PREPARATION AND NOVEL APPLICATIONS OF TRIHALOMETHYL CARBINOLS

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ABSTRACT

Trihalomethyl carbinols have been widely used in organic chemistry and pharmaceutical chemistry as useful intermediates in the preparation of a wide variety of functional groups. Since the discovery of the Jocic reaction in 1897, significant effort has been put into the research of the reaction mechanism as well as the application of trichloromethyl carbinols. Upon deprotonation, the resultant *gem*-dichloroepoxide serves as a key intermediate to furnish a wide variety of organic molecules. These possible products include: carboxylic acids, amides, esters, heterocycles, etc. Herein, we report a convenient one-pot method to convert primary alcohols to their corresponding trichloromethyl carbinols using Dess-Martin periodinane in chloroform followed by the addition of a commercially available guanidine base 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD). A variation of this one-pot method was also developed when basic conditions are not suitable. This method exhibit great functional group tolerance, as well as absolute stereochemical fidelity. By bypassing the formation and the isolation of the intermediate aldehyde, this operationally simple method also reduces preparation time and limits waste associated with workup and purification.

In addition, a one-pot method to furnish primary, secondary and tertiary amides from their corresponding trichloromethyl carbinols was developed. Notably, when used in conjunction

with our one-pot trichloromethyl carbinol conversion procedure, this represents the first method to access one-carbon homologated amides from any primary alcohols or aldehydes in two steps. This method boasts excellent compatibility with a wide range of function groups including aryl, alkyl, alkenyl, chiral substituents, and unprotected amino acids.

Thirdly, we report a method to generate primary alcohols from the corresponding trichloromethyl carbinols. Similar to the amide homologation procedure, this showcases a two-step method to convert primary alcohols and aldehydes to their corresponding one-carbon homologated alcohols. The excellent substrate scope and ease of operation make this method an attractive and versatile approach to one-carbon homologation.

Finally, we report some preliminary results on the enantioselective trihalomethylation of aldehydes. A series of chiral catalysts and Lewis aci.ds were screened. Some catalyst systems showed excellent potential, matching the current best published results in asymmetric trifluoromethylations of aldehydes.

DEDICATION

In loving memory of 李世江 先生.

LIST OF ABBREVIATIONS AND SYMBOLS

$[\alpha]_D^{20}$	Specific rotation
^{13}C NMR	Carbon NMR spectrum
$CDCl_3$	Chloroform-*d*
CERT	Ceramide trafficking
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
E	Entgegen (opposite, *trans*-)
ee	Enantiomeric excess
Equiv	Equivalent
^{19}F NMR	Fluorine NMR spectrum
Et	Ethyl
g	Gram

GC-MS	Gas chromatography-mass spectrometry
h	Hour
HRMS	High resolution mass spectrometry
^{1}H NMR	Proton NMR spectrum
IC_{50}	50% median inhibition concentration
M	Molar
µL	Microliter
mL	Milliliter
mmol	Millimole
mol	Mole
Nu^{-}	Nucleophile
NMR	Nuclear magnetic resonance
p-	*Para*-
pK_a	Acidity constant
Ph	Phenyl
(*R*)-	Rectus (clockwise)
rt	Room temperature
(*S*)-	Sinister (counterclockwise)

t-	*tert-*
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TCA	Trichloroacetic acid
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofuran
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
TTA	Trimethylsilyl trichloroacetate

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1.1. Background

Zicojin Jocic reported the first transformation of a trichloromethyl carbinol to its carboxylic acid derivative in 1897.[1] After stirring the 2,2,2-trichloro-1-phenylethanol (**1**) in 10% aqueous

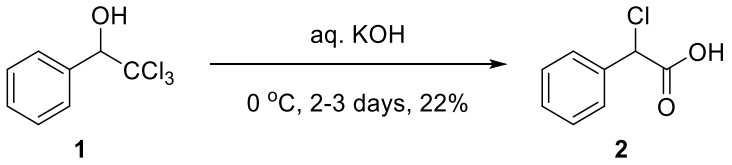
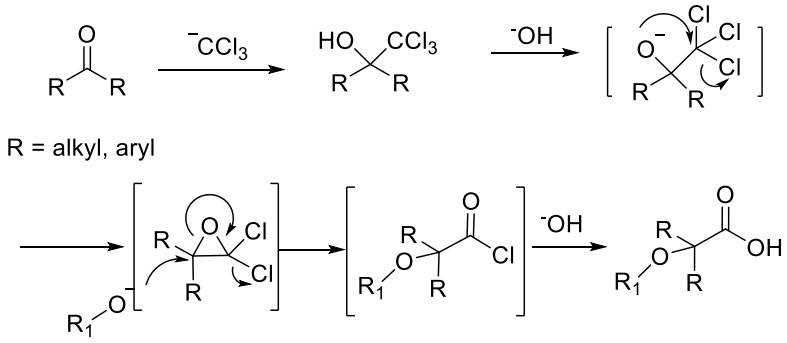


Figure 1.1 Conversion of 2,2,2-trichloro-1-phenylethanol to 2-chloro-2-phenylacetic acid by Zicojin Jocic

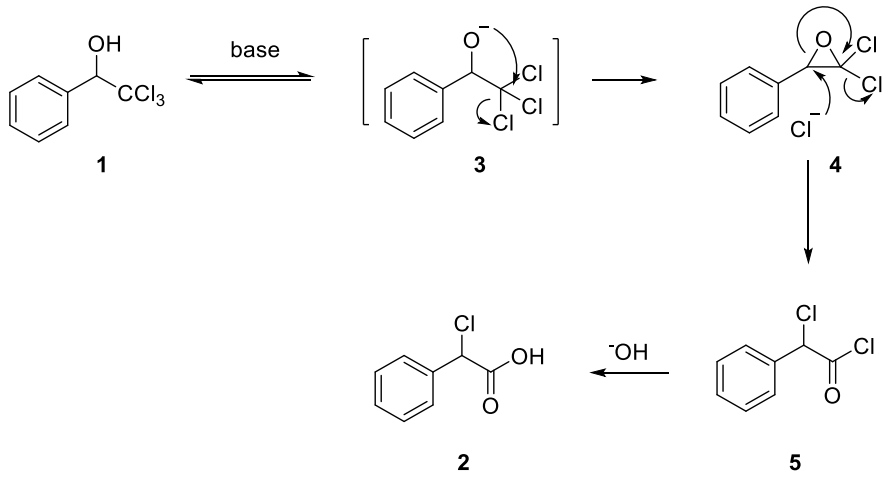


Scheme 1.1 The Bargellini reaction

KOH, 2-chloro-2-phenylacetic acid (**2**) was formed and isolated in 27% yield (Figure 1.1). The Bargellini reaction is similar, but involves formation of a tertiary trichloromethyl carbinol instead of a secondary trichloromethyl carbinol (Scheme 1.1).[2] However, it wasn't until the mid

[1] Jocic, Z. *Zh. Russ. Fiz. Khim. Ova*. **1897**, *29*, 97-99.
[2] Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329-339.

to late 1900s, by the work of Wilkins Reeve, when this reaction mechanism was investigated (Scheme 1.2).[3,4] Reeve reported that the reaction of 2,2,2-trichloroethanol with aqueous potassium hydroxide did not proceed at 0 ºC, however, it progressed slowly at 25 ºC. Through

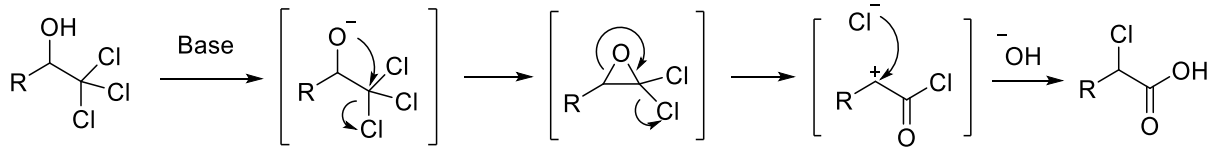


Scheme 1.2 The proposed mechanism for the formation of **2**

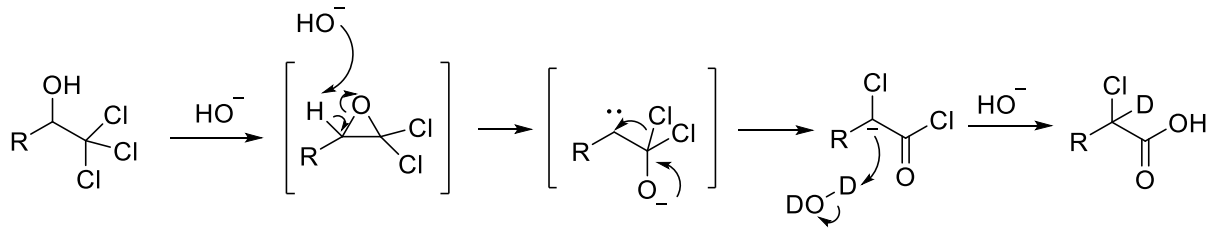
the addition of radioactive chloride ion to the reaction, Reeve concluded that the α-chloride product was formed predominantly (83%) by an intramolecular rearrangement by examining the products.

Reeve also proposed several possible reaction mechanisms and did a number of mechanistic studies to confirm the correct mechanism. He first concluded that it is necessary for the starting trichlorocarbinol to have an α-proton since the reaction did not proceed under his experimental conditions with tertiary trichlorocarbinols. It is a requirement for the reaction to be carried out in basic and aqueous conditions. Lastly, the reaction proceeded through the intramolecular 1,2-chloride shift.

[3] Reeve, W.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem*. **1980**, *58*, 485-493.
[4] Reeve, W.; Bianchi, R. J.; McKee, J. R. *J. Org. Chem*. **1975**, *40*, 339-342.

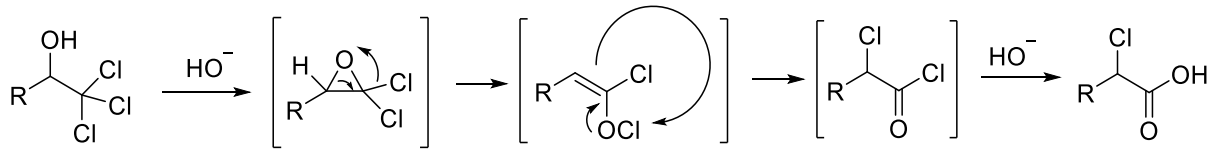


Scheme 1.3. The carbonium ion mechanism

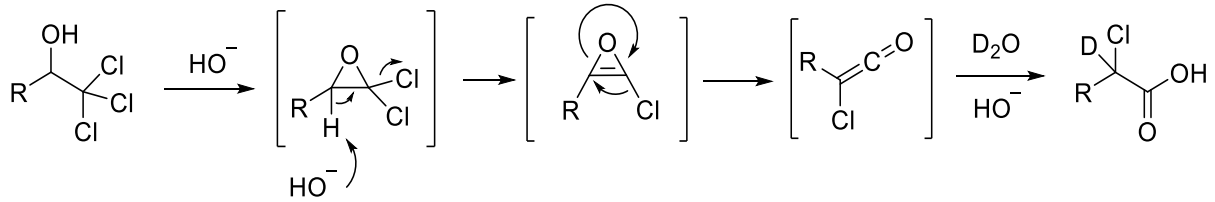


Scheme 1.4. The carbene mechanism

The mechanisms considered by Reeve include: the carbonium ion mechanism (Scheme 1.3), the carbene mechanism (Scheme 1.4), the enol hypochlorite mechanism (Scheme 1.5), and the chlorooxirene mechanism (Scheme 1.6). Reeve performed a test reaction with neopentyl



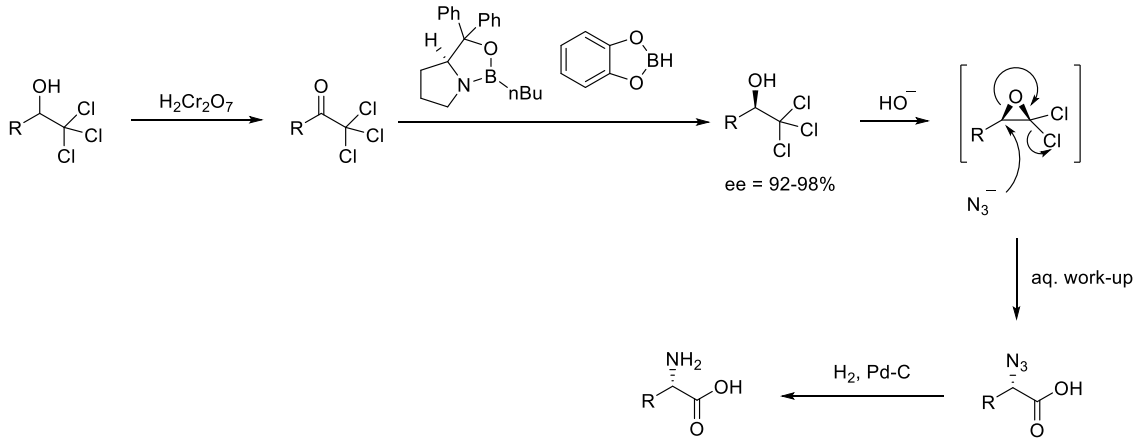
Scheme 1.5. The enol hypochlorite mechanism



Scheme 1.6. The chlorooxirene mechanism

trichloromethyl carbinols and found no rearrangement occurred during the reaction. The carbonium ion mechanism also did not explain the necessity for a base to be included in the

reaction. To test the carbene mechanism, Reeve carried out the reaction in deuterium oxide and found no deuterium substitution at the α-position of the acyl chloride. Therefore, the carbene mechanism was deemed improbable. Nextly, Reeve suggested the mechanism could involve an enol hypochlorite intermediate. The migration of chloride on the *gem*-dichloroepoxide intermediate to the oxygen forms the enol hypochlorite which then chlorinates the α-carbon. However, this mechanism doesn't explain why this reaction fails with tertiary trichlorocarbinols. In addition, Reeve was not able to trap this enol hypochlorite intermediate with a variety of reducing agents. Lastly, Reeve proposed a chlorooxirene mechanism by which the *gem*-dichloroepoxide intermediate forms a highly strained chlorooxirene species, which then undergoes intramolecular 1,2-chloride shift to generate a chloroketene intermediate. Hydrolysis of the chloroketene should yield the α-chlorocarboxylic acid. This mechanism was also quickly excluded due to the fact that the α-hydrogen was not replaced by deuterium when the reaction was carried out in D_2O.[3] Revee concluded that the mechanism of the Jocic reaction by



Scheme 1.7 The Corey-Link reaction.

intramolecular chloride substitution could not be established, since none of the reaction mechanisms examined was fully consistent with the observed reaction outcome.

Corey and Link contributed in this area of chemistry, utilizing the *gem*-dichloroepoxide intermediate to report a method to prepare asymmetric α-azido acids, α-amino acids, and α-hydroxy acids from trichloromethyl carbinols (Scheme 1.7).[5,6]

1.1.1. Applications of Trichloromethyl Carbinols

Trichloromethyl carbinols can be used to prepare amino acids,[7,8,9] azidoacids,[8] carboxylic acids,[10,11,12] amides,[13] heterocycles such as halofurans,[14] substituted azetidines,[15] substituted thiazolidinones[16], and other useful organic compounds.[17,18] Romo, *et al.* reported an enantioselective synthesis of potent α-glucosidase inhibitors (IC_{50} = 48-170 nM) schulzeines B and C starting from the Wynberg lactone.[19] Snowden, *et al.* recently showcased a concise synthesis for HPA-12, a potent CERT inhibitor using a trichloromethyl carbinol as a key intermediate.[20] Trichloromethyl carbinols are also useful in the agriculture industry. For instance, dicofol， first manufactured by Rohm and Haas Company in 1957, is a tertiary trichloromethyl carbinol, which is currently being used as an insecticide on fruits and crops

[5] Corey, E. J.; Link, J. O. *Tetrahedron Lett,* **1992**, *33*, 3431-3434.
[6] Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett*. **1992**, *33*, 3435-3438.
[7] Scaffidi, A.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem*. **2004**, *57*, 723-732.
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[11] Cafiero, L. R.; Snowden, T. S. *Org. Lett*. **2008**, *10*, 3853-3856.
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[14] Ram, N. R.; Kumar, N. *Tetrahedron Lett.* **2008**, *49*, 799-802.
[15] Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3146-3150.
[16] Blanchet, J.; Zhu, J. *Tetrahedron Lett.* **2004**, *45*, 4449-4452.
[17] Li, J.; Xu, X.; Zhang, Y. *Tetrahedron Lett*. **2003**, *44*, 9349-9351.
[18] Snowden, T. S. *ARKIVOC*, **2012**, *ii*, 24-40.
[19] Liu, G.; Romo, D. *Org. Lett*. **2009**, *11*, 1143-1146.
[20] Snider, J. R.; Entrekin, J. T.; Snowden, T. S.; Dolliver, D. *Synthesis*, **2013**, *45*, 1899-1903.

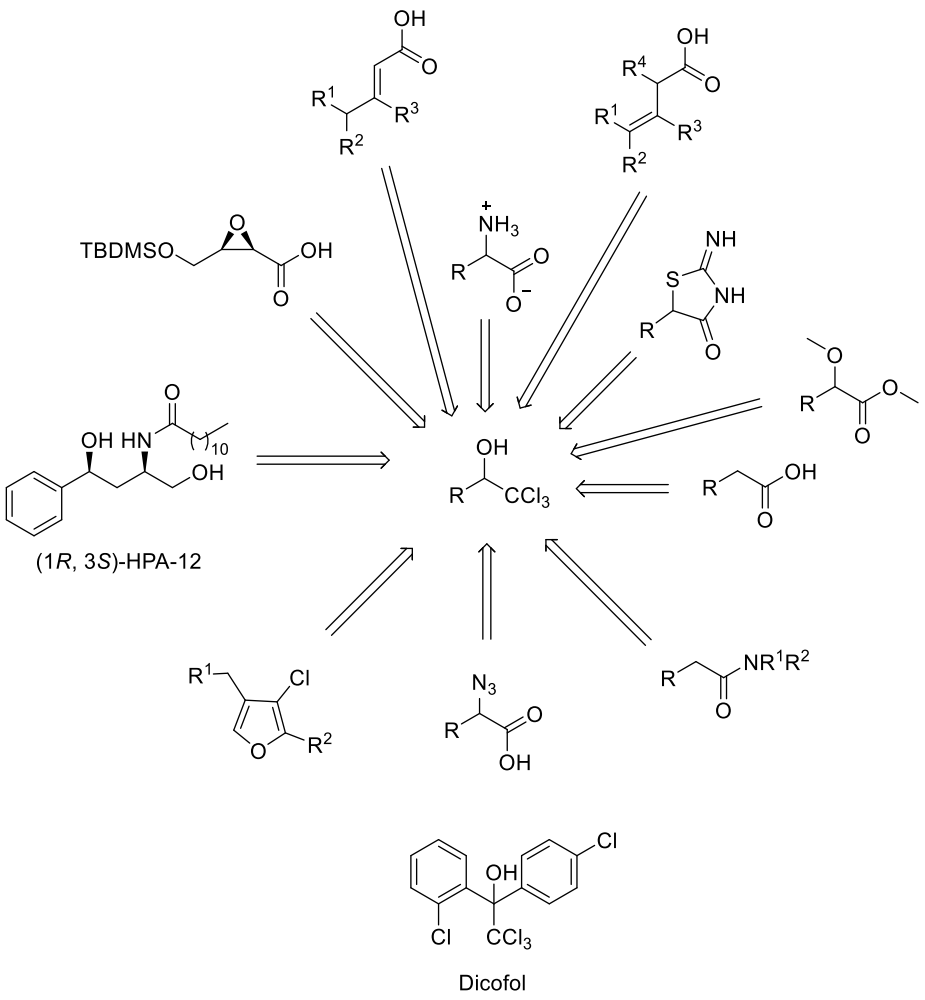


Figure 1.2. Applications of trichloromethyl carbinols.

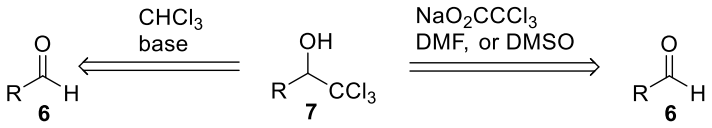
(Figure 1.2).[21] The versatility of trichloromethyl carbinols also makes them attractive functionalities for organic synthesis.

1.1.2. Preparation of Trichloromethyl Carbinols from Aldehydes

Traditionally, trichloromethyl carbinols (**7**) are prepared by the nucleophilic addition of trichloromethide carbanion to the corresponding aldehydes (**6**) (Scheme 1.8). Generation of the

[21] Hoekstra, P. F.; Burnison, B. K.; Garrison, A. W.; Neheli, T.; Muir, D. C. G. *Chemosphere*, **2006**, *64*, 174-177,

trichloromethide can either be achieved through the deprotonation of chloroform (pK_a = 13.6)[22]



Scheme 1.8 Methods to prepare trichloromethyl carbinols from aldehydes

with an appropriate base,[23,24] or through the decarboxylation of sodium trichloroacetate[25] in either DMF or DMSO. The formation of the trichlorocarbinol is faster when treating chloroform with a base; however, it is not compatible with enolizable aldehydes, which are subject to aldol reactions. The presence of the base will generate the corresponding enolate and therefore promote unwanted side reactions.

Many aldehydes are unstable because they are highly electrophilic. For example, aldehydes can undergo homoaldol type reactions, readily form hydrates and hemiacetals, and are able to disproportionate into the corresponding carboxylic acids and alcohols by a Canizzaro-type reaction,[26] among others. However, alcohols are generally more stable, and this makes them attractive to develop a method to convert the primary alcohols to their corresponding trichloromethyl carbinols in one pot without the need to isolate the intermediate aldehydes. This one-pot strategy would eliminate the isolation and purification of the less-stable aldehyde, resulting in a more efficient and economical process.

1.2. Preparation of Trichloromethyl Carbinols from Primary Alcohols

[22] Scharlin, P. *Acta. Chemica. Scandinavica A* **1986**, *40*, 207-209.
[23] Wyvratt, J. M.; Hazen, G. G.; Weinstock, L. M. *J. Org. Chem*. **1987**, *52*, 944-945.
[24] Aggarwal, V. K.; Mereu, A. *J. Org. Chem*. **2002**, *65*, 7211-7212.
[25] Atkins, P. J.; Gold, V.; Marsh, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1239-1245.
[26] Cannizzaro, S. *Liebigs Ann.* **1853**, *88*, 129-130.

1.2.1. Objectives

Our objectives were to synthesize the desired trichloromethyl carbinols in one pot from the corresponding primary alcohol, with comparable or better isolated yields than the standard two-step procedures, and with a broad scope that is able to tolerate a wide range of substituents.

1.2.2. Determination of the Oxidation Conditions for the Alcohols

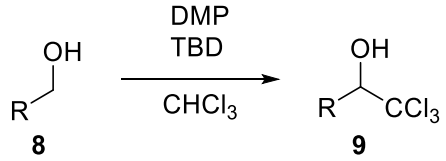
We envisioned that we could oxidize the alcohol to its corresponding aldehyde and subsequently promote the nucleophilic addition of the trichloromethide (generated *in situ*) to the aldehyde in the same reaction flask. With that in mind, a few oxidation protocols were tested. Because of the *in situ* generation of trichloromethide requires either chloroform, DMF or DMSO, we focused on oxidations that are compatible with those solvents. The modification of DMSO-based oxidation[27,28] was unsuccessful. The first oxidation attempted was the activation of DMSO with trichloroacetic anhydride following Albright and Goldman's report on oxidation of alcohols with dimethyl sulfoxide and acetic anhydride;[28] however, no oxidation was observed. A less polar byproduct was formed overnight with the starting material remaining. The next oxidation condition tested was the Swern oxidation. The oxidation went smoothly, furnishing the desired aldehyde. Encouraged by this result, we included sodium trichloroacetate in the reaction and found that this condition was able to furnish the desired trichloromethyl carbinol. However, the complete consumption of starting aldehyde was not able to be achieved. We also attempted the Swern oxidation with TBD or TMG as the base and chloroform as the solvent, envisioning that the base would deprotonate chloroform to generate the

[27] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
[28] Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416-2423.

trichloromethide *in situ*. However, a mixture of products was formed as well as the incomplete consumption of aldehyde after 48 h.

We next examined the oxidation protocol using Dess-Martin Periodinane (DMP).[29] The oxidation is typically carried out in dichloromethane, but we envisioned that by substituting the dichloromethane with chloroform, and using a base that is capable of deprotonating chloroform, the trichloromethide that is required for the nucleophilic addition could be generated *in situ.* Gratifyingly, we were able to obtain the desired trichloromethyl carbinols of aryl substrates in 83-87% yields (Table 1.1).

Table 1.1. Screening of primary alcohols for the one-pot conversion to trichloromethyl carbinols



8 **9**

Compound	R	Product	Yield[a]
8a	4-CH_3OPh	**9a**	83%
8b	Ph	**9b**	87%
8c	4-NO_2Ph	**9c**	85%

[a] Reactions carried out with 1.2 equivalent of DMP, 3.2 equivalent of TBD and 0.6 M concentration

1.2.3. Sources of Trichloromethide for the Trichloromethylation

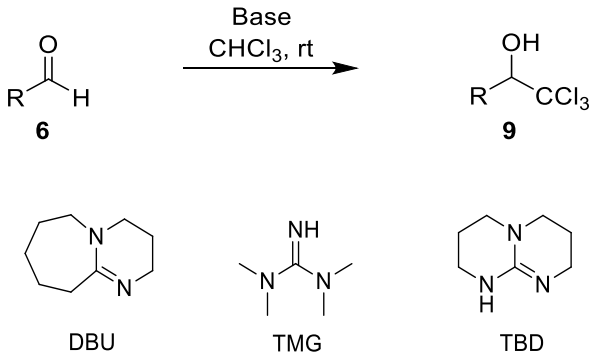
1.2.3.1. Screening of Bases Suitable for the One-Pot Conditions

Aggarwal reported that amidines such as DBU are able to promote the generation of trichloromethide from chloroform and furnish aryl trichloromethyl carbinols in high yield.[24] With that information in mind, we screened several bases and determined that neither triethylamine (TEA) nor 1,1,3,3-tetramethylguanidine (TMG) would generate the desired

[29] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277-7287.

product in satisfactory yield (Table 1.2). On the other hand, DBU and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) gave comparable and appealing results at high

Table 1.2. Screening of bases for trichloromethylation of benzaldehydes in chloroform



entry	R	[**6**][a] (M)	base	time (h)	**9**:**6** (%)[b]
1	Ph	2.5	Et_3N	24	<5:95
2	Ph	2.5	DBU	1	82:18
3	Ph	2.5	DBU	16	>98:2
4	Ph	2.5	TMG	1	23:77
5	Ph	2.5	TMG	24	86:14
6	Ph	2.5	TBD	1	90:10
7	Ph	2.5	TBD	3	>98:2
8	Ph	0.67	DBU	24	45:55
9	Ph	0.67	TBD	3	>98:2
10	4-CH_3OPh	0.67	DBU	24	26:74
11	4-CH_3OPh	0.67	TBD	24	87:13

[a]Reactions were conducted by treating **6** (0.50 mmol) with the corresponding base (0.60 mmol) in $CHCl_3$. [b] Relative percentages of **6** and **9** were determined by ^1H NMR analyses of crude reaction mixtures.

concentration (2.5 M). However, since the required oxidant DMP had limited solubility at 2.5 M concentration, we had to carry out the oxidation at 0.67 M concentration where the reaction could achieve homogeneity. We then retested the efficiency of the bases at this lower substrate concentration and discovered that TBD was a superior base to DBU, since TBD gave comparable conversion at both concentrations, whereas DBU was markedly less effective under the more dilute reaction conditions.

With the optimal base identified, we then started to optimize other reaction conditions. When the base was present at the outset with DMP and the primary alcohol, the yield of the desired trichloromethyl carbinols was unsatisfactory presumably due to the coordination of the guanidine to the acetoxyperiodinane intermediate. However, when TBD was added after the oxidation of the primary alcohol was complete, as indicated by TLC, the yield was much improved and comparable to the yield of the trichloromethylation from the aldehyde. We chose to use 3.3 equivalents of TBD, because 2 equivalents of base are necessary to neutralize the acetic acid that is generated during the oxidation. Using 2 equivalents of NaOH and 1.3 equivalents of TBD did not generate the desired product. We also tried to use the commercially available 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene as the base in hope of being able to recycle the base after the reaction. However, the yield was low with the base on solid support.

1.2.3.2. Generation of Trichloromethide from Sodium Trichloroacetate

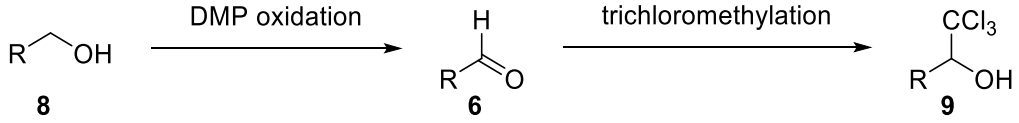
The new one-pot oxidation-trichloromethylation procedure was found to be compatible with substrates possessing an α-stereocenter exemplified by (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (**8p**). When basic conditions lead to undesired byproduct formation, instead of utilizing a base to deprotonate chloroform, the required trichloromethide can be formed by the decarboxylation of sodium trichloroacetate buffered with trichloroacetic acid.[6]

1.2.4. Comparison to the Two-Step Procedure

We also compared the yields from the conventional two-step synthesis of trichloromethyl carbinols from primary alcohols by oxidation and subsequent trichloromethylation to our new

one-pot synthesis (Table 1.3). Gratifyingly, we found that the one-pot protocol was able to afford the desired trichloromethyl carbinols in comparable yield to the traditional two-step process but with shorter overall preparation times.

Table 1.3 Comparative study of conventional two-step vs. outlined one-pot preparations of trichloromethyl carbinols from primary alcohols



			DMP oxidation[a]		trichloromethylation[b]			
entry	cmpnd	R	time (h)	yield (%)	time (h)	yield (%)	product	combined yield[c]/ one-pot yield (%)
1	**8b**	Ph	6	96	18	93	**9b**	89/87
2	**8f**	$PhCH_2CH_2$	8	94	24	87	**9f**	82/71
3	**8k**	thiophen-2-yl	4	72	48	78	**9k**	56/61
4	**8l**	*E*-PhCH=CH	4	81	12	84	**9l**	68/62

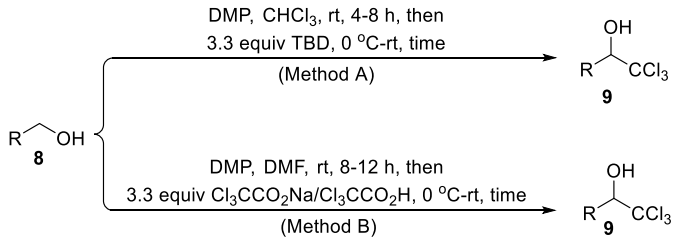
[a]1.2 equiv of DMP, CH_2Cl_2, 4-8 h, followed by flash chromatography purification. [b]1.5 equiv Cl_3CCO_2Na, DMF, 0 °C to rt, 12-48 h, followed by flash chromatography purification. [c]Reactions were conducted on a 1.0 mmol scale.

1.2.5. Results

Two different methods were employed in the one-pot oxidation-trichloromethylation procedure. Method A uses DMP and chloroform for the oxidation step, upon completion of the oxidation, 3.3 equivalents of TBD is added to the reaction mixture to generate the required trichloromethide *in situ* through the deprotonation of chloroform. The generated trichloromethide then attacks the electrophilic carbonyl carbon in the aldehyde intermediate to furnish the desired trichloromethyl carbinol. Method B employs DMP as the oxidant but the reaction is carried out in DMF as the solvent. Upon completion of the oxidation, 3.3 equivalents of trichloroacetic acid and sodium trichloroacetate each were added. The trichloroacetate

undergoes decarboxylation in DMF to generate the trichloromethide *in situ*. The resultant trichloromethide then attacks the aldehyde intermediate to afford the target trichloromethyl

Table 1.4 One-pot oxidation-trichloromethylation of primary alcohols



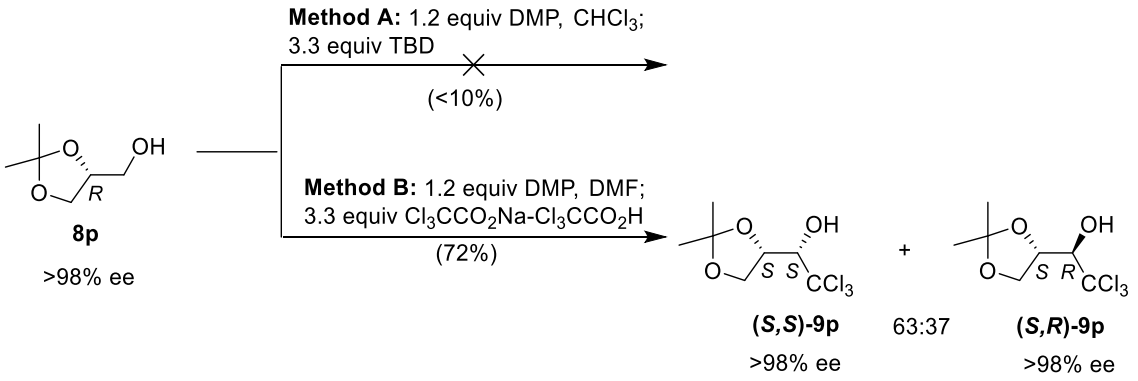
entry	Compd[a]	R	Method[b,c]	time (h)	product	yield (%)[d]
1	**8a**	4-CH_3OPh	A	24	**9a**	83
2	**8b**	Ph	A	8	**9b**	87
3	**8c**	4-NO_2Ph	A	6	**9c**	85
4	**8d**	4-CF_3Ph	A	8	**9d**	86
5	**8e**	2-naphthyl	A	16	**9e**	84
6	**8f**	$PhCH_2CH_2$	A	30	**9f**	71
7	**8f**	$PhCH_2CH_2$	B	36	**9f**	61
8	**8g**	$CH_3(CH_2)_8$	A	30	**9g**	60
9	**8g**	$CH_3(CH_2)_8$	B	16	**9g**	34
10	**8h**	$TBSO(CH_2)_4$	A	25	**9h**	62
11	**8i**	Cy	A	14	**9i**	73
12	**8j**	2-furyl	A	18	**9j**	70
13	**8k**	thiophen-2-yl	A	48	**9k**	61
14	**8k**	thiophen-2-yl	B	48	**9k**	34
15	**8l**	*E*-PhCH=CH	A	18	**9l**	62
16	**8l**	*E*-PhCH=CH	B	20	**9l**	55
17	**8m**	$(CH_3)_2C$=CH	A	18	**9m**	80
18	**8n**	Ph—≡	A	10	**9n**	34
19	**8n**	Ph—≡	B	16	**9n**	27
20	**8o**	$CH_3(CH_2)_4$—≡	A	12	**9o**	<10
21	**8o**	$CH_3(CH_2)_4$—≡	B	16	**9o**	18

[a]All reactions were conducted on a 1 mmol scale. [b]Method A: 1.2 equiv of DMP, $CHCl_3$, 4-8 h, then 3.3 equiv TBD, 0 °C to rt, 6-48 h. [c]Method B: 1.2 equiv of DMP, DMF, 4-8 h, then 3.3 equiv Cl_3CCO_2Na, 3.3 equiv Cl_3CCO_2H, 0 °C to rt, 16-48 h. [d]Yield of purified product.

carbinol. Method A was able to afford the desired trichloromethyl carbinols in higher yield (60-87%) than the ones obtained from method B; however, method A is not compatible with base-sensitive substrates or enolizable substrates. Therefore, method B was employed with those

substrates to afford acceptable yields ranging between 62-71%. Unfortunately, we were not able to obtain high yields with the alkynyl substrates using either set of conditions due to the formation of several byproducts after any base was added to the ynal intermediates (Table 1.4).

We also investigated (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (**8p**) to determine if our one-pot protocol would affect substrates that possess an α-stereocenter. Our initial attempts involved treating **8p** with DMP in chloroform and subsequently adding TBD to the reaction. However, a complicated mixture of polar byproducts were formed instead of the desired trichlorocarbinol. We reasoned that this might be due to deprotonation of the acidic proton at the α-position under the basic reaction conditions, promoting unwanted side reactions. We then treated **8p** with DMP in DMF while subsequently adding 2 equivalents of sodium trichloroacetate and 2 equivalents of trichloroacetic acid as the buffered source of the trichloromethide. We were able to obtain a 63:37 mixture of the **(*S*, *R*)-9p** and the **(*S*, *S*)-9p** diastereomers in 72% combined yield (Scheme 1.9). This combined yield was slightly higher than the trichloromethylation of the (*R*)-isopropylidene glyceraldehyde **10** with trichloroacetic acid and sodium trichloroacetate as previously reported by Schmidt and Oliver (Figure 1.3) (70%).[10] To unequivocally prove that the stereocenter was not racemized during the reaction,



Scheme 1.9. The one-pot trichloromethyl carbinol conversion of **11p**

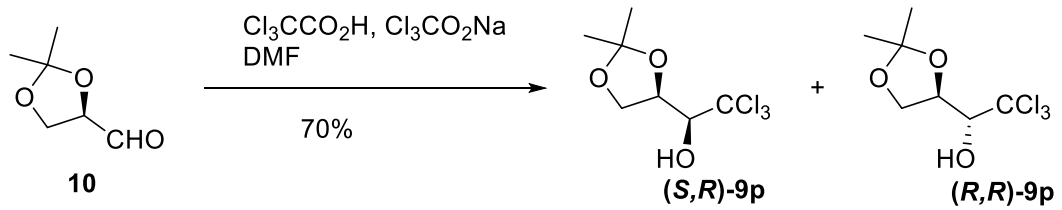


Figure 1.3. Trichloromethylation of (*R*)-isopropylidene glyceraldehyde

we converted the trichlorocarbinols into their corresponding Mosher's ester derivatives.[30] ^{1}H, ^{19}F and ^{13}C NMR analysis of the Mosher's ester derivatives confirmed that each was a single stereoisomer. Thus the new one-pot conversion procedure is able to furnish trichloromethyl carbinols bearing sensitive racemizable chiral centers with complete stereochemical fidelity.

1.3. Conclusion

We developed a method to convert a wide range of primary alcohols to their corresponding trichloromethyl carbinols. The board substrate scope, the ability to use the more stable alcohol as the starting material instead of the less stable aldehyde, and the generally high yields make this an appealing method for accessing trichloromethyl carbinols, which are useful building blocks and precursors to a wide variety of organic molecules.

1.4. Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments at 360 or 500 MHz, 125.4 MHz, and 338 MHz, respectively. Mass spectra were recorded on an AutoSpec-Ultima_NT mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a Mel-Temp 1001D capillary melting point

[30] a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549. b) Myers, A. G.; Bryant, H. Y.; Chem, H. *Organic Synthesis*; Wiley & Sons: New York, 2004; pp 509-516.

apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL® IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. Dess−Martin periodinane was prepared by the method of Boeckman, *et al.*[31] The Celite® was purchased from Fisher Scientific. The silica gel (SiliaFlash® F60) was purchased from Silicycle (230-400 mesh). The anhydrous chloroform was purchased from EMD Millipore and was used directly without further purification. All reagents were used directly as obtained from commercial sources unless otherwise noted.

General Procedure for the Preparation of Trichloromethyl Carbinols from Primary Alcohols

Method A

To a solution of primary alcohol (1.0 mmol) in anhydrous $CHCl_3$ (1.5 mL) was added Dess-Martin periodinane (509 mg, 1.20 mmol) at 0 ºC under an argon atmosphere. The reaction mixture was brought to room temperature and allowed to stir until starting alcohol was consumed, as determined by TLC analysis (~2 h). TABD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) (446 mg, 3.20 mmol) was added in 3 portions over 5 minutes and stirred very rapidly at 0 ºC. After 6-8 h, the mixture was monitored by TLC. If corresponding aldehyde remained, one equivalent of TABD was added with vigorous stirring. After completion of the reaction as indicated by TLC (~16-20 h), the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and precipitated solids were filtered through a bed of Celite™. The filter cake was washed three times with CH_2Cl_2. The filtrate was separated and the aqueous layer was washed with dichloromethane (3 x 5 mL). The combined organic layers were dried

[31] Boeckman, Jr., R. K.; Shao, P.; Mullins, J. J. *Organic Syntheses*, Wiley & Sons: New York, **2004**, pp. 696−707.

over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of ethyl acetate/hexanes to afford the corresponding trichloromethyl carbinols.

Method B

To a stirring solution of primary alcohol (1.0 mmol) in anhydrous DMF (1.5 mL) was added Dess-Martin periodinane (509 mg, 1.20 mmol) at 0 ^{o}C under an atmosphere of argon. The reaction temperature was brought to room temperature and the reaction was allowed to stir until starting primary alcohol was consumed completely. The reaction was cooled to 0 ^{o}C before the addition of sodium trichloroacetate (604 mg, 3.30 mmol) and trichloroacetic acid (539 mg, 3.30 mmol). The reaction was then allowed to warm to room temperature and stirred until the corresponding aldehyde was consumed (12-48 h). After the reaction was complete, the reaction mixture was diluted with satd. $NaHCO_3$ (5 mL) and ethyl acetate (10 mL) and was filtered through a bed of Celite^{TM}. The organic layer was separated and the aqueous layer was further washed with ethyl acetate (3 x 5 mL). The combined organic layer was washed with DI H_2O (3 x 5 mL) and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of ethyl acetate/hexanes to afford the corresponding trichloromethyl carbinols.

General Procedure for the Preparation of Mosher's Esters from Trichloromethyl Carbinols ((*R*,*S*)-9p and (*S*,*S*)-9p)

To a dry 10 mL round-bottom flask equipped with a stir bar was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (44 mg, 0.18 mmol) and anhydrous benzene (2 mL). The benzene was then evaporated under reduced pressure. The flask was back-filled with argon then CH_2Cl_2 (1 mL) was added followed by oxalyl chloride (22 μL, 0.26 mmol) and DMF (2 μL, 0.03 mmol). The reaction was stirred under argon for 30 min. The flask was then cooled to 0 °C and excess oxalyl chloride and CH_2Cl_2 were evaporated to afford (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride. CH_2Cl_2 (1 mL) was added to the residue upon completion of evaporation. In a separate 10 mL round-bottom flask, **(*R*,*S*)-9p** / **(*S*,*S*)-9p** (20 mg, 0.08 mmol), triethylamine (50 μL, 0.36 mmol), DMAP (2 mg, 0.02 mmol) and CH_2Cl_2 (0.5 mL) were added. This mixture was transferred by cannula into the (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride at 0 °C, and the reaction was mixed until starting trichloromethyl carbinol was consumed, as indicated by TLC (~3 h). Once complete, the reaction mixture was diluted with saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (5 mL) and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with 8:2 hexane/EtOAc as the eluent to afford the corresponding Mosher's ester derivative.

2,2,2-Trichloro-1-(4-methoxyphenyl)ethanol (9a)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 83% yield (212 mg); m.p. 44-45 °C; IR (solid): 3511, 3019, 2840, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.14 (d, *J* = 4.1

Hz, 1H), 3.82 (s, 3H), 3.61 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 130.3, 127.0, 113.1, 103.3, 84.0, 55.2; HRMS *m/z* was calcd. for $C_9H_9OCl_3$, 253.9668; found 253.9665.

2,2,2-trichloro-1-phenylethanol (9b)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 87% yield (196 mg); IR (film): 3446, 3055, 2984, 2901, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.71 – 7.53 (m, 2H), 7.50 – 7.34 (m, 3H), 5.22 (s, 1H), 3.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.8, 129.4, 129.2, 127.8, 103.0, 84.4; HRMS *m/z* calcd. for $C_8H_7Cl_3O$, 223.9562; found 223.9563.

2,2,2-Trichloro-1-(4-nitrophenyl)-ethanol (9c)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as an off-white solid in 85% yield (230 mg); m.p. 107-108 °C; IR (film): 3568, 3054, 2986, 1525, 1350, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 5.34 (d, *J* = 3.5 Hz, 1H), 3.64 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.4, 141.5, 130.4, 122.8, 102.0, 83.4; HRMS *m/z* calcd. for $C_8H_6Cl_3NO$, 268.9413; found 268.9406.

2,2,2-Trichloro-1-(4-(trifluoromethyl)phenyl)ethanol (9d)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 86% yield (253 mg); m.p. 34-35 °C; IR (solid): 3422, 3055, 2986,

1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 5.28 (d, *J* = 3.7 Hz, 1H), 3.38 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.4, 131.4 (q, *J* = 35.8 Hz), 129.7, 124.7 (q, *J* = 3.7 Hz), 122.8 (q, *J* = 270.4 Hz), 102.5, 83.8; ^{19}F NMR ($CDCl_3$, 360 MHz): δ -62.7; HRMS *m/z* calcd. for $C_8H_6F_3O$, 175.0371; found 175.0373 which corresponds to $[M\text{-}CCl_3]^+$.

2,2,2-Trichloro-1-napthalen-2-yl-ethanol (9e)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as an off-white solid in 84% yield (232 mg); m.p. 93-94 °C; IR (solid): 3486, 3049, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.09 (s, 1H), 7.94 – 7.83 (m, 3H), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.58 – 7.49 (m, 2H), 5.40 (d, *J* = 3.9 Hz, 1H), 3.37 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 133.6, 132.4, 132.2, 129.2, 128.3, 127.6, 127.3, 126.8, 126.3, 126.0, 103.1, 84.5; HRMS *m/z* was calcd. for $C_{12}H_9OCl_3$, 273.9712; found 273.9713.

1,1,1-Trichloro-4-phenylbutan-2-ol (9f)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 71% yield (180 mg); IR (film): 3439, 3028, 2936, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 – 7.12 (m, 5H), 3.98 (ddd, *J* = 10.0, 5.5, 1.8 Hz, 1H), 2.99 (ddd, *J* = 13.8, 9.1, 4.7 Hz, 1H), 2.86 – 2.71 (m, 2H), 2.47 – 2.31 (m, 1H), 2.04 – 1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.7, 128.6, 128.5, 126.3, 104.1, 82.0, 32.9, 31.9; HRMS *m/z* calcd. for $C_{10}H_{11}Cl_3O$, 251.9875; found 251.9885.

1,1,1-Trichloroundecan-2-ol (9g)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 60% yield (165 mg); IR (film): 3431, 2926, 2856, 1461, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.00 (ddd, *J* = 9.4, 5.6, 1.9 Hz, 1H), 2.65 (dd, *J* = 5.6, 1.5 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.63 (m, 2H), 1.50 – 1.41 (m, 1H), 1.37 – 1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.4, 83.0, 31.9, 31.5, 29.5, 29.4, 29.3, 29.2, 26.1, 22.7, 14.1; HRMS *m/z* calcd. for $C_{10}H_{21}O$, 157.1592; found 157.1586 which corresponds to $[M\text{-}CCl_3]^+$.

6-{(*tert*-Butyldimethylsilyl)oxy}-1,1,1-trichlorohexan-2-ol (9h)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 62% yield (208 mg); IR (film): 3580, 3053, 2956, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.01 (ddd, *J* = 9.0, 5.6 , 1.8 Hz, 1H), 3.66 (m, 2H), 2.89 (s, 1H), 2.14 – 2.04 (m, 1H), 1.78 – 1.48 (m, 5H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.3, 83.1, 63.0, 32.2, 31.2, 22.8, 19.2, 18.4, -5.3; HRMS *m/z* calcd. for $C_8H_{16}Cl_3SiO_2$ $[M\text{-}C_4H_9]^+$, 276.9985; found 276.9977.

2,2,2-Trichloro-1-cyclohexylethanol (9i)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 73% yield (169 mg); IR (film): 3577, 3053, 2986, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.86 (d, *J* = 2.2 Hz, 1H), 2.78 (d, *J* = 6.0 Hz, 1H), 2.15 – 1.96 (m, 2H), 1.82 – 1.64 (m, 4H), 1.48 – 1.14 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.2, 86.4,

39.9, 32.9, 26.7, 26.5, 26.0, 25.9; HRMS *m/z* was calcd. for $C_7H_{13}O$ $[M\text{-}CCl_3]^+$, 113.0966; found 113.0965.

2,2,2-Trichloro-1-furan-2-yl-ethanol (9j)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 70% yield (151 mg); m.p. 34-35 °C. IR (film): 3431, 2922, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, *J* = 1.6 Hz, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.44 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.24 (d, *J* = 7.3 Hz, 1H), 3.34 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 148.4, 143.1, 110.9, 110.7, 101.2, 79.3; HRMS *m/z* was calcd. for $C_6H_5Cl_3O_2$, 213.9355; found 213.9352.

2,2,2-Trichloro-1-thiophen-2-ylethanol (9k)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as an off-white solid in 61% yield (140 mg); m.p. 29-30 ºC; IR (film): 3422, 3060, 2912, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.48 (d, *J* = 4.7 Hz, 1H), 3.30 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (CDCl3, 125 MHz): δ 137.3, 129.1, 127.1, 126.3, 102.5, 81.6; HRMS *m/z* was calcd. for $C_6H_5Cl_3SO$, 229.9127; found 229.9122.

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol (9l)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as an off-white solid in 62% yield (156 mg); m.p. 62-63 ºC; IR (film): 3474, 3054,

2985, 2305 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.29 – 7.38 (m, 3H), 6.91 (d, *J* = 15.9 Hz, 1H), 6.38 (dd, *J* = 15.9, 5.9 Hz, 1H), 4.78 (t, *J* = 5.9 Hz, 1H), 2.98 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.8, 135.6, 128.7, 128.6, 126.9, 122.6, 102.8, 83.4; HRMS *m/z* calcd. for $C_{10}H_9Cl_3O$, 249.9719; found 249.9729.

1,1,1-Trichloro-4-methylpent-3-en-2-ol (9m)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 80% yield (163 mg); m.p. 85-86 ºC; IR (film): 3577, 2981, 2918, 1671, 1455, 1382 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.36 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.78 (dd, *J* = 8.2, 6.0 Hz, 1H), 2.67 (d, *J* = 6.0 Hz, 1H), 1.82 (d, *J* = 9.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.5, 119.5, 103.6, 79.5, 26.1, 19.2; HRMS *m/z* calcd. for $C_5H_9Cl_3O$, 201.9719; found 85.0652 which corresponds to $[M\text{-}CCl_3]^+$.

1,1,1-Trichloro-4-phenylbut-3-yn-2-ol (9n)

The crude material (prepared following Method A) was purified by flash chromatography through silica gel using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 34% yield (85 mg); IR (film): 3434, 2253, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 – 7.47 (m, 2H), 7.42 – 7.29 (m, 3H), 5.04 (d, *J* = 9.0 Hz, 1H), 3.10 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.0, 129.4, 128.4, 121.2, 101.1, 88.1, 83.0, 75.8; HRMS *m/z* calcd. for $C_{10}H_7Cl_3O$, 247.9562; found 247.9559.

1,1,1-trichloronon-3-yn-2-ol (9o)

The crude material (prepared following Method B) was purified by flash chromatography through silica gel using 98:2 hexane/EtOAc as the eluent. The indicated compound was

obtained as a colorless oil in 18% yield (45 mg); IR (film): 3387, 2932, 2860, 1621, 1379 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (dt, *J* = 8.8, 1.9 Hz, 1H), 2.95 (d, *J* = 8.8 Hz, 1H), 2.26 (td, *J* = 7.1, 1.9 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.43 – 1.26 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 101.6, 89.8, 75.4, 74.6, 30.9, 27.7, 22.1, 18.6, 13.9; HRMS *m/z* calcd. for $C_8H_{13}O$ $[M\text{-}CCl_3]^+$, 125.0966; found 125.0968.

(*R*)-2,2,2-trichloro-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol ((*R,S*)-9p)

The crude material (prepared following Method B) was purified by flash chromatography through a plug of 1% pyridine saturated silica gel using 95:5 hexane/EtOAc as the eluent. A ca. 2:1 mixture of diastereomers **((*R,S*)-9p)** and **((*S,S*)-9p)** was obtained in 72% yield (178 mg). Pure **((*R,S*)-9p)** was obtained as a white crystal after recrystalization from 0 °C hexane; Mosher's ester of **((*R,S*)-9p)** was prepared following General Procedure for the Preparation of Mosher's Esters from Trichloromethyl Carbinols described above. No racemization was indicated in ^{19}F NMR spectrum; m.p.:80-82 °C; $[\alpha]_D^{20}$ = +21.3 (c 3.8, $CHCl_3$); IR (film): 3446, 2987, 2934, 1646, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.59 (ddd, J = 3.0, 6.0, 6.0 Hz, 1H), 4.36 (dd, J = 4.0, 3.5 Hz, 1H), 4.27 (dd, J = 6.5, 9.0 Hz, 1H), 4.10 (dd, J = 6.5, 9.0 Hz, 1H), 3.06 (d, J = 4.0 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.23, 100.61, 82.43, 75.14, 64.73, 26.32, 25.33; HRMS *m/z* calcd. for $C_7H_{11}Cl_3O_3$, 247.9774, found 131.0708 which corresponds to $[M\text{-}CCl3]^+$.

(*S*)-2,2,2-trichloro-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol ((*S,S*)-9p)

The crude material (prepared following Method B) was purified by flash chromatography through a plug of 1% pyridine saturated silica gel using 95:5 hexane/EtOAc as the eluent. A ca. 2:1 mixture of diastereomers **((*R,S*)-9p)** and **((*S,S*)-9p)** was obtained in 72% yield (178 mg).

Pure **((*S,S*)-9p)** was obtained as a colorless oil. Mosher's ester of **((*S,S*)-9p)** was prepared following General Procedure for the Preparation of Mosher's Esters from Trichloromethyl Carbinols described above. No racemization was indicated in ^{19}F NMR spectrum; $[\alpha]_D^{20}$ = +10.5 (c 2.0, $CHCl_3$); IR (film): 3481, 2989, 2937, 1769, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.57 (ddd, J = 2.5, 6.5, 6.5 Hz, 1H), 4.25 (dd, J = 6.5, 8.5 Hz, 1H), 3.98 (dd, J = 2.5, 8.5 Hz, 1H), 3.91 (dd, J = 7, 8.5 Hz, 1H), 3.72 (d, J = 8.5 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 110.92, 101.33, 81.14, 73.24, 68.40, 26.06, 25.66; HRMS *m/z* calcd. for $C_7H_{11}Cl_3O_3$, 247.9774, found 131.0708 which corresponds to $[M\text{-}CCl3]^+$.

CHAPTER 2. PREPARATION OF ONE-CARBON HOMOLOGATED AMIDES FROM TRICHLOROMETHYL CARBINOLS

2.1 Background

2.1.1. Jocic Reaction

In 1897, Zicojin Jocic reported the generation of 2-chloro-2-phenylacetic acid (**2**) in low yield from 2,2,2-trichloro-1-phenylethanol (**1**) when **1** was stirred in ice-cold aqueous

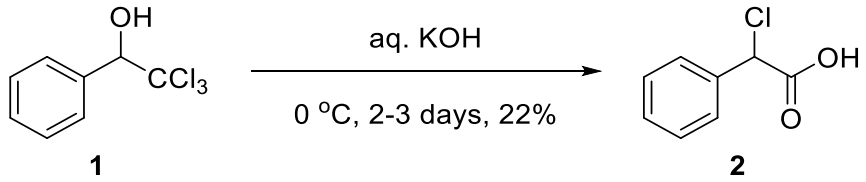
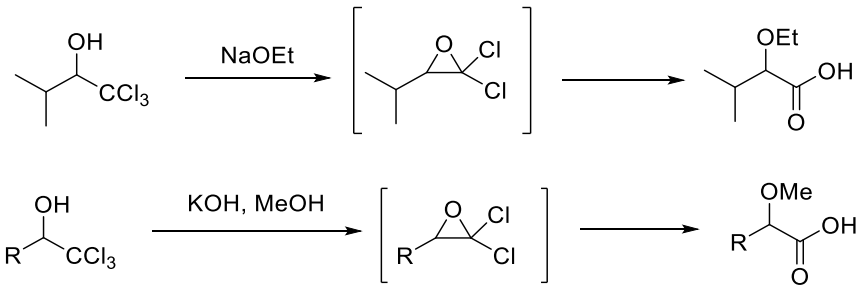


Figure 2.1 Conversion of 2,2,2-trichloro-1-phenylethanol to 2-chloro-2-phenylacetic acid



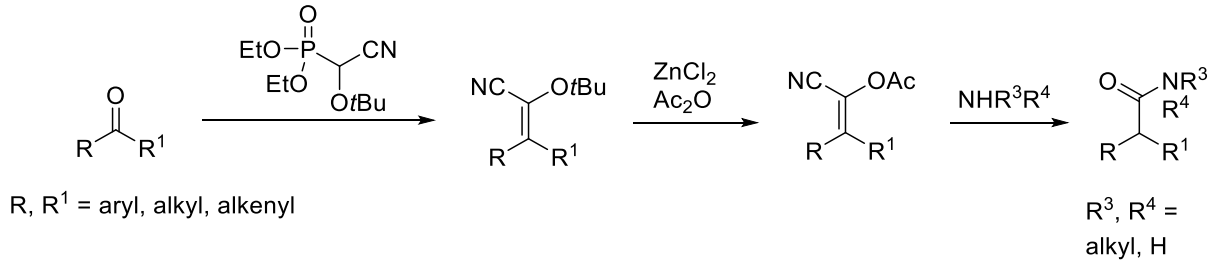
Scheme 2.1 Reaction pathways as proposed by McElvain, et al. and Weizmann, et al.

KOH for several days (Figure 2.1). About fifty years later, McElvain, *et al.*[32] and Weizmann, *et al.*[33] both suggested that the transformation proceeds through a *gem*-dichloroepoxide

[32] McElvain, S. M.; Stevens, C. L. *J. Am. Chem. Soc.* **1947**, *69*, 2667-2670.
[33] Weizmann, C.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153-1158.

intermediate (Scheme 2.1). However, the reaction mechanism was not extensively studied until Reeve's work from 1980.[3] Researchers have tried to isolate the reactive *gem*-dichloroepoxide. However, the half-life of this intermediate is so short that only a handful of *gem*-dichloroepoxides have been isolated and characterized to date.[34] In 2005, Cvetovich, *et al.* at Merck reported a short-lived (half-life ~ 5 min) species giving an IR signal at 758 cm^{-1} using React-IR.[35] They attributed this species to the *gem*-dichloroepoxide. However, they too were not able to detect this intermediate using NMR spectroscopy.

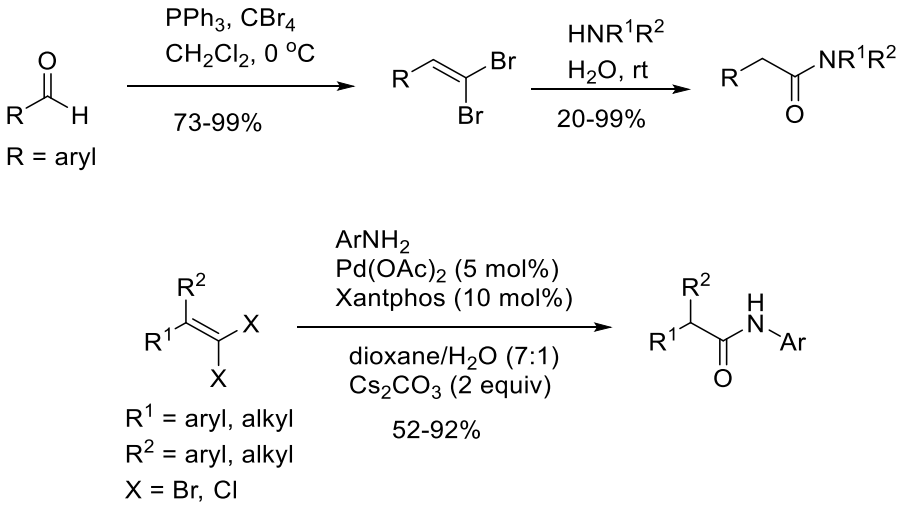
2.1.2. Published Methods to Prepare One-Carbon Homologated Amides



Scheme 2.2. The three-step one-carbon homologated amide synthesis reported by Watt, et al.

Methods to prepare homologated amides go through either dihaloalkenes[36,37] or aldehydes.[38,39,40] However, most of these methods are limited to the type of aldehydes used, or

[34] a) Mloston, G.; Romanski, J.; Swiatek, A.; Heimgartner, H. *Helv. Chim. Acta.* **1999**, *82*, 946-956. b) Scaffidi, A.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem.* **2006**, *59*, 426-433.
[35] Cvetovich, R. J.; Chung, J. Y. L.; Kress, M. H.; Amato, J. S.; Matty, L.; Weingarten, M. D.; Tsay, F.-R.; Li, Z.; Zhou, G. *J. Org. Chem*. **2005**, *70*, 8560-8563.
[36] Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925-9932.
[37] Ye, W.; Mo, J.; Zhao, T.; Xu, B. *Chem. Commun*. **2009**, 3246-3248.
[38] Bonne, D.; Dekane, M.; Zhu, J. *J. Am. Chem. Soc*. **2005**, *127*, 6926-6927.
[39] Shen, W.; Kunzer, A. *Org. Lett*. **2002**, *4*, 1315-1317.
[40] Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, *99*, 182-186.



Scheme 2.3. Amide formation from dihaloalkenes.[36,37]

are not general methods to prepare a variety of amides. For instance, the method developed by Kim, *et al.* is only applicable to aryl aldehydes.[36,39] The one-carbon homologation utilizing the Horner-Emmons modification of the wittig reaction followed by the cleavage of the t-butyl ether and solvolysis as reported by Watt, *et al.* is a three step process; however, it is compatible with alkenyl, aryl and alkyl substrates (Scheme 2.2).[40] The conversion reported by Xu, *et al.* is limited to aryl amines and therefore only able to furnish *N*-aryl substituted carboxamides

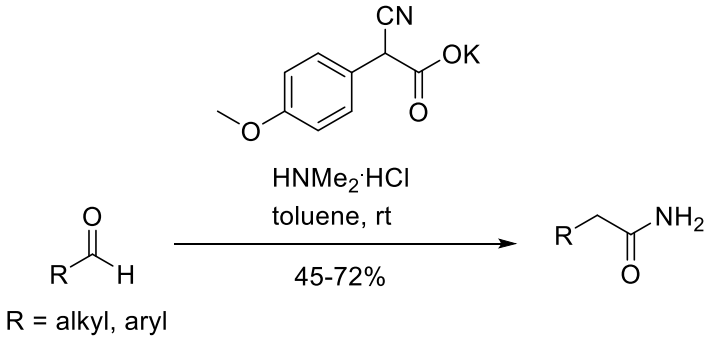


Figure 2.2. Formation of one-carbon homologated primary amides from aldehydes

(Scheme 2.3).[37] Finally, the homologation methodology developed by Zhu, *et al.* is limited to the formation of primary carboxamides (Figure 2.2).[38]

2.1.3. Preparation of One-Carbon Homologated Carboxylic Acids from Trichloromethyl Carbinols

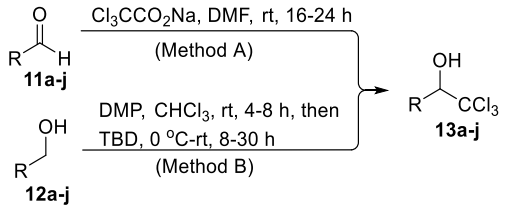
Cafiero and Snowden developed a method to afford one-carbon homologated carboxylic acids from the corresponding trichloromethyl carbinols.[11] We envisioned that it would be possible to expand on this chemistry by using an amine as the second nucleophile to add to the acyl chloride and furnish the corresponding amide. With our trichloromethyl carbinol chemistry, by way of the acyl chloride intermediate, we would be able to access primary, secondary, and tertiary amides from the same trichloromethyl carbinol or the corresponding alcohols/aldehydes. The wide substrate compatibility and the broad scope of this chemistry was expected to make this method very attractive.

2.2. Preparation of One-Carbon Homologated Amides

2.2.1. Preparation of Trichloromethyl Carbinols

The trichloromethyl carbinols were either prepared from the aldehydes using the conditions reported by the buffered conditions reported by Corey,[6] or from the primary alcohols using the one-pot conversion to trichloromethyl carbinols developed in the Snowden group.[51] A total of

Table 2.1. Preparation of trichloromethyl carbinols from aldehydes (**11a-j**) or primary alcohols (**12a-j**)



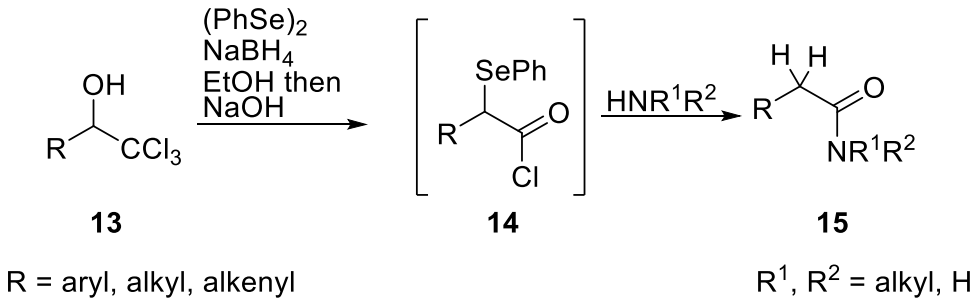
reactant	R	method[a,b]	product	yield[c]
11a	Ph	A	**13a**	96%
11b	4-CF_3Ph	A	**13b**	92%
11c	4-CH_3OPh	A	**13c**	97%
11d	$PhCH_2CH_2$	A	**13d**	89%
11e	$CH_3(CH_2)_{10}$	A	**13e**	88%
11f	Cy	A	**13f**	87%
11g	2-furyl	A	**13g**	95%
11h	Thiophen-2-yl	A	**13h**	93%
11i	*(E)*-$(CH_3)_2CHCH=CH$	A	**13i**	93%
11j	*(E)*-PhCH=CH	A	**13j**	90%
12a	Ph	B	**13a**	87%
12b	4-CF_3Ph	B	**13b**	86%
12c	4-CH_3OPh	B	**13c**	83%
12d	$PhCH_2CH_2$	B	**13d**	71%
12e	$CH_3(CH_2)_{10}$	B	**13e**	60%
12f	Cy	B	**13f**	73%
12g	2-furyl	B	**13g**	70%
12h	Thiophen-2-yl	B	**13h**	61%
12i	*(E)*-$(CH_3)_2CHCH=CH$	B	**13i**	68%
12j	*(E)*-PhCH=CH	B	**13j**	62%

[a] Method A: 1.5 equiv of Cl_3CCO_2Na, 1.5 equiv of Cl_3CCO_2H, 0 °C to RT, 6−24 h. [b] Method B: 1.2 equiv of Dess-Martin periodinane (DMP), $CHCl_3$, 4−8 h, and then 3.3 equiv of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 0 °C to RT, 8−30 h. [c] Yield of purified product.

20 trichloromethyl carbinols were prepared with yields ranging from 60-97% (Table 2.1).

2.2.2. Determination of Conditions to Generate the Homologated Amides

Snowden and Shamshina researched the solvents required to generate the *gem*-dichloroepoxide from the corresponding trichloromethyl carbinols.[41] They concluded that only polar protic solvents were capable of allowing formation of the *gem*-dichloroepoxide. The key

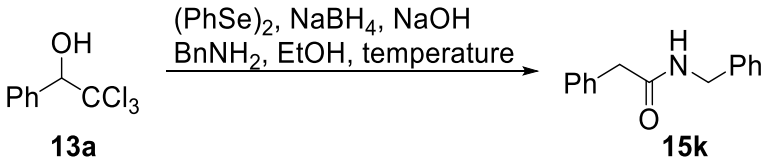


Scheme 2.4. Conceptual mechanism for the formation of **15** from **13**

to this method is to tune the relative reactivities of the nucleophiles so the substitutions of the two electrophilic intermediates will take place at the correct carbon with the desired nucleophile. As conceived, the important nucleophiles in the reaction would include $PhSeB(OEt)_3^-$, HO^-, Cl^-, EtOH, EtO^-, and HNRR' (Scheme 2.4). We envisioned that by carrying out the reaction in a polar protic solvent (EtOH), the nucleophilicity of hydroxide anion as well as chloride would be suppressed due to hydrogen bonding interactions. Building upon the previously reported reaction conditions, using the phenyl trichloromethyl carbinol **13a** as the starting material, we started our investigation with 3 equivalents of NaOH at 45 ^oC along with 2.2 equivalents of amine. The reaction did not go to completion even after 60 h. We then increased the temperature to 55 ^oC to find the reaction went to completion with 86% yield (Table 2.2). The reaction temperature was then increased further to 65 ^oC; however, the yield

[41] Shamshina, J. L. New Synthetic Applications of Trichloromethylcarbinols. Synthesis of Small Molecule Natural Products. Ph. D. Dissertation, the University of Alabama, Tuscaloosa, AL, 2008

Table 2.2. Optimization studies



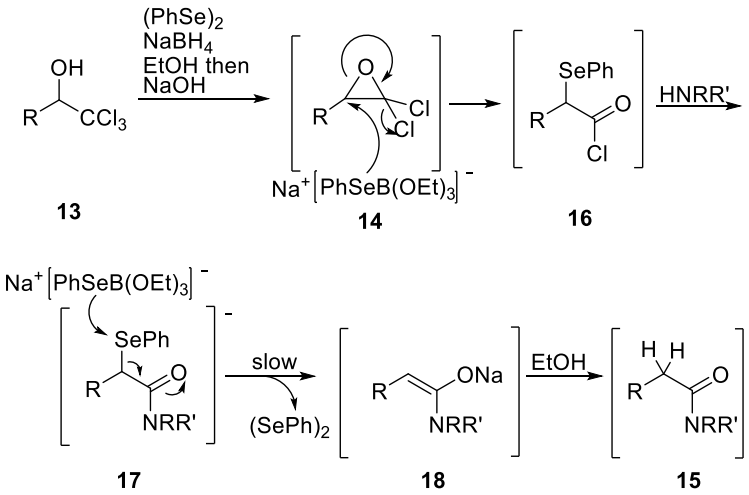
13a **15k**

entry[a]	NaOH	$BnNH_2$	temp. (°C)	Yield[b]
1	3.0 equiv	2.2 equiv	65	87%
2	3.0 equiv	2.2 equiv	55	86%
3	3.0 equiv	2.2 equiv	45	63%[c]
4	4.0 equiv	2.2 equiv	55	25%[d]
5	2.0 equiv	2.2 equiv	55	54%[c]
6	2.5 equiv	2.2 equiv	55	87%
7	2.5 equiv	1.1 equiv	55	89%

[a] 1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then x equiv of NaOH, y equiv of amine ($BnNH_2$), 45-65 °C, 36 h. [b] Yield of purified product. [c] Reaction not completed after 60 h. [d] Phenylacetic acid (44 %) was the major product.

showed no improvement. Next, we shifted our attention to optimizing the amount of the base used in the reaction. When 4.0 equivalents of NaOH was used, the desired product was isolated in only 25% yield, and phenylacetic acid was formed in 44% yield, presumably because the hydroxide anion was outcompeting the amine as the second nucleophile in the nucleophilic acyl substitution. When 2.0 equivalents of NaOH was used, the reaction did not go to completion because of insufficient amount of base in the reaction required to fully generate the requisite *gem*-dichloroepoxide. We also found that 2.5 equivalents of NaOH had comparable results to using 3.0 equivalents. Finally, when 1.1 equivalents of amine was used instead of 2.2 equivalents, the yield was unchanged. Therefore, we determined that the optimal reaction conditions for the homologation required 2.5 equivalents of NaOH, 1.1 equivalents of the amine, and 55 °C as the reaction temperature.

2.2.3. Reaction Mechanism



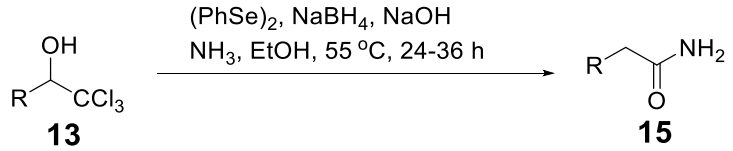
Scheme 2.5 Proposed reaction mechanism for the formation of **15** from trichloromethyl carbinols **13**

Upon deprotonation, the *gem*-dichloroepoxide intermediate **14** is attacked by the phenylselenium triethoxyborate[42] generated *in situ* to form the α-phenylselenyl substituted acyl chloride **16** (Scheme 2.5). This intermediate then undergoes nucleophilic acyl substitution by the amine to afford the α-substituted amide **17**. This amide furnishes the target amide **15** through dephenylselenation and subsequent protonation. Experimental supports for this reaction mechanism are the isolable intermediate **17**, as well as the requirement for two equivalents of phenylselenyltriethoxyborate complex for the reaction to reach completion.

[42] a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697-2699. b) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, *18*, 4365-4367. c) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem*. **1981**, *46*, 2605-2610.

2.2.4. Results

Table 2.3. Conversions of trichloromethyl carbinols to primary amines



13 **15**

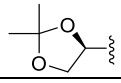
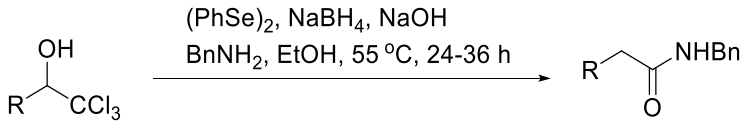
Cmpd.	R	Product	Yield
13a	Ph	**15a**	88%
13b	4-CF_3Ph	**15b**	90%
13c	4-CH_3OPh	**15c**	86%
13d	$PhCH_2CH_2$	**15d**	85%
13e	$CH_3(CH_2)_{10}$	**15e**	80%
13f	cy	**15f**	92%
13g	2-furyl	**15g**	75%
13h	Thiophen-2-yl	**15h**	90%
13i	(*E*)-$(CH_3)_2CHCH$=CH	**15i**	86%
13j	(*E*)-PhCH=CH	**15j**	74%
24		**25b**	75%

Table 2.4. Conversions of trichloromethyl carbinols to secondary amines



13 **15**

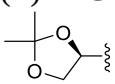
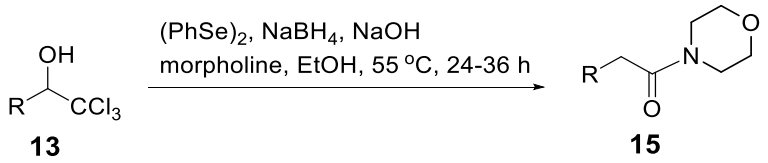
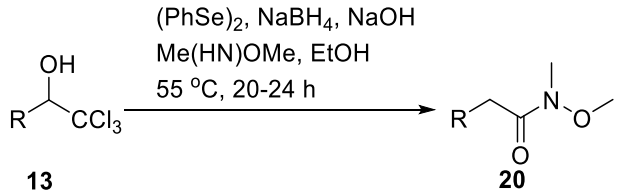
Cmpd.	R	Product	Yield
13a	Ph	**15k**	89%
13b	4-CF_3Ph	**15l**	95%
13c	4-CH_3OPh	**15m**	87%
13d	$PhCH_2CH_2$	**15n**	85%
13e	$CH_3(CH_2)_{10}$	**15o**	96%
13f	cy	**15p**	93%
13g	2-furyl	**15q**	83%
13h	Thiophen-2-yl	**15r**	92%
13i	(*E*)-$(CH_3)_2CHCH$=CH	**15s**	96%
13j	(*E*)-PhCH=CH	**15t**	82%
24		**25a**	80%

Table 2.5. Conversions of trichloromethyl carbinols to tertiary amines



Cmpd.	R	Product	Yield
13a	Ph	**15u**	88%
13b	4-CF_3Ph	**15v**	88%
13c	4-CH_3OPh	**15w**	81%
13d	$PhCH_2CH_2$	**15x**	84%
13e	cy	**15y**	95%
13f	2-furyl	**15z**	75%
13g	Thiophen-2-yl	**15aa**	91%
13h	(*E*)-$(CH_3)_2CHCH$=CH	**15bb**	82%
13i	(*E*)-PhCH=CH	**15cc**	78%

Table 2.6. Conversion of trichloromethyl carbinols to Weinreb amides



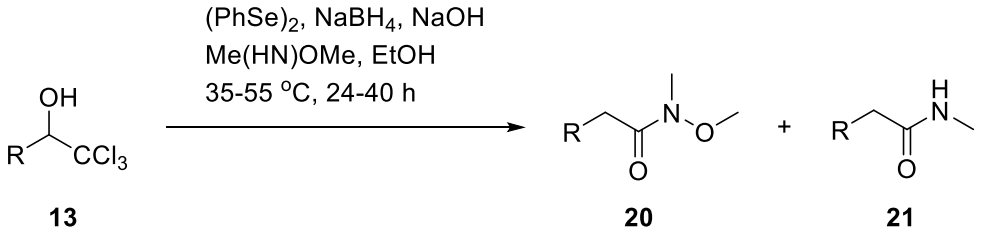
compound	R	product[a]	yield[b]
13a	Ph	**20a**	83%
13b	4-CF_3Ph	**20b**	89%
13c	4-CH_3OPh	**20c**	76%
13d	$PhCH_2CH_2$	**20d**	87%
13f	Cy	**20e**	75%

[a]1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then 3.3 equiv of NaOH, 1.1 equiv MeONHMe·HCl, 55 °C, 20−24 h. [b]Yield of purified product.

After the optimal reaction conditions were established, 20 trichloromethyl carbinols were prepared and screened for the conversion of primary, secondary and tertiary amides (Tables 2.3-2.5). The primary amides were prepared using ammonia saturated ethanol, whereas the secondary amides were prepared using benzylamine. Morpholine was used to prepare the

tertiary amides. With the successful preparation of the primary, secondary and tertiary amides, preparation of Weinreb amides was attempted. With aryl and aliphatic substrates, we were able to prepare the corresponding Weinreb amides in high yields (Table 2.6). However, we observed the formation of *N*-methylamides from some other substrates (Table 2.7). This could be

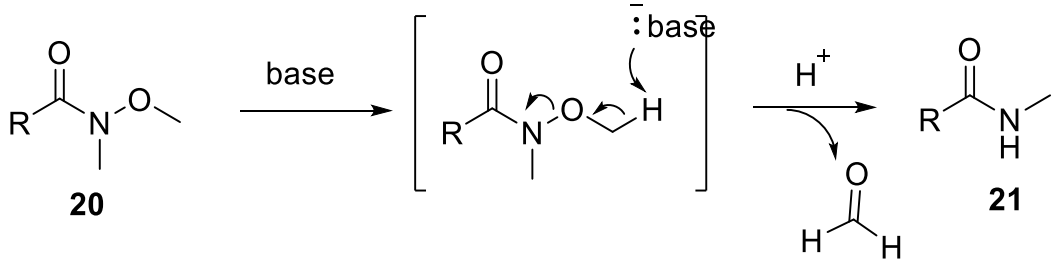
Table 2.7. Formation of *N*-methylamides **23** as a byproduct



13 **20** **21**

compound	R	product[a]	Yield of **21**[b]
13g	2-furyl	**21g**	ND[c]
13h	Thiophen-2-yl	**21h**	53%
13i	(*E*)-$(CH_3)_2$CHCH=CH	**21i**	51%
13j	(*E*)-PhCH=CH	**21j**	ND[c]

[a]1.3 equiv of $(PhSe)_2$, 2.8 equiv of $NaBH_4$, abs EtOH, rt, 30 min, then 3.3 equiv of NaOH, 1.1 equiv MeONHMe·HCl, 35-55 °C, 24−40 h. [b]Yield of purified product. [c]Formation of **21** was noted but not isolated.



Scheme 2.6. Elimination of formaldehyde from Weinreb amides in the presence of a base

explained by Graham's report on the E2 elimination of formaldehyde from Weinreb amides (Scheme 2.6).[43] Graham also reported that this E2 elimiation can be completely suppressed by

[43] Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269-6272.

enolization. Therefore, the conversion to Weinreb amides is compatible with substrates that are readily enolizable or with fast conversion times (18-24 h). With non-enolizable substrates or substrates that require extended reaction times, the demethoxylated product will be generated as a major byproduct.

As another example, an α-amino acid, L-homoserine, was used as the second nucleophile in the reaction. Since L-homoserine possesses a hydroxyethyl moiety and a carboxylate functionality, those groups could compete with the amino group that is the desired nucleophile in the epoxide substitution and in the nucleophlic acyl substitution steps. Gratifyingly, we were able to form the target amide **22** in 89% yield (Figure 2.3) with the generation of no byproducts.

To further strengthen this method, we examined the possibility of carrying out this homologation-amidation method on a chiral enolizable substrate. It is worth noting that the chiral substrate **24** was able to be converted to its homologated amides **25a** and **25b** in great

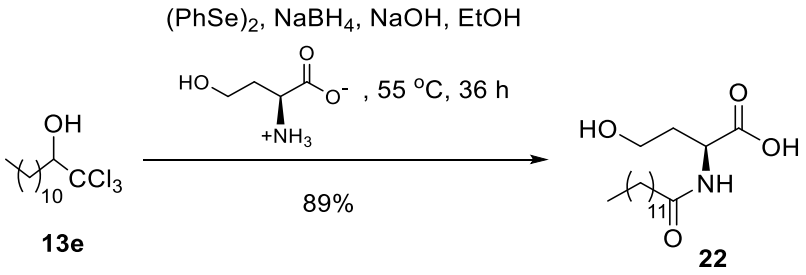


Figure 2.3. Formation of **22** using L-homoserine

yields (80% and 75% yield) (Tables 2.3, 2.4) without any racemization of the chiral center based on Mosher's amide analysis.[30] The ^{1}H, ^{13}C and ^{19}F NMR spectra confirmed that each of the Mosher's amide was a single stereoisomer.

2.3. Conclusion

We were able to develop a general method to convert trichloromethyl carbinols to their corresponding amides in high yield and great functional group tolerance. Notably, this marks the first general method to furnish either one-carbon homologated primary, secondary, or tertiary amides from the corresponding aldehyde or primary alcohol in just two operational steps.

2.4. Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments at 360 or 500 MHz, 125.4 MHz, and 338 MHz, respectively. Mass spectra were recorded on an AutoSpec-Ultima_NT mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a Mel-Temp 1001D capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL® IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. Dess−Martin periodinane was prepared by the method of Boeckman, *et al.*[31] The Celite® was purchased from Fisher Scientific. The silica gel (SiliaFlash® F60) was purchased from Silicycle (230-400 mesh). The anhydrous chloroform was purchased from EMD Millipore and was used directly without further purification. All reagents were used directly as obtained from commercial sources unless otherwise noted.

General Procedures for the Preparation of Trichloromethyl Carbinols (13a-13j)

Method A: Trichloromethyl carbinols in entries (**13a**–**13j)** were prepared by the method of Corey and Link from the respective aldehydes. Yields and reaction times are unoptimized. The

following serves as a general procedure. To a solution of aldehyde (1.0 mmol) in 1.35 mL of anhydrous DMF was added trichloroacetic acid (1.5 mmol) then sodium trichloroacetate (1.5 mmol) with stirring at room temperature. Initially rapid evolution of CO_2 was observed. After 6–8 h, the mixture was monitored by TLC. If starting material remained, one equivalent of sodium trichloroacetate and one equivalent of trichloroacetic acid were added. After an additional 4–8 h, the mixture was diluted with 5 mL of diethyl ether and washed with saturated aqueous sodium bicarbonate. Precipitated solids were filtered and washed three times with diethyl ether. The filtrate was washed two more times with sodium bicarbonate solution and once with brine. The organic phase was dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with hexanes/ethyl acetate to afford the corresponding trichloromethyl carbinol.

Method B: To a solution of primary alcohol **12a**-**12j** (1.0 mmol) in anhydrous $CHCl_3$ (1.5 mL) was added Dess–Martin periodinane (509 mg, 1.20 mmol) at 0 ^oC under an argon atmosphere. The reaction mixture was brought to room temperature and allowed to stir until the starting alcohol was consumed, as determined by TLC analysis (typically 4-8 hours). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) (446 mg, 3.20 mmol) was added in three portions over 5 mins and stirred very rapidly at 0 ^oC. After 6-8 h, the mixture was monitored by TLC. If corresponding aldehyde remained, one equivalent of TBD was added with vigorous stirring. After completion of the reaction, as indicated by TLC (~ 16-20 h), the mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The precipitated solids were filtered on a bed of diatomaceous earth and the filter cake was rinsed with CH_2Cl_2. The filtrate was separated, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined

organic layers were dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography using indicated ratios of ethyl acetate/hexanes to afford the corresponding trichloromethyl carbinols **16**.

1,1,1–Trichlorotridecan–2–ol (13e).

The crude material was purified by flash chromatography through silica gel, using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 88% yield (267.3 mg); IR (film): 3579, 2927, 2856, 1461, 1265, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.0 (ddd, 1H, *J* = 9.4, 5.3, 1.7 Hz), 2.65 (d, 1H, *J* = 5.3 Hz), 2.16 – 1.91 (m, 1H), 1.70 – 1.55 (m, 2H), 1.53 – 1.40 (m, 1H), 1.36 – 1.17 (m, 16H), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.4, 83.0, 31.9, 31.5, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 26.1, 22.7, 14.1; HRMS *m/z* calcd for $C_{12}H_{25}O$ $[M–CCl_3]^+$, 185.1905; found 185.1901.

(*E*)–1,1,1–Trichloro–5–methylhex–3–en–2–ol (13i).

The crude material was purified by flash chromatography through silica gel, using 95:5 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 93% yield (202.3 mg); IR (film): 3366, 2964, 2871, 1643, 1266, 972, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 5.99 (ddd, 1H, *J* = 15.5, 6.7, 1.0 Hz), 5.59 (ddd, 1H, *J* = 15.5, 6.7, 1.4 Hz), 4.52 (t, 1H, *J* = 6.0 Hz), 2.78 (dd, 1H, *J* = 6.0, 2.9 Hz), 2.44 – 2.33 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.1, 121.0, 103.1, 83.5, 31.1, 21.8, 21.8; HRMS *m/z* calcd for $C_6H_{11}O$ $[M–CCl_3]^+$, 99.0810; found 99.0807.

General Procedure for the Preparation of One–Carbon Homologated Primary Amides (15a-15j) from Trichloromethyl Carbinols

Diphenyldiselenide (1.3 mmol, 406 mg) was added to a 50 mL dry pressure tube temporarily fit with a rubber septum and equipped with a magnetic stir bar. Ammonia saturated absolute ethanol (4 mL) was added followed by the rapid addition of $NaBH_4$ (2.8 mmol, 106 mg) under argon. Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then neat trichloromethyl carbinol **13** (1.0 mmol) was added, followed by the addition of freshly powdered NaOH (2.5 mmol, 100.0 mg) under argon. The rubber septum was quickly replaced with a Teflon screw cap and the solution was heated in a 55 °C oil bath for 24–36 hours. After completion of the reaction as indicated by TLC, the ethanolic ammonia was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL ethyl acetate and 5 mL H_2O. The resulting solution was cooled to 0 °C and adjusted to pH 1 with 1 N HCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous sodium sulfate, and then concentrated by rotary evaporation. The crude material was purified by flash chromatography through a small plug of silica using the specified eluent, affording the corresponding primary amide.

2–Phenylacetamide (15a).

The crude material was purified by flash chromatography through silica gel using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated product was obtained as an off–white solid in 88% yield (119.1 mg); m.p. 156–157 °C; IR (solid): ν 3349, 3163, 3031, 2923, 2804, 1633, 1411, 1285, 1181, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 – 7.33 (m, 2H), 7.33 – 7.26 (m, 3H), 5.68 (brs, 1H), 5.39 (brs, 1H), 3.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 134.8, 129.4, 129.0, 127.4, 43.3; HRMS *m/z* calcd for C_8H_9NO, 135.0684; found 135.0689.

2–{4–(Trifluoromethyl)phenyl}acetamide (15b).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 90% yield (183.7 mg); m.p. 148–150 °C; IR (solid): ν 3352, 3166, 2924, 2806, 1634, 1413, 1323, 1132, 1064, 1019, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 5.69 (brs, 1H), 5.40 (brs, 1H), 3.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.1, 138.7, 129.9 (q, *J* = 32.4 Hz), 129.7, 125.8 (q, *J* = 3.7 Hz), 122.9 (q, *J* = 276.3 Hz), 42.8; ^{19}F NMR ($CDCl_3$, 360 MHz): δ –62.6; HRMS *m/z* calcd for $C_9H_8F_3NO$, 203.0558; found 203.0556.

2–(4–Methoxyphenyl)acetamide (15c).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 86% yield (142.2 mg); m.p. 189–190 °C; IR (solid): ν 3345, 3168, 2972, 2940, 2807, 1631, 1509, 1411, 1298, 1204, 1180, 1023, 811, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 5.37 (brs, 2H), 3.81 (s, 3H), 3.53 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 159.0, 130.5, 126.9, 114.5, 55.3, 42.4; HRMS *m/z* calcd for $C_9H_{11}NO_2$, 165.0790; found 165.0793.

4–Phenylbutanamide (15d).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as an off–white solid in 85% yield (138.7 mg); m.p. 80–81 °C; IR (solid): ν 3380, 3198, 3023, 2944, 2861, 1645, 1418, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500

MHz): δ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 6.0 (brs, 1H), 5.55 (brs, 1H), 2.66 (t, 2H, *J* = 7.5 Hz), 2.20 (t, 2H, *J* = 7.5 Hz), 2.00 – 1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 141.3, 128.4, 128.3, 125.9, 35.0, 34.9, 26.8; HRMS *m/z* calcd for $C_{10}H_{13}NO$, 163.0997; found 163.0998.

Tridecanamide (15e).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 80% yield (170.5 mg); m.p. 93–95 °C; IR (solid): ν 3356, 3188, 2916, 2849, 1631, 1466, 1416, 1136, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.68 (brs, 1H), 5.46 (brs, 1H), 2.21 (t, 2H, *J* = 7.5 Hz), 1.63 (dd, 2H, *J* = 14.8, 7.5 Hz), 1.40 – 1.18 (m, 18H), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.7, 36.0, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 25.5, 22.7, 14.1; HRMS *m/z* calcd for $C_{13}H_{27}NO$, 213.2093; found 213.2100.

2–Cyclohexylacetamide (15f).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 92% yield (130.4 mg); m.p. 160–162 °C; IR (solid): ν 3349, 3183, 2922, 2846, 1623, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.44 (brs, 1H), 5.39 (brs, 1H), 2.08 (d, 2H, *J* = 6.7 Hz), 1.89 – 1.60 (m, 6H), 1.38 – 1.21 (m, 2H), 1.21 – 1.06 (m, 1H), 0.96 (qd, 2H, *J* = 13.0, 3.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.7, 44.0, 35.2, 33.1, 26.2, 26.0; HRMS *m/z* calcd for $C_8H_{15}NO$, 141.1154; found 141.1152.

2–(Furan–2–yl)acetamide (15g).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a grey solid in 75% yield (93.8 mg); m.p. 108–109 °C; IR (solid): ν 3351, 3175, 2808, 1641, 1406, 1288, 1143, 1072, 1011, 945, 903, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, 1H, *J* = 1.5 Hz), 6.35 (dd, 1H, *J* = 3.1, 1.5 Hz), 6.24 (d, 1H, *J* = 3.1 Hz), 5.97 (brs, 1H), 5.71 (brs, 1H), 3.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 148.6, 142.5, 110.8, 108.5, 35.8; HRMS *m/z* calcd for $C_6H_7NO_2$, 125.0477; found 125.0480.

2–(Thiophen–2–yl)acetamide (15h).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a grey solid in 90% yield (127.6 mg). m.p. 150–151 °C; IR (solid): ν 3348, 3164, 2909, 2812, 1634, 1407, 1284, 1134, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (dd, 1H, *J* = 5.1, 1.2 Hz), 7.00 (dd, 1H, *J* = 5.1, 3.5 Hz), 6.97 (dd, 1H, *J* = 3.5, 1.2 Hz), 5.88 (brs, 1H), 5.65 (brs, 1H), 3.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 136.1, 127.4, 125.6, 37.0; HRMS *m/z* calcd for C_6H_7NOS, 141.0248; found 141.0250.

(*E*)–5–Methylhex–3–enamide (15i).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 86% yield (109.4 mg); m.p. 87–88 °C; IR (solid): ν 3349, 3177, 2958, 2868, 2805, 1630, 1409, 967, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.87 (brs, 1H), 5.64 (dd, 1H, *J* = 15.3, 6.4 Hz), 5.63 (brs, 1H), 5.55 – 5.42 (m, 1H), 2.94 (d, 2H, *J* = 6.9 Hz), 2.33 (dq, 1H, *J* = 13.4, 6.9 Hz), 1.00 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 174.2, 143.4, 119.6, 39.9, 31.0, 22.2; HRMS *m/z* calcd for $C_7H_{13}NO$, 127.0997; found 127.1002.

(*E*)–4–Phenylbut–3–enamide (15j).

The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 74% yield (119.3 mg) in 9:1 isomeric ratio. Characteristic data of major product; m.p. 105–106 °C; IR (solid): ν 3378, 3191, 3032, 2912, 2848, 1641, 1410, 1259, 963, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.50 – 7.10 (m, 5H), 6.55 (d, 1H, *J* = 15.8 Hz), 6.28 (dt, 1H, *J* = 15.8, 7.2 Hz), 5.90 (brs, 1H), 5.72 (brs, 1H), 3.17 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 136.5, 134.7, 128.6, 127.8, 126.3, 122.2, 40.2; HRMS *m/z* calcd for $C_{10}H_{11}NO$, 161.0841; found 161.0842.

General Procedure for the Preparation of One–Carbon Homologated Secondary Amides (15k-15t) from Trichloromethyl Carbinols

Diphenyldiselenide (1.3 mmol, 406 mg) was added to a dry round–bottom flask equipped with stir bar under a blanket of argon. Deoxygenated absolute ethanol (purged for 30 minutes with argon) (4 mL) was then added, followed by the rapid addition of $NaBH_4$ (2.8 mmol, 106 mg). Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then neat trichloromethyl carbinol **13** (1.0 mmol) was added, followed by the additions of freshly powdered NaOH (2.5 mmol, 100 mg) and benzylamine (1.1 mmol, 118 mg) under argon. The mixture was heated in a 55°C oil bath and allowed to react at this temperature for 24–36 hours while monitoring by TLC for consumption of starting material and 2-phenylselanylamide **17**. After completion of the reaction, as indicated by TLC (typically 24-36 h), ethanol was removed

by rotary evaporation and the amorphous solids were dissolved in 5 mL saturated aqueous NH_4Cl, and the solution was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated by rotary evaporation. The crude material was purified by flash chromatography through a small plug of silica using the specified eluent, affording the corresponding pure secondary amide.

***N*–Benzyl–2–phenylacetamide (15k).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 89% yield (200.5 mg); m.p. 116–117 °C; IR (solid): ν 3284, 2925, 1637, 1549, 1489, 1448, 1025, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40 – 7.20 (m, 8H), 7.16 (d, 2H, *J* = 7.6 Hz), 5.79 (brs, 1H), 4.39 (d, 2H, *J* = 5.8 Hz), 3.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 138.1, 134.8, 129.4, 129.0, 128.6, 127.4, 127.4, 127.3, 43.8, 43.5; HRMS *m/z* calcd for $C_{15}H_{15}NO$, 225.1154; found 225.1160.

***N*–Benzyl–2–(4–(trifluoromethyl)phenyl)acetamide (15l).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated product was obtained as a white solid in 95% yield (278.6 mg); m.p. 135–136 °C; IR (solid): ν 3241, 3066, 2929, 2856, 1626, 1554, 1330, 1124, 1068, 1015, 822, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (d, 2H, *J* = 8.0 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 7.34 – 7.22 (m, 3H), 7.19 (d, 2H, *J* = 6.9 Hz), 5.90 (brs, 1H), 4.40 (d, 2H, *J* = 5.8 Hz), 3.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7, 138.9, 137.9, 129.7, 129.5 (q, *J* = 32.5 Hz), 128.7, 127.6, 127.6, 125.8 (q, *J* = 3.8 Hz),

124.1 (q, J = 272.0 Hz), 43.8, 43.3; ^{19}F NMR ($CDCl_3$, 360 MHz): δ –62.5; (HRMS *m/z* calcd for $C_{16}H_{14}F_3NO$, 293.1027; found 293.1028.

***N*–Benzyl–2–(4–methoxyphenyl)acetamide (15m).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated product was obtained as an off–white solid in 87% yield (222.4 mg); m.p. 132–133 ºC; IR (solid): ν 3288, 3069, 3032, 2840, 1633, 1584, 1508, 1459, 1298, 1241, 1180, 1029, 809, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.21 (m, 3H), 7.16 (d, 4H, J = 8.4 Hz), 6.87 (d, 2H, J = 8.4 Hz), 5.73 (brs, 1H), 4.40 (d, 2H, J = 5.8 Hz), 3.79 (s, 3H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 158.9, 138.2, 130.5, 128.6, 127.5, 127.4, 126.7, 114.5, 55.3, 43.5, 42.9; HRMS *m/z* calcd for $C_{16}H_{17}NO_2$, 255.1259; found 255.1264.

***N*–Benzyl–4–phenylbutanamide (15n).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 85% yield (215.3 mg); m.p. 75–76 °C; IR (solid): ν 3285, 3066, 3025, 2920, 2868, 1639, 1543, 1453, 1266, 1209, 1076, 1025, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.20 (m, 7H), 7.19 – 7.09 (m, 3H), 5.96 (brs, 1H), 4.37 (d, 2H, J = 5.6 Hz), 2.62 (t, 2H, J = 7.4 Hz), 2.17 (t, 2H, J = 7.4 Hz), 2.09 – 1.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.5, 141.4, 138.3, 128.6, 128.4, 128.3, 127.7, 127.4, 125.9, 43.4, 35.7, 35.1, 27.0; HRMS *m/z* calcd for $C_{17}H_{19}NO$, 253.1467; found 253.1470.

***N*–Benzyltridecanamide (15o).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a white solid in 96% yield (291.3 mg); m.p. 80–81 °C; IR (solid): ν 3295, 3073, 3032, 2916, 2848, 1637, 1550, 1457, 1238, 1029, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 5.74 (brs, 1H), 4.44 (d, 2H, *J* = 5.6 Hz), 2.20 (t, 2H, *J* = 7.5 Hz), 1.70 – 1.60 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.9, 138.5, 128.7, 127.8, 127.5, 43.6, 36.8, 31.9, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 29.3, 25.8, 22.7, 14.1; HRMS *m/z* calcd for $C_{20}H_{33}NO$, 303.2562; found 303.2570.

N–Benzyl–2–cyclohexylacetamide (15p).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a white solid in 93% yield (214.8 mg); m.p. 132–134 °C; IR (solid): ν 3276, 3065, 2923, 1639, 1450, 1265, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.30 (m, 2H), 7.30 – 7.24 (m, 3H), 5.70 (brs, 1H), 4.44 (d, 2H, *J* = 5.7 Hz), 2.07 (d, 2H, *J* = 7.1 Hz), 1.89 – 1.80 (m, 1H), 1.78 – 1.72 (m, 2H), 1.72 – 1.61 (m, 3H), 1.34 – 1.22 (m, 2H), 1.19 – 1.07 (m, 1H), 0.99 – 0.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 138.5, 128.7, 127.8, 127.5, 44.9, 43.6, 35.4, 33.2, 26.2, 26.1; HRMS *m/z* calcd for $C_{15}H_{21}NO$, 231.1623; found 231.1624.

***N*–Benzyl–2–(furan–2–yl)acetamide (15q).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 83% yield (178.2 mg); m.p. 88–89 °C; IR (solid): ν 3279, 3069, 3028, 2934, 2885, 1645, 1545, 1247, 1073, 1007, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz):

δ 7.36 (dd, 1H, *J* = 1.8, 0.6 Hz), 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 1H) 7.23 – 7.16 (m, 2H), 6.33 (dd, 1H, *J* = 3.0, 1.9 Hz), 6.22 (dd, 1H, *J* = 3.0, 0.5 Hz), 6.10 (brs, 1H), 4.42 (d, 2H, *J* = 5.8 Hz), 3.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 148.6, 142.4, 138.0, 128.6, 127.4, 127.4, 110.7, 108.5, 43.5, 36.2; HRMS *m/z* calcd for $C_{13}H_{13}NO_2$, 215.0946; found 215.0950.

_N_–Benzyl–2–(thiophen–2–yl)acetamide (15r).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 92% yield (212.8 mg); m.p. 102–103 °C; IR (solid): ν 3268, 3073, 3024, 2919, 1645, 1550, 1410, 1352, 1254, 1025, 840, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.27 (m, 2H), 7.27 – 7.18 (m, 4H), 6.96 (dd, 1H, *J* = 5.1, 3.5 Hz), 6.92 (dd, 1H, *J* = 3.5, 0.9 Hz), 6.06 (brs, 1H), 4.41 (d, 2H, *J* = 5.8 Hz), 3.80 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7, 137.9, 136.0, 128.6, 127.5, 127.4, 127.4, 127.3, 125.6, 43.6, 37.5; HRMS *m/z* calcd for $C_{13}H_{13}NOS$, 231.0718; found 231.0727.

(*E*)–*N*–Benzyl–5–methylhex–3–enamide (15s).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated product was obtained as a grey solid in 96% yield (208.6 mg); m.p. 36–37 °C; IR (solid): ν 3298, 3069, 3034, 2958, 2930, 2868, 1638, 1545, 1456, 1323, 1246, 1026, 968, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 – 7.30 (m, 2H), 7.29 – 7.23 (m, 3H), 5.96 (brs, 1H), 5.59 (dd, 1H, *J* = 15.4, 6.7 Hz), 5.53 – 5.46 (m, 1H), 4.43 (d, 2H, *J* = 5.7 Hz), 2.97 (d, 2H, *J* = 6.7 Hz), 2.31 (dq, 1H, *J* = 13.4, 6.7 Hz), 0.98 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 143.4, 138.3,

128.7, 127.6, 127.4, 119.6, 43.5, 40.4, 31.0, 22.2; HRMS *m/z* calcd for $C_{14}H_{19}NO$, 217.1467; found 217.1472.

(*E*)–*N*–Benzyl–4–phenylbut–3–enamide (15t).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated product was obtained as an off–white solid in 82% yield (205.8 mg) as 9:1 isomeric ratio. Characteristic data of major compound; m.p. 113–114 °C; IR (solid): ν 3246, 3063, 3028, 2930, 2822, 1629, 1551, 1448, 1349, 1242, 1066, 1022, 963, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.20 (m, 10H), 6.51 (d, 1H, *J* = 15.9 Hz), 6.29 (dt, 1H, *J* = 15.9, 7.2 Hz), 6.09 (brs, 1H), 4.43 (d, 2H, *J* = 5.8 Hz), 3.17 (dd, 2H, *J* = 7.2, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 138.0, 136.5, 134.6, 128.6, 128.5, 127.7, 127.4, 126.3, 122.3, 43.6, 40.7; HRMS *m/z* calcd for $C_{17}H_{17}NO$, 251.1310; found 251.1311.

General Procedure for the Preparation of One–Carbon Homologated Tertiary Amides (15u-15cc) from Trichloromethyl Carbinols

Diphenyldiselenide (1.3 mmol, 406 mg) was added to a dry round–bottom flask equipped with stir bar under a blanket of argon. Deoxygenated absolute ethanol (purged for 30 minutes with argon) (4 mL) was then added, followed by the rapid addition of $NaBH_4$ (2.8 mmol, 106 mg). Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then neat trichloromethyl carbinol **13** (1.0 mmol) was added, followed by the additions of freshly powdered NaOH (2.5 mmol, 100 mg) and morpholine (1.1 mmol, 95.8 mg) under argon. The mixture was heated in a 55°C oil bath and allowed to react at this temperature for 24–36 hours while monitoring by TLC for consumption of starting material and 2-phenylselanylamide **17**.

After completion of the reaction, as indicated by TLC (typically 24-36 h), ethanol was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL saturated aqueous NH_4Cl, and the solution was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated by rotary evaporation. The crude material was purified by flash chromatography through a small plug of silica using the specified eluent, affording the corresponding pure tertiary amide.

1–Morpholino–2–phenylethanone (15u).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 88% yield (180.1 mg); m.p. 62–63 °C; IR (solid): ν 3028, 2961, 2896, 2850, 1642, 1433, 1272, 1227, 1111, 1033, 960, 848, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.29 (m, 2H), 7.28 – 7.21 (m, 3H), 3.73 (s, 2H), 3.64 (s, 4H), 3.51 – 3.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 134.7, 128.7, 128.4, 126.8, 66.7, 66.3, 46.4, 42.0, 40.7; HRMS *m/z* calcd for $C_{12}H_{15}NO_2$, 205.1103; found 205.1099.

1–Morpholino–2–(4–(trifluoromethyl)phenyl)ethanone (15v).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a yellow oil in 88% yield (240.5 mg); IR (film): ν 2916, 2248, 1644, 1461, 1327, 1117, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 7.59 (d, 2H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 3.77 (s, 2H), 3.70 – 3.62 (m, 4H), 3.59 – 3.53 (m, 2H), 3.49 – 3.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.7, 138.9, 129.4 (q, J = 32.5 Hz), 129.2, 125.7 (q, J = 3.8 Hz), 124.1

(q, J = 272.4 Hz), 66.8, 66.4, 46.5, 42.2, 40.2; ^{19}F ($CDCl_3$, 360 MHz): δ –62.5; HRMS *m/z* calcd for $C_{13}H_{14}F_3NO_2$, 273.0977; found 273.0977.

2–(4–Methoxyphenyl)–1–morpholinoethanone (15w).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 81% yield (190.6 mg); IR (film): ν 2964, 2911, 2857, 1634, 1513, 1459, 1362, 1247, 1178, 1114, 1035, 964, 787, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15 (d, 2H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 3.79 (s, 3H) 3.66 (s, 2H), 3.63 (s, 4H), 3.49 – 3.44 (m, 2H), 3.44 – 3.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 169.9, 158.4, 129.5, 126.7, 114.1, 66.7, 66.4, 55.2, 46.4, 42.0, 39.8; HRMS *m/z* calcd for $C_{13}H_{17}NO_3$, 235.1208; found 235.1217.

1–Morpholino–4–phenylbutan–1–one (15x).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 84% yield (196.7 mg); IR (film): ν 3024, 2962, 2922, 2857, 1642, 1436, 1361, 1237, 1116, 1068, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.25 (m, 2H), 7.20 – 7.16 (m, 3H), 3.67 – 3.56 (m, 6H), 3.35 (t, 2H, J = 4.8 Hz), 2.67 (t, 2H, J = 7.4 Hz), 2.28 (t, 2H, J = 7.4 Hz), 2.02 – 1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 141.5, 128.4, 128.3, 125.8, 66.8, 66.5, 45.8, 41.8, 35.1, 32.0, 26.4; HRMS *m/z* calcd for $C_{14}H_{19}NO_2$, 233.116; found 233.118.

2–Cyclohexyl–1–morpholinoethanone (15y).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was

obtained as a white solid in 95% yield (200.7 mg); m.p. 64–65 °C; IR (solid): ν 2920, 2849, 1632, 1427, 1274, 1229, 1112, 1032, 973, 898, 795, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.62 – 3.52 (m, 6H), 3.41 (d, 2H, *J* = 4.1 Hz), 2.21 (t, 2H, *J* = 6.4 Hz), 1.78 – 1.55 (m, 6H), 1.28 – 1.16 (m, 2H), 1.13 – 1.02 (m, 1H), 0.96 (q, 2H, *J* = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 66.8, 66.6, 46.2, 41.7, 40.3, 34.9, 33.2, 26.1, 26.0; HRMS *m/z* calcd for $C_{12}H_{21}NO_2$, 211.1572; found 211.1579.

2–(Furan–2–yl)–1–morpholinoethanone (15z).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 3:7 hexanes/EtOAc as the eluent. The indicated compound was obtained as a light yellow oil in 75% yield (146.6 mg); IR (film): ν 3031, 2924, 2858, 1655, 1547, 1245, 1014, 907, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.35 (dd, 1H, *J* = 1.8, 0.7 Hz), 6.33 (dd, 1H, *J* = 3.1, 1.8 Hz)), 6.19 (dd, 1H, *J* = 3.1, 0.7 Hz)), 3.77 (s, 2H), 3.67 – 3.62 (m, 4H), 3.61 (t, 2H, *J* = 5.0 Hz), 3.53 (t, 2H, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.2, 148.5, 141.8, 110.6, 107.6, 66.7, 66.6, 46.6, 42.3, 33.9; HRMS *m/z* calcd for $C_{10}H_{13}NO_3$, 195.0895; found 195.0903.

1–Morpholino–2–(thiophen–2–yl)ethanone (15aa).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 91% yield (192.5 mg); m.p. 59–60 °C; IR (solid): ν 2961, 2896, 2853, 1641, 1438, 1270, 1227, 1110, 1066, 1030, 957, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 (dd, 1H, *J* = 5.1, 1.0 Hz), 6.95 (dd, 1H, *J* = 5.1, 3.5 Hz), 6.89 (dd, 1H, *J* = 2.2, 1.0 Hz), 3.88 (s, 2H), 3.65 (s, 4H), 3.56 (t, 2H, *J* = 4.7 Hz), 3.49 (t, 2H, *J* = 4.7 Hz); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 168.4, 136.2, 126.8, 125.9, 124.7, 66.6, 66.3, 46.5, 42.2, 34.8; HRMS *m/z* calcd for $C_{10}H_{13}NO_2S$, 211.0667; found 211.0659.

(*E*)–5–Methyl–1–morpholinohex–3–en–1–one (15bb).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 82% yield (161.4 mg); IR (flim): ν 2959, 2863, 1645, 1433, 1272, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.51 – 5.47 (m, 2H), 3.68 – 3.63 (m, 4H), 3.61 (t, 2H, *J* = 4.7 Hz), 3.45 (t, 2H, *J* = 4.7 Hz), 3.07 (d, 2H, *J* = 4.7 Hz), 2.34 – 2.26 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2, 141.2, 119.6, 66.9, 66.7, 46.2, 41.9, 37.6, 31.1, 22.3; HRMS *m/z* calcd for $C_{11}H_{19}NO_2$, 197.1416; found 197.1414.

(*E*)–1–Morpholino–4–phenylbut–3–en–1–one (15cc).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as a white solid in 78% yield (180.1 mg); m.p.: 92–93 °C; IR (solid): ν 3443, 2856, 1636, 1437, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 – 7.19 (m, 5H), 6.48 (d, 1H, *J* = 16.0 Hz), 6.32 (dt, 1H, *J* = 16.0, 6.6 Hz), 3.72 – 3.62 (m, 6H), 3.54 – 3.48 (m, 2H), 3.30 (dd, 2H, *J* = 6.6, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 136.8, 133.0, 128.5, 127.5, 126.2, 122.7, 66.9, 66.6, 46.3, 42.1, 37.7; HRMS *m/z* calcd for $C_{14}H_{17}NO_2$, 231.1259; found 231.1259.

General Procedure for the Preparation of One–Carbon Homologated Weinreb Amide Derivatives (20a-20e) from Trichloromethyl Carbinols

Diphenyldiselenide (1.3 mmol, 406 mg) was added to a dry round–bottom flask equipped with stir bar under a blanket of argon. Deoxygenated absolute ethanol (purged for 30 minutes

with argon) (4 mL) was then added, followed by the rapid addition of $NaBH_4$ (2.8 mmol, 106 mg). Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then neat trichloromethyl carbinol **13** (1.0 mmol) was added, followed by the additions of freshly powdered NaOH (3.3 mmol, 132 mg) and *N,O*–dimethylhydroxylamine hydrochloride (1.1 mmol, 107.3 mg) under argon. The mixture was heated in a 55 °C oil bath and allowed to react at this temperature for 20-24 hours while monitoring by TLC for consumption of starting material and 2-phenylselanylamide **17**. After completion of the reaction, as indicated by TLC (typically 20-24 h), ethanol was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL saturated aqueous NH_4Cl, and the solution was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated by rotary evaporation. The crude material was purified by flash chromatography through a small plug of silica using the specified eluent, affording the corresponding pure Weinreb amide derivative.

***N*–Methoxy–*N*–methyl–2–phenylacetamide (20a).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 1:9 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 83% yield (148.7 mg); IR (film): ν 3031, 2938, 2856, 1644, 1456, 1383, 1292, 1175, 1103, 1004, 934, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.25 (m, 4H), 7.25 – 7.20 (m, 1H), 3.76 (s, 2H), 3.58 (s, 3H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 134.9, 129.2, 128.4, 126.6, 61.1, 39.3, 32.1; HRMS *m/z* calcd for $C_{10}H_{13}NO_2$, 179.0946; found 179.0942.

***N*–Methoxy–*N*–methyl–2–(4–(trifluoromethyl)phenyl)acetamide (20b).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 1:9 hexanes/EtOAc as the eluent. The indicated compound was obtained as a white solid in 89% yield (219.7 mg); m.p. 34–35 °C; IR (solid): ν 2974, 3944, 2833, 1661, 1414, 1382, 1322, 1109, 1062, 867, 822, 793, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 3.82 (s, 2H), 3.65 (s, 3H), 3.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.4, 139.0, 129.7, 129.2 (q, *J* = 32.5 Hz), 125.3 (q, *J* = 3.7 Hz), 123.1 (q, *J* = 264.3 Hz), 61.3, 39.0, 32.3; ^{19}F ($CDCl_3$, 360 MHz): δ –62.5; HRMS *m/z* calcd for $C_{11}H_{12}F_3NO_2$, 247.0820; found 247.0822.

***N*–Methoxy–2–(4–methoxyphenyl)–*N*–methylacetamide (20c).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 1:9 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 76% yield (159.3 mg); IR (film): ν 2970, 2941, 2838, 1648, 1513, 1437, 1384, 1297, 1248, 1177, 1031, 787 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 3.78 (s, 3H), 3.70 (s, 2H), 3.61 (s, 3H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.7, 158.4, 130.2, 126.9, 113.9, 61.2, 55.2, 38.4, 32.2; HRMS *m/z* calcd for $C_{11}H_{15}NO_3$, 209.1052; found 209.1053.

***N*–Methoxy–*N*–methyl–4–phenylbutanamide (20d).**

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 1:9 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 87% yield (180.3 mg); IR (film): ν 3027, 2938, 2866, 1637, 1189, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.31 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 3.62 (s, 3H), 3.17 (s, 3H), 2.68 (t, 2H, *J* = 7.5 Hz), 2.42 (t, 2H, *J* = 7.5 Hz), 2.02 – 1.93 (m, 2H); ^{13}C

NMR ($CDCl_3$, 125 MHz): δ 174.4, 141.8, 128.5, 128.3, 125.8, 61.1, 35.3, 32.2, 31.2, 26.0; HRMS *m/z* calcd for $C_{12}H_{17}NO_2$, 207.1259; found 207.1265.

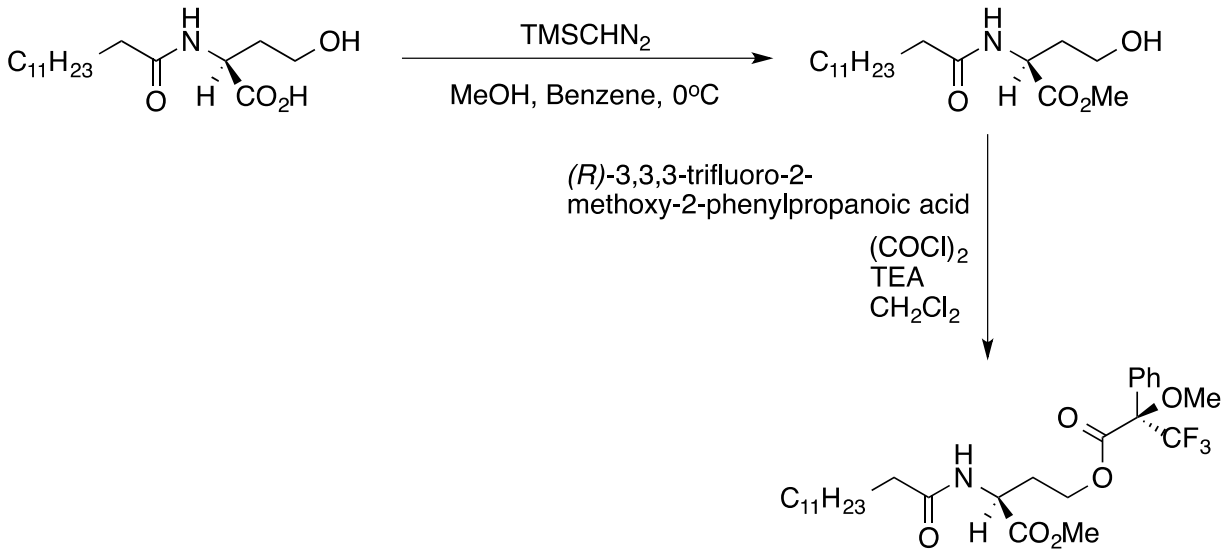
2–Cyclohexyl–*N*–methoxy–*N*–methylacetamide (20e).

The crude material was purified by flash chromatography through silica gel, using hexane to remove diphenyldiselenide then 1:9 hexanes/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 75% yield (139.1 mg); IR (film): ν 2980, 2928, 2855, 1652, 1375, 1243, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 3.64 (s, 3H), 3.14 (s, 3H), 2.26 (d, 2H, J = 6.6 Hz), 1.84 – 1.71 (m, 1H), 1.70 – 1.53 (m, 5H), 1.32 – 1.06 (m, 3H), 1.00 – 0.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.0, 61.1, 39.3, 34.4, 33.3, 26.2, 26.1, 26.0; HRMS *m/z* calcd for $C_{10}H_{19}NO_2$, 185.1416; found 185.1416.

Preparation of *N*–Tridecanoyl–L–homoserine (22) from L–homoserine.

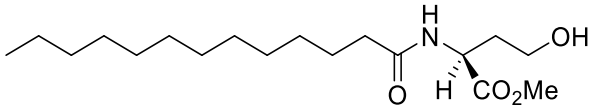
Diphenyldiselenide (1.30 mmol, 406 mg) was added to a dry round–bottom flask equipped with stir bar under a blanket of argon. Deoxygenated absolute ethanol (purged for 30 minutes with argon) (4 mL) was then added, followed by the rapid addition of $NaBH_4$ (2.80 mmol, 106 mg). Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then neat trichloromethyl carbinol **13** (1.0 mmol) was added, followed by the additions of freshly powdered NaOH (3.30 mmol, 132 mg) and L–homoserine (1.10 mmol, 131 mg) under argon. The mixture was heated in a 55 °C oil bath and allowed to react at this temperature for 36 hours while monitoring by TLC for consumption of starting material and 2-phenylselanylamide **17**. After completion of the reaction, as indicated by TLC, ethanol was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL ethyl acetate and 5 mL H_2O. The

resulting solution was cooled to 0 °C and adjusted to pH 1 with 1 N HCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous sodium sulfate, and then concentrated by rotary evaporation. The crude material was purified by flash chromatography through silica gel, using 1:9 EtOAc/hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated product was obtained as a white solid in 89% yield (280.7 mg); m.p. 103–104 °C; $[\alpha]_D^{21} = -23.1^o$ cm^3 g^{-1} dm^{-1} (*c* = 1.0 in CH_3OH); IR (solid): ν 3394, 3310, 2915, 2850, 1701, 1650, 1539, 1290 cm^{-1}; ^1H NMR (DMSO d_6, 500 MHz): δ 12.40 (brs, 1H), 7.96 (d, 1H, *J* = 7.6 Hz), 4.25 (ddd, 1H, *J* = 12.3, 9.1, 4.4 Hz), 3.48 – 3.36 (m, 2H), 2.09 (t, 2H, *J* = 7.5 Hz), 1.89 – 1.80 (m, 1H), 1.74 – 1.64 (m, 1H), 1.47 (t, 2H, *J* = 6.2 Hz), 1.29 – 1.21 (m, 19H), 0.86 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (DMSO d_6, 125 MHz): δ 174.0, 172.4, 57.3, 49.0, 35.0, 34.1, 31.3, 29.0, 29.0, 29.0, 29.0, 28.8, 28.7, 28.6, 25.2, 22.1, 13.9; HRMS *m/z* calcd for $C_{17}H_{31}NO_3$, 297.2304; found 297.2302 which corresponds to $[M–H_2O]$.



Scheme 2.7 Conversion of **22** to the corresponding methyl ester and subsequently the Mosher's ester derivative.

General procedure for the formation of methyl ester from 22



To a chilled stirred solution of **22** (0.16 mmol, 50 mg) in 0.3 mL methanol and 1.1 mL benzene was added $TMSCHN_2$ (0.19 mmol, 95 μL) at 0ºC. The ice bath was removed, and the mixture was stirred at rt for 5 min. After completion of the reaction, as indicated by TLC (~30 min), solvents were removed by rotary evaporation. The crude reaction mixture was purified by flash chromatography through a plug of pyridine-saturated silica gel, using 1:1 EtOAc/hexane as the eluent. The methyl carboxylate was obtained as a white solid in 75% yield (39 mg); m.p. 71–72 °C; $[\alpha]_D^{20}$ = +3.63º $cm^3\,g^{-1}\,dm^{-1}$ (*c* = 1.1 in CH_2Cl_2); IR (solid): ν 3419, 3314, 2915, 2848, 1730, 1647, 1539, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.34 (d, 1H, *J* = 7.5 Hz), 4.76 (ddd, 1H, *J* = 11.0, 7.7, 3.7 Hz), 3.78 (s, 3H), 3.69 (s, 1H), 3.62 – 3.46 (m, 2H), 2.35 – 2.22 (m, 2H), 2.22 – 2.14 (m, 1H), 1.68 – 1.55 (m, 4H), 1.31 – 1.22 (m, 19H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.3, 173.3, 58.1, 52.6, 49.4, 36.5, 36.1, 31.9, 29.6, 29.6, 29.6, 29.4, 29.3, 29.3, 29.2, 25.6, 22.7, 14.1; HRMS *m/z* calcd for $C_{18}H_{35}NO_4$, 329.2566; found 329.2567.

No racemization was indicated in the NMR spectra of the corresponding Mosher ester derivative.[30]

Preparation of (*R*)–2,2,2–trichloro–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)ethanol (24a) and its (*R*,*S*)–diastereomer (24b):

(*R*)–Isopropylidine–D–mannitol was purchased from Sigma–Aldrich and used without further purification. (*R*)–2,2–dimethyl–1,3–dioxolane–4–carbaldehyde **10** was prepared according to procedures reported by Schmid and Bryant. To a 0 °C solution of sodium

trichloroacetate (245 mg, 1.50 mmol) and trichloroacetic acid (278 mg, 1.50 mmol) in 2 mL of DMF was added **10** (130 mg, 1.00 mmol) dissolved in 1 mL of DMF. After stirring for 15 min., the mixture was warmed to room temperature then stirred rapidly for 12 hours while monitoring by TLC for consumption of starting material. After judged complete, the mixture was diluted with 5 mL of EtOAc and washed with saturated aqueous $NaHCO_3$. Precipitated solids were filtered and rinsed three times with EtOAc. The combined organic phase was dried with sodium sulfate, and the EtOAc was evaporated under reduced pressure. The crude material was purified by flash chromatography through silica gel, using 9:1 hexanes/EtOAc as eluent. The (*R*,*R*)–isomer was obtained as a white solid in 44% yield (110.8 mg), and the (*R*,*S*)–isomer was obtained as a colorless oil in 22% yield (55.6 mg). The physical and analytical data for both isomers were identical to that previously reported.[15] (*R*)–2,2,2–Trichloro–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)ethanol (**24a**): m.p. 81–82 °C, (lit[4] m.p. 82–83 °C); $[\alpha]_D^{20}$ = +21.3 $cm^3\,g^{-1}\,dm^{-1}$ (*c* = 3.8 g cm^{-3} in $CHCl_3$); IR (solid): ν 3371, 2985, 1375, 1150, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.62 – 4.56 (m, 1H), 4.36 (dd, 1H, *J* = 4.0, 3.5 Hz), 4.27 (dd, 1H, *J* = 8.7, 6.3 Hz), 4.09 (dd, 1H, *J* = 8.7, 6.3 Hz), 3.10 (dd, 1H, *J* = 4.0, 3.5 Hz), 1.48 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.2, 100.6, 82.4, 75.1, 64.7, 26.3, 25.3; HRMS *m/z* calcd for $C_6H_8Cl_3O$, 232.2539; found 232.9546 which corresponds to $[M–CH_3]^+$.

(*S*)–2,2,2–Trichloro–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)ethanol (**24b**):

$[\alpha]_D^{20}$ = +10.5° $cm^3\,g^{-1}\,dm^{-1}$ (*c* = 2.0 in $CHCl_3$); IR (film): ν 3446, 2987, 2934, 1374, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.57 (ddd, *J* = 2.5, 6.5, 6.5 Hz, 1H), 4.25 (dd, *J* = 6.5, 8.5 Hz, 1H), 3.98 (dd, *J* = 2.5, 8.5 Hz, 1H), 3.91 (dd, *J* = 7, 8.5 Hz, 1H), 3.72 (d, *J* = 8.5 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 110.9, 101.3, 81.1, 73.2, 68.4, 26.1, 25.7; HRMS *m/z* calcd for $C_7H_{11}Cl_3O_3$, 246.9696; found 246.9701.

(*S*)–*N*–Benzyl–2–(2,2–dimethyl–1,3–dioxolan–4–yl)acetamide (25a).

Diphenyldiselenide (1.30 mmol, 406 mg) was added to a dry round–bottom flask equipped with stir bar under a blanket of argon. Deoxygenated absolute ethanol (purged for 30 minutes with argon) (4 mL) was then added, followed by the rapid addition of $NaBH_4$ (2.80 mmol, 106 mg). Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then a mixture of diastereomers **24a** and **24b** (1 mmol) was added, followed by the additions of freshly powdered NaOH (2.50 mmol, 100 mg) and benzylamine (1.10 mmol, 118 mg) under argon. The mixture was heated in a 55°C oil bath and allowed to react at this temperature for 36 hours while monitoring by TLC for consumption of starting material and 2-phenylselanylamide **17**. After completion of the reaction, ethanol was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL satd NH_4Cl and extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate, and then concentrated by rotary evaporation. The crude material was purified by flash chromatography through a plug of pyridine-saturated silica gel, using hexane to remove diphenyldiselenide then 2:8 hexanes/EtOAc as the eluent. The indicated compound was obtained as an off–white solid in 80% yield (199.3 mg); m.p. 38–39 °C; $[\alpha]_D^{24} = -9.6^o$ cm^3 g^{-1} dm^{-1} (*c* = 3.3 in CH_2Cl_2); IR (solid): ν 3276, 3084, 3032, 2984, 2871, 1637, 1567, 1369, 1217, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35 – 7.30 (m, 2H), 7.29 – 7.25 (m, 3H), 6.43 (brs, 1H), 4.45 (d, 2H, *J* = 5.7 Hz), 4.44 – 4.40 (m, 1H), 4.12 (dd, 1H, *J* = 8.1, 6.1 Hz), 3.63 (dd, 1H, *J* = 8.1, 7.0 Hz), 2.57 – 2.46 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 138.2, 128.6, 127.6, 127.4, 109.3, 72.5, 69.1, 43.4, 40.5, 26.8, 25.5; EIMS (*m/z*): 249.1, 234.1, 191.1, 174.1, 149.1, 119.1, 106.1, 91; HRMS *m/z* calcd for $C_{14}H_{19}NO_3$, 249.1365; found 249.1372.

(*S*)–2–(2,2–Dimethyl–1,3–dioxolan–4–yl)acetamide (**25b**)

Diphenyldiselenide (1.30 mmol, 406 mg) was added to a 50 mL dry pressure tube temporarily fit with a rubber septum and equipped with a magnetic stir bar. Ammonia saturated absolute ethanol (4 mL) was added followed by the rapid addition of $NaBH_4$ (2.80 mmol, 106 mg) under argon. Shortly after the addition, the initial yellow solution turned colorless, indicating complete reduction of diphenyldiselenide. The solution stirred at room temperature for 30 minutes, then a mixture of diastereomers **24a** and **24b** (1 mmol) was added, followed by the addition of freshly powdered NaOH (2.50 mmol, 100.0 mg) under argon. The rubber septum was quickly replaced with a Teflon screw cap and the solution was heated in a 55 °C oil bath for 36 hours. After completion of the reaction as indicated by TLC, the ethanolic ammonia was removed by rotary evaporation and the amorphous solids were dissolved in 5 mL ethyl acetate and 5 mL saturated aqueous NH_4Cl. The resulting solution was cooled to 0 °C and adjusted to pH 4 with 1 N HCl and then saturated with solid NaCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous sodium sulfate, and then concentrated by rotary evaporation. The crude material was purified by flash chromatography through a small plug of pyridine-saturated silica gel, using hexane to remove diphenyldiselenide then 95:5 EtOAc/MeOH as the eluent. The indicated compound was obtained as a white solid in 75% yield (119.4 mg); m.p. 105–106 °C, (lit[16] m.p. 106–108 °C); $[\alpha]_D^{24} = -15.0^o$ cm^3 g^{-1} dm^{-1} (*c* = 0.4 in CH_2Cl_2), (lit[5] $[\alpha]_D^{24} = -15.4^o$ cm^3 g^{-1} dm^{-1} (*c* = 1.0 in $CHCl_3$); IR (solid): ν 3364, 3192, 2993, 1640, 1252, 1156, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 6.14 (brs, 1H), 5.83 (brs, 1H), 4.46 – 4.38 (m, 1H), 4.14 (dd, 1H, *J* = 8.3, 6.1 Hz), 3.63 (dd, 1H, *J* = 8.3, 6.8 Hz), 2.55 (dd, 1H, *J* = 15.3, 7.7 Hz), 2.46 (dd, 1H, *J* = 15.3, 4.8 Hz), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 172.5, 109.4, 72.3, 69.1, 40.1, 26.9, 25.5; HRMS *m/z* calcd for $C_6H_{10}NO_3$, 144.0661; found 144.0664 which corresponds to $[M–CH_3]^+$.

General Procedure for the Diol Deprotection of Dioxolanes 25a and 25b to Form the Corresponding 3,4–Dihydroxyamides (25aa and 25bb)

The isopropylidine was cleaved following the procedure reported by Lavallee , *et al.*[44] Yields and reaction times are unoptimized. A solution of homologated amide **25a** or **25b** (1 mmol) in 1.1 mL of 80% AcOH in H_2O was heated to 40ºC (bath temperature) under argon. When the starting material was consumed, as indicated by TLC (~1 h), saturated aqueous $NaHCO_3$ was *slowly* added to quench the reaction. All solvents were evaporated under reduced pressure at 45 ºC, and the resulting solid was rinsed with acetone and filtered. The filtrate was concentrated to obtain the corresponding diols. No further purification was necessary. The characterization data for compounds **25aa**, **25bb** are given below.

(*S*)-*N*-benzyl-3,4-dihydroxybutanamide (25aa)

The indicated compound was obtained as a white solid in 98% yield (204.9 mg). m.p. 114–115 °C; $[a]_D^{20} = –12.5^o$ cm^3 g^{-1} dm^{-1} (*c* = 1.7 in acetone); IR (solid): ν 3299, 3084, 2920, 1634, 1095, 734 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 500 MHz): δ 7.66 (brs, 1H), 7.33 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 4.41 (d, 2H, *J* = 5.9 Hz), 4.31 (brs, 1H), 4.03 – 3.96 (m, 1H), 3.74 (brs, 1H), 3.48 (d, 2H, *J* = 5.5 Hz), 2.48 (dd, 1H, *J* = 14.8, 4.1 Hz), 2.36 (dd, 1H, *J* = 14.8, 8.2 Hz); ^{13}C NMR ($(CD_3)_2CO$, 125 MHz): δ 172.5, 140.5, 129.2, 128.3, 127.7, 70.3, 66.8, 43.4, 40.4; HRMS *m/z* calcd for $C_{11}H_{15}NO_3$, 209.1052; found 209.1061.

No racemization was indicated in the NMR spectra of the corresponding Mosher diester

[44] Lavallee, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679–682.

derivative;[30]

(*S*)-3,4-dihydroxybutanamide (25bb)

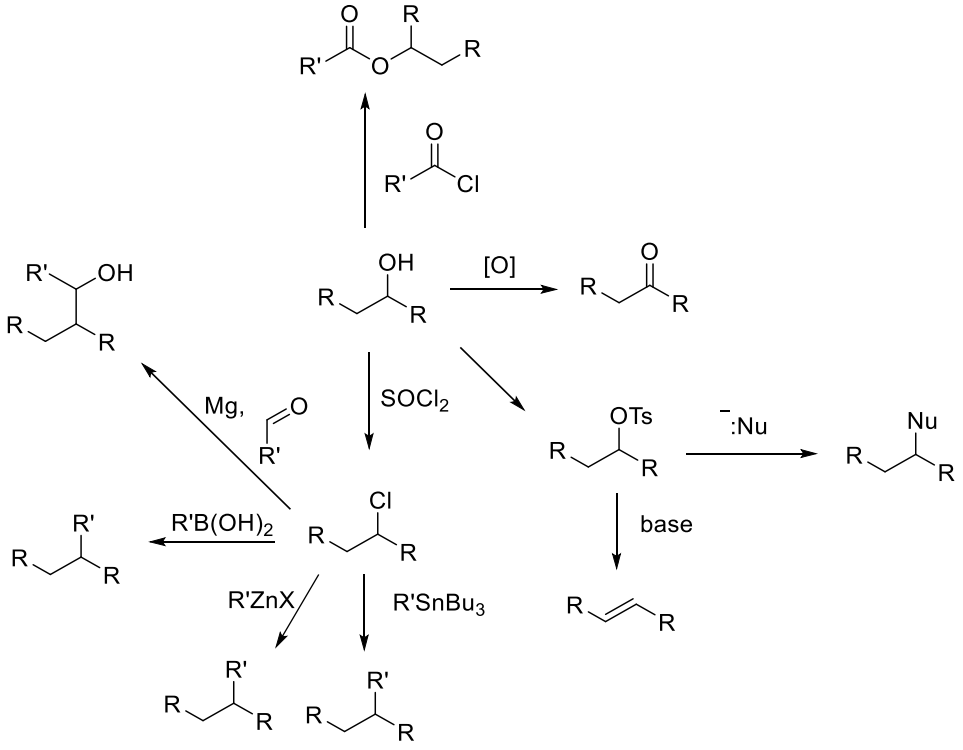
The indicated compound was obtained as a colorless oil in 42% yield (42.5 mg). $[a]_D^{21} = -6.8^o$ $cm^3\ g^{-1}\ dm^{-1}$ (*c* = 1.07 in acetone); IR (film): ν 3369, 2925, 1666, 1409, 867 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 500 MHz): δ 6.92 (brs, 1H), 6.31 (brs, 1H), 4.31 (d, 1H, *J* = 3.0 Hz), 3.98 – 3.90 (m, 1H), 3.71 – 3.64 (m, 1H), 3.46 (t, 1H, *J* = 4.8 Hz), 2.41 (dd, 1H, *J* = 15.1, 4.1 Hz), 2.29 (dd, 1H, *J* = 15.1, 8.3 Hz); ^{13}C NMR ($(CD_3)_2CO$, 125 MHz): δ 173.9, 69.2, 65.8, 38.7; HRMS *m/z* calcd for $C_4H_7NO_2$, 101.0477; found 101.0477 which corresponds to $[M–H_2O]$.

No racemization was indicated in the NMR spectra of the corresponding Mosher diester derivative;[30]

CHAPTER 3. PREPARATION OF ONE-CARBON HOMOLOGATED ALCOHOLS FROM TRICHLOROMETHYL CARBINOLS

3.1. Introduction

The homologation of alcohols is attractive, because it is one way to elongate the carbon chain to get access to higher carbon compounds. This enables generation of the desired intermediates with the correct number of carbons for further conversion to other useful organic



Scheme 3.1. Some examples of possible reactions with alcohols

structures or to furnish desired alcohol targets. Alcohols are useful synthetic handles that can be transformed into a wide variety of compounds. For instance, alcohols can be oxidized into aldehydes, ketones and carboxylic acids, can be reduced to alkenes and alkanes, can be halogenated into the corresponding halides, and can act as a nucleophile in nucleophilic substitution reactions (Scheme 3.1). Because of the versatility in reactivity of alcohols, a simple one-carbon homologation should prove itself to be valuable in organic synthesis.

3.2. Current Methods for the Preparation of One-Carbon Homologated Alcohols from Aldehydes or Alcohols

Few general methods exist to prepare one-carbon homologated alcohols directly from the corresponding aldehydes or alcohols. Aldehydes have been converted by the methylenation-hydroboration-oxidation method reported by Lebel and Ladjel is limited to only aliphatic

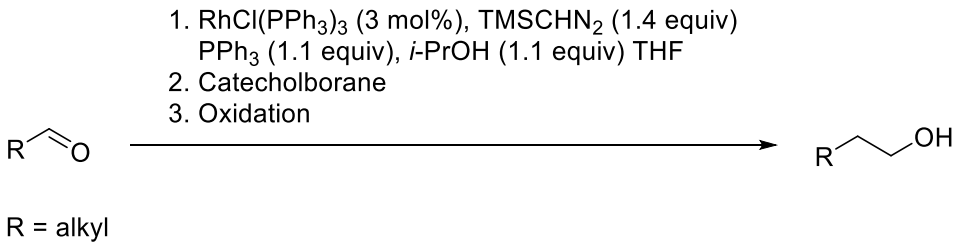
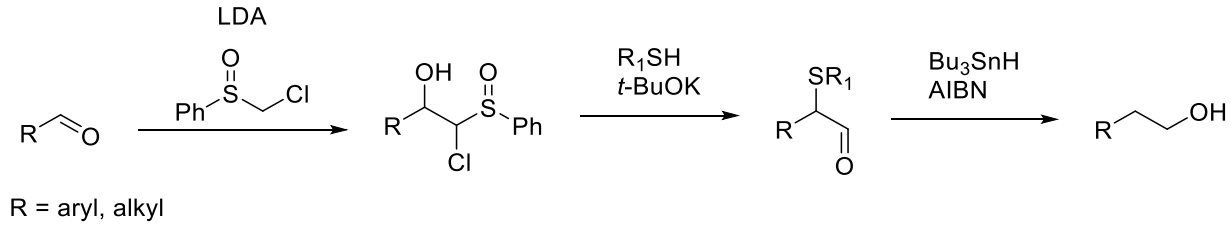


Figure 3.1. The methylenation-hydroboration cascade developed by Lebel and Ladiel[45]



Scheme 3.2 Satoh and Kubota's homologation method[46]

substrates whereas the aromatic substrates afforded low yields of a combination of the primary and secondary alcohols (Figure 3.1) .[45] Furthermore, the homologation method via the generation and desulfurization of an α-thioaldehyde intermediate reported by Satoh and Kubota was not compatible with alkenyl substrates (Scheme 3.2).[46] We envisioned that by applying our trichloromethyl carbinol chemistry, we could access a series of one-carbon homologated alcohols by the reduction of the acyl chloride intermediate. Combining this with the previously reported one-pot synthesis of trichloromethyl carbinols from primary alcohols, this will be the first two-step method reported for the one-carbon homologation of a primary alcohol to the corresponding homologated primary alcohol.

3.3. Preparation of One-Carbon Homologated Alcohols from Trichloromethyl Carbinols

3.3.1. Determination of Reaction Conditions for the Homologation

We explored the possibility of this transformation based on the amide homologation methodology we previously developed. Using a reducing agent compatible with the necessary protic conditions, we envisioned that it would reduce both the *gem*-dichloroepoxide and the intermediate acyl chloride to afford the desired primary alcohol. We chose 2-propanol as the solvent because lithium borohydride was not compatible at 40 ^{o}C or reflux temperature in methanol, and at reflux temperature in ethanol. There were complications stemming from excessive H_2 evolution from lithium borohydride when the reaction was carried out in those solvents at elevated temperature. We also attempted using *tert*-butyl alcohol and 2,2,2-trifluoroethanol. However, we observed the detrichloromethylation-reduction product when the

[45] Lebel, H.; Ladjel, C. *J. Organomet. Chem*. **2005**, *690*, 5198-5205.
[46] Satoh, T.; Kubota, K. *Tetrahedron Lett*. **2000**, *41*, 2121-2124.

reaction was carried out in *tert*-butyl alcohol. In addition, no reaction was observed when 2,2,2-trifluoromethanol was used as the solvent, presumably because of the acidity of the trifluoromethanol (pK_a = 12.5).[47] Therefore, the reaction solvent was limited to 2-propanol, since protic solvents are required for the generation of the intermediate *gem*-dichloroepoxide. The choice of the reducing agent was set to be lithium borohydride because sodium borohydride was not able to reduce the acyl chloride intermediate. Failing to reduce the acyl chloride intermediate results in the formation of the carboxylic acid instead of the desired alcohol because of the nucleophilic acyl substitution between hydroxide and the acid chloride intermediate.[11] With the reagents decided, we moved to optimizing the reaction conditions. We started with the reaction at 40 ^{o}C, with 3 equivalents of NaOH and 3 equivalents of lithium borohydride and with phenyl trichloromethyl carbinol as the starting material. The yield was acceptable. Unfortunately, a mixture of primary and secondary homologated alcohols was formed. We then tested the reaction at reflux in 2-propanol to find the reaction rate was vastly increased. The starting material was completely consumed after 45 minutes to 2 h instead of the 16-22 h when the reaction was carried out at 40 ^{o}C. However, the yield was slightly lower when the reaction was carried out at reflux. Furthermore, some substrates were not compatible with the elevated temperature where they formed a complicated mixture of byproducts.

3.3.2. Generation of the Secondary Alcohol as a Byproduct

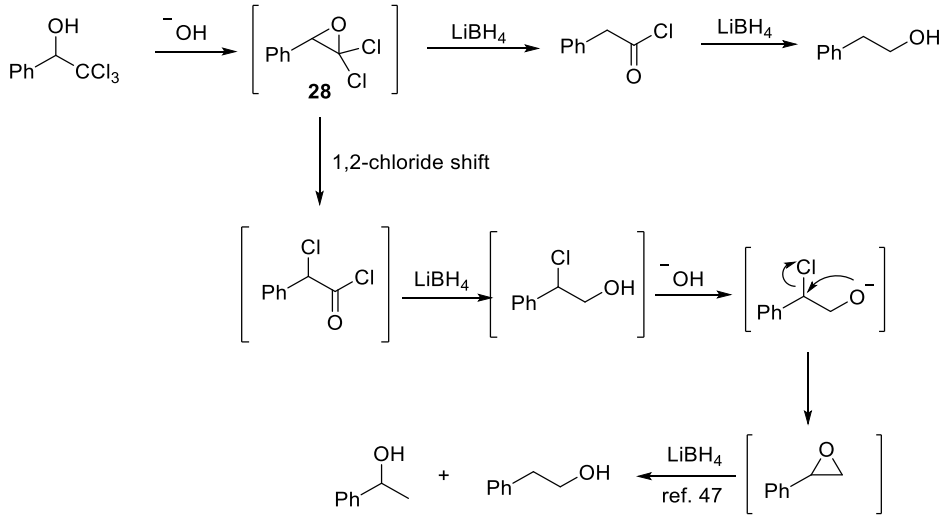
Most of the substrates tested behaved predictably, forming the desired one-carbon homologated alcohol in high yields. However, with electron-rich aryl substrates, namely the phenyl, 4-methoxyphenyl, and the naphthyl substrates, we observed the formation of the

[47] Roberts, C. W.; Macbee, E. T.; Hataway, C. E. *J. Org. Chem.* **1956**, *21*, 1369-1370.

homologated secondary alcohol along with the desired primary alcohol. We reasoned that this byproduct originated from a 1,2-chloride shift of the *gem*-dichloroepoxide **28** (Scheme 3.3).

3.3.2.1. 1,2-Chloride Shift

The 1,2-chloride shift was first reported by Reeve , *et al.* in 1979.[3] This resulted in the formation of the epoxide, and upon reduction with lithium borohydride, a mixture of the primary and the secondary alcohols are formed as the products. Surprisingly, the position of the methoxy substituent on the ring didn't seem to have an effect. The homologation of either the 3- or the 4-methoxyphenyl trichlorocarbinols with 4 equivalents of $LiBH_4$, 3 equivalents of NaOH

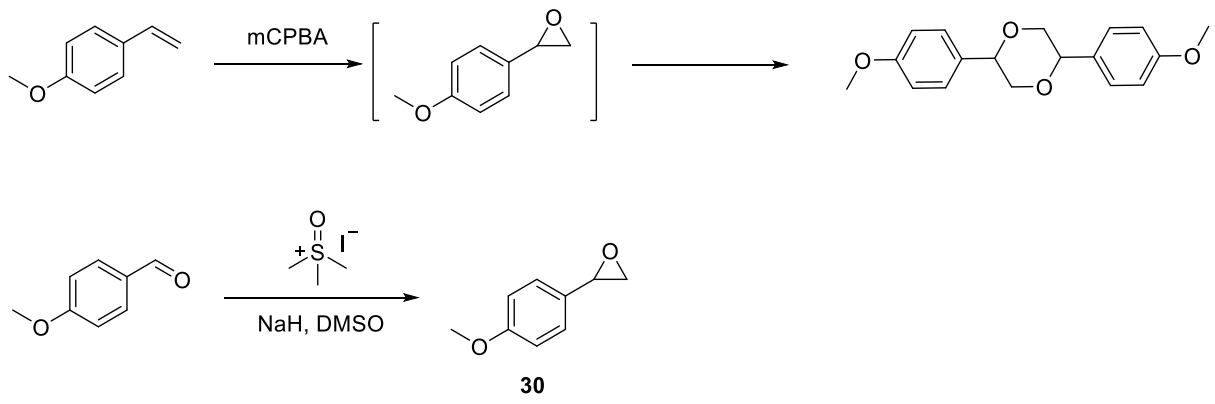


Scheme 3.3. The competing pathways for the generation of both primary and secondary alcohols

at 40 ^{o}C in 2-propanol afforded similar product distributions of the corresponding primary and secondary alcohols. We proposed a competing reaction mechanism pathway for the formation of the two products (Scheme 3.3).

3.3.2.2. Experimental Investigation of the Generation of the Secondary Alcohol Byproduct

To investigate the possible mechanism for the formation of the secondary alcohol product, we carried out a GC-MS investigation of reaction intermediates at various time points. A reaction was set up using 2,2,2-trichloro-1-(4-methoxyphenyl)ethan-1-ol as the starting material, 4 equivalents of $LiBH_4$, 3 equivalents of NaOH, in 2-propanol at reflux temperature. Aliquots (1 mL) were taken every 5 minutes. Each aliquot was carefully quenched with saturated NH_4Cl (1 mL) and the organic phase was dried with a small amount of anhydrous magnesium sulfate. The dried organic phase was then carefully filtered through a Pasteur pipette with a small piece of cotton, using EtOAc to aid the filtration (~1 mL). Each of these aliquots was analyzed by GC-MS (inlet temp, 200 ^oC; split, split ratio 30; oven temperature program: 40 ^oC, 20 ^oC/min to 200 ^oC, hold for 32 min; column: Rtx-wax, 30 m x 250 µm x 0.5 µm, 0.4 mL/min; EI source temperature 190 ^oC). In time points 15 and 20 minutes, an ion with a mass of 150 was detected. We hypothesized that this would be the 4-methoxystyrene oxide. We then prepared 4-methoxystyrene oxide and reduced the oxirane with lithium borohydride. There are reports that lithium borohydride reduction of styrene oxides affords a mixture of primary and



Scheme 3.4 Methods attempted to synthesize *p*-methoxystyrene oxide[48]

secondary alcohols.[48] We first attempted the preparation with 4-methoxystyrene and mCPBA. Unfortunately, the desired oxirane was not formed; instead, we obtained the 1,4-dioxane as reported by Masesane, *et al.*[49] Instead of the direct oxidation, we prepared 4-methoxystyrene oxide from 4-methoxybenzaldehyde via a Corey-Chaykovsky reaction (Scheme 3.4),[50] and this oxirane **30** was then reduced with lithium borohydride in 2-propanol at 40 ^{o}C. These conditions replicated the reaction conditions in the homologation procedure. We found that this reduction afforded the primary and secondary alcohols in a 0.9:1 ratio with quantitative yield when 1 equivalent of lithium borohydride was used. When the reaction was carried out with 4 equivalents of lithium borohydride in 2-propanol at 40 ^{o}C, a mixture of primary and secondary alcohol with a ratio of 1.4:1 was obtained. However, an increased amount of impurities was also observed in the ^{1}H NMR of the crude reaction mixture. HRMS studies were then conducted on both the pure 4-methoxystyrene oxide and the species detected from the aliquots. The fragmentation patterns of each species are in agreement with each other (Figure 3.2). With this information in hand, we surmised that there are indeed two pathways in this transformation. One pathway involves the reduction of the acyl chloride to afford the desired primary alcohol whereas the second pathway goes through the aryl oxirane intermediate and gives rise to the secondary alcohol along with the desired primary alcohol (page 69).

We then moved our attention to tuning the reaction conditions to improve the ratio of the primary and the secondary alcohols. We tried different ratios of sodium hydroxide and lithium borohydride, as well as carrying out the reaction at different concentrations. Unfortunately,

[48] a) Fuchs, R. J. Am. Chem. Soc. 1956, 78, 5612-5613. b) Soai, K.; Ookawa, A. *J. Org. Chem*. **1986**, *51*, 4000-4005.
[49] Mazimba, O,; Majinda, R. R.; Masesane, I. B. *Bull. Chem. Soc. Ethiop.* **2011**, *25*, 299-304.
[50] Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 8504-8505.

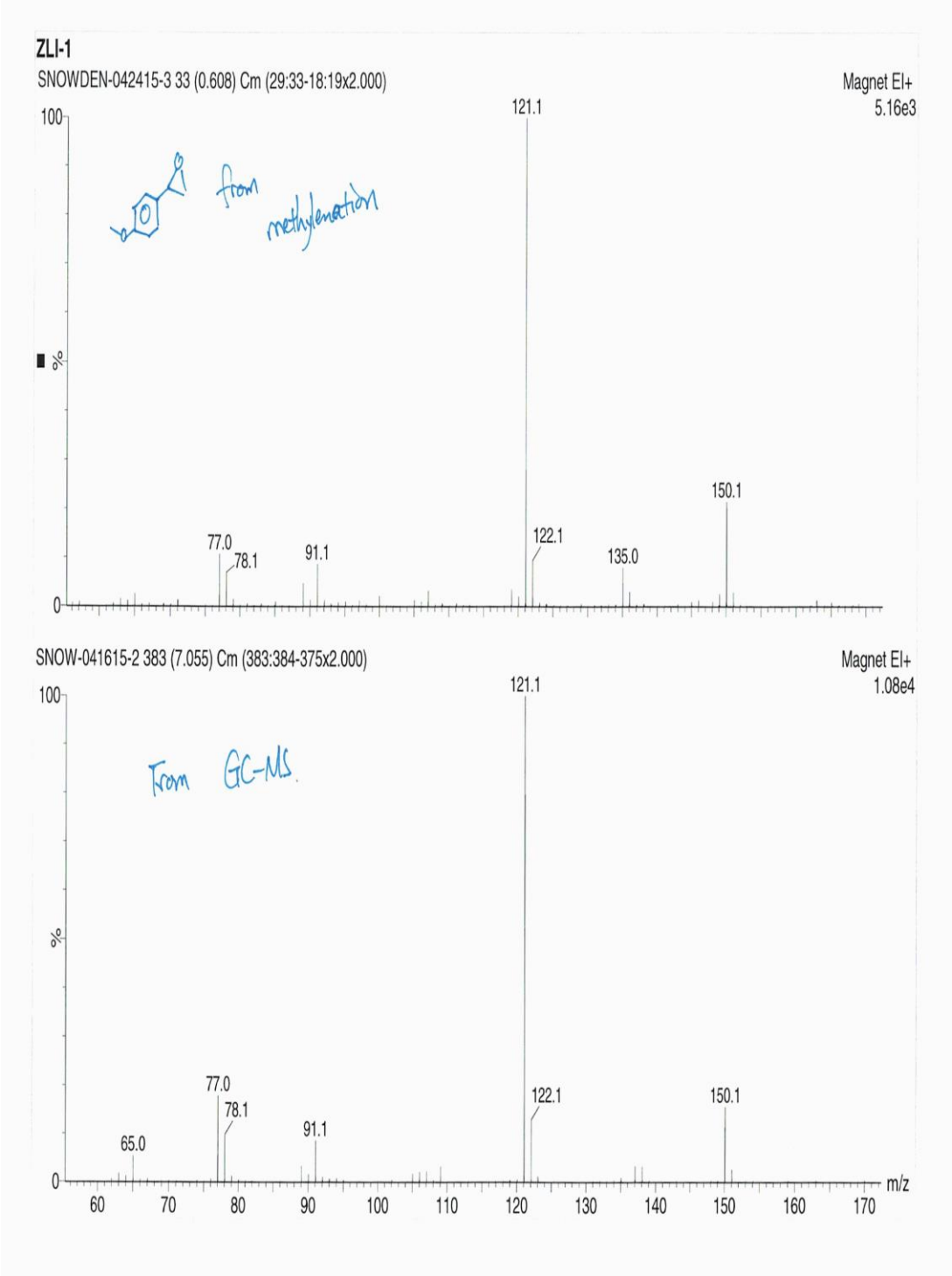
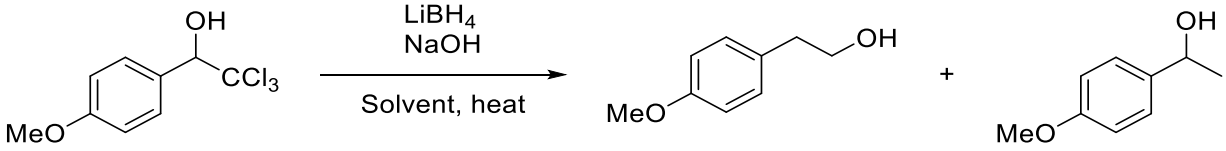


Figure 3.2. High-res mass spectra for the authentic 4-methoxystyrene oxide and the intermediate obtained from the reaction aliquots at t = 15 min, and t = 20 min.

Table 3.1. Optimization studies



LiBH4 (eq)	NaOH (eq)	Solvent[a]	Heat	Time	Yield[b]	Primary	secondary
4	3	IPA	40C	15h	99%	70%	29%
3	3	IPA	40C	36h	99%	66%	33%
3	3	IPA	Reflux	1h	94%	63%	31%
5	3	IPA	Reflux	45min	94%	60%	34%
4	4	IPA	Reflux	30min	93%	47%	47%
4	3	IPA	40C	24h	91%	62%	29%
3	3	IPA	40C	24h	89%	61%	28%
3	3	IPA	40C	16h	88%	55%	33%[c]
3	3.5	IPA	40C	30h	86%	60%	26%
3	3	IPA	40C	<16h	86%	57%	29%[d]
4	3	IPA	Reflux	1.5h	85%	54%	31%
4	1	IPA	Reflux	1h	81%	51%	30%
4	3 (LiOH)	IPA	Reflux	1h	81%	55%	26%
2	3	IPA	40C	22h	75%	50%	25%
3	3	IPA	Reflux	1h	72%	51%	21%
3	2	IPA	Reflux	2h	70%	50%	20%
3	2 (Cs2CO3)	IPA	Reflux	2h	62%	46%	16%
3	3	IPA	Reflux	45min	54%	41%	13%
4	2	IPA (with 2eq LiOTf)	Reflux	5h	54%	40%	14%
3	2	IPA	40C	65h	48%	32%	16%[e]
4	3 (LiOH), 1 LiOTf	EtOH	40C	24h	33%	25%	7%
3	4	IPA	40C	13h	26%	22%	4%[f]
4	3(Cs2CO3)	IPA	Reflux	1h	99%	68%	31%

[a] The reaction was run at 0.25 M concentraton unless otherwise noted. [b]isolated yield. [c]0.125 M concentration. [d]0.5 M concentration. [e]Did not go to completion. [f]32% detrichloromethylation-reduction product was isolated.

there was little effect on the ratio of the primary to secondary alcohols formed (Table 3.1).

3.3.3. Results

The trichloromethyl carbinols used in these reactions were reported previously.[11,12,13,51] However, an unexpected product was obtained (Figure 3.3) when 2-benzylprop-2-en-1-ol **31** was subjected to the one-pot oxidation-trichloromethylation conditions reported previously.[51] Attempts were made to understand the formation of **32**. We did not observe any formation of **32** when the reaction was carried out in two separate steps (oxidation, isolation of the aldehyde, then trichloromethylation of the aldehyde). Treatment of **33n** with 0.5 equivalent of DMP afforded the corresponding trichloromethyl ketone. Ultimately, the results of our investigation was inconclusive. Fortunately, the ester **32** was able to undergo transesterification and conversion to the desired

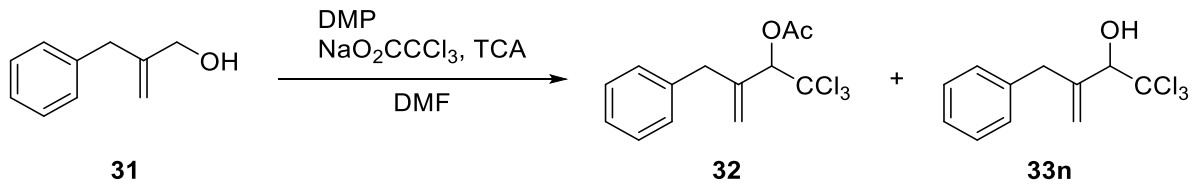
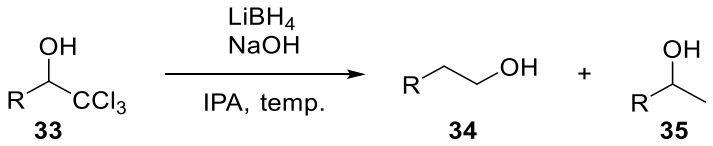


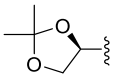
Figure 3.3. Unexpected byproduct for 2-benzylprop-2-en-1-ol from the one-pot conversion to trichloromethyl carbinol

trichloromethyl carbinol **33n** when stirred with 20 mol% PTSA in MeOH at 40 ^{o}C for three days (unoptimized). No side reaction was observed in the transesterification. We subjected 16 trichloromethyl carbinols to our method and examined the outcome of the homologation. The homologation yields were satisfactory to excellent, ranging from 75-95%. With three of the substrates (cinnamyl, phenyl, and 4-methoxyphenyl substituted trichloromethyl carbinols), a mixture of primary and secondary alcohols was obtained (Table 3.2). This is attributed to the styrene oxide generated from 1,2-chloride shift. Optimization studies were conducted; however,

[51] Gupta, M. K.; Li, Z.; Snowden, T. S. *J. Org. Chem.* **2012**, *77*, 4854-4860.

Table 3.2 Homologation results



cmpd.	R	Reaction time at reflux	Yield at reflux	Reaction time at 40 °C	Yield at 40 °C
33a	4-NO_2Ph	30min	84%	19h	90%
33b	$CH_3(CH_2)_{10}$	2h	90%	20h	95%
33c	$PhCH_2CH_2$	45min	72%	18h	85%
33d	(*E*)-PhCH=CH	2h	64%[a]	20h	68%[b]
33e	4-CF_3Ph	2.5h	78%	18h	89%
33f	Ph	1h	76%[c]	20h	83%[d]
33g	4-CH_3OPh	30min	55%[e]	22h	70%[f]
33h	cy	1h	73%	18h	86%
33i		1.5h	0%[g]	21h	75%
33j	2-furyl	3h	86%	26h	89%
33k	Thiophene-2-yl	2h	88%	20h	89%
33l	$(CH_3)_2C=CH$	3h	80%	32h	80%
33m	3-pyridyl	2h	85%	20h	85%
33n	$PhCH_2C=CH_2$	3h	0%[g]	22h	84%
33o	$CH_2=CH(CH_2)_8$	NA	NA	22h	82%
33p	4-*N*$(CH_3)_2$Ph	1h	59%[h]	16h	96%

[a] the secondary alcohol was obtained in 18% yield [b] the secondary alcohol was obtained in 17% yield. [c] the secondary alcohol was obtained in 19% yield. [d] the secondary alcohol was obtained in 16% yield. [e] the secondary alcohol was obtained in 26% yield. [f] the secondary alcohol was obtained in 29% yield. [g] a complicated mixture was formed, no desired product was isolated. [h] the detrichloromethylation-reduction product formed in 41% yield.

tuning the reaction conditions failed to promote the exclusive formation of the primary alcohol.

3.4. Conclusion

We developed a novel method to prepare one-carbon homologated alcohol from primary alcohols or aldehydes in two steps. This method exhibits broad substrate scope, great

conversion, and broad functional group tolerance. The simplicity of the operations and availability of the reagents also make this method attractive for organic synthesis.

3.5. Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments at 360 or 500 MHz, 125.4 MHz, and 338 MHz, respectively. Mass spectra were recorded on an AutoSpec-Ultima_NT mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a Mel-Temp 1001D capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL® IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. Dess−Martin periodinane was prepared by the method of Boeckman, *et al.*[31] The Celite® was purchased from Fisher Scientific. The silica gel (SiliaFlash® F60) was purchased from Silicycle (230-400 mesh). The anhydrous chloroform was purchased from EMD Millipore and was used directly without further purification. Isopropanol (anhydrous, 99.5%) was obtained from Sigma-Aldrich. Lithium borohydride (95%) was obtained from Strem Chemicals, Inc. All reagents were used directly as obtained from commercial sources unless otherwise noted.

The trichloromethyl carbinols **33a-o** were prepared based on previously reported procedures except for **33p** which gave poor conversion with both the Corey-Link procedure[5] or the Aggarwal procedure.[24]

General Procedure for the Preparation of 33p from 4-(Dimethylamino)benzaldehyde

This procedure was based on a modification of the method reported by Wyvratt, Hazen, and Weinstock.[23] The following serves as a general procedure: to a solution of 4-

(dimethylamino)benzaldehyde (149 mg, 1.00 mmol) in $CHCl_3$ (0.25 mL, 2.25 mmol) and DMF (0.6 mL) cooled to -10 ^oC under an atmosphere of argon was added dropwise a solution of KOH (39 mg, 0.70 mmol) in MeOH (0.15 mL). The reaction was stirred at -10 ^oC under an atmosphere of argon for 16 h before being poured into a solution of 1 N HCl (2 mL) and toluene (2 mL) at -10 ^oC. This mixture was stirred at -5 ^oC for 30 mins and slowly warmed to room temperature. The resulting mixture was diluted with additional toluene (10 mL) and the organic phase was separated. The organic layer was washed with H_2O (2 x 5 mL), followed by sat. $NaHCO_3$ (5 mL). The organic phase was dried with anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel using 8:2 hexane/EtOAc as the eluent to obtain the desired trichlorocarbinol **33p** in 75% yield as a yellow solid. m.p. 159-161 ^oC, IR (solid): 3420, 2890, 1614, 1525, 1358 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, 2H, J = 8.9 Hz), 6.70 (d, 2H, J = 8.9 Hz), 5.13 (s, 1H), 3.18 (brs, 1H), 2.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.1, 129.9, 122.1, 111.2, 104.0, 84.6, 40.3. HRMS *m/z* calcd. for $C_{10}H_{12}Cl_3NO$, 266.9984; found 266.9981.

General Procedure for the Preparation of Trichloromethyl Carbinols from Primary Alcohols

Method A: To a solution of primary alcohol (1.0 mmol) in anhydrous DMF (1.5 mL) was added Dess–Martin periodinane (509 mg, 1.20 mmol) at 0 ^oC under an atmosphere of argon. The reaction mixture was slowly warmed to room temperature and allowed to stir until starting alcohol was consumed, as determined by TLC (~2 h) analysis. Upon cooling the reaction mixture to 0 ^oC, trichloroacetic acid (539 mg, 3.30 mmol) and sodium trichloroacetate (604 mg, 3.30 mmol) were added quickly. The solution was warmed slowly to room temperature and

after 6-8 h, the mixture was monitored by TLC. If corresponding aldehyde remained, one equivalent each of trichloroacetic acid and sodium trichloroacetate was added with stirring. After completion of the reaction, as indicated by TLC (typically 20-26 h), the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL). The precipitated solids were filtered through a bed of diatomaceous earth. The filter cake was washed three times with EtOAc. The filtrate was separated, and the aqueous layer was washed with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of EtOAc/hexanes to afford the corresponding trichloromethyl carbinols **33**.

Method B: To a solution of primary alcohol (1.0 mmol) in anhydrous $CHCl_3$ (1.5 mL) was added Dess–Martin periodinane (509 mg, 1.20 mmol) at 0 ^oC under an atmosphere of argon. The reaction mixture was slowly warmed to room temperature and allowed to stir until starting alcohol was consumed, as determined by TLC analysis (~2 h). The reaction mixture was cooled to 0 ^oC and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) (446 mg, 3.2 mmol) was added in 3 portions over 5 minutes with rapid stirring. The solution was warmed slowly to room temperature and after 6-8 h, the mixture was monitored by TLC. If corresponding aldehyde remained, one equivalent of TBD was added with vigorous stirring. After completion of the reaction, as indicated by TLC (typically 14-20 h), the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The precipitated solids were filtered through a bed of diatomaceous earth. The filter cake was washed three times with CH_2Cl_2. The filtrate was separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, vacuum filtered through a

fritted funnel, and the solvent was evaporated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of EtOAc/hexanes to afford the corresponding trichloromethyl carbinols **33**.

General Procedure for the Preparation of One-Carbon Homologated Primary Alcohols from Trichloromethyl Carbinols at 40 ºC

The trichloromethyl carbinol **33** (0.5 mmol) was added to a 10 mL two-neck dry round bottom flask equipped with a magnetic stir bar and a reflux condenser under a blanket of argon. Anhydrous 2-propanol (IPA) (2 mL) was then added, followed by the addition of $LiBH_4$ (2.0 mmol, 44 mg), and freshly powdered NaOH (1.5 mmol, 60 mg). The reaction mixture was heated to 40 °C (oil bath temperature) and allowed to react at this temperature for 24 hours while monitoring by TLC for the consumption of starting material. It is worth noting that the corresponding isopropylester intermediate will appear by TLC analysis towards the end of the reaction as a high Rf spot. It is critical for this intermediate to disappear prior to quenching the reaction to ensure complete conversion to the desired product. After completion of the reaction as indicated by TLC (typically 16-24 h), the reaction was cooled to rt and quenched with sat. NH_4Cl (5 mL) and the aqueous phase was saturated with NaCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and concentrated under reduced pressure. The crude material was purified by flash chromatography with indicated ratios of EtOAc/hexanes to afford the homologated alcohols.

General Procedure for the Preparation of One-Carbon Homologated Primary Alcohols from Trichloromethyl Carbinols at 85 ºC

The trichloromethyl carbinol **33** (0.5 mmol) was added to a 10 mL two-neck dry round bottom flask equipped with a magnetic stir bar and a reflux condenser under a blanket of argon. Anhydrous 2-propanol (IPA) (2 mL) was then added, followed by the addition of $LiBH_4$ (2.0 mmol, 44 mg), and freshly powdered NaOH (1.5 mmol, 60 mg). The reaction mixture was heated to 85 °C (oil bath temperature) and allowed to react at this temperature for 30 min to 3 hours while monitoring by TLC for the consumption of starting material. It is worth noting that the corresponding isopropylester intermediate will appear by TLC analysis towards the end of the reaction as a high Rf spot. It is critical for this intermediate to disappear prior to quenching the reaction to ensure complete conversion to the desired product. After completion of the reaction as indicated by TLC (typically 30 min–3 h), the reaction was cooled to rt and quenched with sat. NH_4Cl (5 mL) and the aqueous phase was saturated with NaCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and concentrated under reduced pressure. The crude material was purified by flash chromatography with indicated ratios of EtOAc/hexanes to afford the homologated alcohols.

Preparation of *p*-methoxystyrene oxide 30

This procedure was modified from the method reported by Tsuchiya, Kumamoto and Ishikawa.[50] Sodium hydride (6.00 mmol, 240 mg, 60% suspension in oil) was placed in a 25 mL dry round bottom flask equipped with a magnetic stir bar. Anhydrous DMSO (8 mL) was added followed by trimethylsulfonium iodide (6.00 mmol, 1.22g). This mixture was stirred at rt under Ar for 30 min, at which time, the reaction mixture was cooled to 0 ^oC and *p*-anisaldehyde (5 mmol, 0.6 mL) solution in DMSO (1.5 mL) was added. After the addition was complete, the ice bath was removed and the reaction was allowed to stir at rt under Ar for 2 h. The reaction was

then quenched with H_2O (10 mL), and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with H_2O (20 mL x 3) and brine (20 mL), dried with anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and concentrated under reduced pressure. The crude material was purified by Kugelrohr distillation (173 ^oC, 0.1 mm) to afford the *p*-methoxystyrene oxide as a colorless oil in 80% yield (600 mg, 4.0 mmol).

Reduction of *p*-methoxystyrene oxide 30

p-Methoxystyrene oxide **30** (75 mg, 0.5 mmol) was dissolved in 2 mL of dry isopropanol. To this solution was added lithium borohydride (44 mg, 2.0 mmol). This reaction mixture was heated to 40 ^oC (oil bath temperature) and allowed to react under an atmosphere of Ar for 12 hours. The reaction was then quenched with sat. NH_4Cl (5 mL), and the aqueous phase was saturated with NaCl. The product was extracted with ethyl acetate (5 × 10 mL), dried with anhydrous magnesium sulfate, vacuum filtered through a fritted funnel, and concentrated under reduced pressure. The crude material was purified by flash chromatography with 2:8 EtOAc/hexanes to afford a 0.9:1 mixture of **34g** and **35g** in 98% combined yield (75 mg, 0.49 mmol). The ratio of **34g** and **35g** also agrees with the ratio obtain from the ^1H NMR spectrum of the crude material.

2-(4-Nitrophenyl)ethan-1-ol (34a)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 90% yield (75 mg). IR (film): 3388, 1642, 1511, 1348, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, 2H, *J* = 8.6 Hz), 7.41 (d, 2H, *J* = 8.6 Hz), 3.93 (t, 2H, *J* = 6.5 Hz), 2.98 (t, 2H, *J* = 6.5

Hz), 1.46 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.8, 146.7, 129.8, 123.7, 62.9, 38.9; HRMS *m/z* calcd. for $C_8H_9NO_3$, 167.0582; found 167.0585.

Tridecan-1-ol (34b)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 95% yield (95 mg). m.p. 30-32 ºC; IR (solid): 3400, 2919, 1646, 1467 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.61-3.67 (m, 2H), 1.53-1.60 (m, 2H), 1.23-1.37 (m, 20H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 63.1, 32.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.6, 29.4, 29.3, 25.7, 22.7, 14.1; HRMS *m/z* calcd. for $C_{13}H_{27}O$ $[M–H]^-$, 199.2062; found 199.2070.

4-Phenylbutan-1-ol (34c)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 85% yield (64 mg). IR (film): 3398, 2936, 1644, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14-7.32 (m, 5H), 3.66 (dd, 2H, *J* = 6.5, 6.3 Hz), 2.65 (dd, 2H, *J* = 7.2, 7.8 Hz), 1.65-1.76 (m, 2H), 1.56-1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.3, 128.4, 128.3, 125.7, 62.7, 35.6, 32.3, 27.5; HRMS *m/z* calcd. for $C_{10}H_{14}O$, 150.1045; found 150.1040.

(*E*)-4-Phenylbut-3-en-1-ol (34d)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound **30d** was obtained as a colorless oil in 68% yield (50 mg) along with **31d** (12 mg, 17% yield). IR (film): 3403, 2919, 1641, 1493, 1045, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18-7.40 (m, 5H), 6.51 (d, 1H, *J* = 16 Hz), 6.21 (dt, 1H, *J* = 7, 16 Hz), 3.77 (t, 2H, *J* = 6.3 Hz), 2.47-2.53 (m, 2H), 1.45 (brs, 1H); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 137.2, 132.7, 128.5, 127.2, 126.3, 126.0, 62.0, 36.3; HRMS *m/z* calcd. for $C_{10}H_{12}O$, 148.0888; found 148.0887.

(*E*)-4-Phenylbut-3-en-2-ol (35d)

White solid (12 mg, 17% yield), m.p. 39-40 ºC; IR (solid): 3343, 2972, 1494, 1449, 1142, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.36 (m, 2H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 1H), 6.57 (d, 1H, *J* = 16.0 Hz), 6.27 (dd, 1H, *J* = 16.0, 6.4 Hz), 4.53-4.46 (m, 1H), 1.38 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.7, 133.6, 129.4, 128.6, 127.6, 126.5, 68.9, 23.4; HRMS *m/z* calcd. for $C_{10}H_{12}O$, 148.0888; found 148.0887.

2-(4-(Trifluoromethyl)phenyl)ethan-1-ol (34e)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 89% yield (84 mg). IR (film): 3408, 2953, 1639, 1327, 1163, 1122 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.57 (d, 2H, *J* = 8.0 Hz), 7.35, (d, 2H, *J* = 8.0 Hz), 3.89, (t, 2H, *J* = 6.5 Hz), 2.92 (t, 2H, *J* = 6.5 Hz), 1.54 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.9, 129.3, 128.8 (q, *J* = 32.5 Hz), 125.4 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272 Hz), 63.2, 38.9; HRMS *m/z* calcd. for $C_9H_9OF_3$, 190.0605; found 190.0607.

2-Phenylethanol (34f)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound **30f** was obtained as a colorless oil in 83% yield (51 mg) along with **31f** (9.8 mg, 16% yield). IR (film): 3346, 2932, 2875, 1496, 1454, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.43 (m, 5H), 3.80 (t, 2H, *J* = 6.5 Hz),

2.83 (t, 2H, *J* = 6.5 Hz), 1.88 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.5, 128.9, 128.5, 126.3, 63.5, 39.1; HRMS *m/z* calcd. for $C_8H_{10}O$, 122.0732; found 122.0729.

1-Phenylethan-1-ol (35f)

Colorless oil (9.8 mg, 16% yield), IR (film): 3351, 2972, 2925, 1452, 1205, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.40 (m, 4H), 7.27-7.30 (m, 1H), 4.91 (q, 1H, *J* = 6.5 Hz), 1.77 (brs, 1H), 1.51 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.8, 128.5, 127.5, 125.4, 70.4, 25.2; HRMS *m/z* calcd. for $C_8H_{10}O$, 122.0732; found 122.0729.

2-(4-Methoxyphenyl)ethanol (34g)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound **30g** was obtained as a colorless oil in 70% yield (52 mg) along with **31g** (23 mg, 29% yield).

IR (film): 3396, 2934, 1612, 1513, 1247, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, 2H, *J* = 8.3 Hz), 6.84 (d, 2H, *J* = 8.3 Hz), 3.75-3.83 (m, 2H), 3.77 (s, 3H), 2.79 (t, 2H, *J* = 6.6 Hz), 1.75 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.2, 130.4, 129.9, 128.6, 114.0, 63.7, 55.2, 38.2; HRMS *m/z* calcd. for $C_9H_{12}O_2$, 152.0837; found 152.0840.

1-(4-Methoxyphenyl)ethanol (35g)

Colorless oil, (23 mg, 29% yield), IR (film): 3254, 2934, 1622, 1381, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, 2H, *J* = 8.1 Hz), 6.88 (d, 2H, *J* = 8.1 Hz), 4.85 (t, 1H, *J* = 6.3 Hz), 3.80 (s, 3H), 1.87 (brs, 1H), 1.47 (dd, 3H, *J* = 6.3, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 138.0, 126.6, 113.8, 70.0, 55.3, 25.0; HRMS *m/z* calcd. for $C_9H_{12}O_2$, 152.0837; found 152.0831.

2-Cyclohexylethanol (34h)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 86% yield (55 mg). IR (film): 3346, 2922, 2851, 1448, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.67 (dt, 2H, *J* = 6.9, 1.0 Hz), 1.96 (brs, 1H), 1.57-1.77 (m, 5H), 1.44 (q, 2H, *J* = 6.9 Hz), 1.32-1.42 (m, 1H), 1.06-1.28 (m, 3H), 0.84-0.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 60.7, 40.3, 33.3, 29.5, 26.6, 26.5, 26.2, 25.8; HRMS *m/z* calcd. for C_8H_{14} [M–H_2O], 110.1096; found 110.1099.

(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (34i)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 75% yield (55 mg). $[\alpha]^{20}_D$ = +2.45° (*c* = 1.1, $CHCl_3$); IR (film): 3420, 2933, 1646, 1373, 1219, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.23-4.29 (m, 1H), 4.08 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.75-3.84 (m, 2H), 3.59 (dd, 1H, *J* = 8.1, 7.5 Hz), 2.16 (brs, 1H), 1.79-1.84 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.1, 75.1, 69.4, 60.5, 35.6, 26.9, 25.6; HRMS *m/z* calcd. for $C_7H_{13}O_3$ [M–H]$^-$, 145.0865, found 145.0857.

2-(Furan-2-yl)ethan-1-ol (34j)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a light yellow oil in 86% yield (48 mg). IR (film): 3350, 2956, 2925, 1507, 1146, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (dd, 1H, *J* = 1.8, 0.7 Hz), 6.31 (dd, 1H, *J* = 3.1, 1.8 Hz), 6.09-6.12 (m, 1H), 3.87

(t, 2H, *J* = 6.1 Hz), 2.90 (t, 2H, *J* = 6.1Hz), 1.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.8, 141.5, 110.3, 106.5, 61.1, 31.6; HRMS *m/z* calcd. for $C_6H_8O_2$, 112.0524; found 112.0522.

2-(Thiophen-2-yl)ethan-1-ol (34k)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a light yellow oil in 88% yield (56 mg). IR (film): 3348, 2926, 2878, 1439, 1241, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (dd, 1H, *J* = 5.1, 1.2 Hz), 6.96 (dd, 1H, *J* = 5.1, 3.4 Hz), 6.87-6.89 (m, 1H), 3.85 (t, 2H, *J* = 6.3 Hz), 3.08 (dt, 2H, *J* = 6.3, 0.7 Hz), 1.84 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.7, 127.0, 125.5, 123.9, 63.4, 33.3; HRMS *m/z* calcd. for C_6H_8OS, 128.0296; found 128.0294.

4-Methylpent-3-en-1-ol (34l)

The crude material was purified by flash chromatography through silica gel using 8:2 pentane:Et_2O as the eluent. The indicated compound was obtained as a colorless oil in 80% yield (40 mg). IR (film): 3343, 2969, 2927, 2875, 1454, 1376, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.08-5.16 (m, 1H), 3.58-3.67 (m, 2H), 2.28 (q, 2H, *J* = 6.7 Hz), 1.73 (s, 3H), 1.65 (s, 3H), 1.34 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.2, 122.0, 62.5, 31.6, 25.8, 17.9; HRMS *m/z* calcd. For $C_6H_{12}O$, 100.0888; found 100.0890.

2-(Pyridin-3-yl)ethan-1-ol (34m)

The crude material was purified by flash chromatography through silica gel using 80:15:5 hexane/EtOAc/TEA followed by 90:5:5 EtOAc/MeOH/TEA as the eluent. The indicated compound was obtained as a white solid in 85% yield (52 mg). m.p. 130-132 ^{o}C IR (solid): 3376, 2931, 1652, 1427, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.45 (s, 1H), 8.43 (d, 1H, *J*

= 4.2 Hz), 7.57 (d, 1H, *J* = 7.8 Hz), 7.22 (dd, 1H, *J* = 7.8, 4.9 Hz), 3.88 (t, 2H, *J* = 6.5 Hz), 2.86 (t, 2H, *J* = 6.5 Hz), 2.39 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.2, 147.6, 136.6, 134.5, 123.4, 62.9, 36.3; HRMS *m/z* calcd. for C_7H_9NO, 123.0684; found 123.0686.

3-Benzylbut-3-en-1-ol (34n)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 84% yield (68 mg). IR (film): 3337, 2917, 1495, 1453, 1056, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.32 (m, 2H), 7.17-7.24 (m, 3H), 4.93-4.95 (m, 1H), 4.90-4.92 (m, 1H), 3.70 (t, 2H, *J* = 6.5 Hz), 3.38 (s, 2H), 2.27 (dt, 2H, *J* = 6.5, 0.6 Hz), 1.33 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.4, 139.2, 129.0, 128.4, 126.3, 113.8, 60.4, 42.9, 38.6; HRMS *m/z* calcd. for $C_{11}H_{14}O$, 162.1045; found 162.1045.

11-Dodecene-1-ol (34o)

CAUTION: exposure to this compound may trigger eczema flare-ups. The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 82% yield (76 mg). IR (film): 3349, 3077, 2925, 2853, 1641, 1465, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.80 (ddt, 1H, *J* = 17.1, 10.2, 6.7 Hz), 4.98 (dq, 1H, *J* = 17.1, 1.7 Hz), 4.90-4.94 (m, 1H), 3.62 (t, 2H, *J* = 6.6 Hz), 2.16 (brs, 1H), 2.00-2.06 (m, 2H), 1.52-1.59 (m, 2H), 1.22-1.41 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.2, 114.1, 63.0, 33.8, 33.7, 29.6, 29.5, 29.4, 29.4, 29.1, 28.9, 25.7; HRMS *m/z* calcd. for $C_{12}H_{24}O$, 184.1827; found 184.1819.

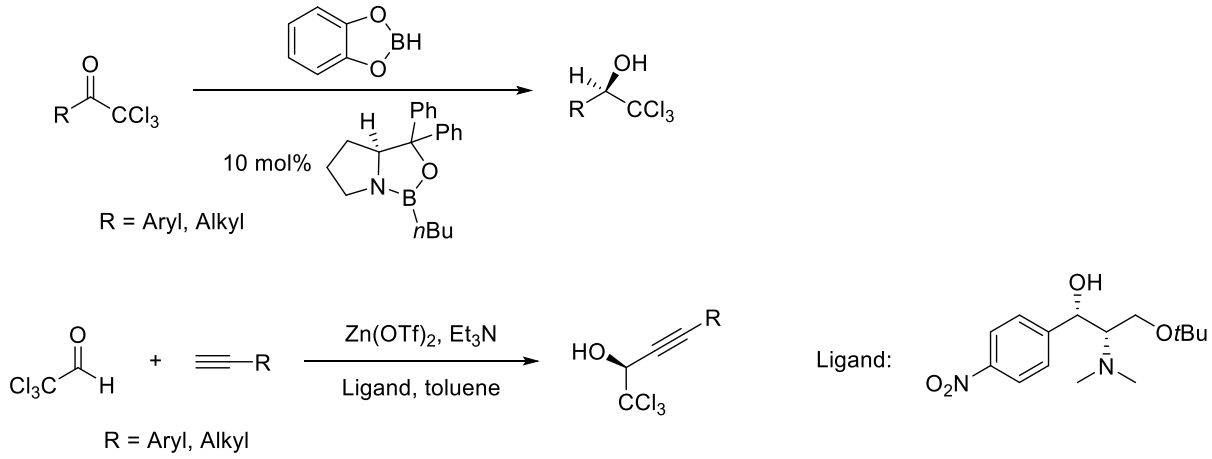
2-(4-(Dimethylamino)phenyl)ethan-1-ol (34p)

The crude material was purified by flash chromatography through silica gel using 80:15:5 hexane/EtOAc/TEA followed by 90:5:5 EtOAc/MeOH/TEA as the eluent. The indicated compound was obtained as a yellow solid in 96% yield (79 mg). m.p. 56-57 ^{o}C IR (solid): 3366, 2928, 1616, 1348, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 (d, 2H, *J* = 8.7 Hz), 6.72 (d, 2H, *J* = 8.7 Hz), 3.81 (t, 2H, *J* = 6.5 Hz), 2.92 (s, 6H), 2.78 (t, 2H, *J* = 6.5 Hz), 2.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.5, 129.7, 126.1, 113.1, 64.0, 40.8, 38.2; HRMS *m/z* calcd. for $C_{10}H_{15}NO$, 165.1154; found 165.1149.

CHAPTER 4. PROGRESS TOWARDS ENANTIOSELECTIVE TRIHALOMETHYLATION OF ALDEHYDES

4.1. Introduction

4.1.1. Procedures for the synthesis of Chiral Trichloromethyl Carbinols



Scheme 4.1 Current procedures to synthesize chiral trichloromethyl carbinols

Even though many methods to prepare trichloromethyl carbinols have been reported since Howard's preparation in 1925,[52] the preparation for chiral trichloromethyl carbinols has not been heavily reported. Corey and Link published the first and the only general method to date for the synthesis of chiral trichloromethyl carbinols via CBS reduction of the corresponding trichloromethyl ketones in 1992.[8] One other published method to synthesize chiral

[52] Howard, J. W. *J. Am. Chem. Soc.* **1925**, *47*, 455-456.

trichloromethyl propargyl alcohol was developed by Jiang and Si in 2004. Through subsequent reduction methods, the corresponding alkenyl and alkyl trichloromethyl carbinols can be prepared.[53] However, the chiral ligand used in the transformation is not commercially available, and the source of the trichloromethyl group originates from choral, which is a controlled substance and not available from domestic vendors. Aside from these methods (Scheme 4.1), no other general method has been published regarding the synthesis of chiral trichloromethyl carbinols.

4.1.2. Applications of Chiral Trichloromethyl Carbinols

Chiral trichloromethyl carbinols are used as building blocks for the synthesis of useful organic compounds such as α-amino acids,[8] α-hydroxy carboxylic acids,[5] chiral mono-substituted

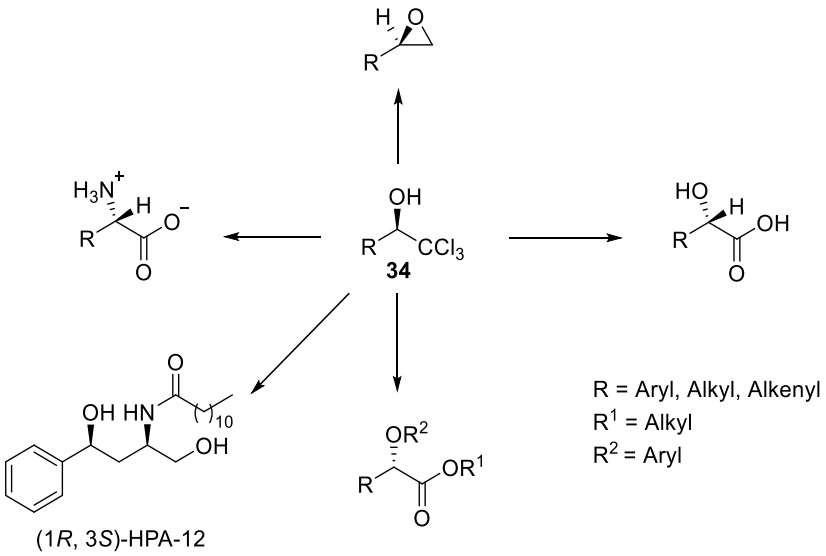


Figure 4.1 Applications of chiral trichloromethyl carbinols **34**

[53] Jiang, B.; Si, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 669-674.

oxiranes,[54] and chiral hydroxyl acid esters (Figure 4.1). Some examples of these applications are important to synthetic organic chemists. For instance, the synthesis of chiral mono-substituted oxiranes through chiral trichloromethyl carbinols circumvents the poor enantioselectivity of current asymmetric epoxidation of terminal alkenes.[55] Snowden, et al. devised a concise synthesis route to synthesize HPA-12, a potent CERT inhibitor, from the Wynberg lactone, which is derived from a chiral trichloromethyl carbinol.[20] Because of these aforementioned applications, a simple, general method to access chiral trichloromethyl carbinols will be attractive to organic chemists.

4.1.3. Procedures for the Synthesis of Chiral Trifluoromethyl Carbinols

The development of the synthesis of chiral trifluoromethyl carbinols has attracted a lot of attention due to the useful properties that fluorine possesses in organic molecules. The trifluoromethyl group increases the lipophilicity of the molecule, therefore it usually gives the molecule increased bioavailability. It is one of only a few, and unquestionably the most common functional groups that is strongly electron withdrawing yet lipophilic. This gives it a valued utility in the design of drugs and materials. This aspect of the trifluoromethyl group makes it attractive to organic chemists, especially agrochemical and medicinal chemists.

Because of the aforementioned attractive properties, trifluoromethylation has been a hotly studied subject since 1992.[56] In 1999, Iseki, *et al.* reported an asymmetric trifluoromethylation protocol using a chiral triaminosulfonium salt; however, the ee's obtained were modest at best, with the highest being 52%.[57] Langlois, *et al.* investigated a series of trifluoromethylation

[54] E. J. Corey, C. J. Helai, *Tetrahedron Lett.* **1993**, *34*, 5227-5230.
[55] Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064.
[56] McClinton, M. A.; McClinton, D. A.; *Tetrahedron* **1992**, *48*, 6555-6666.
[57] Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231-8234.

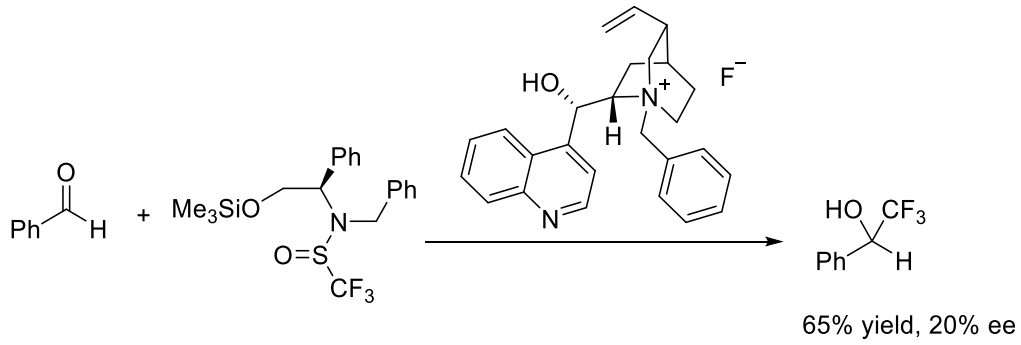
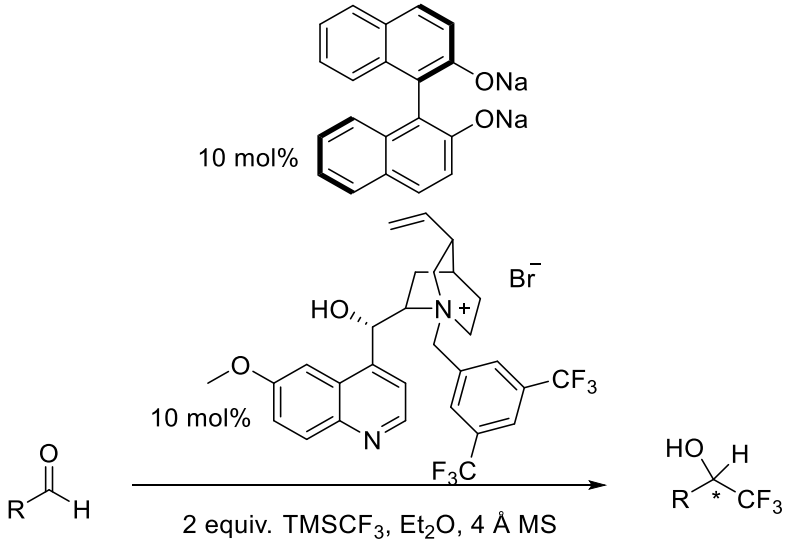


Figure 4.2 Langlois' asymmetric trifluoromethylation procedure

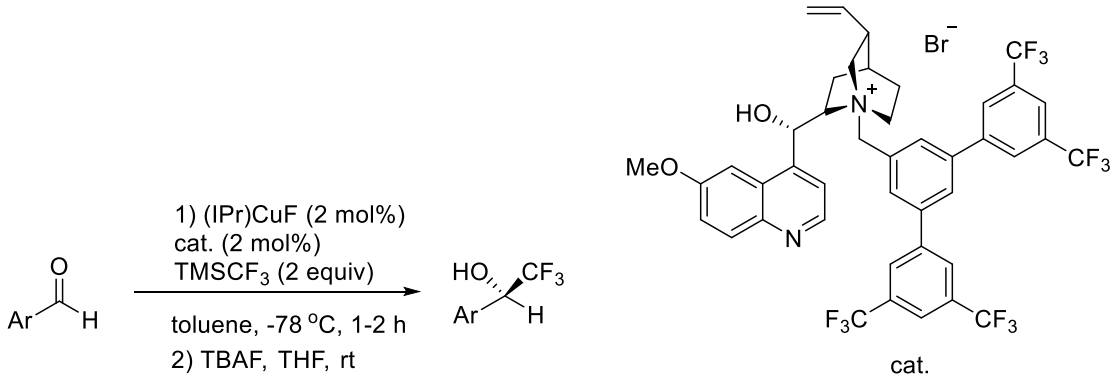
Table 4.1 Asymmetric trifluoromethylation of aromatic aldehydes reported by Feng, et al.



Entry	Aldehyde	Yield (%)	ee (%)
1	2-Naphthaldehyde	85	71
2	Benzaldehyde	72	56
3	4-Methylbenzaldehyde	87	60
4	4-Chlorobenzaldehyde	72	50
5	4-Methoxybenzaldehyde	87	41
6	Piperonal	95	46
7	4-Fluorobenalzdehyde	86	57

reagents used with a cinchonium fluoride catalyst (Figure 4.2); however, the highest ee they were able to obtain was 20% with 65% yield.[58] Fuchikami reported the enantioselective trifluoromethylation using a cinchona alkaloid as the chiral catalyst and Ruppert's reagent[59] as the trifluoromethylation agent. However, the yield and ee were low (49% and 9%,

Table 4.2 Enantioselective trifluoromethylation reported by Wu, *et al.*



Ar	yield (%)	ee (%)	Ar	yield (%)	ee (%)
2-Naphthyl	90	75	4-PhC_6H_4	90	66
1-Naphthyl	88	60	3-$PhOC_6H_4$	87	60
C_6H_5	80	60	4-$MeOC_6H_4$	85	67
2-pyridyl	89	42	3-$MeOC_6H_4$	89	74
4-BrC_6H_4	81	57	2-$MeOC_6H_4$	88	73
3-BrC_6H_4	82	52	6-MeO-2-naphthyl	83	53
4-ClC_6H_4	83	51	3,4-$O(CH_2)C_6H_3$	92	81
3-ClC_6H_4	83	51	3,4-$O(CH_2)_2C_6H_3$	92	79
4-FC_6H_4	79	45	4-$(C_3H_5O)C_6H_4$	80	67
3-FC_6H_4	87	51	4-$C_2H_5SC_6H_4$	85	73
4-MeC_6H_4	88	68			

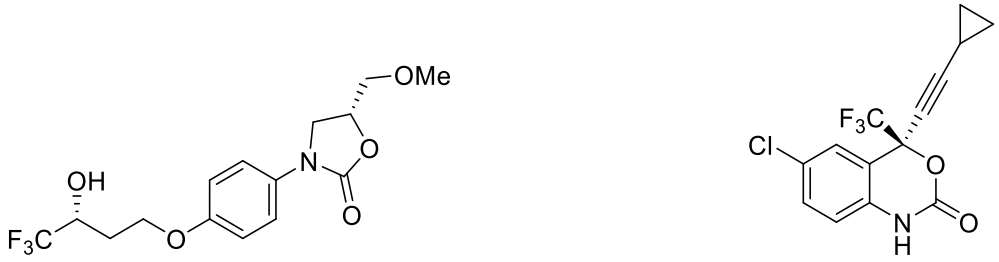
respectively).[60] One of the best catalyst system on the asymmetric trifluoromethylation of aldehydes was reported by Feng, *et al.*in 2007, which had moderate yield and ee (Table 4.1).[61]

[58] Roussel, S.; Billard, T.; Langlois, B. R.; Saint-James, L. *Eur. J. Org. Chem.* **2005**, *11*, 939-944.
[59] a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195-2198. b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757-786.
[60] Hagiwara, T.; Kobayashi, T.; Fuchikami, T. *Nippon Kagaku Kaishi* **1997**, *12*, 869-875.
[61] Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron*, **2007**, *63*, 6822-6826.

Most recently, in 2013, Wu, et al. reported a catalyst system using quaternary ammonium bromide and (IPr)CuF with Ruppert's reagent. Wu reported up to 92% yield and up to 71% ee on aryl substrates (Table 4.2).[62]

4.1.4. Applications of Chiral Trifluoromethyl Carbinols

Trifluoromethyl carbinols have received a lot of attention particularly in the pharmaceutical and the agrochemical industries. As direct examples, the chiral trifluorocarbinol moiety can be



Befloxatone Efavirenz

Figure 4.3 Drugs that have the chiral trifluorocarbinol moiety

found in the anti-depressent Befloxatone[63] and the anti-HIV drug Efavirenz[64] (Figure 4.3). It can also: give access to Mosher's acid **36**[30], a useful reagent to determine the enantiomeric excess of alcohols and amines; be present in glucocorticoid receptor agonists such as ZK 216348;[65] be found in molecules that exhibit anticonvulsant activities (**37**, **38**) that have

[62] Wu, S.; Guo, J.; Sohail, M.; Cao, C.; Chen, F-X. *J. Fluorine Chem.* **2013**, *148*, 19-29.
[63] a) Rabasseda, X.; Sorbera, L. A.; Castaner, J. *Drugs Fut.* **1999**, *24*, 1057-1067; b) Wouters, J.; Moureau, F.; Evrard, G.; Koenig, J.-J.; Jegham, S.; George, P.; Durant, F. *Bioorg. Med. Chem*. **1999**, *7*, 1683-1693.
[64] a) Ren, J.; Milton, J.; Weaver, K. L.; Short, S. A.; Stuart, D. I.; Stammers, D. K. *Structure*, **2000**, *8*, 1089-1094. b) Pedersen, O. S.; Pedersen, E. B. *Synthesis*, **2000**, 479-495.
[65] Schacke, H.; Schottelius, A.; Docke, W. D.; Strhlke, P.; Jaroch, S.; Schmees, N.; Rehwinkel, H.; Hennekes, H.; Asadullah, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 227-232.

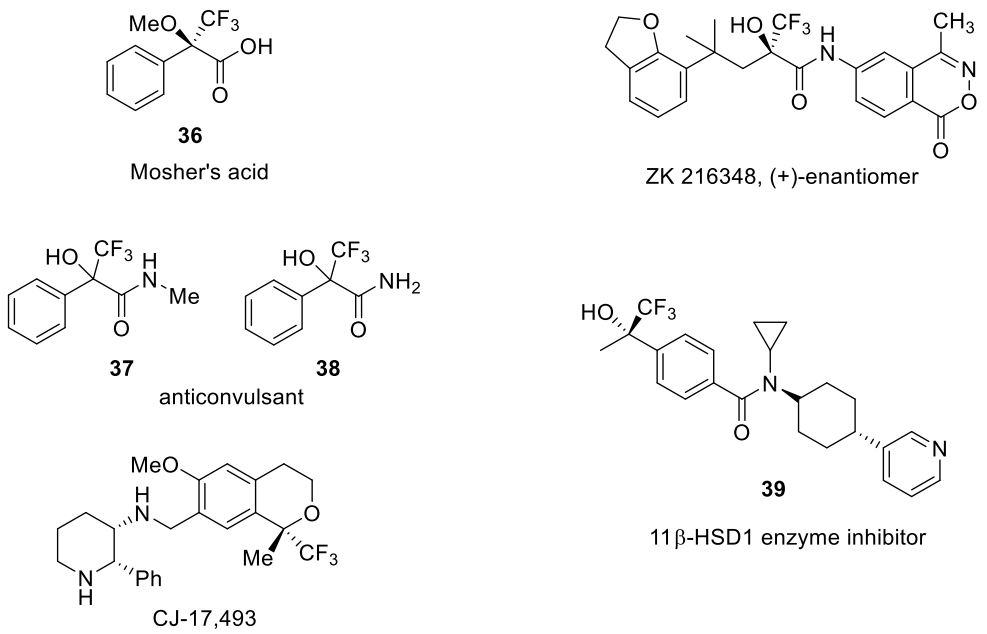


Figure 4.4 Molecules that possess chiral trifluoromethyl carbinols as key fragments

activities comparable to phenytoin;[66] serve as a key moiety of a novel class of 11*β*-HSD1 (11 *β*-hydroxysteroid dehydrogenase type I) enzyme inhibitors (**39**) which have high potential for treating type II diabetes;[67] and last but not least, it is a fragment found in CJ-17,493, an NK-1 receptor antagonist that has shown promise to treat several diseases such as migraine, depression, and asthma (Figure 4.4).[68]

4.2. Preparation of Chiral Trihalomethyl Carbinols

4.2.1. Objective

[66] Schenck, H. A.; Lenkowski, P. W.; Choudhury-Mukherjee, I.; Ko, S.-H.; Stables, J. P.; Patel, M. K.; Brown, M. L. *Bioorg. Med. Chem*. **2004**, *12*, 979-993.
[67] Julian, L. D.; Wang, Z.; Bostick, T.; Caille, S.; Choi, R.; DeGraffenreid, M.; Di, Y.; He, X.; Hungate, R. W.; Jaen, J. C.; Liu, J.; Monshouwer, M.; McMinn, D.; Rew, Y.; Sudom, A.; Sun, D.; Tu, H.; Ursu, S.; Walker, N.; Yan, X.; Ye, Q.; Powers, J. P. *J. Med. Chem.* **2008**, *51*, 3953-3960.
[68] Caron, S.; Do, N. M.; Sieser, J. E.; Arpin, P.; Vazquez, E. *Org. Process Res. Dev.* **2007**, *11*, 1015-1024.

Even though there have been a lot of investigations on asymmetric trifluoromethylations on carbonyls for almost 20 years, researchers have only made significant progress on the asymmetric trifluoromethylation of ketones to furnish the tertiary trifluoromethyl carbinols. The selectivity for asymmetric trifluoromethylation of aldehydes, however, has been poor. Most notably, asymmetric trifluoromethylations with Lewis acids have been particularly poor.[69] We decided to screen a series of ligands and Lewis acids for the enantioselective trifluoromethylation of aldehydes in hope of improving upon the ee for the current best results (71%)[61] as well as broaden the scope of the reaction (*vide supra*).

4.2.2. Screening of Chiral Catalysts

Asymmetric trifluoromethylation has been investigated by a number of research groups, as described previously. We decided to consider these findings as well as published successful procedures to generate asymmetric cyanohydrins using TMSCN, in hope that the cyanide addition would be analogous to the trihalomethide addition. This seems plausible, in part, because the most attractive sources of trihalomethides were determined to be (trichloromethyl)trimethylsilane and commercially available Ruppert's reagent.[59] These are reagents that could potentially mimic TMSCN successfully employed in the enantioselective cyanation of aldehydes.

[69] Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633-2644.

Belokon and North have done extensive work on the asymmetric cyanation of aldehydes with TMSCN with salen type catalysts **40**.[70] Saa[71], Katsuki[72] and Nakai[73] reported successful

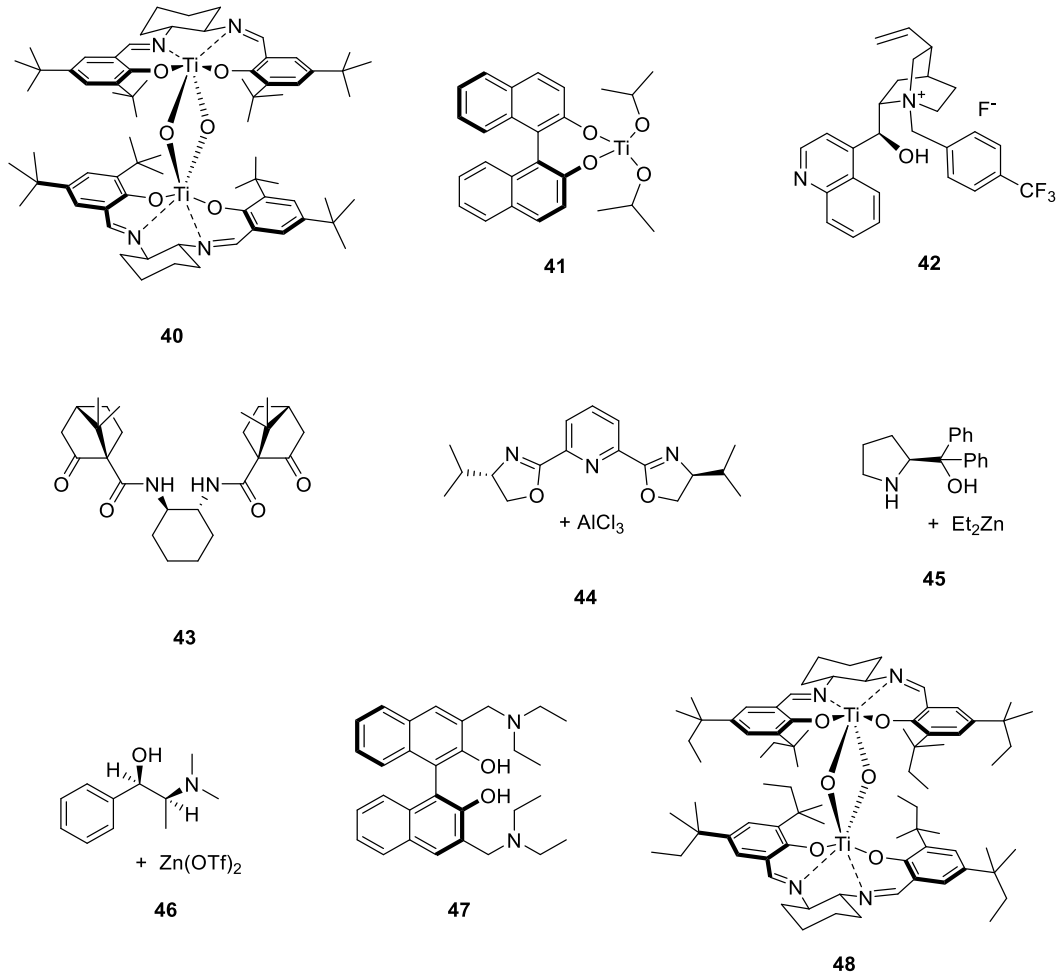


Figure 4.5 Ligands screened

[70] a) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968 -3973. b) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301-3312. c) Belokon, Y.; Moscalenko, M.; Ikonnikov, N.; Yashkina, L.; Antonov, D.; Vorontsov, E.; Rozenberg, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3245-3250. d) Belokon, Y. N.; Chusov, D.; Borkin, D. A.; Yashkina, L. V.; Dmitriev, A. V.; Katayev, D.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2328-2333. e) Belokon, Y. N.; Clegg, W.; Harrington, R. W.; North M.; Young, C. *Inorg. Chem*. **2008**, *47*, 3801-3814.

[71] Casas, J.; Najera, C.; Sansano, J. M.; Gonzalez, J.; Saa, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699-702.

[72] Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 207-217.

[73] Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6229-6232.

asymmetric cyanations with BINOL type ligands (**41**, **47**). Iovel, *et al.* reported a Pybox-$AlCl_3$ complex (**44**) that showed excellent conversion of aldehydes to their corresponding chiral cyanohydrins.[74] Shioiri developed a series of chiral quaternary ammonium fluoride phase transfer catalysts (**42**) which could potentially be used in asymmetric trihalomethylation reactions.[75] Last but not least, Uang developed a 1,2-diphenylethylenediamine linked catalyst (**43**) which was able to furnish the chiral cyanohydrin in high yield (72-92%) and high ee (87-97%) (Figure 4.5).[76]

A test reaction was conducted with racemic BINOL, Ti(O*i*Pr)$_4$, TBD and benzaldehyde in chloroform. The starting material was consumed in 4 h. (*S*)-BINOL (20 mol%) was then used on benzaldehyde, with TBD/chloroform as the source of the trichloromethide. However, the yield was low (42%) and the ee was low as well (19%). Unfortunately, no reaction was observed with the Pybox-$AlCl_3$ complex **44**, the *N*-methylephedrine/zinc system **46**, or the (*S*)-diphenyl(pyrrolidin-2-yl)methanol/zinc system **45**. The cinchona alkaloid catalyst **42** was also tested at 30% catalyst loading in DCM; however, the yield was low (8%) as well as the ee (10%). In addition to the commercially available salen ligands, a *t*-amyl salen ligand **48** was also prepared according to Bu's reported procedure.[77] However, the yield and ee we obtained from the enantioselective trichloromethylation reaction were lower (62% and 12%, respectively) than the ones obtained from the same conversion with the conventional salen-Ti **40** complex

[74] Iovel, I.; Popelis, Y.; Fleisher, M.; Lukevics, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1279-1285.
[75] a) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835-2838. b) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett*. **1993**, *34*, 1507-1510.
[76] a) Hwang, C.-D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762-6763. b) Chang, C.-W.; Yang, C.-T.; Hwang, C.-D.; Uang, B.-J. *Chem. Commun.* **2002**, 54-55.
[77] Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702-2704.

under the same condition (88% and 33%, respectively). It is also worth noting that the salen-Ti monomer was not active in the chiral induction.

4.2.3. Screening of Metal Cations as Lewis Acids

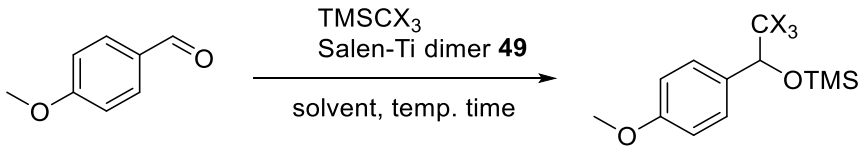
In chiral catalyst development, metal cations have been used as Lewis acids in the catalysis.[78] Belokon and North reported salen-type catalysts with Ti (IV) and V(V) ions.[7070] Iovel's Pybox complex uses Al (III) as the Lewis acid.[74] We prepared the BINOLAM **47** and attempted the trifluoromethylation at 0 ^{o}C in toluene with 3 equivalents of Ruppert's reagent, 10 mol% catalyst loading with 10 mol% of Et_2AlCl as the Lewis acid, 40 mol% of Ph_3PO and 200 mg/mmol of 4 Å molecular sieves as Saa's procedures suggested.[71] Unfortunately, very little conversion was observed after 85 h. The V(V) coordinated salen was also prepared for testing. However, the test reaction run in toluene did not consume all the starting material after 48 h. It is worth noting that Mn (II) coordinated salen (Jacobsen's catalyst) was also tested for trichloromethylation, however, no reaction was observed after 18 h. The best Lewis acid from the list was Ti (IV) which afforded >90% yield, 33% ee on the enantioselective trichloromethylation of 4-methoxybenzaldehyde, and 82% yield, 43% ee on the enantioselective trifluoromethylation of 4-methoxybenzaldehyde.

4.2.4. Determination of Reaction Conditions

After screening the catalysts shown in Figure 4.5, we decided to optimize the reaction conditions using the salen-Ti(IV) complex. Using 4-methoxybenzaldehyde as the starting

[78] *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer-Verlag: Berlin, 1999.

Table 4.3 Determination of reaction conditions



X	Solvent	Temp.	Cat. loading	Time (h)	Yield	ee
F	DCM	rt	10 mol%	24	60%	0%
F	DCM	-50 °C	20 mol%	78	82%	43%
Cl	DCM	rt	10 mol%	18	95%	15%
Cl	DCM	0 °C	10 mol%	48	98%	14%
Cl	THF	rt	10 mol%	40	92%	20%
Cl	THF	0 °C	10 mol%	48	90%	11%
Cl	toluene	rt	10 mol%	72	80%	25%
Cl	toluene	45 °C	10 mol%	120	~10%[a]	NA
Cl	DCM	rt	20 mol%	18	>90%	33%
Cl	DCM	rt	50 mol%	18	>90%	30%

[a] 88% of the starting material was recovered

material, assuming it might be more difficult to functionalize due to its less electrophilic carbonyl, we tested the trihalomethylations with the salen-Ti(IV) dimeric complex at a variety of reaction conditions and found dichloromethane to be the superior solvent (Table 4.3). Importantly, the salen-Ti monomer was found to be ineffective in the induction of chirality, furnishing exclusively racemic TMS protected trichloromethyl carbinols when the reaction was carried out at rt in DCM.

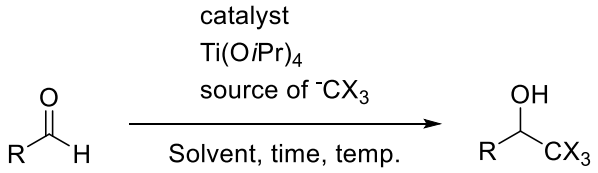
4.2.5. Determination of Enantiomeric Excess

The outcome of the trihalomethylation was determined by converting the trihalomethyl silyloxy product to its corresponding Mosher's ester using (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid.[30] By converting enantiomers to their corresponding diastereomers, we were able to determine the ee of the reaction from the relative integrations of peaks in the ^{1}H-NMR spectrum as well as in the ^{19}F-NMR spectrum.

4.2.6. Results

After the determination of reaction conditions, we screened a few aromatic aldehydes for the trihalomethylations (Table 4.4). This result was promising in that it showed moderate selectivity

Table 4.4 Preliminary results for the asymmetric trihalomethylation of aldehydes



54 **55**

cmpd	R	Source of $^-CX_3$	Cat.	Temp.	Solvent	Time	Yield	ee
55a	Ph	TBD/$CHCl_3$	*S*-BINOL	rt	$CHCl_3$	5h	42%	19%
55b	4-CH_3OPh	$TMSCF_3$	**49**	-50 ^oC	DCM	78h	82%	43%
55c	4-CH_3OPh	$TMSCCl_3$	**49**	rt	DCM	18h	>90%	33%
55d	4-NO_2Ph	$TMSCCl_3$	**49**	rt	DCM	18h	>90%	<10%

on the trihalomethylation. Electron-rich substrate seemed to give higher selectivity in comparison to the electron-poor substrate presumably due to the stronger interaction with the chiral catalyst to promote the asymmetric induction, outcompeting the background reaction.

4.3. Conclusion

We obtained preliminary results for a novel catalyst system to be used in the asymmetric trihalomethylation of aldehydes. Although the enantioselectivity was moderate, it is comparable to the best ee's yet reported, and the yields have been excellent with the easily prepared catalysts. With optimization, we believe that this catalytic system could have potential to furnish the desired chiral trihalomethyl carbinols with high yield and appealing stereocontrol.

4.4. Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker instruments at 360 or 500 MHz, 125.4 MHz, and 338 MHz, respectively. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. The Celite® was purchased from Fisher Scientific. The silica gel (SiliaFlash® F60) was purchased from Silicycle (230-400 mesh). All reagents were used directly as obtained from commercial sources unless otherwise noted. $Ti(OiPr)_4$ was obtained from Sigma-Aldrich and used without purification.

General procedure for the preparation of trichloromethyltrimethylsilane

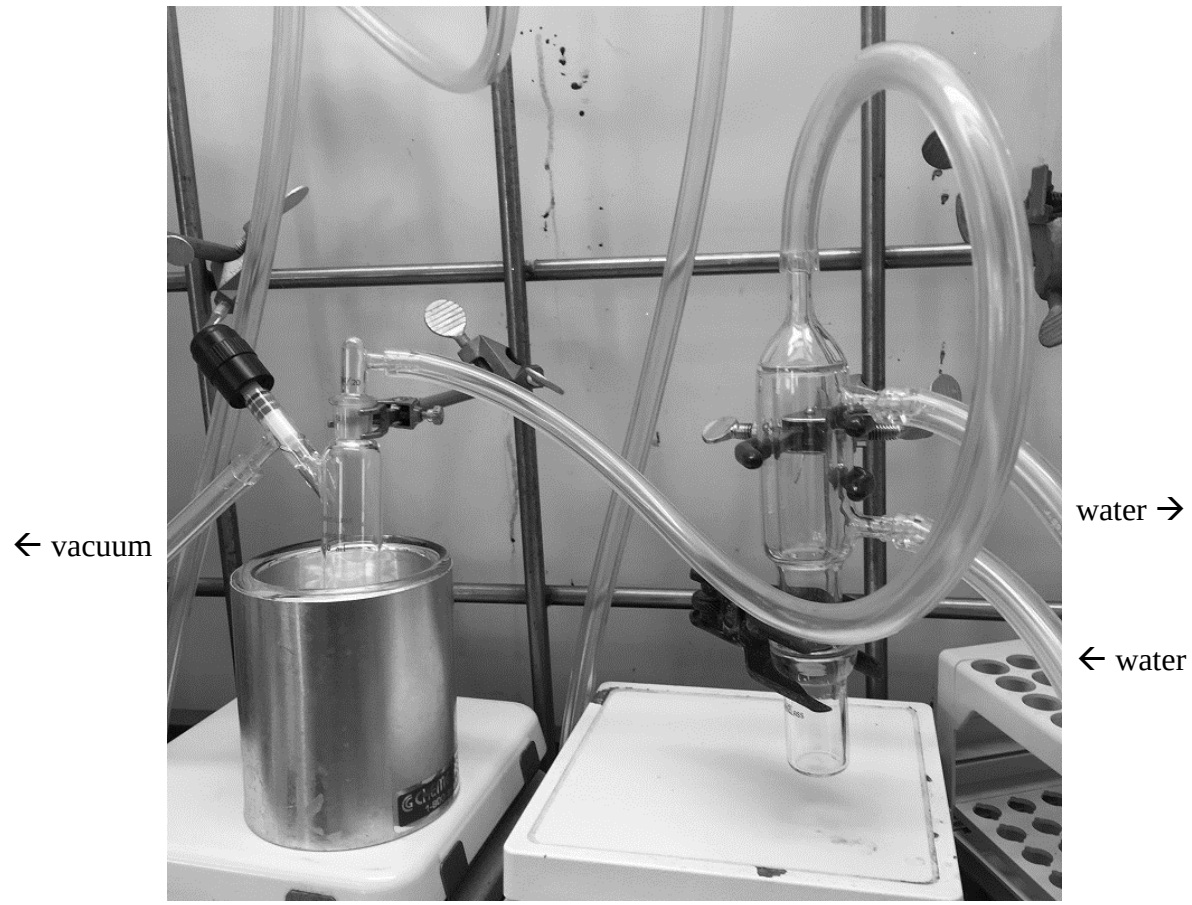
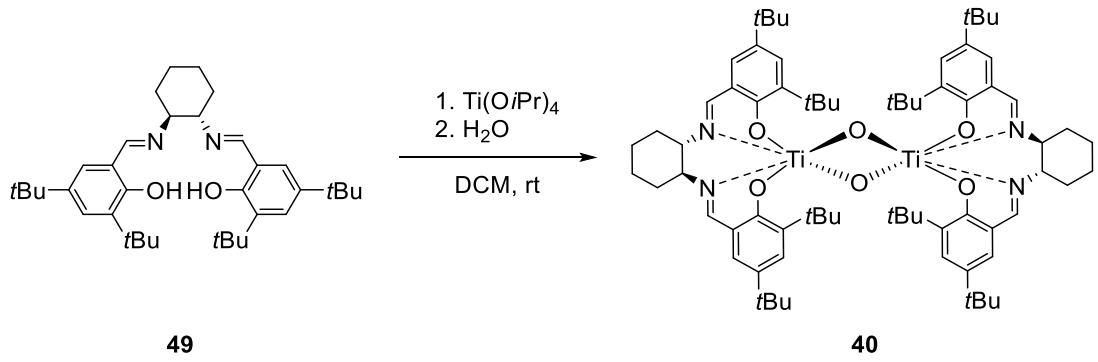


Figure 4.6 Set up of the sublimation apparatus

Trimethylsilyl trichloroacetate (TTA) was prepared following the method reported by Alper and Goldberg.[79] To a 2 neck round bottom flask equipped with a reflux condenser and a magnetic stir bar was added triethylamine (1.2 mL, 8.6 mmol) and THF (20 mL), followed by TTA (10.0 g, 42 mmol). The reaction was heated to 70 ^{o}C and stirred under an atmosphere of argon for 4h. The THF was then carefully distilled from the reaction mixture with a short-path distillation head (replacing the reflux condenser) and the resultant brown residue was dissolved with pentane (10 mL). The organic layer was washed with 1N HCl (10 mL) and H_2O (10 mL x 3), and dried with anhydrous sodium sulfate. The pentane was carefully evaporated with a slow stream of air to obtain a brown solid. This brown solid was sublimed (Figure 4.6) at 70 ^{o}C under high vacuum (~0.1 mm) to obtain the desired trichloromethyltrimethylsilane as a white crystalline solid.

General procedure for the preparation of the salen dimeric complexes



49 **40**

Figure 4.7 Synthesis of the salen-Ti(IV) dimeric complex

[79] Goldberg, Y.; Alper, H. *J. Org. Chem.* **1992**, *57*, 3731-3732.

The preparation method was adopted from the method published by Belokon, *et al*.[80] The commercially available salen ligand **49** was dissolved in DCM. To this solution, 1 equivalent $Ti(OiPr)_4$ was added dropwise. The reaction was stirred at rt under an atmosphere of argon for 2 h. 1 equivalent of H_2O was then added and stirred at rt for an additional 3 hours (Figure 4.7). The DCM was then evaporated and the yellow residue was collected as the dimeric complex **40**. The addition of H_2O is crucial for the generation of the dimeric complex.[70] The catalyst obtained without the addition of H_2O was the monomeric complex and was not active. Attempts were made to purify this dimeric complex by washing the residue with DCM or water,[70a] however, the catalyst obtained was inactive.

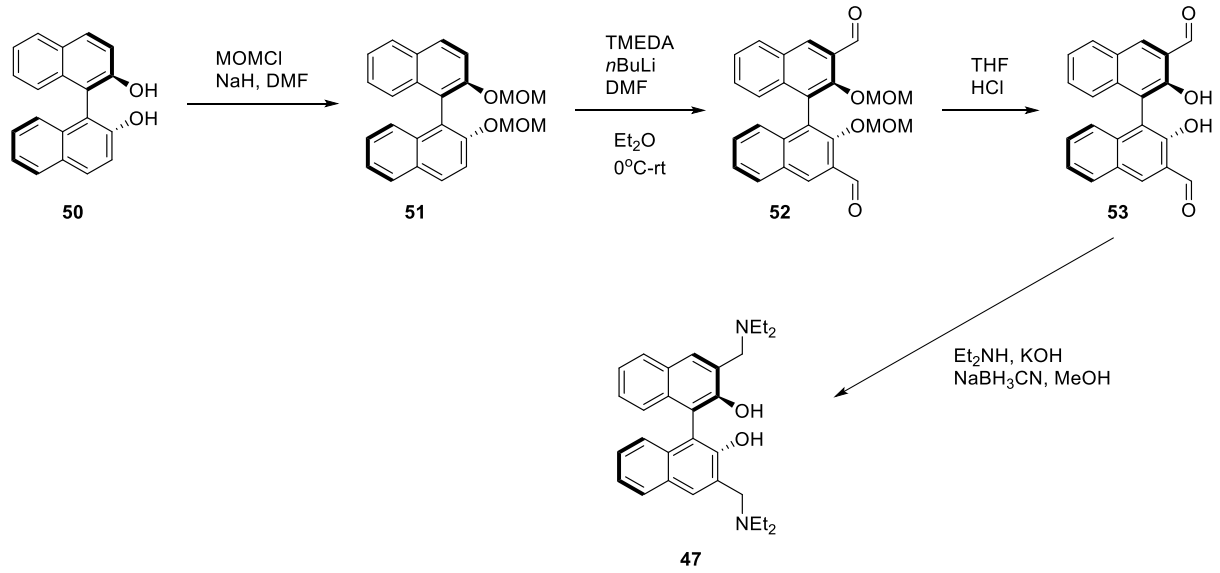
To synthesize the vanadium-salen complex, the commercially available salen ligand was dissolved in 3:2 EtOH:DCM. A $VOSO_4 \cdot 5H_2O$ in H_2O solution was then added dropwise at rt under an atmosphere of argon. This solution was refluxed for 4 h and then cooled to rt and stirred for 12 h while the septum on the reaction flask was removed for aerial oxidation. After 12 h, the solvent was evaporated under reduced pressure and the residue was dissolved in DCM and then washed with water three times. The organic layer was dried with anhydrous sodium sulfate and then evaporated to obtain the salen-V(V) complex as a light-green solid.

[80] Belokon, Y. N.; Cabeda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C .; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968-3973.

General procedure for the preparation of the BINOLAM 47 (Scheme 4.2)

MOM protection

A solution of (*R*)-BINOL **50** (1.95g, 6.8 mmol) in 20 mL DMF was added in portions over 5 minutes to a stirred suspension of NaH (1.15g, 48 mmol) in 20 mL DMF at 0 ^{o}C. After 30 min,



Scheme 4.2 Synthesis of the BINOLAM ligand **47**

MOMCl (2.4 mL, 31 mmol) was added and the ice bath was removed after 5 min. An additional 0.3 mL of MOMCl was added and the reaction mixture was stirred at rt for 3 h under an atmosphere of argon. This mixture was then poured into 160 mL of H_2O and extracted with 120 mL of Et_2O three times. The ether layer was washed with H_2O (50 mL x 4), sat. Na_2CO_3 (50 mL) and dried with anhydrous sodium sulfate. The solvent was then removed under reduced pressure and the pure MOM-protected BINOL **51** was obtained in 94% yield (2.4g, 6.4 mmol) by recrystallization from methanol.

Aldehyde synthesis

The MOM-protected BINOL **51** (2.25g, 6.0 mmol) and anhydrous TMEDA (3.59 mL, 23.8 mmol) were dissolved in anhydrous ether (157 mL) under an atmosphere of argon. The reaction was cooled to 0 ^{o}C with an ice bath. A 1.48 M solution of *n*BuLi in hexane (16 mL, 23.8 mmol) was added dropwise. The reaction was stirred at 0 ^{o}C for 1 h. Anhydrous DMF (2.25 mL, 29 mmol) was then added and the reaction was stirred at rt for 2 h. When the reaction was complete, the reaction was acidified to pH = 5 with 1N HCl. The organic layer were separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by flash column chromatography with 8:2 hexanes:EtOAc as the eluent. The protected aldehyde was obtained as a white solid in 27% yield (700mg, 1.62 mmol).

Deprotection of the protected dialdehyde **52**

The aldehyde **52** (500 mg, 1.39 mmol) was dissolved in THF and cooled to 0 ^{o}C in an ice bath. Conc. HCl (5 mL) was then added dropwise with stirring. The ice bath was then removed, the reaction was stirred at rt for 3h. This reaction mixture was extracted with EtOAc (10 mL x 7). The combined organic layers were washed with H_2O (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by flash column chromatography with 8:2 hexanes:EtOAc as the eluent. The deprotected dialdehyde **53** was obtained as a yellow solid in 78% yield (370 mg, 1.08 mmol).

Reductive amination

To a solution of diethylamine (0.28 mL, 2.6 mmol) in MeOH (2 mL) was added KOH (56 mg, 1 mmol). When the KOH pellets dissolved, the dialdehyde **53** (340 mg, 1 mmol) was added

and stirred at rt under an atmosphere of argon. When the starting material was consumed as judged by TLC (~2 h), a solution of $NaBH_4$ (114 mg, 3 mmol) in MeOH (0.5 mL) was added dropwise. The reaction was stirred at rt for 0.5 h. KOH (75 mg) was then added and stirred until all pellets dissolved. This solution was then filtered, diluted with H_2O (10 mL) and brine (10 mL). The methanol was evaporated, and the aqueous phase was extracted with Et_2O (20 mL x 3). The combined organic phase was dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude material was purified by flash column chromatography with 96:4 $CHCl_3$:MeOH as the eluent. The BINOLAM **47** was obtained as a yellow solid in 18% yield (82 mg, 0.18 mmol).

General procedure for the trichloromethylation of benzaldehyde with (*S*)-BINOL

In a dry 10 mL round bottom flask with a magnetic stir bar, combine $Ti(OiPr)_4$ (30 µL, 0.1 mmol), (*S*)-BINOL (28 mg, 0.1 mmol), benzaldehyde (50 µL, 0.5 mmol) and $CHCl_3$ (1 mL). This reaction mixture was stirred at rt under an atmosphere of argon for 1h. TBD (140 mg, 1 mmol) was then added in one portion. The reaction was monitored by TLC (typically ~5 h). When the reaction was judged complete, the reaction was quenched with sat. NH_4Cl, extracted with DCM (10 mL x 3). The combined organic phase was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of EtOAc/hexanes to afford the corresponding trichloromethyl carbinols.

2,2,2-trichloro-1-phenylethanol (55a)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 42%

yield (47 mg); IR (film): 3446, 3055, 2984, 2901, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.71 – 7.53 (m, 2H), 7.50 – 7.34 (m, 3H), 5.22 (s, 1H), 3.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.8, 129.4, 129.2, 127.8, 103.0, 84.4; HRMS *m/z* calcd. for $C_8H_7Cl_3O$, 223.9562; found 223.9563.

General procedure for the trifluoromethylation of aldehydes 54 with catalyst 49

In a dry 10 mL round bottom flask with a magnetic stir bar, combine the catalyst **49** (50 mg, 0.05 mmol), the starting aldehyde **54** (0.5 mmol), and $CHCl_3$ (1 mL). This solution was stirred at -50 ºC under an atmosphere of argon at rt for 1 h. $TMSCF_3$ (148 μL, 1 mmol) was then added dropwise over 1 min. The reaction was allowed to react at -50 ºC until the reaction was complete as indicated by TLC (54-78 h). The reaction was then quenched by passing the reaction mixture through a pad of silica gel to remove the catalyst **49**, and the solvent was removed under reduced pressure. The residue was diluted with THF (5 mL) and 1N HCl (5 mL) and stirred at rt until the TMS protected trifluoromethyl carbinol has been converted to the free trifluoromethyl carbinol as indicated by TLC analysis (~1 h). The THF was evaporated under reduced pressure and the residue was extracted with EtOAc (10 mL x 5). The combined organic phase was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of EtOAc/hexanes to afford the corresponding trifluoromethyl carbinols.

2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (55b)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a colorless oil in 82% yield (84 mg); ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.40 (d, 2H, J = 8.9 Hz), 6.93 (d, 2H, J = 8.9 Hz),

4.97 (qd, 1H, J = 6.7, 4.4 Hz), 3.83 (s, 3H), 2.51 (d, 1H, 4.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.9, 129.2, 126.7, 124.8 (q, J = 281.9 Hz), 114.4, 72.6 (q, J = 31.8 Hz), 55.5; ^{19}F NMR ($CDCl_3$, 360 MHz): δ -78.5 (d, 3F, J = 6.7 Hz).

General procedure for the trichloromethylation of aldehydes 54 with catalyst 49

In a dry 10 mL round bottom flask with a magnetic stir bar, combine the catalyst **49** (50 mg, 0.05 mmol), the starting aldehyde **54** (0.5 mmol), and $CHCl_3$ (1 mL). This solution was stirred under an atmosphere of argon at rt for 30 minutes. $TMSCCl_3$ (192 mg, 1 mmol) was then added in one portion. The reaction was allowed to react at rt until the reaction was complete as indicated by TLC (16-20 h). The reaction was then quenched by passing the reaction mixture through a pad of silica gel to remove the catalyst **49**, and the solvent was removed under reduced pressure. The residue was diluted with THF (5 mL) and 1N HCl (5 mL) and stirred at rt until the TMS protected trichlorocarbinol has been converted to the free trichloromethyl carbinol as indicated by TLC analysis (~1 h). The THF was evaporated under reduced pressure and the residue was extracted with EtOAc (10 mL x 5). The combined organic phase was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified through flash column silica gel chromatography with indicated ratios of EtOAc/hexanes to afford the corresponding trichloromethyl carbinols.

2,2,2-Trichloro-1-(4-methoxyphenyl)ethanol (55c)

The crude material was purified by flash chromatography through silica gel using 9:1 hexane/EtOAc as the eluent. The indicated compound was obtained as a white solid in 88% yield (112 mg); m.p. 44-45 °C; IR (solid): 3511, 3019, 2840, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.14 (d, J = 4.1 Hz, 1H), 3.82 (s, 3H),

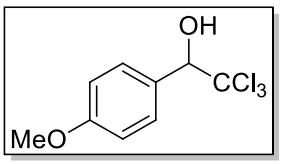
3.61 (d, J = 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 130.3, 127.0, 113.1, 103.3, 84.0, 55.2; HRMS *m/z* was calcd. for $C_9H_9OCl_3$, 253.9668; found 253.9665.

2,2,2-Trichloro-1-(4-nitrophenyl)-ethanol (55d)

The crude material was purified by flash chromatography through silica gel using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as an off-white solid in 94% yield (127 mg); m.p. 107-108 °C; IR (film): 3568, 3054, 2986, 1525, 1350, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 5.34 (d, J = 3.5 Hz, 1H), 3.64 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.4, 141.5, 130.4, 122.8, 102.0, 83.4; HRMS *m/z* calcd. for $C_8H_6Cl_3NO$, 268.9413; found 268.9406.

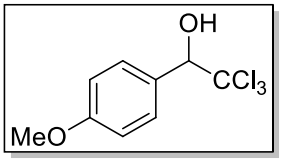
APPENDIX

A1.1. APPENDIX A. ^{1}H, ^{13}C, ^{19}F NMR SPECTRA


OH
CCl3
MeO

(9a)

7.539
7.522
7.260
6.926
6.909
5.147
5.139
3.820
3.618
3.610
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
f1 (ppm)


OH
CCl3
MeO

(9a)

160.215
130.318
126.998
113.144
103.345
84.002
77.254
77.000
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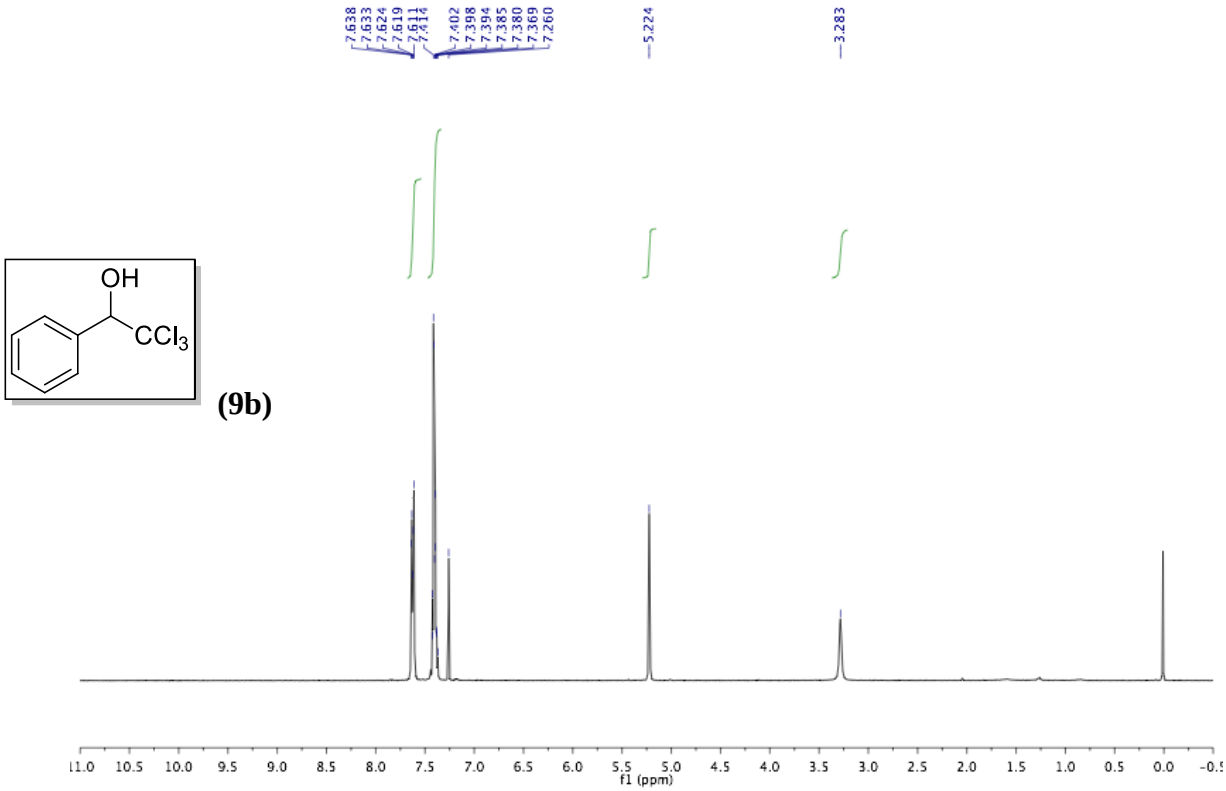
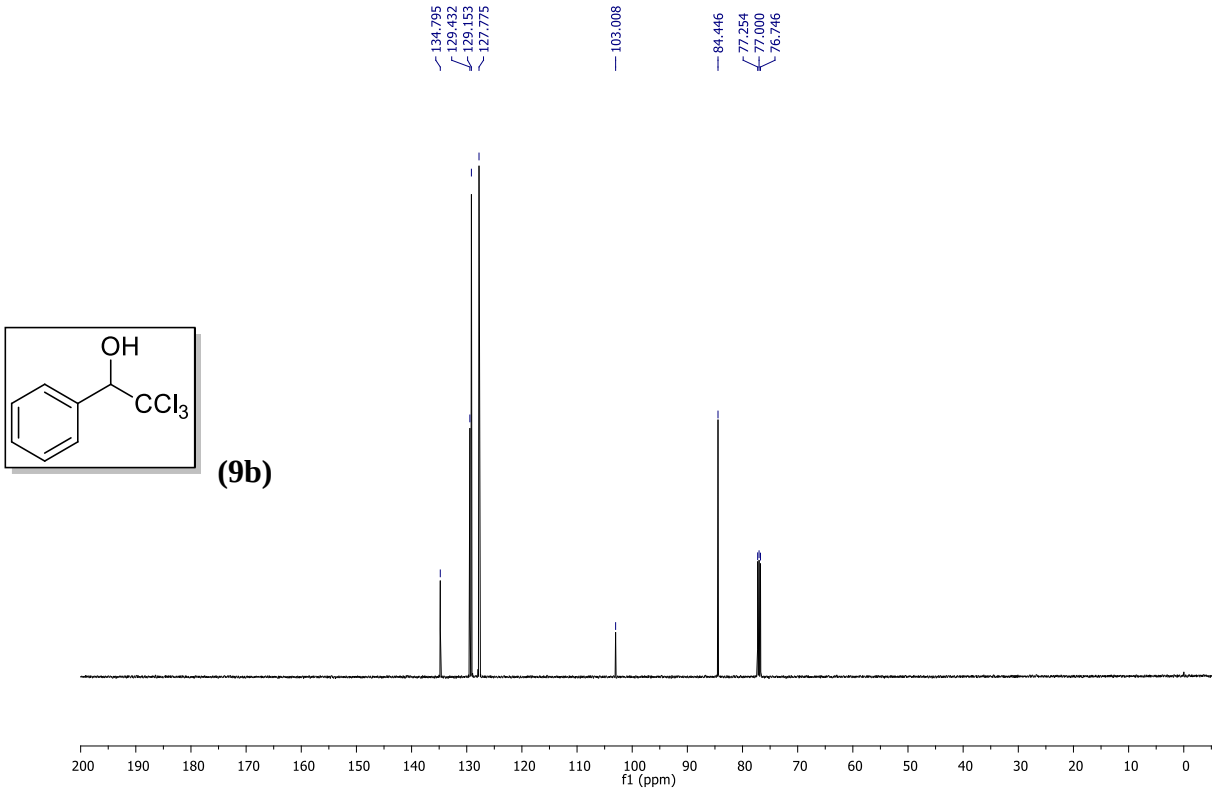
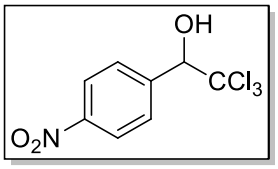
f1 (ppm)


7.638
7.633
7.624
7.619
7.611
7.414
7.402
7.398
7.394
7.385
7.380
7.369
7.260
5.224
3.283
OH
CCl3
f1 (ppm)

(9b)

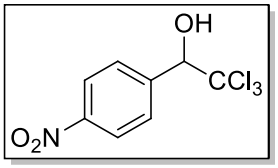

134.795
129.432
129.153
127.775
103.008
84.446
77.254
77.000
76.746
OH
CCl3
f1 (ppm)

(9b)


OH
CCl3
O2N

(9c)

8.235
8.231
8.221
8.217
7.834
7.817
7.260
5.347
5.340
3.647
3.640
f1 (ppm)


OH
CCl3
O2N

(9c)

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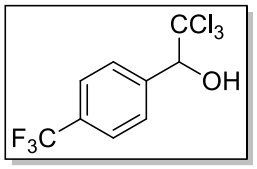
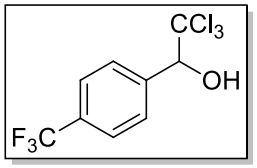
141.484
130.362
122.778
101.966
83.364
77.254
77.000
76.746
f1 (ppm)


CCl3
OH
F3C

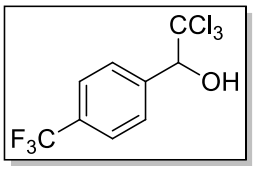
(9d)

7.775
7.774
7.751
7.669
7.646
7.260
5.288
5.278
3.383
3.372
f1 (ppm)


CCl3
OH
F3C

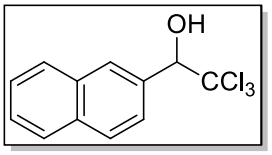
(9d)

138.448
138.439
131.701
131.442
131.182
129.720
124.971
124.768
124.739
124.709
124.678
83.855
77.254
77.000
76.746
f1 (ppm)


CCl3
OH
F3C

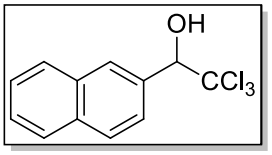
(9d)

-62.719
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


OH
CCl3

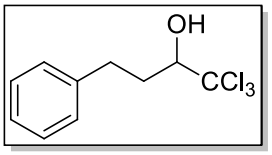
(9e)

8.091
7.877
7.728
7.528
7.260
5.403
5.392
3.379
3.368
f1 (ppm)


OH
CCl3

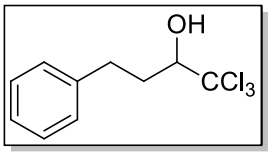
(9e)

133.614
132.394
132.207
129.154
128.321
127.608
127.331
126.770
126.275
126.026
103.071
84.476
77.254
77.000
76.745
f1 (ppm)


OH
CCl3

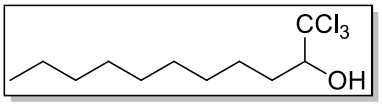
(9f)

7.320
7.305
7.290
7.242
7.228
7.213
7.199
3.993
3.989
3.982
3.978
3.973
3.969
3.962
2.839
2.819
2.778
2.762
2.367
1.991
1.981
1.971
1.963
1.961
1.953
1.943
0.000
f1 (ppm)


OH
CCl3

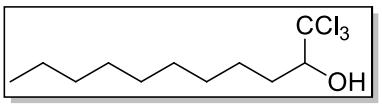
(9f)

140.673
128.557
128.471
126.251
104.080
81.960
77.254
77.000
76.746
32.900
31.920
f1 (ppm)


CCl3
OH

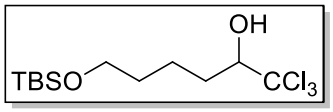
(9g)

7.260
4.025
4.019
4.009
4.004
3.998
3.993
3.983
3.977
2.664
2.660
2.660
2.648
2.648
2.644
2.032
2.017
2.006
1.472
1.417
1.274
0.901
0.883
0.863
f1 (ppm)


CCl3
OH

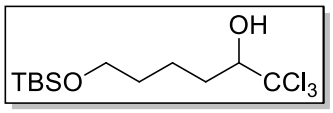
(9g)

104.412
83.043
77.254
77.000
76.746
31.867
31.536
29.507
29.449
29.295
29.270
26.110
22.659
14.087
-0.020
f1 (ppm)

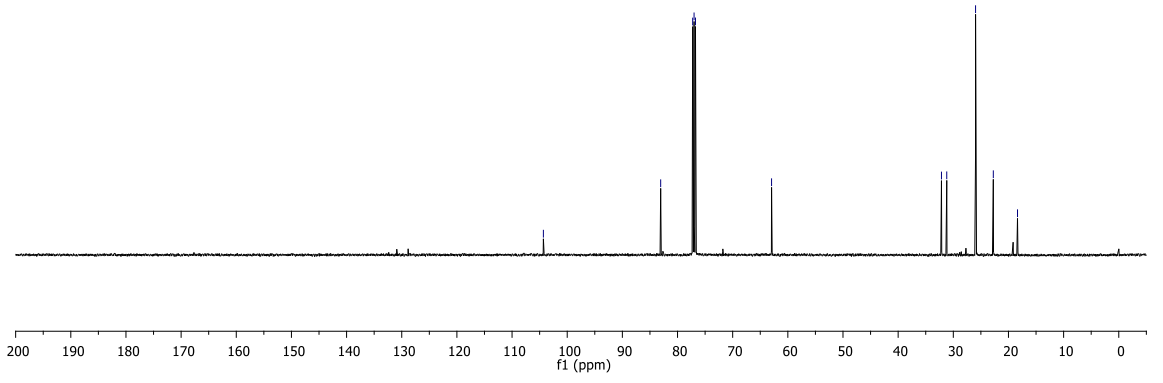

OH
TBSO
CCl3

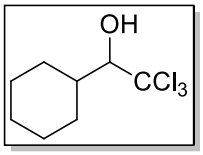
(9h)

7.260
4.015
4.005
3.995
3.662
3.651
3.639
2.894
2.088
2.070
2.061
1.674
1.612
1.557
1.539
0.898
0.058
f1 (ppm)


OH
TBSO
CCl3

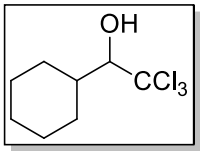
(9h)


104.319
83.053
77.254
77.000
76.746
62.949
32.147
31.187
25.965
22.746
18.359
f1 (ppm)


OH
CCl3

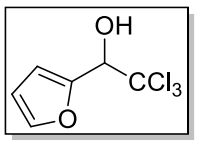
(9i)

7.260
3.861
3.855
2.793
2.776
2.066
2.045
2.025
1.725
1.343
1.308
1.295
1.288
1.282
1.270
1.261
1.245
1.237
1.214
1.205
1.181
1.171
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)


OH
CCl3

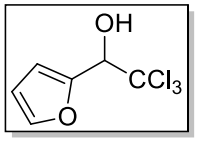
(9i)

104.162
86.403
77.254
77.000
76.746
39.929
32.899
26.672
26.532
26.030
25.912
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
CCl3
O

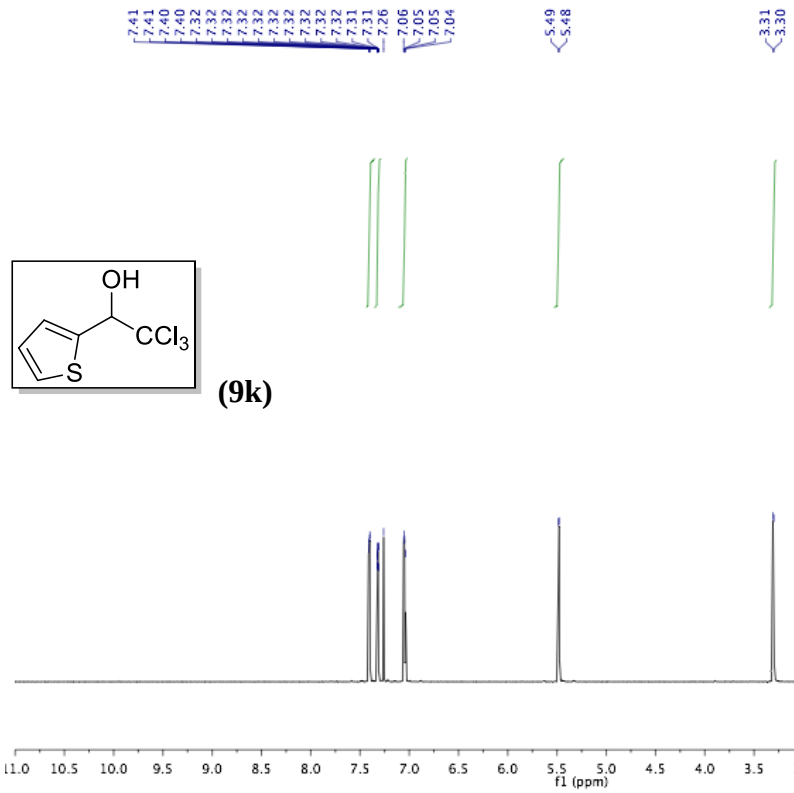
(9j)

7.475
7.472
7.260
6.614
6.608
6.443
6.439
6.436
6.433
5.247
5.232
3.345
3.330
f1 (ppm)

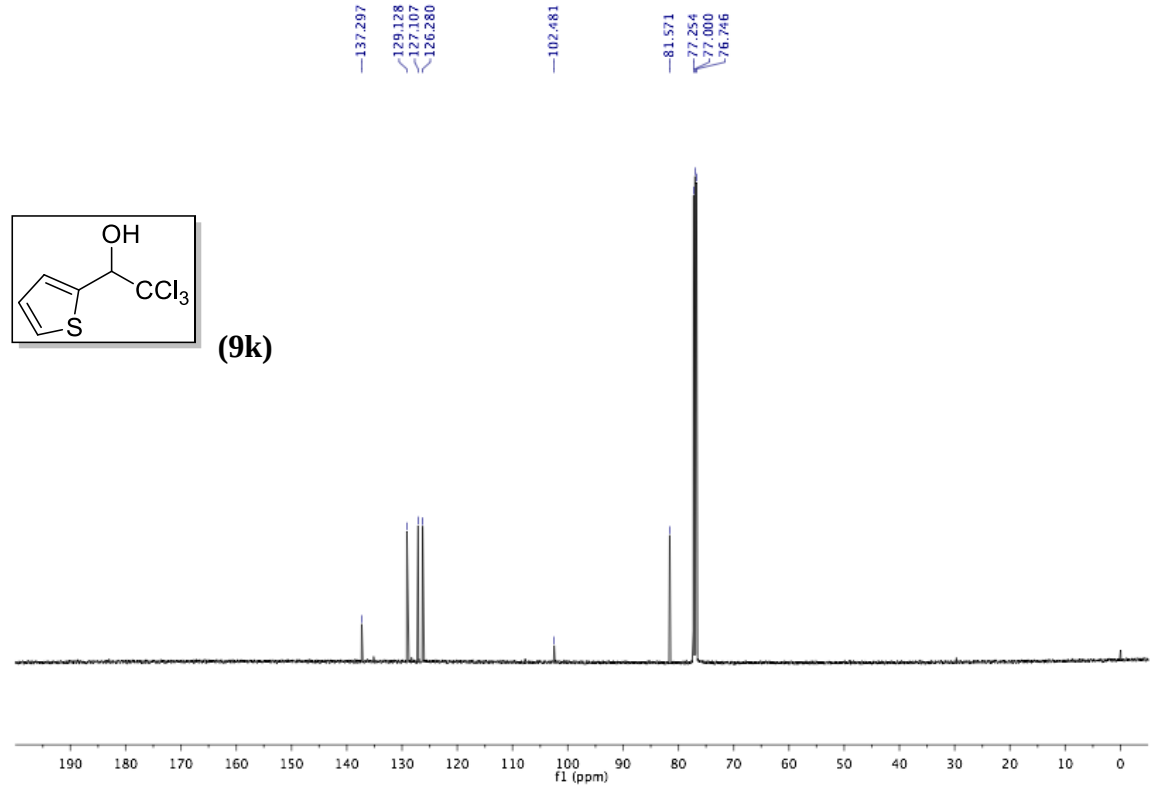

OH
CCl3
O

(9j)

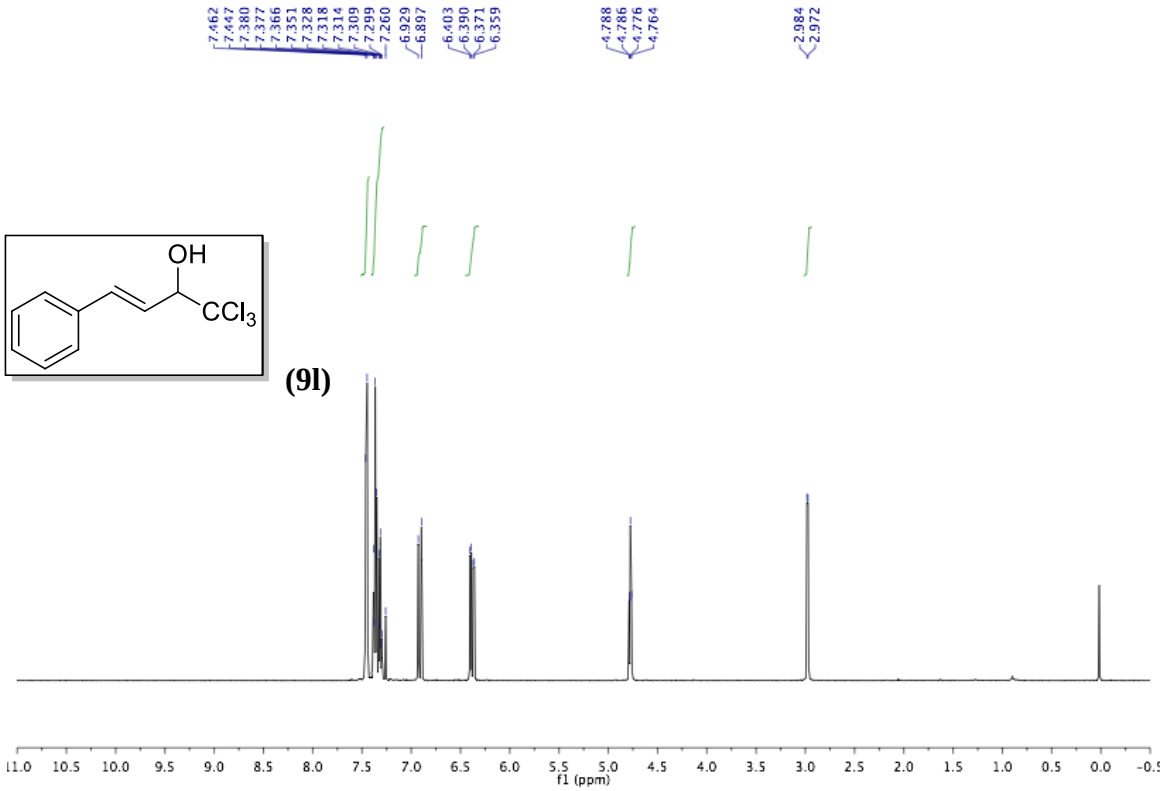
148.379
143.061
110.876
110.690
101.208
79.320
77.254
77.000
76.746
f1 (ppm)

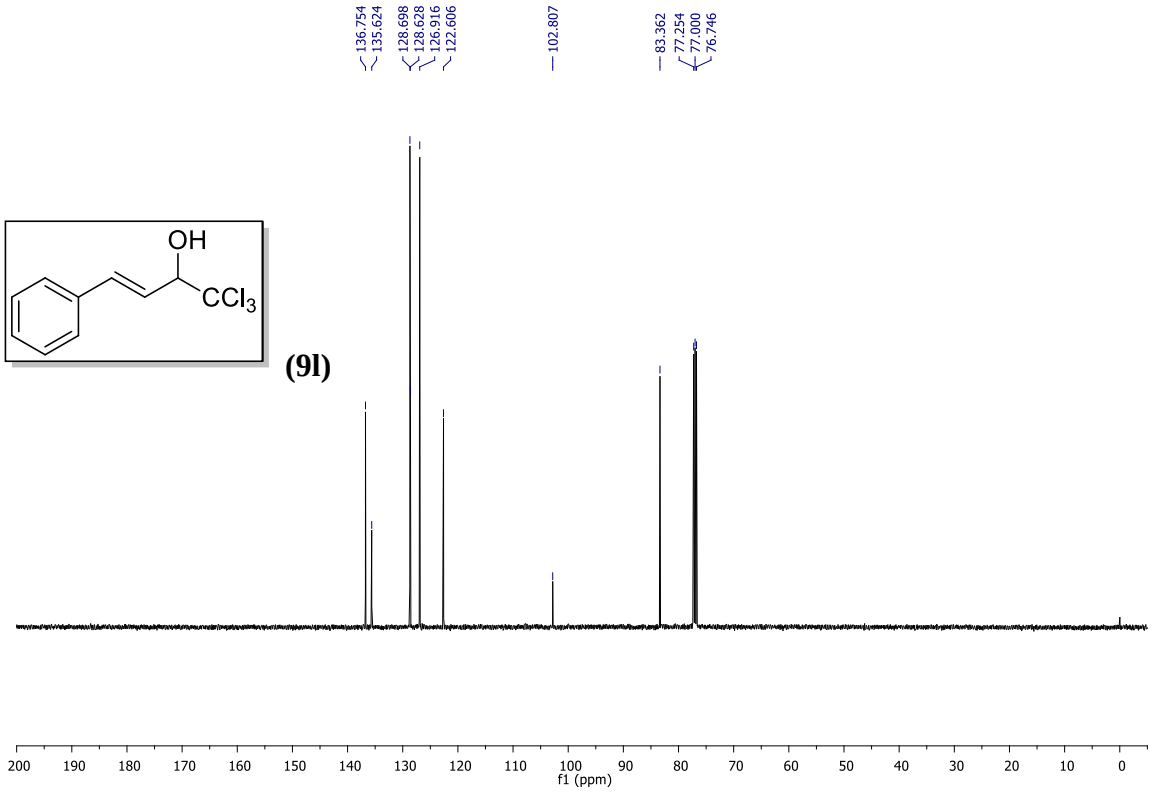

7.41
7.41
7.40
7.40
7.32
7.32
7.32
7.32
7.32
7.32
7.32
7.32
7.31
7.31
7.26
7.06
7.05
7.05
7.04
5.49
5.48
3.31
3.30
OH
CCl3
S
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

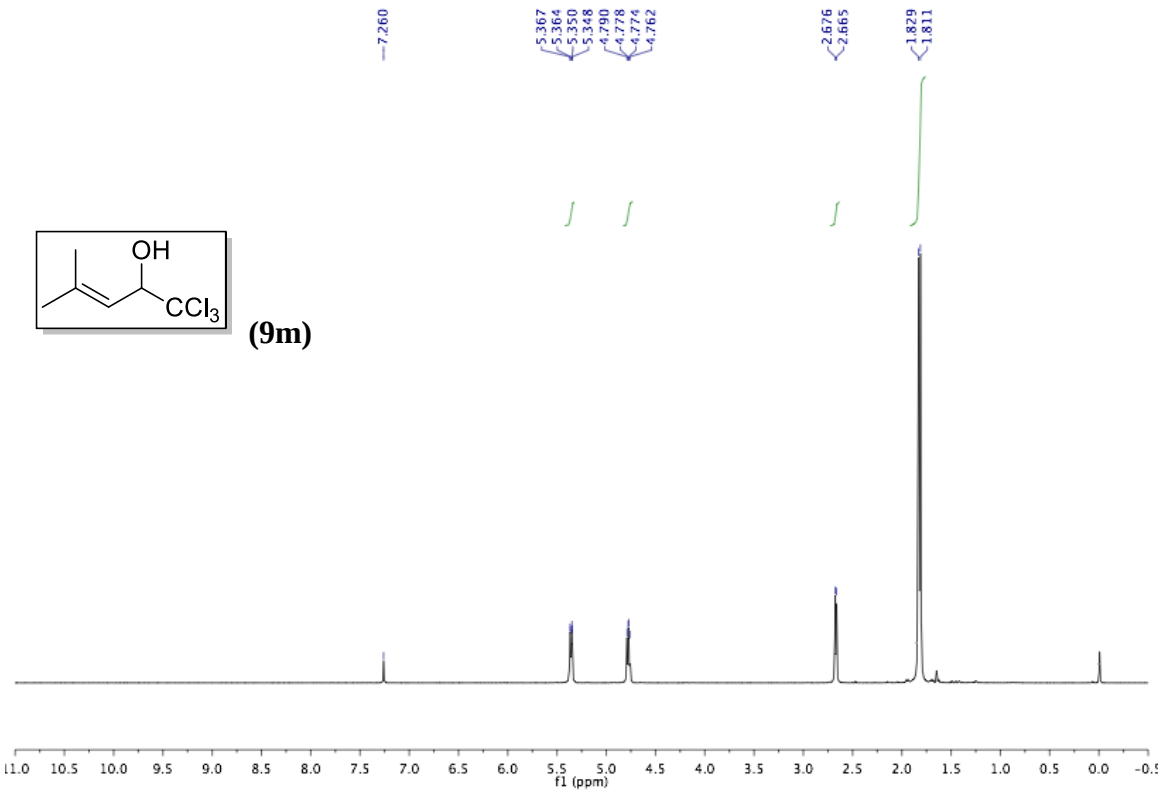
(9k)


137.297
129.128
127.107
126.280
102.481
81.571
77.254
77.000
76.746
OH
CCl3
S
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

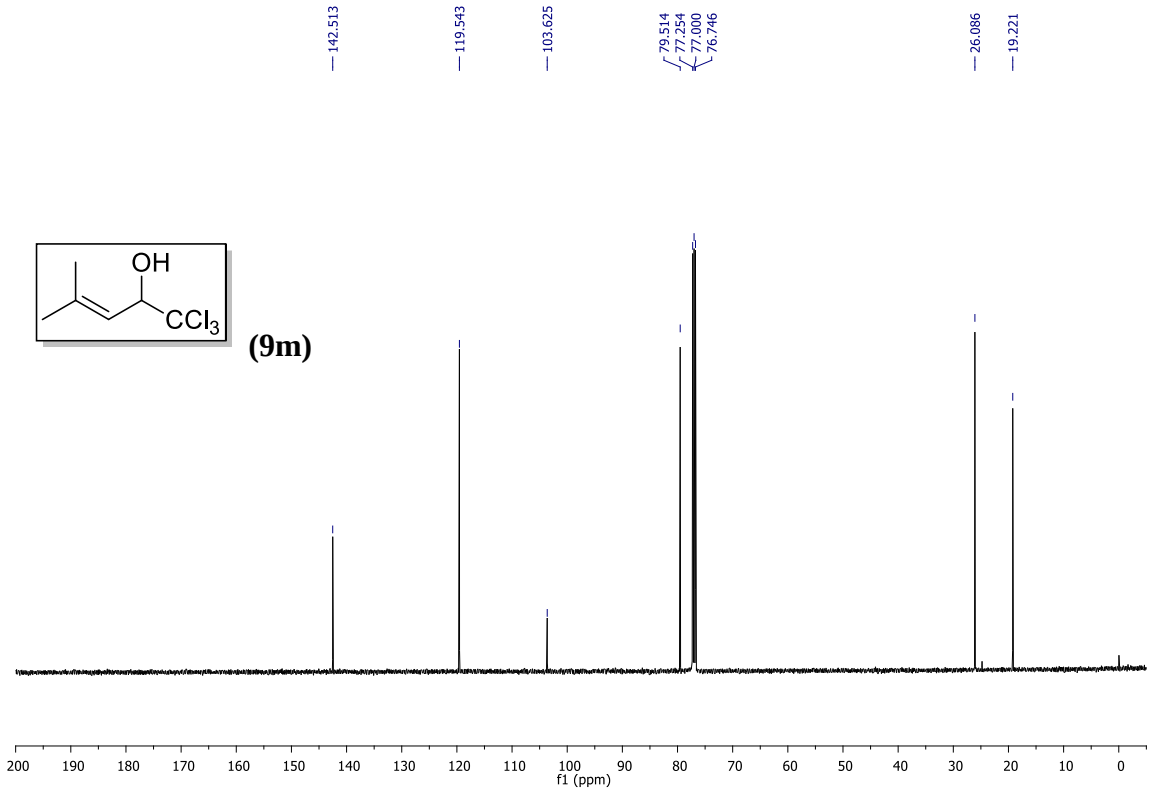
(9k)


7.462
7.447
7.380
7.377
7.366
7.351
7.328
7.318
7.314
7.309
7.299
7.260
6.929
6.897
6.403
6.390
6.371
6.359
4.788
4.786
4.776
4.764
2.984
2.972
OH
CCl3
(9l)
f1 (ppm)

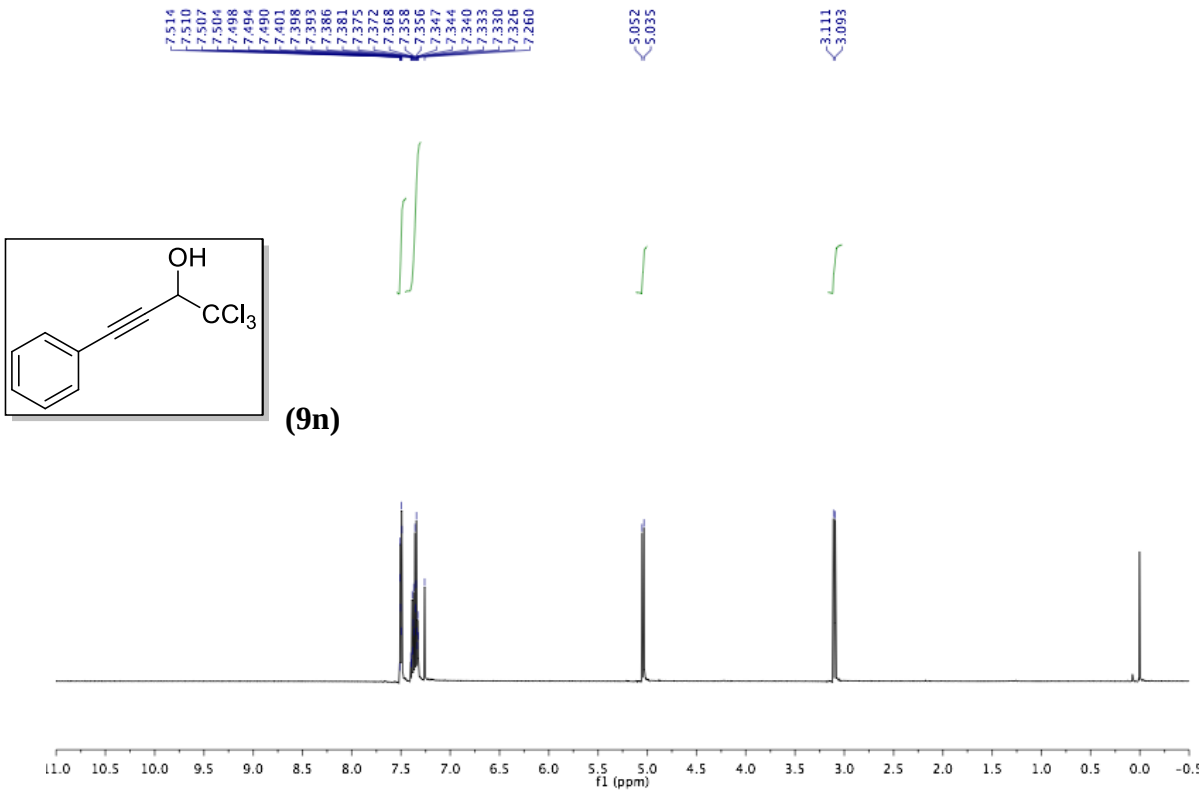

136.754
135.624
128.698
128.628
126.916
122.606
102.807
83.362
77.254
77.000
76.746
OH
CCl3
(9l)
f1 (ppm)


7.260
5.367
5.364
5.350
5.348
4.790
4.778
4.774
4.762
2.676
2.665
1.829
1.811
OH
CCl3
f1 (ppm)

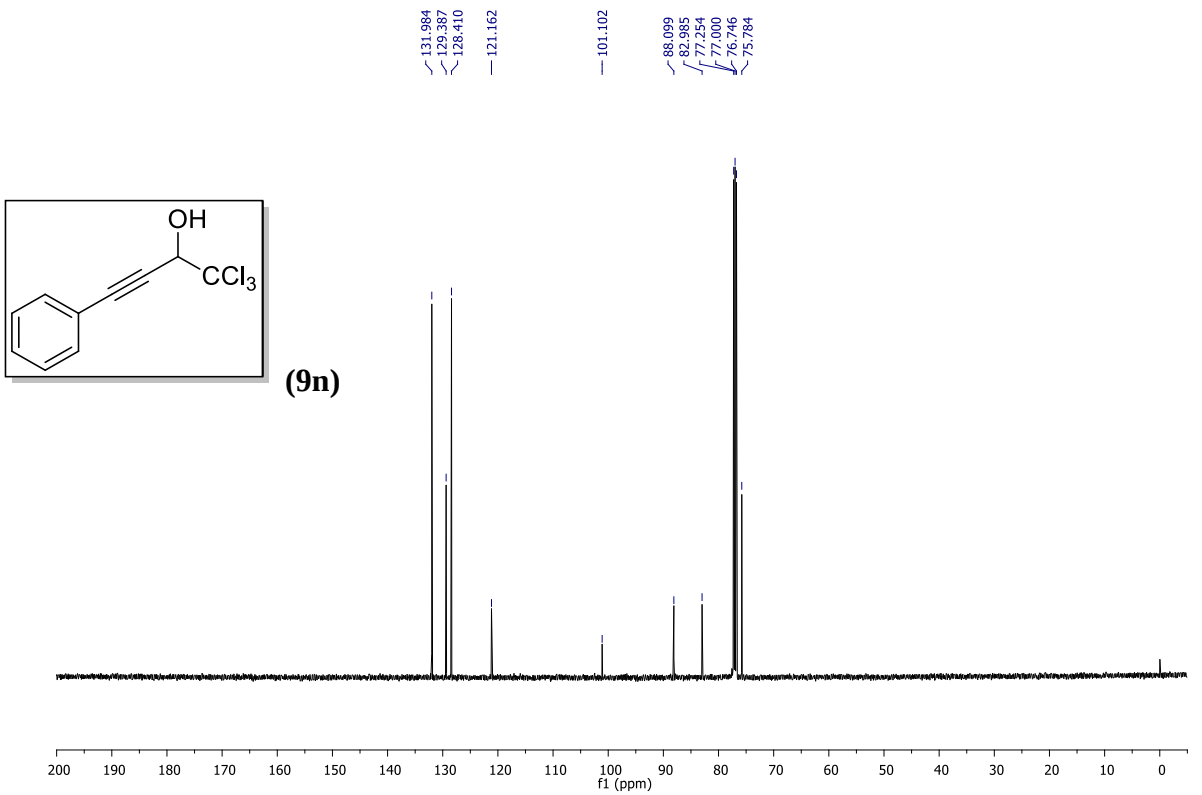
(9m)


142.513
119.543
103.625
79.514
77.254
77.000
76.746
26.086
19.221
OH
CCl3
f1 (ppm)

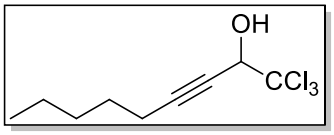
(9m)


7.514
7.510
7.507
7.504
7.498
7.494
7.490
7.401
7.398
7.393
7.386
7.381
7.375
7.372
7.368
7.358
7.356
7.347
7.344
7.340
7.333
7.330
7.326
7.260
5.052
5.035
3.111
3.093
OH
CCl3
f1 (ppm)

(9n)

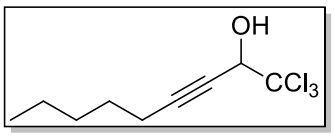

131.984
129.387
128.410
121.162
101.102
88.099
82.985
77.254
77.000
76.746
75.784
OH
CCl3
f1 (ppm)

(9n)


OH
CCl3

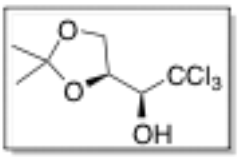
(9o)

7.260
4.795
4.791
4.788
4.778
4.774
4.770
2.959
2.942
2.273
2.263
2.259
1.377
1.340
1.296
0.910
0.895
0.881
f1 (ppm)


OH
CCl3

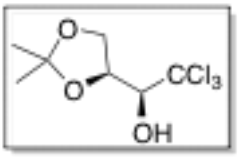
(9o)

101.6
89.8
77.3
77.0
76.7
75.4
74.6
30.9
27.7
22.1
18.6
13.9
f1 (ppm)


O
O
CCl3
OH

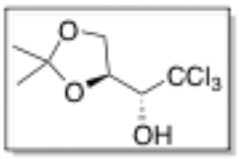
((*S*,*S*)-9p)

7.260
4.608
4.602
4.596
4.589
4.583
4.576
4.357
4.273
4.256
4.101
4.083
3.061
3.053
1.474
1.393
f1 (ppm)


O
O
CCl3
OH

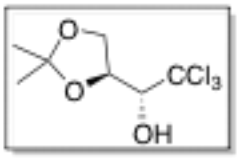
((*S*,*S*)-9p)

109.21
100.63
82.38
77.00
76.75
75.14
64.70
26.30
25.32
f1 (ppm)


O
O
CCl3
OH

((*S*,*R*)-9p)

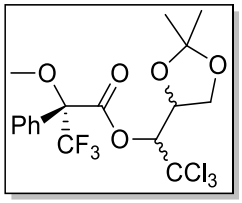
7.260
4.588
4.584
4.575
4.570
4.561
4.556
3.976
3.972
3.925
3.911
3.908
3.894
3.732
3.715
1.491
1.435
f1 (ppm)

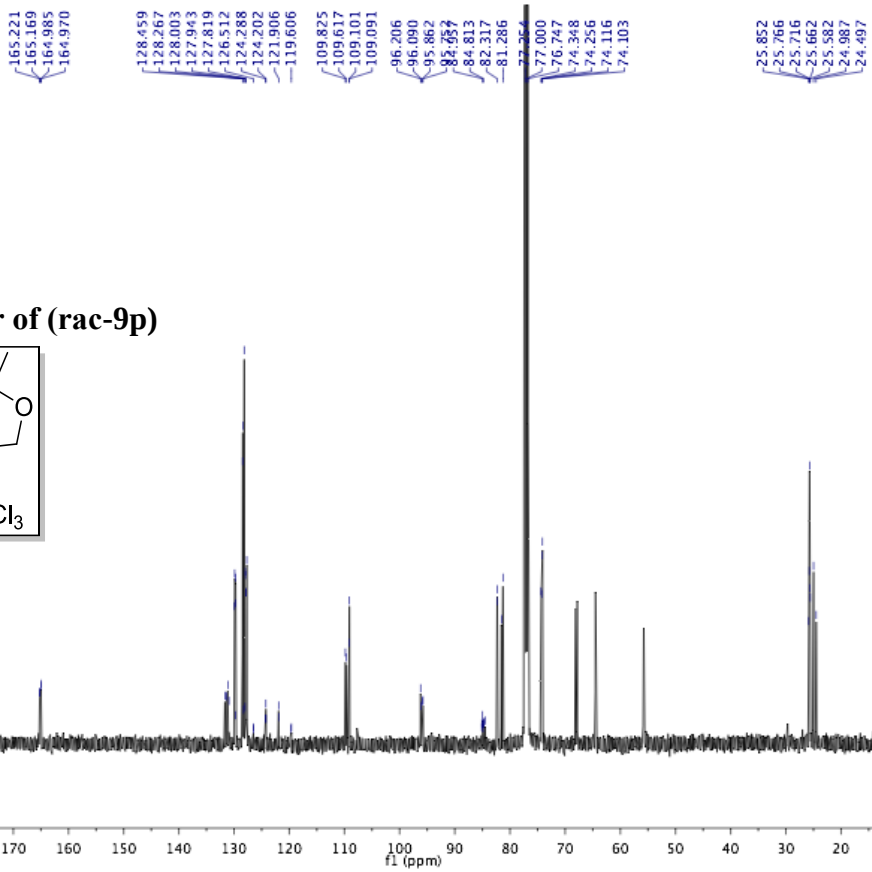

O
O
CCl3
OH

((*S*,*R*)-9p)

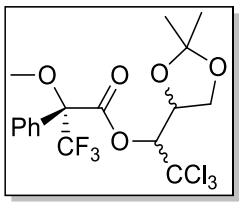
110.918
101.331
81.140
76.746
73.240
68.401
26.057
25.656
f1 (ppm)

Mosher's ester of (rac-9p)



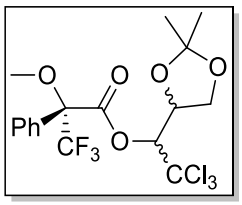


Mosher's ester of (rac-9p)



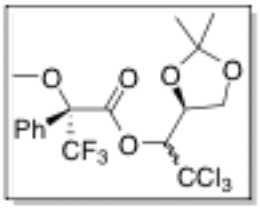
-70.92
-71.27
-71.32
-71.55

Mosher's ester of (rac-9p)

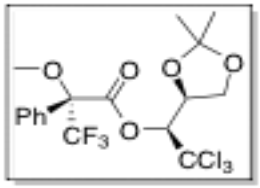


-71.32
-71.55

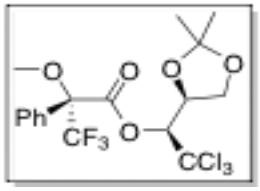
Mosher's ester of diastereomeric mixture (*S,R)*-9p/(*R,R)*-9p



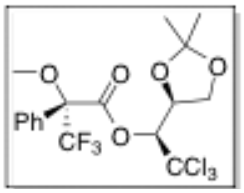
Mosher's ester of ((*S*,*S*)-9p)

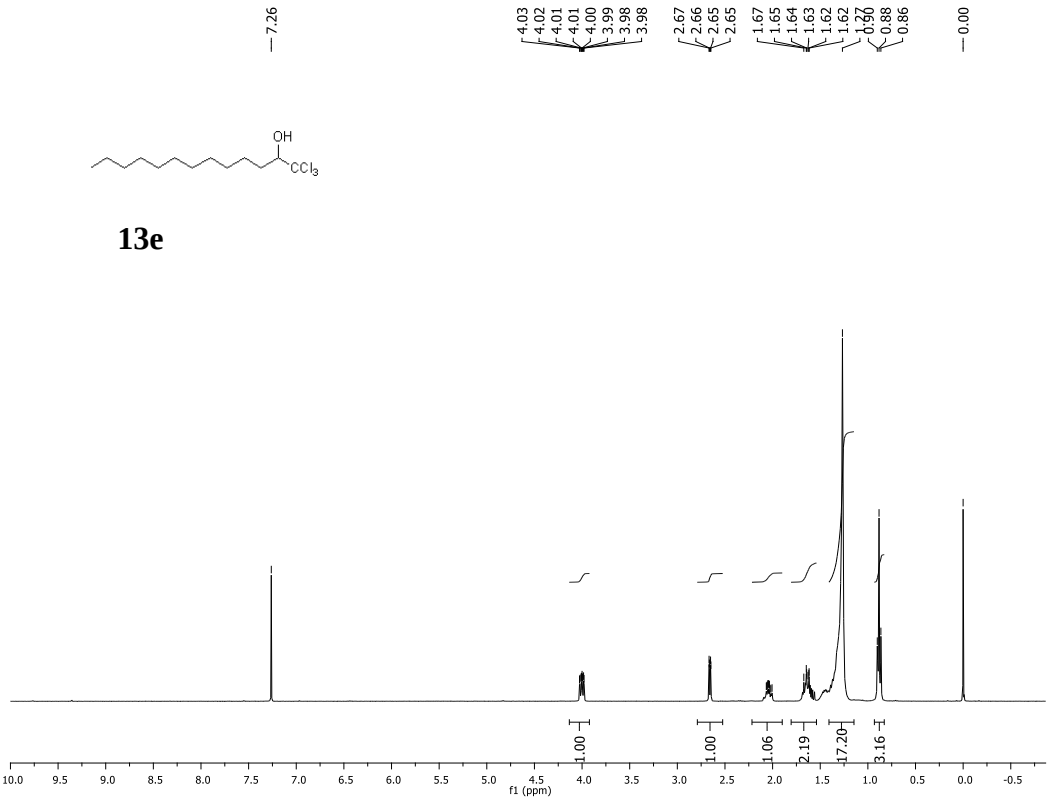


Mosher's ester of ((*S*,*S*)-9p)

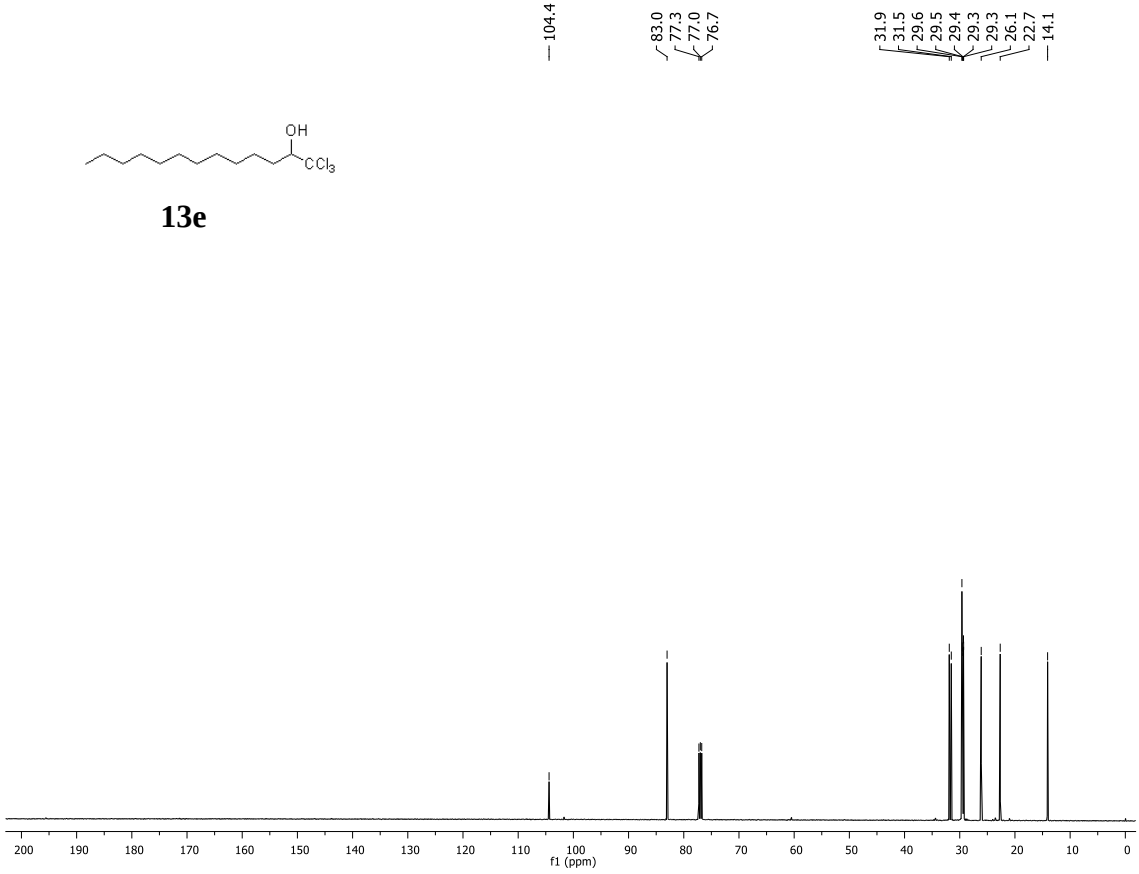


Mosher's ester of ((*S*,*S*)-9p)

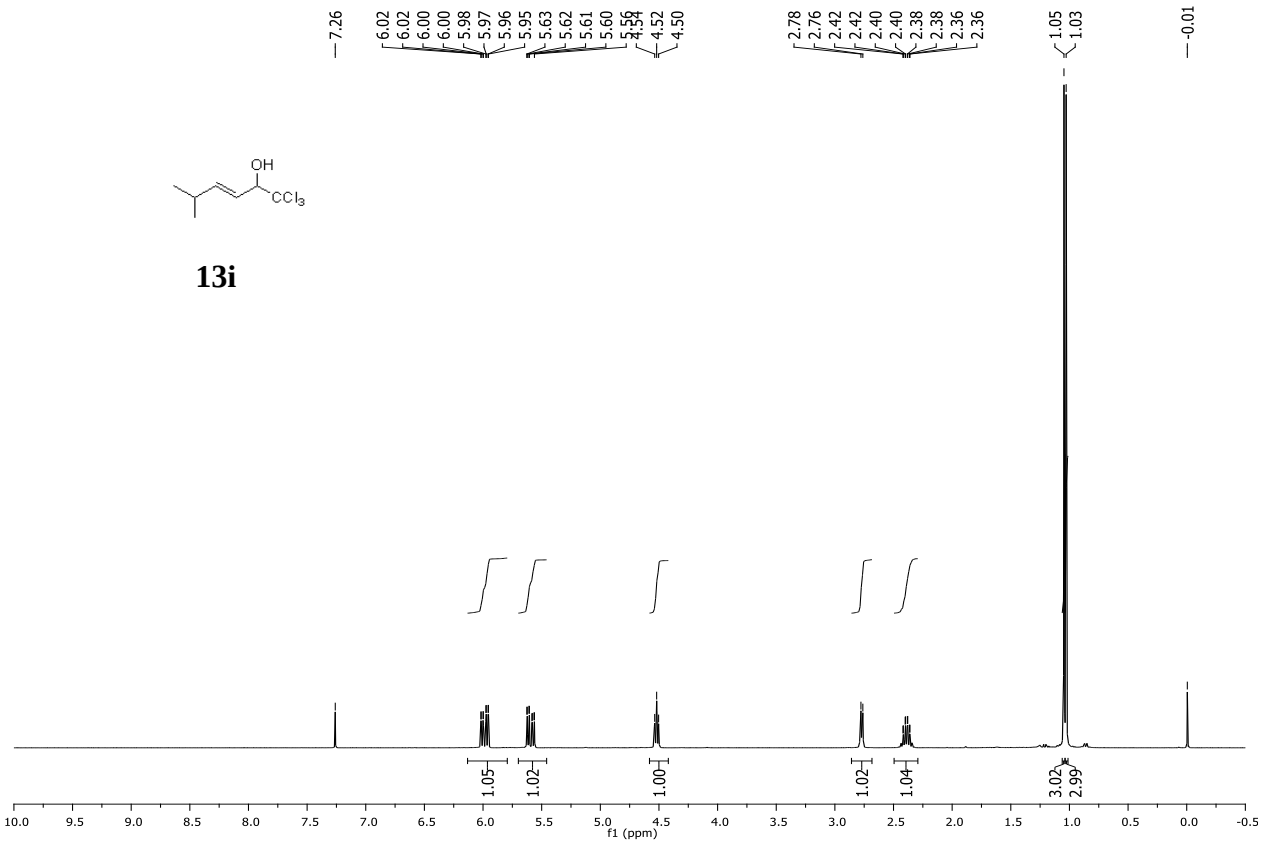



7.26
4.03
4.02
4.01
4.01
4.00
3.99
3.98
3.98
2.67
2.66
2.65
2.65
1.67
1.65
1.64
1.63
1.62
1.62
1.27
0.90
0.88
0.86
0.00
OH
CCl3
1.00
1.00
1.06
2.19
17.20
3.16
f1 (ppm)

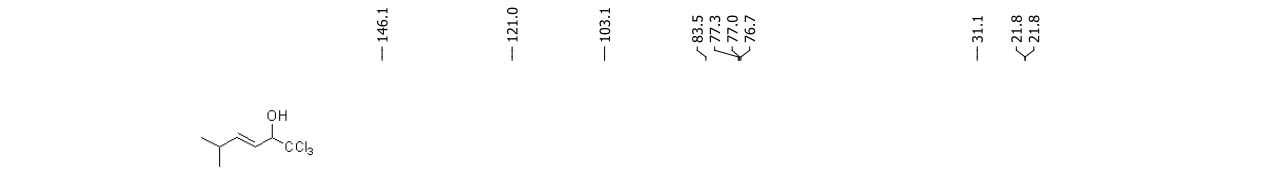
13e


104.4
83.0
77.3
77.0
76.7
31.9
31.5
29.6
29.5
29.4
29.3
29.3
26.1
22.7
14.1
OH
CCl3
f1 (ppm)

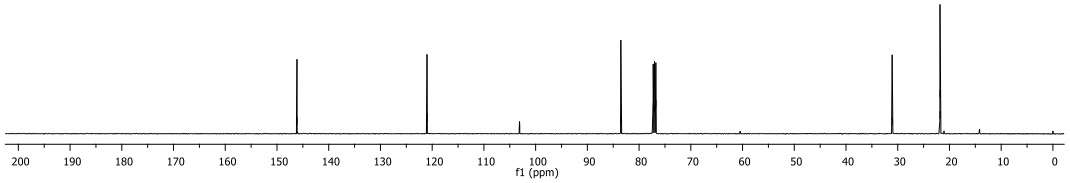
13e

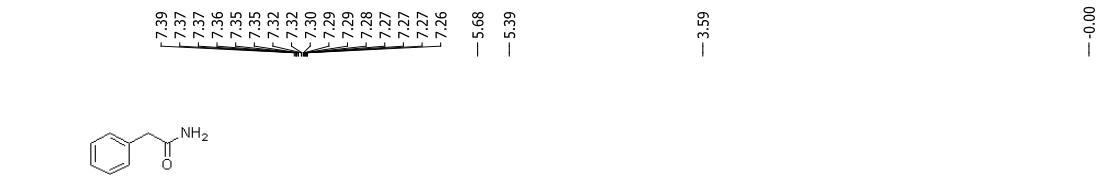

7.26
6.02
6.02
6.00
6.00
5.98
5.97
5.96
5.95
5.63
5.62
5.61
5.60
4.54
4.52
4.50
2.78
2.76
2.42
2.42
2.40
2.40
2.38
2.38
2.36
2.36
1.05
1.03
-0.01
OH
CCl3
1.05
1.02
1.00
1.02
1.04
3.02
2.99
f1 (ppm)

13i


146.1
121.0
103.1
83.5
77.3
77.0
76.7
31.1
21.8
21.8
OH
CCl3

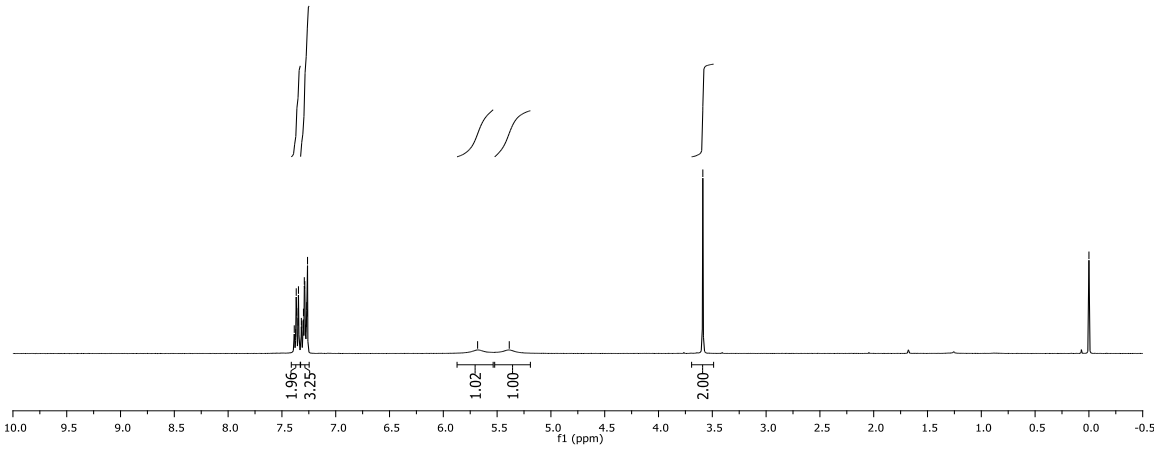
13i


f1 (ppm)

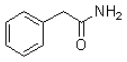

7.39
7.37
7.37
7.36
7.35
7.35
7.32
7.32
7.30
7.29
7.29
7.28
7.27
7.27
7.27
7.26
5.68
5.39
3.59
0.00

NH2
O

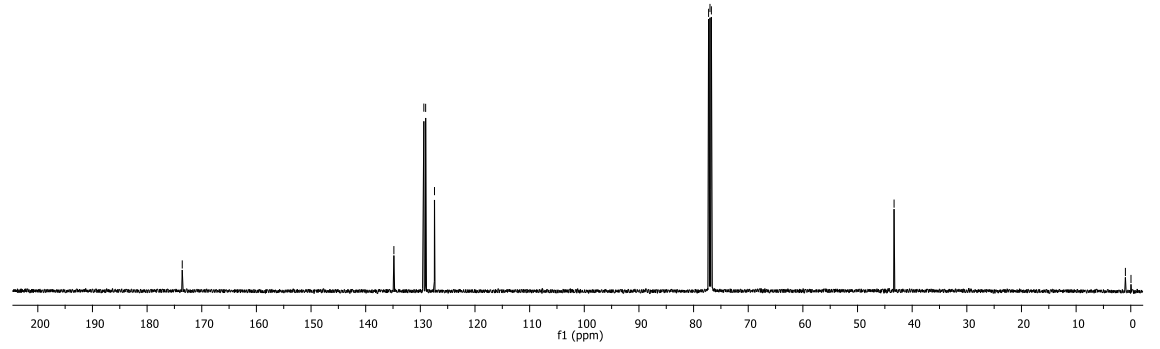
15a

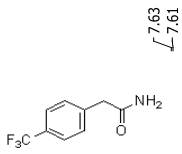

1.96
3.25
1.02
1.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


173.6
134.8
129.4
129.0
127.4
77.3
77.0
76.7
43.3
1.0
0.0

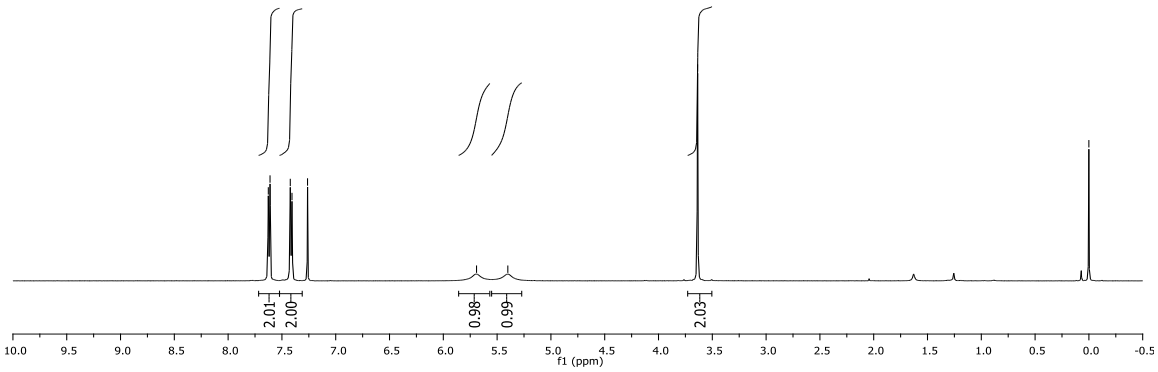

NH2
O

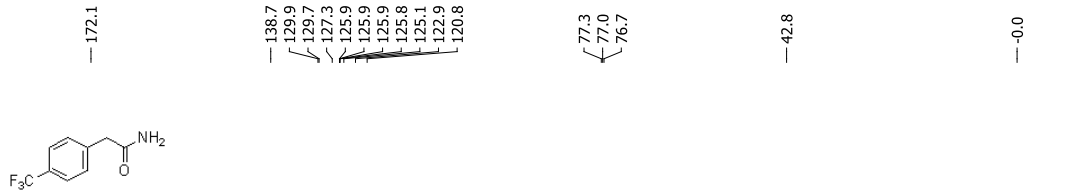
15a


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.63
7.61
7.42
7.41
7.26
5.69
5.40
3.64
0.00
NH2
O
F3C

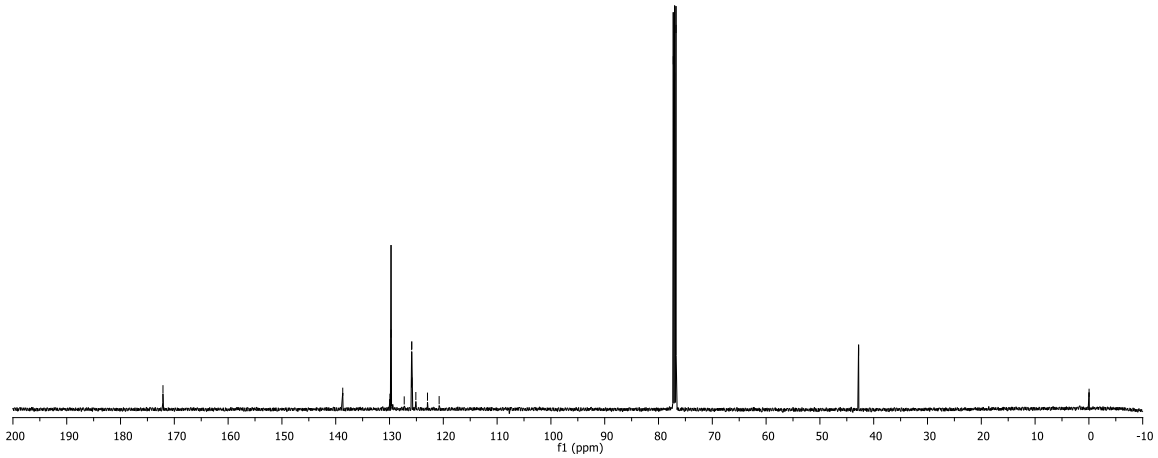
26b

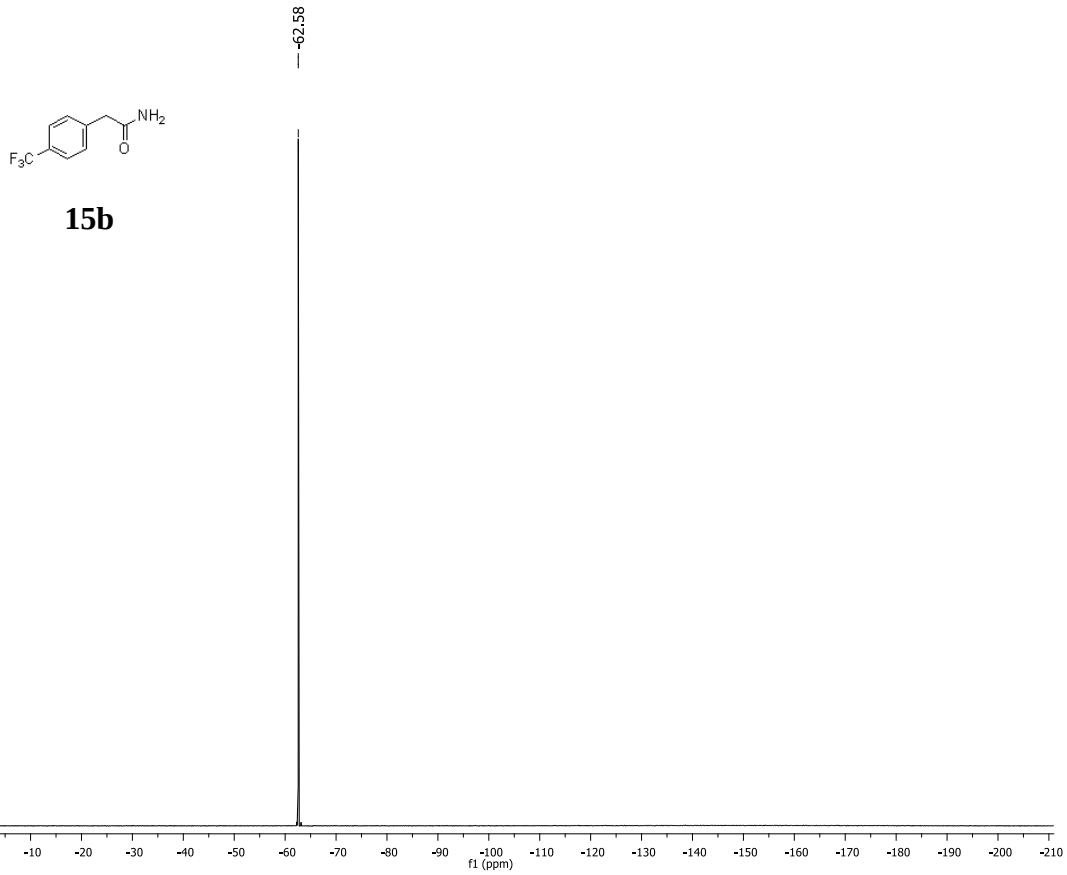

2.01
2.00
0.98
0.99
2.03
f1 (ppm)


172.1
138.7
129.9
129.7
127.3
125.9
125.9
125.9
125.8
125.1
122.9
120.8
77.3
77.0
76.7
42.8
-0.0

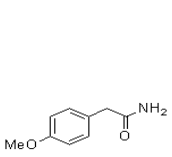
NH2
O
F3C

15b

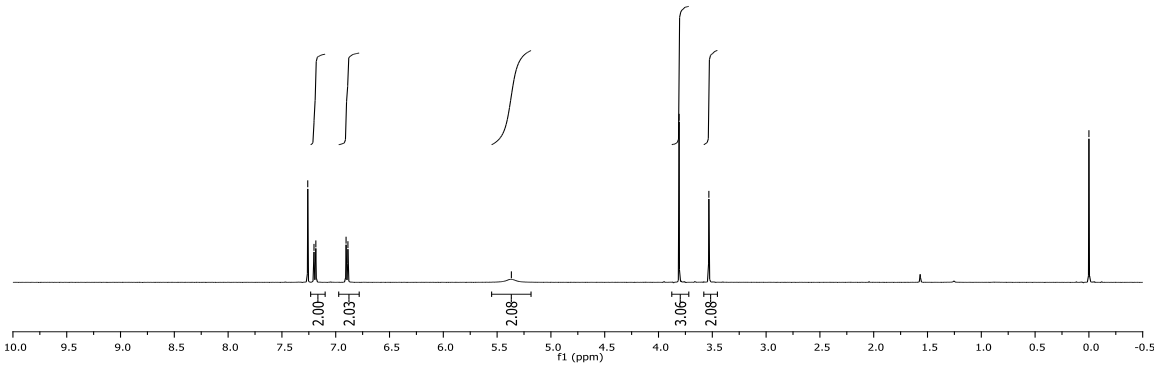

f1 (ppm)


-62.58
NH2
O
F3C
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

15b

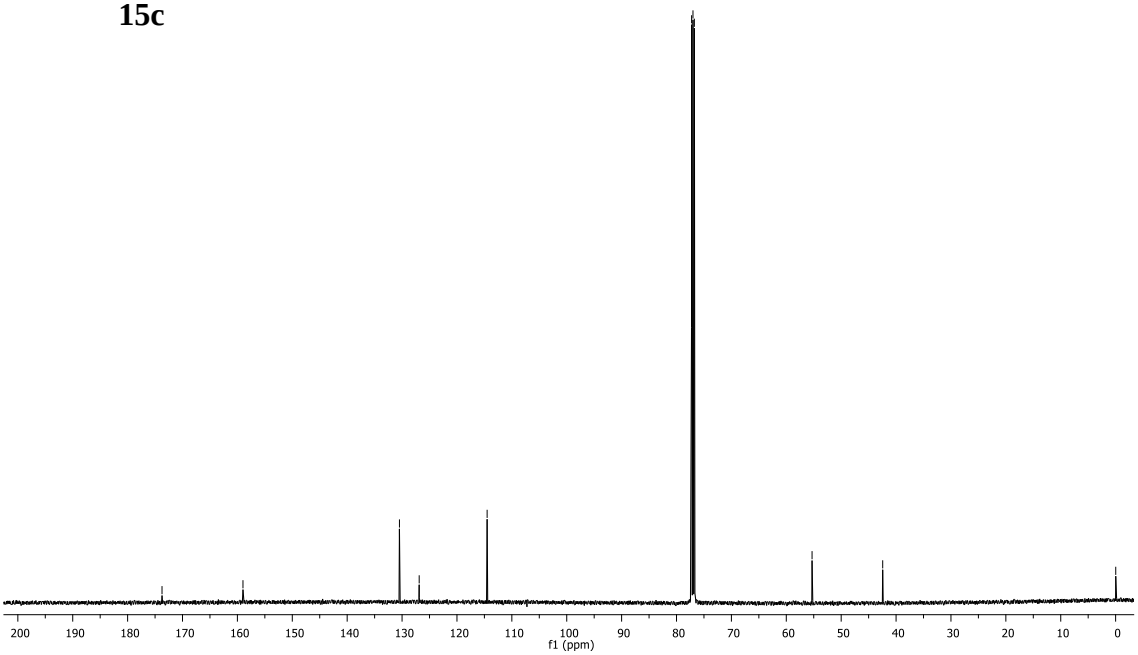

7.26
7.20
7.18
6.90
6.89
5.37
3.81
3.53
0.00
NH2
O
MeO

15c


2.00
2.03
2.08
3.06
2.08
f1 (ppm)

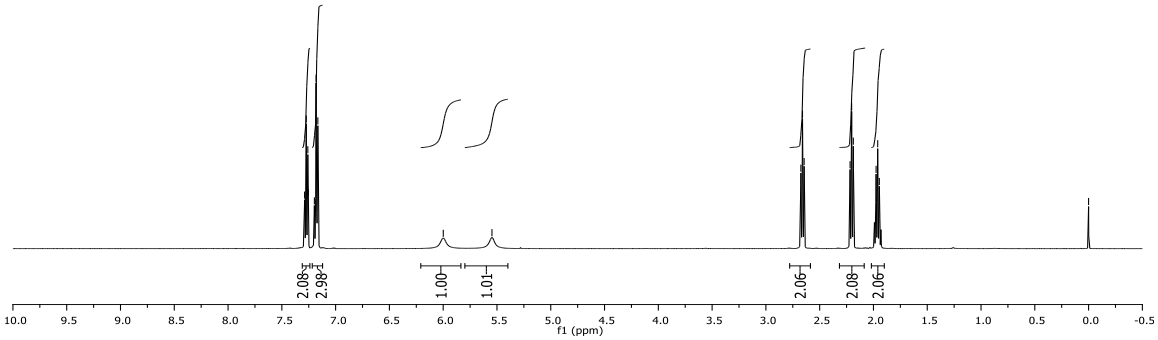

173.7
159.0
130.5
126.9
114.5
77.3
77.0
76.7
55.3
42.4
0.0
NH2
O
MeO

15c

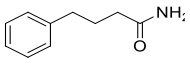

f1 (ppm)


7.29
7.27
7.26
7.25
7.20
7.18
7.17
6.00
5.55
2.67
2.66
2.64
2.22
2.20
2.19
1.98
1.96
1.95
0.00
NH2
O

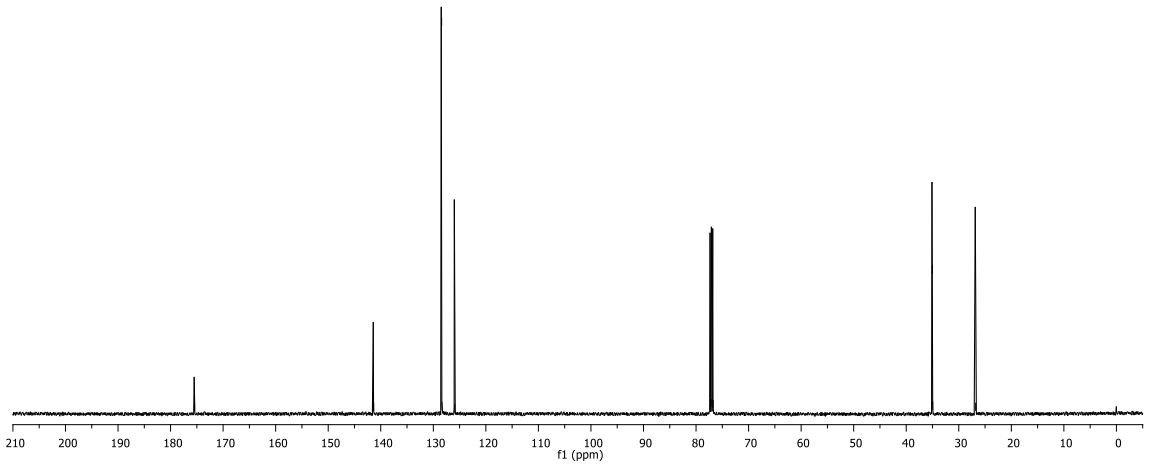
15d

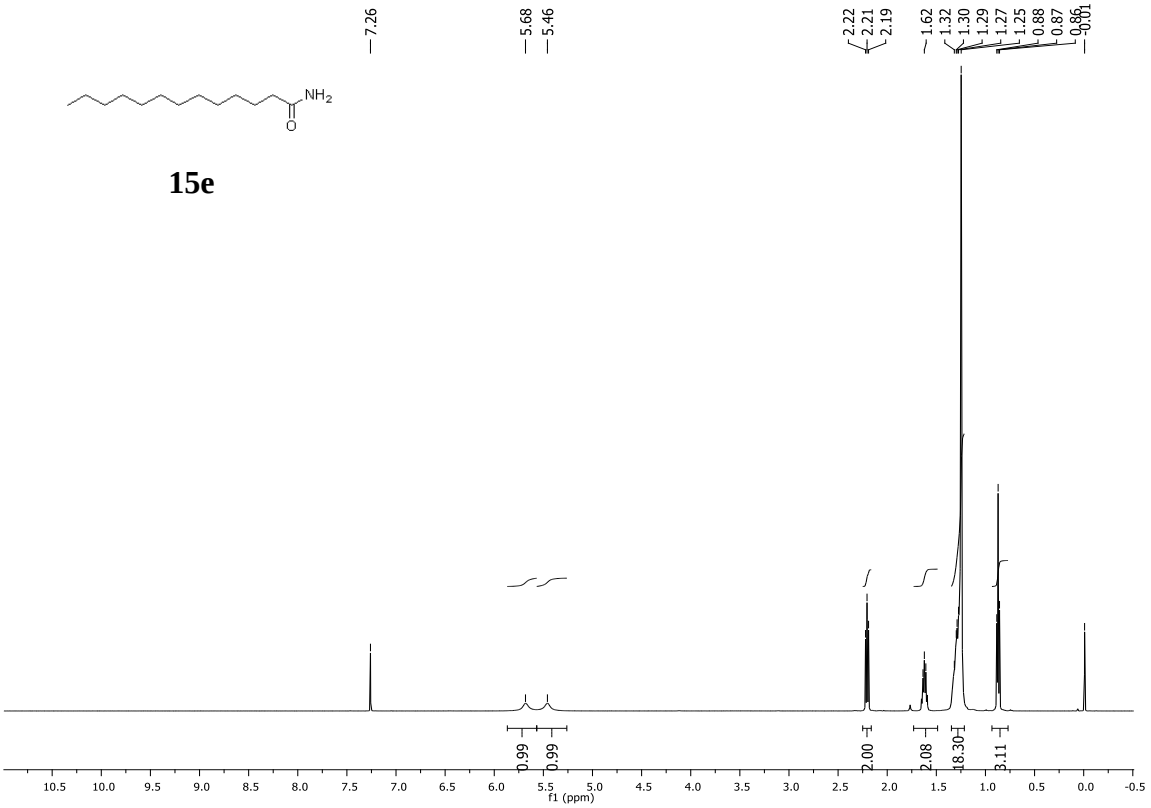

2.08
2.98
1.00
1.01
2.06
2.08
2.06
f1 (ppm)


175.4
141.3
128.4
128.3
125.9
77.3
77.0
76.7
35.0
34.9
26.8

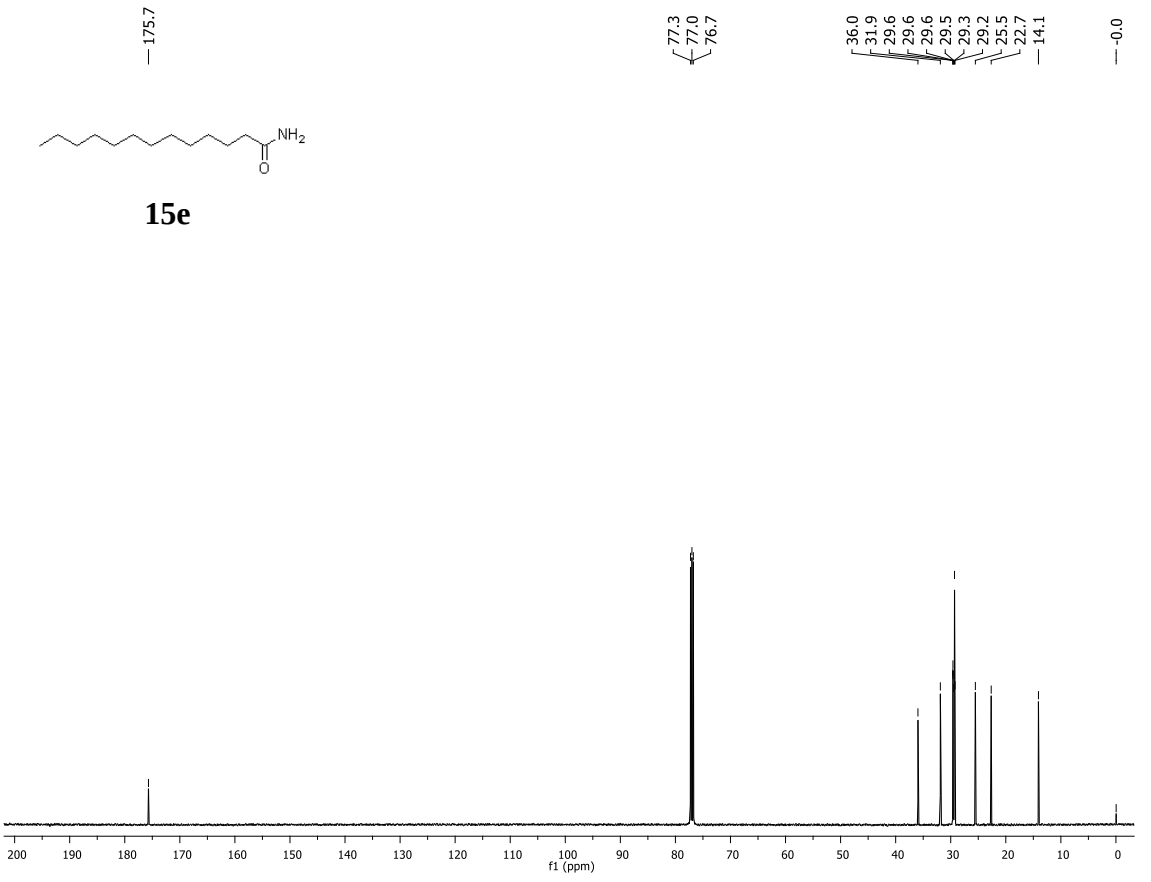

NH2
O

15d

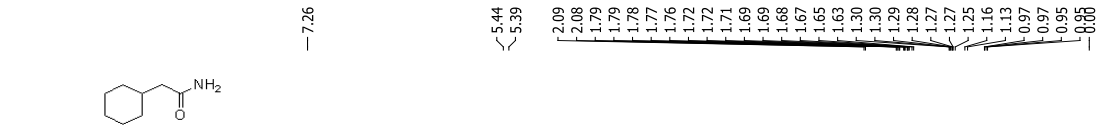

f1 (ppm)


7.26
5.68
5.46
2.22
2.21
2.19
1.62
1.32
1.30
1.29
1.27
1.25
0.88
0.87
0.86
0.01
NH2
O
0.99
0.99
2.00
2.08
18.30
3.11
f1 (ppm)

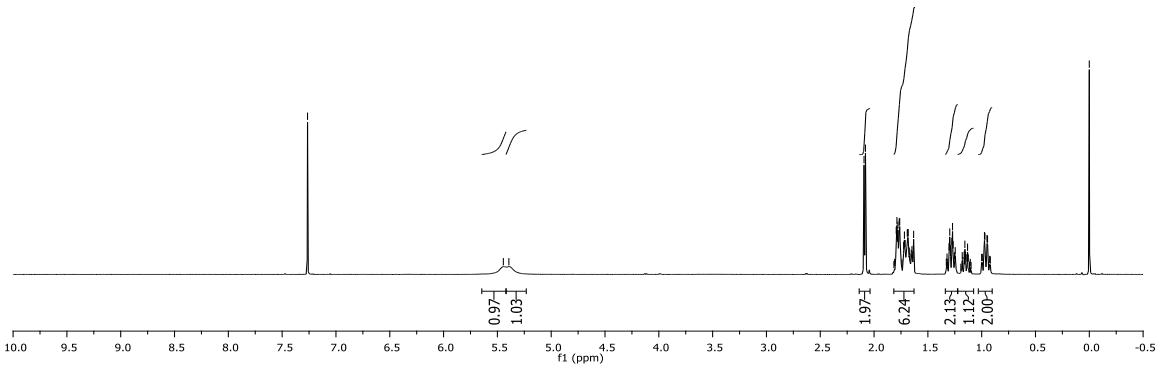
15e


175.7
77.3
77.0
76.7
36.0
31.9
29.6
29.6
29.6
29.5
29.3
29.2
25.5
22.7
14.1
-0.0
NH2
O
f1 (ppm)

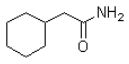
15e


7.26
5.44
5.39
2.09
2.08
1.79
1.79
1.78
1.77
1.76
1.72
1.72
1.71
1.69
1.69
1.68
1.67
1.65
1.63
1.30
1.29
1.28
1.27
1.27
1.25
1.16
1.13
0.97
0.97
0.95
0.00
NH2
O

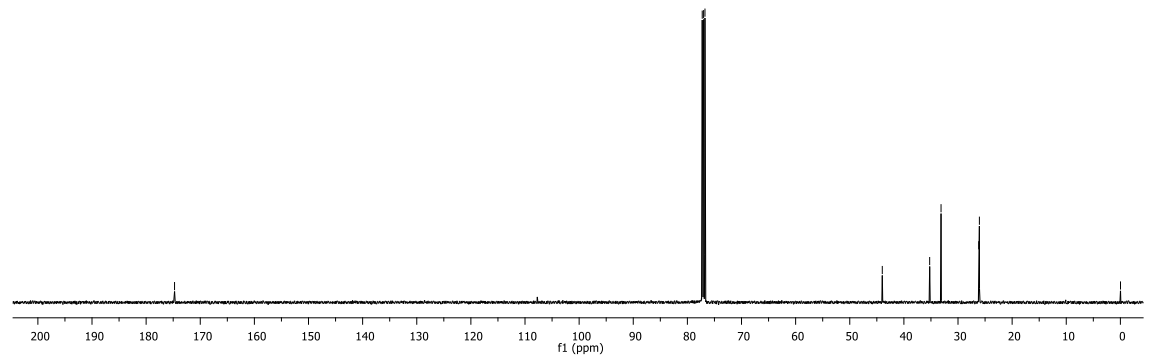
15f

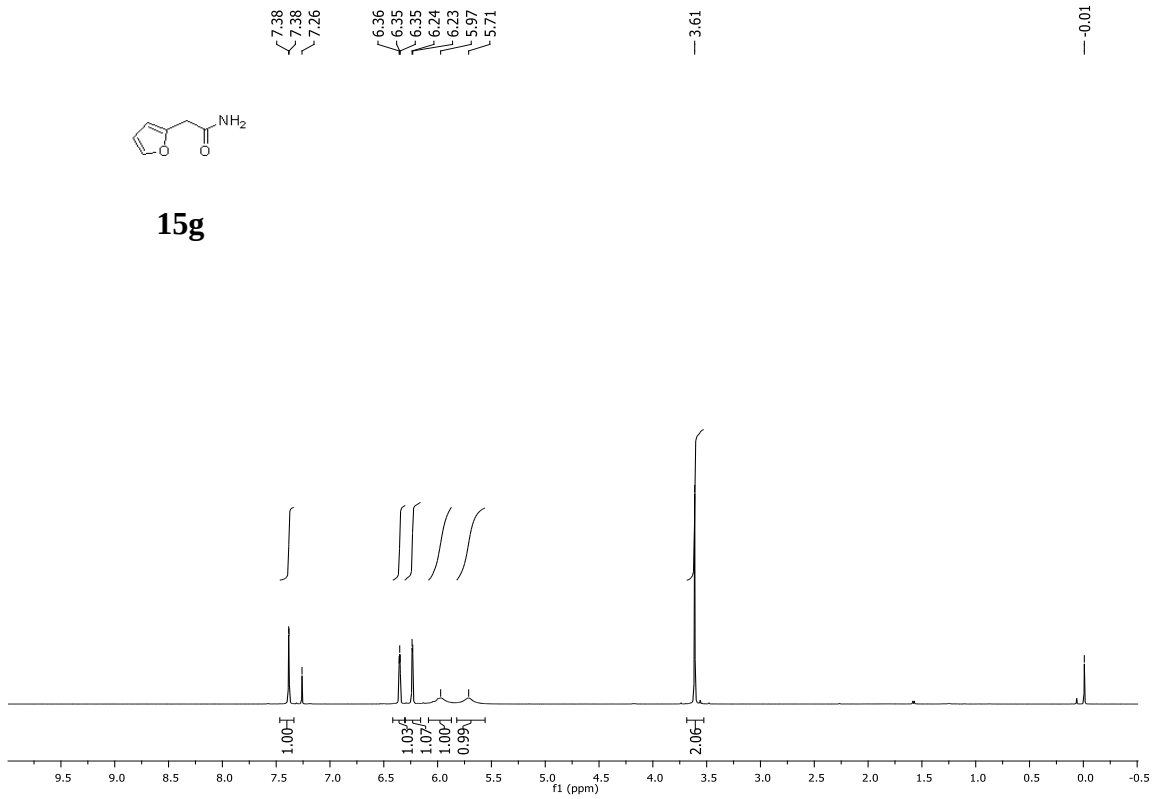

0.97
1.03
1.97
6.24
2.13
1.12
2.00
f1 (ppm)


174.7
77.3
77.0
76.8
44.0
35.2
33.1
26.2
26.0
-0.0

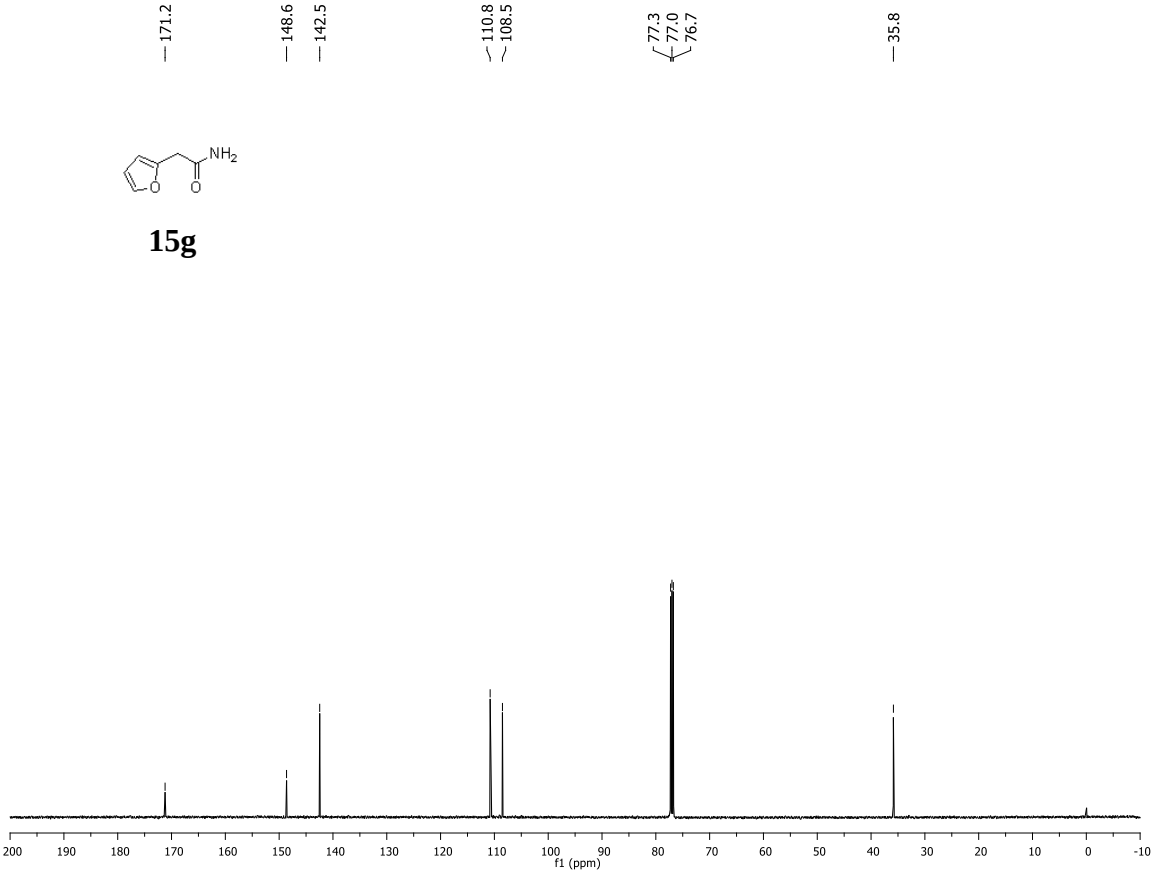

NH2
O

15f


f1 (ppm)


7.38
7.38
7.26
6.36
6.35
6.35
6.24
6.23
5.97
5.71
3.61
-0.01
NH2
O
O
1.00
1.03
1.07
1.00
0.99
2.06
f1 (ppm)

15g

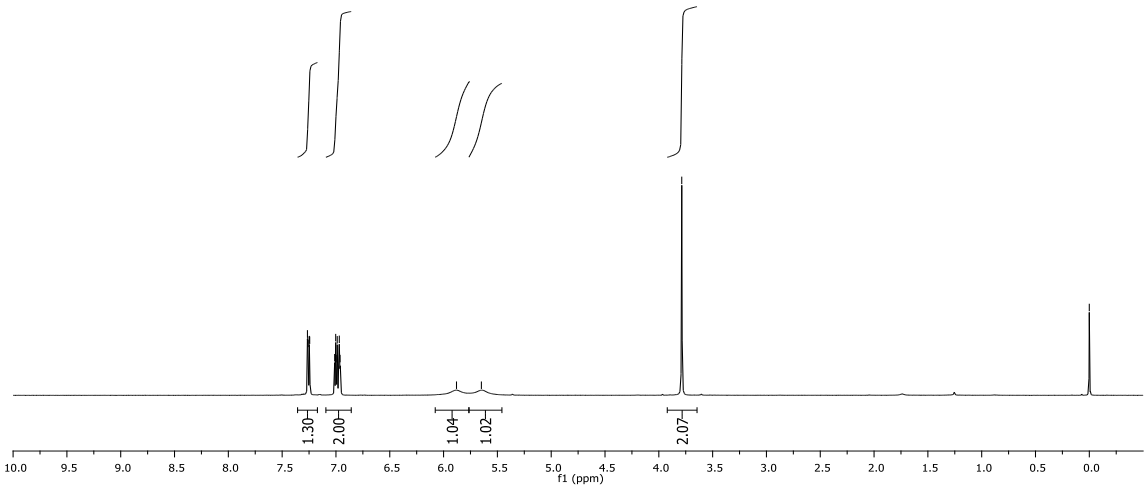

171.2
148.6
142.5
110.8
108.5
77.3
77.0
76.7
35.8
NH2
O
O
f1 (ppm)

15g

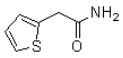

7.27
7.26
7.26
7.25
7.24
7.01
7.00
7.00
6.99
6.97
6.96
5.88
5.65
3.79
0.00

NH2
S
O

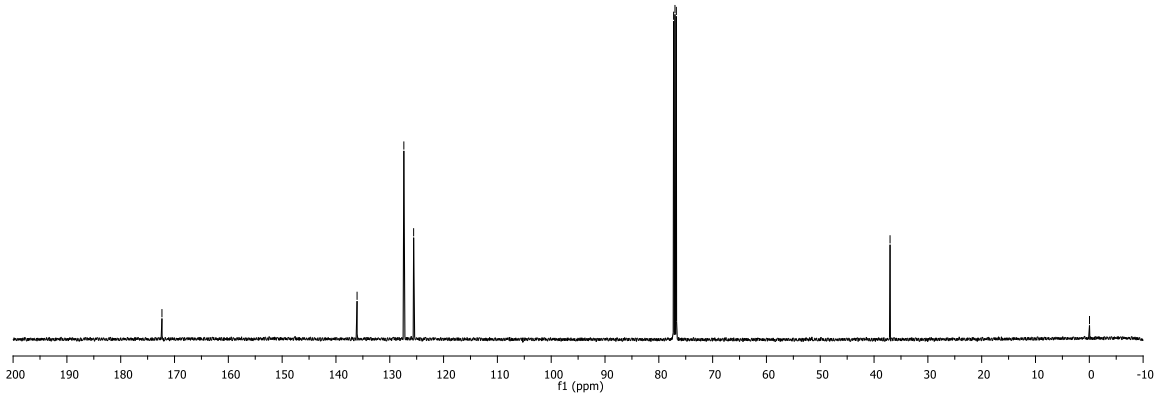
15h

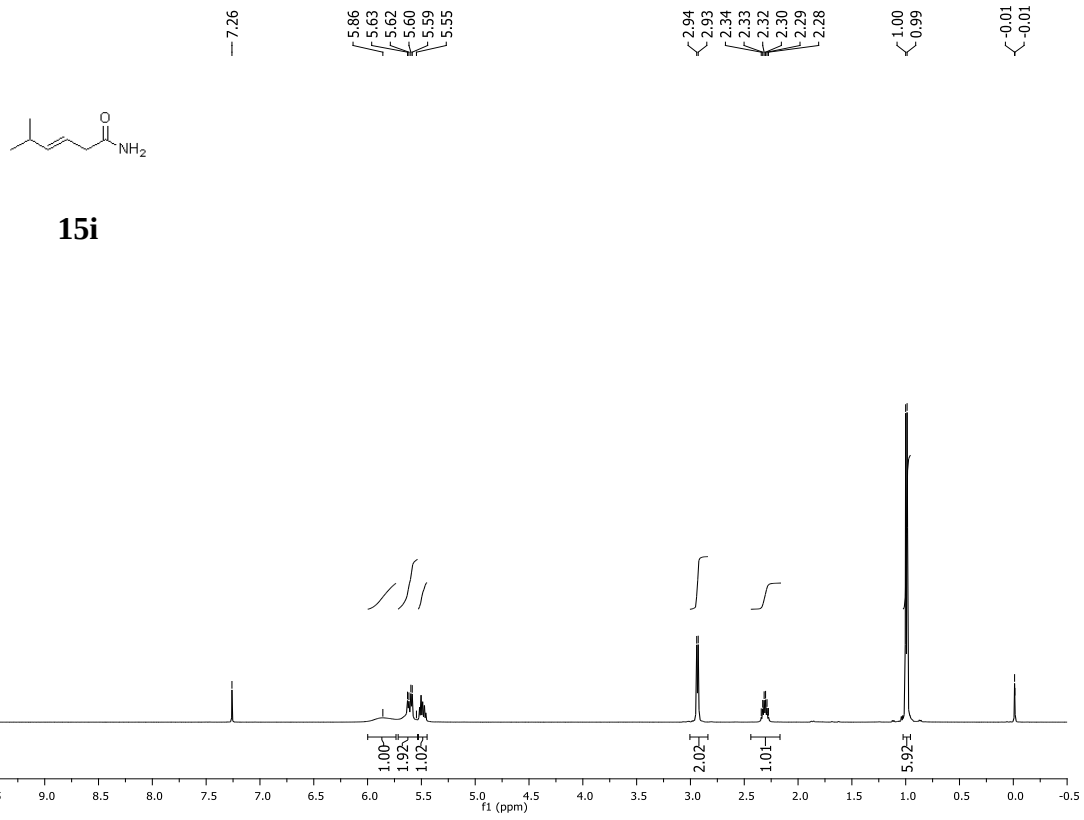

1.30
2.00
1.04
1.02
2.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.3
136.1
127.4
125.6
77.3
77.0
76.7
37.0
-0.0

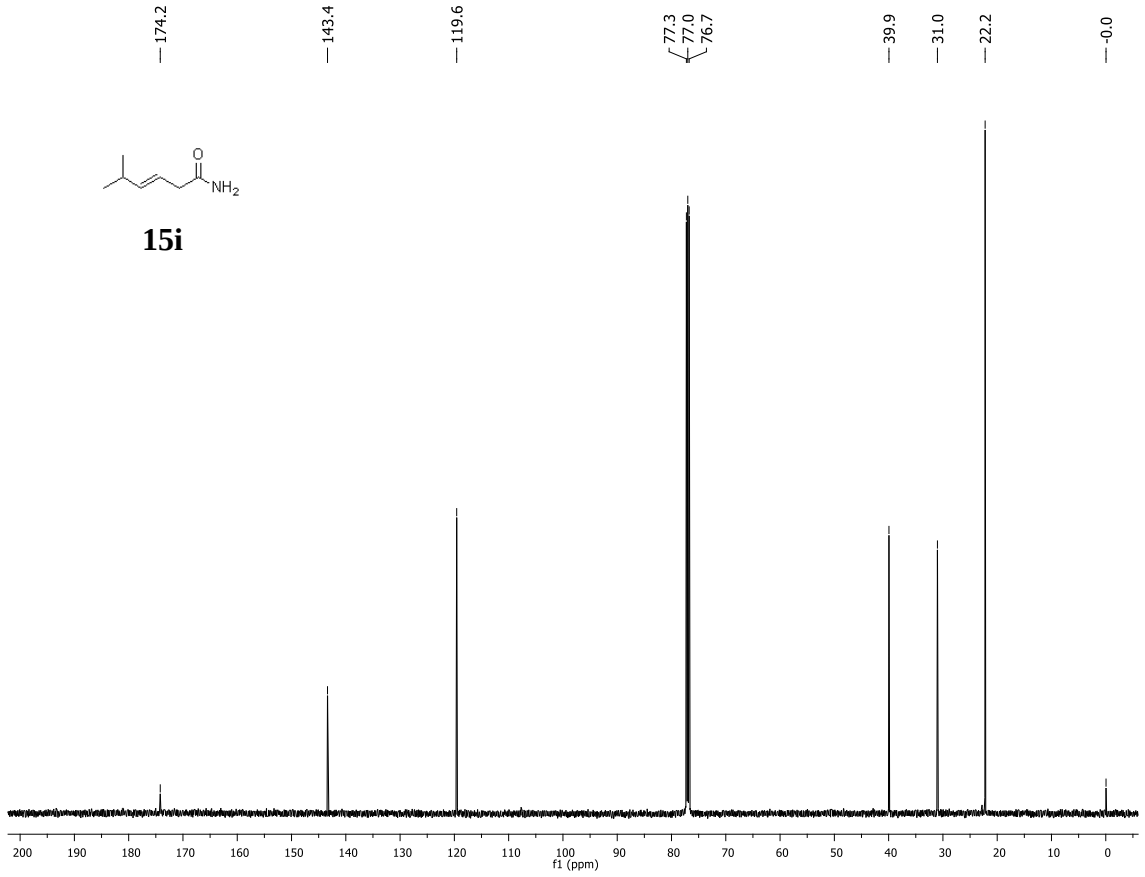

NH2
S
O

15h

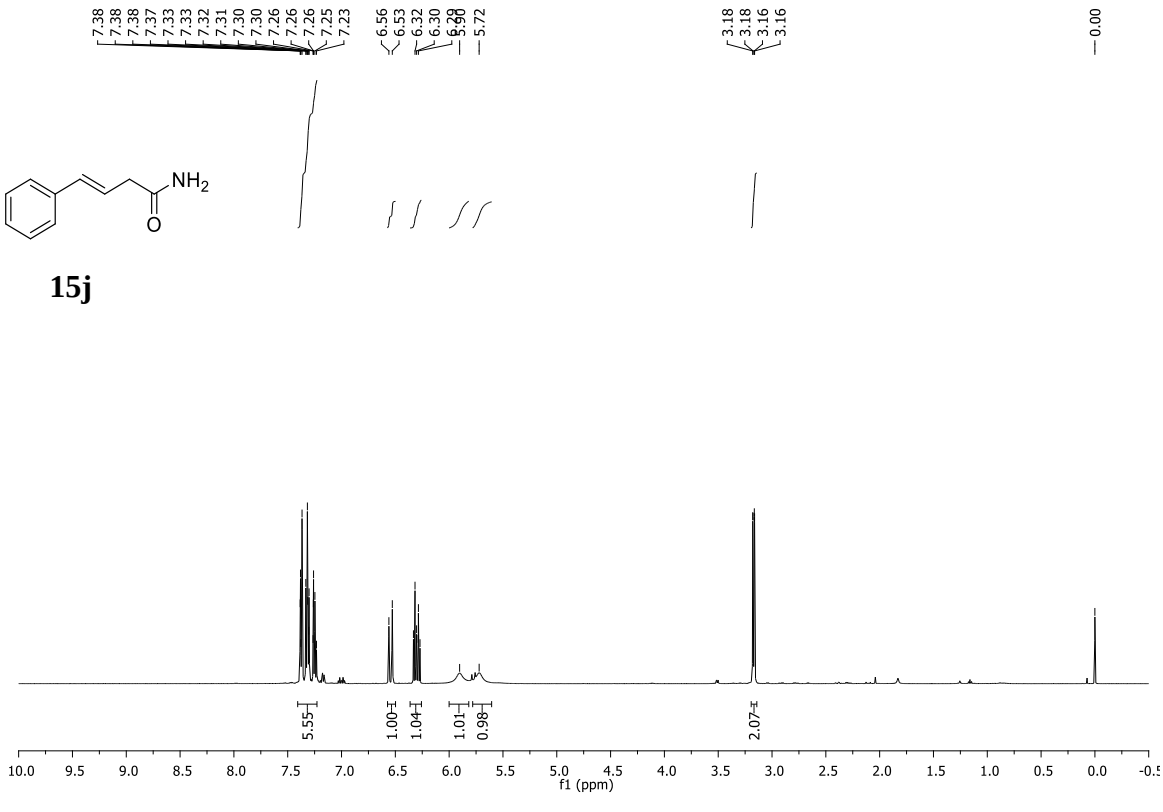

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
5.86
5.63
5.62
5.60
5.59
5.55
2.94
2.93
2.34
2.33
2.32
2.30
2.29
2.28
1.00
0.99
-0.01
-0.01
O
NH2
1.00
1.92
1.02
2.02
1.01
5.92
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)

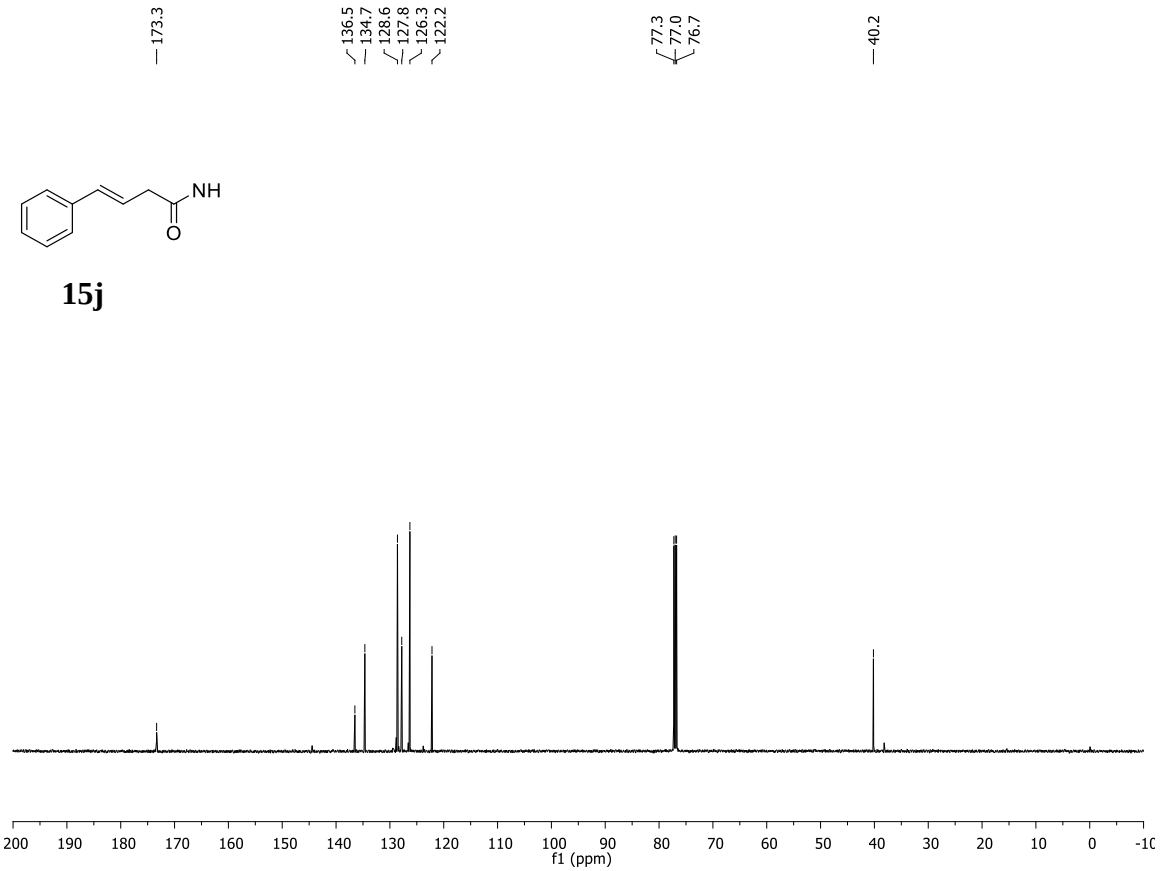
15i


174.2
143.4
119.6
77.3
77.0
76.7
39.9
31.0
22.2
-0.0
O
NH2
f1 (ppm)

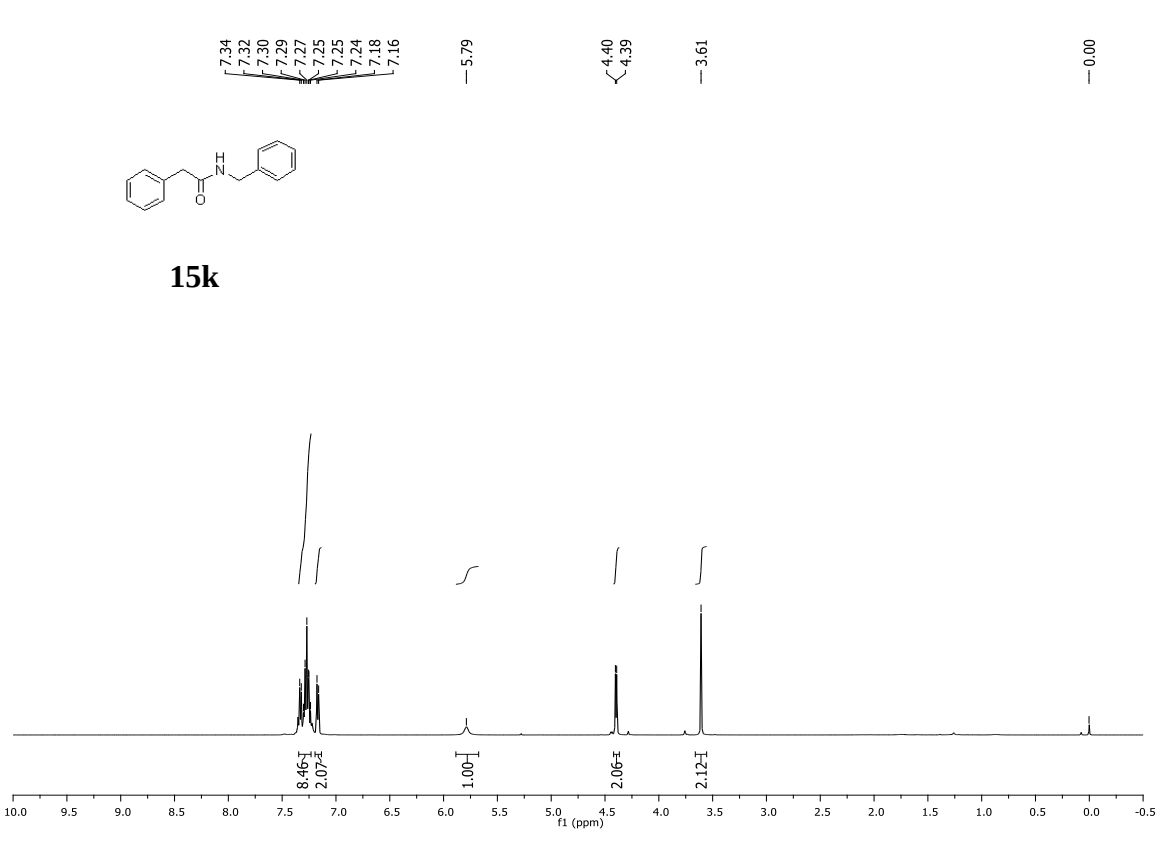
15i


7.38
7.38
7.38
7.37
7.33
7.33
7.32
7.31
7.30
7.30
7.26
7.26
7.25
7.23
6.56
6.53
6.32
6.30
5.90
5.72
3.18
3.18
3.16
3.16
0.00
NH2
O
5.55
1.00
1.04
1.01
0.98
2.07
f1 (ppm)

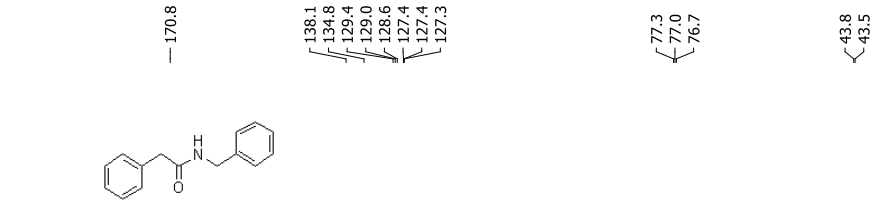
15j


173.3
136.5
134.7
128.6
127.8
126.3
122.2
77.3
77.0
76.7
40.2
NH
O
f1 (ppm)

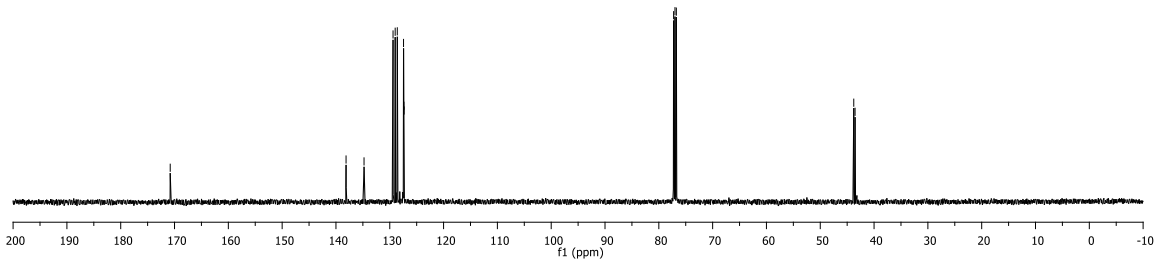
15j

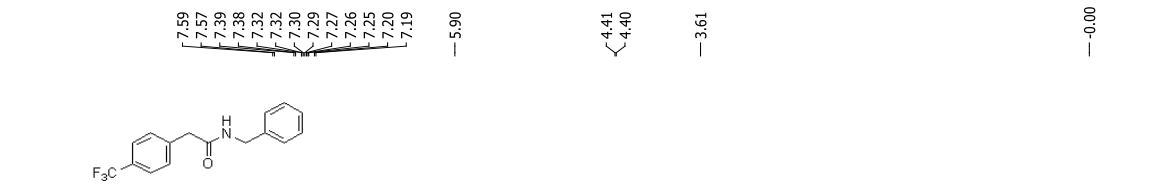

7.34
7.32
7.30
7.29
7.27
7.25
7.25
7.24
7.18
7.16
5.79
4.40
4.39
3.61
0.00
N
H
O
8.46
2.07
1.00
2.06
2.12
f1 (ppm)

15k

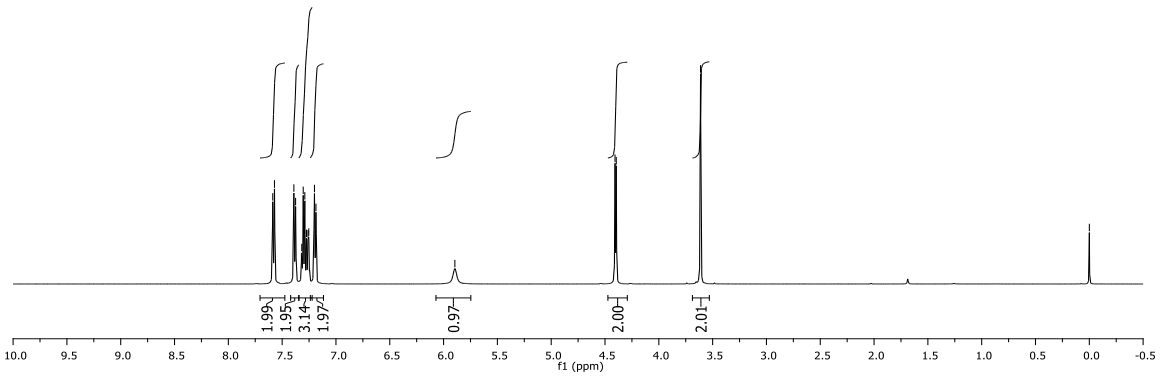

170.8
138.1
134.8
129.4
129.0
128.6
127.4
127.4
127.3
77.3
77.0
76.7
43.8
43.5

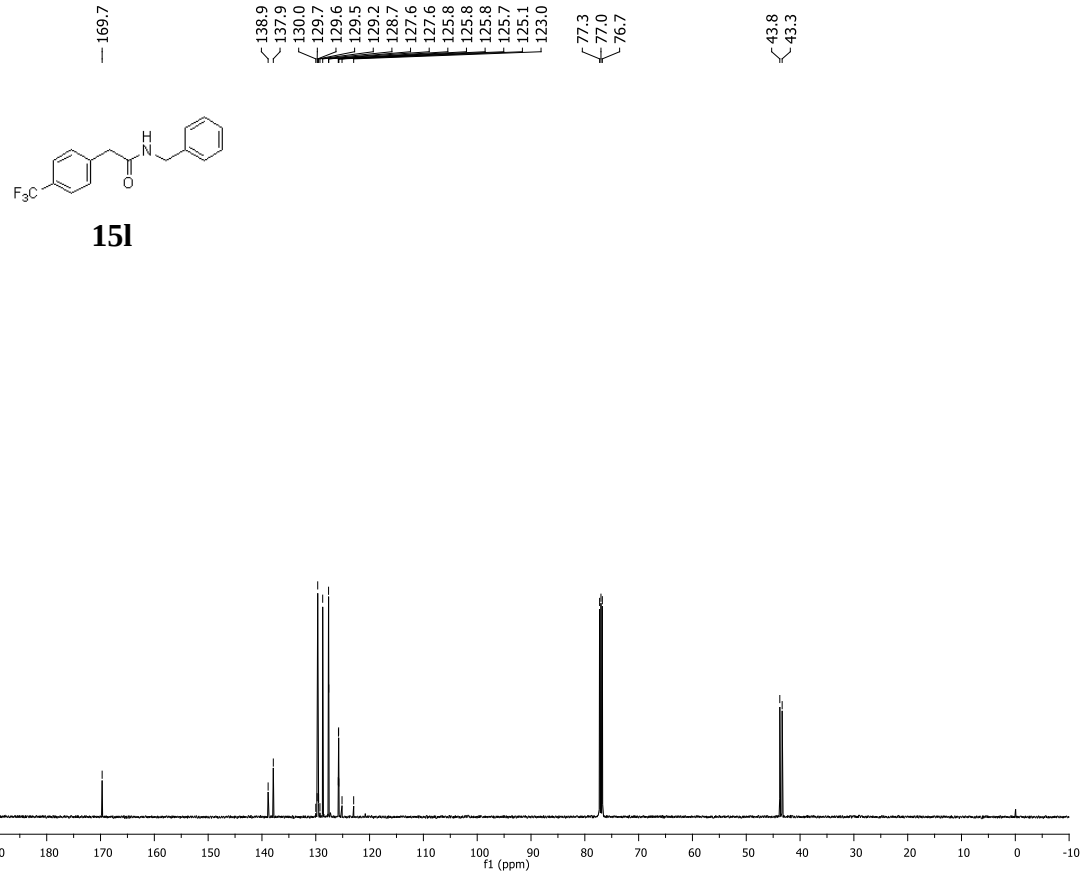
15k


f1 (ppm)

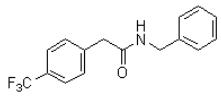

7.59
7.57
7.39
7.38
7.32
7.32
7.30
7.29
7.27
7.26
7.25
7.20
7.19
5.90
4.41
4.40
3.61
-0.00

15l


1.99
1.95
3.14
1.97
0.97
2.00
2.01
f1 (ppm)

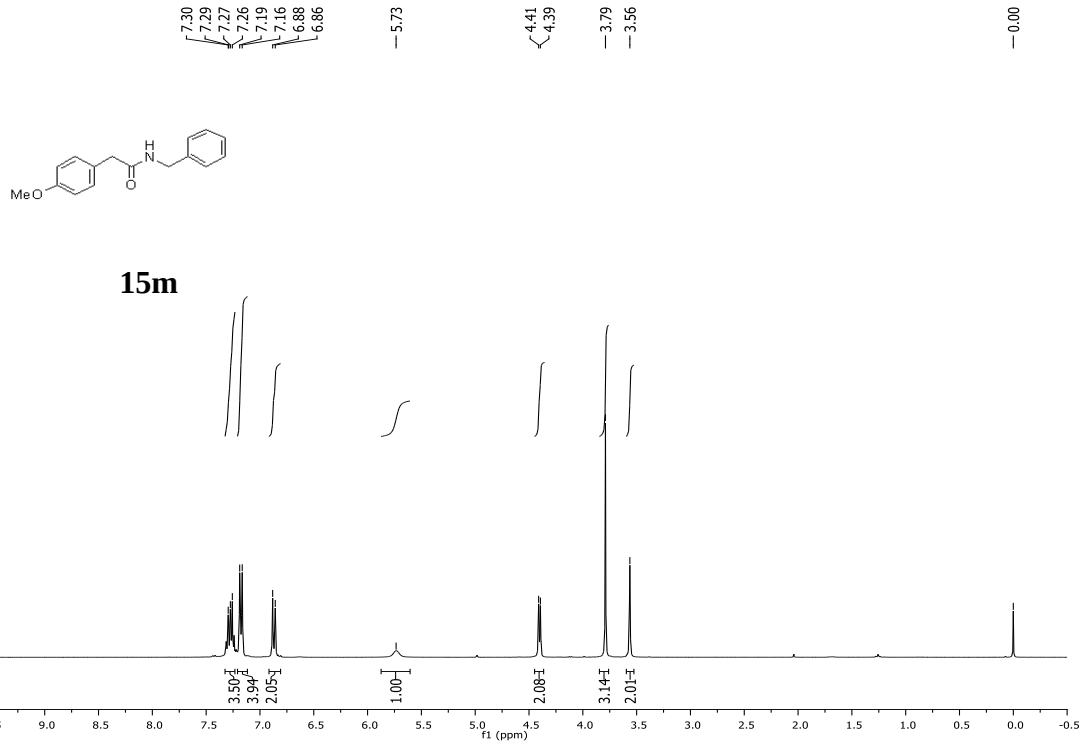

169.7
138.9
137.9
130.0
129.7
129.6
129.5
129.2
128.7
127.6
127.6
125.8
125.8
125.8
125.7
125.1
123.0
77.3
77.0
76.7
43.8
43.3
H
N
O
F3C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

15l

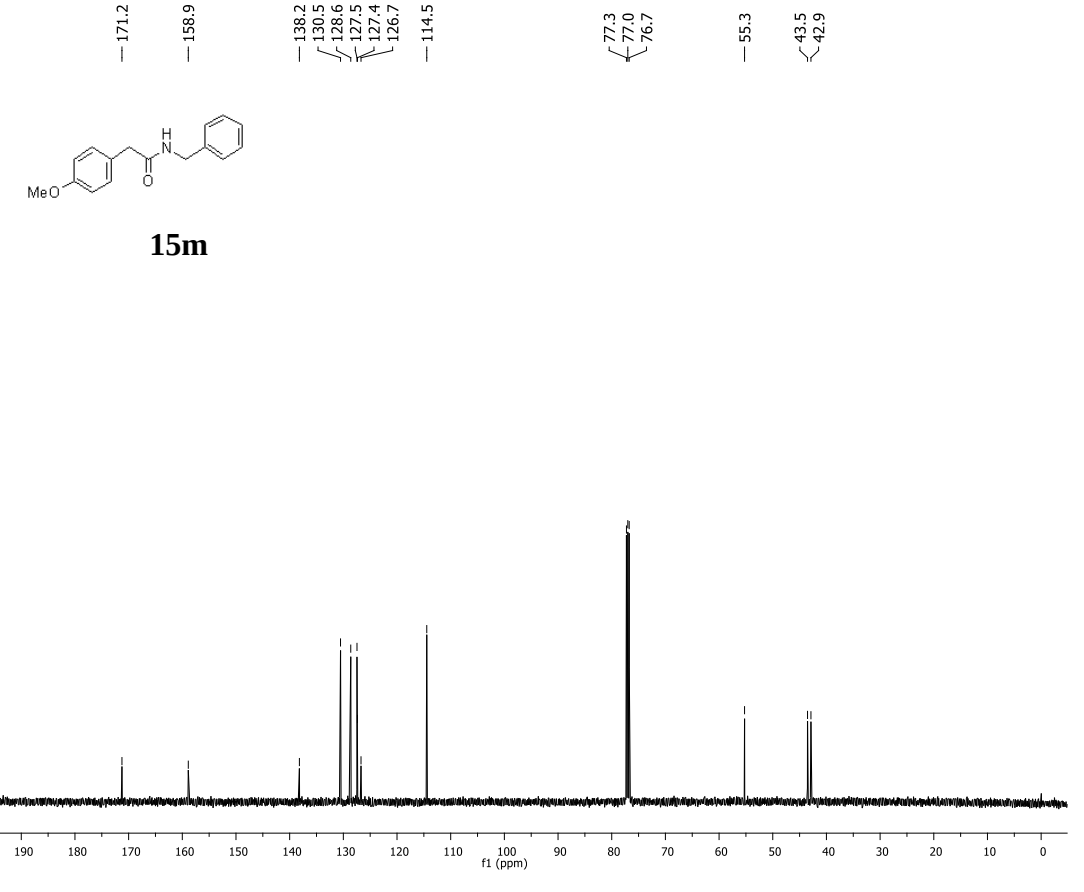

F3C
H
N
O

15l

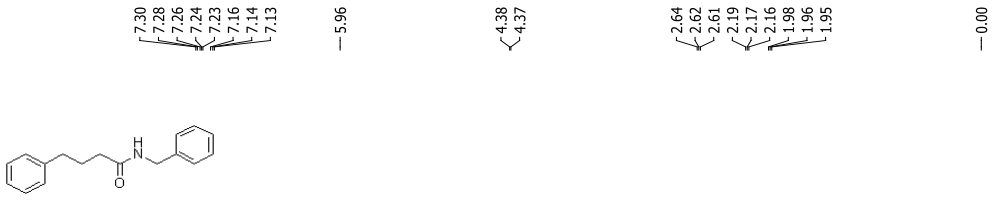
-62.52
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


7.30
7.29
7.27
7.26
7.19
7.16
6.88
6.86
5.73
4.41
4.39
3.79
3.56
0.00
MeO
H
N
O
3.50
3.94
2.05
1.00
2.08
3.14
2.01
f1 (ppm)

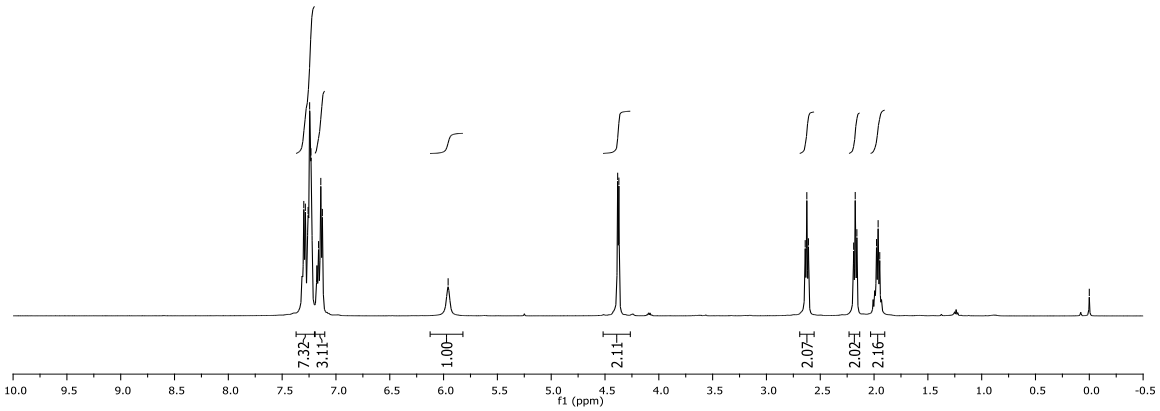
15m


171.2
158.9
138.2
130.5
128.6
127.5
127.4
126.7
114.5
77.3
77.0
76.7
55.3
43.5
42.9
MeO
H
N
O
f1 (ppm)

15m

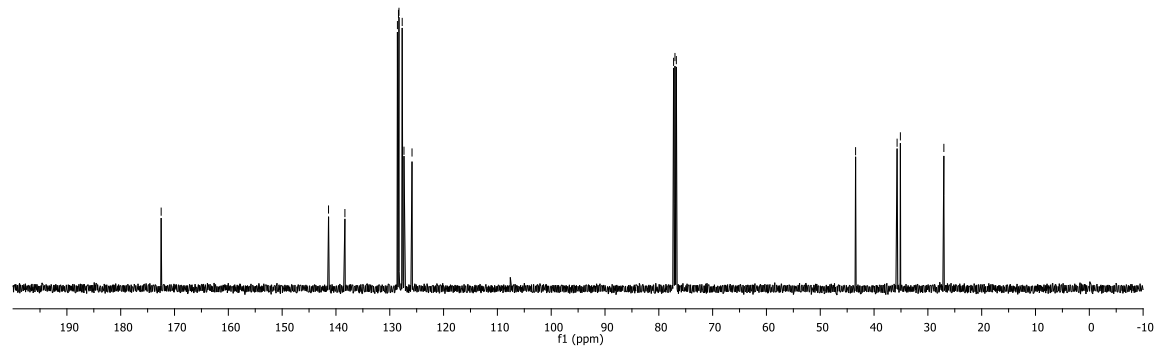

7.30
7.28
7.26
7.24
7.23
7.16
7.14
7.13
5.96
4.38
4.37
2.64
2.62
2.61
2.19
2.17
2.16
1.98
1.96
1.95
0.00

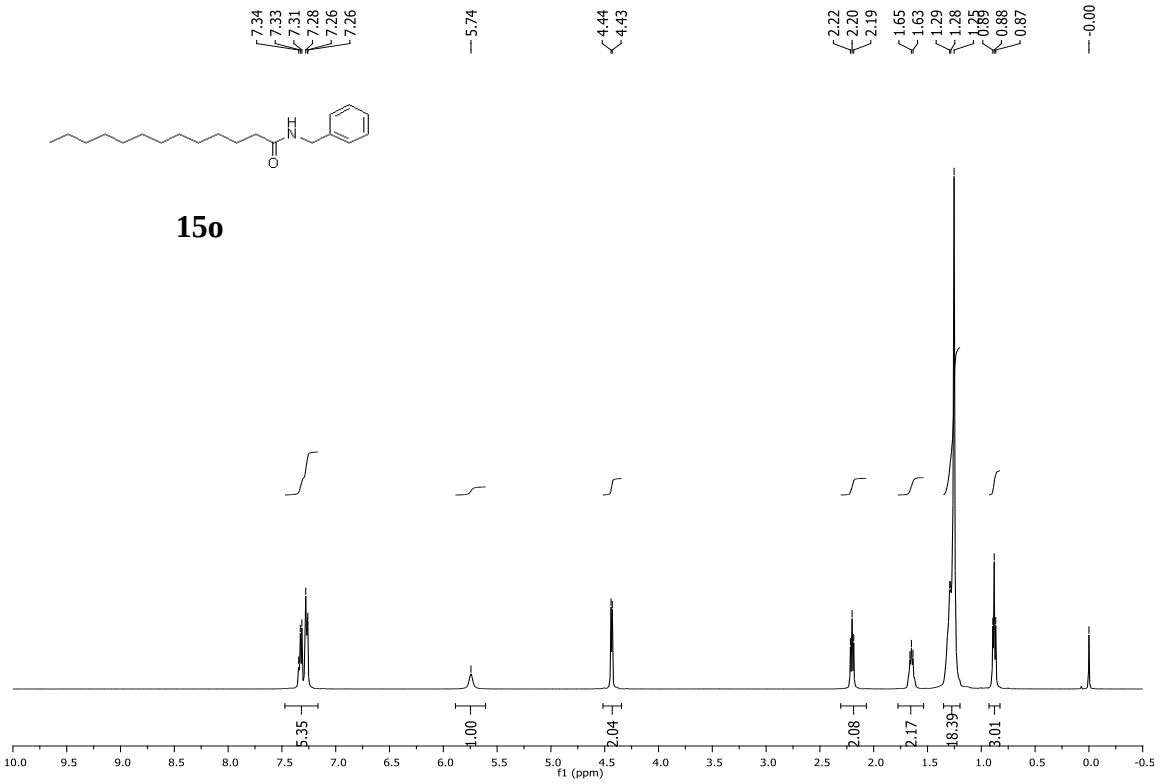
15n


7.32
3.11
1.00
2.11
2.07
2.02
2.16
f1 (ppm)

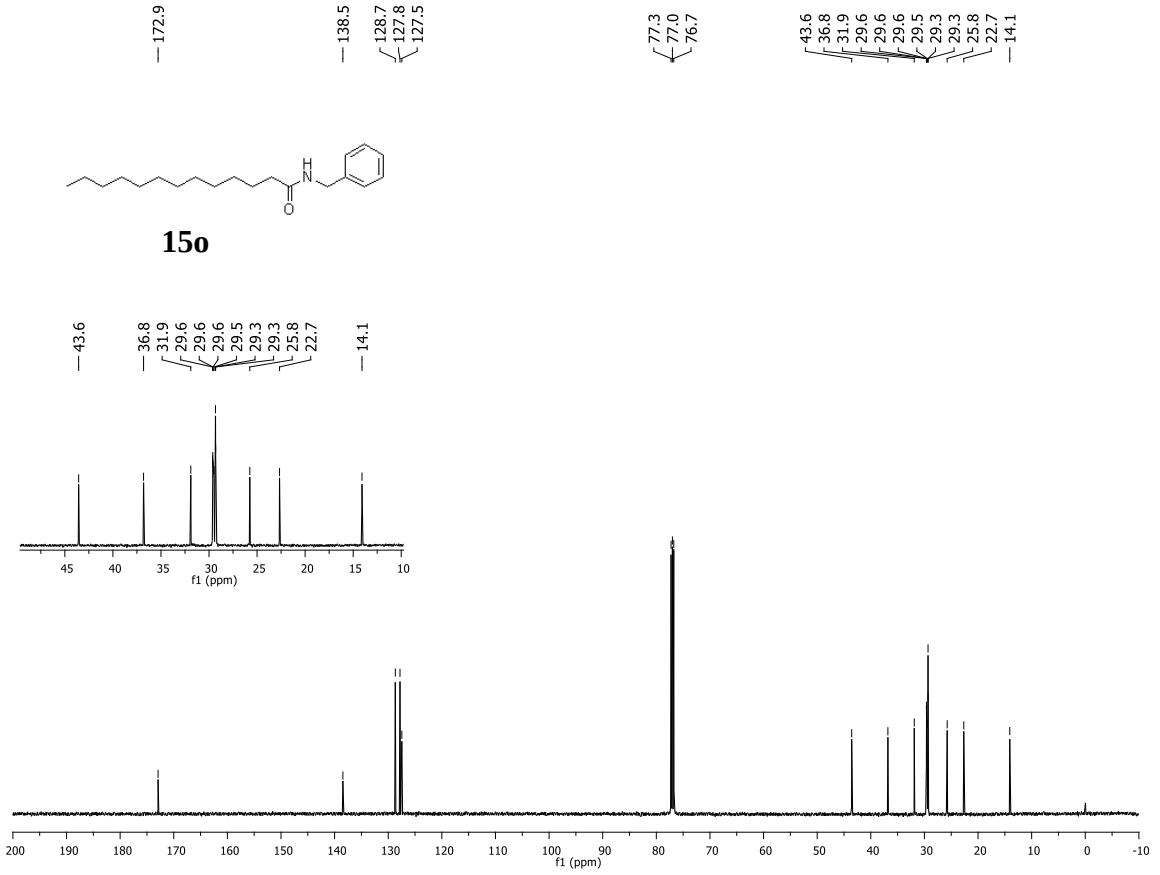

172.5
141.4
138.3
128.6
128.4
128.3
127.7
127.4
125.9
77.3
77.0
76.7
43.4
35.7
35.1
27.0

15n


f1 (ppm)

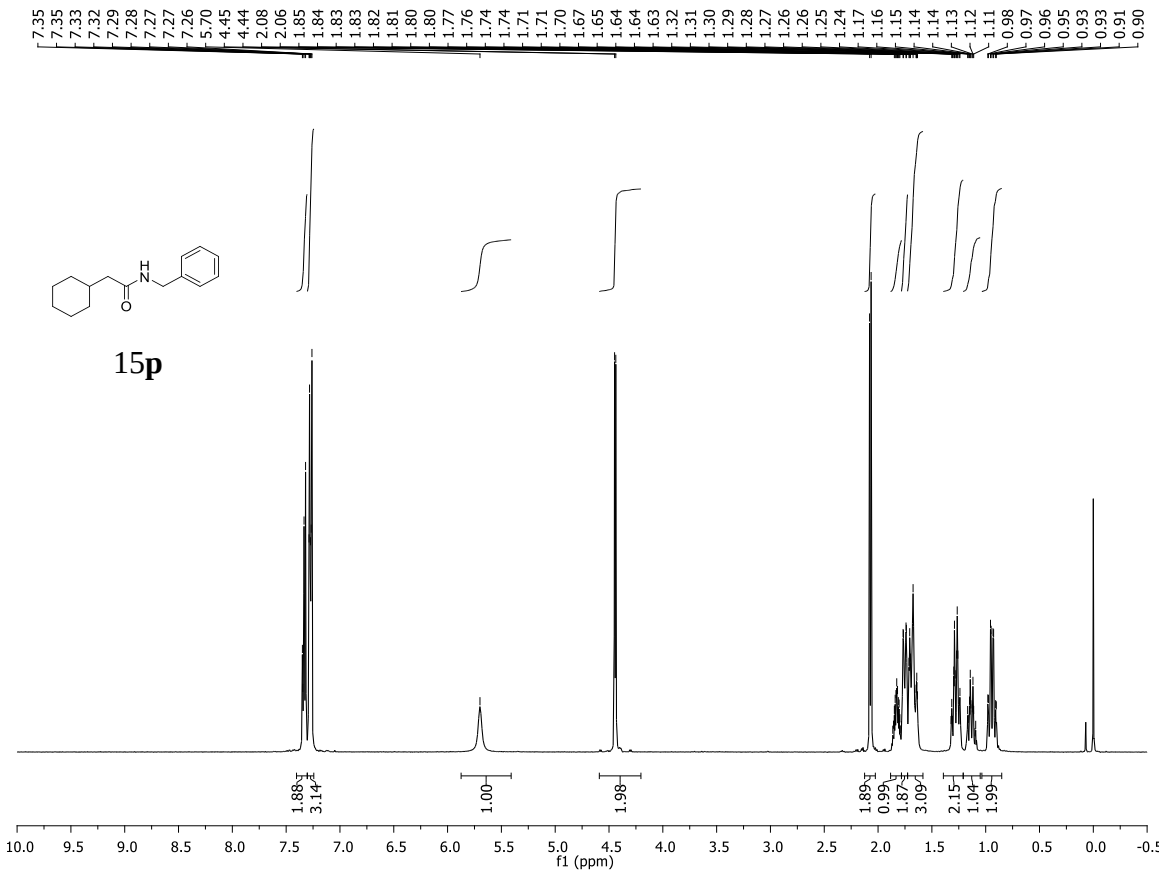

7.34
7.33
7.31
7.28
7.26
7.26
5.74
4.44
4.43
2.22
2.20
2.19
1.65
1.63
1.29
1.28
0.88
0.87
-0.00
5.35
1.00
2.04
2.08
2.17
18.39
3.01
f1 (ppm)

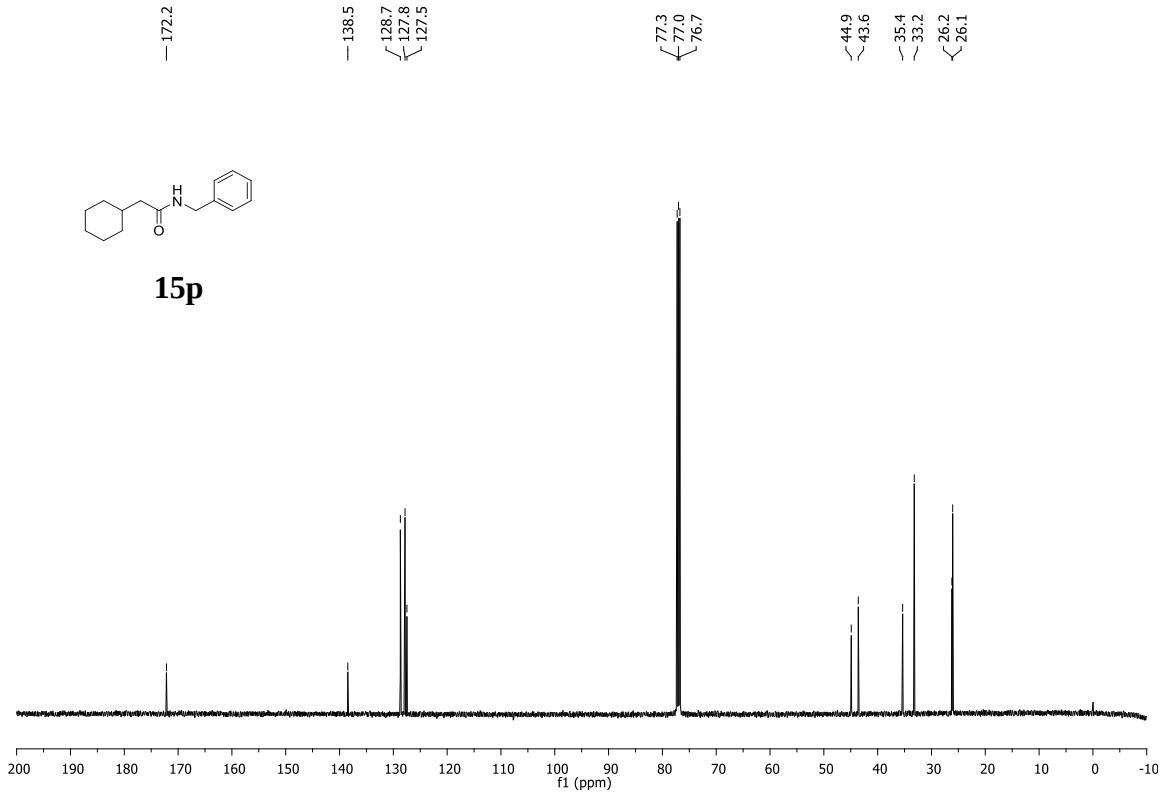
15o

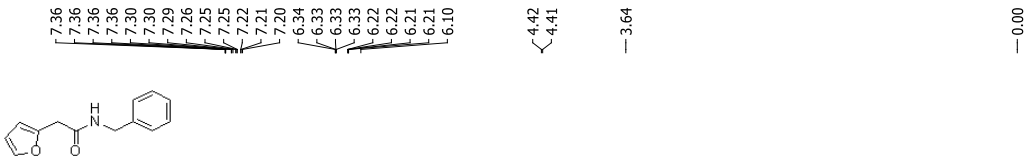

172.9
138.5
128.7
127.8
127.5
77.3
77.0
76.7
43.6
36.8
31.9
29.6
29.6
29.6
29.5
29.3
29.3
25.8
22.7
14.1
f1 (ppm)

15o

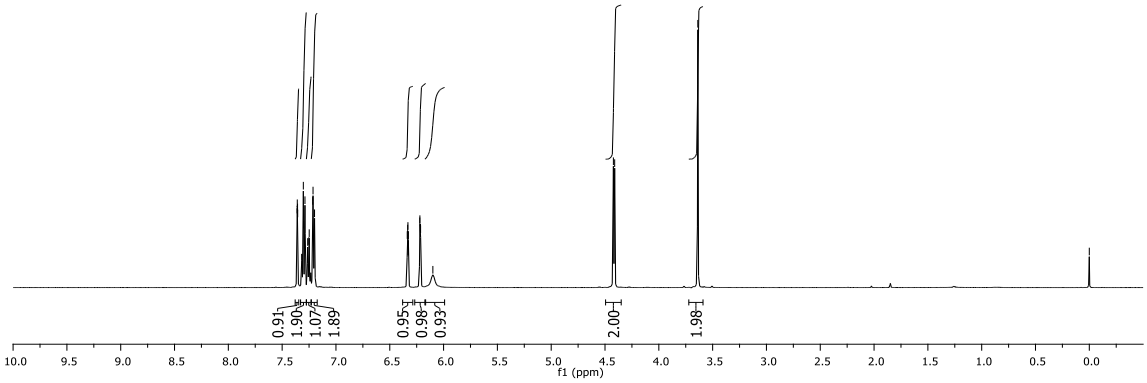
43.6
36.8
31.9
29.6
29.6
29.6
29.5
29.3
29.3
25.8
22.7
14.1
f1 (ppm)


7.35 7.35 7.33 7.32 7.29 7.28 7.27 7.27 7.26 5.70 4.45 4.44 2.08 2.06 1.85 1.84 1.83 1.83 1.82 1.81 1.80 1.80 1.77 1.76 1.74 1.74 1.71 1.71 1.70 1.67 1.65 1.64 1.64 1.63 1.32 1.31 1.30 1.29 1.28 1.27 1.26 1.26 1.25 1.24 1.17 1.16 1.15 1.14 1.14 1.13 1.12 1.11 0.98 0.97 0.96 0.95 0.93 0.93 0.91 0.90
15p
1.88 3.14 1.00 1.98 1.89 0.99 1.87 3.09 2.15 1.04 1.99
f1 (ppm)

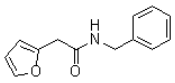

172.2 138.5 128.7 127.8 127.5 77.3 77.0 76.7 44.9 43.6 35.4 33.2 26.2 26.1
15p
f1 (ppm)


7.36
7.36
7.36
7.36
7.30
7.30
7.29
7.26
7.25
7.25
7.22
7.21
7.20
6.34
6.33
6.33
6.33
6.22
6.22
6.21
6.21
6.10
4.42
4.41
3.64
0.00

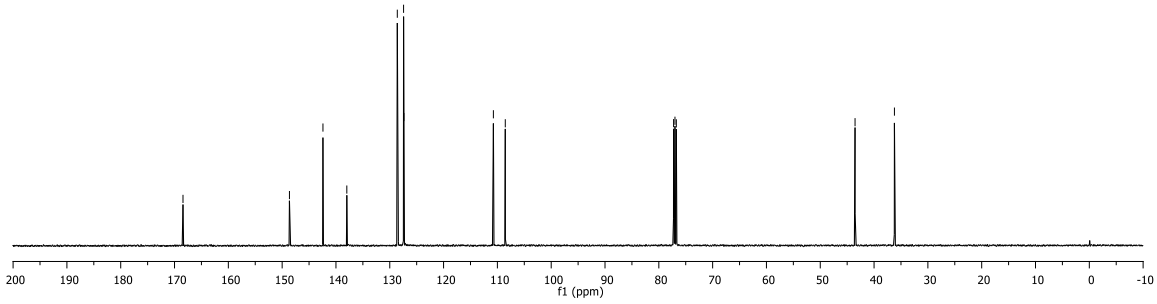
15q


0.91
1.90
1.07
1.89
0.95
0.98
0.93
2.00
1.98
f1 (ppm)

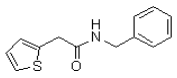

168.4
148.6
142.4
138.0
128.6
127.4
127.4
110.7
108.5
77.3
77.0
76.7
43.5
36.2



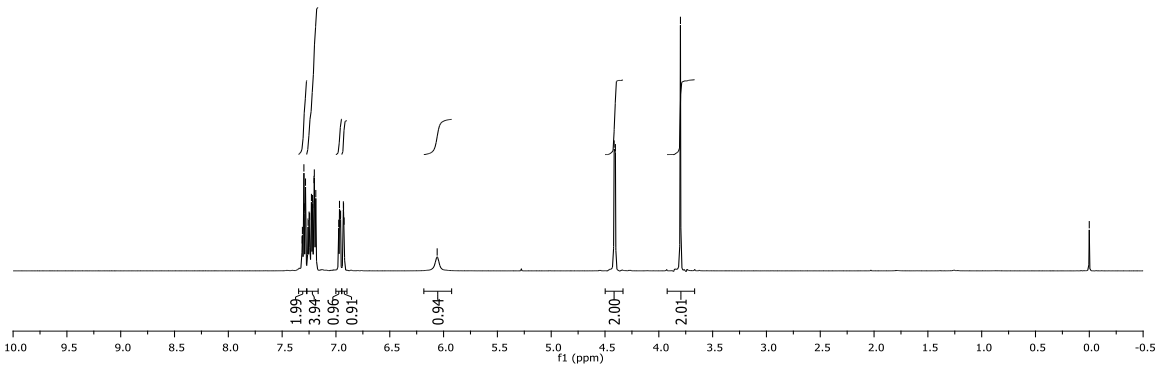
15q


f1 (ppm)

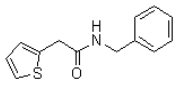

7.31
7.31
7.30
7.29
7.28
7.26
7.25
7.24
7.23
7.23
7.22
7.22
7.20
7.20
7.19
6.97
6.97
6.96
6.96
6.93
6.93
6.92
6.06
4.41
4.40
3.80
0.00



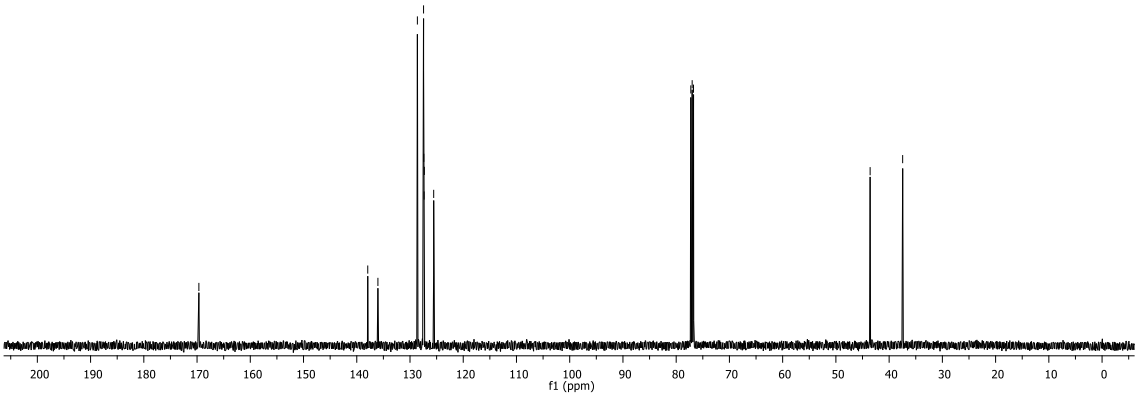
15r

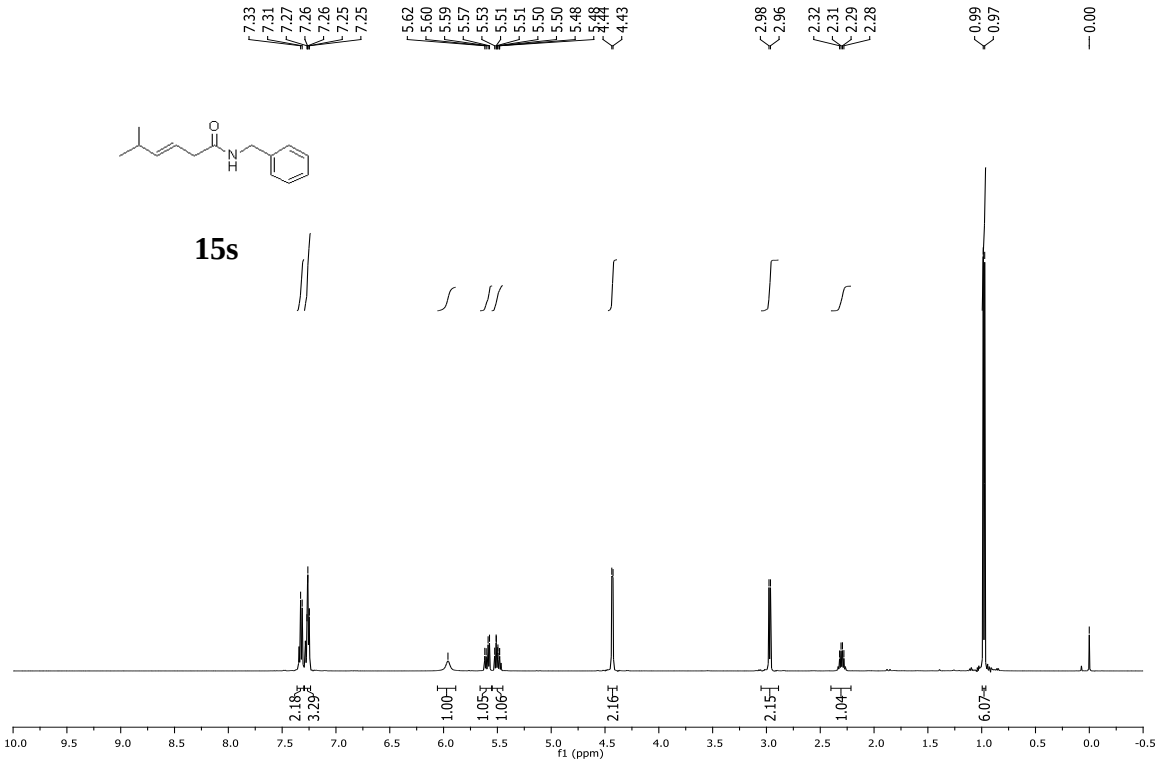

1.99
3.94
0.96
0.91
0.94
2.00
2.01
f1 (ppm)


169.7
137.9
136.0
128.6
127.5
127.4
127.4
127.3
125.6
77.3
77.0
76.7
43.6
37.5



15r


f1 (ppm)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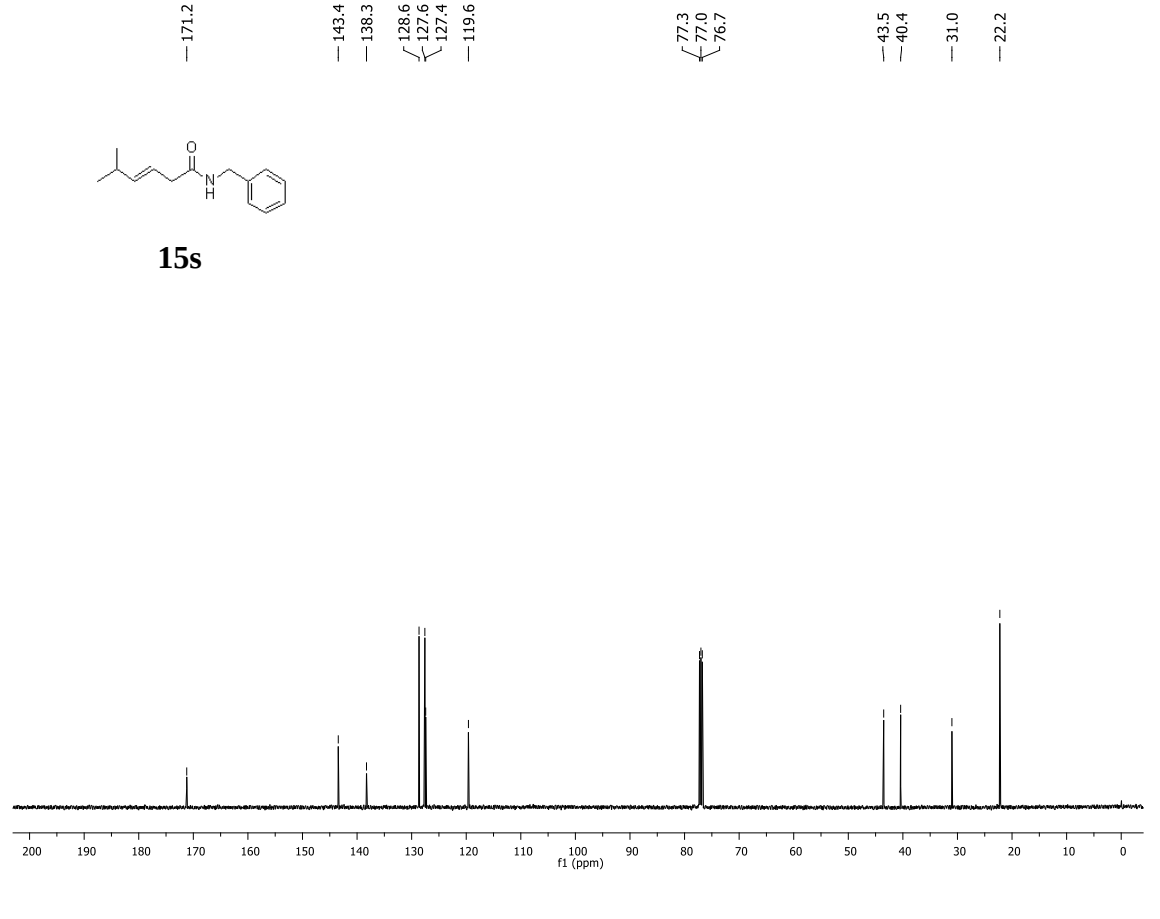
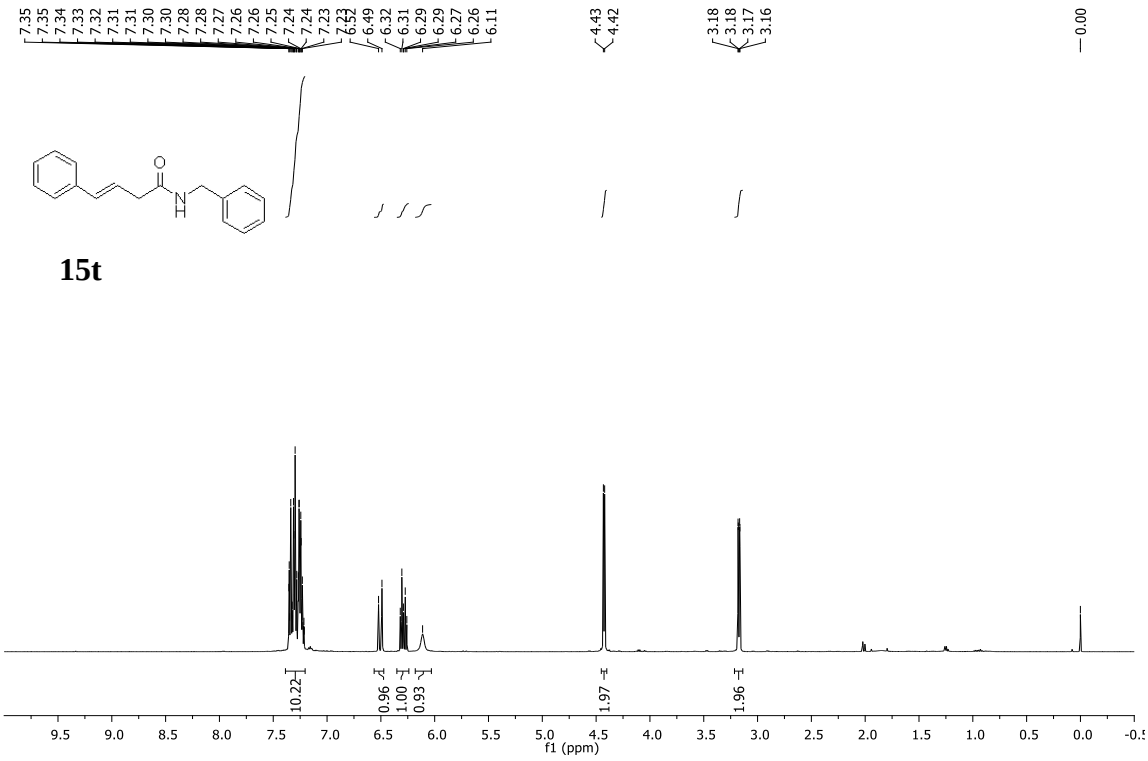
7.31
7.27
7.26
7.26
7.25
7.25
5.62
5.60
5.59
5.57
5.53
5.51
5.51
5.50
5.50
5.48
4.44
4.43
2.98
2.96
2.32
2.31
2.29
2.28
0.99
0.97
0.00
O
N
H
2.18
3.29
1.00
1.05
1.06
2.16
2.15
1.04
6.07
f1 (ppm)

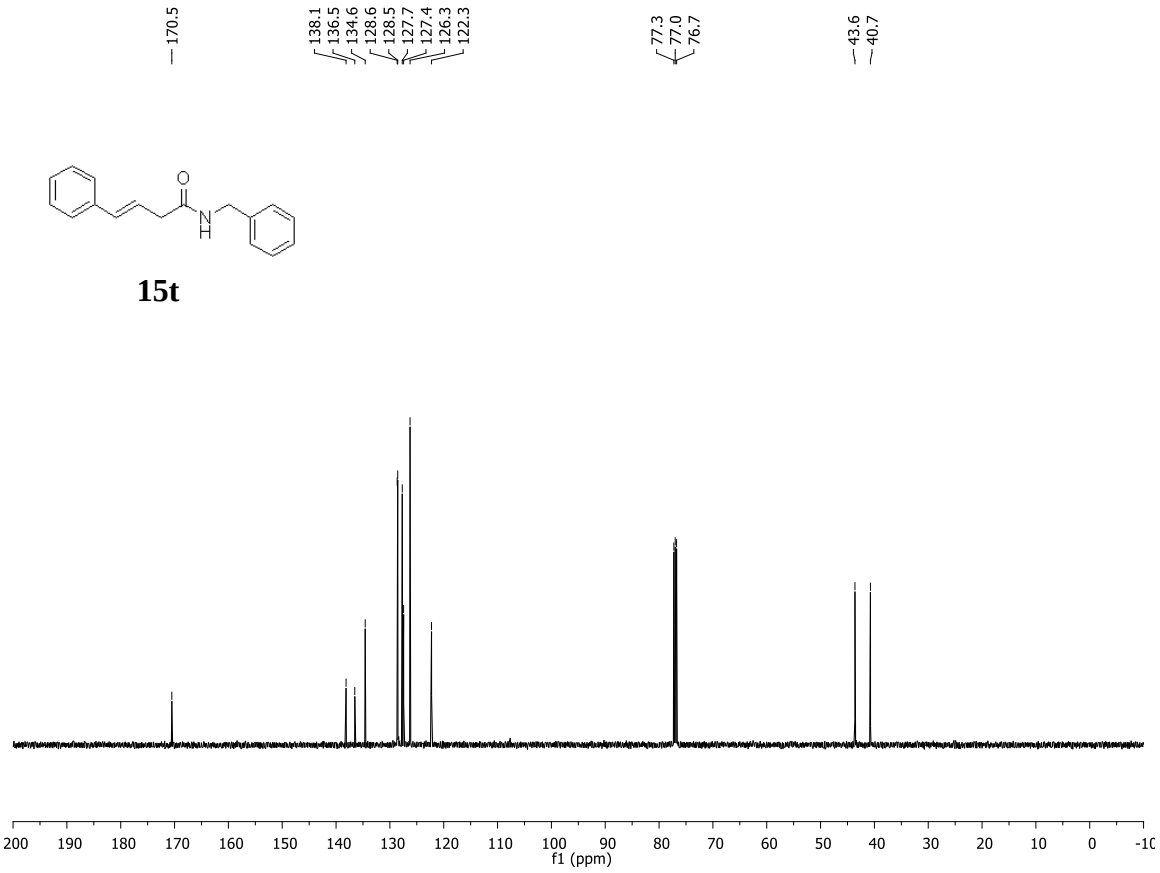
15s


171.2
143.4
138.3
128.6
127.6
127.4
119.6
77.3
77.0
76.7
43.5
40.4
31.0
22.2
O
N
H
f1 (ppm)

15s


7.35
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.28
7.27
7.26
7.26
7.25
7.24
7.24
7.23
7.23
6.52
6.49
6.32
6.31
6.29
6.29
6.27
6.26
6.11
4.43
4.42
3.18
3.18
3.17
3.16
0.00
O
N
H
10.22
0.96
1.00
0.93
1.97
1.96
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
f1 (ppm)

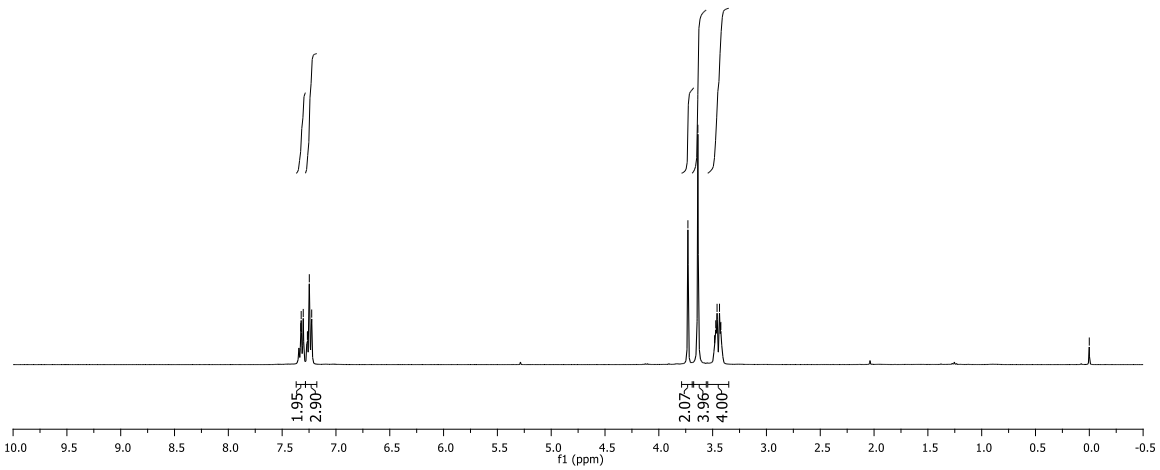
15t


170.5
138.1
136.5
134.6
128.6
128.5
127.7
127.4
126.3
122.3
77.3
77.0
76.7
43.6
40.7
O
N
H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

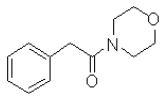
15t


7.33
7.32
7.30
7.27
7.26
7.25
7.23
3.73
3.64
3.48
3.47
3.46
3.44
3.43
3.42
0.00

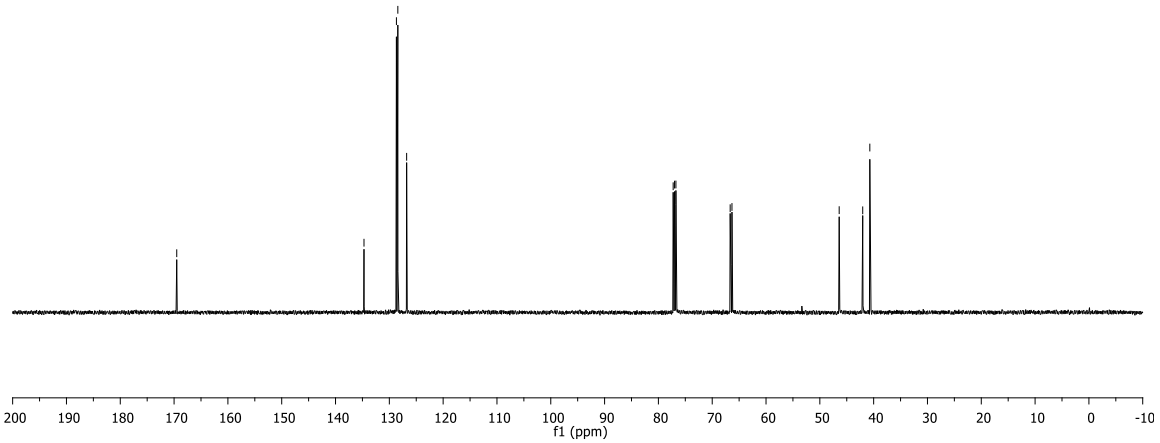
15u

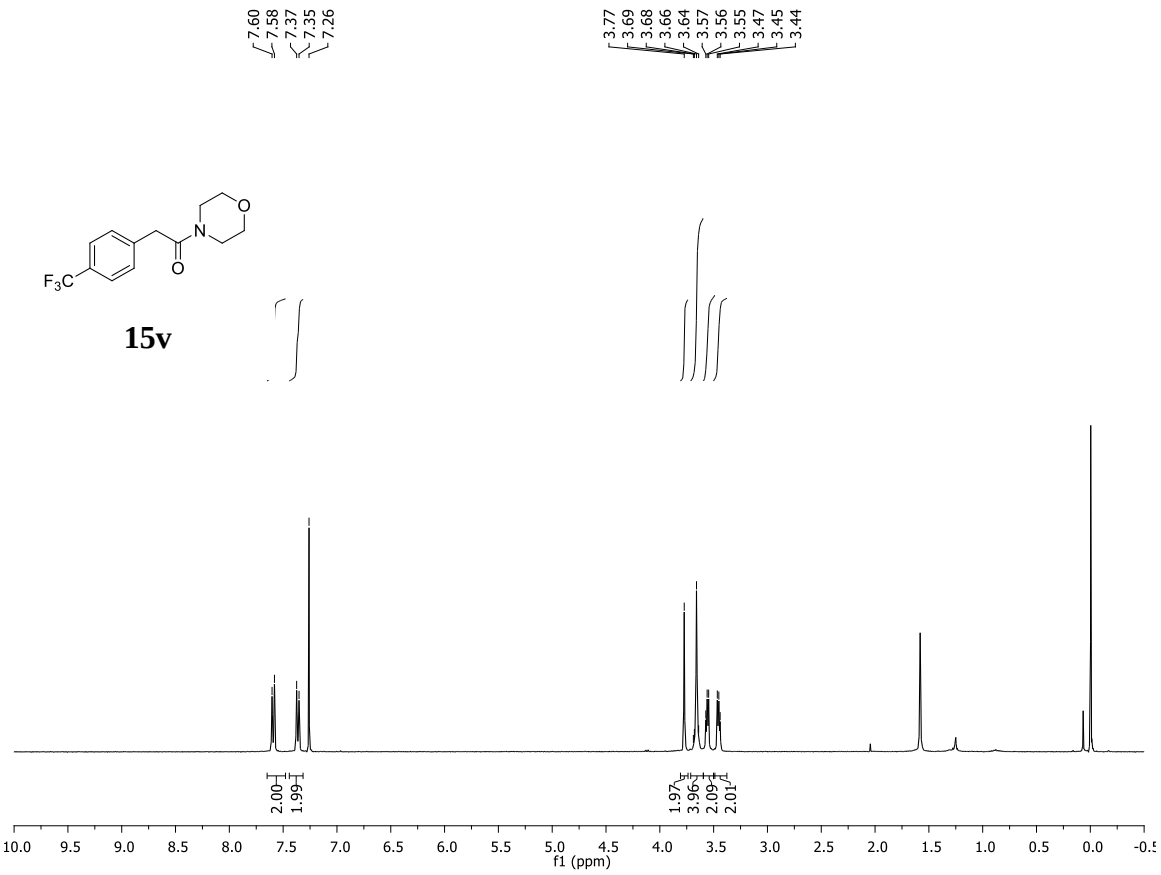

1.95
2.90
2.07
3.96
4.00
f1 (ppm)

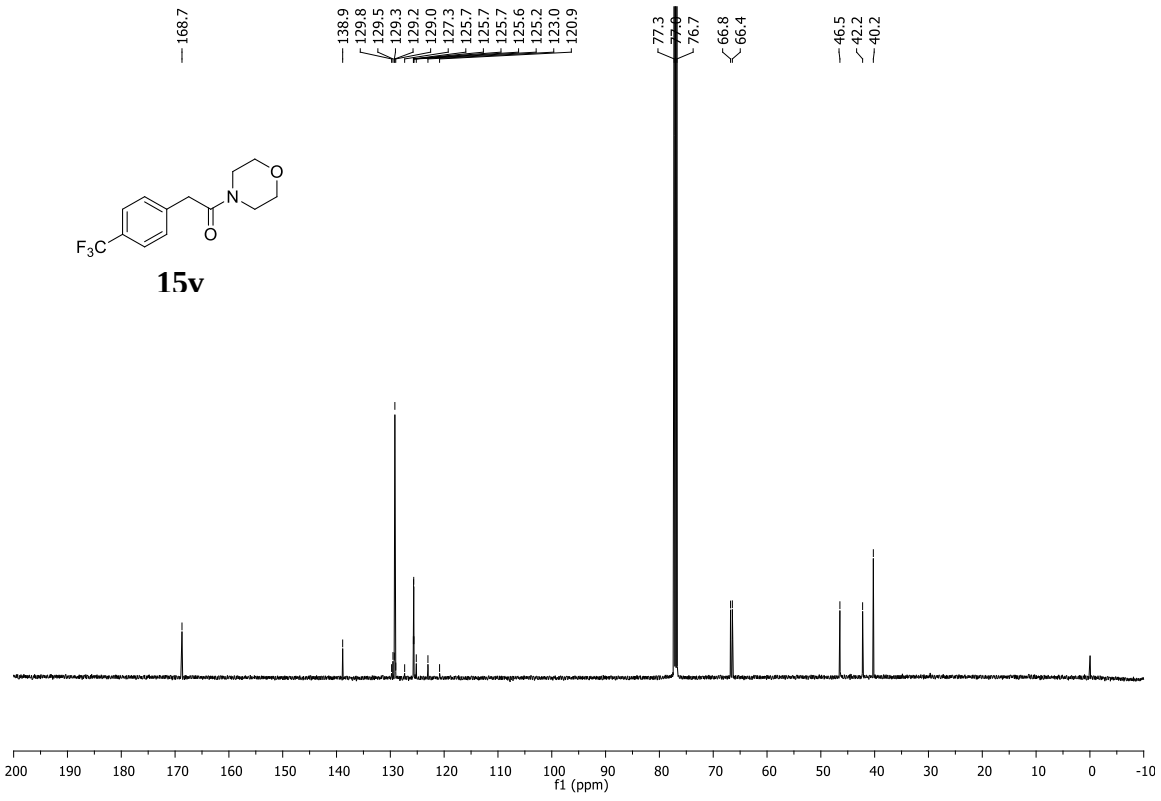

169.5
134.7
128.7
128.4
126.8
77.3
77.0
76.7
66.7
66.3
46.4
42.0
40.7

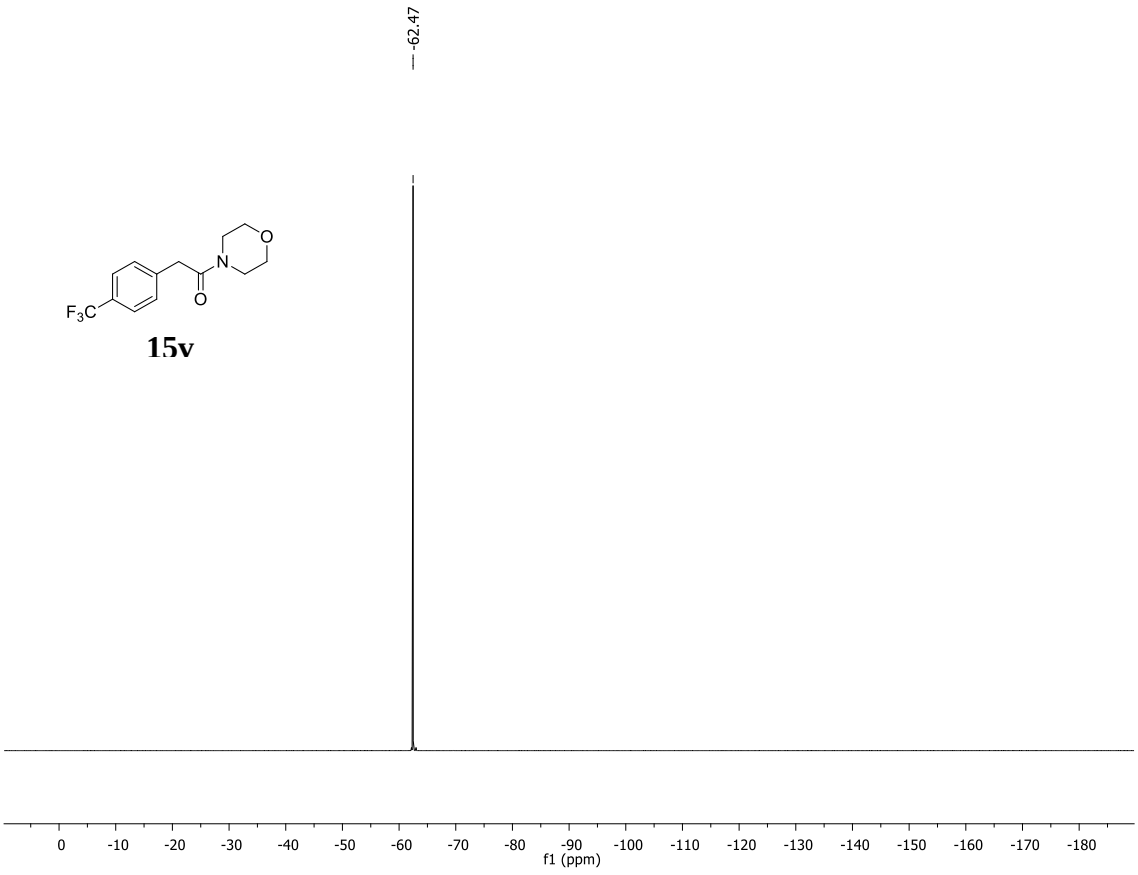


15u

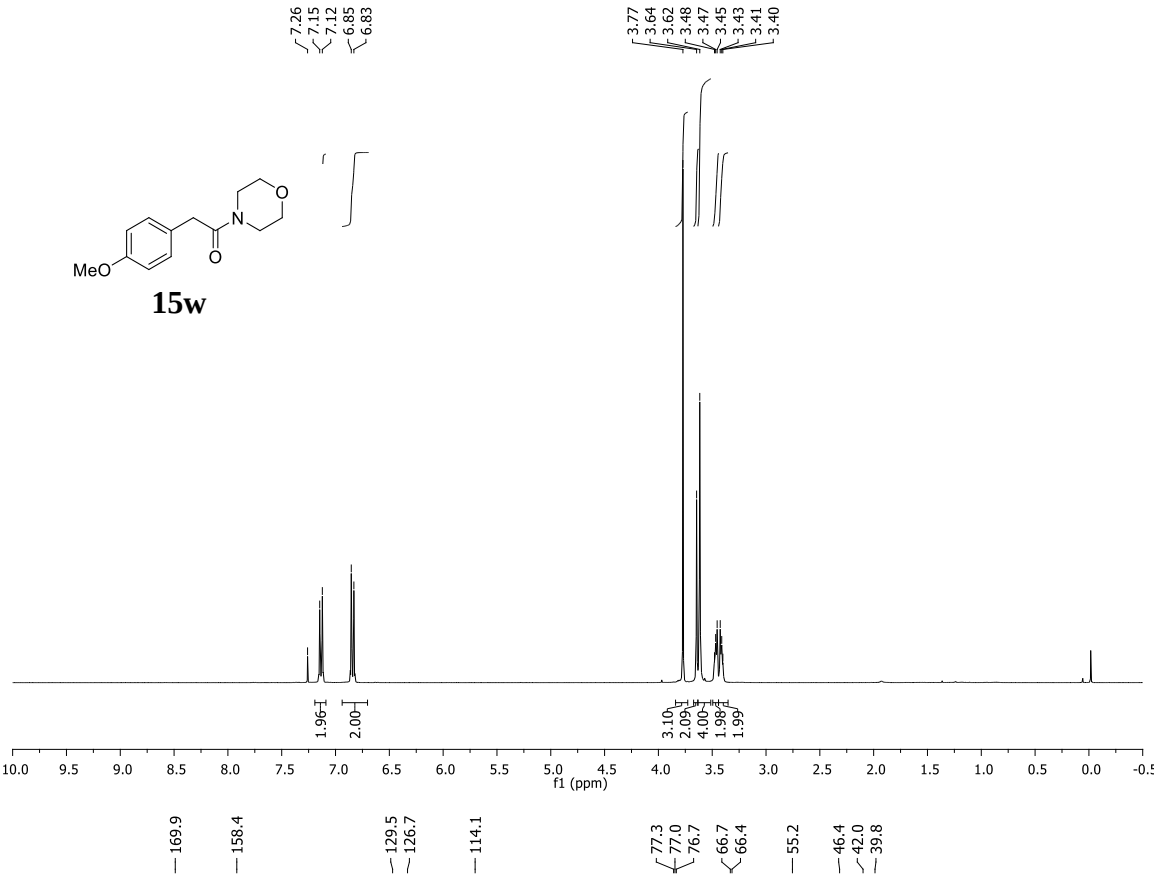

f1 (ppm)


7.60
7.58
7.37
7.35
7.26
3.77
3.69
3.68
3.66
3.64
3.57
3.56
3.55
3.47
3.45
3.44
O
N
O
F3C
15v
2.00
1.99
1.97
3.96
2.09
2.01
f1 (ppm)

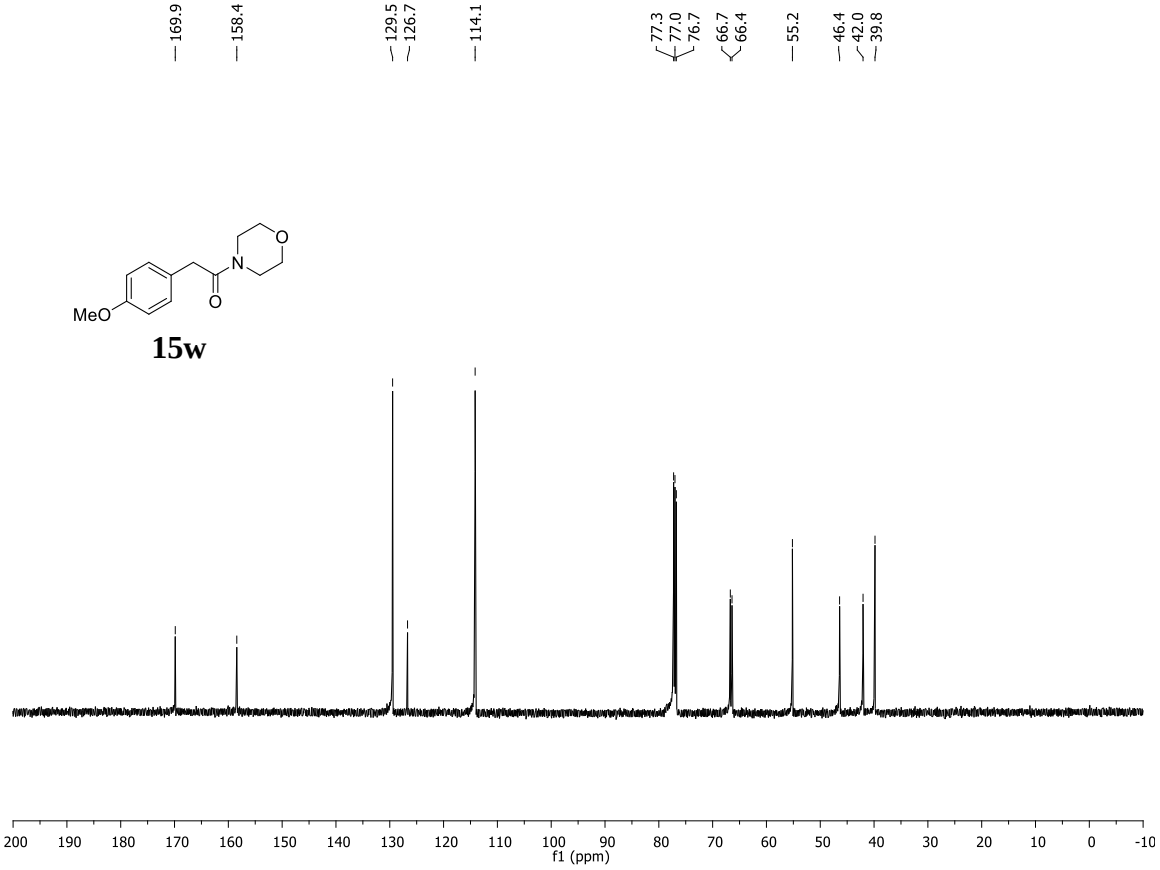

168.7
138.9
129.8
129.5
129.3
129.2
129.0
127.3
125.7
125.7
125.7
125.6
125.2
123.0
120.9
77.3
77.0
76.7
66.8
66.4
46.5
42.2
40.2
O
N
O
F3C
15v
f1 (ppm)


-62.47
O
N
O
F3C
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

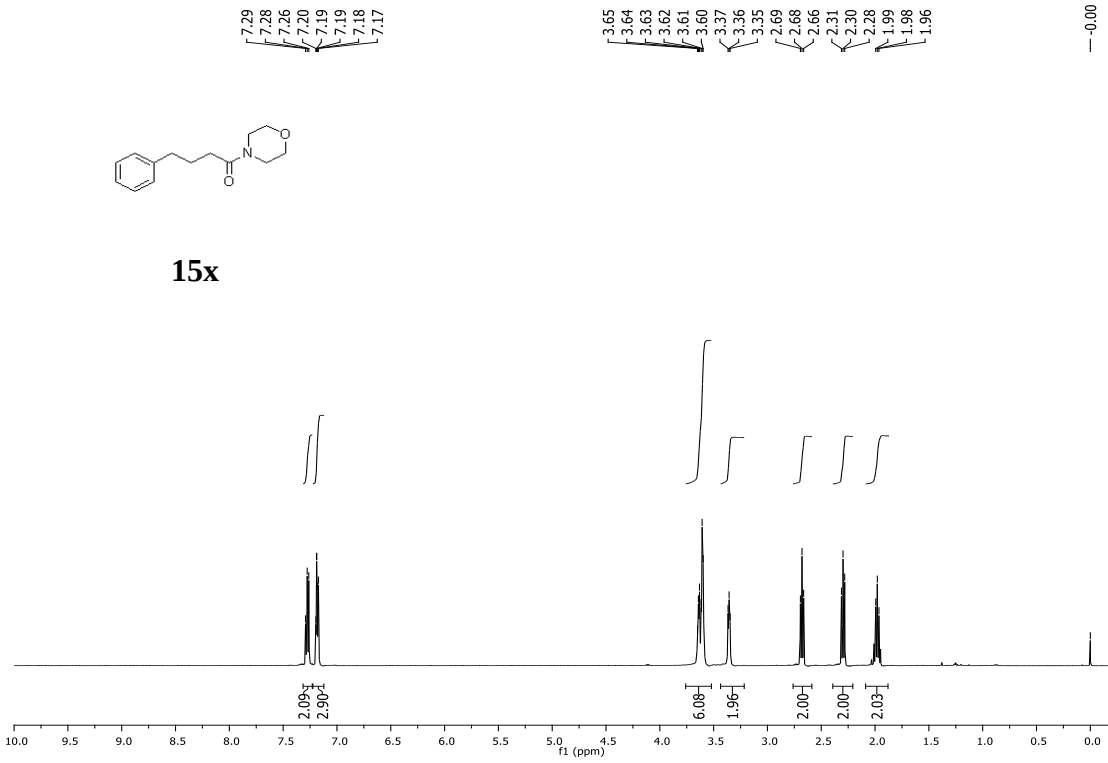
15v


7.26
7.15
7.12
6.85
6.83
3.77
3.64
3.62
3.48
3.47
3.45
3.43
3.41
3.40
MeO
O
N
O
1.96
2.00
3.10
2.09
4.00
1.98
1.99
f1 (ppm)

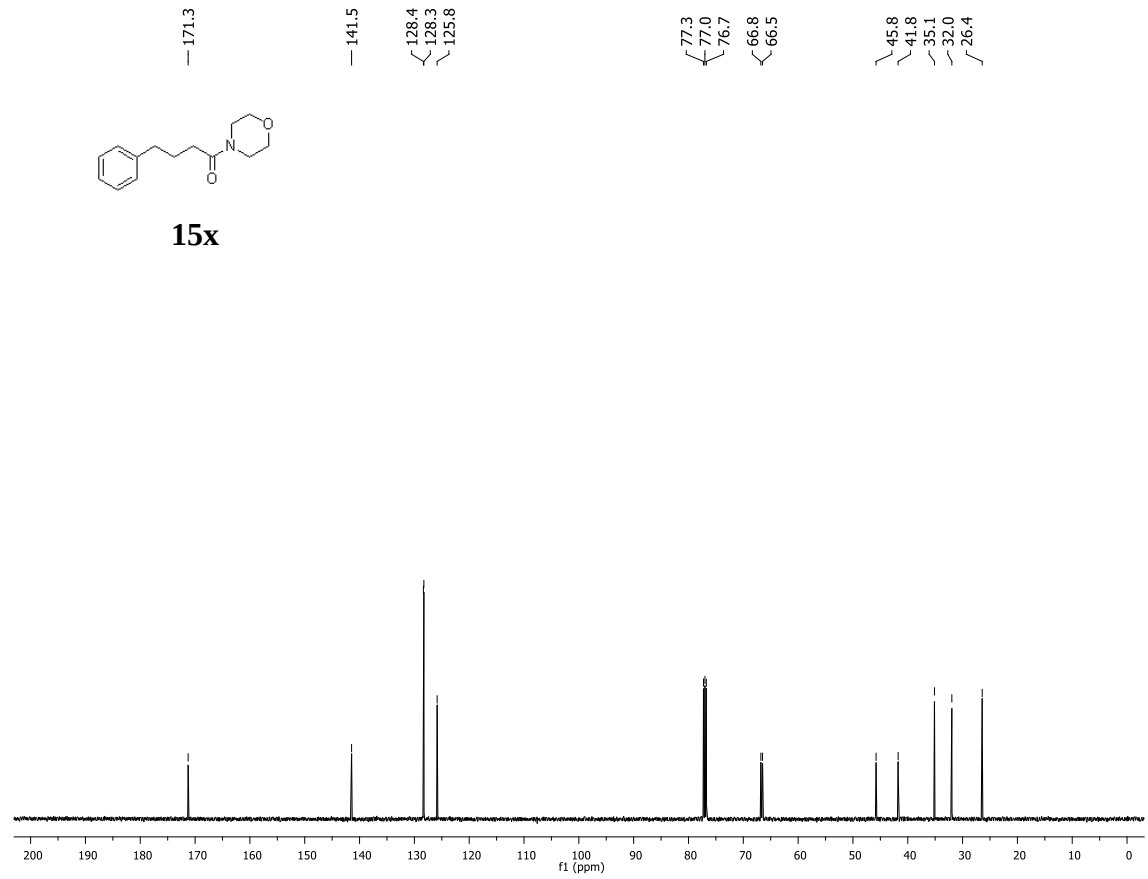
15w


169.9
158.4
129.5
126.7
114.1
77.3
77.0
76.7
66.7
66.4
55.2
46.4
42.0
39.8
MeO
O
N
O
f1 (ppm)

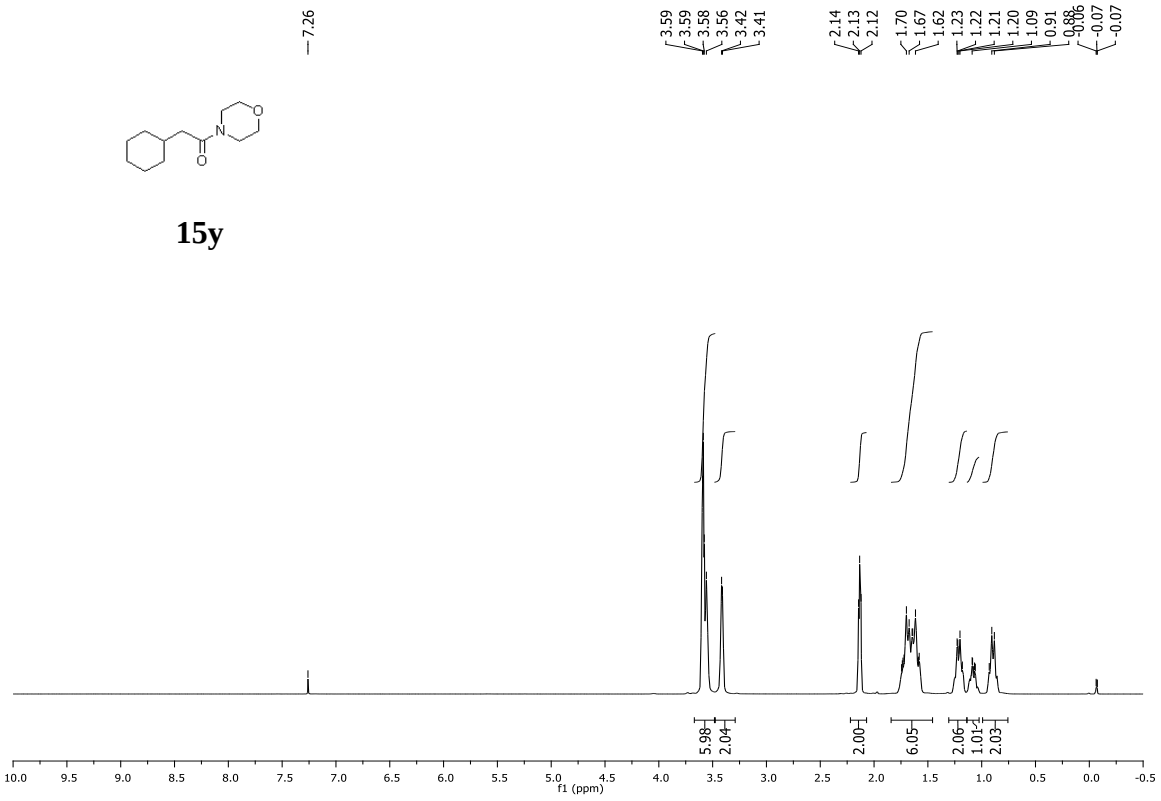
15w


7.29
7.28
7.26
7.20
7.19
7.19
7.18
7.17
3.65
3.64
3.63
3.62
3.61
3.60
3.37
3.36
3.35
2.69
2.68
2.66
2.31
2.30
2.28
1.99
1.98
1.96
-0.00
O
N
O
2.09
2.90
6.08
1.96
2.00
2.00
2.03
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)

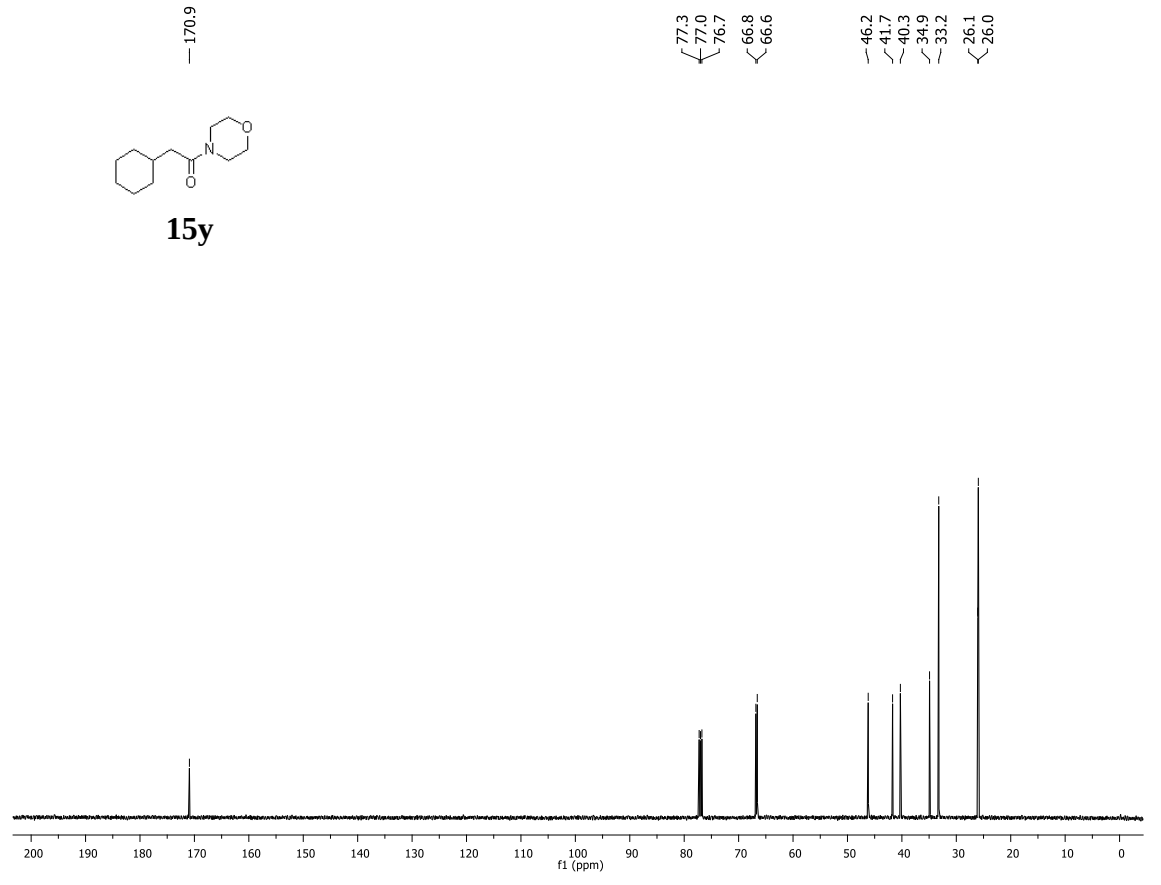
15x


171.3
141.5
128.4
128.3
125.8
77.3
77.0
76.7
66.8
66.5
45.8
41.8
35.1
32.0
26.4
O
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

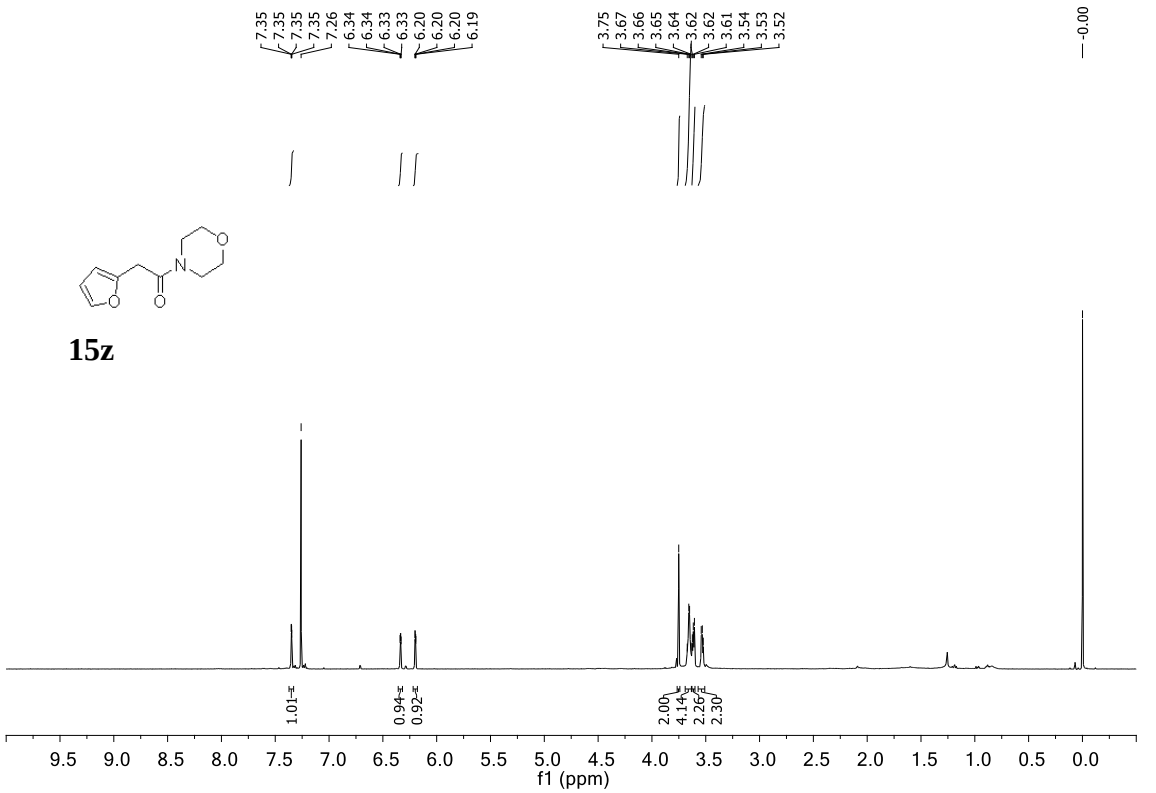
15x


7.26
3.59
3.59
3.58
3.56
3.42
3.41
2.14
2.13
2.12
1.70
1.67
1.62
1.23
1.22
1.21
1.20
1.09
0.91
0.88
0.86
-0.07
-0.07
5.98
2.04
2.00
6.05
2.06
1.01
2.03
f1 (ppm)

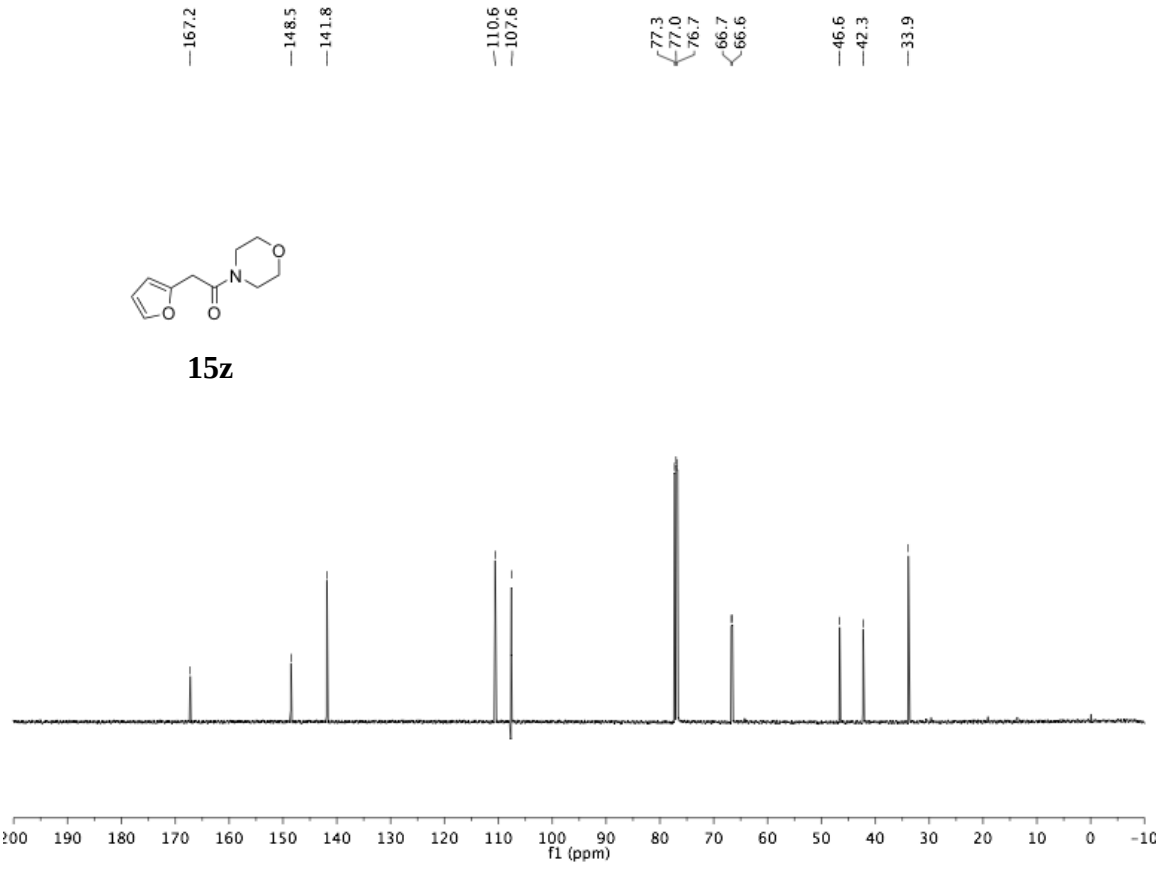
15y


170.9
77.3
77.0
76.7
66.8
66.6
46.2
41.7
40.3
34.9
33.2
26.1
26.0
f1 (ppm)

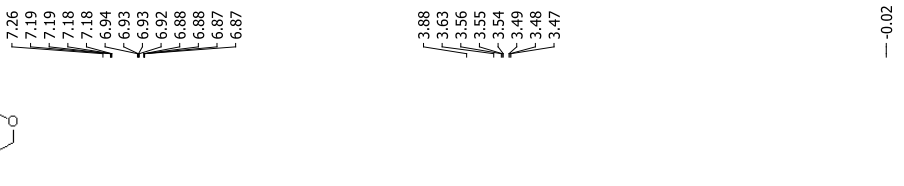
15y


7.35
7.35
7.35
7.35
7.26
6.34
6.34
6.33
6.33
6.20
6.20
6.20
6.19
3.75
3.67
3.66
3.65
3.64
3.62
3.62
3.61
3.54
3.53
3.52
-0.00
1.01
0.94
0.92
2.00
4.14
2.26
2.30
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
f1 (ppm)

15z


167.2
148.5
141.8
110.6
107.6
77.3
77.0
76.7
66.7
66.6
46.6
42.3
33.9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

15z


7.26
7.19
7.19
7.18
7.18
6.94
6.93
6.93
6.92
6.88
6.88
6.87
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3.88
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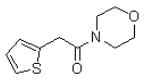
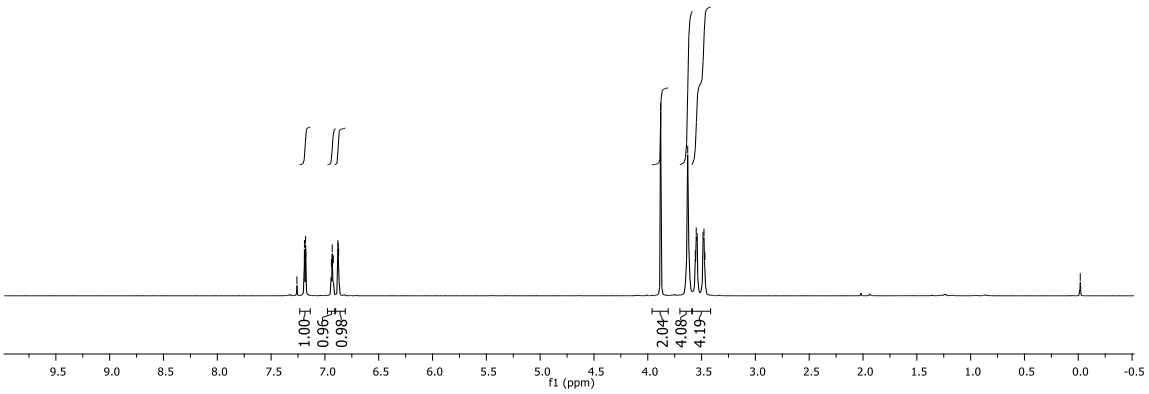
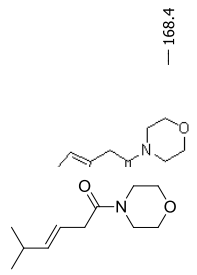
3.55
3.54
3.49
3.48
3.47
-0.02


O
N
O
S

15aa

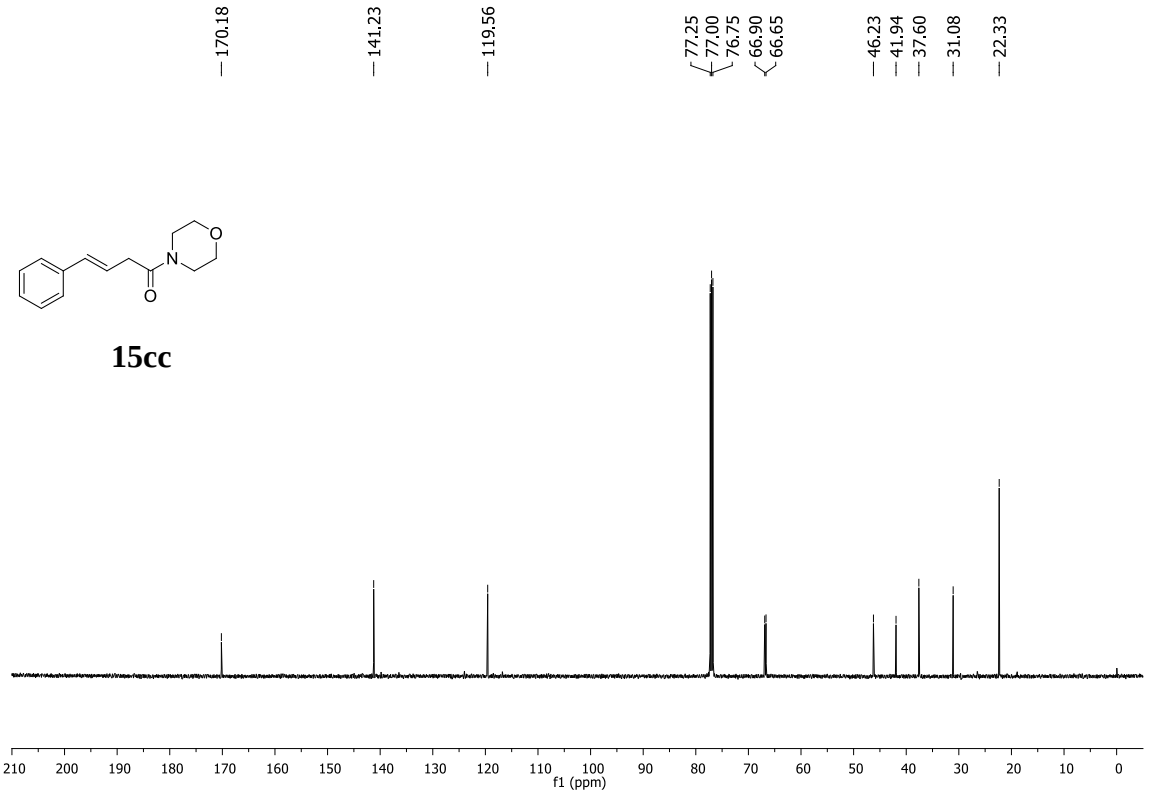

1.00
0.96
0.98
2.04
4.08
4.19
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

15aa

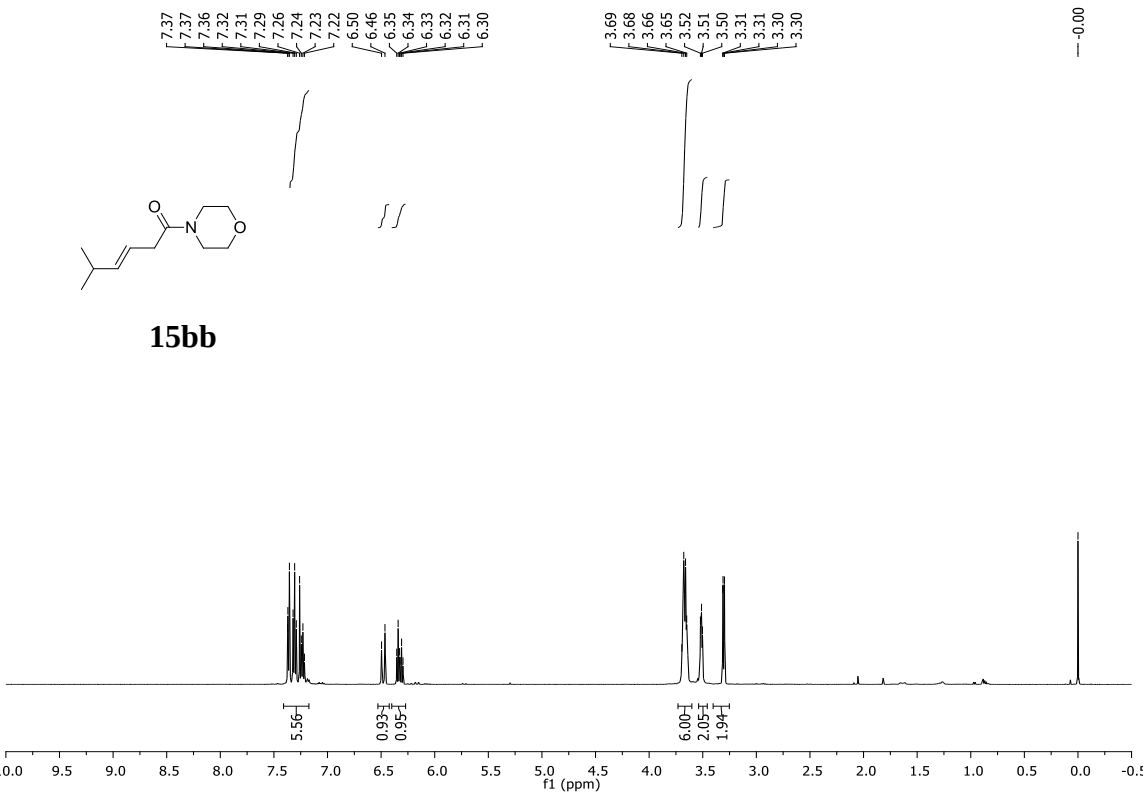


15bb

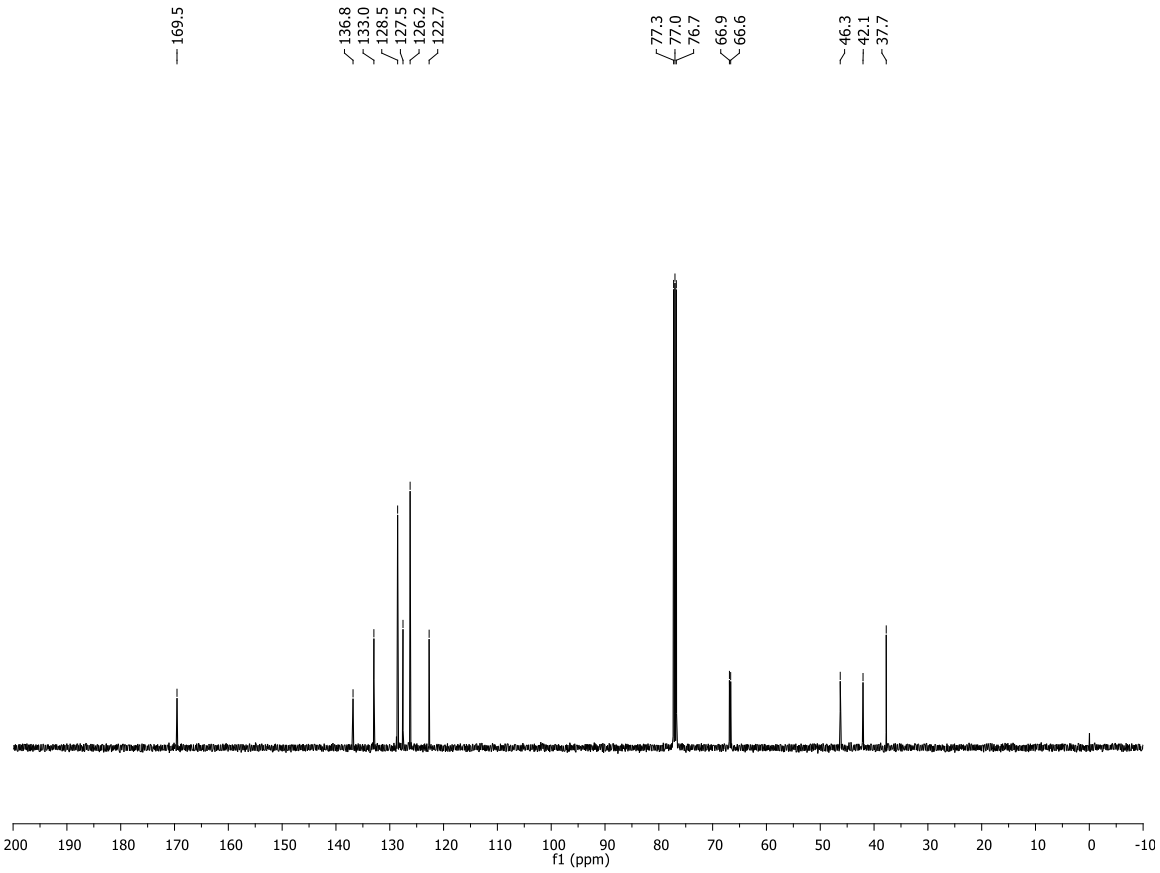
168.4
136.2
126.8
125.9
124.7
77.3
77.0
76.7
66.6
66.3
46.5
42.2
34.8
f1 (ppm)
7.26
5.50
5.49
5.49
5.49
5.48
3.67
3.66
3.65
3.64
3.63
3.62
3.61
3.60
3.46
3.45
3.44
3.07
3.06
2.33
2.32
2.30
2.29
2.29
2.28
2.27
0.99
0.97
2.02
4.03
2.09
2.04
1.92
0.97
6.00
f1 (ppm)

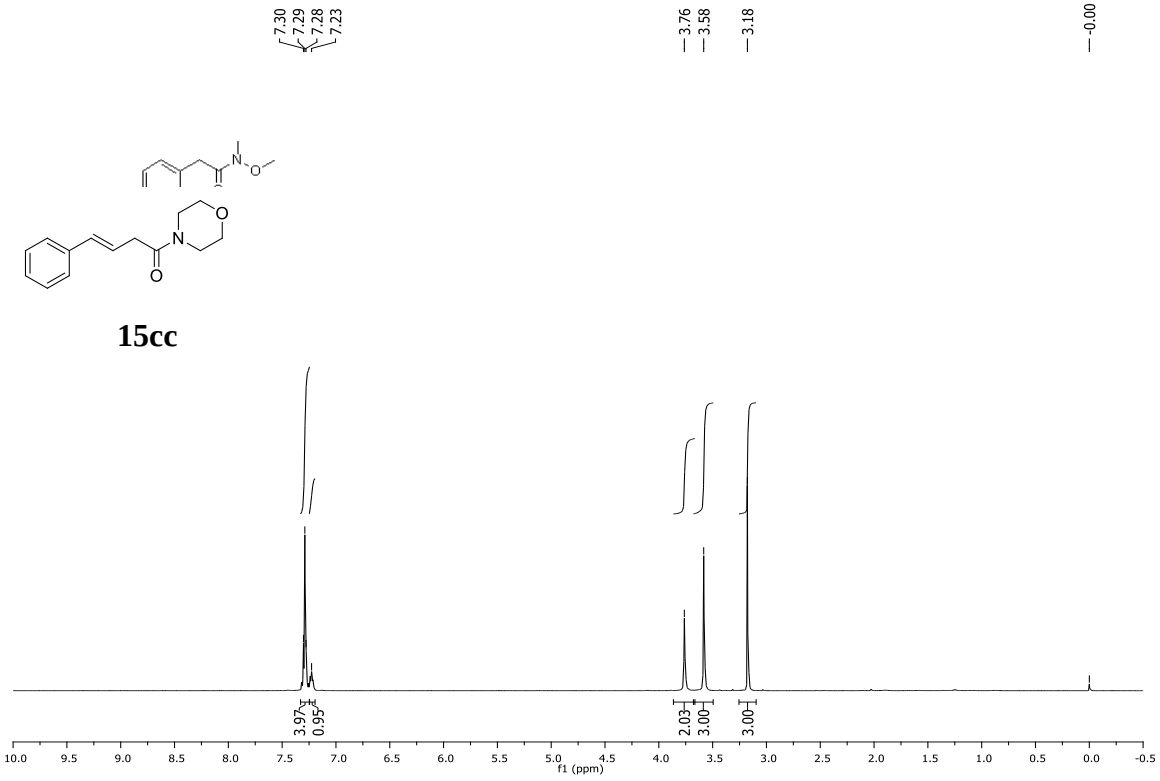

170.18
141.23
119.56
77.25
77.00
76.75
66.90
66.65
46.23
41.94
37.60
31.08
22.33
f1 (ppm)

15cc

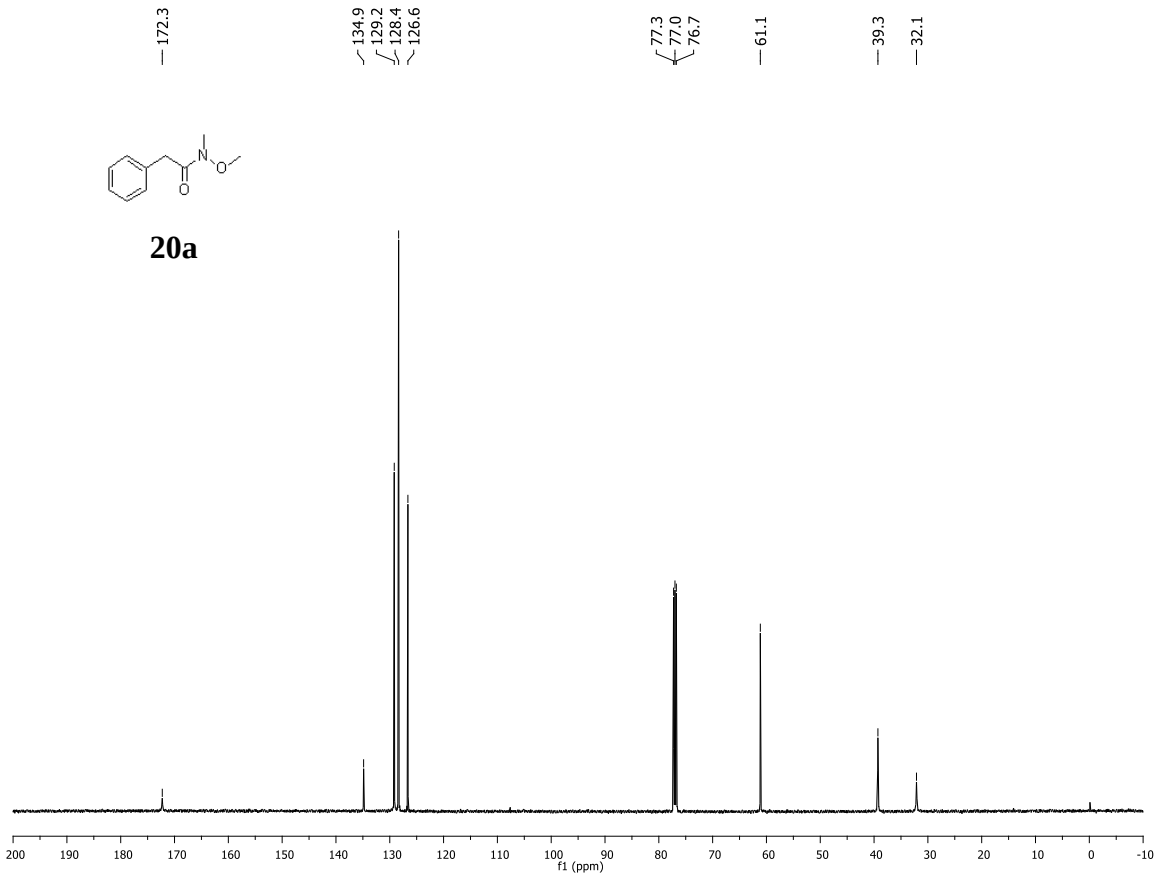

7.37
7.37
7.36
7.32
7.31
7.29
7.26
7.24
7.23
7.22
6.50
6.46
6.35
6.34
6.33
6.32
6.31
6.30
3.69
3.68
3.66
3.65
3.52
3.51
3.50
3.31
3.31
3.30
3.30
0.00
5.56
0.93
0.95
6.00
2.05
1.94
f1 (ppm)

15bb

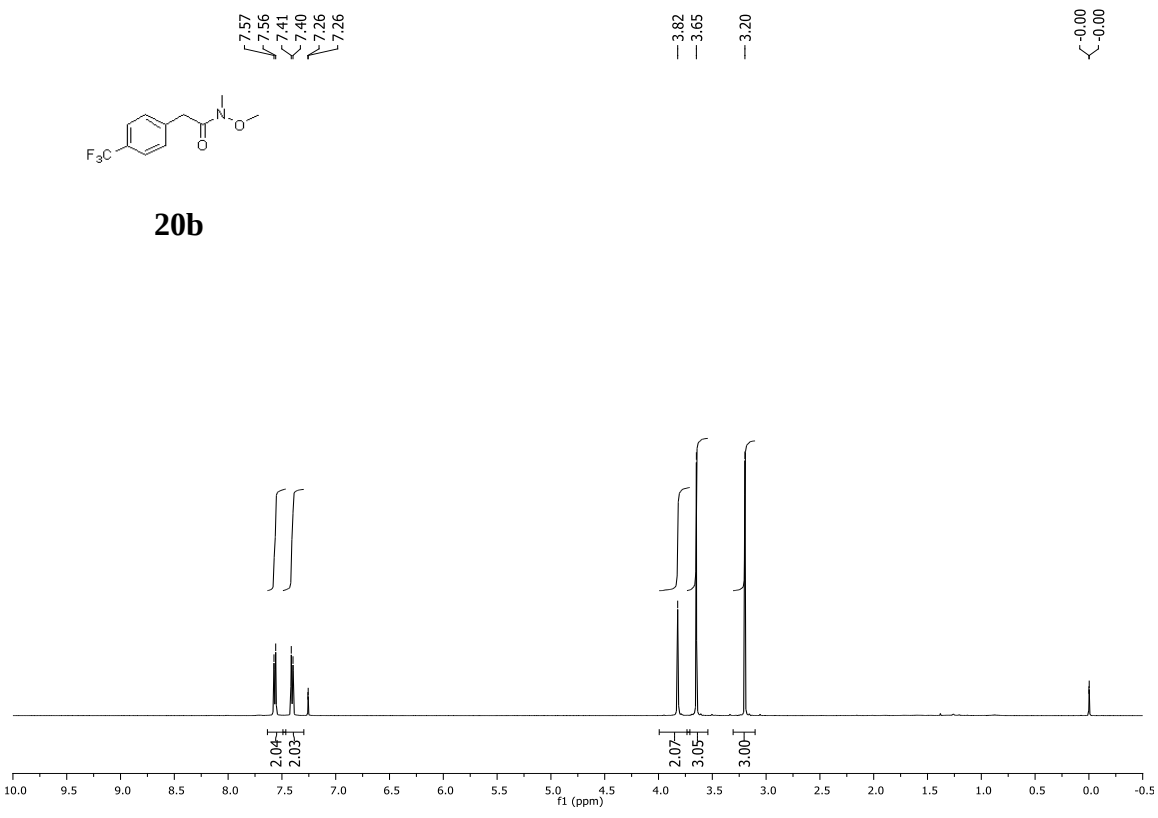

169.5
136.8
133.0
128.5
127.5
126.2
122.7
77.3
77.0
76.7
66.9
66.6
46.3
42.1
37.7
f1 (ppm)


7.30
7.29
7.28
7.23
3.76
3.58
3.18
-0.00
3.97
0.95
2.03
3.00
3.00
f1 (ppm)

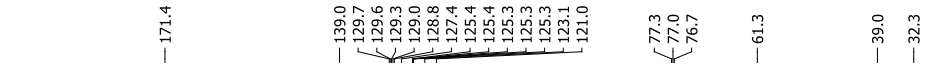
15cc

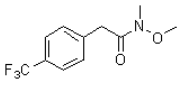

172.3
134.9
129.2
128.4
126.6
77.3
77.0
76.7
61.1
39.3
32.1
f1 (ppm)

20a

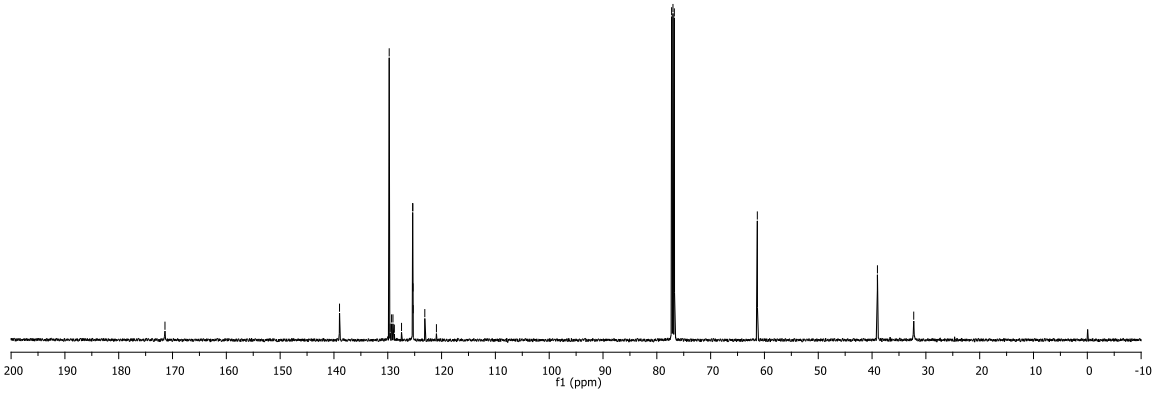

7.57
7.56
7.41
7.40
7.26
7.26
3.82
3.65
3.20
-0.00
-0.00
2.04
2.03
2.07
3.05
3.00
f1 (ppm)

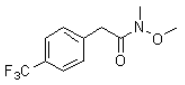
20b


171.4
139.0
129.7
129.6
129.3
129.0
128.8
127.4
125.4
125.4
125.3
125.3
125.3
123.1
121.0
77.3
77.0
76.7
61.3
39.0
32.3


N
O
O
F3C

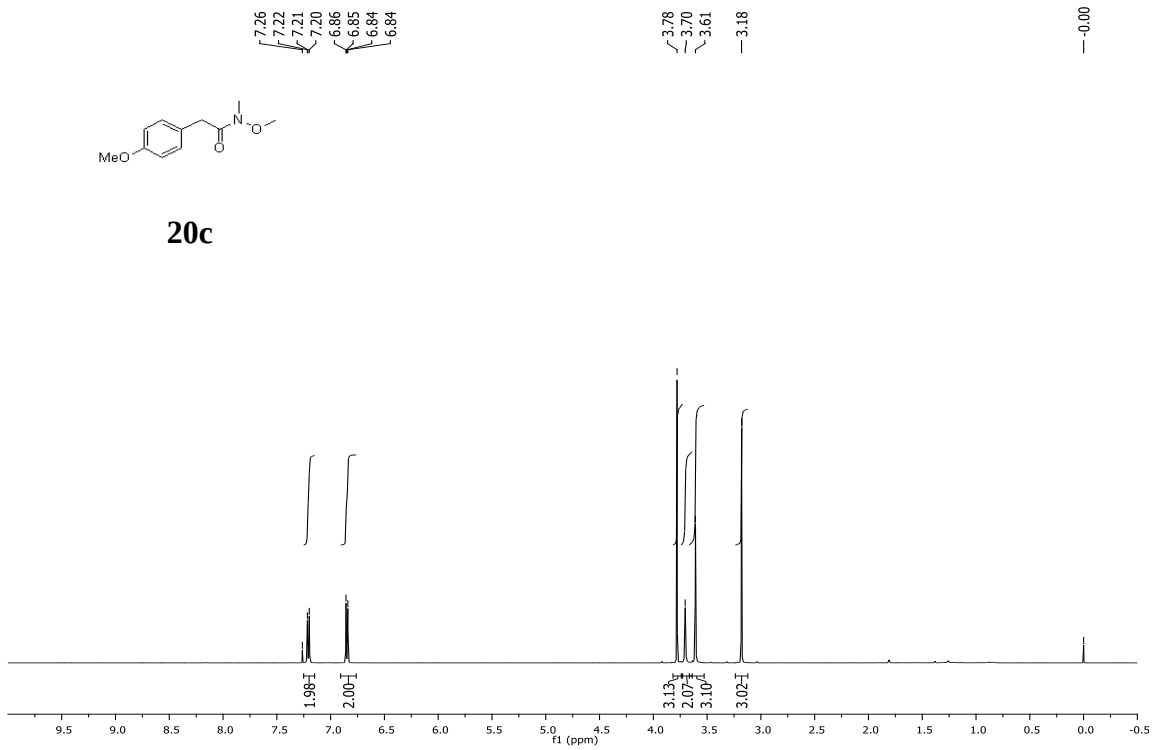
20b


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

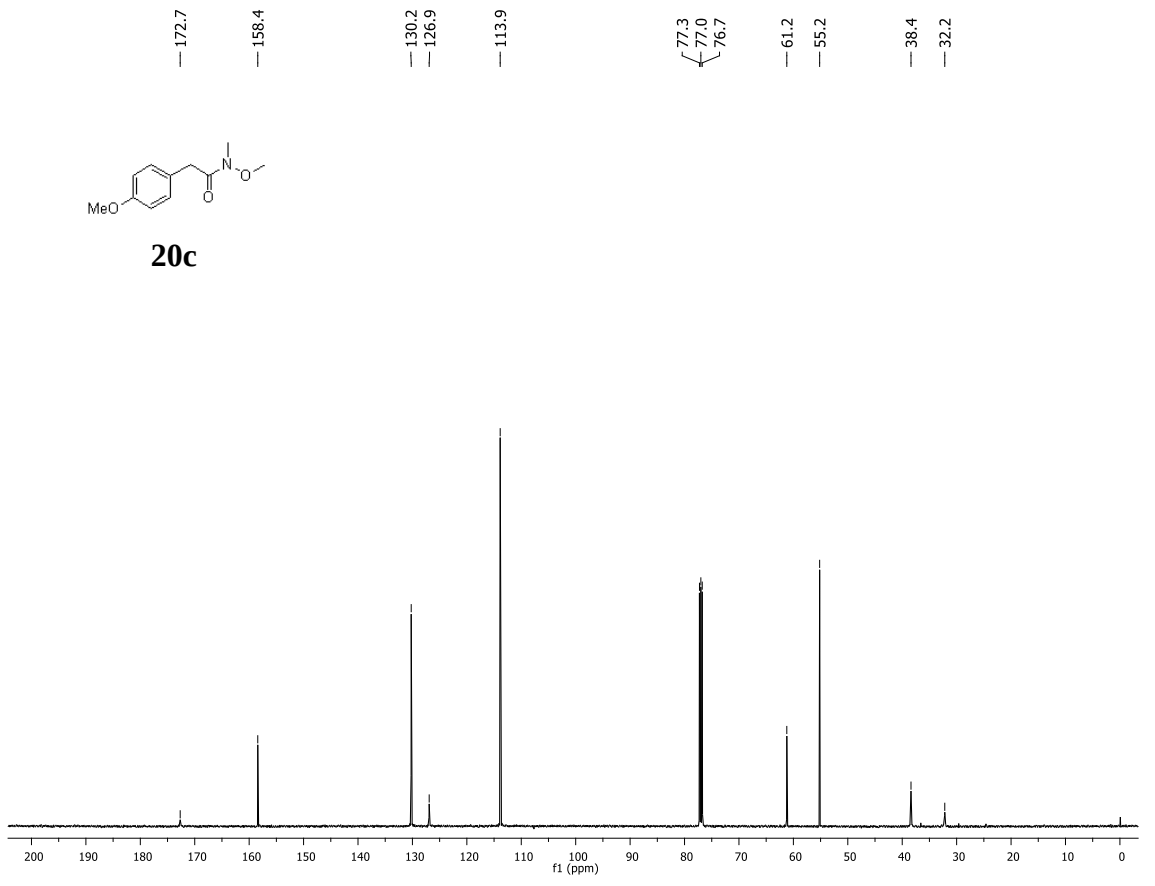


20b

-62.5
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

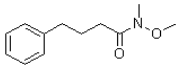

7.26
7.22
7.21
7.20
6.86
6.85
6.84
6.84
3.78
3.70
3.61
3.18
-0.00
MeO
1.98
2.00
3.13
2.07
3.10
3.02
f1 (ppm)

20c

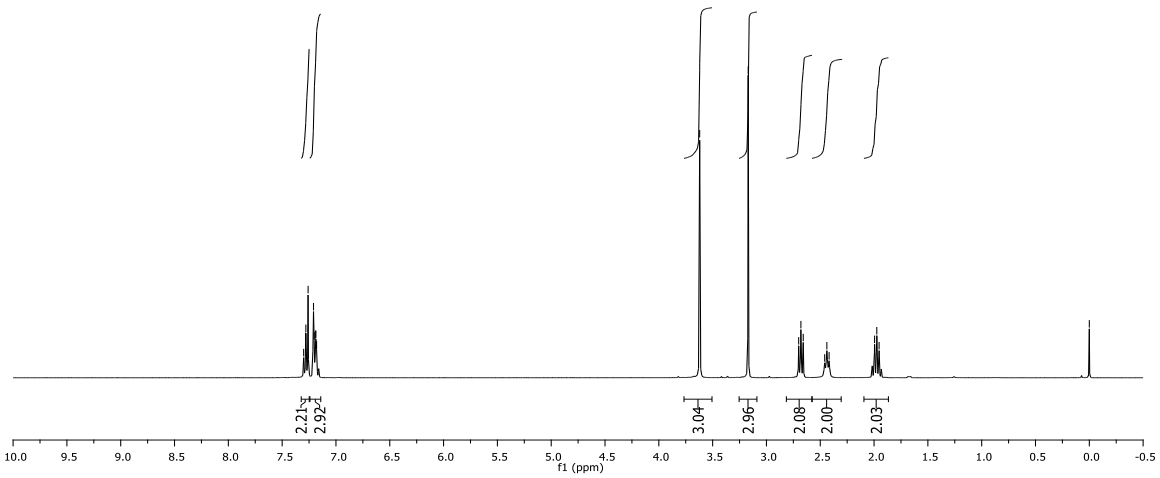

172.7
158.4
130.2
126.9
113.9
77.3
77.0
76.7
61.2
55.2
38.4
32.2
MeO
f1 (ppm)

20c

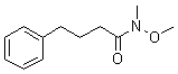

7.30
7.28
7.28
7.26
7.21
7.20
7.19
7.19
7.18
3.62
3.17
2.70
2.68
2.66
2.44
2.42
2.00
1.97
1.95
-0.00



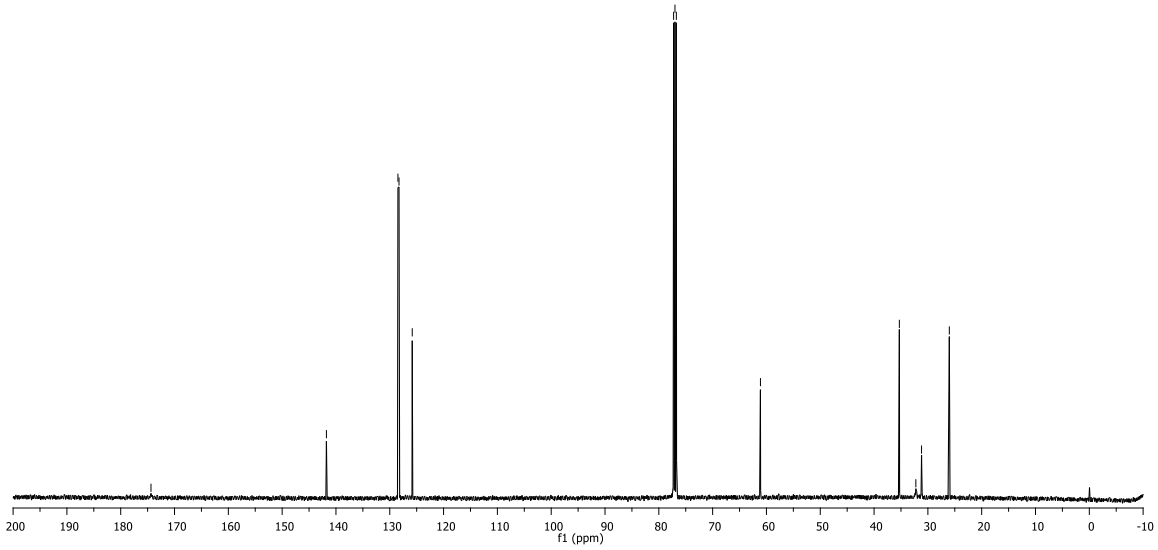
20d

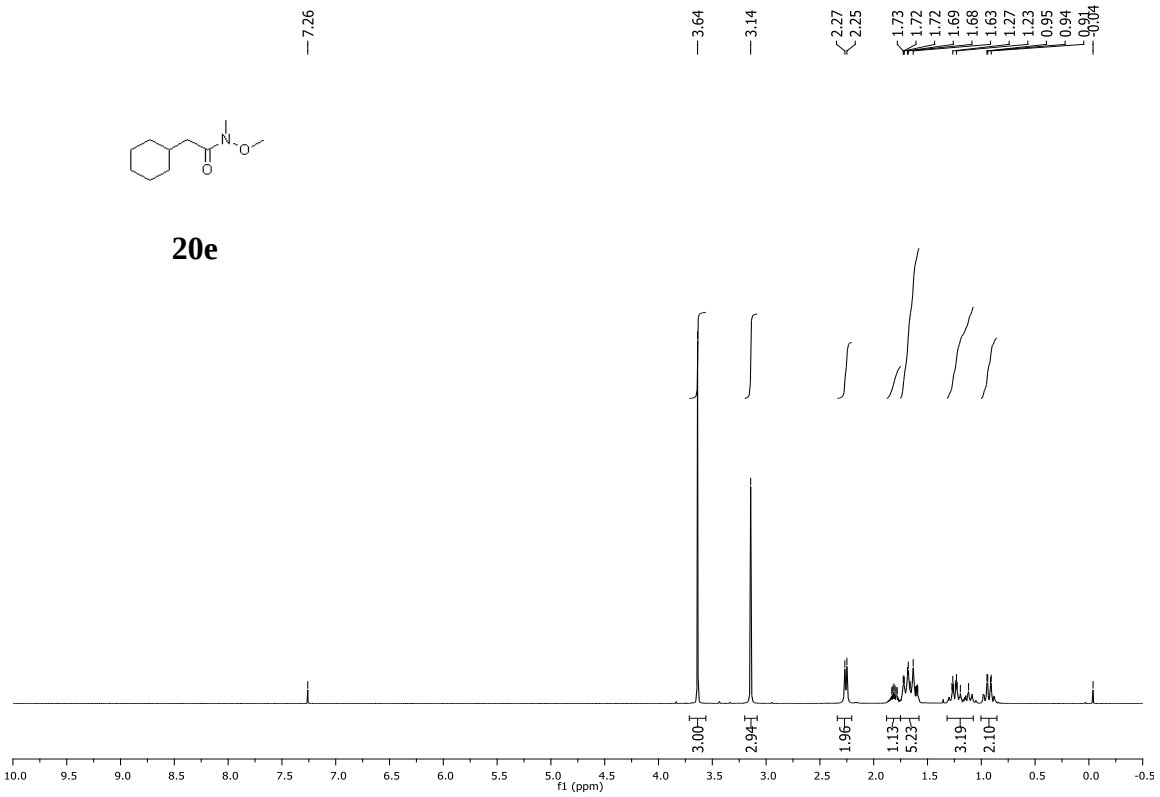

2.21
2.92
3.04
2.96
2.08
2.00
2.03
f1 (ppm)


174.4
141.8
128.5
128.3
125.8
77.3
77.0
76.7
61.1
35.3
32.2
31.2
26.0

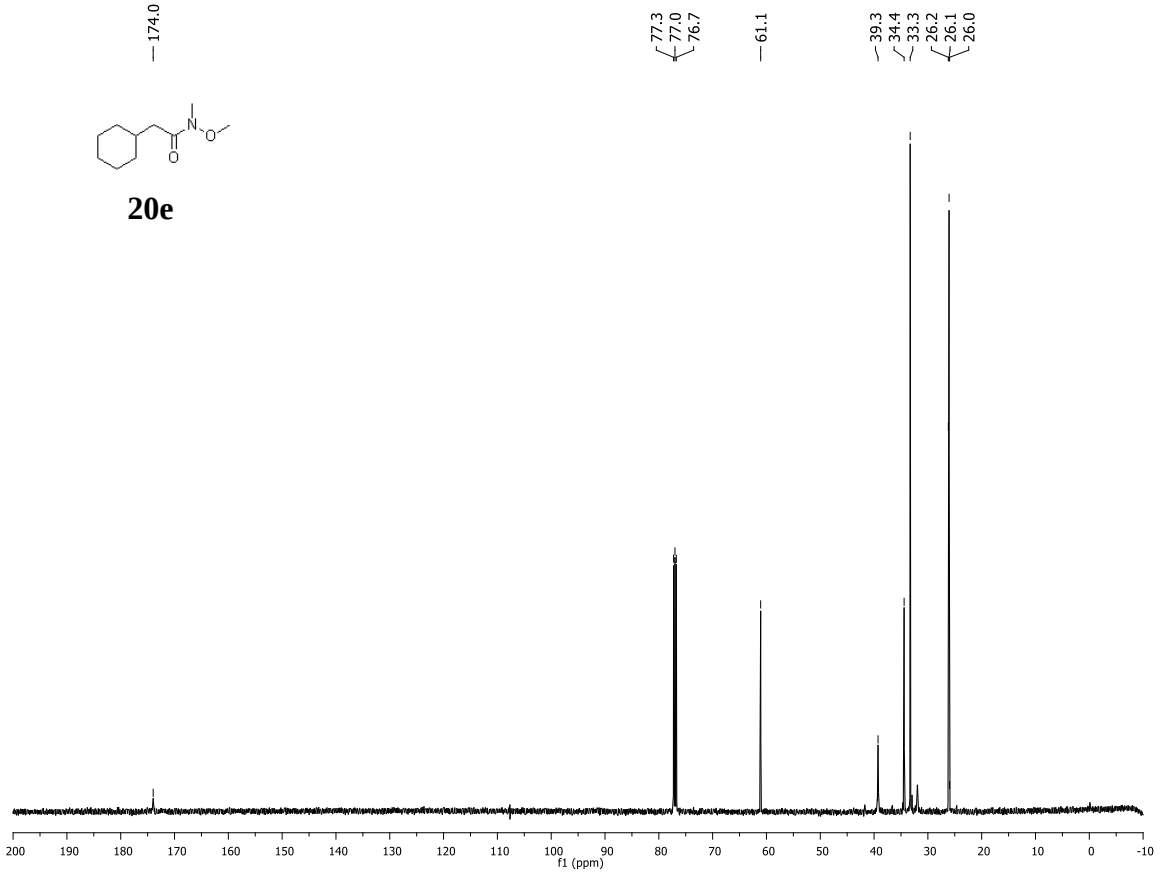


20d

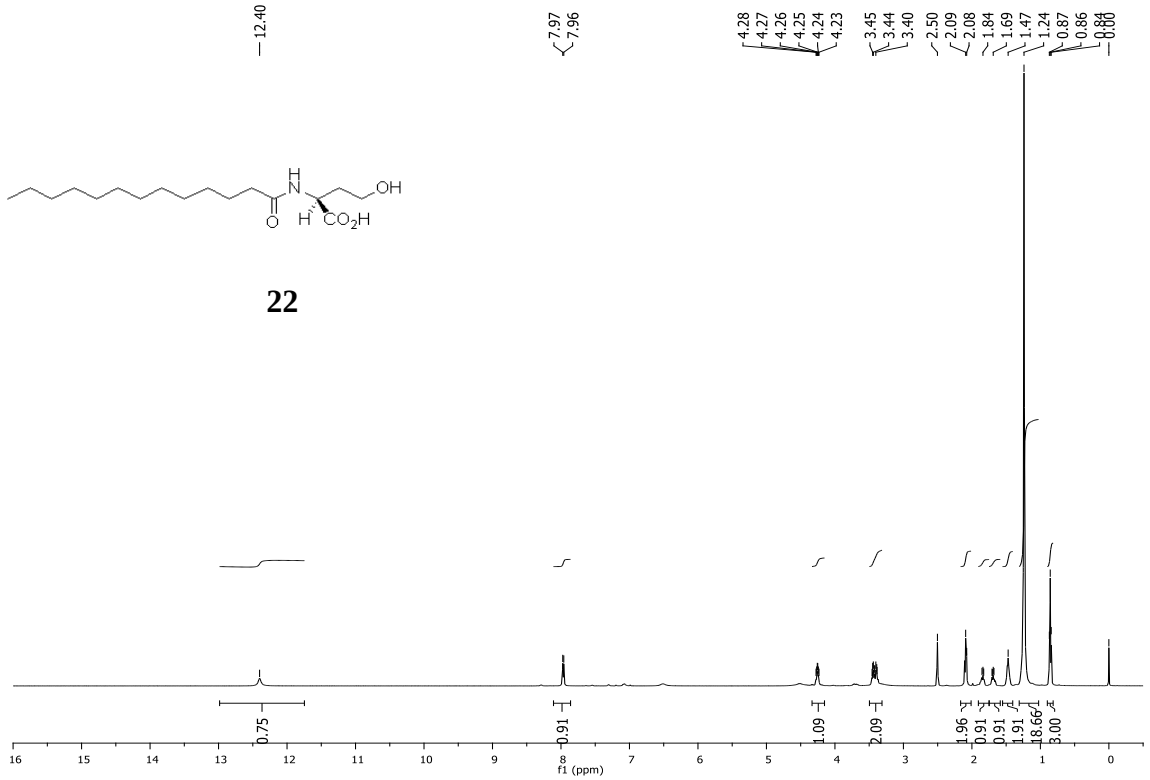

f1 (ppm)


7.26
3.64
3.14
2.27
2.25
1.73
1.72
1.72
1.69
1.68
1.63
1.27
1.23
0.95
0.94
0.91
0.04
3.00
2.94
1.96
1.13
5.23
3.19
2.10
f1 (ppm)

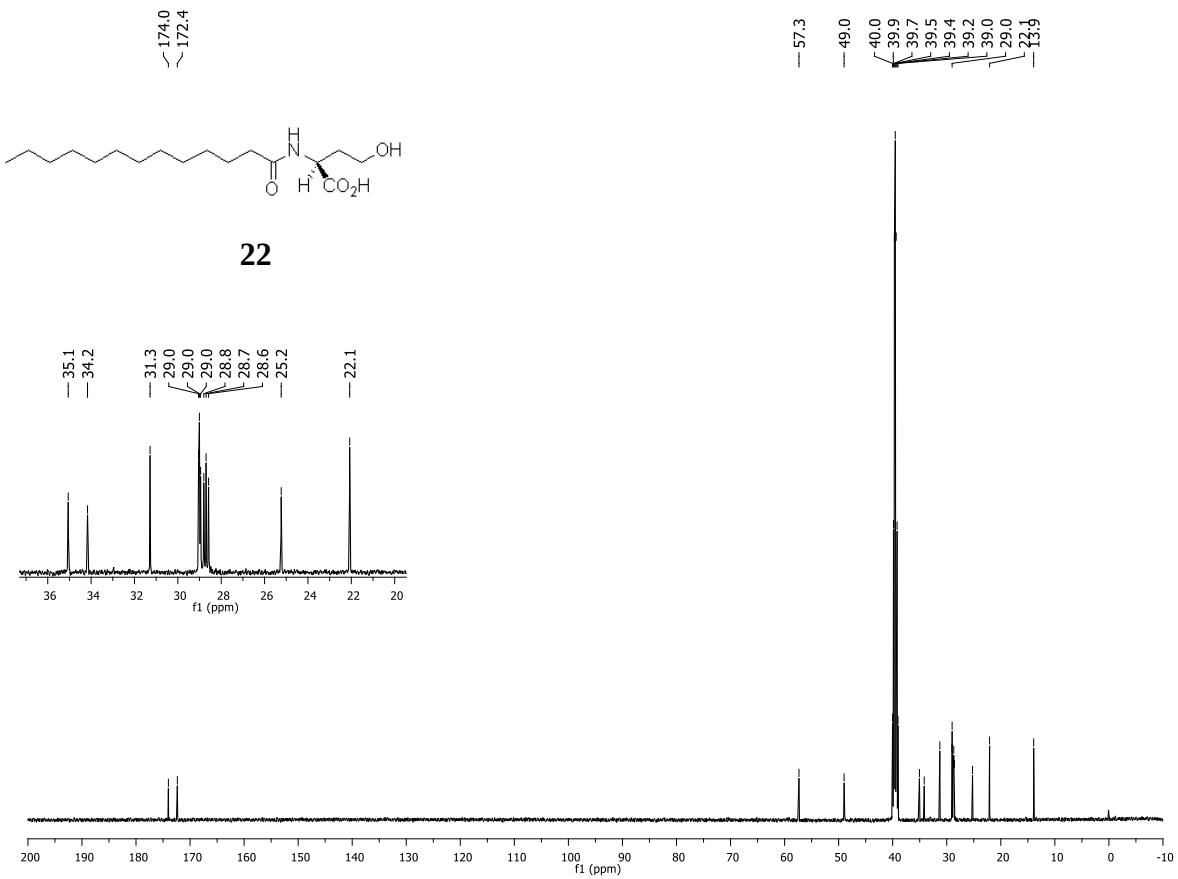
20e


174.0
77.3
77.0
76.7
61.1
39.3
34.4
33.3
26.2
26.1
26.0
f1 (ppm)

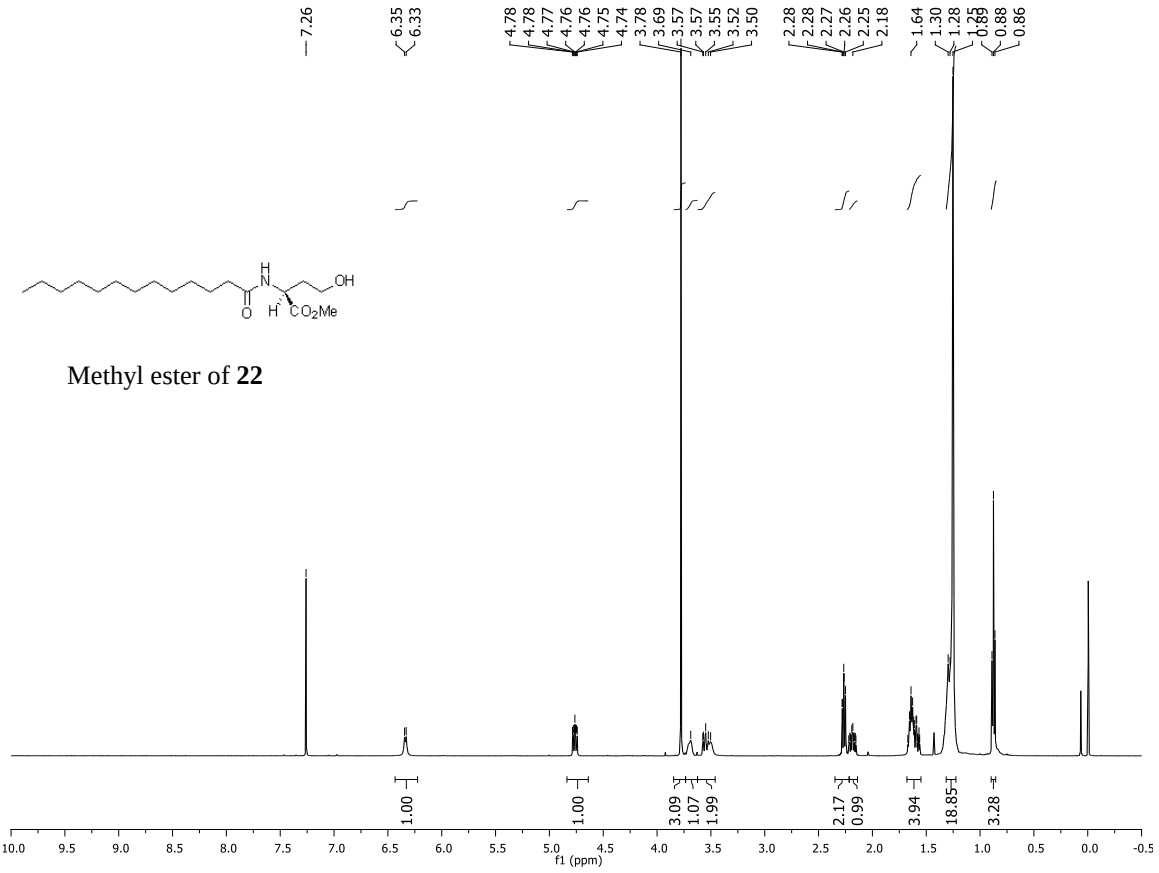
20e


12.40
7.97
7.96
4.28
4.27
4.26
4.25
4.24
4.23
3.45
3.44
3.40
2.50
2.09
2.08
1.84
1.69
1.47
1.24
0.87
0.86
0.75
0.91
1.09
2.09
1.96
0.91
0.91
1.91
18.66
3.00
f1 (ppm)

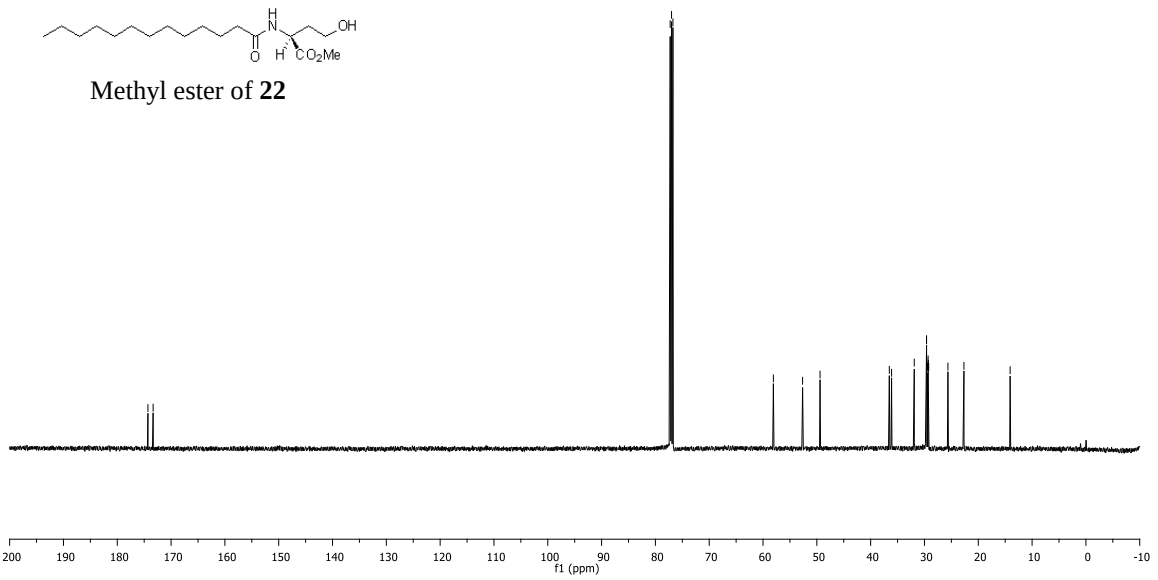
22


174.0
172.4
57.3
49.0
40.0
39.9
39.7
39.5
39.4
39.2
39.0
29.0
22.1
13.9
35.1
34.2
31.3
29.0
29.0
29.0
28.8
28.7
28.6
25.2
22.1
f1 (ppm)
f1 (ppm)

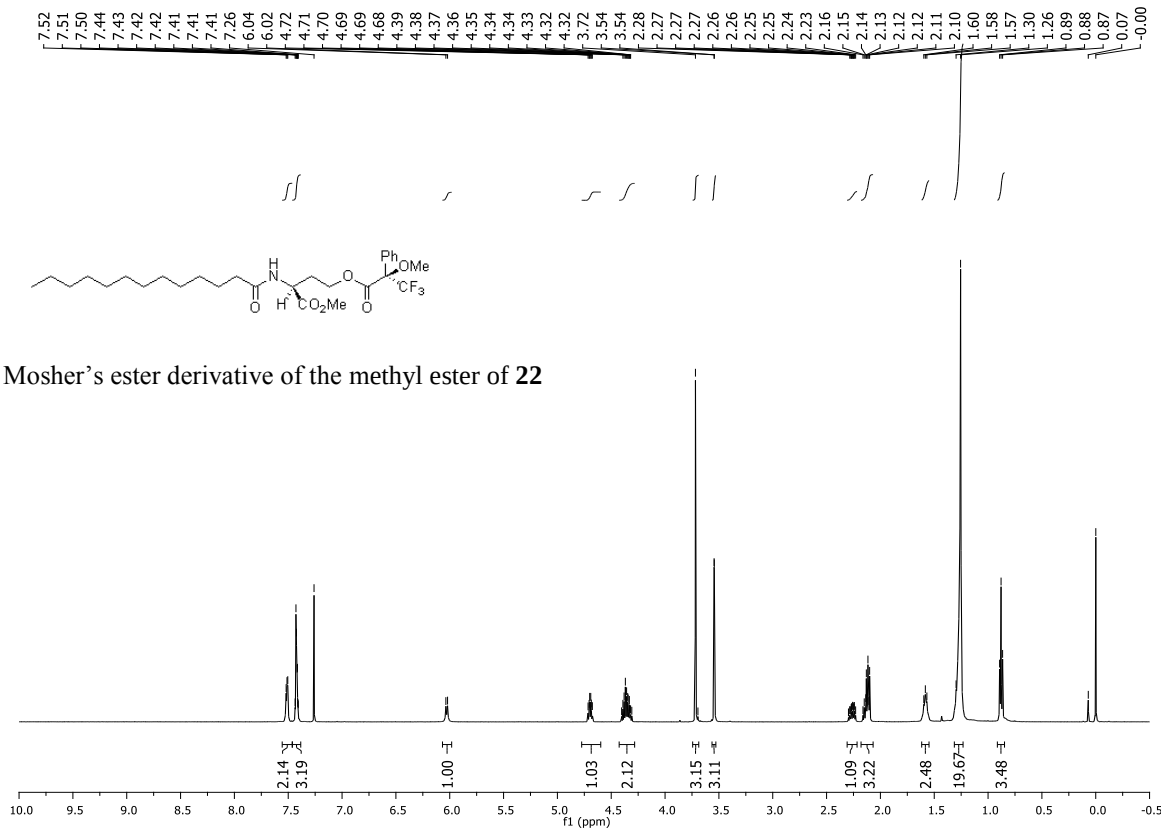
22



Methyl ester of **22**

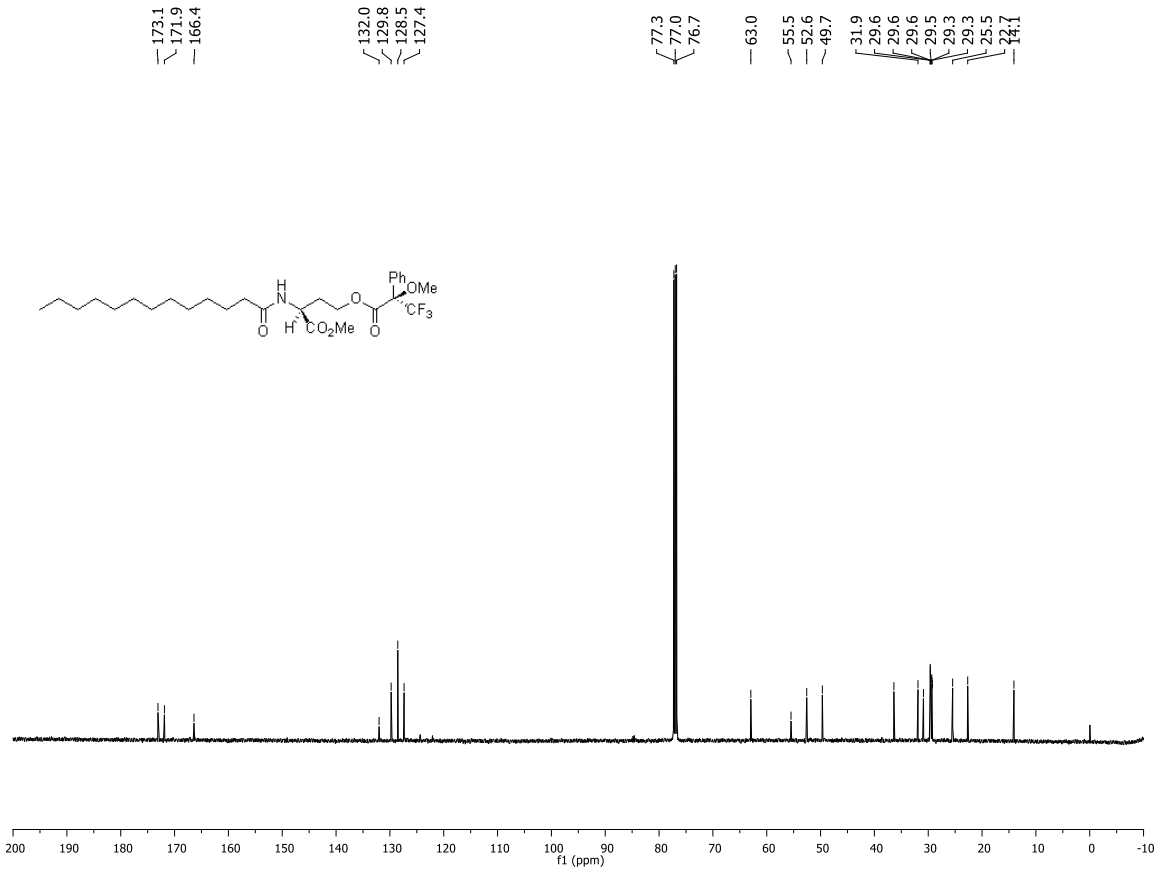


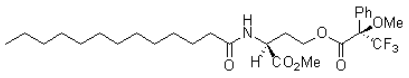
Methyl ester of **22**



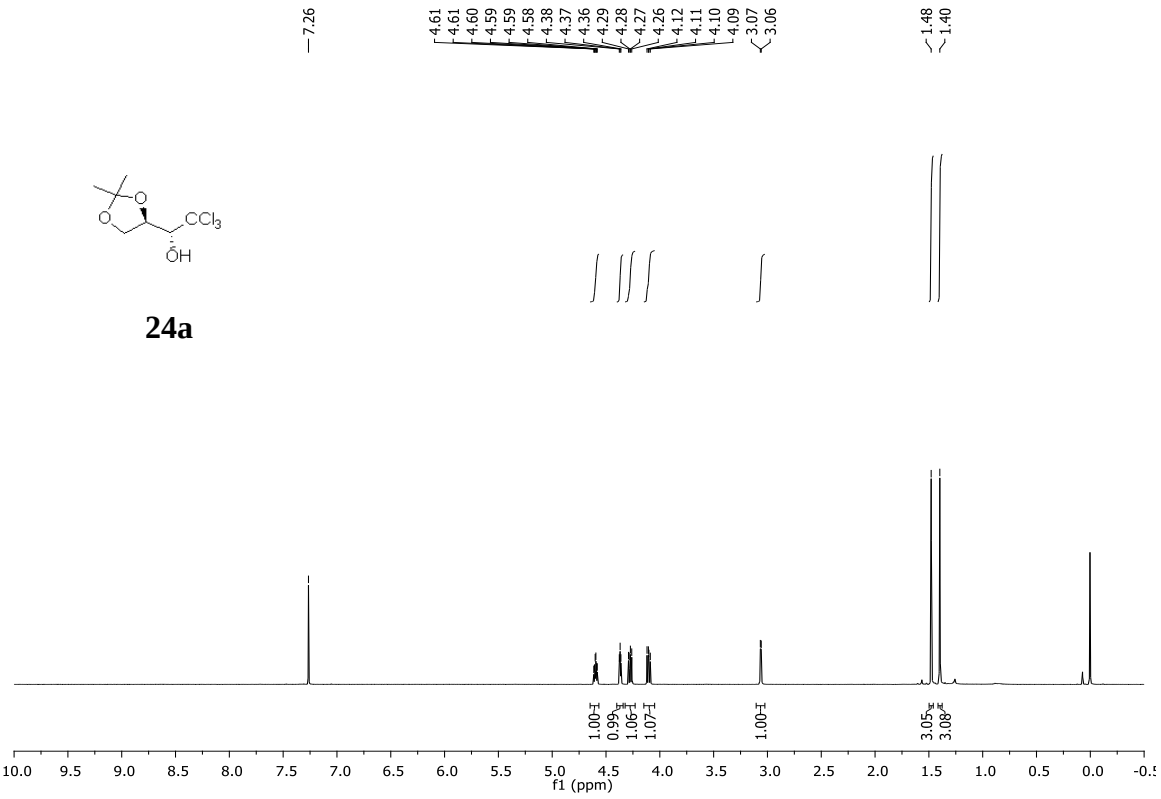
Mosher's ester derivative of the methyl ester of **22**

Mosher's ester derivative of the methyl ester of **22**

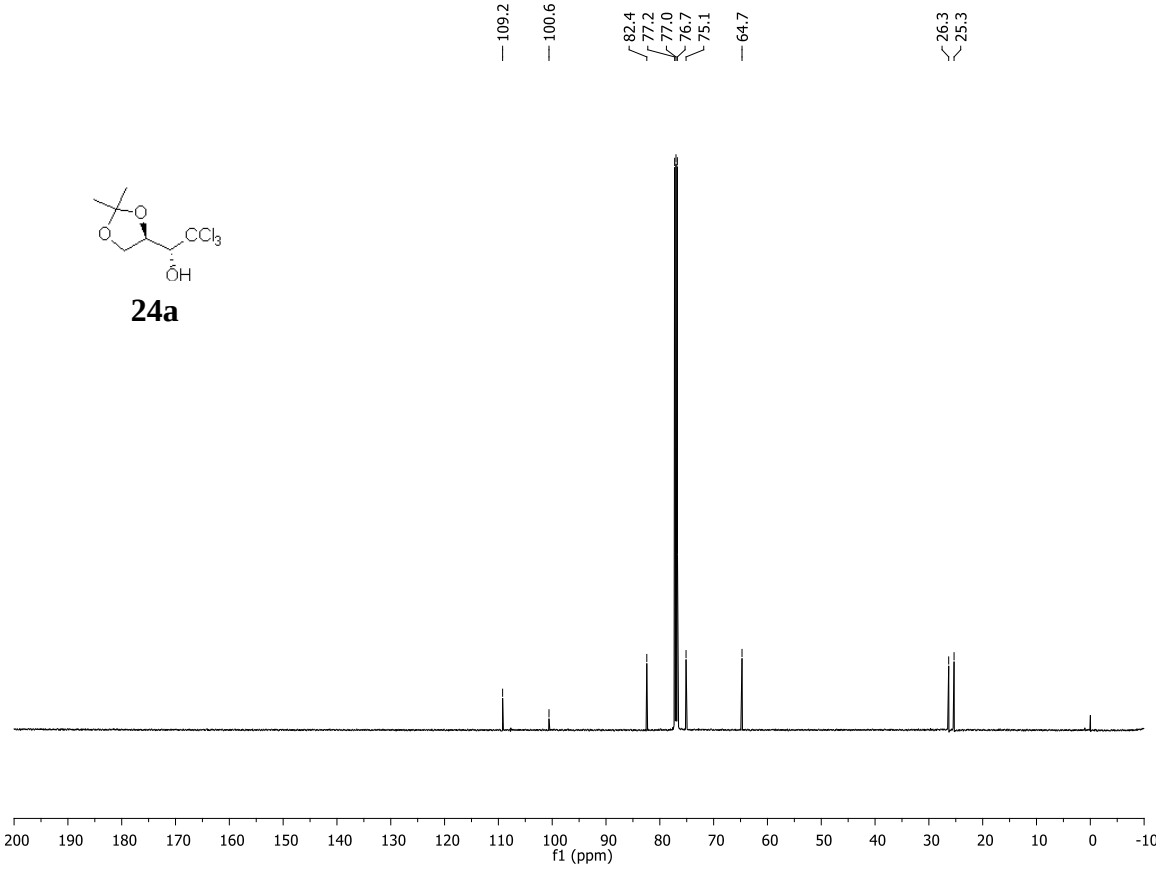

173.1
171.9
166.4
132.0
129.8
128.5
127.4
77.3
77.0
76.7
63.0
55.5
52.6
49.7
31.9
29.6
29.6
29.6
29.5
29.3
29.3
25.5
22.7
14.1
Ph
OMe
CF3
H
N
O
CO2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



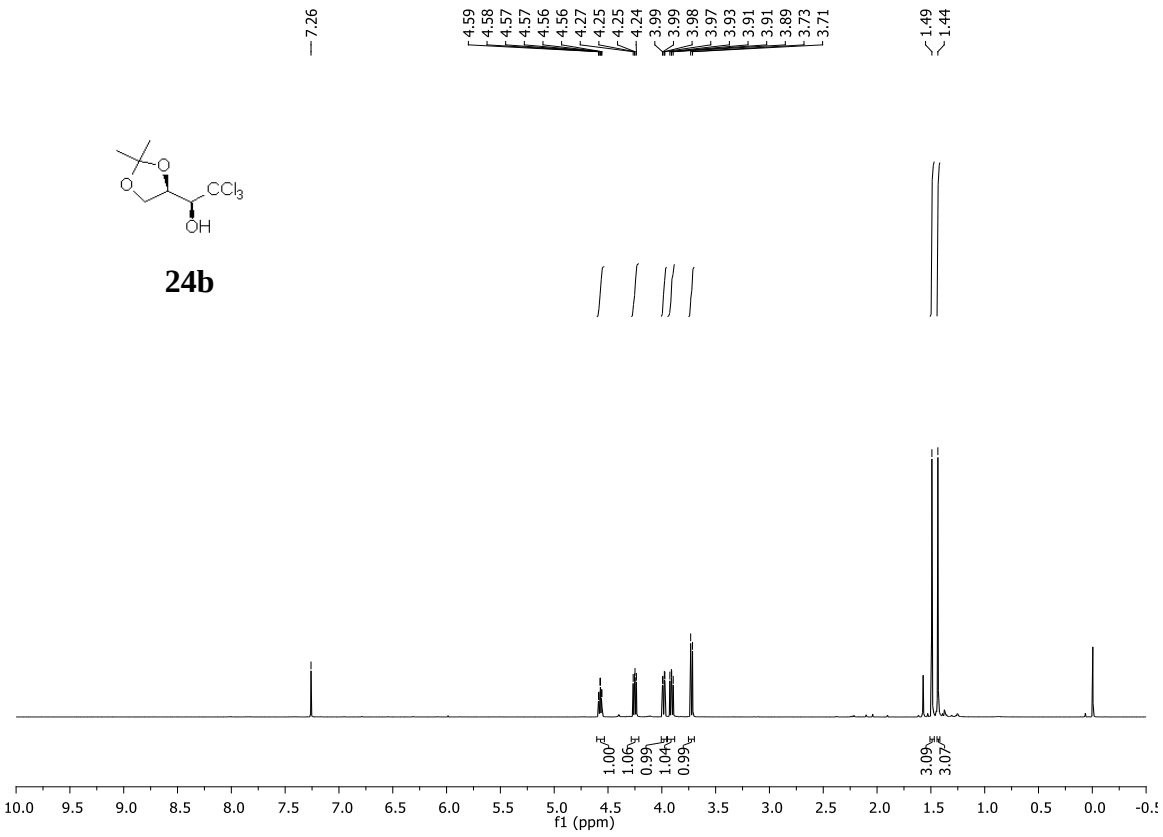
Mosher's ester derivative of the methyl ester of **22**


7.26
4.61
4.61
4.60
4.59
4.59
4.58
4.38
4.37
4.36
4.29
4.28
4.27
4.26
4.12
4.11
4.10
4.09
3.07
3.06
1.48
1.40
CCl3
OH
1.00
0.99
1.06
1.07
1.00
3.05
3.08
f1 (ppm)

24a

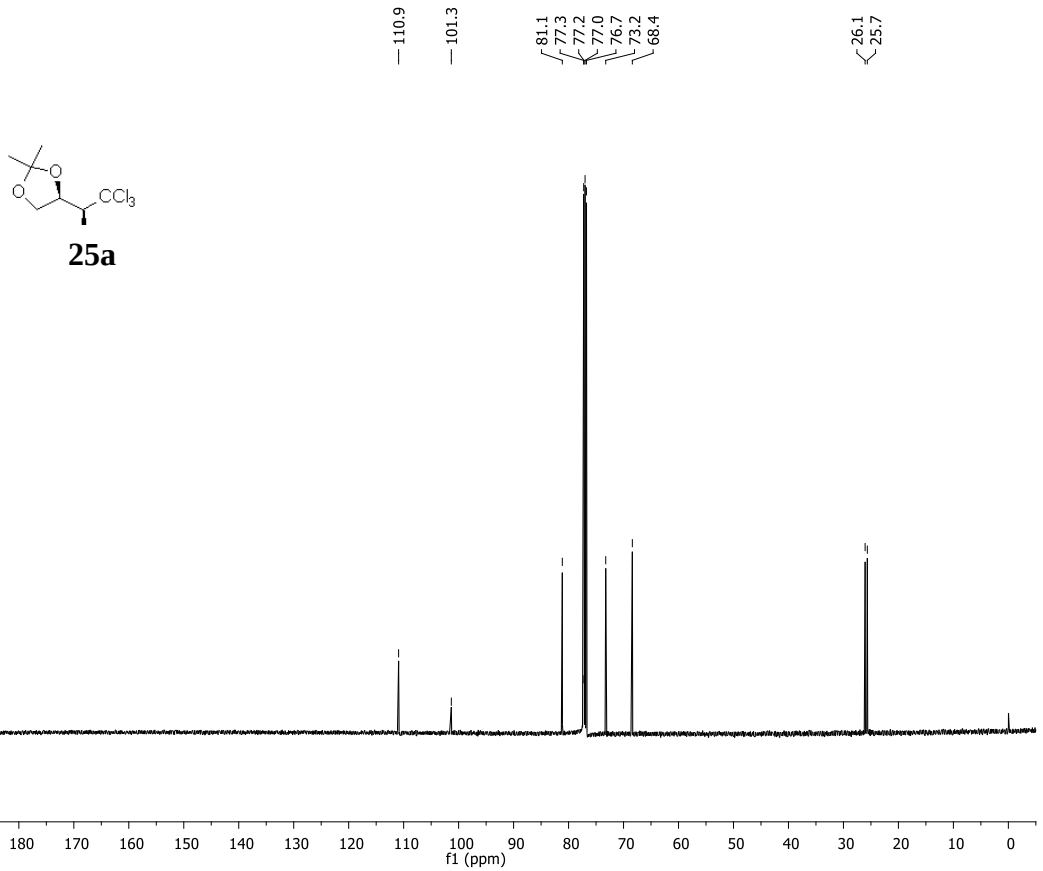

109.2
100.6
82.4
77.2
77.0
76.7
75.1
64.7
26.3
25.3
CCl3
OH
f1 (ppm)

24a

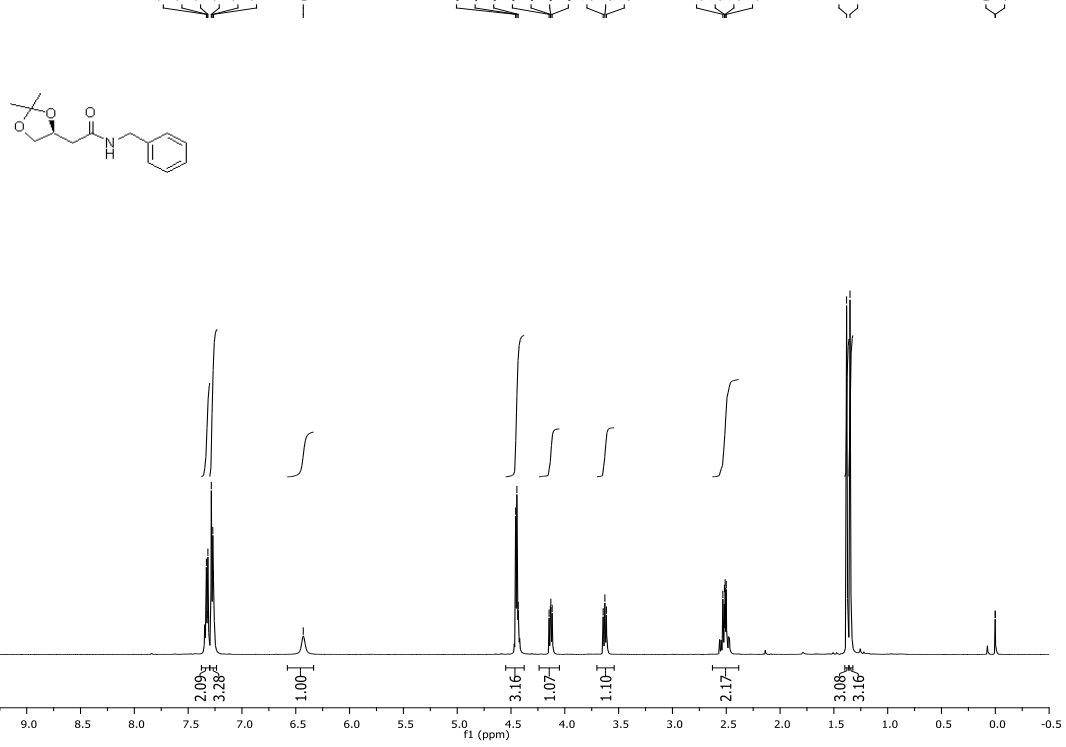

7.26
4.59
4.58
4.57
4.57
4.56
4.56
4.27
4.25
4.24
3.99
3.99
3.98
3.97
3.93
3.91
3.91
3.89
3.73
3.71
1.49
1.44
O
O
CCl3
OH
1.00
1.06
0.99
1.04
0.99
3.09
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

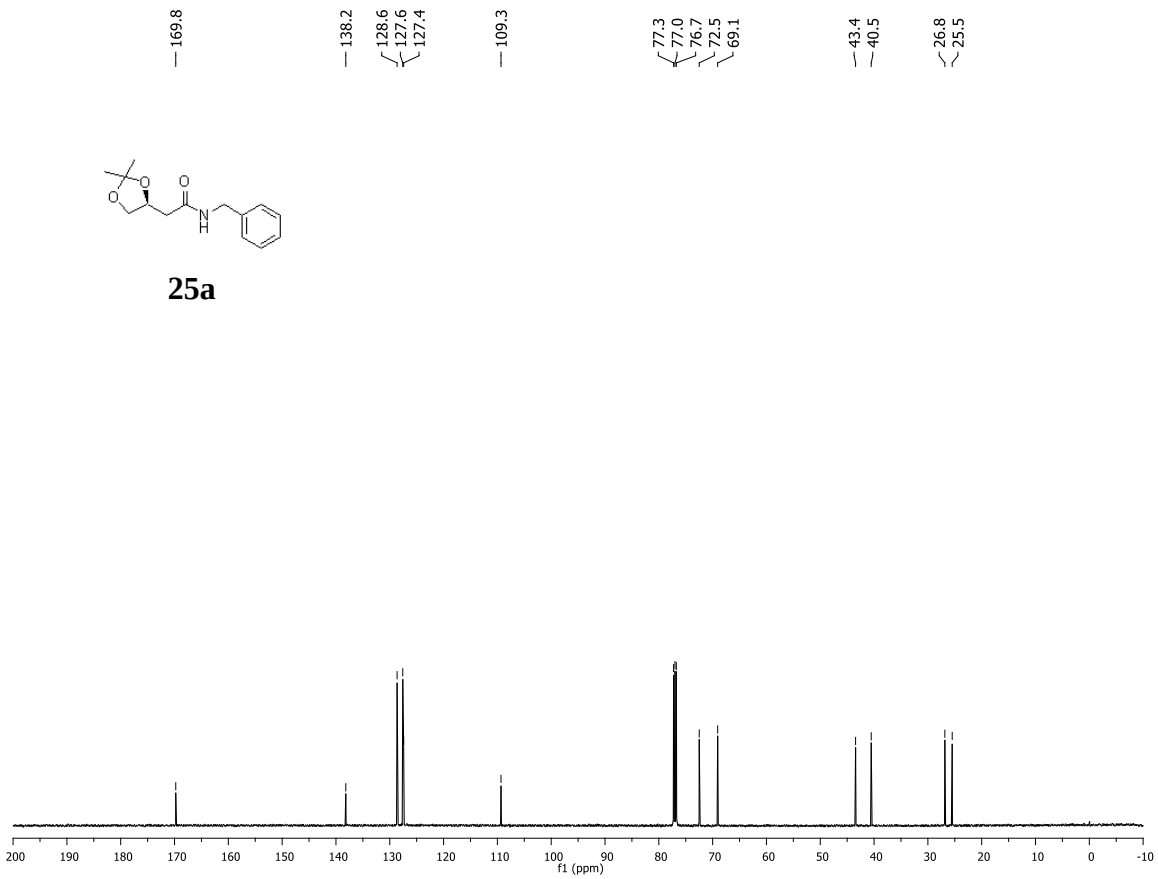
24b

24b

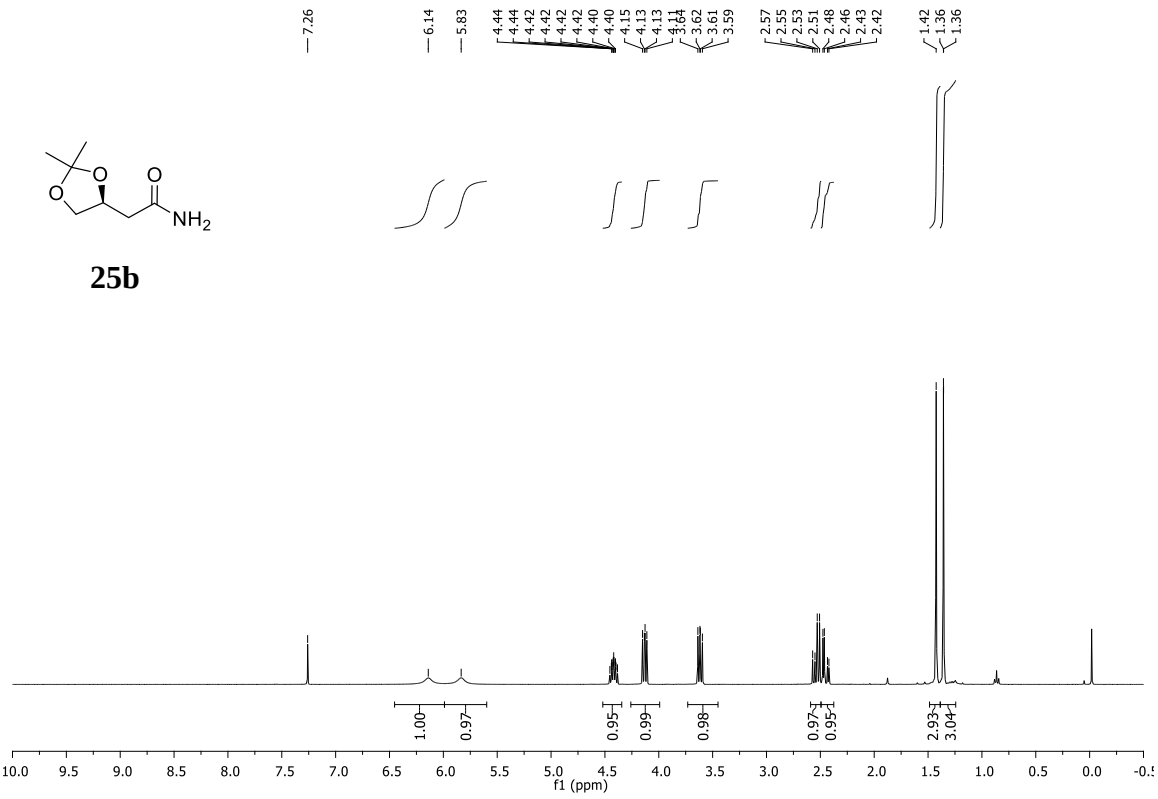

110.9
101.3
81.1
77.3
77.2
77.0
76.7
73.2
68.4
26.1
25.7
CCl3
f1 (ppm)

25a

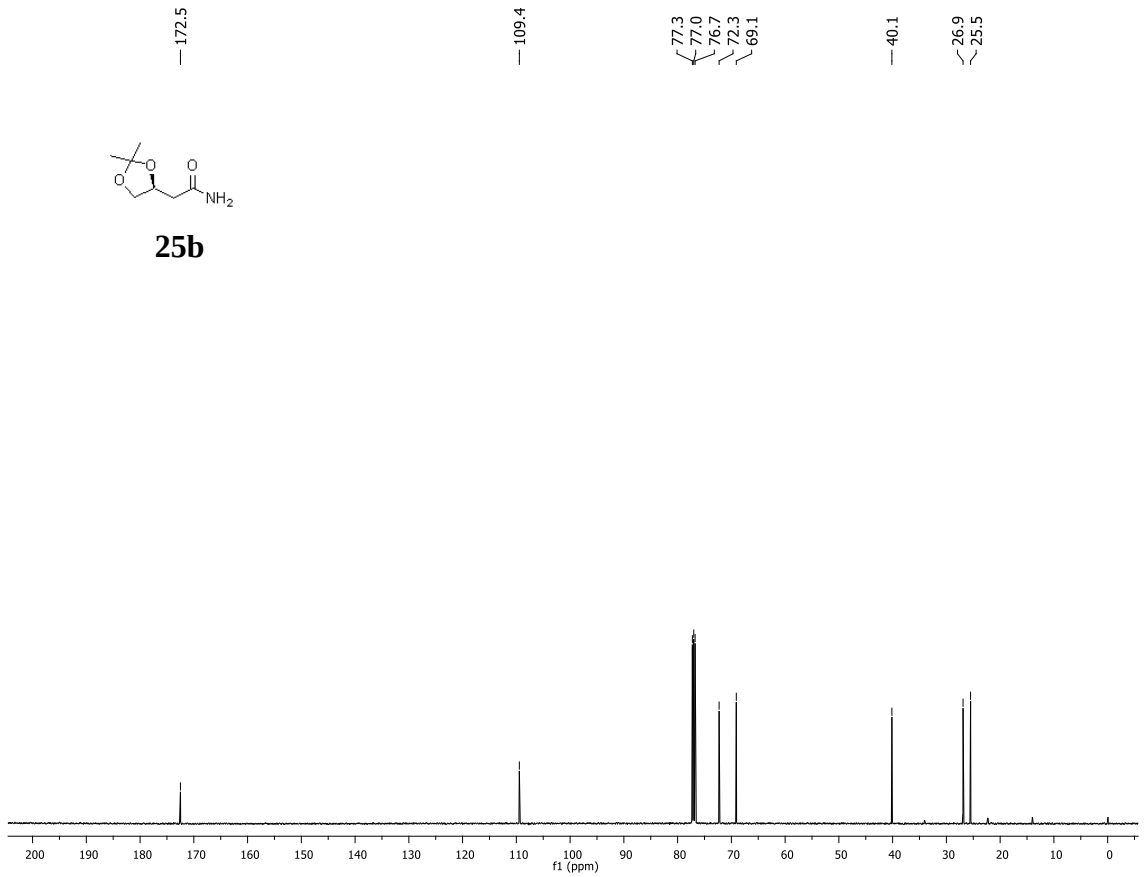

7.33
7.32
7.32
7.28
7.27
7.26
6.43
4.46
4.45
4.43
4.15
4.13
4.13
4.12
3.64
3.63
3.61
2.53
2.52
2.51
2.50
1.38
1.35
0.00
-0.00
O
N
H
2.09
3.28
1.00
3.16
1.07
1.10
2.17
3.08
3.16
f1 (ppm)


169.8
138.2
128.6
127.6
127.4
109.3
77.3
77.0
76.7
72.5
69.1
43.4
40.5
26.8
25.5
f1 (ppm)

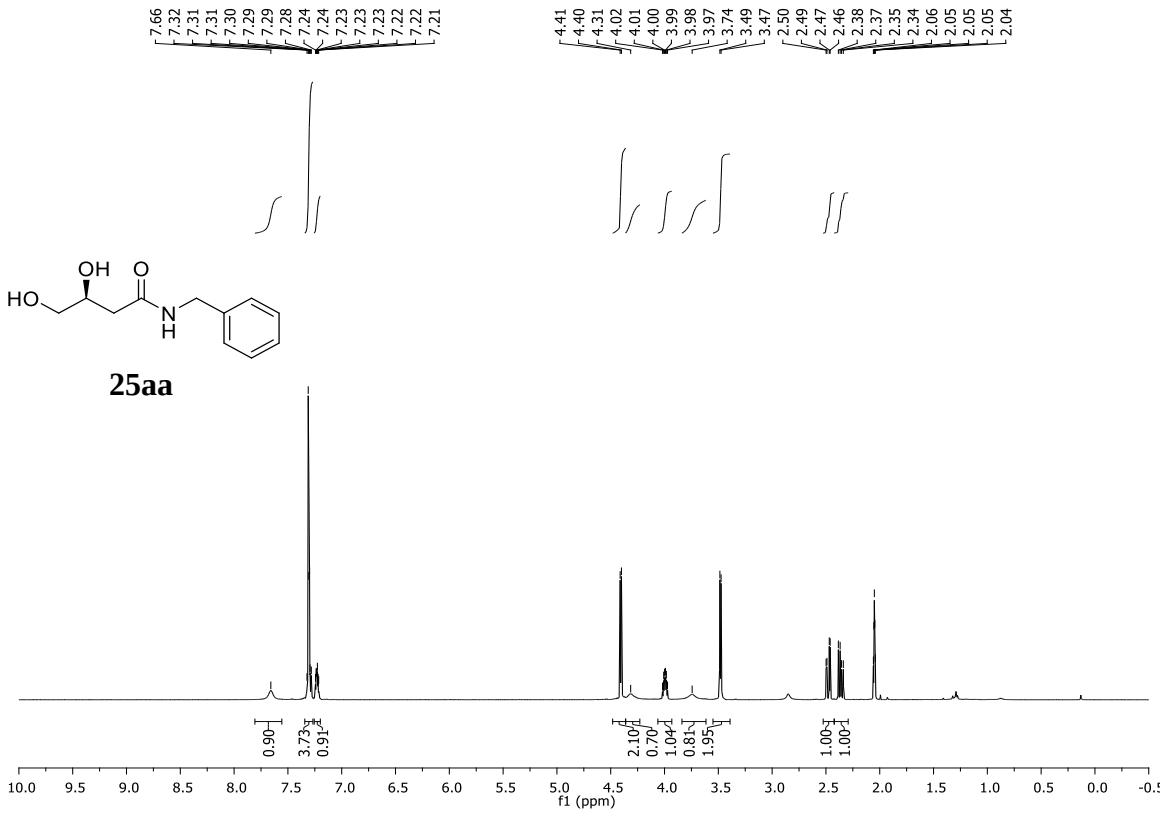
25a


7.26
6.14
5.83
4.44
4.42
4.40
4.15
4.13
3.62
3.61
3.59
2.57
2.55
2.53
2.51
2.48
2.46
2.43
2.42
1.42
1.36
1.00
0.97
0.95
0.99
0.98
0.97
0.95
2.93
3.04
f1 (ppm)

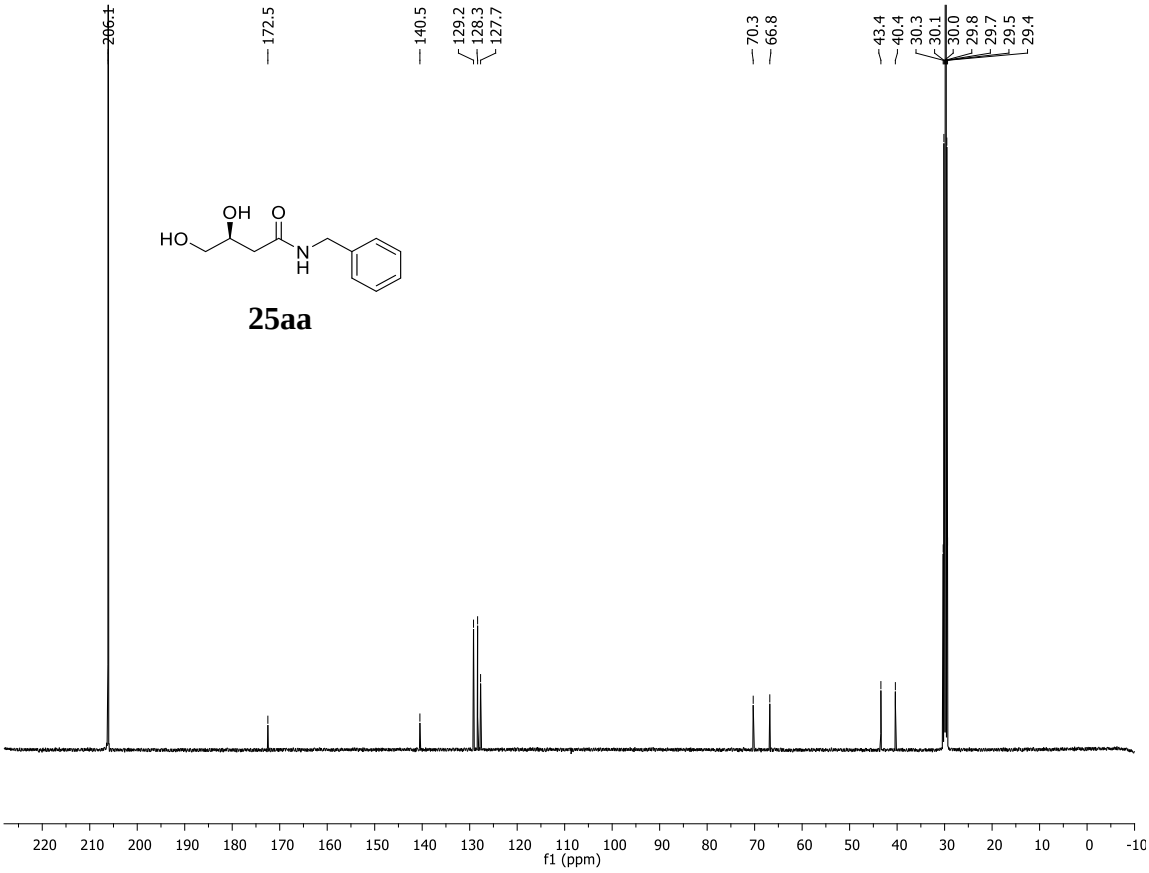
25b


172.5
109.4
77.3
77.0
76.7
72.3
69.1
40.1
26.9
25.5
O
O
O
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

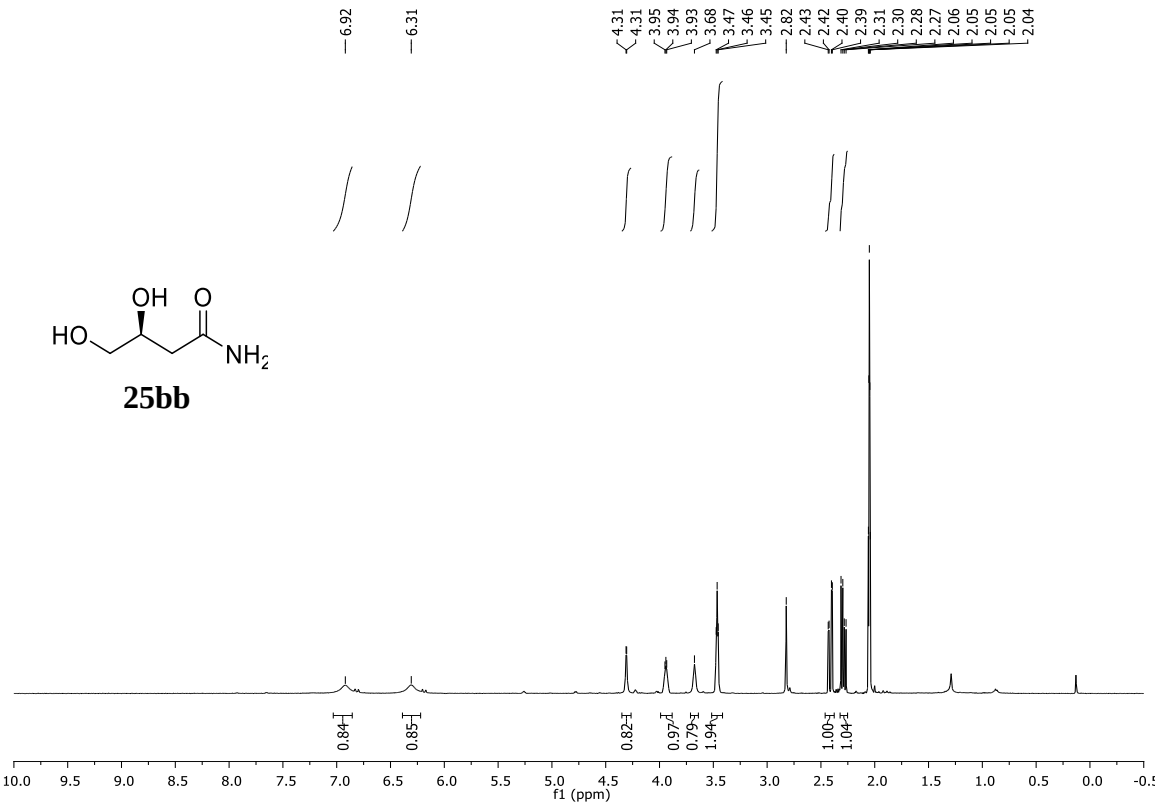
25b


7.66
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.24
7.24
7.23
7.23
7.22
7.22
7.21
4.41
4.40
4.31
4.02
4.01
4.00
3.99
3.98
3.97
3.74
3.49
3.47
2.50
2.49
2.47
2.46
2.38
2.37
2.35
2.34
2.06
2.05
2.05
2.05
2.04
OH
O
HO
N
H
0.90
3.73
0.91
2.10
0.70
1.04
0.81
1.95
1.00
1.00
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
f1 (ppm)

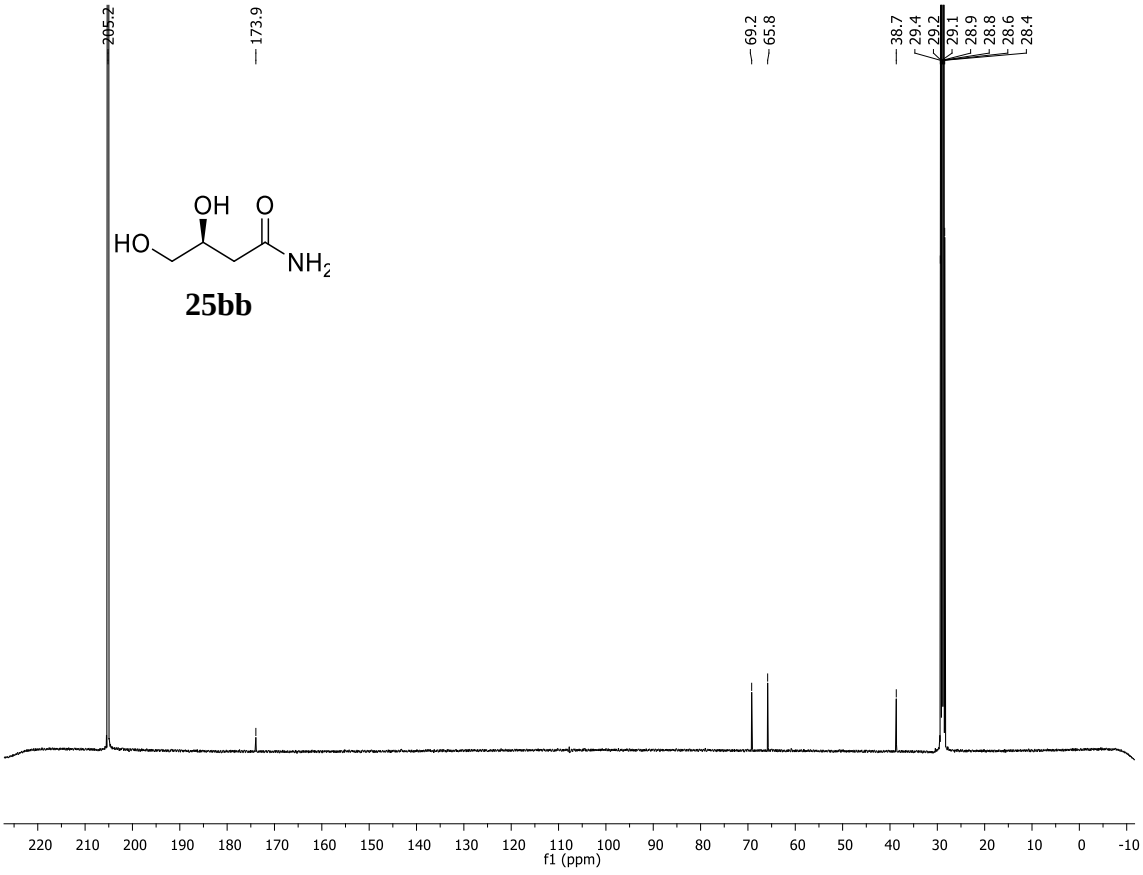
25aa


206.1
172.5
140.5
129.2
128.3
127.7
70.3
66.8
43.4
40.4
30.3
30.1
30.0
29.8
29.7
29.5
29.4
OH
O
HO
N
H
f1 (ppm)

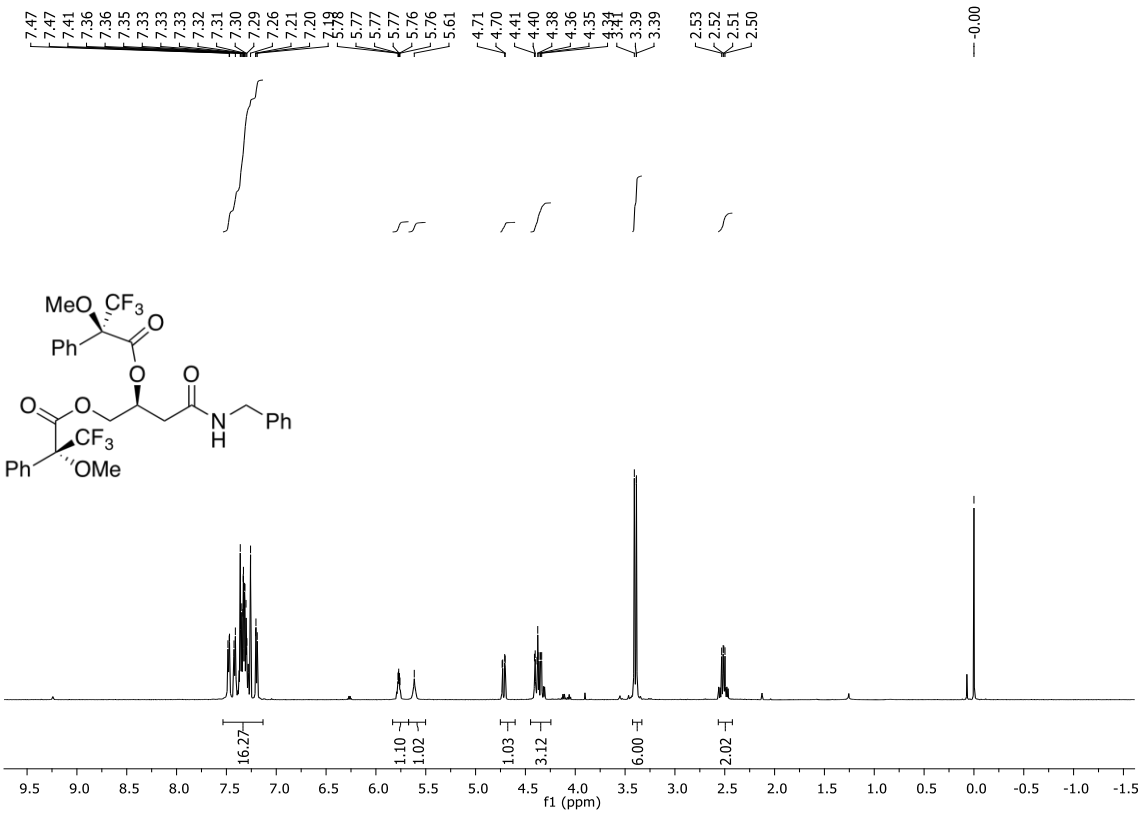
25aa

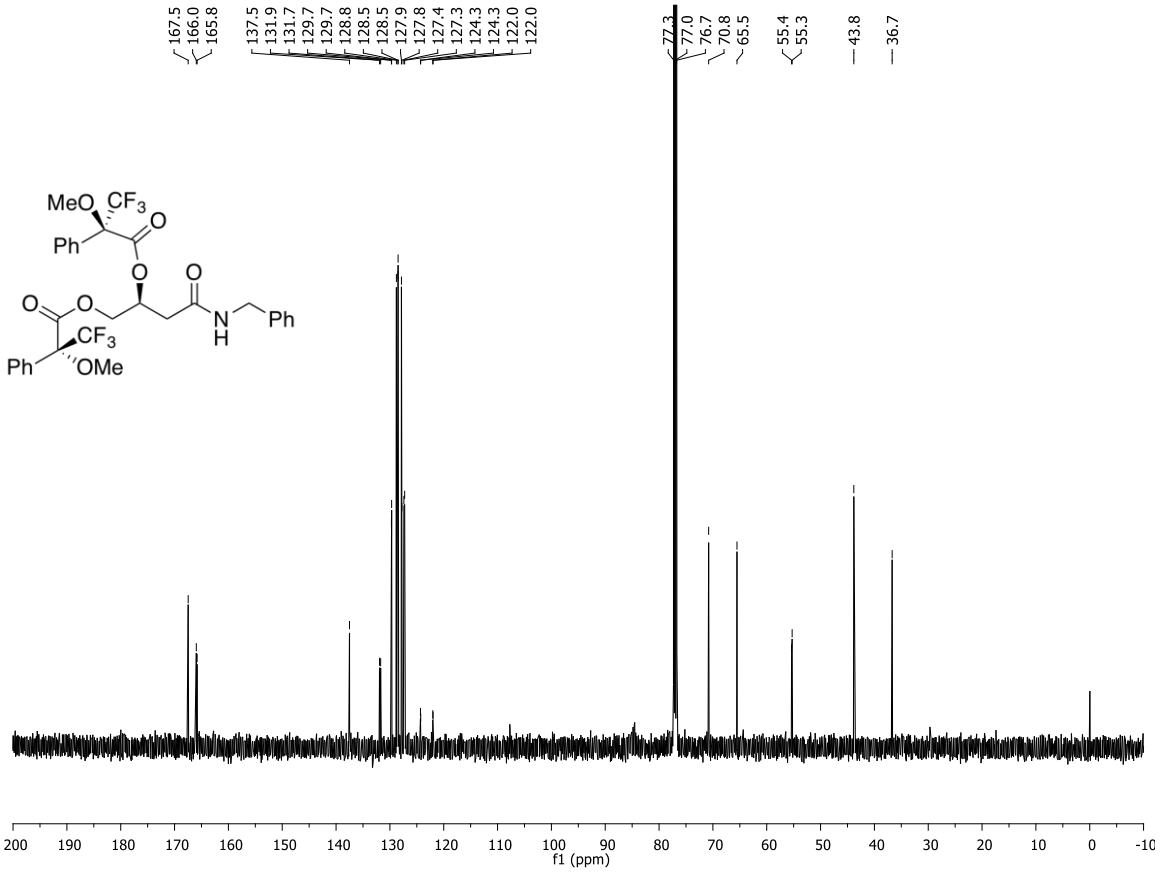

6.92
6.31
4.31
4.31
3.95
3.94
3.93
3.68
3.47
3.46
3.45
2.82
2.43
2.42
2.40
2.39
2.31
2.30
2.28
2.27
2.06
2.05
2.05
2.05
2.04
OH
O
HO
NH2
0.84
0.85
0.82
0.97
0.79
1.94
1.00
1.04
f1 (ppm)

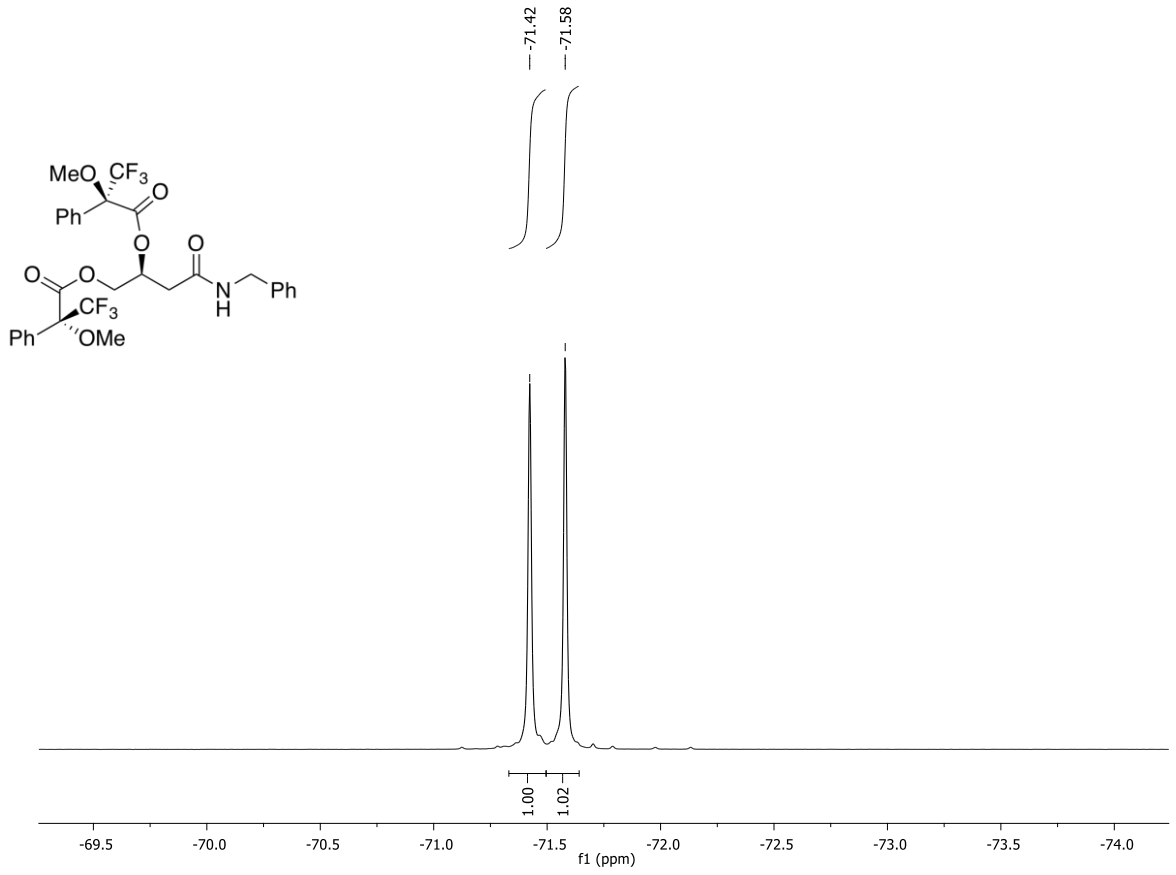
25bb

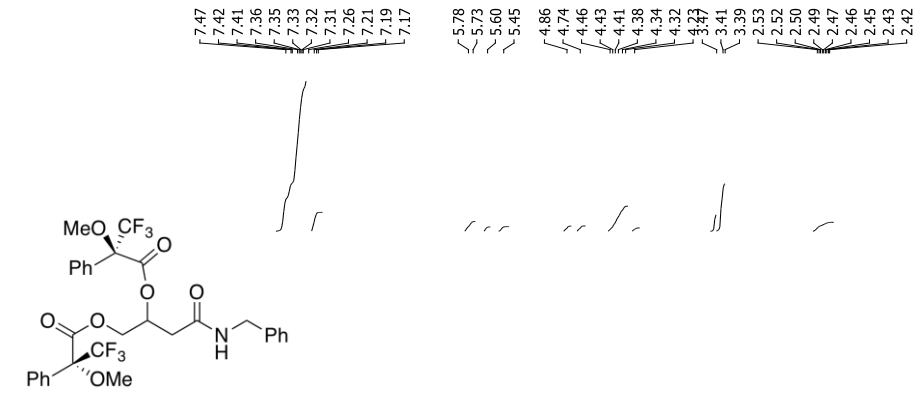

205.2
173.9
69.2
65.8
38.7
29.4
29.2
29.1
28.9
28.8
28.6
28.4
OH
O
HO
NH2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

25bb

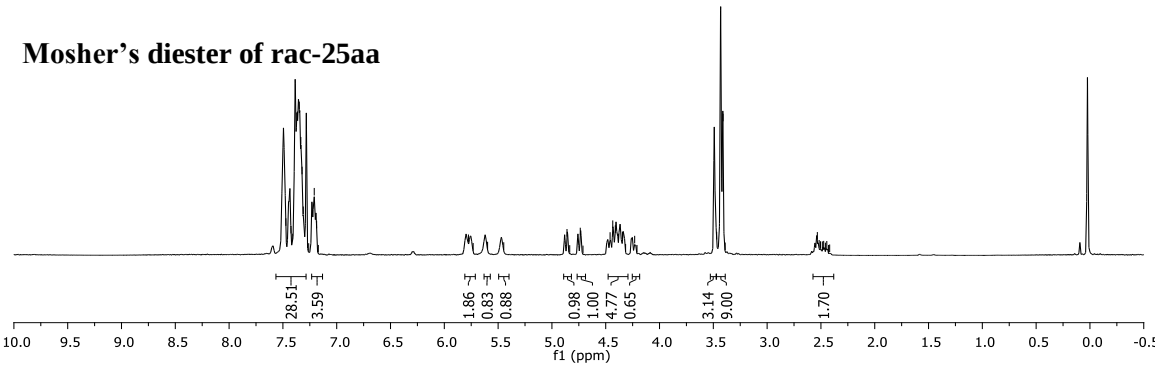

7.47
7.47
7.41
7.36
7.36
7.35
7.33
7.33
7.33
7.32
7.31
7.30
7.29
7.26
7.21
7.20
5.78
5.77
5.77
5.77
5.76
5.76
5.61
4.71
4.70
4.41
4.40
4.38
4.36
4.35
4.34
4.34
3.41
3.39
3.39
2.53
2.52
2.51
2.50
-0.00
MeO
CF3
Ph
O
O
O
O
O
N
H
Ph
CF3
Ph
OMe
16.27
1.10
1.02
1.03
3.12
6.00
2.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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
-1.0
-1.5
f1 (ppm)

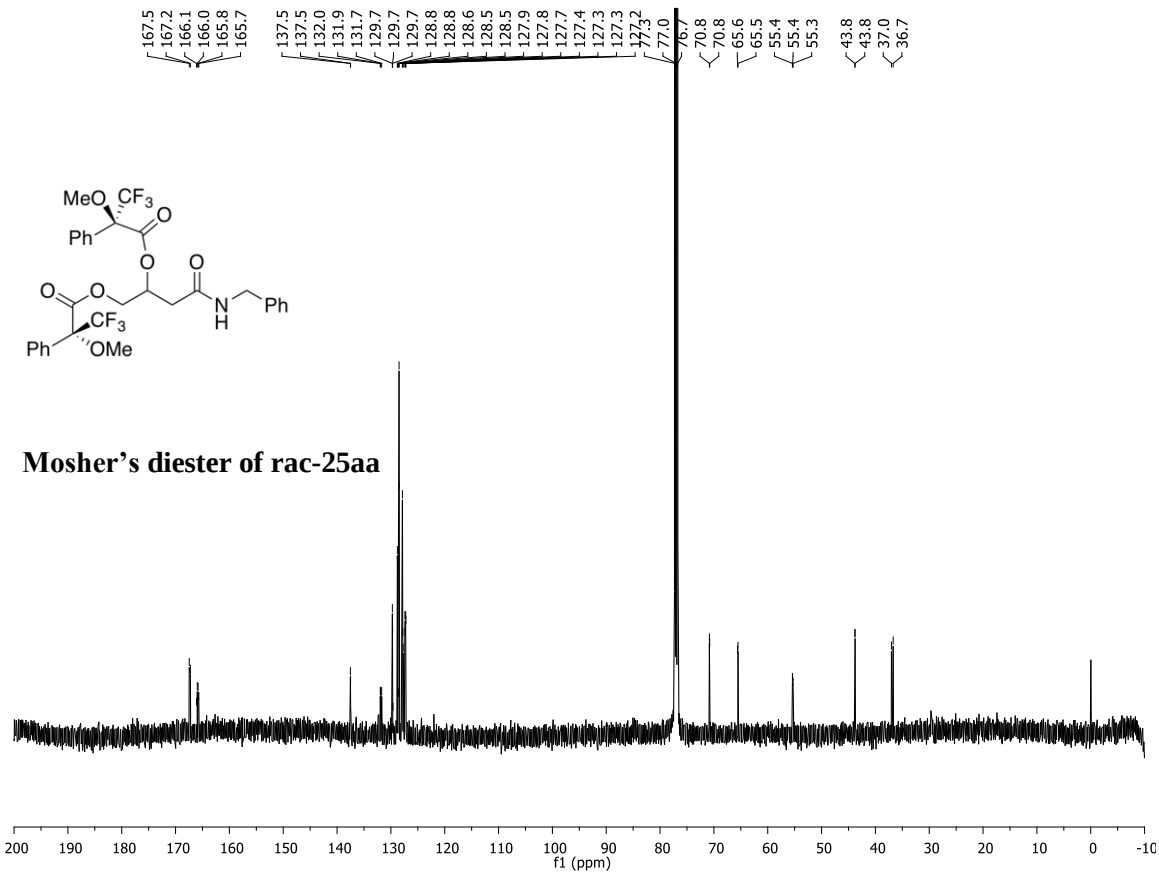

167.5
166.0
165.8
137.5
131.9
131.7
129.7
129.7
128.8
128.5
128.5
127.9
127.8
127.4
127.3
124.3
124.3
122.0
122.0
77.3
77.0
76.7
70.8
65.5
55.4
55.3
43.8
36.7
MeO
CF3
Ph
O
O
O
O
O
N
H
Ph
CF3
Ph
OMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-71.42
-71.58
MeO
CF3
Ph
O
O
O
O
O
N
H
Ph
CF3
Ph
OMe
1.00
1.02
-69.5
-70.0
-70.5
-71.0
-71.5
-72.0
-72.5
-73.0
-73.5
-74.0
f1 (ppm)

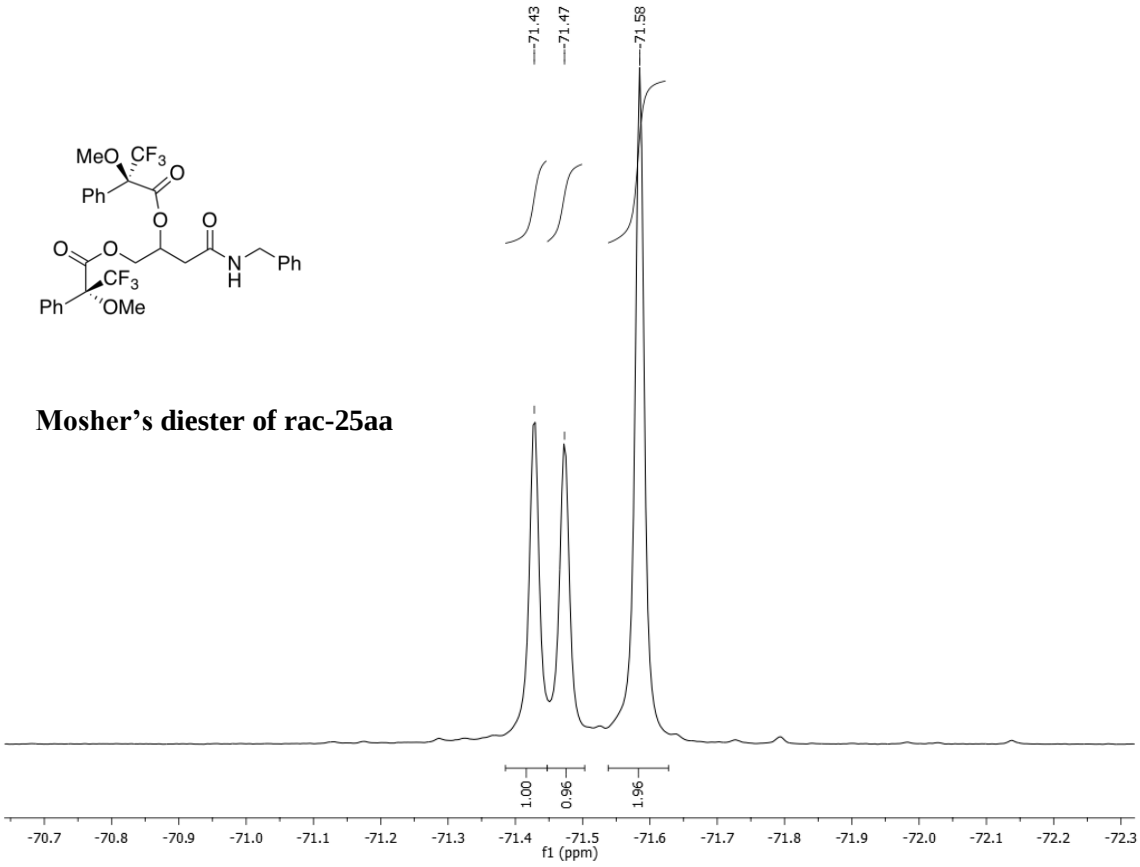


Mosher's diester of rac-25aa

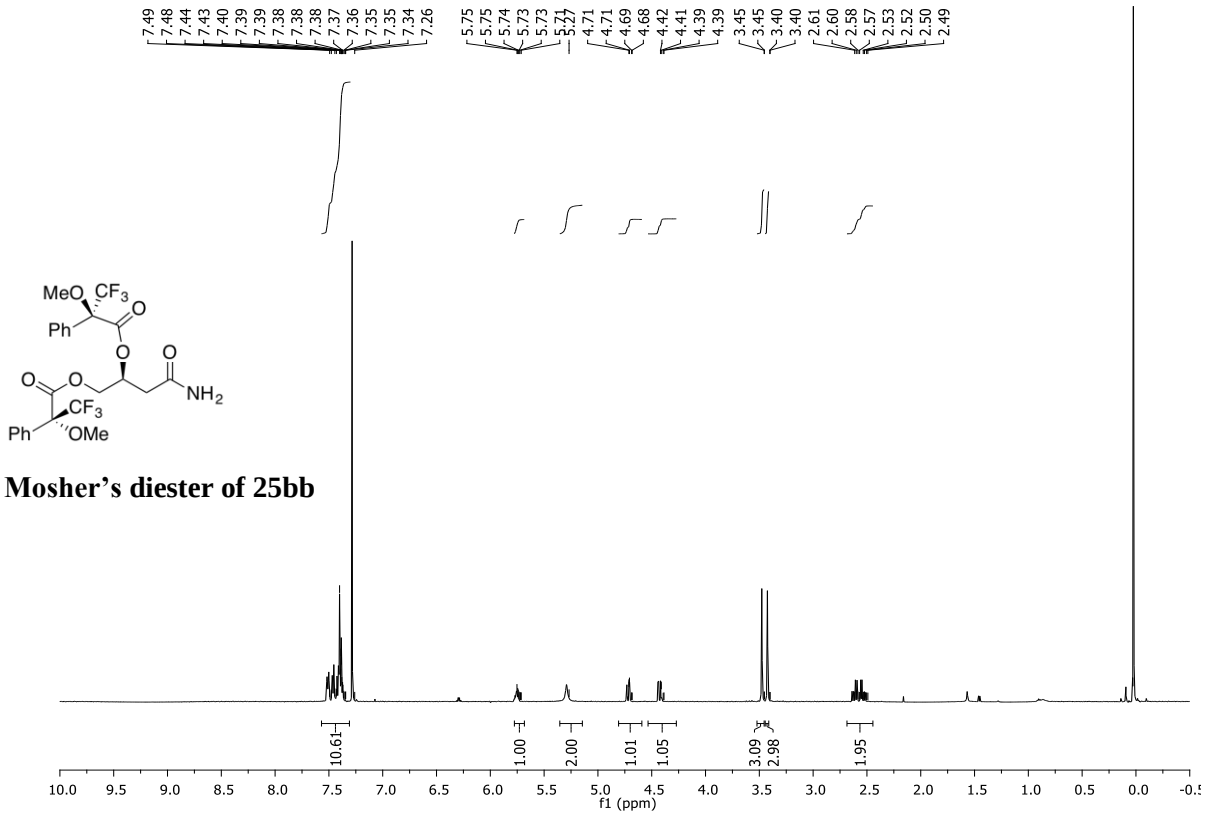




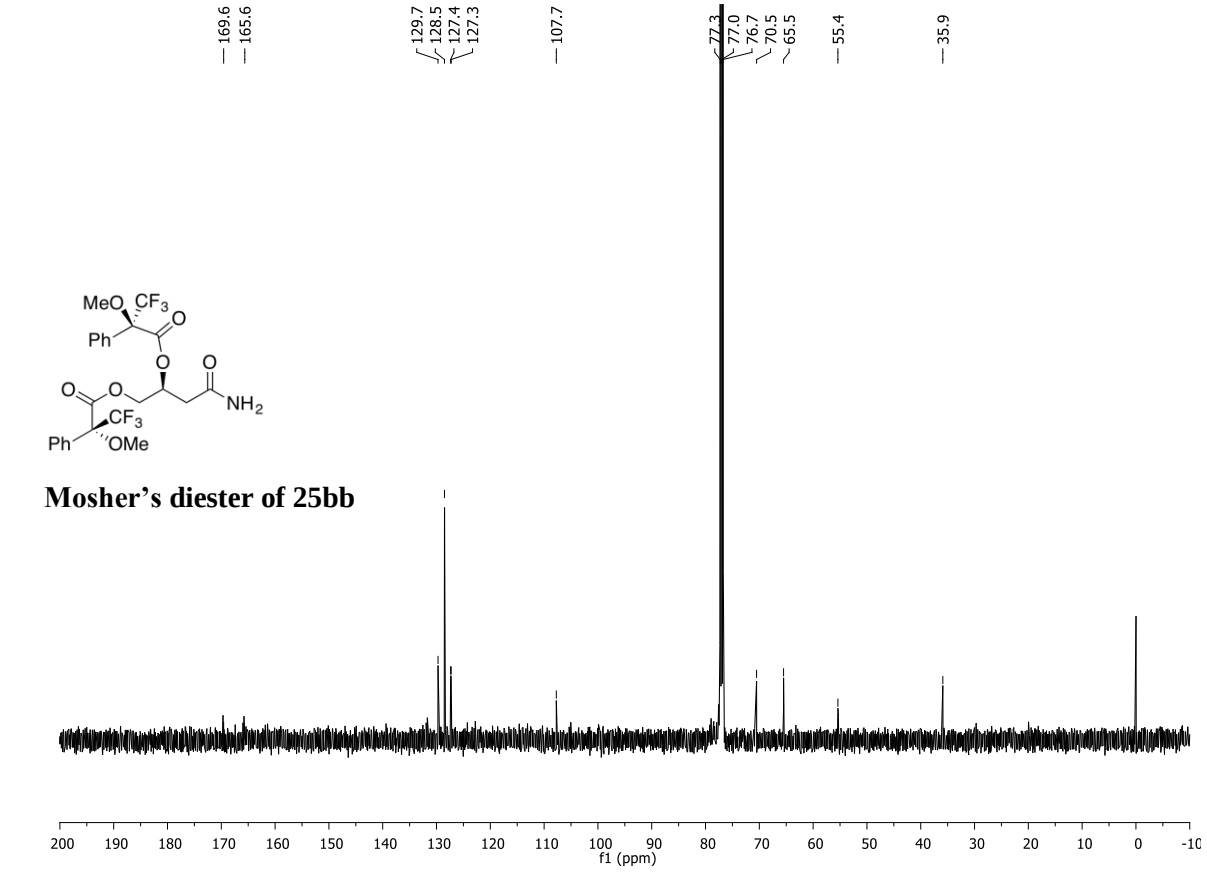
Mosher's diester of rac-25aa



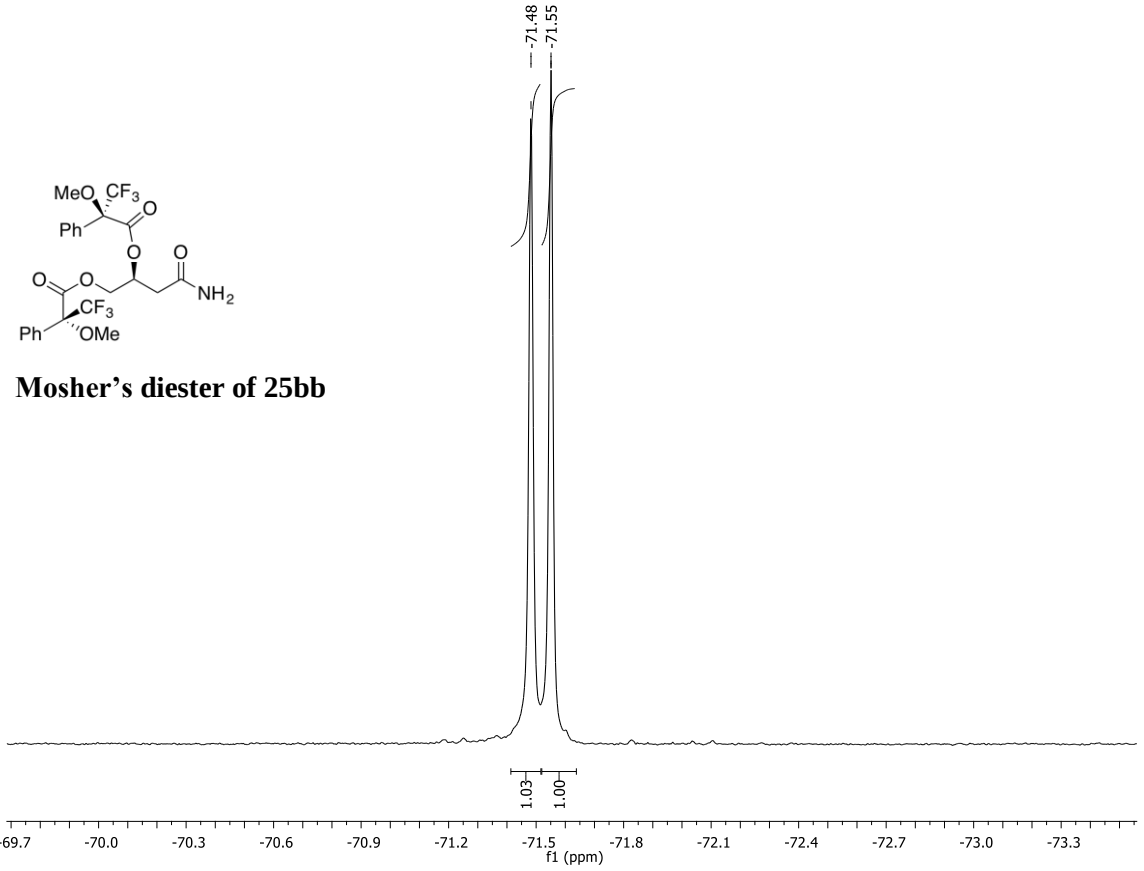
Mosher's diester of rac-25aa



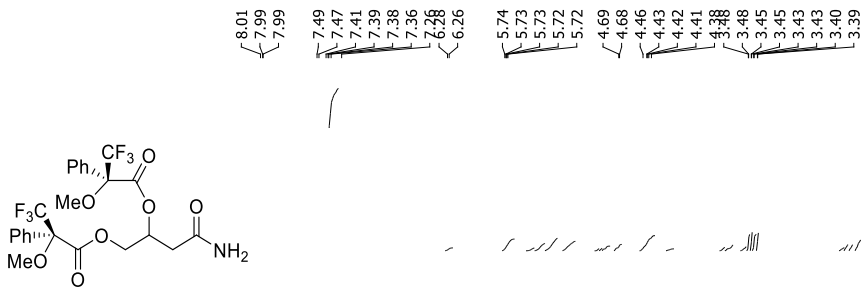
Mosher's diester of 25bb



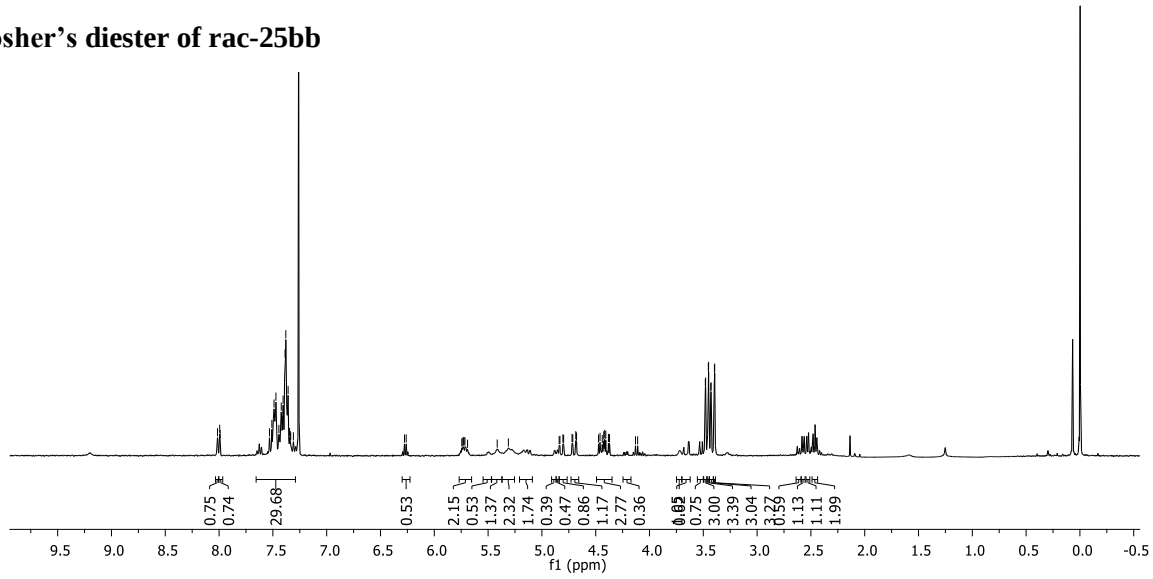
Mosher's diester of 25bb

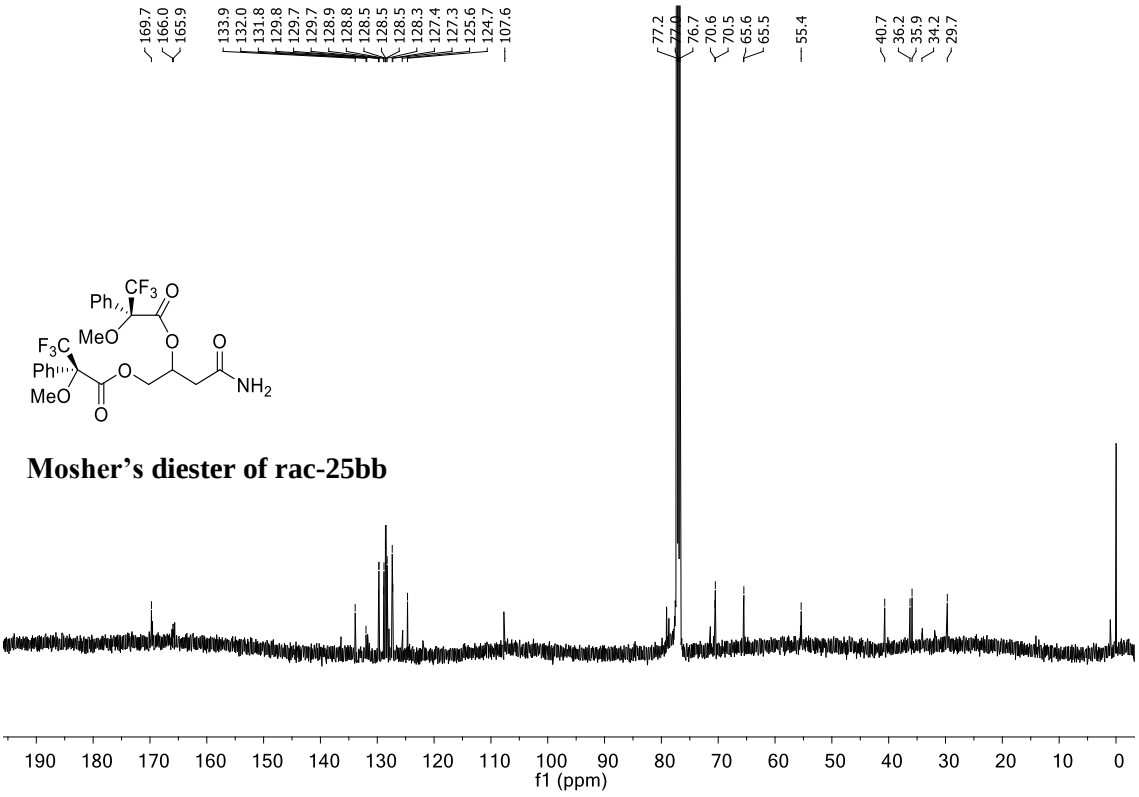


Mosher's diester of 25bb

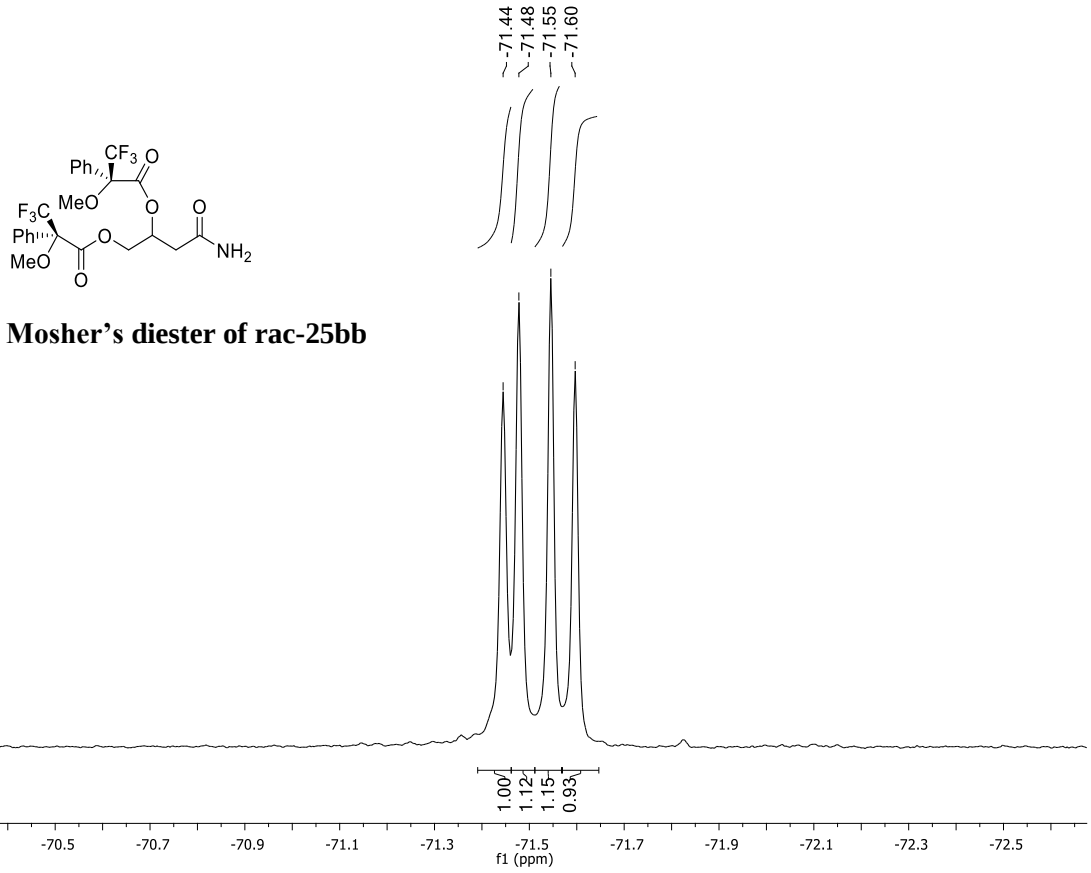


Mosher's diester of rac-25bb

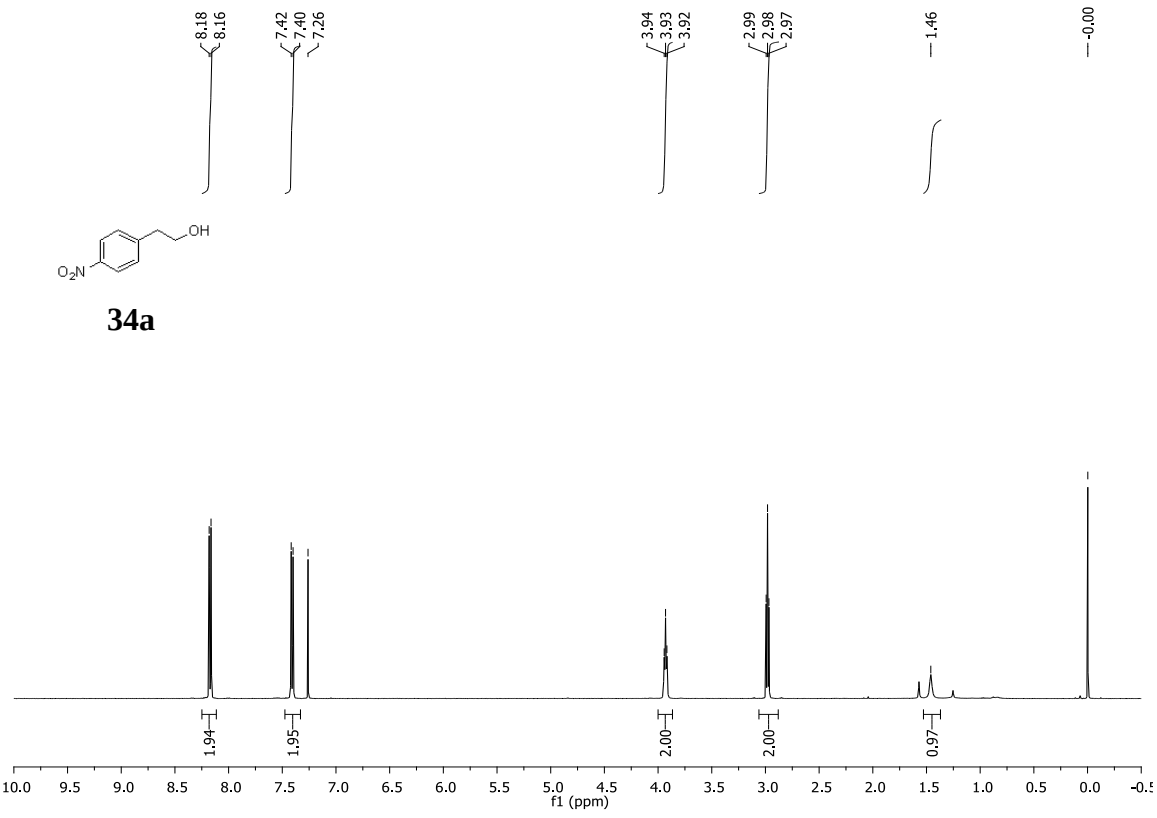




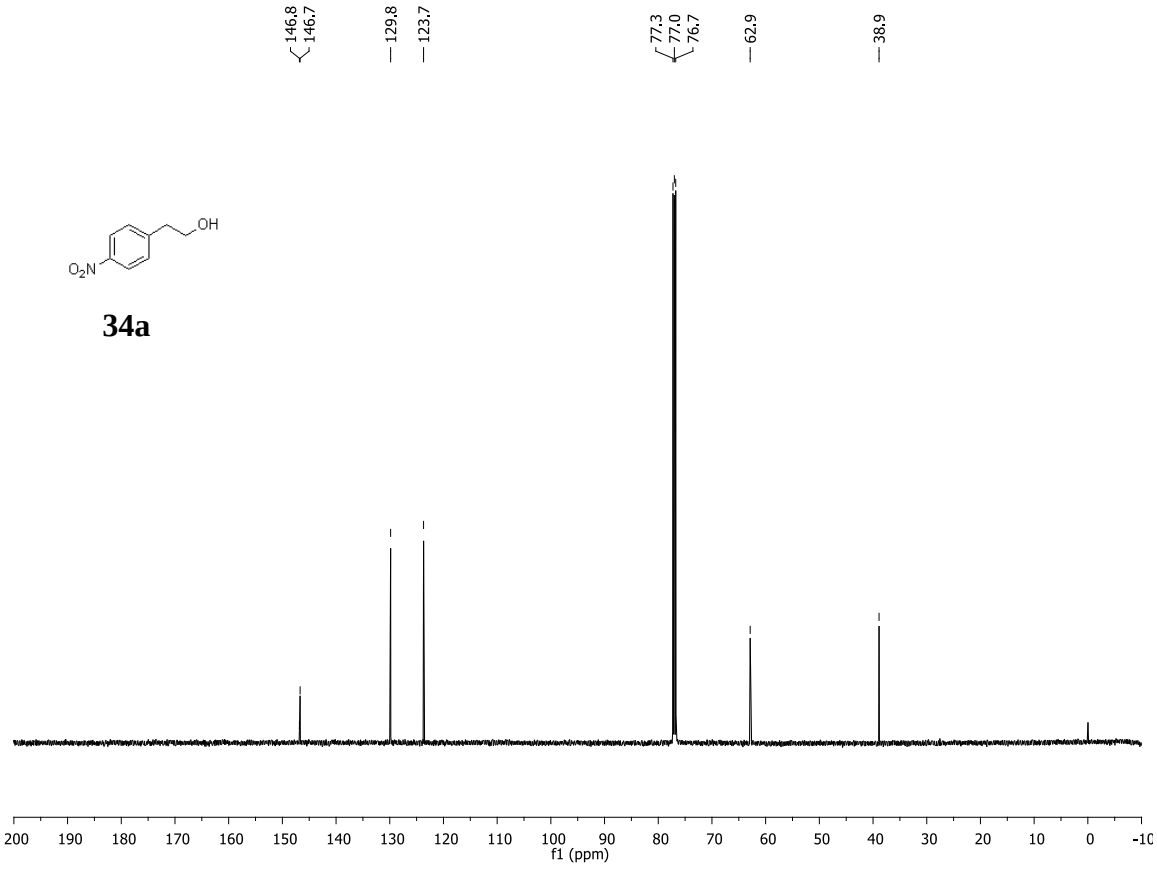
Mosher's diester of rac-25bb



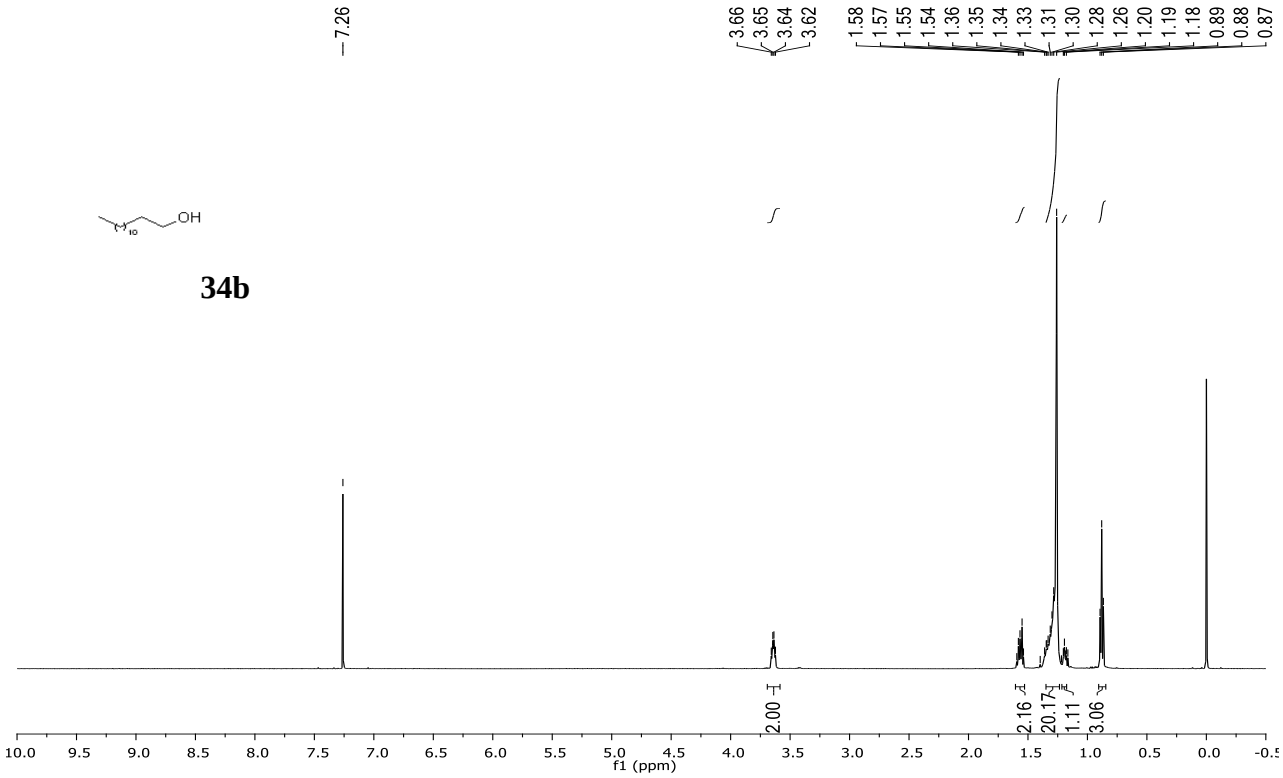
Mosher's diester of rac-25bb


8.18
8.16
7.42
7.40
7.26
3.94
3.93
3.92
2.99
2.98
2.97
1.46
0.00
OH
O2N
1.94
1.95
2.00
2.00
0.97
f1 (ppm)

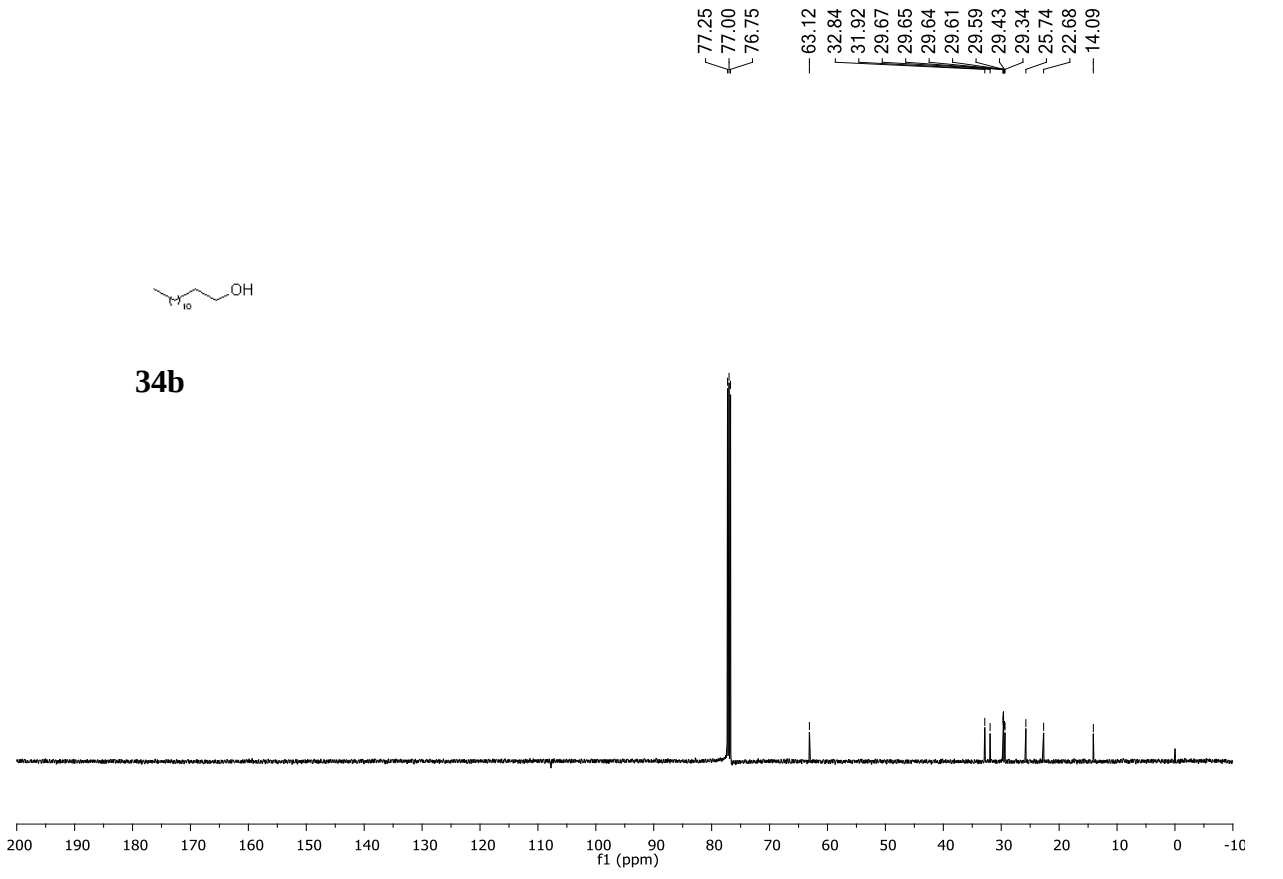
34a


146.8
146.7
129.8
123.7
77.3
77.0
76.7
62.9
38.9
OH
O2N
f1 (ppm)

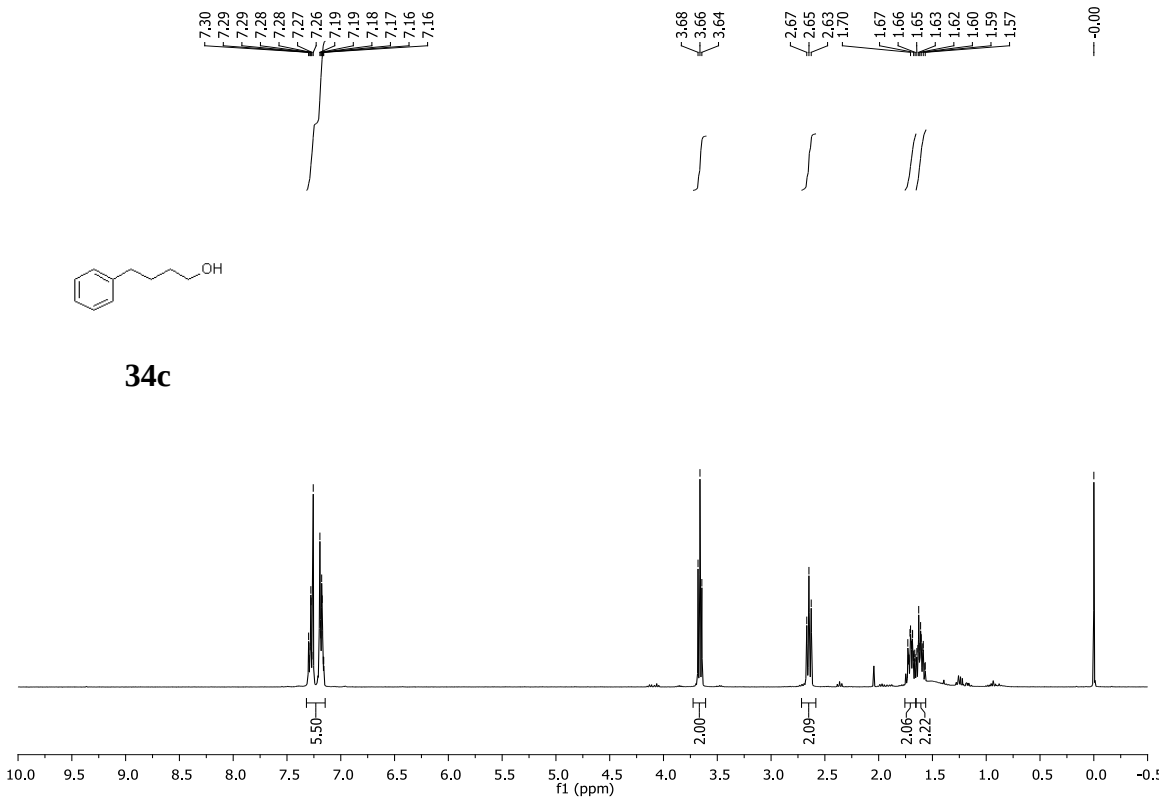
34a


7.26
3.66
3.65
3.64
3.62
1.58
1.57
1.55
1.54
1.36
1.35
1.34
1.33
1.31
1.30
1.28
1.26
1.20
1.19
1.18
0.89
0.88
0.87
OH
10
2.00
2.16
20.17
1.11
3.06
f1 (ppm)

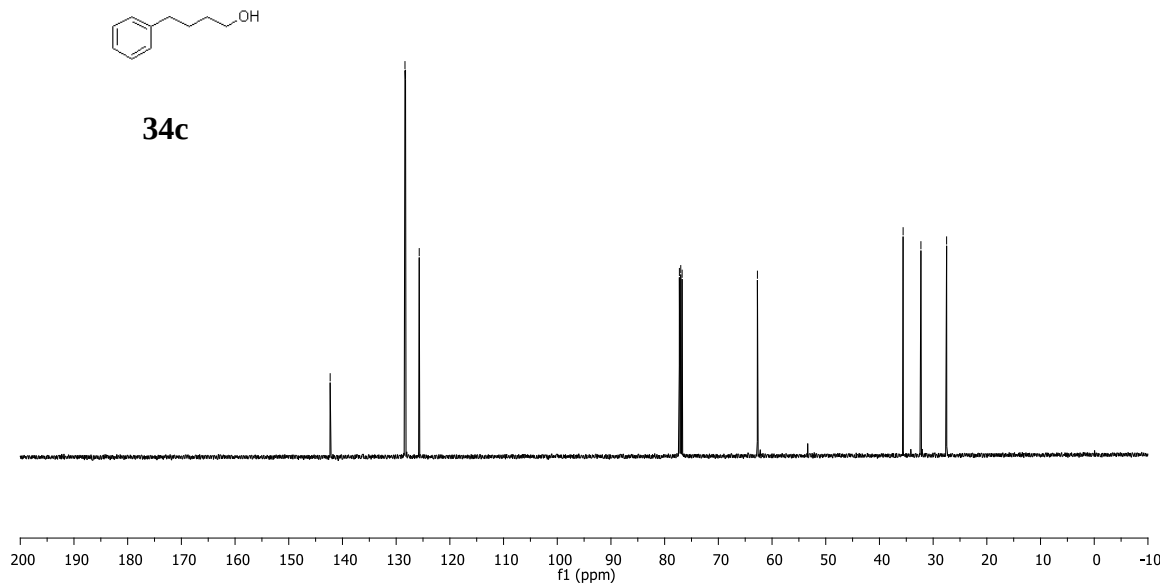
34b


77.25
77.00
76.75
63.12
32.84
31.92
29.67
29.65
29.64
29.61
29.59
29.43
29.34
25.74
22.68
14.09
OH
10
f1 (ppm)

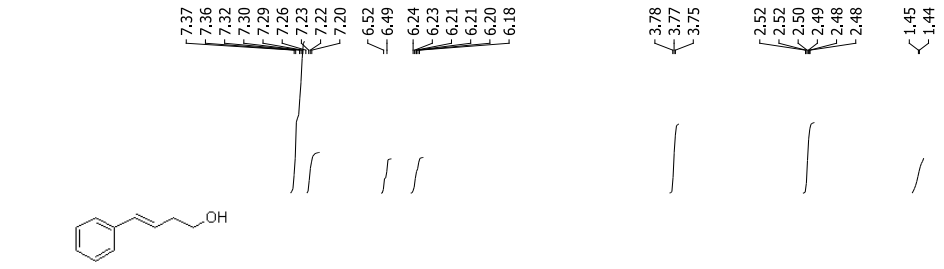
34b


7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.19
7.19
7.18
7.17
7.16
7.16
3.68
3.66
3.64
2.67
2.65
2.63
1.70
1.67
1.66
1.65
1.63
1.62
1.60
1.59
1.57
0.00
OH
5.50
2.00
2.09
2.06
2.22
f1 (ppm)

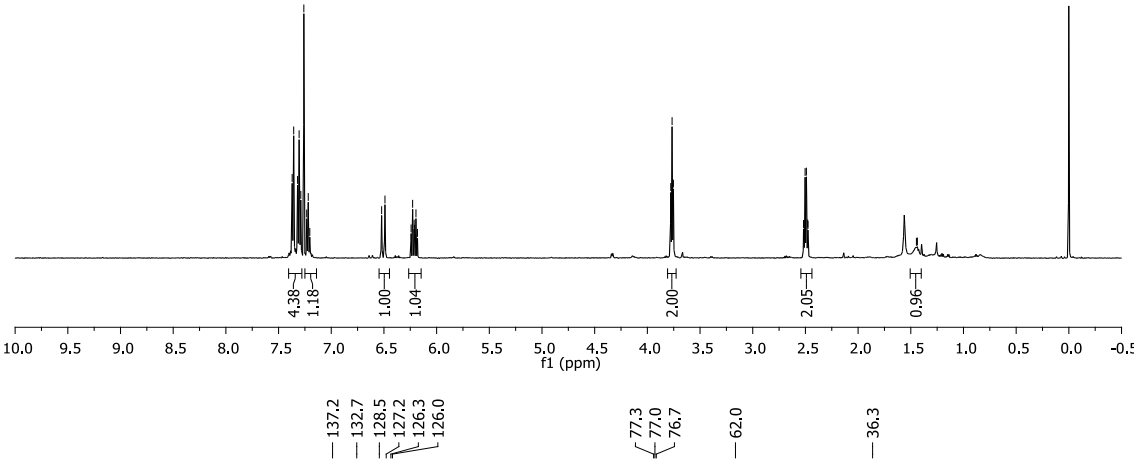
34c

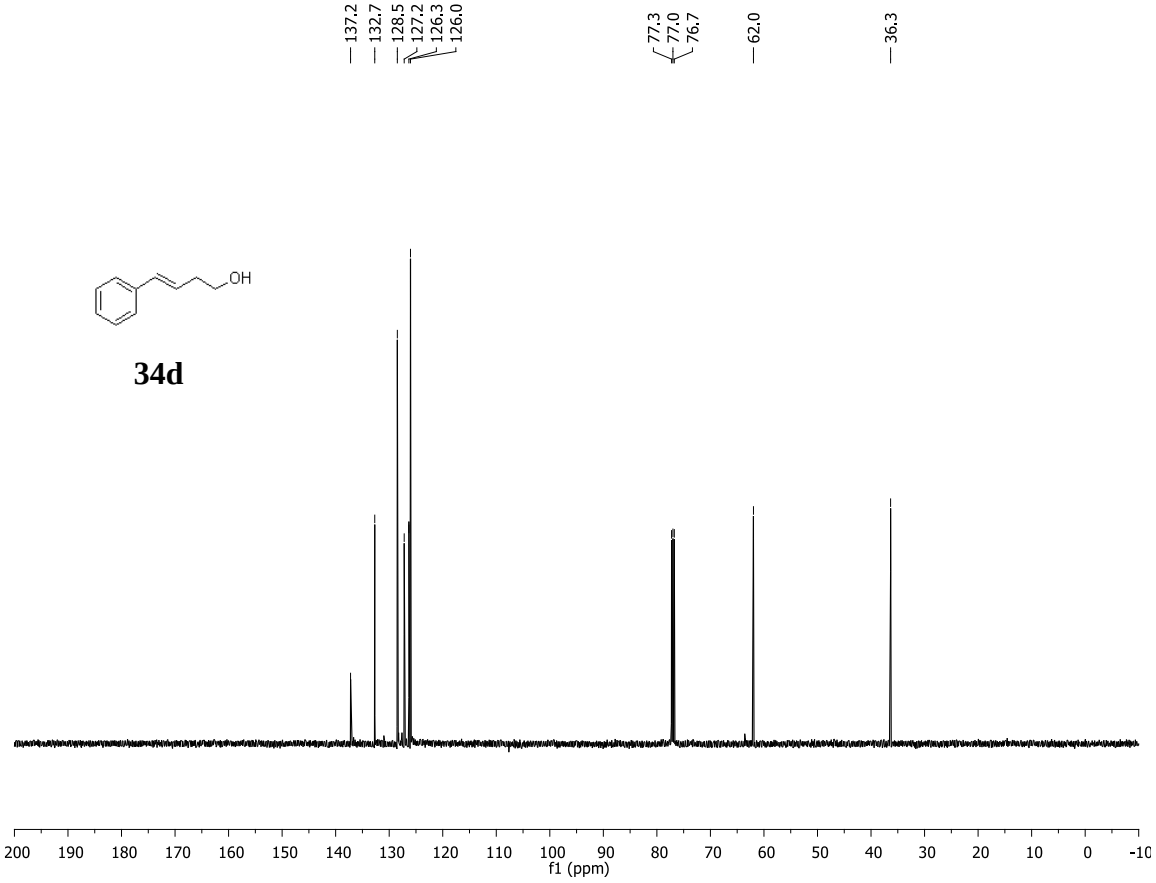

142.3
128.4
128.3
125.7
77.3
77.0
76.7
62.7
35.6
32.3
27.5
OH
f1 (ppm)

34c

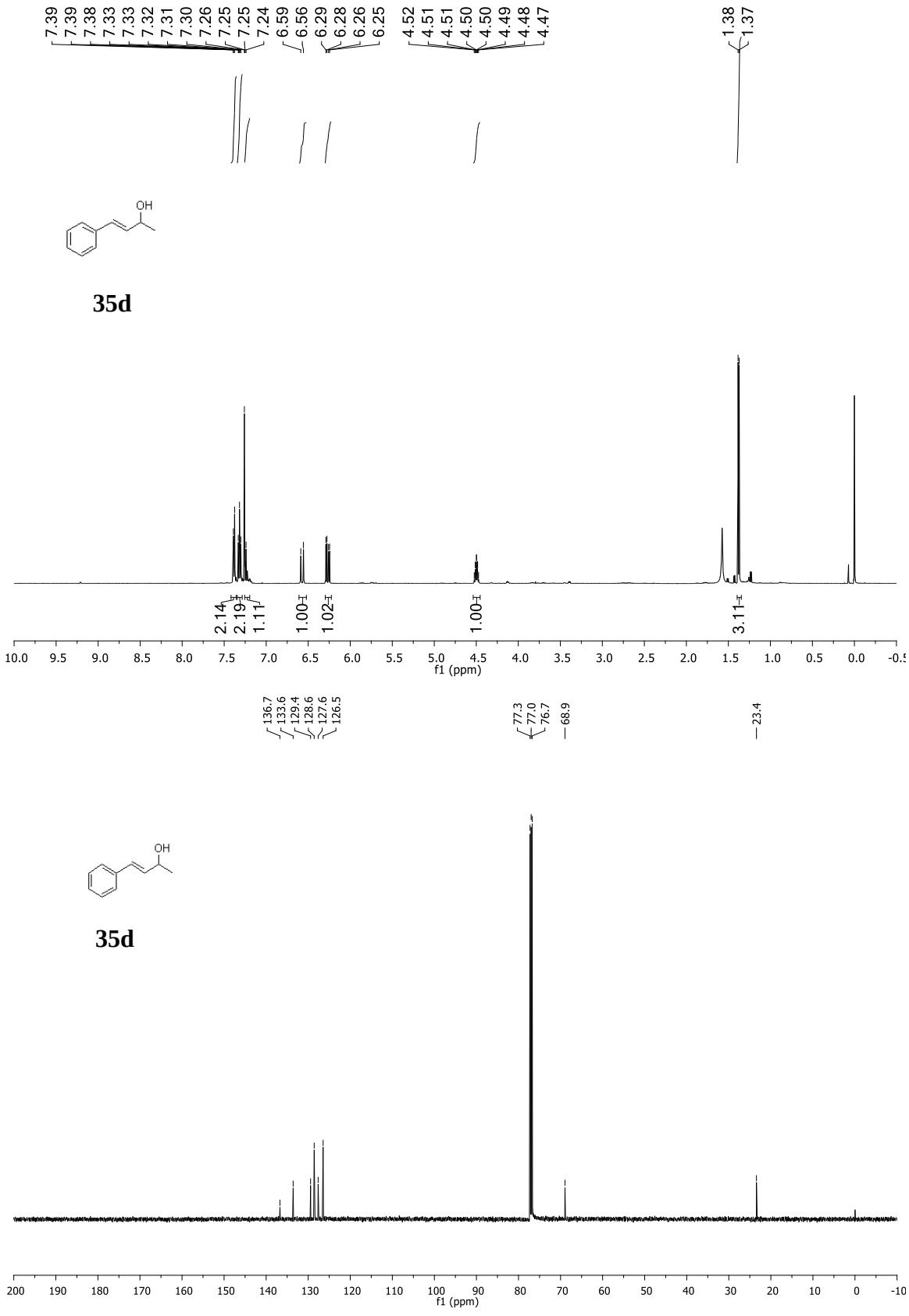

7.37
7.36
7.32
7.30
7.29
7.26
7.23
7.22
7.20
6.52
6.49
6.24
6.23
6.21
6.21
6.20
6.18
3.78
3.77
3.75
2.52
2.52
2.50
2.49
2.48
2.48
1.45
1.44
OH

34d


4.38
1.18
1.00
1.04
2.00
2.05
0.96
f1 (ppm)

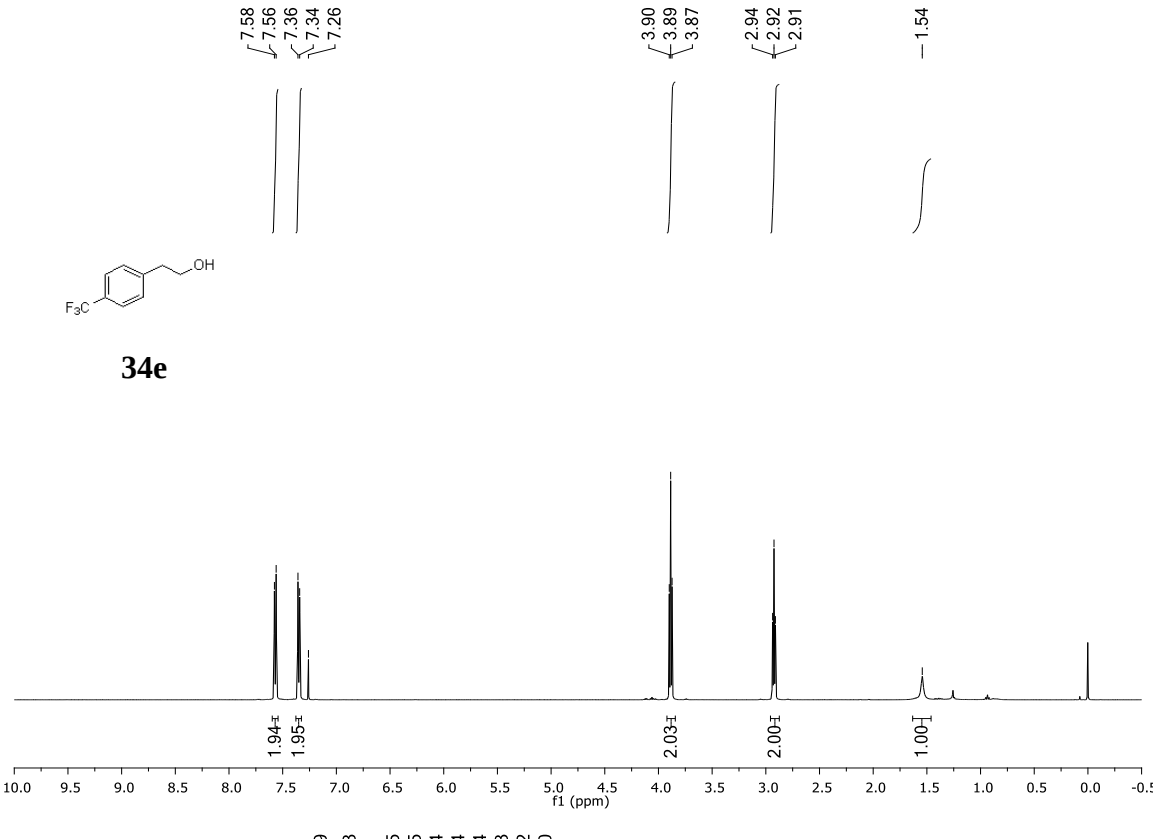

137.2
132.7
128.5
127.2
126.3
126.0
77.3
77.0
76.7
62.0
36.3
OH
f1 (ppm)

34d

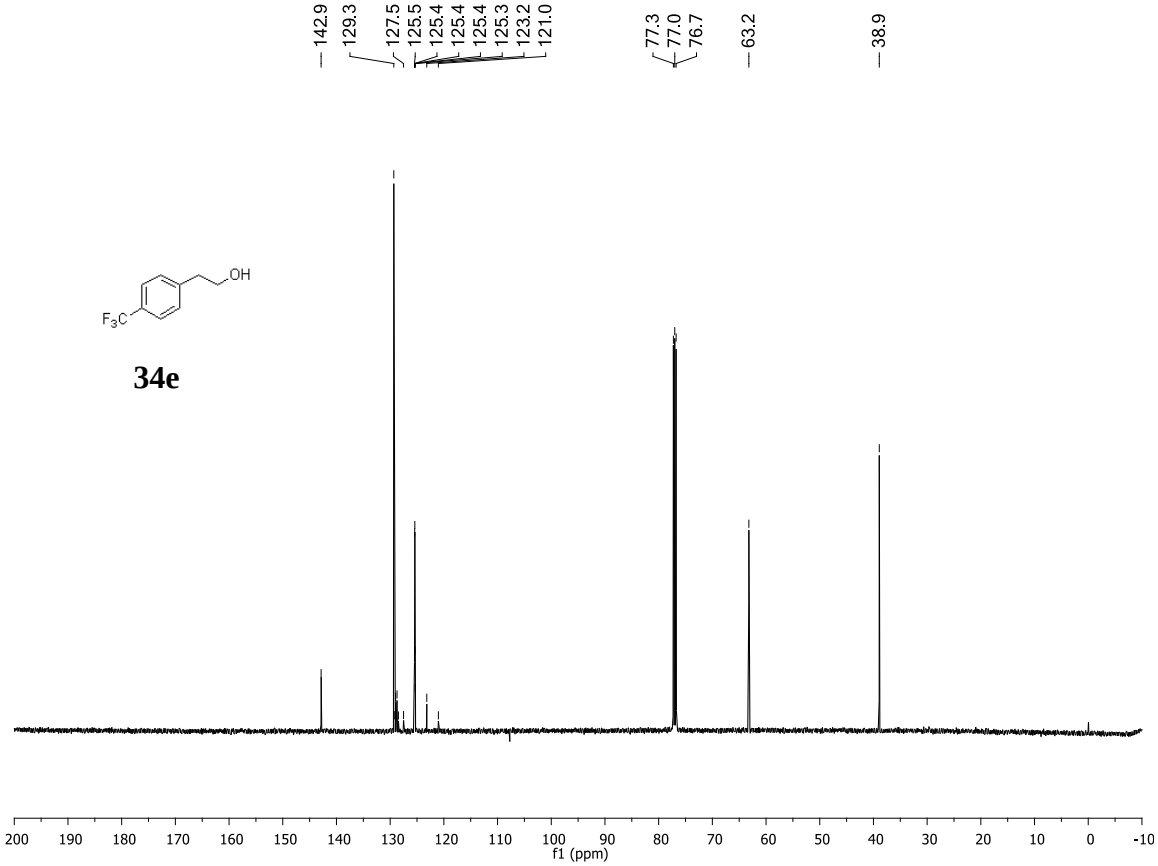

7.39
7.39
7.38
7.33
7.33
7.32
7.31
7.30
7.26
7.25
7.25
7.24
6.59
6.56
6.29
6.28
6.26
6.25
4.52
4.51
4.51
4.50
4.50
4.49
4.48
4.47
1.38
1.37
OH
2.14
2.19
1.11
1.00
1.02
1.00
3.11
f1 (ppm)
136.7
133.6
129.4
128.6
127.6
126.5
77.3
77.0
76.7
68.9
23.4
OH
f1 (ppm)

35d

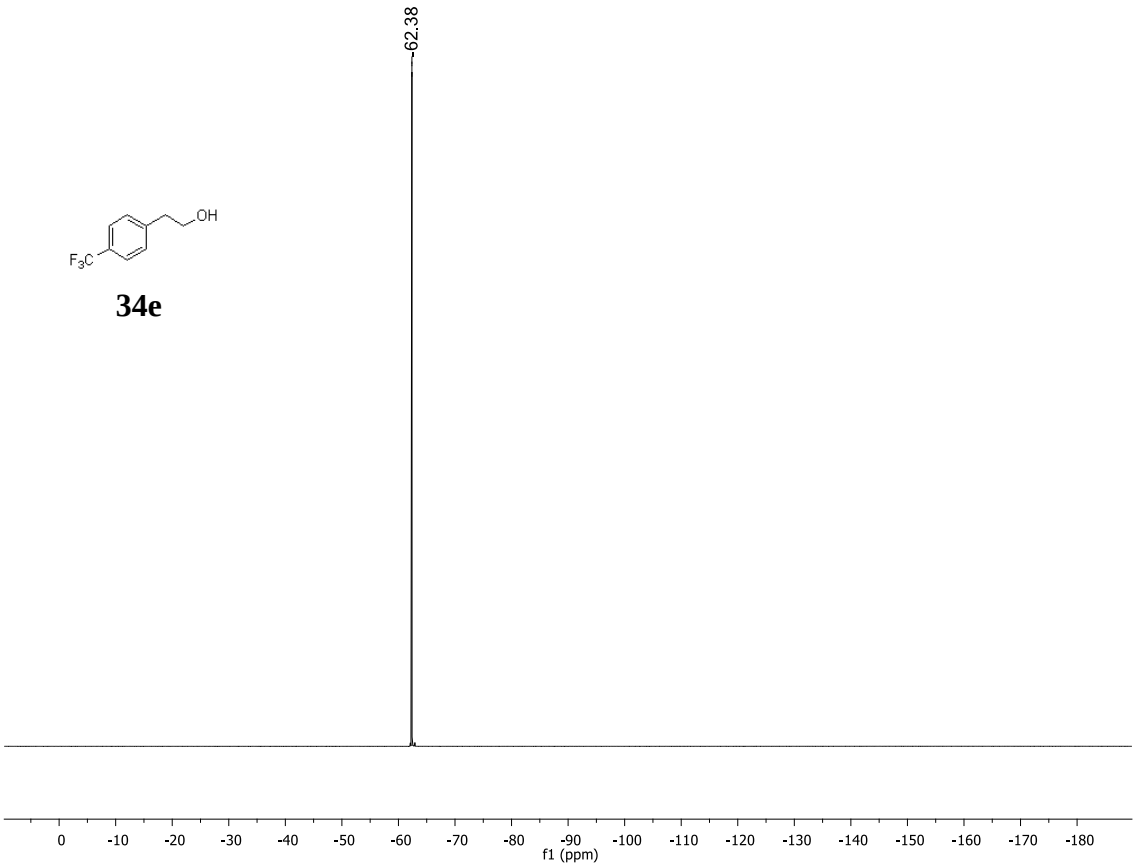
35d


7.58
7.56
7.36
7.34
7.26
3.90
3.89
3.87
2.94
2.92
2.91
1.54
OH
F3C
1.94
1.95
2.03
2.00
1.00
f1 (ppm)

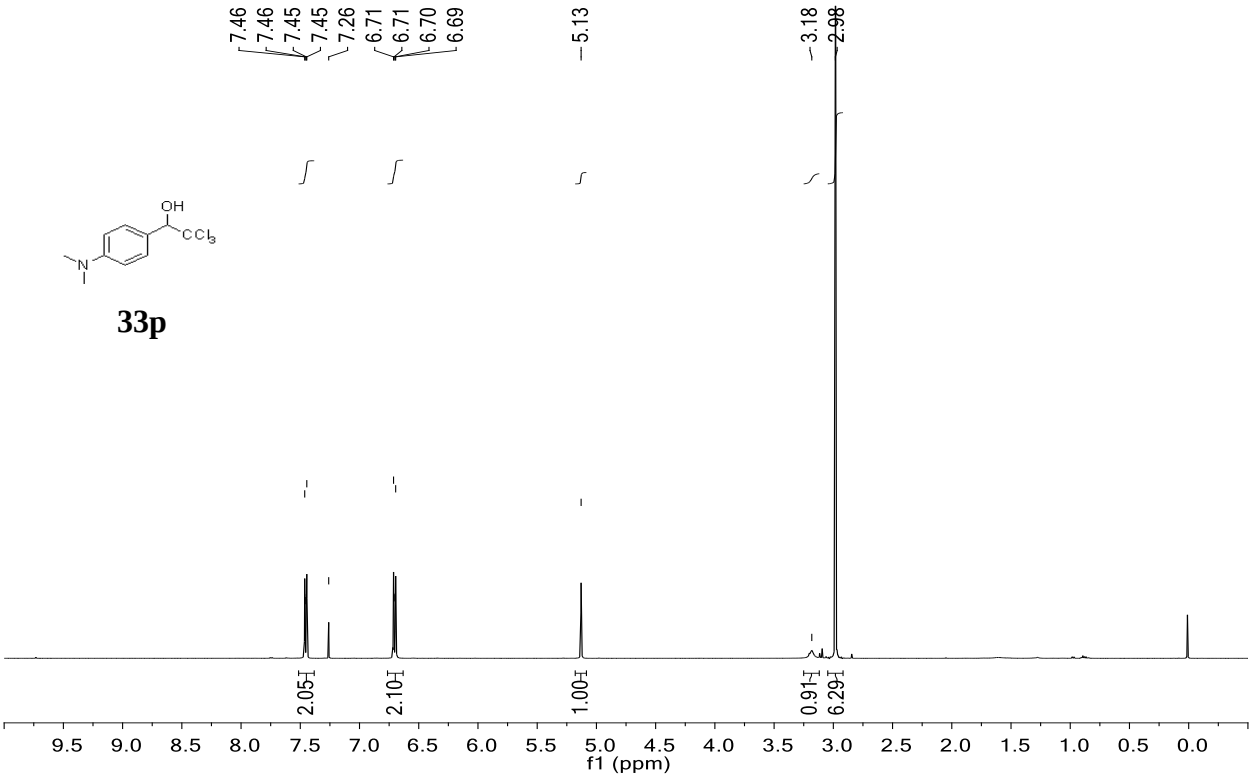
34e


142.9
129.3
127.5
125.5
125.4
125.4
125.4
125.3
123.2
121.0
77.3
77.0
76.7
63.2
38.9
OH
F3C
f1 (ppm)

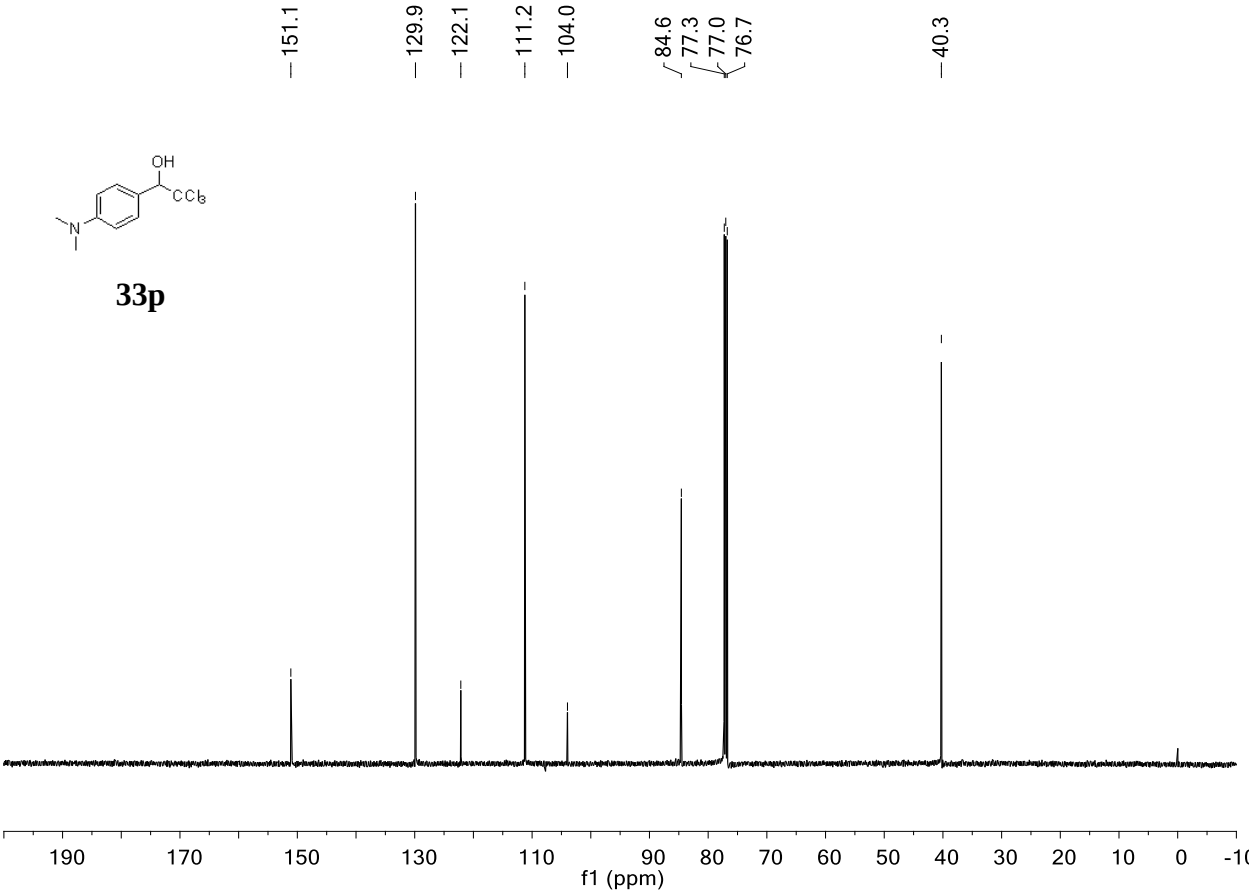
34e


-62.38
OH
F3C
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

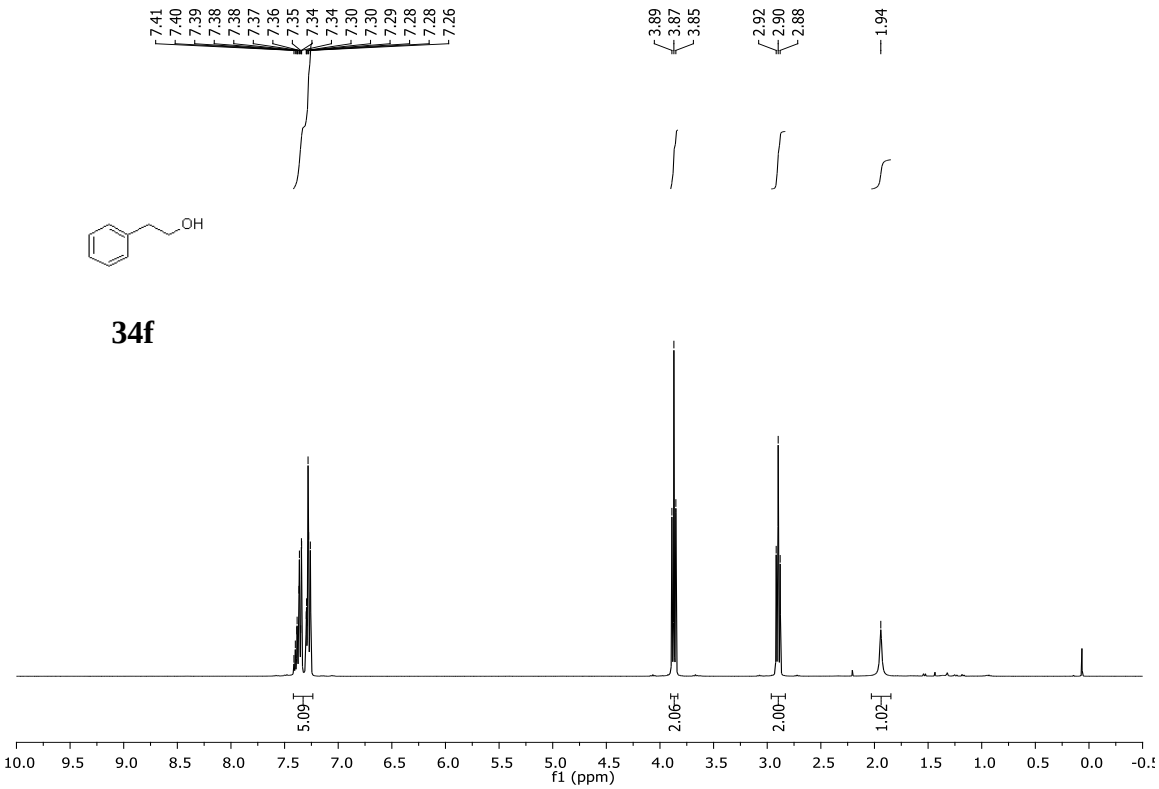
34e


7.46
7.46
7.45
7.45
7.26
6.71
6.71
6.70
6.69
5.13
3.18
2.98
OH
CCl3
N
2.05
2.10
1.00
0.91
6.29
f1 (ppm)

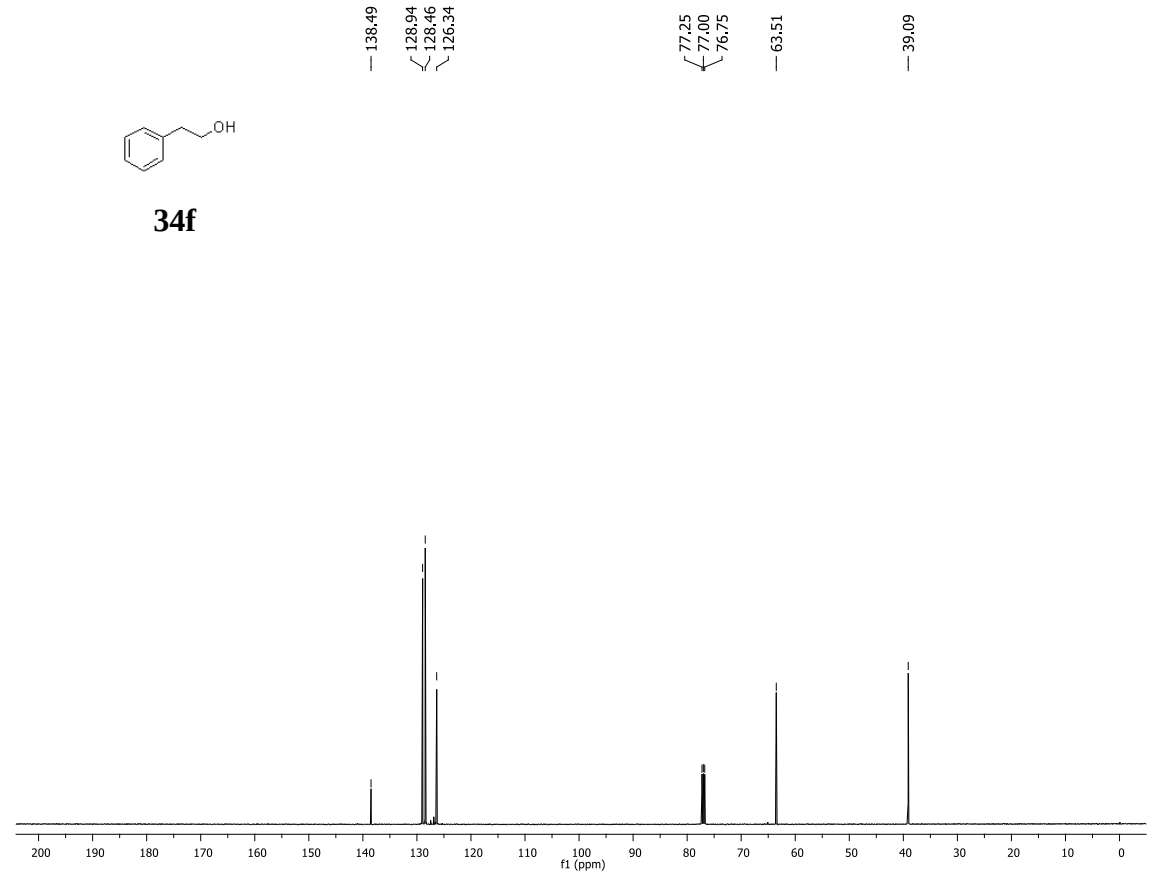
33p


151.1
129.9
122.1
111.2
104.0
84.6
77.3
77.0
76.7
40.3
OH
CCl3
N
f1 (ppm)

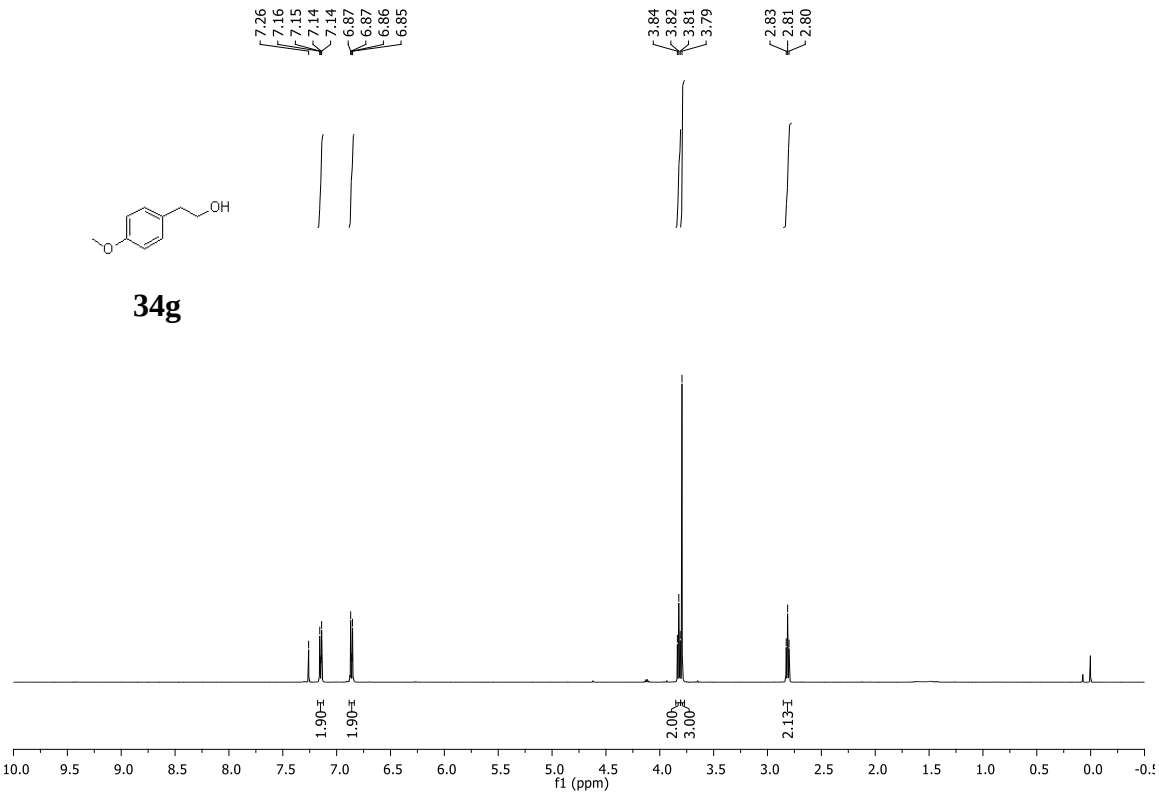
33p


7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.34
7.30
7.30
7.29
7.28
7.28
7.26
3.89
3.87
3.85
2.92
2.90
2.88
1.94
OH
5.09
2.06
2.00
1.02
f1 (ppm)

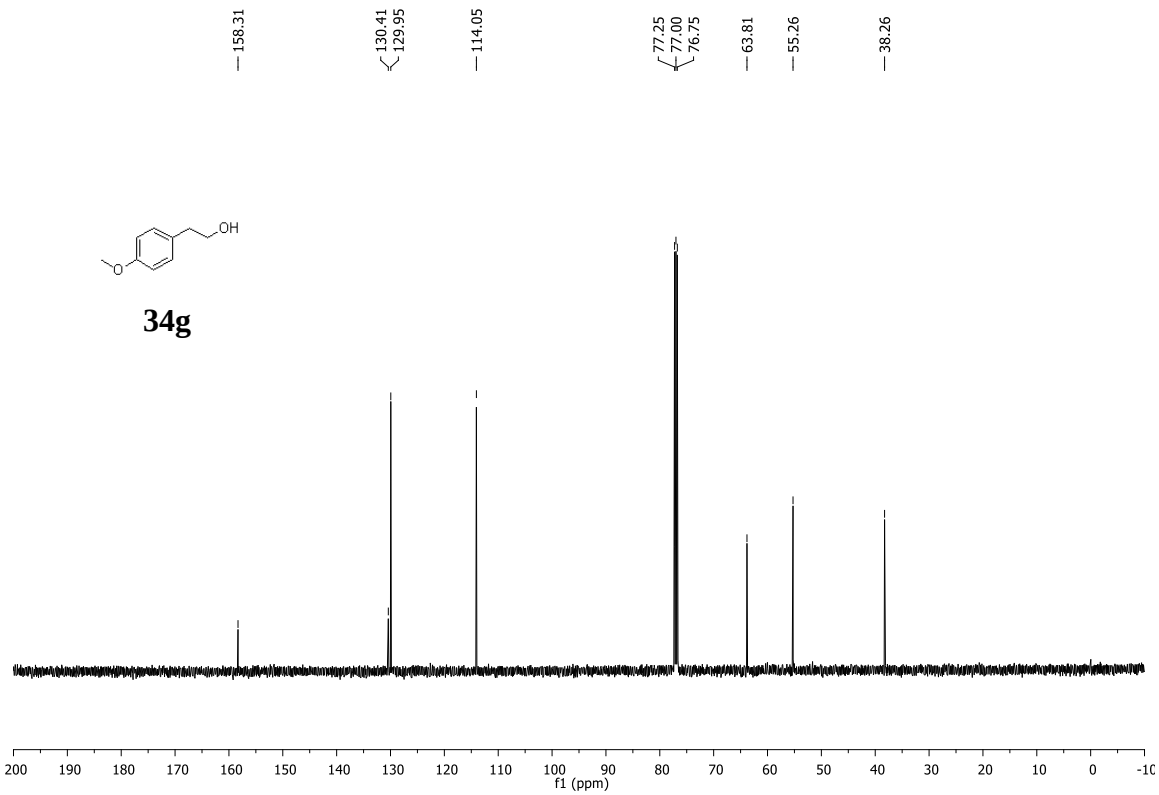
34f


138.49
128.94
128.46
126.34
77.25
77.00
76.75
63.51
39.09
OH
f1 (ppm)

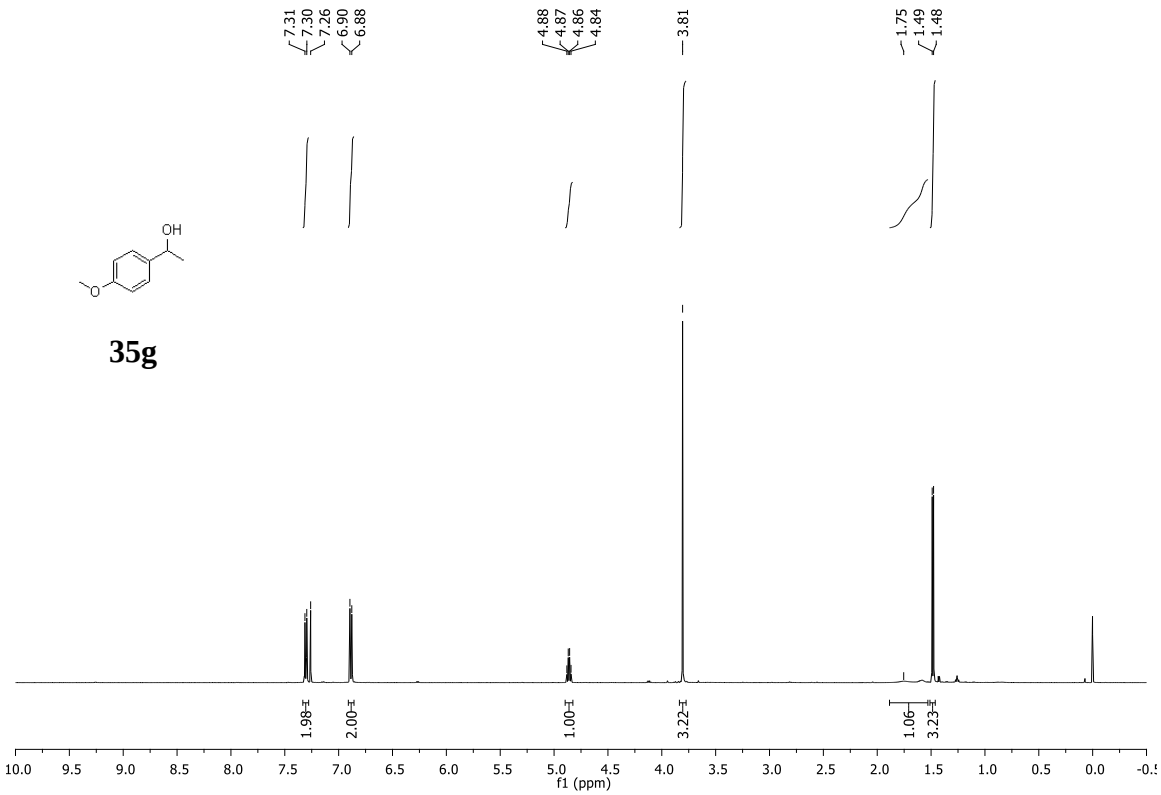
34f


7.26
7.16
7.15
7.14
7.14
6.87
6.87
6.86
6.85
3.84
3.82
3.81
3.79
2.83
2.81
2.80
OH
O
1.90
1.90
2.00
3.00
2.13
f1 (ppm)

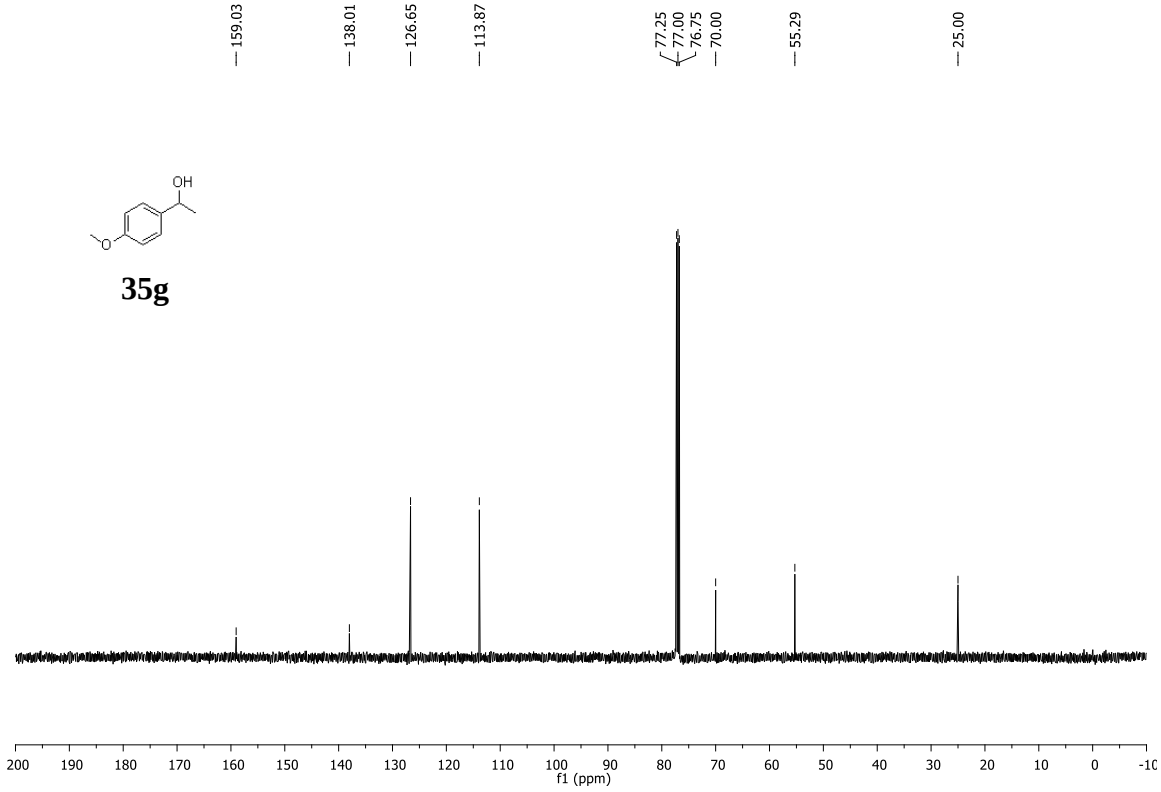
34g


158.31
130.41
129.95
114.05
77.25
77.00
76.75
63.81
55.26
38.26
OH
O
f1 (ppm)

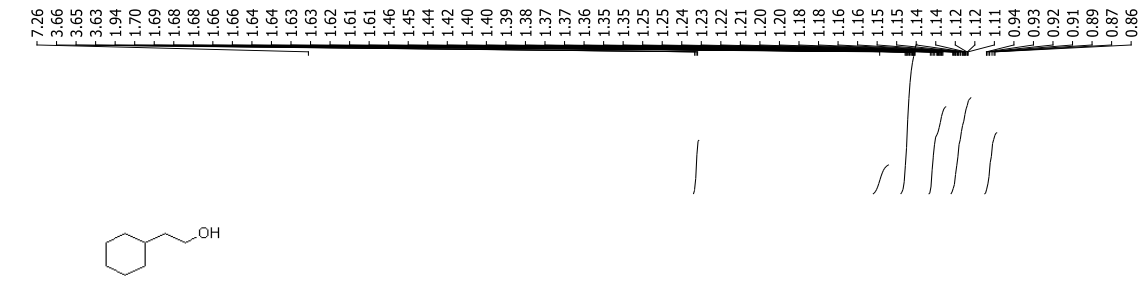
34g


7.31
7.30
7.26
6.90
6.88
4.88
4.87
4.86
4.84
3.81
1.75
1.49
1.48
OH
O
1.98
2.00
1.00
3.22
1.06
3.23
f1 (ppm)

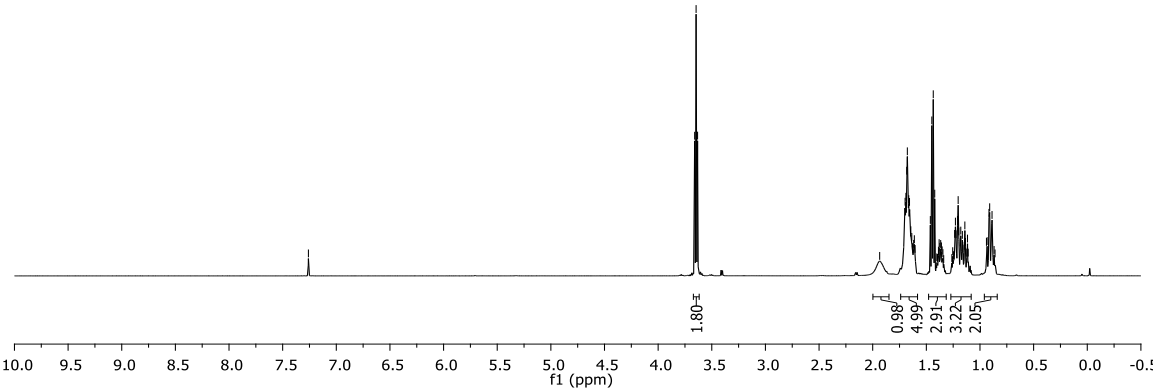
35g


159.03
138.01
126.65
113.87
77.25
77.00
76.75
70.00
55.29
25.00
OH
O
f1 (ppm)

35g

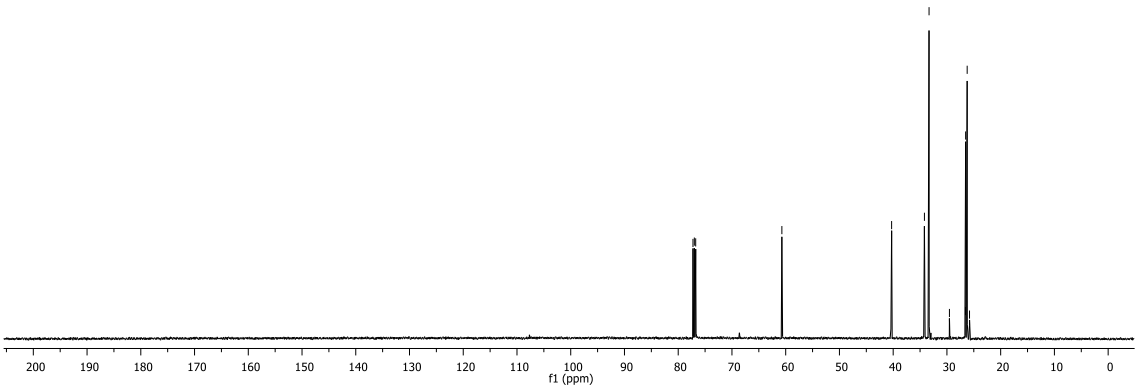

7.26
3.66
3.65
3.63
1.94
1.70
1.69
1.68
1.68
1.66
1.66
1.64
1.64
1.63
1.63
1.62
1.61
1.61
1.46
1.45
1.44
1.42
1.40
1.40
1.39
1.38
1.37
1.37
1.36
1.35
1.35
1.25
1.25
1.24
1.23
1.22
1.21
1.20
1.20
1.18
1.18
1.16
1.16
1.15
1.15
1.14
1.14
1.12
1.12
1.11
0.94
0.93
0.92
0.91
0.89
0.87
0.86
OH

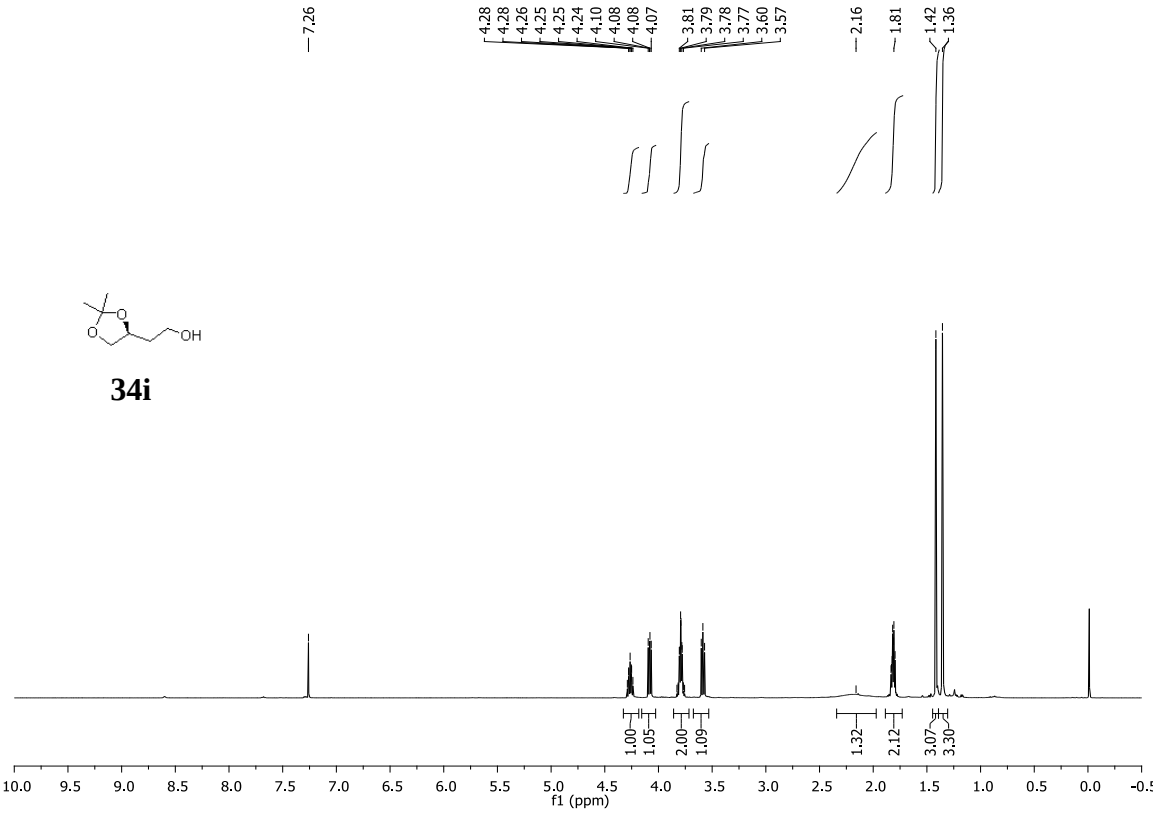
34h


1.80
0.98
4.99
2.91
3.22
2.05
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
f1 (ppm)

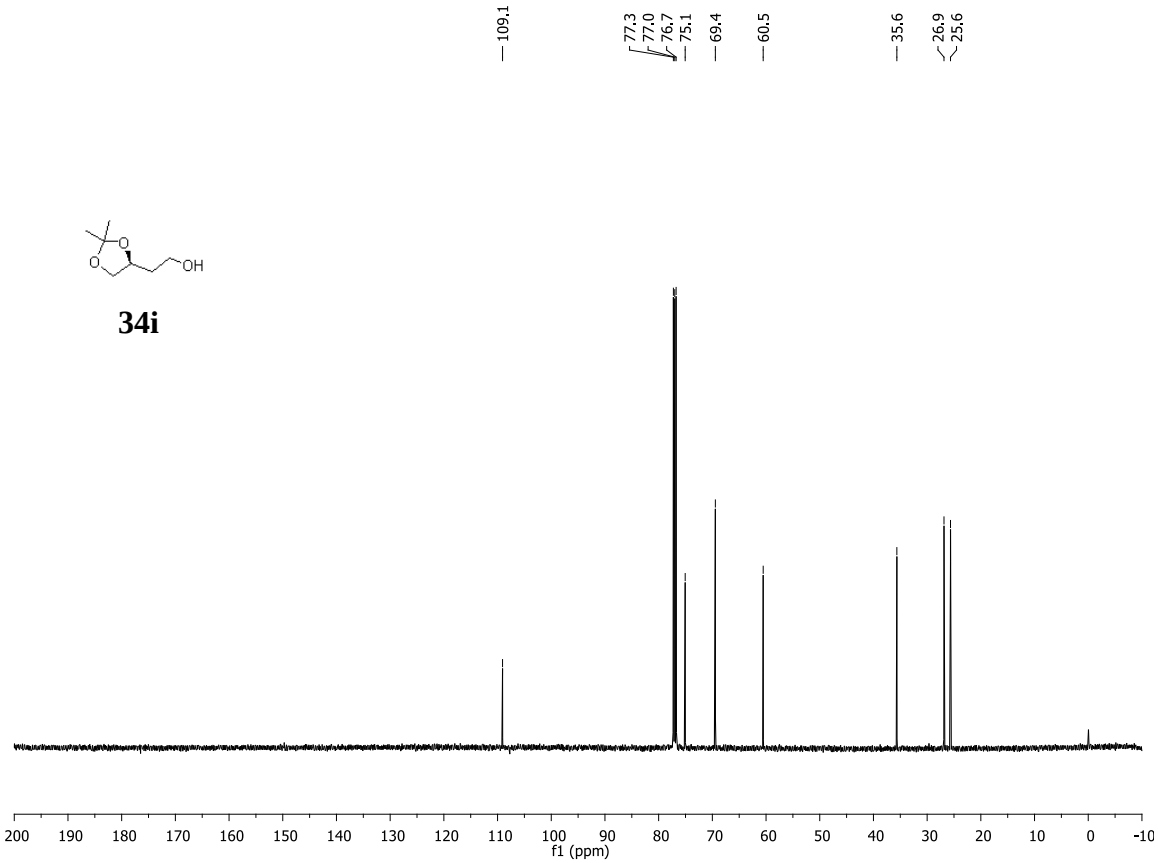

77.25
77.00
76.75
60.71
40.29
33.33
29.53
26.55
26.52
26.23
25.79
OH

34h

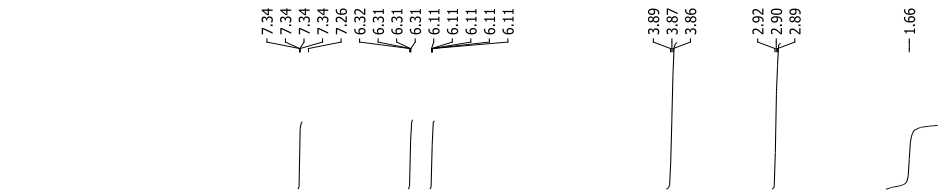

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

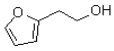

7.26
4.28
4.28
4.26
4.25
4.25
4.24
4.10
4.08
4.08
4.07
3.81
3.79
3.78
3.77
3.60
3.57
2.16
1.81
1.42
1.36
OH
1.00
1.05
2.00
1.09
1.32
2.12
3.07
3.30
f1 (ppm)

34i

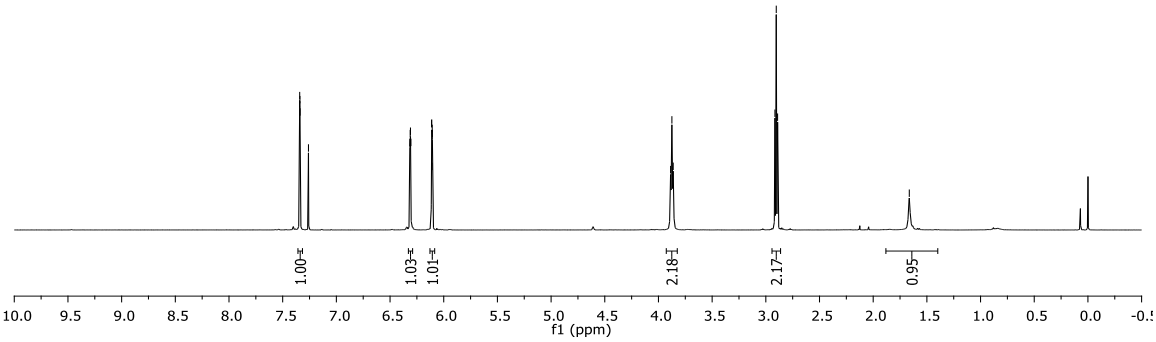

109.1
77.3
77.0
76.7
75.1
69.4
60.5
35.6
26.9
25.6
OH
f1 (ppm)

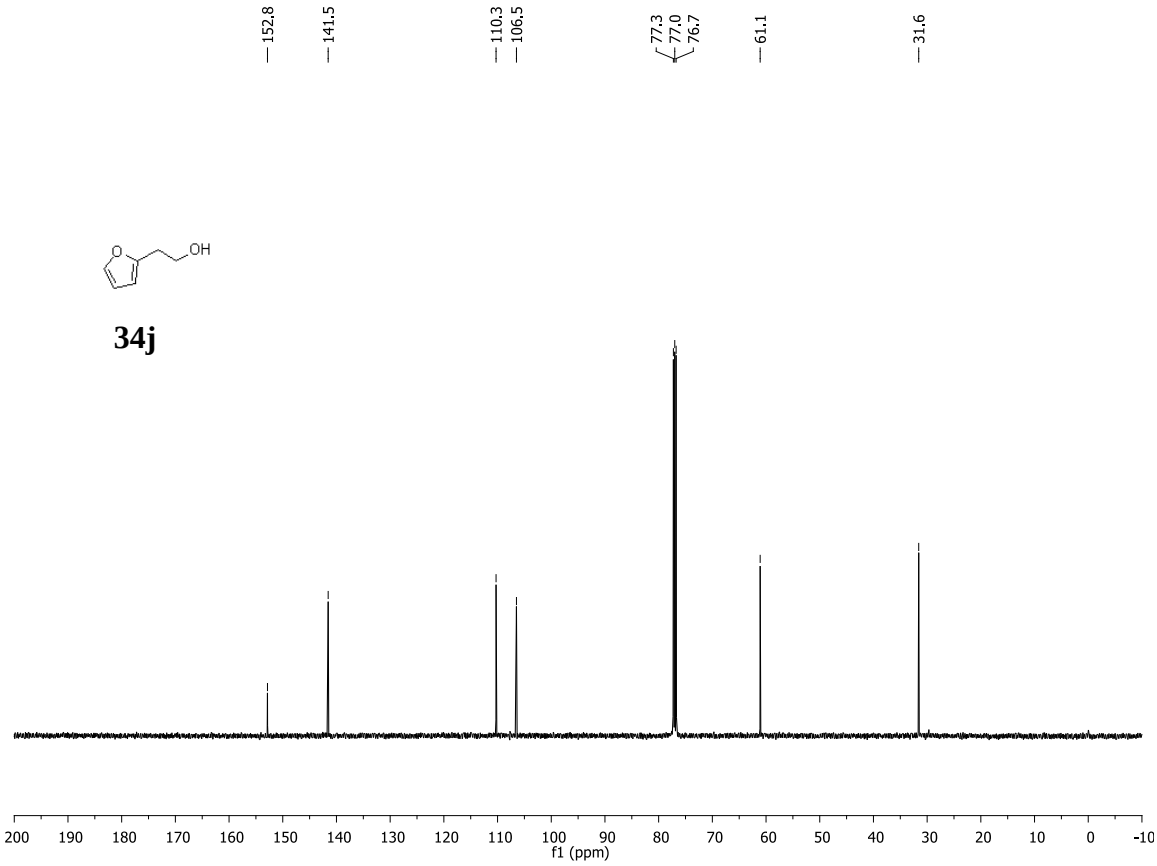
34i


7.34
7.34
7.34
7.34
7.26
6.32
6.31
6.31
6.31
6.11
6.11
6.11
6.11
6.11
3.89
3.87
3.86
2.92
2.90
2.89
1.66


O
OH

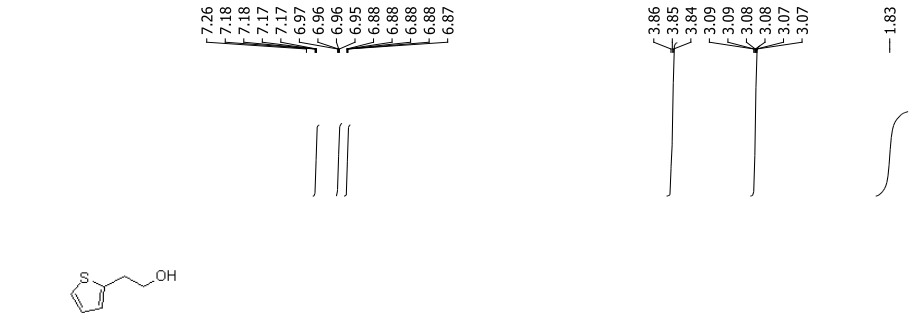
34j


1.00
1.03
1.01
2.18
2.17
0.95
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
f1 (ppm)


152.8
141.5
110.3
106.5
77.3
77.0
76.7
61.1
31.6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

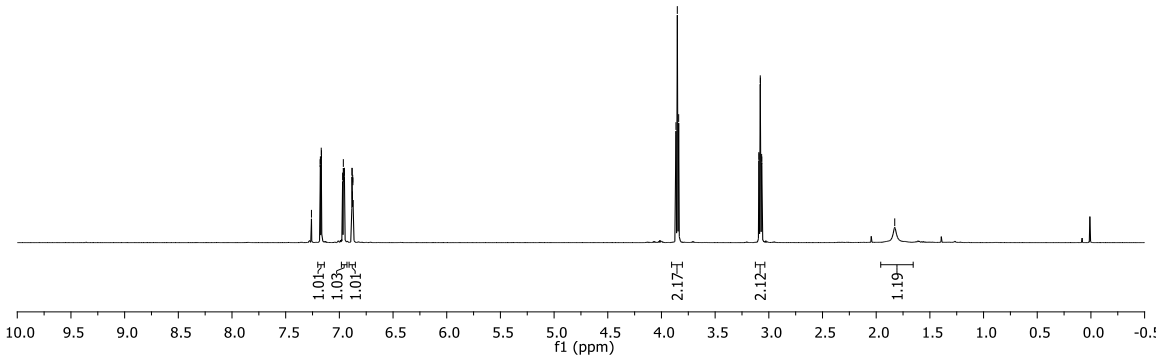
O
OH

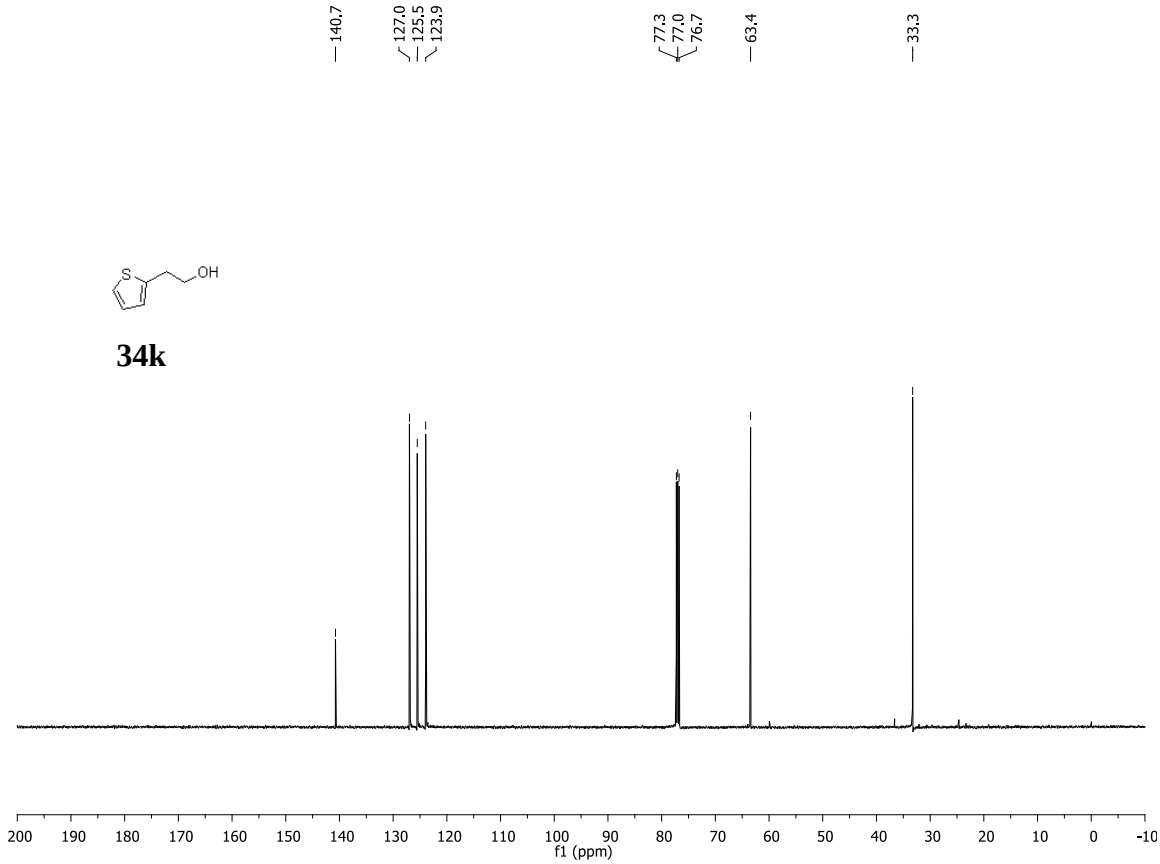
34j


7.26
7.18
7.18
7.17
7.17
6.97
6.96
6.96
6.95
6.88
6.88
6.88
6.88
6.87
3.86
3.85
3.84
3.09
3.09
3.08
3.08
3.07
3.07
1.83

S
OH

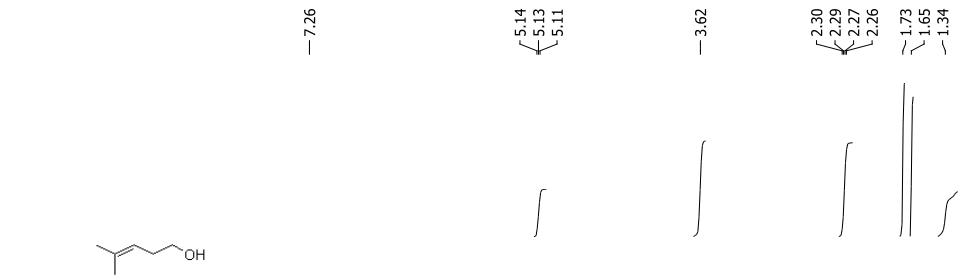
34k


1.01
1.03
1.01
2.17
2.12
1.19
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
f1 (ppm)

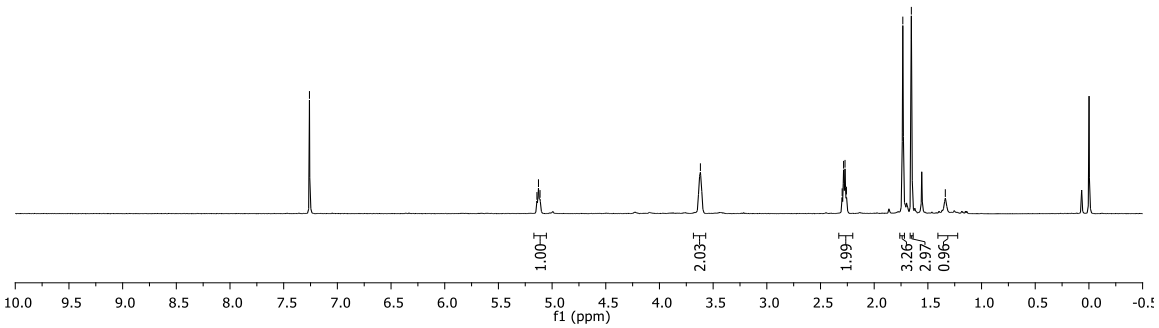

140.7
127.0
125.5
123.9
77.3
77.0
76.7
63.4
33.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

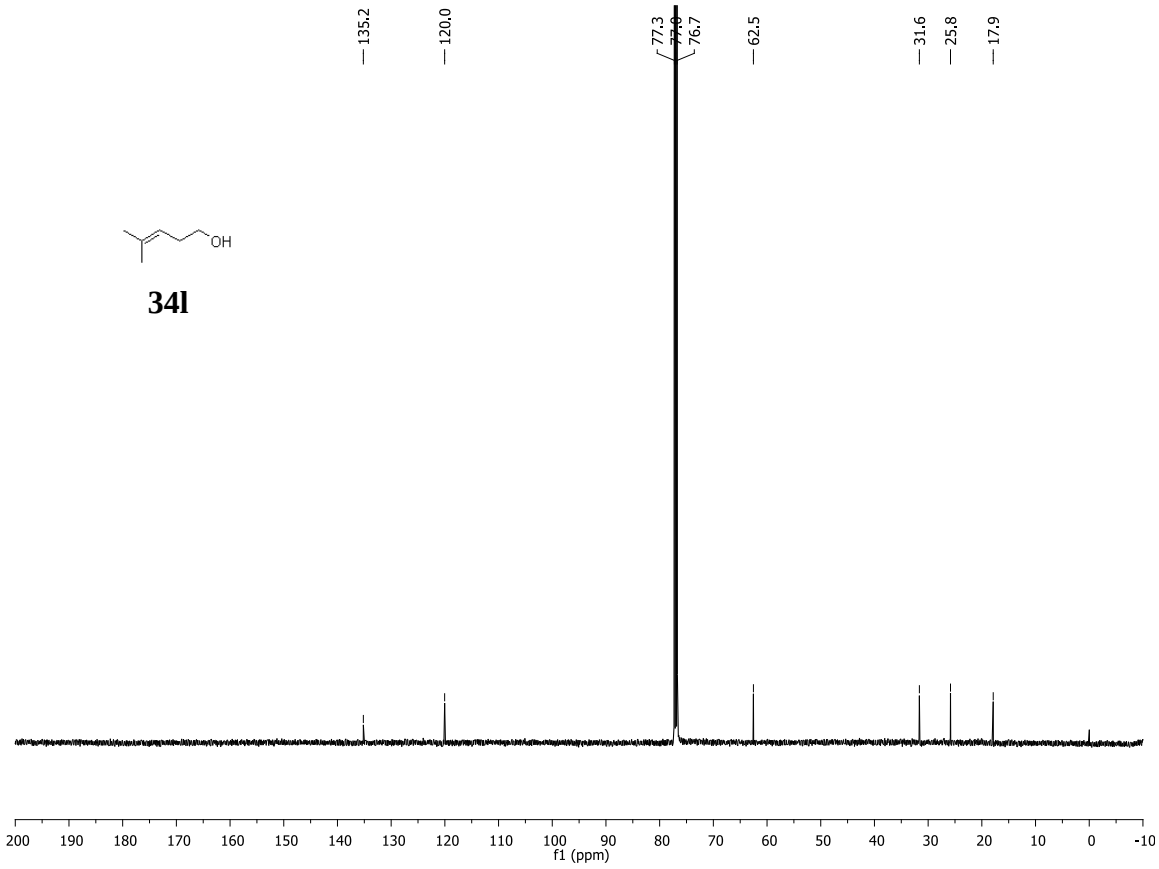
S
OH

34k

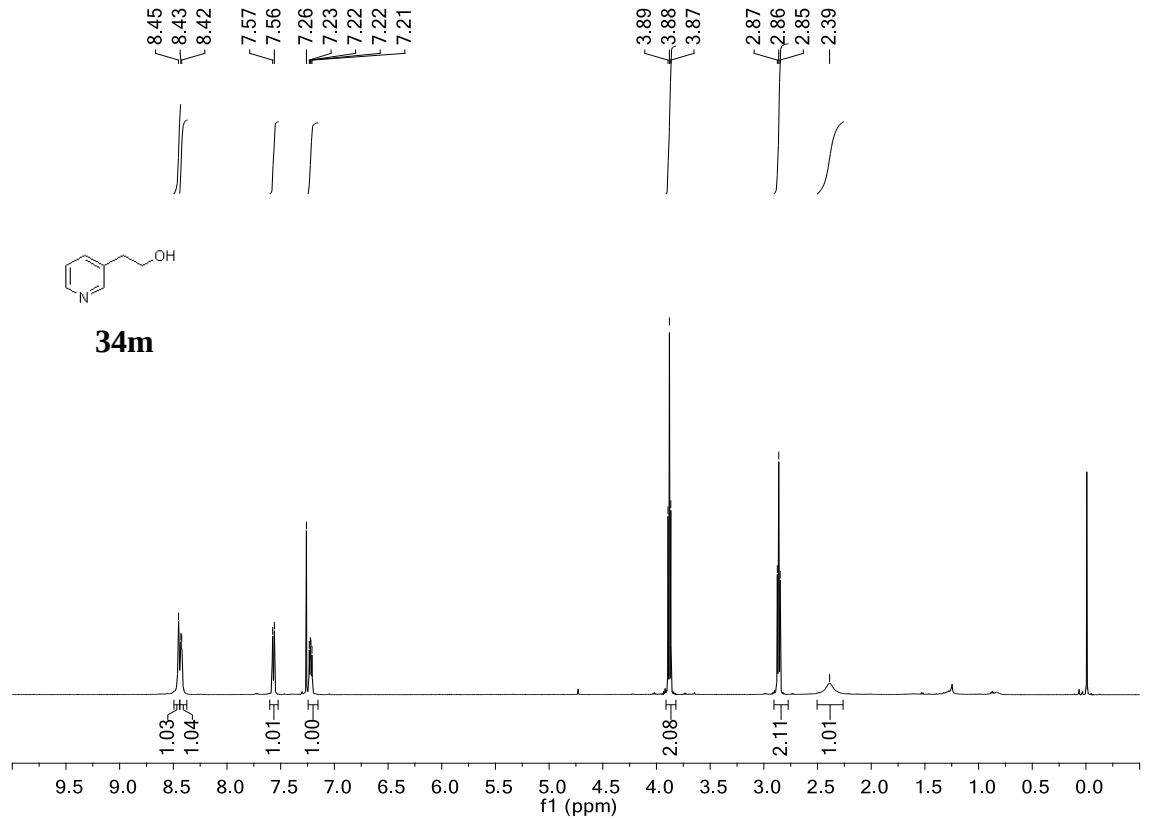

7.26
5.14
5.13
5.11
3.62
2.30
2.29
2.27
2.26
1.73
1.65
1.34
OH

34l

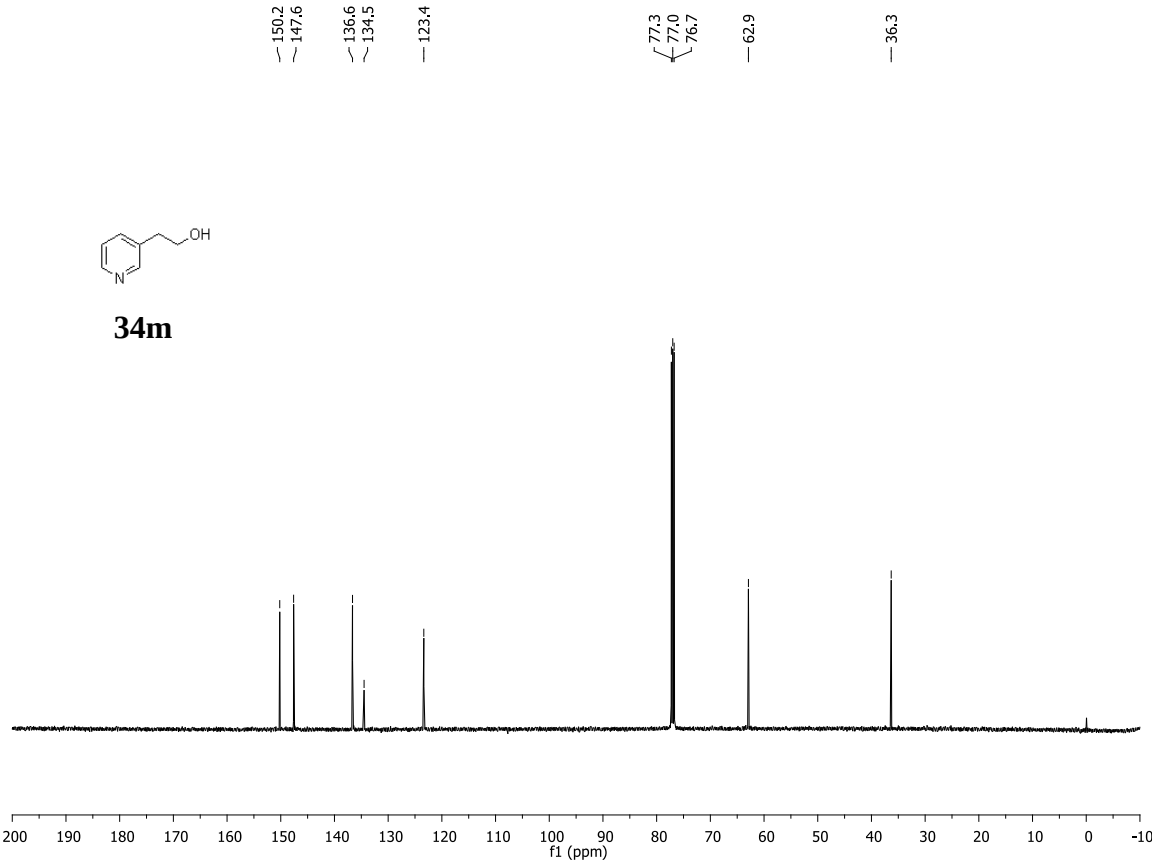

1.00
2.03
1.99
3.26
2.97
0.96
f1 (ppm)


135.2
120.0
77.3
77.0
76.7
62.5
31.6
25.8
17.9
OH
f1 (ppm)

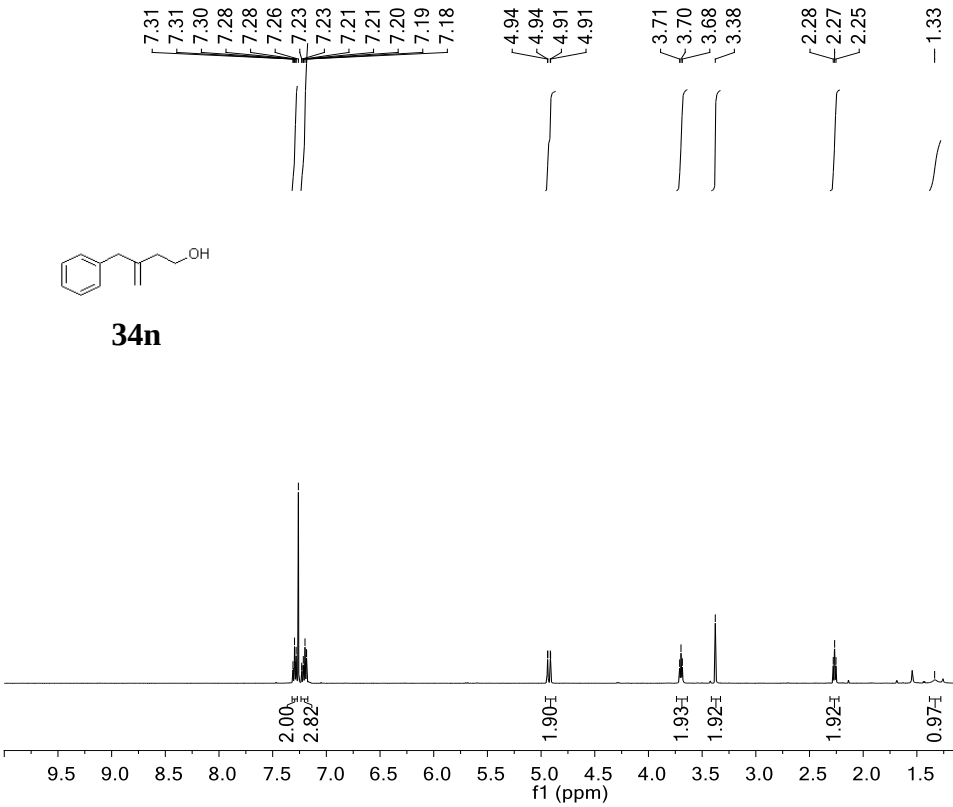
34l


8.45
8.43
8.42
7.57
7.56
7.26
7.23
7.22
7.22
7.21
3.89
3.88
3.87
2.87
2.86
2.85
2.39
OH
N
1.03
1.04
1.01
1.00
2.08
2.11
1.01
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
f1 (ppm)

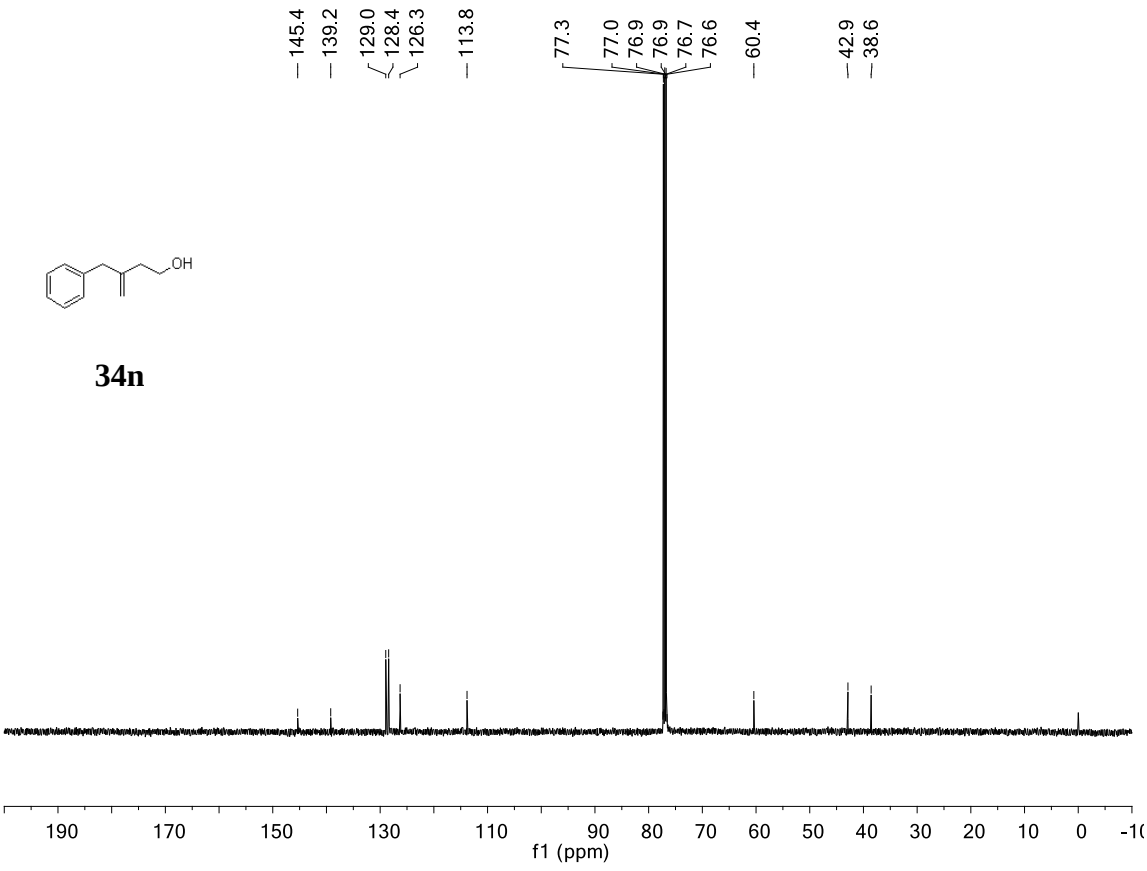
34m


150.2
147.6
136.6
134.5
123.4
77.3
77.0
76.7
62.9
36.3
OH
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

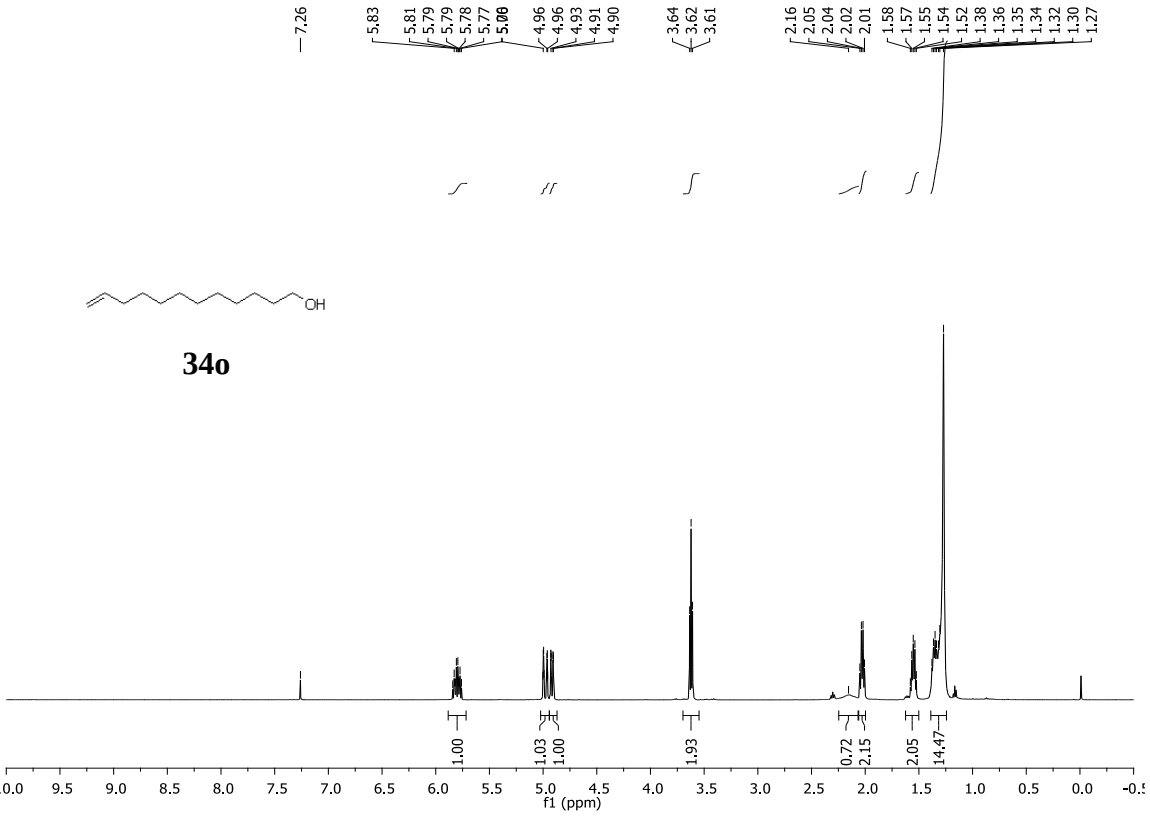
34m


7.31
7.31
7.30
7.28
7.28
7.26
7.23
7.23
7.21
7.21
7.20
7.19
7.18
4.94
4.94
4.91
4.91
3.71
3.70
3.68
3.38
2.28
2.27
2.25
1.33
OH
2.00
2.82
1.90
1.93
1.92
1.92
0.97
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
f1 (ppm)

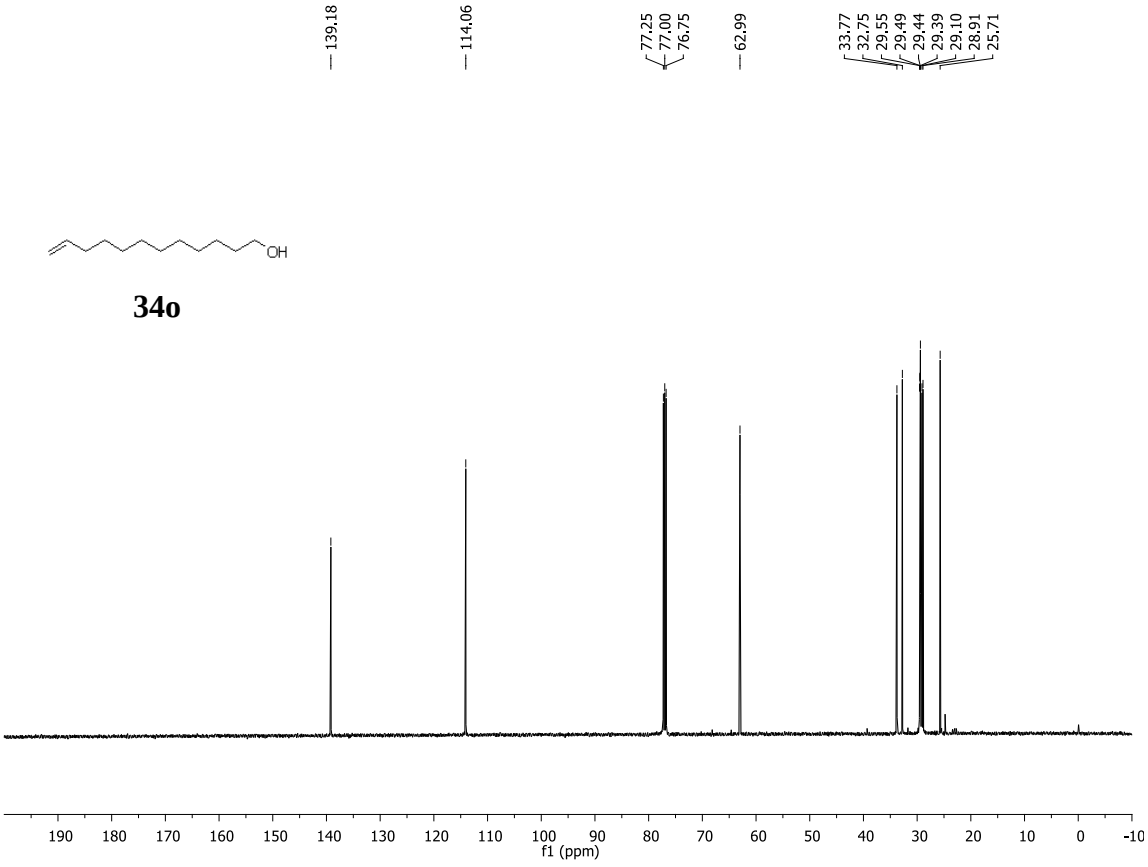
34n


145.4
139.2
129.0
128.4
126.3
113.8
77.3
77.0
76.9
76.9
76.7
76.6
60.4
42.9
38.6
OH
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -1(
f1 (ppm)

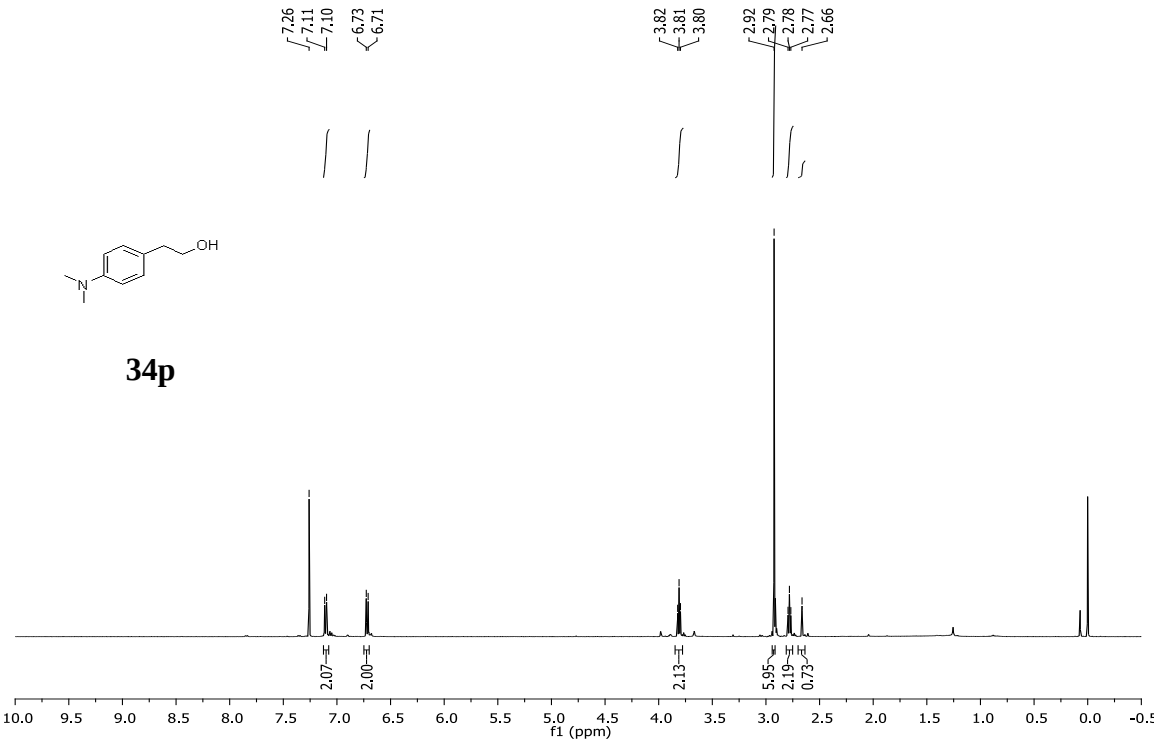
34n

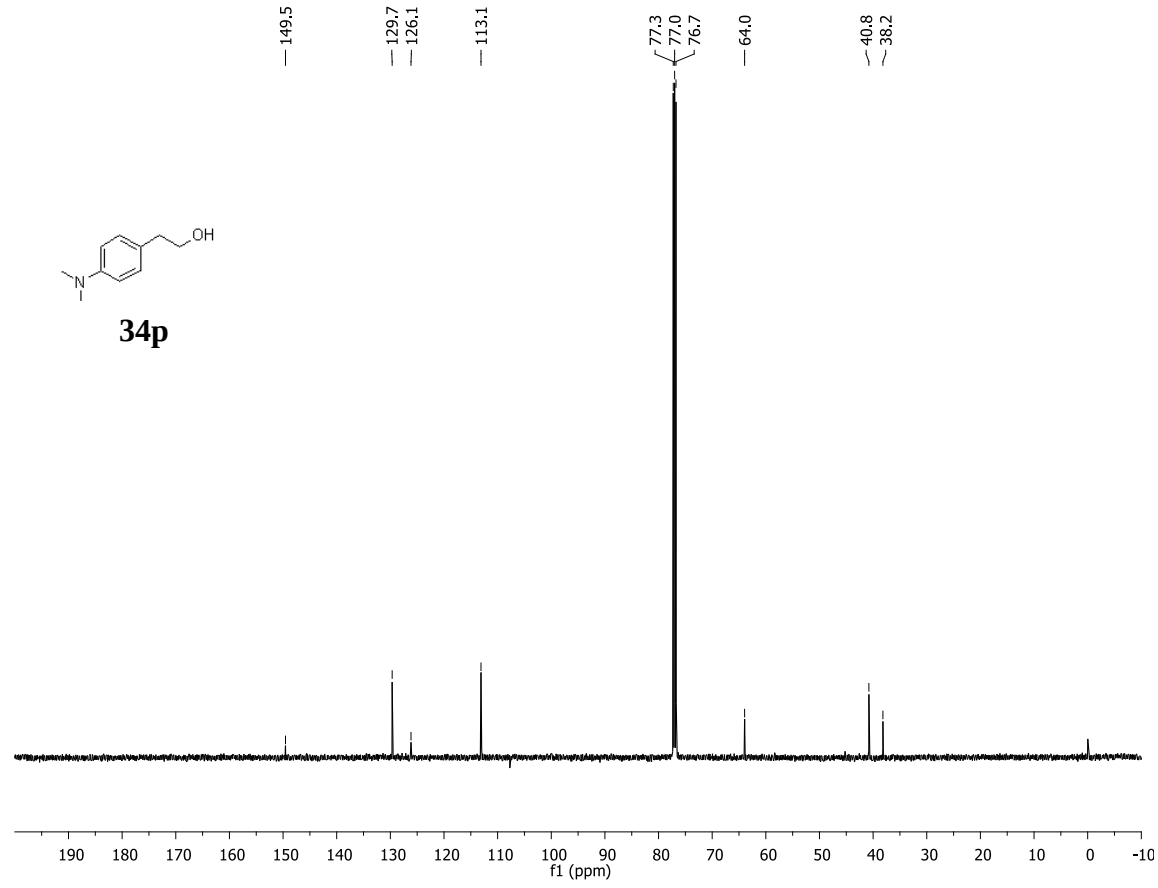

7.26
5.83
5.81
5.79
5.78
5.77
5.00
4.96
4.96
4.93
4.91
4.90
3.64
3.62
3.61
2.16
2.05
2.04
2.02
2.01
1.58
1.57
1.55
1.54
1.52
1.38
1.36
1.35
1.34
1.32
1.30
1.27
OH
1.00
1.03
1.00
1.93
0.72
2.15
2.05
14.47
f1 (ppm)

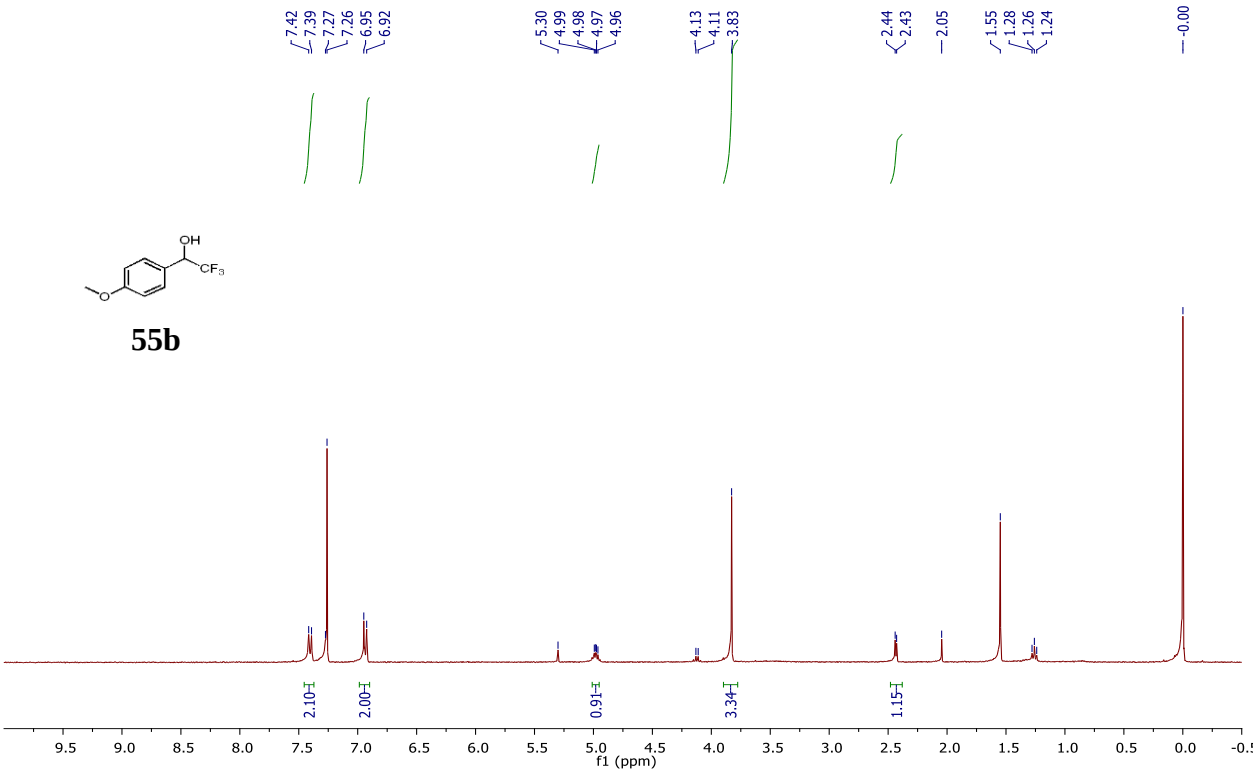
34o

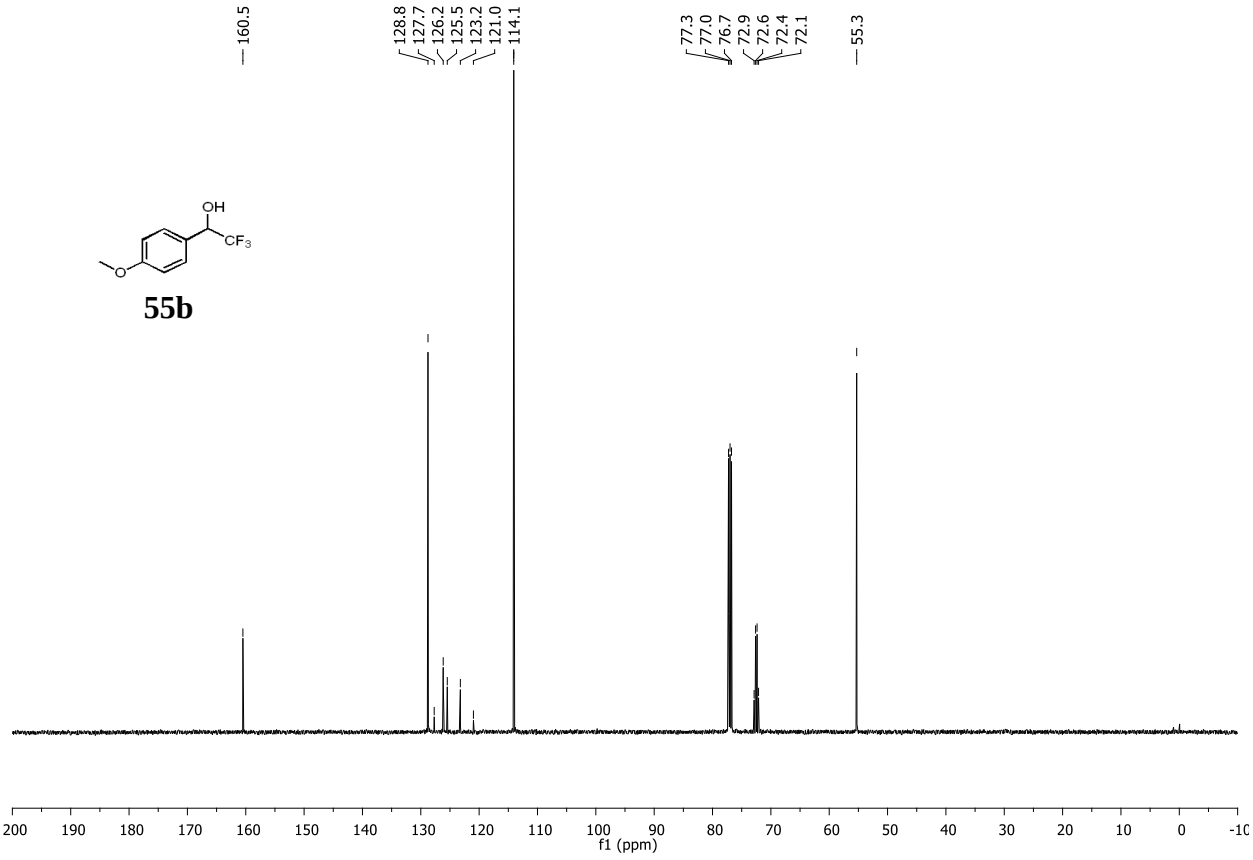

139.18
114.06
77.25
77.00
76.75
62.99
33.77
32.75
29.55
29.49
29.44
29.39
29.10
28.91
25.71
OH
f1 (ppm)

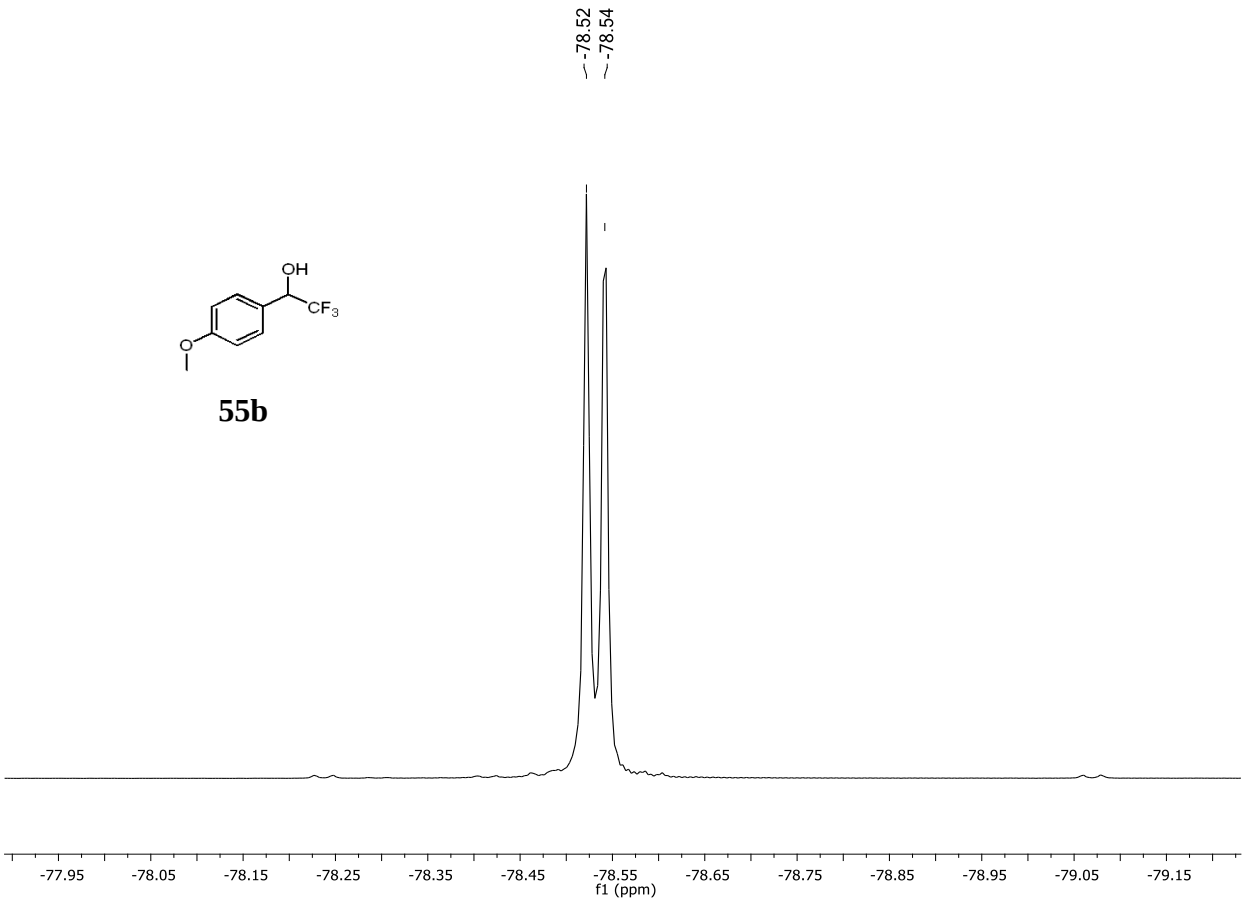
34o


7.26
7.11
7.10
6.73
6.71
3.82
3.81
3.80
2.92
2.79
2.78
2.77
2.66
OH
N
34p
2.07
2.00
2.13
5.95
2.19
0.73
f1 (ppm)

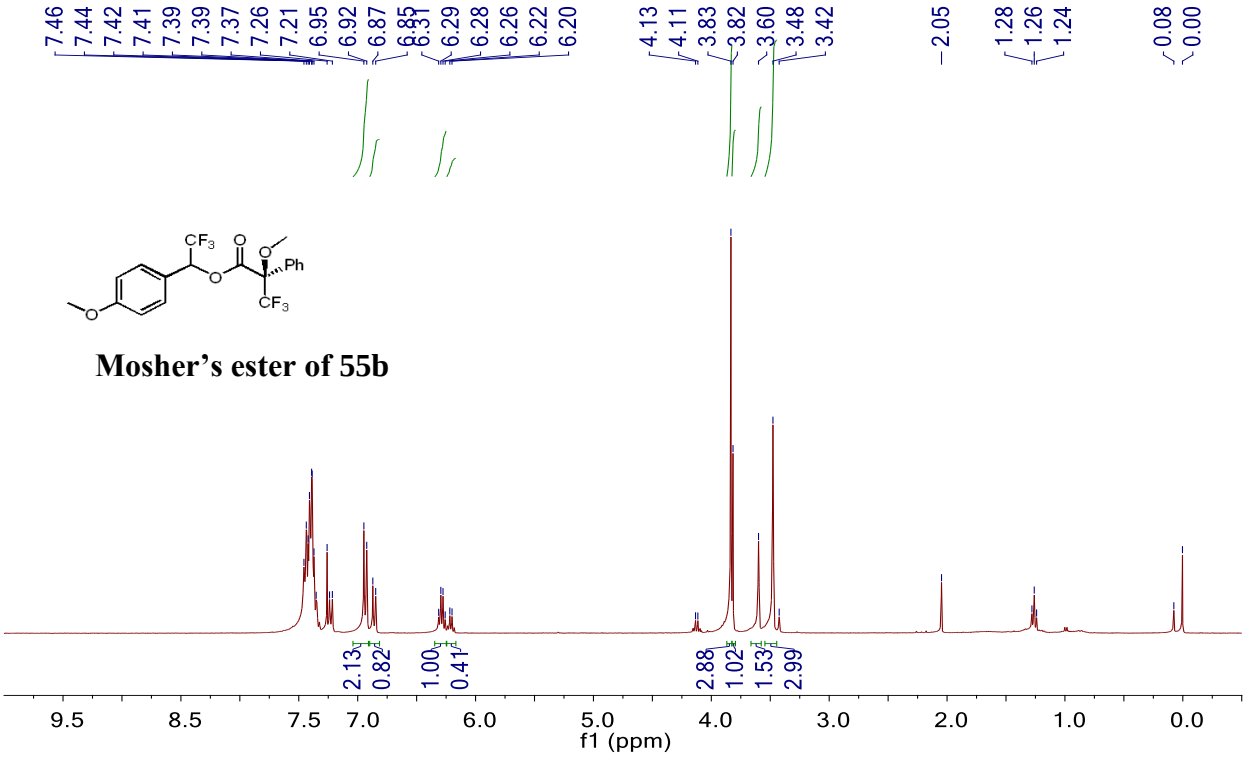

149.5
129.7
126.1
113.1
77.3
77.0
76.7
64.0
40.8
38.2
OH
N
34p
f1 (ppm)


7.42
7.39
7.27
7.26
6.95
6.92
5.30
4.99
4.98
4.97
4.96
4.13
4.11
3.83
2.44
2.43
2.05
1.55
1.28
1.26
1.24
0.00
OH
CF3
O
55b
2.10
2.00
0.91
3.34
1.15
f1 (ppm)

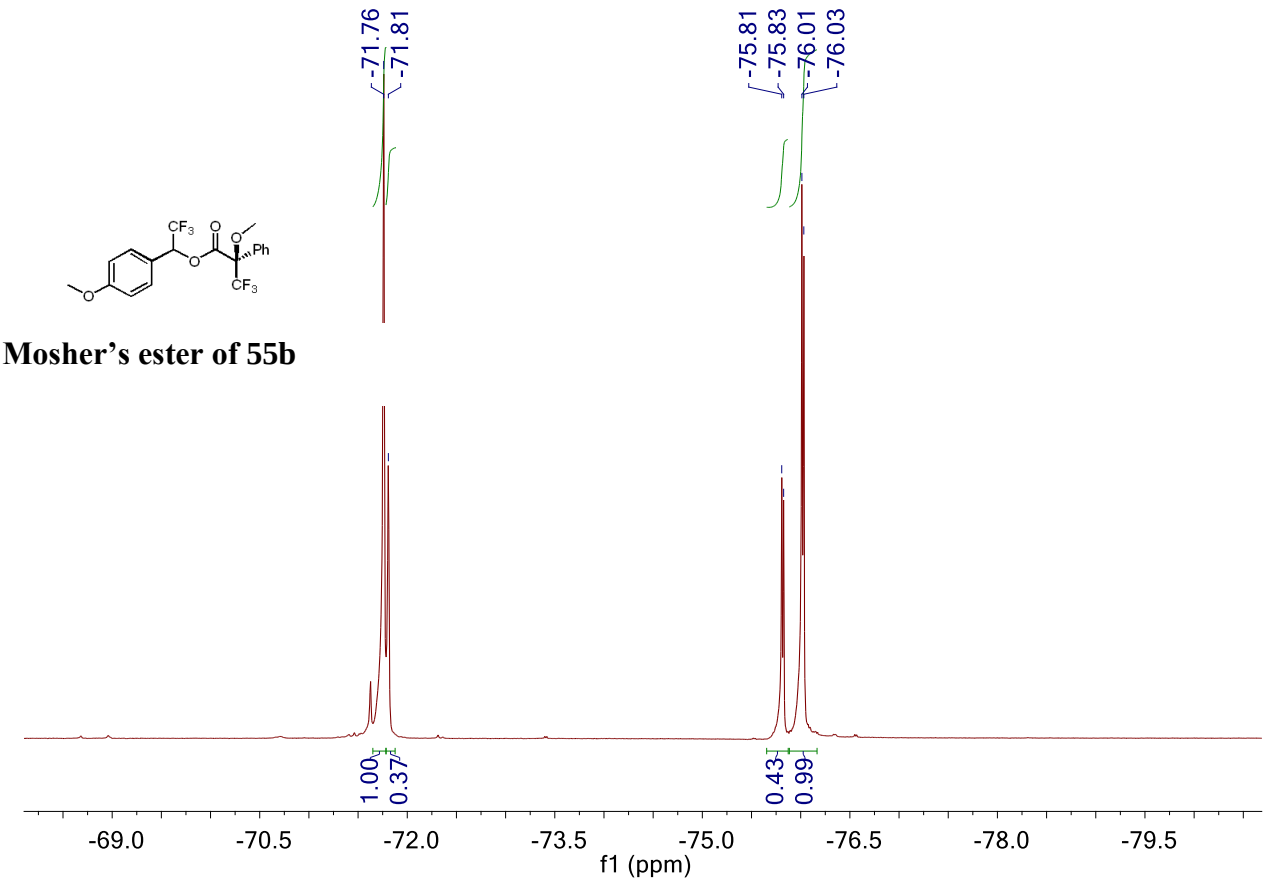

160.5
128.8
127.7
126.2
125.5
123.2
121.0
114.1
77.3
77.0
76.7
72.9
72.6
72.4
72.1
55.3
OH
CF3
O
55b
f1 (ppm)


-78.52
-78.54
OH
CF3
O
-77.95
-78.05
-78.15
-78.25
-78.35
-78.45
-78.55
-78.65
-78.75
-78.85
-78.95
-79.05
-79.15
f1 (ppm)

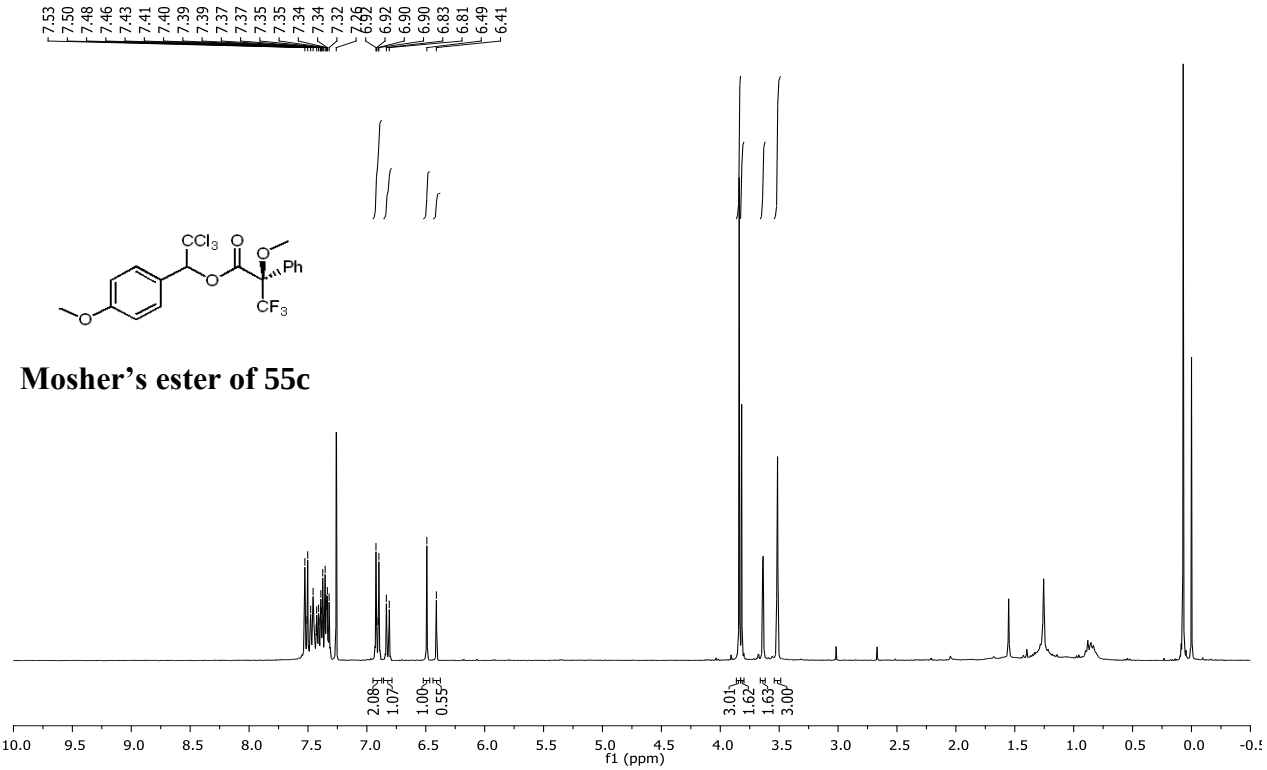
55b



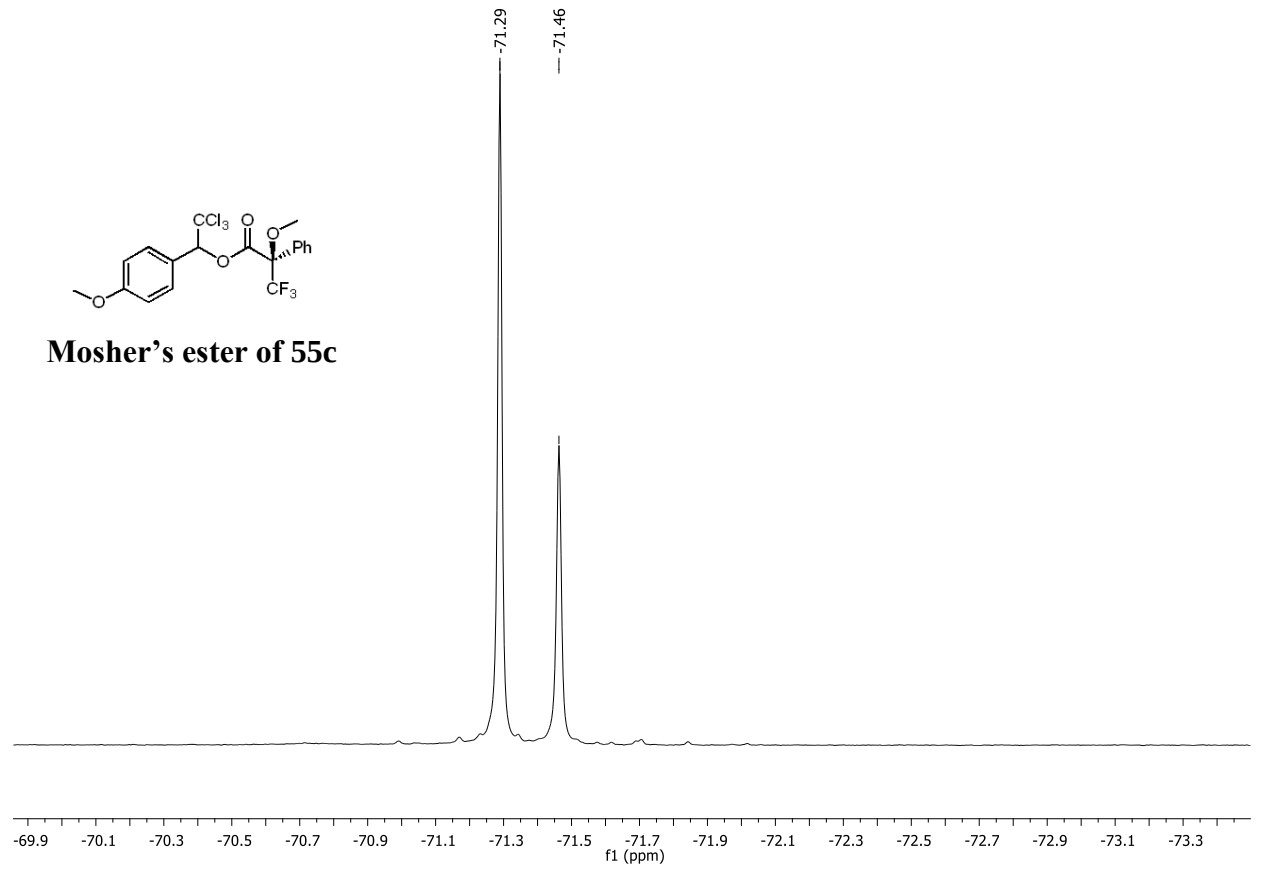
Mosher's ester of 55b



Mosher's ester of 55b

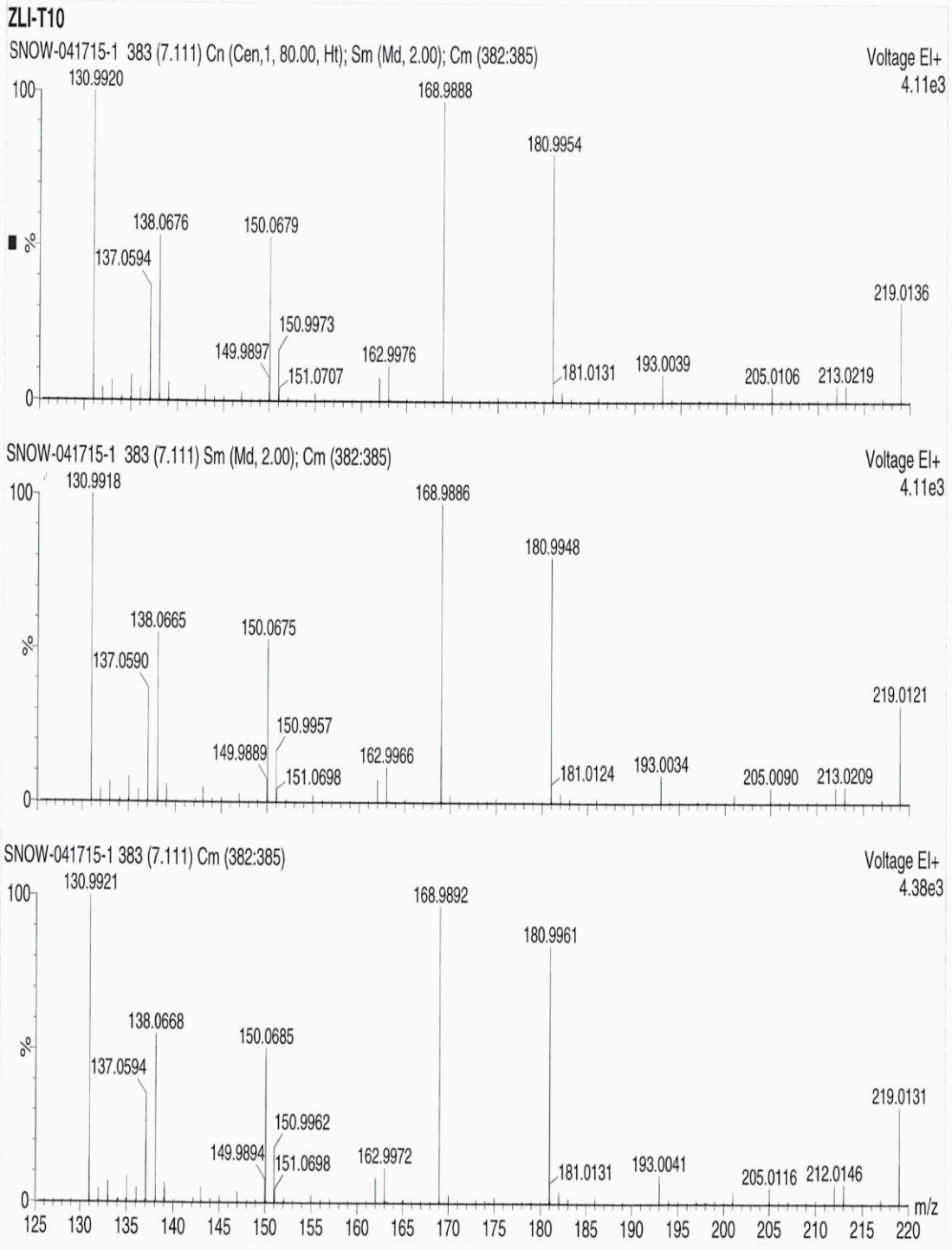


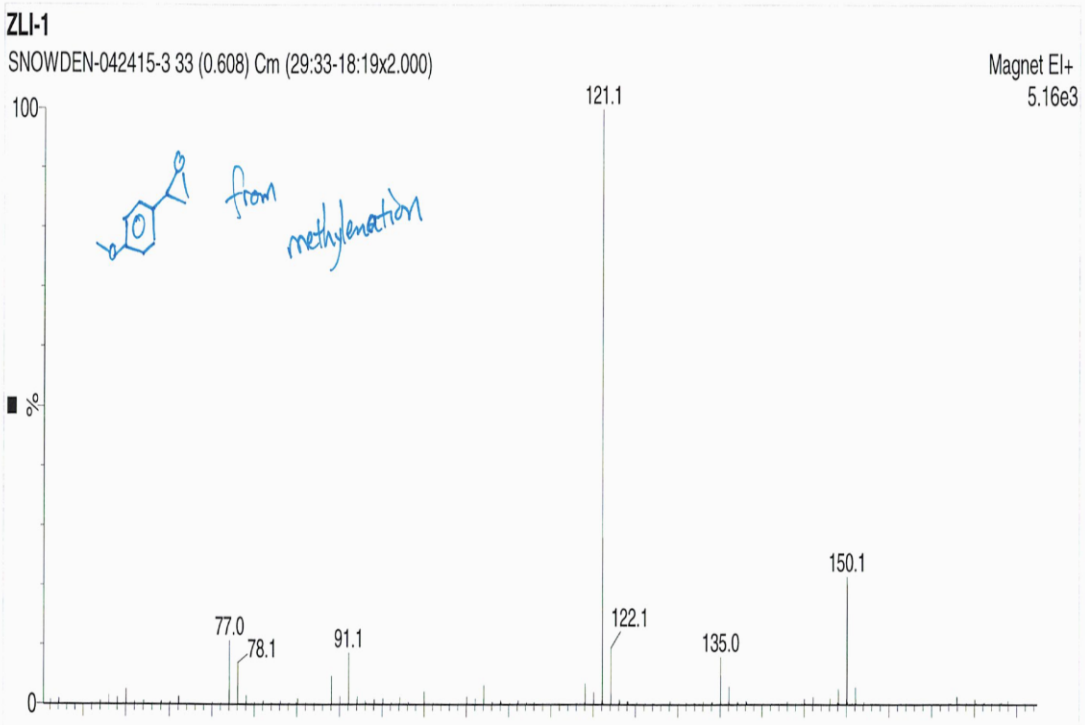
Mosher's ester of 55c

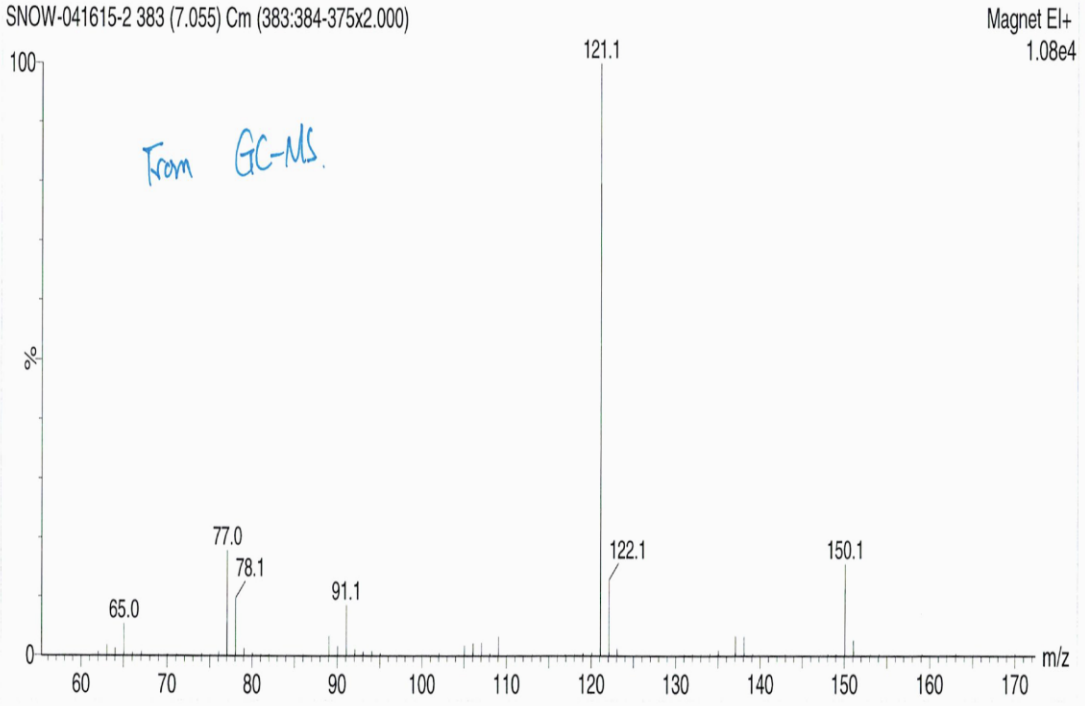


Mosher's ester of 55c

A1.2. APPENDIX B. GC-LRMS, GC-HRMS SPECTRA




ZLI-1
SNOWDEN-042415-3 33 (0.608) Cm (29:33-18:19x2.000)
Magnet EI+
5.16e3
121.1
100
from methylenation
%
150.1
77.0
78.1
91.1
122.1
135.0
0

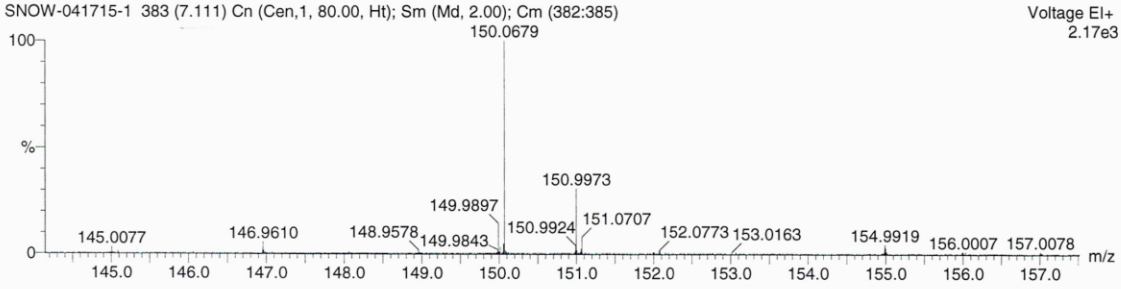

SNOW-041615-2 383 (7.055) Cm (383:384-375x2.000)
Magnet EI+
1.08e4
121.1
100
From GC-MS.
%
77.0
78.1
91.1
122.1
150.1
65.0
0
m/z
60
70
80
90
100
110
120
130
140
150
160
170

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

ZLI-T10
SNOW-041715-1 383 (7.111) Cn (Cen,1, 80.00, Ht); Sm (Md, 2.00); Cm (382:385)



Minimum:				-1.5		
Maximum:		3.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
150.0679	150.0681	-0.2	-1.2	5.0	1	C9 H10 O2