Titanium-mediated Carbometallation of Homoallylic Alcohols

Approved By:

Dr. Joseph Ready

Dr. Chuo Chen

Dr. Lazslo Kurti

Dr. Uttam Tambar

_____

To My Parents and the giants that we stand upon

Titanium-mediated Carbometallation of Homoallylic Alcohols

by

Bo Peng

Thesis

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

Master of Science

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

November, 2011

Titanium-mediated Carbometallation of Homoallylic Alcohols

Bo Peng, M.S.

The University of Texas Southwestern Medical Center at Dallas, 2011

Mentor: Dr. Joseph M. Ready

Addition of zinc dichloride as an additive allows for the titanium-mediated carbometallation of homoallylic alcohols with Grignard reagents. The zinc dichloride additive successfully inhibits the β-hydride elimination of the titanium intermediate. The unsaturated products are obtained in up to 90 percent yield and up to >20 to 1 ratio of the carbometallation to oxidative arylation products. Subsequent electrophilic trapping is possible with elemental halides to yield the respective halohydrin products or oxidation to yield the diol products. The reaction is tolerant of both alkyl and aryl substituents on the homoallylic alcohol. This reaction allows ready access to unsaturated secondary alcohols or further functionalized products from an initial homoallylic alcohol.

Table of Contents

List of Schemes

List of Tables

List of Appendices

List of Abbreviations and Terminology

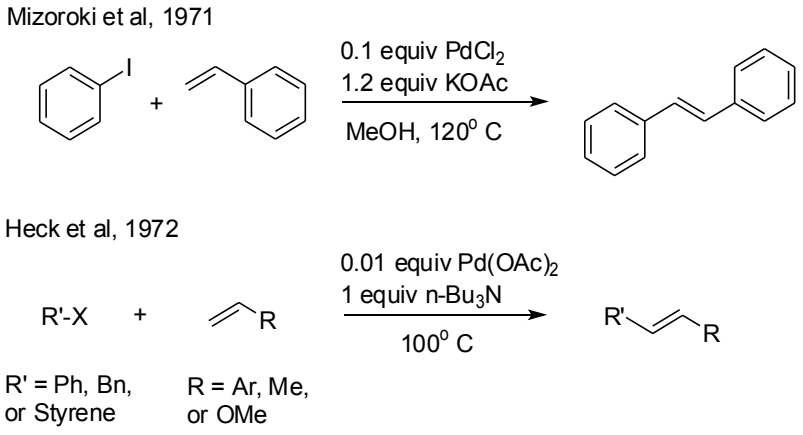
Ac	acetyl
anhyd.	anhydrous
aq.	Aqueous
Ar	aryl (substituted aromatic ring)
Bn	benzyl
br	broad
BuLi	butyl lithium
Bz	benzoyl
calc	calculated
cat.	Catalytic
ca	cerca (approximately)
°C	degrees Celsius
conc.	concentrated
Cy	cyclohexyl
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dba	dibenzylideneacetone
DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dt	doublet of triplets
E^+	electrophile (denotes any electrophile in general)
ee	enantiomeric excess
eq.	equation
equiv	equivalent
ES+	electrospray, positive ionization mode
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
FT-IR	Fourier transform infrared
g	gram
GC	gas chromatography
h	hour
[H]	reductant

Hg mm	millimeter of mercury (760 Hg mm = 1 atm = 760 Torr)
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
hν	light
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
M	molar
m	multiplet or medium
[M]	metal
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
m/z	mass / charge
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
n-Bu	butyl
Nu	nucleophile
o-	ortho
[O]	oxidant
OAc	acetate
OTf	triflate
p.	page
p-	para
Ph	phenyl
PCC	pyridinium chlorochromate
PhH	benzene

PhMe	toluene
PMB (MPM)	*p*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	part per million
pyr	pyridine
q	quartet
rac	racemic
R_f	retention factor in chromatography
rt	room temperature
s	singlet or strong
t	triplet
t-Bu	tert-butyl
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
tol	toluene
T_r	retention time
p-TsOH	*p*-toluenesulfonic acid
Ts	toluenesulfonyl
UV	ultraviolet
w	weak
X	halide

Chapter One: Introduction

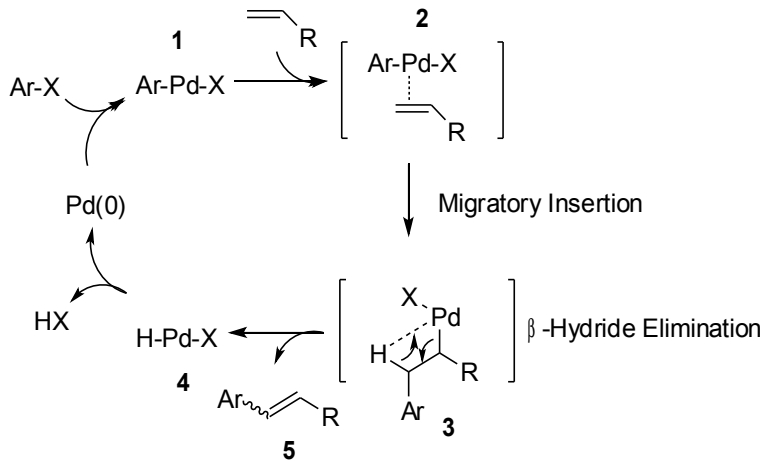
Forming carbon-carbon bonds is a fundamental operation in the creation of new organic molecules. The development of palladium-catalyzed reaction in order to create such bonds was a major advancement in organometallic chemistry in the latter half of the 20th Century. The recent Nobel Prize awarded in 2010 to Drs. Negishi, Heck, and Suzuki for palladium-catalyzed cross-coupling recognizes the importance of these innovative reactions. Palladium-mediated cross-coupling reactions are able to create bonds between naturally unreactive starting materials, which offers an advantage by tolerating a wide range of chemical groups. After their discovery, palladium-catalyzed cross coupling reactions have seen widespread use for the synthesis of both small molecules and complex natural products.[1]



Scheme 1: Heck Reaction

The Heck reaction was first reported in 1972 for the creation of substituted olefins from unsaturated halides and alkenes by the Heck group.[2] The reaction is related to work reported earlier by the Mizoroki group on the Pd(II)-catalyzed coupling of iodobenzene and styrene

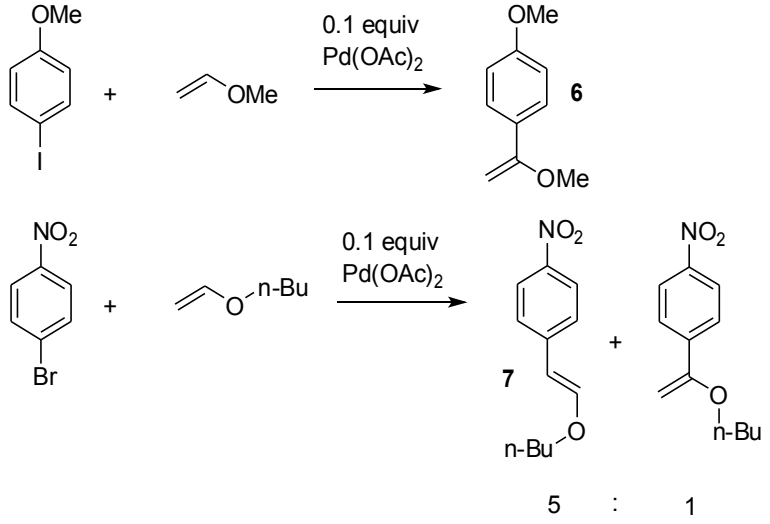
(Scheme 1).[3] In the coupling reaction reported by the Heck group, Pd(II) catalyst is used along with a *n*-Bu_3N amine base to attach the aryl, benzyl, or styryl halide to the alkene. The reactions proceed through a general process involving palladium insertion into the carbon-halogen bond of the aryl halide to form the organopalladium intermediate **1** (Scheme 2). This intermediate is then able to undergo migratory insertion into the olefin bond by attaching the aryl group to the terminal carbon of the olefin and forming **3**. This insertion occurs regioselectively as a result of the preference for insertion to occur in an anti-Markovnikov fashion for simple olefins.[1] The product of the reaction is formed when β-hydride elimination occurs from **3** to form the olefin **5**. The last step to complete the catalytic cycle is regeneration of the Pd(0) catalyst which occurs reductive elimination to release HX.



Scheme 2: Mechanism of Heck Reaction

Although the original reaction reported the usage of Pd(II), the active catalyst is currently thought to be Pd(0), which is commonly generated in situ through reduction by phosphine ligands.[4] Insertion of olefins into the Pd-Ar bond is electronically controlled except for simple olefins and aryl halides where steric interactions dominate.[1] By varying between electron

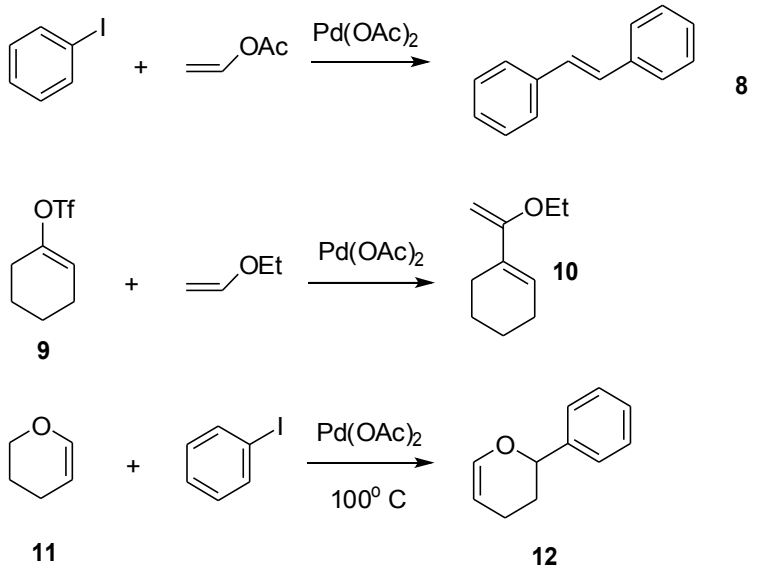
donating or withdrawing substituents, the regioselectivity of the insertion can be reversed so that insertion occurs into the α-carbon instead of the terminal β-carbon to give either the Markovnikov or anti-Markovnikov product (Scheme 3).[1] The general trend is that weakly coordinating ligands and electron rich olefins such as enol ethers and enol carboxylates prefer the Markovnikov product while electron withdrawing substituents cause the anti-Markovnikov product to dominate. The data showed also that the trans configuration of the olefin is favored for the product due to the conformation during the β-hydride elimination preferring the two remaining substituents be non-eclipsed.[2]



Scheme 3: Regioselectivity of Heck Reaction

Due to its synthetic utility, much work has been conducted on extending the applicability of the Heck reaction. Aryl triflates and boronic acids have been demonstrated as competent coupling partners in place of the original aryl halides with analogous palladium insertion into the carbon-heteroatom bond (Scheme 4).[1,5] As to the other partner of the coupling reaction, enol ethers, enol carboxylates, enamines, and enamides all have been shown to contain double bonds

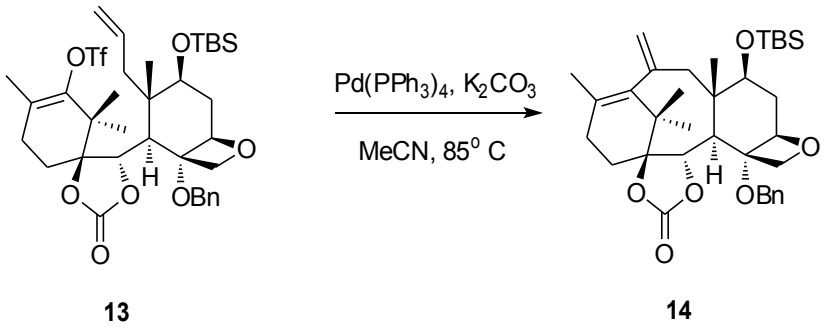
amenable to insertion into the active palladium intermediate **1**.[1] Cyclic versions of these substrates have also been utilized and due to easier β-hydride elimination from the γ-position, the unconjugated olefin is the result with the net effect being that the olefin has "walked". Under heated conditions, this process of β-hydride elimination and migratory insertion causes the most conjugated double bond to be formed. In addition, usage of acetates and silyl groups on the olefin partner can allow for bidirectional functionalization. In these cases the elimination occurs of the directing group rather than the normal β-hydride elimination. The intermediate after elimination can then undergo another Heck reaction. Vinyl acetate can be used as an ethylene substitute in this manner and addition to both ends occurs (Scheme 4).



Scheme 4: Extended Substrates for Heck Reaction

Total syntheses have utilized intramolecular Heck reactions to perform ring closure. Two of the more well known examples are the Danishefsky Group's synthesis of Taxol and the Overman Group's synthesis of morphine.[6,7] Both syntheses utilized the Heck reaction to perform

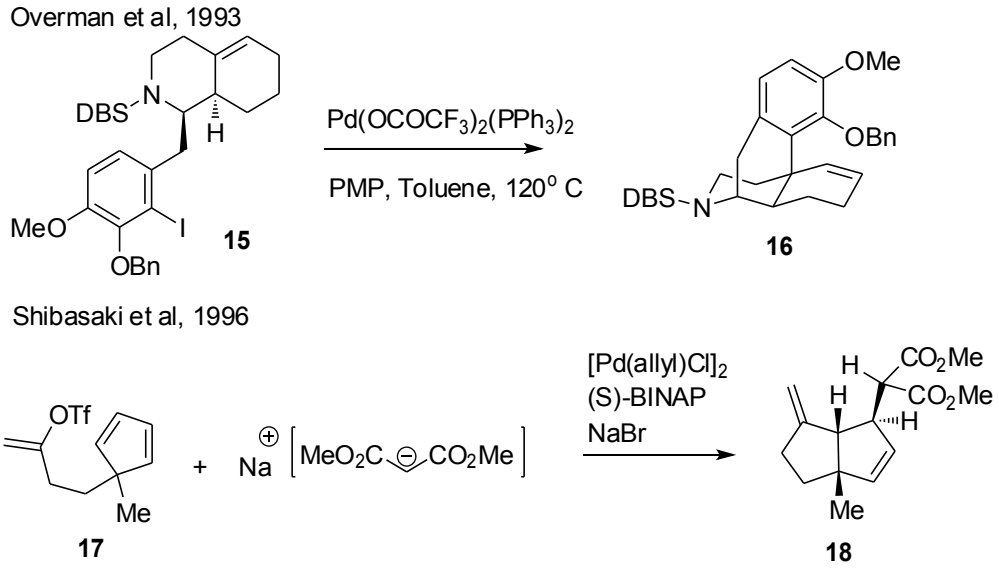
cyclization closures on the core skeletons.



13 **14**

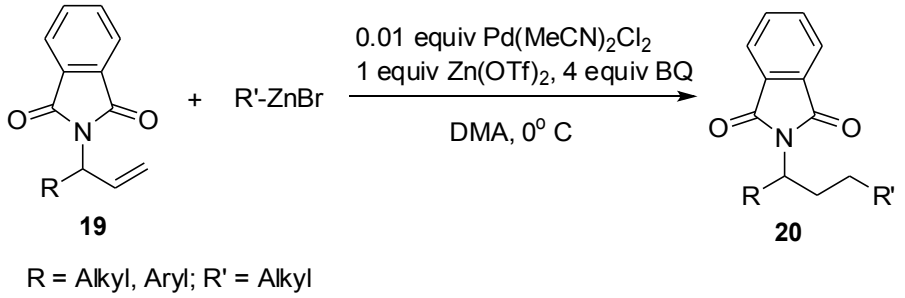
Scheme 5: Danishefsky Group Taxol Synthesis

For the Danishefsky synthesis of Taxol, this involved coupling of a terminal olefin and enol triflate for closure of the 8-membered central ring of **14 (**Scheme 5).[6] The Heck reaction was utilized after the previous failure to close the ring by both the Barbier reaction and Nozaki-Hiyama-Kishi coupling. Intermediate **13** was then synthesized containing both an enol triflate and an olefin intended to be the two partners for the Heck reaction. The exocyclic methylene was seen as the product due to the proclivity for triflate partners for Markovnikov addition and prefernce for the exocyclic addition to the olefin. The Heck reaction ring closure for **14** was the final step in completing the core structure and integral to their synthetic route.



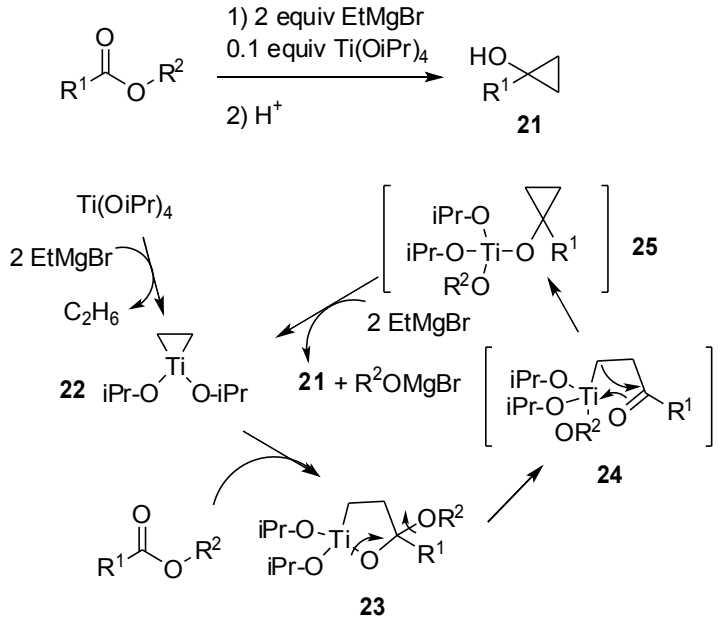
Scheme 6: Overman Group and Shibasaki Group Syntheses

In the Overman synthesis of morphine, Heck coupling is used to form the final 6-membered ring portion of the morphine skeleton (Scheme 6).[7] This approach for forming quaternary carbons in polycyclic structures was also used by their group for the synthesis of gelsemine.[8] The reaction creates a quaternary carbon center from the formation of a bond between the iodobenzene and the trisubstituted cyclic olefin of **15**. This approach to forming quartenary centers in polycyclic systems has been expanded through both tandem reactions by nucleophilic attack and use of chiral ligands to perform asymmetric versions of the Heck reaction. A great example is work by the Shibasaki group involving asymmetric Heck reactions with nucleophilic trapping to form chiral functionalized bicyclic systems from non-chiral starting materials in one step.[9]



Scheme 7: Sigman Group Alkylation

One drawback of the Heck reaction is that rapid β-hydride elimination occurs from the reaction intermediate in order to release the product. This causes the product to always be a reformed substituted olefin. As a result, the saturated product is normally not accessed under the Heck reaction conditions. Recently a report by the Sigman group has shown that usage of alkylzinc reagents is able to provide reductive coupling using palladium catalysis (Scheme 7).[10] The reaction reported by the Sigman group is applicable to both allylic amines and alcohols and yields the corresponding saturated product **20** from the insertion operation of the alkyl group of the alkylzinc reagent. Suppression of the undesired β-hydride elimination was thought to be from transmetallation of the zinc reagent to displace titanium in the intermediate analogous to **3**.

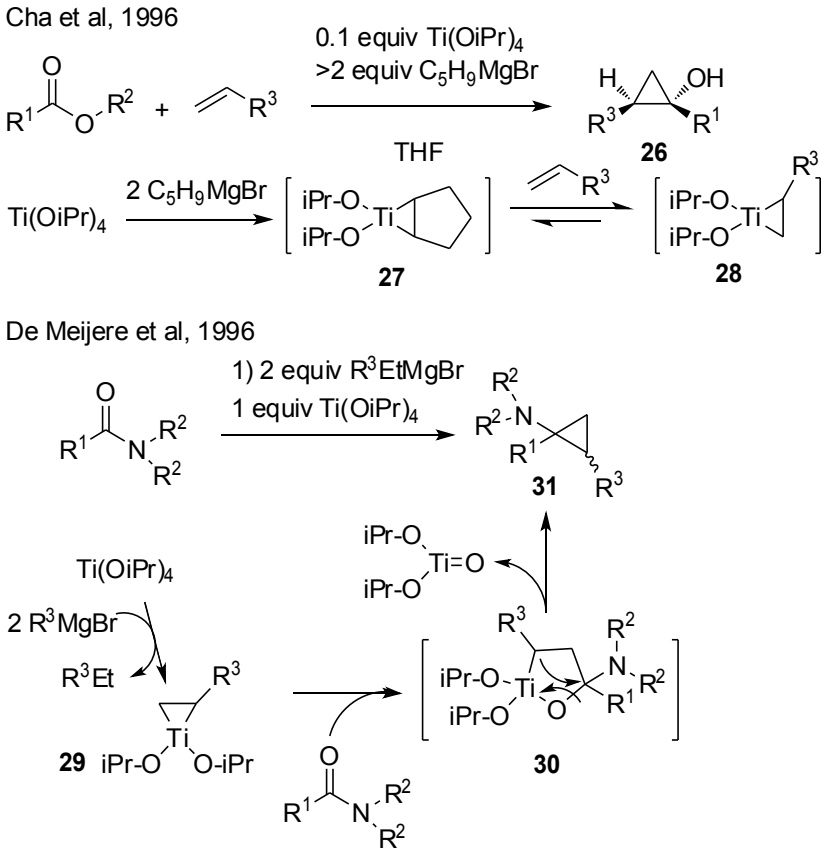


Scheme 8: Kulinkovich Reaction

The Kulinkovich cyclopropanation was reported in 1989 as a convenient method of synthesizing cyclopropanols from esters.[11] The reaction relies on activation of titanium alkoxides with Grignard reagents to generate the active titanocyclopropane **22** (Scheme 8). Insertion of the carbonyl bond into the weakest carbon-titanium bond gives the titanocycle intermediate **23** that is key to the reaction. From intermediate **23**, a rearrangement causes elimination of the ester substituent to advance to **24**. A second insertion of the newly formed ketone into the carbon-titanium bond occurs to yield the cyclopropanol **25**. The titanium alkoxide in **25** can then be displaced by more Grignard reagent to release the product as a magnesium alkoxide. The titanium alkoxide is then reactivated into the cyclopropyl titanium **22** to continue the catalytic cycle.

More substituted Grignard reagents are able to give more functionalized cyclopropanols as products. The resulting products were seen to give a pronounced bias for the *cis* isomer of the

product. This is attributed to an agostic interaction in intermediate **24** controlling the ring contraction step, which is disrupted when chelating substituents are introduced.[12] Interestingly, substrates preferentially underwent β-hydride elimination when an abstractable proton was present instead of regenerating to the cyclopropyl titanium **22**. These substrates required stoichiometric amounts of titanium added to the reaction due to the lack of turnover to the titanocyclopropane. Unfortunately, low selectivity in the ratio of *E* to *Z* isomers were seen in these cases.

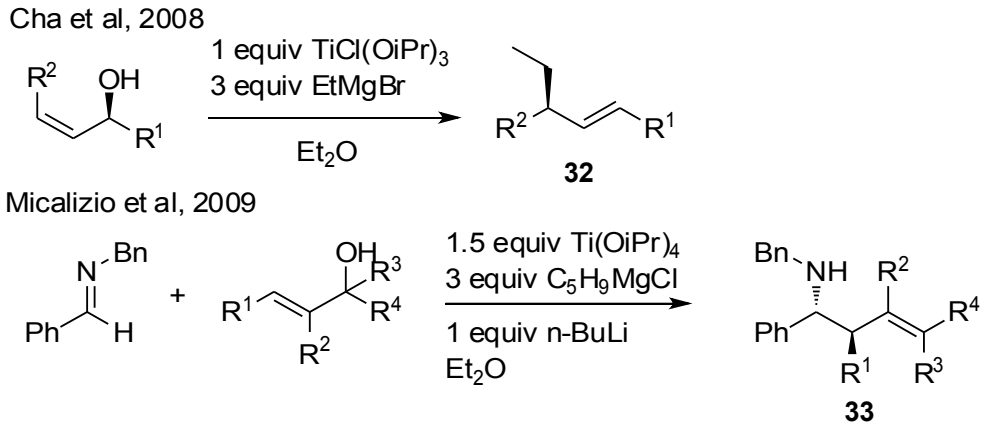


Scheme 9: Kulinkovich Reaction Modifications

Recent improvements to the Kulinkovich reaction by Cha and De Meijere have expanded the range of the reaction. The Cha group has shown that cyclopentyl Grignard can act as a

sacrificial reagent and undergo olefin exchange with a more valuable substituted olefin to generate a substituted titanocyclopropane **28**.[13] In this case, the cyclopentyl Grignard is used to generate the cyclopentyl bicyclometallocyclopropane **27** which then exchanges with the relevant olefin to be inserted to give the active reagent **28** (Scheme 9). This intermediate is then able to undergo the cyclopropanation as usual. By using the cyclopentyl Grignard as the activating reagent, the substituted olefin does not need to be used in excess nor does the analogous Grignard reagent need to be generated.

The De Meijere variant of the reaction has shown that amides can be utilized instead of esters to give the aminocyclopropane product **31**. A difference in the reaction is that the ring contraction occurs with loss of the oxotitanium from intermediate **30** rather than the amine in the key step (Scheme 9).[14] Unfortunately, the oxotitanium that is eliminated can not be regenerated into the active species **29** and 2 equivalents of the relevant Grignard reagent are necessary.



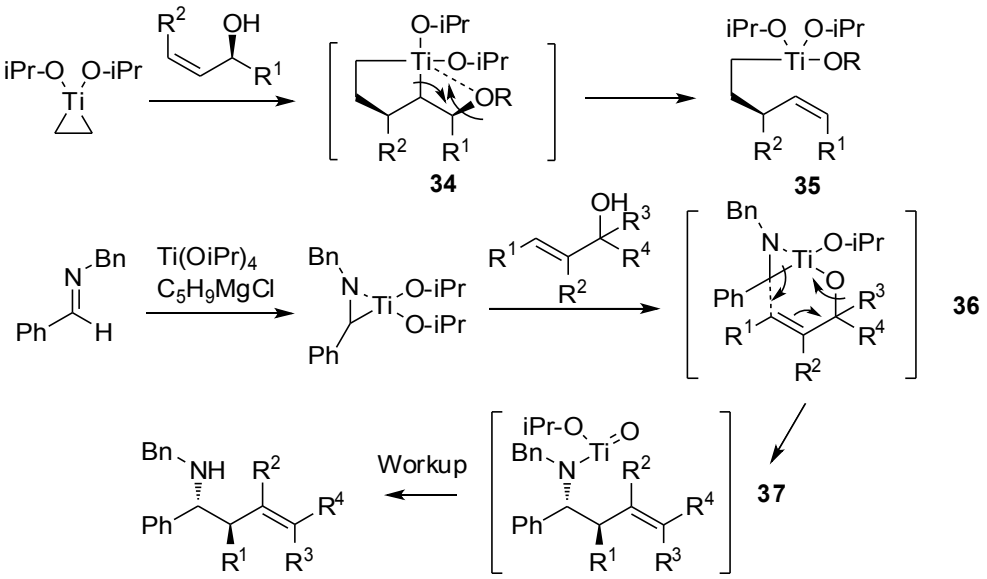
Scheme 10: Titanium-mediated Additions

As both titanium and and palladium are able to undergo migratory insertions and β-hydride eliminations, investigations into using titanium to mimick known reactions of palladium catalysis were undertaken. Extension of the reactivity of titanium alkoxides apart from cycloproponation has resulted in alkylations and imine cross-coupling reactions of allylic alcohols. These reactions are similar to the Heck reactions of olefins with directing groups although the coupling partners are somewhat different.

The Cha group has developed alkylation reactions of chiral allylic alcohols.[15] The ethylation reaction is able to install an ethyl substituent stereoselectively in the β position to create a new stereocenter (Scheme 10). The reaction proceeds in a diastereoselective manner to give a *syn* addition to form **34** (Scheme 11). Titanium alkoxide elimination proceeds to form the alkyl titanium **35** which is then worked up into the product **32**. The operation is similar to Heck coupling of enol carboxylates. The elimination of the titanium alkoxide is similar to loss of palladium acetates in Scheme 4. The drawback of this transformation is that the initial chiral alcohol center is lost during the reaction when elimination of the titanium alkoxide occurs. Turnover of the reaction is impossible because of this elimination; and the titanium reagent is required in stoichiometric quantity.

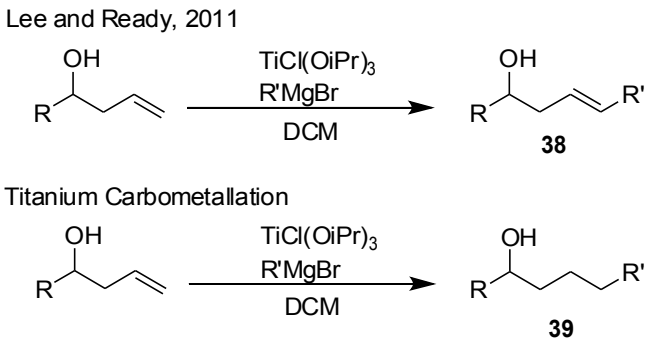
Micalizio and coworkers reported the reductive cross-coupling of allylic alcohols and imines as a pathway to access the homoallylic amines.[16] The imines were utilized as a surrogate for an olefin to undergo exchange with the initially formed intermediate **27**. The lithium alkoxide of the starting allylic alcohol needed to be preformed for addition to occur successfully; and a stoichiometric amount of the titanium is used due to formation of the titanium oxide which cannot be turned over. After the formation of **36**, Micalizio proposes a [3,3] metallo-

rearrangement in order to form the product intermediate **37** that is then worked up into the observed product. Evidence for the rearrangement lies in the stereochemical outcome of the reaction. The observed diastereoselectivity for the *trans* product and also the transfer of stereochemical information when the starting material is scalemic points to a chair-like transition state that minimizes the allylic strain and non-bonding interactions.



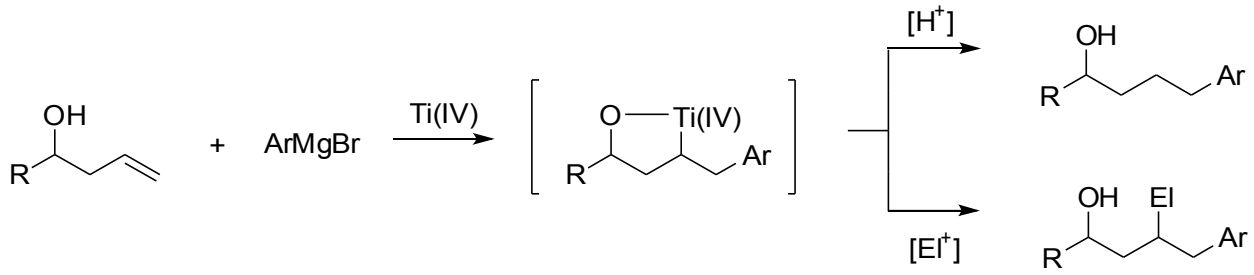
Scheme 11: Proposed Titanium Addition Mechanisms

The ability to suppress elimination reactions of titanacycle intermediates would allow for both saturated and possibly more advanced products to be accessed using titanium alkoxides. As both the β-hydride elimination and β-alkoxide eliminations have been observed to create unreactive titanium species, by preventing this process it is hoped the reactive titanacycle intermediate analogous to **34** can be preserved until workup. With the titanacycle in hand, it is possible that subsequent trapping with other reagents or a secondary transformation in the same pot could be performed.



Scheme 12: Titanium-mediated Oxidative Arylation and Carbometallation of Homoallylic Alcohols

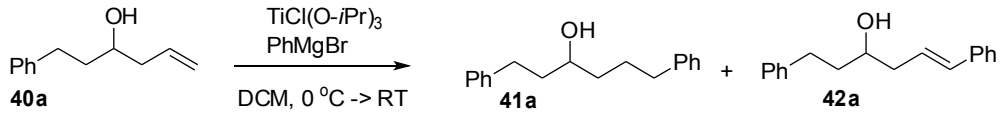
Previous work in the Ready group by Dr. Kathleen Lee on the titanium-mediated oxidative arylation of homoallylic alcohols had shown that the oxidative arylation product **38** is accessed across a broad range of substrates and Grignard reagents using excess titanium(IV) and aryl Grignard reagents (Scheme 12).[17] The reaction was thought to proceed with addition of an aryl titanium reagent across the olefin and then β-hydride elimination to give the *trans* olefin. In most cases, this elimination was rapid and as a consequence gave the oxidative arylation product **38** exclusively from the reaction. However, for certain conditions and substrates, the carbometallation product **39** was isolated in significant quantities. This realization pointed to the possibility that the β-hydride elimination was not occurring completely in all cases and that possibly a significant amount of a titanocycle intermediate was present in the reaction solution before final workup. If the β-hydride elimination could be slowed or prevented successfully, then workup would give exclusively the carbometallation product **39**. The possibility that additional reactions could be performed on the intermediate was also intriguing in order to develop more complex transformations or alternative trapping protocols.



Scheme 13: Electrophilic Trapping

The development of titanium carbometallation of homoallylic alcohols was pursued due to its novelty and potential utility. Reports of reductive hydroarylation in high selectivity or addition of two new substituents to an olefin through titanium-mediated addition were not present at the start of the project. As the reaction would result in functionalization with a new carbon-carbon single bond, the products possible with this reaction would be different than for Heck reactions or the titanium addition reactions reported by the Cha and Micalizio groups. This could prove valuable in the pursuit of more advanced products or similar products due to the ease with which the starting materials can be made. In addition if interception of the reaction intermediate with other reagents such as electrophiles was successful, the reaction has the potential to create additional complexity in the products and improve its scope and utility (Scheme 13).

The starting point for this investigation into the titanium-mediated carbometallation of homoallylic alcohols was the reaction utilizing 1-phenylhex-5-en-3-ol **40a** as the model substrate and addition of 1 equivalent each of the titanium chlorotriisopropoxide and the phenylmagnesium bromide Grignard reagent. The 1 equivalent of Grignard reagent needed to deprotonate for the active alkoxide species was held to be independent of the stoichiometry for the reaction. The initial conditions gave a conversion of 75 percent by GC and a 2:3 mixture of the carbometalation product **41a** and the oxidative arylation product **42a**.

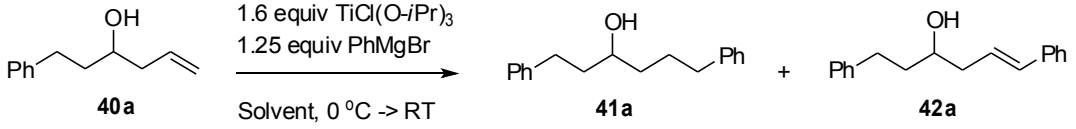


PhMgBr	$TiCl(OiPr)_3$	Conversion (GC)	Relative Yield (GC)	Relative Yield (GC)
1 equiv	1 equiv	75%	34%	66%
1.25 equiv	1.6 equiv	81%	82%	18%

Table 1: Stoichiometry Optimization

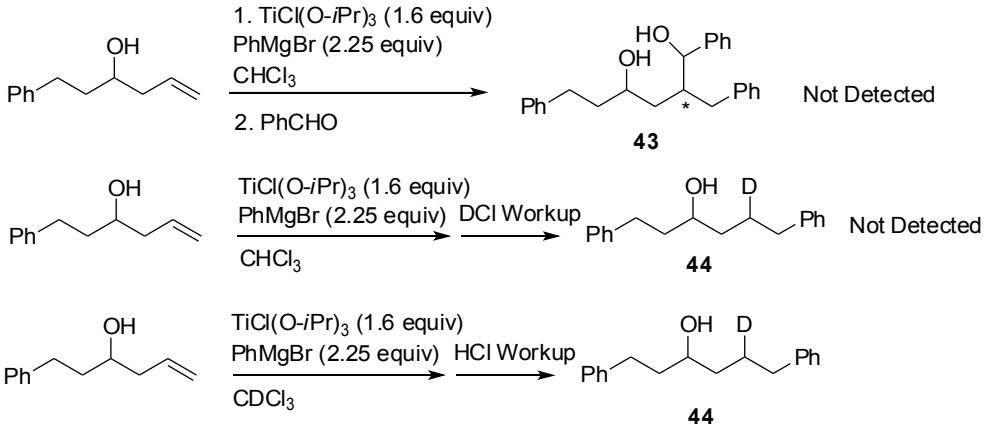
As the selectivity for the desired carbometallation product was low, varying the stoichiometry of the reaction was attempted first in order to boost the conversion and selectivity of the reaction (Table 1). Improving both the conversion and ratio of the carbometallation product was found to require excess amounts of both the titanium chlorotriisopropoxide and the phenyl Grignard reagent. A ratio of 1.6 equivalents of the titanium chlorotriisopropoxide to 1.25 equivalents of the phenylmagnesium bromide was found to give the best conversion of 81 percent. However, the ratio for the carbometallation product **41a** to the oxidative arylation

product **42a** still was only found to be 5 to 1.



Solvent	Conversion (GC)	Relative Yield (GC)	Relative Yield (GC)
Dichloromethane	81%	82%	18%
Toluene/Chloroform	97%	74%	26%
Dichoromethane/Chloroform	97%	70%	30%
Chloroform	65%	89%	11%

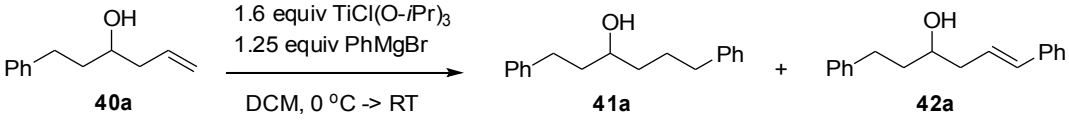
Table 2: Solvent Screen



Scheme 14: Trapping in Chloroform

Changing the solvent showed that coordinating polar solvents such as ethyl ether and tetrahydrofuran would shut the reaction down completely. Toluene was tolerated, but it hindered both the conversion of **40a** and formation of the desired carbometallation product **41a**. Chloroform was found to give a superior ratio for the carbometallation product of 9 to 1 (Table 2). The reaction was found to proceed in lower conversion of 65 percent but the best ratio

ascertained thus far. An attempt was made to trap the reaction with aldehydes as target electrophiles to access diol product **43** while using chloroform as the solvent(Scheme 14). However, no trapping was seen to the expected diol **43**. When workup with DCl was used, little incorporation of deuterium for **44** was also seen. Switching to run the reaction in $CDCl_3$ revealed that in situ quenching of the reaction was occurring as the product was deuterated even with a normal HCl workup.



40a **41a** **42a**

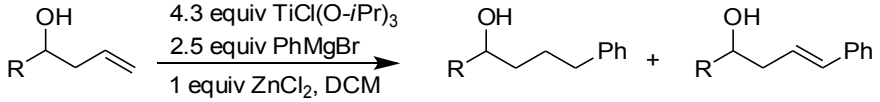
Additive	Conversion (GC)	Relative Yield (GC)	Relative Yield (GC)
1 equiv $CaCl_2$	>99%	21%	79%
1 equiv CuCl	>99%	49%	51%
1 equiv $CuCl_2$	49%	53%	47%
1 equiv LiCl	69%	32%	68%
1 equiv $ZnBr_2$	**64%**	**>99%**	**<1%**
1 equiv $ZnCl_2$	**96%**	**98%**	**2%**

Table 3: Additive Screening

After reverting back to using dichloromethane as the reaction solvent, additives were screened in order to make the reaction more selective. A screen of inorganic salts revealed that zinc dibromide and zinc dichloride gave excellent selectivity for the carbometallation product over the oxidative arylation with addition of 1 equivalent of the salts to the reaction (Table 3). As the zinc dibromide gave lower conversion, the zinc dichloride was chosen as the additive to be used subsequently. By adding 1 equivalent of zinc dichloride as an additive, the title reaction was

found to improve the carbometallation reaction from the model substrate **40a** to 75 percent yield and greater than 20 to 1 selectivity for **41a** over **42a** (Table 4). Addition of the zinc dichloride was found to slow the rate of the reaction significantly from the original reaction time of 4 hours before use an additive. By following the reaction with GC sampling, high conversion was found to require over 12 hours. In order for the maximum amount of starting material to be consumed, the reactions were required to be stirred for 2 days at room temperature for complete consumption of the homoallylic alcohol.

Scaling the procedure to 0.4 mmol scale with these conditions showed the isolated yields of the product were lower than that of the reactions on smaller scale. Yields were in the 50 to 60 percent range consistently after having been 70 to 80 percent when conducted on 0.1 mmol scale. The Cha group added additional titanium chlorotriisopropoxide before attempting trapping in order to sequester reactive magnesium oxides.[18] Addition of 3 equivalents of titanium chlorotriisopropoxide was added to the reaction before workup during attempts to trap with electrophiles. While this did not improve aldehyde trapping, in our case the yield of the regular carbometallation product **42a** was observed to be improved. This modification along with some tweaking of the stoichiometry to 1.3 equivalents of titanium chlorotriisopropoxide and 1.5 equivalents of Grignard reagent gave a much better yield upon scaleup and raised the yield to 90 percent for the title substrate.



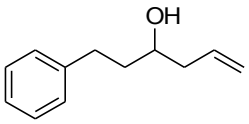
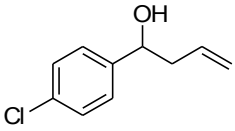
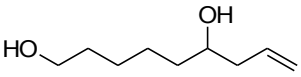
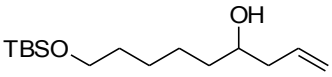
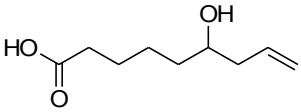
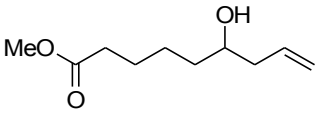
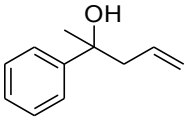
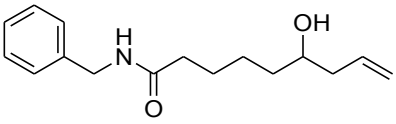
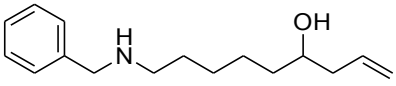
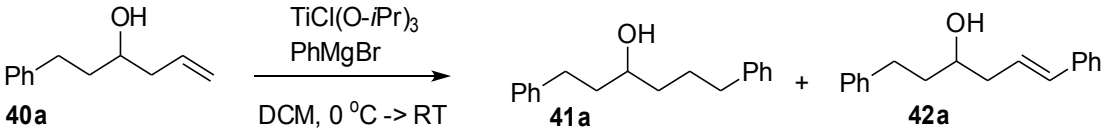
Substrate	Conversion	Yield	Selectivity
	>99%	90%	>20:1
	98%	88%	>20:1
	92%	88%	11:1
	>99%	59%	15:1
	93%	58%	9:1
	95%	50%	>20:1
	37%	13%	6:1
	>99%	24%	1:1
	78%	15%	1:1

Table 4: Substrate Scope

After settling on conditions for the model substrate, a second substrate, chlorophenyl butenol **40b**, was tested which contained an aryl homoallylic alcohol. The reaction proceeded smoothly and the desired product was isolated in 88 percent yield and >20:1 selectivity for the carbometallation product (Table 4). Additional substrates as indicated in Table 4 were tested at this time in order to establish the scope of starting materials that were compatible with the established reaction conditions. Tolerance of protected alcohols and esters was found to be good with somewhat lower yields and selectivities (**40e** and **40g**). When a second deprotonatable group was present on the substrate, such as an alcohol or carboxylic acid, the yield was impacted adversely along with selectivity (**40d** and **40f**). In mixed substrates with both an homoallylic alcohol and allylic alcohol, low selectivity between the possible products was present. This finding unfortunately showed that chemoselectivity for possibly differentiating between multiple allylic and homoallylic alcohols on a single substrate is unlikely. The reaction utilizing a tertiary homoallylic alcohol **40c**, proceeded with both low conversion and selectivity. The amide and amine substrates did not react well under the optimized reaction conditions to yield the desired carbometallation product selectively. This was surprising as these substrates had been amenable to the oxidative arylation version of the reaction previously.



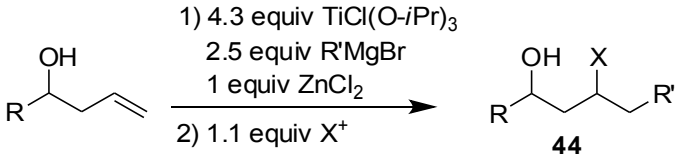
PhMgBr	$TiCl(OiPr)_3$	Conversion (GC)	Relative Yield (GC)	Relative Yield (GC)
1 equiv	0.5 equiv	45%	59%	41%
1.5 equiv	0.1 equiv	11%	40%	60%

Table 5: Catalytic Titanium Addition

From previously proposed mechanisms by Cha and Micalizio, the reaction was believed to be redox neutral for the titanium chlorotriisopropoxide during the titanium carbometallation reaction.[15,16] As the generation of the active titanium and subsequent addition keeps the titanium center in the +4 oxidation state, a transmetallation to zinc might release titanium halotriisopropoxide that could re-enter the catalytic cycle. Use of a catalytic amount of titanium chlorotriisopropoxide was attempted and showed turnover was not occurring. Catalytic amounts of titanium chlorotriisopropoxide caused the conversion to scale exactly to the amount of titanium chlorotriisopropoxide added. As the titanium reagent was unable to turnover, the titanium species was shown to not re-enter the catalytic cycle.

Chapter Three: Intermediate Trapping

After seeing that addition of DCl was able to trap for the deuterated product, usage of electrophiles was attempted in order to access more substituted products. Initially electrophiles were utilized as it was believed that the intermediate would be reactive enough to cause addition to a suitable electrophile. Unfortunately, initial trapping with aldehydes and acid chlorides showed that this was not the case and no reaction occurred. Heating the reactions resulted in the acetate products when acid chlorides were used. What eventually worked was addition of bromine or iodine to the crude solution in order to obtain the halohydrin products **44a** to **44d** (Table 6). The addition was found to proceed well at 0 ºC and to give good yields of 59 to 76 percent. One disappointment was that low diastereoselectivity was observed with ratios never becoming higher than 1:2.



44

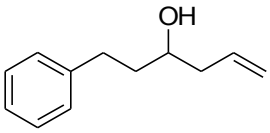
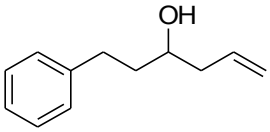
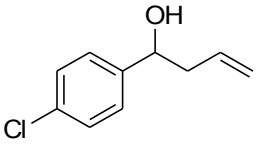
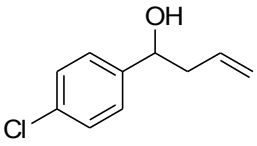
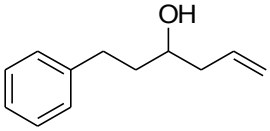
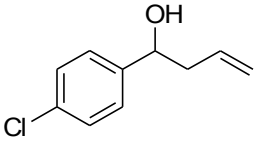
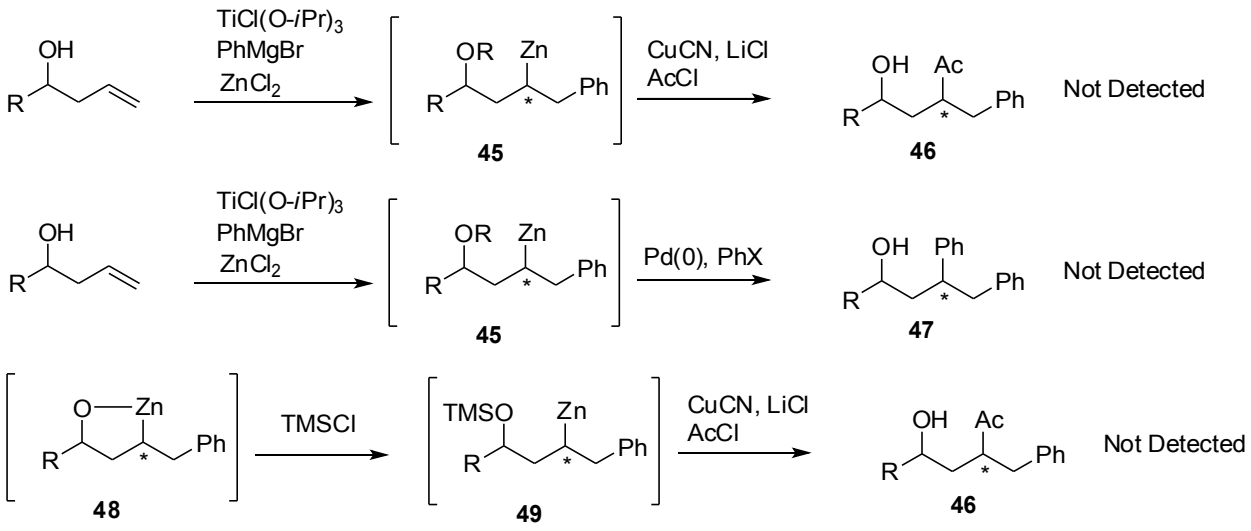
	Substrate	X^+ =	X=	Yield	Selectivity
44a		Br_2	Br	76%	1:1.3 dr
44b		I_2	I	72%	1:1.5 dr
44c		Br_2	Br	76%	1:1.9 dr
44d		I_2	I	59%	1:1.4 dr
44e		tBuOOH	OH	75%	1:1.1 dr
44f		tBuOOH	OH	55%	1:1.2 dr

Table 6: Successful Functionalizations

Other attempts to trap the reaction intermediate to provide useful products involved use of oxidants, azodicarboxylates, and transition metal-catalyzed cross-coupling. Oxidant screening found that tert-butyl zinc peroxide and tert-butyl hydroperoxide were able to oxidize the crude reaction mixture to the diol **44e**/**44f**. Yields were good for **44e** and **44f,** but the diastereoselectivity was low and only ratios near 1:1 were observed. Use of other oxidants such

as DDQ was found to give a mixture of products that were not cleanly converted. Azodicarboxylates were envisioned to be very reactive electrophiles in order to access aminoalcohol derivatives. Trapping was conducted as with the aldehydes and acid chlorides, but no isolation of the desired product occurred.



Scheme 15: Unsuccessful Cross-couplings

The final intermediate obtained by the carbometallation reaction was believed to be an alkylzinc species **53** due to transmetallation with the added zinc dichloride. This would give an alkylzinc species as the final intermediate before workup in order to explain the lack of β-hydride elimination. Alkylzinc species have been widely used as coupling partners in the Negishi coupling and also used for copper-catalyzed coupling with electrophiles.[19,20] Ideally, the reaction mixture would be transferred directly to the additional reagents needed for the cross coupling.

Use of Cu(I) has been demonstrated for the coupling of alkylzinc species and acid chlorides by the Rieke group.[19] In their work, alkylzinc reagents were generated through

oxidative insertions of zinc into carbon-halide bonds. As our intermediate is believed to already have the preformed zinc bond, the copper chloride, lithium chloride, and acid chloride coupling partner based on their conditions were added directly to the reaction mixture. No reactivity to generate **46** was seen even with use of THF as the solvent and heating to 80 ^{o}C (Scheme 15). Trimethylchlorosilane was utilized by the Heathcock group to disrupt zinc enolate bonds in their intermediates.[21] This approach was tried on the crude reaction mixture in case a zinc-oxygen bond of **48** was hindering coupling and the reaction was heated again with the relevant coupling reagents. Again, no reactivity was observed.

Negishi coupling of the intermediate with iodobenzene was attempted as an alternative coupling for the alkylzinc species **47**. Substituted alkylzinc partners have previously been reported to react in good yield with arylhalides using palladium catalysts.[20] The crude reaction mixture was transferred to a second flask with catalytic palladium triphenylphosphine and iodobenzene. No reactivity was observed after 4 hours stirring so the reaction was heated to 40 ^{o}C overnight (Scheme 15). After quenching, only the carbometallation product was recovered and none of the coupling product **47** was detected. Trimethylchlorosilane was again tried as an additive before attempting the coupling reaction and the mixture was stirred at 40 ^{o}C with the Negishi coupling reagents. Again, no additional products were observed after workup.

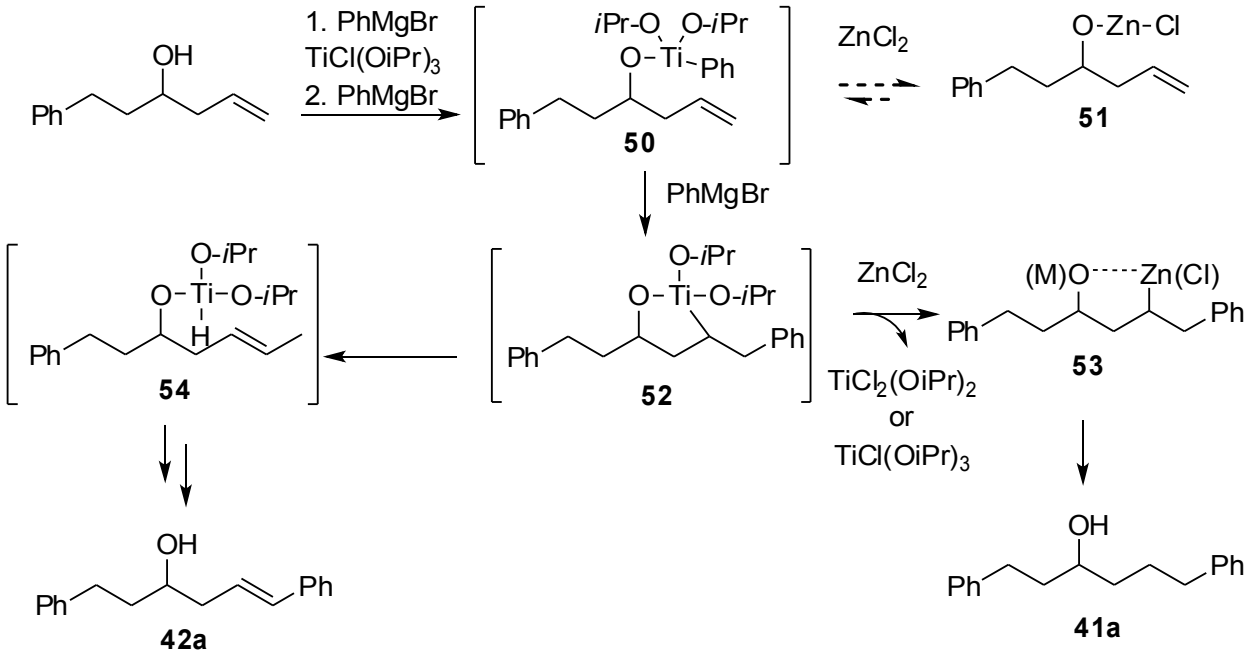
Chapter Four: Reactivity Encountered

The titanium-mediated carbometallation of homoallylic alcohols was found to be accessible under mild conditions and a limited amount of further advanced products resulted from addition of secondary reagents after reaction completion. Zinc dichloride was able to suppress the β-hydride elimination behavior that is usually seen with use of titanium isopropoxides after addition across the double bond. Substrate compatibility showed that the presence of an amide or amine group hindered conversion to the desired products. Tertiary homoallylic alcohols also exhibited low conversion from the starting material to the desired product. The halohydrin and diol products resulting from trapping of the intermediate resulted in low diastereoselectivity which differs from previously observed behavior for titanium-mediated addition reactions.

Mixed substrates containing both allylic alcohols and homoallylic alcohols were tested. The results showed that chemoselectivity in the reaction was low between the two possible pathways for addition. Surprisingly, tertiary homoallylic alcohols such as **40c** showed much lower conversion than expected and low selectivity between the carbometallation and oxidative arylation products. Deprotonatable groups were tolerated to an extent but both having another alcohol or having a carboxylic acid adversely affected the yield/selectivity to some extent.

The benzamide and benzamine substrates (**40h** and **40i**) were shown to have greatly reduced reactivity and no selectivity in the ratio of carbometallation to oxidative arylation products. As these substrates have performed well previously in the oxidative arylation reaction, it is unclear why they were not compatible with the conditions used successfully on the other

substrates.[17] As the carboyxlic acid, diol, and ester were all tolerated to a much better extent, chelation effects can probably be ruled out.



Scheme 16: Proposed Mechanism

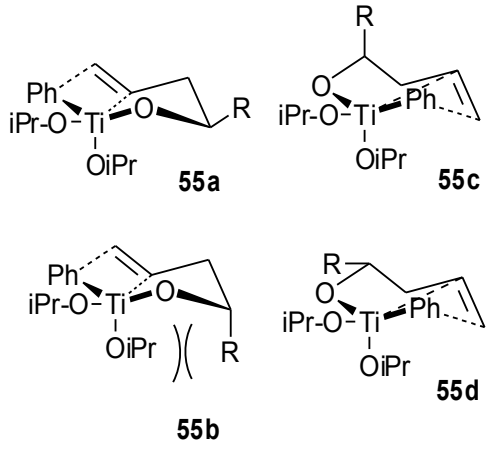
Initially, the reaction was believed to be redox neutral after insertion of the Grignard reagent and transmetallation from the titanium alkoxide **52** to the zinc alkoxide **53** (Scheme 15). Recently, the Ma group has reported a titanium-catalyzed asymmetric alkynylation that they believe involves a titanium to zinc transmetallation in order to turnover the reaction.[22] However, the lack of turnover exhibited in our reaction when using catalytic amounts of titanium chlorotriisopropoxide (Table 5) served to not support that an active titanium(IV) species is released by transmetallation to **53**. The specificity for zinc salts in the +2 oxidation state for suppression of β-hydride elimination posits that an equilibrium between the two metals is responsible for the proposed transmetallation.

A significant increase in the duration of the reaction from 4 hours to over 48 hours for conversion of the starting material to cease hints that the relative concentration of the reactive insertion intermediate **50** is lower when zinc chloride is added to the reaction (Scheme 16). Bearing this in mind, a working hypothesis is that transmetallation occurs rapidly between the zinc and titanium species **50** and **51** or **52** and **53** on a faster time scale than both the titanium insertion from **50** to **52** and β-hydride elimination from **52** to **54**. In situ quenching by deutero-chloroform (Scheme 14) reveals that the deuterium is attached in the β position for **44**. This supports that a metal-carbon bond exists in this position for the intermediate **52** or **53**.

The reaction scheme proposed by the Sigman group for their reported reductive coupling of homoallylic amines contains a transmetallation between an organopalladium species and an alkylzinc.[10] An analogous process is invoked for explaining intermediate **53** although in this case the zinc species is believed to displace the titanium isopropoxide. The lack of activity towards coupling conditions onward from **53** does not rule out the existence of an alkylzinc species as the predominant intermediate. As the reaction was carried through in order to perform the second coupling step in a pseudo one-pot process, there could be a surfeit of metals that is hindering any coupling to occur.

Trapping of the purported zinc intermediate **53** proved to require much more reactive conditions than expected. Initially, it was hoped that fairly common electrophiles such as aldehydes and acid chlorides could be added to provide the diol and hydroxyketone products. However, even with addition of chlorosilanes in order to ensure the alkylzinc species by breaking a possible zinc to oxygen bond, no trapping was seen to occur. As alkylzinc species are known to

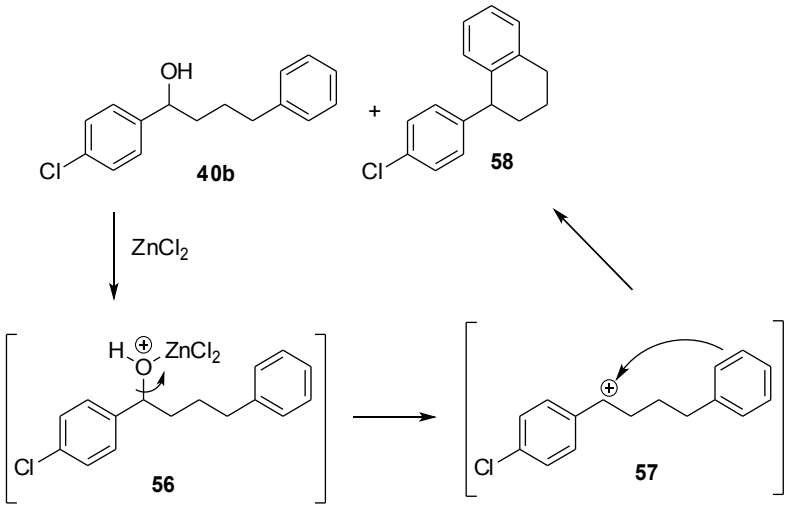
be somewhat less reactive than the corresponding magnesium reagents, the need for very active eletrophilic halides for reaction to occur is understandable. The stability of alkylzincs may be exploitable in order to perform careful purification to the pure alkylzinc species in order to perform the desired coupling reactions.



Scheme 17: Possible Transition States

Diastereoselectivity with all of the reagents that were able to trap the reaction intermediate was very dissapointing. In contrast to previously reported work by Kulinkovich, Cha, and Micalizio, little diastereoselectivity was seen when trapping by halides or oxidants was performed. As the trapping reactions are believed to occur with displacement of the metal-carbon bond in **52** or **53**, the indication is that the the formation of **52** may not occur diastereoselectively. This possibly causes **52** or **53** to form as a mixture of the syn and anti diastereomers after addition across the olefin. As there are no substituents on the olefin at the time of the migratory insertion, it is possible there is a lack of significant allylic strain to differentiate the possible conformers when undergoing the chair-like transition state proposed by Micalizio.[16] Drawing out the possible 7-membered transition states seems to indicate only 1 of the 4 possible diastereomers, **55b,** experiences allylic 1,3 strain and the amount of strain might

be tenous at best (Scheme 17). The reported styrene coupling of homoallylic alcohols by Cha also presents this issue, although substituted styrenes with chelating substituents were found to be a partial solution in their case.[23]



Scheme 18: Benzylic Cation Cyclization

An interesting side reaction was seen with the aryl homoallylic alcohol **40b**. By utilizing an acidic workup, the expected carbometallation was not recovered in high yield. Instead, a cyclized product **58** was obtained as the major product (Scheme 18). The occurrence of this product was unexpected, but a short literature search revealed that this behavior has been observed before by the Angle group.[24] $ZnCl_2$ was able to cause a benzylic cation cyclization reaction to occur when tested by the Angle group. During the workup, it is believed that free zinc salt was able to cause formation of a cationic intermediate **57** through loss of a zinc oxide. Workup with saturated Na_2SO_3 was found to be successful in preventing the cyclization to be the major product.

Chapter Five: Conclusion

In conclusion, addition of zinc dichloride as an additive allows for the titanium-mediated carbometallation of homoallylic alcohols with Grignard reagents. The zinc dichloride additive successfully inhibits the β-hydride elimination of the titanium intermediate. The unsaturated products are obtained in up to 90 percent yield and up to >20 to 1 ratio of the carbometallation to oxidative arylation products. Subsequent electrophilic trapping is possible with elemental halides to yield the respective halohydrin products or oxidation to yield the diol products. The reaction is tolerant of both alkyl and aryl substituents on the homoallylic alcohol. This reaction allows ready access to unsaturated secondary alcohols or further functionalized products from an initial homoallylic alcohol.

Future work that is possible for further improvements on this reaction lie in improving the several results that were less than ideal and possibly extending the scope of the reaction further. Substrates such as tertiary homoallylic alcohols, benzamides, and benzamines need to be tested again to see if their failure to react as expected is something that can be fixed. Hydroalkylation is an additional reaction mode that needs to be explored for compatibility of alkyl Grignard reagents. Internal homoallylic alcohols or chelating aryl Grignards also could be interesting cases to see if diastereoselectivity can be obtained by influencing the hypothesized transition state. The addition of chiral ligands to the reaction would be interesting to try and form an enantioselective version of the reaction when stereocenters are formed if diastereoselectivity is not enforceable.

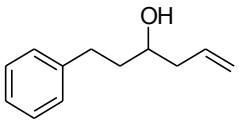
The coupling reactions could be revisited by attempting purifications under inert atmosphere to remove the extraneous chemical species at the end of the reaction sequence. This would presumably give the active alkylzinc intermediate without having the remaining titanium and magnesium byproducts in the solution. Investigating if any reagents could turnover the reaction and regenerate the active titanium species could be an alternative solution to decreasing the amount of other metals left after the reaction. This would decrease the titanium loading and be applicable to related reactions that require stoichiometric quantities of the titanium isopropoxides..

Appendix One: Experimental Details

General Experimental**:**

All reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. Zinc dichloride was fused using a butane torch under vacuum before the addition of other reagents. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Yields were reported with adjustment for recovered starting material. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography (TLC) and/or gas chromatography (GC). TLC analysis was performed with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). GC was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID
detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies. 1H and 13C NMR spectra were recorded on Varian Inova-500 or Inova-400 spectrometer in CDCl3 unless otherwise specified. Chemical shifts are reported relative to internal chloroform (CDCl3: 1H, δ = 7.26, 13C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet), sep (septet), and m for multiplet. For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Low-resolution mass spectra were acquired on an Agilent 1100 Series LC/MS equipped with a ZORBAX Eclipse XDB-C18 analytical column from Agilent (4.6 x 150mm, 5μm, Part #: 993967-902) and attached to an MSD VL series mass detector equipped with an electrospray ionization source (ESI).

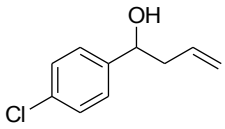
General Procedure for Synthesis of Homoallylic Alcohols **40** from Corresponding Aldehydes:

40a) 

3-phenyl-propionaldehyde (95%, 677 mg, 5 mmol) was dissolved in 10 ml of dichloromethane under nitrogen atmosphere. The solution was then cooled to -78° C and 1.2 equivalents (6 ml, 1M in diethyl ether) of allyl magnesium bromide was added slowly by syringe pump over 1 hour. The solution was allowed to warm to room temperature and stirred for an additional 7 hours. The reaction was quenched by addition of 20 ml of 1M HCl and stirred for 15 min. The organic layer was then seperated and the remaining aqueous layer was extracted by 2x20ml portions of dichloromethane. The organic layers were then pooled and dried over Na_2SO_4. The solution was filtered and solvent removed by rotary evaporation. Flash chromatography of the residue using a gradient of 5% to 15% EtOAc in hexanes yielded 792 mg (90%) of 1-phenyl-hex-5-en-3-ol **40a**.

1H NMR (500 MHz): δ 7.40 – 7.21 (m, 5H), 5.97 – 5.80 (m, 1H), 5.26 – 5.13 (m, 2H), 3.73 (d, J = 3.2, 1H), 2.81 (tdd, J = 15.1, 11.5, 7.7, 2H), 2.45 – 2.20 (m, 2H), 2.09 (s, 1H), 1.93 – 1.77 (m, 2H).

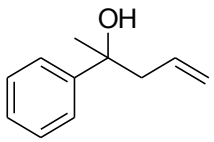
13C NMR (126 MHz): δ 32.34, 38.73, 42.35, 70.29, 118.40, 126.11, 128.72, 135.00, 142.39.

40b) 

4-chlorophenyl-benzaldehyde (98%, 1.406 g, 10 mmol) and 11 ml of 1M allylmagnesium bromide in diethyl ether yielded 1.706 g (93%) of 1-(4-chlorophenyl)-but-3-en-1-ol **40b**.

1H NMR (400 MHz): δ 7.39 – 7.19 (m, 5H), 5.77 (dt, J = 16.9, 7.2, 1H), 5.17 (d, J = 4.8, 1H), 4.74 – 4.68 (m, 1H), 2.55 – 2.38 (m, 2H),.

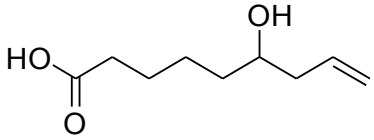
13C NMR (101 mhz): δ 44.07, 72.80, 119.04, 127.46, 128.74, 133.34, 134.23, 142.54.

40c) 

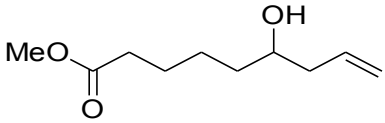
Acetophenone (99%, 600mg, 5 mmol) and 5.5 ml of 1M allylmagnesium bromide in diethyl ether yielded 443 mg (54.6%) of 2-phenylpent-4-en-2-ol **40c**.

1H NMR (400 MHz) δ 7.52 – 7.17 (m, 5H), 5.73 – 5.52 (m, 1H), 5.23 – 5.05 (m, 2H), 2.69 (dd, *J* = 13.6, 6.3, 1H), 2.59 – 2.42 (m, 1H), 2.00 (s, 1H), 1.55 (d, *J* = 3.3, 4H).

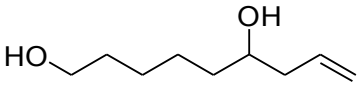
13C NMR (101 MHz) δ 147.83, 133.88, 128.40, 126.84, 124.98, 119.74, 77.58, 77.26, 76.95, 73.85, 48.68, 30.14.

40d) 

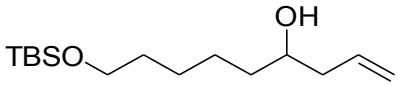
Synthesized as previously reported.[17]

40e) 

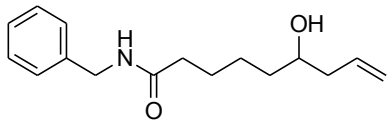
Synthesized as previously reported.[17]

40f) 

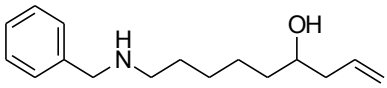
Synthesized as previously reported.[17]

40g) 

Synthesized as previously reported.[17]

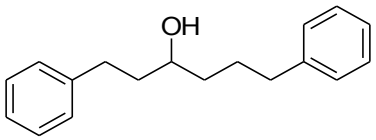
40h) 

Synthesized as previously reported.[17]

40i) 

Synthesized as previously reported.[17]

General Procedure for Titanium-mediated Carbometallation of Homoallylic Alcohols **41**:

41a) 

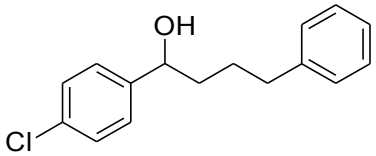
$ZnCl_2$ (98%, 0.4mmol, 52 mg, 1 equivalent) was fused under vacuum with a butane torch. After cooling under vacuum, nitrogen was used to fill the flask before addition of 1-phenyl-hex-5-en-3-ol **40a** (72mg, 0.4mmol) and 2 ml of dichloromethane. The solution was cooled to 0^o C and 1 equivalent of phenylmagnesium bromide (0.4 mmol, 133 ul, 3M in diethyl ether) was added to the solution. The solution was stirred for 5 min before addition of $TiCl(OiPr)_3$ (95%, 130 ul, 0.52 mmol, 1.3 equivalents). The solution was stirred for 30 min with warming to room temperature and then recooled to 0^o C. An additional 1.5 equivalents of phenyl magnesium bromide (0.6 mmol, 200 ul, 3M in diethyl ether) was then added to the solution. The solution was stirred for

38 hours as a dark brown color evolved. An additional 3 equivalents of $TiCl(OiPr)_3$ (300 ul, 1.2 mmol) was added and the reaction was stirred for 4 hours at room temperature. The reaction was quenched by addition of 4 ml 1M HCl and stirred until all solids were dissolved. The organic layer was seperated and the aqueous layer was extracted by an additional 3x8 ml portions of dichloromethane. The organic layers were pooled and dried over Na_2SO_4 before filtration and rotary evaporation of the solvent. The residue was flash chromatographed using a gradient of 5% to 15% EtOAc in hexanes to yield 92 mg (90.2%) of 1,6-diphenyl-hexan-3-ol **41a**.

1H NMR (500 MHz) δ 7.39 – 7.14 (m, 9H), 3.76 – 3.61 (m, 1H), 2.82 (dd, *J* = 9.5, 5.6, 1H), 2.78 – 2.57 (m, 3H), 1.91 – 1.64 (m, 4H), 1.64 – 1.43 (m, 3H).

13C NMR (126 MHz) δ 142.62, 142.41, 128.88, 128.79, 128.72, 128.63, 126.42, 126.13, 126.08, 77.65, 77.40, 77.14, 71.48, 39.36, 37.38, 36.16, 32.35, 27.76.

EI-MS: Calc. 254.37, Found 234.

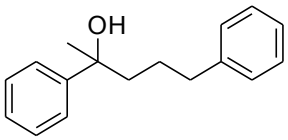
41b) 

73 mg of **41a** yielded 79 mg (75.7%) of 1-(4-chlorophenyl)-4-phenylbutan-1-ol **41b**.

1H NMR (500 MHz) δ 7.43 – 7.13 (m, 12H), 4.70 – 4.60 (m, 0H), 2.66 (t, *J* = 7.2, 1H), 1.88 – 1.68 (m, 3H), 1.61 (dd, *J* = 10.8, 7.5, 1H).

13C NMR (126 MHz) δ 143.39, 142.36, 133.37, 128.86, 128.84, 128.81, 128.69, 128.63, 127.57, 127.51, 126.11, 77.62, 77.37, 77.11, 74.05, 74.03, 38.85, 35.96, 27.74.

EI-MS: Calc. 260.76, Found 240.9.

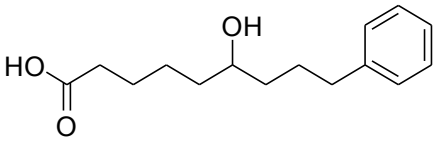
41c) 

66 mg of **40c** yielded 34 mg (36.6%) of 2,5-diphenylpentan-2-ol **41c**.

1H NMR (400 MHz, cdcl3) δ 7.55 – 6.98 (m, 21H), 5.61 (d, *J* = 8.3, 1H), 5.24 – 5.00 (m, 2H), 2.77 – 2.38 (m, 5H), 1.92 – 1.72 (m, 3H), 1.72 – 1.35 (m, 15H), 1.25 (s, 3H).

13C NMR (101 MHz) δ 148.00, 147.82, 142.44, 133.86, 128.72, 128.59, 128.46, 128.39, 128.36, 127.60, 126.93, 126.84, 126.76, 126.41, 125.92, 125.24, 124.97, 124.95, 119.75, 77.56, 77.24, 76.92, 74.86, 74.37, 73.84, 48.66, 43.88, 36.25, 30.48, 30.15, 25.98.

EI-MS: Calc. 240.34, Found 221.

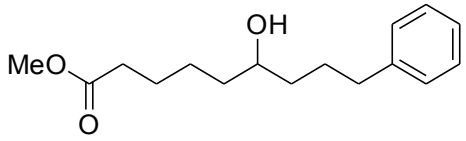
41d) 

69 mg of **40d** yielded 88mg (88%) of 6-hydroxy-9-phenylnonanoic acid **41d.**

1H NMR (500 MHz) δ 7.46 – 7.10 (m, 2H), 3.63 (dd, *J* = 12.3, 6.0, 2H), 2.73 – 2.54 (m, 1H), 2.24 (s, 0H), 1.62 – 1.29 (m, 2H).

13C NMR (101 MHz) δ 142.66, 133.05, 128.88, 128.86, 128.83, 128.81, 128.76, 128.71, 128.62, 128.58, 128.50, 127.44, 126.29, 125.93, 77.67, 77.35, 77.03, 71.74, 71.26, 62.74, 41.42, 37.52, 37.25, 36.99, 36.13, 32.79, 27.73, 25.96, 25.65, 25.59, 25.57.

EI-MS: Calc. 250.33, Found: 217.

41e) 

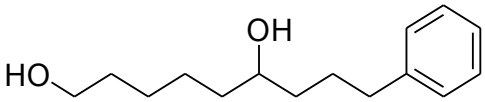
75 mg of **40e** yielded 63 mg (59.4%) of methyl 6-hydroxy-9-phenylnonanoate **41e**.

1H NMR (400 MHz) δ 7.32 – 7.10 (m, 6H), 3.70 – 3.53 (m, 4H), 2.68 – 2.54 (m, 2H), 2.31 (t, *J* = 7.4, 2H), 1.84 – 1.72 (m, 1H), 1.72 – 1.53 (m, 5H), 1.45 (qdd, *J* = 11.6, 8.5, 4.0, 6H), 1.37 – 1.15 (m, 3H).

13C NMR (101 MHz) δ 174.40, 142.55, 128.79, 128.61, 128.52, 128.35, 126.21, 125.96, 77.56, 77.24, 76.92, 71.75, 51.75, 37.26, 37.23, 36.08, 34.20, 29.92, 27.69, 25.38, 25.06.

EI-MS: Calc. 264.36, Found 235.

41f)



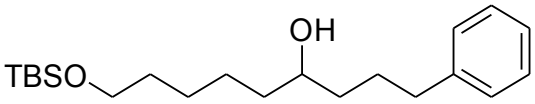
56 mg of **40f** yielded 59 mg (58.1%) of 9-phenylnonane-1,6-diol **41f**.

1H NMR (400 MHz) δ 7.45 – 7.00 (m, 5H), 3.64 (dd, *J* = 11.8, 6.5, 3H), 2.62 (t, *J* = 7.6, 1H), 2.32 (s, 1H), 1.71 – 1.10 (m, 19H), 0.95 – 0.73 (m, 2H).

13C NMR (101 MHz) δ 128.76, 128.61, 128.51, 126.30, 125.95, 104.98, 77.55, 77.23, 76.91, 71.95, 63.13, 41.44, 37.58, 37.28, 36.10, 32.89, 29.92, 27.69, 25.98, 25.71, 25.61.

EI-MS: Calc. 236.35, Found 201.

41g)

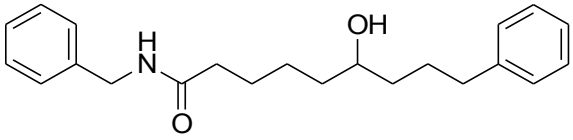


100mg of **40g** yielded 53 mg (50%) of 9-((tert-butyldimethylsilyl)oxy)-1-phenylnonan-4-ol **41g**.

1H NMR (500 MHz) δ 7.38 – 7.14 (m, 2H), 3.63 (t, *J* = 6.5, 2H), 2.66 (d, *J* = 2.3, 1H), 1.87 – 1.62 (m, 0H), 1.63 – 1.28 (m, 1H), 0.92 (s, 2H), 0.08 (s, 1H).

13C NMR (126 MHz) δ 142.66, 128.67, 128.55, 125.98, 77.56, 77.30, 77.05, 72.04, 63.46, 37.73, 37.27, 36.17, 33.07, 27.77, 26.26, 26.13, 25.70, 18.66, -4.98.

EI-MS: Calc. 350.61, Found 201.

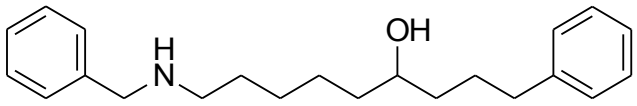
41h) 

105 mg of **40h** yielded 33 mg (24.3%) of N-benzyl-6-hydroxy-9-phenylnonanamide **41h.**

1H NMR (400 MHz) δ 7.29 (ddd, *J* = 12.9, 12.4, 6.0, 6H), 4.40 (d, *J* = 5.6, 3H), 3.71 (d, *J* = 4.2, 1H), 2.61 (s, 0H), 2.53 – 2.12 (m, 0H), 1.87 – 1.31 (m, 1H).

13C NMR (101 MHz) δ 173.40, 173.38, 138.50, 137.46, 133.22, 129.69, 129.04, 129.02, 128.99, 128.92, 128.88, 128.85, 128.78, 128.74, 128.72, 128.69, 128.67, 128.64, 128.60, 128.55, 128.53, 128.49, 128.48, 128.35, 128.20, 128.18, 128.15, 128.07, 128.04, 128.01, 127.99, 127.77, 127.73, 127.62, 127.53, 127.49, 127.46, 126.59, 126.41, 126.38, 126.36, 126.32, 125.95, 120.00, 115.71, 77.63, 77.32, 77.05, 77.00, 71.63, 71.07, 43.99, 43.82, 41.44, 37.28, 37.14, 36.77, 36.72, 36.69, 36.58, 36.11, 27.74, 25.73, 25.70, 25.67, 25.51, 25.46, 25.44.

EI-MS: Calc. 339.47, Found 338.

41i) 

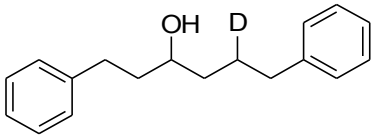
100 mg of **40i** yielded 26 mg (15.3%) of 9-(benzylamino)-1-phenylnonan-4-ol **41i**.

1H NMR (400 MHz) δ 7.42 – 7.12 (m, 29H), 4.42 (d, *J* = 5.6, 0H), 3.79 (s, 0H), 3.60 (d, *J* = 86.5, 1H), 2.76 – 2.51 (m, 0H), 2.51 – 2.13 (m, 0H), 1.41 (ddd, *J* = 80.7, 41.1, 14.2, 1H).

13C NMR (101 MHz) δ 137.47, 133.25, 129.73, 129.47, 128.95, 128.77, 128.73, 128.71, 128.63, 128.61, 128.57, 128.55, 128.52, 128.44, 128.08, 127.76, 127.51, 127.48, 127.44, 126.62, 126.32, 125.95, 120.03, 115.77, 77.60, 77.28, 76.97, 71.23, 53.89, 49.12, 43.86, 41.46, 41.44, 41.43, 36.96, 36.77, 29.70, 27.41, 25.71.

EI-MS: Calc. 325.49, Found 324.

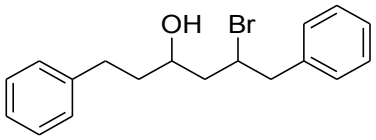
44)



1H NMR (500 MHz) δ 7.35 – 7.15 (m, 9H), 3.66 (s, 1H), 2.87 – 2.57 (m, 4H), 1.89 – 1.67 (m, 4H), 1.64 – 1.48 (m, 3H).

General Procedure for Titanium-mediated Carbometallation of Homoallylic Alcohols with Trapping to Substituted Alcohols **44**:

44a)



$ZnCl_2$ (0.4 mmol, 52 mg, 1 equivalent) was fused under vacuum with a butane torch. After cooling under vacuum, nitrogen was used to fill the flask before addition of 1-phenyl-hex-5-en-3-ol (72mg, 0.4 mmol) and 2 ml of dichloromethane. The solution was cooled to 0° C and 1 equivalent of phenylmagnesium bromide (135 ul, 3M in diethyl ether) was added to the solution. The solution was stirred for 5 min before addition of $TiCl(OiPr)_3$ (95%, 130 ul, 0.52 mmol, 1.3 equivalents). The solution was stirred for 30 min with warming to room temperature and then recooled to 0° C. An additional 1.5 equivalents of phenyl magnesium bromide (200 ul, 3M in

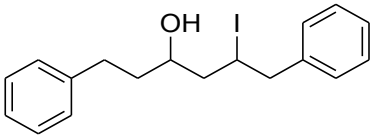
diethyl ether) was then added to the solution. The solution was stirred for 2 days as a dark brown color evolved. The reaction was cooled to 0° C and 1.5 equivalents of bromine (15 ul) was added to the reaction. The solution was stirred for 4 hours at 0° C before addition of 4 ml Na_2SO_3 solution. The solution was stirred for 2 hours before the organic layer was seperated and the aqueous layer was extracted by an additional 2x4 ml portions of diethyl ether. The organic layers were pooled and dried over Na_2SO_4 before filtration and rotary evaporation of the solvent. The residue was flash chromatographed using a gradient of 5% to 15% EtOAc in hexanes to yield 96 mg (76%) of 1,6-diphenyl-5-bromo-hexan-3-ol **44a**. Seperation of diastereomers required use of prep-HPLC.

1H NMR (500 MHz) δ 7.48 – 7.11 (m, 47H), 4.62 – 4.51 (m, 1H), 4.40 – 4.26 (m, 3H), 4.11 – 4.01 (m, 1H), 3.95 (s, 3H), 3.35 – 3.10 (m, 7H), 2.87 – 2.61 (m, 11H), 2.21 – 2.03 (m, 6H), 2.00 – 1.67 (m, 18H).

13C NMR (126 MHz) δ 129.51, 128.73, 128.65, 127.20, 126.22, 77.53, 77.28, 77.02, 70.37, 54.11, 45.91, 45.81, 38.80, 31.89.

EI-MS: Calc. 333.26, Found 356.8.

44b)

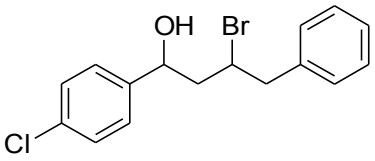


72 mg of **40a** with iodine trapping yielded 105 mg (72%) of 5-iodo-1,6-diphenylhexan-3-ol **44b**.

1H NMR (400 MHz) δ 7.40 – 7.06 (m, 10H), 4.61 – 4.46 (m, 0H), 4.31 (dd, *J* = 13.7, 7.5, 0H), 4.20 – 4.03 (m, 0H), 3.92 (ddd, *J* = 24.6, 8.6, 5.6, 1H), 3.39 – 3.28 (m, 0H), 3.21 (dd, *J* = 10.7, 7.1, 1H), 2.86 – 2.53 (m, 2H), 2.25 – 2.10 (m, 1H), 2.10 – 1.93 (m, 1H), 1.90 – 1.72 (m, 2H), 1.72 – 1.56 (m, 2H).

13C NMR (101 MHz) δ 183.38, 141.98, 141.90, 139.78, 139.67, 129.30, 129.25, 128.80, 128.73, 128.72, 128.71, 128.63, 128.58, 127.57, 127.14, 127.10, 126.35, 126.22, 126.19, 126.10, 104.98, 77.61, 77.29, 76.97, 71.70, 71.63, 70.64, 60.68, 48.14, 47.46, 47.29, 46.76, 41.54, 39.55, 38.78, 38.58, 35.85, 33.18, 32.40, 31.82, 14.45.

EI-MS: Calc. 380.26, Found 402.8.

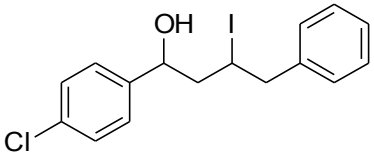
44c) 

73 mg of **40b** yielded 103 mg (76%) of 3-bromo-1-(4-chlorophenyl)-4-phenylbutan-1-ol **44c**. Seperation of diastereomers required use of prep-HPLC.

1H NMR (500 MHz) δ 7.45 – 7.12 (m, 10H), 5.02 (d, *J* = 10.3, 2H), 4.58 (d, *J* = 1.9, 2H), 3.92 (dd, *J* = 10.4, 4.3, 2H), 3.66 (t, *J* = 9.8, 2H), 3.22 (dd, *J* = 15.7, 7.0, 1H), 2.66 – 2.39 (m, 2H), 2.21 – 1.82 (m, 6H).

13C NMR (126 MHz) δ 129.47, 129.12, 128.70, 127.92, 127.21, 77.53, 77.27, 77.02, 72.91, 53.01, 46.70, 45.82.

EI-MS: Calc. 339.65, Found 351.9.

44d) 

73 mg of **40b** with iodine trapping yielded 90 mg (59%) of 1-(4-chlorophenyl)-3-iodo-4-phenylbutan-1-ol **44d.**

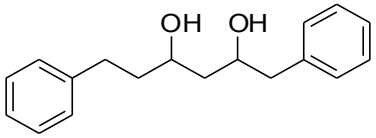
1H NMR (400 MHz) δ 7.42 – 7.00 (m, 15H), 4.90 (dd, *J* = 7.9, 6.0, 1H), 4.11 (d, *J* = 7.1, 0H),

3.86 – 3.73 (m, 1H), 3.28 – 3.07 (m, 2H), 2.68 – 2.53 (m, 1H), 2.45 – 2.31 (m, 1H), 2.06 (ddd, *J* = 12.2, 7.9, 3.4, 2H), 1.25 (t, *J* = 7.1, 1H).

13C NMR (101 MHz) δ 183.42, 142.51, 141.48, 139.40, 137.20, 134.11, 134.04, 129.18, 129.10, 128.82, 128.81, 128.76, 128.69, 127.94, 127.70, 127.44, 127.16, 126.40, 125.50, 77.59, 77.28, 76.96, 74.24, 73.23, 47.83, 47.49, 43.32, 32.21.

EI-MS: Calc. 386.66, Found 240.9.

44e)



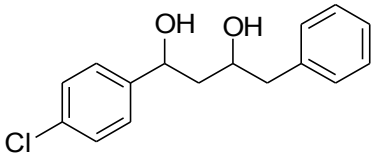
72 mg of **40a** with tert-butyl hydroperoxide trapping yielded 81 mg (75%) of 1,6-diphenylhexane-2,4-diol **44e**.

1H NMR (400 MHz) δ 7.43 – 7.07 (m, 22H), 4.18 (tt, *J* = 12.0, 5.8, 1H), 4.12 – 3.96 (m, 2H), 3.96 – 3.78 (m, 1H), 2.89 – 2.54 (m, 8H), 2.29 (d, *J* = 17.0, 7H), 1.96 – 1.49 (m, 10H), 1.35 – 1.16 (m, 2H).

13C NMR (101 MHz) δ 142.20, 129.65, 129.58, 128.89, 128.68, 128.65, 128.62, 126.89, 126.85, 126.09, 126.05, 77.57, 77.25, 76.93, 74.22, 72.20, 70.49, 69.02, 44.93, 44.28, 42.59, 42.13, 39.78, 39.26, 32.43, 31.90.

EI-MS: Calc. 270.37, Found 235.

44f)



73 mg of **40b** with tert-butyl hydroperoxide trapping yielded 61mg (55%) of 1-(4-chlorophenyl)-

4-phenylbutane-1,3-diol **44f**.

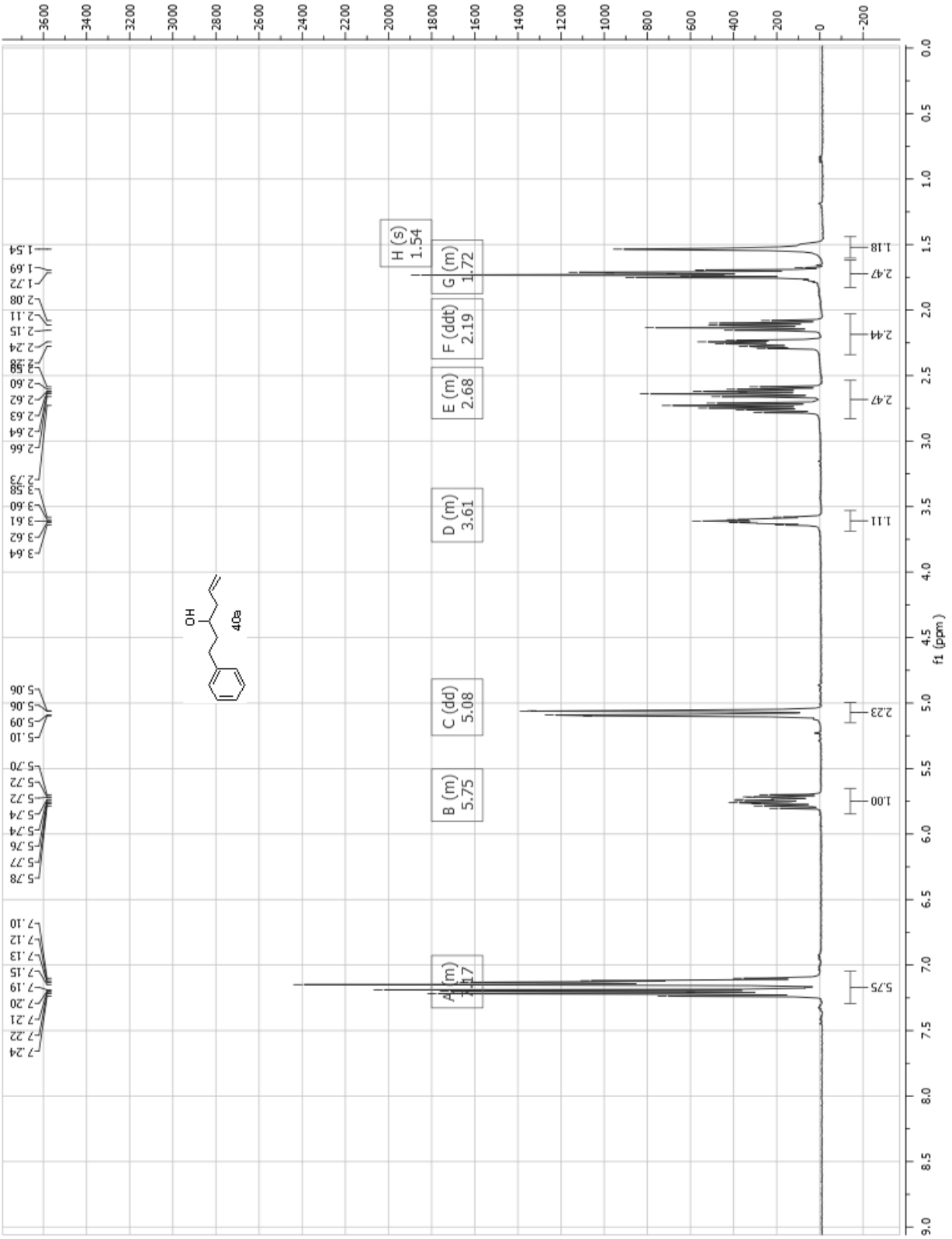
1H NMR (500 MHz) δ 7.44 – 7.14 (m, 22H), 5.11 (s, 1H), 4.94 (dd, *J* = 8.8, 3.5, 1H), 4.18 (d, *J* = 4.6, 1H), 4.10 (s, 1H), 3.66 (s, 1H), 3.16 (s, 1H), 2.89 – 2.74 (m, 4H), 2.64 (s, 1H), 2.10 (s, 1H), 2.01 – 1.92 (m, 2H), 1.92 – 1.83 (m, 2H), 1.61 (d, *J* = 14.3, 4H), 1.30 (d, *J* = 27.5, 9H), 0.94 – 0.83 (m, 3H).

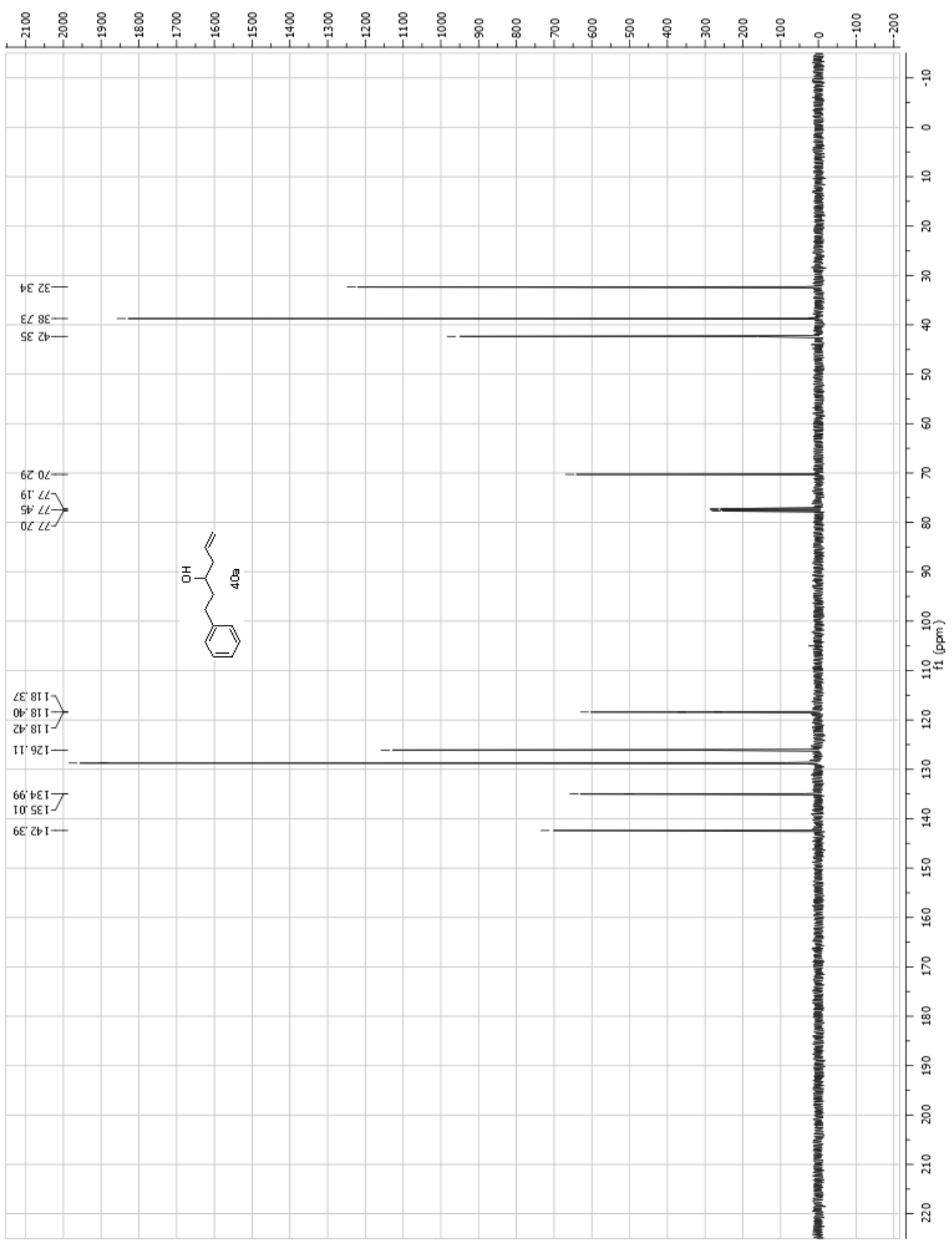
13C NMR (101 MHz) δ 129.64, 129.57, 128.96, 128.95, 128.80, 128.75, 127.33, 127.15, 74.55, 73.79, 71.21, 70.23, 45.16, 44.83, 44.21, 44.20, 29.92.

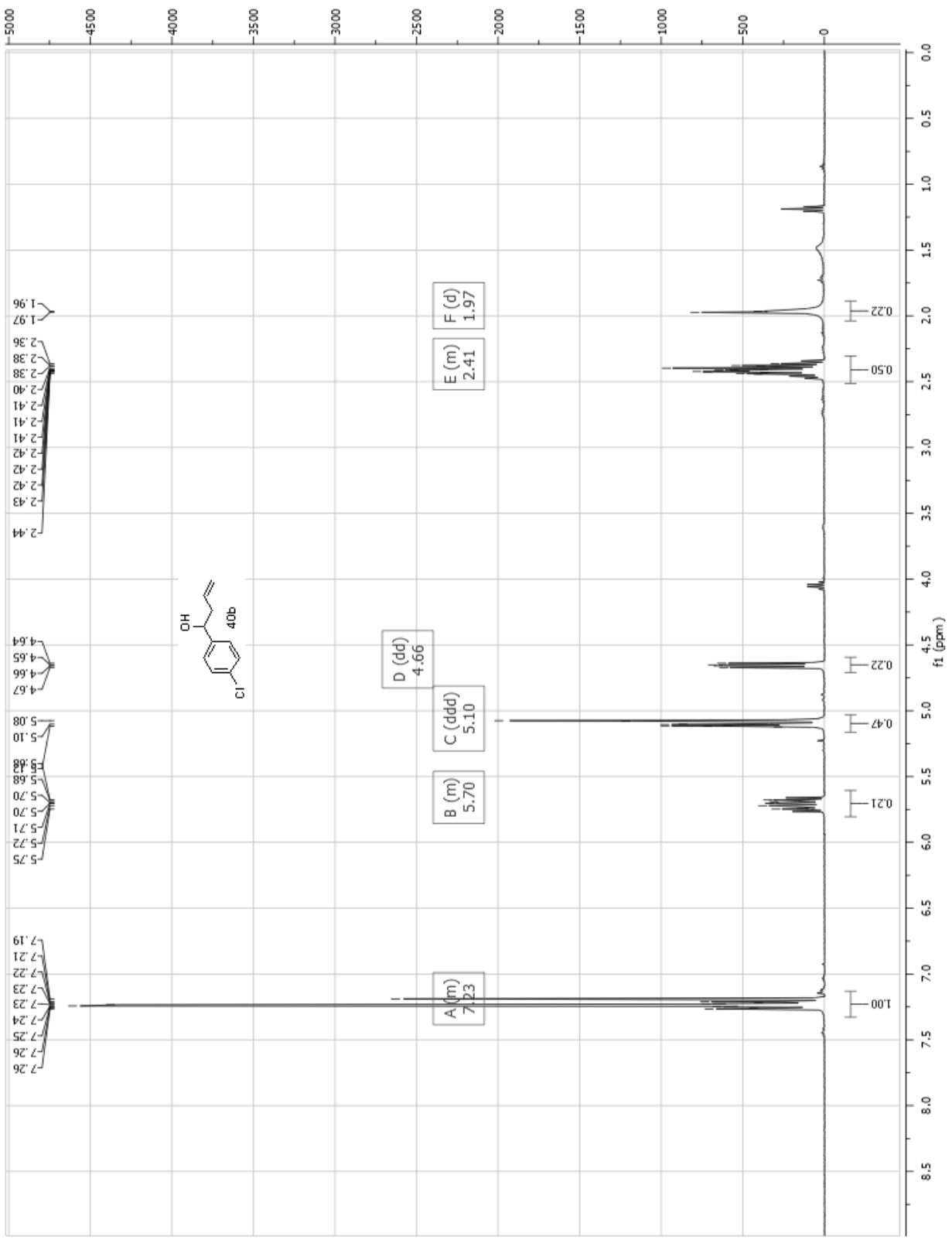
EI-MS: Calc. 276.76, Found 304.1.

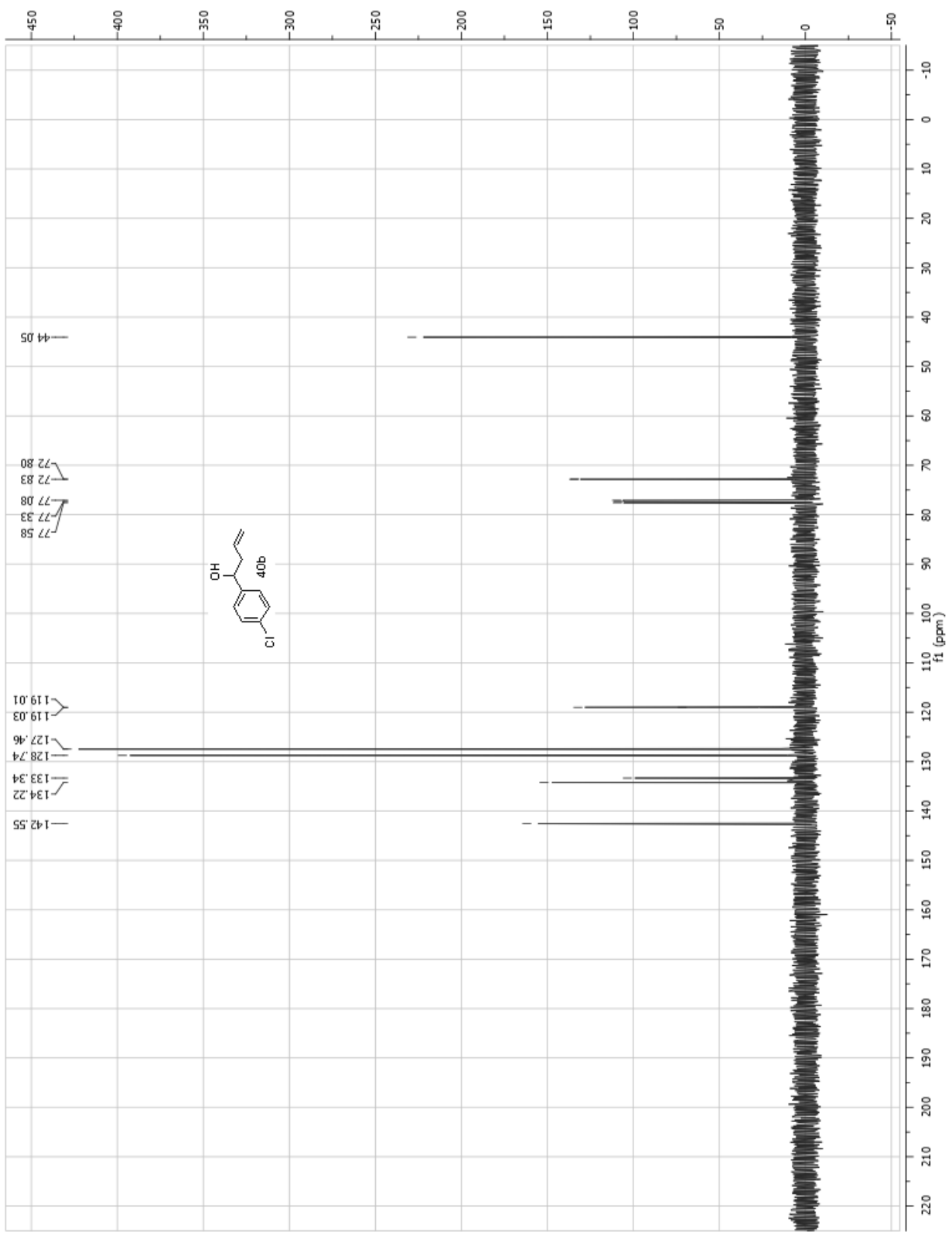
Appendix Two: NMR Spectra

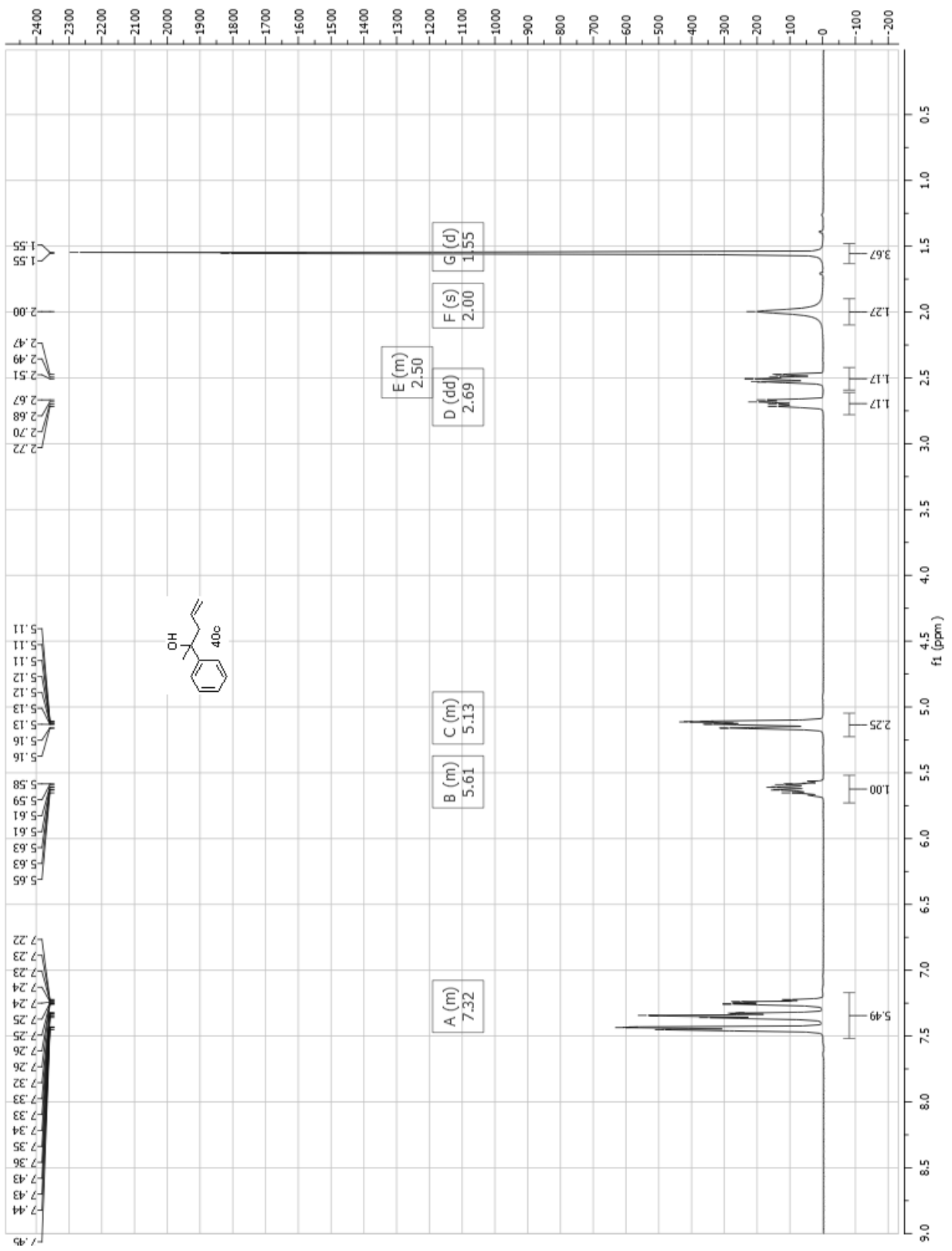
Spectra were analyzed using MestReNova 5.

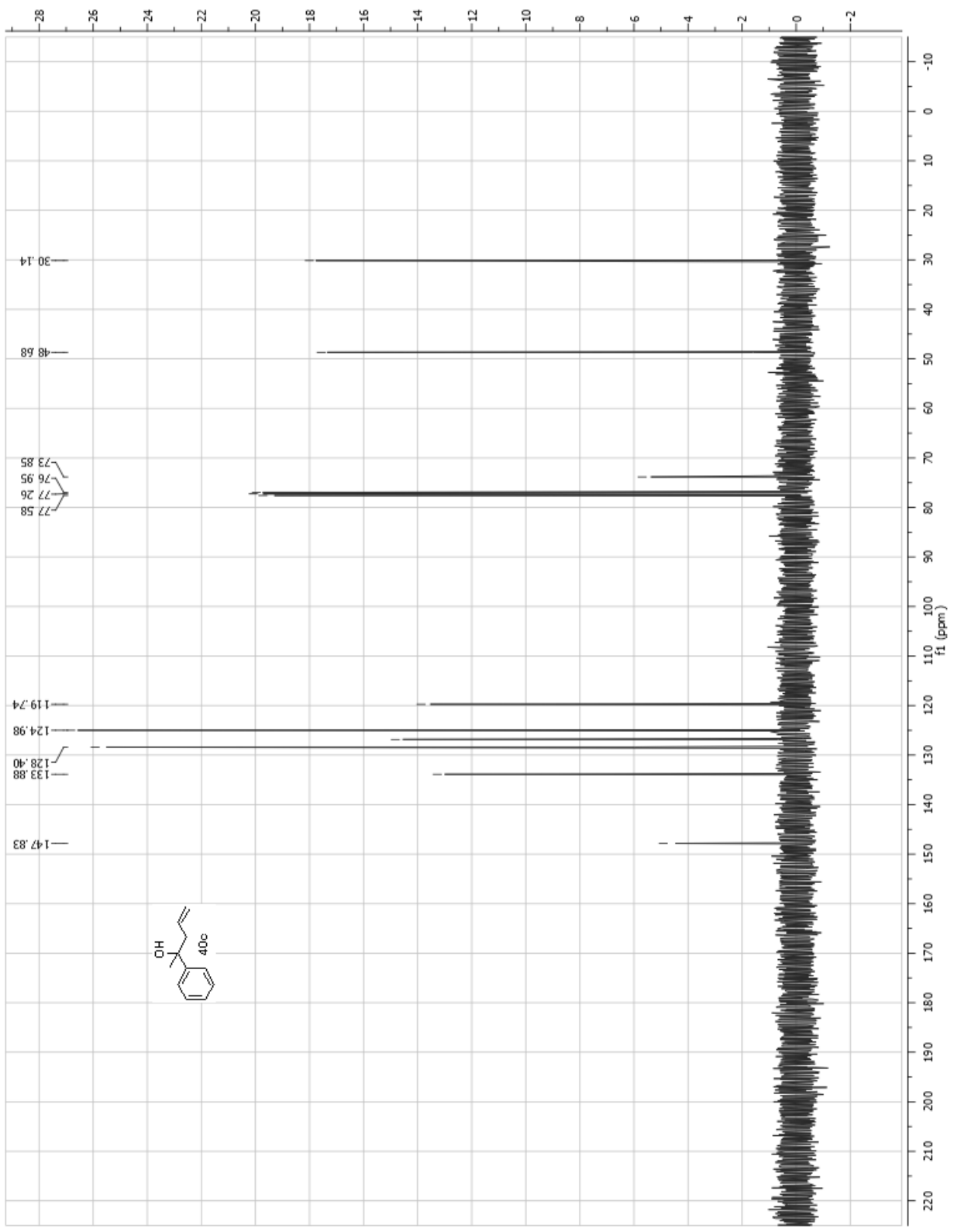


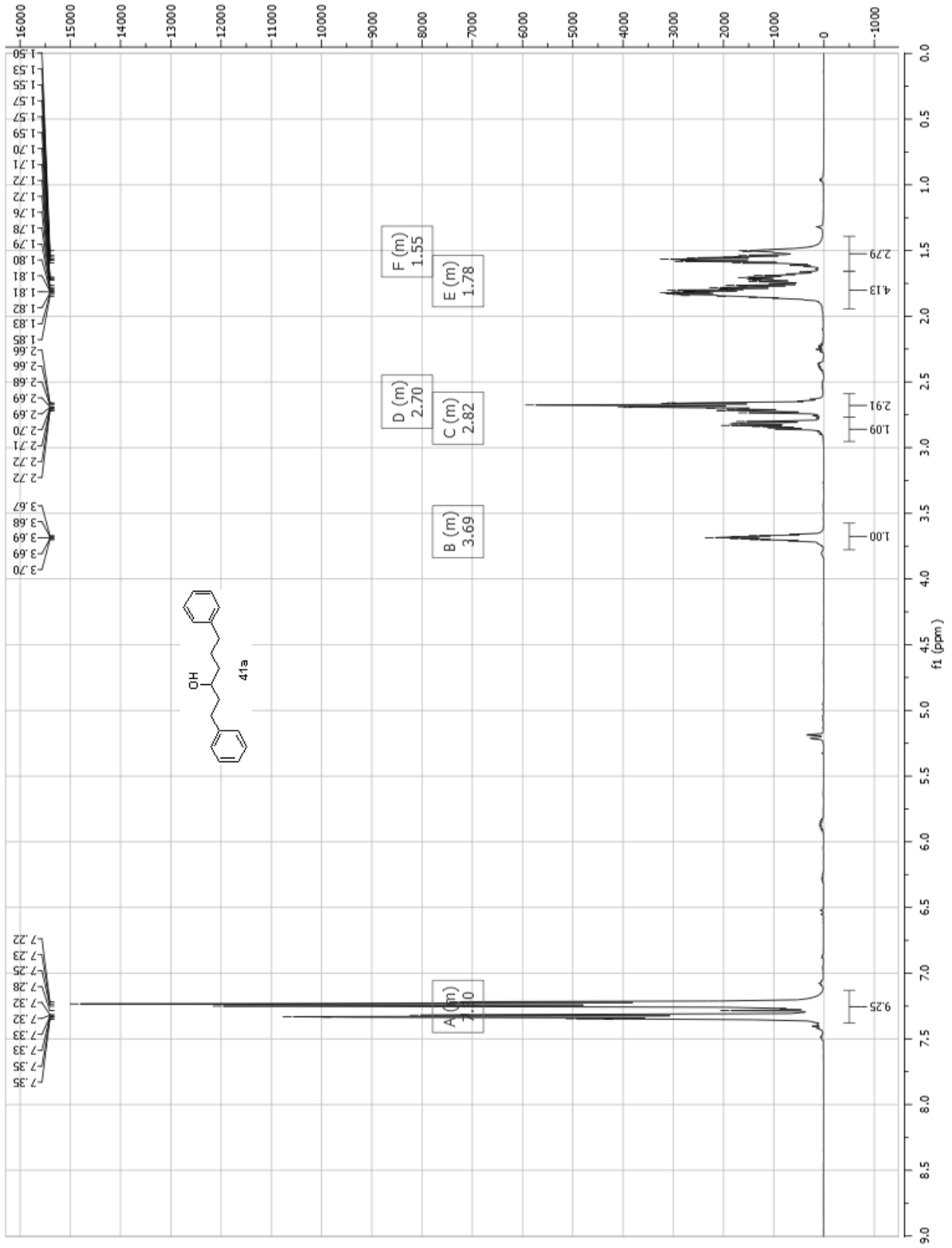

142.39
135.01
134.99
126.11
118.40
118.37
77.70
77.45
77.19
70.29
42.35
38.73
32.34
OH
40a
f1 (ppm)

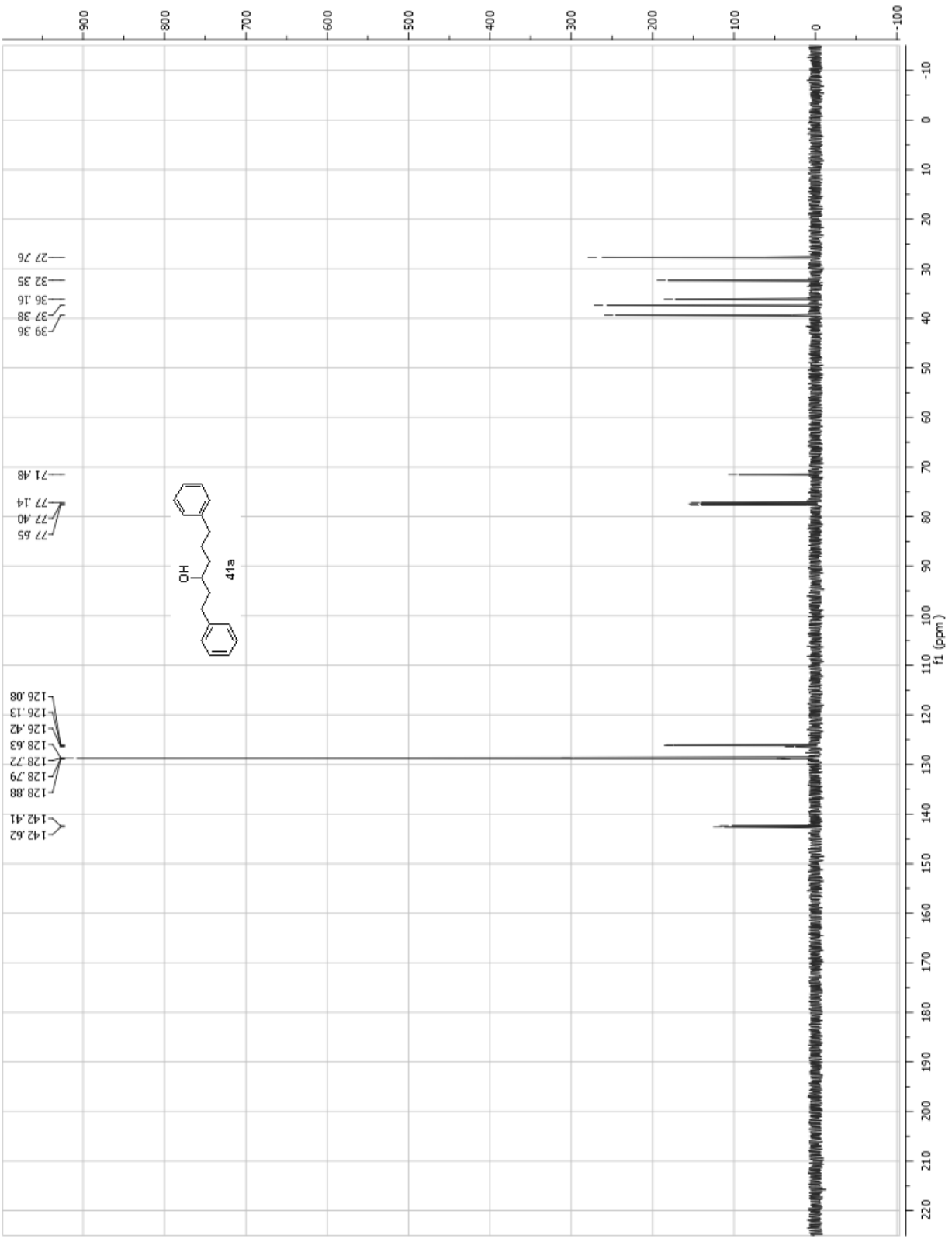

A (m) 7.23
B (m) 5.70
C (ddd) 5.10
D (dd) 4.66
E (m) 2.41
F (d) 1.97
OH
Cl
40b
f1 (ppm)

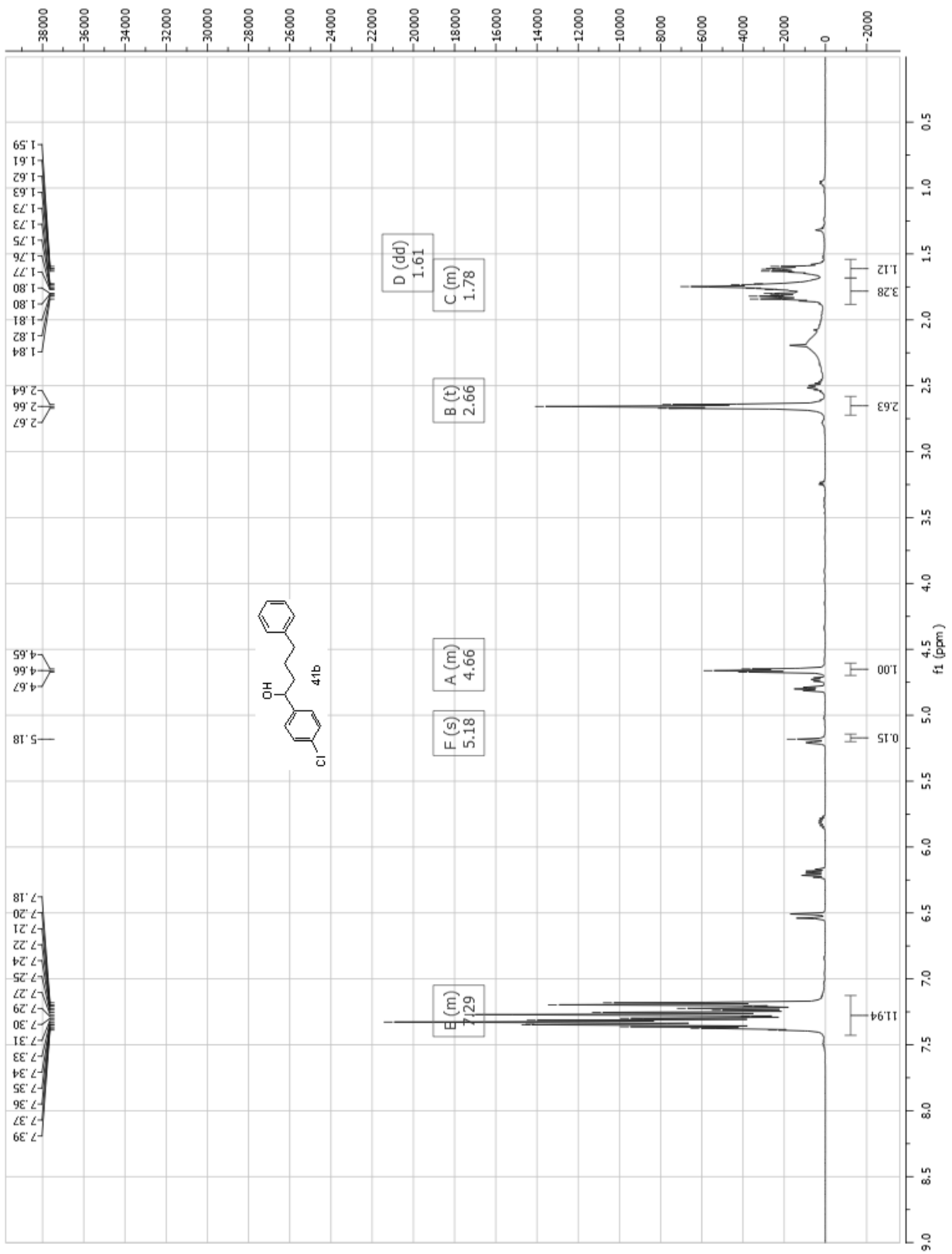

44.05
72.80
72.83
77.08
77.33
77.58
119.01
119.03
127.46
128.74
133.34
134.22
142.55
OH
40b
Cl
f1 (ppm)

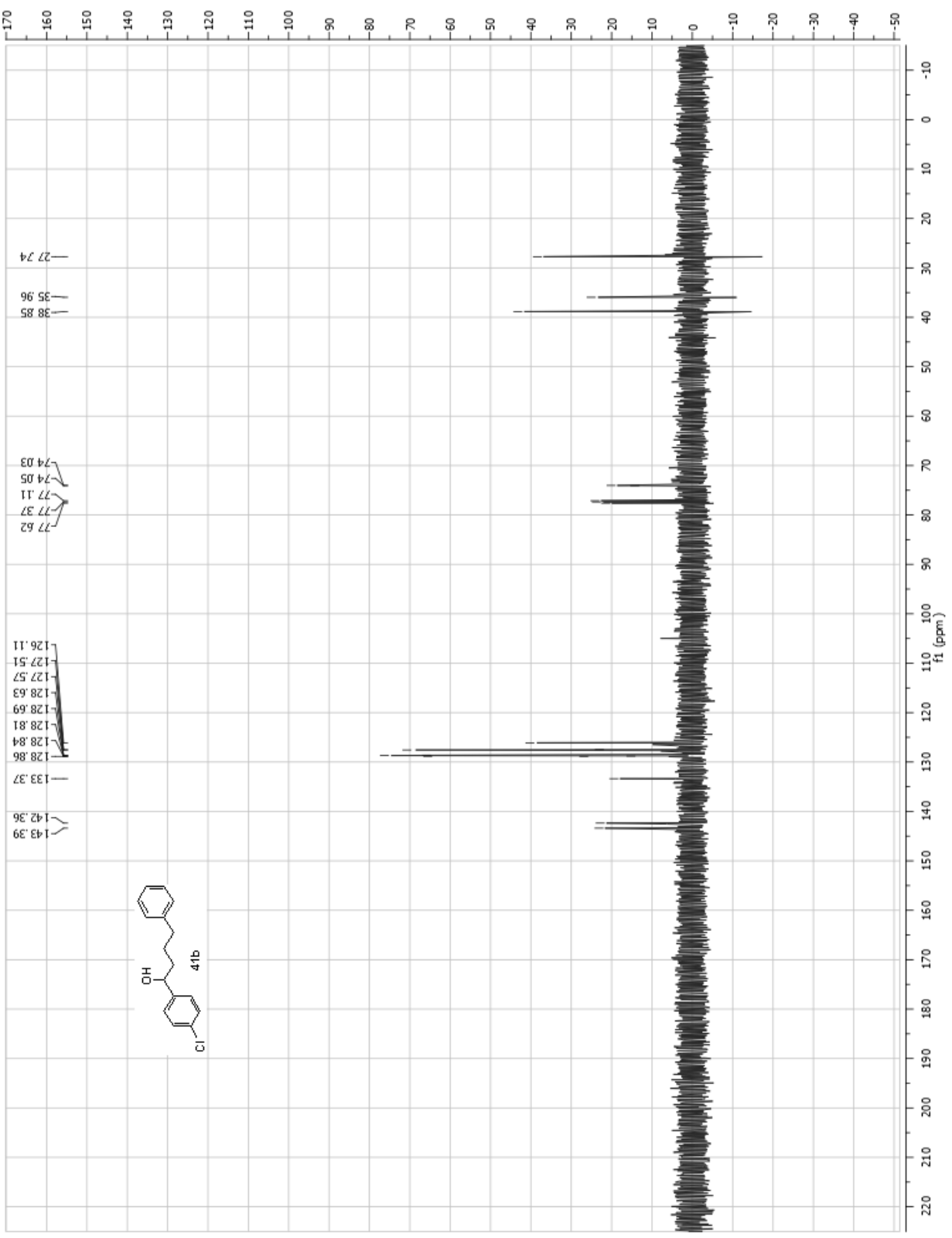

OH
40o
A (m) 7.32
B (m) 5.61
C (m) 5.13
D (dd) 2.69
E (m) 2.50
F (s) 2.00
G (d) 1.55
f1 (ppm)

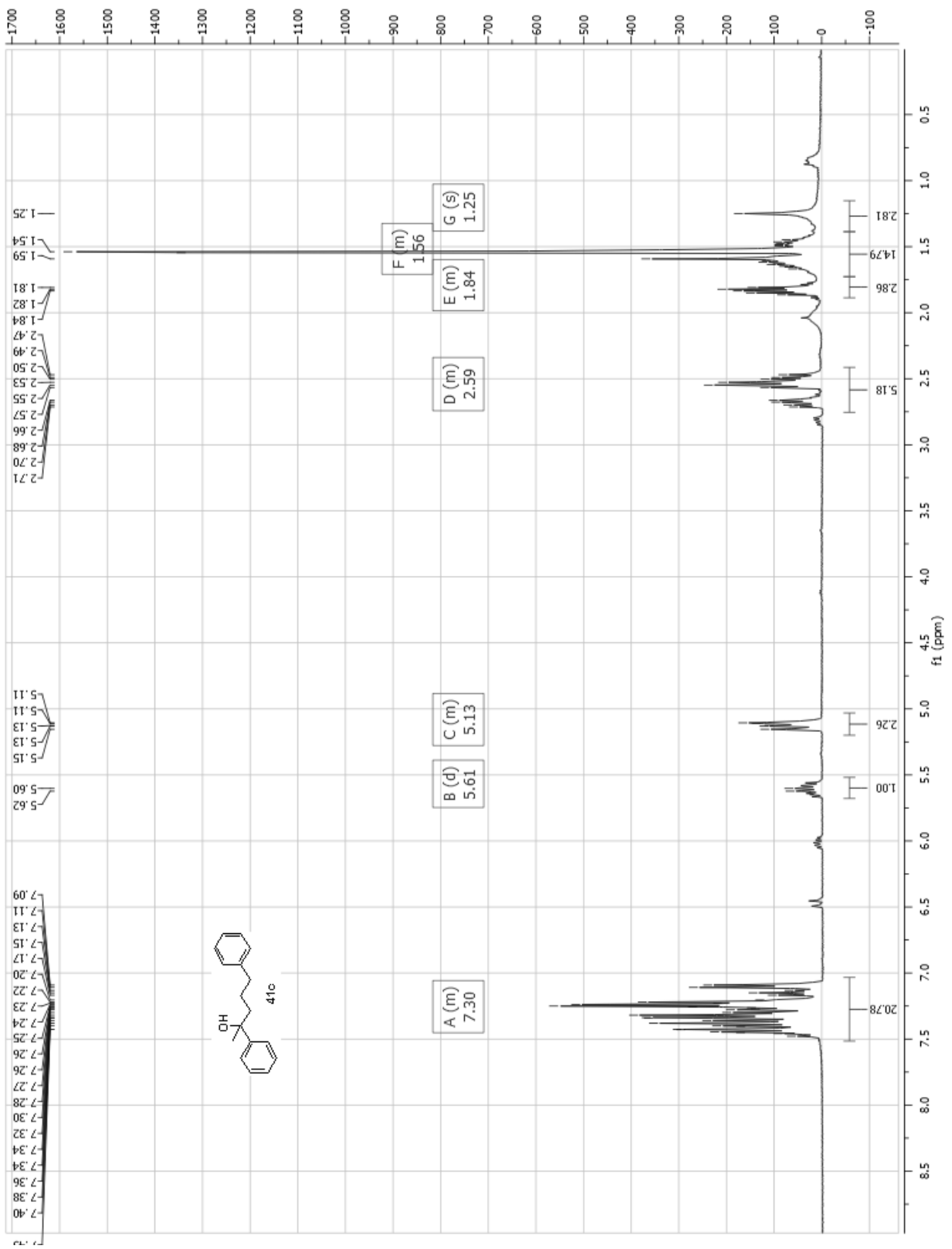

147.83
133.88
128.40
124.98
119.74
77.58
77.26
76.95
73.85
48.58
30.14
OH
40c
f1 (ppm)

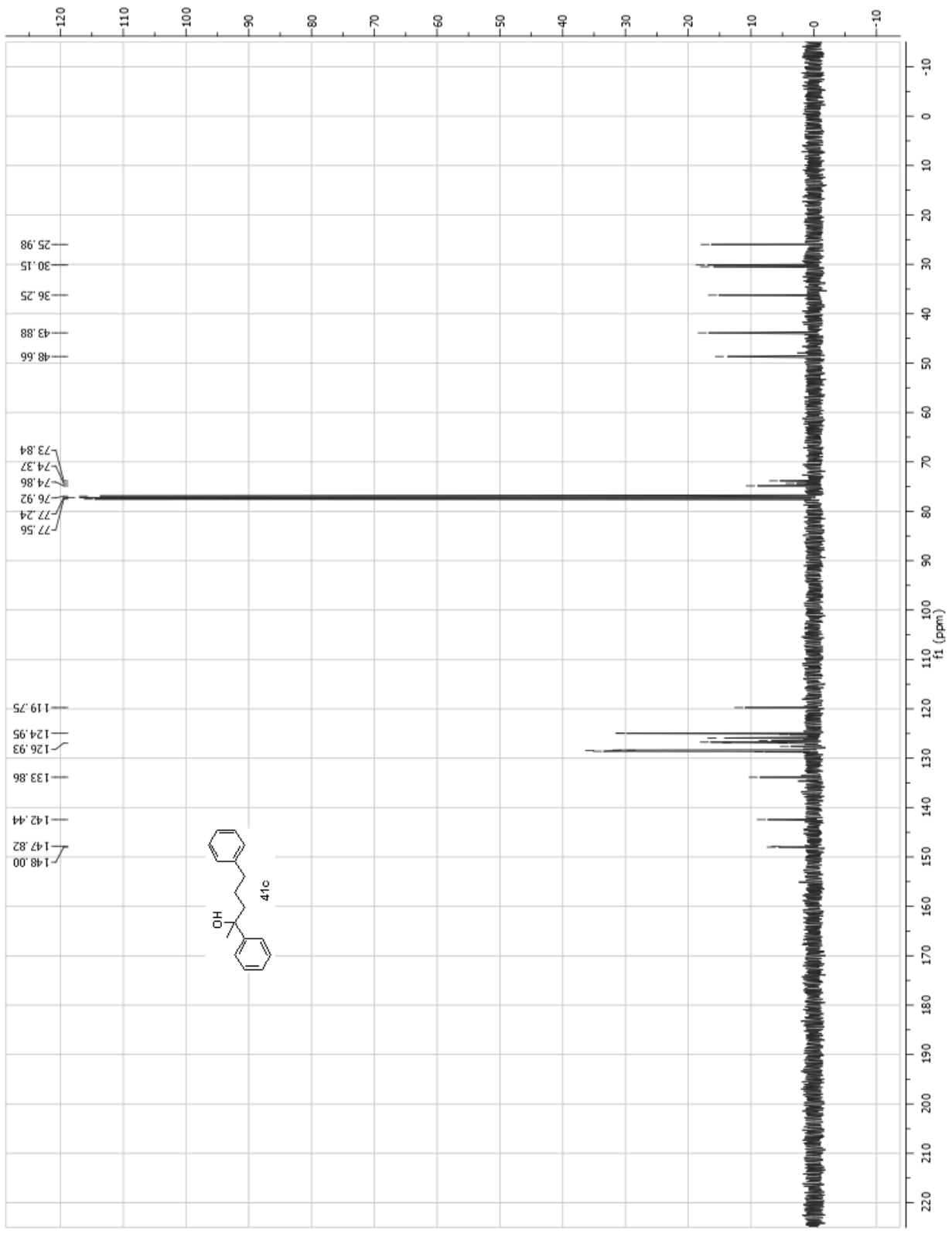

OH
41a
A (m)
7.30
B (m)
3.69
C (m)
2.82
D (m)
2.70
E (m)
1.78
F (m)
1.55
9.25
1.00
2.91
1.09
4.13
2.79
f1 (ppm)

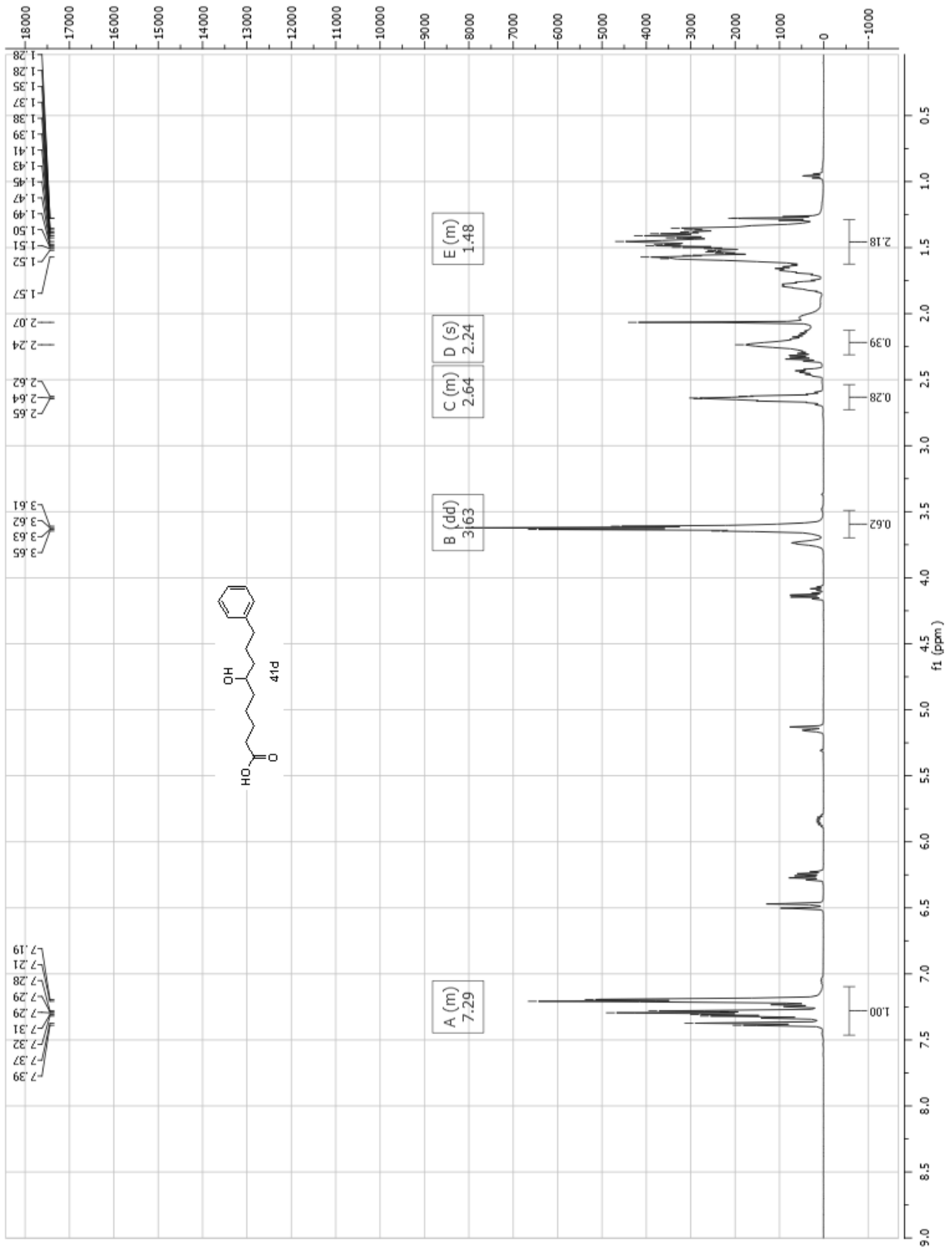

142.62
142.41
128.88
128.79
128.72
128.63
126.42
126.13
126.08
77.65
77.40
77.14
71.48
39.36
37.38
36.16
32.35
27.76
OH
41a
f1 (ppm)

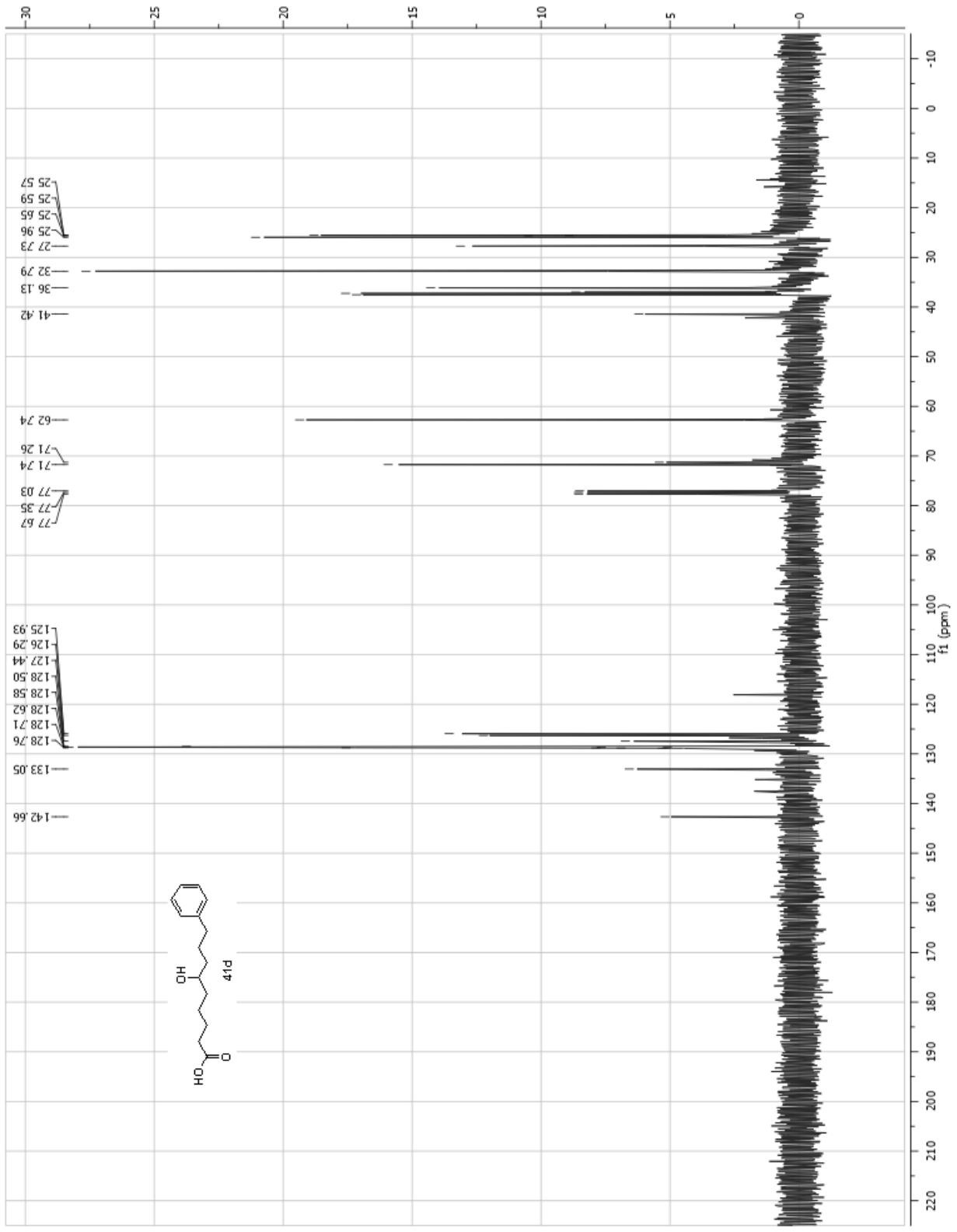

41b
OH
Cl
D (dd) 1.61
C (m) 1.78
B (t) 2.66
A (m) 4.66
F (s) 5.18
E (m) 7.29
f1 (ppm)

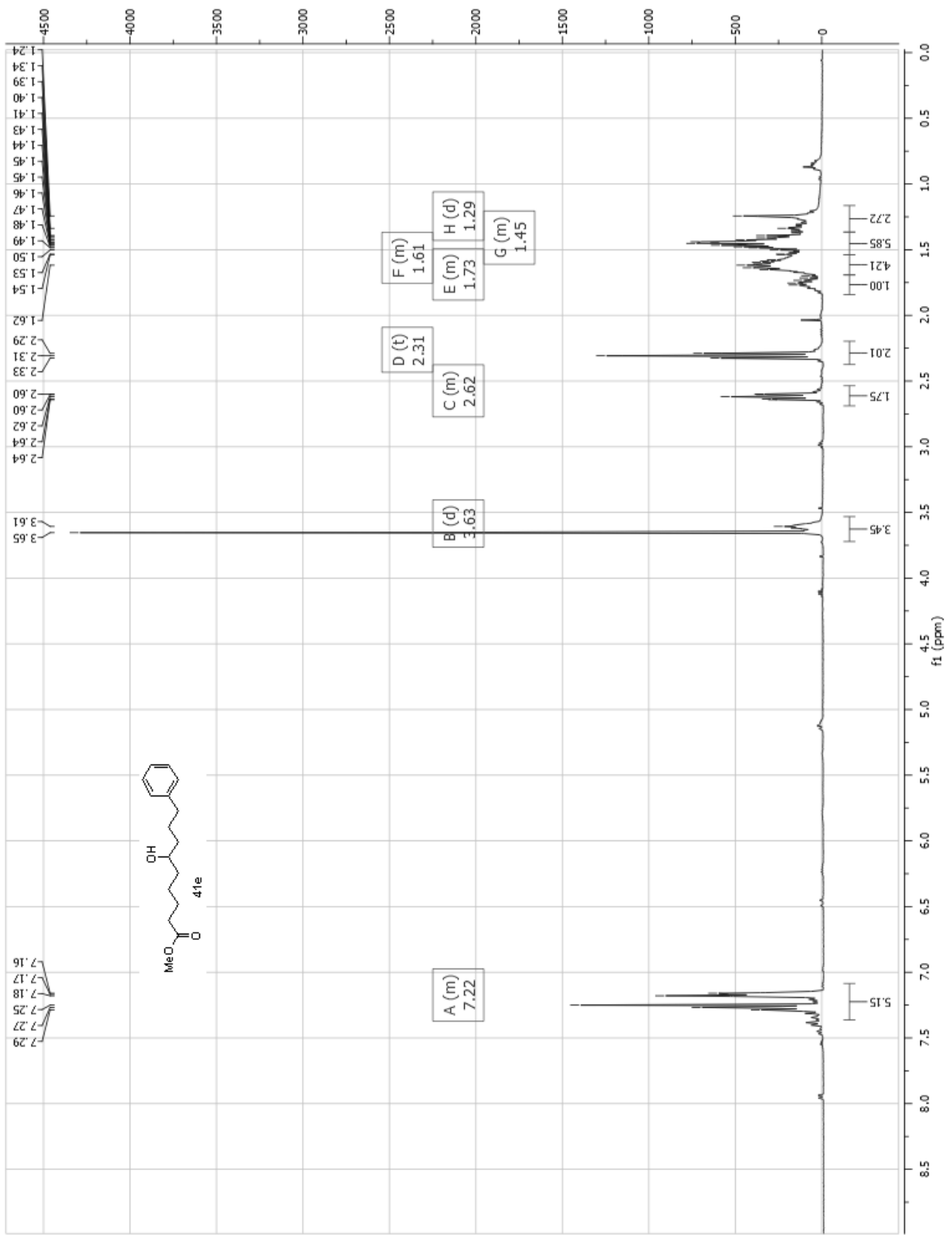

41b
OH
Cl
143.39
142.36
133.37
128.86
128.84
128.81
128.69
128.63
127.57
127.51
126.11
77.62
77.37
77.11
74.05
74.03
38.85
35.96
27.74
f1 (ppm)

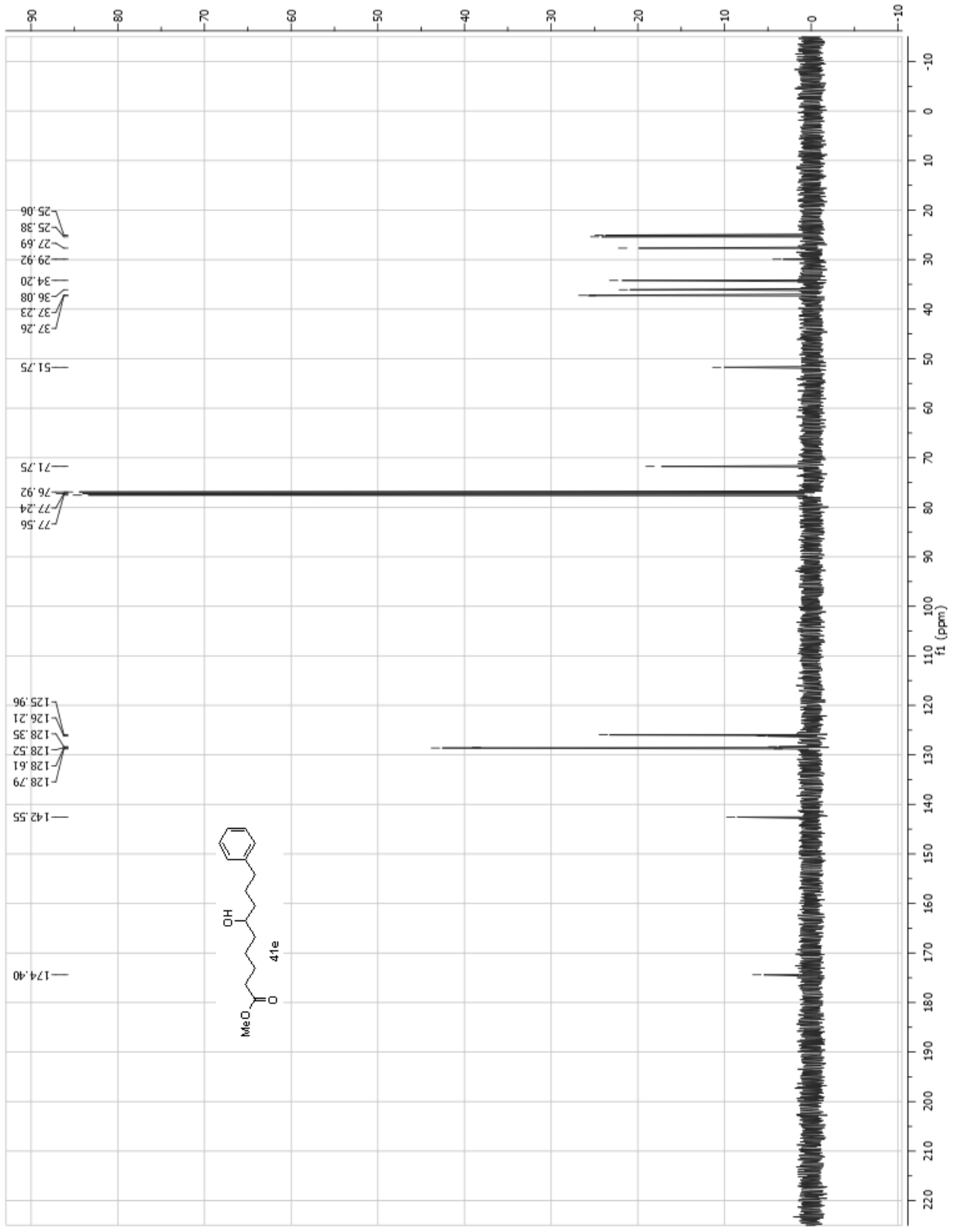

A (m) 7.30
B (d) 5.61
C (m) 5.13
D (m) 2.59
E (m) 1.84
F (m) 1.56
G (s) 1.25
41c
OH
20.78
1.00
2.26
5.18
2.86
14.79
2.81
f1 (ppm)

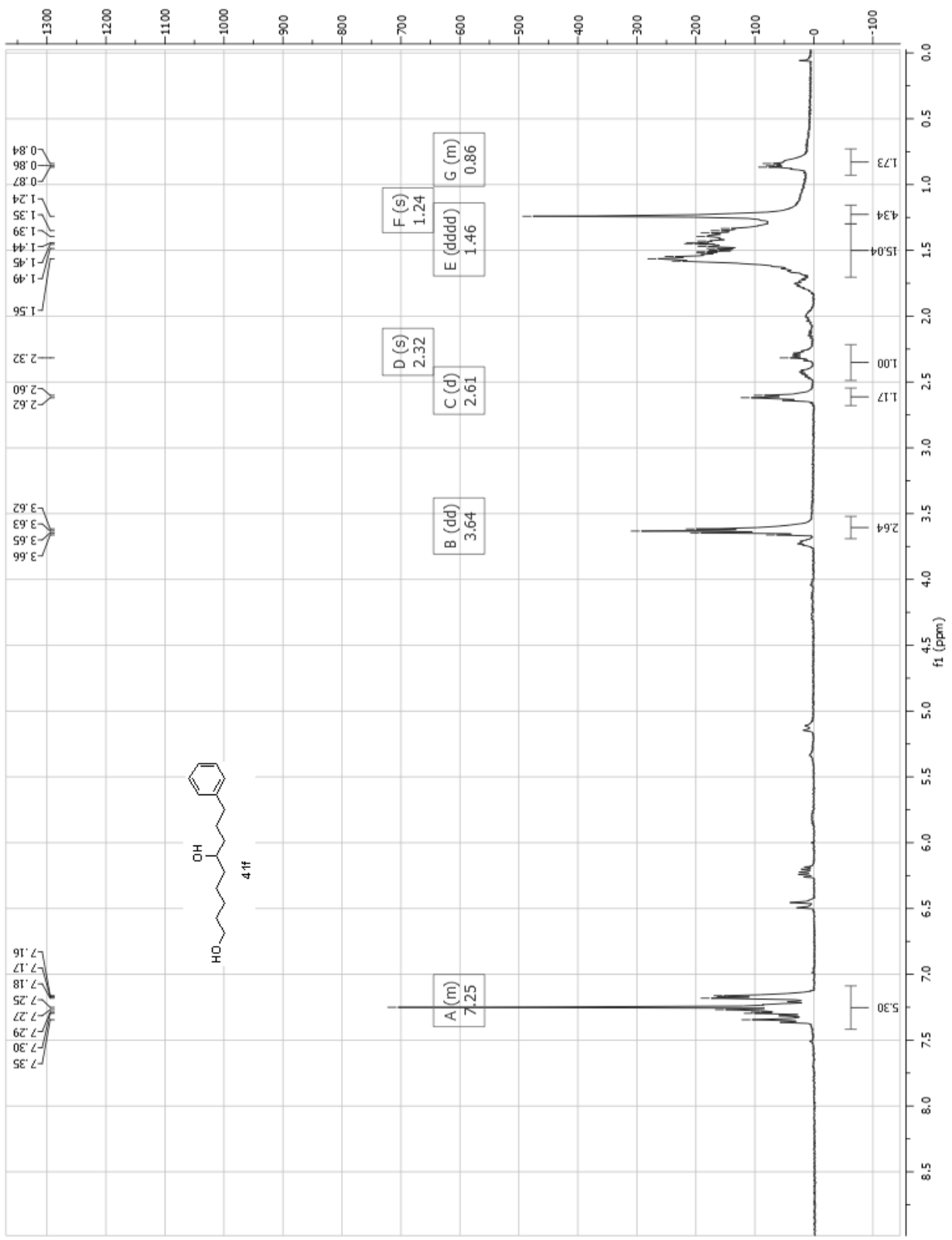

25.98
30.15
36.25
43.88
48.66
73.84
74.37
74.86
76.92
77.24
77.56
119.75
124.95
126.93
133.86
142.44
147.82
148.00
OH
41c
f1 (ppm)

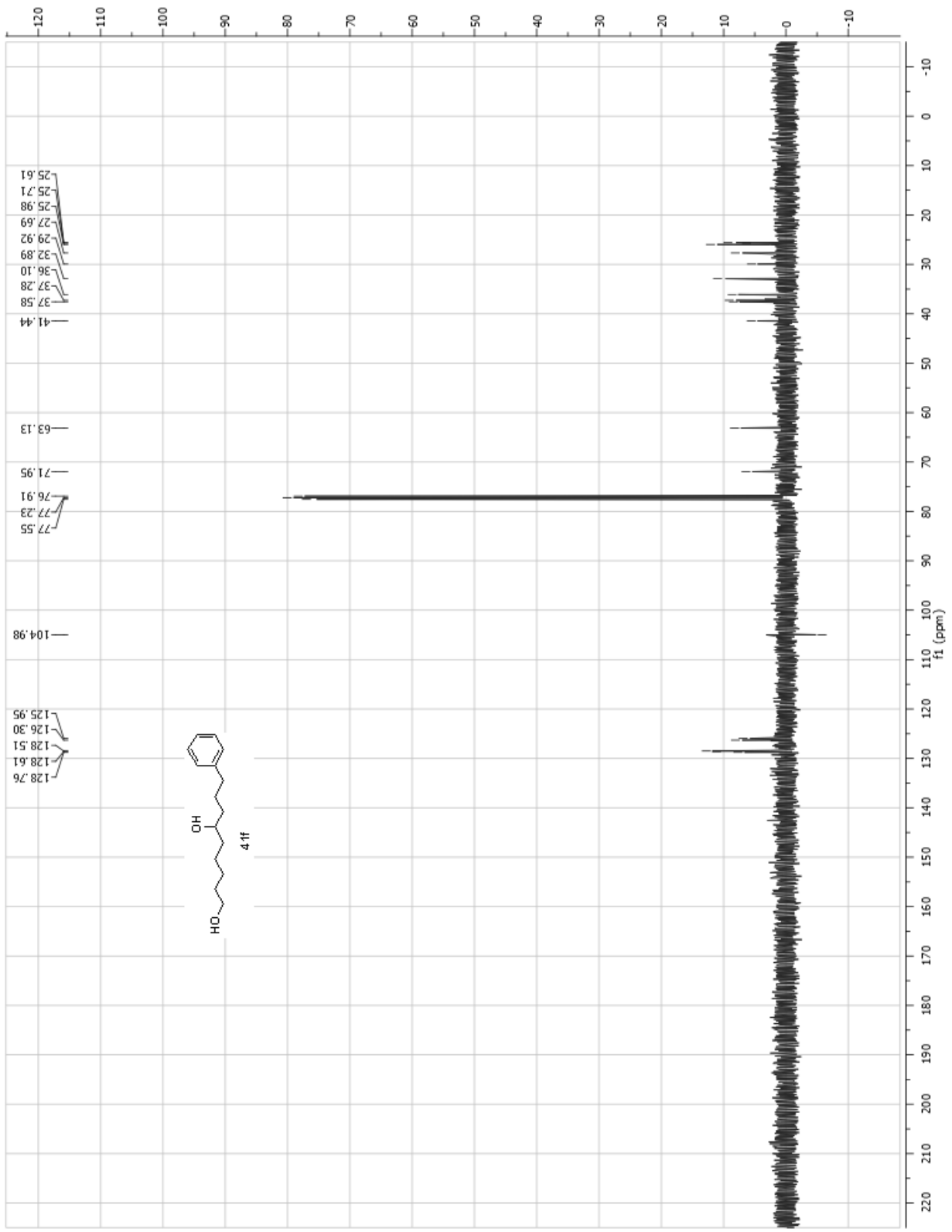

A (m) 7.29
B (dd) 3.63
C (m) 2.64
D (s) 2.24
E (m) 1.48
1.00
0.62
0.28
0.39
2.18
41d
f1 (ppm)

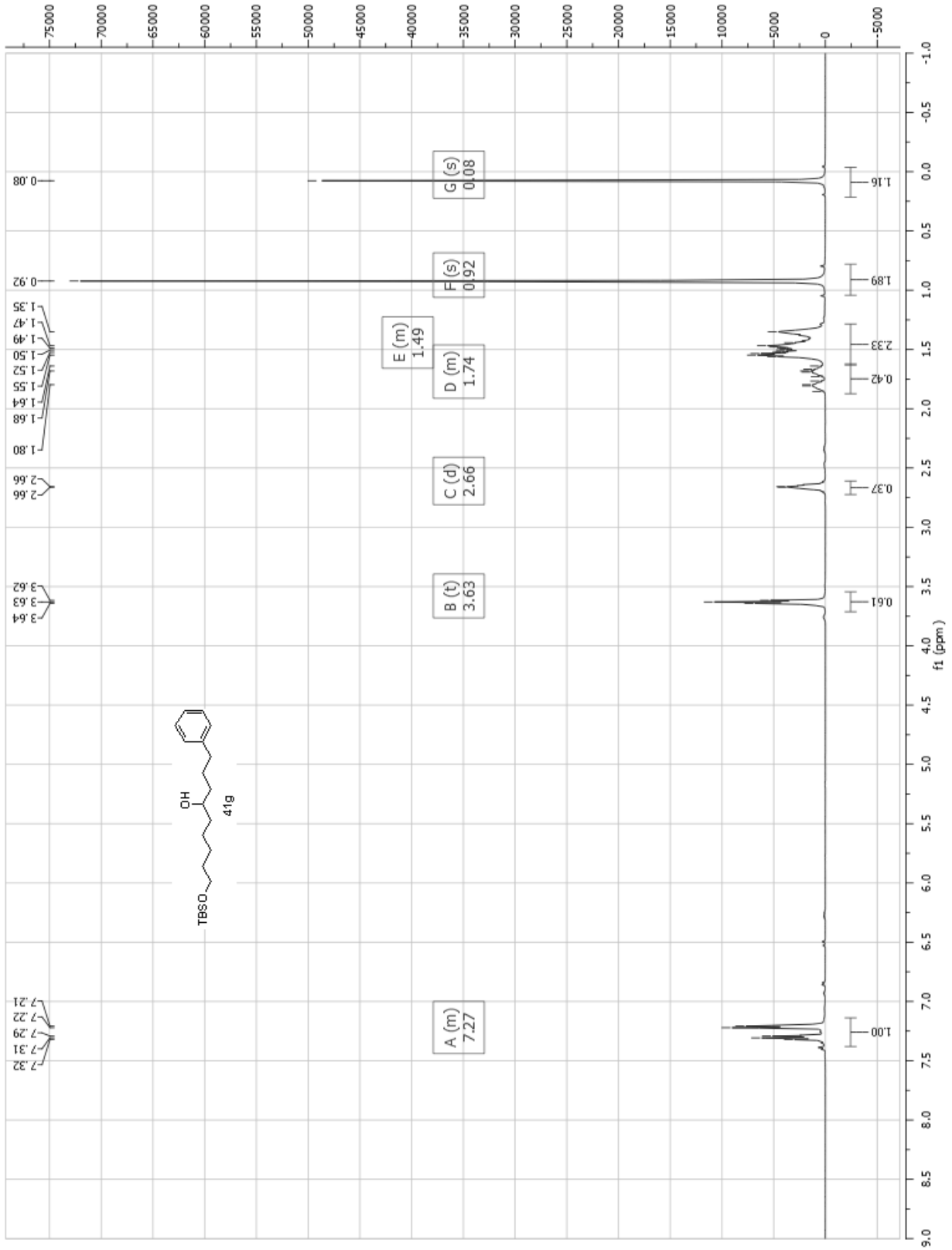

142.66
133.05
128.76
128.71
128.62
128.58
128.50
127.44
126.29
125.93
77.67
77.35
77.03
71.74
71.26
62.74
41.42
36.13
32.79
27.73
25.96
25.65
25.59
25.57
HO
O
OH
41d
f1 (ppm)

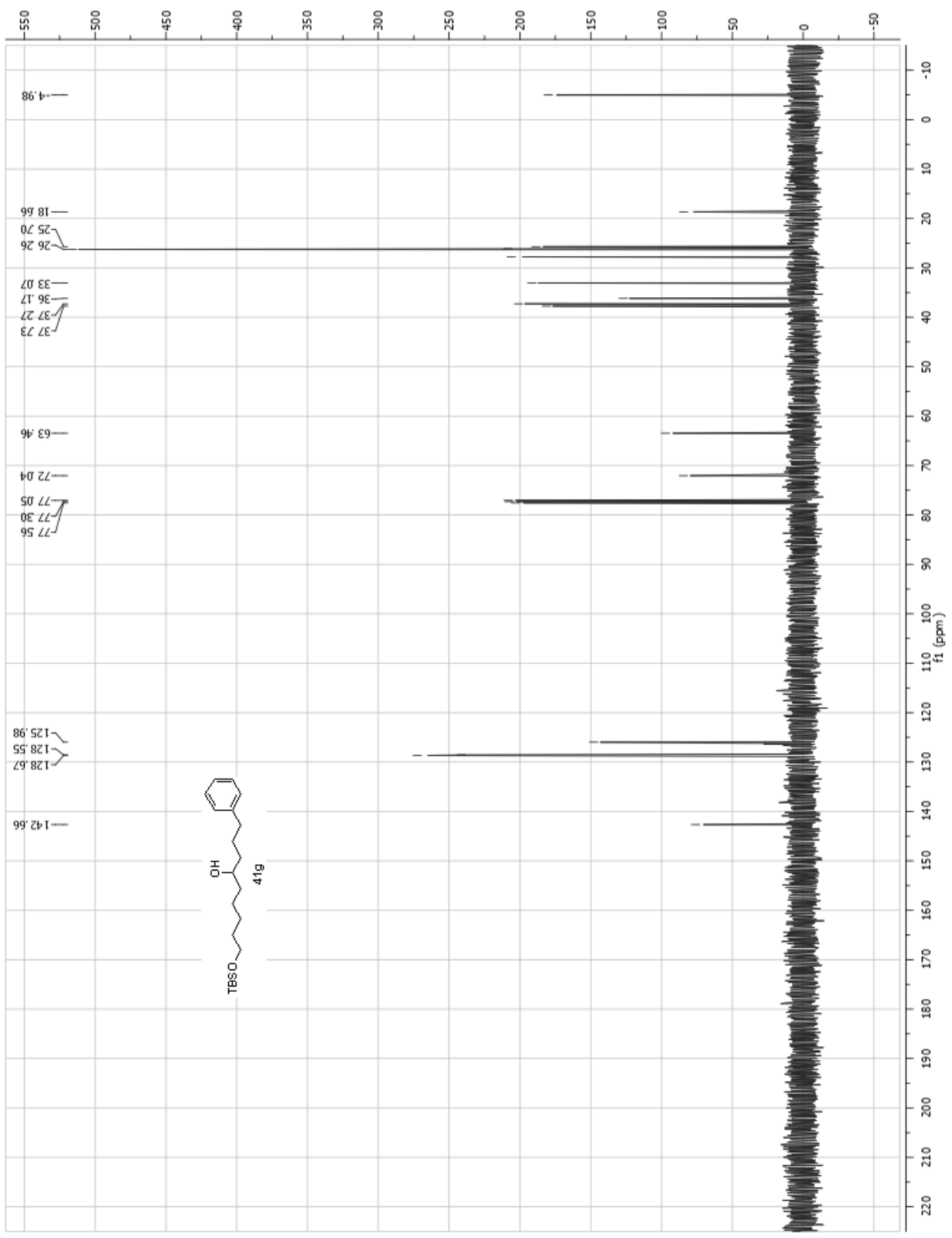

A (m) 7.22
B (d) 3.63
C (m) 2.62
D (t) 2.31
E (m) 1.73
F (m) 1.61
G (m) 1.45
H (d) 1.29
41e
MeO
OH
O
f1 (ppm)

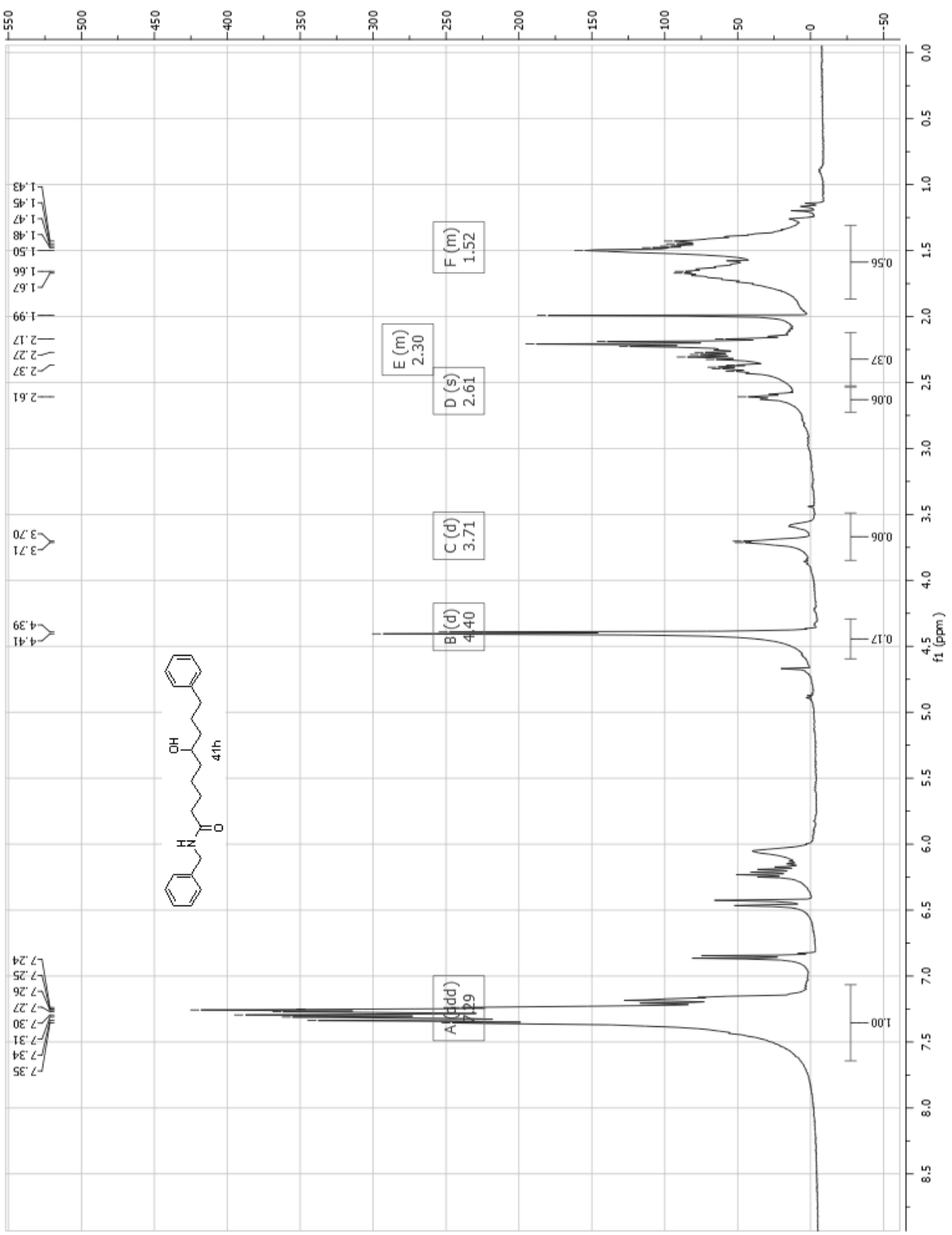

174.40
142.55
128.79
128.61
128.52
128.35
126.21
125.96
77.56
77.24
76.92
71.75
51.75
37.26
37.23
36.08
34.20
29.92
27.69
25.38
25.06
MeO
O
OH
41e
f1 (ppm)

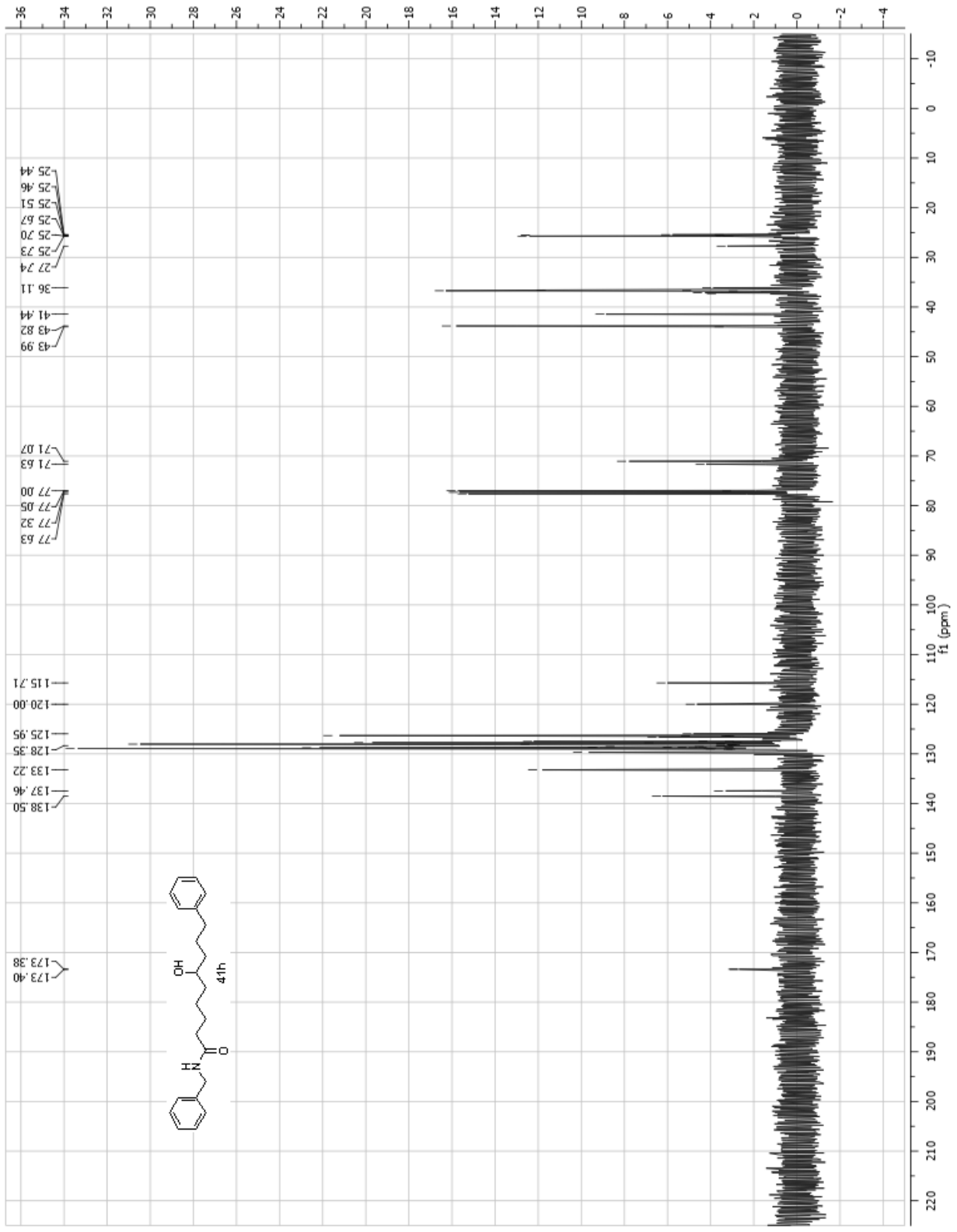

A (m) 7.25
B (dd) 3.64
C (d) 2.61
D (s) 2.32
E (dddd) 1.46
F (s) 1.24
G (m) 0.86
OH
HO
41f
f1 (ppm)

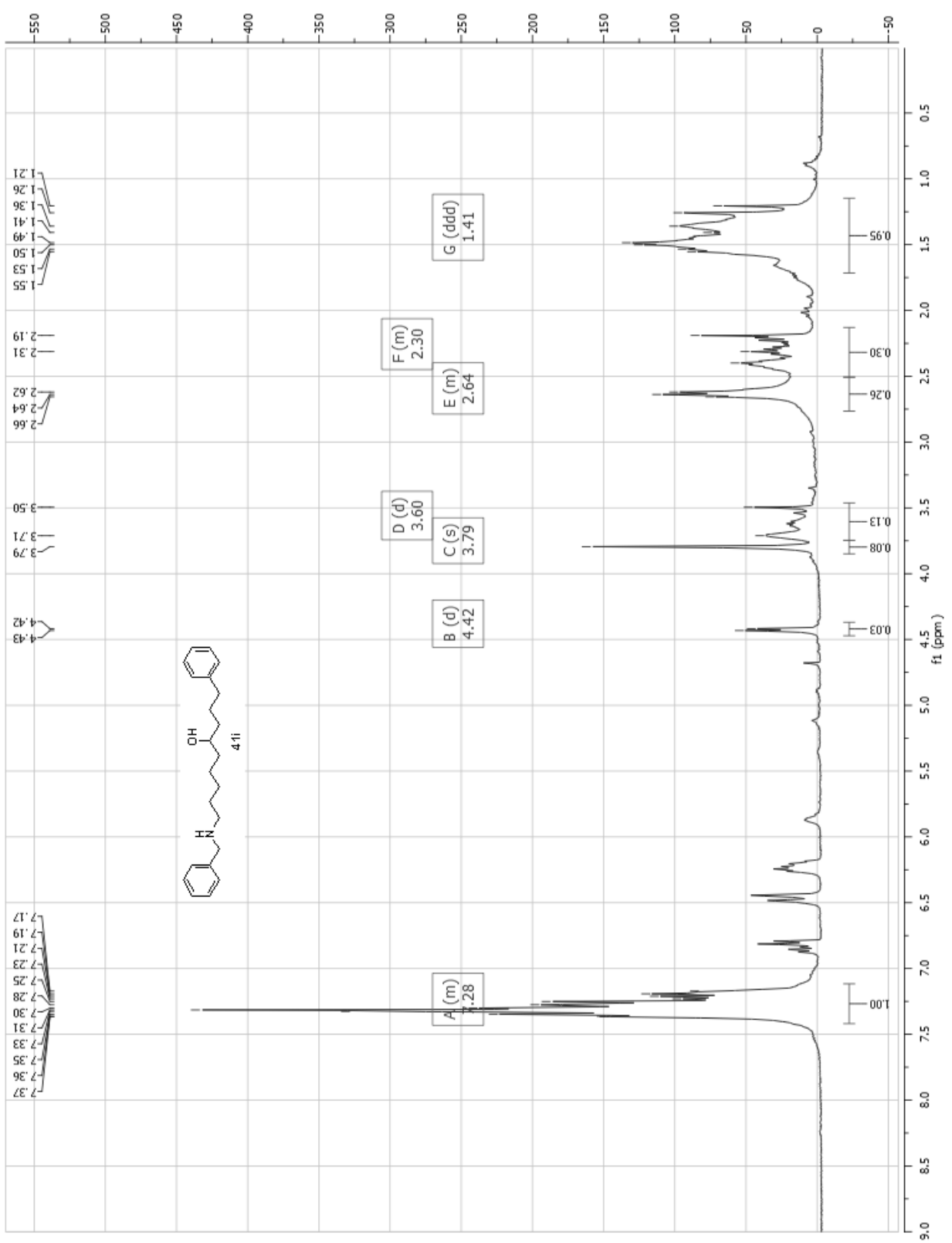

25.61
25.71
25.98
27.69
29.92
32.89
36.10
37.28
37.58
41.44
63.13
71.95
76.91
77.23
77.55
104.98
125.95
126.30
128.51
128.61
128.76
OH
HO
41f
f1 (ppm)

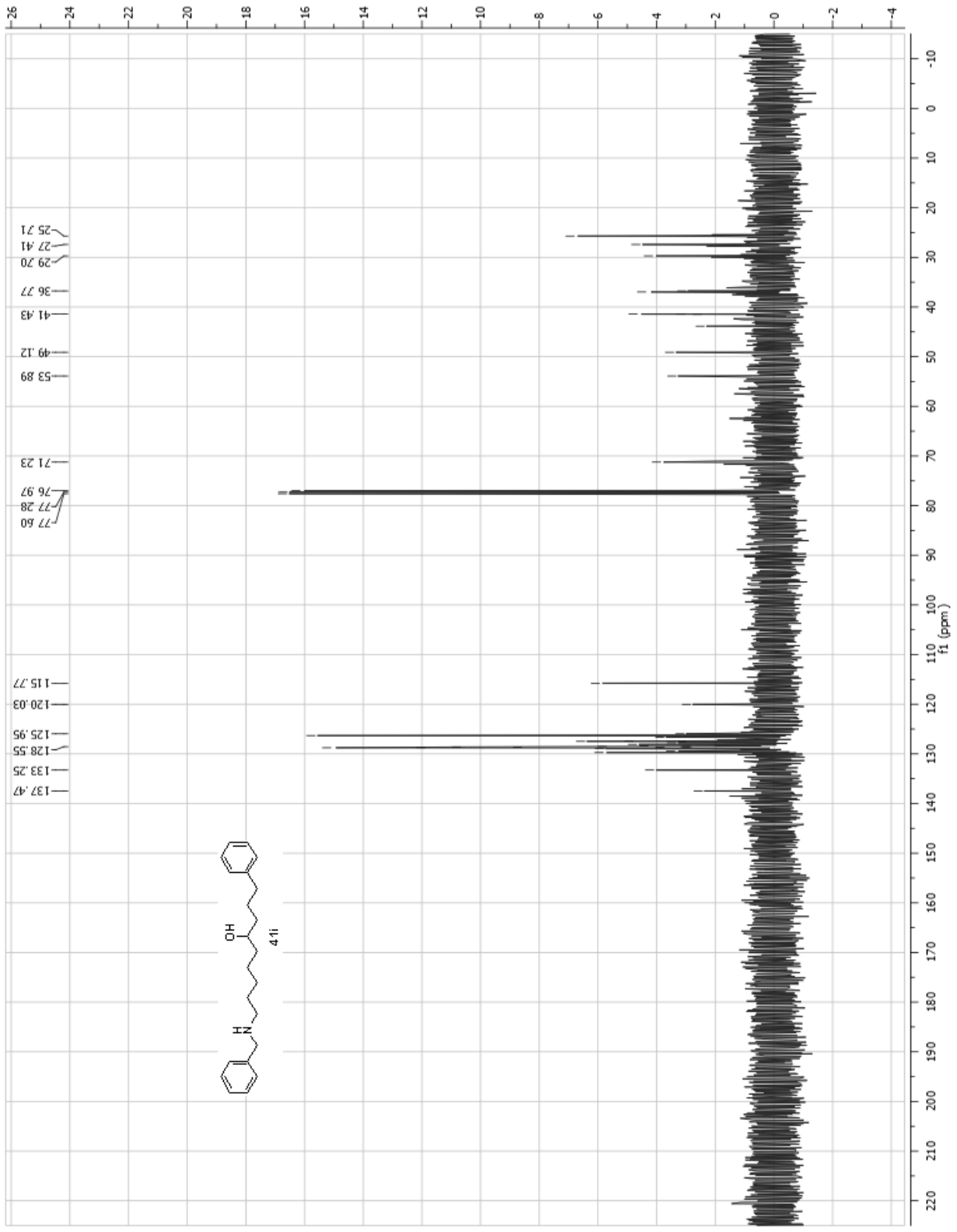

A (m) 7.27
B (t) 3.63
C (d) 2.66
D (m) 1.74
E (m) 1.49
F (s) 0.92
G (s) 0.08
TBSO
OH
41g
f1 (ppm)

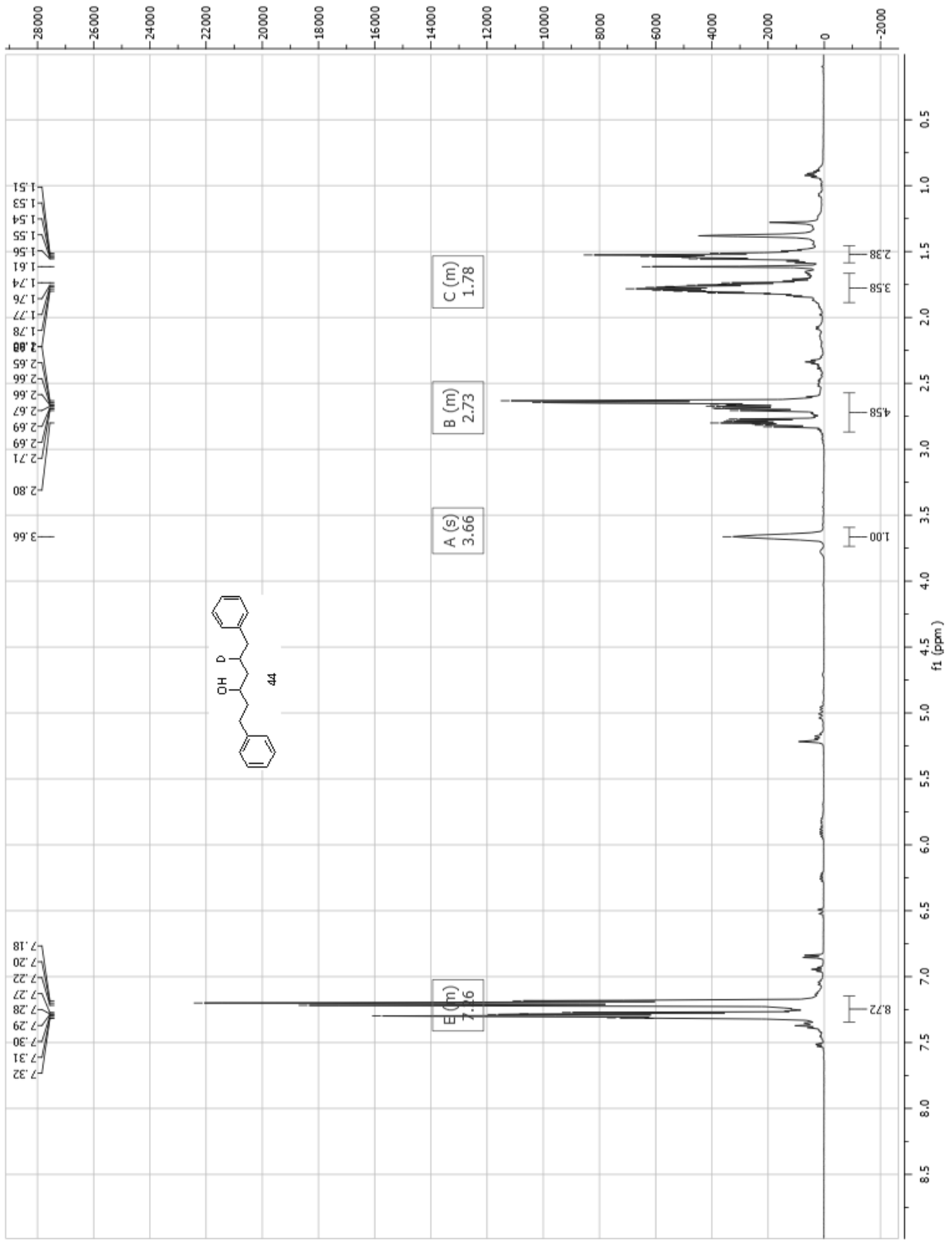

-4.98
18.66
25.70
26.26
33.07
36.17
37.27
37.73
63.46
72.04
77.05
77.30
77.56
125.98
128.55
128.67
142.66
OH
TBSO
41g
f1 (ppm)

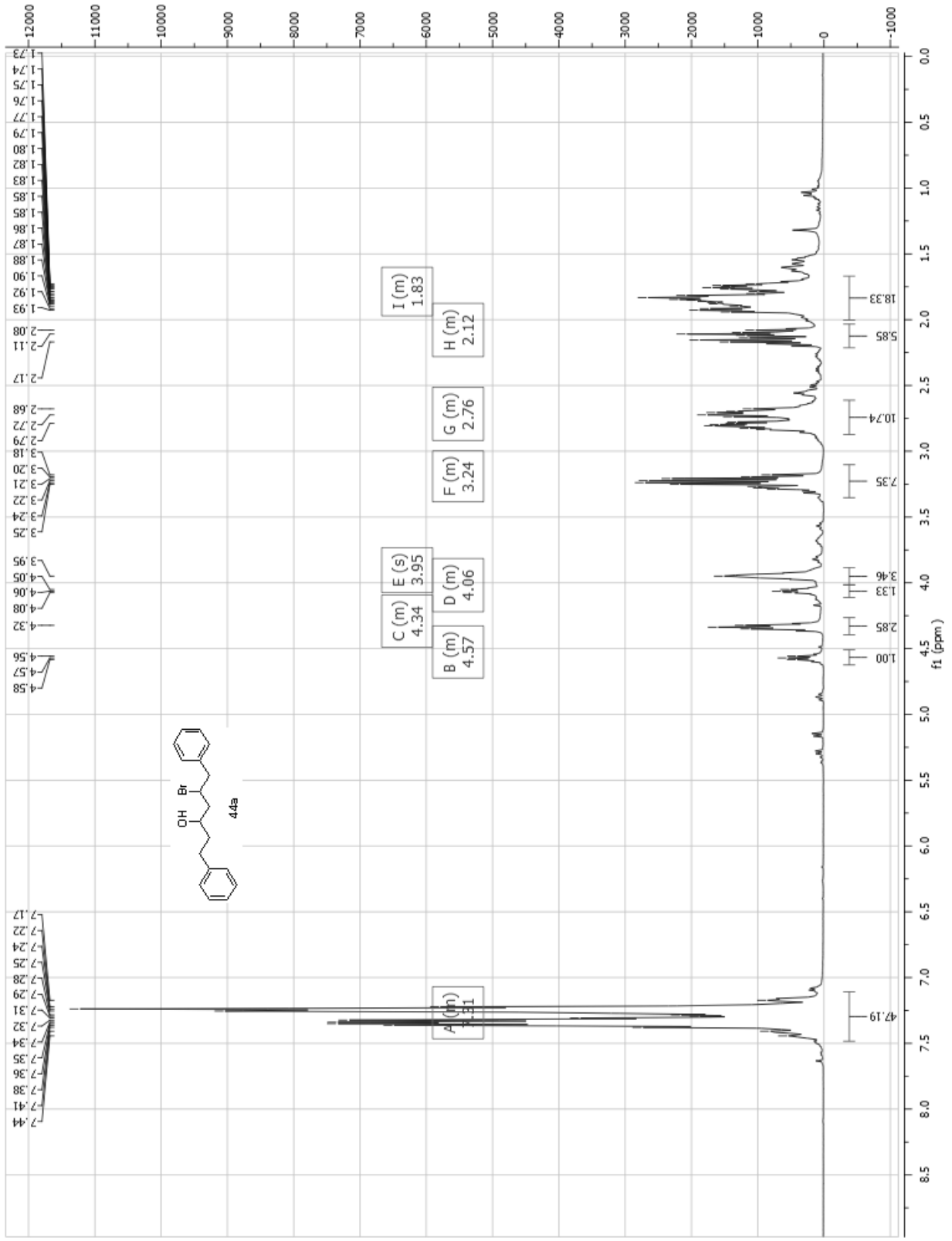

A (ddd) 7.29
B (d) 4.40
C (d) 3.71
D (s) 2.61
E (m) 2.30
F (m) 1.52
41h
OH
H N
O
f1 (ppm)

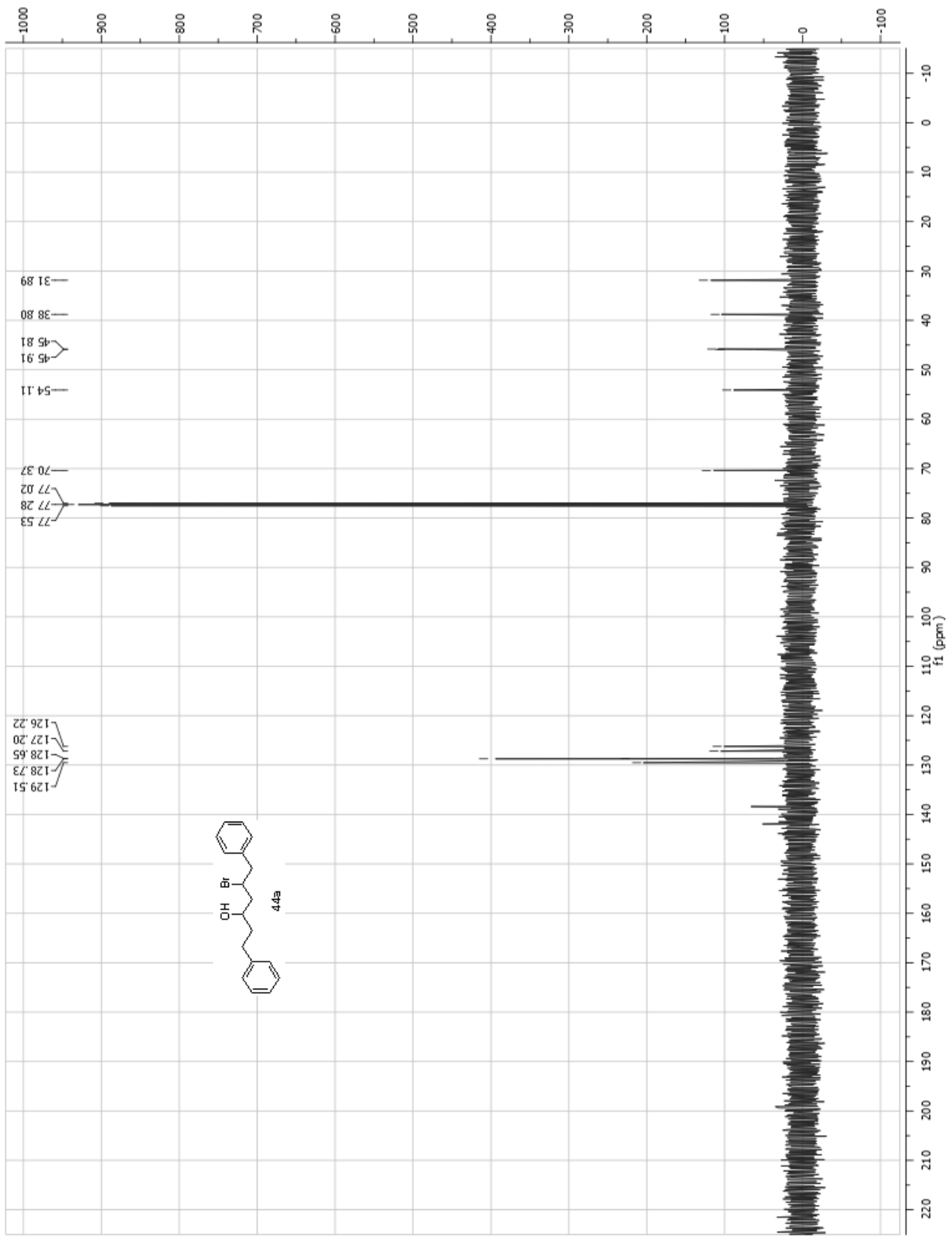

41h
f1 (ppm)

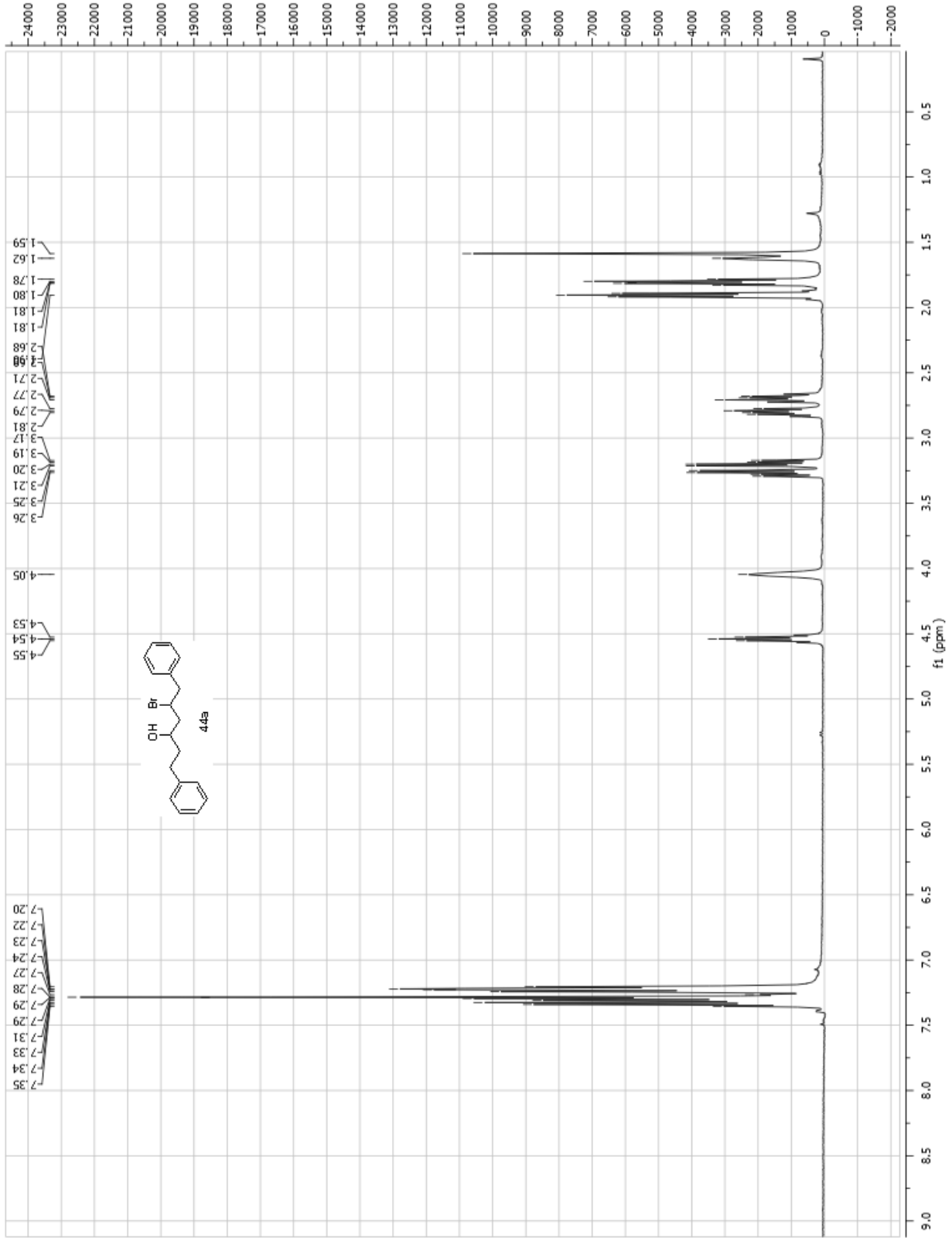

A (m) 7.28
B (d) 4.42
C (s) 3.79
D (d) 3.60
E (m) 2.64
F (m) 2.30
G (ddd) 1.41
1.00
0.95
0.30
0.26
0.13
0.08
0.03
OH
H
N
41i
f1 (ppm)


137.47
133.25
128.55
125.95
120.03
115.77
77.60
77.28
76.97
71.23
53.89
49.12
41.43
36.77
29.70
27.41
25.71
OH
H
N
41i
f1 (ppm)

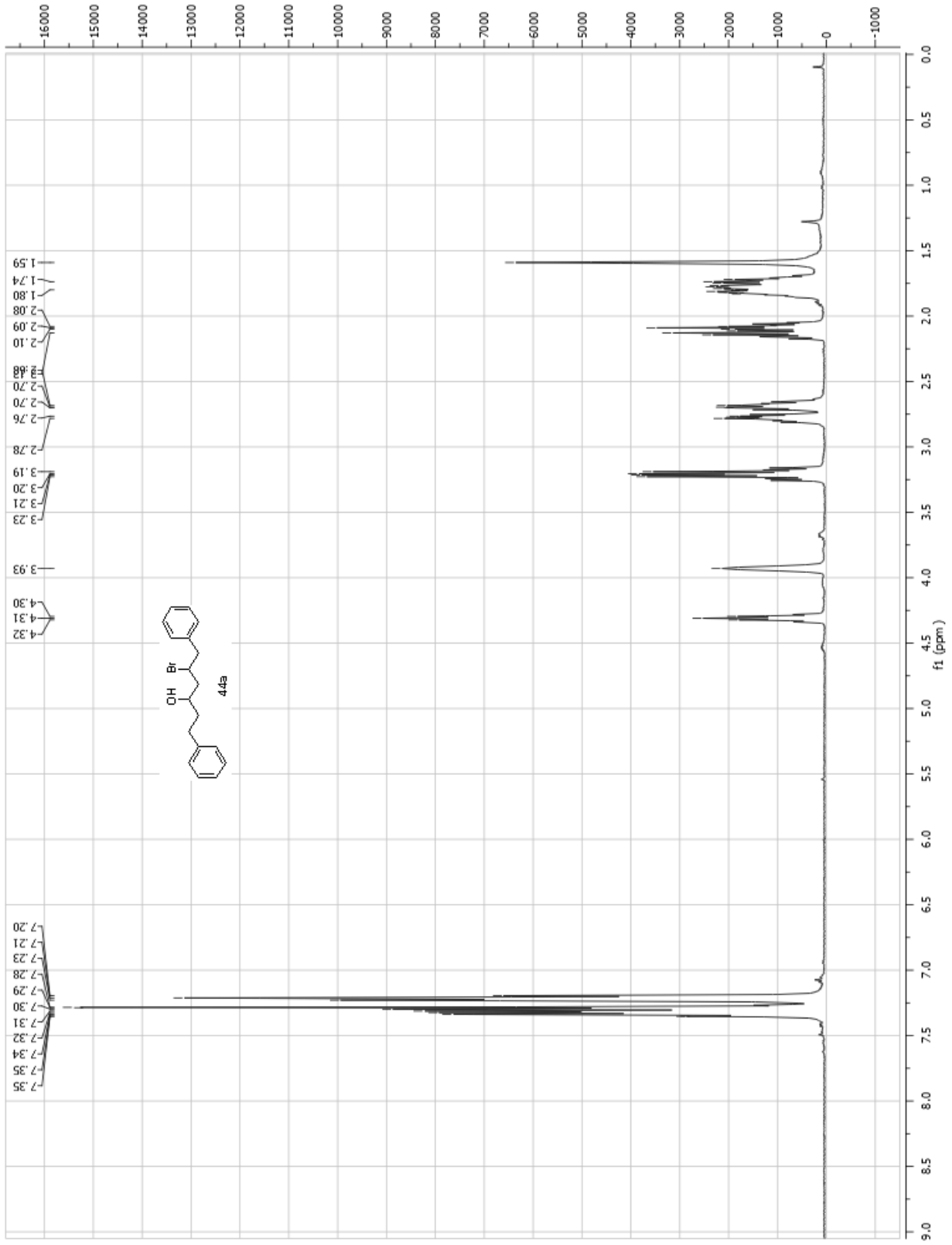

A (s) 3.66
B (m) 2.73
C (m) 1.78
E (m) 7.16
OH
D
44
f1 (ppm)


OH Br
44a
A (m) 7.31
B (m) 4.57
C (m) 4.34
E (s) 3.95
D (m) 4.06
F (m) 3.24
G (m) 2.76
H (m) 2.12
I (m) 1.83
47.19
18.33
5.85
10.74
7.35
3.46
1.33
2.85
1.00
f1 (ppm)

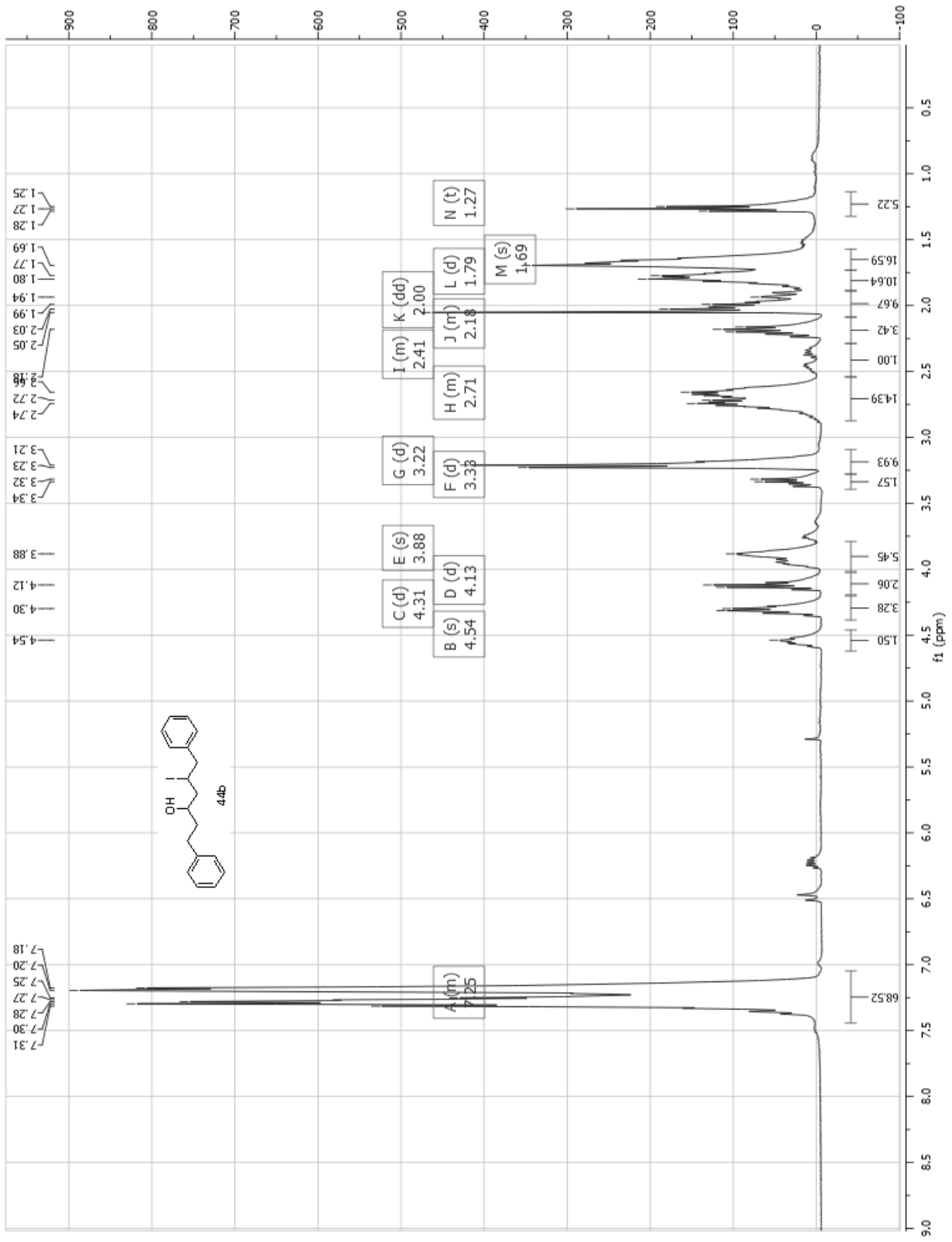

31.89
38.80
45.91
45.81
54.11
70.37
77.28
77.02
77.53
126.22
127.20
128.65
128.73
129.51
Br
OH
44a
f1 (ppm)

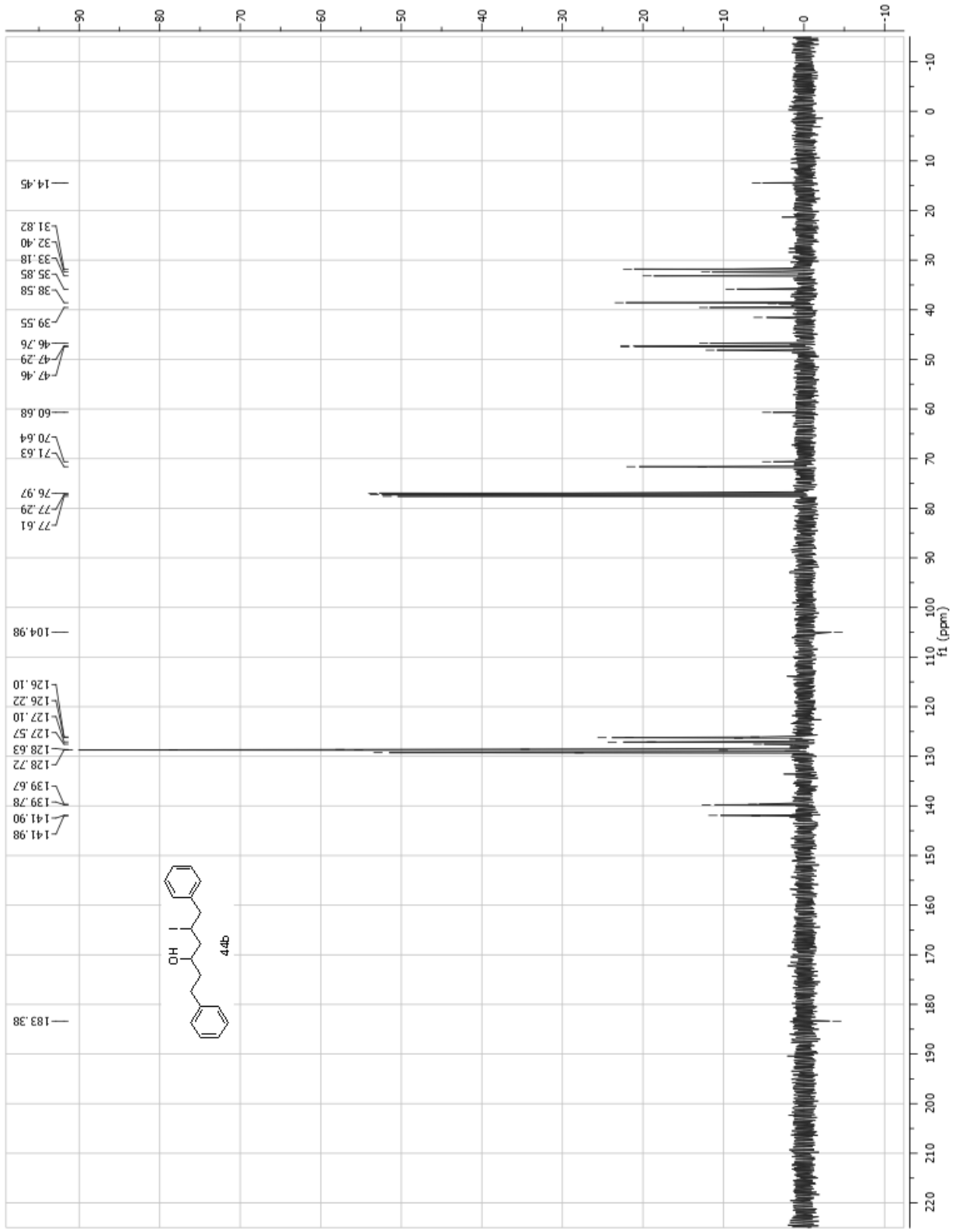


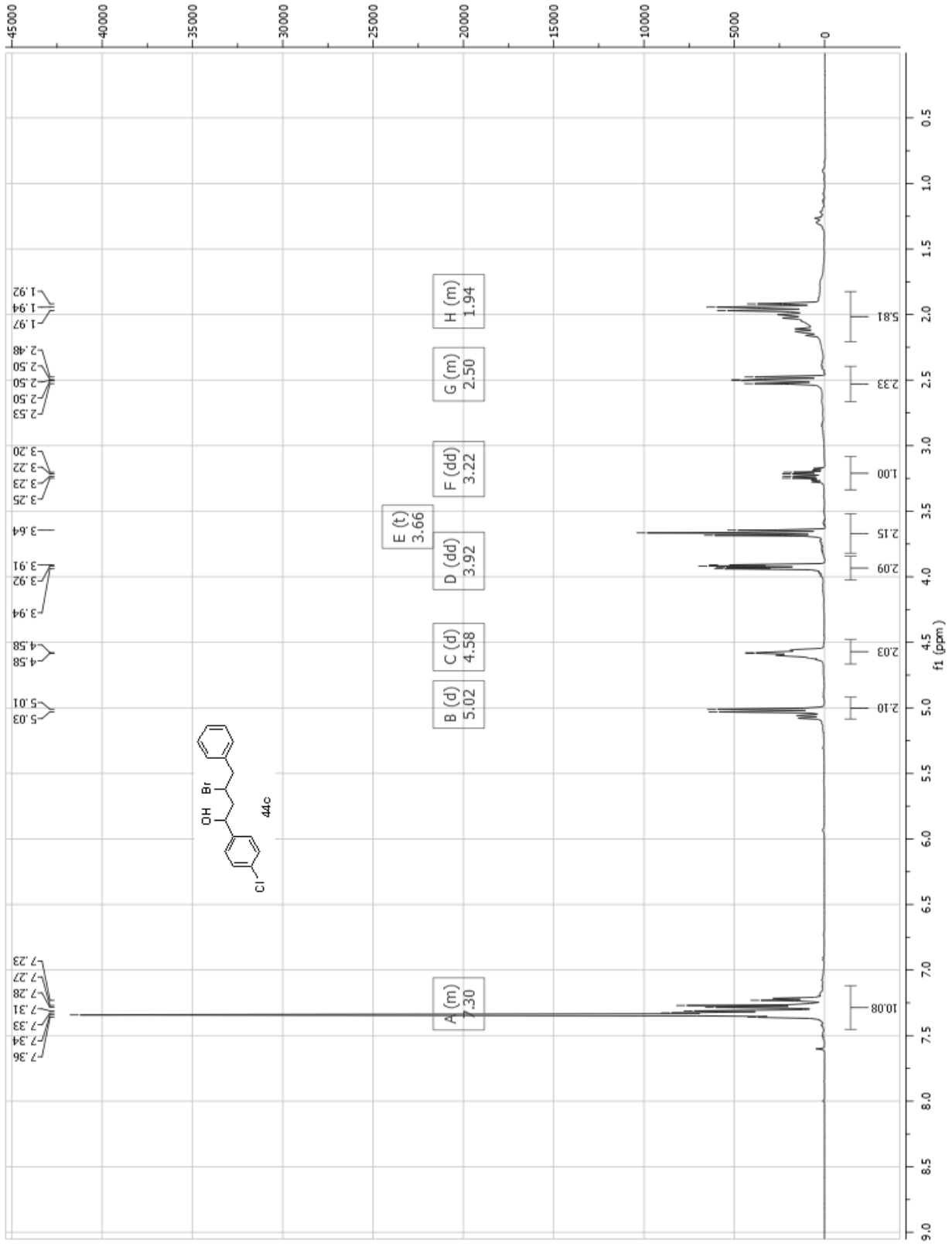
Diastereomer 1

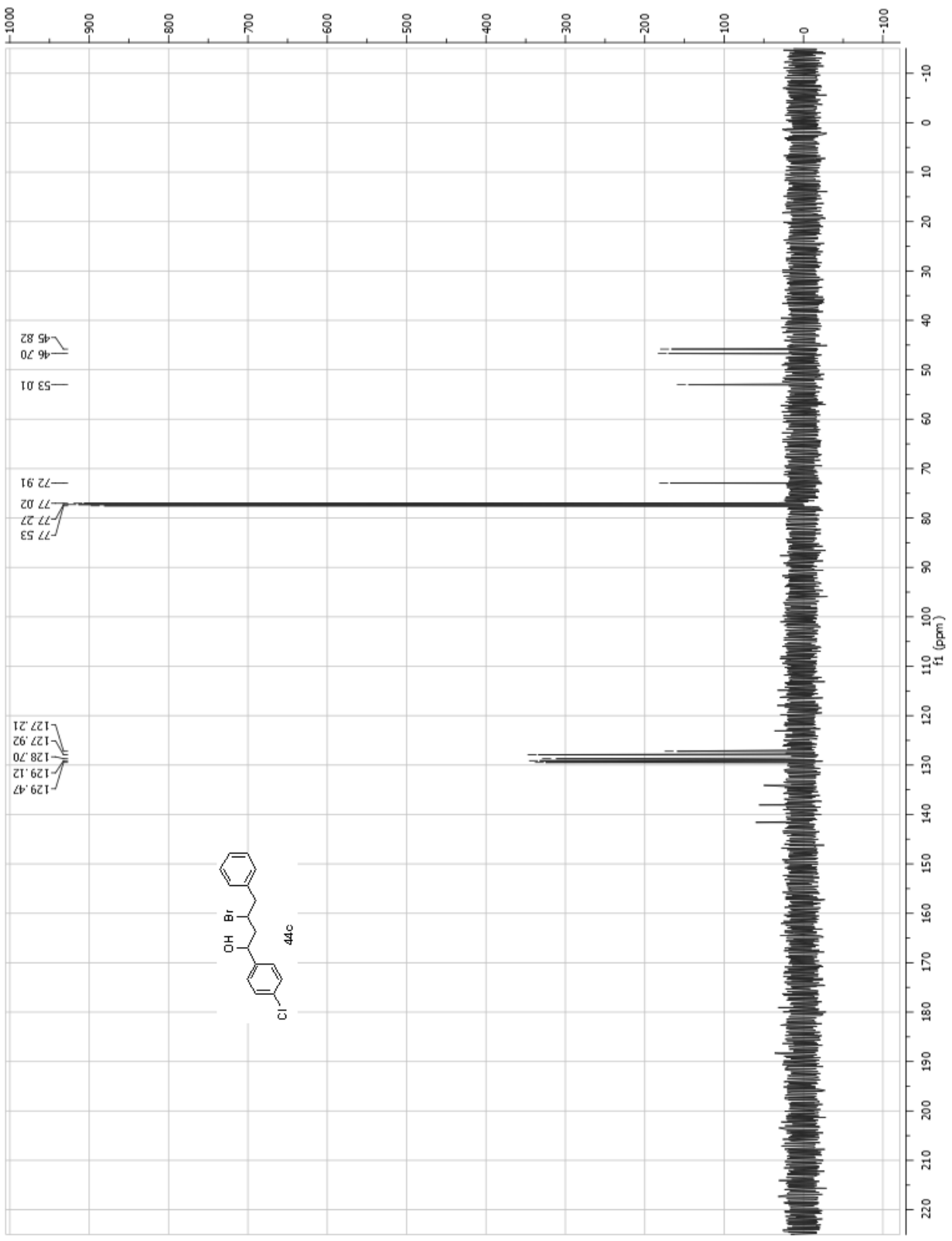


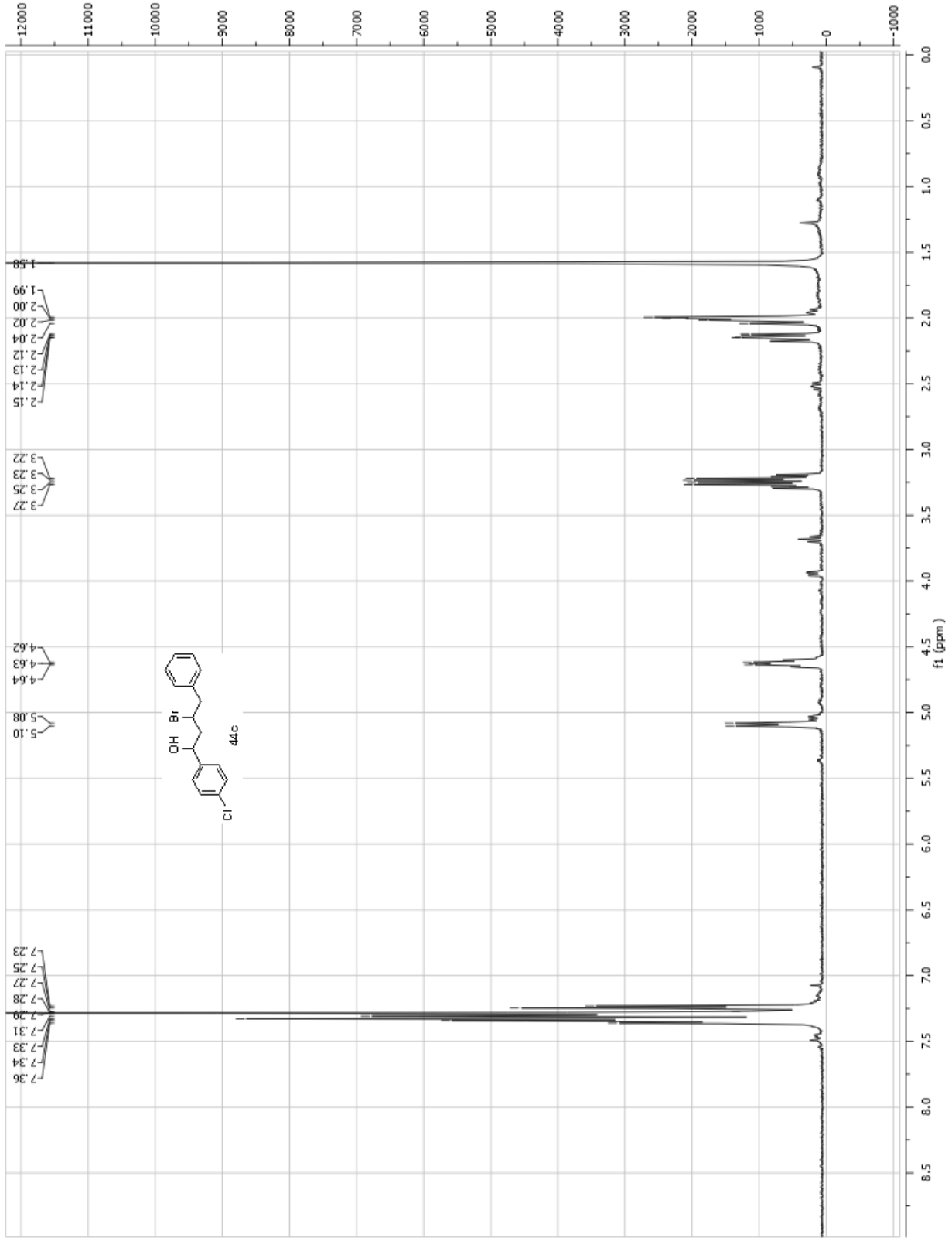
Diastereomer 2


A (m) 7.25
B (s) 4.54
C (d) 4.31
D (d) 4.13
E (s) 3.88
F (d) 3.38
G (d) 3.22
H (m) 2.71
I (m) 2.41
J (m) 2.18
K (dd) 2.00
L (d) 1.79
M (s) 1,69
N (t) 1.27
44b
f1 (ppm)

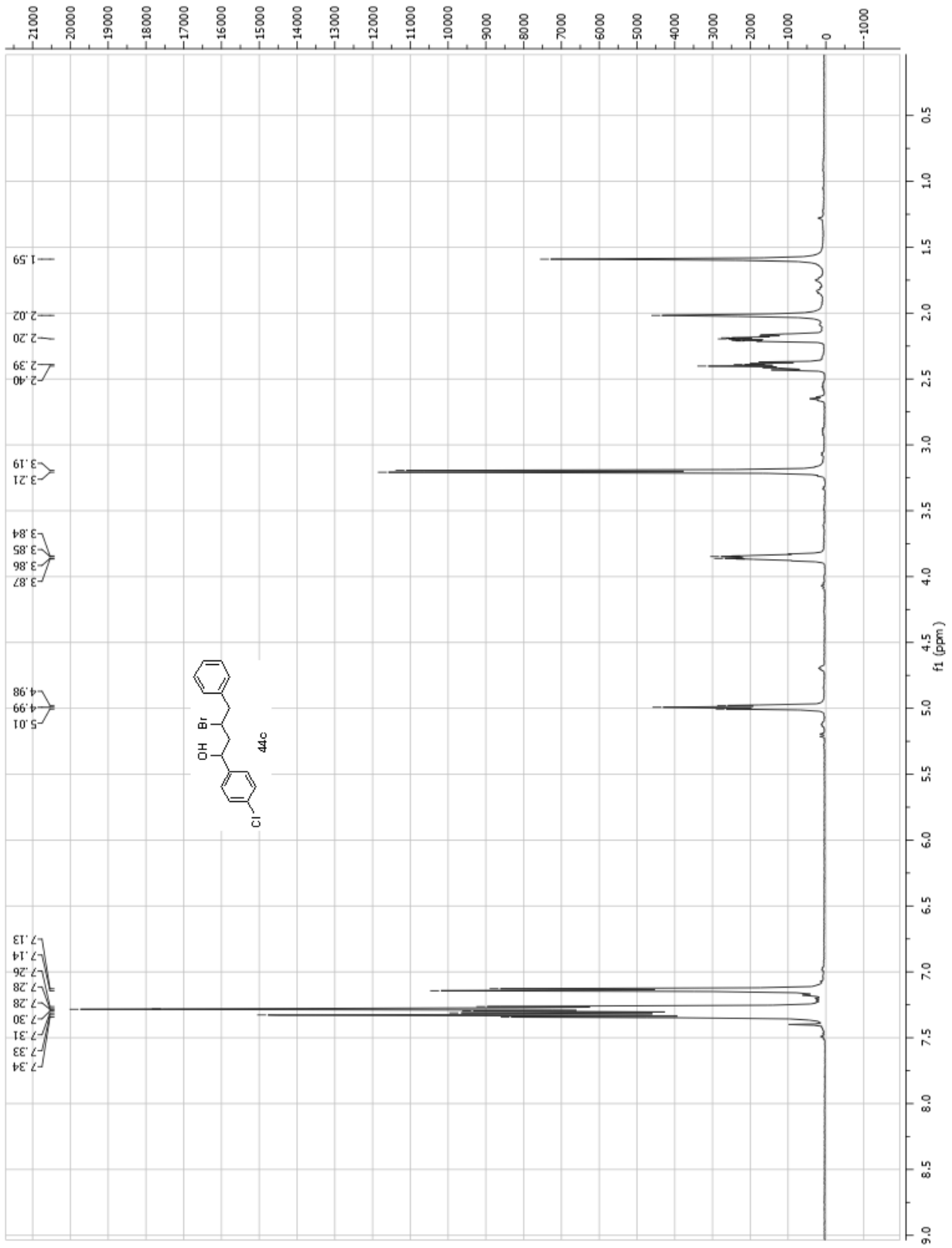

14.45
31.82
32.40
33.18
35.85
38.58
39.55
46.76
47.29
47.46
60.68
70.64
71.63
76.97
77.29
77.61
104.98
126.10
126.22
127.10
127.57
128.63
128.72
139.67
139.78
141.90
141.98
183.38
OH
44b
f1 (ppm)


A (m) 7.30
B (d) 5.02
C (d) 4.58
D (dd) 3.92
E (t) 3.66
F (dd) 3.22
G (m) 2.50
H (m) 1.94
OH Br
Cl
44c
f1 (ppm)

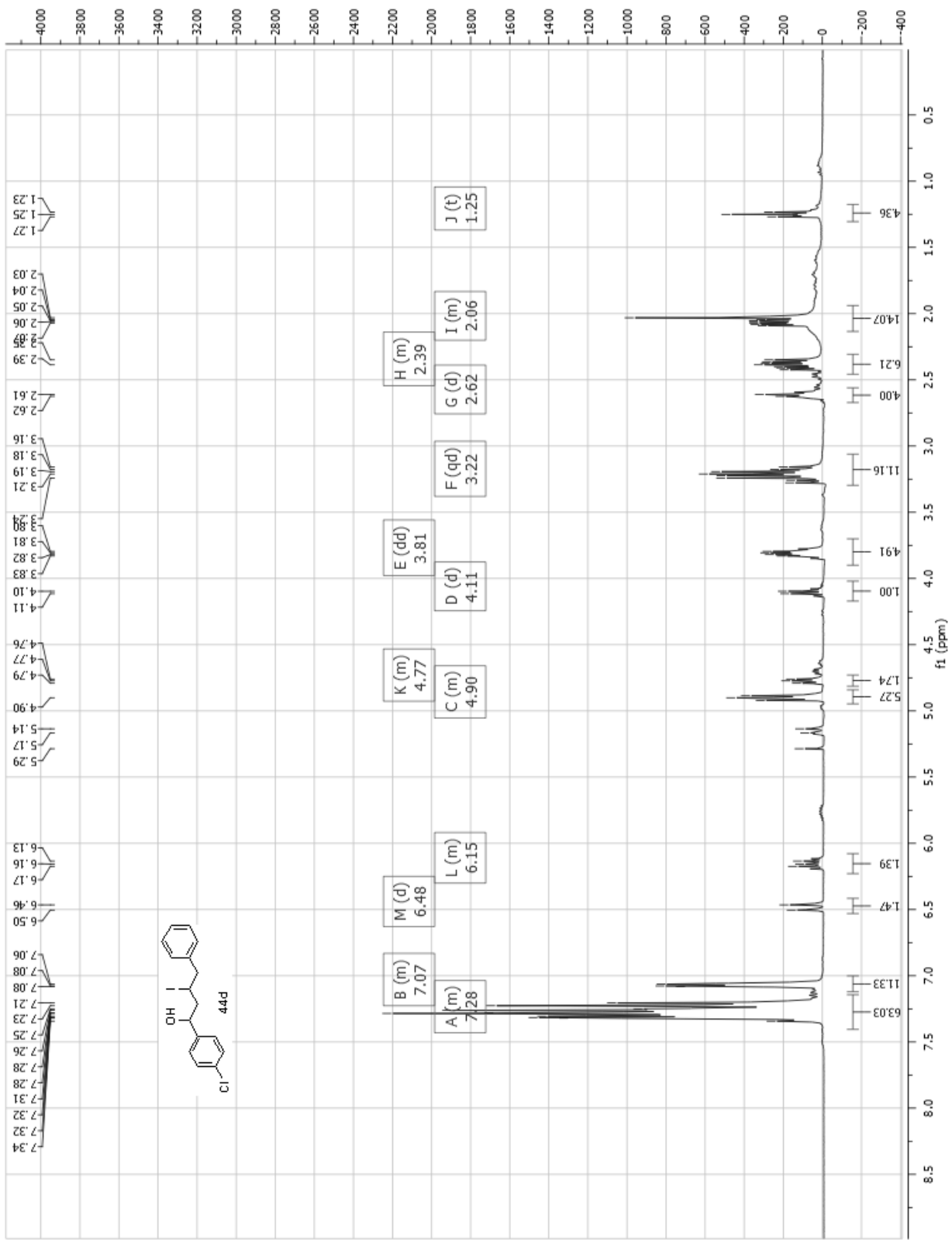

46.82
46.70
53.01
72.91
77.02
77.27
77.53
127.21
127.92
128.70
129.12
129.47
OH Br
Cl
44c
f1 (ppm)

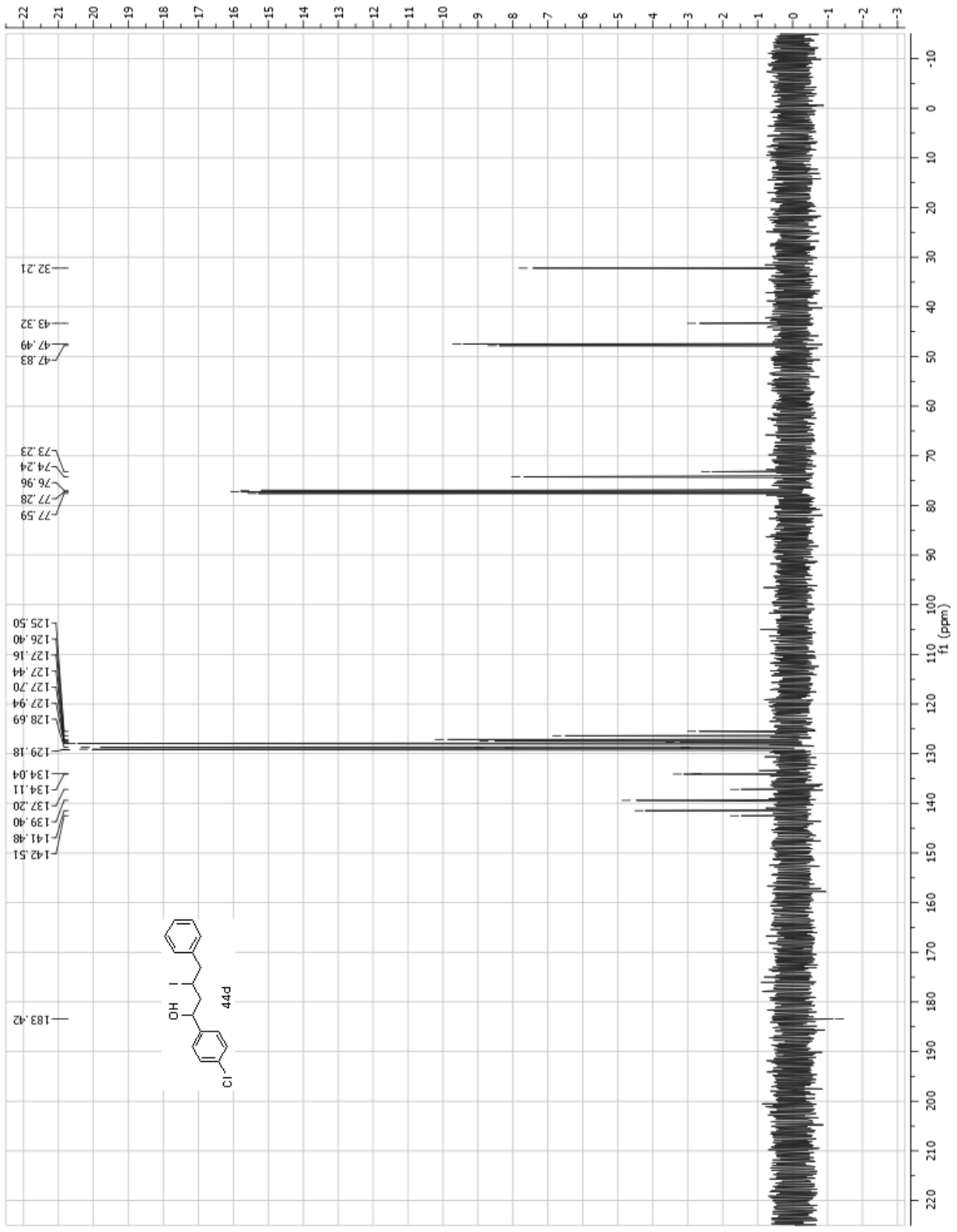


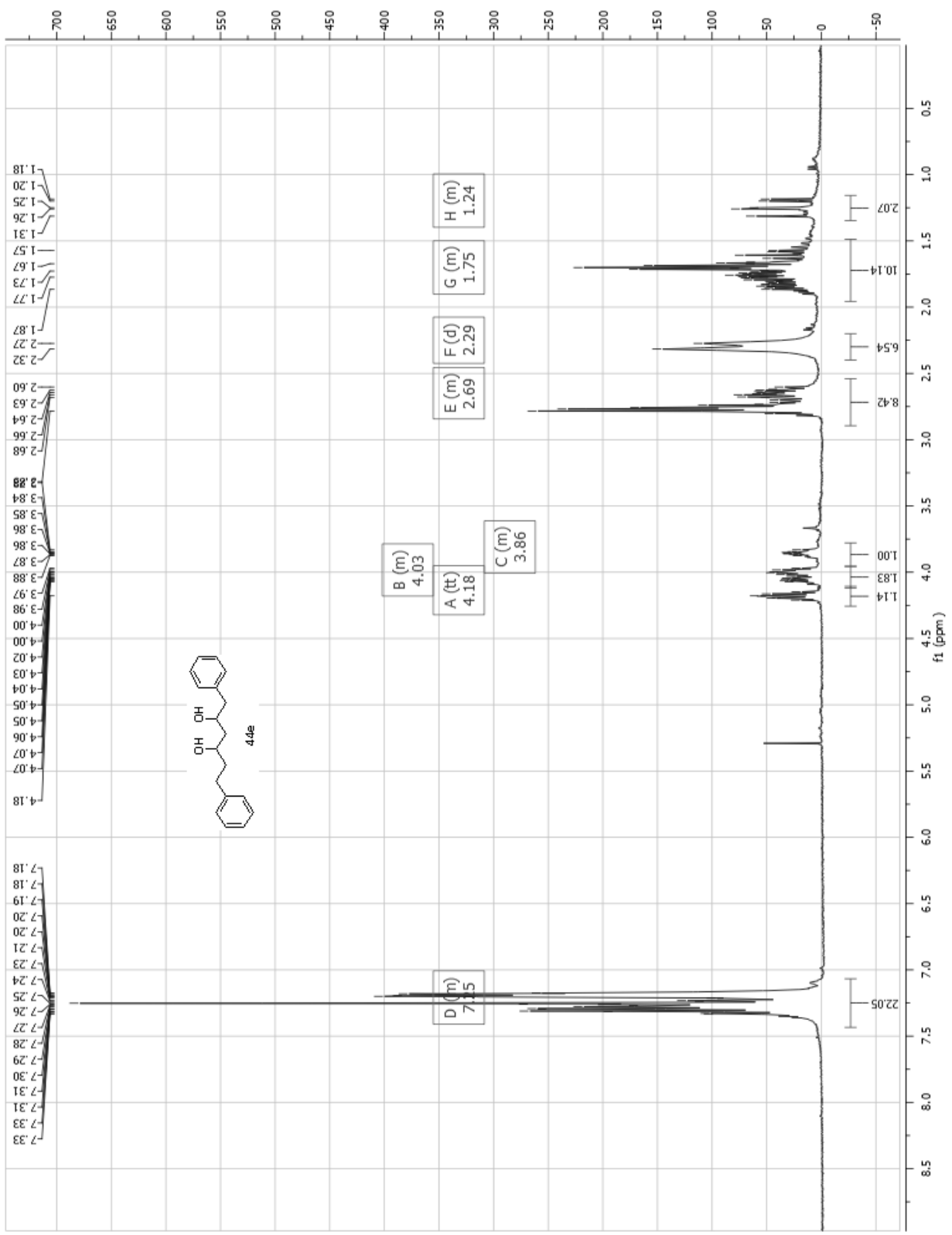
Diastereomer 1

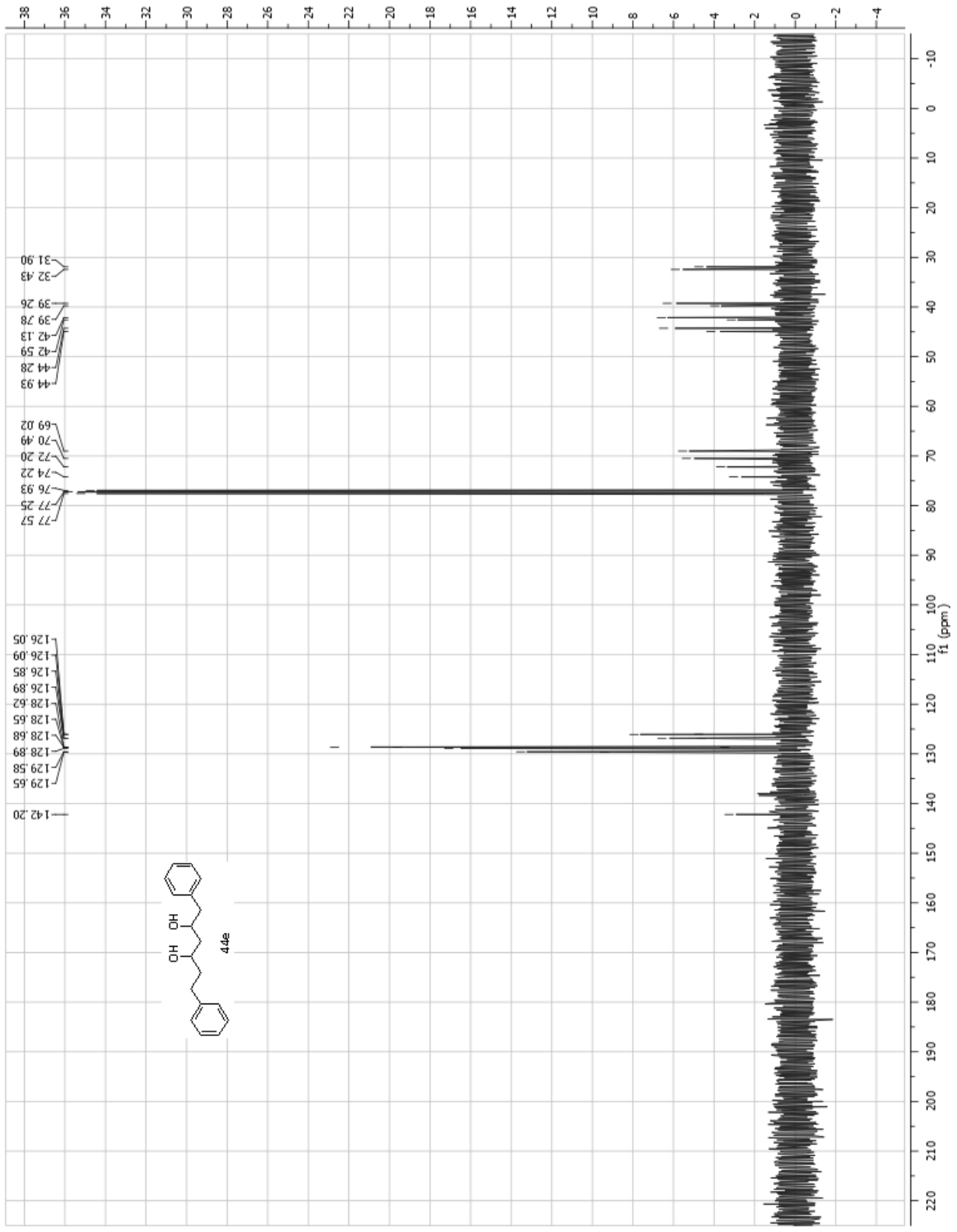


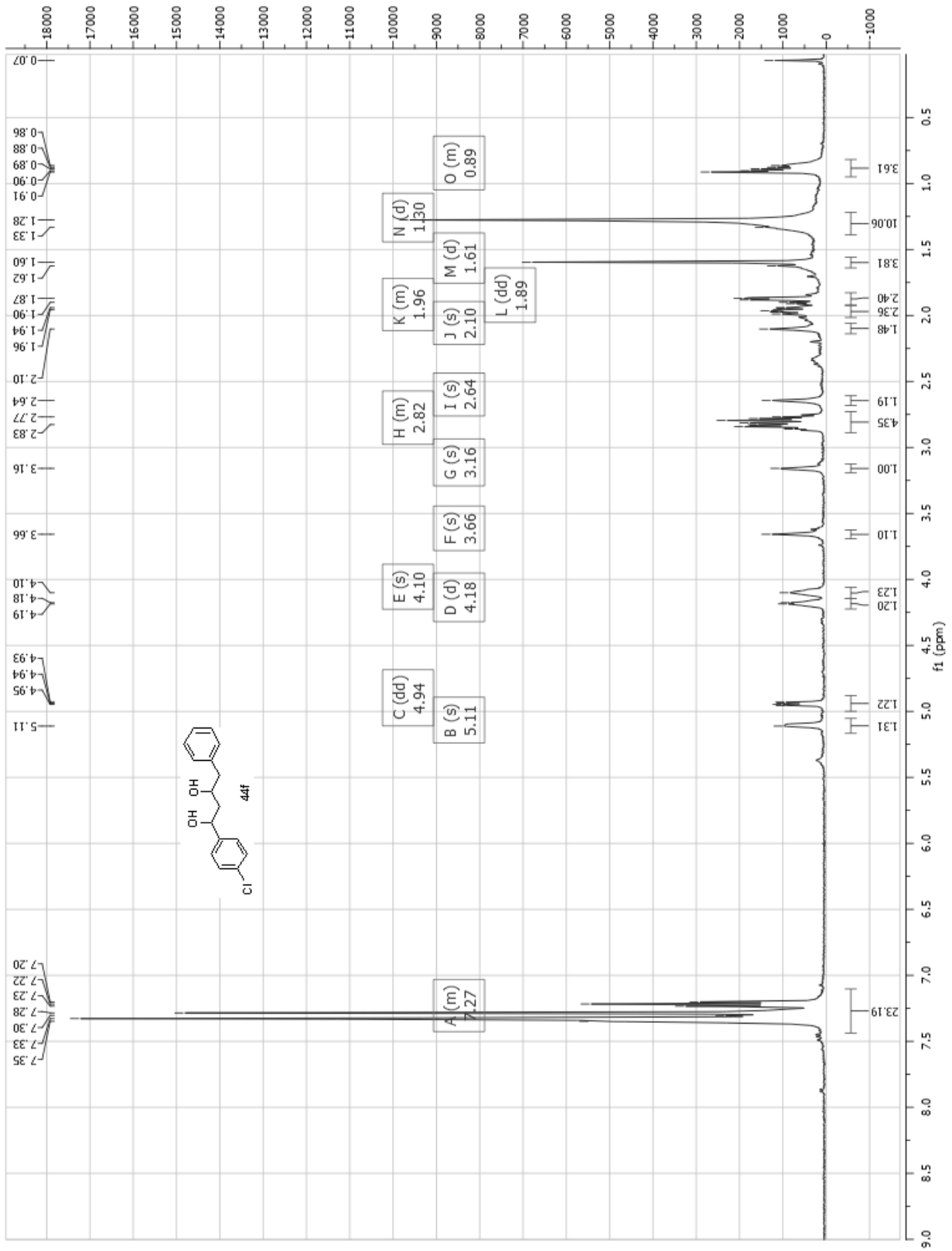
Diastereomer 2

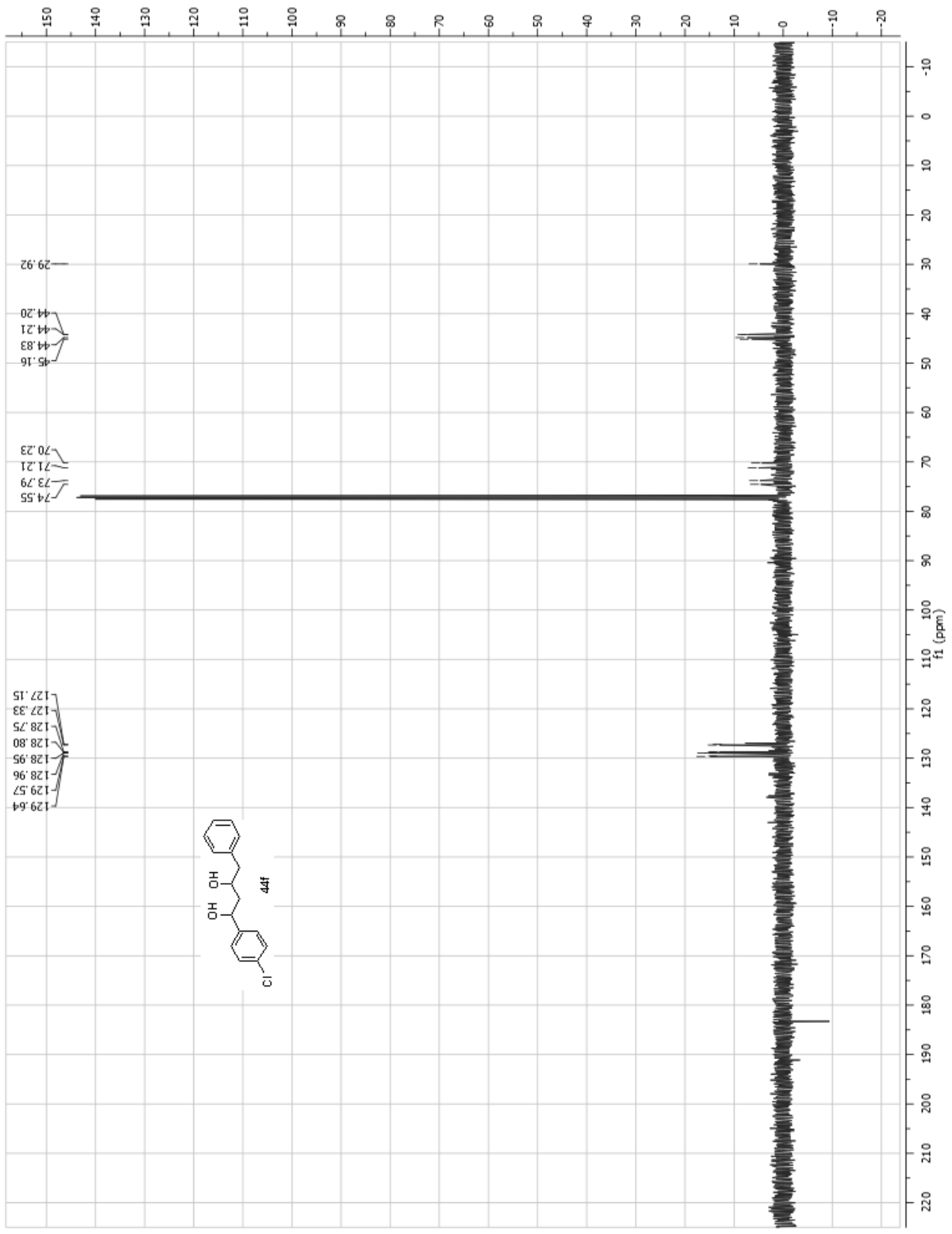

A (m) 7.28
B (m) 7.07
C (m) 4.90
D (d) 4.11
E (dd) 3.81
F (qd) 3.22
G (d) 2.62
H (m) 2.39
I (m) 2.06
J (t) 1.25
K (m) 4.77
L (m) 6.15
M (d) 6.48
OH
Cl
44d
f1 (ppm)


183.42
142.51
141.48
139.40
137.20
134.11
134.04
129.18
128.69
127.94
127.70
127.44
127.16
126.40
125.50
77.59
77.28
76.96
74.24
73.23
47.83
47.49
43.32
32.21
OH
Cl
44d
f1 (ppm)


D (m) 7.15
A (tt) 4.18
B (m) 4.03
C (m) 3.86
E (m) 2.69
F (d) 2.29
G (m) 1.75
H (m) 1.24
22.05
1.14
1.83
1.00
8.42
6.54
10.14
2.07
OH
OH
44e
f1 (ppm)


31.90
32.43
39.26
39.78
42.13
42.59
44.28
44.93
69.02
70.49
72.20
74.22
76.93
77.25
77.57
126.05
126.09
126.85
126.89
128.62
128.65
128.68
128.89
129.58
129.65
142.20
OH
OH
44e
f1 (ppm)


A (m) 7.27
B (s) 5.11
C (dd) 4.94
D (d) 4.18
E (s) 4.10
F (s) 3.66
G (s) 3.16
H (m) 2.82
I (s) 2.64
J (s) 2.10
K (m) 1.96
L (dd) 1.89
M (d) 1.61
N (d) 1.30
O (m) 0.89
44f
OH
OH
Cl
f1 (ppm)


29.92
44.20
44.21
44.83
45.16
70.23
71.21
73.79
74.55
127.15
127.33
128.75
128.80
128.95
128.96
129.57
129.64
OH
OH
Cl
44f
f1 (ppm)

Bibliography:

1. Daves, G.D. Jr.; Hallberg, A. *Chem.Rev.* **1989**, 89, p. 1433-1445
2. Heck, R.F.; Nolley, J.P. Jr. *J . Org. Chem.*, **1972**, Vol. 37, No. 14, p. 2320-2322
3. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Japan*, **1971**, Vol.44 , No.2, p. 581
4. Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 21, No. 11, p. 2177
5. White, C.M.; Delcamp, J.H.; Brucks, A.P. *J. Am. Chem. Soc.*, **2008**, 130, p. 11270-11271
6. Danishefsky, S.J.; Masters, J.J.; Young, W.B.; Link, J.T.; Snyder, L.B.; Magee, T.V.; Jung, D.K.; Isaacs, R.C.A.; Bornmann, W.G.; Alaimo, C.A.; Coburn, C.A.; Di Grandi, M.J. *J. Am. Chem. Soc*. **1996**, 118, p. 2843-2859
7. Hong, C.Y.; Kado, N.; Overman, LE. *J. Am. Chem. Soc*. **1993**,115, p. 11028-11029
8. Earley, W.G.; Jacobsen, J.E.; Madin, A.; Meier, G.P.; O'Donnell, C.J.; Oh, T.; Old, D.W.; Overmann, L.E.; Sharp, M.J. *J. Am. Chem. Soc*., **2005**, 127, 51, p. 18046–18053
9. Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1996**, 118, p. 7108-7116
10. DeLuca, R.J.; Sigman, M.S. *J. Am. Chem. Soc*. **2011**, 133, p. 11454–11457
11. Kulinkovich, O.G.; De Meijere, A. *Chem. Rev.* **2000**, 100, p. 2789-2834
12. Wu, Y.D.; Yu, Z.X.; *J. Am. Chem. Soc.*, **2001**, 123, 24, p. 5777–5786
13. Lee, J.; H. Kim, H.; Cha, J.K. *J. Am. Chem. Soc*., **1996**, 118, p. 4198-4199
14. Chaplinski, V.; De Meijere, A. *Angew. Chem. Int. Ed.,* **1996**, 35, No. 4, p. 413-414
15. Lysenko, I.L.; Kim, K.; Lee, H.G.; Cha, J.K. *J. Am. Chem. Soc*. **2008**, 130, p. 15997–16002
16. Takahashi, M.; McLaughlin, M.; Micalizio, G.C. *Angew. Chem. Int. Ed*. **2009**, 48, p. 3648 – 3652
17. Lee, K.; Ready, J.M.; *Angew. Chem. Int. Ed*. **2011**, 50, p. 2111-2114

18. Das, P.P.; Lysenko, I.L.; Cha, J.K. *Angew. Chem. Int. Ed*. **2011**, 50, p. 9459 –9461

19. Rieke, R.D.; Hanson, M.V.; Brown, J.D. *J. Org. Chem*. **1996**, 61, p. 2726-2730

20. King, A.O.; Nobuhisa, O.; Negishi, E.I, *J. Chem. Soc., Chem. Comm*., **1977**, 19, p. 683-684

21. Hansen, M.M.; Bartlett, P.A.; Heathcock, C.H. *Organometallics* **1987**, 6, p. 2069-2074

22. Zhang, G.W.; Meng, W.; Ma, H.; Nie, J.; Zhange, W.Q.; Ma, J.A. *Angew. Chem. Int. Ed*. **2011**, 50, p. 3538 –3542

23. Balakrishnan, M.; Cha, J.K. *Tet. Lett.,* **2010**, 51, p. 5571–5573

24. Angle, S.R.; Louie, M.S. *J. Org. Chem*. **1991**, 56, p. 2853-2866