DEVELOPMENT OF NOVEL FLUOROUS TAGGING REAGENTS AND PROGRESS TOWARDS (4*S*,8*S*,12*S*)-4,8,12-TRIMETHYLNONADECANOL

by

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DEVELOPMENT OF NOVEL FLUOROUS TAGGING REAGENTS AND PROGRESS TOWARDS (4*S*,8*S*,12*S*)-4,8,12-TRIMETHYLNONADECANOL

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The configuration of methyl groups within polyisoprenoid motifs of natural products continue to be difficult to assign. The *syn*/*anti* relationships of methyl groups within oligoisoprenoids have been shown to produce reliable differences in ^{1}H and ^{13}C NMR spectra. However, the data set requires expanion to include longer polyisoprenoid motifs and the stereopurity of these samples needs to be higher.

Herein, we describe the advancements towards making a more comprehensive data set of oligoisoprenoids in high stereopurity through a fluorous mixture synthesis. Four new fluorous tagging reagents were synthesized and demonstrated to separate otherwise identical compounds. From which a simple method was developed to evaluate the potential of future fluorous tags. Additionally, the known reaction conditions for aryl thionocarbonate ester formation were optimized to reduce the presence of byproduct; increasing the isolatable yield. Finally, an iterative reaction scheme utilizing a highly selective (96 % de, +99 % ee) iridium catalyzed crotylation reaction was used towards the synthesis of (4S,8S,12S)-4,8,12,-trimethyl-nonadecanol.

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AIBN	Azobisisobutyronitrile
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DIBAL	Diisobutylaluminium Hydride
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
F-HPLC	Fluorous High Performance Liquid Chromatography
FBS	Fluorous Biphasic System
FID	Free Induction Decay
FMS	Fluorous Mixture Synthesis
FSPE	Fluorous Solid Phase Extraction
^{F}PMB	Fluorous p-Methoxybenzyl Ether
^{F}TIPS	Fluorous Triisopropylsilane
MPM	β-D-mannosyl phosphomycoketide
SASA	Solvent Accessible Surface Area
TBSOTf	*t*-Butyldimethylsilyl Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

PREFACE

I would like to start out by thanking my M.S. thesis advisor Dr. Dennis Curran, who has guided me over the past four years. His teachings during my time within the Curran group will be an invaluable asset to build off of as my career progresses. I am grateful for all of the assistance and opportunities he has given me. I also want to thank my B.S. advisor, P.J. Persichinni III, who piqued my interested in organic chemistry. Without whom I may have wandered aimlessly through my academic and professional careers.

Being a member of the Curran group has been a joy, and I would like to thank all of the members for their advice and friendship over the years. I want to particularly acknowledge Dr. Edmund Yeh and Dr. Mantosh Sinha for their assistance, knowledge, and patience during my first year to help me begin my research; and for their continued efforts over the years since then, whenever I have had a question. I am also grateful to Dr. Xinyu Liu and Dr. Scott Nelson for being on my committee and offering their advice towards my project and career goals.

Finally, I would like to thank my family, both immediate and extended, for letting me know that I will always have someone there for me if I need help. To my brother, Jim Tush, thank you for helping take care of me when I was little; and I hope one day when we are not as busy that we will get to know one another better. I would especially like to thank my parents, Bill and Susan Budavich. Their continued love and support over the years has been priceless

along my journey. I cannot even begin to show enough love and appreciation that I have for them in these few sentences.

1.0 Introduction

1.1 Fluorous Chemistry

In 1994, Horváth and Rábai introduced the term *fluorous* to describe highly fluorinated solvents and solids that are immiscible in aqueous or common organic solvents. Using this phase property, they were able to efficiently recycle a highly fluorinated rhodium catalyst for hydroformylation reactions.[1,2] Later Curran and Gladysz proposed a formal definition of *fluorous*: "of, relating to, or having the characteristics of highly fluorinated saturated organic materials, molecules, or molecular fragments."[3,4] Since Horváth and Rábai's paper, other reaction schemes have made use of a fluorous biphasic system (FBS) to separate metal catalysts such as cobalt, nickel, and tin complexed with highly fluorinated ligands from reaction mixtures.[5,6] Further advancements led to fluorous synthesis techniques in which the target organic molecules are made with the aid of fluorous protecting groups.[7] The fluorinated products are then partitioned into a fluorous solvent, while any remaining reagents or byproducts stay in the organic solvent.

In lieu of a liquid-liquid biphase, molecules bearing fluorous tags can be retained on fluorous silica gel during a solid phase extraction while the non-fluorous components are eluted.[8,9] A *fluorous tag* is defined as "a portion or domain of a molecule that is rich in sp^3 carbon-fluorine bonds and exerts primary control over the separability characteristics of the molecule in fluorous separation techniques."[3] The main benefit of fluorous solid phase extraction (FSPE) over liquid-liquid extraction is the reduction of fluorine content required for the molecule to be partitioned to the fluorous media.[8–10] This becomes particularly useful for larger organic molecules which would require "heavier" fluorous tags to dissolve preferentially in a fluorous

solvent. The fluorinated motif of the molecule only needs to bind to the stationary phase as opposed to the molecule being solvated by a fluorous solvent.[9,10]

1.1.1 Fluorous Mixture Synthesis

To help identify viable fluorous tags, Curran and Luo separated a mixture of amides (**1a-i**) on fluorous silica gel (silica-$OSi(Me)_2(CH_2)_nR_f$).[9] The amides only differed by perfluoroalkyl chain length. A heptyl substituent was used as a standard for where the amides would elute without any fluorine atoms. Using a Fluofix 120E analytical column ($SiC(CF_3)_2CF_2CF_2CF_3$) with a gradient methanol-water mobile phase, **1a-i** were separated with resolution between each amide and baseline resolution after **1d** (Figure 1).[9]

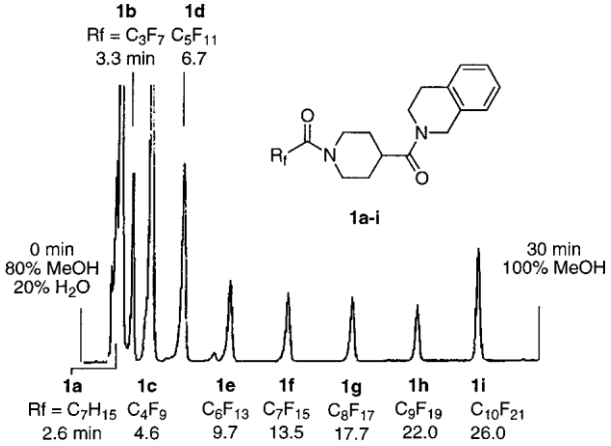
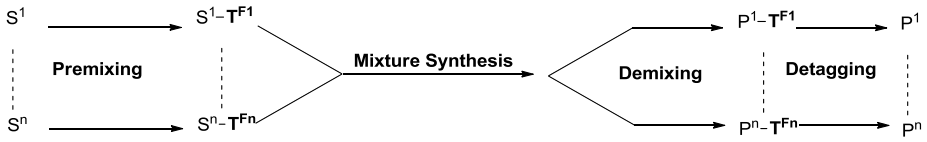


Figure 1. HPLC trace of **1a-i** on a Fluofix 120E[9]

This work led Curran and co-workers to further demonstrate the utility of fluorous stationary phases through fluorous mixture synthesis (FMS).[11] FMS allows multiple isomers to undergo a series of reactions in the solution-phase by encoding each isomer with a unique fluorous tag. There are four stages in a FMS: premixing, mixture synthesis, demixing, and detagging (Scheme 1).[11,12]

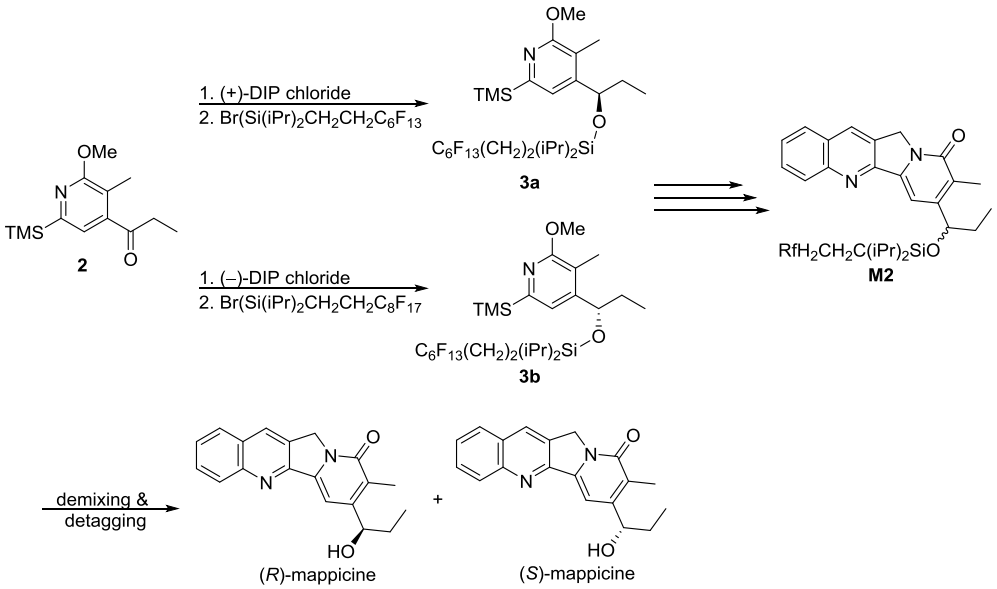
Scheme 1. Four Step Strategy of FMS



During the premixing stage the substrates (**S$^{1—n}$**) are labeled with a unique fluorous tag (**T^{Fn}**). The tagged substrates are combined in equal parts and the average molecular weight of the substrates is used for stoichiometry calculations during all subsequent reactions during the mixture synthesis stage. At or near the end of the synthesis, the fluorous mixture is demixed using a fluorous HPLC (F-HPLC) column yielding each quasiisomer.[13] Quasiisomers are almost isomers in that they contain slightly different substituents, such as fluorous tags, and can vary in stereochemistry.[14] In the final step of FMS, the fluorous tag is removed resulting in each desired product in high purity, free from the other isomers.

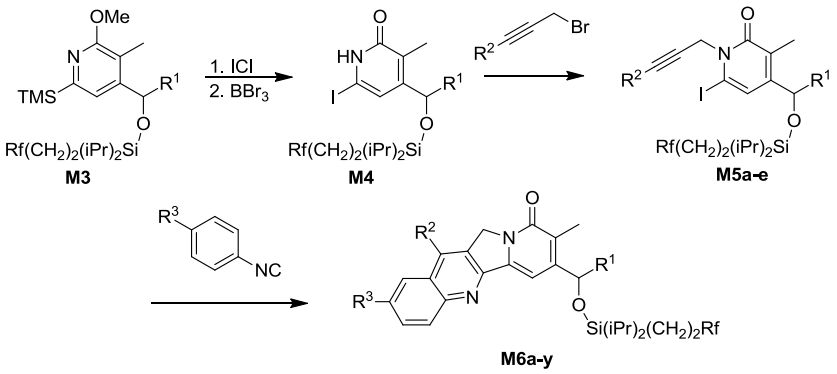
The power of FMS lies in its ability to react similar substrates, such as enantiomers, in one pot as opposed to parallel syntheses. To prove the concept of quasiracemic synthesis, Curran and coworkers synthesized (*R*) and (*S*)-mappicine with >98% ee in 8 steps where the first two reactions were done in parallel to set the stereocenter and add a fluorous tag (Scheme 2).[11] The quasiisomers **3a** and **3b** were then mixed together and undergo four transformations to reach **M2** which is then demixed and detagged to yield (*R*) and (*S*)-mappicine.

Scheme 2. FMS of (*R*) and (*S*)-mappicine[11]



Using the same synthetic scheme, a library of 100 mappicine derivatives was generated through FMS.[11] Instead of encoding for enantiomers, the four fluorous tags assigned the variation in alkyl group attached to the racemic silyl ether (Scheme 3). The fluorous mixture **M4** was split into five portions, then each was reacted with a different propargyl bromide to yield five fluorous mixtures (**M5a-e**). Again each fluorous mixture was split into five portions to react with five different isonitriles to yield 25 fluorous mixtures (**M6a-y**) each containing four compounds that were purified by F-HPLC.[11] This "mix/split" method was later used to synthesize (+)-murisolin and fifteen of its stereoisomers.[15]

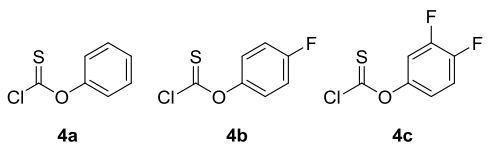
Scheme 3. Library synthesis of mappicine derivatives using FMS



FMS has also been combined with other solution-phase mixture tags to expand the number of substrates reacted simultaneously.[16] By combining four fluorous tags with four oligoethylene glycol tags, Wilcox, Curran, and coworkers were able to synthesize sixteen stereoisomers of murisolin (including twelve new ones).[16] A significant aspect of their mixture synthesis was that each set of tags was able to cause separation independently from the other tag; during the first demixing step, F-HPLC or reverse phase chromatography, both sets of tags resulted in four fractions each containing four quasiisomers of the other tag.[16] Double tagging strategies using only fluorous tags and with separation based on the combined fluorine contents were used in the syntheses of lagunapyrones, cytostatins, and passifloricins.[17–19] Recently, Curran and coworkers reported the synthesis of 16 stereoisomers of macrosphelide in which four fluorous groups were used to encode eight stereocenters.[14] In this binary tagging strategy, -C_2F_5, C_4F_9, C_6F_{13}, and C_8F_{17} were used to make fluorous PMB (^{F}PMB) and fluorous TIPS (^{F}TIPS) protecting groups. Overlap in fluorine content caused up to 4 quasiisomers to elute together during the demixing stage. However by removing the ^{F}TIPS group, a second demixing step based on the ^{F}PMB tags provided each stereoisomer.[14]

1.1.2 Ultra-Light Fluorous Tagging Reagents

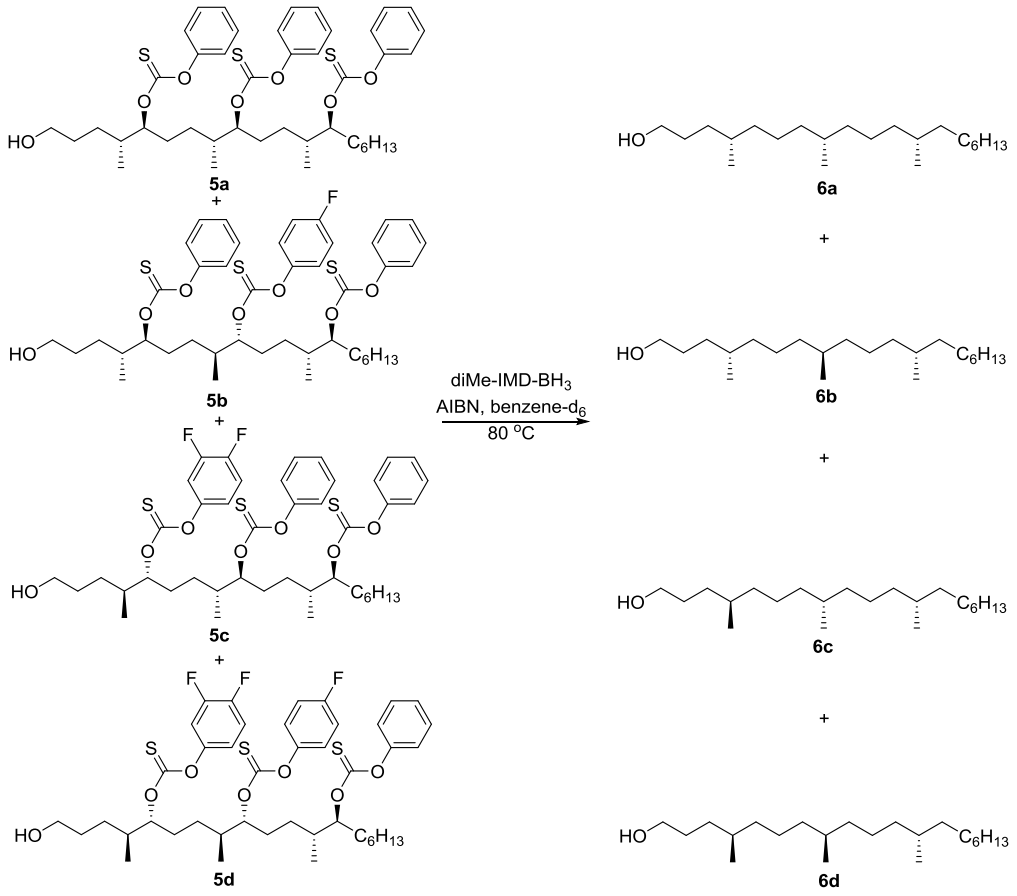
This work shows how FMS is an alternative tool for synthesizing multiple stereoisomers by increasing the linear sequence to tag, demix, and detag in order to avoid parallel syntheses of each stereoisomer. As the number of stereocenters increases for a target molecule, the number of stereoisomers increases exponentially by the power of two and a FMS becomes more powerful. However, FMS becomes problematic if the fluorine content increases to an extent where the quasiisomers have a molecular weight that is too high and become insoluble. Also enough sites on the target molecule need to be present to attach the fluorous tags. To make target molecules that lack functional groups, Dr. E. Kumli proposed the idea of using fluorinated xanthates combined with Barton-McCombie deoxygenation after demixing to result in "traceless" tags.[12] Expanding on the traceless tag approach, Dr. E. Yeh used fluorinated *O*-phenyl chlorothionocarbonates (**4a-c**) to tag secondary alcohols in a iterative approach towards **5a-d** that were demixed and deoxygenated at the end of the FMS to yield **6a-d** (Scheme 4).[12] Yeh showed that the methyl groups of **6a-d** differ in chemical shifts based on differences in their *syn*/*anti* relationship to each other by using a 700 MHz NMR analysis with very precise shimming and Traficante processing of the FID data.[12] If the small differences between *syn*- and *anti*-methyl groups prove to be reliable, then this will be a powerful tool in determining the structure of other natural products without having to synthesize all of the isomers.



4a **4b** **4c**

Figure 2. *O*-phenyl chlorothionocarbonate tags used by Yeh[12]

Scheme 4. Detagging of the 4 quasiisomers of 4,8,12- trimethylnonadecanol[12]



Tags **4a-c** were used in combination to encode and separate **5a-d** despite varying by only 1 fluorine atom. Then through Barton-McCombie deoxygenation of **5a-d** the 4 isomers of 4,8,12-trimethylnonadecanol (**6a-d**) were isolated. Fluorinated triisopropylsilane (^{F}TIPS) are considered to be "light" fluorous tags based on their low fluorine content (5-17 fluorine atoms) [14] which corresponds with a lighter molecular weight; compared to metal catalysts that would be tagged with over 30 fluorine atoms to be removed by extraction.[1,10] *O*-Phenyl chlorothionoformates have less fluorine content (0-3 fluorine atoms) than ^{F}TIPs and were referred to as "ultra-light" fluorous tags by Yeh.[12] These ultra-light fluorous tags address the problem of needing a site on a target molecule to label and decrease the risk of solubility issues. However, Yeh made only four

stereoisomers with his tags. More fluorinated *O*-phenyl chlorothionoformates need to be developed to increase the number of possible combinations of tagged products. This is important because several natural products have side chains that are higher oligomers of **6**.

1.2 Saturated Polyisoprenoid Natural Products

Many natural products contain a saturated polyisoprenoid motif (Figure 3).[20–25] Due to the lack of functional groups, single isomers of polyisoprenoids are difficult to synthesize. Huo and Negishi were able to achieve a 74 % selectivity in a 4-step procedure for one isoprenoid iteration.[26] The stereochemistry of natural products containing polyisoprenoids with multiple stereocenters is difficult to assign by spectroscopy. The lack of functional groups prevents the use of NMR techniques, such as Mosher ester analyses, that can determine the configuration of a stereocenter.[27] Long range auxiliaries that impart anisotropic effects on polyisoprenoids, similar to using Mosher ester, were unable to distinguish all 3 stereocenters of 4,8,12,16-tetramethylheptadecanol by NMR experiments.[28] Currently, the best method to determine the stereochemistry of a polyisoprenoid natural product is through synthesis of all possible stereoisomers. The chemical shifts, optical rotations, and especially the biological activities of each stereoisomer are directly compared to those of the natural product to find a match, since the exact stereochemistry cannot be predicted when only examining the data from the natural product.

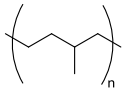
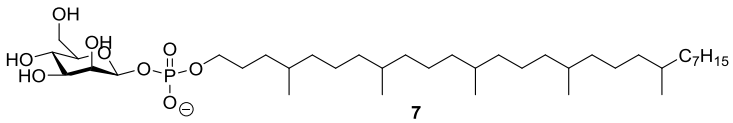


Figure 3. Saturated polyisoprenoid motif

1.2.1 β-D-Mannosyl Phosphomycoketide

Moody and coworkers isolated β-D-mannosyl phosphomycoketide (MPM) **7** from the cell walls of *Mycobacterium tuberculosis* in 2000.[23] MPM is a potent antigen; the polyisoprenoid motif has strong binding with the CD1c protein located on an antigen presenter cell while the phosphate sugar group binds to the T-cell receptor.[29] Crich and Dudkin first developed a method for forming the phosphate sugar in the β conformation before describing a synthesis of **7** with a stereorandom polyisoprenoid motif.[30,31]

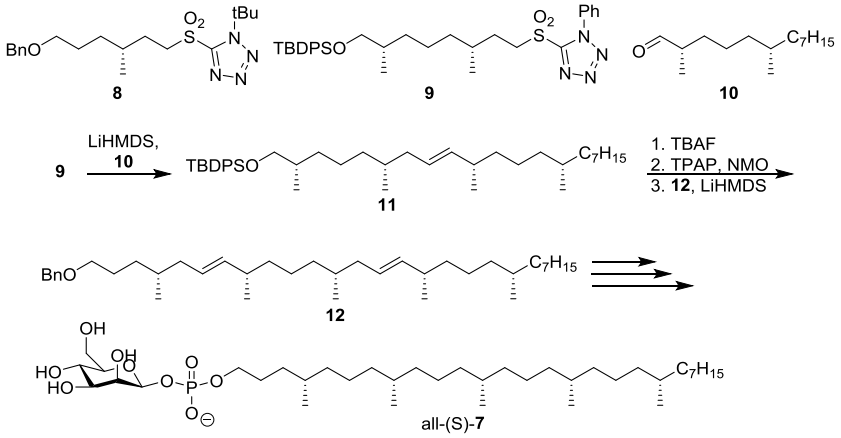


7

Figure 4. Structure of β-D-mannosyl phosphymycoketide

In 2004, Moody and coworkers described the biosynthetic pathway of the mycoketide portion, polyisoprenoid, of **7** to be repetitive which would lead to the same configuration at each methyl stereocenter.[32] Based on these results Feringa and coworkers synthesized the all-(*S*)-MPM in 6.7 % yield by a convergent synthesis with a longest linear sequence of 18 steps (Scheme 5).[24] A copper-catalyzed 1,4-addition of MeMgBr was used to establish the configuration at the methyl positions. [33,34]

Scheme 5. Synthesis of all-(*S*)-MPM[24]



The binding constant of the all-(S)-MPM to T cells matched that of the natural product within the margin of error.[24] However, to prove which stereoisomer of MPM is the molecule isolated from *Mycobacterium tuberculosis*, the other stereoisomers need to be ruled out. Based on Scheme 5, 172 reactions would need to be performed to synthesize all 32 isomers of the polyisoprenoid motif before adding the phosphate sugar moiety (Figure 5). Dr. Yeh's iterative FMS of polyisoprenoid motifs would more than halve the number of reactions (61 total steps) required to synthesize, demix, and detag the 32 stereoisomers of the polyisoprenoid.[12] The iterative approach has 3 reactions that are repeated: crotylation of an aldehyde to add the methyl stereocenter and terminal alkene of **13**; fluorous tagging of the secondary alcohol **16**; hydroformylation of the terminal alkene to extend the alkyl chain and form **15** (Scheme 6).[12]

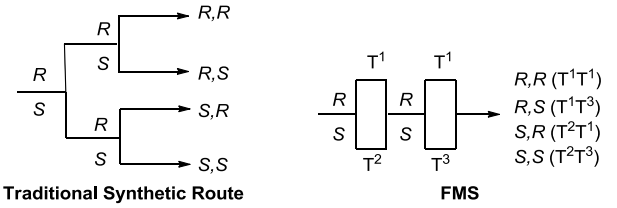
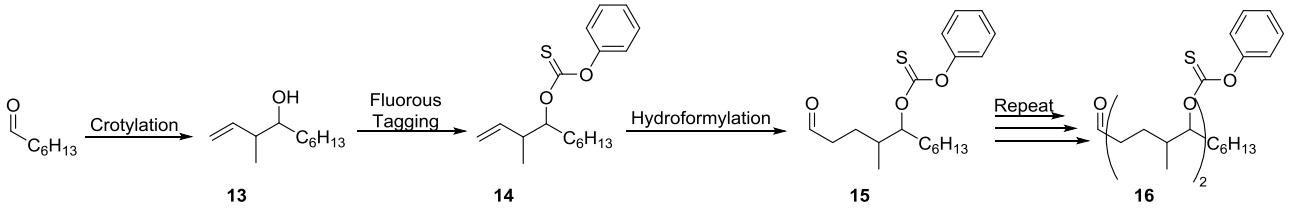


Figure 5. Synthetic routes for the synthesis of stereoisomer libraries[17]

Scheme 6. Iterative Synthesis of Isoprenoids



The crotylation step establishes the configurations of the methyl and alcohol stereocenters through a chair-like 6-membered transition state; the configuration of the alcohol is determined by the chiral ligand on the crotylating agent (**17-20**) and the methyl group is *syn* or *anti* to the alcohol based on the Z/E relationship respectively (Figure 6 and 7).[35–39] During the synthesis of 4,8,12-trimethylnonadecanol, both Brown and Roush crotylboration reagents were used.[12] Brown's reagent exhibited better selectivity than Roush's reagent; however, **19** and **20** can be stored for long durations which make them a more appealing choice for an iterative scheme.[12,35,37,39] Therefore, Yeh used both **19** and **20** in the synthesis of **6a-d** to have consistent selectivity during each crotylation.[12]

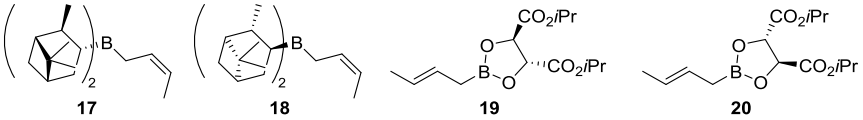


Figure 6. Brown's (*Z*)-crotyldiisopinocampheylboranes **(17 & 18)** and Roush's diisopropyl tartrate (*E*)-crotylboronates **(19 & 20)**

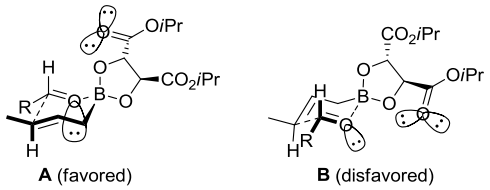
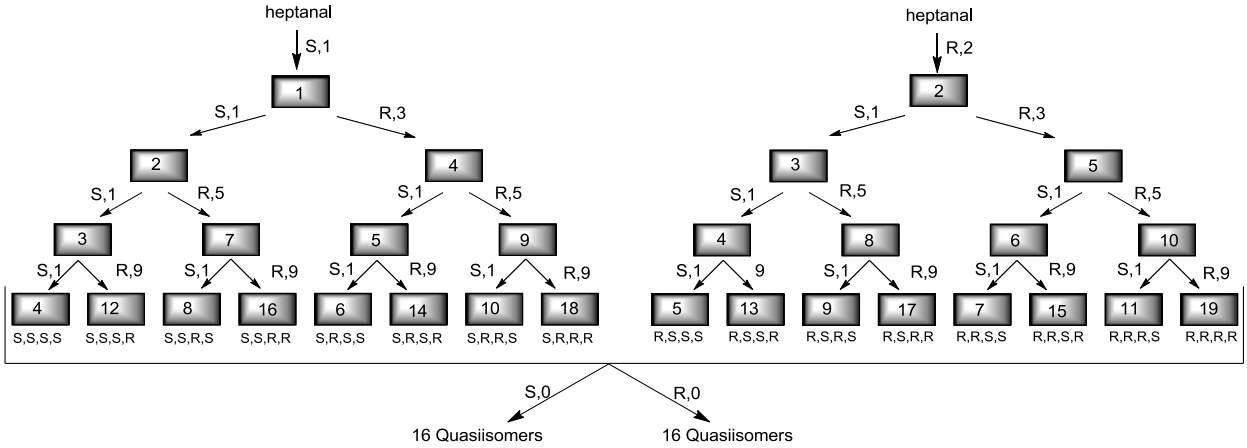


Figure 7. Transition state of the crotylboration reaction based on **20.**[39]

Our long range goal is to synthesize the 32 isomers of MPM by FMS with the smallest total fluorine content possible. In principle, this can be achieved by using tags that contain 0, 1, 2, 3, 5, and 9 fluorine atoms. Based on Schemes 1 and 6, each cycle begins with an aldehyde that

is split into two equal portions. In the first cycle, heptanal is crotylated to obtain the two enantiomers which are given tags of 1 and 2 fluorine content (Scheme 7). The tagged products are then mixed in equal portions to undergo hydroformylation. The newly formed aldehyde mixture is then split into equal portions and the cycle repeated. This time the added tags have fluorine contents of 1 and 3. Each cycle of this iterative approach doubles the number of quasiisomers. In order to tag for this half of the quasiisomers' fluorine content increases by 1 and the other half's fluorine content is increased above the quasiisomers in the first half. Extending this approach through 4 cycles results in 16 quasiisomers that contain between 4 and 19 fluorine atoms (Scheme 7). The final cycle of the FMS splits the mixture of aldehydes into equal parts. Each half is crotylated to form the methyl centers in MPM, but this time the alcohols are tagged with *O*-phenyl chlorothionoformate and they remain separate from each other for the remaining steps. This is done to avoid any possible solubility issues that might arise from adding the next tag, which would contain 17 fluorines. The final steps include hydroformylation, reduction to the alcohol, adding the phosphate sugar, removing the protecting groups from the sugar, demixing, and deoxygenation of the polyisoprenoid motif.

Scheme 7. The tagging strategy for the FMS of MPM: R and S denote the enantiomer being formed. The numbers designate the fluorine content of each tag. And the numbers in the box represents the total fluorine content of the aldehydes which are combined and split for the next cycle.



Prior to starting the FMS of MPM, additional fluorous tags need to be synthesized and tested for stability under reaction conditions. Most importantly the tagged products need to be separable on an F-HPLC column. Additionally, the crotylation reagents need to be more selective than the Roush reagents in order to have a high percentage of the desired isomer. Using the selectivity observed by Yeh with **19** and **20** (89:11), after 5 iterations the major stereoisomer is present in only 55 % with the next 4 most prevalent isomers occurring in 7 %. The crotylation reagents need to be stable long enough to store for consistent yields and selectivity between cycles; and the byproduct of the reaction needs to be separable from the product.[12]

2.0 Results & Discussion

2.1 Synthesis and Evaluation of New Ultra-Light Fluorous Thionocarbonate Tags

Yeh used the term ultra-light fluorous tag to describe his low fluorine-content aryl thionocarbonate groups.[40] We define an *ultra-light fluorous tag* as a group or substituent with little to no fluorine content that exerts primary control over separation of a tagged molecule from other tagged molecules using fluorous separation techniques. While the tags with only a few fluorines might better be called "fluorinated" rather than "fluorous", they still dictate the separation on a fluorous HPLC column. For this reason we refer to them as fluorous tags.

2.1.1 Synthesis and Evaluation of Tagging Reagents

The first goal towards FMS of MPM side chain isomers was to increase the repertoire of ultra-light fluorous tags, hereafter simply called tags. In addition to the successful tagging reagents **4a-c**, Yeh had evaluated the performance of tagging reagents **21a-c**[*] and **4d** (Figure 8).[12,40] The three reagents containing one fluorine atom (**4b**, **21a**, and **21b**) differed by their location of fluorine on the aryl ring. Yeh combined all seven of these tagging reagents with a secondary alcohol to create a set of tagged compounds.[12,40] The expected product from **21c** was not observed by NMR analysis; the fluorous tag appeared to have eliminated perfluorophenoxide after addition to the alcohol. When the tagged compounds were mixed and then separated on F-HPLC, the *meta*- and

[*] Aryl chlorothionoformates that were either not used within this work or were not successful tagging reagents are part of the **21** set, in order to keep reagents **4** labeled succinctly.

para-substituted tagged alcohols eluted as one peak while the *ortho*-substituted analog eluted between the unfluorinated and *m*/*p*-fluorophenyl products. However, when **4a**, **4b**, and **21a** were used in a FMS of **6**, sufficient separation of the quasiisomers was not achieved.[12,40]

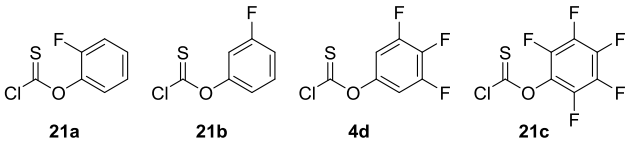


Figure 8. Fluorous tagging reagents used by Yeh

We selected for evaluation seven new tagging reagents with 3, 5, and 9 fluorine atoms (Figure 9). Yeh already assessed a tagging reagent with three fluorine atoms on the phenyl ring (**4d**), and we evaluated complementary reagents containing a *meta*- or *para*-CF_3 group (**4e** and **21e**) and a *para*-OCF_3 group (**4f**). To obtain tagging reagents with 5 fluorine atoms, we extended the perfluoroalkyl chain of **4e** and **21e** by one CF_2 unit to give *meta*- and *para*-(pentafluoroethyl)phenyl chlorothionocarbontes **4g** and **21g**. Extending the perfluoroalkyl chain another two CF_2 units gave *meta*- and *para*-(nonafluorobutyl)phenyl chlorothionocarbonates (**4h** and **21h**).

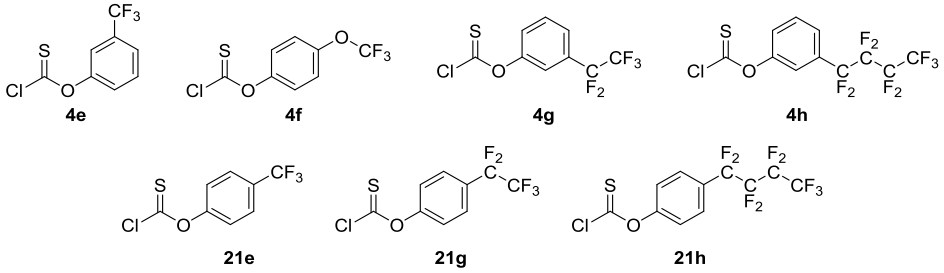
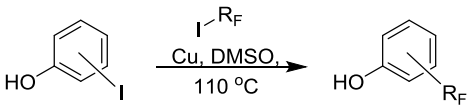


Figure 9. Proposed set of fluorous tagging reagents to synthesize and evaluate

The procedure developed by Williams and coworkers to form the chlorothionocarbonates combines a phenol with thiophosgene under basic conditions.[41] The phenols needed for **4e**, **4f**, and **21e** are commercially available, while the *meta*- (**22h**) and *para*-substituted perfluorobutyl- (**23h**) and *meta*-perfluoroethyl phenols (**22g**) are available from published procedures.[42,43] Following procedures developed by Matsui,[43] 5 equiv of pentafluoroethyl iodide (C_2F_5I) was

condensed at -78 °C and added to a DMSO solution of *m*-iodophenol and 3 equiv of copper powder in a sealed tube at 0 °C. The mixture was heated to 110 °C for 48 h before being cooled to rt and poured into H_2O. After workup and column chromatography, the *m*-(pentafluoroethyl)phenol **22g** was obtained in 64 % yield (Scheme 8).[43] A similar procedure was used to make **22h** and **23h**; however, because nonafluorobutyl iodide (C_4F_9I) is a liquid at rt, only 1.25 equiv of this reagent was used and a sealed tube was unnecessary in the synthesis of *m*/*p*-(nonafluorobutyl)phenols. The corresponding phenols **22h** and **23h** were isolated in 70 % and 62 % yields, respectively.

Scheme 8. Synthesis of perfluoroalkylphenols

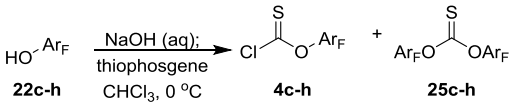


Substitution	R_F	Product	Yield
meta	pentafluoroethyl	**22g**	64 %
meta	nonafluorobutyl	**22h**	70 %
para	nonafluorobutyl	**23h**	62 %

With the necessary phenols obtained, we synthesized the fluorous chlorothionocarbonates (Scheme 9), then directly reacted them individually with alcohol **24** to make the tagged alcohols (Table 1). To make the tagging reagent **4c**, 3,4-difluorophenol was dissolved in an aqueous NaOH solution.[41] The resulting mixture was added to a solution of thiophosgene (1.2 equiv) in chloroform at 0 °C. The reaction progress was followed by TLC. The more polar 3,4-difluorophenol disappeared, leaving the 3,4-difluorophenyl chlorothionocarbonte (**4c**) along with byproduct, *O*,*O*-bis(3,4-difluorophenyl)thiono-carbonate (**25c**). The presence of the **25c** does not interfere with the following tagging reaction and so the product was initially used crude. However, the byproduct was found to coelute with the desired product during column chromatography. Thus **4c** was eventually purified by column chromatography; but we were

unable to back calculate the yield for forming **4c**. This process was repeated to yield the other tagging reagents **4d-h**.

Scheme 9. Synthesis of fluorinated aryl chlorothionocarbonates



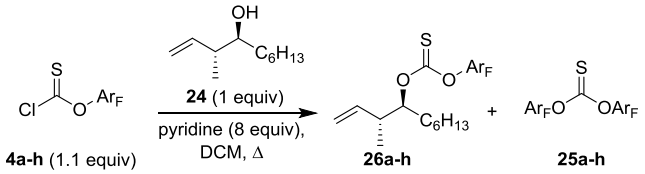
22c-h **4c-h** **25c-h**

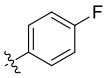
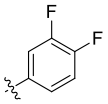
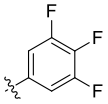
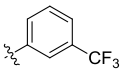
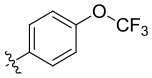
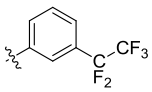
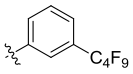
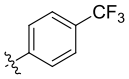
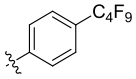
Based on Robins and coworkers procedure, the secondary alcohol (**24**) was reacted with excess **4c** and pyridine in dichloromethane to form the tagged alcohol **26c** (Table 1).[44] The reaction progress was monitored by TLC and ^{1}H NMR spectroscopy. On TLC analysis, the product **26c** does not overlap with either starting materials **4c** and **24**; however, **25c** forms during the tagging reaction and the tagged alcohol **26c** and *O,O*-bis(3,4-difluorophenyl) thionocarbonate have similar retention factors. Conversion of the **24** to **25c** can be discerned easily by crude ^{1}H NMR spectroscopy. The carbinol proton signal occurs at 3.39 ppm for the untagged secondary alcohol while the carbinol signal of the tagged product is at 5.34 ppm. After column chromatography, the desired product could be isolated as pure. However, this required discarding the contaminated fractions containing **25c** reducing the isolatable yield of **26c**.

In addition to needing to reduce the amount of diaryl byproduct, the reaction conditions when used with the other tagging reagents gave varying yields (0-72 %). To optimize the reaction the concentrations of the reagents were varied, other solvents were tested, the reaction temperature was increased, and DMAP was added to help catalyze the reaction. In the end, decreasing the amount of **4c** to 1.1 equiv, increasing the amount of pyridine to 8 equiv, and heating the reaction mixture to reflux in a 0.2 M solution of DCM for 16 hours resulted in 50 % isolated yield of the tagged alcohol **26c** (Table 1). Despite the reduction in the amount of 3,4-difluorophenyl chlorothionocarbonate used, there was still some **25c** formed. However, the

decreased amount of **4c** resulted in an increased amount of product **26c** recovered after chromatography.

Table 1. Synthesis of tagging reagents and the tagging of alcohol **24**



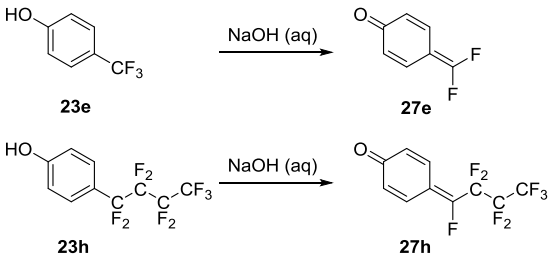
Entry	Ar_F	Ar_F Abbreviation	Tagging Reagent	Diaryl Thionocarbonate	Tagged Alcohol	Yield of Tagged Alcohol
1		Ar_a	**4a**[a]	**25a**	**26a**	90 %
2		Ar_b	**4b**[a]	**25b**	**26b**	79 %
3		Ar_c	**4c**	**25c**	**26c**	50 %
4		Ar_d	**4d**	**25d**	**26d**	79 %
5		Ar_e	**4e**	**25e**	**26e**	77 %
6		Ar_f	**4f**	**25f**	**26f**	81 %
7		Ar_g	**4g**	**25g**	**26g**	70 %
8		Ar_h	**4h**	**25h**	**26h**	84 %
9			**21e**[b]			
10			**21h**[b]			

a) commercially available b) tagging reagents not formed

Following this procedure 1.1 equiv of the other tagging reagents (**4a,b,d-h**) were reacted with **24** and 8 equiv of pyridine in refluxing DCM. The isolated yields of pure tagged alcohols are shown in Table 1. The commercially available tagging reagents **4a** and **4b** gave **26a** and **26b** in good yields of 90 % and 79 % respectively (Entries 1 & 2). Tagging reagent **4d** yielded **26d** in 79 %, similarly **26e** and **26f** were obtained in 77 % and 81 % yields (Entries 4,5, & 6). We isolated **26g** in a yield of 70 % and the yield of **26h** was 84 % (Entries 7 & 8). The byproducts **25a-h** were not isolated during purification of **24a-h**.

In contrast to the successes with **4a-h**, tagging reagents **21e** and **21h** (entries 9 and 10) were not formed when the phenols **23e** and **23h** with NaOH (aq) were in the presence of thiophosgene. The ^{1}H and ^{19}F NMR data of the tagging reagents from entries 9 and 10 show complex aromatic proton and fluorine signals. When a non-nucleophilic base, DBU, or NaH was used instead of aqueous NaOH, complex NMR spectra were again observed. Based on precedent, [45] we suspect that the phenoxides of **23e** and **23h** eliminate fluoride forming highly reactive **27e** and **27h** more rapidly than they add to thiophosgene (Scheme 10). We concluded that *p*-perfluoroalkyl phenols are not good perspective tag components; however, all the other motifs in Table 1 are suitable.

Scheme 10. Proposed decomposition of *p*-(perfluoroalkyl)phenols by elimination of fluoride



2.1.2 Separation of Tagged Alcohols

Compounds that vary in fluorine content are known to separate by F-HPLC; however, we needed to demonstrate that the new fluorous tagging reagents **4e-h** could separate quasiisomers.[9,11,12] In Table 1 we synthesized a set of tagged alcohols **26a-h** that are identical with the exception of the fluorinated aryl group. The eight tagged alcohols were combined in equal mole portions, and this mixture (**M7**) was injected onto an analytical F-HPLC column (FluoroFlash, 4.6 mm i.d., 150 mm length, 5 μm) using an isocratic mobile phase of acetonitrile and water. The resulting chromatogram is shown in Figure 10. Additionally, each tagged alcohol was individually injected onto the F-HPLC column to assign the elution order of the mixture. As expected, the tagged alcohols eluted based on their total fluorine content with **26a** having zero fluorine atoms coming first and **26h** having nine fluorines coming last. None of the quasiisomers overlapped using the isocratic mobile phase, suggesting that the labelled compounds will be isolatable on a semi-preparative scale with a gradient mobile phase to elute the last two compounds faster.

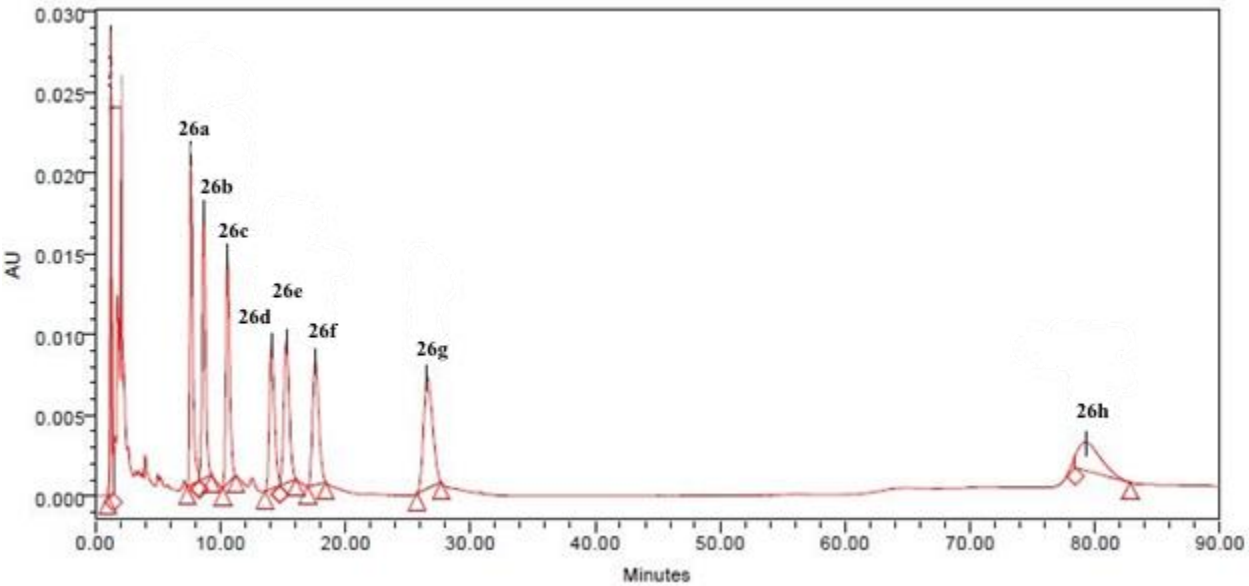


Figure 10. F-HPLC Trace of **M7** (60:40 acetonitrile-water, 1 mL/min, injection size = 10 μL of 1 mg/mL **M7** in acetonitrile)

Interestingly, the three compounds which had a three fluorine atoms **26d** (14.1 min), **26e** (15.3 min), and **26f** (17.6 min) were separable from each other by more than 1 min. We postulated that the difference in retention on the F-HPLC column was due to how accessible the fluorine atoms on **26d**, **26e**, and **26f** are to the stationary phase. To test this notion, we modeled the fluorinated phenol groups (Ar_FOH) that are present in tagged alcohols **26a-h**. The remainder of these molecules (alcohol component) us the same, so it was omitted to simplify the model. The fluorinated phenols were constructed using the molecular modeling program Scigress (Table 2). From the phenol structures, the solvent accessible surface area (SASA) was calculated by using the COSMO solvation model.[46] By finding the difference in the SASA between the fluorinated phenols and phenol, we obtained an estimate of the fluorine surface area that is accessible by the stationary phase. The estimated solvent accessible fluorine surface area of the 3,4,5-trifluorophenol, 3-(trifluoromethyl)phenol, and 4-(trifluoromethoxy)phenol increases in the same order they elute off the F-HPLC column. This shows that the total fluorine surface area is not necessarily the same between fluorous tags containing the same number of fluorines.

Table 2. Retention Times Compared to Estimated Solvent Accessible Surface Area of Phenol Groups[a]

Ar_FOH	Solvent Accessible Surface Area (Å^2)[a]	Difference from Phenol (Å^2)	t_r (min)	k[b]	$log\left(\frac{k}{k_{Ph}}\right)$
Phenol	128	0	7.67	4.94	0.000
4-Fluorophenol	137	9	8.67	5.72	0.063
3,4-Difluorophenol	144	16	10.58	7.20	0.164
3,4,5-Trifluorophenol	151	23	14.11	9.94	0.303
3-(Trifluorometyl)phenol	168	40	15.27	10.84	0.341
4-(Trifluoromethoxy)phenol	179	51	17.60	12.65	0.408
3-(Pentafluoroethyl)phenol	195	67	26.59	19.61	0.599
3-(Nonafluorobutyl)phenol	249	121	79.31	60.48	1.088

a) Cacluated by COSMO solvation model[46] b) t_0 = 1.25 min

The coefficient of determination (r^2) was used to determine how accurate this assessment was by plotting the fluorine surface (the difference from phenol) area against the retention time. The retention factor (k) measures how long the tagged alcohols reside in the stationary phase relative to the mobile phase (Equation 1). The retention factor is corrected to account for only the effect of fluorine by dividing by the retention factor of tagged alcohol **26a**, and the data is plotted as a logarithmic value to fit a straight line (Figure 11). The coefficient of determination (0.9863) is close to 1. This means that the accessible fluorine surface area of each tagged alcohol, calculated by this model, corresponds closely with the difference in retention times between compounds. While this simplified model does not take into account all of the factors that might affect the retention time, it provided a proof of concept into why quasiisomers containing equal numbers of fluorine atoms vary in retention time. The method is simple to apply and can quickly predict the viability of new tags.

Equation 1. Calculation of the retention factor

$$k = \frac{(t_r - t_0)}{t_0}$$

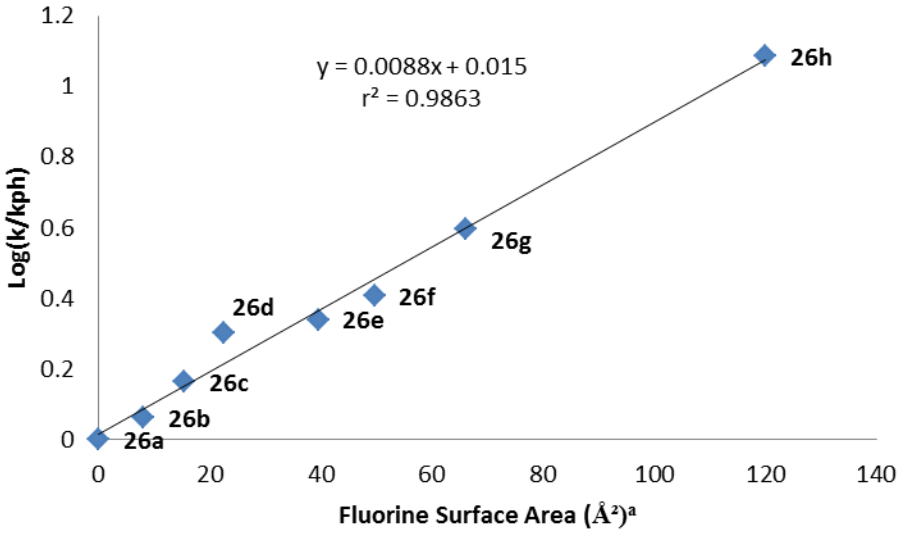


Figure 11. Tagged alcohols Tagged alcohols **26a-h** plotted based on accessible fluorine surface area plotted based on accessible fluorine surface area
a) ($Å^2$ Ar_FOH) – ($Å^2$ PhOH)

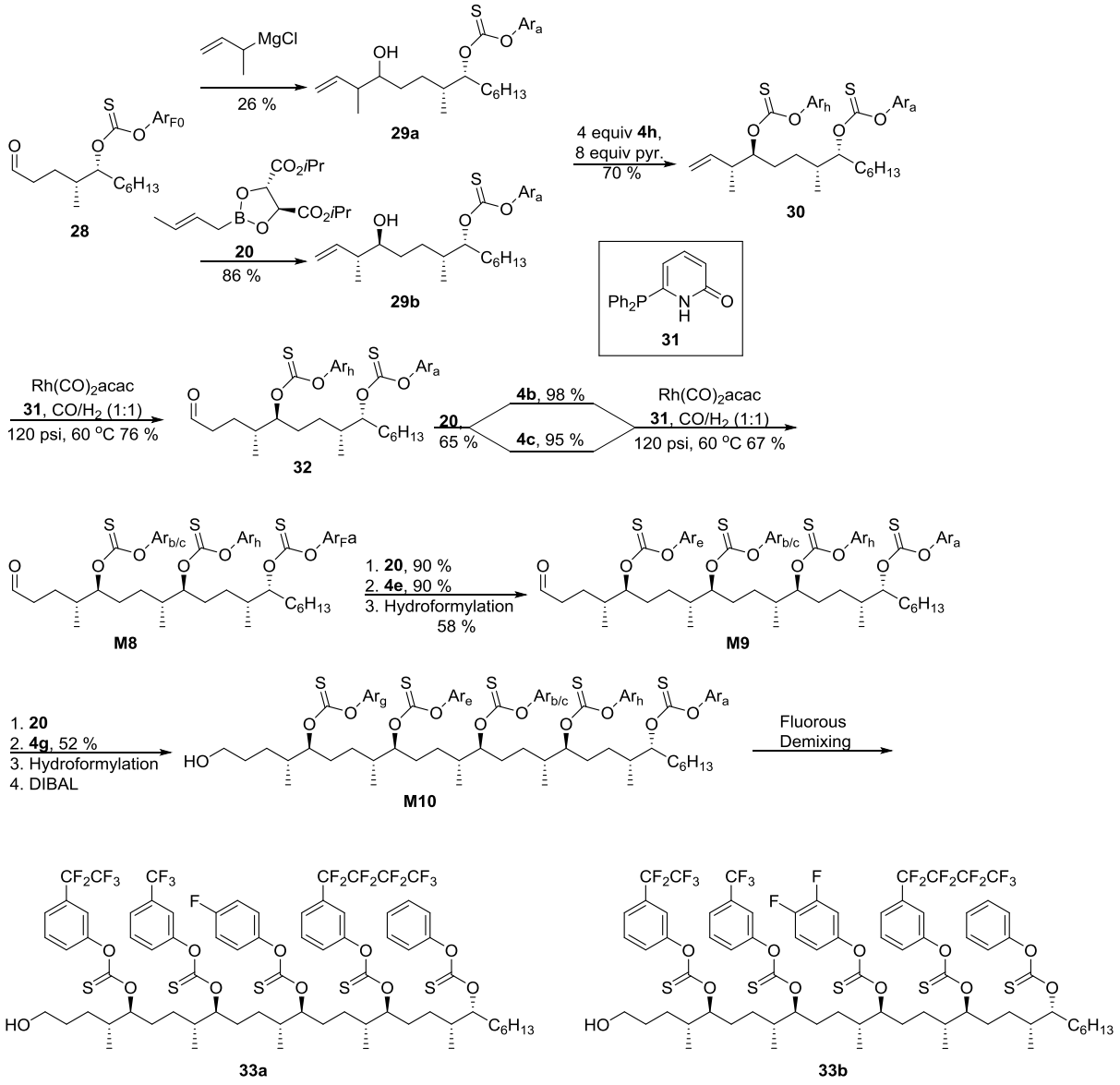
2.1.3 Combinatorial Effect of the Fluorous Tags

With the retention time of **26h** and to a lesser extent **26g** being considerably longer than the rest of the tagged alcohols under isocratic conditions, we needed to make sure that when the tags were used combinatorially that the more heavily fluorinated compounds would preparatively separate with only a 1 fluorine atom difference. Thus the FMS of **M10** was attempted to create two quasiisomers containing 18 and 19 fluorine atoms to inject onto an F-HPLC column (Scheme 10). Aldehyde **28** was obtained from Dr. Yeh and reacted separately with both the allyl Grignard reagent and the Roush reagent (**20**) to give alcohol **29a** (26 %) and **29b** (86 %) respectively. Alcohols **29a** and **29b** were combined to give a mixture of isomers that was enriched in the configuration of **29b**. We used 4 equiv of **4h** and 8 equiv of pyridine to tag a 0.2 M solution of **29** in refluxing DCM, and after workup and purification **30** was obtained in a 70 %

yield. The tagging conditions used throughout Scheme 10 were prior to the optimized conditions in Section 2.1.1.

The hydroformylation conditions in Scheme 11, developed by Breit and coworkers, were the same used by Yeh when making **6a-d**.[12,47,48] Alkene **30** was hydroformylated under these conditions in an autoclave for 18 h. The crude material was purified by column chromatography to give **32** and 41 % of the starting material remained unreacted. Out of the reacted material, 76 % was converted into the desired aldehyde **32**. The recovered **30** was resubjected to the hydroformylation conditions, after 36 h starting material still remained. Additional rhodium catalyst and ligand **31** were added to the reaction mixture and the autoclave was charged with CO/H_2 (1:1, 120 psi) for another 18 h. The crude NMR spectrum showed no presence of **30** and after purification **32** was isolated in 55 % yield.

Scheme 11. Iterative approach to a tagged polyisoprenoid chain



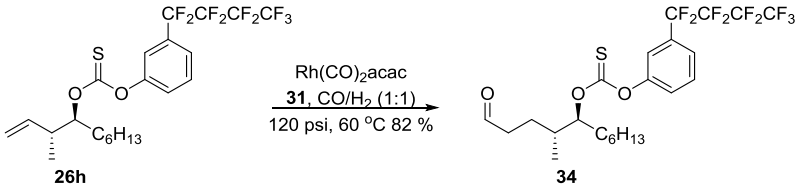
Continuing the synthesis, aldehyde **32** was crotylated with Roush reagent **20** in 65 % yield and split into equal portions. Half the secondary alcohol was tagged with reagent **4b** in 98 % yield and the other half was tagged with **4c** in 90 % yield. These two tagged compounds were mixed together in a 1:1 ratio and hydroformylated to **M8**. The reaction mixture still contained starting material **32** after 20 h, resulting in an overall yield of 44 % of **M8** after separation. After accounting for the recovered starting material, the yield of the terminal alkenes that had reacted

was 67 %. The next iteration crotylated **M8** in 90 % yield, followed by tagging with **4e** in 90 % yield and hydroformylation in 58 % yield to result in **M9**. In the final iteration **M9** was crotylated with **20**, and the resulting alcohol was tagged with **4g** in 52 % yield. The tagged alcohol was hydroformylated and the aldehyde reduced to **M10** in 43 % yield using DIBAL over two steps.

2.1.4 Hydroformylation

Yeh reported 80-83 % yields for five hydroformylation reactions during his first and second attempt at the FMS of **6a-d**.[12,40] While Breit and coworkers observed between 82 % and quantitative yields for a variety of terminal alkenes, except for alkenes containing secondary and tertiary amides (65 % and 36 % respectively).[48] Yet, all of the hydroformylation reactions in Scheme 11 had unreacted starting material remaining after 20 h. The hydroformylation ligand is highly selective for the linear product versus the branched aldehyde.[47,48] No branched product was detected during the hydroformylation reactions thus we do not expect the problem to be between rhodium and the ligand. Using 1.2 equivalents of $Rh(CO)_2acac$ and 6 equivalents of **31** showed complete conversion of starting material to **M9** after 36 hours. Additionally the hydroformylation of **26h** gave the aldehyde **34** in 82 % yield (Scheme 12). This rules out that the Ar_{F9} group by itself poisons the catalyst, but for the first three iterations this was the main difference from the experiments by Dr. Yeh. The aldehyde appears to decompose if the reaction goes longer than 1.5-2 days. Thus, the best approach is to use catalytic amounts of rhodium and ligand, and stop the reaction after 20 hours. If starting material is recovered, then the hydroformylation can be repeated. Alternatively, if the amount of terminal alkene is small stoichiometric amounts of rhodium and **31** may become more convenient.

Scheme 12. Hydroformylation of **26h**



2.1.5 Model Reactions: Fluorous HPLC

In Scheme 10, **M10** was expected to have two fractions with a combination of tags resulting in total fluorine contents of 18 and 19 atoms. Product **M10** was injected onto an analytical F-HPLC column (FluoroFlash, 4.6 mm i.d., 150 mm length, 5 µm). Unexpectedly, the F-HPLC trace of **M10** showed the presence of four compounds, not two (Figure 12). A semi-prep scale F-HPLC demixing of the mixture gave the four compounds in 70 % total recovery. ^{19}F NMR analysis was used to identify the tags of each fraction. The compounds retained at 8.9 and 10.2 min contain ^{19}F NMR signals for *m*-(C_4F_9)phenyl, *m*-(CF_3)phenyl, phenyl, and either 4-fluorophenyl (8.9 min) or 3,4-difluorophenyl (10.2 min). Thus these products have a total fluorine content of 13 and 14 atoms, respectively. The other two compounds at 21.5 and 25.1 minutes are the expected tagged alcohols with a total fluorine content of 18 (**33a**) and 19 (**33b**) atoms, respectively. Examination of the ^{19}F NMR data from samples **M9** to **M10** showed the expected fluorine signals until the last step, DIBAL reduction. After the reduction, the two fluorine signals that correspond to the pentafluoroethyl group integrated to <5 fluorine atoms while the other fluorous tags have the correct values. This reveals that the thionocarbonate containing 3-(pentafluoroethyl)phenyl was partially decomposed during the reduction; but by ^{1}H NMR analysis the thionocarbonate group was not completely degraded as no carbinol signal for the free alcohol was observed. Fortunately the possibility of separating 16 quasiisomers is very promising based on these results.

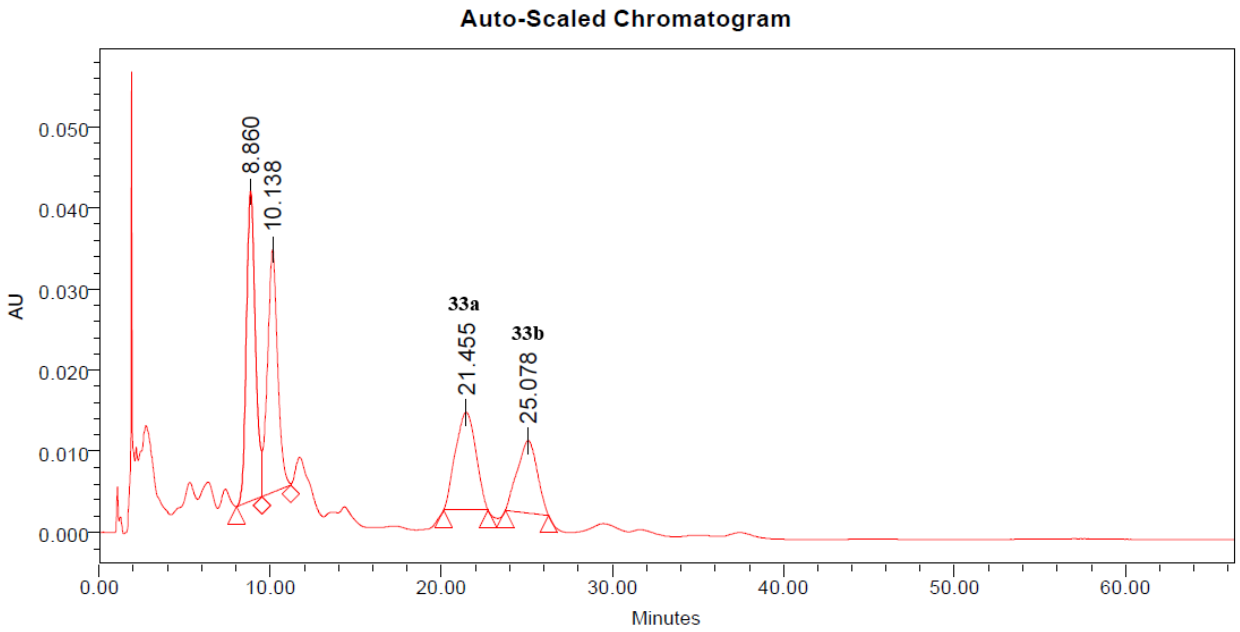


Figure 12. F-HPLC trace of **M10** eluted with a 9:1 acetonitrile-water mobile phase

Based on the observed yields during the synthesis of **M10** and the improved tagging procedures in Table 1, a suitable method was obtained for a FMS of oligoisoprenoids with our set of tagging reagents (**4a-h**). Equally important is that the fluorous tags function collectively when multiple tags encode one compound; rather than the Ar_F groups with higher fluorine content masking the effect of Ar_b and Ar_c resulting in no separation of the peaks at 21.4 and 25.1 (Figure 12).

2.2 Progress Towards Oligoisoprenoids

The overarching target molecule of the project, β-D-mannosyl phosphomycoketide, contains an oligoisoprenoid motif of five repeating units. Using the same synthetic scheme shown before of aldehyde crotylation to form the methyl stereocenter, tagging/protecting of the secondary alcohol, linear hydroformylation of the terminal alkene to yield an aldehyde, and iterating these three steps to the desired chain length we planned to make MPM. First the crotylation conditions need to be improved upon from Yeh's synthesis in order to maintain a high stereopurity of the desired stereoisomer after five iterations.[12]

2.2.1 Leighton's Crotylation Reagent

In 2011, Leighton and coworkers reported the use of $Sc(OTf)_3$ to catalyze the crotylsilylation of aldehydes using enantiomeric crotylsilanes **35a** and **35b**.[49] Scandium triflate increases the yield and decreases the reaction time, while maintaining a high enantioselectivity. Shortly thereafter, mixtures of Leghton reagents **35a** or **35b** with $Sc(OTf)_3$ became commercially available.

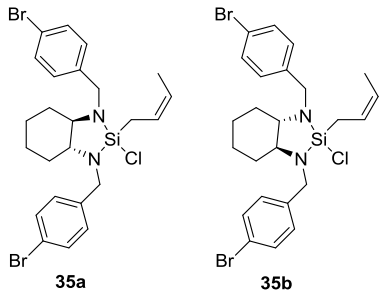


Figure 13. Leighton's enantiomeric crotylsilation reagents **35a** and **35b** which make the *syn*-(*R*,*R*) and *syn*-(*S*,*S*) products, respectively

Following the procedures by Leighton and coworkers, we synthesized the moisture sensitive **35b** using equal portions of (*S*,*S*)-N,N'-bis(4-bromobenzyl)-1,2-diaminocyclyhexane and *Z*-crotyltrichlorosilane with 2 equiv of DBU at 0 °C .[49] The spectra of this reagents matched the reported ^{1}H and ^{13}C NMR data for **35b** by Leighton. To determine the enantio- and diastereoselectivities of the Leighton's reagents, we first made a crotylation standard by addition of the Grignard reagent, 1-methyl-2-propenylmagnesium chloride, to a solution of heptanal in THF at 0 °C to produce **24** in 53 % yield (Scheme 13). Using **36**, a GC method was developed with a chiral column to separate the four stereoisomers (racemates of *syn*/*anti* isomers) to calculate the ratios. Next, the homemade **35b** and $Sc(OTf)_3$ were added to a solution of heptanal in DCM at -5 °C. The solution was stirred for 3 h and quenched with 2 N HCl to result in **(*S*,*S*)-24** in 64 % yield. This procedure was repeated for the commercially available **35b** to give **(*S*,*S*)-24** in 68 % yield. The products were injected onto a chiral GC column. Additionally a sample of

the racemic **24** was spiked with the **(*S,S*)-24** to prove the correlation of peaks between the racemic and enantioenriched samples. The homemade reagent gave an enantioselectivity of the *syn*-isomer in an 88:12 (*S,S*:*R,R*) ratio with 1 % of the *anti*-isomer (Table 3). Commercial **35b** resulted in a selectivity of 92:8 in favor of the *S,S* enantiomer with 0.5 % of the diastereomer. The enantiomer, **(*R,R*)-24** was also made using **35a** which gave a selectivity of 94:6 with <1 % of the diastereomers.

Scheme 13. Crotylation of heptanal for selectivity analysis

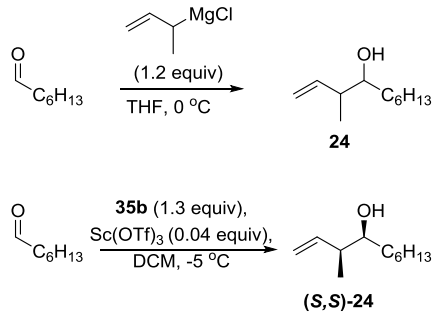


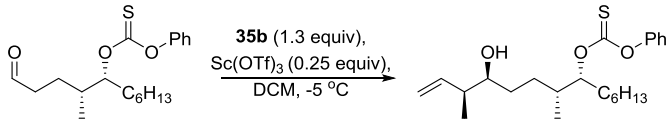
Table 3. Stereoselectivities of **35a** and **35b** in the formation of **24** determined by chiral GC analyses

Crotylation Reagent	(*S,S*)-24	(*R,R*)-24	(*R,S*)-24	(*S,R*)-24
homemade-**35b**	81 %	18 %	1 %	0 %
commercial-**35b**	92 %	7.5 %	0.5 %	0 %
commericla-**35a**	4.3 %	95 %	0.3 %	0.4 %

Leighton's reagents gave excellent diastereoselectivity and a better enantioselectivity (84 % ee) than the Roush reagents (78 % ee). Unlike the Brown reagents, which needs to be synthesized and used immediately, the Leighton reagents can be stored under argon.[12,40,49] However, when Leighton's reagents was used to crotylate an aldehyde containing the thionocarbonate tags (**36**), we observed decomposition of the thionocarbonyl group. The decomposition presumably occurs through a side reaction with the silane byproduct. However, by increasing the catalyst loading from 4 % to 25 % the crotylation reaction finished in 1 h or

less and the thionocarbonate tag survived in product **37** (Scheme 14). The ^{13}C NMR spectrum of **37** contained a minor diastereomer whose peaks integration corresponded to the amount expected of 15 % which demonstrated that as the oligoisoprenoid length increases our selectivity does not diminish. While the Leighton's reagent gave the desired stereocenter in a good selectivity of 92 %, after five iterations the final product would be enriched with only 66 % of the target isomer. This led us to explore another option.

Scheme 14. Crotylsilation of a tagged aldehyde



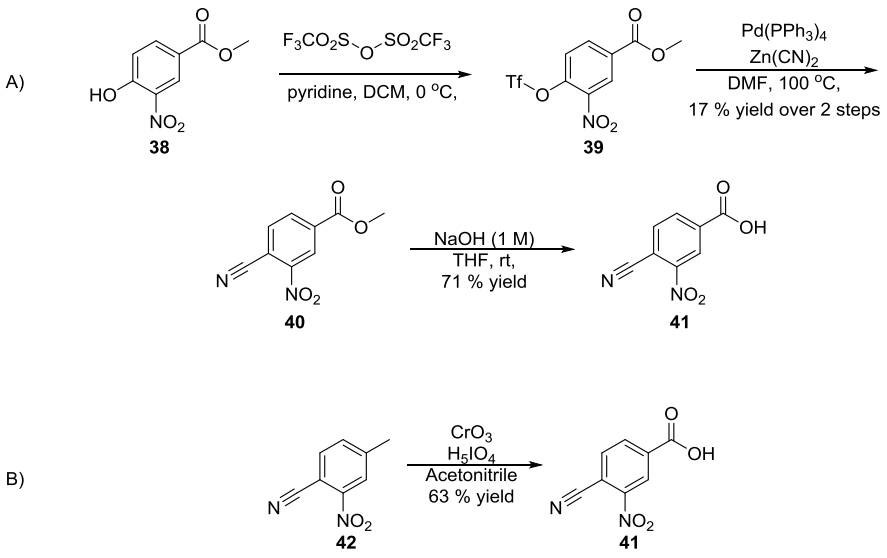
36 **37**

2.2.2 Krishe's Crotylation Catalyst

Chiral crotylboration and crotylsilation reagents require multiple manipulations to be generated and are used in super-stoichiometric amounts in reactions with aldehydes.[35,39] The crotylation product then needs to be purified from an excess amount of reagent-derived byproduct. In an effort to circumvent these issues, Krische utilized metal-catalyzed crotylations with a chiral iridium or ruthenium complex and but-3-en-2-yl acetate or 1,3-butadiene, respectively.[50–53] The iridium complex **43a** provided better enantio- and diastereselectivity. In 2009 Krische demonstrated that the iridium catalyst when used *in situ* with 3-phenylpropanal resulted in (3*R*,4*S*)-4-methyl-1-phenylhex-5-en-3-ol with 98 % ee, but only a de of 83 %, on par with the Leighton reagent.[51] Fortunately in 2011 Krische showed that the iridium catalyst could be formed and isolated through column chromatography; and by using the preformed catalyst the diastereoselectivity increased to >95 % de.[54]

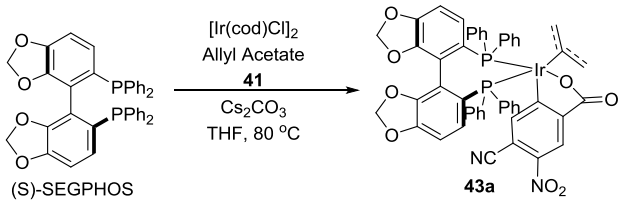
In order to examine the iridium catalyst **43a** for the crotylation of heptanal, we needed to first synthesize the 4-cyano-3-nitro-benzoic acid (**41**). Jung and coworkers had reported several routes towards this benzoic acid.[55] We tried the longer method A first, because we had the materials on hand (Scheme 15). Negishi coupling was used to transform the hydroxy group of **38** into the nitrile **40**, followed by deprotection of the carboxylic acid to result in **41** in an overall yield of 12 %. Due to the low yields of step 2 of method A, we switched to method B. This method involved the oxidation of 4-methyl-2-nitrobenzonitrile (**42**) to the carboxylic acid **41** which resulted in a more convenient workup and purification in addition to a better yield (63 %).

Scheme 15. Synthesis of 4-cyano-3-nitro-benzoic acid



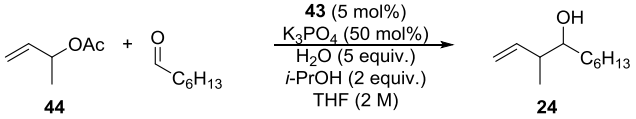
Following the procedure by Krische in Scheme 16, (*S*)-SEGPHOS was combined with $[Ir(cod)Cl]_2$, allyl acetate, **41**, cesium carbonate, and dissolved in THF in a sealed tube and heated to 80 °C.[54] After 2 h, the reaction product was purified by column chromatography. Finally, the (*S*)-iridium catalyst **43a** was recrystallized to result in a yield of 62 %. Using the same procedure, (*R*)-SEGPHOS was used to make the other enantiomer of the iridium catalyst (**43b**) in 67 % yield.

Scheme 16. Formation of the chiral iridium catalyst **43a** using (*S*)-SEGPHOS



To test the efficacy of the catalysts, we used the published reaction conditions for the crotylation of heptanal with but-3-en-2-yl acetate (**44**) to yield **24** (Table 4). After 48 h, catalyst **43a** gave **(*S*,*R*)-24** in 47 % isolated yield with an exceptional degree of selectivity (+99 % ee , 96 % de) determined by GC equipped with a chiral column (Entry 1). In an effort to shorten the 48 h reaction time, the reaction was repeated and temperatures were increased to 70 °C and 85 °C. After 20 h the mixtures were cooled and GC samples prepared. At 70 °C, **(*S*,*R*)-24** was isolated in 37 % yield with only a slight decrease in the diastereoselectivity to result in a 96 % de with +99 % ee (Entry 2). Increasing the temperature of the reaction to 85 °C results in a significant decrease in the selectivity to 88 % de and 98 % ee (Entry 3). By increasing the reaction temperature to 70 °C, we were able to reduce the reaction time by half while the stereoselectivity of the reaction was barely affected. The crotylation using the (*R*)-iridium catalyst **43b** was then conducted at 70 °C to yield **(*R*,*S*)-24** in 64 % with 96 % de and +99 % ee (Entry 4).

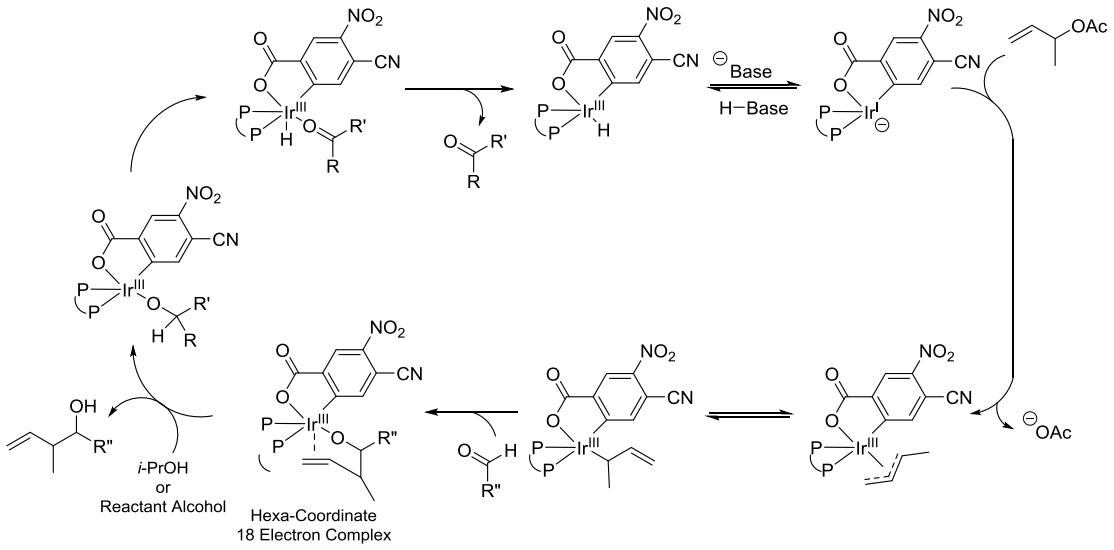
Table 4. Crotylation reaction using Krische's Iridium catalyst



Entry	Catalyst	Product	T (°C)	Time (h)	ee (%)	de (%)
1	43a	(*S*,*R*)-24	60	48	+99	96
2	43a	(*S*,*R*)-24	70	20	+99	96
3	43	(*S*,*R*)-24	85	20	98	88
4	43b	(*R*,*S*)-24	70	20	+99	96

Krische proposes that the iridium catalysts **43a** and **43b** form a new C-C bond through a transfer hydrogenation reaction (Scheme 17).[51] The catalyst coordinates with the aldehyde and forms the hexa-coordinated 18-electron complex which is unable to undergo β-hydride elimination. The homo-allylic alcohol is exchanged for isopropanol resulting in the desired product and upon β-hydride elimination of the 16-electron complex involving isopropanol the catalyst is regenerated.

Scheme 17. Krische's postulated catalytic mechanisms for the iridium-catalyzed hydrogenative coupling[51]



Krische's iridium catalysts **43a** and **43b** provides significantly better stereoselectivity with heptanal compared to the crotylborylation and crotylsilation reagents. The reaction time is longer with the iridium catalysts than the Roush or Leighton reagents, but we were able to reduce reaction duration by half compared to the published procedure without compromising the stereoselectivity. Additionally, catalysts **43a** and **43b** are stable to air, making them more convenient to make and use than the other crotylation reagents.

2.2.3 (4S,8S,12S)-4,8,12,-Trimethylnonadecanol

The goal of this work was to establish the means to eventually synthesize the stereoisomers of MPM (**7**) to discover the exact configuration of the natural product and to obtain high resolution ^{1}H and ^{13}C NMR spectra of oligoisoprenoids to create a data set for the possible combinations of *syn* and *anti*-methyl groups. We decided to first synthesize oligoisoprenoids containing only the (*S*)-methyl stereocenters based on recent publications. Scharf and coworkers cocrystalized synthetic **all-(*S*)-7** with the major histocompatibility complex CD1c.[56,57] While Ly and coworkers measured the activation of T cells by **all-(*S*)-7** and **45-47** (Figure 14).[58] The **all-(*S*)-7** showed the most activation of the T cell, the oligoisoprenoid with one (*S*)-methyl stereocenter (**45**) exhibited some activation of the T cell in higher concentrations, while **46** and **47** showed no activity. These results along with previous analyses provide strong evidence that the **all-(*S*)-7** is the natural product.

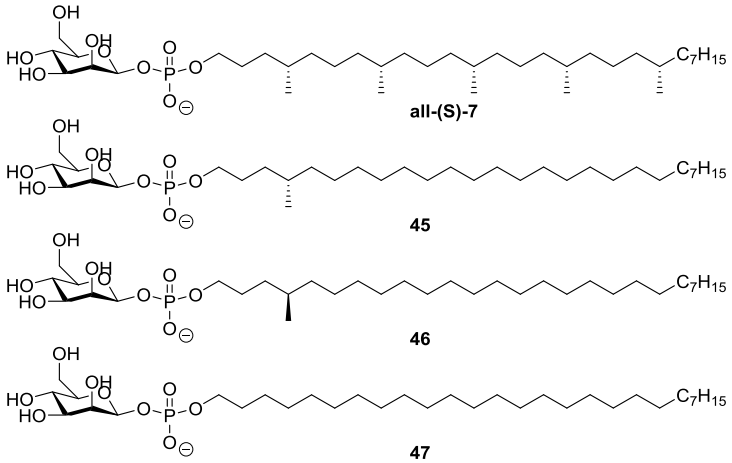


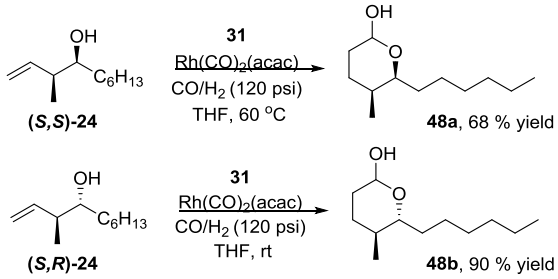
Figure 14. Ly and coworkers molecules used for T cell activation

In 2013 Li and coworkers reported a highly stereocontrolled synthesis of the **all-(*S*)-7** in >96 % stereopurity in 23 steps while the previous report by van Summeren and coworkers had a stereopurity of >89 % but in only 18 steps.[57] Our plan was to synthesize the oligoisoprenoid side

of **all-(*S*)-7** using **43b**. Since this scheme was not a FMS, we decided to try the iterative cycle without protection of the secondary alcohol. Breit and coworkers had shown that the rhodium hydroformylation that we use in our iterative approach can be used with an unprotected alcohol; however, their substrate had a trityl group nearby that sterically prevented cyclization.[48]

The results of hydroformylation of unprotected alcohols **24** are shown in Scheme 18. Alcohol **(*S,S*)-24** was added to a solution of **31** and $Rh(CO)_2(acac)$ in THF, placed into a Parr apparatus, and charged with an atmosphere of CO/H_2. The mixture was heated to 60 °C for 18 h before cooling to rt and purifying through flash chromatography. Upon NMR analysis of the sample we observed the formation of **48a** isolated in 68 % yield. The reaction was repeated with **(*S,R*)-24** without heating the mixture and **48b** was isolated in 90 %. Thus the hydroformylation succeeds, but the product aldehydes prefer to exist as lactols with the neighboring OH group.

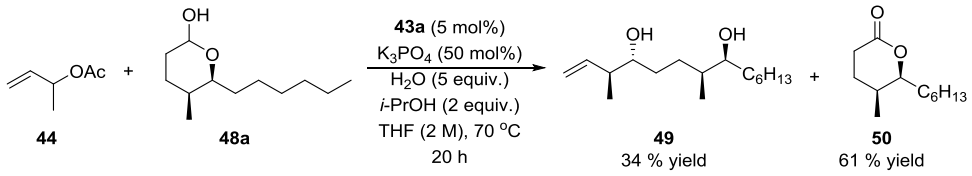
Scheme 18. Linear hydroformylation of terminal alkenes with unprotected secondary alcohols



Lactols are in equilibrium with their aldehyde and transformations such as the Wittig reaction have been used to only react with the aldehyde.[59] Thus we decided to attempt the catalytic crotylation of the first synthesized lactol. Crotylation of lactol **48a** with butenyl acetate and Krische's catalyst **43a** was conducted under the standard conditions for 20 h at 70 °C (Scheme 19). All of **48a** was consumed and two new products were formed. These were separated by flash chromatography. The minor product isolated in 34 % yield was the crotylation product **49** with the new stereocenters formed assumed to be (*S,R*) as expected from using

43a.The major product was the oxidized lactone **50**, isolated in 61 % yield, and characterized by 1D and 2D NMR analyses.

Scheme 19. Crotylation of lactol **48a** using iridium catalyst **43a**

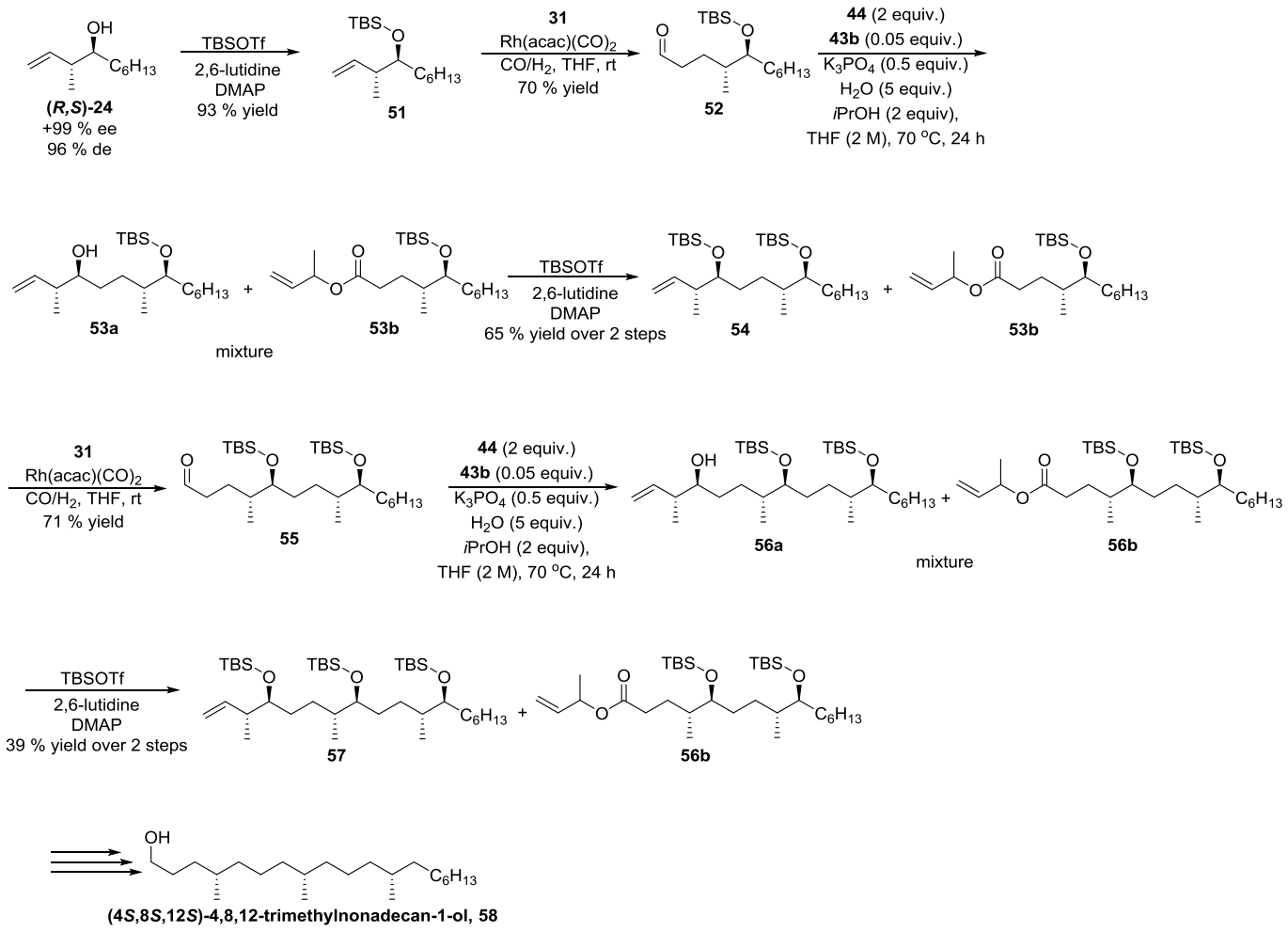


The *syn* relationship of **48a** forces it to have one alkyl group in the axial position with the other being in the more favorable equatorial while **48b** can have both groups in the equatorial position. Thus the equilibrium favors the lactol formation compared to the open aldehyde, which could result in equal or higher amounts of lactone. During the catalytic cycle in Scheme 16, the iridium catalyst is reduced by isopropanol. In Scheme 19, **48a** is being oxidized to the lactone in place of isopropanol to regenerate the iridium catalyst. To prevent the oxidization of the lactol, the equivalents of isopropanol could be increased or switched to a more reactive reducing agent. We decided to continue the synthesis by protecting the secondary alcohol of **(*R*,*S*)-24** with TBSOTf as the next goal.

The synthesis of (4*S*,8*S*,12*S*)-4,8,12,-trimethylnonadecanol began with the crotylation of heptanal using catalyst **43b** to yield **(*R*,*S*)-24** which we had already synthesized in Table 4. Following TBSOTf protection with 2,6-lutidine and DMAP, **51** was selectively hydroformylated to form the linear product using the 6-DPPon ligand (**31**) and (acetylacetaonato)dicarbonylrhodium under a CO/H_2 (120 psi) atmosphere to form **52** in 70 % yield (Scheme 20).[47,48] The second iteration aldehyde (**52**) was crotylated; however, the change in polarity that the TBS ether provided to **53a** compared to the purification of **(*R*,*S*)-24** caused the product to coelute with a byproduct, the but-3-en-2-yl ester **53b**. After TBS protection **54** was easily purified, isolated in 65 % yield over two steps, and the ^{13}C NMR data showed no

diastereomer peak for the carbinol signals. Then **54** was hydroformylated using the same procedure as before to yield **55** in 71 % yield. During the third iteration we observed the ester byproduct (**56b**) from the crotylation reaction again and after TBS protection isolated **57** over two steps in 39 % yield. We concluded the project at **57** with known procedures for reaching **58** in five more steps; and enough material to extend the oligoisoprenoid chain length to 4 and 5 units.

Scheme 20. Synthesis towards (4*S*,8*S*,12*S*)-4,8,12,-trimethylnonadecanol (**57**)



While we pushed the synthesis through to reach **57** we wanted to eventually go back and improve the crotylation reaction to reduce the formation byproducts. Undesired oxidation was

one of the issues observed during crotylation of both the lactols and the TBS protected alcohols. Isopropanol is not the most reactive reducing agent within the reaction mixture. The other complication arose from the hydrolysis of **44** but-3-en-2-ol, which would then react with our aldehydes to eventually form an ester.

2.3 Conclusions

Four new fluorous tags have been developed that achieved good separation from one another while keeping the target molecules relatively low in molecular weight. The addition of the aryl chlorothionocarbonates onto secondary alcohols has been optimized for high yields while minimizing byproduct formation, which can coelute with the desired product. From these experiments we collected data and created a simple new calculation to evaluate a tag's potential to cause separation on a F-HPLC column.

Evaluation of various crotylation reagents demonstrated that Krische's iridium catalyst resulted in the highly enantio- and diastereoselective products at some cost to the overall yield compared to the Brown, Roush, and Leighton reagents. Then, using Krische's catalyst we synthesized late-stage precursor to (4*S*,8*S*,12*S*)-4,8,12,-trimethylnonadecanol and other oligoisoprenoids in high stereopurity.

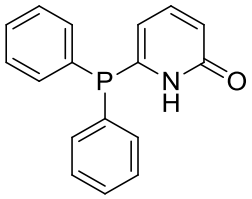
3.0 EXPERIMENTAL

Commercial chemicals and solvents were used as received, except as follows. Dichloromethane, tetrahydrofuran, diethyl ether, and toluene were dried by passing through an activated alumina column. All reactions were carried out under an inert atmosphere of dry argon, unless stated otherwise. (4*S*,5*S*)-Diisopropyl 2-((*E*)-but-2-en-1-yl)-1,3,2-dioxaborolane-4,5-dicarboxylate (**20**) was obtained as a solution (1 M) in toluene from Dr. Yeh.[40] The EZ-CrotylMix contains Leighton's crotylation reagents (**34a** and **34b**) and 4 mol% $Sc(OTf)_3$.

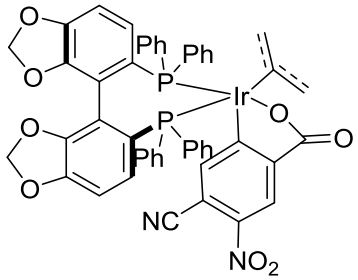
All reactions were followed by TLC or ^1H NMR spectroscopy. TLC analysis was performed by illumination with a UV lamp (254 nm) or by staining with a PMA solution in ethanol and heating. All flash chromatography was performed on a CombiFlash instrument from Teledyne Isco, using pre–packed silica gel cartridges. For reactions involving fluorous mixtures calculations are based on the average molecular weight of the starting materials in the mixture assuming equal parts of each component.

^1H NMR spectra were recorded on a Bruker Avance 300, 400, 500, 600, and 700 MHz instruments using deuterated chloroform as solvent, unless otherwise indicated. ^{13}C NMR spectra were measured on Bruker Avance instruments at 75, 100, 125, 150, and 175 MHz. ^{19}F NMR spectra were measured on Bruker Avance instruments at 376 MHz. The chemical shifts in spectra were measured in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak ($CDCl_3$: ^1H = 7.26 ppm, ^{13}C = 77.00 ppm) or tetramethylsilane (^1H = 0.00 ppm). Unless otherwise noted, NMR spectra were recorded at rt. HPLC analyses and separations were performed on a Waters 600E system with a Waters 2487 dual λabsorption detector using a FluoroFlash™ (PF-C8) column. Infrared (IR) spectra were taken on a Mattson Genesis FT-IR

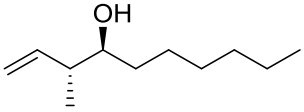
spectrometer as thin film on NaCl plate and the peaks are reported in wave numbers (cm^{-1}). Gas Chromatorgraphy (GC) was ran on an Agilent Technologies 6850 Network System GC fitted with a chiral Varian capillary column (25 M, 0.25 mm, 0.25μm, CP750215).



6-(Diphenylphosphino)pyridine-2(1H)-one (31): The ligand for the Rh catalyzed hydroformylation reaction was synthesized in a 3-step procedure from 2,6-dichloropyridine by Breit and coworkers.[48]

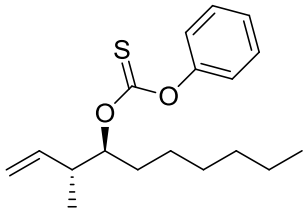


Krische's Iridium Catalyst (43a): The iridium catalyst was synthesized following a one-step procedure using (*S*)-SEGPHOS $[Ir(cod)Cl]_2$, allyl acetate, 4-CN-3-NO_2-BzOH (**42**), and Cs_2CO_3 in THF at 80 °C by Gao and coworkers.[54] The enantiomer **43b** was synthesized following the same procedures using (*R*)-SEGPHOS.



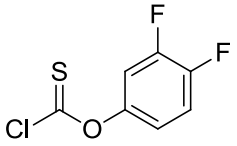
Typical Procedure 1: The Roush Crotylboration of Aldehydes via (3*R*,4*S*)-3-Methyldec-1-en-4-ol ((*R*,*S*)-24): The procedure was followed as used by Yeh[13]: Powdered 4 Å molecular sieves (20 mg/mL) were added to a solution of Roush reagent (**20**, 26.27 mL, 1 M, 3 equiv) in toluene and then the solution was cooled to –78 °C. After 10 min, heptanal (1.0 g, 1.22 mL, 1

equiv) was added neat and the resulting solution was stirred at –78 °C for 3 h. 2 N NaOH (4 mL) was added to quench the reaction over 20 min at 0 °C. The mixture was then filtered through a pad of celite. The aqueous layer was extracted with diethyl ether (10 mL, 3 times). The combined organic layers were dried with K_2CO_3 and concentrated. The crude product was purified by column chromatography (9:1 hexane-diethyl ether) to yield 1.45 g (97 %) of the title compound as a colorless oil. The ^{1}H NMR data matched the values reported by Yeh.[13] ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.75 (ddd, *J* = 8.2, 10.8, 16.6 Hz, 1 H), 5.12 (d, *J* = 10.5 Hz, 1 H), 5.11 (d, *J* = 17.5 Hz, 1 H), 3.39 (s, m, 1 H), 2.21 (ddq, *J* = 6.9, 10.5, 10.5 Hz, 1 H), 1.20—1.60 (m, 11 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 6.5 Hz, 3 H).



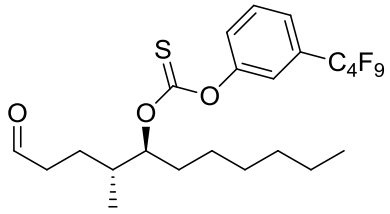
Typical Procedure 2: Thionocarbonate Formation via *O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-phenyl carbonothioate (26a). Anhydrous pyridine (0.19 mL, 8 equiv) was added to (3*R*,4*S*)-3-methyldec-1-en-4-ol (0.05g, 0.2 M) in CH_2Cl_2 rt. *O*-Phenyl chlorothionoformate (45 μL, 1.1 equiv) was added dropwise into the reaction mixture, which was heated to 40 °C (16 h). The reaction was allowed to cool to rt followed by aqueous layer extraction with CH_2Cl_2 (10 mL, 3 times). The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by column chromatography (hexanes-ehtyl acetate gradient). The pure carbonothioate was obtained as a clear oil in 90 % yield (0.215 g). The ^{1}H NMR data matched the values reported by Yeh.[13] ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ =7.41 (t, *J* = 7.8 Hz, 2 H), 7.28 (t, *J* = 8.6 Hz, 1 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 5.78 (ddd, *J* = 7.9, 10.3, 17.1 Hz, 1 H), 5.37 (dt, *J* = 4.4, 8.7 Hz, 1 H), 5.11 (d, *J* = 17.9 Hz, 1 H), 5.10 (d, *J* = 10.2 Hz,1 H) 2.65 (ddq, *J* =

6.4, 6.7, 6.7 Hz, 1 H) 1.55-1.80 (m, 2 H), 1.200-1.500 (m, 8 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.5 Hz, 3 H).



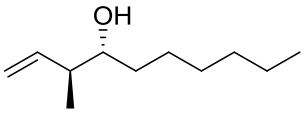
Typical Procedure 3: Synthesis of *O*-3,4-Difluorophenyl Chlorothionoformate (4c).

The procedure was followed as developed by Yeh[13]: A solution of 3,4-difluorophenol (0.27 g, 2.07 mmol, 1.1 equiv) in NaOH aq. (1.6 mL, 1.25 M) was added to thiophosgene (0.14 mL, 1.82 mmol, 1 equiv) in $CHCl_3$ (4 mL). The biphasic mixture was vigorously stirred for 1.5 h at 0 °C. The reaction was quenched using 1 N HCl, the organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.25 (q, *J* = 9.1 Hz, 1 H), 7.04 (ddd, *J* = 2.8, 6.5, 9.6 Hz, 1 H), 6.92 (m, 1 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –132.73 (m, 1 F), –137.82 (m,1 F).

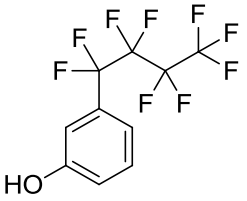


Typical Procedure 4: Rhodium Catalyzed Hydroformylation of *O*-((4*R*,5*S*)-4-Methyl-1-oxoundecan-5-yl) *O*-(3-(perfluorobutyl)phenyl) carbonothioate(34). The pyridine ligand **31** (0.186 g, 35 mol%) and $Rh(CO)_2$acac (0.035 g, 7 mol%) were added to THF (3 mL) under Ar, and the resulting mixture was stirred at room temp. After 10 min, **26h** (0.997 g, 1.90 mmol, 0.1 M) in THF was added to the premixed catalysts in THF. The resulting mixture was transported to the pressure vessel and stirred at 60 °C under 120 psi of CO/H_2 for 20h. After complete consumption of the starting alkene, the solvent was evaporated under reduced pressure and the

crude mixture was purified via column chromatography giving **34** in 82 % yield (0.863 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.81 (t, *J* = 1.4 Hz, 1 H), 7.49-7.60 (m, 2 H), 7.31-7.36 (m, 2 H), 5.30 (dt, *J* = 4.3, 8.7 Hz, 1 H), 2.40-2.65 (m, 2 H), 2.02 (m 1 H), 1.20-1.88 (m, 12 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.96 (tt, *J* = 3.4, 10.2 Hz, 3 F), –111.00 (m, 2 F), –122.71 (m, 2 F), –125.56 (m, 2 F).

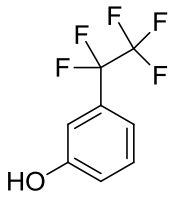


Typical Procedure 5: Krische Crotylation of Aldehydes via (3*S*,4*R*)-3-Methyldec-1-en-4-ol ((*S*,*R*)-24): Isopropanol (134 μL, 2 equiv), K_3PO_4 (0.093 g, 0.5 equiv), H_2O (79 μL, 5 equiv), iridium catalyst **43a** (0.046 g, 0.05 equiv), heptanal (122 μL, 1 equiv), and butenyl acetate **44** (222 μL, 2 equiv) were added to a sealed tube and dissolved in THF (2.0 M). The sealed tube was fitted with a rubber septum, purged with Ar, and septum removed as the screw cap closed the system. The reaction mixture was stirred for 30 min behind a blast shield and then heated to 70 °C for 20 h. The sealed tube was cooled prior to opening, and the crude mixture was purified by flash chromatography (hexane : diethyl ether gradient) to yield **(*S*,*R*)-24** in 37 % with +99 % ee and 96 % de. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.76 (ddd, *J* = 8.2, 10.9, 16.7 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.11 (d, *J* = 17.6 Hz, 1), 3.39 (s, 1 H), 2.21 (m, 1 H), 1.23-1.62 (m, 11 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).



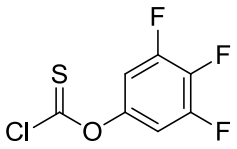
3-(1,1,1,2,2,3,3,4,4-Nonafluorobutyl)phenol (22h). Perfluorobutyl iodide (4.96 g, 2.42 mL, 14.06 mmol) and copper powder (2.418 g, 38.06 mmol) were added to a solution of 3-

iodophenol (2.500 g, 11.25 mmol, 0.5 M) in DMSO. The reaction mixture was stirred and heated for 20 hours at 110 °C. The mixture was poured into water (45 mL); celite (2.4 g) was added to the aqueous solution before filtering through a pad of celite and was washed with diethyl ether. The aqueous layer was extracted with diethyl ether (20 mL, 3 times). The organic layers were combined and dried over anhydrous sodium sulphate. The drying agent was removed and the crude solution was concentrated under reduced pressure. The crude oil was purified via column chromatography (8:2 hexanes-ethyl acetate).The 3-(perfluorobutyl)phenyl was obtained in 63 % yield (4.40 g) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.61 (m, 2H), 7.39 (m, 2H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.95 (t, *J* = 10.2 Hz, 3 F), –111.00 (t, *J* = 13.7 Hz, 2 F), –122.7 (m, 2 F), –125.55 (m, 2 F).

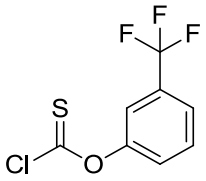


3-(1,1,1,2,2-Pentafluoroethyl)phenol (22g). Copper powder (13.103 g, 206.18 mmol) was added to a DMSO solution of 3-iodophenol (13.543, 60.94 mmol, 0.3 M) in a sealed tube and chilled to 0 °C. Perfluoroethyl iodide (13.9 mL, 115.79 mmol) was condensed at –78 °C and added to the sealed tube. The sealed tube was capped and warmed to rt before heating to 110°C for 48 h. The mixture was poured into water (45 mL); celite (2.4 g) was added to the aqueous solution before filtering through a pad of celite and was washed with diethyl ether. The aqueous layer was extracted with diethyl ether (50 mL, 3 times). The organic layers were combined and dried over anhydrous sodium sulphate. The drying agent was removed and the crude solution was concentrated under reduced pressure. The crude oil was purified via column chromatography (8:2 hexanes-ethyl acetate) to yield 8.21 g (63.5 %) of the 3-

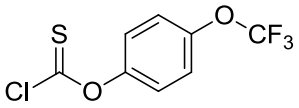
(perfluoroethyl)phenol as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.36 (t, *J* = 7.9 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.05 (m, 2H), 6.03 (s, 1H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –84.77 (3 F), –115.87 (2 F).



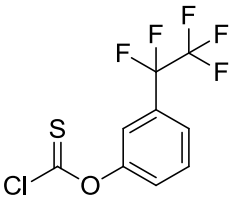
***O*-3,4,5-Trifluorophenol chlorothionoformate (4d).** Typical procedure 3 was followed using 3,4,5-trifluorophenol (0.190 g, 1.283 mmol, 1.1 equiv) and thiophosgene (0.09 mL, 1.174 mmol, 1 equiv). Following extraction and concentration the crude product was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.87 (t, *J* = 6.4 Hz, 2 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –130.78 (m, 2 F), –160.27 (tt, *J* = 6.0, 20.5 Hz, 1 F).



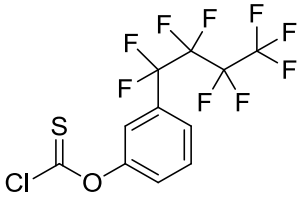
***O*-3-(Trifluoromethyl)phenol chlorothionoformates (4e).** Typical procedure 3 was followed using 3-(trifluoromethyl)phenol (0.037 mL, 0.305 mmol, 1.2 equiv) and thiophosgene (0.019 mL, 0.254 mmol, 1 equiv). Following extraction and concentration the crude product was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.57-7.64 (m, 2 H), 7.43 (s, 1H), 7.36 (m, 1H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.73 (s, 3 F).



***O*-4-(Trifluoromethoxy)phenol chlorothionoformate (4f).** Typical procedure 3 was followed using 4-(trifluoromethoxy)phenol (0.037 mL, 0.278 mmol, 1.2 equiv) and thiophosgene (0.018 mL, 0.232 mmol, 1 equiv). Following extraction and concentration the crude product was was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.31 (d, *J* = 8.8 Hz, 2 H), 7.19 (dt, *J* = 2.7, 10.2 Hz, 2 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –58.08 (s, 3 F).

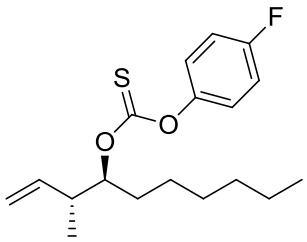


***O*-3-(1,1,1,2,2-Pentafluoroethyl)phenol chlorothionoformate (4g).** Typical procedure 3 was followed using 3-(pentafluoroethyl)phenol (0.200, 0.942 mmol, 1 equiv) and thiophosgene (0.089 mL, 1.131 mmol, 1.2 equiv). Following extraction and concentration the crude product was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.56-7.64 (m, 2H), 7.42 (s, 1 H), 7.38 (dt, *J* = 1.9, 7.2 Hz, 1 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –84.82 (s, 3 F), –115.03 (s, 2 F).

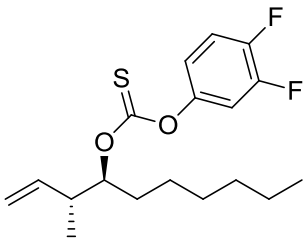


***O*-3-(1,1,1,2,2,3,3,4,4-Nonafluorobutyl)phenol chlorothionoformate (4h).** Typical procedure 3 was followed using 3-(nonafluorobutyl)phenol (0.062 g, 0.380 mmol, 1 equiv) and thiophosgene (0.035 mL, 0.456 mmol, 1.2 equiv). Following extraction and concentration the crude product

was purified by column chromatography (hexanes : ethyl acetate gradient). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.56-7.66 (m, 2 H), 7.40 (s, 1H), 7.38 (m, 1H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.96 (tt, *J* = 3.4, 10.2 Hz, 3 F), –111.00 (m, 2 F), –122.71 (m, 2 F), –125.55 (m, 2 F).

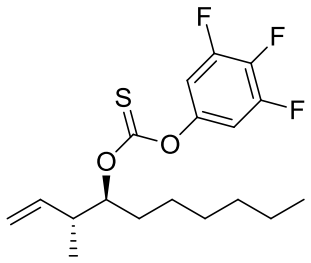


***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-4-fluorophenyl carbonothioate (26b).** Typical procedure 2 was followed using *O*-4-fluorophenol chlorothionoformate (45 μL, 0.323 mmol, 1.1 equiv), (3*R*,4*S*)-3-methyldec-1-en-4-ol (0.050 g, 0.294 mmol, 1 equiv) and anhydrous pyridine (190 μL, 2.35mmol, 8 equiv) in DCM (0.2 M)to yield the title compound in 79 % yield (0.232 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.02-7.12 (m, 4 H), 5.78 (ddd, *J* = 7.9, 10.5, 16.9 Hz, 1 H), 5.35 (dt, *J* = 4.7, 8.2 Hz, 1 H), 5.11 (d, *J* = 17.0 Hz, 1 H), 5.10 (d, *J* = 10.6 Hz, 1 H);^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –115.92 (m, 1 F).

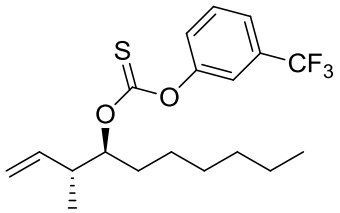


***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-3,4-difluorophenyl carbonothioate (26c).** Typical procedure 2 was followed using *O*-3,4-difluorophenol chlorothionoformate (0.065 g, 0.312 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.050 g, 0.294mmol, 1 equiv), and anhydrous pyridine (190 μL, 2.35mmol, 8 equiv) in DCM (0.2 M) to yield the title compound in 50 % yield (0.050 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.19 (q, *J* = 9.2 Hz, 1 H), 6.97 (ddd, *J* = 2.9, 6.7, 10.3 Hz, 1H), 6.84 (m, 1 H), 5.77 (m, 1 H), 5.34 (dt, *J* = 4.1, 9.3 Hz, 1H), 5.12 (d, *J* = 17.0

Hz, 1 H), 5.11 (d, 11.1 Hz, 1 H), 2.64 (m, 1 H), 1.59-1.78 (m, 2 H), 1.21-1.42 (m, 8 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –134.22 (m, 1 F), –139.81 (m, 1 F).

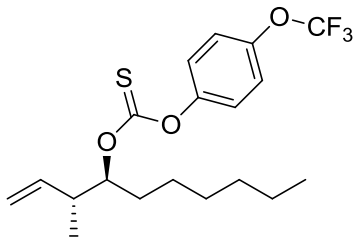


***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-3,4,5-trifluorophenyl carbonothioate (26d).** Typical procedure 2 was followed using *O*-3,4,5-trifluorophenol chlorothionoformate (0.072 g, 0.318 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.049g, 0.290 mmol, 1 equiv), and anhydrous pyridine (187 μL, 2.32 mmol, 8 equiv) to yield the title compound in 79 % yield (0.083 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.79 (m, 2 H), 5.77 (ddd, *J* = 7.9, 9.7, 17.6 Hz, 1 H) 5.32 (dt, *J* = 4.7, 8.2 Hz, 1H), 5.12 (d, *J* = 16.1 Hz, 1 H), 5.11 (d, 11.6 Hz, 1 H), 2.63 (m, 1 H), 1.59-1.78 (m, 2 H), 1.21-1.42 (m, 8 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –132.50 (m, 2 F), –139.81 (t, *J* = 5.9, 20.6 Hz, 1 F).

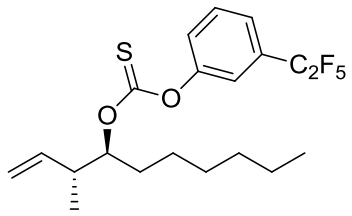


***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-3-(trifluoromethyl)phenyl carbonothioate (26e).** Typical procedure 2 was followed using *O*-3-(trifluoromethyl)phenol chlorothionoformate (0.078 g, 0.326 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.050g, 0.293mmol, 1 equiv), and anhydrous pyridine (190 μL, 2.35 mmol, 8 equiv) to yield the title compound in 81 % yield (0.089 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.50-7.58 (m, 2 H), 7.37 (s, 1H), 7.29 (m, 1H),

5.77 (ddd, *J* = 7.9, 9.8, 17.7 Hz, 1 H) 5.35 (dt, *J* = 4.7, 8.3 Hz, 1H), 5.12 (d, *J* = 16.9 Hz, 1 H), 5.11 (d, 10.8 Hz, 1 H), 2.65 (m, 1 H), 1.60-1.80 (m, 2 H), 1.22-1.43 (m, 8 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.64 (s, 3 F).

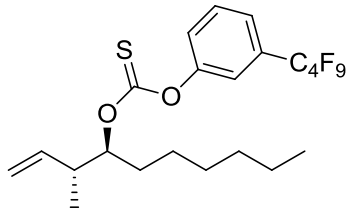


***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-4-(trifluoromethoxy)phenyl carbonothioate (26f).** Typical procedure 2 was followed using *O*-4-(trifluoromethoxy)phenol chlorothionoformate (0.091 g, 0.355 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.055g, 0.323mmol, 1 equiv), and anhydrous pyridine (209 μL, 2.58 mmol, 8 equiv) to yield the title compound in 77 % yield (0.126 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.25 (d, *J* = 8.4 Hz, 2 H), 7.12 (dt, *J* = 2.9, 10.2, 2 H), 5.77 (ddd, *J* = 7.9, 10.6, 16.9 Hz, 1 H) 5.35 (dt, *J* = 4.7, 8.3 Hz, 1H), 5.11 (d, *J* = 17.6 Hz, 1 H), 5.10 (d, 10.6 Hz, 1 H), 2.64 (m, 1 H), 1.59-1. 80 (m, 2 H), 1.21-1.44 (m, 8 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –58.06 (m, 1 F).



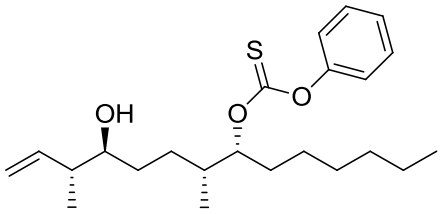
***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-3-(pentafluoroethyl)phenyl carbonothioate (26g).** Typical procedure 2 was followed using *O*-3-(pentafluoroethyl)phenol chlorothionoformate (0.094 g, 0.323 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.050g, 0.294mmol, 1 equiv), and anhydrous pyridine (190 μL, 2.35 mmol, 8 equiv) to yield the title compound in 70 % yield (0.126 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.49-7.56 (m, 2 H), 7.29-7.37 (m, 2 H), 5.76

(ddd, *J* = 8.0, 9.7, 17.8 Hz, 1 H) 5.35 (dt, *J* = 4.7, 8.1 Hz, 1H), 5.11 (d, *J* = 17.3 Hz, 1 H), 5.10 (d, 10.3 Hz, 1 H), 2.65 (m, 1 H), 1.59-1. 80 (m, 2 H), 1.21-1.44 (m, 8 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –84.66 (s, 3 F), –114.83 (s, 2 F).



***O*-((3*R*, 4*S*)-3-Methyldec-1-en-4-yl) *O*-3-(pentafluoroethyl)phenyl carbonothioate (26h).**

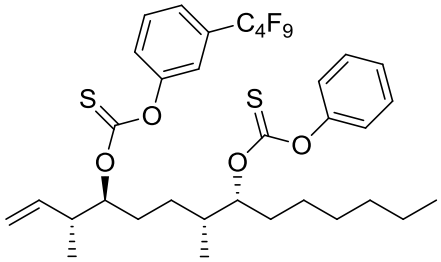
Typical procedure 2 was followed using *O*-3-(nonafluorobutyl)phenol chlorothionoformate (0.126 g, 0.323 mmol, 1.1 equiv), (3*R*,4*S*)-3-Methyldec-1-en-4-ol (0.050 g, 0.294 mmol, 1 equiv), and anhydrous pyridine (190 μL, 2.35 mmol, 8 equiv) to yield the title compound in 84 % yield (0.130 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.43-7.56 (m, 2 H), 7.29-7.36 (m, 2 H), 5.77 (ddd, *J* = 7.8, 10.8, 16.7 Hz, 1 H) 5.35 (dt, *J* = 4.7, 8.2 Hz, 1H), 5.11 (d, *J* = 17.5 Hz, 1 H), 5.11 (d, 10.2 Hz, 1 H), 2.65 (m, 1 H), 1.59-1. 80 (m, 2 H), 1.21-1.44 (m, 8 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.96 (tt, *J* = 3.4, 10.2 Hz, 3 F), –111.00 (m, 2 F), –122.71 (m, 2 F), –125.56 (m, 2 F).



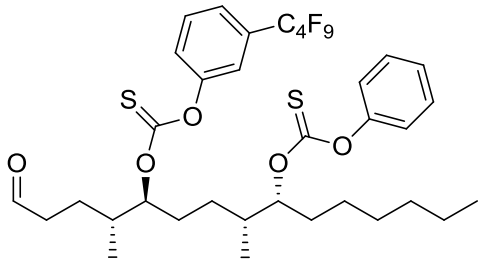
***O*-((11*S*,12*R*)-11-Hydroxy-8,12-dimethyltetradec-13-en-7-yl) *O*-phenyl carbonothioate (29).**

Typical procedure 1 was followed using aldehyde **26h** (0.995 g, 3.10 mmol, 1 equiv) and the Roush reagent **20** (9.31 mL, 9.31 mmol, 1 M) in toluene to obtained the title compound in nearly quantitative yield (1.160 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.41 (t, *J* = 7.8 Hz, 2 H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2 H), 5.76 (ddd, *J* = 8.3, 10.6, 16.7 Hz, 1 H), 5.38 (dt, *J*

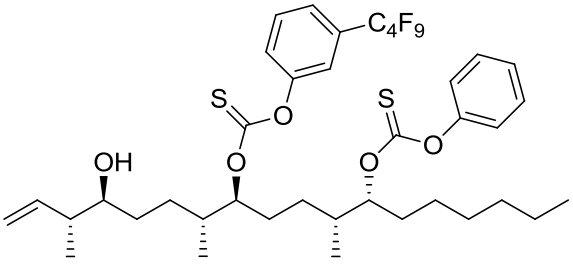
= 4.2, 8.4 Hz, 1 H), 5.09-5.22 (m, 2 H), 3.39 (m, 1 H), 2.23 (m, 1 H), 1.58-1.94 (m, 4 H), 1.20-1.40 (m, 10 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.5 Hz, 3 H).



***O*,*O*'-((3*R*,4*S*)-3,7-Dimethyltetradec-1-ene-4,8-diyl) *O*'-(3-(perfluorobutyl)phenyl) *O*-phenyl dicarbonothioate (30). 29** *O*-3-(nonafluorobutyl)phenol chlorothionoformate (8.36 g, 21.4 mmol, 4 equiv) was added dropwise to (2.10 g, 5.35 mmol, 1 equiv) and anhydrous pyridine (3.46 mL, 42.8 mmol, 8 equiv) in DCM (1.0 M). The reaction mixture refluxed (40 °C) for 2h. The crude mixture was concentrated and purified via column chromatography (hexanes : diethyl ether gradient) without aqueous workup. The product was further purified by precipitation of the diaryl thionocarbonate byproduct in concentrated hexane solution to yield the title compound in 70 % yield (2.78 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.26-7.59 (m, 7 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 5.71-5.88 (m, 1 H), 5.37 (m, 2 H), 5.14 (d, *J* = 17.3 Hz, 1 H), 5.14 (d, *J* = 10.8 Hz, 1 H), 2.66 (m, 1 H), 1.90 (m, 1 H), 1.79 (m, 2 H), 1.54-1.68 (m, 2 H), 1.18-1.43 (m, 10 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.1 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.97 (t, *J* = 9.5 Hz, 3 F), –110.94 (t, *J* = 12.9 Hz, 2 F), –122.68 (m, 2 F), –125.56 (m, 2 F).

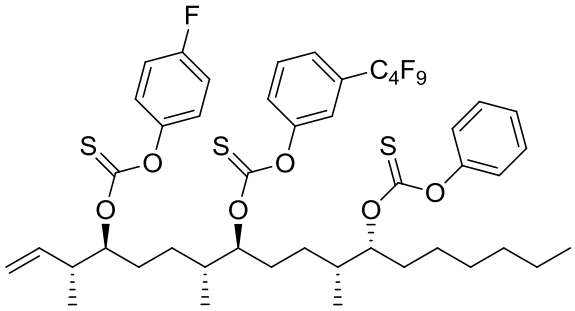


***O*,*O*'-((4*R*,5*S*)-4,8-Dimethyl-1-oxopentadecane-5,9-diyl) *O*'-(3-(perfluorobutyl)phenyl) *O*-phenyl dicarbonothioate (32).** Typical procedure 4 was followed using alkene **30**(2.78 g, 3.72 mmol, 1 equiv), 6-DPPon (0.365 g, 1.302 mmol, 0.35 equiv), and (acetylacentato)dicarbonyl rhodium (0.069 g, 0.260 mmol, 0.07 equiv). After 18 h, TLC showed that significant amount of **30** was unreacted and the reaction mixture was placed back under a pressurized atmosphere of CO/H_2 (150 psi) for 3 days. TLC still showed that a significant amount of alkene remained. The crude mixture was purified following typical procedure 4 to yield the title compound in 45 % yield (0.038g) with 1.154 g of the alkene **30** recovered. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.81 (s, 1 H), 7.26-7.59 (m, 7 H), 7.09 (d, *J* = 7.7 Hz, 2 H), 5.25-5.46 (m, 2 H), 2.56 (m, 2 H), 1.22-2.06 (m, 18 H), 1.01 (m, 6 H), 0.89 (t, *J* = 6.4 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.97 (t, *J* = 9.6 Hz, 3 F), –110.91 (t, *J* = 12.1 Hz, 2 F), –122.68 (m, 2 F), –125.57 (m, 2 F).

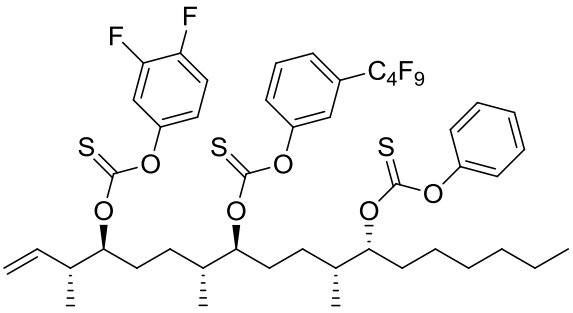


***O*,*O*'-((11*S*,12*R*,15*S*,16*R*)-15-Hydroxy-8,12,16-trimethyloctadec-17-ene-7,11-diyl) *O*'-(3-(perfluorobutyl)phenyl) *O*-phenyl dicarbonothioate (32.2).** Typical procedure 1 was followed using **32** (1.868 g, 2.404 mmol, 1 equiv) and the Roush reagent **20** (7.21 mL, 7.21 mmol, 1 M) in toluene to obtained the title compound in 65 % yield (1.303 g). ^{1}H NMR ($CDCl_3$, 400 MHz,

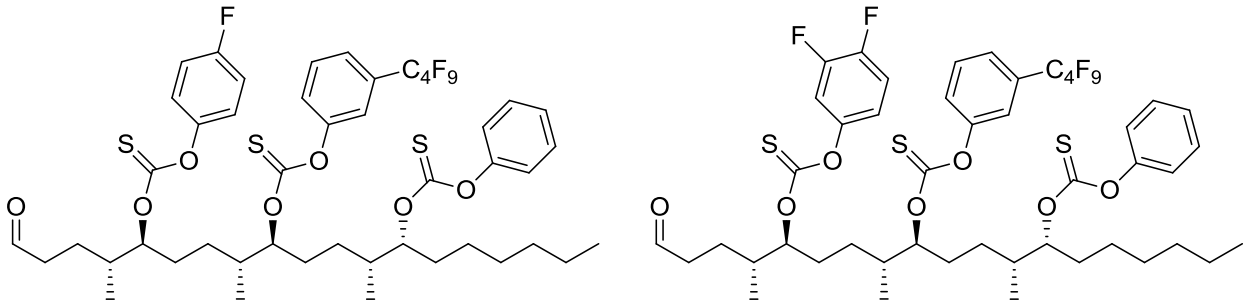
ppm) δ = 7.47-7.54 (m, 2 H), 7.27-7.42 (m, 5 H), 7.06-7.12 (m, 2 H), 5.66-5.81 (m, 1 H), 5.25-5.45 (m, 2 H), 5.06-5.16 (m, 2 H), 3.39 (m, 1 H), 2.21 (m, 1 H), 2.03 (m, 1 H), 1.91 (m, 1 H), 1.79 (m, 2 H), 1.47-1.74 (m, 4 H), 1.21-1.43 (m, 12 H), 0.97-1.06 (m, 9 H), 0.89 (t, *J* = 6.0 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.97 (t, *J* = 9.6 Hz, 3 F), –110.91 (t, *J* = 12.1 Hz, 2 F), –122.68 (m, 2 F), –125.57 (m, 2 F).



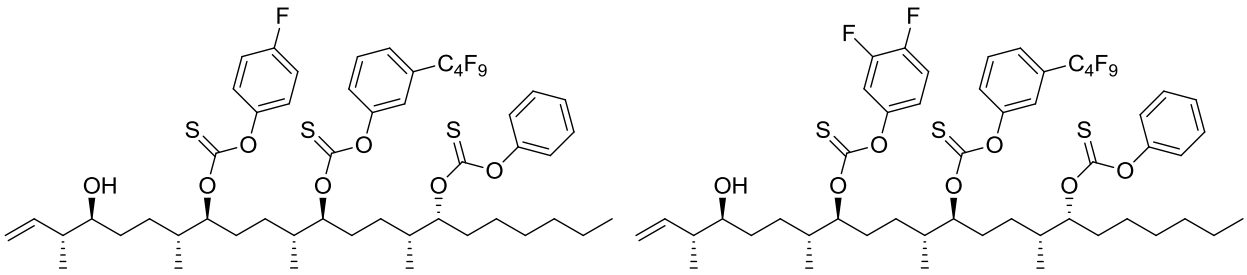
***O*''-(4-Fluorophenyl) *O*'-(3-(perfluorobutyl)phenyl) *O*-phenyl *O*,*O*',*O*''-((3*R*,4*S*,7*R*,8*S*)-3,7,11-trimethyloctadec-1-ene-4,8,12-triyl) tricarbonothioate (32.3).** *O*-4-fluorophenol chlorothionoformate (0.63 mL, 4.51 mmol, 4 equiv) was added dropwise to **32.2** (0.940 g, 1.129 mmol, 1 equiv) and anhydrous pyridine (0.73 mL, 9.03 mmol, 8 equiv)in DCM (1.0 M). The reaction mixture refluxed (40 °C) for 2h. The crude mixture was concentrated and purified via column chromatography (hexanes : diethyl ether gradient) without aqueous workup. The product was further purified by precipitation of the diaryl thionocarbonate byproduct in concentrated hexane solution to yield the title compound quantitatively (1.112 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 7.00-7.65 (m, 13 H), 5.78 (m, 1 H), 5.37 (m, 3 H), 5.08-5.18 (m, 2 H), 2.65 (m, 1 H), 2.02 (m, 1 H), 1.50-1.97 (m, 10 H), 1.22-1.45 (m, 10 H), 1.11 (m, 3 H), 1.00 (m, 6 H), 0.88 (t, *J* = 6.7 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.98 (t, *J* = 9.5 Hz, 3 F), –110.89 (t, *J* = 13.2 Hz, 2 F), –115.91 (m, 1 F), –122.66 (m, 2 F), –125.57 (m, 2 F).



***O*''-(3,4-Difluorophenyl) *O*'-(3-(perfluorobutyl)phenyl) *O*-phenyl *O*,*O*',*O*''-((3*R*,4*S*,7R,8*S*)-3,7,11-trimethyloctadec-1-ene-4,8,12-triyl) tricarbonothioate 32.4.** *O*-3,4-difluorophenol chlorothionoformate (0.64 mL, 4.51 mmol, 4 equiv) was added dropwise to **32.2** (0.940 g, 1.129 mmol, 1 equiv) and anhydrous pyridine (0.73 mL, 9.03 mmol, 8 equiv) in DCM (1.0 M). The reaction mixture refluxed (40 °C) for 2h. The crude mixture was concentrated and purified via column chromatography (hexanes : diethyl ether gradient) without aqueous workup. The product was further purified by precipitation of the diaryl thionocarbonate byproduct in concentrated hexane solution to yield the title compound in 98 % yield (1.113 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.78-7.64 (m, 12 H), 5.78 (m, 1 H), 5.26-5.47 (m, 3 H), 5.07-5.18 (m, 2 H), 2.65 (m, 1 H), 2.02 (m, 1 H), 1.50-1.97 (m, 10 H), 1.23-1.40 (m, 10 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 0.95-1.03 (m, 6 H), 0.88 (t, *J* = 6.7 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.99 (t, *J* = 8.6 Hz, 3 F), –110.90 (t, *J* = 13.6 Hz, 2 F), –122.68 (m, 2 F), –125.57 (m, 2 F), –134.22 (m, 1 F), 139.78 (m, 1 F).

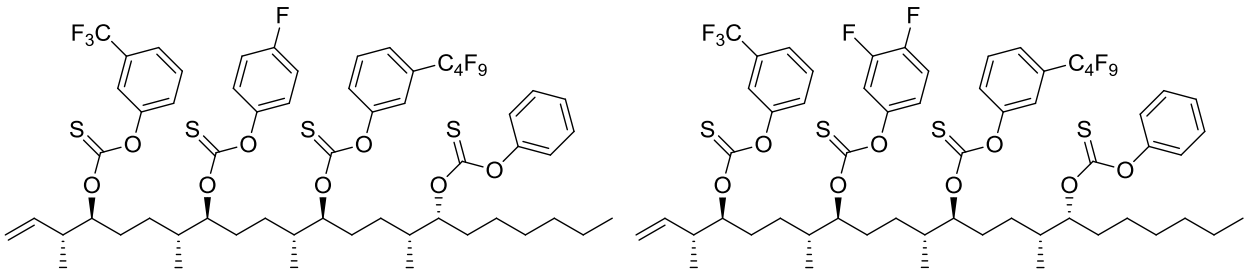


Fluorous Mixture M8. Typical procedure 4 was followed using alkenes **32.3** (1.112 g, 1.126 mmol, 1 equiv) and **32.4** (1.113 g, 1.108 mmol, 0.94 equiv), 6-DPPon (0.230 g, 0.823 mmol, 0.7 equiv), and (acetylacentato)dicarbonyl rhodium (0.043 g, 0.165 mmol, 0.14 equiv) to yield the fluorous mixture in 44 % yield (1.060) with starting material recovered. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.79 (m, 1H), 6.78-7.53 (m, 12.5 H), 5.26-5.47 (m, 3 H), 2.42-2.65 (m, 2 H), 2.01 (m, 1H), 1.50-1.97 (m, 11 H), 1.23-1.40 (m, 10 H), 0.95-1.06 (m, 9 H), 0.88 (t, *J* = 6.5 Hz, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.97 (m, 3 F), –110.89 (t, *J* = 12.9 Hz, 2 F), –115.80 (m, 0.5 F), –122.67 (m, 2 F), –125.57 (m, 2 F), –134.11 (m, 0.5 F), 139.65 (m, 0.5 F).

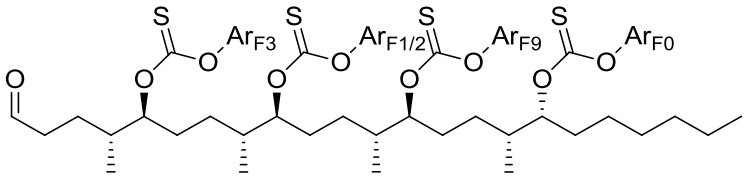


Fluourous Mixture M8.2. Equivalents based on lowest MW alkene in the fluorous mixture. Typical procedure 1 was followed using **M8** (1.060 g, 1.042 mmol, 1 equiv) and the Roush reagent **22** (7.21 mL, 7.21 mmol, 1 M) in toluene to obtained the title compound in 90 % yield (1.006 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.78-7.53 (m, 12.5 H), 5.73 (m, 1 H), 5.26-5.47 (m, 3 H), 5.06-5.17 (m, 2 H), 3.38 (m, 1 H), 2.20 (m, 1 H), 1.46-2.10 (m, 12 H), 1.22-1.44 (m, 12 H), 0.94-1.07 (m, 12 H), 0.89 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –80.98 (t, *J* = 9.0 Hz, 3

F), –110.86 (t, *J* = 12.9 Hz, 2 F), –115.96 (m, 0.5 F), –122.65 (m, 2 F), –125.54 (m, 2 F), –134.25 (m, 0.5 F), 139.84 (m, 0.5 F).

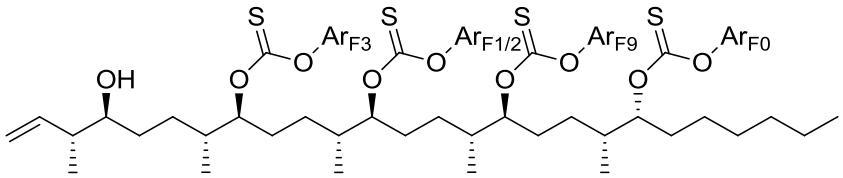


Fluorous Mixture M8.3. Equivalents based on lowest MW alkene in the fluorous mixture. *O*-3-(trifluoromethyl)phenol chlorothionoformate (0.67 mL, 3.82 mmol, 4 equiv) was added dropwise to **M8.2** (1.024 g, 0.955 mmol, 1 equiv) and anhydrous pyridine (0.62 mL, 7.64 mmol, 8 equiv) in DCM (1.0 M). The reaction mixture refluxed (40 °C) for 2h. The crude mixture was concentrated and purified via column chromatography (hexanes : diethyl ether gradient) without aqueous workup. The product was further purified by precipitation of the diaryl thionocarbonate byproduct in concentrated hexane solution to yield the title compound in 90 % yield (1.113 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.78-7.63 (m, 16.5 H), 5.78 (m, 1 H), 5.27-5.46 (m, 4 H), 5.08-5.17 (m, 2 H), 2.66 (m, 1 H), 2.02 (m, 2 H), 1.52-1.96 (m, 12 H), 1.22-1.44 (m, 12 H), 1.11 (m, 3 H), 1.01 (m, 9 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.66 (t, *J* =6.1 Hz, 3 F), –80.98 (t, *J* = 8.2 Hz, 3 F), –110.87 (t, *J* = 12.8 Hz, 2 F), –115.89 (m, 0.5 F), –122.66 (m, 2 F), –125.55 (m, 2 F), –134.22 (m, 0.5 F), 139.79 (m, 0.5 F).

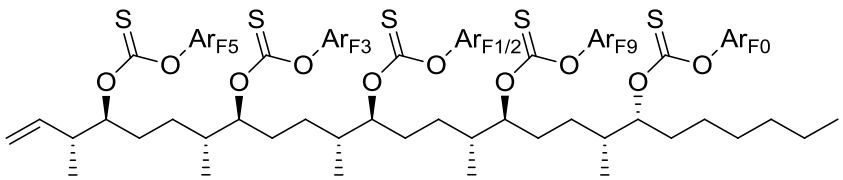


Fluorous Mixture M9. Equivalents based on lowest MW alkene in the fluorous mixture. Typical procedure 4 was followed using fluorous mixture **M8.3** (0.759 g, 0.594 mmol, 1 equiv),

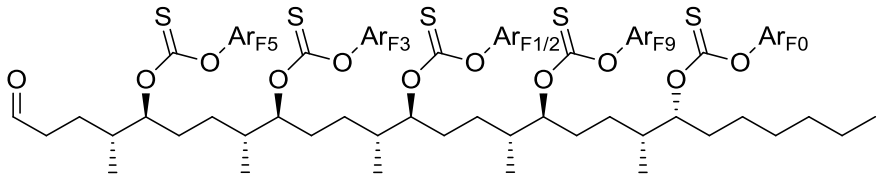
6-DPPon (0.133 g, 0.475 mmol, 0.8 equiv), and (acetylacentato)dicarbonyl rhodium (0.031 g, 0.119 mmol, 0.2 equiv) to yield the fluorous mixture in 57 % yield (0.449) with starting material recovered. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.79 (s, 1 H), 6.79-7.57 (m, 16.5 H), 5.26-5.46 (m, 4 H), 2.43-2.65 (m , 2 H), 2.02 (m, 2 H), 1.48-1.96 (m, 14 H), 1.23-1.44 (m, 12 H), 0.95-1.06 (m, 12 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.63 (t, *J* =6.9 Hz, 3 F), –80.97 (t, *J* = 8.9 Hz, 3 F), –110.90 (t, *J* = 12.2 Hz, 2 F), –115.85 (m, 0.5 F), –122.69 (m, 2 F), –125.58 (m, 2 F), –134.17 (m, 0.5 F), 139.71 (m, 0.5 F).



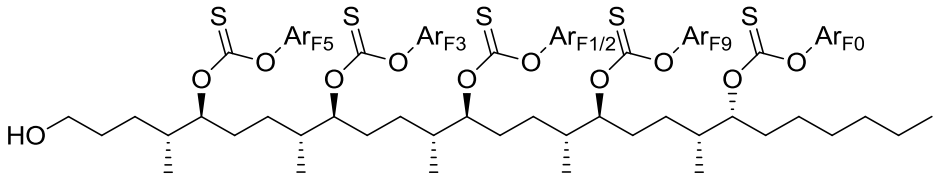
Fluorous Mixture M9.2. Equivalents based on lowest MW alkene in the fluorous mixture. Typical procedure 1 was followed using **M9** (0.375 g, 0.287 mmol, 1 equiv) and the Roush reagent **22** (0.86 mL, 0.86 mmol, 1 M) in toluene to obtained the title compound with ~1 equiv ethyl acetate by ^{1}H NMR (0.458 g).The viscous oil had been under vacuum for over 24 h, and the small amount of ethyl acetate was expected to have no effect on the subsequent reaction. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.79-7.57 (m, 16.5 H), 5.73 (ddd, *J* = 8.3, 10.4, 17.1 Hz, 1 H), 5.26-5.45 (m, 4 H), 5.13 (d, *J* = 9.8 Hz, 1 H), 5.12 (d, *J* = 19.2 Hz, 1 H), 3.33 (m, 1 H), 2.20 (m, 1 H), 2.02 (m, 2 H), 1.48-1.96 (m, 14 H), 1.23-1.44 (m, 14 H), 0.95-1.06 (m, 15 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.61 (t, *J* =6.1 Hz, 3 F), –80.97 (t, *J* = 8.8 Hz, 3 F), –110.90 (m, 2 F), –115.87 (m, 0.5 F), –122.69 (m, 2 F), –125.59 (m, 2 F), –134.19 (m, 0.5 F), 139.77 (m, 0.5 F).



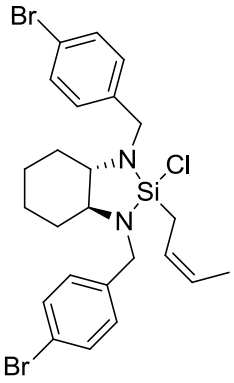
Fluorous Mixture M9.3. Equivalents based on lowest MW alkene in the fluorous mixture. *O*-3-(pentafluoroethyl)phenol chlorothionoformate (0.376 g, 1.30 mmol, 4 equiv) was added dropwise to **M9.2** (0.442 g, 0.324 mmol, 1 equiv) and anhydrous pyridine (0.21 mL, 2.60 mmol, 8 equiv) in DCM (1.0 M). The reaction mixture refluxed (40 °C) for 2h. The crude mixture was concentrated and purified via column chromatography (hexanes : diethyl ether gradient) without aqueous workup. The product was further purified by precipitation of the diaryl thionocarbonate byproduct in concentrated hexane solution to yield the title compound in 88 % yield (0.462 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.78-7.65 (m, 20.5), 5.74 (m, 1 H), 5.24-5.45 (m, 5 H), 5.08-5.16 (m, 2 H), 2.02 (m, 2 H), 1.48-1.96 (m, 15 H), 1.23-1.44 (m, 14 H), 0.95-1.06 (m, 15 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.65 (m, 3 F), –80.98 (m, 3 F), –84.63 (m, 3 F), –110.92 (m, 2 F), –114.85 (m, 2 F), –115.89 (m, 0.5 F), –122.69 (m, 2 F), –125.59 (m, 2 F), –134.18 (m, 0.5 F), 139.73 (m, 0.5 F).



Fluorous Mixture M9.4. Equivalents based on lowest MW alkene in the fluorous mixture. Typical procedure 4 was followed using fluorous mixture **M9.3** (0.175 g, 0.108 mmol, 1 equiv), 6-DPPon (0.024 g, 0.086 mmol, 0.8 equiv), and (acetylacentato)dicarbonyl rhodium (0.006 g, 0.216 mmol, 0.2 equiv) to yield the fluorous mixture in 71 % yield (0.1261) with starting material recovered. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.79 (s, 1 H), 6.78-7.65 (m, 20.5), 5.24-5.45 (m, 5 H), 2.54 (m, 2 H), 2.02 (m, 2 H), 1.48-1.96 (m, 15 H), 1.23-1.44 (m, 16 H), 0.95-1.06 (m, 15 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.65 (m, 3 F), –80.98 (m, 3 F), –84.66 (m, 3 F), –110.93 (m, 2 F), –114.78 (m, 2 F), –115.86 (m, 0.5 F), –122.70 (m, 2 F), –125.60 (m, 2 F), –134.16 (m, 0.5 F), 139.75 (m, 0.5 F).

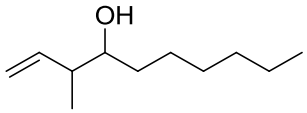


Fluorous Mixture M10. Equivalents based on lowest MW alkene in the fluorous mixture. DIBAL-H (0.010 g, 0.076 mmol, 1 equiv) was added to the fluorous mixture **M9.4** (0.126 g, 0.076 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred and allowed to reach rt over an hour. Saturated Rochelle's salt (1 mL) was added to quench the reaction and the aqueous layer was extracted using diethyl ether (10 mL, 3 times). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified via column chromatography (hexane-ether gradient) to yield 0.055 g (43 %) of **M11**. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 6.78-7.65 (m, 20.5), 5.24-5.45 (m, 5 H), 3.42 (m, 2 H), 2.02 (m, 2 H), 1.48-1.96 (m, 17 H), 1.23-1.44 (m, 16 H), 0.95-1.06 (m, 15 H), 0.88 (m, 3 H); ^{19}F ($CDCl_3$, 376 MHz, ppm) δ = –62.60 (m, 3 F), –80.97 (m, 3 F), –84.66 (m, 3 F), –110.92 (m, 2 F), –114.82 (m, 2 F), –115.88 (m, 0.5 F), –122.69 (m, 2 F), –125.59 (m, 2 F), –134.19 (m, 0.5 F), 139.77 (m, 0.5 F).



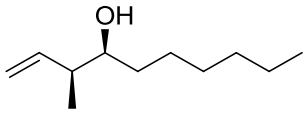
Leighton's (*S*,*S*)-*cis*-crotylation reagent 35b. All liquids were purged with argon prior to use. Based on the procedure reported by Leighton and coworkers,[54] (*S*,*S*)-N,N'-bis(4-bromobenzyl)-1,2-diaminocyclohexane (10.00 g, 21.44 mmol, 1 equiv) and CH_2Cl_2 (75 mL) was placed in a round bottom flask equipped with a drain at the bottom and cooled to 0 °C. DBU (6.54 mL,

43.75 mmol, 2 equiv) was slowly added to the reaction pot, followed by dropwise addition of *cis*-crotyltrichlorosilane (3.31 mL, 21.88 mmol, 1 equiv). The reaction mixture was removed from the ice bath and stirred overnight (16 h). The mixture was concentrated under reduced pressure and the residue was dissolved in freshly distilled pentane (75 mL). The drain of the flask was connected to a fine glass frit that drained into a 3 neck round bottom flask. A simple distillation system with a receiving flask chilled to –78 °C was attached to one of the necks on the round bottom and the system was placed under vacuum and purged with argon. The pentane solution was filtered through the fine glass frit and the pentane was evaporated from the filtrate via distillation under reduced pressure at rt. The oil was dissolved in a minimal amount of pentane (4 mL) and crystals had formed when chilled to –78 °C. The pentane was removed by evaporation via reduced pressure at –60 °C overnight (16 hrs); however the product was in oil form again. The oil was placed in the freezer –20 °C for 36 h and had recrystallized to yield 1.1 g (9.6 %) of the title compound. [Note: Evaporation of CH_2Cl_2 seemed to trap a significant amount of product in the salt that formed. During filtration step, air had leaked into the system and all of the material exposed to air had been discarded. The system was cleaned, dried, and purged with argon before continuing.] ^{1}H NMR ($CDCl_3$, 700 MHz, ppm) δ = 7.42 (m, 4 H), 7.27 (m, 4 H), 5.42 (m, 1 H), 5.29 (m, 1 H), 4.13 (d, *J* = 16.2 Hz, 1 H), 4.00 (d, *J* = 15.0 Hz, 1 H), 3.84 (d, *J* = 3.1 Hz, 1 H), 3.82 (d, *J* = 4.4 Hz, 1 H), 2.78 (m, 1 H), 2.71 (m, 1 H), 1.77 (m, 1 H), 1.69-1.74 (m, 1 H), 1.55-1.67 (m, 5 H), 1.23-1.33 (m, 1 H), 1.11 (m, 2), 0.86-1.01 (m, 3 H).



3-Methyldec-1-en-4-ol (24). Chloro(1-methyl-2-propenyl)magnesium (1.05 mL, 0.5 M) in THF was added slowly to heptanal (61 μL, 0.437 mmol, 1 equiv) in THF (4.3 mL) at 0 °C. The

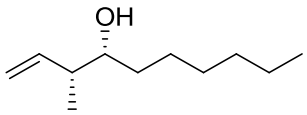
mixture was stirred and warmed to rt for 30 min. Reaction mixture was washed with DI water and extracted with diethyl ether (5 mL, 3 times). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.79 (m, 1 H), 5.11 (d, *J* = 14.1 Hz, 1 H), 5.08 (d, *J* = 15.5 Hz, 1 H), 3.49 (m, *syn*, 0.67 H), 3.39 (m, *anti*, 0.33 H), 2.16-2.32 (m, 1 H), 1.49 (m, 2 H), 1.20-2.40 (m, 8 H), 1.03 (m, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H).



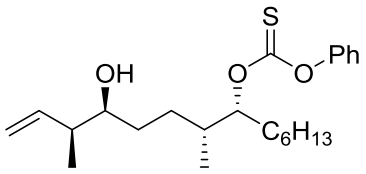
(3*S*,4*S*)-3-Methyldec-1-en-4-ol ((*S*,*S*)-24). In a glove box **35b** (0.160 g, 0.285 mmol, 1.3 equiv) and scandium triflate (0.027 g, 0.055 mmol, 0.25 equiv) were added to a dry round bottom flask. Under argon, the mixture was dissolved in DCM (0.1 M) and chilled to -10 °C. Heptanal (30 μL, 0.219 mmol, 1 equiv) was added dropwise to the solution and stirred for 16 h. The reaction mixture was quenched with HCl (2 N) and diluted with ether. The solid diamine dihydrochloride was filtered through celite and the filtrate was extracted with ether (3 times), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes : ethyl acetate gradient). The alkene was injected onto a chiral GC column to yield a selectivity of the title compound in 82:18 er. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.80 (ddd, *J* = 7.5, 10.0, 17.6 Hz, 1 H), 5.08 (d, *J* = 16.7 Hz, 1 H), 5.08 (d, *J* = 11.0, 1 H), 3.49 (m, 1 H), 2.28 (m, 1 H), 1.48 (m, 2 H), 1.20-1.40 (m, 8 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

The above procedure was repeated using the commercial (*S*,*S*)-*cis*-EZ crotyl mix **35b** (0.165 g, 1.3 equiv), scandium triflate (0.021 g, 0.21 equiv), and heptanal (30 μL, 0.219 mmol, 1 equiv) in CH_2Cl (2.1 mL) to yield the title compound in 92:8 er. ^{1}H NMR ($CDCl_3$, 400 MHz,

ppm) δ = 5.79 (m, 1 H), 5.07 (d, *J* = 16.0 Hz, *trans*, 1 H), 5.07 (d, *J* = 11.6 Hz, *cis*, 1 H), 3.48 (s, 1 H), 2.26 (m, 1 H), 1.46 (m, 2 H), 1.21-1.39 (m, 8 H), 1.01 (d, *J* = 1.01 Hz, 3 H), 0.88 (t, *J* = 6.0 Hz, 3 H).

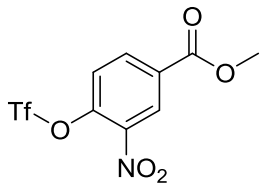


(3*R*,4*R*)-3-Methyldec-1-en-4-ol ((*R*,*R*)-24. In a glove box (*R*,*R*)-*cis*-EZ crotyl mix **35a** (0.165 g, 1.3 equiv) and scandium triflate (0.021 g, 0.21 equiv) were added to a a dry round bottom flask. Under argon, the mixture was dissolved in DCM (0.1 M) and chilled to -10 °C. Heptanal (30 μL, 0.219 mmol, 1 equiv) was added dropwise to the solution and stirred for 16 h. The reaction mixture was quenched with HCl (2 N) and diluted with ether. The solid diamine dihydrochloride was filtered through celite and the filtrate was extracted with ether (3 times), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes : ethyl acetate gradient). The alkene was injected onto a chiral GC column to yield a selectivity of the title compound in 96:4 er. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.79 (ddd, *J* = 7.5, 10.0, 17.7 Hz, 1 H), 5.07 (d, *J* = 16.3 Hz, 1 H), 5.07 (d, *J* = 11.2 Hz, 1 H), 3.48 (s, 1 H), 2.26 (m, 1 H), 1.47 (m, 2 H), 1.22-1.39 (m, 8 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

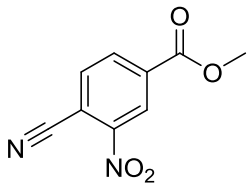


O-((7R,8R,11S,12S)-11-hydroxy-8,12-dimethyltetradec-13-en-7-yl) O-phenyl carbonothioate (37): In a glove box **35b** (0.087 g, 1.3 equiv) and scandium triflate (0.015 g, 0.25 equiv) were added to a dry round bottom flask. Under argon, the mixture was dissolved in DCM (0.1 M) and chilled to -10 °C. **36** (0.040 g, 0,119 mmol, 1 equiv) was added dropwise to

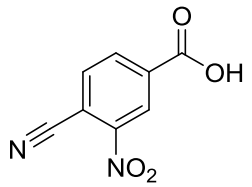
the solution and stirred for 16 h. The reaction mixture was quenched with HCl (2 N) and diluted with ether. The solid diamine dihydrochloride was filtered through celite and the filtrate was extracted with ether (3 times), washed with brine, dried over $MgSO_4$, and concentreated under reduced pressure. The crude material was purified by flash chromatography (hexanes : ethyl acetate gradient). ^{13}C NMR ($CDCl_3$, 175 MHz, ppm) δ = 195.19, 153.33, 140.86, 129.42, 126.37, 122.00, 115.44, 89.00, 74.87, 43.54, 36.05, 31.73, 31.67, 30.52, 29.68, 29.17, 29.08, 25.46, 22.56, 14.64, 14.54, 14.17, 14.05.



Methyl 3-nitro-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (39): Following the procedure by Jung and coworkers,[55] 4-Hydroxy-3-nitro-benzoic acid methyl ester (8.28 g, 42.0 mmol) and pyridine (10.15 mL, 126.0 mmol) were dissolved in dichloromethane (168 mL, 0.25 M). The yellow mixture was cooled to 0°C and trifluoromethane sulfonic anhydride (7.77 mL, 46.2 mmol) was added dropwise within 60 minutes at 0°C-5°C. After 90 minutes at 5°C the reaction mixture was washed with aqueous hydrochloric acid (2M), then with aqueous sodium hydrogen carbonate (10% w/v) and finally with brine. The organic phase was dried over sodium sulfate and concentrated to yield **39** (15.27 g) as a yellow oil which was used in the next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ = 8.80 (s, 1H), 8.40 (d, 1H), 7.58 (d, 1H), 4.00 (s, 3H) ppm.



Methyl 4-cyano-3-nitrobenzoate (40): 39 (7.34 g, 22.3 mmol), zinc cyanide (1.57 g, 13.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.29 g, 1.11 mmol) were suspended in N,N-dimethylformamide (223 ml, 0.1 M). The reaction mixture was stirred for 3 hours at 100°C under an argon atmosphere. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: cyclohexane / ethyl acetate 3:1) to **40** (0.81 g, 17.6 % yield). ^{1}H-NMR (400 MHz, CDCl3): 8.92 (s, 1H), 8.48 (d, 1H), 8.04 (d, 1H), 4.03 (s, 3H) ppm.

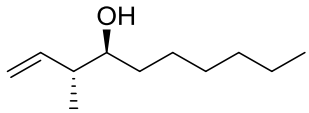


4-Cyano-3-nitrobenzoic acid (41):

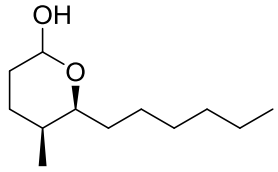
Method A[55]: 40 (0.686 g, 3.33 mmol) was dissolved in tetrahydrofuran (4.1 mL, 0.8 M) and aqueous sodium hydroxide (1M) (3.99 ml) was added. The reaction mixture was stirred at 25°C for 4 hours. Then the reaction mixture was diluted with water (38 ml) and acidified with aqueous hydrochloric acid (1M). The mixture was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (hexanes : ethyl acetate gradient) to yield **41** as a yellow solid in 0.535g (83.7 %). ^{1}H-NMR (400 MHz, DMSO-d6): 13.00 (bs, 1H), 8.79 (s, 1H), 8.40 (d, 1H), 8.30 (d, 1H) ppm

Method B[55]: Under Ar , H5IO6 (7.38 g, 32.4 mmol) was dissolved in CH3CN (0.2 M) and stirred for 15 mins. CrO3 (0.370 g, 3.70 mmol) and 4-cyano-3-nitro-toluene (1.50 g, 9.25 mmol)

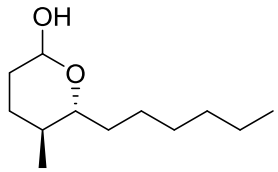
were added. The resulting mixture was stirred at rt overnight. The reaction mixture was filtered through celite, and silica gel was added to the filtrate and concentrated. The crude was dry loaded onto the combiflash for purification with hexane-ethyl acetate gradient (80:20-50:50). The product was a white solid isolated in 62 % yield (1.11 g).



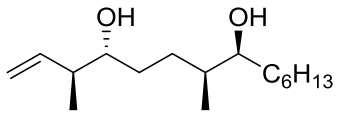
(3*R*,4*S*)-3-Methyldec-1-en-4-ol ((*R*,*S*)-24): Typical procedure 5 was followed using **44** (1.11 mL, 8.76 mmol), heptanal (0.61 mL, 4.38 mmol), isopropanol (0.67 mL, 8.75 mmol), H_2O (0.39 mL, 21.89 mmol), K_3PO_4 (0.465 g, 2.19 mmol), **43b** (0.229 g, 0.219 mmol) to yield the title compound in 64 % yield (0.474 g) in +99 % ee and 96 % de. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.76 (ddd, *J* = 8.2, 10.8, 16.7 Hz, 1 H), 5.12 (d, *J* = 10.5 Hz, 1 H), 5.11 (d, *J* = 17.3 Hz, 1 H), 3.39 (s, 1 H), 2.21 (m, 1 H), 1.23-1.62 (m, 11 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).



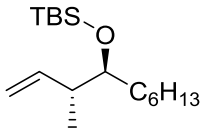
(5S,6S)-6-hexyl-5-methyltetrahydro-2H-pyran-2-ol (48a): Typical procedure 4 was followed using **(*S*,*S*)-24** (0.125 g, 0.734 mmol), **31** (0.072 g, 0.257 mmol), and $Rh(CO)_2(acac)$ (0.014 g, 0.051 mmol) to yield target compound in 68 % (0.100 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) Major Isomer (~66 %): δ = 4.69 (dd, *J* = 1.6, 9.2 Hz, 1 H), 3.48 (m, 1 H), 2.05 (tt, *J* = 4.3, 13.2 Hz, 1 H), Minor Isomer (~33 %): δ = 5.24 (br, 1 H), 4.03 (m, 1 H), 1.84 (tt, *J* = 4.0, 13.4 Hz, 1 H), Overlapping Signals: δ = 1.2-1.79 (m, 15.21 H), 0.93 (m, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H).



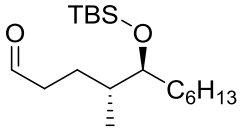
(5S,6R)-6-hexyl-5-methyltetrahydro-2H-pyran-2-ol (48b): Typical procedure 4 was followed using **(*S,R*)-24** (0.094 g, 0.552 mmol), **31** (0.054 g, 0.193 mmol), and $Rh(CO)_2(acac)$ (0.011 g, 0.039 mmol) to yield target compound quantitatively (0.110 g). ^{1}H NMR ($CDCl_3$, 700 MHz, ppm) Major Isomer (~62 %): δ = 4.68 (m, 1 H), 3.07 (d, *J* = 6.1 Hz, 1 H), 3.03 (dt, *J* = 2.5, 9.1 Hz, 1H), 0.82 (d, 6.6 Hz, 3 H), Minor Isomer (~38 %): δ = 5.31 (s, 1 H), 3.57 (dt, *J* = 2.5, 9.1 Hz, 1 H), 2.50 (s, 1 H), 0.85 (d, *J* = 6.5 Hz, 3 H), Overlapping Signals: δ = 1.17-1.90 (m, 14 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 175 MHz, ppm) δ = 103.84, 96.48, 91.58, 85.24, 81.65, 74.27, 44.36, 38.85, 36.25, 34.78, 34.18, 33.44, 32.99, 32.87, 31.90, 31.88, 31.58, 30.26, 29.51, 29.47, 26.46, 26.39, 25.21, 25.14, 22.67, 22.64, 18.09, 17.21, 14.12, 11.89, 11.39



(3S,4R,7S,8S)-3,7-dimethyltetradec-1-ene-4,8-diol (49): Typical procedure 5 was followed using **48a** (0.096 g, 0.478 mmol), **44** (121 μL, 0.956 mmol), isopropanol (73 μL, 0.956 mmol), H_2O (43 μL, 2.39 mmol), K_3PO_4 (0.051 g, 239 mmol), and **43a** (0.025 g, 0.024 mmol) to yield **49** in 34 % yield (0.042 g). The majority of **48a** was converted into **50** (0.061 g, 64 %). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.76 (ddd, *J* = 8.2, 11.0, 16.4 Hz, 1 H), 5.12 (d, *J* = 11.0 Hz, 1 H), 5.11 (d, *J* = 17.2, 1 H), 3.52 (m, 1 H), 3.40 (m, 1 H), 2.22 (m, 1 H), 1.66 (br, 2 H), 1.23-1.56 (m, 15 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.89 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ = 140.38, 116.41, 75.21, 74.70, 44.22, 38.21, 37.82, 34.35, 31.84, 29.40, 29.06, 26.27, 22.62, 16.33, 14.08, 13.68.

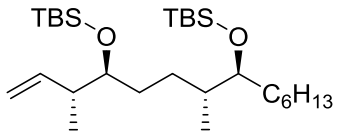


tert-Butyldimethyl(((3*R*,4*S*)-3-methyldec-1-en-4-yl)oxy)silane (51): TBSOTf (0.26 mL, 1.12 mmol, 1.1 equiv) was added to a solution of **(*S*,*R*)-24** (0.174 g, 1.03 mmol, 1 equiv) and 2,6-lutadine (177 μL, 1.53 mmol, 1.5 equiv) in DCM (2 mL, 0.5 M) at rt. After 14 h, TLC showed remaining **(*S*,*R*)-24** and DMAP (0.025 g, 0.204 mmol, 0.2 equiv) was added to the reaction mixture along with another 1.5 equiv of 2,6-lutadine and 1.1 equiv of TBSOTf. Starting material was no longer visible by TLC analysis after an hour. The mixture was poured into water (1:1 DCM to H_2O). The organic layer was separated, and the aqueous layer was extracted with DCM (3 times). The organic layers were combined, dried over Na_2SO_4, and purified by flash chromatography (hexanes : ethyl acetate) to yield **51** in 93 % (0.269 g). ^{1}H NMR ($CDCl_3$, 600 MHz, ppm) δ = 5.78 (ddd, *J* = 7.9, 9.6, 17.9 Hz, 1 H), 4.98 (d, *J* = 13.3 Hz, 1 H), 4.98 (d, *J* = 14.3 Hz, 1H), 3.51 (m, 1H), 2.29 (m, 1 H), 1.18-1.38 (m, 11 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.88 (m, 12 H), 0.04 (s, 6 H). ^{13}C NMR ($CDCl_3$, 150 MHz, ppm) δ = 141.12, 114.13, 75.83, 43.07, 33.56, 31.87, 29.49, 25.93, 25.67, 22.63, 18.16, 15.36, 14.09, -4.29, -4.47. HRMS (TOF ES) calcd for $C_{17}H_{37}OSi$ $[M]^+$: 285.2614, found: 285.2647.



(4R,5S)-5-((tert-butyldimethylsilyl)oxy)-4-methylundecanal (52) Typical procedure 4 was followed using **51** (0.500 g, 1.757 mmol), **31** (0.217 g, 0.777 mmol), and $Rh(CO)_2(acac)$ (0.038 g, 0.144 mmol) to yield **52** in 70 % (0.388 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.77 (t, *J* = 1.9 Hz, 1 H), 3.51 (m, 1 H), 2.30-2.54 (m, 2 H), 1.77 (m, 1 H), 1.50-1.61 (m, 2 H), 1.18- 1.45 (m, 11 H), 0.88 (m, 15 H), 0.03 (d, *J* = 4.8 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ =197.20,

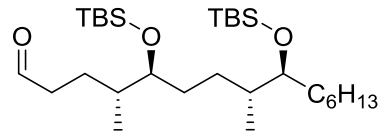
75.92, 42.16, 37.62, 32.80, 31.90, 29.56, 25.92, 25.58, 24.30, 22.64, 18.13, 14.93, 14.09, -4.30, -4.49. HRMS (TOF ES) calcd for $C_{18}H_{37}O_2Si$ $[M]^+$: 313.2563, found: 313.2592.



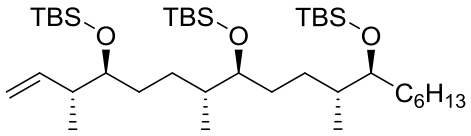
(5S,6R,9S)-9-((R)-but-3-en-2-yl)-5-hexyl-2,2,3,3,6,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecane (54): Typical procedure 5 was followed using **52** (1.079 g, 3.43 mmol), **44** (0.87 mL, 6.86 mmol), **43b** (0.179 g, 0.172 mmol), K_3PO_4 (0.364 g, 1.72 mmol), H_2O (0.31 mL, 17.15 mmol), isopropanol (0.53 mL, 6.86 mmol). After column chromatography (hexanes : ethyl acetate gradient), the product was an impure mixture. The semi-pure material was taken on to the next step (TBS protection) to create a polarity difference between mixture components (**53a** and **53b**).

The crotylation product mixture (1.063 g, 2.868 mmol) was assumed to be **53a** for calculation purposes was dissolved in DCM (5.7 mL). DMAP (0.070 g, 0.574 mmol), 2,6-lutidine (0.50 mL, 4.3 mmol) was added to the mixture solution followed by the addition of TBSOTf (0.99 mL, 4.3 mmol). The reaction mixture was stirred at rt for 14 h, TLC showed the disappearance of one of the mixture spots. The mixture was poured into water (1:1 DCM to H_2O). The organic layer was separated, and the aqueous layer was extracted with DCM (3 times). The organic layers were combined, dried over Na_2SO_4, and purified by flash chromatography (hexanes : ethyl acetate) to yield **54** in 65 % (0.914 g) over two steps. 0.346 g (0.899 mmol, 31 %) of the byproduct **53b** was isolated. ^{1}H NMR ($CDCl_3$, 700 MHz, ppm) δ = 5.79 (ddd, J = 8.0, 9.7, 17.9 Hz, 1 H), 4.99 (d, J = 11.8 Hz, 1 H), 4.99 (d, J = 16.1 Hz, 1 H), 3.50 (m, 1 H), 2.29 (m, 1 H), 1.43-1.51 (m, 2 H), 1.17-1.41 (m, X H), 0.99 (d, J = 6.9 Hz, 3 H), 0.89 (m, 21 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.04 (s, 6 H), 0.03 (d, J = 4.8 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 175 MHz, ppm) δ =

140.98, 114.25, 76.00, 43.00, 38.56, 32.38, 31.91, 31.79, 29.54, 28.29, 25.98, 25.95, 25.94, 25.91, 22.66, 18.16, 15.62, 14.92, 14.08, -4.27, -4.34, -4.41, -4.44



(4R,5S,8R,9S)-5,9-bis((tert-butyldimethylsilyl)oxy)-4,8-dimethylpentadecanal (55): Typical procedure 4 was followed using **54** (0.914 g, 1.89 mmol), **31** (0.184 g, 0.660 mmol), and $Rh(CO)_2(acac)$ (0.034 g, 0.132 mmol) to yield **55** in 71 % (0.691 g). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ = 9.77 (s, 1 H), 3.49 (m, 2 H), 2.32-2.55 (m, 2 H), 1.76 (m, 1 H), 1.16-1.62 (m, 17 H), 0.83-0.91 (m, 27 H), 0.01-0.05 (m, 12 H). ^{13}C NMR ($CDCl_3$, 150 MHz, ppm) δ = 31.90, 25.93, 22.65, 18.14, 14.09, -4.36, -4.42, -4.48.



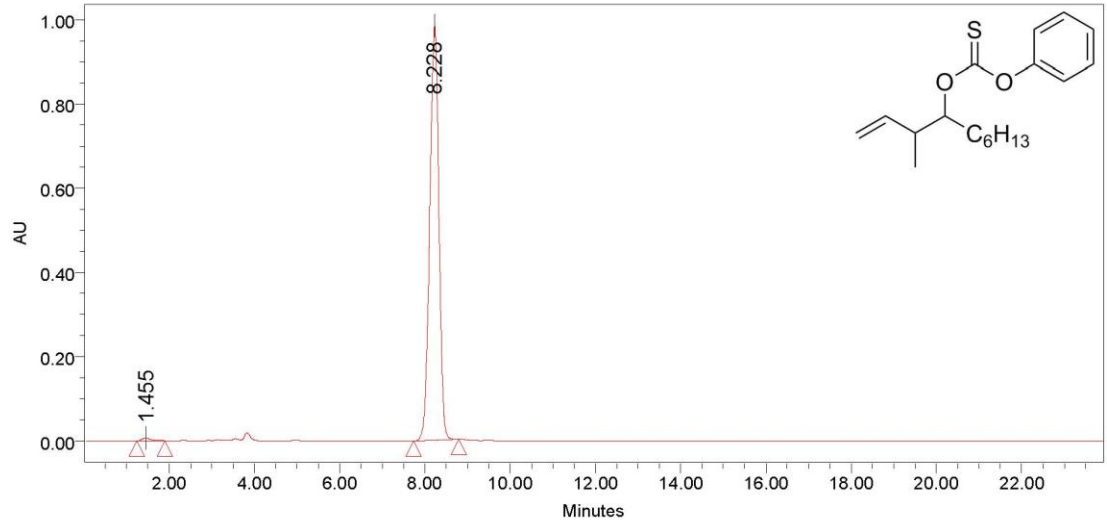
(5S,6R,9S,10R,13S)-13-((R)-but-3-en-2-yl)-9-((tert-butyldimethylsilyl)oxy)-5-hexyl-2,2,3,3,6,10,15,15,16,16-decamethyl-4,14-dioxa-3,15-disilaheptadecane (57): Typical procedure 5 was followed using **55** (0.686 g, 1.33 mmol), **44** (0.34 mL, 2.67 mmol), **43b** (0.070 g, 0.067 mmol), K_3PO_4 (0.141 g, 0.666 mmol), H_2O (120 μL, 6.66 mmol), isopropanol (204 μL, 2.66 mmol). After column chromatography (hexanes : ethyl acetate gradient), the product was an impure mixture. The semi-pure material was taken on to the next step (TBS protection) to create a polarity difference between mixture components (**56a** and **56b**).

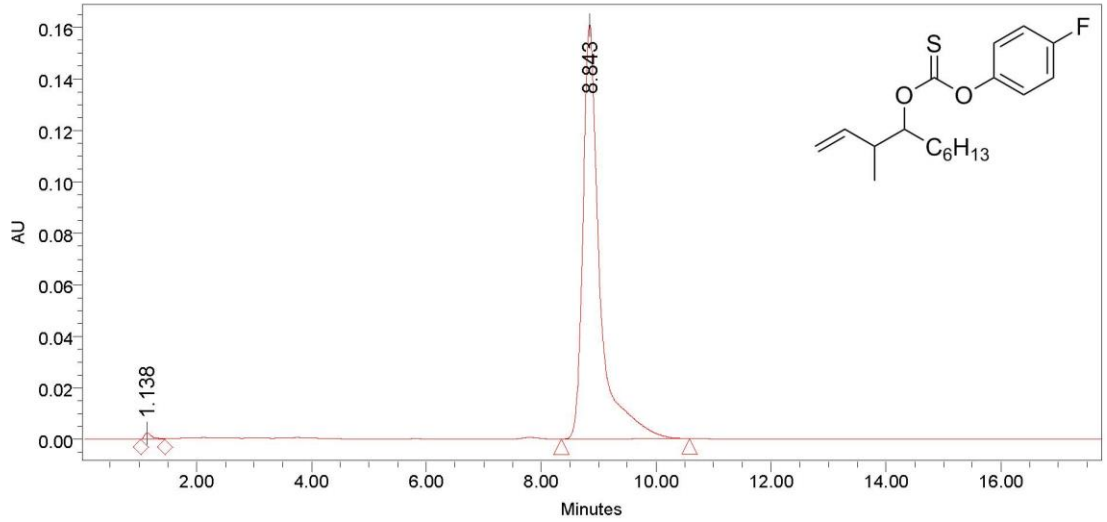
The crotylation product mixture (0.761 g, 1.33 mmol) was assumed to be **56a** for calculation purposes was dissolved in DCM (2.7 mL). DMAP (0.033 g, 0.266 mmol), 2,6-lutidine (170 μL, 1.47 mmol) was added to the mixture solution followed by the addition of TBSOTf (107 μL, 1.47 mmol). The reaction mixture was stirred at rt for 14 h, TLC showed the

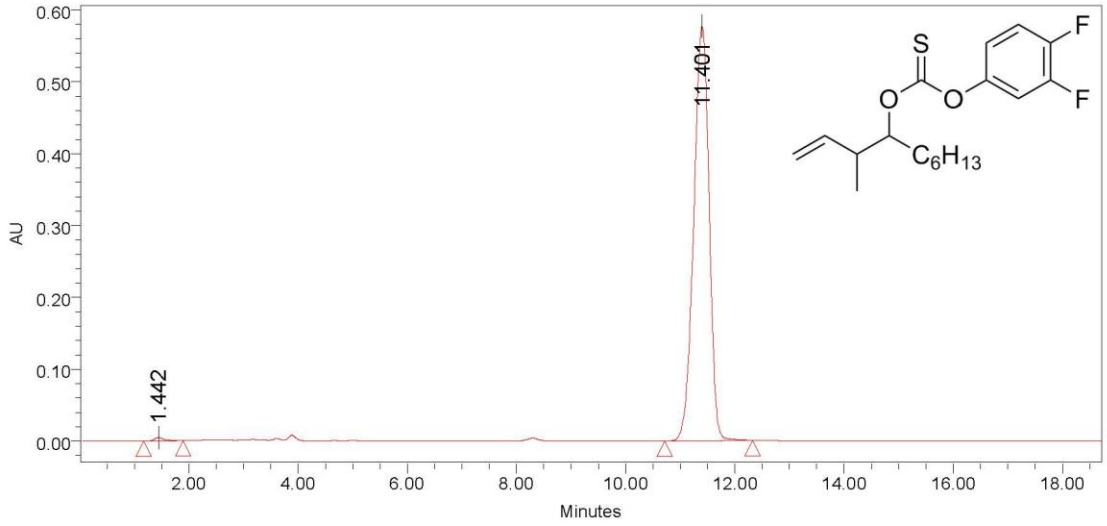
disappearance of one of the mixture spots. The mixture was poured into water (1:1 DCM to H-$_2$O). The organic layer was separated, and the aqueous layer was extracted with DCM (3 times). The organic layers were combined, dried over Na_2SO_4, and purified by flash chromatography (hexanes : ethyl acetate) to yield **57** in 39 % (0.353 g) over two steps. 0.202 g (0.345 mmol, 26 %) of the byproduct **56b** was isolated as well as 7 % starting material (**55**). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = 5.79 (ddd, *J* = 8.0, 9.7, 17.9 Hz, 1 H), 4.99 (d, *J* = 12.3 Hz, 1 H), 4.99 (d, *J* = 15.9 Hz, 1 H), 3.42-3.53 (m, 3 H), 2.29 (m, 1 H), 1.14-1.52 (m, 23 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.82-0.91 (m, 33 H), 0.01-0.05 (m, 18 H). ^{1}H NMR ($CDCl_3$, 100 MHz, ppm) δ = 140.97, 114.27, 77.22, 76.01, 42.95, 38.75, 38.41, 32.17, 31.92, 31.84, 30.64, 29.53, 28.80, 28.10, 26.03, 25.95, 22.67, 18.15, 15.73, 14.11, 14.89, 14.10, -4.24, -4.31, -4.35, -4.38, -4.46.

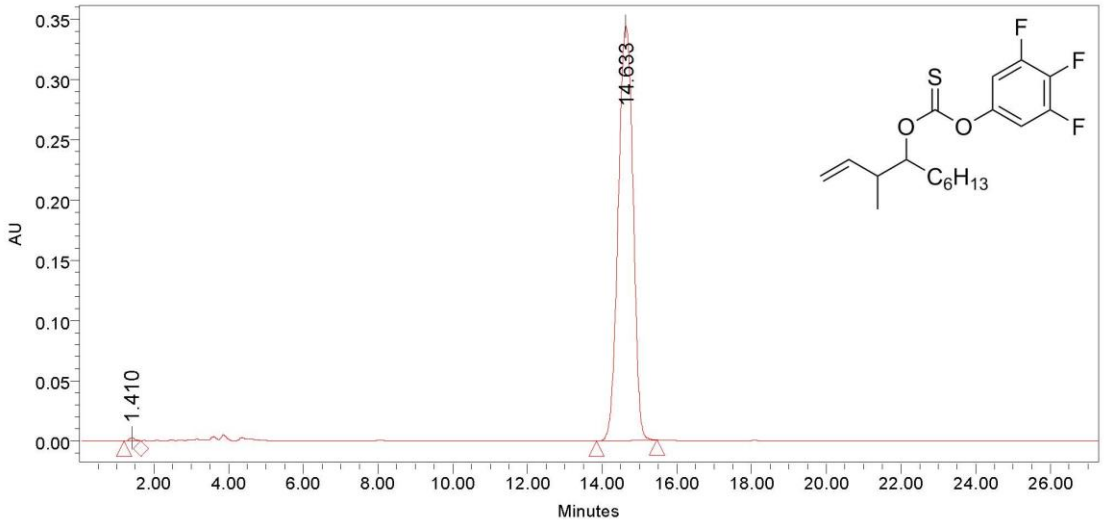
APPENDIX A

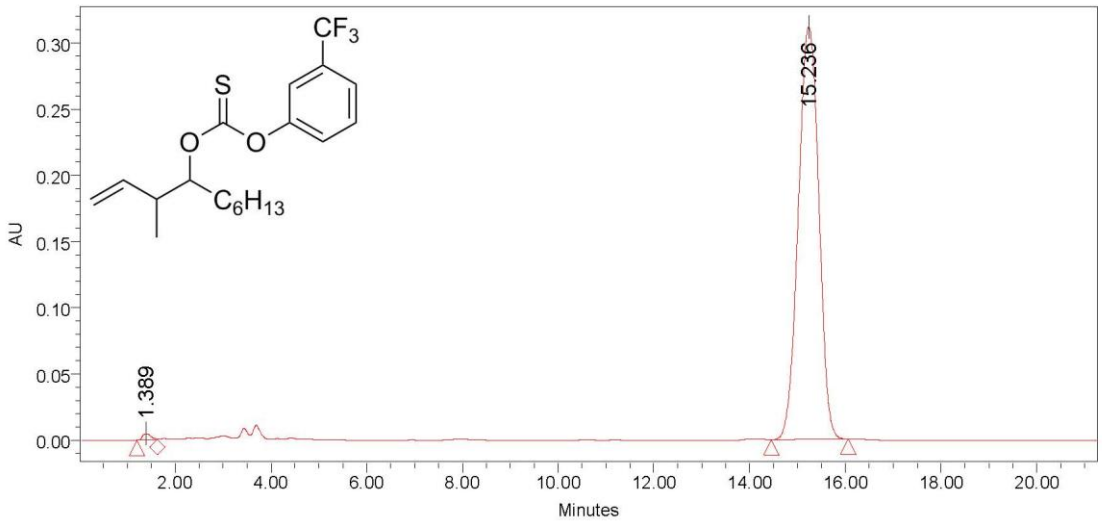
FLUOROUS HPLC CHROMATOGRAMS

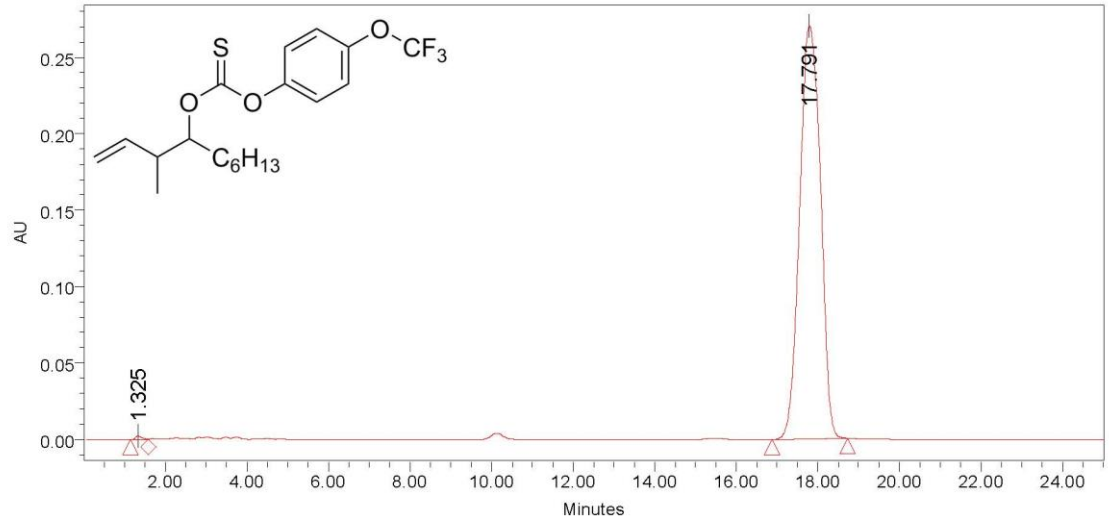


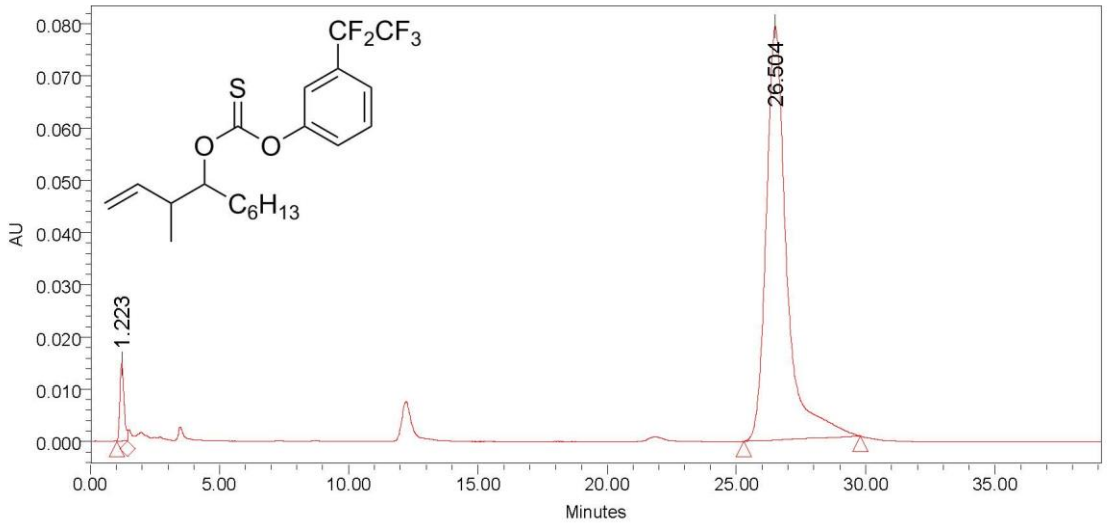


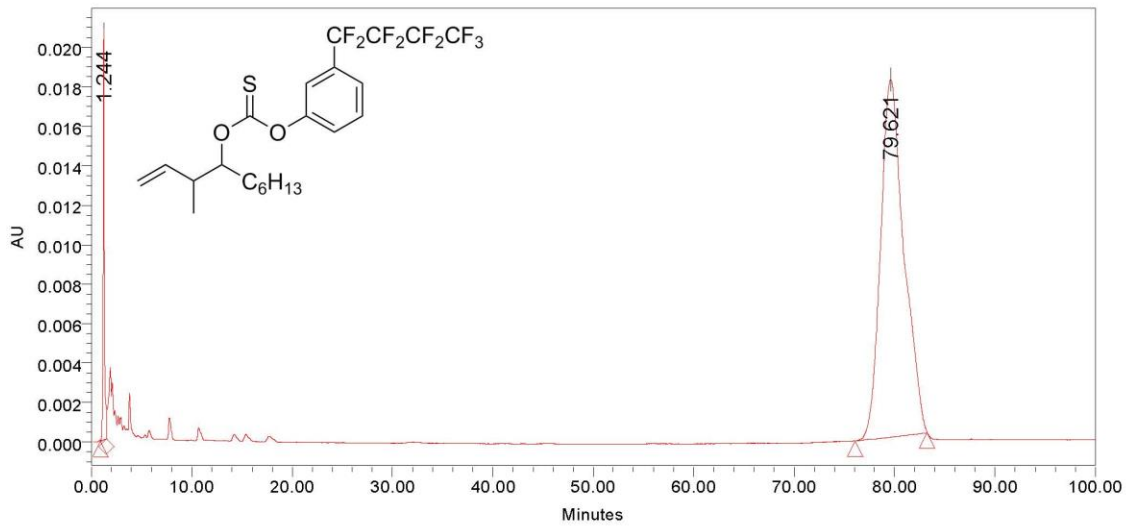

11.401
1.442
AU
Minutes
S
O
O
F
F
C_6H_{13}


14.633
1.410
AU
Minutes
F
F
F
S
O
O
C_6H_{13}


15.236
1.389
AU
Minutes
CF_3
S
O
O
C_6H_{13}

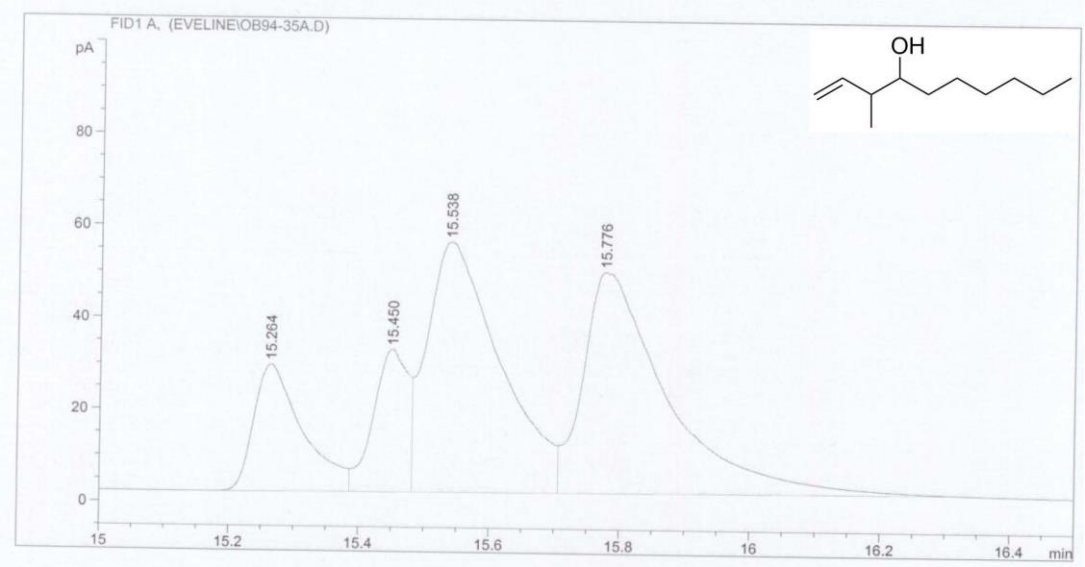

S
O
O
O
CF3
C6H13
17.791
1.325
AU
0.25
0.20
0.15
0.10
0.05
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
Minutes

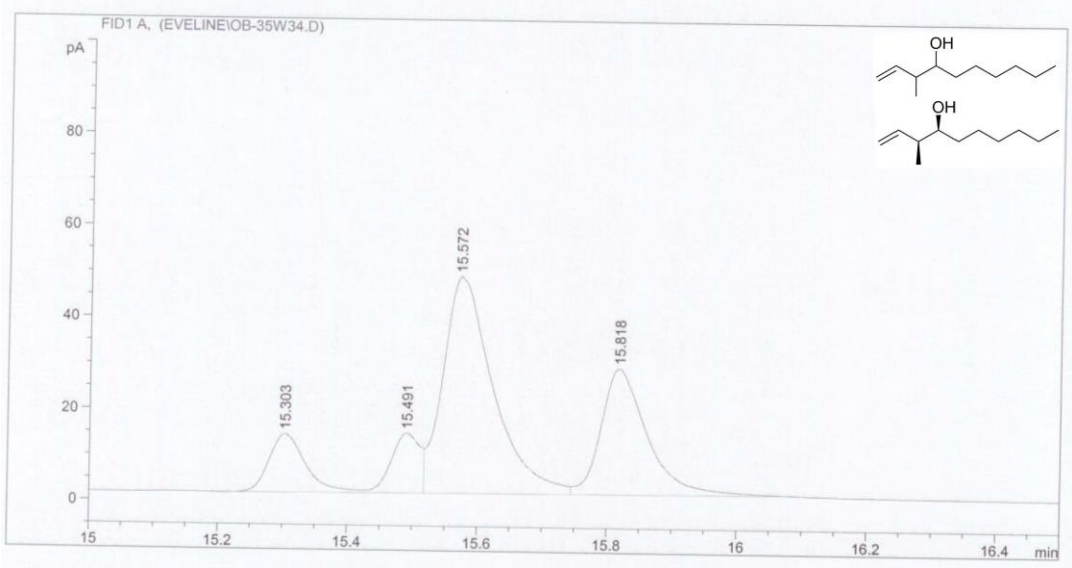

CF2CF3
S
O
O
C6H13
26.504
1.223
AU
0.080
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00
Minutes


CF2CF2CF2CF3
S
O
O
C6H13
1.244
79.621
AU
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
100.00
Minutes

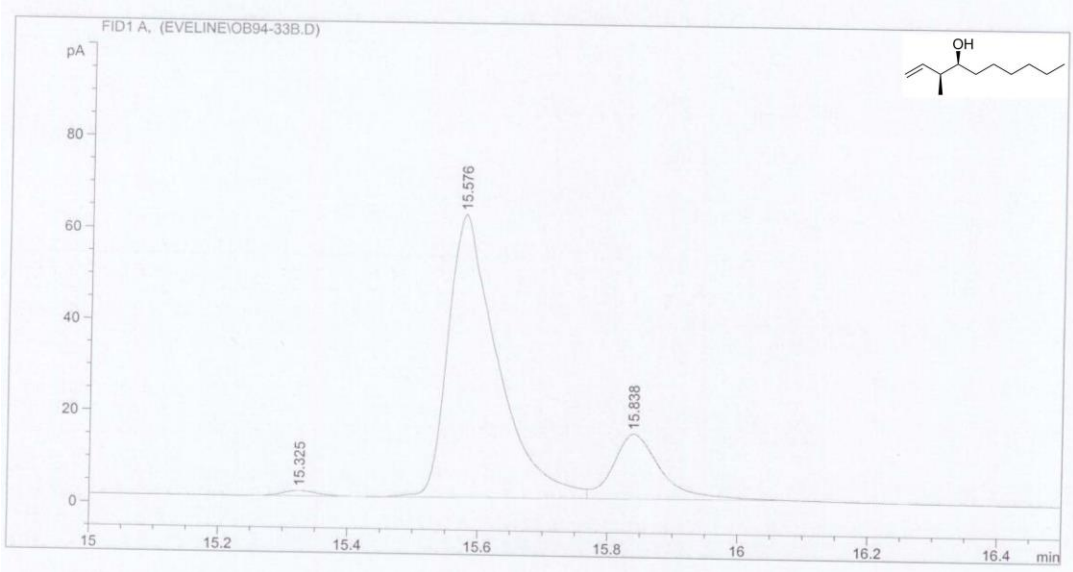
APPENDIX B

CHIRAL GC CHROMATOGRAMS

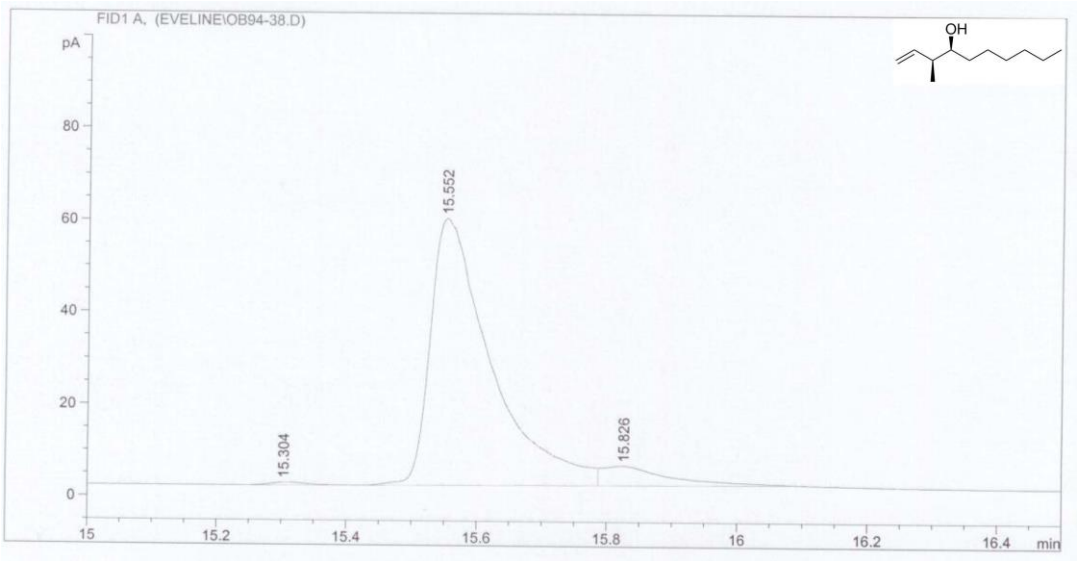


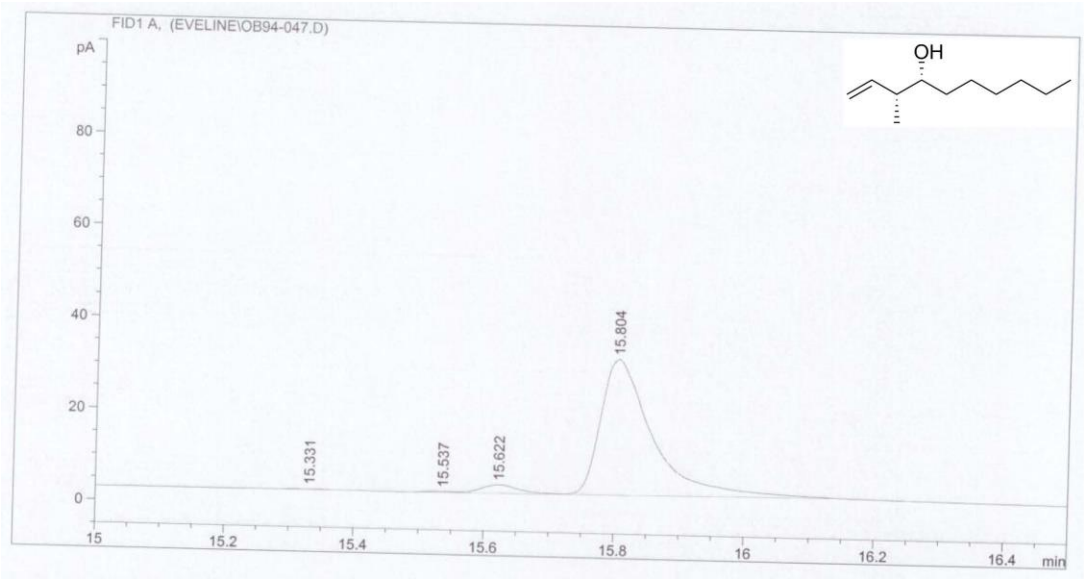


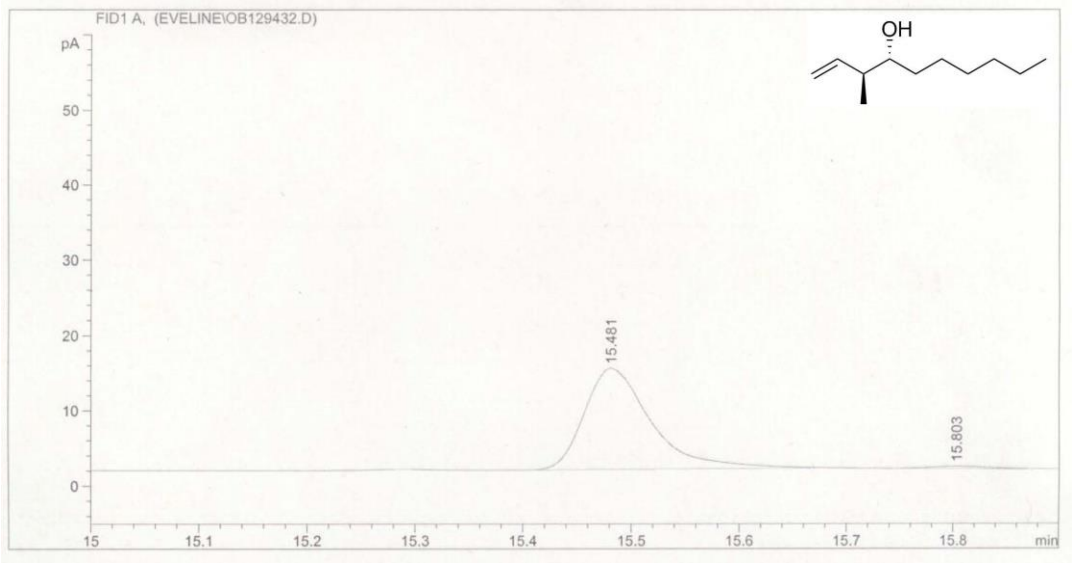
From homemade 35b

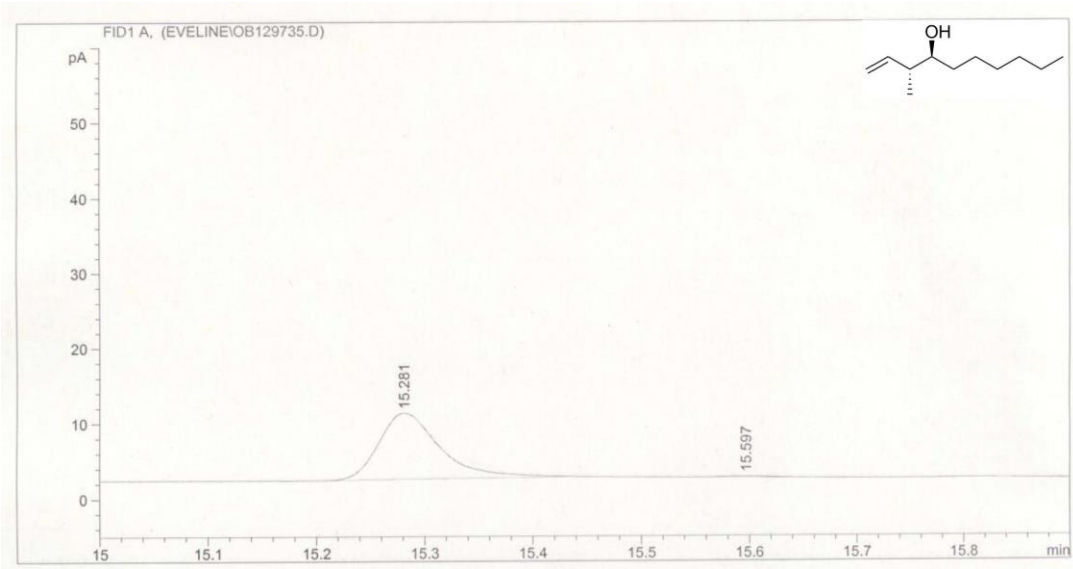


From commercial 35b






FID1 A, (EVELINE\OB129432.D)
pA
50
40
30
20
10
0
15.481
15.803
15
15.1
15.2
15.3
15.4
15.5
15.6
15.7
15.8
min
OH


FID1 A, (EVELINE\OB129735.D)
pA
50
40
30
20
10
0
15.281
15.597
15
15.1
15.2
15.3
15.4
15.5
15.6
15.7
15.8
min
OH

APPENDIX C

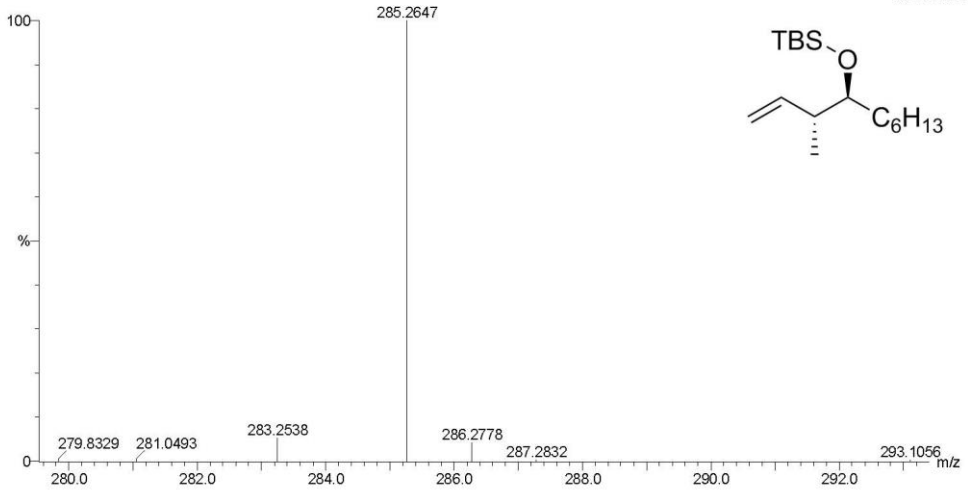
HIGH RESOLUTION MASS SPECTROMETRY

Single Mass Analysis
Tolerance = 1000.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-17 H: 0-37 O: 0-1 Si: 1-1

BUDAVICH-OB-129-069-CURRAN
72467ASAP 96 (0.993) AM (Cen,3, 85.00, Ar,8000.0,0.00,0.70); Sm (SG, 5x3.00); Cm (92:105)

08-Aug-201411:48:27
TOF MS ES+
6.27e+002



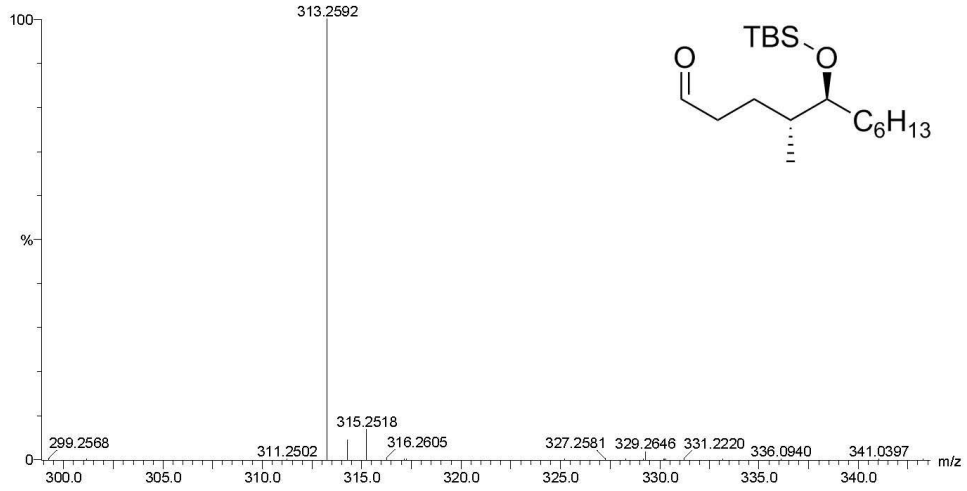
Minimum:				-1.5		
Maximum:		1000.0	1000.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
285.2647	285.2614	3.3	11.6	0.5	214.6	C17 H37 O Si

Single Mass Analysis
Tolerance = 1000.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-18 H: 0-37 O: 0-2 Si: 1-1

BUDAVICH-OB-129-075-CURRAN
72468ASAP 89 (0.921) AM (Cen,3, 85.00, Ar,8000.0,0.00,0.70); Sm (SG, 5x3.00); Cm (86:91)

08-Aug-201412:03:02
TOF MS ES+
6.75e+003



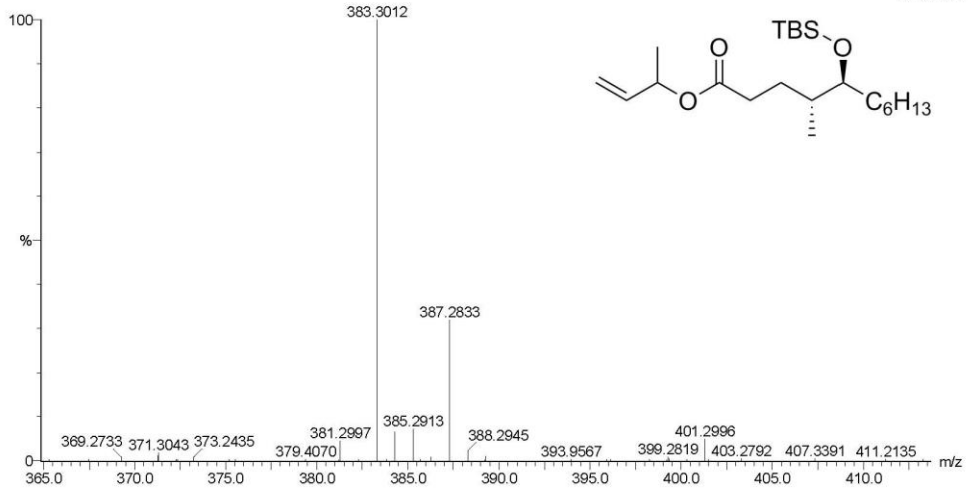
Minimum:				-1.5		
Maximum:		1000.0	1000.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
313.2592	313.2563	2.9	9.3	1.5	1459.3	C18 H37 O2 Si

Single Mass Analysis
Tolerance = 1000.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-22 H: 0-44 O: 0-3 Si: 1-1

BUDAVICH-OB-129-077-F51-59-CURRAN
72469ASAP 185 (1.912) AM (Cen,3, 85.00, Ar,8000.0,0.00,0.70); Sm (SG, 5x3.00); Cm (178:213)

08-Aug-201412:10:28
TOF MS ES+
6.71e+002

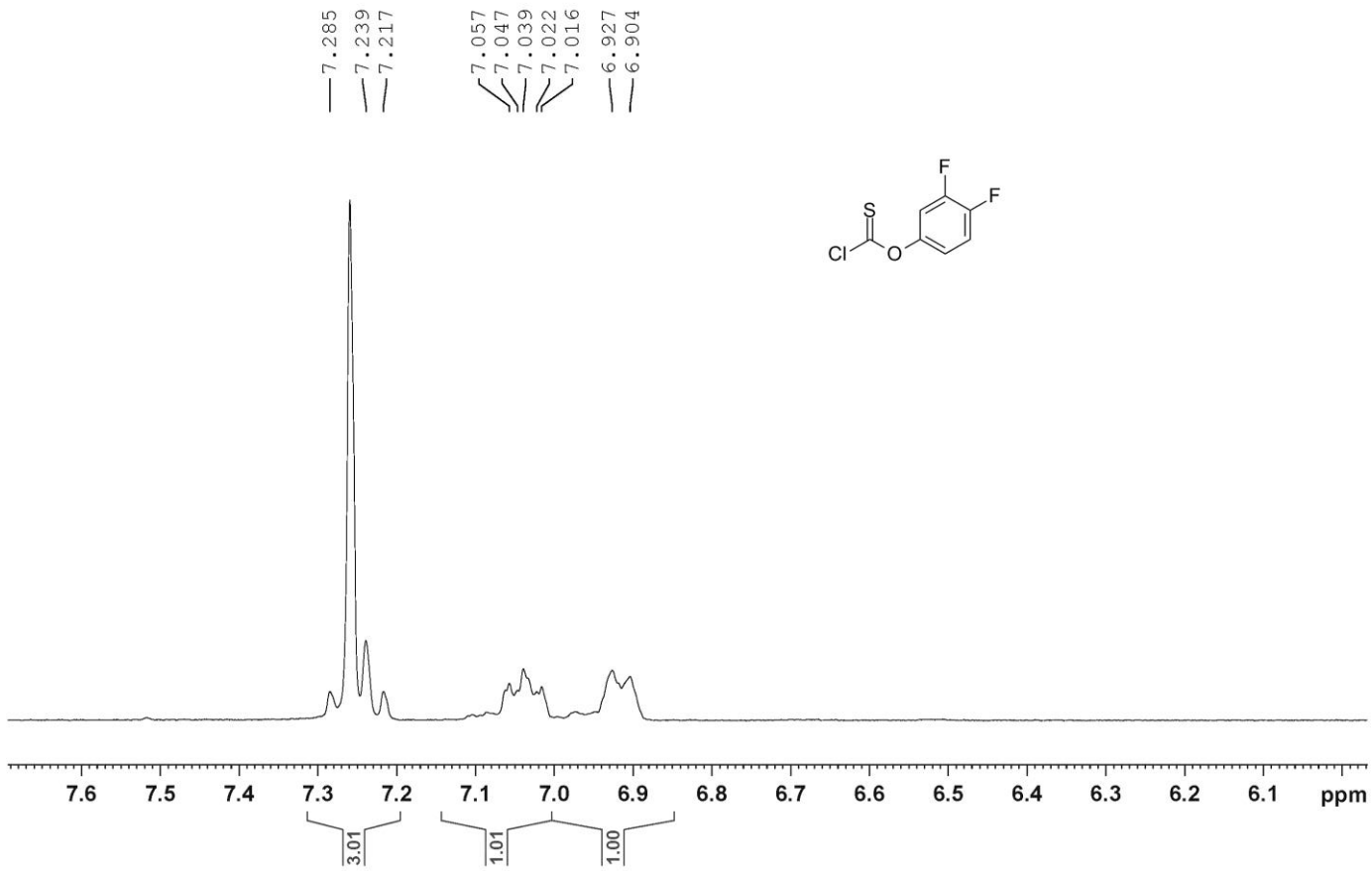


Minimum:				-1.5		
Maximum:		1000.0	1000.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
383.3012	383.2981	3.1	8.1	2.5	125.9	C22 H43 O3 Si

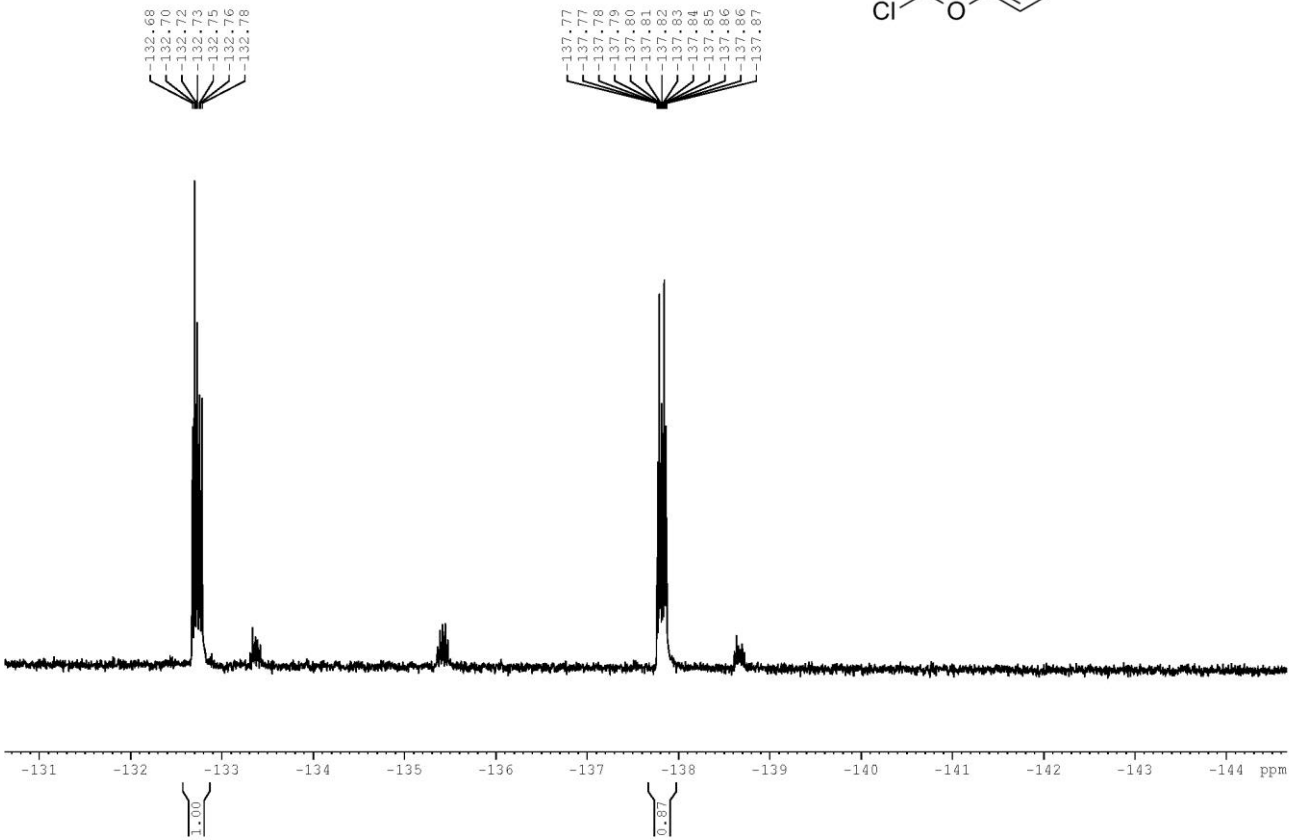
APPENDIX D

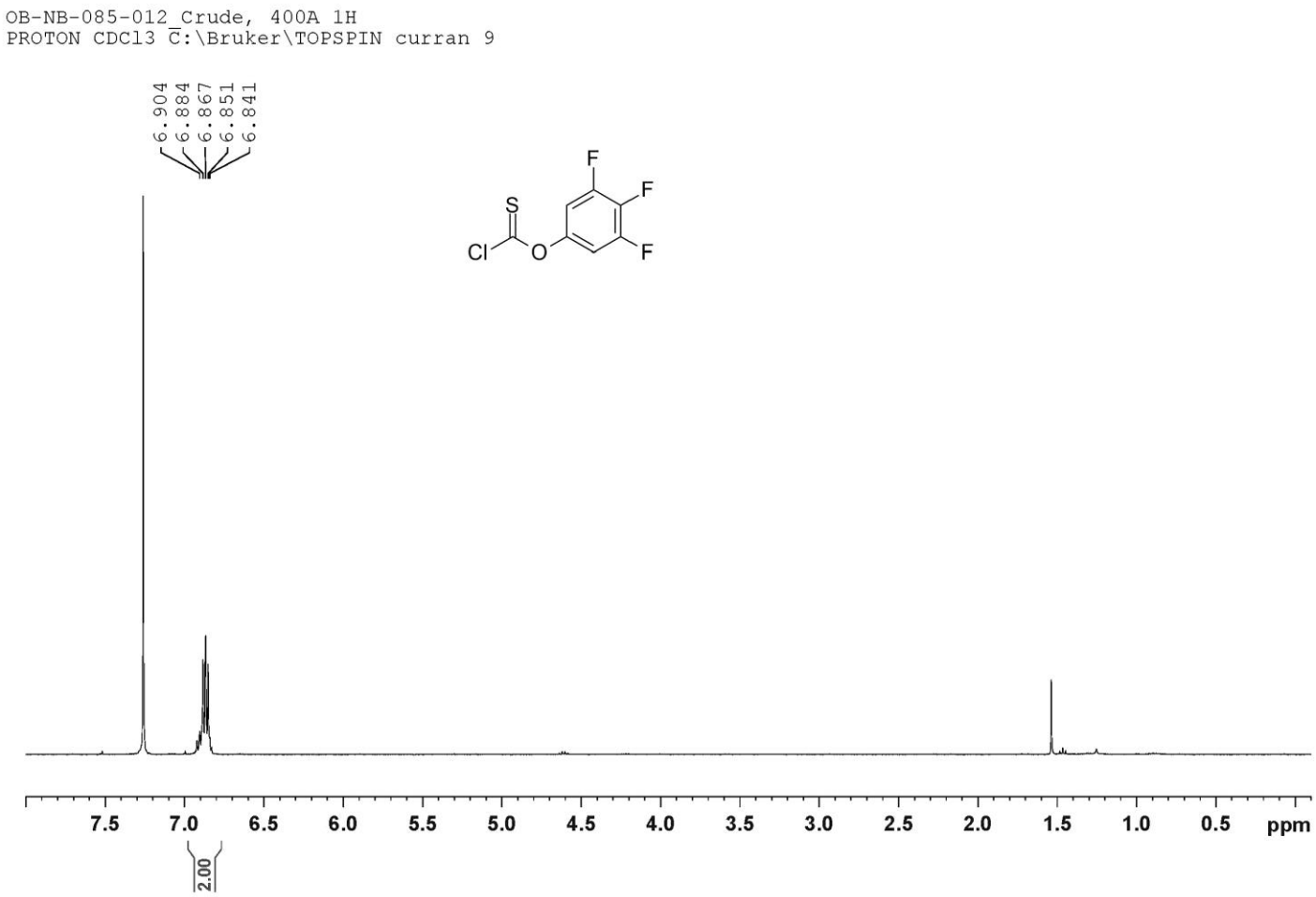
NMR SPECTROSCOPY

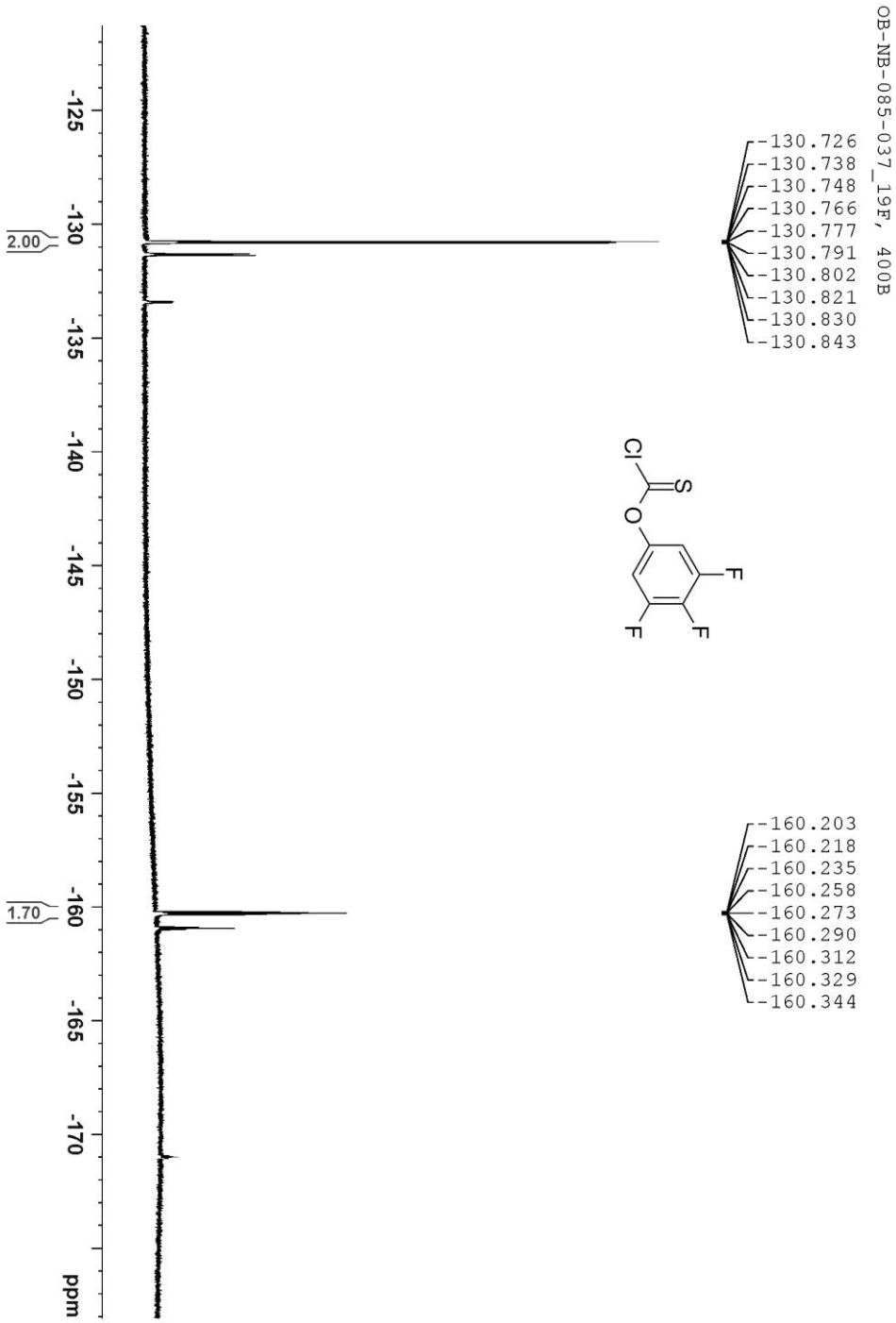
OB-NB-085-046, 1H, 400A



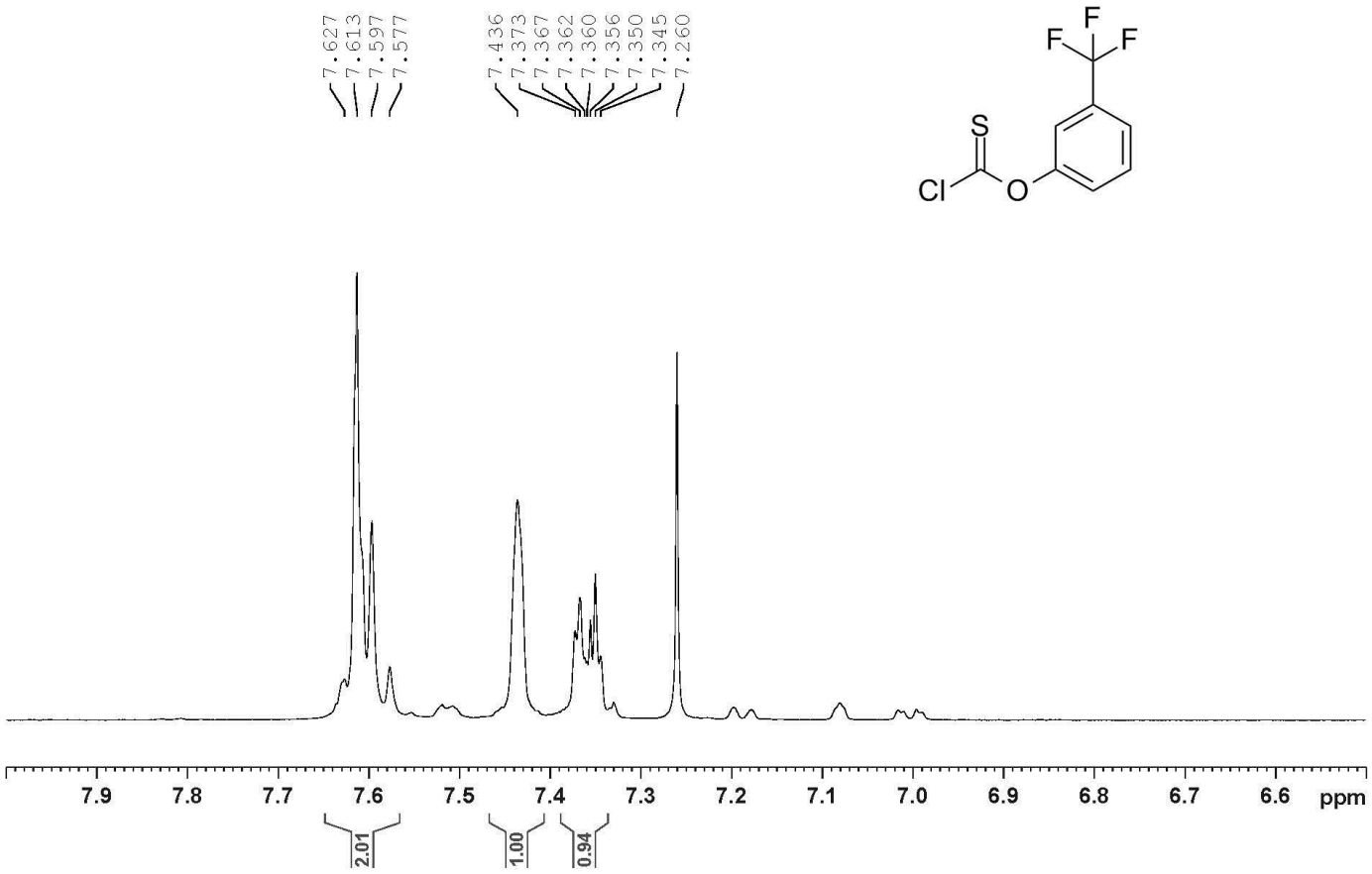
OB-NB-085-008_Crude_Fluorine, 19F, 400B, 05/23/11



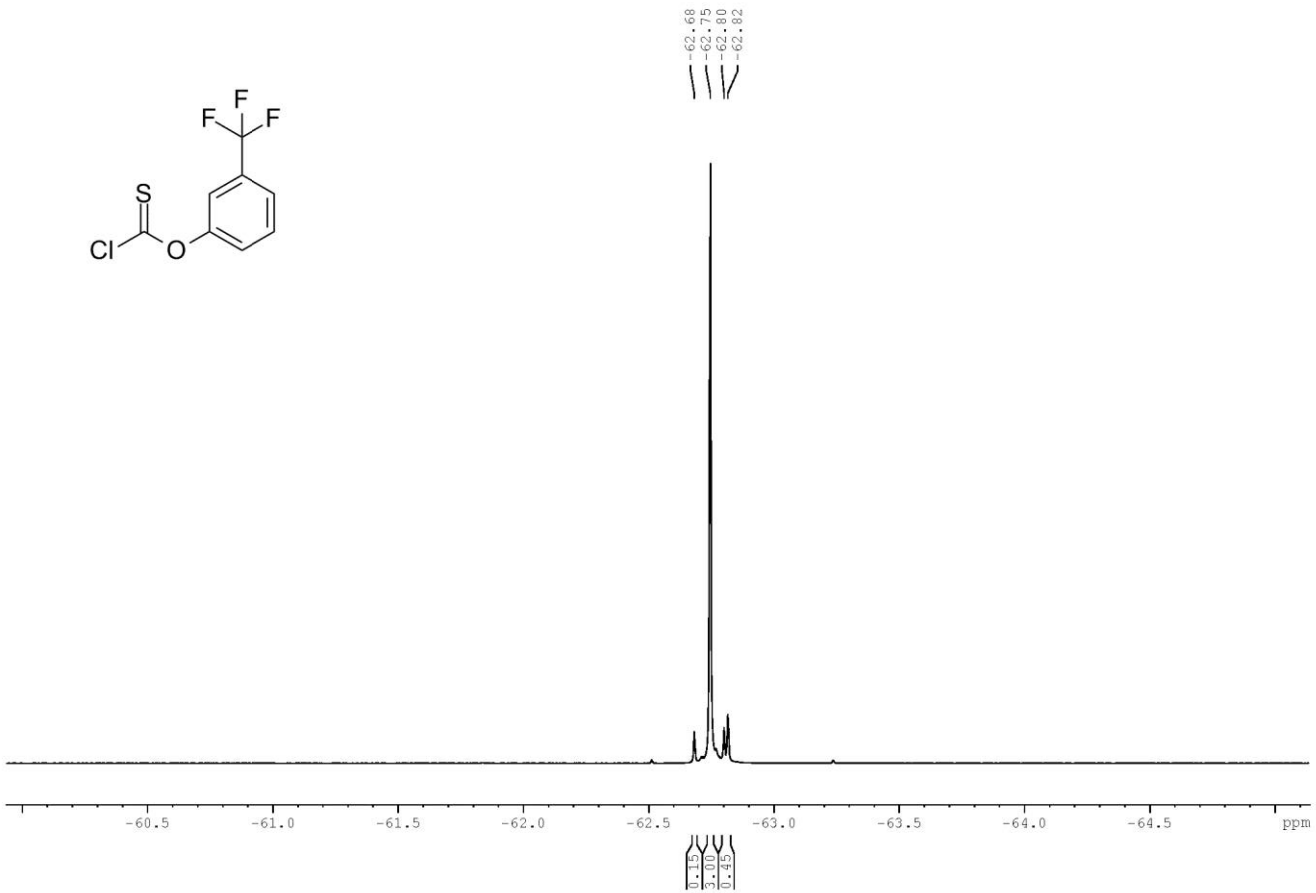

OB-NB-085-012_Crude, 400A 1H
PROTON CDCl3 C:\Bruker\TOPSPIN curran 9
6.904
6.884
6.867
6.851
6.841
F
F
F
S
Cl
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00


OB-NB-085-037_19F, 400B
-130.726
-130.738
-130.748
-130.766
-130.777
-130.791
-130.802
-130.821
-130.830
-130.843
-160.203
-160.218
-160.235
-160.258
-160.273
-160.290
-160.312
-160.329
-160.344
2.00
1.70
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
ppm
Cl
S
O
F
F
F

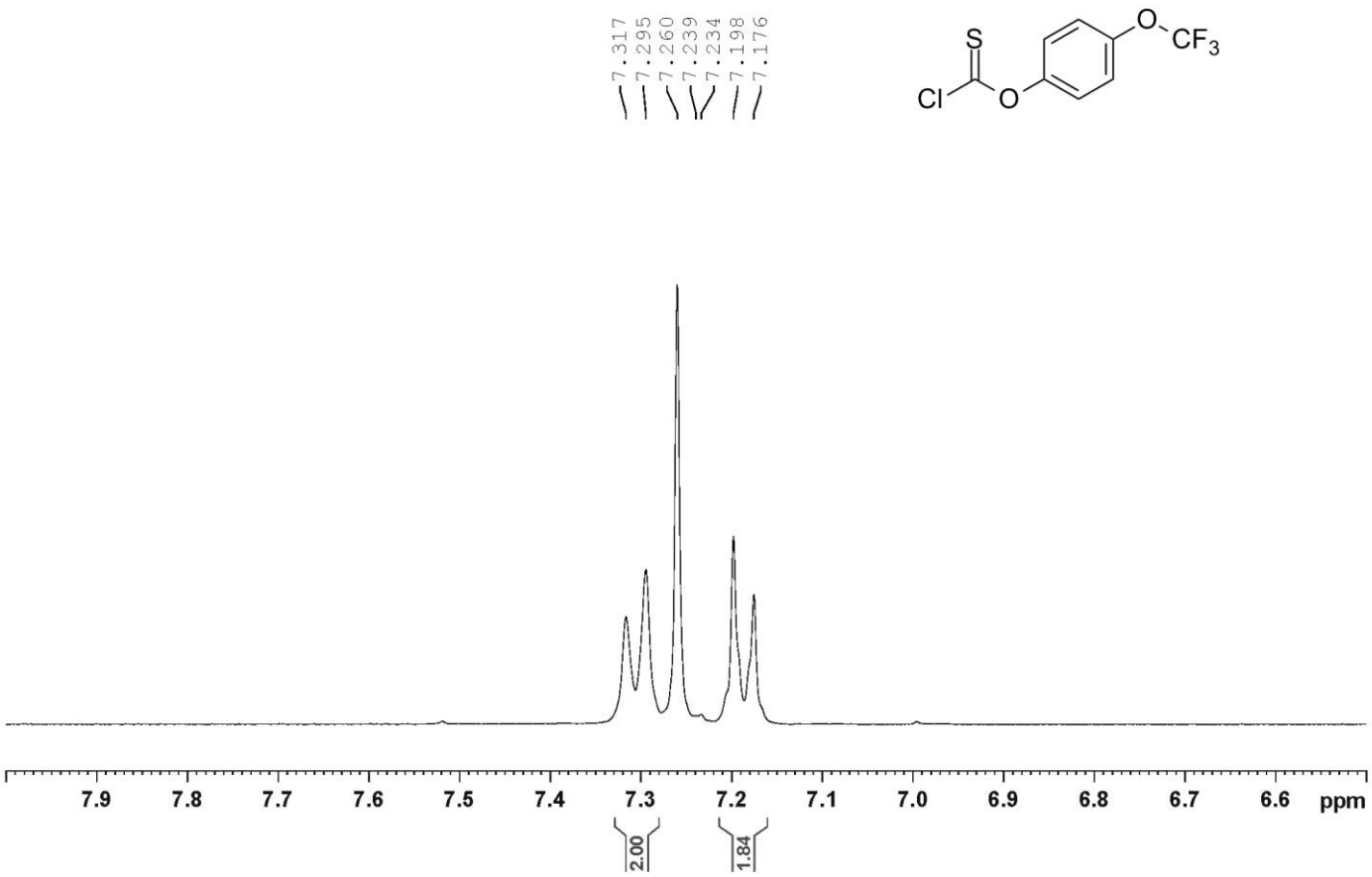
OB-NB-094-026, 1H, 400B



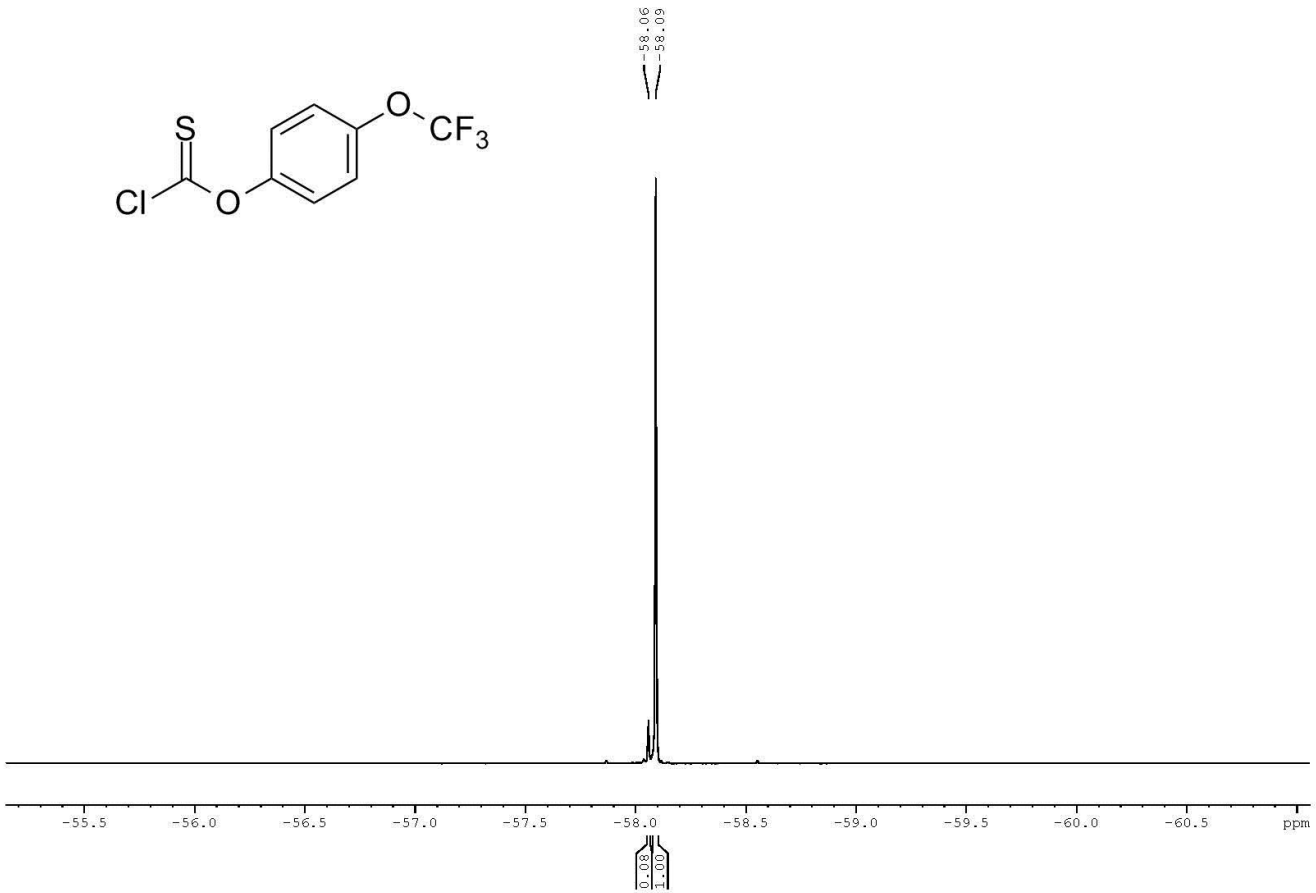
OB-NB-094-026, 19F, 400B

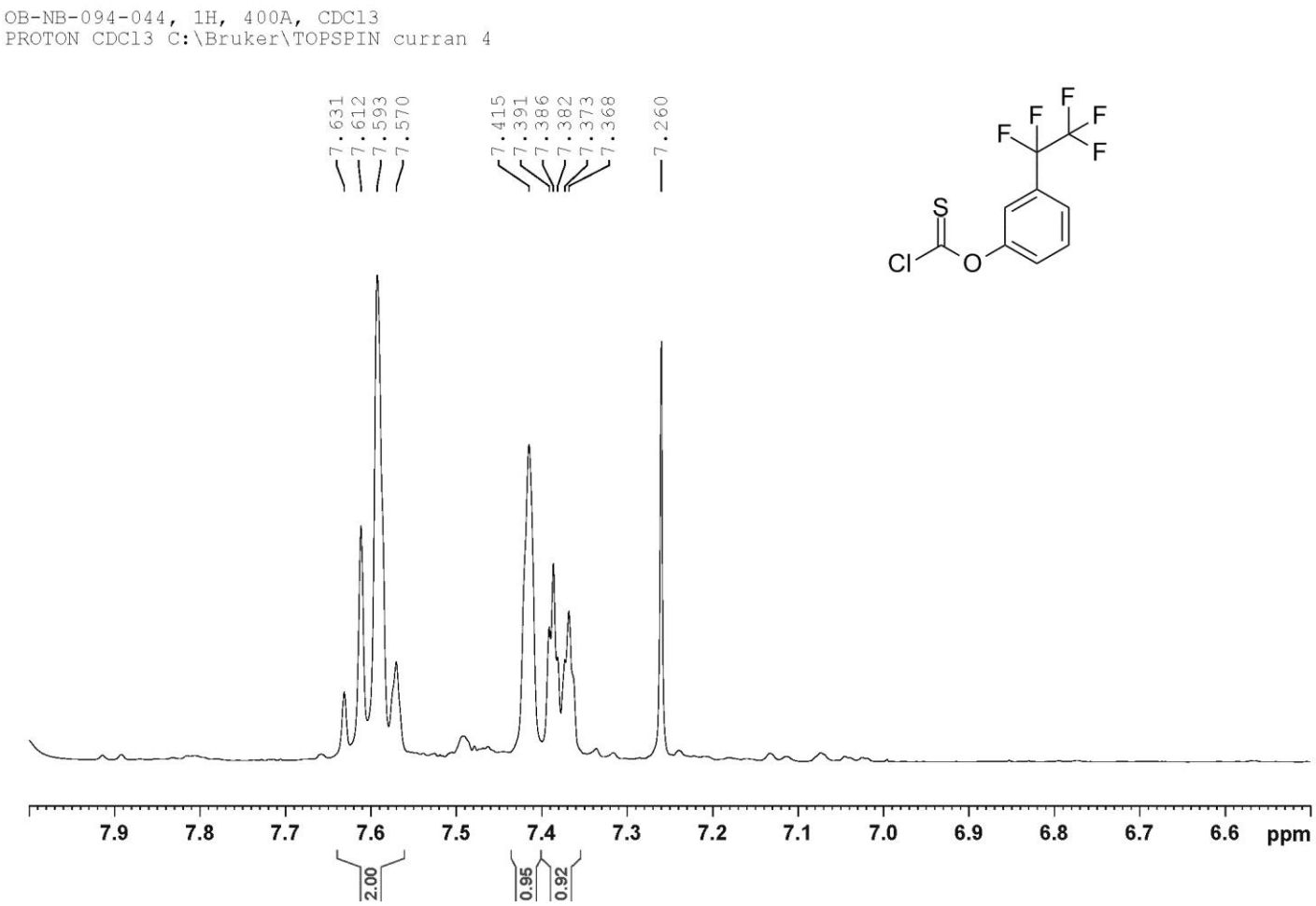


OB-NB-094-086, 1H, 400A, CDCl3

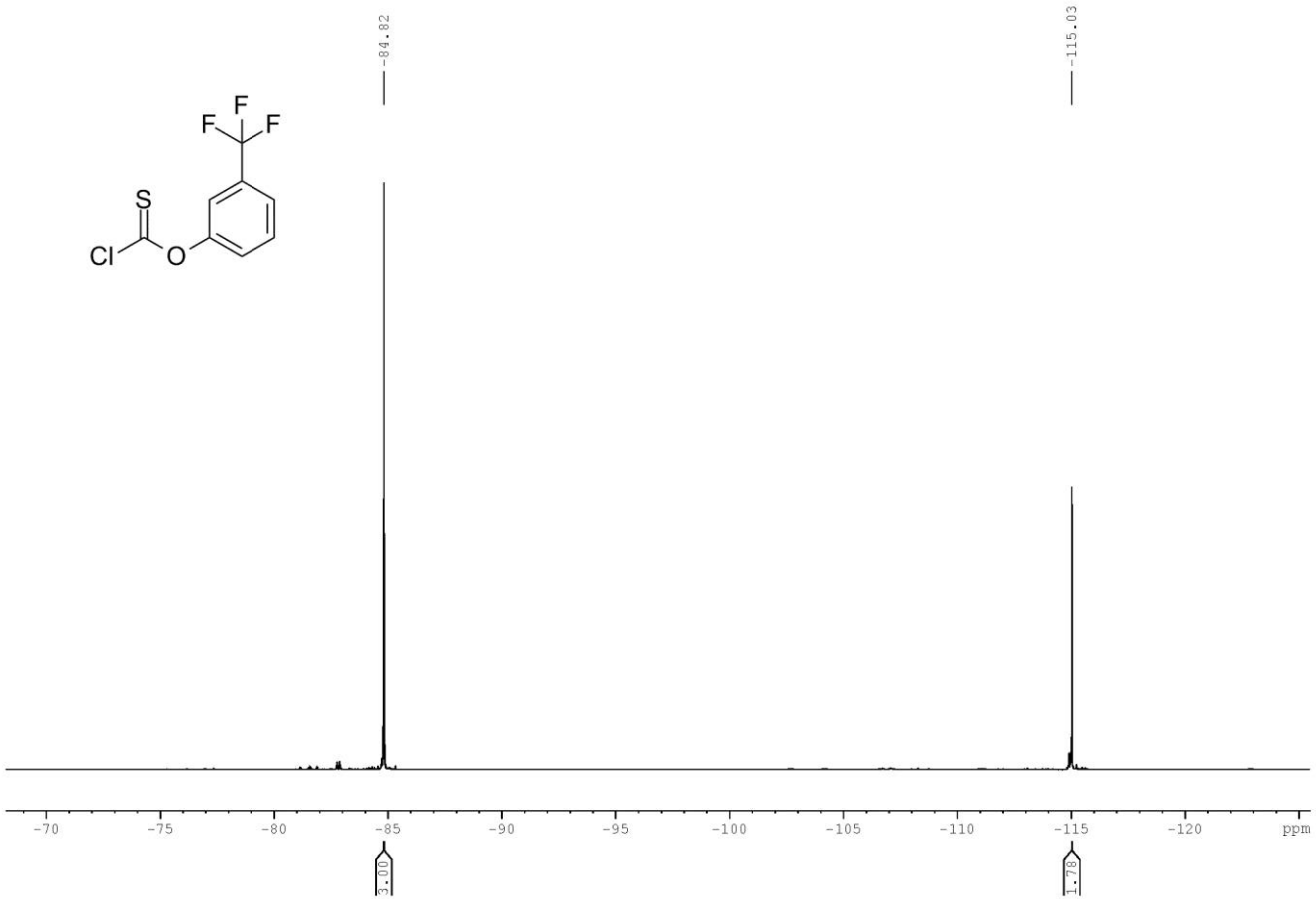


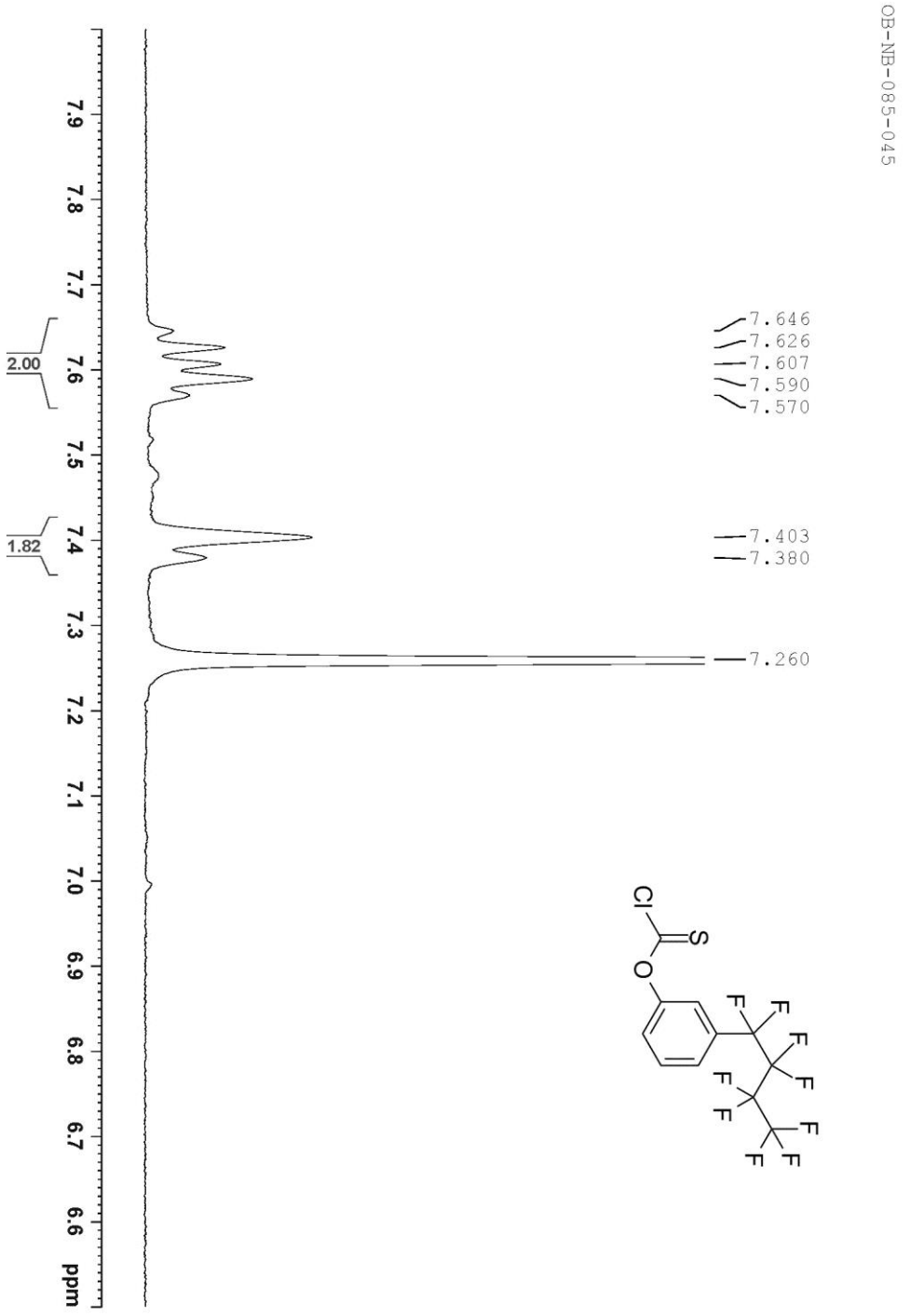
OB-NB-094-086, 19F, 400A, CDCl3

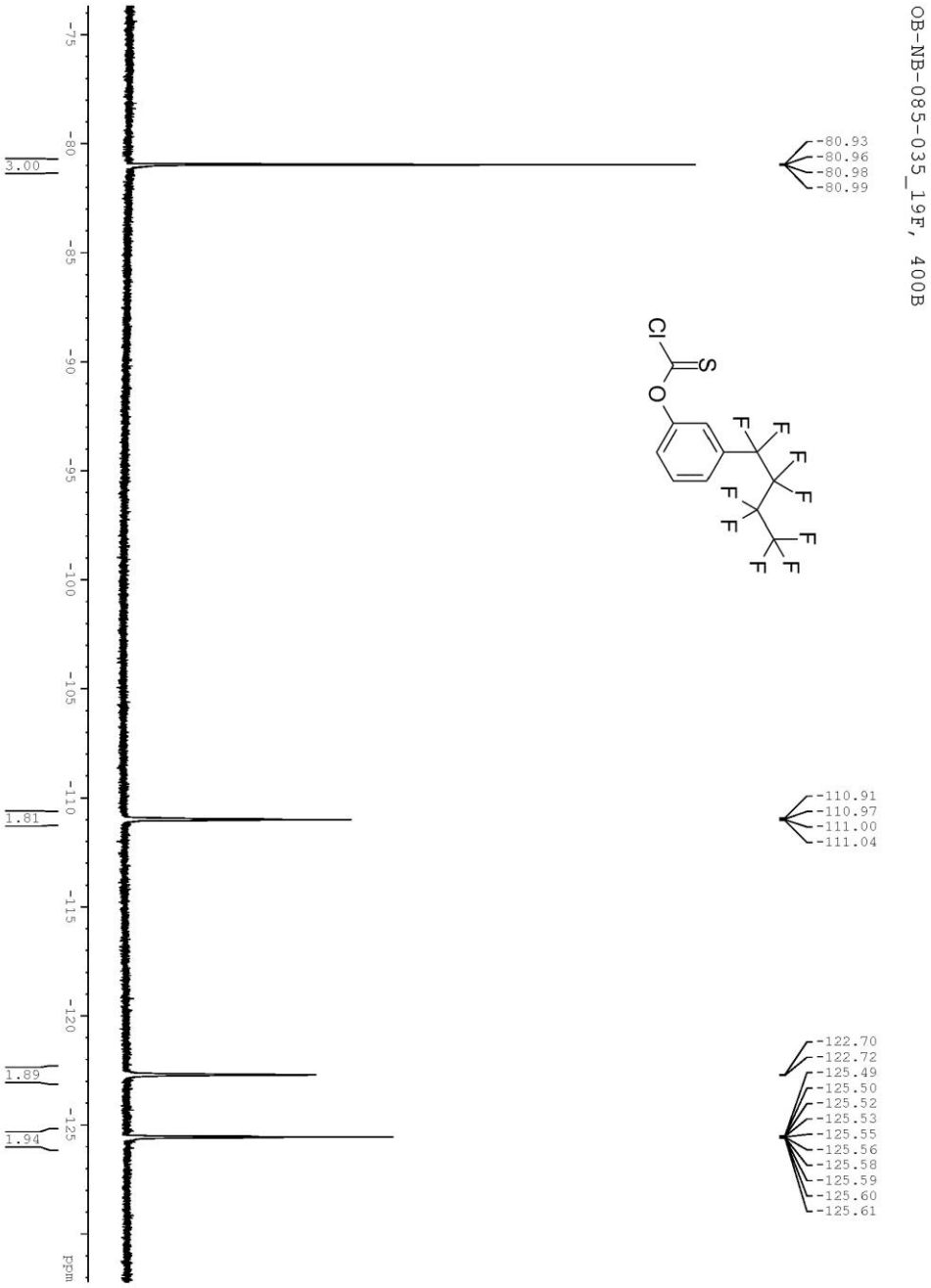



OB-NB-094-044, 1H, 400A, CDCl3
PROTON CDCl3 C:\Bruker\TOPSPIN curran 4
7.631
7.612
7.593
7.570
7.415
7.391
7.386
7.382
7.373
7.368
7.260
F
F
F
F
F
S
Cl
O
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm
2.00
0.95
0.92

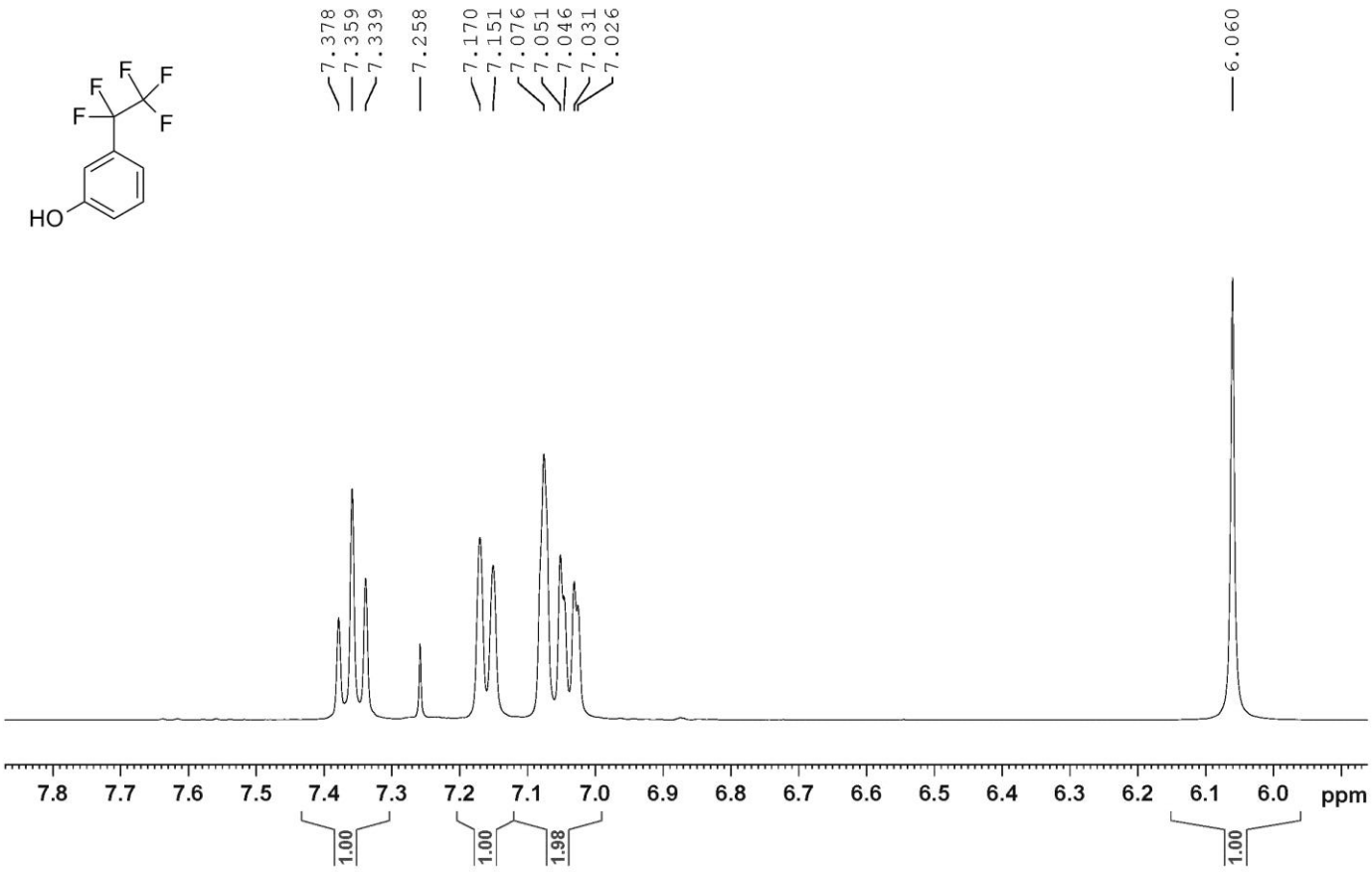
OB-NB-094-044, 19F, 400B, CDCl3

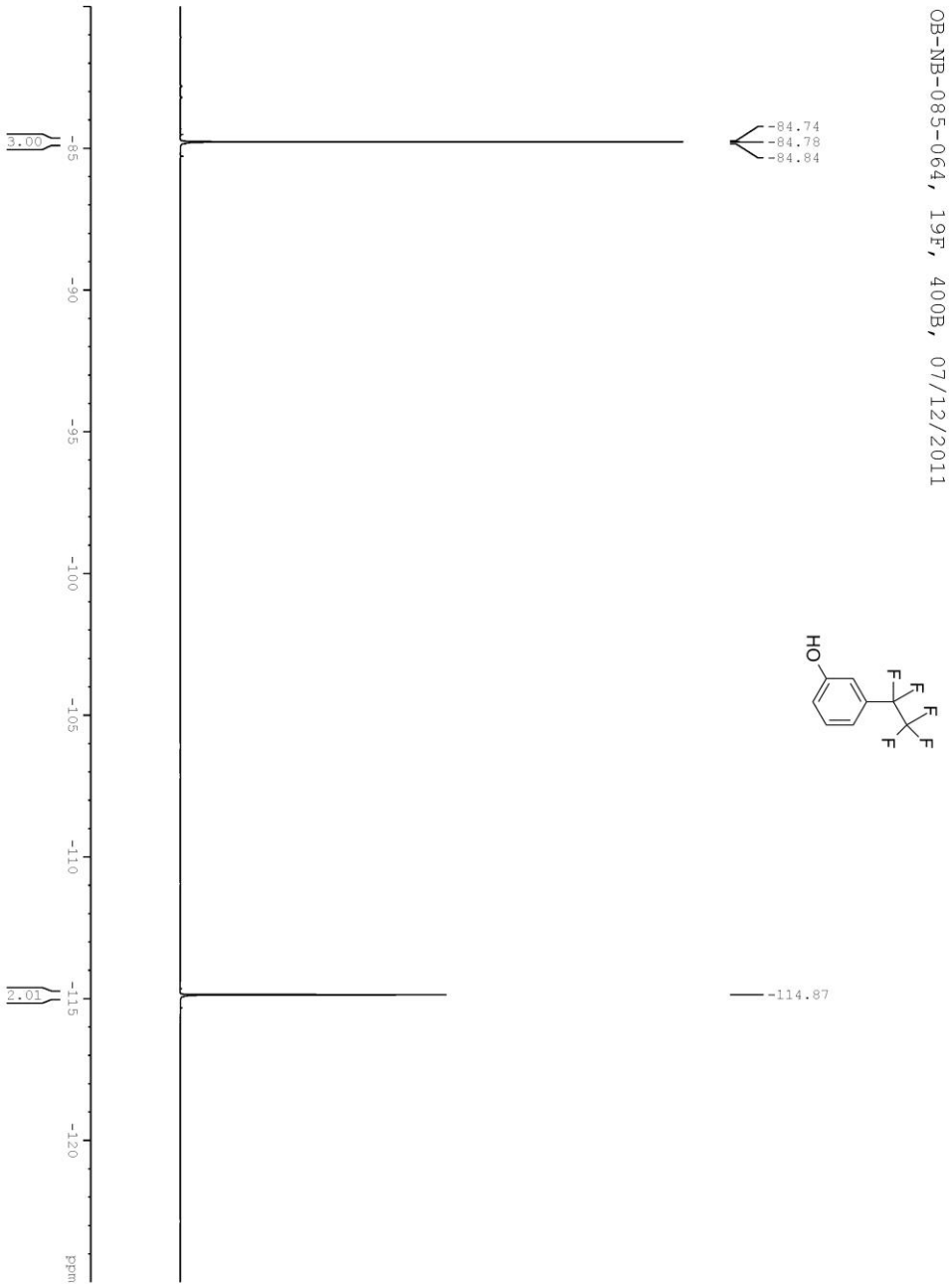


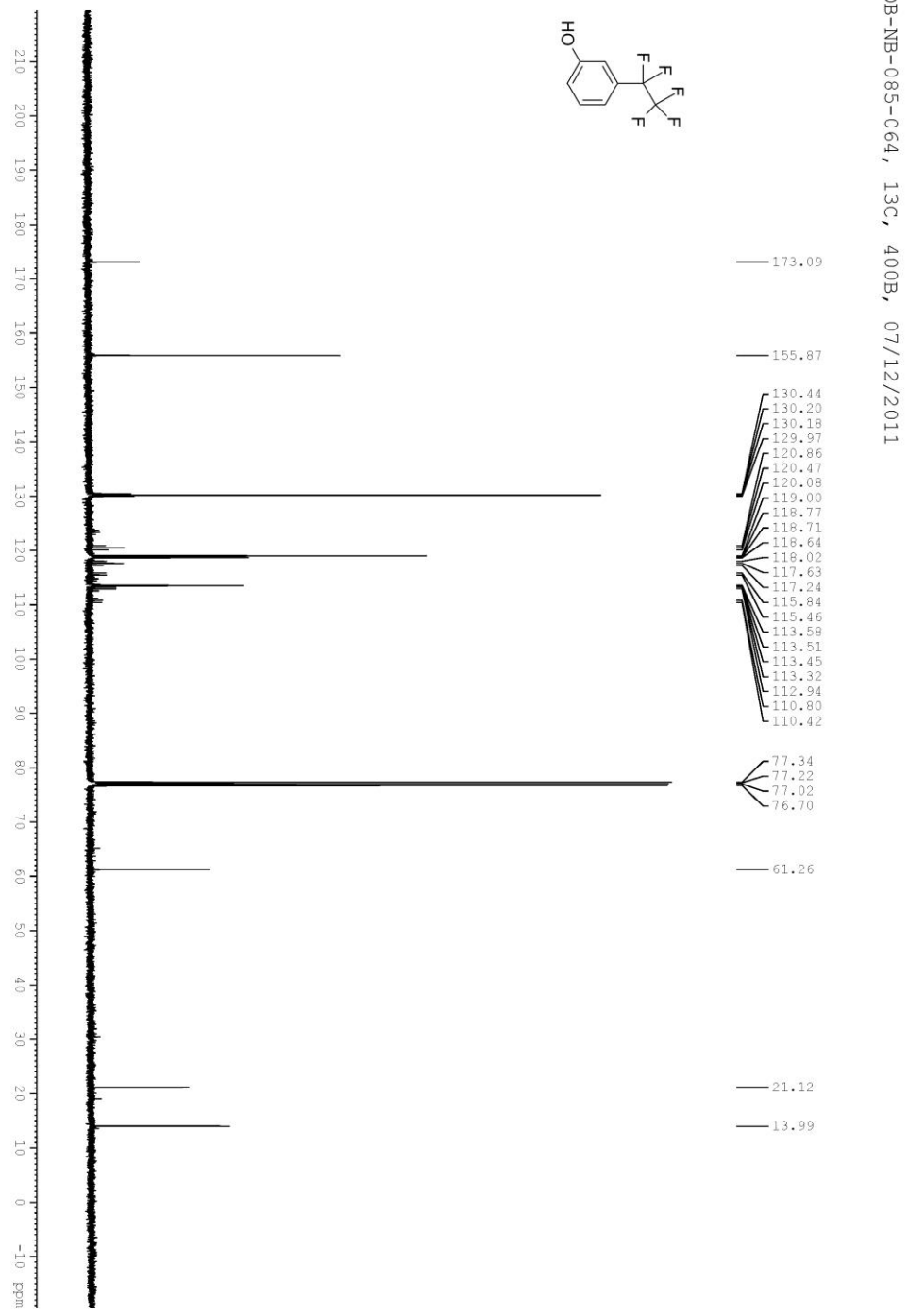

OB-NB-085-045
7.646
7.626
7.607
7.590
7.570
7.403
7.380
7.260
2.00
1.82
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm
Cl
S
O
F
F
F
F
F
F
F
F
F

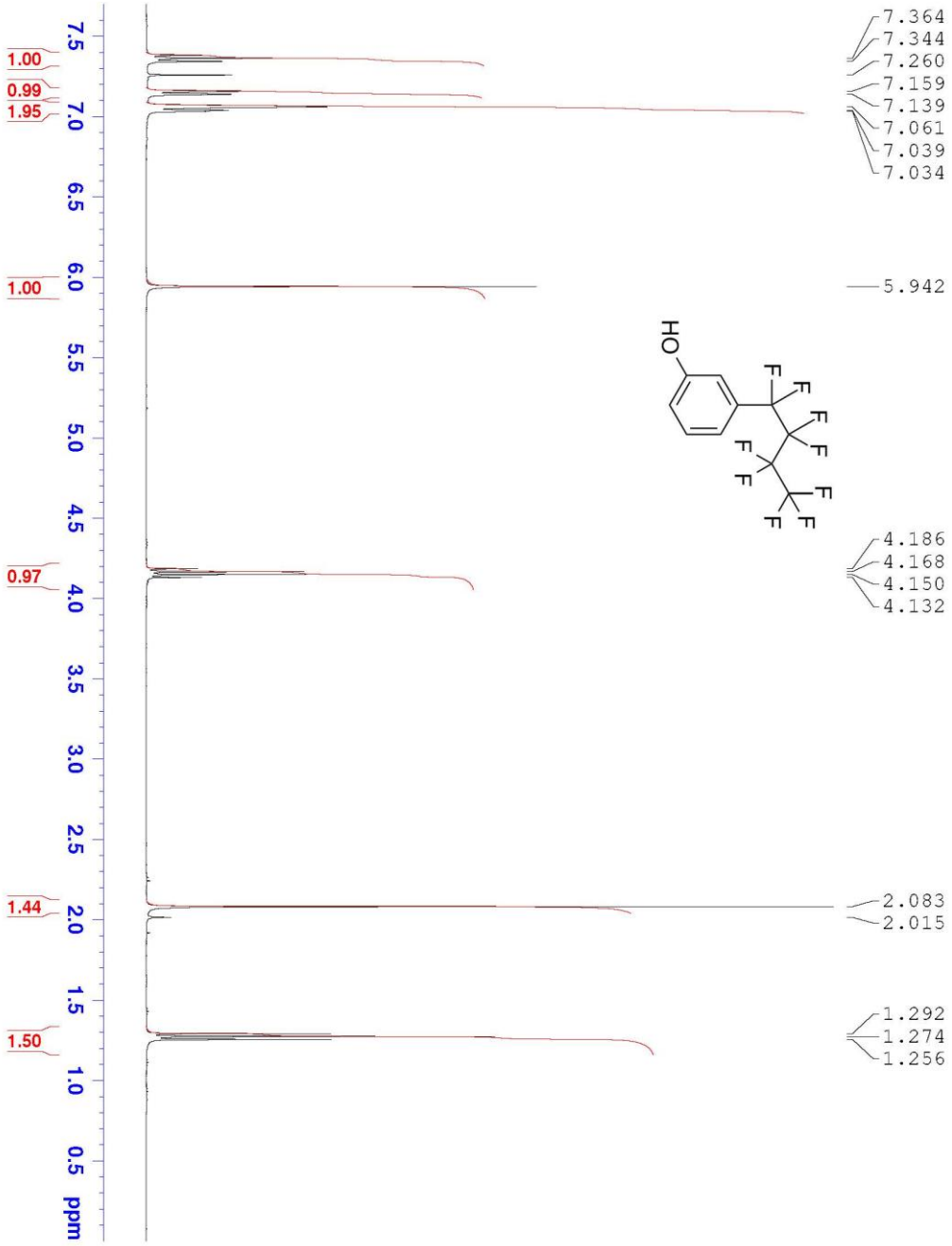

OB-NB-085-035_19F, 400B
-80.93
-80.96
-80.98
-80.99
-110.91
-110.97
-111.00
-111.04
-122.70
-122.72
-125.49
-125.50
-125.52
-125.53
-125.55
-125.56
-125.58
-125.59
-125.60
-125.61
3.00
1.81
1.89
1.94
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
ppm
Cl
S
O
F

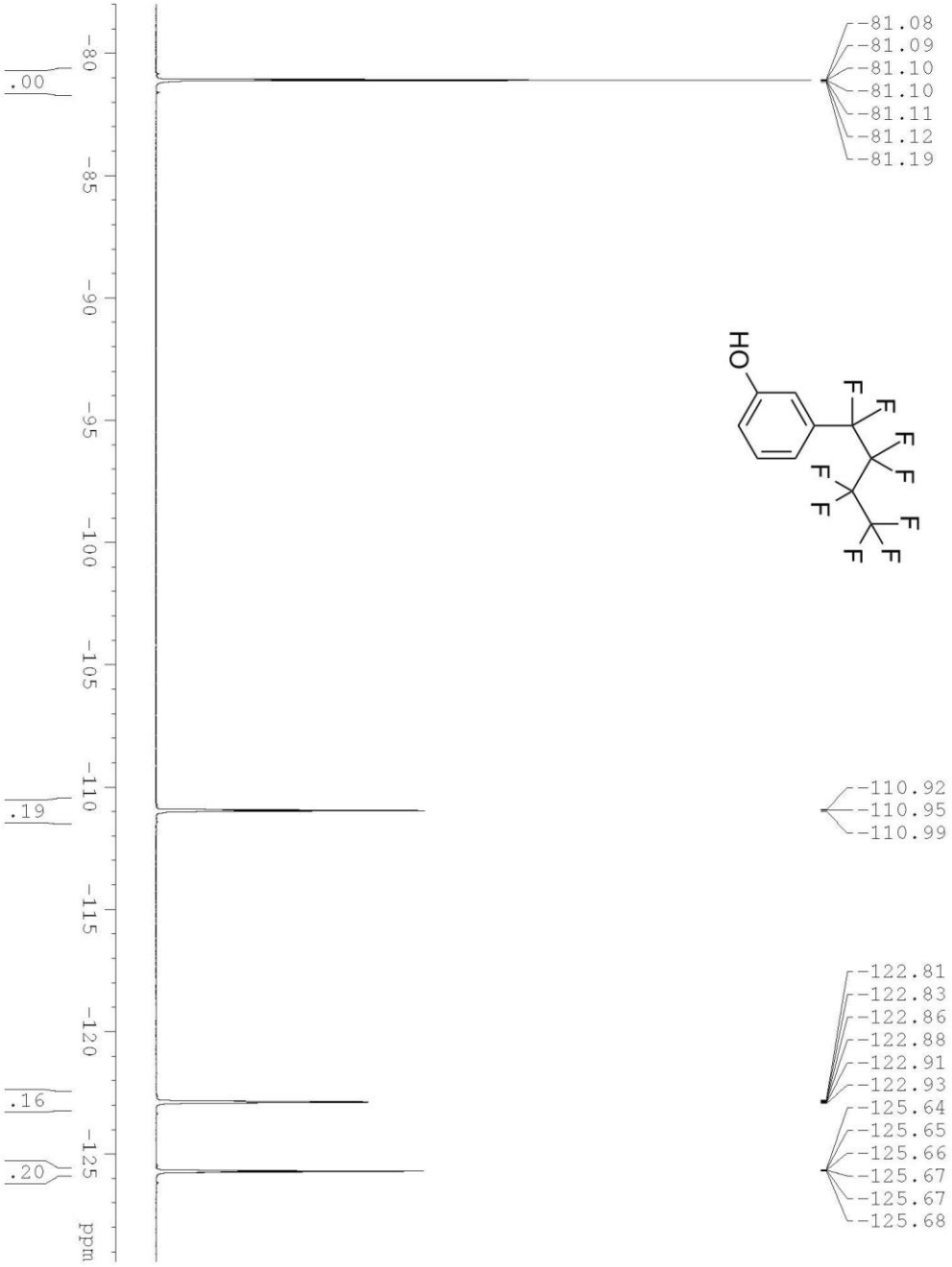
OB-NB-085-064, 1H, 400B, 07/12/2011

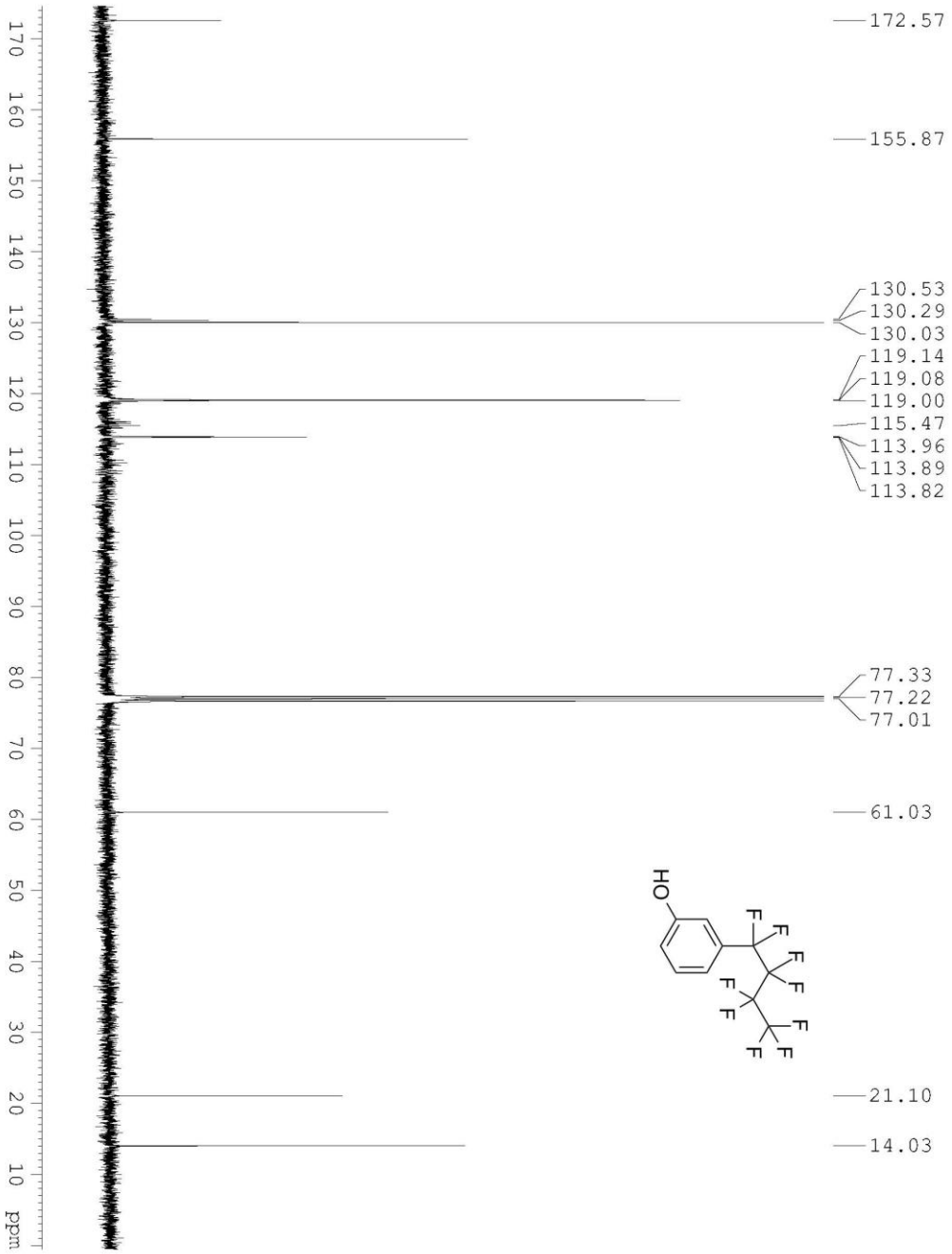


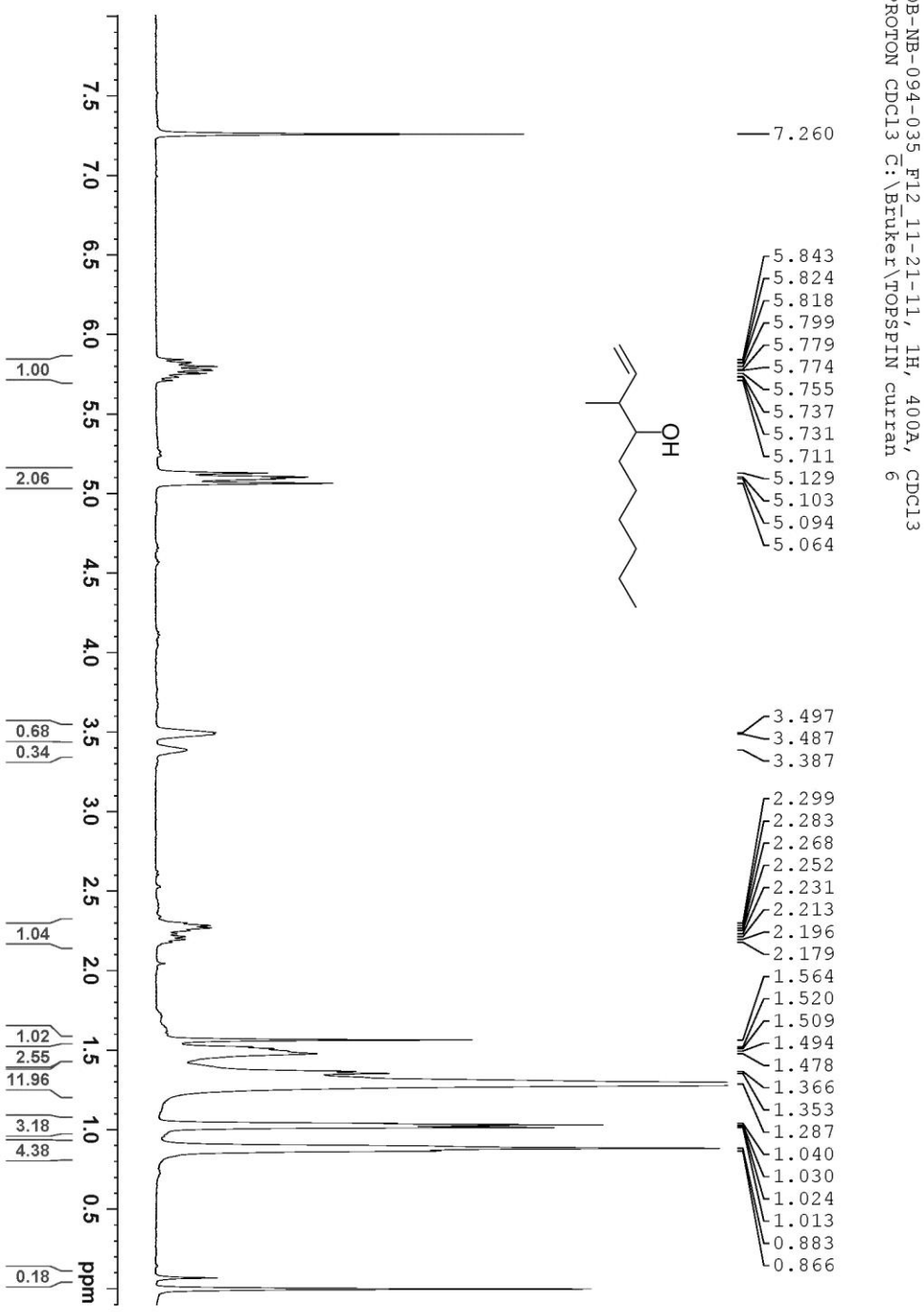

OB-NB-085-064, 19F, 400B, 07/12/2011
-84.74
-84.78
-84.84
-114.87
HO
F
F
F
F
F
3.00
2.01
-85
-90
-95
-100
-105
-110
-115
-120
ppm

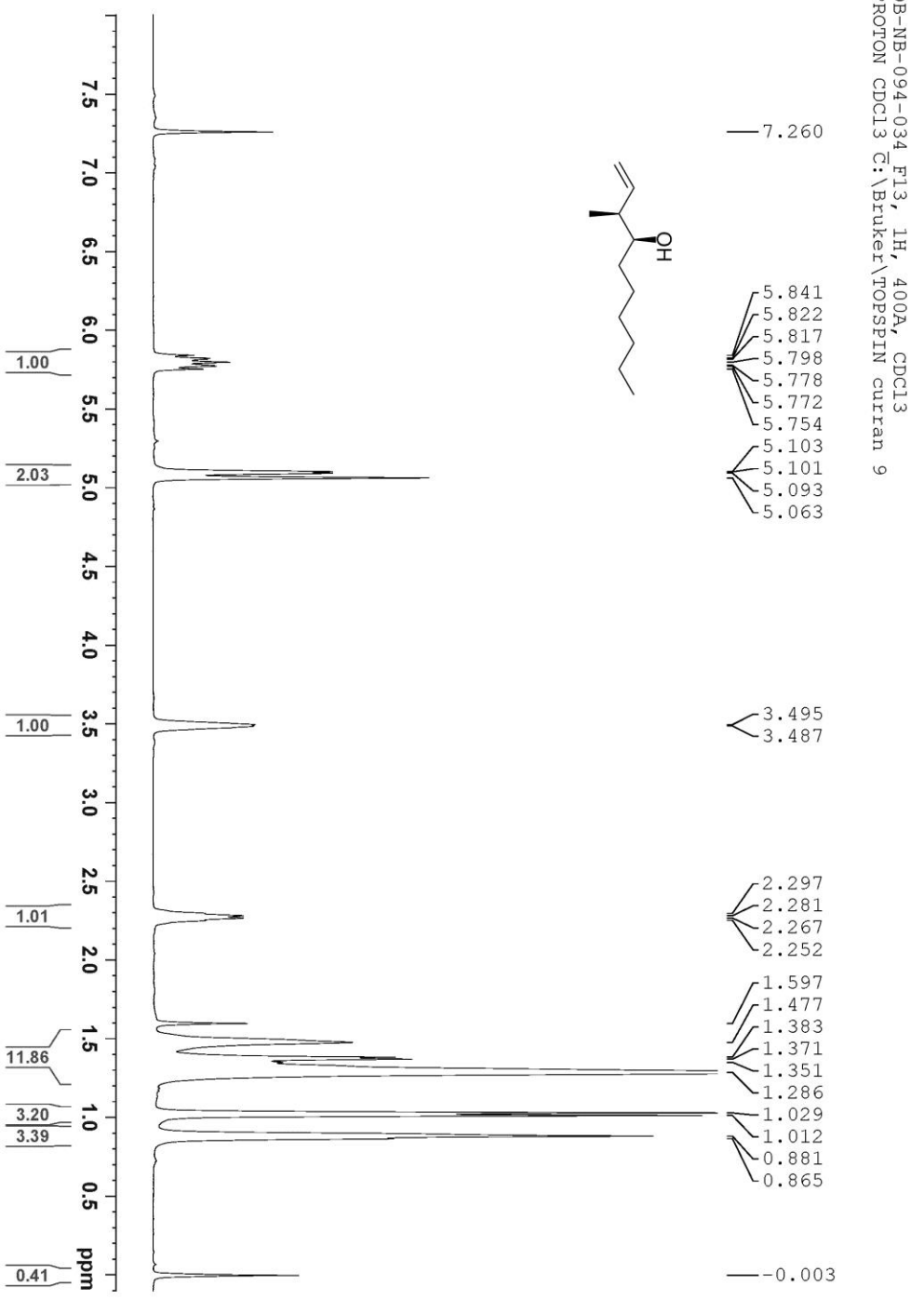

OB-NB-085-064, 13C, 400B, 07/12/2011
HO
F
F
F
F
F
173.09
155.87
130.44
130.20
130.18
129.97
120.86
120.47
120.08
119.00
118.77
118.71
118.64
118.02
117.63
117.24
115.84
115.46
113.58
113.51
113.45
113.32
112.94
110.80
110.42
77.34
77.22
77.02
76.70
61.26
21.12
13.99
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

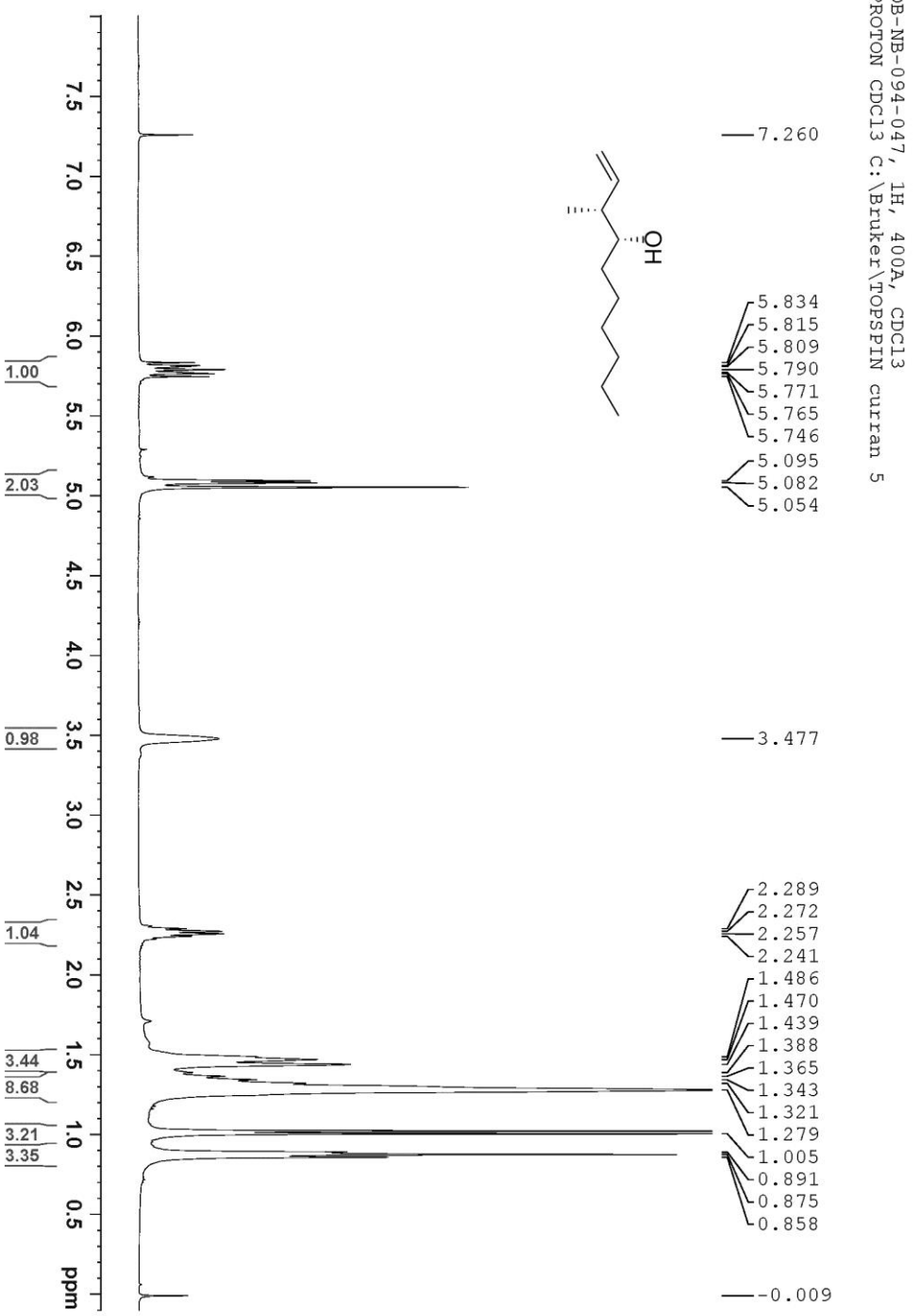

7.364
7.344
7.260
7.159
7.139
7.061
7.039
7.034
5.942
4.186
4.168
4.150
4.132
2.083
2.015
1.292
1.274
1.256
1.00
0.99
1.95
1.00
0.97
1.44
1.50
OH
F
ppm

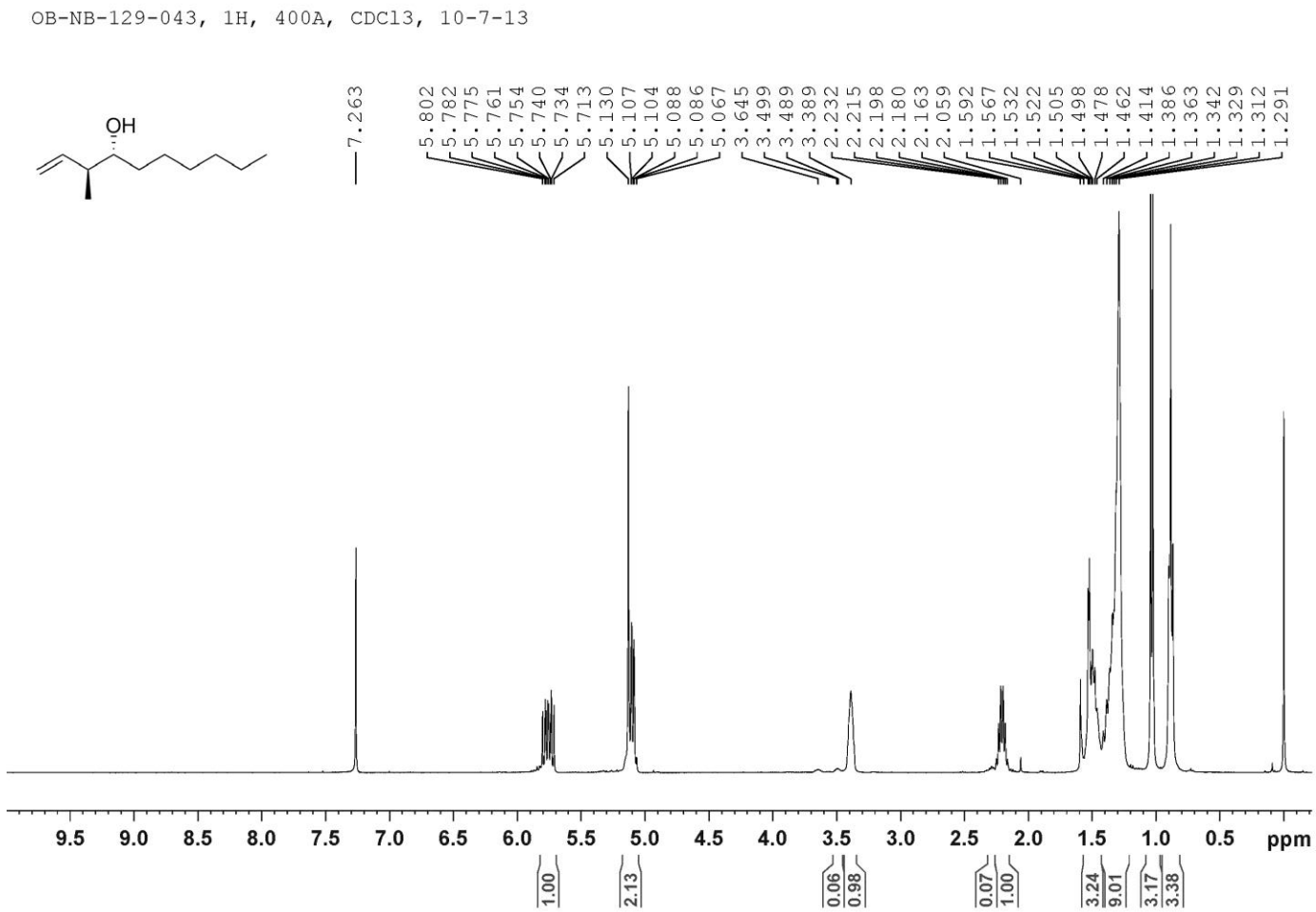

-81.08
-81.09
-81.10
-81.10
-81.11
-81.12
-81.19
-110.92
-110.95
-110.99
-122.81
-122.83
-122.86
-122.88
-122.91
-122.93
-125.64
-125.65
-125.66
-125.67
-125.67
-125.68
.00
.19
.16
.20
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
ppm
HO
F


172.57
155.87
130.53
130.29
130.03
119.14
119.08
119.00
115.47
113.96
113.89
113.82
77.33
77.22
77.01
61.03
21.10
14.03
HO
F
F
F
F
F
F
F
F
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

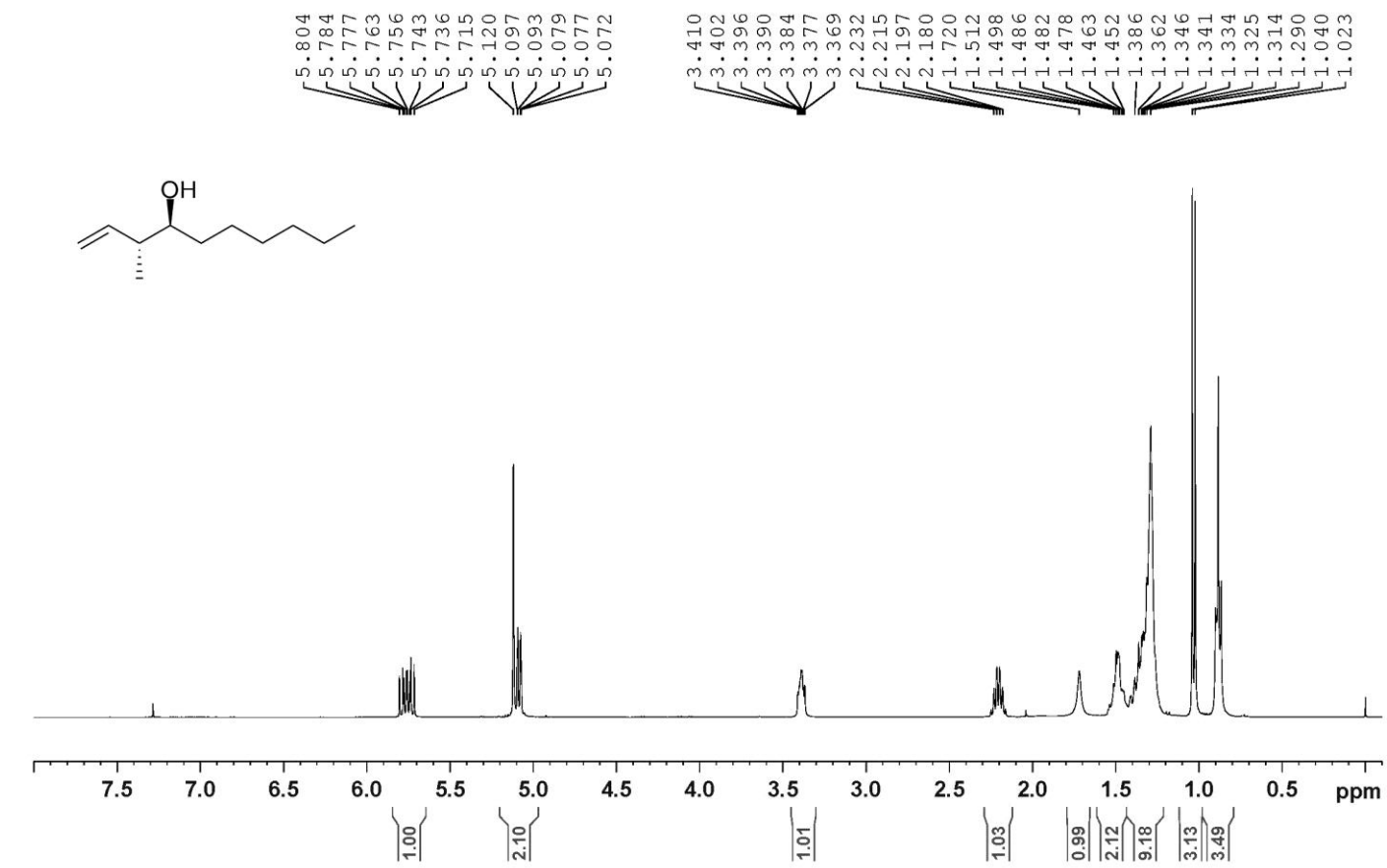

OB-NB-094-035 F12 11-21-11, 1H, 400A, CDCl3
PROTON CDCl3 C:\Bruker\TOPSPIN curran 6
7.260
5.843
5.824
5.818
5.799
5.779
5.774
5.755
5.737
5.731
5.711
5.129
5.103
5.094
5.064
3.497
3.487
3.387
2.299
2.283
2.268
2.252
2.231
2.213
2.196
2.179
1.564
1.520
1.509
1.494
1.478
1.366
1.353
1.287
1.040
1.030
1.024
1.013
0.883
0.866
OH
1.00
2.06
0.68
0.34
1.04
1.02
2.55
11.96
3.18
4.38
0.18
ppm

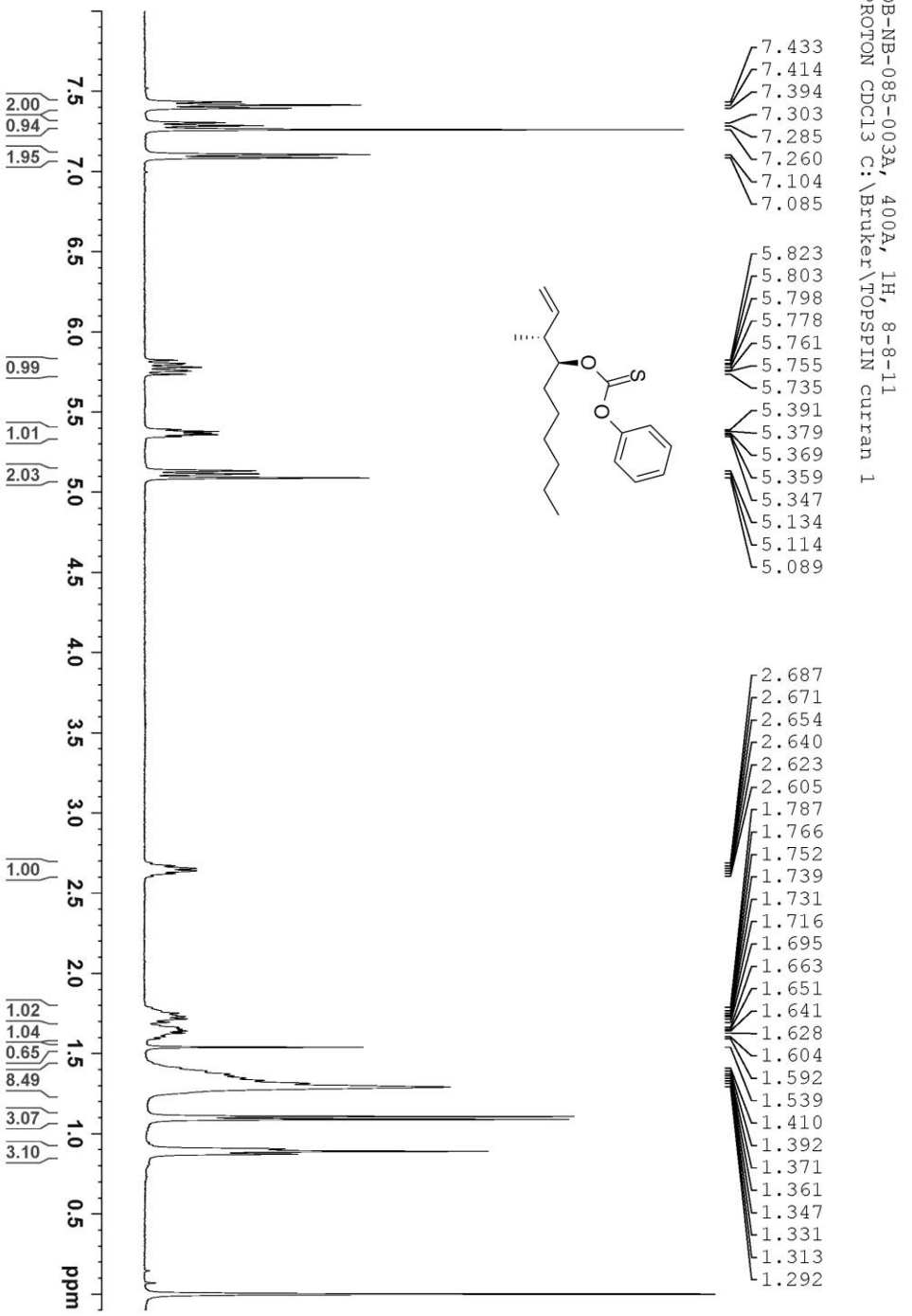

OB-NB-094-034 F13, 1H, 400A, CDCl3
PROTON CDCl3 C:\Bruker\TOPSPIN curran 9
7.260
5.841
5.822
5.817
5.798
5.778
5.772
5.754
5.103
5.101
5.093
5.063
3.495
3.487
2.297
2.281
2.267
2.252
1.597
1.477
1.383
1.371
1.351
1.286
1.029
1.012
0.881
0.865
-0.003
OH
1.00
2.03
1.00
1.01
11.86
3.20
3.39
0.41
ppm

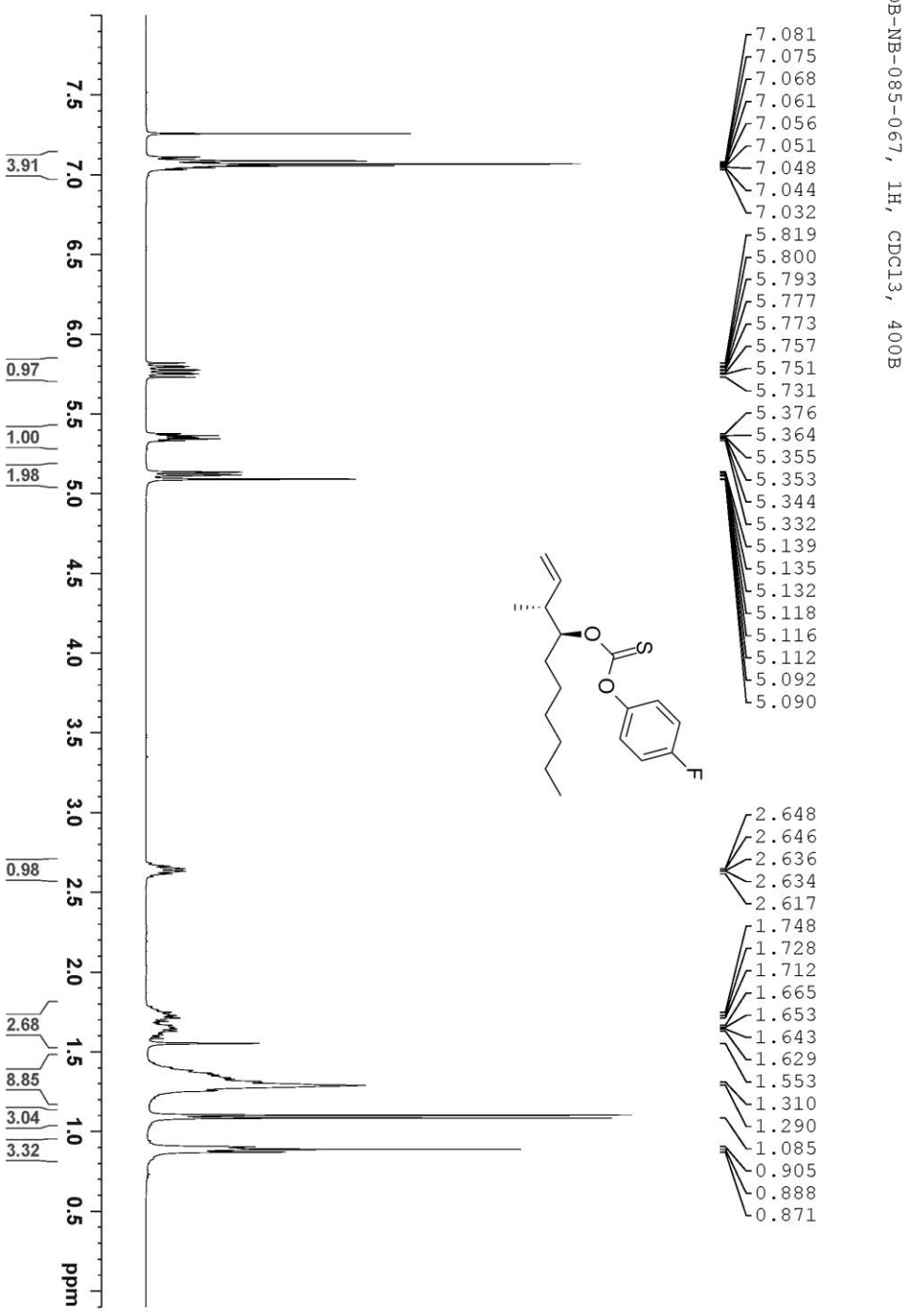

OB-NB-094-047, 1H, 400A, CDC13
PROTON CDC13 C:\Bruker\TOPSPIN curran 5
OH
7.260
5.834
5.815
5.809
5.790
5.771
5.765
5.746
5.095
5.082
5.054
3.477
2.289
2.272
2.257
2.241
1.486
1.470
1.439
1.388
1.365
1.343
1.321
1.279
1.005
0.891
0.875
0.858
-0.009
1.00
2.03
0.98
1.04
3.44
8.68
3.21
3.35
ppm


OB-NB-129-043, 1H, 400A, CDCl3, 10-7-13
OH
7.263
5.802
5.782
5.775
5.761
5.754
5.740
5.734
5.713
5.130
5.107
5.104
5.088
5.086
5.067
3.645
3.499
3.489
3.389
2.232
2.215
2.198
2.180
2.163
2.059
1.592
1.567
1.532
1.522
1.505
1.498
1.478
1.462
1.414
1.386
1.363
1.342
1.329
1.312
1.291
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 ppm
1.00
2.13
0.06
0.98
0.07
1.00
3.24
9.01
3.17
3.38

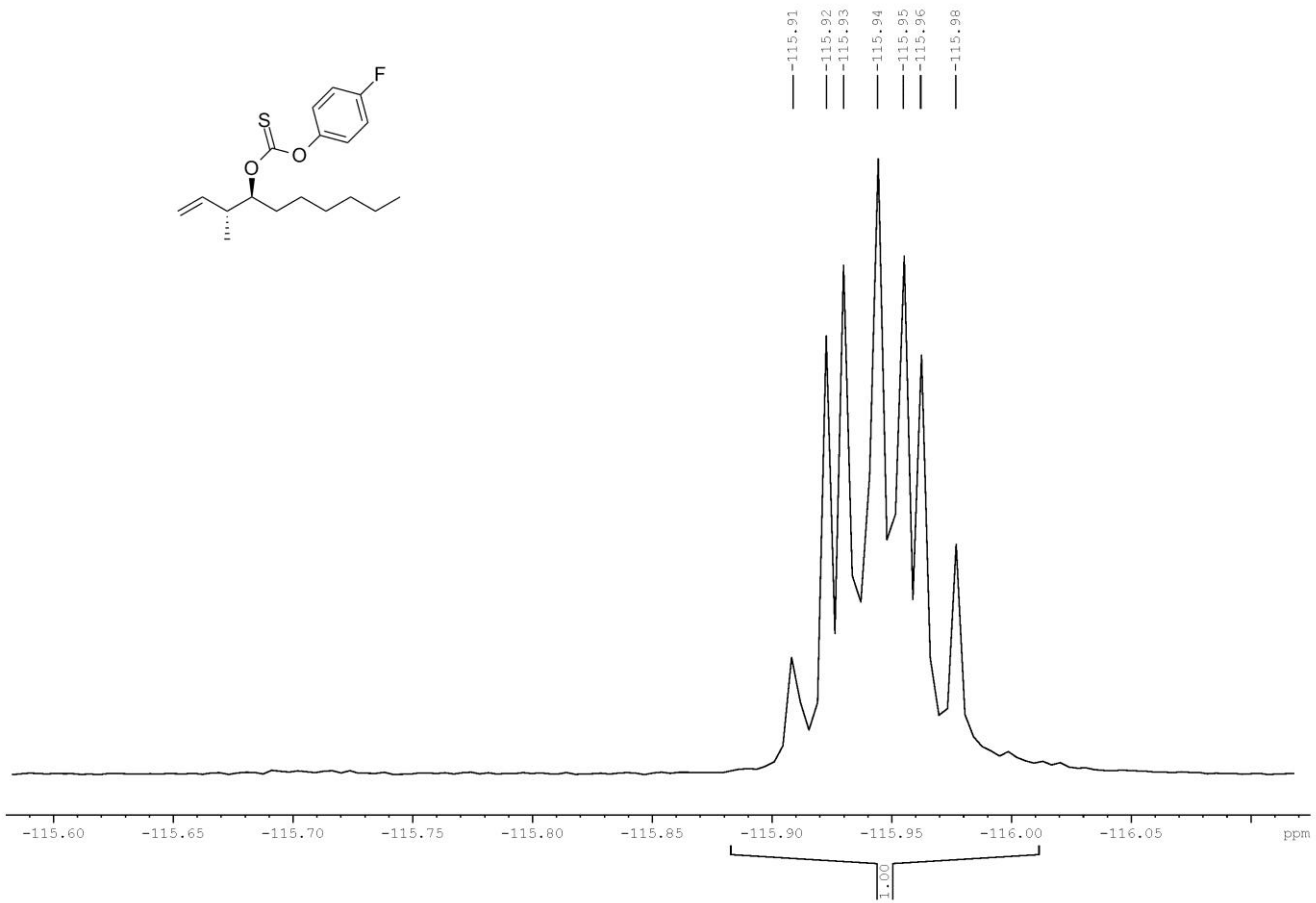
OB-NB-08-079, 1H, CDCl3, 400B

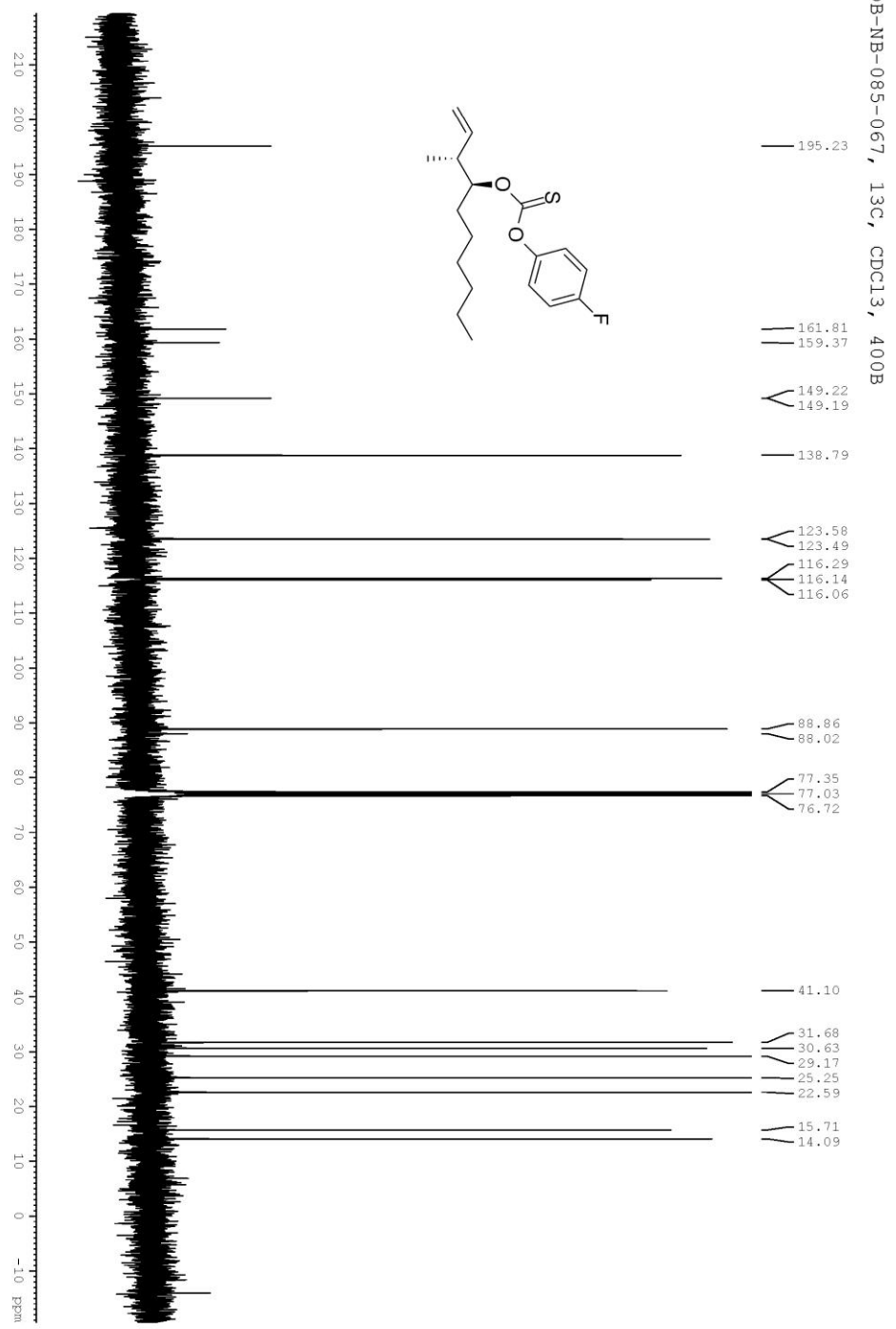



OB-NB-085-003A, 400A, 1H, 8-8-11
PROTON CDCl3 C:\Bruker\TOPSPIN curran 1
7.433
7.414
7.394
7.303
7.285
7.260
7.104
7.085
5.823
5.803
5.798
5.778
5.761
5.755
5.735
5.391
5.379
5.369
5.359
5.347
5.134
5.114
5.089
2.687
2.671
2.654
2.640
2.623
2.605
1.787
1.766
1.752
1.739
1.731
1.716
1.695
1.663
1.651
1.641
1.628
1.604
1.592
1.539
1.410
1.392
1.371
1.361
1.347
1.331
1.313
1.292
2.00
0.94
1.95
0.99
1.01
2.03
1.00
1.02
1.04
0.65
8.49
3.07
3.10
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
ppm

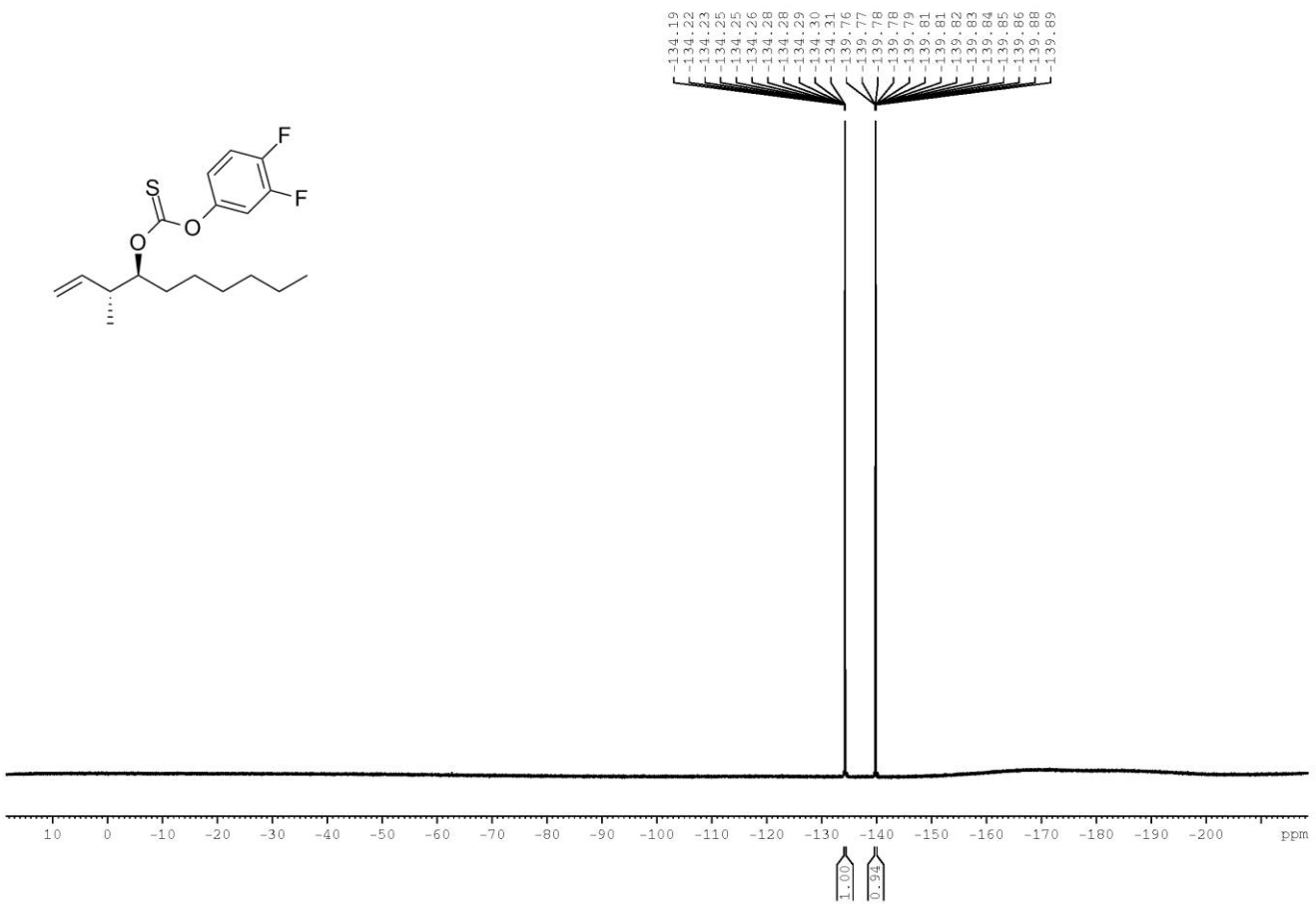

OB-NB-085-067, 1H, CDCl3, 400B
7.081
7.075
7.068
7.061
7.056
7.051
7.048
7.044
7.032
5.819
5.800
5.793
5.777
5.773
5.757
5.751
5.731
5.376
5.364
5.355
5.353
5.344
5.332
5.139
5.135
5.132
5.118
5.116
5.112
5.092
5.090
2.648
2.646
2.636
2.634
2.617
1.748
1.728
1.712
1.665
1.653
1.643
1.629
1.553
1.310
1.290
1.085
0.905
0.888
0.871
3.91
0.97
1.00
1.98
0.98
2.68
8.85
3.04
3.32
ppm
O
S
O
F

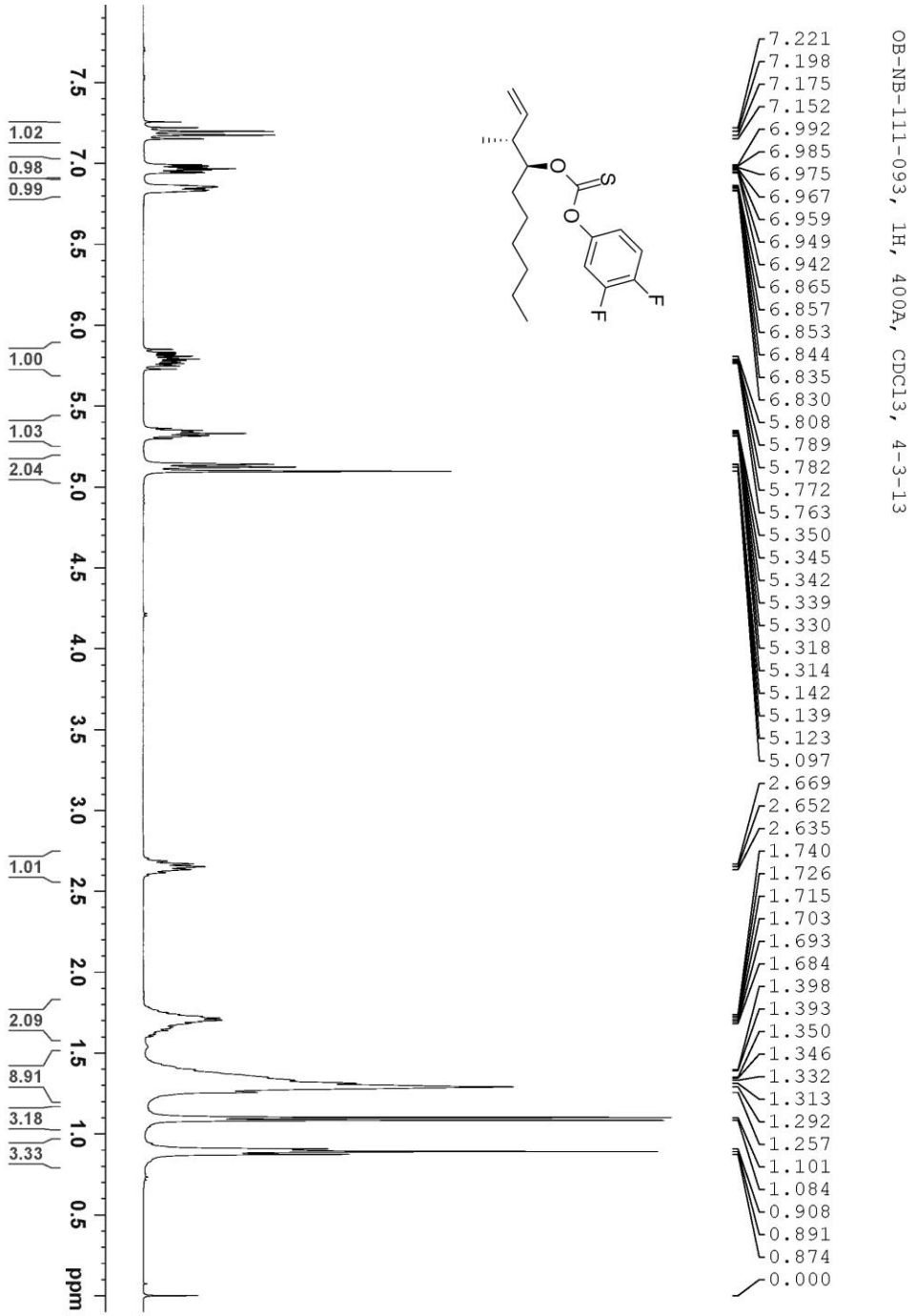
OB-NB-085-067, 19F, CDCl3, 400B



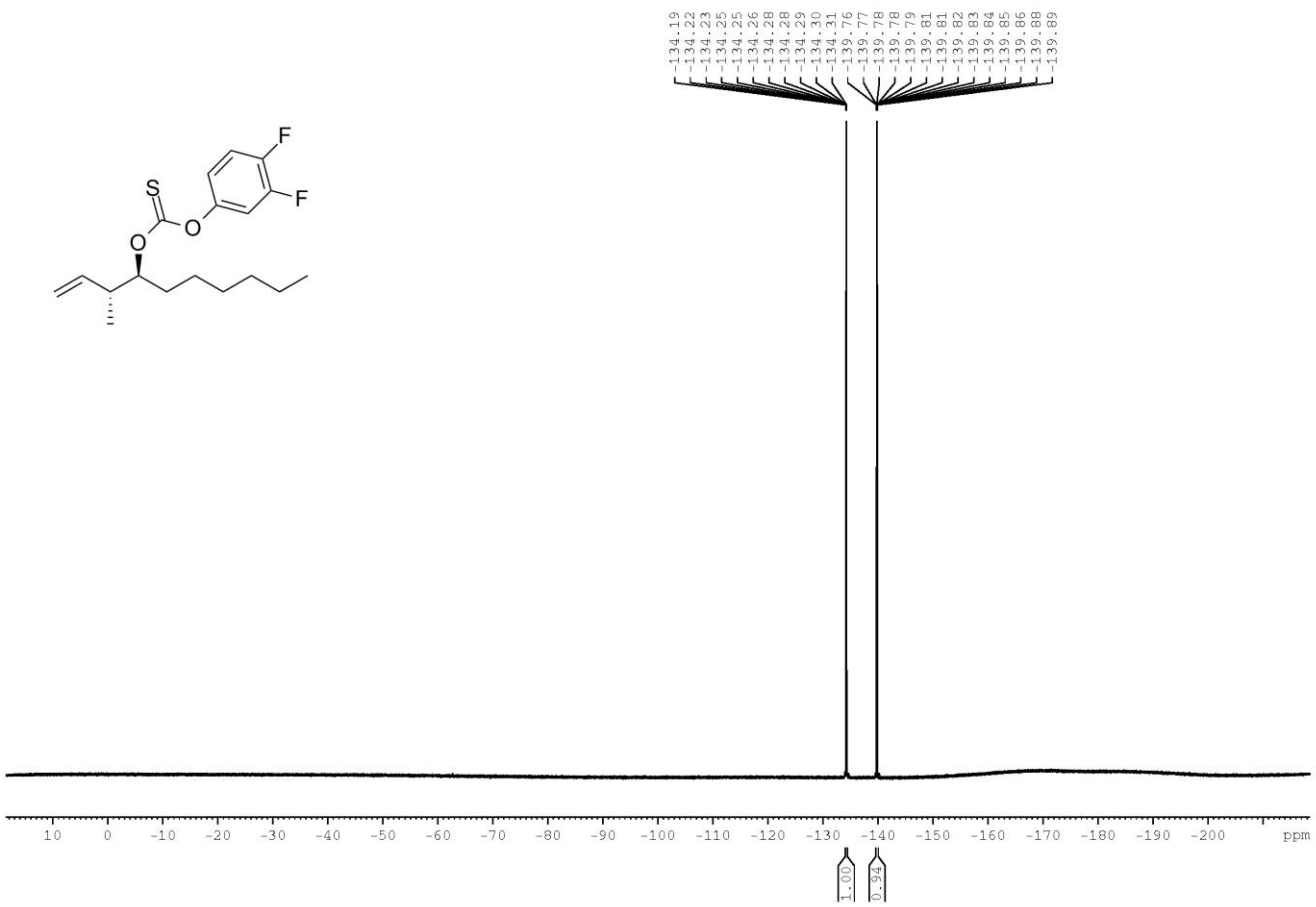

OB-NB-085-067, 13C, CDC13, 400B
195.23
161.81
159.37
149.22
149.19
138.79
123.58
123.49
116.29
116.14
116.06
88.86
88.02
77.35
77.03
76.72
41.10
31.68
30.63
29.17
25.25
22.59
15.71
14.09
O
S
O
F
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

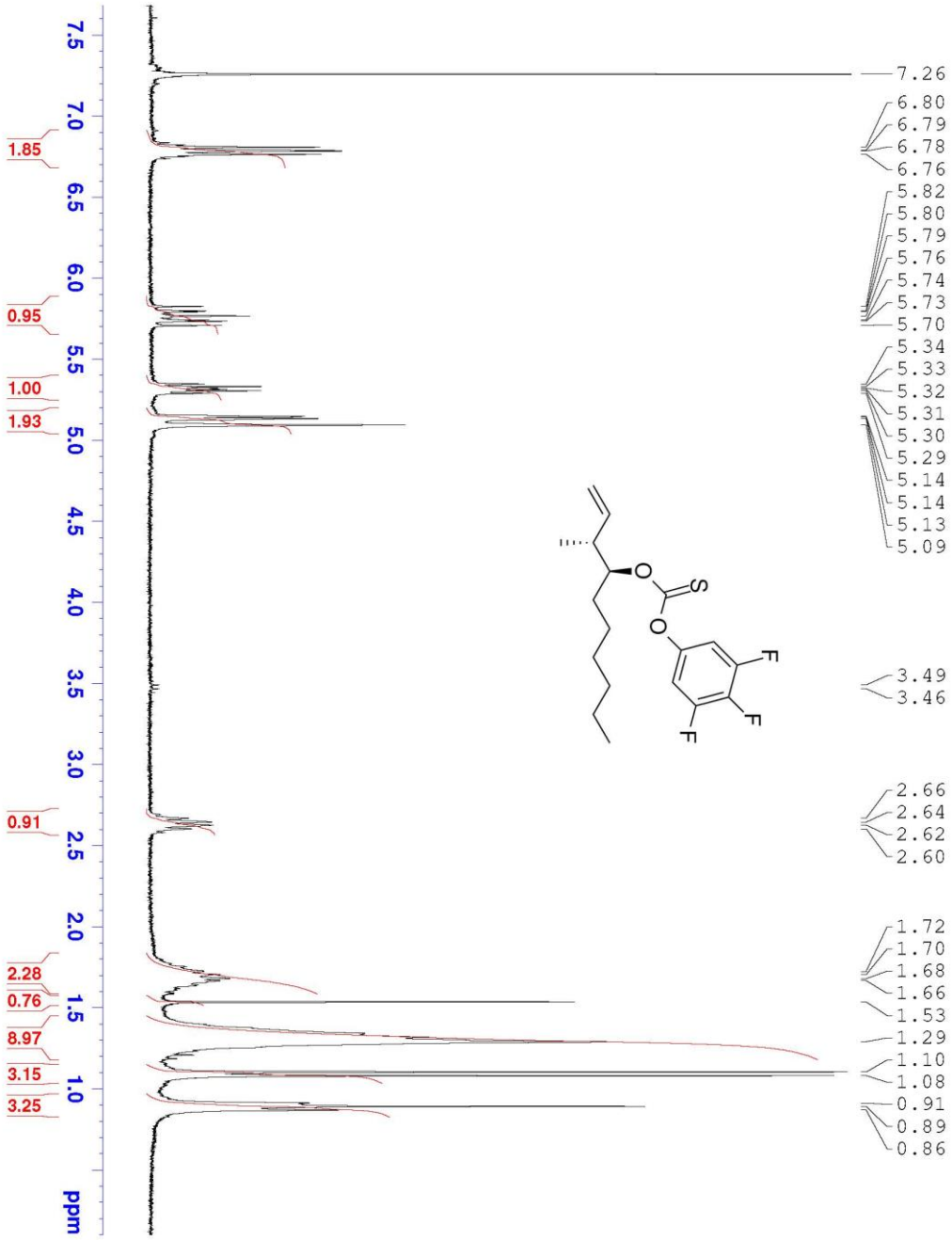
OB-NB-111-093, 19F, 400A, CDCl3, 4-3-13

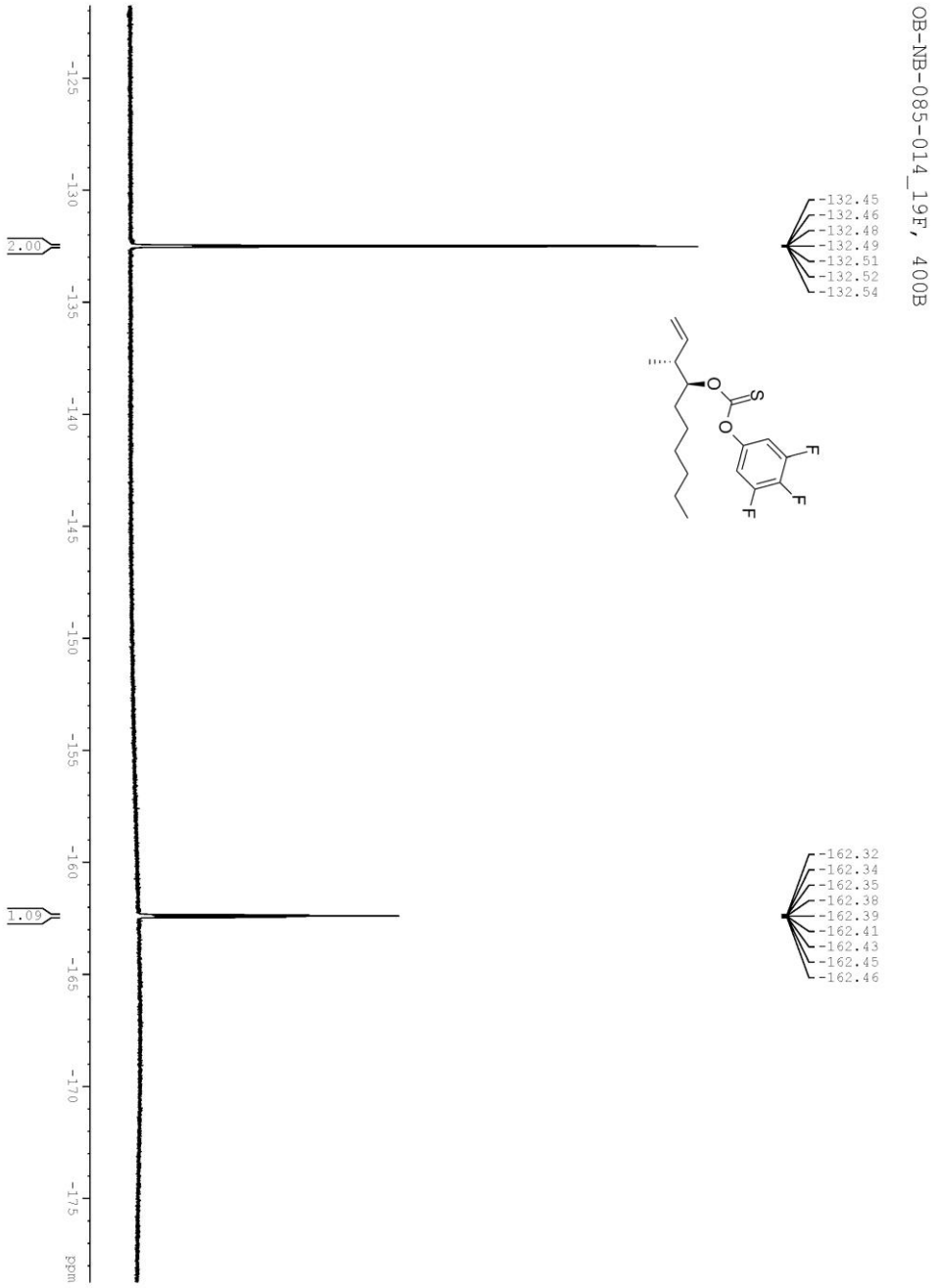


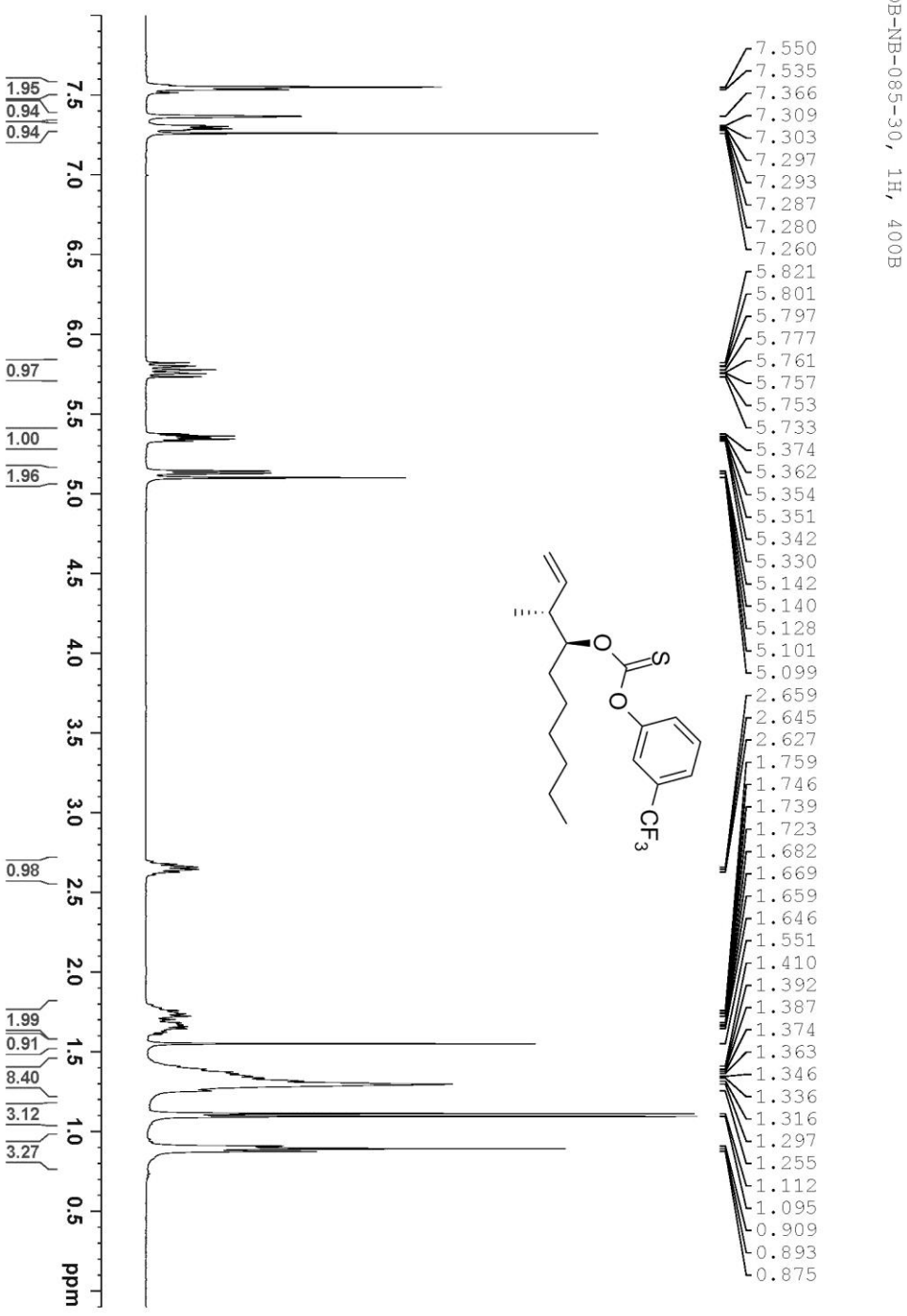

OB-NB-111-093, 1H, 400A, CDCl3, 4-3-13
7.221
7.198
7.175
7.152
6.992
6.985
6.975
6.967
6.959
6.949
6.942
6.865
6.857
6.853
6.844
6.835
6.830
5.808
5.789
5.782
5.772
5.763
5.350
5.345
5.342
5.339
5.330
5.318
5.314
5.142
5.139
5.123
5.097
2.669
2.652
2.635
1.740
1.726
1.715
1.703
1.693
1.684
1.398
1.393
1.350
1.346
1.332
1.313
1.292
1.257
1.101
1.084
0.908
0.891
0.874
0.000
1.02
0.98
0.99
1.00
1.03
2.04
1.01
2.09
8.91
3.18
3.33
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
ppm
O
S
O
F
F

OB-NB-111-093, 19F, 400A, CDCl3, 4-3-13

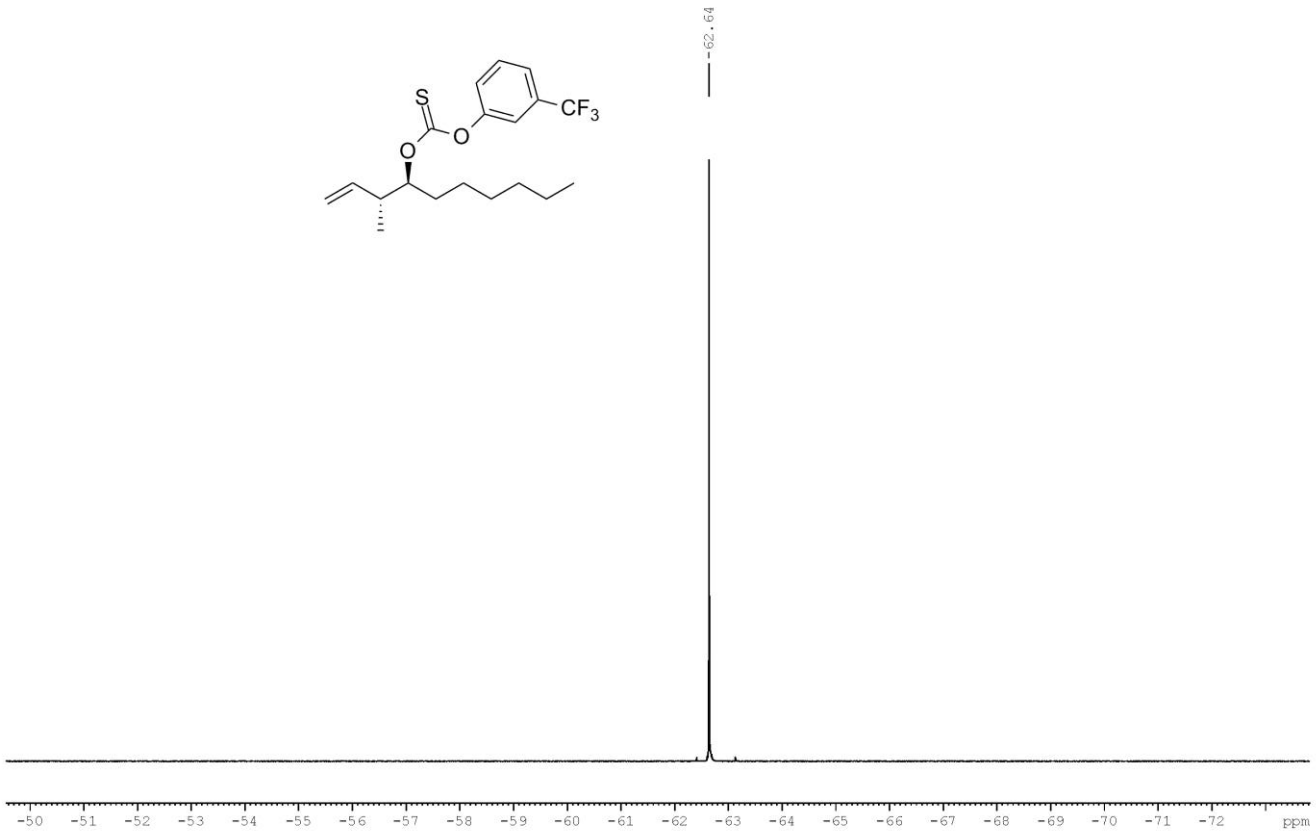


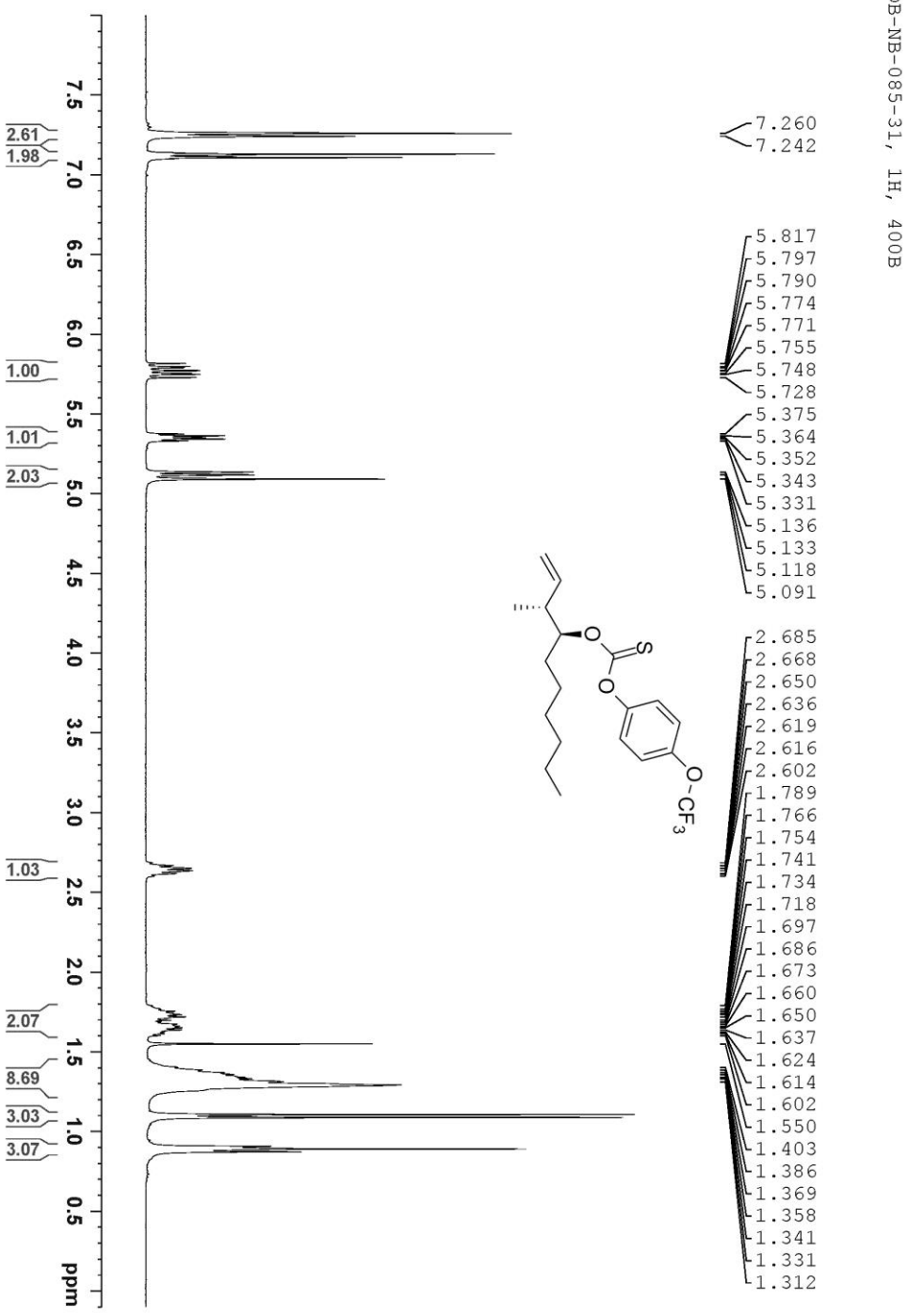

7.26
6.80
6.79
6.78
6.76
5.82
5.80
5.79
5.76
5.74
5.73
5.70
5.34
5.33
5.32
5.31
5.30
5.29
5.14
5.14
5.13
5.09
3.49
3.46
2.66
2.64
2.62
2.60
1.72
1.70
1.68
1.66
1.53
1.29
1.10
1.08
0.91
0.89
0.86
1.85
0.95
1.00
1.93
0.91
2.28
0.76
8.97
3.15
3.25
ppm
O
S
O
F
F
F


OB-NB-085-014_19F, 400B
-132.45
-132.46
-132.48
-132.49
-132.51
-132.52
-132.54
-162.32
-162.34
-162.35
-162.38
-162.39
-162.41
-162.43
-162.45
-162.46
2.00
1.09
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
ppm

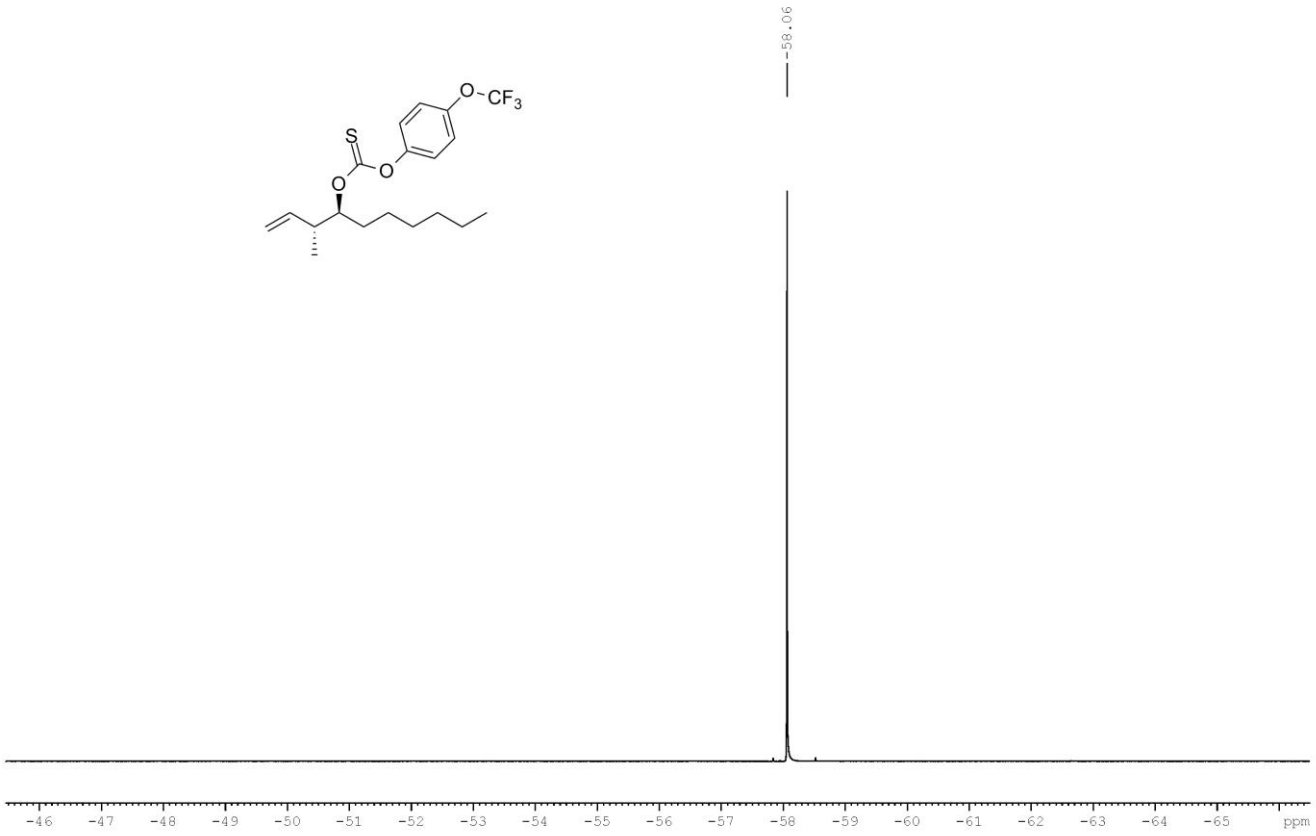

OB-NB-085-30, 1H, 400B
7.550
7.535
7.366
7.309
7.303
7.297
7.293
7.287
7.280
7.260
5.821
5.801
5.797
5.777
5.761
5.757
5.753
5.733
5.374
5.362
5.354
5.351
5.342
5.330
5.142
5.140
5.128
5.101
5.099
2.659
2.645
2.627
1.759
1.746
1.739
1.723
1.682
1.669
1.659
1.646
1.551
1.410
1.392
1.387
1.374
1.363
1.346
1.336
1.316
1.297
1.255
1.112
1.095
0.909
0.893
0.875
1.95
0.94
0.94
0.97
1.00
1.96
0.98
1.99
0.91
8.40
3.12
3.27
O
S
O
CF3
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
ppm

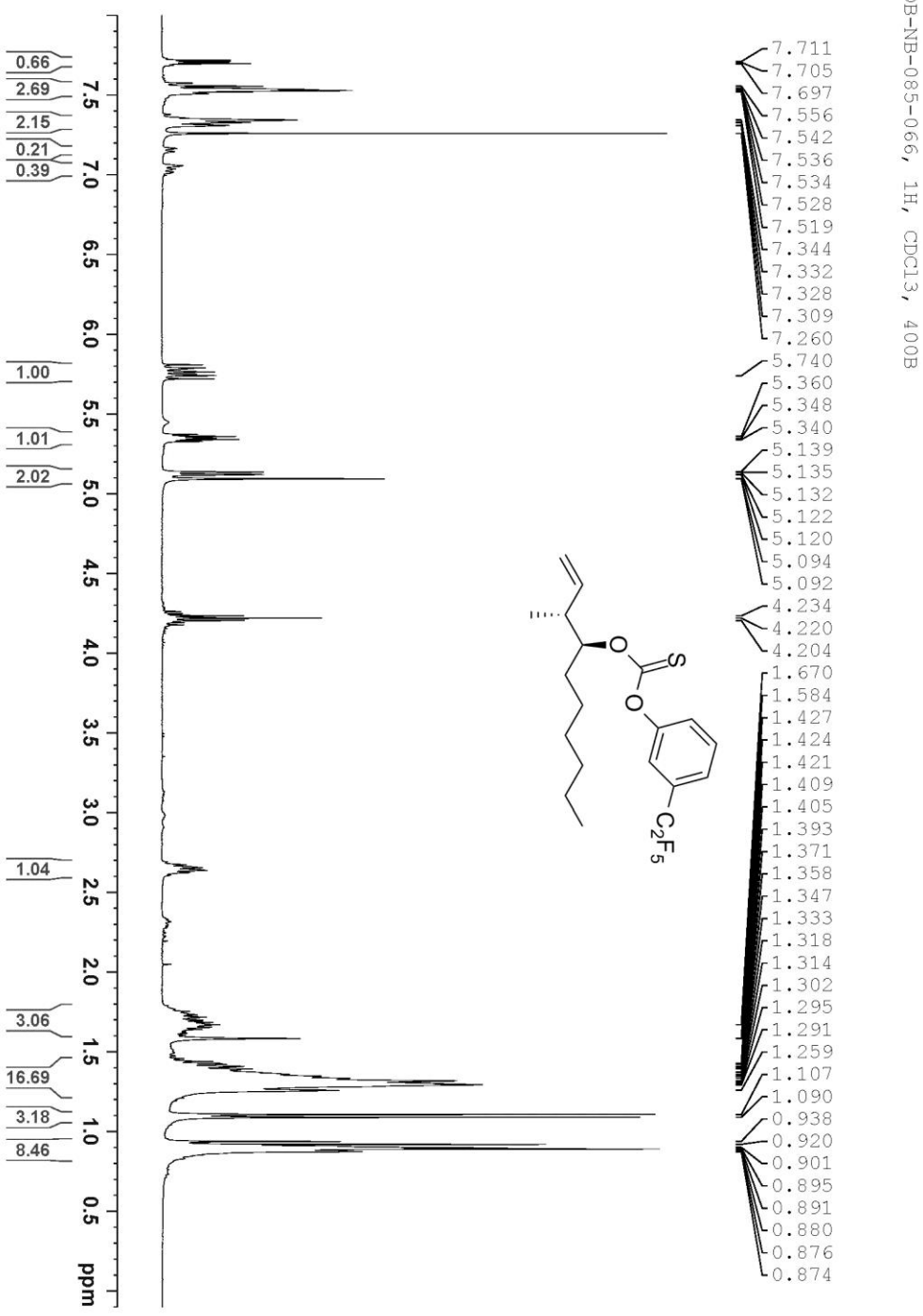
OB-NB-085-30_19F, 400B



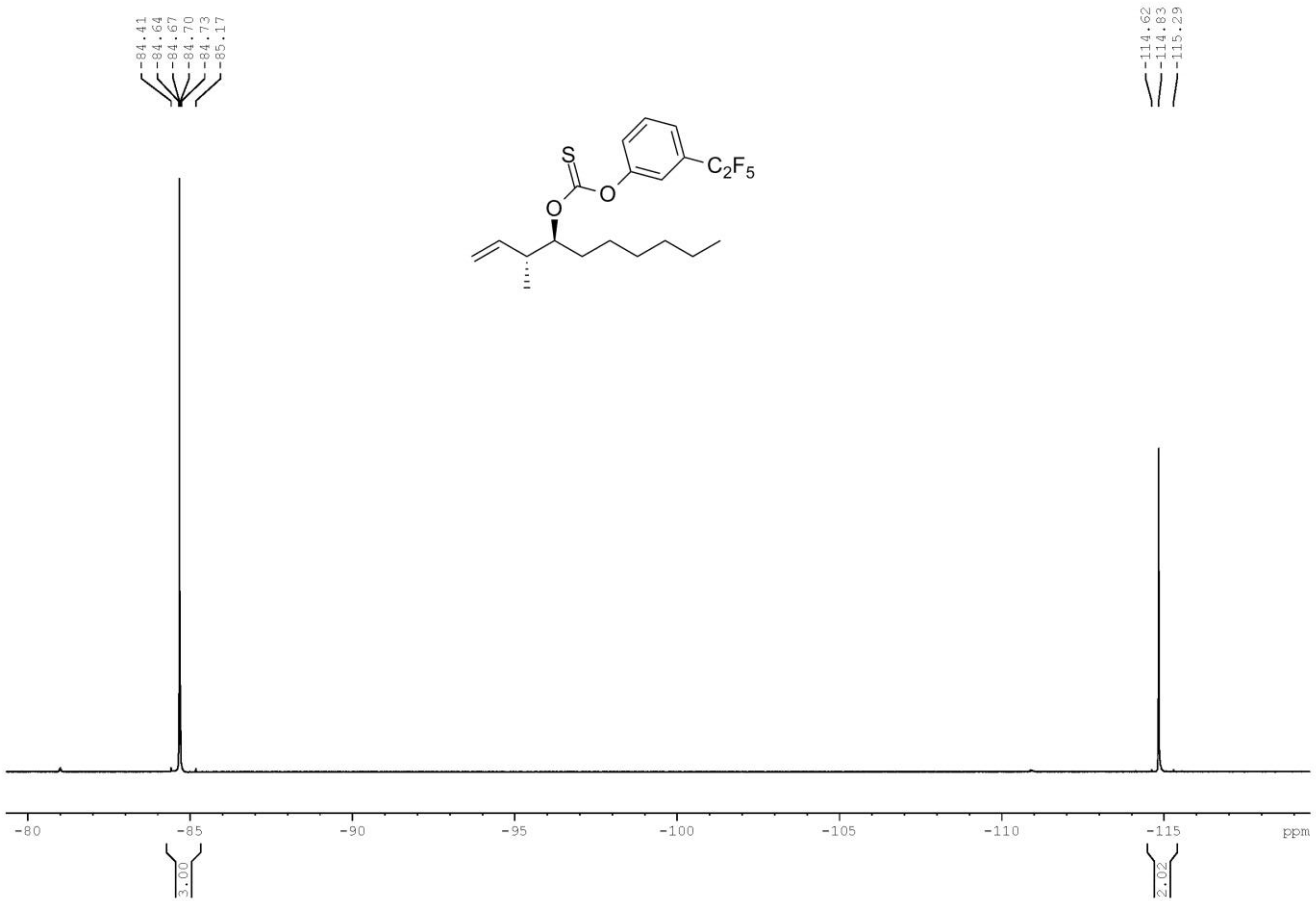

OB-NB-085-31, 1H, 400B
7.260
7.242
5.817
5.797
5.790
5.774
5.771
5.755
5.748
5.728
5.375
5.364
5.352
5.343
5.331
5.136
5.133
5.118
5.091
2.685
2.668
2.650
2.636
2.619
2.616
2.602
1.789
1.766
1.754
1.741
1.734
1.718
1.697
1.686
1.673
1.660
1.650
1.637
1.624
1.614
1.602
1.550
1.403
1.386
1.369
1.358
1.341
1.331
1.312
2.61
1.98
1.00
1.01
2.03
1.03
2.07
8.69
3.03
3.07
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
ppm
O
S
O
O-CF3

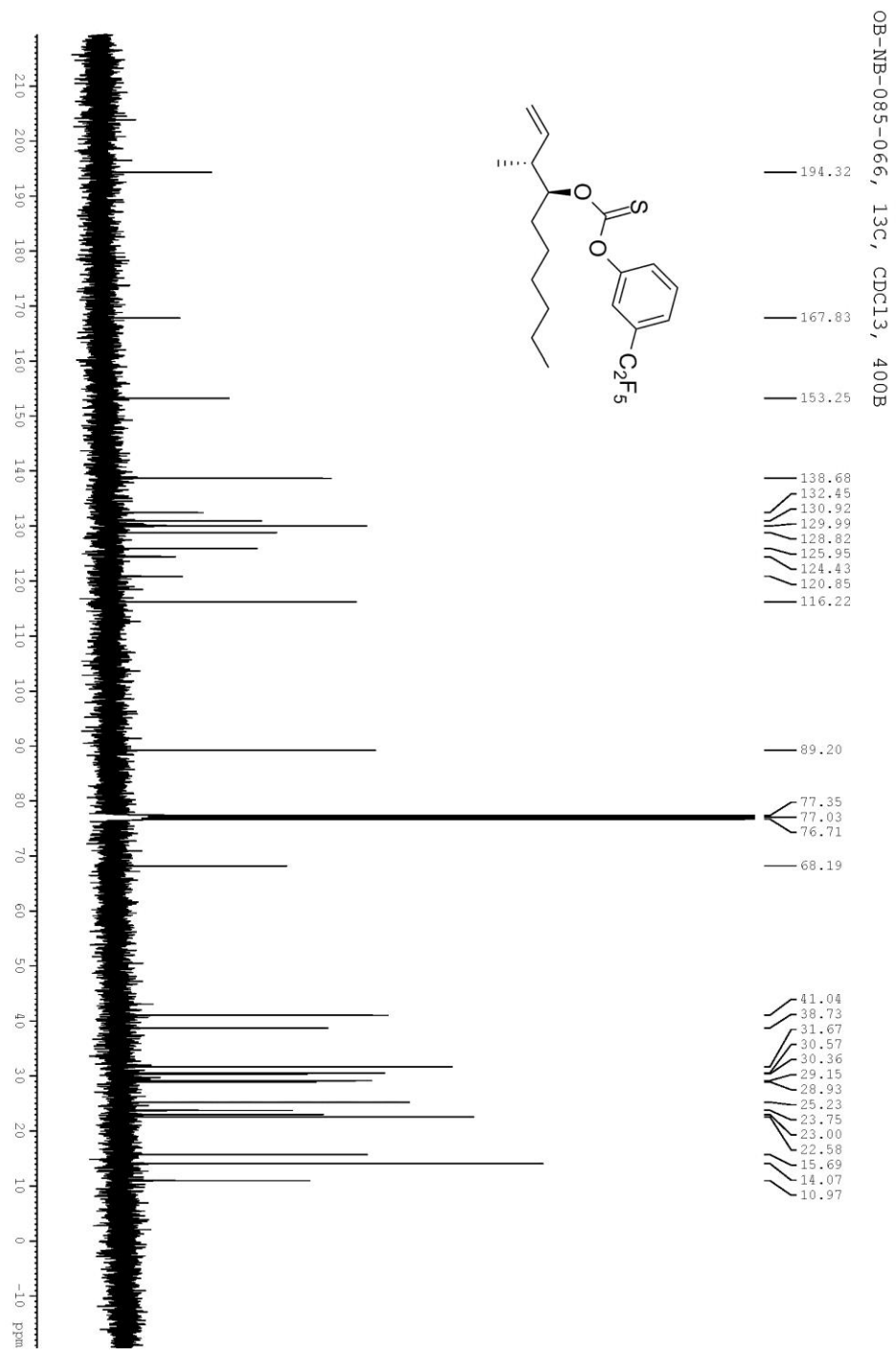
OB-NB-085-31, 19F, 400B

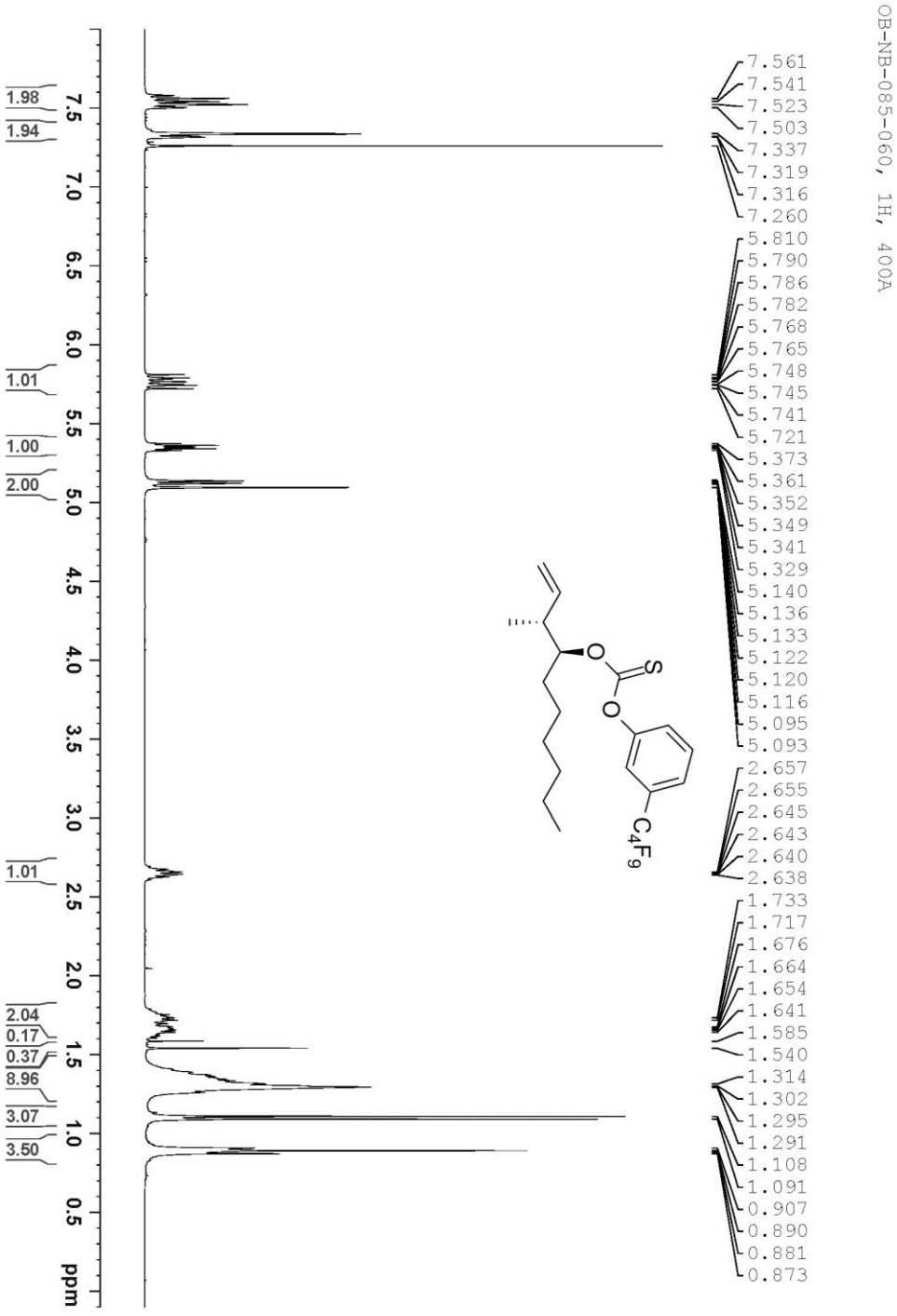


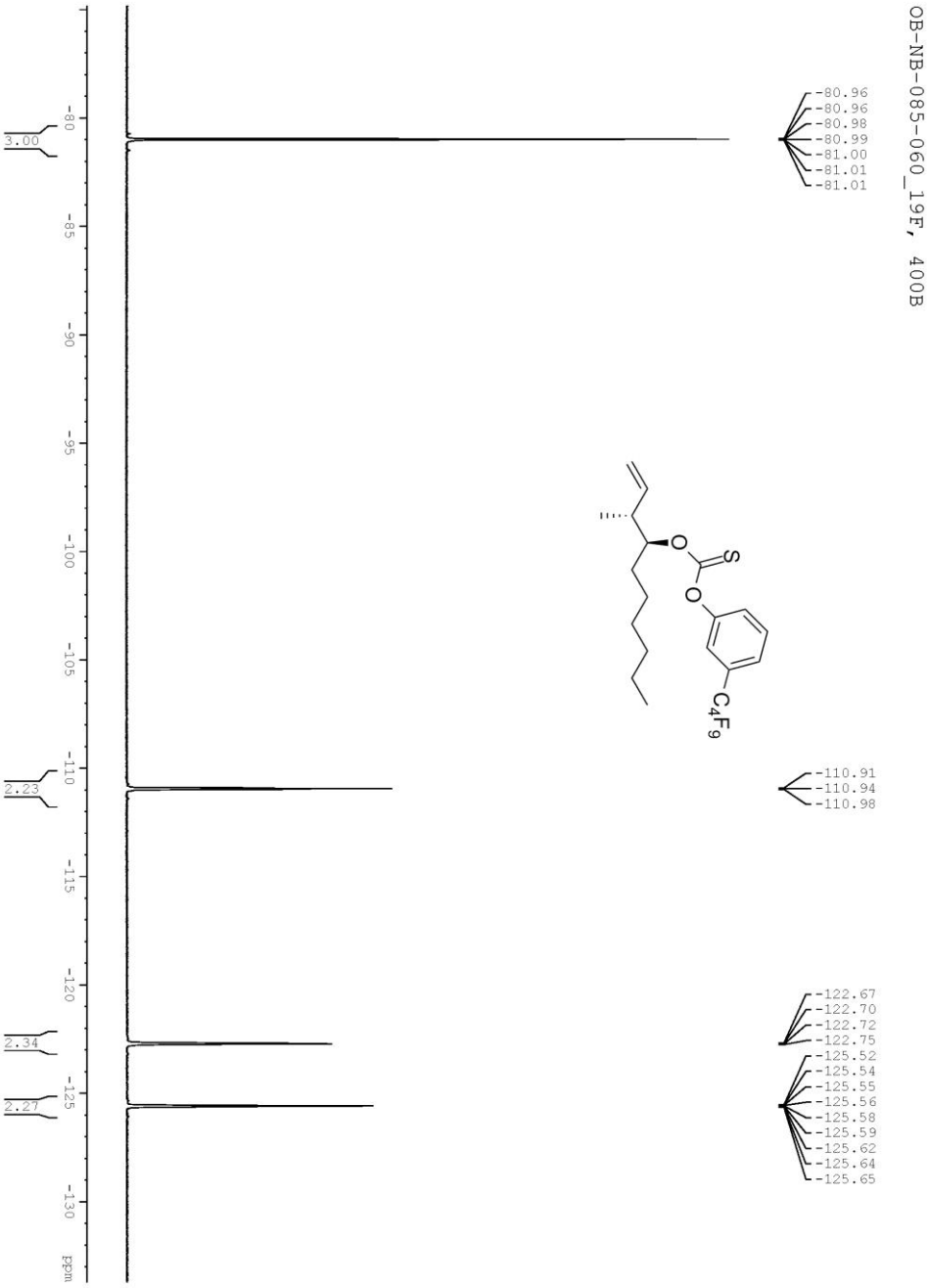

OB-NB-085-066, 1H, CDCl3, 400B
7.711
7.705
7.697
7.556
7.542
7.536
7.534
7.528
7.519
7.344
7.332
7.328
7.309
7.260
5.740
5.360
5.348
5.340
5.139
5.135
5.132
5.122
5.120
5.094
5.092
4.234
4.220
4.204
1.670
1.584
1.427
1.424
1.421
1.409
1.405
1.393
1.371
1.358
1.347
1.333
1.318
1.314
1.302
1.295
1.291
1.259
1.107
1.090
0.938
0.920
0.901
0.895
0.891
0.880
0.876
0.874
0.66
2.69
2.15
0.21
0.39
1.00
1.01
2.02
1.04
3.06
16.69
3.18
8.46
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
ppm
O
S
O
C2F5

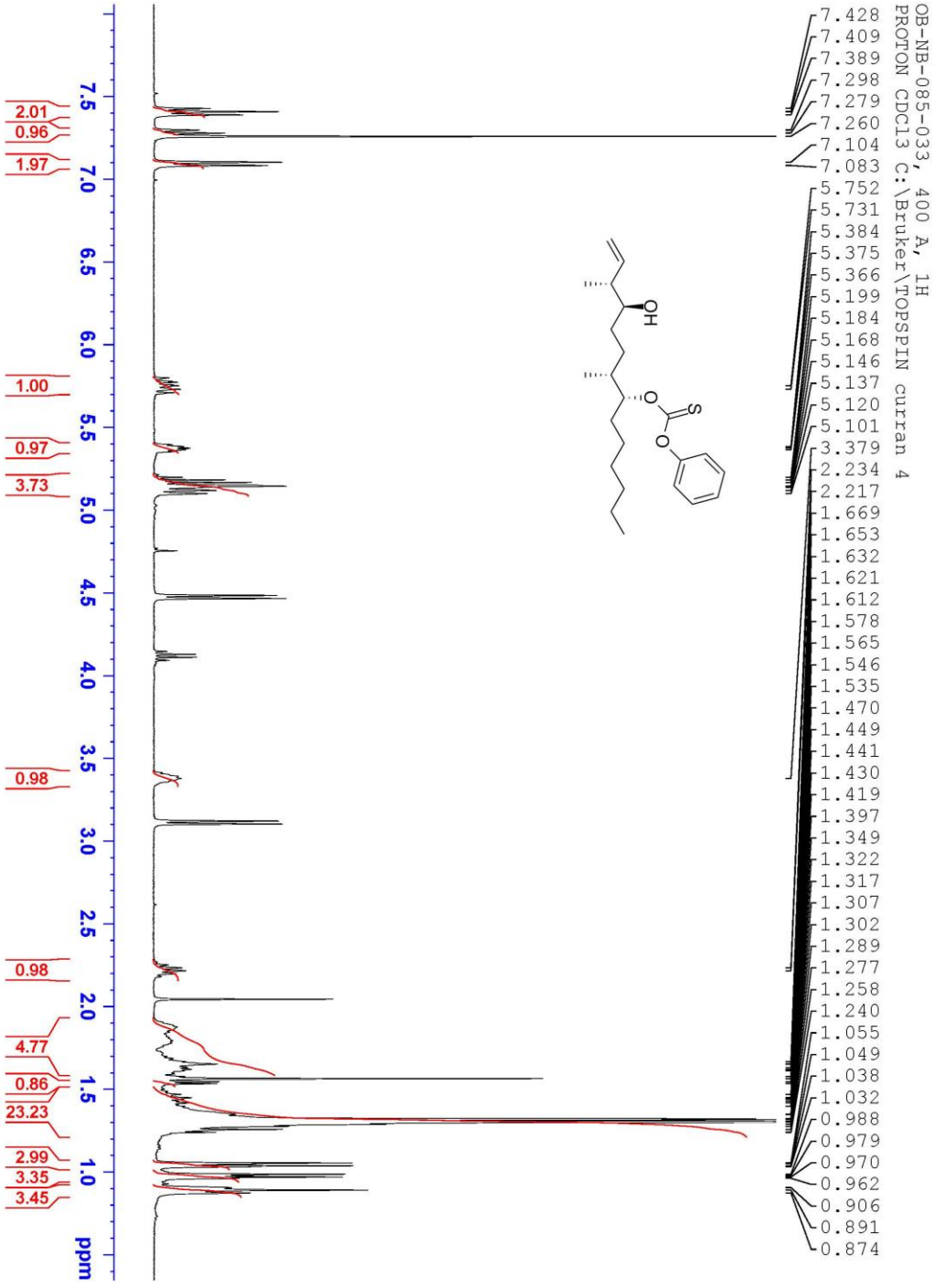
OB-NB-085-066, 19F, CDCl3, 400B

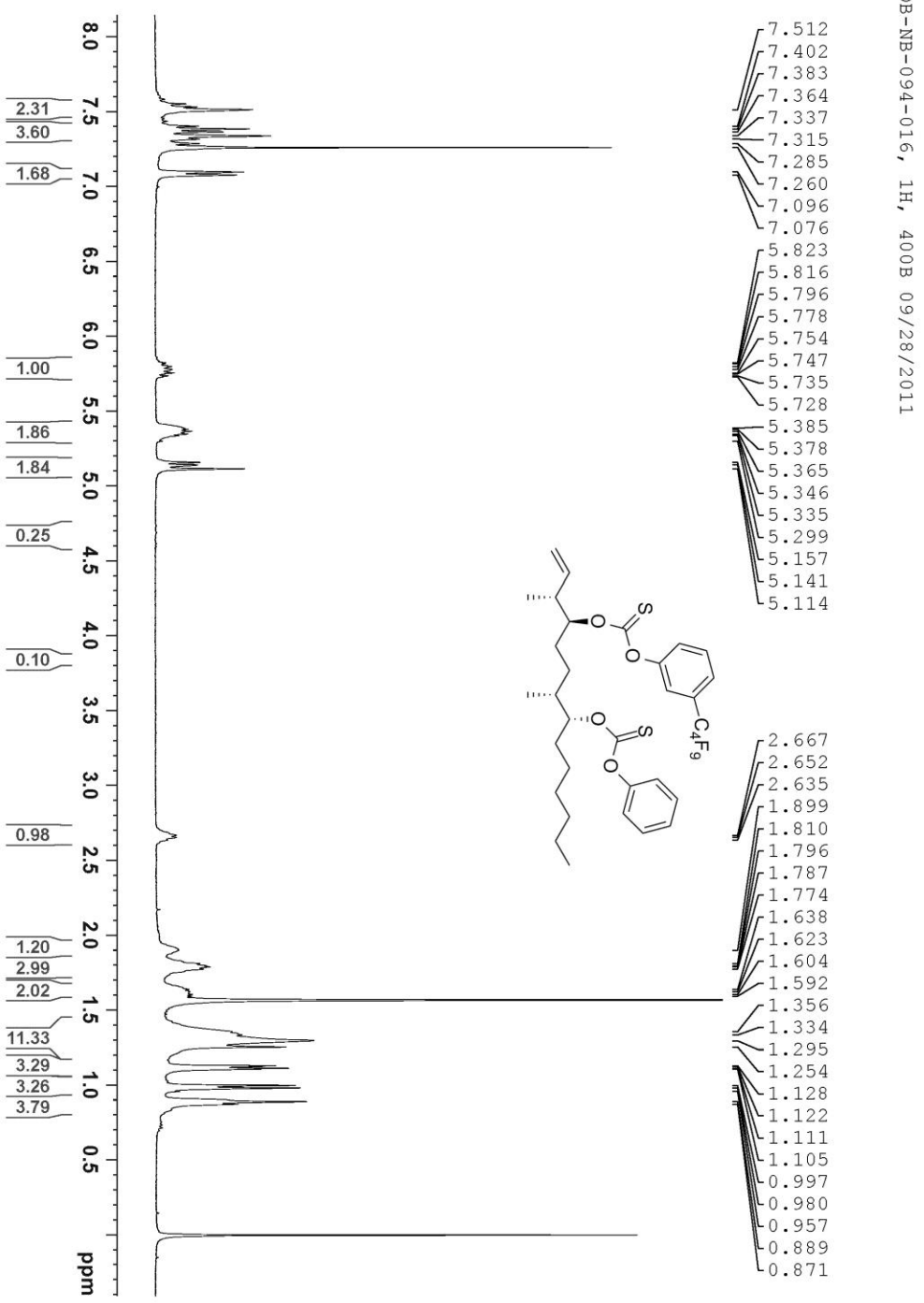


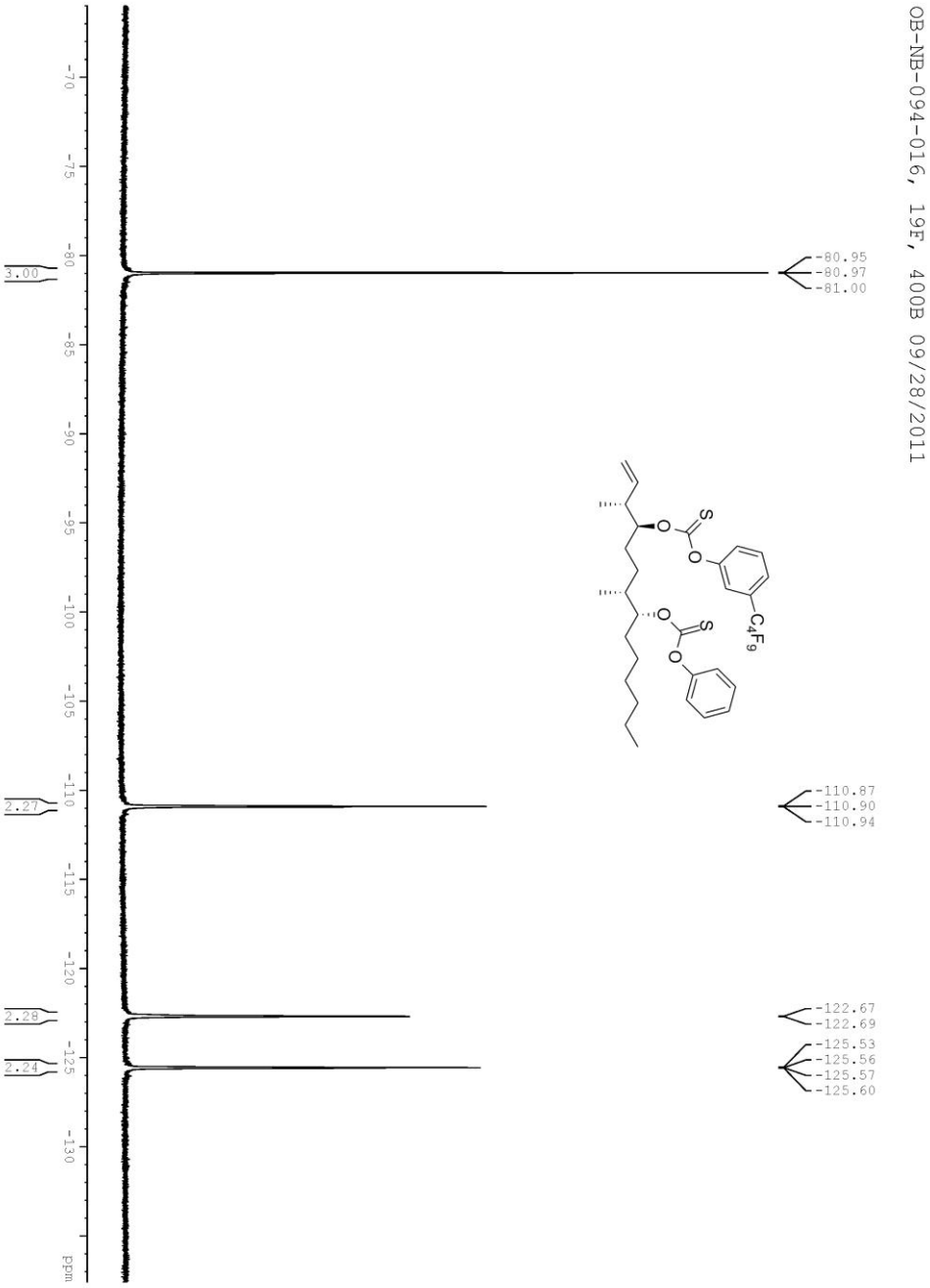

OB-NB-085-066, 13C, CDC13, 400B
194.32
167.83
153.25
138.68
132.45
130.92
129.99
128.82
125.95
124.43
120.85
116.22
89.20
77.35
77.03
76.71
68.19
41.04
38.73
31.67
30.57
30.36
29.15
28.93
25.23
23.75
23.00
22.58
15.69
14.07
10.97
O
S
O
C2F5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

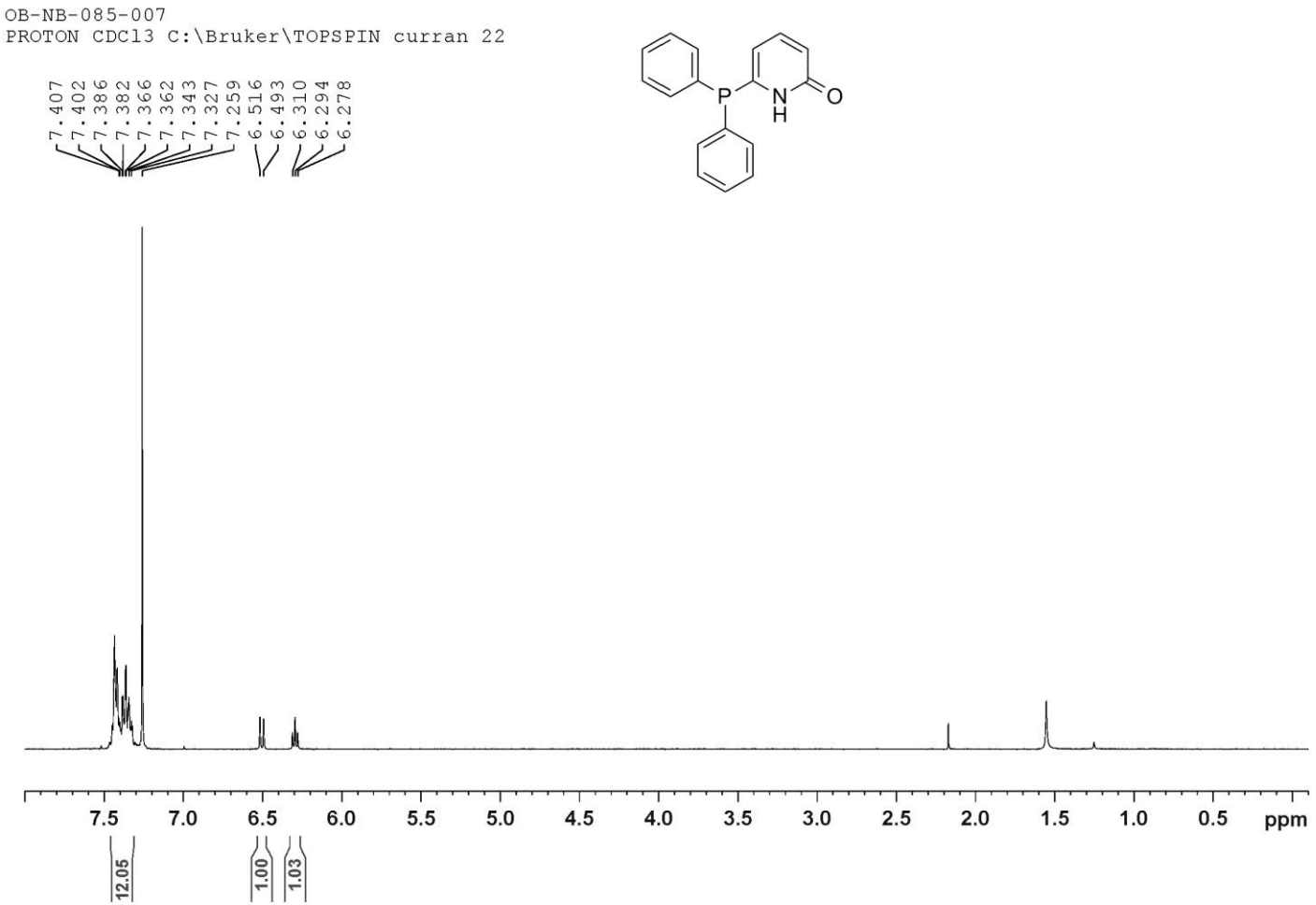

OB-NB-085-060, 1H, 400A
7.561
7.541
7.523
7.503
7.337
7.319
7.316
7.260
5.810
5.790
5.786
5.782
5.768
5.765
5.748
5.745
5.741
5.721
5.373
5.361
5.352
5.349
5.341
5.329
5.140
5.136
5.133
5.122
5.120
5.116
5.095
5.093
2.657
2.655
2.645
2.643
2.640
2.638
1.733
1.717
1.676
1.664
1.654
1.641
1.585
1.540
1.314
1.302
1.295
1.291
1.108
1.091
0.907
0.890
0.881
0.873
O
S
O
C4F9
1.98
1.94
1.01
1.00
2.00
1.01
2.04
0.17
0.37
8.96
3.07
3.50
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
ppm

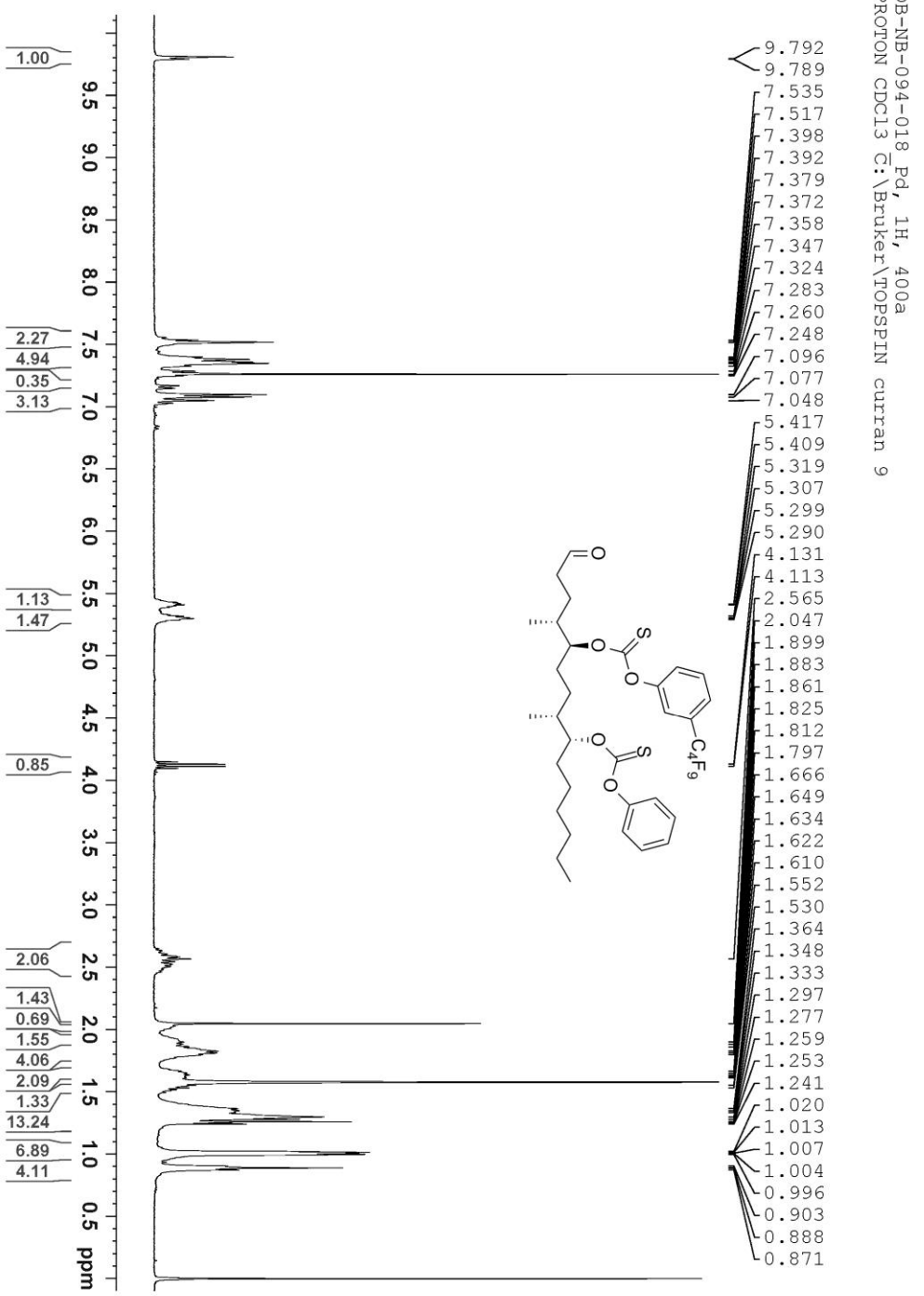

OB-NB-085-060_19F, 400B
-80.96
-80.96
-80.98
-80.99
-81.00
-81.01
-81.01
-110.91
-110.94
-110.98
-122.67
-122.70
-122.72
-122.75
-125.52
-125.54
-125.55
-125.56
-125.58
-125.59
-125.62
-125.64
-125.65
3.00
2.23
2.34
2.27
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
ppm
O
S
O
C4F9

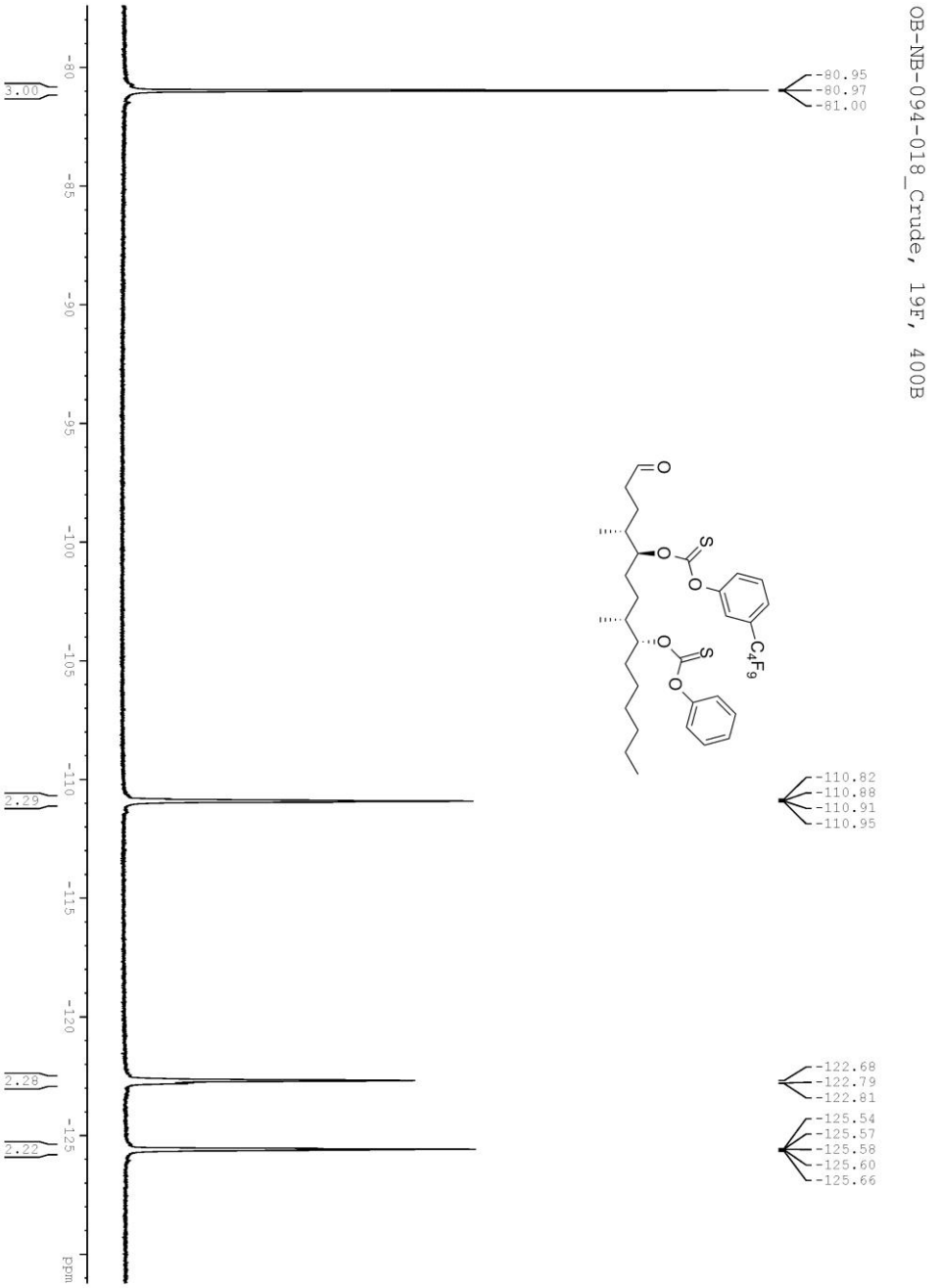

OB-NB-085-033, 400 A, 1H
PROTON CDC13 C:\Bruker\TOPSPIN curran 4
7.428
7.409
7.389
7.298
7.279
7.260
7.104
7.083
5.752
5.731
5.384
5.375
5.366
5.199
5.184
5.168
5.146
5.137
5.120
5.101
3.379
2.234
2.217
1.669
1.653
1.632
1.621
1.612
1.578
1.565
1.546
1.535
1.470
1.449
1.441
1.430
1.419
1.397
1.349
1.322
1.317
1.307
1.302
1.289
1.277
1.258
1.240
1.055
1.049
1.038
1.032
0.988
0.979
0.970
0.962
0.906
0.891
0.874
OH
O
S
O
2.01
0.96
1.97
1.00
0.97
3.73
0.98
0.98
4.77
0.86
23.23
2.99
3.35
3.45
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
ppm

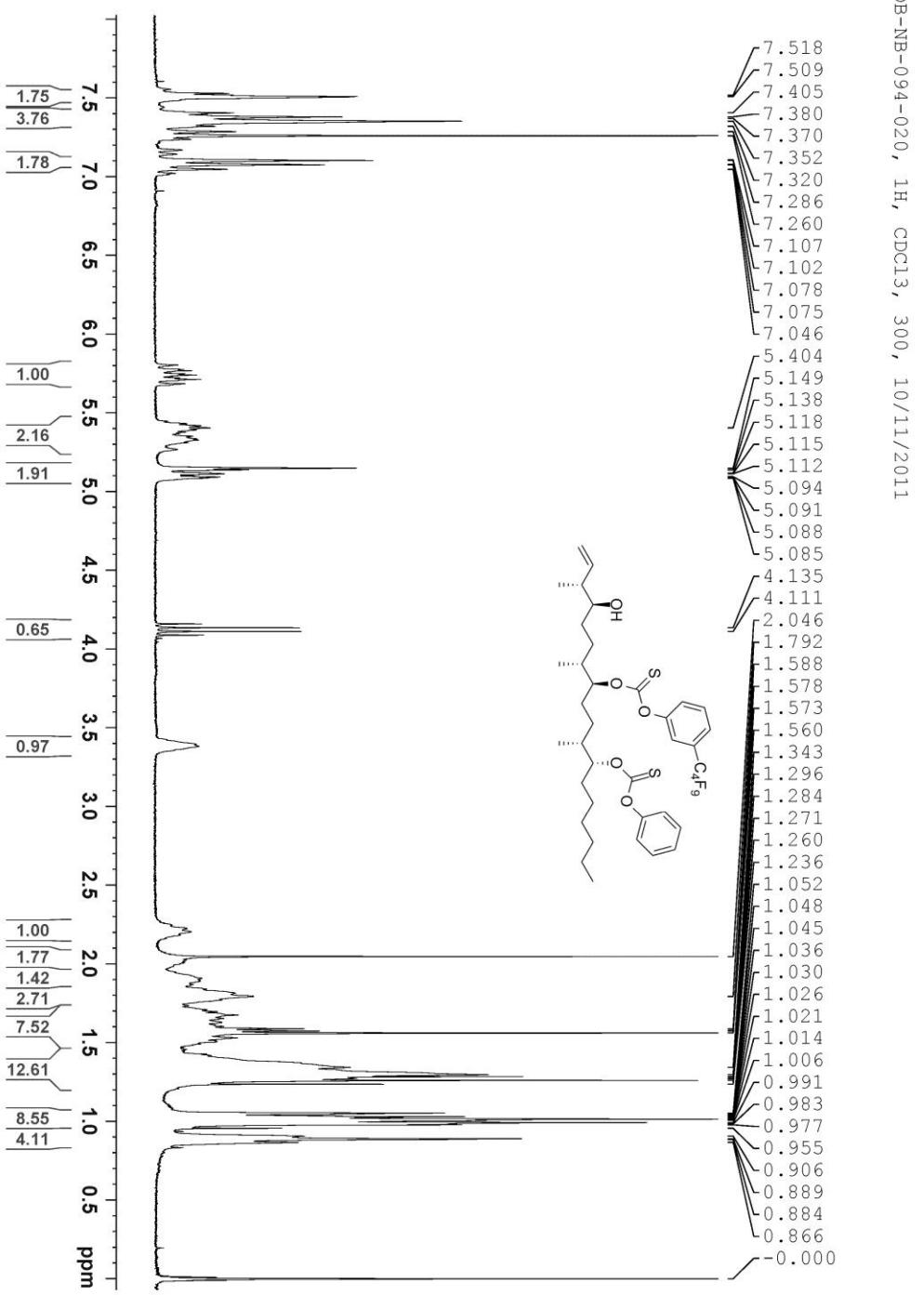

OB-NB-094-016, 1H, 400B 09/28/2011
7.512
7.402
7.383
7.364
7.337
7.315
7.285
7.260
7.096
7.076
5.823
5.816
5.796
5.778
5.754
5.747
5.735
5.728
5.385
5.378
5.365
5.346
5.335
5.299
5.157
5.141
5.114
2.667
2.652
2.635
1.899
1.810
1.796
1.787
1.774
1.638
1.623
1.604
1.592
1.356
1.334
1.295
1.254
1.128
1.122
1.111
1.105
0.997
0.980
0.957
0.889
0.871
2.31
3.60
1.68
1.00
1.86
1.84
0.25
0.10
0.98
1.20
2.99
2.02
11.33
3.29
3.26
3.79
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
ppm
S
O
O
O
S
O
O
C4F9

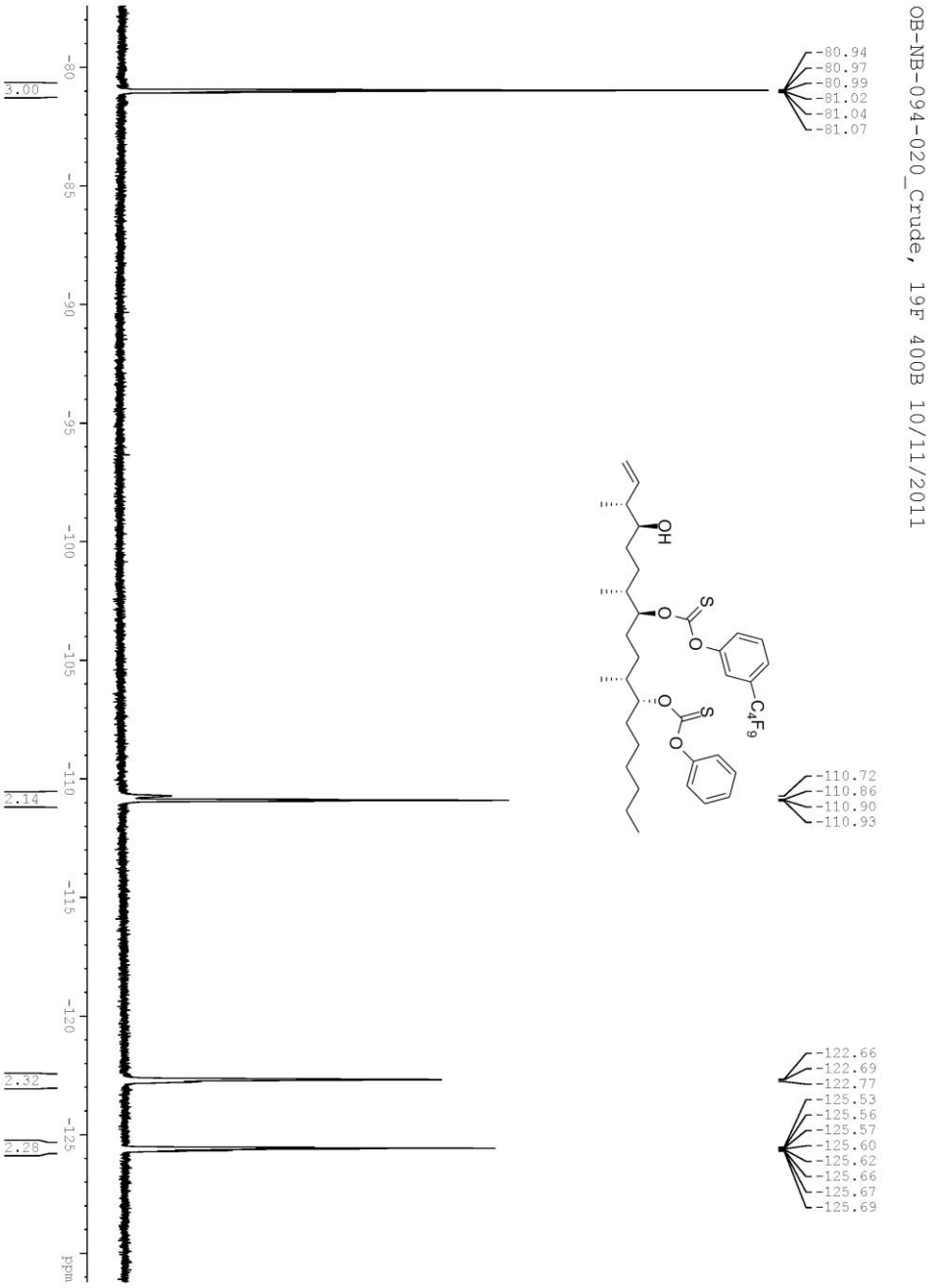

OB-NB-094-016, 19F, 400B 09/28/2011
-80.95
-80.97
-81.00
-110.87
-110.90
-110.94
-122.67
-122.69
-125.53
-125.56
-125.57
-125.60
3.00
2.27
2.28
2.24
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
ppm

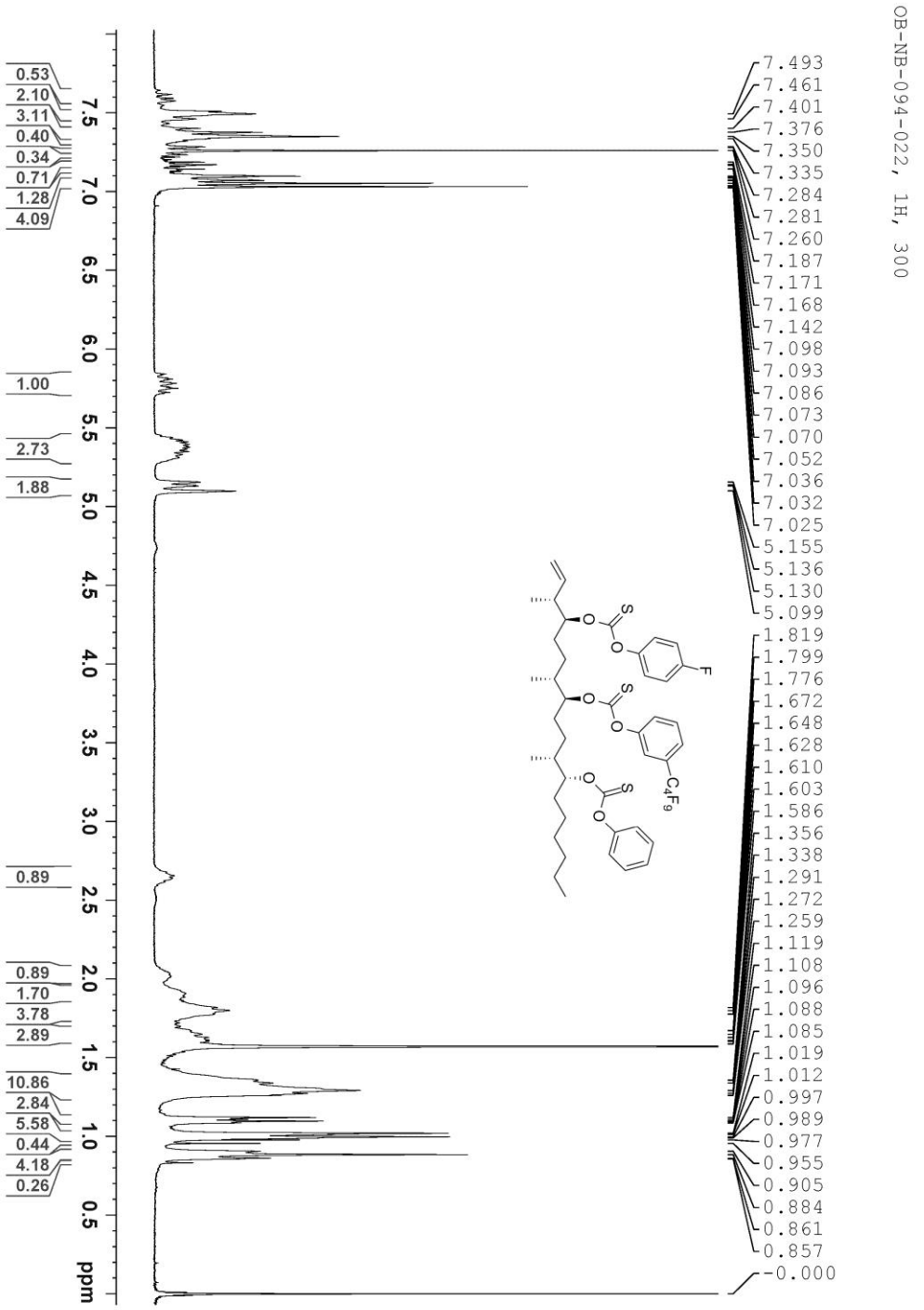

OB-NB-085-007
PROTON CDCl3 C:\Bruker\TOPSPIN curran 22
7.407
7.402
7.386
7.382
7.366
7.362
7.343
7.327
7.259
6.516
6.493
6.310
6.294
6.278
P
N
H
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
12.05
1.00
1.03

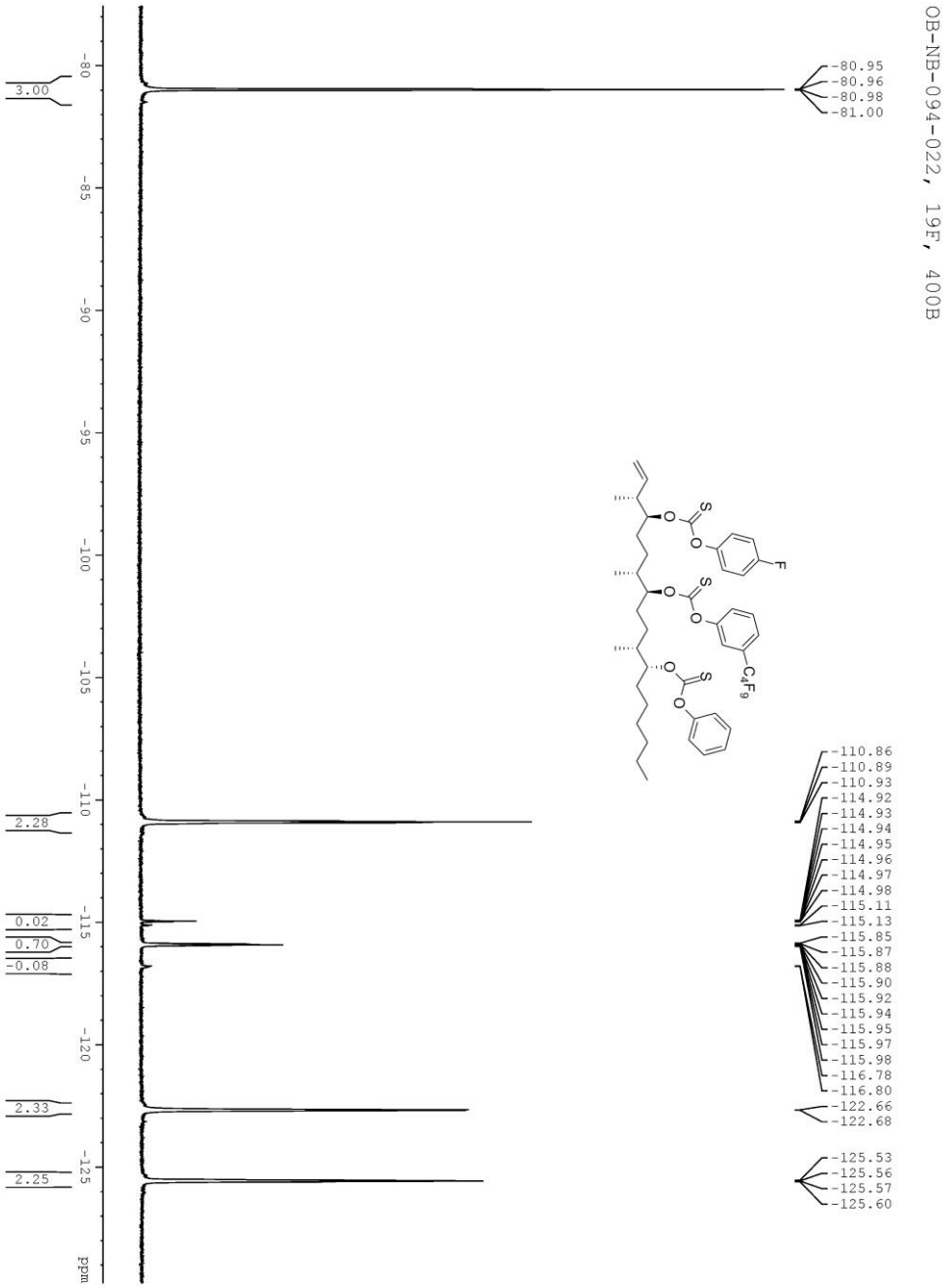

OB-NB-094-018 Pd, 1H, 400a
PROTON CDCl3 C:\Bruker\TOPSPIN curran 9
9.792
9.789
7.535
7.517
7.398
7.392
7.379
7.372
7.358
7.347
7.324
7.283
7.260
7.248
7.096
7.077
7.048
5.417
5.409
5.319
5.307
5.299
5.290
4.131
4.113
2.565
2.047
1.899
1.883
1.861
1.825
1.812
1.797
1.666
1.649
1.634
1.622
1.610
1.552
1.530
1.364
1.348
1.333
1.297
1.277
1.259
1.253
1.241
1.020
1.013
1.007
1.004
0.996
0.903
0.888
0.871
1.00
2.27
4.94
0.35
3.13
1.13
1.47
0.85
2.06
1.43
0.69
1.55
4.06
2.09
1.33
13.24
6.89
4.11
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
ppm
O
S
O
O
O
S
O
C4F9

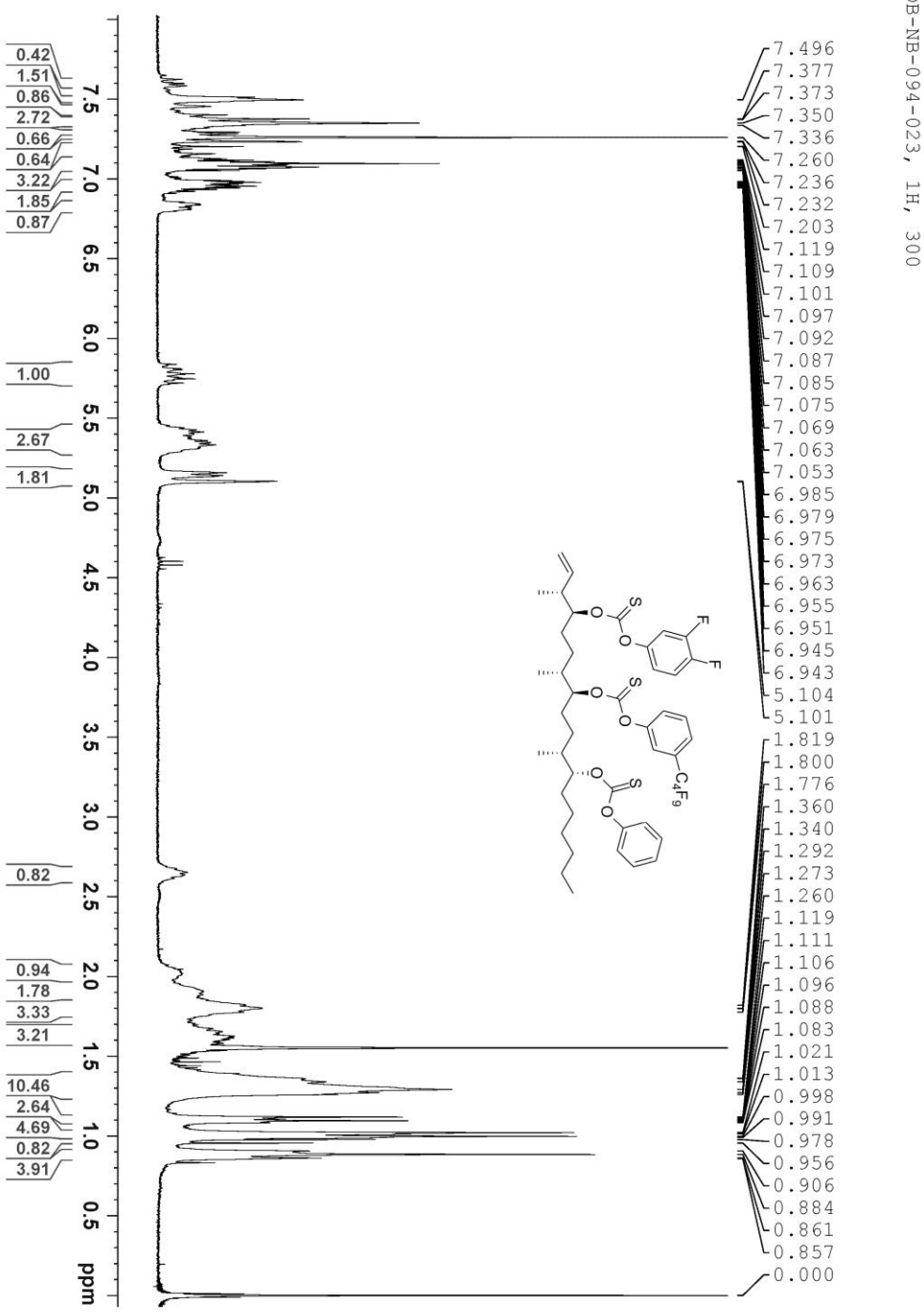

OB-NB-094-018_Crude, 19F, 400B
-80.95
-80.97
-81.00
-110.82
-110.88
-110.91
-110.95
-122.68
-122.79
-122.81
-125.54
-125.57
-125.58
-125.60
-125.66
3.00
2.29
2.28
2.22
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
ppm

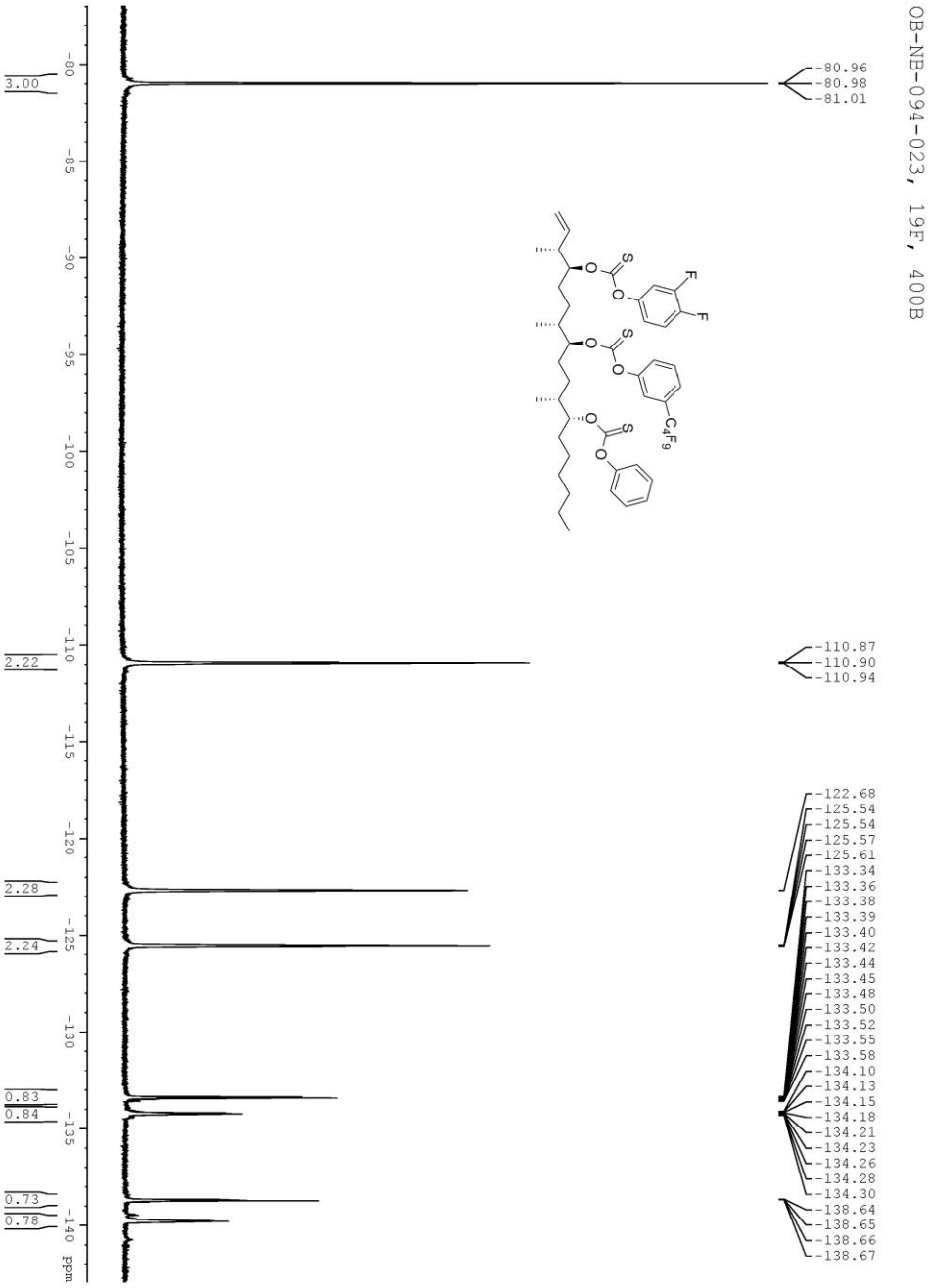

OB-NB-094-020, 1H, CDCl3, 300, 10/11/2011
7.518
7.509
7.405
7.380
7.370
7.352
7.320
7.286
7.260
7.107
7.102
7.078
7.075
7.046
5.404
5.149
5.138
5.118
5.115
5.112
5.094
5.091
5.088
5.085
4.135
4.111
2.046
1.792
1.588
1.578
1.573
1.560
1.343
1.296
1.284
1.271
1.260
1.236
1.052
1.048
1.045
1.036
1.030
1.026
1.021
1.014
1.006
0.991
0.983
0.977
0.955
0.906
0.889
0.884
0.866
-0.000
1.75
3.76
1.78
1.00
2.16
1.91
0.65
0.97
1.00
1.77
1.42
2.71
7.52
12.61
8.55
4.11
ppm
OH
S
O
O
C4F9

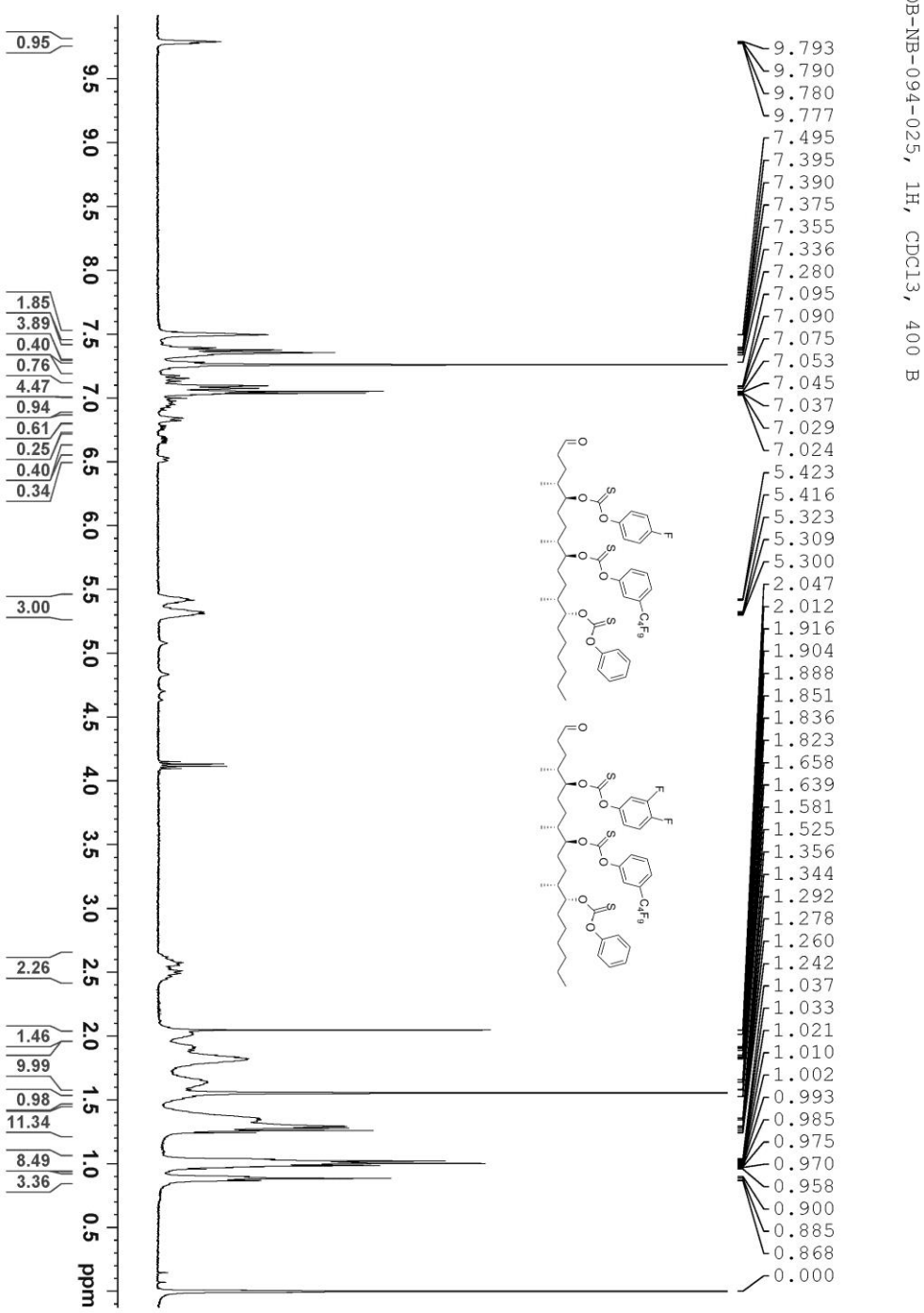

OB-NB-094-020_Crude, 19F 400B 10/11/2011
-80.94
-80.97
-80.99
-81.02
-81.04
-81.07
-110.72
-110.86
-110.90
-110.93
-122.66
-122.69
-122.77
-125.53
-125.56
-125.57
-125.60
-125.62
-125.66
-125.67
-125.69
OH
S
O
O
S
O
O
C4F9
3.00
2.14
2.32
2.28
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
ppm

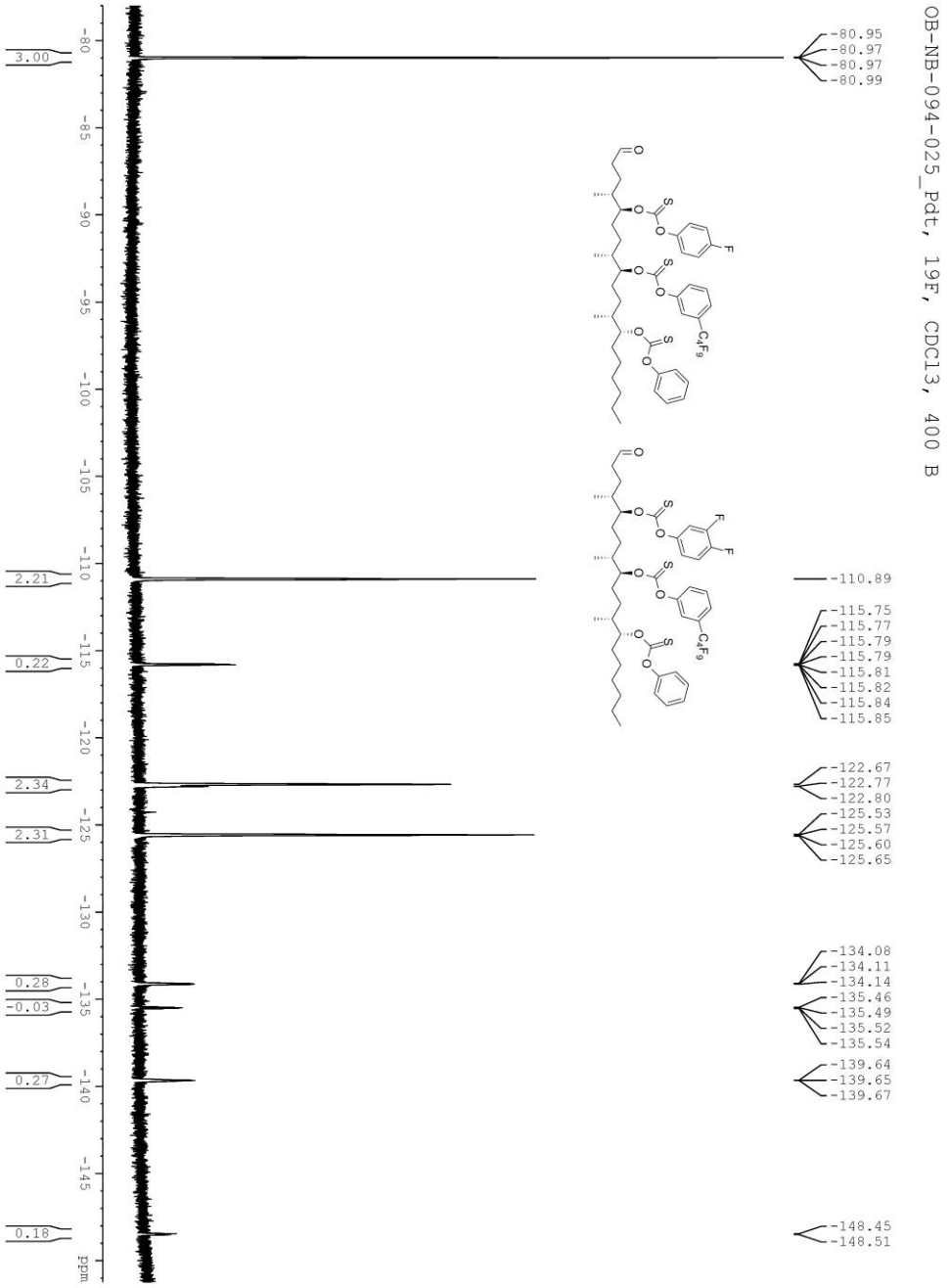

OB-NB-094-022, 1H, 300
7.493
7.461
7.401
7.376
7.350
7.335
7.284
7.281
7.260
7.187
7.171
7.168
7.142
7.098
7.093
7.086
7.073
7.070
7.052
7.036
7.032
7.025
5.155
5.136
5.130
5.099
1.819
1.799
1.776
1.672
1.648
1.628
1.610
1.603
1.586
1.356
1.338
1.291
1.272
1.259
1.119
1.108
1.096
1.088
1.085
1.019
1.012
0.997
0.989
0.977
0.955
0.905
0.884
0.861
0.857
-0.000
0.53
2.10
3.11
0.40
0.34
0.71
1.28
4.09
1.00
2.73
1.88
0.89
0.89
1.70
3.78
2.89
10.86
2.84
5.58
0.44
4.18
0.26
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
ppm
F
C4F9

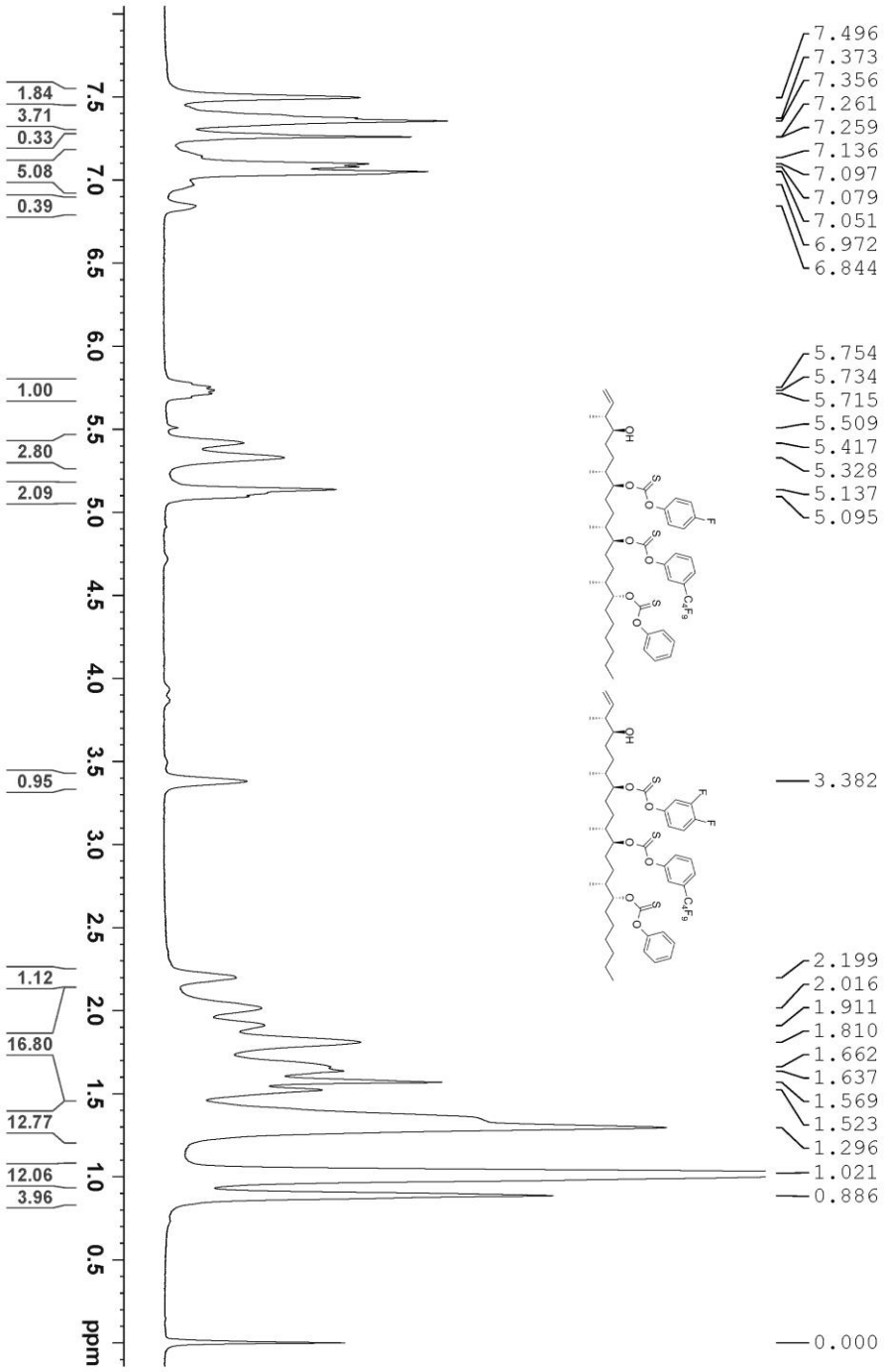

OB-NB-094-022, 19F, 400B
-80.95
-80.96
-80.98
-81.00
-110.86
-110.89
-110.93
-114.92
-114.93
-114.94
-114.95
-114.96
-114.97
-114.98
-115.11
-115.13
-115.85
-115.87
-115.88
-115.90
-115.92
-115.94
-115.95
-115.97
-115.98
-116.78
-116.80
-122.66
-122.68
-125.53
-125.56
-125.57
-125.60
3.00
2.28
0.02
0.70
-0.08
2.33
2.25
ppm


OB-NB-094-023, 1H, 300
7.496
7.377
7.373
7.350
7.336
7.260
7.236
7.232
7.203
7.119
7.109
7.101
7.097
7.092
7.087
7.085
7.075
7.069
7.063
7.053
6.985
6.979
6.975
6.973
6.963
6.955
6.951
6.945
6.943
5.104
5.101
1.819
1.800
1.776
1.360
1.340
1.292
1.273
1.260
1.119
1.111
1.106
1.096
1.088
1.083
1.021
1.013
0.998
0.991
0.978
0.956
0.906
0.884
0.861
0.857
0.000
0.42
1.51
0.86
2.72
0.66
0.64
3.22
1.85
0.87
1.00
2.67
1.81
0.82
0.94
1.78
3.33
3.21
10.46
2.64
4.69
0.82
3.91
ppm

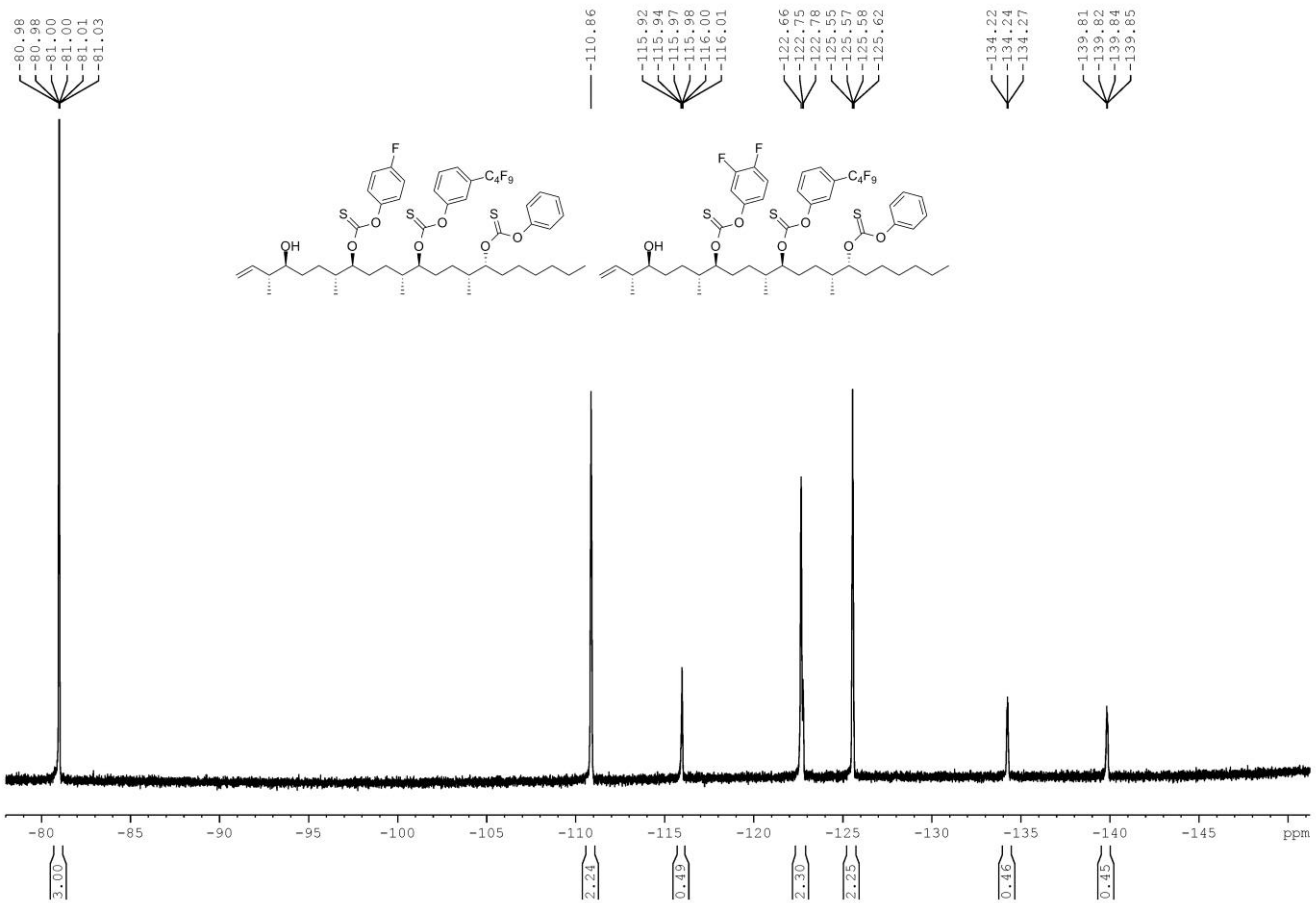

OB-NB-094-023, 19F, 400B
-80.96
-80.98
-81.01
-110.87
-110.90
-110.94
-122.68
-125.54
-125.54
-125.57
-125.61
-133.34
-133.36
-133.38
-133.39
-133.40
-133.42
-133.44
-133.45
-133.48
-133.50
-133.52
-133.55
-133.58
-134.10
-134.13
-134.15
-134.18
-134.21
-134.23
-134.26
-134.28
-134.30
-138.64
-138.65
-138.66
-138.67
3.00
2.22
2.28
2.24
0.83
0.84
0.73
0.78
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
ppm

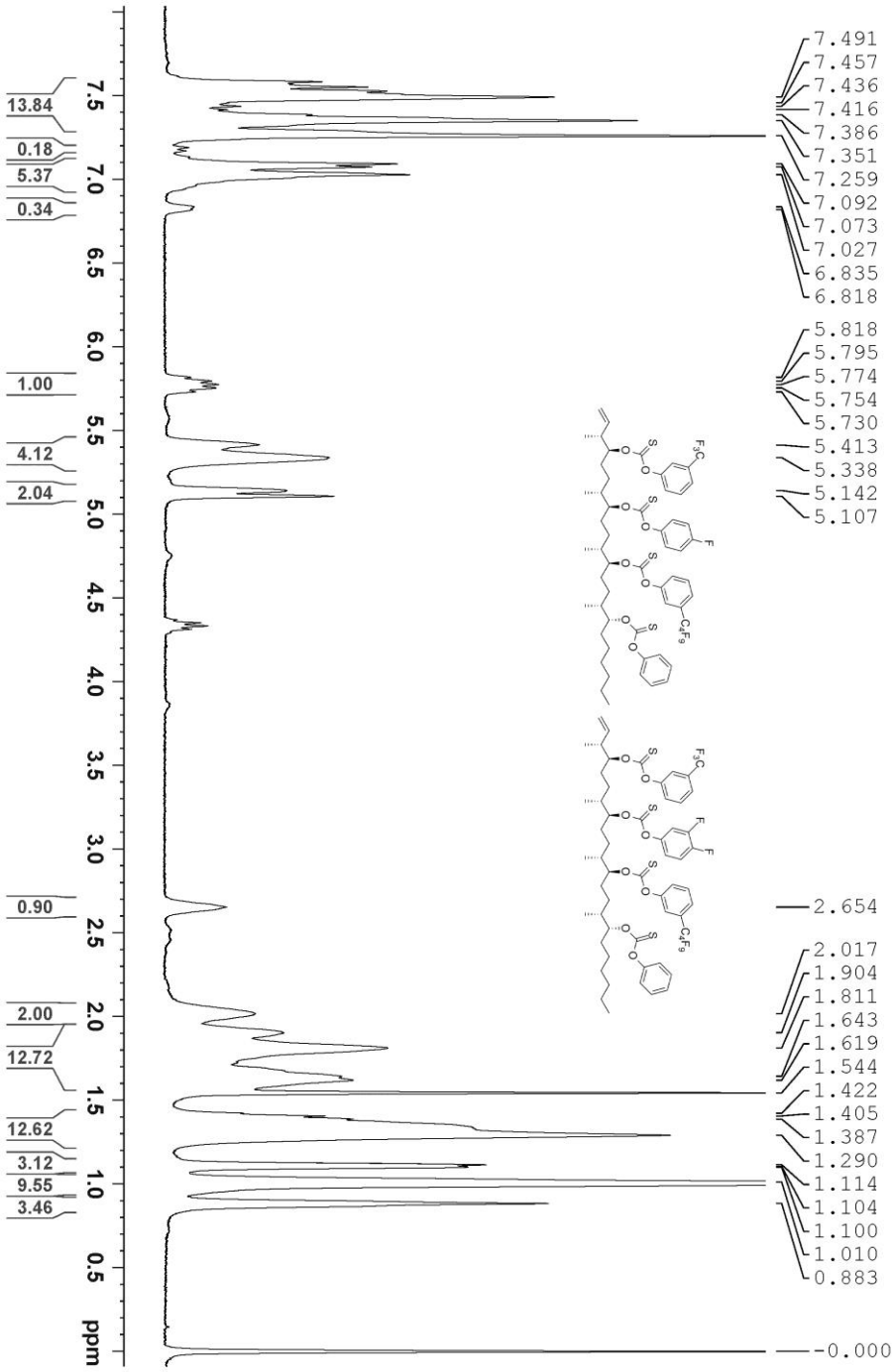

OB-NB-094-025, 1H, CDCl3, 400 B
9.793
9.790
9.780
9.777
7.495
7.395
7.390
7.375
7.355
7.336
7.280
7.095
7.090
7.075
7.053
7.045
7.037
7.029
7.024
5.423
5.416
5.323
5.309
5.300
2.047
2.012
1.916
1.904
1.888
1.851
1.836
1.823
1.658
1.639
1.581
1.525
1.356
1.344
1.292
1.278
1.260
1.242
1.037
1.033
1.021
1.010
1.002
0.993
0.985
0.975
0.970
0.958
0.900
0.885
0.868
0.000
0.95
1.85
3.89
0.40
0.76
4.47
0.94
0.61
0.25
0.40
0.34
3.00
2.26
1.46
9.99
0.98
11.34
8.49
3.36
ppm

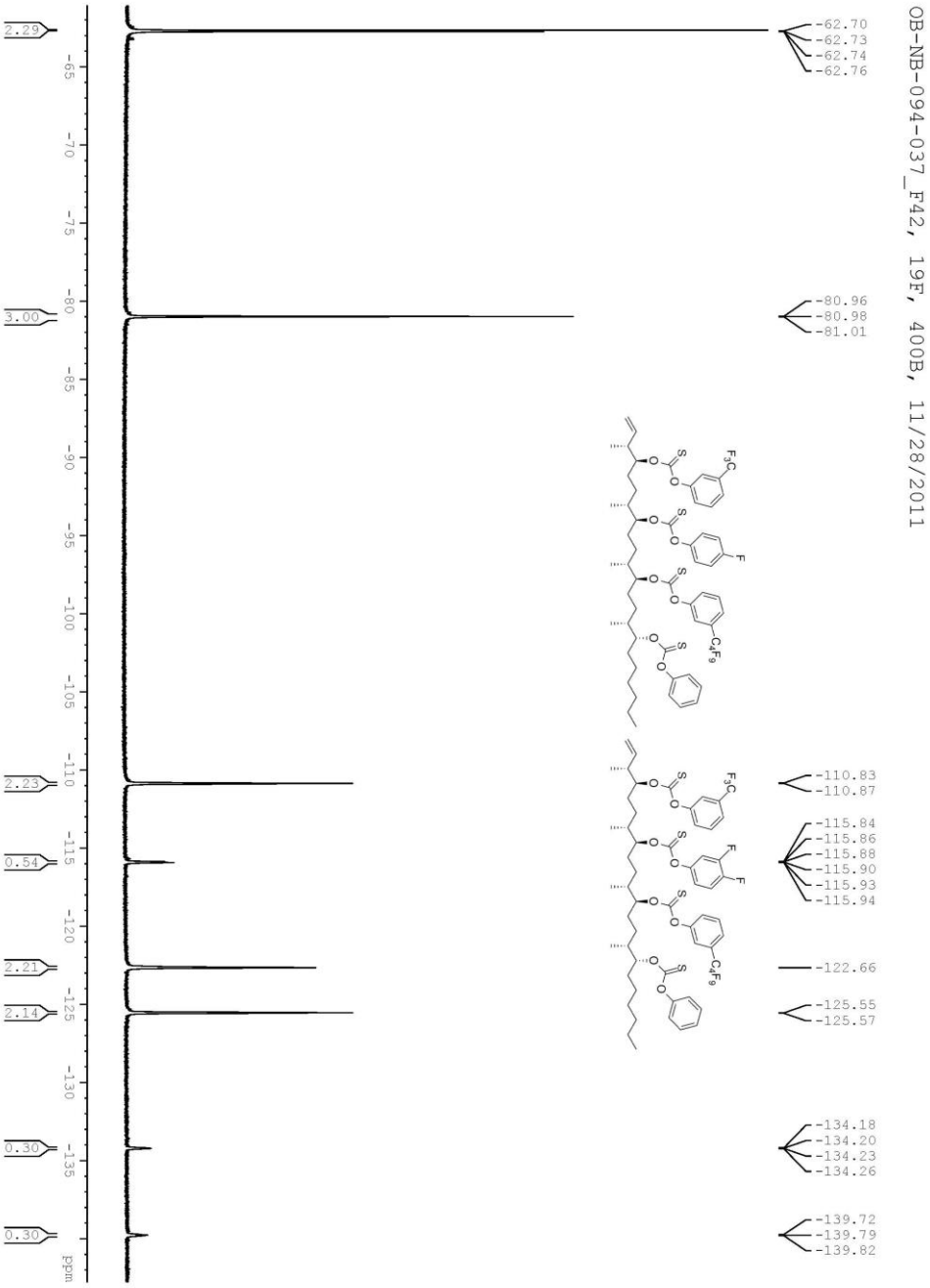

OB-NB-094-025_Pdt, 19F, CDCl3, 400 B
-80.95
-80.97
-80.97
-80.99
-110.89
-115.75
-115.77
-115.79
-115.79
-115.81
-115.82
-115.84
-115.85
-122.67
-122.77
-122.80
-125.53
-125.57
-125.60
-125.65
-134.08
-134.11
-134.14
-135.46
-135.49
-135.52
-135.54
-139.64
-139.65
-139.67
-148.45
-148.51
3.00
2.21
0.22
2.34
2.31
0.28
0.03
0.27
0.18
ppm

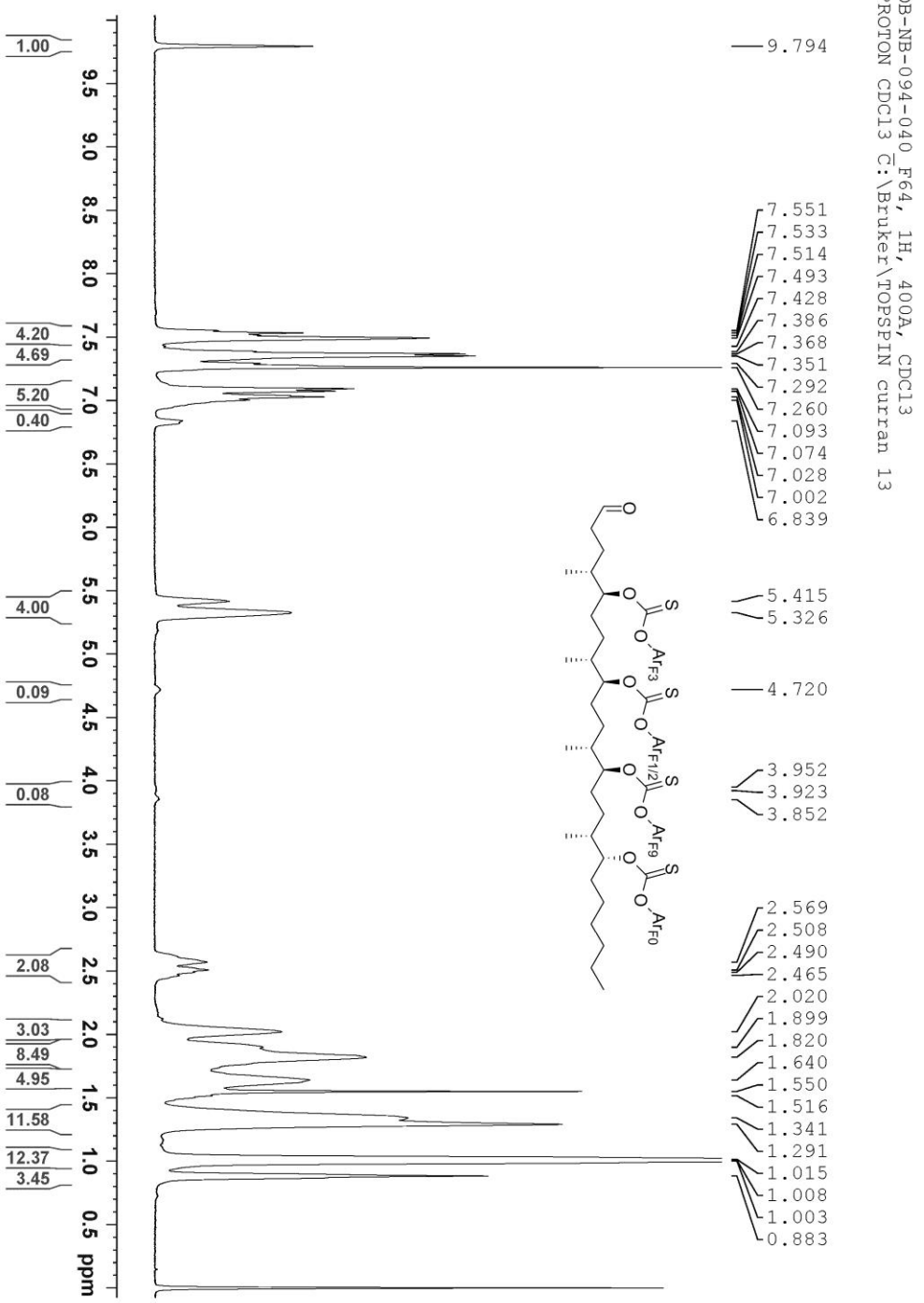

OB-NB-094-036 F59, 1H, 400A, CDCl3
PROTON CDCl3 C:\Bruker\TOPSPIN curran 10
7.496
7.373
7.356
7.261
7.259
7.136
7.097
7.079
7.051
6.972
6.844
5.754
5.734
5.715
5.509
5.417
5.328
5.137
5.095
3.382
2.199
2.016
1.911
1.810
1.662
1.637
1.569
1.523
1.296
1.021
0.886
0.000
1.84
3.71
0.33
5.08
0.39
1.00
2.80
2.09
0.95
1.12
16.80
12.77
12.06
3.96
ppm

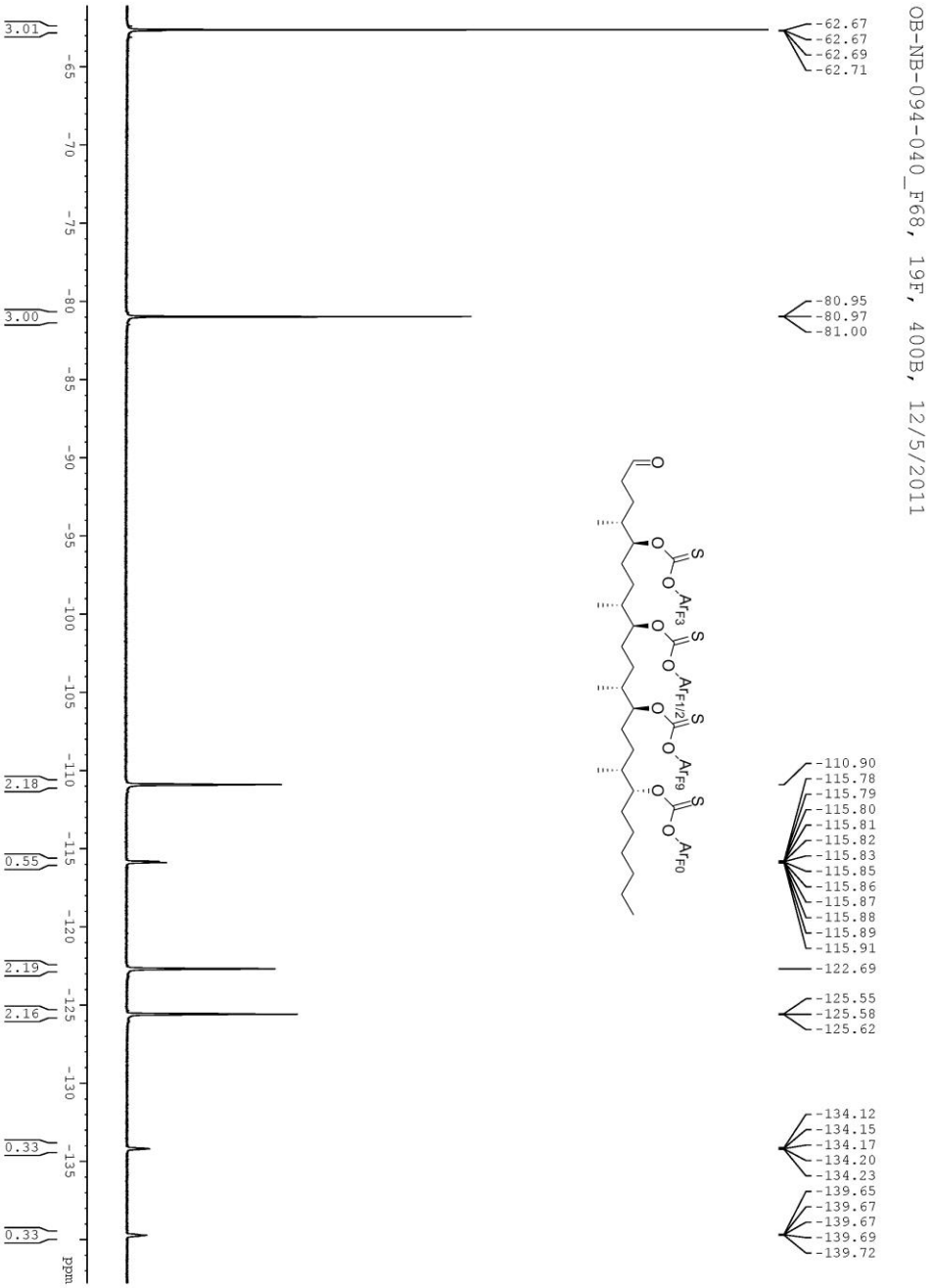
OB-NB-094-036_F57, 19F, CDCl3, 400B, 11/21/11

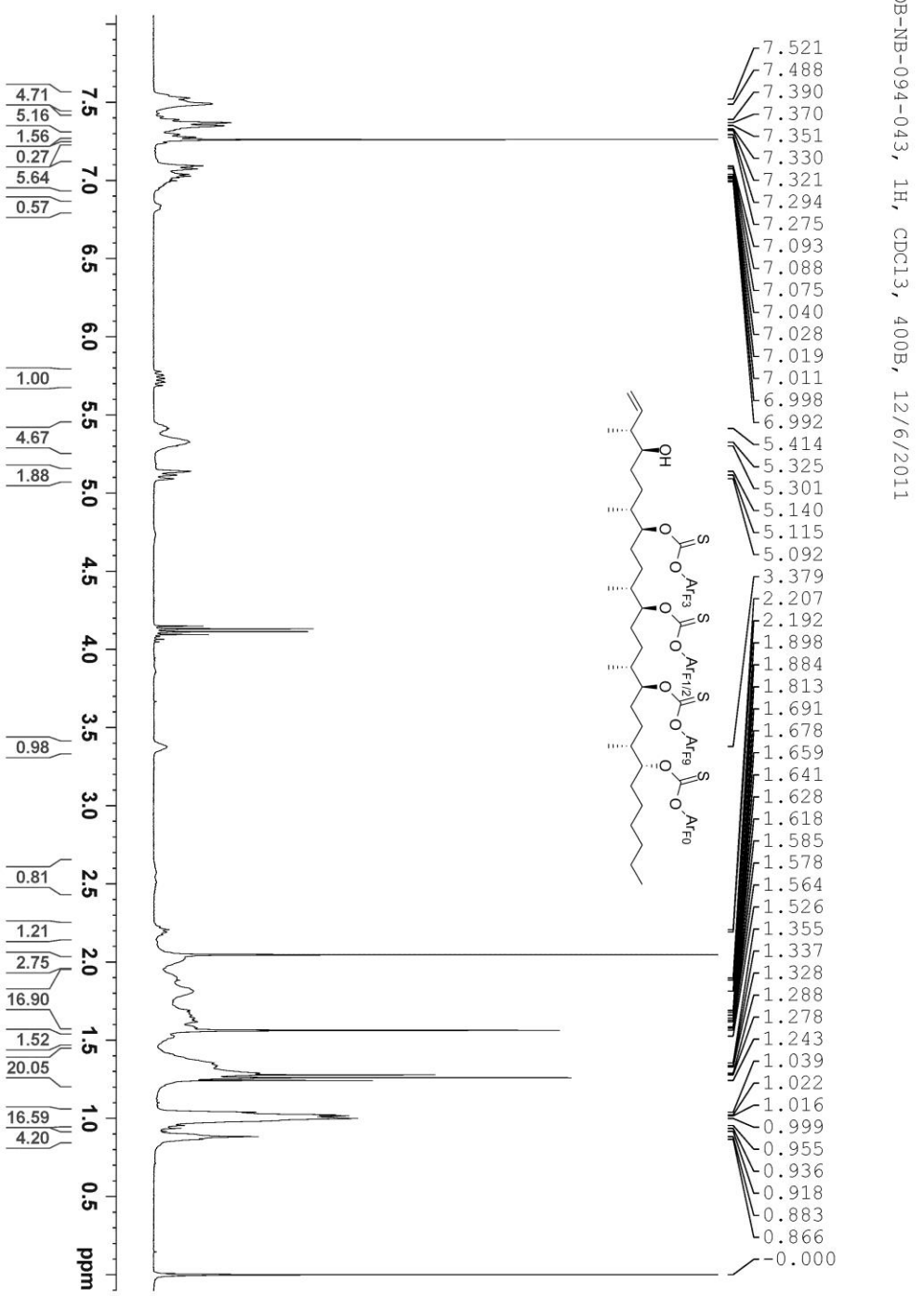


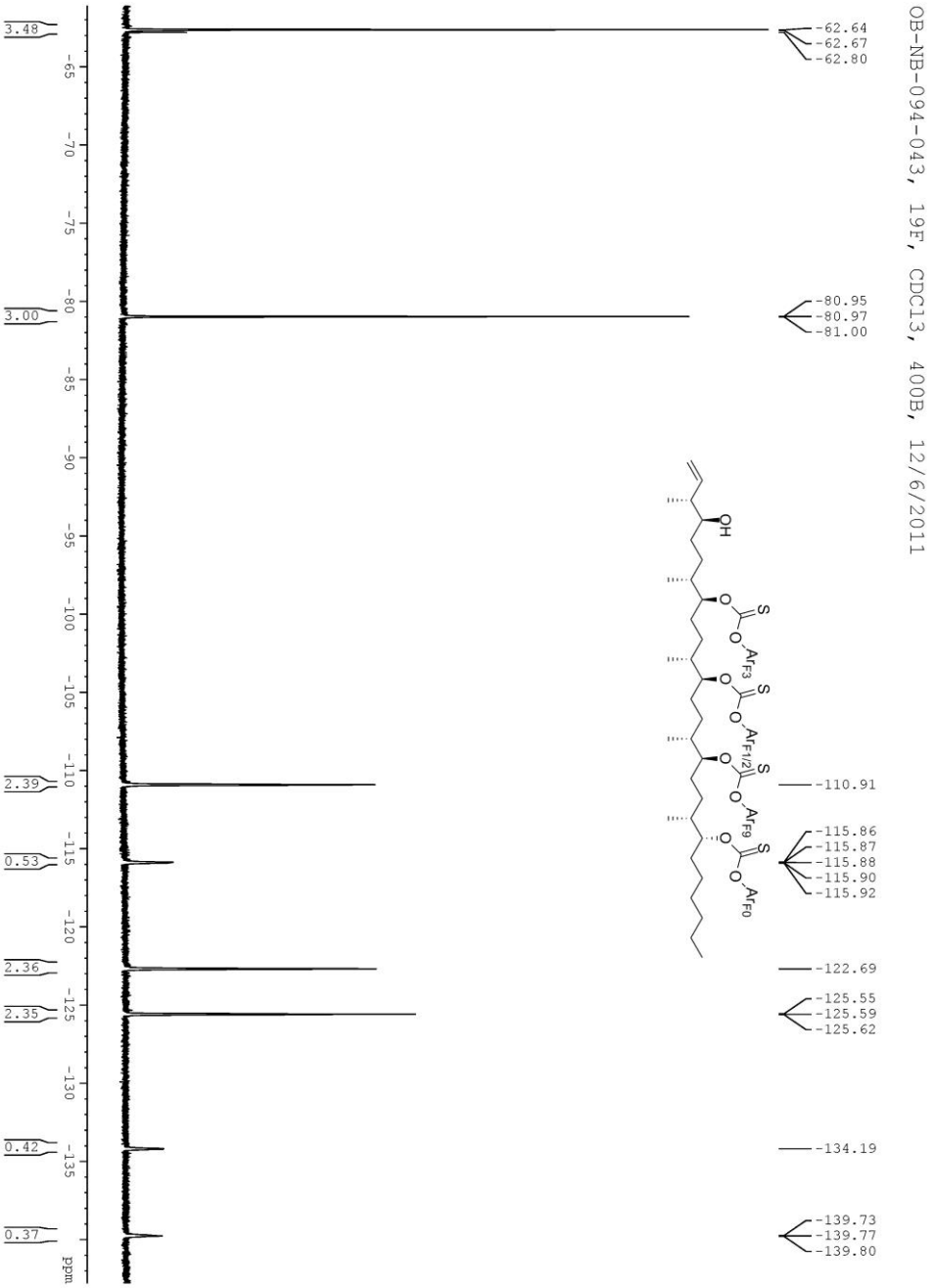

OB-NB-094-037_F42, 1H, 400A, CDCl3
PROTON CDCl3 C:\Bruker\TOPSPIN curran 6
7.491
7.457
7.436
7.416
7.386
7.351
7.259
7.092
7.073
7.027
6.835
6.818
5.818
5.795
5.774
5.754
5.730
5.413
5.338
5.142
5.107
2.654
2.017
1.904
1.811
1.643
1.619
1.544
1.422
1.405
1.387
1.290
1.114
1.104
1.100
1.010
0.883
-0.000
13.84
0.18
5.37
0.34
1.00
4.12
2.04
0.90
2.00
12.72
12.62
3.12
9.55
3.46
ppm

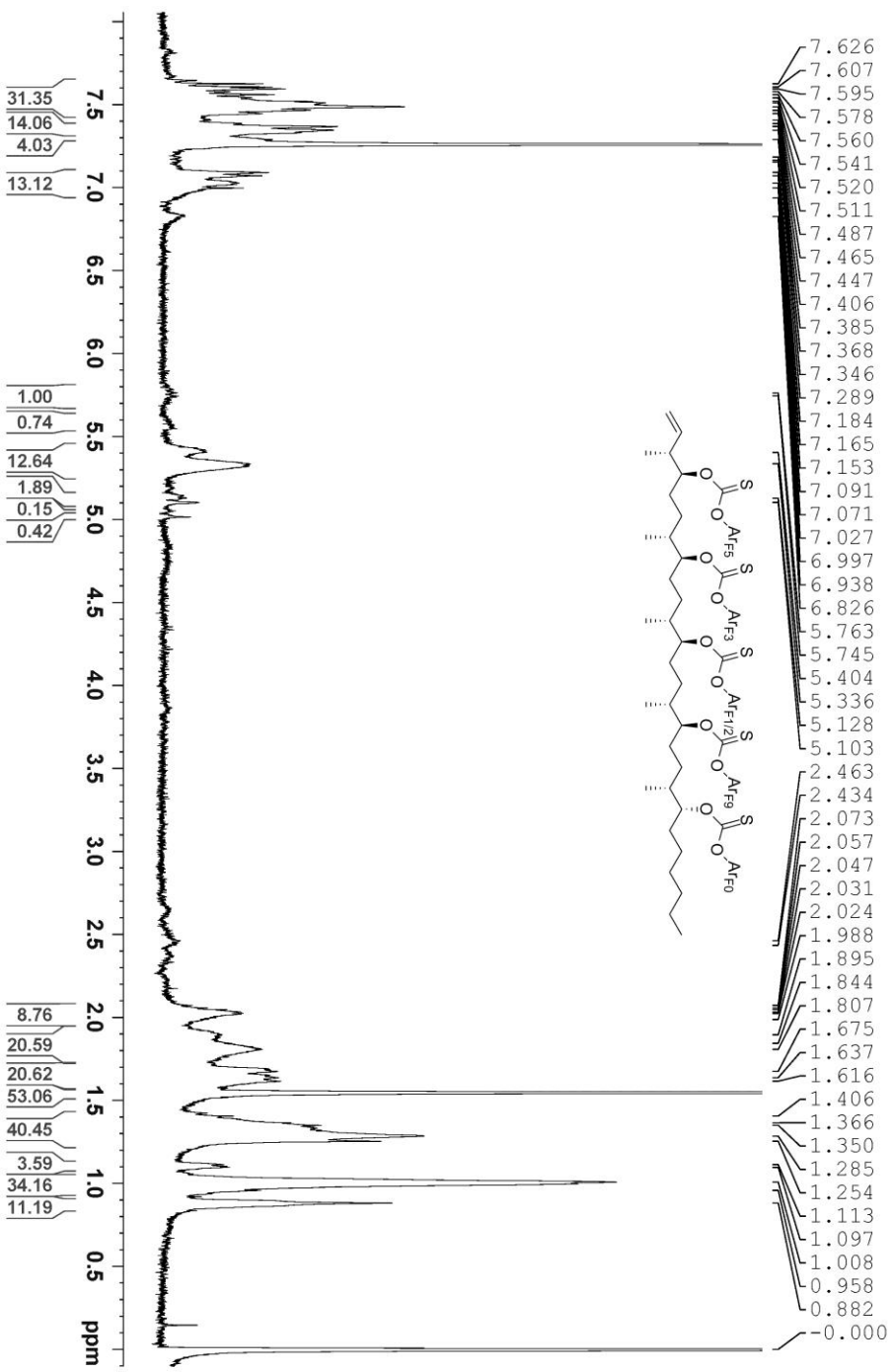

OB-NB-094-037_F42, 19F, 400B, 11/28/2011
-62.70
-62.73
-62.74
-62.76
-80.96
-80.98
-81.01
-110.83
-110.87
-115.84
-115.86
-115.88
-115.90
-115.93
-115.94
-122.66
-125.55
-125.57
-134.18
-134.20
-134.23
-134.26
-139.72
-139.79
-139.82
2.29
3.00
2.23
0.54
2.21
2.14
0.30
0.30
ppm

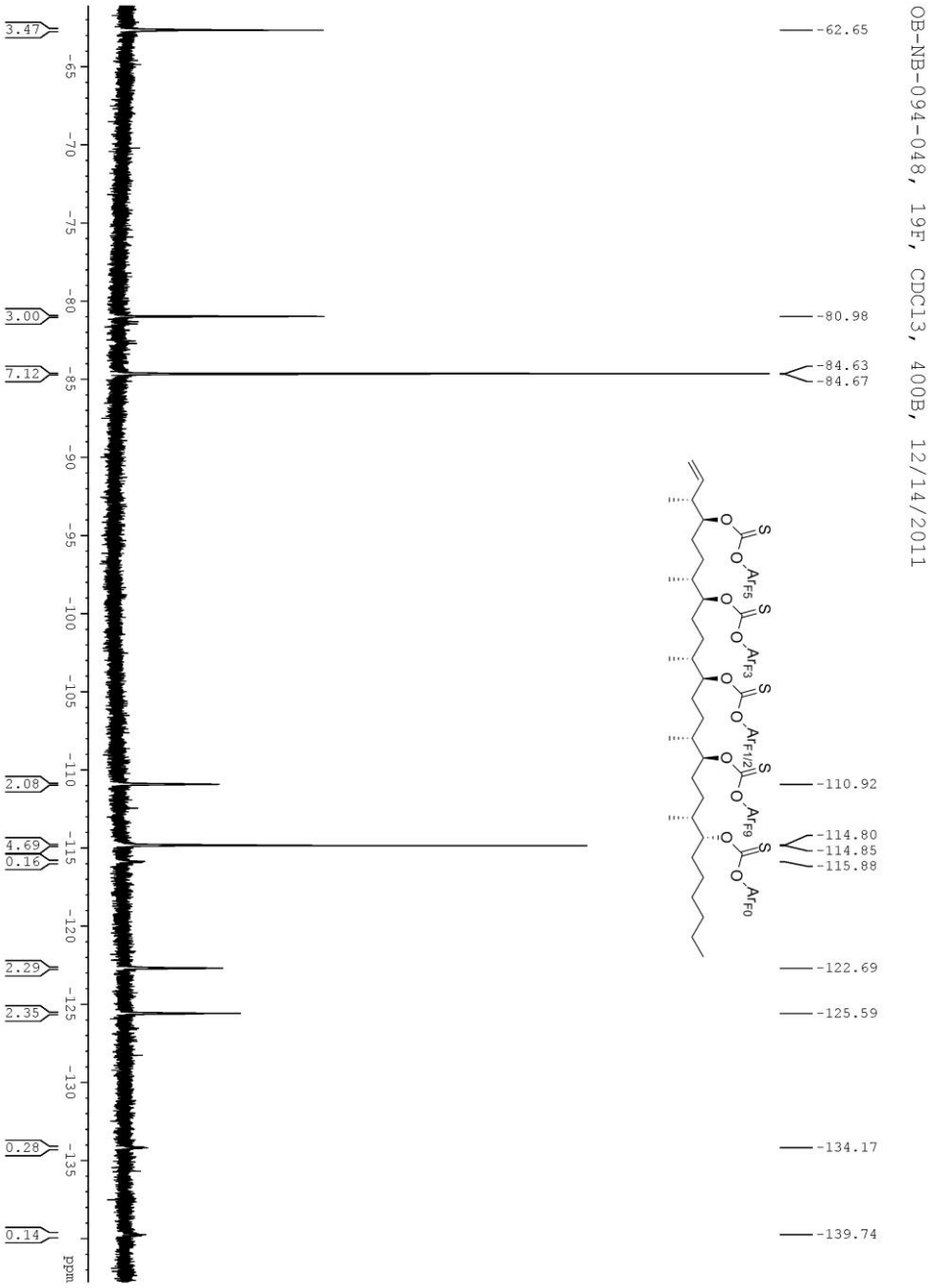

OB-NB-094-040 F64, 1H, 400A, CDC13
PROTON CDC13 C:\Bruker\TOPSPIN curran 13
9.794
7.551
7.533
7.514
7.493
7.428
7.386
7.368
7.351
7.292
7.260
7.093
7.074
7.028
7.002
6.839
5.415
5.326
4.720
3.952
3.923
3.852
2.569
2.508
2.490
2.465
2.020
1.899
1.820
1.640
1.550
1.516
1.341
1.291
1.015
1.008
1.003
0.883
1.00
4.20
4.69
5.20
0.40
4.00
0.09
0.08
2.08
3.03
8.49
4.95
11.58
12.37
3.45
ppm

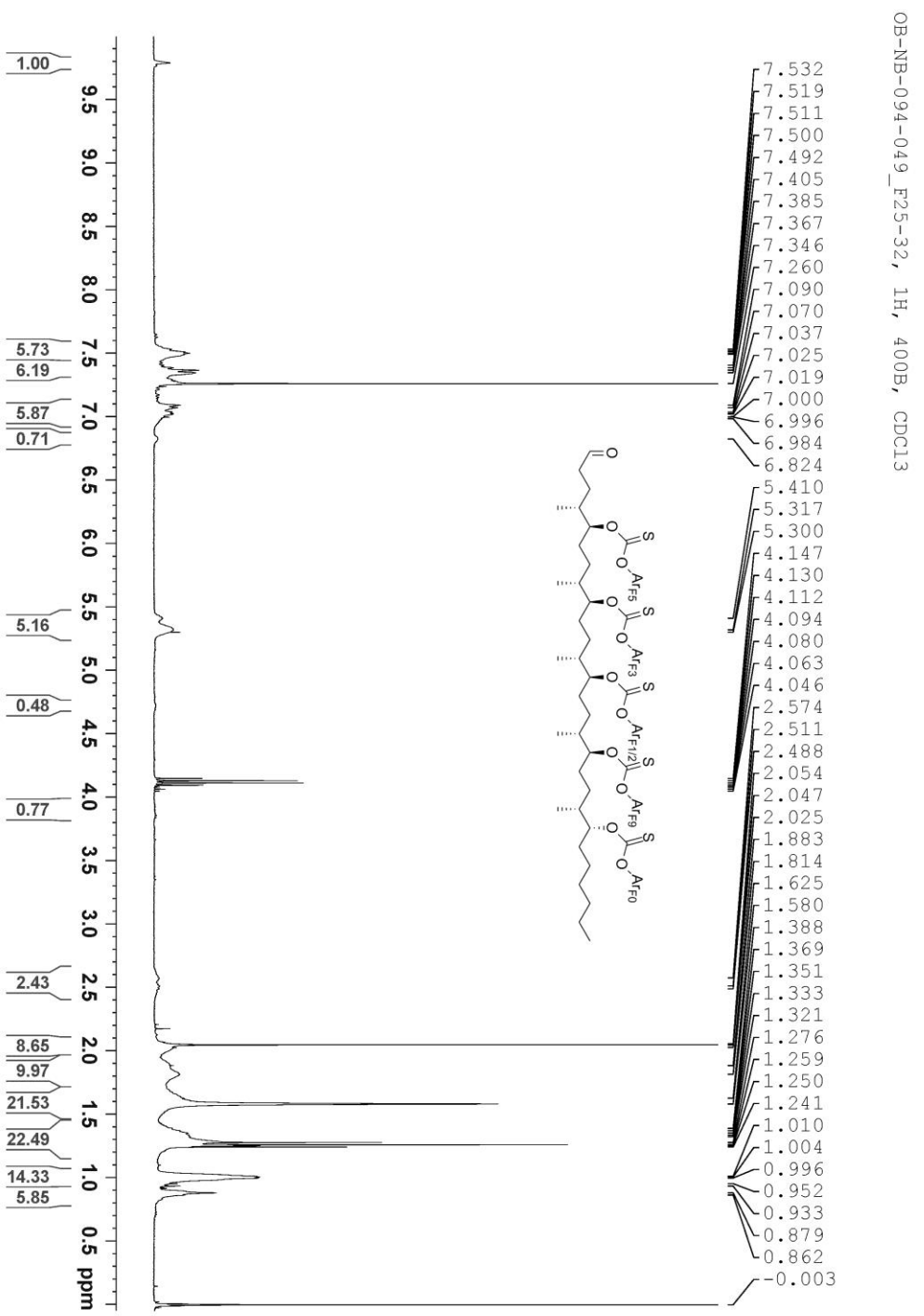

OB-NB-094-040_F68, 19F, 400B, 12/5/2011
-62.67
-62.67
-62.69
-62.71
-80.95
-80.97
-81.00
-110.90
-115.78
-115.79
-115.80
-115.81
-115.82
-115.83
-115.85
-115.86
-115.87
-115.88
-115.89
-115.91
-122.69
-125.55
-125.58
-125.62
-134.12
-134.15
-134.17
-134.20
-134.23
-139.65
-139.67
-139.67
-139.69
-139.72
3.01
3.00
2.18
0.55
2.19
2.16
0.33
0.33
ppm

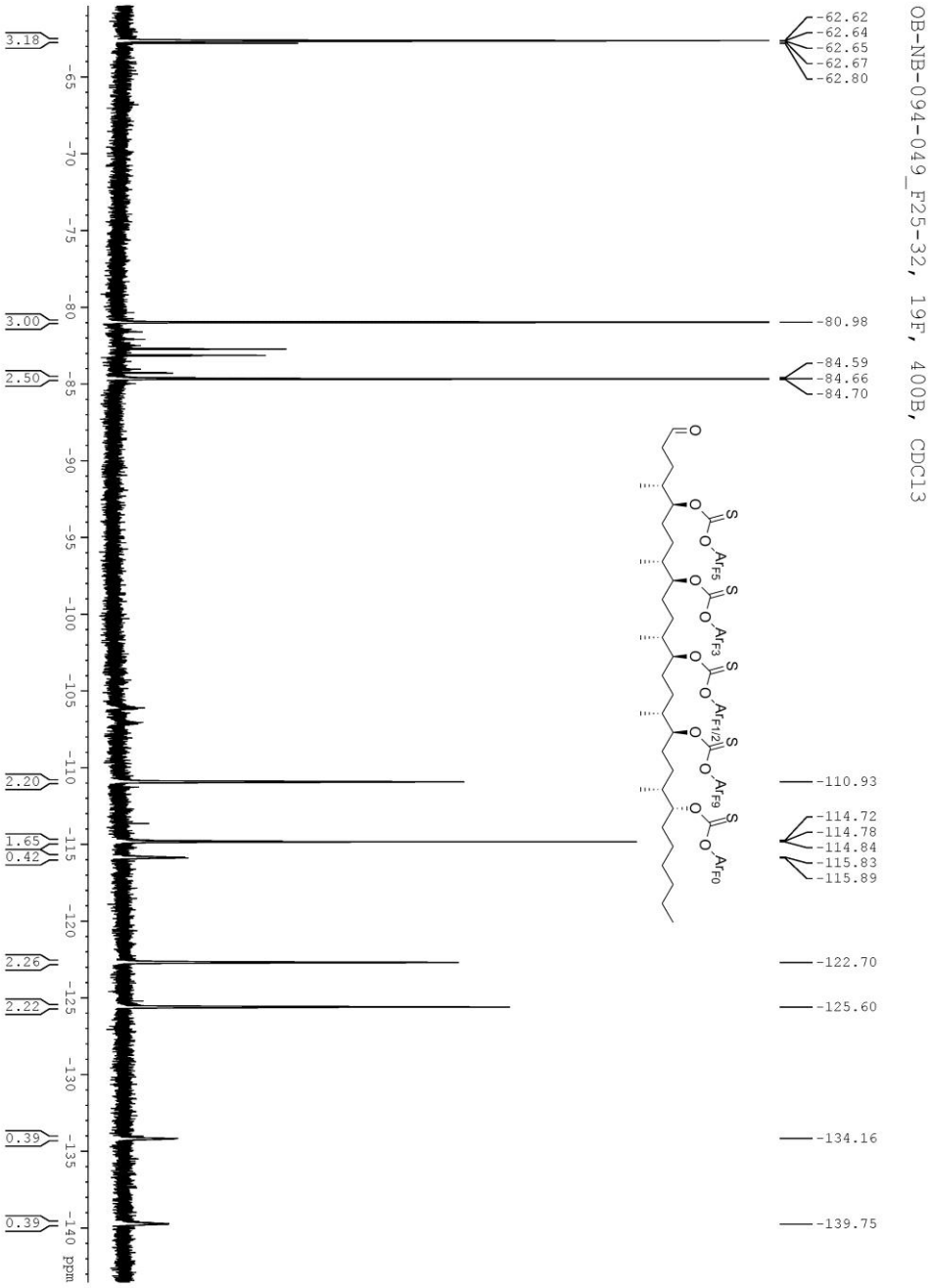

OB-NB-094-043, 1H, CDCl3, 400B, 12/6/2011
7.521
7.488
7.390
7.370
7.351
7.330
7.321
7.294
7.275
7.093
7.088
7.075
7.040
7.028
7.019
7.011
6.998
6.992
5.414
5.325
5.301
5.140
5.115
5.092
3.379
2.207
2.192
1.898
1.884
1.813
1.691
1.678
1.659
1.641
1.628
1.618
1.585
1.578
1.564
1.526
1.355
1.337
1.328
1.288
1.278
1.243
1.039
1.022
1.016
0.999
0.955
0.936
0.918
0.883
0.866
-0.000
4.71
5.16
1.56
0.27
5.64
0.57
1.00
4.67
1.88
0.98
0.81
1.21
2.75
16.90
1.52
20.05
16.59
4.20
ppm
OH
S
O
ArF3
ArF1/2
ArF9
ArF0

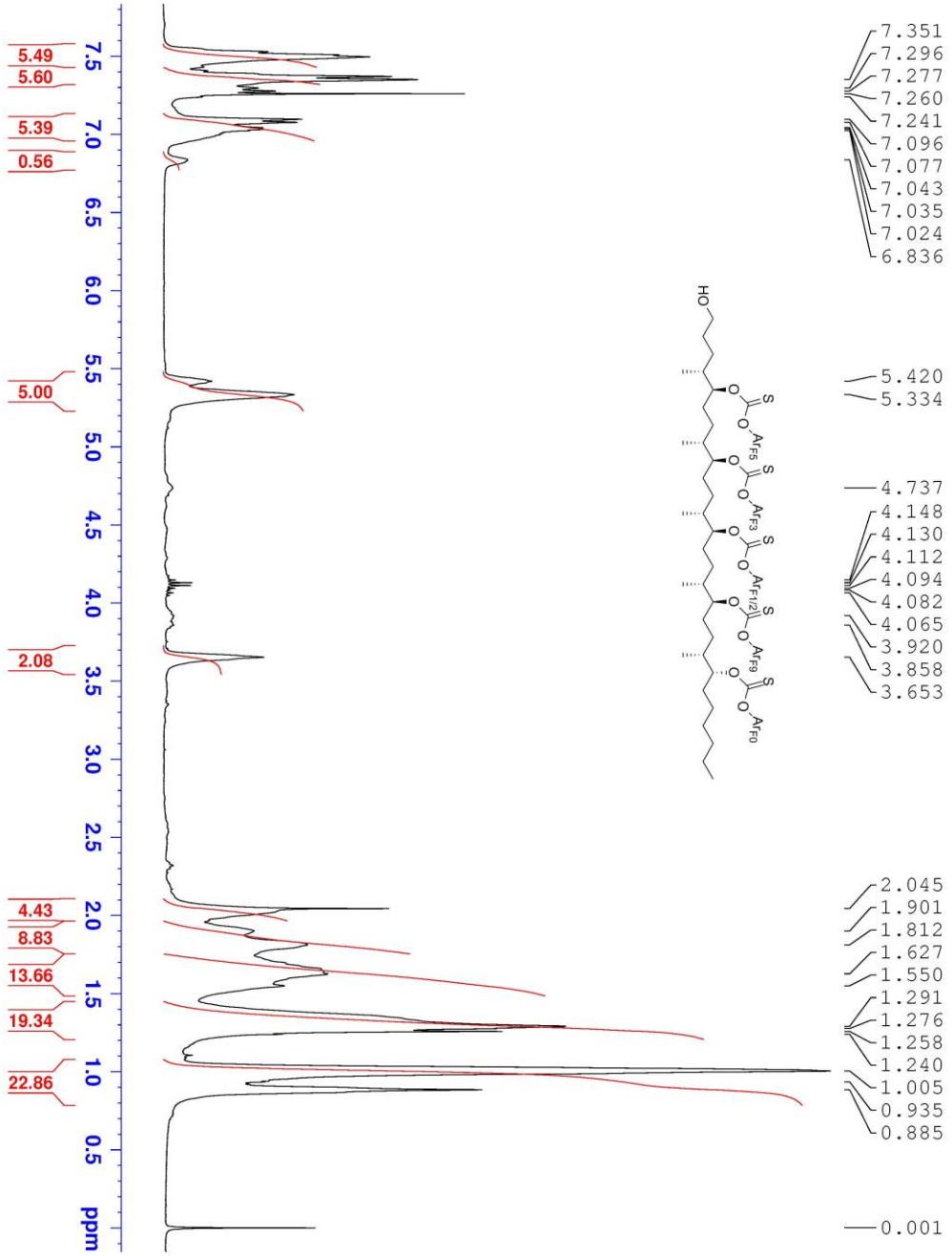

OB-NB-094-043, 19F, CDCl3, 400B, 12/6/2011
-62.64
-62.67
-62.80
-80.95
-80.97
-81.00
-110.91
-115.86
-115.87
-115.88
-115.90
-115.92
-122.69
-125.55
-125.59
-125.62
-134.19
-139.73
-139.77
-139.80
3.48
3.00
2.39
0.53
2.36
2.35
0.42
0.37
ppm

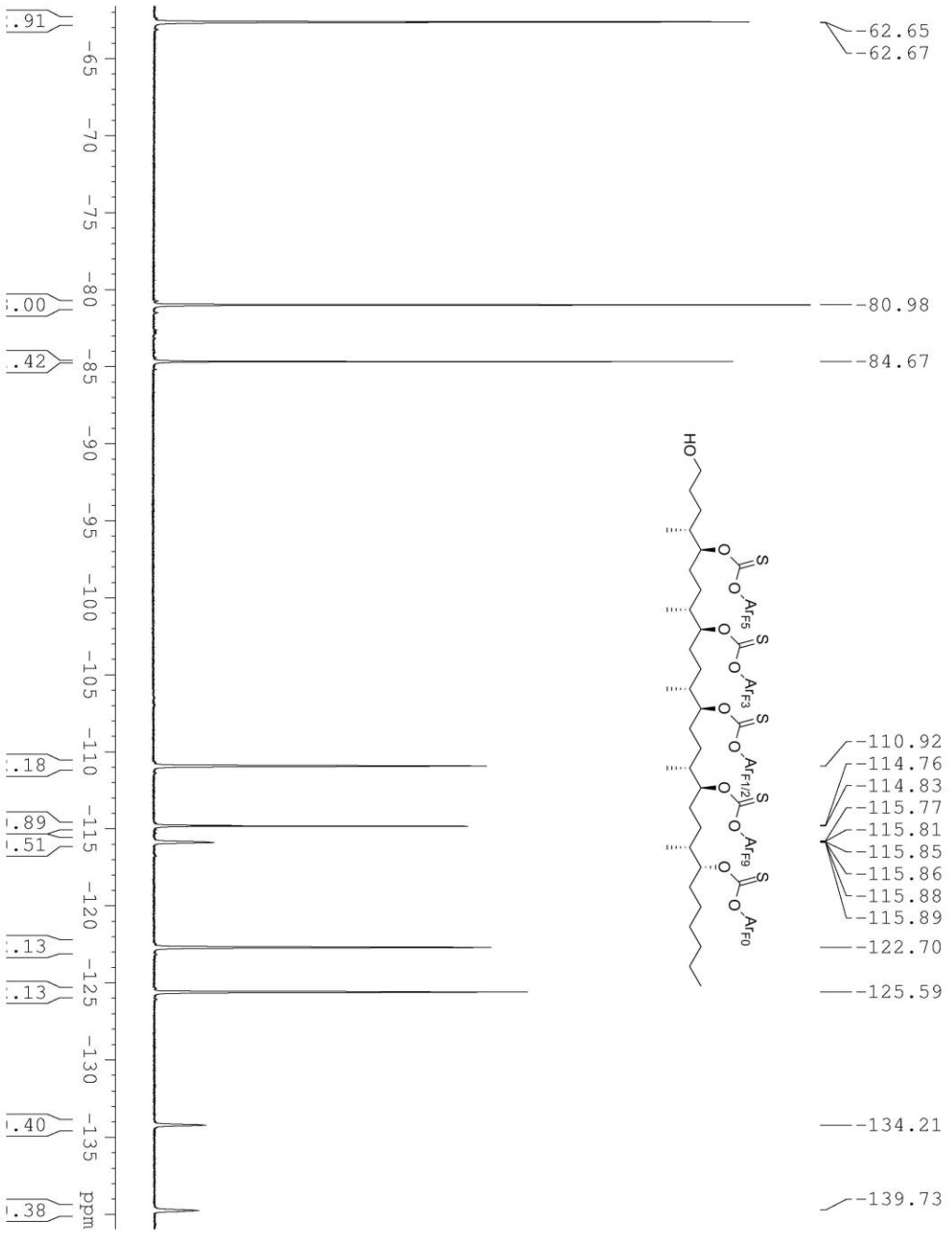

OB-NB-094-048, 1H, 400A, CDC13
PROTON CDC13 C:\Bruker\TOPSPIN curran 8
7.626
7.607
7.595
7.578
7.560
7.541
7.520
7.511
7.487
7.465
7.447
7.406
7.385
7.368
7.346
7.289
7.184
7.165
7.153
7.091
7.071
7.027
6.997
6.938
6.826
5.763
5.745
5.404
5.336
5.128
5.103
2.463
2.434
2.073
2.057
2.047
2.031
2.024
1.988
1.895
1.844
1.807
1.675
1.637
1.616
1.406
1.366
1.350
1.285
1.254
1.113
1.097
1.008
0.958
0.882
-0.000
31.35
14.06
4.03
13.12
1.00
0.74
12.64
1.89
0.15
0.42
8.76
20.59
20.62
53.06
40.45
3.59
34.16
11.19
ppm

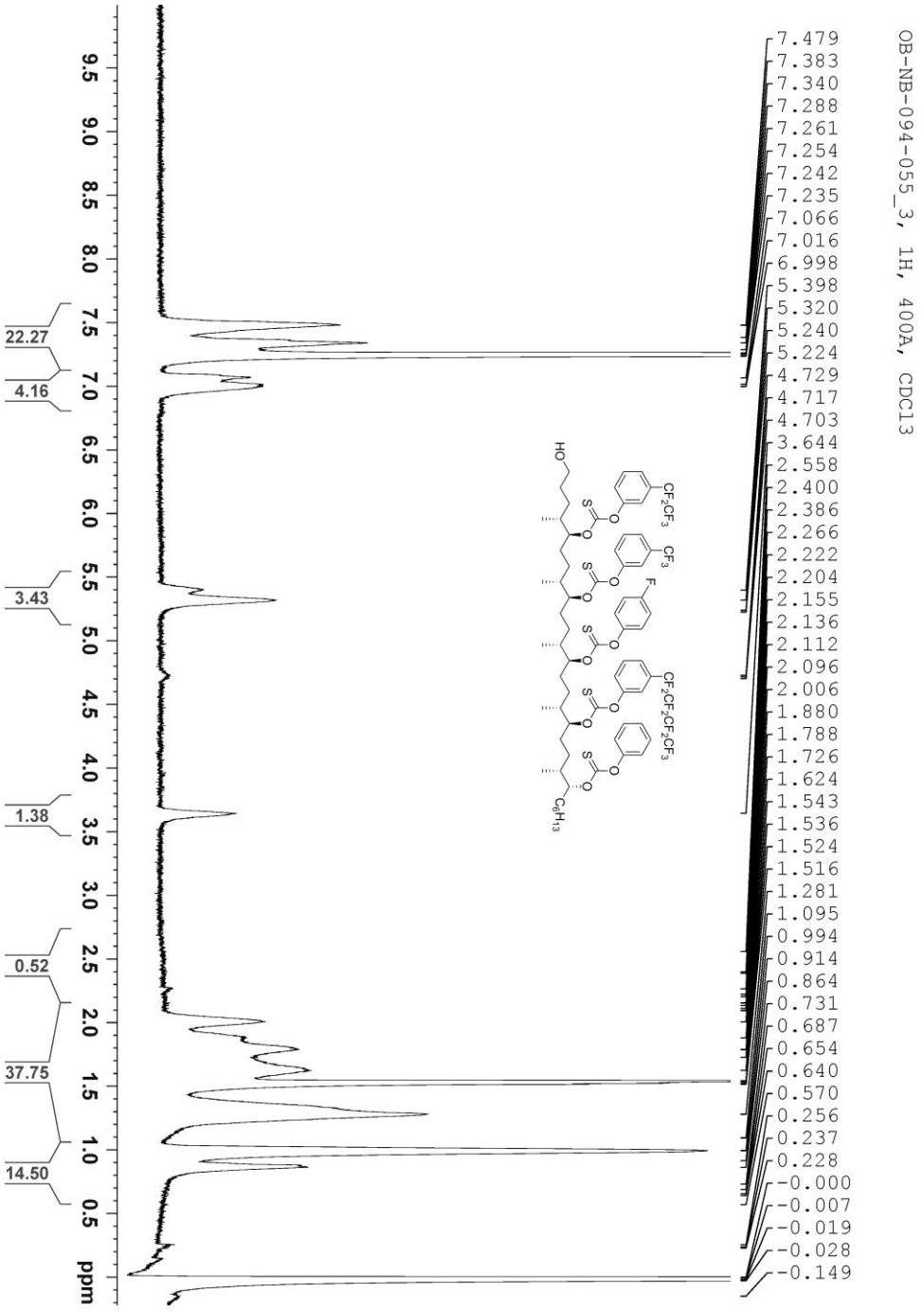

OB-NB-094-048, 19F, CDCl3, 400B, 12/14/2011
-62.65
-80.98
-84.63
-84.67
-110.92
-114.80
-114.85
-115.88
-122.69
-125.59
-134.17
-139.74
3.47
3.00
7.12
2.08
4.69
0.16
2.29
2.35
0.28
0.14
ppm

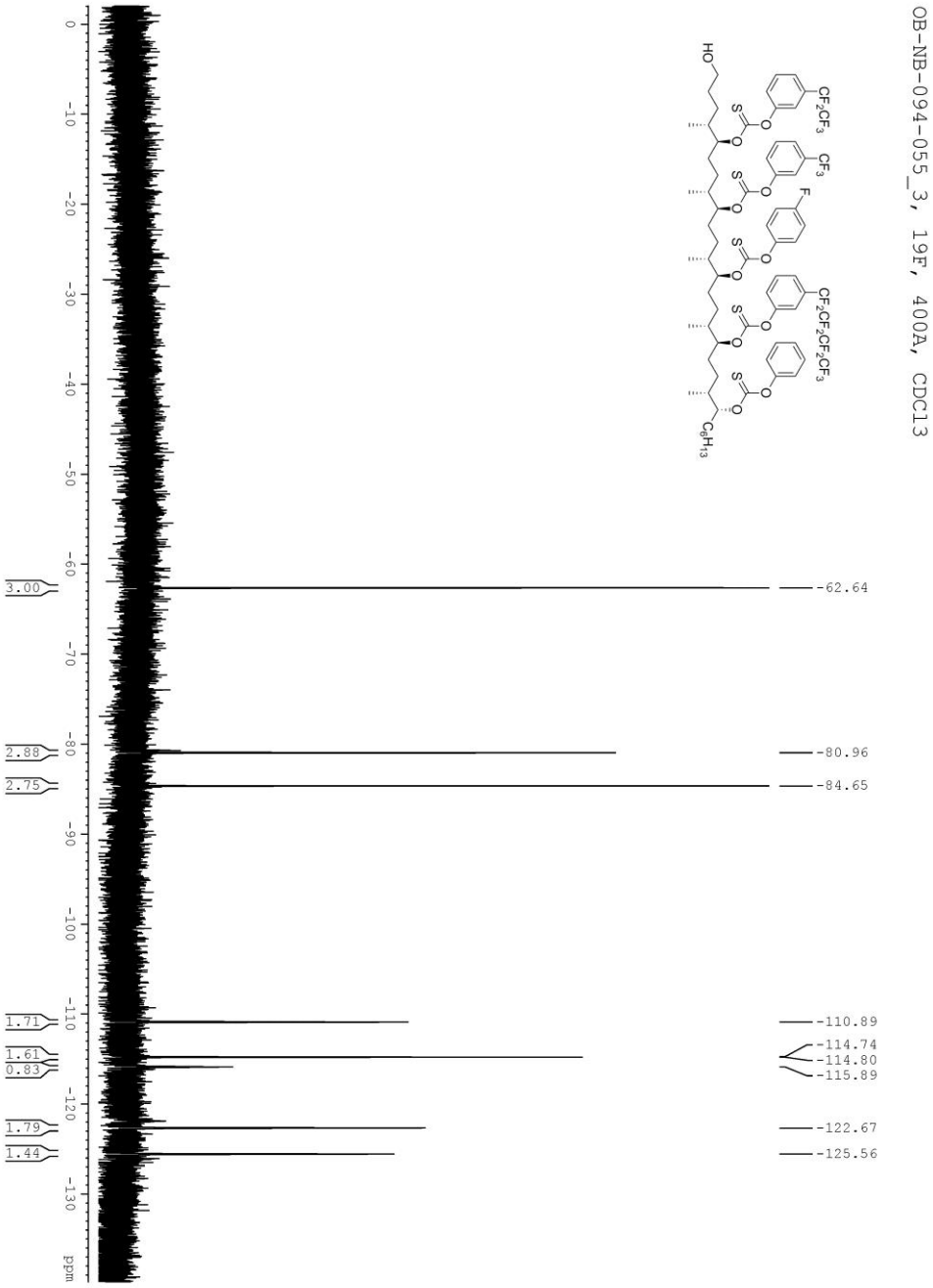

OB-NB-094-049_F25-32, 1H, 400B, CDC13
7.532
7.519
7.511
7.500
7.492
7.405
7.385
7.367
7.346
7.260
7.090
7.070
7.037
7.025
7.019
7.000
6.996
6.984
6.824
5.410
5.317
5.300
4.147
4.130
4.112
4.094
4.080
4.063
4.046
2.574
2.511
2.488
2.054
2.047
2.025
1.883
1.814
1.625
1.580
1.388
1.369
1.351
1.333
1.321
1.276
1.259
1.250
1.241
1.010
1.004
0.996
0.952
0.933
0.879
0.862
-0.003
1.00
5.73
6.19
5.87
0.71
5.16
0.48
0.77
2.43
8.65
9.97
21.53
22.49
14.33
5.85
ppm

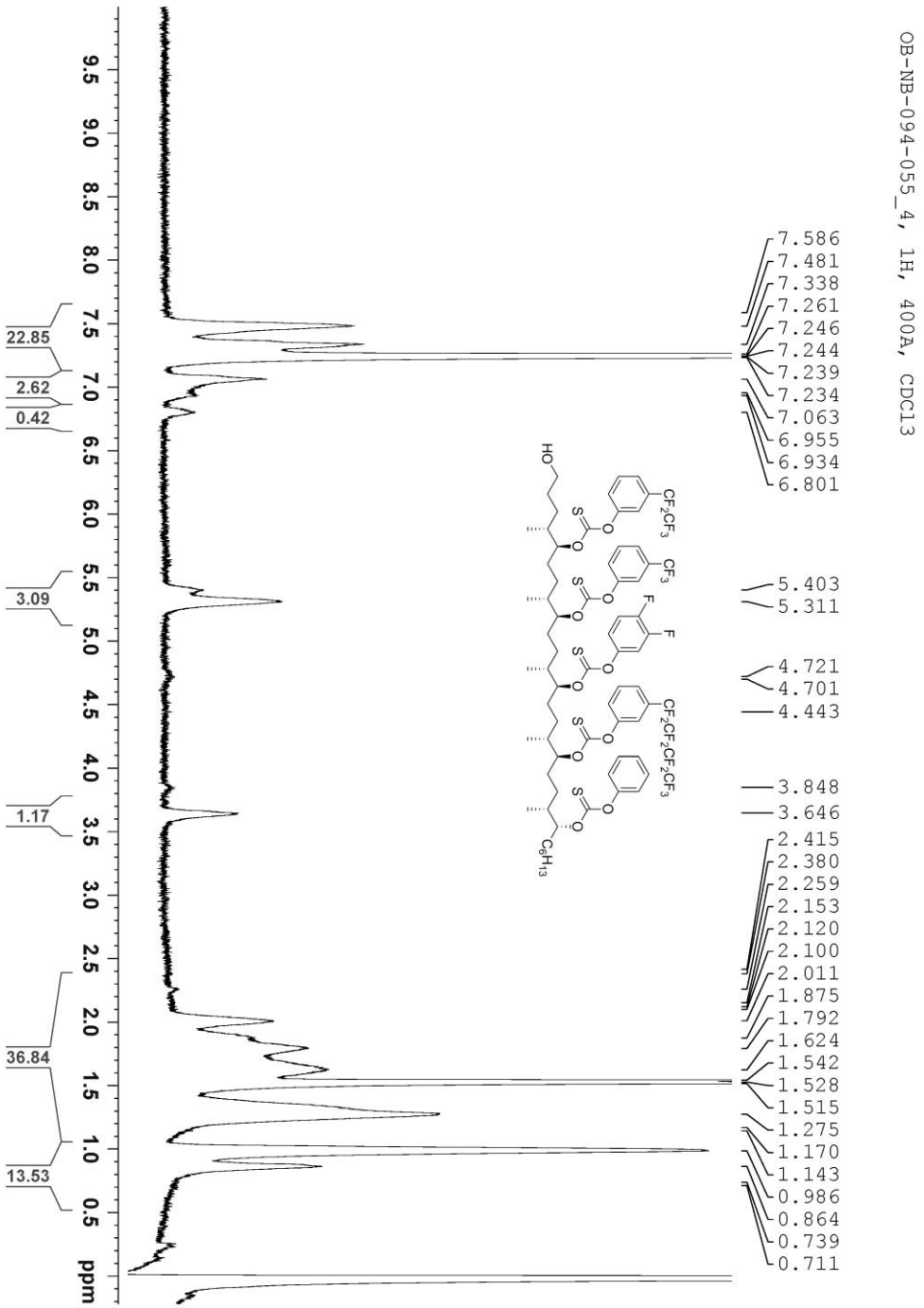

OB-NB-094-049_F25-32, 19F, 400B, CDC13
-62.62
-62.64
-62.65
-62.67
-62.80
-80.98
-84.59
-84.66
-84.70
-110.93
-114.72
-114.78
-114.84
-115.83
-115.89
-122.70
-125.60
-134.16
-139.75
3.18
3.00
2.50
2.20
1.65
0.42
2.26
2.22
0.39
0.39
ppm

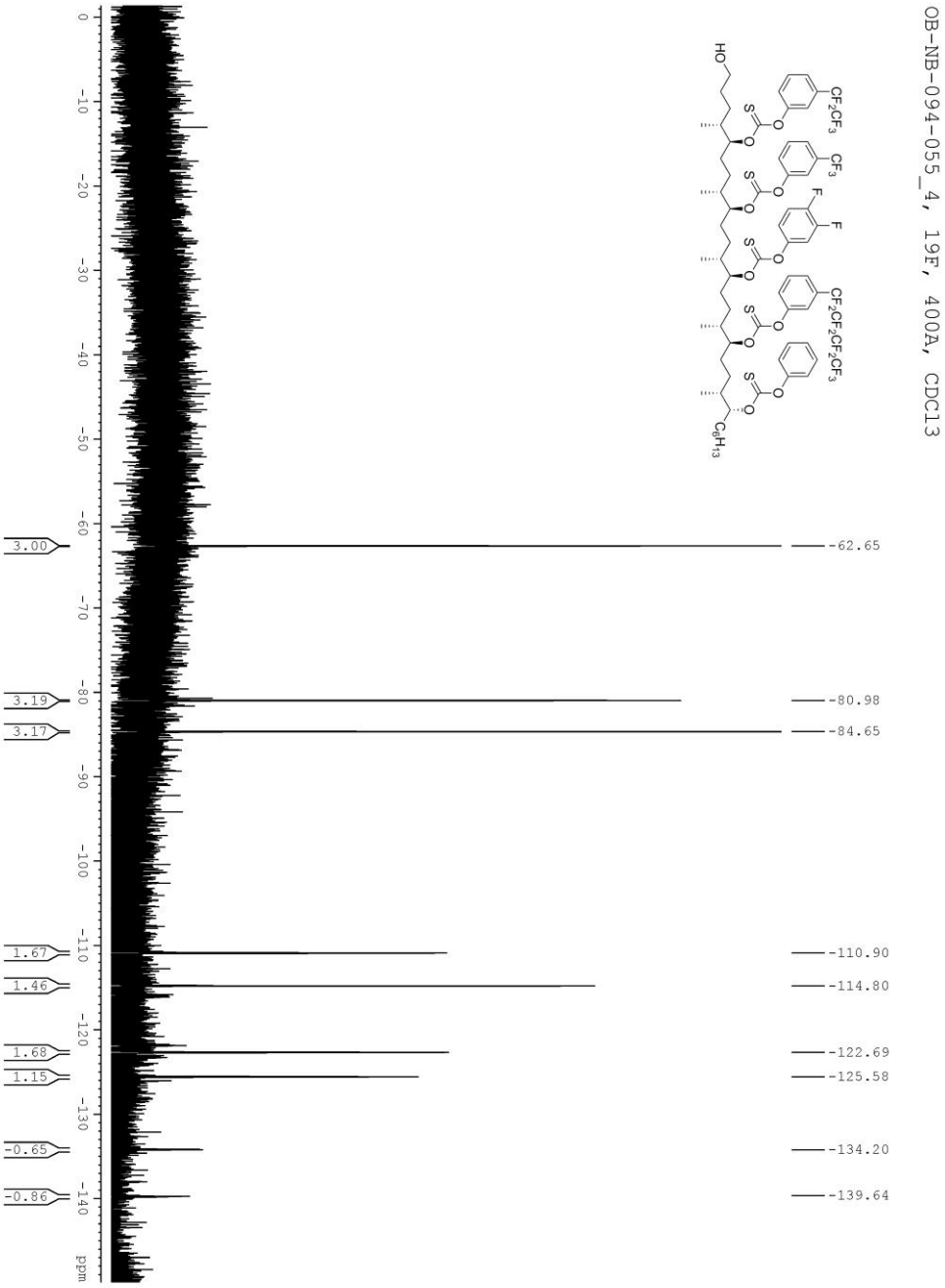

5.49
5.60
5.39
0.56
5.00
2.08
4.43
8.83
13.66
19.34
22.86
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
7.351
7.296
7.277
7.260
7.241
7.096
7.077
7.043
7.035
7.024
6.836
5.420
5.334
4.737
4.148
4.130
4.112
4.094
4.082
4.065
3.920
3.858
3.653
2.045
1.901
1.812
1.627
1.550
1.291
1.276
1.258
1.240
1.005
0.935
0.885
0.001
HO
S
O
ArF5
ArF3
ArF12
ArF9
ArF0

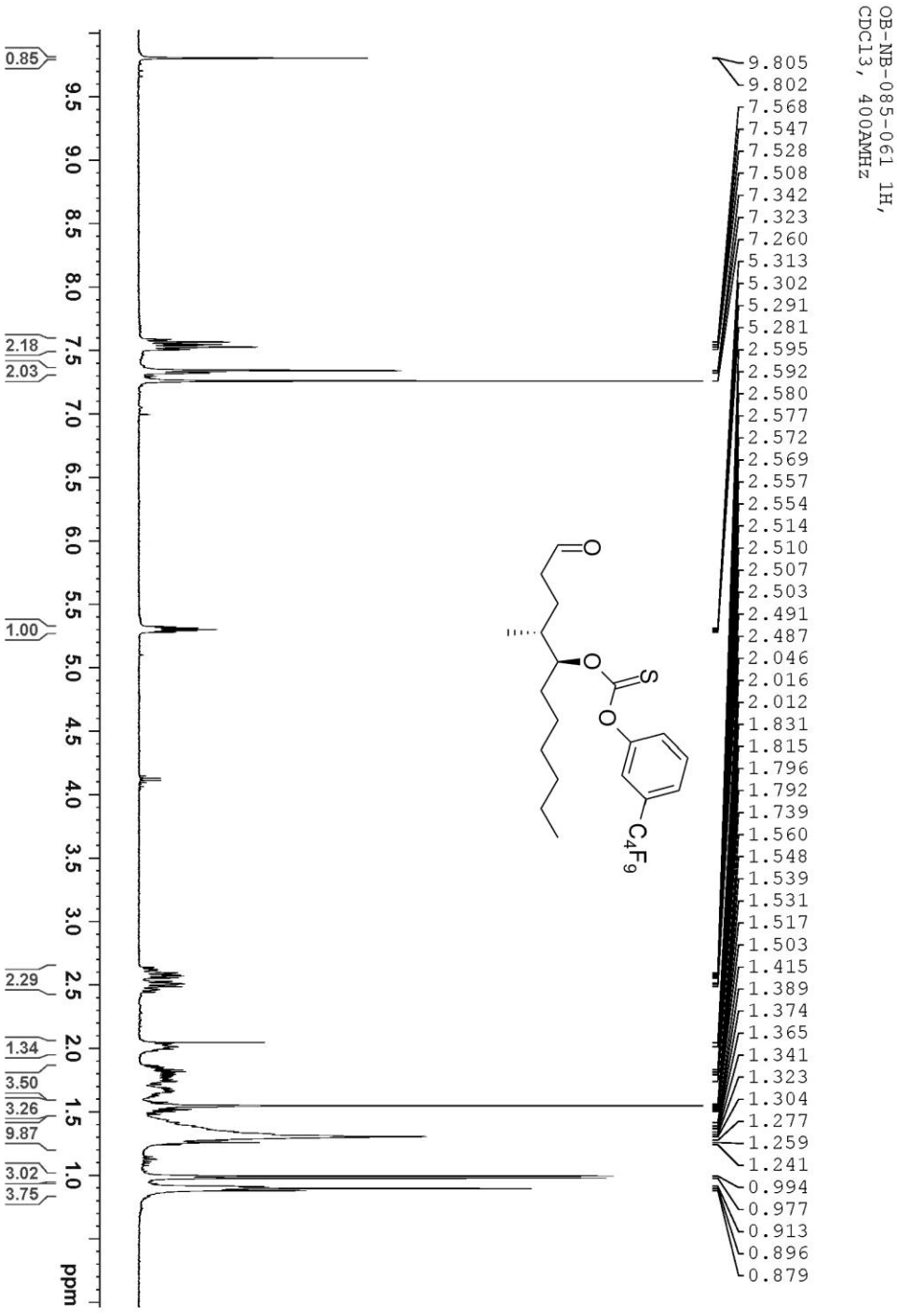

-62.65
-62.67
-80.98
-84.67
-110.92
-114.76
-114.83
-115.77
-115.81
-115.85
-115.86
-115.88
-115.89
-122.70
-125.59
-134.21
-139.73
HO
S
O
ArF5
ArF3
ArF12
ArF9
ArF0
ppm

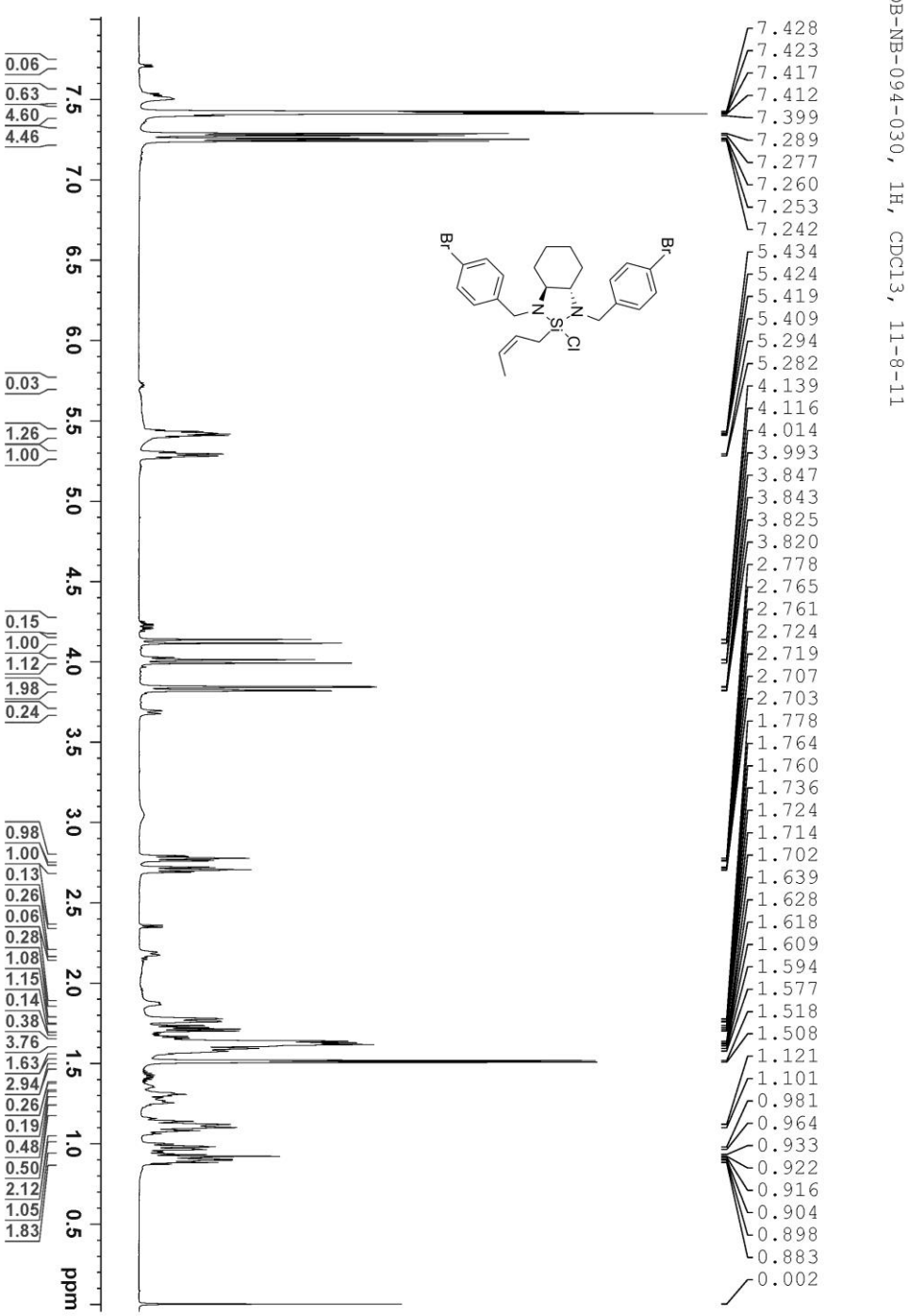

OB-NB-094-055_3, 1H, 400A, CDCl3
7.479
7.383
7.340
7.288
7.261
7.254
7.242
7.235
7.066
7.016
6.998
5.398
5.320
5.240
5.224
4.729
4.717
4.703
3.644
2.558
2.400
2.386
2.266
2.222
2.204
2.155
2.136
2.112
2.096
2.006
1.880
1.788
1.726
1.624
1.543
1.536
1.524
1.516
1.281
1.095
0.994
0.914
0.864
0.731
0.687
0.654
0.640
0.570
0.256
0.237
0.228
-0.000
-0.007
-0.019
-0.028
-0.149
22.27
4.16
3.43
1.38
0.52
37.75
14.50
ppm

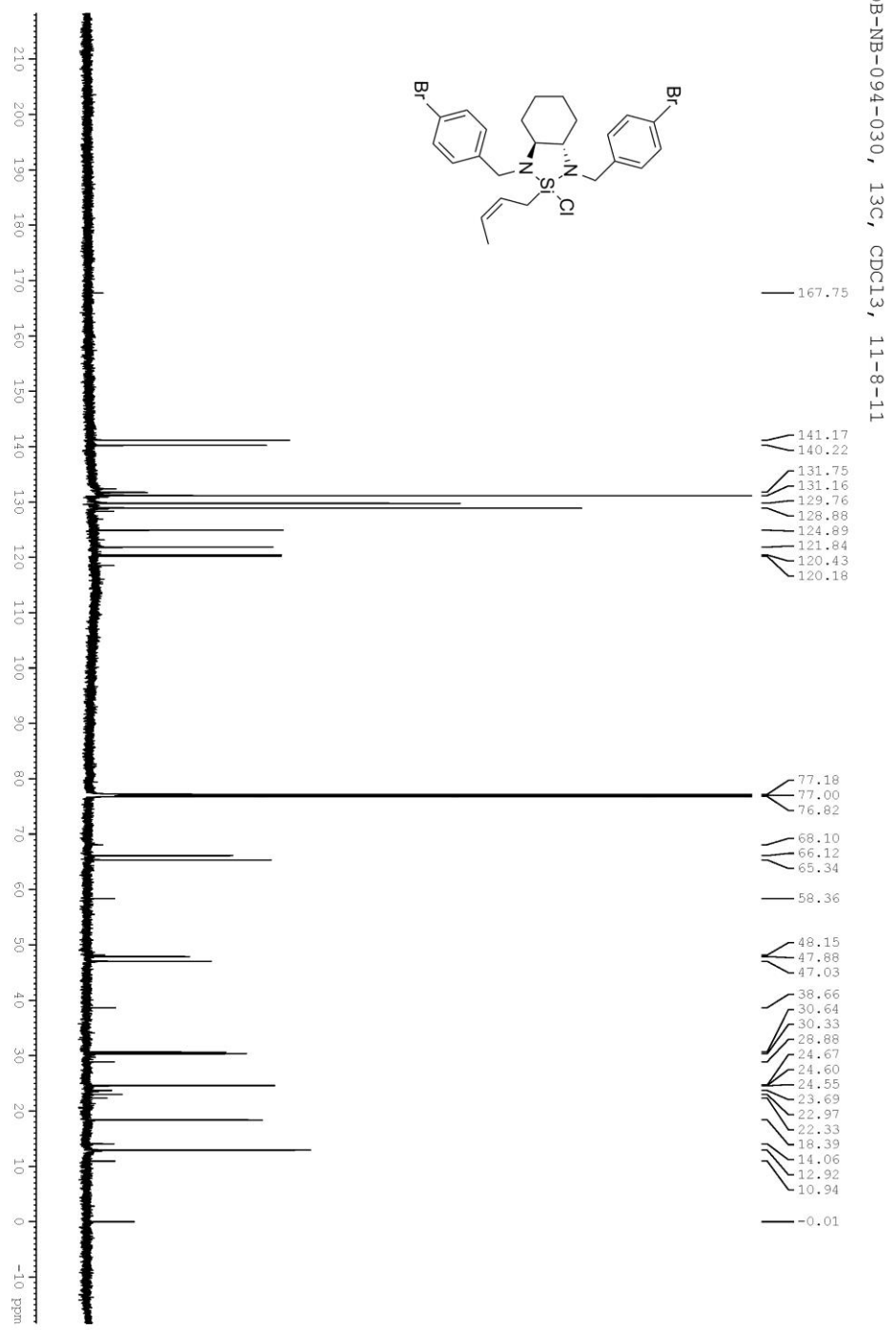

OB-NB-094-055_3, 19F, 400A, CDC13
HO
CF2CF3
CF3
F
CF2CF2CF2CF3
C6H13
-62.64
-80.96
-84.65
-110.89
-114.74
-114.80
-115.89
-122.67
-125.56
3.00
2.88
2.75
1.71
1.61
0.83
1.79
1.44
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

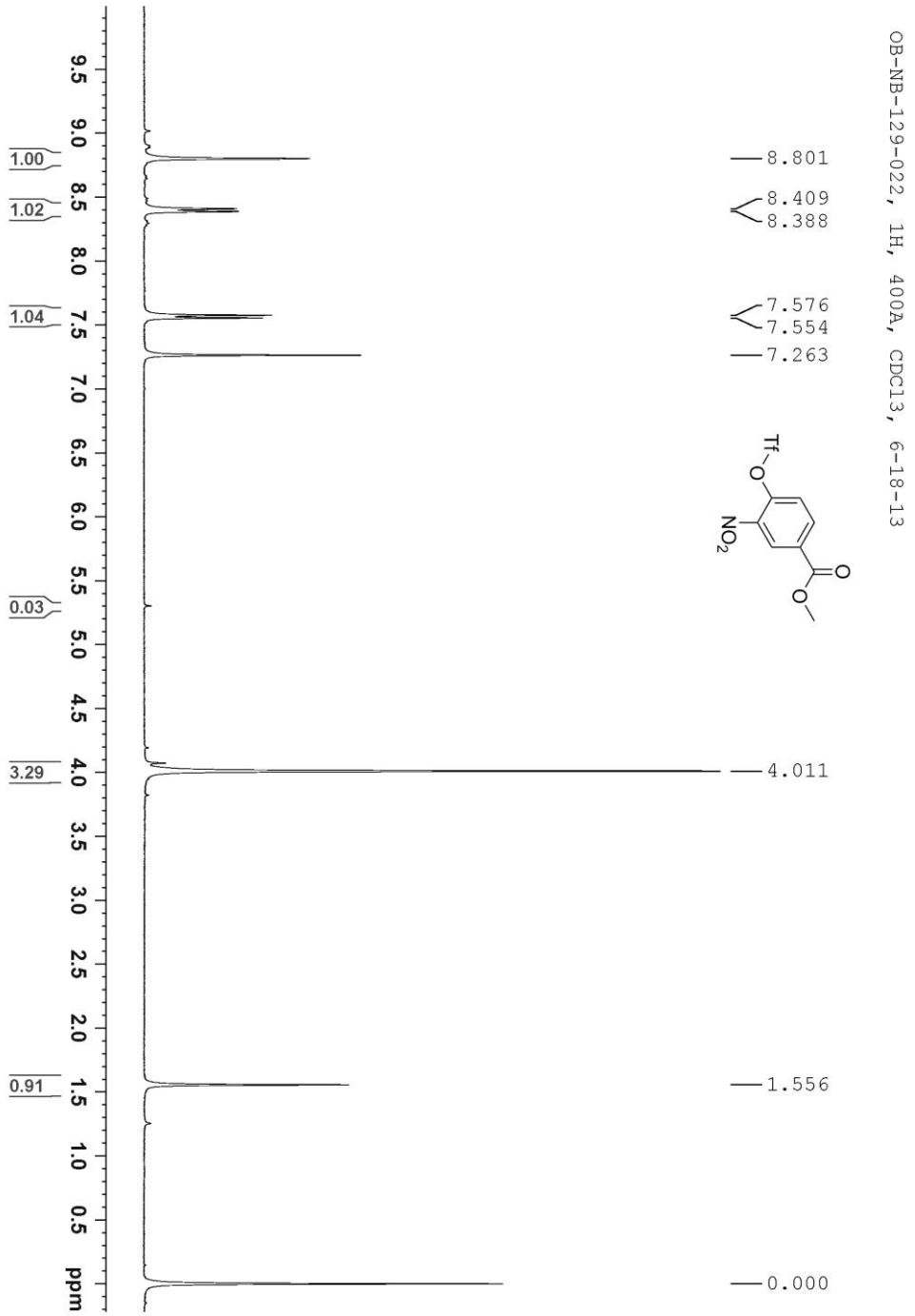

OB-NB-094-055_4, 1H, 400A, CDCl3
7.586
7.481
7.338
7.261
7.246
7.244
7.239
7.234
7.063
6.955
6.934
6.801
5.403
5.311
4.721
4.701
4.443
3.848
3.646
2.415
2.380
2.259
2.153
2.120
2.100
2.011
1.875
1.792
1.624
1.542
1.528
1.515
1.275
1.170
1.143
0.986
0.864
0.739
0.711
22.85
2.62
0.42
3.09
1.17
36.84
13.53
ppm

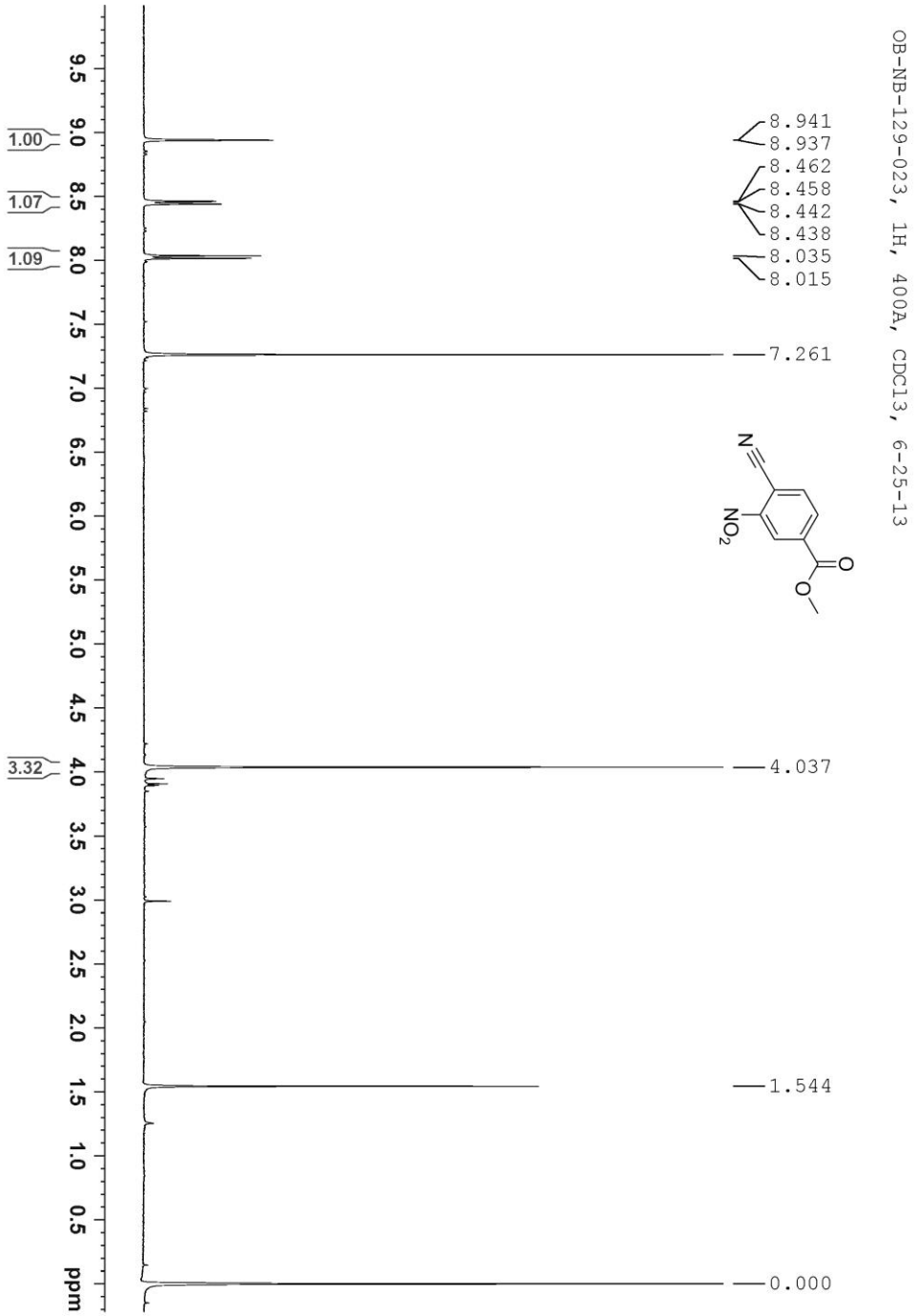

OB-NB-094-055_4, 19F, 400A, CDC13
-62.65
-80.98
-84.65
-110.90
-114.80
-122.69
-125.58
-134.20
-139.64
3.00
3.19
3.17
1.67
1.46
1.68
1.15
-0.65
-0.86
ppm

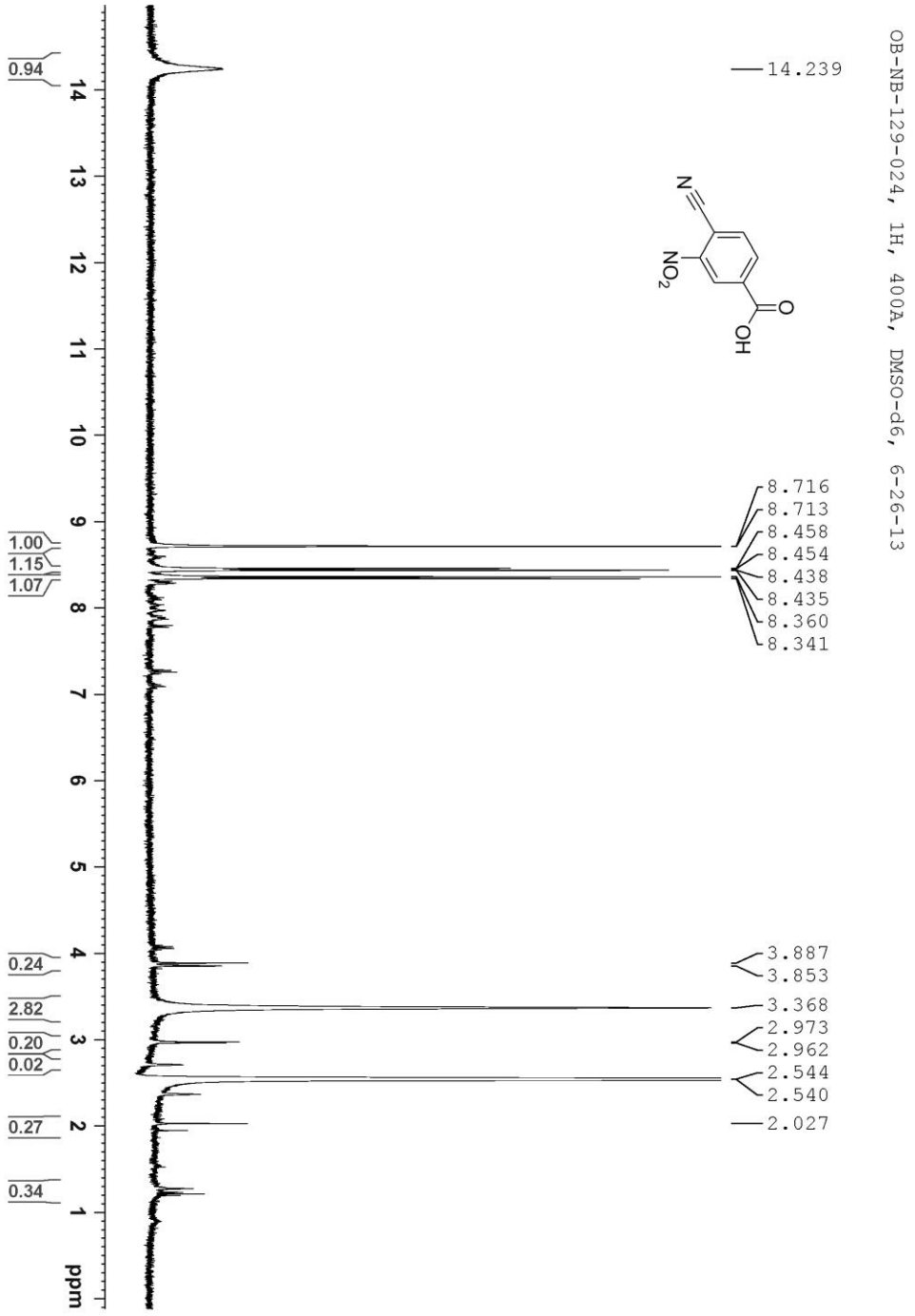

OB-NB-085-061 1H,
CDCl3, 400AMHz
9.805
9.802
7.568
7.547
7.528
7.508
7.342
7.323
7.260
5.313
5.302
5.291
5.281
2.595
2.592
2.580
2.577
2.572
2.569
2.557
2.554
2.514
2.510
2.507
2.503
2.491
2.487
2.046
2.016
2.012
1.831
1.815
1.796
1.792
1.739
1.560
1.548
1.539
1.531
1.517
1.503
1.415
1.389
1.374
1.365
1.341
1.323
1.304
1.277
1.259
1.241
0.994
0.977
0.913
0.896
0.879
0.85
2.18
2.03
1.00
2.29
1.34
3.50
3.26
9.87
3.02
3.75
ppm
O
O
S
O
C4F9

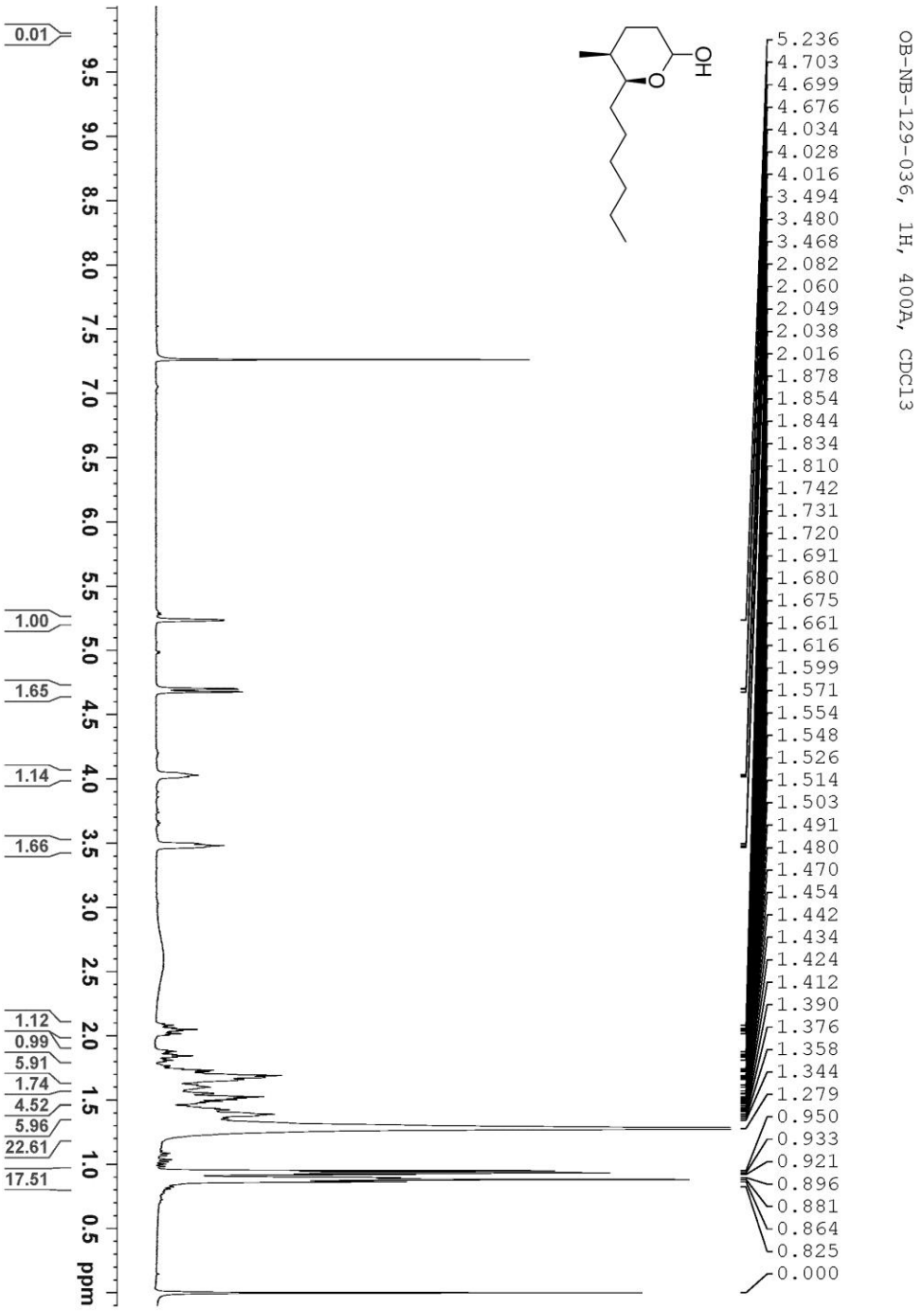

OB-NB-094-030, 1H, CDCl3, 11-8-11
7.428
7.423
7.417
7.412
7.399
7.289
7.277
7.260
7.253
7.242
5.434
5.424
5.419
5.409
5.294
5.282
4.139
4.116
4.014
3.993
3.847
3.843
3.825
3.820
2.778
2.765
2.761
2.724
2.719
2.707
2.703
1.778
1.764
1.760
1.736
1.724
1.714
1.702
1.639
1.628
1.618
1.609
1.594
1.577
1.518
1.508
1.121
1.101
0.981
0.964
0.933
0.922
0.916
0.904
0.898
0.883
0.002
Br
Br
N
N
Si
Cl
0.06
0.63
4.60
4.46
0.03
1.26
1.00
0.15
1.00
1.12
1.98
0.24
0.98
1.00
0.13
0.26
0.06
0.28
1.08
1.15
0.14
0.38
3.76
1.63
2.94
0.26
0.19
0.48
0.50
2.12
1.05
1.83
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
ppm

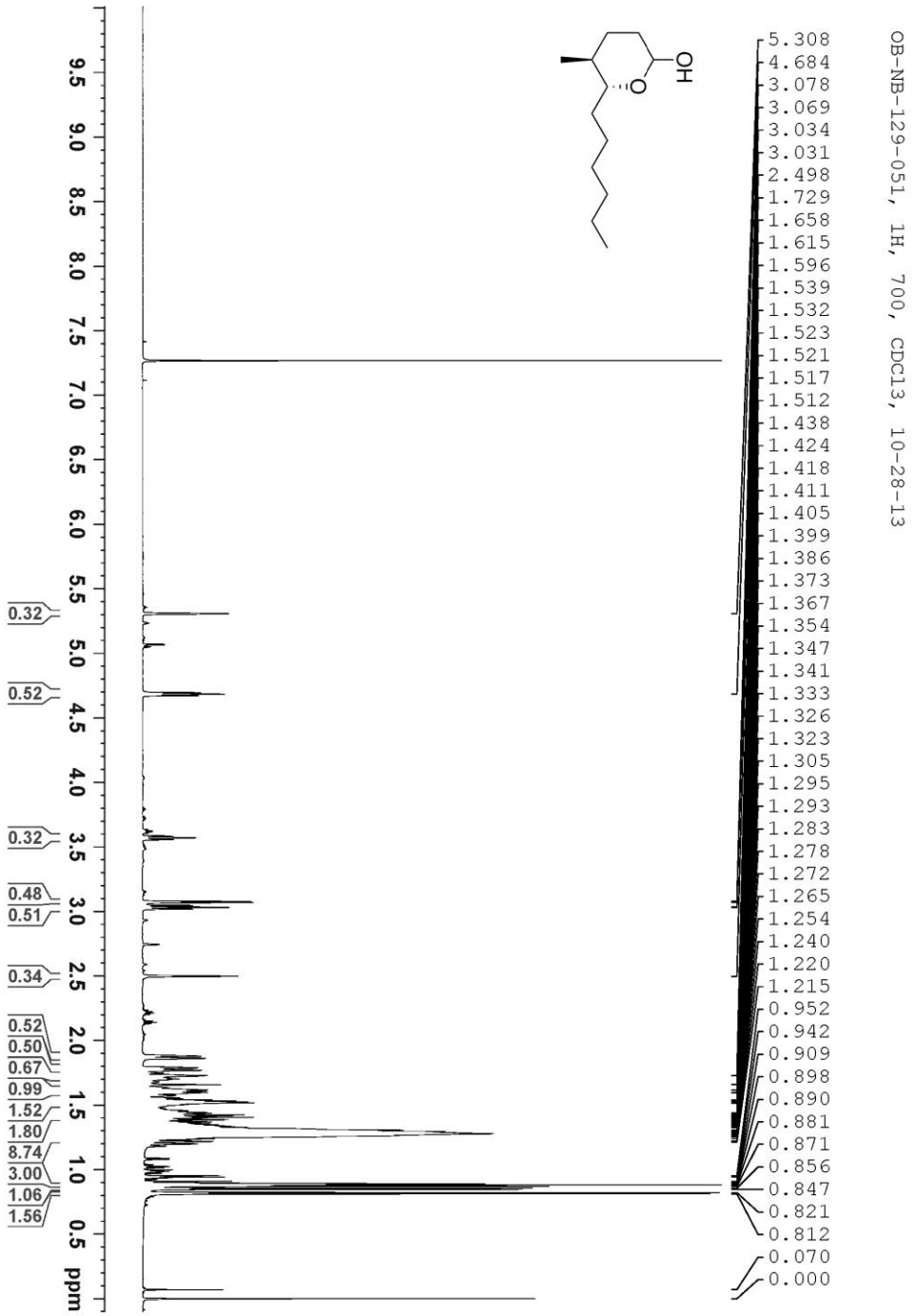

OB-NB-094-030, 13C, CDCl3, 11-8-11
Br
Br
N
N
Si
Cl
167.75
141.17
140.22
131.75
131.16
129.76
128.88
124.89
121.84
120.43
120.18
77.18
77.00
76.82
68.10
66.12
65.34
58.36
48.15
47.88
47.03
38.66
30.64
30.33
28.88
24.67
24.60
24.55
23.69
22.97
22.33
18.39
14.06
12.92
10.94
-0.01
ppm

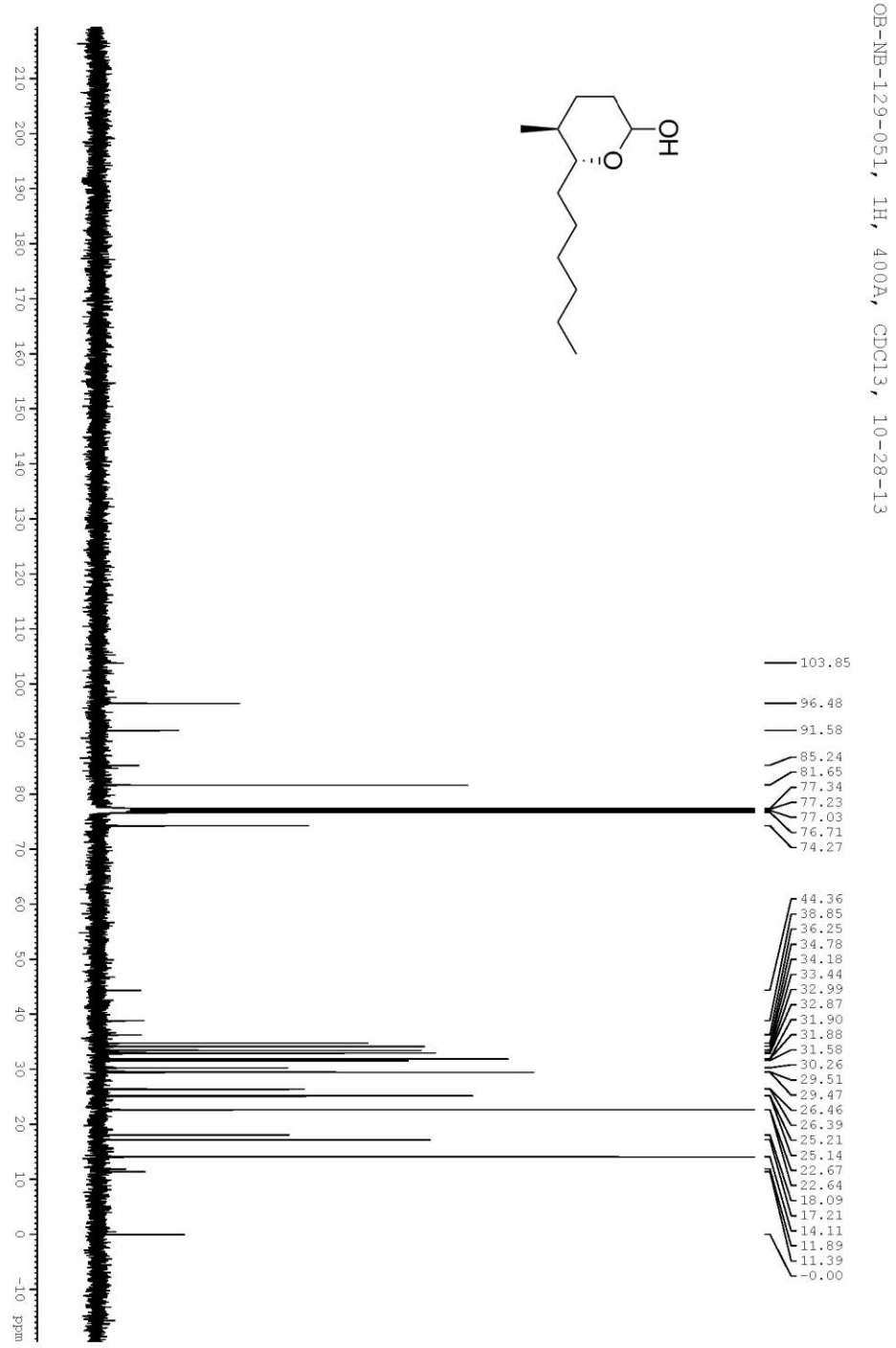

OB-NB-129-022, 1H, 400A, CDCl3, 6-18-13
8.801
8.409
8.388
7.576
7.554
7.263
4.011
1.556
0.000
Tf
O
NO2
O
O
1.00
1.02
1.04
0.03
3.29
0.91
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

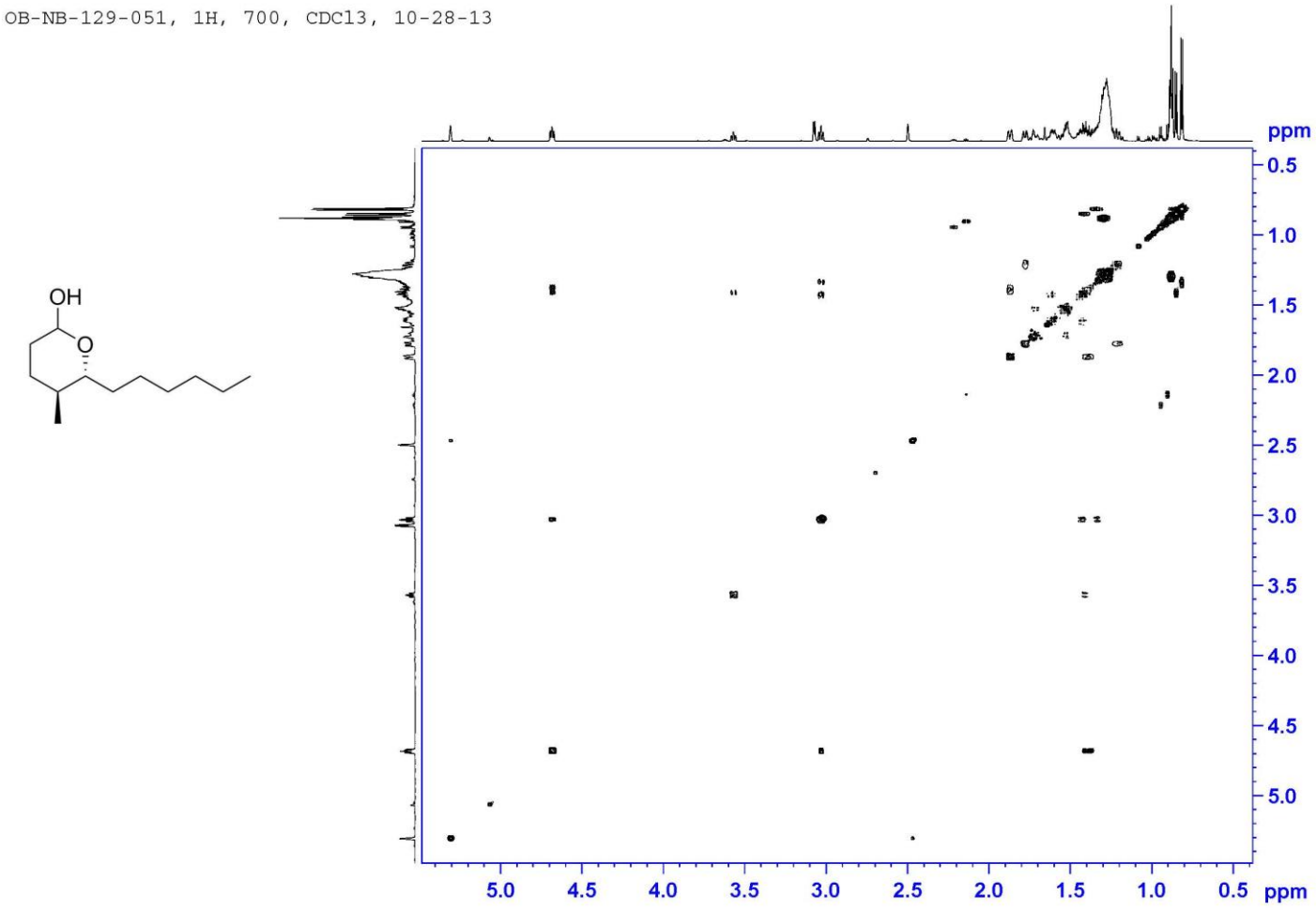

OB-NB-129-023, 1H, 400A, CDCl3, 6-25-13
8.941
8.937
8.462
8.458
8.442
8.438
8.035
8.015
7.261
4.037
1.544
0.000
1.00
1.07
1.09
3.32
ppm


OB-NB-129-024, 1H, 400A, DMSO-d6, 6-26-13
14.239
8.716
8.713
8.458
8.454
8.438
8.435
8.360
8.341
3.887
3.853
3.368
2.973
2.962
2.544
2.540
2.027
0.94
1.00
1.15
1.07
0.24
2.82
0.20
0.02
0.27
0.34
ppm

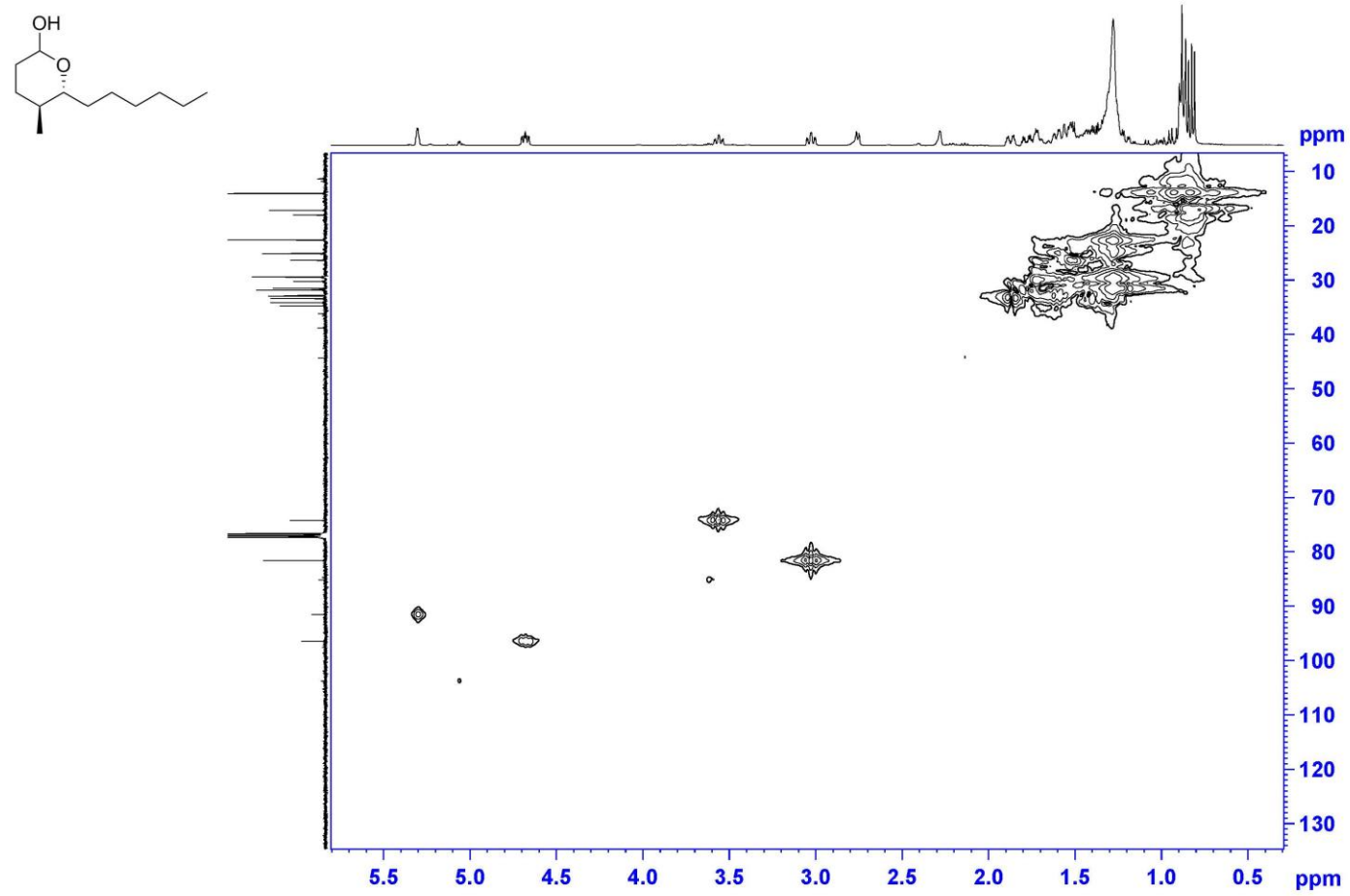

OB-NB-129-036, 1H, 400A, CDCl3
5.236
4.703
4.699
4.676
4.034
4.028
4.016
3.494
3.480
3.468
2.082
2.060
2.049
2.038
2.016
1.878
1.854
1.844
1.834
1.810
1.742
1.731
1.720
1.691
1.680
1.675
1.661
1.616
1.599
1.571
1.554
1.548
1.526
1.514
1.503
1.491
1.480
1.470
1.454
1.442
1.434
1.424
1.412
1.390
1.376
1.358
1.344
1.279
0.950
0.933
0.921
0.896
0.881
0.864
0.825
0.000
OH
O
0.01
1.00
1.65
1.14
1.66
1.12
0.99
5.91
1.74
4.52
5.96
22.61
17.51
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 ppm

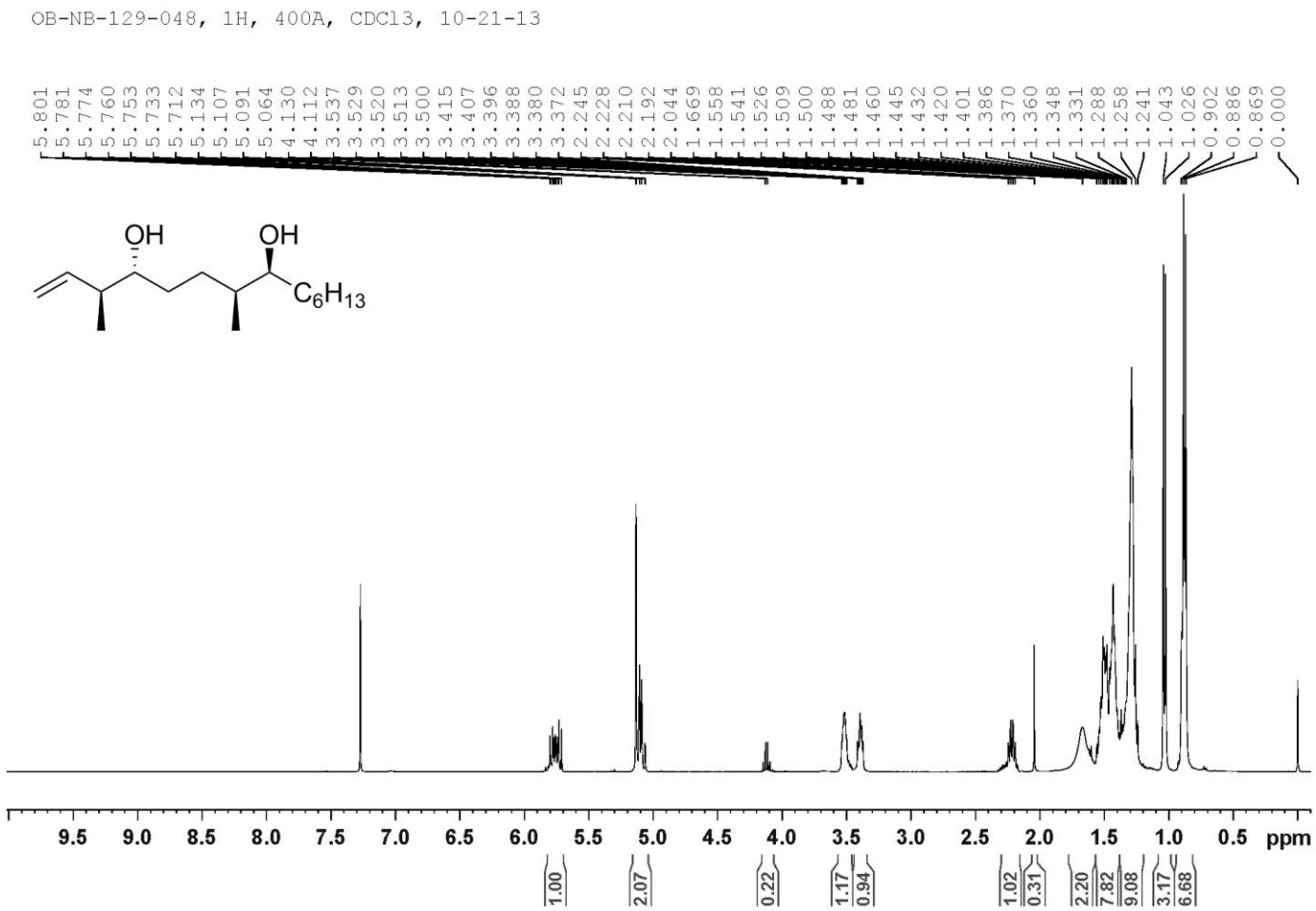

OB-NB-129-051, 1H, 700, CDCl3, 10-28-13
5.308
4.684
3.078
3.069
3.034
3.031
2.498
1.729
1.658
1.615
1.596
1.539
1.532
1.523
1.521
1.517
1.512
1.438
1.424
1.418
1.411
1.405
1.399
1.386
1.373
1.367
1.354
1.347
1.341
1.333
1.326
1.323
1.305
1.295
1.293
1.283
1.278
1.272
1.265
1.254
1.240
1.220
1.215
0.952
0.942
0.909
0.898
0.890
0.881
0.871
0.856
0.847
0.821
0.812
0.070
0.000
OH
O
0.32
0.52
0.32
0.48
0.51
0.34
0.52
0.50
0.67
0.99
1.52
1.80
8.74
3.00
1.06
1.56
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 ppm

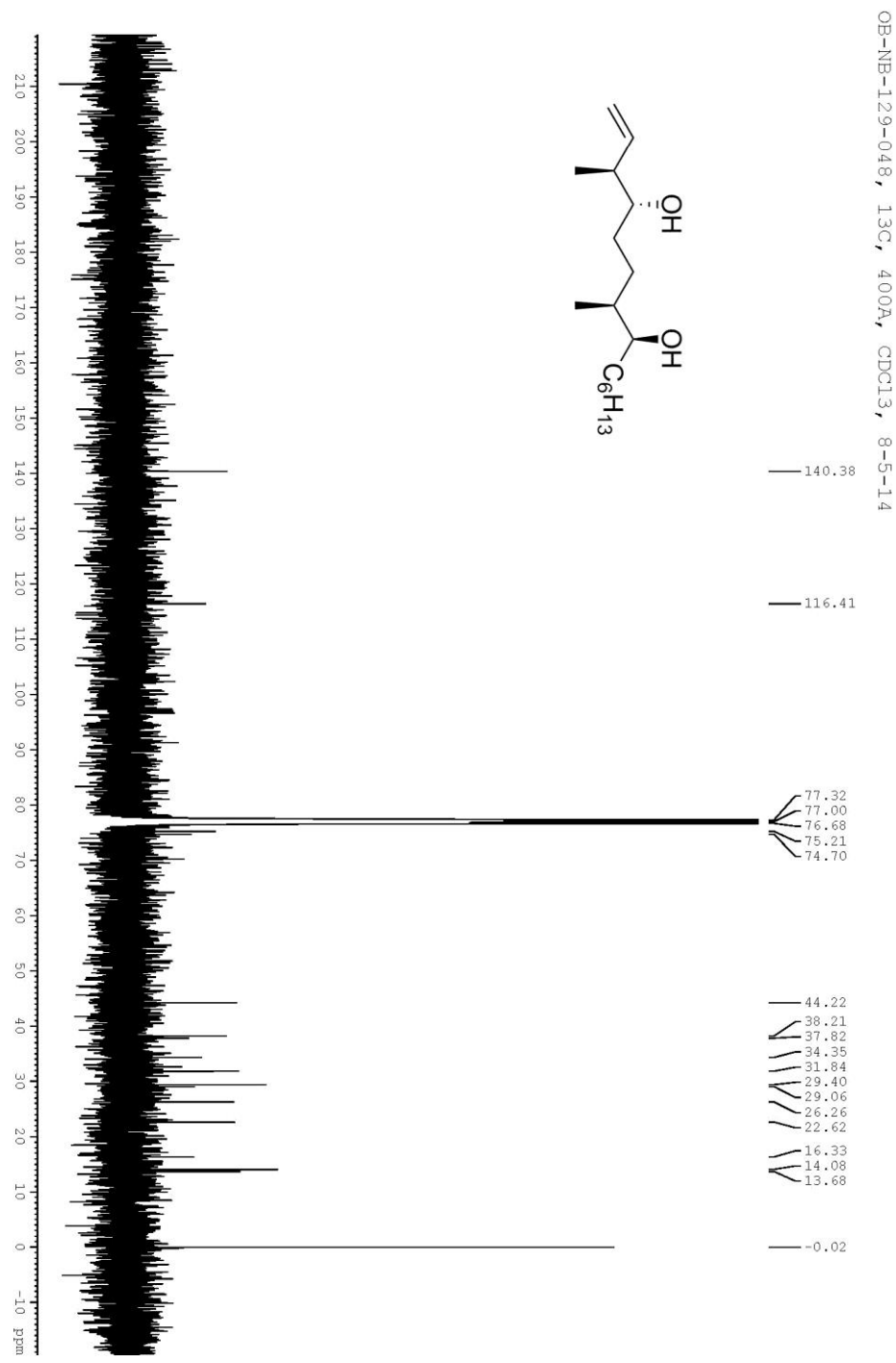

OB-NB-129-051, 1H, 400A, CDCl3, 10-28-13
HO
O
103.85
96.48
91.58
85.24
81.65
77.34
77.23
77.03
76.71
74.27
44.36
38.85
36.25
34.78
34.18
33.44
32.99
32.87
31.90
31.88
31.58
30.26
29.51
29.47
26.46
26.39
25.21
25.14
22.67
22.64
18.09
17.21
14.11
11.89
11.39
-0.00
ppm

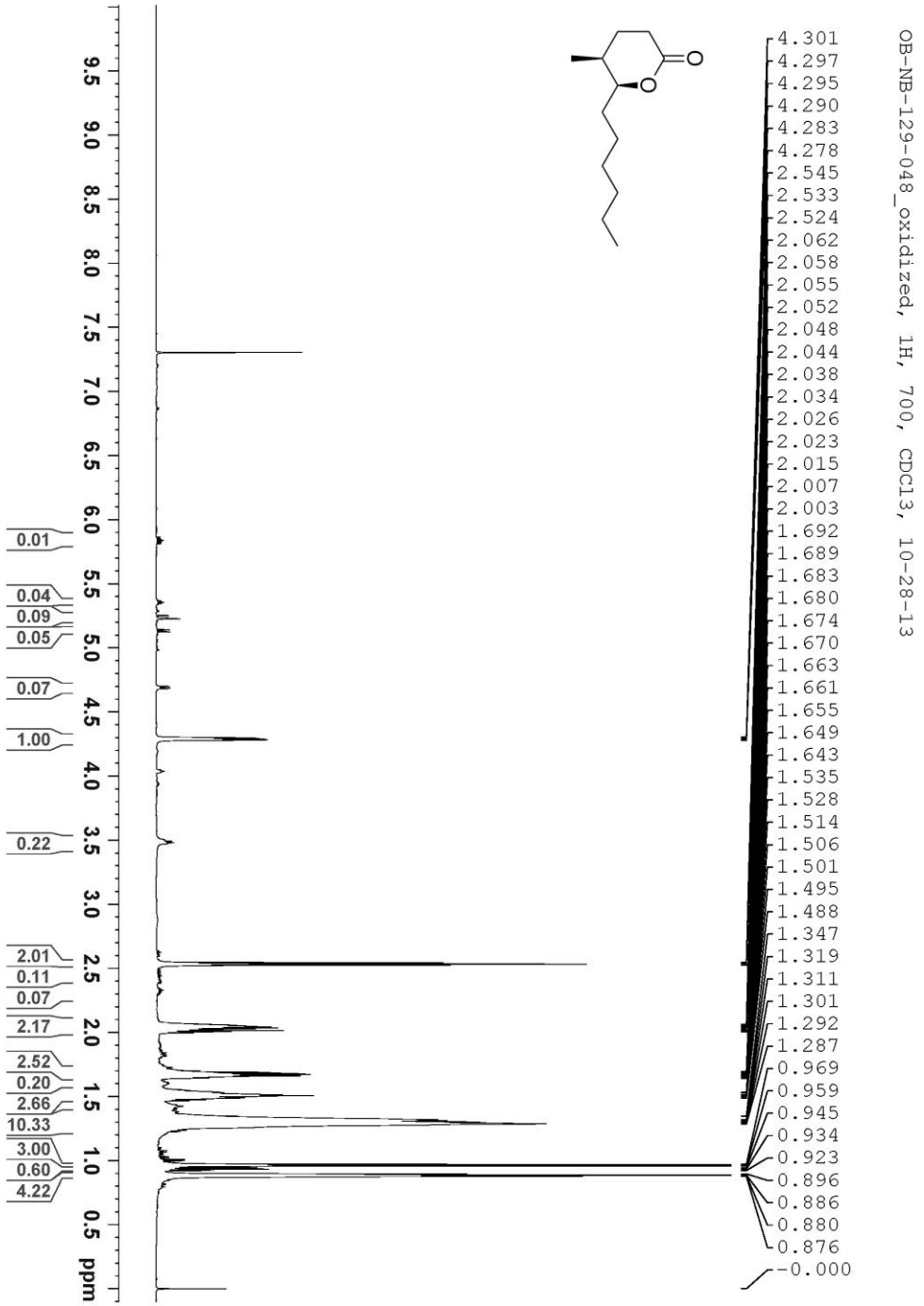

OB-NB-129-051, 1H, 700, CDCl3, 10-28-13
OH
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

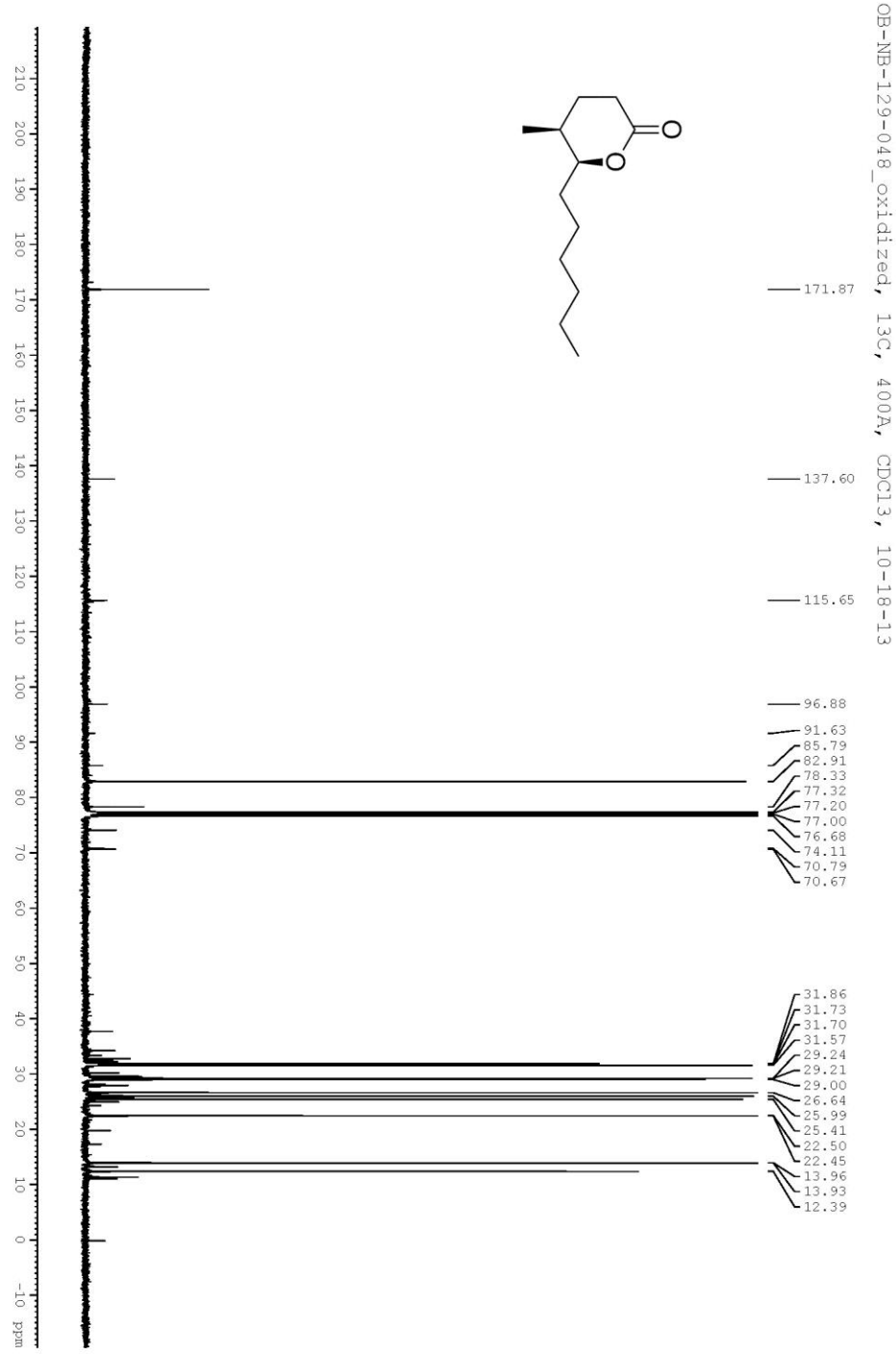
OB-NB-129-051, 1H, 400A, CDCl3, 10-28-13



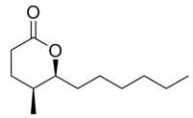

OB-NB-129-048, 1H, 400A, CDCl3, 10-21-13
5.801
5.781
5.774
5.760
5.753
5.733
5.712
5.134
5.107
5.091
5.064
4.130
4.112
3.537
3.529
3.520
3.513
3.500
3.415
3.407
3.396
3.388
3.380
3.372
2.245
2.228
2.210
2.192
2.044
1.669
1.558
1.541
1.526
1.509
1.500
1.488
1.481
1.460
1.445
1.432
1.420
1.401
1.386
1.370
1.360
1.348
1.331
1.288
1.258
1.241
1.043
1.026
0.902
0.886
0.869
0.000
OH
OH
C6H13
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
ppm
1.00
2.07
0.22
1.17
0.94
1.02
0.31
2.20
7.82
9.08
3.17
6.68

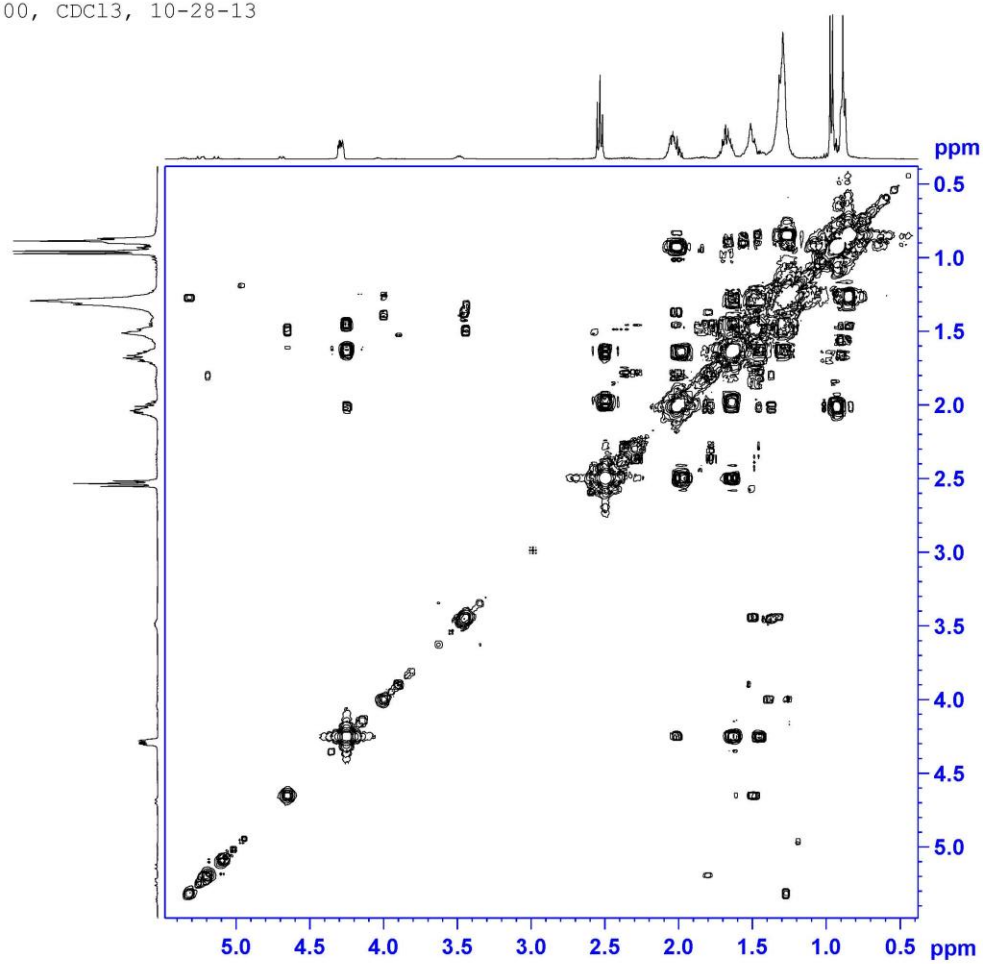

OB-NB-129-048, 13C, 400A, CDC13, 8-5-14
OH
OH
C6H13
140.38
116.41
77.32
77.00
76.68
75.21
74.70
44.22
38.21
37.82
34.35
31.84
29.40
29.06
26.26
22.62
16.33
14.08
13.68
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


OB-NB-129-048_oxidized, 1H, 700, CDCl3, 10-28-13
4.301
4.297
4.295
4.290
4.283
4.278
2.545
2.533
2.524
2.062
2.058
2.055
2.052
2.048
2.044
2.038
2.034
2.026
2.023
2.015
2.007
2.003
1.692
1.689
1.683
1.680
1.674
1.670
1.663
1.661
1.655
1.649
1.643
1.535
1.528
1.514
1.506
1.501
1.495
1.488
1.347
1.319
1.311
1.301
1.292
1.287
0.969
0.959
0.945
0.934
0.923
0.896
0.886
0.880
0.876
-0.000
0.01
0.04
0.09
0.05
0.07
1.00
0.22
2.01
0.11
0.07
2.17
2.52
0.20
2.66
10.33
3.00
0.60
4.22
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 ppm

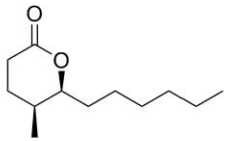

OB-NB-129-048_oxidized, 13C, 400A, CDCl3, 10-18-13
171.87
137.60
115.65
96.88
91.63
85.79
82.91
78.33
77.32
77.20
77.00
76.68
74.11
70.79
70.67
31.86
31.73
31.70
31.57
29.24
29.21
29.00
26.64
25.99
25.41
22.50
22.45
13.96
13.93
12.39
ppm

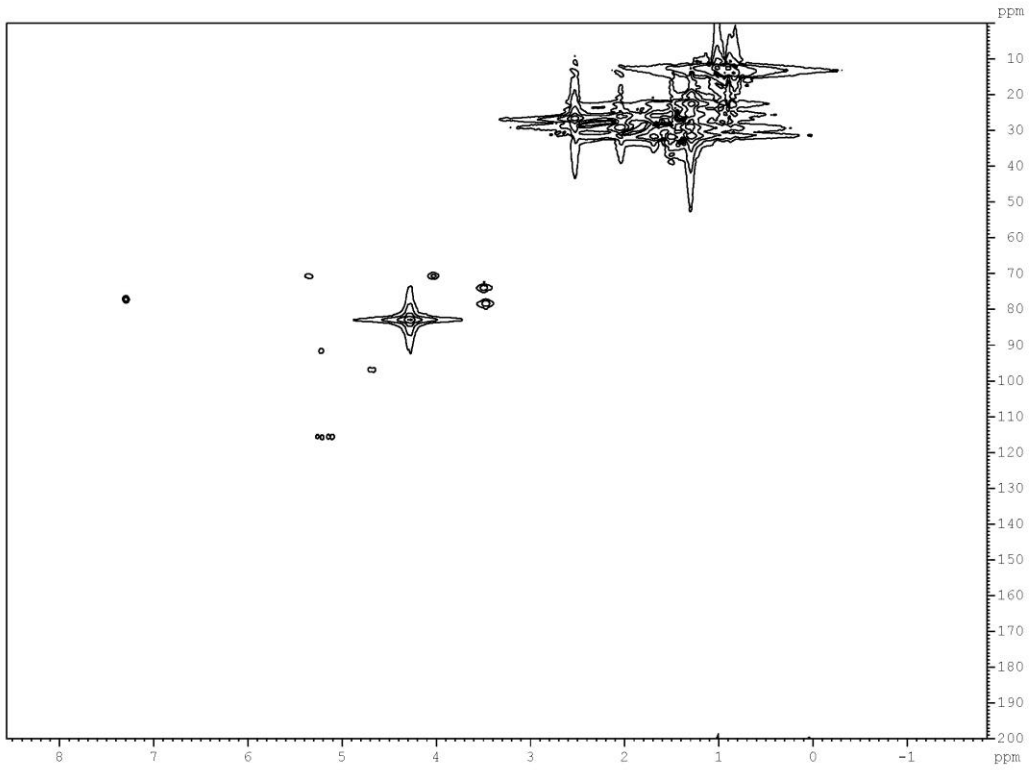
OB-NB-129-048_oxidized, COSY, 700, CDCl3, 10-28-13



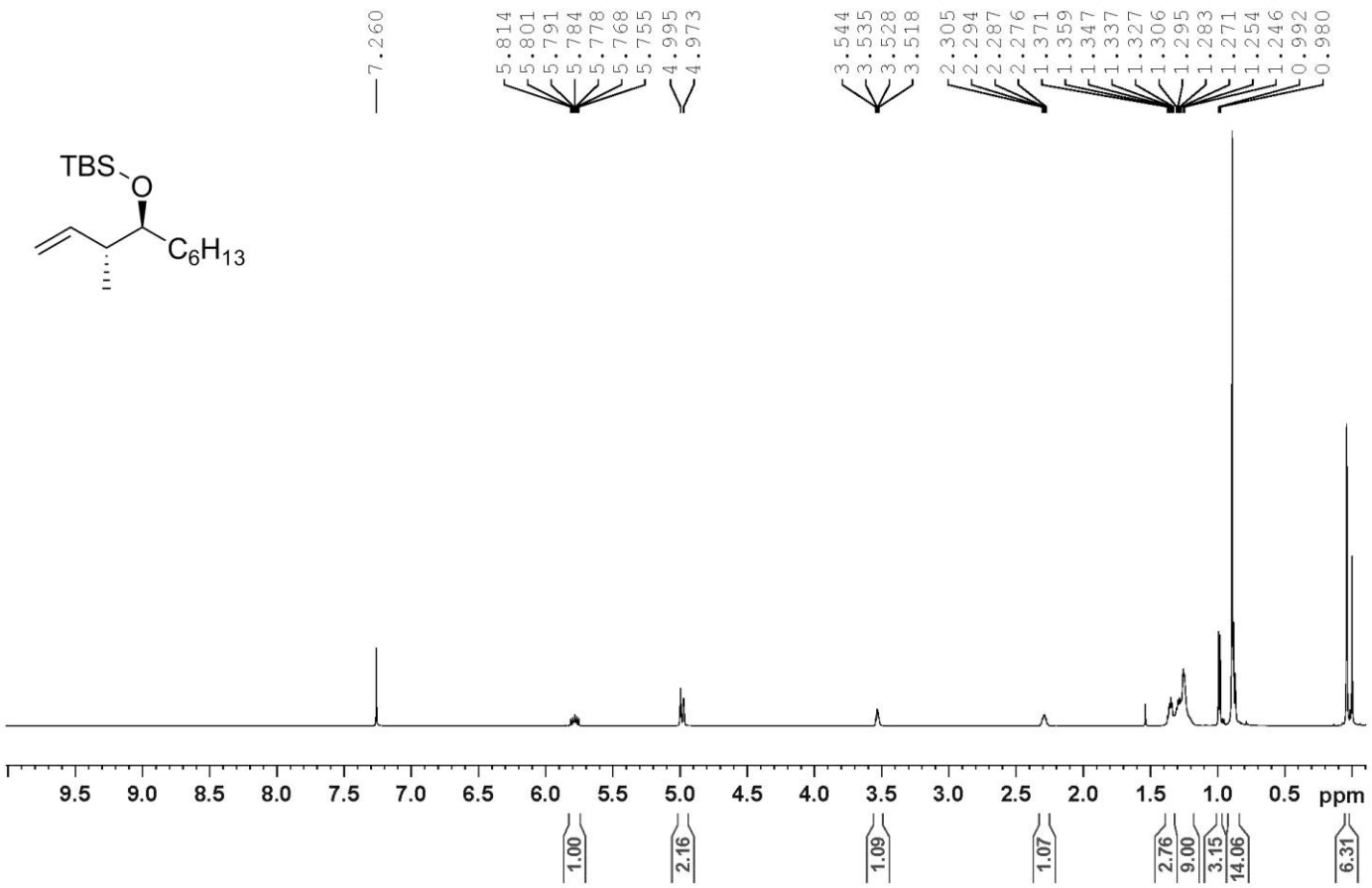


OB-NB-129-048_oxidized, HMQC, 400A, CDCl3, 10-18-13

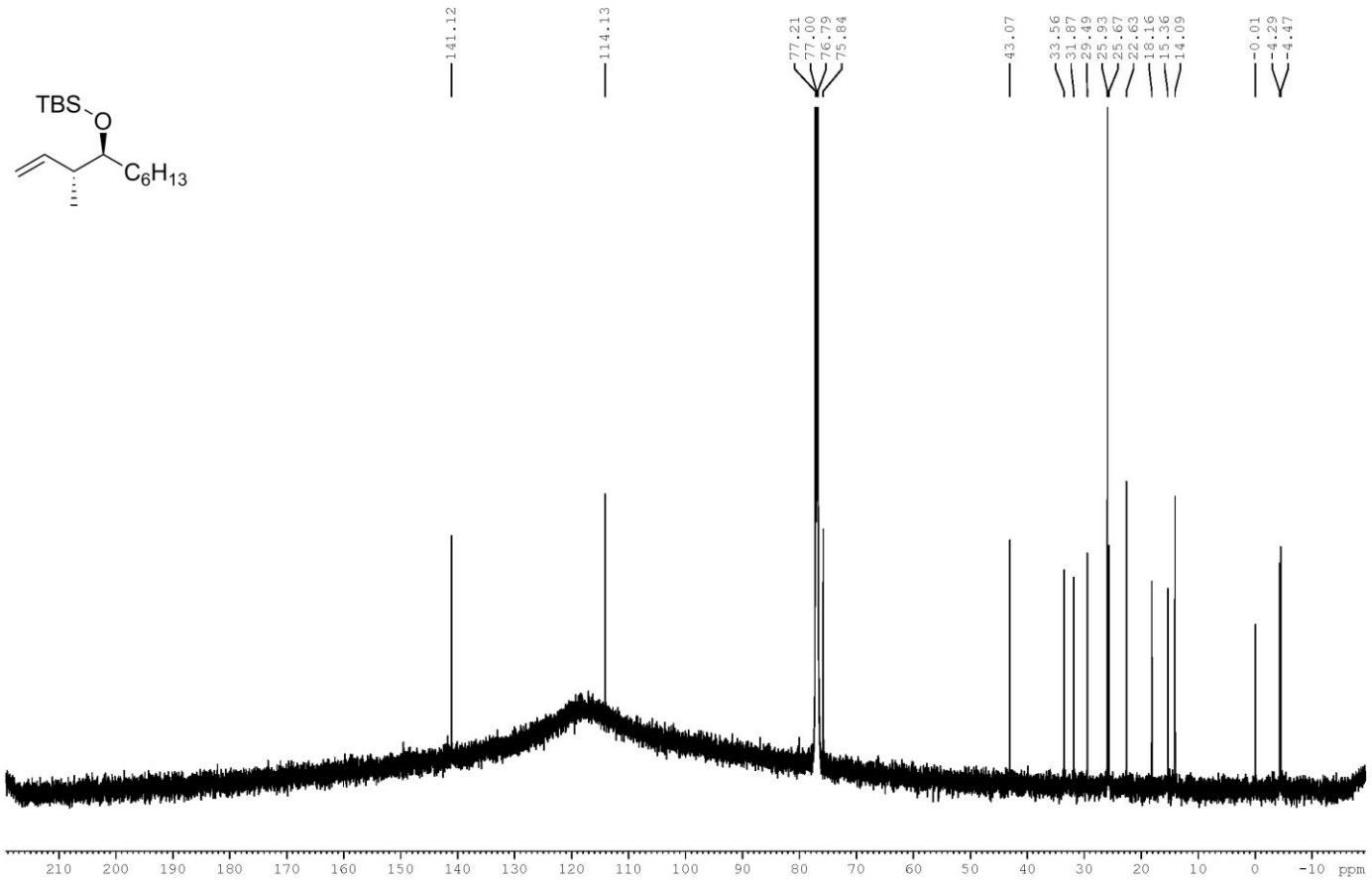


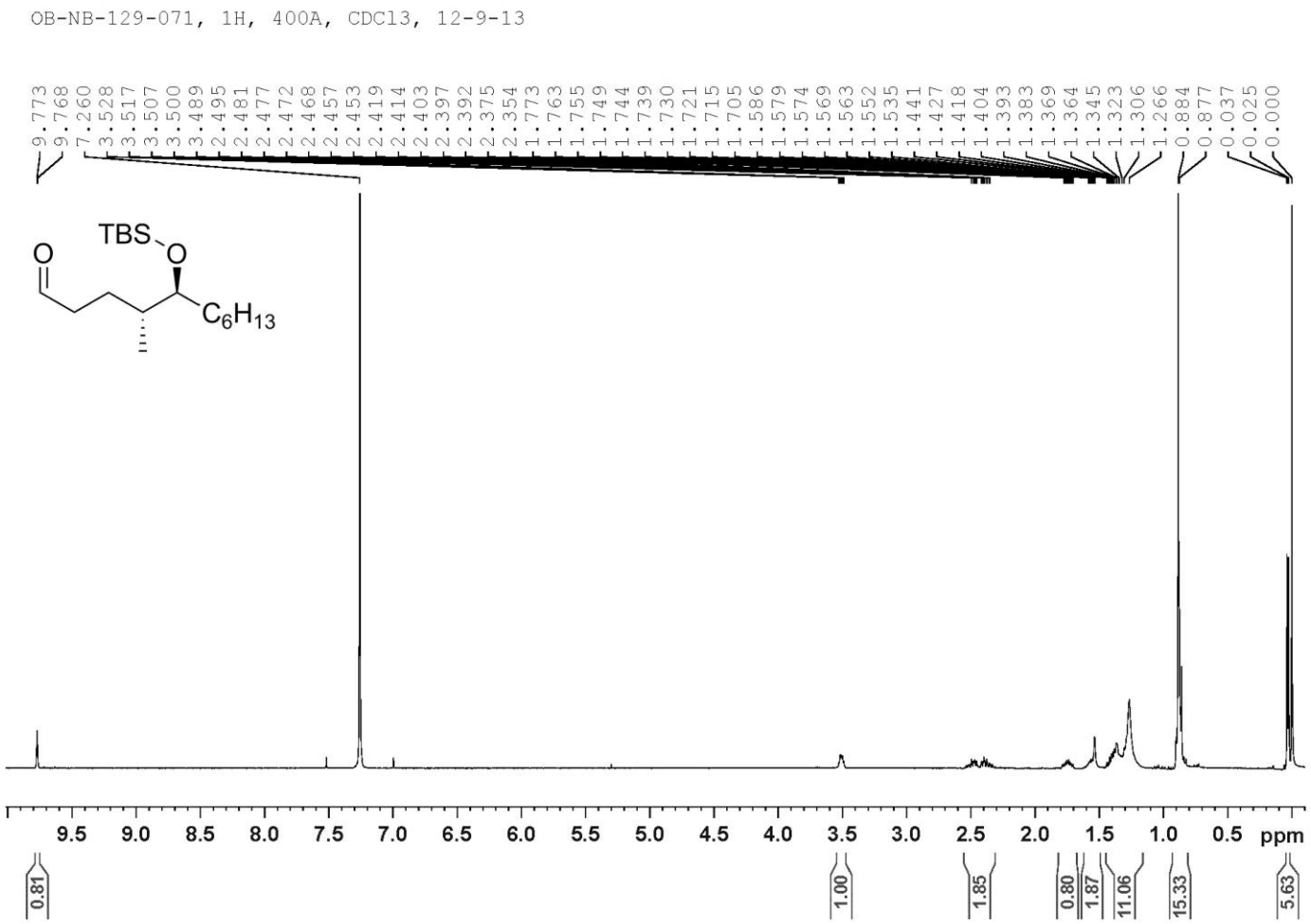


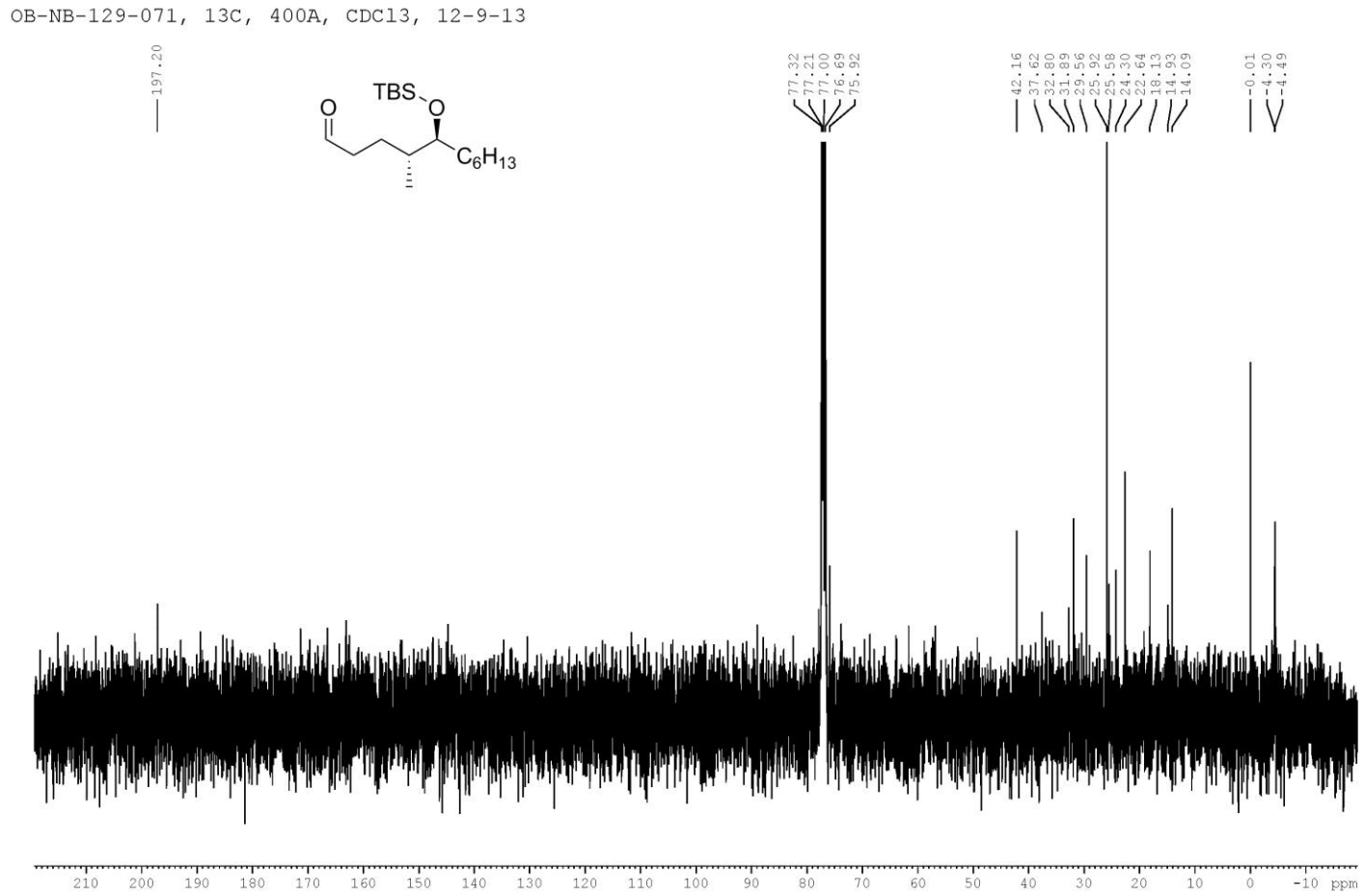
OB-NB-129-069, 1H, 600, CDCl3, 8-4-14

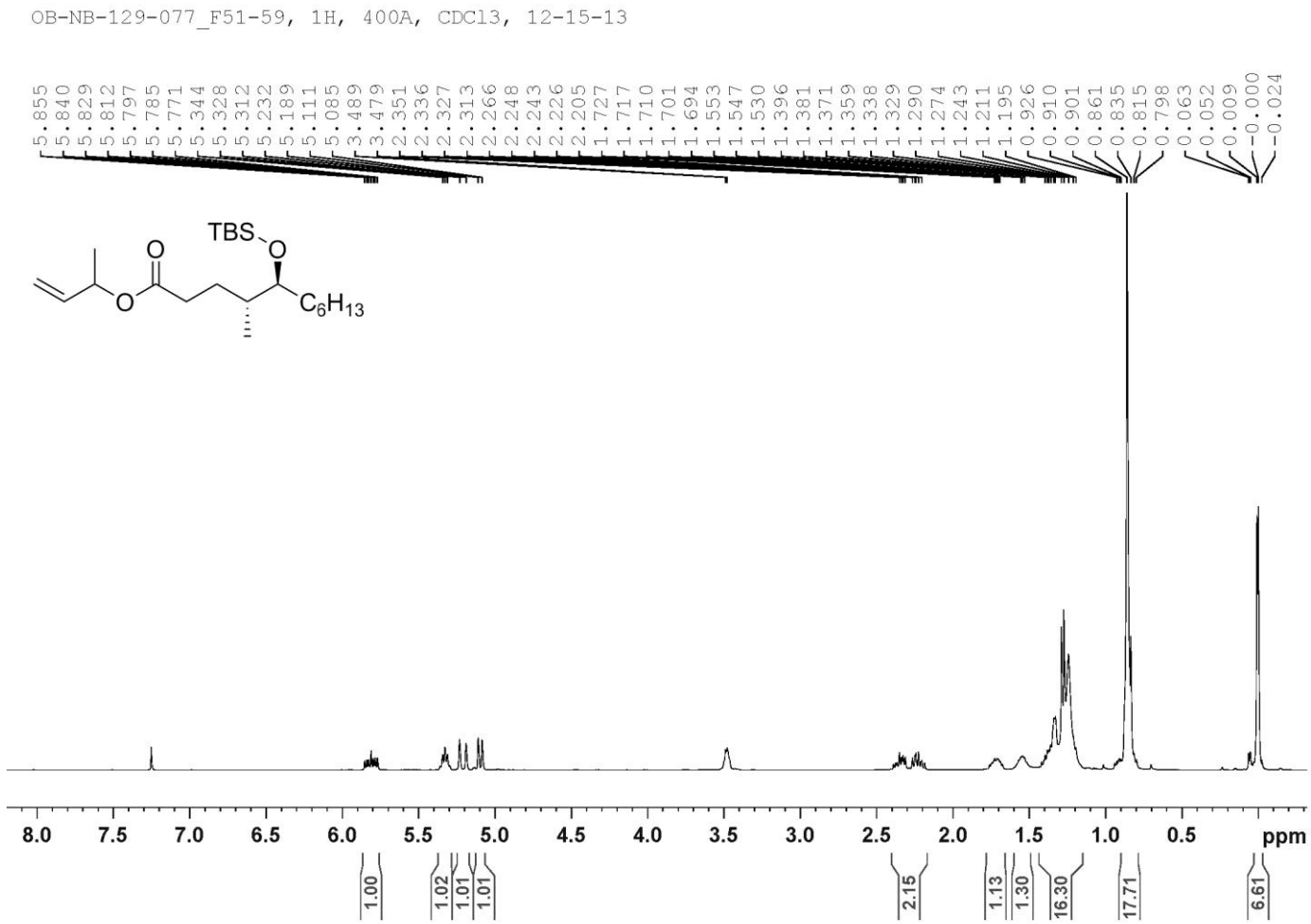


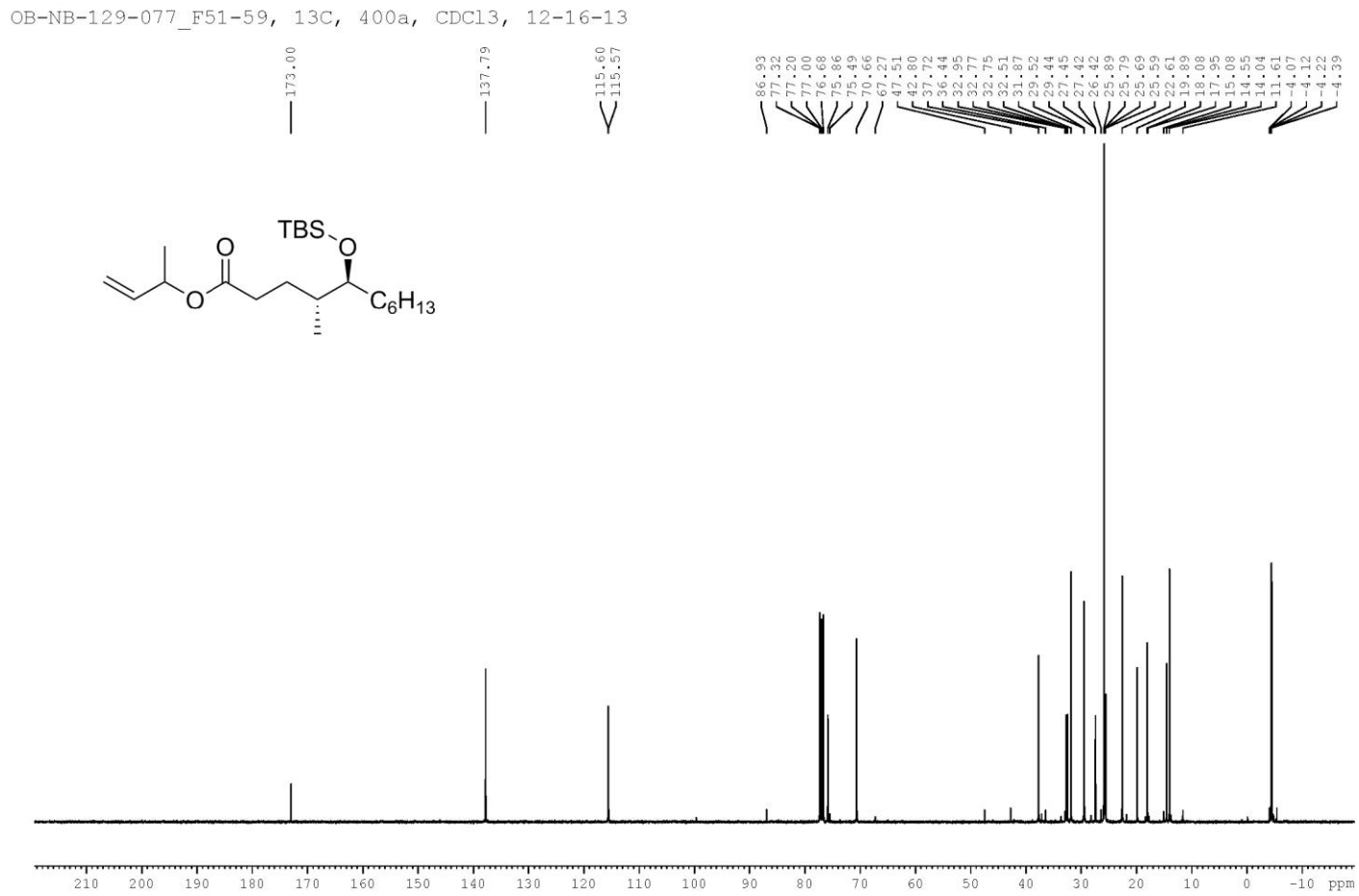
OB-NB-129-069, 13C, 600, CDCl3, 8-4-14

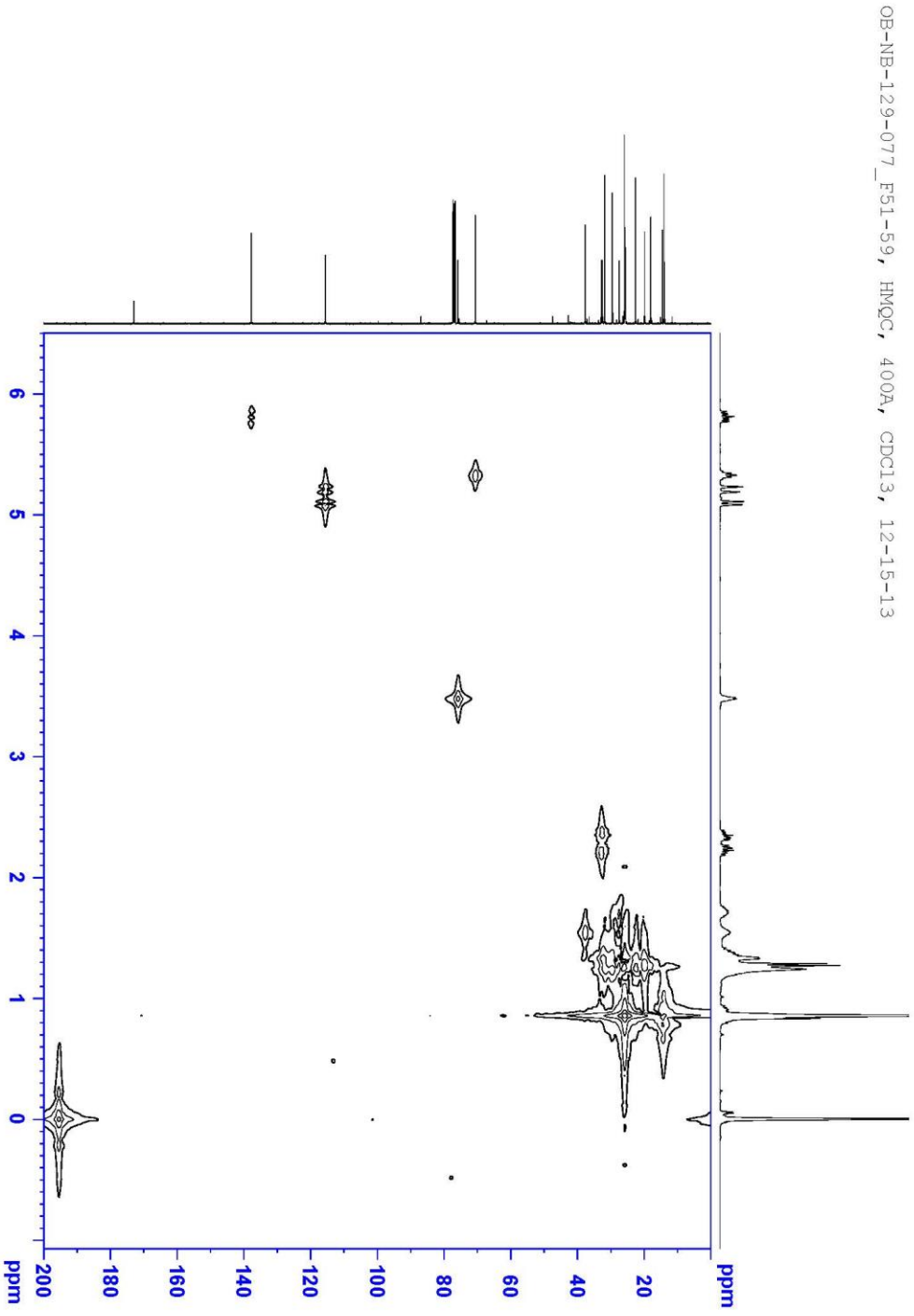


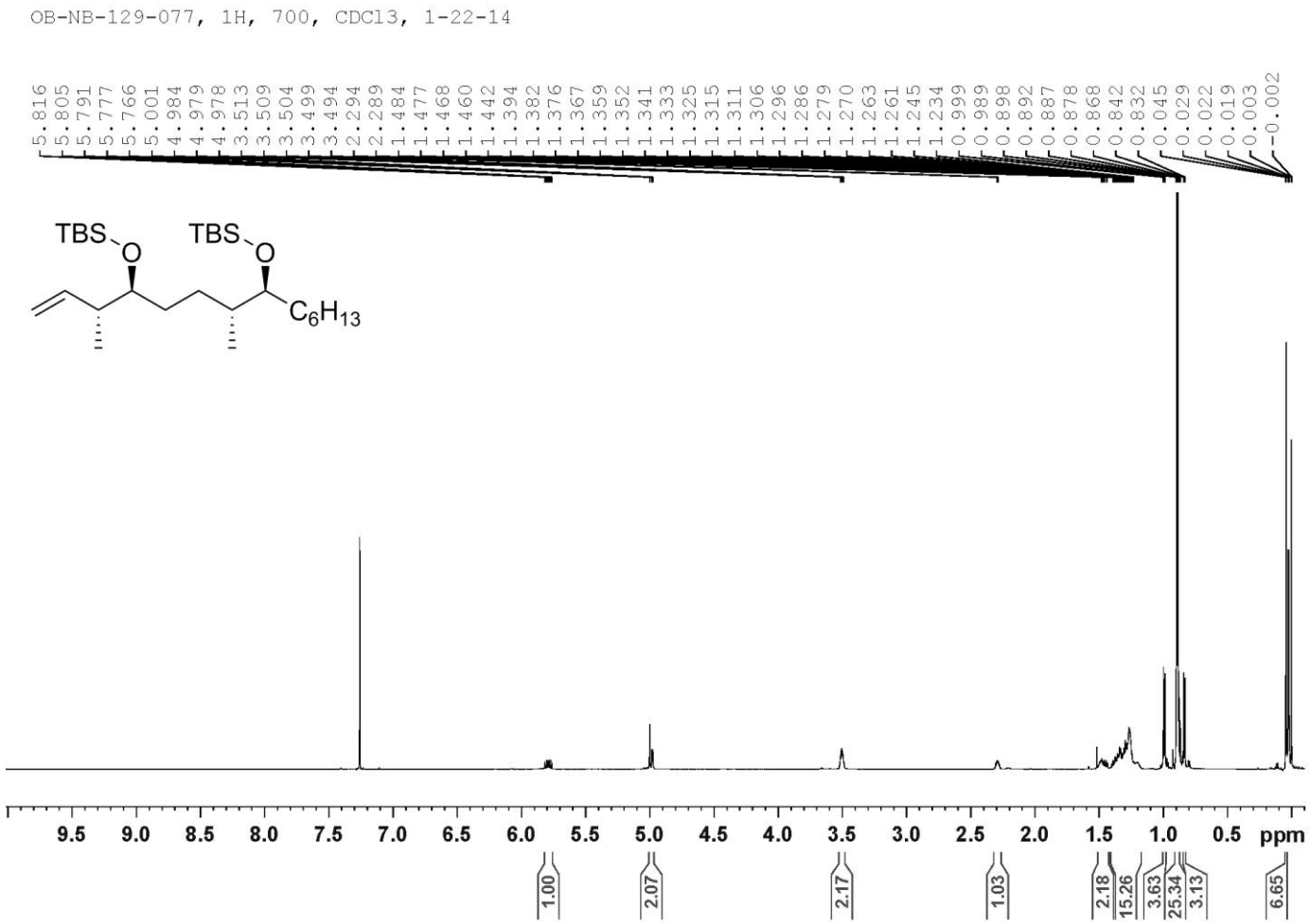

OB-NB-129-071, 1H, 400A, CDCl3, 12-9-13
9.773
9.768
7.260
3.528
3.517
3.507
3.500
3.489
2.495
2.481
2.477
2.472
2.468
2.457
2.453
2.419
2.414
2.403
2.397
2.392
2.375
2.354
1.773
1.763
1.755
1.749
1.744
1.739
1.730
1.721
1.715
1.705
1.586
1.579
1.574
1.569
1.563
1.552
1.535
1.441
1.427
1.418
1.404
1.393
1.383
1.369
1.364
1.345
1.323
1.306
1.266
0.884
0.877
0.037
0.025
0.000
TBS
O
O
C6H13
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
ppm
0.81
1.00
1.85
0.80
1.87
11.06
15.33
5.63

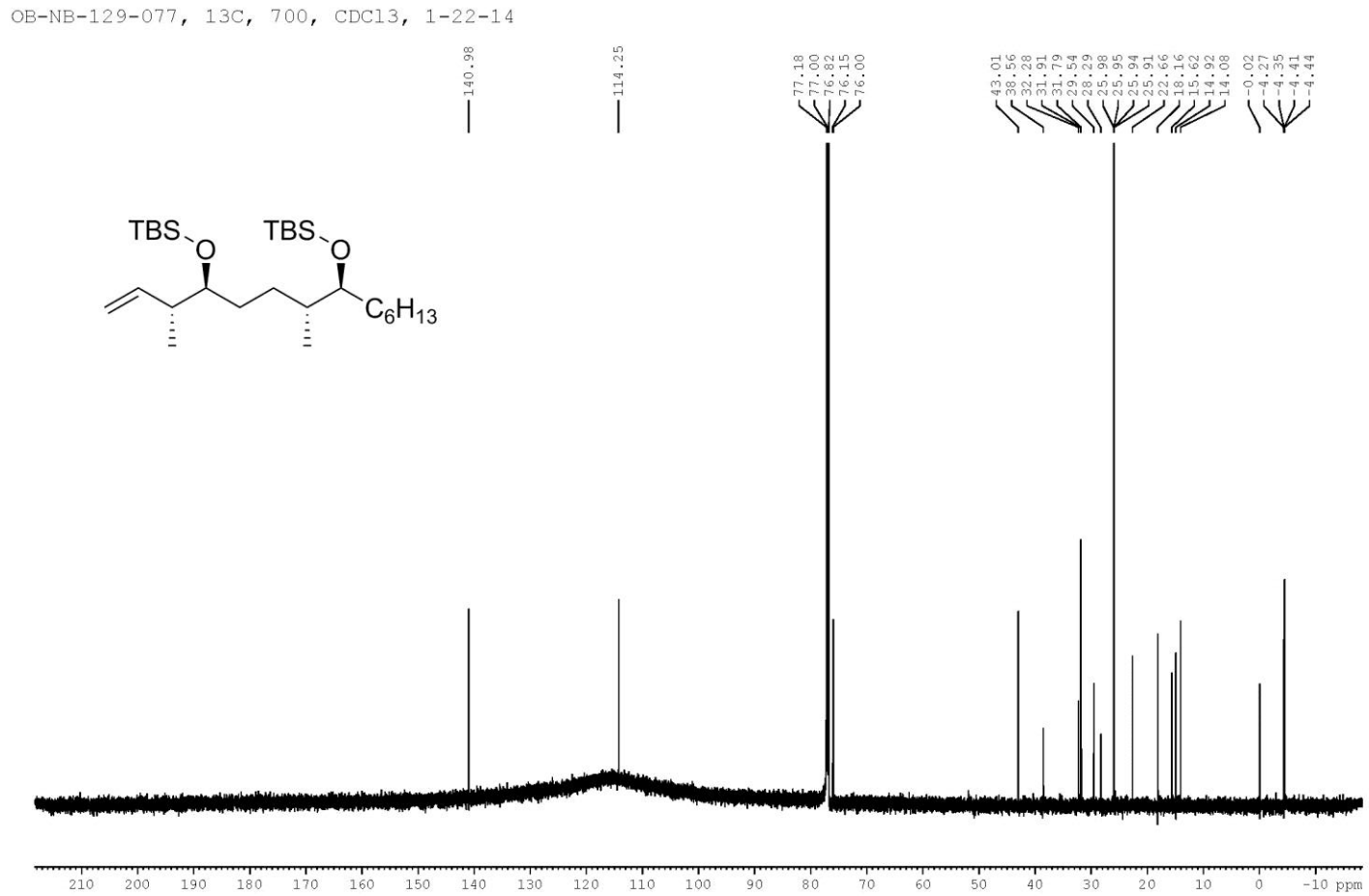

OB-NB-129-071, 13C, 400A, CDCl3, 12-9-13
197.20
TBS
O
O
C6H13
77.32
77.21
77.00
76.69
75.92
42.16
37.62
32.80
31.89
29.56
25.92
25.58
24.30
22.64
18.13
14.93
14.09
-0.01
-4.30
-4.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

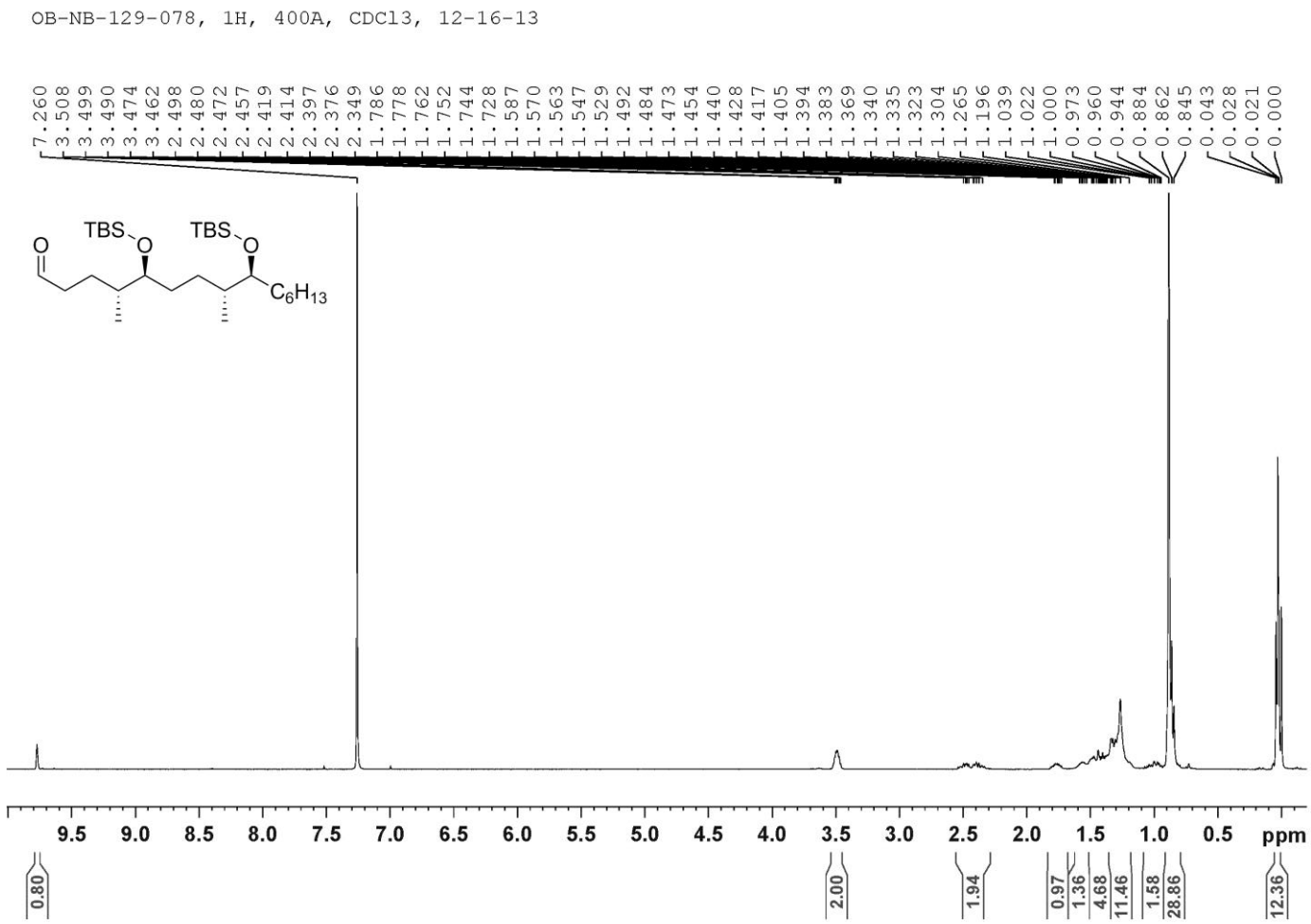

OB-NB-129-077_F51-59, 1H, 400A, CDCl3, 12-15-13
5.855
5.840
5.829
5.812
5.797
5.785
5.771
5.344
5.328
5.312
5.232
5.189
5.111
5.085
3.489
3.479
2.351
2.336
2.327
2.313
2.266
2.248
2.243
2.226
2.205
1.727
1.717
1.710
1.701
1.694
1.553
1.547
1.530
1.396
1.381
1.371
1.359
1.338
1.329
1.290
1.274
1.243
1.211
1.195
0.926
0.910
0.901
0.861
0.835
0.815
0.798
0.063
0.052
0.009
-0.000
-0.024
TBS
O
O
O
C6H13
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
ppm
1.00
1.02
1.01
1.01
2.15
1.13
1.30
16.30
17.71
6.61

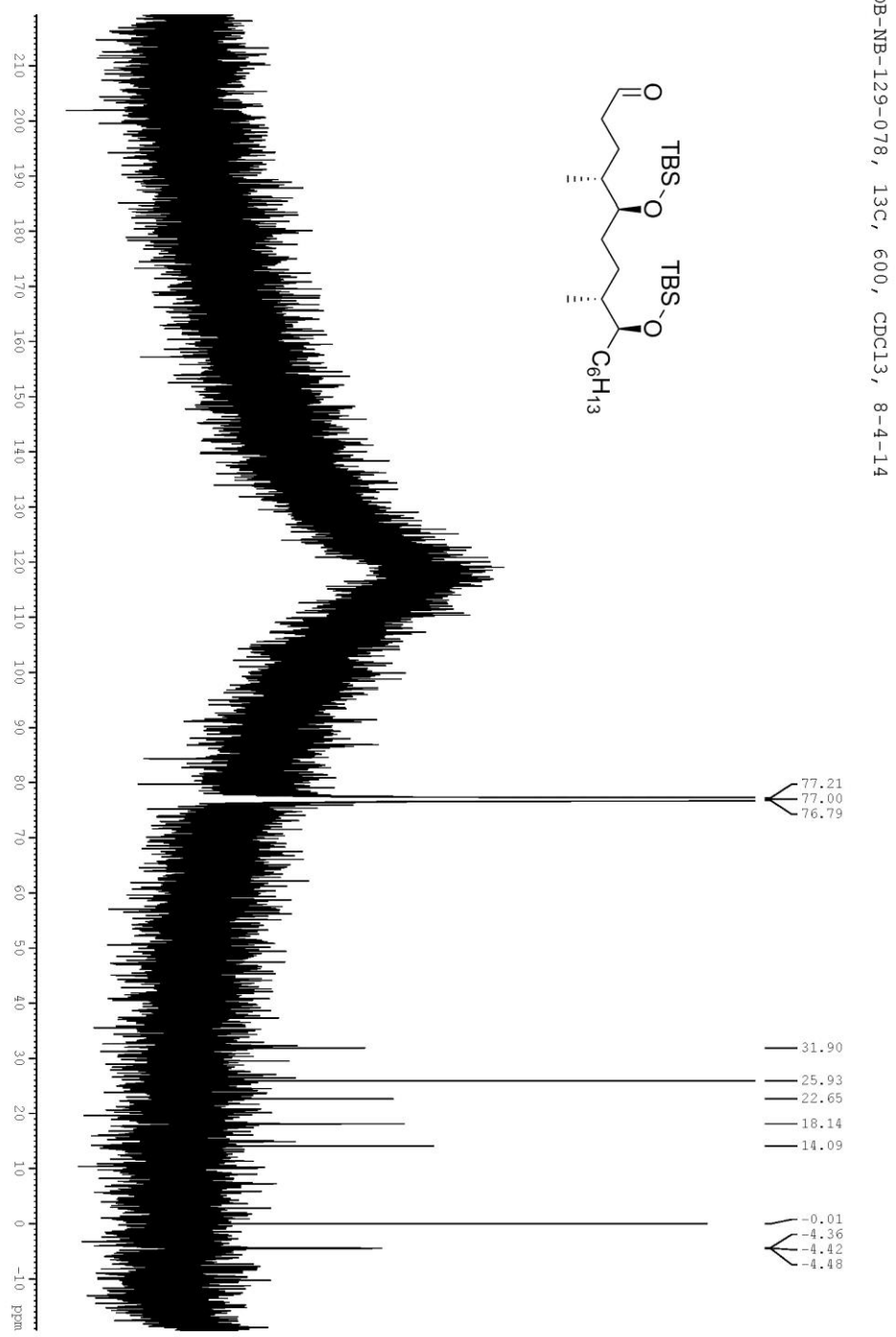

OB-NB-129-077_F51-59, 13C, 400a, CDCl3, 12-16-13
173.00
137.79
115.60
115.57
86.93
77.32
77.20
77.00
76.68
75.86
75.49
70.66
67.27
47.51
42.80
37.72
36.44
32.95
32.77
32.75
32.51
31.87
29.52
29.44
27.45
27.42
26.42
25.89
25.79
25.69
25.59
22.61
19.89
18.08
17.95
15.08
14.55
14.04
11.61
-4.07
-4.12
-4.22
-4.39
TBS
O
O
O
C6H13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

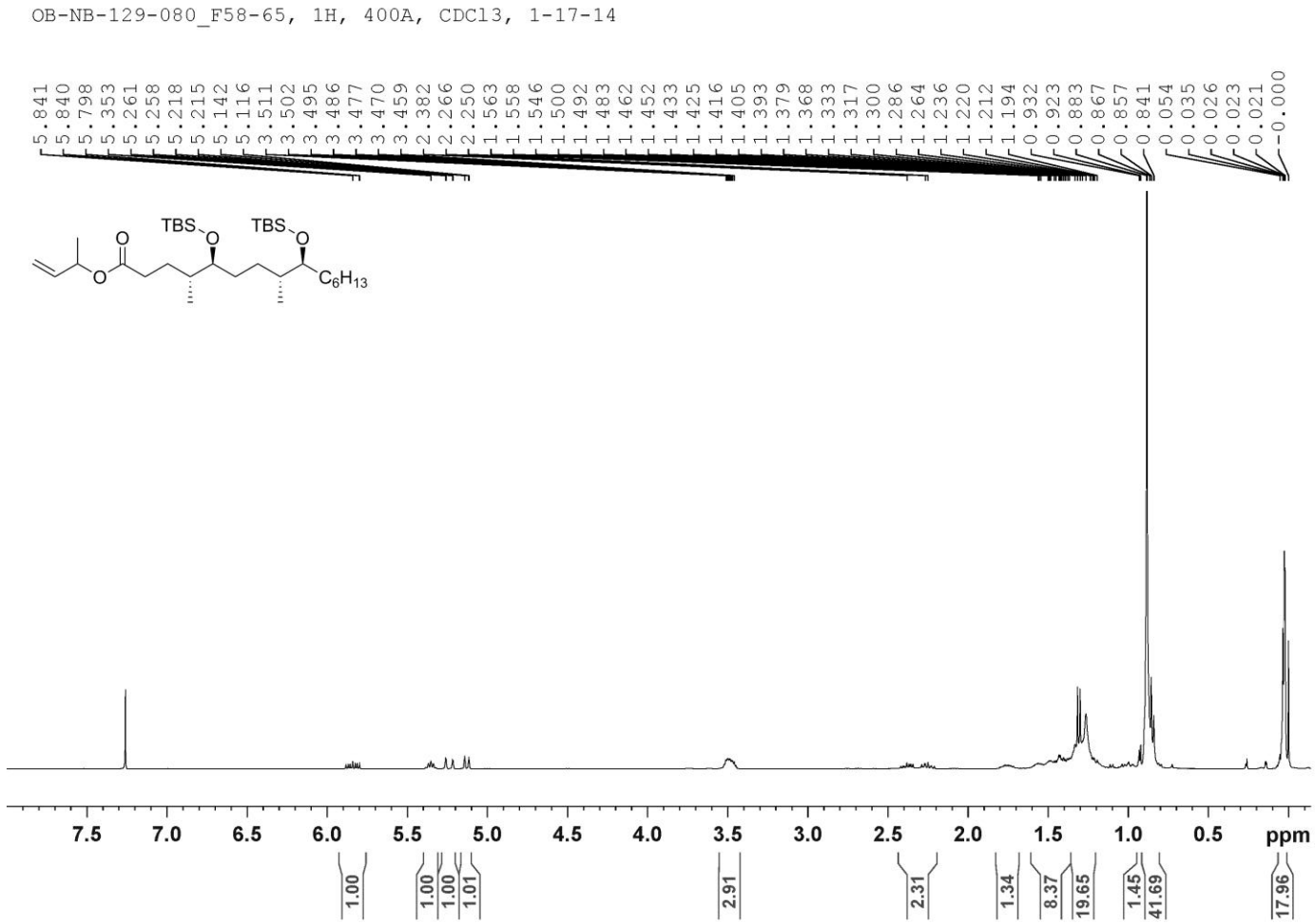

OB-NB-129-077_F51-59, HMQC, 400A, CDCl3, 12-15-13
ppm
ppm
200
180
160
140
120
100
80
60
40
20
6
5
4
3
2
1
0


OB-NB-129-077, 1H, 700, CDCl3, 1-22-14
5.816
5.805
5.791
5.777
5.766
5.001
4.984
4.979
4.978
3.513
3.509
3.504
3.499
3.494
2.294
2.289
1.484
1.477
1.468
1.460
1.442
1.394
1.382
1.376
1.367
1.359
1.352
1.341
1.333
1.325
1.315
1.311
1.306
1.296
1.286
1.279
1.270
1.263
1.261
1.245
1.234
0.999
0.989
0.898
0.892
0.887
0.878
0.868
0.842
0.832
0.045
0.029
0.022
0.019
0.003
-0.002
TBS
O
TBS
O
C6H13
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
ppm
1.00
2.07
2.17
1.03
2.18
15.26
3.63
25.34
3.13
6.65


OB-NB-129-077, 13C, 700, CDCl3, 1-22-14
140.98
114.25
77.18
77.00
76.82
76.15
76.00
43.01
38.56
32.28
31.91
31.79
29.54
28.29
25.98
25.95
25.94
25.91
22.66
18.16
15.62
14.92
14.08
-0.02
-4.27
-4.35
-4.41
-4.44
TBS
O
TBS
O
C6H13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm


OB-NB-129-078, 1H, 400A, CDCl3, 12-16-13
7.260
3.508
3.499
3.490
3.474
3.462
2.498
2.480
2.472
2.457
2.419
2.414
2.397
2.376
2.349
1.786
1.778
1.762
1.752
1.744
1.728
1.587
1.570
1.563
1.547
1.529
1.492
1.484
1.473
1.454
1.440
1.428
1.417
1.405
1.394
1.383
1.369
1.340
1.335
1.323
1.304
1.265
1.196
1.039
1.022
1.000
0.973
0.960
0.944
0.884
0.862
0.845
0.043
0.028
0.021
0.000
TBS
O
TBS
O
O
C6H13
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
ppm
0.80
2.00
1.94
0.97
1.36
4.68
11.46
1.58
28.86
12.36


OB-NB-129-078, 13C, 600, CDC13, 8-4-14
TBS
TBS
C6H13
77.21
77.00
76.79
31.90
25.93
22.65
18.14
14.09
-0.01
-4.36
-4.42
-4.48
ppm


OB-NB-129-080_F58-65, 1H, 400A, CDCl3, 1-17-14
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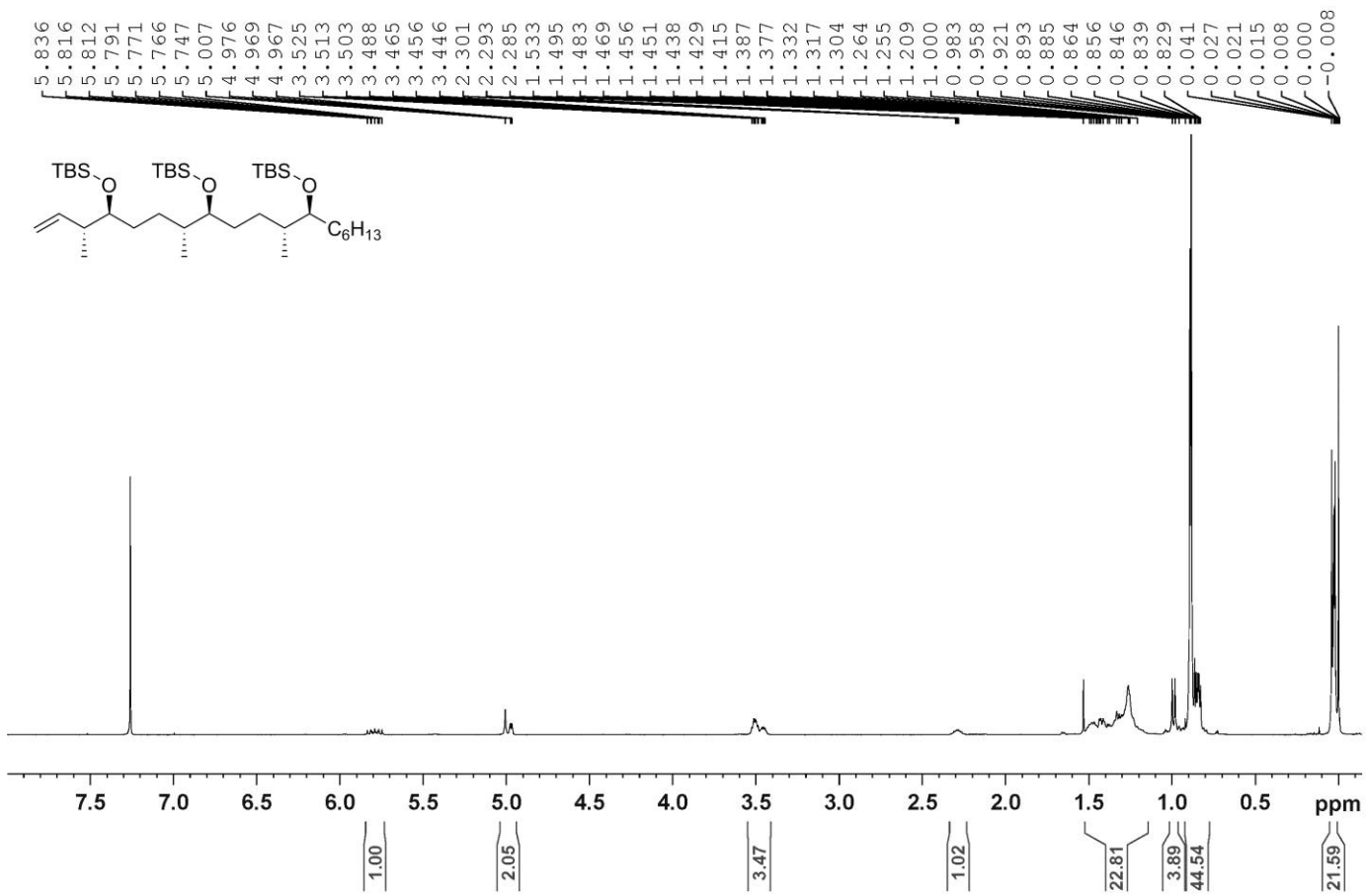
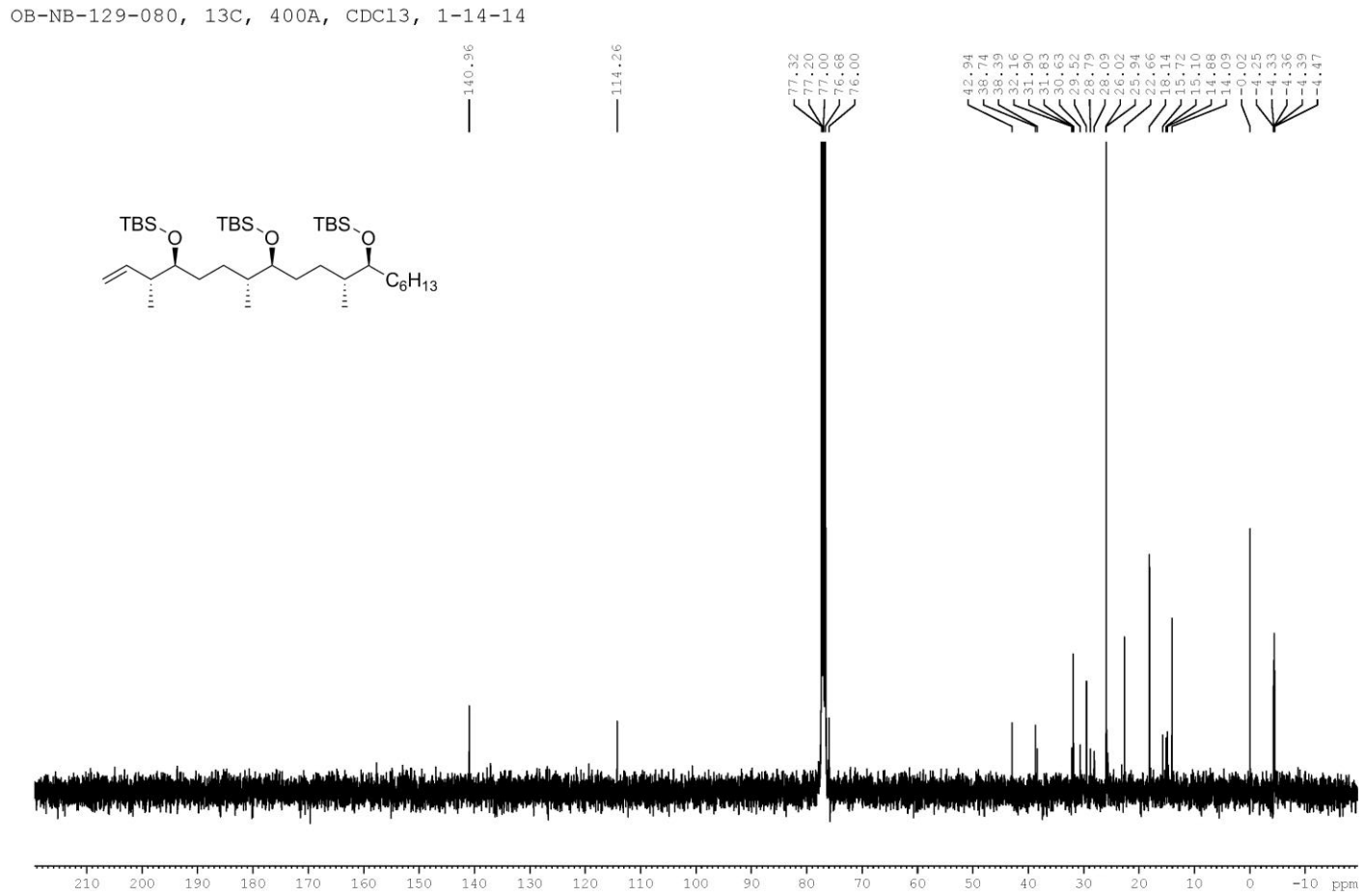
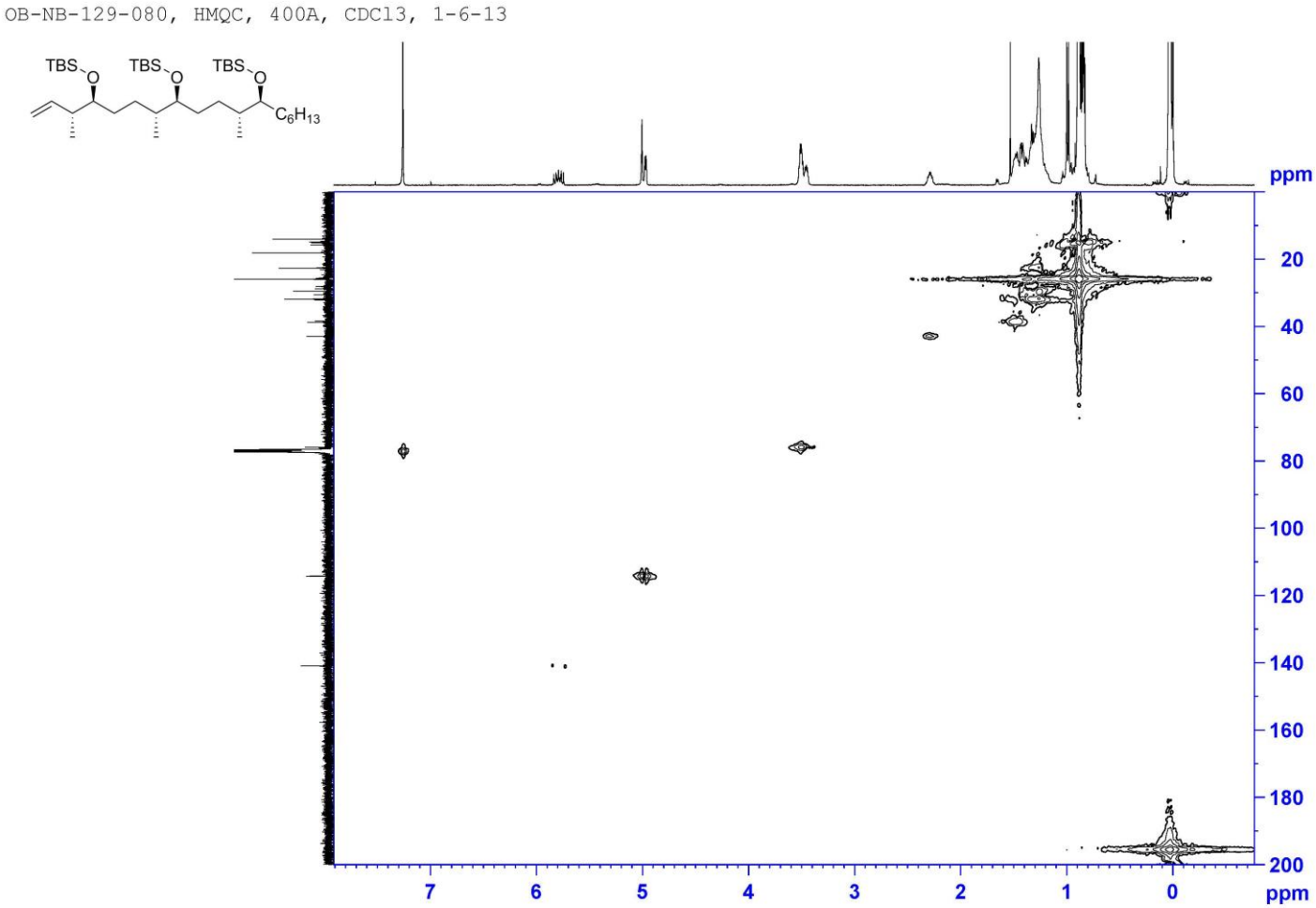
5.840
5.798
5.353
5.261
5.258
5.218
5.215
5.142
5.116
3.511
3.502
3.495
3.486
3.477
3.470
3.459
2.382
2.266
2.250
1.563
1.558
1.546
1.500
1.492
1.483
1.462
1.452
1.433
1.425
1.416
1.405
1.393
1.379
1.368
1.333
1.317
1.300
1.286
1.264
1.236
1.220
1.212
1.194
0.932
0.923
0.883
0.867
0.857
0.841
0.054
0.035
0.026
0.023
0.021
-0.000
TBS
O
TBS
O
O
O
C6H13
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
ppm
1.00
1.00
1.00
1.01
2.91
2.31
1.34
8.37
19.65
1.45
41.69
17.96

OB-NB-129-080, 1H, 400A, CDCl3, 1-6-14




OB-NB-129-080, 13C, 400A, CDCl3, 1-14-14
140.96
114.26
77.32
77.20
77.00
76.68
76.00
42.94
38.74
38.39
32.16
31.90
31.83
30.63
29.52
28.79
28.09
26.02
25.94
22.66
18.14
15.72
15.10
14.88
14.09
-0.02
-4.25
-4.33
-4.36
-4.39
-4.47
TBS
O
TBS
O
TBS
O
C6H13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm


OB-NB-129-080, HMQC, 400A, CDCl3, 1-6-13
TBS
TBS
TBS
C_6H_{13}
ppm
20
40
60
80
100
120
140
160
180
200
7
6
5
4
3
2
1
0
ppm

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