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Vertical Diversity-Oriented Synthesis with Dibenzylideneacetones

Multivariate Optimization and Diversity Exploration

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Phenias Buhire

KJE-3900 Masters thesis in Organic Chemistry, May 2015

AKNOWLEDGEMENTS

First of all I thank God for creating and keeping us alive up this moment.

Secondly, I would like to thank my supervisor Assoc. Prof. Jørn H.Hansen for motivating me. He was always available for me and offered guidance and advice. His constructive advice helped me to complete the presented work. I am grateful to work under your supervision.

I would like to thank my co-supervisor Prof Tore Lejon for his guidance, help and encouragement during the lab work. The first part of the project was very challenging and it could not be completed without his guidance.

I would like also to thank Dr Taye Beyene Demissie for providing me DFT data and Dr Johan Isaksson for helping me with 2D-NMR spectra.

Many thanks goes to engineers Jostein Johansen, Truls Ingebrigtsen and Arnfinn Kvarsnes for giving me help with HRMS, GC-MS and IR.

I also wish to thank Dr. Muhammad Zeeshan for his advice and guidance both in chemistry and social life.

I am also grateful to Yngve Guttormsen for his friendship and help with diverse thing.

Another thank goes to my office co-worker, lab-fellow, Aya Ismael for her moral support.

Lastly, I thank my family Ernest, Marceline, and my younger sister Denise for their moral social support.

ABSTRACT

DOS was planned from dibenzylideneacetone to generate compound library with structural diversity, which can undergo further transformations. In the presented work, dibenzylideneacetone was cyclized under Robinson Annulation reaction. The resulting cyclization product was optimized using Multivariate response surface method. Response surface analysis helped to determine both significant variables used during the optimization process and to generate a model describing the variation of response according to the experimental variables.

The Robinson Annulation product was studied in a range of transformations, for instance Hydrogenation, Krapcho decarboxylation, inverse electron demand Diels-Alder, Luche reduction and Alkylation reaction. All the attempted reactions were found successful, except reduction and cycloaddition reactions. Further work on unsuccessful reactions could not be carried out due to time constraints. Various new compounds were synthesized during this work.

Dibenzylideneacetone can play various functions in synthetic chemistry as precursor to other compounds. It is used to make ligands, for instance dibenzylideneacetonedipalladium (0) which is utilized as a homogeneous catalyst in organic synthesis. Dibenzylideneacetone can be used to synthesize heterocyclic organic compounds. There is no available research conducted to explore its benefits to synthesize compound libraries.

LIST OF ABBREVIATIONS

^{1}H-NMR	Proton nuclear magnetic resonance
^{13}C-NMR	Carbon nuclear magnetic resonance
GC	Gas chromatography
MS	Mass spectrometry
HRMS	High-Resolution Mass Spectrometry
IR	Infrared (spectroscopy)
TLC	Thin layer chromatograph
δ	Delta, used in NMR data report to signify chemical shift.
EI	Electron ionization
ppm	Part per million
cm^{-1}	Reciprocal centimeters
DOS	Diversity-Oriented –Synthesis
TOS	Targeted – Oriented Synthesis
EWG	Electron-Withdrawing Group
EDG	Electron- Donating Group
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
IEDDA	Inverse Electrons Demand Diels-Alder
TBE	Tricyclic Bis-Enones
EtOAc	Ethyl acetate
DBU	1,8-Diazabicyclo[5.4.0] undec-7-ene
DMF	N,N dimethylformamide
DMSO	Dimethylsulfoxide

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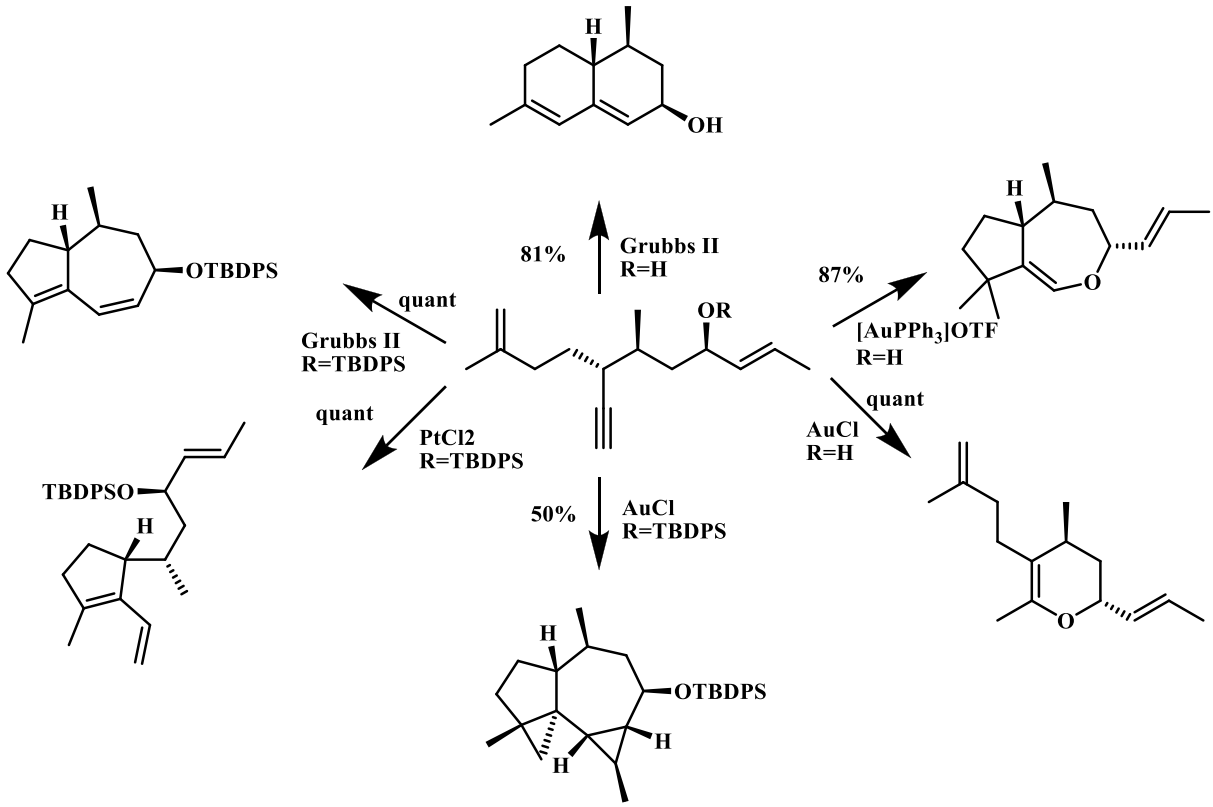
1. INTRODUCTION

1.1. Diversity-oriented library synthesis (DOS)

There has been a significant revolution in library construction and synthetic methods development of new drugs in the last decades[1]. Target-oriented synthesis (TOS) focuses on transformation of one region to produce a specific molecule. The TOS method has been used since in many year to build compound libraries, but it was recently considered as a relatively weak strategy for library design. [1-2] Diversity-oriented library synthesis (DOS), which aims to produce chemical libraries that are representative of compounds that have large structural diversity, was introduced to complement TOS. Stereochemical, skeletal, appendage and functional groups diversity describe the structural diversity of a molecule.[2- 5] . Example of DOS is given in ***scheme 1*** where different reagents were used to transform one aliphatic compound to six distinct compounds with skeletal and stereochemical diversity.

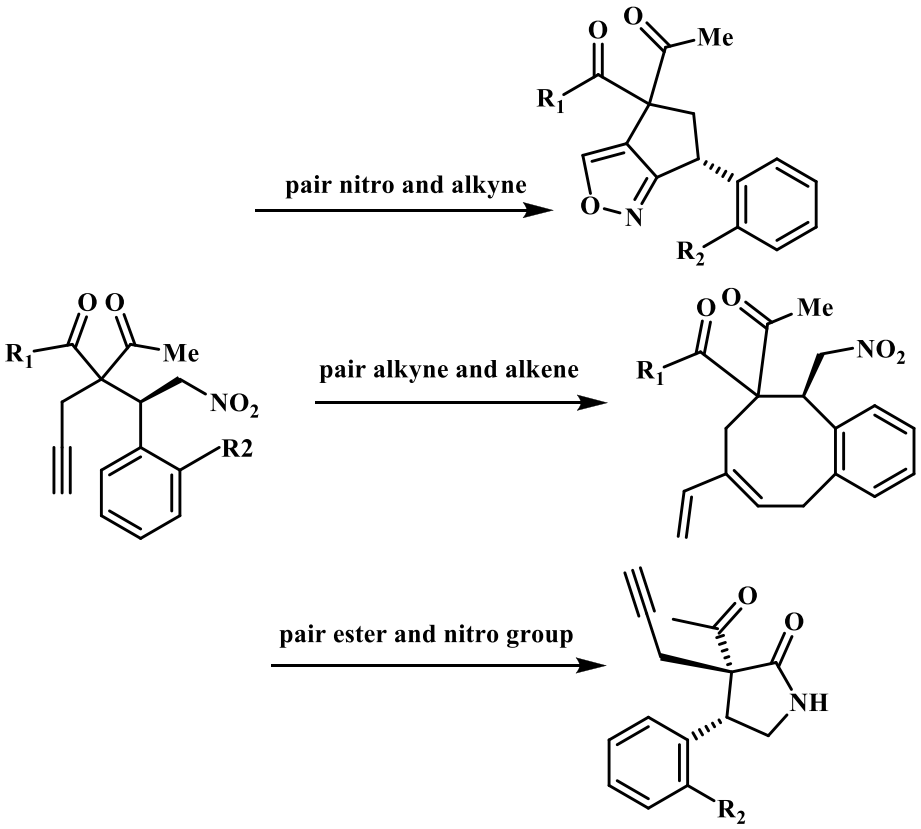


Scheme 1: A ring- distortion strategy to construct stereochemically complex and structurally diverse compounds from natural product.[6]

1.1.1. Synthetic strategies for skeletal diversity.

There are two kind of strategies, a reagent-based strategy (RBS) and a substrate-based strategy (SBT) that are used to generate skeletal molecular diversity.

In RBS, different reagents are used to transform one molecule into many compounds with skeletal diversity.[2,4,7] Example of a RBS is given in ***scheme 2*** where some functional groups (alkyne, nitro and ester) of compound **17** were paired with various reagents to generate compounds with different skeletons.



Scheme 2: Different pairing reactions of the densely functionalized compound 17 gave access to distinct molecular scaffolds 18-20. [8]

Whereas, SBT involves the use of the same reagents to transform different compounds containing pre-encoded information into distinct products.[2] Example of a SBT to generate molecular diversity is shown in ***Fig 1*** where three different compounds are transformed to various compounds with the same reagent.

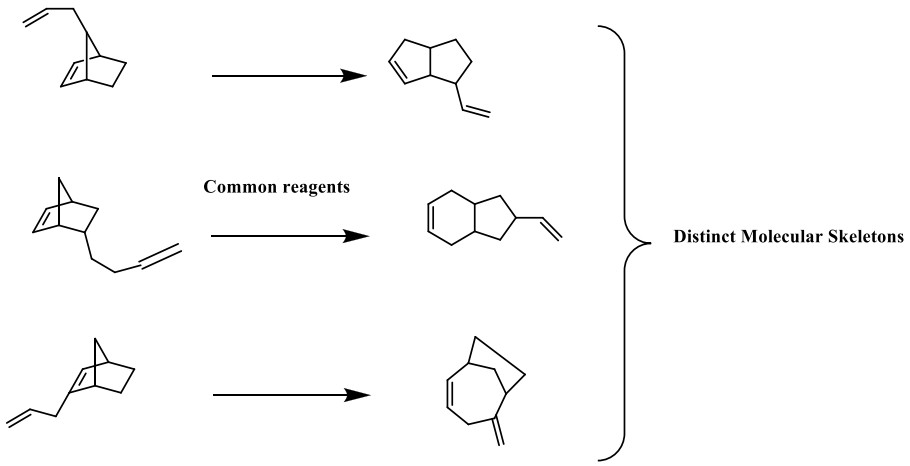


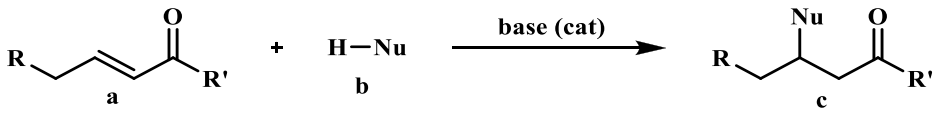
Fig 1: Substrate- based strategy.[2]

1.2. Robinson Annulation

The Robinson Annulation reaction is useful in synthesis of cyclic organic compounds. This reaction is a combination of Michael addition and intramolecular Aldol condensation reaction.[9]

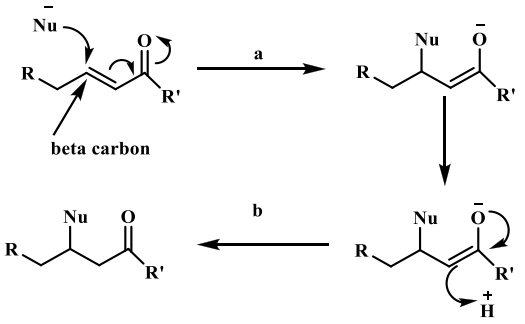
The reaction involving a base catalyzed addition of a nucleophile (Michael donor) to activated π-system (Michael acceptor), refers to the Michael addition reaction. The π-system is activated when it is attached to an electron withdrawing group or negative charge stabilizing group. Nucleophile can be generated with deprotonation of CH-activated compounds like β-dicarbonyl, ketones, aldehyde and nitrile compounds. Michael reaction which involves direct attack of a nucleophile to β-carbon of α, β unsaturated carbonyl compounds is called conjugate addition or 1, 4-addtion.[10, 9] An example of Michael addition reaction and mechanism is shown in ***scheme 3*** and ***4.***

Nucleophile **b** attacks directly β -carbon of unsaturated compound **a** to produce compound **c.** Base can deprotonate hydrogen of nucleophile before or after nucleophile attack. Mechanism of this reaction is shown in ***scheme 4***.



Scheme 3: Michael reaction scheme.

Mechanism of 1,4 conjugate addition Michael reaction is shown in steps **a** and **b** in ***scheme 4*** After nucleophile attack to β-carbon of unsaturated ketone **a**, electrons are delocalized in conjugated system **b** followed with protonation of α—carbon of unsaturated ketone.



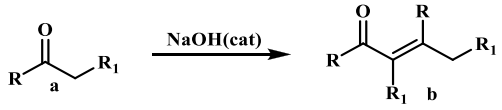
Scheme 4: Conjugate addition mechanism.

Tremendous progress has been made in fields of stereoselective and catalytic Michael reactions. Asymmetric organocatalytic Michael reaction has been used in targeted and diversity oriented synthesis to generate optical active natural products. [11-12] Oxa-Michael reaction that involves the addition of an oxygen of a nucleophile to activated π-system compounds has been used to produce stereoselective compounds. [13-14] Aza-Michael reaction (conjugate addition of amines to α, β unsaturated compounds) has been used to synthesize stereoselecive cyclic or acyclic nitrogen chiral compounds [15] and optical active chiral amines compounds.[16-17] Sulfa-Michael reaction has been used to synthesize compouds with highly enantioselective organocatalylic sulfa compounds.[18] Phospha-Michael reaction has been used to synthesize a recylable catalysis [19] and a magnetic recylable heterogeneous organic base.[20]

Aldol reaction

The reaction allows molecular diversification by the reaction of enols or enolates with carbonyl compounds (ketones and aldehydes), refers as Aldol reaction. The resulting β-hydroxy carbonyl product undergo acidic or basic hydrolysis to give α, β unsaturated enones.[21-22] Example of Aldol condensation reaction is shown in ***scheme 5.***

Base deprotonates the hydrogen of α-carbon of ketone compound **a** to generate enolate of compound **a.** The reaction between compound a and its enolate forms β-hydroxy ketone which undergo dehydration to give α, β unsaturated ketone (**b**).



Scheme 5. Aldol reaction

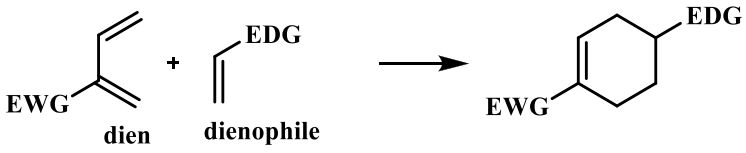
1.3 Inverse electron demand Diels-Alder reaction (IEDDA).

IEDDA [4+2] cycloaddition reaction is a useful reaction to synthesize six membered ring compounds.

The reaction involving an electron–poor diene (4π electrons) and an electron-rich dienophile group (2π electrons) refers to [4+2] cycloaddition IEDDA reaction. Dien is a conjugated double while a dienophile can be a double or a triple bond. Substituted diene with electron-withdrawing group and a dienophile with an electron–donating group have been seen to improve the reaction rate. The local symmetry of molecular orbitals involved in reaction can be used to explain the stereospecificity of the reaction. Molecular orbitals involving in reaction are HOMO of a dienophile and LUMO of a diene. [23-28]

Example of IEDDA reaction is shown in ***scheme 7*** and orbital overlap ***(Fig 2).***

Electrons flow from dienophile to dien in ***scheme 7***. Electron withdrawing group (EWG) and electron donating group (EDG) activates compounds containing them.



Scheme 6. Inverse electrons demand Diels-Alder.

Molecular orbital overlap between HOMO of an electron rich dienophile and LUMO of an electron poor dien is shown in ***Fig 2***

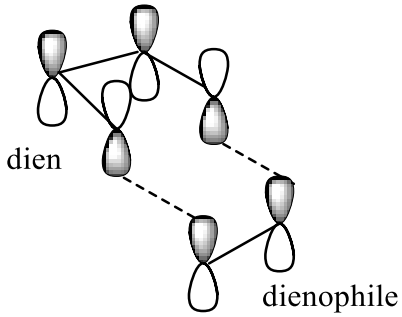


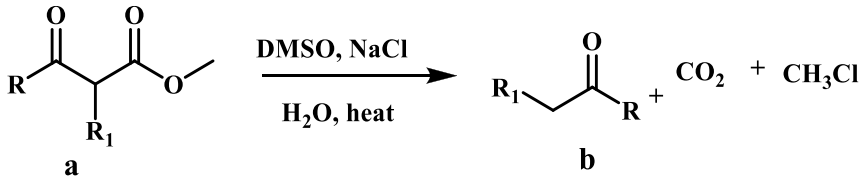
Fig 2: Molecular orbital overlap in IEDDA

1.4 Krapcho reaction.

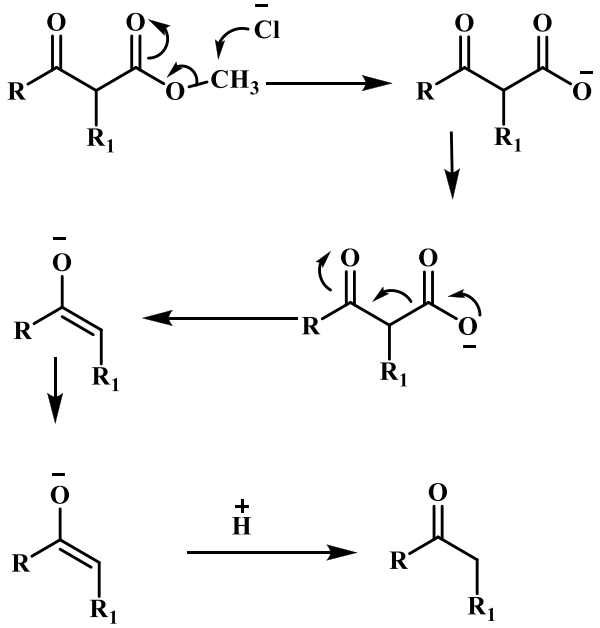
The reaction is a useful to remove an ester group from organic compounds.

The alkali salt promoted loss of alkoxylcarbonyl group from esters by heating in a polar aprotic solvent refers to Krapcho decarboxylation reaction.[29- 31]

Example of Krapcho reaction and mechanism is shown in ***scheme 7*** and ***8*** Chlorine ion (Cl^-) takes away methyl of ester of compound **a** and promotes the cleavage of ester group to generate compound **b,** see ***scheme 7*** The removal of ester methyl group and its cleavage occurs simultaneously, see mechanism in ***scheme 8***.



Scheme 7: Reaction equation



Scheme 8: Proposed salt-assisted Krapcho decarboxylation mechanism

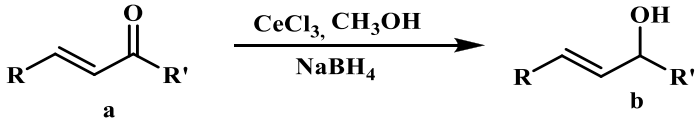
1.5 Luche Reduction

The reaction is usefully in reduction of ketones of α, β unsaturated ketones compounds.

The reaction that involves a combination of lanthanide and sodium borohydride to reduce α, β unsaturated compounds to the corresponding alcohols, refers to Luche reduction.

Lanthanide catalyzes the formation of alkoxyborohydride and its coordination to oxygen of a solvent makes proton of alcohol to be more acidic which makes it easy to be abstracted by oxygen atom of the carbonyl group.[32-33]. Example of Luche reduction reaction is shown in ***scheme 9***.

Cerium (Ce^{3+}) coordinates to oxygen of methanol and facilitates the formation of methoxyborohydride. Coordination of $Ce^{3+}$to oxygen of carbonyl compound **a**, which makes carbon of carbonyl group electron deficient, which is then attacked by methoxyborohydride to generate compound **b**, see ***scheme 9***.

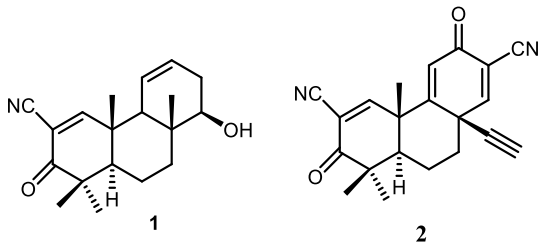


Scheme 9*:* Reaction equation

1.6 Uses of bis-enone compounds

Enones play various important roles in synthetic organic chemistry, some used, as basis compounds to make other compounds and others are medicines used to treat diverse diseases.

Tricyclic bis-enones (TBE-31) derivatives are types of enones, which have been used in medicine to treat different diseases such as cancer, inflammation, neurological disorders, and pathologies involving oxidative stress and to stimulate bones and cartilage growth.[34 - 37]



TBE-31 and its derivatives

1.7 Response surface method and its principles

The yield obtained after running experiment is influenced with a number of experimental variables (eg. Concentration of reagent, temperature, pH). The problem is to know how experimental variables contribute to observed results and how to adjust them in order to improve the yield. By means of response surface modelling, it is possible to determine the response surface model describing the variation of yield according to experimental variables and their settings. With response surface analysis it is possible to see how the yield varies according to variation of experimental variables, which helps to find out the optimum conditions.[38-42]

1.7.1. Variables, experimental domain and experimental screening.

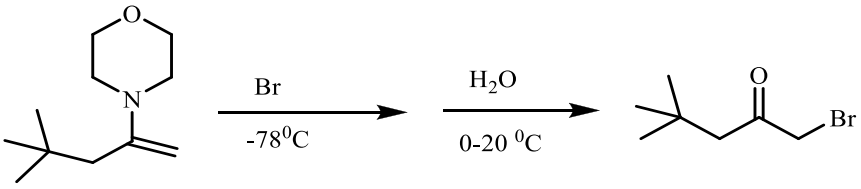
The term variable refers to experimental factors like, rate of adding reagents, reaction temperature, pH of the reaction, solvents, concentration of reactants and stirring rate. Variable, which can be changed to any value over its range of variation, refers to a quantitative variable. During a synthetic process, experimenter can decide the minimum and maximum value for all experimental variables that are used. Experimental domain refers to fixed experimental space between minimum and maximum value of the variation of the experimental variables.[42]

Experimental variables influence the obtained yield in a different way and some may not have a significant influence on response, the problem is to predict which variables are more important. Experimental screening aims to identify significant experimental variables. In screening it is possible to find out both individual and interaction effect of variables on the yield. The experimental screening results help to know which variables should be controlled.[42-44]

1.7.2 Experimental design

By means of two-level factorial design, each experimental variable can take two values, one at low level and another at high level. A full factorial design is a type of two-level factorial design, which shows all possible combinations of levels of experimental variables. A full factorial design representing a number of variable **m** studied at two level a number of possible experiment to run is represented with $\mathbf{2^m}$.[42,41]

Example of experimental design: Bromination of an enamine.



Scheme 10: Bromination reaction.[42]

First step is to determine variables and experimental domain before designing an experiment.

Table1 shows variables (x_1, x_2 and x_3) and their experimental domain where each variable has low level (-) and high level (+).

***Table 1*:** Variables and experimental domain.

Variables	experimental domain	
	(-) low level	(+) high level
x_1: bromine concentration (mol/dm^3)	0.25	0.50
x_2: bromination time (min)	2	5
x_3: hydrolysis time (min)	5	10

Experimental design full factorial design.

For a full factorial design, a number of possible runs is z^m where **z** represents levels of each variable and **m** is a number of all variables involved in reaction. In case of bromination of enamine possible runs is $\mathbf{2^3}$. All possible combination of settings of experimental variables is shown in ***table 2.***

***Table 2*:** Full factorial design 2^3

Exp no	x_1	x_2	x3
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	-	-	+
7	-	+	+
8	+	+	+

1.7.3 Taylor polynomial model

The model can be used to evaluate the influence of each experimental variable on the response and assess the significance of each term in the model.

The model describes the variation of response (y) in experimental domain according to settings of experimental variables (x_1, x_2, … etc). Taylor polynomial model is written as:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \beta_{12} x_1 x_2 + \ldots \beta_{ij} x_i x_j + \ldots + \beta_{11} x^2_1 + \ldots \beta_{kk} x_k + e$$

Polynomial model coefficients ($\beta_0, \beta_1, \beta_2, \ldots, \beta_{ij \ldots}$ etc) are called model parameters which can be estimated with multiple linear regression method.

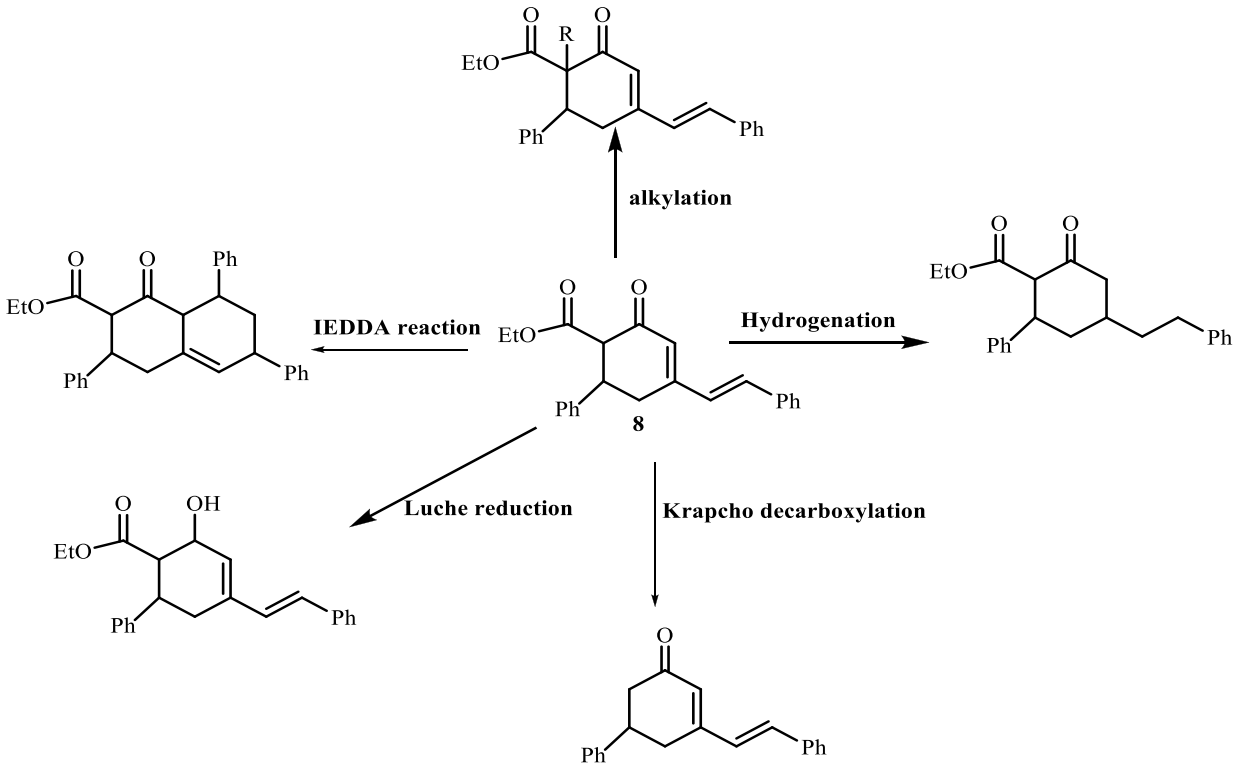
Estimation of the response when all variables are set zero is represented with β_0, linear coefficients $\beta_1, \ldots \beta_k$ are measures of the linear dependence of the corresponding variables and cross- coefficients (β_{ij}) measure interactive effect between between concerning variables.[42 - 47]

1.8 Purpose of thesis

The present project had following purposes

- To explore compound **8** in a range of standard transformations to achieve vertical diversity for future library design.
- To use multivariate response surface method to determine optimal experimental conditions for compound **8** in the project ***scheme 12***.

Scheme 11: shows different reactions, which could checked whether, are possible for compound **8.** Hydrogenation, krapcho, Inverse electron demand Diels-Alder (IEDDA), alkylation and Luche reduction reaction are expected reaction which compound **8** could be undergo.



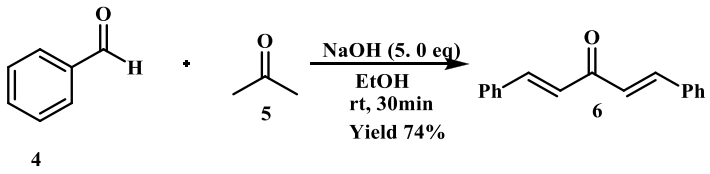
Scheme 11: Summary of the project reactions

2. RESULTS AND DISCUSSION

2.1 Synthesis of dibenzylideneacetone

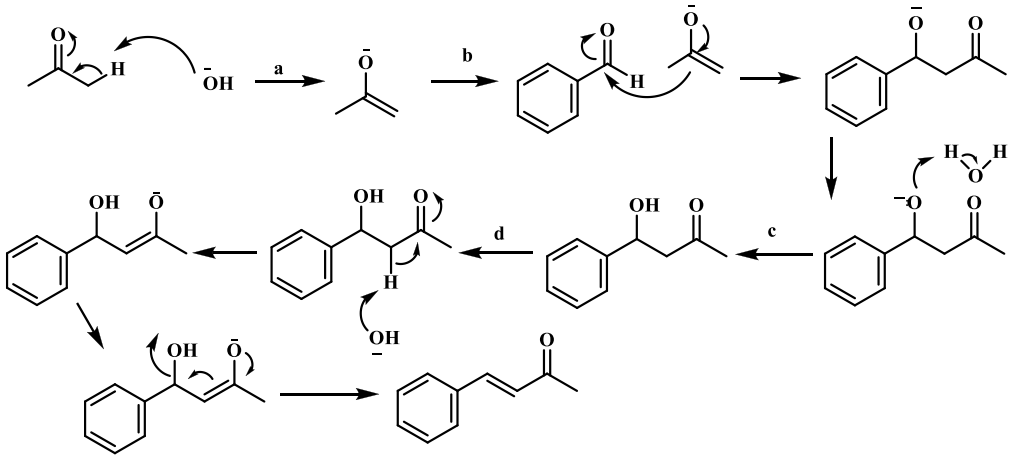
This section describes synthetic results of dibenzylideneacetone, which was the basic material in next step (synthesis of compound **8).**

Compound **6** was synthetized according to the general procedure described in literature. Compound was collected as yellow crystals in 74% yield. Spectroscopic data were recorded and found similar to one reported in literature. The reaction between benzaldehyde and acetone was catalyzed by sodium hydroxide to form dibenzylideneacetone, see ***scheme 12***.



***Scheme 12*:** Synthesis of dibenzylidene acetone.

Mechanism is shown in ***scheme 13*** in step **a-d.** Hydroxide deprotonates acetone to generate enolate (**a),** enolate formed attacks benzaldehyde (**b)** to generate ion which is protonated in step **c** to form β-hydroxy ketone. In step **d**, β-hydroxyketone undergoes Aldol condensation reaction to generate α, β unsaturated ketone.



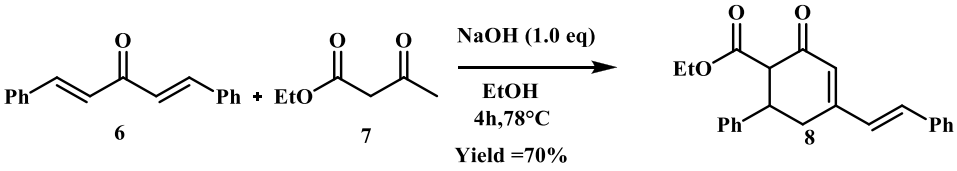
Scheme 13: Suggested mechanism of compound **6**. [48,49]

2.2 Synthesis of compound 8

This section describes synthetic results of compound **8**, which was the main product of this work. Compound **8** was studied in a range of standard transformations.

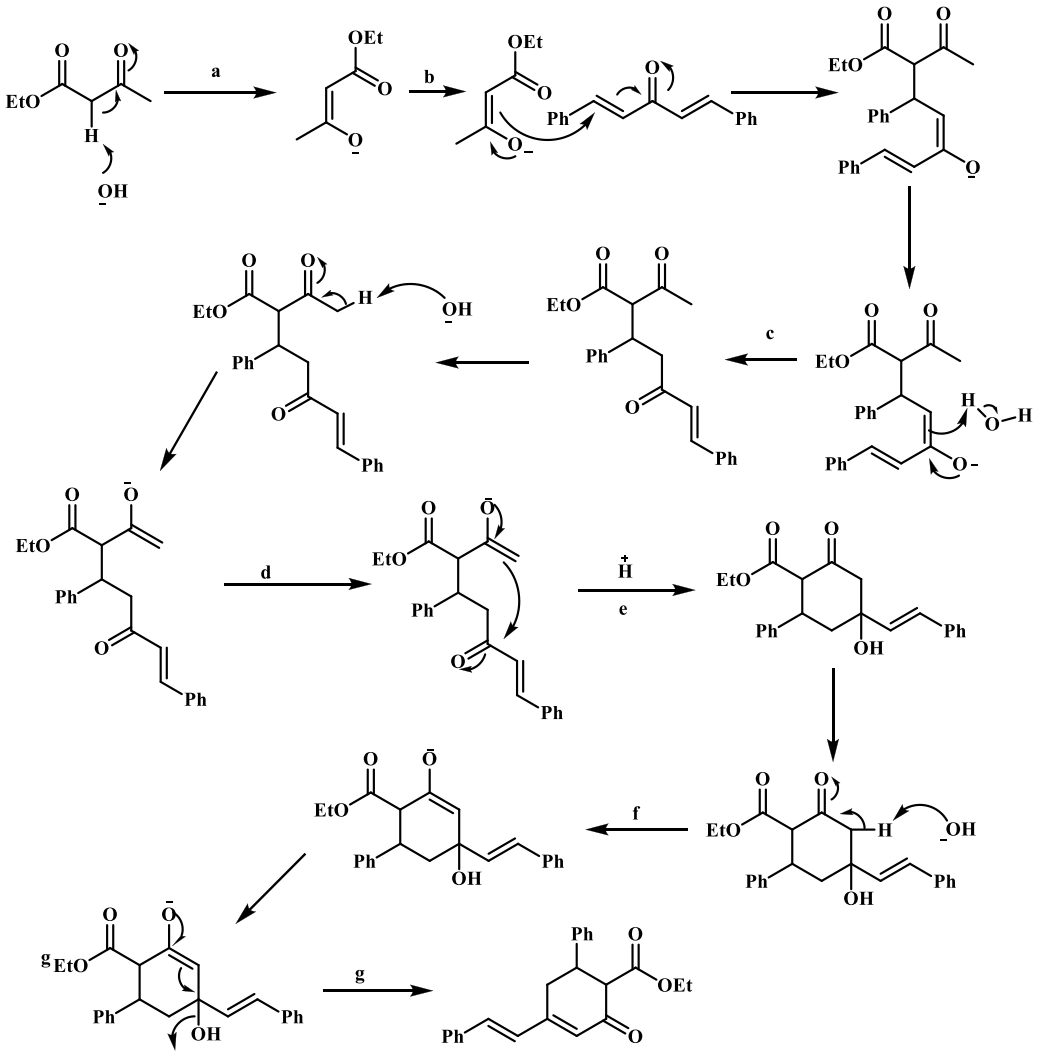
The synthesis was done according to experimental procedures described in literature.[50, 51] Precipitate was observed at the end of the reaction. The amount of the compound isolated depends on the amount of water added to induce crystallization and the time given for crystallization process. The final compound after crystallization was collected as yellow crystals. Spectroscopic data was recorded, which showed the presence of the compound **8** in 70% yield.

The reaction between dibenzylideneacetone, compound **6** and ethyl acetoacetate under basic condition in ethanol formed compound **8,** see ***scheme 14.***



***Scheme 14*:** Synthesis of compound **8**.

Mechanism of compound **8** is shown in ***scheme 15*** in step **a – g.** Base deprotonates compound **7** to form enolate in step **a,** formed enolate attacks directly β-carbon of unsaturated ketone **6** in step **b** to generate an ion which is protonated in step **c** to produce Robinson product**.** Robinson compound undergoes intramolecular Aldol cyclization reaction to form β-hydroxyl ketone followed with its condensation in step **d - g** to generate final Robinson cyclization product.



Scheme 15: Suggested mechanism of compound **8**. [52]

2.3. Multivariate response surface model of compound 8

This section presents discussion and presentation of variable choice and experimental domain, experimental design, results, experimental screening and response surface analysis of compound **8** (**scheme 14**) under optimization process.

2.3.1. Variables and experimental domain

Determination of variable and experimental domain is usefully in experimental design.

Variables used in synthesis of compound **8** are concentration of dibenzylideneacetone (DA) and ethyl acetoacetate (EAA) (mmol), reaction temperature and amount of base (mmol). Variables are represented with x_1, x_2 and x_3 following their above written order. DA and EAA were combined in one variable x_1 which is the ratio of their millmoles. The combination of EAA and DA in one variable was done in order to reduce number of variables and experiments. The choice of three variables (x_1, x_2 and x_3) instead of four variables helped to run eight experiments instead of 16 experiments. After choosing variables, the followed step was to decide their experimental domain. Each variable was taken at its low level (-) and high level (+). Variables and experimental domain are shown in ***table 3***.

Table 3: Experimental settings

Variables	Experimental domain	
	(-) level	(+) high level
X_1: amount of DA/EAA (mmol/mmol)	0.83	1
X_2: Reaction temperature (℃)	68	78
X_3: Amount of sodium hydroxide (mmol)	1.80	4.25
Amount of variable at low and high level, DA (0.3 g, 0.74 g), EAA (0.2 g, 0.41g) and NaOH (0.072g, 0.17g).		

2.3.2. Experimental design

During experiments, three variables were used and each variable has two values, one at low level and another at high level, a two-level full factorial design 2^3 was a suitable experimental design. A full factorial design 2^3 shows all 8 possible combination of settings of the experimental variables. Verification of each variable effect on the response was the basic factor to decide experimental design order. In two consecutive experiments, two variables were kept constant in order to check the contribution of the third variable. Experiments one and two, were chosen as first experiments to run in order to check whether experimental domain chosen could be explored or not. Experiments 3 and 4 were carried out to check the contribution of the variable x_1, 5 and 6 were run in order to verify the effect of variable x_3 on response and the influence of the variable x_3 on the response was checked in experiments 7 and 8. A number of possible experiment in 2^3 is shown in ***table 4.***

Table 4**:** Full factorial design 2^3

Exp no	variables		
	x_1	x_2	x_3
1	-	-	-
2	+	+	+
3	+	+	-
4	-	+	-
5	+	-	-
6	+	-	+
7	-	+	+
8	-	-	+

2.3.3 Results presentation and discussion

This section presents data recorded with gas chromatography after injection of different amount of product dissolved in 1mL of internal standard (0.00295 M), calibration curve and results obtained after optimization.

Different amount of compound **8** (see experimental section page **54**, ***table 10***) was dissolved in 1mL of internal standard (phenyl cyclohexane) in order to produce a calibration curve that was used to measure yield. Data recorded with G.C are represented in ***table 5.*** A_p represents peak area of the product and A_{is} peak area of internal standard.

Table 5**:** Results given by gas chromatography after injection of one microliter of internal standard and product.

Standard mmol/mL	Internal std (mmol /mL)	c_p /c_{is}	A_{is}	A_p	A_p/A_{is}
0.0042	0.00295	1.424	567.294	171.204	0.3018
0.0314	0.00295	10.644	573.784	855.422	1.4908
0.052	0.00295	17.627	569.732	1394.098	2.4469
0.0729	0.00295	24.712	565.630	1798.053	3.1788
0.0958	0.00295	32.474	558.107	2223.020	3.9831

Chromatograms can be found in appendix 9-13 (t_R: around 4.2 min for internal standard and 9.8 min for analyte).

Calibration curve produced from data in ***table 5*** is shown in ***Fig 4.***

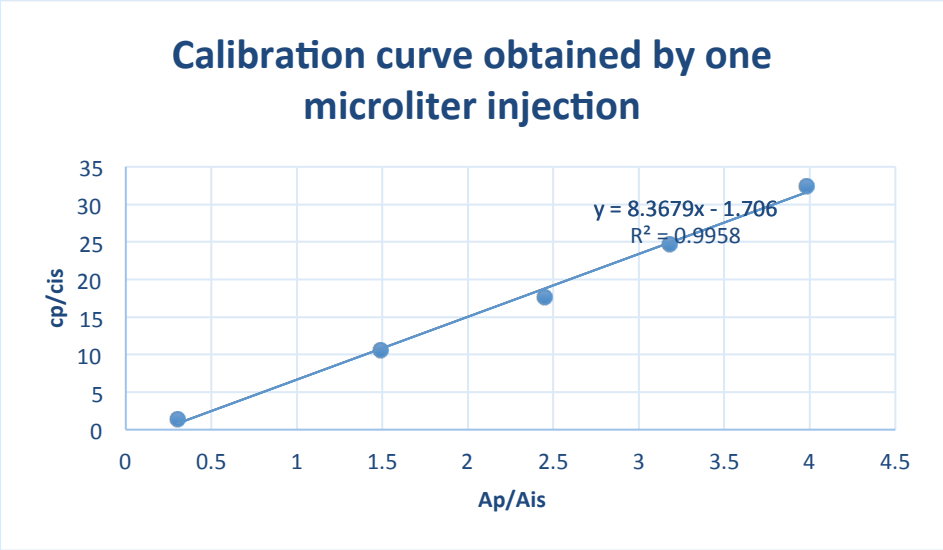


Fig 4: Calibration curve.

Since running several experiments for optimization process, results are presented in ***table 6*** and ***7.*** Data recorded from gas chromatograph after injection of samples ***(table 6)***, (C_{is}) presents concentration of internal standard injected and its peak area (A_{is}), peak area of analyte (A_x). The ratio of peak analyte and internal standard peak area (A_x/A_{is}), ratio of analyte concentration and internal standard (Cx/Cis), this ratio was calculated from calibration curve (an example of Cx/Cis calculation can be seen in experimental section (page **55-56** and concentration of analyte in sample (C_x reaction). Concentration of analyte was calculated according to dilution of each sample during the preparation of gas chromatograph sample. An example for ($C_{x\ (reaction)}$) calculation can be seen in experimental section (page **55-56**).

Results presented in ***table 6*** are discussed in part of the ***table 7***, which has detailed information about experiment settings, and yield.

***Table 6*:** Data recorded with gas chromatograph.

Exp no	C_{is} (mmol/mL)	A_x	A_{is}	A_x/A_{is}	C_x/C_{is}	$C_{x(}$reaction) (mmol/mL)	Appendix
1	0.00295	165.46	721.65	0.229	0.210	0.0078	14
2	0.00295	209.67	688.97	0.304	0.841	0.0896	15
3	0.00295	214.14	734. 18	0.292	0.737	0.0789	16
4	0.00295	190.08	705.73	0.269	0.545	0.0354	17
5	0.00295	210.16	746.22	0.282	0.654	0.0700	18
6	0.00295	182.79	705.76	0.259	0.461	0.0494	19
7	0.00295	165.74	684.6	0.242	0.319	0.0212	20
8	0.00295	118.38	617.6	0.192	0.1	<0.0015	21
9	0.00295	217.84	724.69	0.301	0.813	0.0871	22

Chromatograms can be found in appendix 14-22 (t_R: around 4.2 min for internal standard and 9.8 min for analyte).

The yield was first measured after crystallization of compound **8**, but it was decided to measure the yield from reaction mixture with calibration curve in order to reduce errors that could be made during isolation of compound.

Methyl benzoate was the first internal standard tried, but it was a big difference between retention times between product and internal standard. Phenyl cyclohexane has boiling point, which is higher than methyl benzoate was used as internal standard. First results, the yield was over 100 % for reactions run at high temperature.

The reaction mixture started to precipitate at the end of the reaction due to evaporation of solvent during the reaction, this was the main cause of the first results observed. This problem was solved by adding more solvent at the end of the reaction and a 50 mL volumetric flask was used to measure exact volume, this methodology worked for samples with DA at high concentration, sample at low concentration gave negative results and it was decided to change amount of the solvent for samples with DA at low concentration during the reaction and the preparation of gas chromatography samples.

DA at high concentration, reactions were run in ethanol (30.00 mL) the same amount used to make the calibration curve, 12.00 mL at low concentration and during the preparation of gas chromatograph samples, 50 mL volumetric flask was used for samples at high concentration and 25 mL at low concentration. The use of different amount of the solvent gave results presented in ***table 7***

Results presented in ***table 7*** show experiments (Exp) with variables at their low level (-) and high level (+). Results of experiment number one (EXP no 1) and number two show a big difference between variables at their low level (15%) and high level (86%). Variables at their high level (Exp no 2) gave the highest yield 86%, the combination gave the lowest yield (4%) is in Exp number eight with variable x_3 at high level and other variables at low level. Combination of x_1 and x_2 at high level and x_3 at low level (Exp no 3) gave also good result. It is not possible to draw any direct conclusion about individual or interactive effects of variables on response results in ***table 7.*** The conclusion will be taken after experimental screening and response surface model analysis.

Table 7: Experimental settings and their yield

Exp no	X_1	X_2	X_3	Y%
1	-	-	-	15
2	+	+	+	86
3	+	+	-	76
4	-	+	-	69
5	+	-	-	67
6	+	-	+	48
7	-	+	+	40
8	-	-	+	4
9	1.5	1	1.5	84

2.3.4 Screening and response surface analysis.

This section discusses data obtained after screening and response surface analysis of results presented in ***table 7***.

After screening, response surface model describing the variation of response according to variables was determined. Evaluation the model coefficients helped to identify significant variables. Important variables are x_1 and x_2 with coefficients 19 and 17 and there is no big difference between their coefficients. Variable x_3 with coefficient (-6) is less significant than other variables. Model coefficients are shown in ***table 8.***

$y = 54 + 19\,x_1 + 17\,x_2 - 6\,x_3$ (response surface model)

54.22 is estimated response when all variables are set to zero.

Table 8: model parameters.

Variables coefficients	
X_1	19
X_2	17
X_3	-6

Response surface analysis (**Fig 5**) showed clearly contribution of variables one response. Variables x_1 and x_2 have high influence on response, variable x_3 has not big influence ***Fig 5*** shows how response varies in surface according to variation of x_1 and x_2 when x_3 is constant. The variation of response is proportional to variation of variables (x_1 and x_2).

Response is around 20% in domain around (–) and it increases as domain varies up to around (+). Optimum conditions is located in domain (around +1) with yield around 80%).

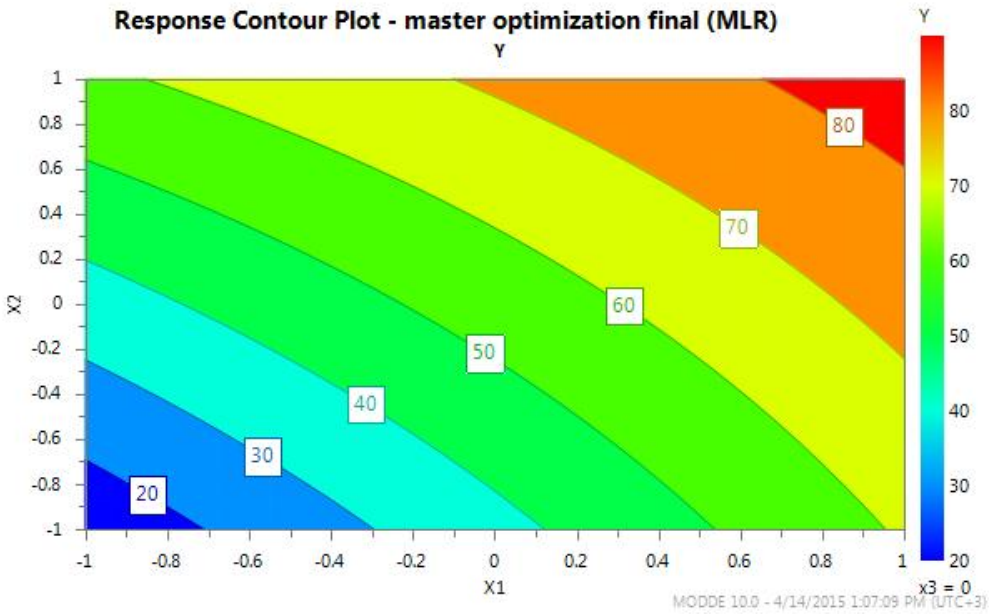
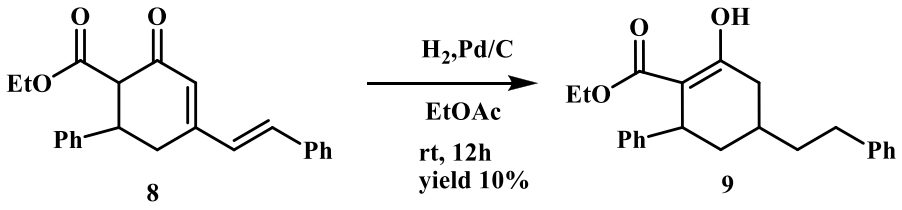


Fig 5: Response contour plot shows variation of yield when x_3 is constant

2.4 Hydrogenation of compound 8

This part describes the synthetic result of compound **9** in ***scheme 17***. The synthesis followed experimental procedure described in literature[53,54]., minor modifications were done. TLC showed two diastereoisomers and the column was run several times to separate them but separation was not successful. Spectroscopic data were recorded and confirmed that hydrogenation of compound **8** gave an enol compound **9**. ^{1}HNMR of the compound **9** showed a peak with chemical shift above 12 ppm, ^{13}C-NMR did not show a peak at ppm (185-220) for ketone.

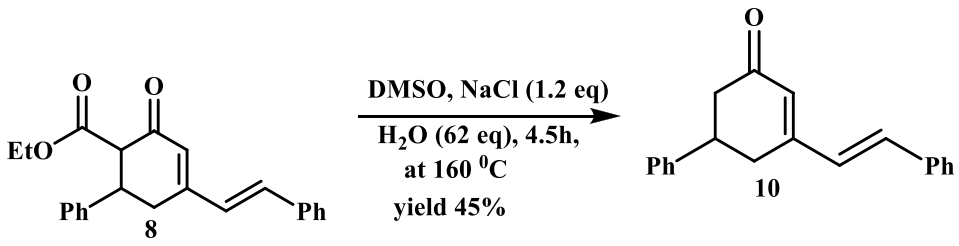
Palladium on carbon used as a catalyst that provides the reaction surface, hydrogen bond (H-H) is cleaved and each hydrogen is attached to palladium surface by palladium hydrogen bond. Compound **8** is also absorbed onto palladium surface. Thus, syn addition of hydrogens to compound **8** occurs to generate compound **9.** Synthetic reaction of compound **9** is shown in ***scheme 15***.



Scheme 15: Synthesis of compound **9**

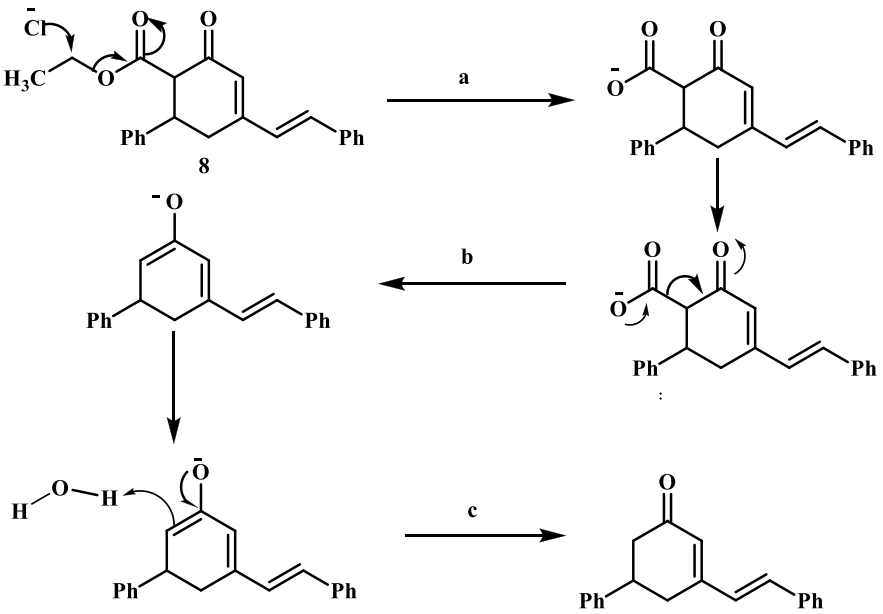
2.5Decarboxylation of compound 8

This section describes the obtained result of compound **10** in ***scheme 18.*** The synthesis was performed according to experimental procedures described in literature [55-60]. Reaction was run in the same experimental conditions described in literature but it was not successful. Reaction was carried out by heating compound **8** in DMSO and water at 160 ℃, and 200 ℃ for 2 days and stopped without completion. Experimental conditions were changed, sodium chloride was added and 10:1 ratio of NaCl : compound **8** was used as reported in literature and the reaction mixture was heated 160 ℃ but reaction was not found successful. Although reaction was successful when sodium chloride (1.2 eq), and compound **8** (1.0 eq) was used. Compound **10** was isolated and collected as colorless crystals (yield 10 %). Spectroscopic data were recorded and confirmed compound **10.** Synthesis of compound **9** is shown in ***scheme 16.***



***Scheme 16*:** Synthesis of compound **10**

Mechanism of compound **10** is shown in three steps (**a, b** and **c**). The chlorine ion (Cl^-), takes away ester methylene of compound **8** in step **a** and promotes cleavage of ester group to generate enolate formed in step **b.** In step **c** enolate is protonated to form final decarboxylation product, as shown in ***scheme 17.***

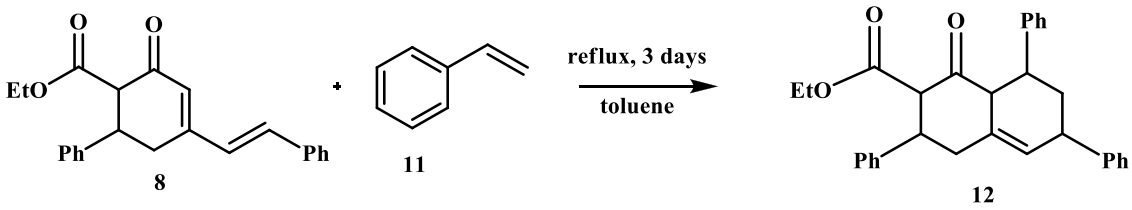


***Scheme 17*:** Suggested mechanism for compound **10**

2.6 Inverse electrons demand Diel-Alder reaction

This part describes results obtained during the attempt of inverse electrons demand Diels-Alder reaction to produce compound **12**, ***scheme 18.*** The synthesis followed experimental procedures described in literature [27, 61-64]. The reaction mixture was refluxed in toluene for 3 days and heated at 130 ℃ in dioxane. Information from crude ^{1}HNMR was not clear to confirm that the reaction was successful. HRMS showed a small peak 451.2268, which is the exact mass of compound 12, but it was not enough proof to confirm the presence of compound **12** and it was decided to stop the work on this experiment.

Compound **8** and styrene was heated in toluene but reaction was not successful, ***scheme 18.*** Electrons were expected to flow from styrene HOMO to LUMO of compound **8**, followed by cyclization in a single transition state to form a six membered ring.

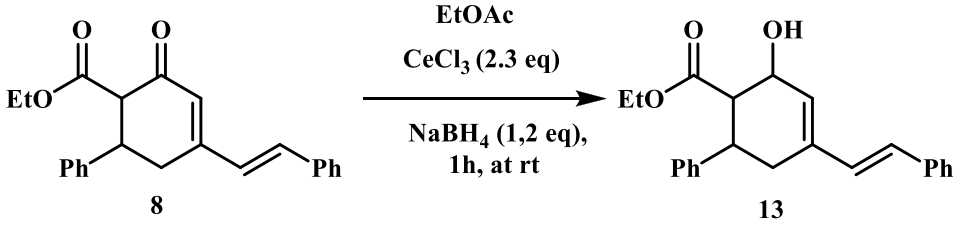


Scheme 18: Synthesis of compound **12**

2.7 Luche reduction reaction

This section describes results obtained during the reduction of compound **8** in ***scheme 19.*** Reaction was run according to experimental procedure described in in literature [32]. Information from crude ^{1}H NMR, ***Fig 4*** was not clear to confirm the presence of compound **13** and it was difficult to draw any conclusion on the success of the reaction .It was decided to stop work on this stage.

Cerium (Ce^{3+}) coordinates to oxygen of carbonyl group and increases electophilicity of carbonyl carbon. Hydride (H^-) attacks activated carbonyl carbon to generate alcohol. Synthesis of compound **13** is shown in ***scheme 19.***



Scheme 19: Synthesis of compound **13**

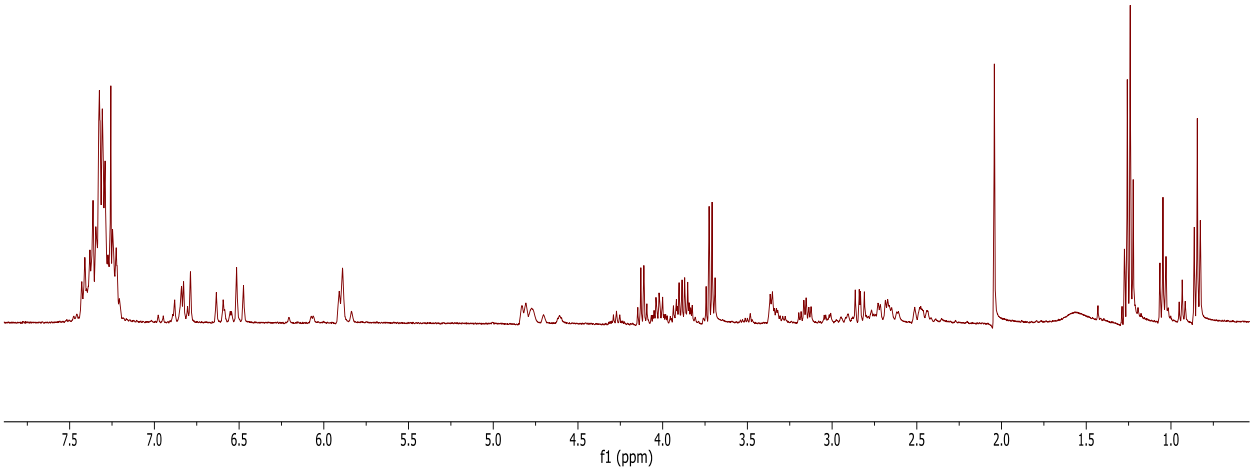
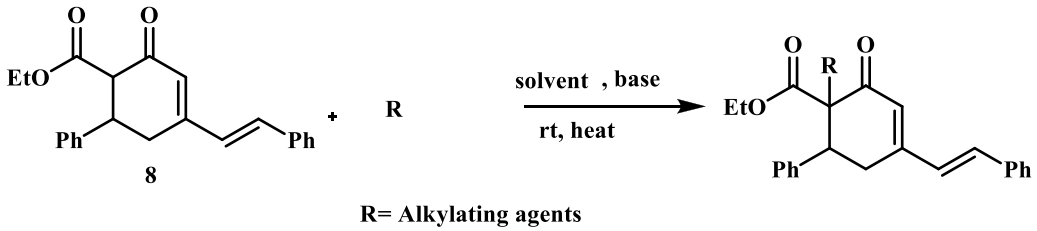


***Fig 4*:** Crude ^{1}H-NMR spectra of compound **13**

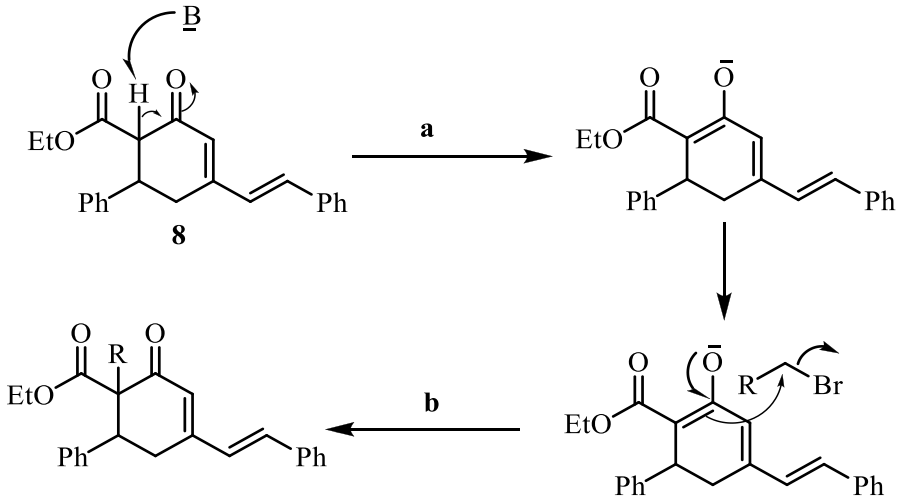
2.8 Alkylation of compound 8

This part presents results obtained by alkylating compound **8** with different selected R-group to generate compounds (**15**, **17**, **19**, 21, **23**, and **25**). Alkylating was performed according to ***scheme 20.*** Base deprotonates compound **8** to form enolate which substitutes bromine.



Scheme 20: Alkylation scheme.

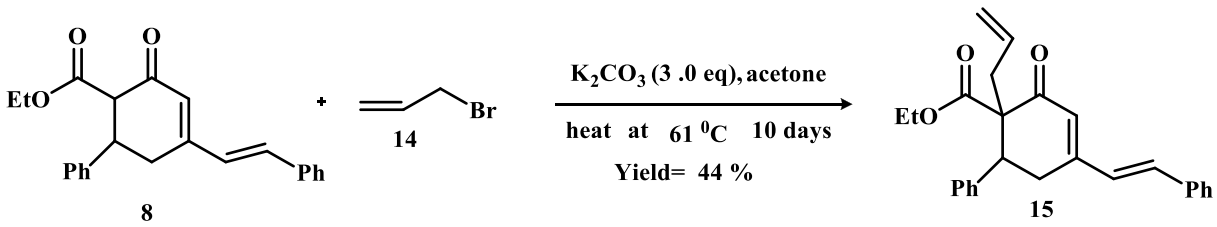
Alkylation of compound **8** follows an S_N2 mechanism and it is done in step **a** and **b (*scheme* 21).** Base (B^-) deprotonates compound **8** in step **a** to form enolate. An S_N2 reaction between enolate and alkyl bromide generates alkylated compound in step **b.**



Scheme 21: Alkylation mechanism

2.8.1 Alkylation with allyl bromide

Compound **8** was converted to compound **15** according to ***scheme 22.***



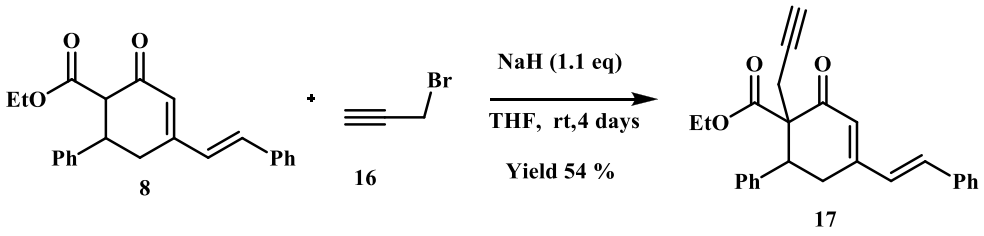
***Scheme 22*:** Synthesis of compound **15**

The reaction was run according to general experimental procedure described in literature[65]. Two bases were used to check their influence on reaction rate. With DBU, the reaction was ran at room temperature for 24 hours as it was reported in literature but was found unsuccessful. The reaction mixture was heated at 40 ℃ and TLC analysis showed the presence of product, the reaction temperature was raised to 62 ℃, after 5 days the reaction did not finish. Potassium carbonate was also used to check if the reaction time could be improved, but no changes happened but the reaction was left to run until the full conversion of compound **8** was observed. The reaction finished after 10 days.

The reaction was also ran in $CHCl_3$ to check whether the solvent could enhance the rate of the reaction but no difference was observed. The rate of the reaction might be slow due to steric effect of compound **8** and the bases used.

2.8.2 Alkylation with propargyl bromide

This part describes alkylation results of compound **8** in ***scheme 23.***

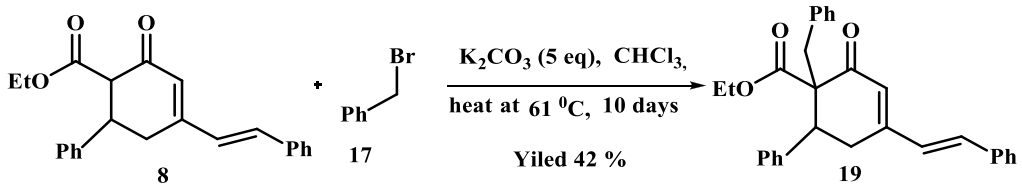


Scheme 23: Synthesis of compound **17**

Since low reaction rate observed in the alkylation with ally bromide, it was decided to use a strong and less bulky base in order to improve the reaction rate. Sodium hydride was used and the full conversion of compound **8** was observed after four days with TLC analysis. Spectroscopic data were recorded and confirmed compound **17.**

2.8.3 Alkylation with benzyl bromine.

This section describes results obtained after alkylation of compound **8** with benzyl bromide. Alkylation was done according to ***scheme 26.***

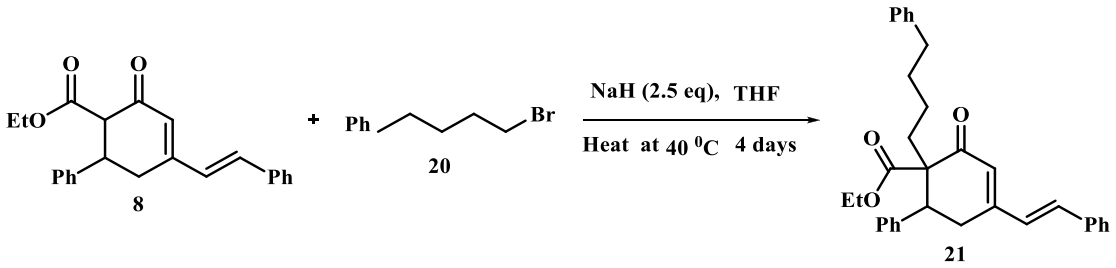


Scheme 24: Synthesis of compound **19**

The synthesis followed experimental procedures reported in literature [65], minor modifications were done. The reaction was first run with sodium hydride after 4 days TLC analysis, showed no reaction. ^{1}H NMR of benzyl bromide was run and showed that benzyl bromide has water which might disturb the reactivity of sodium hydride. The reaction was run with potassium carbonate, monitored with TLC and left to run for 10 days. Compound **19** was collected as yellow viscous liquid. Spectroscopic data were recorded and confirmed compound **19.**

2.8.4 Alkylation with 1-bromo 4-phenyl butane

Compound **8** was converted to compound **21** according to ***scheme 25.***

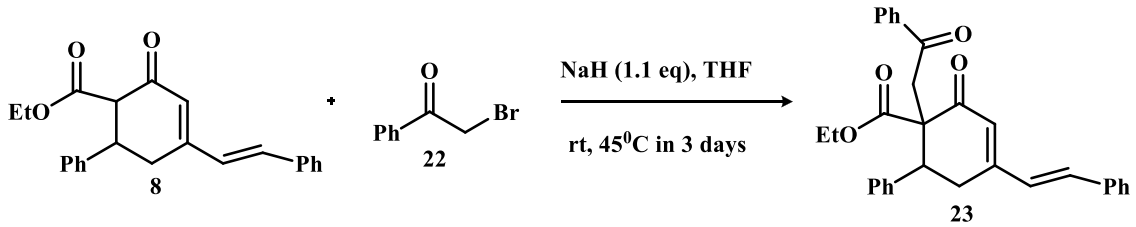


***Scheme 25*:** Synthesis of compound **21**

The amount of sodium hydride was doubled and the reaction was heated to check if the problem of the reaction rate encountered in previous alkylation reactions can be improved, but no difference was observed. Information from crude ^{1}H NMR and HRMS confirmed the presence of compound **21.** Crude ^{1}H-NMR shows extra peaks to compound **8** at ppm (7.34 - 7.11, 3.44 -3.40, 1.92-1.76, and 1.3-1.27), these peaks may be evidence of compound **21.** HRMS confirms clearly compound **21.** The column was run to separate compound but separation was not successfully.

2.7.5 Alkylation with 2-bromoacetophenone

Compound **8** was alkylated according to ***scheme 26.***



Scheme 26: Synthesis compound **23**

The reaction was run with sodium hydride (1.1 eq) at room temperature and heated but no result found. The amount of base was doubled to check whether it could affect, but it did not help. Crude ^{1}H NMR, did not show compound **23.** It only shows staring materials**.**

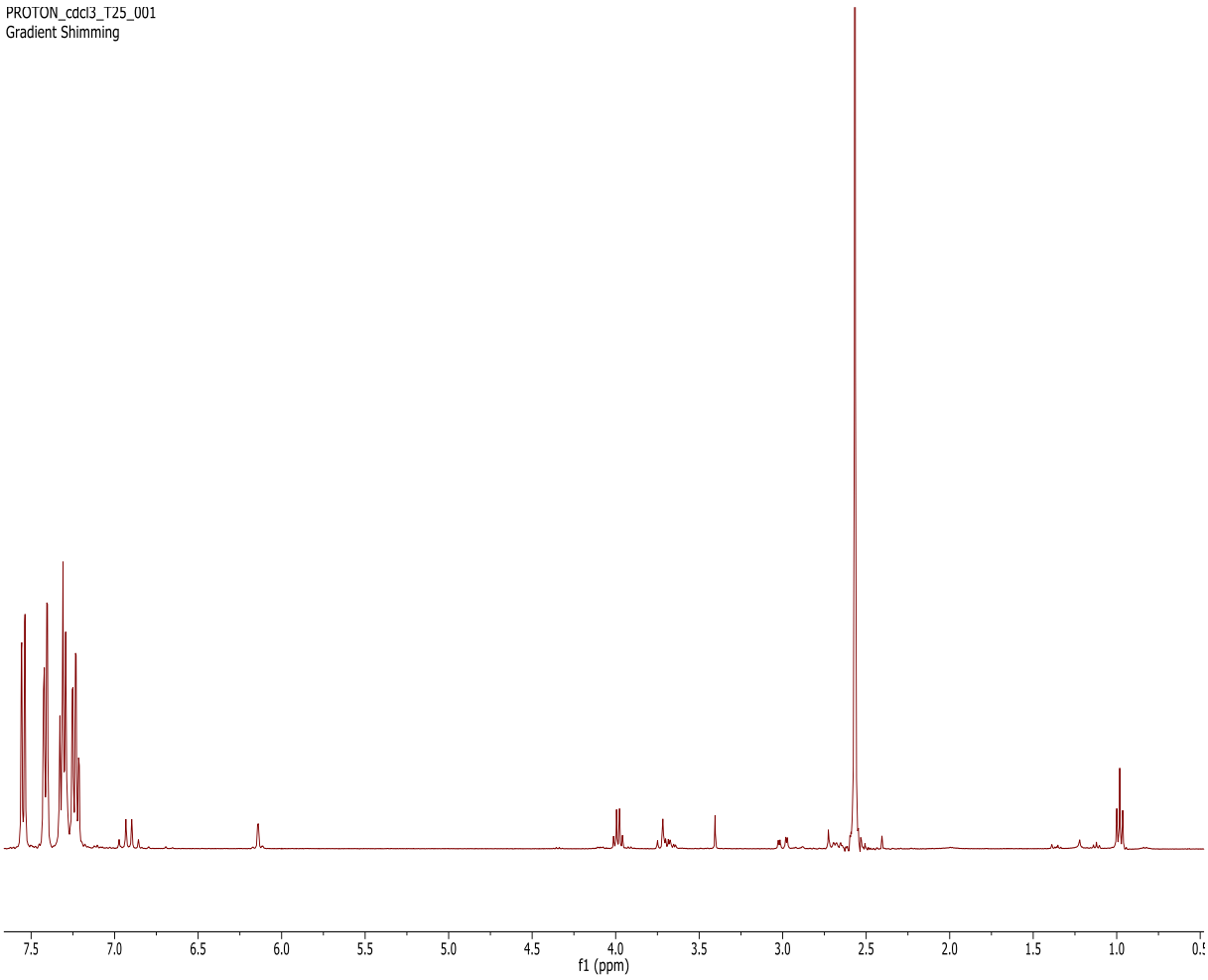
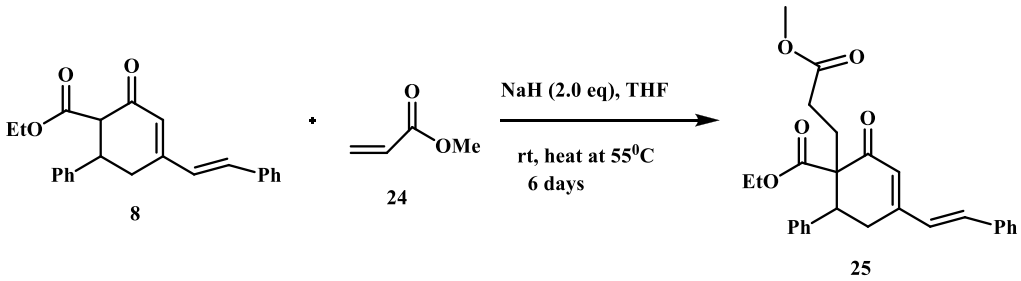


Fig 6: Crude ^{1}H-NMR for compound **23**

2.8.5 Alkylation with methyl acrylate

This section describes results after alkylation of compound **8** with methyl acrylate. Alkylation was done according to ***scheme 27.***



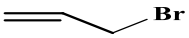
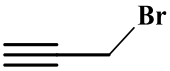
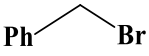
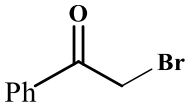
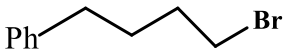
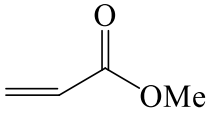
Scheme 27: Synthesis of compound **25**

The reaction was first run at room temperature, then heated at 55 ℃, and stopped after 5 days without completion. Crude ^{1}H NMR and HRMS confirmed the presence of compound **25.** Crude ^{1}H-NMR is hard to interpret but it shows two single peaks at 3.65 and 3.60 ppm, for (CH_3O^-), one peak may be for starting material (compound **24**) another for compound **25.** It also shows a peak at 2.57-2.44 ppm, which is most likely, result of alkylation. The column was run to separate compound 25 with starting materials but separation was not successfully.

Alkylation results obtained are summarized in ***table 9.***

Alkylation catalyzed by DBU (compound **15**) was purified at the first time because it was expected to run other reaction in order to observe full conversion of alkylated compound. Alkylation catalyzed by NaH (compound **19**) was not purified due to result, which was not good and compound **23** and **25** separation was not successfully.

***Table 9**:* Summary of alkylation results

Alkylation agents	**Conditions** **base / solvent**	**Compound**	**Yield (%)**
	DBU/ DMF	15	Not purified
	K_2CO_3/ aceton		44
	NaH/THF	17	54
	NaH/THF	19	Not purified
	K_2CO_3/$CHCl_3$	19	42
	NaH/ THF	21	Not successful
	NaH/THF	23	Not purified
	NaH/THF	25	Not purified

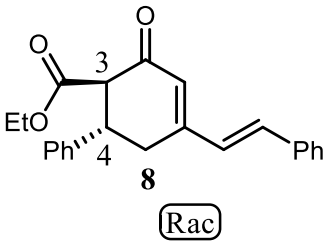
2.9 Relative Stereochemistry of compound 8, 15 and 17

Many of the products obtained contain multiple stereocenters. Therefore, studies were conducted to determine the relative stereochemistry of these.

Stereochemistry of compound 8.

NMR data did not help us to determine the relative stereochemistry of compound **8** due to overlap between hydrogen 3 and 4. (see NMR in Appendix 55-60).

NMR data was supported with information from DFT calculations carried out by Dr Taye Demissie which confirms that the major diastereomer has anti at positions 3 and 4. After collecting and analyzing the above information the correct stereochemistry of compound **8** shown below was decided.



8

Rac

The more stable anti-diastereomer calculated by DFT is 4.21kcal/mol is more stable than the syn- diastereomer. The most stable conformer of compound **8** predicted by DFT is shown in ***Fig 7***.

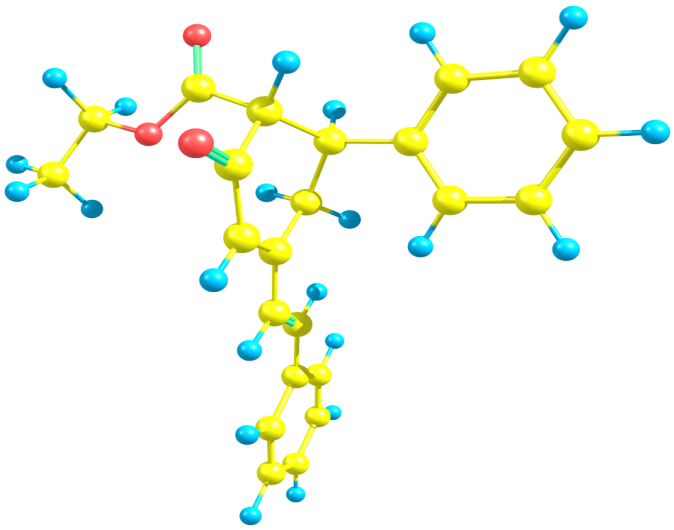
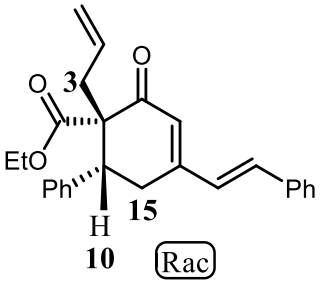


Fig 7. Most stable conformer of anti-**8** predicted by DFT.

Stereochemistry of compound 15

Analysis of NMR spectra (gHMBC) and NOESY shows that hydrogen 3 and 10 are close to each other, (see NMR in Appendix 61-66).

DFT calculations done by Dr Taye showed that syn-diastereomer of compound **15** is 1.81kcal/mol less stable than anti-diastereomer. The syn-diastereomer showed by NOESY is shown below.



The syn-conformer of compound **15** predicted by DFT is shown in ***Fig 8.***

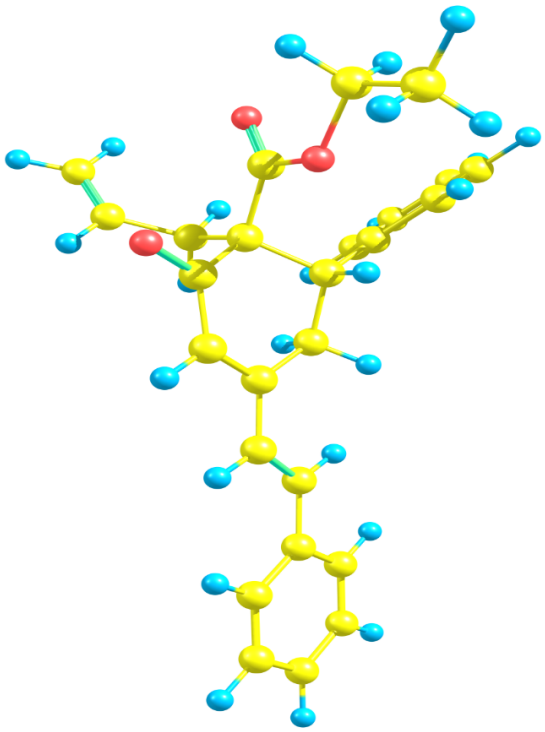
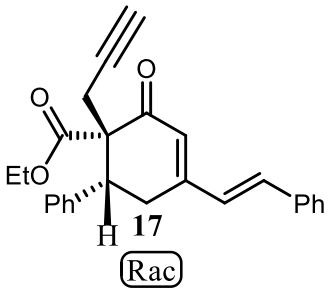


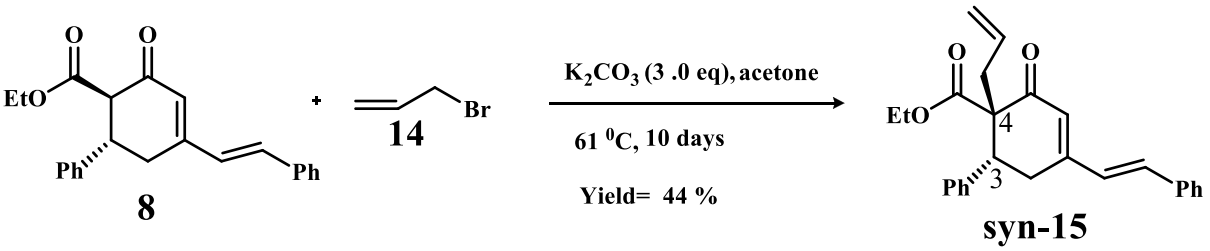
Fig 8: Syn-diasteomer predicted by DFT.

Stereochemistry of compound 17



Information from NMR spectra (gHMBC) confirmed that CH- 3 and 9 coupled, and NOESY showed hydrogen 3 and 9 are close to each other, (see NMR spectra in appendix 67-72). After collecting and analyzing the above information the relative stereochemistry of compound **17** shown below was decided, and is consistant with that of 15.

Evidence for kinetic alkylation of compound 8



The phenyl group on position 3 directs the alkylation face of the intermediate enolate formed. Alkylation is more favored to the less hindered face, opposite to that of phenyl. Alkylation taking place on opposite side of phenyl on position 3 gives the kinetic product. DFT calculations done by Dr Taye showed that the thermodynamic product is the anti-diastereomer opposite to what the NOESY studies indicated. Experimental syn-anti-diastereomer showed by DFT are shown in ***Fig 9.***

There are two possible transition states (TS1 and TS2) in the alkylation of compound 8 with allyl bromide. The transition state giving the kinetic product has lower energy than the other giving the thermodynamic product. The energy difference between the thermodynamic and kinetic products is 1.81kcal/mol (***Fig 9***).

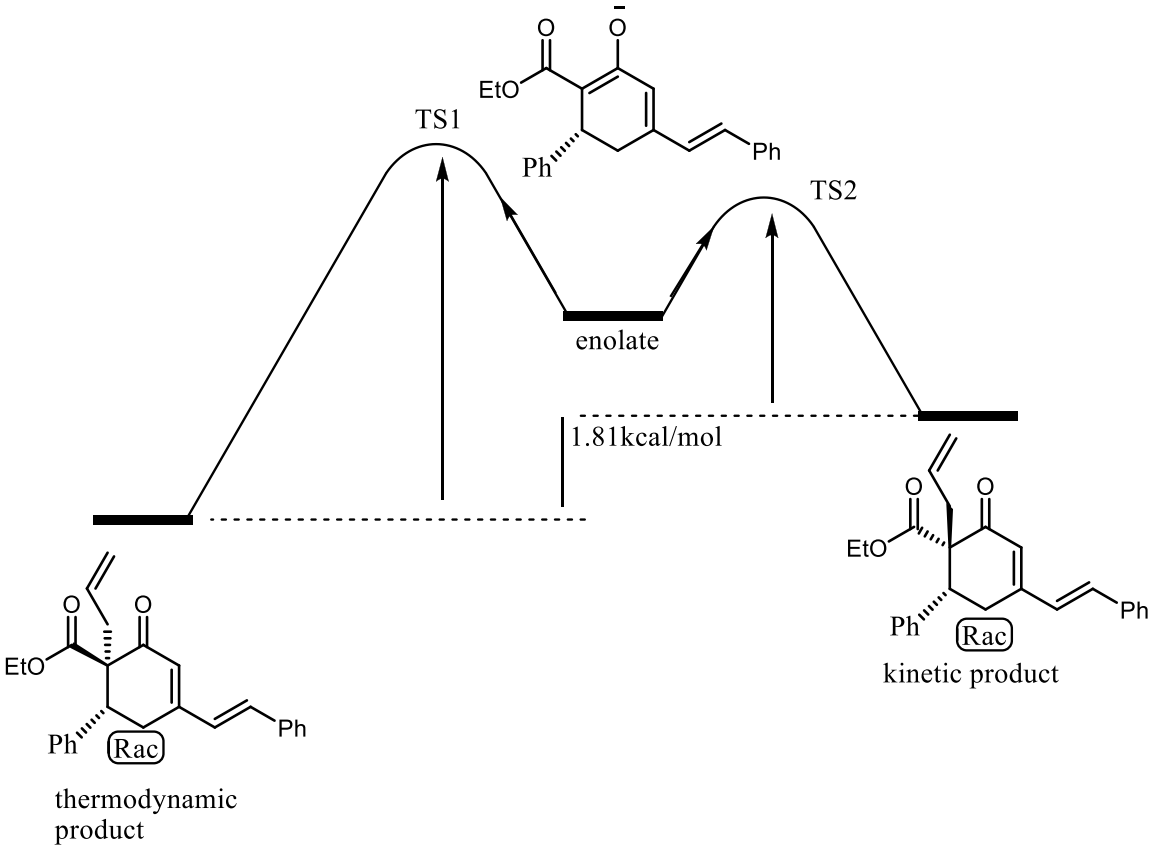
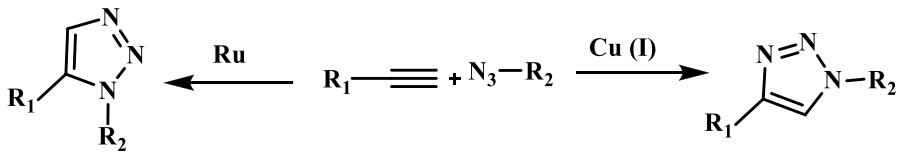


Fig 9: Thermodynamic and kinetic products

3. FUTURE DIRECTIONS

Compound **8** synthesized during this work has larger chemical space. Our chemical library can be extended by exploring its remaining structural diversity and its derivatives. Compound still has many functional groups (ester, ketone, conjugated system and aromatic system) that can be transformed to make heterocyclic compounds, other functional groups may be introduced that can undergo further functionalization. Alkene and alkyne compounds (**15** and **17**) introduced in compound **8** can also be explored to generate other compounds particularly side chains.

An example of side chains compound **17** can undergo 1,3 dipolar cycloaddition between azides and alkyne to generate triazoles which are important compounds in medicinal chemistry[66]. (***Scheme 28***).



Scheme 28: Suggested triazoles formation [66].

4 .CONCLUSION

The first part of the presented work was to develop and optimize the synthesis of compound **8**, which was successful. The second part was to explore the reactivity diversity of compound **8** in order to build future chemical libraries for biological profiling around this versatile scaffold. During the study of compound **8** in a range of transformations, many reactions were done. Successful alkylation appears to only occur with less crowded and activated alkyl halides. Compounds shown in ***Fig 8*** were synthesized successfully. The relative stereochemistry of alkylating product **8**, **15** and **17** was determined by NMR and DFT calculations; also the kinetics of the reaction was determined for compound **15** by DFT calculation.

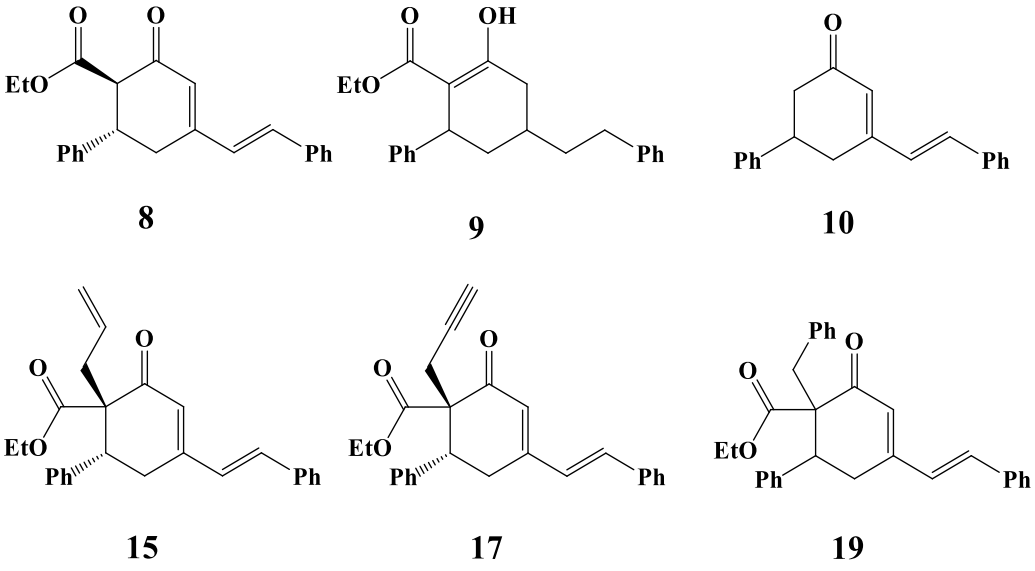


Fig 8*:* Compounds synthesized successfully during the presented work

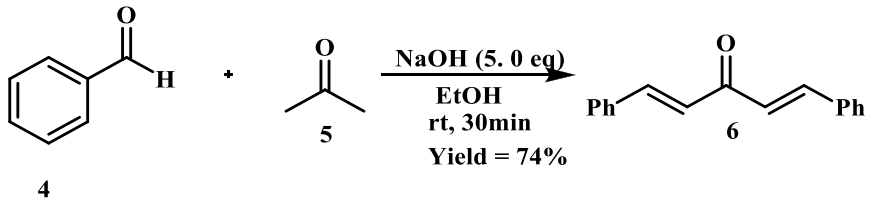
5. EXPERIMENTAL SECTION

Reagents used were purchased from Sigma-Aldrich and others were previously synthesized in our laboratories.

^{1}H NMR (400 MHz and ^{13}C NMR (101 MHz), spectra were recorded on a Varian Mercury 400 plus spectrometer (400 MHz) using $CDCl_3$ as solvent. Spectra were processed with MestReNova software. Chemicals shifts (δ) are reported in parts per millions (ppm) and multiplicities are given as a singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), and multiplet (m). Infrared spectra were recorded on a Varian 700e FT-IR spectrometer and bands are reported in wavenumber (cm^{-1}). High-resolution MS was recorded on a Thermo electron LTQ Orbitrap XL +Electrospray ion source (ION-MAX). GC-MS analyses were conducted using a Thermo Scientific ITQ 1100 +Trace GC Utra. GC-FID analyses were conducted with an Agilent technology 7820A gas chromatograph instrument. The melting point was measured with Bu̇chi 535 instrument.

All reactions were performed under inert conditions. Glassware and stir bars were dried oven at 110℃ in 2 days and put under vacuum before their use. Reagents were transferred in reaction flasks under inert nitrogen or argon atmospheres. The progression of the reactions were monitored with TLC on 60 F254 silica gel plates and visualization of spots on TLC was carried out with UV, Potassium permanganate, molybdic acid and vanillin stains.

Synthesis of compound 6



In a 100 mL beaker with a stir bar, sodium hydroxide (5.20 g, 0.13 mol, 4.3 eq) was dissolved in water (50 mL) and ethanol (96%, 40mL) at room temperature. Benzaldehyde (5.31 g, 0.05mol, 1.7 eq) and acetone (1.46 g, 0.03 mol, 1.0 eq) were dissolved in ethanol (96%, 4.22 mL). Half of the benzaldehyde-acetone mixture previously prepared was added drop-wise to the sodium hydroxide solution with stirring. The rest was added after six minutes and the reaction was stopped after ten minutes. The crude material was isolated as yellow crystals with a Büchner funnel and washed with 3 x 100 mL of water.

The crude was purified by recrystallization. The crude material was transferred to a 250 mL beaker with a stir bar and 150 mL of 70% ethanol was added. Heating was done until boiling, then more solvent was added until all material was dissolved. The reaction mixture was cooled in an ice bath, and the resulting crystals were collected with a Büchner funnel to yield yellow , flaky crystals (8.70 g, 74%).

^{1}H- NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 16.0 Hz, 2H), 7.63 – 7.60 (m, 4H), 7.43-7.39 (m, 6H), 7.09 (d, J = 16.0 Hz, 2H).

The data is consistent with literature [67]

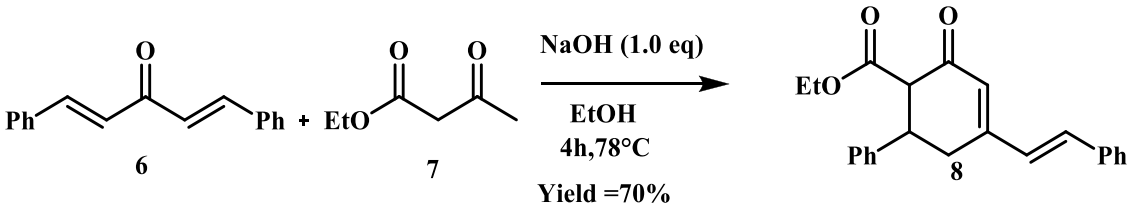
^{13}C- NMR (101 MHz, $CDCl_3$) δ 188.9, 143.5, 134.6, 130.5, 129.0, 128.4, 125.5.

GC-MS: t_R = 9.44 min, M^+ = 234

IR (cm^{-1}): 3056, 3027, 1649, 1626, 1590, 1573, 1495, 1447, 1332, 1284, 1100, 1076, 1186.

Spectra can found in Appendix 1-4

Synthesis of compound 8



In a 100 mL round bottomed flask equipped with a reflux condenser and a stir bar, dibenzylidene acetone (740 mg, 3.15 mmol, 1.75 eq), ethyl acetoacetate (410 mg, 3.15 mmol, 1.75 eq) and sodium hydroxide (72 mg, 1.80 mmol, 1.0 eq) and 30 mL of 96% ethanol was refluxed for 4 hours at 78°C. After reflux, small amount of water was added to reaction mixture, and allowed to cool for 2 days in refridgerator. The crude material was collected with a Bùhner funnel, washed with water. The crude was purified by recrystallization. Reflux in ethanol 70% was done until all material was fully dissolved, then cooled in an ice bath, and crystals were collected with a Bùhner funnel, yield (0.77 g, 70%).

Melting point: 132-134 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 2H), 7.35-7.33 (m, 8H), 6.97 (ABq, 2H), 6.20 (s, 1H), 4.05 (q, 2H), 3.76 – 3.73 (m, 2H), 3.05 (dd, J = 4Hz, 1H), 2.74-2.69 (m, 1H), 1.04 (t, J = 4 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$) ppm 194.1, 169.2, 155.7, 140.9, 136.1, 135.5, 1239.5, 128.9, 128.8, 127.5, 127.4, 126.8, 60.9, 60.2, 43.9, 33.4, 13.9.

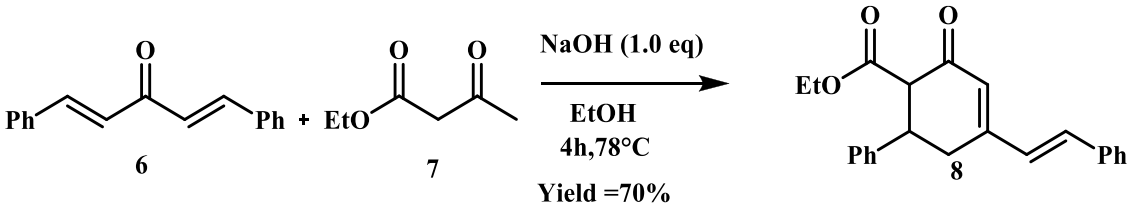
HRMS (ESI): *m/z*: $[M+H]^+$, calculated: 347.1642, Found: 347.1640

IR (cm^{-1}) 3061, 3030, 2982, 2903, 1737, 1657, 1618, 1585, 1495, 1453, 1383, 1304, 1255, 1173, 1143, 1585, 1174, 1143.

Spectra be found in appendix 5-8

Multivariate Optimization of Robinson Annulation

During the optimization process, the yield was measured using GC based on a calibration curve determined in advance.



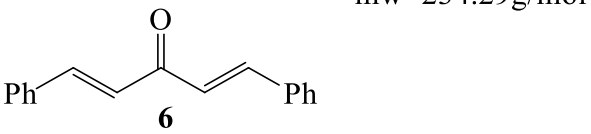
Calibration curve

The Robinson Annulation product made previously was used as product and a phenyl cyclohexane stock solution was used as internal standard to make a calibration curve.

Preparation of internal standard

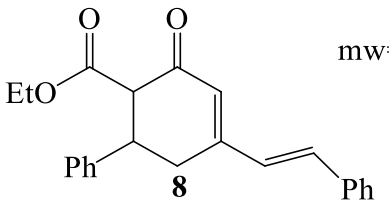
Phenyl cyclohexane (0.095 g, 5.9×10^{-4}mol) was diluted in ethyl acetate (9.00 mL) to make a solution (0.059 M). 1.00 mL from the first solution was also diluted in ethyl acetate (9.00 mL) to make a solution (5.90×10^{-3}M) and, finally, 1.00 mL from the second solution wasdiluted in ethyl acetate (1.00 mL) to make a solution (2.95×10^{-3}M).

Preparation of product



mw=234.29g/mol

dibenzylideneacetone



mw= 346.42g/mol

Product

Concentration of the product was calculated theoretically from dibenzylideneacetone (DA).

The first step was to calculate the concentration of DA in reaction mixture at the beginning of the reaction in order to determine the concentration of the product.

In reaction, ethanol (90%, 30 mL), DA (0.74 g, 3.15 mmol), ethyl acetoacetate (0.41 g, 3.15 mmol, 0.40 mL), was mixed with sodium hydroxide and heated for 4h.

Total volume of reaction mixture (V_t) equals to solvent (30 mL) and ethyl acetoacetate (0.40 mL).

V_t (30+0.4) mL =30.4 mL = 3.04×10^{-2}L. (V_t = total volume of reaction mixture)

Moles (n) of dibenzylideneacetone in reaction mixture.

n = (0.74 g /234.29 g/mol) = 3.15×10^{-3} moles

Concentration (C) of dibenzylideneacetone in reaction mixture

C= (3.15 mol x 10^{-3}/3.04 x 10^{-2} L) = 1.04×10^{-1} M.

If all amount of dibenzylideneacetone (1.04×10^{-1} M) is converted to product, the expected yield is 100 %. The expected yield at 100 % was calculated theoretically from DA. Molecular weight of compound **6** is 234.29 g/mol and product **8** is 346.42 g/mol. Amount of compound **6 (**1.04×10^{-1} M) in reaction mixture is 0.74 g and expected yield of product **8** is

Yield (100 %) = 0.74 g x346.42g/mol / 234.29 g/mol = 1.09 g

After calculating expected yield at 100 %, the yield expected at 10 % was calculated.

The yield at 10%: 1.09 g /10 = 0.109 g in 1L

After calculating the expected yield at 10 % in 1L of reaction mixture, the yield expected at 10 % in 1 mL of reaction mixture was calculated.

Yield expected in 1mL is 109 mg/30.4 mL = 3.58 mg

Dibenzylideneacetone (0.30 g, 1.28 mmol) and ethyl acetoacetate (0.20 g, 1.54mmol, 0.20 mL) was also used and expected yield (10 %) of product **8** in 1 mL is 1.46 mg (calculation refer to compound **6** with 0.74 g).

Various amount of the product was measured (***table 10)*** and dissolved in 1.00 mL of internal standard (0.00295M) to run gas chromatograph. Data recorded with GC and determined calibration curve can be found in results section (page **27-28**).

In ***table 10***, (10 %) was calculated from compound **6** (0.30 g) and other from compound **6** (0.74 g).

Table 10: Amount of product **8** calculated

Yield %	amount (mg)	concentration (mmol/mL)
10 %	1.50	$4.2 X10^{-3}$
30 %	10.80	$3.14 X10^{-2}$
51%	18.40	$5.34 X10^{-2}$
70 %	25.10	$7.29 X10^{-2}$
92%	32.80	$9.53X10^{-2}$

Experimental procedure, preparation of G.C samples and calculation of analyte concentration.

General procedure

A round-bottomed flask equipped with a stir bar, a reflux condenser, ethanol, dibenzylideneacetone, ethyl acetoacetate and sodium hydroxide was heated for 4h. Experimental variables with their levels are shown in ***table 11.***

Table 11: Experimental variables

Variables	low level	high level
dibenzylideneacetone (mg)	300	740
ethyl acetoacetate (mg)	200	410
temperature (℃)	68	78
sodium hydroxide (mg)	72	170

Amount of the solvent used in reaction was decided according to the amount of dibenzylideneacetone, experiments with high concentration were performed in ethanol (30 mL) and 12 mL at low concentration.

General procedure for the preparation of gas chromatograph samples

When the reaction was stopped, the product started to precipitate, ethyl acetate was used to dissolve the precipitate, wash the reaction flask and to complete the transfer of reaction mixture into a volumetric flask. A 50 mL volumetric flask was used for experiments with dibenzylideneacetone at high concentration and 25 mL at low concentration.

In a separation funnel, around 8 mL of water was transferred in first, 1mL of the reaction mixture from round bottomed flask and 10 mL of EtOAc was added. Separation funnel was shaked, and then organic layer was separated from aqueous layer. In some experiments, organic layer was washed more than once with water. Organic layer was dried on sodium sulfate and the drying agent was filtered off.

The reaction mixture (0.5 mL) was mixed with 0.5 mL of internal standard solution (0.0059M) to run the gas chromatography.

Calculations of the sample concentration from the calibration curve

C_x/C_{is} is calculated from regression linear of calibration curve, Y= 8.3679x-1.706.

($Y= C_x/C_{is}$)

$C_x = YC_{is}$

Two examples that show how the sample concentration was calculated with calibration curve are shown below.

One for sample at high concentration (+): Exp no 2 (see *table 6 on page 21)*

1. Concentration of internal standard (C_{is}) = 0.00295 M

2. Peak area of internal standard (A_{is}) = 688.97

3. Peak area of analyte (A_x) = 209.67

4. Ax/A_{is} = 0.304

C_x/C_{is} = 0.304 x 8.3679 -1.706 = 0.84

C_x= (C_x/C_{is}) Cis = 0.84 x 0.00295 = 0.00247M

During the preparation of G.C samples, all reaction mixture with dibenzylideneacetone at high concentration was dissolved in 50 mL of the solvent, 1mL of the reaction mixture from 50mL was washed with water and extracted with ethyl acetate (10 mL), and 0.5 mL of the sample was mixed with 0.5 mL of internal standard to run gas chromatograph.

$C_{x\ (reaction)} = (C_x/C_{is})\ C_{is}$ x2x11x1.65 at high concentration

C_x (reaction) = 0.00247 x 11 x 2 x1.65 = 0.0896 mmol/mL

Yield % = 0.0896 x 100/ 0.104 = 86 % (reported in ***table 7 page 30)***

Example 2 a sample at low concentration (-): Exp no 7 (*table 6 page 29*)

1. Concentration of internal standard (C_{is}) = 0.00295 mmol/mL

2. Peak area of internal standard (A_{is}) = 684.6

3. Peak area of analyte (A_x) = 165.74

4. Ax/A_{is} = 0.242

C_x/C_{is} = 0.242 x 8.3679 -1.706 =0.319

C_x= (C_x/C_{is}) Cis = 0.319 x 0.00295 =0.00094 mmol/mL

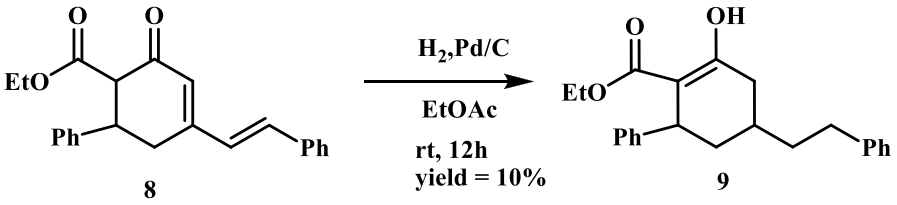
During the preparation of G.C samples, all reaction mixture with dibenzylideneacetone at low concentration was dissolved in the solvent (25 mL), 1mL of the reaction mixture from 25 mL was washed with water and extracted with ethyl acetate (10 mL), and 0.5 mL of the sample was mixed with 0.5 mL of internal standard to run gas chromatography.

$C_{x\ (reaction)} = {}_(C_x\backslash C_{is})\ c_{is}$ x2 x11 at low concentration

C_x (reaction) = 0.00094mmol/mL x 11 x 2 = 0.0207mmol/mL.

Yield % = 0.0207 x 100/0.0512 = 40 % (***table 7, page30***)

Hydrogenation of compound 8



In a 50 mL round bottomed flask, (346 mg, 1.0 mmol, 1.0 eq) of starting material and 10% Pd /C (35 mg) was dissolved in ethyl acetate (7 mL) and stirred under hydrogen atmosphere at room temperature for 12 hours .The catalyst was filtered off by simple filtration and the filter was washed by ethyl acetate (30 mL) and ethanol(30 mL), the filtrate was collected and concentrated on rotavapor.

The compound was purified with the column chromatography (3 % ethyl acetate in pentane) and collected as colorless crystals yield (34 mg, 10%),

Melting point: 84-86 ℃

^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 7.28 – 7.26 (m, 2H), 7.19 – 7.13 (m, 6H), 6.97 (d, *J* = 8Hz, 2H), 4.04-3.96 (m, 2H), 2.52 – 2.48 (m, 4H), 1.87-1.86 (m, 1H), 1.68 (d, *J* = 12Hz, 1H) 1.64-1.54(m, 2H), 1.54-1.52(m, 3H) 0.97 (t, *J* = 8 Hz, 3H).

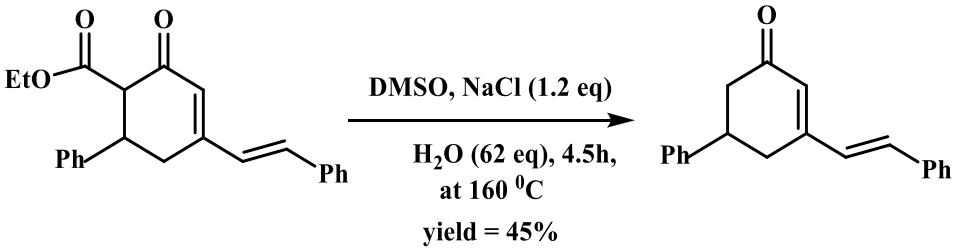
^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.2, 172.3, 146.1, 142.1, 128.3, 127.9, 125.6, 99.4, 60.1, 38.6, 38.1, 37.5 35.8, 32.9, 27.2, 14.0.

HRMS (ESI): *m/z*: $[M+H]^+$, calculated: 351.1955, found: 351.1955

IR (cm^{-1}): 3027, 2925, 1642, 1620, 1493, 1419, 1404, 13411275, 1212, 1155, 1118.

Spectra can be found in appendix 23-26

Decarboxylation of compound 8



In a 25mL two necked round bottomed flask equipped with a stir bar, a reflux condenser and a gas bubble, compound **2.5** (440 mg, 1.3 mmol, 1.0 eq) , DMSO (13 mL), water (1.5mL) and NaCl (74mL, 83 mmol, 1.2 eq) was heated at 160 °C for 4hours, reaction was mixture was cooled to room temperature in 30 min, then transferred to separator funnel and mixed with ice cooled water (140mL), the product was extracted with ethyl acetate (3x30mL). The collected extracts were washed with distilled water (5 x 50 mL) and dried over sodium sulfate.

The drying agent was filtered off and the filtrate was concentrated on rotavapor. The compound was recrystallized in heptane, collected as yellow crystals and dried on vacuum after 3 days (yield, 0.2 g, 45%).

Melting point: 112-114 ℃

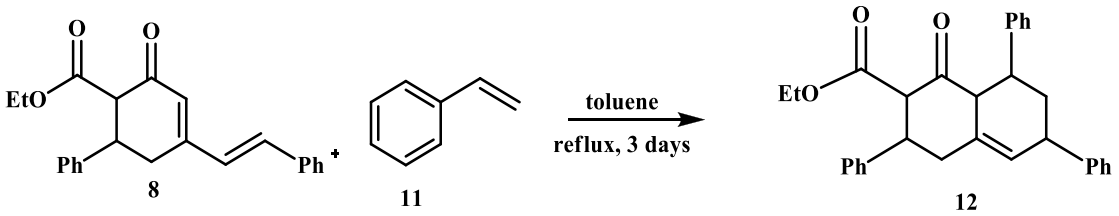
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.47 (m, 2H), 7.41 – 7.28 (m, 8H), 6.98 (ABq, 2H), 6.18 (s, 1H), 3.42-3.37 (m, 1H), 3.02 (dd, , *J* = 4, 12 Hz, 2H), 2.73 – 2.64 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 155.9, 143.4, 135.8, 135.6, 129.2, 128.8, 127.9, 44.4, 41.0, 33.1

HRMS (ESI): *m/z*: $[M+H]^+$, calculated: 275.1433, found: 275.1430

Spectra can be found in Appendix 27-29

Inverse electron demand Diels-Alder reaction



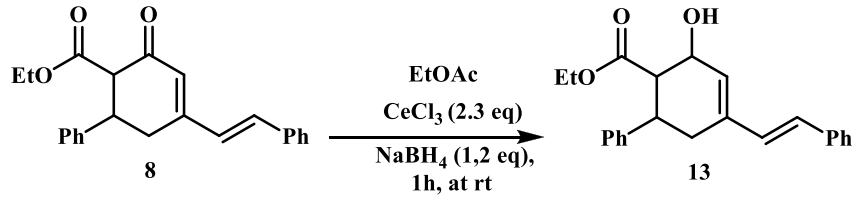
In a 25 mL two necked round bottomed flask equipped with a stir bar and a reflux condenser, toluene 8 mL, compound **11** (346 mg, 1 mmol, 1.0 eq), and styrene (104.15 mg, 8.6 mmol, 8.6 eq) was refluxed in 3 days and heated at 130 ℃ in dioxane in 2 days. Solvents were removed under reduced pressure.

Crude ^{1}H-NMR was recorded but it does not show compound **12,** but HRMS shows it**.**

HRMS (ESI): *m/z*: $[M+H]^{+}$, calculated 451.2268, found: 451.2268

Spectra can be found in appendix 30-31

Reduction of compound 8



In a 25mL round bottomed flask, starting material (300 mg, 0.86mmol, 1 eq), $CeCl_3.7H_2O$ mL (780 mg, 2.09 mmol, 2.3 eq) was dissolved in ethyl acetate (5 mL), $NaBH_4$ (40 g, 1.03 mmol, 1.2 eq) was slowly added under stirring, the reaction ran for 1hour at room temperature. Isolation was done by hydrolysis followed by extraction with diethyl ether. Ether extracts were dried over sodium sulfate, then drying agent was filtered off and the reaction mixture was concentrated on rotavapor.

Crude ^{1}H-NMR can be found in Appendix 32

Alkylation of compound 8 with allyl bromide

Two experimental procedures were attempted during the alkylation of compound **8** with allyl bromide.

Procedure one

In a 25 mL two necked round bottomed flask equipped with a stir bar dried in 2 days in oven at 110 ℃ compound **8** (104 mg, 0.3 mmol, 1.0 eq) dissolved in dry DMF (4 mL), DBU (46 mg, 0.3 mmol, 1.0 eq) was added under stirring, the resulting mixture was cooled in an ice bath and allyl bromide (55 mg, 0.45 mmol, 1.5 eq) was drop-wisely added under stirring during 4 min.

The reaction mixture was stirred at room temperature for 24 hours, heated at 40℃ overnight, next day, the temperature raised at 62℃, reaction was left to run more 4 days and stopped without completion

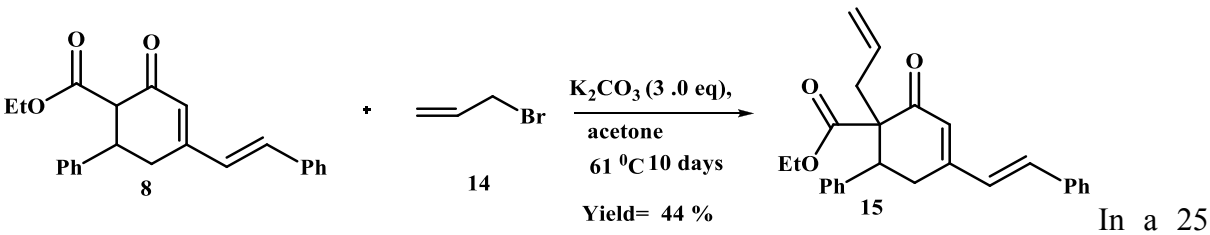
Isolation of the product: the reaction mixture was poured into water (10mL), and the product was extracted with $CHCl_3$ (2x10mL). The $CHCl_3$ extracts were washed with water (5x10mL), then dried over Na_2SO_4 and the drying agent was filtered off. The reaction mixture was concentrated on rotavapor.

Crude ^{1}H-NMR was recorded.

HRMS (ESI): *m/z*: $[M+H]^+$, calculated: 387.1955, found: 387.1959

Spectra can be found in appendix 33-34.

Procedure two



In a 25 mL two necked round bottomed flask equipped with a stir bar, compound **2.5** (104 mg, 0.3 mmol, 1 eq), K_2CO_3 anhydrous (123 mg, 0.89 mmol, 3 eq), allyl bromide (220 mg, 1.81 mmol, 6 eq) was dissolved in acetone dry (5 mL) , the mixture was stirred at room temperature overnight. The next day, the reaction was heated at 55℃ and finished after 10 days.

Isolation of the product: K_2CO_3 was filtered off after cooling the reaction mixture at room temperature, washed with $CHCl_3$, the filtrate was poured into water (10 mL) and the solution was acidified with 2MHCl (5 mL). The product was extracted with $CHCl_3$ (3 x 10 mL). $CHCl_3$ extracts were dried over sodium sulfate and the reaction mixture was concentrated on rotavapor.

The crude material was recrystallized in ethanol (70%), collected as colorless crystals and dried on high vacuum overnight (yield: 44 mg, 42%).

Melting point: 134-136 ℃

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49- 7.47 (m, 2H), 7.37-7.32 (m, 6H), 7.27 – 7.25 (m, 2H), 6.99 (ABq, 2H), 6.24 (s, 1H), 5.67-5.62 (m, 1H), 5.17-5.16 (m, 2H), 4.18 - 4.10 (m, 2H), 3.58 (dd, *J* = 8, 24 Hz, 1H), 3.36-3.31 (m, 1H), 3.08 (dd, *J* = 4, 16 Hz, 1H), 2.89 (dd, *J* = 16, 24 Hz, 1H), 2.31(dd, *J* = 2, 24 Hz, 1H), 1.19 (t, *J* = 8 Hz, 3H).

^{13}C-NMR (100 MHz, CDCl3): δ 190.0, 170.3, 156.9, 139.7, 135.8, 133.7, 129.3, 128.7, 128.6, 128.5, 127.6, 127.4, 119.5, 61.3, 60.8, 44.9, 35.7, 29.9, 13.8

HRMS (ESI): *m/z*: $[M+H]^+$, calculated: 387.1955, found: 387.1954

IR (cm^{-1}) 1734, 1713, 1646, 1612, 1588, 1495, 1451, 1428, 1387, 1337, 1275, 1255, 1219, 1190, 1115.

Spectra can be found in appendix 35-38

Alkylation with propargyl bromide, benzyl bromide, 1-bromoacetophenone, 1-bromo-4-phenylbutane and methyl acrylate.

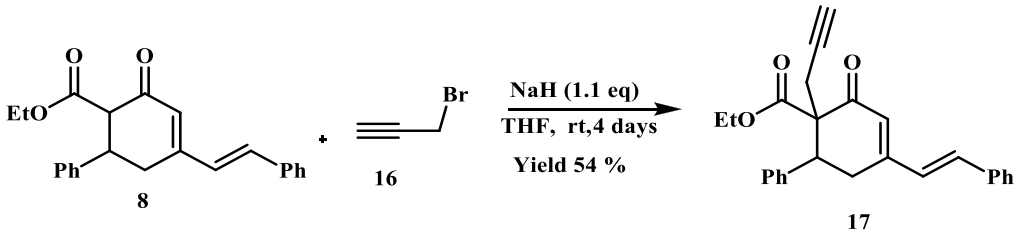
General procedure for alkylation

Reactions were performed in anhydrous conditions and under nitrogen gas atmosphere in glassware and stir bars, which were dried in oven at 110 ℃ in 2 days. Glassware were also dried under vacuum before transferring reactants in reaction flask. Under nitrogen atmosphere, NaH 60% in mineral oil was washed with hexane two times, then cooled in an ice bath. Dry THF was added and the mixture was stirred around 5 min. Compound **8** dissolved in dry TFH was added drop-wise, reaction stirred around 8 min, alkylating reagent was carefully added and the resulting mixture was stirred around 10 min. The ice bath was removed and reaction was stirred at room temperature and heated at various temperature in some cases. Isolation of the product: Sodium hydride was quenched with saturated ammonium chloride (ca 15 mL), then reaction mixture was transferred into a separatory

funnel, water (ca,10mL) was added and the product was extracted with diethyl ether (3 x10 mL).

Diethyl ether extracts were washed with brine (3 x10 mL) and dried over sodium sulfate. The drying agent was filtered off and the reaction mixture was concentrated on rotavapor. The compound was purified by crystallization or column chromatography.

Alkylation with propargyl bromide



Sodium hydride 60% in mineral oil (33mg, 0.83 mmol, 1.1 eq) washed with hexane (2x4mL), THF dry (4mL), compound **8** (260 mg, 0.75 mmol, 1 eq) dissolved in THF dry (3 mL) and propargyl bromide (500mg, 4.3 mmol, 4.2 eq) was added and the resulting mixture was stirred in 4 days.

The compound was crystallized in ethanol (70 %), collected as colorless crystals and dried on vacuum overnight after three days (yield: 140 mg, 54%).

Melting point: 133-135 ℃

^{1}H- NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.40-7.32 (m, 8H), 7.03 (ABq, 2H), 6.29 (s, 1H), 4.15-4.10 (m, 2H), 4.03 (dd, *J* =4, 16 Hz, 1H), 3.40-3.36 (m, 1H), 3.21 (dd, *J* = 2, 20 Hz, 1H), 2.97 (dd, *J* = 12, 16 Hz, 1H), 2.34 (dd, *J* =16, 20 Hz, 1H), 2.13 (dd, *J* = 2, 4 Hz, 1H), 1.18 (t, *J* = 8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 194.1, 169.0, 157.1, 139.0, 136.3, 135.8, 129.3, 128.9, 128.7, 128.6, 128.3, 127.9, 127.4, 127.1, 80.4, 71.5, 61.6, 60.3, 44.9, 29.2, 21.6, 13.9

HRMS (ESI): *m/z*: $[M+H]^+$,calculated: 385.1798, found:385.1802

IR (cm^{-1}) 3283, 3029, 1729, 1651, 1612, 1587, 1495, 1452, 1417, 1387, 1308, 1277, 1257, 1224, 1212, 1197, 1178, 1121.

Spectra can be found in appendix 39-42

Alkylation with benzyl bromide

Two experimental procedures were attempted during the alkylation of compound **8** with benzyl bromide.

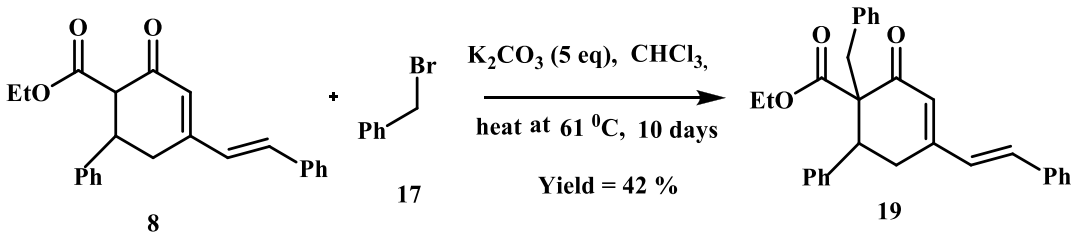
General procedure for alkylation.

Sodium hydride 60% in mineral oil (33 mg, 0.83 mmol, 1.1 eq) washed with hexane (2 x 4 mL), dry THF (4 mL), compound **8** (260 mg, 0.75 mmol, 1.0 eq) dissolved in dry THF (3 mL) and benzyl bromide (716 mg, 4.18 mmol, 5.6 eq) was added. The reaction was run for 4 days and stopped without completion. Crude ^{1}H-NMR was recorded.

HRMS (ESI): *m/z:* calculate ($C_{30}H_{28}O_3Na$): 459.1931, found: 459.1929

Spectra can be found in Appendix 43-44.

Procedure two



In a 25 mL two necked round bottomed flask equipped with a stir bar and a reflux condenser were dried in oven in 2 days, then dried again with the vacuum around 20 min. Under nitrogen gas atmosphere, compound **8** (335 mg, 0.96 mmol, 1 eq), K_2CO_3 anhydrous (700 mg, 5.06 mmol, 5.1 eq), benzyl bromide (830 mg, 4.86 mmol, 5.0 eq) and $CHCl_3$ (12 mL) was transferred in reaction flask according to their written order. The reaction mixture was heated at 61℃ in 24 hours. The reaction was left to run for 10 days where TLC showed big spot of the product compared to one of compound 8

Isolation of the product: K_2CO_3 was filtered off after cooling the reaction mixture at room temperature, washed with $CHCl_3$, the filtrate was poured into water (10 mL) and the solution was acidified with 2MHCl (10 mL). The organic layer was separated from aqueous phase, dried on Na_2SO_4, and the reaction mixture was concentrated on rotavapor.[65]

The compound was purified with column chromatograph (3.5% EtOAc in pentane) and collected as yellow viscous liquid, yield (140 mg, 42%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8 Hz, 2H), 7.37– 7.34 (m, 4H), 7.27-7.24 (m, 3H), 7.20 – 7.15 (m, 4H), 7.10 (d, *J* = 8 Hz, 2H), 6.95 (ABq, 2H), 6.28 (s,1H), 4.25-4.23 (m, 2H), 3.89 (d, *J* = 12 Hz, 1H), 3.46 (dd, *J* = 8, 16 Hz, 1H), 3.30-3.22 (m, 1H), 2.87 (d, *J* = 16 Hz, 1H), 2.79 (dd, *J* = 20, 28 Hz, 1H), 1.26 (t, *J* = 8 Hz, 3H).

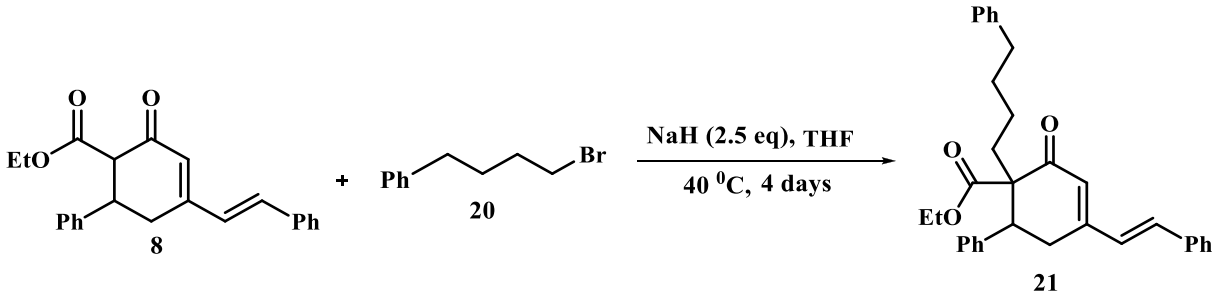
^{13}C-NMR (100 MHz, CDCl3): δ 196.7, 170.7, 156.4, 140.8, 137.8, 136.8, 136.0, 135.8, 131.0, 129.4, 129.0, 128.9, 128.6, 128.5, 128.2, 127.6, 127.3, 126.5, 125.3, 61.9, 61.6, 44.5, 36.9, 31.0, 13.8

HRMS (ESI): *m/z*: $[M+H]^+$, calculated:437.2111, found: 437.2113

IR (cm^{-1}) 3029, 1737, 1650, 1616, 1589, 1495, 1452, 1387, 1262, 1183, 1164, 1121.

Spectra can be found in Appendix 45-48

Alkylation with 1-bromo 4-phenylbutane

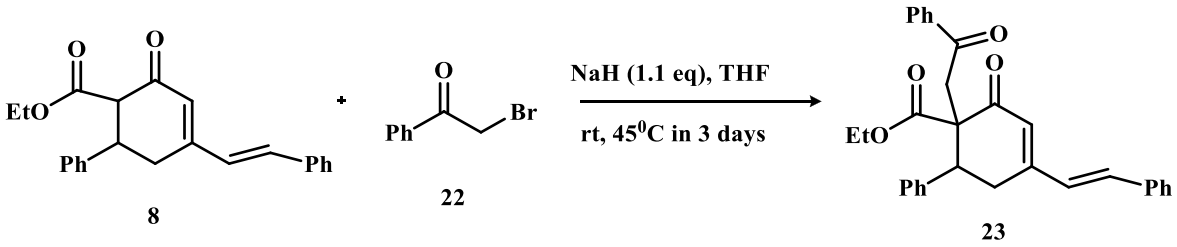


Sodium hydride 60% in mineral oil (28 mg, 0.71 mmol, 2.5 eq) was washed with dry THF (2x4mL), compound **8** (100 mg, 0.28 mmol, 1.0 eq) dissolved in dry THF (3 mL) and 1-bromo 4- phenyl butane (180 mg, 0.85 mmol, 3.0 eq) was added. The reaction mixture ran at room temperature overnight, the next day, the reaction was heated at 40 ℃ and left to run for 3 days and stopped without completion. Crude ^{1}H-NMR was recorded.

HRMS (ESI): *m/z*: $[M+H]^+$, calculated = 479.2581, found =479.2583.

Spectra can be found in Appendix 49-50.

Alkylation with 1-bromoacetophenone

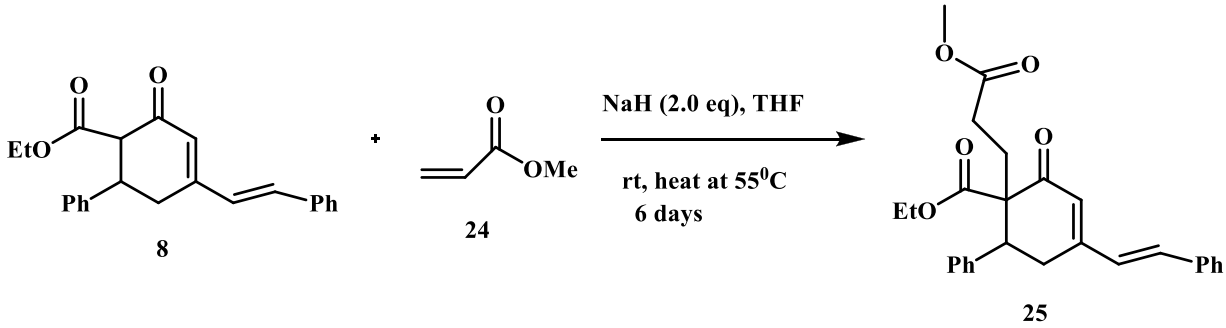


Sodium hydride 60% in mineral oil (33 mg, 0.83 mmol, 1.1 eq) was washed with dry THF (2x4mL), compound **8** (260 mg, 0.75 mmol, 1eq) dissolved in THF dry (3 mL), and 2-bromoacetophenone (747 mg, 3.75 mmol, 5.0 eq) was drop-wisely added and reaction ran overnight. The next day, the reaction was heated at 40 ℃ and left to run for 2 days further. After 3 days, no reaction happened and the reaction was stopped.

The reaction was repeated by doubling amount of Sodium hydride (66 mg, 1.66 mmol, 2.2 eq), and was refluxed but it changed nothing. Crude ^{1}H NMR was recorded. HRMS does not show the product.

Spectra can be found in appendix 51-52.

Alkylation with methyl acrylate



Sodium hydride 60% in mineral oil (21 mg, 0.54 mmol, 1.93 eq) was washed with hexane (2x4 mL), Robinson annulation product (100 mg, 0.28 mmol, 1.0 eq) dissolved in dry THF (3 mL) and methyl acrylate (37 mg, 0.43 mmol, 1.5 eq) was added and reaction ran overnight at room temperature. The next day, the reaction was heated at 45℃ and ran for 6 days.

Crude 1H-NMR was recorded.

Crude HRMS (ESI): *m/z*: $[M+H]^+$, calculated for $[C_{27}H_{28}O_5Na]$ = 455.1829, found =455.1829

Spectra can be found in appendix 53-54.

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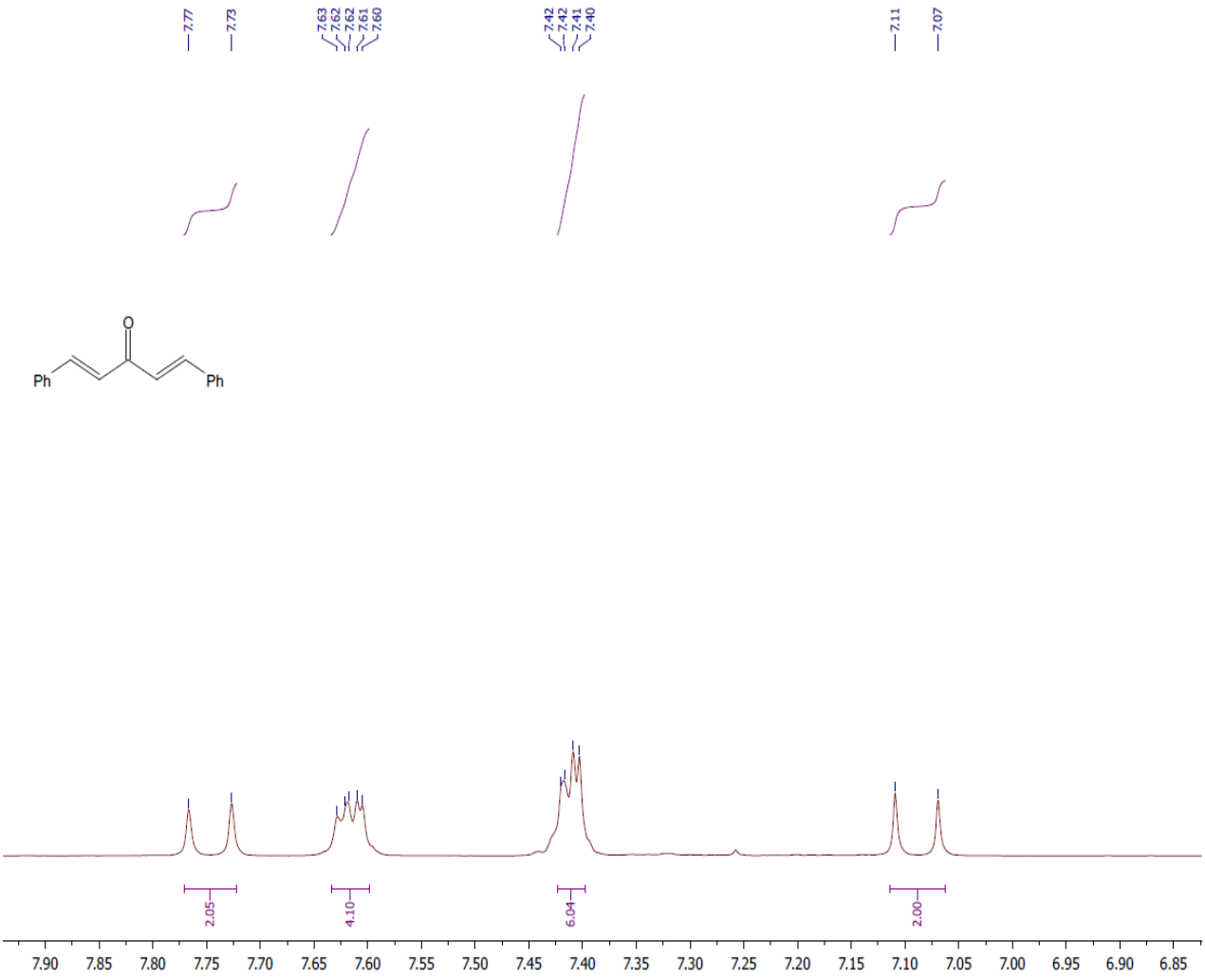
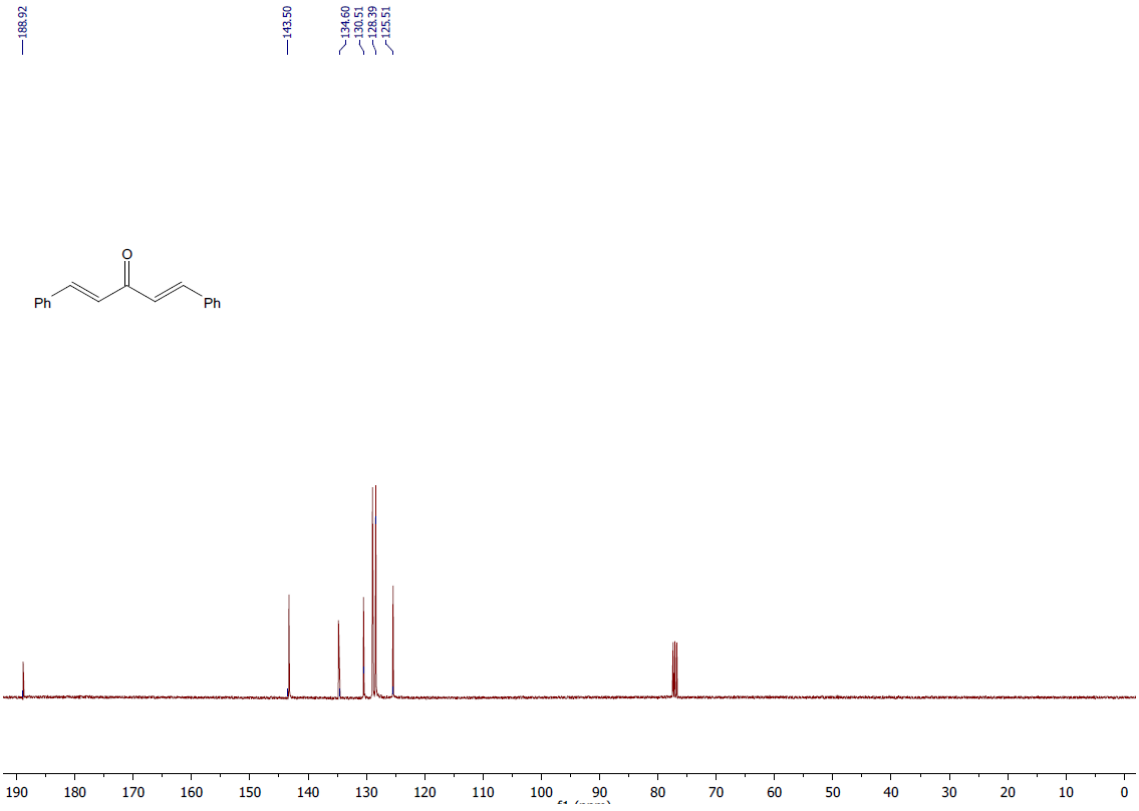
(67) B.S.Furniss, A. J. H., P.W.G.Smith and A.R.Tatachell *VOGEL'S, Textbook of Organic chemistry*. fifth edition ed.; 1991.

APPENDICES

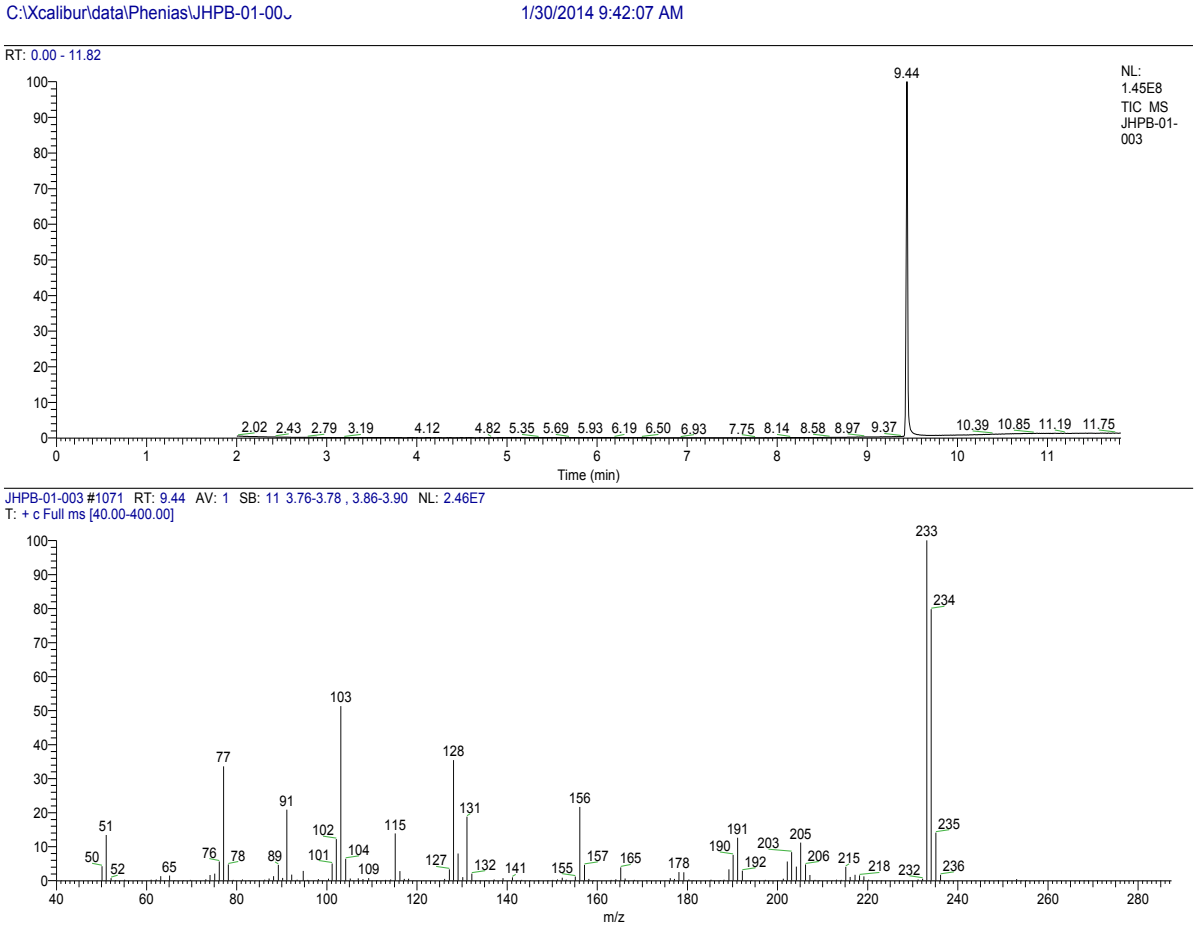
Appendix 1



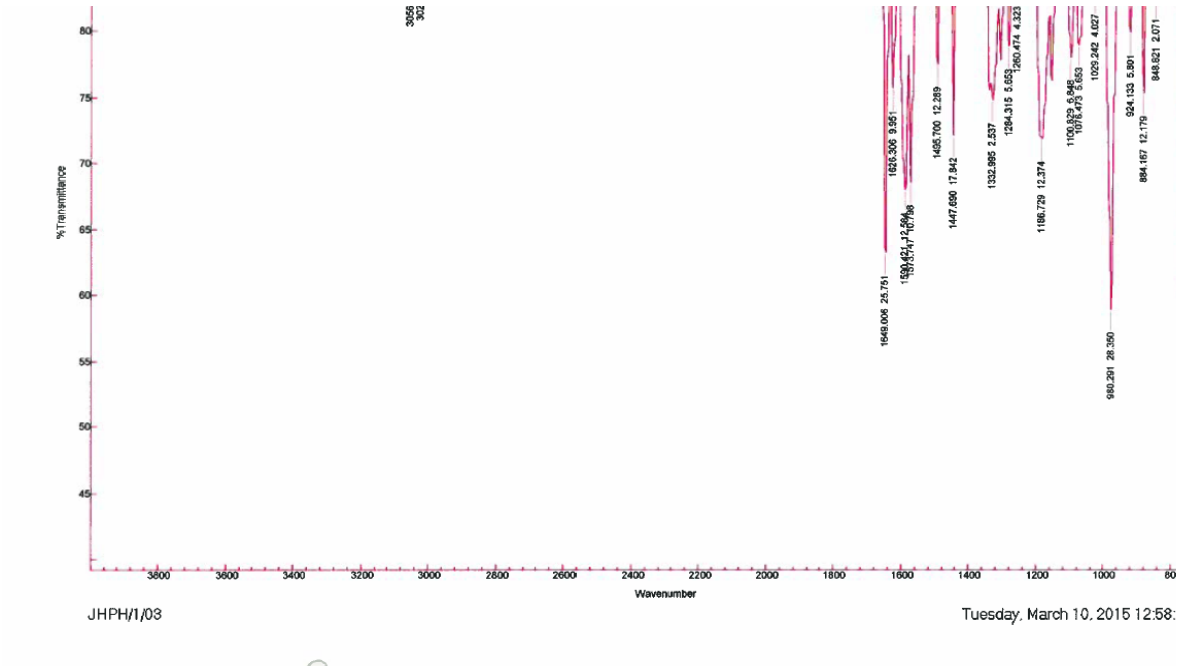
Appendix 2


188.92
143.50
134.60
130.51
128.39
125.51
O
Ph
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

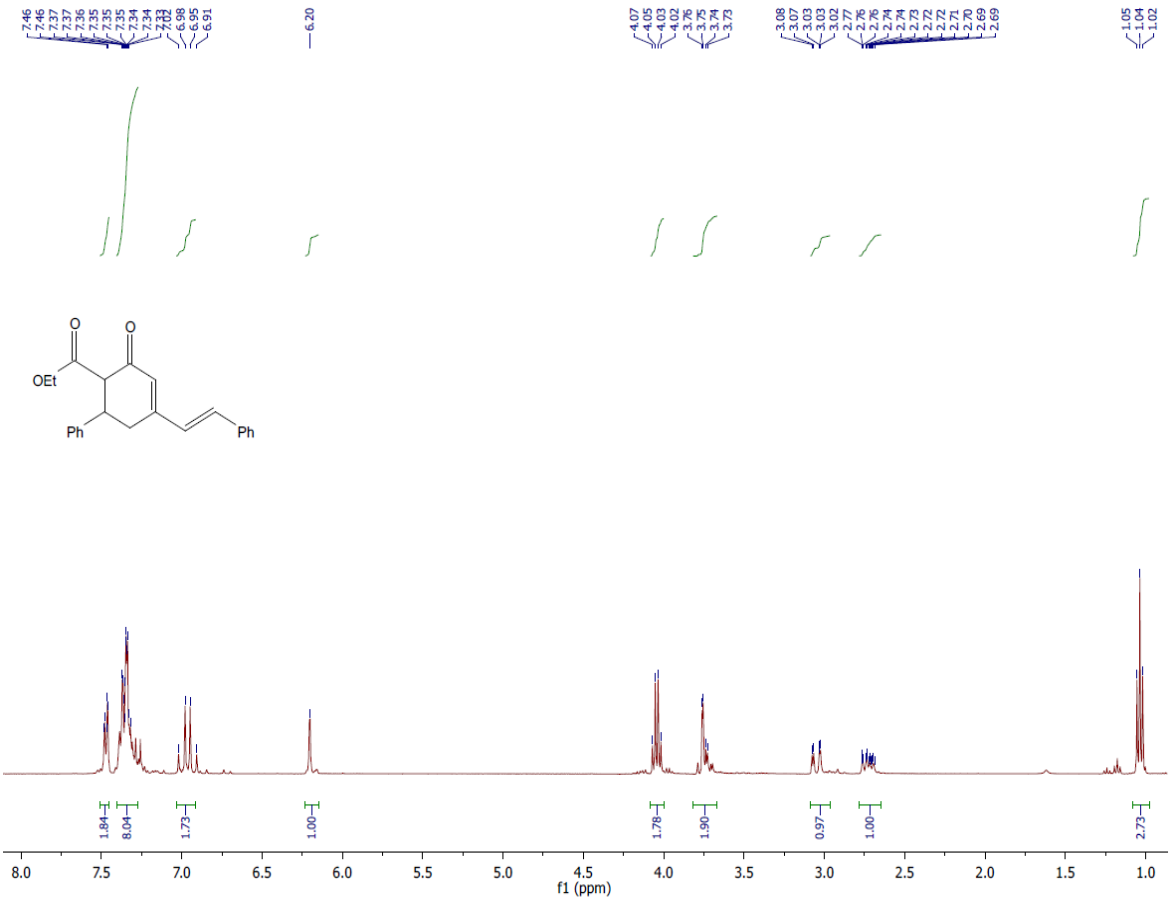
Appendix 3


C:\Xcalibur\data\Phenias\JHPB-01-00
1/30/2014 9:42:07 AM
RT: 0.00 - 11.82
9.44
NL:
1.45E8
TIC MS
JHPB-01-
003
2.02 2.43 2.79 3.19 4.12 4.82 5.35 5.69 5.93 6.19 6.50 6.93 7.75 8.14 8.58 8.97 9.37 10.39 10.85 11.19 11.75
Time (min)
JHPB-01-003 #1071 RT: 9.44 AV: 1 SB: 11 3.76-3.78 , 3.86-3.90 NL: 2.46E7
T: + c Full ms [40.00-400.00]
233
234
103
77
128
91
131
156
51
102
115
191
205
203
235
190
104
50
52
65
76
78
89
101
109
127
132
141
155
157
165
178
192
206
215
218
232
236
m/z

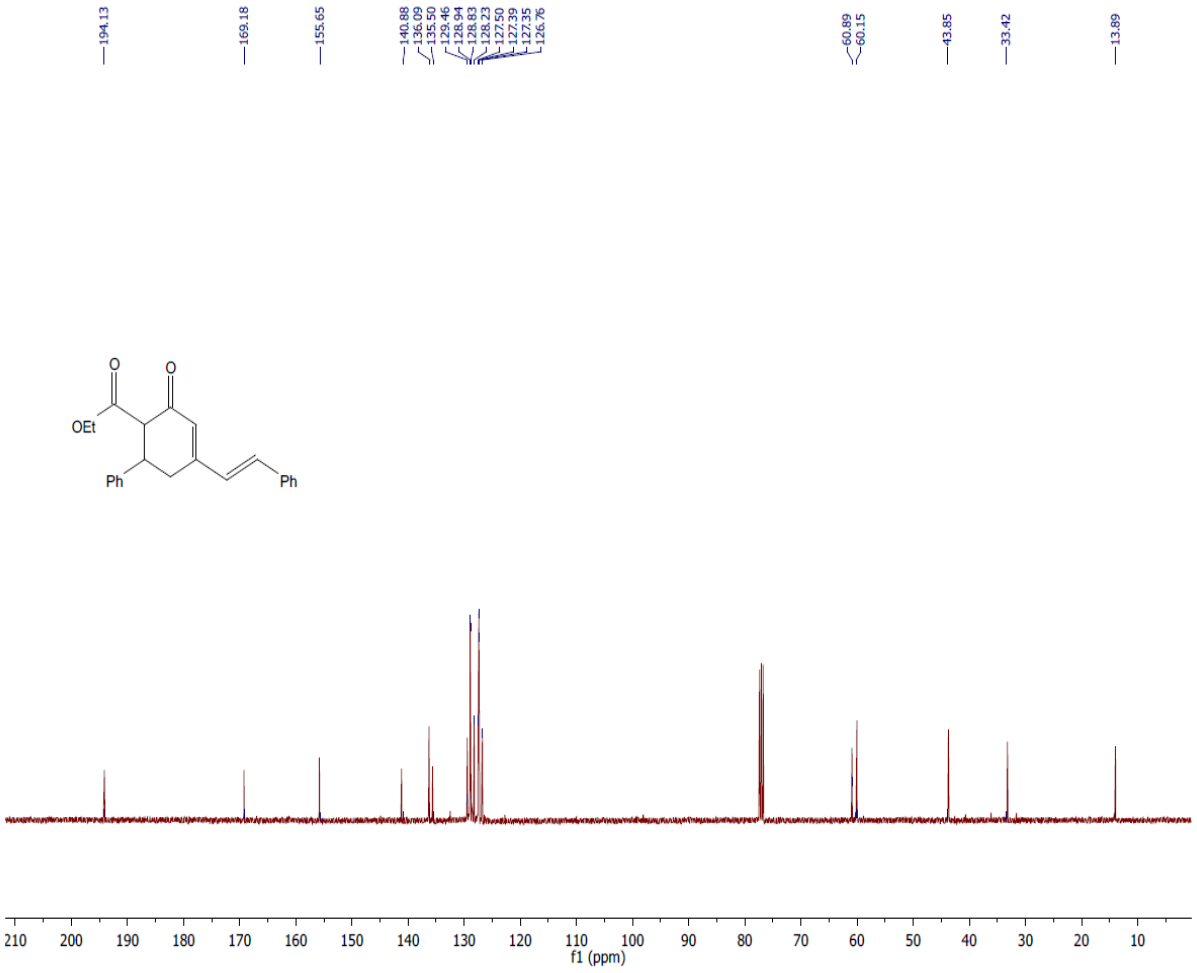
Appendix 4


%Transmittance
Wavenumber
JHPH/1/03
Tuesday, March 10, 2015 12:58:

Appendix 5

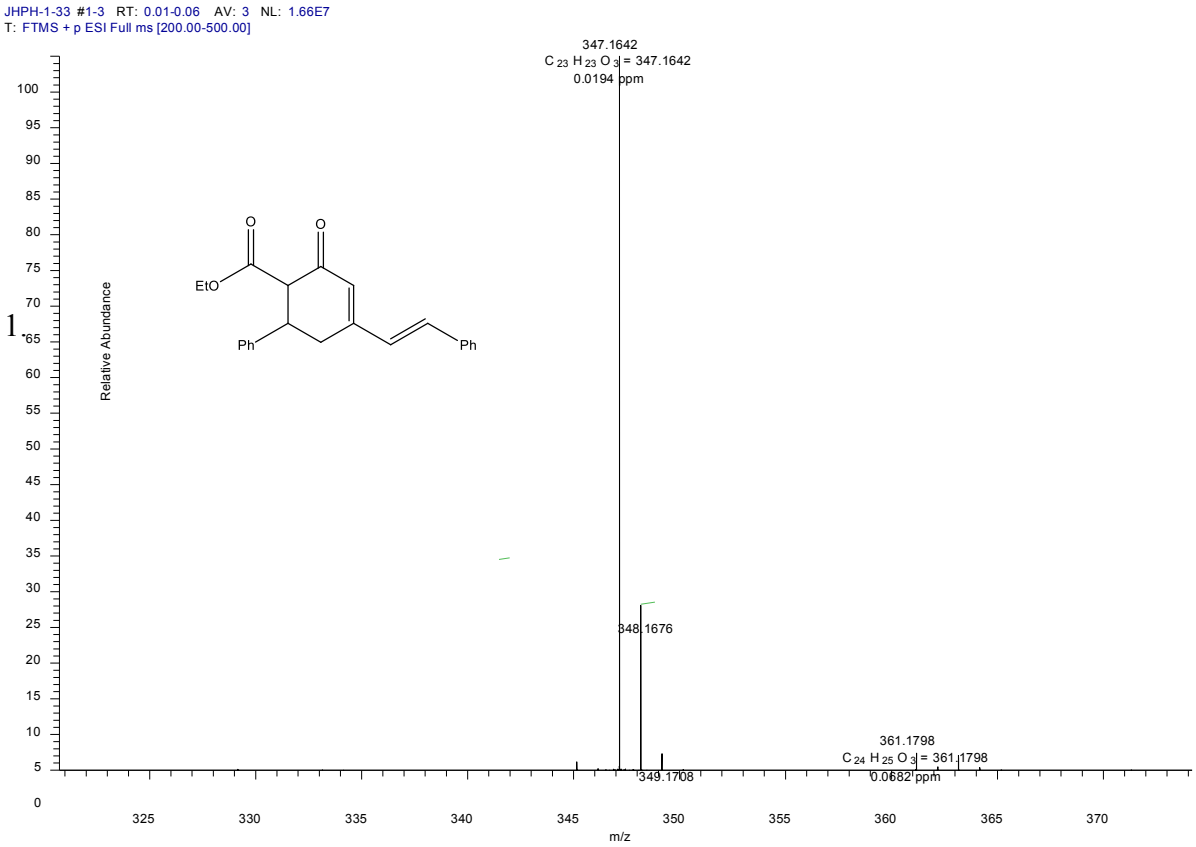

7.46
7.46
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.34
7.33
7.02
6.98
6.95
6.91
6.20
4.07
4.05
4.03
4.02
3.76
3.75
3.74
3.73
3.08
3.07
3.03
3.03
3.02
2.77
2.76
2.76
2.74
2.74
2.73
2.72
2.72
2.71
2.70
2.69
2.69
1.05
1.04
1.02
O
O
OEt
Ph
Ph
1.84
8.04
1.73
1.00
1.78
1.90
0.97
1.00
2.73
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

Appendix 6

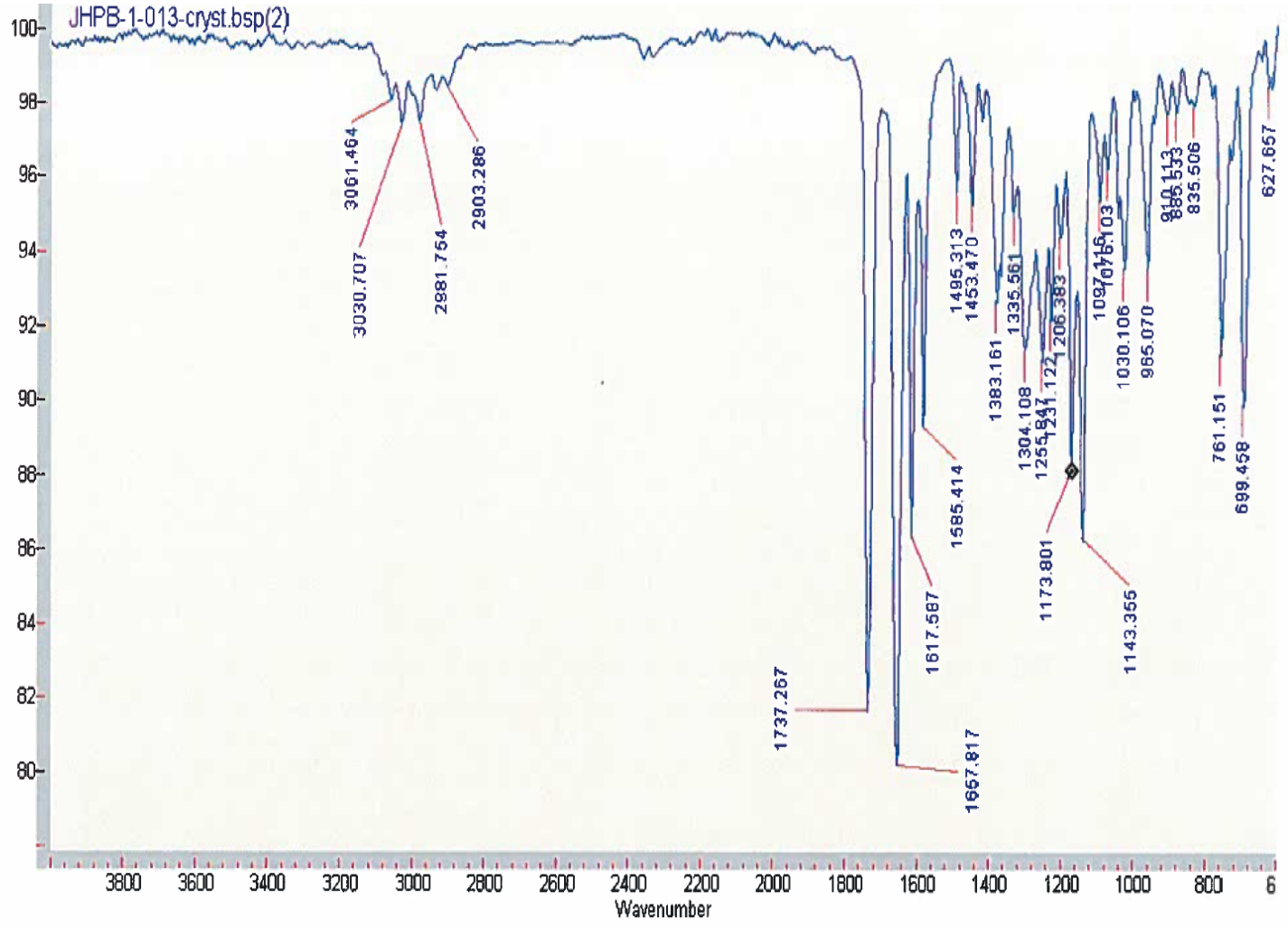

194.13
169.18
155.65
140.88
136.09
135.50
129.46
128.94
128.83
128.23
127.50
127.39
127.35
126.76
60.89
60.15
43.85
33.42
13.89
O
O
OEt
Ph
Ph
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Appendix 7

1.


JHPH-1-33 #1-3 RT: 0.01-0.06 AV: 3 NL: 1.66E7
T: FTMS + p ESI Full ms [200.00-500.00]
347.1642
C 23 H 23 O 3 = 347.1642
0.0194 ppm
348.1676
349.1708
361.1798
C 24 H 25 O 3 = 361.1798
0.0682 ppm
Relative Abundance
m/z
EtO
Ph
Ph

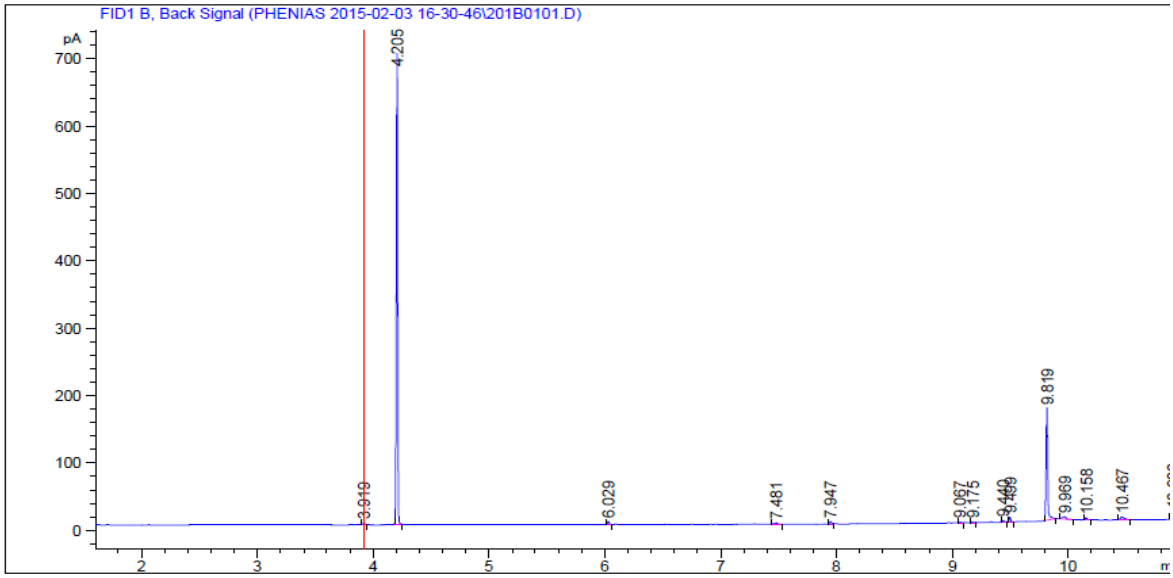
Appendix 8


JHPB-1-013-cryst.bsp(2)
100
98
96
94
92
90
88
86
84
82
80
3061.464
3030.707
2981.754
2903.286
1737.267
1667.817
1617.587
1585.414
1496.313
1453.470
1383.161
1335.561
1304.108
1255.841
1231.122
1206.383
1173.801
1143.355
1097.116
1076.103
1030.106
965.070
910.113
885.133
835.506
761.151
699.458
627.657
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
Wavenumber

Appendix 9

Data File C:\CHEM32\1\DATA\PHENIAS 2015-02-03 16-30-46\201B0101.D
Sample Name: JHPH-1-INT1.5

```
==========================================================================
Acq. Operator    : Jostein                          Seq. Line :   1
Acq. Instrument : Agilent 7820A                      Location : Vial 201
Injection Date   : 2/3/2015 4:32:18 PM                    Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-03 16-30-46\PHENIAS.M
Last changed     : 4/10/2014 9:57:40 AM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   3.919 BB    0.0128    2.67117    3.25254  0.32992
   2   4.205 BB    0.0128  567.29431  691.28265 70.06750
   3   6.029 BB    0.0161    4.81489    4.65252  0.59470
   4   7.481 BB    0.0214    2.64301    1.77188  0.32644
   5   7.947 BB    0.0178    4.12294    3.68972  0.50923
   6   9.067 BB    0.0151    1.00245    1.05096  0.12381
   7   9.175 BB    0.0154    1.19768    1.22884  0.14793
   8   9.440 BB    0.0185    2.74417    2.20155  0.33894
   9   9.499 BB    0.0156    6.77618    6.83063  0.83694
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	9.819	BB	0.0161	171.20459	164.98840	21.14577
11	9.969	BB	0.0368	7.50087	3.31799	0.92645
12	10.158	BB	0.0219	4.12302	2.95363	0.50924
13	10.467	BB	0.0354	9.56947	3.95645	1.18194
14	10.906	BB	0.0303	21.21800	10.36642	2.62067
15	11.000	BB	0.0259	2.75698	1.58635	0.34052
Totals :				809.63971	903.13053	

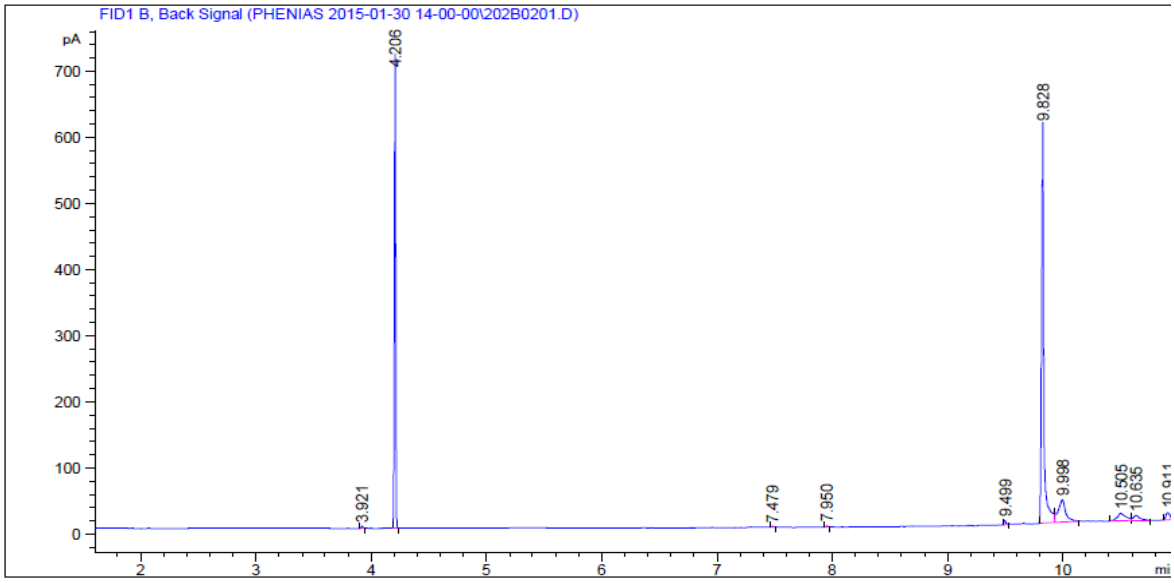
==========

*** End of Report ***

Appendix 10

Data File C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\202B0201.D
Sample Name: JHPH-1-IN10.8

```
======================================================================
Acq. Operator    : Jostein                      Seq. Line :   2
Acq. Instrument : Agilent 7820A                  Location : Vial 202
Injection Date  : 1/30/2015 2:19:41 PM               Inj :   1
                                                Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\PHENIAS.M
Last changed     : 4/10/2014 9:57:40 AM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```

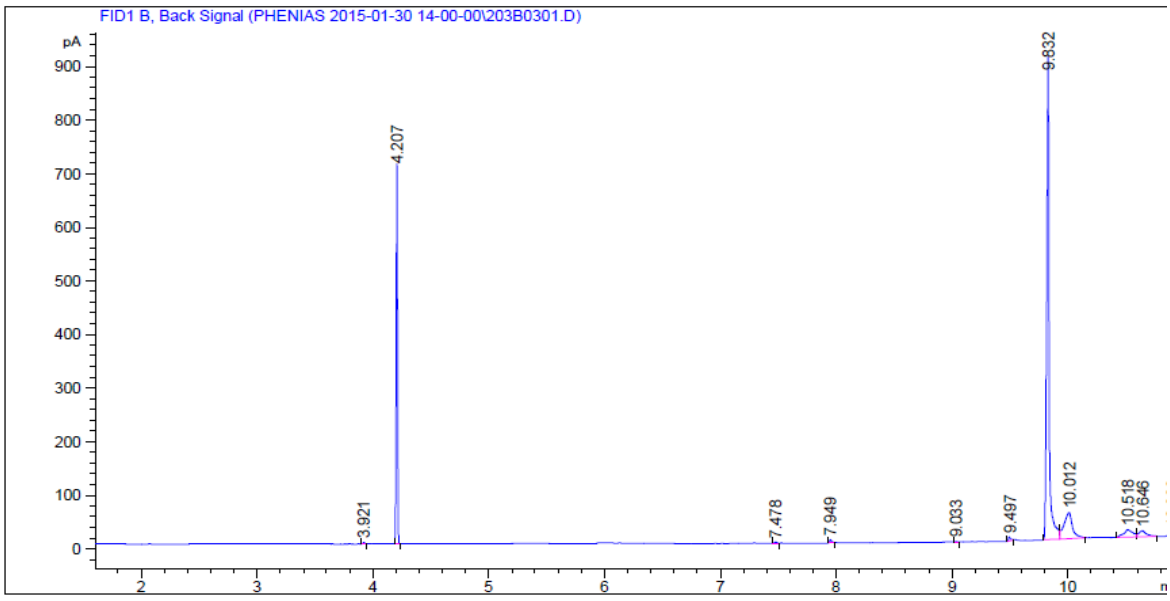



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.921	BB	0.0124	2.67578	3.37758	0.15611
2	4.206	BB	0.0126	573.78455	710.01965	33.47659
3	7.479	BB	0.0153	1.84556	1.91186	0.10768
4	7.950	BB	0.0186	2.95080	2.35184	0.17216
5	9.499	BB	0.0173	8.06830	6.66154	0.47073
6	9.828	BB	0.0214	855.42230	601.85376	49.90832
7	9.998	BB	0.0603	150.86433	33.67999	8.80195
8	10.505	BV	0.0676	58.11494	11.52935	3.39063
9	10.635	VB	0.0532	32.54914	7.84701	1.89903

Appendix 11

```
Data File C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\203B0301.D
Sample Name: JHPH-1-IN18.4

    ======================================================================
    Acq. Operator    : Jostein                        Seq. Line :   3
    Acq. Instrument : Agilent 7820A                    Location : Vial 203
    Injection Date   : 1/30/2015 2:37:12 PM                Inj :   1
                                                     Inj Volume : 1 µl
    Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\PHENIAS.M
    Last changed     : 4/10/2014 9:57:40 AM by Jostein
    Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
    Last changed     : 2/26/2015 3:26:37 PM by Jostein
```

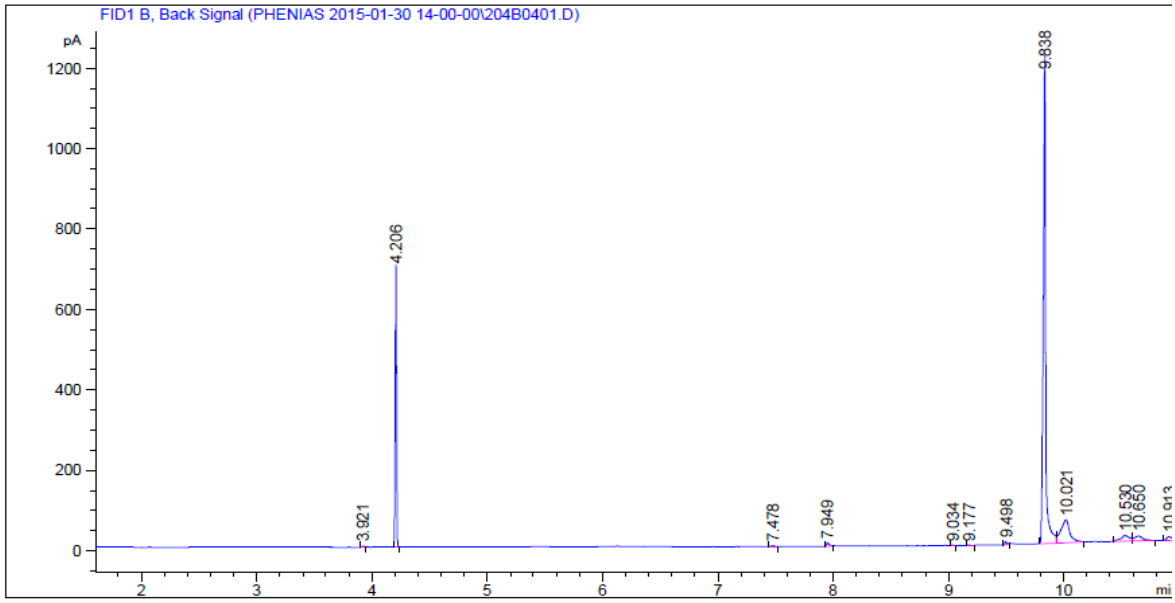



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 B, Back Signal

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]    [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1   3.921 BB    0.0126    2.68608    3.33104  0.11200
       2   4.207 BB    0.0135  569.73163  702.81805 23.75676
       3   7.478 BB    0.0165    1.96760    1.83674  0.08205
       4   7.949 BB    0.0208    8.64574    6.01655  0.36051
       5   9.033 BB    0.0150    1.00040    1.06391  0.04171
       6   9.497 BB    0.0189    9.00774    7.04152  0.37561
       7   9.832 BV    0.0238 1394.09839  895.86224 58.13135
       8  10.012 VB    0.0701  247.14240   48.31278 10.30538
       9  10.518 BV    0.0684   72.20488   13.75519  3.01081

Agilent 7820A 4/21/2015 12:16:18 PM Jostein                    Page   1 of 2
```

Appendix 12

Data File C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\204B0401.D
Sample Name: JHPH-1-IN25.1

```
==========================================================================
Acq. Operator    : Jostein                        Seq. Line :   4
Acq. Instrument : Agilent 7820A                    Location : Vial 204
Injection Date   : 1/30/2015 2:54:43 PM                Inj :   1
                                                  Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\PHENIAS.M
Last changed     : 4/10/2014 9:57:40 AM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```



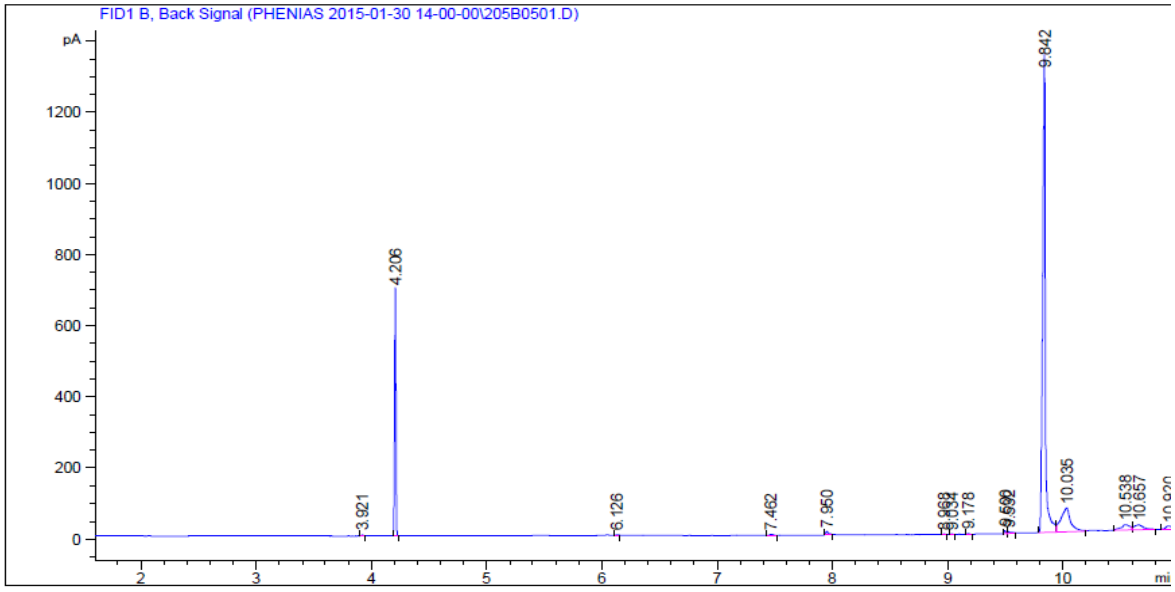

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.921	BB	0.0131	2.57792	3.31417	0.08938
2	4.206	BB	0.0135	565.63000	695.21283	19.61065
3	7.478	BB	0.0218	3.12047	2.04876	0.10819
4	7.949	BB	0.0225	13.95266	8.79829	0.48375
5	9.034	BB	0.0142	1.04368	1.10702	0.03618
6	9.177	BB	0.0216	1.47929	1.13818	0.05129
7	9.498	BB	0.0194	9.65727	7.33026	0.33482
8	9.838	BV	0.0221	1798.05334	1209.52942	62.33932
9	10.021	VB	0.0758	308.37207	56.41247	10.69140

Appendix 13

Data File C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\205B0501.D
Sample Name: JHPH-1-IN32.8

```
==========================================================================
Acq. Operator    : Jostein                          Seq. Line :   5
Acq. Instrument : Agilent 7820A                      Location : Vial 205
Injection Date  : 1/30/2015 3:12:20 PM                   Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\PHENIAS 2015-01-30 14-00-00\PHENIAS.M
Last changed    : 4/10/2014 9:57:40 AM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed    : 2/26/2015 3:26:37 PM by Jostein
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.921	BB	0.0124	2.63318	3.32231	0.07669
2	4.206	BB	0.0126	558.10748	692.54004	16.25393
3	6.126	BB	0.0148	1.26188	1.26836	0.03675
4	7.462	BB	0.0254	4.41757	2.40964	0.12865
5	7.950	BB	0.0249	17.73021	10.28973	0.51636
6	8.968	BB	0.0183	1.37446	1.12129	0.04003
7	9.034	BB	0.0157	1.49996	1.39744	0.04368
8	9.178	BB	0.0191	2.11113	1.72459	0.06148
9	9.500	BV	0.0159	8.72911	8.01440	0.25422

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	9.532	VB	0.0431	14.91013	4.63402	0.43423
11	9.842	BV	0.0251	2223.02002	1332.93518	64.74166
12	10.035	VB	0.0763	395.00220	67.50288	11.50376
13	10.538	BV	0.0646	79.81427	14.97949	2.32445
14	10.657	VB	0.0676	79.39468	14.19604	2.31223
15	10.920	BV	0.0575	39.05586	9.66827	1.13744
16	11.016	VB	0.0292	4.61558	2.45076	0.13442
Totals :				3433.67774	2168.45442	

Appendix14

```
=====================================================================
Acq. Operator    : Jostein                          Seq. Line :   1
Acq. Instrument : Agilent 7820A                      Location : Vial 201
Injection Date   : 2/27/2015 12:56:41 PM                 Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-27 12-52-55\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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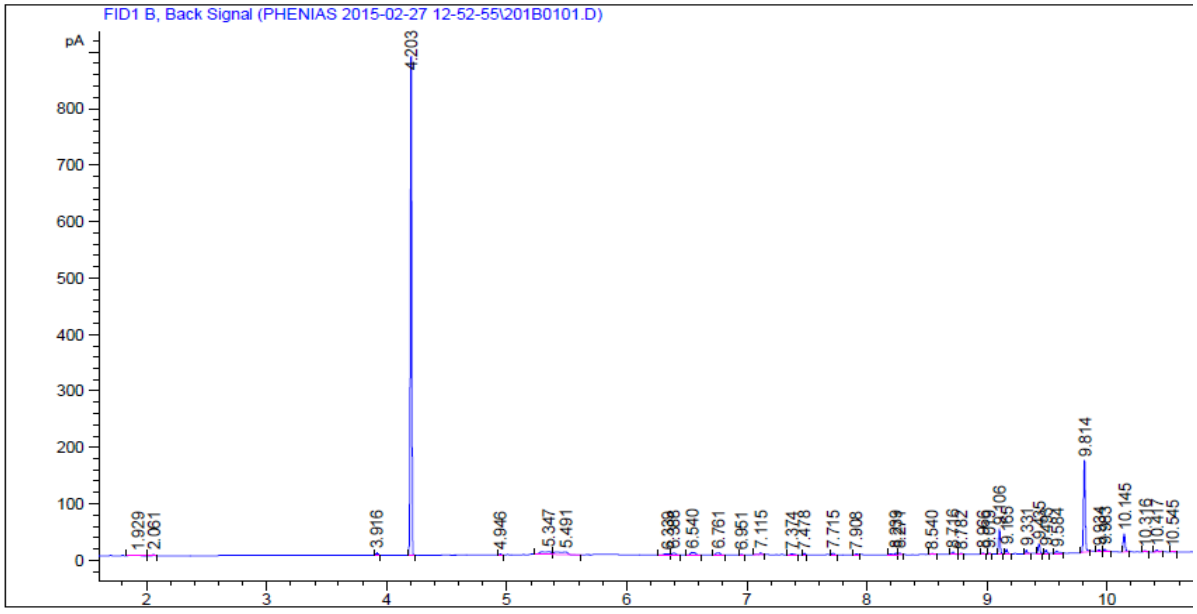



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

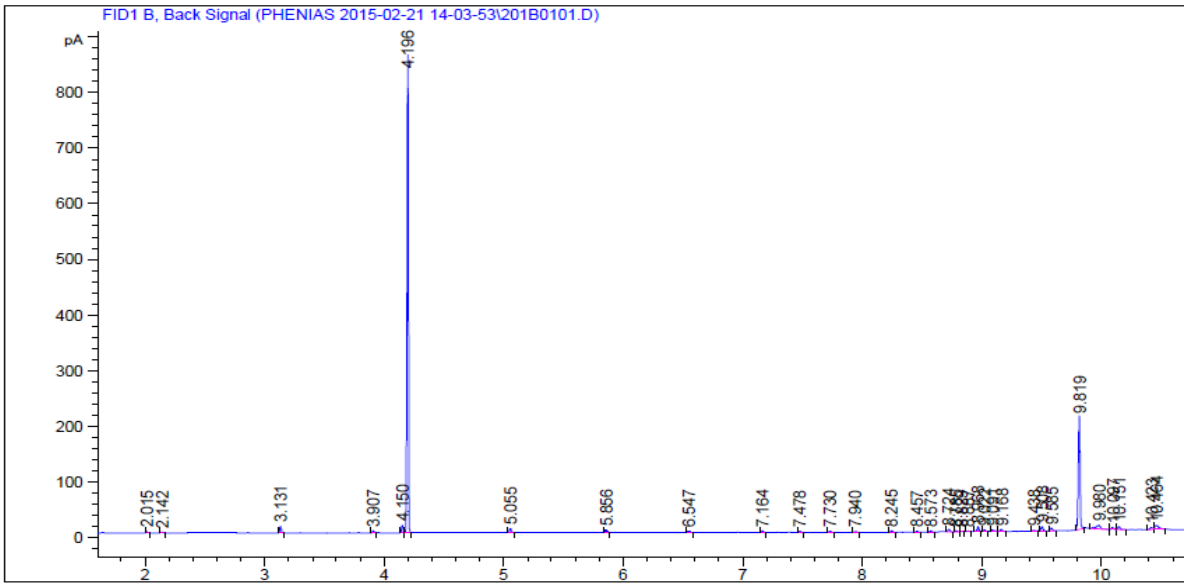
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   1.929 BV    0.0496    5.01739    1.43321  0.41161
   2   2.061 VB    0.0117    1.44247    1.97610  0.11833
   3   3.916 BB    0.0133    3.33363    4.18921  0.27348
   4   4.203 BB    0.0130  721.65240  862.70410 59.20154
   5   4.946 BB    0.0135    1.60321    1.96480  0.13152
   6   5.347 BV    0.0750   33.09170    5.37544  2.71471
   7   5.491 VB    0.0817   30.73035    4.86684  2.52100
   8   6.339 BV    0.0410    6.49872    2.19153  0.53313
   9   6.388 VB    0.0337    7.24228    3.39461  0.59413

ilent 7820A 4/21/2015 12:22:54 PM Jostein                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	6.540	BB	0.0376	11.84778	4.21491	0.97195
11	6.761	BB	0.0315	7.80510	3.52144	0.64030
12	6.951	BB	0.0156	1.00764	1.01305	0.08266
13	7.115	BB	0.0222	4.78992	3.20367	0.39295
14	7.374	BB	0.0303	2.99886	1.51181	0.24601
15	7.478	BB	0.0143	2.35795	2.48517	0.19344
16	7.715	BB	0.0175	3.05858	2.80113	0.25091
17	7.908	BB	0.0208	1.87197	1.36590	0.15357
18	8.239	BV	0.0274	5.20751	2.68695	0.42720
19	8.271	VB	0.0153	2.57668	2.65211	0.21138
20	8.540	BB	0.0213	2.51946	1.87672	0.20669
21	8.716	BB	0.0225	6.22609	4.09550	0.51076
22	8.782	BB	0.0154	1.73463	1.77080	0.14230
23	8.966	BB	0.0170	2.52525	2.40924	0.20716
24	9.019	BB	0.0143	1.72195	1.81079	0.14126
25	9.106	BB	0.0156	44.15569	44.22349	3.62236
26	9.165	BB	0.0193	10.12017	8.11772	0.83022
27	9.331	BB	0.0163	6.75257	6.39598	0.55395
28	9.435	BB	0.0164	18.29283	17.17098	1.50067
29	9.493	BB	0.0172	6.78845	6.01354	0.55690
30	9.584	BB	0.0258	7.14306	3.96416	0.58599
31	9.814	BB	0.0167	165.46027	162.07898	13.57371
32	9.934	BV	0.0184	3.16953	2.56054	0.26002
33	9.983	VB	0.0251	6.12437	3.66236	0.50242
34	10.145	BB	0.0193	36.39503	30.88533	2.98571
35	10.316	BB	0.0188	3.33334	2.78385	0.27345
36	10.417	BB	0.0303	6.35268	2.99950	0.52115
37	10.545	BB	0.0196	1.22048	1.02067	0.10012
38	10.896	BB	0.0344	15.88582	6.43830	1.30321
39	10.992	BB	0.0234	2.07459	1.35756	0.17019
40	11.530	BV	0.0435	6.34805	2.35324	0.52077
41	11.613	VB	0.0298	2.67406	1.38325	0.21937
42	11.769	BB	0.0345	7.82311	3.54479	0.64178

Appendix 15

```
========================================================================
Acq. Operator    : Jostein                          Seq. Line :   1
Acq. Instrument : Agilent 7820A                      Location : Vial 201
Injection Date   : 2/21/2015 2:04:40 PM                  Inj :   1
                                                   Inj Volume : Manually
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-21 14-03-53\PHENIAS-MANUAL.M
Last changed     : 2/17/2015 1:24:30 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```




```
========================================================================
                          Area Percent Report
========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   0.841 BV S 6.75e-3  865.65747 2323.57666  2.30393
   2   0.866 VBAS 8.41e-3 3.55928e4  7.05299e4  94.72944
   3   2.015 BB    0.0106    1.87374    2.65267  0.00499
   4   2.142 BB    0.0138    1.24377    1.48480  0.00331
   5   3.131 BB    0.0145   10.37320   11.55639  0.02761
   6   3.907 BB    0.0126    3.18970    3.97419  0.00849
   7   4.150 BV    0.0148   12.49193   13.50740  0.03325
   8   4.196 VB    0.0127  688.97052  846.08569  1.83368
   9   5.055 BB    0.0154    7.70003    7.87864  0.02049

ilent 7820A 4/21/2015 12:46:50 PM Jostein                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	5.856	BB	0.0158	4.77922	4.70756	0.01272
11	6.547	BB	0.0174	4.05768	3.74694	0.01080
12	7.164	BB	0.0178	3.39157	3.04828	0.00903
13	7.478	BB	0.0146	2.10531	2.32409	0.00560
14	7.730	BB	0.0184	3.20815	2.75657	0.00854
15	7.940	BB	0.0234	2.25200	1.47693	0.00599
16	8.245	BB	0.0188	3.47291	2.88743	0.00924
17	8.457	BB	0.0208	2.38495	1.73905	0.00635
18	8.573	BB	0.0187	2.61116	2.07924	0.00695
19	8.724	BB	0.0213	5.67562	4.22500	0.01511
20	8.785	BB	0.0161	2.11380	2.03531	0.00563
21	8.829	BB	0.0166	1.15081	1.00418	0.00306
22	8.887	BB	0.0173	1.73866	1.52038	0.00463
23	8.968	BB	0.0191	11.14441	8.62549	0.02966
24	9.022	BB	0.0177	4.51441	3.64015	0.01201
25	9.091	BB	0.0208	5.17923	3.43381	0.01378
26	9.168	BB	0.0211	5.26001	3.95670	0.01400
27	9.438	BB	0.0199	1.87781	1.45116	0.00500
28	9.508	BB	0.0207	10.67572	7.84550	0.02841
29	9.585	BB	0.0216	7.08716	5.15522	0.01886
30	9.819	BB	0.0161	209.67017	201.74879	0.55803
31	9.980	BB	0.0411	16.49112	5.95299	0.04389
32	10.097	BV	0.0186	4.10640	3.47133	0.01093
33	10.151	VB	0.0198	6.97085	5.43547	0.01855
34	10.423	BV	0.0254	5.56994	3.42674	0.01482
35	10.464	VB	0.0365	20.01490	7.76097	0.05327
36	10.901	BB	0.0336	35.85453	15.83327	0.09543
37	11.537	BB	0.0420	5.45697	2.01256	0.01452
Totals :				3.75731e4	7.40539e4	

==========

Appendix 16

```
==========================================================================
Acq. Operator    : Jostein                          Seq. Line :   4
Acq. Instrument : Agilent 7820A                      Location : Vial 204
Injection Date   : 2/27/2015 1:49:02 PM                   Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-27 12-52-55\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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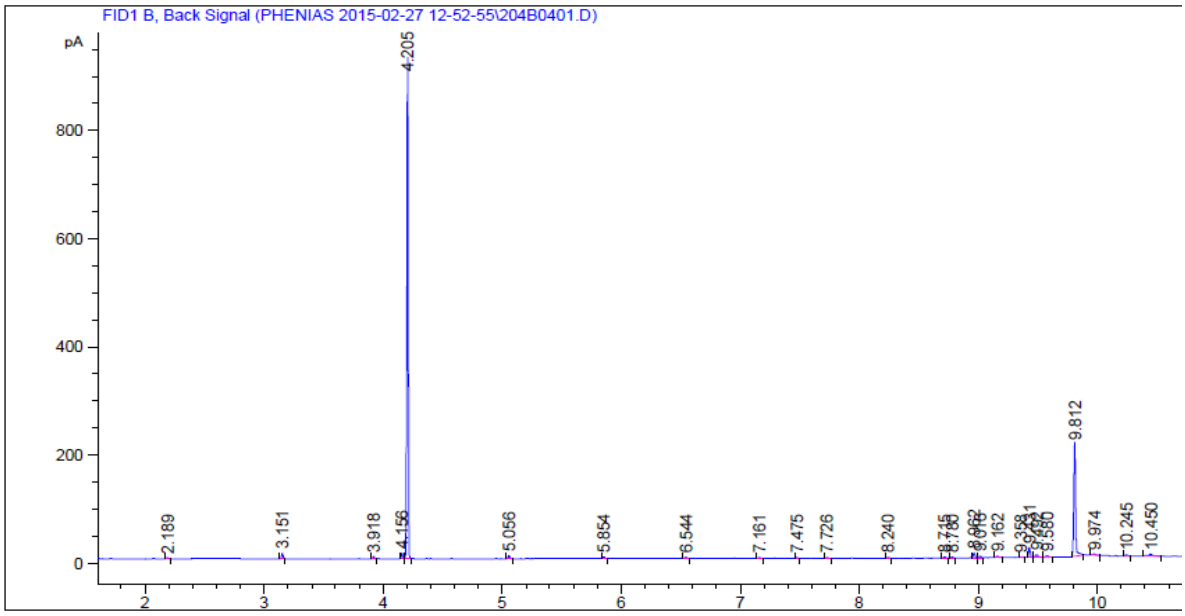


```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   2.189 BB    0.0130    1.52028    1.81891  0.13898
   2   3.151 BB    0.0145    9.05649   10.09521  0.82793
   3   3.918 BB    0.0130    3.38641    4.40315  0.30958
   4   4.156 BV    0.0149    9.18117    9.85419  0.83933
   5   4.205 VB    0.0127  734.18250  901.82819 67.11798
   6   5.056 BB    0.0155    5.37569    5.43706  0.49144
   7   5.854 BB    0.0158    3.23973    3.20840  0.29617
   8   6.544 BB    0.0174    2.86238    2.64243  0.26167
   9   7.161 BB    0.0171    2.17049    2.05621  0.19842

gilent 7820A 4/21/2015 1:21:00 PM Josteir                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	7.475	BB	0.0137	2.13956	2.37319	0.19560
11	7.726	BB	0.0188	2.05677	1.81162	0.18803
12	8.240	BB	0.0174	2.19134	1.90201	0.20033
13	8.715	BB	0.0197	2.53363	2.09064	0.23162
14	8.780	BB	0.0152	2.32528	2.42502	0.21257
15	8.962	BB	0.0156	8.98788	9.05151	0.82166
16	9.016	BB	0.0156	2.88755	2.90302	0.26398
17	9.162	BB	0.0219	3.59760	2.56974	0.32889
18	9.358	BB	0.0164	1.17432	1.10472	0.10735
19	9.431	BB	0.0157	18.11456	18.09301	1.65601
20	9.492	BB	0.0238	7.48010	5.00781	0.68382
21	9.580	BB	0.0243	4.26648	2.66324	0.39004
22	9.812	BB	0.0160	214.13348	207.34979	19.57580
23	9.974	BB	0.0307	4.41593	2.12421	0.40370
24	10.245	BB	0.0178	3.33030	2.99379	0.30445
25	10.450	BB	0.0389	10.28720	3.69745	0.94044
26	10.887	BB	0.0355	16.65232	6.86814	1.52233
27	10.985	BB	0.0257	16.31905	9.85480	1.49187
Totals :				1093.86851	1226.22745	

Appendix 17

```
========================================================================
Acq. Operator    : Jostein                          Seq. Line :   5
Acq. Instrument  : Agilent 7820A                     Location : Vial 205
Injection Date   : 2/27/2015 2:06:37 PM                 Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-27 12-52-55\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method  : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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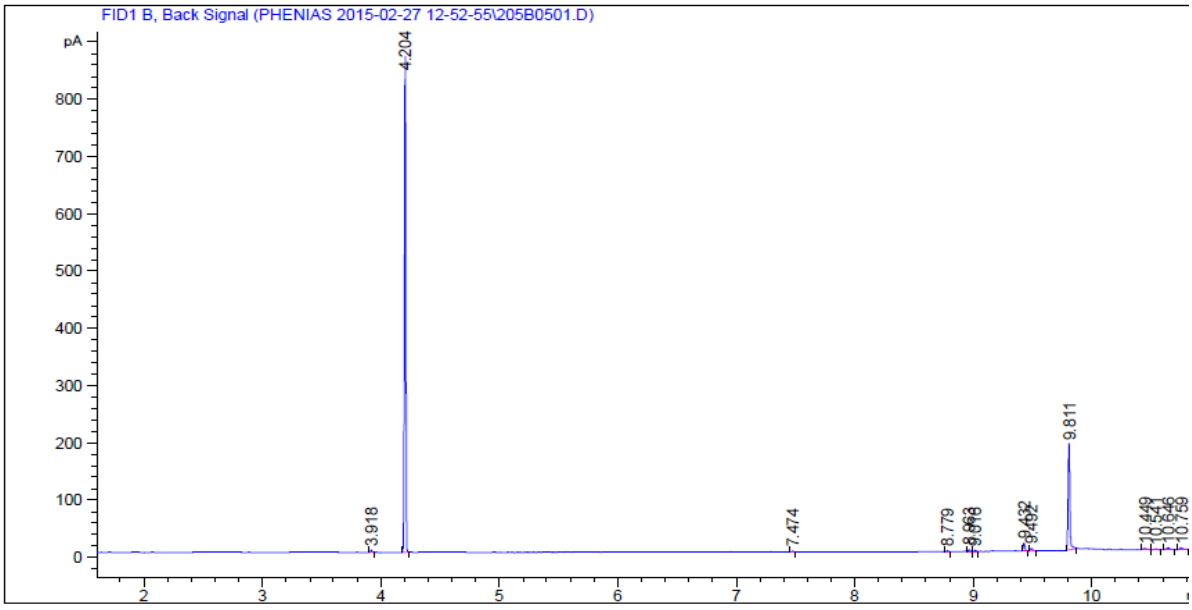


```
========================================================================
                        Area Percent Report
========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   3.918 BB    0.0134    3.26312    4.05003  0.32379
   2   4.204 BB    0.0137  705.72748  850.73743 70.02810
   3   7.474 BB    0.0150    2.09359    2.23047  0.20774
   4   8.779 BB    0.0159    1.64636    1.61691  0.16337
   5   8.963 BB    0.0161    3.30095    3.17282  0.32755
   6   9.016 BB    0.0152    2.08592    2.17022  0.20698
   7   9.432 BB    0.0161   14.19856   13.73551  1.40890
   8   9.492 BB    0.0184    6.39446    5.17705  0.63451
   9   9.811 BB    0.0161  190.08430  183.56302 18.86173

ilent 7820A 4/21/2015 1:16:42 PM Jostein                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	10.449	BB	0.0314	6.58970	3.07385	0.65388
11	10.541	BB	0.0251	2.62708	1.57230	0.26068
12	10.646	BB	0.0325	7.46712	3.44305	0.74095
13	10.759	BB	0.0308	7.59524	3.63028	0.75366
14	10.883	BB	0.0374	21.92809	8.93804	2.17589
15	10.985	BV	0.0258	8.29215	4.78173	0.82282
16	11.056	VV	0.0278	5.01501	2.63353	0.49763
17	11.101	VB	0.0333	8.83780	3.72179	0.87696
18	11.206	BB	0.0330	6.13745	2.69428	0.60901
19	11.761	BB	0.0383	4.49324	1.87924	0.44586
Totals :				1007.77763	1102.82154	

Appendix 18

```
========================================================================
Acq. Operator    : Jostein                          Seq. Line :   7
Acq. Instrument : Agilent 7820A                      Location : Vial 207
Injection Date   : 2/27/2015 2:41:45 PM                  Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-27 12-52-55\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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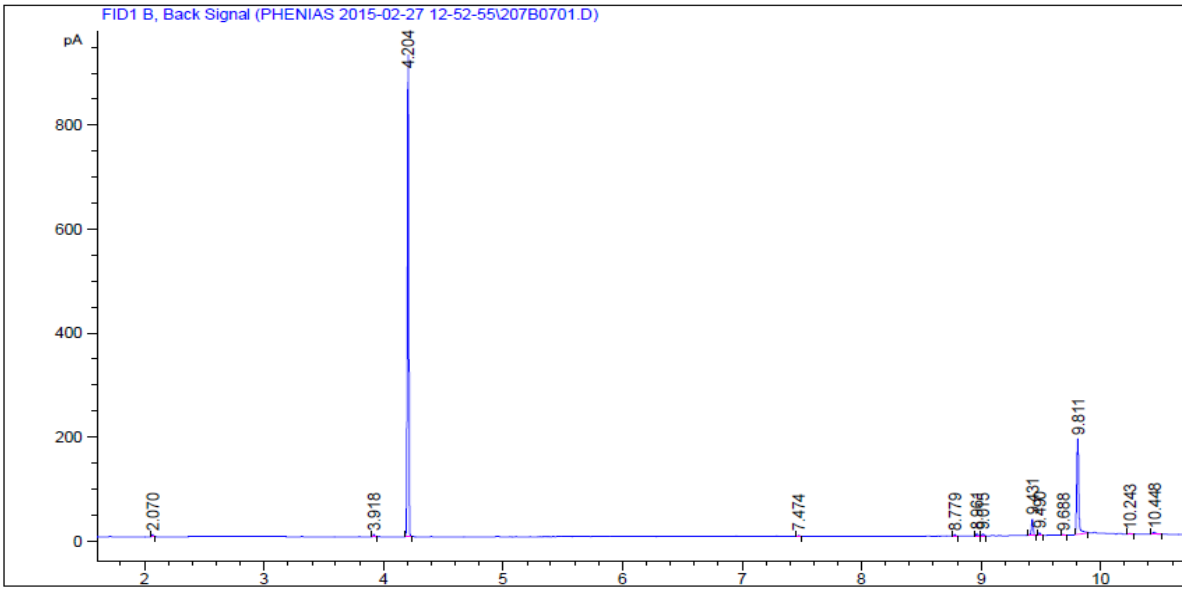


```
========================================================================
                        Area Percent Report
========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]       [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   2.070 BB    0.0126    3.32957    4.14831  0.31875
   2   3.918 BB    0.0124    3.50189    4.43173  0.33524
   3   4.204 BB    0.0135  746.21600  912.34235 71.43679
   4   7.474 BB    0.0146    2.21803    2.45175  0.21234
   5   8.779 BB    0.0153    2.49012    2.58100  0.23838
   6   8.961 BB    0.0147    4.09210    4.46391  0.39175
   7   9.015 BB    0.0159    3.63376    3.56648  0.34787
   8   9.431 BB    0.0161   32.40655   31.16247  3.10235
   9   9.490 BB    0.0177    5.96440    5.06685  0.57098

gilent 7820A 4/21/2015 1:17:54 PM Josteir                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	9.688	BB	0.0173	1.12120	1.04951	0.10733
11	9.811	BB	0.0182	210.16580	182.33894	20.11960
12	10.243	BB	0.0176	1.23788	1.20048	0.11851
13	10.448	BB	0.0313	7.93005	3.84415	0.75916
14	10.887	BB	0.0304	17.05905	8.59351	1.63310
15	10.982	BB	0.0279	3.21585	1.74872	0.30786
Totals :				1044.58228	1168.99017	

Appendix 19

```
=========================================================================
Acq. Operator    : Jostein                          Seq. Line :   8
Acq. Instrument  : Agilent 7820A                     Location : Vial 208
Injection Date   : 3/2/2015 1:41:27 PM                   Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-03-02 11-35-11\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method  : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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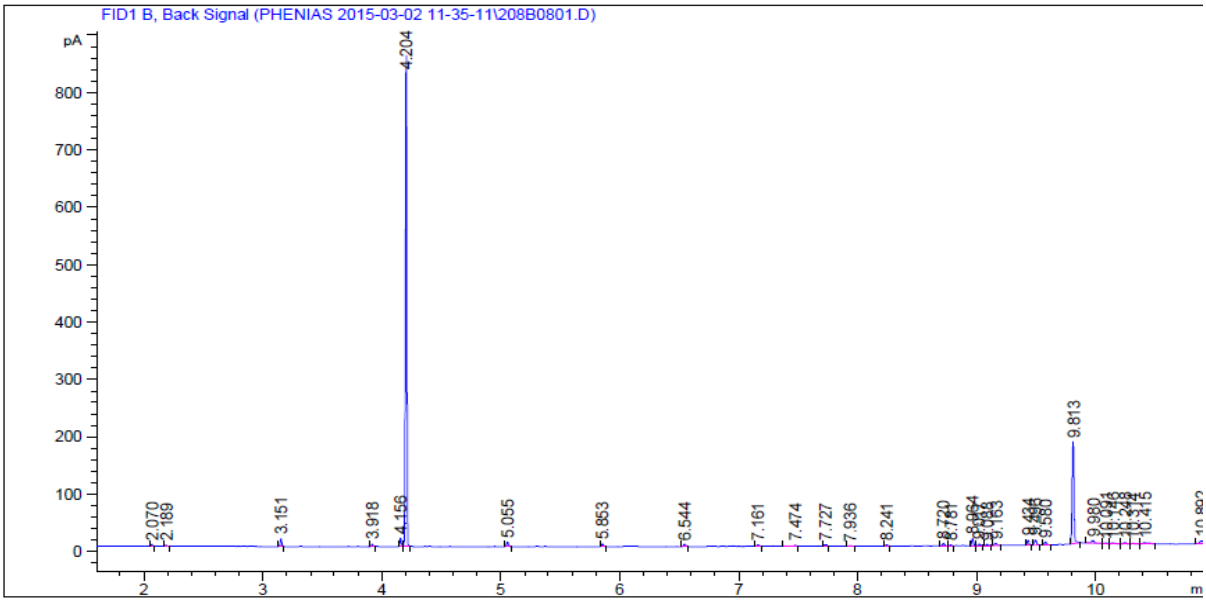


```
=========================================================================
                        Area Percent Report
=========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   2.070 BB    0.0128    2.83640    3.43584  0.26570
   2   2.189 BB    0.0133    1.67221    1.93872  0.15664
   3   3.151 BB    0.0143   11.93146   13.50189  1.11768
   4   3.918 BB    0.0125    3.30989    4.13513  0.31006
   5   4.156 BV    0.0147   13.03720   14.22022  1.22126
   6   4.204 VB    0.0137  705.76172  847.56567 66.11245
   7   5.055 BB    0.0154    7.74872    7.90463  0.72586
   8   5.853 BB    0.0156    4.75477    4.78070  0.44540
   9   6.544 BB    0.0175    4.07641    3.74364  0.38186

lent 7820A 4/21/2015 1:25:38 PM Josteir                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	7.161	BB	0.0177	3.23917	2.92381	0.30343
11	7.474	BB	0.0230	3.44893	2.21127	0.32308
12	7.727	BB	0.0171	3.09216	2.74872	0.28966
13	7.936	BB	0.0235	1.76212	1.15143	0.16507
14	8.241	BB	0.0182	3.21859	2.79896	0.30150
15	8.720	BB	0.0209	5.32557	4.04820	0.49887
16	8.781	BB	0.0160	1.62896	1.58417	0.15259
17	8.964	BB	0.0155	12.40091	12.58014	1.16166
18	9.017	BB	0.0166	3.07947	2.85964	0.28847
19	9.088	BB	0.0194	3.02805	2.29225	0.28365
20	9.163	BB	0.0211	4.77721	3.59788	0.44751
21	9.434	BB	0.0156	8.76069	8.81868	0.82066
22	9.496	BB	0.0206	11.66445	8.60108	1.09267
23	9.580	BB	0.0202	6.76750	5.13194	0.63395
24	9.813	BB	0.0169	182.79004	176.42859	17.12292
25	9.980	BB	0.0293	8.70604	4.29245	0.81554
26	10.091	BV	0.0182	1.70118	1.47662	0.15936
27	10.146	VB	0.0244	2.82261	1.75524	0.26441
28	10.248	BV	0.0214	3.20698	2.36224	0.30041
29	10.314	VB	0.0217	1.81826	1.25221	0.17033
30	10.415	BB	0.0429	8.61570	2.81280	0.80708
31	10.892	BV	0.0430	16.66260	5.30838	1.56087
32	10.988	VB	0.0262	9.77739	5.76890	0.91590
33	11.527	BB	0.0376	4.09365	1.61244	0.38347
Totals :				1067.51704	1165.64451	

Appendix 20

```
=====================================================================
Acq. Operator    : Jostein                          Seq. Line :   6
Acq. Instrument : Agilent 7820A                      Location : Vial 206
Injection Date   : 2/27/2015 2:24:10 PM                  Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-27 12-52-55\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
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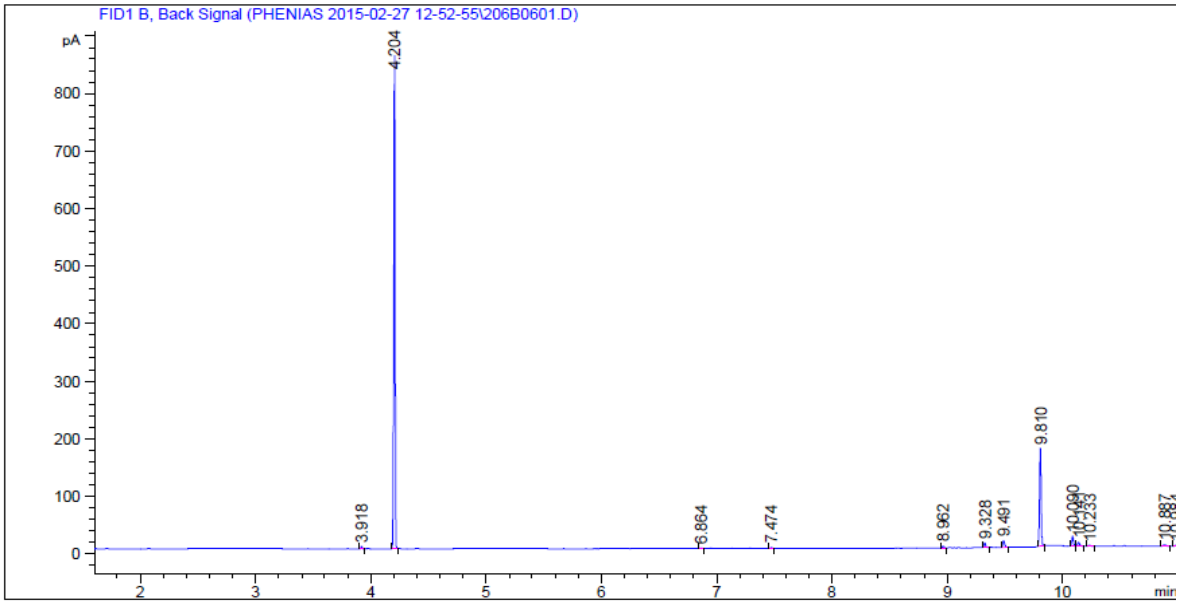
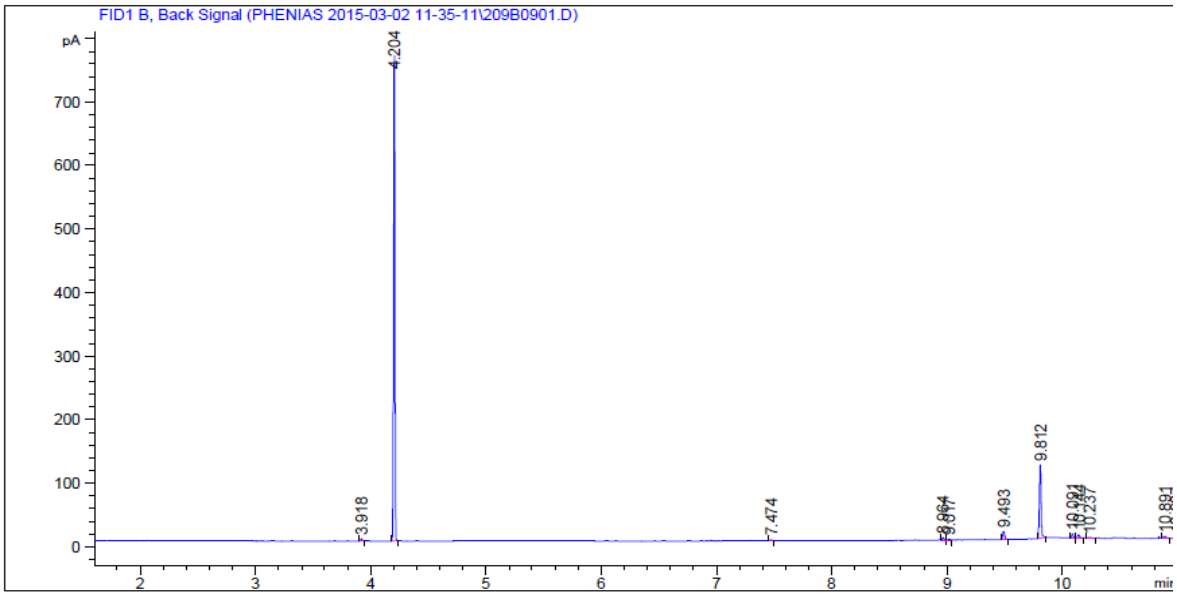



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   3.918 BB    0.0125     3.20407    4.02834  0.34838
   2   4.204 BB    0.0135   684.30444  842.60162 74.40394
   3   6.864 BB    0.0144     1.01609    1.13484  0.11048
   4   7.474 BB    0.0155     2.13432    2.16976  0.23206
   5   8.962 BB    0.0155     3.23918    3.29862  0.35219
   6   9.328 BB    0.0163     8.25296    8.34767  0.89734
   7   9.491 BB    0.0182    13.06686   11.37514  1.42075
   8   9.810 BB    0.0155   165.74506  168.36539 18.02134
   9  10.090 BV    0.0166    18.46226   17.11541  2.00739

Agilent 7820A 4/21/2015 1:19:16 PM Jostein                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	10.141	VB	0.0195	7.92749	6.30199	0.86195
11	10.233	BB	0.0254	1.97092	1.26390	0.21430
12	10.887	BB	0.0294	4.60555	2.41681	0.50076
13	10.984	BB	0.0251	2.47444	1.47844	0.26904
14	11.762	BB	0.0329	3.31168	1.54862	0.36008
Totals :				919.71531	1071.44655	

Appendix 21

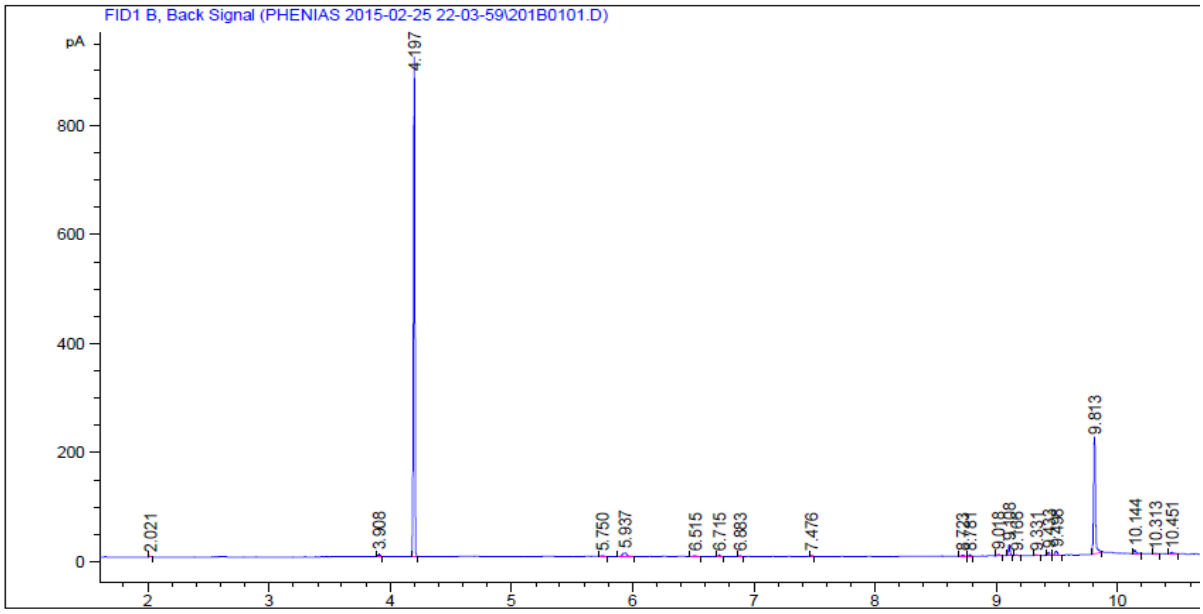
```
======================================================================
Acq. Operator    : Jostein                          Seq. Line :   9
Acq. Instrument  : Agilent 7820A                     Location : Vial 209
Injection Date   : 3/2/2015 1:59:06 PM                    Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-03-02 11-35-11\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
Analysis Method  : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1   3.918 BB    0.0125    2.89816    3.64637  0.36895
   2   4.204 BB    0.0135  617.60034  756.91400 78.62399
   3   7.474 BB    0.0141    1.87148    2.00751  0.23825
   4   8.964 BB    0.0158    4.24097    4.20964  0.53990
   5   9.017 BB    0.0172    1.37217    1.21388  0.17468
   6   9.493 BB    0.0173   14.14788   12.44869  1.80110
   7   9.812 BB    0.0161  118.37987  114.40845 15.07042
   8  10.091 BV    0.0167    7.14616    6.56510  0.90975
   9  10.144 VB    0.0197    6.66224    5.22090  0.84814

Agilent 7820A 4/21/2015 1:26:55 PM Jostein                  Page   1 of 2
```

Appendix 22

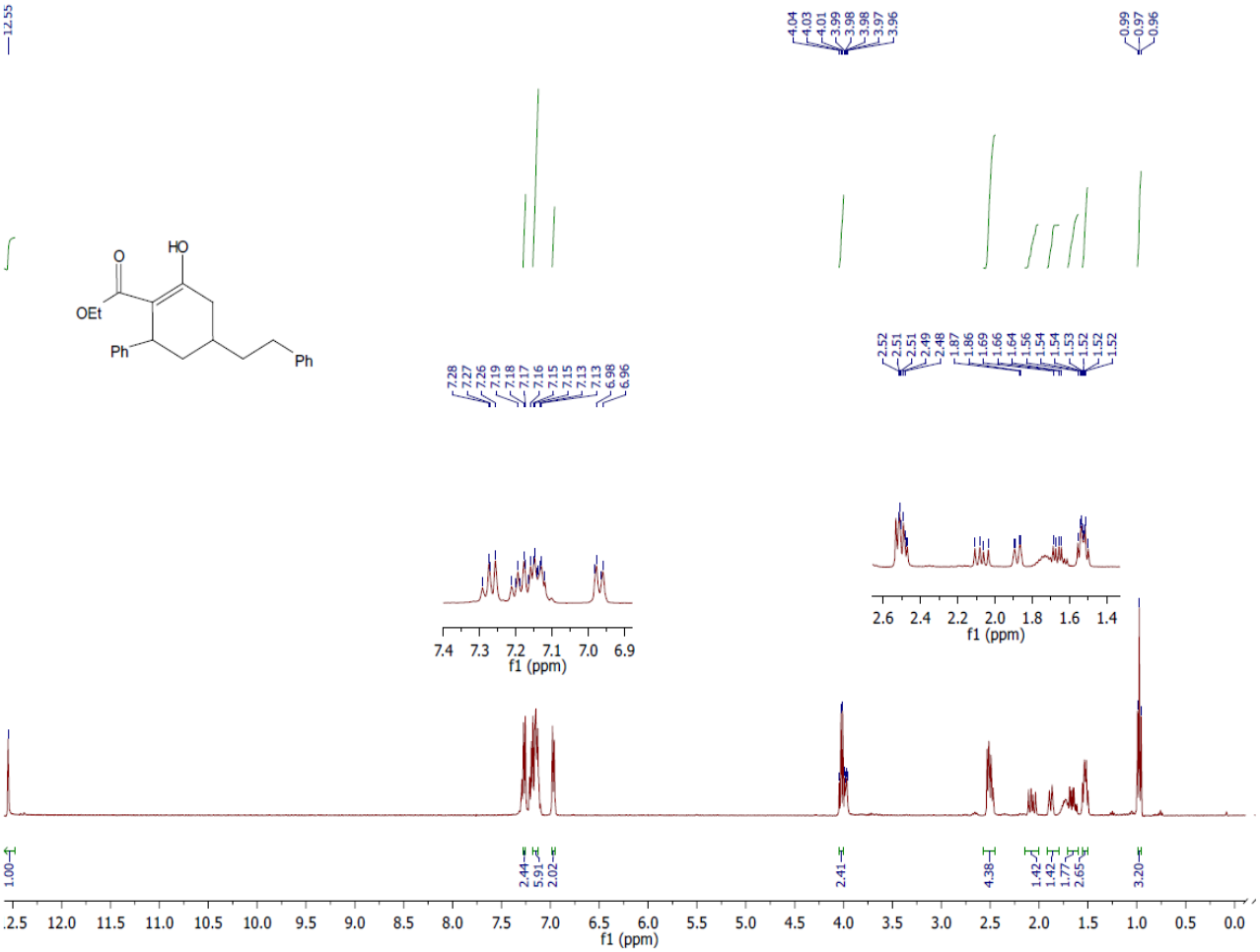
```
=====================================================================
Acq. Operator    : Jostein                          Seq. Line :   1
Acq. Instrument : Agilent 7820A                      Location : Vial 201
Injection Date   : 2/25/2015 10:04:46 PM                 Inj :   1
                                                   Inj Volume : Manually
Acq. Method      : C:\CHEM32\1\DATA\PHENIAS 2015-02-25 22-03-59\PHENIAS-MANUAL.M
Last changed     : 2/17/2015 1:24:30 PM by Jostein
Analysis Method : C:\CHEM32\1\METHODS\PHENIAS.M
Last changed     : 2/26/2015 3:26:37 PM by Jostein
```



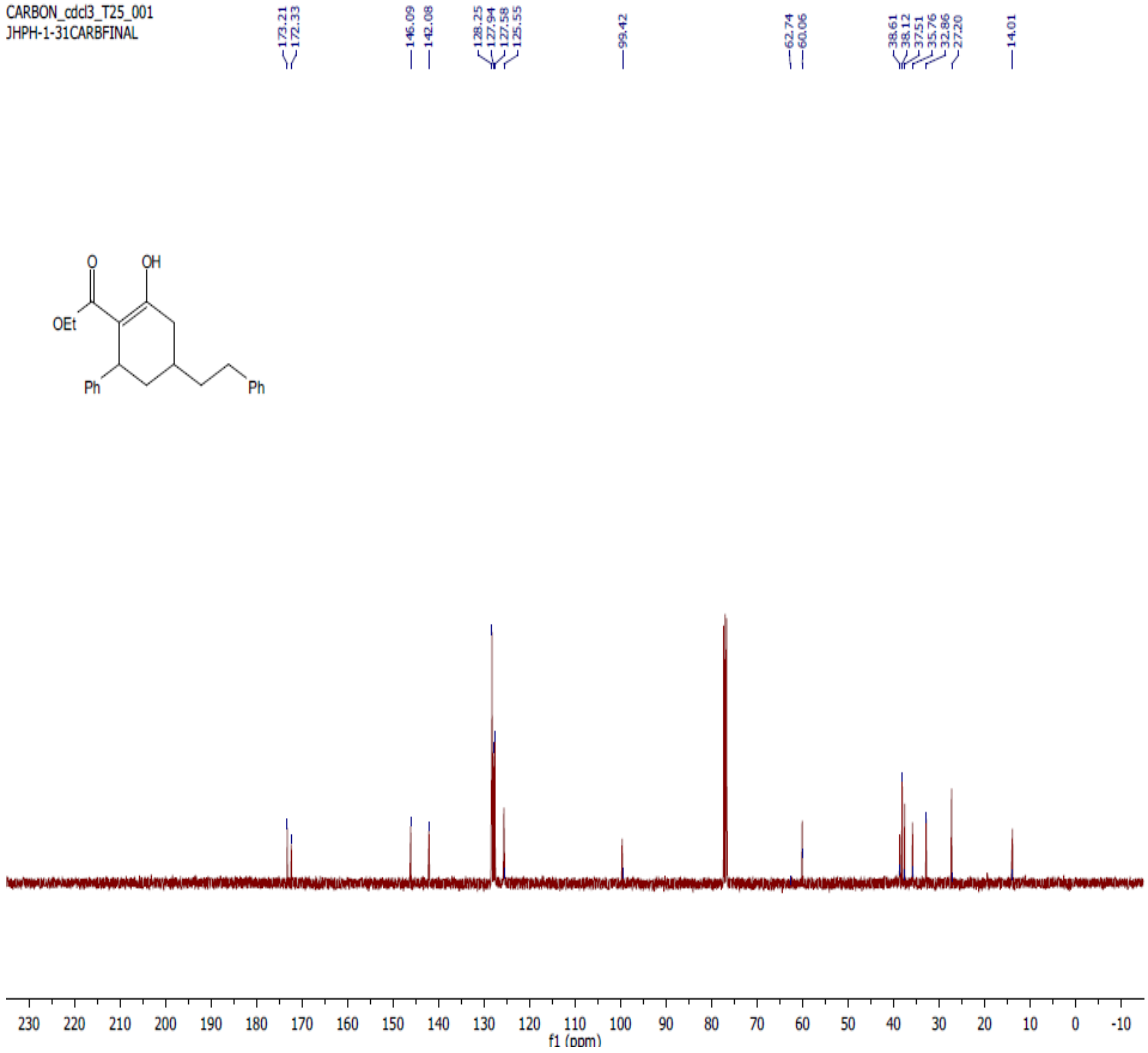

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   0.852 BBAS 7.28e-3 1815.38196 4336.31934 63.12681
   2   2.021 BB    0.0121    1.15358    1.51217  0.04011
   3   3.908 BB    0.0133    3.33325    4.20108  0.11591
   4   4.197 BB    0.0126  724.69727  896.66766 25.20011
   5   5.750 BB    0.0274    2.77699    1.60061  0.09657
   6   5.937 BB    0.0414   16.69599    6.62520  0.58057
   7   6.515 BB    0.0323    3.63522    1.45684  0.12641
   8   6.715 BB    0.0160    3.07195    2.98474  0.10682
   9   6.883 BB    0.0162    2.13552    2.03512  0.07426

.lent 7820A 4/21/2015 12:26:18 PM Jostein                    Page   1 of 2
```

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
10	7.476	BB	0.0148	2.03349	2.20676	0.07071
11	8.723	BB	0.0195	2.06343	1.55338	0.07175
12	8.781	BB	0.0144	2.08642	2.16597	0.07255
13	9.018	BB	0.0154	2.90697	2.98700	0.10108
14	9.108	BB	0.0154	19.05077	19.47408	0.66246
15	9.166	BB	0.0190	2.05297	1.69211	0.07139
16	9.331	BB	0.0177	2.24365	1.80336	0.07802
17	9.433	BB	0.0157	5.73573	5.70206	0.19945
18	9.498	BB	0.0239	10.43080	6.97172	0.36271
19	9.813	BB	0.0152	217.84288	211.26018	7.57511
20	10.144	BB	0.0217	9.99339	6.59562	0.34750
21	10.313	BB	0.0188	1.55826	1.29829	0.05419
22	10.451	BB	0.0320	5.87665	2.76904	0.20435
23	10.894	BB	0.0323	13.10189	6.09707	0.45560
24	10.989	BB	0.0248	1.70383	1.12901	0.05925
25	11.766	BB	0.0341	4.20736	1.93731	0.14630
Totals :				2875.77022	5529.04569	

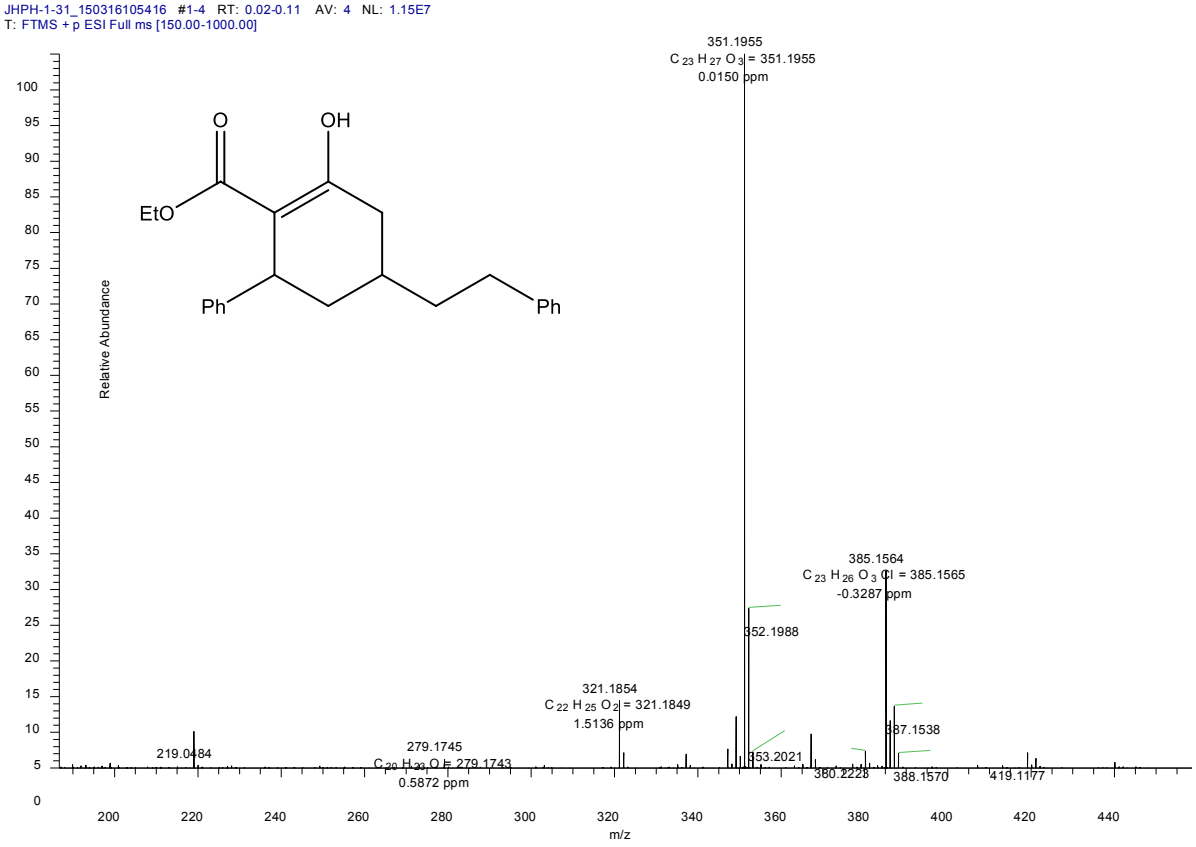
Appendix 23


12.55
4.04
4.03
4.01
3.99
3.98
3.98
3.97
3.96
0.99
0.97
0.96
O
HO
OEt
Ph
Ph
7.28
7.27
7.26
7.19
7.18
7.17
7.16
7.15
7.15
7.13
7.13
6.98
6.96
2.52
2.51
2.51
2.49
2.48
1.87
1.86
1.69
1.66
1.64
1.56
1.54
1.54
1.53
1.52
1.52
1.52
7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
2.6 2.4 2.2 2.0 1.8 1.6 1.4
f1 (ppm)
1.00
2.44
5.91
2.02
2.41
4.38
1.42
1.42
1.77
2.65
3.20
.2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

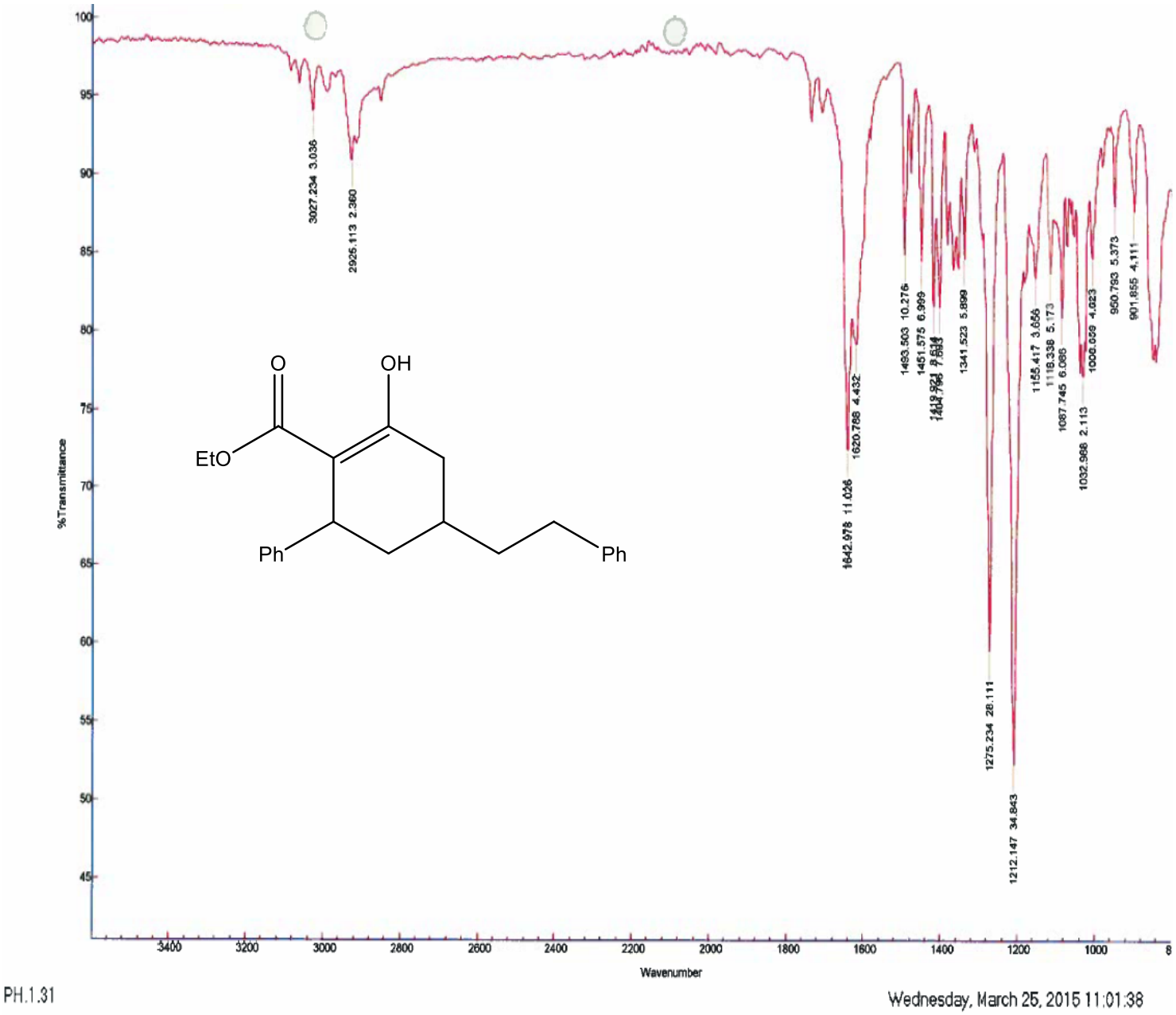
Appendix 24


CARBON_cdcl3_T25_001
JHPH-1-31CARBFINAL
173.21
172.33
146.09
142.08
128.25
127.94
127.58
125.55
99.42
62.74
60.06
38.61
38.12
37.51
35.76
32.86
27.20
14.01
O
OH
OEt
Ph
Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

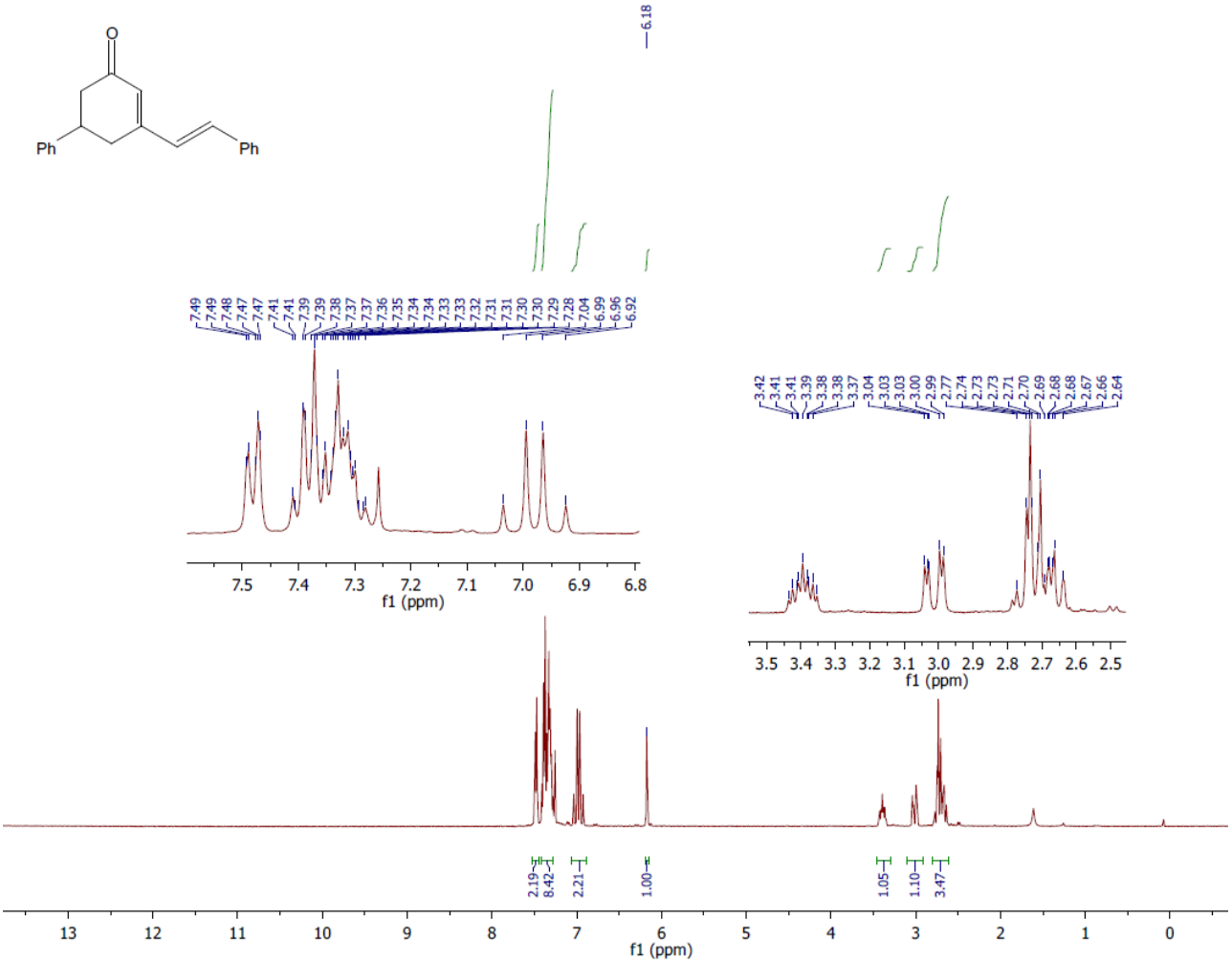
Appendix 25


JHPH-1-31_150316105416 #1-4 RT: 0.02-0.11 AV: 4 NL: 1.15E7
T: FTMS + p ESI Full ms [150.00-1000.00]
351.1955
C 23 H 27 O 3 = 351.1955
0.0150 ppm
O
OH
EtO
Ph
Ph
Relative Abundance
385.1564
C 23 H 26 O 3 Cl = 385.1565
-0.3287 ppm
352.1988
321.1854
C 22 H 25 O 2 = 321.1849
1.5136 ppm
387.1538
219.0484
279.1745
C 20 H 23 O = 279.1743
0.5872 ppm
353.2021
380.2228
388.1570
419.1177
m/z

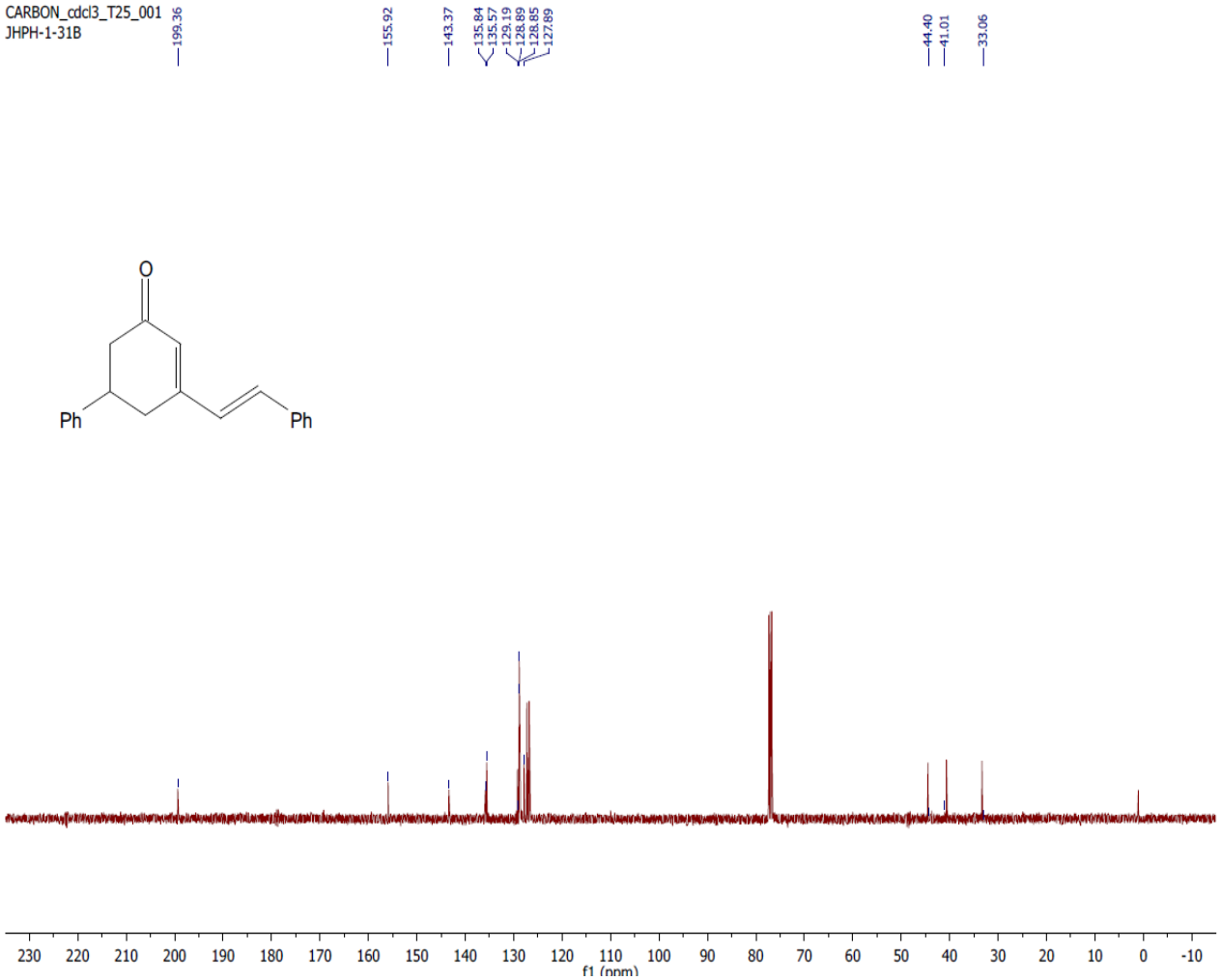
Appendix 27


%Transmittance
Wavenumber
3027.234 3.036
2926.113 2.360
1842.978 11.026
1620.788 4.432
1493.503 10.276
1451.575 6.999
1341.523 5.899
1275.234 28.111
1212.147 34.843
1155.417 3.656
1118.338 5.173
1087.745 6.086
1032.966 2.113
1006.659 4.623
950.793 5.373
901.855 4.111
O
OH
EtO
Ph
Ph
PH.1.31
Wednesday, March 25, 2015 11:01:38

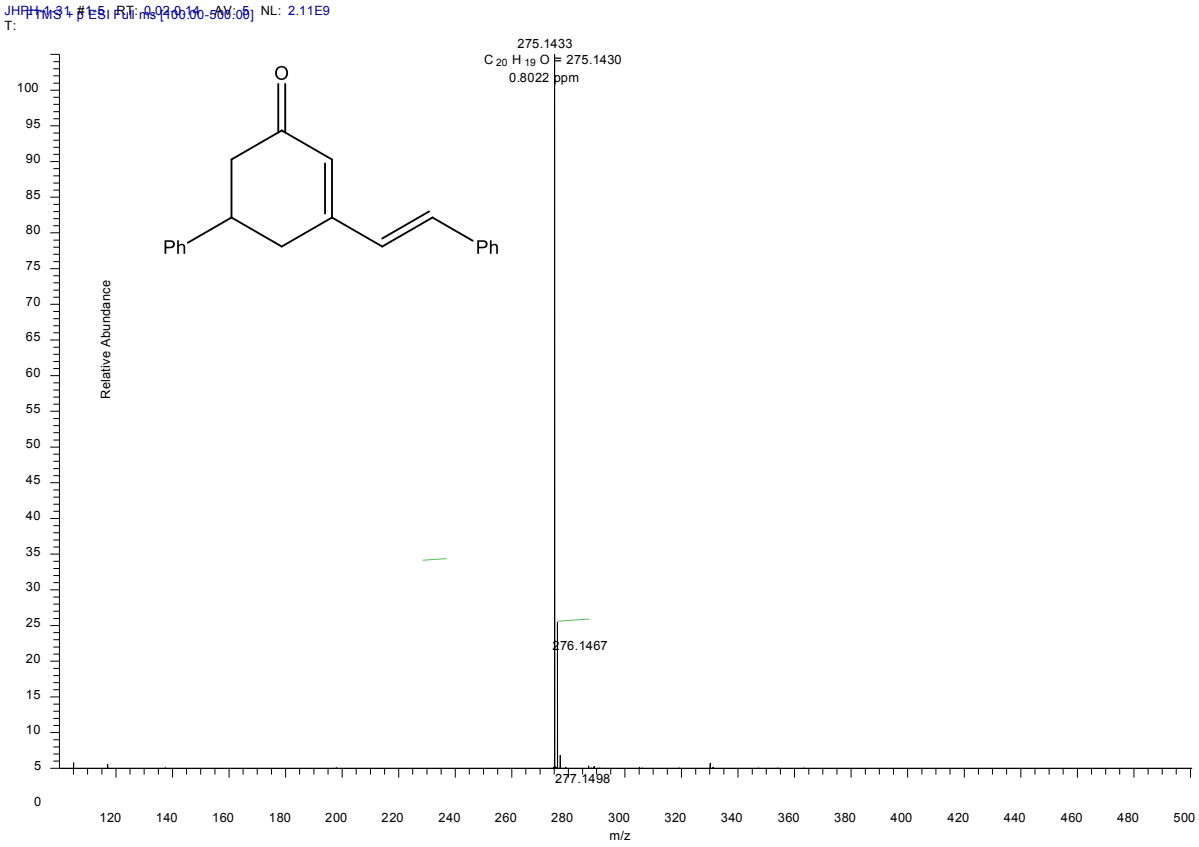
Appendix 27


O
Ph
Ph
6.18
7.49 7.49 7.48 7.47 7.47 7.41 7.41 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.34 7.34 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.28 7.04 6.99 6.96 6.92
3.42 3.41 3.41 3.39 3.38 3.38 3.37 3.04 3.03 3.03 3.00 2.99 2.77 2.74 2.73 2.73 2.71 2.70 2.69 2.68 2.68 2.67 2.66 2.64
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5
f1 (ppm)
2.19
8.42
2.21
1.00
1.05
1.10
3.47
13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

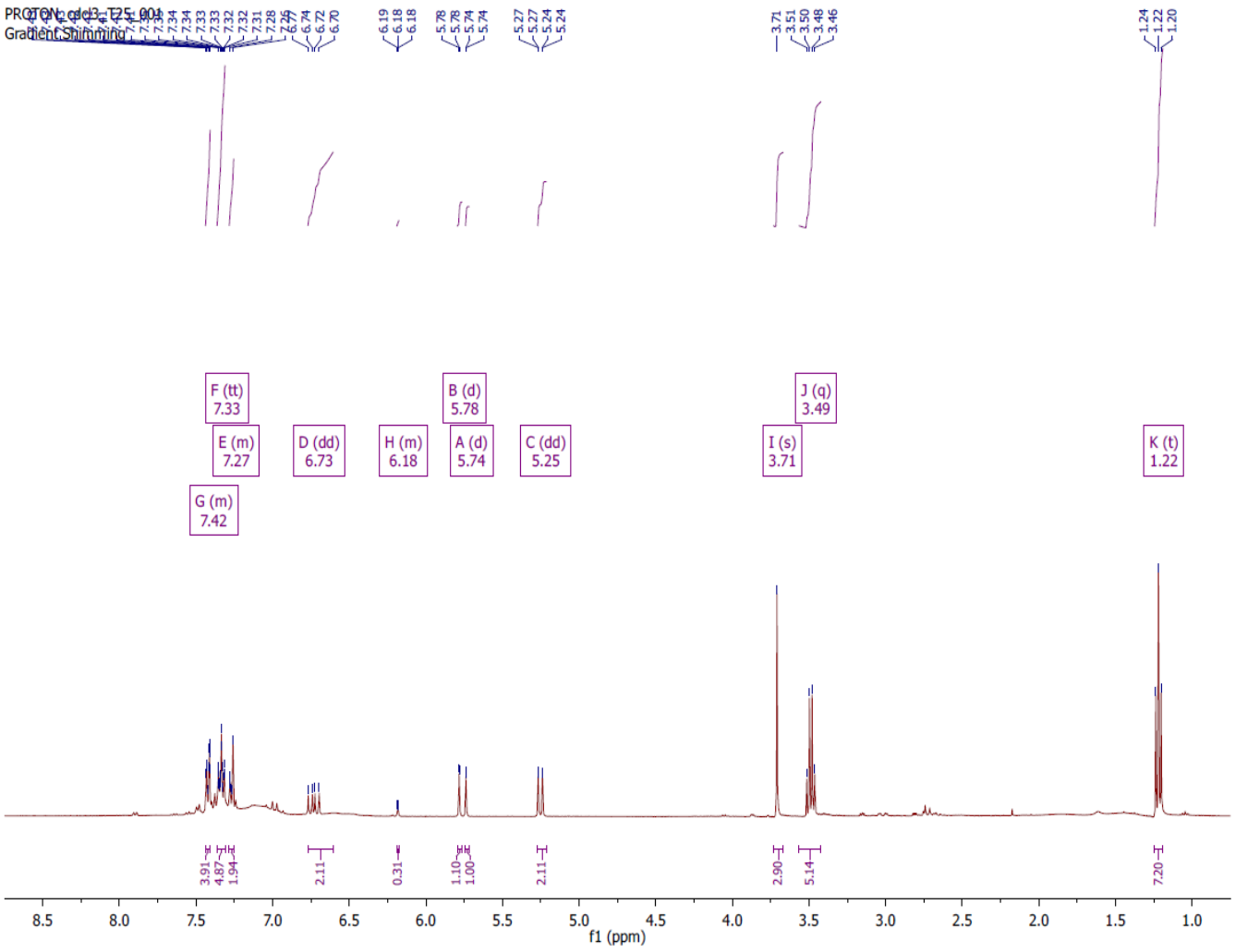
Appendix 28


CARBON_cdcl3_T25_001
JHPH-1-31B
199.36
155.92
143.37
135.84
135.57
129.19
128.89
128.85
127.89
44.40
41.01
33.06
O
Ph
Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

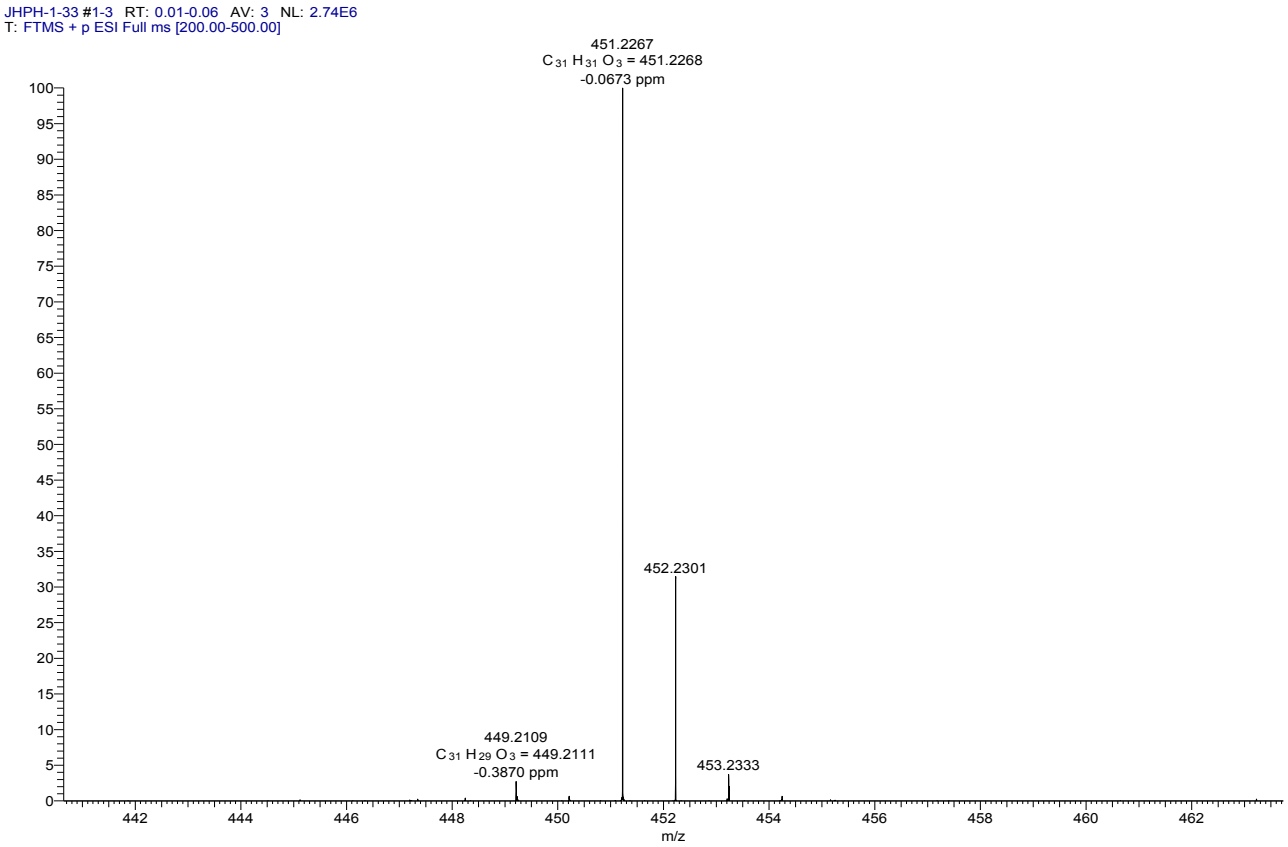
Appendix 29


NL: 2.11E9
T:
275.1433
C 20 H 19 O = 275.1430
0.8022 ppm
O
Ph
Ph
Relative Abundance
276.1467
277.1498
m/z

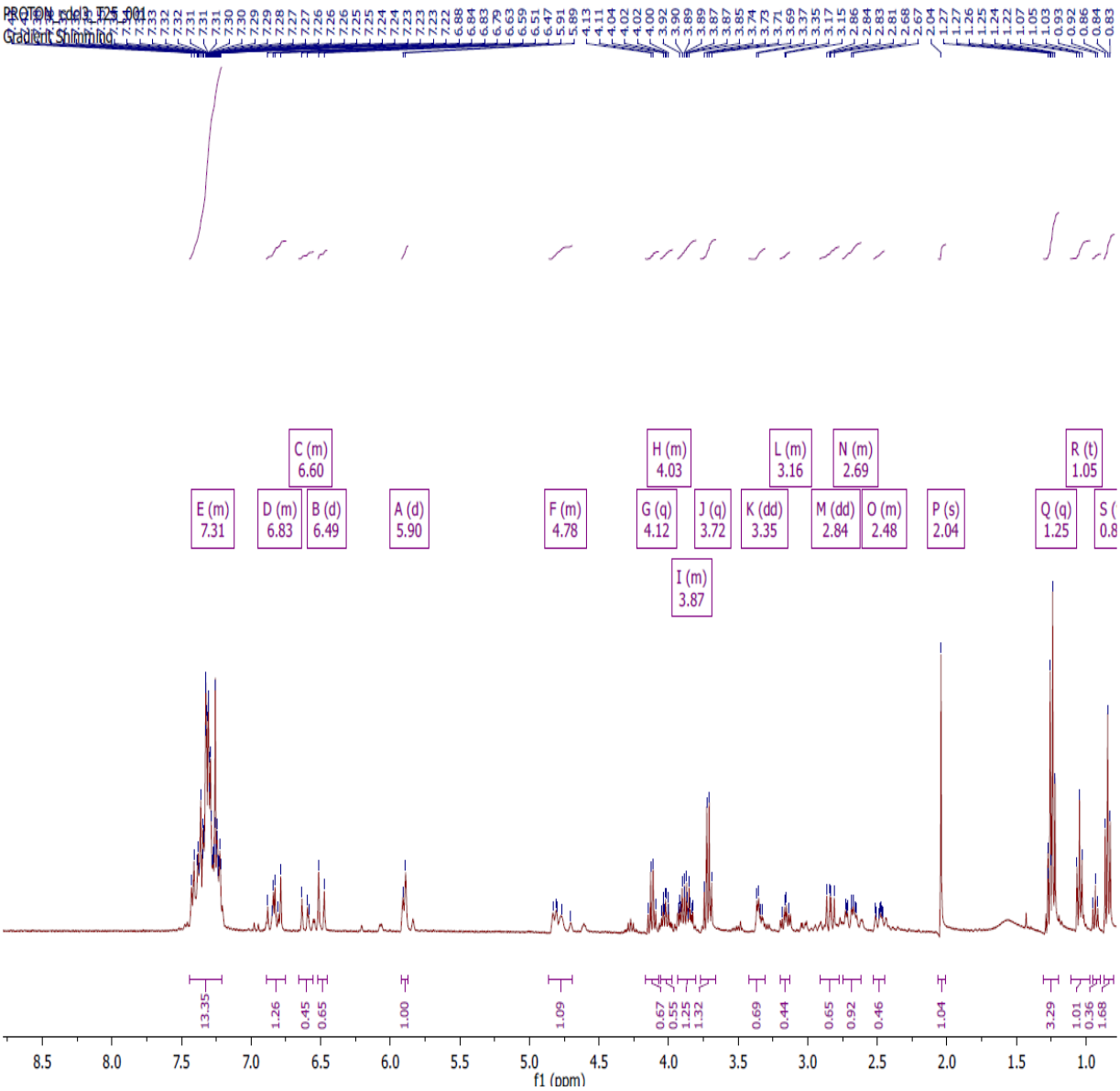
Appendix 30


F (tt) 7.33
E (m) 7.27
G (m) 7.42
D (dd) 6.73
H (m) 6.18
B (d) 5.78
A (d) 5.74
C (dd) 5.25
J (q) 3.49
I (s) 3.71
K (t) 1.22
f1 (ppm)

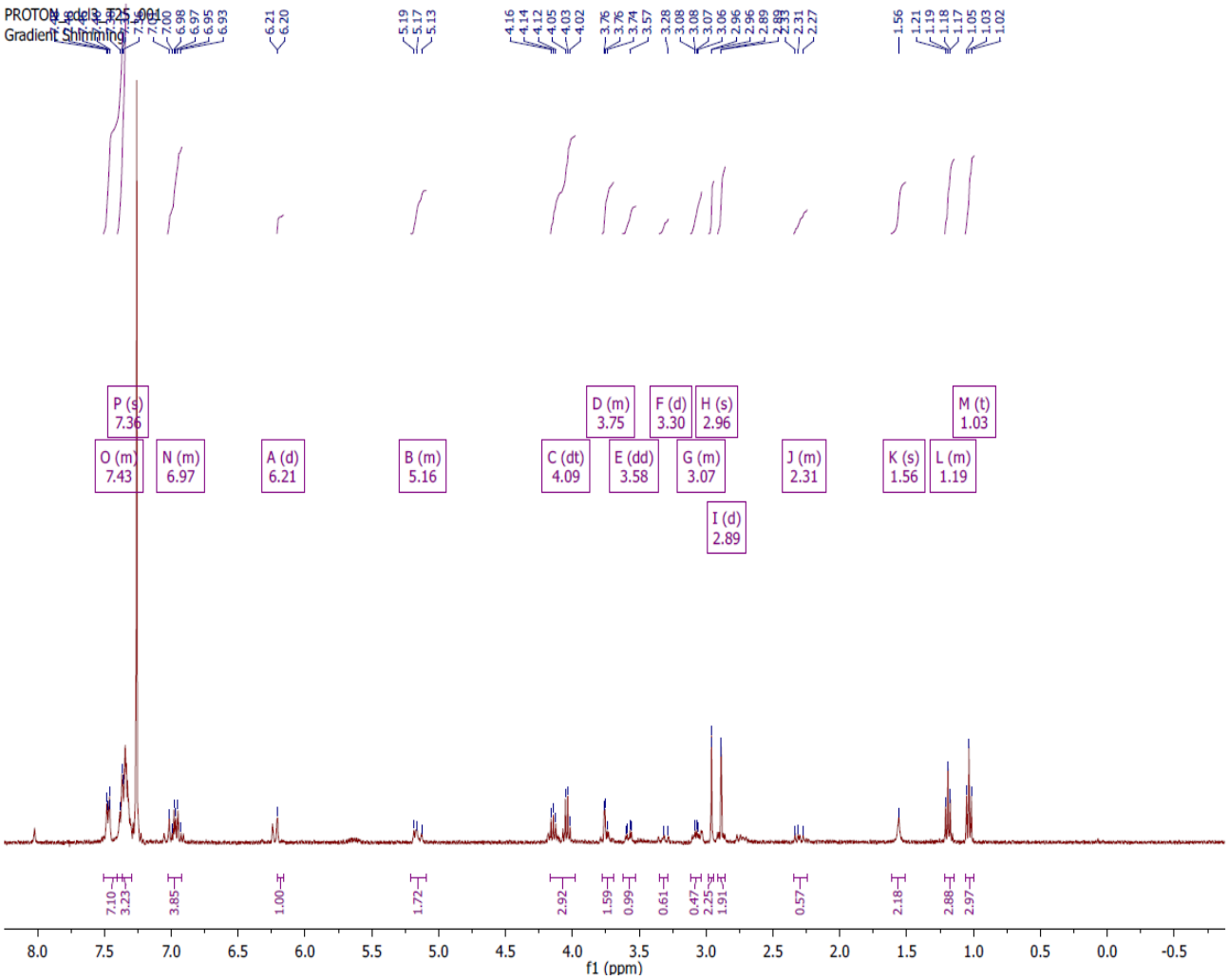
Appendix 31


JHPH-1-33 #1-3 RT: 0.01-0.06 AV: 3 NL: 2.74E6
T: FTMS + p ESI Full ms [200.00-500.00]
451.2267
C31 H31 O3 = 451.2268
-0.0673 ppm
452.2301
449.2109
C31 H29 O3 = 449.2111
-0.3870 ppm
453.2333
m/z

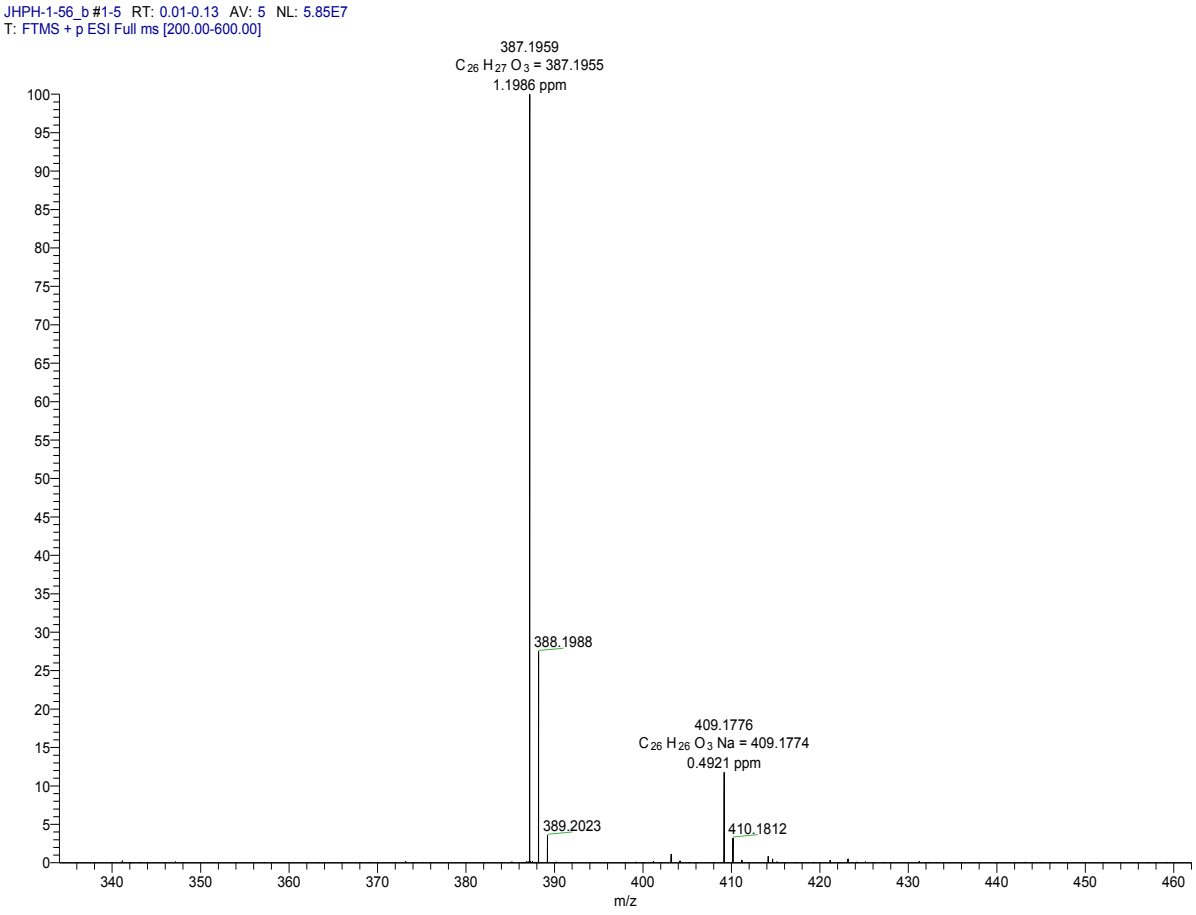
Appendix 32


C (m) 6.60
H (m) 4.03
L (m) 3.16
N (m) 2.69
R (t) 1.05
E (m) 7.31
D (m) 6.83
B (d) 6.49
A (d) 5.90
F (m) 4.78
G (q) 4.12
J (q) 3.72
K (dd) 3.35
M (dd) 2.84
O (m) 2.48
P (s) 2.04
Q (q) 1.25
I (m) 3.87
13.35
1.26
0.45
0.65
1.00
1.09
0.67
0.55
1.25
1.32
0.69
0.44
0.65
0.92
0.46
1.04
3.29
1.01
0.36
1.68
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

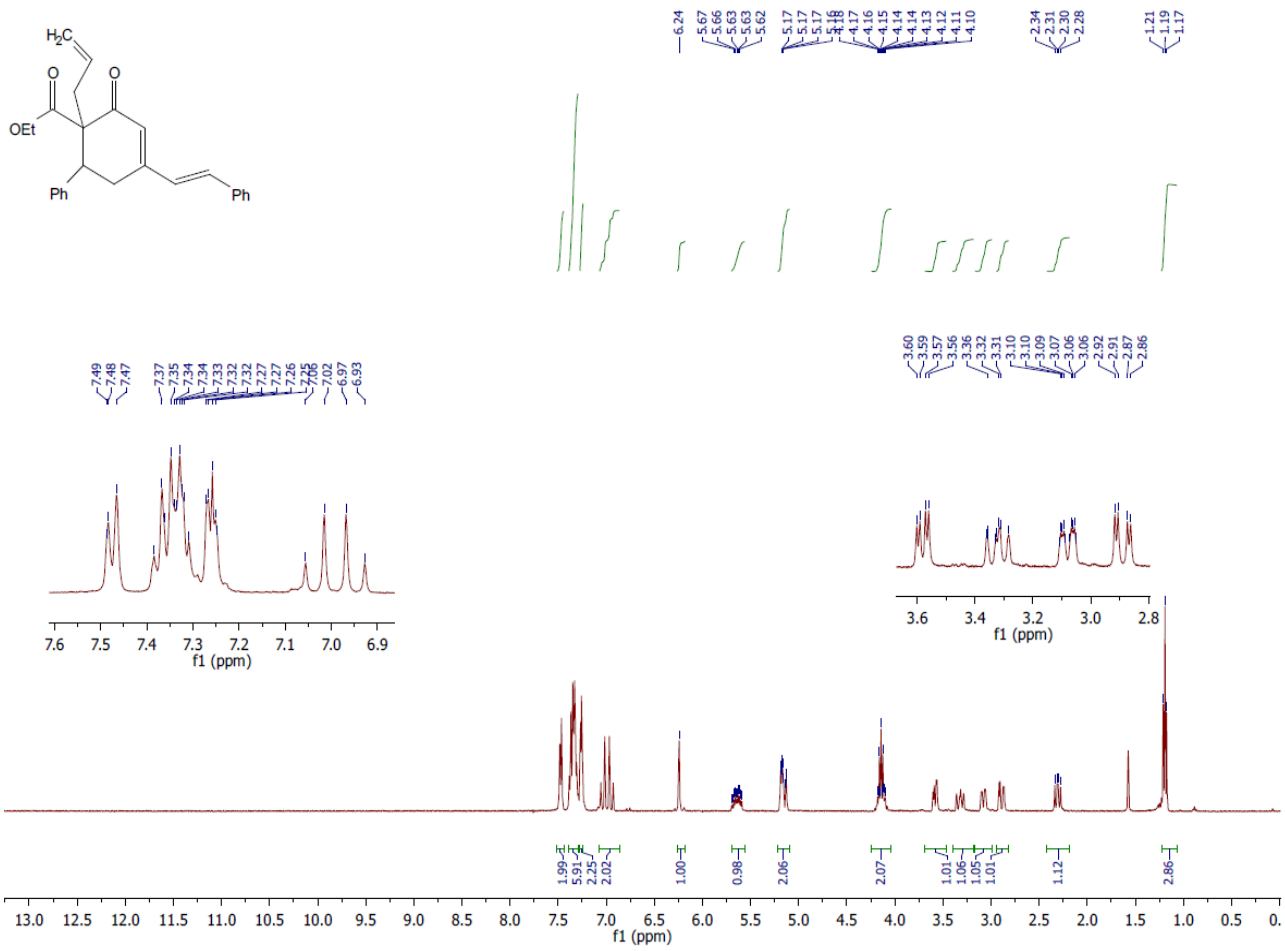
Appendix 33


PROTON.cde|3_T25_001
Gradient Shimming
P (s) 7.36
O (m) 7.43
N (m) 6.97
A (d) 6.21
B (m) 5.16
C (dt) 4.09
D (m) 3.75
E (dd) 3.58
F (d) 3.30
G (m) 3.07
H (s) 2.96
I (d) 2.89
J (m) 2.31
K (s) 1.56
L (m) 1.19
M (t) 1.03
f1 (ppm)

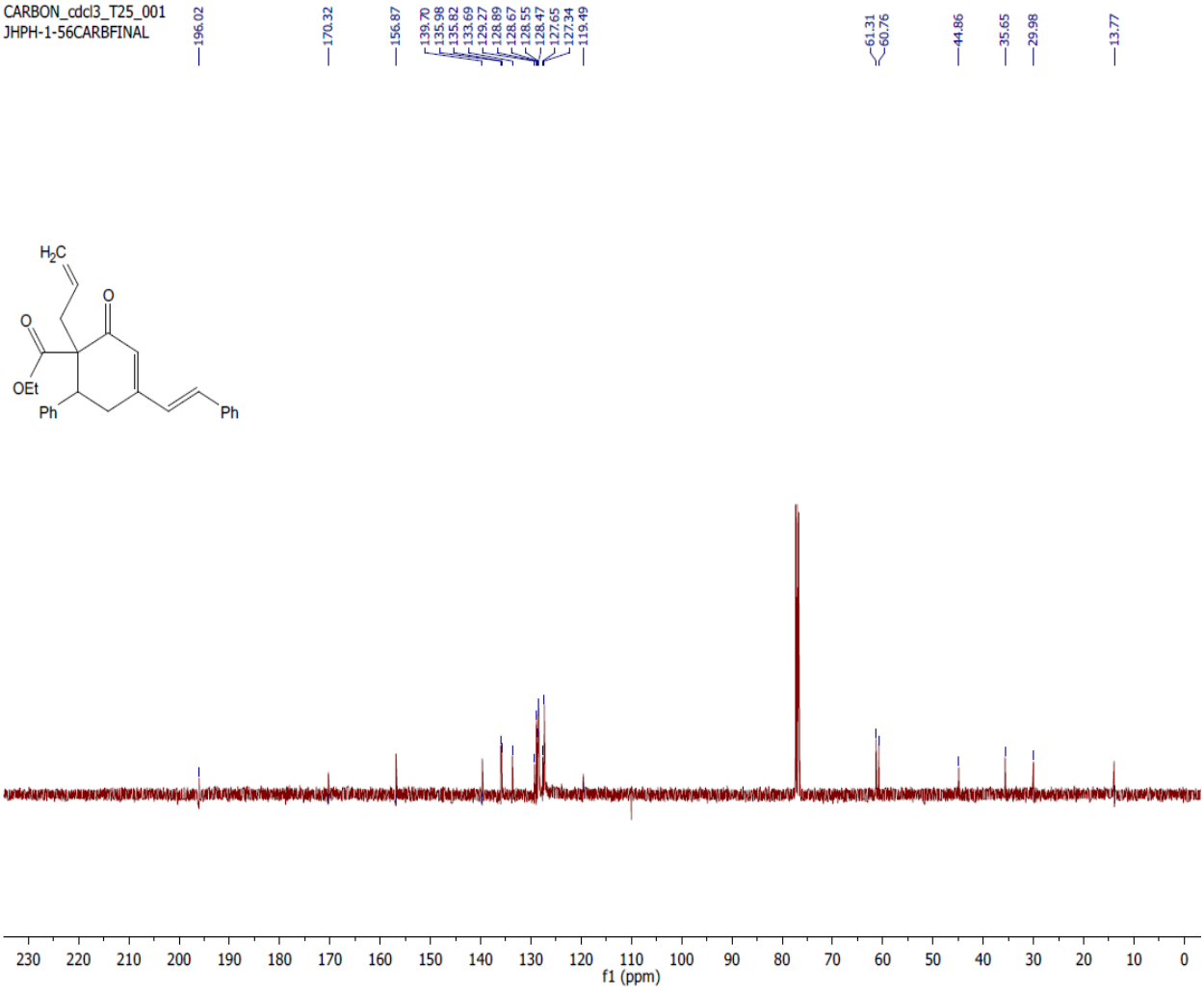
Appendix 34


JHPH-1-56_b #1-5 RT: 0.01-0.13 AV: 5 NL: 5.85E7
T: FTMS + p ESI Full ms [200.00-600.00]
387.1959
C26 H27 O3 = 387.1955
1.1986 ppm
388.1988
409.1776
C26 H26 O3 Na = 409.1774
0.4921 ppm
389.2023
410.1812
m/z

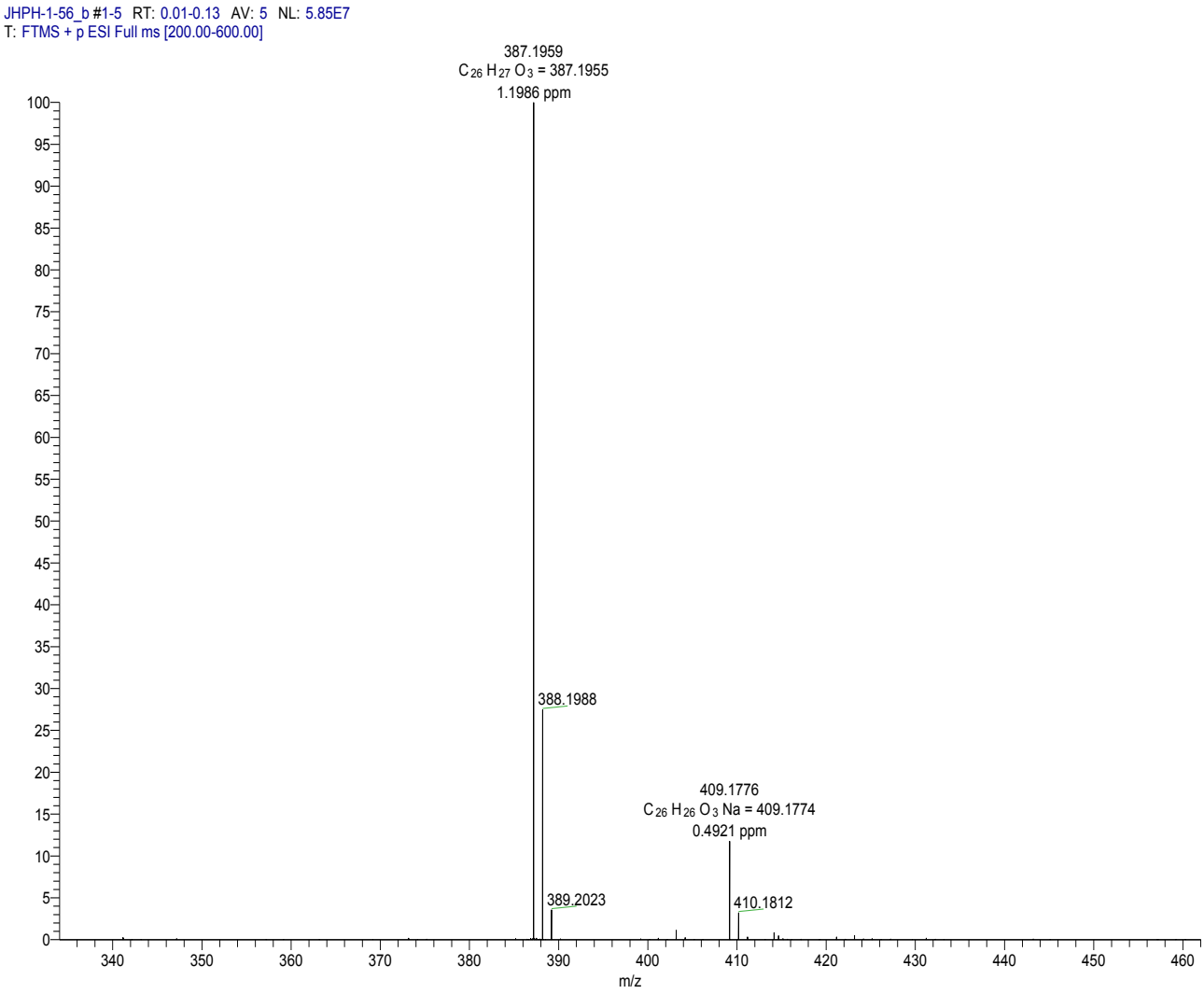
Appendix 35



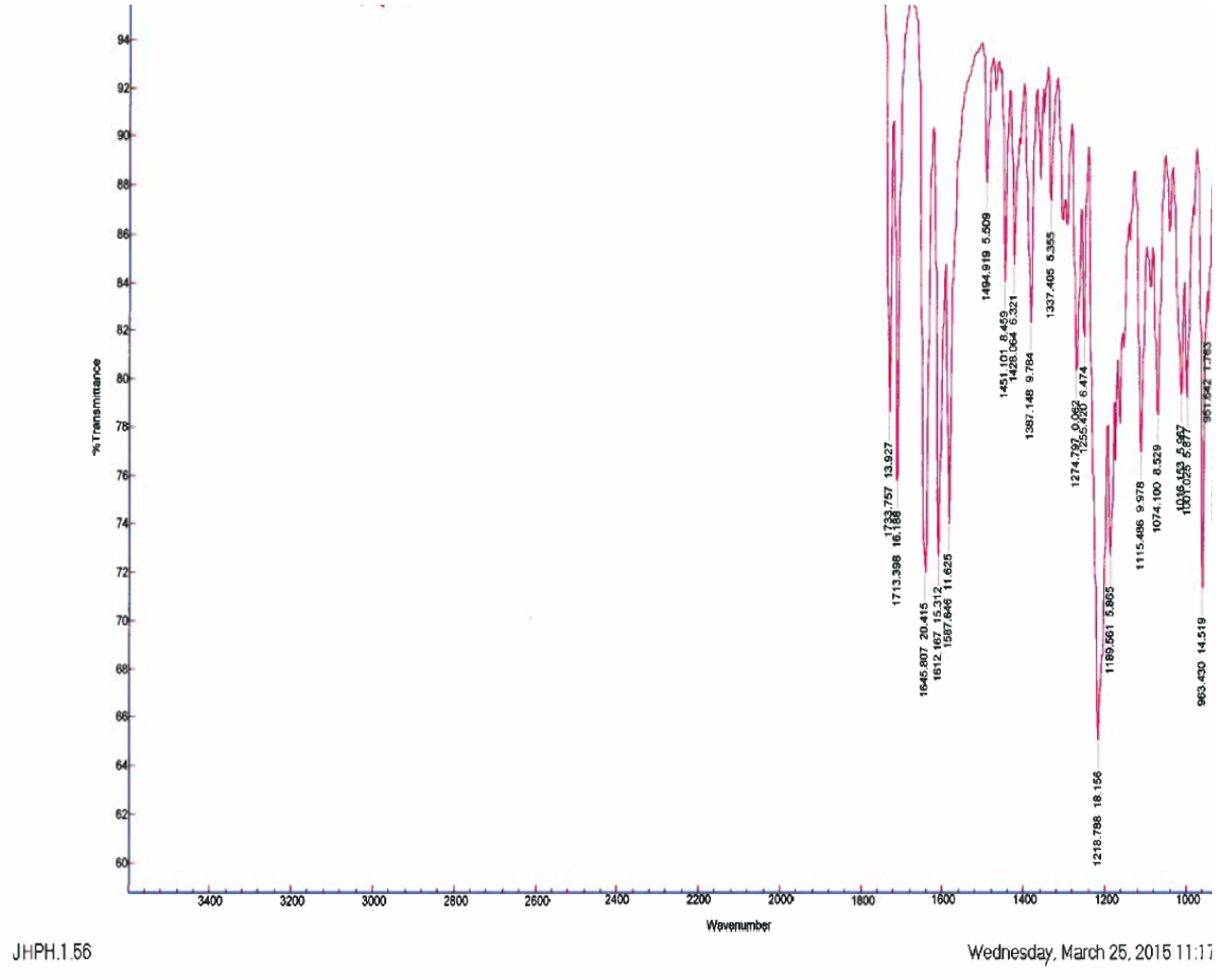
Appendix 36


CARBON_cdcl3_T25_001
JHPH-1-56CARBFINAL
196.02
170.32
156.87
139.70
135.98
135.82
133.69
129.27
128.89
128.67
128.55
128.47
127.65
127.34
119.49
61.31
60.76
44.86
35.65
29.98
13.77
H2C
O
O
OEt
Ph
Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

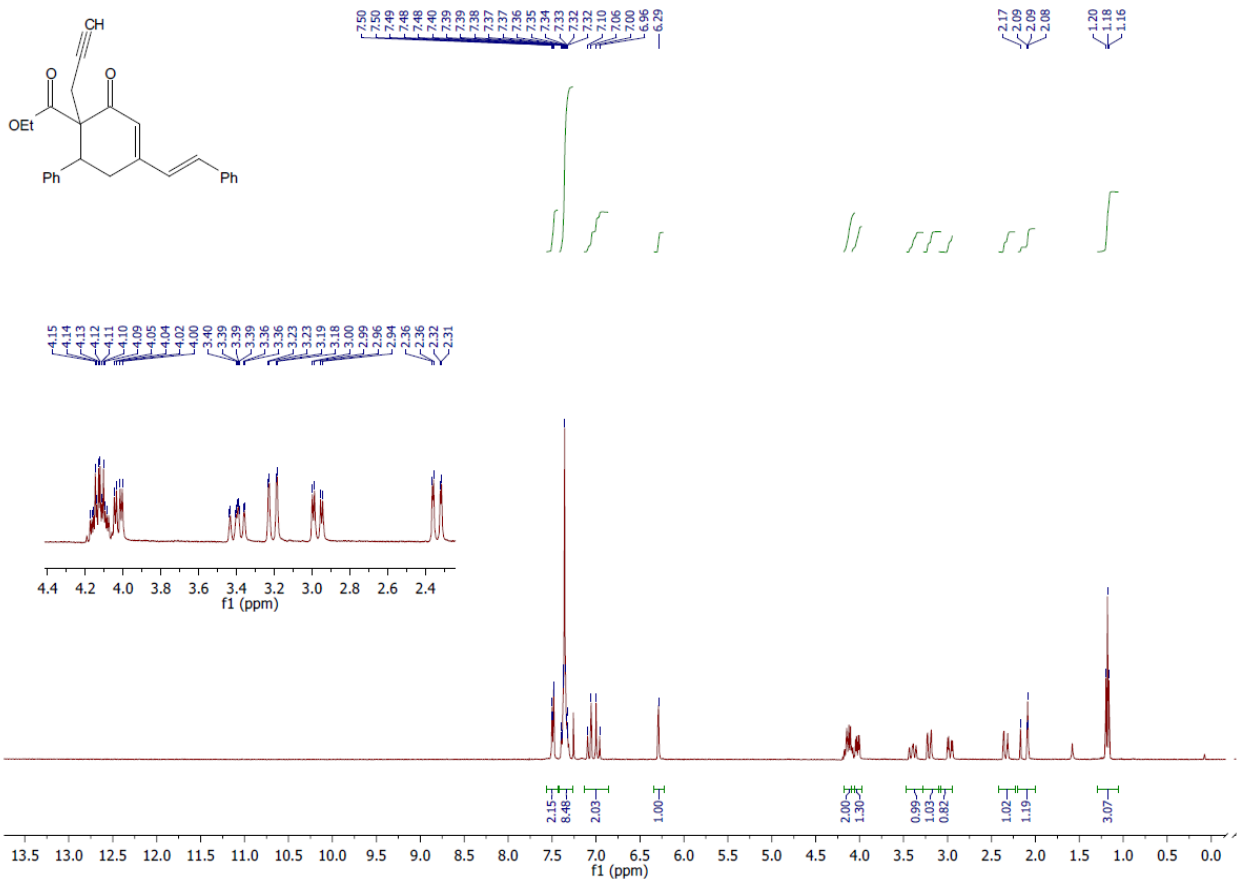
Appendix 37


JHPH-1-56_b #1-5 RT: 0.01-0.13 AV: 5 NL: 5.85E7
T: FTMS + p ESI Full ms [200.00-600.00]
387.1959
C26 H27 O3 = 387.1955
1.1986 ppm
388.1988
409.1776
C26 H26 O3 Na = 409.1774
0.4921 ppm
389.2023
410.1812
m/z

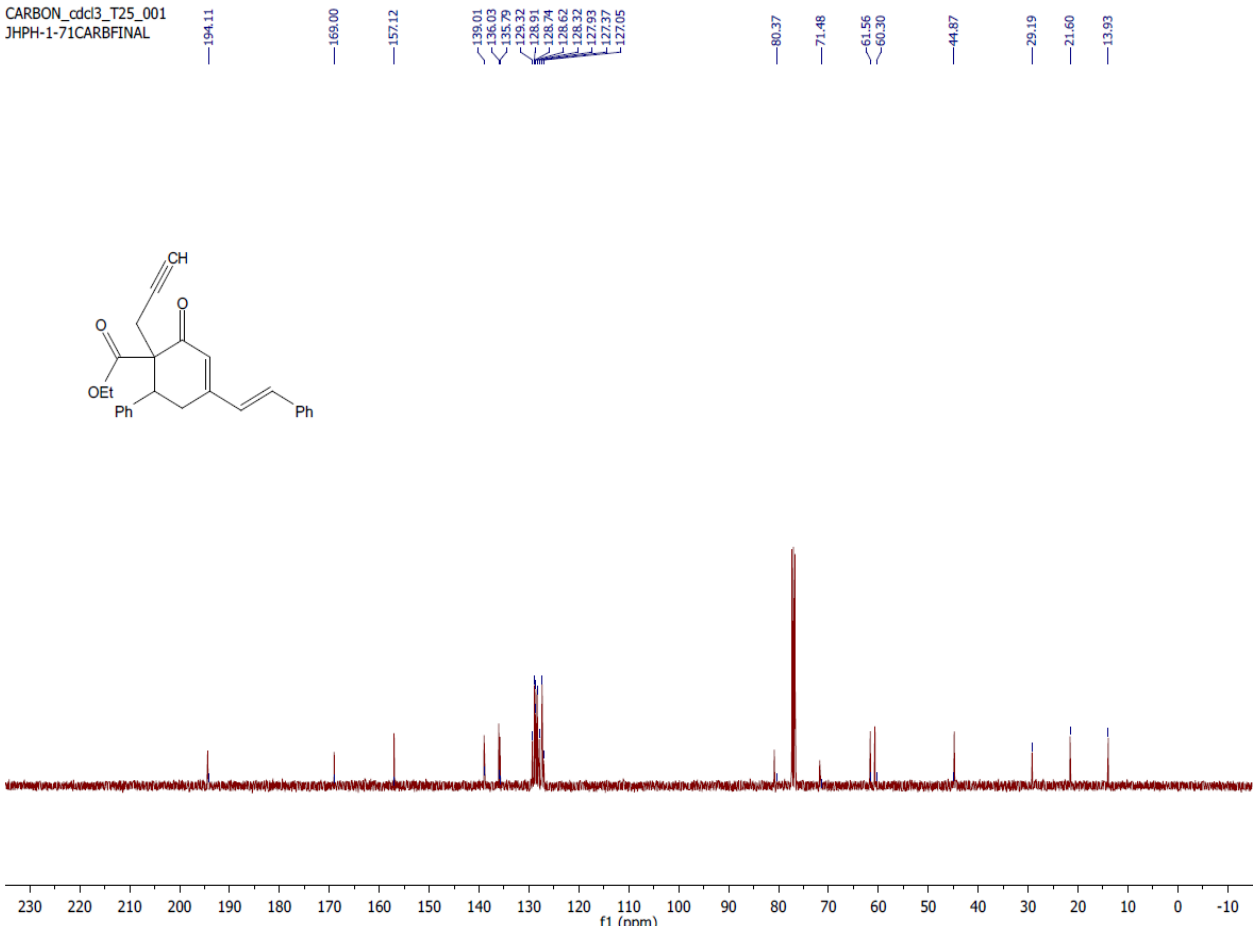
Appendix 38


%Transmittance
Wavenumber
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
1733.757 13.927
1713.398 16.188
1645.807 20.415
1612.167 15.312
1587.646 11.625
1494.919 5.509
1451.101 8.459
1428.064 6.321
1387.148 9.784
1337.405 5.355
1274.792 9.062
1255.420 6.474
1189.561 5.865
1218.788 18.156
1115.486 9.978
1074.100 8.529
1016.153 5.957
1001.026 5.877
963.430 14.519
JHPH.1.56
Wednesday, March 25, 2015 11:17

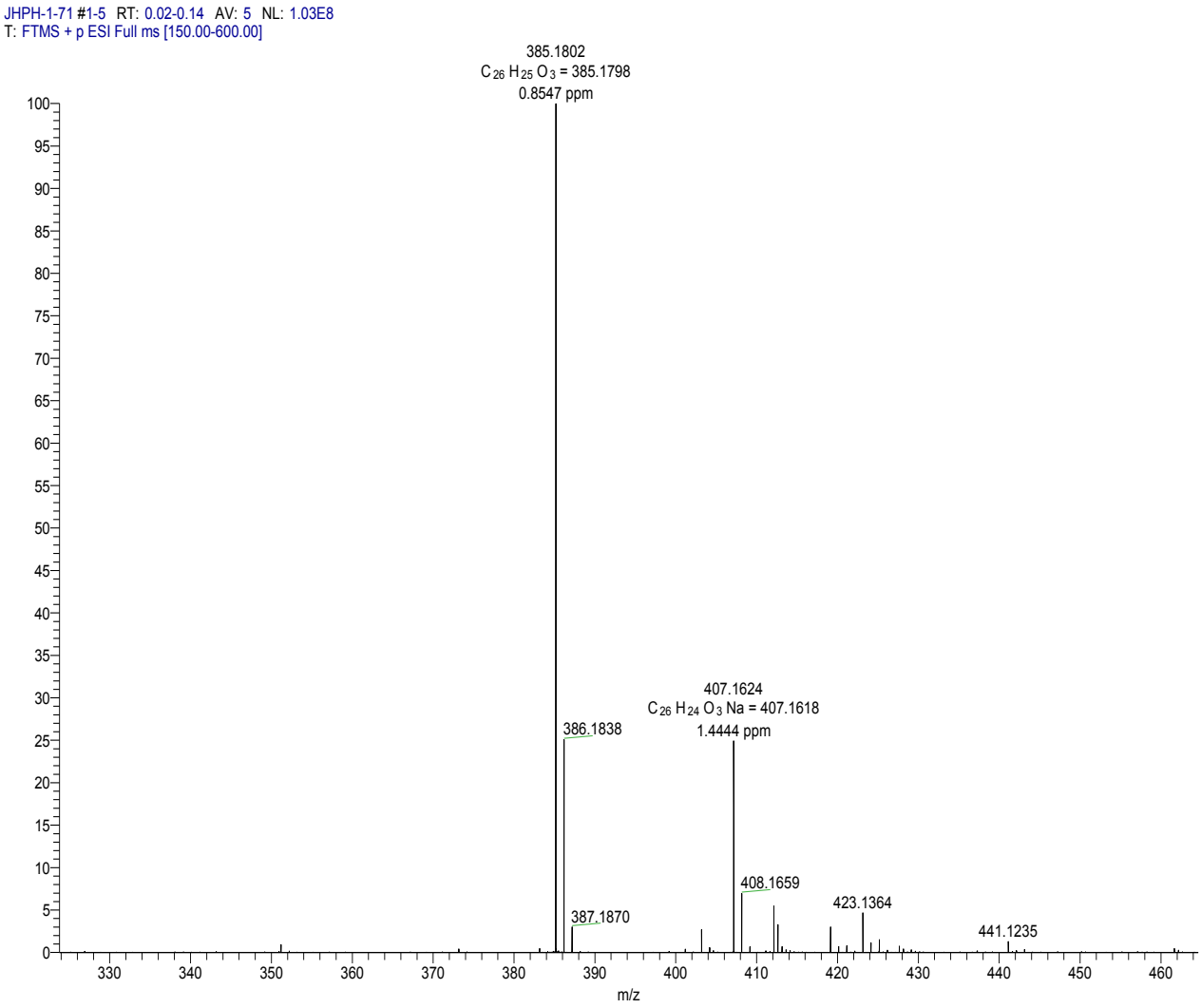
Appendix 39


CH
O
O
OEt
Ph
Ph
7.50 7.50 7.49 7.48 7.48 7.40 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.34 7.33 7.32 7.10 7.06 7.00 6.96 6.29
2.17 2.09 2.09 2.08
1.20 1.18 1.16
4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.05 4.04 4.02 4.00 3.40 3.39 3.39 3.36 3.36 3.23 3.23 3.19 3.18 3.00 2.99 2.96 2.94 2.36 2.36 2.32 2.31
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4
f1 (ppm)
2.15 8.48 2.03 1.00 2.00 1.30 0.99 1.03 0.82 1.02 1.19 3.07
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

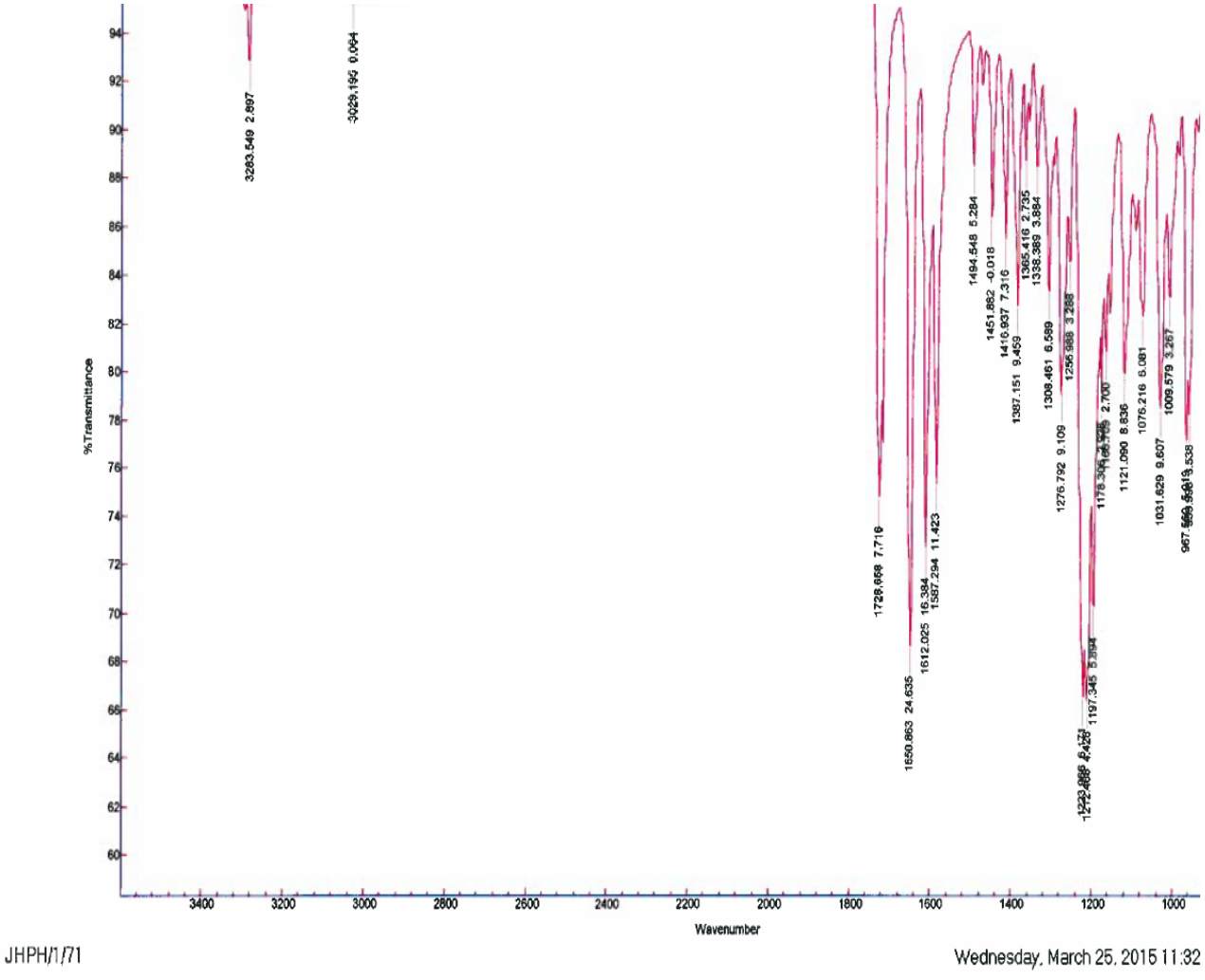
Appendix 40

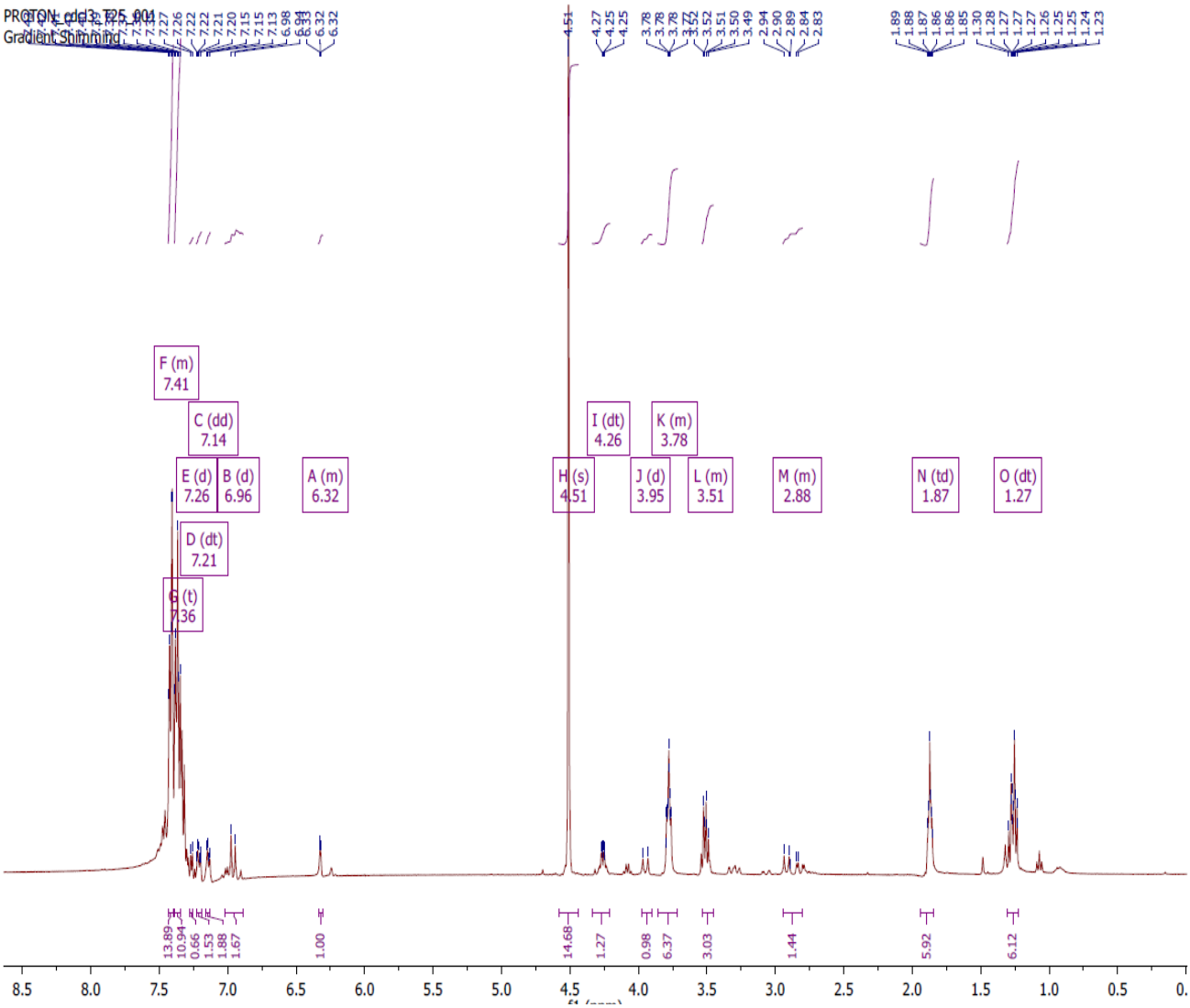

CARBON_cdcl3_T25_001
JHPH-1-71CARBFINAL
194.11
169.00
157.12
139.01
136.03
135.79
129.32
128.91
128.74
128.62
128.32
127.93
127.37
127.05
80.37
71.48
61.56
60.30
44.87
29.19
21.60
13.93
CH
O
O
OEt
Ph
Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Appendix 41

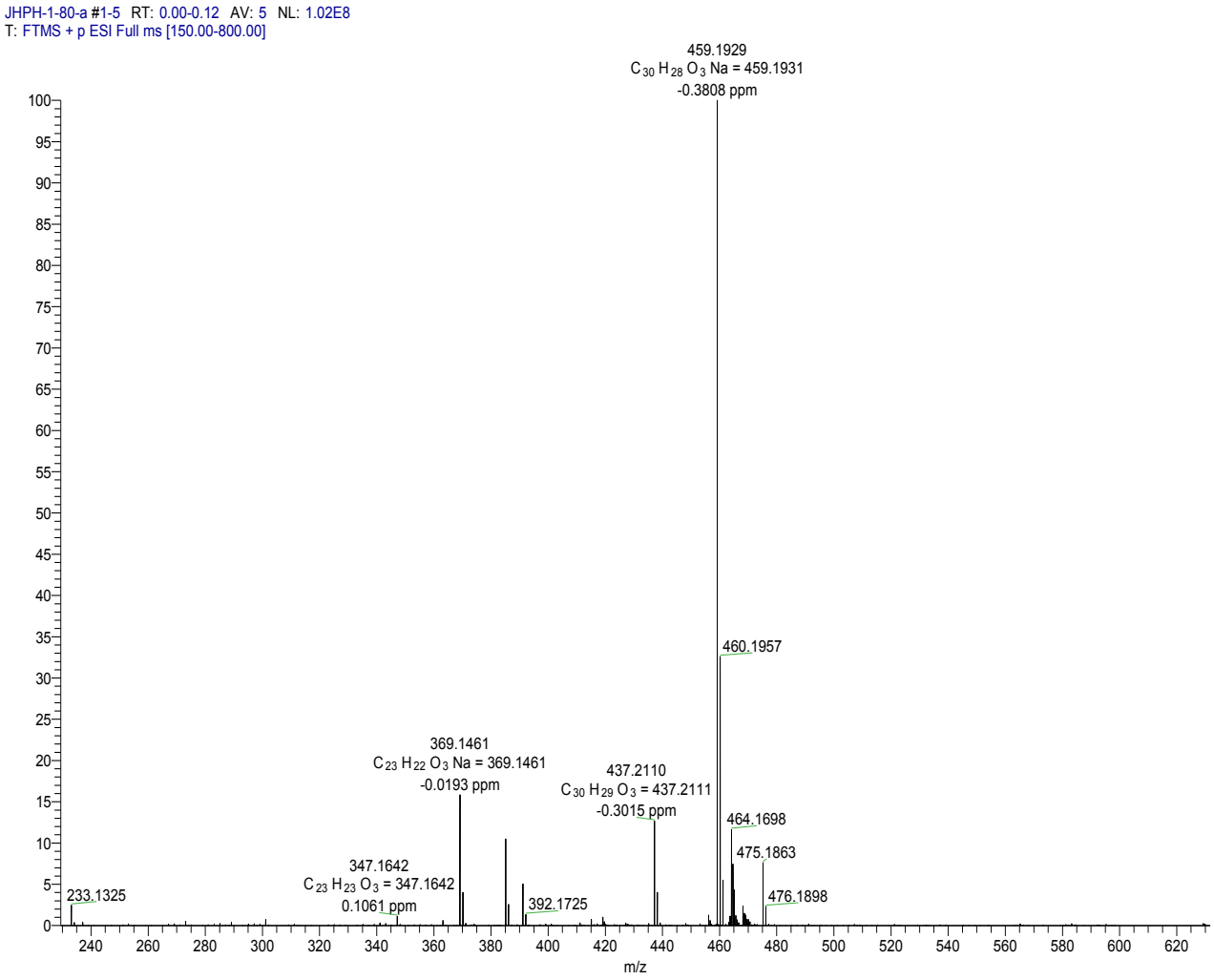

JHPH-1-71 #1-5 RT: 0.02-0.14 AV: 5 NL: 1.03E8
T: FTMS + p ESI Full ms [150.00-600.00]
385.1802
C26 H25 O3 = 385.1798
0.8547 ppm
407.1624
C26 H24 O3 Na = 407.1618
1.4444 ppm
386.1838
387.1870
408.1659
423.1364
441.1235
m/z

Appendix 42

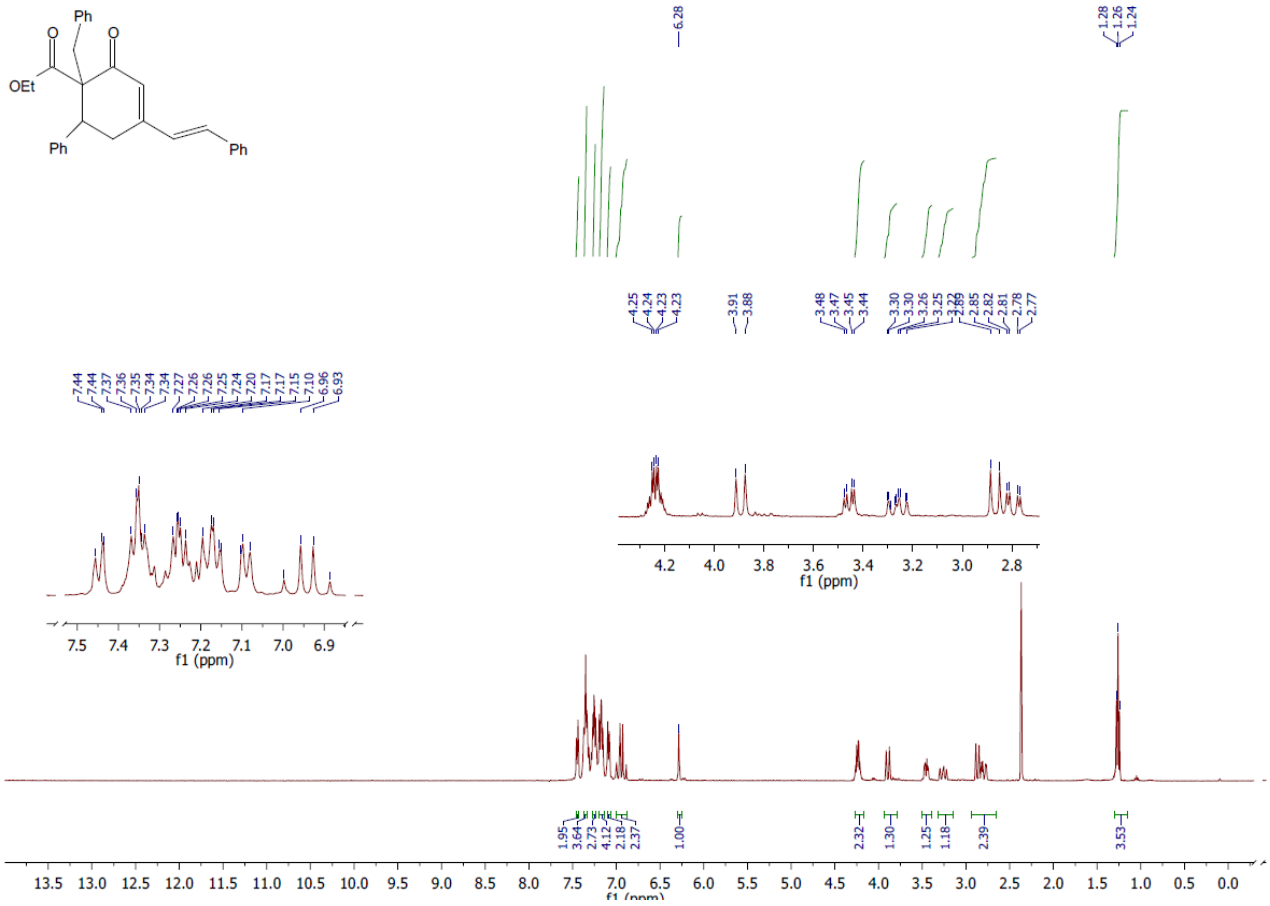

%Transmittance
Wavenumber
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
3283.549 2.897
3029.195 0.064
1728.668 7.716
1650.863 24.635
1612.025 16.384
1587.294 11.423
1494.548 5.284
1451.882 -0.018
1416.937 7.316
1387.151 9.459
1365.416 2.795
1338.389 3.884
1308.461 6.589
1276.792 9.109
1197.345 5.394
1121.090 8.836
1076.216 6.081
1031.629 9.607
1009.579 3.267
JHPH/1/71
Wednesday, March 25, 2015 11:32


PROTON cdcl3 T25 001
Gradient Shimming
F (m) 7.41
C (dd) 7.14
E (d) 7.26
B (d) 6.96
A (m) 6.32
D (dt) 7.21
G (t) 7.36
I (dt) 4.26
K (m) 3.78
H (s) 4.51
J (d) 3.95
L (m) 3.51
M (m) 2.88
N (td) 1.87
O (dt) 1.27
13.89
10.94
0.66
1.53
1.88
1.67
1.00
14.68
1.27
0.98
6.37
3.03
1.44
5.92
6.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.

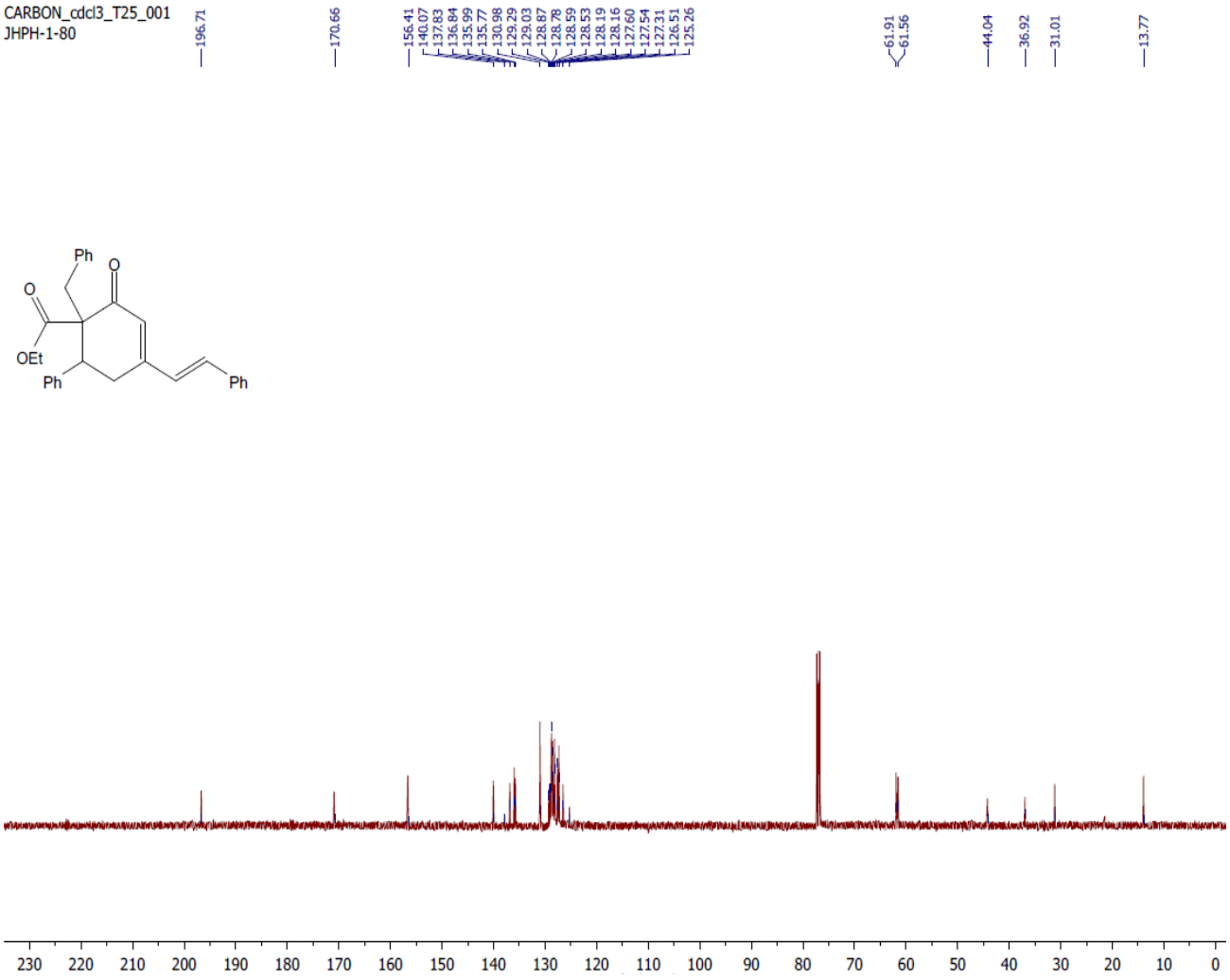
Appendix 44


JHPH-1-80-a #1-5 RT: 0.00-0.12 AV: 5 NL: 1.02E8
T: FTMS + p ESI Full ms [150.00-800.00]
459.1929
C30 H28 O3 Na = 459.1931
-0.3808 ppm
460.1957
369.1461
C23 H22 O3 Na = 369.1461
-0.0193 ppm
437.2110
C30 H29 O3 = 437.2111
-0.3015 ppm
464.1698
475.1863
347.1642
C23 H23 O3 = 347.1642
0.1061 ppm
233.1325
392.1725
476.1898
m/z

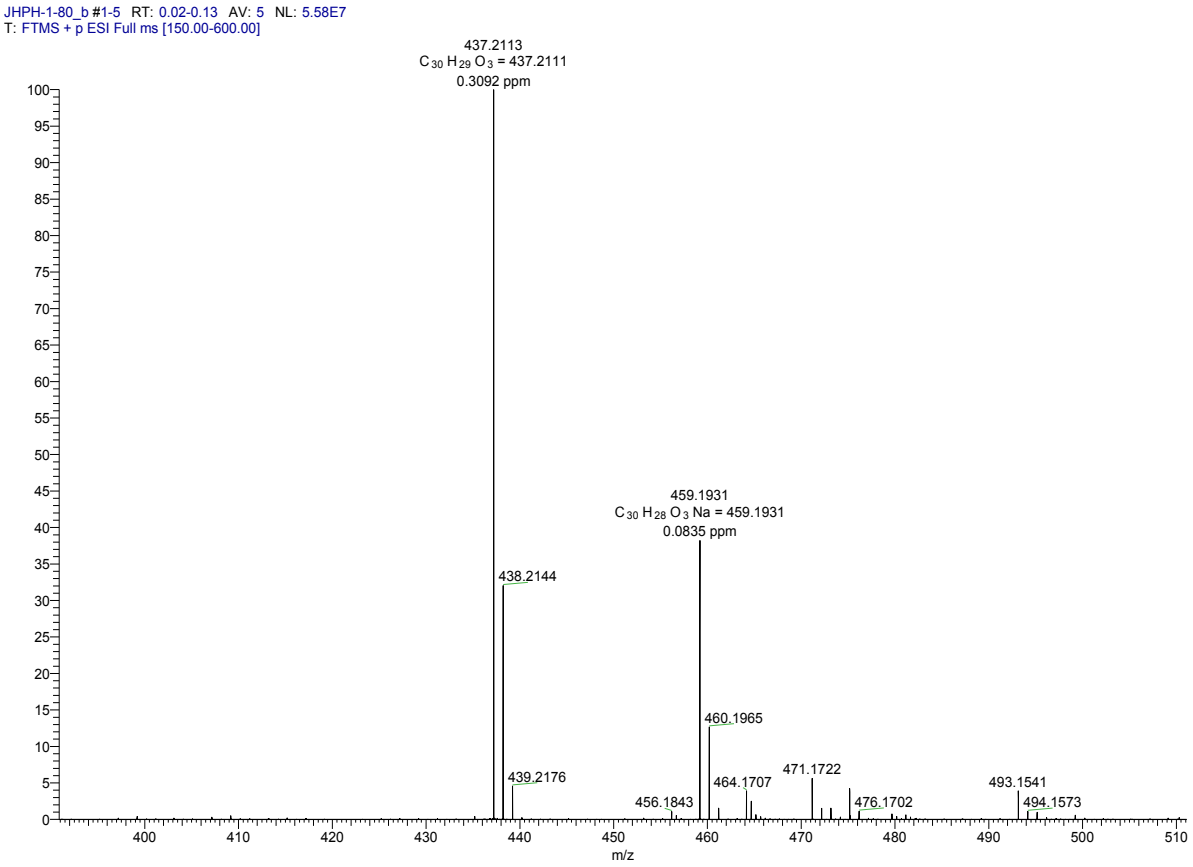
Appendix 45


Ph
O
O
OEt
Ph
Ph
6.28
1.28
1.26
1.24
4.25
4.24
4.23
4.23
3.91
3.88
3.48
3.47
3.45
3.44
3.30
3.30
3.26
3.25
2.85
2.82
2.81
2.78
2.77
7.44
7.44
7.37
7.36
7.35
7.34
7.34
7.27
7.26
7.26
7.25
7.24
7.20
7.17
7.17
7.15
7.10
6.96
6.93
7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
f1 (ppm)
1.95
3.64
2.73
4.12
2.18
2.37
1.00
2.32
1.30
1.25
1.18
2.39
3.53
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

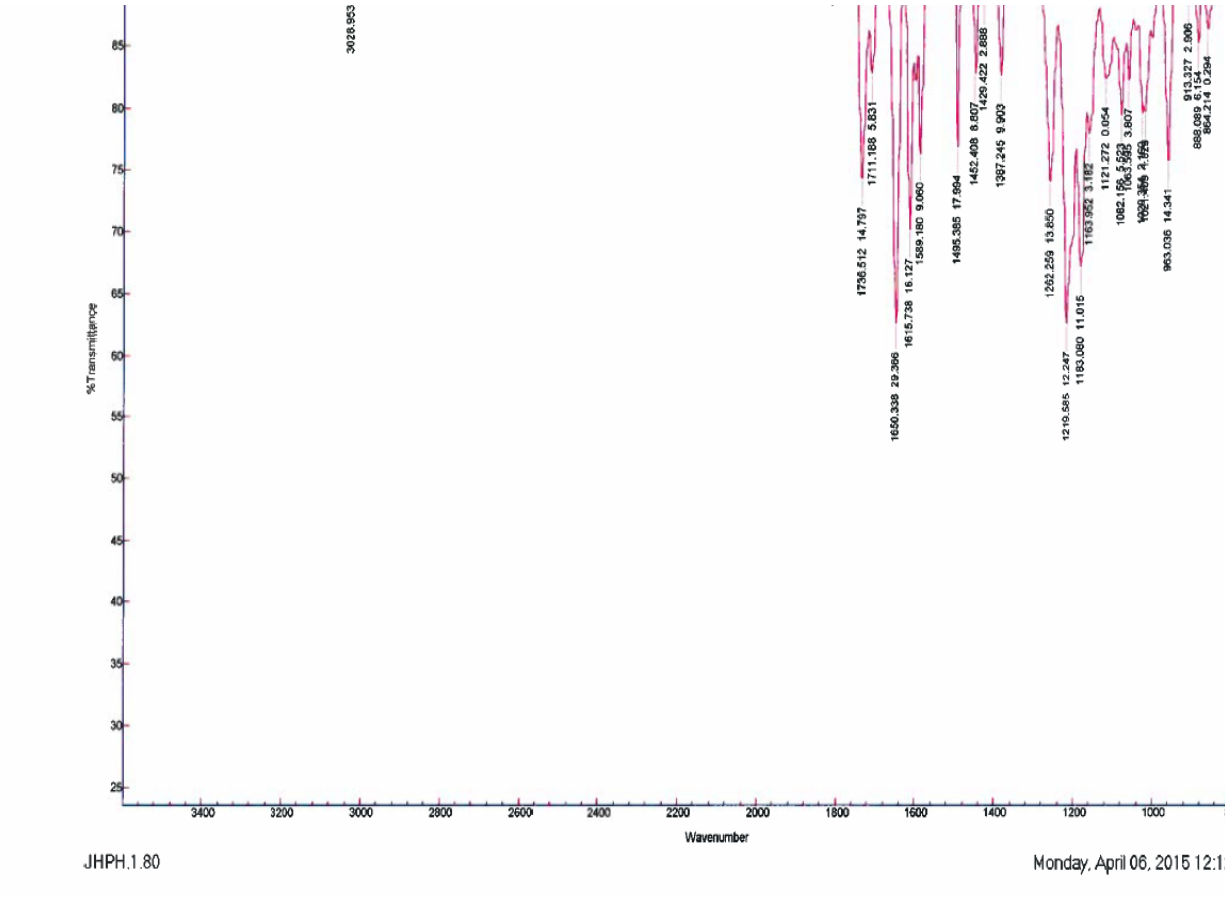
Appendix 46


CARBON_cdcl3_T25_001
JHPH-1-80
196.71
170.66
156.41
140.07
137.83
136.84
135.99
135.77
130.98
129.29
129.03
128.87
128.78
128.59
128.53
128.19
128.16
127.60
127.54
127.31
126.51
125.26
61.91
61.56
44.04
36.92
31.01
13.77
Ph
O
O
OEt
Ph
Ph
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

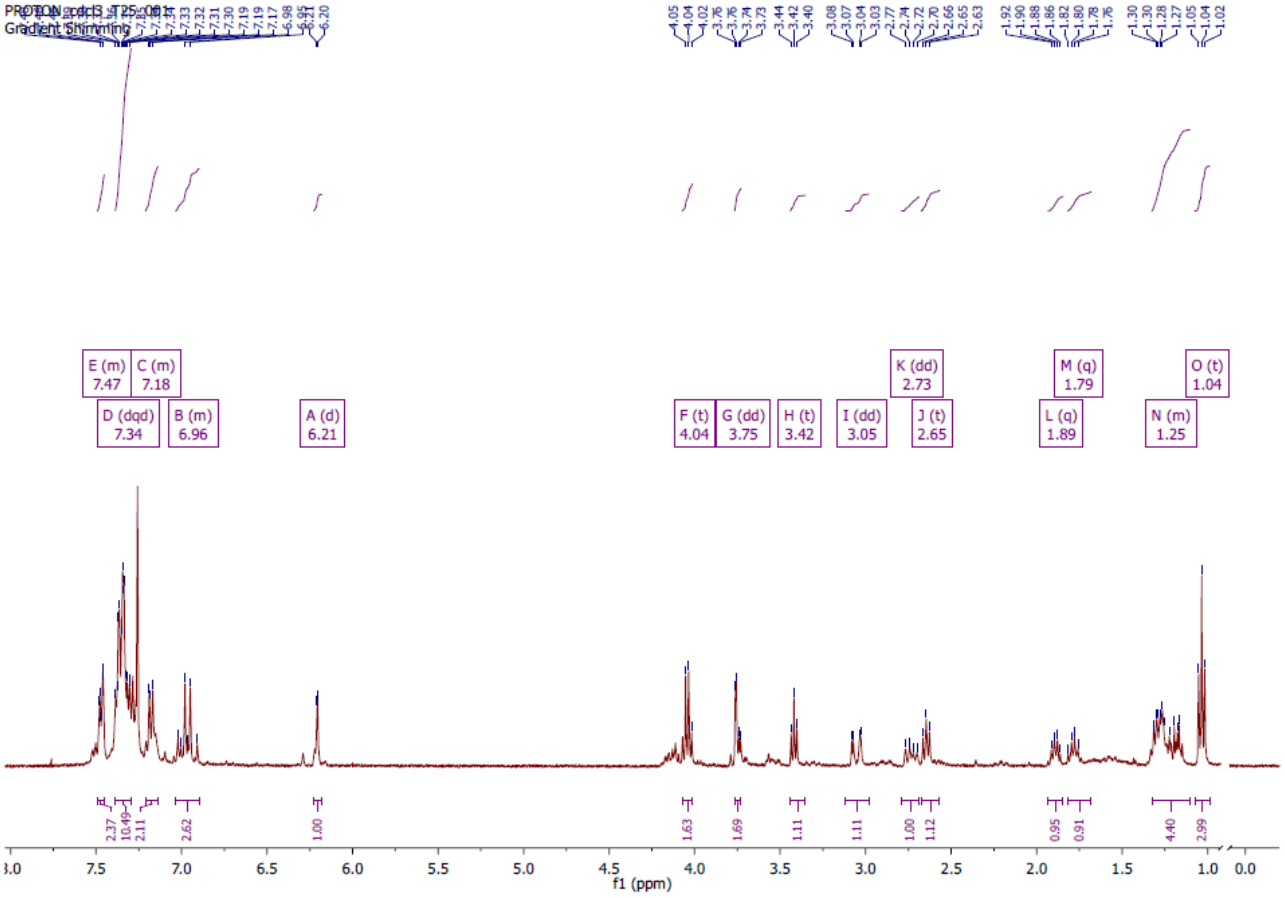
Appendix 47


JHPH-1-80_b #1-5 RT: 0.02-0.13 AV: 5 NL: 5.58E7
T: FTMS + p ESI Full ms [150.00-600.00]
437.2113
C30 H29 O3 = 437.2111
0.3092 ppm
459.1931
C30 H28 O3 Na = 459.1931
0.0835 ppm
438.2144
460.1965
439.2176
471.1722
464.1707
456.1843
476.1702
493.1541
494.1573
m/z

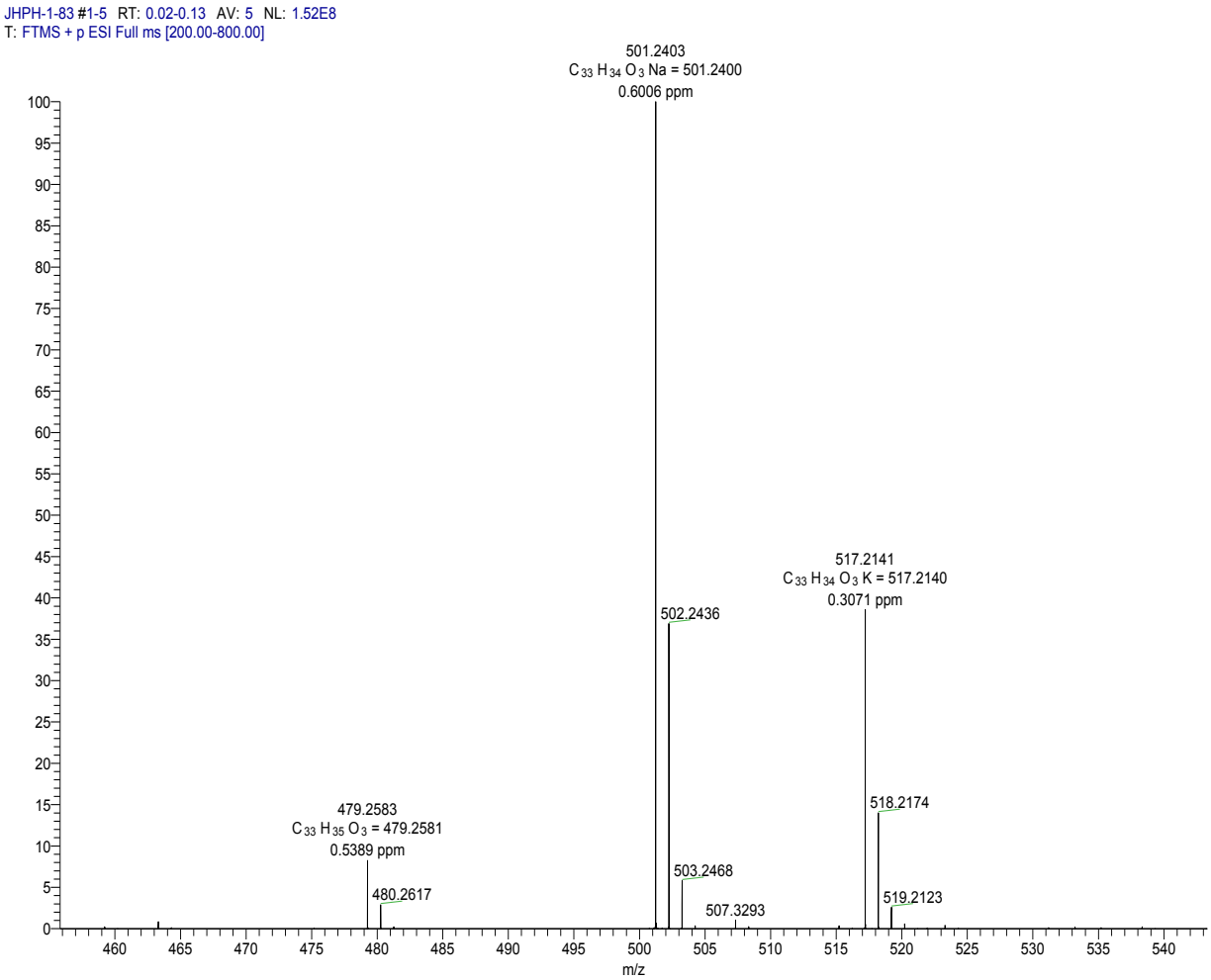
Appendix 48


%Transmittance
Wavenumber
JHPH.1.80
Monday, April 06, 2015 12:1

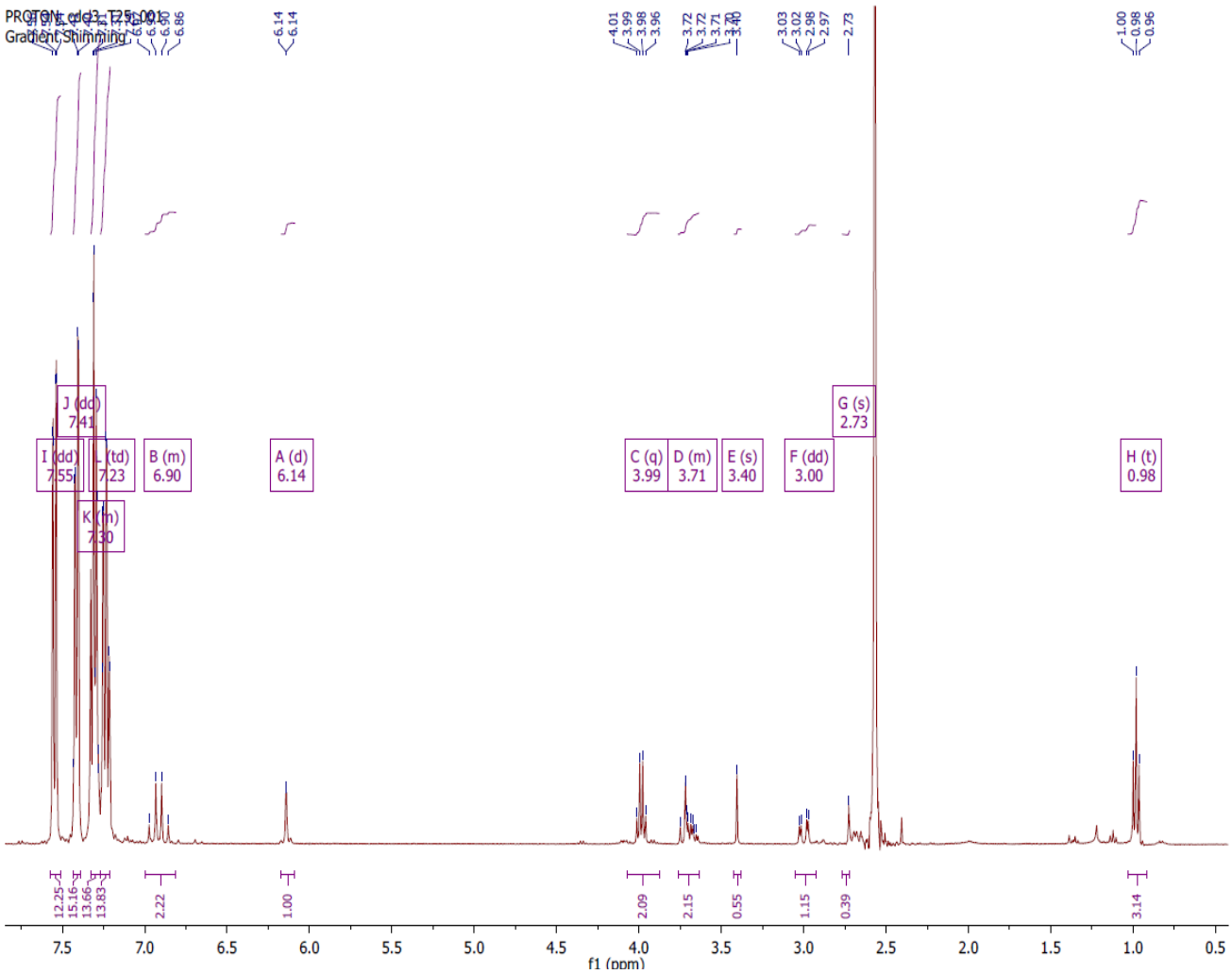
Appendix 49


PROTON cdcl3 T25_001
Gradient Shimming
E (m) 7.47
C (m) 7.18
D (dqd) 7.34
B (m) 6.96
A (d) 6.21
K (dd) 2.73
M (q) 1.79
O (t) 1.04
F (t) 4.04
G (dd) 3.75
H (t) 3.42
I (dd) 3.05
J (t) 2.65
L (q) 1.89
N (m) 1.25
f1 (ppm)

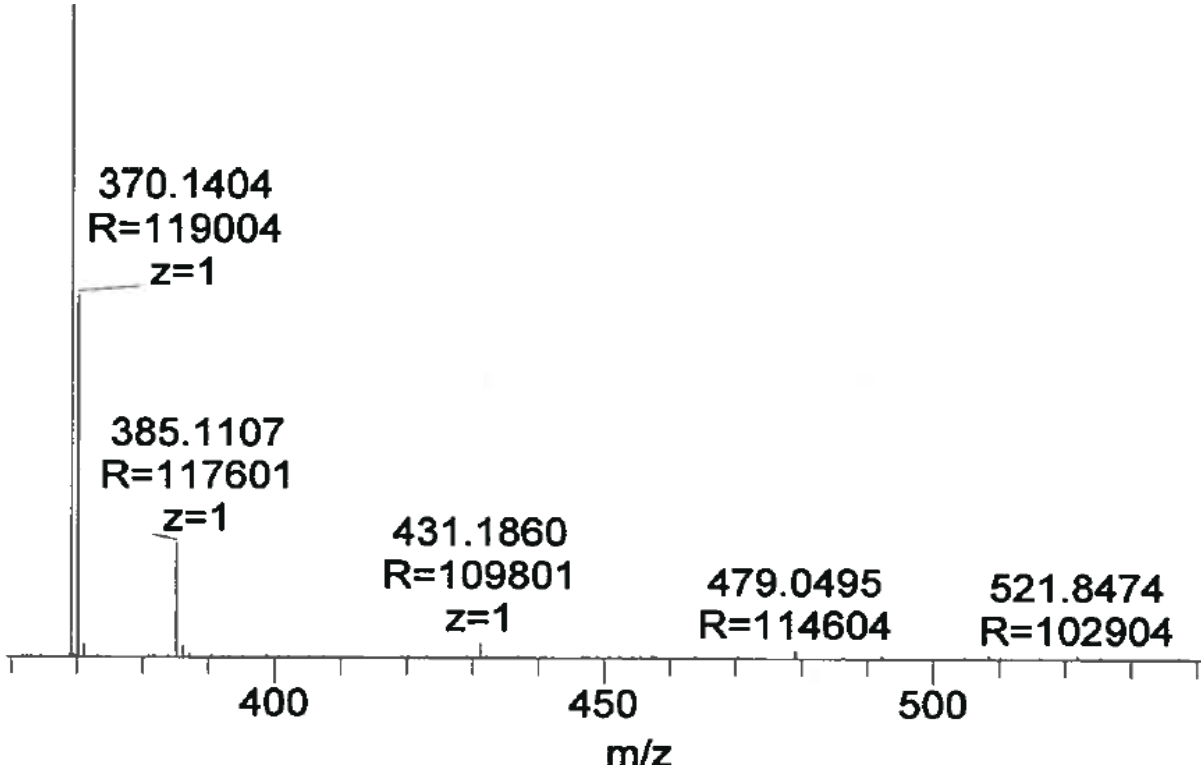
Appendix 50


JHPH-1-83 #1-5 RT: 0.02-0.13 AV: 5 NL: 1.52E8
T: FTMS + p ESI Full ms [200.00-800.00]
501.2403
C33 H34 O3 Na = 501.2400
0.6006 ppm
517.2141
C33 H34 O3 K = 517.2140
0.3071 ppm
502.2436
479.2583
C33 H35 O3 = 479.2581
0.5389 ppm
518.2174
503.2468
480.2617
519.2123
507.3293
m/z

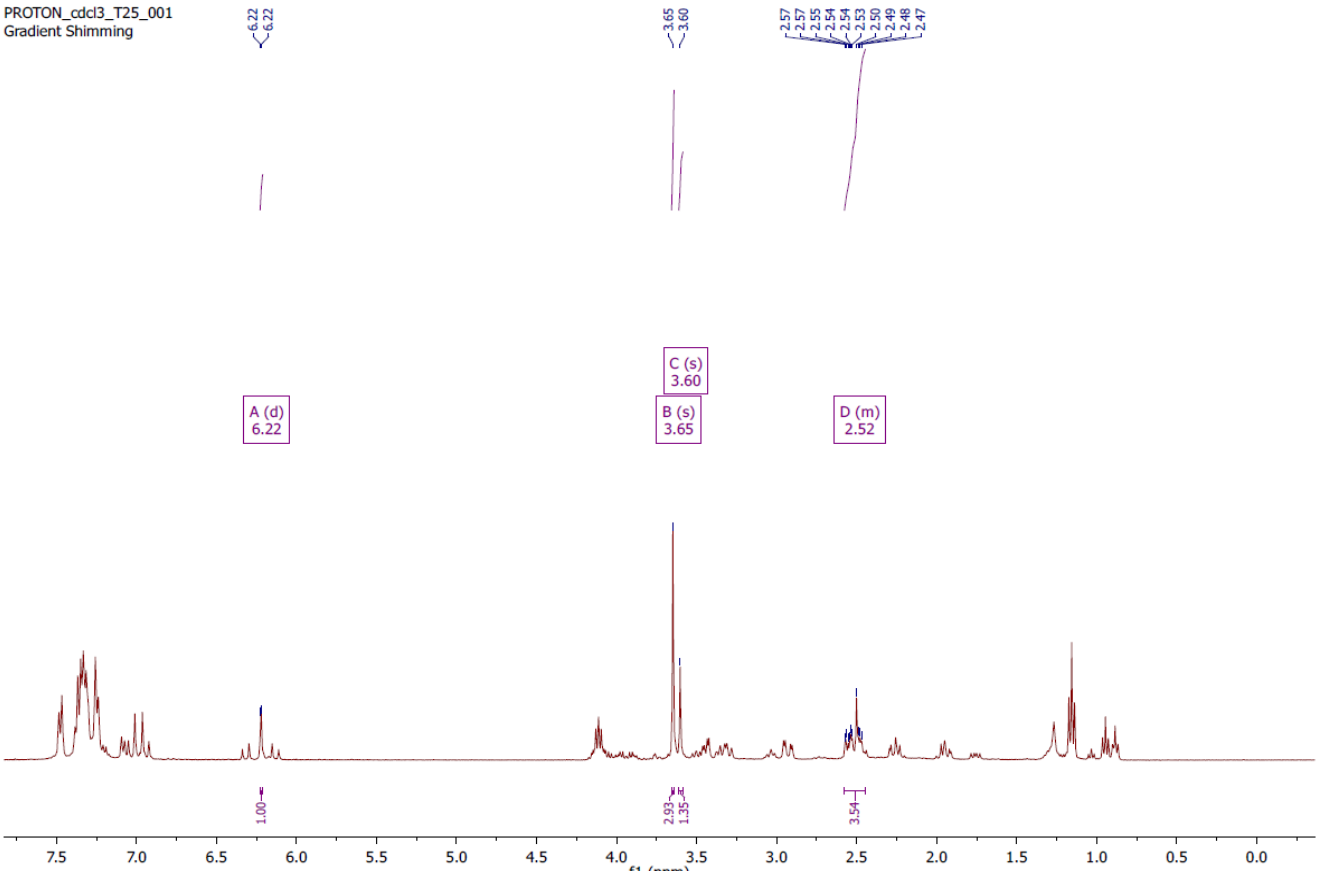
Appendix 51


PROTON_cdcl3_T25_001
Gradient Shimming
J (dd) 7.41
I (dd) 7.55
L (td) 7.23
K (m) 7.30
B (m) 6.90
A (d) 6.14
C (q) 3.99
D (m) 3.71
E (s) 3.40
F (dd) 3.00
G (s) 2.73
H (t) 0.98
f1 (ppm)

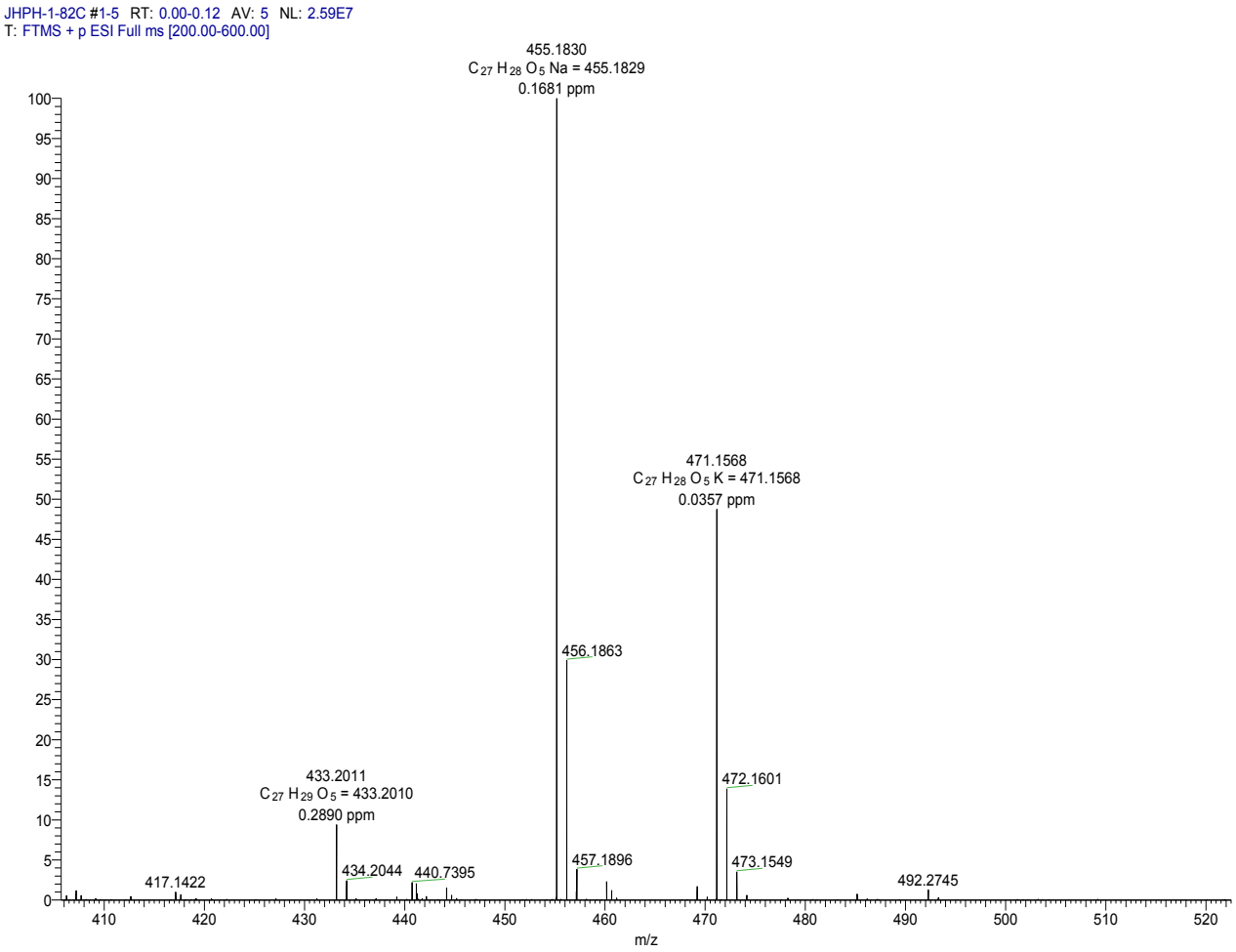
Appendix 52


370.1404
R=119004
z=1
385.1107
R=117601
z=1
431.1860
R=109801
z=1
479.0495
R=114604
521.8474
R=102904
400
450
500
m/z

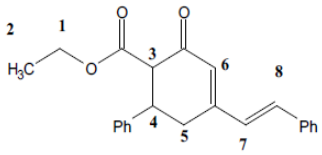
Appendix 53

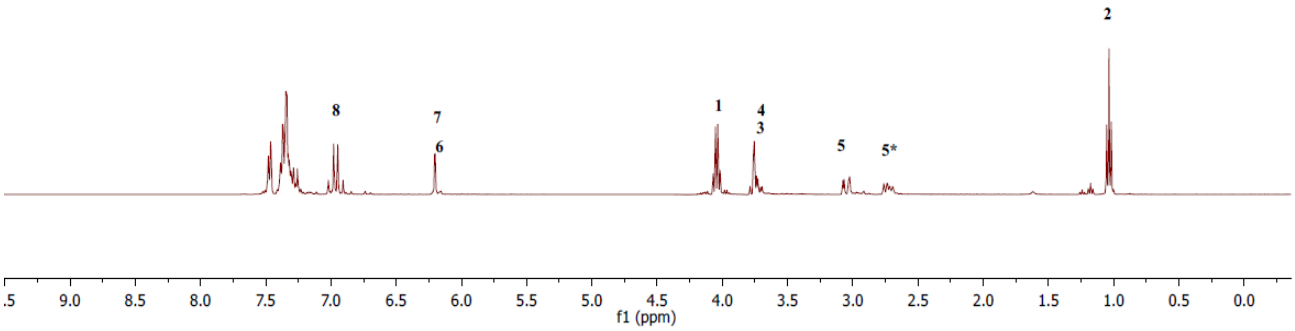

PROTON_cdcl3_T25_001
Gradient Shimming
6.22
6.22
3.65
3.60
2.57
2.57
2.55
2.54
2.54
2.53
2.50
2.49
2.48
2.47
C (s)
3.60
A (d)
6.22
B (s)
3.65
D (m)
2.52
1.00
2.93
1.35
3.54
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Appendix 54

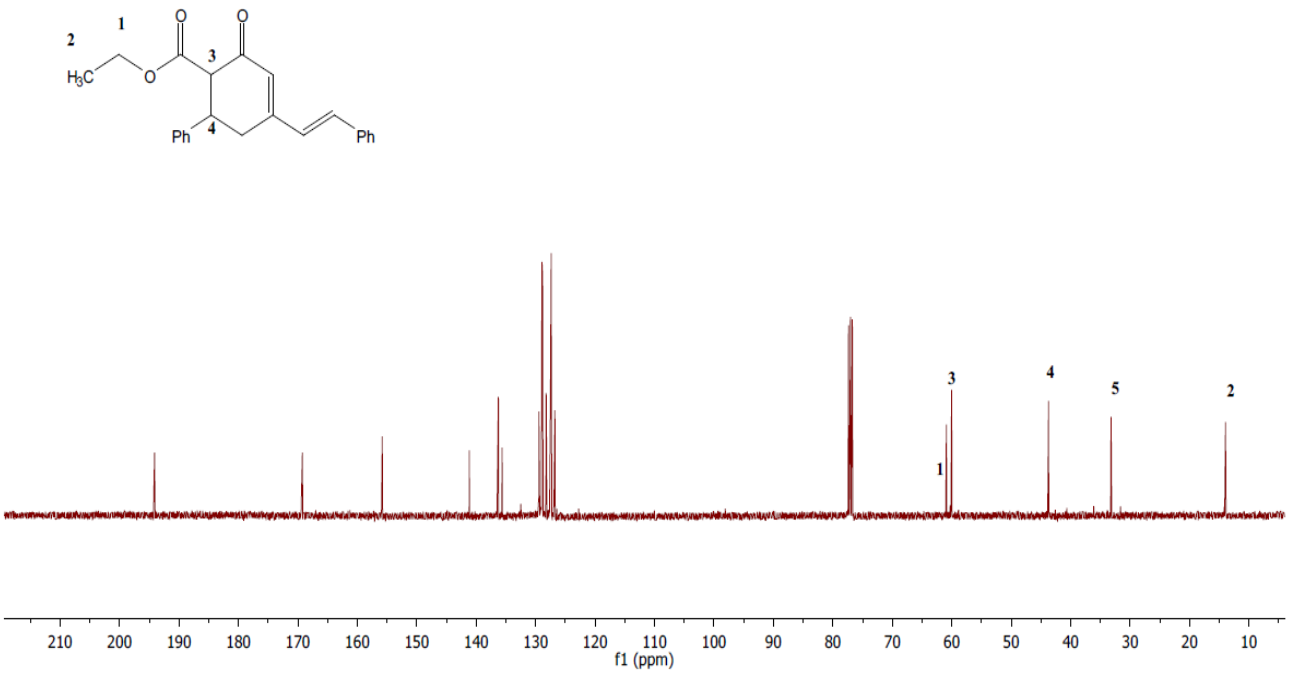

JHPH-1-82C #1-5 RT: 0.00-0.12 AV: 5 NL: 2.59E7
T: FTMS + p ESI Full ms [200.00-600.00]
455.1830
C27 H28 O5 Na = 455.1829
0.1681 ppm
471.1568
C27 H28 O5 K = 471.1568
0.0357 ppm
456.1863
433.2011
C27 H29 O5 = 433.2010
0.2890 ppm
472.1601
457.1896
473.1549
434.2044
440.7395
417.1422
492.2745
m/z

Appendix 55

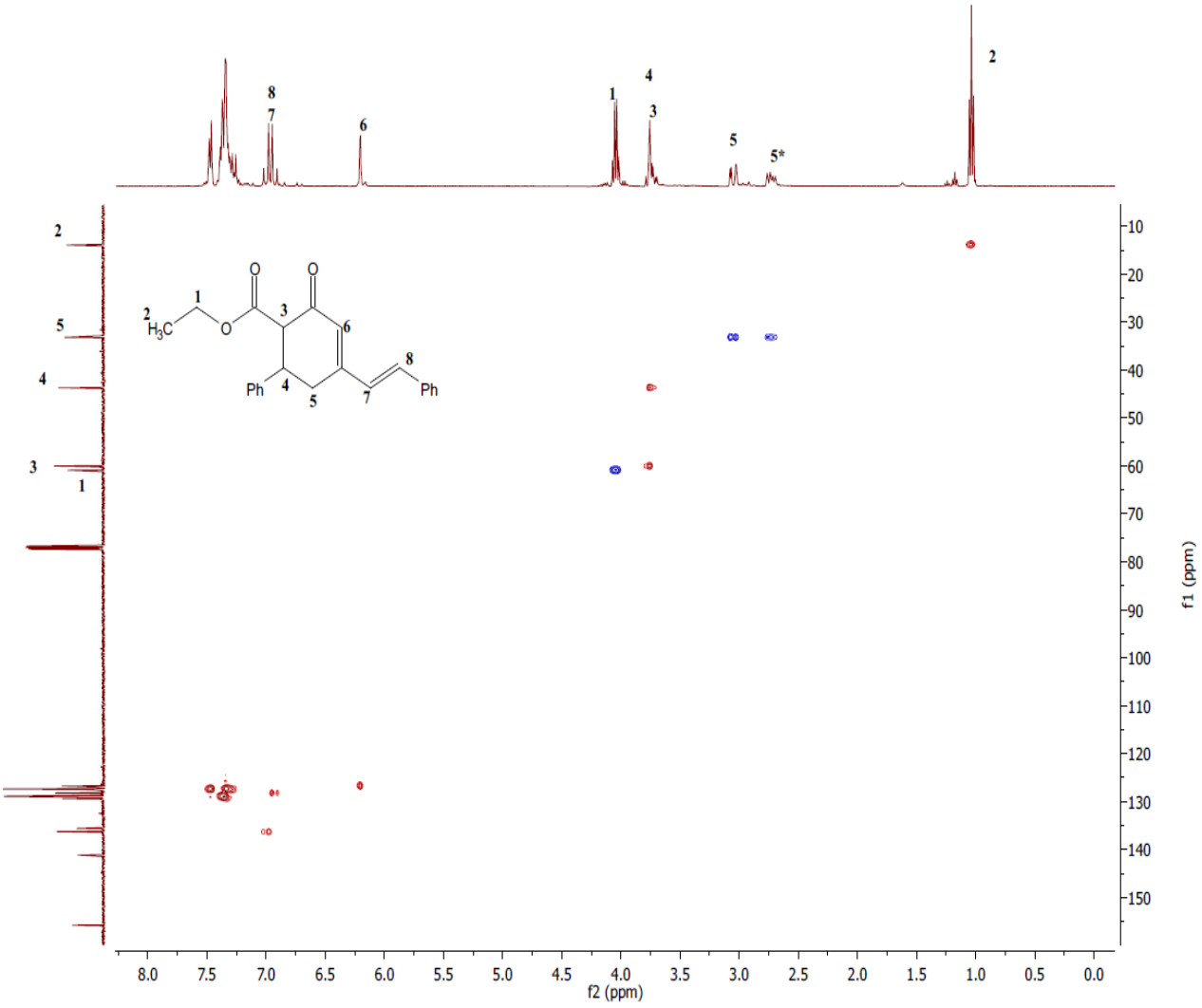

2
1
O
O
3
6
8
H3C
O
Ph
4
5
7
Ph


2
8
7
6
1
4
3
5
5*
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

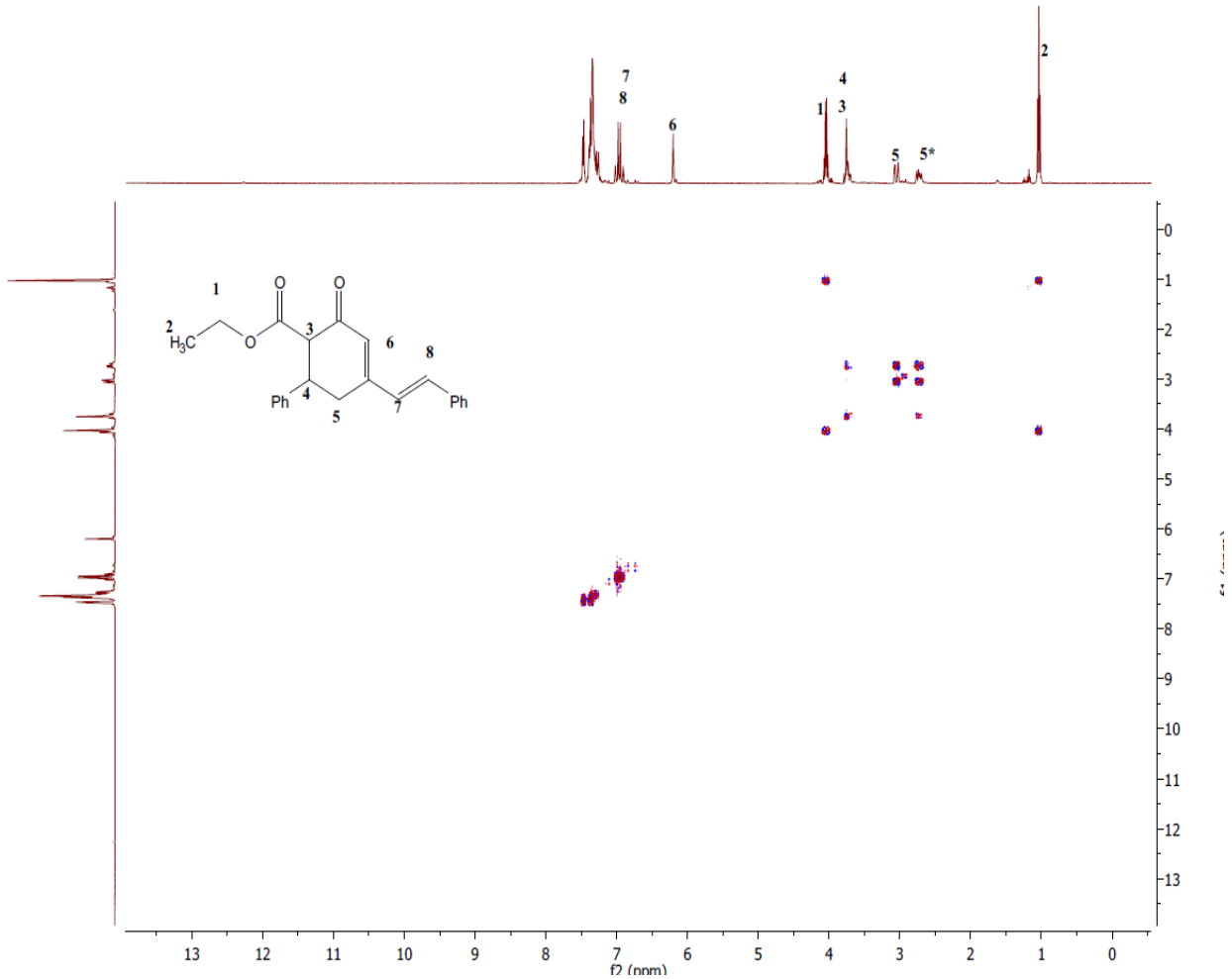
Appendix 56


1
2
3
4
Ph
Ph
H3C
O
O
O
1
3
4
5
2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

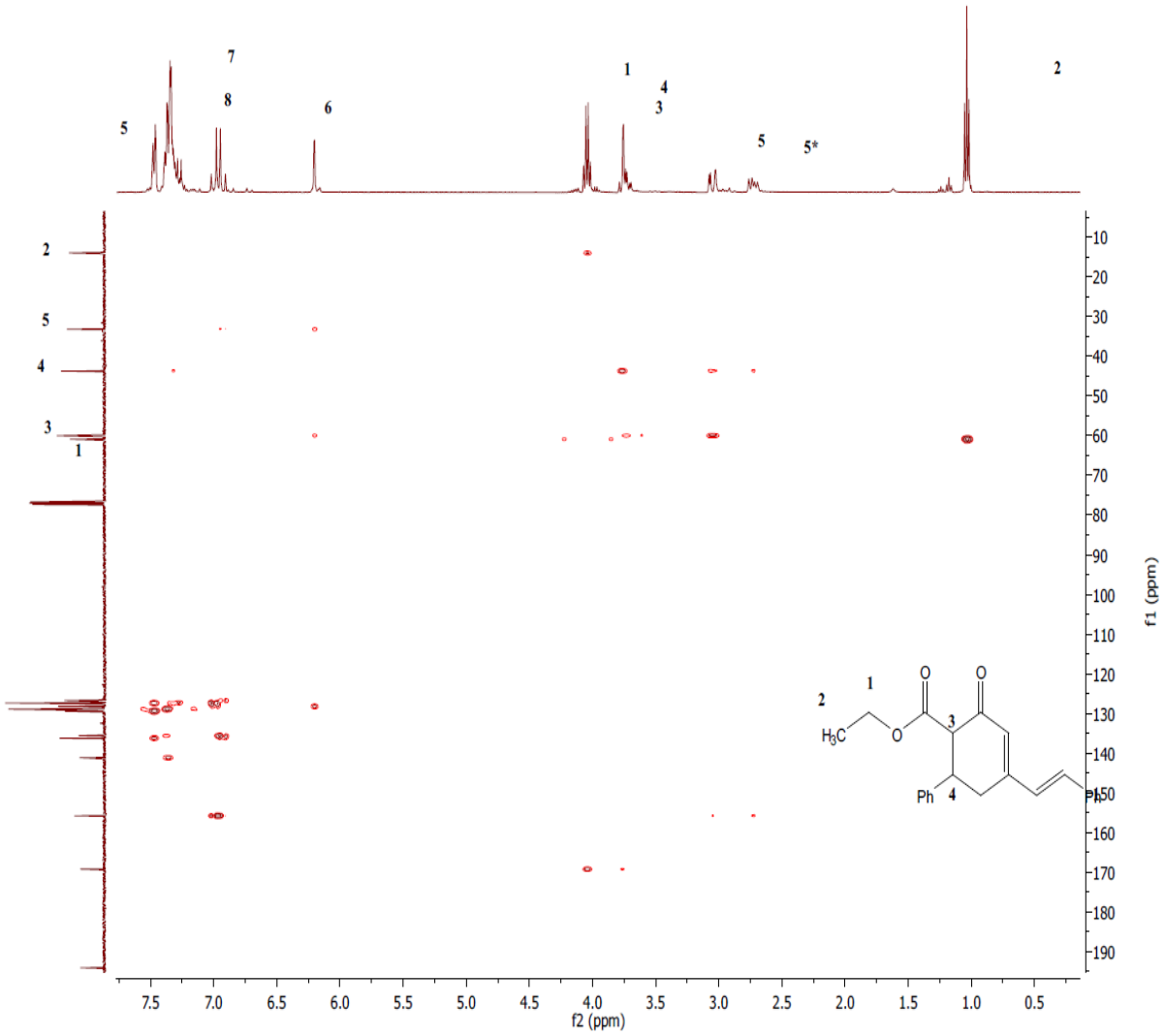
Appendix 57 (gHSQC)



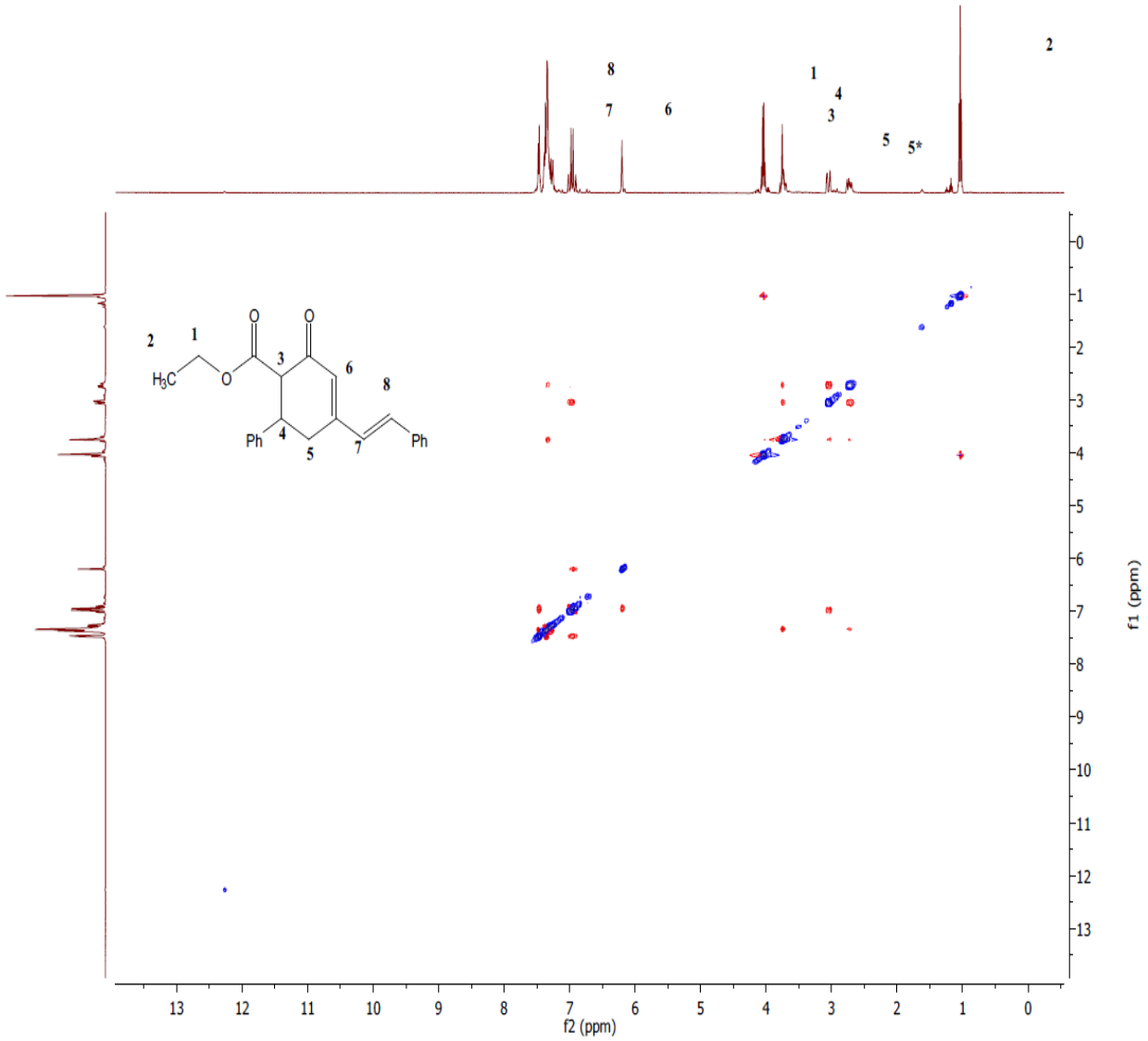
Appendix 58 (gDQCOSY)



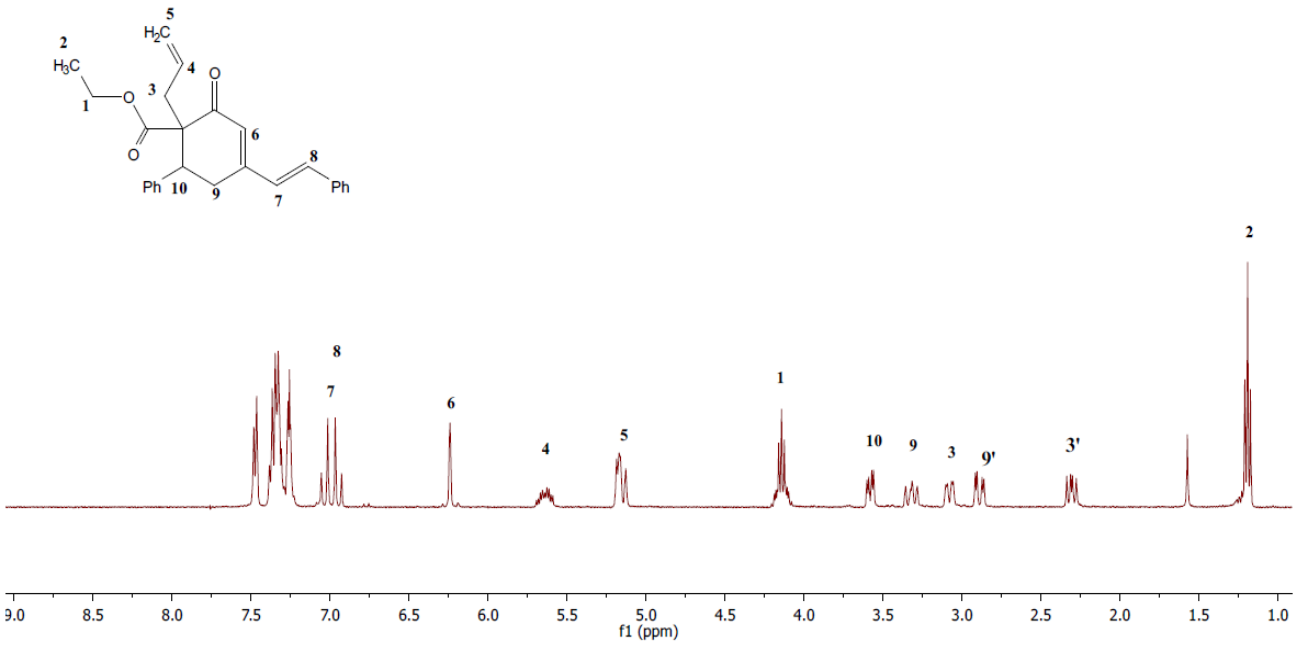
Appendix 59 (gHMBC)



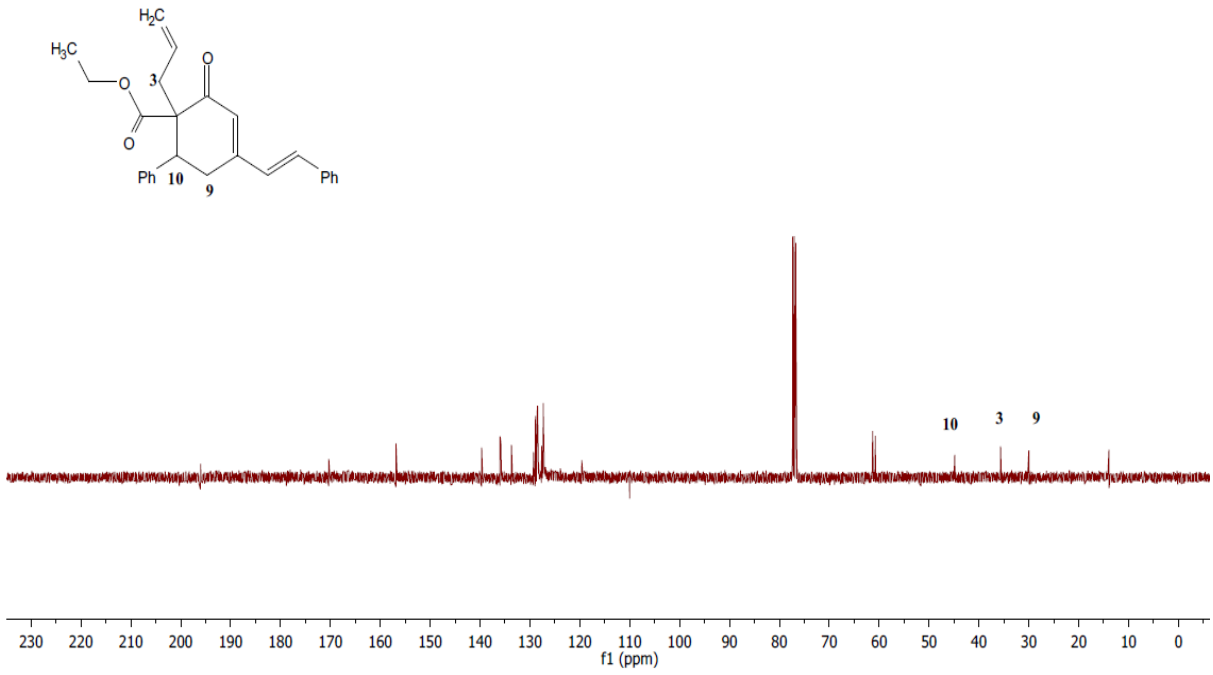
Appendix 60 (NOESY)



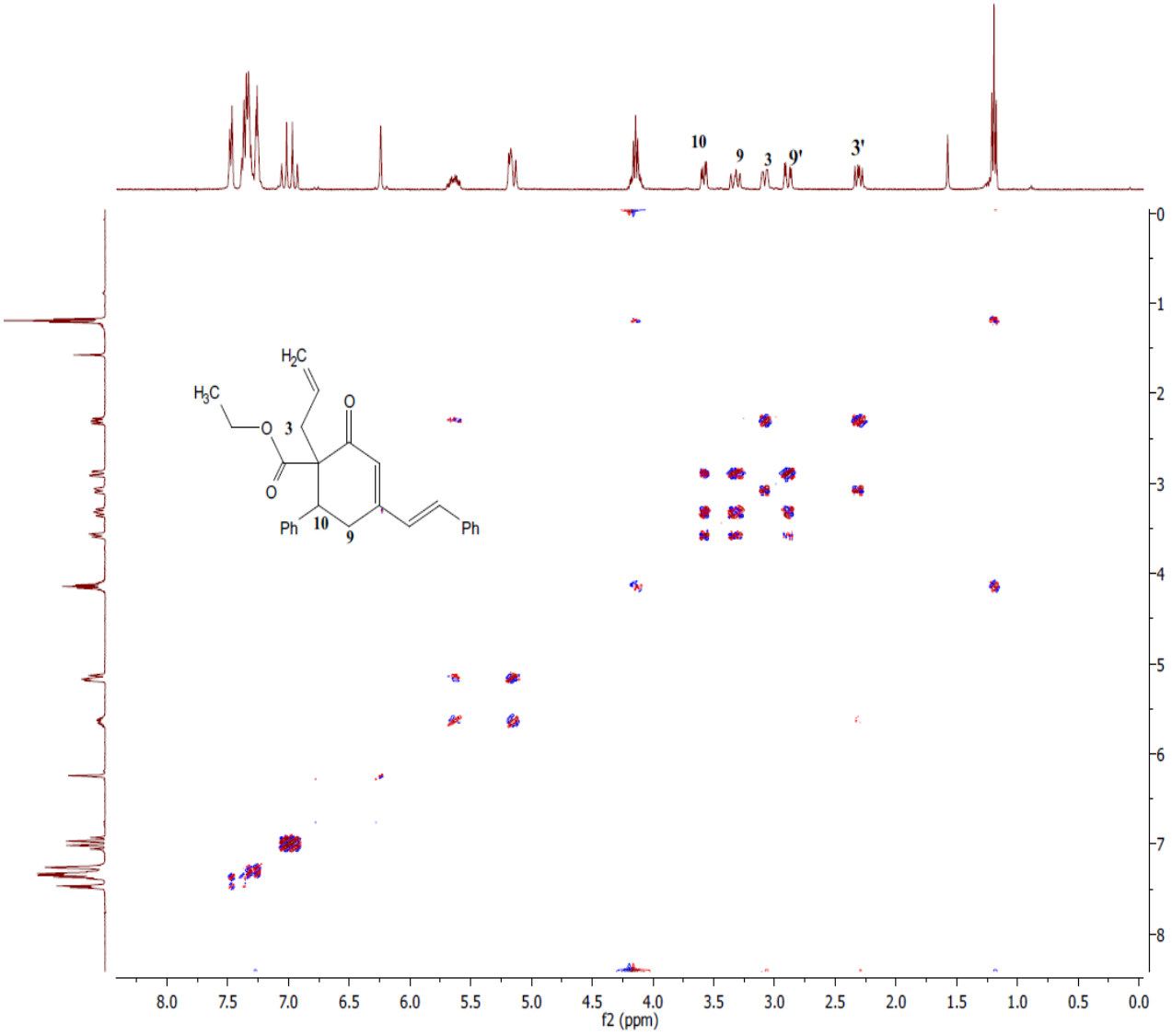
Appendix 61


2
H3C
1
O
5
H2C
4
3
O
O
6
8
Ph
10
9
7
Ph
2
8
7
6
4
5
1
10
9
3
9'
3'
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

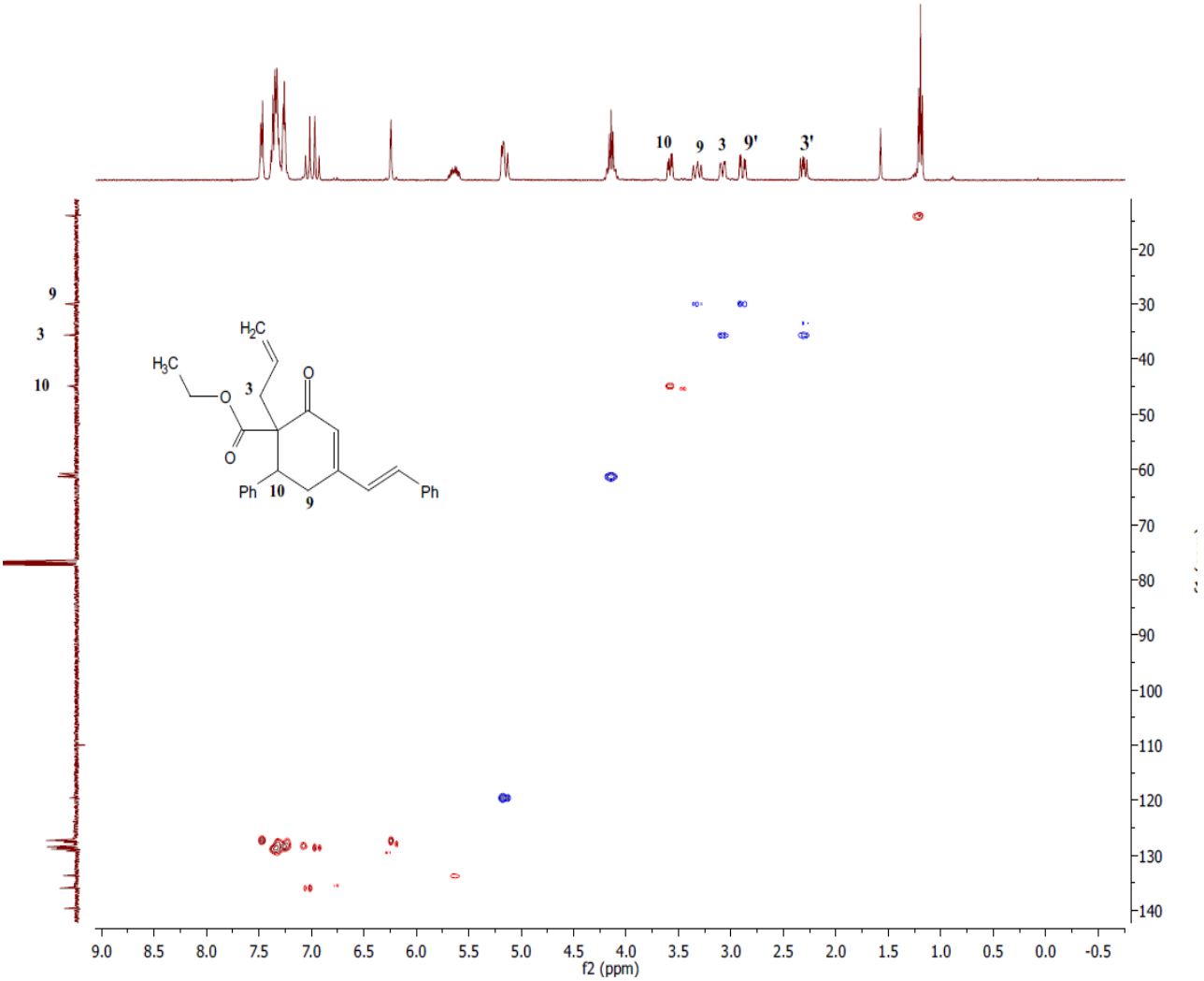
Appendix 62


H2C
H3C
O
3
O
O
Ph
10
9
Ph
10
3
9
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

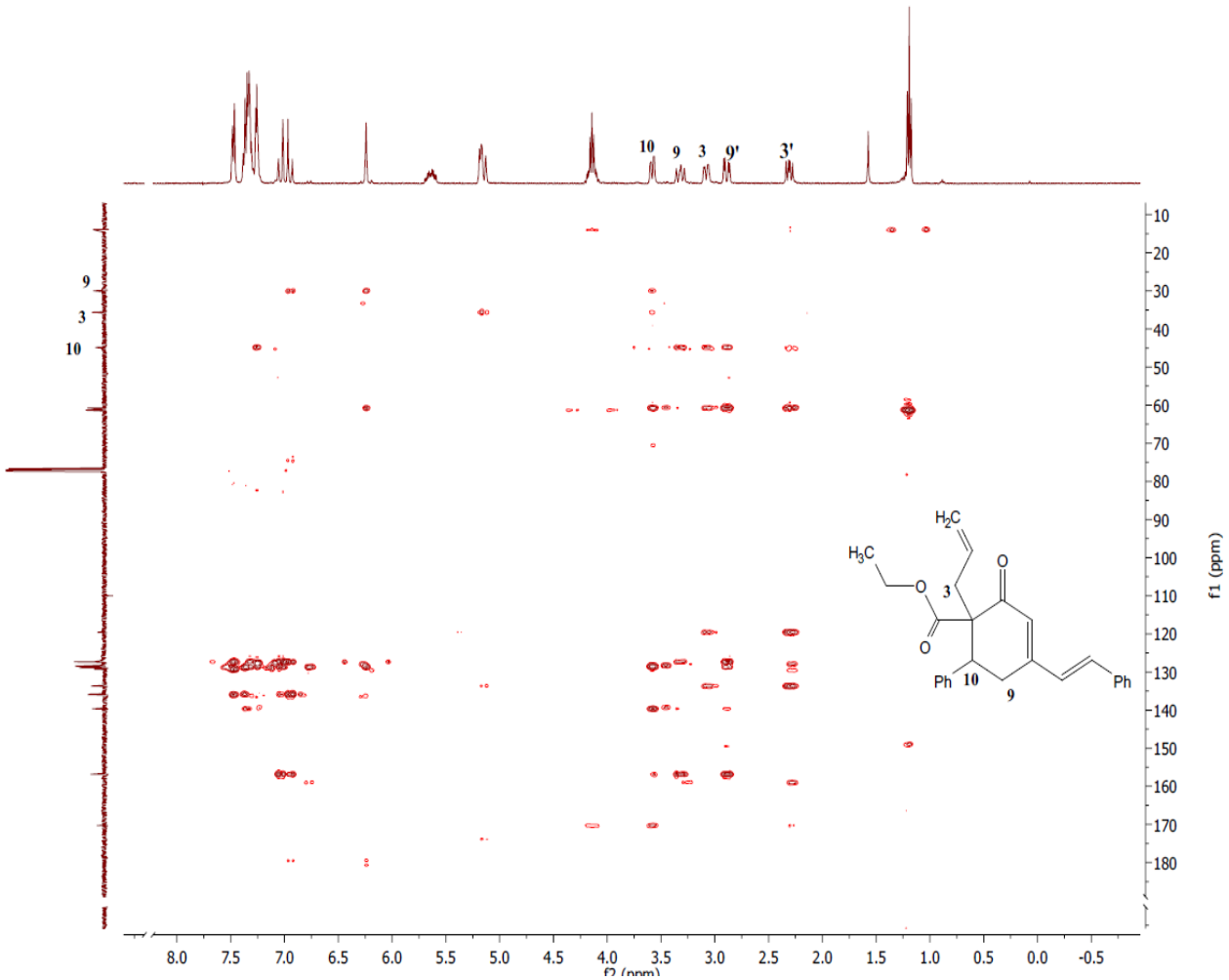
Appendix 63 (gDQCOSY)



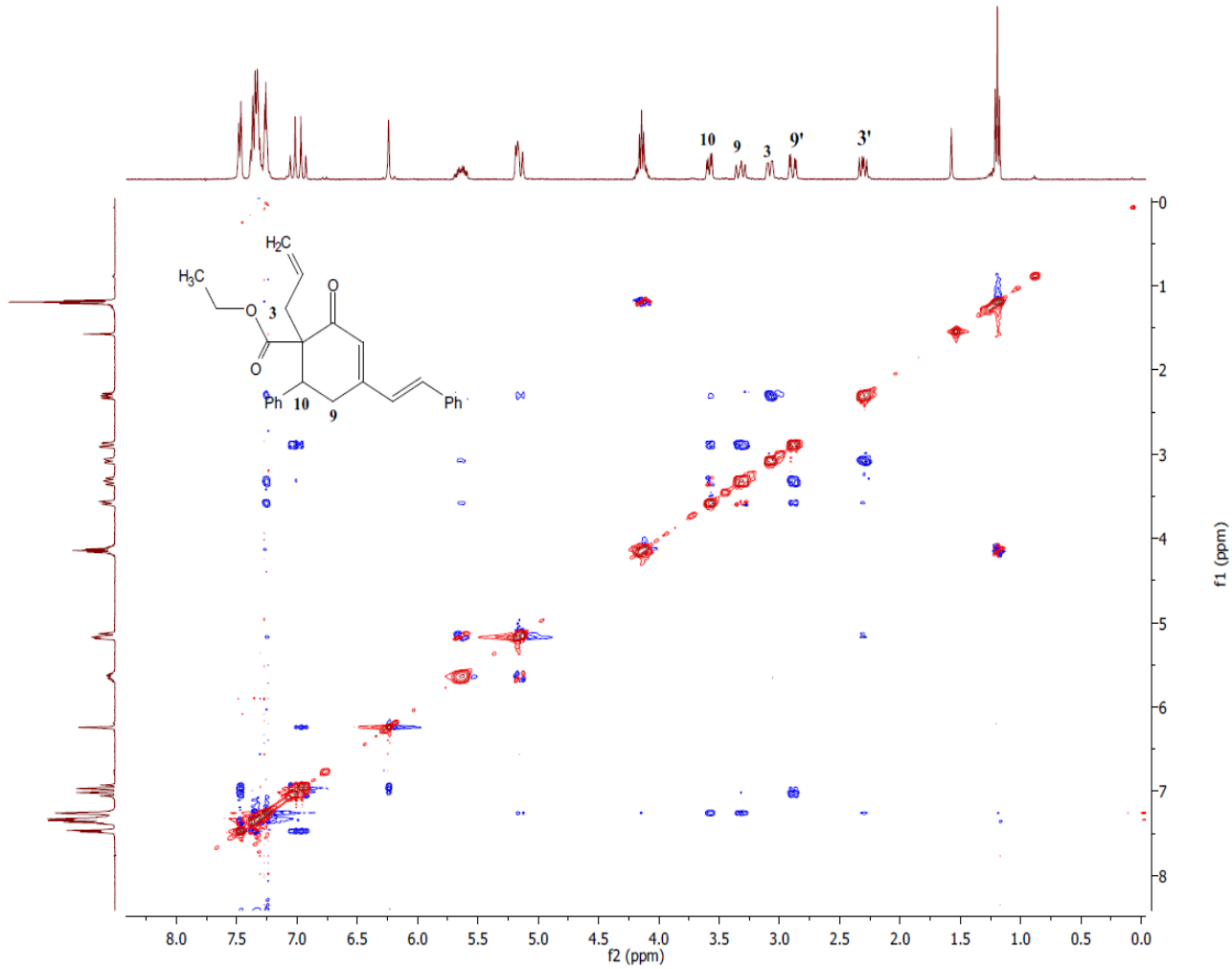
Appendix 64 (gHSQC)



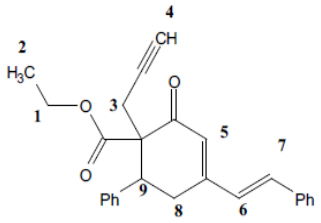
Appendix 65 (gHMBC)

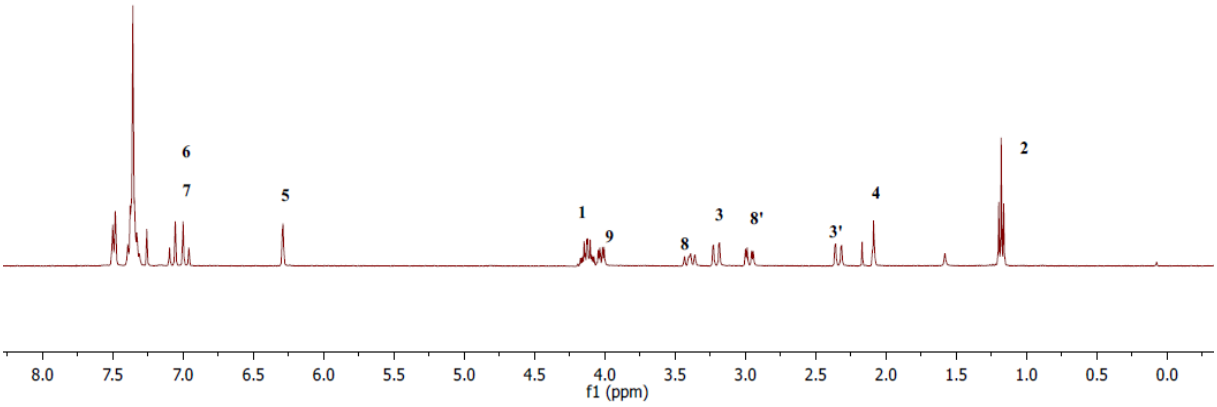


Appendix 66 (NOESY)

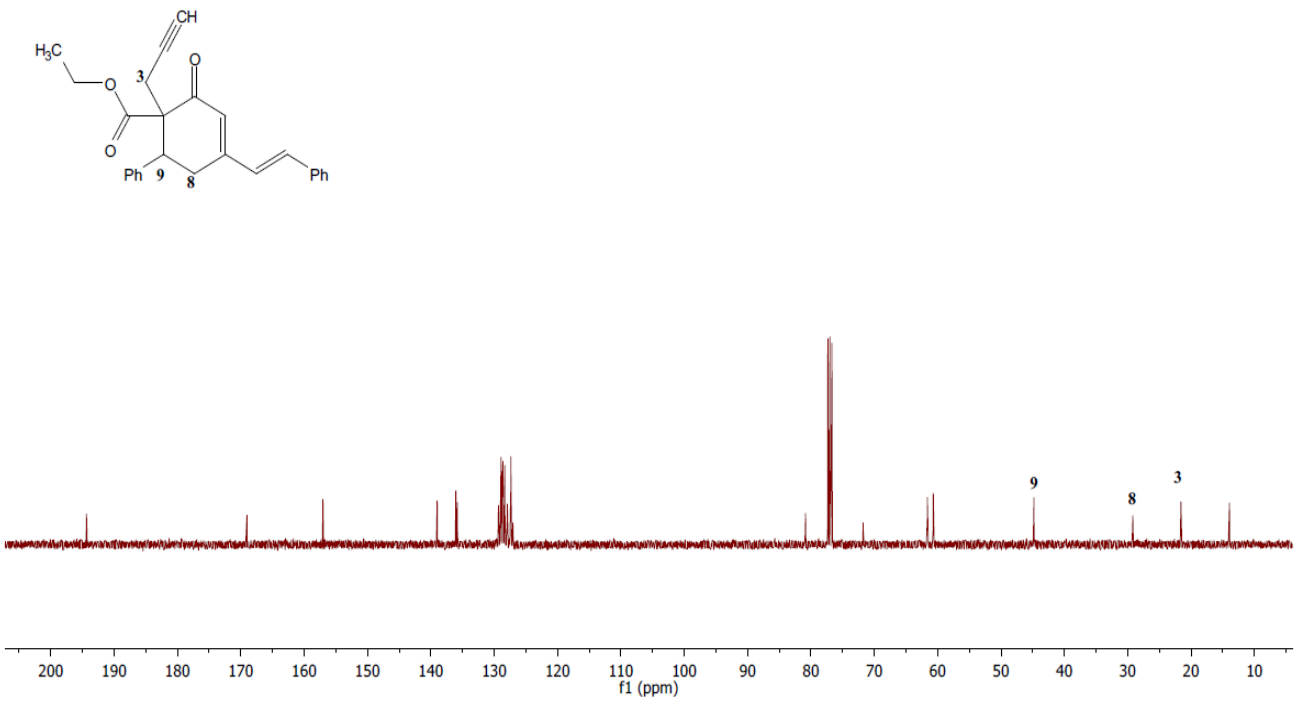


Appendix 67

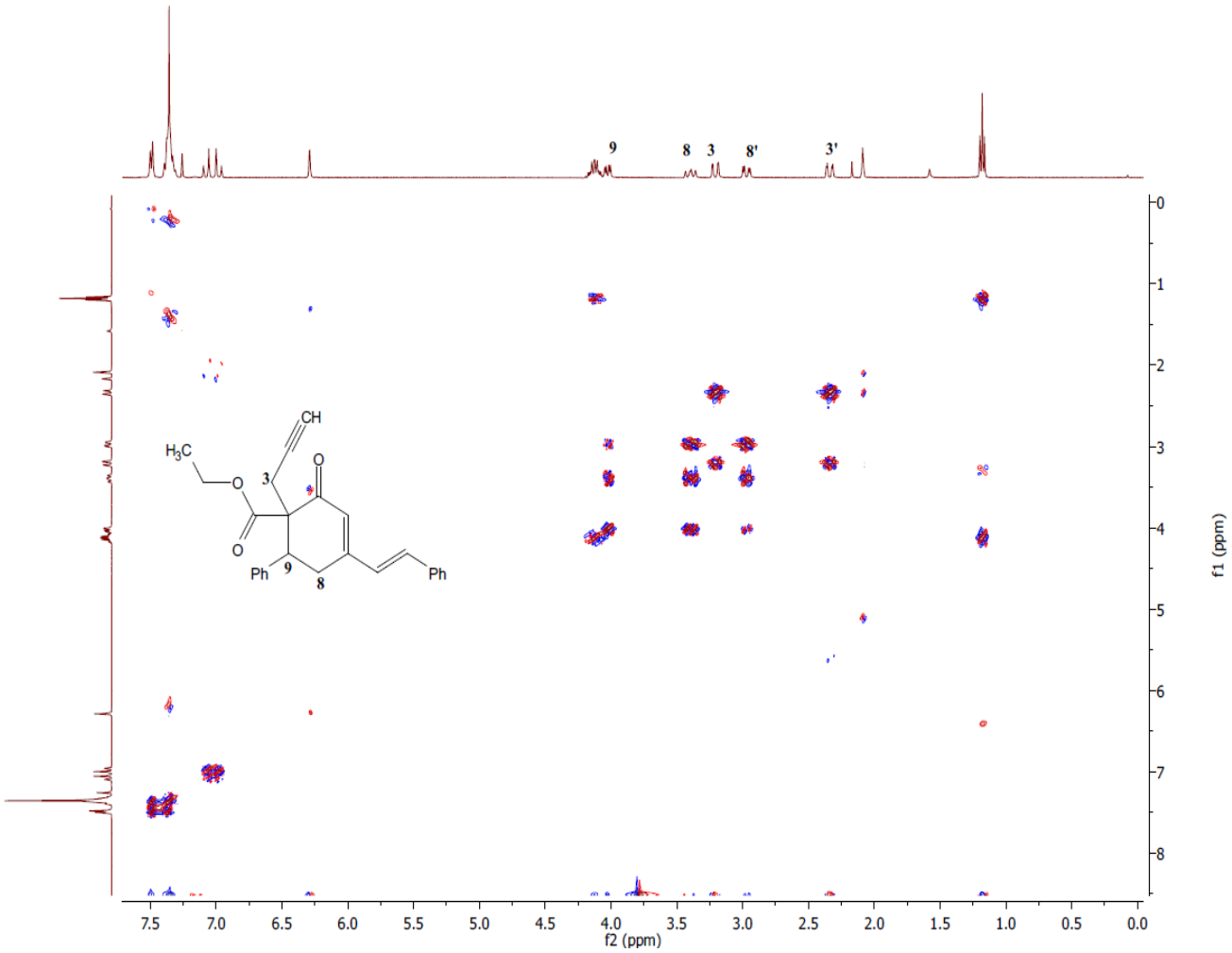

4
CH
2
H3C
1
O
3
O
5
7
O
Ph
9
8
6
Ph


6
7
5
1
9
8
3
8'
3'
4
2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

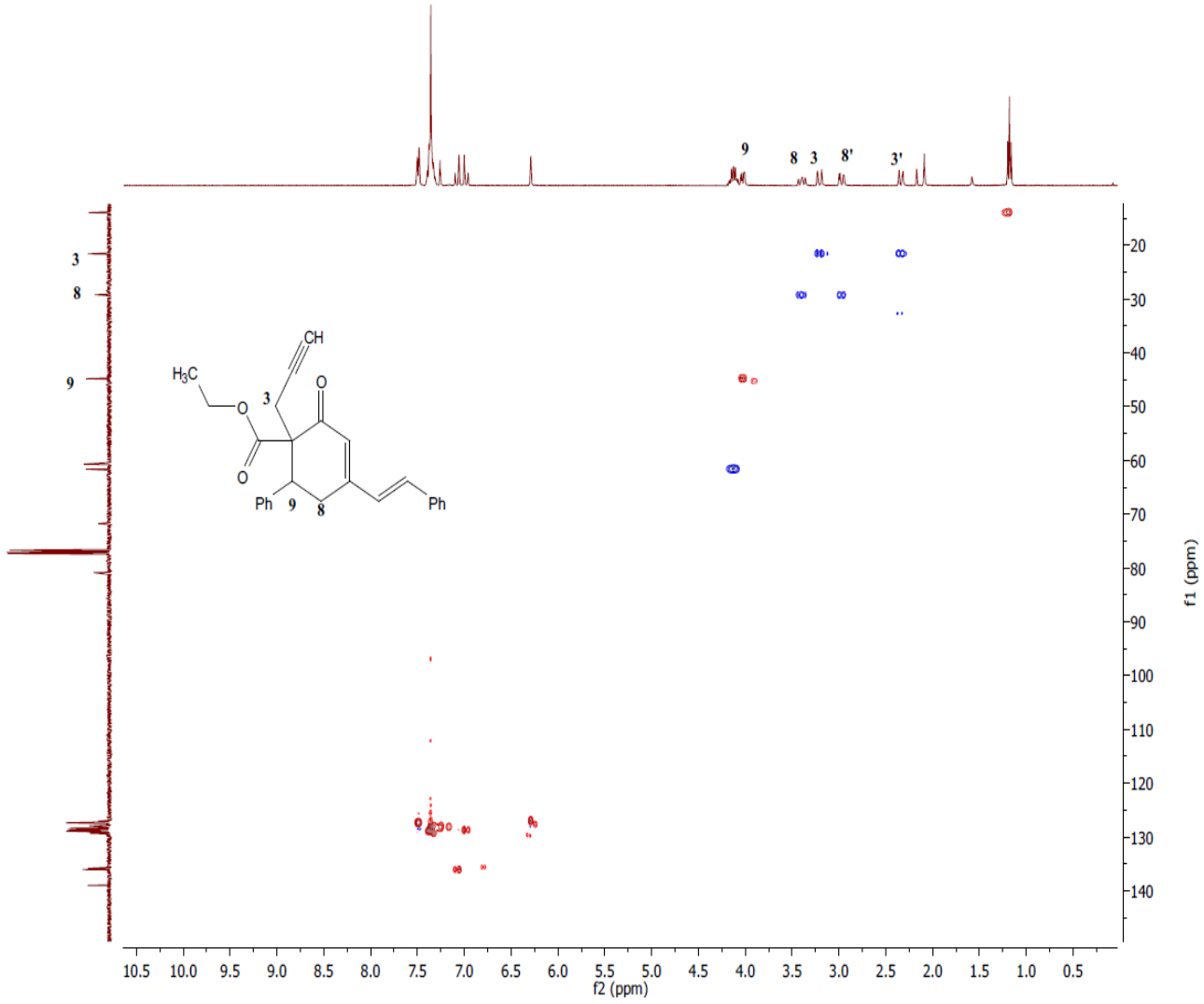
Appendix 68


CH
H3C
O
3
O
O
Ph
9
8
Ph
9
8
3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

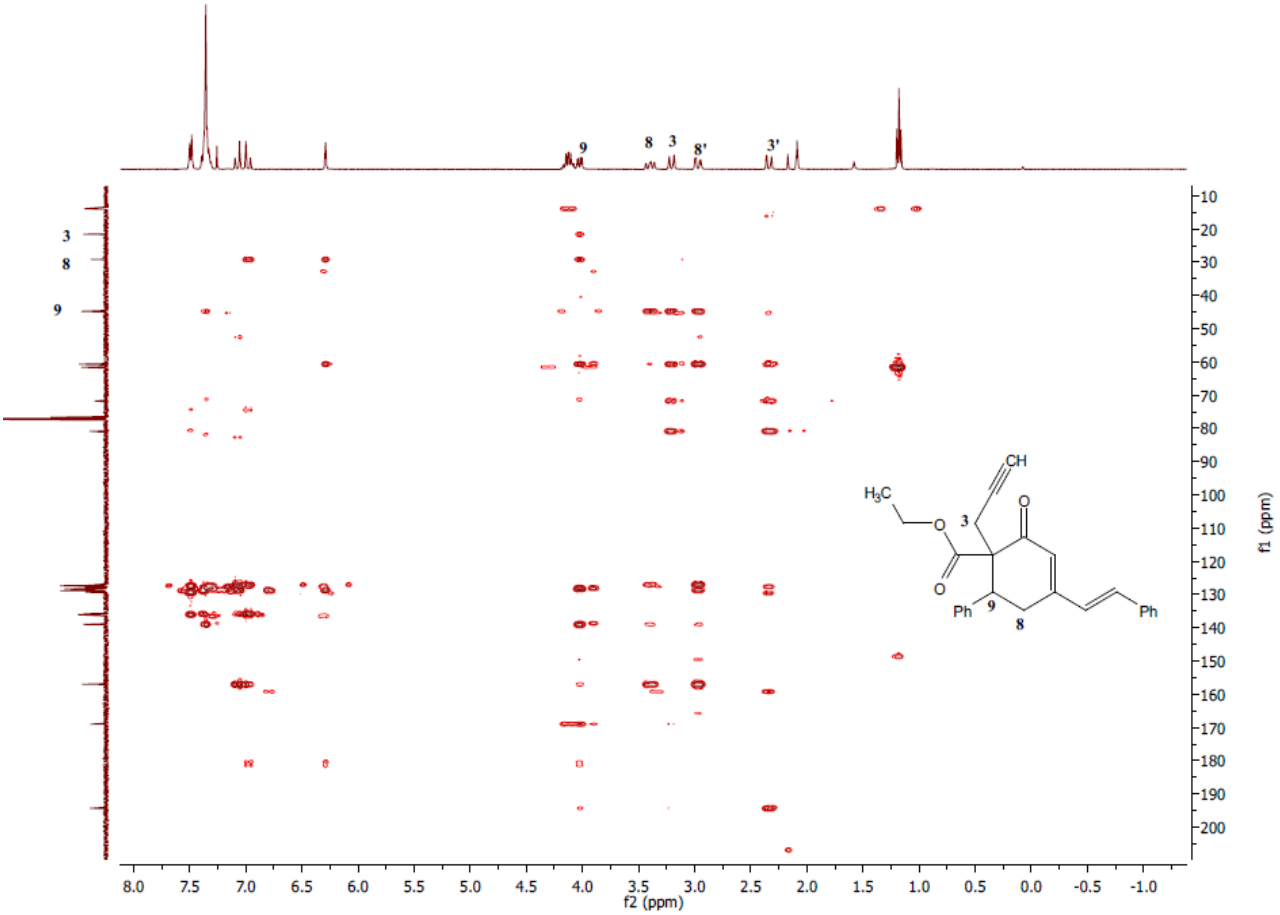
Appendix 69 (gDQCOSY)



Appendix 70 (gHSQC)



Appendix 71 (gHMBC)



Appendix 72 (NOESY)