2, 156.0, 146.3, 132.1, 121.5, 115.9, 113.2, 60.5, 55.3, 45.5, 37.2, 14.3.
FTIR (NaCl, thin film), cm^{-1}:	2980, 2938, 2826, 2781, 1738, 1608, 1506.
HRMS $(EI)^+$:	Calcd. for $C_{13}H_{19}NO_3$ $[M^{\bullet}]^+$: 244.1313. 237.1364. Found: 237.1366.
TLC (20% EtOAc–Hex), R_f:	Ethyl (2-(*N*,*N*-dimethylamino)-5-methoxyphenyl)acetate **182**: 0.39 (UV, $KMnO_4$).



183
43%
2:1
(2-alk:4-alk)

Ethyl (1-(*N*,*N*-dimethylamino)naphthalen-2-yl)acetate *ortho*-**183**:

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.13 – 8.02 (m, 1H), 7.93 – 7.82 (m, 1H), 7.68 (d, J_1 = 8.4 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.40 (d, J_1 = 8.4 Hz, 1H), 4.21 (q, J_1 = 7.1 Hz, 2H), 3.88 (s, 2H), 3.05 (s, 6H), 1.29 (t, J_1 = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 172.2, 147.2, 134.8, 132.8, 131.6, 128.9, 128.8, 126.1, 125.6, 125.4, 124.5, 60.7, 43.8, 38.6, 14.4.

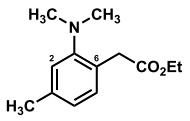
FTIR (NaCl, thin film), cm^{-1}: 3050, 2979, 2926, 2832, 1733, 1386.

HRMS $(ES)^+$: Calcd. for $C_{16}H_{19}NO_2Na$ $[M + Na]^+$: 280.1313. Found: 280.1306.

TLC (20% EtOAc–Hex), R_f: Ethyl (1-(*N*,*N*-dimethylamino)naphthalen-2-yl)acetate *ortho*-**183**: 0.63 (UV, $KMnO_4$)

Ethyl (4-(*N*,*N*-dimethylamino)naphthalen-1-yl)acetate *para*-**183**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	8.36 – 8.24 (m, 1H), 8.03 – 7.92 (m, 1H), 7.58 – 7.45 (m, 2H), 7.34 (dt, J_1 = 7.7, J_2 = 0.6 Hz, 1H), 7.05 (d, J_1 = 7.6 Hz, 1H), 4.17 (q, J=*1* = 7.1 Hz, 2H), 4.01 (d, J_1 = 0.6 Hz, 2H), 2.90 (s, 6H), 1.25 (t, J_1 = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	172.1, 150.9, 133.4, 129.3, 128.0, 126.2, 125.3, 125.1, 124.9, 124.4, 113.8, 61.0, 45.4, 39.2, 14.4.
FTIR (NaCl, thin film), cm^{-1}:	3050, 2979, 2926, 2832, 1733, 1386.
HRMS $(ES)^+$:	Calcd. for $C_{16}H_{19}NO_2Na$ $[M + Na]^+$: 280.1313. Found: 280.1306.
TLC (20% EtOAc–Hex), R_f:	Ethyl (4-(*N*,*N*-dimethylamino)naphthalen-1-yl)acetate *para*-**183**: 0.54 (UV, $KMnO_4$).



184
65%
2:1
(6-alk:2-alk)

Ethyl (2-(*N*,*N*-dimethylamino)-4-methylphenyl)acetate **184**:

Isolated as a mixture of regioisomers, asterisk denotes minor peaks.

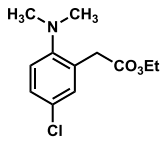
^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.19* (t, J_1 = 7.8 Hz, 1H), 7.16 (d, J_1 = 8.1 Hz, 1H), 7.07* (d, J_1 = 8.2 Hz, 1H), 6.99 (s, 1H), 6.97* (d, J_1 = 7.8 Hz, 1H), 6.90 (d, J_1 = 7.6 Hz, 1H), 4.19 (q, J_1 = 7.1 Hz, 2H), 4.19* (q, J_1 = 7.1 Hz, 2H), 3.90* (s, 2H), 3.73 (s, 2H), 2.66 (s, 6H), 2.66* (s, 6H), 2.35 (s, 3H), 2.29* (s, 3H), 1.28 (t, J_1 = 7.1 Hz, 3H), 1.28* (t, J_1 = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$), δ: 172.7, 172.6, 153.6, 152.9, 138.4, 137.7, 130.7, 129.6, 129.1, 127.6, 127.2, 125.9, 124.5, 120.9, 118.2, 117.9, 113.2, 109.7, 60.5, 45.4, 36.9, 34.0, 21.4, 20.2, 14.3.

FTIR (NaCl, thin film), cm^{-1}: 2979, 2937, 2826, 2781, 1732, 1609, 1507.

HRMS $(ES)^+$: Calcd. for $C_{13}H_{19}NO_2Na$ $[M + Na]^+$: 244.1313. Found: 244.1309.

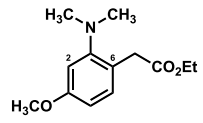
TLC (20% EtOAc–Hex), R_f:	Ethyl (2-(*N*,*N*-dimethylamino)-4-methylphenyl)acetate **184**: 0.57 (UV, $KMnO_4$).



185
29%

Ethyl (5-chloro-2-(*N*,*N*-dimethylamino)phenyl)acetate **185**:

^{1}H NMR (300 MHz, $CDCl_3$), δ:	7.24 – 7.16 (m, 2H), 7.06 (d, J_1 = 8.4 Hz, 1H), 4.17 (q, J_1 = 7.1 Hz, 2H), 3.68 (s, 2H), 2.61 (s, 6H), 1.25 (t, J_1 = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	171.9, 151.8, 130.8, 129.1, 128.0, 121.6, 113.5, 60.9, 45.0, 37.0, 14.4.
FTIR (NaCl, thin film), cm^{-1}:	2982, 2941, 2787, 1734, 1490.
HRMS $(EI)^+$:	Calcd. for $C_{12}H_{16}ClNO_2$ $[M^{\bullet}]^+$: 241.0869. Found: 241.0859.
TLC (10% EtOAc–Hex), R_f:	Ethyl (5-chloro-2-(*N*,*N*-dimethylamino)phenyl)acetate **185**: 0.46 (UV, $KMnO_4$).



186
51%
2:1
(6-alk:2-alk)

Ethyl (2-(*N*,*N*-dimethylamino)-4-methoxyphenyl)acetate **186**:

Isolated as a mixture of regioisomers, asterisk denotes minor peaks.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.21* (t, J_1 = 8.2 Hz, 1H), 7.16 (d, J_1 = 8.4 Hz, 1H), 6.80* (d, J_1 = 8.1 Hz, 1H), 6.71 (d, J_1 = 2.6 Hz, 1H), 6.65* (d, J_1 = 8.3 Hz, 1H), 6.61 (dd, J_1 = 8.3, J_2 = 2.7 Hz, 1H), 4.17 (q, J_1 = 7.1 Hz, 2H), 4.17* (d, J_1 = 7.1 Hz, 2H), 3.79 (s, 2H), 3.79* (s, 2H), 3.78* (s, 2H), 3.67, (s, 2H), 2.66* (s, 6H), 2.64 (s, 6H), 1.26 (t, J_1 = 7.1 Hz, 3H), 1.26* (t, J_1 = 7.1 Hz, 3H).

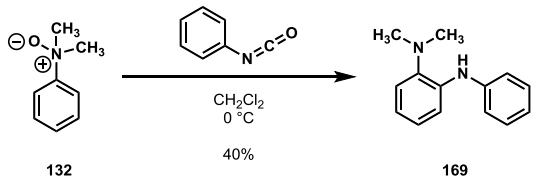
^{13}C NMR (75 MHz, $CDCl_3$), δ: 172.9, 172.8, 159.5, 158.6, 154.3, 154.2, 131.5, 128.1, 122.3, 119.0, 112.2, 108.1, 106.8, 106.0, 60.5, 60.3, *55.6, 55.3, 45.1, 44.0, 36.5, 31.4, 14.3.

FTIR (NaCl, thin film), cm^{-1}: 2960, 2938, 2782, 1735, 1610, 1506.

HRMS $(ES)^+$: Calcd. for $C_{13}H_{19}NO_3H$ $[M + H]^+$: 238.1143. Found: 238.1456.

TLC (10% EtOAc–Hex), R_f:	Ethyl (2-(*N*,*N*-dimethylamino)-4-methoxyphenyl)acetate **186**: 0.35 (UV, $KMnO_4$).

*Procedure for the Synthesis of Aminated N,N-Dimethylaniline **169***



132 169

<u>N^1,N^1-Dimethyl-N^2-phenylbenzene-1,2-diamine **169**:</u>

A solution of phenyl isocyanate (0.150 mL, 1.20 mmol, 1.2 equiv.) in dichloromethane (50 mL) was added dropwise over six hours to a stirred, cooled solution of the *N*,*N*-dimethylaniline-*N*-oxide **69** (137 mg, 1.00 mmol, 1.0 equiv., dried by azeotropic distillation with benzene) in dichloromethane (50 mL) at 0 °C. The resultant solution slowly turned red and was stirred 0 °C for 6 h whereupon the solution was allowed to slowly rise to 22 °C over the next 8 h. After this period, silica gel (ca. 3 mL) was added. The resultant suspension was stirred for 30 min, allowed to settle, then the yellow solution was filtered and concentrated. The crude product mixture was suspended in hexane such that a solid white byproduct is removed and the yellow extract passed through a small plug of silica gel (hexane) to afford the N^1,N^1-dimethyl-N^2-phenylbenzene-1,2-diamine **169** (83.9 mg, 40%) after concentration as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37–7.26 (m, 3H), 7.19 – 7.13 (m, 2H), 7.11 (dd, J_1 = 7.8, J_2 = 1.5 Hz, 1H), 7.03 – 6.89 (m, 2H), 6.85 (td, J_1 = 7.6, J_2 = 1.5 Hz, 1H), 6.57 (s, 1H), 2.68 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$), δ:	129.4, 129.2, 124.2, 120.9, 120.0, 119.8, 118.4, 116.8, 114.5, 112.8, 44.3, 40.8.
FTIR (NaCl, thin film), cm^{-1}:	3354, 3040, 2939, 2826, 2360, 1592, 1512.
HRMS $(ES)^+$:	Calcd. for $C_{14}H_{16}N_2H$ $[M + H]^+$: 213.1392. Found: 213.1387.
TLC (10% EtOAc–Hex), R_f:	N^1,N^1-Dimethyl-N^2-phenylbenzene-1,2-diamine **169**: 0.63 (UV, $KMnO_4$).

Chapter 3

EFFORTS TOWARD A TOTAL SYNTHESIS OF PSIGUADIAL A

3.1 Introduction to the Meroterpenoid Psiguadials

In 2010, Ye and coworkers described the natural products psiguadial A (**190**) and psiguadial B (**191**) (**Figure 3.1**).[1a] These meroterpenoids were isolated from the ethanol extracts from the leaves of *Psidium guajava*, the common guava tree. Two years later in 2012, Ye and coworkers published a second report detailing the structures of psiguadial C (**192**) and psiguadial D (**193**) again isolated from the leaves of the same species of small tropical tree.[1b] All structures reported with absolute configuration were elucidated by means of NMR, HRMS, X-ray diffraction, and quantum chemical CD calculations.

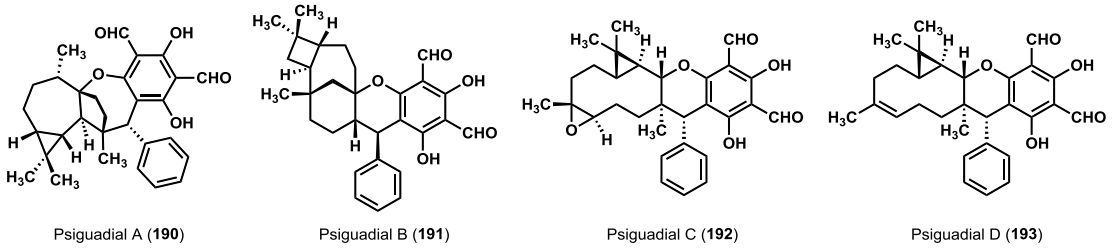


Figure 3.1 Psiguadials A, B, C, and D

Prior to the isolation of psiguadials A–D, the leaves of *P. guajava* had been used for the treatment of diarrhea and hyperglycemia in traditional Chinese medicines. Pharmacological and clinical research groups have sought to understand the safety and

efficacy of materials and extracts of *P. guajava* in recent years.[2] Previous phytochemical investigations of this plant had led to the isolation of more than 50 compounds including triterpenoids, sesquiterpenoids, flavonoids and novel sesquiterpenoid-based meroterpenoids.[3] Given the well-known medicinal uses of the parent plants leaves, the psiguadials were examined for their biological activity. The antitumor activities of the psiguadial were detected in doxorubicin-sensitive and -resistant human hepatoma cells (HepG2 and HepG2/ADM). Psiguadials A (**190**), B (**191**), C (**192**), and D (**193**) exhibited potent inhibitory effects on the growth of HepG2 cells (IC_{50} = 61, 45, 104, and 128 nM, respectively). Testing the biological activity against doxorubicin-resistant HepG2/ADM cell lines, the researchers found the natural products exhibited far weaker activity. These data lead the authors to speculate that these meroterpenoids are substrates for the P-glycoprotein pump which is overexpressed in HepG2/ADM.[1b]

3.2 Prior Synthesis of Psiguadials

In 2014, Tran and Cramer described a brief synthesis of psiguadial A (**190**) (**Figure 3.2**).[4] Retrosynthetic analysis in this biomimetic synthesis divided the meroterpenoid psiguadial A (**190**) in to its constituent halves: sesquiterpene and polyketide. The sequence began with (+)-2-carene (**194**) transformed in seven steps to (+)-bicyclogermacrene **195**. The synthesis was completed with an acid catalyzed carbocation cascade reaction between **195**, phloroglucinol **196**, and benzaldehyde with a 1% yield of psiguadial A (**190**) and a 7% yield psiguadial D (**193**) detected via NMR (using 1,3,5-trimethoxybenzene as internal standard). To date, Tran and Cramer's synthesis is the only published synthesis of psiguadial A (**190**) and D (**193**).

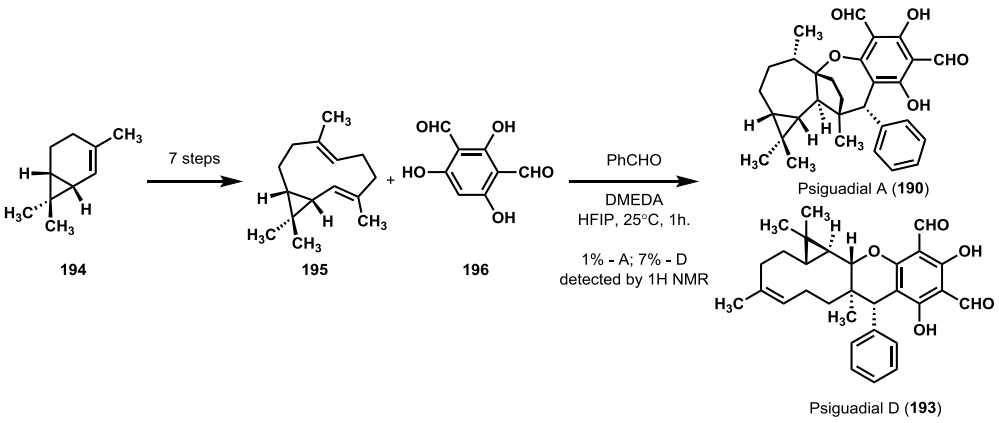


Figure 3.2 Tran and Cramer's Biomimetic Synthesis of Psiguadial A

The acid-mediated carbocation cascade reaction in Tran and Cramer's synthesis mimics the proposed biosynthesis from Ye and coworkers (**Figure 3.3**).[1b] The plausible biosynthesis begins with benzoyl-CoA (**197**) condensed with one molecule of malonyl-CoA and two molecules of methylmalonyl-CoA. Then cyclization and enolization would lead to the formation of intermediate **198**. Intermediate **198** could be oxidized and then generate the carbocation **199**. In parallel, geranyl phosphate (**200**) would form bicyclogermacrene **195** via a cyclase. As a cationic initiator, the carbocation **199** could respectively couple with the cyclic **195**, to generate the carbocations **201** through **203**, eventually affording psiguadial A (**190**).

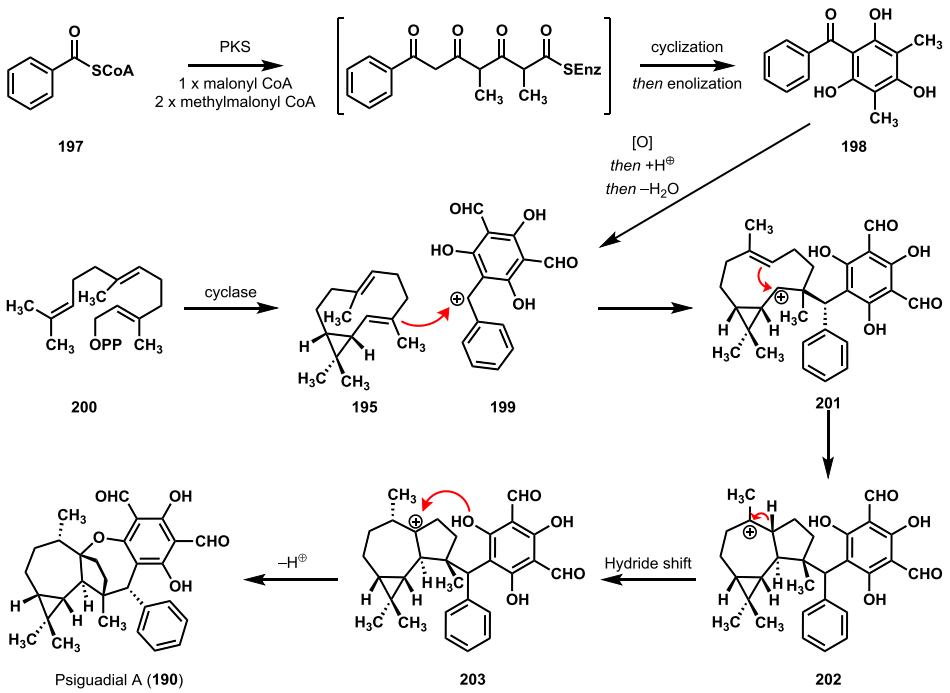
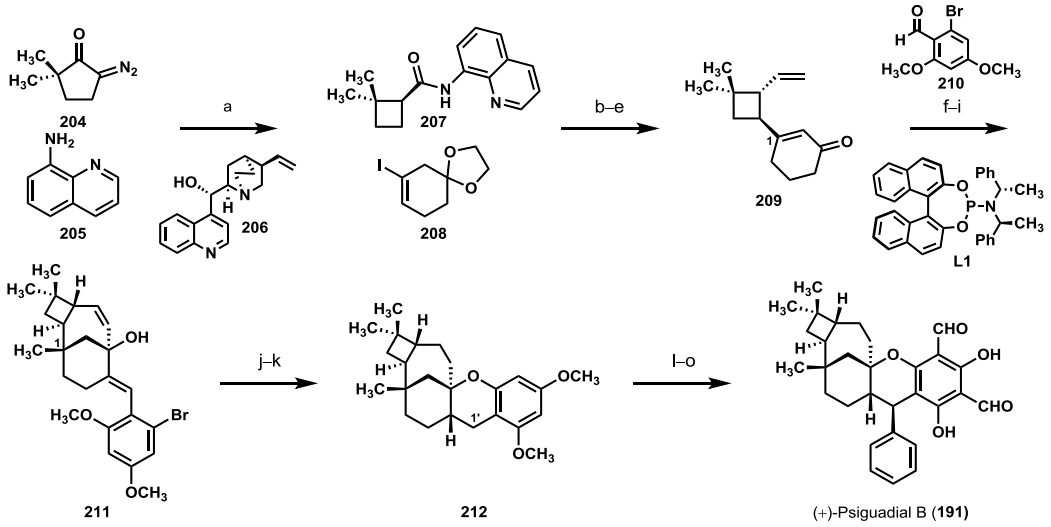


Figure 3.3 Ye's Proposed Biosynthesis of Psiguadial A

In 2016, Reisman and coworkers completed the first enantioselective total synthesis of the meroterpenoid (+)-psiguadial B (**191**) (**Figure 3.4**)[5]. The synthesis began with the photolysis of 2,2-dimethylcyclopentanone (**204**) in the presence of a chiral catalyst ((+)-cinchonine, **206**) and 8-aminoquinoline (**205**) to produce the tandem Wolff rearrangement/catalytic asymmetric ketene addition product **207**. The amide **207** was coupled with the iodide **208**. This coupled amide was reduced to the corresponding aldehyde, epimerized under basic conditions, then finally telescoped through a Wittig olefination and hydrolysis to afford the vinyl enone **209**. Copper catalyzed asymmetric conjugate addition installed the methyl group at the C1 all-carbon quaternary center. Subsequent aldol condensation with **210**, treatment with vinyllithium and ring-closing metathesis provided the fully assembled A–B–C ring system **211**. Hydrogenation with Crabtree's catalyst and copper catalyzed

intramolecular *O*-arylation constructed the pentacycle **212**. Completion of the synthesis installed the phenyl group at C1' in two steps and formylation of the polyketide derived ring in two steps to yield (+)-psiguadial B (**191**) in 15 steps.



(a) **206**, h*ν* (254 nm), THF, 62%. (b) $Pd(OAc)_2$, Ag_2CO_3, TBME, 90 °C, 72%. (c) $Cp_2Zr(H)Cl$, THF. (d) KOH, MeOH, 70% over two steps. (e) Ph_3PCH_2, then 5M HCl, 88%. (f) CuTC, **L1**, Me_3Al, Et_2O, –35 °C, 94%. (g) **210**, KOH, MeOH, 80 °C, 92%. (h) vinyllithium, THF, –78 °C, 80%. (i) HG-II, 1,4-BQ, PhH, 80 °C, 93%. (j) Crabtree's cat, H_2, CH_2Cl_2, 90%. (k) CuI, 2,2'-bipy., KO*t*-Bu, DMF, 120 °C, 75%. (l) DDQ, $EtO(CH_2)_2OH$, MeCN, CH_2Cl_2, 0 °C to rt. 60%, 2 cycles. (m) $Ph_2Cu(CN)Li_2$, BF_3•OEt_2, Et_2O, –78 to –45 °C, 90%. (n) pyr•HCl, 200 °C, 62%. (o) CH_3OCHCl_2, $TiCl_4$, CH_2Cl_2, –78 °C to rt, 50%.

Figure 3.4 Reisman's Synthesis of (+)-Psiguadial B

3.3 Retrosynthetic Analysis of Psiguadial A

At the core of psiguadial A (**190**) lies an interesting 3-7-7-6 fused ring system with a bridging five-membered ring. The molecule contains five contiguous stereogenic centers with seven in total. The western half of the molecule is terpene-based and fully reduced without any oxidation or obvious synthetic handle, while the eastern half is polyketide-based and contains a high level of oxidation. The central seven-membered ring is an oxepane and links the western seven-member and eastern

six-membered rings. Given these diverse structural features, psiguadial A (**190**) presents us with a considerable synthetic challenge.

We hoped to develop a convergent strategy toward psiguadial A (**190**) that would allow us to join a functionalized diphenyl methane unit with a suitably modified terpenoid fragment. Retrosynthetic analysis of the key step began by targeting the oxygen-containing heterocyclic seven-membered oxepane (**Figure 3.5**, highlighted in **red**). If one considers a simple oxidation level change at C3 (**213**, a carbonyl highlighted in **blue**), the key sequence in the synthesis we envisioned would be forming the seven-member ring via two successive Michael addition reactions (**214**) involving an intermolecular addition of an enolate to an *ortho*-quinone methide (*o*-QM), substrates **215** and **216** respectively, followed by an intramolecular oxa-Michael addition.

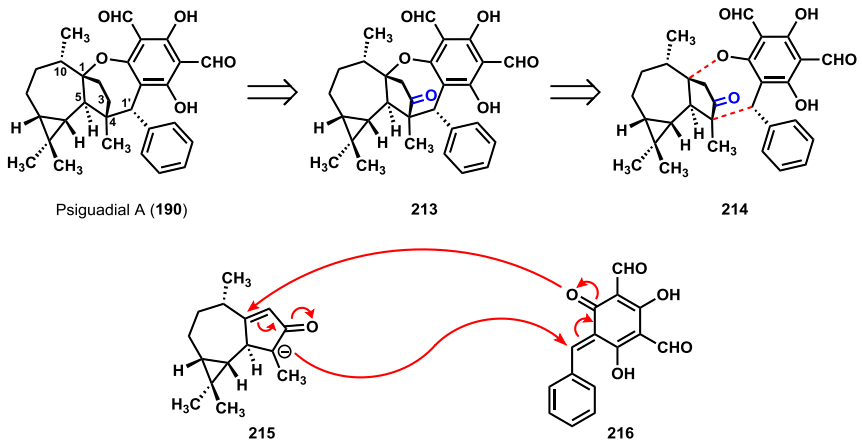


Figure 3.5 Retrosynthetic Analysis of Psiguadial A

We recently describe an enolate–*ortho*-quinone methide coupling reaction in which silyl enol ethers and/or silyl ketene acetals of type **217** are joined smoothly and

diastereoselectivity with silyl protected phenolic benzyl chlorides of type **218** under the action of anhydrous fluoride to give a variety of functionalized β–(2-hydroxyphenyl)-carbonyl **221** compounds (**Figure 3.6**).[6] One substrate we described in that work (**223**) is suitably functionalized to serve as the diphenyl methane unit in our intended synthesis of psiguadial A, and the stereochemical outcomes (and proposed predictive model based on these results) of the reaction are consistent with the stereochemical requirements of our intended synthetic strategy. This modular, convergent strategy gives us maximum flexibility for the production of a diverse array of analogues for structure-function, target identification, and other critical biological studies of this family of natural products.

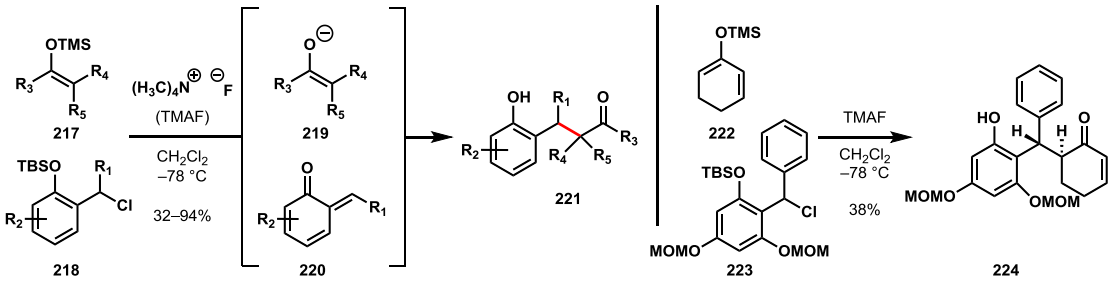


Figure 3.6 Enolate–*ortho*-Quinone Methide Reaction

Further simplification of the silyl enol ether **225** and silyl protected phenolic benzyl chloride **223** to commercially available materials is as follows. The silyl enol ether **225** could result from redox adjustment of the cyclopentenone **226** then generation of the enolate, and trapping with silyl protecting group (**Figure 3.7**). The amide **227** reacting with a lithiated allene is expected to undergo a Nazarov cyclization to form the cyclopentenone **226**. The asymmetric version of this Nazarov cyclization would require a chiral auxiliary on the lithiated allene to impart asymmetry.[7]

Continuing the retrosynthesis, the conjugated amide **227** would result from the hydrolysis of alcohol **228**. The dimethyl cyclopropane unit in **228** could be installed via a Simmons-Smith reaction from the allylic alcohol **229**. Formation of the seven-membered ring would result from ring closing metathesis of the di-olefin **230**. An aldol reaction between acrolein and the enolate of **231** would install the three carbon side chain. Commercially available (±)-citronellic acid (**232**) would begin racemic synthesis toward **225** and be the scaffold for developing the synthetic route. (–)-Citronellic acid would be the starting material of the enantioselective synthesis, making use of the chiral pool.

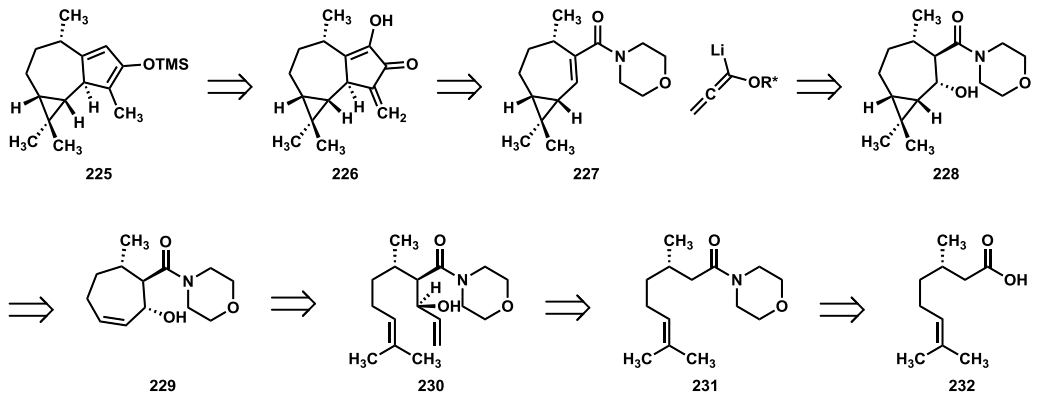


Figure 3.7 Retrosynthetic Analysis of Silyl Enol Ether **225**

Retrosynthetic analysis of the silyl protected phenolic benzyl chloride **223** is shown below (**Figure 3.8**). First, simple functional group conversion of the benzylic alcohol **233** to benzylic chloride **223**. Phenyl Grignard would add to the aldehyde **234** producing benzylic alcohol **233**. The synthesis of the aldehyde **234** would begin with 2,4,6-trihydroxybenzaldehyde (**236**), the doubly protected with MOM **235** and the last phenol protected with TBS.

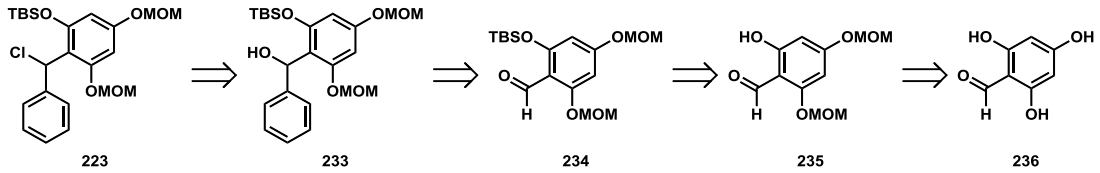


Figure 3.8 Retrosynthetic Analysis of Silyl Protected Phenolic Benzyl Chloride **233**

3.4 Preliminary Synthesis of Terpene Derived Silyl Enol Ether 225

Initial efforts have been directed toward the synthesis of the racemic silyl enol ether **225** the terpenoid unit of the natural product. We converted commercially available (±)-citronellic acid (**232**) into the morpholine amide **231** using straightforward carbonyl chemistry (**Figure 3.9**).[8] Next, an aldol reaction[9] between the lithium enolate derived from **231** and acrolein gave the adduct **230** as a mixture of inseparable diastereomers. This amide enolate was reactive toward acrolein at low temperature (–78 °C) and did not require warming to accomplish the aldol reaction. Continuing the synthesis, a ring closing metathesis under the action of the Grubbs second generation catalyst[10] gave the cycloheptenol **229** as a mixture of partially separable diastereomers. The diastereomers are rendered inconsequential after hydrolysis in the coming steps.

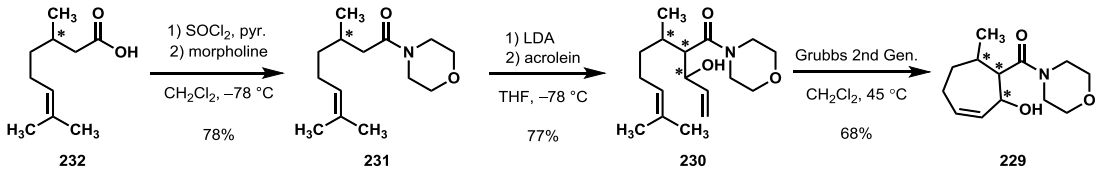


Figure 3.9 Synthesis of Allylic Alcohol **229**

At this point in the sequence, we envisioned two separate paths that could lead to the conjugated amide **227** (**Figure 3.10**). The first path involved a Furukawa-

modified Simmons-Smith reaction producing **228**.[11] Although in this racemic synthesis, the allylic alcohol **229** was a mixture of inseparable diastereomers, when the enantiopure (–)-citronellic acid was employed, only two diastereomer could arise. Our hypothesis was with the allylic alcohol **229** in hand, conditions could be developed for a directed Furukawa-modified Simmons-Smith reaction to install the *gem*-dimethyl cyclopropane with the correct stereochemistry.[11] Cyclopropanation is highly diastereoselective and occurs from the less hinder face of a double bond or is delivered to the face of a double bong having the closer proximity to a functional group (directing effect, *cis*-diastereoselectivity).[11] The stereochemical outcome to cycloalkenols depends on the ring size. Five-, six-, and seven-membered cycloalkenols give rise to high *cis*-diastereoselectivity, while larger rings produce high levels of *anti*-diastereoselectivity. If necessary conditions exist to favor the *anti*-diastereoselectivity in smaller rings thus allowing us to access the reverse of the directing effect.[11]

To our delight, cyclopropanation with diethyl zinc and diiodomethane to produce **237** was consistently successful. Yet, this product lacked the *gem*-dimethyl cyclopropane functionality we desired. We intended to make the conjugated amide after hydrolysis, but were disappointed to discover that elimination with Martin's sulfurane dehydrating agent[12] to **238** gave ring opening and fragmentation of the cyclopropane.

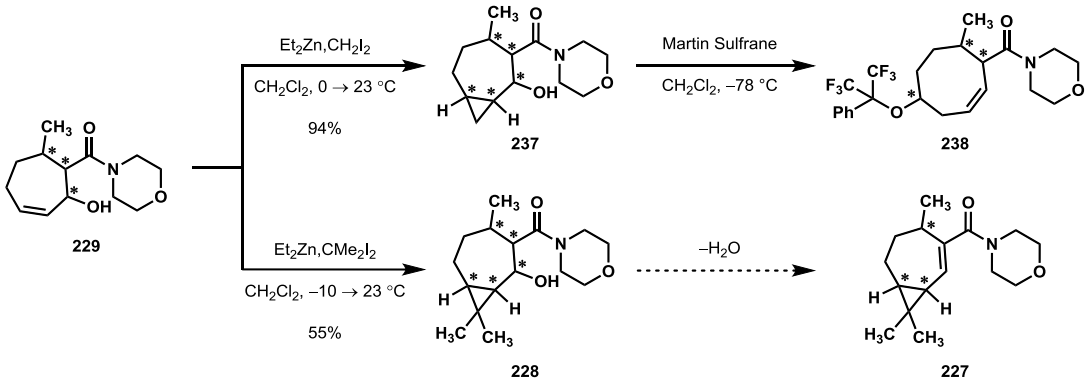


Figure 3.10 Efforts Toward the Synthesis of Conjugated Amide **227**

Investigations to install the *gem*-dimethyl functionality seen in **228** with diethyl zinc and 2,2-diiodopropane were undertaken (**Figure 3.10**). Reproducibility of this reaction proved to be a challenge. The synthesis was hampered by the inconsistent results of reactions employing 2,2-diiodopropane and diethyl zinc. 2,2-Diiodopropane was not stable to storage in our hands and required preparation within hours of use; treatment of an ethereal solution of acetone hydrazone with iodine and immediate purification and use of the product is required. Although acetone hydrazone is readily available, we wished to avoid the hazards associated with neat, anhydrous hydrazine (described in an *Organic Syntheses* protocol of this reagent).[13]

The second path involved a Corey-Chaykovski cyclopropanation to install the dimethyl cyclopropane (**Figure 3.11**). In this sequence, the allylic alcohol **229** was treated with methanesulfonyl chloride to give the corresponding mesylate, which was treated with DBU in hot benzene to furnish the diene **239**. Diastereomers resulting from the aldol reaction (**231** → **230**) are rendered inconsequential after formation of the diene **239**, with the conserved methyl-bearing stereogenic center originating from citronellic acid. Sulfur ylides (Corey-Chaykovsky cyclopropanation) have been used

to generate dimethyl cyclopropanes in several instances, and demonstrate a preference for 1,6-addition of sulfoxonium ylides to extended enones.[14] In our hands, 1,6-addition of sulfoxonium ylides (isopropyl shown and methyl) yielded no detectable cyclopropanation product **227**.

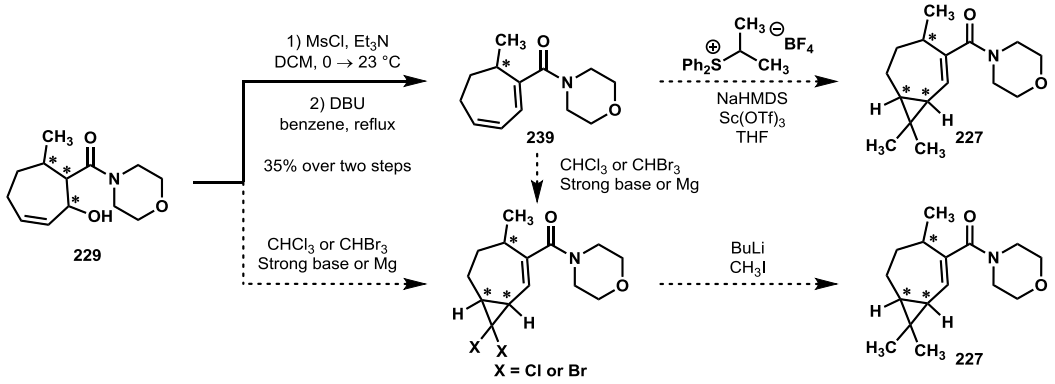


Figure 3.11 Progress Toward the Synthesis of Conjugated Amide **227**

Finally, attempts at installing a g*em*-dihalocyclopropane were undertaken on **229** and **239** (**Figure 3.11**).[15] In this method, a dihalocarbene is generated from chloro- or bromoform under basic conditions. The carbene generated reacts with an olefin to produce the *gem*-dihalocyclopropane. Halogen-metal exchange with substituent methylation would provide the *gem*-dimethylcyclopropane functionality. Generation of the dihalocarbene reacting with **229** or **239** produced no detectable *gem*-dihalocyclopropanation products.

3.5 Efforts Toward a Model System of Psiguadial A

Concurrent with our efforts toward the synthesis of silyl enol ether **225** and ultimately psiguadial A (**190**), we pursued a model system to further refine our conditions for the key enolate–*o*-QM reaction (**Figure 3.12**). By testing the silyl enol

ether **240** and benzyl chloride **223**, we could examine diastereoselectivity of the enolate–*o*-QM reaction (**241)**, optimize the conditions to perform the oxa-Michael ring-closure (**242**) as well as address any complications that may arise from possible [1,5]-sigmatropic rearrangements (e.g., hydride shifts)[16] on the cyclopentadiene **240**.

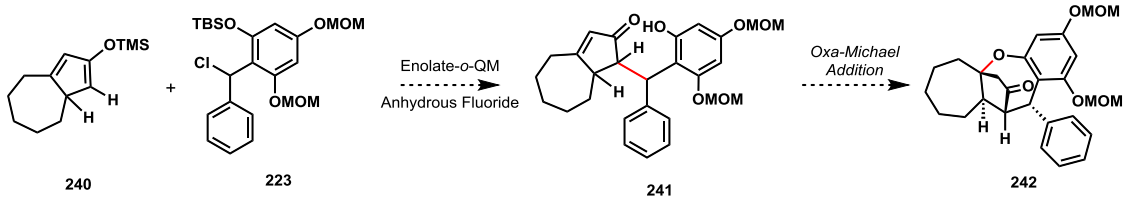


Figure 3.12 Model System of Psiguadial A

3.5.1 Synthesis of Silyl Enol Ether 248

Construction of **240** began with alkylation of cycloheptanone (**243**) by deprotonation with LDA and treatment of the resultant enolate with allyl bromide to give the allyl ketone **244** (**Figure 3.13**). This reaction appears trivial but requires specific purification protocols for all the starting materials (cycloheptanone, and allyl bromide) as described by Armarego and Chai.[17] A straightforward Wacker-Tsuji oxidation[18] gave the corresponding diketone **245**. Intramolecular aldol condensation[19] via treatment with heterogeneous anhydrous sodium methoxide in benzene gave the cyclopentenone **246**. More traditional homogeneous conditions such as sodium methoxide and methanol or THF were far less efficient.

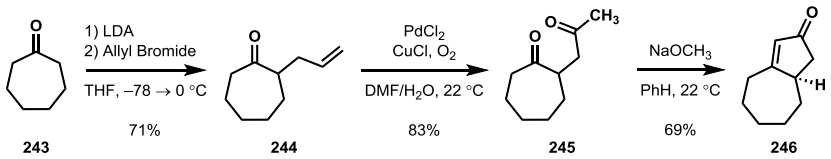


Figure 3.13 Synthesis of Cyclopentenone **246**

Treatment of the cyclopentenone **246** with trimethylsilyl trifluoromethanesulfonate and pyridine provided the thermodynamic product, the silyl enol ether **247** (**Figure 3.14**) in 90% yield. This structural assignment was confirmed by ^{1}H, ^{13}C (ATP), COSY, HMBC, and HSQC NMR studies, and we assume the extended enolate leading to **247** is lower energy than the cross conjugated enolate leading to the desired silyl enol ether **248**.

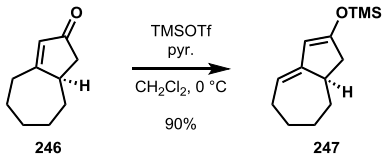


Figure 3.14 Synthesis of Diene **247**

We overcame this problem by treating the cyclopentenone **246** with LDA (deprotonation at C4) and trapping the resultant enolate with trimethylchlorosilane to give the desired silyl enol ether **248** (**Figure 3.15**). Employing a strong, hindered base like LDA at low temperatures typically favors formation of the kinetic enolate while using a weaker base such as pyridine and at higher temperatures typically favors the formation of the thermodynamic enolate. Quantitative yields of the trapped kinetic enolate **248** could be achieved with a non-aqueous workups; the crude mixture was concentrated, triturated with hexane, and filtered with through a pad of celite. Optimal

yields in the forthcoming enolate–*o*-QM reaction were achieved by using the purified silyl ether within one hour of its isolation.

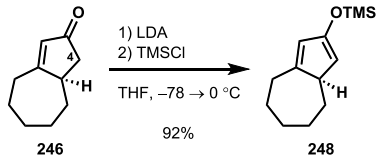


Figure 3.15 Synthesis of Silyl Enol Ether **248**

3.5.2 Synthesis of Silyl Protected Benzyl Chloride 223

Generation of the *o*-QM precursor **223** began with protection of 2,4,6-trihydroxy benzaldehyde (**236**) and elaboration utilizing chemistry developed during our previous exploration of *o*-QM methodology. First, 2,4,6-trihydroxybenzaldehyde (**236**) was protected with chloromethyl methyl ether (commercially available) and Hünig's base to give the phenol **235** (**Figure 3.16**). Treatment of the resulting phenol **235** with triethylamine, followed by slow addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate, protected the remaining phenol to produce the silylated aldehyde **234**. Poor yields resulted when *tert*-butyldimethylchlorosilane was used. Alkylation of the aldehyde **234** with freshly prepared phenylmagnesium bromide provided the benzyl alcohol **233**. Using phenylmagnesium bromide and short reaction times were critical for high reaction yields. Alkyllithium additions to aldehydes are accompanied by silyl group migration. Utilizing the phenylmagnesium bromide, we did not detect the migration of the *tert*-butyldimethylsilane from the phenol to the newly formed benzyl alcohol.

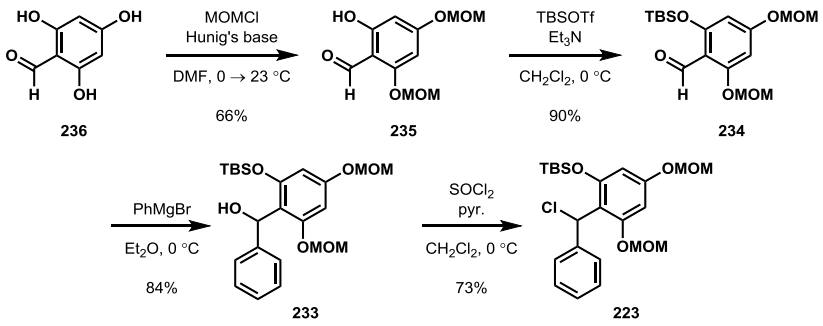


Figure 3.16 Synthesis of Silyl Protected Benzyl Chloride **223**

Conversion of the benzyl alcohol **233** to the benzyl chloride **223** is complicated by the tendency of the chloride to decompose upon standing and/or in the presence of base. Reaction of the chloride with trace amounts of water causes polymerization to occur, resulting in a hard, transparent red plastic. Residual pyridine displaces the chloride to form an orange pyridinium salt, which is isolable and bench stable, but incompatible with the enolate–*o*-QM reaction conditions. These problems were overcome by treatment of the benzyl alcohol **233** with thionyl chloride and pyridine in diethyl ether at 0 °C, followed by filtration through a pad of acidic alumina (2 grams) topped with a pad of silica gel (2 grams). This two-layer filter effectively quenches residual thionyl chloride, filters out the pyridinium salts, and removes excess pyridine to provide the benzyl chloride **223** in consistent and reproducible 70–75% yields (**Figure 3.16**). As with the silyl enol ethers, optimal yields were achieved by using the pure chloride within one hour of its creation. Yields of the coupling product **241** deteriorate rapidly even with careful storage of the chloride **223** at –20 °C.

3.5.3 Efforts Toward the Synthesis of Keto Phenol 241 and Oxepane 242

The enolate–*o*-QM reaction was expected to follow an open transition state, consistent with our previous studies (**Figure 3.17**). We expected the enolate (**A**) to

approach the *o*-QM (**B**) at the less hindered face to give a single stereochemical arrangement at C4. The stereochemistry at C1' would arise from the steric environment in the *o*-QM and then set the E/Z configuration of the *o*-QM when generated (**E-B** and **Z-B**). We expected only two diastereomers (**241A** and **241B**) rather than four possible diastereomers possible when making two contiguous stereogenic centers.

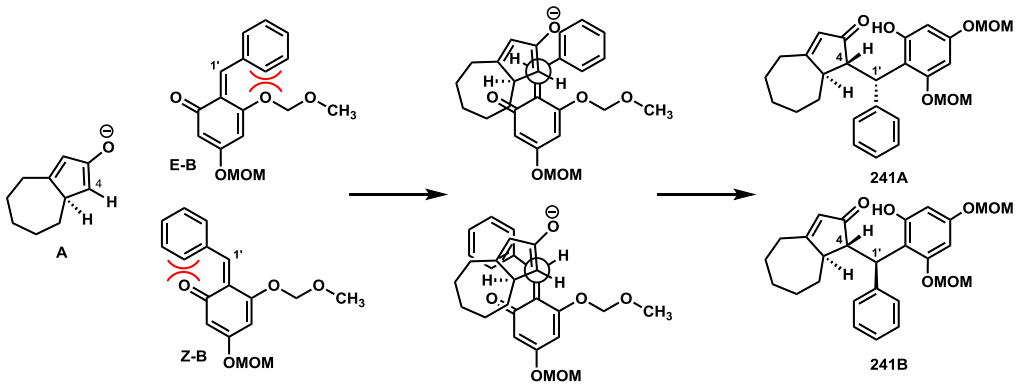


Figure 3.17 Stereochemical Outcomes of Enolate–*o*-QM Reaction

With the requisite the silyl enol ether **248** and benzyl chloride **223** in hand, the enolate–*o*-QM reaction provided an unoptimized yield of 46% of the keto phenols **241A** and **241B** as a mixture of separable diastereomers (d.r. = 1.5:1) (**Figure 3.18**).

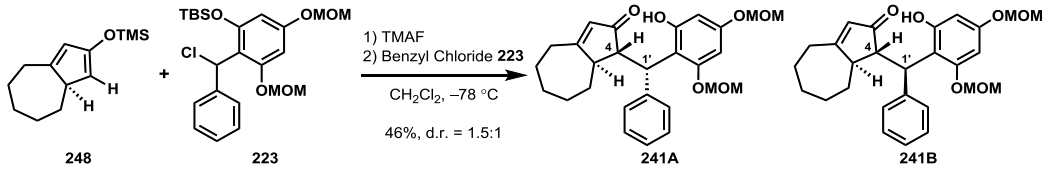
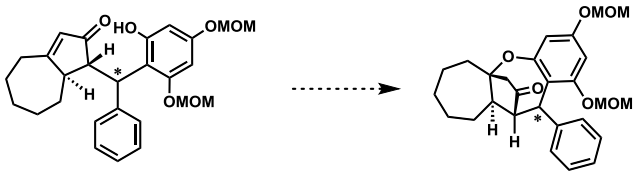


Figure 3.18 Synthesis of Keto Phenols **241A** and **241B**

A wide variety of Brønsted acids, Lewis acids, amine bases, phosphines and inorganic bases have all been used successfully in previous oxa-Michael reactions.[20] Quinine and other cinchona alkaloids had been previously explored and utilized on similar oxa-Michael substrates with great success by Dinter, Haabe and Hintermann.[21] The mixture of diastereomers of the keto phenol **241** was exposed to a variety of Lewis acids, bases, and bifunctional catalysts (**Table 3.1**) to induce the desired oxa-Michael addition. Initial success was found with refluxing toluene, quinine-HCl and potassium carbonate. Subsequently, potassium carbonate alone was found to be sufficient to produce, at first glance, the desired oxa-Michael addition.

Table 3.1 Screening Conditions for oxa-Michael Addition of Keto Phenol **241**



241 **242**

Reagent	Solvent	Temperature	Result
pyrrolidine	$CDCl_3$	50 °C	No Reaction
piperidine	$CDCl_3$	50 °C	No Reaction
piperdine-AcOH	$CDCl_3$	50 °C	No Reaction
DABCO	$CDCl_3$	50 °C	No Reaction
$NaOCH_3$	$CDCl_3$	50 °C	No Reaction
$NaOCH_3$	CH_3OH	50 °C	No Reaction
DABCO-$Sn(OTf)_2$	$CDCl_3$	50 °C	No Reaction
TfOH	CH_3CN	22 °C	Dec. (MOM removal)
$TiCl_4$	CH_3CN	22 °C	Dec. (MOM removal)
TMSOTf	CH_3CN	22 °C	Dec. (MOM removal)
$ZnCl_2$	CH_3CN	22 °C	No Reaction

Quinine-HCl K_2CO_3	$PhCH_3$	110 °C (48h)	27% (99% BRSM)
K_2CO_3	$PhCH_3$	110 °C (24h)	22%

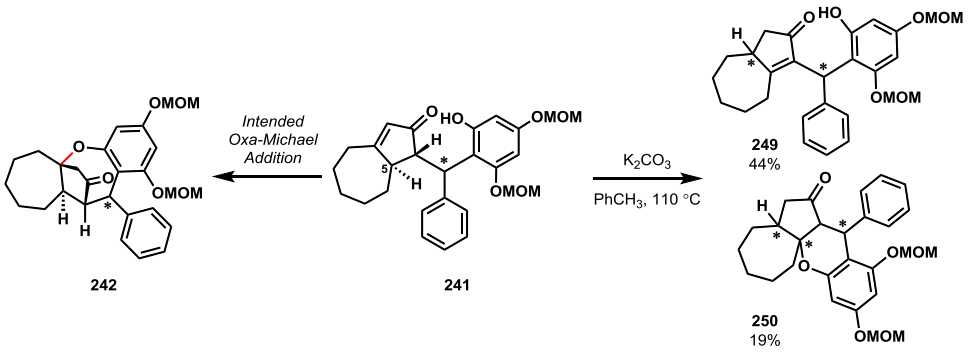


Figure 3.19 Synthesis of Keto Phenol **249** and Tetrahydropyran **250**

The starting materials and the products of the reaction were constitutional isomers so analysis of the reaction with HRMS did not prove useful. Instead, after careful analysis by ^{1}H, ^{13}C, COSY, HSQC, and HMBC NMR, we concluded that an oxa-Michael addition did occur, however the heterocycle formed was a six-membered ring and not the desired seven-membered ring. We presume that under the basic reaction conditions, the keto phenol **241** is deprotonated at C5, isomerizes to keto phenol **249** and then the phenolic oxygen engages the new cyclopentenone in an oxa-Michael addition to form the six-membered tetrahydropyran **250**. In the reaction, **241** was fully consumed and the keto phenol **249** along with the tetrahydropyran **250** were isolated together in the same reaction mixture.

3.5.4 Synthesis of Silyl Enol Ether 252

A modification of the silyl enol ether **248** was undertaken to stop this isomerization and subsequent incorrect oxa-Michael addition. We hoped that replacing one of the protons on C4 with a methyl functionality would stop the isomerization of the cyclopentenone ring seen in the keto phenol **241**. Additionally the modification produced a model system that more closely resembled the natural product.

Synthesis of the silyl enol ether **252** started with interception of the known cyclopentenone **246** (**Figure 3.20**). Treatment of **246** with LDA then methyl iodide produced the enone **251** as mixture a diastereomers (**251A** major diastereomer shown, d.r. = 4.5:1). The relative stereochemistry of each alkylation product was inferred by nOe analysis of pure samples. The major diastereomer resulted from addition of the methyl group at the *exo* face of the molecule. This fact confirmed our assumptions regarding the inherent stereochemical bias that might be expected in enolate chemistry on such a platform.

The resulting diastereomers from the alkylation reaction (**246** → **251**) are rendered inconsequential after treating enone **251** with another equivalent of LDA and then trapping with trimethylchlorosilane to give **252**. As with the proton version, quantitative yields of the trapped silyl enol ether **252** could be achieved with non-aqueous workups; the crude mixture was concentrated, triturated with hexane, and filtered with celite. Optimal yields in the forthcoming enolate–*o*-QM reaction were achieved by using pure silyl enol ether within one hour of its creation.

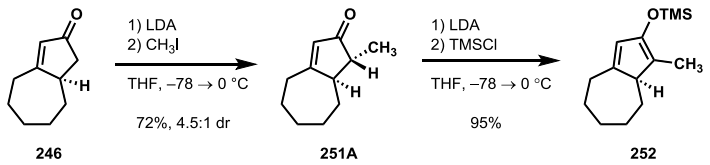


Figure 3.20 Synthesis of Silyl Enol Ether **252**

As we had previously discovered, subjecting the cyclopentenone **251** to trimethylsilyl trifluoromethanesulfonate provided the incorrect silyl enol ether **253** (**Figure 3.21**). We confirmed the structure of the silyl enol ether **253** with ^{1}H, ^{13}C, COSY, HMBC, and HSQC NMR.

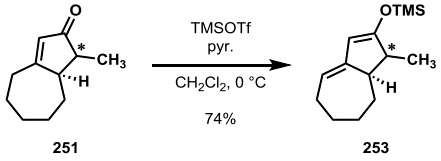


Figure 3.21 Synthesis of Silyl Enol Ether **253**

3.5.5 Synthesis and Investigations of Keto Phenol 254

With the benzyl chloride **223** and the methyl modified silyl enol ether **252** in hand, the enolate–*o*-QM reaction provided an unoptimized yield of 34% of the keto phenols **254A** and **254B** as a mixture of separable diastereomers (d.r. = 1:1) (**Figure 3.22**). All precautions were taken to limit the amount of impurities and water from the reaction, yet yields vary due to the instability of the starting materials.

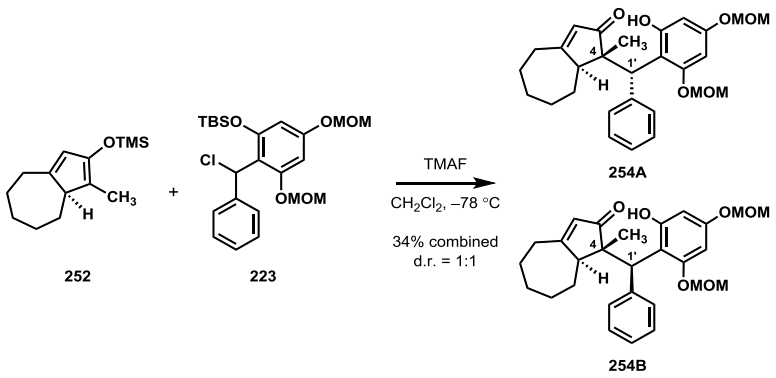


Figure 3.22 Synthesis of Keto Phenols **254A** and **254B**

3.5.5.1 Determining Stereochemistry of Keto Phenol 254 with X-ray Crystallography

With keto phenol **254** in hand, we sought a method to confirm the stereochemistry at the dibenzylic carbon C1' of the two diastereomers. NMR techniques for determining the relative stereochemistry, nOe, were attempted. The results with nOe proved to be misleading. Given the nature of nOe and our molecule, there was too much rotation about the C4/C1' bond for meaningful results. We would need a more structurally rigid molecule to truly evaluate the relative stereochemistry with NMR techniques.

We noticed that while concentrating keto phenol **254A**, the molecule would become an amorphous solid for a moment and then become a thick oil. We thought that, if we could modify the keto phenol **254A** we could produce a crystalline material. We hoped to produce X-ray quality crystals and determine the stereochemistry of the dibenzylic carbon C1' of the two diastereomers by analysis via X-ray diffraction.

The phenol function was an obvious point of modification for the keto phenol **254A** to obtain a more crystalline derivative. Thus, the less polar diastereomer keto phenol **254A** was functionalized with *para*-nitrobenzoyl chloride to produce the solid

nitro ester **255** (**Figure 3.23**). The nitro ester **255** was crystallized by pentane/dichloromethane layering to provide X-ray quality crystals. Single crystal X-ray crystallography confirmed the absolute stereochemistry of the dibenzylic carbon C1' (**Figure 3.24**), and confirmed our assumption that the alkylation event took place via the *exo* face of enolate **252.**

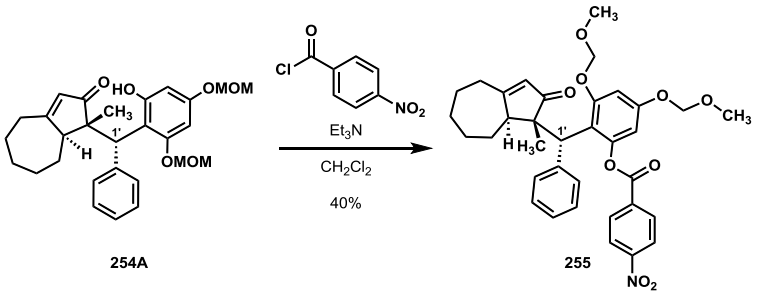


Figure 3.23 Synthesis of Nitro Ester **255**

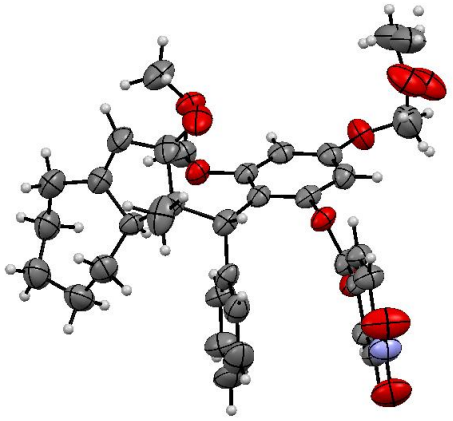


Figure 3.24 Crystal Structure of Nitro Ester **255**

The second, more polar diastereomer **254B** was functionalized at the phenol with *para*-nitrobenzoyl chloride and *para*-iodobenzoyl chloride (**256** shown, **Figure**

3.25). All attempts at crystallization did not produce X-ray quality materials. We have assumed that this second diastereomer bears the inverted stereochemistry at the dibenzylic carbon C1'.

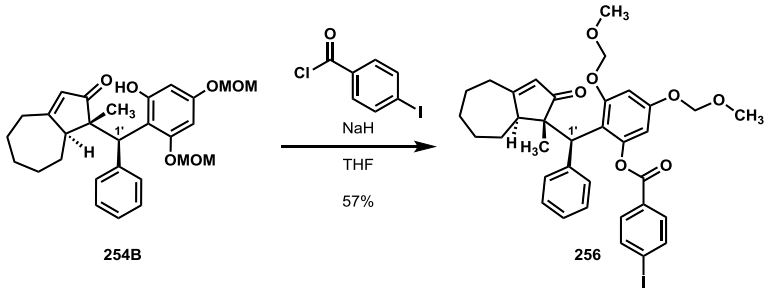


Figure 3.25 Synthesis of Iodo Ester **256**

3.5.5.2 Optimizing the Synthesis of Keto Phenol 254A

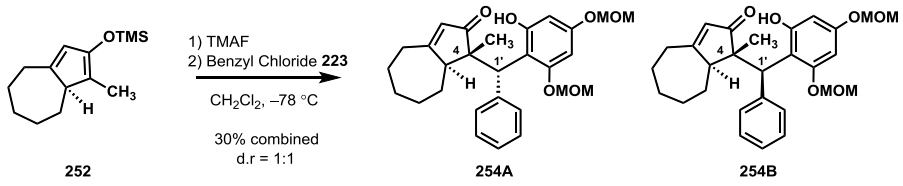
We sought to improve the yields for the enolate–*o*-QM reaction to produce keto phenol **254A**. We looked at a number of factors (1) addition sequence in the reaction, (2) varying the leaving group on the *o*-QM precursor, (3) varying the silyl on the enolate precursor, and (4) scalability of the reaction. We investigated changing the protocols for the enolate–*o*-QM reaction described in the 2015 paper.[6]

3.5.5.2.1 Addition Sequence Enolate–*ortho*-Quinone Methide Reaction

First, the general addition sequence protocol called for rapidly adding the cooled (–78 °C) anhydrous fluoride in dichloromethane to a mixture of enolate (ex. **248** or **252**) and *o*-QM (**223**) precursors in cooled (–78 °C) dichloromethane. In this addition sequence, both the enolate and *o*-QM are generated and consumed simultaneously.

We tested whether changing the addition sequence may improve the overall yield of the reaction or diastereoselectivity. We thought that adding the *o*-QM precursor to a mixture of premade desilylated enolate and excess anhydrous fluoride may increase the yield.

First, 2.0 equiv. of cooled (–78 °C) anhydrous fluoride in dichloromethane was added to 1.0 equiv. of the cooled (–78 °C) silyl enol ether **252** in dichloromethane (**Figure 3.26**); this mixture should rapidly desilylate and generate our enolate *in situ*. The addition of the fluoride caused an intense color change in the reaction mixture, from clear pale yellow to dark red. Next, we added 0.8 equiv. of the benzyl chloride **223** in dichloromethane to the reaction mixture. Because the benzyl chloride **223** was not precooled, the solution ran down the side of the flask, such that it was cooled as it entered the bulk mixture. The excess anhydrous fluoride in the reaction mixture should rapidly generate the *o*-QM and we expect the *o*-QM to be consumed by the excess enolate. We observed a gradual color change in the reaction mixture as the benzyl chloride **223** was added (dark red to brown/green).



252 **254A** **254B**

Figure 3.26 Optimization via Addition Sequence of Enolate– *ortho*-Quinone Methide Reaction

Application of this protocol did not increase the yield or diastereoselectivity of the reaction to produce **254A,** but did simplify the preparation of the benzyl chloride and the mechanical material manipulations required.

3.5.5.2.2 Leaving Group on *ortho*-Quinone Methide Precursor

Second, we looked at changing the chloride leaving group on the *o*-QM precursor and to test these analogues in the enolate–*o*-QM reaction, including the methyl ether **257**, the acetate **258**, the monochloroacetate **259**, and the trifluoroacetate **260** (**Figure 3.27**).

The reactivity of the leaving group is influenced by the stability of the anion created and the strength of the bond broken. The trend holds that the relative rates of solvolysis for the leaving groups is methoxide < acetate < monochloroacetate < chloride < trifluoroacetate.[22] This is similar to what we observed. The methyl ether **257**, acetate **258**, and monochloroacetate **259** in the enolate–*o*-QM reaction returned none of the keto phenol **254**, instead only desilylated the starting materials. The trifluoroacetate **260** analog in the enolate–*o*-QM reaction produced the desired coupling products, but with no overall improvement in reaction yield. This analog proved to be less bench stable than the chloride counterpart and decomposed upon concentration.

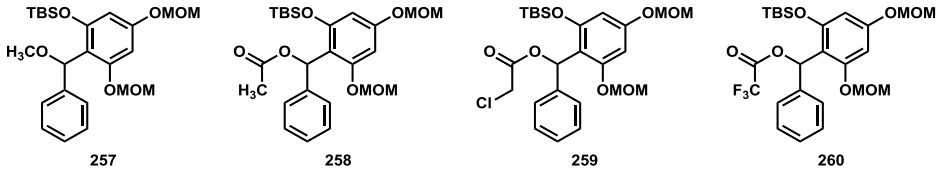


Figure 3.27 Analogues of *ortho*-Quinone Methide Precursor

3.5.5.2.3 Silyl Group on Enolate Precursor

The third modification to improve the enolate–*o*-QM reaction involved changing the silyl group of the enolate precursor from a trimethylsilyl (TMS) to a triethylsilyl (TES) (**Figure 3.28**).

Generating enolates with LDA and trapping them with trimethylchlorosilane or triethylchlorosilane is equally effective but produces a stoichiometric amount of lithium chloride salts. Removal of these salts can be achieved by an aqueous workup of the reaction mixture.

Our TMS silyl enol ether analogues **248** and **252** are prone to hydrolysis during an aqueous workup attempting to remove the generated salts. The TMS analogues were purified by concentration then trituration with hexanes, followed by filtration with celite. This method omits any water producing a dry product, but may still contain trace amounts of salts or other impurities that would be removed in an aqueous workup. The byproduct trimethylsilanol is removed with drying under vacuum.

The TES analog can withstand an aqueous workup, which allows for all of the salts and other impurities to be removed. This method requires water and subsequent drying of the organic solution. We could achieve comparable yields trapping with TESCl. Checking the purity of the TES analog **261** with NMR revealed that, unlike the TMS analog **252**, the degradation byproduct of TESCl, triethylsilanol, remained even after drying under vacuum. After all this work, employing the TES analog **261** in the enolate–*o*-QM reaction produced no noticeable increase in the yield of the reaction, regardless of which addition sequence was employed.

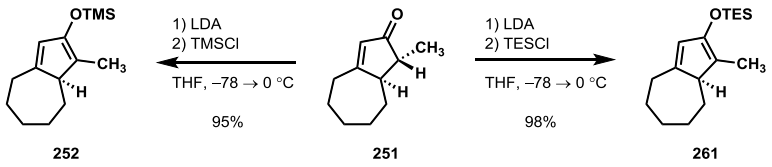


Figure 3.28 Analogues of Enolate Precursors

3.5.5.2.4 Scalability of Enolate–*ortho*-Quinone Methide Reaction

We tested the scalability of the enolate–*o*-QM reaction. Initially reaction were carried out at approximately 1.0 mmol of TMAF (100 mg scale) and yields at this scale ranged from 20 to 30%. We were pleased that scaling up to 6.0 mmol of TMAF (600 mg scale) resulted in reactions with comparable yields. The largest reaction we completed was 10.7 mmol of TMAF (1.00 g) and the yield of the reaction remained consistent.

3.5.6 Efforts Toward the Synthesis of Oxepane 262

As before, potassium carbonate alone was found to be sufficient to produce, at first glance, a new product. After careful analysis with ^{1}H, ^{13}C, COSY, HSQC, and HMBC NMR experiments, we concluded that an oxa-Michael addition (**262**) did not occur. Instead, we produced the six-member heterocyclic hemiketal **263** (**Figure 3.29**). First, we believe that deprotonation at C5 occurred, which broke conjugation, and then the phenolic oxygen did a 1,2-addition to the carbonyl group.

Similar to the previously attempted oxa-Michael addition, the keto phenol **254** was screened against a wide variety of Brønsted acids, Lewis acids, amine bases, metal hydrides, and inorganic bases to produce the desired oxa-Michael addition product oxepane **262**. None of the desired oxa-Michael addition product **262** was ever detected.

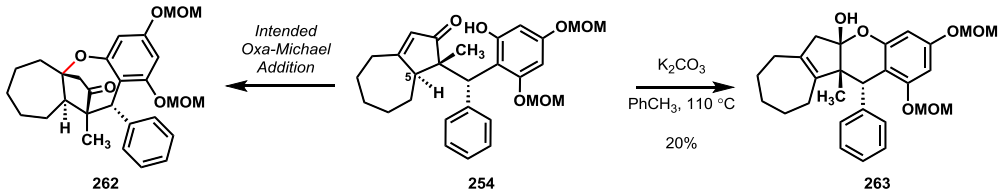


Figure 3.29 Synthesis of Hemiketal **263**

3.5.7 Efforts Toward the Synthesis of Oxepane 269

The six-member hemiketal functionality was confirmed via the analogous methyl ether hemiketal **270**. The synthesis of methyl ether hemiketal **270** began with producing the methyl ether protected *o*-QM precursor **267**.

The sequence began with 2,4,6-trimethoxybenzaldehyde undergoing mono demethylation (not shown) via standard conditions[23] to provide aldehyde **264** (**Figure 3.30**). Treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine to aldehyde **264** provided the silylated aldehyde **265**, which was then reacted with Grignard reagent, phenyl magnesium bromide, to yield the benzyl alcohol **266**.

The use of thionyl chloride to convert alcohols to chlorides produces a stoichiometric amount of acid (HCl). Previously using an acid sensitive protecting group (MOM) for our phenyl alcohols required the use of base (pyridine) to sequester the acid generated in the reaction. We hypothesized that using protecting groups that are not acid sensitive, we would not need to buffer the reaction with base. Thionyl chloride without base provided the benzyl chloride **267** in quantitative yields. This method did not require a filtration step to remove the pyridinium chloride salt.

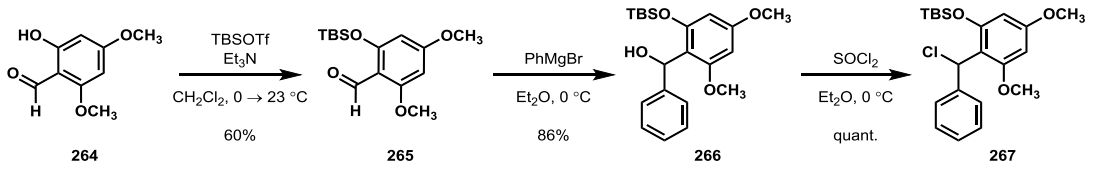


Figure 3.30 Synthesis of Benzyl Chloride **267**

The benzyl chloride **267** and the silyl enol ether **252** was subjected to anhydrous fluoride to induce the enolate–*o*-QM reaction yielding 35% of the keto phenol **268** as an inseparable mixture of diastereomers (d.r. = 1:1) (**Figure 3.31**). The keto phenol **268** was as difficult to analysis via ^{1}H NMR. In chloroform-*d*, **268** provided a mixture of rotamers, but switching to DMSO-d_6, we could slow the rotation and collect cleaner spectra.

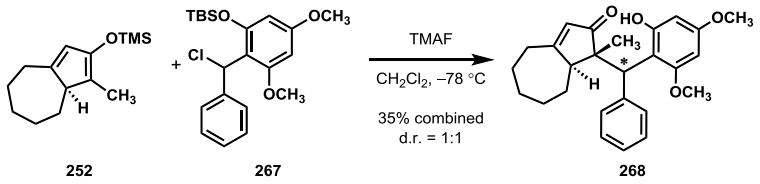


Figure 3.31 Synthesis of Keto Phenol **268**

Subjecting the mixture of diastereomers of the keto phenol **268** to potassium carbonate in refluxing toluene produced the hemiketal **270** and not the intended oxa-Michael addition product the oxepane **269** (**Figure 3.32**). This product was slowly allowed to solidify (slow evaporation in dichloromethane) to produce X-ray quality crystals (**Figure 3.33**). The diastereomer that crystallized exhibited inverted stereochemistry at the dibenzylic carbon C1' but the stereochemistry at C4 was consistent with our alkylation model and expectations.

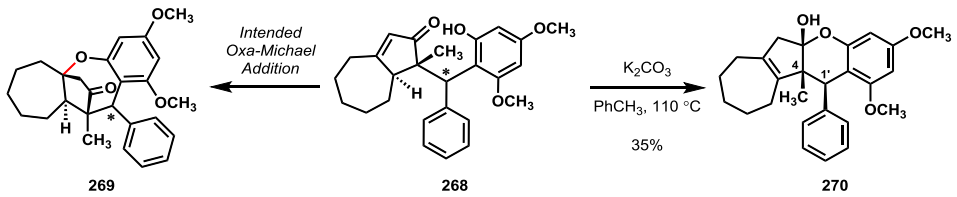


Figure 3.32 Synthesis of Hemiketal **270**

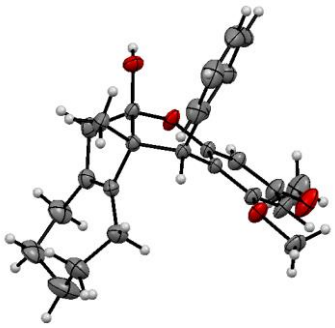


Figure 3.33 Crystal Structure of Hemiketal **270**

3.5.8 Synthesis of Keto Phenol 272

We sought to synthesize an analog of the *o*-QM precursor that contained only the required silylated phenolic oxygen for the enolate–*o*-QM reaction. In a previous publication, we synthesized the benzyl chloride **271**.[6] Treating the silyl enol ether **252** and the benzyl chloride **271** with anhydrous fluoride to induce the enolate–*o*-QM reaction yielded 31% of the keto phenol **272** as a mixture of inseparable diastereomers (d.r. = 1:1) (**Figure 3.34**). We would use this model in later scout reactions because of the easy and quick access to the keto phenol scaffold.

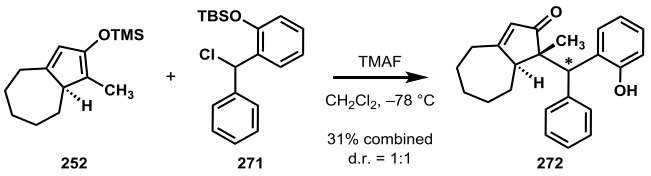


Figure 3.34 Synthesis of Keto Phenol **272**

3.6 Amended Syntheses of Model System Toward Seven-Member Oxepanes

After failing to detect the desired oxa-Michael addition products, we began a reevaluation to synthesize the heterocyclic seven-member oxepane ring contained within psiguadial A (**190**).

3.6.1 Efforts Toward the Synthesis of Seven-Membered Oxepane via S_N' Cyclization

Initially, we thought an adjustment in redox level of the carbonyl carbon was needed (**Figure 3.35**, carbon highlighted in **red**). Reduction of the enone functionally to the allylic alcohol would lower the electrophilicity of this carbon atom. Selection of the appropriate diastereomer, the *exo* reduction product **273**, would not allow an S_N2 displacement reaction to take place directly on this reduced carbon atom. We imagined that activation of the allylic alcohol **273** with an appropriate leaving group may induce an S_N' type reaction to generate the oxepane **274**.[24]

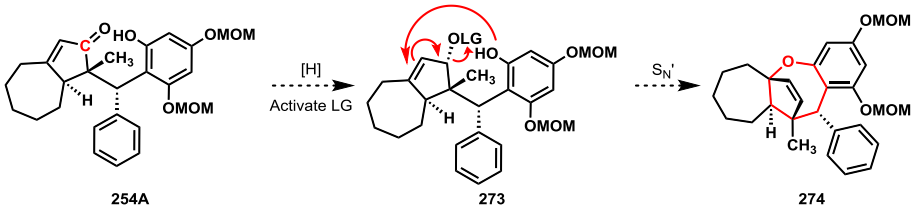


Figure 3.35 Proposed Synthesis – Reduction, Activation, and S_N'

The synthesis to test our idea to form the heterocyclic seven-member oxepane ring via S_N' mechanism began with protection of the keto phenol **254A** (**Figure 3.36**). It is known that silylating a hydroxyl group with *tert*-butyldimethylsilyl trifluoromethanesulfonate, in the presence of an ester or ketone, may make a silyl enol ether, and that not all reactions proceed as expected.[25] In our hands, protection of the keto phenol **254A** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine produced the silylated hemiketal **275**.

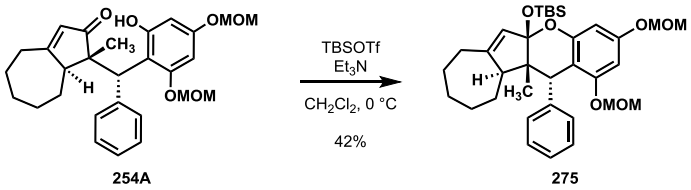


Figure 3.36 Synthesis of Silylated Hemiketal **275**

Protection of the phenol functionality was not observed with amine bases and required forcing conditions[26] (KH or NaH in THF) to product the hindered oxide. Treatment of **254A** with sodium hydride then addition of *tert*-butyldimethylchlorosilane protected the phenol as the corresponding silyl ether **276** (**Figure 3.37**).

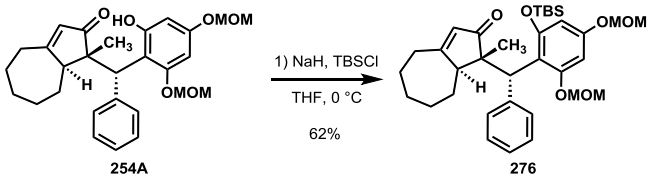


Figure 3.37 Synthesis of Silylated Phenol **276**

Methods for the 1,2-reduction of the enone functionality were investigated. Reduction of **276** with $NaBH_4$, Luche conditions ($NaBH_4$ and $CeCl_3 \cdot 7H_2O$), and LAH in tetrahydrofuran returned only starting material. Reduction with LAH in diethyl ether produced a mixture of separable diastereomers the allylic alcohols **277A** and **277B** (d.r. = 1.3:1) (**Figure 3.38**). We were able to achieve a stereoselective reduction of **278** with diisobutylaluminum hydride to produce the allylic alcohol **279** (**Figure 3.39**).

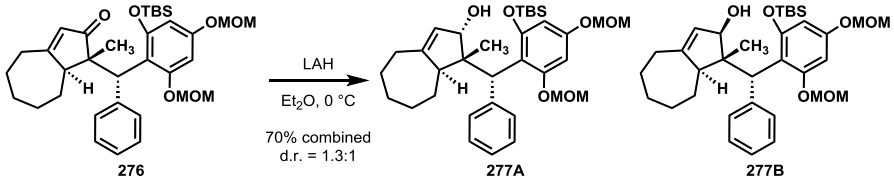


Figure 3.38 Synthesis of Allylic Alcohols **277A** and **277B**

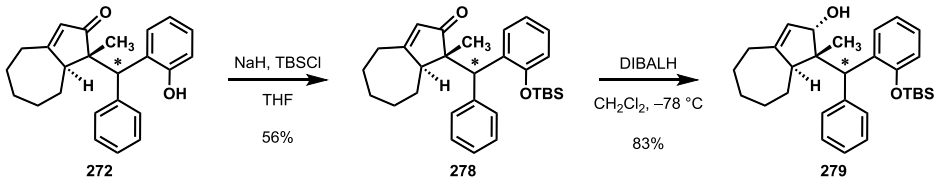


Figure 3.39 Synthesis of Allylic Alcohol **279**

With allylic alcohol **277A** in hand, conditions to activate the leaving group and induce the S_N' displacement reaction were investigated. Attempts at isolating either the triflate, mesylate, or tosyl versions of the activated allylic alcohol all resulted in the elimination product, diene **280** (**Figure 3.40**). We noticed that the allylic alcohol

precursor (**277**) itself was acid-sensitive, and upon prolonged storage would also gradually eliminate the elements of water to generate the diene **280**.

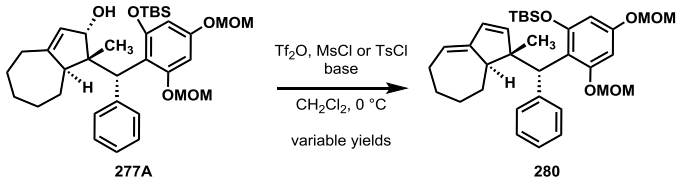


Figure 3.40 Efforts Toward Activating Allylic Alcohol **277A**

We observed quantitative conversion of **277A** to the diene **280** upon treatment with aqueous acidic conditions (1N HCl in THF, **Figure 3.41**). Under anhydrous acidic conditions (*p*-TSA in dichloromethane), elimination via a S_N1 mechanism was observed producing the tetrahydropyran **281**. We also observed the loss a MOM group under these reaction conditions. Under these conditions, with no TBS protected allylic alcohol **282**, the unprotected phenol is captured by the carbocation to produce the tetrahydropyran **283** (**Figure 3.42**).

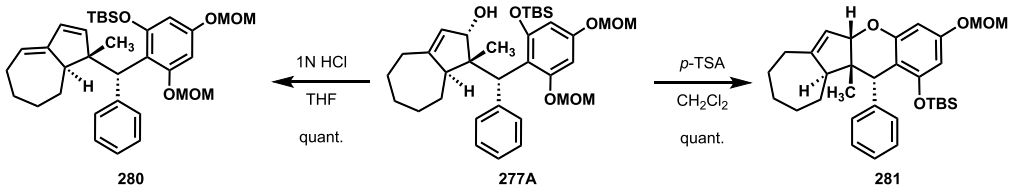


Figure 3.41 Variable Activity of Allylic Alcohol **277A** Under Different Acidic Conditions

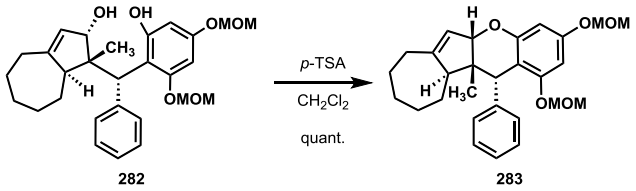


Figure 3.42 Synthesis of Tetrahydropyran **283**

3.6.2 Efforts Toward the Synthesis of Seven-Membered Oxepane via Carbocation Capture

Intrigued by the prospect of generating a discreet carbocation, we sought to capitalize on this discovery. Returning to our synthetic route, we considered the reactivity of the allylic alcohol **277A** and the diene **280** and reviewed the cation cascade sequence in the proposed biosynthesis of psiguadial A (**190**). From this, we developed new synthetic routes utilizing epoxides as carbocation precursors toward seven-member oxepanes.

3.6.2.1 Chemoselective Epoxidation of Diene 280

Epoxides can be useful synthetic intermediates in order to introduce functionality to an olefin. Ring opening of epoxides can be executed under acidic or basic conditions. This flexible reactivity of the epoxide ring can impart stereospecific bond formations. Under basic conditions, steric forces dominate such that the ring opening occurs at the less substituted site due to access afforded the incoming nucleophile. Under acidic conditions, electronic forces dominate such that significant cleavage of the C-O bond in the transition state will open the epoxide and place the resulting carbocation on the more substituted site.

In the first route, we start with the diene **280** and conduct an electrophilic chemoselective epoxidation to produce the epoxide **284** (**Figure 3.43**). In our hands,

we imagined opening the epoxide **284** under acidic conditions will place the carbocation on most substituted position and will capture one of the phenolic oxygens (MOM protected or not) to produce the seven-membered oxepane **285**.

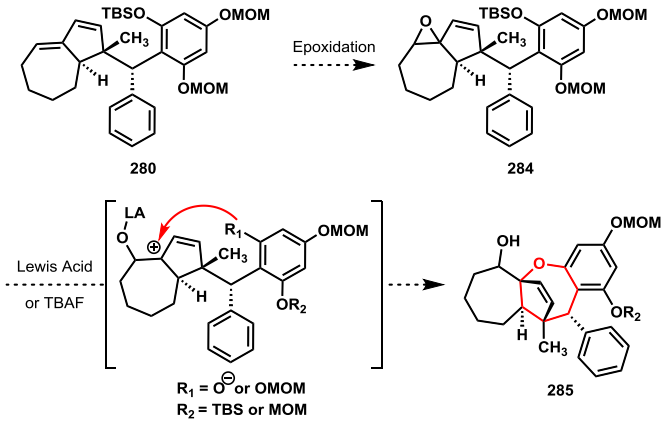


Figure 3.43 Proposed Synthesis – Chemoselective Epoxidation and Carbocation Capture

Synthesis toward the seven-member oxepane **285** began with electrophilic chemoselective epoxidation of the diene **280** to give the epoxide **284**. It is well-known that the epoxidation of a diene with electrophilic epoxidation reagents will generate and epoxide on the more substituted (more nucleophilic) olefin.[27] Epoxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) was investigated.

We isolated several products during the course of optimization and isolation of the desired product (**Figure 3.44**). We isolated the ester **286**, the ketone **287**, and the ether **288**. All products show that the epoxidation did occur at the correct olefin. The ester **286** is the result of *m*-CPBA's byproduct, 3-chlorobenzoic acid, being acidic enough to open the epoxide,[28] generate the carbocation, and capturing the 3-

chlorobenzoate anion. Recrystallization of *m*-CPBA and buffering the solution stopped the production of the ester **286**.

The ketone **287** resulted from the epoxide opening then undergoing a hydride shift to quench the carbocation and produce the ketone. The ether **288** resulted from the epoxide opening then isomerization of the second olefin, and shift of the carbocation, which captures one of the phenolic oxygens. Cooling the solution, short reaction times, and using neutralized TLC and silica gel sequestered the production of these two byproducts.

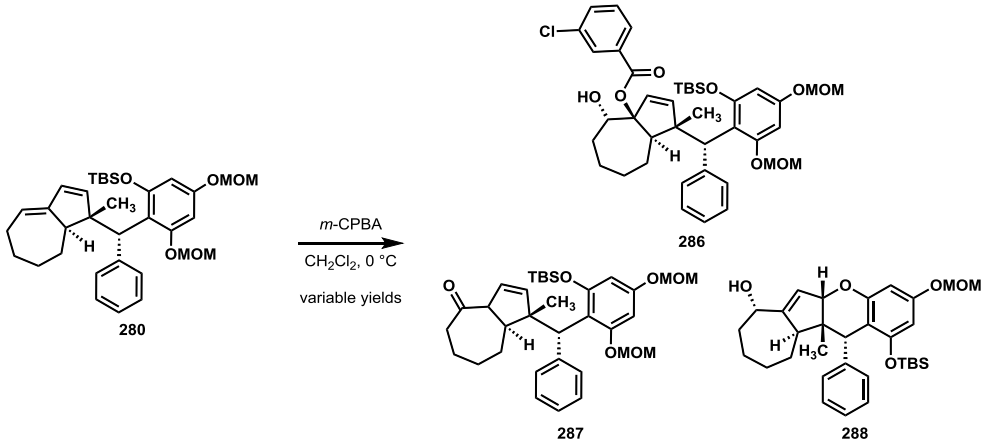


Figure 3.44 Optimization of Chemoselective Epoxidation of Diene **280**

We isolated the epoxide **284** by developing optimized reaction conditions (**Figure 3.45**). Unfortunately, as we saw during the prior attempts with unoptimized conditions, this epoxide proved to be too acid sensitive to be synthetically viable. Screening Lewis acidic conditions (example: $ZnCl_2$ or $BF_3{\cdot}Et_2O$) returned a mixture of

the known products **287** and **288**. This acid sensitivity has been seen in similar vinyl epoxides in fused ring structures.[29]

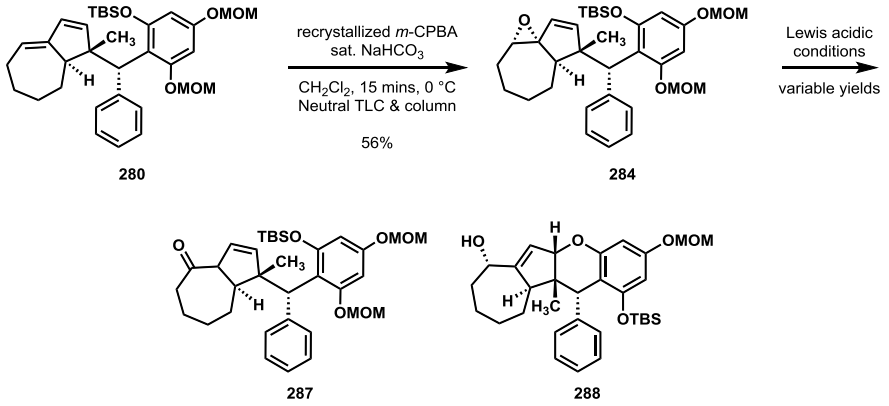


Figure 3.45 Synthesis of Epoxide **284** and Attempts at Carbocation Capture

Efforts to chemoselectively reduce the diene **280** were taken. We hypothesized that the single reduction of the diene **280** would remove the acid sensitivity of the resulting epoxide product. Hydrogenation with Wilkinson's catalyst[30] and diimide reduction[31] were investigated (**Figure 3.46**). A review of the literature convinced us that other methods such as heterogeneous catalysts like Pd/C or Pt with H_2 or homogeneous catalyst with Crabtree's catalyst[32] would over reduce and provide the wrong product.

Typically, stereoselective hydrogenations carried out with homogenous catalyst are dictated by a substituent directing effect or by steric approach control. Selective reductions of unconjugated double bonds can be reduced preferentially over conjugated double bonds.[33] In our hands, reduction of the diene **280** with Wilkinson's catalyst under an atmosphere of hydrogen gas returned only the starting material,

diene **290**. We suspect this is due to sterics, as seen in other systems that failed with similar conditions.[34]

Hydrogen transfer from diimide was investigated. Simple alkenes are reduced efficiently by diimide (HN=NH) which is an unstable hydrogen donor that is generated *in situ*. Reduction with diimide chemoselectively prefers more stained double bonds and terminal over internal double bonds. To avoid the need to produce possibly explosive materials, such as potassium azodicarboxylate, we synthesized and used *o*-nitrobenzenesulfonylhydrazide (NBSH), a mild diimide reagent.[35] Subjecting the diene **280** to NBSH reduction provided an inseparable mixture of **290** as three products (NMR). We believe that this mixture contains one fully reduced, and two types of partial reduction products.

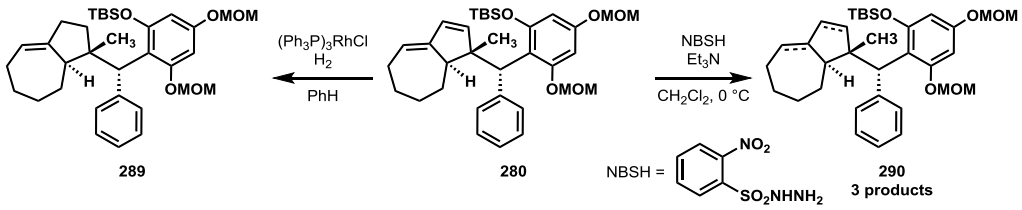


Figure 3.46 Efforts Toward a Chemoselective Reduction of Diene **280**

3.6.2.2 Efforts Toward the Synthesis of Seven-Membered Oxepane Via Directed Epoxidation

The stereoselective epoxidation of with peroxycarboxylic acids has been studied extensively.[36] Hydroxy groups exert a directive effect on epoxidation and favor approach from the side of the double bond closest to the hydroxyl group.[37] Hydrogen bonding between the hydroxyl group and the peroxide reagent stabilize the

transition state. This produces a strong directing effect that can exert stereochemical control that can overcome steric effects.

We developed a sequence for forming the seven-member oxepane **292** via directed epoxidation of the allylic alcohol **277**, then like with the diene **280**, under acidic conditions, capture of the carbocation with one of the phenolic oxygens (**Figure 3.47**).

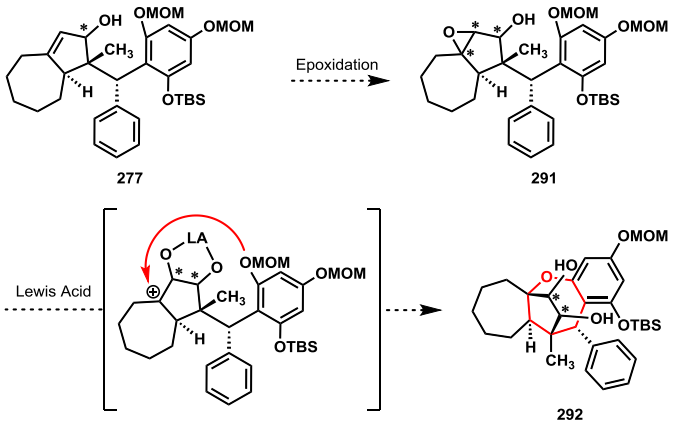


Figure 3.47 Proposed Synthesis – Directed Epoxidation and Carbocation Capture

Our efforts toward the oxepane **292** started with the directed epoxidation of the allylic alcohol **277**. Since the diastereomers of **277** can be separated, we selected the major diastereomer of **277A** for the directed epoxidation (**Figure 3.48**). Application of the optimized epoxidation conditions previously developed, we were able to isolate the product of the directed epoxidation **291**. Screening with Lewis acidic conditions to produce the oxepane **292**, we did not detect the desired product (one example shown with $ZnCl_2$ in dichloromethane).

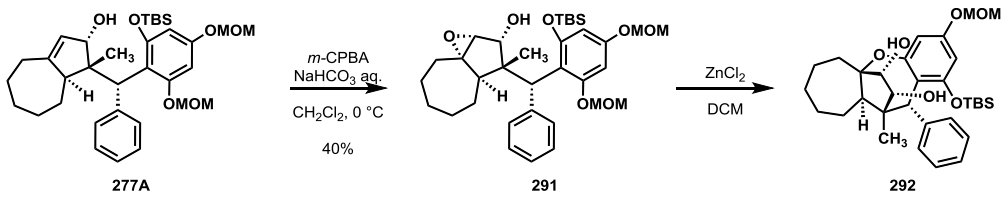


Figure 3.48 Directed Epoxidation of Allylic Alcohol **277A**

The allylic alcohol **277B** was also treated with epoxidation conditions to produce **293** (**Figure 3.49**). Screening with Lewis acids, we did not detect the desired product oxepane **292**. The epoxy alcohol **293** was treated with tetrabutylammonium fluoride to desilylate the molecule and produce the oxepane **294** (ex. shown in **Figure 3.48**). Deprotection with TBAF or HF has been shown to mediate intramolecular epoxide ring openings.[38] In our hands, none of the desired oxepane **294** was detected.

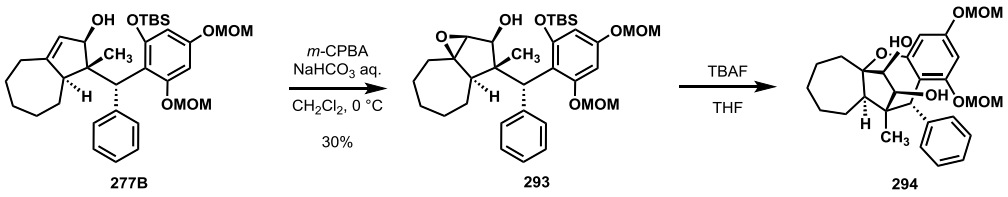


Figure 3.49 Directed Epoxidation of Allylic Alcohol **277B**

3.6.2.3 Efforts Toward Seven-Member Oxepane Via Simple Epoxide 296

Modifying the carbocation capture chemistry we tried to carry out with the diene **280**, we sought to simplify the approach. We envisioned that directly going toward the olefin **295** and epoxidation of this product would produce the epoxide **296** (**Figure 3.50**). We hoped that this would remove some of the sensitive substrates we were experiencing with the diene **280**. With this approach, we would still need to

open the epoxide under acidic conditions, but we did not expect this starting material to be as acid sensitive as the diene derived version.

Direct reduction of the enone to the olefin was investigated. In this method, we would not need to produce the known acid sensitive allylic alcohols. Instead, we envisioned with the olefin **295** in hand, we could epoxidized this, then generate our tertiary carbocation, which could then be captured by one of the phenolic oxygens to produce the oxepane **297**.

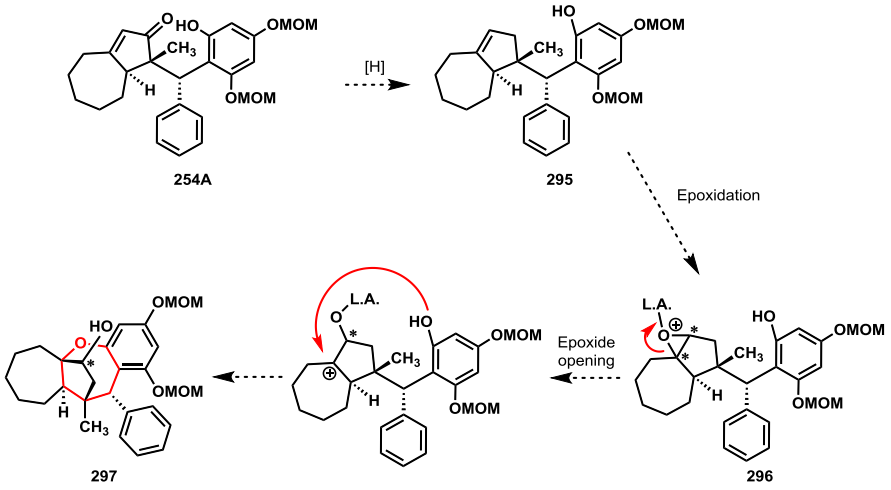


Figure 3.50 Proposed Revised Synthesis – Reduction, Epoxidation, and Carbocation Capture

Several methods exist for reductive deoxygenation of carbonyl groups to methylene. The Clemmensen reduction[39] is a classical reaction involving zinc and hydrochloric acid and works well with aryl ketones. Reduction of α,β-unsaturated ketones is less straightforward producing a mixture of rearranged products. Another drawback of this method in our molecule is the use of strong acid (HCl). In our

formal synthesis, the strong acid sensitive MOM protecting groups would be cleavage under these conditions.

The Wolff-Kishner reduction[40] is another method we considered for reductive deoxygenation of carbonyl groups to methylene. In this reaction, the carbonyl group is converted to the hydrazone with hydrazine, then undergoes a base-catalyzed decomposition to the methylene group. The related Caglioti reaction[41] involves the reduction of tosylhydrazones with a hydride source to produce the methylene. With both reactions, the mechanism is believed to proceed via a diimide intermediate. Reduction of α,β-unsaturated hydrazones or tosylhydrazones will give an alkene with the double bond located between the former carbonyl carbon and the α-carbon. All attempts to functional the carbonyl groups with tosylhydrazine, on our system returned starting material.

Reductive desulfurization of thioketals is another method we investigated to convert the carbonyl group to a methylene (**Figure 3.51**). In this method, the cyclic thioketal **296** is formed from the reaction of a ketone and ethanedithiol and then reduced with excess Raney nickel. As a method to form our desired methylene group, this route was advantageous for two reasons: it lacked the strong acidic conditions seen in the Clemmensen reaction and was expected to isomerize as had been seen in other molecules of this type in the Wolff-Kishner and Caglioti reactions.

Creation of the cyclic thioketal **296** proved to be a challenge. All attempts at procuring the desired thioketal products returned only starting material. We varied the conditions and took inspiration from other reported cyclizations that reported success.[42] This conditions included a variety of Brønsted acids (*p*-TSA, TfOH), Lewis acids ($BF_3 \cdot Et_2O$, $ZnCl_2$), solvents (Et_2O, PhH, AcOH) and a range of

temperatures (0 → reflux, bomb reactor for temperatures greater than the boiling point of the solvent). We made and reacted 1,2-ethanedithiobis(trimethylsilane)[43] ($[TMSSCH_2]_2$) with our substrate in the presence of zinc iodide, but recovered only the starting material.

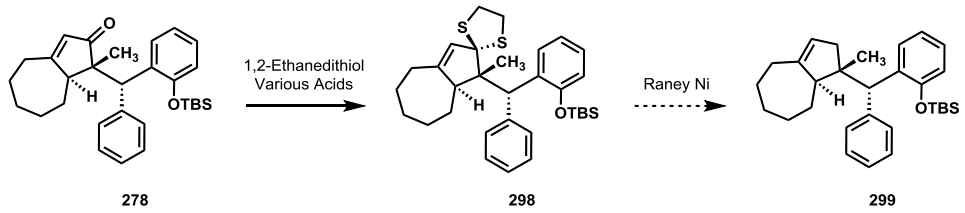


Figure 3.51 Efforts Toward the Synthesis of Olefin 2**99**

The *tert*-butyldimethyl protecting group is not stable under some conditions to install a thioketal. We swapped the *tert*-butyldimethyl protecting group protecting on the phenolic oxygen for the acetate **300** and screened conditions to create the cyclic hemiketal **301** (**Figure 3.52**). We did not detect the production of the desired hemiketal **301**.

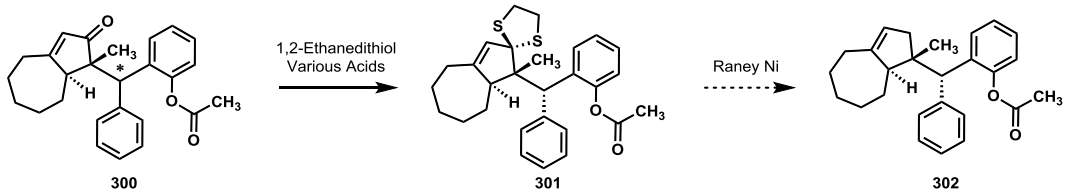


Figure 3.52 Efforts Toward the Synthesis of Olefin **302**

3.7 Current Efforts Toward a Model System of Psiguadial A

To recap, our first attempts at the oxa-Michael reaction isomerized our enone to produce the wrong oxa-Michael addition product. The second attempt at the oxa-Michael produced a hemiketal. Our attempts at the S_N' reaction gave elimination products. Being inspired by the carbocation cascade sequence in the biosynthesis, we tried to produce and then capture two varieties of a carbocation with one of the phenolic oxygens.

Our current synthetic strategy was developed to easily make the oxepane **303** and complete the synthesis of the model system of psiguadial A (**190**) (**Figure 3.53**). In this sequence, we sought to place the synthetic handles to make the seven-member ring exactly where we want a coupling event to occur. To achieve this control, we will start the sequence with the known silyl enol ether **252** and the bromide analog of the *o*-QM precursor chloride **309**.

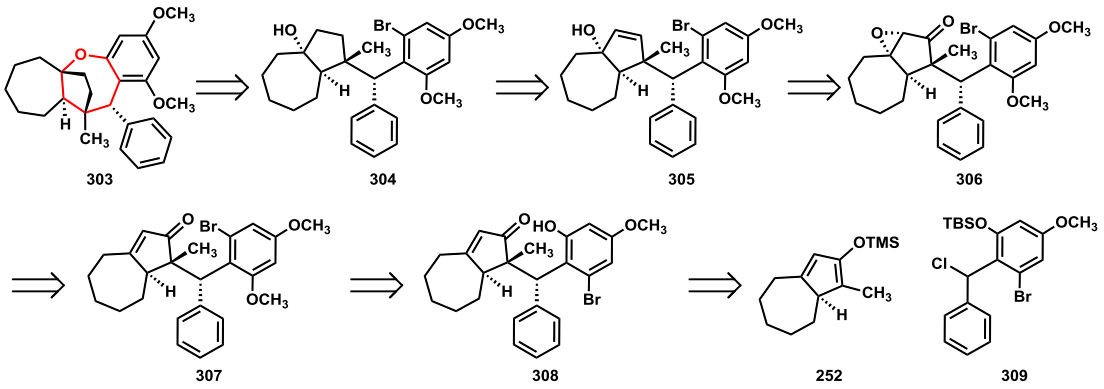


Figure 3.53 Retrosynthetic Analysis of Oxepane **303**

3.7.1 Efforts Toward the Synthesis of Oxepane 303 via Copper Catalyzed Intramolecular *O*-Arylation

The sequence to make the right hand bromide analog chloride **309** began with formylation of 1-bromo-3,5-dimethoxybenzene (**310**) with phosphoric trichloride and DMF to produce the aldehyde **311** (**Figure 3.54**). One of the methyl ethers were cleaved with exactly 1.0 equiv. of boron tribromide to give the phenol **312**. From here we follow chemistry we have previously worked out. The phenol **312** is protected with *tert*-butyldimethylsilyl trifluoromethanesulfonate and trimethylamine to provide the aldehyde **313** which is then treated with phenyl magnesium bromide giving **314** and finally thionyl chloride to provide the benzyl chloride **309** (yet to be completed).

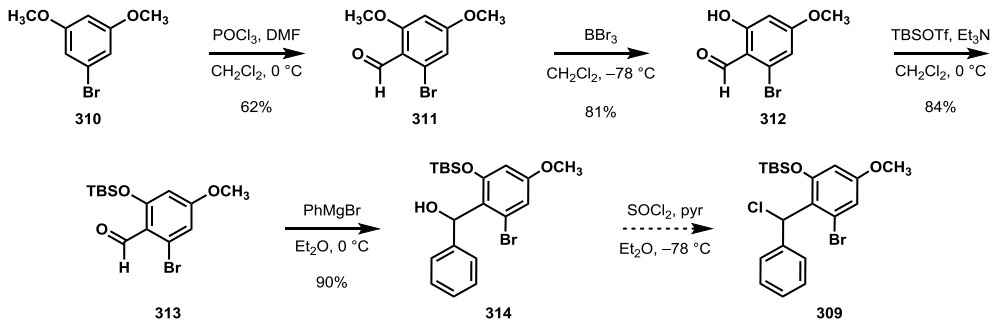


Figure 3.54 Proposed Synthesis of Benzyl Chloride **309**

Continuing the synthesis, we expect the benzyl chloride **309**, the silyl enol ether **252** and anhydrous fluoride to produce the desired enolate–*o*-QM reaction product the keto phenol **308** (**Figure 3.55**). We contest that reaction will produce the correct stereogenic center at C4, but we hope for the correct stereochemistry at C1', the benzylic carbon. We will protect the phenol to the methyl ether **307** and then, with nucleophilic epoxidation conditions, we will produce the epoxy ketone **306**.

Treatment with hydrazine hydrate and then acid will lead to a Wharton transposition to produce the tertiary allylic alcohol **305**.[44] Reduction of the olefin will give way to the penultimate product **304**. We envision that copper catalyzed intramolecular *O*-arylation[45] will provide us with the oxepane **303** and complete the sequence.

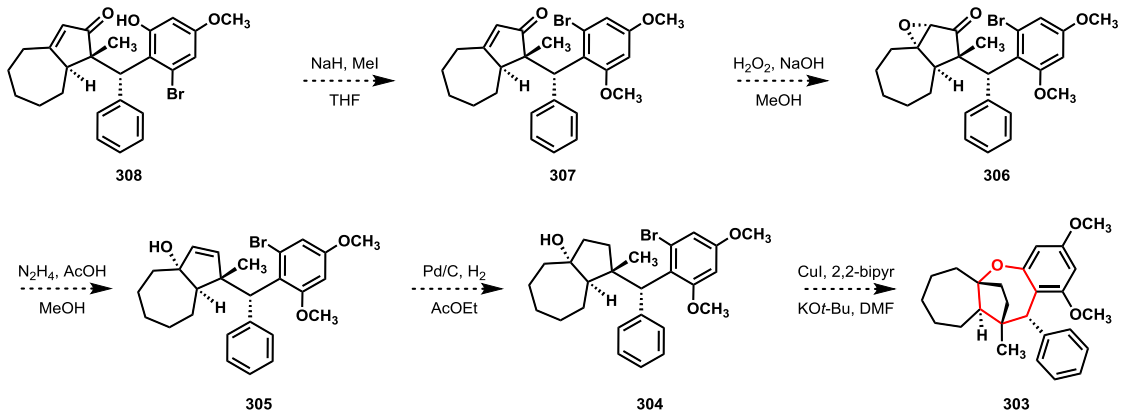


Figure 3.55 Proposed Synthesis of Oxepane **303**

We have previously attempted to produce compounds with the epoxy ketone functionality similar to the epoxy ketone **306**. Our attempts to epoxidize the silylated phenol **276** yielded a mixture of products (**Figure 3.56**). In the same reaction mixture, we isolated the keto phenol **254A**, the hemiketal **263**, the epoxy hemiketal **315**, and the epoxy phenol **316**. Rationalizing the four products, we believe under basic conditions, the silylated phenol **276** will give the deprotected keto phenol **254A**. We understood at the onset of the epoxidation that under basic conditions, base hydrolysis of the silyl ether was possible.[46] Similar to our attempts at producing an oxa-Michael addition under basic conditions, the keto phenol **254A** will isomerize to give the

hemiketal **263**. A small amount of the deprotected epoxy phenol **316** was formed, but we isolated an equal amount of the epoxy hemiketal **315**. The epoxy hemiketal **315** is the result of **316** completing a 1,2-addtion to the carbonyl functionality. Attempts to epoxidize without deprotection of the silylated phenol **276** with *tert*-butyl hydrogen peroxide and DBU returned only starting material.

With nOe experiments, we were able to determine that the relative stereochemistry of the epoxy hemiketal **315** has the methyl at C4 and epoxide at C1-C2 on opposite sides of the molecule. We believe this is due to the sterics imposed by the seven-member ring on to the nucleophilic peroxide.

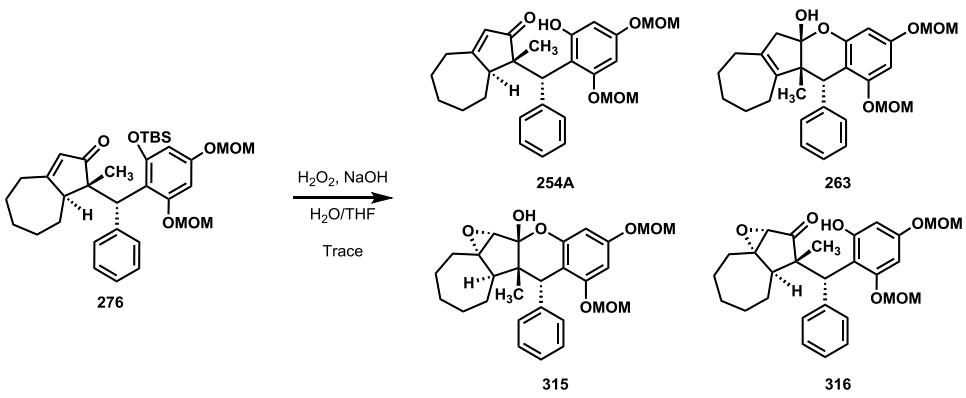


Figure 3.56 Efforts Toward the Epoxidation of Silylated Phenol **276**

With the knowledge gained from our attempts at epoxidation of the silylated phenol **276**, we have begun to scout the reaction sequence toward the epoxy ketone **306** without the bromide analog. Protection of the keto phenol **272** with sodium hydride and methyl iodide produced separable diastereomers of the methyl ether **317** (single diastereomer shown, **317A**, **Figure 3.57**). As we learned before, protection

with TBS and acetate would result in deprotection, thus modifying the protecting group was necessary. Continuing the scout sequence, we were pleased to see the epoxidation of the enone functionally produced the single product epoxy ketone **318**. We again confirmed the relative stereochemistry of the epoxide to be opposite the methyl group at C4.

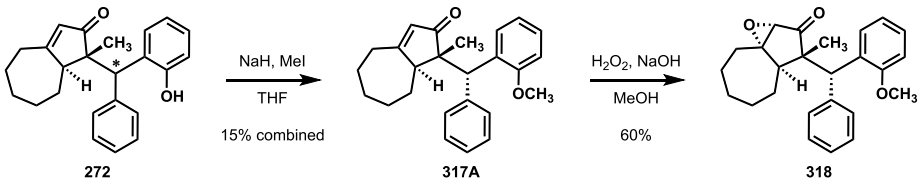


Figure 3.57 Synthesis of Epoxy Ketone **318**

3.8 Second Generation Synthesis of Silyl Enol Ether 225

Once we complete the model system, we will return to the total synthesis toward psiguadial A (**190**). We have developed a new strategy to create the terpene derived left hand half of the natural product, the silyl enol ether **225** (**Figure 3.58**). The advantage and beauty of this synthetic sequence is that we are buying the cyclopropane from the chiral pool.

The synthesis toward the silyl enol ether **255** will begin with (+)-3-carene (**316**). An advantage of starting with (+)-3-carene (**316**) is twofold (1) we will not have to install and set the stereochemistry of the *gem*-dimethyl cyclopropane functionality and (2) (+)-3-carene (**316**) is a member of the chiral pool and is relatively inexpensive. Ozonolysis of (+)-3-carene (**316**) will provide keto aldehyde **317**. We expect we will need to protect the aldehyde functionality either as the cyclic or acyclic

ketal. In order to make the seven-member ring **319** via an intramolecular aldol condensation, we believe we will need to transform the ketone to the keto ester **318** with Mander's reagent. This transformation will insure that the seven-member ring is formed over the five-member by making a more nucleophilic partner for the required aldol condensation. Intramolecular aldol condensation will provide the first seven-member ring found in the natural product. With careful 1,4-reduction, and stereoselective alkylation we hope to stereoselectively install the methyl group seen in ketone **320**.

If we can generate the ketone **320**, the rest of the synthesis parallels the model system we have previously developed and implemented in the lab. Treatment of **320** with LDA and steric approach controlled alkylation will provide ketone **321**. Wacker oxidation of **321** will give diketone which will then be subjected to intramolecular aldol condensation to generate the cyclopentenone **322**. Another treatment with LDA and alkylation with methyl iodide will generate another stereogenic center in the cyclopentenone **323**, but will be rendered inconsequential after another treatment with LDA. Trapping the enolate with a chlorosilane will provide the silyl enol ether **225**.

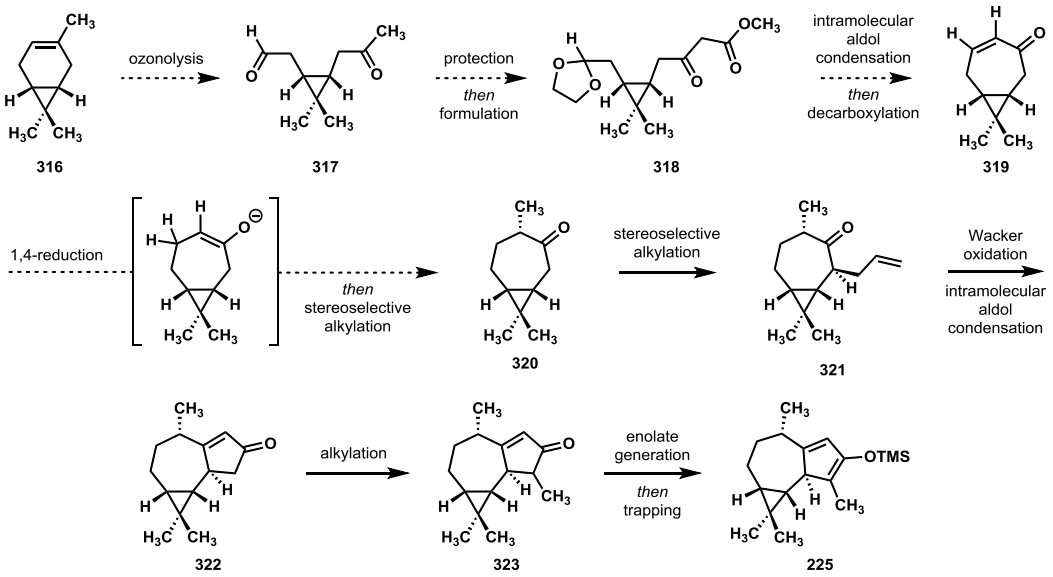


Figure 3.58 Second Generation Synthesis Toward Silyl Enol Ether **225**

3.9 Summary

Complex meroterpenoid psiguadial A (**190**) has promising anti-cancer properties and possess a genuine synthetic challenge. Progress has been made towards the total synthesis of psiguadial A (**190**) in a first generation synthesis of the terpene derived half silyl enol ether **225**. A second generation synthesis of the terpene fragment has been developed and the last five steps parallel our model system. The model system has demonstrated one of the key steps, the enolate–*o*-QM reaction, within the psiguadial A (**190**) synthesis. The development of the model has revealed our original designs, formation of the seven-member oxepane, cannot be formed via an oxa-Michael addition. We developed several synthetic sequences for forming the oxepane; the S_N' method, the attempted carbocation capture, and copper-catalyzed intramolecular *O*-arylation.

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EXPERIMENTAL PROCEDURE

General Information: All reactions were performed in single-neck oven- or flame-dried round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 10 Torr (diaphragm vacuum pump) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 230-400 mesh, Sorbent Technologies) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous acidic dinitrophenylhydrazine solution (DNP), acidic ethanolic *p*-anisaldehyde solution (Anis.), ceric ammonium molybdate (CAM), or aqueous basic potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (215 °C, 10–30 s). Flash chromatography was performed as described by Still et al.[1], employing silica gel (60-Å pore size, 40–63 μm, standard grade, Sorbent Technologies).

Materials: Commercial reagents and solvents were used as received with the following exceptions. Triethylamine, dichloromethane, ethyl ether, dimethylsulfoxide, tetrahydrofuran, hexane, toluene, and benzene were purified by the

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method of Pangborn, et. al.[2] 2-Chloropropanoate, 3-methyl-2-butanone, hexamethyldisilazane, and *N*,*N*-diisopropylamine were distilled from calcium hydride under an atmosphere of argon at 760 Torr. Hexamethylphosphoramide (HMPA) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (0.1 Torr) and stored under argon. The molarity of solutions of *n*-butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[3] Where noted, solvents were deoxygenated before use by bubbling with argon for 20 minutes.

Instrumentation: Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR), and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on Varian Mercury 300 MHz/75 MHz, Varian INOVA 500 MHz/125 MHz, Bruker CryoPlatform 400 MHz/100/376 MHz, or Bruker SMART 600 MHz/151 MHz NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, CD_2HOD: δ 3.31, CD_3SOCD_2H: δ 2.50). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.00, CD_3OD: δ 49.00, CD_3SOCD_3: δ 39.52). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectra were obtained using a

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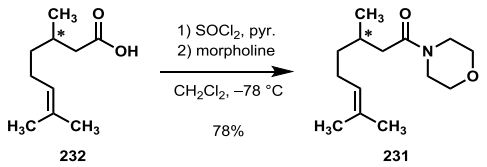
Perkin Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard and data are represented as frequency of absorption (cm^{-1}). Optical rotations were determined using a JASCO-DIP-370 polarimeter equipped with a sodium lamp source (589 nm). Reported readings are the average of three determinations for each sample. High-resolution mass spectra were obtained using an Agilent 1100 quaternary LC system coupled to an Agilent 6210 LC/MSD-TOF fitted with an ESI or an APCI source, or Thermo Q-Exactive Orbitrap using electrospray ionization (ESI) or a Waters GCT Premier spectrometer using chemical ionization (CI).

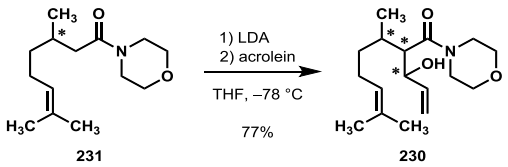


Morpholine Amide **231**:

Thionyl chloride (0.938 mL, 12.9 mmol, 1.1 equiv.) was slowly added to a cooled (–78 °C) solution of (±)-citronellic acid **232** (2.00 g, 11.7 mmol, 1.0 equiv.) and pyridine (1.70 mL, 21.9 mmol, 1.8 equiv.) in dichloromethane (100 mL). The mixture was warmed to 22 °C, stirred for 2 h, and then cooled to –78 °C whereupon anhydrous morpholine (2.03 mL, 23.1 mmol, 2.0 equiv.) was added via syringe. The mixture was warmed to 22 °C and stirred for 30 min. The resultant mixture was slowly diluted with water (40 mL) and the resulting biphasic mixture was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 50% ethyl acetate–hexane) to provide the morpholine amide **231** (2.20 g, 78%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.07 (tq, J_1 = 7.0, J_2 = 1.5 Hz, 1H), 3.63 (tt, J_1 = 5.9, J_2 = 2.6 Hz, 6H), 3.53 – 3.29 (m, 2H), 2.29 (ddd, J_1 = 14.5, J_2 = 5.8, J_3 = 1.3 Hz, 1H), 2.18 – 2.05 (m, 2H), 2.00 – 1.94 (m, 3H), 1.66 (s, 3H), 1.61 – 1.55 (m, 3H), 1.42 – 1.34 (m, 1H), 0.94 (d, J_1 = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	171.4, 131.5, 124.4, 67.0, 66.7, 46.3, 42.0, 40.3, 37.1, 30.1, 25.7, 25.5, 19.8, 17.7.
FTIR (NaCl, thin film), cm^{-1}:	2962, 2918, 2853, 2727, 1644, 1636.
HRMS $(ES)^+$:	Calcd. for $C_{14}H_{25}NO_2Na$ $[M + Na]^+$: 262.1783. Found: 262.1787.
TLC (20% EtOAc–Hex), R_f:	Morpholine Amide **231**: 0.15 (CAM, $KMnO_4$).



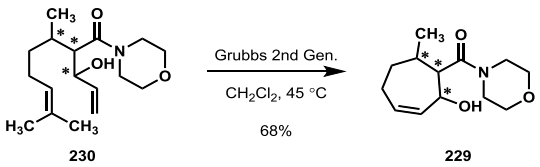
Alkylated Amide **230**:

n-Butyllithium (2.30 M solution in hexane, 2.18 mL, 5.00 mmol, 1.2 equiv.) was added to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (0.819 mL, 8.09 mmol, 1.4 equiv.) in THF (40 mL). The mixture was warmed to 0 °C for 15 min, then cooled to –78 °C whereupon a solution of the amide **231** (1.00 g, 4.17 mmol, 1.0 equiv.) in THF (20 mL) was added via cannula. The mixture was stirred at –78 °C for 2 h whereupon acrolein (0.306 mL, 4.58 mmol, 1.1 equiv.) was added dropwise via syringe. The mixture was stirred at –78 °C for 15 min, then warmed to 23 °C, and stirred for 1 h. The resultant mixture was slowly diluted with water (40 mL) and the resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide an inseparable mixture of diastereomers the alkylated amide **230** (0.953 g, 77%, mixture of two major diastereomers) as a clear colorless oil.

Alkylated amide **230** was isolated as a mixture of diastereomers, asterisk denotes minor peaks.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.71 (dddt, J_1 = 13.6, J_2 = 10.5, J_3 = 5.2, J_4 = 1.6 Hz, 2H), 5.28 (p, J_1 = 1.7 Hz, 1H), 5.22* (p, J_1 = 1.7 Hz, 1H), 5.16 – 4.90 (m, 4H), 4.54* (s, 2H),

	4.34 (s, 2H), 3.74 – 3.51 (m, 12H), 3.44 (dq, J_1 = 9.9, J_2 = 4.8, J_3 = 4.1 Hz, 4H), 2.47 (ddd, J_1 = 17.0, J_2 = 9.6, J_3 = 3.1 Hz, 2H), 2.27 (dd, J_1 = 14.5, J_2 = 5.6 Hz, 2H), 2.20 – 1.79 (m, 8H), 1.63 (s, 6H), 1.59 – 1.51 (m, 6H), 1.32 (qd, J_1 = 6.3, J_2 = 2.4 Hz, 2H), 1.24 – 1.12 (m, 2H), 1.03 (dd, J_1 = 6.7, J_2 = 1.4 Hz, 3H), 0.91 (dd, J_1 = 6.6, J_2 = 1.4 Hz, 3H), 0.86 (d, J_1 = 6.8 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	174.0, 171.3*, 140.0, 131.7*, 131.6*, 131.5*, 124.4, 124.2, 124.0, 115.0*, 115.0, 70.9, 70.8*, 67.0, 66.7*, 66.7, 50.3*, 49.7, 46.7, 46.7, 46.3*, 41.9*, 41.8, 40.3, 37.1, 35.0*, 33.6, 32.8, 32.3, 30.0, 25.7, 25.6*, 25.5*, 25.0, 19.8, 17.8, 17.7*, 17.6*, 16.6.
FTIR (NaCl, thin film), cm^{-1}:	3390, 2964, 2917, 2856, 1601, 1424.
HRMS $(ES)^+$:	Calcd. for $C_{17}H_{29}NO_3Na$ $[M + Na]^+$: 318.2045. Found: 318.2043.
TLC (20% EtOAc–Hex), R_f:	Alkylated Amide **230**: 0.20 (CAM, $KMnO_4$).



230 **229**

Allylic Alcohol **229**:

The second generation Grubbs catalyst (44.0 mg, 0.0518 mmol, 0.025 equiv.) was added to a solution of the amide **230** (0.61 g, 2.1 mmol, 1 equiv.) in dichloromethane (25 mL). The resultant brown solution was heated to reflux for 40 h, then was cooled and concentrated. Purification of the residue by flash column chromatography (20 → 100% ethyl acetate–hexane) provided a partially separable mixture of diastereomers the allylic alcohol **229** (343 mg, 68%, mixture of two major diastereomers) of a pale yellow oil that slowly solidified.

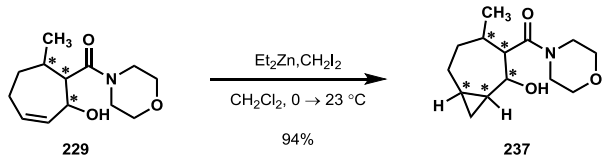
Allylic alcohol **229** was typically isolated as a mixture of diastereomers, asterisk denotes minor peaks.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.91 – 5.58 (m, 4H), 4.79 (br d, J_1 = 9.6 Hz, 1H), 4.69* (br d, J_1 = 9.4 Hz, 1H), 3.83 – 3.53 (m, 12H), 3.53 – 3.45 (m, 4H), 3.02 (dd, J_1 = 9.6, J_2 = 4.7 Hz, 1H), 2.72 – 2.56* (m, 1H), 2.25 – 2.06 (m, 4H), 1.75 – 1.55 (m, 4H), 1.00 (d, J_1 = 7.0 Hz, 3H), 0.91* (d, J_1 = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: Single diastereomer: 173.0, 135.3, 129.4, 67.0, 66.7, 51.4, 46.3, 41.9, 33.5, 32.2, 24.7, 15.4.

FTIR (NaCl, thin film), cm^{-1}: 3363, 2957, 2913, 2857, 1615, 1464, 1441.

HRMS $(EI)^+$:	Calcd. for $C_{13}H_{21}NO_3$ $[M^\bullet]^+$: 239.1521. Found: 239.1527.
TLC (20% EtOAc–Hex), R_f:	Allylic alcohol **229**: 0.03 (CAM, $KMnO_4$).



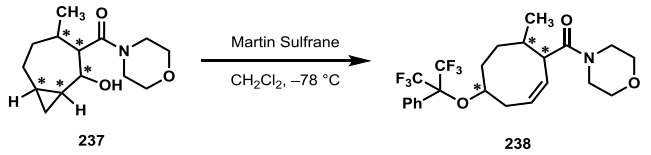
229 237

Cyclopropane **237**:

Diethyl zinc (0.45 M solution in diethyl ether, 3.81 mL, 1.72 mmol, 2.0 equiv.) was added to a cooled (–10 °C) solution of a single diastereomer of the allylic alcohol **229** (205 mg, 0.858 mmol, 1.0 equiv.) in dichloromethane (35 mL) and stirred for 10 min whereupon diiodomethane (0.919 g, 3.43 mmol, 4.0 equiv.) was added neat. The mixture was stirred for 2 h with warming to 22 °C. During the course of the 2 h, a white precipitate began to form in solution. The resultant mixture was slowly quenched with water (2.0 mL), then diluted with ethyl acetate (20 mL) and 1 N aqueous hydrogen chloride solution (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (50% ethyl acetate–hexane) to provide the cyclopropane **237** (205 mg, 94%, single diastereomer) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.84 – 3.46 (m, 8H), 2.82 (dd, J_1 = 10.1, J_2 = 9.1 Hz, 1H), 2.36 (s, 1H), 2.21 – 2.11 (m, 1H), 1.95 – 1.80 (m, 1H), 1.73 (ddd, J_1 = 14.1, J_2 = 6.8, J_3 = 3.3 Hz, 1H), 1.27 (dt, J_1 = 14.1, J_2 = 11.6 Hz, 1H), 0.95 – 0.78 (m, 7H), 0.40 – 0.25 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ:	173.9, 75.9, 67.2, 66.8, 56.3, 46.9, 42.2, 37.7, 37.6, 29.7, 21.8, 21.4, 14.5, 14.1.
TLC (50% EtOAc–Hex), R_f:	Cyclopropane **237**: 0.26 (CAM).



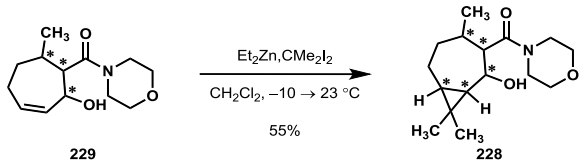
237 238

Amide **238**:

A solution of a single diastereomer of the cyclopropane **237** (56.0 mg, 0.221 mmol, 1.0 equiv.) in dichloromethane (2.0 mL) was added to a cooled (–78 °C) solution of Martin sulfurane (213 mg, 0.317 mmol, 1.4 equiv.) in dichloromethane (3.0 mL). The mixture was stirred at –78 °C for 2 h, then warmed to 22 °C over 30 min. The resultant mixture was concentrated and the residue directed purified by flash column chromatography (10% ethyl acetate–hexane) to provide the amide **238** as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.72 – 7.62 (m, 2H), 7.50 – 7.38 (m, 3H), 6.10 – 6.00 (m, 1H), 5.68 – 5.50 (m, 1H), 3.91 (ddt, J_1 = 11.0, J_2 = 7.5, J_3 = 3.7 Hz, 1H), 3.73 – 3.49 (m, 8H), 2.58 – 2.35 (m, 2H), 2.02 – 1.94 (m, 1H), 1.90 – 1.74 (m, 2H), 1.69 – 1.51 (m, 1H), 1.33 – 1.14 (m, 2H), 0.81 (d, J_1 = 6.8 Hz, 3H).

^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.75 (d, J_1 = 10.3 Hz), –70.13 (d, J_1 = 10.3 Hz).



gem-Dimethylcyclopropane **228**:

Diethyl zinc[4] (0.475 M solution in diethyl ether, 0.704 mL, 0.669 mmol, 2.0 equiv.) was added to a cooled (–10 °C) solution of the allylic alcohol **229** (40.0 mg, 0.167 mmol, 1.0 equiv.) in dichloromethane (5.0 mL) and stirred for 10 min whereupon diiodopropane[5] (197 mg, 0.666 mmol, 4.0 equiv.) in dichloromethane (2.0 mL) was added. The mixture was stirred at –78 °C for 2h whereupon diethyl zinc (0.475 M solution in diethyl ether, 0.704 mL, 0.669 mmol, 2.0 equiv.) was added. The mixture was stirred for 14 h with warming to 22 °C. A white precipitate began to form after the second addition of diethyl zinc. The resultant mixture was quenched with water (2.0 m) and diluted with diethyl ether (20 mL) and 1 N aqueous hydrogen chloride solution (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate–hexane) to provide an inseparable mixture of diastereomers the *gem*-dimethylcyclopropane **228** (26.0 mg, 55%, d.r. = 1:1) as a clear, colorless oil.

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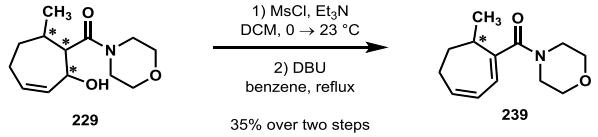
4. Titrated the day of with I_2, LiCl, and THF.

5. 2,2-Diiodopropane made fresh (0.02 mmol scale, 16% diiodo) (a) Redies, K. M.; Fallon, T.; Oestreich, M. *Organometallics*, **2014**, *33*, 3235.

gem-Dimethylcyclopropane **228** was isolated as a mixture of diastereomers, asterisk denotes minor peaks.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	4.80 (d, J_1 = 6.1 Hz, 1H), 4.39* (d, J_1 = 5.2 Hz, 1H), 4.08 (s, 1H), 3.98* (s, 1H), 3.81 – 3.38 (m, 16H), 2.72 (dd, J_1 = 4.3, J_2 = 1.1 Hz, 1H), 2.54 (d, J_1 = 10.6 Hz, 1H), 2.26* (dq, J_1 = 11.0, J_2 = 3.7 Hz, 1H), 2.10* (q, J_1 = 3.4 Hz, 1H), 1.89 – 1.57 (m, 8H), 1.34 (s, 3H), 1.31* (s, 3H), 1.14 (d, J_1 = 7.4 Hz, 3H), 1.03 (s, 3H), 1.02* (s, 3H), 0.85* (d, J_1 = 6.7 Hz, 3H), 0.65* (dddd, J_1 = 14.5, J_2 = 11.4, J_3 = 7.6, J_4 = 3.5 Hz, 2H), 0.56 – 0.41 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	176.4*, 175.7, 73.9*, 70.9, 67.2*, 67.1, 67.0*, 66.8, 52.9*, 49.8, 46.7, 46.6*, 42.0, 41.9, 38.5, 36.1, 34.2, 33.1*, 30.9, 30.8*, 30.5*, 30.4, 29.9, 29.8, 29.0*, 24.1*, 23.8, 23.1*, 22.1, 19.4, 17.2, 17.0, 16.6*.
HRMS $(ES)^+$:	Calcd. for $C_{16}H_{27}NO_3Na$ $[M + Na]^+$: 304.1889. Found: 304.1881.
TLC (50% EtOAc–Hex), R_f:	*gem*-Dimethylcyclopropane **228**: 0.73 ($KMnO_4$).

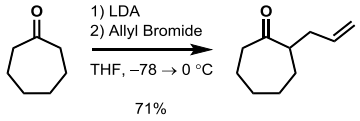


229 239

Conjugated Amide **239**:

Methanesulfonyl chloride (0.952 mL, 12.3 mmol, 3.0 equiv.) was added dropwise to a cooled (0 °C) solution of the allylic alcohol **229** (0.980 g, 4.10 mmol, 1.0 equiv.) and triethylamine (2.86 mL, 21 mmol, 5.0 equiv.) in dichloromethane (40 mL). The mixture was stirred at 0 °C for 30 min, then warmed to 22 °C and stirred for 2 h. The resultant mixture was partitioned between 1 N aqueous hydrogen chloride solution (20 mL) and ethyl acetate (40 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution filtered and the filtrated was concentrated. The residue was dissolved in benzene (40 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.22 mL, 8.21 mmol, 2.0 equiv.) added via syringe. The mixture was heated to reflux for 6 h. The resultant mixture was cooled to room temperature and partitioned between 1 N aqueous hydrogen chloride solution (20 mL) and ethyl acetate (40 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the conjugated amide **239** (0.324 g, 35%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	6.01 – 5.91 (m, 1H), 5.82 – 5.68 (m, 2H), 3.72 – 3.44 (m, 8H), 2.99 – 2.83 (m, 1H), 2.38 (dddd, J_1 = 6.8, J_2 = 4.7, J_3 = 2.9, J_4 = 1.2 Hz, 2H), 1.89 – 1.68 (m, 2H), 1.03 (d, J_1 = 7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	172.7, 143.1, 137.4, 123.9, 123.1, 67.0, 36.1, 30.6, 27.6, 18.5.
HRMS $(ES)^+$:	Calcd. for $C_{13}H_{19}NO_2H$ $[M + H]^+$: 222.1494. Found: 222.1484.
TLC (50% EtOAc–Hex), R_f:	Conjugated Amide **239**: 0.60 (CAM, $KMnO_4$).



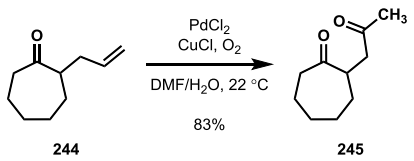
243 **244**

Allyl Ketone **244**:

n-Butyllithium (1.95 M solution in hexane, 117 mL, 32.0 mmol, 1.2 equiv.) was added dropwise via syringe to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (5.24 mL, 37.4 mmol, 1.4 equiv.) in THF (100 mL). The mixture was warmed to 0 °C for 15 min, then cooled to –78 °C whereupon a solution of cycloheptanone **243** (3.16 mL, 3.00 g, 26.7 mmol, 1 equiv.) in THF (10 mL) was added dropwise via cannula addition. The mixture was stirred at –78 °C for 1 h whereupon a solution of allyl bromide (3.24 mL, 4.53 g, 37.4 mmol, 1.4 equiv.) in THF (10 mL) was added dropwise via cannula addition. The reaction mixture was stirred at –78 °C for 1 h, then warmed to 23 °C, and stirred for 1h. The resultant mixture was partitioned between 1 N aqueous hydrogen chloride solution (50 mL) and hexane (100 mL). The resulting biphasic mixture was extracted with hexane (3 x 25 mL). The combined organic extracts were washed with water (10 mL) then saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (0 → 5% diethyl ether–hexane) to provide the allyl ketone **244** (2.90 g, 71%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.79 – 5.65 (m, 1H), 5.05 – 4.97 (m, 2H), 2.55 (tt, J_1 = 7.7, 6.2, 2.8 Hz, 1H), 2.50 – 2.39 (m, 3H), 2.11 – 2.01 (m, 1H), 1.92 – 1.78 (m, 4H), 1.67 – 1.55 (m, 1H), 1.42 – 1.24 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	215.8, 136.4, 116.7, 51.7, 43.2, 36.4, 30.7, 29.6, 28.8, 24.4.
FTIR (NaCl, thin film), cm^{-1}:	2931, 2855, 1735, 1697, 1454, 1401, 1231.
HRMS $(CI)^+$:	Calcd. for $C_{10}H_{16}OH$ $[M + H]^+$: 153.1279. Found: 153.1275.
TLC (20% EtOAc–Hex), R_f:	Allyl Ketone **244**: 0.66 (Anis, $KMnO_4$).



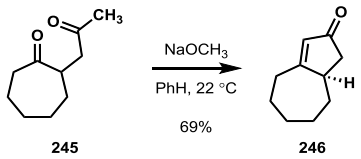
244 245

Diketone **245**:

Oxygen was bubbled for 1 h through a dark suspension of palladium(II) chloride (109 mg, 0.615 mmol, 0.036 equiv.) and copper(I) chloride (2.04 g, 20.6 mmol, 1.2 equiv.) in a mixture of *N*,*N*-dimethylformamide/water (7:1, 20.0 mL) during which the reaction mixture changed colors; dark black to forest green. After 1 h, the allyl ketone **244** (2.61 g, 17.2 mmol, 1.0 equiv.) was added neat to the resultant green suspension, and stirred rapidly under an atmosphere of oxygen for 6 h during which, the mixture darkens to black and returns to green. The resultant mixture was partitioned between 3 N aqueous hydrogen chloride solution (25 mL) and diethyl ether (25 mL). The resulting biphasic mixture was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were washed sequentially with 10% aqueous lithium chloride solution (3 x 10 mL), water (10 mL), and saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 20% ethyl acetate–hexane) to provide the diketone **245** (2.40 g, 83%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.19 – 3.09 (m, 1H), 3.04 (dd, J_1 = 17.6, J_2 = 8.8 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.46 – 2.30 (m, 2H), 2.14 (s, 3H), 1.94 – 1.84 (m, 1H), 1.84 – 1.62 (m, 4H), 1.61 – 1.47 (m, 1H), 1.37 – 1.16 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	214.9, 207.7, 46.6, 46.1, 43.5, 31.4, 30.3, 29.6, 29.0, 23.5.
FTIR (NaCl, thin film), cm^{-1}:	2931, 2855, 1735, 1697, 1454, 1401, 1231.
HRMS $(CI)^+$:	Calcd. for $C_{10}H_{16}O_2H$ $[M + H]^+$: 169.1229. Found: 169.1224.
TLC (20% EtOAc–Hex), R_f:	Diketone **245**: 0.30 (Anis, CAM).



245 246

Cyclopentenone **246**:

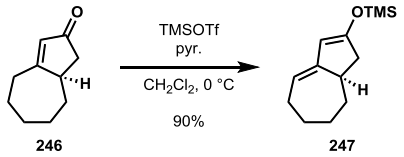
Solid, anhydrous sodium methoxide (3.31 g, 61.3 mmol, 2.5 equiv.) was added to a solution of the diketone **245** (4.15 g, 25.7 mmol, 1. 0 equiv.) in benzene (300 mL, 0.08 M). The mixture was stirred for 25 h, over which time the mixture darkened. The resultant heterogeneous mixture was concentrated to half its original volume. The mixture was partitioned between 1 N aqueous hydrogen chloride solution (50 mL) and diethyl ether (50 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (25 mL) and saturated aqueous sodium chloride solution (25 mL) and dried over anhydrous sodium sulfate. The dry solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the cyclopentenone **246** (2.58 g, 69%) as a clear, dark yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.81 (s, 1H), 2.90 (bs, 1H), 2.79 – 2.49 (m, 3H), 2.01 – 1.84 (m, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.56 (m, 3H), 1.49 – 1.29 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 208.9, 187.9, 129.7, 44.4, 44.4, 34.3, 32.7, 30.3, 28.5, 26.4.

FTIR (NaCl, thin film), cm^{-1}: 2923, 2852, 1710, 1460, 1377.

HRMS $(ES)^+$:	Calcd. for $C_{10}H_{14}OH$ $[M + H]^+$: 151.1123. Found: 151.1129.
TLC (20% EtOAc–Hex), R_f:	Cyclopentenone **246**: 0.22 (UV, CAM).

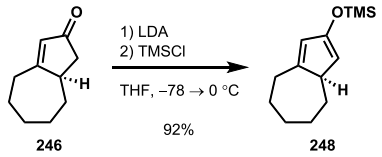


246 247

Silyl Enol Ether **247**:

Trimethylsilyl trifluoromethanesulfonate (0.450 mL, 2.48 mmol, 2.5 equiv. was added slowly via syringe to a cooled (0 °C) solution of the cyclopentenone **246** (0.150 mg, 0.998 mmol, 1.0 equiv.) and pyridine (0.600 mL, 7.45 mmol, 7.0 equiv.) in dichloromethane (3.0 mL). The mixture was stirred at 0 °C for 30 min, and then concentrated. The residue was triturated with hexane, filtered with celite, and then concentrated to provide the silyl enol ether **247** (197 mg, 90%) as a clear, orange oil.

^{1}H NMR (600 MHz, $CDCl_3$), δ:	5.40 (ddd, J_1 = 8.3, J_2 = 4.6, J_3 = 2.4 Hz, 1H), 5.12 (s, 1H), 2.90 – 2.80 (m, 1H), 2.78 – 2.65 (m, 1H), 2.16 – 2.11 (m, 1H), 2.10 – 2.05 (m, 2H), 2.03 – 1.96 (m, 1H), 1.80 – 1.70 (m, 2H), 1.56 – 1.46 (m, 1H), 1.39 – 1.31 (m, 1H), 1.31 – 1.21 (m, 1H), 0.23 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	160.3, 152.6, 115.7, 108.9, 42.3, 40.8, 35.5, 32.5, 29.5, 29.2, 0.2.
HRMS $(CI)^+$:	Calcd. for $C_{10}H_{14}OH$ $[M – TMS + H]^+$: 151.1123. Found: 151.1128.
TLC (20% EtOAc–Hex), R_f:	Silyl Enol Ether **247**: 0.90 (UV, $KMnO_4$).



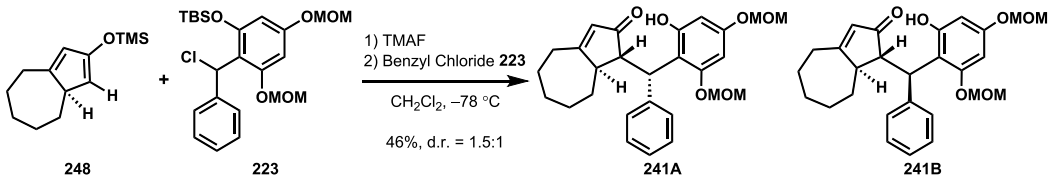
Silyl Enol Ether **248**:

n-Butyllithium (2.50 M solution in hexane, 0.764 mL, 1.91 mmol, 1.2 equiv.) was added to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (0.268 mL, 2.60 mmol, 1.3 equiv.) in THF (20 mL). The mixture was warmed to 0 °C for 15 min, cooled to –78 °C whereupon a solution of the cyclopentenone **246** (200 mg, 1.33 mmol, 1.0 equiv.) in THF (2.0 mL) was added dropwise via cannula addition. The reaction mixture was stirred –78 °C for 45 min whereupon trimethylchlorosilane (0.258 mL, 1.76 mmol, 1.2 equiv.) was added dropwise via syringe. The resultant solution was stirred at –78 °C for 5 min, then warmed to 0 °C, and stirred for 30 min. The resultant mixture was concentrated, the residue was triturated with hexane, filtered with celite, and then concentrated to provide the silyl enol ether **248** (300 mg, 92%) as a clear, pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.79 (t, J_1 = 1.6 Hz, 1H), 4.95 (t, J_1 = 2.0 Hz, 1H), 3.24 – 2.93 (m, 1H), 2.73 – 2.44 (m, 2H), 2.04 – 1.97 (m, 1H), 1.84 – 1.79 (m, 1H), 1.75 – 1.68 (m, 1H), 1.68 – 1.63 (m, 1H), 1.63 – 1.55 (m, 1H), 1.55 – 1.46 (m, 1H), 1.36 – 1.27 (m, 1H), 1.17 – 1.03 (m, 1H), 0.23 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$), δ: 156.2, 154.4, 125.3, 108.8, 52.3, 31.1, 30.9, 30.6, 30.2, 28.1, 0.1.

TLC (20% EtOAc–Hex), R_f: Cyclopentenone **248**: 0.22 (UV, CAM).



Keto Phenol **241**:

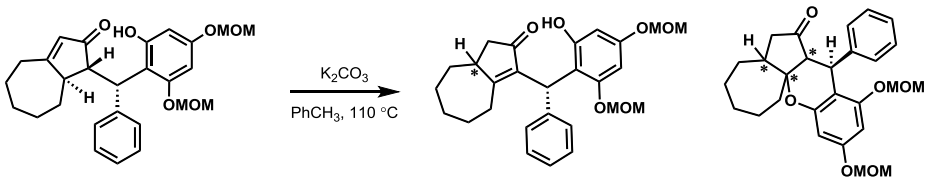
A cooled (–78 °C) solution of tetramethylammonium fluoride (TMAF, 186 mg, 2.00 mmol, 2.05 equiv.) in dichloromethane (2.0 mL) was added rapidly via cannula to a cooled (–78 °C) solution of the silyl enol ether **248** (217 mg, 0.976 mmol, 1.0 equiv.) in dichloromethane (2.0 mL). During the addition, an intense color changed occurred: clear orange to dark red. The reaction was stirred for 2 min whereupon a solution of the benzyl chloride **223** (354 mg, 0.781 mmol, 0.80 equiv.) in dichloromethane (5.0 ml) at 23 °C was slowly added to the reaction flask via cannula addition. The benzyl chloride solution was added to the flask in a manner that caused the solution to run down the side of the reaction flask. This method cooled the benzyl chloride solution before participating in the reaction. Addition of benzyl chloride caused a gradual color change in the reaction mixture: dark red to cloudy brown/green. The mixture was stirred at –78 °C for 1h, and then quenched by the addition of acetic acid (100 μL). The resultant mixture was warmed to 23 °C, and then diluted with ethyl acetate (20 mL) and water (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was absorbed on to silica gel. The purification of the residue was completed by flash column chromatography (10 → 40% ethyl acetate–hexane) to provide separable diastereomers of the keto phenol **241A** and **241B** (97.0 mg and 64.0 mg respectively, 46% combined yield, d.r = 1.5:1) as a clear, colorless oil.

Keto Phenol **241A**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	9.23 (s, 1H), 7.20 (dd, J_1 = 8.2, J_2 = 6.5 Hz, 2H), 7.16 – 7.09 (m, 1H), 6.99 – 6.91 (m, 2H), 6.40 (d, J_1 = 2.5 Hz, 1H), 6.39 (d, J_1 = 2.5 Hz, 1H), 6.04 (s, 1H), 5.23 (s, 1H), 5.14 (d, J_1 = 1.7 Hz, 2H), 5.11 (s, 2H), 3.48 (s, 3H), 3.36 (s, 3H), 3.21 (s, 1H), 2.74 (s, 3H), 2.14 (dd, J_1 = 13.5, J_2 = 7.2 Hz, 1H), 1.86 – 1.70 (m, 3H), 1.65 (dt, J_1 = 11.3, J_1 = 7.2 Hz, 2H), 1.58 – 1.51 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	211.9, 187.6, 157.7, 157.1, 156.0, 140.3, 129.5, 128.4, 127.3, 126.1, 114.0, 100.6, 95.3, 94.9, 94.6, 60.2, 56.3, 56.3, 53.2, 36.8, 33.3, 31.2, 31.1, 29.9, 27.7, 27.7.
FTIR (KBr, thin film), cm^{-1}:	3318, 2925, 2851, 1672, 1607.
HRMS $(ES)^+$:	Calcd. for $C_{27}H_{32}O_6H$ $[M + H]^+$: 453.2272. Found: 453.2264.
TLC (20% EtOAc–Hex), R_f:	Keto Phenol **241A**: 0.11 (CAM, $KMnO_4$).

Keto Phenol **241B**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.44 (s, 1H), 7.31 (t, J_1 = 7.8 Hz, 3H), 7.28 – 7.24 (m, 2H), 7.19 (t, J_1 = 7.1 Hz, 1H), 6.41 (d, J_1 = 2.5 Hz, 1H), 6.24 (d, J_1 = 2.4 Hz, 1H), 5.90 (s, 1H), 5.20 (dd, J_1 = 32.6, J_2 = 6.5 Hz, 2H), 5.09 (s, 2H), 5.00 (d, J_1 = 4.5 Hz, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 3.23 (t, J_1 = 4.1 Hz, 1H), 2.97 (s, 1H), 2.67 (t, J_1 = 5.9 Hz, 2H), 1.90 (s, 1H), 1.84 – 1.54 (m, 3H), 1.70 – 1.59 (m, 2H), 1.50 (d, J_1 = 9.7 Hz, 1H)
^{13}C NMR (101 MHz, $CDCl_3$), δ:	212.0, 188.5, 157.9, 156.8, 156.7, 142.3, 128.8, 128.3, 127.8, 126.2, 112.2, 100.8, 95.6, 95.3, 94.5, 56.9, 56.5, 56.3, 50.0, 37.8, 34.8, 33.3, 31.7, 31.1, 27.9, 27.4, 22.8.
TLC (20% EtOAc–Hex), R_f:	Keto Phenol **241B**: 0.06 (CAM, $KMnO_4$).



241A

249
44%

250
19%

Keto Phenol **249** and Tetrahydropyran **250**:

Potassium carbonate (10.0 mg, 0.0723 mmol, 1.2 equiv.) was added a solution of the keto phenol **241A** (26.0 mg, 0.576 mmol, 1.0 equiv.) in anhydrous toluene (2.0 mL). The reaction mixture was degassed with bubbling argon and heated to reflux (110 °C) for 20 h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the keto phenol **249** (11.4 mg, 44%, mixture of diastereomers, separable on HPLC) as a clear, colorless oil and the tetrahydropyran **250** (5.1 mg, 19%, mixture of diastereomers, separable on HPLC) as a clear, colorless solid.

NMR data of the diastereomeric mixtures of keto phenol **249** and tetrahydropyran **250** were collected, asterisk denotes minor peaks.

The reaction was repeated with other diastereomer keto phenol **241B**. This other diastereomer produced similar products to keto phenol **249** and tetrahydropyran **250**.

Keto Phenol **249**:

^{1}H NMR (400 MHz, $CDCl_3$), δ: Mixture of diastereomers: 9.16 (s, 1H), 9.07* (s, 1H), 7.29 – 7.13 (m, 7H), 7.06 – 6.91 (m, 3H), 6.44 (dd, J_1 = 9.4, J_2 = 2.5 Hz, 2H), 6.37 (t, J_1 = 2.2 Hz, 2H), 5.89* (s, 1H), 5.87 (s, 1H), 5.22 – 5.16 (m, 4H), 5.14 (dd, J_1 = 3.2, J_2 = 1.2 Hz,

4H), 3.48* (s, 3H), 3.47 (s, 3H), 3.45* (s, 3H), 3.43 (s, 3H), 3.15 – 3.06* (m, 1H), 3.01 (dt, J_1 = 13.1, 5.9 Hz, 4H), 2.95* (s, 1H), 2.89* (d, J_1 = 6.4 Hz, 1H), 2.84* (d, J_1 = 6.4 Hz, 1H), 2.79 (d, J_1 = 6.4 Hz, 1H), 2.74 (d, J_1 = 6.3 Hz, 1H), 2.21 (d, J_1 = 2.3 Hz, 1H), 2.16 (d, J_1 = 2.3 Hz, 1H), 2.12 – 1.95 (m, 4H), 1.95 – 1.81 (m, 4H), 1.80 – 1.70 (m, 5H), 1.65 – 1.56 (m, 4H), 1.56 – 1.39 (m, 4H).

Major diastereomer: 9.16 (s, 1H), 7.26 (s, 2H), 7.21 – 7.10 (m, 1H), 7.01 (dt, J_1 = 8.1, 1.2 Hz, 2H), 6.42 (d, J_1 = 2.5 Hz, 1H), 6.36 (d, J_1 = 2.4 Hz, 1H), 5.89 (s, 1H), 5.18 (d, J_1 = 1.4 Hz, 2H), 5.13 (d, J_1 = 1.3 Hz, 2H), 3.47 (s, 3H), 3.43 (s, 3H), 3.09 – 2.91 (m, 3H), 2.76 (dd, J_1 = 19.0, J_2 = 6.4 Hz, 1H), 2.18 (dd, J_1 = 19.0, J_2 = 2.3 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.91 – 1.81 (m, 1H), 1.80 – 1.68 (m, 2H), 1.59 (t, J_1 = 9.6 Hz, 2H), 1.54 – 1.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: Mix of diastereomer: 211.8, 211.5*, 186.9, 186.6*, 157.9, 157.9*, 157.8*, 157.8, 156.9*, 156.7, 140.3, 140.0*, 139.1, 128.4, 128.3*,

126.8*, 126.8, 126.2, 126.1*, 110.7*, 110.4, 101.0*, 100.9, 95.3, 95.3*, 95.2, 95.1*, 94.6*, 94.5, 56.5, 56.5*, 56.3*, 56.3, 43.7*, 43.6, 43.5*, 43.4, 35.4*, 34.7*, 34.6, 34.6, 32.1*, 31.7*, 31.3, 31.0, 30.7, 30.0*, 29.8, 28.2, 26.6, 25.8*.

Major diastereomer: 211.7, 186.8, 157.8, 157.7, 156.6, 140.2, 138.9, 128.3, 126.6, 126.1, 110.3, 100.8, 95.1, 95.1, 94.4, 56.4, 56.2, 43.4, 43.3, 34.4, 31.2, 30.9, 29.7, 28.1, 26.5.

FTIR (KBr, thin film), cm^{-1}: 3285, 2911, 2850, 1670, 1615, 1492, 1152.

HRMS $(ES)^+$: Calcd. for $C_{27}H_{32}O_6H$ $[M + H]^+$: 453.2272. Found: 453.2273.

TLC (20% EtOAc–Hex), R_f: Keto Phenol **249**: 0.35 (UV, CAM, $KMnO_4$).

Tetrahydropyran **250**:

^1H NMR (400 MHz, $CDCl_3$), δ: Major diastereomer: 7.22 (dd, J_1 = 8.5, J_2 = 6.6 Hz, 2H), 7.12 (td, J_1 = 7.0, J_2 = 6.6, J_3 =1.5 Hz, 3H), 6.34 (s, 2H), 5.23 – 5.06 (m, 2H), 4.99 – 4.84 (m, 2H), 4.73 (s, 1H), 3.51 (s, 3H), 3.08 (s, 3H), 2.66 (d, J_1 = 1.2 Hz, 1H), 2.47 (dd, J_1 =

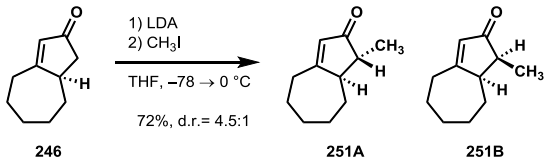
18.5, J_2 = 7.8 Hz, 1H), 2.22 (tt, J_1 = 10.5, J_2 = 8.2 Hz, 1H), 2.17 – 1.90 (m, 3H), 1.86 – 1.60 (m, 5H), 1.49 – 1.33 (m, 2H), 0.98 (ddd, J_1 = 14.6, J_2 = 10.0, J_3 = 4.3 Hz, 1H).

Minor diastereomer: 7.25 (t, J_1 = 7.4 Hz, 2H), 7.20 – 7.11 (m, 3H), 6.36 (d, J_1 = 2.4 Hz, 1H), 6.30 (d, J_1 = 2.3 Hz, 1H), 5.16 (s, 2H), 4.98 – 4.87 (m, 2H), 4.73 (s, 1H), 3.52 (s, 3H), 3.09 (s, 3H), 2.81 – 2.70 (m, 2H), 2.55 (t, J_1 = 9.9 Hz, 1H), 2.16 – 2.00 (m, 2H), 1.89 (s, 1H), 1.80 (d, J_1 = 13.9 Hz, 1H), 1.56 – 1.43 (m, 3H), 1.17 – 0.99 (m, 3H), 0.74 (q, J_1 = 8.0, J_2 = 7.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: Mix of diastereomers: 215.4*, 215.0, 157.7, 157.7*, 156.5, 156.4*, 155.1, 154.8*, 144.4, 144.4, 128.1*, 128.0, 127.6, 125.7*, 125.7, 103.7, 103.6*, 98.0*, 97.9, 95.6, 94.5, 93.8*, 93.8*, 86.2*, 83.2, 62.8, 58.2*, 56.2, 56.2*, 55.9, 45.6, 44.0*, 43.4, 42.6*, 37.8, 37.3*, 33.5, 33.0, 32.6*, 30.5, 30.3, 29.7*, 26.6, 26.5, 25.9*, 23.3, 22.0*.

FTIR (KBr, thin film), cm^{-1}: 2921, 2850, 1746, 1615, 1492, 1450.

HRMS $(ES)^+$:	Calcd. for $C_{27}H_{32}O_6H$ $[M + H]^+$: 453.2272. Found: 453.2270.
TLC (30% EtOAc–Hex), R_f:	Tetrahydropyran **250**: 0.68 (CAM, $KMnO_4$).



Methyl Cyclopentenone **251**:

n-Butyllithium (2.50 M solution in hexane, 0.875 mL, 2.20 mmol, 1.1 equiv.) was added to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (0.362 mL, 2.60 mmol, 1.3 equiv.) in THF (20 mL). The solution was warmed to 0 °C for 15 min, cooled to –78 °C whereupon a solution of the cyclopentenone **246** (0.300 g, 2.00 mmol, 1.0 equiv.) in THF (5.0 mL) was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 45 min whereupon methyl iodide (0.174 mL, 2.80 mmol, 1.4 equiv.) was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 5 min, then warmed to 0 °C and stirred for 30 min. The resultant mixture was slowly quenched with saturated aqueous ammonium chloride (20 mL) and diluted with diethyl ether (20 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 20% ethyl acetate–hexane) to provide separable diastereomers of the methyl cyclopentenones **251A** and **251B** (238 mg, 72%, combined yield, d.r. = 4.5:1) as a clear, colorless oil.

The diastereomers of methyl cyclopentenone **251** were not typically separated, due to the stereochemistry being rendered inconsequential in the forthcoming reaction.

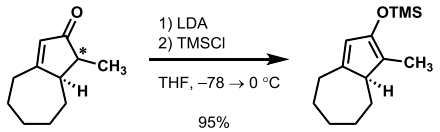
Methyl Cyclopentenone **251A**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	5.87 (s, 1H), 2.97 – 2.91 (m, 1H), 2.88 – 2.77 (m, 1H), 2.71 – 2.61 (m, 1H), 2.55 (p, J_1 = 7.2 Hz, 1H), 2.01 – 1.85 (m, 2H), 1.82 – 1.71 (m, 1H), 1.69 – 1.57 (m, 1H), 1.49 – 1.36 (m, 1H), 1.35 – 1.24 (m, 2H), 1.19 – 1.12 (m, 1H), 1.06 (d, J_1 = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	212.3, 187.0, 128.2, 48.3, 46.0, 33.1, 30.3, 29.9, 29.8, 26.0, 12.3.
FTIR (KBr, thin film), cm^{-1}:	2924, 2852, 1699, 1605, 1455.
HRMS $(CI)^+$:	Calcd. for $C_{11}H_{16}OH$ $[M + H]^+$: 165.1279. Found: 165.1280.
TLC (20% EtOAc–Hex), R_f:	Methyl Cyclopentenone **251A**: 0.40 (UV, CAM, $KMnO_4$).

Methyl Cyclopentenone **251B**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	5.85 (s, 1H), 2.75 – 2.59 (m, 2H), 2.50 – 2.43 (m, 1H), 2.03 – 1.90 (m, 2H), 1.84 – 1.63 (m, 4H), 1.53 – 1.41 (m, 3H), 1.16 (d, J_1 = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	211.2, 185.6, 128.6, 53.5, 49.7, 32.9, 32.3, 31.0, 28.5, 27.1, 13.9.
TLC (20% EtOAc–Hex), R_f:	Methyl Cyclopentenone **251B**: 0.33 (UV, CAM, $KMnO_4$).



251 252

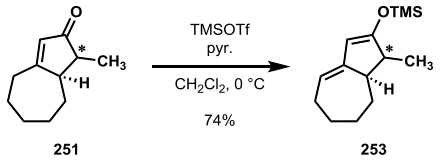
Silyl Enol Ether **252**:

n-Butyllithium (2.39 M solution in hexane, 0.489 mL, 1.17 mmol, 1.1 equiv.) was added to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (0.179 mL, 1.28 mmol, 1.3 equiv.) in THF (8 mL). The solution was warmed to 0 °C for 15 min, cooled to –78 °C whereupon a solution of the methyl cyclopentenone **251** (175 mg, 1.07 mmol, 1.0 equiv.) in THF (2 mL) was added dropwise via cannula addition. The reaction mixture was stirred at –78 °C for 30 min whereupon trimethylsilyl chloride (0.163 mL, 1.28 mmol, 1.2 equiv.) was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 5 min, then warmed to 0 °C, and stirred for 30 min. The resultant mixture was concentrated, the residue was triturated with hexane, filtered with celite, and concentrated to provide the silyl enol ether **252** (250 mg, 95%) as a clear, orange oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.77 (s, 1H), 2.68 (dd, J_1 = 9.8, J_2 = 4.0 Hz, 1H), 2.63 – 2.46 (m, 2H), 2.03 – 1.96 (m, 1H), 1.83 – 1.74 (m, 1H), 1.69 (s, 3H), 1.64 – 1.57 (m, 2H), 1.54 – 1.43 (m, 2H), 1.40 – 1.29 (m, 1H), 1.09 – 0.97 (m, 1H), 0.19 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 152.2, 147.9, 124.9, 118.2, 54.3, 31.1, 30.8, 29.8, 29.4, 28.4, 9.8, 0.5.

FTIR (KBr, thin film), cm^{-1}:	2958, 2921, 2851, 1708, 1646, 1251.
HRMS $(CI)^+$:	Calcd. for $C_{14}H_{24}OSiH$ $[M + H]^+$: 237.1675. Found: 237.1672.
TLC (20% EtOAc–Hex), R_f:	Silyl Enol Ether **252**: 0.85 (UV, CAM).



251 253

Silyl Enol Ether **253**:

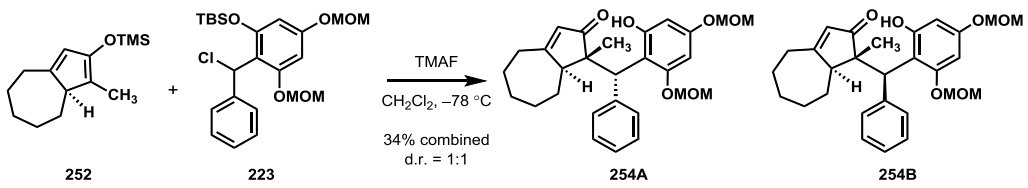
Trimethylsilyl trifluoromethanesulfonate (0.480 mL, 2.63 mmol, 2.5 equiv.) was added slowly via syringe to a cooled (0 °C) solution of the cyclopentenone **251** (0.174 mg, 1.06 mmol, 1.0 equiv.) and pyridine (0.636 mL, 7.42 mmol, 7.0 equiv.) in dichloromethane (10 mL). The mixture was stirred at 0 °C for 30 min, then concentrated. The residue was triturated with hexane, filtered with celite, and concentrated to provide the silyl enol ether **253** (187 mg, 74%) as a clear, orange oil.

^{1}H NMR (600 MHz, $CDCl_3$), δ: 5.38 (ddd, J_1 = 7.6, J_2 = 4.3, J_3 = 2.1 Hz, 1H), 5.07 (s, 1H), 2.36 – 2.19 (m, 2H), 2.18 – 2.12 (m, 1H), 1.81 – 1.74 (m, 2H), 1.53 – 1.44 (m, 1H), 1.34 – 1.22 (m, 2H), 1.07 (d, J_1 = 6.7 Hz, 3H), 0.23 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$), δ: 163.8, 150.9, 115.6, 107.4, 50.3, 48.1, 34.5, 32.4, 29.6, 29.3, 18.2, 0.1.

TLC (20% EtOAc–Hex), R_f: Silyl Enol Ether **253**: 0.90 (UV, $KMnO_4$).

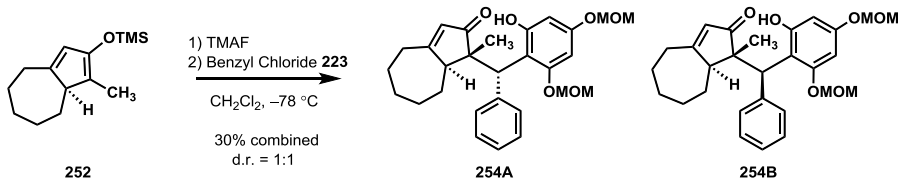
General Addition Sequence – Premix Starting Materials



Keto Phenols **254A** and **254B**:

A cooled (–78 °C) solution of tetramethylammonium fluoride (TMAF, 99.7 mg, 1.07 mmol, 2.05 equiv.) in dichloromethane (2.0 mL) was added rapidly via cannula addition to a cooled (–78 °C) solution of the benzyl chloride **223** (236mg, 0.521 mmol, 1.0 equiv.) and the silyl enol ether **252** (123 mg, 0.521 mmol, 1.0 equiv.), in dichloromethane (3 mL). Addition of TMAF produced an intense color change: yellow to dark red to pale green. The mixture was stirred at –78 °C for 1 h and then quenched by the addition of acetic acid (50 μL). Addition of acetic acid produced a color change: pale green to yellow. The resultant mixture was warmed to 22 °C and then absorbed on to silica gel. Purification was completed by flash column chromatography (10 → 40% ethyl acetate–hexane) to provide separable diastereomers of the keto phenols **254A** and **254B** (43.0 mg and 41.0 mg respectively, 34% combined yield, d.r. = 1:1) as a clear, thick oil.

Stepwise Addition of Starting Materials



252 **254A** **254B**

A cooled (–78 °C) solution of tetramethylammonium fluoride (TMAF, 186 mg, 2.00 mmol, 2.05 equiv.) in dichloromethane (2.0 mL) was added rapidly via cannula to a cooled (–78 °C) solution of the silyl enol ether **248** (217 mg, 0.976 mmol, 1.0 equiv.) in dichloromethane (2.0 mL). During the addition, an intense color changed occurred: clear orange to dark red. The mixture was stirred for 2 min whereupon a solution of the benzyl chloride **223** (354 mg, 0.781 mmol, 0.80 equiv.) in dichloromethane (5.0 ml) at 23 °C was slowly added to the reaction flask via cannula addition. The benzyl chloride solution was added to the flask in a manner that caused the solution to run down the side of the reaction flask. This method cooled the benzyl chloride solution before participating in the reaction. Addition of benzyl chloride caused a gradual color change in the reaction mixture: dark red to cloudy brown/green. The reaction mixture was stirred at –78 °C for 1 h, and then quenched by the addition of acetic acid (100 μL). The resultant mixture was warmed to 23 °C, then diluted with ethyl acetate (20 mL) and water (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was absorbed on to silica gel. The purification of the residue was completed by flash column chromatography (10 → 40% ethyl acetate–hexane) to provide separable diastereomers

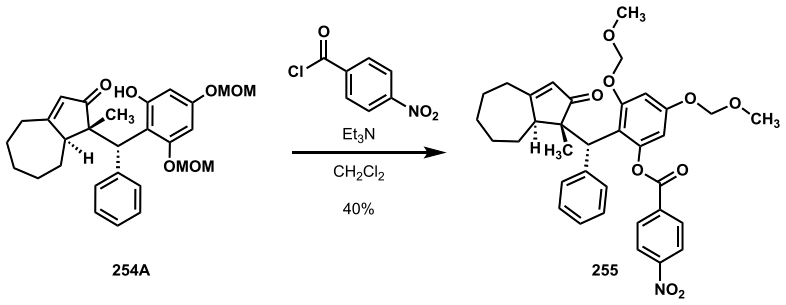
of the keto phenols **241A** and **241B** (97.0 mg and 64.0 mg respectively, 46% combined yield, d.r = 1.5:1) as a clear, thick oil.

Keto Phenol **254A**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	10.12 (s, 1H), 7.20 – 7.08 (m, 3H), 6.93 (d, J_1 = 7.5 Hz, 2H), 6.39 (d, J_1 = 2.5 Hz, 1H), 6.36 (d, J_1 = 2.5 Hz, 1H), 6.08 (s, 1H), 5.22 – 5.10 (m, 5H), 3.49 – 4.46 (m, 6H), 3.23 (s, 1H), 3.05 (dd, J_1 = 17.7, J_2 = 6.8 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.11 – 1.96 (m, 3H), 1.89 – 1.80 (m, 1H), 1.60 – 1.49 (m, 2H), 1.48 – 1.38 (m, 2H), 0.98 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	216.8, 186.7, 157.8, 157.4, 156.9, 140.7, 128.3, 127.9, 127.1, 126.1, 112.4, 100.7, 95.3, 94.6, 58.5, 56.5, 56.3, 41.4, 34.4, 31.8, 30.4, 29.8, 26.7, 26.2, 22.9, 22.8, 14.3.
HRMS $(FD)^+$:	Calcd. for $C_{28}H_{34}O_6$ $[M^{\bullet}]^+$: 466.2355. Found: 466.2336.
TLC (40% EtOAc–Hex), R_f:	Keto Phenol **254**: 0.46 (CAM).

Keto Phenol **254B**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.24 – 7.08 (m, 5H), 6.50 (d, J_1 = 2.4 Hz, 1H), 6.17 (d, J_1 = 2.4 Hz, 1H), 6.02 (s, 1H), 5.33 (s, 1H), 5.30 – 5.17 (m, 2H), 5.11 (d, J_1 = 1.7 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 3H), 3.00 – 2.89 (m, 1H), 2.64 – 2.44 (m, 1H), 2.00 – 1.73 (m, 3H), 1.64 (d, J_1 = 5.3 Hz, 2H), 1.52 (q, J_1 = 12.7, 12.2 Hz, 1H), 1.41 (t, J_1 = 12.8 Hz, 1H), 1.37 – 1.17 (m, 3H), 1.04 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	214.1, 185.9, 157.8, 157.5, 156.5, 140.6, 128.8, 128.4, 127.2, 126.5, 112.0, 99.2, 96.0, 95.2, 94.6, 60.6, 56.7, 56.6, 56.4, 52.3, 43.4, 34.0, 31.8, 30.0, 28.1, 26.3, 22.7.
FTIR (KBr, thin film), cm^{-1}:	3058, 2926, 2853, 1673, 1614.
HRMS $(FD)^{+}$:	Calcd. for $C_{28}H_{34}O_6$ $[M^{\bullet}]^{+}$: 466.2355. Found: 466.2336.
TLC (40% EtOAc–Hex), R_f:	Keto Phenol **254B**: 0.37 (CAM).



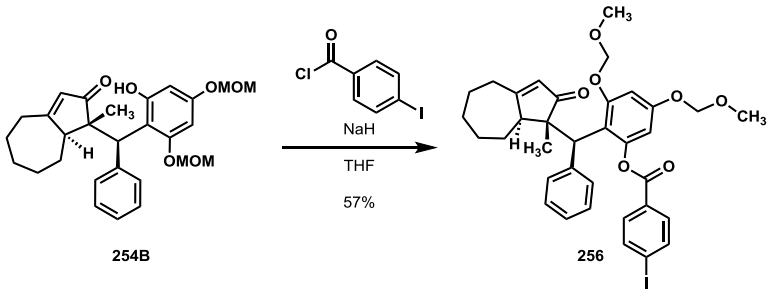
254A 255

Nitro Ester **255**:

4-Nitrobenzoyl chloride (20.0 mg, 0.111 mmol, 1.2 equiv.) was added to a solution of the keto phenol **254A** (0.043 g, 0.0922 mmol, 1.00 equiv.) and triethylamine (0.018 mL, 0.129 mmol, 1.4 equiv.) in dichloromethane (2.0 mL). The mixture was stirred until judged complete via TLC. When judged complete (about 1 h), the resultant mixture was diluted with water (5 mL) and the resulting biphasic mixture was extracted with dichloromethane (3 x 5mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the nitro ester **255** (22.0 mg, 40% yield) as an orange crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.36 – 8.29 (m, 2H), 8.29 – 8.22 (m, 2H), 7.05 (s, 5H), 6.77 (d, J_1 = 2.5 Hz, 1H), 6.49 (d, J_1 = 2.5 Hz, 1H), 5.76 (s, 1H), 5.11 (d, J = 0.9 Hz, 2H), 5.06 – 5.01 (m, 1H), 4.93 – 4.84 (m, 1H), 4.66 (s, 1H), 3.62 (s, 1H), 3.45 (s, 3H), 3.38 (s, 3H), 3.14 – 3.06 (m, 1H), 2.80 (dd, J_1 = 17.7, J_2 = 6.4 Hz, 1H), 2.54 – 2.45 (m, 1H), 1.93 – 1.83

	(m, 1H), 1.81 – 1.70 (m, 2H), 1.54 – 1.41 (m, 2H), 1.35 – 1.18 (m, 2H), 1.13 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	211.8, 184.1, 162.8, 156.9, 150.8, 150.0, 141.5, 135.4, 131.5, 129.3, 128.0, 126.7, 126.1, 123.6, 118.1, 104.6, 102.0, 95.2, 94.7, 56.4, 56.4, 56.1, 52.6, 48.3, 34.8, 33.4, 31.7, 31.2, 30.3, 29.8, 28.8, 26.2, 25.4, 22.8.
FTIR (KBr, thin film), cm^{-1}:	2924, 2853, 1745, 1698, 1611, 1528.
HRMS $(FD)^+$:	Calcd. for $C_{35}H_{37}NO_9$ $[M^{\bullet}]^+$: 615.2468. Found: 615.2463.
TLC (20% EtOAc–Hex), R_f:	Nitro Ester **255**: 0.06 (CAM).



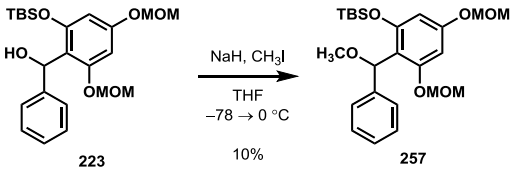
254B 256

Iodo Ester **256**:

Clean, dry sodium hydride (3.40 mg, 0.141 mmol, 1.5 equiv.) was slowly added to a cooled (0 °C) solution of the keto phenol **254B** (44.0 mg, 0.0943 mmol, 1.0 equiv.) in tetrahydrofuran (3.0 mL) and stirred for 5 min. During this time, gas evolved and the color of the solution changed: clear pale yellow to clear dark yellow. After 5 min, 4-iodobenzoyl chloride (182 mg, 1.51 mmol, 2.0 equiv.) was added to the mixture. After the addition, the solution slowly changed in color: clear dark yellow to pale yellow. The reaction was stirred until judged complete via TLC. When judged complete (about 2 h), the resultant mixture was carefully diluted with saturated aqueous sodium bicarbonate solution (5 mL) and diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the iodo ester **256** (39.0 mg, 57%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.94 (d, J_1 = 8.3 Hz, 2H), 7.87 (d, J_1 = 8.3 Hz, 2H), 7.08 (t, J_1 = 7.5 Hz, 2H), 7.00 (t, J_1 = 7.2 Hz, 1H), 6.90 (d, J_1 = 7.8 Hz, 2H), 6.68 (d, J_1 =

	2.2 Hz, 2H), 6.00 (s, 1H) , 5.17 (s, 2H), 4.86 (s, 1H), 4.78 – 4.59 (m, 2H), 3.76 (d, J_1 = 10.1 Hz, 1H), 3.50 (d, J_1 = 5.8 Hz, 3H), 2.97 (s, 3H), 2.86 (dd, J_1 = 17.3, J_2 = 6.9 Hz, 1H), 2.66 – 2.48 (m, 1H), 1.97 – 1.70 (m, 3H), 1.68 – 1.47 (m, 2H), 1.43 – 1.16 (m, 3H), 0.99 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	212.9, 185.6, 164.8, 157.5, 157.2, 151.3, 142.2, 138.2, 137.4, 137.4, 131.8, 128.8, 127.9, 127.7, 127.5, 127.4, 125.4, 118.1, 103.7, 102.7, 102.1, 101.0, 94.9, 56.5, 56.2, 55.8, 51.4, 45.6, 33.7, 31.4, 29.9, 28.6, 26.4, 22.7.
HRMS $(ES)^+$:	Calcd. for $C_{35}H_{37}O_7IH$ $[M + H]^+$: 697.1657. Found: 697.1656.
TLC (40% EtOAc–Hex), R_f:	Iodo Ester **256**: 0.57 (CAM).



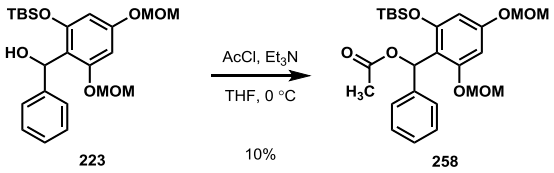
Methyl Ether **257**:

Clean, dry sodium hydride (12.0 mg, 0.499 mmol, 1.1 equiv.) was added to a cooled (–78 °C) solution of the benzyl alcohol **223** (197 mg, 0.453 mmol, 1.0 equiv.) in tetrahydrofuran (5.0 mL) and stirred for 15 min. During this time, gas evolved and the color of the solution changed: clear pale yellow to clear orange. After 15 min, methyl iodide (45.0 μL, 0.713 mmol, 1.5 equiv.) was added. After the addition, the solution slowly changed in color: clear orange to pale yellow. The reaction was warmed to 0 °C and stirred until judged complete via TLC (typically 1 h). When judged complete, the resultant mixture was carefully diluted with saturated aqueous sodium bicarbonate solution (5 mL) and diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 5 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (5 mL) and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate–hexane) to provide the methyl ether **257** (20.0 mg, 10%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.41 (dd, J_1 = 8.1, J_2 = 1.6 Hz, 2H), 7.25 (t, J_1 = 7.6 Hz, 2H), 7.13 (t, J_1 = 7.3 Hz, 1H), 6.46 (s, 1H), 6.41 (d, J_1 = 2.2 Hz, 1H), 6.31 (d, J_1 = 2.2 Hz, 1H), 5.16 (s, 2H), 5.09 – 4.93 (m, 2H), 3.77

(s, 3H), 3.50 (s, 3H), 3.26 (s, 3H), 0.93 (d, J_1 = 2.7 Hz, 9H), 0.08 (s, 3H), –0.14 (s, 3H).

TLC (20% EtOAc–Hex), R_f: Methyl Ether **257**: 0.20 (CAM).



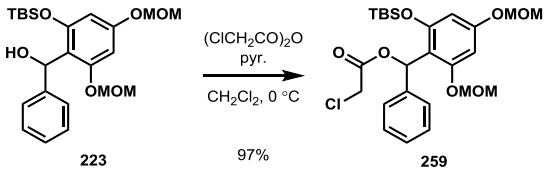
Acetate **258**:

Acetyl chloride (40.0 μL, 0.562 mmol, 1.2 equiv.) was slowly added to a cooled (0 °C) mixture containing benzyl alcohol **223** (205 mg, 0.472 mmol, 1.0 equiv.), triethylamine (132 μL, 0.946 mmol, 2.0 equiv.), and THF (5.0 mL). The reaction mixture was warmed to 23 °C and stirred until the reaction was jugdged complete via TLC (about 6h). The reaction mixture was quenched with water (5.0 mL) and diluted with diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5.0 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane; isocratic) to provide the acetate **258** (25.0 mg, 10%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.53 (s, 1H), 7.32 – 7.20 (m, 5H), 6.43 (d, J_1 = 2.2 Hz, 1H), 6.32 (d, J_1 = 2.3 Hz, 1H), 5.13 (d, J_1 = 0.8 Hz, 2H), 5.10 – 4.95 (m, 2H), 3.49 (s, 3H), 3.28 (s, 3H), 2.16 (s, 3H), 0.91 (s, 9H), 0.27 (s, 3H), 0.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 170.6, 158.6, 157.5, 155.7, 140.9, 127.9, 126.6, 125.8, 125.8, 113.1, 100.6, 96.4, 94.7, 94.2, 69.1, 56.2, 56.1, 25.8, 21.4, 18.3, -3.9, –4.1.

TLC (20% EtOAc–Hex), R_f: Acetate **258**: 0.15 (CAM).



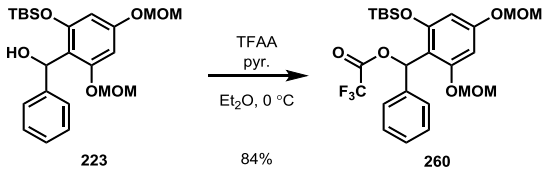
Monochloroacetate **259**:

Chloroacetic anhydride (14.8 mg, 0.0870 mmol, 1.5 equiv.) was added to a cooled (0 °C) solution of the benzyl alcohol **223** (252 mg, 0.580 mmol, 1.0 equiv.) and pyridine (125 μL, 1.45 mmol, 2.5 equiv.) in dichloromethane (16 mL). The mixture was warmed to 23 °C and stirred until the reaction was jugdged complete via TLC (about 2 h). Once judged complete, the resultant mixture was diluted with water (5.0 mL) and diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5.0 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the monochloroacetate **259** (289 mg, 97%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.56 (s, 1H), 7.31 – 7.16 (m, 5H), 6.42 (d, J_1 = 2.2 Hz, 1H), 6.30 (d, J_1 = 2.3 Hz, 1H), 5.30 (s, 2H), 5.11 (d, J_1 = 0.8 Hz, 2H), 5.09 – 4.96 (m, 2H), 3.47 (s, 3H), 3.27 (s, 3H), 0.88 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 166.8, 158.9, 157.7, 155.7, 140.0, 128.0, 126.9, 125.8, 112.1, 100.4, 96.3, 94.7, 94.3, 71.1, 56.2, 56.2, 53.6, 41.4, 25.8, 18.3, –3.9, –4.1.

TLC (20% EtOAc–Hex), R_f: Monochloroacetate **259**: 0.20 (CAM).

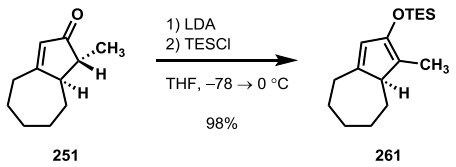


Trifluoroacetate **260**:

Trifluoroacetic anhydride (200 μL, 1.42 mmol, 1.5 equiv.) was added to a cooled (0 °C) solution of the benzyl alcohol **223** (400 mg, 0.920 mmol, 1.0 equiv.) and pyridine (200 μL, 2.32 mmol, 2.5 equiv.) in diethyl ether (10 mL). The mixture was stirred at 0 °C for 30 min. The resultant mixture was diluted with cold (0 °C) water (2.0 mL). The resultant biphasic mixture was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were sequentially washed with cold water (2 x 5.0 mL), 0.01 N aqueous hydrogen chloride solution (2 x 5.0 mL), cold water (5.0 mL), saturated aqueous sodium bicarbonate solution (5.0 mL) and finally dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the trifluoroacetate **260** (412 mg, 84%) as a clear, colorless oil which was used without further purification. Upon standing for >30 min the neat material would begin to decompose, changing color to a clear, light red oil and eventually a thick red plastic.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.60 (s, 1H), 7.38 – 7.16 (m, 5H), 6.43 (d, J_1 = 2.2 Hz, 1H), 6.32 (d, J_1 = 2.3 Hz, 1H), 5.12 (s, 2H), 5.09 – 5.01 (m, 2H), 3.48 (s, 3H), 3.29 (s, 3H), 0.88 (s, 9H), 0.25 (s, 3H), 0.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	159.4, 157.7, 155.8, 138.7, 128.6, 128.2, 127.3, 125.6, 110.6, 100.3, 96.1, 94.7, 94.2, 73.6, 56.3, 56.1, 25.7, 18.3, –4.1, –4.2.
^{19}F NMR (376 MHz, $CDCl_3$), δ:	–74.7.
TLC (20% EtOAc–Hex), R_f:	Trifluoroacetate **260**: 0.30 (CAM).



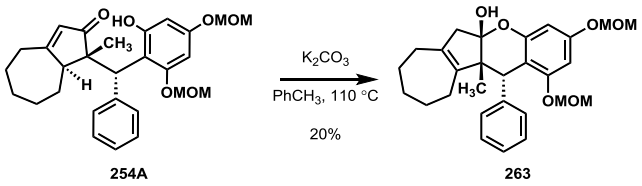
251 261

Silyl Enol Ether **261**:

n-Butyllithium (2.30 M solution in hexane, 0.890 mL, 2.04 mmol, 1.2 equiv.) was added to a cooled (–78 °C) solution of *N*,*N*-diisopropylamine (0.156 mL, 2.13 mmol, 1.3 equiv.) in THF (14 mL). The solution was warmed to 0 °C for 15 min, cooled to –78 °C whereupon a solution of the methyl cyclopentenone **251** (280 mg, 1.71 mmol, 1.0 equiv.) in THF (2 mL) was added dropwise via cannula addition. The reaction mixture was stirred at –78 °C for 30 min whereupon triethylsilyl chloride (0.343 mL, 2.04 mmol, 1.2 equiv.) was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 5 min, then warmed to 0 °C, and stirred for 30 min. The resultant mixture was concentrated. The residue was triturated with hexane, filtered with celite, and concentrated to provide the silyl enol ether **261**(470 mg, 98%) as a clear, orange oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.78 (s, 1H), 2.66 (dd, J_1 = 9.8, J_2 =4.0 Hz, 1H), 2.55 (dt, J_1 = 17.0, J_2 =6.1 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.81 – 1.73 (m, 1H), 1.73 – 1.70 (m, 3H), 1.60 (ddt, J_1 =10.8, J_2 =9.4, J_3 =3.9 Hz, 3H), 1.47 (ddt, J_1 = 13.7, J_2 =11.0, J_3 = 3.0 Hz, 2H), 1.41 – 1.29 (m, 2H), 0.98 (t, J_1 = 7.9 Hz, 9H), 0.72 – 0.62 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	152.2, 148.2, 124.8, 117.6, 54.3, 31.1, 30.8, 29.8, 29.3, 28.4, 9.7, 6.8, 6.8, 5.3.
TLC (20% EtOAc–Hex), R_f:	Silyl Enol Ether **261**: 0.86 (CAM).



254A 263

Hemiketal **263**:

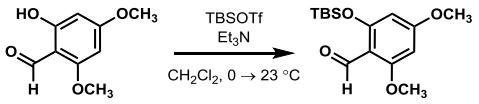
Potassium carbonate (32.0 mg, 0.232 mmol, 1.5 equiv.) was added a solution of the keto phenol **254** (70.0 mg, 0.150 mmol, 1.0 equiv.) in anhydrous toluene (3.0 mL). The mixture was degassed with bubbling argon and heated to reflux (110 °C) for 17h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (5 → 40% ethyl acetate–hexane) to provide the hemiketal **263** (14.0 mg, 20% yield) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.24 – 7.03 (m, 5H), 6.46 (d, J_1 = 2.3 Hz, 1H), 6.39 (d, J_1 = 2.3 Hz, 1H), 5.16 – 5.02 (m, 4H), 4.17 (s, 1H), 3.46 (s, 3H), 3.28 (s, 3H), 2.85 (d, J_1 = 16.4 Hz, 1H), 2.66 (s, 1H), 2.52 (d, J_1 = 16.4 Hz, 1H), 2.08 – 2.01 (m, 2H), 1.96 – 1.82 (m, 3H), 1.82 – 1.74 (m, 1H), 1.54 – 1.47 (m, 2H), 1.46 – 1.33 (m, 2H), 1.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 157.3, 155.1, 153.8, 142.1, 140.1, 135.1, 129.4, 127.5, 126.3, 113.4, 108.9, 100.2, 97.9, 94.7, 94.3, 63.5, 59.5, 56.3, 56.1, 53.9, 46.3, 30.9, 29.8, 27.7, 26.8, 26.6, 21.8.

FTIR (KBr, thin film), cm^{-1}: 3446, 2923, 2851, 1616, 1595, 1493, 1448.

HRMS $(FD)^+$:	Calcd. for $C_{28}H_{34}O_6$ $[M^\bullet]^+$: 466.2355. Found: 466.2340.
TLC (20% EtOAc–Hex), R_f:	Hemiketal **263**: 0.27 (CAM).



264 **265**

Aldehyde **265**:

tert-Butyldimethylsilyl trifluoromethanesulfonate (2.27 mL, 9.88 mmol, 2.0 equiv.) was added to a cooled (0 °C) solution of the phenol aldehyde **264**[6] (0.900 g, 4.94 mmol, 1.0 equiv.) and triethylamine (2.07 mL, 14.8 mmol, 3.0 equiv.) in dichloromethane (25 mL). The mixture was warmed to 23 °C and stirred for 16 h. The resultant mixture was diluted with water (20 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the aldehyde **265** (0.886 g, 60% yield) as a clear, pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.28 (d, J_1 = 2.9 Hz, 1H), 6.04 (t, J_1 = 2.5 Hz, 1H), 5.92 (t, J_1 = 2.6 Hz, 1H), 3.81 (d, J_1 = 3.4 Hz, 3H), 3.76 (d, J_1 = 3.2 Hz, 3H), 0.95 (d, J_1 = 3.2 Hz, 9H), 0.21 (d, J_1 = 3.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 187.9, 165.7, 163.1, 161.6, 111.4, 97.7, 91.8, 55.9, 55.4, 25.7, 18.4, –4.3.

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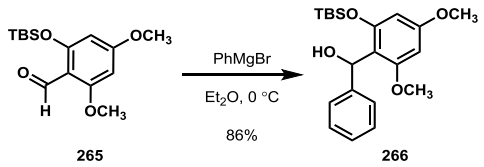
6. Roelens, F.; Huvaere, K.; Dhooge, W.; Cleemput, M. V.; Comhaire, F.; Keukeleire, D. D. *Eur. J. Med. Chem.* **2005**, *40*, 1042.

FTIR (KBr, thin film), cm^{-1}:	2931, 2885, 2858, 2775, 1684, 1601, 1572.
HRMS $(FD)^+$:	Calcd. for $C_{15}H_{24}O_4SiH$ $[M + H]^+$: 297.1522. Found: 297.1533.
TLC (20% EtOAc–Hex), R_f:	Aldehyde **265**: 0.42 (CAM).



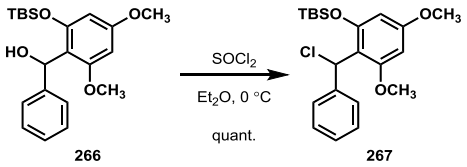
265 266

Benzyl Alcohol **266**:

Bromobenzene (0.693 mL, 6.57 mmol, 2.2 equiv.) was added to a solution of magnesium turnings (washed with 1 N aqueous hydrogen chloride solution then dried, 0.164 g, 6.83 mmol, 2.3 equiv.) in diethyl ether (10 mL). The mixture was slowly heated to reflux (35 °C) for 1 h. During which time the solution changed in color: clear, colorless to cloudy, brown. The mixture was cooled to room temperature and added via cannula addition to a cooled (0 °C) solution of the aldehyde **265** (0.886 g, 2.99 mmol, 1.0 equiv.) in diethyl ether (20 mL). The resultant mixture was stirred at 0 °C for 15 mins and then slowly quenched with saturated aqueous ammonium chloride solution (5.0 mL). The mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the benzyl alcohol **266** (1.03 g, 86%) as a clear, pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.33 – 7.29 (m, 2H), 7.28 – 7.23 (m, 3H), 7.18 (t, J_1 = 7.3 Hz, 1H), 6.18 (d, J_1 = 11.7 Hz, 1H), 6.16 (d, J_1 = 2.3 Hz, 1H), 6.10 (d, J_1 = 2.3 Hz, 1H), 4.07 (d, J_1 = 11.7 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 0.89 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	160.2, 159.3, 154.5, 145.1, 127.9, 126.5, 125.9, 114.8, 97.7, 92.3, 68.7, 55.8, 55.4, 25.9, 18.3, –3.8, –4.2.
FTIR (KBr, thin film), cm^{-1}:	3555, 2955, 2932, 2858, 1607, 1588, 1464.
HRMS $(FD)^+$:	Calcd. for $C_{21}H_{30}O_4Si$ $[M^{\bullet}]^+$: 374.1913. Found: 374.1913.
TLC (20% EtOAc–Hex), R_f:	Benzyl alcohol **266**: 0.40 (CAM, $KMnO_4$).

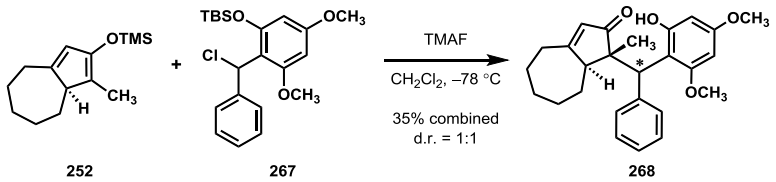


266 267

Benzyl Chloride **267**:

Thionyl chloride (0.058 mL, 0.799 mmol, 1.2 equiv.) was added dropwise to a cooled (0 °C) solution of the benzyl alcohol **266** (250 mg, 0.668 mmol, 1.0 equiv.) in diethyl ether (60 mL) and stirred for 30 min. The resultant mixture was concentrated to provide the benzyl chloride **267** (266 mg, quantitative yield) as a clear, pale yellow oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.50 – 7.40 (m, 2H), 7.30 (t, J_1 = 7.2 Hz, 2H), 7.22 (t, J_1 = 7.2 Hz, 1H), 6.85 (s, 1H), 6.16 (d, J_1 = 2.4 Hz, 1H), 6.12 (d, J_1 = 2.3 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 0.96 (s, 9H), 0.29 (s, 3H), 0.27 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	160.0, 155.3, 141.3, 127.8, 127.1, 126.7, 113.0, 97.5, 92.4, 55.8, 55.8, 55.4, 25.9, 18.5, –3.7, –4.0.
HRMS $(FD)^+$:	Calcd. for $C_{21}H_{29}O_3SiCl$ $[M^{\bullet}]^+$: 392.1575. Found: 392.1587.
TLC (20% EtOAc–Hex), R_f:	Benzyl Chloride **267**: 0.45 ($KMnO_4$).



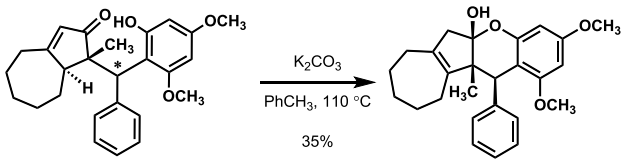
252 267 268

Keto Phenol **268**:

A cooled (–78 °C) solution of tetramethylammonium fluoride (TMAF, 97.1 mg, 1.04 mmol, 2.05 equiv.) in dichloromethane (2.0 mL) was added rapidly via cannula addition to a cooled (–78 °C) solution of the silyl enol ether **252** (120 mg, 0.508 mmol, 1.0 equiv.) and benzyl chloride **267** (199 mg, 0.508 mmol, 1.0 equiv.) in dichloromethane (2.0 mL). No intense color change was seen. The mixture was stirred at –78 °C for 1 h, and then quenched by the addition of acetic acid (50 μL). The resultant mixture was warmed to 23 °C and then the mixture was absorbed on to silica gel. Purification of the residue was completed by flash column chromatography (15 → 20% ethyl acetate–hexane) to provide an inseparable mixture of diastereomers of the keto phenol **268** (72.0 mg, 35% combined yield, d.r. = 1.1) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: Mixture of diastereomers and rotamers in $CDCl_3$: 7.37 – 6.90 (m, 10H), 6.12 (s, 2H), 5.97 (s, 4H), 5.17 (s, 2H), 3.83 (s, 6H), 3.73 (s, 6H), 3.51 (d, J_1 = 29.3 Hz, 2H), 3.35 (s, 2H), 2.94 (d, J_1 = 17.2 Hz, 2H), 2.60 – 2.42 (m, 2H), 1.90 (d, J_1 = 13.4 Hz, 4H), 1.83 – 1.65 (m, 6H), 1.59 – 1.34 (m, 6H), 1.05 (s, 6H).

^{1}H NMR (400 MHz, DMSO-d_6), δ:	Mixture of diastereomers: 9.52 (s, 1H), 9.31 (s, 1H), 7.11 – 7.03 (m, 4H), 7.03 – 6.96 (m, 1H), 6.84 (dd, J_1 = 19.2, 7.6 Hz, 4H), 6.11 (dd, J_1 = 10.6, J_2 = 2.4 Hz, 2H), 6.00 (d, J_1 = 2.4 Hz, 2H), 5.93 (d, J_1 = 9.8 Hz, 2H), 4.97 (d, J_1 = 11.6 Hz, 2H), 3.75 (s, 3H), 3.69 (s, 6H), 3.54 (d, J_1 = 9.9 Hz, 1H), 3.41 (s, 3H), 2.70 (dd, J_1 = 17.6, J_2 =11.1 Hz, 2H), 1.91 – 1.54 (m, 8H), 1.54 – 1.01 (m, 10H), 0.80 (s, 3H), 0.75 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	Mixture of diastereomers and rotamers in $CDCl_3$: 215.0, 186.2, 171.2, 160.1, 159.2, 156.6, 140.6, 128.8, 128.4, 126.9, 126.2, 109.9, 95.2, 91.1, 60.4, 57.2, 55.7, 55.2, 52.8, 43.1, 34.7, 34.0, 31.7, 31.6, 30.0, 29.1, 27.7, 26.1, 25.3, 22.7, 22.4, 21.1, 14.2, 14.2.
FTIR (KBr, thin film), cm^{-1}:	3280, 2924, 2852, 1670, 1602, 1453.
HRMS $(FD)^+$:	Calcd. for $C_{26}H_{30}O_4$ $[M^{\bullet}]^+$: 406.2144. Found: 406.2138.
TLC (20% EtOAc–Hex), R_f:	Keto Phenol **268**: 0.11 (CAM, $KMnO_4$).

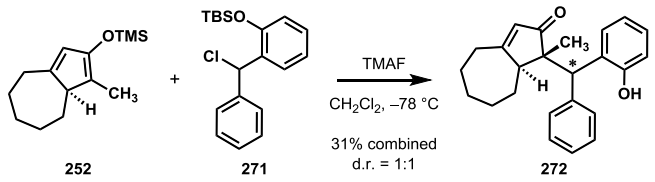


268 270

Hemiketal **270**:

Potassium carbonate (15.1 mg, 0.109 mmol, 1.2 equiv.) was added a solution of the keto phenol **268** (37.0 mg, 0.0910 mmol, 1.0 equiv.) in anhydrous toluene (2.0 mL). The reaction mixture was degassed with bubbling argon and heated to reflux (110 °C) for 23h. The resultant mixture was cooled to room temperature and directly purified by flash column chromatography (5% ethyl acetate–hexane) to provide the hemiketal **270** (13.0 mg, 35% yield) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.32 – 7.23 (m, 4H), 7.22 – 7.15 (m, 1H), 6.16 (d, J_1 = 2.3 Hz, 1H), 6.03 (d, J_1 = 2.3 Hz, 1H), 4.26 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 2.88 – 2.53 (m, 2H), 2.48 (s, 1H), 2.03 – 1.93 (m, 3H), 1.82 (dd, J_1 = 15.4, J_2 = 8.2 Hz, 1H), 1.63 – 1.33 (m, 4H),1.24 – 1.13 (m, 2H), 1.03 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	160.0, 157.3, 156.9, 143.3, 140.4, 134.7, 129.5, 128.7, 126.9, 111.2, 108.4, 93.7, 92.0, 55.9, 55.7, 55.4, 50.0, 41.1, 31.3, 30.0, 27.2, 26.9, 25.5, 20.0.
TLC (20% EtOAc–Hex), R_f:	Hemiketal **270**: 0.42 (CAM).



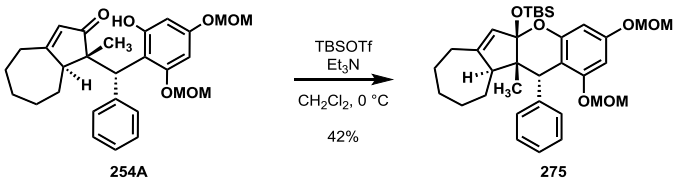
Keto Phenol **272**:

A cooled (–78 °C) solution of tetramethylammonium fluoride (TMAF, 500 mg, 5.36 mmol, 2.05 equiv.) in dichloromethane (10 mL) was added rapidly via cannula addition to a cooled (–78 °C) solution of the benzyl chloride **271** (875 mg, 2.63 mmol, 1.0 equiv.) and silyl enol ether **252** (619 mg, 2.62 mmol, 1.0 equiv.) in dichloromethane (10 mL). The mixture was stirred at –78 °C for 1h, and then quenched by the addition of acetic acid (0.200 mL). The resultant mixture was warmed to 22 °C and diluted with water (10 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 40% ethyl acetate–hexane) to provide a mixture of inseparable diastereomers of the keto phenol **272** (280 mg, 31% combined, d.r. = 1:1) as a clear, colorless oil.

Keto phenol **272** was isolated as a mixture of diastereomers, asterisk denotes minor peaks.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.24 – 7.06 (m, 12H), 6.90 – 6.76 (m, 6H), 5.89* (s, 1H), 5.80 (s, 1H), 5.03 (d, J_1 = 1.8 Hz, 1H), 4.53* (s, 1H), 3.47* (d, J_1 = 10.7 Hz, 1H), 3.41 (d, J_1 = 10.4 Hz, 1H), 2.90* (d, J_1 = 7.0 Hz, 1H), 2.85* (d, J_1 = 7.0 Hz, 1H), 2.66 (d, J_1 = 6.7 Hz,

	1H), 2.61 (d, J_1 = 6.6 Hz, 1H), 2.56 – 2.41 (m, 3H), 1.99 – 1.66 (m, 13H), 1.59 – 1.42 (m, 6H), 1.05 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	Mixture of Diastereomers: 216.2*, 215.1, 188.2*, 187.7, 154.9, 154.1*, 141.0, 140.9*, 130.1, 130.0*, 129.5, 128.5, 128.4*, 128.2, 128.2*, 128.0, 127.9*, 127.7, 127.2, 126.8, 126.3, 120.1*, 119.8, 118.6*, 116.4, 60.6, 56.8*, 55.9, 51.1, 49.3*, 33.8*, 33.2, 31.7*, 31.5, 31.1, 30.2*, 30.0, 29.1, 28.1*, 26.1*, 25.9, 22.8, 21.2*, 21.1, 14.3, 14.3*.
HRMS $(ES)^+$:	Calcd. for $C_{34}H_{26}O_2H$ $[M+H]^+$: 347.2011. Found: 347.2018.
TLC (20% EtOAc–Hex), R_f:	Keto Phenol **272**: 0.11 (CAM).



254A 275

Silylated Hemiketal **275**:

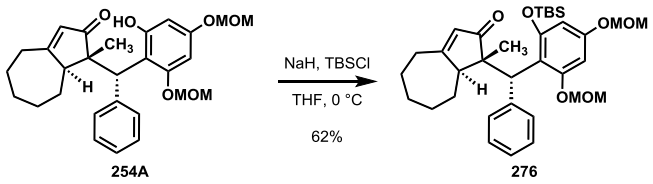
tert-Butyldimethylsilyl trifluoromethanesulfonate (0.017 mL, 0.0729 mmol, 2.0 equiv.) was added dropwise to a cooled (0 °C) solution of the keto phenol **254A** (17.0 mg, 0.0364 mmol, 1.0 equiv.) and triethylamine (0.012 mL, 0.0802 mmol, 2.2 equiv.) in dichloromethane (2.0 mL) and stirred for 3 h. The resultant mixture was concentrated. The residue was purified by flash column chromatography (20 → 40% ethyl acetate–hexane) to provide the silylated hemiketal **275** (9.00 mg, 42%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.24 – 7.20 (m, 2H), 7.12 (dd, J_1 = 8.2, J_2 = 6.4 Hz, 2H), 7.09 – 7.02 (m, 1H), 6.28 (d, J_1 = 2.4 Hz, 1H), 6.20 (d, J_1 = 2.4 Hz, 1H), 5.49 (s, 1H), 5.12 (s, 2H), 4.85 (dd, J_1 = 60.2, J_2 = 6.6 Hz, 2H), 4.02 (s, 1H), 3.48 (s, 3H), 2.94 (s, 3H), 2.66 – 2.48 (m, 2H), 2.19 – 2.07 (m, 1H), 1.93 (d, J_1 = 8.1 Hz, 1H), 1.84 (d, J_1 = 10.2 Hz, 1H), 1.77 – 1.59 (m, 2H), 1.47 – 1.27 (m, 4H), 0.76 (s, 9H), 0.73 (s, 3H), 0.24 (s, 3H), 0.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 157.0, 155.9, 155.3, 151.3, 143.5, 130.3, 127.2, 126.5, 125.6, 110.8, 108.3, 97.5, 95.8, 94.7, 93.7, 56.3, 55.7, 55.2, 52.3, 42.3, 32.4, 31.9, 30.6,

29.9, 27.3, 26.7, 25.9, 25.8, 19.0, 18.1, –2.5, –2.8.

TLC (50% EtOAc–Hex), R_f: Silylated Hemiketal **275**: 0.90 (CAM).

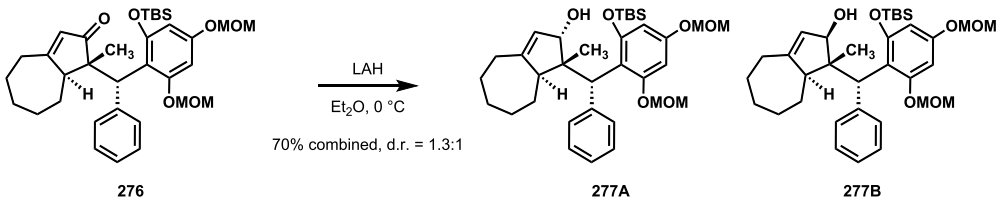


Silylated Phenol **278**:

Clean, dry sodium hydride (22.0 mg, 0.917 mmol, 1.5 equiv.) was slowly added to a cooled (0 °C) solution of the keto phenol **254A** (280 mg, 0.600 mmol, 1.0 equiv.) in THF (10 mL) and stirred for 5 min. During this time, gas evolved and the color of the solution changed: clear pale yellow to clear red. After 5 min, tetrabutyldimethylchlorosilane (182 mg, 1.51 mmol, 2.0 equiv.) was added neat to the mixture. After the addition, the color of the solution slowly changed: clear, red to cloudy, yellow. The mixture was stirred until judged complete via TLC. When judged complete, the mixture was carefully diluted with water (5 mL) and ethyl acetate (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide the silylated phenol **278** (214 mg, 62%) as a clear, colorless oil which slowly solidified to a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.40 – 7.29 (m, 2H), 7.20 (t, J_1 = 7.3 Hz, 2H), 7.16 – 7.07 (m, 1H), 6.49 (d, J_1 = 2.5 Hz, 1H), 6.26 (d, J_1 = 2.4 Hz, 1H), 5.70 (s, 1H), 5.11 – 4.98 (m, 3H), 4.83 – 4.73 (m, 2H), 3.58 (d, J_1 = 9.5 Hz, 1H), 3.43 (d, J_1 = 2.3 Hz, 6H), 2.90 (dd,

	J_1 = 17.6, J_2 = 6.3 Hz, 1H), 2.54 – 2.36 (m, 1H), 1.93 – 1.73 (m, 2H), 1.64 – 1.39 (m, 2H), 1.23 (s, 3H), 1.18 (d, J_1 = 13.6 Hz, 1H), 1.00 (s, 9H), 0.95 – 0.75 (m, 3H), 0.34 (s, 3H), 0.21 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	212.1, 182.6, 156.5, 156.4, 155.0, 142.7, 129.8, 127.8, 126.0, 125.7, 117.1, 101.2, 96.3, 95.0, 94.7, 56.5, 56.4, 56.1, 53.5, 47.9, 33.6, 31.8, 30.4, 27.7, 26.5, 26.2, 25.2, 18.6, –3.6, –3.7.
FTIR (KBr, thin film), cm^{-1}:	2927, 2855, 1700, 1606, 1586, 1153.
HRMS $(ES)^+$:	Calcd. for $C_{34}H_{48}O_6SiH$ $[M + H]^+$: 581.3293. Found: 581.3295.
TLC (40% EtOAc–Hex), R_f:	Silylated phenol **278**: 0.75 (CAM, $KMnO_4$).



276 277A 277B

Allylic Alcohols **277A** and **277B**:

A solution of the silylated phenol **276** (400 mg, 0.689 mmol, 1.0 equiv.) in diethyl ether (5.0 mL) was slowly added to a cooled (0 °C) slurry of lithium aluminum hydride (40.0 mg, 1.05 mmol, 1.5 equiv.) in diethyl ether (15 mL). Upon addition, the reaction bubbled and released gas. The reaction was stirred until judged complete via TLC (15 min). When judged complete, the mixture was slowly quenched with methanol (2.0 mL), then diluted with water (2.0 mL) and ethyl acetate (10 mL). The biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate–hexane) to provide separable diastereomers of allylic alcohols **277A** and **277B** (166 mg and 120 mg respectively, 70% combined yield, d.r. = 1.4:1) as a clear, colorless oil.

Allylic Alcohol **277A**:

^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.41 (d, J_1 = 7.8 Hz, 2H), 7.18 (t, J_1 = 7.8 Hz, 2H), 7.05 (t, J_1 = 7.3 Hz, 1H), 6.37 (d, J_1 = 2.4 Hz, 1H), 6.35 (d, J_1 = 2.4 Hz, 1H), 5.46 (s, 1H), 5.28 (s, 1H), 5.16 – 5.06 (m, 2H), 4.69 – 4.52 (m, 3H), 3.48 (s, 3H), 3.29 – 3.21 (m, 1H), 3.01

(s, 3H), 2.62 (d, J_1 = 16.0, J_2 = 7.2 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.86 – 1.76 (m, 1H), 1.69 – 1.50 (m, 4H), 1.39 – 1.29 (m, 2H), 1.21 – 1.17 (m, 2H), 1.15 (s, 3H), 1.06 (s, 9H), 0.38 (s, 3H), 0.28 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$), δ: 158.1, 156.7, 154.8, 154.4, 145.8, 128.3, 127.7, 124.8, 122.3, 118.2, 100.6, 97.2, 94.8, 94.2, 83.6, 56.0, 56.0, 55.6, 53.4, 43.6, 32.5, 31.7, 30.5, 29.7, 27.6, 26.6, 26.6, 25.9, 18.3, 18.0, –3.3, –4.5.

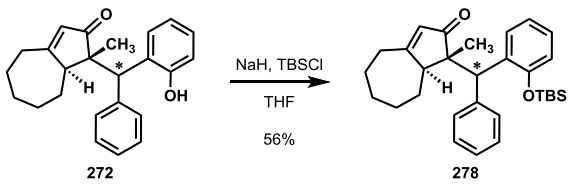
HRMS $(ES)^+$: Calcd. for $C_{34}H_{50}O_6H$ $[M + H]^+$: 583.3449. Found: 583.3459.

TLC (40% EtOAc–Hex), R_f: Allylic Alcohol **277A**: 0.73 (Anis.).

Allylic Alcohol **277B**:

^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.32 – 7.23 (m, 2H), 7.18 (t, J_1 = 7.7 Hz, 2H), 7.07 (t, J_1 = 7.3 Hz, 1H), 6.43 (d, J_1 = 2.4 Hz, 1H), 6.39 (d, J_1 = 2.4 Hz, 1H), 5.56 (s, 1H), 5.38 – 5.28 (m, 1H), 5.15 – 5.05 (m, 2H), 4.92 (s, 1H), 4.73 (dd, J_1 = 44.4, J_2 = 6.7 Hz, 2H), 3.47 (s, 3H), 3.18 (s, 3H), 3.11 – 3.02 (m, 1H), 2.52

	(dd, J_1 = 16.0, J_2 = 7.6 Hz, 1H), 2.30 – 2.17 (m, 2H), 1.85 – 1.76 (m, 2H), 1.68 – 1.55 (m, 3H), 1.35 – 1.28 (m, 3H), 1.03 (s, 9H), 0.83 (s, 3H), 0.35 (s, 3H), 0.27 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	156.7, 155.5, 149.1, 144.1, 129.7, 127.7, 125.1, 125.1, 118.6, 101.2, 98.1, 95.5, 94.9, 79.6, 56.9, 56.4, 56.1, 56.1, 45.5, 32.3, 31.7, 30.3, 29.9, 28.5, 27.1, 27.0, 26.1, 18.6, 15.9, –3.4, –4.0.
HRMS $(ES)^+$:	Calcd. for $C_{34}H_{50}O_6H$ $[M + H]^+$: 583.3449. Found: 583.3452.
TLC (40% EtOAc–Hex), R_f:	Allylic Alcohol **277B**: 0.55 (Anis.).



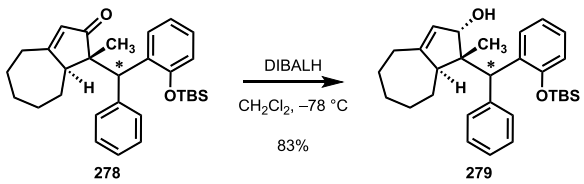
272 278

Silylated Phenol **278**:

Clean, dry sodium hydride (50.0 mg, 2.08 mmol, 1.5 equiv.) was slowly added to a cooled (0 °C) solution of the keto phenol **272** (457 mg, 1.32 mmol, 1.0 equiv.) in tetrahydrofuran (15 mL) and stirred for 5 min. During this time, gas evolved and the color of the solution changed: clear, pale yellow to clear, red. After 5 min, tetrabutyldimethylchlorosilane (400 mg, 2.65 mmol, 2.0 equiv.) was added neat to the mixture. After the addition, the color of the solution slowly changed: clear, red to cloudy, yellow. The mixture was stirred until judged complete via TLC (15 min). When judged complete, the reaction was carefully quenched with saturated aqueous ammonium chloride solution (15 mL) and diluted with diethyl ether (10 mL). The biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide separable diastereomers of the silylated phenol **278** (397 mg, 65% combined yield, d.r. = 4.5:1) as a clear, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$), δ: Major diastereomer: 7.30 (dd, J_1 = 7.7, J_2 = 1.7 Hz, 1H), 7.15 – 7.10 (m, 5H), 6.94 (td, J_1 = 7.5, J_2 = 1.3 Hz, 1H), 6.83 (dd, J_1 = 8.1, J_2 = 1.3 Hz, 1H), 5.77 (s, 1H), 5.08 (s, 1H), 3.26 (d, J_1 = 10.3 Hz, 1H), 2.57 (dddd, J_1 = 17.8, J_2 = 7.0, J_3 = 2.6,

	J_4 = 1.2 Hz, 1H), 2.49 – 2.39 (m, 1H), 1.97 – 1.84 (m, 3H), 1.54 – 1.41 (m, 3H), 1.36 – 1.20 (m, 3H), 1.03 (s, 9H), 0.98 (s, 3H), 0.27 (s, 3H), 0.11 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	Major diastereomer: 213.8, 186.0, 154.4, 140.9, 132.3, 130.1, 129.8, 128.3, 127.7, 127.3, 126.0, 120.6, 119.0, 55.7, 50.8, 48.8, 33.0, 31.1, 30.0, 29.2, 26.1, 22.7, 21.0, –3.7, –3.9.
HRMS $(ES)^+$:	Calcd. for $C_{30}H_{40}O_2SiH$ $[M + H]^+$: 461.2876. Found: 461.2884.
TLC (20% EtOAc–Hex), R_f:	Silylated Phenol **278**: 0.50 (CAM).



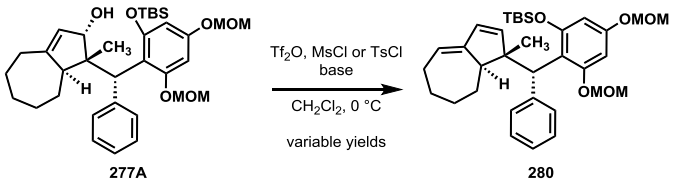
Allylic Alcohol **279**:

Diisobutylaluminum hydride (1.20 M in dichloromethane, 0.506 mL, 0.607 mmol, 2.0 equiv.) was slowly added to a cooled (–78 °C) solution of the silylated phenol **278** (140 mg, 0.303 mmol, 1.0 equiv.) in dichloromethane (5.0 mL) and stirred for 1 h whereupon another aliquot of diisobutylaluminum hydride (1.20 M in dichloromethane, 0.506 mL, 0.607 mmol, 2.0 equiv.) was added. The mixture was stirred with warming to 0 °C over 1h. The resultant mixture was carefully quenched with methanol (1.0 mL). The mixture was diluted with saturated aqueous potassium sodium tartrate solution (10 mL), warmed to room temperature, and stirred for 1 h. The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL) and then dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 20% ethyl acetate–hexane) to provide the single diastereomer of the allylic alcohol **279** (117 mg, 83%, single diastereomer) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.96 (dd, J_1 = 7.8, J_2 = 1.8 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.25 – 7.20 (m, 2H), 7.18 – 7.12 (m, 1H), 7.11 – 7.06 (m, 1H), 6.98 (t, J_1 = 7.5 Hz, 1H), 6.80 (dd, J_1 = 8.0, J_2 = 1.4 Hz, 1H) 5.45 (d, J_1 = 2.7 Hz, 1H), 4.98 (s, 1H), 4.05 (s, 1H), 2.86 (d, J_1 = 10.6 Hz, 1H), 2.62 (dd, J_1 = 16.2, J_2 =

	7.1 Hz, 1H), 2.09 – 1.93 (m, 1H), 1.81 (d, J_1 = 11.7 Hz, 1H), 1.65 (dd, J_1 = 13.8, J_2 = 6.9 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.45 – 1.29 (m, 1H), 1.13 (s, 3H), 1.02 (s, 9H), 0.92 – 0.79 (m, 1H), 0.74 (q, J_1 = 11.6, J_2 = 10.9 Hz, 1H), 0.80 – 0.68 (m, 1H), 0.25 (s, 3H), 0.13 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	154.6, 153.2, 142.5, 133.9, 130.6, 130.0, 127.8, 127.3, 126.2, 123.0, 121.1, 119.3, 100.1, 83.8, 57.4, 53.4, 47.5, 32.4, 31.7, 30.8, 26.8, 26.6, 26.2, 26.1, 18.6, 18.3, –3.7, –3.8.
HRMS $(ES)^+$:	Calcd. for $C_{30}H_{41}OSi$ $[M – OH]^+$: 445.2921. Found: 445.2929.
TLC (20% EtOAc–Hex), R_f:	Allylic Alcohol **279**: 0.61 (Anis.)

*General Procedure for Activating Allylic Alcohol **277A**:*

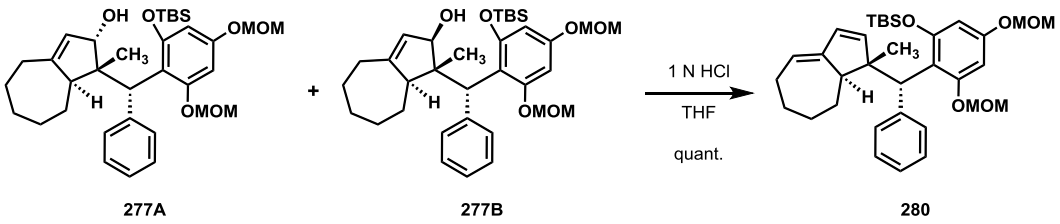


Diene **280**:

Activating agent (Ex. Tf_2O, MsCl, or TsCl, 1.0 equiv.) was added to a cooled (0 °C) solution of the allylic alcohol **277A** (1.0 equiv.) and base (Ex. pyr. or Et_3N, 1.2 equiv.) in dichloromethane and stirred for some time (10 min to 1h). The reaction mixture was quenched with water and diluted with ethyl acetate. The resulting biphasic mixture was extracted with ethyl acetate and the combined organic fractions were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the diene **280** (variable yields) as a clear colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.44 – 7.35 (m, 2H), 7.12 (t, J_1 = 7.6 Hz, 2H), 7.06 – 6.96 (m, 1H), 6.44 (d, J_1 = 5.7 Hz, 1H), 6.39 (d, J_1 = 2.4 Hz, 1H), 6.34 (d, J_1 = 2.4 Hz, 1H), 5.97 (d, J_1 = 5.7 Hz, 1H), 5.63 (dt, J_1 = 7.2, J_2 = 3.5 Hz, 1H), 5.14 – 5.02 (m, 2H), 4.88 (d, J_1 = 6.9 Hz, 1H), 4.81 (s, 1H), 4.69 (d, J_1 = 6.9 Hz, 1H), 3.46 (s, 3H), 3.15 (s, 3H), 2.97 – 2.84 (m, 1H), 2.05 (s, 2H), 1.98 – 1.93 (m, 1H), 1.94 – 1.85 (m, 1H), 1.81 – 1.73 (m, 1H), 1.37 – 1.27

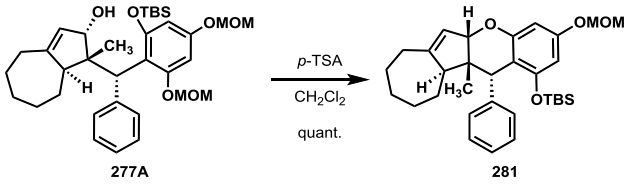
	(m, 3H), 1.08 (s, 9H), 0.86 (s, 3H), 0.37 (s, 3H), 0.32 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	157.4, 156.6, 155.0, 152.3, 145.6, 144.3, 131.8, 130.1, 127.2, 125.0, 121.0, 118.0, 100.3, 97.0, 94.9, 94.3, 56.2, 56.1, 56.0, 50.1, 46.7, 30.2, 29.5, 28.5, 28.3, 26.2, 24.1, 18.6, –3.4, –3.9.
FTIR (KBr, thin film), cm^{-1}:	2956, 26928, 2856, 1604, 1586.
HRMS $(ES)^+$:	Calcd. for $C_{34}H_{48}O_5SiH$ $[M + H]^+$: 565.3349. Found: 565.3345.
TLC (20% EtOAc–Hex), R_f:	Diene **280**: 0.66 (UV, CAM, $KMnO_4$)



277A 277B 280

Diene **280**:

1 N Aqueous hydrogen chloride solution (3 drops) was added to a solution of the allylic alcohol **277A** (5.00 mg, 0.00858 mmol, 1.0 equiv.), the allylic alcohol **277B** (5.00 mg, 0.00858 mmol, 1.0 equiv.) in THF (2.0 mL) and stirred for 20 h. The resultant mixture was judged complete via TLC by comparison of previously isolated diene **280**. The mixture was concentrated to provide the diene **280** (10.0 mg, quantitative yield) as a clear, colorless oil.



Tetrahydropyran **281**:

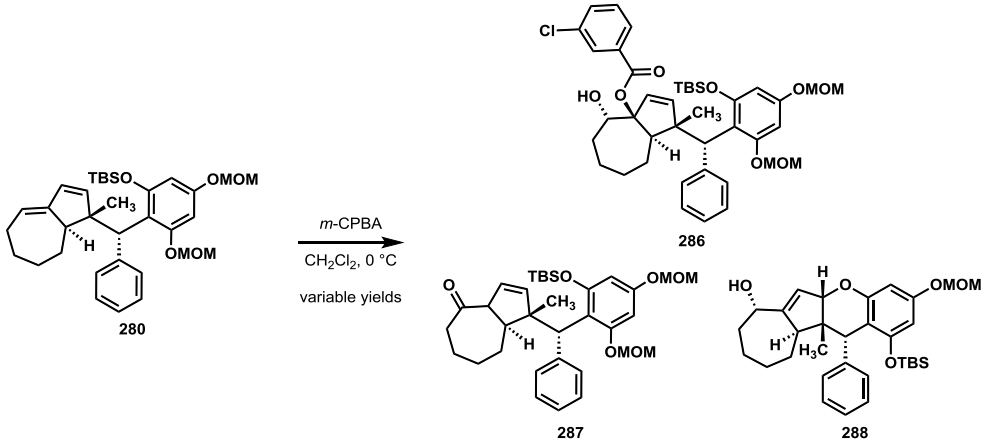
p-Toluenesulfonic acid (1 grain) was added to a solution of the allylic alcohol **277A** (5.00 mg, 0.00858 mmol, 1.0 equiv.) in dichloromethane (2.0 mL) and stirred for 18h. The resultant mixture was judged complete via TLC by comparison of previously isolated tetrahydropyran **281**. The mixture was concentrated to provide the tetrahydropyran **281** (5.00 mg, quantitative yield) as a clear, pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.18 – 7.00 (m, 5H), 6.39 (d, J_1 = 2.4 Hz, 1H), 6.16 (d, J_1 = 2.4 Hz, 1H), 5.50 – 5.26 (m, 1H), 5.23 – 4.97 (m, 2H), 4.24 (d, J_1 = 2.5 Hz, 1H), 4.14 (s, 1H), 3.47 (s, 3H), 2.48 (d, J_1 = 10.9 Hz, 1H), 2.33 (dd, J_1 = 16.2, J_2 = 6.5 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.66 (dd, J_1 = 12.2, J_2 = 6.0 Hz, 1H), 1.59 – 1.45 (m, 5H), 1.10 (s, 4H), 0.91 (s, 9H), 0.60 – 0.47 (m, 1H), 0.18 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$), δ: 158.3, 158.0, 156.7, 154.5, 143.7, 129.6, 127.7, 125.9, 119.7, 116.2, 101.5, 98.7, 94.8, 92.1, 56.1, 53.2, 50.1, 47.6, 31.5, 30.4, 27.7, 26.6, 26.1, 25.6, 18.5, –3.9, –4.0.

FTIR (KBr, thin film), cm^{-1}:	2954, 2926, 2855, 1611, 1587.
HRMS $(ES)^+$:	Calcd. for $C_{32}H_{44}O_4SiH$ $[M + H]^+$: 521.3087. Found: 521.3073.
TLC (20% EtOAc–Hex), R_f:	Tetrahydropyran **281**: 0.80 (CAM, $KMnO_4$).

General Procedure Toward Optimization of Chemoselective Epoxidation



Ester **286**, Ketone **287**, Alcohol **288**:

meta-Chloroperoxybenzoic acid (*m*-CPBA, 1.1 – 2.0 equiv.) was added to a cooled (0 °C) solution of the diene **280** (1.0 equiv.), sodium bicarbonate (solid or saturated solution, 0.0 – 4.0 equiv.) in dichloromethane and stirred for 0.25 – 4 h. The resultant mixture was diluted with saturated aqueous sodium thiosulfate solution and stirred for 15 min. The resulting biphasic mixture extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 20% ethyl acetate–hexane) to provide a mixture of ester **286** (white crystalline solid), ketone **287** (clear, pale oil), alcohol **288** (clear, pale oil) with variable yields (10 – 21%).

Ester **286**:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.03 (t, J_1 = 1.9 Hz, 1H), 7.95 (dt, J_1 = 7.8, J_2 = 1.4 Hz, 1H), 7.54 (ddd, J_1 = 8.1, J_2 = 2.2, J_3 =

	1.1 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.16 (dd, J_1 = 8.3, J_2 = 6.8 Hz, 2H), 7.11 – 7.01 (m, 1H), 6.73 (d, J_1 = 5.9 Hz, 1H), 6.40 (d, J_1 = 2.4 Hz, 1H), 6.34 (d, J_1 = 2.3 Hz, 1H), 5.67 (d, J_1 = 5.9 Hz, 1H), 5.11 – 5.00 (m, 2H), 4.94 (d, J_1 = 7.0 Hz, 1H), 4.84 – 4.69 (m, 3H), 3.45 (s, 3H), 3.17 (s, 3H), 2.36 (dd, J_1 = 12.3, J_2 = 4.2 Hz, 1H), 2.00 (dt, J_1 = 13.0, J_2 = 6.3 Hz, 1H), 1.90 (dt, J_1 = 13.2, J_2 = 6.8 Hz, 1H), 1.80 – 1.59 (m, 6H), 1.30 – 1.16 (m, 2H), 1.10 (s, 9H), 1.00 (s, 3H), 0.38 (s, 3H), 0.34 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	157.3, 156.7, 155.1, 147.1, 143.2, 134.7, 133.1, 132.5, 130.1, 129.9, 129.9, 129.8, 127.9, 127.5, 125.5, 116.7, 100.2, 96.9, 94.8, 94.3, 85.8, 81.0, 56.1, 55.5, 45.9, 45.7, 36.2, 34.8, 31.6, 29.2, 26.2, 25.7, 25.4, 24.6, 21.7, 20.1, 18.7, 11.6, –3.4, –3.9.
FTIR (KBr, thin film), cm^{-1}:	3523, 2955, 3930, 2858, 1718, 1604.
HRMS $(ES)^+$:	Calcd. for $C_{41}H_{53}O_8ClSiH$ $[M + H]^+$: 737.3276. Found: 737.3271.

TLC (20% EtOAc–Hex), R_f: Ester **286**: 0.38 (CAM).

Ketone **287**:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.48 – 7.40 (m, 2H), 7.15 (dd, J_1 = 8.3, J_2 = 6.8 Hz, 2H), 7.07 (d, J_1 = 7.3 Hz, 1H), 6.54 (dd, J_1 = 6.0, J_2 = 1.8 Hz, 1H), 6.39 (d, J_1 = 2.5 Hz, 1H), 6.32 (d, J_1 = 2.4 Hz, 1H), 5.57 (dd, J_1 = 6.0, J_2 = 2.3 Hz, 1H), 5.12 – 5.02 (m, 2H), 4.93 (d, J_1 = 7.0 Hz, 1H), 4.79 – 4.70 (m, 2H), 3.93 (dt, J_1 = 11.0, J_2 = 2.2 Hz, 1H), 3.45 (s, 3H), 3.19 (s, 3H), 2.81 – 2.63 (m, 1H), 2.48 – 2.40 (m, 1H), 2.38 – 2.17 (m, 1H), 2.08 – 1.62 (m, 5H), 1.36 – 1.26 (m, 1H), 1.07 (s, 9H), 0.79 (s, 3H), 0.35 (s, 3H), 0.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 215.3, 157.3, 156.7, 154.9, 145.3, 144.0, 130.3, 127.3, 125.2, 124.6, 117.1, 100.1, 96.8, 94.8, 94.2, 59.6, 56.2, 56.1, 47.1, 45.2, 42.2, 26.2, 25.7, 25.6, 23.8, 22.8, 18.6, –3.4, –3.9.

FTIR (KBr, thin film), cm^{-1}: 2955, 2929, 2856, 1699, 1603.

HRMS $(ES)^+$: Calcd. for $C_{34}H_{48}O_6SiH$ $[M + H]^+$: 581.3298. Found: 581.3291.

TLC (20% EtOAc–Hex), R_f: Ketone **287**: 0.28 (CAM).

Alcohol **288**:

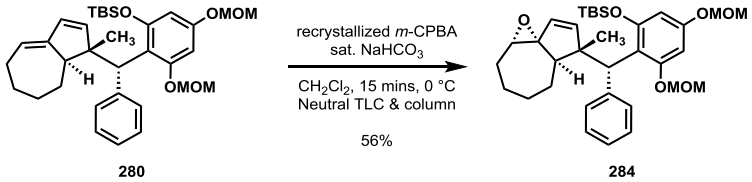
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.10 (dt, J_1 = 13.9, J_2 = 7.1 Hz, 5H), 6.41 – 6.27 (m, 1H), 6.14 (d, J_1 = 2.3 Hz, 1H), 5.63 (q, J_1 = 1.6 Hz, 1H), 5.18 – 5.06 (m, 2H), 4.74 (d, J_1 = 1.8 Hz, 1H), 3.98 (s, 1H), 3.55 (s, 1H), 3.48 (s, 3H), 2.46 (d, J_1 = 10.1 Hz, 1H), 1.84 – 1.48 (m, 4H), 1.47 – 1.35 (m, 2H), 1.23 (d, J_1 = 14.8 Hz, 3H), 1.16 (s, 3H), 0.89 (s, 9H), 0.16 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 157.5, 156.9, 156.5, 154.5, 142.7, 130.8, 127.2, 125.9, 124.5, 114.0, 100.8, 97.9, 94.8, 89.9, 69.7, 56.2, 52.1, 50.0, 47.0, 35.0, 29.9, 29.9, 28.6, 26.0, 25.3, 23.3, 18.4, –3.9, –4.1.

FTIR (KBr, thin film), cm^{-1}: 3400, 2923, 2850, 1761, 1618.

HRMS $(ES)^+$: Calcd. for $C_{32}H_{44}O_5SiH$ $[M + H]^+$: 537.3036. Found: 537.3030.

TLC (20% EtOAc–Hex), R_f: Alcohol **288**: 0.17 (CAM).



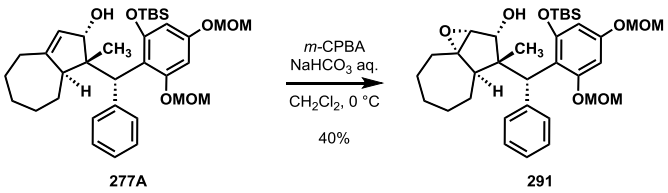
Vinyl Epoxide **284**:

Recrystallized *meta*-chloroperoxybenzoic acid (9.50 mg, 0.0551 mmol, 1.2 equiv.) was added to a cooled (0 °C) solution of the diene **280** (26.0 mg, 0.0460 mmol, 1.0 equiv.), saturated aqueous sodium bicarbonate solution (2.5 mL), and dichloromethane (2.5 mL) and stirred vigorously for 40 min. The resultant mixture was diluted with saturated aqueous sodium thiosulfate solution (3.0 mL) and stirred for 15 min. The resulting biphasic mixture was extracted with dichloromethane(3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (neutralized column, 10% ethyl acetate–hexane) to provide the vinyl epoxide **284** (15.0 mg, 56%) as a clear, colorless oil.

The vinyl epoxide is acid sensitive and will decompose to ketone **287** or alcohol **288**, if the column/TLC is not neutralized.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.46 – 7.36 (m, 2H), 7.14 (t, J_1 = 7.5 Hz, 2H), 7.06 (t, J_1 = 7.2 Hz, 1H), 6.94 (d, J_1 = 5.9 Hz, 1H), 6.43 (d, J_1 = 2.4 Hz, 1H), 6.35 (d, J_1 = 2.4 Hz, 1H), 5.39 (d, J_1 = 5.9 Hz, 1H), 5.17 – 5.03 (m, 2H), 5.01 (d, J_1 = 6.9 Hz, 1H), 4.88 (s, 1H), 4.85 (d, J_1 = 6.9 Hz, 1H), 3.46 (s, 3H), 3.25 (s, 3H), 2.34 – 2.15 (m, 2H), 1.87 – 1.35 (m, 8H),

	1.07 (s, 9H), 0.93 (s, 3H), 0.36 (s, 3H), 0.30 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	157.3, 156.7, 155.2, 150.9, 143.6, 130.3, 128.5, 127.4, 127.4, 125.5, 125.4, 117.1, 100.4, 96.9, 94.9, 94.4, 72.4, 59.4, 56.2, 56.1, 54.5, 48.1, 45.3, 30.3, 28.3, 26.3, 26.2, 26.1, 26.0, 26.0, 24.3, 23.9, 23.6, 22.8, 18.7, 14.3, –3.4, –3.8.
TLC (40% EtOAc–Hex), R_f:	Vinyl Epoxide **284**: 0.70 (Neutralized plate, CAM).

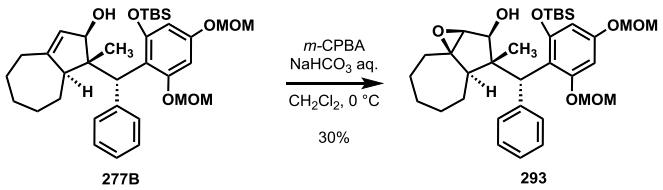


Epoxy Alcohol **291**:

Recrystallized *meta*-chloroperoxybenzoic acid (*m*-CPBA, 13.0 mg, 0.0753 mmol, 2.0 equiv.) was added to a cooled (0 °C) solution of the allylic alcohol **277A** (22.0 mg, 0.0377 mmol, 1.0 equiv.), saturated aqueous sodium bicarbonate solution (1.0 mL), and dichloromethane (2.0 mL) and vigorously stirred for 4 h. The resultant mixture was diluted with water (4.0 mL) and diethyl ether (5.0 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 2.0 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (1.0 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 10% ethyl acetate–hexane) to provide the epoxy alcohol **291** (9.00 mg, 40%) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.31 (d, J_1 = 8.0 Hz, 2H), 7.13 (t, J_1 = 7.7 Hz, 2H), 7.00 (t, J_1 = 7.3 Hz, 1H), 6.34 (d, J_1 = 2.5 Hz, 1H), 6.31 (d, J_1 = 2.5 Hz, 1H), 5.34 – 4.96 (m, 2H), 4.59 (dd, J_1 = 48.2, J_2 = 6.8 Hz, 2H), 4.15 (dd, J_1 = 10.1, J_2 = 3.5 Hz, 1H), 3.65 (d, J_1 = 3.5 Hz, 1H), 3.46 (s, 3H), 3.03 (s, 3H), 2.63 – 2.37 (m, 2H), 2.09 – 1.93 (m, 1H), 1.83 – 1.63 (m, 2H), 1.53 – 1.41 (m, 2H), 1.21 (s, 3H), 1.09

	(s, 9H), 1.00 – 0.77 (m, 3H), 0.38 (s, 3H), 0.29 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	158.1, 156.8, 154.9, 145.2, 128.9, 127.3, 124.5, 118.0, 100.4, 97.2, 94.8, 94.3, 77.3, 75.8, 69.0, 59.7, 56.1, 55.8, 54.6, 43.8, 33.8, 31.3, 30.6, 27.3, 26.2, 26.1, 18.9, 18.4, –3.2, –4.3.
FTIR (KBr, thin film), cm^{-1}:	3468, 2928, 2856, 1604, 1585.
HRMS $(ES)^+$:	Calcd. for $C_{34}H_{50}O_7SiH$ $[M + H]^+$: 599.3399. Found: 599.3390.
TLC (20% EtOAc–Hex), R_f:	Epoxy Alcohol **291**: 0.20 (Anis.).

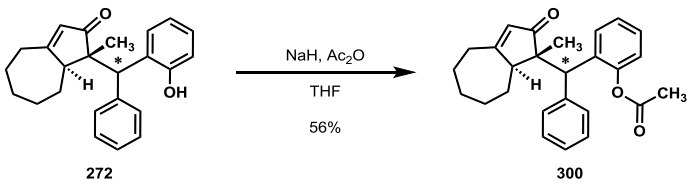


Epoxy Alcohol **293**:

Recrystallized *meta*-chloroperoxybenzoic acid (*m*-CPBA, 14.0 mg, 0.0811 mmol, 2.0 equiv.) was added to a cooled (0 °C) solution of the allylic alcohol **277B** (23.0 mg, 0.0395 mmol, 1.0 equiv.) and solid sodium bicarbonate (13.0 mg, 0.155 mmol, 4.0 equiv.) in dichloromethane (3.0 mL) and vigorously stirred for 4 h. The resultant mixture was diluted with saturated aqueous sodium thiosulfate solution (2.0 mL) and stirred for 15 min. The resulting biphasic mixture was extracted with diethyl ether (3 x 2.0 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (5.0 m), saturated aqueous sodium chloride solution (5.0 mL), and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the epoxy alcohol **293** (7.00 mg, 30%) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.33 (d, J_1 = 7.5 Hz, 2H), 7.19 (t, J_1 = 7.5 Hz, 2H), 7.10 (t, J_1 = 7.5 Hz, 1H), 6.45 (d, J_1 = 2.5 Hz, 1H), 6.34 (d, J_1 = 2.4 Hz, 1H), 5.08 (d, J_1 = 3.4 Hz, 2H), 4.91 (d, J_1 = 6.8 Hz, 1H), 4.87 – 4.73 (m, 2H), 4.68 (s, 1H), 3.46 (s, 3H), 3.40 (d, J_1 = 1.9 Hz, 1H), 3.23 (s, 3H), 2.46 (dd, J_1 = 9.1, J_2 = 4.6 Hz, 1H), 2.35 (d, J_1 = 7.3 Hz, 1H), 2.09

	– 1.93 (m, 1H), 1.83 – 1.57 (m, 4H), 1.55 – 1.45 (m, 3H), 1.03 (s, 9H), 0.97 (s, 3H), 0.35 (s, 3H), 0.26 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	157.1, 156.6, 155.2, 143.2, 129.8, 127.7, 125.4, 117.1, 100.6, 97.3, 95.0, 94.7, 76.1, 68.4, 67.3, 56.2, 56.0, 49.9, 49.1, 48.8, 32.4, 29.7, 28.1, 27.7, 26.0, 25.8, 24.1, 18.5, 17.5, –3.6, –4.1.
FTIR (KBr, thin film), cm^{-1}:	3468, 2928, 2856, 1604, 1585.
TLC (20% EtOAc–Hex), R_f:	Epoxy Alcohol **293**: 0.13 (CAM).



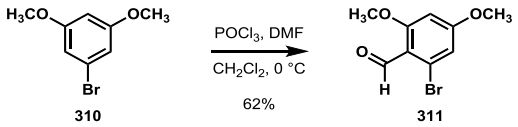
272 300

Acetate **300**:

Clean, dry sodium hydride (10.0 mg, 0.417 mmol, 1.5 equiv.) was slowly added to a cooled (0 °C) solution of the keto phenol **272** (100 mg,0.289 mmol, 1.0 equiv.) in tetrahydrofuran (5 mL) and stirred for 5 min. During this time, gas evolved and the color of the solution changed: clear, pale yellow to clear, red. After 5 min, acetic anhydride (55.0 μL, 0.577 mmol, 2.0 equiv.) was added. After the addition, the color of the solution slowly changed: clear, red to clear, yellow. The reaction was stirred until judged complete via TLC (1h). When judged complete, the mixture was carefully quenched with water (5.0 mL) and diluted with diethyl ether (5.0 mL). The biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10 → 20% ethyl acetate–hexane) to provide a mixture of inseparable diastereomers of the acetate **300** (63.0 mg, 56%, d.r. = 1.5:1) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: Mixture of diastereomers: 7.46 – 6.93 (m, 16H), 5.96 (q, J_1 = 1.5 Hz, 1H), 5.83 (d, J_1 = 1.8 Hz, 1H), 4.67 (s, 1H), 4.49 (s, 1H), 3.52 – 3.35 (m, 2H), 2.92 (dd, J_1 = 17.7, J_2 = 6.7 Hz, 1H), 2.70 (dd, J_1 = 18.0, J_2 = 6.7 Hz, 1H), 2.50 (dddd, J_1 = 20.5, J_2 = 11.2, J_3 = 7.2, J_4 = 2.2 Hz, 2H), 2.23

	(d, J_1 = 7.9 Hz, 2H), 2.07 (s, 3H), 2.00 – 1.86 (m, 2H), 1.86 – 1.42 (m, 6H), 1.14 (s, 3H), 1.05 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	Mixture of diastereomers: 213.1, 212.6, 186.0, 184.2, 168.7, 149.5, 148.9, 140.9, 140.4, 134.0, 134.0, 129.8, 129.2, 128.1, 128.0, 127.9, 127.6, 127.6, 127.3, 126.8, 126.4, 125.7, 125.5, 123.4, 123.3, 110.1, 55.4, 55.3, 52.0, 50.7, 50.1, 33.5, 33.1, 31.7, 31.4, 31.1, 30.1, 29.9, 29.2, 29.0, 28.0, 26.1, 25.9, 22.9, 22.8, 21.1, 21.0, 14.3, 11.6.
HRMS $(ES)^+$:	Calcd. for $C_{26}H_{28}O_3H$ $[M + H]^+$: 389.2117. Found: 389.2115.
TLC (20% EtOAc–Hex), R_f:	Acetate **300**: 0.20 (Anis.).

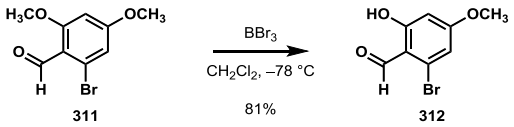


Bromo Aldehyde **311**:

Phosphorus oxychloride ($POCl_3$, 27.9 mL, 299 mmol, 2.6 equiv.) was slowly added to a cooled (0 °C) solution of 1-bromo-3,5-dimethoxybenzene **310** (25.0 g, 115 mmol, 1.0 equiv.) in DMF (110 mL) and stirred for 10 min. The mixture was then0 warmed to 23 °C and stirred for 30 min. The mixture was then warmed to 100 °C and stirred for 4 h. The resultant mixture was cooled to room temperature and poured over ice. A solid slowly crystalized over 15 h, was filtered, and washed with a minimum amount of water (<5 mL). The solid was dissolved in benzene (5 mL) and lyophilized with liquid nitrogen. The solid was recrystallized (25% ethyl acetate–hexane) to provide the bromo aldehyde **311** (14.9 g, 53%) as pale tan crystals. Concentration and recrystallization of the mother liquor provided additional bromo aldehyde **311** (2.67 g, 9%).

^{1}H NMR (600 MHz, $CDCl_3$), δ:	10.30 (s, 1H), 6.77 (d, J_1 = 2.2 Hz, 1H), 6.42 (d, J_1 = 2.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	189.2, 164.6, 163.8, 127.5, 117.1, 111.7, 98.3, 56.3, 56.0.
HRMS $(ES)^+$:	Calcd. for $C_9H_9O_3BrH$ $[M + H]^+$: 244.9813. Found: 244.9812.

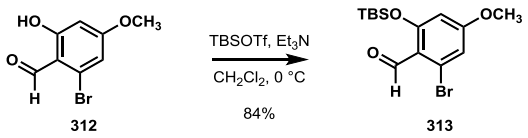
TLC (20% EtOAc–Hex), R_f: Bromo Aldehyde **311**: 0.16 ($KMnO_4$).



Phenol Aldehyde **312**:

Boron tribromide (1.0 M BBr_3 in dichloromethane, 8.16 mL, 8.16 mmol, 1.0 equiv.) was slowly added to a cooled (–78 °C) solution of the bromo aldehyde **311** (2.00 g, 8.16 mmol, 1.0 equiv.) in dichloromethane (14 mL). The mixture was slowly warmed to 23 °C over 2 h. The resultant mixture was carefully quenched with water (10 mL) and diluted with ethyl acetate (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5 → 10% ethyl acetate–hexane) to provide the phenol aldehyde **312** (1.42 g, 81%) as a white crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$), δ:	12.46 (s, 1H), 10.10 (s, 1H), 6.74 (d, J_1 = 2.4 Hz, 1H), 6.37 (d, J_1 = 2.3 Hz, 1H), 3.84 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ:	189.2, 164.6, 163.8, 127.5, 117.1, 111.7, 98.3, 56.3, 56.0.
HRMS $(ES)^+$:	Calcd. for $C_8H_7O_3BrH$ $[M + H]^+$: 230.9657. Found: 230.9655.
TLC (20% EtOAc–Hex), R_f:	Phenol Aldehyde **312**: 0.63 ($KMnO_4$).

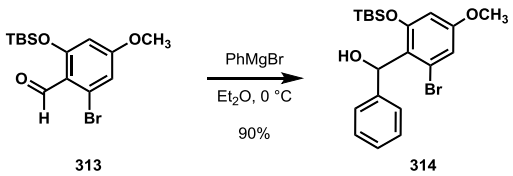


Silylated Aldehyde **312**:

tert-Butyldimethylsilyl trifluoromethanesulfonate (1.98 mL, 8.66 mmol, 2.0 equiv.) was slowly added to a cooled (0 °C) solution of the phenol aldehyde **312** (1.00 g, 4.33 mmol, 1.0 equiv.) and triethylamine (1.50 mL, 10.8 mmol, 2.5 equiv.) in dichloromethane (40 mL) and stirred until the reaction was judged complete via TLC. When judged complete (about 1 h), the mixture was diluted with saturated aqueous ammonium chloride solution (20 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate–hexane) to provide the silylated aldehyde **313** (1.26 g, 84%) as a clear, pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	10.29 (s, 2H), 6.82 (d, J_1 = 2.4 Hz, 1H), 6.33 (d, J_1 = 2.4 Hz, 1H), 3.82 (s, 3H), 1.01 (s, 9H), 0.27 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	188.9, 164.0, 161.0, 125.8, 119.5, 113.7, 105.8, 55.9, 25.8, 18.5, –4.1.
HRMS $(ES)^+$:	Calcd. for $C_{14}H_{21}O_3BrSiH$ $[M + H]^+$: 345.0522. Found: 345.0522.

TLC (20% EtOAc–Hex), R_f: Silylated Aldehyde **313**: 0.69 ($KMnO_4$).



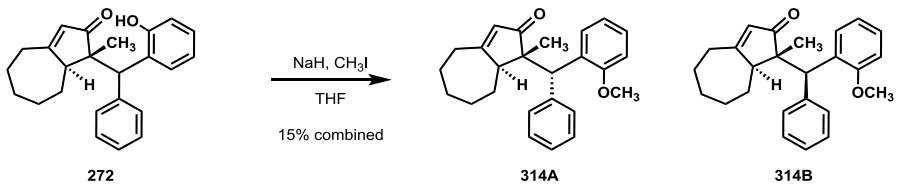
313 314

Benzyl Alcohol **314**:

Bromobenzene (0.680 mL, 6.38 mmol, 2.2 equiv.) was added to a solution of magnesium turnings (washed with 1 N aqueous hydrogen chloride solution then dried, 169 mg, 6.96 mmol, 2.4 equiv.) in diethyl ether (10 mL) and heated to reflux for 1 h. During the course of the reaction, the color solution darkened. The resultant mixture was cooled to room temperature and slowly added via cannula addition to a cooled (0 °C) solution of the silylated aldehyde **313** (1.00 g, 2.90 mmol, 1.0 equiv.) in diethyl ether (20 mL). The resultant mixture was stirred at 0 °C for 15 min then carefully quenched with saturated aqueous ammonium chloride solution (5.0 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate–hexane) to provide the benzyl alcohol **314** (1.11 g, 90%) as a clear, pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.29 – 7.24 (m, 4H), 7.24 – 7.16 (m, 1H), 6.80 (d, J_1 = 2.5 Hz, 1H), 6.40 (d, J_1 = 2.5 Hz, 1H), 6.24 (d, J_1 = 11.6 Hz, 1H), 3.97 (d, J_1 = 11.6 Hz, 1H), 3.78 (s, 3H), 0.75 (s, 9H), 0.20 (s, 3H), –0.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	159.7, 155.5, 143.6, 128.2, 127.0, 126.0, 125.2, 125.0, 110.5, 105.9, 74.1, 55.7, 25.7, 18.3, –3.8, –4.5.
HRMS $(ES)^+$:	Calcd. for $C_{20}H_{26}O_2BrSi$ $[M + H – H_2O]^+$: 405.0880. Found: 405.0883.
TLC (20% EtOAc–Hex), R_f:	Benzyl Alcohol **314**: 0.66 (CAM, $KMnO_4$).



272 314A 314B

Methyl Ethers **314A** and **214B**:

Clean, dry sodium hydride (29.0 mg, 1.21 mmol, 1.5 equiv.) was slowly added to a solution of the keto phenol **272** (280 mg, 0.808 mmol, 1.0 equiv.) in THF (15 mL) and stirred for 5 min. During this time, gas evolved and the color of the solution changed: clear pale yellow to clear red. After 5 min, methyl iodide (100 μL, 1.62 mmol, 2.0 equiv.) was added. After the addition, the color of the solution slowly changed: clear, red to clear, yellow. The mixture was stirred until judged complete via TLC (14 h). When judged complete, the resultant mixture was carefully quenched with saturated aqueous ammonium chloride solution (15 mL) and diluted with ethyl acetate (10 mL). The biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with saturated aqueous sodium chloride solution (10 mL) and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% diethyl ether/hexane) to provide separable diastereomers of the methyl ethers **314A** and **314B** (21 mg and 24.0 mg respectively, 15% combined yield, d.r. = 1:1) both as a clear, colorless oil.

Methyl Ether **314A**:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.25 – 7.06 (m, 9H), 6.92 (td, J_1 = 7.5, 1.2 Hz, 1H), 6.86 (dd, J_1 = 8.2, 1.2 Hz, 1H), 5.79 (q, J_1 = 1.6 Hz, 1H), 5.04 (s, 1H), 3.75 (s, 3H), 3.40 – 3.31 (m, 1H), 2.72 – 2.58 (m, 1H), 2.46 (ddt, J_1 =

15.7, J_2 =11.1, J_3 = 2.1 Hz, 1H), 1.99 – 1.78 (m, 3H), 1.73 – 1.65 (m, 1H), 1.54 – 1.39 (m, 2H), 1.39 – 1.17 (m, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 213.9, 186.1, 157.8, 141.5, 130.5, 130.1, 129.5, 128.0, 127.7, 127.6, 125.9, 120.1, 111.1, 55.7, 55.6, 51.1, 33.1, 31.7, 31.2, 30.0, 29.0, 26.0, 22.8, 21.2, 14.3.

HRMS $(ES)^+$: Calcd. for $C_{25}H_{28}O_2H$ $[M + H]^+$: 361.2168. Found: 361.2163.

TLC (30% Et_2O–Hex), R_f: Methyl Ether **314A**: 0.14 (CAM).

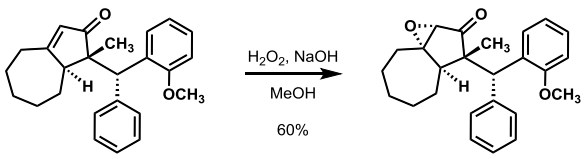
Methyl Ether **314B**:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.32 – 6.97 (m, 7H), 6.83 (t, J_1 = 7.5 Hz, 1H), 6.74 (d, J_1 = 8.2 Hz, 1H), 5.88 (s, 1H), 4.67 (s, 1H), 3.63 (s, 3H), 3.39 (dd, J_1 = 10.3, J_2 = 2.3 Hz, 1H), 2.83 (dd, J_1 = 17.6, J_2 = 6.6 Hz, 1H), 2.52 – 2.40 (m, 1H), 1.96 – 1.85 (m, 1H), 1.84 – 1.60 (m, 4H), 1.32 – 1.21 (m, 4H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ: 213.1, 184.1, 157.2, 142.1, 130.9, 129.9, 128.2, 128.0, 127.8, 127.3, 126.2, 120.0, 110.9, 55.8,

55.5, 52.6, 49.1, 33.5, 31.7, 31.4, 30.2, 28.1, 26.1, 22.8, 22.7, 14.3.

TLC (30% Et_2O–Hex), R_f: Methyl Ether **314B**: 0.11 (CAM).



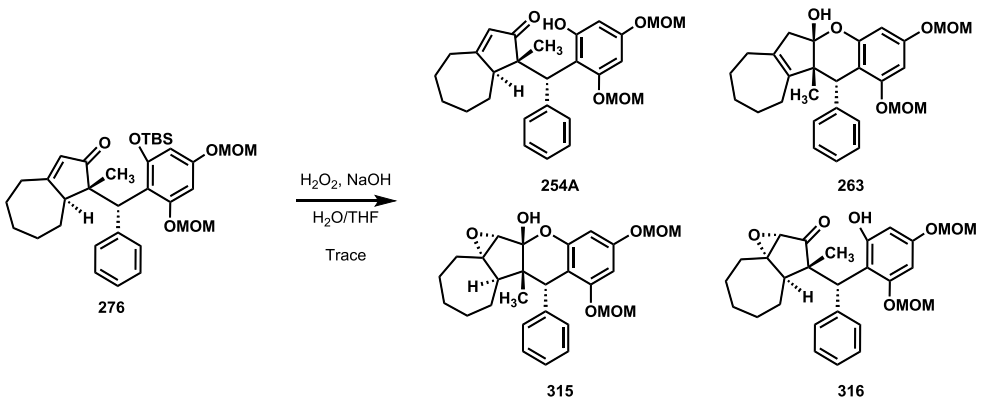
314A 315

Epoxy Ketone **315**:

6 N Aqueous sodium hydroxide solution (50.0 μL, 0.291 mmol, 5.0 equiv.) was added dropwise to a solution of the methyl ether **314** (21.0 mg, 0.0583 mmol, 1.0 equiv.) and hydrogen peroxide (30%, 25.0 μL, 0.175 mmol, 3.0 equiv.) in methanol (2.0 mL) and stirred for 14 h. Additional hydrogen peroxide (30%, 70.0 μL, 0.583 mmol, 10 equiv.), and 6 N aqueous sodium hydroxide solution (50.0 μL, 0.291 mmol, 5.0 equiv.) was added and the reaction continued to stir for 5 h. The resultant mixture was quenched with saturated aqueous sodium thiosulfate solution/saturated aqueous sodium chloride solution (2.0 mL) and stirred for 15 min. The reaction mixture was then extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate–hexane) to provide the epoxy ketone **315** (13.2 mg, 60%) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 – 7.34 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.07 (m, 3H), 6.99 – 6.71 (m, 2H), 5.00 (s, 1H), 3.78 (s, 3H), 3.28 (s, 1H), 2.91 – 2.67 (m, 1H), 2.11 – 1.98 (m, 1H), 1.90 – 1.77 (m, 2H), 1.77 – 1.65 (m, 2H), 1.53 – 1.45 (m, 1H), 1.35 – 1.20 (m, 4H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ:	212.3, 157.2, 142.0, 131.0, 130.2, 130.2, 128.0, 127.7, 126.1, 120.3, 110.8, 71.0, 63.1, 57.1, 55.5, 48.2, 48.0, 33.1, 31.1, 30.1, 29.9, 27.2, 25.8, 20.9.
HRMS $(ES)^+$:	Calcd. for $C_{25}H_{28}O_3H$ $[M + H]^+$: 377.2117. Found: 377.2116.
TLC (30% EtOAc–Hex), R_f:	Epoxy Ketone **315**: 0.17 (CAM).



Epoxy Hemiketal **315** and Epoxy Phenol **316**:

Hydrogen peroxide (30%, 0.190 mL) was slowly added to a cooled (0 °C) solution of the silylated ketone **276** (26.0 mg, 0.0448 mmol, 1.0 equiv.) and 6 N aqueous sodium hydroxide solution (0.112 mL, 0.672 mmol, 15 equiv.) in water/THF (1:1, 2.0 mL) and stirred for 20 h. The resultant mixture was carefully quenched with saturated aqueous sodium thiosulfate solution (1.0 mL) and stirred for 15 mins. The mixture was diluted with ethyl acetate (2.0 mL). The resulting biphasic mixture was extracted with diethyl ether (3 x 2.0 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (1.0 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate–hexane) to provide the keto phenol **254A** (1.00 mg) as a clear, colorless oil; the hemiketal **263** (1.00 mg) as a white crystalline solid; the epoxy hemiketal **315** (5.00 mg) as a white solid; and the epoxy phenol **316** (5.00 mg) as a white crystalline solid.

Epoxy Hemiketal **315**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.22 – 7.01 (m, 5H), 6.49 (d, J_1 = 2.3 Hz, 1H), 6.32 (d, J_1 = 2.3 Hz, 1H), 5.17 – 5.06 (m, 2H), 4.87 (d, J_1 = 6.6 Hz, 1H), 4.72 (d, J_1 = 6.6 Hz, 1H), 3.96 (s, 1H), 3.49 – 3.47 (m, 1H), 3.46 (s, 3H), 3.40 (s, 1H), 2.93 (s, 3H), 2.78 (s, 1H), 2.13 (dd, J_1 = 12.3, J_2 = 2.7 Hz, 1H), 2.02 (dd, J_1 = 14.5, J_2 = 12.2 Hz, 1H), 1.67 (dd, J = 11.6, 5.7 Hz, 2H), 1.51 – 1.39 (m, 4H), 1.22 (s, 3H), 1.09 (dd, J = 14.7, J_2 = 11.2 Hz, 1H), 1.01 – 0.95 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	157.4, 155.2, 152.8, 143.2, 126.2, 112.0, 103.9, 100.0, 97.9, 94.7, 93.8, 70.7, 68.7, 56.3, 56.2, 55.7, 51.2, 47.2, 33.2, 30.9, 29.7, 26.5, 26.1, 22.7.
HRMS $(ES)^+$:	Calcd. for $C_{28}H_{34}O_7H$ $[M+H]^+$: 483.2383. Found: 483.2363.
TLC (40% EtOAc–Hex), R_f:	Epoxy Hemiketal **315**: 0.66 (CAM).

Epoxy Phenol **316**:

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.25 – 7.08 (m, 5H), 6.52 (d, J_1 = 2.4 Hz, 1H), 6.39 (d, J_1 = 2.5 Hz, 1H), 5.18 – 5.01 (m, 2H), 4.90 (d, J_1 = 6.6 Hz, 1H), 4.72 (d, J_1 = 6.6 Hz, 1H), 4.22 (s, 1H), 3.97 (s, 1H), 3.47 (s, 3H), 2.96 – 2.90 (m, 1H), 2.88 (s, 3H), 2.27 (dt, J_1 = 14.6, J_2 = 7.2 Hz, 1H), 1.74 (dt, J_1 = 14.7, J_2 = 5.2 Hz, 1H), 1.64 – 1.56 (m, 2H), 1.52 – 1.36 (m, 3H), 1.32 (s, 3H), 1.24 – 1.18 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ:	213.2, 157.2, 157.0, 156.0, 141.3, 127.8, 126.6, 117.6, 102.5, 99.7, 94.5, 93.8, 91.1, 79.5, 56.3, 55.7, 51.9, 51.7, 46.5, 36.0, 29.9, 26.9, 26.2, 22.7, 22.2, 19.7.
TLC (40% EtOAc–Hex), R_f:	Epoxy Phenol **316**: 0.44 (CAM).

Appendix A

PERMISSION FOR PUBLISHED WORK

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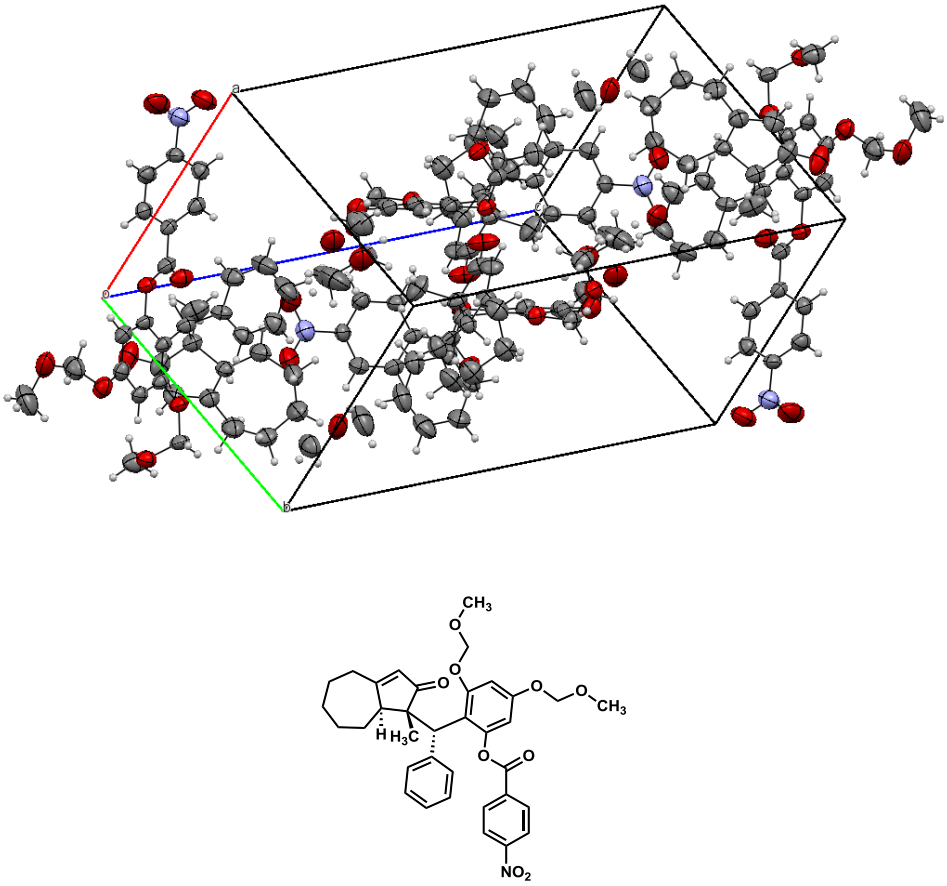
Metal-Free Functionalization of *N*,*N*-Dialkylanilines via Temporary Oxidation to *N*,*N*-Dialkylaniline *N*-Oxides and Group Transfer, Lewis, R. S.; Wisthoff, M. W.; Grissmerson, J.; Chain, W. J. *Org. Lett.* **2014**, 16, 3832–3835.
Direct Link: http://pubs.acs.org/doi/abs/10.1021%2Fol501813s

Appendix B

CRYSTAL STRUCTURE DATA FOR NITRO ESTER 255 AND HEMIKETAL 270



ORTEP view of the Nitro Ester **255** unit cell.

Data Collection and Reduction

A specimen of $C_{35}H_{37}NO_9$, approximate dimensions 0.028 mm x 0.151 mm x 0.337 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 17.17 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 11609 reflections to a maximum θ angle of 43.27° (1.12 Å resolution), of which 2241 were independent (average redundancy 5.180, completeness = 99.6%, R_{int} = 3.45%, R_{sig} = 2.78%) and 1986 (88.62%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 11.0048(3) Å, $\underline{b}$ = 11.2247(3) Å, $\underline{c}$ = 24.9243(7) Å, β = 93.796(2)°, volume = 3072.03(15) $Å^3$, are based upon the refinement of the XYZ-centroids of 6066 reflections above 20 σ(I) with 7.108° < 2θ < 86.30°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.800. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5986 and 0.7485.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z = 4 for the formula unit, $C_{35}H_{37}NO_9$. The final anisotropic full-matrix least-squares refinement on F^2 with 420 variables converged at R1 = 3.98%, for the observed data and wR2 = 10.76% for all data. The goodness-of-fit was 1.061. The largest peak in the final difference electron density synthesis was 0.131 $e^-/Å^3$ and the largest hole was -0.152 $e^-/Å^3$ with an RMS

deviation of 0.032 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.331 g/cm^3 and F(000), 1304 e^-.

*Experimental Details for Nitro Ester **255***

Crystal Details

Chemical Formula	$C_{35}H_{37}NO_9$	
Formula Weight	615.65 g/mol	
Temperature	200(2) K	
Wavelength	1.54178 Å	
Crystal Size	0.028 x 0.151 x 0.337 mm	
Crystal System	monoclinic	
Space Group	P 1 21/n 1	
Unit Cell Dimensions	a = 11.0048(3) Å	α = 90°
	b = 11.2247(3) Å	β = 93.796(2)°
	c = 24.9243(7) Å	γ = 90°
Volume	3072.03(15) $Å^3$	
Z	4	
Density (calculated)	1.331 g/cm^3	
Absorption Coefficient	0.792 mm^{-1}	
F(000)	1304	

Data Collection and Structure Refinement

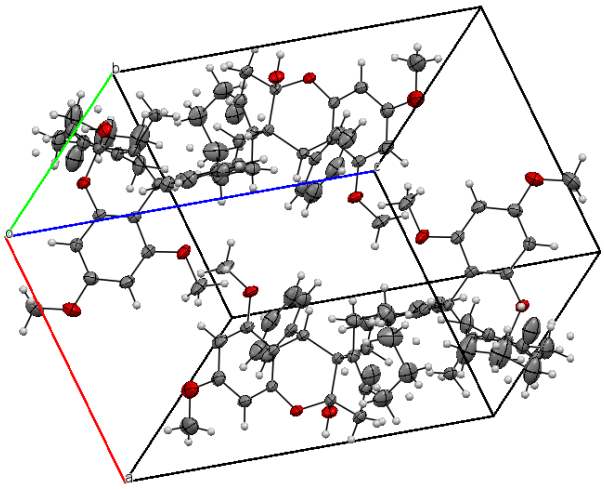
Theta Range for Data Collection	3.55 to 43.27°
Index Ranges	-9<=h<=9, -9<=k<=9, -19<=l<=22
Reflections Collected	11609
Independent Reflections	2241 [R(int) = 0.0345]

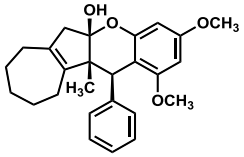
Coverage of Independent Reflections	
	99.6%
Absorption Correction	multi-scan
Max. and Min. Transmission	0.7485 and 0.5986
Structure Solution Technique	direct methods
Structure Solution Program	SHELXS-97 (Sheldrick 2008)
Refinement Method	Full-matrix least-squares on F^2
Refinement Program	SHELXL-2014/7 (Sheldrick, 2014)
Function Minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data/Restraints/Parameters	2241 / 5 / 420
Goodness-of-Fit on F^2	1.061
Final R Indices	1986 data; R1 = 0.0398, wR2 = 0.1037
	$I>2\sigma(I)$
	all data R1 = 0.0452, wR2 = 0.1076
Weighting Scheme	$w=1/[\sigma^2(F_o^2)+(0.0597P)^2+1.7898P]$
	where $P=(F_o^2+2F_c^2)/3$
Largest Diff. Peak and Hole	0.131 and -0.152 $eÅ^{-3}$
R.M.S. deviation from mean	0.032 $eÅ^{-3}$

Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters ($Å^2$)

	x/a	y/b	z/c	U(eq)
C1	0.4331(3)	0.2968(3)	0.64341(14)	0.0505(10)
C2	0.3053(4)	0.3257(4)	0.61963(18)	0.0628(11)
C3	0.2199(4)	0.2533(4)	0.64686(17)	0.0623(11)
C4	0.2785(3)	0.1715(4)	0.67704(15)	0.0538(10)
C5	0.4142(3)	0.1789(3)	0.67440(14)	0.0469(10)
C6	0.2196(3)	0.0770(4)	0.70933(17)	0.0736(12)
C7	0.2907(4)	0.9615(3)	0.71680(16)	0.0696(12)
C8	0.3922(4)	0.9675(4)	0.76052(17)	0.0785(12)
C9	0.5047(4)	0.0354(4)	0.74614(17)	0.0793(13)
C10	0.4855(3)	0.1648(3)	0.72905(16)	0.0668(11)
C11	0.4630(4)	0.4001(3)	0.68385(16)	0.0805(13)
C12	0.5316(3)	0.3001(3)	0.60161(14)	0.0470(10)
C13	0.6641(3)	0.1179(4)	0.61689(14)	0.0558(10)
C14	0.7702(5)	0.0638(4)	0.63603(17)	0.0750(12)
C15	0.8630(4)	0.1287(6)	0.66065(19)	0.0896(14)
C16	0.8494(5)	0.2500(6)	0.66559(17)	0.0842(13)
C17	0.7426(5)	0.3050(4)	0.64678(16)	0.0654(11)
C18	0.6480(3)	0.2400(4)	0.62226(13)	0.0479(10)
C19	0.5008(3)	0.2641(3)	0.54256(14)	0.0409(9)
C20	0.5643(3)	0.3210(3)	0.50384(19)	0.0433(9)
C21	0.5524(3)	0.2997(3)	0.44933(18)	0.0489(10)
C22	0.4730(4)	0.2114(3)	0.43190(17)	0.0474(10)
C23	0.4060(3)	0.1502(3)	0.46811(18)	0.0451(9)
C24	0.4203(3)	0.1756(3)	0.52264(17)	0.0406(9)
C25	0.7678(4)	0.3866(4)	0.52113(14)	0.0483(10)
C26	0.9621(4)	0.4601(3)	0.56237(14)	0.0502(10)
C27	0.0368(3)	0.5471(4)	0.58499(14)	0.0517(10)
C28	0.9908(4)	0.6607(4)	0.58844(14)	0.0478(10)
C29	0.8749(4)	0.6891(3)	0.56970(16)	0.0576(10)
C30	0.8001(3)	0.6002(4)	0.54773(14)	0.0505(10)
C31	0.8433(3)	0.4850(3)	0.54410(13)	0.0409(9)
C32A	0.4829(10)	0.2550(15)	0.3377(5)	0.0798(19)
C33A	0.2857(8)	0.3061(14)	0.3091(8)	0.115(5)
C32B	0.493(4)	0.264(6)	0.343(2)	0.0798(19)
C33B	0.312(4)	0.336(7)	0.304(3)	0.115(5)
C34	0.2816(3)	0.0168(3)	0.54228(15)	0.0538(10)
C35	0.0888(3)	0.1110(4)	0.53557(17)	0.0727(12)

N1	0.0689(4)	0.7546(4)	0.61291(13)	0.0690(10)
O1	0.1722(3)	0.7288(3)	0.62950(12)	0.0895(10)
O2	0.0276(3)	0.8547(3)	0.61644(14)	0.1092(12)
O3	0.6469(2)	0.41135(18)	0.52155(9)	0.0481(6)
O4	0.8069(2)	0.2943(2)	0.50499(10)	0.0649(8)
O5	0.4534(2)	0.1755(2)	0.37905(12)	0.0645(7)
O6A	0.4064(5)	0.3461(3)	0.33185(15)	0.0966(14)
O6B	0.4215(15)	0.2602(12)	0.2967(6)	0.0966(14)
O7	0.3558(2)	0.1167(2)	0.55969(9)	0.0494(6)
O8	0.1800(2)	0.04885(19)	0.50892(10)	0.0578(7)
O9	0.2823(3)	0.4012(3)	0.58490(13)	0.0887(9)





ORTEP view of the Hemiketal **270** unit cell.

*Crystallographic Experimental for Hemiketal **270***

Data Collection and Reduction

A specimen of $C_{26}H_{30}O_4$, approximate dimensions 0.222 mm x 0.527 mm x 0.622 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 1.43 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 56768 reflections to a maximum θ angle of 27.45° (0.77 Å resolution), of which 9864 were independent (average redundancy 5.755, completeness = 99.3%, R_{int} = 7.20%, R_{sig} = 5.44%) and 6759 (68.52%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.609(3) Å, b = 13.784(4) Å, c = 13.877(4) Å, α = 71.647(5)°, β = 79.292(5)°, γ = 72.813(5)°, volume = 2175.5(10) $Å^3$, are based upon the refinement of the XYZ-centroids of 7887 reflections above 20 σ(I) with 4.835° < 2θ < 47.82°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.902. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6722 and 0.7456.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 4 for the formula unit, $C_{26}H_{30}O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 555 variables converged at R1 = 9.69%, for the observed data and wR2 = 31.47% for all data. The goodness-of-fit was 1.025. The largest peak in the final difference electron density synthesis was 1.248 $e^-/Å^3$ and the largest hole was -0.815 $e^-/Å^3$ with an RMS deviation

of 0.102 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.241 g/cm^3 and F(000), 872 e^-.

*Experimental Details for Hemiketal **270***

Crystal Details

Chemical Formula	$C_{26}H_{30}O_4$	
Formula Weight	406.50 g/mol	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal Size	0.222 x 0.527 x 0.622 mm	
Crystal System	triclinic	
Space Group	P -1	
Unit Cell Dimensions	a = 12.609(3) Å	α = 71.647(5)°
	b = 13.784(4) Å	β = 79.292(5)°
	c = 13.877(4) Å	γ = 72.813(5)°
Volume	2175.5(10) $Å^3$	
Z	4	
Density (calculated)	1.241 g/cm^3	
Absorption Coefficient	0.082 mm^{-1}	
F(000)	872	

Data Collection and Structure Refinement

Theta Range for Data Collection	1.55 to 27.45°
Index Ranges	-16<=h<=16, -17<=k<=17, -17<=l<=17
Reflections Collected	56768
Independent Reflections	9864 [R(int) = 0.0720]

Coverage of Independent Reflections	
	99.3%
Absorption Correction	multi-scan
Max. and Min. Transmission	0.7465 and 0.6722
Structure Solution Technique	direct methods
Structure Solution Program	SHELXS-97 (Sheldrick 2008)
Refinement Method	Full-matrix least-squares on F^2
Refinement Program	SHELXL-2014/7 (Sheldrick, 2014)
Function Minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data/Restraints/Parameters	9864 / 96 / 555
Goodness-of-Fit on F^2	1.025
Final R Indices	6759 data; R1 = 0.0969, wR2 = 0. 2799
	$I>2\sigma(I)$
	all data R1 = 0.1291, wR2 = 0.3147
Weighting Scheme	$w=1/[\sigma^2(F_o^2)+(0.1945P)^2+2.5885P]$
	where $P=(F_o^2+2F_c^2)/3$
Largest Diff. Peak and Hole	1.248 and -0.815 $eÅ^{-3}$
R.M.S. deviation from mean	0.102 $eÅ^{-3}$

Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters ($Å^2$)

	x/a	y/b	z/c	U(eq)
C1	0.9520(2)	0.4118(2)	0.9329(2)	0.0250(6)
C2	0.9852(3)	0.3174(3)	0.0257(3)	0.0348(8)
C3	0.8976(3)	0.2586(3)	0.0377(3)	0.0352(7)
C4	0.8769(4)	0.1759(3)	0.1343(3)	0.0521(10)
C5	0.8921(6)	0.0665(5)	0.1217(5)	0.0710(14)
C6	0.8034(6)	0.0575(5)	0.0662(5)	0.0898(14)
C4'	0.8769(4)	0.1759(3)	0.1343(3)	0.0521(10)
C5'	0.7779(19)	0.134(2)	0.136(2)	0.0710(14)
C6'	0.8034(6)	0.0575(5)	0.0662(5)	0.0898(14)
C7	0.8013(5)	0.1202(4)	0.9569(4)	0.0707(12)
C8	0.7651(3)	0.2386(3)	0.9340(3)	0.0403(8)
C9	0.8484(3)	0.2873(2)	0.9525(2)	0.0288(6)
C10	0.8954(3)	0.3712(2)	0.8688(2)	0.0247(6)
C11	0.8030(2)	0.4584(2)	0.8076(2)	0.0231(6)
C12	0.7255(2)	0.5174(2)	0.8786(2)	0.0230(6)
C13	0.6115(2)	0.5624(2)	0.8658(2)	0.0264(6)
C14	0.5417(3)	0.6180(3)	0.9302(3)	0.0344(8)
C15	0.5847(3)	0.6280(3)	0.0110(3)	0.0323(7)
C16	0.6961(3)	0.5845(3)	0.0267(2)	0.0280(7)
C17	0.7644(2)	0.5304(2)	0.9583(2)	0.0233(6)
C18	0.9844(3)	0.3175(3)	0.7966(3)	0.0307(7)
C19	0.4625(3)	0.5941(3)	0.7668(3)	0.0405(9)
C20	0.5455(4)	0.6889(4)	0.1589(4)	0.0588(12)
C21	0.8448(3)	0.5150(3)	0.6161(3)	0.0339(8)
C22	0.8833(3)	0.5802(3)	0.5265(3)	0.0409(9)
C23	0.9221(3)	0.6627(3)	0.5292(3)	0.0397(9)
C24	0.9196(3)	0.6817(3)	0.6220(3)	0.0400(8)
C25	0.8811(3)	0.6176(3)	0.7109(3)	0.0334(7)
C26	0.8445(2)	0.5318(2)	0.7097(2)	0.0249(6)
C27	0.1299(2)	0.9254(2)	0.4212(2)	0.0239(6)
C28	0.0960(3)	0.0161(3)	0.3270(2)	0.0308(7)
C29	0.2068(3)	0.0298(3)	0.2706(3)	0.0311(7)
C30	0.2129(4)	0.1319(3)	0.1928(3)	0.0481(10)
C31	0.2926(5)	0.1327(5)	0.0981(5)	0.0491(14)
C32	0.4160(4)	0.0921(4)	0.1190(4)	0.0674(15)
C33	0.4446(4)	0.9721(4)	0.1554(3)	0.0491(10)
C30'	0.2129(4)	0.1319(3)	0.1928(3)	0.0481(10)

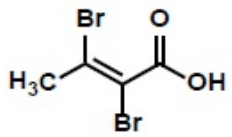
C31'	0.3217(8)	0.1571(8)	0.1820(9)	0.0491(14)
C32'	0.4160(4)	0.0921(4)	0.1190(4)	0.0674(15)
C34	0.4110(3)	0.9242(3)	0.2668(3)	0.0346(8)
C35	0.2889(3)	0.9439(2)	0.3028(2)	0.0249(6)
C36	0.2430(2)	0.8585(2)	0.3850(2)	0.0224(6)
C37	0.3208(2)	0.7976(2)	0.4712(2)	0.0231(6)
C38	0.3271(2)	0.8734(2)	0.5267(2)	0.0223(6)
C39	0.4233(2)	0.8621(2)	0.5710(2)	0.0263(6)
C40	0.4260(3)	0.9294(3)	0.6258(3)	0.0353(8)
C41	0.3326(3)	0.0127(3)	0.6343(3)	0.0340(8)
C42	0.2383(3)	0.0282(3)	0.5891(2)	0.0285(7)
C43	0.2375(2)	0.9575(2)	0.5364(2)	0.0230(6)
C44	0.2220(3)	0.7820(3)	0.3353(3)	0.0293(7)
C45	0.6117(3)	0.7669(3)	0.5977(3)	0.0400(9)
C46	0.2573(4)	0.1657(4)	0.6937(4)	0.0566(12)
C47	0.3456(3)	0.6004(3)	0.5213(3)	0.0404(9)
C48	0.3182(4)	0.5090(3)	0.5840(4)	0.0536(11)
C49	0.2405(4)	0.5113(3)	0.6680(3)	0.0518(11)
C50	0.1909(4)	0.6055(4)	0.6898(3)	0.0501(11)
C51	0.2164(3)	0.6984(3)	0.6285(3)	0.0364(8)
C52	0.2936(3)	0.6969(2)	0.5425(2)	0.0281(7)
O1	0.87466(18)	0.49228(19)	0.97633(18)	0.0319(5)
O2	0.03892(18)	0.45422(19)	0.87733(18)	0.0328(5)
O3	0.57712(19)	0.54783(19)	0.78474(18)	0.0343(6)
O4	0.5097(2)	0.6826(2)	0.0718(2)	0.0510(7)
O5	0.13981(17)	0.97676(19)	0.49532(18)	0.0308(5)
O6	0.05285(18)	0.86578(18)	0.46655(18)	0.0312(5)
O7	0.51037(18)	0.78011(18)	0.55706(19)	0.0327(5)
O8	0.3433(2)	0.0746(2)	0.6901(3)	0.0532(8)

Appendix C

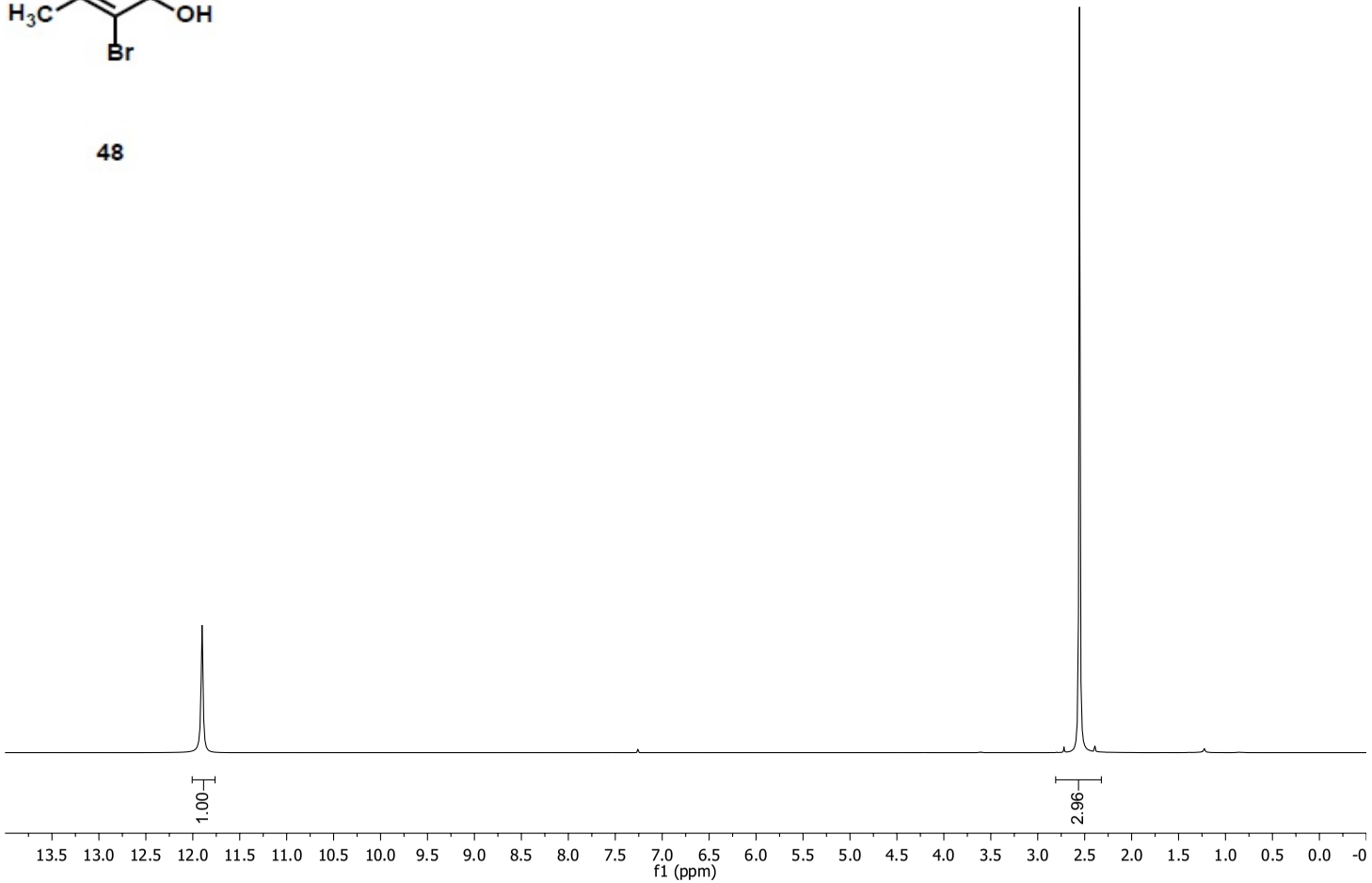
CATALOG OF SPECTRA

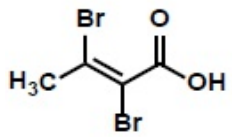
49
HO
1.09
1.94
3.79
1.91
3.76
0.93
f1 (ppm)

137.4
120.0
108.2
66.8
64.6
35.5
31.0
24.9
f1 (ppm)
49

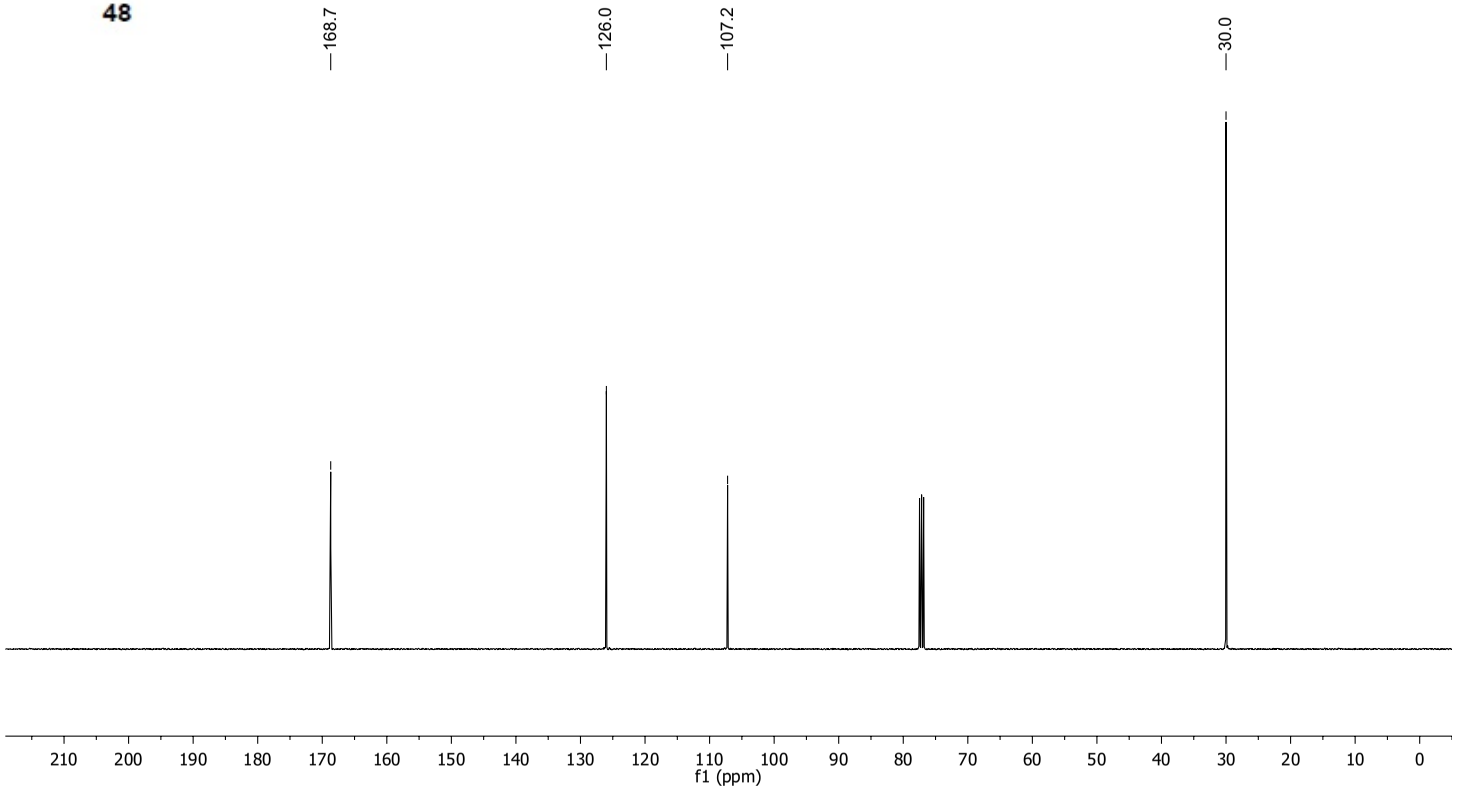

Br
O
H3C
OH
Br

48

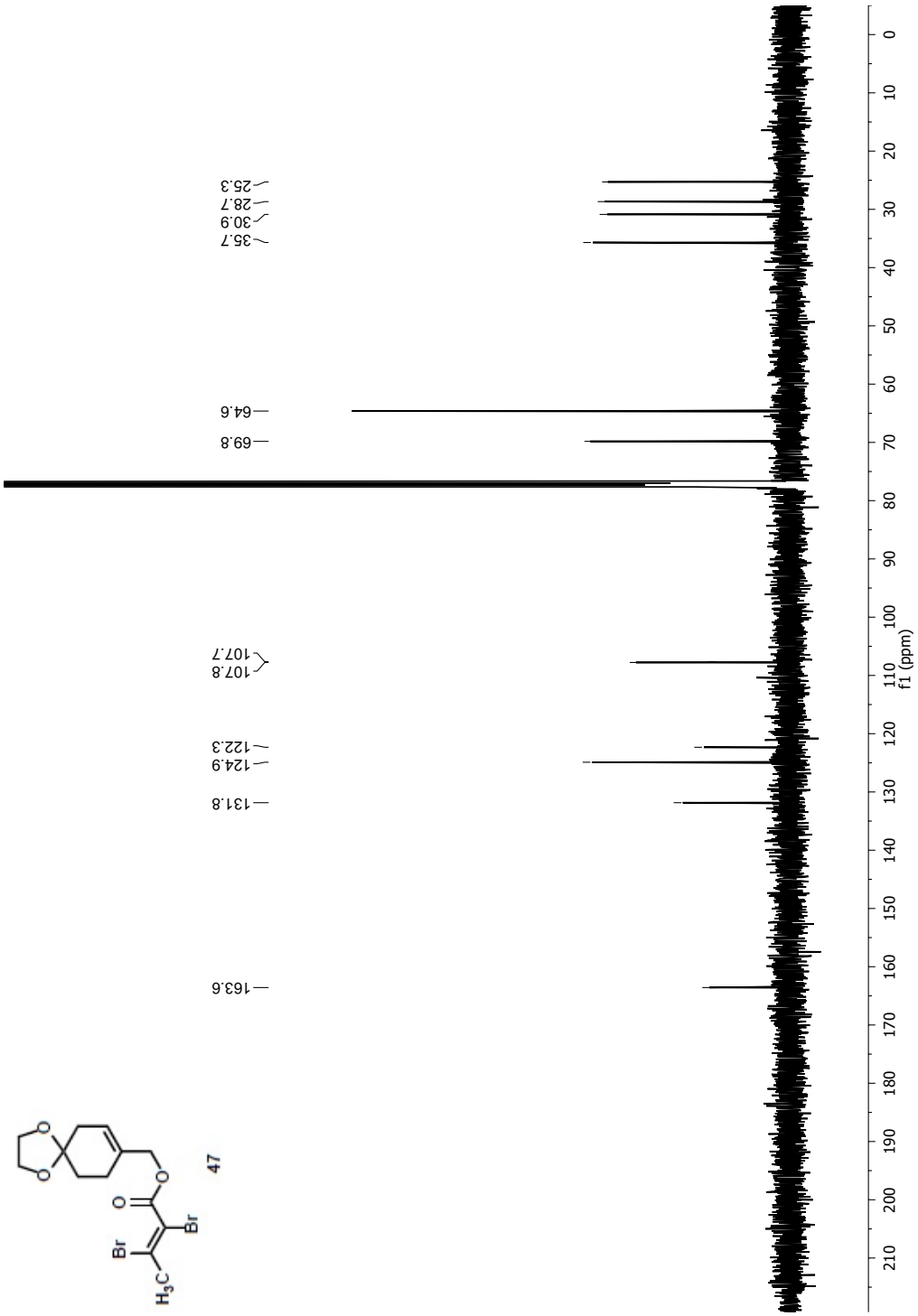

1.00
2.96
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


Br
O
H3C
OH
Br

48

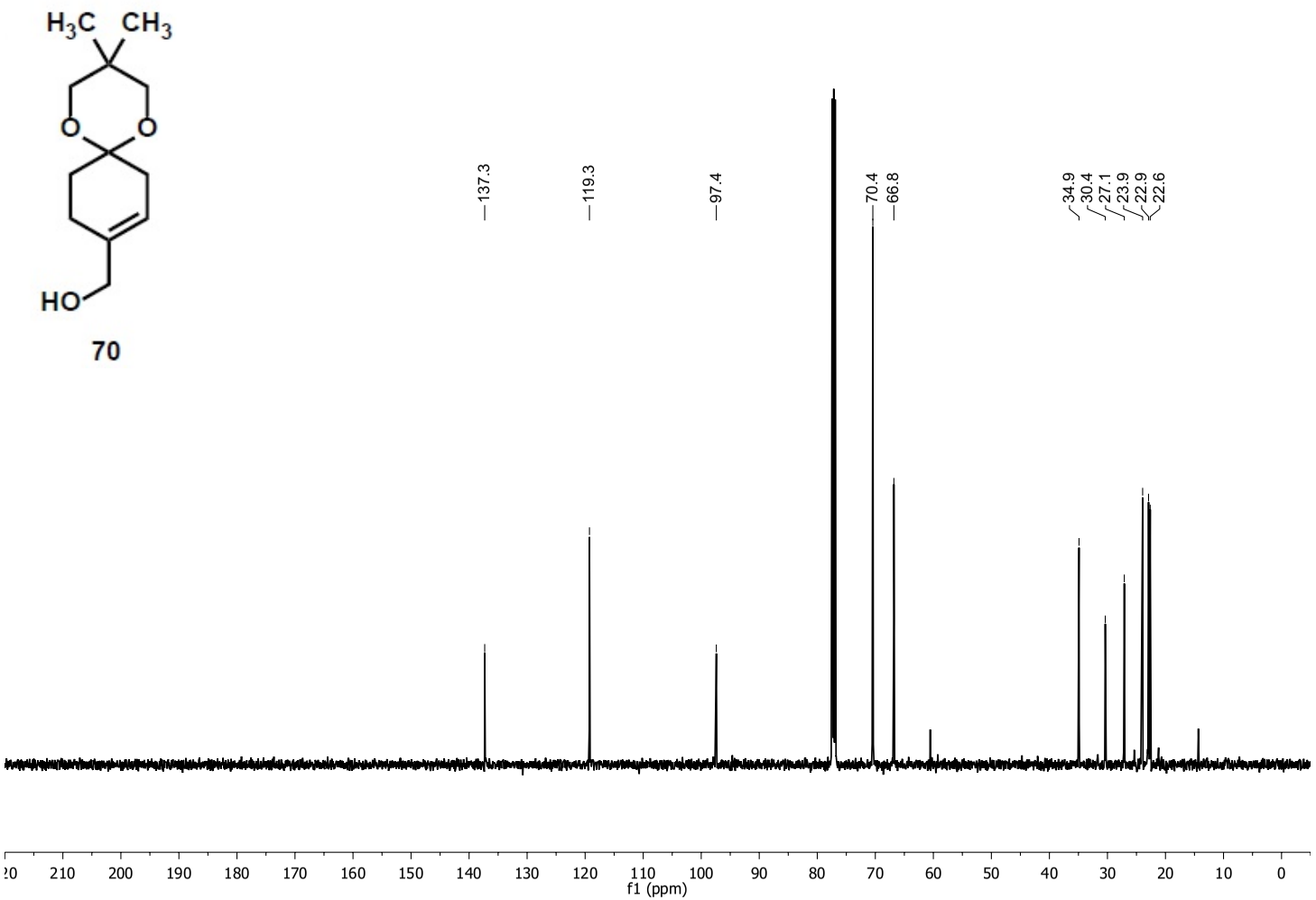

168.7
126.0
107.2
30.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

47
Br
O
Br
H_3C
0.92
1.71
4.00
2.58
3.87
2.07
f1 (ppm)

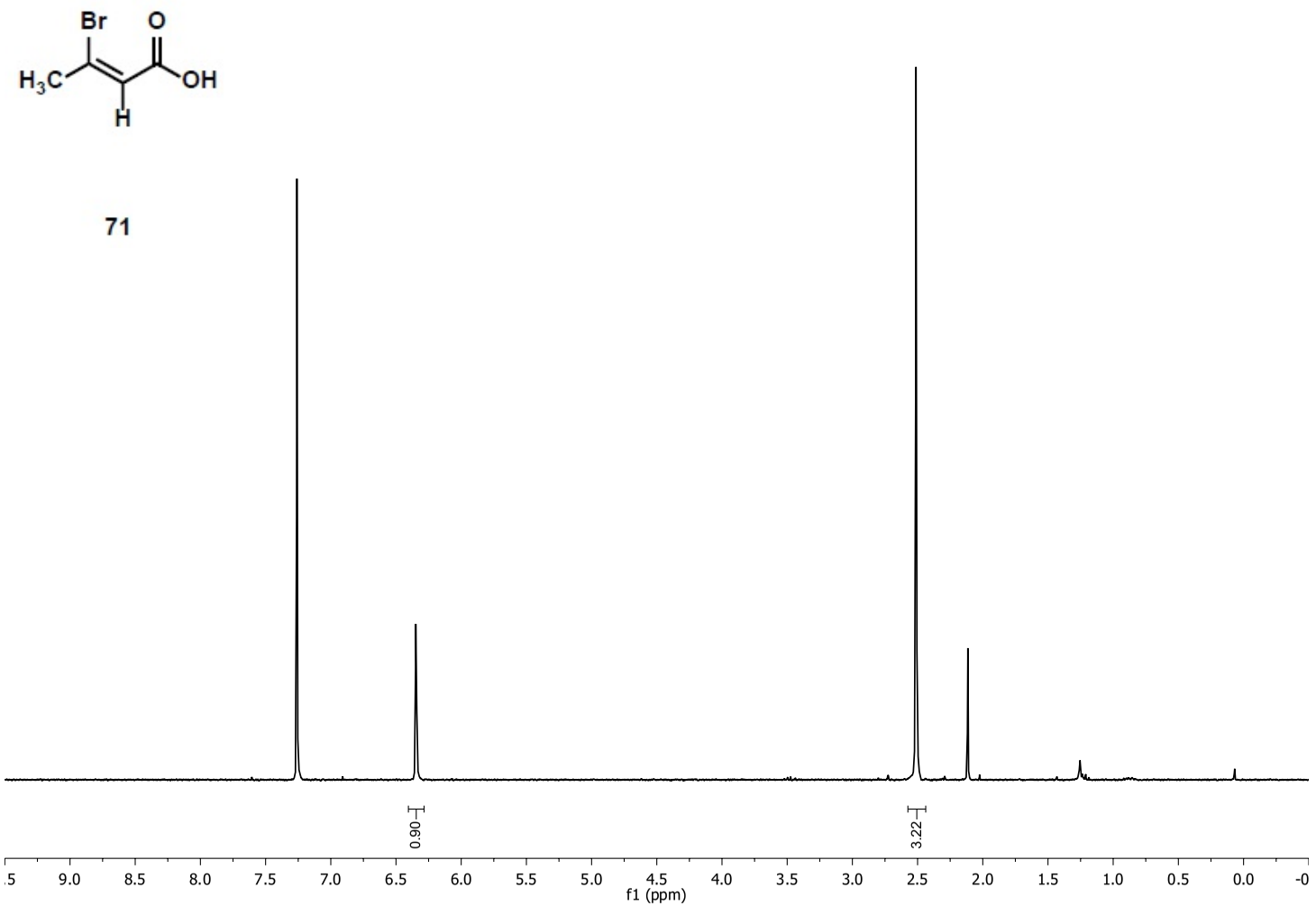

163.6
131.8
124.9
122.3
107.8
107.7
64.6
69.8
35.7
30.9
28.7
25.3
f1 (ppm)
47

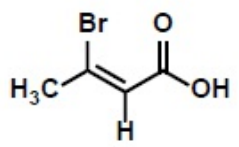
68
H3C
0.96
2.09
4.04
4.36
3.00
2.37
f1 (ppm)

H3C CH3
O
O
HO
70
0.96
2.00
4.36
2.08
2.12
2.71
2.94
3.29
f1 (ppm)

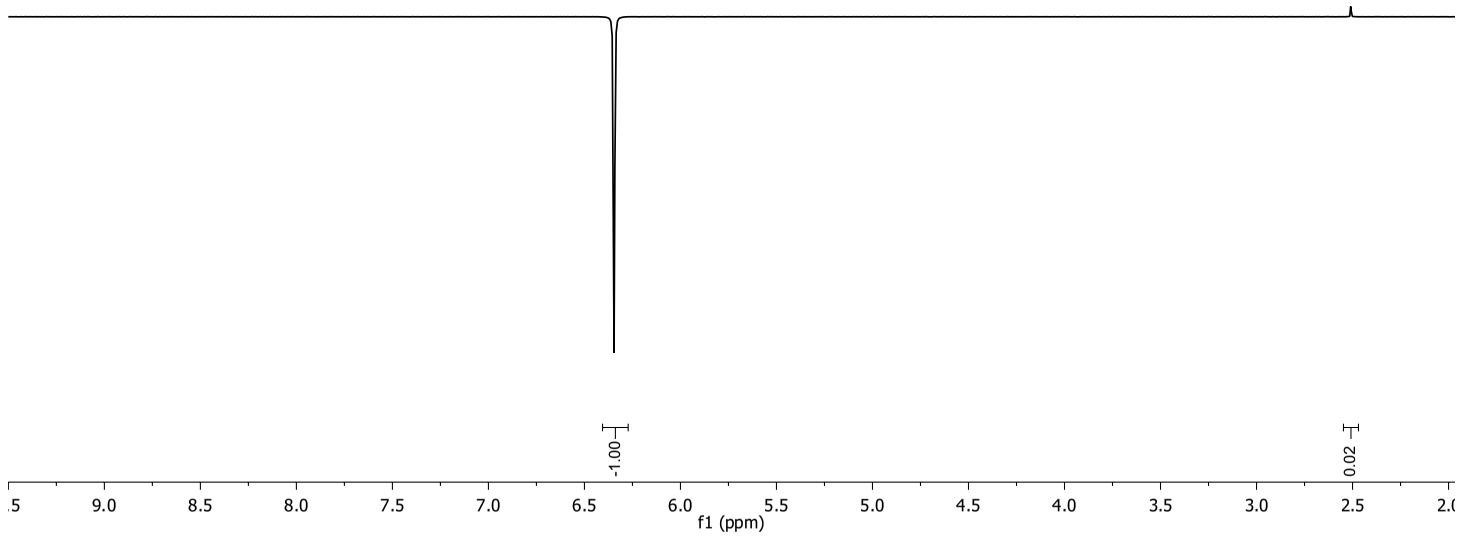

H3C CH3
O
O
HO
137.3
119.3
97.4
70.4
66.8
34.9
30.4
27.1
23.9
22.9
22.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

70


Br
O
H3C
OH
H
71
0.90
3.22
f1 (ppm)



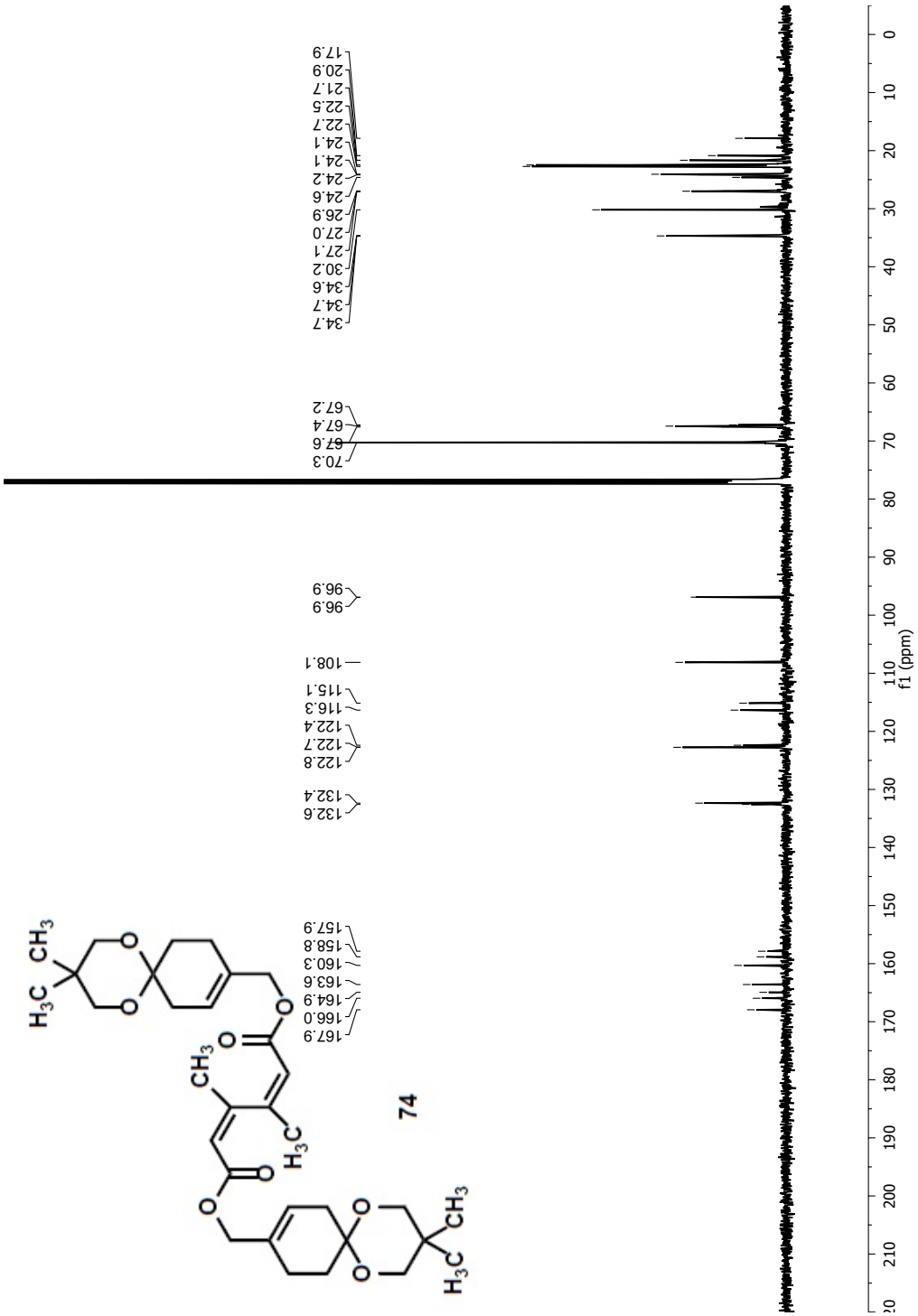
71

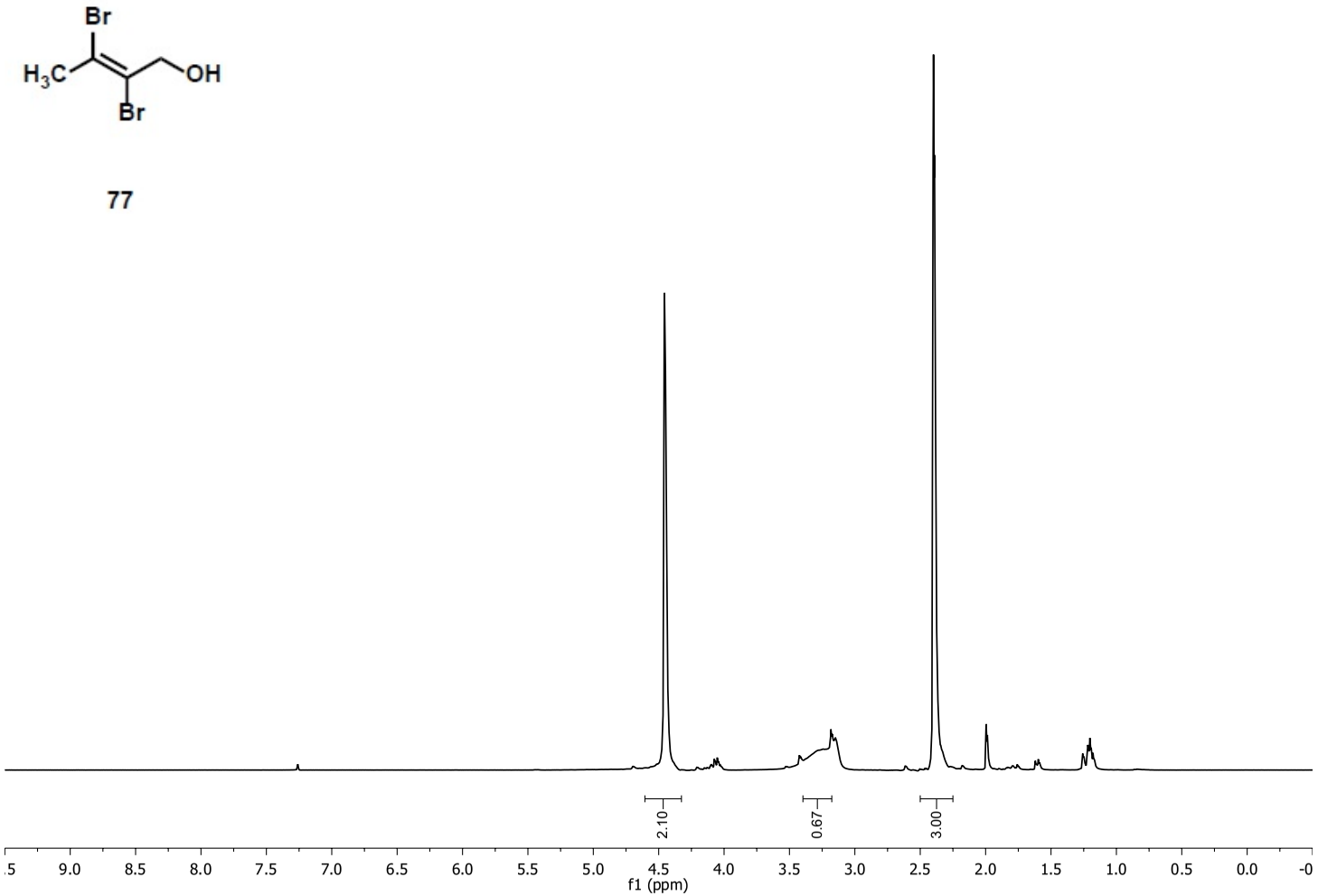


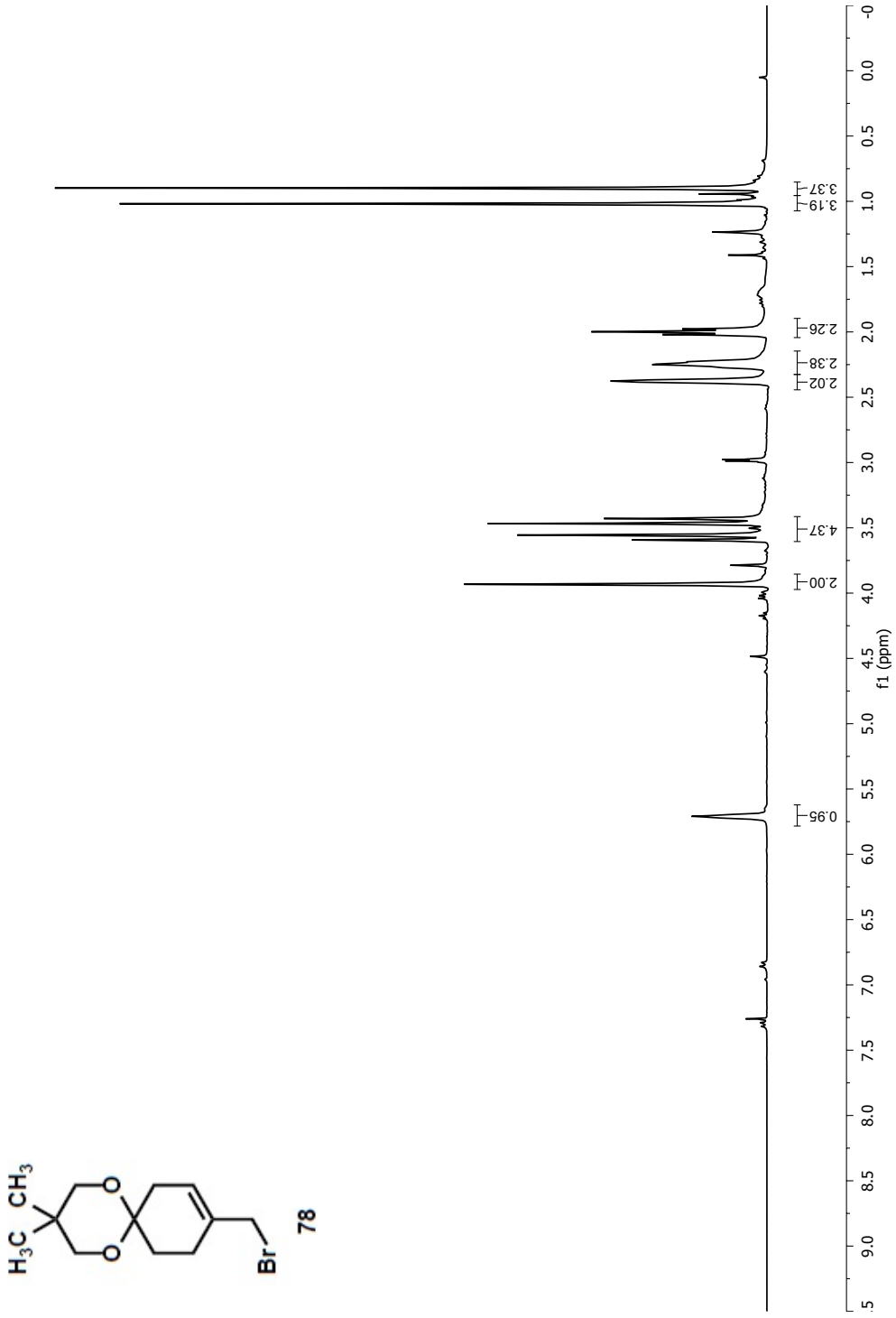
H3C CH3
O
O
O
O
Br
H
H3C
72
3.11
2.99
3.27
2.07
2.13
3.13
4.25
1.98
1.03
1.00
f1 (ppm)

H3C CH3
O
O
O
O
Br
H3C
72
164.1
137.0
132.4
123.1
120.0
97.1
70.4
67.9
34.8
31.2
30.4
27.2
24.3
22.9
22.6
f1 (ppm)

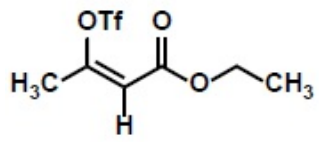
74
4.04
4.00
9.88
4.13
3.53
3.84
7.02
6.85
7.29
f1 (ppm)


74
f1 (ppm)


Br
H3C
OH
Br
77
2.10
0.67
3.00
f1 (ppm)

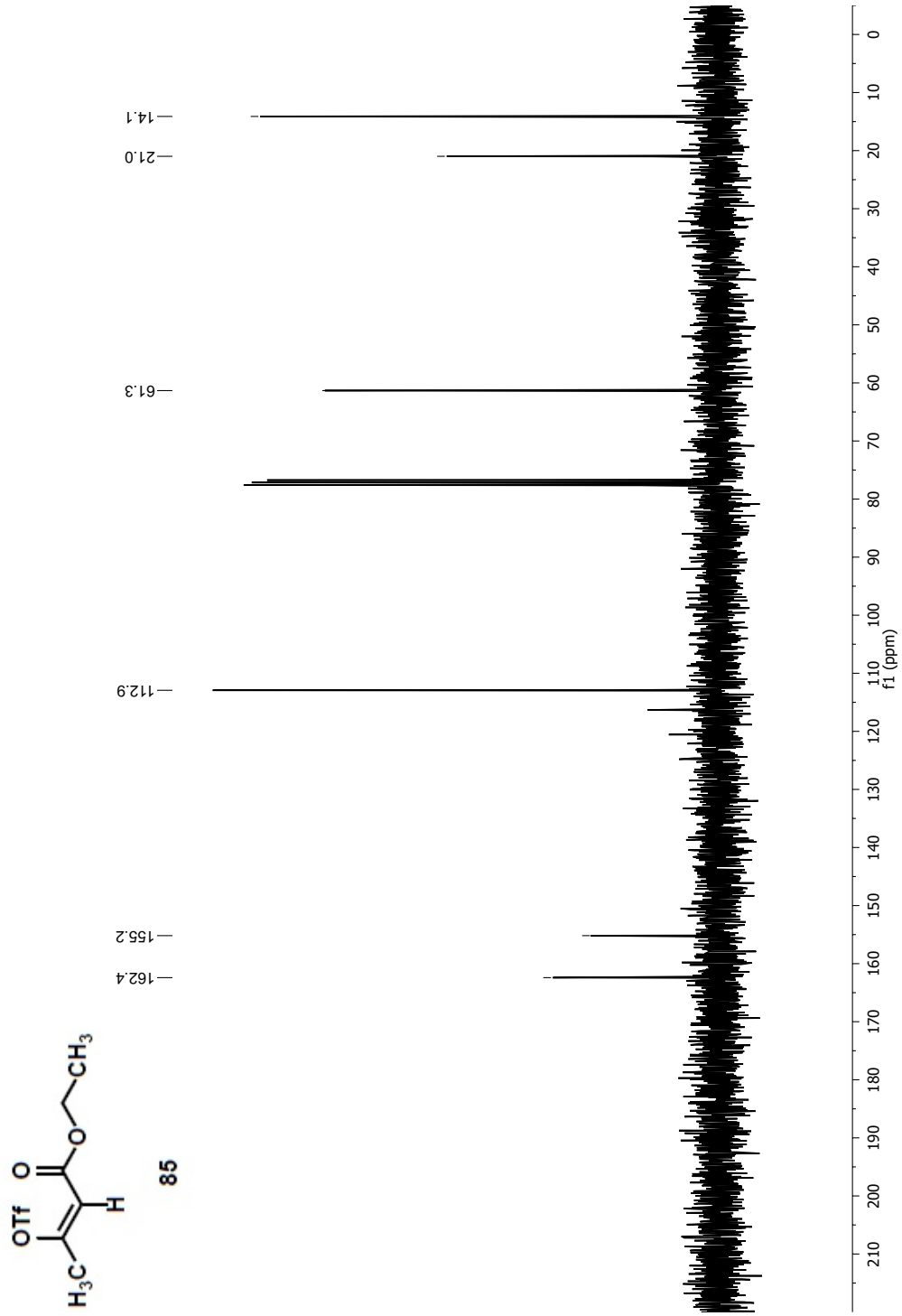

H3C CH3
O
O
Br
78
3.37
3.19
2.26
2.38
2.02
4.37
2.00
0.95
f1 (ppm)

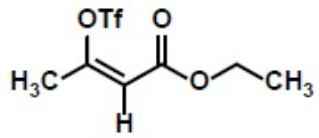
H3C
CH3
O
O
O
Br
Br
H3C
79
3.60
3.41
2.91
2.06
2.53
2.74
4.89
1.99
1.97
0.97
f1 (ppm)


OTf
O
H3C
O
CH3
H

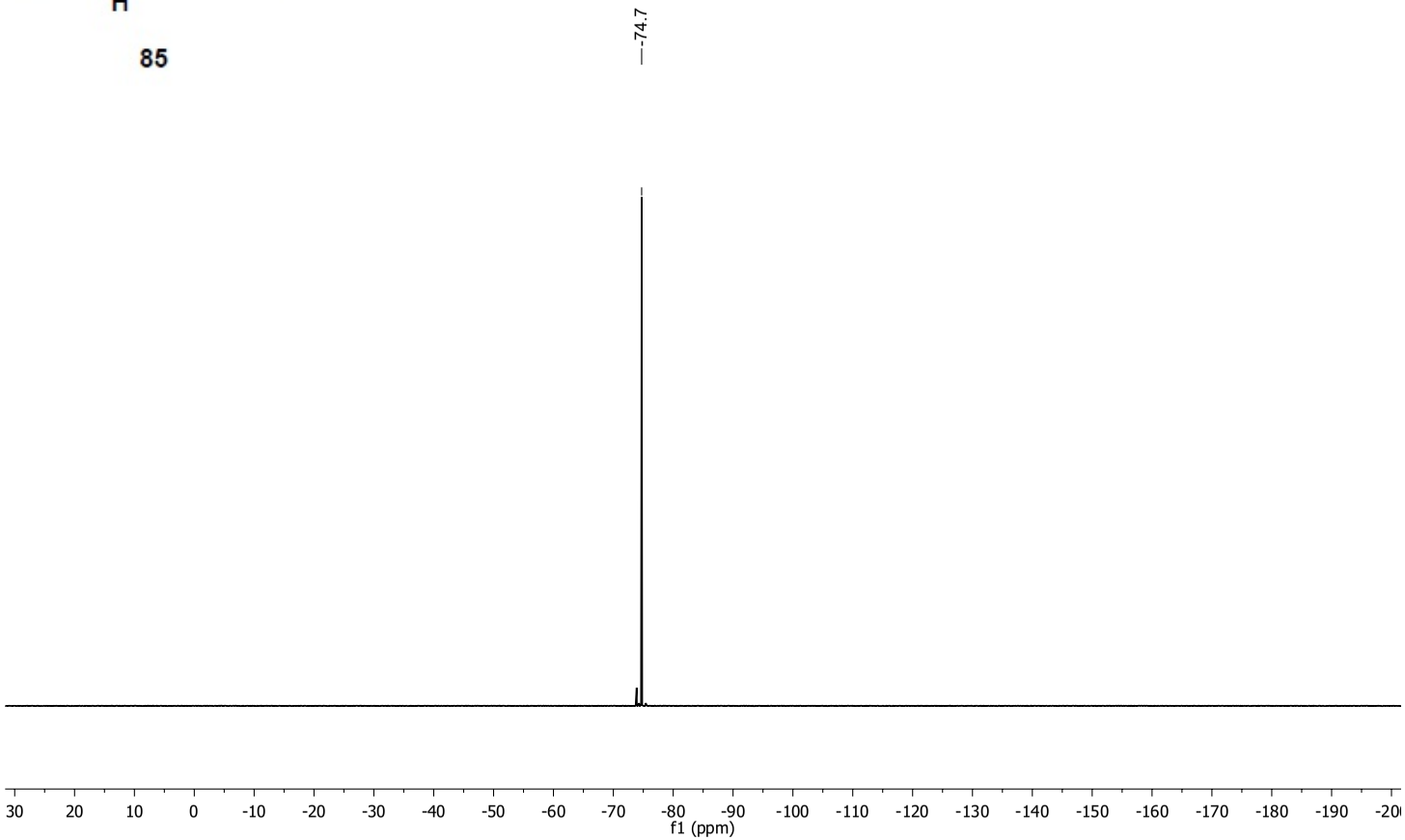
85

0.83
2.00
3.10
3.34
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

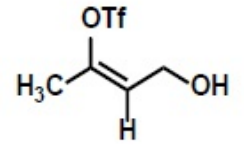

OTf
O
O
CH3
H
H3C
85
162.4
155.2
112.9
61.3
21.0
14.1
f1 (ppm)


OTf
O
H3C
O
CH3
H

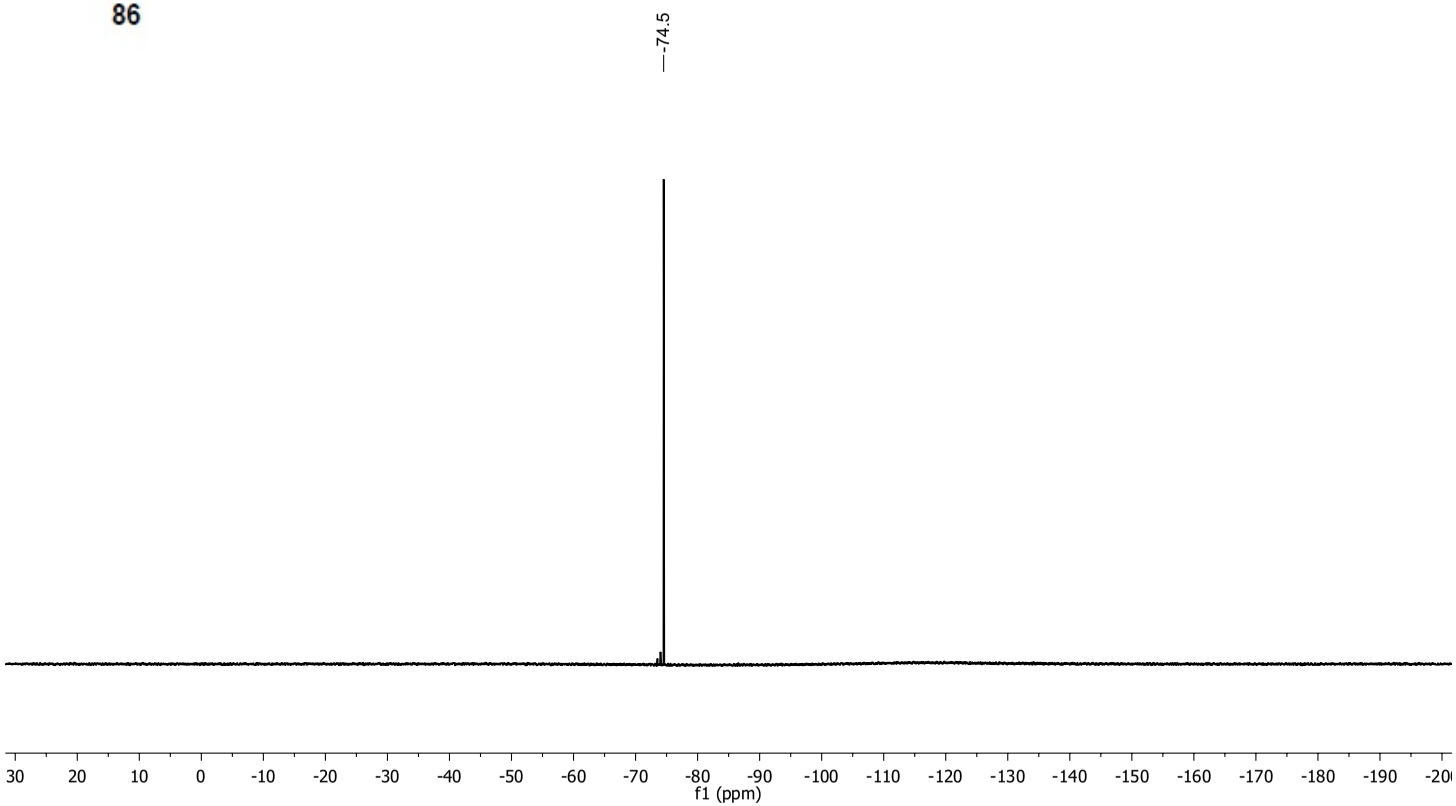
85


-74.7
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

OTf
OH
H
H3C
86
3.08
2.00
0.83
f1 (ppm)

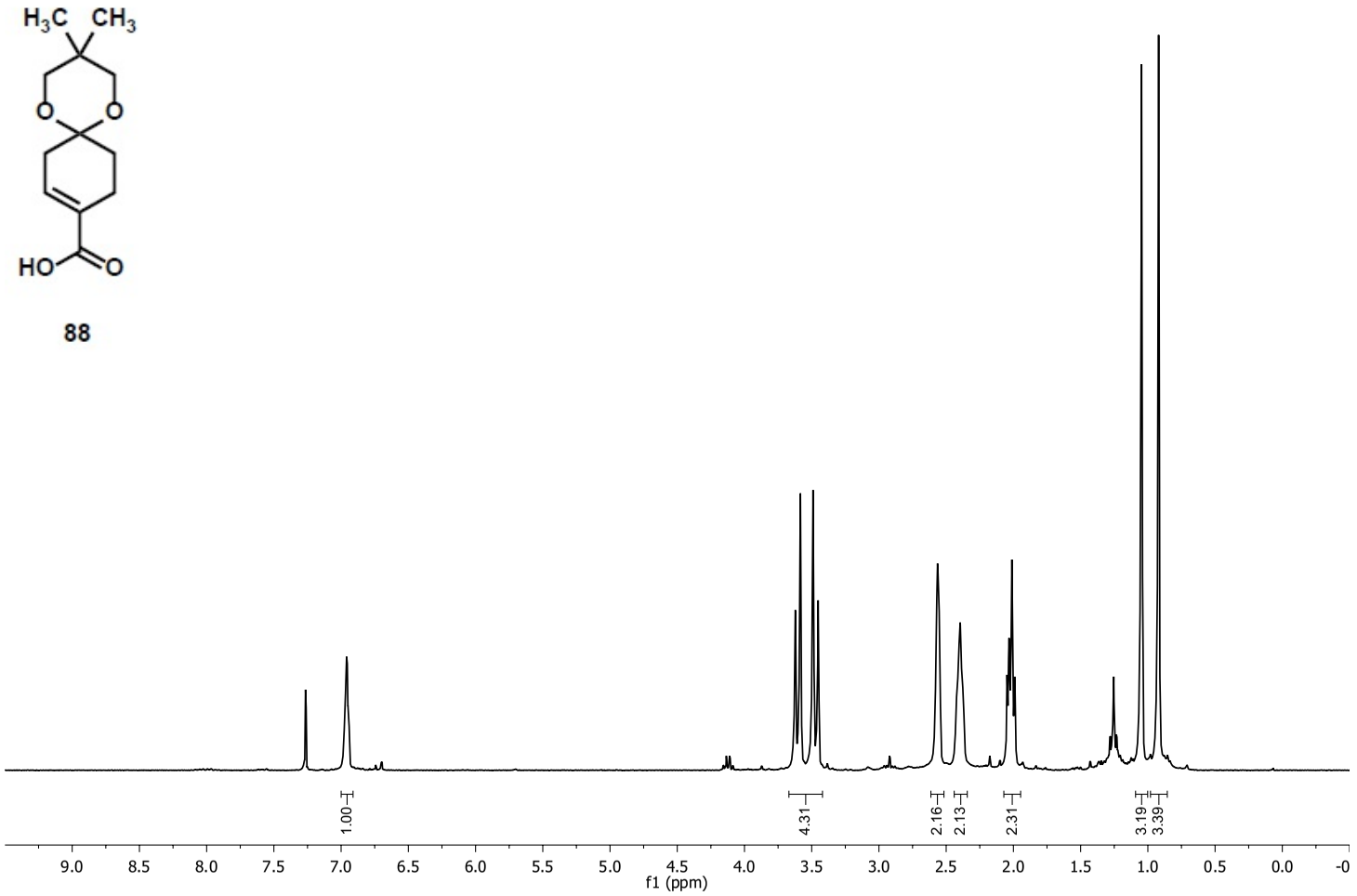

OTf
H3C
OH
H

86


-74.5
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

H3C CH3
O
O
O
H
87
0.92
1.00
4.30
2.09
2.10
2.31
3.32
3.41
f1 (ppm)

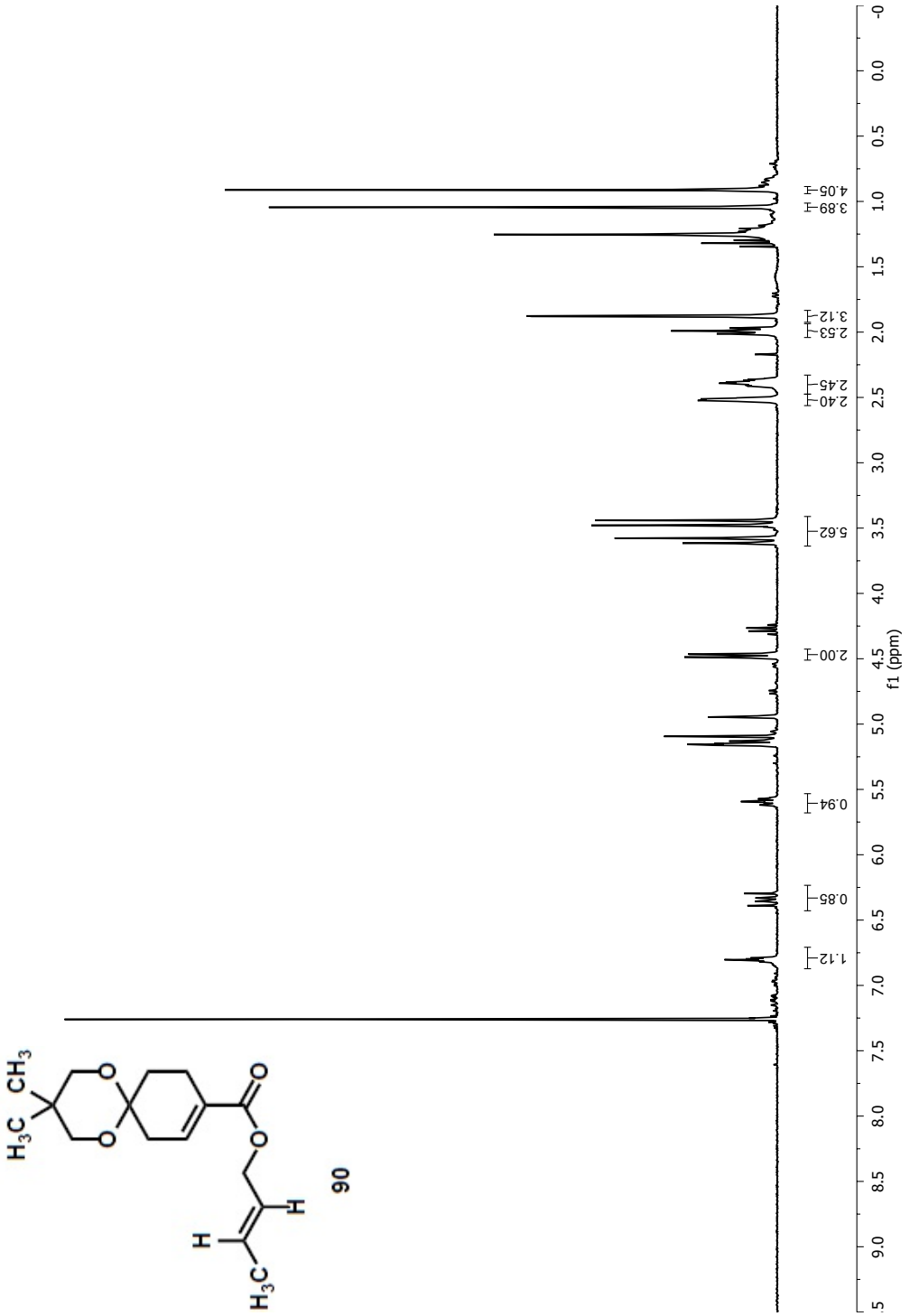
193.2
146.9
140.8
97.0
70.4
36.8
30.2
25.8
22.9
22.4
19.5
f1 (ppm)
H3C
CH3
O
O
O
H
87


H3C CH3
O
O
HO
O
88
1.00
4.31
2.16
2.13
2.31
3.19
3.39
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

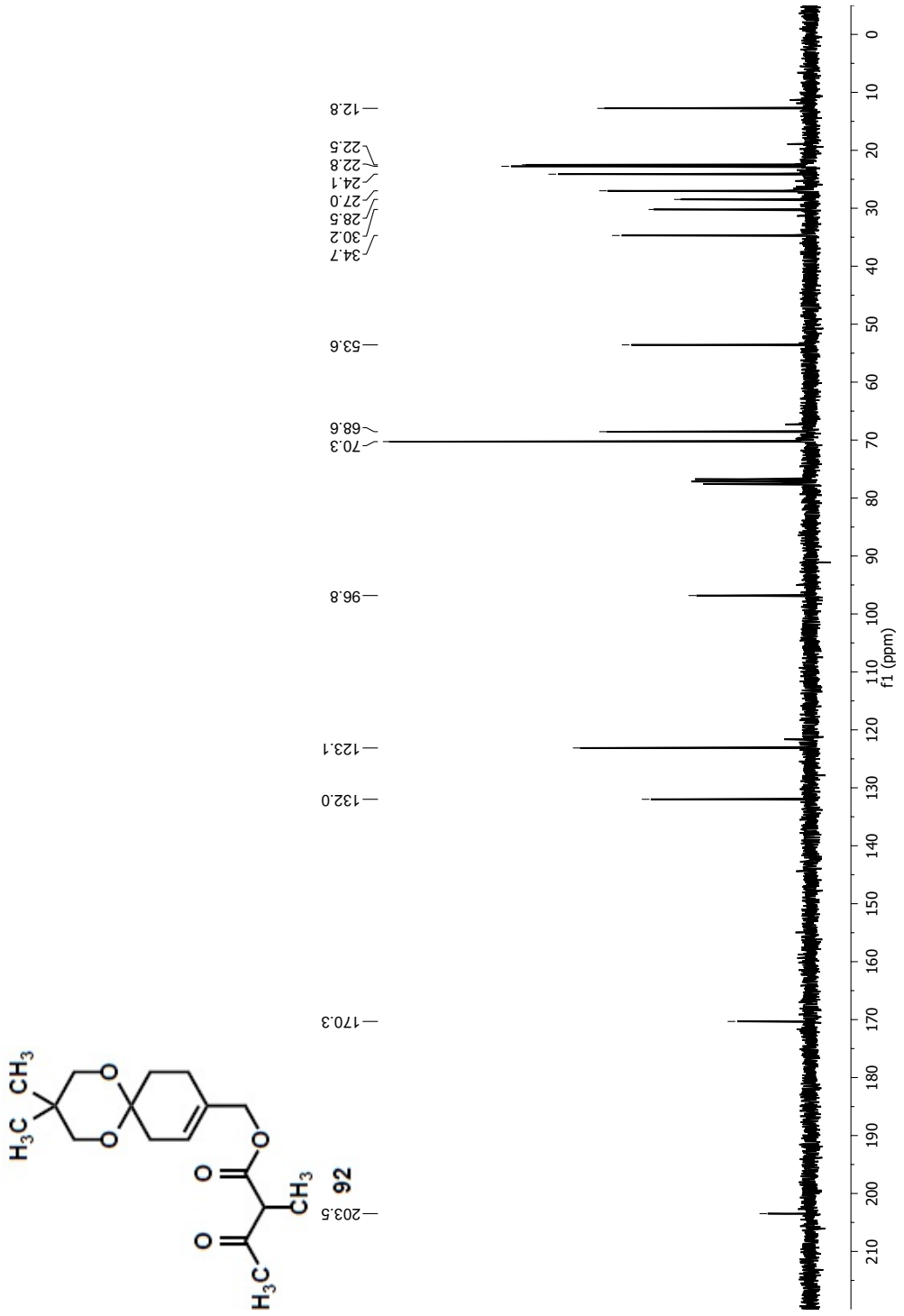
H3C CH3
O
O
HO
O
88
172.1
138.7
129.4
96.6
70.5
35.9
30.3
26.9
22.9
22.6
22.3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

H3C CH3
O
O
O
O
OTf
H
H3C
89
1.00
1.00
1.91
4.35
1.94
2.02
2.86
1.94
2.91
3.06
f1 (ppm)

-74.4
f1 (ppm)
89


H3C CH3
O
O
O
O
H
H
H3C
90
4.05
3.89
3.12
2.53
2.45
2.40
5.62
2.00
0.94
0.85
1.12
f1 (ppm)

H3C CH3
O
O
O
O
CH3
O
H3C
92
1.02
2.00
5.21
2.21
2.57
2.30
2.88
2.93
3.21
3.56
f1 (ppm)

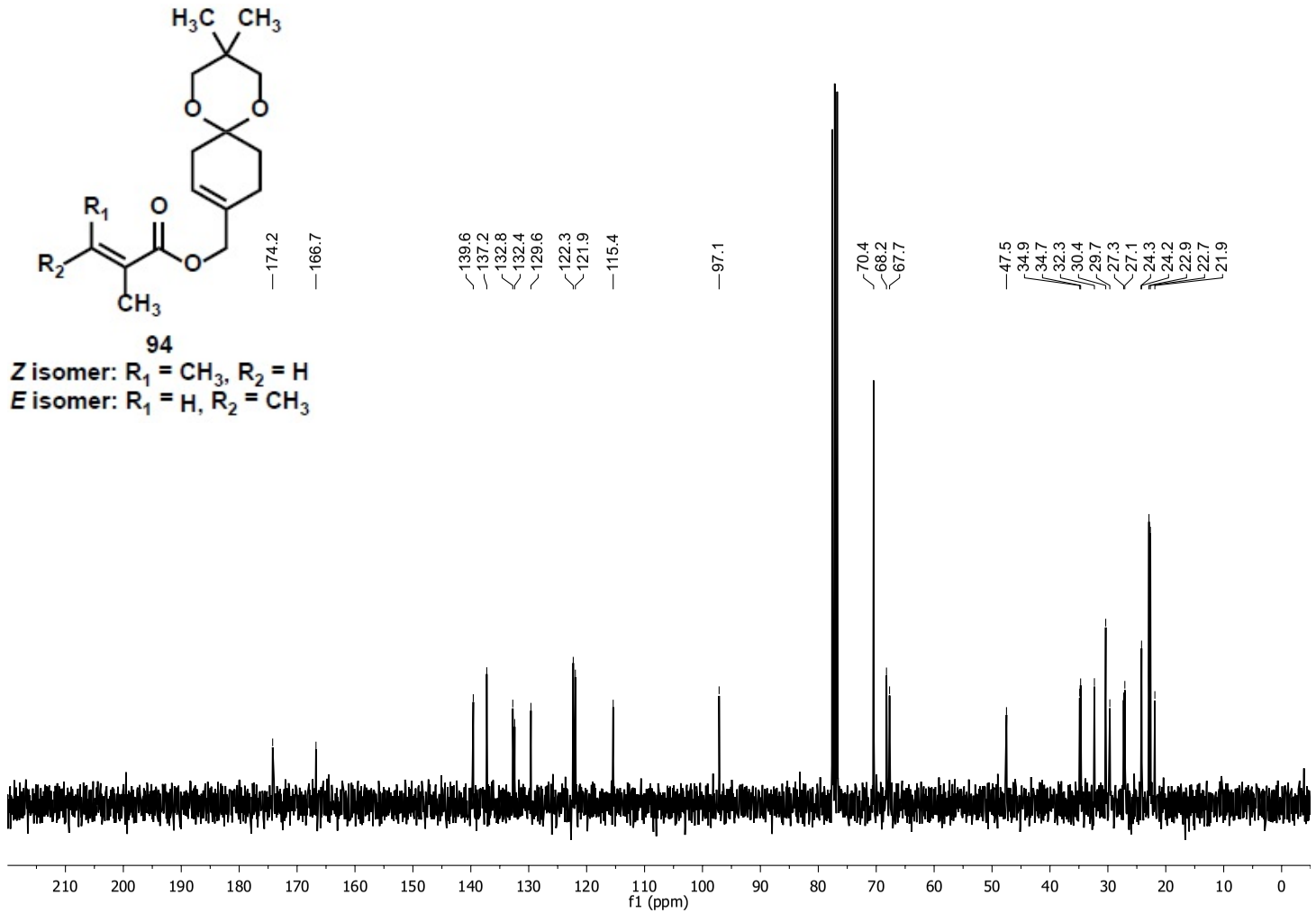

92
203.5
170.3
132.0
123.1
96.8
70.3
68.6
53.6
34.7
30.2
28.5
27.0
24.1
22.8
22.5
12.8
f1 (ppm)

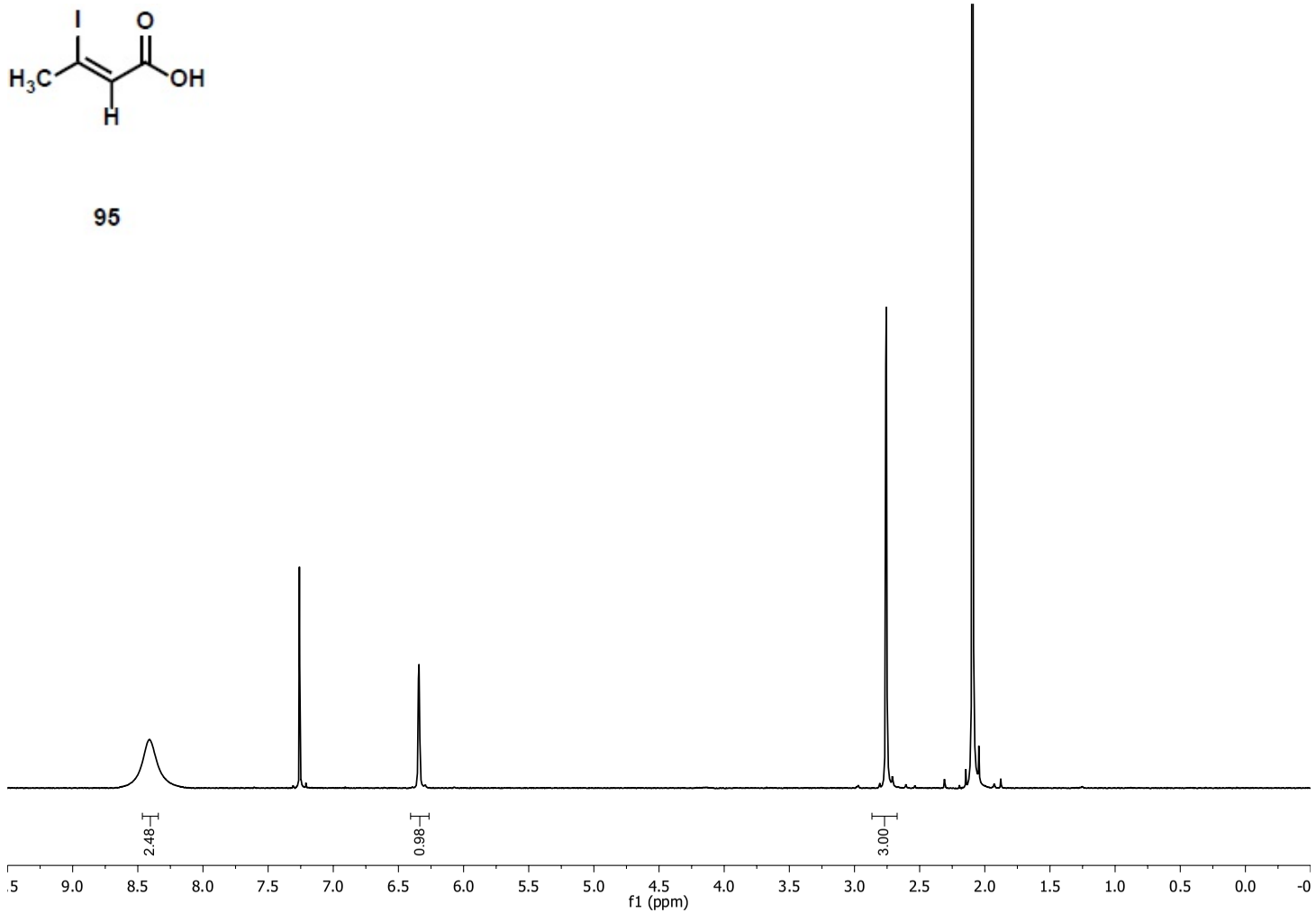
H3C CH3
O
O
O
OTf O
CH3
H3C
93
3.77
3.16
5.11
5.07
2.07
4.78
2.00
0.96
f1 (ppm)

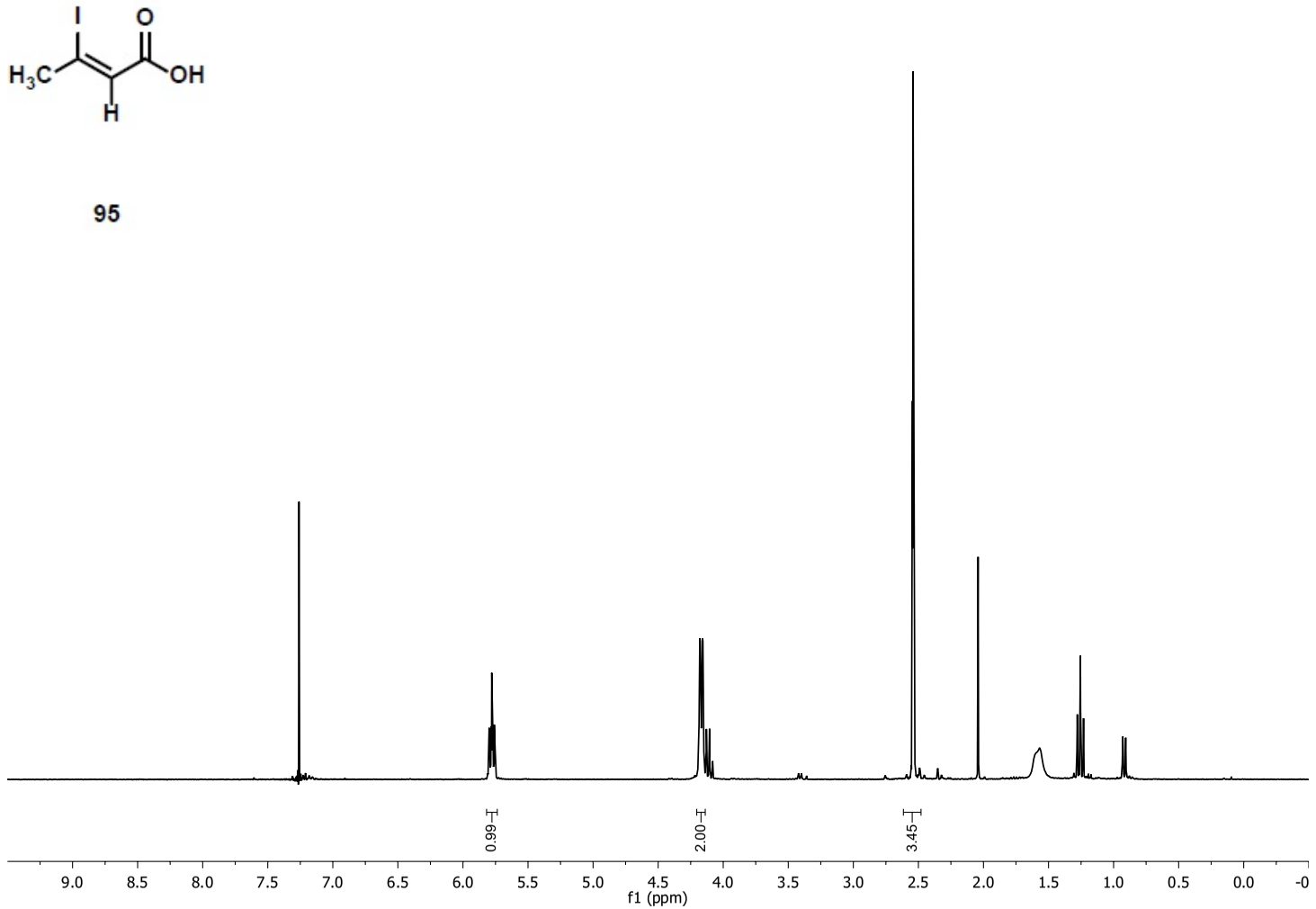
165.1
147.8
131.9
123.4
121.8
96.9
70.3
68.8
34.8
30.3
27.0
24.2
22.8
22.5
17.7
15.3
f1 (ppm)
93

-74.7
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)
H3C
CH3
O
O
O
O
OTf
CH3
H3C
93

H3C CH3
O
O
O
O
R1
R2
CH3
94
Z isomer: R1 = CH3, R2 = H
E isomer: R1 = H, R2 = CH3
1.06
1.00
2.24
4.50
9.70
5.24
2.70
6.50
4.95
7.04
8.17
f1 (ppm)

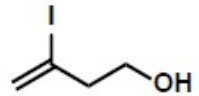

H3C CH3
O
O
R1
O
R2
O
CH3
94
Z isomer: R1 = CH3, R2 = H
E isomer: R1 = H, R2 = CH3
174.2
166.7
139.6
137.2
132.8
132.4
129.6
122.3
121.9
115.4
97.1
70.4
68.2
67.7
47.5
34.9
34.7
32.3
30.4
29.7
27.3
27.1
24.3
24.2
22.9
22.7
21.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


I
O
H3C
OH
H
95
2.48
0.98
3.00
f1 (ppm)

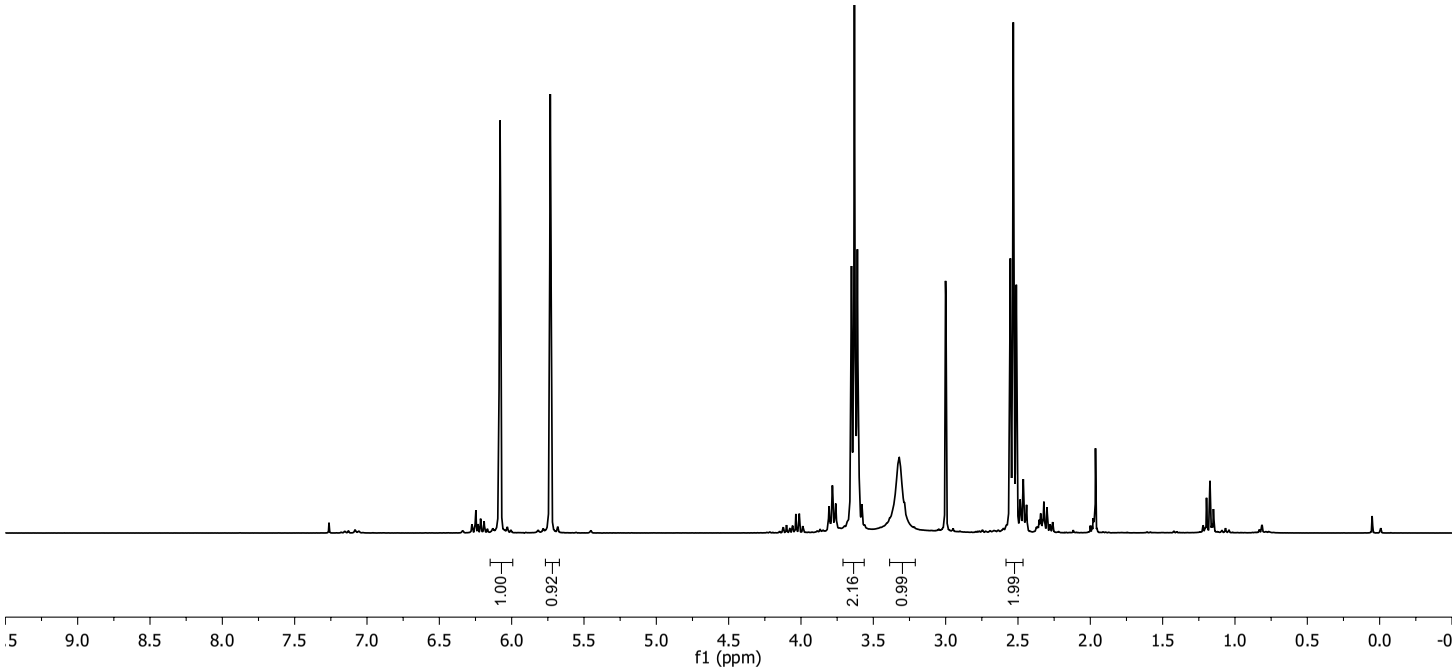

I
O
H3C
OH
H
95
0.99
2.00
3.45
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

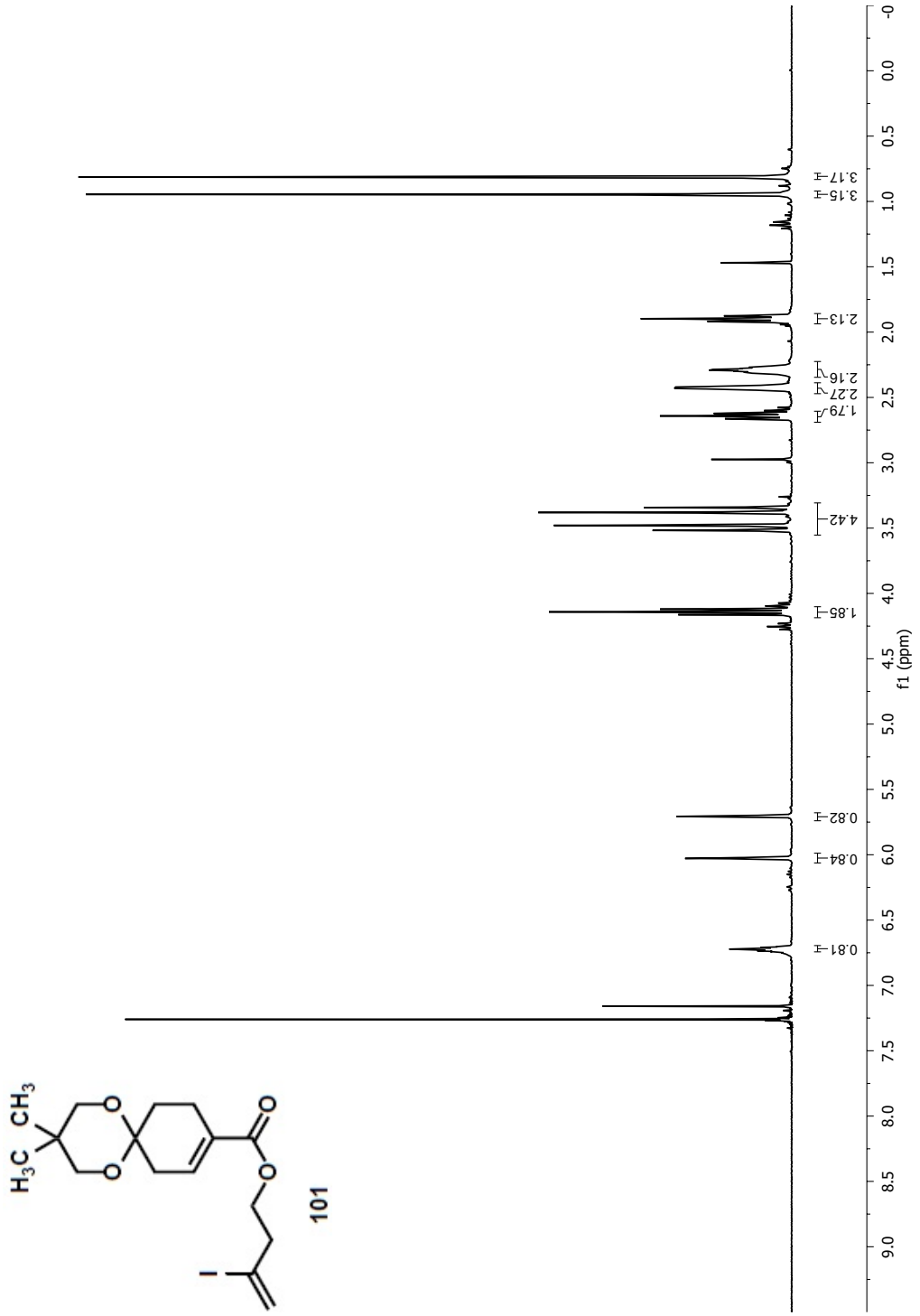
H3C CH3
O
O
O
O
H
I
H3C
98
0.97
0.88
2.00
4.36
5.07
2.15
2.13
3.17
3.23
f1 (ppm)

166.6
136.5
130.3
129.7
104.2
96.6
70.5
68.8
35.8
33.9
30.3
26.8
22.9
22.7
22.6
f1 (ppm)
98


I
OH

100

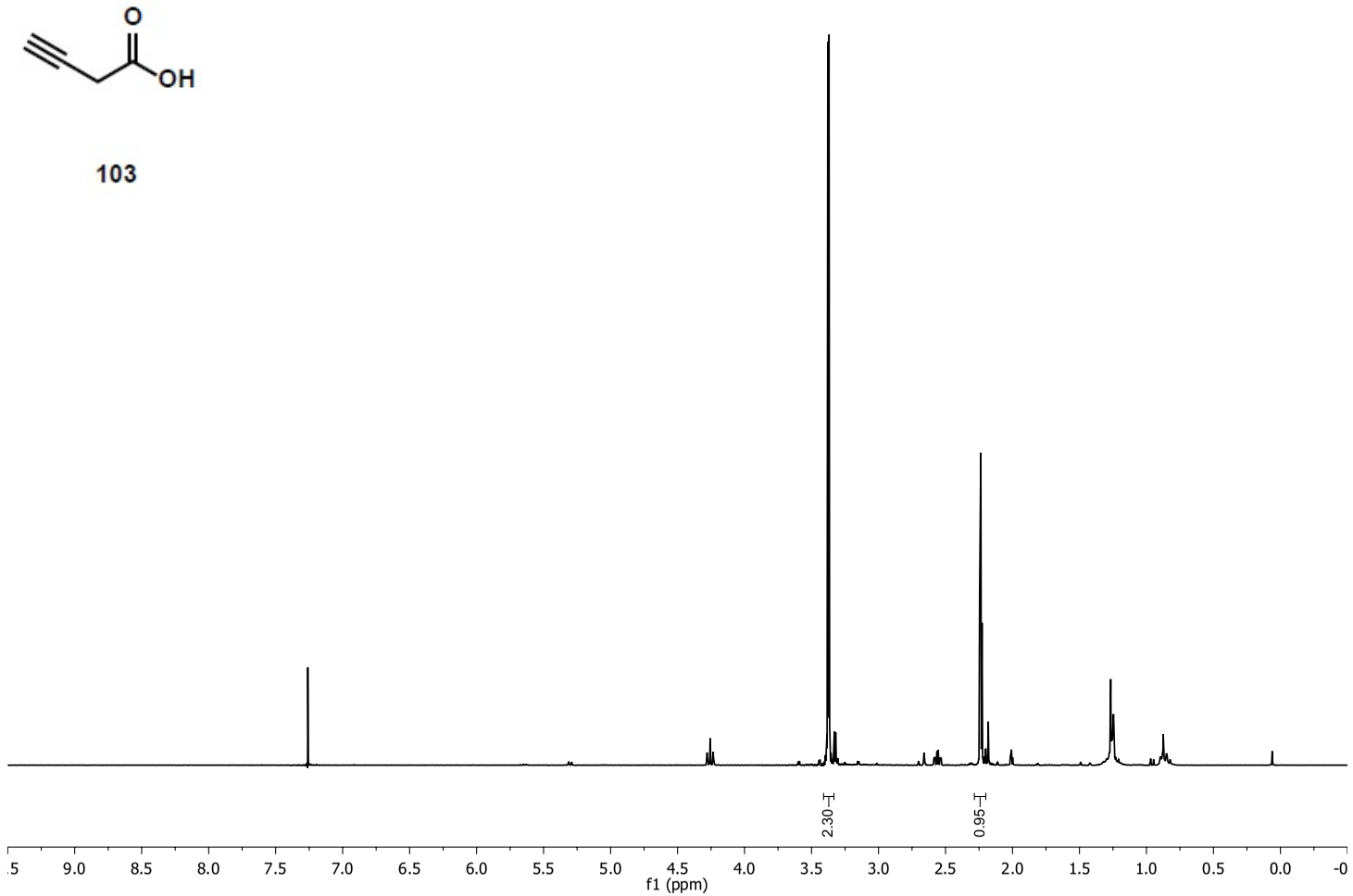

1.00
0.92
2.16
0.99
1.99
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


H3C CH3
O
O
O
O
I
101
3.17
3.15
2.13
2.16
2.27
1.79
4.42
1.85
0.82
0.84
0.81
f1 (ppm)

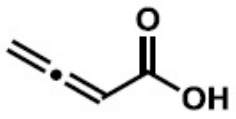
166.6
136.3
129.8
128.5
128.1
105.9
96.6
70.5
62.7
44.5
35.8
30.3
26.8
22.9
22.7
22.6
f1 (ppm)
101

H3C CH3
O
O
O
O
O
O
O
O
H3C CH3
102
2.00
1.54
1.41
4.45
10.69
2.90
4.85
4.99
5.49
9.24
8.35
f1 (ppm)

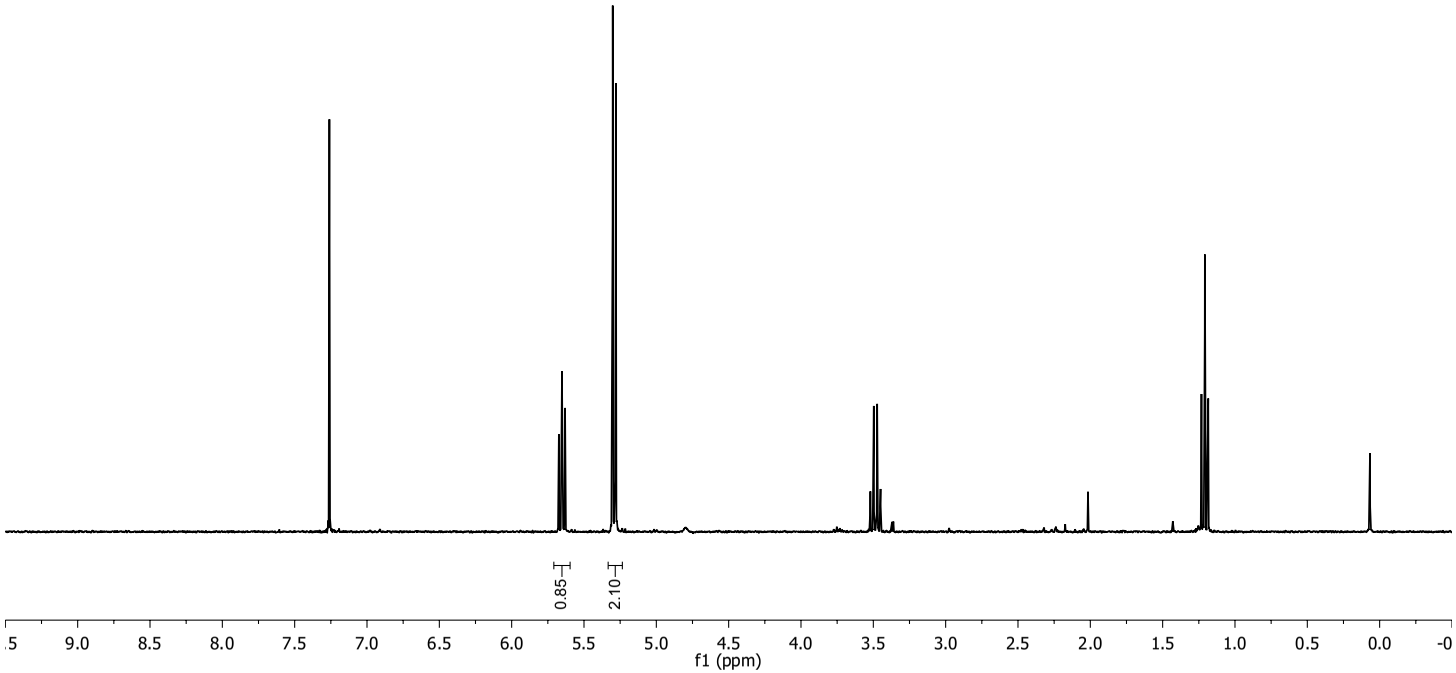
H3C CH3
O
O
O
O
O
O
O
O
H3C CH3
102
166.8
142.7
136.0
130.0
114.6
96.7
70.5
63.4
35.8
33.4
30.3
26.9
22.9
22.7
22.6
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

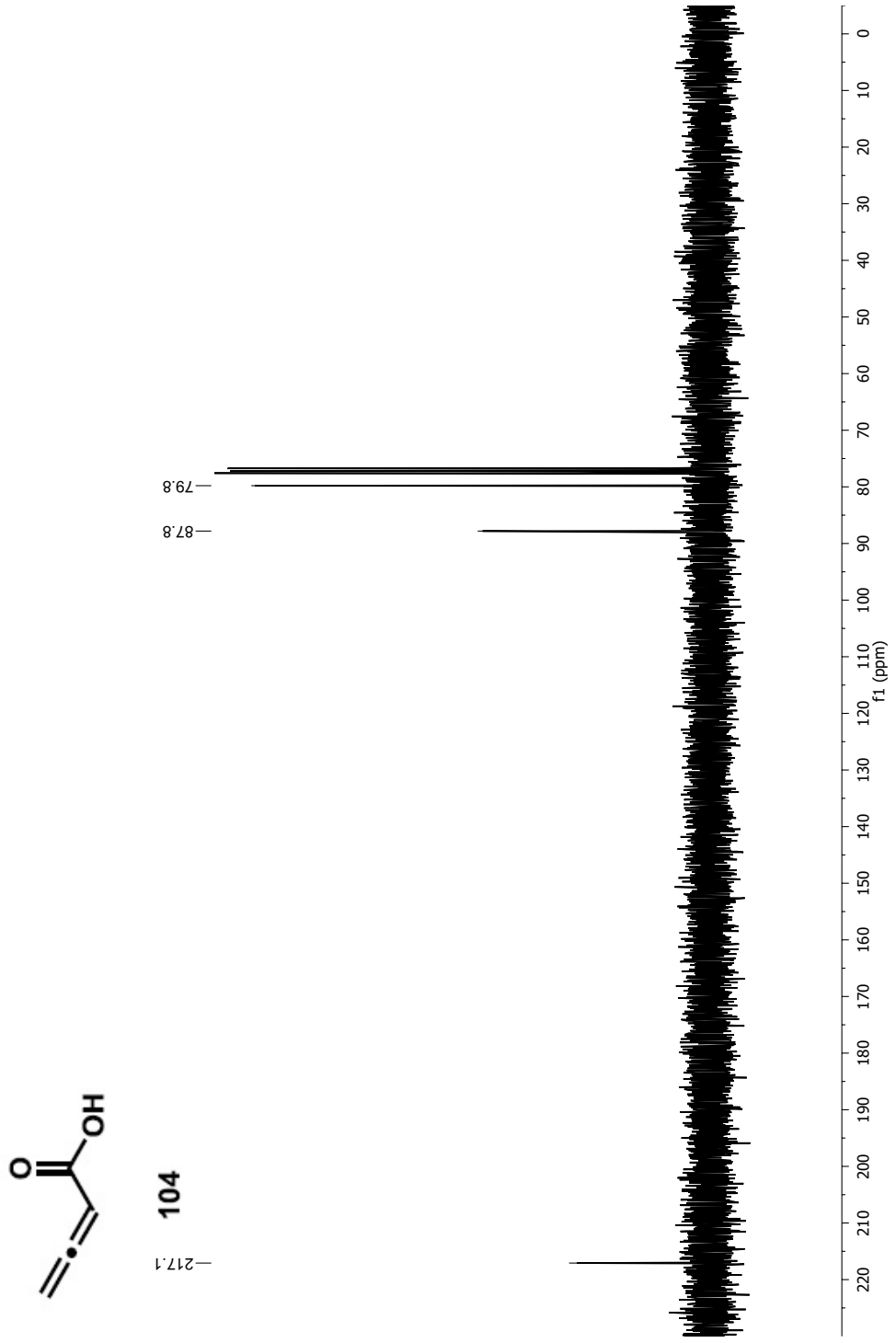

O
OH
103
2.30
0.95
f1 (ppm)

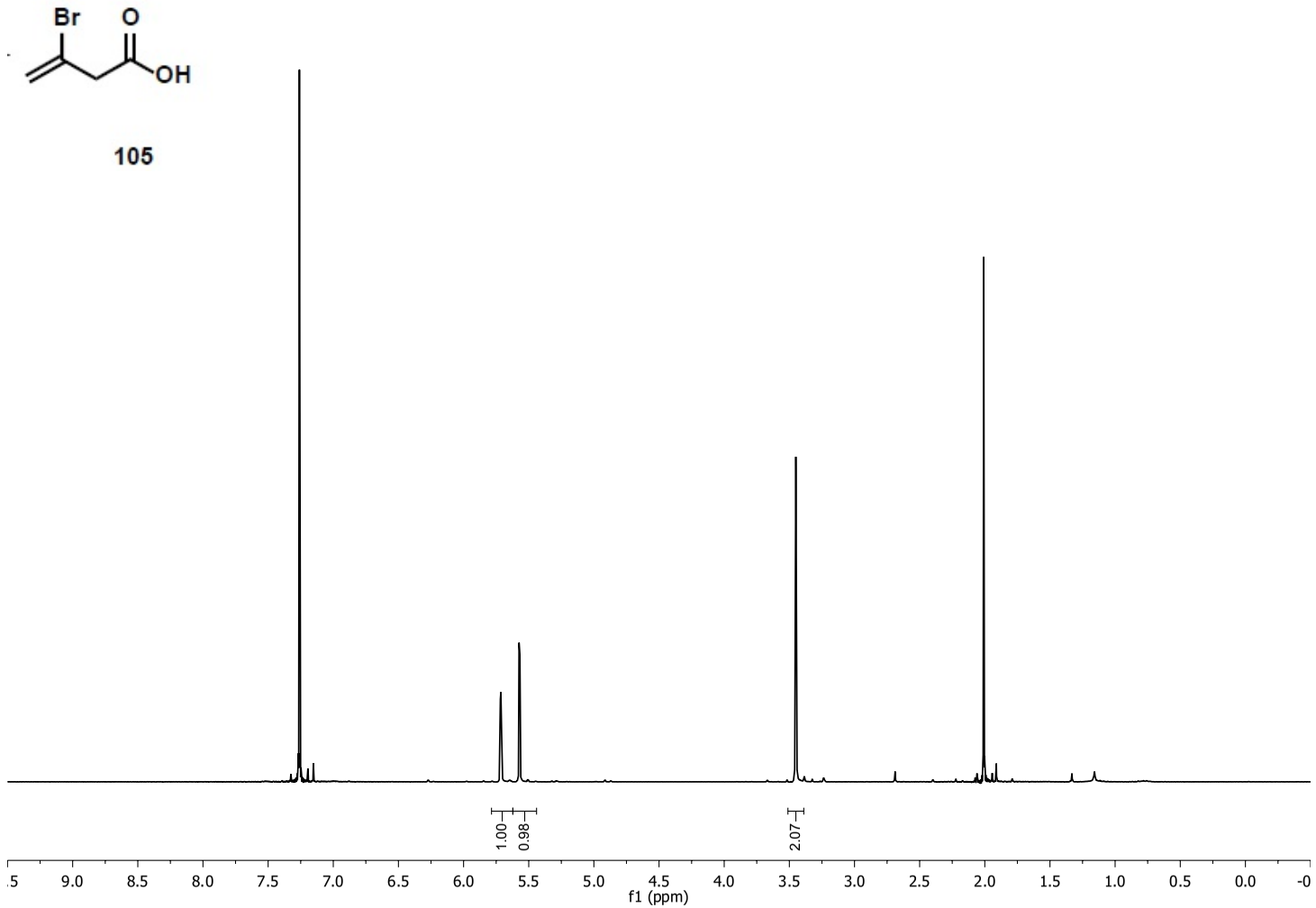
O
OH
103
174.3
74.9
72.5
25.7
f1 (ppm)


O
OH

104


0.85
2.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


104
217.1
87.8
79.8
f1 (ppm)


Br
O
OH
105
1.00
0.98
2.07
f1 (ppm)

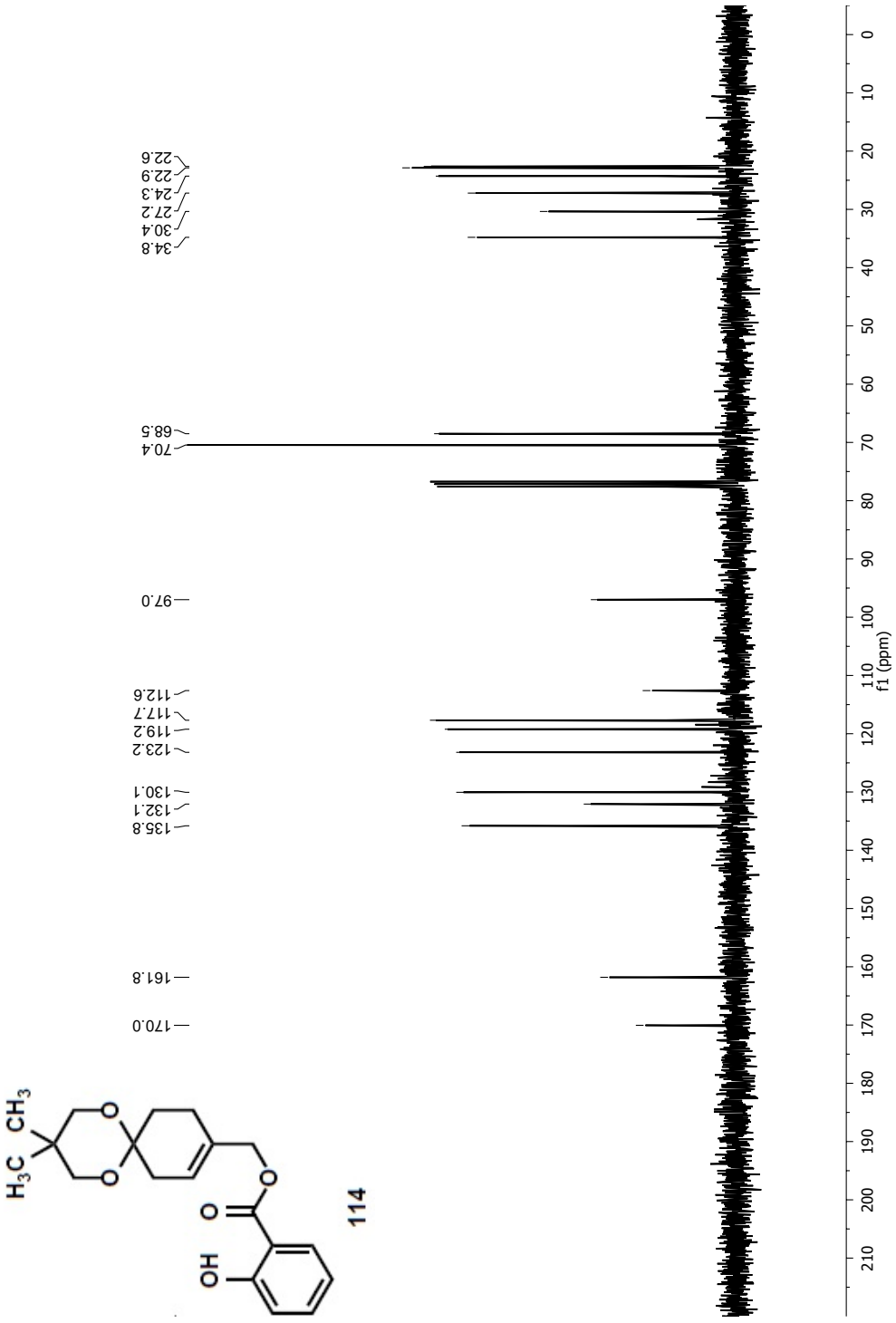
H3C CH3
O
O
O
O
Cl
107
3.20
3.12
2.79
2.17
2.12
1.09
4.38
1.99
1.04
1.12
f1 (ppm)

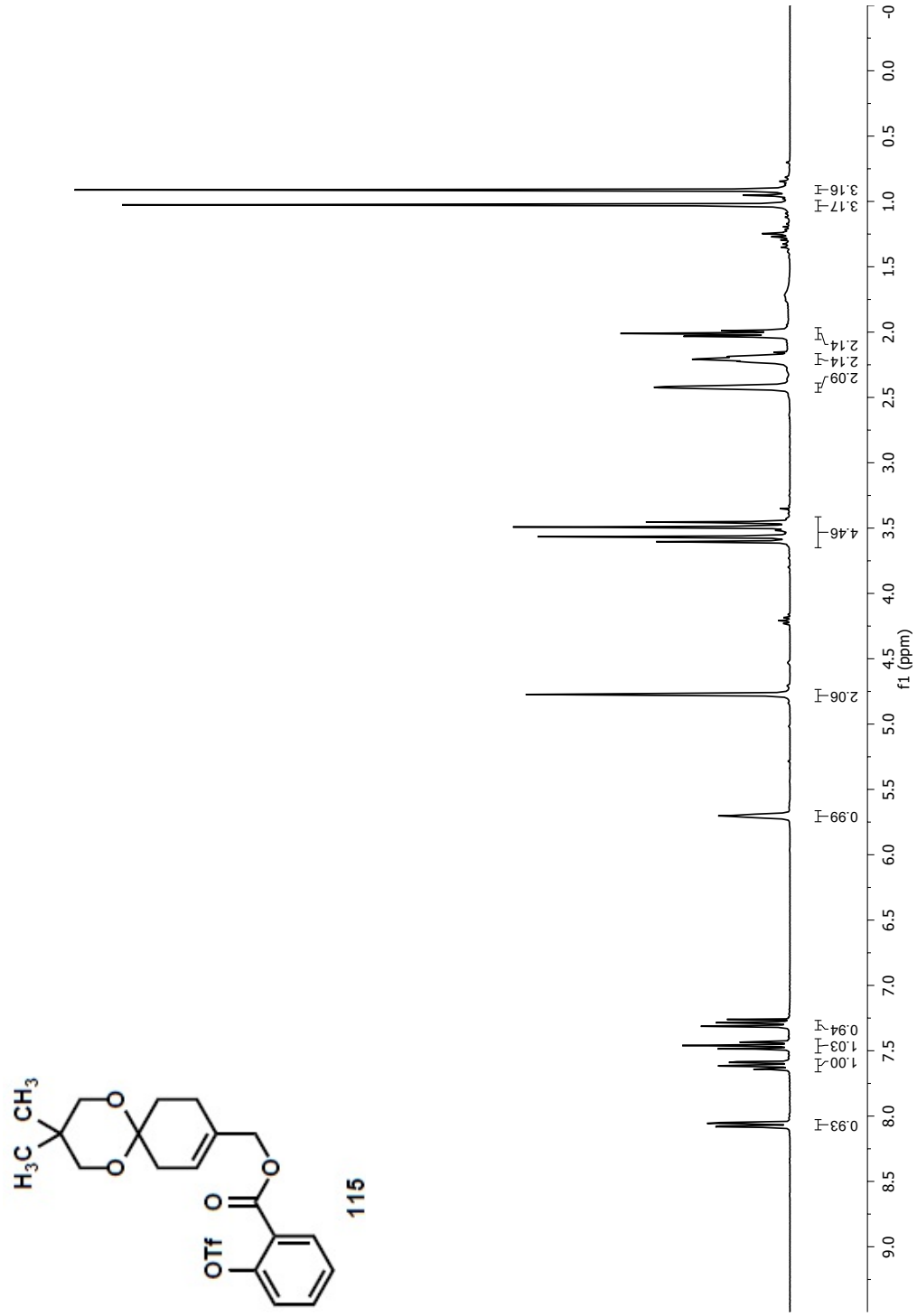
168.6
134.3
132.1
131.7
123.8
123.0
116.7
96.9
96.9
70.3
69.0
68.5
44.7
34.8
34.7
30.3
27.1
27.0
24.1
24.1
22.8
22.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)
H3C CH3
O
O
O
O
Cl
107

H3C CH3
O
O
O
O
I
111
0.91
0.97
1.05
1.00
1.04
2.13
4.58
2.18
2.22
2.83
3.08
3.01
f1 (ppm)

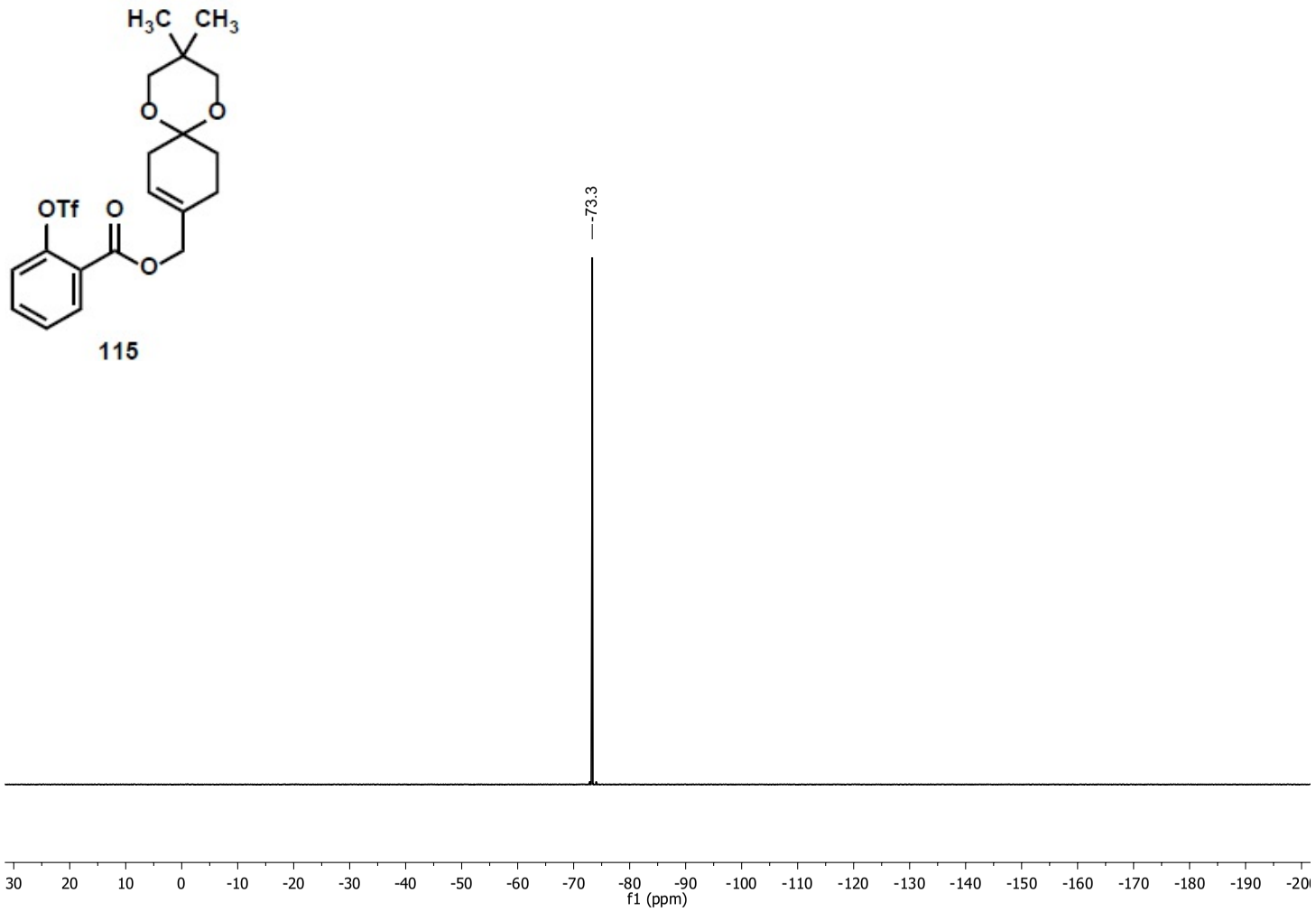
H3C CH3
O
O
O
O
113
1.94
2.14
1.00
1.06
2.20
4.68
2.21
2.18
2.29
3.16
3.14
f1 (ppm)

H3C CH3
O
O
O
O
OH
114
3.61
2.60
2.37
2.21
4.63
2.17
1.04
0.93
1.04
1.00
0.96
0.80
f1 (ppm)

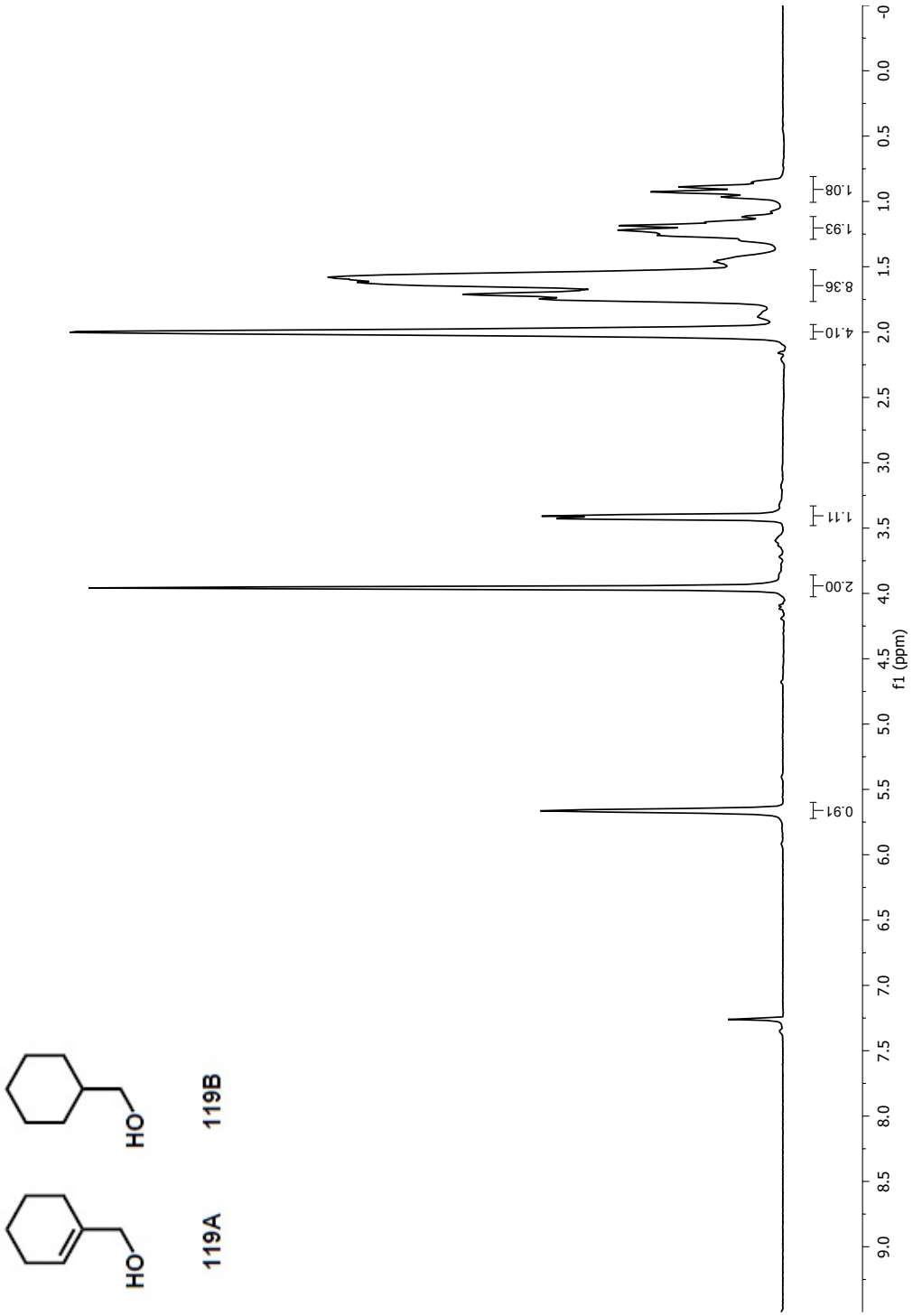

H3C CH3
O
O
O
O
OH
114
170.0
161.8
135.8
132.1
130.1
123.2
119.2
117.7
112.6
97.0
70.4
68.5
34.8
30.4
27.2
24.3
22.9
22.6
f1 (ppm)

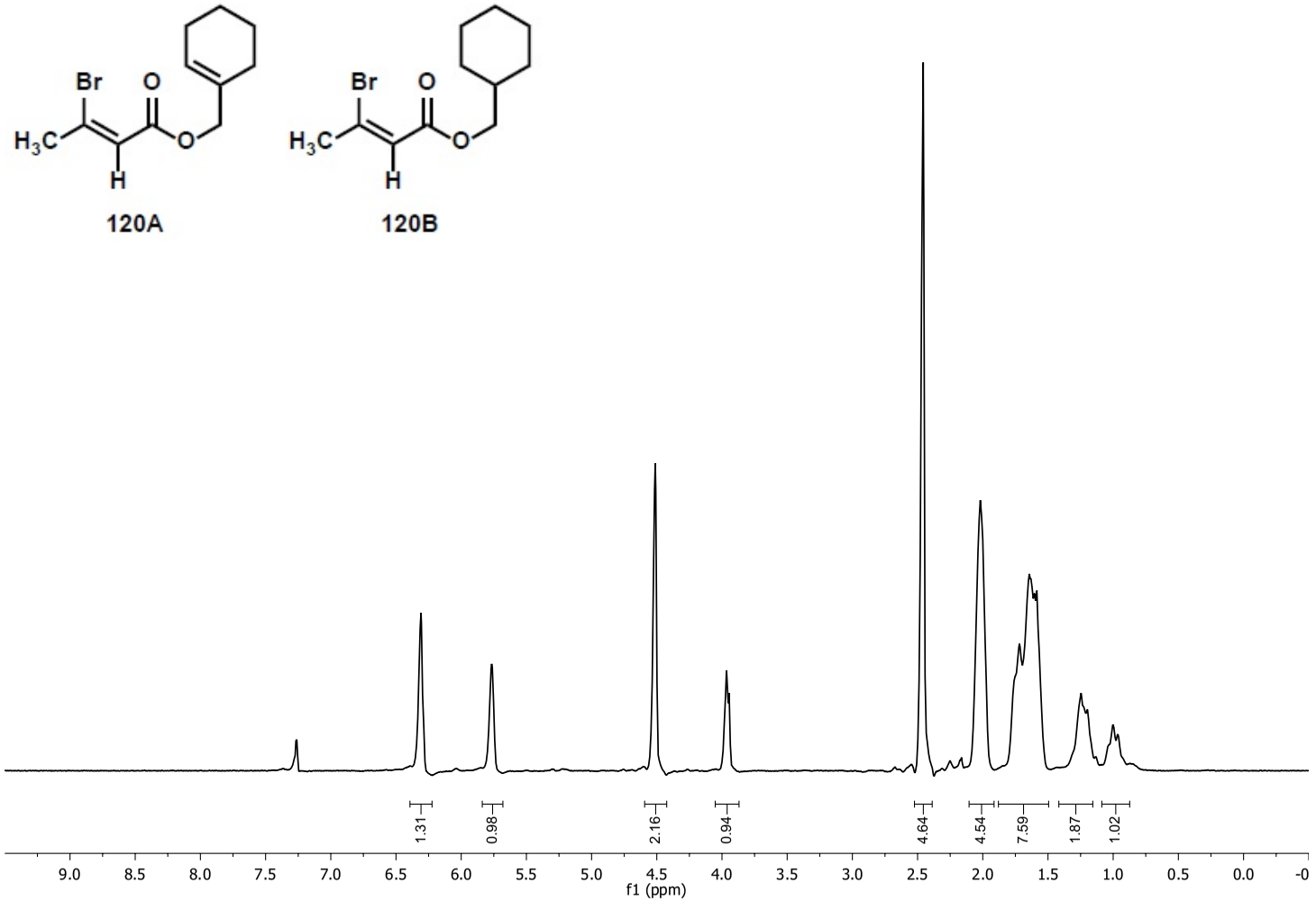

H3C CH3
O
O
O
O
OTf
115
3.16
3.17
2.14
2.14
2.09
4.46
2.06
0.99
0.94
1.03
1.00
0.93
f1 (ppm)

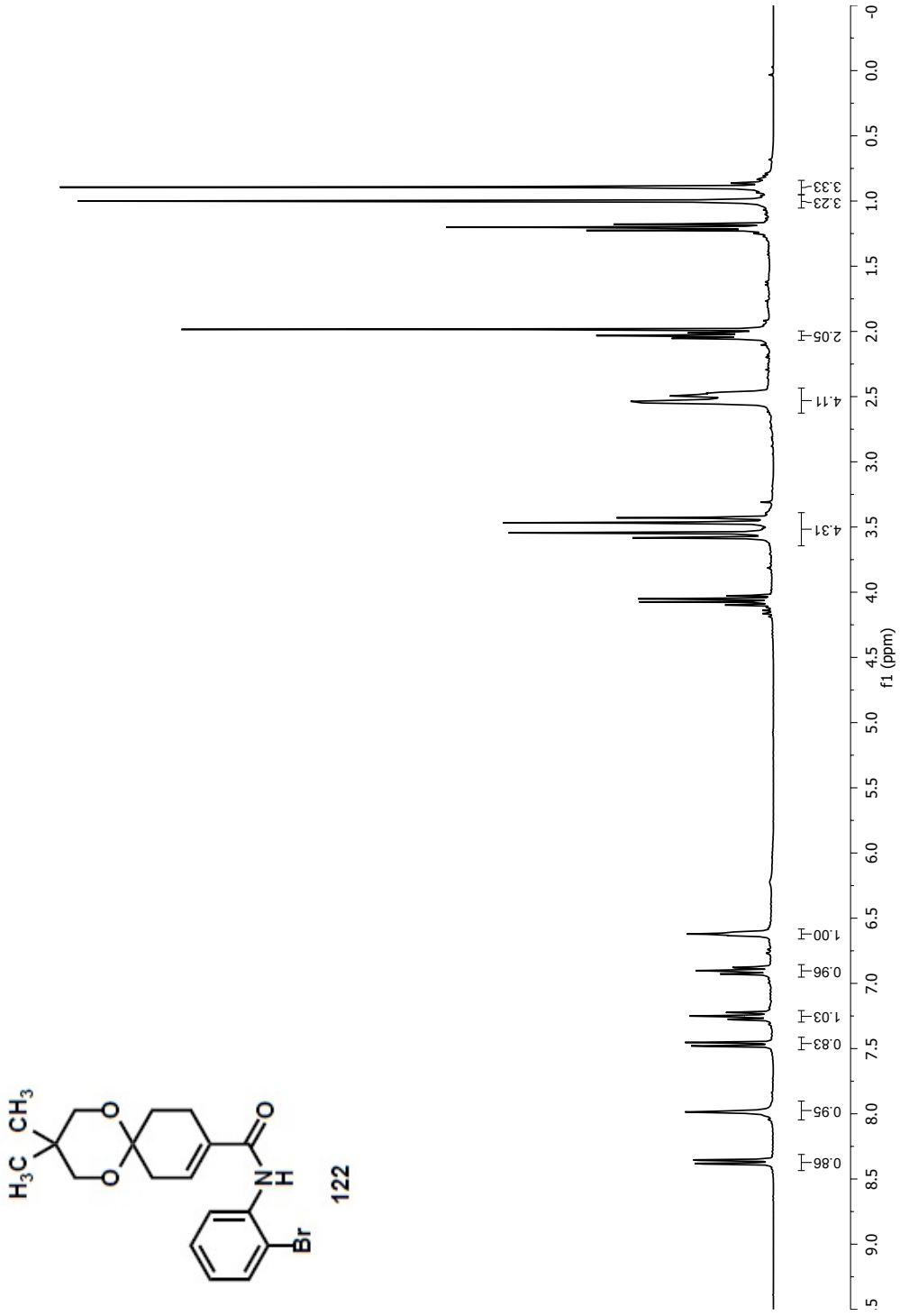
H3C CH3
O
O
O
O
OTf
115
163.6
148.5
134.3
132.7
132.0
128.5
124.8
123.8
122.8
116.7
97.0
70.4
69.3
34.9
30.3
27.1
24.3
22.9
22.6
f1 (ppm)


H3C CH3
O
O
OTf
O
O
115
-73.3
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

OCH3
O
O
Br
H
H3C
116
1.00
1.04
2.32
1.15
3.53
4.58
3.48
f1 (ppm)


HO
119B
HO
119A
0.91
2.00
1.11
4.10
8.36
1.93
1.08
f1 (ppm)

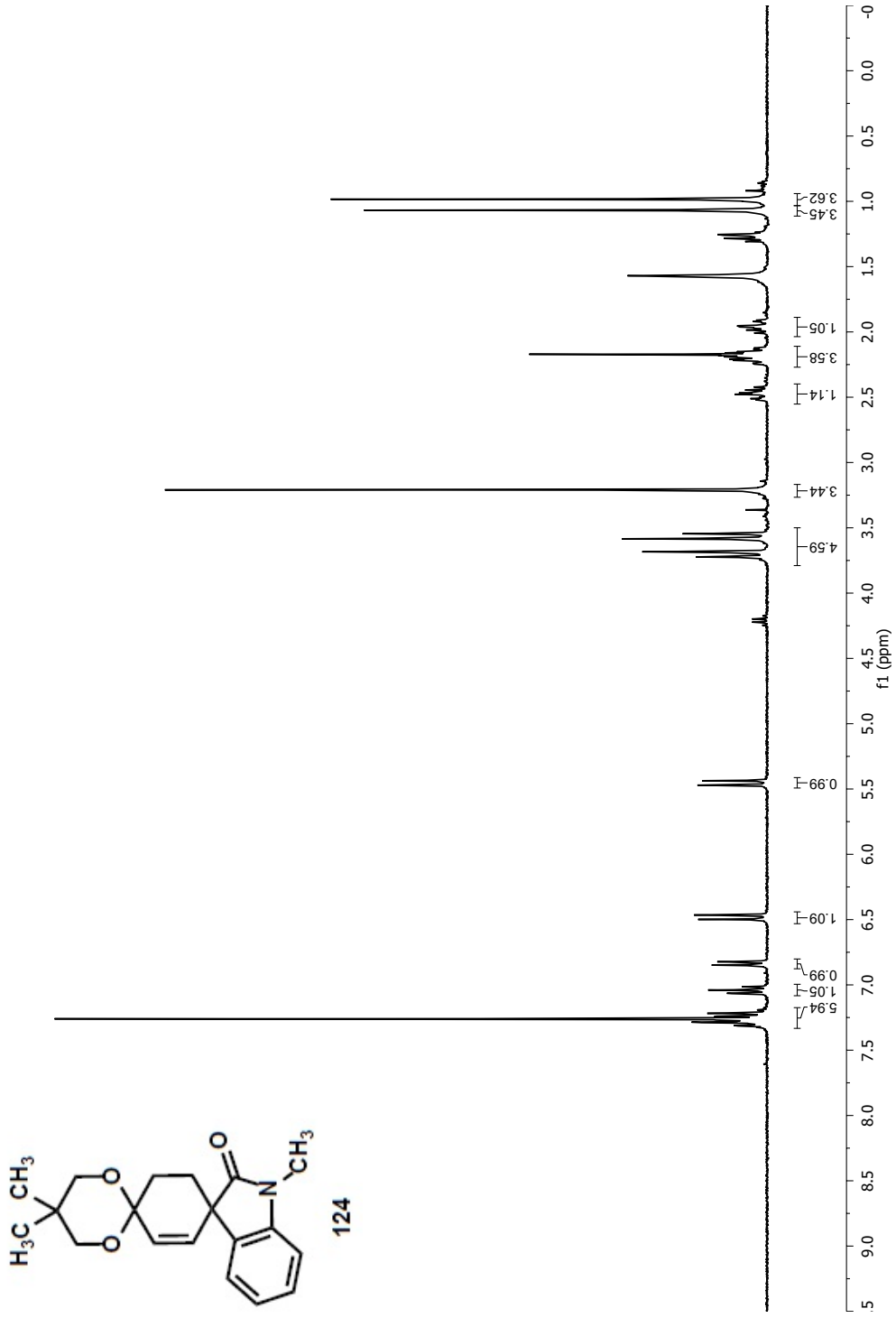

Br
O
H3C
O
H
120A
Br
O
H3C
O
H
120B
1.31
0.98
2.16
0.94
4.64
4.54
7.59
1.87
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

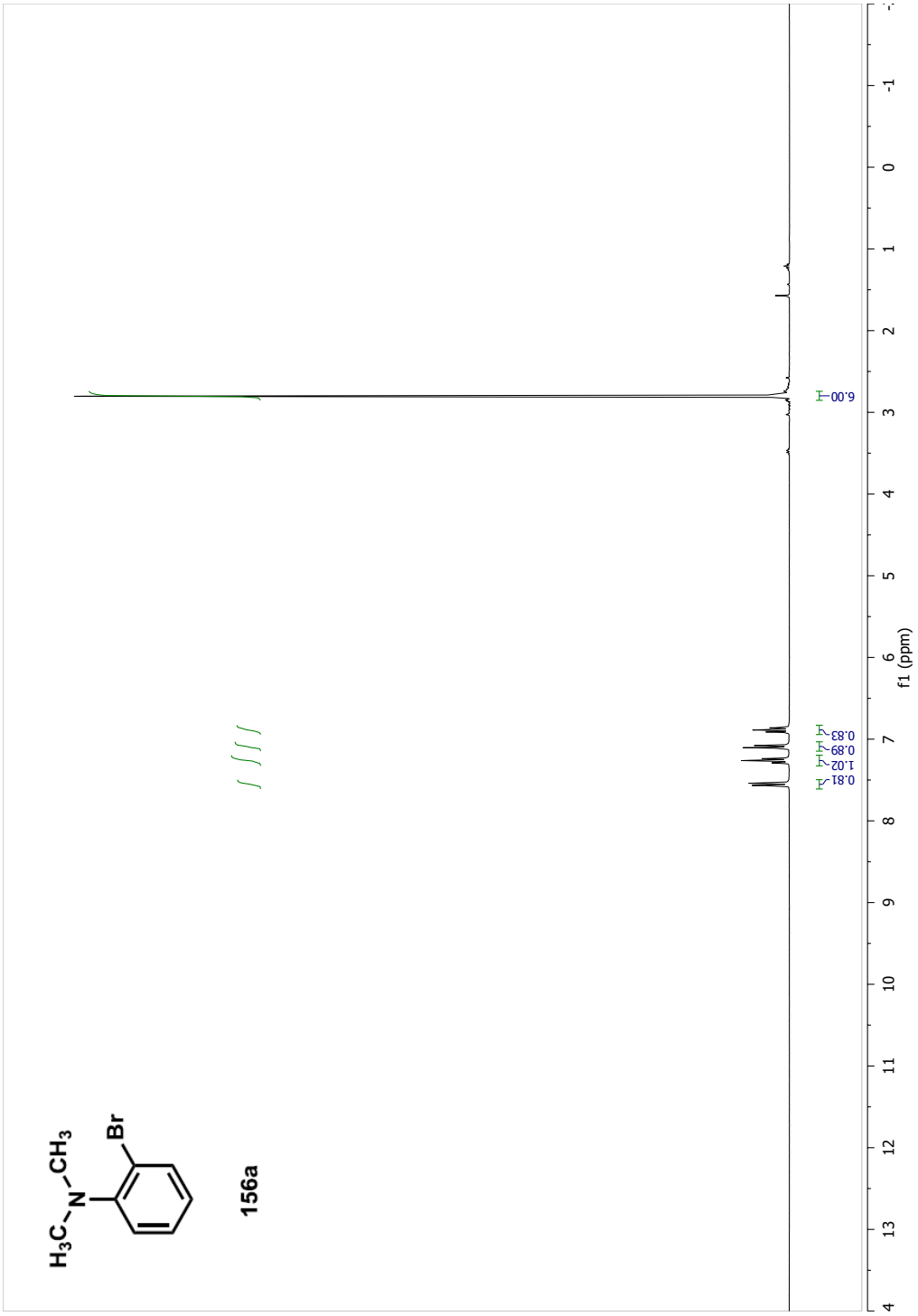

H3C CH3
O
O
O
N
H
Br
122
3.33
3.23
2.05
4.11
4.31
1.00
0.96
1.03
0.83
0.95
0.86
f1 (ppm)

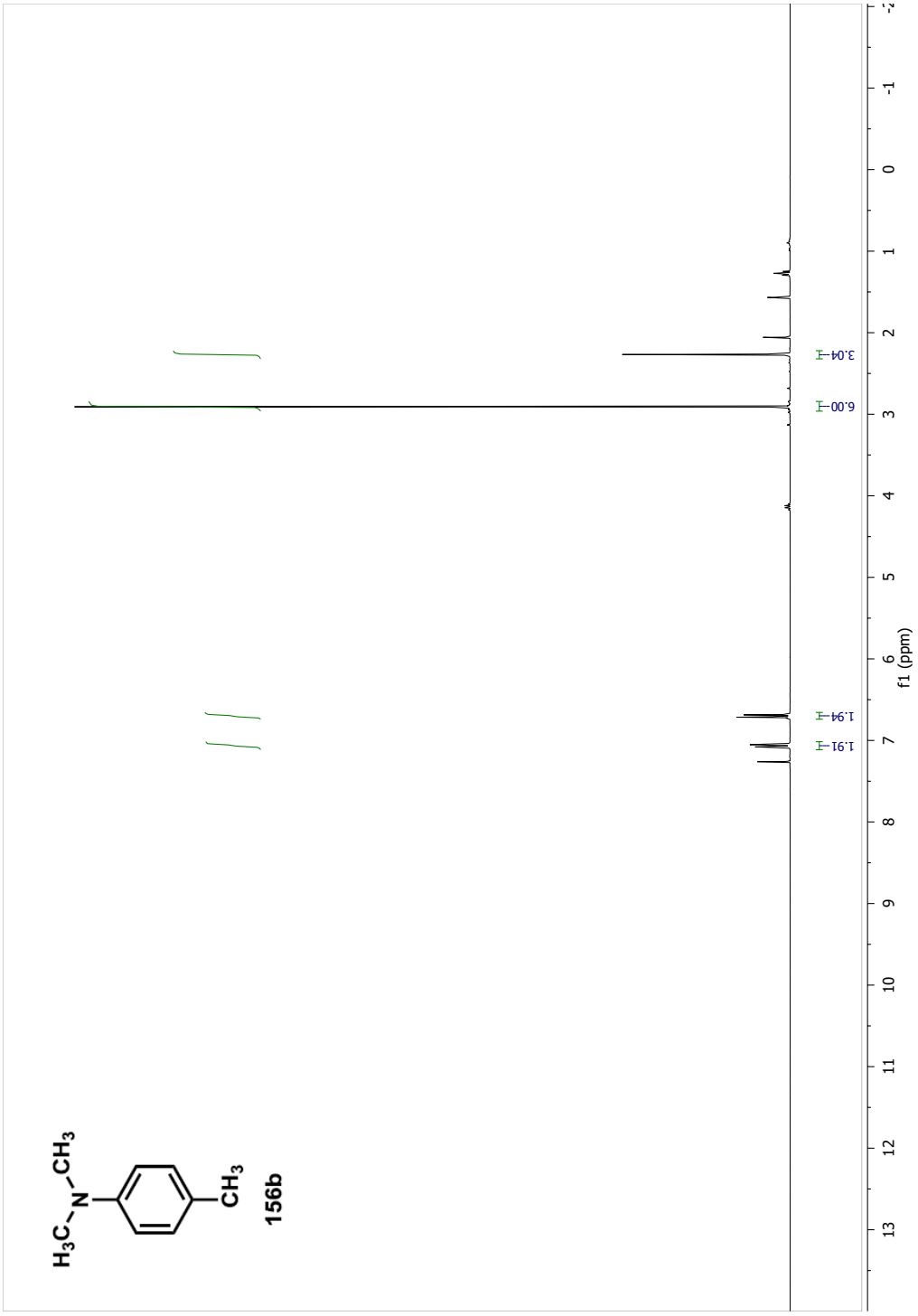
171.0
165.3
135.8
133.2
132.1
131.5
128.4
124.9
121.7
113.6
96.4
70.3
60.3
35.2
30.2
27.1
22.7
22.7
22.4
21.0
14.2
f1 (ppm)
H3C CH3
O
O
O
N
H
Br
122

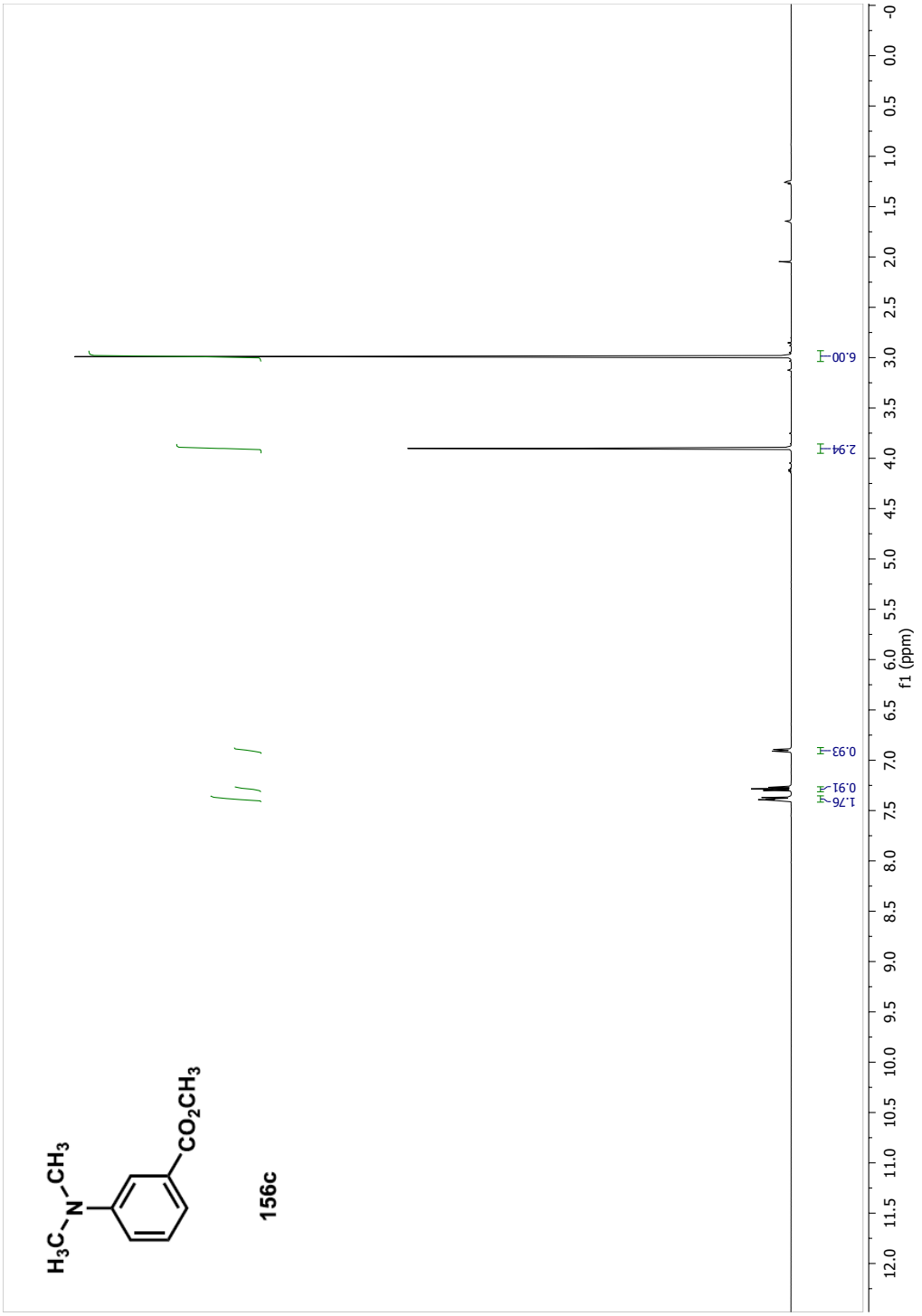
H3C CH3
O
O
O
N
CH3
Br
123
8.19
2.50
4.35
3.48
4.66
1.00
2.25
1.29
1.02
f1 (ppm)

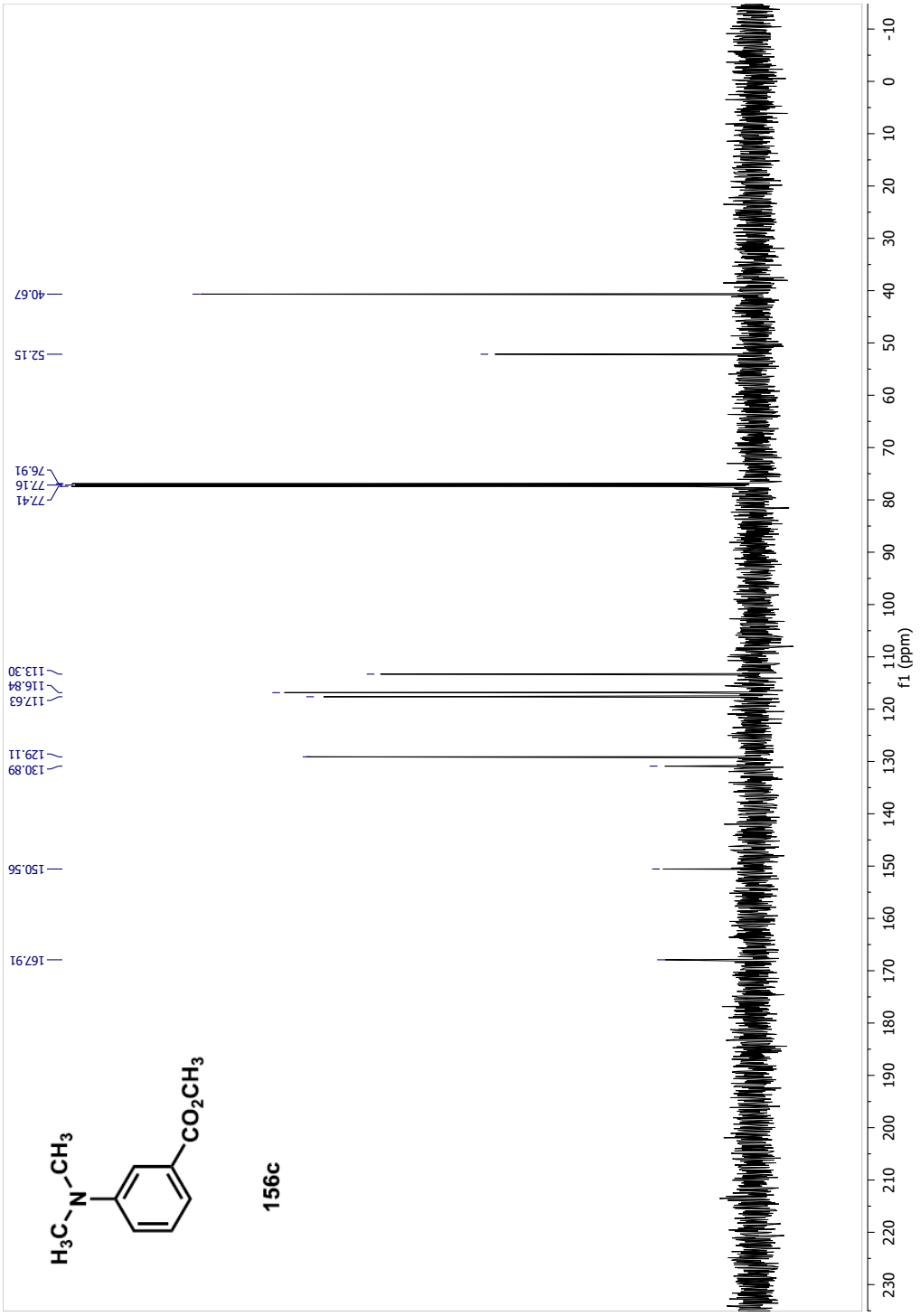
171.7
133.7
133.7
129.9
128.9
128.4
122.7
96.3
70.1
36.6
33.6
30.1
28.0
24.3
22.7
22.7
f1 (ppm)
123

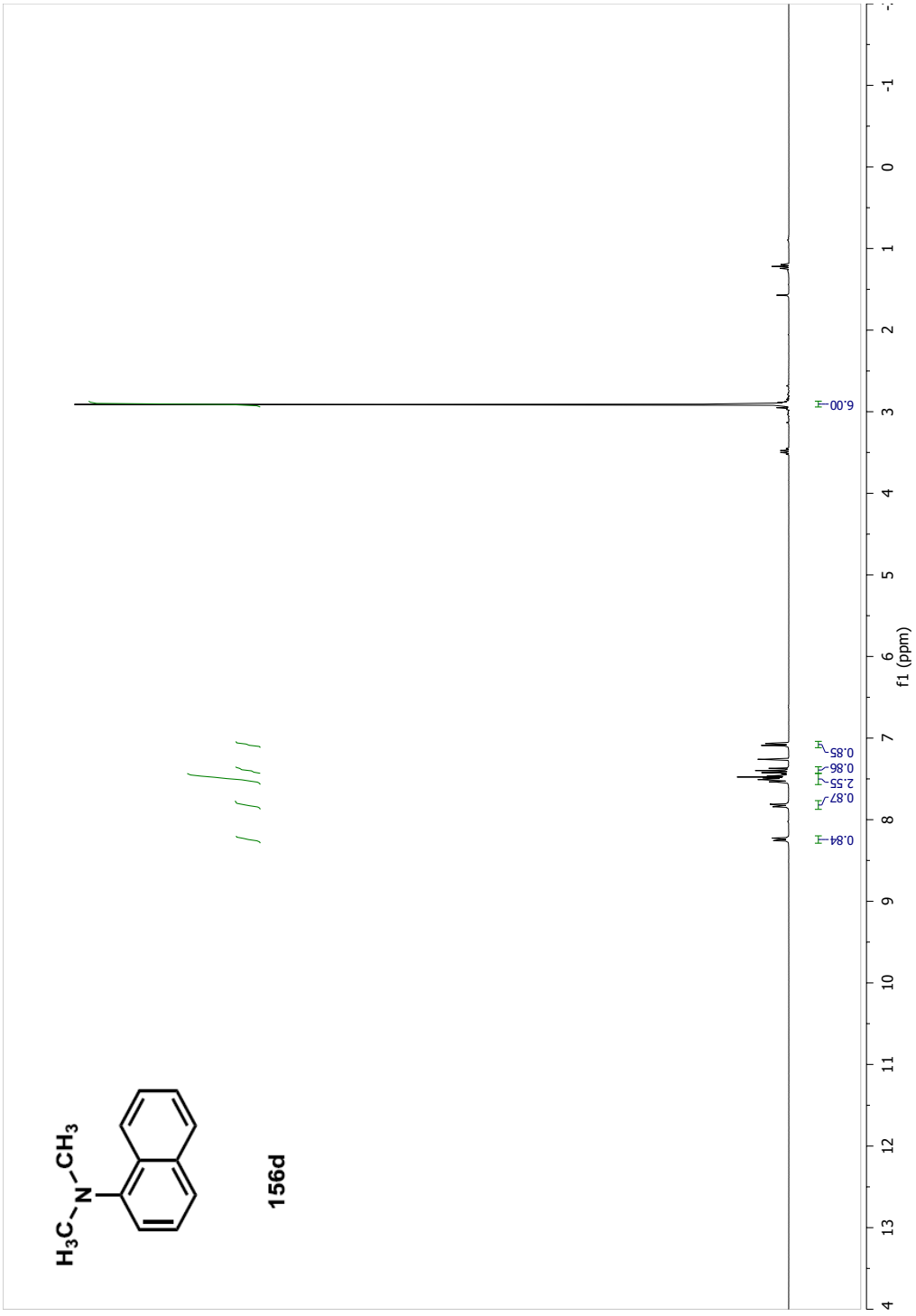

H3C CH3
O
O
O
N
CH3
124
5.94
1.05
0.99
1.09
0.99
3.44
4.59
1.14
3.58
1.05
3.45
3.62
f1 (ppm)

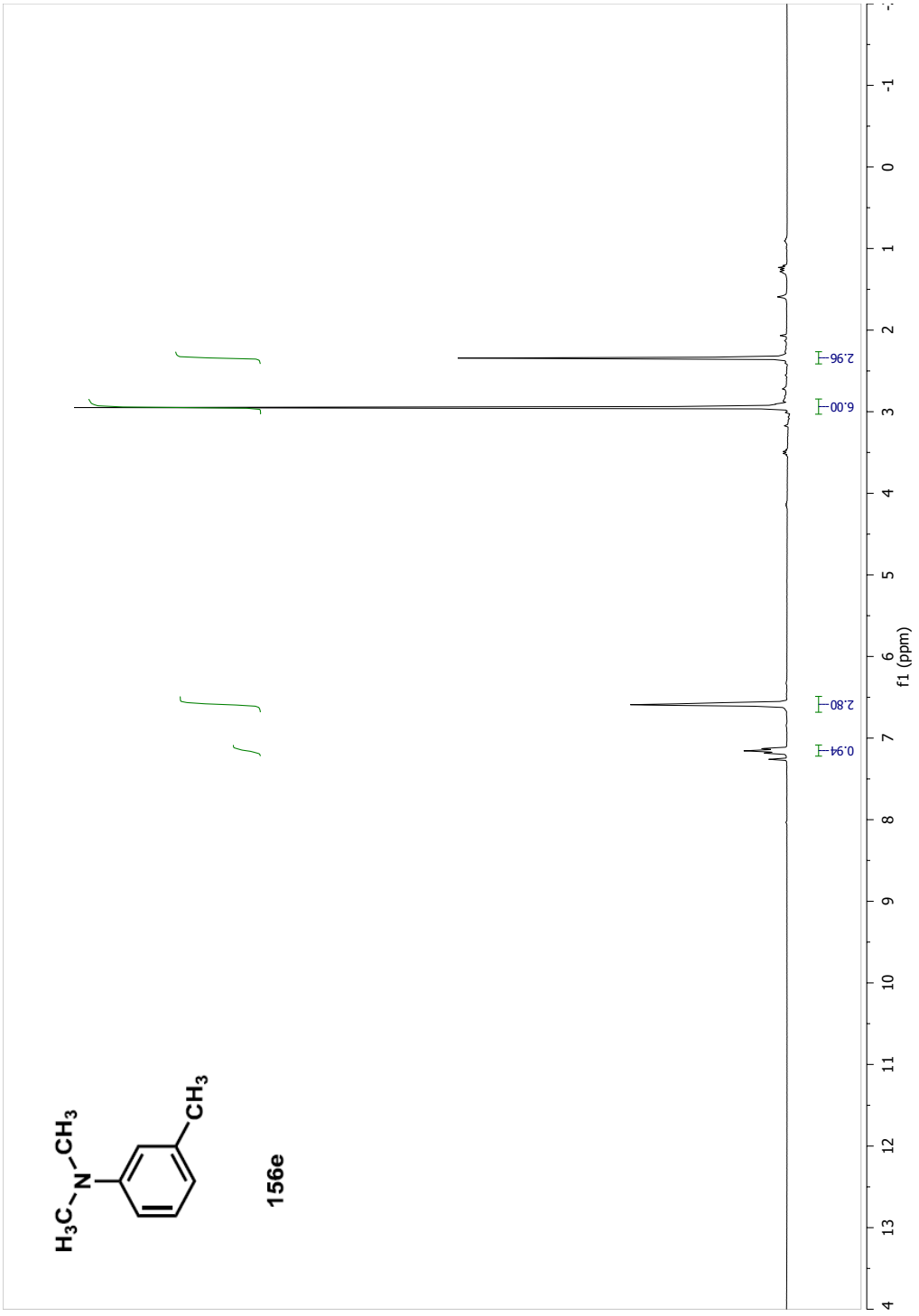

156a
6.00
0.81
1.02
0.89
0.83
f1 (ppm)

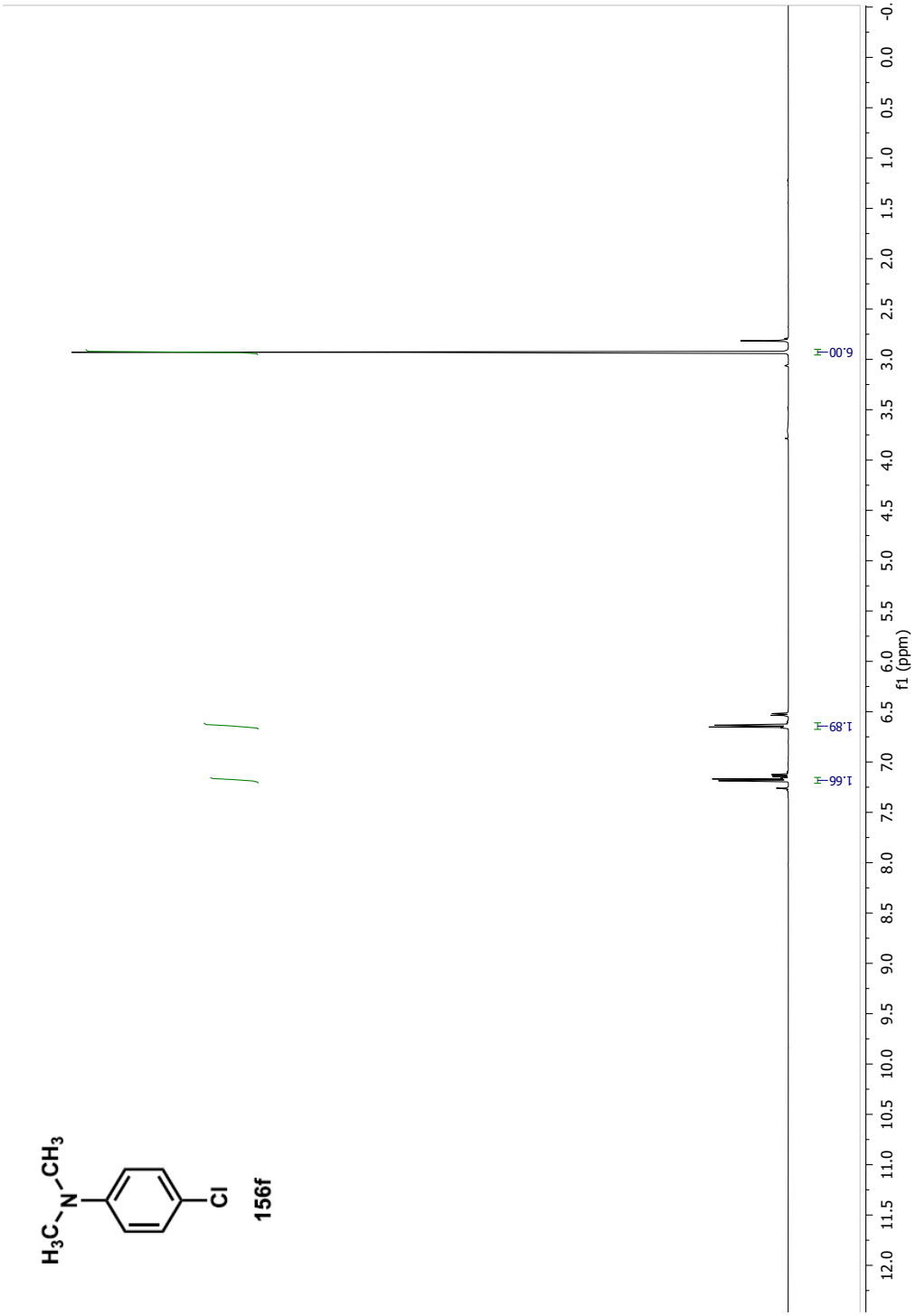

3.04
6.00
1.94
1.91
f1 (ppm)
156b


156c
6.00
2.94
0.93
1.76
0.91
f1 (ppm)

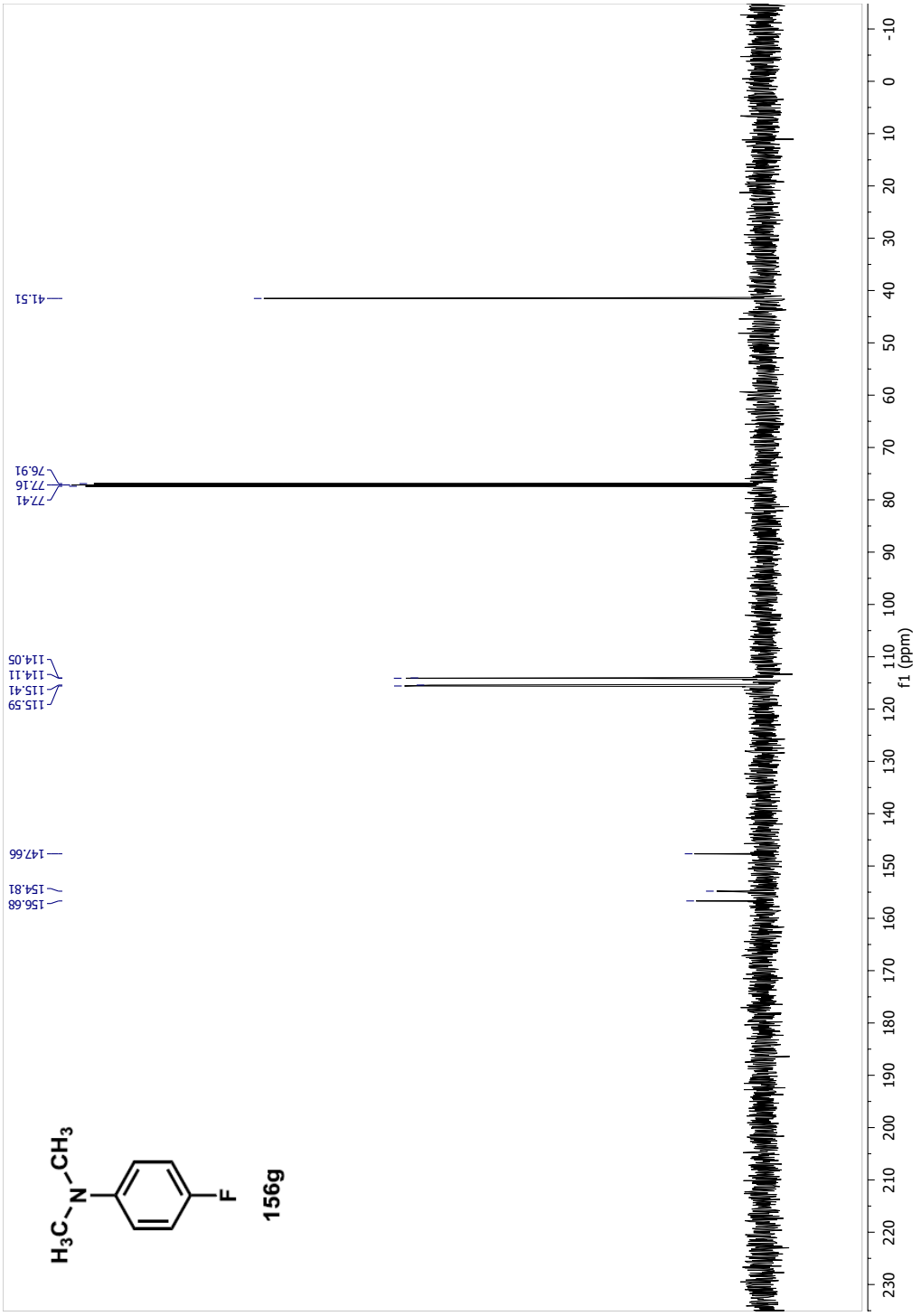

40.67
52.15
76.91
77.16
77.41
113.30
116.84
117.63
129.11
130.89
150.56
167.91
156c
f1 (ppm)

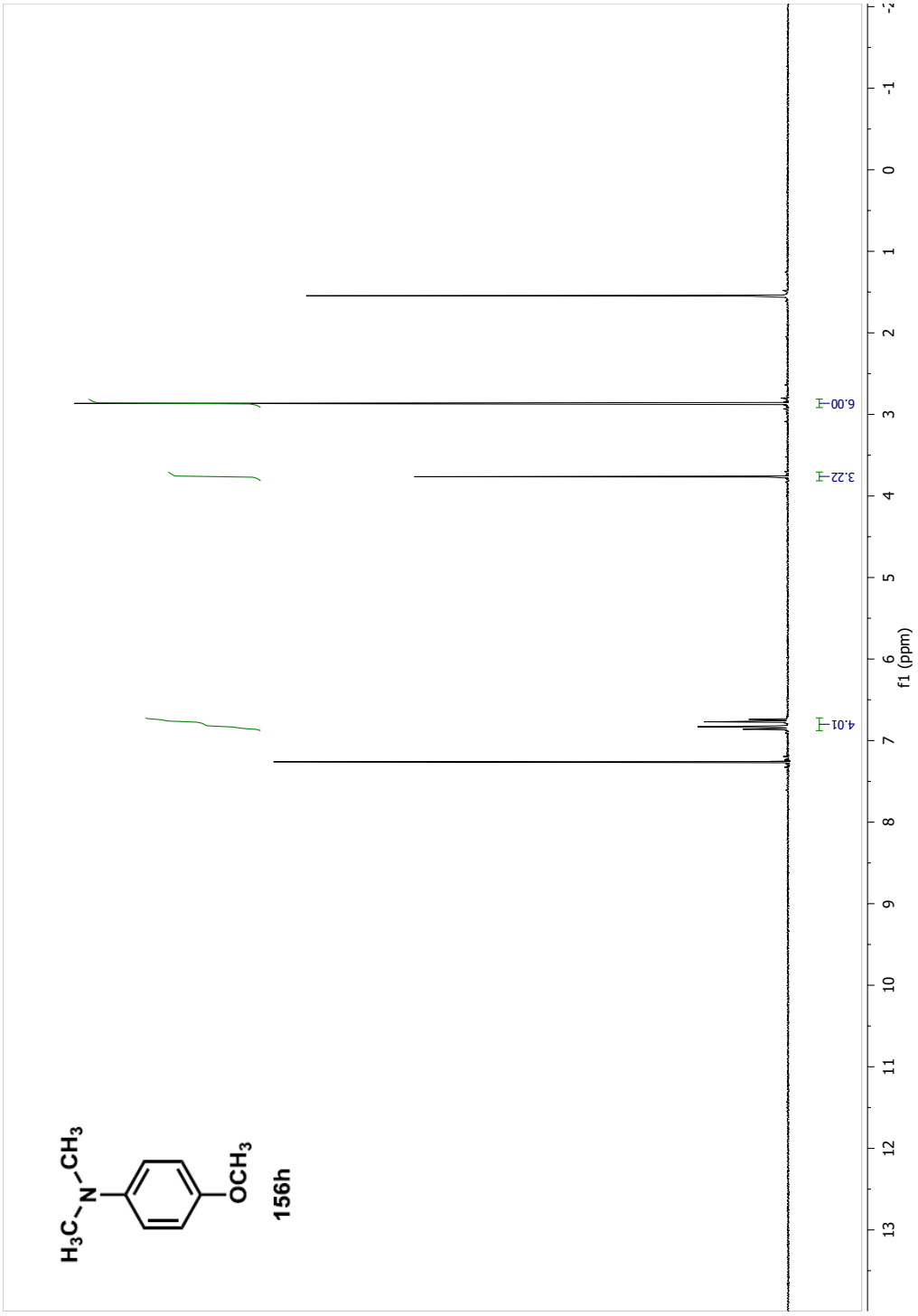

H3C
N
CH3
156d
6.00
0.84
0.87
2.55
0.86
0.85
f1 (ppm)

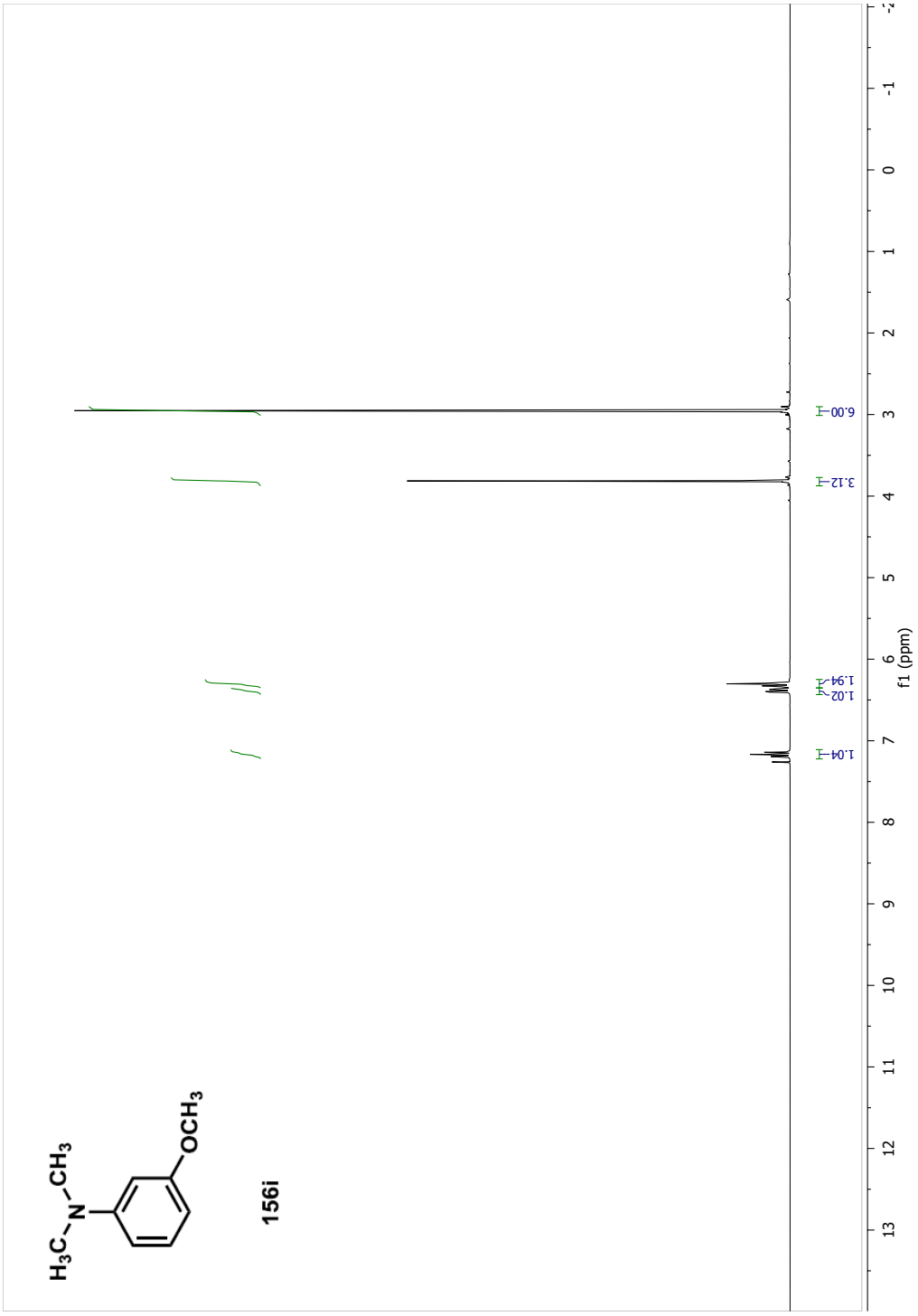

2.96
6.00
2.80
0.94
f1 (ppm)
156e

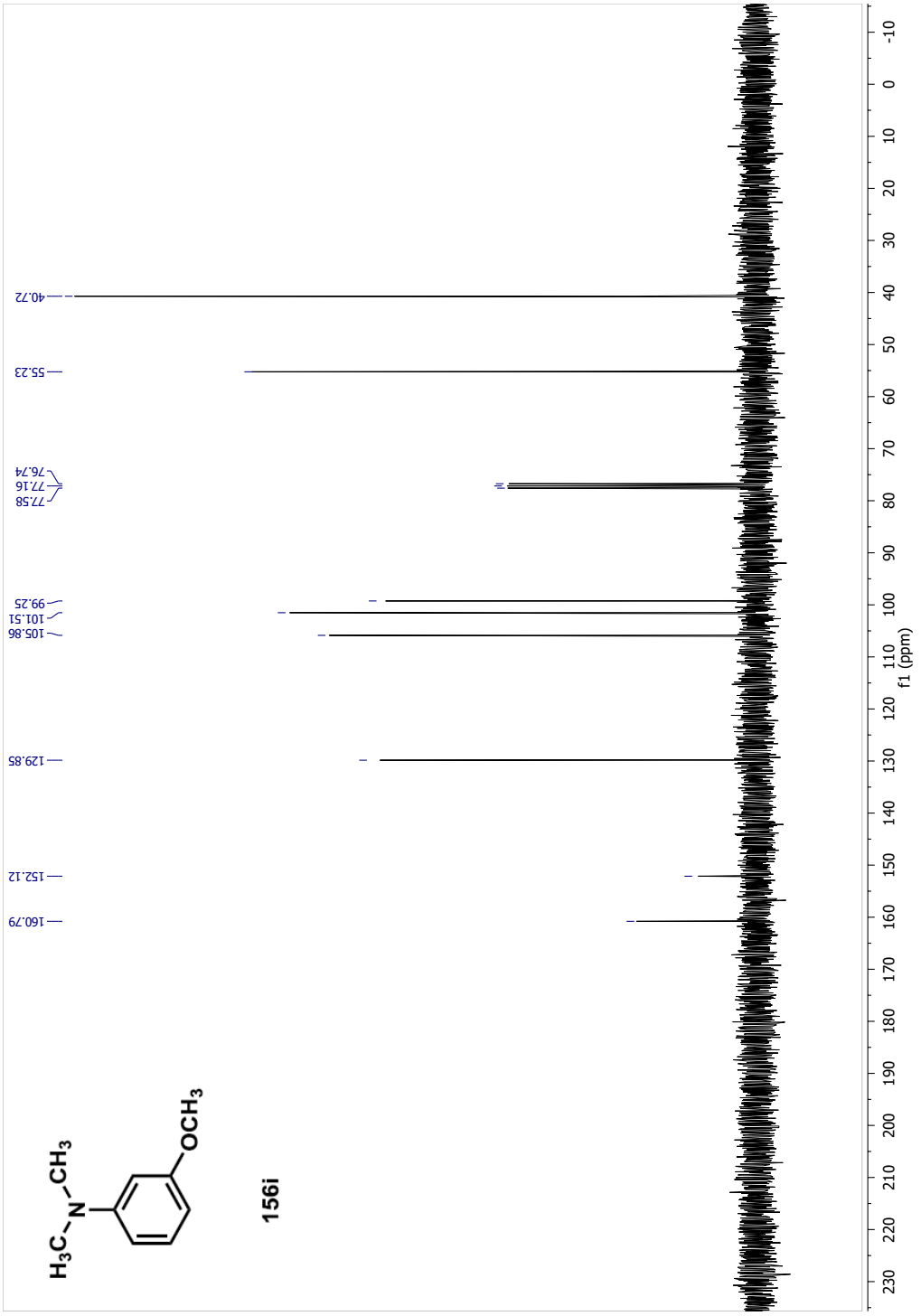

6.00
1.89
1.66
f1 (ppm)
H3C
CH3
N
Cl
156f

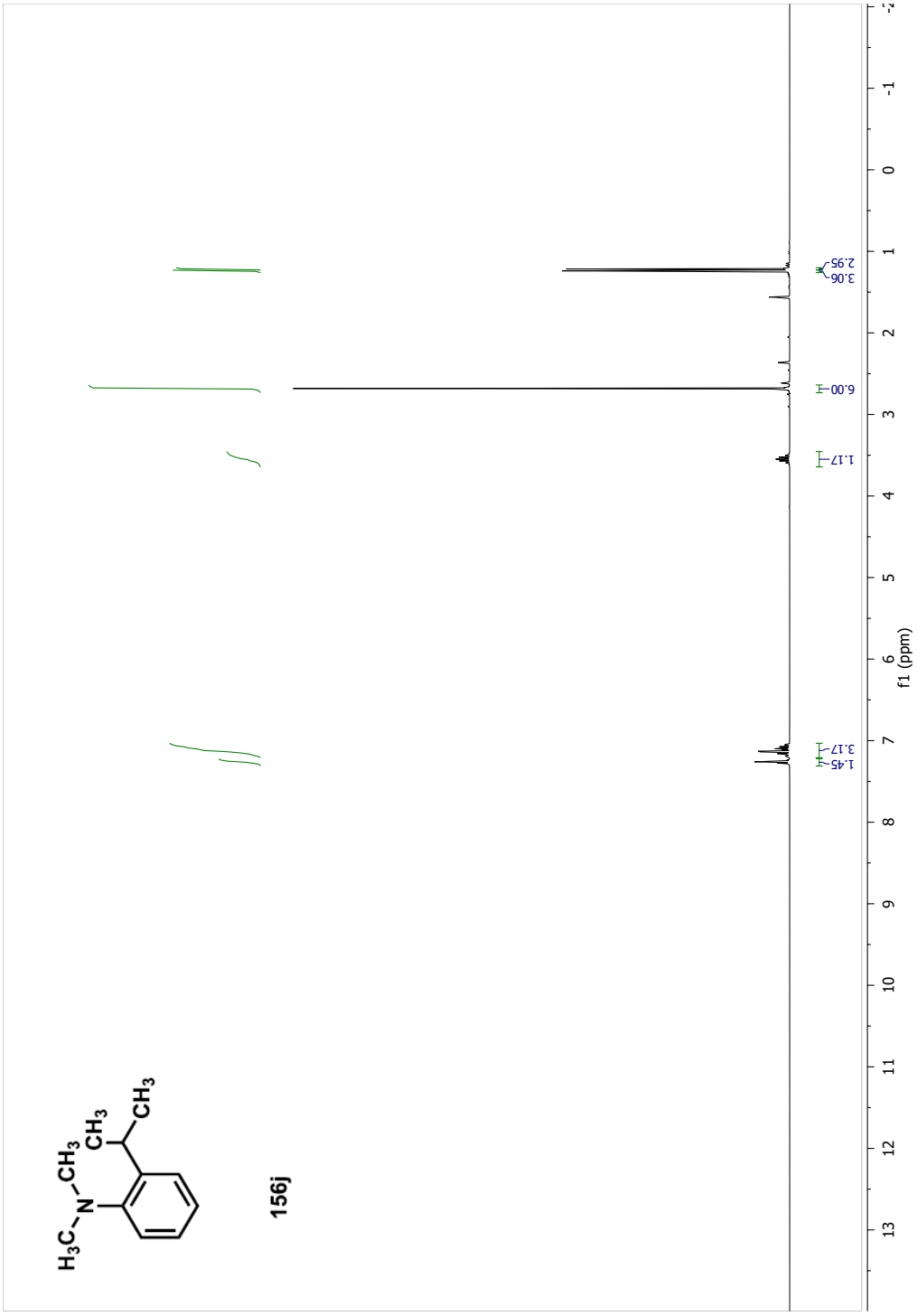

H3C
N
CH3
F
156g
6.00
1.84
1.77
f1 (ppm)

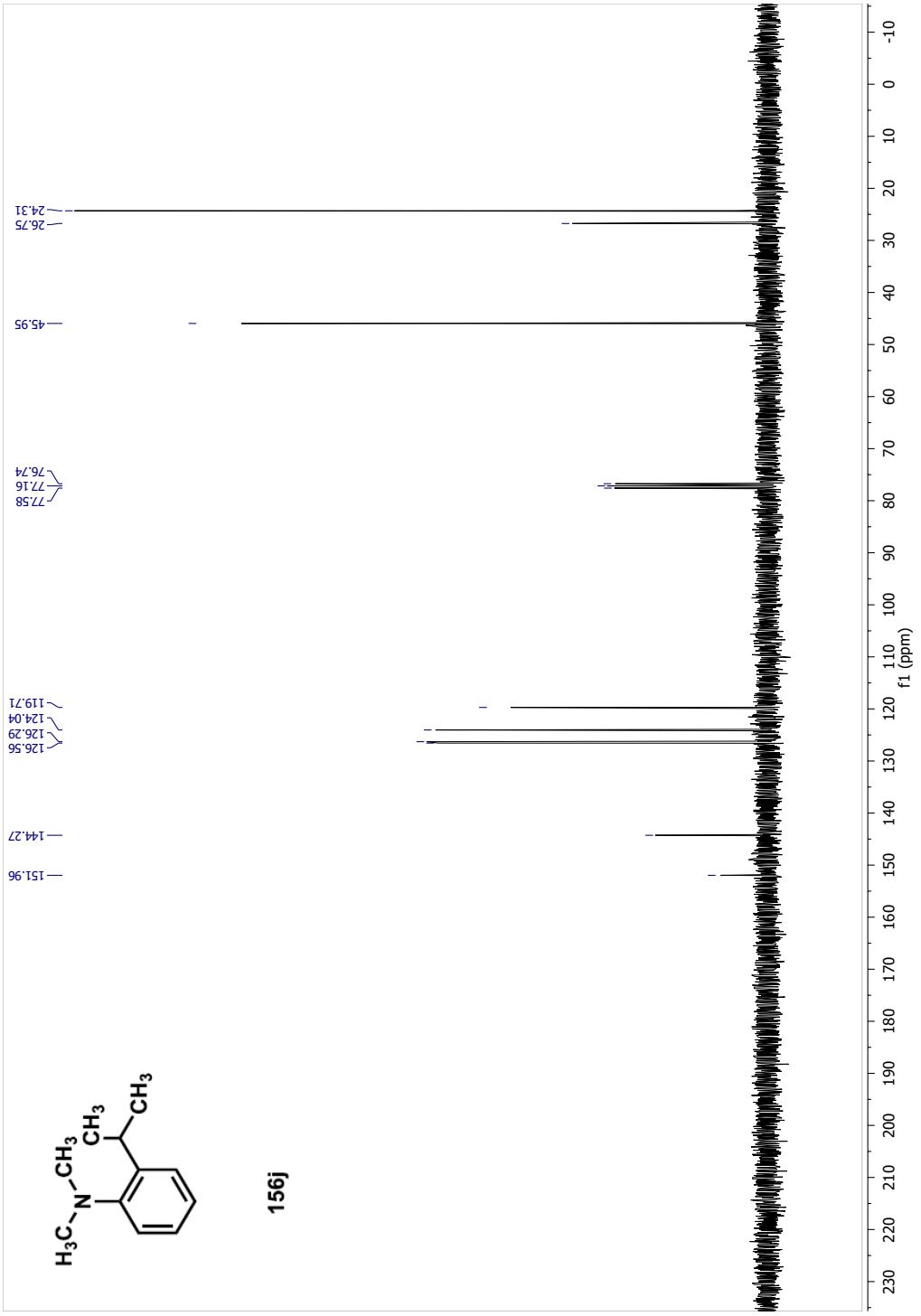

41.51
77.41
77.16
76.91
115.59
115.41
114.11
114.05
147.66
154.81
156.68
f1 (ppm)
156g

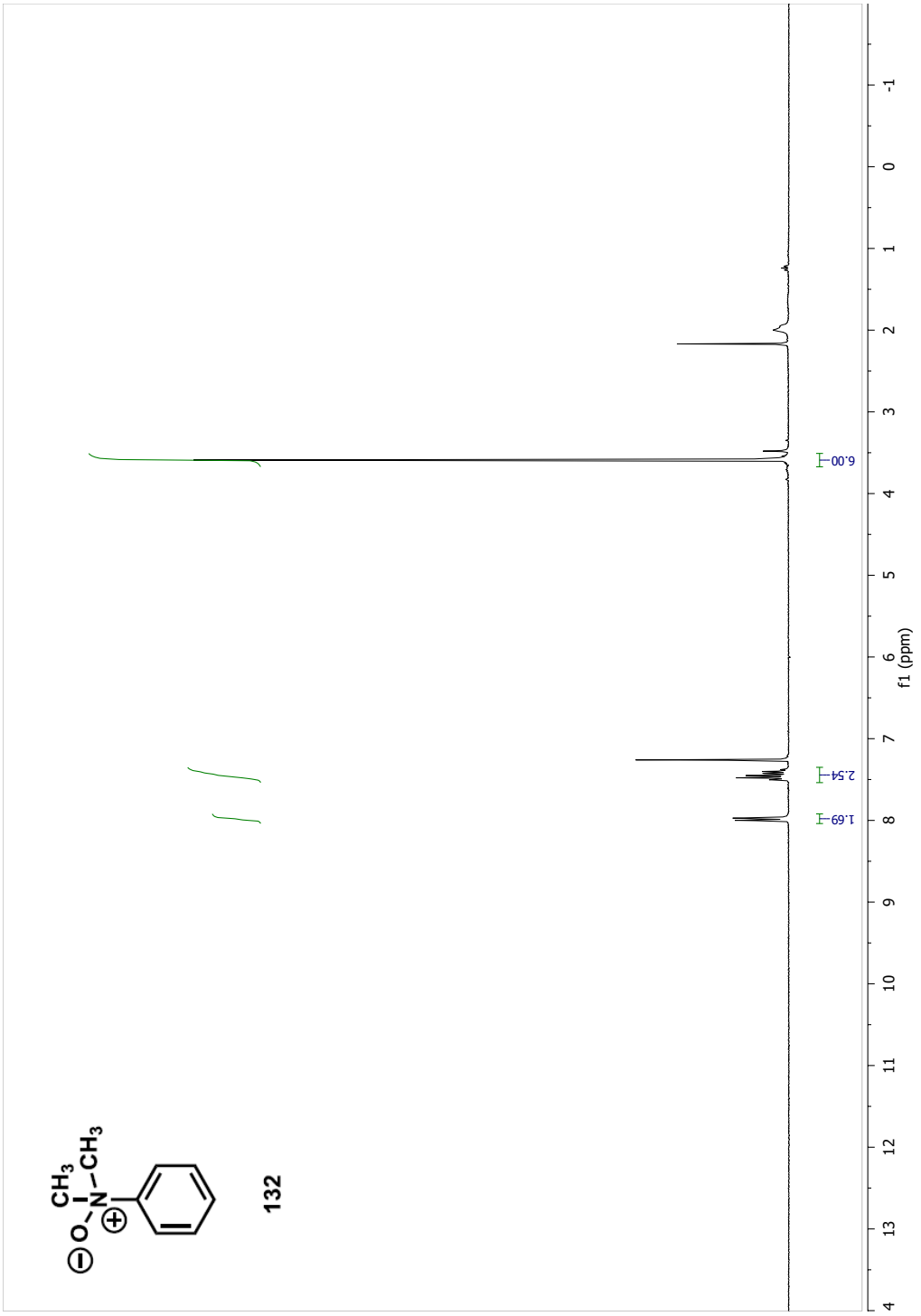

H3C
N
CH3
OCH3
156h
6.00
3.22
4.01
f1 (ppm)

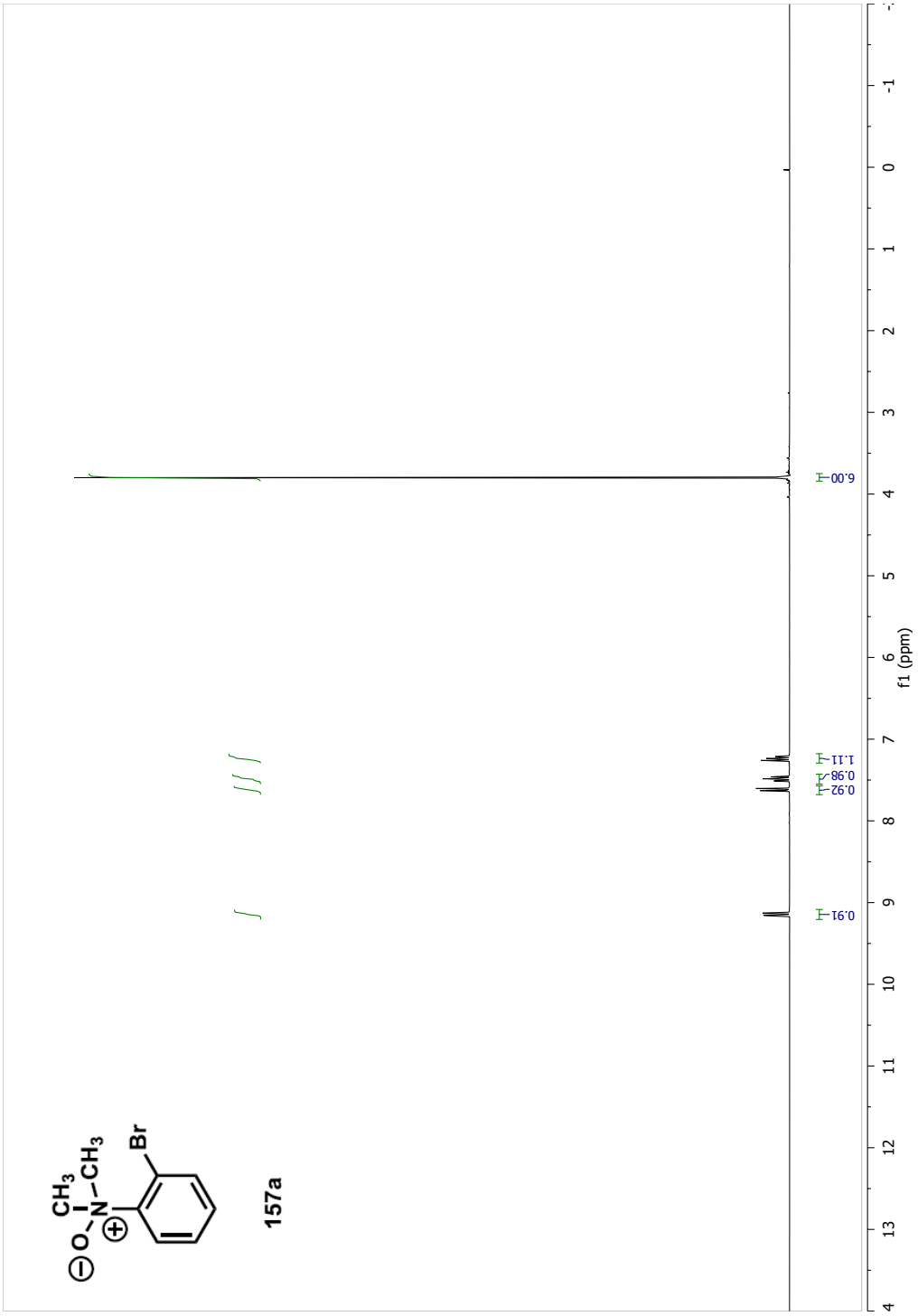

156i
6.00
3.12
1.94
1.02
1.04
f1 (ppm)

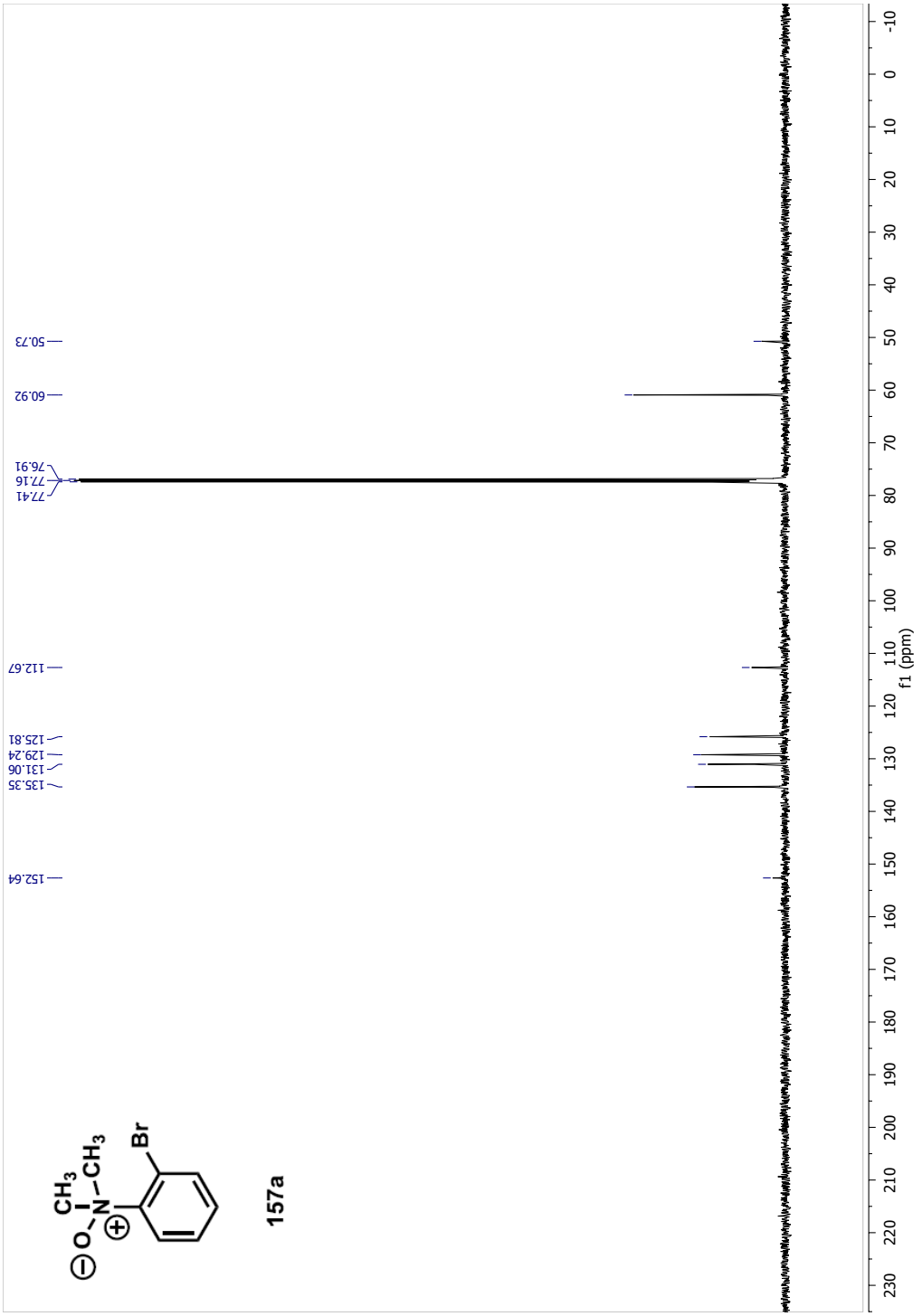

40.72
55.23
76.74
77.16
77.58
99.25
101.51
105.86
129.85
152.12
160.79
156i
f1 (ppm)

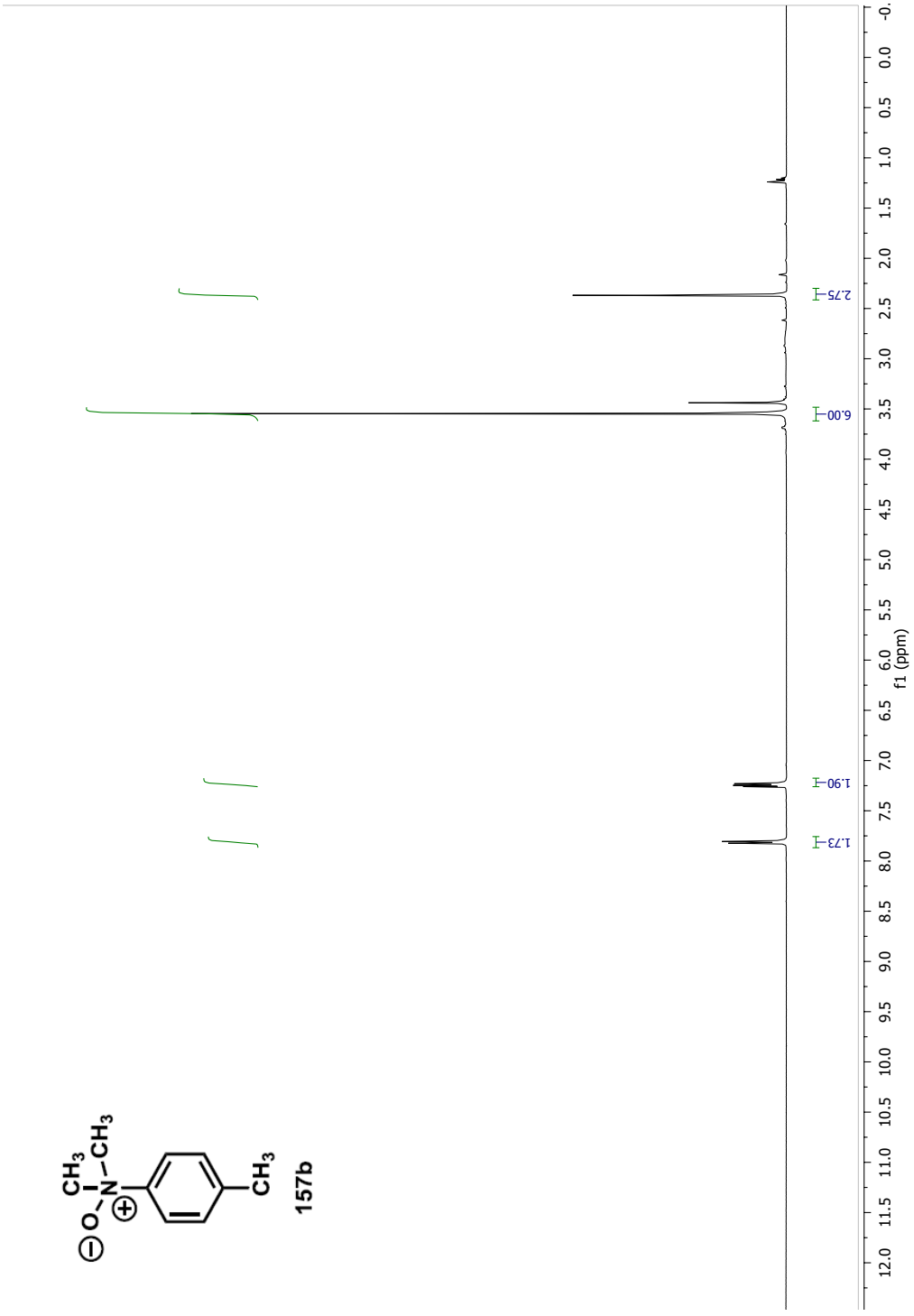

156j
f1 (ppm)
3.06
2.95
6.00
1.17
1.45
3.17

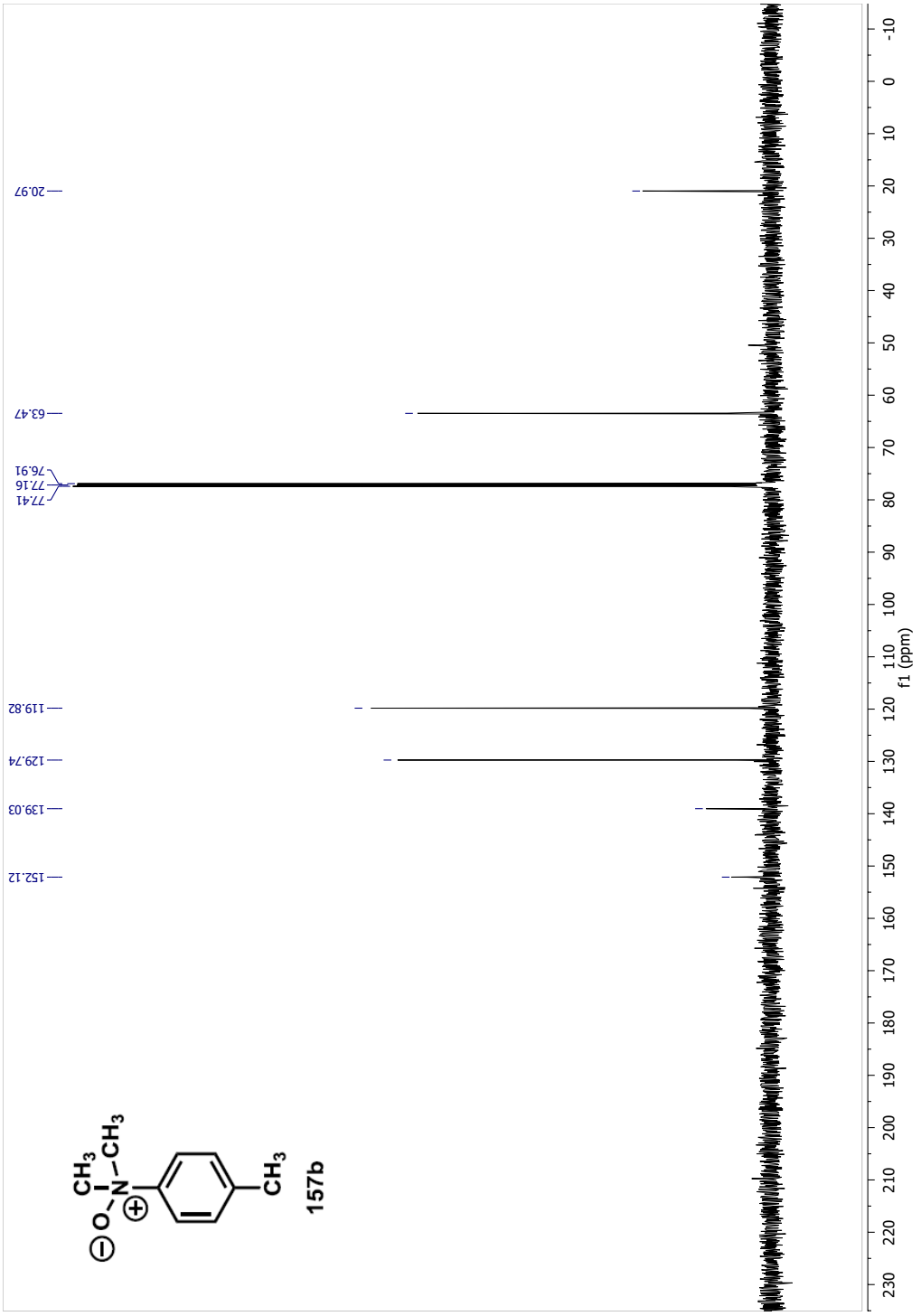

24.31
26.75
45.95
76.74
77.16
77.58
119.71
124.04
126.29
126.56
144.27
151.96
156j
f1 (ppm)


132
6.00
2.54
1.69
f1 (ppm)

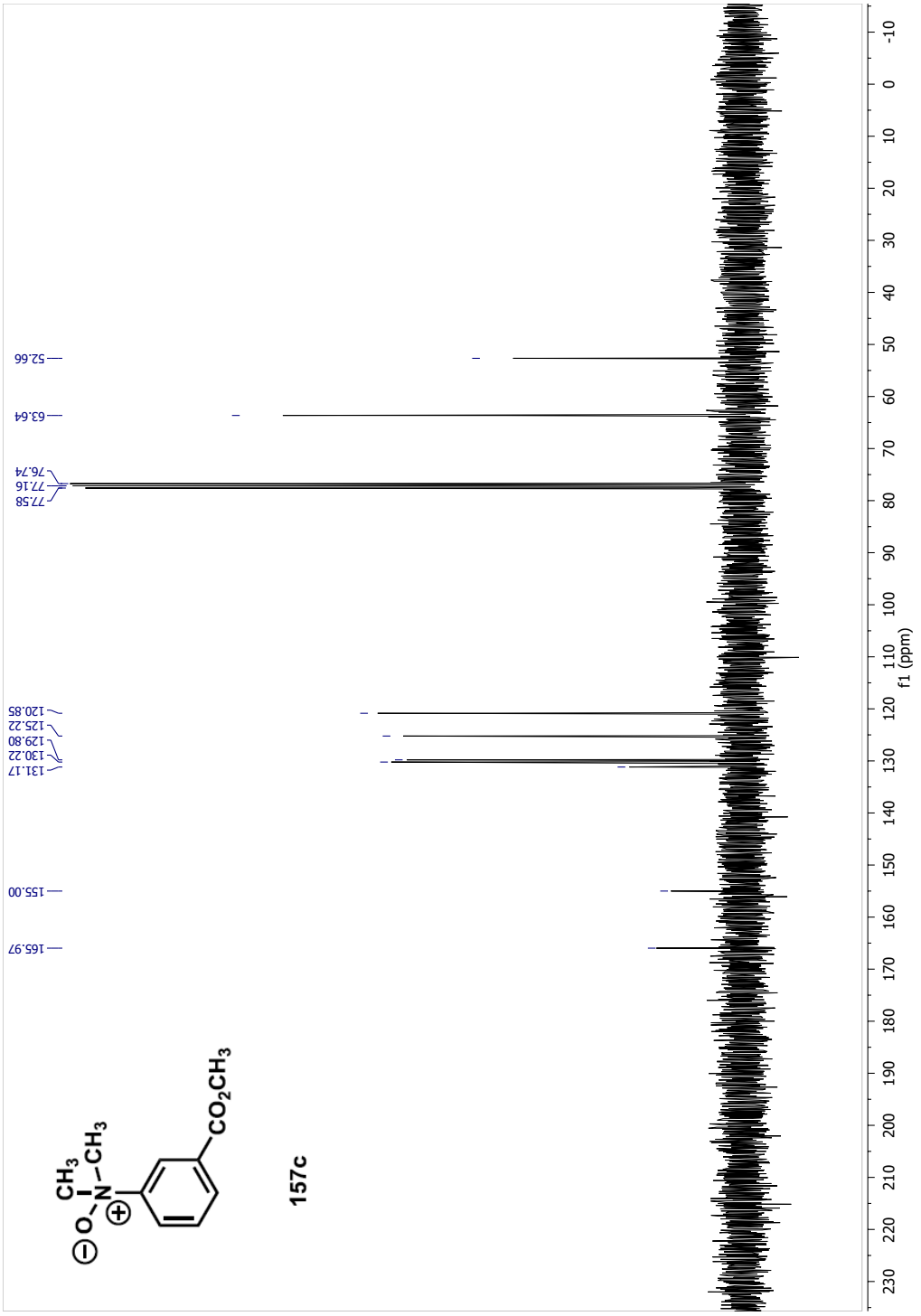

157a
6.00
1.11
0.98
0.92
0.91
f1 (ppm)

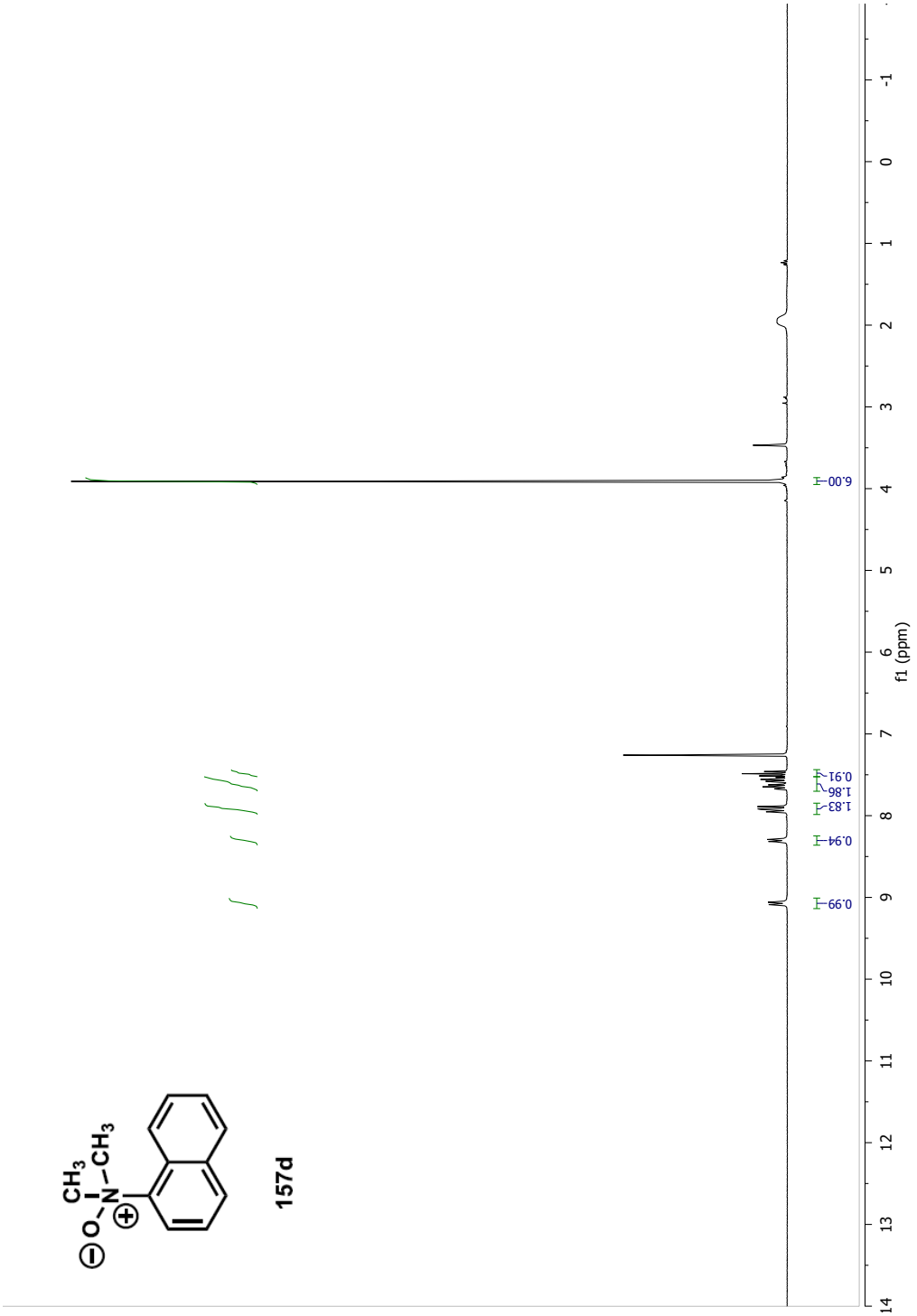

157a
152.64
135.35
131.06
129.24
125.81
112.67
77.41
77.16
76.91
60.92
50.73
f1 (ppm)

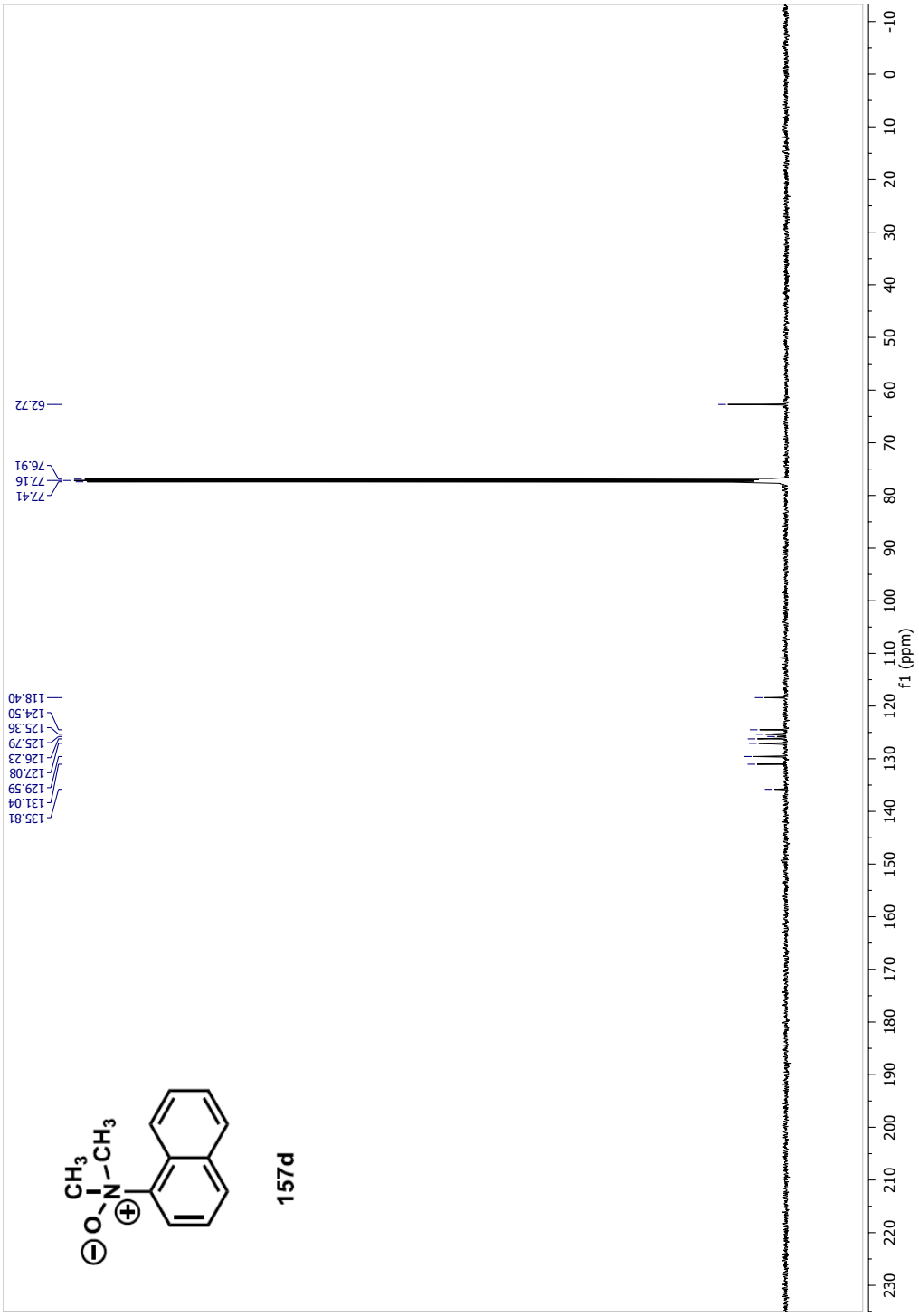

2.75
6.00
1.90
1.73
f1 (ppm)
157b

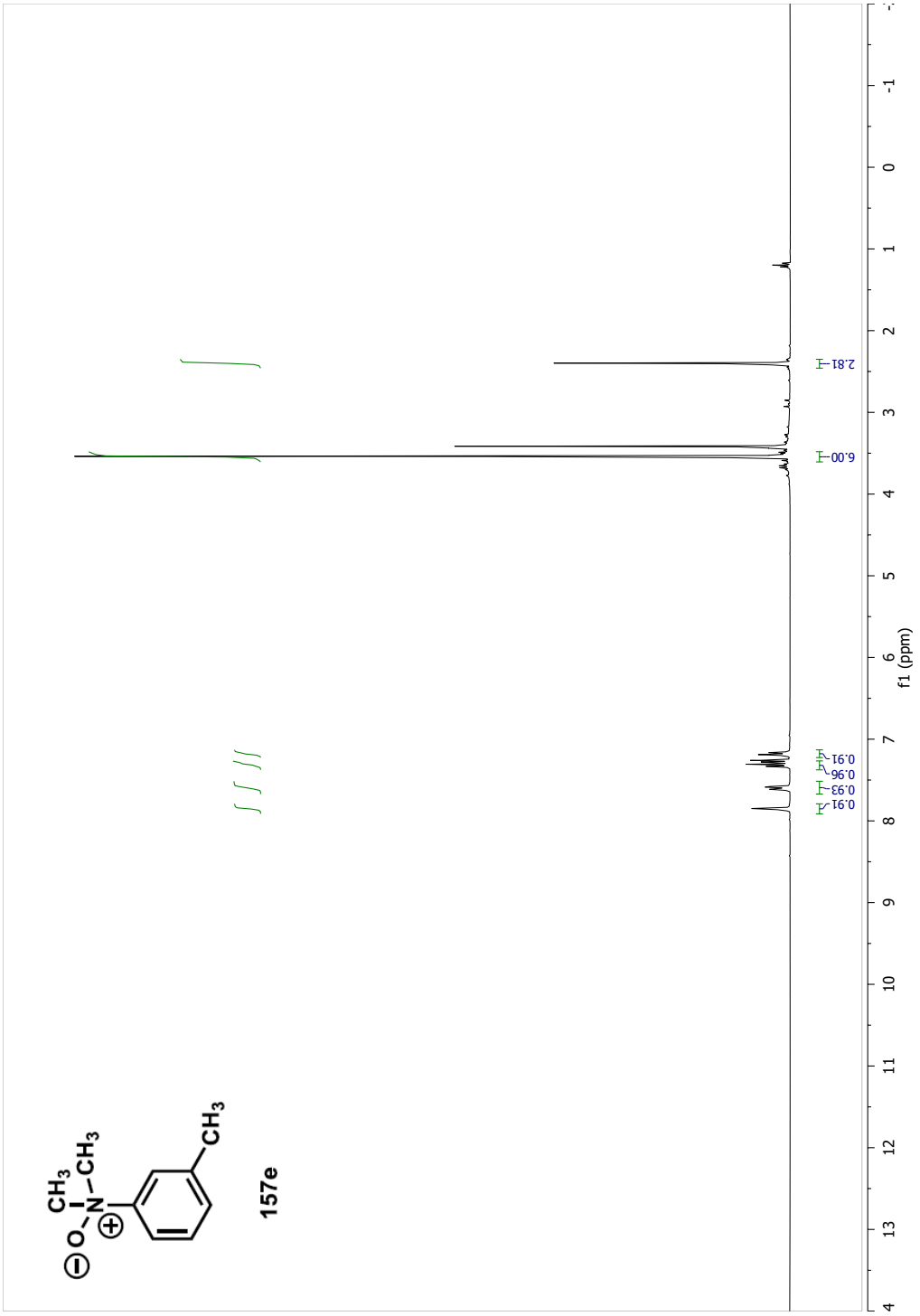

20.97
63.47
76.91
77.16
77.41
119.82
129.74
139.03
152.12
157b
f1 (ppm)

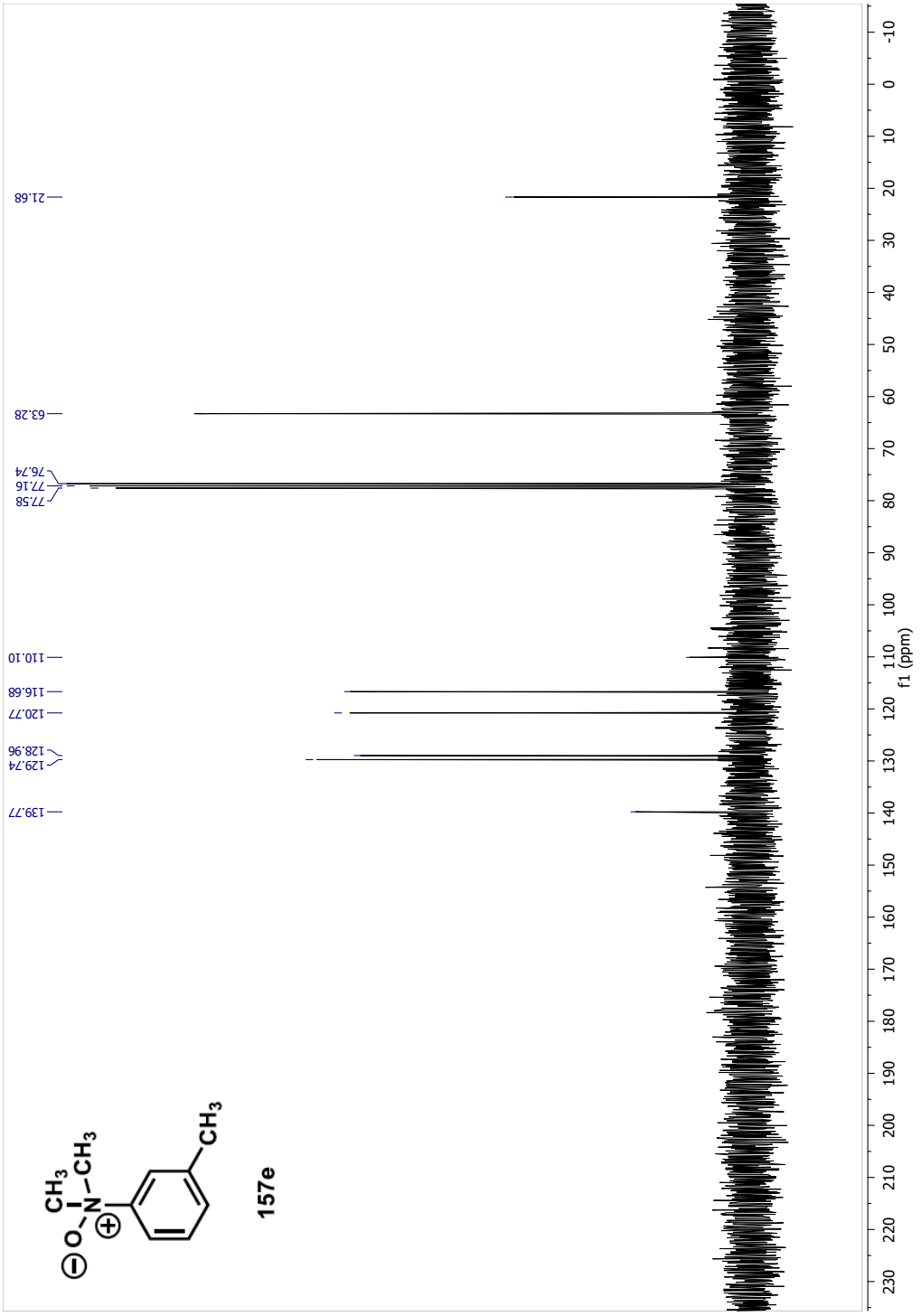
157c
6.00
2.98
1.11
1.04
2.00
f1 (ppm)

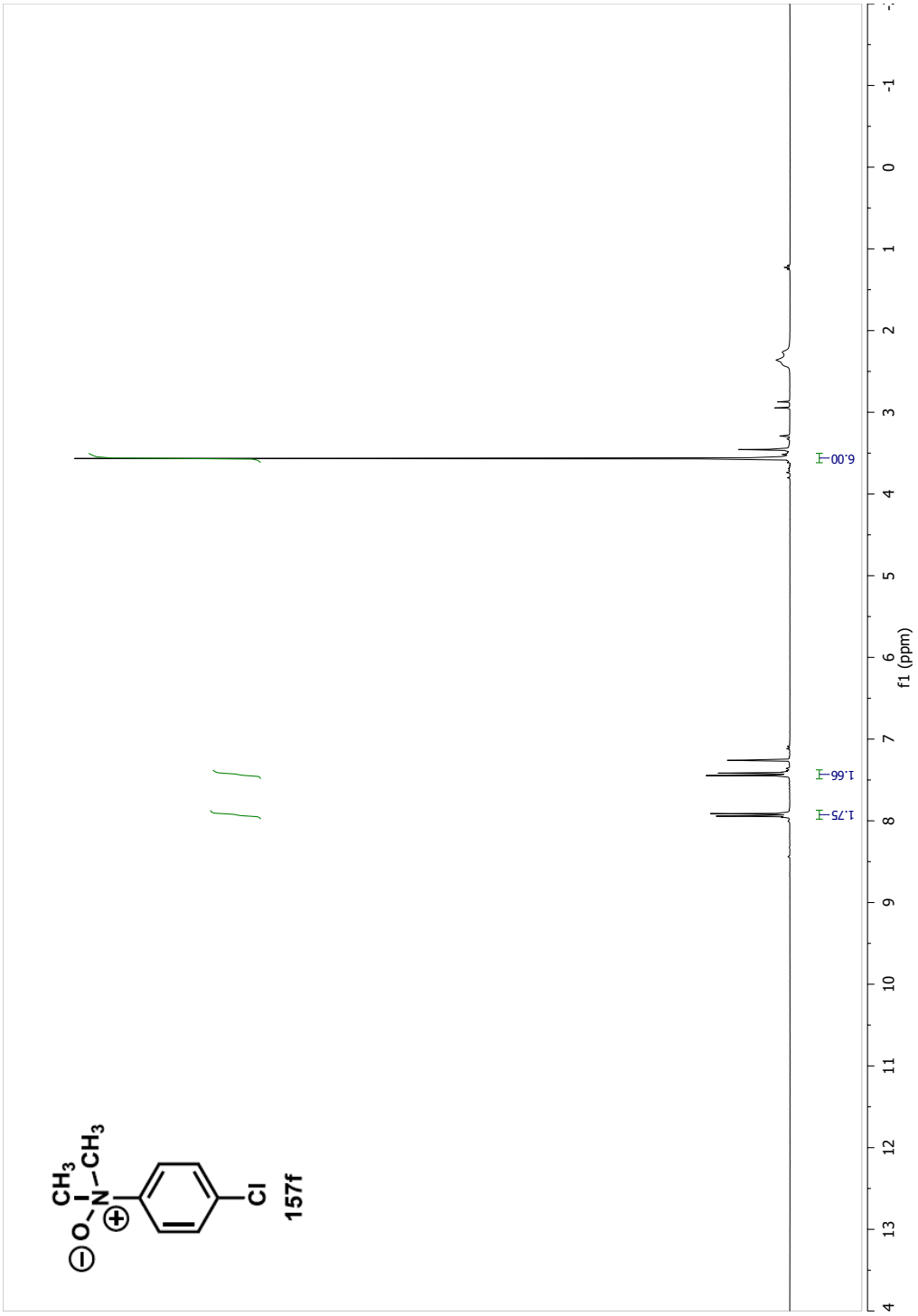

157c
52.66
63.64
77.58
77.16
76.74
120.85
125.22
129.80
130.22
131.17
155.00
165.97
f1 (ppm)

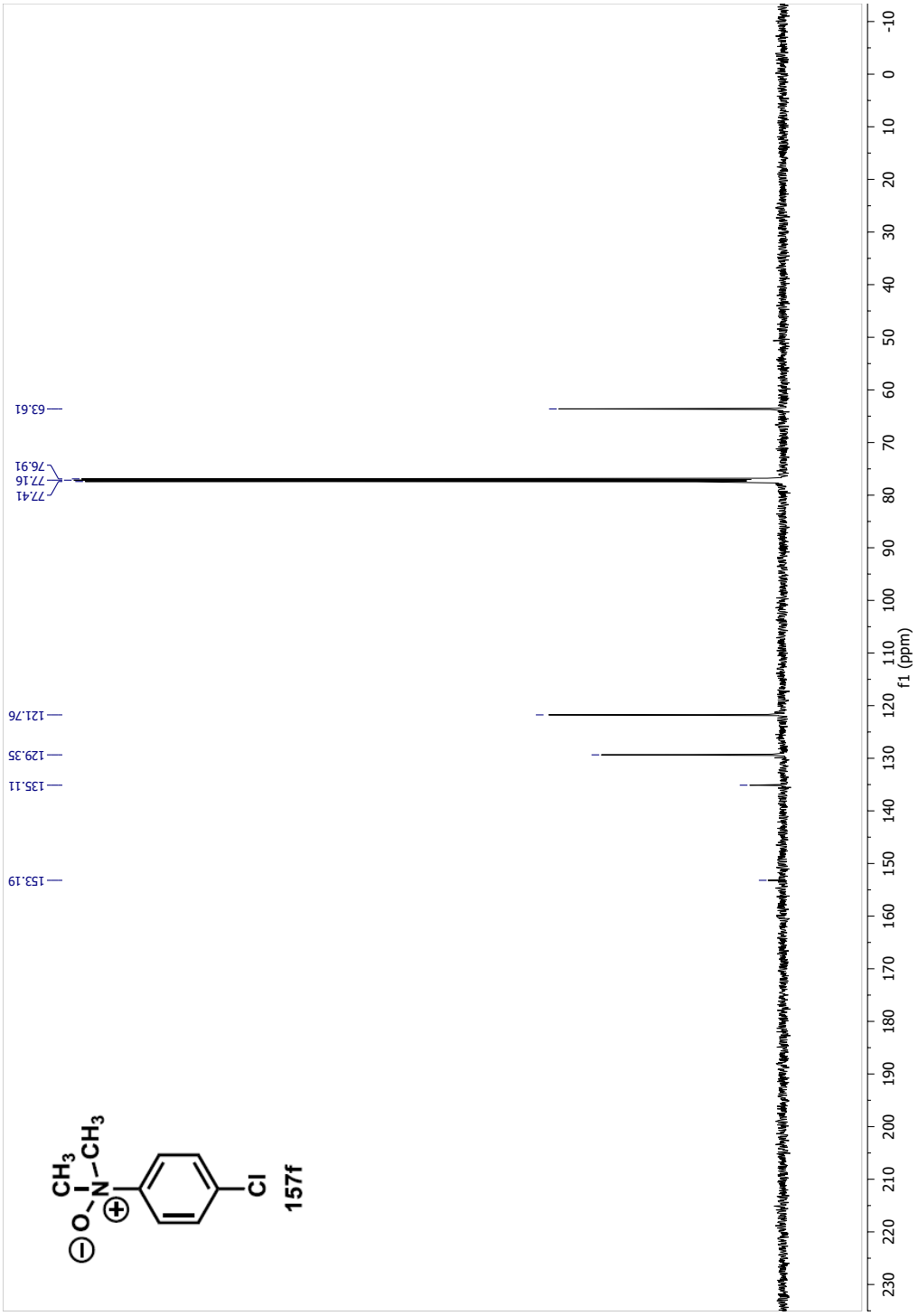

157d
6.00
0.99
0.94
1.83
1.86
0.91
f1 (ppm)


157d
62.72
77.41
77.16
76.91
135.81
131.04
129.59
127.08
126.23
125.79
125.36
124.50
118.40
f1 (ppm)

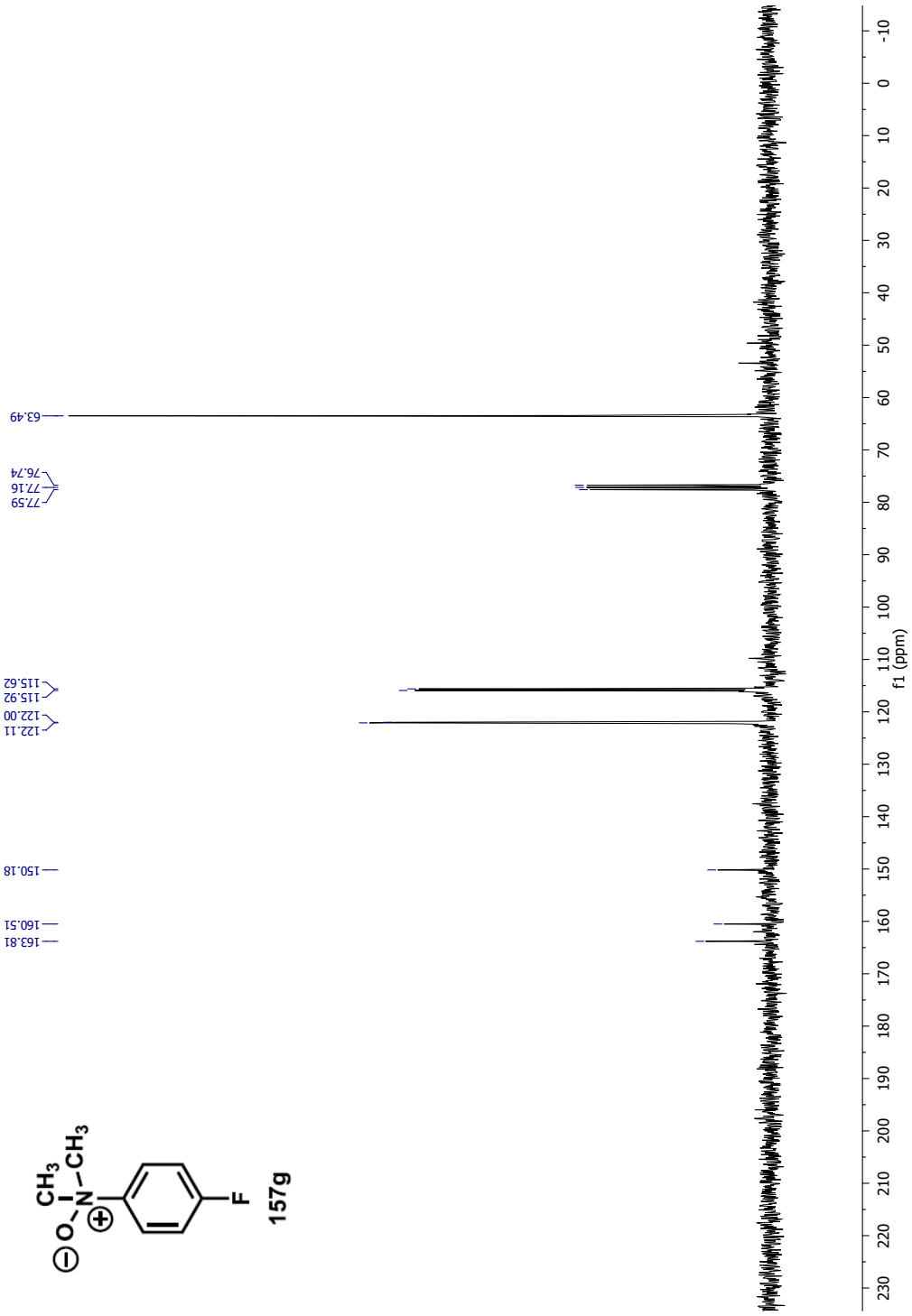

157e
2.81
6.00
0.91
0.96
0.93
0.91
f1 (ppm)

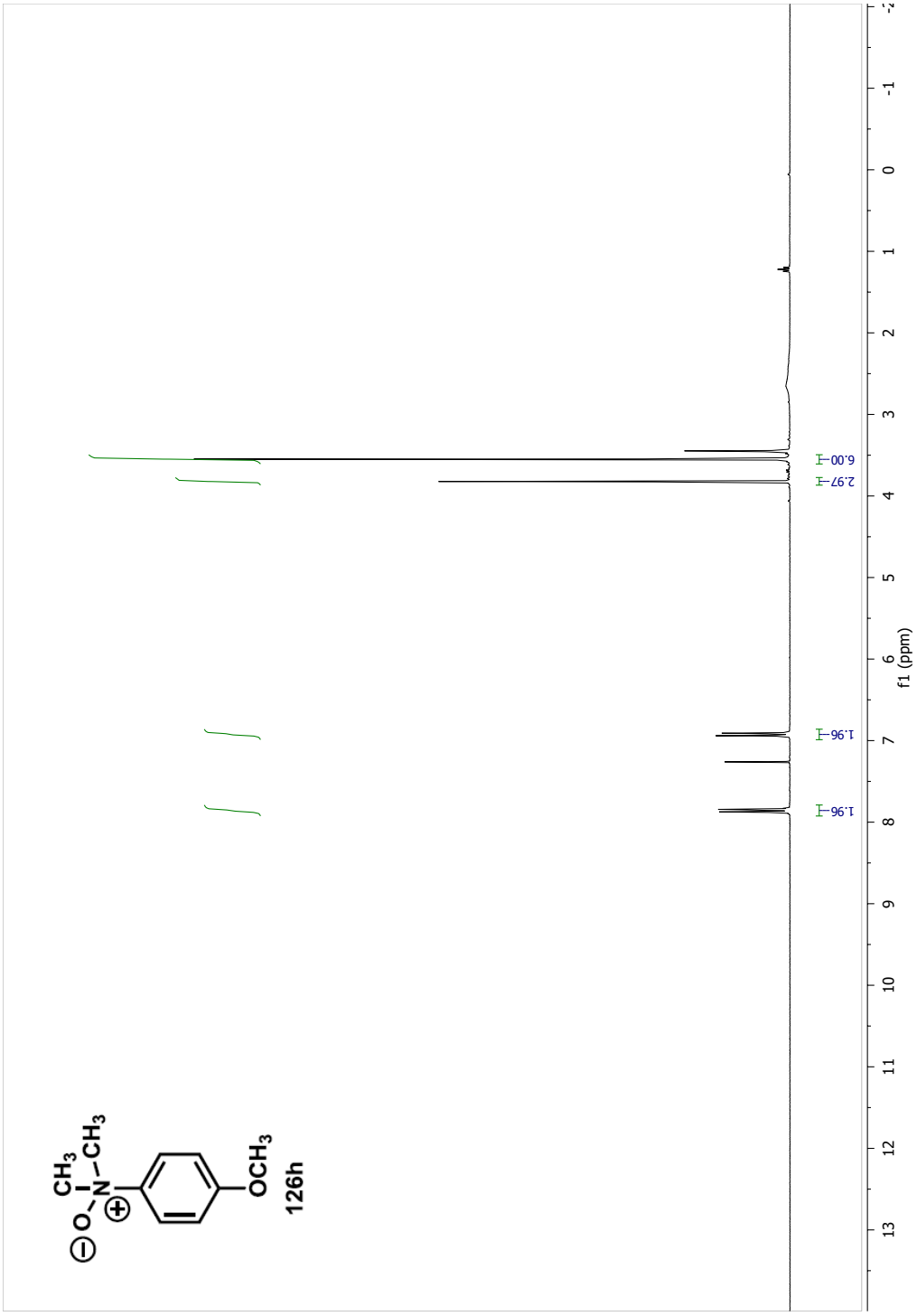

21.68
63.28
76.74
77.16
77.58
110.10
116.68
120.77
128.96
129.74
139.77
f1 (ppm)
157e

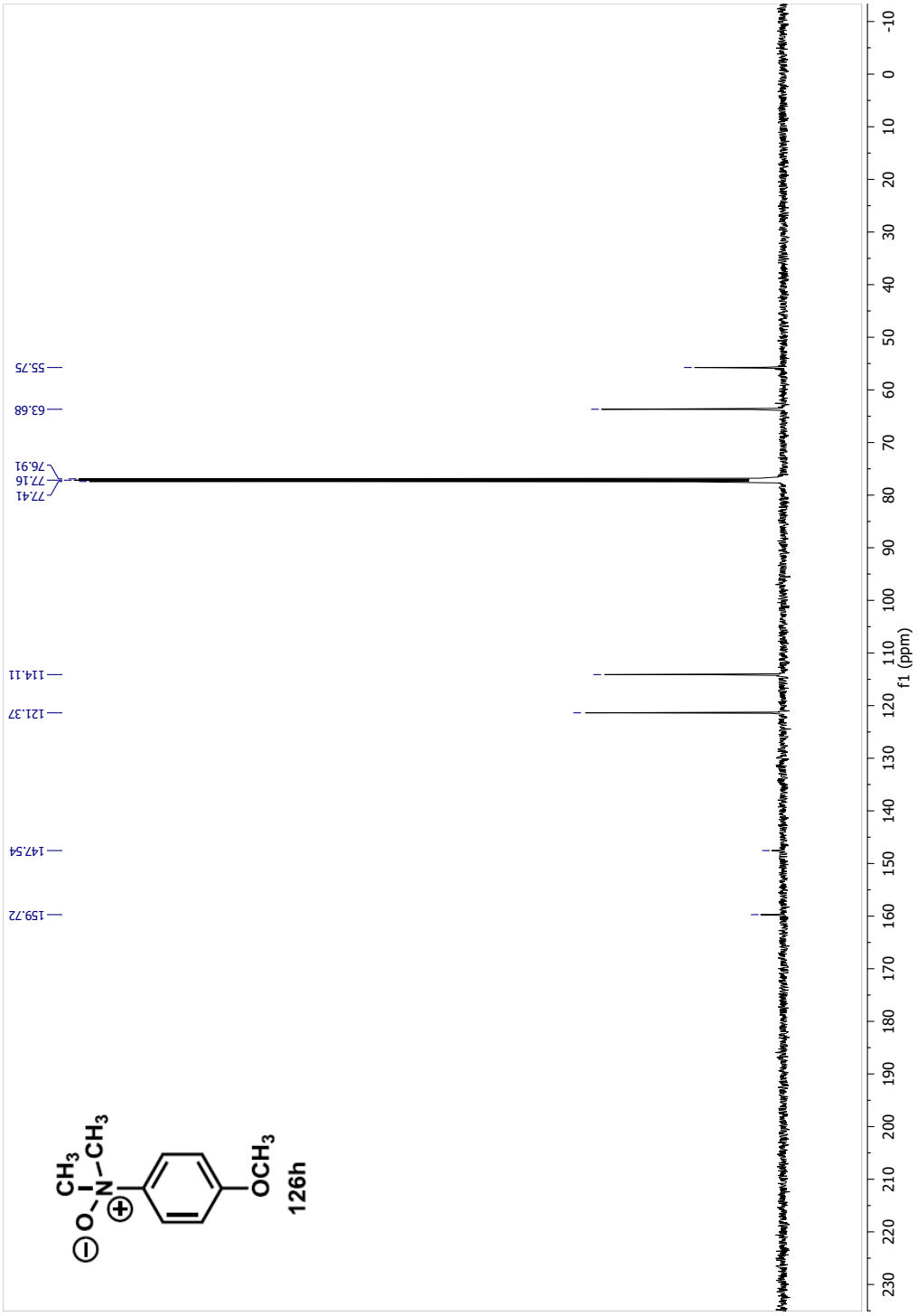

6.00
1.66
1.75
f1 (ppm)
157f

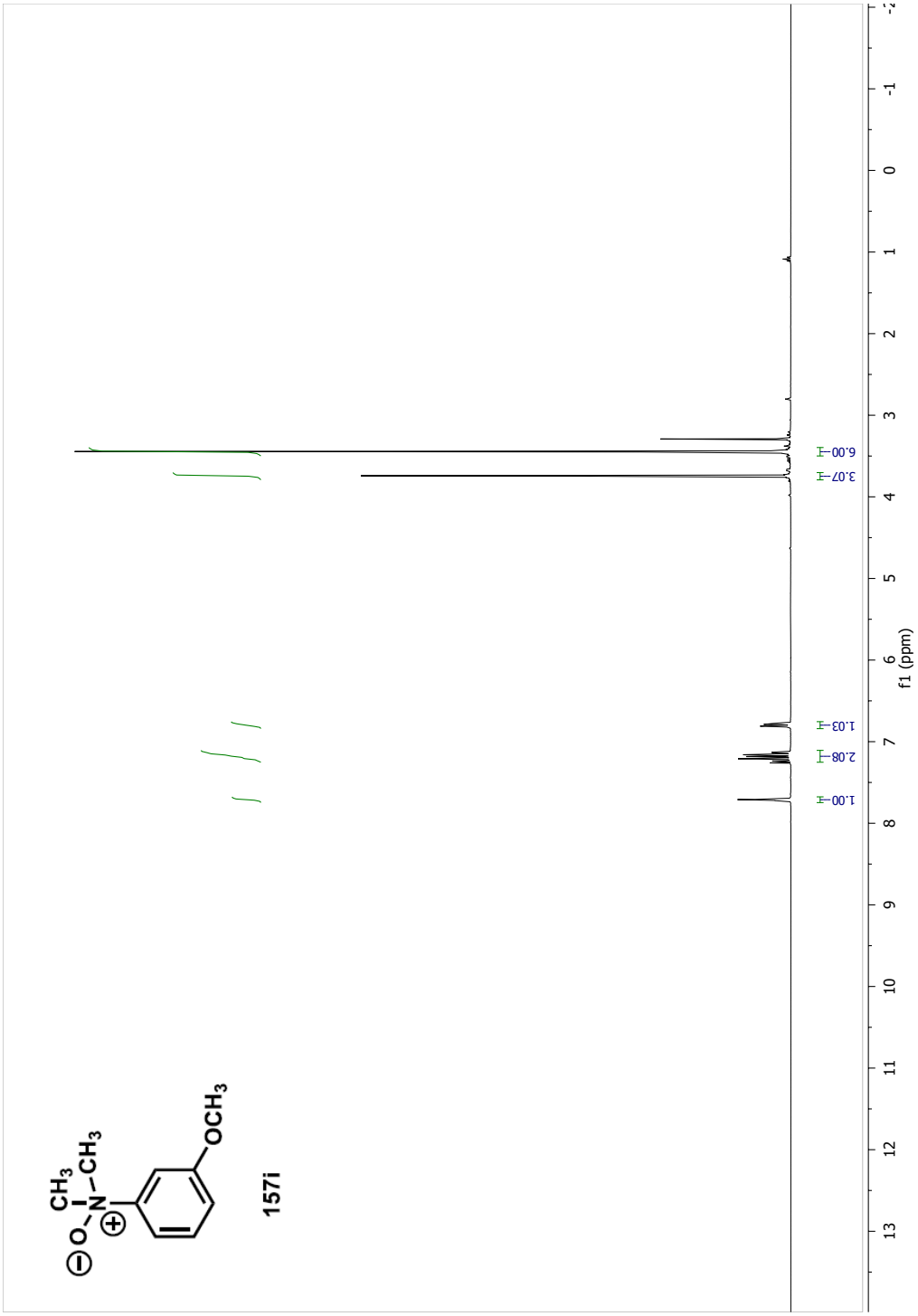

63.61
76.91
77.16
77.41
121.76
129.35
135.11
153.19
f1 (ppm)
157f

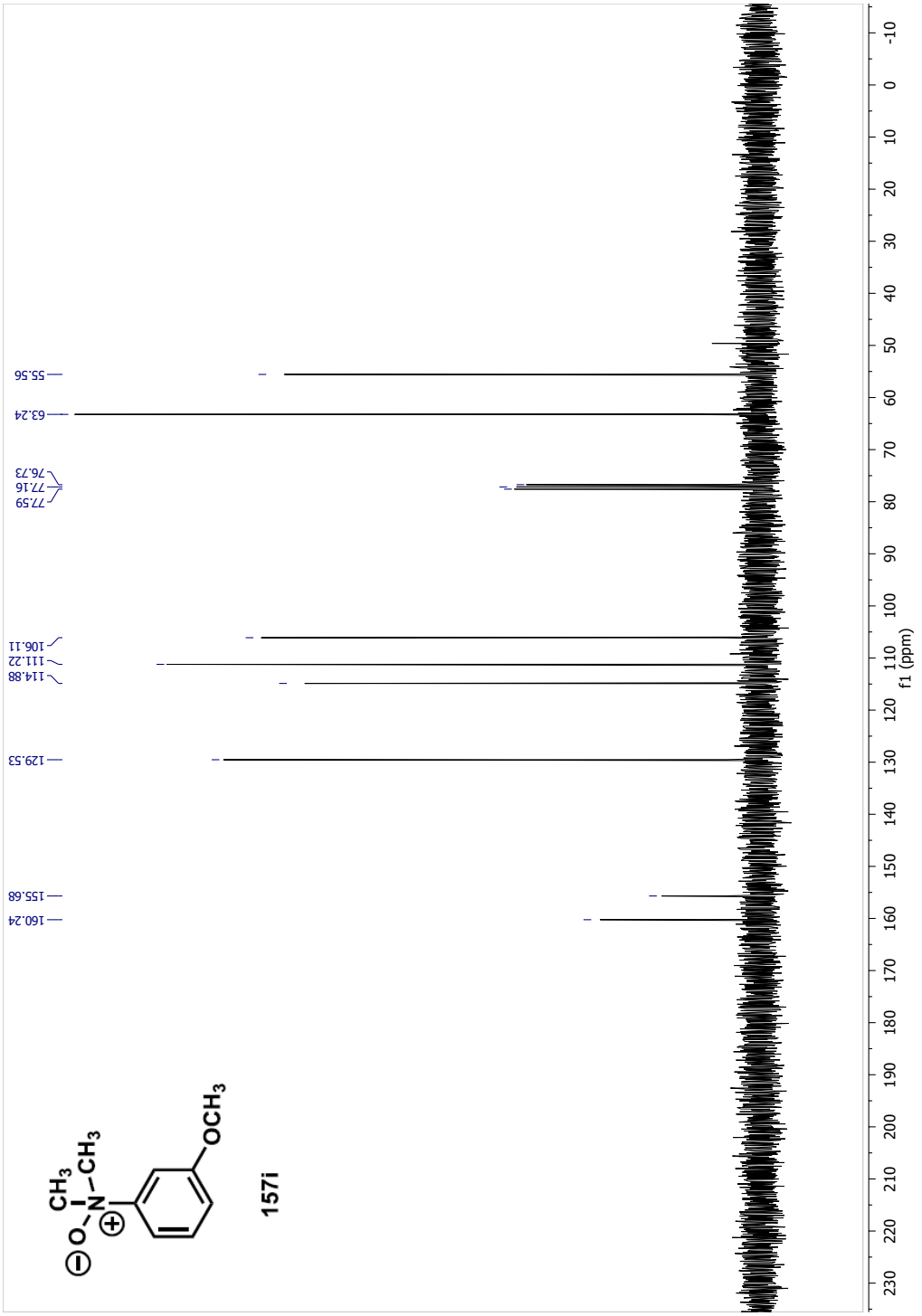
157g

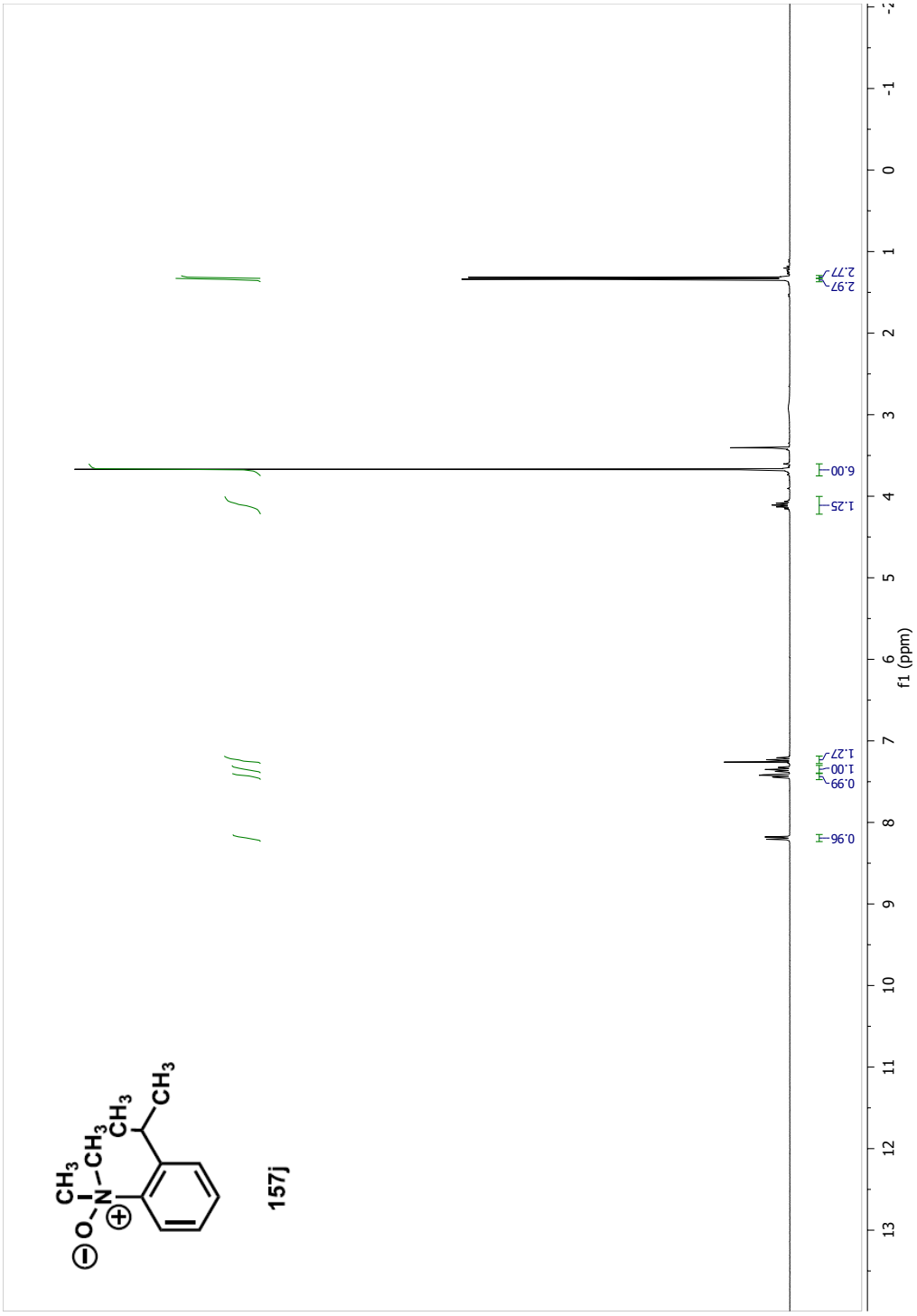

63.49
76.74
77.16
77.59
115.62
115.92
122.00
122.11
150.18
160.51
163.81
f1 (ppm)
157g

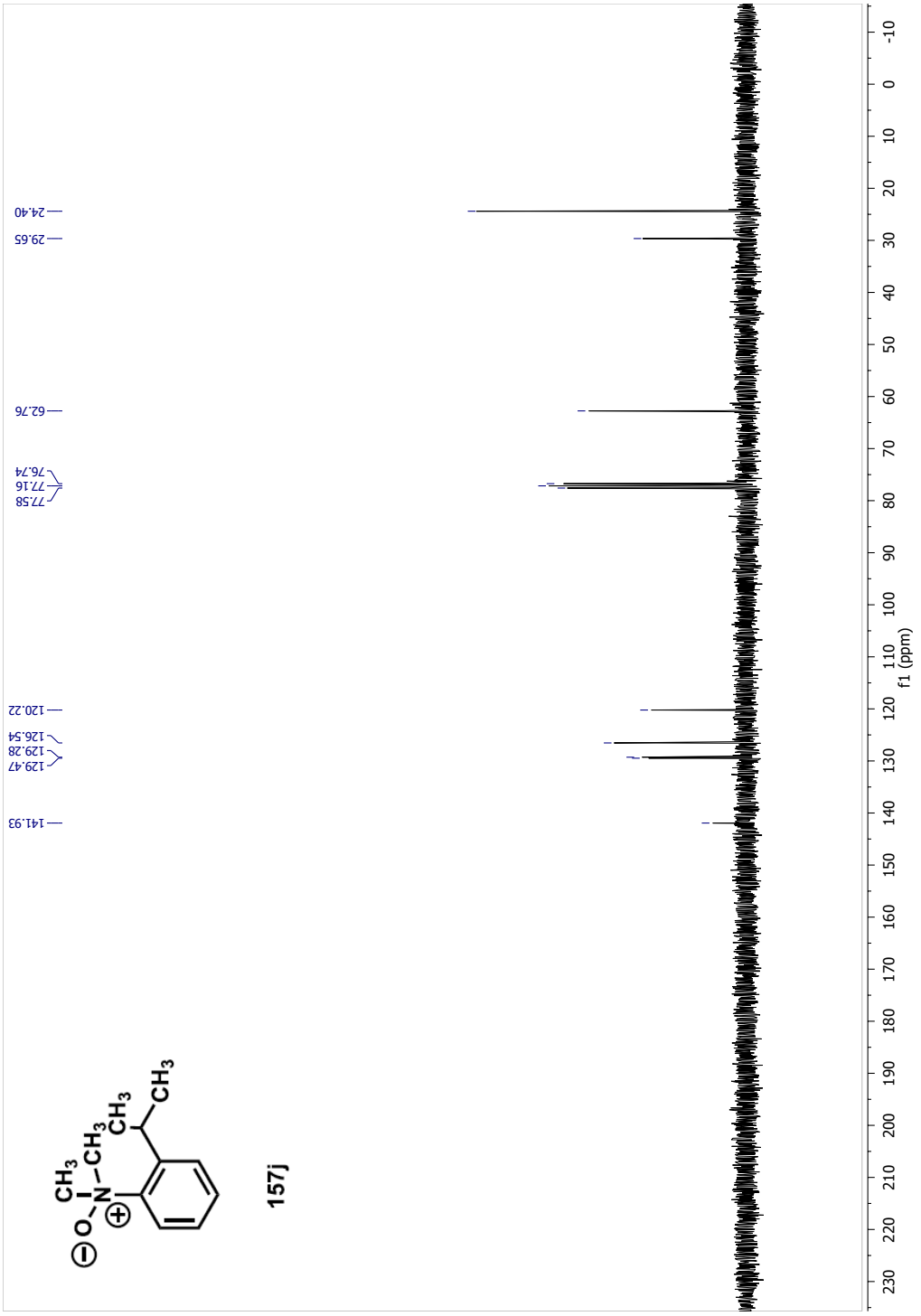

6.00
2.97
1.96
1.96
f1 (ppm)
126h

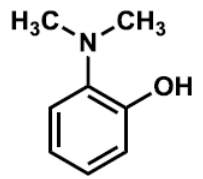

126h
159.72
147.54
121.37
114.11
77.41
77.16
76.91
63.68
55.75
f1 (ppm)


157i
6.00
3.07
1.03
2.08
1.00
f1 (ppm)

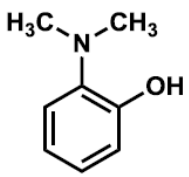

157i
OCH3
CH3
CH3
55.56
63.24
76.73
77.16
77.59
106.11
111.22
114.88
129.53
155.68
160.24
f1 (ppm)


157j
2.97
2.77
6.00
1.25
0.96
1.27
1.00
0.99
f1 (ppm)


157j
24.40
29.65
62.76
76.74
77.16
77.58
120.22
126.54
129.28
129.47
141.93
f1 (ppm)

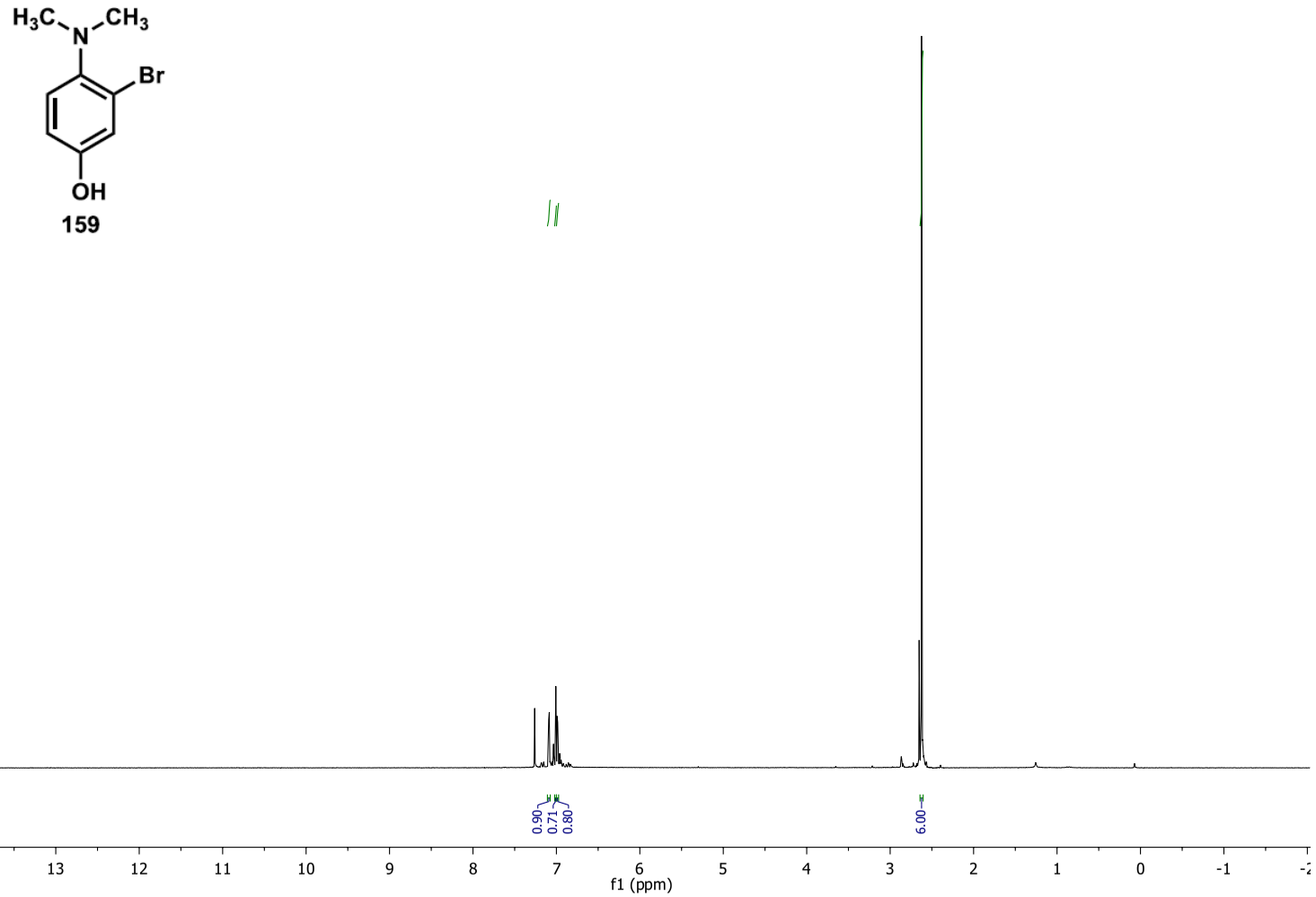


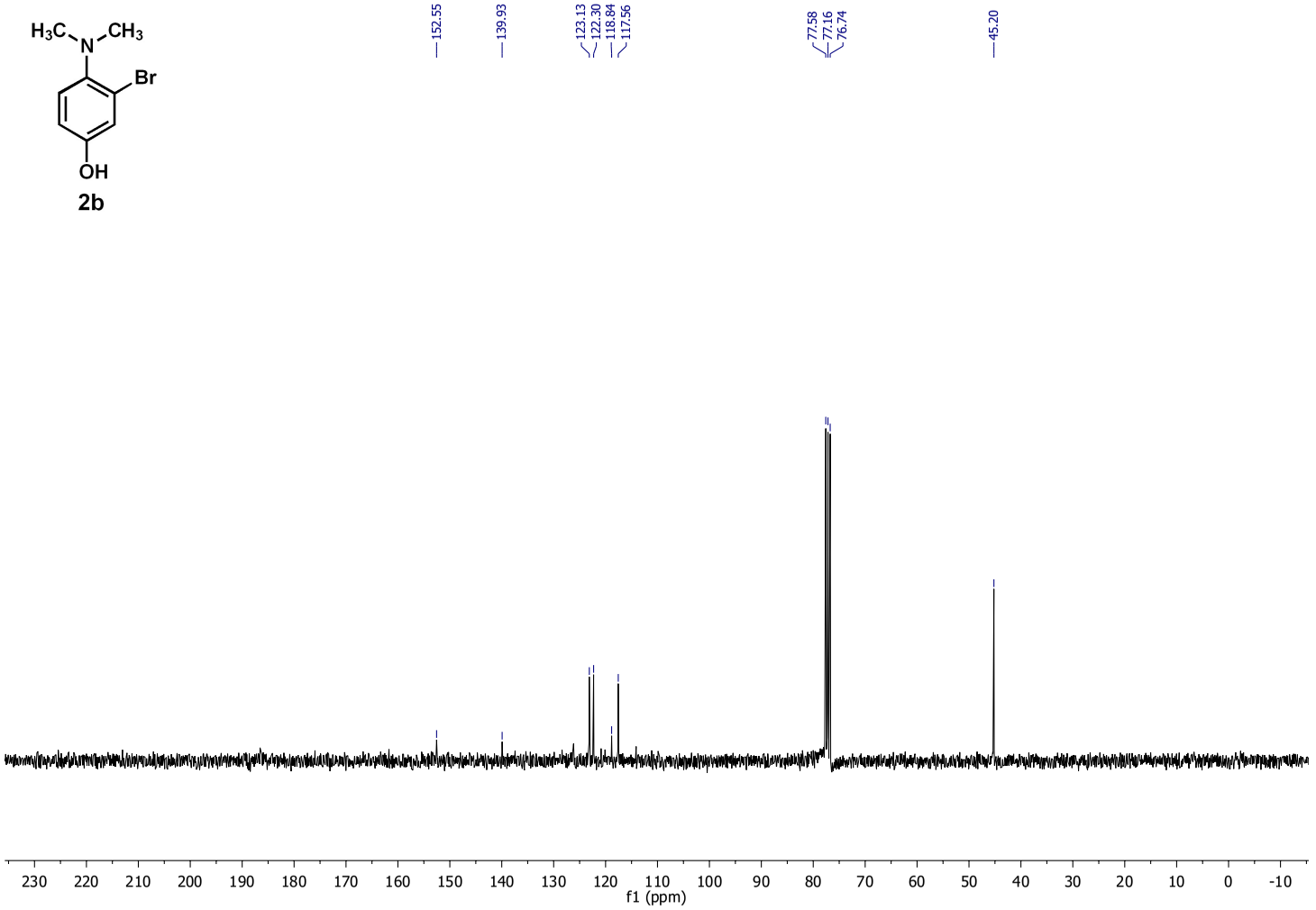
158

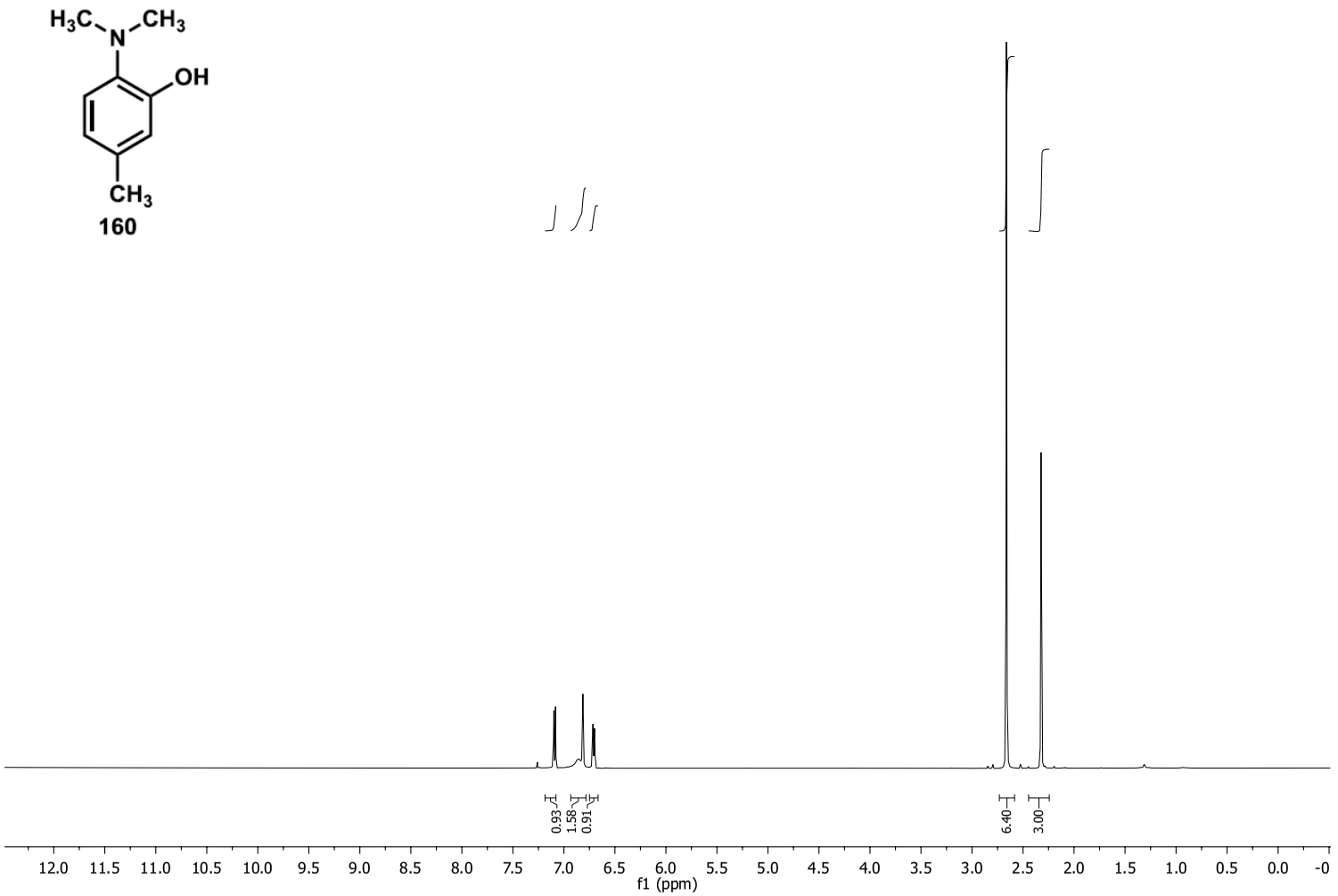

H3C
N
CH3
OH

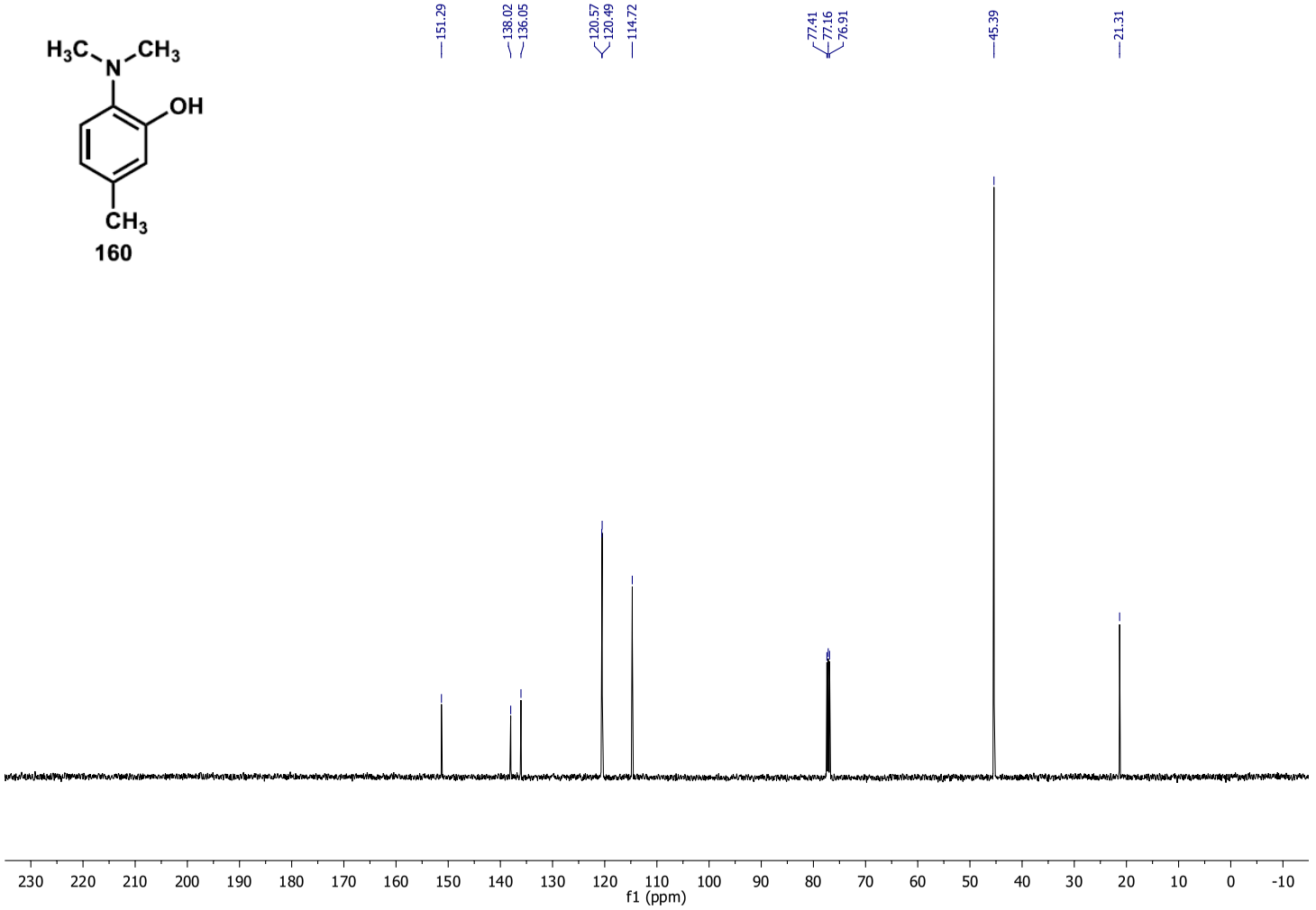
158

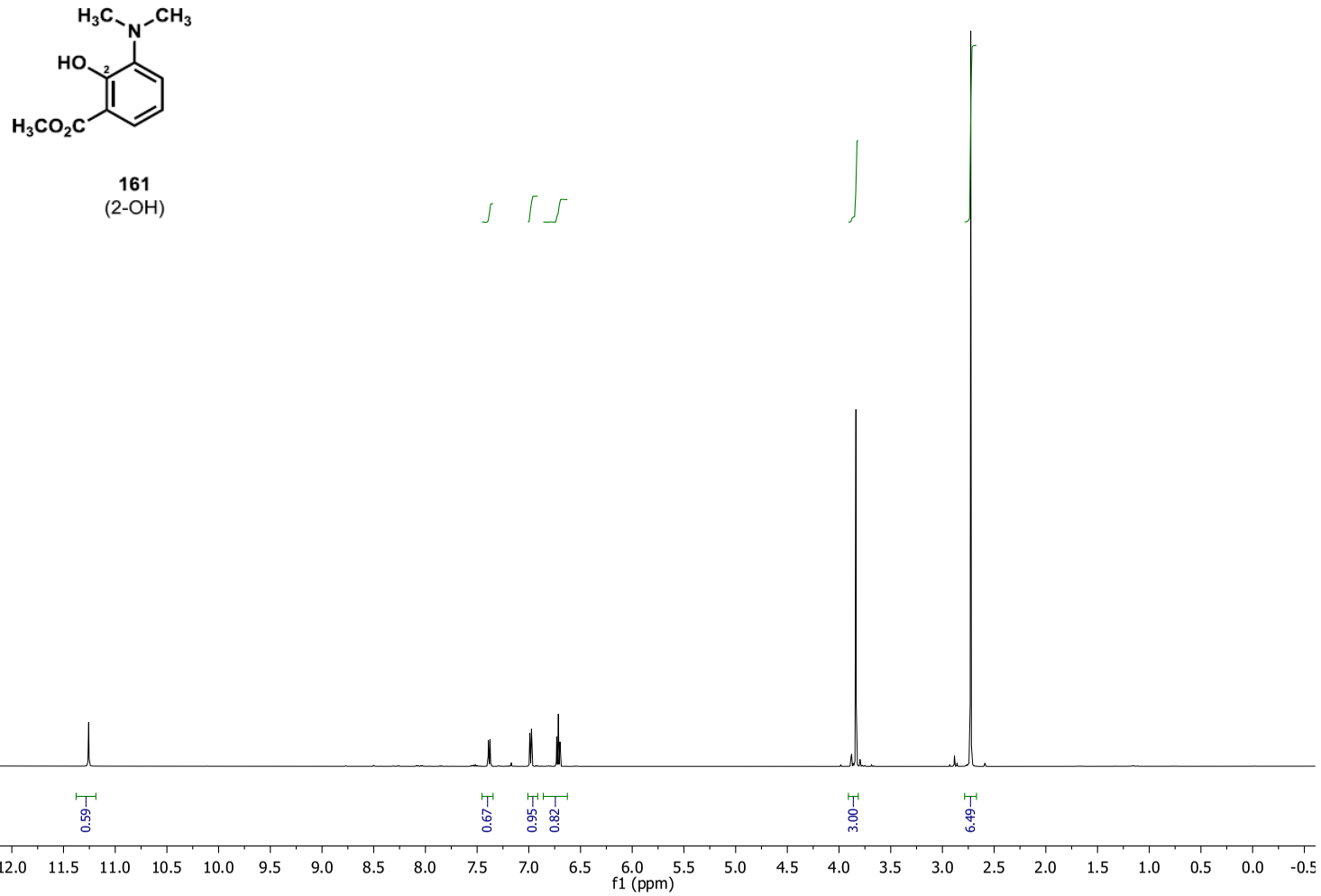
151.61
140.68
126.16
120.84
120.09
114.11
77.58
77.16
76.74
45.31
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

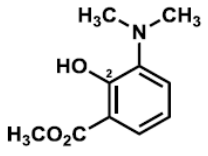

H3C
N
CH3
Br
OH
159
0.90
0.71
0.80
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


H3C
N
CH3
Br
OH
2b
152.55
139.93
123.13
122.30
118.84
117.56
77.58
77.16
76.74
45.20
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OH
CH3
160
0.93
1.58
0.91
6.40
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

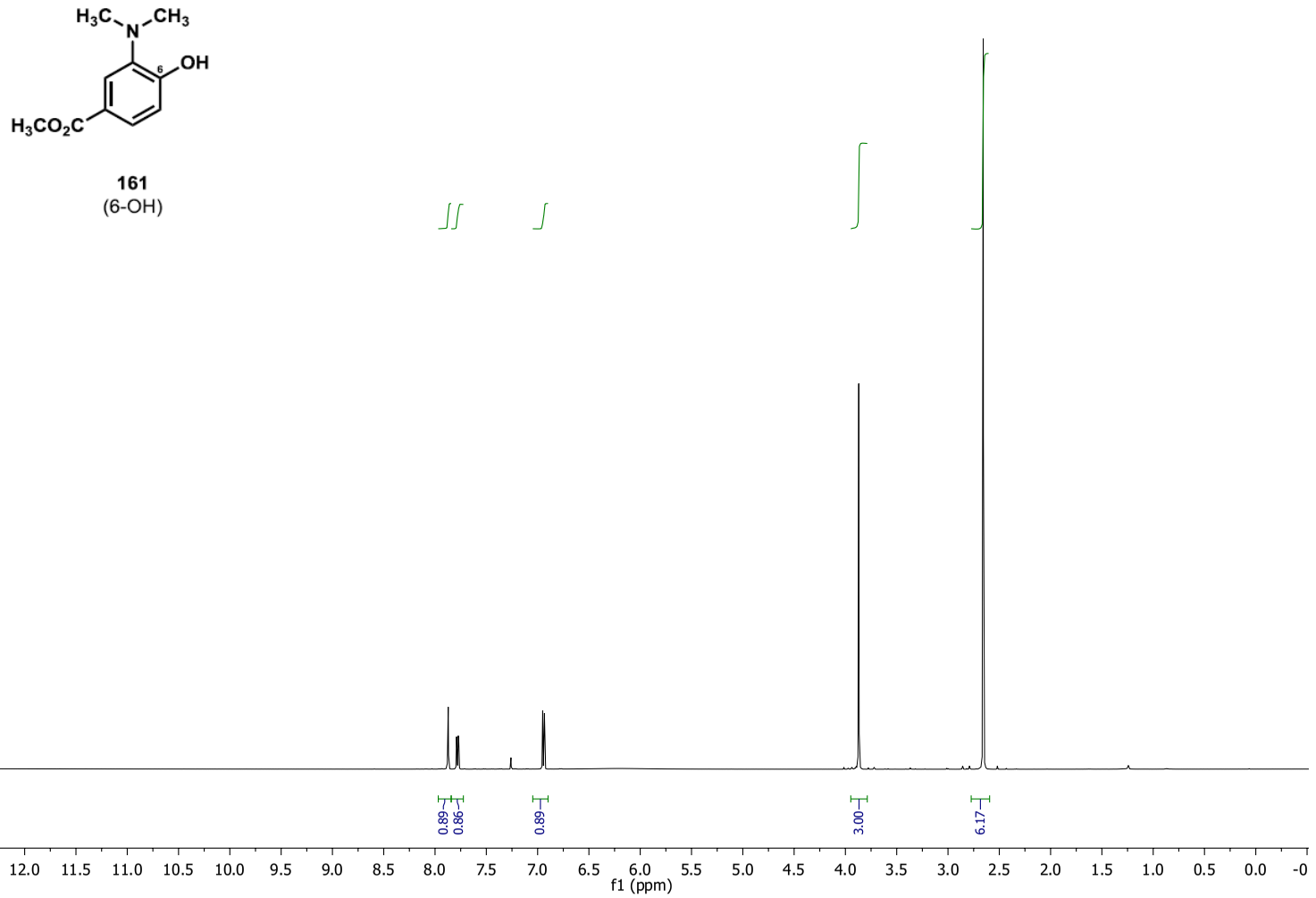

H3C
N
CH3
OH
CH3
160
151.29
138.02
136.05
120.57
120.49
114.72
77.41
77.16
76.91
45.39
21.31
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

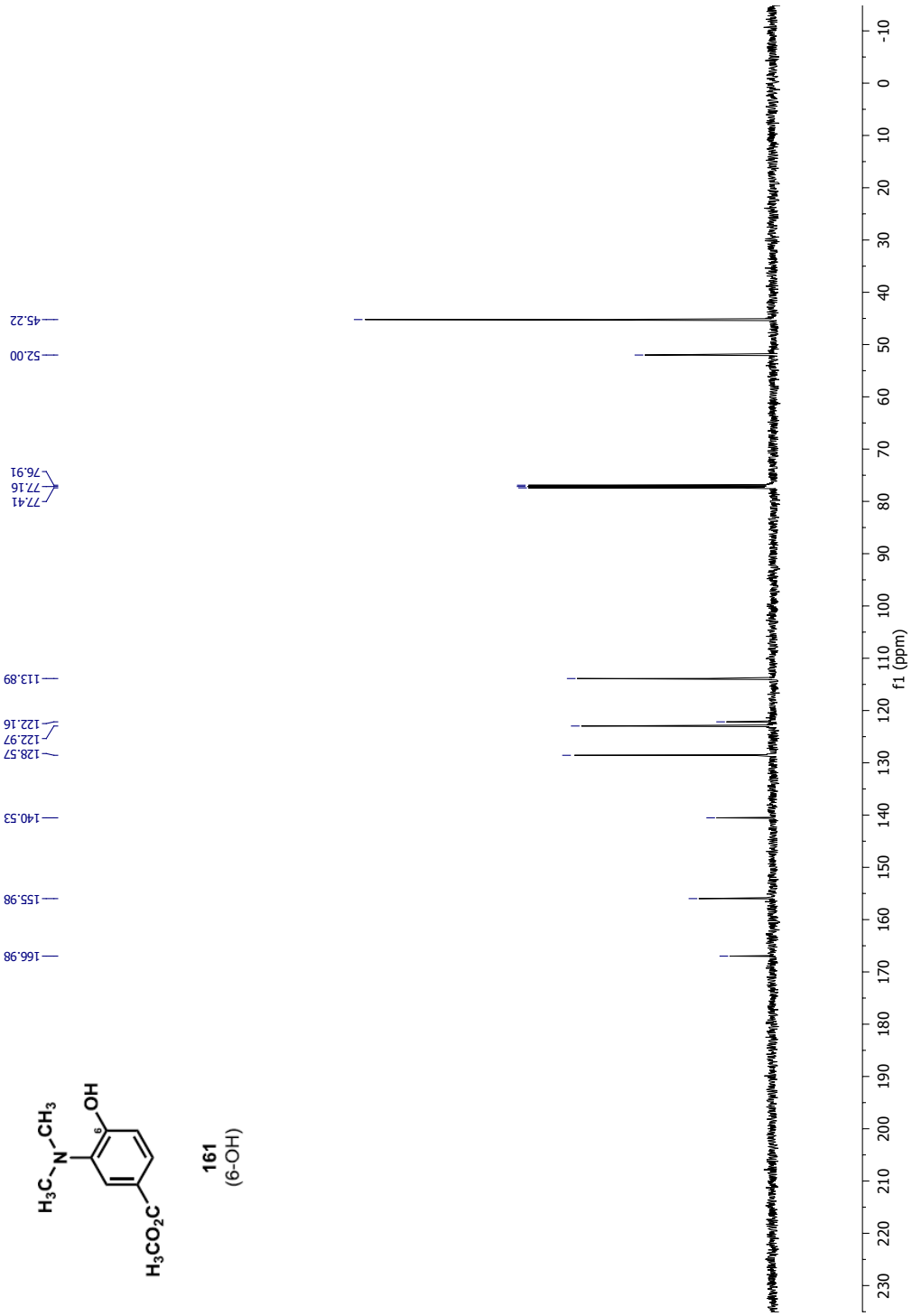

H3C
N
CH3
HO
2
H3CO2C
161
(2-OH)
0.59
0.67
0.95
0.82
3.00
6.49
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


H3C
N
CH3
HO
2
H3CO2C

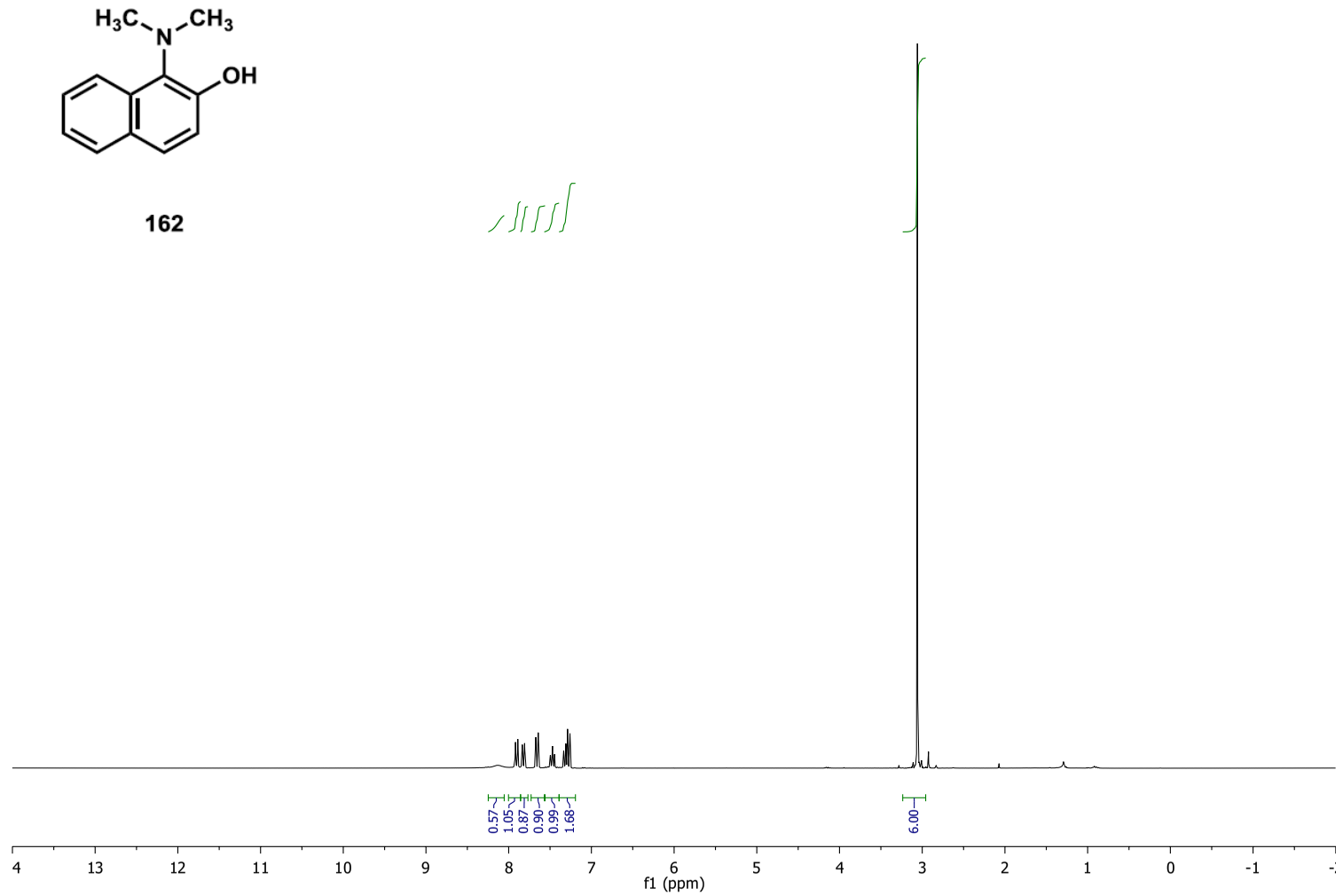
161
(2-OH)

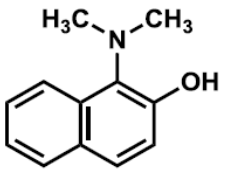
171.45
155.37
142.21
123.48
122.53
118.83
112.30
77.41
77.16
76.91
52.40
43.10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OH
6
H3CO2C
161
(6-OH)
0.89
0.86
0.89
3.00
6.17
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


45.22
52.00
76.91
77.16
77.41
113.89
122.16
122.97
128.57
140.53
155.98
166.98
f1 (ppm)

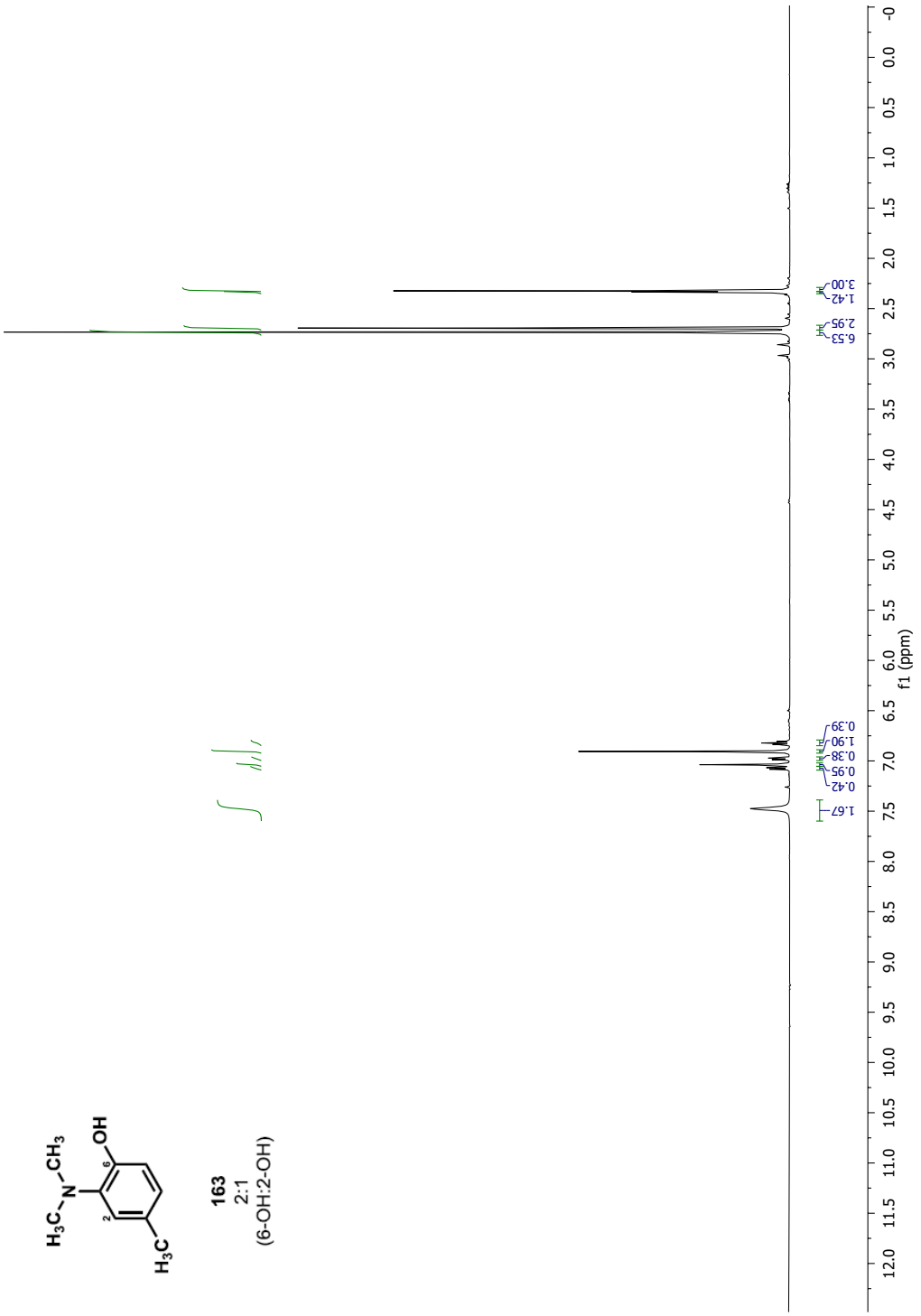
161
(6-OH)

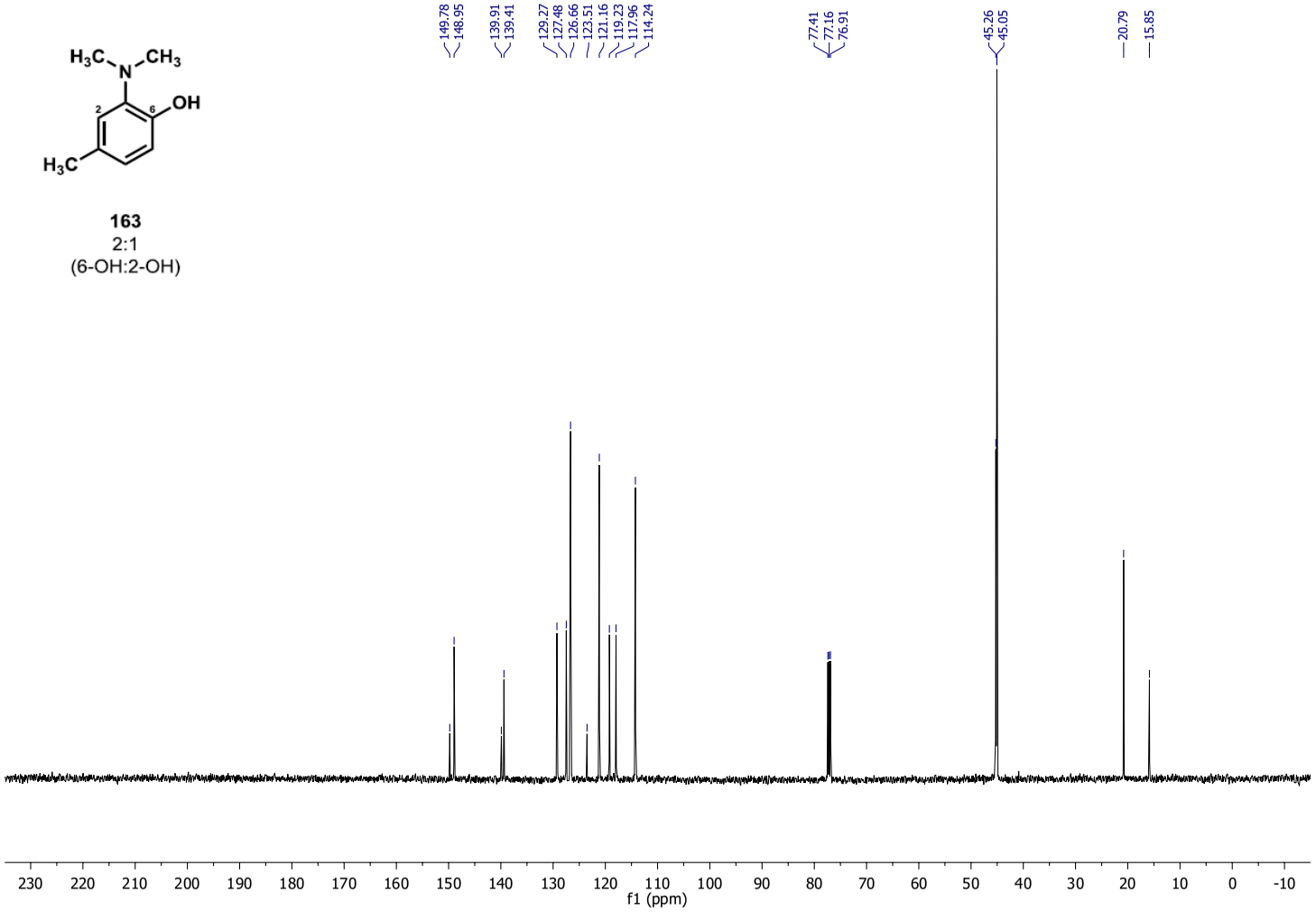

H3C
N
CH3
OH
162
0.57
1.05
0.87
0.90
0.99
1.68
6.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

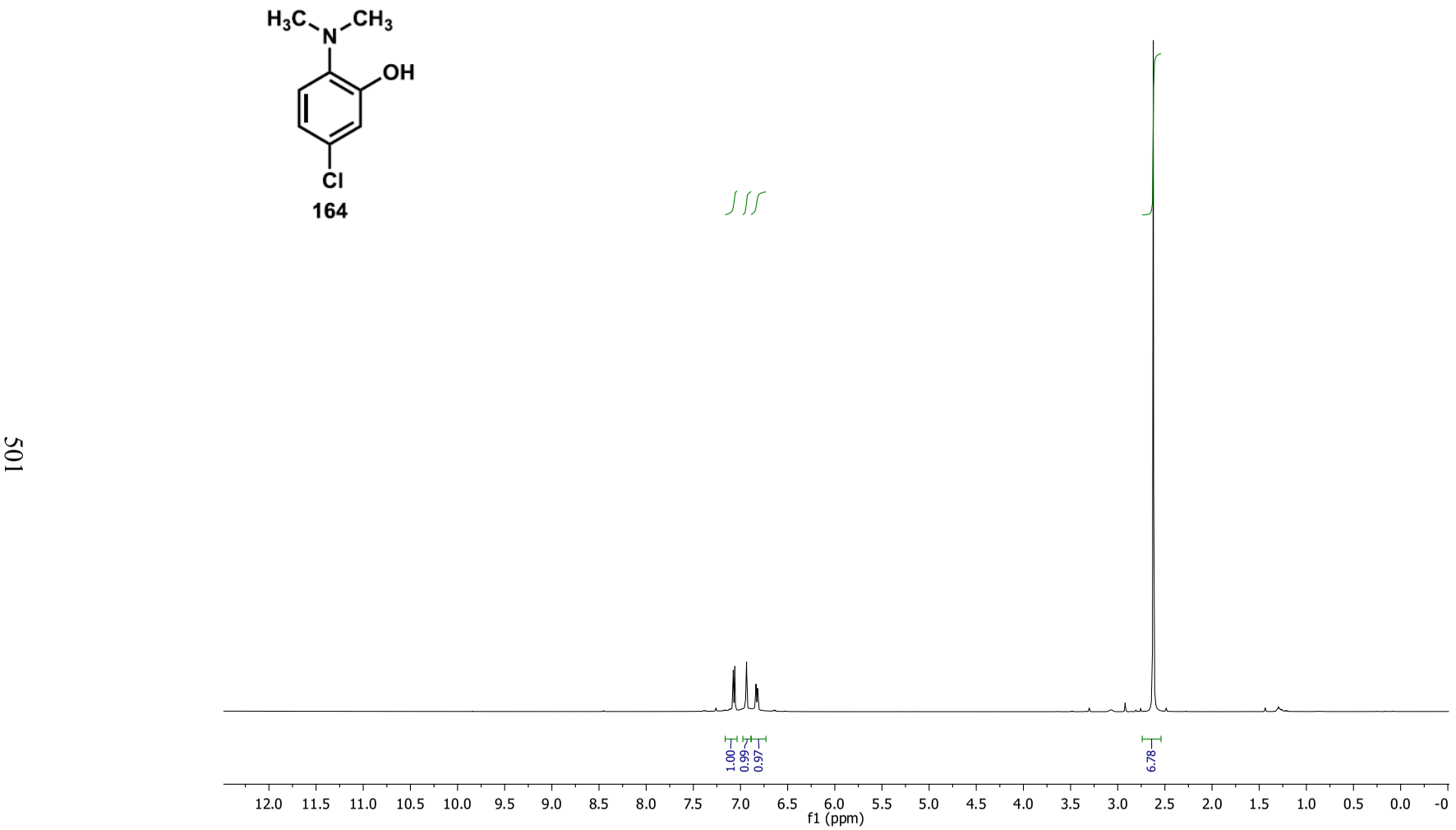

H3C
N
CH3
OH

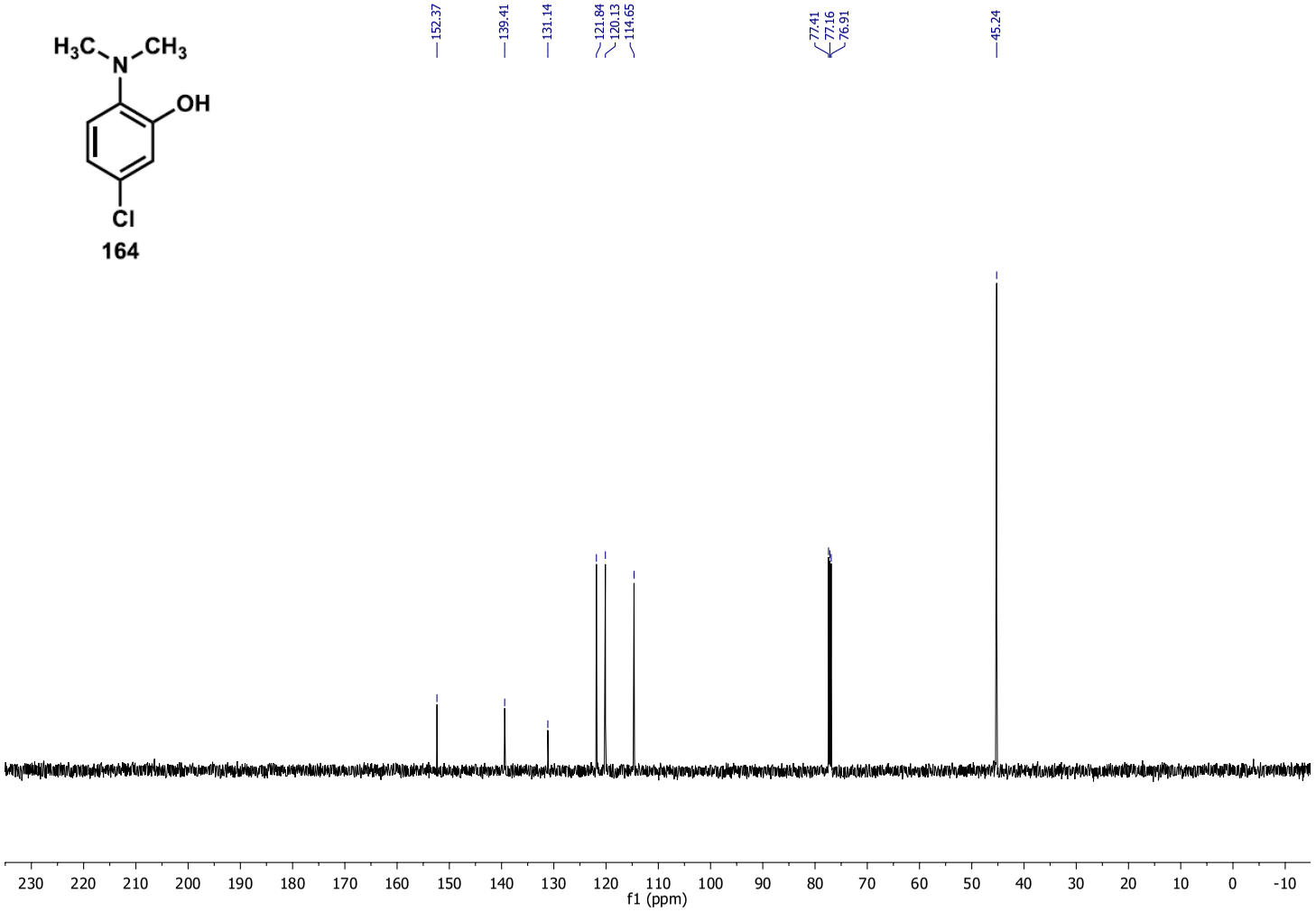
162

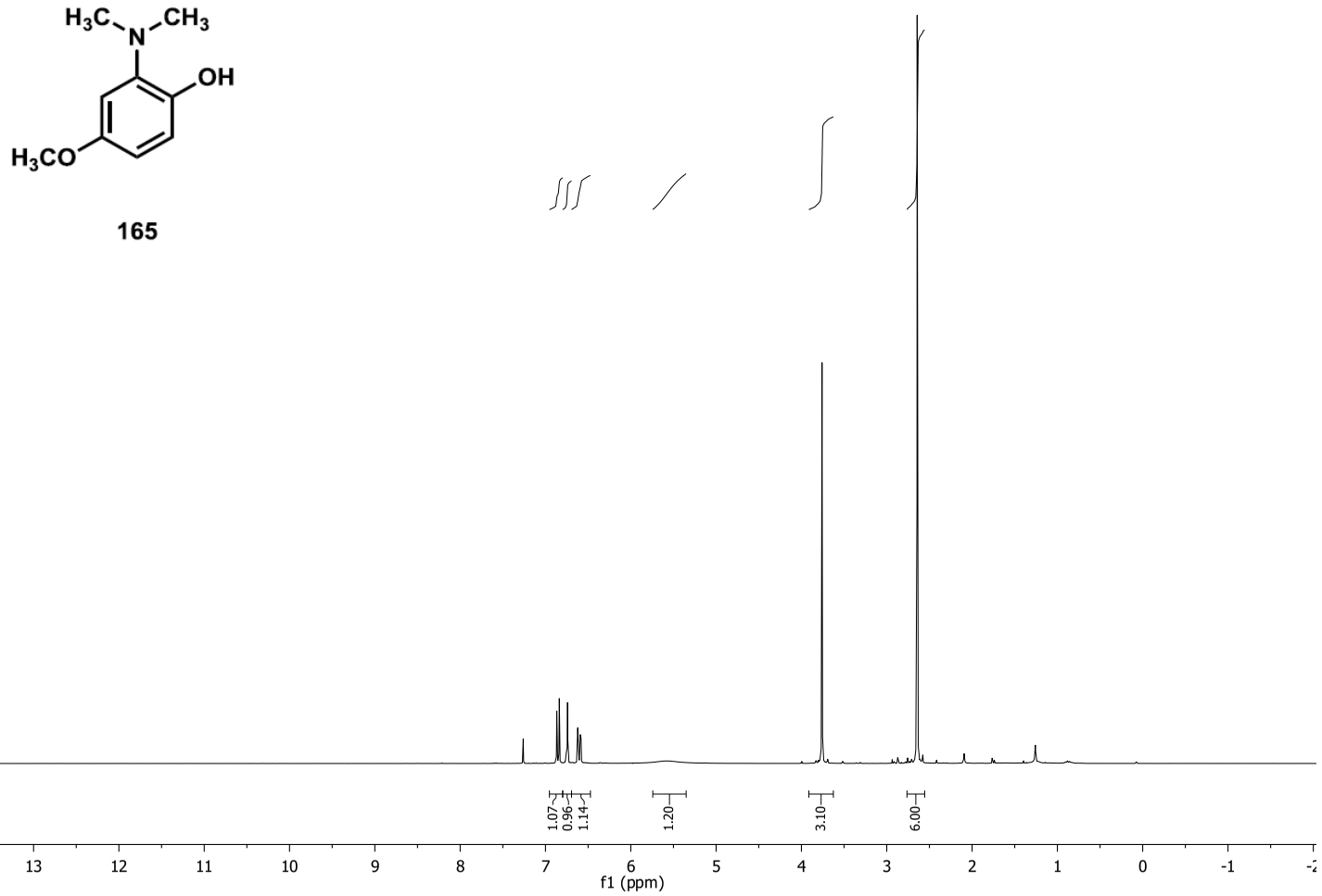
151.80
131.68
129.80
129.64
128.23
126.00
122.54
122.02
116.11
77.58
77.16
76.74
44.02
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

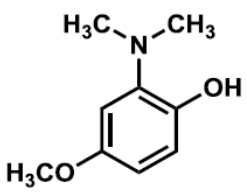

H3C
CH3
N
OH
6
2
H3C
163
2:1
(6-OH:2-OH)
1.67
0.42
0.95
0.38
1.90
0.39
1.42
3.00
2.95
6.53
f1 (ppm)


H3C
N
CH3
2
6
OH
H3C
163
2:1
(6-OH:2-OH)
149.78
148.95
139.91
139.41
129.27
127.48
126.66
123.51
121.16
119.23
117.96
114.24
77.41
77.16
76.91
45.26
45.05
20.79
15.85
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OH
Cl
164
1.00
0.99
0.97
6.78
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

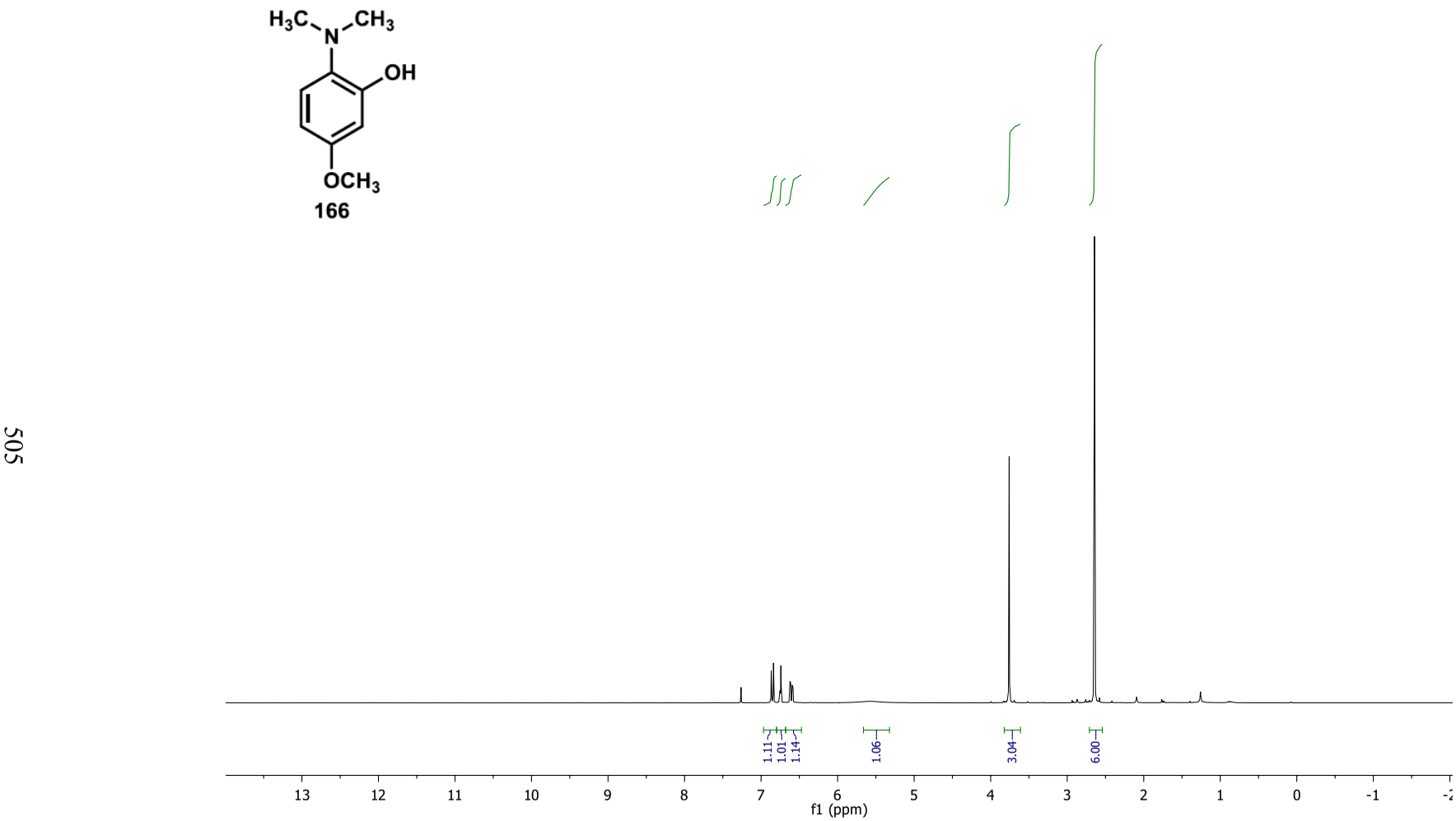

H3C
N
CH3
OH
Cl
164
152.37
139.41
131.14
121.84
120.13
114.65
77.41
77.16
76.91
45.24
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

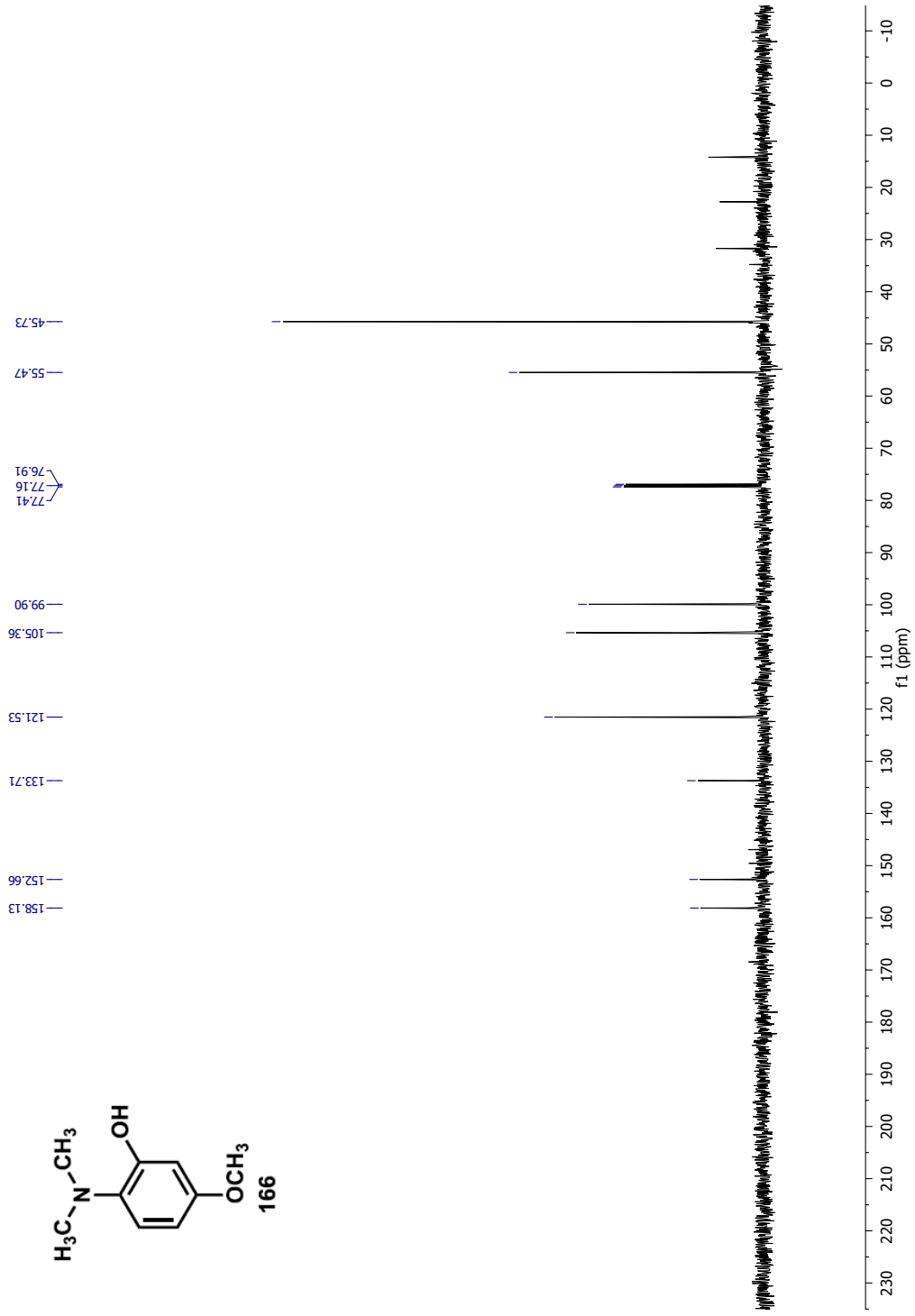

H3C
N
CH3
OH
H3CO
165
1.07
0.96
1.14
1.20
3.10
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

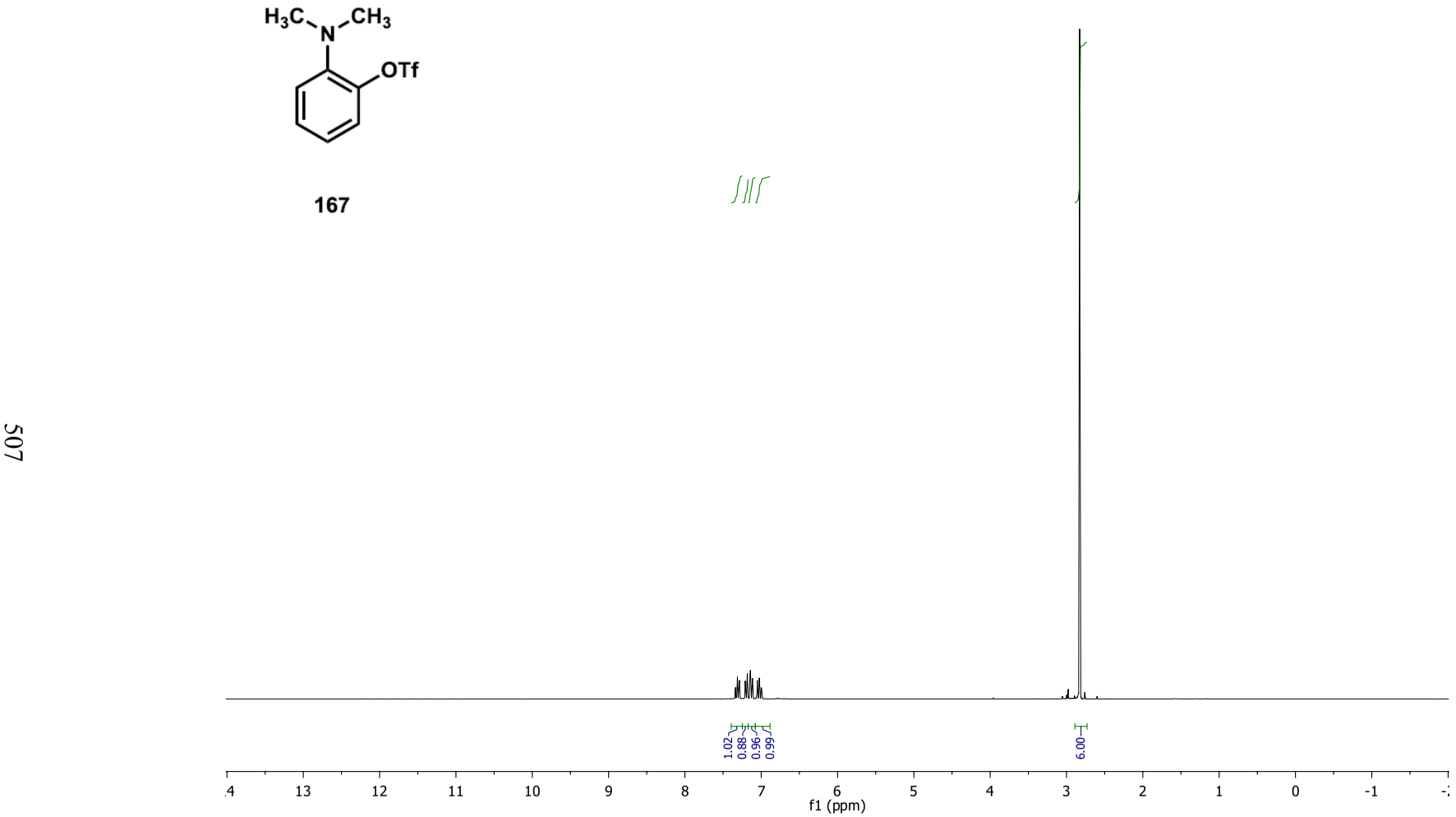

H3C
N
CH3
OH
H3CO

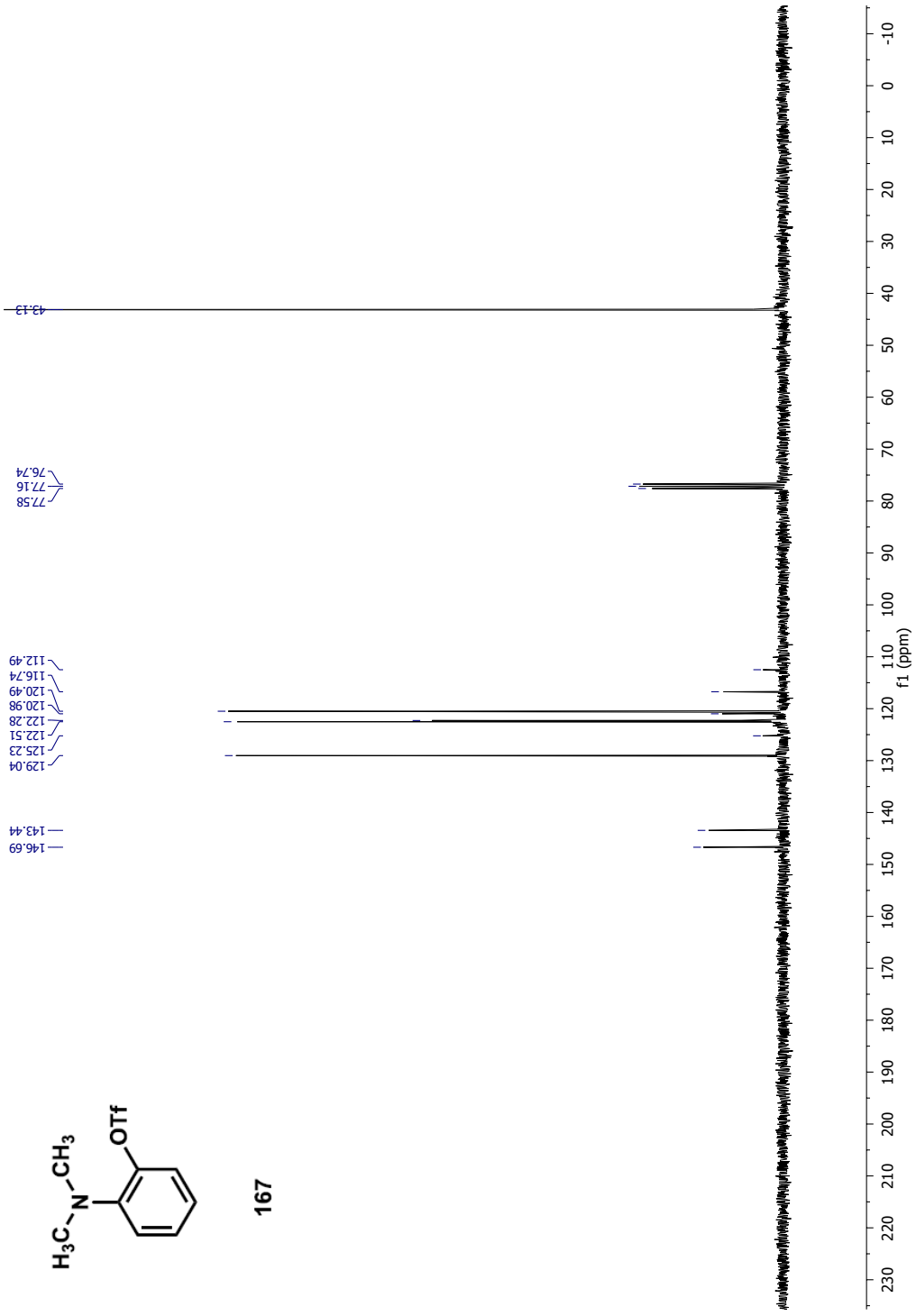
165

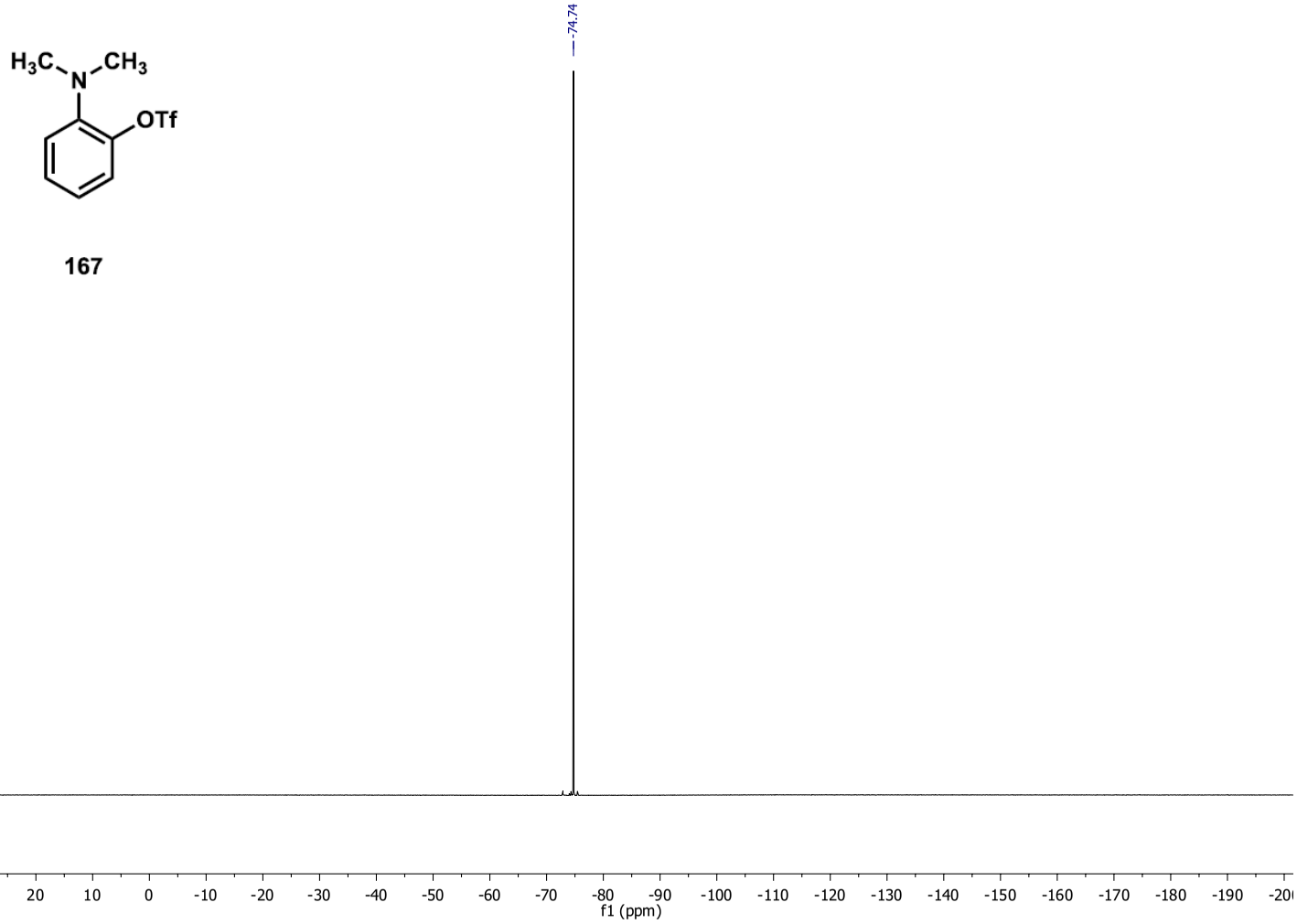
153.35
145.44
141.20
114.24
110.19
107.61
77.58
77.16
76.74
55.94
45.07
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

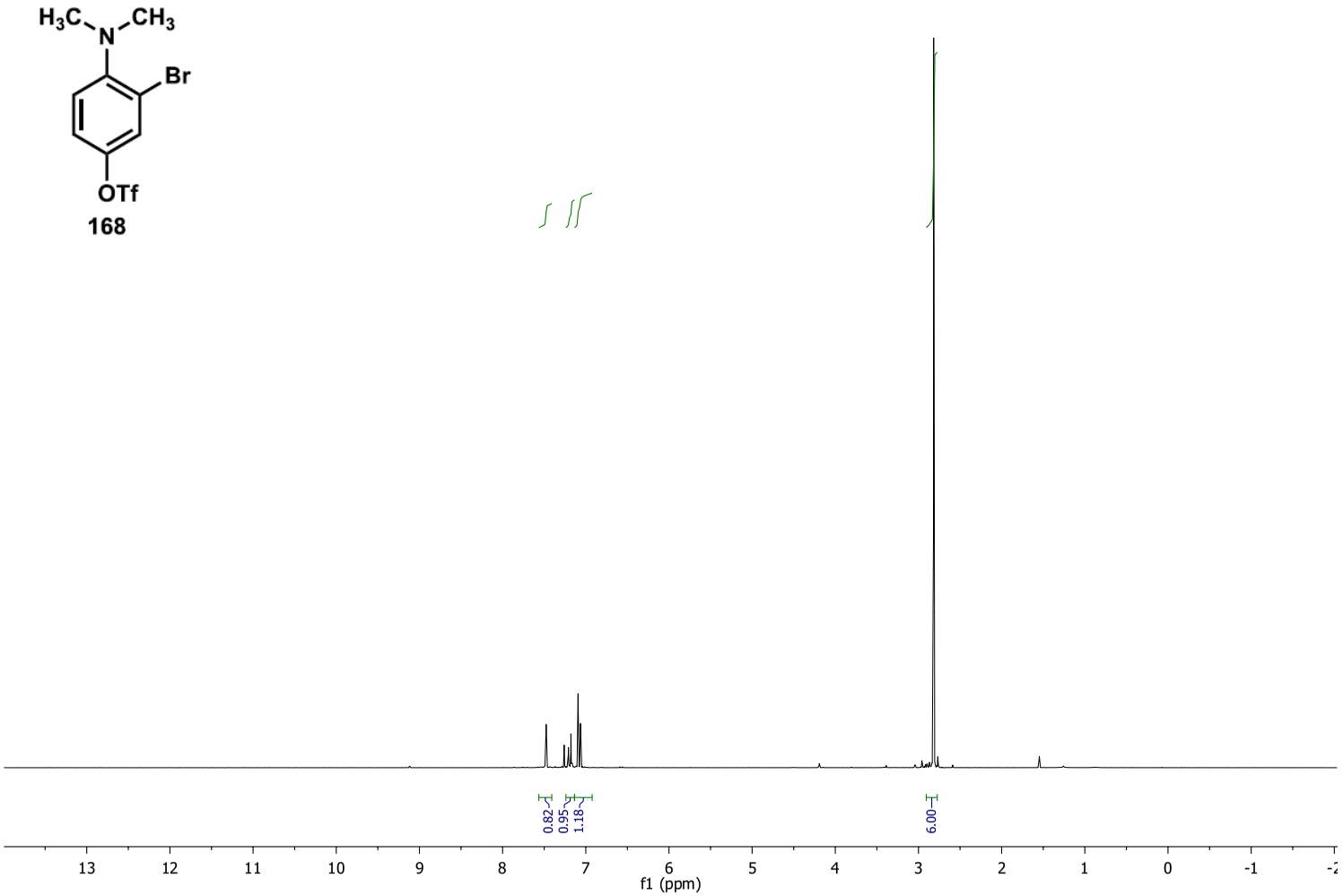

H3C
N
CH3
OH
OCH3
166
1.11
1.01
1.14
1.06
3.04
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

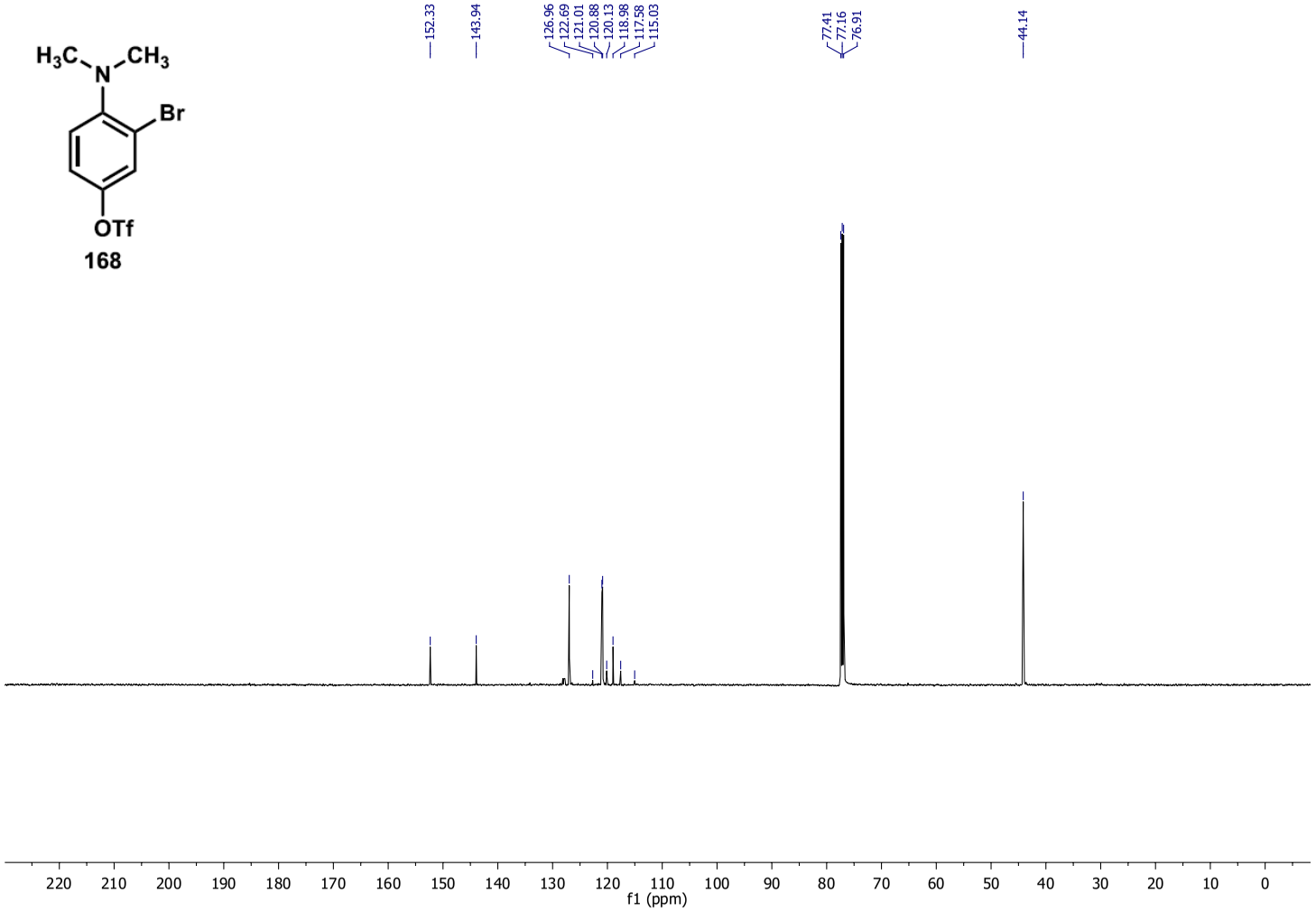

158.13
152.66
133.71
121.53
105.36
99.90
77.41
77.16
76.91
55.47
45.73
f1 (ppm)
OH
CH3
N
H3C
OCH3
166

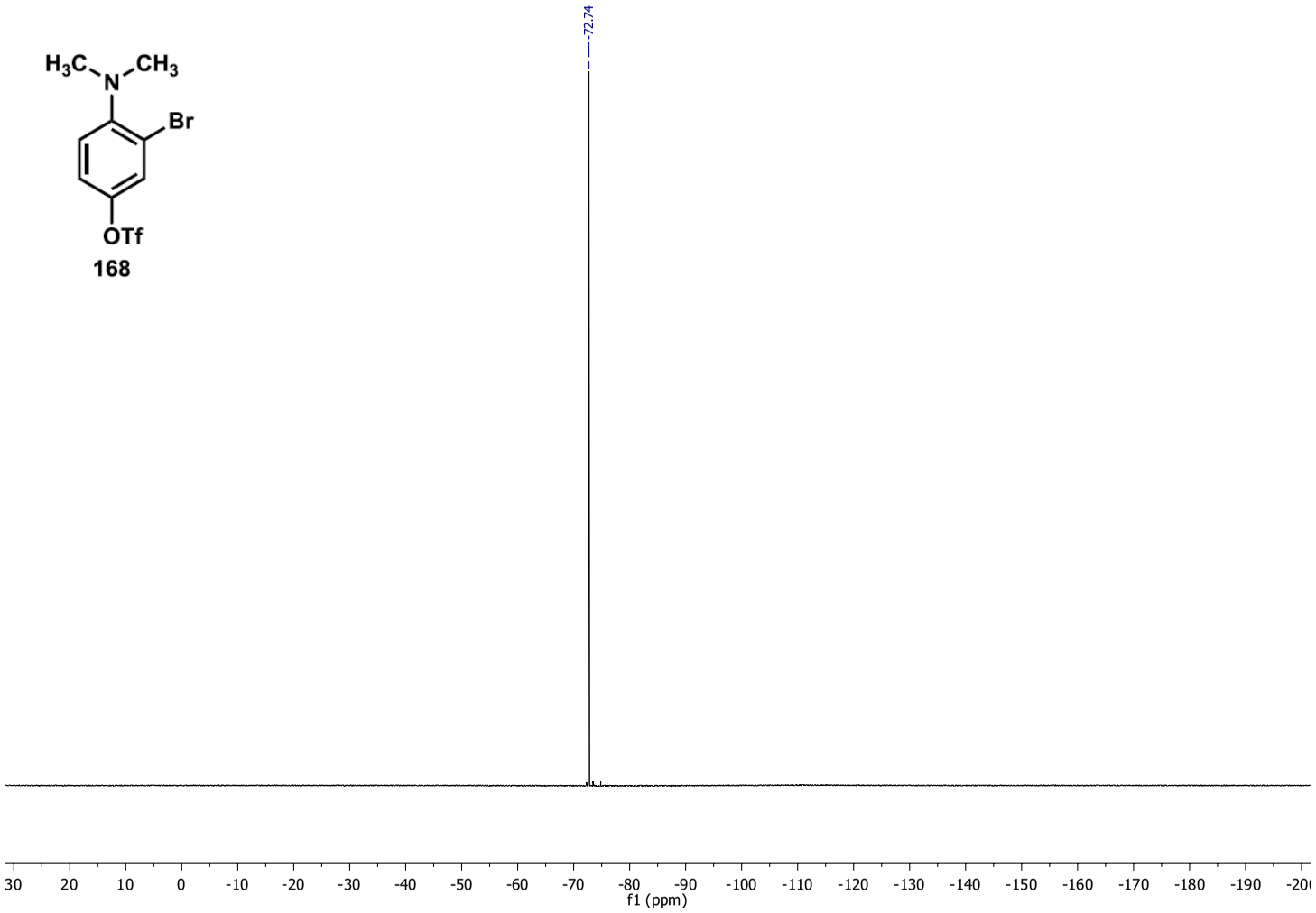

H3C
N
CH3
OTf
167
1.02
0.88
0.96
0.99
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

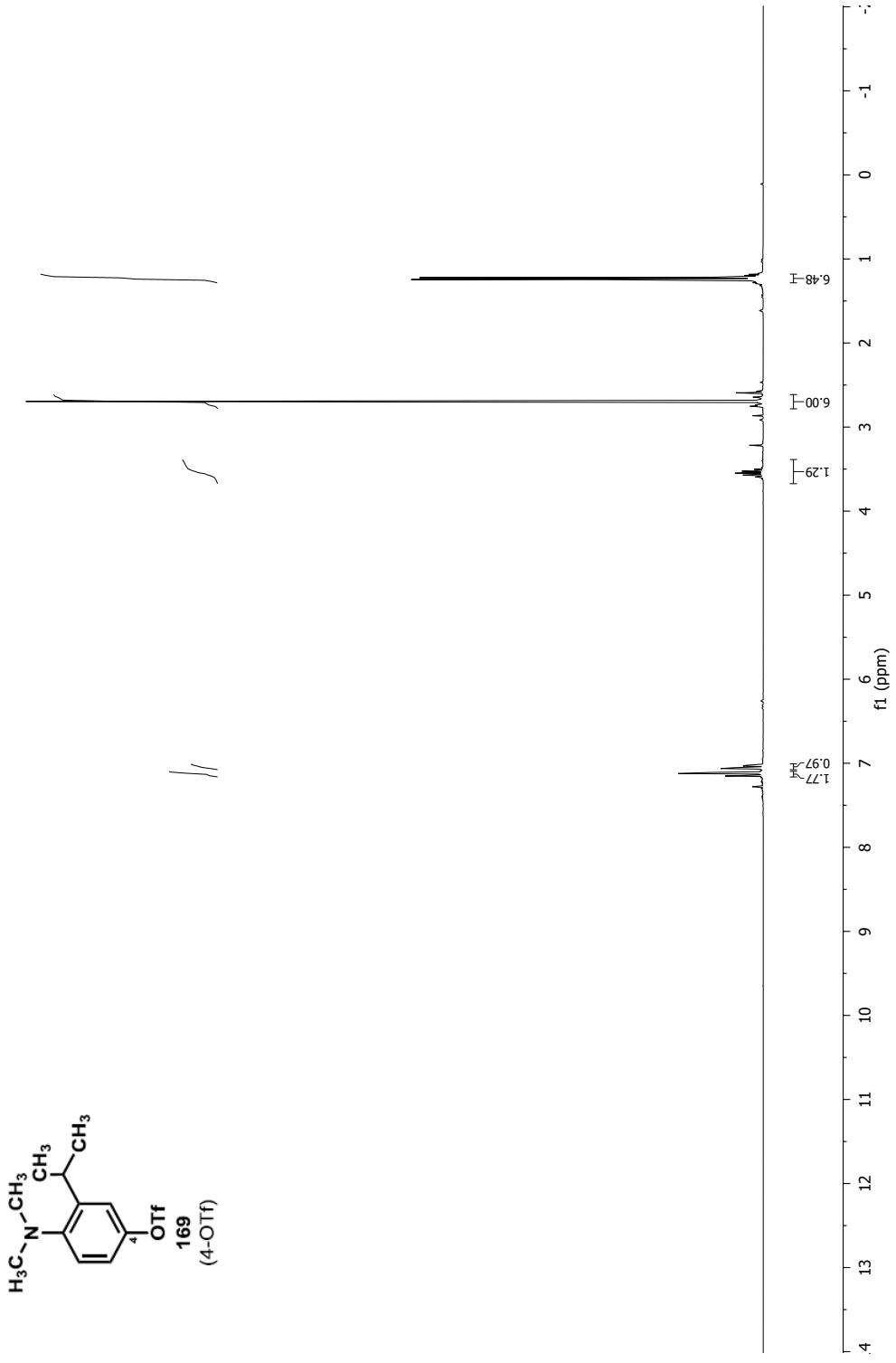

43.13
76.74
77.16
77.58
112.49
116.74
120.49
120.98
122.28
122.51
125.23
129.04
143.44
146.69
f1 (ppm)
167


H3C
N
CH3
OTf
167
-74.74
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

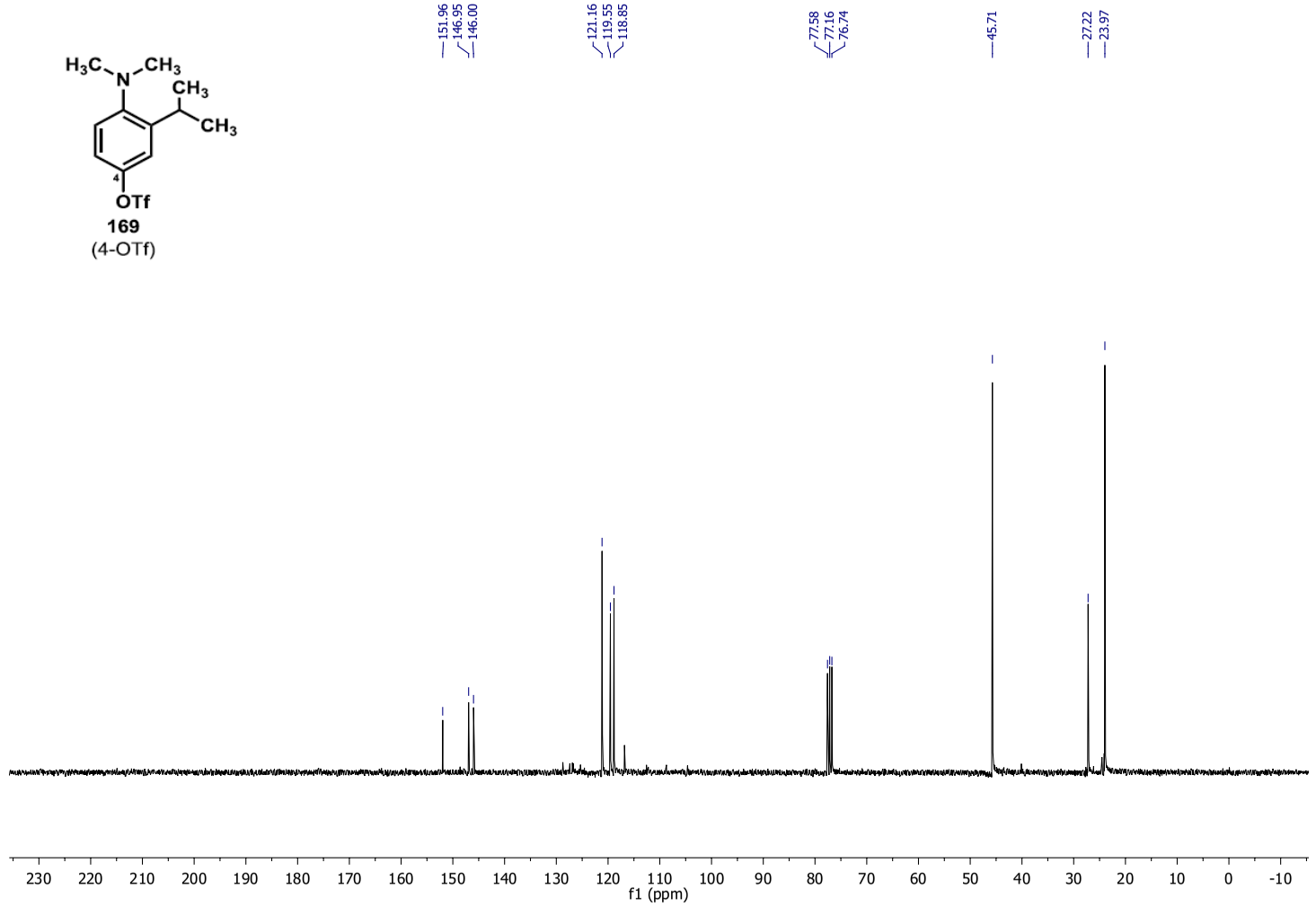

H3C
N
CH3
Br
OTf
168
0.82
0.95
1.18
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

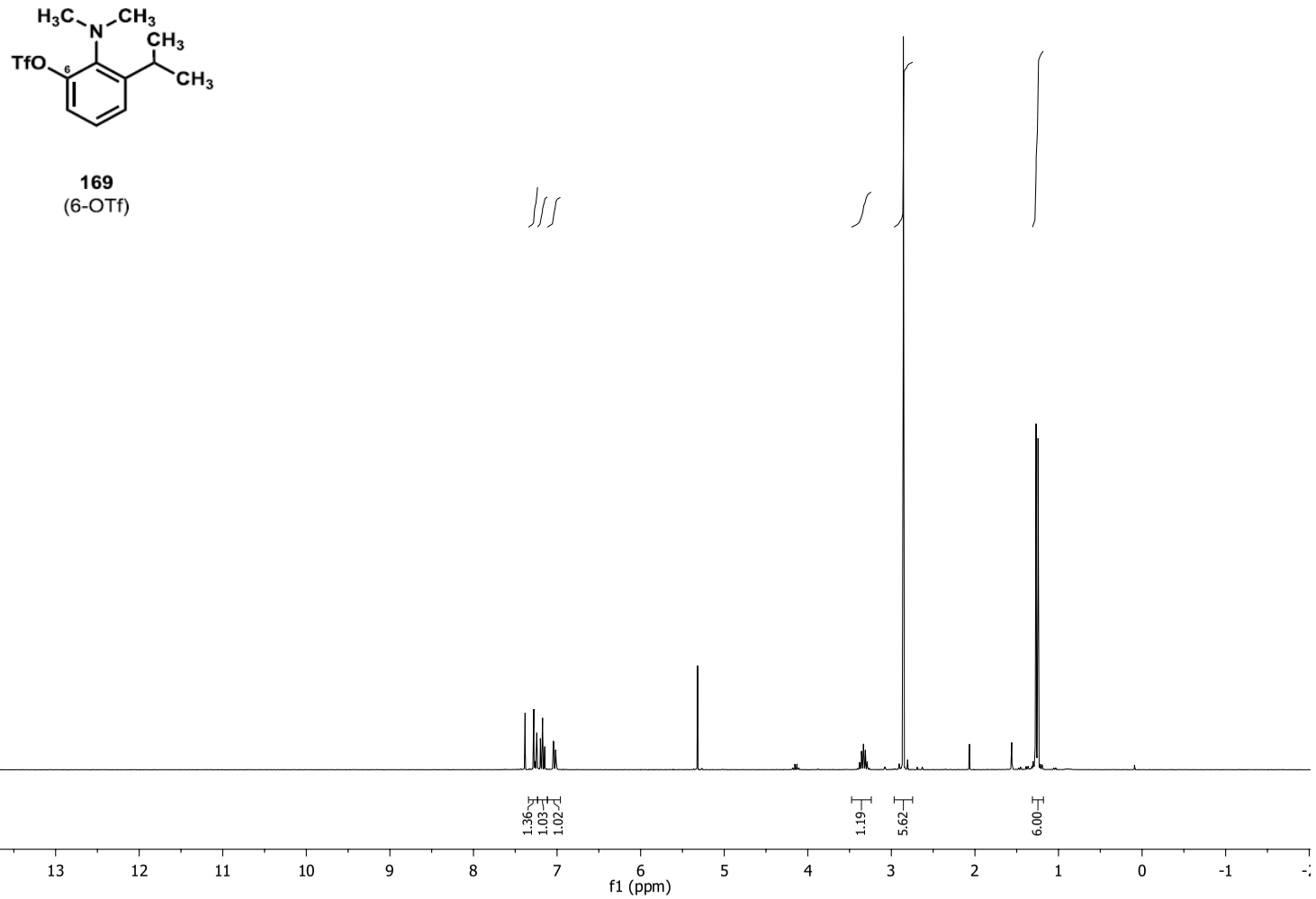

H3C
N
CH3
Br
OTf
168
152.33
143.94
126.96
122.69
121.01
120.88
120.13
118.98
117.58
115.03
77.41
77.16
76.91
44.14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

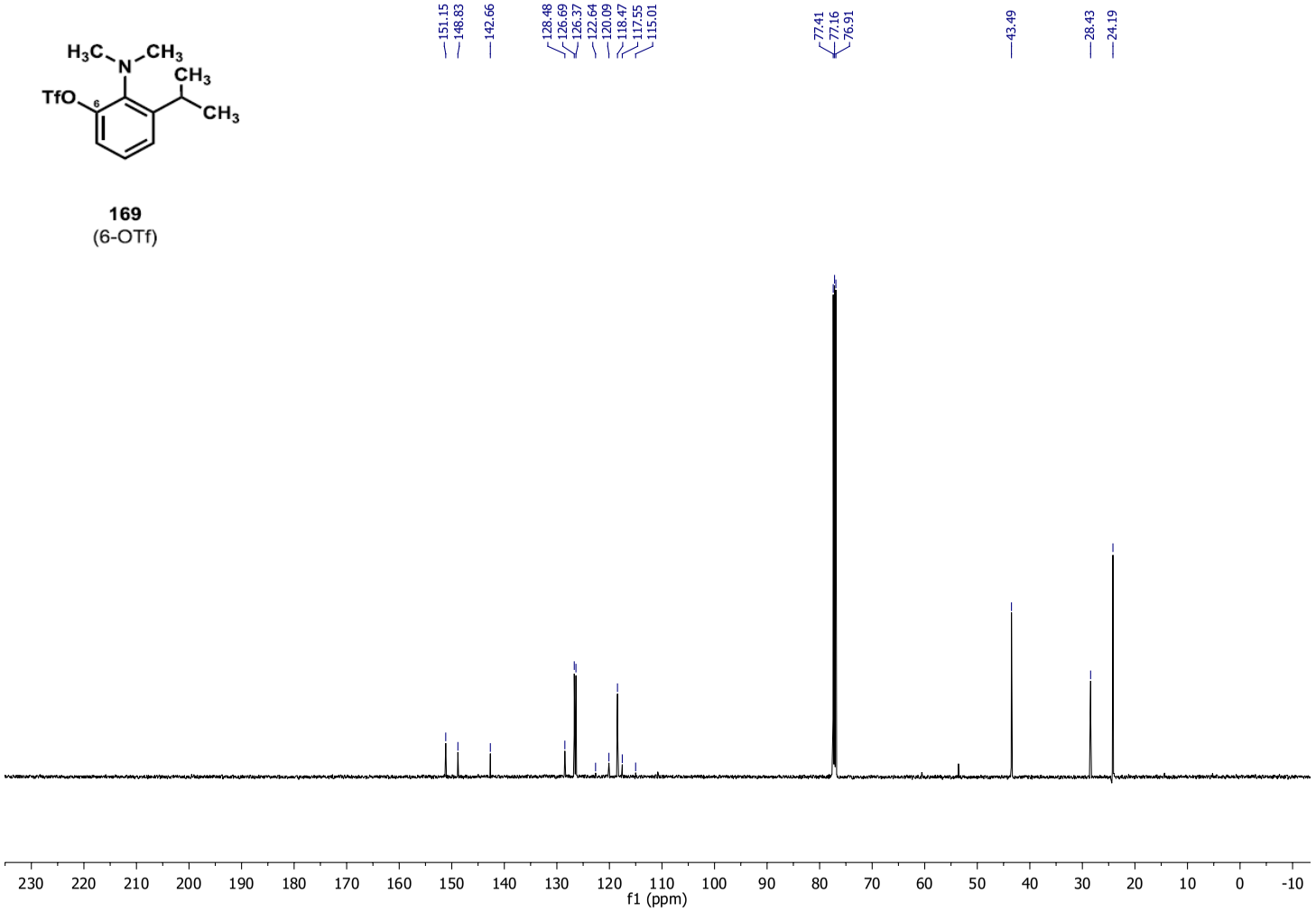

H3C
N
CH3
Br
OTf
168
-72.74
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

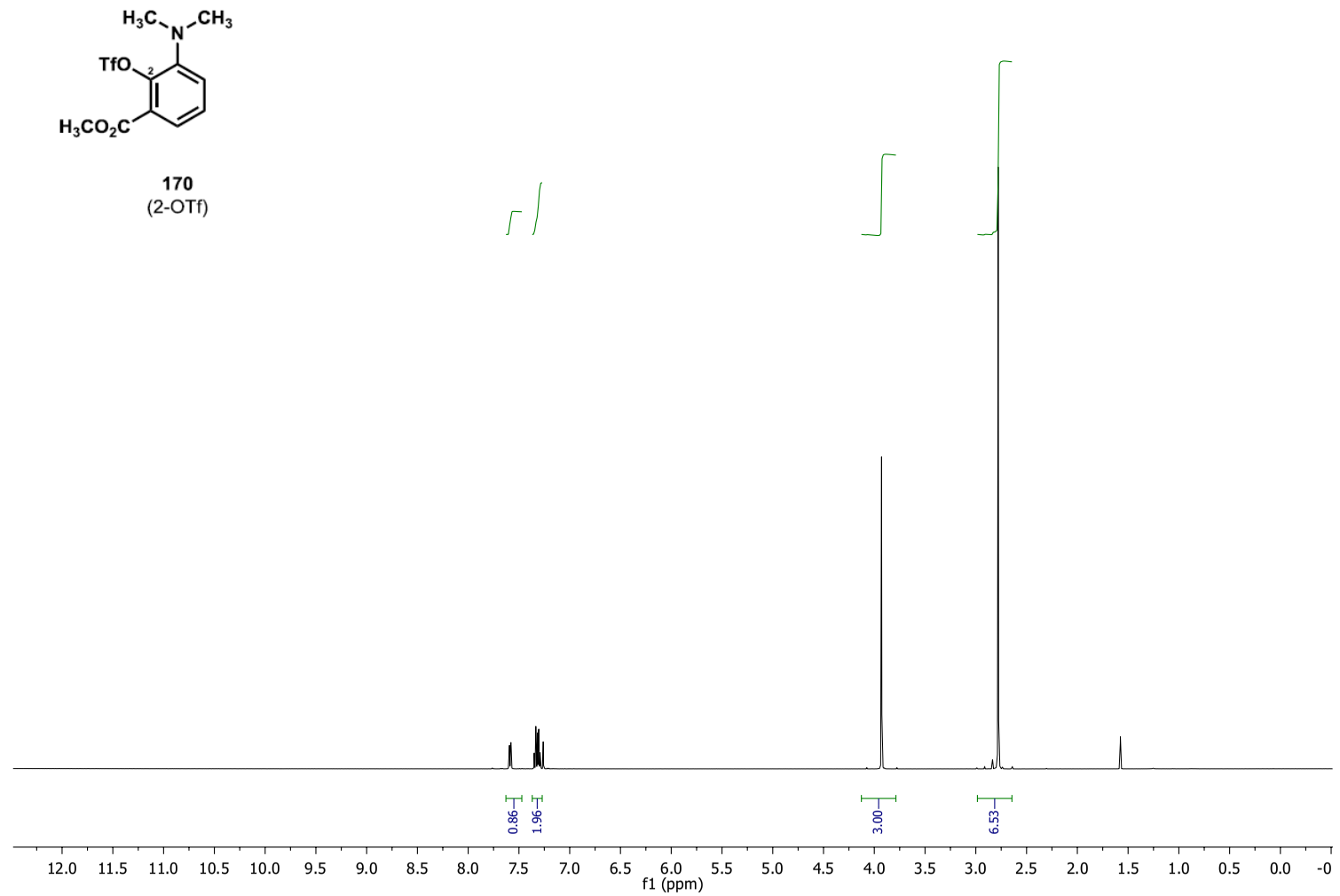


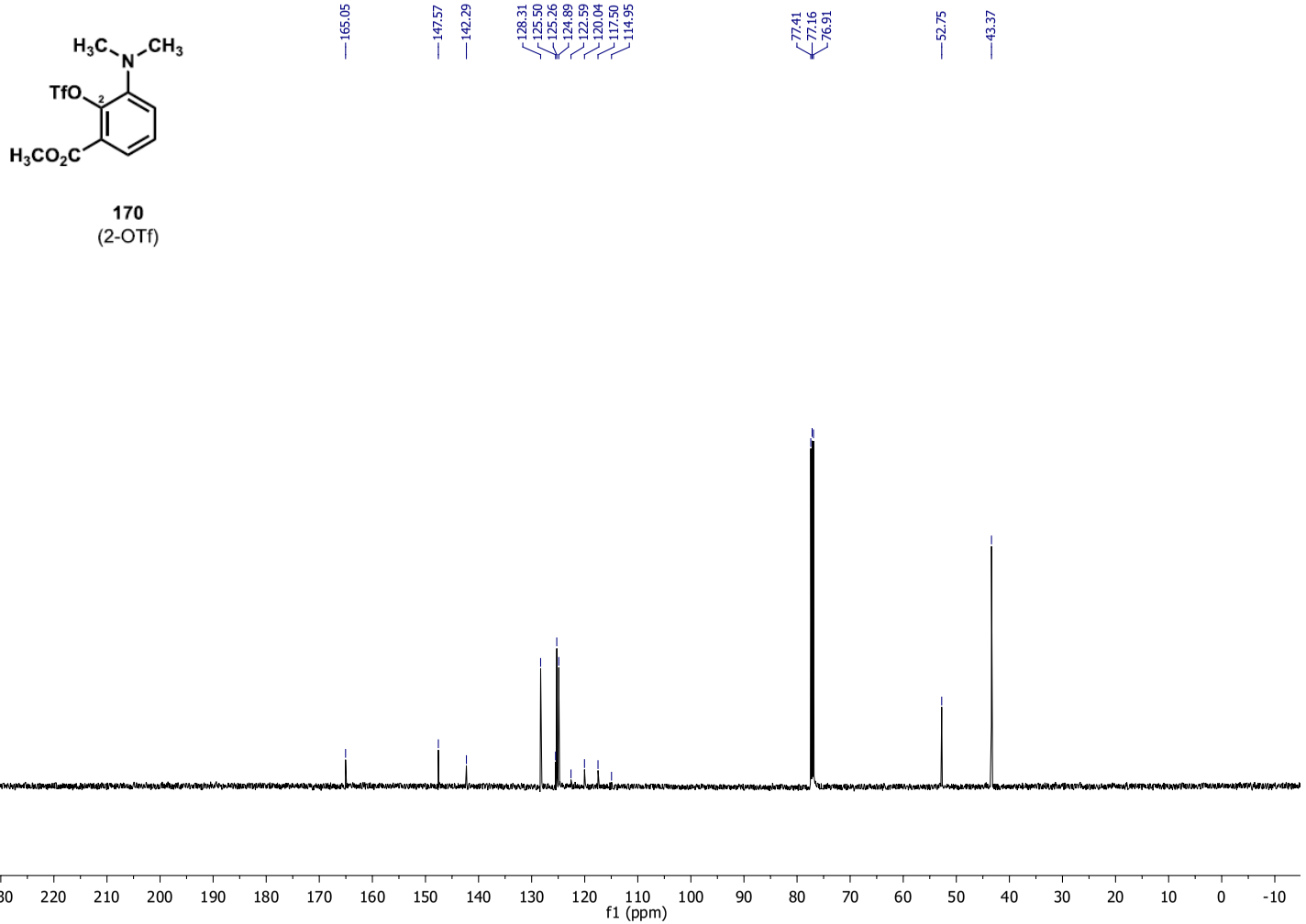
169
(4-OTf)

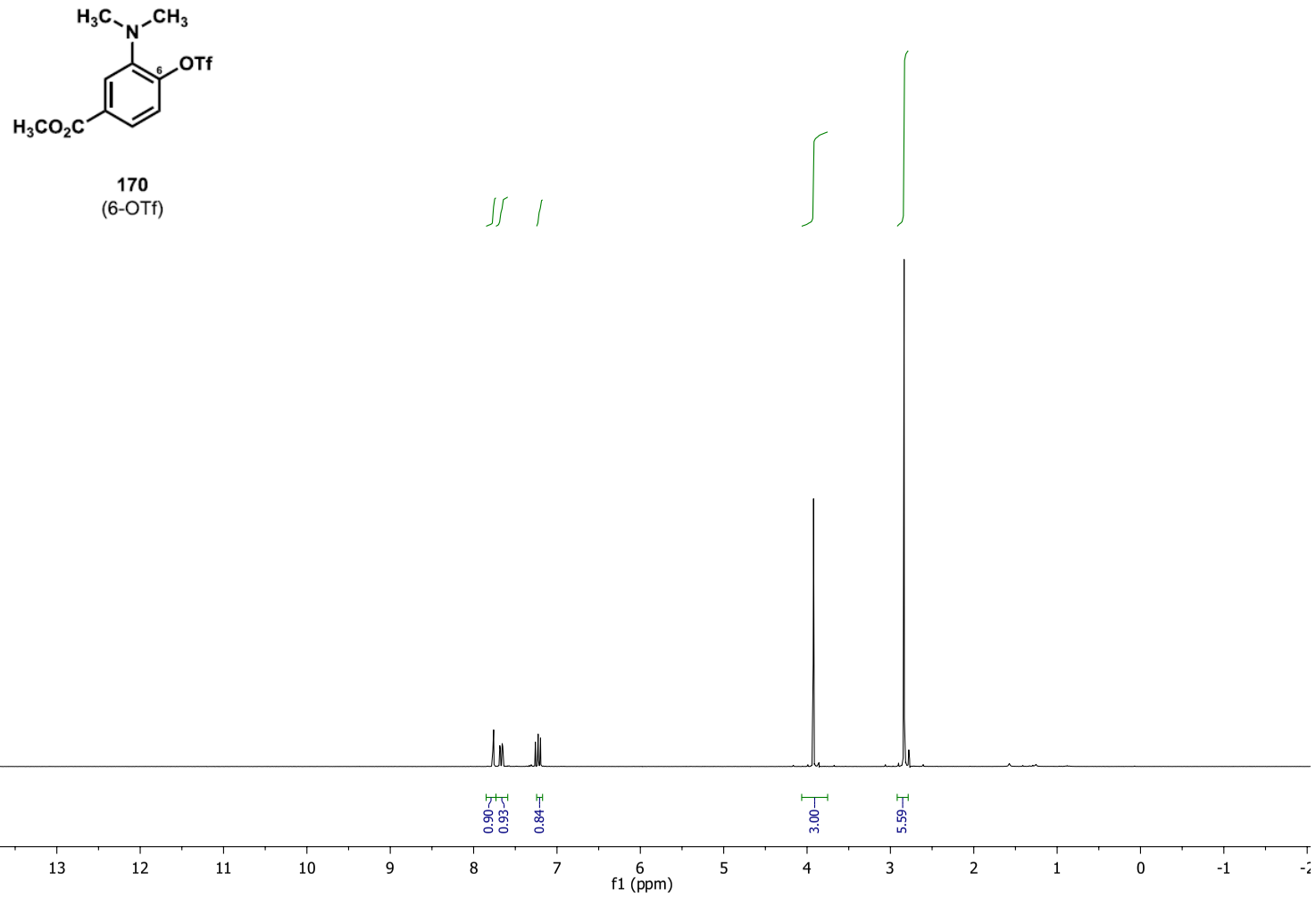

H3C
N
CH3
CH3
CH3
4
OTf
169
(4-OTf)
151.96
146.95
146.00
121.16
119.55
118.85
77.58
77.16
76.74
45.71
27.22
23.97
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

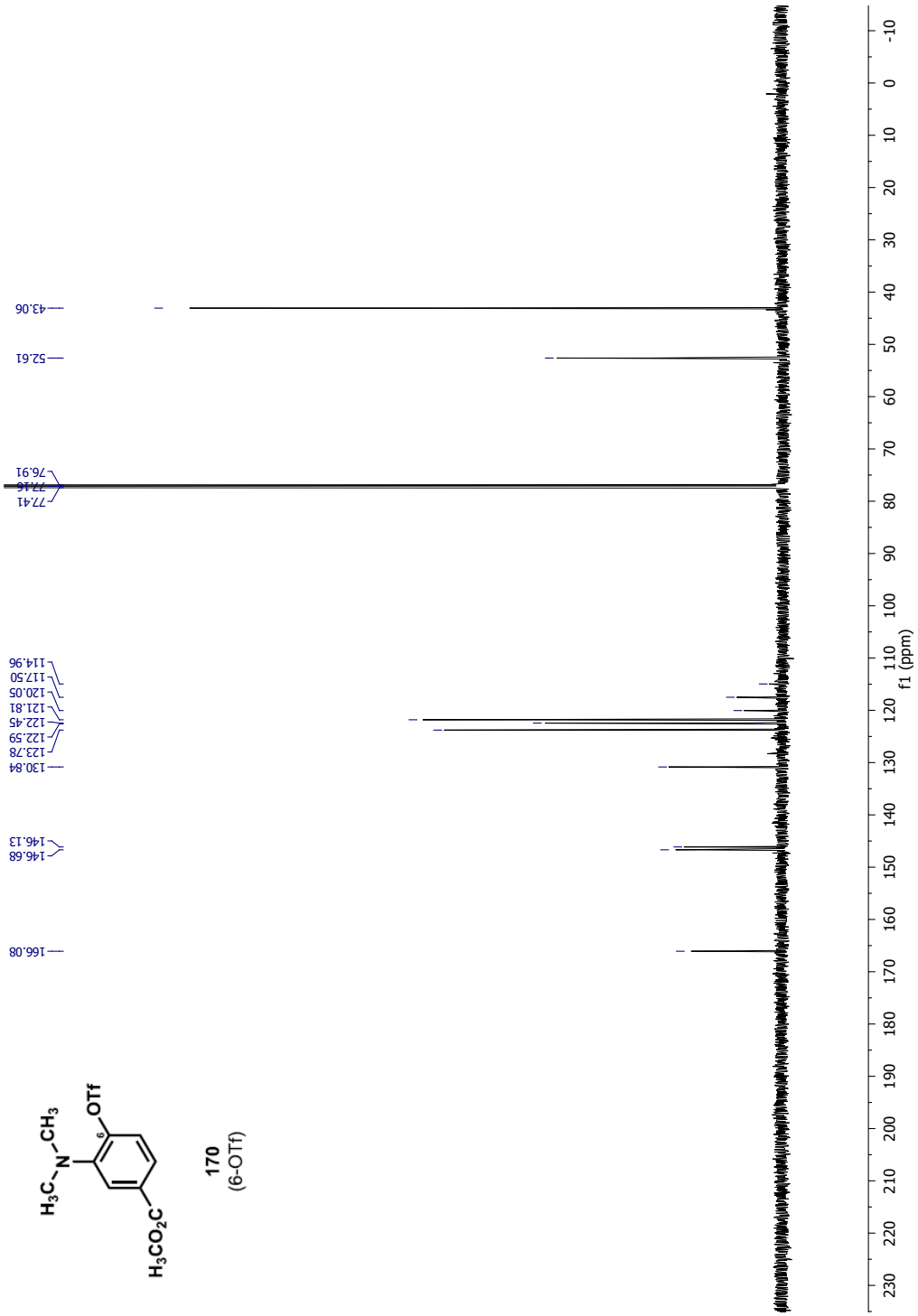

H3C
N
CH3
CH3
TfO
6
CH3
169
(6-OTf)
1.36
1.03
1.02
1.19
5.62
6.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

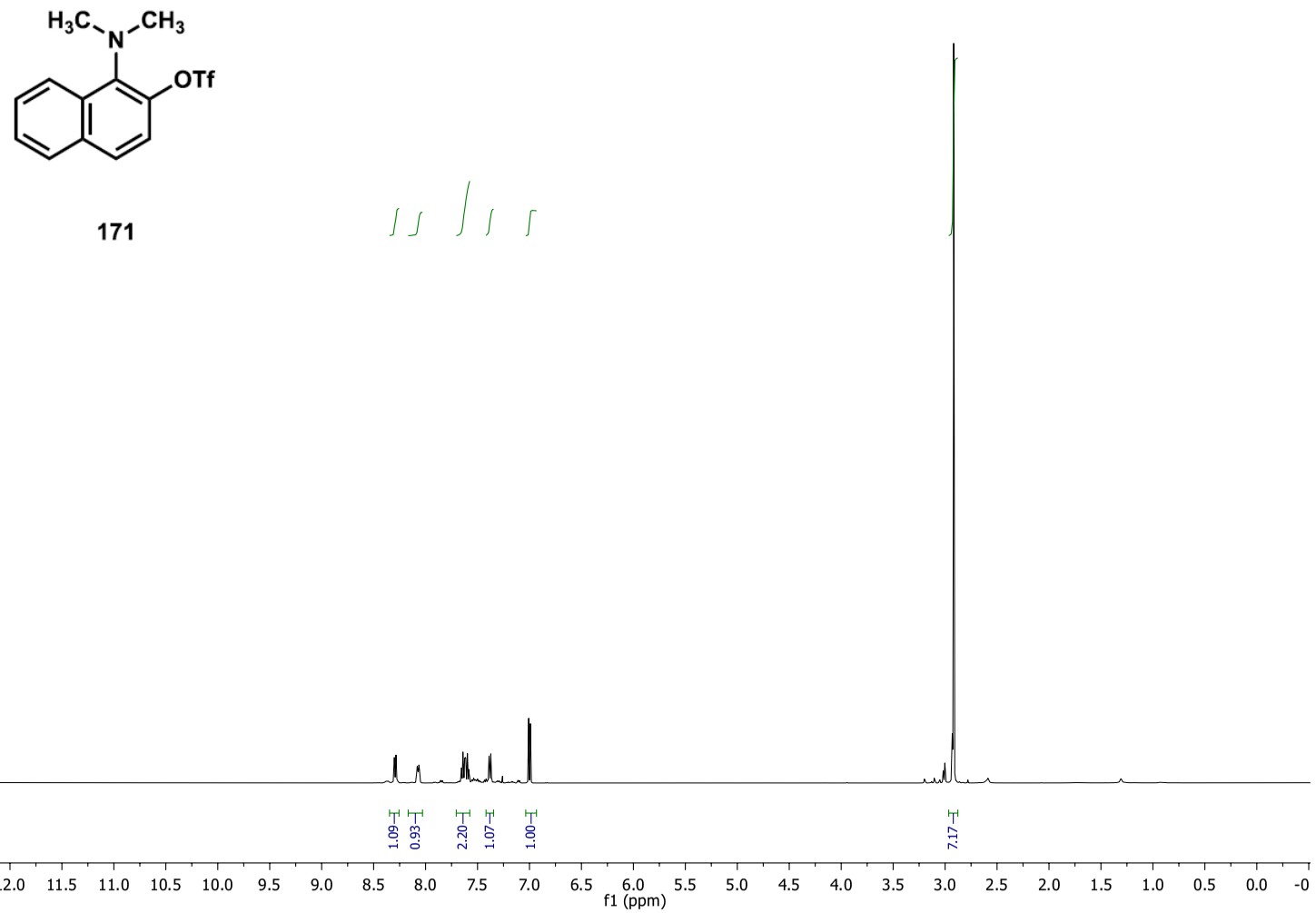

H3C
N
CH3
CH3
TfO
6
CH3
169
(6-OTf)
151.15
148.83
142.66
128.48
126.69
126.37
122.64
120.09
118.47
117.55
115.01
77.41
77.16
76.91
43.49
28.43
24.19
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

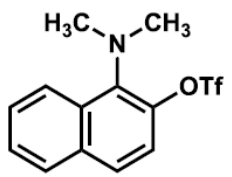

H3C
N
CH3
TfO
2
H3CO2C
170
(2-OTf)
0.86
1.96
3.00
6.53
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


H3C
N
CH3
TfO
2
H3CO2C
170
(2-OTf)
165.05
147.57
142.29
128.31
125.50
125.26
124.89
122.59
120.04
117.50
114.95
77.41
77.16
76.91
52.75
43.37
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OTf
6
H3CO2C
170
(6-OTf)
0.90
0.93
0.84
3.00
5.59
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

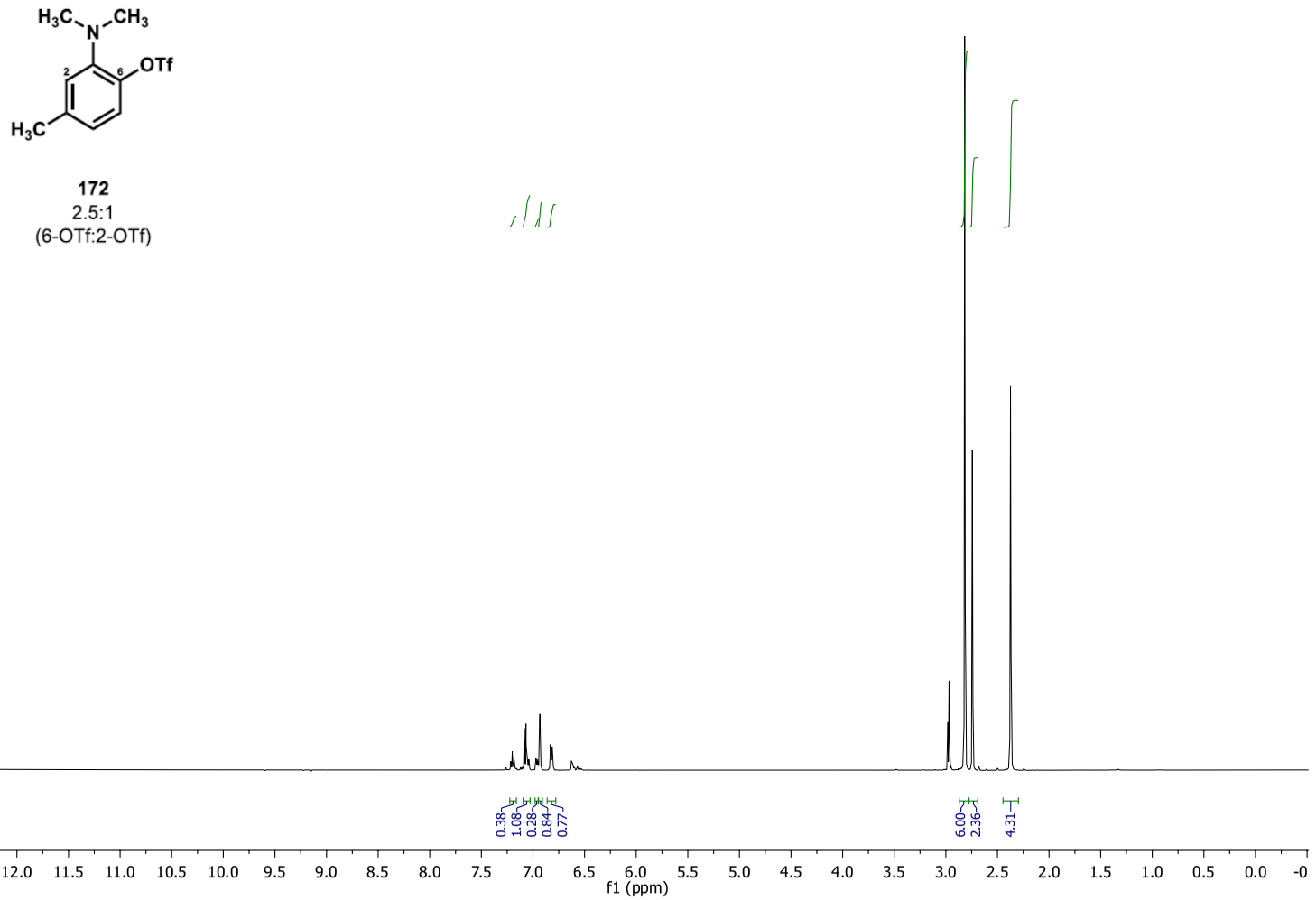

43.06
52.61
76.91
77.16
77.41
114.96
117.50
120.05
121.81
122.45
122.59
123.78
130.84
146.13
146.68
166.08
f1 (ppm)
OTf
6
CH3
N
H3C
H3CO2C
170
(6-OTf)

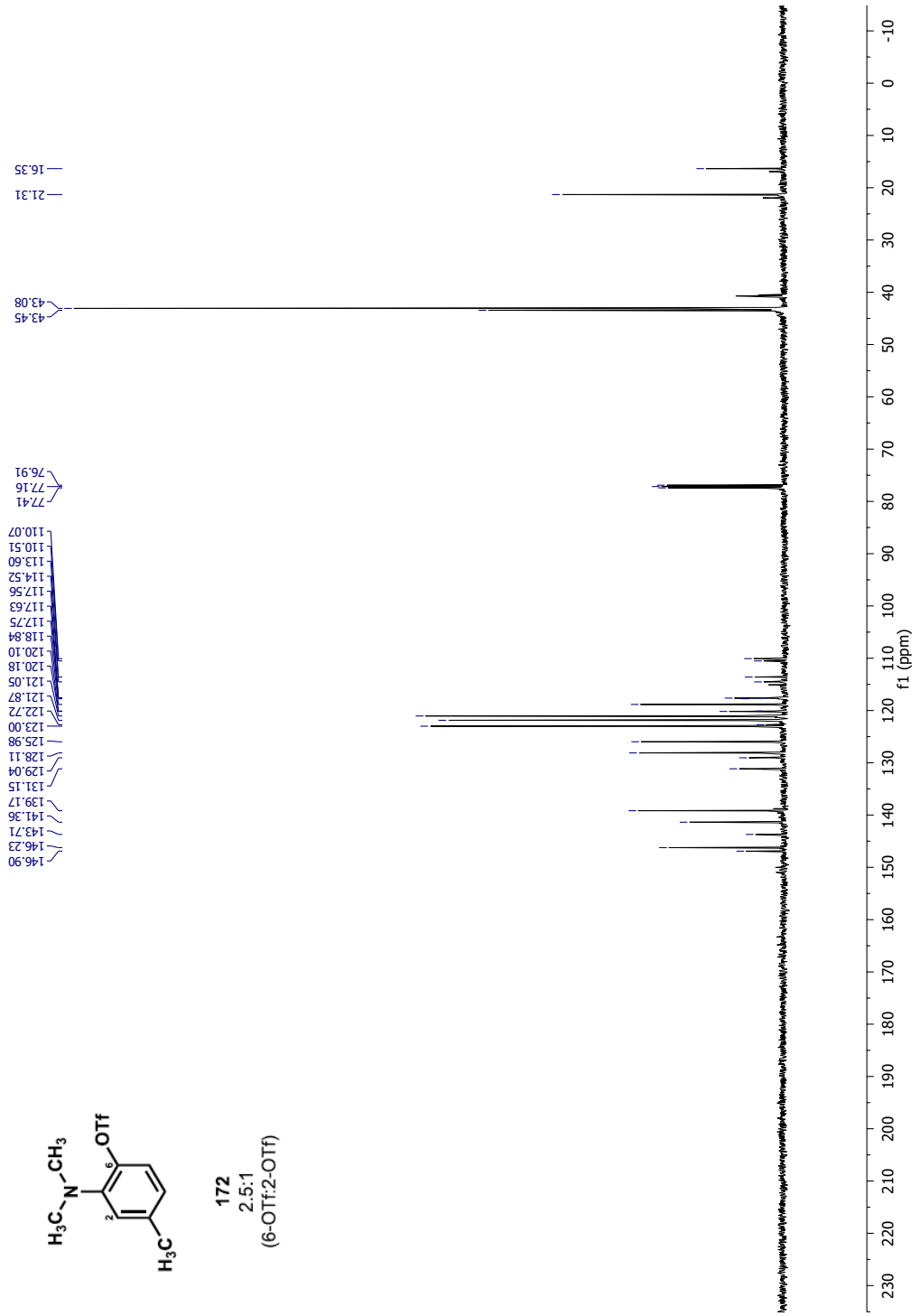

H3C
N
CH3
OTf
171
1.09
0.93
2.20
1.07
1.00
7.17
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

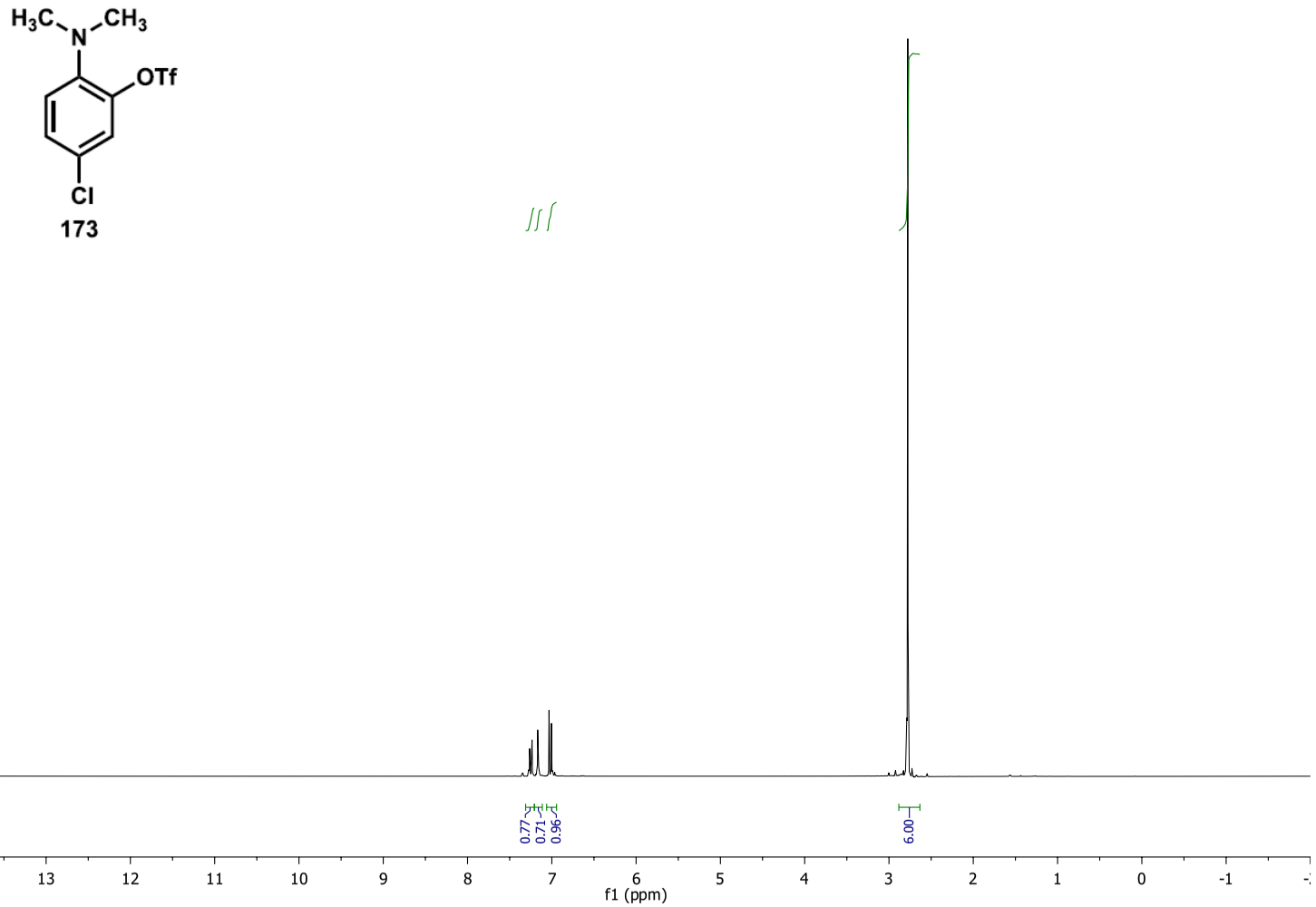

H3C
N
CH3
OTf

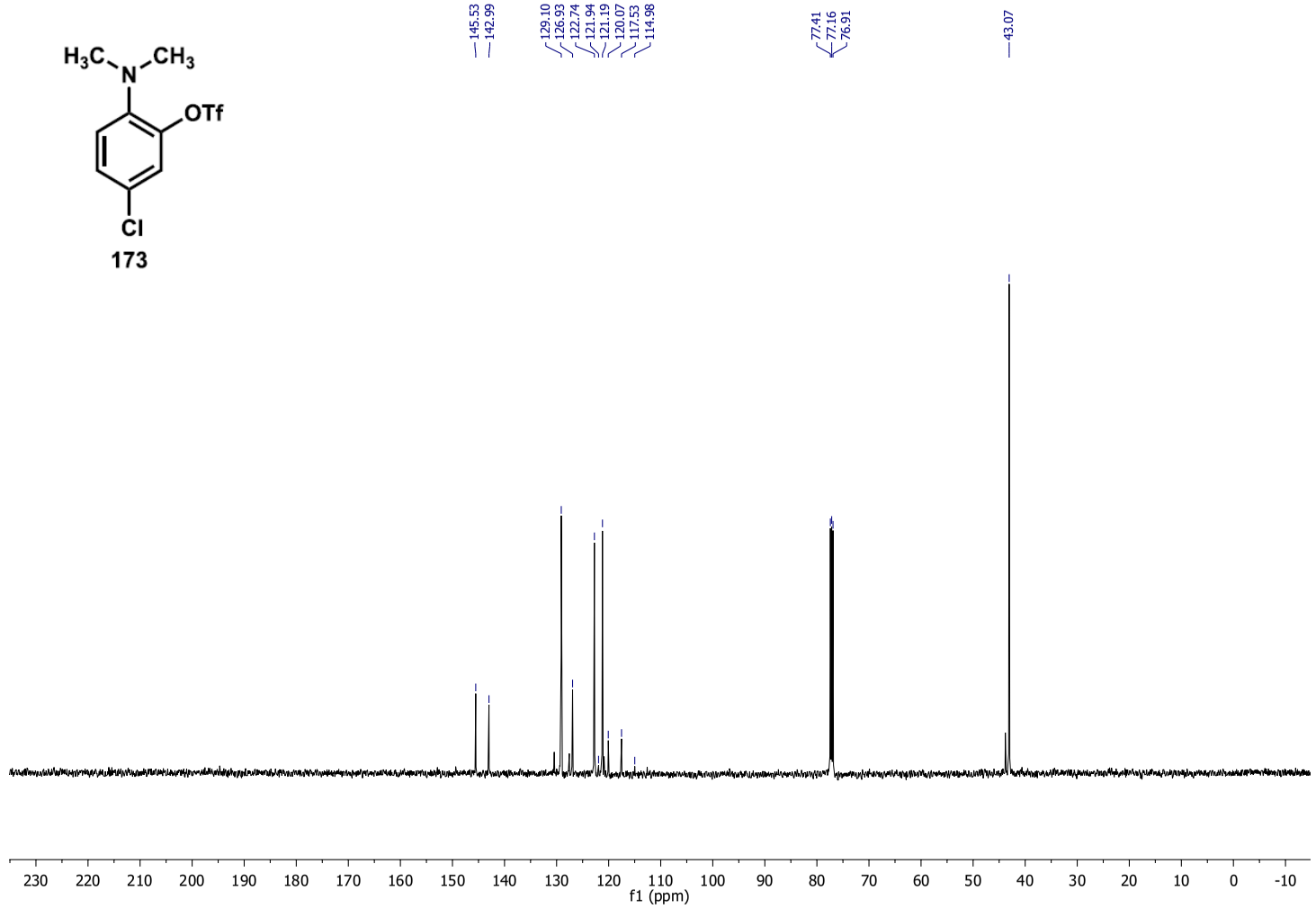
171

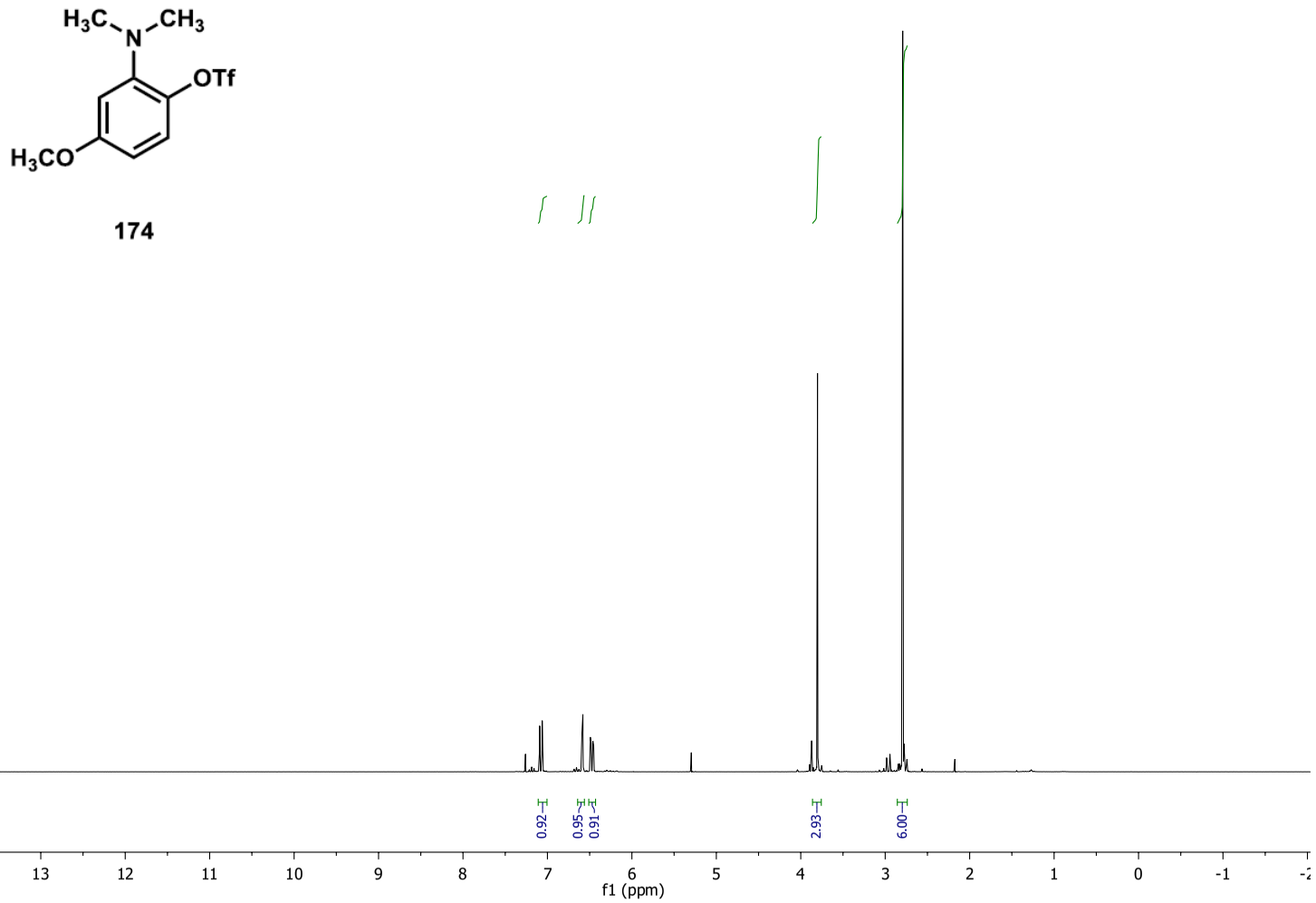
151.47
141.08
129.86
127.66
127.59
126.50
124.90
121.24
119.82
117.90
117.65
114.04
112.76
110.11
77.41
77.16
76.91
45.19
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

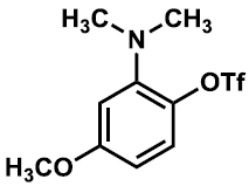

H3C
N
CH3
2
6
OTf
H3C
172
2.5:1
(6-OTf:2-OTf)
0.38
1.08
0.28
0.84
0.77
6.00
2.36
4.31
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


172
2.5:1
(6-OTf:2-OTf)
f1 (ppm)


H3C
N
CH3
OTf
Cl
173
0.77
0.71
0.96
6.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

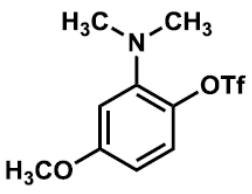

145.53
142.99
129.10
126.93
122.74
121.94
121.19
120.07
117.53
114.98
77.41
77.16
76.91
43.07
H3C
N
CH3
OTf
Cl
173
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OTf
H3CO
174
0.92
0.95
0.91
2.93
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


H3C
N
CH3
OTf
H3CO

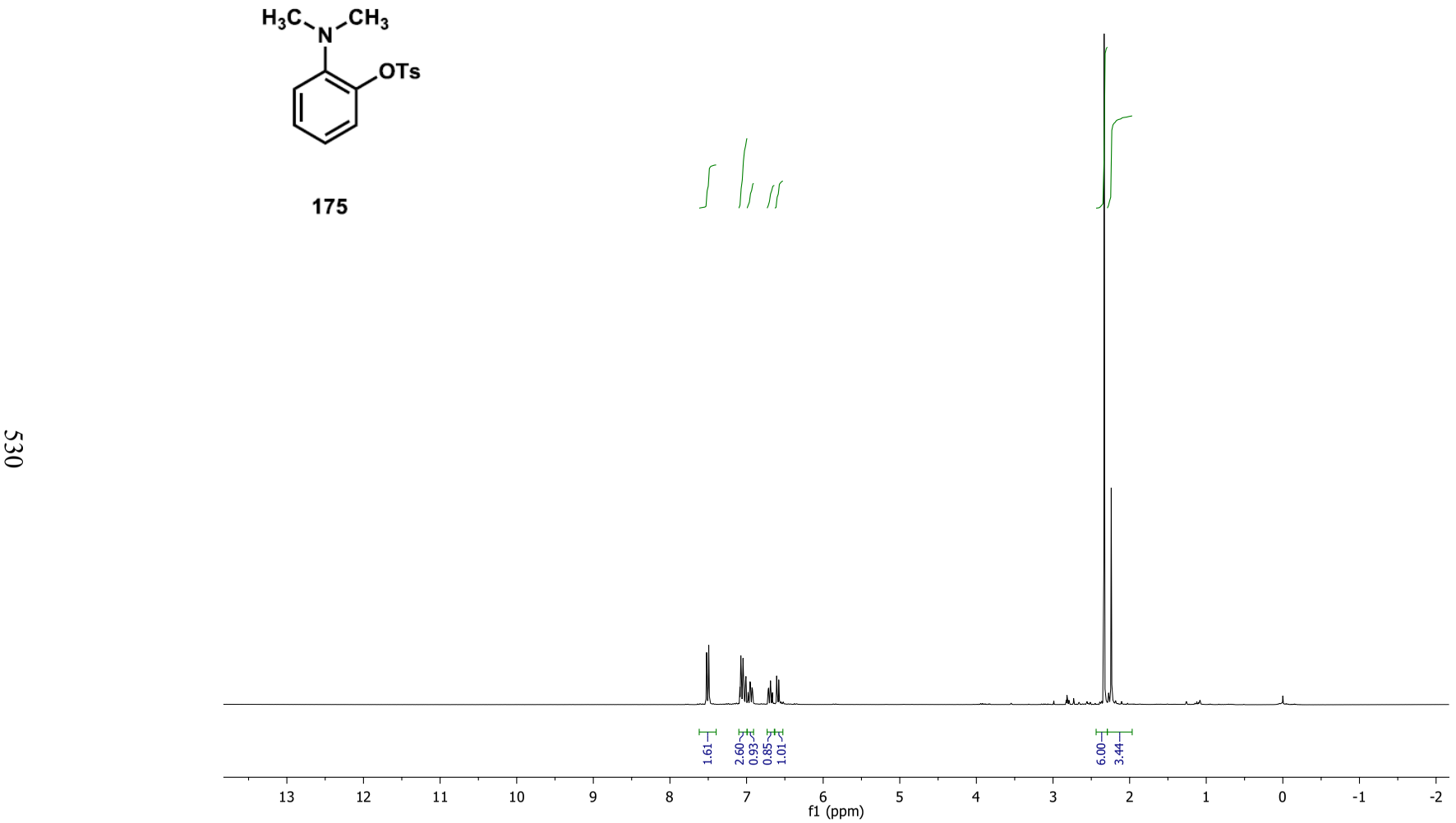
174

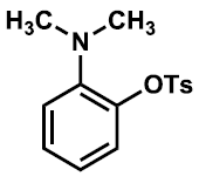
159.72
147.61
136.97
125.23
122.92
120.98
116.73
111.88
106.61
105.93
77.58
77.16
76.74
55.70
43.03
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OTf
H3CO

174

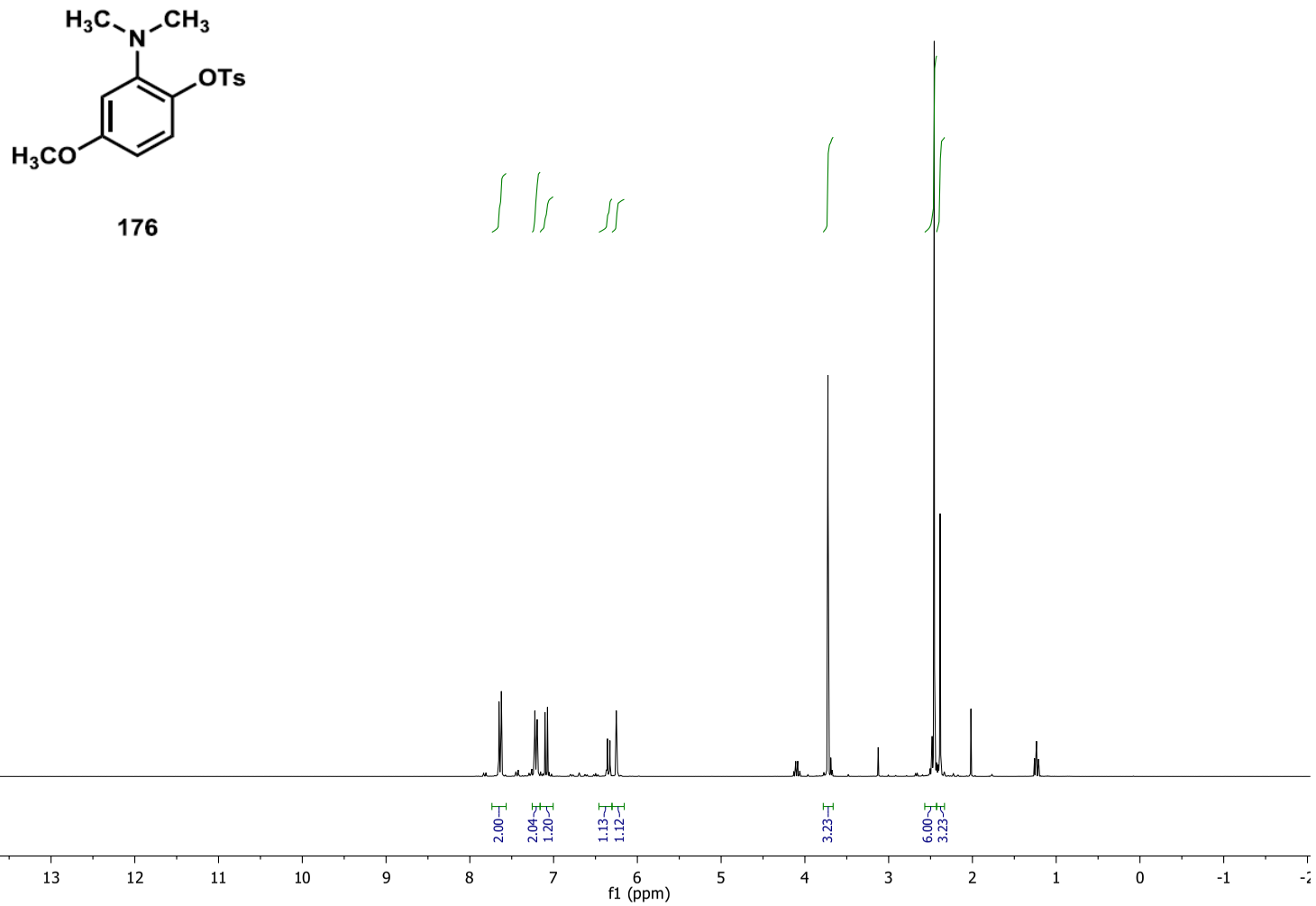
-74.56
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

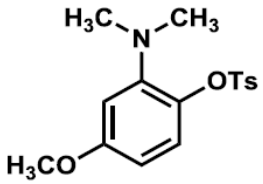

H3C
N
CH3
OTs
175
1.61
2.60
0.93
0.85
1.01
6.00
3.44
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


H3C
N
CH3
OTs

175

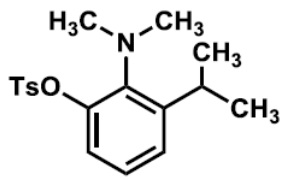
145.79
144.87
141.88
133.51
129.07
128.66
127.79
124.35
121.11
118.87
77.58
77.16
76.74
42.46
21.77
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
N
CH3
OTs
H3CO
176
2.00
2.04
1.20
1.13
1.12
3.23
6.00
3.23
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


H3C
N
CH3
OTs
H3CO

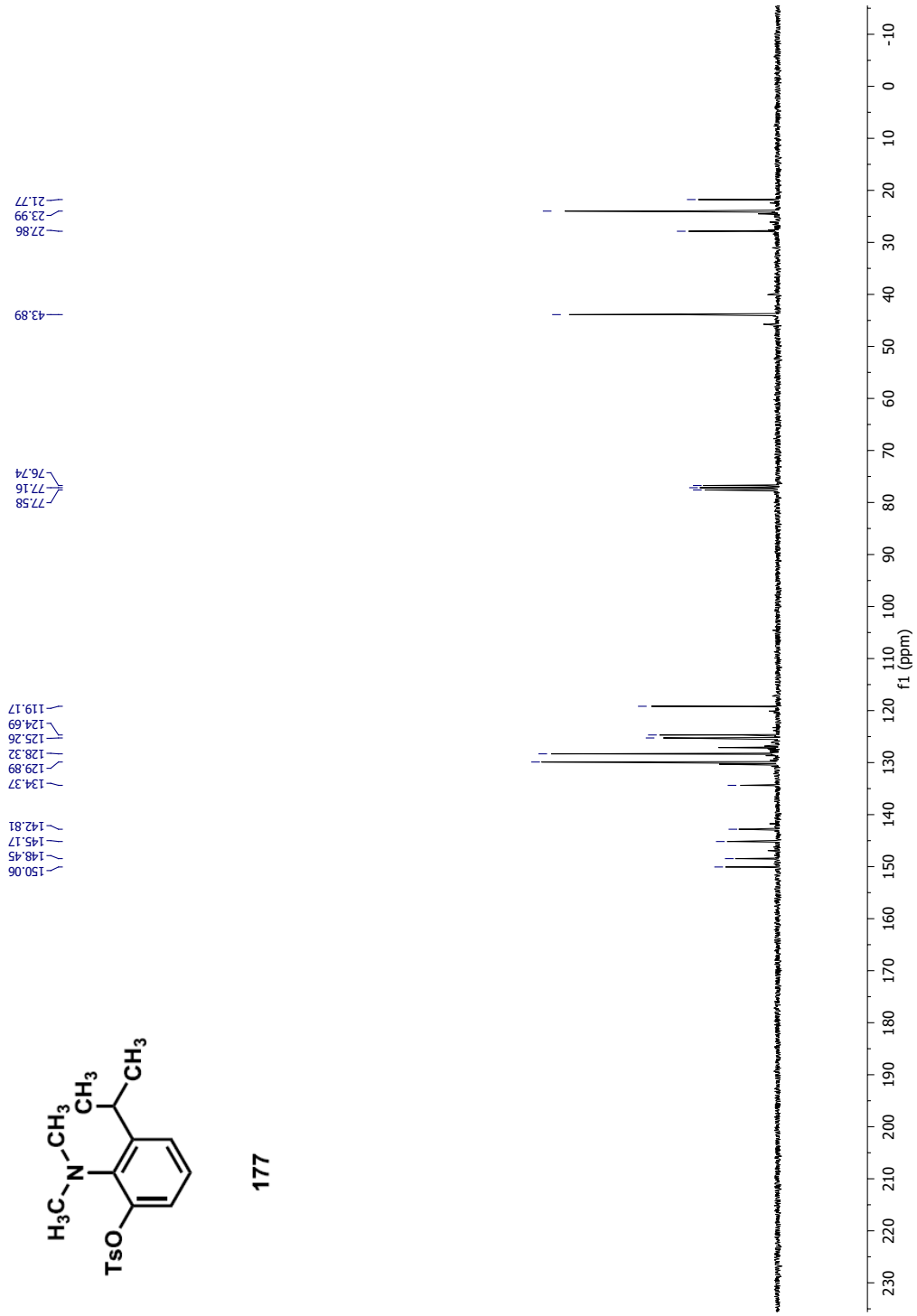
176

158.74
146.56
144.76
135.44
133.28
128.95
128.54
124.77
105.12
104.39
77.58
77.16
76.73
55.41
42.14
21.61
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

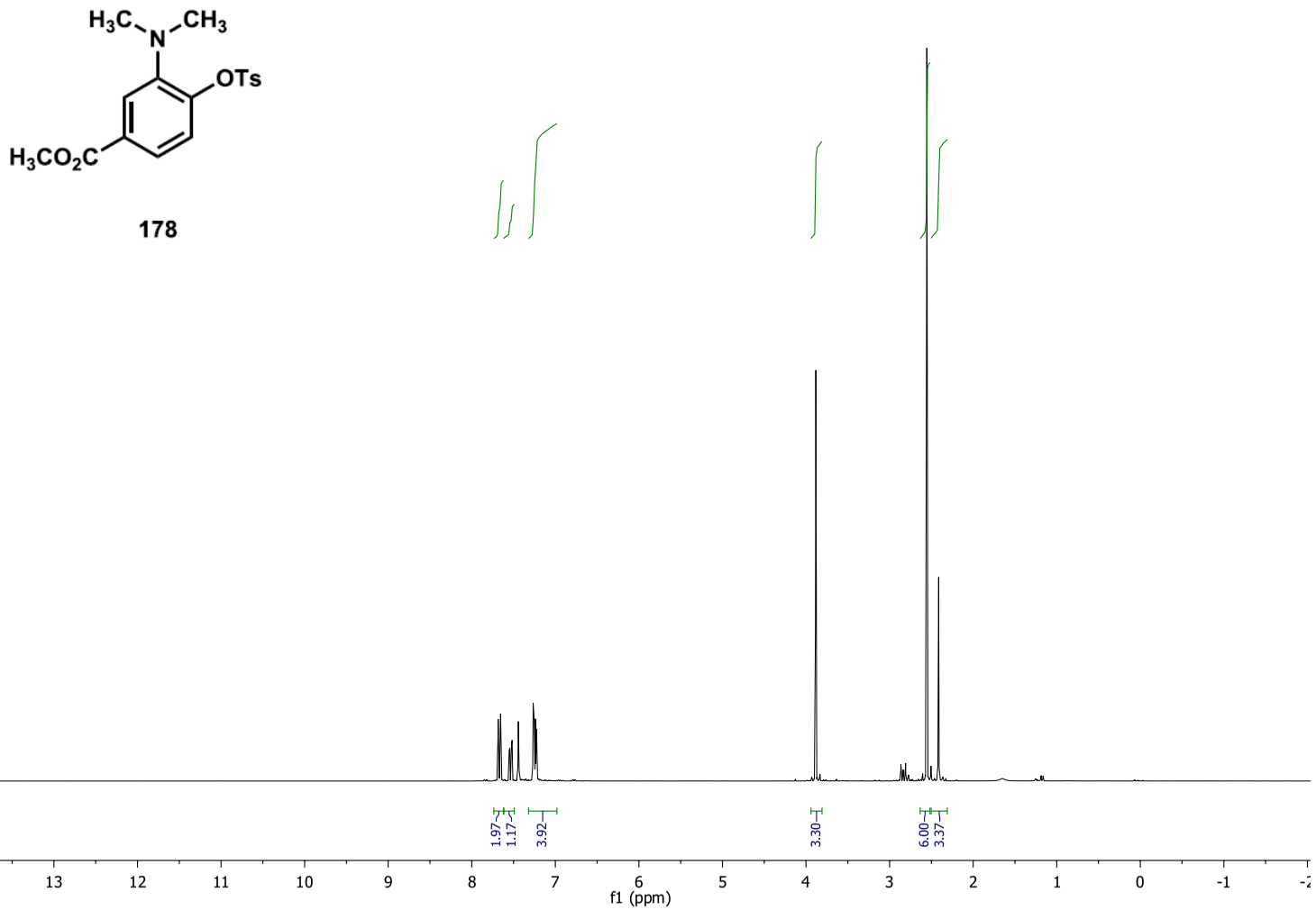

H3C
N
CH3
CH3
TsO
CH3

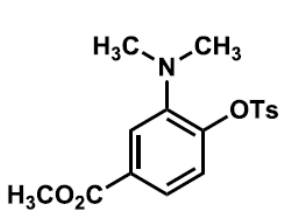
177

1.95
2.18
1.24
1.30
1.09
1.17
6.00
2.98
6.77
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


21.77
23.99
27.86
43.89
76.74
77.16
77.58
119.17
124.69
125.26
128.32
129.89
134.37
142.81
145.17
148.45
150.06
f1 (ppm)

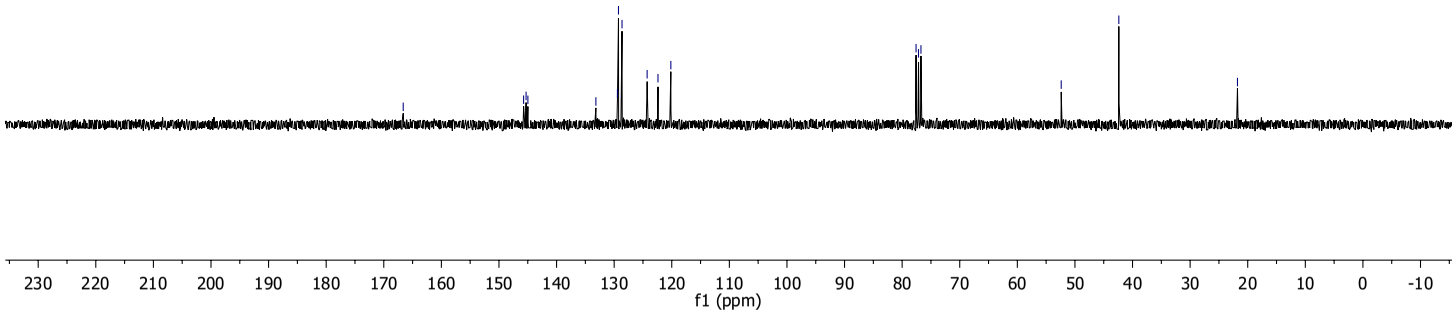
177

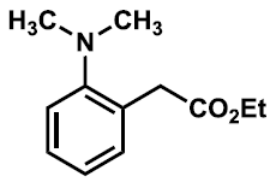

H3C
N
CH3
OTs
H3CO2C
178
1.97
1.17
3.92
3.30
6.00
3.37
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)



178

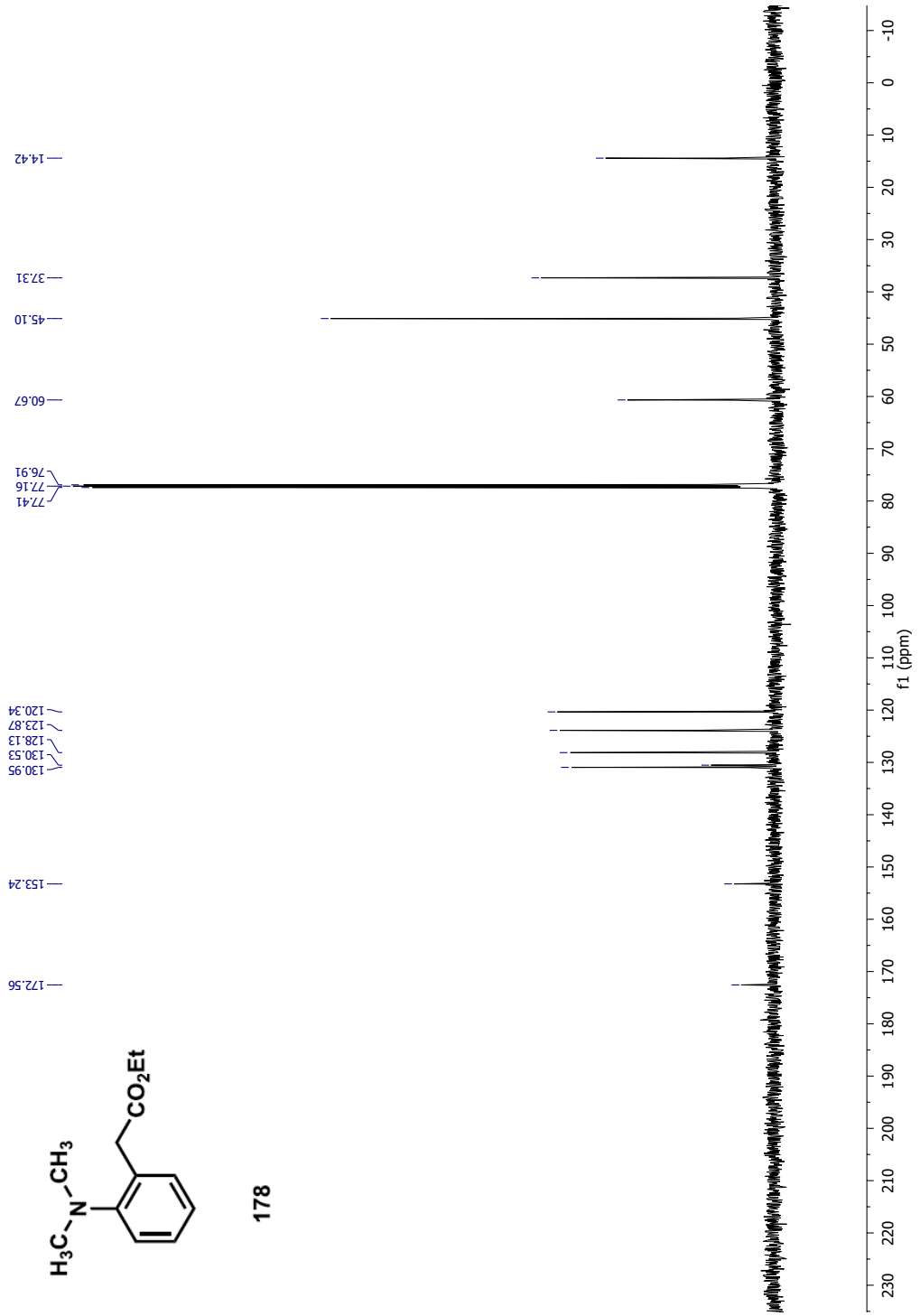
166.62
145.72
145.29
144.98
133.17
129.43
129.25
128.64
124.28
122.39
120.16
77.58
77.16
76.74
52.38
42.38
21.78



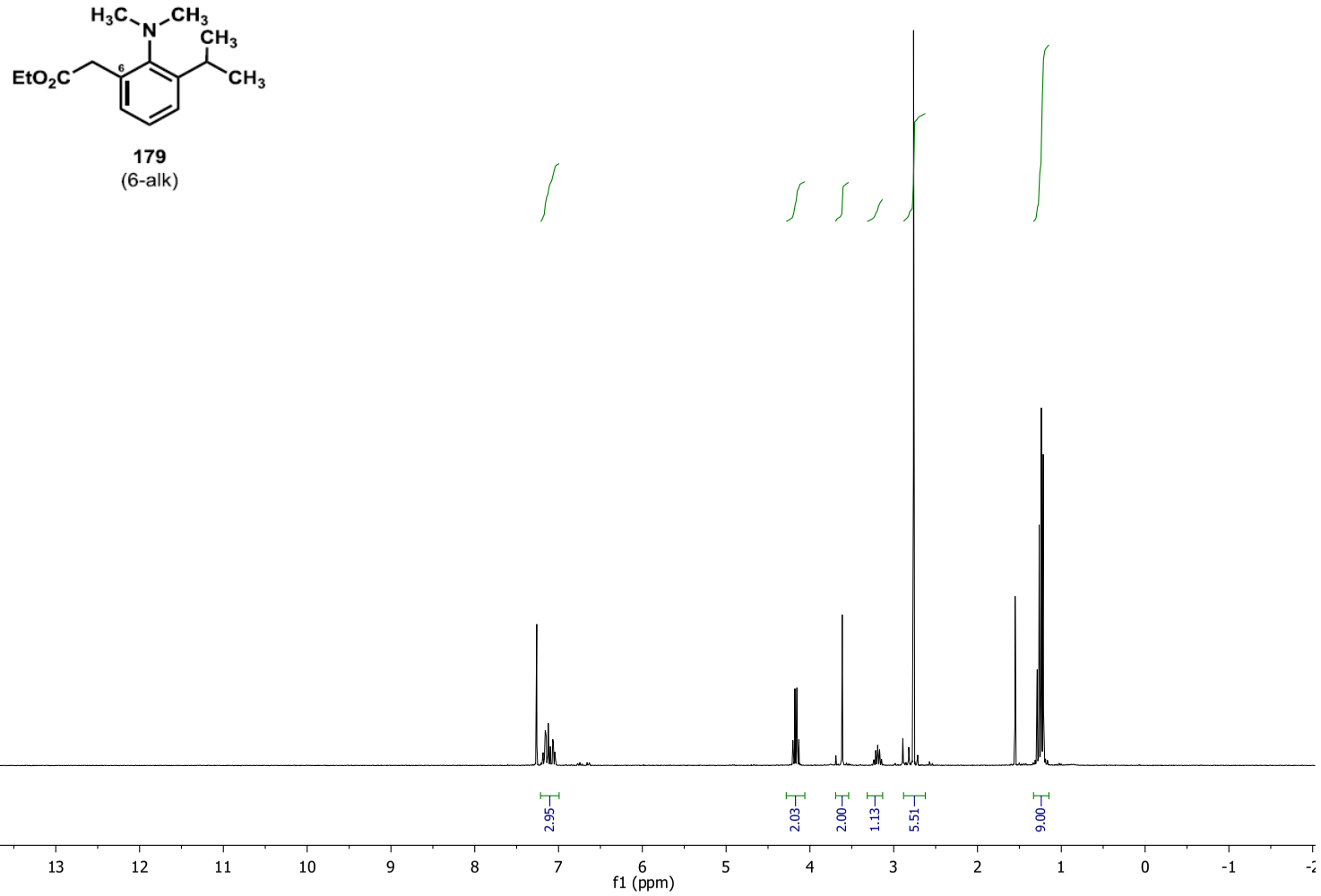

H3C
N
CH3
CO2Et

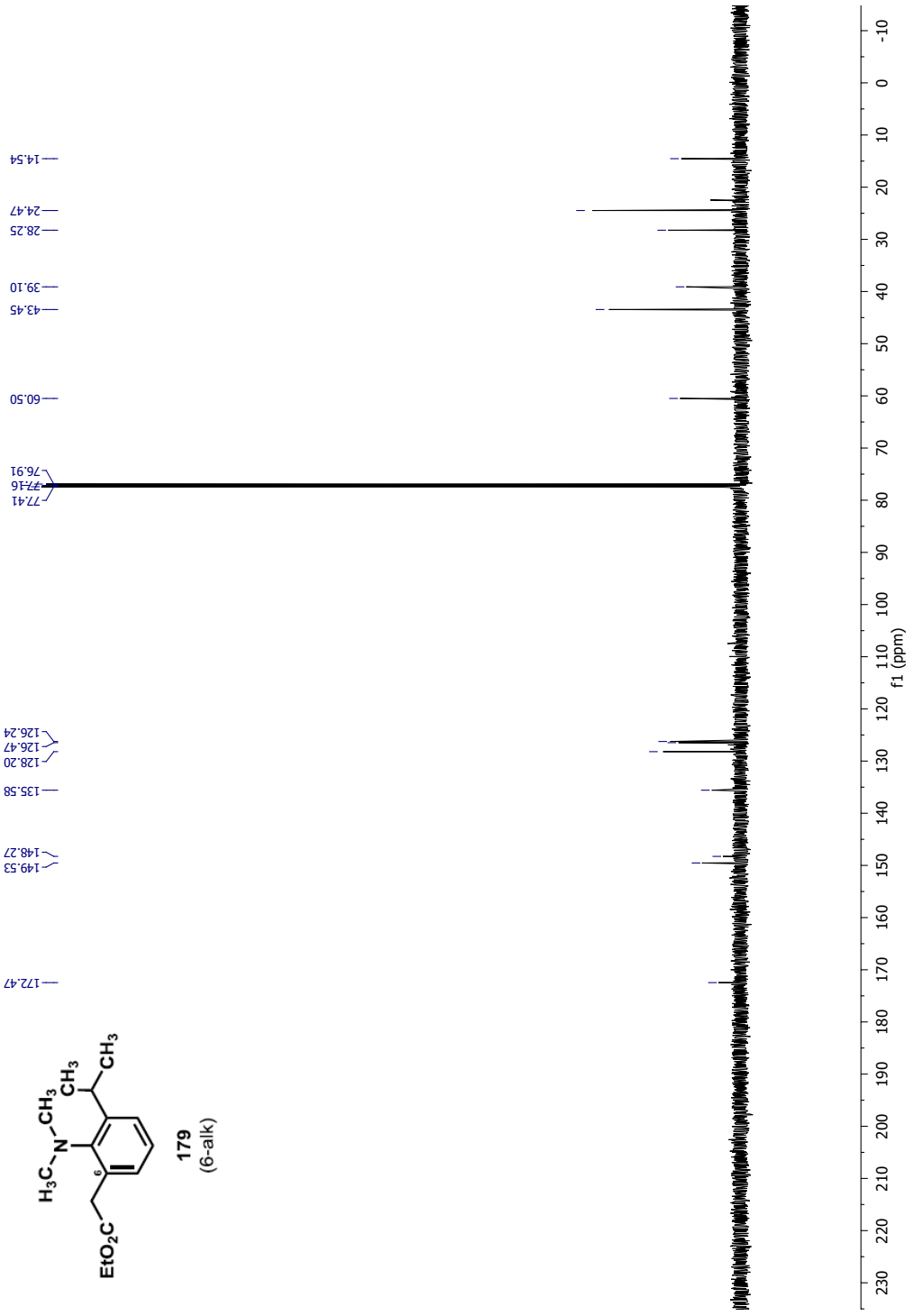
178

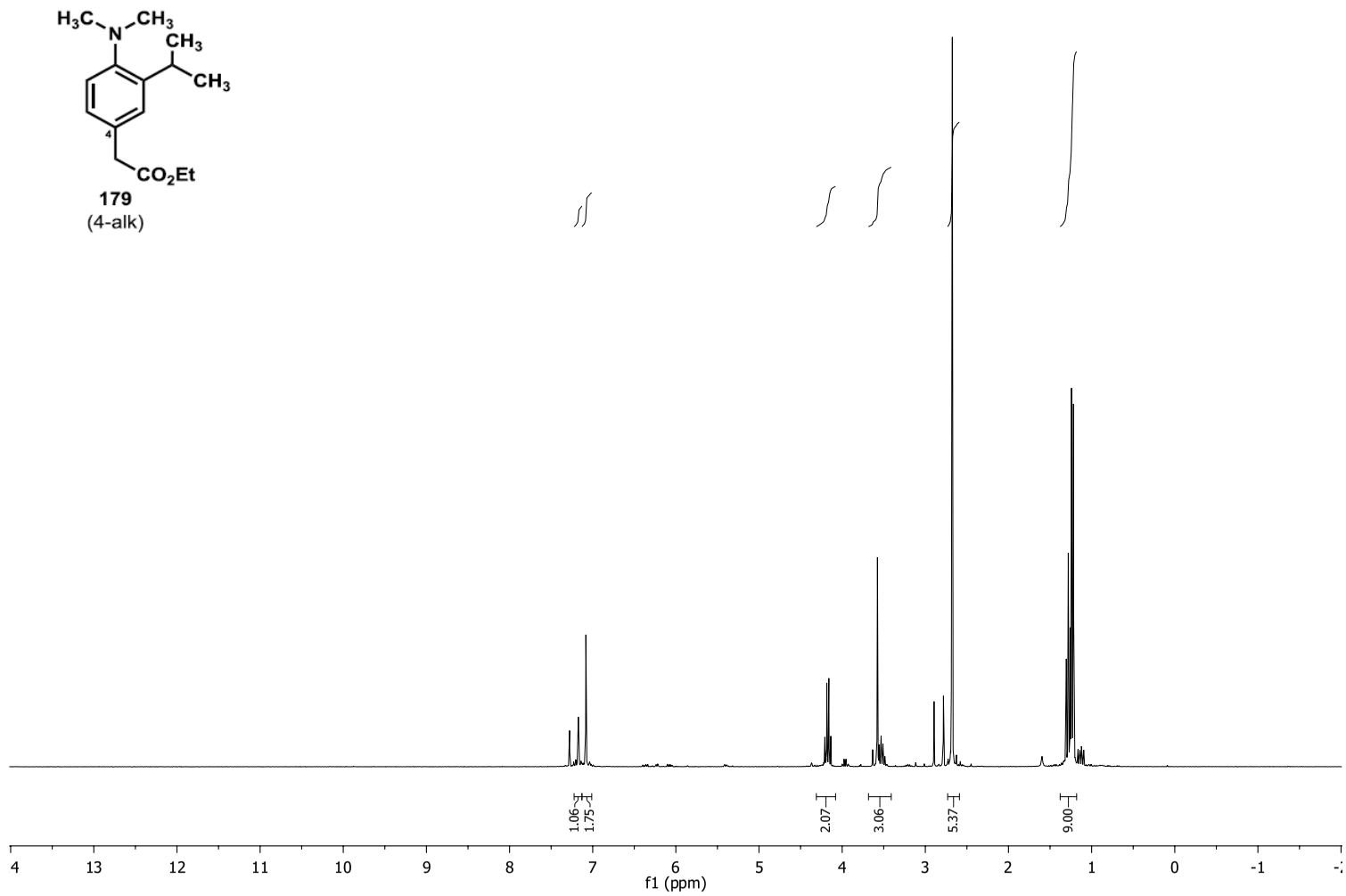
1.68
1.05
0.90
2.00
2.06
5.91
3.68
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

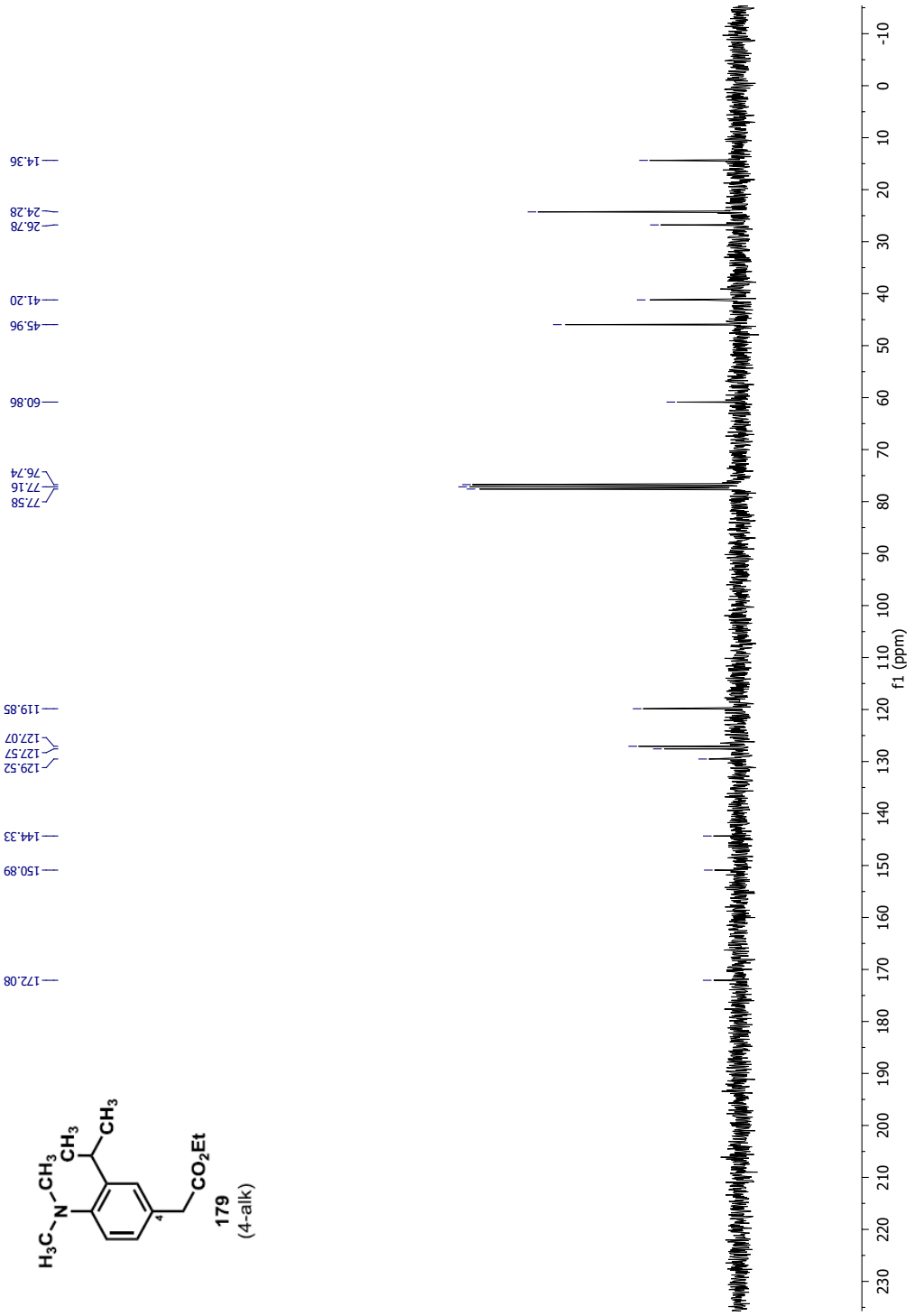

172.56
153.24
130.95
130.53
128.13
123.87
120.34
77.41
77.16
76.91
60.67
45.10
37.31
14.42
f1 (ppm)
CO2Et
CH3
N
H3C

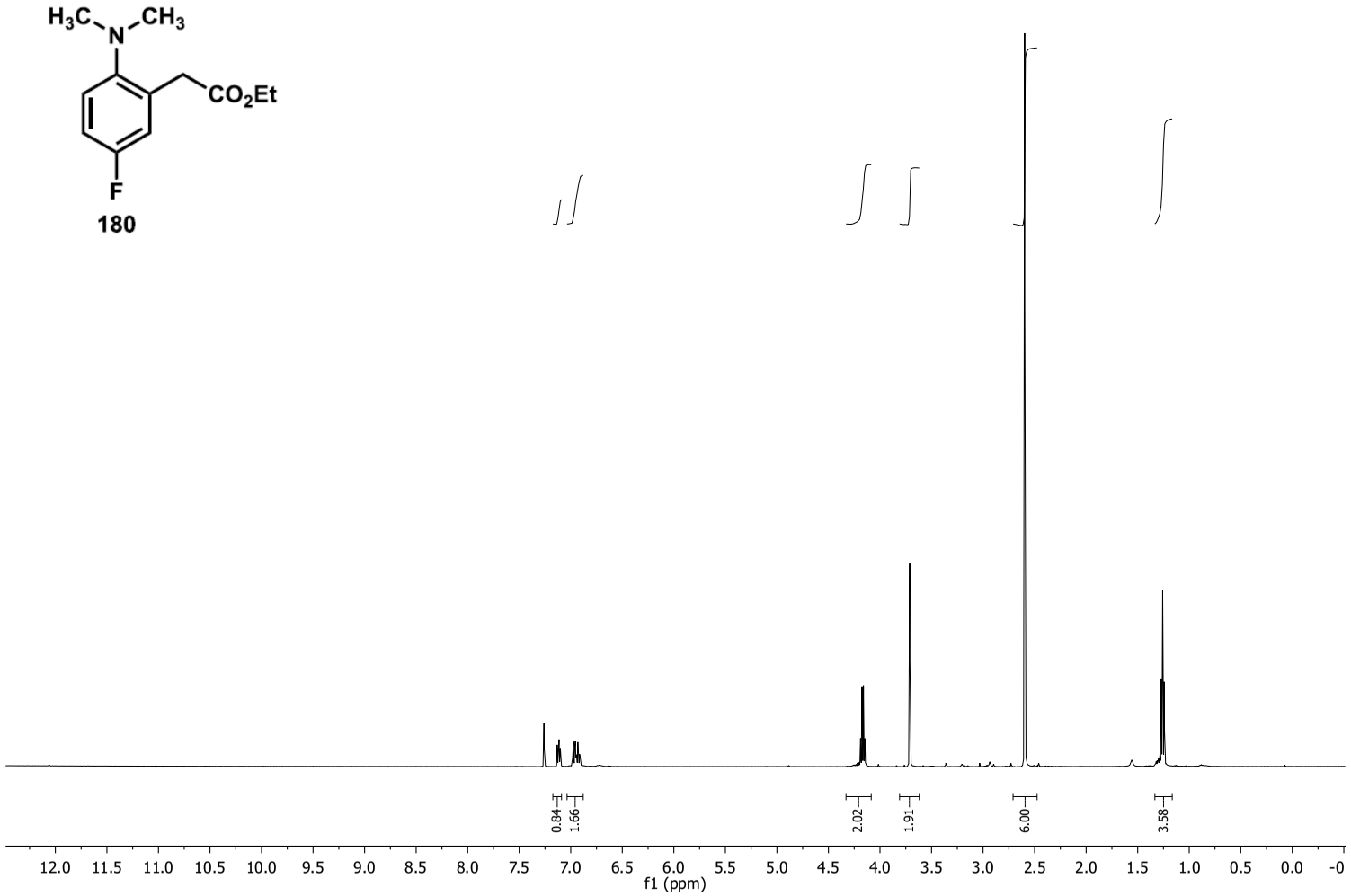
178

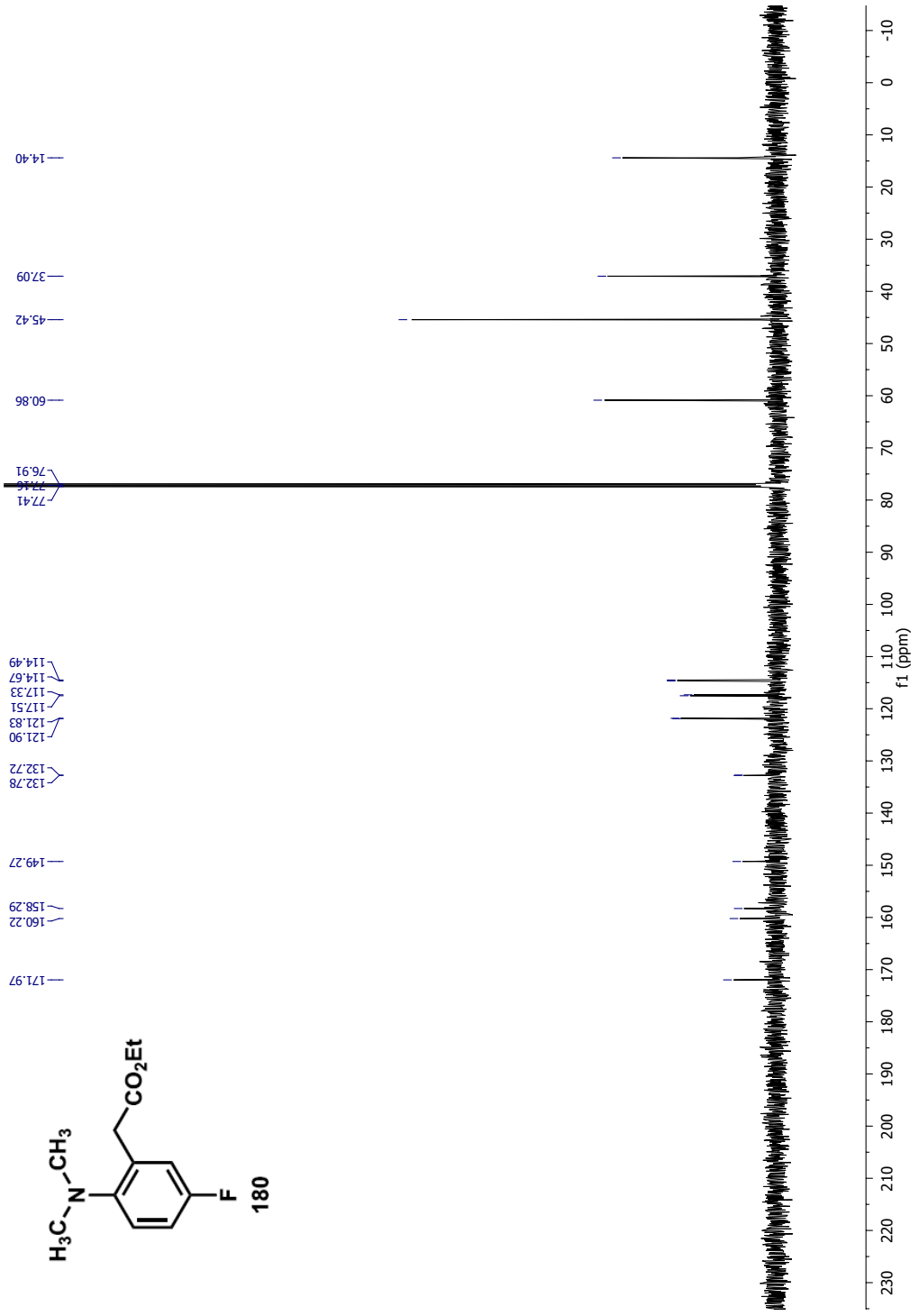

H3C
N
CH3
CH3
EtO2C
6
CH3
179
(6-alk)
2.95
2.03
2.00
1.13
5.51
9.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

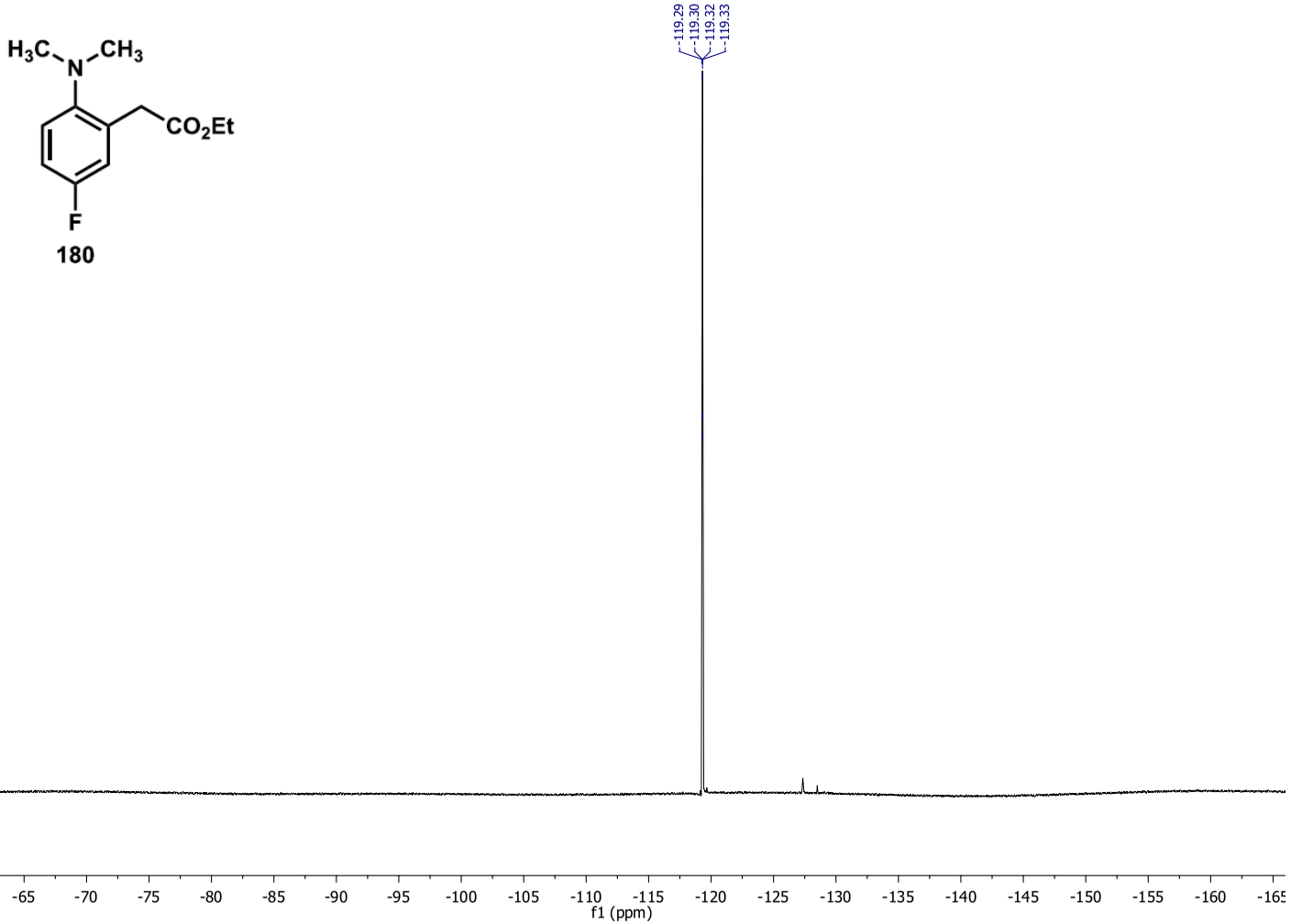

179
(6-alk)
172.47
149.53
148.27
135.58
128.20
126.47
126.24
77.41
76.91
60.50
43.45
39.10
28.25
24.47
14.54
f1 (ppm)

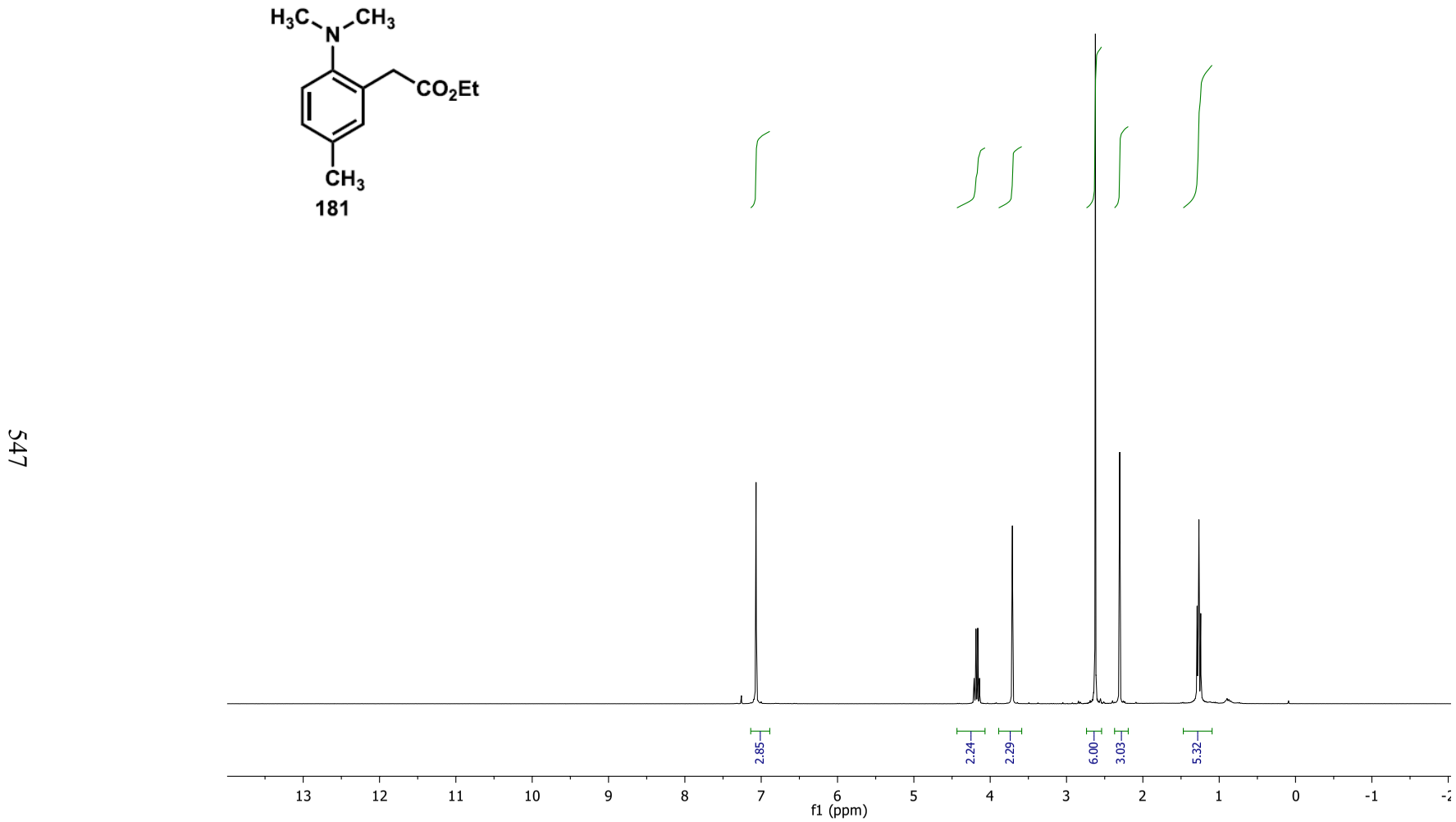

H3C
N
CH3
CH3
CH3
4
CO2Et
179
(4-alk)
1.06
1.75
2.07
3.06
5.37
9.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

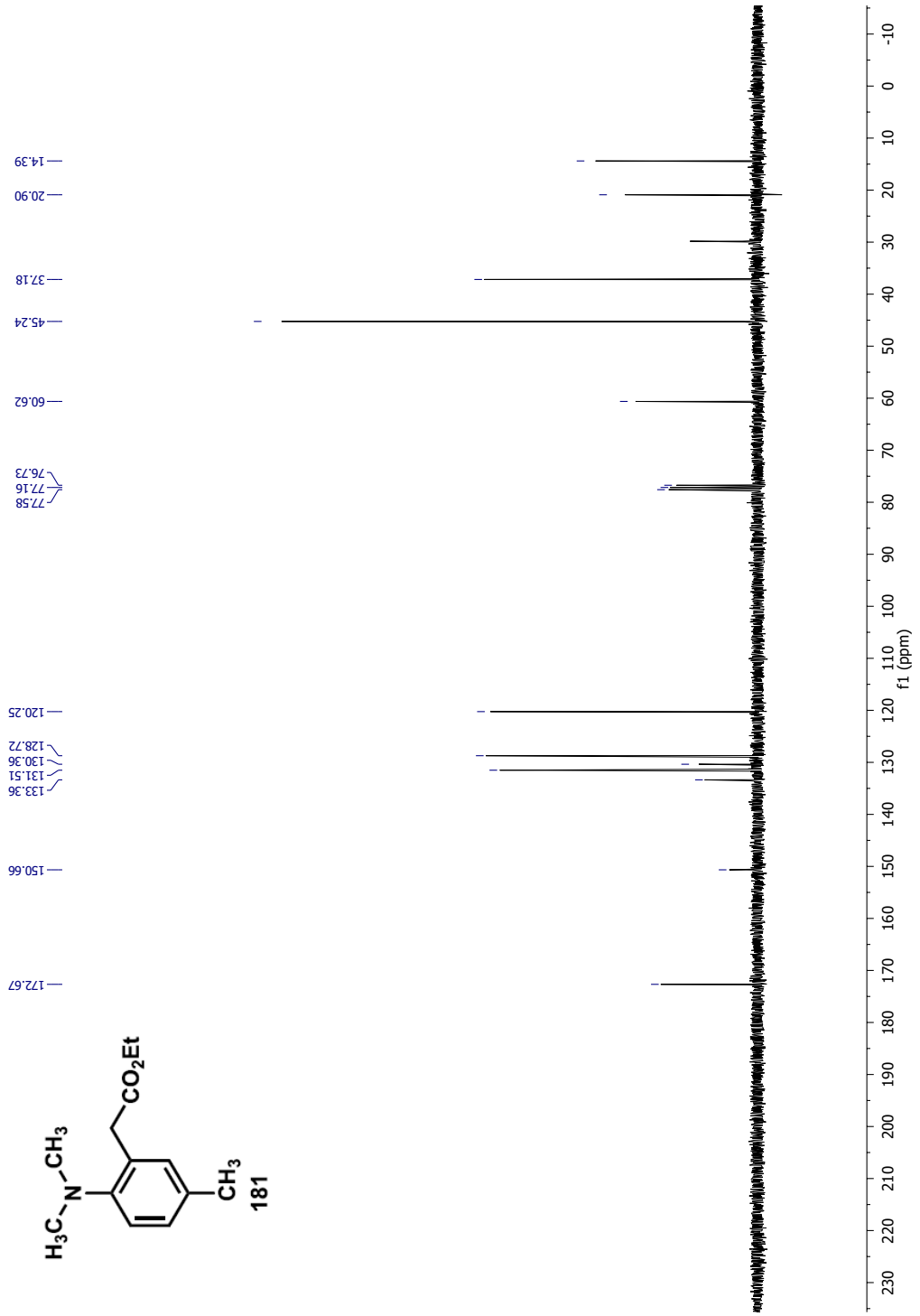

14.36
24.28
26.78
41.20
45.96
60.86
76.74
77.16
77.58
119.85
127.07
127.57
129.52
144.33
150.89
172.08
H_3C
N
CH_3
CH_3
CH_3
CO_2Et
4
179
(4-alk)
f1 (ppm)

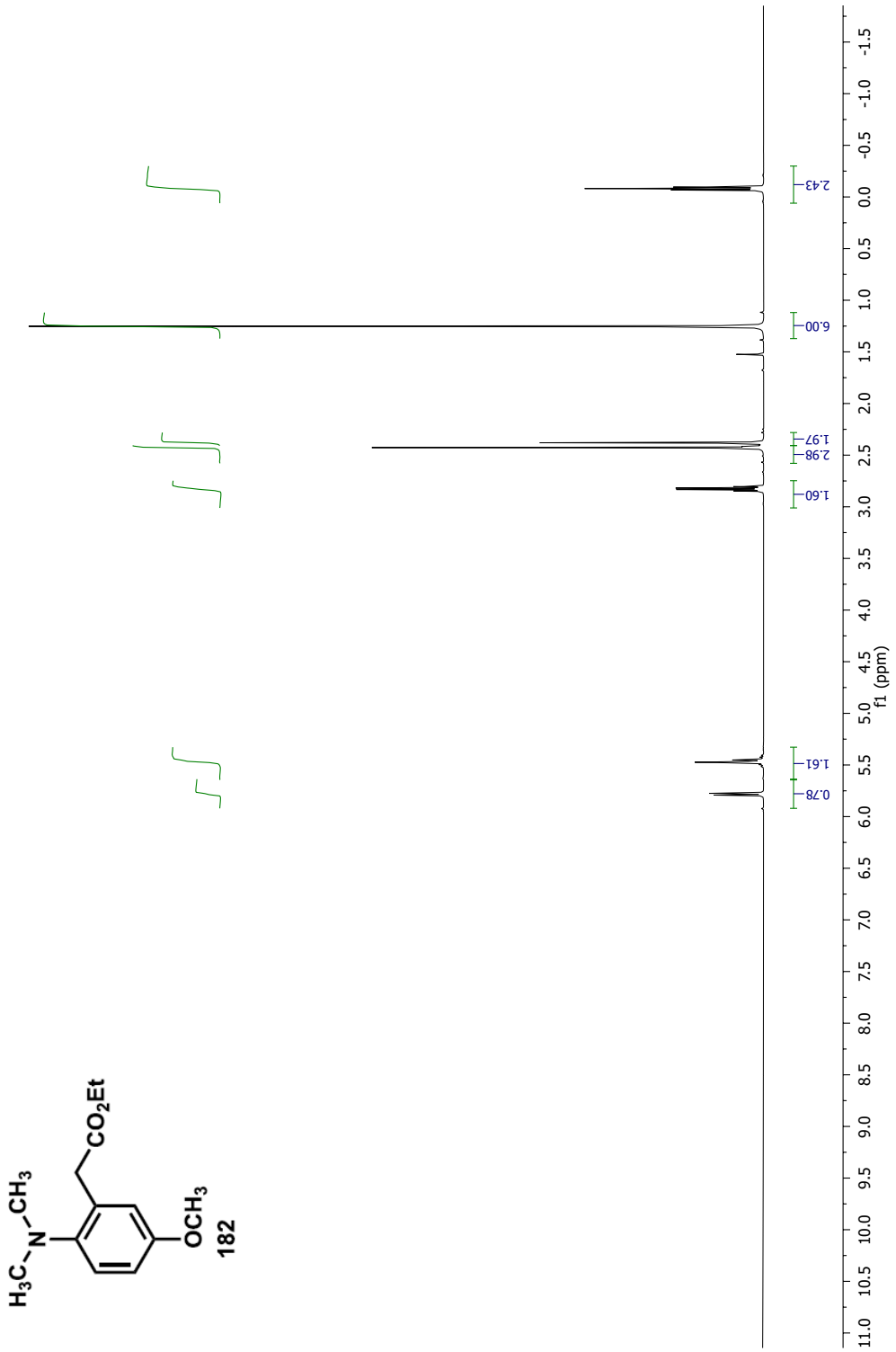

H3C
N
CH3
CO2Et
F
180
0.84
1.66
2.02
1.91
6.00
3.58
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

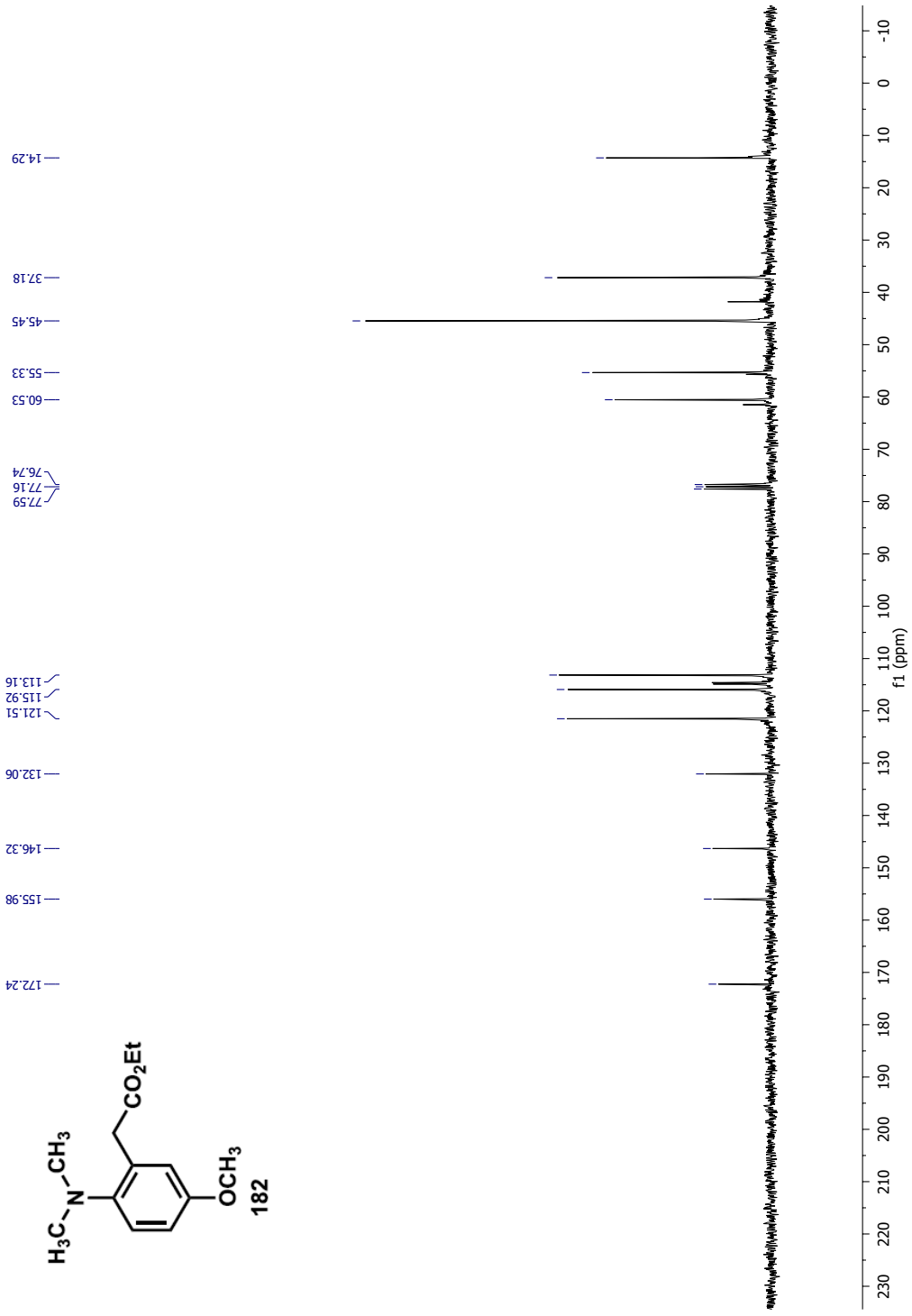

14.40
37.09
45.42
60.86
76.91
77.16
77.41
114.49
114.67
117.33
117.51
121.83
121.90
132.72
132.78
149.27
158.29
160.22
171.97
f1 (ppm)
180

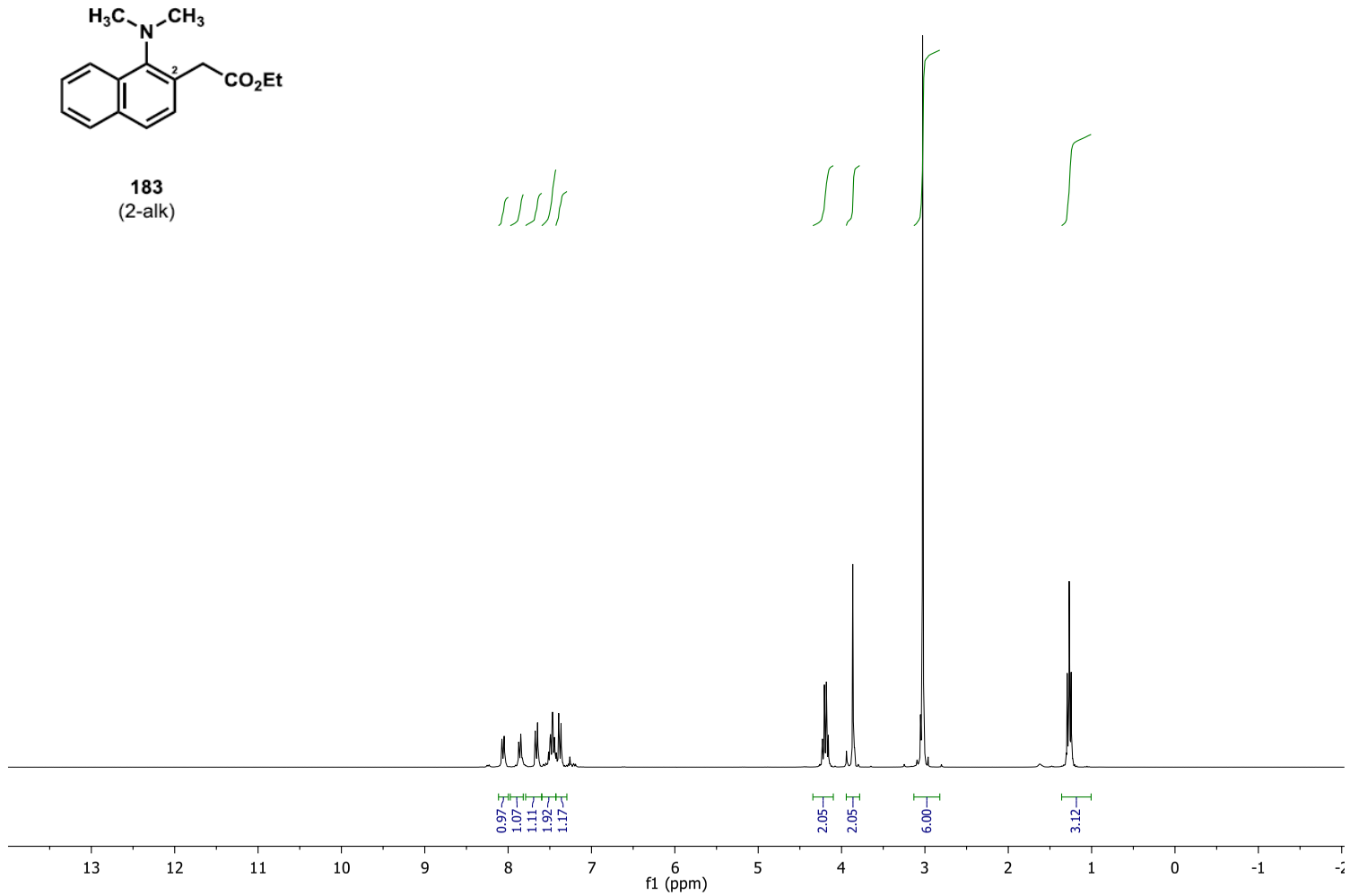

H3C
N
CH3
CO2Et
F
180
-119.29
-119.30
-119.32
-119.33
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
f1 (ppm)

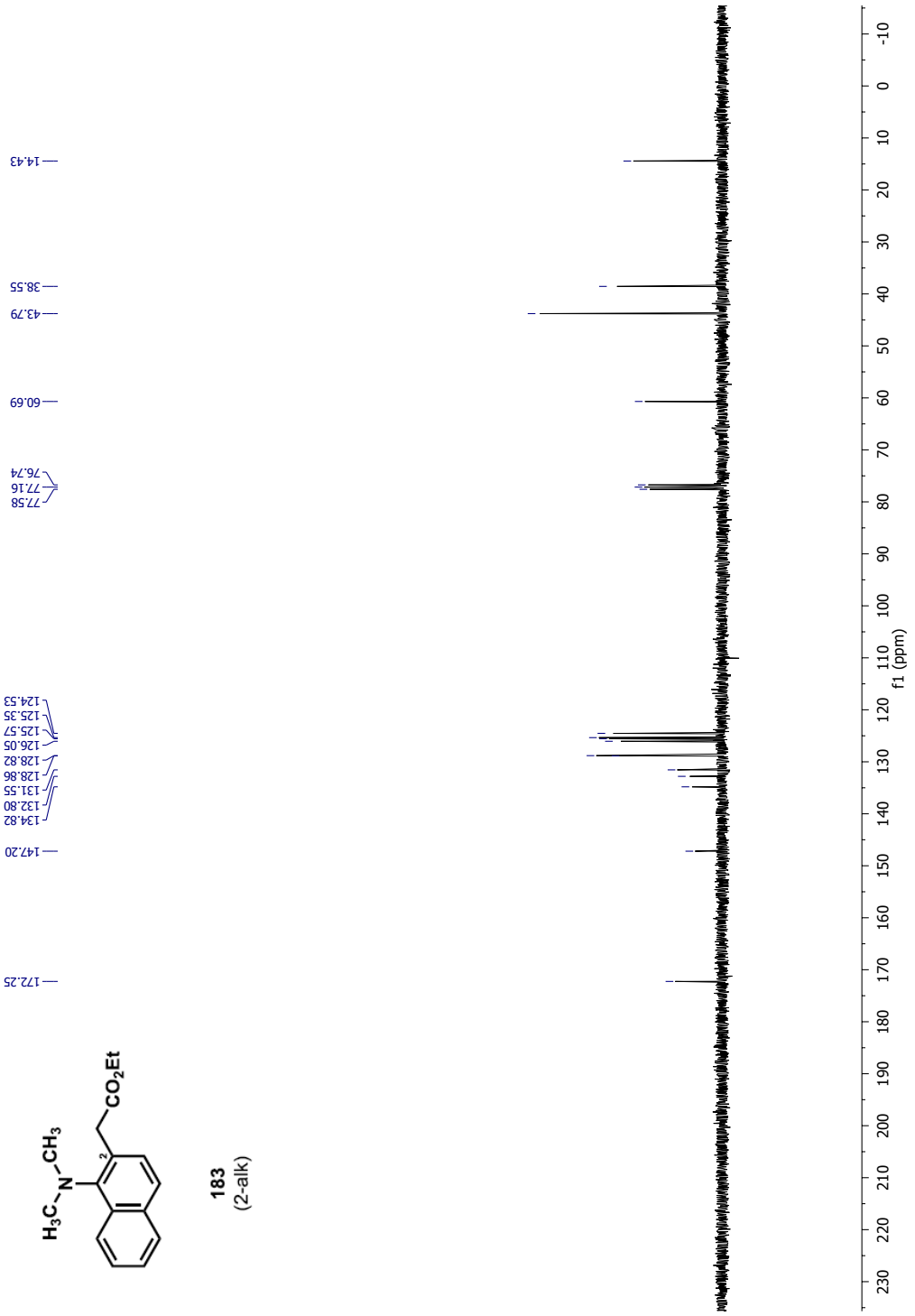

H3C
N
CH3
CO2Et
CH3
181
2.85
2.24
2.29
6.00
3.03
5.32
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

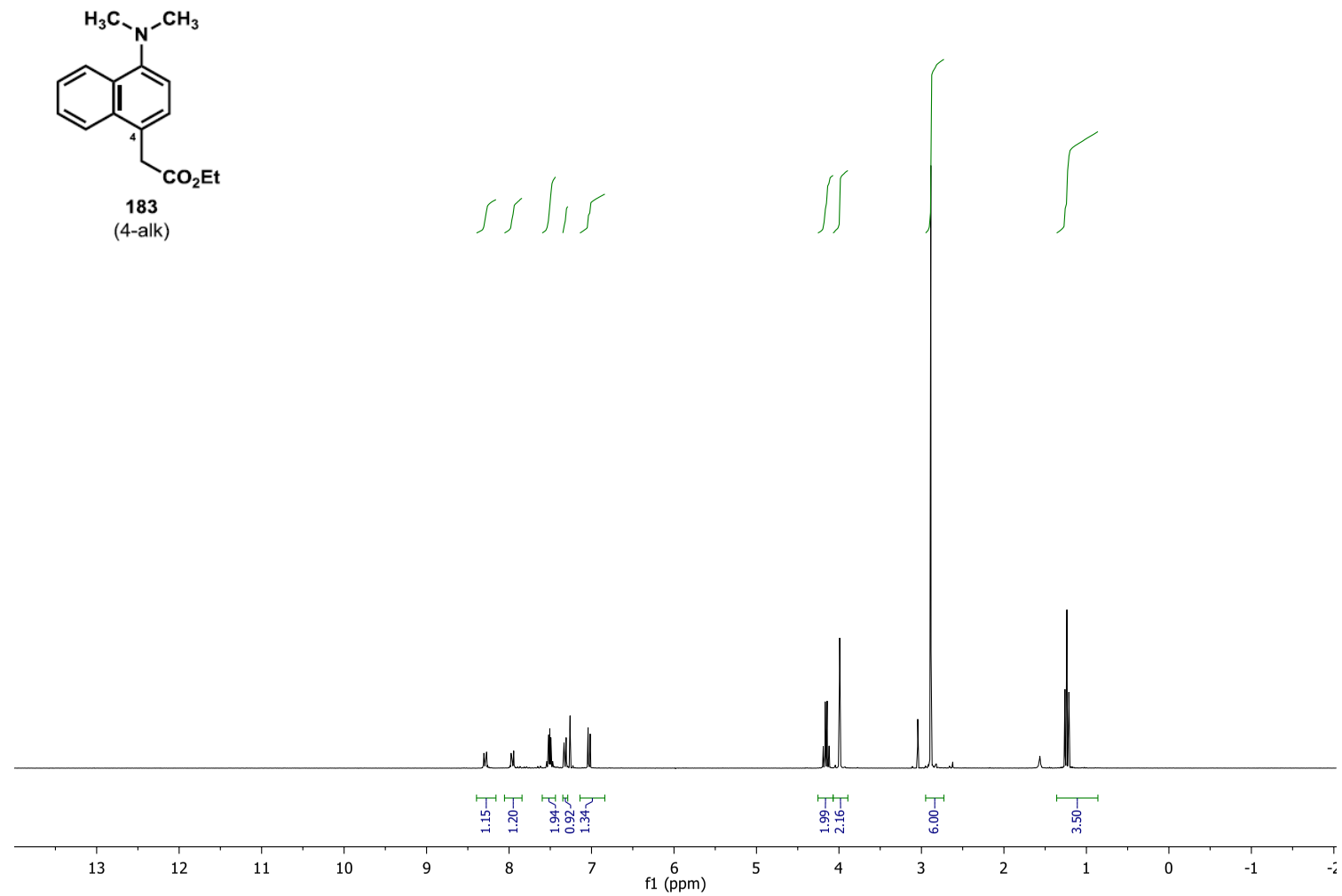

14.39
20.90
37.18
45.24
60.62
76.73
77.16
77.58
120.25
128.72
130.36
131.51
133.36
150.66
172.67
CO2Et
CH3
N
H3C
CH3
181
f1 (ppm)

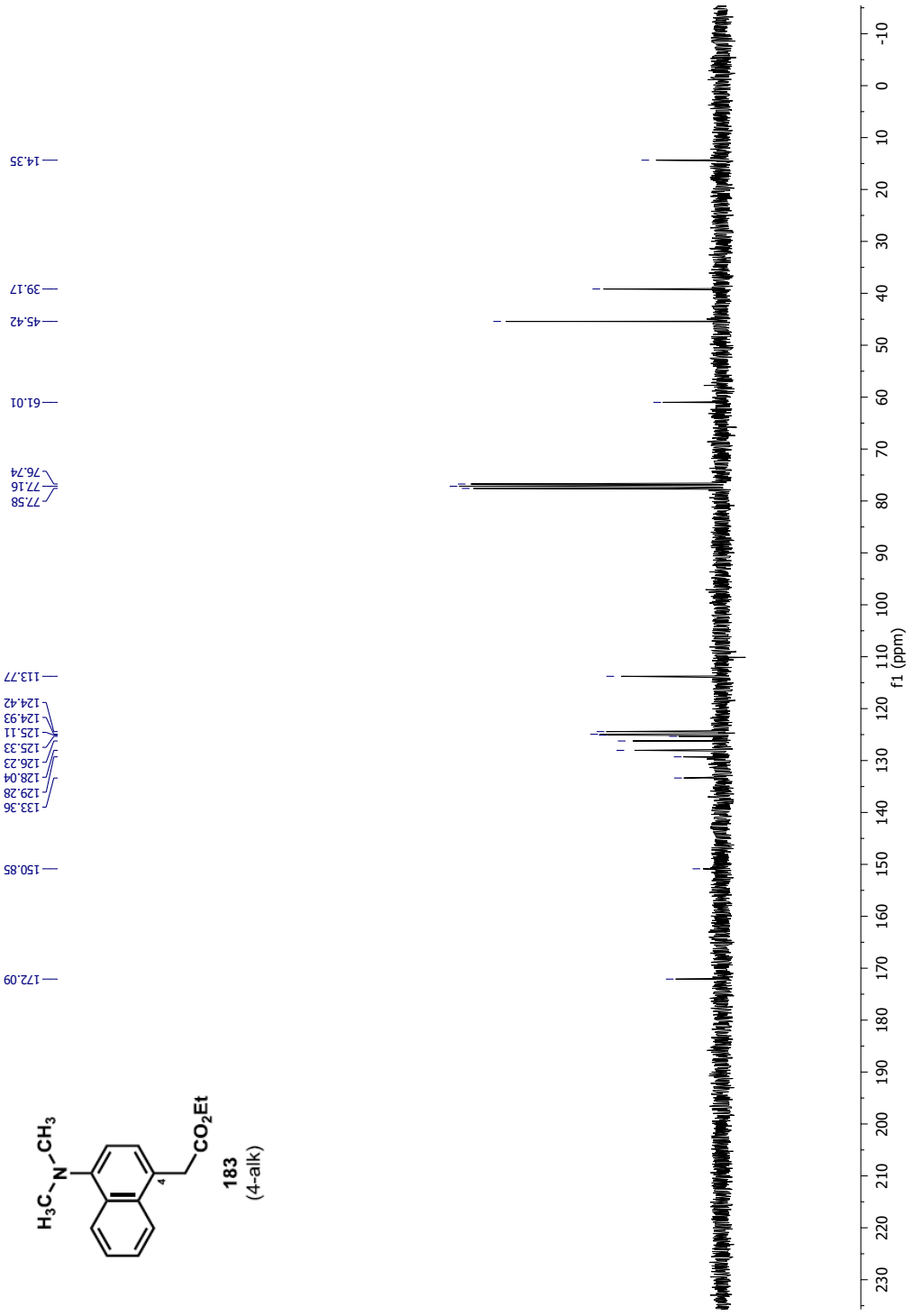

2.43
6.00
1.97
2.98
1.60
1.61
0.78
f1 (ppm)
182

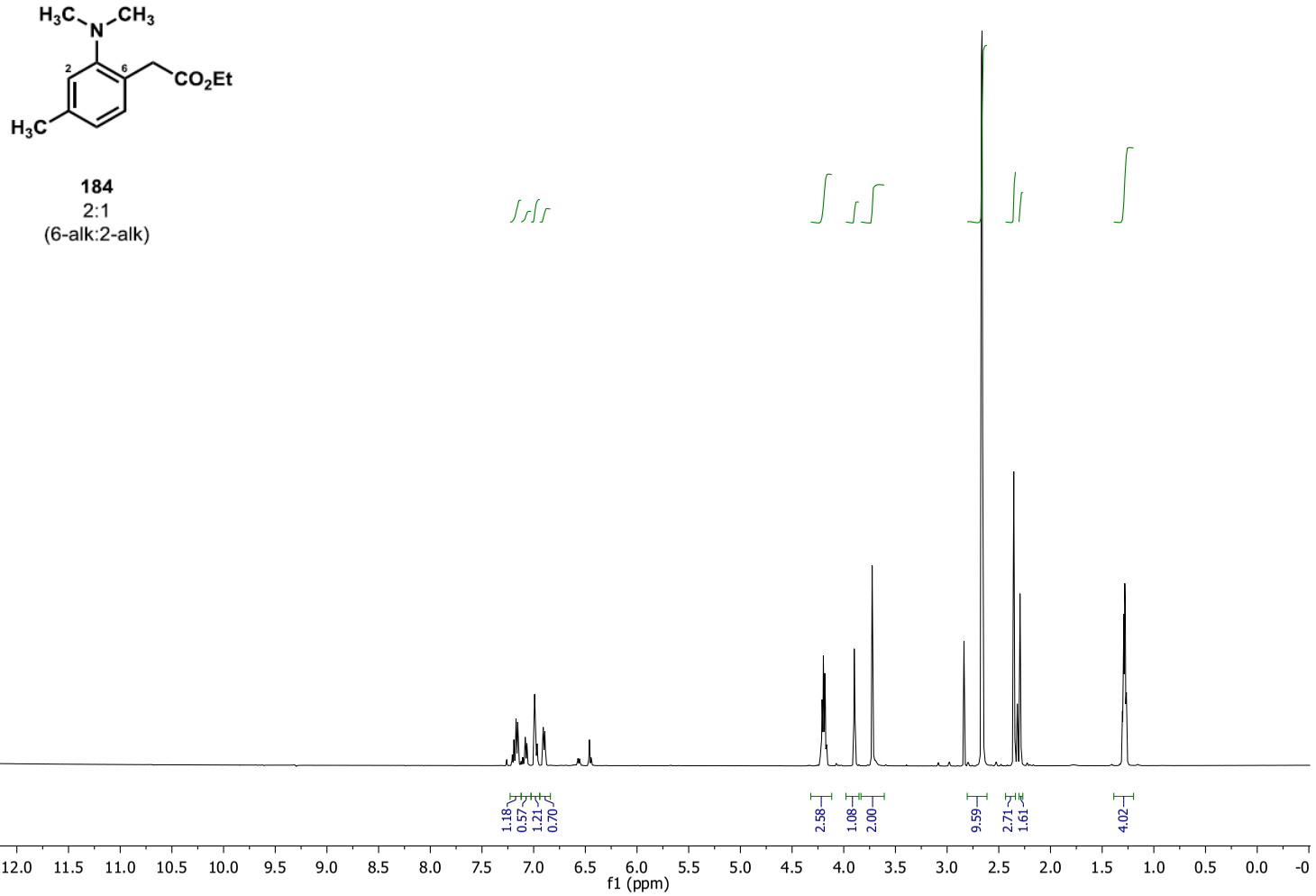

14.29
37.18
45.45
55.33
60.53
76.74
77.16
77.59
113.16
115.92
121.51
132.06
146.32
155.98
172.24
f1 (ppm)
182

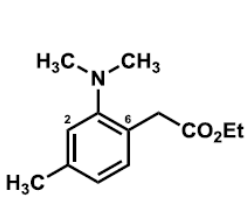

H3C
N
CH3
CO2Et
2
183
(2-alk)
0.97
1.07
1.11
1.92
1.17
2.05
2.05
6.00
3.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


14.43
38.55
43.79
60.69
76.74
77.16
77.58
124.53
125.35
125.57
126.05
128.82
128.86
131.55
132.80
134.82
147.20
172.25
H_3C
N
CH_3
CO_2Et
183
(2-alk)
f1 (ppm)

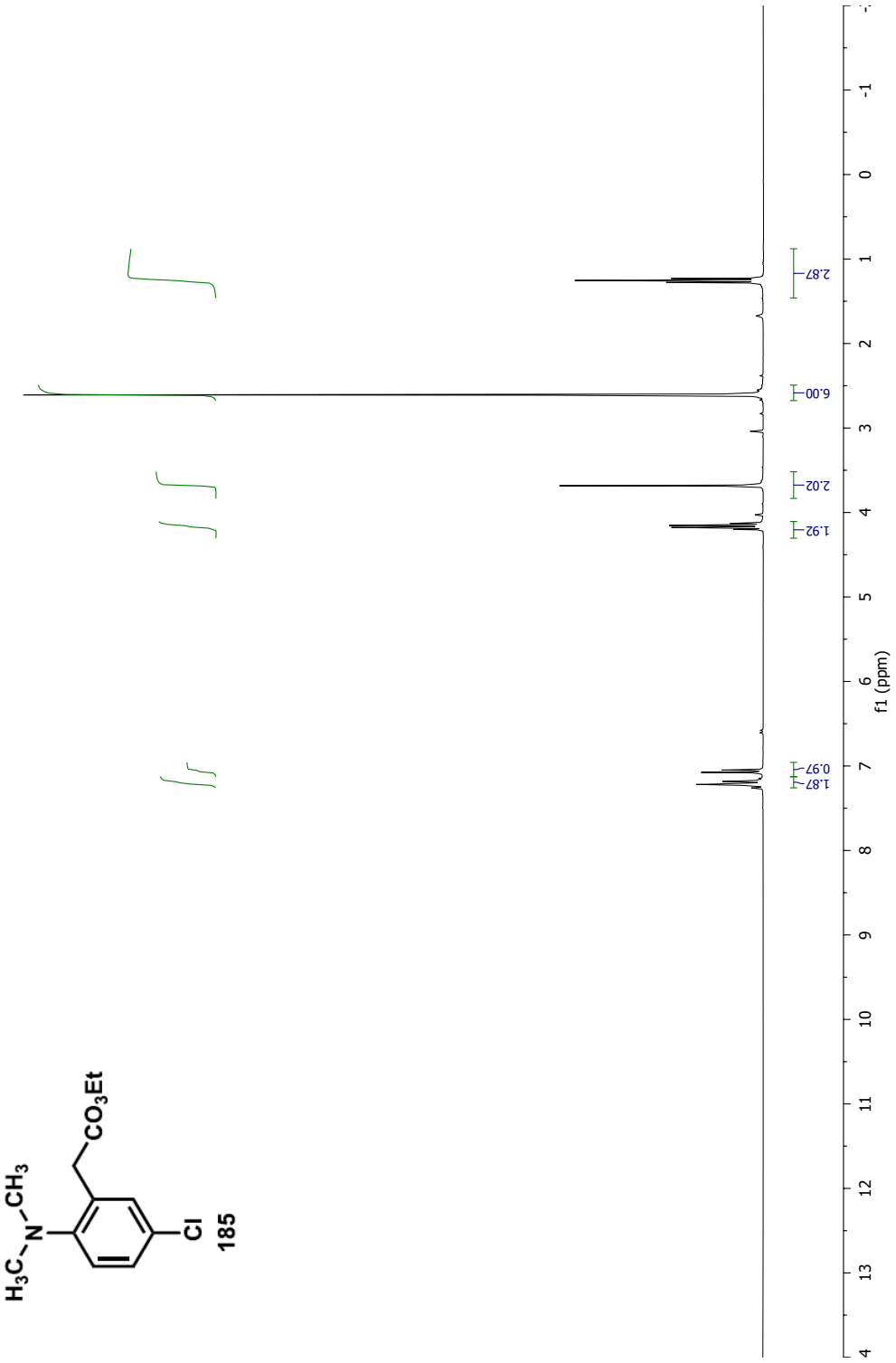

H3C
N
CH3
4
CO2Et
183
(4-alk)
1.15
1.20
1.94
0.92
1.34
1.99
2.16
6.00
3.50
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

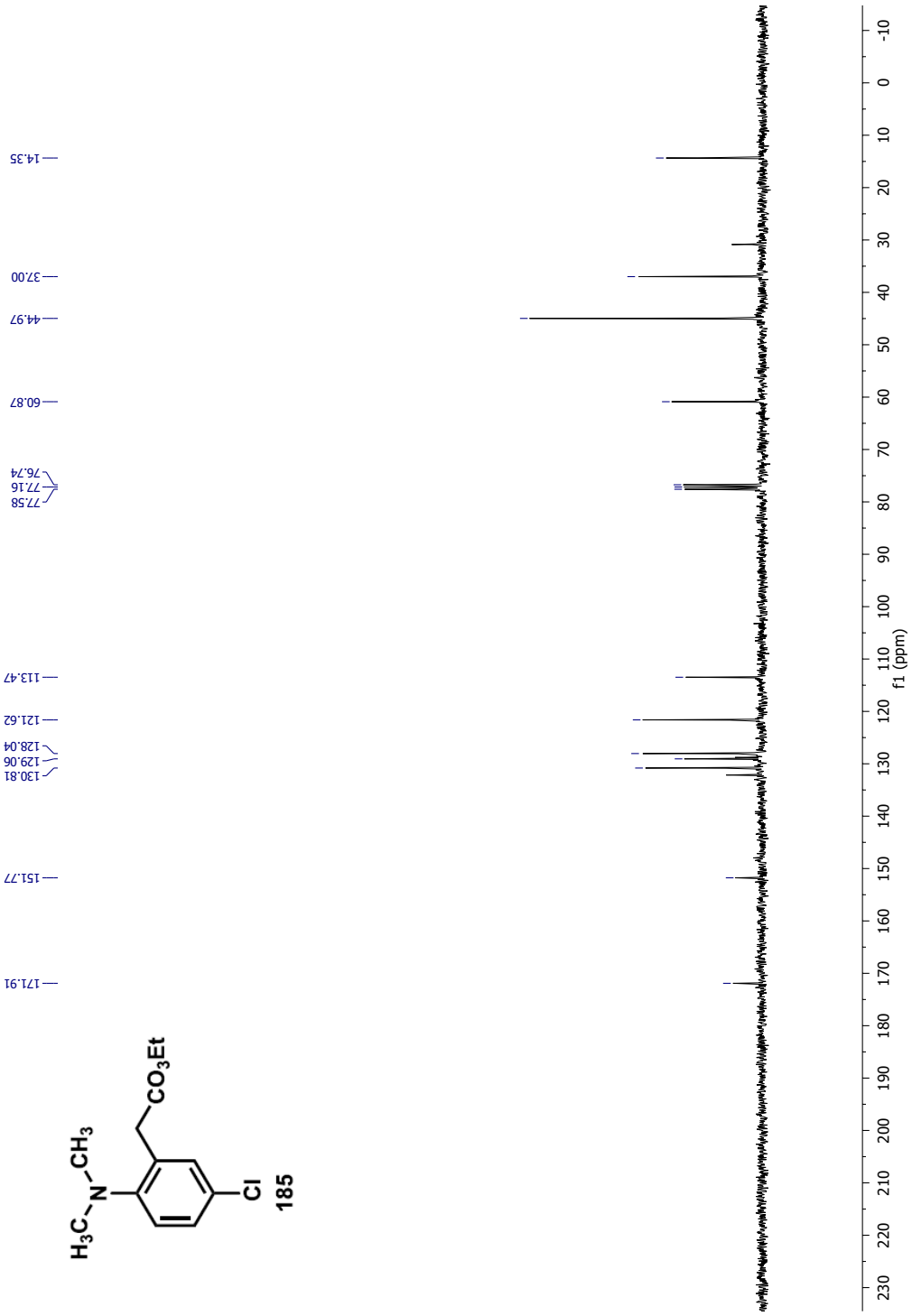

14.35
39.17
45.42
61.01
76.74
77.16
77.58
113.77
124.42
124.93
125.11
125.33
126.23
128.04
129.28
133.36
150.85
172.09
f1 (ppm)
183
(4-alk)

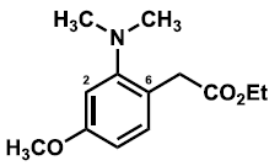

H3C
N
CH3
2
6
CO2Et
H3C
184
2:1
(6-alk:2-alk)
1.18
0.57
1.21
0.70
2.58
1.08
2.00
9.59
2.71
1.61
4.02
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)



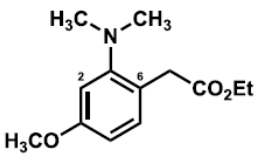
184
2:1
(6-alk:2-alk)


2.87
6.00
2.02
1.92
1.87
0.97
f1 (ppm)
185

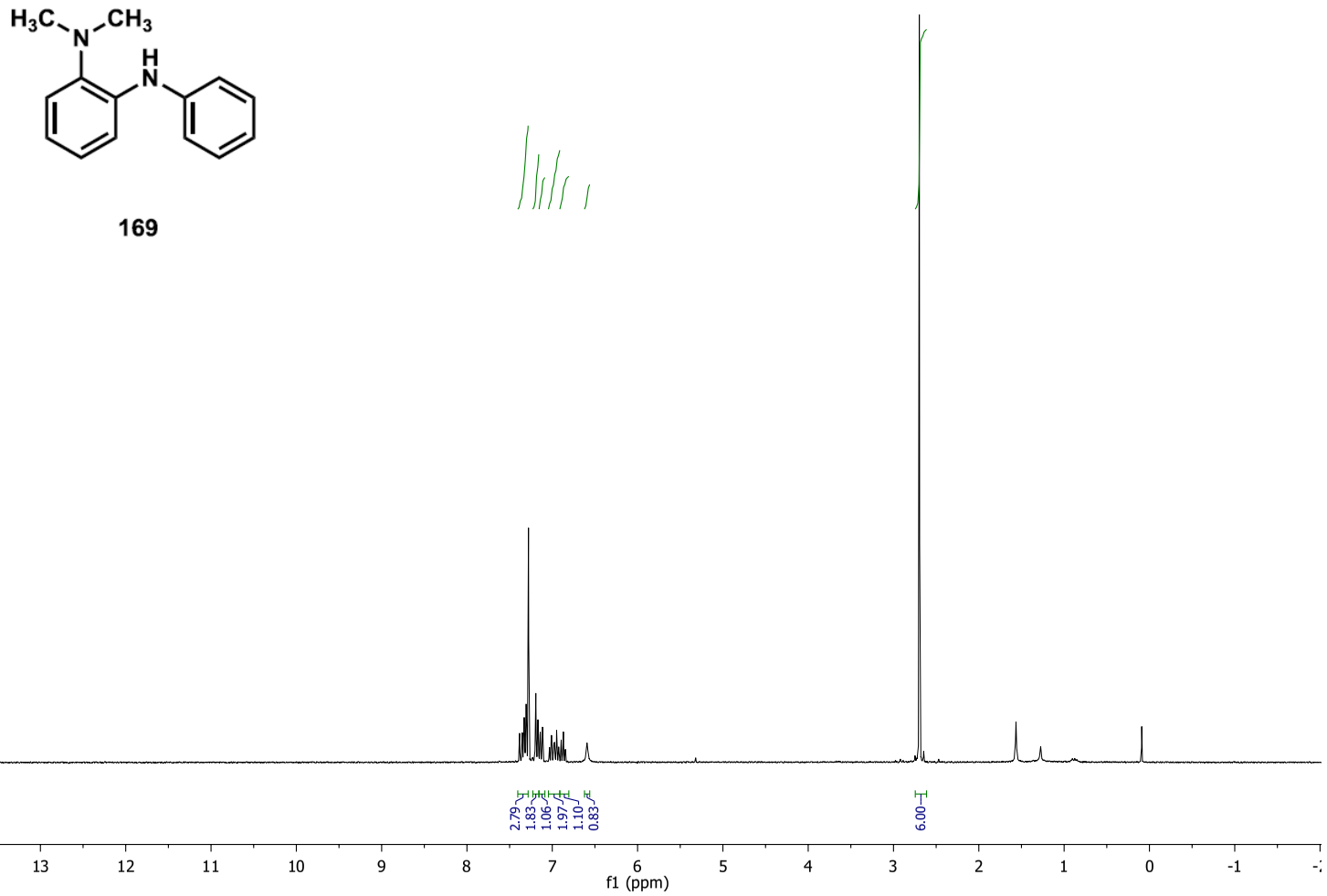

14.35
37.00
44.97
60.87
76.74
77.16
77.58
113.47
121.62
128.04
129.06
130.81
151.77
171.91
f1 (ppm)
185

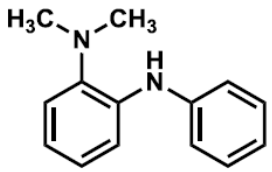


186
2:1
(6-alk:2-alk)



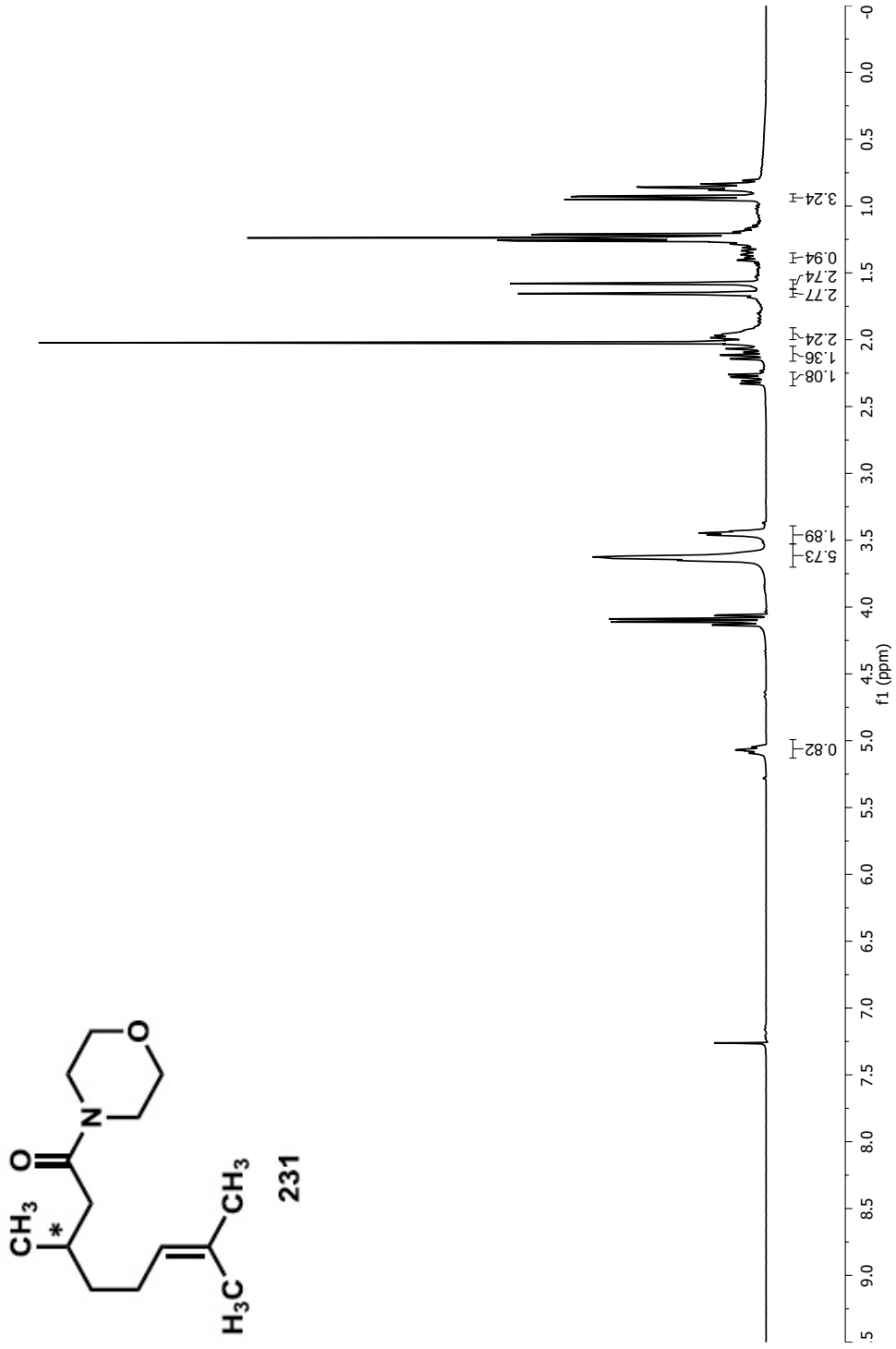
186
2:1
(6-alk:2-alk)


H3C
N
CH3
H
N
169
2.79
1.83
1.06
1.97
1.10
0.83
6.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


H3C
N
CH3
H
N

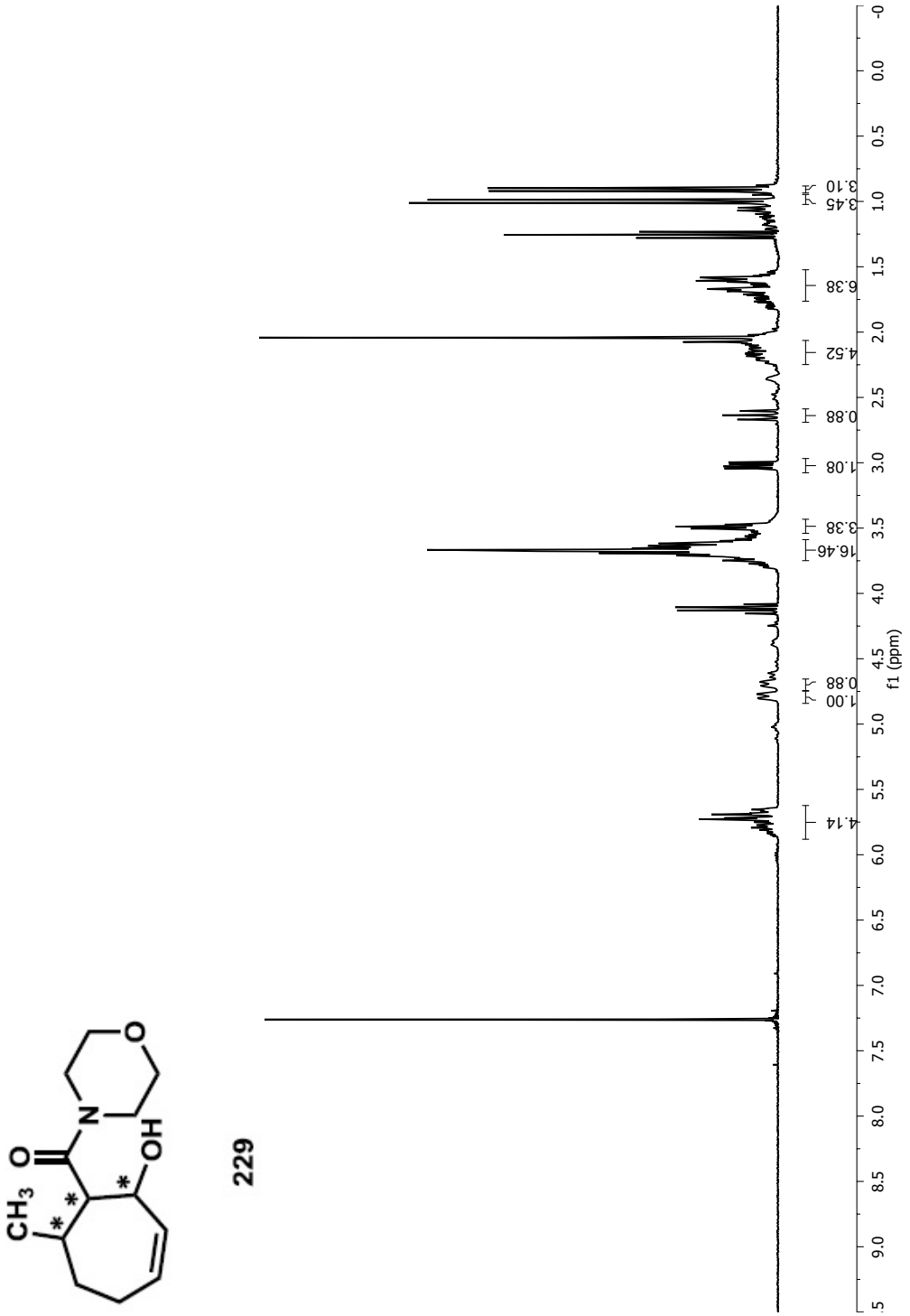
169

129.45
129.20
124.16
120.93
120.04
119.77
118.39
116.76
114.53
112.79
77.58
77.16
76.74
44.27
40.77
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

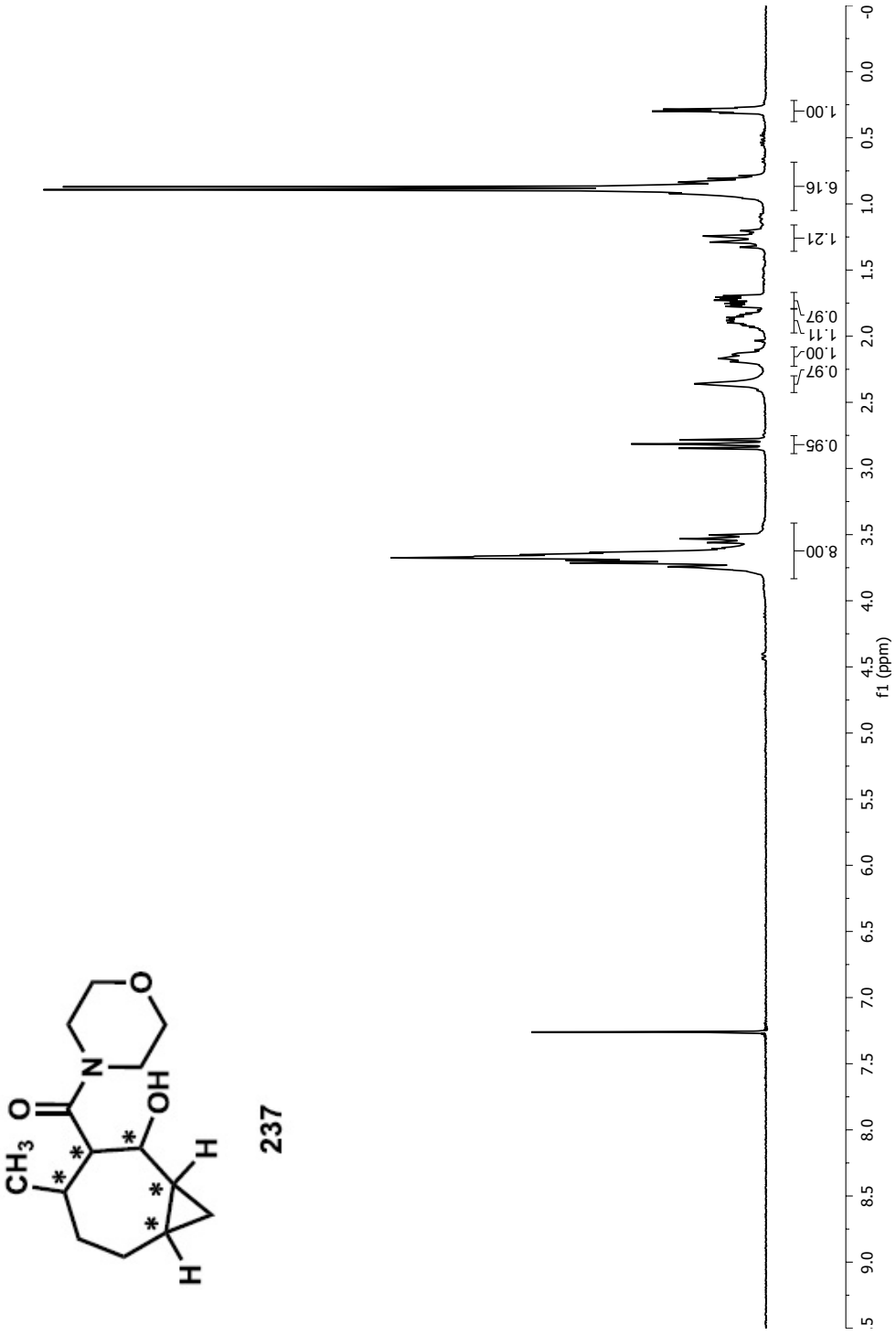

O
N
O
CH3
*
CH3
H3C
231
3.24
0.94
2.74
2.77
2.24
1.36
1.08
1.89
5.73
0.82
f1 (ppm)

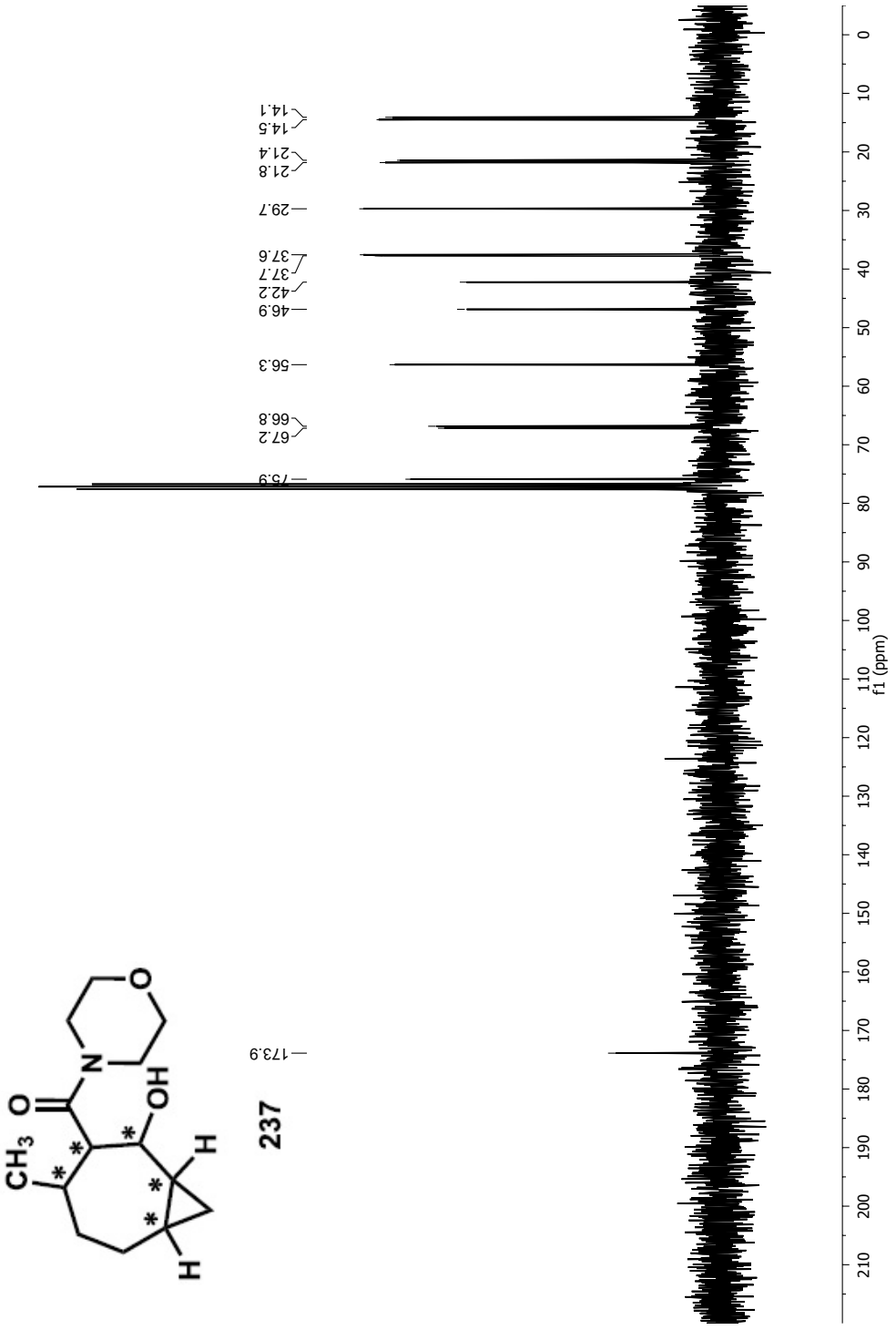
CH3
O
N
OH
CH3
H3C
230
1.65
0.95
0.81
4.01
1.90
2.02
13.14
4.38
2.00
1.33
7.86
6.32
5.63
2.14
2.14
2.61
2.40
2.18
f1 (ppm)

230
174.0
171.3
140.0
131.7
131.6
131.5
124.4
124.2
124.0
115.0
115.0
70.9
70.8
67.0
66.7
66.7
50.3
49.7
46.7
46.7
46.3
41.9
41.8
40.3
37.1
35.0
33.6
32.8
32.3
30.0
25.7
25.6
25.5
25.0
19.8
17.7
16.6
f1 (ppm)

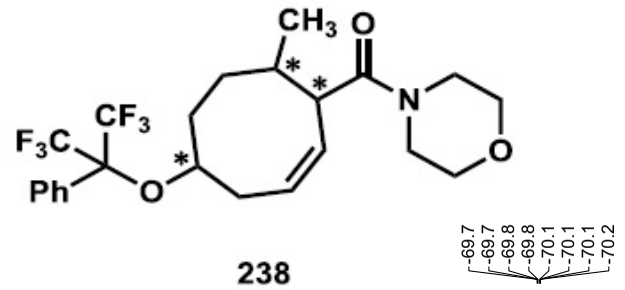

CH3
O
N
O
OH
*
*
*
*
229
4.14
1.00
0.88
16.46
3.38
1.08
0.88
4.52
6.38
3.45
3.10
f1 (ppm)

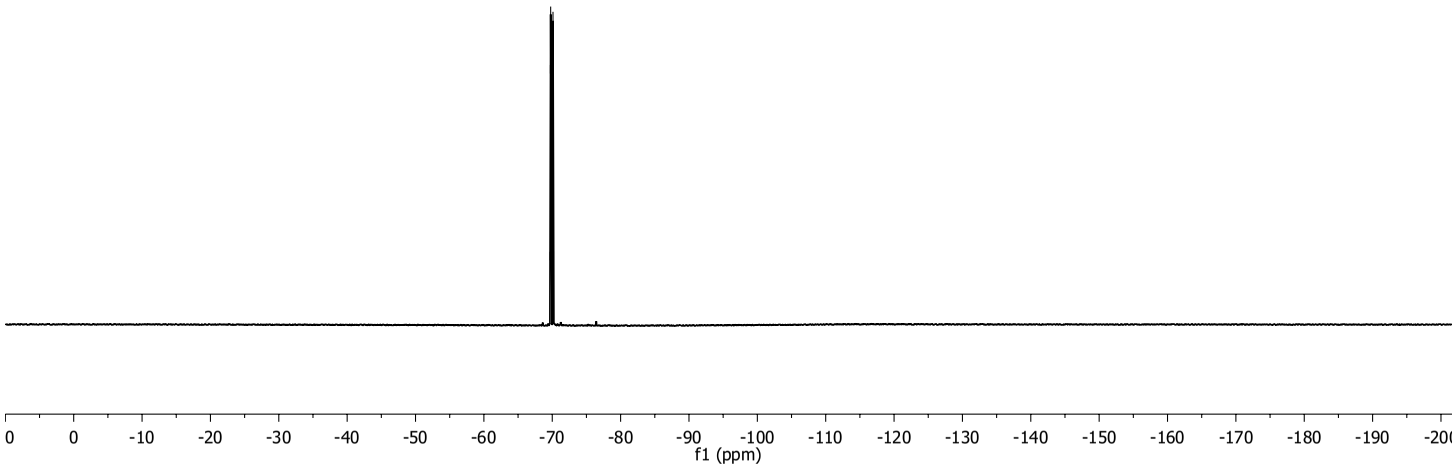
229
173.0
135.3
129.4
67.0
66.7
51.4
46.3
41.9
33.5
32.2
24.7
15.4
f1 (ppm)


O
N
OH
CH3 O
H
H
237
8.00
0.95
0.97
1.00
1.11
0.97
1.21
6.16
1.00
f1 (ppm)


237
173.9
75.9
67.2
66.8
56.3
46.9
42.2
37.7
37.6
29.7
21.8
21.4
14.5
14.1
f1 (ppm)

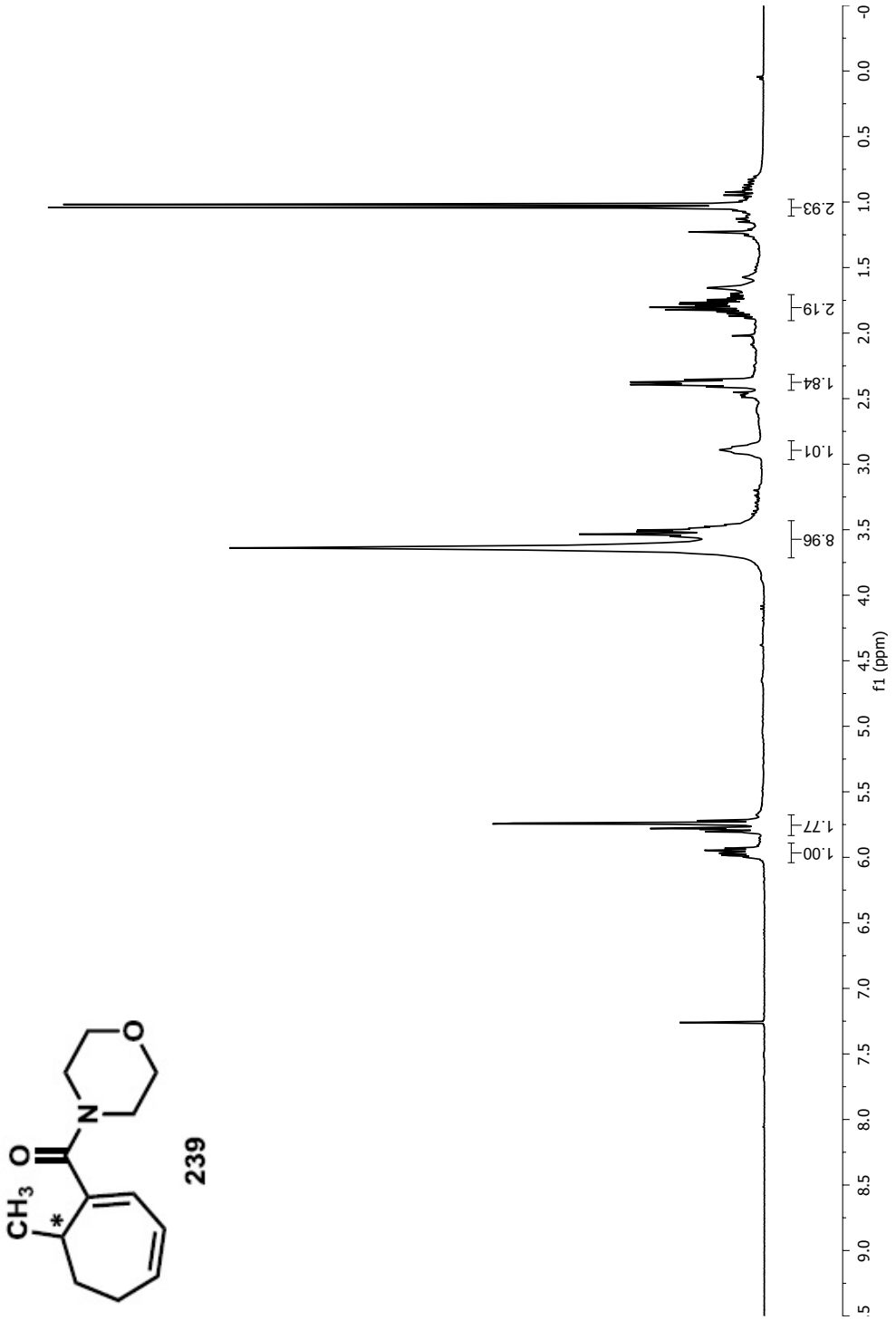
238
CH3
O
N
O
CF3
F3C
Ph
O
3.34
2.44
1.53
1.50
1.37
2.37
9.21
1.13
1.04
1.00
3.50
2.40
f1 (ppm)

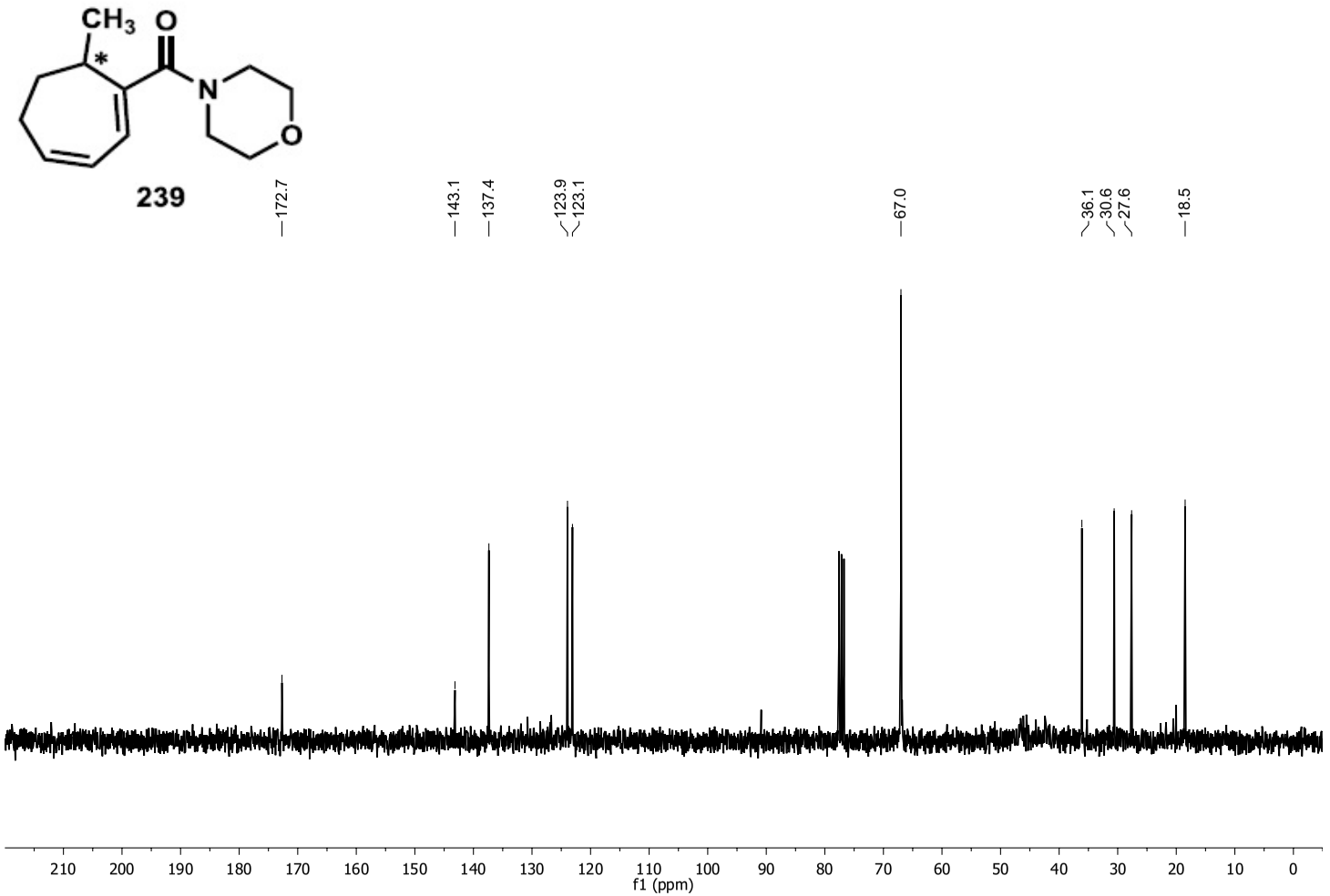

CH3
O
CF3
F3C
Ph
O
N
O
238
-69.7
-69.7
-69.8
-69.8
-70.1
-70.1
-70.1
-70.2


0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

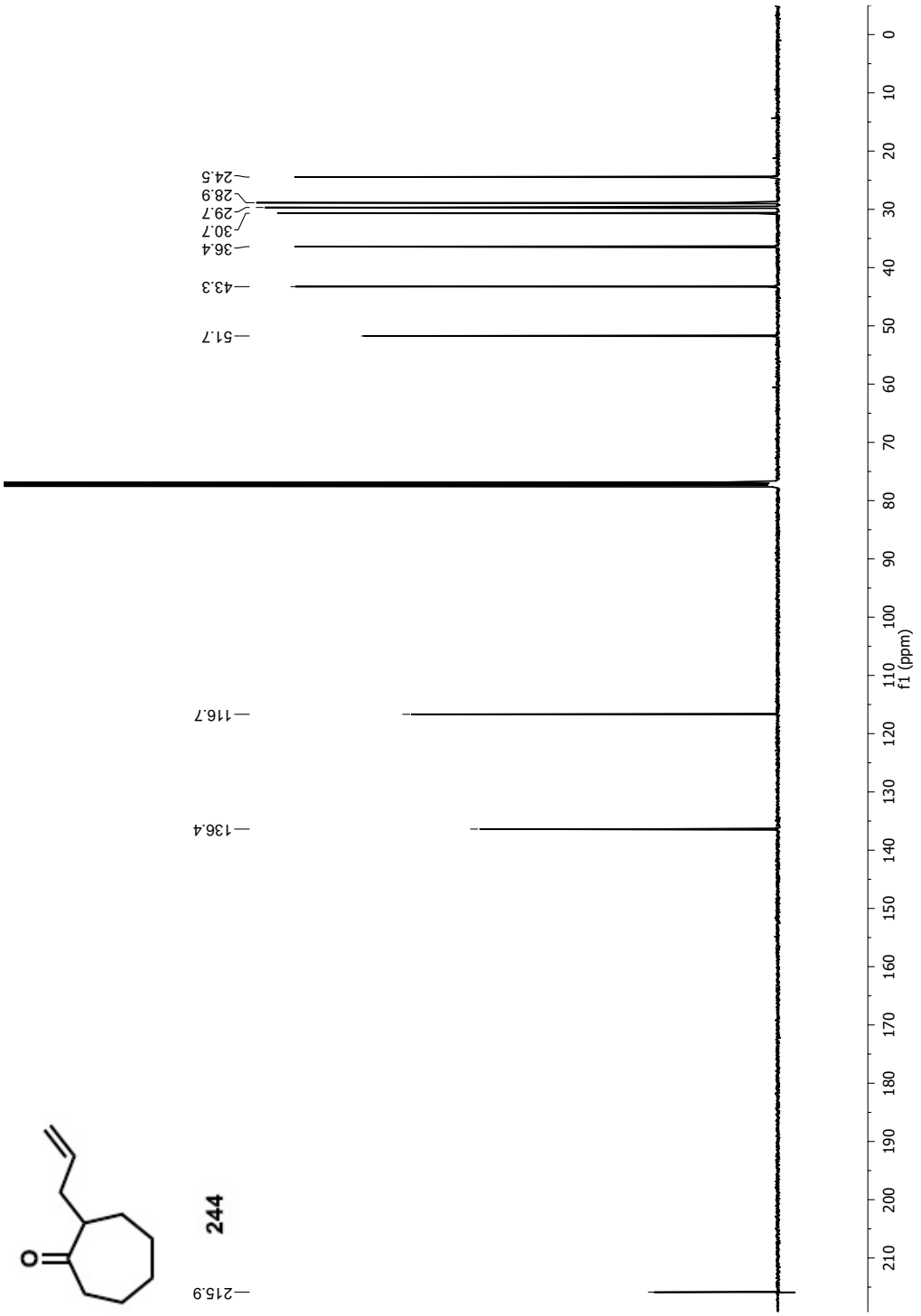
228
f1 (ppm)

16.8
17.0
17.2
19.4
22.1
23.8
29.0
29.9
30.4
30.5
30.8
30.9
33.1
34.2
36.1
38.5
41.9
42.0
46.7
49.8
52.9
66.8
67.0
67.1
67.2
70.9
73.9
175.7
176.4
f1 (ppm)
228


O
N
O
CH3
*
239
2.93
2.19
1.84
1.01
8.96
1.77
1.00
f1 (ppm)

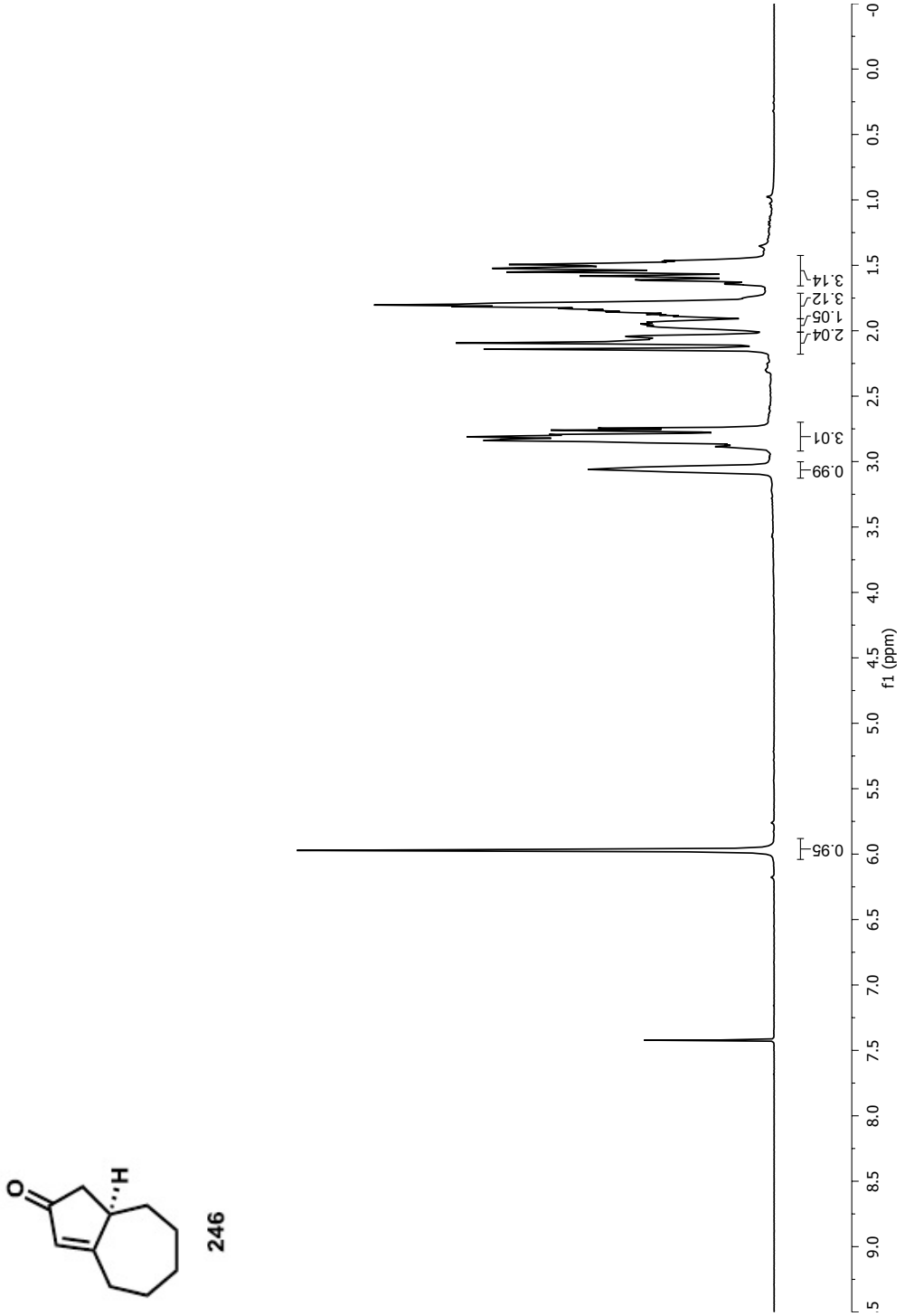

CH3
O
*
N
O
239
172.7
143.1
137.4
123.9
123.1
67.0
36.1
30.6
27.6
18.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

244

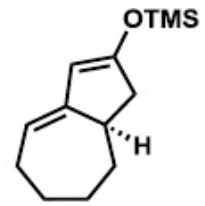

215.9
136.4
116.7
51.7
43.3
36.4
30.7
29.7
28.9
24.5
244
O
f1 (ppm)

245

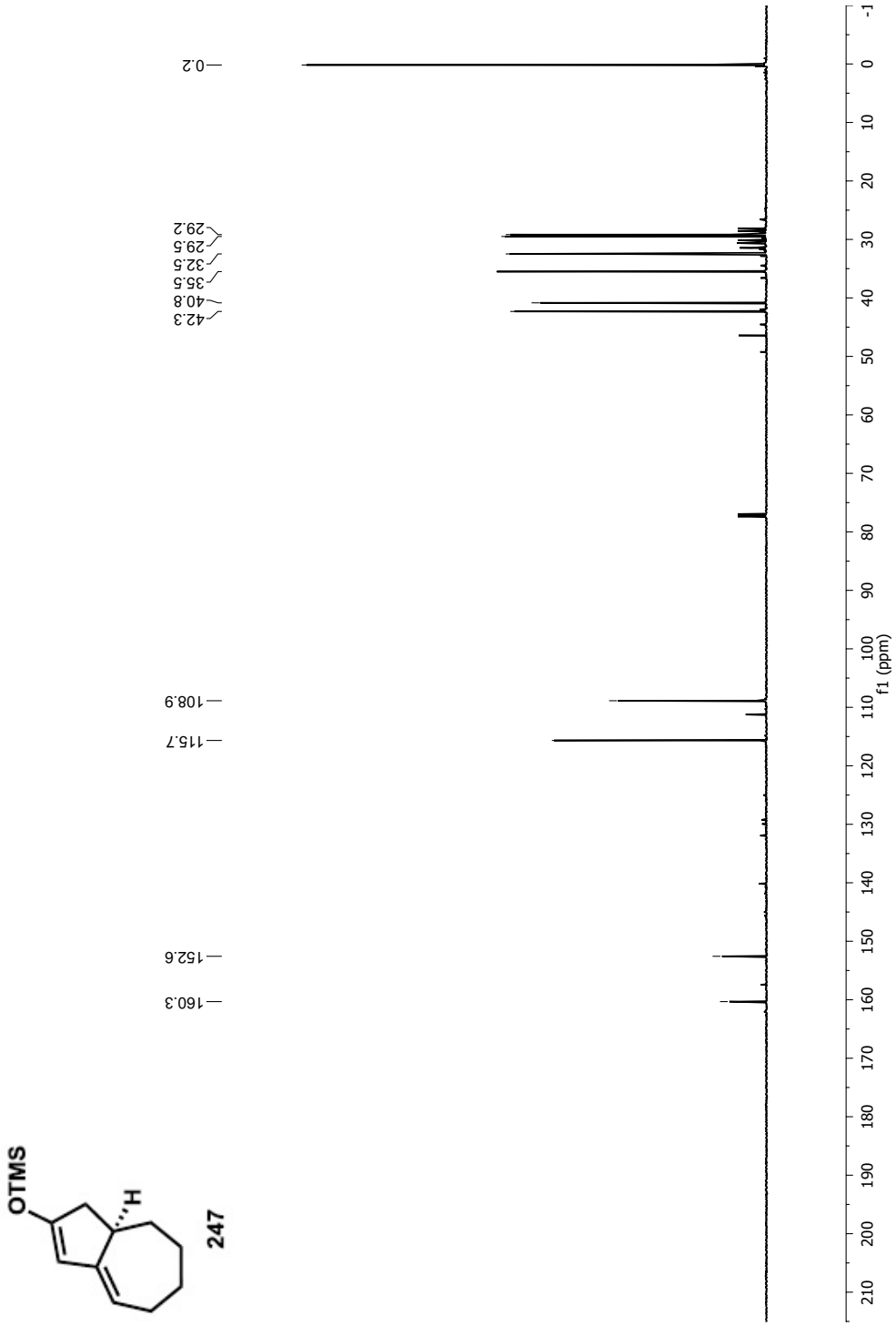
245
214.9
207.7
46.6
46.2
43.6
31.4
30.3
29.6
29.0
23.5
f1 (ppm)


O
H
246
0.95
3.01
0.99
2.04
1.05
3.12
3.14
f1 (ppm)

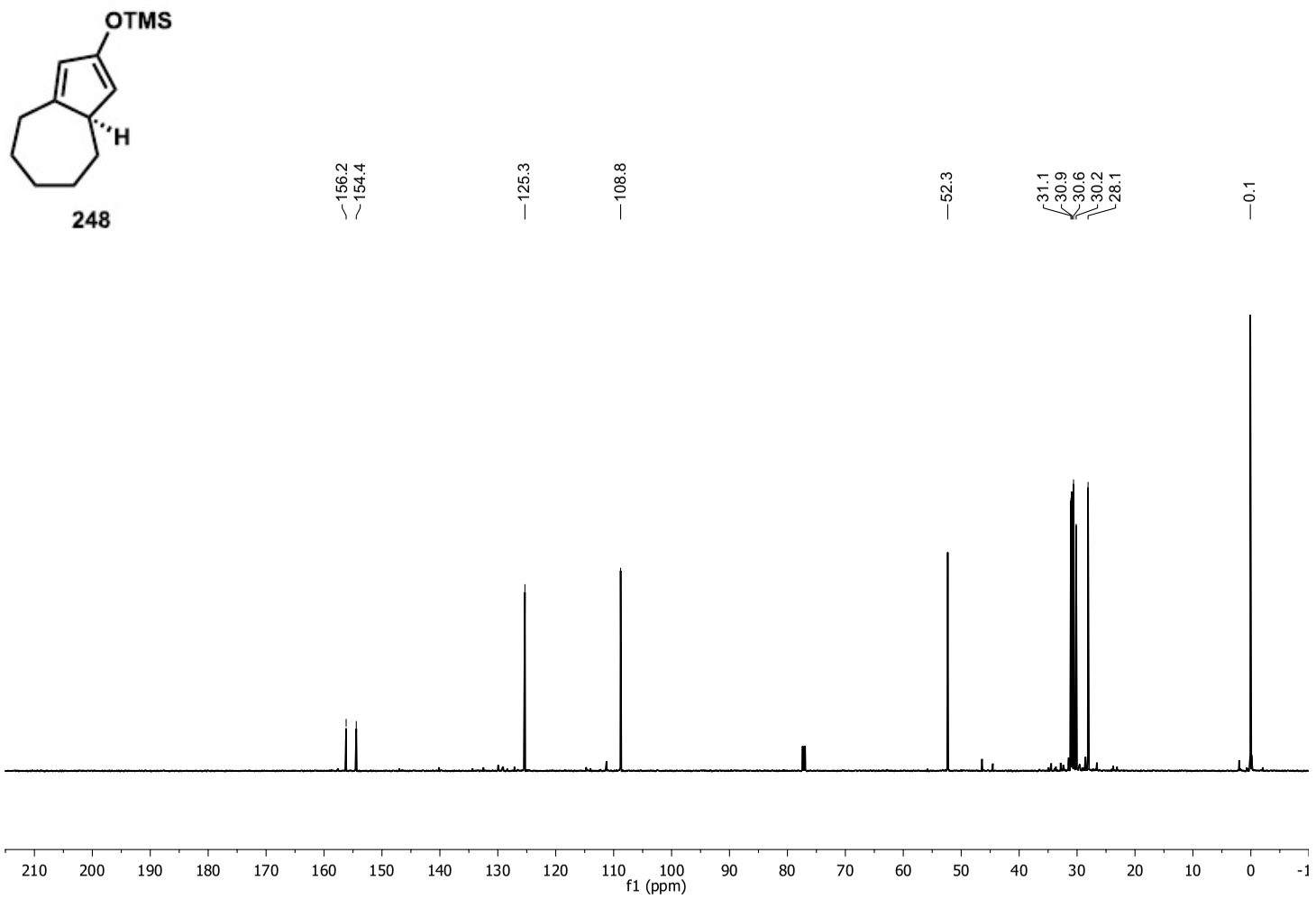
O
H
246
209.0
188.0
129.8
44.5
44.5
34.4
32.8
30.4
28.6
26.5
f1 (ppm)



247


OTMS
H
247
160.3
152.6
115.7
108.9
42.3
40.8
35.5
32.5
29.5
29.2
0.2
f1 (ppm)

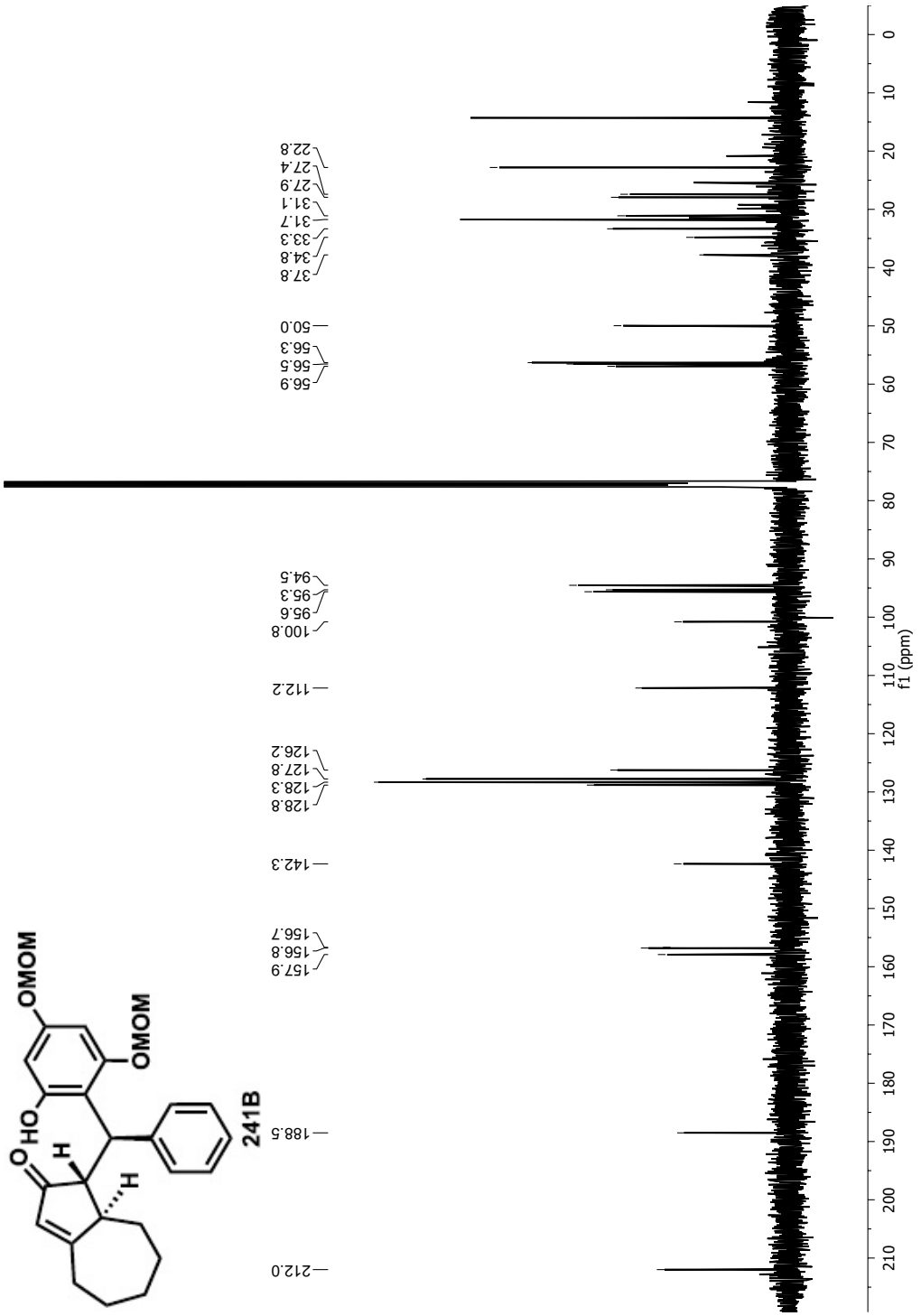
OTMS
H
248
9.64
1.19
1.16
1.39
1.55
1.21
1.48
1.28
1.20
2.31
1.00
0.95
0.85
f1 (ppm)


OTMS
H
248
156.2
154.4
125.3
108.8
52.3
31.1
30.9
30.6
30.2
28.1
0.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

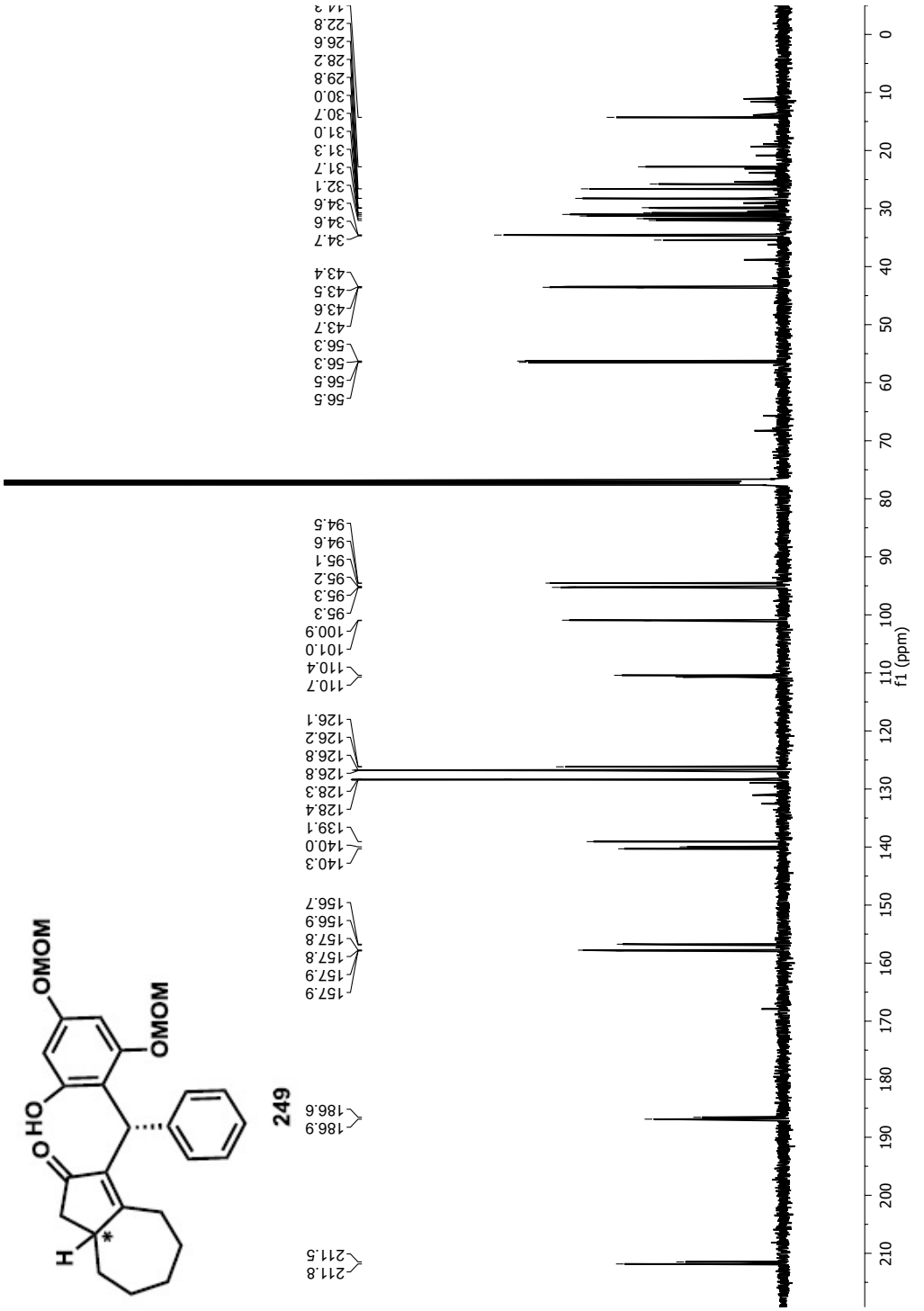
OMOM
OMOM
HO
O
H
H
241A
0.86
2.07
1.03
2.00
1.02
0.95
0.98
1.00
1.93
1.97
3.23
3.07
1.01
3.00
0.95
3.23
2.35
3.27
f1 (ppm)

OMOM
OMOM
HO
O
H
H
241A
211.9
187.6
157.7
157.1
156.0
140.3
129.5
128.4
127.3
126.1
114.0
100.6
95.3
94.9
94.6
60.2
56.3
56.3
53.2
36.8
33.3
31.2
31.1
29.9
27.7
27.7
f1 (ppm)

OMOM
OMOM
HO
O
H
H
241B
0.84
2.73
16.87
1.03
0.98
1.01
1.00
2.02
1.99
0.99
3.28
3.08
1.01
0.59
1.92
0.56
1.20
0.95
f1 (ppm)


OMOM
OMOM
HO
O
H
H
241B
212.0
188.5
157.9
156.8
156.7
142.3
128.8
128.3
127.8
126.2
112.2
100.8
95.6
95.3
94.5
56.9
56.5
56.3
50.0
37.8
34.8
33.3
31.7
31.1
27.9
27.4
22.8
f1 (ppm)

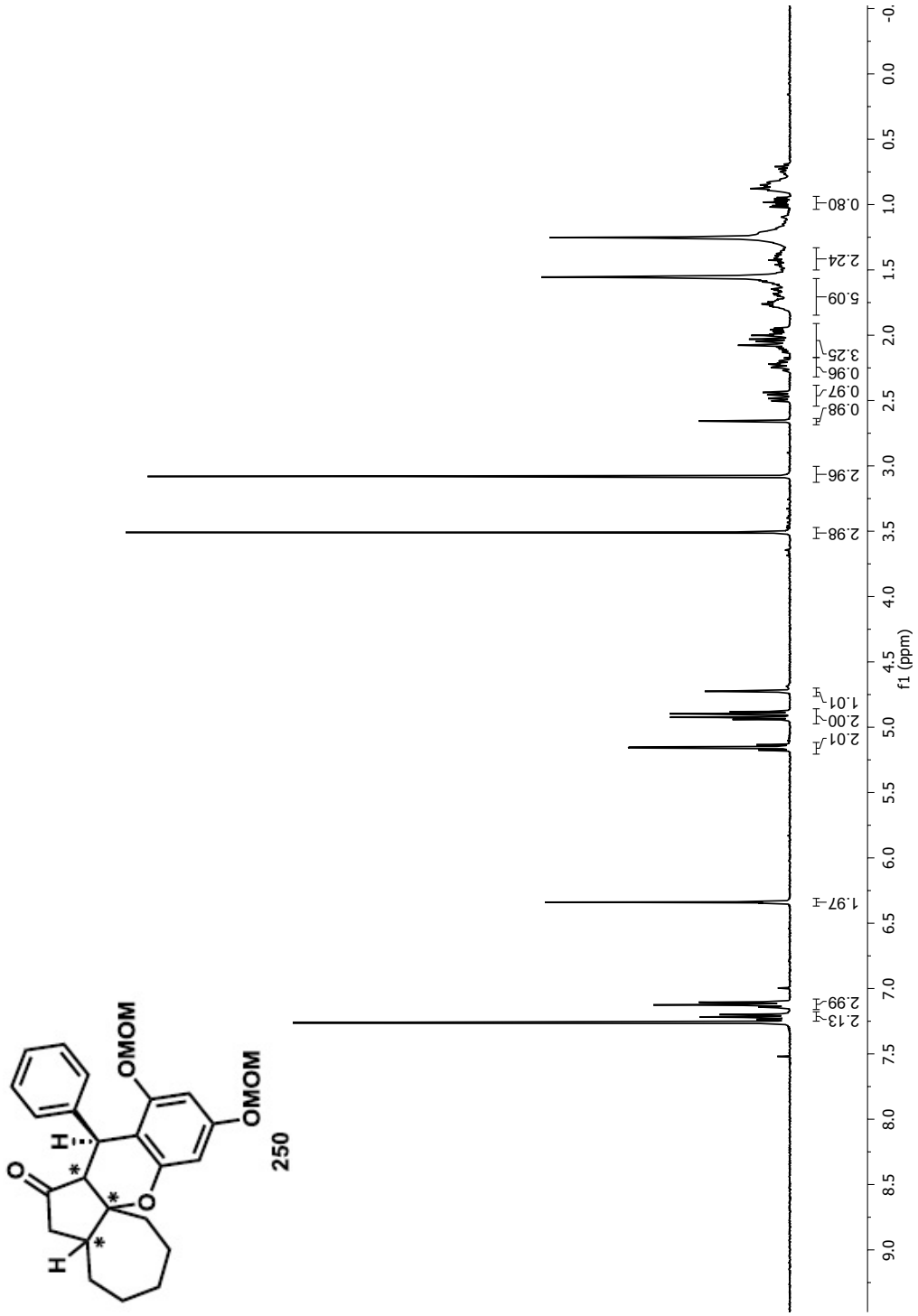
OMOM
OMOM
HO
O
H
*
249
1.07
0.65
3.59
6.67
1.79
1.80
1.10
0.67
3.60
3.79
2.17
3.27
2.19
3.33
0.91
4.17
0.34
0.37
0.50
0.58
0.58
0.63
3.62
3.13
5.01
3.81
3.92
f1 (ppm)


OMOM
OMOM
HO
O
H
*
249
211.8
211.5
186.9
186.6
157.9
157.9
157.8
157.8
156.9
156.7
140.3
140.0
139.1
128.4
128.3
126.8
126.8
126.2
126.1
110.7
110.4
101.0
100.9
95.3
95.3
95.2
95.3
95.1
94.6
94.5
56.5
56.5
56.3
56.3
43.7
43.6
43.5
43.4
34.7
34.6
34.6
32.1
31.7
31.3
31.0
30.7
30.0
29.8
28.2
26.6
22.8
14.2
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

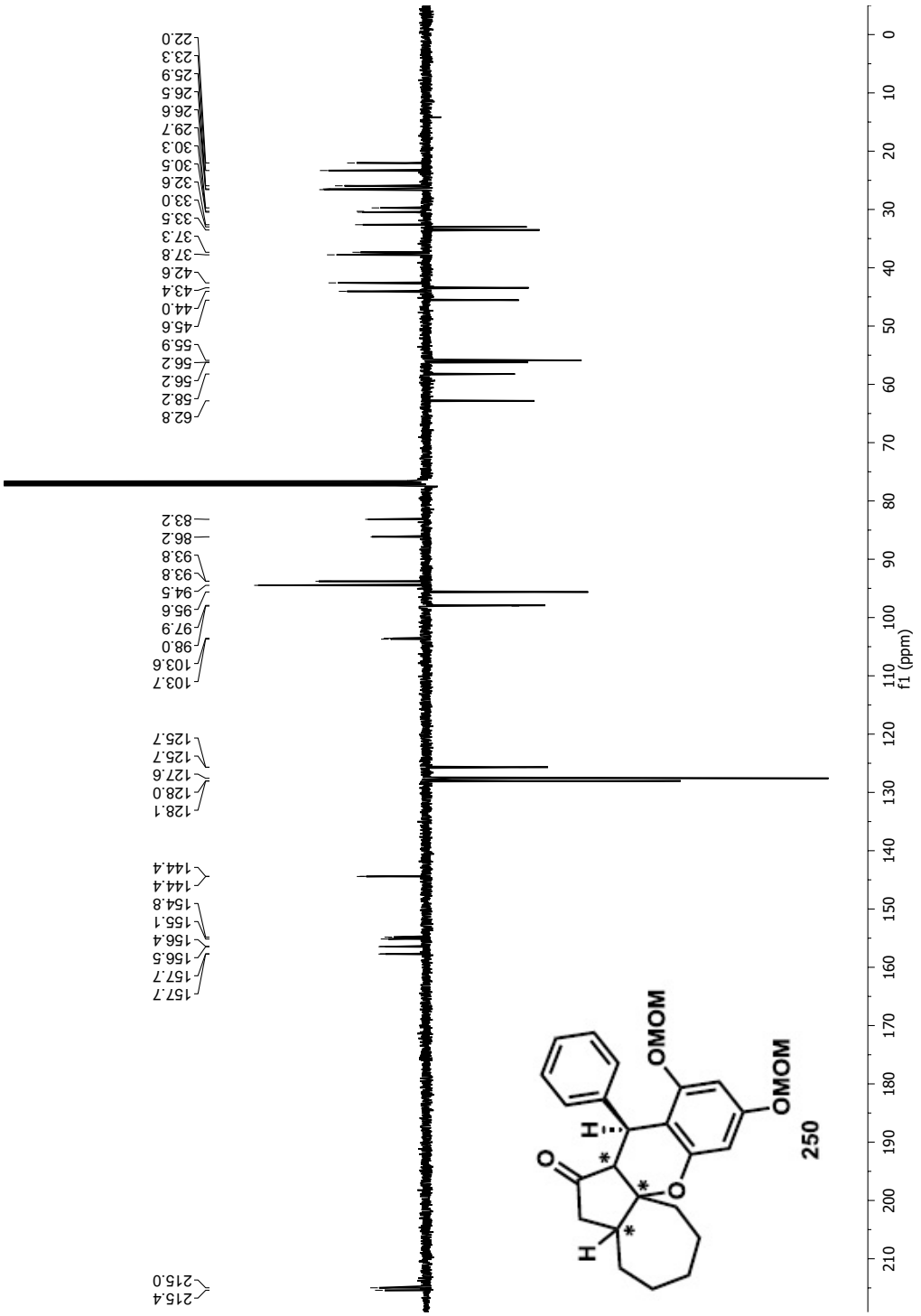
OMOM
OMOM
HO
O
H
*
249
1.11
13.51
1.19
2.32
1.12
1.10
1.14
2.27
2.35
3.48
3.40
3.41
1.08
1.00
0.77
0.87
3.03
1.93
1.94
f1 (ppm)

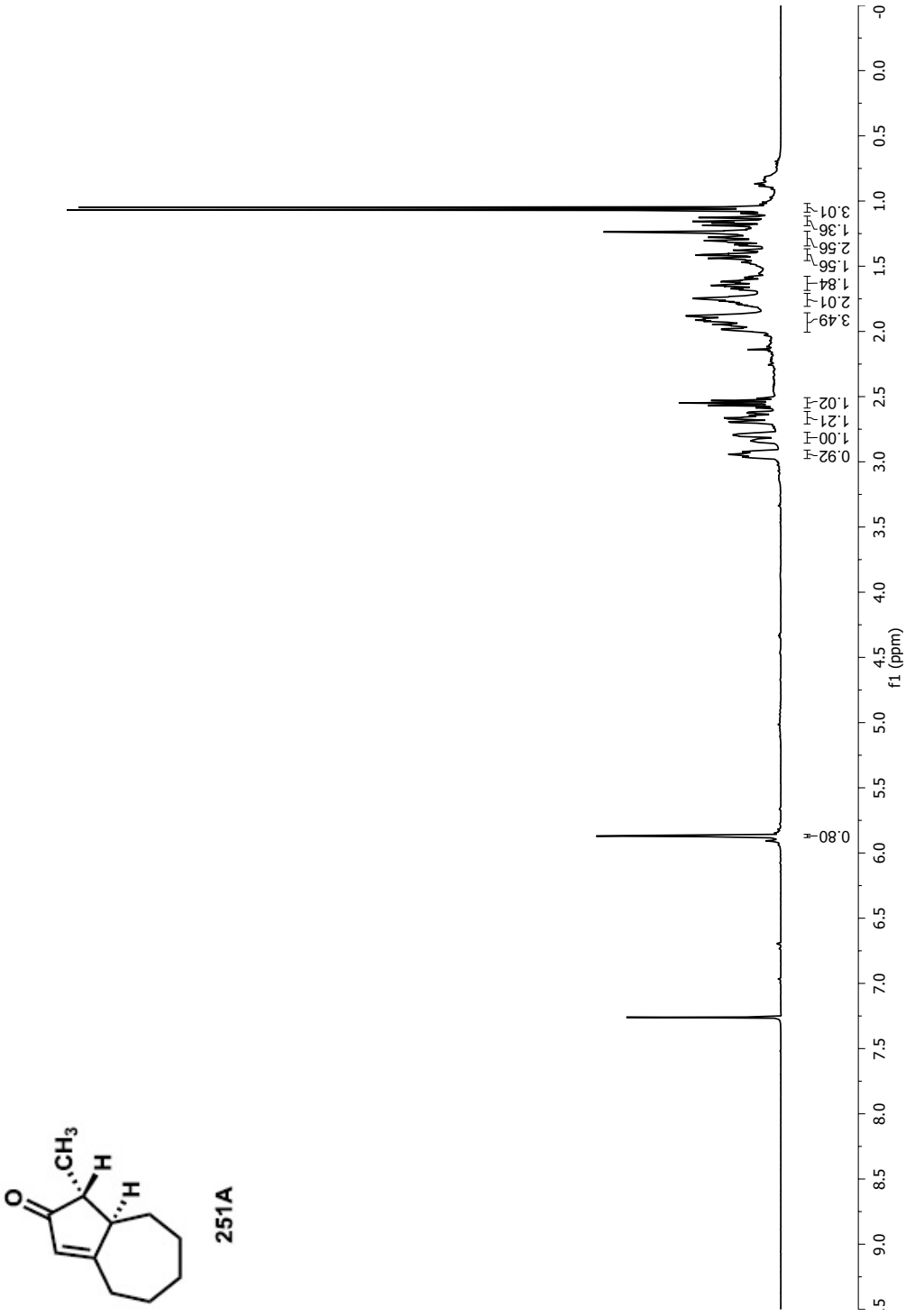
OMOM
OMOM
HO
O
H
*
249
211.7
186.8
157.8
157.7
156.6
140.2
138.9
128.3
126.6
126.1
110.3
100.8
95.1
95.1
94.4
56.4
56.2
43.4
43.3
34.4
31.2
30.9
29.7
28.1
26.5
f1 (ppm)

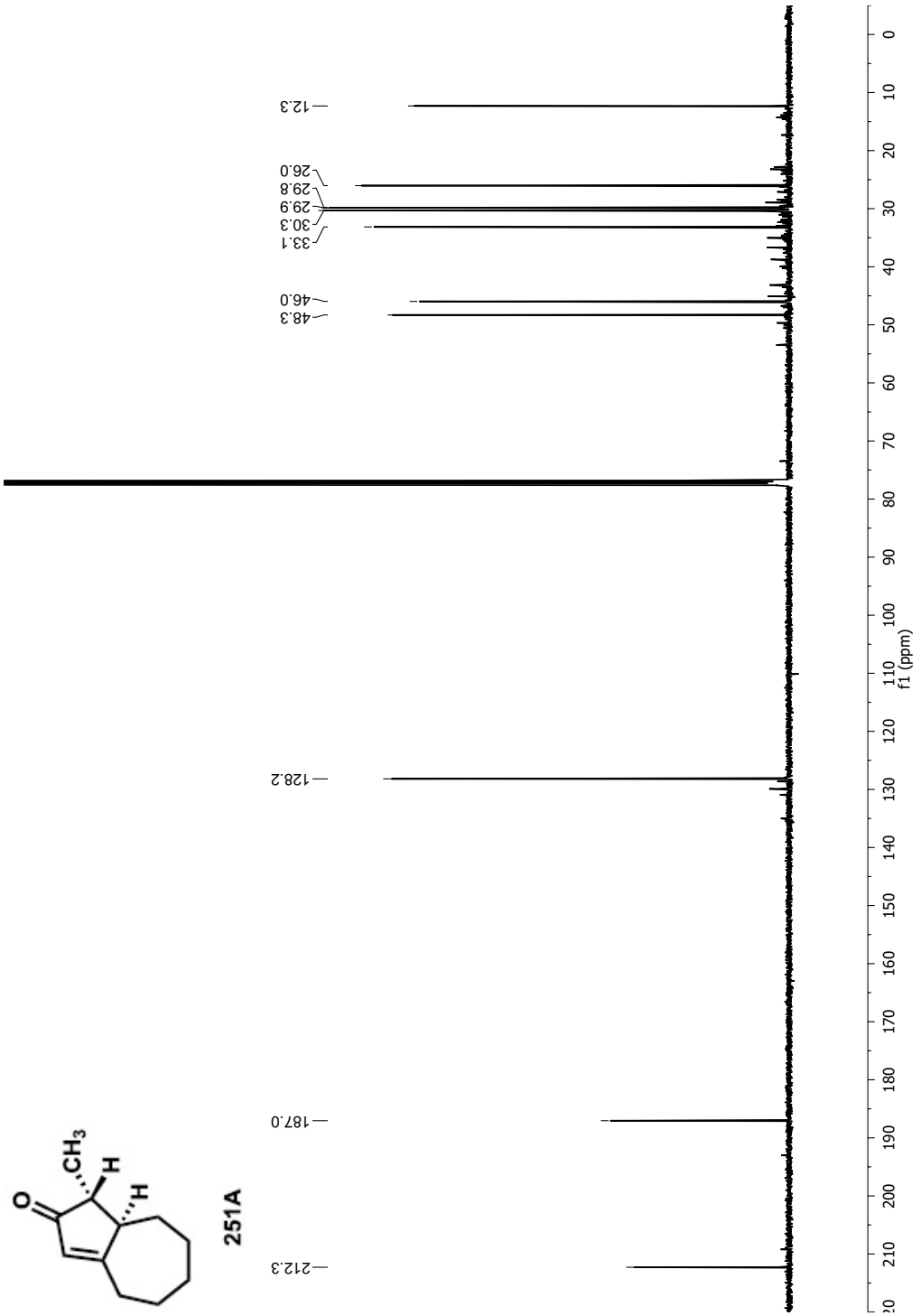
OMOM
OMOM
H
O
O
H
250
5.75
6.42
3.36
1.88
5.16
5.27
1.66
1.73
2.99
3.00
3.11
2.82
4.85
4.39
3.01
8.39
2.15
4.36
2.70
14.35
5.43
f1 (ppm)

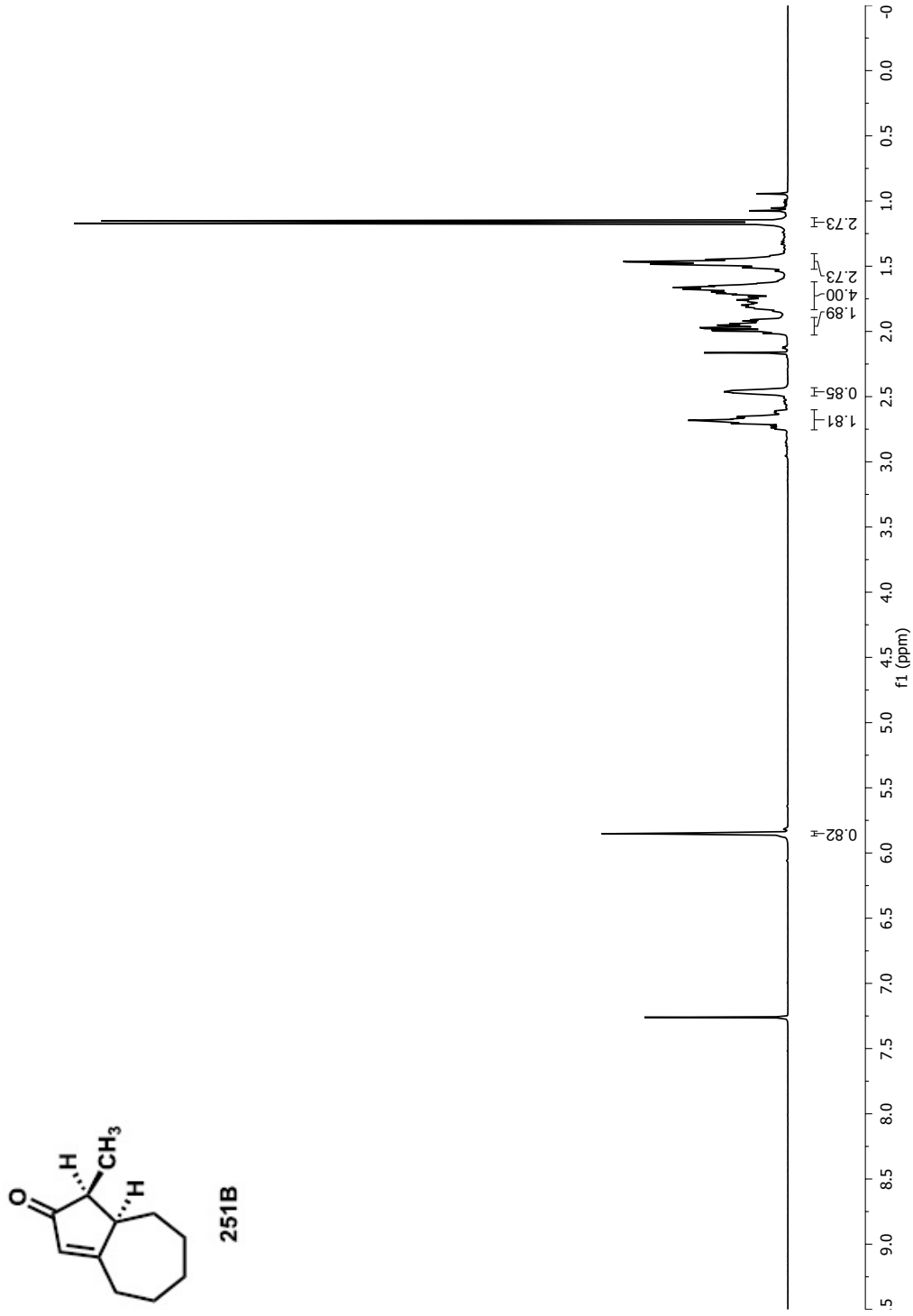

OMOM
OMOM
H
O
H
O
250
2.13
2.99
1.97
2.01
2.00
1.01
2.98
2.96
0.98
0.97
0.96
3.25
5.09
2.24
0.80
f1 (ppm)

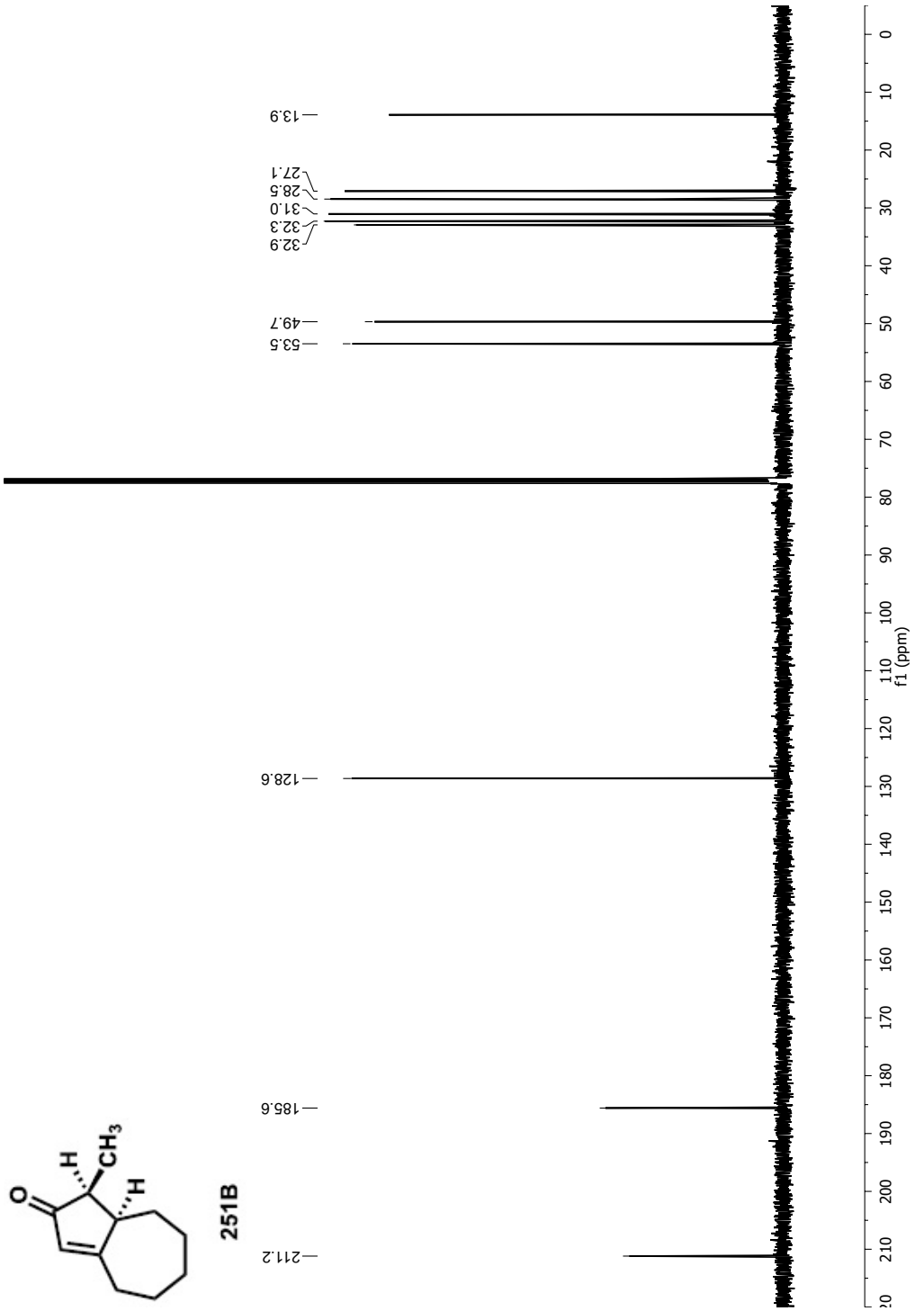
OMOM
OMOM
H
O
O
H
250
2.32
3.04
1.00
0.99
2.04
2.05
1.11
3.05
3.01
1.96
0.97
2.11
0.76
0.81
3.32
3.59
1.06
f1 (ppm)


215.4
215.0
157.7
157.7
156.5
156.4
155.1
154.8
144.4
144.4
128.1
128.0
127.6
125.7
125.7
103.7
103.6
98.0
97.9
95.6
94.5
93.8
93.8
86.2
83.2
62.8
58.2
56.2
56.2
55.9
45.6
44.0
43.4
42.6
37.8
37.3
33.5
33.0
32.6
30.5
30.3
29.7
26.6
26.5
25.9
23.3
22.0
OMOM
OMOM
H
O
O
H
250
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)


CH3
H
H
O
251A
0.80
0.92
1.00
1.21
1.02
3.49
2.01
1.84
1.56
2.56
1.36
3.01
f1 (ppm)


251A
O
CH3
H
H
212.3
187.0
128.2
48.3
46.0
33.1
30.3
29.9
29.8
26.0
12.3
f1 (ppm)

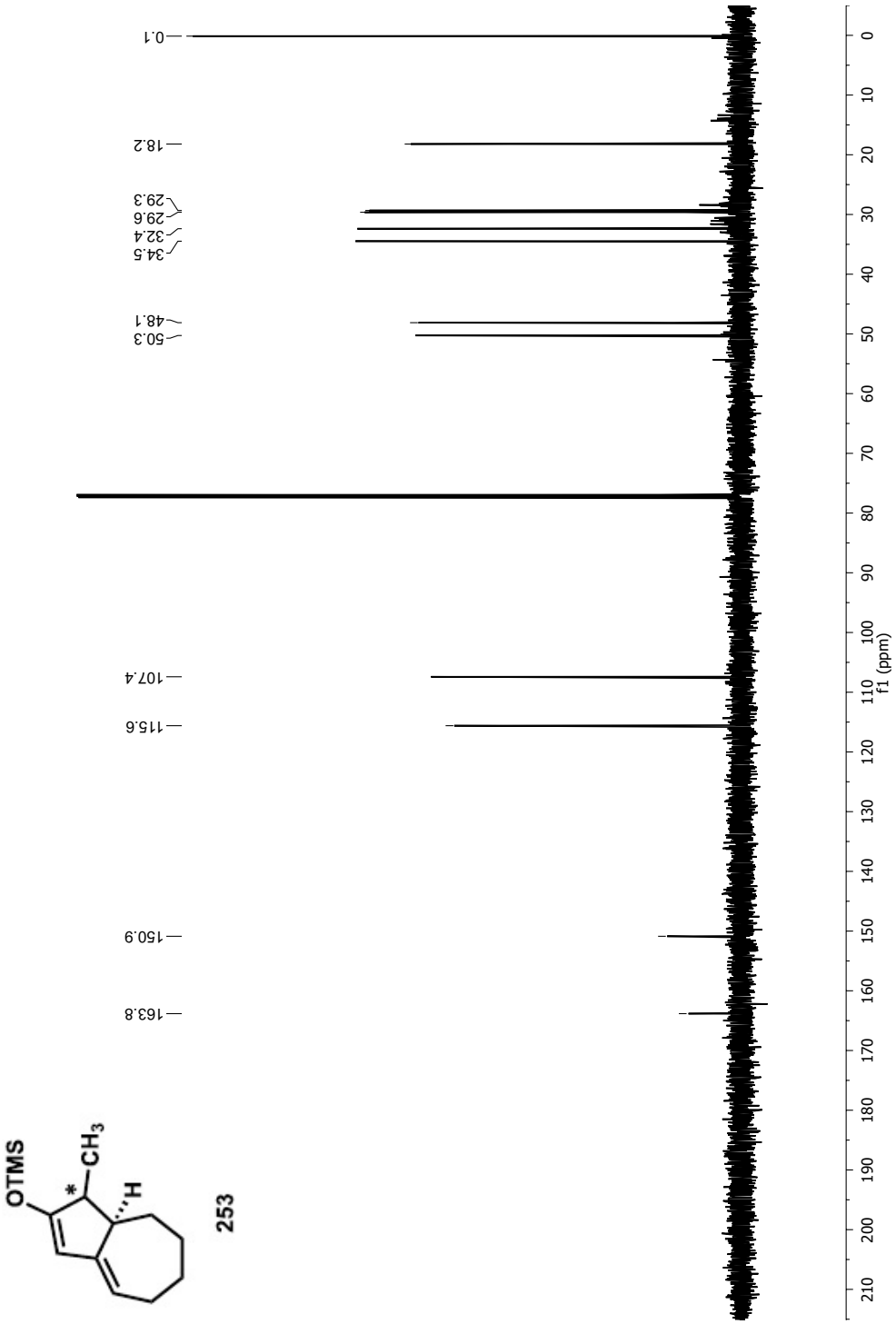

O
H
CH3
H
251B
0.82
1.81
0.85
1.89
4.00
2.73
2.73
f1 (ppm)


251B
211.2
185.6
128.6
53.5
49.7
32.9
32.3
31.0
28.5
27.1
13.9
f1 (ppm)

OTMS
CH3
H
252
9.29
1.09
1.00
1.52
1.78
3.46
1.18
1.11
1.00
1.85
0.75
f1 (ppm)

OTMS
CH3
H
252
152.2
147.9
124.9
118.2
54.3
31.1
30.8
29.8
29.4
28.4
9.8
0.6
f1 (ppm)

OTMS
CH3
H
*
253
9.51
3.00
2.57
1.47
2.05
2.09
1.27
1.84
0.85
0.84
f1 (ppm)


OTMS
CH3
H
253
163.8
150.9
115.6
107.4
50.3
48.1
34.5
32.4
29.6
29.3
18.2
0.1
f1 (ppm)

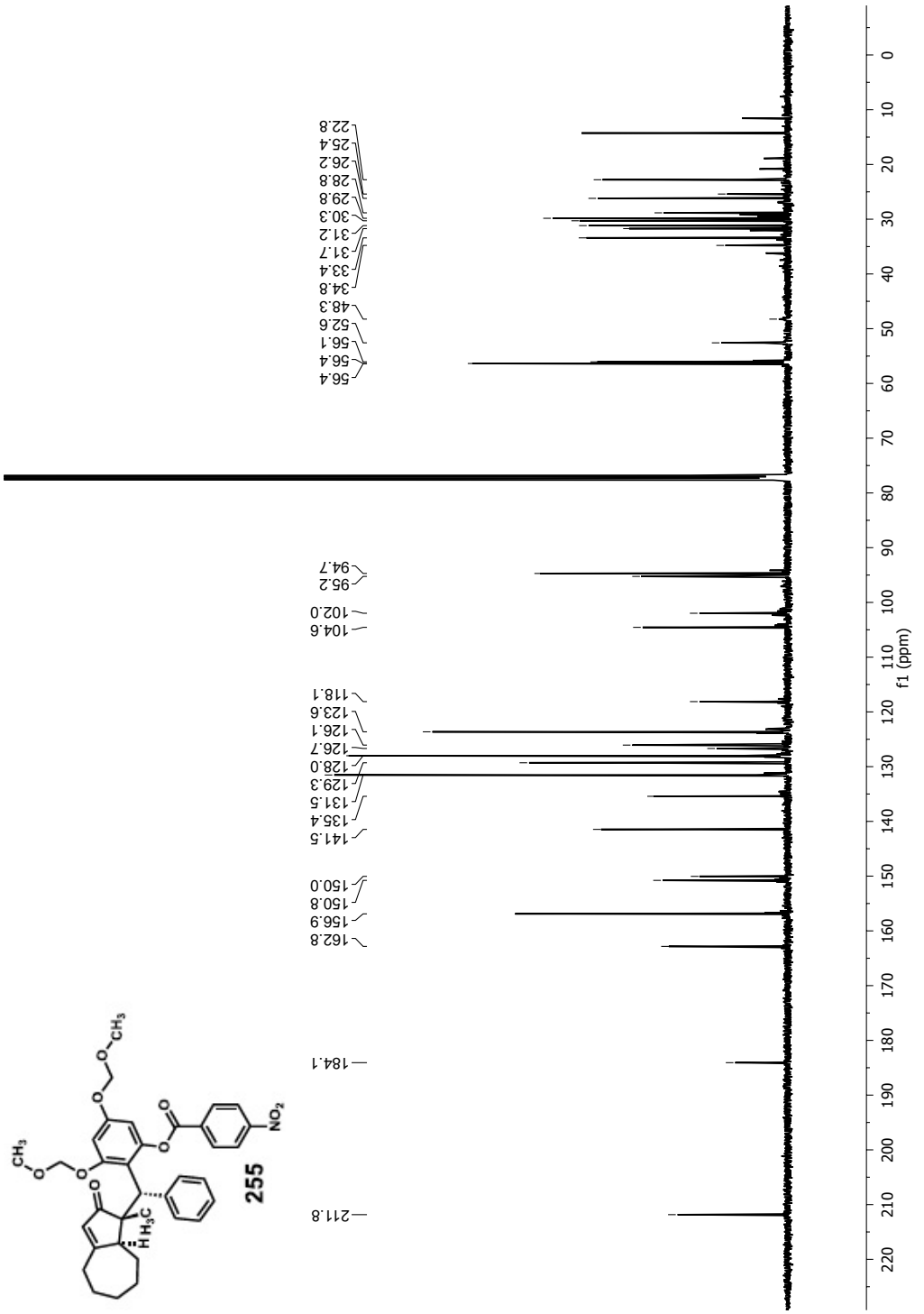
OMOM
OMOM
HO
O
CH3
H
254A
0.58
3.37
2.12
1.32
1.11
1.00
5.84
6.93
0.44
0.96
0.90
3.14
1.04
2.10
1.68
3.25
f1 (ppm)

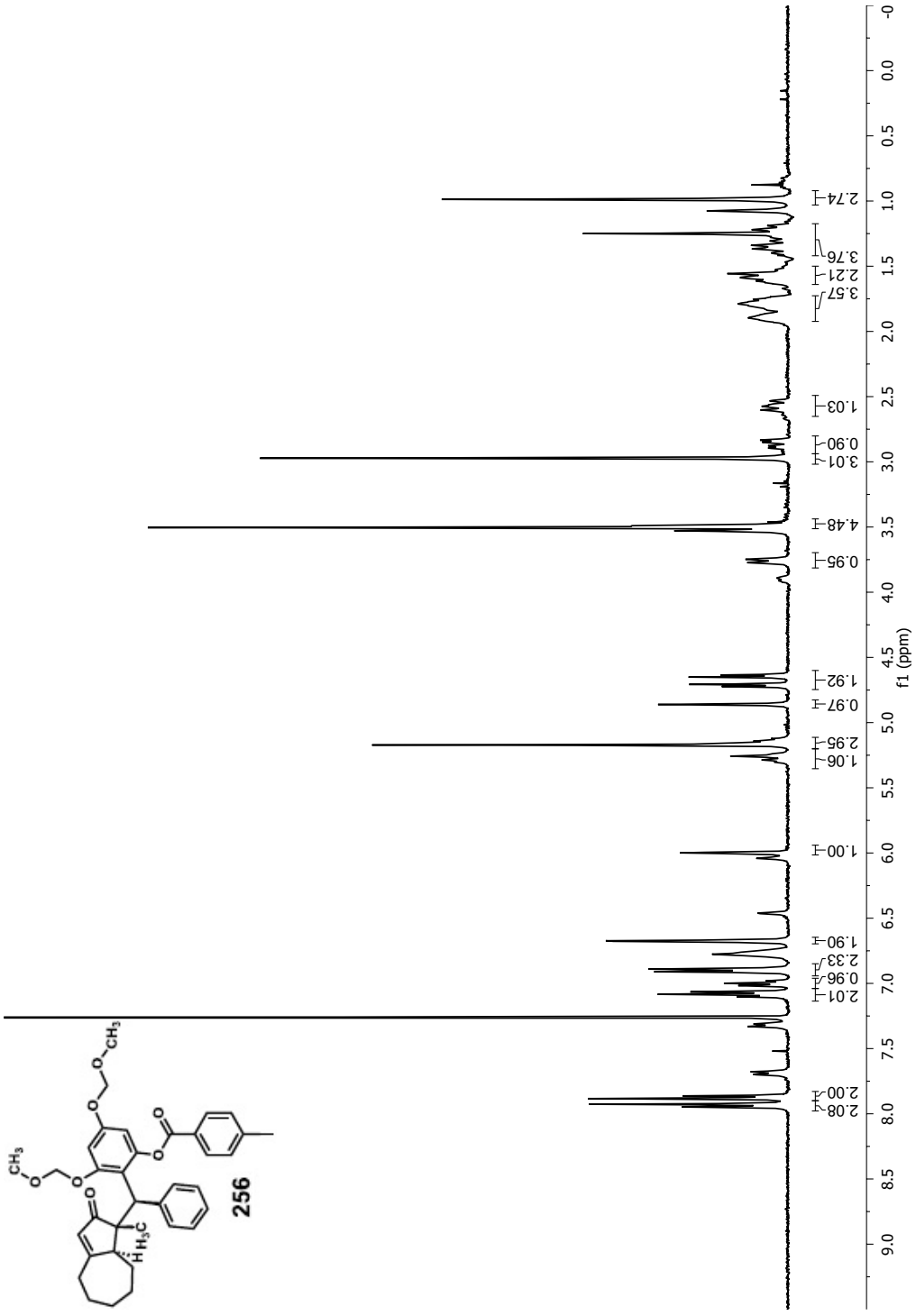
OMOM
OMOM
HO
O
CH3
H
254A
216.8
186.7
157.8
157.4
156.9
140.7
128.3
127.9
127.1
126.1
112.4
100.7
95.3
94.6
58.6
56.5
56.3
41.4
34.4
31.8
30.4
29.9
26.7
26.2
22.9
22.8
14.3
f1 (ppm)

OMOM
OMOM
HO
O
CH3
H
254B
4.57
0.79
0.87
1.00
0.70
2.56
2.41
2.80
3.64
1.40
0.99
3.23
1.69
1.22
1.04
3.31
3.17
f1 (ppm)

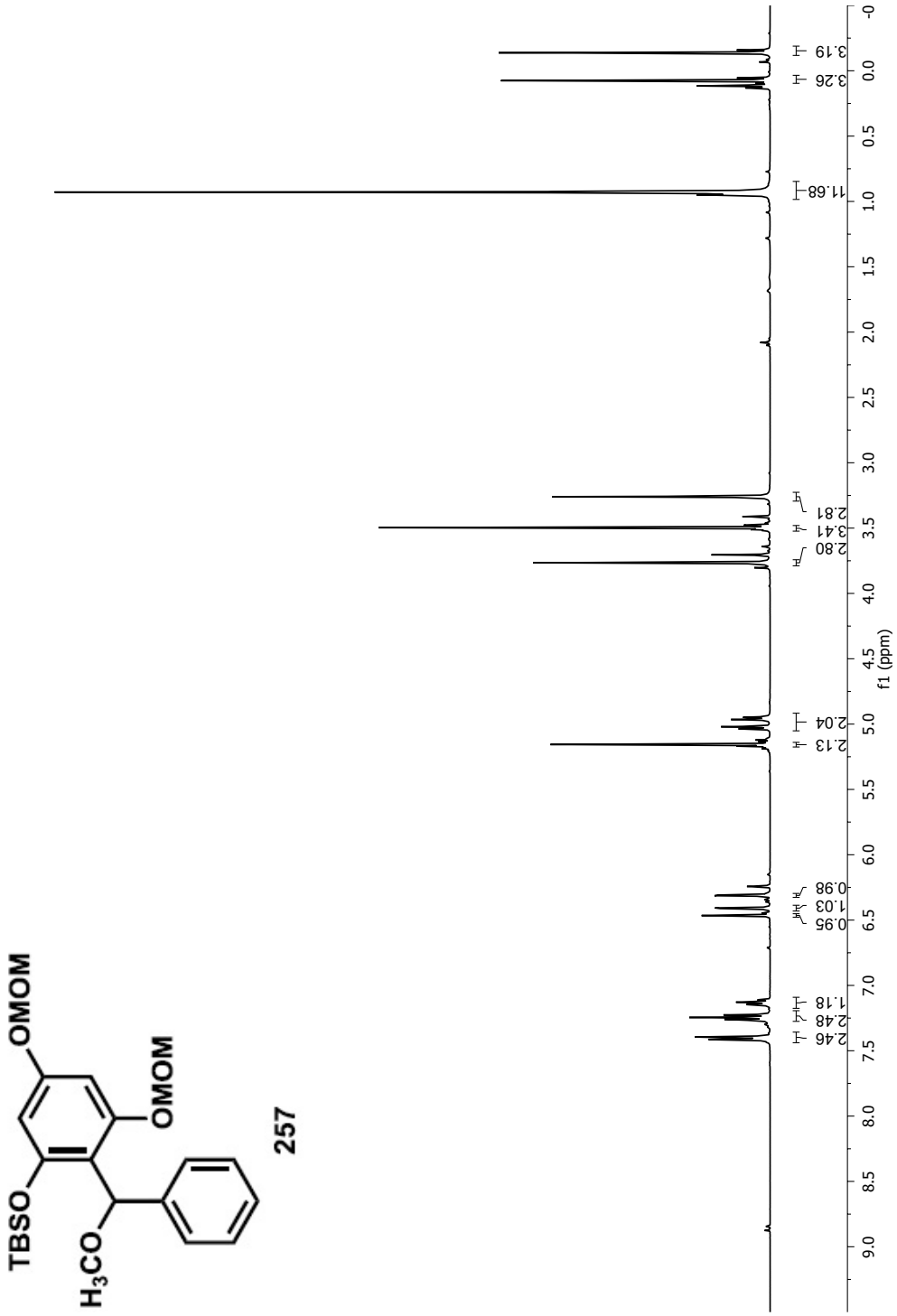
OMOM
OMOM
HO
O
CH3
H
254B
214.1
185.9
157.8
157.5
156.5
140.6
128.8
128.4
127.2
126.5
112.0
99.2
96.0
95.2
94.6
60.6
56.7
56.6
56.4
52.3
43.4
34.0
31.8
30.0
28.1
26.3
22.7
f1 (ppm)

255
f1 (ppm)

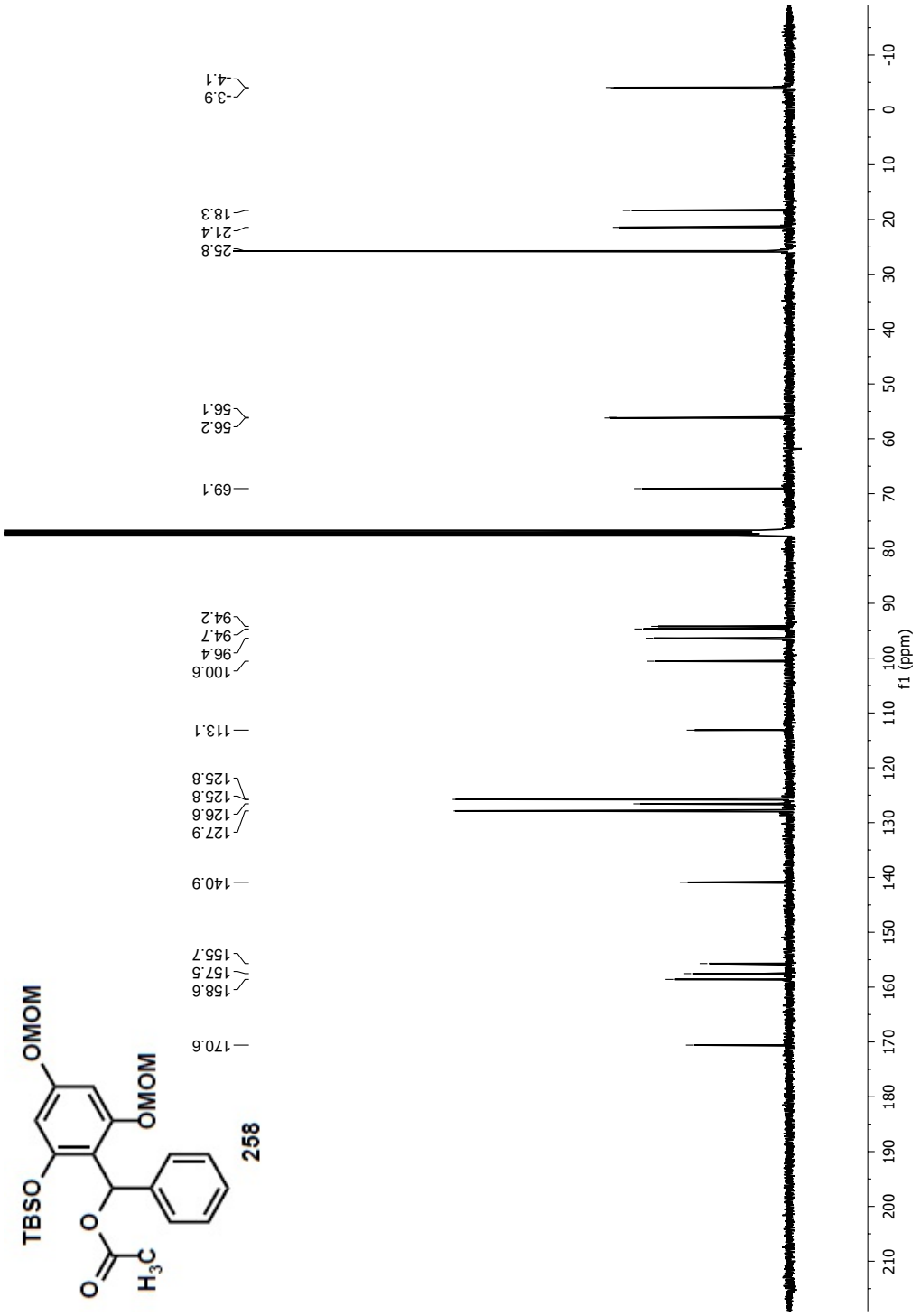

255
211.8
184.1
162.8
156.9
150.8
150.0
141.5
135.4
131.5
129.3
128.0
126.7
126.1
123.6
118.1
104.6
102.0
95.2
94.7
56.4
56.4
56.1
52.6
48.3
34.8
33.4
31.7
31.2
30.3
29.8
28.8
26.2
25.4
22.8
f1 (ppm)

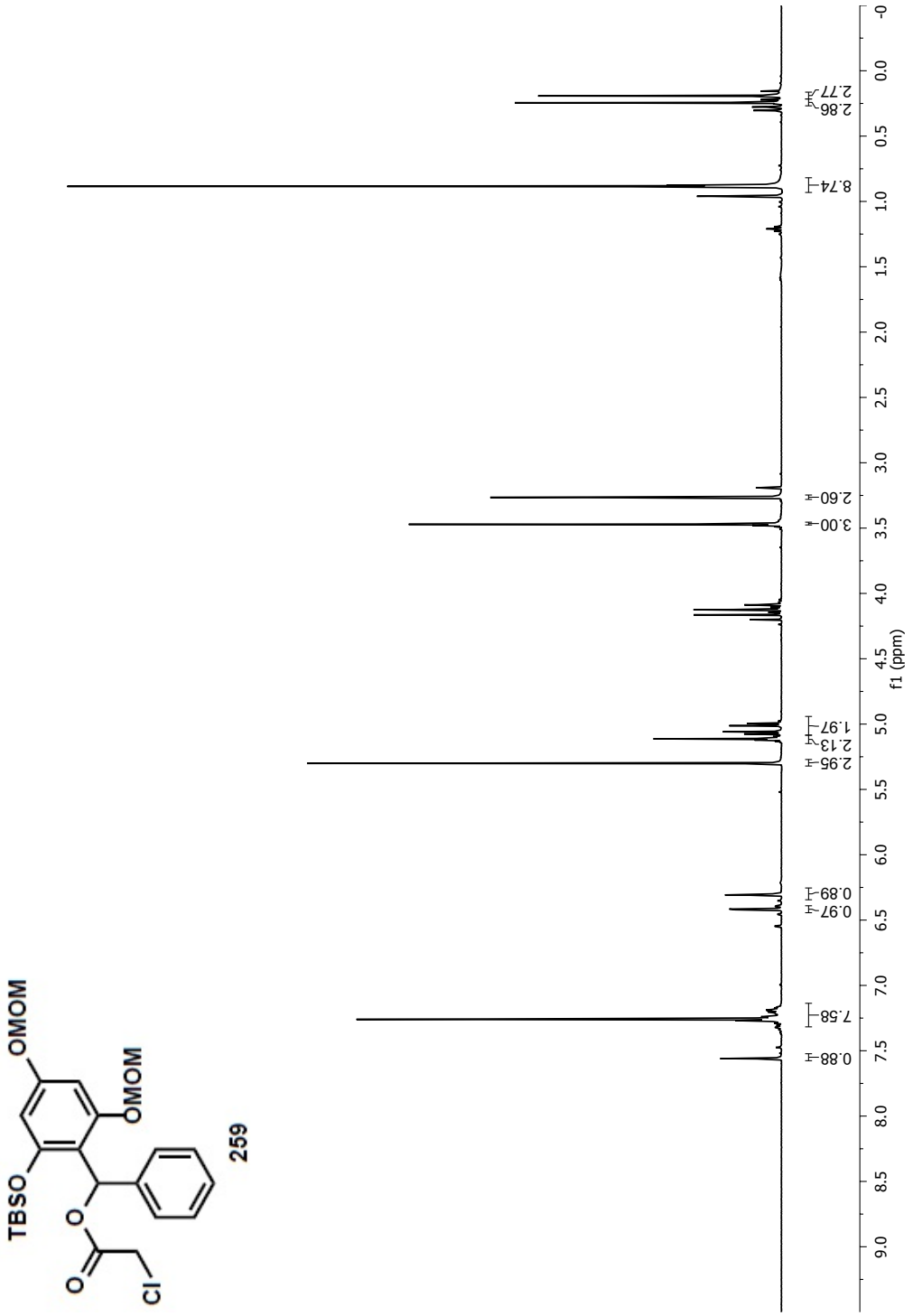

256
2.08
2.00
2.01
0.96
2.33
1.90
1.00
1.06
2.95
0.97
1.92
0.95
4.48
3.01
0.90
1.03
3.57
2.21
3.76
2.74
f1 (ppm)

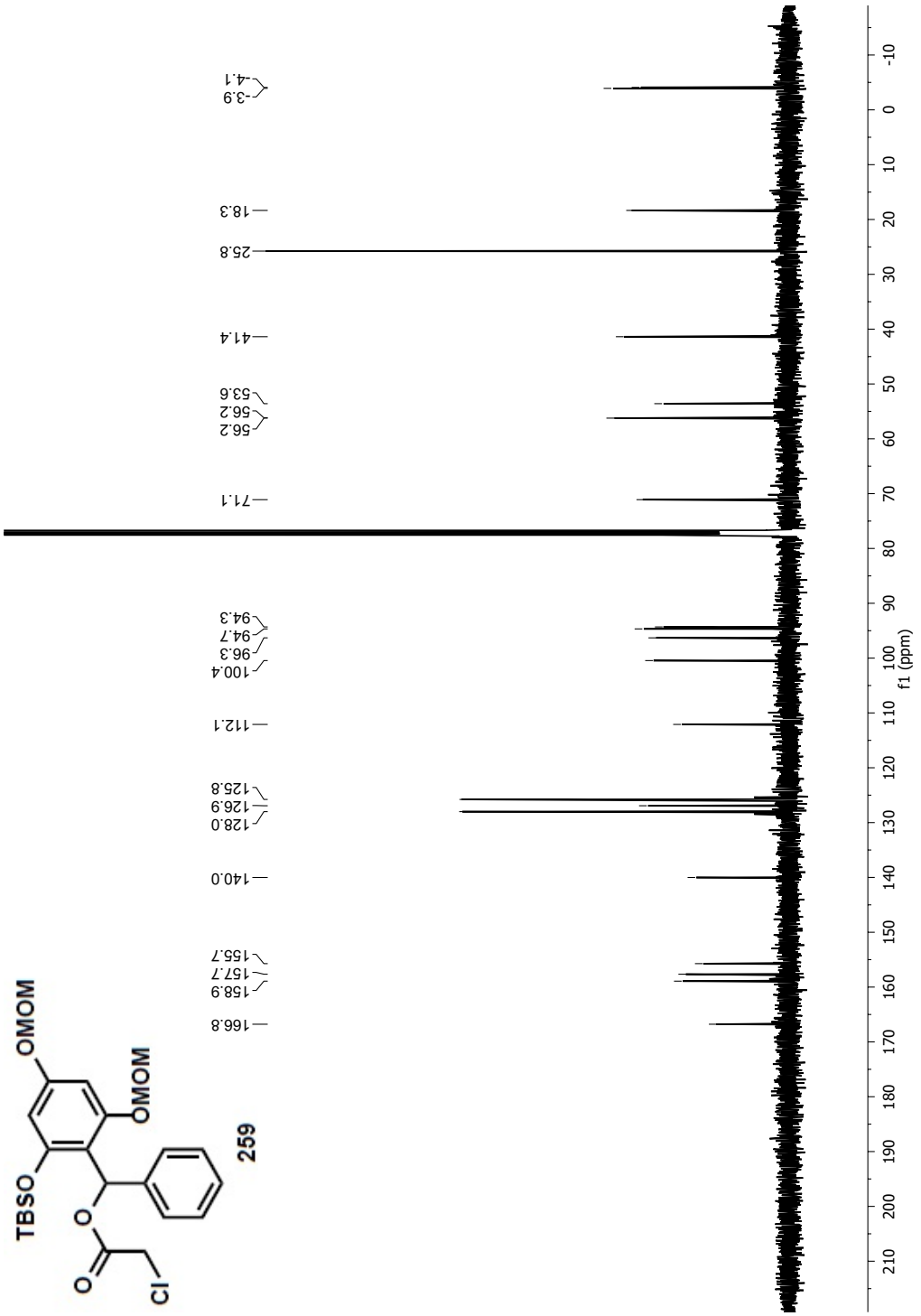
256
212.9
185.6
164.8
157.5
157.2
151.3
142.2
138.2
137.4
137.4
131.8
128.8
127.9
127.7
127.5
127.4
125.4
118.1
103.7
102.7
102.1
101.0
94.9
56.5
56.2
55.8
51.4
45.6
33.7
31.4
29.9
28.6
26.4
22.7
f1 (ppm)


OMOM
OMOM
TBSO
H3CO
257
3.19
3.26
11.68
2.81
3.41
2.80
2.04
2.13
0.95
1.03
0.98
1.18
2.48
2.46
f1 (ppm)

TBSO
OMOM
OMOM
O
O
H3C
258
0.96
5.15
0.97
1.00
2.33
2.20
3.43
2.67
2.96
9.71
3.26
3.08
f1 (ppm)

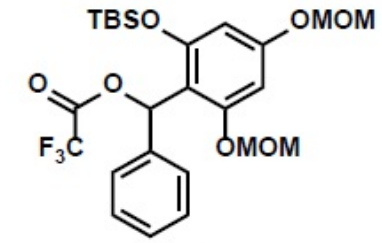

OMOM
OMOM
TBSO
O
O
H3C
258
170.6
158.6
157.5
155.7
140.9
127.9
126.6
125.8
125.8
113.1
100.6
96.4
94.7
94.2
69.1
56.2
56.1
25.8
21.4
18.3
-3.9
-4.1
f1 (ppm)


OMOM
OMOM
TBSO
O
O
Cl
259
8.74
2.77
2.86
2.60
3.00
1.97
2.13
2.95
0.89
0.97
7.58
0.88
f1 (ppm)


OMOM
OMOM
TBSO
O
O
Cl
259
166.8
158.9
157.7
155.7
140.0
128.0
126.9
125.8
112.1
100.4
96.3
94.7
94.3
71.1
56.2
56.2
53.6
41.4
25.8
18.3
-3.9
-4.1
f1 (ppm)

OMOM
OMOM
TBSO
O
O
F3C
260
0.98
6.94
1.02
1.01
2.35
2.05
3.44
3.00
10.43
3.03
2.91
f1 (ppm)

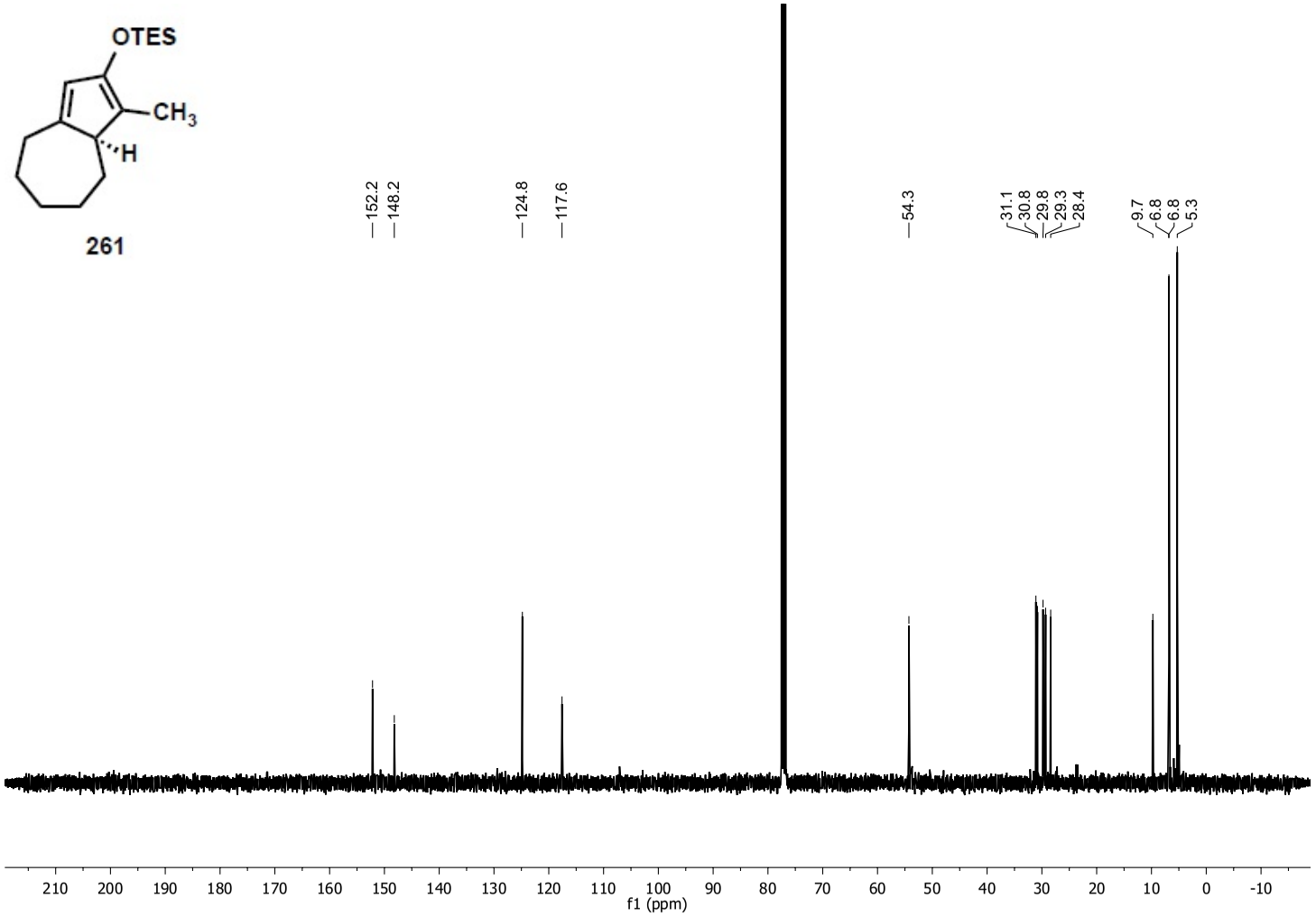
OMOM
OMOM
TBSO
O
O
F3C
260
159.4
157.7
155.8
138.7
128.6
128.2
127.3
125.6
110.6
100.3
96.1
94.7
94.2
73.6
56.3
56.1
25.7
18.3
-4.1
-4.2
f1 (ppm)


TBSO
OMOM
O
O
F3C
OMOM

260

-74.7
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

OTES
CH3
H
261
0.67
1.60
0.73
0.96
0.77
3.00
2.85
1.60
1.97
9.05
5.42
f1 (ppm)


OTES
CH3
H
261
152.2
148.2
124.8
117.6
54.3
31.1
30.8
29.8
29.3
28.4
9.7
6.8
6.8
5.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

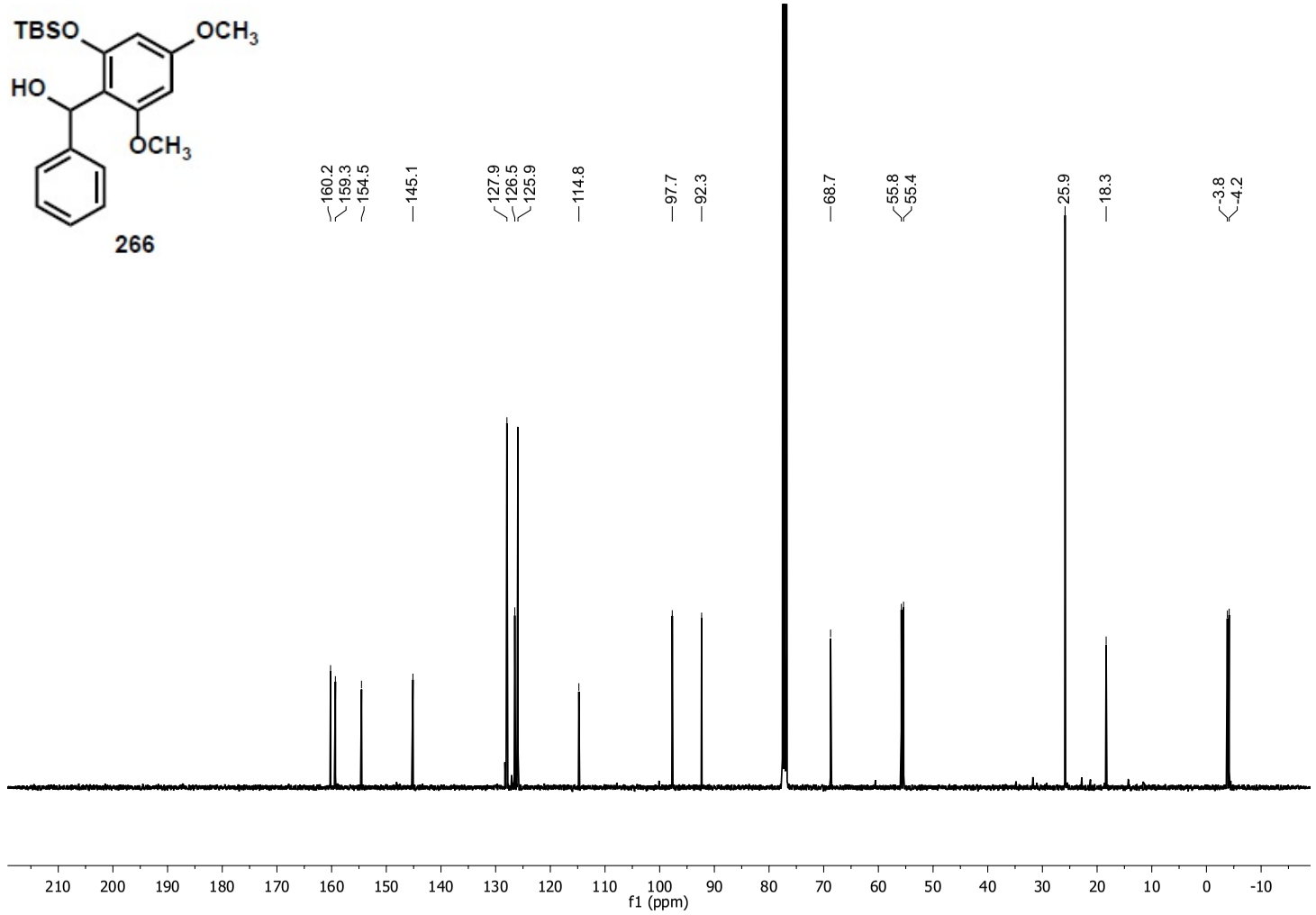
OMOM
OMOM
OH
O
H3C
263
4.98
1.00
0.91
4.42
0.96
2.97
2.82
1.10
0.95
1.04
2.29
2.38
0.89
2.50
1.16
2.94
f1 (ppm)

OMOM
OMOM
OH
O
H3C
263
157.3
155.1
153.8
142.1
140.1
135.1
129.4
127.5
126.3
113.4
108.9
100.2
97.9
94.7
94.3
63.5
59.5
56.3
56.1
53.9
46.3
30.9
29.8
27.7
26.8
26.6
21.8
f1 (ppm)

OCH3
OCH3
TBSO
O
H
265
0.95
0.99
0.98
2.93
3.18
8.97
5.80
f1 (ppm)

OCH3
OCH3
TBSO
O
H
265
187.9
165.7
163.1
161.6
111.4
97.7
91.8
55.9
55.4
25.7
18.4
-4.3
f1 (ppm)

OCH3
OCH3
TBSO
HO
266
2.87
2.94
8.89
2.96
2.92
0.94
0.95
0.96
0.95
2.02
2.62
0.95
f1 (ppm)

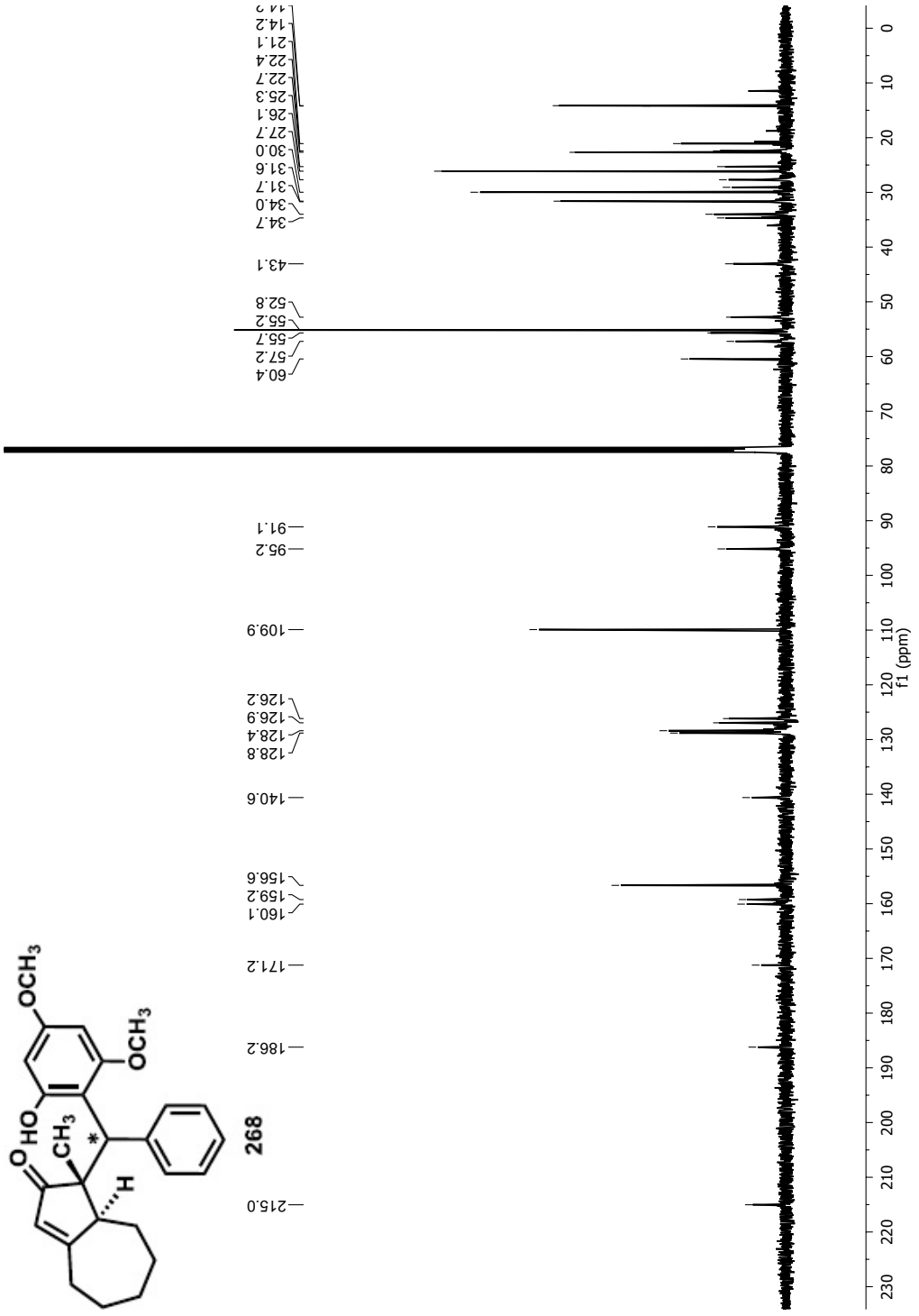

TBSO
OCH3
HO
OCH3
266
160.2
159.3
154.5
145.1
127.9
126.5
125.9
114.8
97.7
92.3
68.7
55.8
55.4
25.9
18.3
-3.8
-4.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

OCH3
OCH3
TBSO
Cl
267
2.96
2.66
8.57
2.98
2.73
0.95
0.96
0.89
0.97
1.91
1.83
f1 (ppm)

TBSO
OCH3
OCH3
Cl
267
161.3
160.0
155.3
141.3
127.8
127.1
126.7
113.0
97.5
92.4
55.8
55.8
55.4
25.9
18.5
-3.7
-4.0
f1 (ppm)

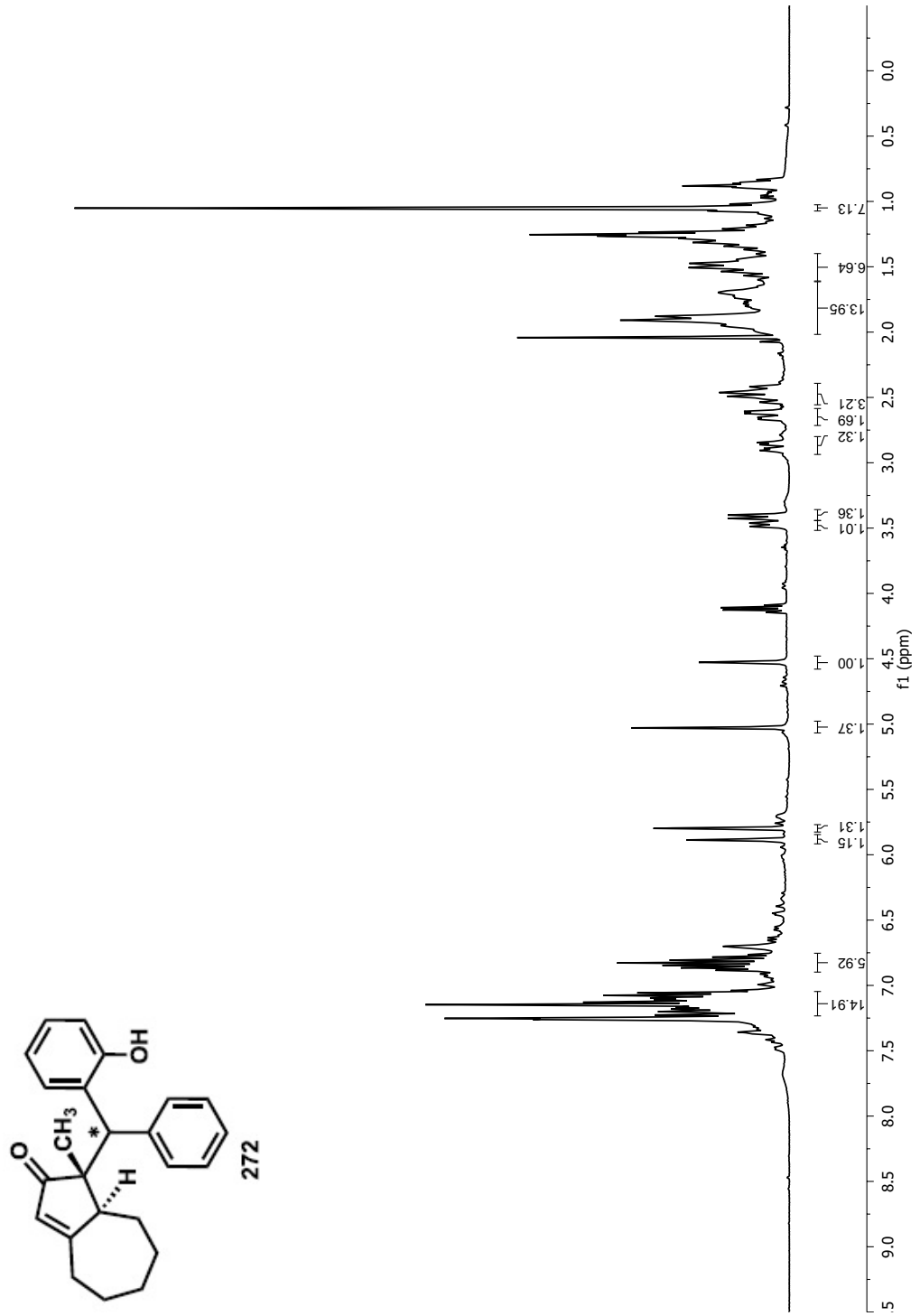
OCH3
OCH3
HO
O
CH3
*
H
268
9.90
1.95
4.31
2.00
4.42
7.25
1.55
1.68
1.40
2.04
4.08
5.51
5.35
7.14
f1 (ppm)

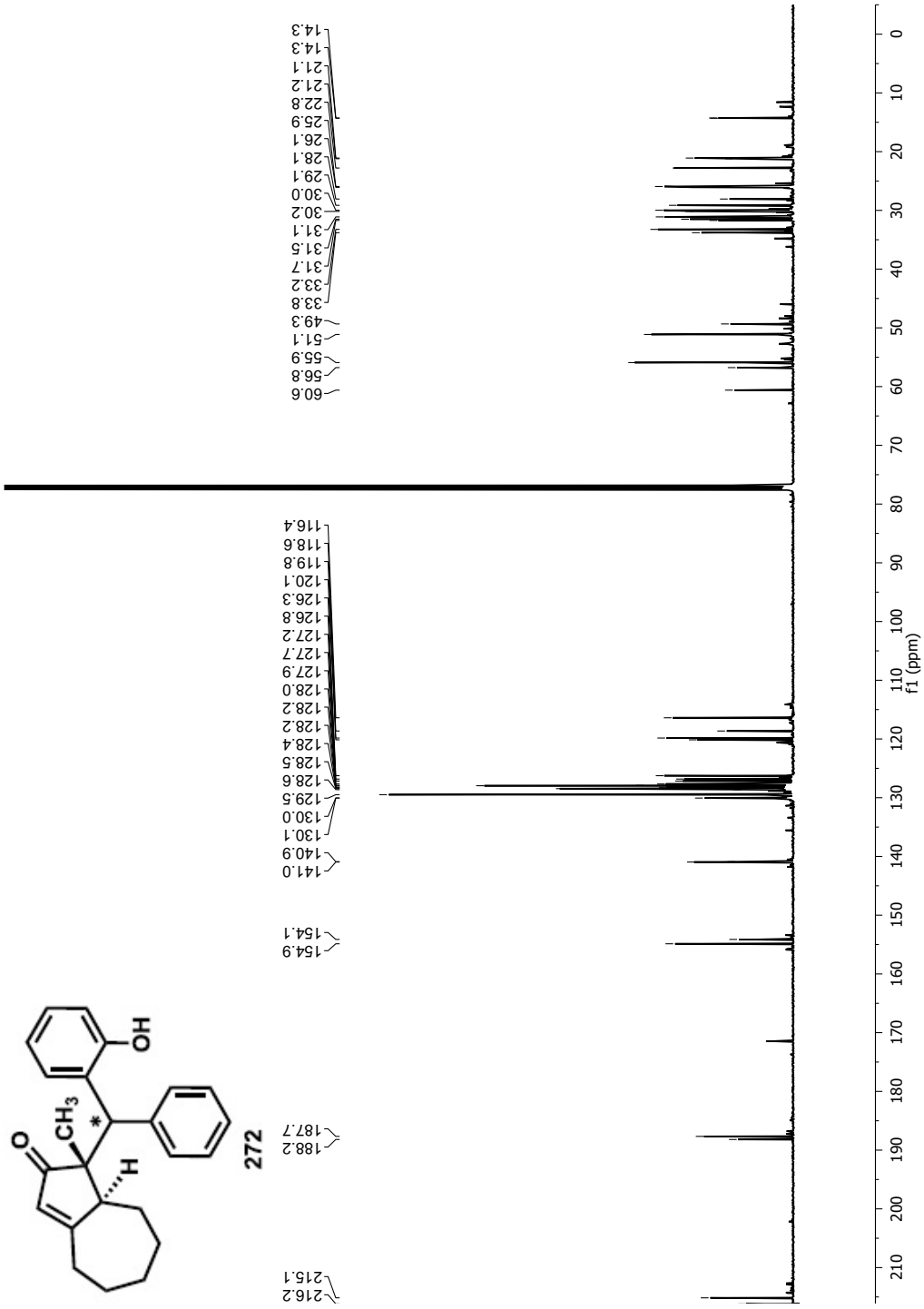
OCH3
OCH3
HO
O
CH3
*
H
268
1.03
1.01
4.16
2.05
2.03
2.03
2.10
2.19
2.07
1.99
2.76
7.94
1.28
3.12
2.25
8.11
9.76
2.98
2.94
f1 (ppm)


OCH3
OCH3
HO
O
CH3
*
H
268
215.0
186.2
171.2
160.1
159.2
156.6
140.6
128.8
128.4
126.9
126.2
109.9
95.2
91.1
60.4
57.2
55.7
55.2
52.8
43.1
34.7
34.0
31.7
31.6
30.0
27.7
26.1
25.3
22.7
22.4
21.1
14.2
14.2
f1 (ppm)

OCH3
OCH3
OH
O
H3C
270
4.46
1.05
0.98
1.00
0.99
3.09
3.04
1.02
0.99
0.97
3.02
1.13
4.36
1.76
3.42
f1 (ppm)

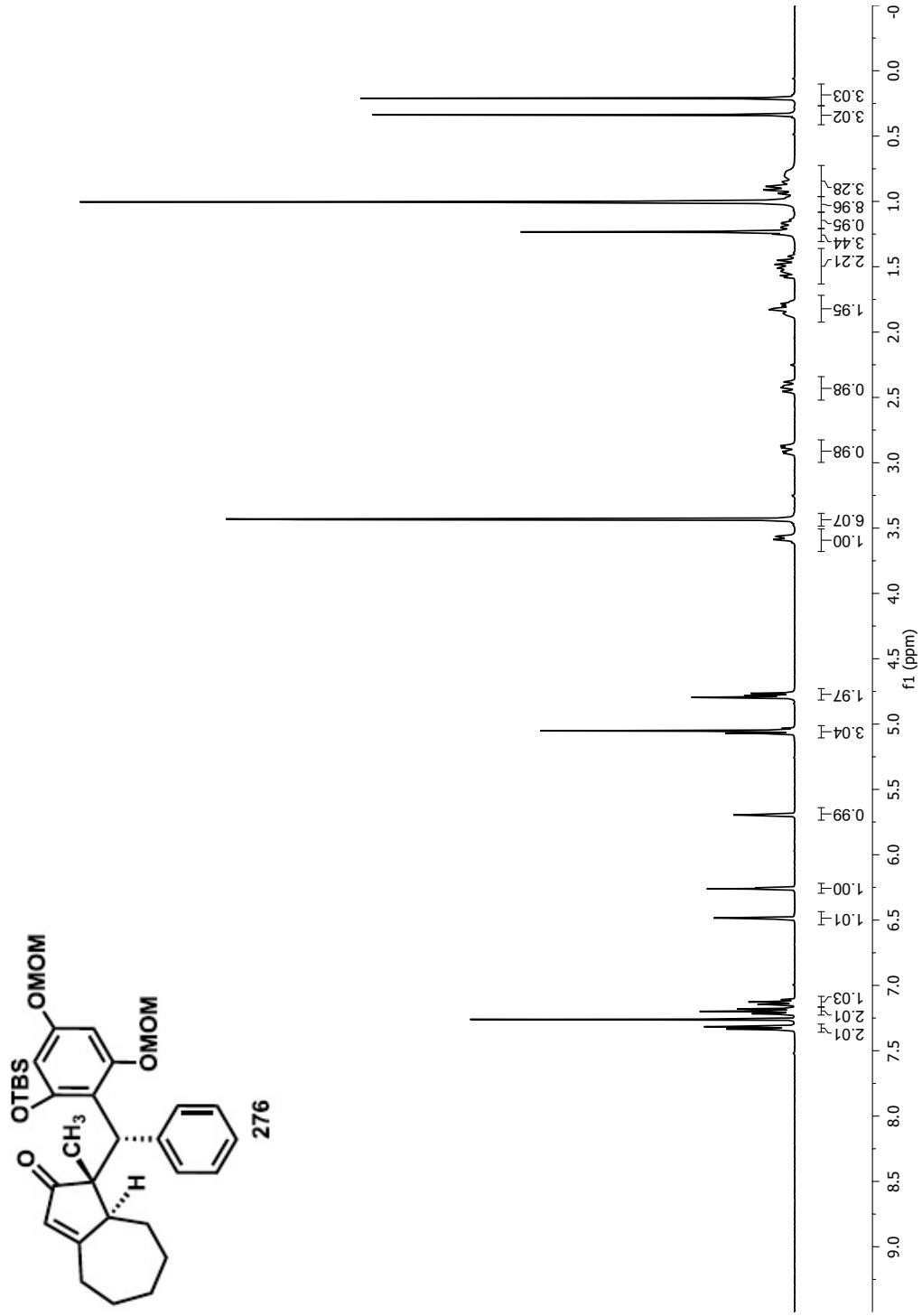
OCH3
OCH3
OH
O
H3C
270
160.0
157.3
156.9
143.3
140.4
134.7
129.5
128.7
126.9
111.2
108.4
93.7
92.0
55.9
55.7
55.4
50.0
41.1
31.3
30.0
27.2
26.9
25.5
20.0
f1 (ppm)

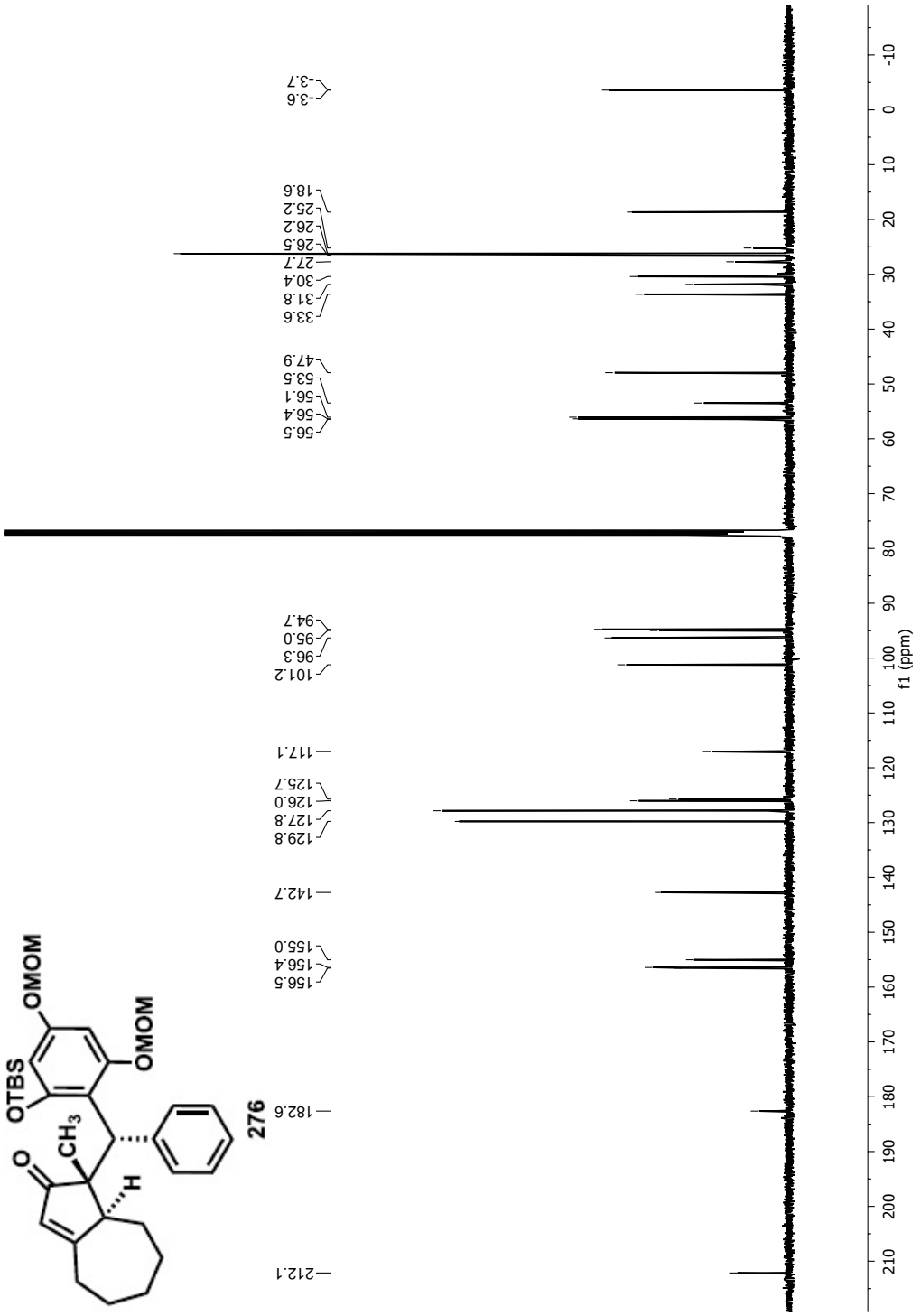

OH
CH3
*
O
H
272
14.91
5.92
1.15
1.31
1.37
1.00
1.01
1.36
1.32
1.69
3.21
13.95
6.64
7.13
f1 (ppm)


272
O
CH3
*
H
OH
216.2
215.1
188.2
187.7
154.9
154.1
141.0
140.9
130.1
130.0
129.5
128.6
128.5
128.4
128.2
128.2
128.0
127.9
127.7
127.2
126.8
126.3
120.1
119.8
118.6
116.4
60.6
56.8
55.9
51.1
49.3
33.8
33.2
31.7
31.5
31.1
30.2
30.0
29.1
28.1
26.1
25.9
22.8
21.2
21.1
14.3
14.3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

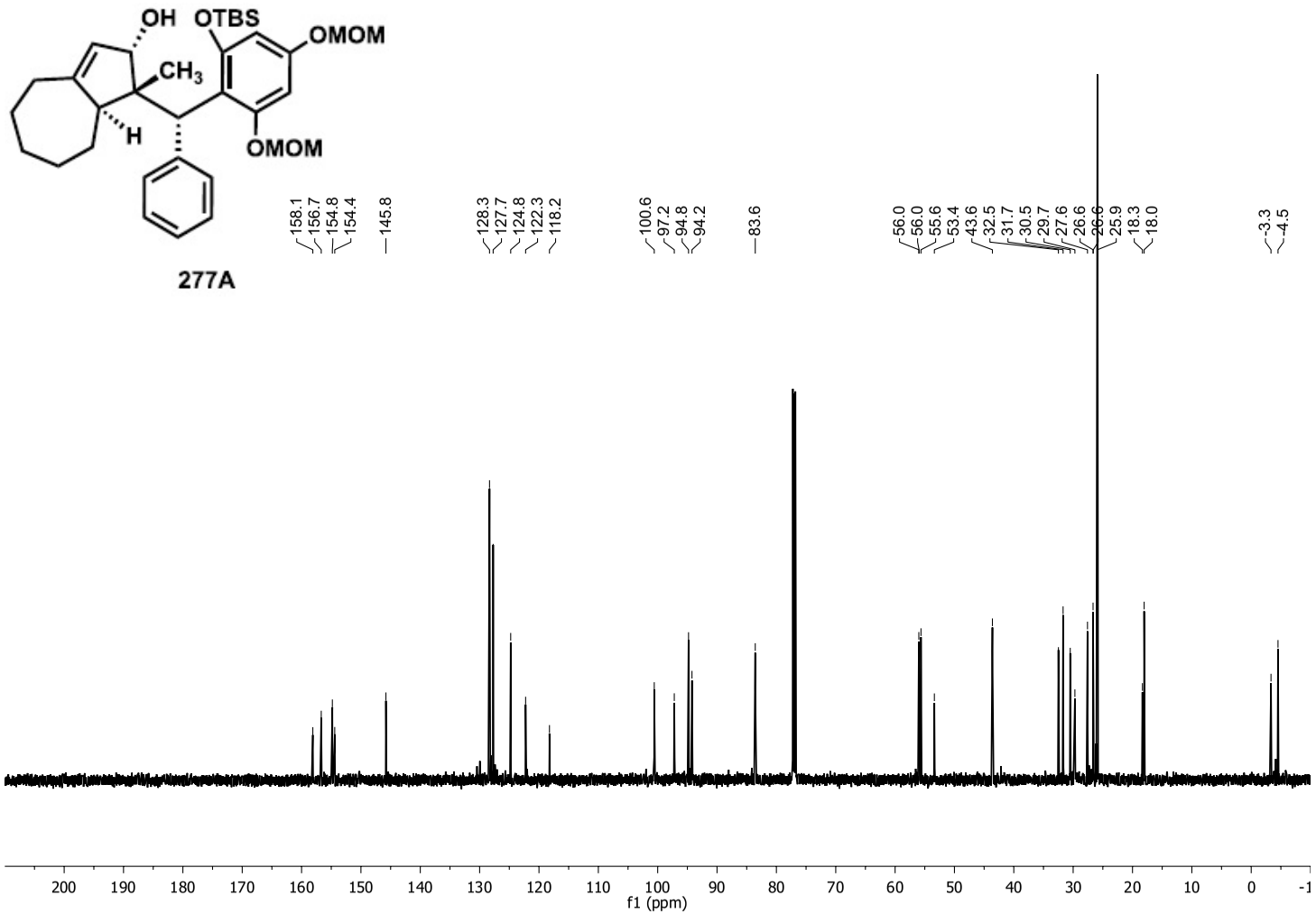
OMOM
OMOM
OTBS
O
H3C
H
275
1.96
1.95
1.00
0.98
1.00
0.96
2.07
1.94
0.97
3.09
2.94
1.95
0.88
0.92
0.86
2.06
4.04
8.72
3.20
2.92
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

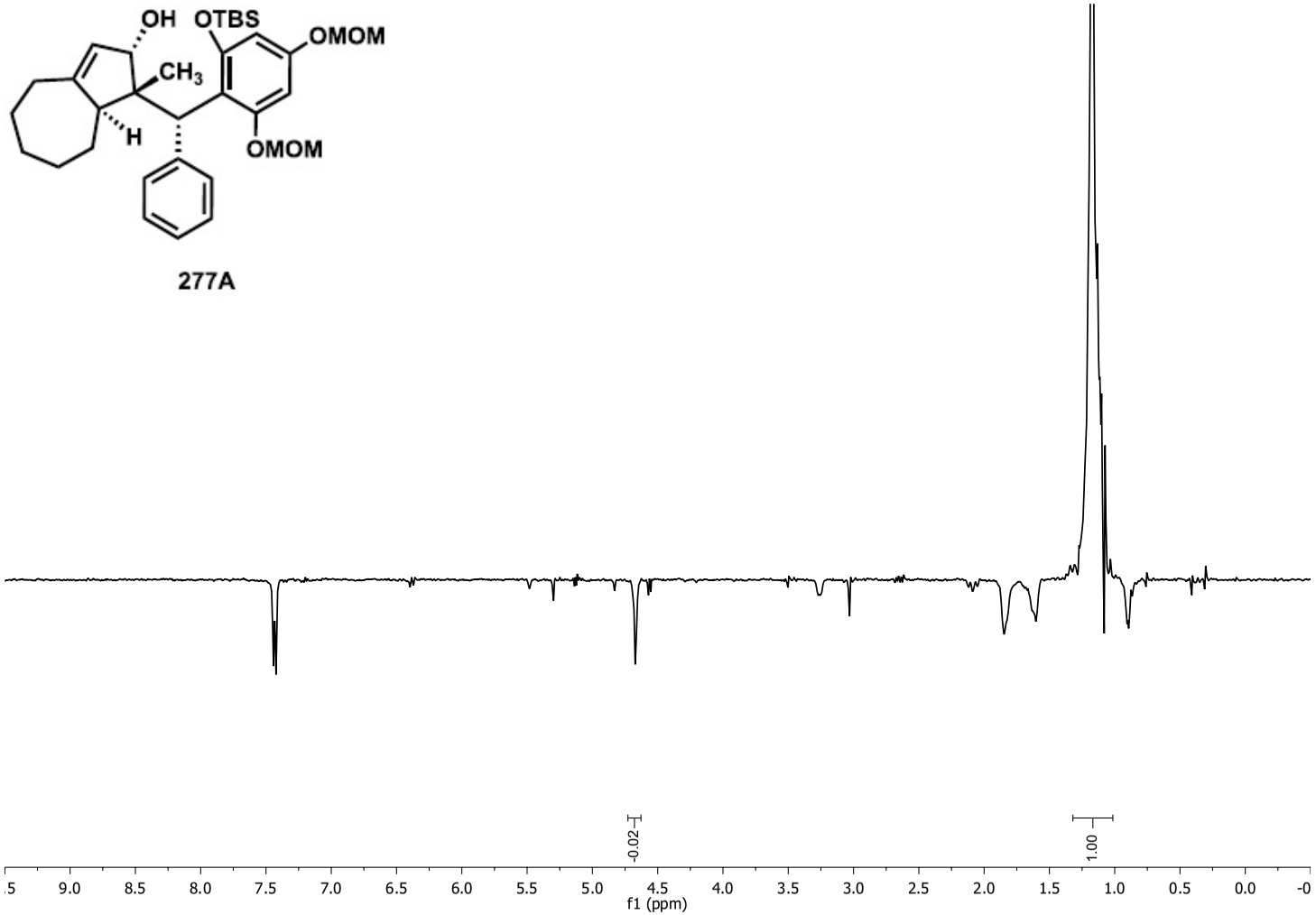
OMOM
OMOM
OTBS
O
H3C
H
275
157.0
155.9
155.3
151.3
143.5
130.3
127.2
126.5
125.6
110.8
108.3
97.5
95.8
94.7
93.7
56.3
55.7
55.2
52.3
42.3
32.4
31.9
30.6
29.9
27.3
26.7
25.9
25.8
19.0
18.1
-2.5
-2.8
f1 (ppm)


OMOM
OTBS
OMOM
CH3
O
H
276
f1 (ppm)


OMOM
OMOM
OTBS
CH3
O
H
276
-3.7
-3.6
18.6
25.2
26.2
26.5
27.7
30.4
31.8
33.6
47.9
53.5
56.1
56.4
56.5
94.7
95.0
96.3
101.2
117.1
125.7
126.0
127.8
129.8
142.7
155.0
156.4
156.5
182.6
212.1
f1 (ppm)

OMOM
OTBS
OMOM
OH
CH3
H
277A
1.94
2.17
1.05
0.96
1.00
2.21
1.04
2.86
3.22
0.94
2.89
1.04
1.22
1.06
4.01
1.96
1.75
3.58
9.45
3.05
2.93
f1 (ppm)


OH
OTBS
OMOM
CH3
H
OMOM
277A
158.1
156.7
154.8
154.4
145.8
128.3
127.7
124.8
122.3
118.2
100.6
97.2
94.8
94.2
83.6
56.0
56.0
55.6
53.4
43.6
32.5
31.7
30.5
29.7
27.6
26.6
26.6
25.9
18.3
18.0
-3.3
-4.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


OH
OTBS
OMOM
CH3
H
OMOM
277A
-0.02
1.00
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

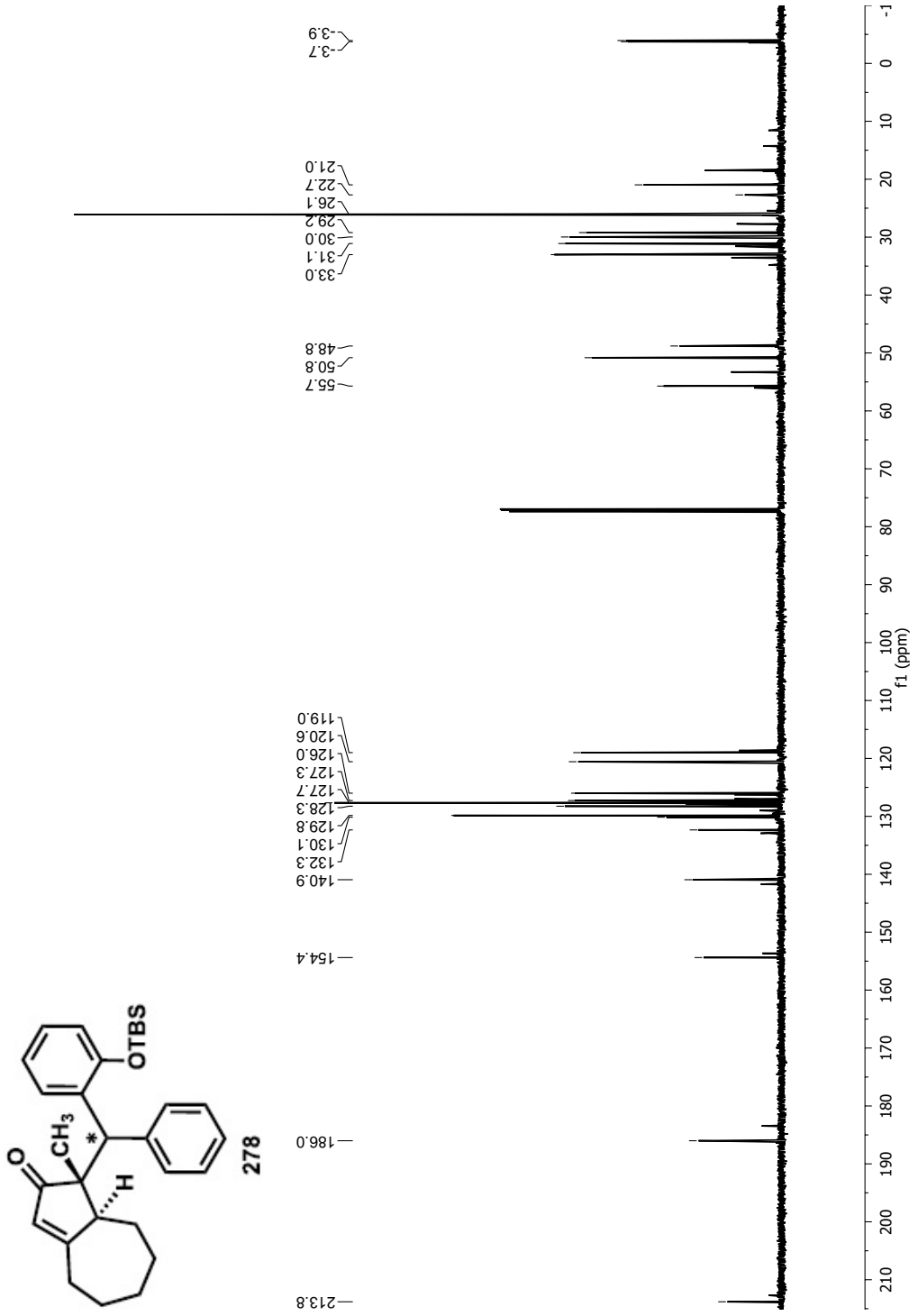
OMOM
OTBS
OMOM
OH
CH3
H
277B
3.15
2.43
1.15
0.95
1.00
0.97
0.95
2.36
0.96
1.96
3.69
2.91
0.98
1.91
0.95
2.43
3.21
3.73
8.99
4.53
2.99
2.93
f1 (ppm)

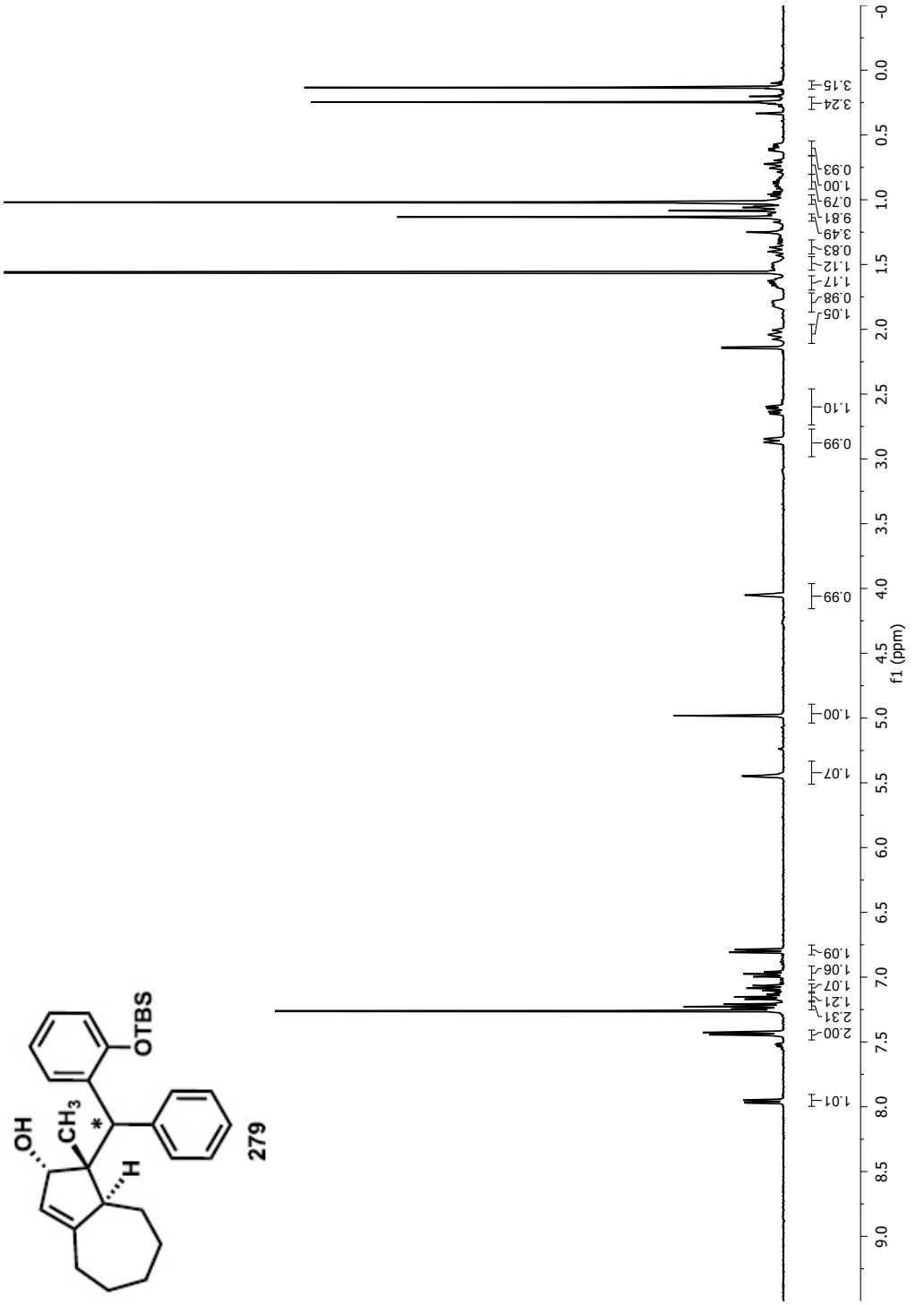
OMOM
OMOM
OTBS
OH
CH3
H
277B
156.7
155.5
149.1
144.1
129.7
127.7
125.1
125.1
118.6
101.2
98.1
95.5
94.9
79.6
56.9
56.4
56.1
56.1
45.5
32.3
31.7
30.3
29.9
28.5
27.1
27.0
26.1
18.6
15.9
-3.4
-4.0
f1 (ppm)

OTBS
CH3
O
H
*

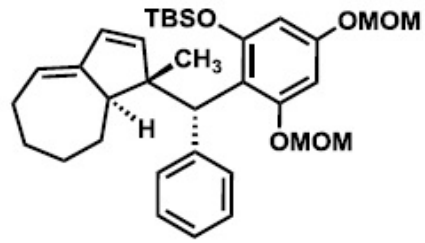
278

1.01
4.76
1.05
1.22
0.94
1.00
0.99
1.03
1.30
3.26
2.60
3.32
8.75
2.71
2.76
2.81
f1 (ppm)


OTBS
CH3
*
O
H
278
213.8
186.0
154.4
140.9
132.3
130.1
129.8
128.3
127.7
127.3
126.0
120.6
119.0
55.7
50.8
48.8
33.0
31.1
30.0
29.2
26.1
22.7
21.0
-3.7
-3.9
f1 (ppm)


OTBS
OH
CH3
*
H
279
f1 (ppm)

OTBS
OH
CH3
H
279
154.6
153.2
142.5
133.9
130.6
130.0
127.8
127.3
126.2
123.0
121.1
119.3
100.1
83.8
57.4
53.4
47.5
32.4
31.7
30.8
26.8
26.6
26.2
26.1
18.6
18.3
-3.7
-3.8
f1 (ppm)


TBSO
OMOM
CH3
H
OMOM

280

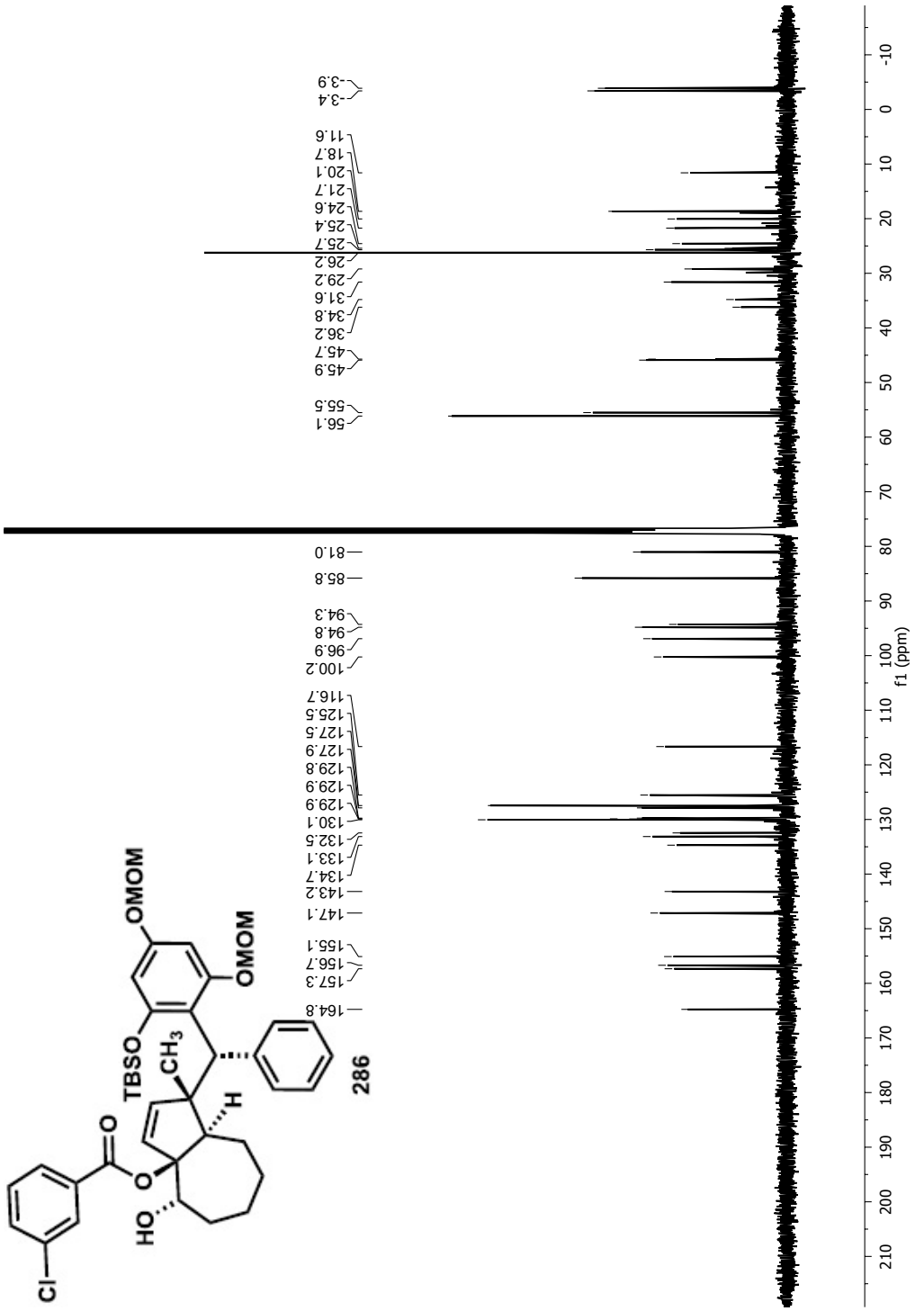
1.85
1.97
1.00
0.93
0.95
0.95
0.91
0.96
2.15
1.00
0.99
1.00
3.05
2.79
0.99
1.10
1.12
0.89
1.00
1.16
3.30
8.54
3.29
2.75
2.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

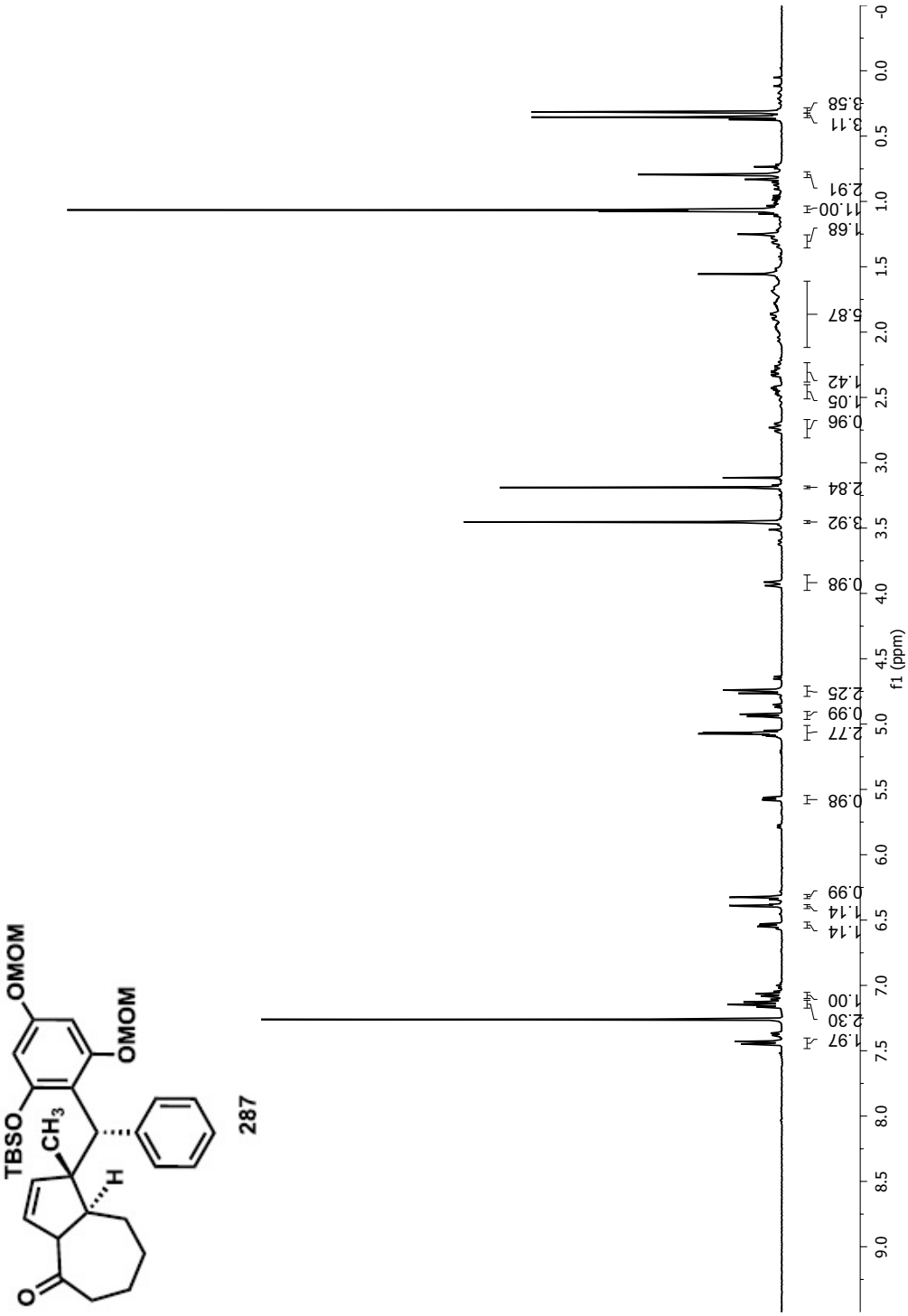
TBSO
OMOM
OMOM
CH3
H
280
157.4
156.6
155.0
152.3
145.6
144.3
131.8
130.1
127.2
125.0
121.0
118.0
100.3
97.0
94.9
94.3
56.2
56.1
56.0
50.1
46.7
30.2
29.5
28.5
28.3
26.2
24.1
18.6
-3.4
-3.9
f1 (ppm)

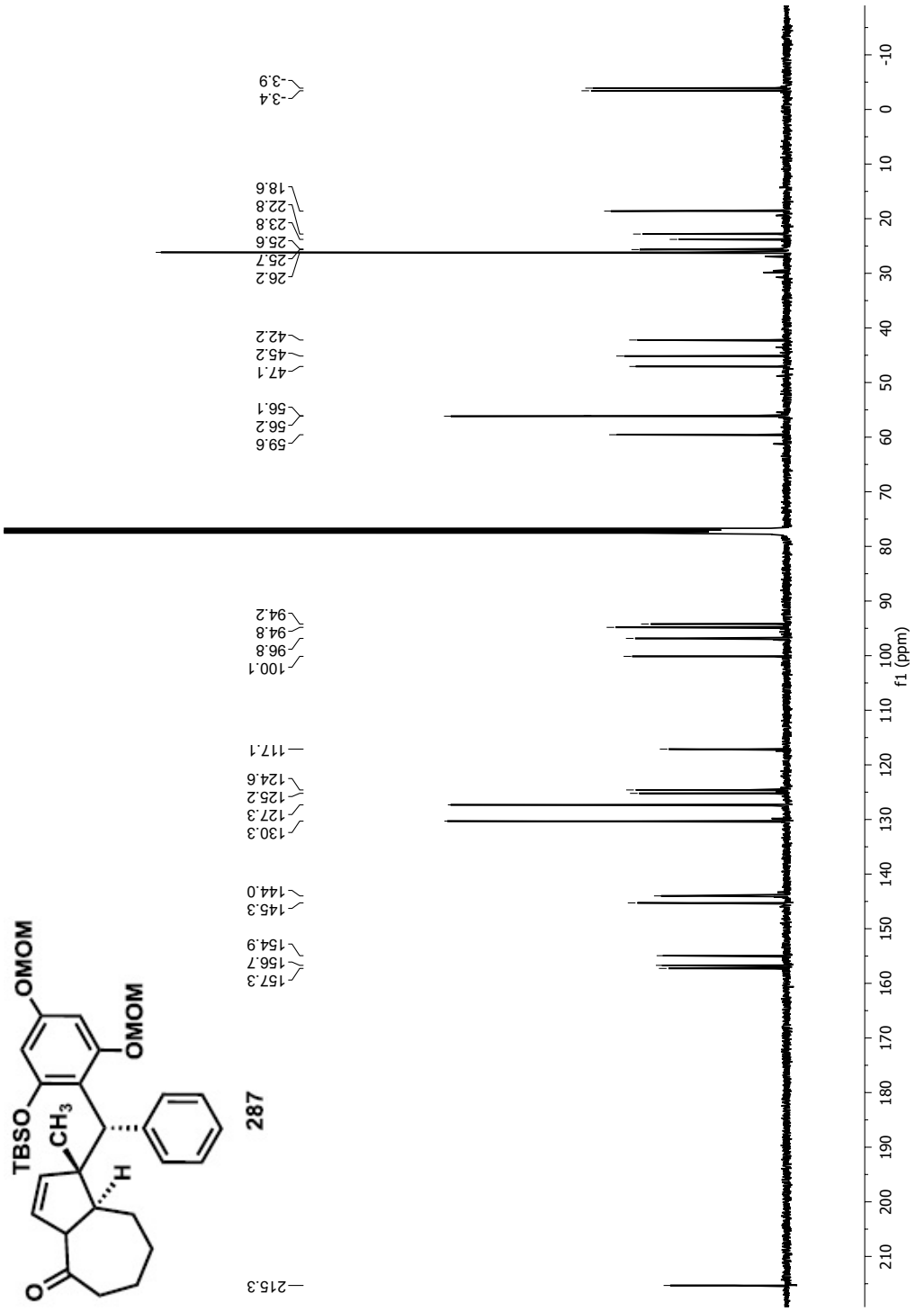
OMOM
OTBS
O
H
H3C
H
281
5.05
1.01
0.95
0.99
2.28
0.99
1.00
1.58
3.30
0.98
1.12
2.02
1.15
4.59
5.13
9.21
0.99
3.09
3.02
f1 (ppm)

OMOM
OTBS
O
H
H3C
H
281
158.3
158.0
156.7
154.5
143.7
129.6
127.7
125.9
119.7
116.2
101.5
98.7
94.8
92.1
56.1
53.2
50.1
47.6
31.5
30.4
27.7
26.6
26.1
25.6
18.5
-3.9
-4.0
f1 (ppm)

OMOM
OMOM
TBSO
CH3
H
O
O
HO
Cl
286
f1 (ppm)


-3.9
-3.4
11.6
18.7
20.1
21.7
24.6
25.4
25.7
26.2
29.2
31.6
34.8
36.2
45.7
45.9
55.5
56.1
81.0
85.8
94.3
94.8
96.9
100.2
116.7
125.5
127.5
127.9
129.8
129.9
129.9
130.1
132.5
133.1
134.7
143.2
147.1
155.1
156.7
157.3
164.8
f1 (ppm)
OMOM
OMOM
TBSO
CH3
H
O
O
HO
Cl
286


OMOM
OMOM
TBSO
CH3
H
O
287
f1 (ppm)


OMOM
OMOM
TBSO
CH3
H
O
287
215.3
157.3
156.7
154.9
145.3
144.0
130.3
127.3
125.2
124.6
117.1
100.1
96.8
94.8
94.2
59.6
56.2
56.1
47.1
45.2
42.2
26.2
25.7
25.6
23.8
22.8
18.6
-3.4
-3.9
f1 (ppm)

OMOM
OTBS
H
O
H3C
H
HO
288
4.74
1.60
1.00
0.95
2.61
1.06
0.95
1.00
3.72
0.90
4.18
1.95
3.72
2.87
9.43
2.98
2.98
f1 (ppm)

OMOM
OTBS
O
H
H3C
H
HO
288
157.5
156.9
156.5
154.5
142.7
130.8
127.2
125.9
124.5
114.0
100.8
97.9
94.8
89.9
69.7
56.2
52.1
50.0
47.0
35.0
29.9
29.9
28.6
26.0
25.3
23.3
18.4
-3.9
-4.1
f1 (ppm)

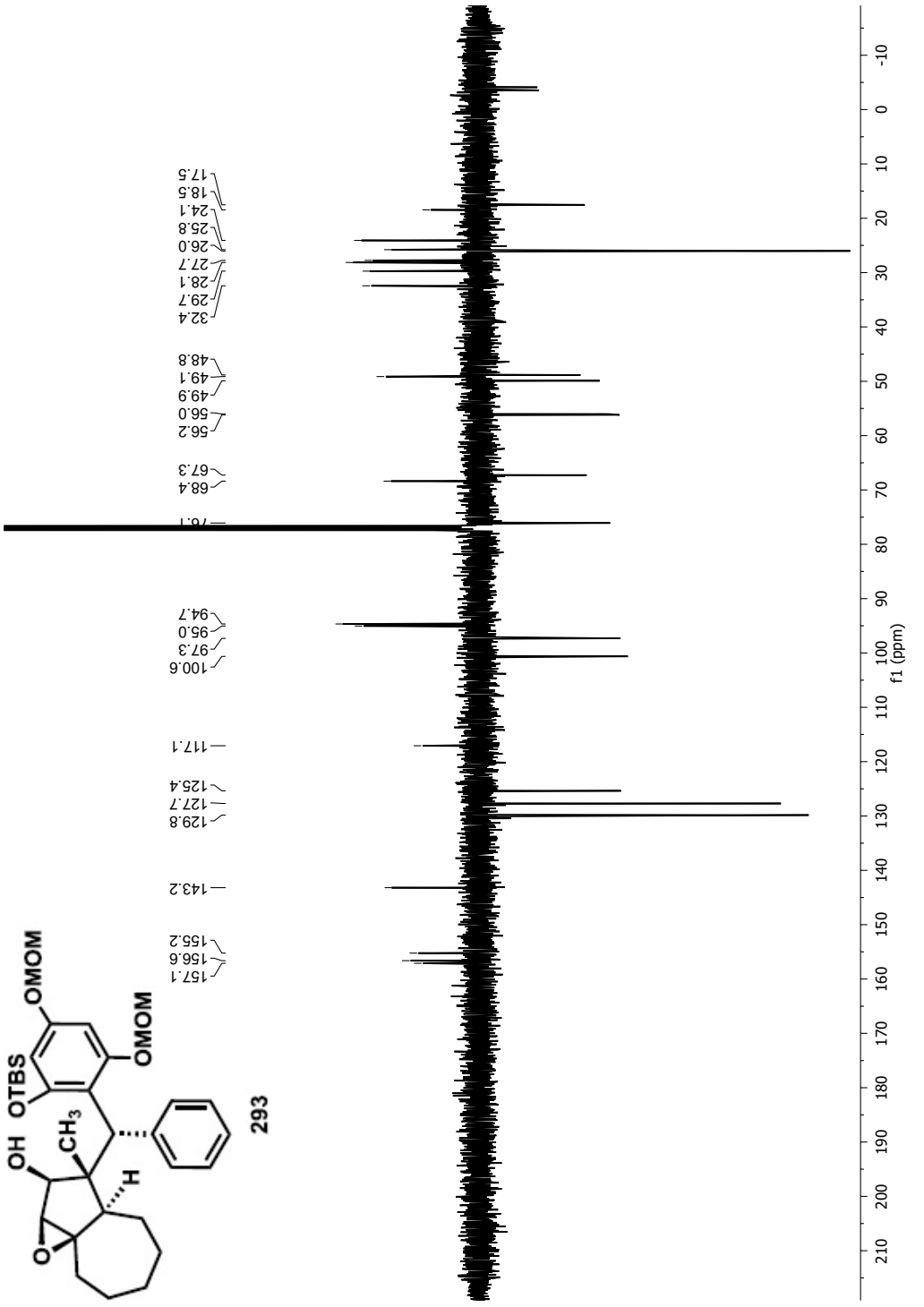
OMOM
OMOM
TBSO
CH3
H
O
284
2.44
2.93
1.44
1.15
1.14
1.37
1.00
2.31
1.13
1.01
1.05
3.38
3.00
2.33
9.46
9.20
4.27
3.91
3.57
f1 (ppm)

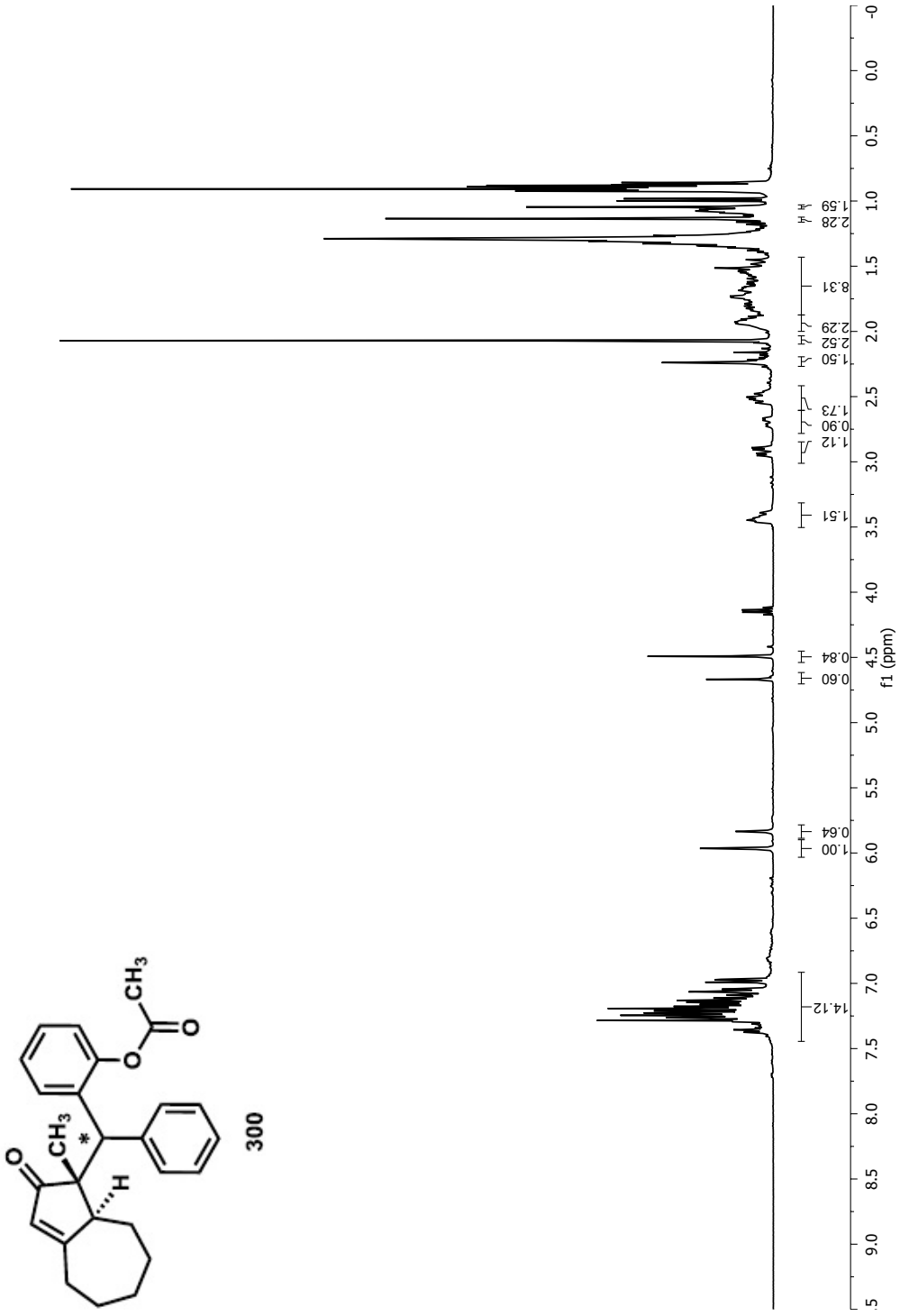
OMOM
OMOM
TBSO
CH3
H
O
284
157.3
156.7
155.2
150.9
143.6
130.3
128.5
127.4
127.4
125.5
125.4
117.1
100.4
96.9
94.9
94.4
72.4
59.4
56.2
56.1
54.5
48.1
45.3
30.3
28.3
26.3
26.2
26.1
26.0
24.3
23.9
23.6
22.8
18.7
14.3
-3.4
-3.8
f1 (ppm)

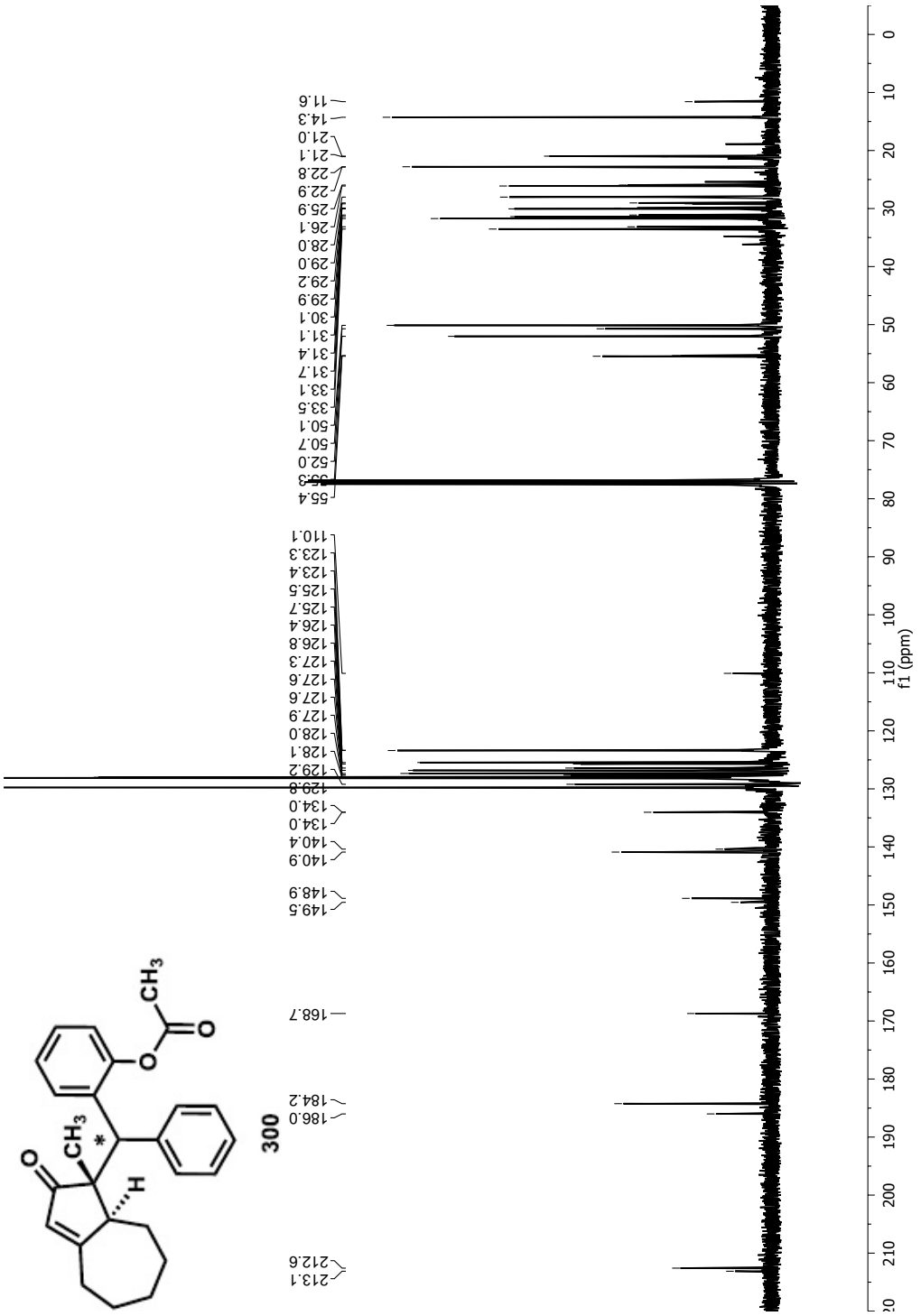
OMOM
OMOM
OTBS
OH
CH3
H
O
291
f1 (ppm)

OMOM
OMOM
OTBS
OH
CH3
H
O
291
158.1
156.8
154.9
145.2
128.9
127.3
124.5
118.0
100.4
97.2
94.8
94.3
77.3
75.8
69.0
59.7
56.1
55.8
54.6
43.8
33.8
31.3
30.6
27.3
26.2
26.1
18.9
18.4
-3.2
-4.3
f1 (ppm)

OMOM
OMOM
OTBS
OH
CH3
H
O
293
1.88
2.46
1.11
0.92
1.00
2.39
0.89
1.84
1.06
3.44
1.08
2.78
0.90
0.99
1.23
4.47
3.79
9.47
2.90
3.07
3.09
f1 (ppm)


OMOM
OTBS
OMOM
OH
CH3
H
O
293
157.1
156.6
155.2
143.2
129.8
127.7
125.4
117.1
100.6
97.3
95.0
94.7
76.1
68.4
67.3
56.2
56.0
49.9
49.1
48.8
32.4
29.7
28.1
27.7
26.0
25.8
24.1
18.5
17.5
f1 (ppm)


CH3
O
O
CH3
*
O
H
300
14.12
1.00
0.64
0.60
0.84
1.51
1.12
0.90
1.73
1.50
2.52
2.29
8.31
2.28
1.59
f1 (ppm)


CH3
O
O
CH3
*
O
H
300
11.6
14.3
21.0
21.1
22.8
22.9
25.9
26.1
28.0
29.0
29.2
29.9
30.1
31.1
31.4
31.7
33.1
33.5
50.1
50.7
52.0
55.4
110.1
123.3
123.4
125.5
125.7
126.4
126.8
127.3
127.6
127.6
127.9
128.0
128.1
129.2
129.8
134.0
134.0
140.4
140.9
148.9
149.5
168.7
184.2
186.0
212.6
213.1
f1 (ppm)

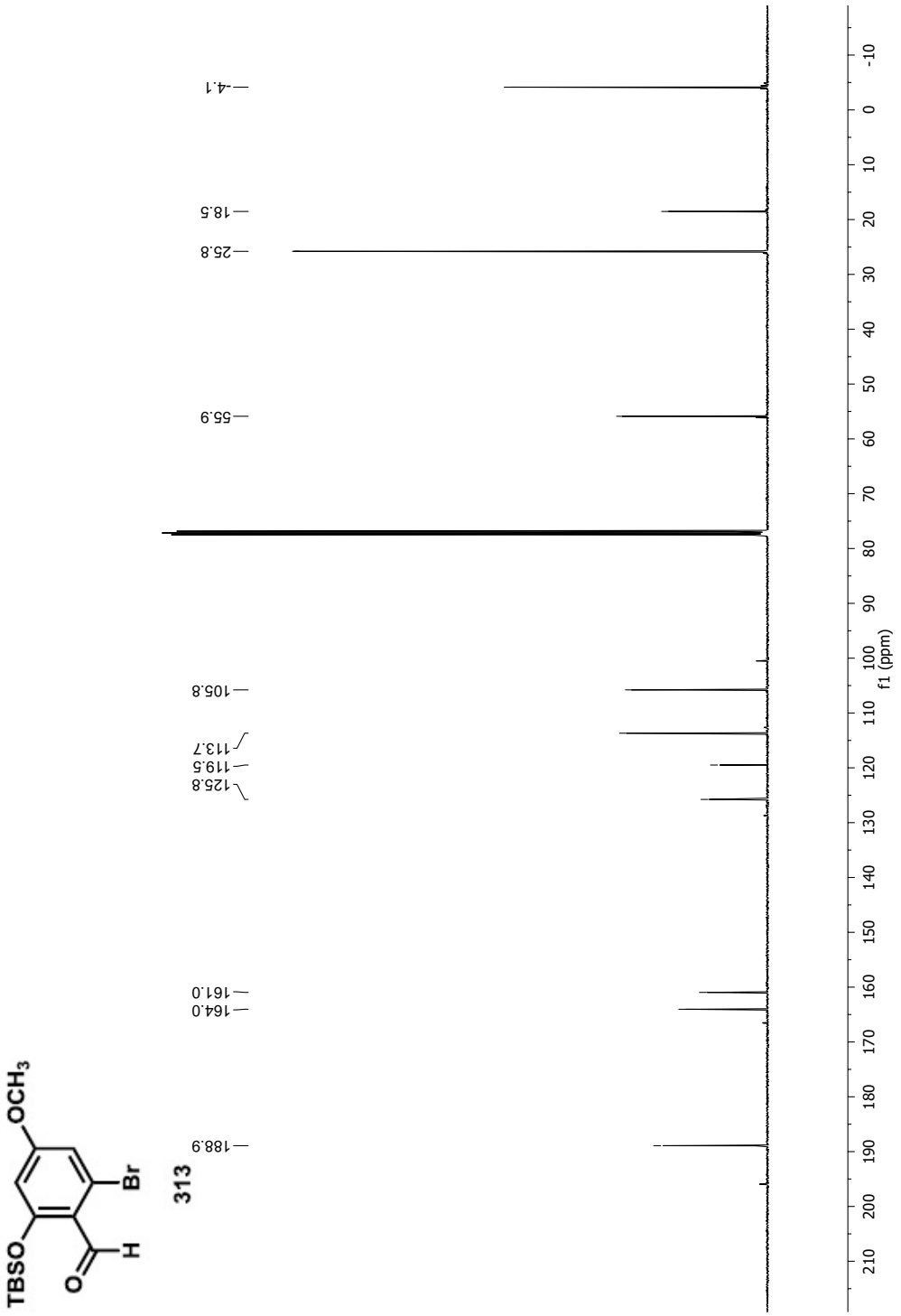
OCH3
Br
H3CO
O
H
311
0.96
1.03
1.00
3.39
3.37
f1 (ppm)

OCH3
Br
H3CO
O
H
311
189.2
164.6
163.8
127.5
117.1
111.7
98.3
56.3
56.0
f1 (ppm)

OCH3
Br
HO
H
O
312
3.32
1.01
1.00
0.97
0.97
f1 (ppm)

OCH3
Br
HO
H
O
312
195.9
166.6
166.5
128.7
113.7
112.7
100.6
56.1
f1 (ppm)

TBSO
OCH3
Br
H
O
313
6.06
9.57
3.02
1.00
1.00
0.96
f1 (ppm)


OCH3
Br
TBSO
O
H
313
188.9
164.0
161.0
125.8
119.5
113.7
105.8
55.9
25.8
18.5
-4.1
f1 (ppm)

OCH3
Br
TBSO
HO
314
4.30
1.11
1.00
0.98
0.97
3.09
0.87
9.28
3.04
3.02
f1 (ppm)

OCH3
Br
TBSO
HO
314
159.7
155.5
143.6
128.2
127.0
126.0
125.2
125.0
110.5
105.9
74.1
55.7
25.7
18.3
-3.8
-4.5
f1 (ppm)

OCH3
CH3
O
H
314A
8.74
1.28
1.30
1.10
1.00
3.00
1.14
1.37
1.29
4.06
1.83
3.29
5.17
3.69
f1 (ppm)

O
CH3
H
OCH3
314A
213.9
186.1
157.8
141.5
130.5
130.1
129.5
128.0
127.7
127.6
125.9
120.1
111.1
55.7
55.6
51.1
33.1
31.7
31.2
30.0
29.0
26.0
22.8
21.2
14.3
f1 (ppm)

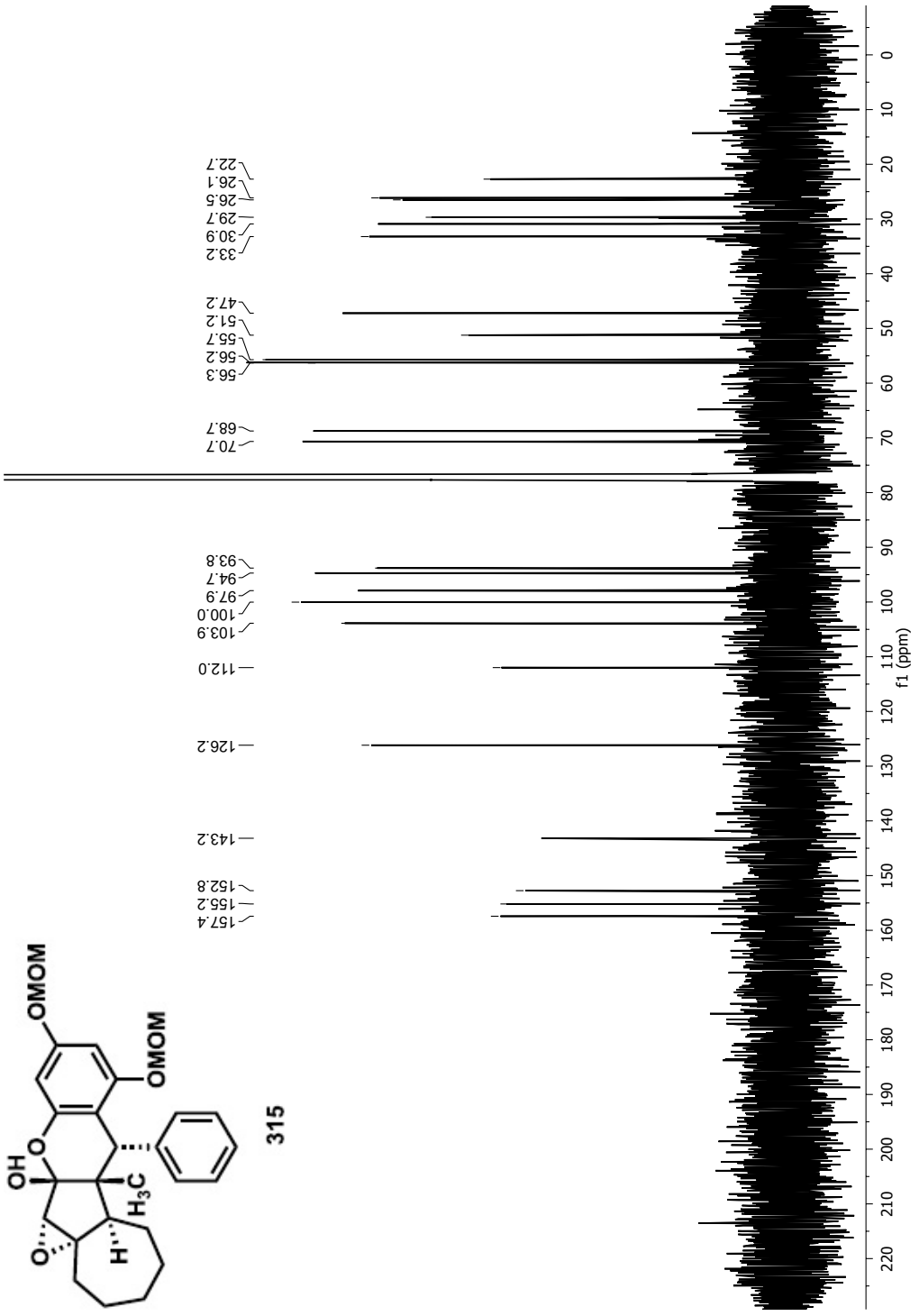
O
CH3
H
OCH3
314B
8.67
1.33
1.09
1.00
1.00
1.04
2.79
0.99
1.07
1.28
3.96
3.95
3.42
f1 (ppm)

314B
213.1
184.1
157.2
142.1
130.9
129.9
128.2
128.0
127.8
127.3
126.2
120.0
110.9
55.8
55.5
52.6
49.1
33.5
31.7
31.4
30.2
28.1
26.1
22.8
22.7
14.3
f1 (ppm)

OCH3
CH3
O
H
O
315
2.03
2.17
3.45
2.10
1.00
3.08
1.00
0.99
0.97
2.02
1.83
0.80
5.14
2.94
f1 (ppm)

OCH3
CH3
O
H
O
315
212.3
157.2
142.0
131.0
130.2
130.2
128.0
127.7
126.1
120.3
110.8
71.0
63.1
57.1
55.5
48.2
48.0
33.1
31.1
30.1
29.9
27.2
25.8
20.9
f1 (ppm)

OMOM
OMOM
OH
O
H3C
O
H
315
5.22
0.93
0.86
2.50
0.87
0.85
0.82
0.92
2.75
0.86
2.46
0.87
1.34
0.86
1.98
3.51
3.80
1.62
1.93
f1 (ppm)


OMOM
OMOM
OH
O
H3C
O
H
315
157.4
155.2
152.8
143.2
126.2
112.0
103.9
100.0
97.9
94.7
93.8
70.7
68.7
56.3
56.2
55.7
51.2
47.2
33.2
30.9
29.7
26.5
26.1
22.7
f1 (ppm)

OMOM
OMOM
OH
CH3
O
H
O
316
5.09
1.00
1.06
2.23
1.04
1.10
1.03
1.02
3.34
1.14
3.10
0.98
1.09
1.97
3.08
3.11
3.33
f1 (ppm)

OMOM
OMOM
OH
CH3
O
H
O
316
213.2
157.2
157.0
156.0
141.3
127.8
126.6
117.6
102.5
99.7
94.5
93.8
91.1
79.5
56.3
55.7
51.9
51.7
46.5
36.0
29.9
26.9
26.2
22.7
22.2
19.7
f1 (ppm)