NTNU – Trondheim
Norwegian University of
Science and Technology

Potential Inhibitors of Tyrosine Kinase 2

Synthesis of Important Intermediates

Lise Bjerkestrand Skaret

Teacher Education with Master of Science
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Supervisor: Odd Reidar Gautun, IKJ
Co-supervisor: Silje Melnes, IKJ

Norwegian University of Science and Technology
Department of Chemistry

Declaration

I hereby declare that the work in this project has been done independently an in accordance with the Examination Regulations at The Norwegian University of Science and Technology (NTNU).

Lise Bjerkestrand Skaret

Trondheim, June 10, 2013

Preface

This project with the title "Potential Inhibitors of Tyrosine Kinase 2 – Synthesis of Important Intermediates" is carried out in cooperation with my supervisors, Associate Professor Odd Reidar Gautun and especially PhD Silje Melnes. It is a continuation of Ragnhild Gard Ohm and Cecilie Surdal`s master`s theses on the same subject, written the spring 2011 and 2012 respectively. It is also a part of Silje Melnes`s doctoral project "Rational Drug Design. Synthesis of Potential Inhibitors of Tyrosine Kinase 2".

I would like to thank Odd Reidar for taking me on this project, even though I`m a student at the LUR-program and missing some subjects that could be relevant for the work. Thanks to Silje for great instruction and patience when I was a fresh chemist. I would also like to thank my lab neighbor Vegard Torp Lien for his patience in relation to my many questions and for never making me feel stupid. Roger Aarvik always made me feel welcome to ask for chemicals, solvent and everything else. I`m greatful for that.

Last, but not least; thank you my dear Mattis for encouragement, care and practical help. It has been a tough first year of our relationship when it comes to lab-related frustration and low energy level, and I don`t know how I would have managed without you.

And thank you my beautiful Leah Angelina, for inspiring me to be ambitious.

Abbreviations and symbols used in this project are listed on page IX.

Abstract

Two different synthesis routes towards target molecule **1** have been investigated.

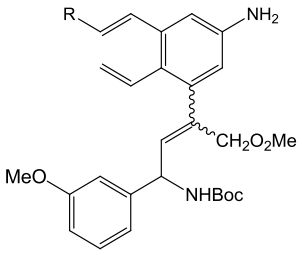

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Figure I; target compound

Synthesis route A (see Figure II) is based on previous work by Ragnhild G. Ohm and Cecilie Surdal. This route gave a total yield of 20% for the synthesis of compound **3**, in a Z/E-mixture in the ratio 1:0.9. The Z/E-mixture was inseparable by column chromatography (except a small amount of the E-isomer), hence a new synthesis route was contemplated.

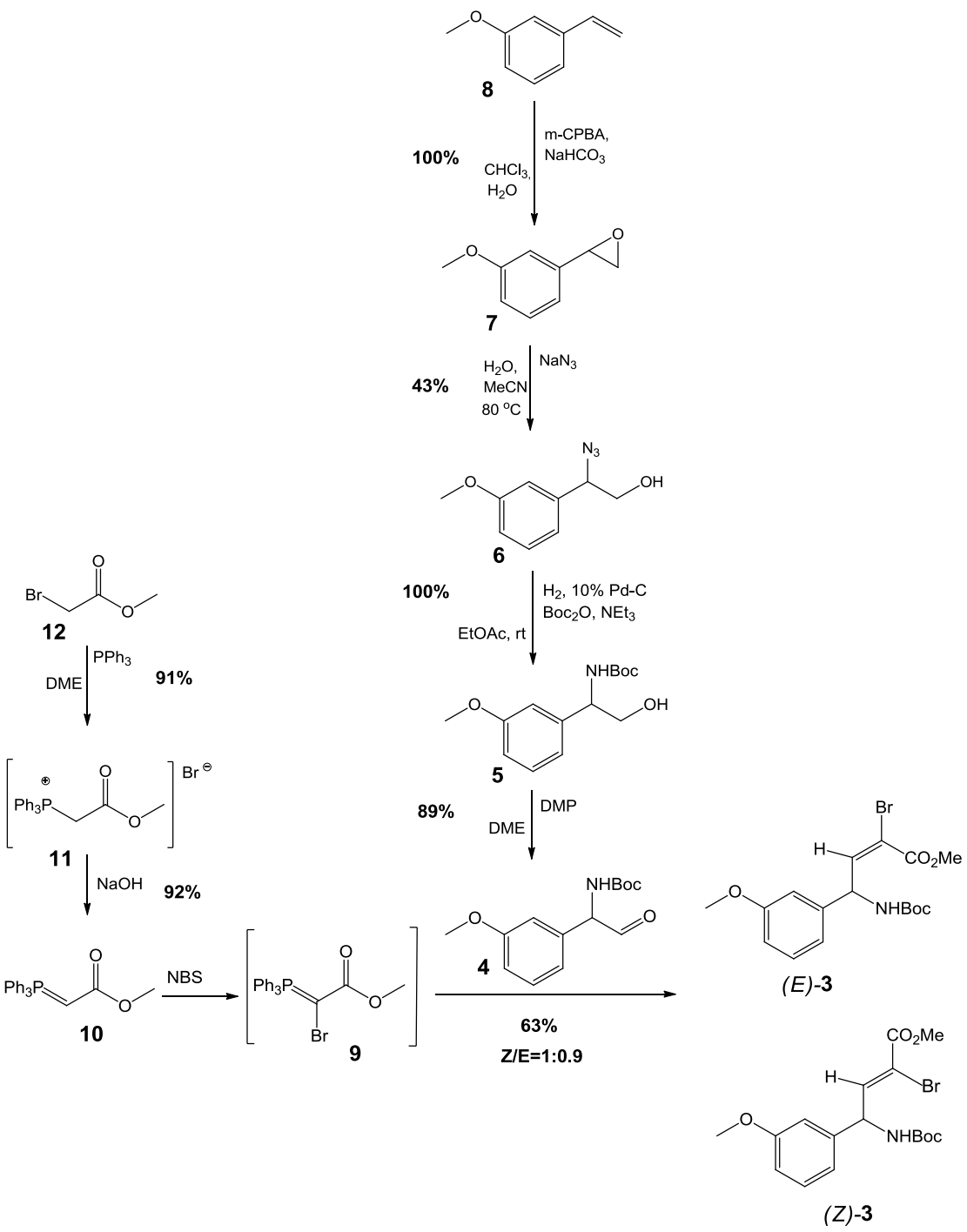

Figure II; Synthesis route A

Synthesis route B was developed to enable synthesis of enantiomerically pure substrates for use in Suzuki -and Hiyama cross-couplings, towards target molecules *(E)*-**1** and *(Z)*-**1.** The first step with condensation between methylpropiolate (**18**) and arylaldehydes **17a** and **17b** was accomplished with yields of 46% and 52% respectively (see Figure III).The second step was a protection of propargylic alcohols **16a** and **16b** with TBDMSCl. This reaction gave yields of 63% and 64% respectively. Subsequent hydrosilylation of the protected **15a** to *(E)*-

14a was attempted, but NMR showed unreacted **15a**. Attempts on hydrosilylation of compound **16a** and **16b** gave a complex mixture and no insulatable product.

The Ritter reaction for amidation of the propargylic alcohol **16a** was attempted, but ^{1}H NMR showed unreacted starting material.

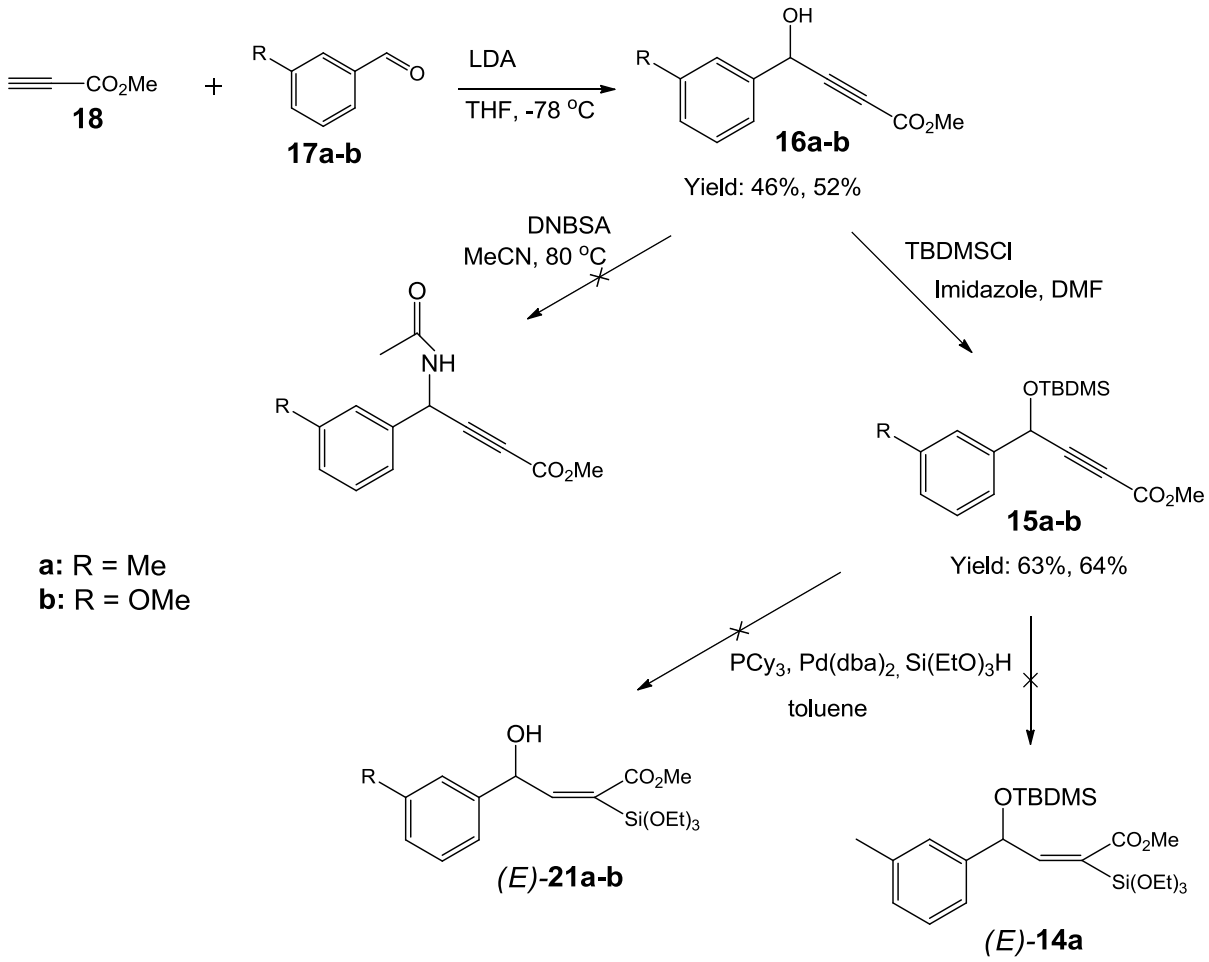

Figure III; Synthesis route B

Sammendrag

To ulike synteseruter mot målmolekyl **1** har blitt studert (se figur I).

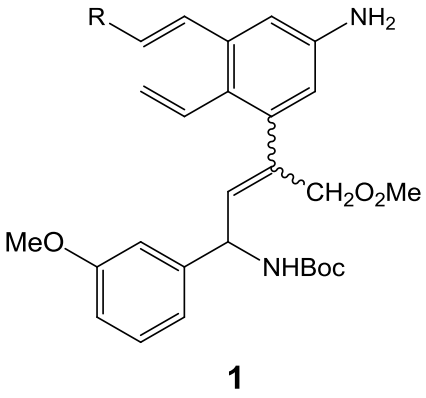

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Figure I; Målmolekylet 1

Synteserute A (se Figur II) er basert på tidligere arbeid av Ragnhild G. Ohm og Cecilie Surdal. Med denne strategien ble forbindelse **3** fremstilt med 20% utbytte, i en blanding av Z - og E isomeren i forholdet 1:0.9. De to isomerene var ikke skillbare ved bruk av kolonne kromatografi (bortstet ra en liten del av E-isomeren). På grunn av dette ble en ny synteserute satt opp.

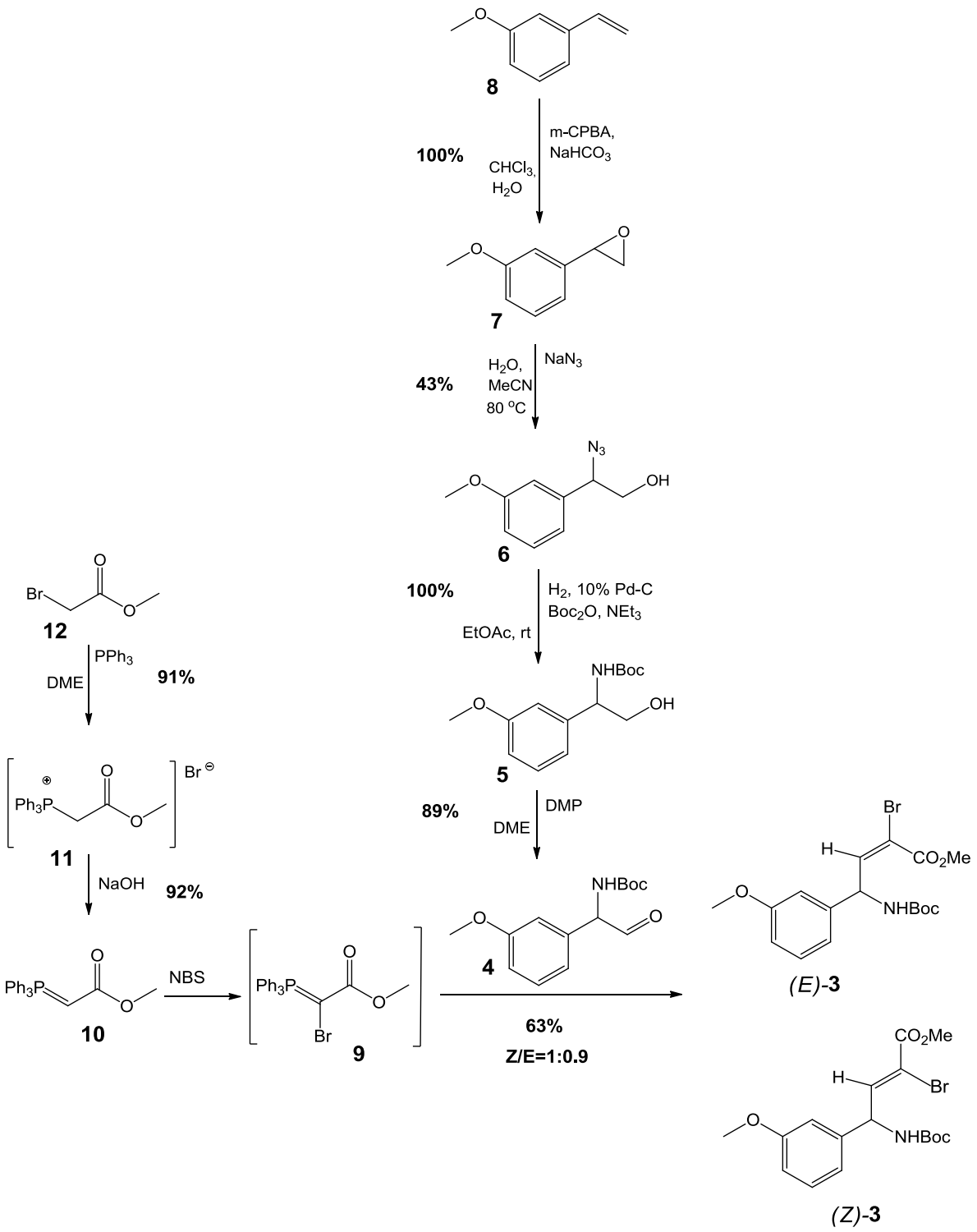


Figure II; Synteserute A

Synteserute B er designet for å kunne danne enantiomert rene substrater som kan brukes i Suzuki –og Hiyama krysskoblinger, som ender med målmolekylet **1** som ren E og ren Z isomer. Det første steget med kondensasjon mellom metylpropiolat (18) og arylaldehydene 17a og 17b ble gjennomført med utbytter på henholdsvis 46 og 52% (se Figur III). Neste steg var en beskyttelsesreaksjon av propargylalkoholene 16a og 16b med TBDMSCl. Denne

reaksjonen gav utbytter på henholdsvis 63 og 64%. Etterfølgende hydrosilylering av den beskyttede forbindelsen 15a til *(E)*-**14a** ble forsøkt, men NMR viste ureagert startmateriale. Forsøk med hydrosilylering av forbindelse 16a og 16b gav en kompleks miks uten isolerbart produkt.

Det ble gjennomført et forsøk med Ritter reaksjonen for amidering av propargylalkoholen 16a, men NMR viste kun ureagert startmateriale.

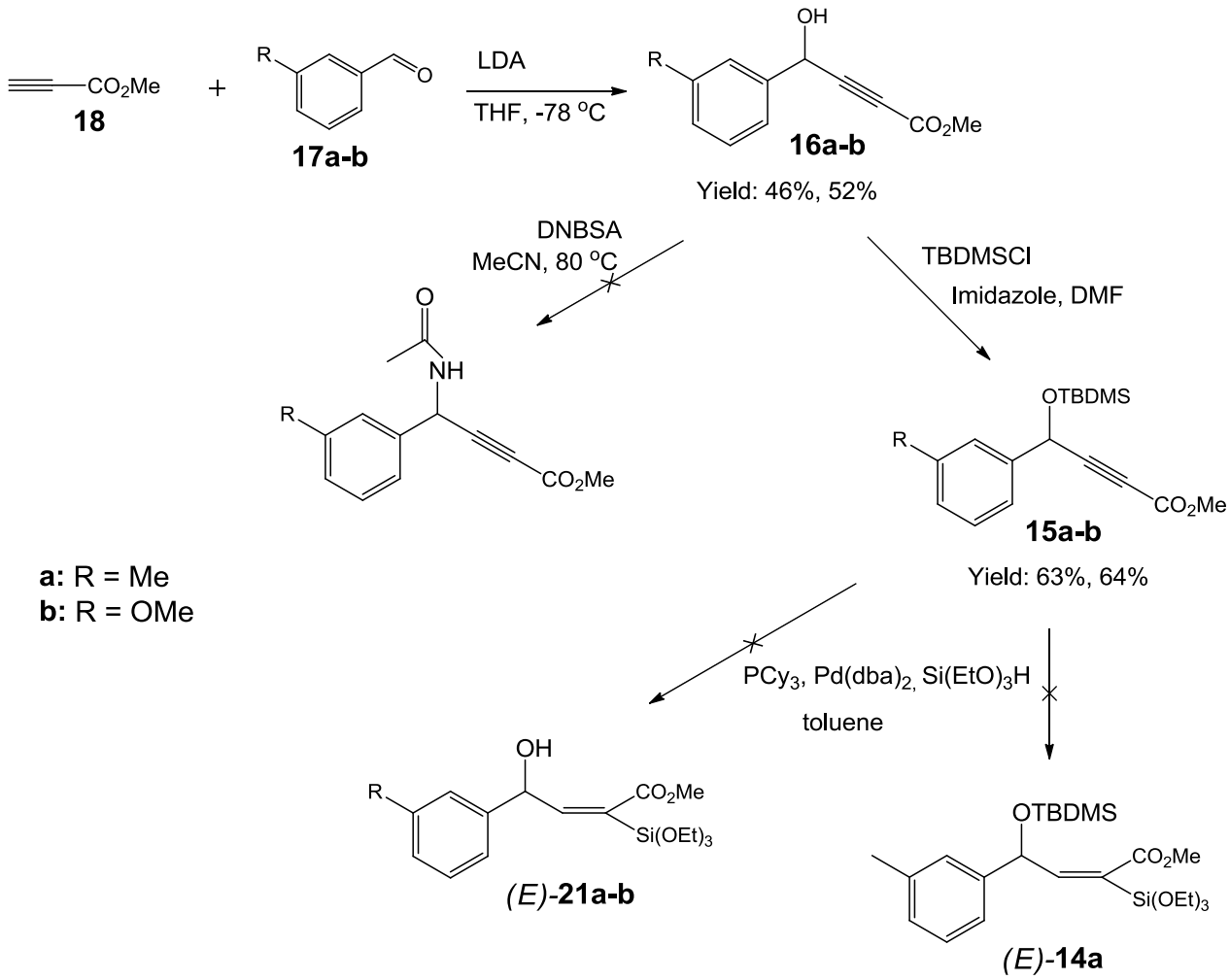


Figure II; Synthesis route B

Abbreviations and symbols

δ	Chemical shift measured in ppm from a reference point
app.	Apparent
atm	Atmosphere
aq	aqueous
Boc	*tert*-Butoxy carbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
C NMR	Carbon Nuclear Magnetic Resonance
COSY	**Co**rrelation **S**pectroscop **Y** – 2D NMR, ^{1}H-^{13}C correlation
d	doublet
DCM	Dichloromethane
DCE	Dichloroethane
dd	doublet of doublets
DMP	Dess-Martin periodinane
DMF	Dimethylformamide
DNBSA	Dinitrobenzenesulphonic acid
EPO	Erythropoietin
equiv.	Equivalent
EtOAc	Ethyl acetate
Fmoc	Fluorenylmethyloxycarbonyl
h	Hours
HF	Hydrogen fluoride
HMBC	Heteronuclear multiple bond correlation
H NMR	Hydrogen Nuclear Magnetic Resonance
HR-MS	High resolution Mass spectroscopy
HSQC	Heteronuclear single-quantum correlation
IBX	o-Iodoxybenzoic acid
IR	Infrared
J	Coupling constant, Hz
Jak	Janus kinase
m-CPBA	*meta*-Chloroperbenzioc acid
mL	millilitre
MM	Multiple myeloma
mmol	millimol

MS	Mass spectroscopy
NEt_3	Triethyl amine
NMR	Nuclear Magnetic Resonance
o.n	Over night
PASSA	Protein Alpha Shape Similarity Analysis (PASSA)
rt	Room temperature
s	singlet
sat.	saturated
STAT	Signal Transducers and Activators of Transcription
t	triplet
TBDMS	*tert*-Butyldimethylsilyl
TLC	Thin layer chromatography
Tyk	Tyrosine kinase

Table of Contents

1. Introduction

Multiple Myeloma (MM) is a disorder in the plasma cells that accounts for approximately 10% of hematologic cancers and about 1% of all cancer deaths worldwide. [1, 2] Treatment with existing drugs only prolongs life to a certain extent, with median survival time after diagnosis of 3-4 years. [2] Tyrosine kinase 2 (Tyk2) has been identified as a potential target for MM cancer therapy, since inhibiting Tyk2 could inhibit the growth and proliferation of MM cells through the *Janus Kinase-Signal Transducers and Activators of Transcription* (Jak STAT) signaling cascade. [3, 4] Tøndel and co-workers have, based on computational work, [3, 5] suggested five different compounds as potential selective inhibitors of Tyk2. Figure 1.1 is showing one of these, which will be the subject of this master`s thesis.

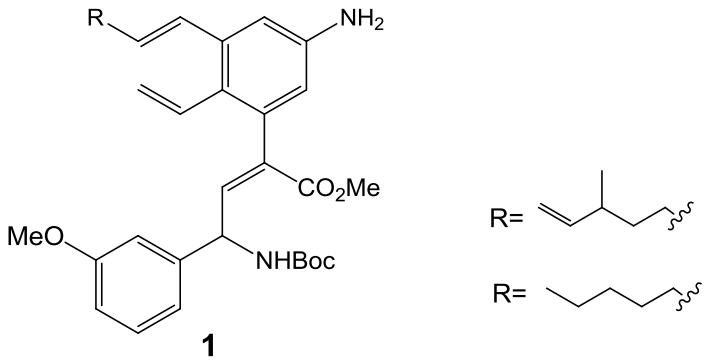


Figure 1.1; Target compound (1) to be synthesized

Retrosynthetic analysis shows that the target compound can be disconnected to compound **2a** and **3**, shown in figure 1.2. The synthesis will involve a Suzuki-Miyaura cross-coupling.

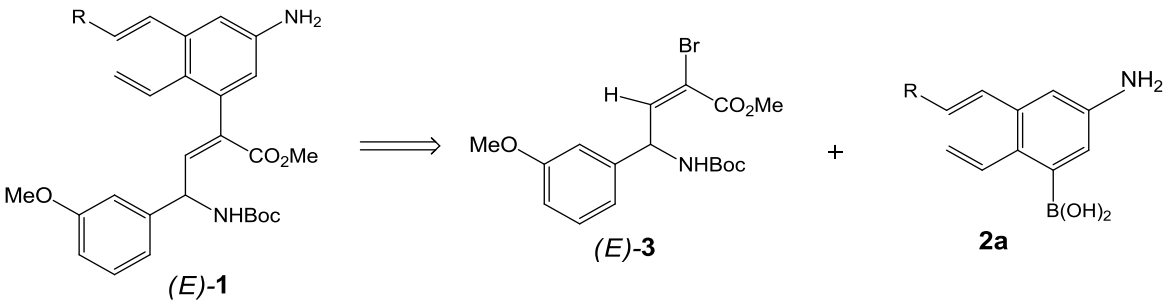


Figure 1.2; Target compound (1) can be disconnected to compounds 3 and 2a

Ohm [6] has earlier in this project shown that the E-isomer of compound **3** can be synthesized and isolated. She did not succeed with the subsequent Suzuki reaction, and other conditions are planned to be tested in this thesis. Surdal [7] attempted to synthesize the Z-isomer of compound **3**, without success, hence the focus will be to synthesize the E-isomer and utilize it

in the cross coupling. An improvement of the synthesis towards both the E and the Z isomers are desirable, but it is assumed that preparation of the E-isomer requires less work and is more likely to result in a successful Suzuki-Miyaura cross coupling.

The synthesis route in this master`s thesis will be based on the reactions developed by Ohm [6] towards compound *(E)*-**3** (Figure 1.2). Improvement of certain steps will be attempted, to produce sufficient *(E)*-**3** for utilization in the Suzuki test reactions.

Compound **2a** (Figure 1.2) is not yet synthesized, and the Suzuki-Miyaura experiments will therefore involve a structurally similar model substrate (see Figure 1.3). This master`s thesis is a part of the project "Rational Drug Design. Synthetic studies toward potential selective inhibitors of tyrosine kinase 2" conducted by Philosophia Doctor Silje Melnes.[8] Melnes did not succeed in the synthesis of compound **2a**. For the purpose of testing the Suzuki-Miyaura cross-coupling with compound *(E)*-**3**, (3-methoxyphenyl)boronic acid, which is commercially available, can be utlilized. [8]

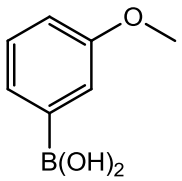


Figure 1.3; (3-methoxyphenyl)boronic acid, a model substrate for use in Suzuki reaction

2 Theory

2.1 Biochemical background

Multiple myeloma (MM) [2] is a cancer affecting the antibody producing plasma cells found in bone marrow. The Jak-STAT cell signaling cascade is shown to play a key role in growth and survival of human MM cancer cells, where Jak is an enzyme family and STAT is a transcription factor family.[9]

The Jak-STAT pathway (shown in igure 2.1) is, among other physiological processes, fundamental for the proliferation of blood cells.[9]

The pathway includes a receptor that has no intrinsic protein kinase activity.[10] The system binds a cytosolic Tyr kinase when occupied by a ligand. For the system that regulates the formation of erythrocytes, the ligand is erythropoietin (EPO). EPO binding makes the plasma membrane receptor dimerize, and the dimer can bind and activate the soluble protein kinase Jak (Janus kinase).

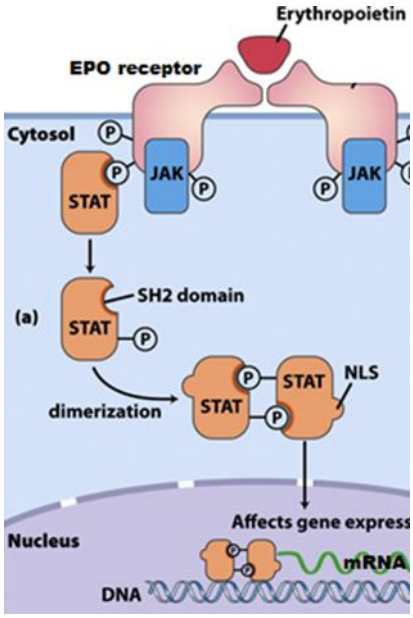


Figure 2.1; The Jak-STAT signaling cascade[10]

Jak then phosphorylates several Tyr residues in the cytoplasmic domain of the EPO receptor in addition to a family of transcription factors, collectively called STATs (Signal Transducers and Activators of Transcription). A domain in STAT (SH2-domain, see figure 2.1) binds the phosphorylated Tyr residues in the EPO receptor, positioning the STAT for phosphorylation by Jak in response to EPO. The phosphorylated STAT forms dimers, exposing a nuclear

localization sequence (NLS) that causes it to be transported into the nucleus. There, STAT induces expression of specific genes essential for erythrocyte maturation.[10]

In all types of cancer, the normal regulation of cell division has become dysfunctional due to defects in one or more genes. [10] It also seems to be the case of MM, where it has been proposed that the phosphorylation of STAT3 is increased by an overactive Jak. This results in increased gene transcription and consequently physiological response, is responsible for the pathogenesis.[9]

Blocking the ATP binding site of the protein kinase Tyk2 by a selective inhibitor might stop the abnormal Jak-STAT activity in the MM cells, and potentially work in anticancer therapy. The general protein kinase structure is shown in figure 2.2.

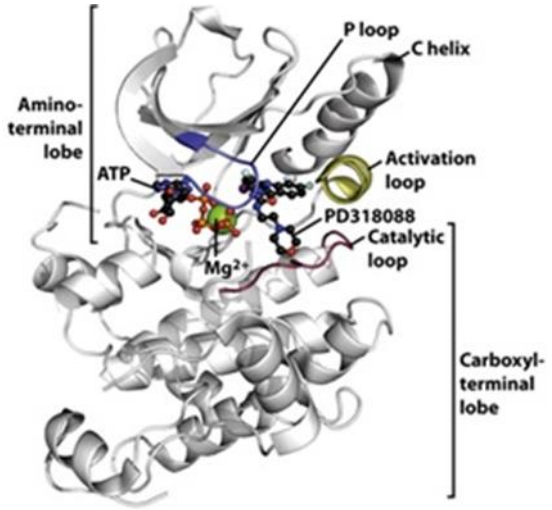


Figure 2.2; Conserved features of the active site of protein kinases, illustrated with a specific inhibitor occupying the substrate binding cleft

The simplest protein kinase inhibitors are ATP analogs that occupy the ATP binding site, but cannot serve as phosphoryl donors. These compounds have a limited clinical usefulness, because they inhibit virtually all protein kinases, causing severe side effects. [10]

Success has earlier been reached in design of a *selective* Tyk-inhibitor, the drug Gleevec, used for treating chronic myelogenous leukemia.[11] Gleevec (or imatinib mesylate, shown in figure 2.3) is an inhibitor with more selectivity because the compound fill parts of the ATP-binding site, but also interact outside this site, with parts of the protein unique to the target protein kinase. [10]

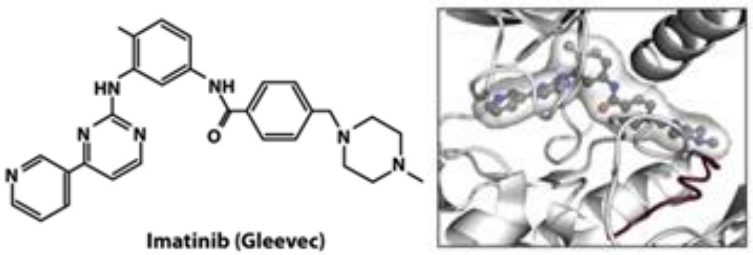


Figure 2.3 The structure of the tyrosine kinase inhibitor Gleevec, and an illustration of its position inside the protein kinase structure where it inhibits the oncogene activity

Tøndel and Drabløs cooperated with the MM research group at NTNU, and suggested five structures as potential selective inhibitors of Tyk2, analogous to Gleevec but for use in treatment of MM.[3, 5] They used homology modeling to predict the 3D structures of the catalytically active kinase domains of Jak2 and Tyk2.[3] In addition they used Protein Alpha Shape Similarity Analysis (PASSA) to find important functional groups for selective inhibition of Tyk2 based. [5] These compounds are not available and need to be synthesized before their action in a biological system can be tested.

2.2 Strategy for preparation of Target Molecules

Synthesis routes with long linear sequences of reactions give low yields[12] ; a linear 10-step sequence with each step giving 90% yield gives only just under 35% overall. Convergent or branching strategies make things better by reducing the longest linear sequence. The bigger the molecule, the easier it is to devise a convergent strategy, and this is what we do when we choose disconnections in the middle of the molecule and at branch points. [12] As seen in Figure 2.4 the retrosynthesis includes two disconnections at branch points, this is the Suzuki reaction between compound **2** and **3** and the Wittig reaction between compound **4** and **9**. The rest of the synthesis strategy is involved with functional group interconversions; from vinylanisole (**8**) to the aminoaldehyde (**4**), and from methyl bromoacetate (**12**) to the bromoylide (**9**). In addition a Boc-protection group is included to prevent side reactions. [13]

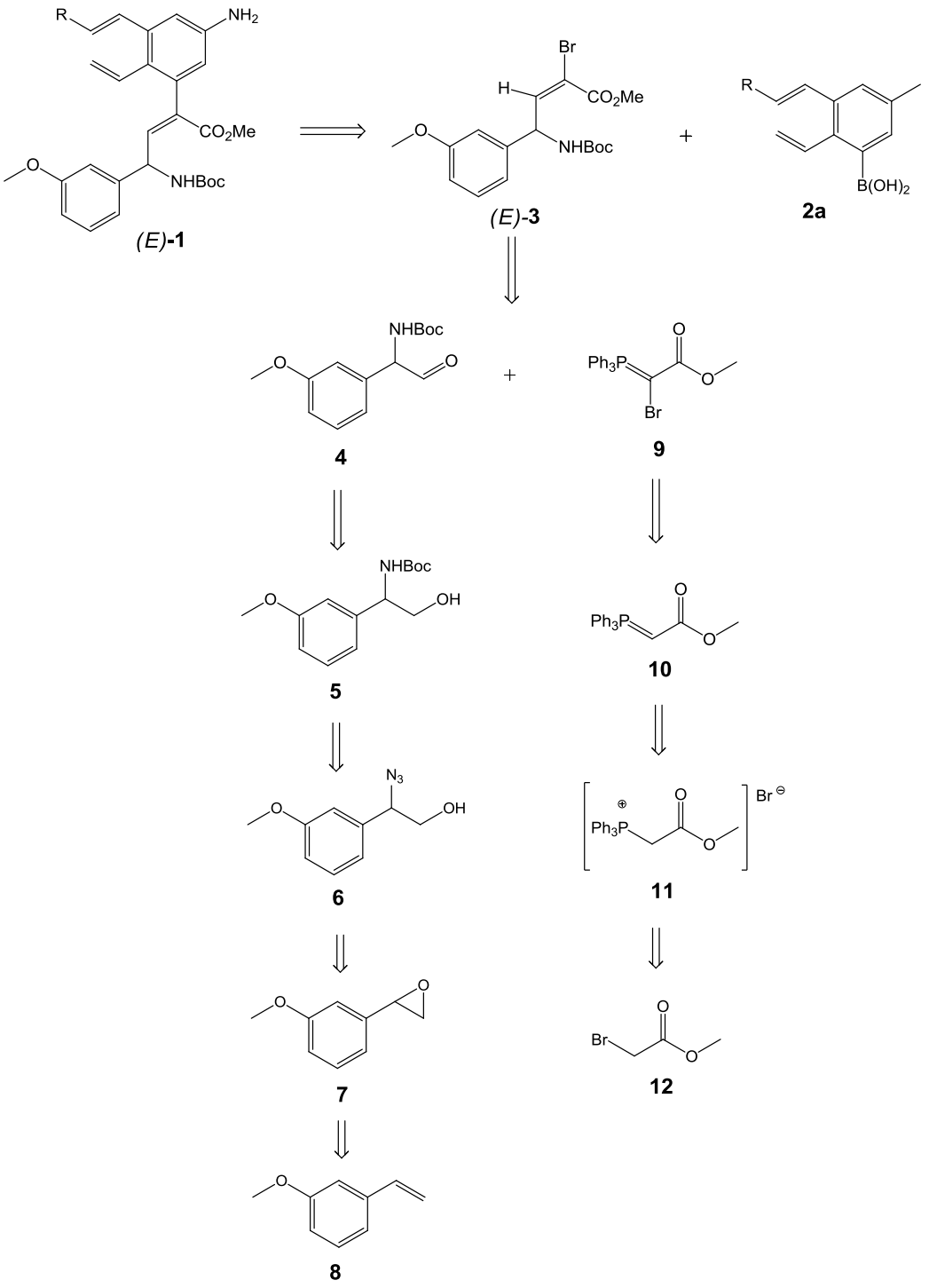


Figure 2.4; Retrosynthesis of target compound (1)

The Suzuki reaction (between compound **2a** and **3**, Figure 2.4) is a palladium-catalyzed cross-coupling reaction in which the organometallic component is a boron compound. These reactions proceed with retention of double-bond configuration in both the boron derivative and the alkenyl halide. The oxidative addition by the alkenyl halide, transfer of the alkenyl group from boron to palladium, and reductive elimination all occur with retention of configuration. [14]

The protected α-aminoaldehyde (**4**) is prepared over the four steps. The first reaction is an epoxidation of 3-vinylanisole by mCPBA (see section 6.3 Experimental). The epoxide (**7**) is subsequently ringopened by NaN_3 (section 6.4), the resulting azide (**6**) is catalytically hydrogenated with Pd-C and H_2-gas and protected with Boc (section 6.5). The fourth step is Dess-Martin oxidation of the protected aminoalcohol (**5**) (section 6.6).

This route for preparation of the α-aminoaldehyde (**4**) is earlier accomplished by Ohm[6] and Surdal[7] with promising results. Oxidation of aminoalcohol (**5**) might have room for improvement; hence oxidation agents PCC [13] and IBX [14] will be tested.

An alternative to the first three steps is the Sharpless asymmetric aminohydroxylation (SAA), where the styrene is converted to the Boc-protected α-aminoalcohol (**5**). [15] This was tested by Ohm and resulted in yields between 20 and 37% for 3-methylstyrene as substrate, and no reaction for 3-vinylanisole as substrate. [6] SAA works best with electron deficient alkenes. [15] The fact that both these styrenes are electron rich, especially 3-vinylanisole, makes the reaction less suitable.

2.2.1 Oxidation of aminoalcohol 5

o-Iodoxybenzoic acid (IBX) and Dess Martin periodinane (DMP) are called periodinanes and are organic derivatives of pentacoordinate iodine(V). DMP has emerged as the reagent of choice for the oxidation of alcohols to the corresponding carbonyl compounds, because of advantages such as mild reaction conditions, high chemoselectivity and tolerance of sensitive functional groups on complex substrates. [15] The reaction mechanism is shown in Figure 2.2.

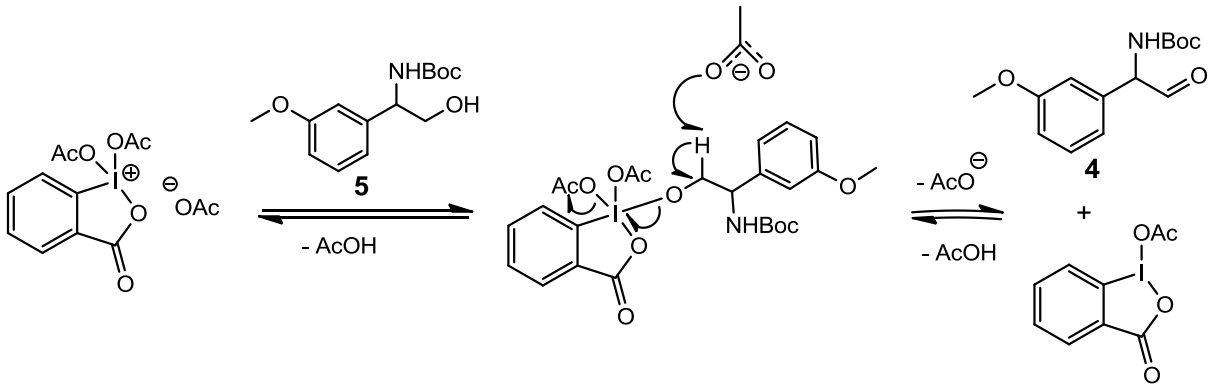


Figure 2.2; Reaction mechanism for Dess Martin oxidation of aminoalcohol 5

The mechanism for the Dess Martin oxidation initiates by the rapid reaction between DMP and the alcohol to give diacetoxyalkoxyperiodinane.[15] It proceeds by the removal of the α-proton of the alcohol by a base (acetate), and the aldehyde is released along with a molecule of iodinane.

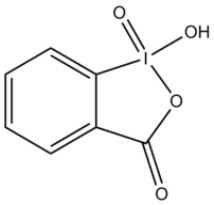


Figure 2.3; *o*-Iodoxybenzoic acid (IBX)

IBX (Figure 2.3) has been known since 1893, but its almost complete insolubility in most organic solvents prevented its widespread use in organic synthesis.[15] More and Finney [16] on the other hand, found that at elevated temperatures, IBX was sufficiently soluble in most organic solvents to permit clean oxidation of alcohols to the corresponding aldehydes and ketones. They regarded EtOAc and DCE as the solvents of choice because they are inert and all byproducts are insoluble at room temperature, such that no purification is required beyond simple filtration. [16] With the use of three equivalents IBX, virtually every alcohol they investigated was converted to the corresponding carbonyl compound in excellent yield, and IBX proved to be insensitive to the presence of air and moisture.

Oxidation with pyridinium chlorochromate (PCC) has the advantages of easy and safe preparation and high capability to convert primary alcohols exclusively to aldehydes with great efficiency [17]. Piancatelli *et al*. [17] reviewed four different mechanisms of the reaction, but the details will not be discussed here.

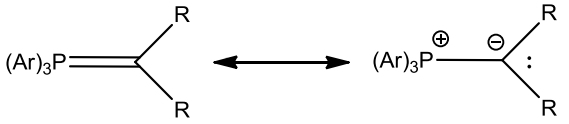
2.2.2 Stereoselective Wittig reaction between bromoylide and aldehyde

The most important method of alkene synthesis is the Wittig reaction, which gives full control over the position of the double bond and some control over its geometry. [12] Reaction between an aldehyde and an ylide gives the alkene, usually the Z-alkene if the R-group (side chain) on the ylide is an alkyl group, and triphenylphosphine oxide.

An ylide is a species with positive and negative charges on adjacent atoms.[12] To prepare the ylide (**10**) for use in the Wittig reaction, triphenylphosphine is reacted with an alkyl halide

(**12**) in an S_N2 reaction to give a phosphonium salt (**11**). Treatment with base, in this synthesis NaOH, gives the phosphonium ylide (**10**).

There are three types of ylides depending on its substituents (originating from the alkyl halide). These are shown in figure 2.4. In the "stabilized" ylides the alkyl halide component has at least one strong electron-withdrawing group (in the case of compound **10** a COOR-group), which stabilizes the formal negative charge on the carbon. [15] "Semi-stabilized" ylides have at least one aryl or alkenyl substituent, and "nonstabilized" ylides usually have only alkyl substituents. "Stabilized" ylides give predominantly (E)-olefins with aldehydes in dipolar aprotic solvents. Whereas "nonstabilized" ylides affords olefins with high (Z)-selectivity, and "semi-stabilized" ylides usually give alkenes with poorer selectivity. [15]



Nonstabilized ylide: R= alkyl, H
Semistabilized ylide: R= aryl, alkenyl, benzyl, allyl, H
Stabilized ylide: R= $-CO_2R$, $-SO_2R$, -CN, -COR

Figure 2.4; Three types of ylides, which have different stereoselectivity [15]

The mechanism for the formation of the alkene is on the other hand open for discussion, due to uncertainty on the source of the stereoselectivity. [12] The presence of a betaine or not is especially a hot topic.[18] This intermediate is included in the reaction mechanism in figure 2.5. The carbanion end of the ylide adds to the aldehyde and the betaine, then cyclizes to the four-membered ring which fragments to give the products. The *Z*-alkene is formed from the *cis* oxaphosphetane [12] and the *E*-alkene from the *trans* oxaphosphetane.[15]

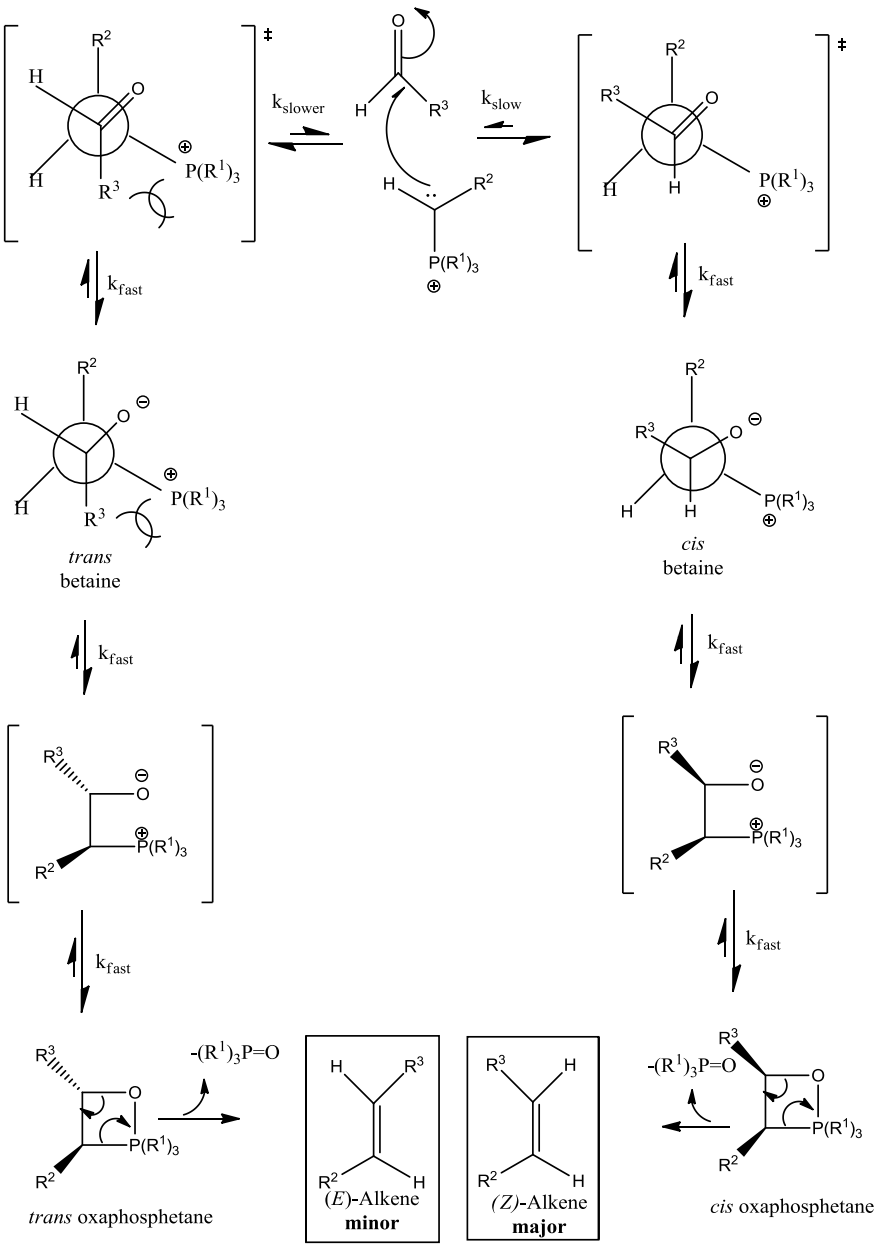


Figure 2.5; Reaction mechanism for the regular Wittig olefination[15]

In the first step an ylide is attacking an aldehyde. This is the rate limiting step and where the stereoselectivity is determined. [15] For the transition state shown at the left there is repulsion between the bulky PR_3-group (triphenylphosphine) and the substituent on the aldehyde, which is not present in the transition state to the right. The *cis*-betaine is generated more rapidly than the *trans*-betaine. Subsequent bond rotation and ring closure of the cis-betaine is forming the cis-oxaphosphetane, before elimination of triphenylphosphine gives the *Z*-alkene as the major product. [15]

The typically observed high E-selectivity in Wittig reactions of ester-stabilized ylides results from a kinetic preference for the formation of *trans*-oxaphosphetane (OPA) (the pathway

leading to the E-alkene), since OPA decomposition to alkene and phosphine oxide is shown to be stereospecific, and is irreversible. [18] Irreversible formation of trans-OPA in reactions of stabilized ylides can be inferred from the fact that *cis*-OPA is formed irreversibly, since trans-OPAs are generally thermodynamically favored over *cis*-OPA and decompose more slowly than *cis*-OPAs, indicating a greater barrier to cycloreversion for *trans*-OPAs.[18]

All factors mentioned above regarding stereoselectivity involve regular Wittig reactions. When α-Aminoaldehyde **4** reacts with bromoylide **9** the resulting alkene is assigned E or Z based on the position of the bromine substituent in relation to the substituent originating from the aldehyde (**4**). According to Cahn–Ingold–Prelog priority rules bromine has higher priority than the ester group, and everything mentioned above concerning E/Z-selectivity in Wittig reactions will be the opposite for haloylides.

When it comes to Wittig reactions with haloylides there is limited literature concerning the E/Z-selectivity. Thiemann *et al.* [19] and Ohno *et al*. [20] found that this type of Wittig reactions give predominantly the Z-isomer, but Ohm [6] reports a stereoselective reaction in favor of the E-isomer. She attributes this selectivity to complexation in the transition state, between the amino group and the carbonyl group on the aldehyde. She also presents amount of solvent as a factor.

Wittig reactions employing haloylides can be complicated because haloylides react easily with traces of acids, including their own conjugate acids, and they decompose upon exposure to moisture. [21] Earlier in this research project, Ohm [6] only got a 33% yield in the preparation of the brominated ylide. To avoid isolation and purification of this unstable compound, the Wittig type reaction implemented in this synthesis route is a procedure with bromination of the ylide and the actual Wittig olefination in one-pot.

In the one-pot procedure the ylide (**10**) is brominated with NBS to form bromoylide (**9**), and the aldehyde (**4**) is added directly to the reaction mixture from the bromination to complete the Wittig coupling. [21, 22]

2.3 New strategy for preparation of Target Molecules

An alternative route to the target compound (**1**) can originate from methyl propiolate (**18**) and arylaldehydes (**17**) as starting material (see Figure 2.6). Similar to the original synthesis route the last step involves a Suzuki cross coupling with compound **2a**. This cross-coupling results in the E-isomer of the target compound. The Z-isomer is originating from the same substrate earlier in the synthesis route, only with one different reaction. In addition to the reactions mentioned, the synthesis includes a condensation between methyl propiolate (**18**) and arylaldehydes (**17**), a protection reaction and a hydrosilylation. An alternative to the protection of the hydroksyl group in compound **16** is the Ritter reaction, where the alcohol is converted to an amide.

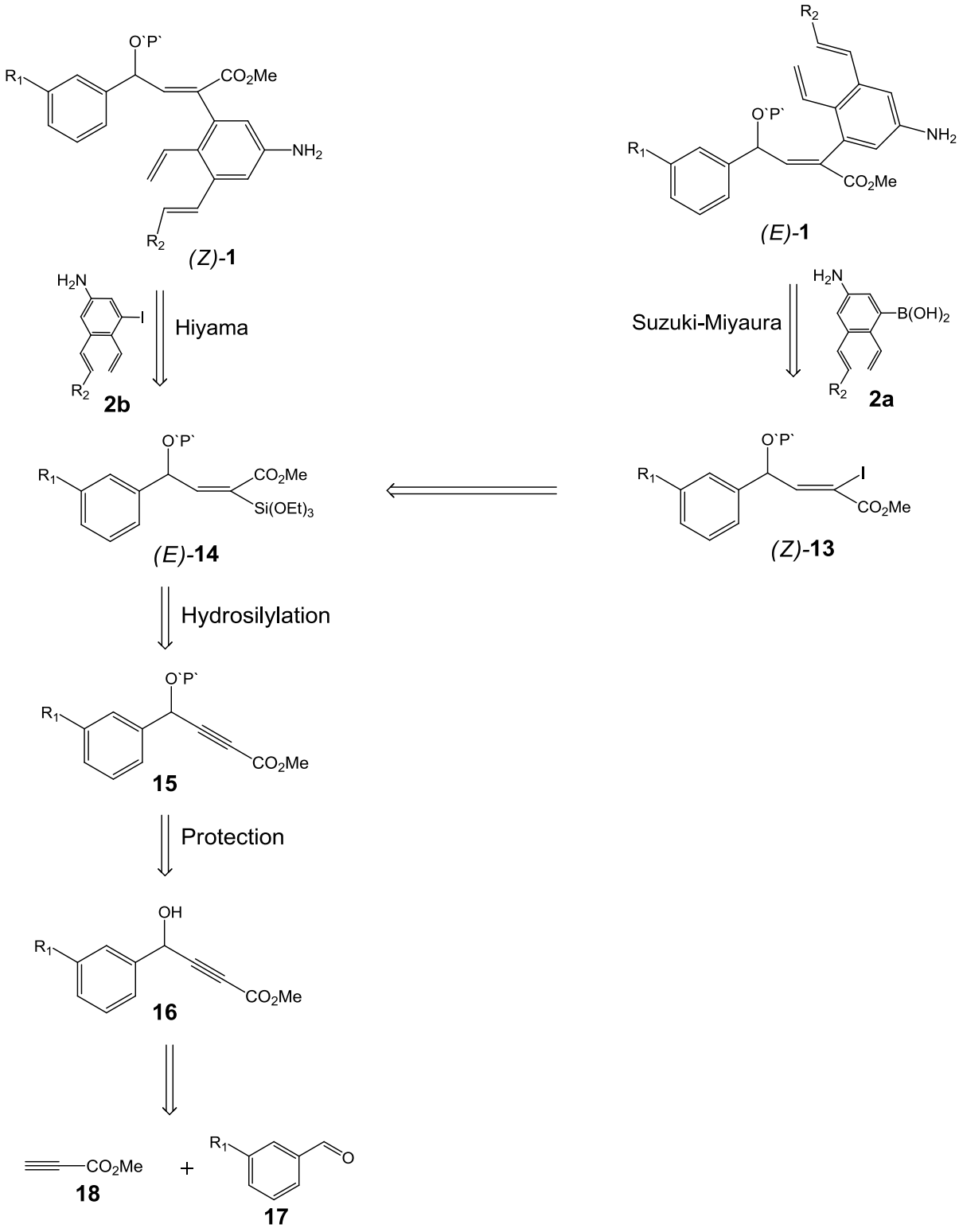


Figure 2.6; Alternative retrosynthesis of target compound (1)

This synthesis route is new, and the reactions are based on separate literature procedures, proven to work with other substrates. In general this route looks more promising than the original route, because it has fewer steps where product can be lost. In comparison to the original synthesis route, this one encompasses the stereoselective synthesis of both the Z -and

the E-isomers of the target compounds from the same substrates towards the end of the synthesis route. The two (three) last steps with hydrosilylation and following Hiyama -or Suzuki-Miyaura coupling is accomplished successfully by Sumida *et al*. utilizing similar substrates. [23] They applied hydrosilylation to alkynes activated by an adjacent electron-withdrawing group, equivalent to compound **15** in figure 2.6.

Suzuki-Miyaura and Hiyama reactions are cross-couplings that enable new carbon-carbon bond formations. [23] From silylalkene *(E)*-**14** (Figure 2.6) Hiyama coupling might be accomplished by addition of an aryliodide (compound **2b** or a model substrate), catalyzed by $PdCl_2(PPh_3)_2$. The silylalkene *(E)*-**14** might also be stereoinverted to *(Z)*-**13** by adding 2 equiv. ICl, before *(Z)*-**13** can be coupled to a boronic acid (compound **2a** or a model substrate) in a Suzuki-Miyaura reaction.

2.3.1 Condensation of methyl-propiolate and aryl aldehydes (17a, 17b)

Alkynylation of carbonyl compounds (**17a** and **17b**) are powerful reactions for forming carbon–carbon bonds. Acetylides can be generated in situ by the addition of n-butyllithium to methyl propiolate. Because n-butyllithium is itself a nucleophile toward aldehydes and ketones, the amount of base used must be controlled carefully. These strongly basic conditions limit the application to base-stable compounds. Satisfactory results might be difficult to obtain due to problems if the very strong base is in access, and it is also moisture sensitive[24].

Midland [25] found that the lithium acetylide salt of methyl or ethyl propiolate may be readily prepared at low temperature by the reaction of the propiolate ester with *n*butyllithium. The acetylenic anion rapidly adds to a variety of aldehydes and ketones to give the methyl or ethyl 4-hydroxy-2-alkynoates upon workup. The addition of the anion to aldehyde or ketones appears to be rapid and quantitative. Workup is facilitated by protonation with acetic acid or saturated ammonium chloride at low temperature

The moieties in the substrates *m*-tolualdehyde (**17a**) and *m*-anisaldehyde (**17b**) which are not desirable for the attack are stabile upon base (see reaction mechanism in Figure 2.7). For convenience commercial LDA is used instead of generating it from BuLi and diisopropylamine.

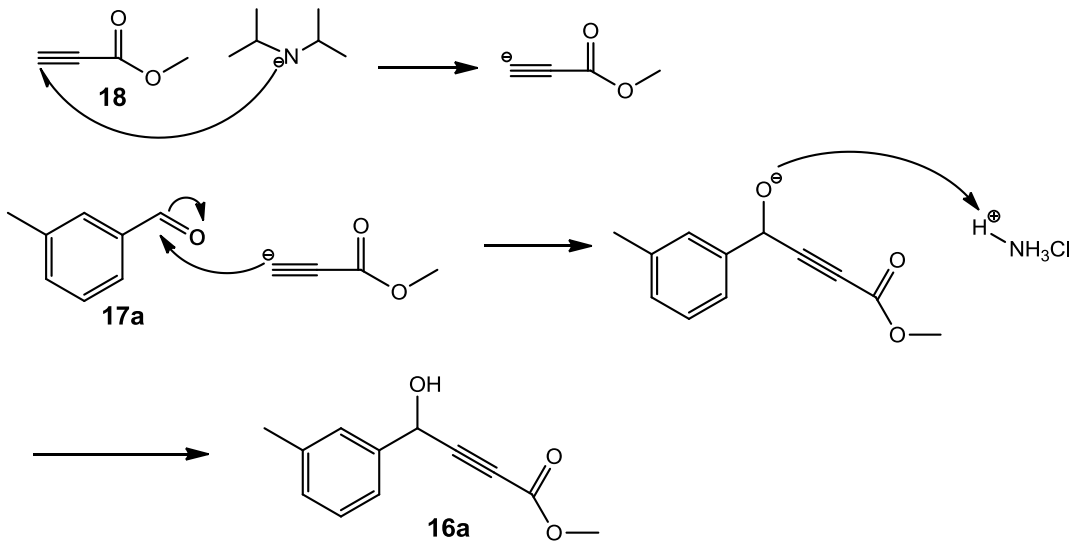


Figure 2.7; Reaction mechanism for condensation between 17a and 18

The reaction mechanism involves deprotonation of methyl propiolate (**18**) by LDA, and subsequent nucleophilic attack by the resulting acetylide anion on the carbonyl carbon. The alkoxide ion is protonated by ammonium chloride in work-up, resulting in a propargylic alcohol (**16a**).

2.3.2 The Ritter reaction

The Ritter reaction is a general method for amidation of alcohols or alkenes with nitriles. The reaction works well in the case of tertiary alcohols, but is more challenging with less substituted centers due to the instability of the intermediate carbocation. Catalytic cycle for the reaction is shown in Figure 2.8. [26]

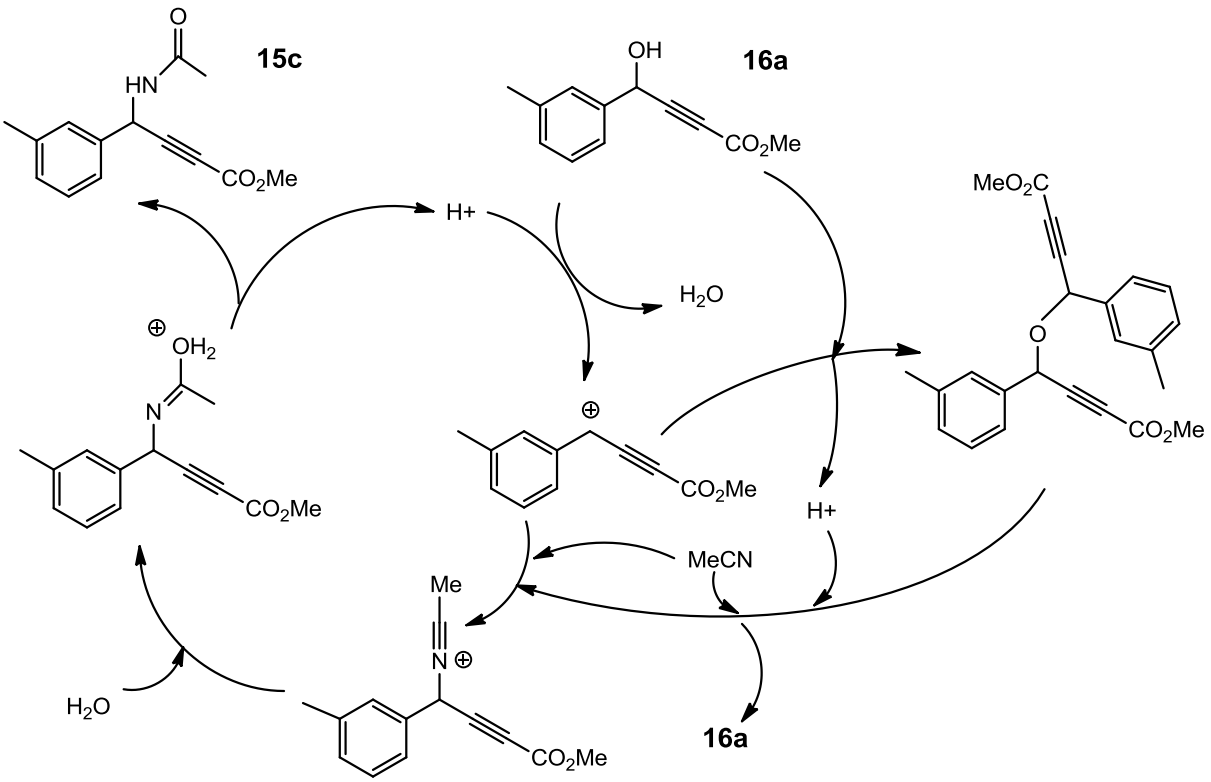


Figure 2.8; Catalytic cycle for Ritter reaction

Protonation of a benzylic alcohol, such as **16a** forms a carbocation. The carbocation is trapped with a molecule of acetonitrile to generate a nitrilium cation. This is captured by the water produced in the first step of the process. Deprotonation affords the product, which is an amide.

Sanz *et al.* [26] found that simple organic acids like 2,4-dinitrobenzenesulphonic acid (DNBSA) catalyzed the Ritter reaction of secondary benzylic alcohols giving rise to the corresponding N-benzylacetamides in high yields. The reaction was reported to be tolerant towards air and moisture, and is an environmentally friendly alternative to metallic catalysts.

2.3.3 Protection of alcohols with tBuMe2SiCl

tert-Butyldimethylsilyl (TBDMS) ethers are the most versatile of all the silicon based protecting groups, when it comes to different reagents and conditions for removal of the group. This can be accomplished by acids, including Lewis acids, complexes of HF with amines, and fluorides. [13] TBDMS ethers are stable to chromatography and they are stable below 0 ^{o}C to strong non-protic bases, such as n-alkyllithiums, Grignard reagents, enolates and metallated sulfones. TBDMSCl is expensive, though it is readily prepared in high yield by the reaction of *tert*-butyllithium with dichloromethylsilane. The steric bulk of the *tert*-butyl group significantly diminishes the rate of silylation with TBDMSCl, so convenient rates are

best achieved by the addition of basic activators such as imidazole and by using dipolar aprotic solvents such as DMF. Primary alcohols react much faster than secondary alcohols, but tertiary alcohols are inert. [13]

2.3.3 Hydrosilylation of alkynes

Silylalkenes serve as a powerful building block in organic synthesis owing to diverse types of valuable transformations, such as Hiyama coupling, which enables new carbon-carbon bond formations. Silylalkene also offers advantages over other metal alkenes in terms of stability, cost and low toxicity. Sumida *et al.* describes a highly regio- and stereoselective hydrosilylation achieved by the use of palladium catalysis. These reactions are generally applicable to alkynes activated by an adjacent electron-withdrawing group, like the ester group in compound **15a**. Sumida *et al.* found that catalysis by $Pd(dba)_2$ and PCy_3 worked ideally providing the (E)-α-isomer in an excellent yield with extremely high regio- and stereoselectivity. [23] The reaction proceeds by the Chalk-Harrod mechanism, with the proton originating from $Si(OEt)_3H$ getting placed in β-position to the ester group (see Figure 2.9). The mechanism involves oxidative addition of silane to Pd(0), regio- and stereoselective hydropalladation to the alkyne, and then reductive elimination to afford the product.[27]

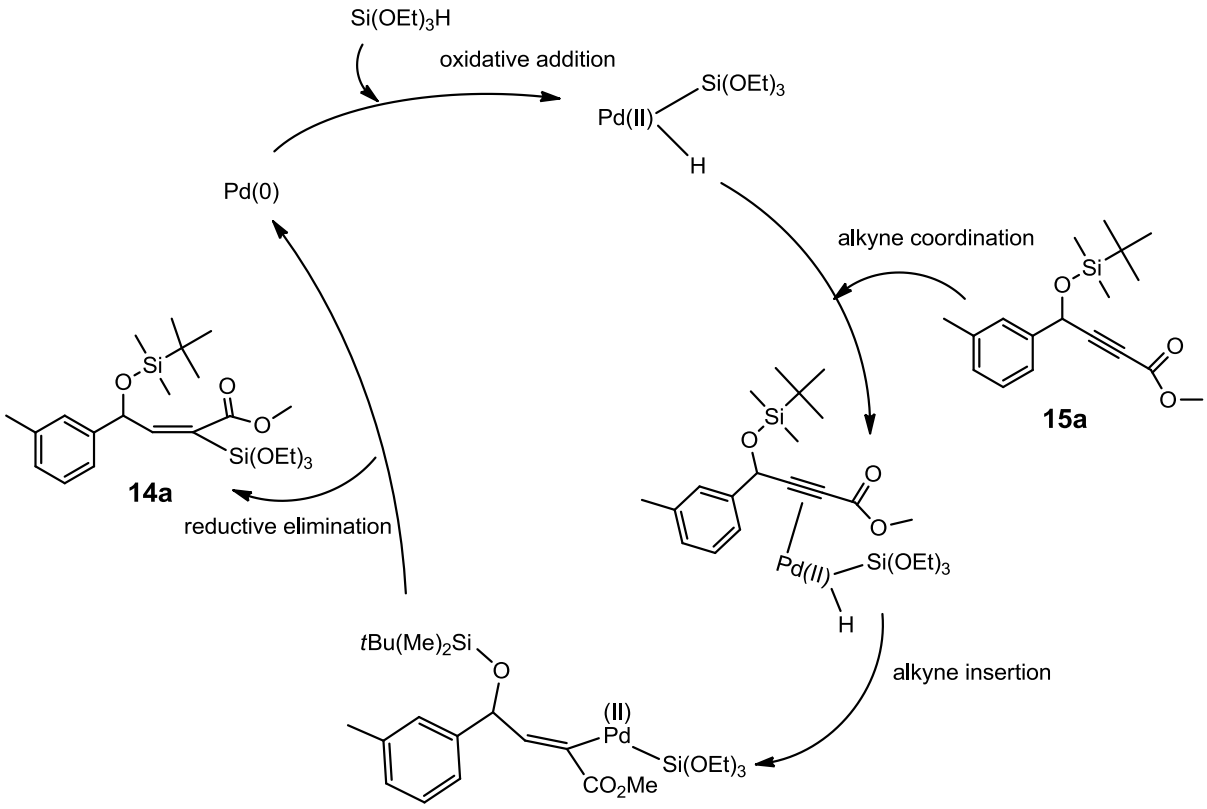


Figure 2.9; Catalytic cycle for hydrosilylation of alkynes[27]

3 Results and Discussion

3.1 Synthesis route A

3.1.1 Overview of synthesis route from 3-vinylanisole to compound 4

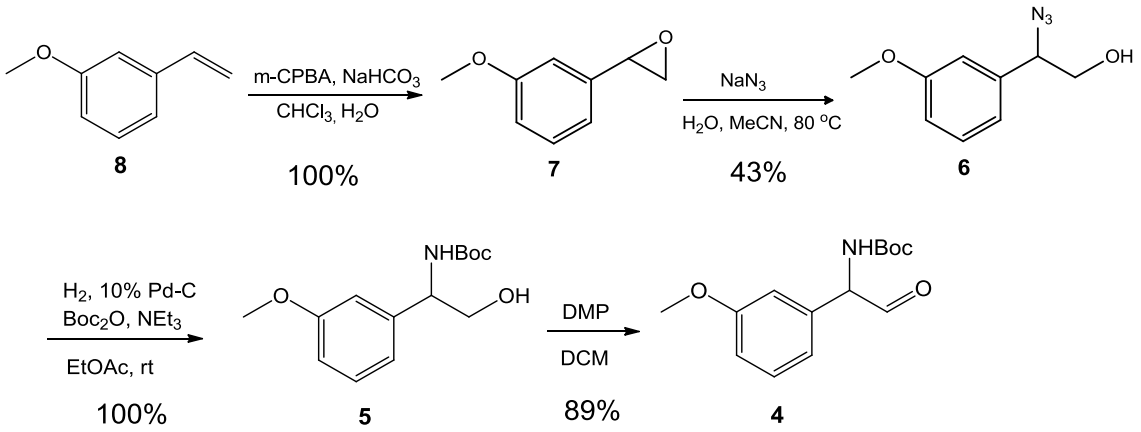


Figure 3.1; Summarized results for the first four reactions in the synthesis route

Table 3.1 gives a summary of the yields for the reactions involved in the synthesis of *tert*-Butyl 1-(3-methoxyphenyl)-2-oxoethylcarbamate (**4**). The experimental procedures for the reactions are described in Chapters 6.3 to 6.6. For a thorough theoretical background of these reactions refer to Ohm [6] and Surdal. [7]

Table 3.1 Summary of the reactions of the first half of the synthesis route, with corresponding sections in experimental. Components of the reaction are accompanied with best yield for the reaction. Total yields for the combined reactions are shown in the column to the right.

Reaction (section in experimental)	Substrate	Reagents	Product	Best yield for reaction (%)	Total yield from 3-vinylanisole (%)
Epoxidation, 6.3	3-vinylanisole	*m*-CPBA	**7**	100	100
Ring-opening, 6.4	**7**	NaN_3	**6**	43	43
Protection, 6.5	**6**	Boc_2O, Pd-C, H_2	**5**	100	43
Oxidation, 6.6	**5**	DMP	**4**	89	38

These four steps of the synthesis route are identical to the reactions described by Surdal [7] and Ohm[6]. As seen in table 3.1 the total yield in the preparation of compound 4 was 38%. The results were as expected, and in comparison to Surdal the yield over these four reactions is improved from 19% [7].

The Dess Martin oxidation was generally tricky due to problems with purification. Column chromatography (10% EtOAc/n-pentane) was implemented, and the different components in the mixture seemed to elude from the column at the same time. The product spot on TLC had

a tail, and the aldehyde was thought to decompose on silica. However, a TLC decomposition test did not confirm this. In the last experiment (entry 3, Table 6.4) $NaHCO_3$ was used in the extraction, which seemed to remove the byproduct very nicely. It was decided not to go through with chromatography, since ^1H NMR spectra already looked nicer than it had done for the other entries after purification. It was thought that product would be lost in the purification process. The yield was calculated from the integrals of the signals originating from the aldehydic proton compared to that from the alcohol.

Test reactions with alternative oxidations were carried out, in hopes of a cleaner purification process.

3.1.2 Test reaction: PCC-oxidation of alcohol 5

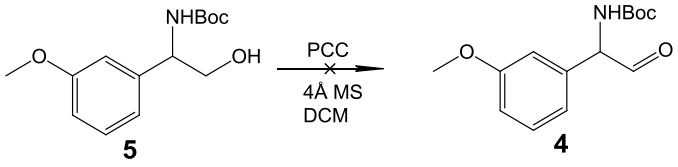


Figure 3.2; The chemical equation for oxidation of alcohol (5)

The experimental procedure is described in Chapter 6.10.

An oxidation of alcohol **5** was attempted in accordance to a general procedure described by Clive et al. [28] The reaction did not give the desired product. See also test reaction with IBX (next section).

3.1.3 Test reaction: IBX-oxidation of alcohol 5

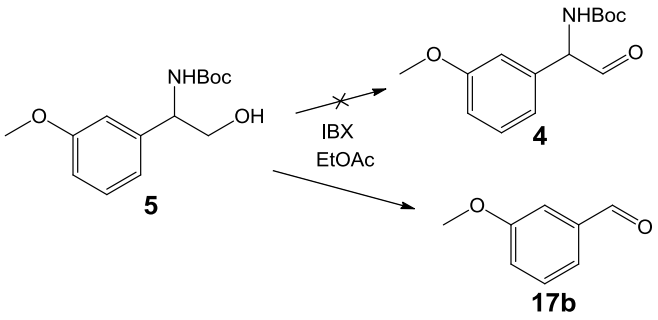


Figure 3.3; The chemical equation for oxidation of alcohol (5) with formation of byproduct (17b)

The experimental procedure is described in Chapter 6.11. The properties of IBX as an oxidation agent are discussed in section 2.2.1.

An oxidation of alcohol **5** was attempted in accordance to the procedure by More and Finney.[16] The reaction did not give the desired product. More and Finney found that virtually every alcohol investigated was converted to the corresponding carbonyl compound, but they were not able to oxidize Fmoc-phenylglycinol to the corresponding aldehyde. This was attributed to the instability of the α-aminoaldehyde.[16] The byproduct 3-methoxybenzaldehyde (**17b**) was isolated by column chromatography (10% EtOAc/n-pentane) and characterized. Compound **17b** is also a recurring byproduct in PCC and Dess-Martin oxidation.

3.1.4 Generation of bromoylide (9) and Wittig-reaction with protected aminoaldehyde

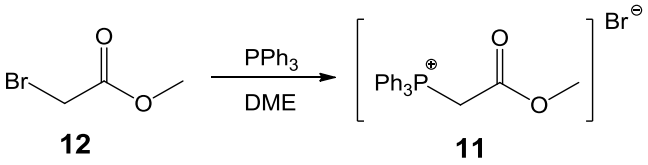


Figure 3.4; The reaction of methyl bromoacetate (12) to form phosphonium salt (11)

The experimental procedure for preparation of phosphonium salt **11** is described in Chapter 6.7. Theoretical background is given in section 2.2.2.

The phosphonium salt **11** was prepared from methyl bromoacetate in 91% yield according to a general procedure described by Boers et al[29].

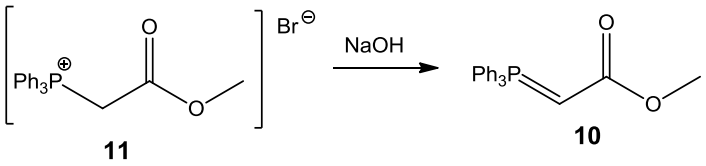


Figure 3.5; The reaction of phosphonium salt (11) to form ylide (10)

The experimental procedure for preparation of ylide **10** is described in Chapter 6.8.

The ylide **10** was prepared from phosphonium salt **11** in 92% yield according to the procedure described by Boers et al. [29]

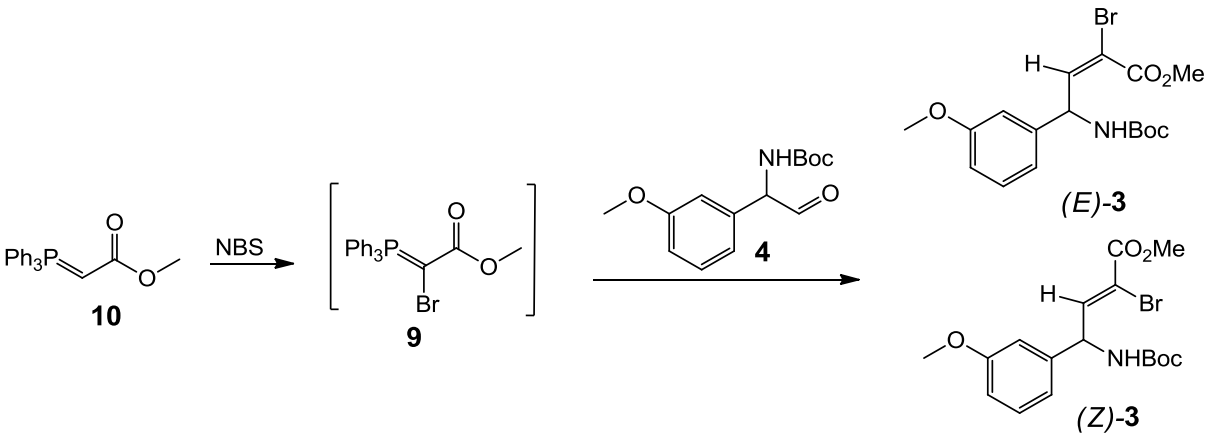


Figure 3.6; The wittig reaction between ylide (10) and aldehyde (4)

Refer to Table 3.2 for reaction conditions and yields for the one pot reaction involving preparation of bromoylide **9** and subsequent Wittig reaction with aminoaldehyde **4.**

The experimental procedure for the reaction is described in Chapter 6.9.

Table 3.2: Quantity of reagents, type of solvent and yield in one-pot generation of bromoylide 9 from ylide 10 and Wittig reaction with protected α-aminoaldehyde 4

Entry	**10** (mmol)	NBS (equiv.)	**4** (equiv.)	solvent	Result (prod., mmol, %)	Z/E selectivity
1	0.39	1.1	1.0	DCM	**3**, 0.205, 53	0.55:1[a]
2	5.73	1.2	1.0	DCM	**3**, 3.33, 60	1:0.4
3	14.3	1.2	0.8	chloroform	Complex mixture	
4	13.80	1.1	0.7	DCM	**3**, 6.6[b], 63	1:0.9

[a] It was not possible to measure the E/Z ratio in the crude, and this is measured after flash column chromatography in the E/Z-mixture, hence it might be loss of some Z-isomer during purification.
[b] The amounts are adjusted by calculations involving ^{1}H NMR-integrals

Compound *(Z/E)*-**3** was prepared in 53-63% yield, according to a general procedure described by Audisio et al. [30] and Brenna et al. [22]

The test reaction (entry 1, Table 3.2) seemed to work well, so the same procedure was used in scale-up. Purification turned out to be difficult, when to spots on TLC were overlapping in the fractions of the column. Different eluation-systems were utilized, both 10-33% EtOAc/n-pentane and 1-2% EtOAc/DCM, but the compounds were still overlapping. It was thought that the compounds in the mixture were Wittig-products with and without bromine respectively. The ^{1}H-NMR spectra showed what seemed to be two different alkene-proton signals (δ 6.75 and 7.4), but none of these were split by a second adjacent proton (which

would have been the case if the alkene was not brominated). Further investigation also showed that the first fractions that were isolated had the exact same ^{1}H-NMR spectra as Ohm [6] reported for her E-alkene. The other compound in the mix was interpreted as the Z-alkene, since the shift value of the alkene proton around 7.4 ppm is in accordance with observations described in the literature. [19]

It was unexpected that the reaction gave a mixture of E and Z, since Ohm had reported the E-isomer exclusively.[6] Ohm used a different procedure with chloroform as solvent and hence a higher reflux temperature. The same one-pot procedure as used in entry 1 and 2, but with chloroform as solvent, was implemented, in hopes of getting the pure E-alkene (entry 3, Table 3.2). This experiment did on the other hand give a complex mixture (see Appendix H.7).

The overall results of the Wittig reaction were disappointing. The fact that the reaction gave both isomers is not necessarily a bad thing, since both isomers are desirable in the target molecule. The problem was the separation of the two. The R_f-value of the two isomers is the same, and all fractions from flash column chromatography except a few at the beginning contain both isomers. Enough E-isomer for characterization was isolated, but the Z-isomer only came in a mixture with E. The next step in the synthesis, the Suzuki reaction, cannot be done successfully with a mixture of isomers. It was decided that the synthesis route was not practical, and a new route was planned. The leftovers of the aminoaldehyde **4** and the ylide **10** were used in a final Wittig reaction, to get a better picture of the actual yield and the ratio between the two isomers. The two isomers was not attempted isolated from each other, and Z:E-selectivity of (1:0.9) was determined by integration of signals assumed to originate from alkene protons in E and Z olefins in the mixture. Total yield of E/Z-mix was 63%.

The fact that the Wittig-reaction gave most of the Z-isomer is according to literature. It is generally the case for stabilized ylides, [15] and experiments with haloylides have shown that the Z-isomer is dominating. [19, 20]

Haloylides generated in situ are in equilibrium with the source ylide, which competes efficiently for an aldehyde. During the condensation with a carbonyl group, the ylide is depleted, because the olefination with ylide is faster than that with haloylide. And the shift in equilibrium brings about the conversion of haloylide to its conjugate acid.[21] Keyser *et al.* [21] experienced increased yields when adding a second base (K_2CO_3) in addition to succinimide anion (originating from NBS), to prevent the formation of the conjugate acid of the haloylide.

$Ph_3P{=}C(Br)CO_2Me$ + $Ph_3P^+CH_2CO_2Me$ ⇌ $Ph_3P{=}CHCO_2Me$ + $Ph_3P^+CH(Br)CO_2Me$

Haloylide (generates brominated olefin) | source ylide (generates olefin without Br) | conjugate acid

It is possible that formation of conjugate acid of the bromoylide **9** is responsible for a modest yield in the one-pot wittig procedure, and it would be productive to add 2.5 equivalents of anhydrous K_2CO_3 before addition of the aldehyde.

When the yield over the two steps in the preparation of compound **10** was 84 % and the Wittig reaction between the aldehyde (**4**) and the ylide (**10**) gave a yield of 63%, the total yield for the synthesis in whole was 20 %. In comparison to Ohm [6] the synthesis route towards and including the preparation of *(E/Z)*-**3** was improved in this project from 6 % to 20 %.

3.2 The new synthesis route from aryl aldehydes and methyl-propiolate

3.2.1 Condensation between methyl-propiolate and arylaldehydes (17a, 17b)

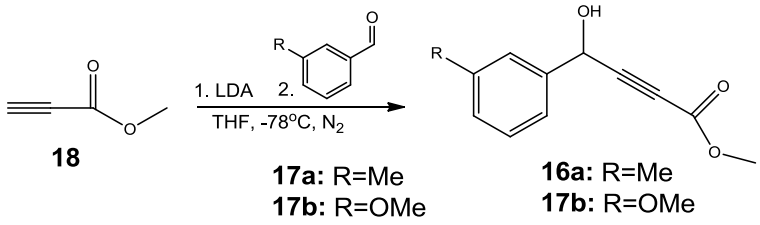


Figure 3.7; The chemical equation for addition of alkynide anion (18) to aldehyde (17a and 17b)

The experimental procedure is described in Chapter 6.12. Refer to Table 3.3 for the reaction conditions and yields of the condensation reaction between methyl propiolate (**18**) and arylaldehydes (**17a** and **17b**) .

Propargylic alcohols **16a** and **16b** were prepared in 46 and 52% yield respectively, in accordance to a general procedure described by YEE, *et al.* [31].

The reaction was also attempted with a procedure involving generation of LDA in situ from BuLi and diisopropylamine, resulting in a complex mixture. This was probably caused by bad quality of the diisopropylamine, considering its brownish coloring.

Table 3.3: Quantity of reagents and solvent, reaction time and yield in addition of methyl-propiolate to aldehydes 17a and 17b.

Entry	Methyl-propiolate (mmol)	aldehyde (compound, equiv.)	Reaction time (h)	Result (prod., mmol, %)
1	2.5	**17a**, 1.05	2.5	**16a**, 23.9, 46
2	50.0	**17a**, 1.05	3	
3	2.5	**17b**, 1.05	4	**16b**, <1.93, <77[a]
4	25.0	**17b**, 1.05	5.5	**16b**, 12.96, 52

[a] The product was not purified, hence the weight is including byproducts

The yields are good, but were expected to be better. An explanation could be instability of the acetylene anions. Midland reported that ethyl esters might be prepared and used at -78 ^{o}C, but the methyl ester (methyl propiolate) should be kept below -100 ^{o}C to achieve good results. This temperature could be maintained with 4:l:l tetrahydrofuran-ether-pentane solvent; 4: 1:l low-boiling petroleum ether-acetone-isopropyl alcohol in liquid nitrogen slush bath.[25]

3.2.2 Ritter rx

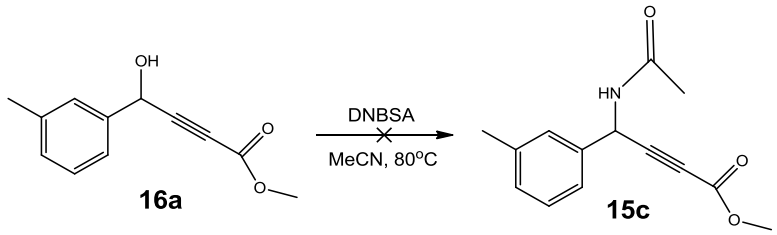


Figure 3.8; The chemical equation for protection of propargyl alchol (16a)

The experimental procedure is described in Chapter 6.13.

An attempt to protect alcohol **16a** was done in accordance to a procedure described by Sanz *et al.* [26] ,but the reaction did not give product, and ^{1}H NMR showed unreacted starting material. Sanz *et al.* [26] did use a wide range of secondary alcohols in their experiments even though the reaction works best with tertiary alcohols. But they did not include propargylic alcohols (like **16a**) in their experiments. Another explanation might be that the reaction was stopped to early.

3.2.3. Protection of alcohols with $tBuMe_2SiCl$

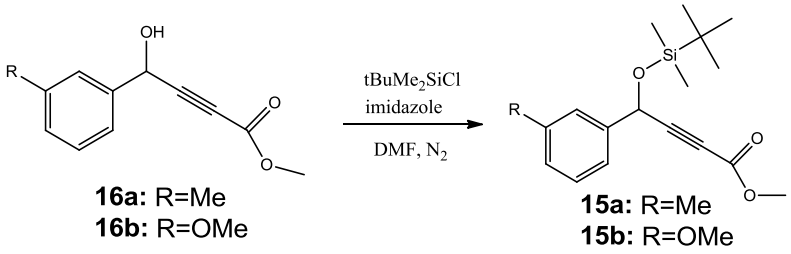


Figure 3.9; The chemical equation for protection of propargyl alchol (16a and 16b)

The experimental procedure is described in Chapter 6.14. Refer to Table 3.4 for reaction conditions and yield of the preparation of **15a** and **15b**.

Protection of propargylic alcohols **16a** and **16b** were accomplished in 63 and 64% yield respectively in accordance to a general procedure described by Nielsen et al. [32]

Table 3.4: Quantity of reagents and solvent, reaction time and yield in protection of alcohols 16a and 16b

Entry	alcohol (compound, mmol)	Imidazole (equiv.)	TBDMSCl (equiv.)	Reaction time (h)	Result (prod., mmol, %)
1	**16a**, 2.15	1.1	1	6	**15a**, 1.35, 63
2	**16a**, 14.8	1.2	1	10.5	**15a**, 8.05, 54
3	**16b**, 1.93	1.1	0.95	5	**15b**, 1.09, 59
4	**16b**, 10.03	1.2	1	9	**15b**, 6.37, 64

3.2.4 Hydrosilylation of alkynes

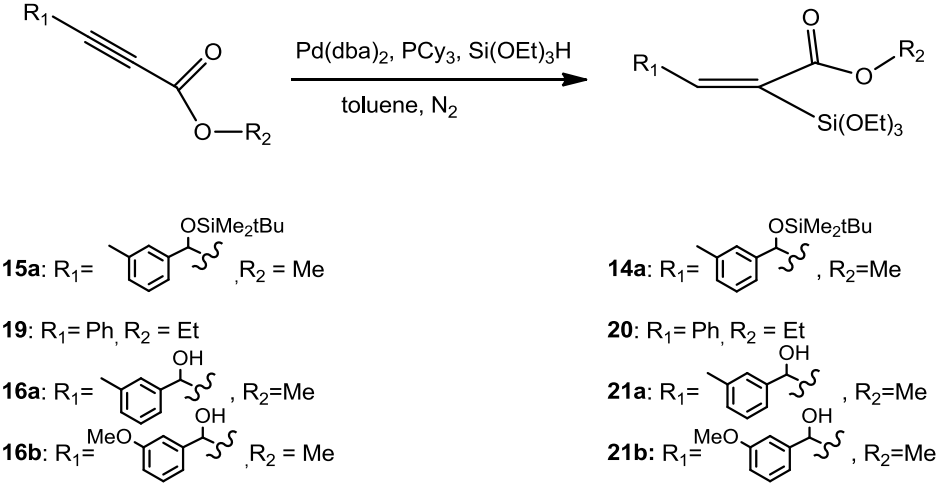


Figure 3.10; The chemical equation for hydrosylolation of alkynes (15 a, 19, 16a and 16b)

The experimental procedures are described in Chapter 6.15 to 6.17. Refer to Table 3.5 for reaction conditions and yields for hydrosilylations on different alkynes.

Table 3.5: Quantity of reagents and solvent, reaction time and yield in hydrosilylation of alkynes 15 a, 19, 16a **and** 16b

Entry	alkyne (compound, mmol)	$Pd(dba)_2$, PCy_3 (mol %)	$Si(OEt)_3H$ (equiv.)	toluene (mL)	Reaction time (h)	Result (prod., mmol, %)
1	**15a**, 0.31	5, 12	1.2	4	overnight	Unreacted **15a**
2	**15a**, 0.87	5, 10	1.2	8	overnight	Unreacted **15a**
3	**19**, 0.61	5, 10	0.9	4	5	**20**, 0.25, 46[a]
4	**16b**, 0.333	10, 10	1.2	3.5	20	Complex mixture
5	**16a**, 0.596	4, 10	1.2	5	4	Complex mixture

[a] the yield is calculated from amount of triethoxysilane added the reaction mixture (limiting reactant), and hence might be higher if equivalents triethoxysilane compared to alkyne in the reaction were 1.2.

The first hydrosilylation attempted was with the protected propargylic alcohol **15a** as substrate. ^{1}H NMR showed unreacted starting material, and it was thought that the catalyst was of bad quality (entry 1 in Table 3.5). $Pd(dba)_2$ is unstable in air, but also in room temperature, and the catalyst had been stored in the glove box (in rt). New catalyst was bought and the reaction attempted again, with the same conditions. But the results were unchanged, as seen in entry 2 (Table 3.5). A test reaction with a substrate (**19**), used by Sumida *et al.* [23] with a nice result, was implemented to see if it was something wrong with the applied techniques. Fortunately, it was not the case, when the reaction gave a pure hydrosilylated product (**20**), in a 46 % yield (entry 3, Table 3.5). The yield is low compared to what Sumida *et al.* reported, but some of this result can be explained by the mistake of adding a too small amount of triethoxysilane compared to the alkyne (**19**). The equivalents of silane were supposed to be 1.2 of that of the alkyne, but a calculation error involving the density of triethoxysilane resulted in addition of only 0.9 equivalents. The yield of 46% is calculated from the amount triethoxysilane added to the reaction mixture, but this might not be a satisfying way to calculate it since the silane was supposed to be in excess.

The success with the test reaction led to the idea that the failed reaction with compound **15a** was caused by steric hindrance (entry 2, Table 3.5). The TBDMS protection group in α-position to the acetylene group could be blocking the triple bond for access by the palladium-silane-complex. A new experiment with the unprotected alcohol **16b** as substrate was then attempted (entry 4, Table 3.5). This reaction gave a complex mixture of products, and it was thought it might be due to compromised inertness of the atmosphere caused by nitrogen leakage overnight. The experiment was repeated with compound **16a** (entry 5, Table 3.5), but

the reaction was stopped before the work day was over, to avoid the same problem. TLC looked different this time, with one colored spot at higher R_f value than the substrate and one UV-active spot with smaller R_f value. After an attempt to isolate the compounds producing the spots of interest by column chromatography ^{1}H NMR showed a complex mixture for both cases. ^{1}H NMR spectra for the fractions giving the UV-active and colored spots in TLC is given in appendix P.1 and P.2 respectively.

The results of entry 4 and 5 (Table 3.5) were disappointing, considering that the protection group could be put on after the hydrosilylation if the reaction had been successful. The result was not surprising though, since the hydroxyl group is a reactive group, and several side reactions could have taken place in addition to a prospective hydrosilylation. Sumida *et al.* did not refer to any entries involving hydroxyl groups in their work. Due to lack of time the experimentation stopped here. If more time was available, other protecting groups than the bulky TBDMS would be explored, and hopefully the hydrosilylation would work on the protected propargylic alcohol.

4 Spectrometric data for new compounds

(Z)-methyl 2-bromo-4-((tert-butoxycarbonyl)amino)-4-(3-methoxyphenyl)but-2-enoate (3)

The Wittig reaction gave a mixture of the E and Z isomers of compound **3**. *(E)*-**3** was isolated and NMR spectra are in accordance to reported data [6]. *(Z)*-**3,** on the other hand, was only obtained in a mixture with *(E)*-**3.** Hence the full characterization of *(Z)*-**3** cannot be presented with certainty. The chemical shifts for the alkene proton and the amine proton were found to differ between *(E)*-**3** and *(Z)*-**3** (indicated in figure 4.1).

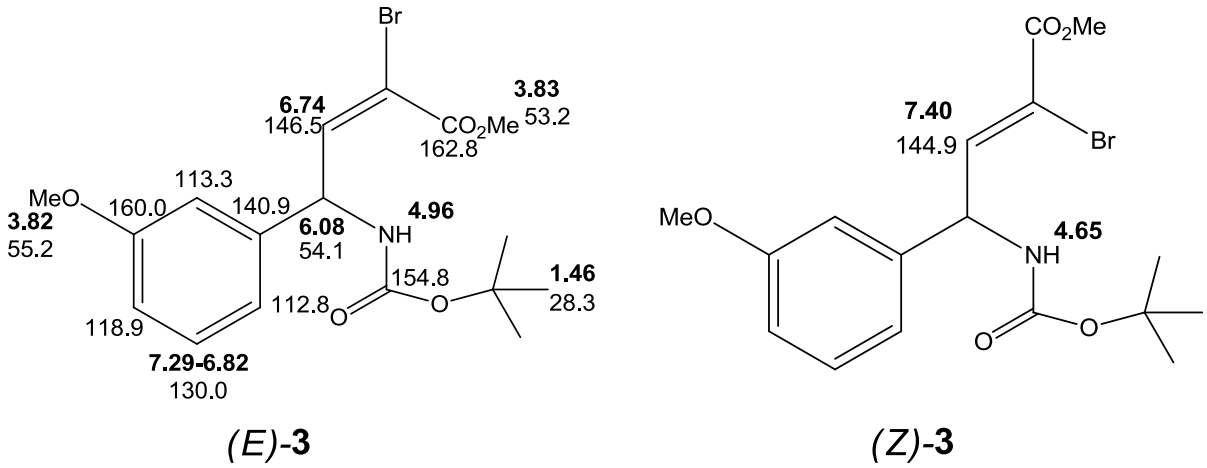


Figure 4.1 Assigned shifts of the known E-isomer [6] and the shifts that are different in the Z-isomer.

Data for the mixture of *(E)*-**3** and *(Z)*-**3**: R_f 0.36 (20% EtOAc/n-pentane).; HRMS (ESI): *m/z* calcd for $C_{17}H_{22}Br\ N\ Na\ O_5$ $(M + Na)^+$ 422.0574, found 422.0575; IR (neat): 3359 (m), 2979 (m), 1713 (s), 1488 (s), 1367 (s), 1239 (s), 1157 (s) cm^{-1}.

Data for (*E*)-**9**: Rf 0.36 (20% EtOAc/n-pentane) IR (neat): 3353 (m), 2977 (m), 1715 (s), 1697 (s), 1487 (s), 1366 (s), 1226 (s), 1158 (s) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 7.29 – 6.82 (4H, m, Ar-H), 6.74 (1H, d, J 9.1 Hz, alkene-CH), 6.08 (1H, app t, J 7.5 Hz, CH), 4.96 (1H, br, NH), 3.83 (3H, s, CO_2CH_3), 3.82 (3H, s, $ArOCH_3$), 1.46 (9H, s, t-Bu). The ^{1}H NMR spectrum (appendix G) is consistent with reported data.[6]

Data for *(Z)*-**9**: R_f 0.36 (20% EtOAc/n-pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* 9.1 Hz, alkene-CH), 7.29 – 6.82 (4H, m, Ar-H), 6.06 (1H, app t, *J* 7.5 Hz, CH), 4.65 (1H, br, NH), 3.82 (3H, s, CO_2CH_3), 3.81 (3H, s, $ArOCH_3$), 1.44 (9H, s, t-Bu). The ^{1}H NMR spectrum of the (*E*)-**9** and *(Z)*-**9** mixture is given in appendix H.

Metyl 4-(tert-butyldimethylsilyl)oxy)-4-(m-tolyl)but-2-ynoate (15a**)**

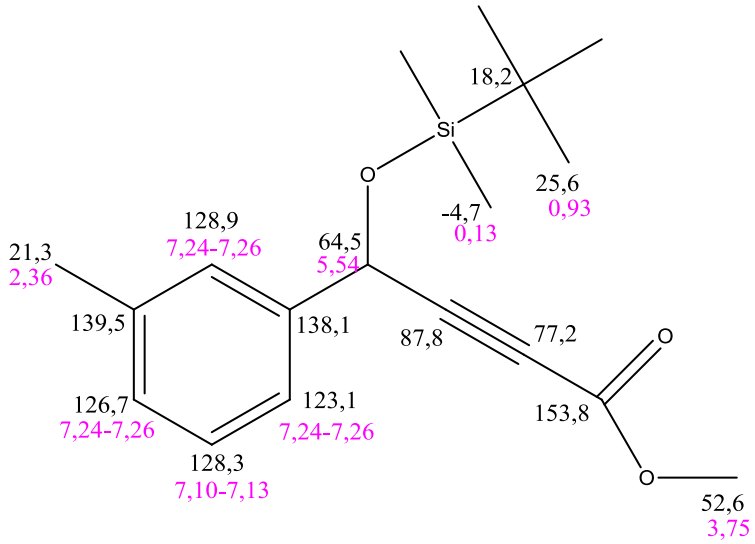


Figure 4.2; Assigned ^{1}H and ^{13}C NMR shifts of 15a

Data for **15a**: R_f 0.87 (20% EtOAc/n-pentane); IR (neat): 2954 (m), 2930 (m), 2858 (m), 2237 (w), 1717 (s), 1601 (m), 1434 (m), 1246 (s), 1044 (s), 836 (s), 778 (s), 751 (s), 695 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.24 (3H, m, ArH), 7.13-7.10 (1H, m, ArH), 5.54 (1H, s, CH), 3.75 (3H, s, OCH_3), 2.36 (3H, s, CH_3), 0.93 (9H, s, CH_3), 0.13 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (R-COOR), 139.5, 138.1 (Ar), 128.9, 128.3, 126.7, 123.1 (ArH), 87.8 (alkyne C), 77.2 (alkyne C), 64.5 ($ArCR_2$), 52.6 (OCH_3), 25.6 (CCH_3), 21.3 ($ArCH_3$), 18.2 (SiC), -4.7 ($SiCH_3$). HRMS (ASAP): calcd for $C_{18}H_{27}O_3$ Si: 319.1729 found 319.1728.

The ^{1}H NMR, ^{13}C NMR, IR and MS spectra are given in appendix M. Assigned ^{1}H and ^{13}C NMR shifts (determined with COSY and HSQC) are indicated in Figure 4.2.

Methyl 4-((tert-butyldimethylsilyl)oxy)-4-(3-methoxyphenyl)but-2-ynoate (15b**)**

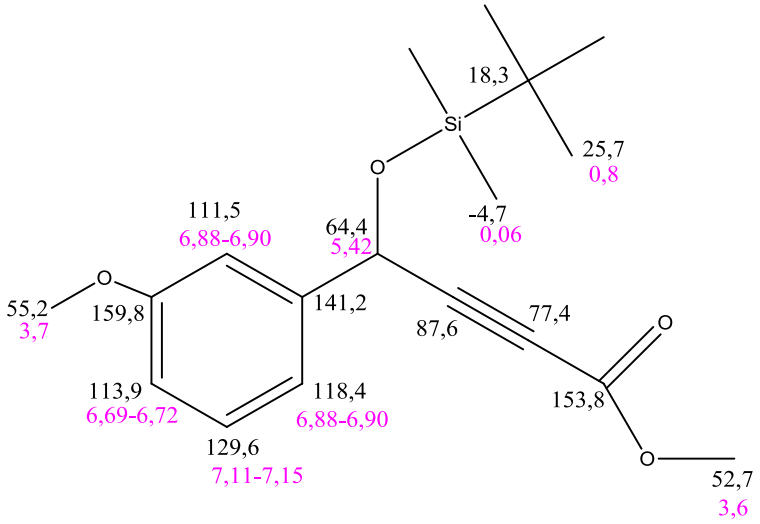


Figure 4.3; Assigned ^{1}H (bottom number) and ^{13}C NMR shifts (top number) of 15b

Data for **15b**: R_f 0.64 (20% EtOAc/n-pentane); IR (neat): 2954 (m), 2930 (m), 2858 (m), 2350 (w), 2236 (m), 1717 (s), 1435 (m), 1246 (s), 1054 (s), 836 (s), 778 (s), 750 (s), 699 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.11 (1H, m, ArH), 6.90-6.88 (2H, m, ArH), 6.72-6.69 (1H, m, ArH), 5.42 (1H, s, CH), 3.70 (3H, s, $ArOCH_3$), 3.60 (3H, s, OCH_3), 0.80 (9H, s, CH_3), 0.06 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (ArO) 153.8 (R-COOR), 141.2 (Ar), 129.6, 118.4, 113.9, 111.5 (ArH), 87.6 (alkyne C), 77.4 (alkyne C), 64.4 ($ArCR_2$), 52.7, 55.2 (OCH_3), 25.7 (CCH_3), 18.3 (SiC), -4.7 ($SiCH_3$).

HRMS (ASAP): calcd for $C_{18}H_{27}O_4Si$: 335.1679 found 335.1680.

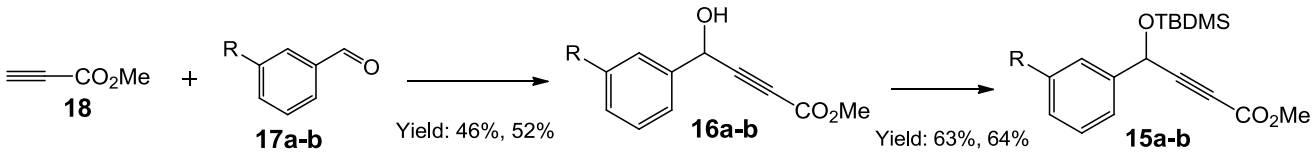
The ^{1}H NMR, ^{13}C NMR, IR and MS spectra are given in appendix N. Assigned ^{1}H NMR and ^{13}C NMR shifts (determined with COSY and HSQC) are indicated in Figure 4.3.

5 Conclusion and Future Work

A summary of the reactions accomplished in this thesis is shown I Table 5.1 for synthesis route A, and in Figure 5.1 for synthesis route B.

Table 5.1; Summarizes the results from synthesis route A. The best achieved yields are shown for each reaction, and also total yields for the reactions combined.

Reaction (section in experimental)	Substrate	Reagents	Product	Highest yield for reaction (%)	Total yield from 3-vinylanisole/methyl bromoacetate (%)
Epoxidation, 6.3	3-vinylanisole	*m*-CPBA	**7**	100	100
Ring-opening, 6.4	**7**	NaN_3	**6**	43	43
Protection, 6.5	**6**	Boc_2O, Pd-C, H_2	**5**	100	43
Oxidation, 6.6	**5**	DMP	**4**	89	38
Preparation of phosphonium salt, 6.7	Methyl bromoacetate	PPh_3	**11**	91	91
Preparation of ylide, 6.8	**11**	NaOH	**10**	92	84
Wittig, 6.9	**10**	NBS, **4**	**3**	63	20 (E/Z mixture)



a: R = Me
b: R = OMe

Figure 5.1; Accomplished reactions in synthesis route B

This master`s thesis was carried out at the end of a five year long project, resulting in Silje Melnes` doctoral thesis. The work done is based on two earlier master`s theses written by Ragnhild G. Ohm and Cecilie Surdal.

There are some inconsistencies with the earlier work when it comes to the E/Z-selectivity in the Wittig reaction. Ohm [6] reported to get the E-isomer exclusively, but the results in this thesis are showing a higher selectivity for the Z-alkene, and all the experiments gave mixtures of both isomers. Synthesis route A (based on Ohm and Surdal`s work) was abandoned because of severe difficulties with purification of the E/Z-mixture, making the product useless

in the following Suzuki reaction. Possible future work could be to verify the results from the Wittig reaction, to be certain that the pure isomer cannot be prepared.

Synthesis route B should be continued with a different OH-protection group than TBDMS. Most probable the hydrosilylation was not accomplished with compound **15** because of steric hindrance, since there was no reaction. The Ritter reaction of the propargylic alcohols is also worth another try, since it was only attempted once in this thesis.

For the project of synthesizing target compound **1** in whole, there is considerable work to be done. It has especially been proven to be difficult to synthesize compound **2a** (and hence **2b**) [8]. One possibility could be to get back to Drabløs and Tøndel and ask if they could do a new calculations with a slightly different substrate (compound X shown in Figure 5.2), which could be easier to synthesize.

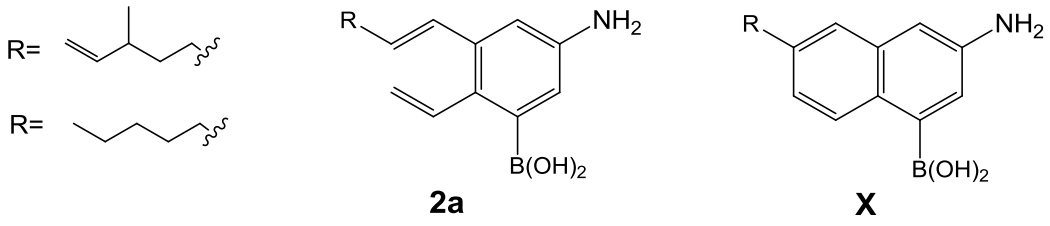


Figure 5.2; Compound 2a is a key intermediate in the synthesis towards target compound 1. Compound X is suggested to replace 2a in the synthesis.

6 Experimental

6.1 Materials

Chemicals were purchased from Sigma-Aldrich and used without further purification. All reactions sensitive to air or moisture were performed under nitrogen atmosphere with dried solvents and reagents. DCM, THF, and Et_2O were dried using MBRAUN solvent purification system (MB SPS-800). DCE and toluene were dried by distillation after treatment with CaH_2, and stored over activated 4 Å molecular sieves. EtOAc was dried by washing with aqueous 5% Na_2CO_3, then with saturated aqueous NaCl, and dryed with $MgSO_4$.

6.2 Analysis methods

^1H and ^{13}C NMR spectra were recorded from Bruker Advance DPX instruments (300/75 MHz and 400/100 MHz). Chemical shifts (δ) are reported in parts per million. Where $CDCl_3$ has been used, shift values for proton are reported with reference to TMS (0.00) via the lock signal of the solvent. Signal patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). ^1H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC).

IR spectra were recorded from a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed (cm^{-1}).

Accurate mass determination, ESI, was performed on Agilent G1969 TOF MS instrument. Samples were injected into the instrument using an Agilent 1100 series HPLC.

TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 312 nm and a 5% solution of molybdophosphoric acid in 96% EtOH for detection. Column chromatography was performed with Silica gel (pore size 60 Å, 230-400 mesh particle size) purchased from Fluka.

6.3 Preparation of Epoxide 7

2-(3-Methoxyphenyl)oxirane (7)

The title compound was prepared in accordance to a procedure described by Li *et al.* [33]

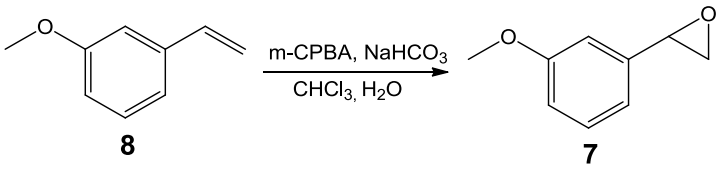


Figure 6.1; The chemical equation for epoxidation of m-vinylanisole (8)

To a mixture of 3-vinylanisole (**8**, 5 g, 37.3 mmol), $CHCl_3$ (80 mL) and $NaHCO_3$ (sat. aq., 80 mL) at 0 °C was added *m*-CPBA (6.73 g, 39 mmol) in portions over 10 min. The reaction mixture was stirred at rt for 2 h. *m*-CPBA (4.02 g, 23 mmol) was again added in portions at 0 °C and the reaction mixture was stirred over night at rt. The reaction mixture was washed with $Na_2S_2O_3$ (sat. aq., 50 mL) and the phases were separated. The water phase was extracted with $CHCl_3$ (50 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq., 50 mL) and H_2O (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **7** (5.60 g, 37.3 mmol, ≈ 100%) as a brown oil. The product was used without further purification.

R_f 0.44 (50% DCM/n-pentane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-6.81 (4H, m, Ar), 3.84 (1H, dd, *J*=4.0, 2.5 Hz, CH), 3.80 (3H, s, OMe), 3.13 (1H, dd, J=5.6, 3.1 Hz, CH_2), 2.78 (1H, dd, *J* = 5.5, 2.4 Hz, CH_2). The ^{1}H NMR spectrum (appendix A) is consistent with reported data.[6]

Table 6.1 gives a summary of the amounts of 3-vinylanisole, m-CPBA, $CHCl_3$ and $NaHCO_3$ used in the preparation of **7**, in addition to reaction times and yields for the reactions.

Table 6.1: Quantity of reagents and solvent, reaction time and yield in epoxidation of 8

Entry	3-vinylanisole (g, mmol)	*m*-CPBA (mmol)	$CHCl_3$, $NaHCO_3$ (mL, mL)	Reaction time (h)	Result (prod., yield)
1	11.80, 88.0	179.8	140, 140	Overnight	**7,** quantitative
2	5, 37.3	39.0	80, 80	4	**7**, quantitative
3	12.42, 92.5	140.0	150, 140	Overnight	**7**, quantitative

6.4 Ring Opening of Epoxide 7 to form Azide 6

2-Azido-2-(3-methoxyphenyl)ethanol (6)

The title compound was prepared in accordance to a procedure by Li et al. [33].

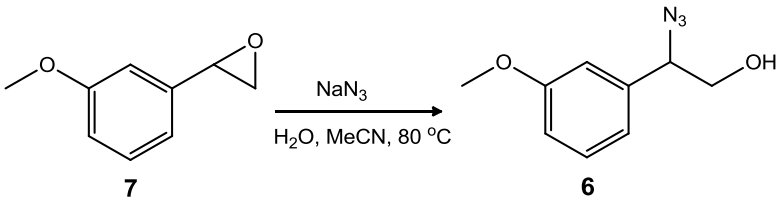


Figure 6.2; The chemical equation for ringopening of epoxide (7)

To a mixture of **7** (6.018 g, 37.3 mmol) in MeCN/H_2O (1:1, 100 mL) was added NaN_3 (7.806 g, 120.1 mmol). The reaction mixture was warmed to 80 °C and stirred for 4 h. After cooling to rt, the two resulting layers were separated. The water phase was extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (10% EtOAc/n-pentane) afforded **6** (3.022 g, 15.6 mmol, 42%) as a yellow oil.

R_f 0.26 (20% EtOAc/n-pentane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.87 (4H, m, Ar), 4.65 (1H, app. dd, *J* = 5.3, 2.1 Hz, C<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$), 3.74 (2H, app. t, *J* = 5.3 Hz, C<u>H</u>$_2$), 1.98 (1H,app. t, *J* = 6 Hz, O<u>H</u>). The ^{1}H NMR spectrum (appendix B) is consistent with reported data.[6] Refer to appendix B for the ^{1}H NMR spectrum.

Table 6.2 gives a summary of the amounts of **7**, NaN_3, CH_3CN and water used in the preparation of **6**, in addition to reaction times and yields for the reactions.

Table 6.2: Quantity of reagents and solvent, reaction time and yield in ring opening of 7

Entry	**7** (g, mmol)	NaN_3 (g, mmol)	CH_3CN, H_2O (mL, mL)	Reaction time (h)	Result (prod., g, mmol, %)
1	17.8, 88[a]	17.189, 264.4	140, 140	4	**6**, 6.43, 33, 38
2	6.02, 37.3[a]	7.806, 120.1	100, 100	Overnight	**6**, 3.022, 15.6, 42
3	14.41, 92.5[a]	18.27, 281.0	200, 200	Overnight	**6**, 7.869, 40.0, 43[b]

[a]The amounts are equivalent to the amounts of 3-vinylanisole used in the preparation of the epoxide (section 6.3), and hence do not agree with the mass of the crude product of **7**. [b]The yield is adjusted by calculations involving ^{1}H NMR-integrals.

6.5 Reduction and protection of azide 6 to form N-Boc amino alcohol 5

tert-Butyl 2-hydroxy-1-(3-methoxyphenyl)ethylcarbamate (5)

The title compound was prepared in accordance to a procedure described by Li *et al.* [33]

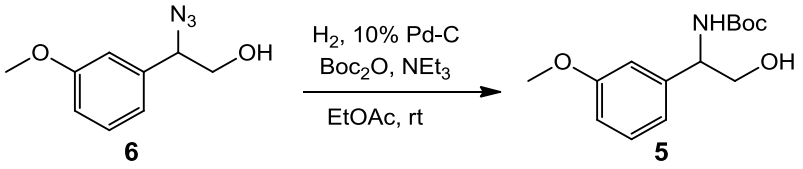


Figure 6.3; The reaction from compound (6) to compound (5)

A mixture of **6** (6.34 g, 31 mmol) and 10 % Pd-C (1.25 g) in EtOAc (anhydrous, 115 mL) was evacuated and put under 1 atm of H_2 (balloon). Boc_2O (6.79 g, 31.1 mmol) and NEt_3 (200µL,

1.43 mmol) were subsequently added, and the resulting suspension was allowed to stir under H_2 at rt. After 19 h, the reaction mixture was filtered through a silica plug pre-packed with EtOAc. The plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford **5** (7.67 g, 28.7 mmol, 93%) as a white powder.

Mp 130 – 132 °C; R_f 0.26 (20% EtOAc/n-pentane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90-6.82 (4H, m, Ar-H), 5.19 (1H, s br, NH), 4.74 (1H, s br, CH), 3.84 (2H, app t, *J* = 5.9 Hz, CH_2OH), 3.81 (3H, s, OCH_3), 2.22 (1H, s, OH), 1.44 (9H, s br, Boc-CH_3). The ^{1}H NMR spectrum (appendix C) is consistent with reported data.[6]

Table 6.3 gives a summary of the amounts of 2-Azido-2-(3-methoxyphenyl)ethanol (**6**), Boc_2O, Pd-C, EtOAc and NEt_3 used in the preparation of **5**, in addition to reaction times and yields for the reactions.

Table 6.3: Quantity of reagents and solvent, reaction time and yield in reduction and protection of 6

Entry	**6** (g, mmol)	Boc_2O (g, mmol)	Pd-C, EtOAc, NEt_3 (g, mL, µL)	Reaction time	Result (prod., g, mmol, %)
1	6.38, 31.0	6.77, 31.0	1.29, 115, 200	Overnight	**5**, 7.67, 28.7, 93
2	3.02, 15.6	3.63, 16,6	0.65, 55, 80	Overnight	**5**, 4.32, 15.6, 100
3	7.89, 40.7	9.02, 41.3	1.5, 60, 200	Overnight	**5**, 6.77, 25.3, 62[a]

[a] Lower yield caused by loss on rotavapor

6.6 Dess-Martin oxidation of 5

tert-Butyl 1-(3-methoxyphenyl)-2-oxoethylcarbamate (4)

The title compound was prepared in accordance to a general procedure described by Myers *et al.* [34]

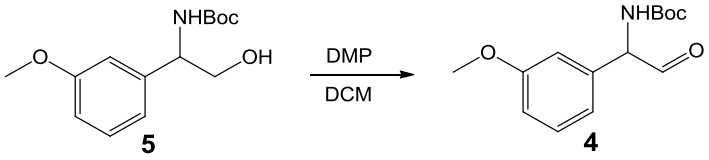


Figure 6.4; The chemical equation for Dess-Martin oxidation of aminoalcohol (5)

A mixture of **5** (4.3 g, 15.6 mmol) and DMP (6.9 g, 16.2 mmol) in DCM (160 mL) was stirred at rt for 3.5 h. $Na_2S_2O_3$ (sat. aq., 75 mL) and EtOAc (75 mL) were added. The mixture was stirred for 10 min, and the layers were separated. The water phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (3 x 50 mL) or $NaHCO_3$ (sat. aq., 3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The

crude product was purified by column chromatography (10% EtOAc/n-pentane) to afford **5** (8.38 g, 11.3 mmol, 73 %) as a yellow oil.

R_f 0.27 (20% EtOAc/n-pentane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (1H, s, CHO), 6.91-6.83 (4H, m, Ar-H), 5.74 (1H, s br, NH), 5.28 (1H, s br, CH), 3.81 (3H, s, OCH_3), 1.44 (9H, s br, Boc-CH_3). The ^{1}H NMR spectrum (appendix D) is consistent with reported data.[6]

Table 6.4 gives a summary of the amounts of **5**, DMP and DCM used in the preparation of **4**, in addition to reaction times and yields for the reactions.

Table 6.4: Quantity of reagents and solvent, reaction time and yield in Dess-Martin oxidation of 5

Entry	**5** (g, mmol)	DMP (g, mmol)	DCM (mL)	Reaction time (h)	Washed with	Result (prod., g, mmol, %)
1	3.105, 11.62	5.0, 11.79	110	Overnight	H_2O	**4**, 1.59, 6.0, 52
2	4.32, 15.6	6.9, 16.27	160	Overnight	H_2O	**4**, 8.38, 11.3[a], 73
3	3.926, 14.69	5.0, 11.79	120	3,5	$NaHCO_3$	**4**, 3.69, 10.5[a+b], 89

[a] The yield is adjusted by calculations involving ^{1}H NMR-integrals. This is taken into consideration in coming reactions were **4** is used as reactant. [b] Purification was not implemented.

6.7 Preparation of the phosphonium salt 11

(2-Methoxyacetyl)triphenylphosphonium bromide (11)

The title compound was prepared in accordance to a procedure described by Boers *et al.*[29] with some modifications.

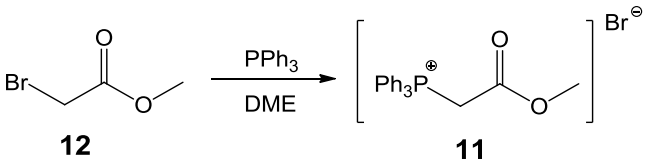


Figure 6.5; The reaction of methyl bromoacetate (12) to form phosphonium salt (11)

Methyl bromoacetate (1.25 mL, 2.02 g, 13.18 mmol) in DCM (100 mL) was added triphenylphosphine (3.457 g, 13.18 mmol). The reaction mixture was stirred at 100 °C (reflux) for 3 h, before cooling to 0 °C. The crystalline precipitate was filtered and washed with toluene, and then dried under vacuum o.n. to afford **11** (5.0 g, 12.04 mmol, 91 %) as a white solid. The crude product was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.67 (m, 15H, Ph), 5.68 (d, *J*(P-H) = 15.5 Hz, 2H, CH_2), 3.61 (s, 3H, OMe). The ^{1}H NMR spectrum (appendix E) is consistent with data reported.[29] Refer to appendix E for the ^{1}H NMR spectrum.

6.8 Preparation of the ylide 10

Methyl 2-(triphenylphosphoranylidene)acetate (10)

The title compound was prepared in accordance to a procedure described by Boers *et al.* [29]

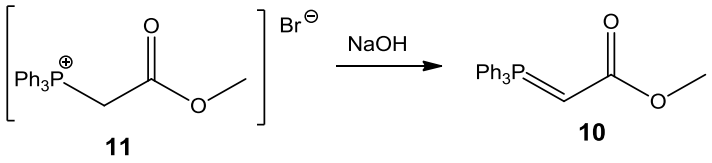


Figure 6.6; The reaction of phosphonium salt (11) to form ylide (10)

Compound **11** (5 g, 12.04 mmol) in DCM (30 mL) was shaken with NaOH (aq, 1M, 20 mL) for 2 min. The layers were separated and the water layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with NaCl (sat. aq., 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **10** (3.705 g, 11.08 mmol, 92%) as a white solid. The crude product was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.49 (m, 15H, Ph), 3.51 (H, OCH_3) ppm (CH not visible). The ^{1}H NMR spectrum (appendix F) is consistent with reported data.[29]

6.9 One-pot generation of 9 and Wittig reaction with 4

(*E*/*Z*)-Methyl 2-bromo-4-((tert-butoxycarbonyl)amino)-4-(3-methoxyphenyl)but-2-enoate (3)

The title compound was prepared in accordance to a general procedure described by Audisio *et al.* [30] and Brenna *et al.* [22] with modifications.

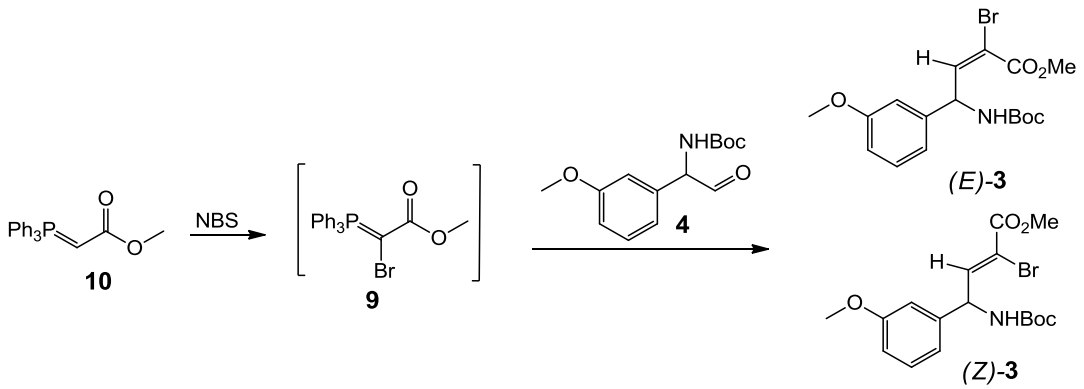


Figure 6.7; The wittig reaction between bromoylide (10) and aldehyde (4)

A solution of methyl(triphenylphosphoranylidene)acetate (**10**) (1.918 g, 5.737 mmol) in DCM (20 mL) was cooled to -13 ^{o}C. NBS (1.186 g, 6.66 mmol) was added, and the reaction mixture was stirred for 1 h. A solution of **4** (1.48 g, 5.58 mmol) in DCM (20 mL) was added. The reaction mixture was warmed to reflux and allowed to stir over night. After cooling to rt, DCM (40 mL) and H_2O (40 mL) were added. The phases were separated. The water phase was extracted with DCM (40 mL). The collected organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification twice by column chromatography (10-33% EtOAc/n-pentane) and then (1-2% EtOAc/DCM) afforded an inseparable mixture of *(Z)*-**3** and *(E)*-**3** (1:0.9, 1.41 g, 3.52 mmol, 63%) as a pale yellow oil.

Data for the mixture of *(E)*-**3** and *(Z)*-**3**: HRMS (ESI): *m/z* calculated for $C_{17}H_{22}Br\ N\ Na\ O_5$ $(M + Na)^+$ 422.0574, found 422.0575; R (neat): 3359 (m), 2979 (m), 1713 (s), 1488 (s), 1367 (s), 1239 (s), 1157 (s) cm^{-1}. The MS and IR spectra are given in appendix H.

Data for (*E*)-**9**: Rf 0.36 (20% EtOAc/n-pentane) IR (neat): 3353 (m), 2977 (m), 1715 (s), 1697 (s), 1487 (s), 1366 (s), 1226 (s), 1158 (s) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 7.29 – 6.82 (4H, m, Ar-H), 6.74 (1H, d, J 9.1 Hz, alkene-CH), 6.08 (1H, app t, J 7.5 Hz, CH), 4.96 (1H, br, NH), 3.83 (3H, s, CO_2CH_3), 3.82 (3H, s, $ArOCH_3$), 1.46 (9H, s, t-Bu). The IR and ^{1}H NMR spectra (appendix G) is consistent with reported data.[6]

Data for *(Z)*-**9**: R_f 0.36 (20% EtOAc/n-pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* 9.1 Hz, alkene-CH), 7.29 – 6.82 (4H, m, Ar-H), 6.06 (1H, app t, *J* 7.5 Hz, CH), 4.65 (1H, br, NH), 3.82 (3H, s, CO_2CH_3), 3.81 (3H, s, $ArOCH_3$), 1.44 (9H, s, t-Bu). The ^{1}H NMR spectrum of the (*E*)-**9** and *(Z)*-**9** mixture is given in appendix H.

Table 6.5 gives a summary of the amounts of **10**, NBS, **4** and solvent used in the coupling to **3** in addition to reaction times and yields for the reactions.

Table 6.5: Quantity of reagents and solvent, reaction time and yield in one-pot generation of 9 and Wittig reaction with 4

Entry	**10** (g, mmol)	NBS (g, mmol)	**4** (g, mmol)	DCM/$CHCl_3$ (mL)	Result (prod., g, mmol %)	Z/E ratio
1	0.1289, 0.39	0.074, 0.42	0.1092, 0.41	3 / -	**3**, 0.082, 0.205, 53	0.55:1[a]
2	1.918, 5.73	1.186, 6.66	1.48, 5.58	40 / -	**3**, 1.335, 3.33, 60	1:0.4
3	4.7818, 14.3	3.148, 17.68	7.251, 11.3[a]	- / 70	Complex mixture	
4	4.614, 13.80	2.769, 15.56	3.689, 10.2	40 / -	**3**, 2.94, 6.6[b], 63	1:0.9

[a]The E/Z ratio was not possible to measure in the crude, because of overlapping peaks. The ratio is therefore measured in a sample after flash column chromatography and there might not some loss of Z-isomer during flash [b] The amounts are adjusted by calculations involving ^{1}H NMR-integrals

6.10 Test reaction: PCC-oxidation of 5

An oxidation of alcohol **5** was attempted in accordance to a general procedure by Clive *et al.*[28]

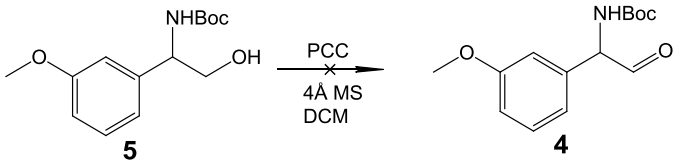


Figure 6.8; The chemical equation for oxidation of alcohol (5)

PCC (0.155 g, 0.72 mmol) and 4Å MS (0.12 g) in DCM (anhydrous, 1 mL) was added **5** (0.102 g, 0.38 mmol) in DCM (anhydrous, 2 mL). The reaction mixture was stirred for 1 h, and then filtered through a silica plug pre-packed with EtOAc/hexane (1:1). The plug was washed with EtOAc/hexane (1:1) and the filtrate was concentrated under reduced pressure.

The reaction did not give the desired product. See also test reaction with IBX (section 6.11).

6.11 Test reaction: IBX-oxidation of 5

An oxidation of alcohol **5** was attempted in accordance to a general procedure given by More and Finney.[16]

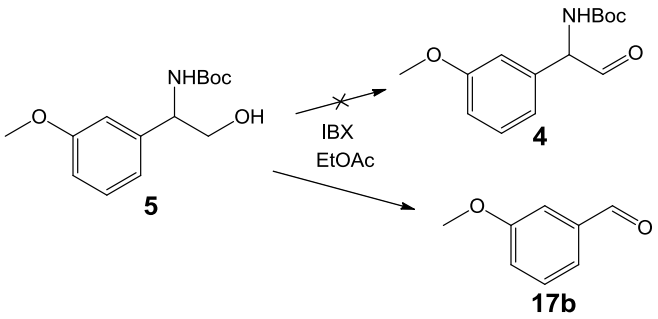


Figure 6.9; The chemical equation for oxidation of alcohol (5) with formation of byproduct (17b)

Aminoalcohol **5** (0.0744 g, 0.278 mmol) in EtOAc (7 mL) was added IBX (0.1537 g, 0.55 mmol), and allowed to stir at 80 ^{o}C for 4 h. After cooling to rt the reaction mixture was filtered through a silica plug pre-packed with EtOAc. The plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure.

The reaction did not give the desired product. The byproduct 3-methoxybenzaldehyde (**17b**) was isolated by column chromatography (10% EtOAc/n-pentane) and characterized. **17b** is also a recurring byproduct in Dess-Martin oxidation (section 6.6).

Data for **17b**: ^{1}H NMR (300 MHz): δ 9.99 (1H, s, CHO), 7.47-7.17 (4H, m, ArH), 3.88 (3H, s, OCH_3). The ^{1}H NMR spectrum (appendix I) is consistent with reported data.[35]

6.12 Condensation between methyl propiolate and aryl aldehydes (17a, 17b)

Methyl 4-hydroxy-4-(m-tolyl)but-2-ynoate (**16a**) and methyl 4-hydroxy-4-(3-methoxyphenyl)but-2-ynoate (**16b**) were prepared in accordance to a general procedure described by Yee *et al.* [31] with modifications.

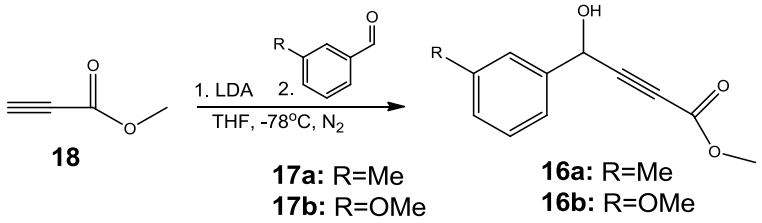


Figure 6.10; The chemical equation for addition of alkynide anion (18) to aldehyde (17a and 17b)

Methyl 4-hydroxy-4-(3-methoxyphenyl)but-2-ynoate (16b)

Methyl propiolate (**18**, 2.20 mL, 25 mmol) was dissolved in THF (anhydrous, 45 mL) under an atmosphere of nitrogen. The solution was cooled to -78 ^{o}C and added LDA (13.13 mL, 26.25 mmol) in drops, and allowed to stir for 1 h. *m*-Anisaldehyde (**17b**, 3.20 mL, 26.25 mmol) was added and the resulting mixture was allowed to stir at -78 ^{o}C for 5.5 h. Water (50 mL) was added and the reaction mixture allowed to reach rt before the the reaction mixture was diluted with EtOAc (100 mL) and the phases separated. The organic layer was washed with NH_4Cl (sat. aq., 3 x 30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (10% EtOAc/n-pentane) to afford **16b** (2.854 g, 12.96 mmol, 52%) as a red oil.

R_f 0.12 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (1H, t, *J* 8.0 Hz, ArH), 7.08-7.06 (2H, m, ArH), 6.90 (1H, dd, *J*=2.4, 8.0 Hz, ArH), 5.55 (1H, d, *J*=6 Hz, CH), 3.83 (3H, s, CH_3), 3.79 (3H, s, CH_3), 2.49 (1H, d, *J*=6.4 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 140.1 (ArC), 153.8 (R$\underline{C}O_2$R) , 129.8, 118.8, 114.5, 112.1 (Ar$\underline{C}$H), 86.7 (alkyne C), 77.4 (alkyne C), 64.0 ($\underline{C}$H), 55.3(OCH_3), 52.9 (OCH_3). The ^{1}H and ^{13}C NMR spectra (appendix J) are consistent with data reported.[36]

Methyl 4-hydroxy-4-(m-tolyl)but-2-ynoate (16a)

The title compound was prepared from **17a** in accordance with the procedure described for preparation of **17b**. The crude product was purified by column chromatography (10% EtOAc/n-pentane) to afford **16a** (4.88 g, 46% yield) as a red oil.

R_f 0.54 (33% EtOAc/n-pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (2H, app. t, *J*=8.0 Hz, ArH), 7.17 (2H, d, *J*= 6.7 Hz, ArH), 5.52 (1H, d, *J*=6 Hz, CH), 3.79 (3H, s, OCH_3), 2.69 (1H, d, *J*=6.4 Hz, OH), 2.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9 (R-COOR), 138.6 (ArC), 138.4 (ArCH), 129.6 (ArCH), 128.7 (ArCH), 127.3 (ArCH), 123.7 (ArCH), 86.9 (alkyne C), 77.4 (alkyne C), 64.2 (CH), 52.9 (OCH_3), 21.3 (CH_3). The ^{1}H NMR data is consistent with data reported.[36] Refer to appendix K for the ^{1}H and 13C NMR spectra.

Table 6.6 gives a summary of the amounts of *m*-tolualdehyde (**17a**)/anisaldehyde (**17b**), methyl-propiolate (**18**), LDA and THF used in the preparation of **16a** and **16b**, in addition to reaction times and yields for the reactions.

Table 6.6: Quantity of reagents and solvent, reaction time and yield in addition of methyl-propiolate to aldehydes 17a and 17b.

Entry	aldehyde (compound, mL, mmol)	Methyl-propiolate (mL, mmol)	LDA (mL, mmol)	THF (mL)	Reaction time (h)	Result (prod., g, mmol %)
1	**17a**, 0.31, 2.6	0.22, 2.5	1.25, 2.5	11	2.5	**16a**, 4.882, 23.9, 46
2	**17a**, 6.19, 52.5	4.40, 50.0	26.25, 52.5	90	3	
3	**17b**, 0.32, 2.63	0.22, 2.5	1.31, 2.63	10	4	**16b**, 0.364[a], <1.93, <77
4	**17b**, 3.20, 26.25	2.20, 25.0	13.125, 26.25	45	5.5	**16b**, 2.854, 12.96, 52

[a] The product was not purified, hence the weight is including byproducts

6.13 Ritter reaction on alcohol 16a

Amidation of alcohol **16a** was attempted in accordance to a procedure described by Sanz *et al.* [26]

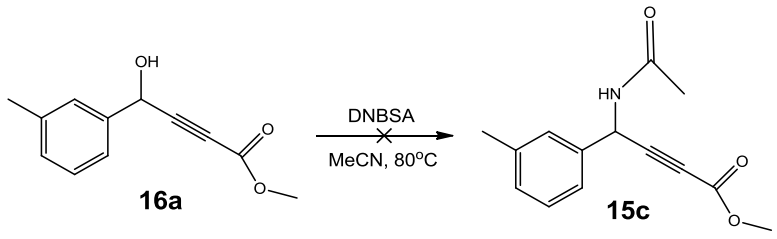


Figure 6.11; The chemical equation for amidation of propargyl alcohol (16a)

Compound **16a** (1.206 g, 1 mmol) was dissolved in MeCN (anhydrous, 2.5 mL). 2,4 Dinitrobenzenesulphonic acid (DNBSA, 0.031 g, 0.1 mmol) was added. The reaction mixture was refluxed (80 ^{o}C) over night. The reaction mixture was concentrated under reduced pressure and ^{1}H NMR showed unreacted **16a** (appendix L).

6.14 Protection of alcohols 16a and 16b

Metyl 4-(tert-butyldimethylsilyloxy)-4-m-tolylbut-2-ynoate (**15a**) and Methyl 4-(tert-butyldimethylsilyloxy)-4-(3-methoxyphenyl)but-2-ynoate (**15b**) were prepared in accordance to a general procedure described by Nielsen *et al.* [32]

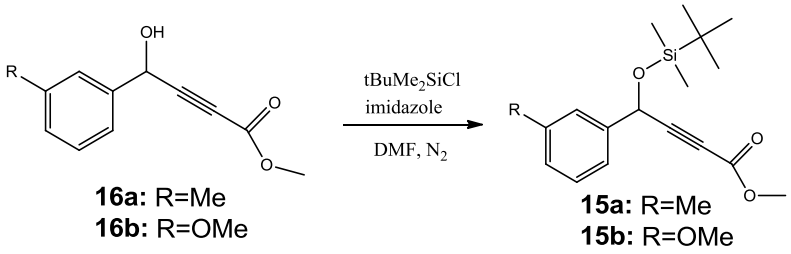


Figure 6.12; The chemical equation for protection of propargyl alcohol (16a and 16b)

Metyl 4-(tert-butyldimethylsilyloxy)-4-m-tolylbut-2-ynoate (15a)

Compound **16a** (0.44 g, 2.15 mmol) was added imidazole (1.1 equiv.) dissolved in DCM (anhydrous, 2 mL). At 0 ^{o}C TBDMS-Cl (0.335 g, 2.22 mmol, 1 equiv.) in DCM (5 mL) was added. The reaction mixture was allowed to stir at 0 ^{o}C for 6 h. H_2O (5 mL) and pentane (5 mL) were added and the phases separated. The water phase was extracted with pentane (40 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10-20% EtOAc/hexane) afforded **15a** (0.429 g, 1.35 mmol, 63%) as a yellow oil.

R_f 0.87 (20% EtOAc/n-pentane); IR (neat): 2954 (m), 2930 (m), 2858 (m), 2237 (w), 1717 (s), 1601 (m), 1434 (m), 1246 (s), 1044 (s), 836 (s), 778 (s), 751 (s), 695 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.24 (3H, m, ArH), 7.13-7.10 (1H, m, ArH), 5.54 (1H, s, CH), 3.75 (3H, s, OCH_3), 2.36 (3H, s, Ar$\underline{C}H_3$), 0.93 (9H, s, SiC($C\underline{H}_3$)$_3$), 0.13 (6H, s, Si$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (R-COOR), 139.5, 138.1 (Ar), 128.9, 128.3, 126.7, 123.1 (ArH), 87.8 (alkyne C), 77.2 (alkyne C), 64.5 (Ar$\underline{C}R_2$), 52.6 (OCH_3), 25.6 ($C\underline{C}H_3$), 21.3 (Ar$\underline{C}H_3$), 18.2 (SiC), -4.7 (Si$\underline{C}H_3$). Assigned shifts determined by 2D-NMR (COSY, HSQC) are shown in figure 4.2.

HRMS (ASAP): calcd for $C_{18}H_{27}O_3$ Si: 319.1729 found 319.1728.

The ^{1}H NMR, ^{13}C NMR, IR and MS spectra are given in appendix M.

Methyl 4-((tert-butyldimethylsilyl)oxy)-4-(3-methoxyphenyl)but-2-ynoate (15b)

The title compound was prepared from **16b** in accordance with the procedure described for preparation of **15a**. The crude product was purified by column chromatography (10-20% EtOAc/hexane) to afford **15b** (59-64% yield) as an orange oil.

R_f 0.64 (20% EtOAc/n-pentane); IR (neat): 2954 (m), 2930 (m), 2858 (m), 2350 (w), 2236 (m), 1717 (s), 1435 (m), 1246 (s), 1054 (s), 836 (s), 778 (s), 750 (s), 699 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.11 (1H, m, ArH), 6.90-6.88 (2H, m, ArH), 6.72-6.69 (1H, m, ArH), 5.42 (1H, s, CH), 3.70 (3H, s, $ArOCH_3$), 3.60 (3H, s, OCH_3), 0.80 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (ArO) 153.8 (R-COOR), 141.2 (Ar), 129.6, 118.4, 113.9, 111.5 (ArH), 87.6 (alkyne C), 77.4 (alkyne C), 64.4 ($ArCR_2$), 52.7, 55.2 (OCH_3), 25.7 (CCH_3), 18.3 (SiC), -4.7 ($SiCH_3$).

HRMS (ASAP): calcd for $C_{18}H_{27}O_4Si$: 335.1679 found 335.1680.

The ^{1}H NMR, ^{13}C NMR, IR and MS spectra are given in appendix N. Assigned ^{1}H NMR and ^{13}C NMR shifts (determined with COSY and HSQC) are indicated in Figure 4.3.

Table 6.7 gives a summary of the amounts of alcohol, imidazole, TBDMSCl and DCM used in the preparation of **15a** and **15b**, in addition to reaction times and yields for the reactions.

Table 6.7: Quantity of reagents and solvent, reaction time and yield in protection of alcohols 16a and 16b

Entry	Alcohol (compound, g, mmol)	Imidazole (g, mmol)	TBDMSCl (g, mmol)	DCM (mL)	Reaction time (h)	Result (prod., g, mmol, %)
1	**16a**, 0.44, 2.15	0.160, 2.35	0.335, 2.22	7	6	**15a**, 0.429, 1.35, 63
2	**16a**, 3.023, 14.8	1.178, 17.3	2.239, 14.8	25	10.5	**15a**, 2.5626, 8.05, 54
3	**16b**, 0.426, 1.93	0.144, 2.12	0.277, 1.84	2	5	**15b**, 0.3659, 1.09, 59
4	**16b**, 2.209, 10.03	0.788, 11.57	1.514, 10.0	25	9	**15b**, 2.13, 6.37, 64

6.15 Attempted hydrosilylation of 15a

(*E*)-Methyl 4-(*tert*-butyldimethylsilyloxy)-4-*m*-tolyl-2-(triethoxysilyl)but-2-enoate (**14a**) was attempted synthesized from **15a** in accordance to a general procedure described by Sumida *et al.*[23]

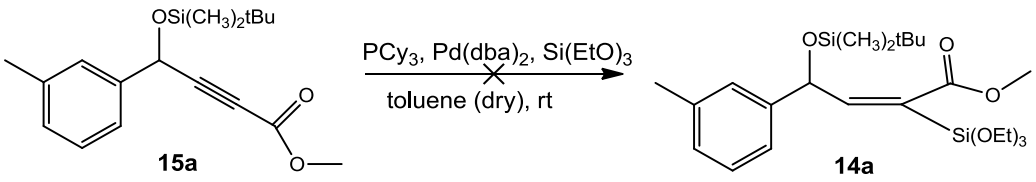


Figure 6.13; The chemical equation for hydrosylolation of alkyne (15a)

$Pd(dba)_2$ (8.5 mg, 5 mol %) and PCy_3 (8.7 mg, 10 mol %) were weighed out under nitrogen atm. Toluene (anhydrous, 2 mL) was added and the mixture via syringe. The reaction mixture was allowed to stir for 10 min. Compound **15a** (0.10 g, 0.31 mmol) in toluene (anhydrous, 2 mL) was degassed and added the reaction mixture via syringe. Triethoxysilane (1.2 equiv., 70 µL) were added by injection and the reaction mixture stirred overnight. The reaction mixture was passed through a florisil plug pre-packed with EtOAc. The plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure.

1H NMR of the crude did not show the desired product, but rather the unreacted **15a**.

6.16 Hydrosilylation test reaction with ethyl 3-phenylpropiolate (19) as substrate

(*E*)-Ethyl 3-phenyl-2-(triethoxysilyl)acrylate (20)

The title compound was prepared in accordance to a procedure described by Sumida et al.[23]

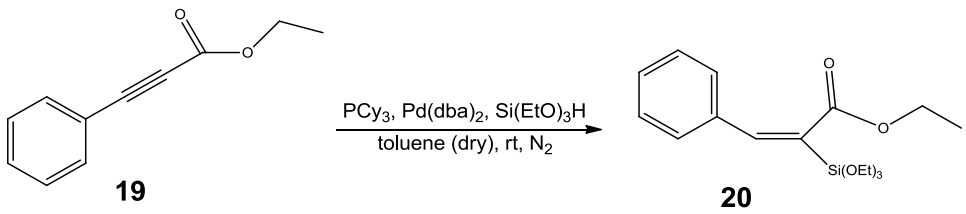


Figure 6.14; The chemical equation for hydrosylolation of alkyne (19)

$Pd(dba)_2$ (16.8 mg, 0.029 mmol) and PCy_3 (17.7 mg, 0.063 mmol) were weighed out under nitrogen atm. Toluene (anhydrous, 2 mL) was added via syringe and the mixture stirred for 10 min. Compound **19** (0.10 mL, 0.61 mmol) in toluene (anhydrous, 2 mL) was evacuated and added the reaction mixture via syringe. Triethoxysilane (0.104 mL, 0.55 mmol) were added by injection and the reaction mixture stirred overnight. The reaction mixture was passed through a florisil plug pre-packed with EtOAc. The plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford **20** (85 mg, 0.25 mmol, 46%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.32–7.29 (5H, m, aromatic), 7.20 (1H, s, alkene-H), 4.21 (2H, q, *J* = 7.0 Hz, -$CO_2C\underline{H}_2CH_3$), 3.93 (6H, q, *J* = 7.0 Hz, -$Si(OC\underline{H}_2CH_3)_3$), 1.26 (9H, t, *J* = 7.0 Hz, -$Si(OCH_2C\underline{H}_3)_3$) 1.22 (3H, t, *J* = 7.0 Hz, -$CO_2CH_2C\underline{H}_3$). The ^{1}H NMR spectrum (appendix O) is consistent with data reported in the literature.[23]

6.17 Attempted hydrosilylation of 16a and 16b

Hydrosilylation with compound **16a** and **16b** as a substrate was attempted in accordance to the general procedure described by Sumida et al.[23232323]

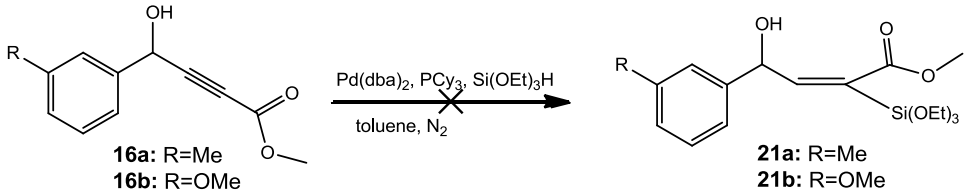


Figure 6.15; The chemical equation for hydrosylolation of alkyne 16a and 16b

$Pd(dba)_2$ (12.8 mg, 0.0223 mmol) and PCy_3 (17.0 mg, 0.0606 mmol) were weighed out under inert atm. Toluene (anhydrous, 2 mL) was added and the mixture stirred for 1 h. Compound **16a** (0.1218 g, 0.596 mmol) in toluene (anhydrous, 2 mL) and triethoxysilane (0.135 mL, 0.715 mmol) were added and the reaction mixture stirred for 4 h. The reaction mixture was passed through a florisil plug pre-packed with EtOAc. The plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure. The crude product was purified with flash column chromatography (10-50% EtOAc:hexane) to afford a complex mixture. Refer to appendix P for the ^{1}H NMR spectrum.

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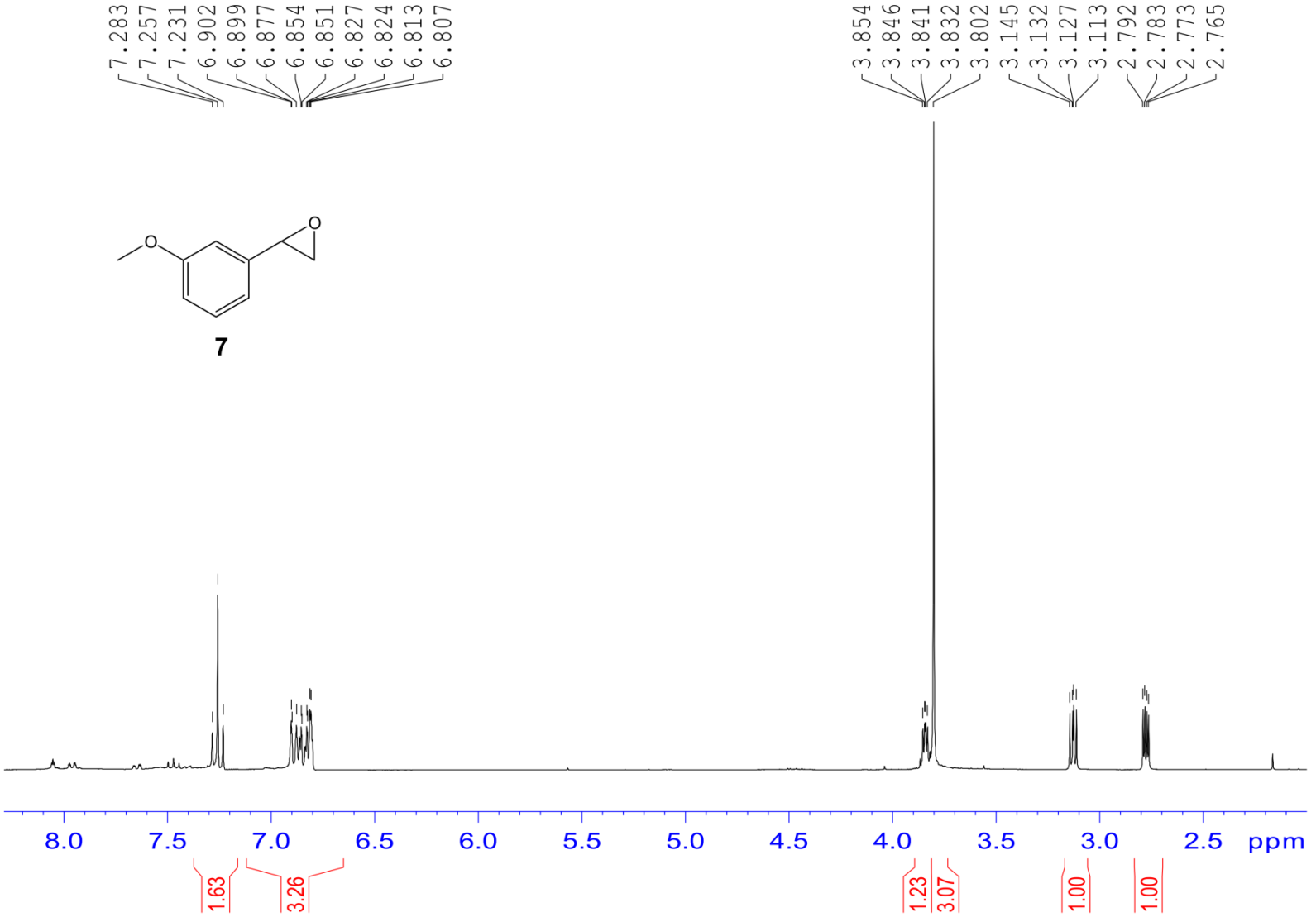
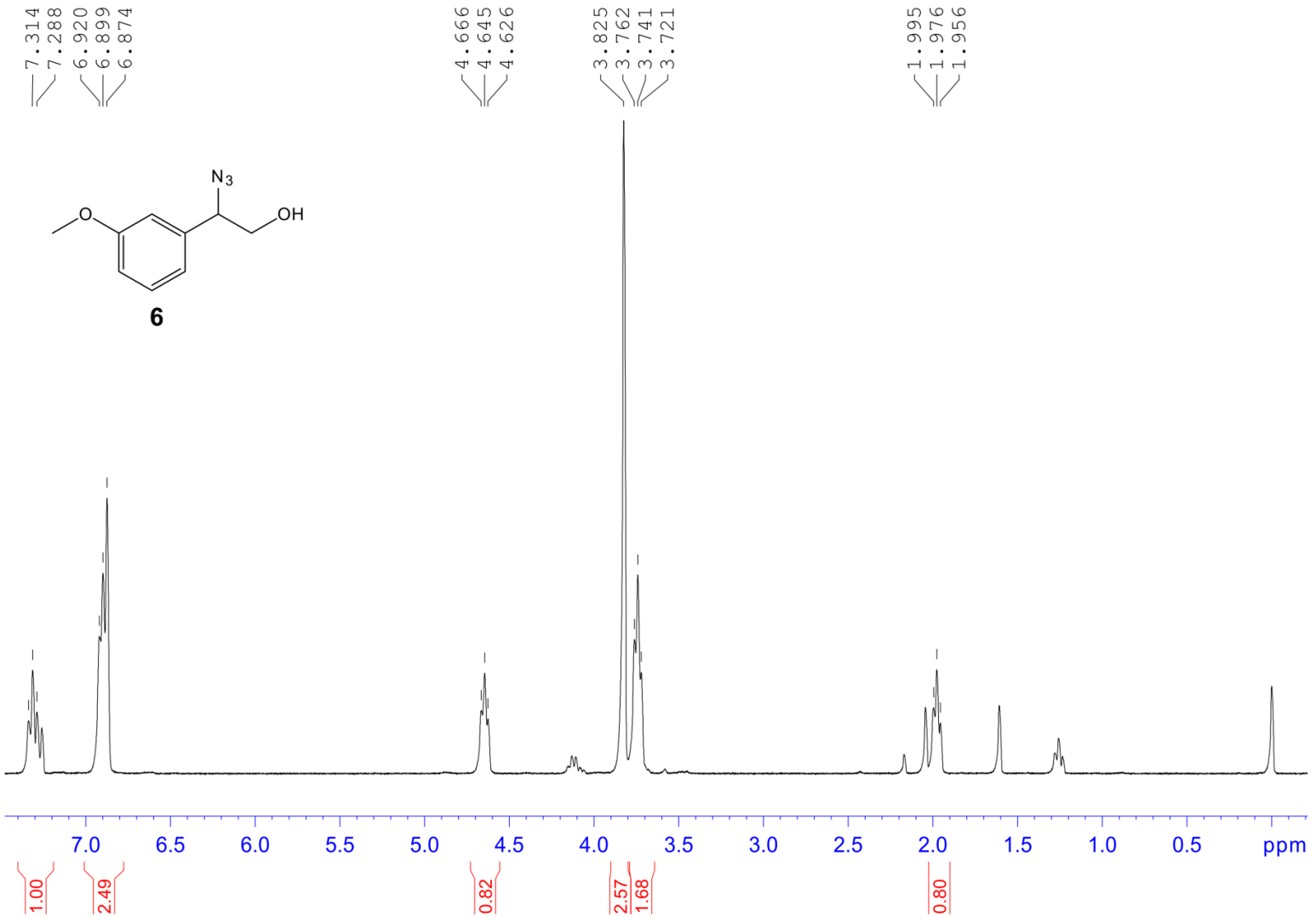
A Spectroscopic data of compound 7



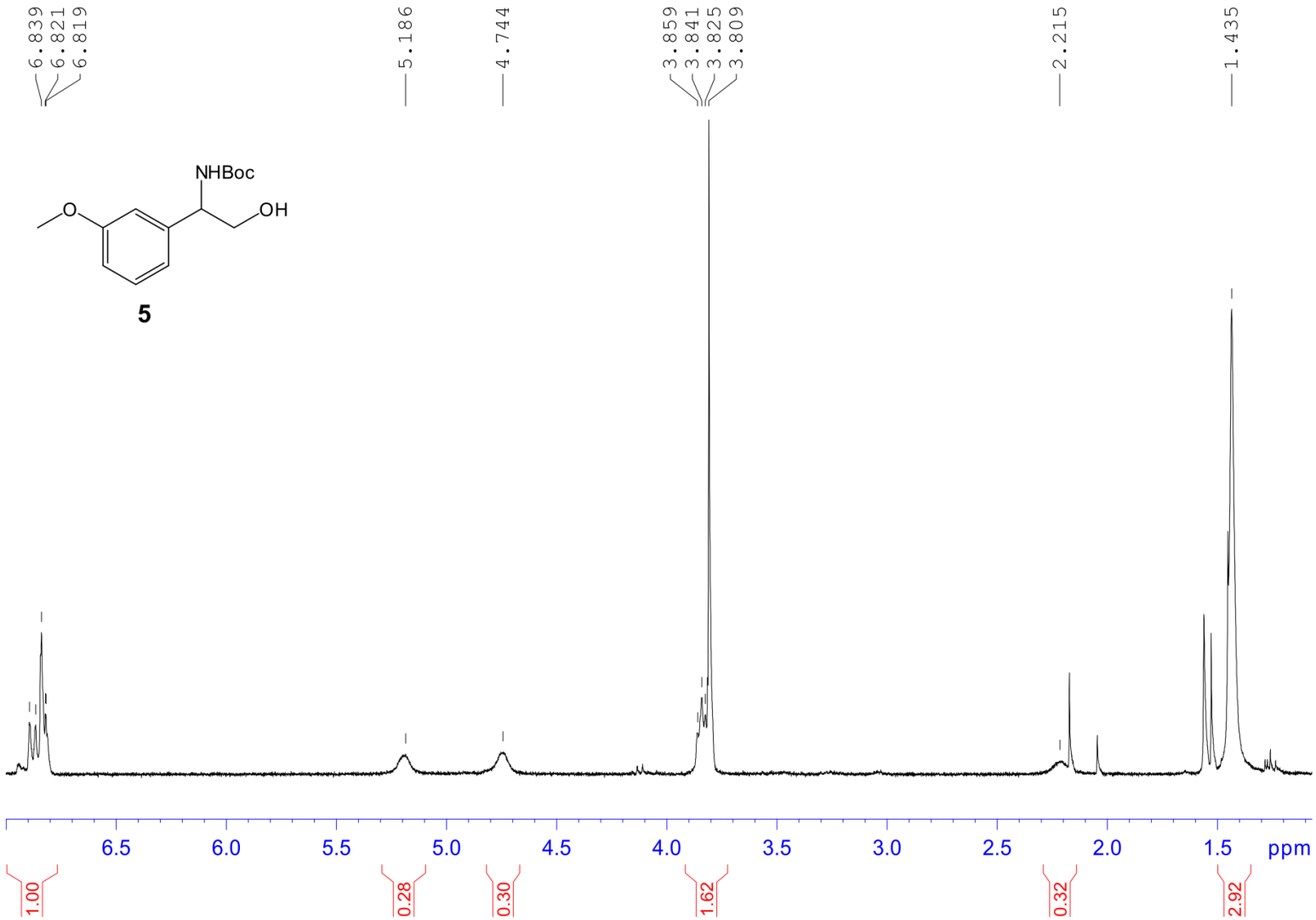
Appendix A; ^{1}H NMR spectrum of compound 7

B Spectroscopic data of compound 6



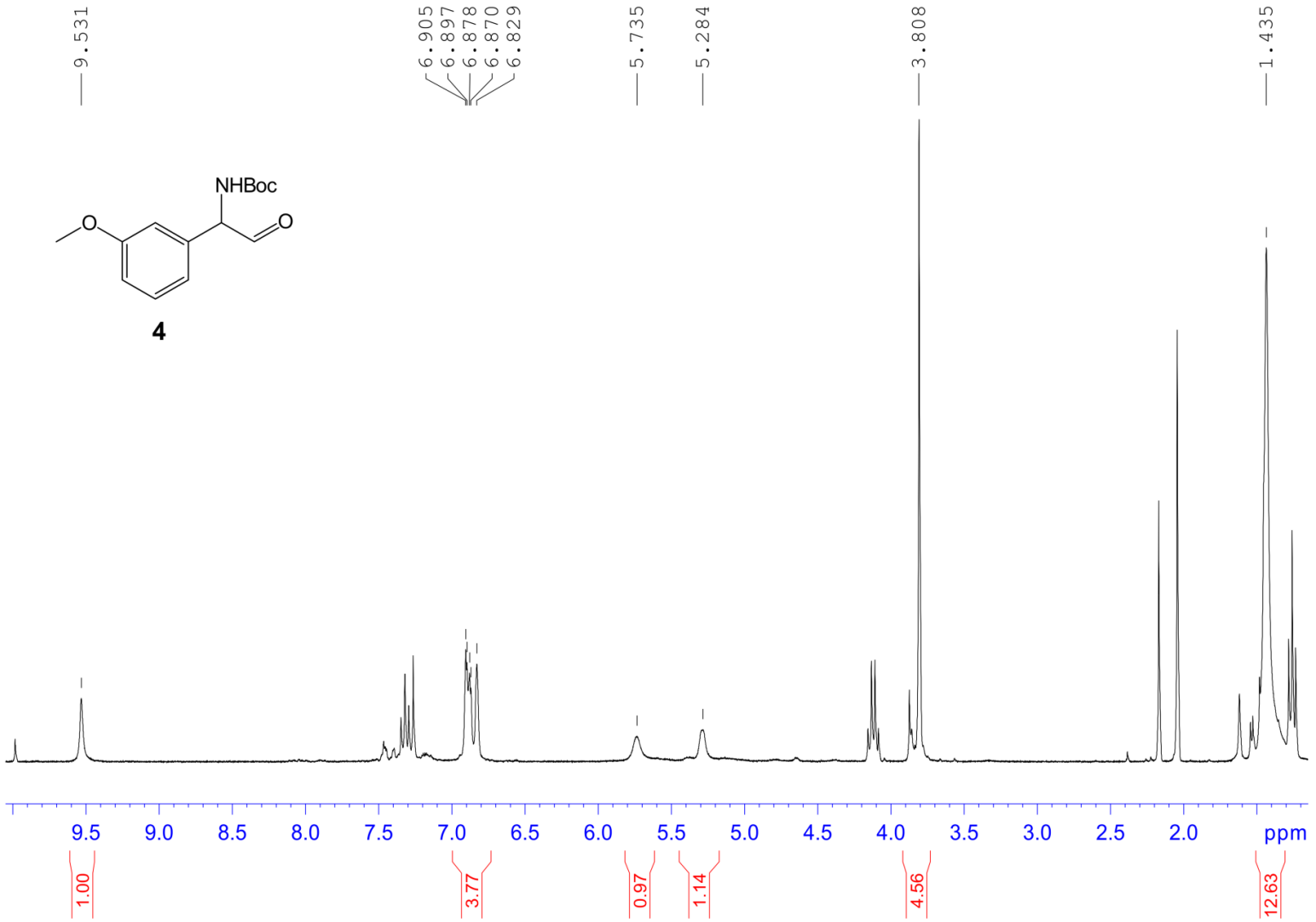
Appendix B; ^{1}H NMR spectrum of compound 6

C Spectroscopic data of compound 5



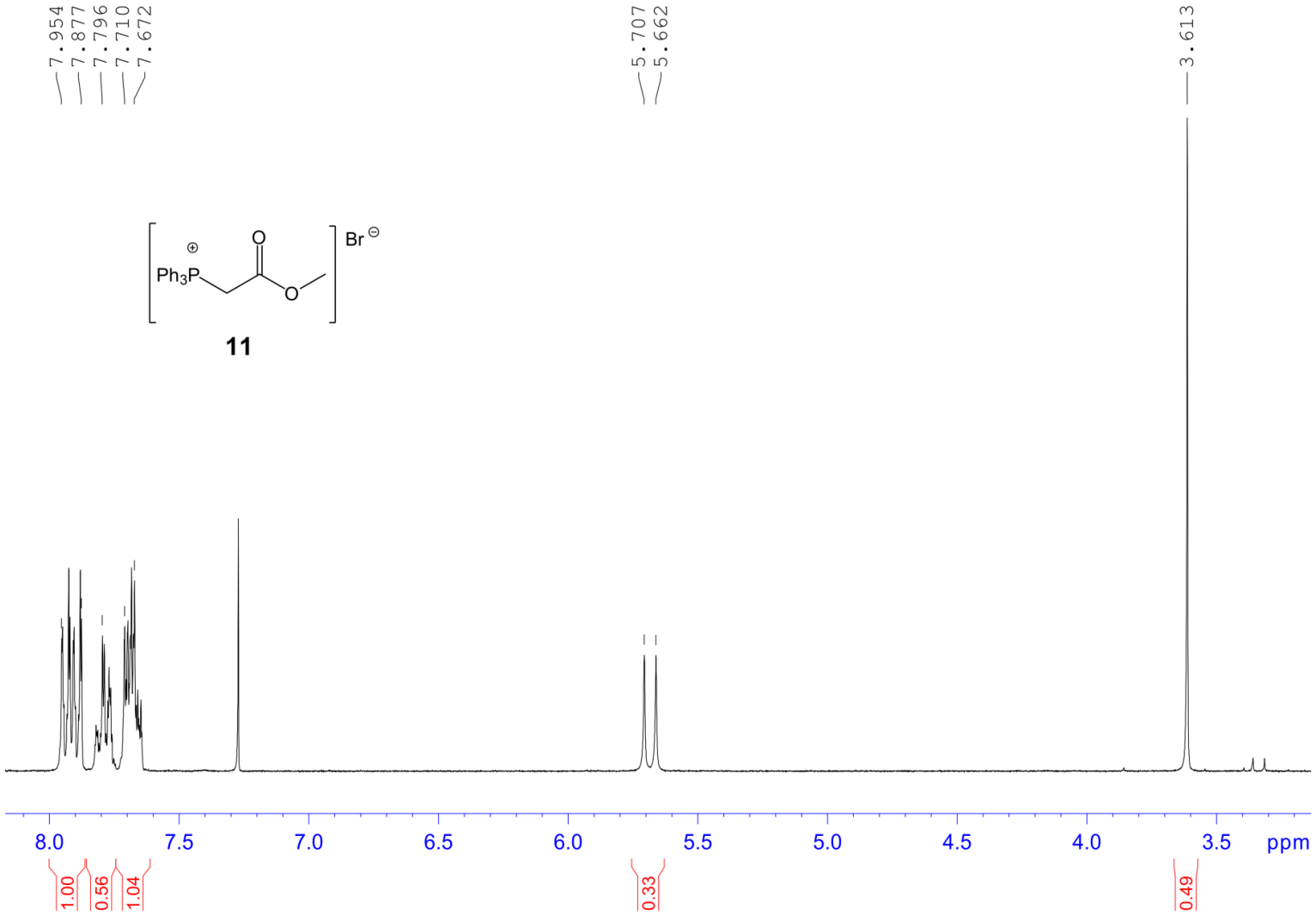
Appendix C; ^{1}H NMR spectrum of compound 5

D Spectroscopic data of compound 4



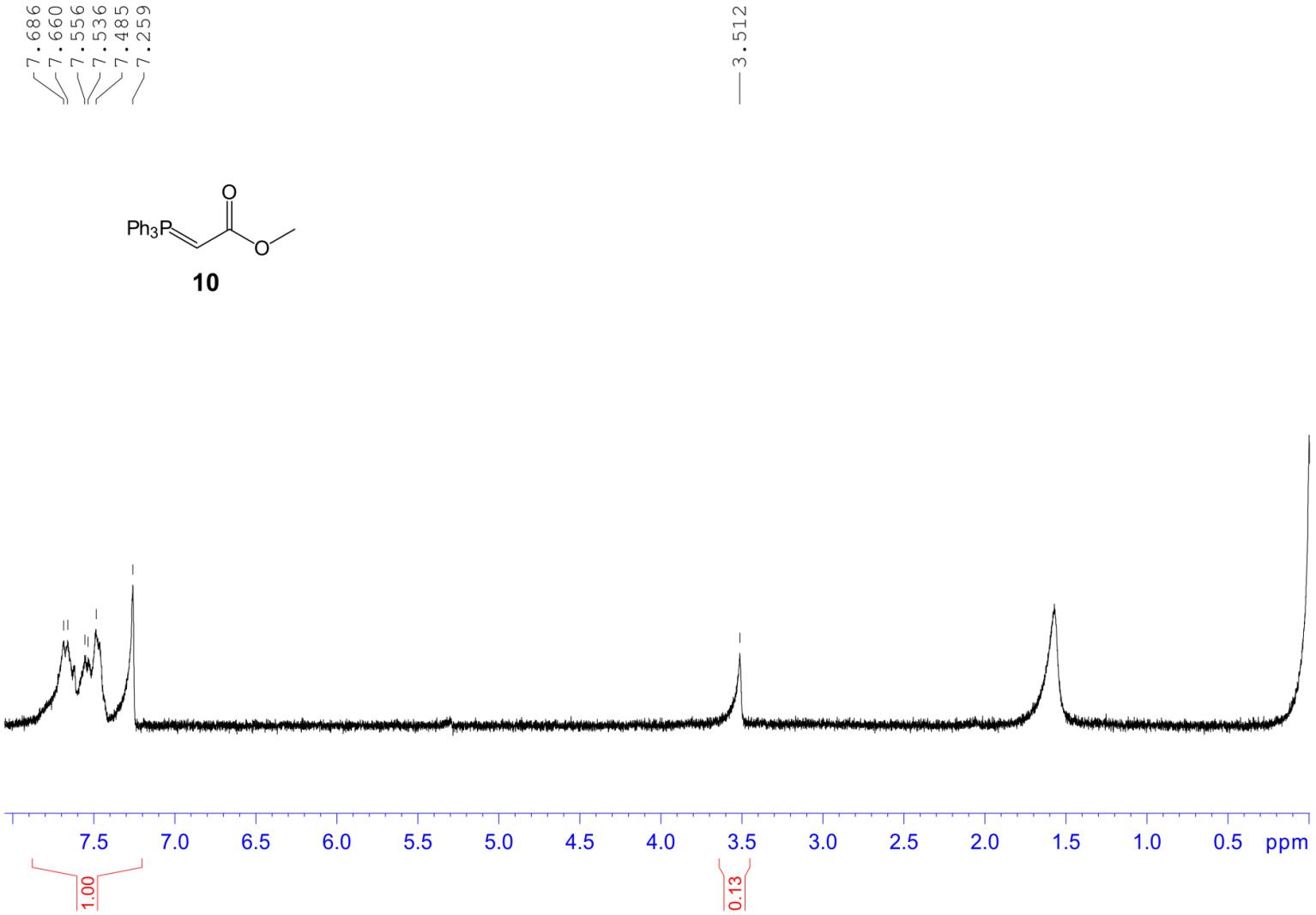
Appendix D; ^{1}H NMR spectrum for compound 4

E Spectroscopic data of compound 11



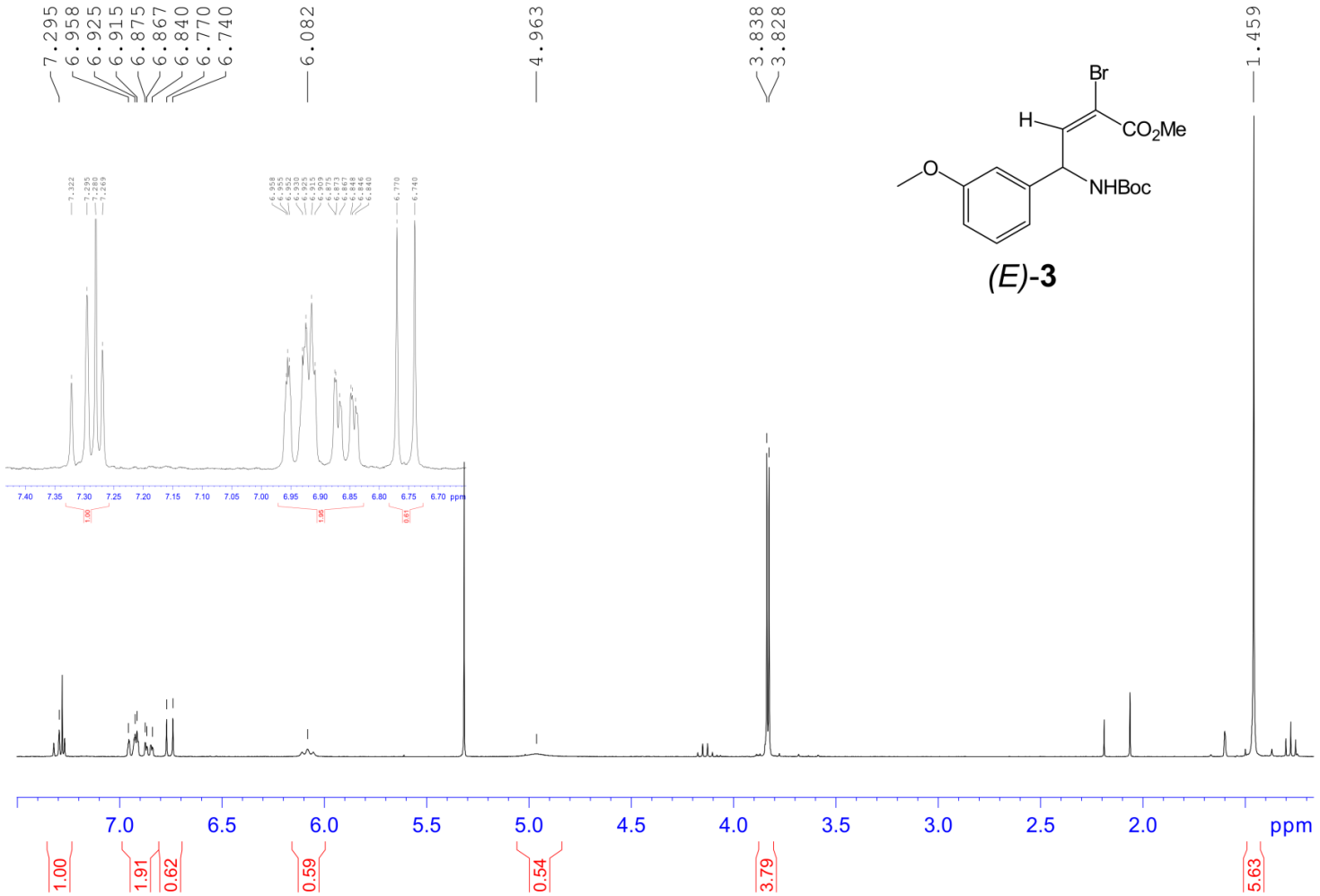
Appendix E; ^{1}H NMR spectrum of compound 11

F Spectroscopic data of compound 10

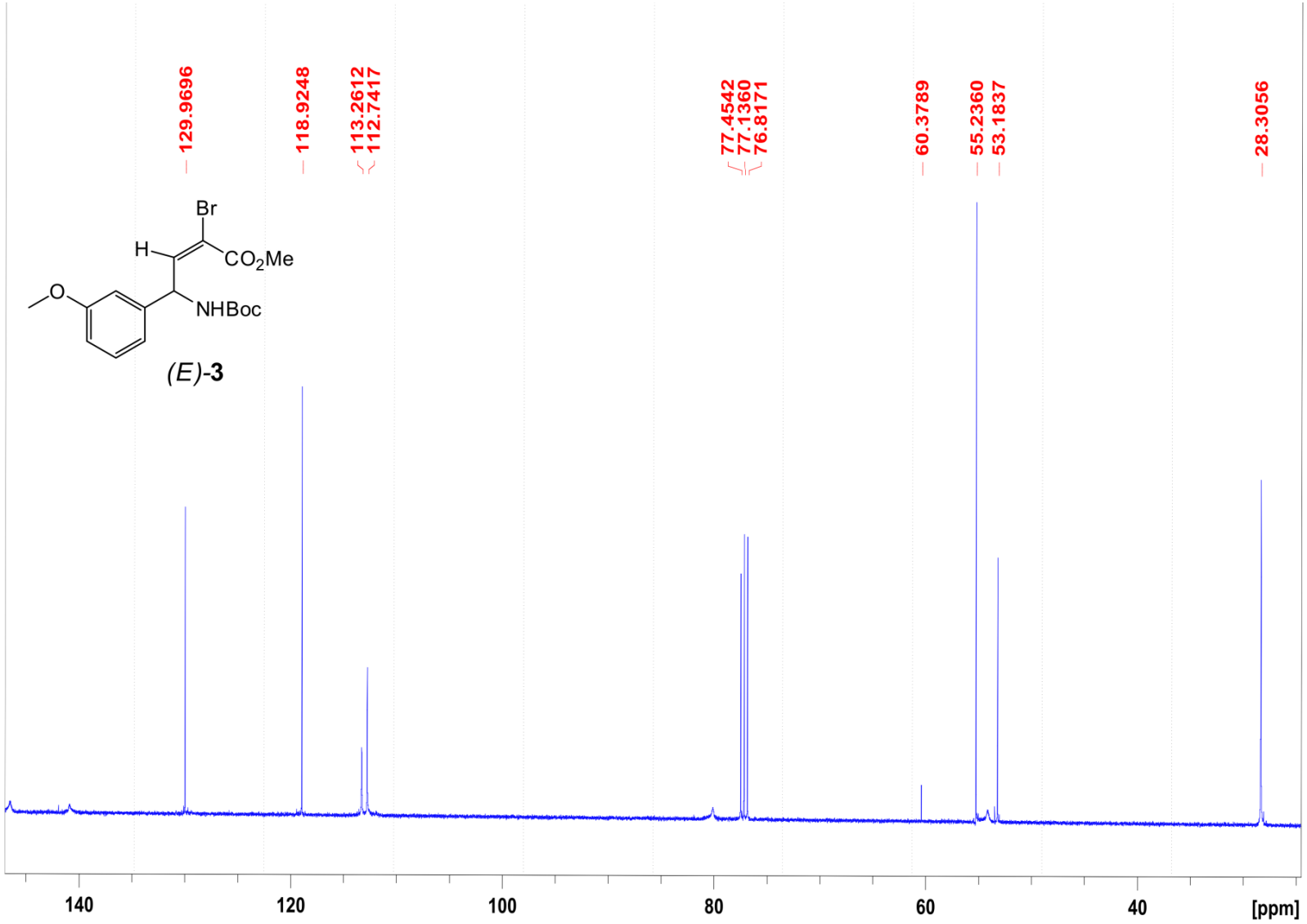


Appendix F; ^{1}H NMR spectrum for compound 10

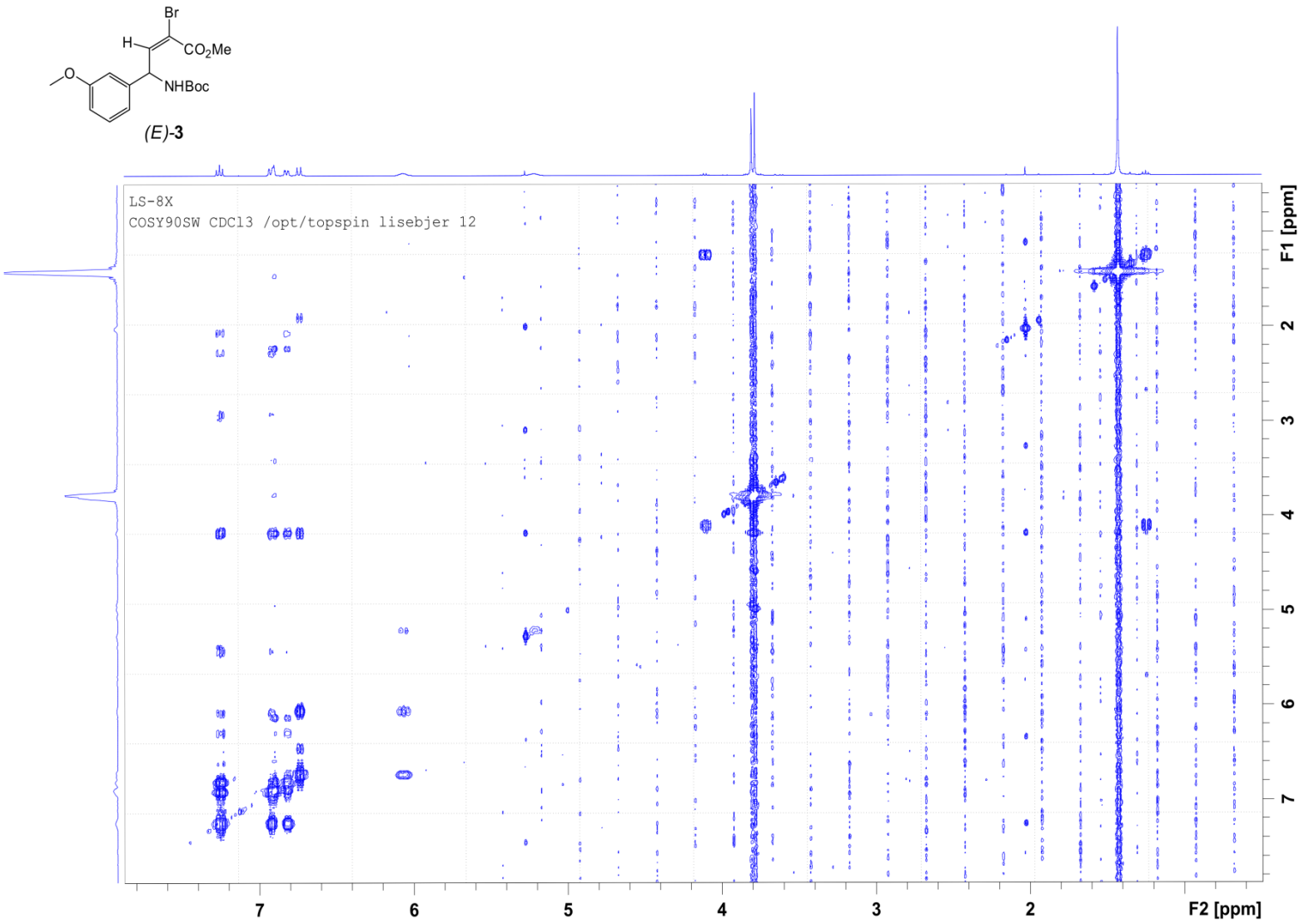
G Spectroscopic data of compound *(E)*-3



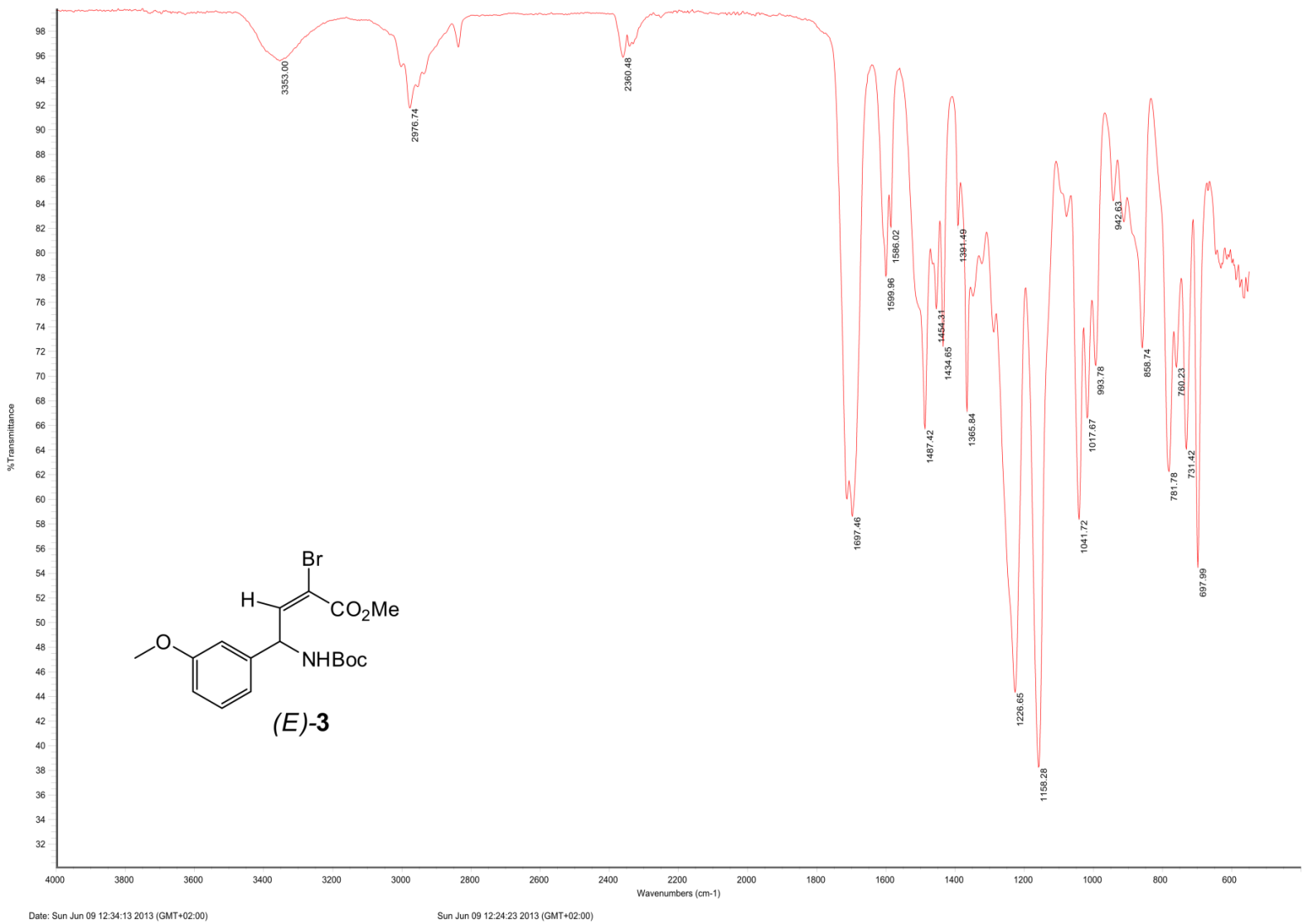
Appendix G.1; ^{1}H NMR spectrum compound *(E)*-3



Appendix G.2; ^{13}C NMR spectrum compound *(E)*-3

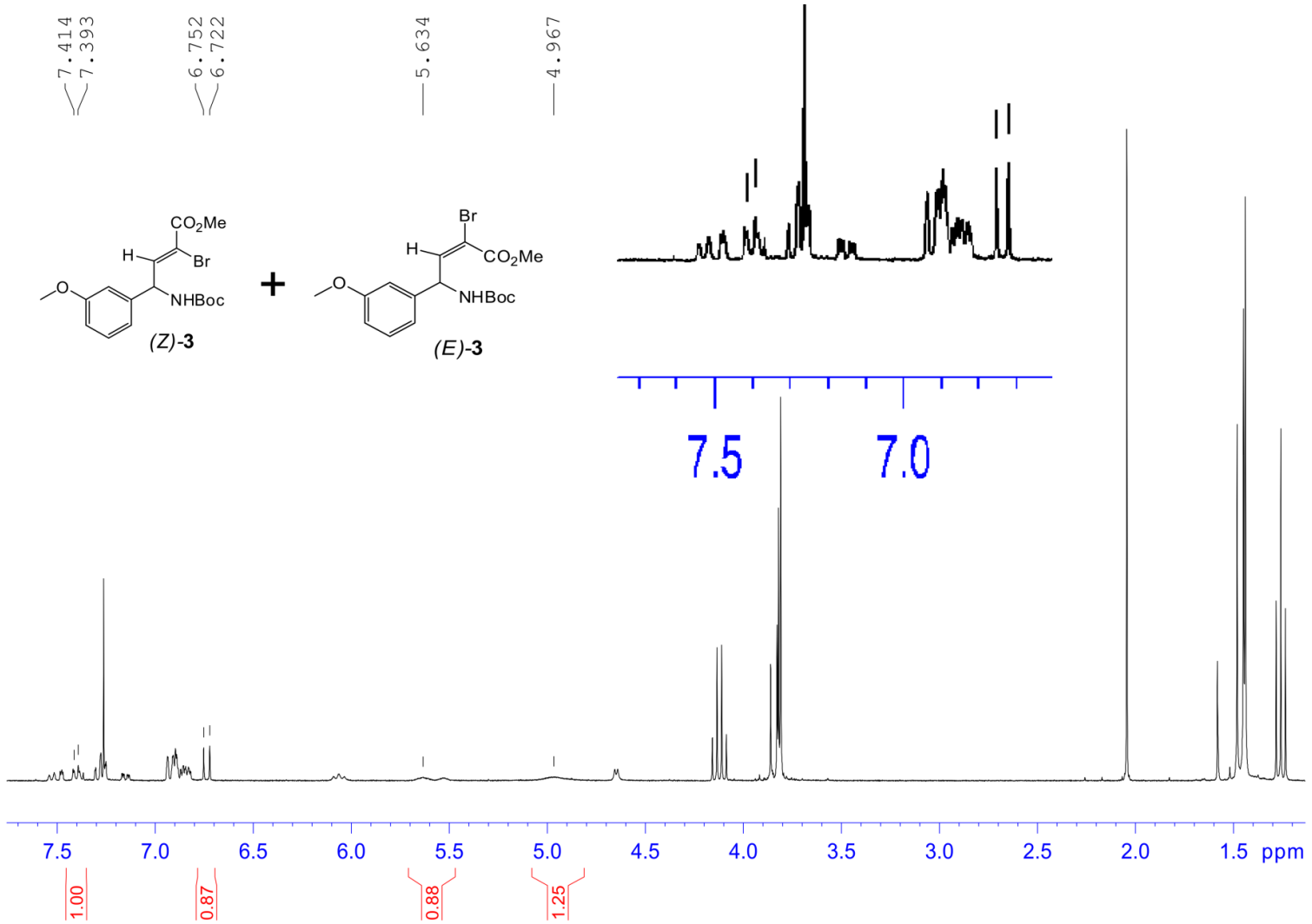


Appendix G.3; COSY spectrum compound *(E)*-3

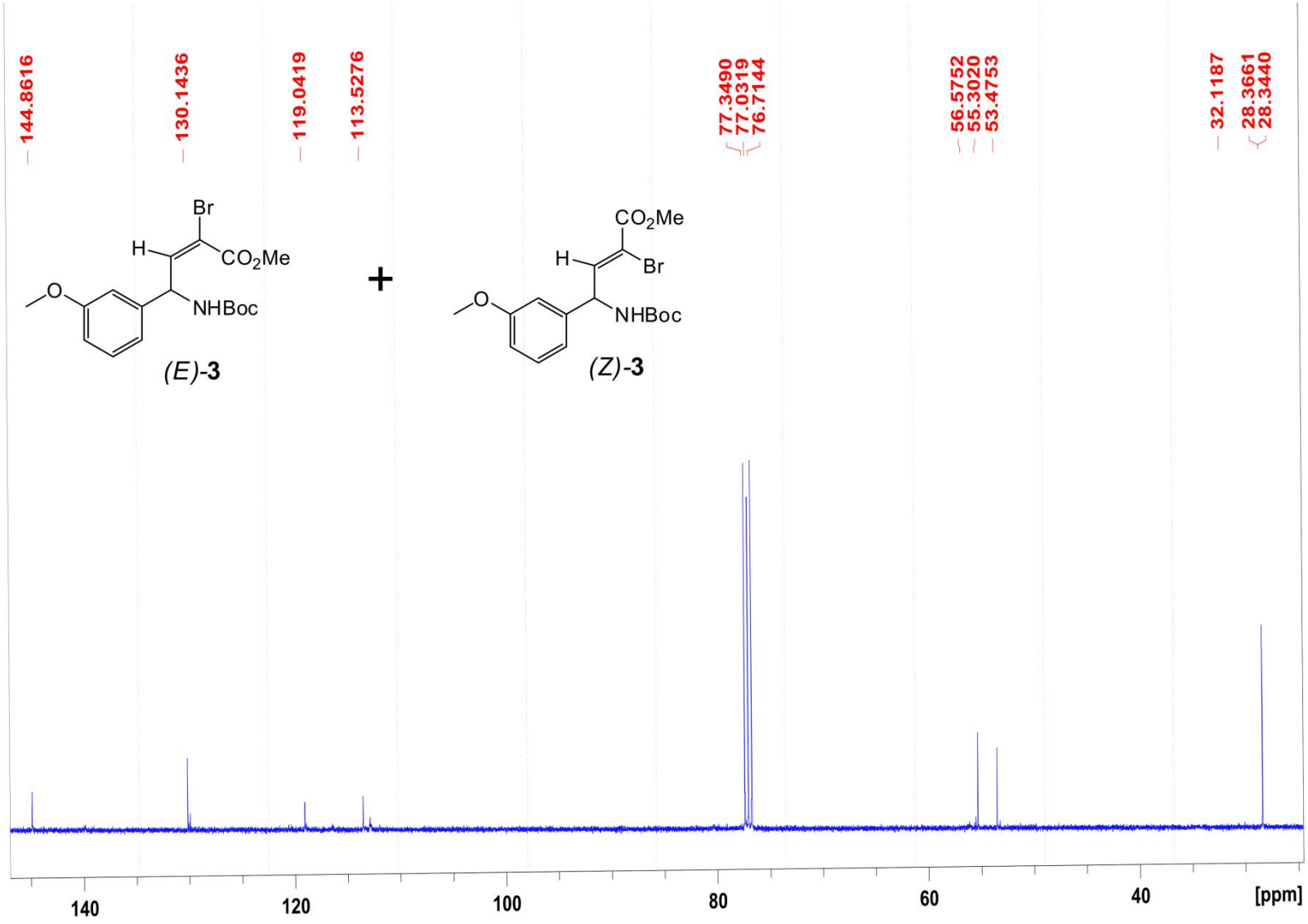


Appendix G.4; IR spectrum *(E)*-3

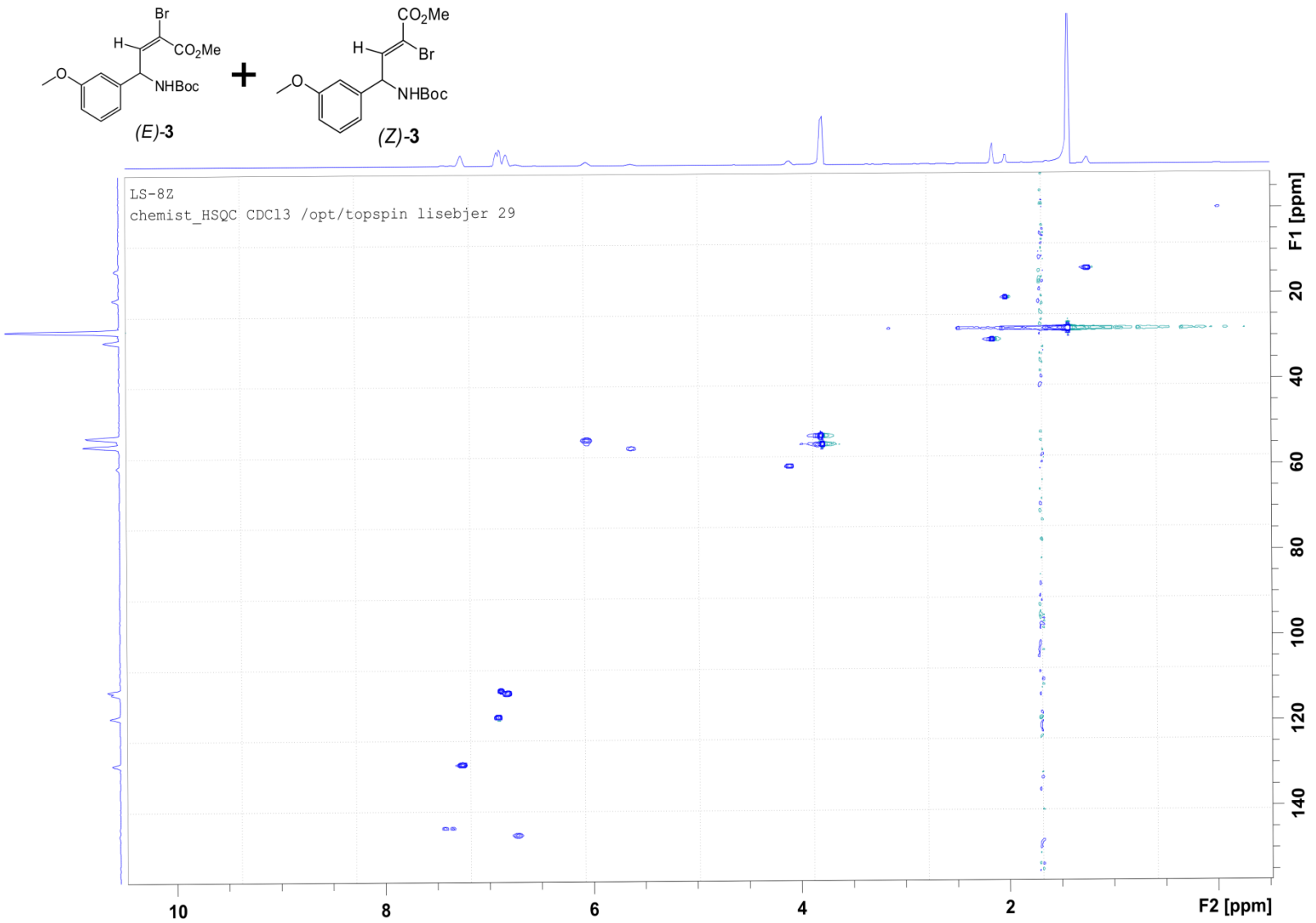
H Spectroscopic data of compound *(E/Z)*-3



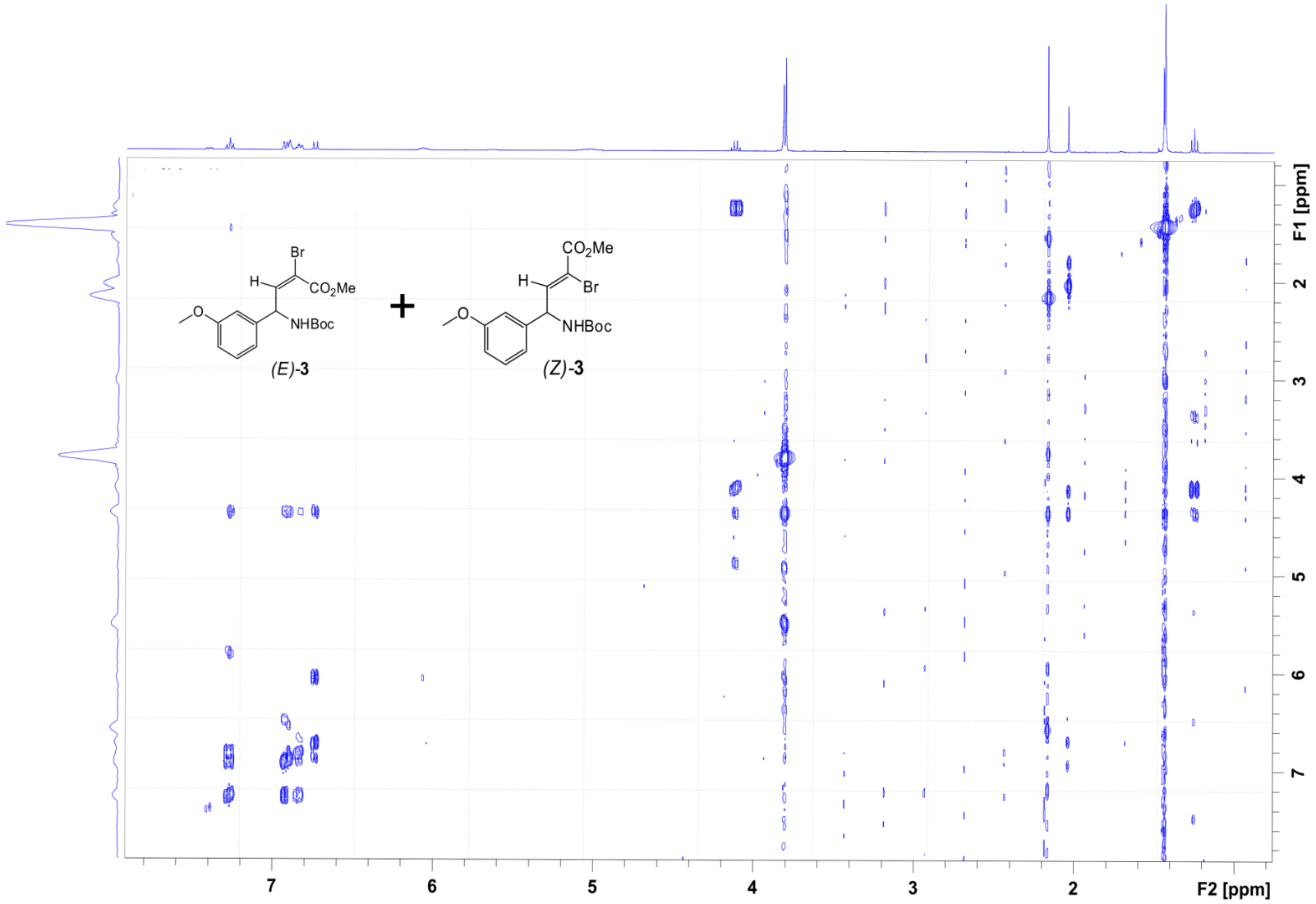
Appendix H; ^{1}H NMR spectrum for compound *(Z/E)*-3



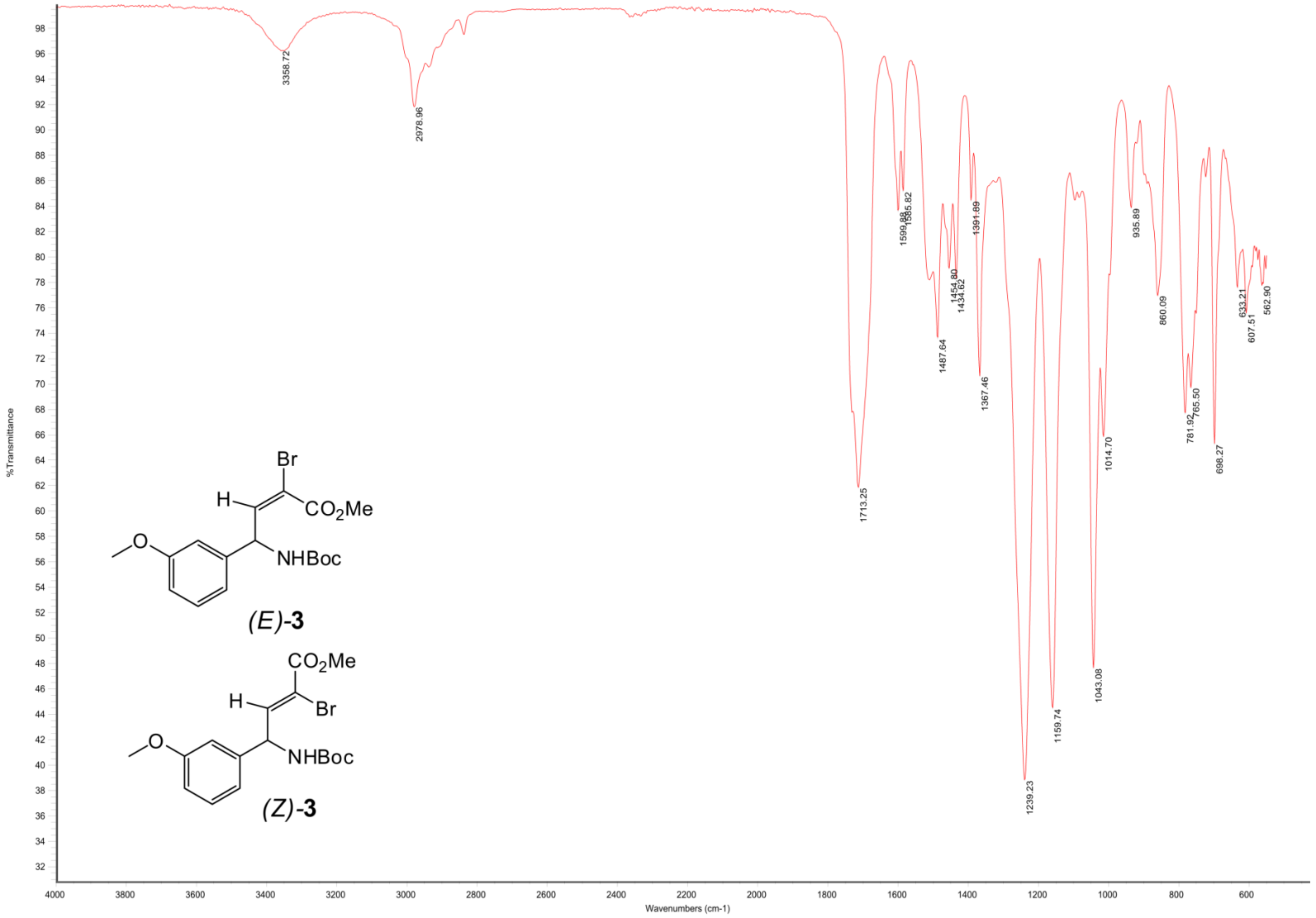
Appendix H.2; C NMR spectrum compound (*E*/*Z*)-3



Appendix H.3; HSQC spectrum compound *(E/Z)*-3



Appendix H.4; COSY spectrum compound *(E/Z)*-3



Appendix H.5; IR spectrum *(E/Z)*-3

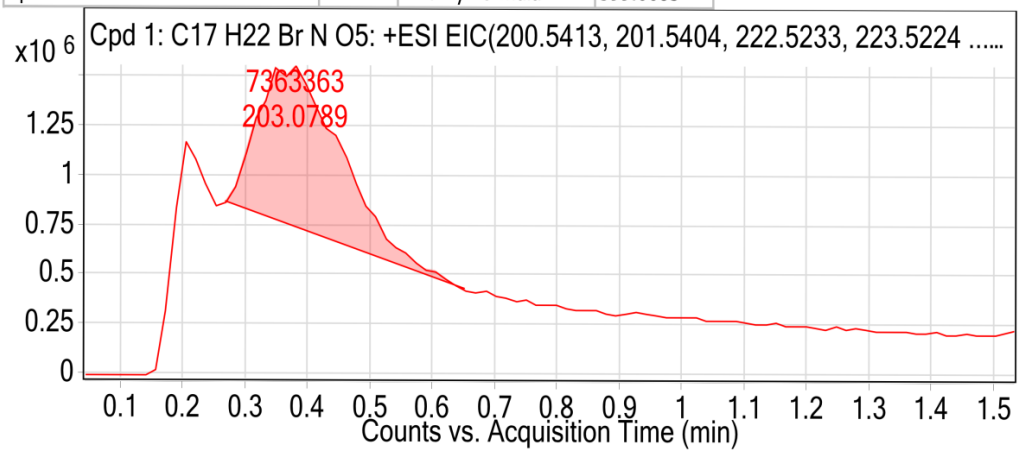
Qualitative Compound Report

Data File	2012_282_002.d	**Sample Name**	2012-282
Sample Type	Sample	**Position**	Vial 91
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	Default.m	**Comment**	

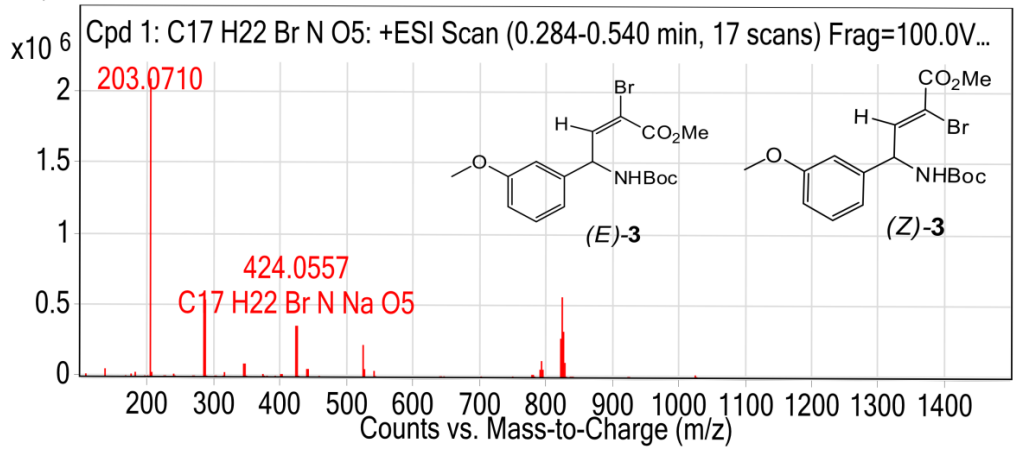
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C17 H22 Br N O5	0.38	399.0683	369499	C17 H22 Br N O5	399.0681	0.32

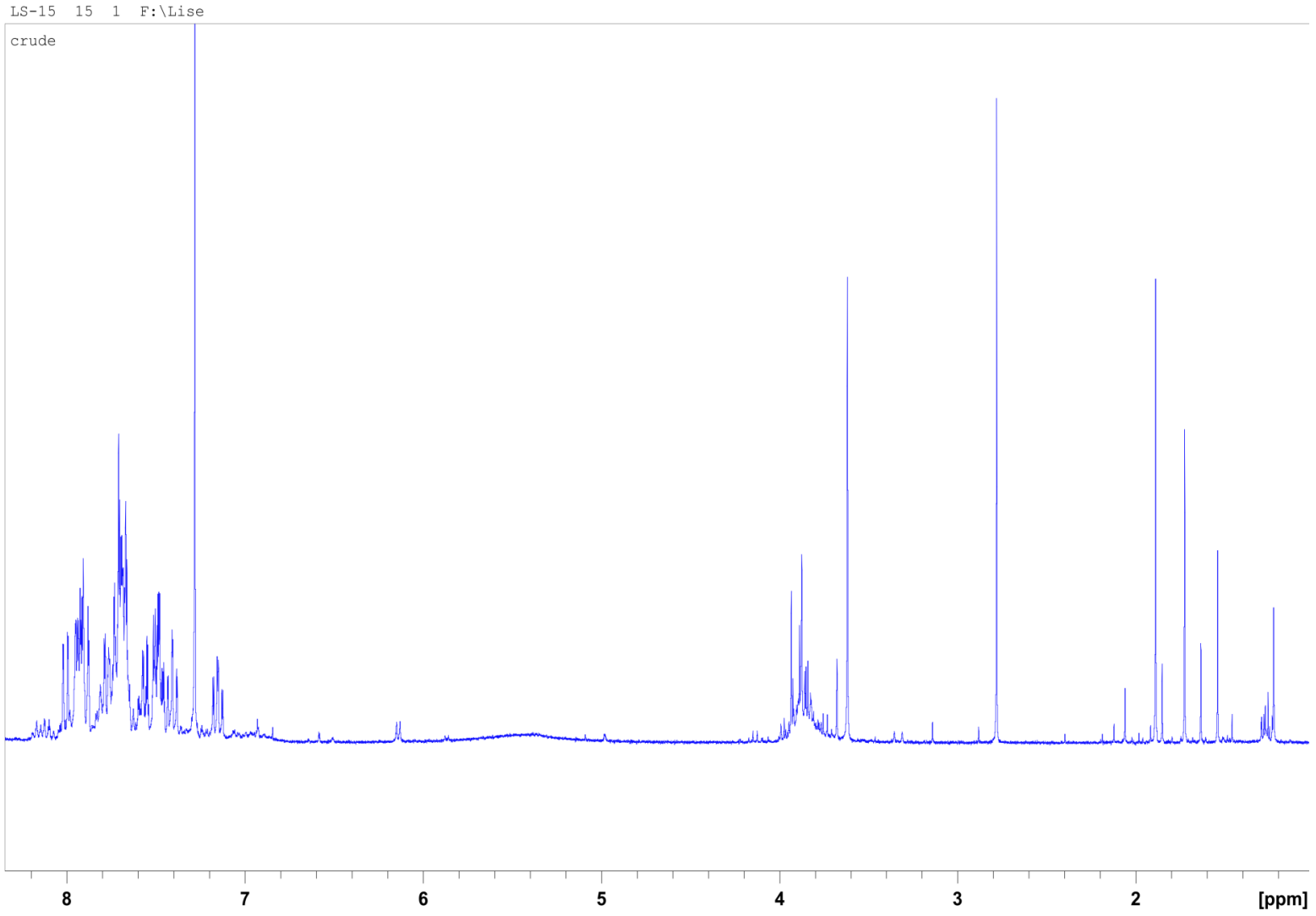
Compound Label	RT	Algorithm	Mass
Cpd 1: C17 H22 Br N O5	0.38	Find By Formula	399.0683



MS Spectrum

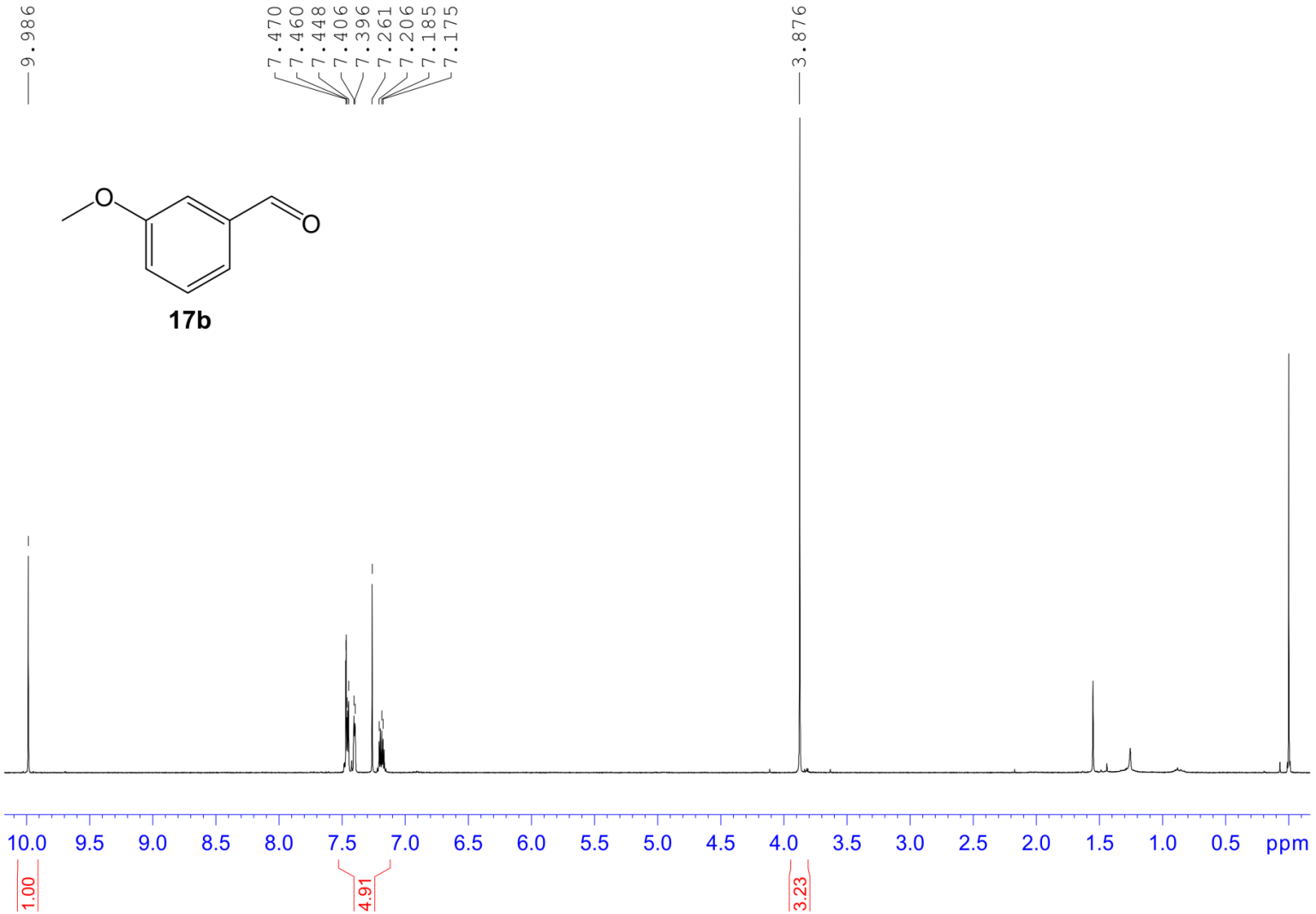


Appendix H.6; MS spectrum for compound *(E/Z)*-3



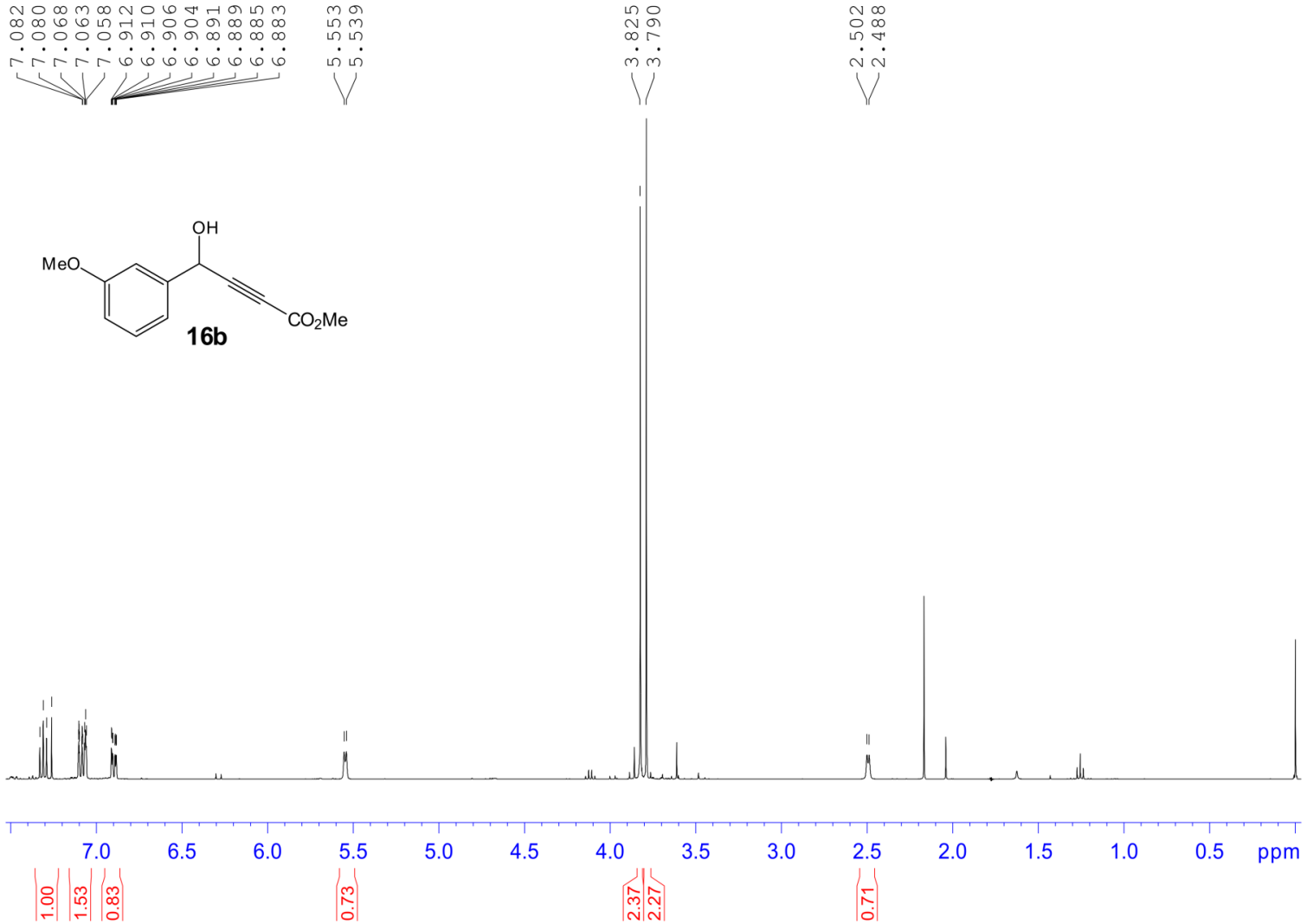
Appendix H.7; ^{1}H NMR spectrum showing complex mixture from Wittig reaction with chloroform as solvent, entry 3 table 6.5

I Spectroscopic data of compound 17b

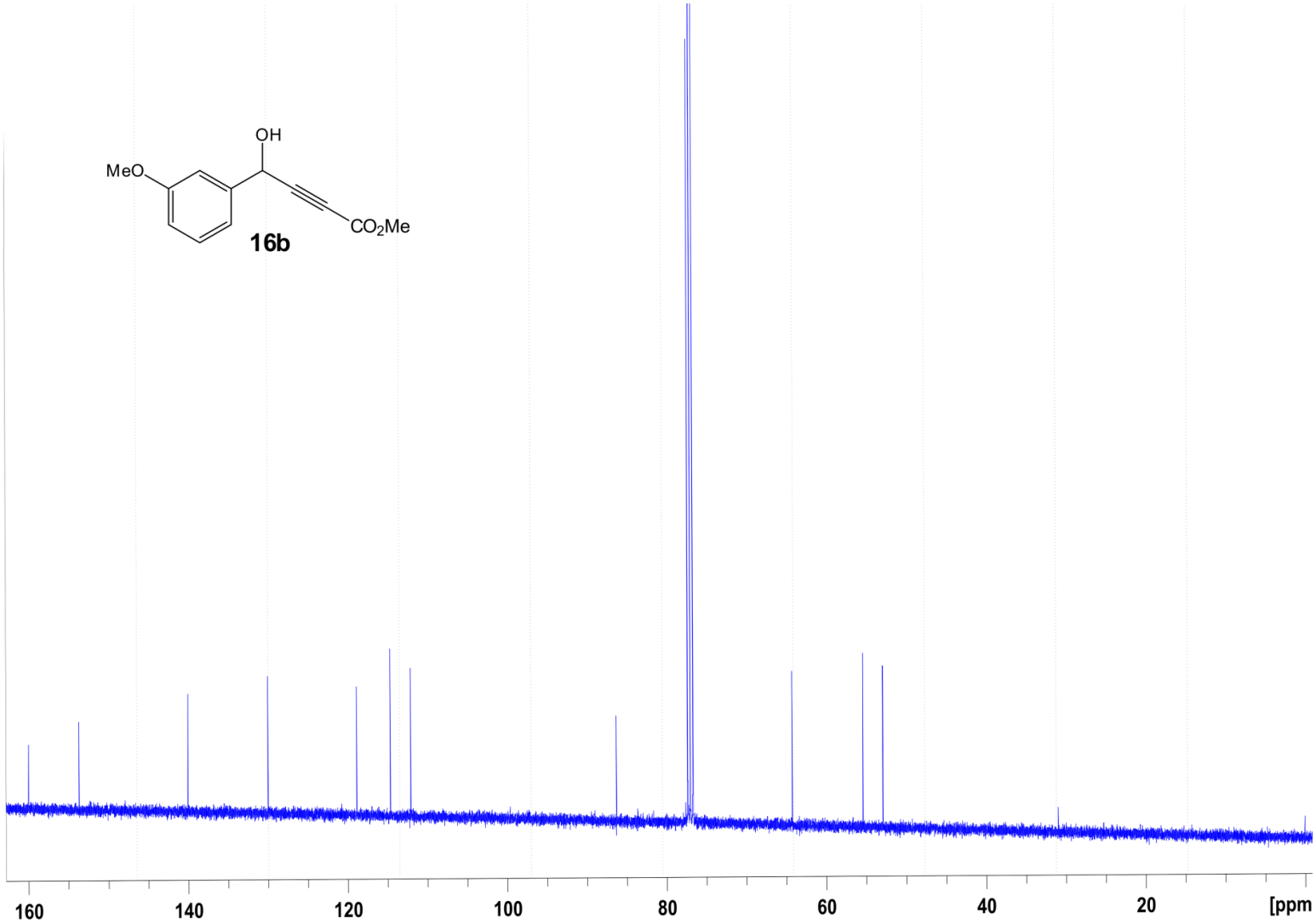


Appendix I; ^{1}H NMR spectrum for compound 17b

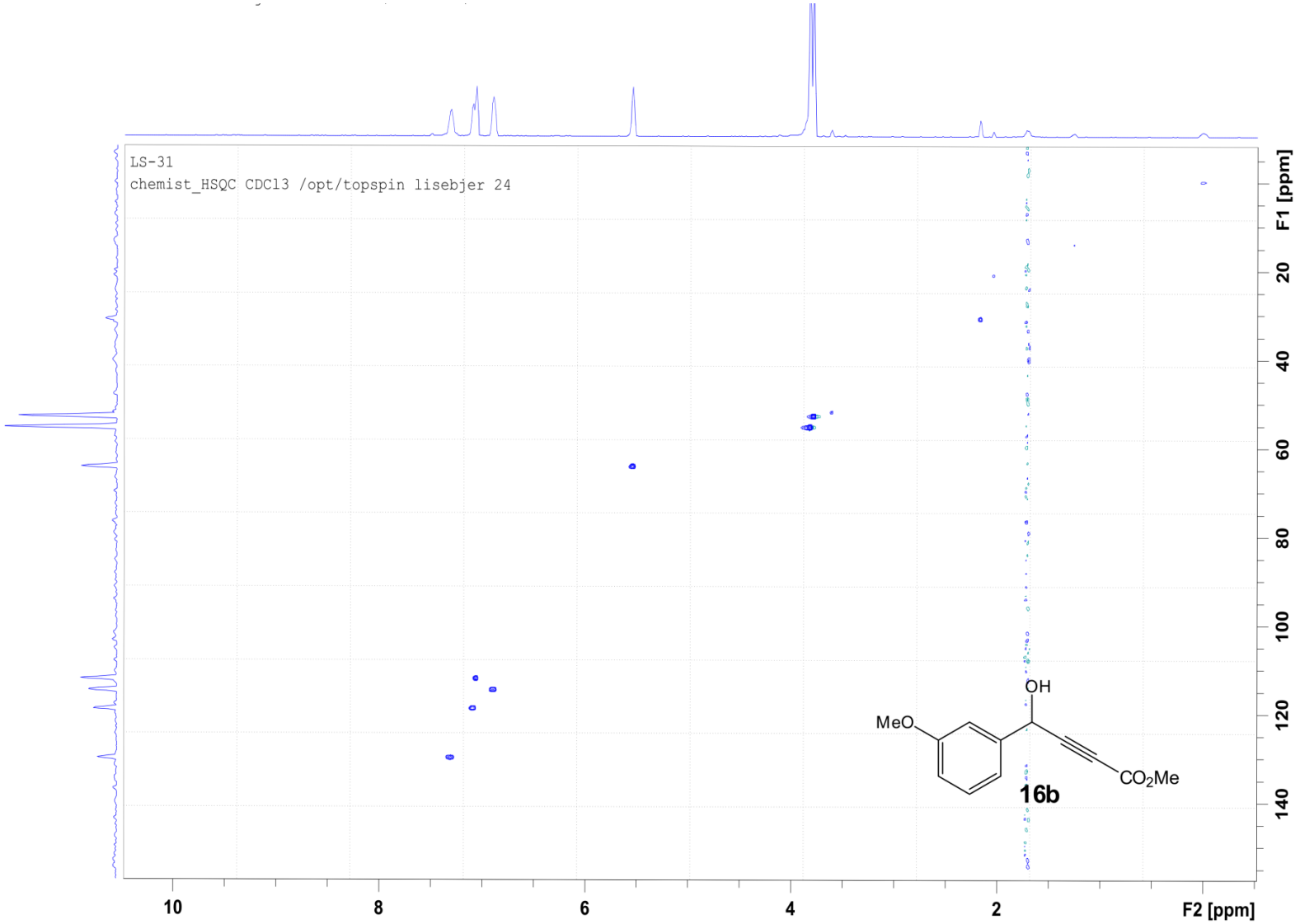
J Spectroscopic data of compound 16b



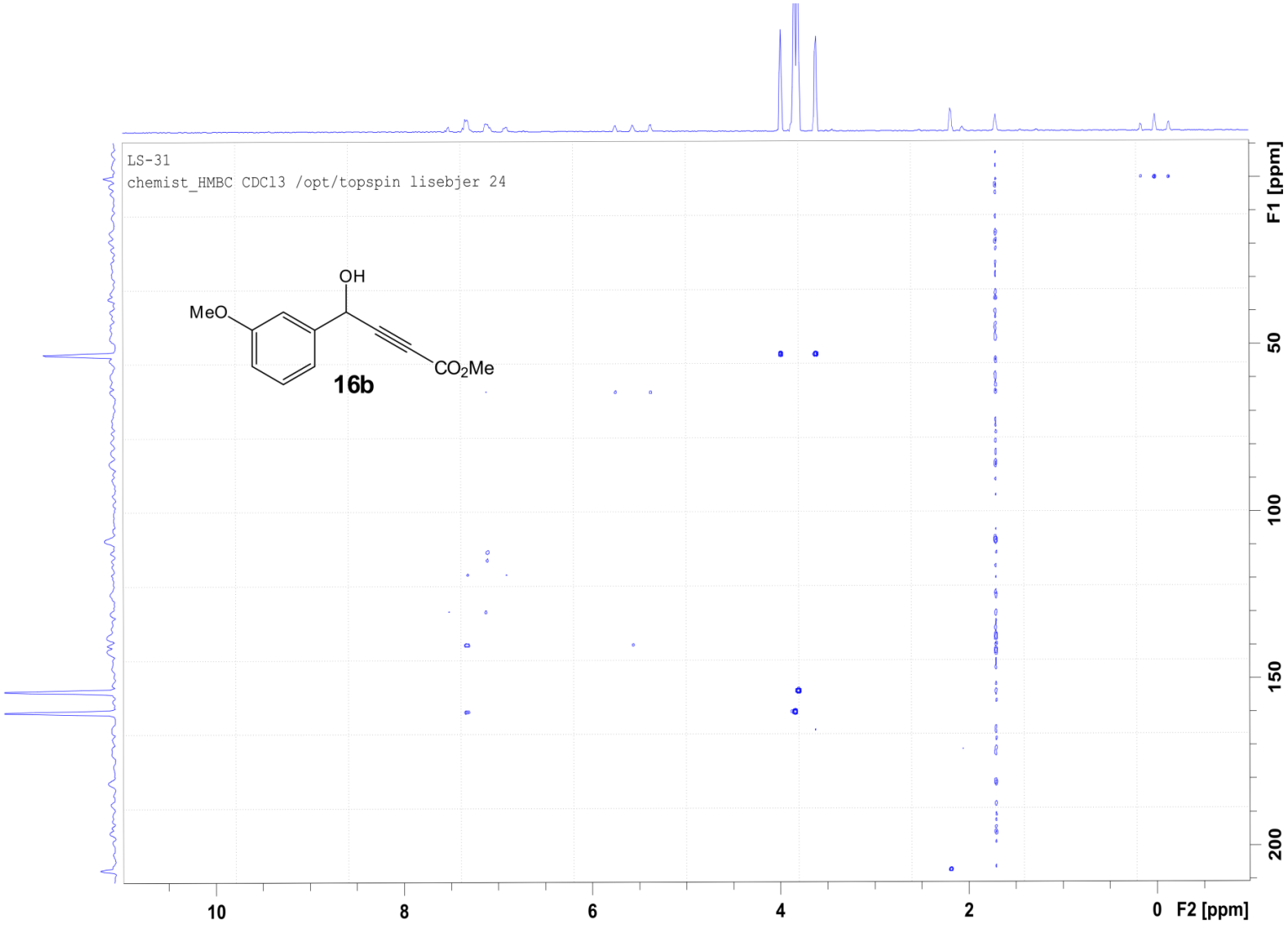
Appendix J.1; ^{1}H NMR spectrum of compound 16b



Appendix J.2; ^{13}C NMR spectrum for compound 16b

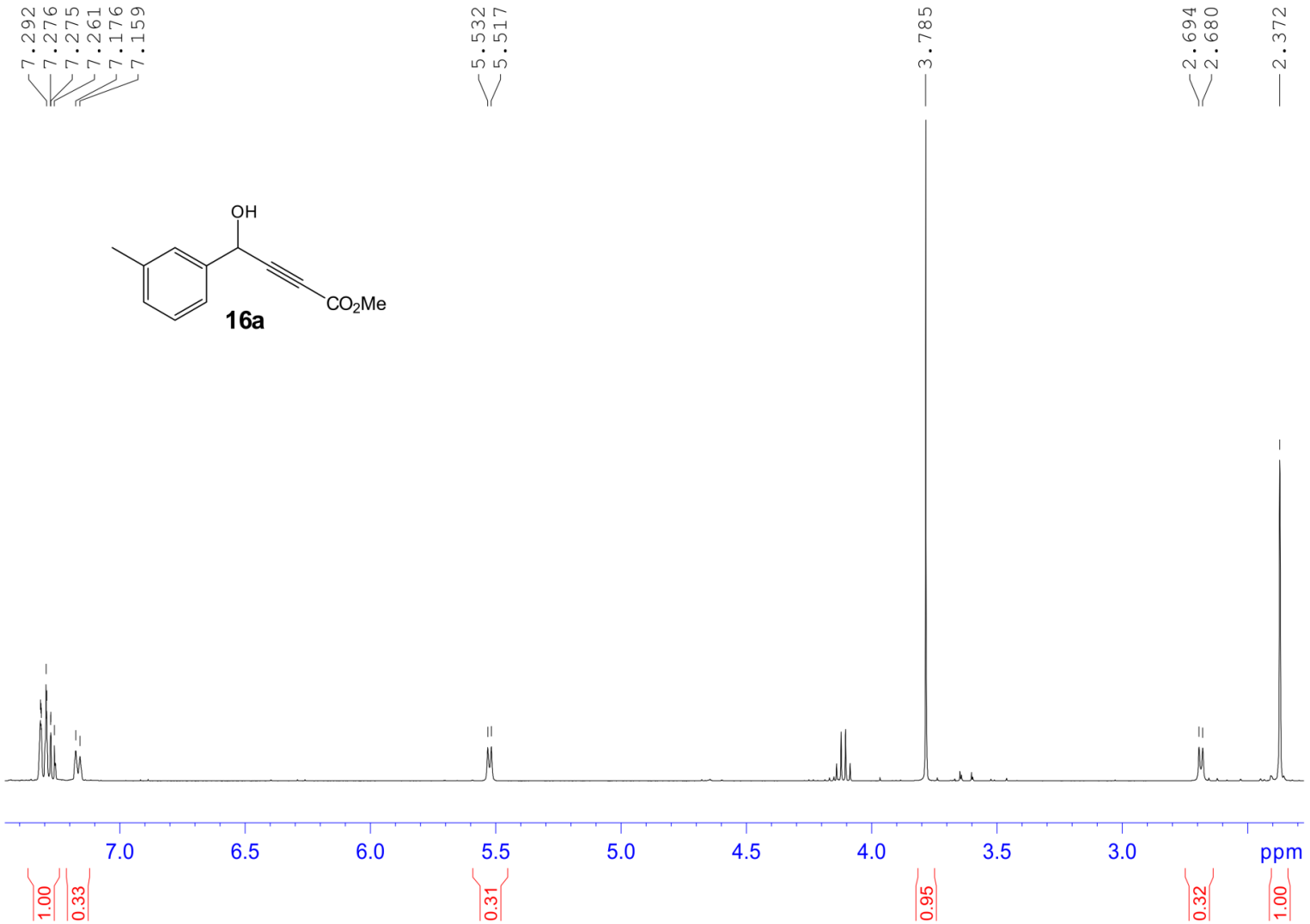


Appendix J.3; HSQC spectrum for compound 16b

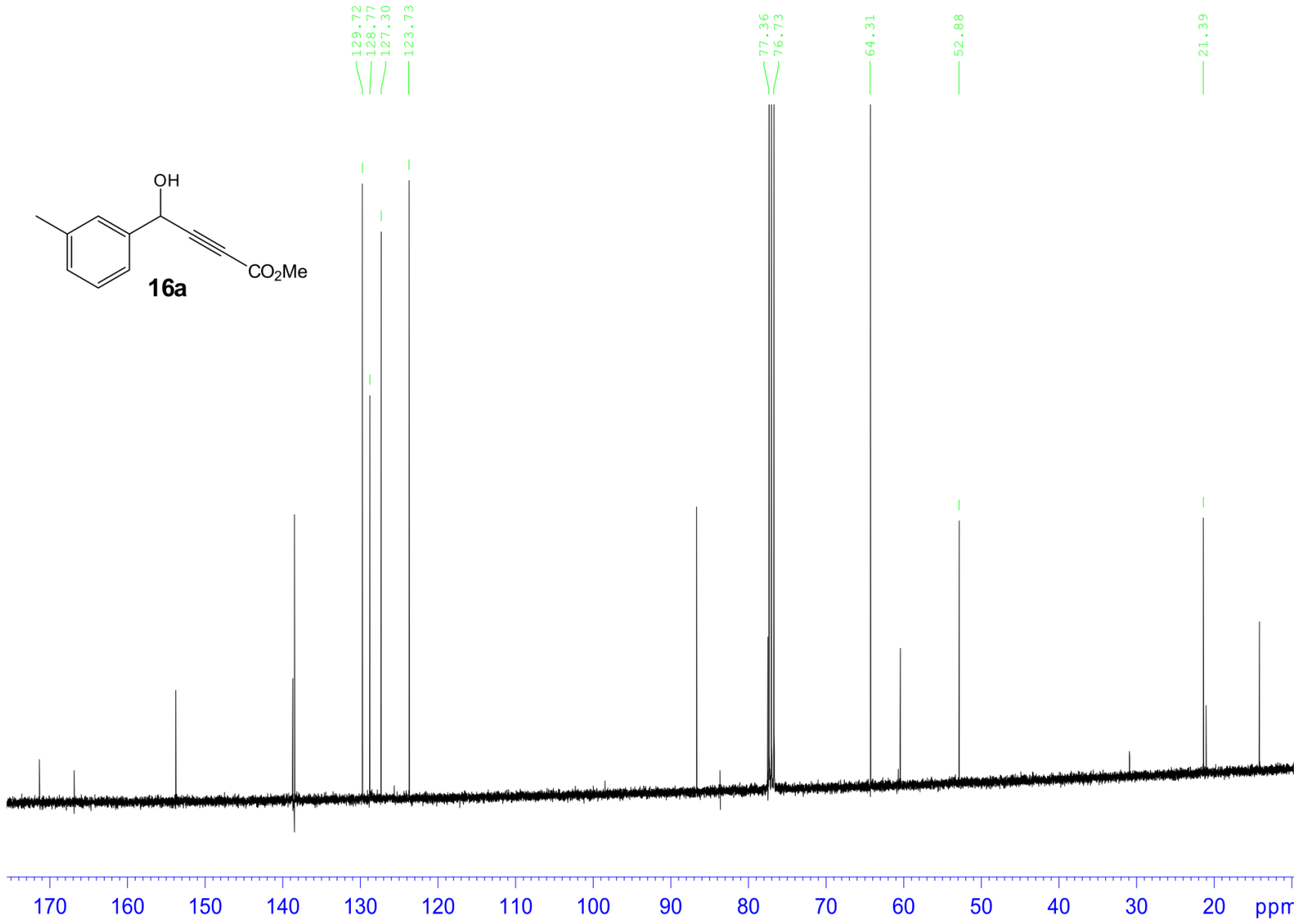


Appendix J.4; HMBC spectrum for compound 16b

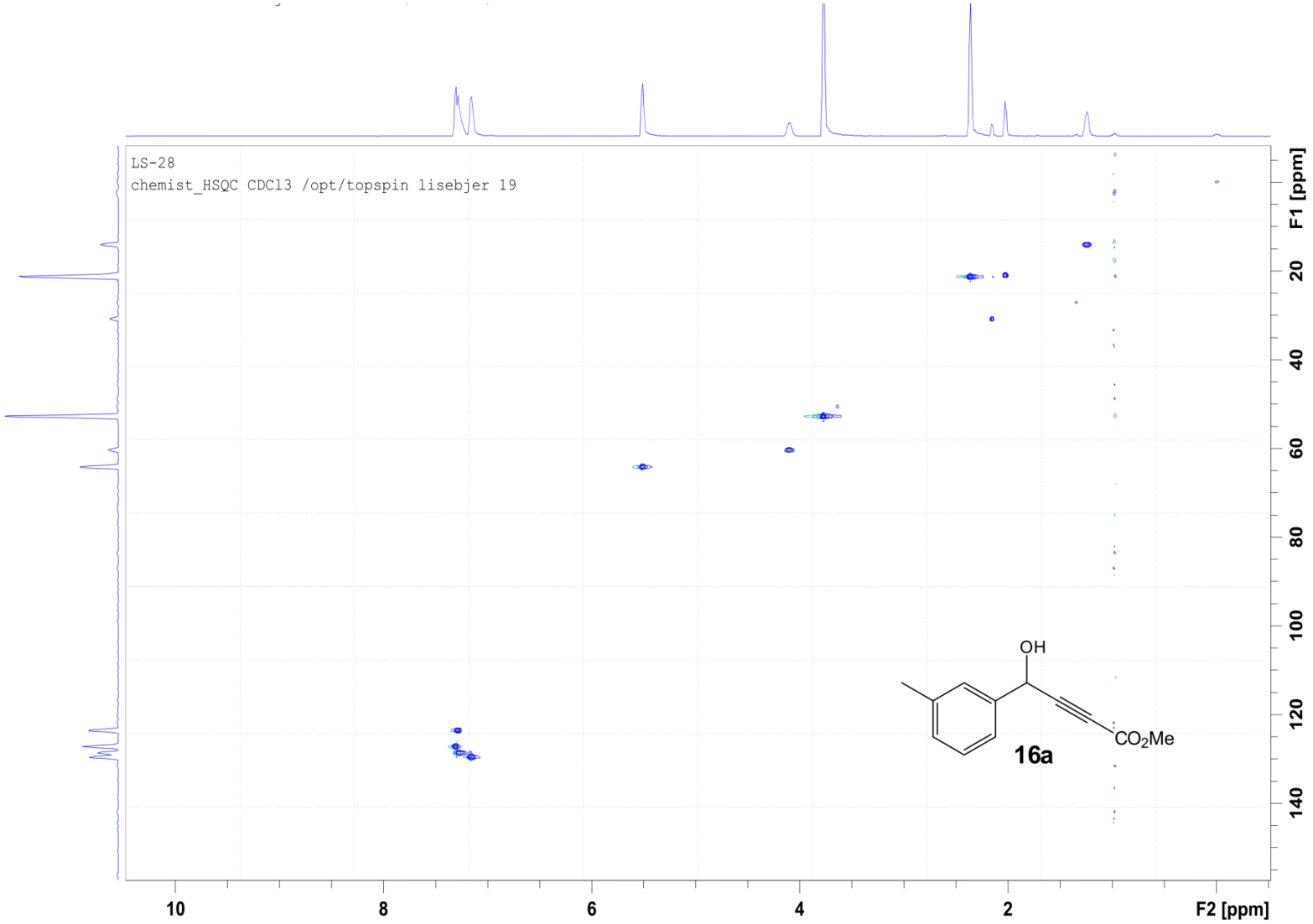
K Spectroscopic data of compound 16a



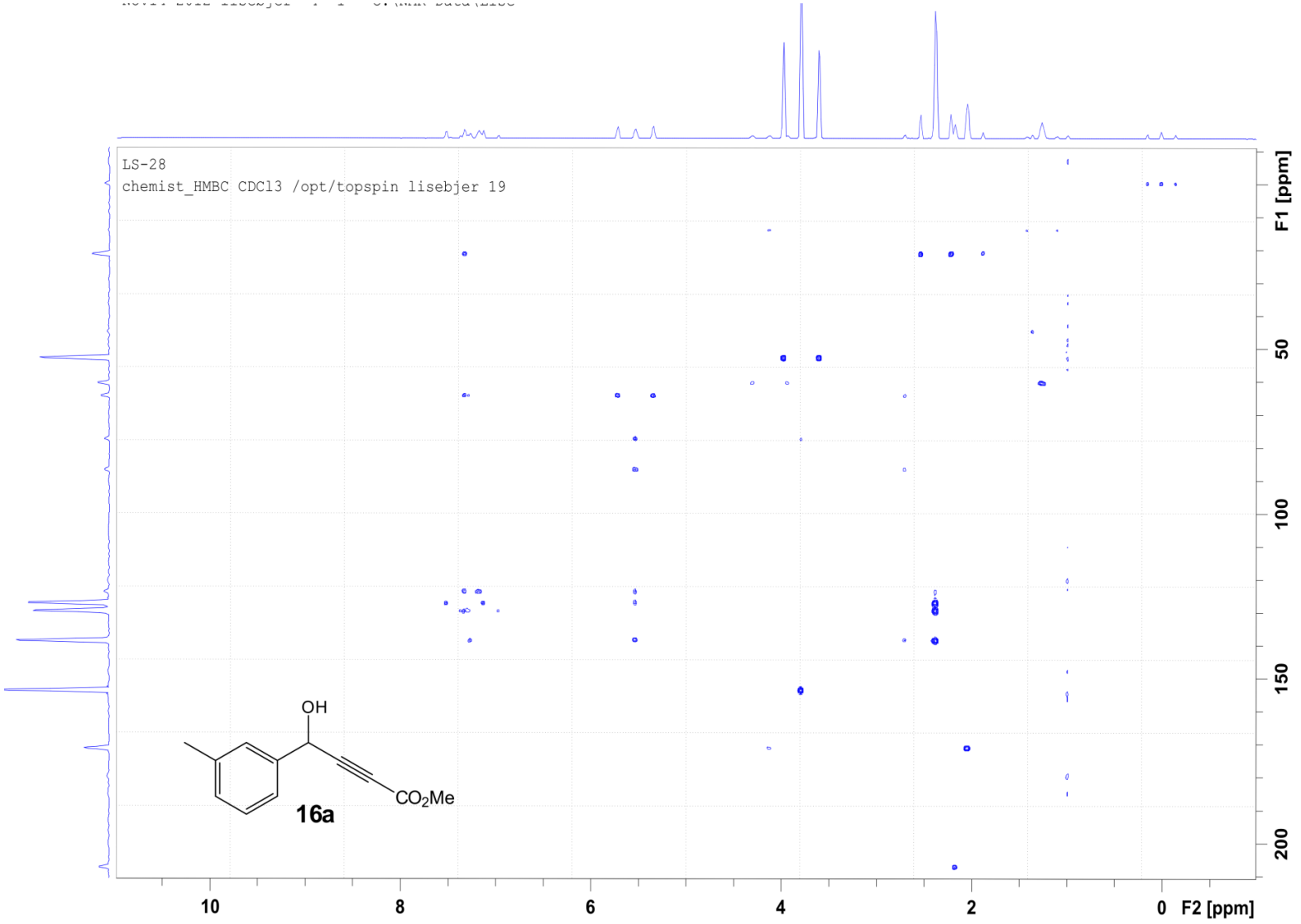
Appendix K.1; ^{1}H NMR spectrum of compound 16a



Appendix K.2; ^{13}C NMR spectrum of compound 16a

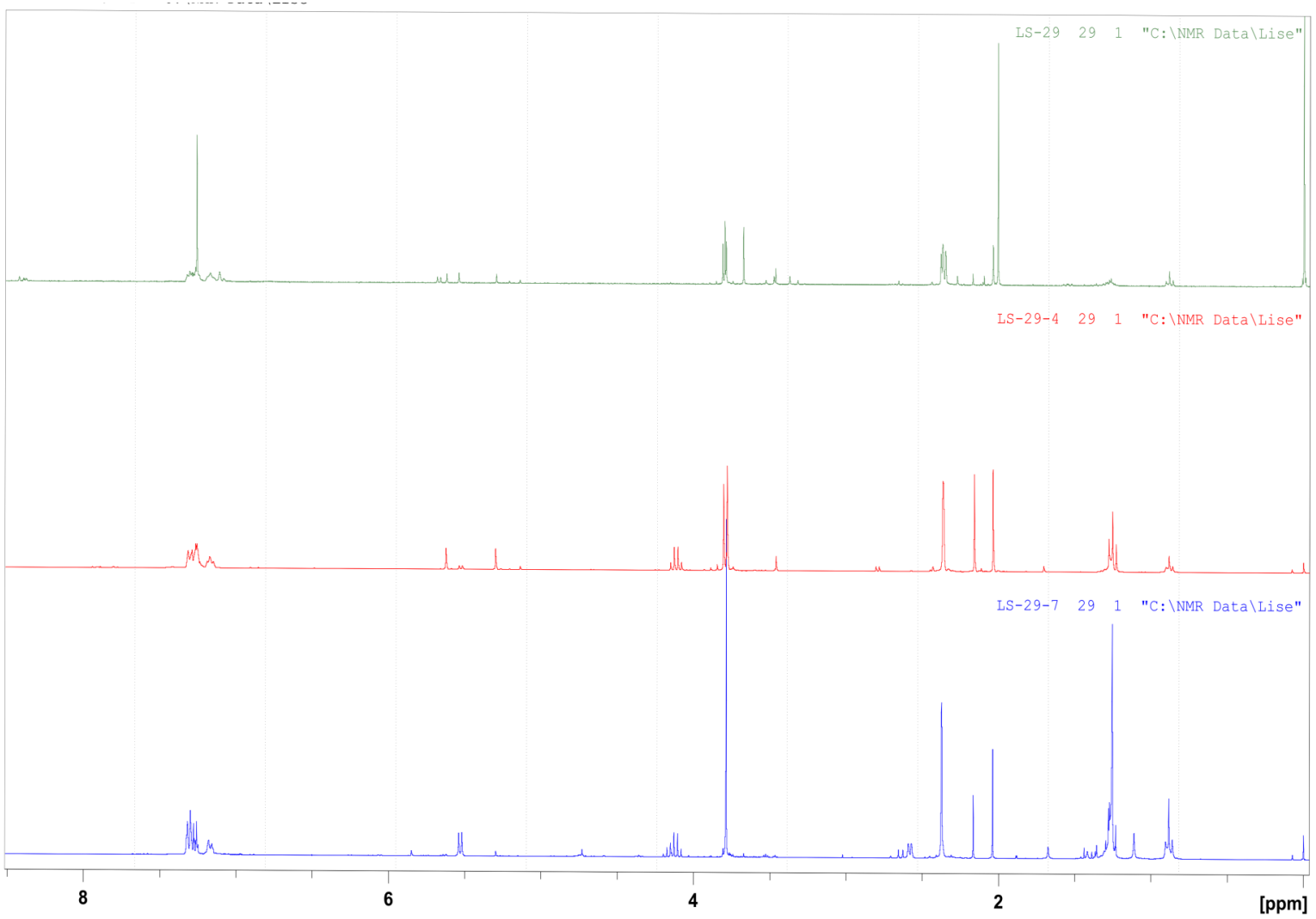


Appendix K.3; HSQC spectrum of compound 16a



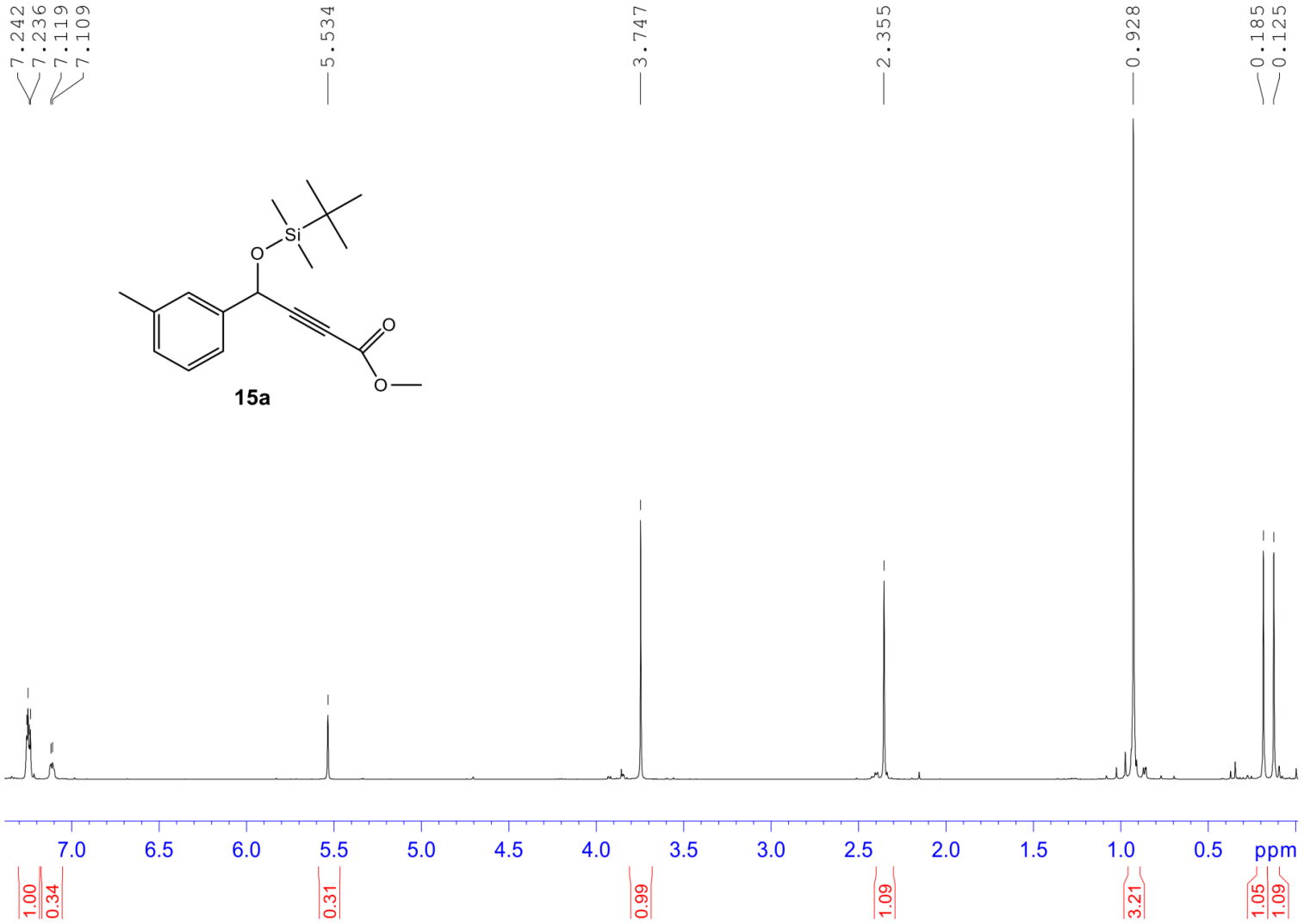
Appendix K.4; HMBC spectrum for compound 16a

L Spectroscopic data from Ritter reaction

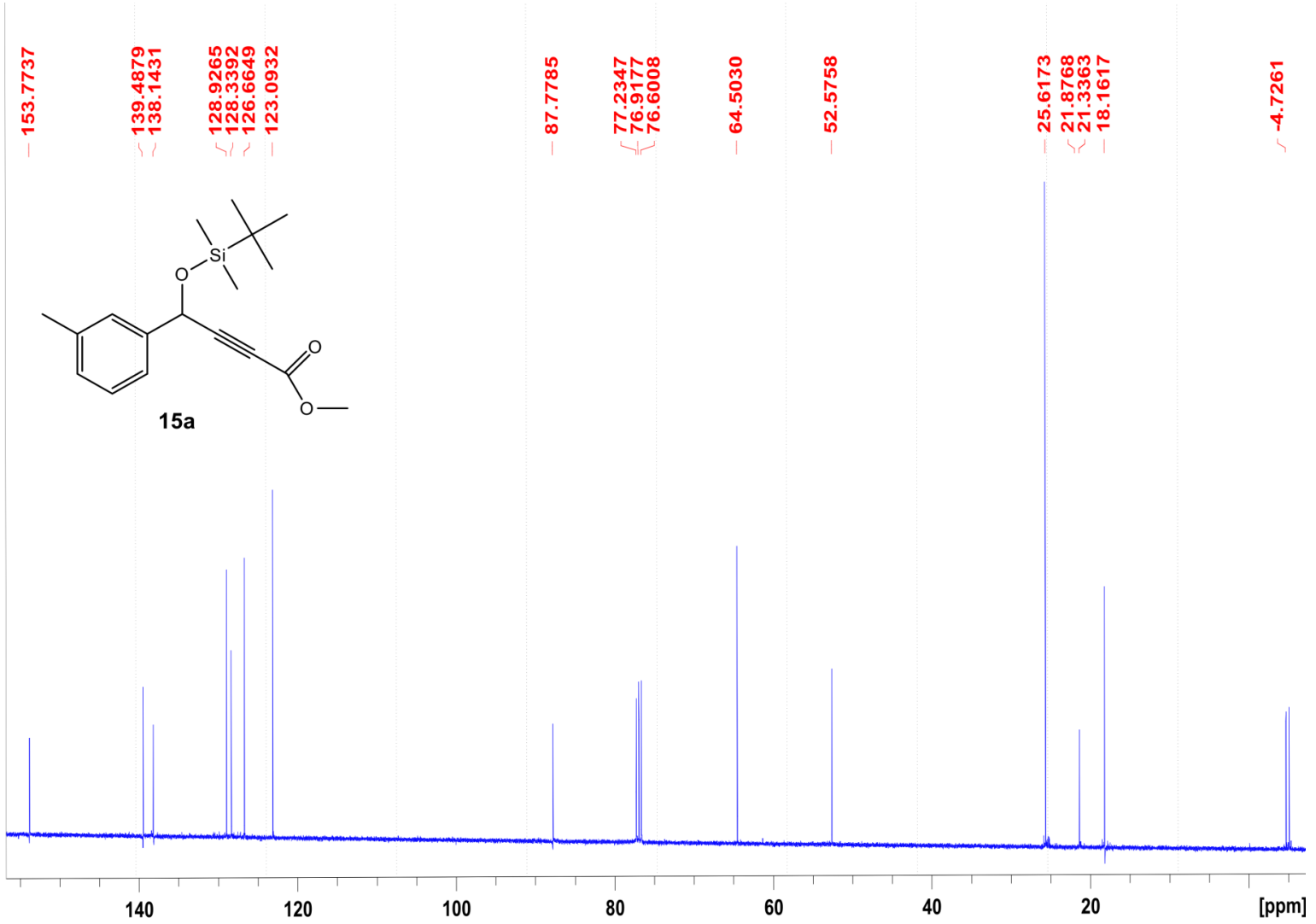


Appendix L; ^{1}H NMR spectrum from Ritter test reaction, crude and two different fractions from flash column chromatography

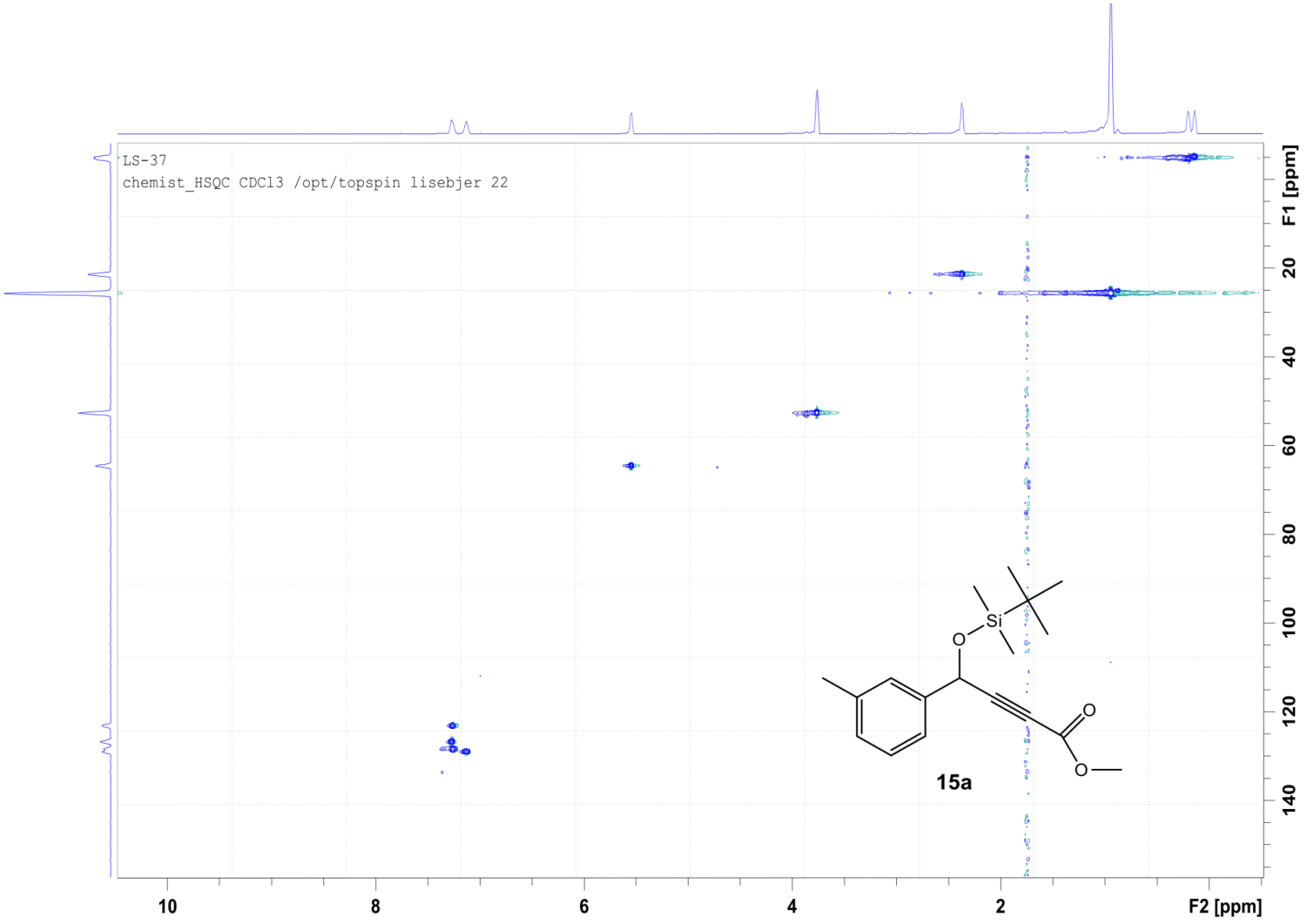
M Spectroscopic data of compound 15a



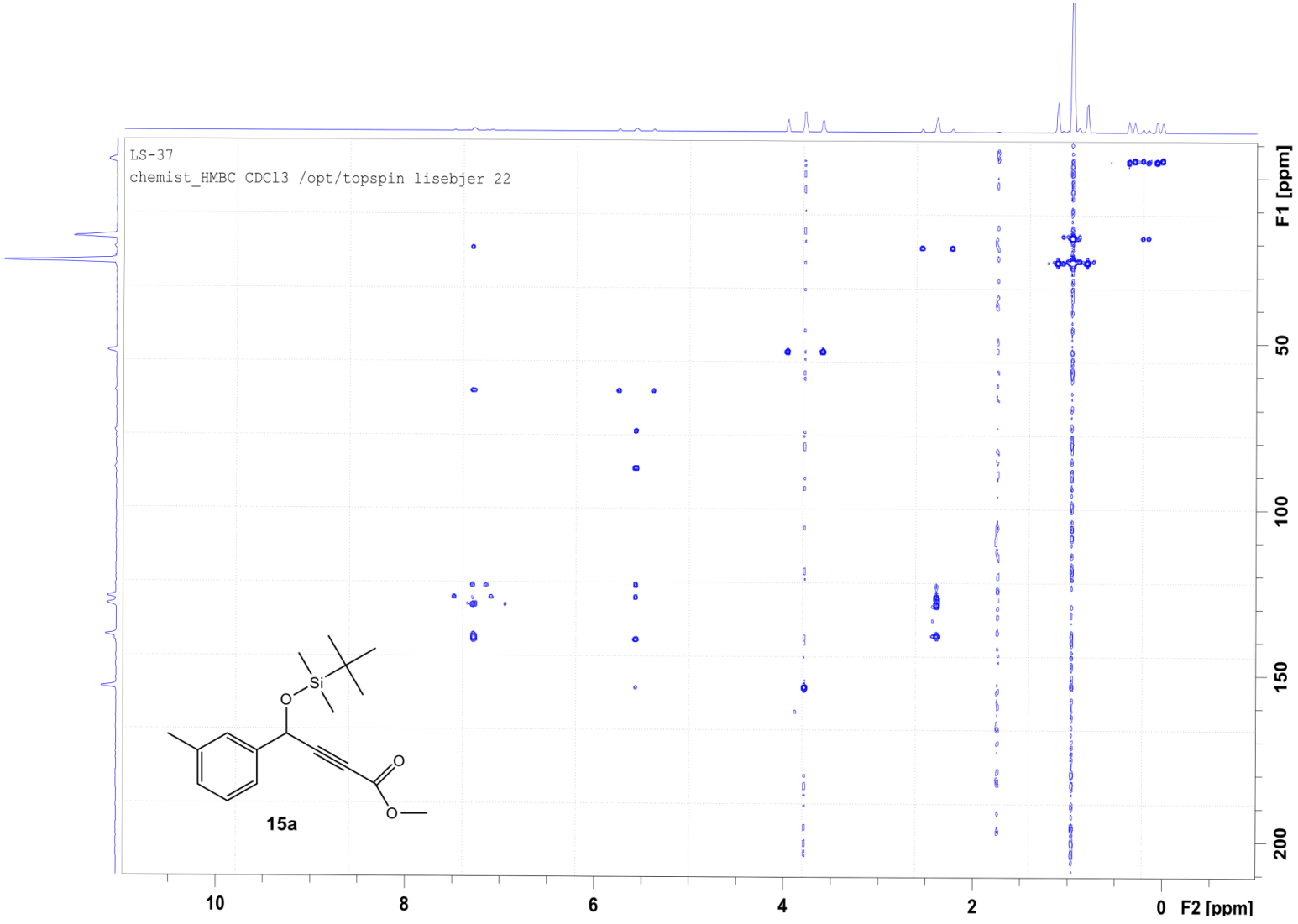
Appendix M.1; ^{1}H NMR spectrum of compound 15a



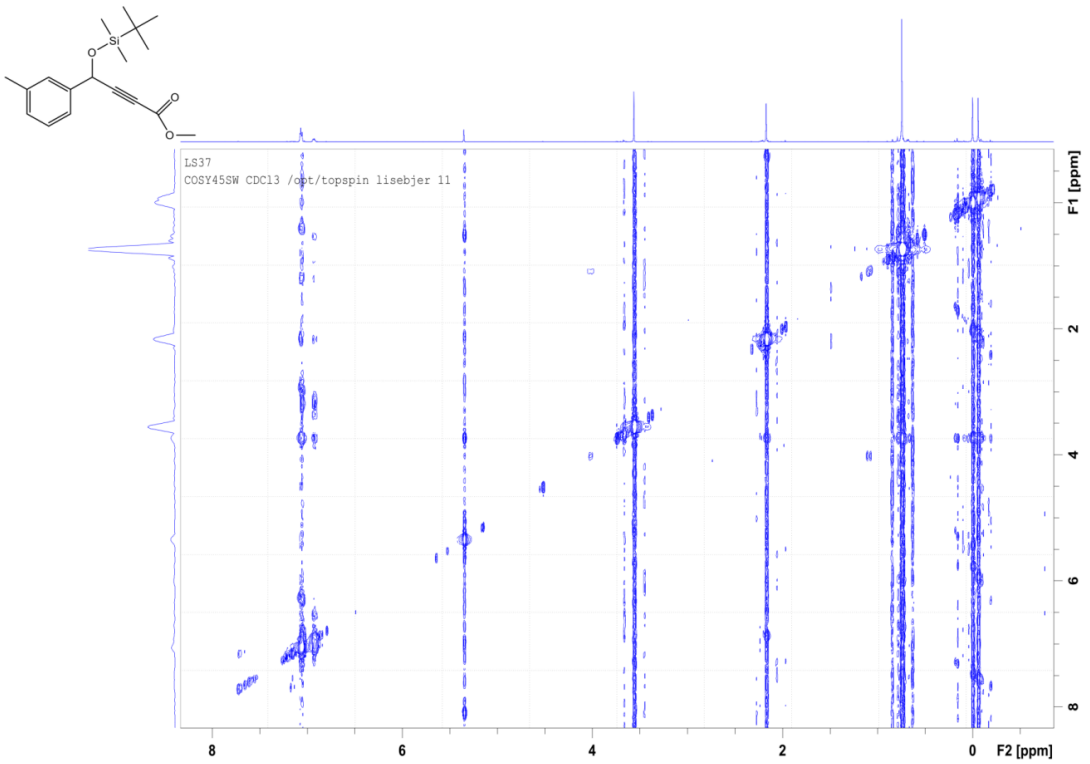
Appendix M.2; ^{13}C NMR spectrum of compound 15a



Appendix M.3; HSQC spectrum of compound 15a

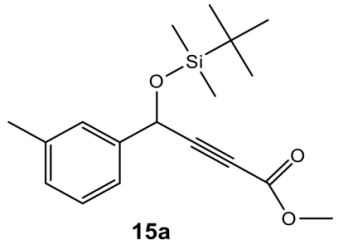


Appendix M.4; HMBC spectrum of compound 15a



Appendix M.5; **COSY spectrum compound** 15a

Elemental Composition Report

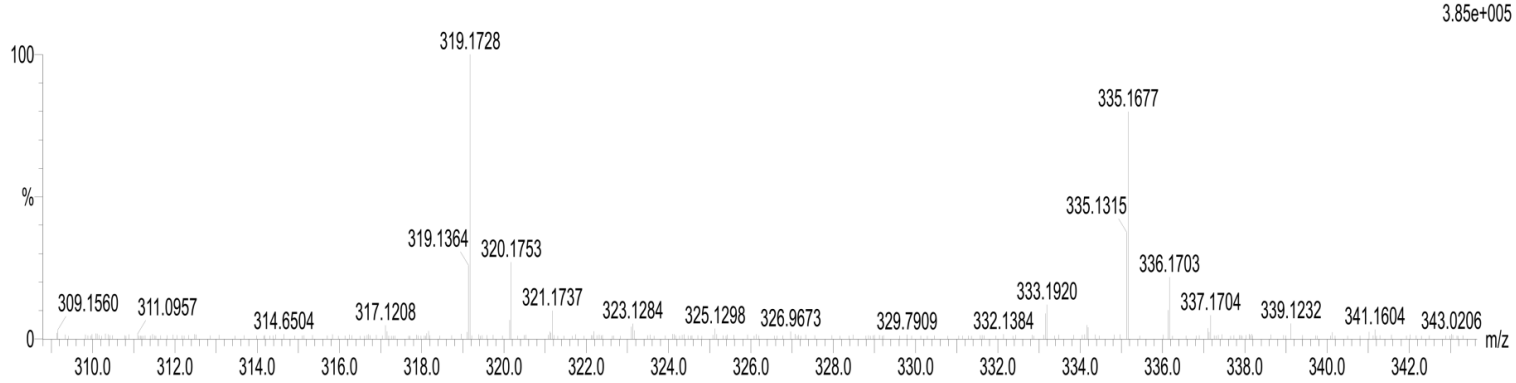


15a

Single Mass Analysis

Tolerance = 2.0 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
2443 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-200 H: 0-1000 N: 0-200 O: 0-200 Si: 0-4
2013-122 45 (0.896) AM2 (Ar,35000.0,0.00,0.00); Cm (24:45)
1: TOF MS ASAP+



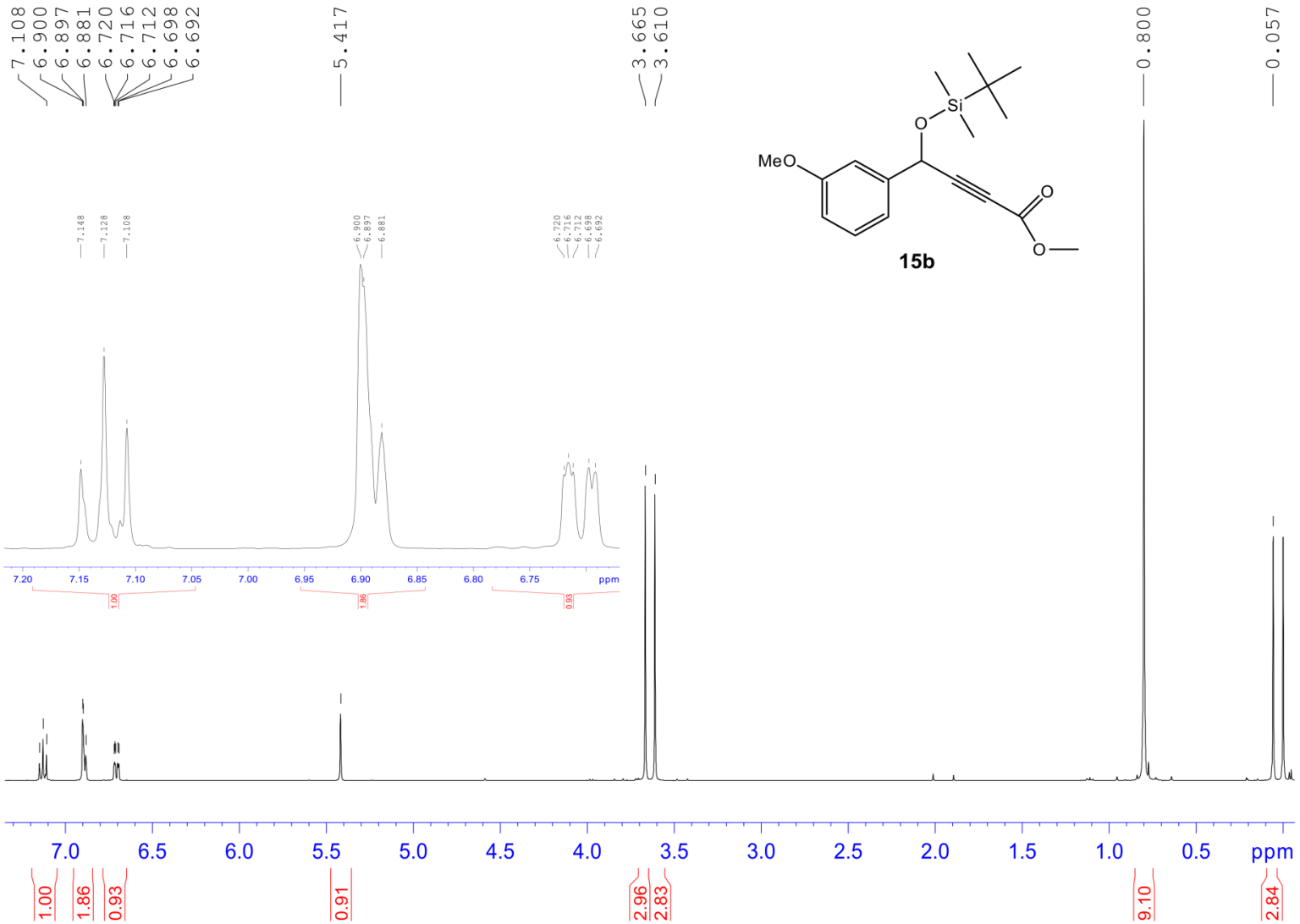
Minimum:				-1.5
Maximum:		5.0	2.0	50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
319.1728	319.1729	-0.1	-0.3	6.5	331.8	0.023	97.74	C18 H27 O3 Si
	319.1730	-0.2	-0.6	3.5	345.1	13.333	0.00	C11 H23 N6 O5
	319.1734	-0.6	-1.9	5.5	338.7	6.909	0.10	C17 H31 Si3
	319.1734	-0.6	-1.9	2.5	335.6	3.833	2.16	C10 H27 N6 O2 Si2

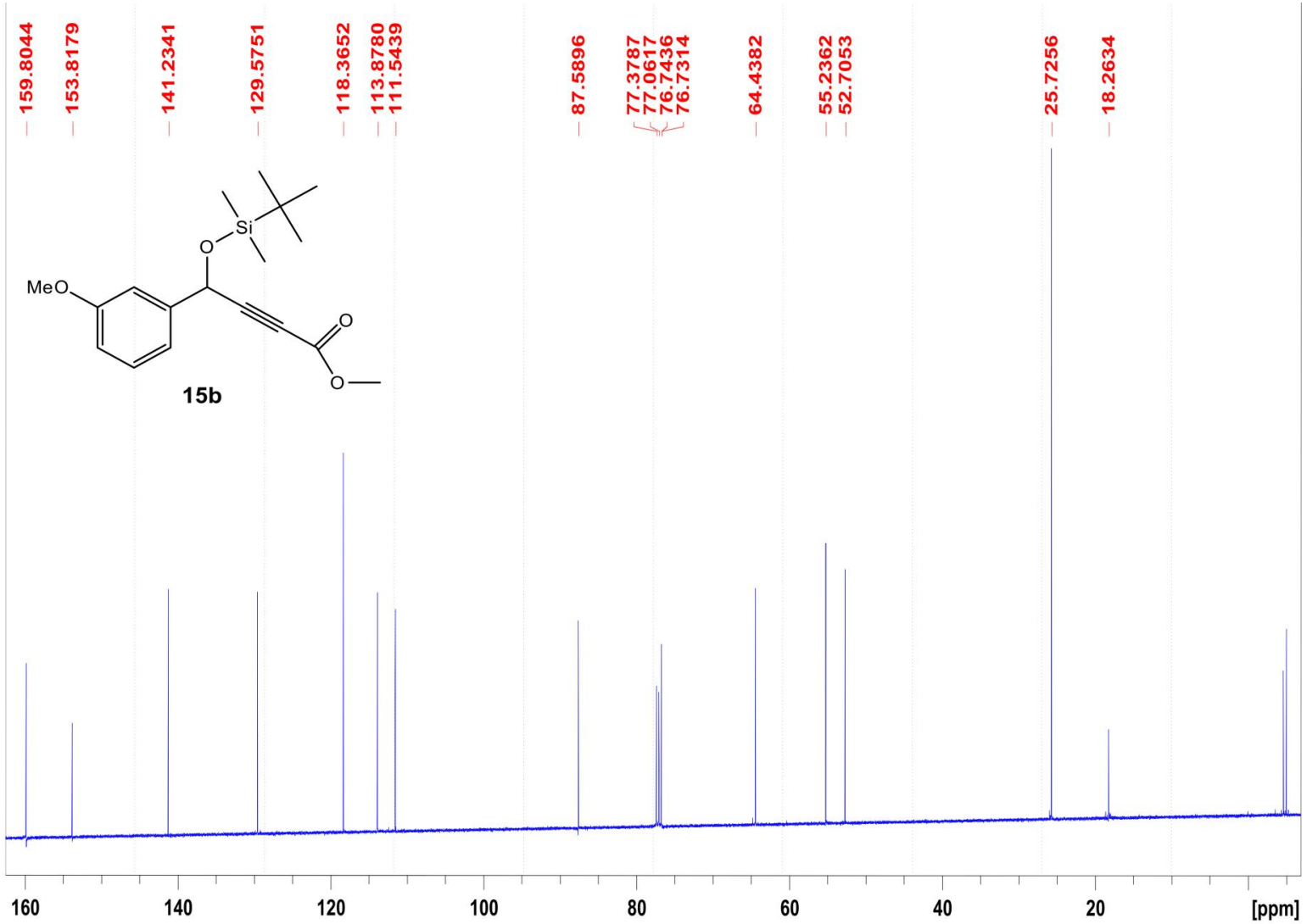
Appendix M.6; MS spectrum of compound 15a

Appendix M.7; IR spectrum of compound 15a

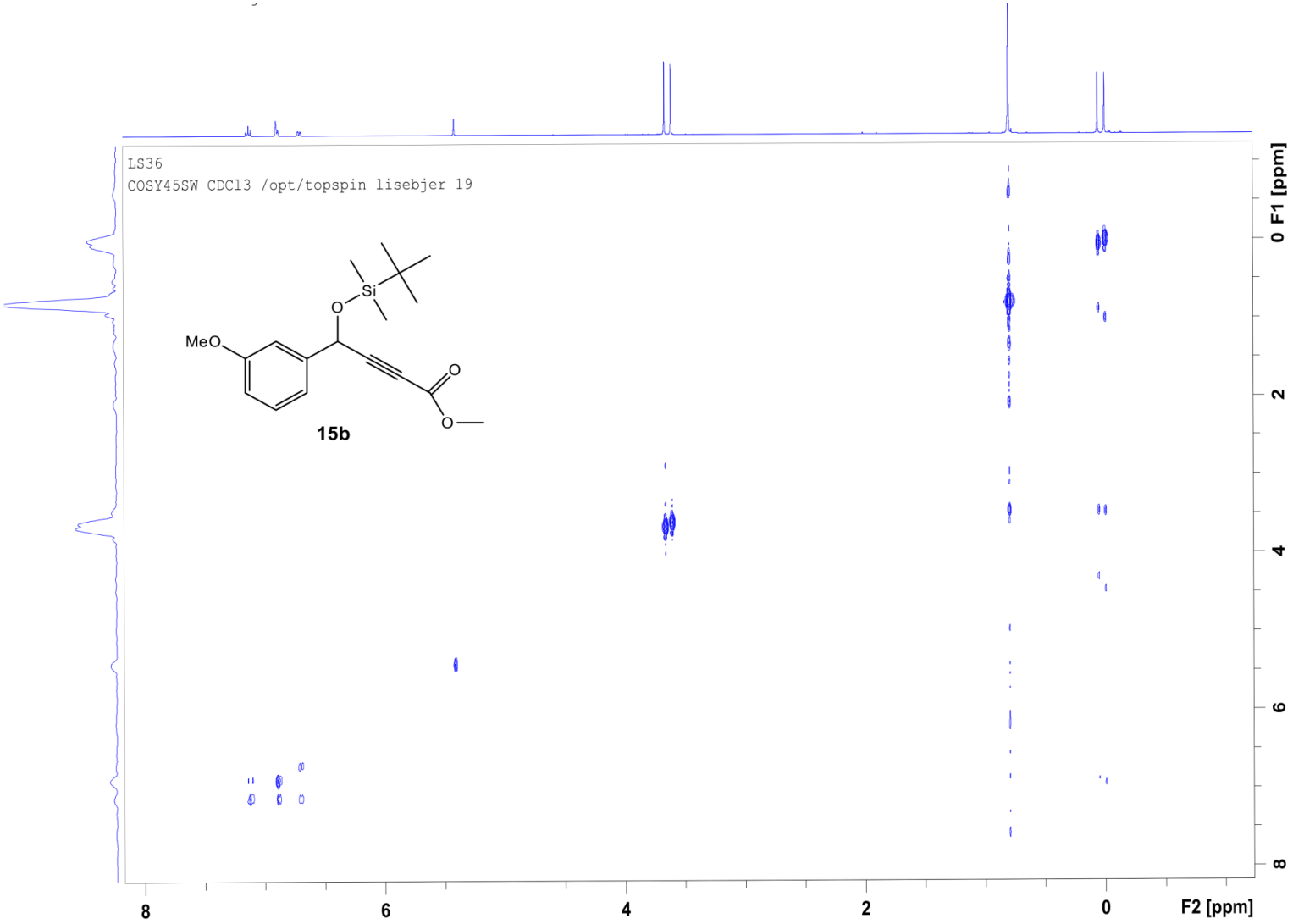
N Spectroscopic data of compound 15b



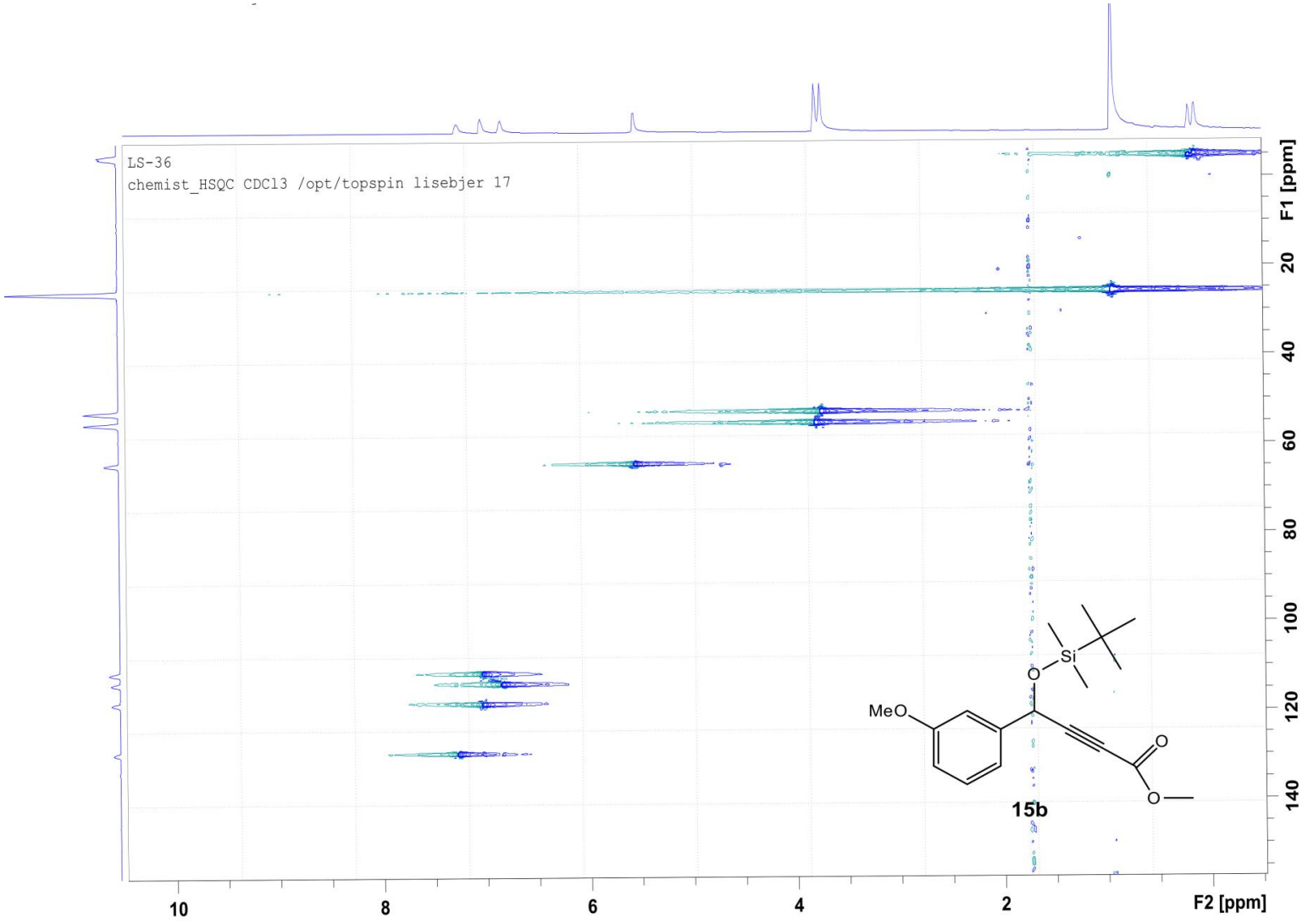
Appendix N.1; ^{1}H NMR spectrum of compound 15b



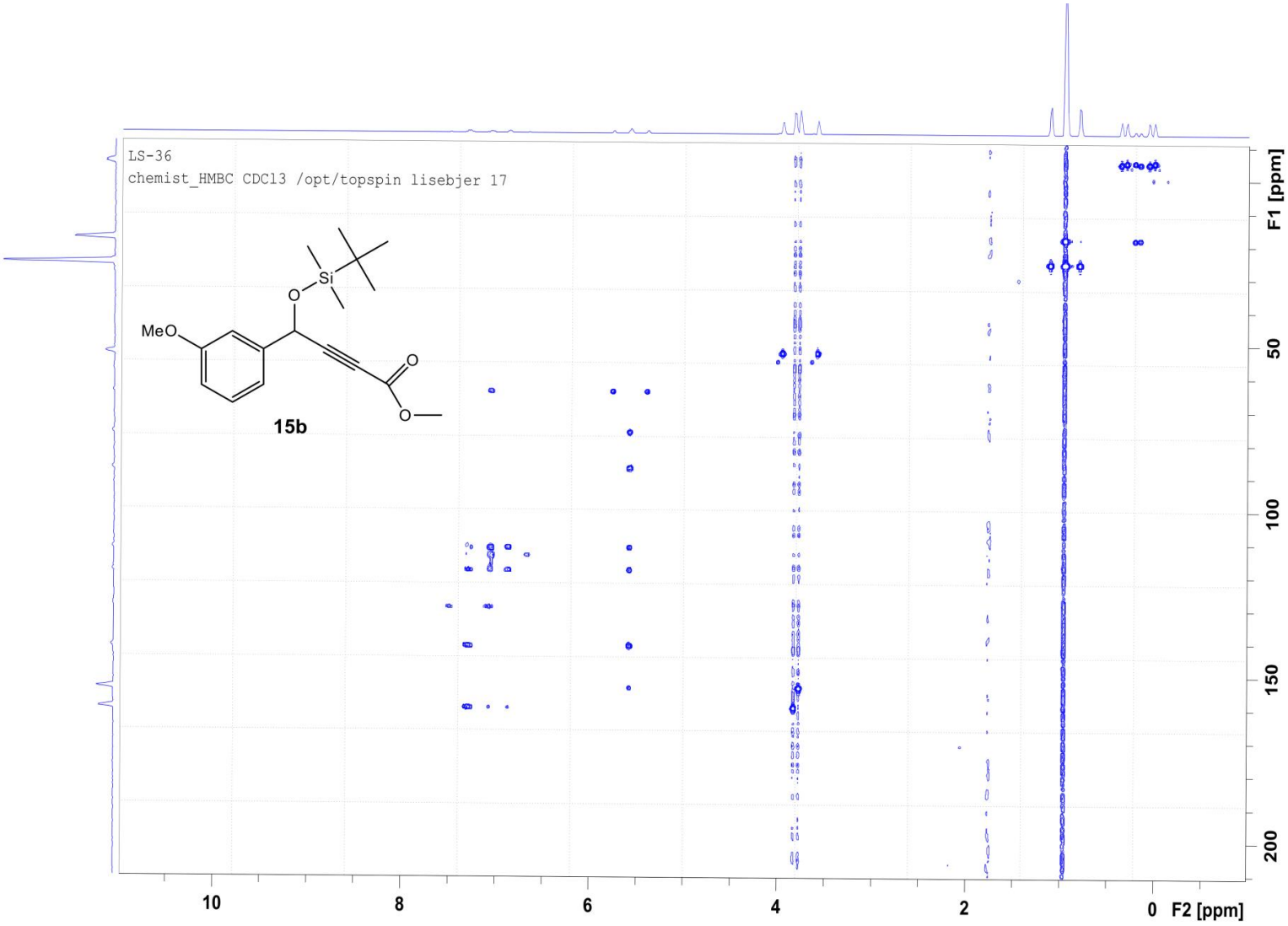
Appendix N.2; ^{13}C NMR spectrum of compound 15b



Appendix N.3; COSY spectrum of compound 15b



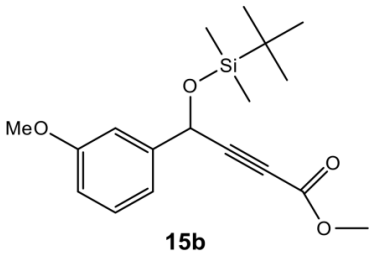
Appendix N.4; HSQC spectrum of compound 15b



Appendix N.5; HMBC spectrum of compound 15b

Single Mass Analysis

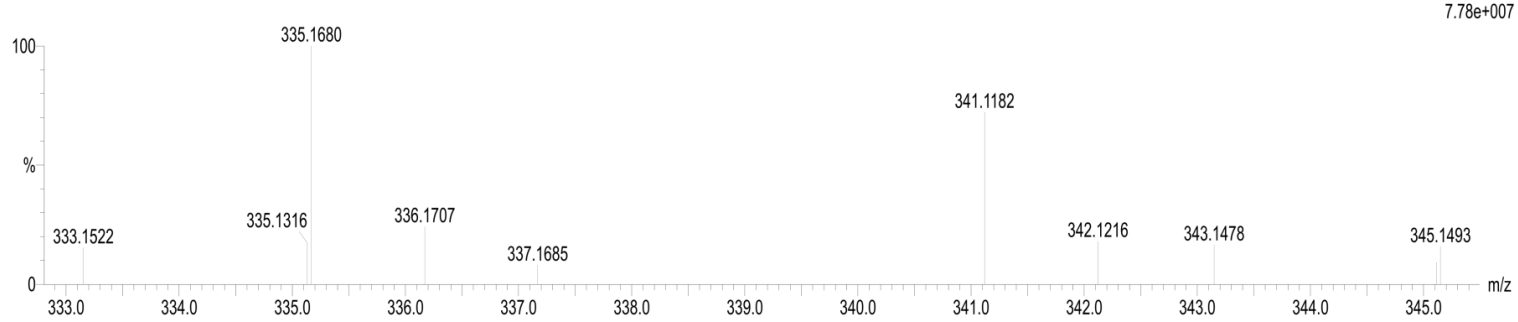
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



15b

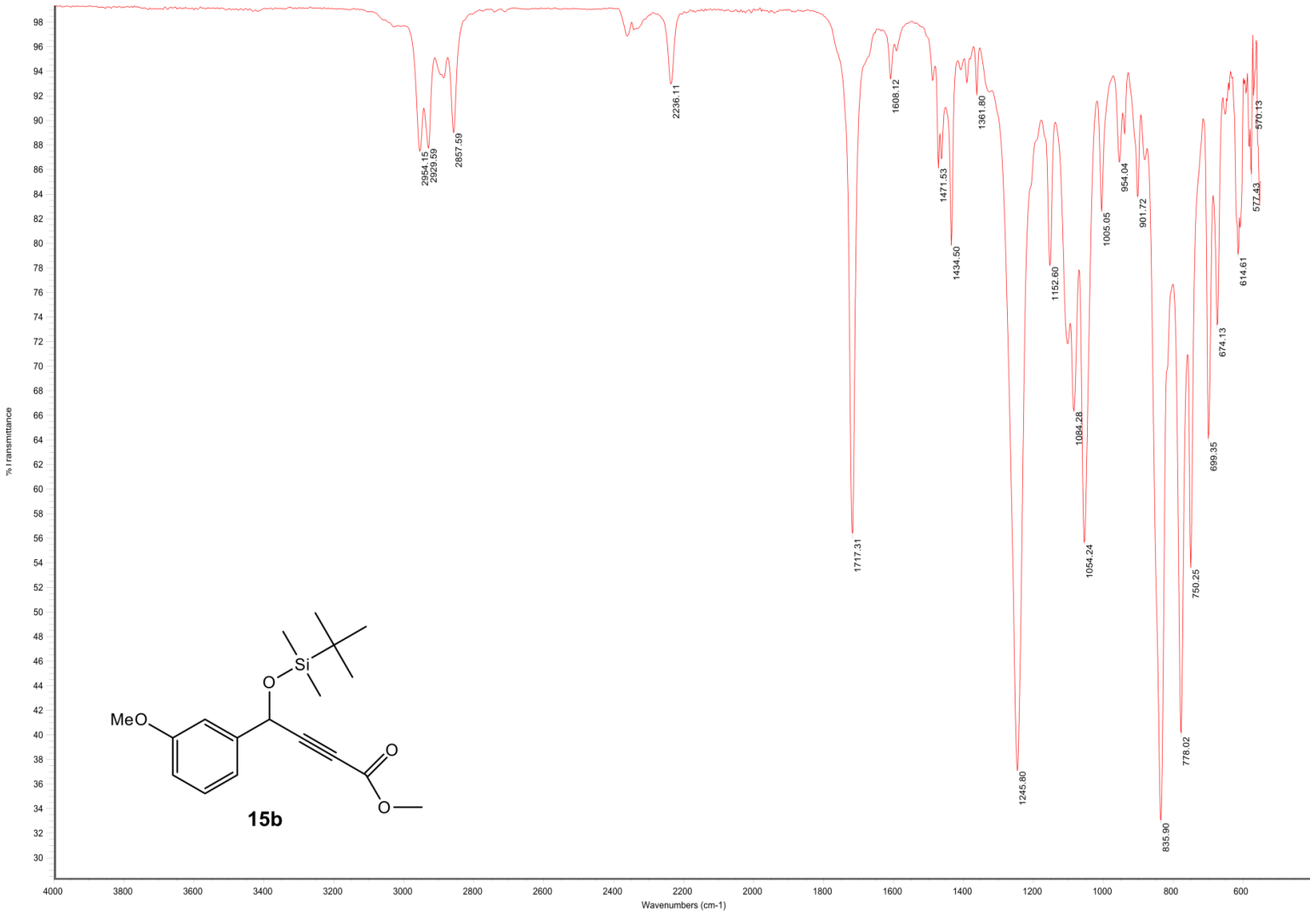
Monoisotopic Mass, Even Electron Ions
23584 formula(e) evaluated with 11 results within limits (up to 10 best isotopic matches for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-200 O: 0-200 S: 0-6 Cl: 0-8 Br: 0-8 Si: 0-2

2012-340 140 (2.740) AM2 (Ar,35000.0,0.00,0.00); Cm (75:198)
1: TOF MS ASAP+



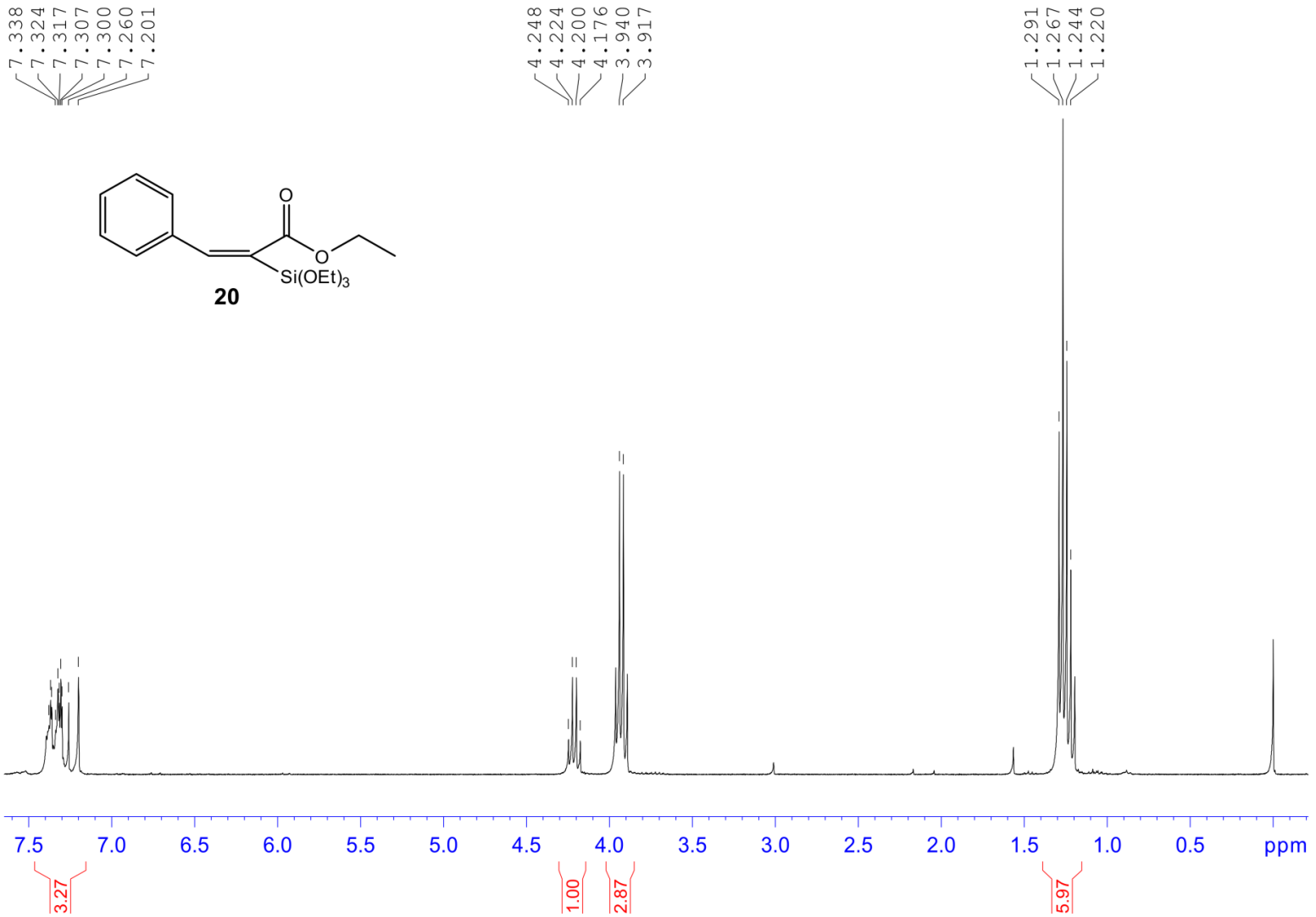
Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
335.1680	335.1679	0.1	0.3	6.5	36.0	0.099	90.59	C18 H27 O4 Si
	335.1681	-0.1	-0.3	6.5	38.3	2.413	8.95	C19 H27 O3 S
	335.1683	-0.3	-0.9	2.5	41.3	5.447	0.43	C10 H27 N6 O3 Si2
	335.1685	-0.5	-1.5	2.5	44.6	8.684	0.02	C11 H27 N6 O2 S Si
	335.1685	-0.5	-1.5	5.5	46.4	10.486	0.00	C18 H31 S Si2
	335.1684	-0.4	-1.2	-0.5	48.3	12.452	0.00	C3 H23 N12 O5 Si
	335.1686	-0.6	-1.8	-0.5	49.7	13.791	0.00	C4 H23 N12 O4 S
	335.1679	0.1	0.3	3.5	50.7	14.844	0.00	C11 H23 N6 O6
	335.1684	-0.4	-1.2	4.5	53.3	17.382	0.00	C7 H20 N14 Cl
	335.1677	0.3	0.9	-1.5	54.5	18.560	0.00	C6 H28 N10 S Cl Si

Appendix N.6; MS spectrum of compound 15b



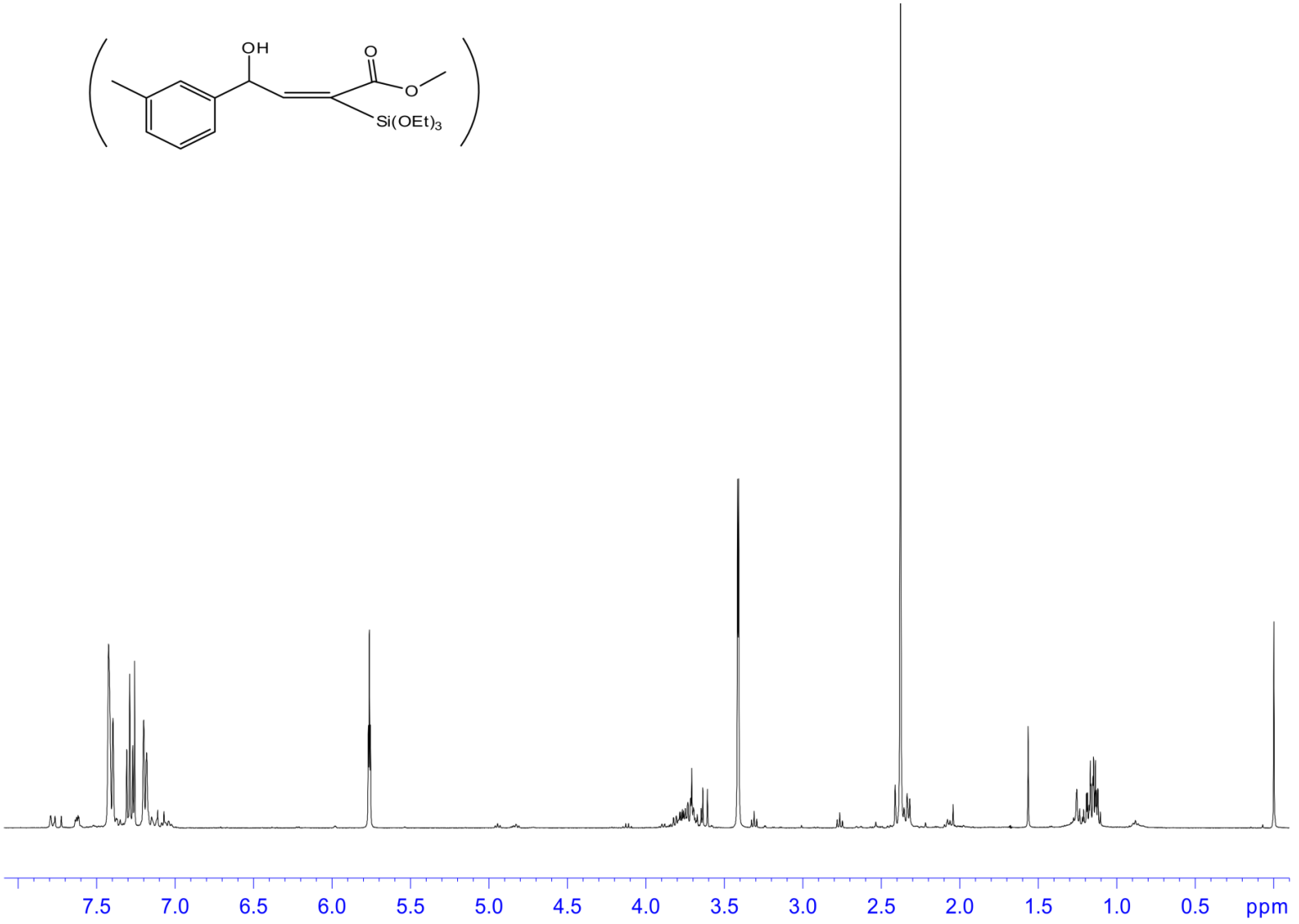
Appendix N.7; IR spectrum of compound 15b

O Spectroscopic data of compound 20

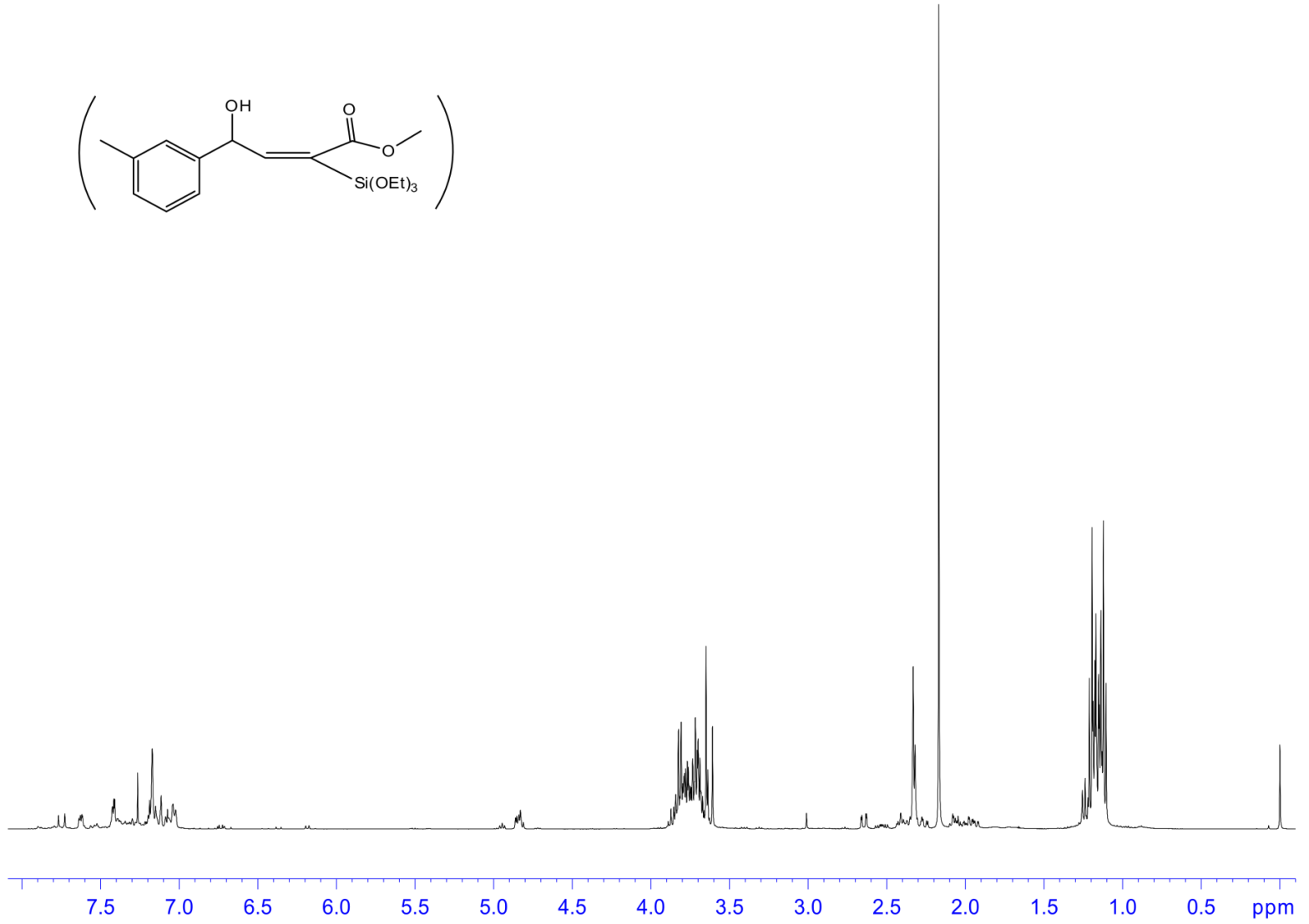


Appendix O; ^{1}H NMR spectrum of compound 20

P Spectroscopic data from attempted hydrosilylation



Appendix P.1; ^{1}H NMR spectrum for the UV-active fraction from attempt on hydrosilylation of compound 16a



Appendix P.2; ^{1}H NMR spectrum for the (UV-active?) fraction from attempt on hydrosilylation of compound 16a