An Approach towards the Asymmetric Total Synthesis of (*R*)-3-Benzylpiperidine.

Thesis submitted in partial fulfillment of the requirements

for the award of the degree of

Masters of Science

In

Chemistry

Submitted by

Sarishti Garg

Roll no: 301402019

Under the guidance of

Dr. Satyendra Kumar Pandey

to the

School Of Chemistry and Biochemistry

Thapar University

Patiala-147004 (Punjab)

INDIA

2016

Certificate

This is to certify that the project entitled **"An Approach towards the Asymmetric Total Synthesis of (*R*)-3-Benzylpiperidine"** being submitted by Sarishti Garg, Roll No: 301402019 in the partial fulfillment of the requirements for the award of degree of Masters of Science in School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under my supervision and guidance. The report has not been submitted for the award of any other degree or certificate in this or any other University.

Dr. Satyendra Kumar Pandey

Assistant Professor

Thapar University, Patiala.

Head of Department,

(Prof. Bonamali Pal)

School of Chemistry and Biochemistry,

Thapar University, Patiala.

Dean of Academic Affairs,

(Prof. S. S. Bhatia)

Thapar University, Patiala.

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled **"An Approach towards the Asymmetric Total Synthesis of (*R*)-3-Benzylpiperidine"** in partial fulfilment of the requirements for the award of the degree of Masters of Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of January to July 2016, under the supervision of **Dr. Satyendra Kumar Pandey**. My thesis has not previously formed the basis for award of any degree, or other similar title or recognisation.

Patiala

Date: 15-07-2016

Sarishti

Sarishti Garg

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

Dr. Satyendra Kumar Pandey

Assistant Professor

Thapar University, Patiala.

Prof. Bonamali Pal

Head, SCBC

Thapar University, Patiala

Acknowledgement

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Sarishti Garg

Abstract

An enantioselective synthectic approach for R-(3-Benzylpiperidine) has been attempted from phenylacetaldehyde employing Michael addition reaction as the key step. The merits of this synthetic approach are high yielding reaction steps.

LIST OF CONTENTS

An Approach towards the Asymmetric Total Synthesis of (*R*)-3-Benzylpiperidine.

1. INTRODUCTION

Benzylpiperidine and their derivatives posses a range of physiological and pharmaceutical activities.[1] Substituted 4-Benzylpiperidine is a drug and research chemical used in scientific studies. It acts as a monoamine releasing agent with 20- to 48-fold selectivity for releasing dopamine versus Serotonin as well as it has a fast onset of action and a short duration.[2] It also functions as a monoamine oxidase inhibator (MAOI) with preference for MAO-A[3] and also exhibit N-methyl-D-asparate (NMDA) antagonists activity[4] as well as high affinity for other central nervous system receptor.[5]

Substituted 2-Benzylpiperidine derivative are known dopamine receptor antagonists and it is a stimulant drug of piperidine class. It boosts norepinephrine levels to round the same extent as d-amphetamine.[6] It has very little effect on dopamine levels, with sits binding affinity for the dopamine transporator[7] around 175 times lower than for the noradrelanine transporator. 2-benzylpiperidine is little used as a stimulant, with its main use being as a synthetic intermediate in the manufacture of other drugs, it has very little effect on the dopamine levels and mainly used as the synthetic intermediate in the manufacture of other drugs.[8-10]

While the 3-Benzylpiperidine and its derivatives substituted at the aromatic ring have emerged as important structural subunit of potential drug candidates in pharmaceutical screening.[11] They have fungicide activity also.[12] Asthma is one of the most common chronic diseases in industrialized nations.[13,14] Clinical studies have linked symptom severity in asthma

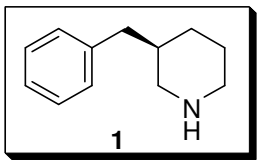


Figure 1: Structure of (*R*)-3-Benzylpiperidine

patients to the gross accumulation of eosinophils in the lungs.[15] Eosinophils are recruited and directed to sites in the body *via* chemo attraction by the chemotactic cytokine (chemokine) eotaxin. Eotaxin binds exclusively to the seven trans membrane G protein-coupled receptor CC chemokine receptor-3 (CCR3), which is predominantly expressed on eosinophils and basophils,[16]

Asthma (AZ-ma) is a chronic (long-term) lung disease that inflames and narrows the airways. Asthma affects people of all ages, but it most often starts during childhood. In the United States, more than 25 million people are known to have asthma and about 7 million of these people are children.

(*S*)-3-(4-fluorobenzyl)piperidine was determined to be an integral part of several CC chemokine receptor-3 (CCR3) antagonists, for example (DPC168),[17] (BMS-570520),[18] (BMS-639623)[19] with potential in the treatment of asthma. DPC168, a benzylpiperidine-substituted aryl urea CCR3 antagonist evaluated in clinical trials, was a relatively potent inhibitor of the 2D6 isoform of cytochrome P-450 (CYP2D6). Replacement of the cyclohexyl central ring with saturated heterocycles provided potent CCR3 antagonists with improved selectivity against CYP2D6. The favorable preclinical profile of DPC168 was maintained in an acetylpiperidine derivative, BMS-570520.[20] The CCR3 antagonists are the opposite enantiomers of 3-Benzylpiperidines.[11] For the purpose of detailed activity studies and biological evaluation, a straightforward and reliable method for the stereoselective syntheses of 3-Benzylpiperidine derivatives are of great utility and interest.

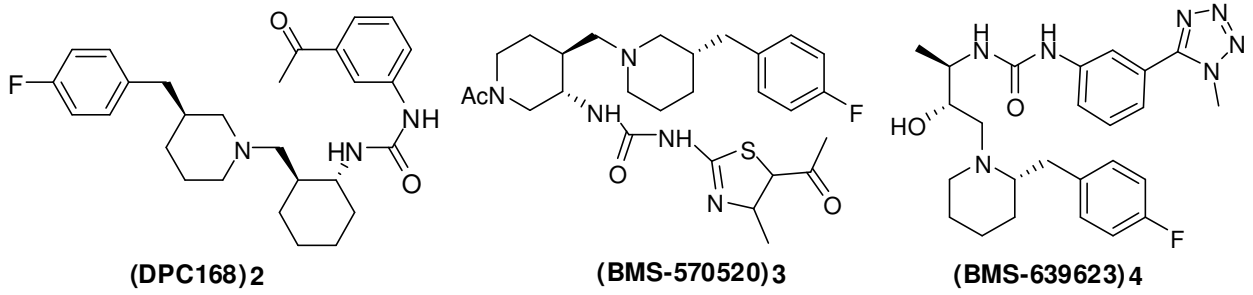


Figure 2: Structure of some 3-benzylpiperidine derivatives.

1.1 Asymmetric, organocatalyzed Michael reactions:

The Michael addition is originally defined by Arthur Michael. It is the nucleophilic addition of carbanion or another nucleophile to *α,β*-unsaturated carbonyl compounds. The conjugate addition of carbanions to *α,β*-unsaturated carbonyl compounds is one of the most fundamental carbon-carbon bond forming reactions in organic synthesis.[21] The Michael Addition is thermodynamically controlled, the reaction donors are active methylenes such as malonates and

nitroalkanes, and the acceptors are activated olefins such as α,β-unsaturated carbonyl compounds.[22]

As α-aminoxylation, tandem *O*-nitroso aldol/Michael reactions, and Mannich reactions earlier catalyzed by the siloxyproline **7**, a highly active proline, so the simple introduction of a siloxy group into the proline structure leads to an increase in the catalytic activity. This higher activity can be attributed to the increased solubility of **7** in organic solvents. The fact that the substitution of a hydroxy group for a siloxy group can dramatically affect catalytic activity prompted to investigate other catalytic systems, and these investigations led to the diphenylprolinol silyl ether **6**.

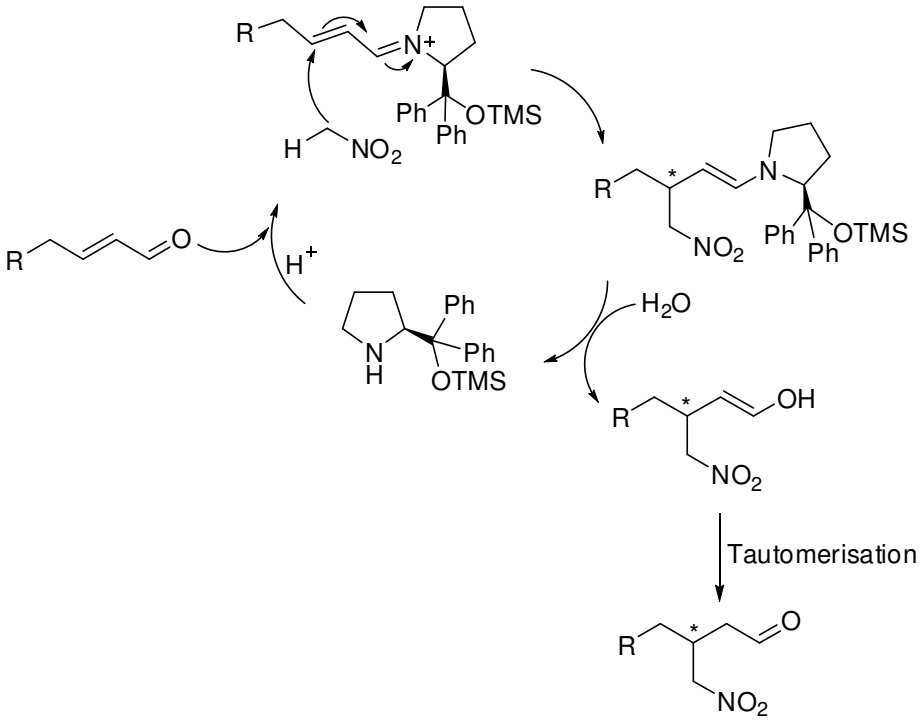


Figure 3: Plausible mechanism for the asymmetric Michael addition.

The parent diphenyl-2-pyrrolidinemethanol (**5**, diphenylprolinol), a commercially available amino alcohol developed by Corey and co-workers, has proved to be a very useful ligand for asymmetric synthesis.[23]

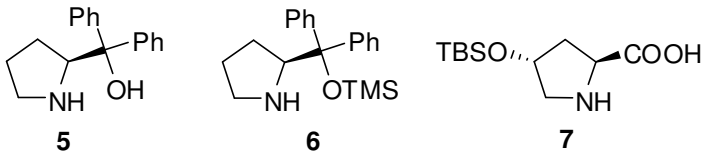
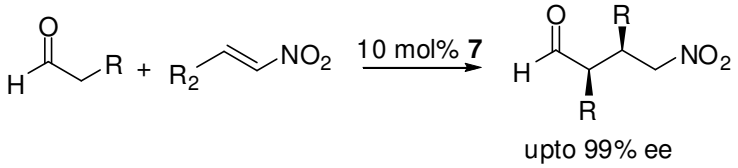


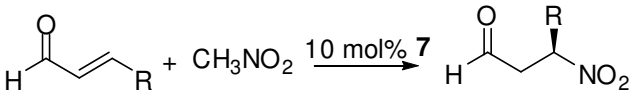
Figure 4: Some proline substituted organocatalysts.

Jorgenson and co-workers studied a highly *syn*- and enantioselective Michael reaction catalyzed by diphenylprolinol silyl ether, in which aldehyde and nitroalkene[24] act as Michael donor and acceptor, respectively (Scheme 1).



Scheme 1: Michael addition reaction of unsaturated nitro alkenes and aldehydes.

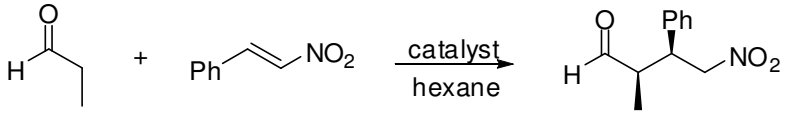
Michael reaction of the reverse combination, in which nitro alkane and α-β unsaturated aldehyde act as donor and acceptor, respectively (Scheme 2).



Scheme 2: Michael addition reaction of unsaturated aldehydes and nitro alkanes.

In spite of considerable effort, most of the Michael reactions of nitroalkanes that have been devised are limited to *α,β*-unsaturated ketones, esters, or amides. Achieving the Michael reaction of *α,β*-unsaturated aldehydes is thought to be difficult because the competitive 1,2-addition reaction occurs readily due to the highly reactive aldehyde. Although these have been limited to *α,β*-unsaturated ketones. For *α,β*-unsaturated aldehydes, Maruoka and co-workers have developed an elegant chiral phase transfer Michael reaction, in which the silyl nitronates prepared from nitroethane and nitropropane were employed instead of the nitroalkanes, but they reported no results for nitromethane.[25] Arvidsson and co-workers reported the Michael reaction of *α,β*-unsaturated aldehydes with nitroalkanes catalyzed by imidazole-containing organocatalyst. The reaction had limited success with nitroethane and nitropropane, but only moderate enantioselectivity (47% ee) with nitromethane.[25]

However, no widely applicable, direct Michael reactions of simple nitroalkanes, and inclusive of nitromethane, with *α,β*-unsaturated aldehydes have been described. The development of more effective asymmetric catalysts in terms of both enantioselectivity and substrate scope is desirable. The Michael reaction of propanal and nitrostyrene was selected as a model.



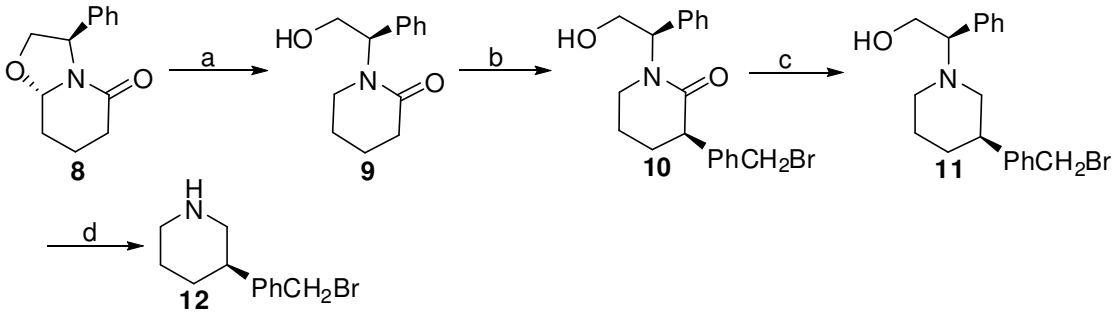
Scheme 3: Michael addition reaction of nitro alkene with aldehyde.

Excellent enantioselectivity (95% ee) was observed when diphenylprolinol **6** was employed,[24] the progress of the reaction was slow, and the yield was unsatisfactory (29%) even after 24 h. The reactivity of the catalyst was increased dramatically along with the enantioselectivity, when the hydroxygroup in **5** was exchanged for a siloxy group. That is, the reaction was complete within 1 h at room temperature in the presence of the diphenyl siloxy proline **6**, and the adduct was afforded in good yield (82%) and with increased enantioselectivity (99% ee). When the reaction was performed at a lower temperature (0-8 ^{o}C), the adduct was obtained in nearly optically pure form (99% ee), in good yield, and also with high diastereoselectivity. The catalyst loading can be reduced to 5 mol% without compromising the enantioselectivity. Excellent results had been obtained with the model system. So, on this basis we use this catalyst in our Scheme for carrying out Michael addition of conjugated aldehyde with nitromethane and conjugated nitroalkene with aldehydes.

2. Review of Literature:

2.1 Micouina, L. *et al.* (1994)[26]

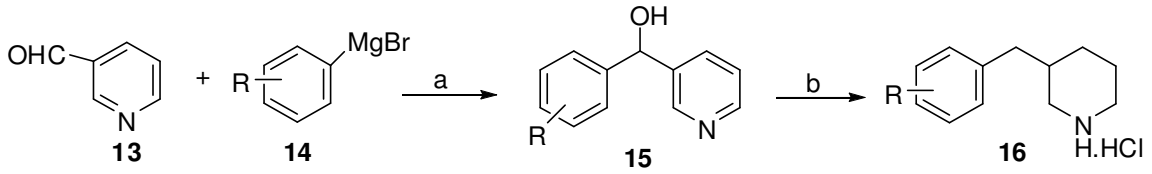
Micouina, L. and co workers discovered a series of 3-substituted piperidines. They explore the reactivity of hydroxy lactam **9** which was obtained in 84% yield by reduction of **8** following the Meyer's procedure. Deprotonation of **9** with *sec*-BuLi followed by addition of benzyl bromide led to substituted products **10**. The amide group of **10** was reduced using $LiAlH_4$ without epimerization at C-3 furnishing piperidine derivatives **11** in excellent yield. Then, hydrogenolysis of **11** was performed with Pearlman catalyst which furnished the 3-substituted piperidine **12** isolated as hydrochloride.



Scheme 4: *Reagents and conditions*: (a) $TiCl_4$, Et_3SiH, MeOH, rt, 4 h, 78%; (b) $PhCH_2Br$, *Sec*-BuLi, THF, -78 ^oC, 2 h, 75%; (c) $LiAlH_4$, THF, 12 h, reflux, 88%; (d) H_2, $Pd(OH)_2$, MeOH, rt, 12 h, 81%.

2.2 Agai, B. *et al*. (2003)[9]

Agai, B. and co workers prepared 3-(substituted benzyl) piperidines starting from readily available pyridine-3-carboxaldehyde **13** and Grignard reagents prepared from mono-, di-, or trisubstituted bromo benzene **14** and continued by a one-pot catalytic deoxygenation and heteroaromatic ring saturation of the aryl-3-pyridylmethanol intermediates **15** (Scheme 5). Addition of **13** to the Grignard-reagents provided **15** in moderate to good yield. The crude products were dissolved in glacial acetic acid and hydrogenated in the presence of 10% Pd/C catalyst. The products were isolated as hydrochloride salts in crystalline form.



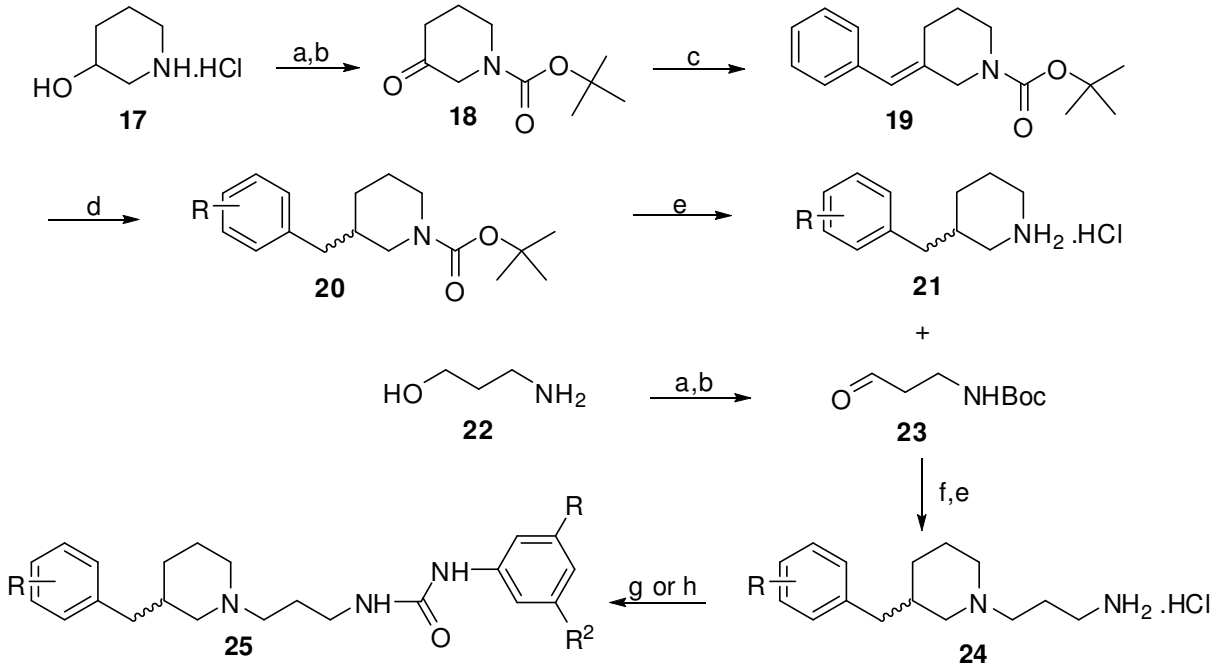
Scheme 5: *Reagents and conditions*: (a) THF, -20 ^oC, 3 h, 75%; (b) i) H_2, Pd/C, MeOH, rt, 12 h, 80%; ii) HCl, MeOH, reflux, 12 h, 85%.

2.3 Varnes, J. G. *et al*. (2004)[17]

Varnes, J. G. and co workers synthesized a series of 3-benzylpiperidine analogues, the 3-benzylpiperidines and their analogues were prepared according to Scheme 6, which depicts the preparation 3-benzylpiperidins-1-yl-n-propylureas from commercially available 3-hydroxypiperidine hydrochloride **17**. Protection of the piperidine nitrogen with Boc_2O and oxidation with tetrapropylammonium perruthenate[29] afforded the 3-piperidone tert-butyl carbamic acid **18**. A Wittig reaction between **18** and an appropriately substituted

benzyltriphenylphosphonium bromide resulted in Olefin **19**, which on reduction under hydrogenation conditions furnished the racemic Boc-protected benzylpiperidine **20**. Chiral 3-(4-fluorobenzyl)-piperidines were prepared upon chiral resolution of 20.[30]

Deprotection of **20** under acidic conditions and reductive amination with Boc-protected 3-aminopropanal **23** and sodium triacetoxyborohydride was followed by acid-mediated cleavage of the resulting Boc-carbamate to give hydrochloride **24**. Urea **25** was obtained by reacting **24** with commercially available 3-substituted phenyl isocyanates in the presence of triethylamine. Where these desired 3-substituted phenyl isocyanates were not commercially available, the corresponding phenolic carbamates were prepared from the appropriately substituted aniline (C_6H_5OCOCl, Et_3N, CH_2Cl_2, 90%) and used instead.[31]

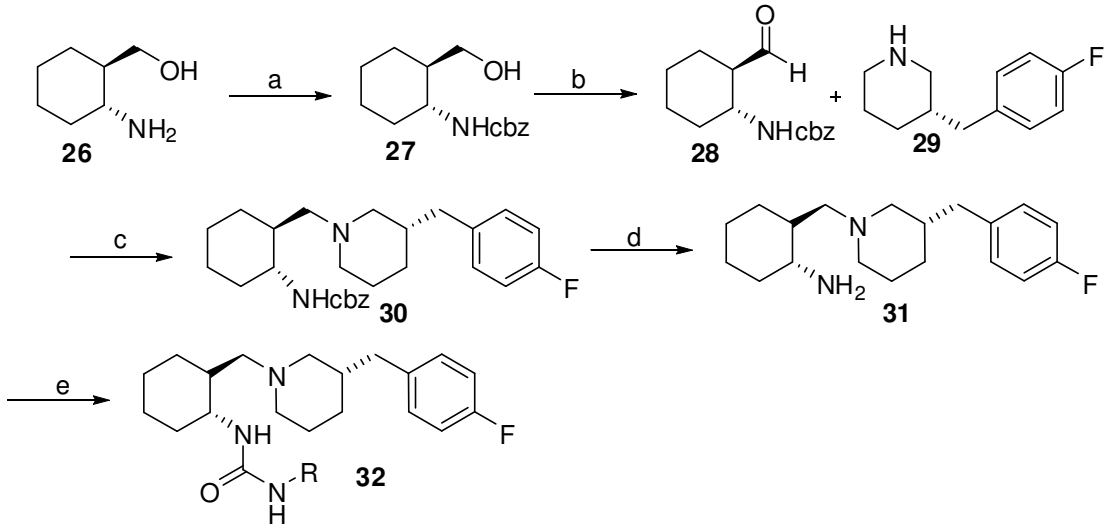


Scheme 6: *Reagents and conditions* (a) Boc_2O, $NaHCO_3$, THF, 14 h, 90%; (b) TPAP, NMO, CH_2Cl_2/CH_3CN, 4A° MS, 1 h, 60-80%; (c) R-$C_6H_4CH_2P^+Ph_3Br^-$, *n*-BuLi, THF, -78 °C, 6-8 h, 60-70%; (d) H_2 (40 psi), Pd/C, MeOH, 12 h, quant; (e) 4M HCl, diox, 3 h, quant.; (f) **23**, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 14 h, 80%; (g) 3-R^1-5-R^2-C_6H_4NCO, Et_3N, CH_2Cl_2, 5 min, 60-85%; (h) 3-R^1-5-R^2-$C_6H_4NHC(O)OC_6H_5$, CH_3CN, 50 °C, 1 h, 55-85%.

2.4 Lucca, D. G. V. *et al.* (2005)[18]

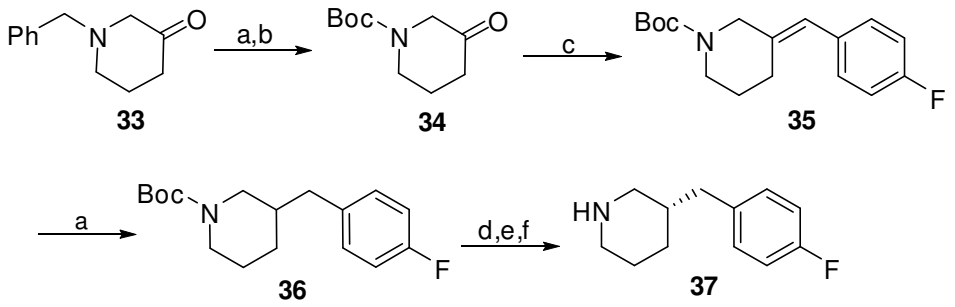
Lucca, D. G. V. and coworkers synthesized a series of substituded 3-benzylpiperidine derivatives starting from the readily available aminoalcohol **26** which was protected as the

benzyl carbamate by treating with benzyl chloroformate to gave the protected amine **27**. The (N-Cbz) amino alcohol was subjected under Swern oxidation conditions to afforded the aldehyde **28**. Reductive amination of **28** with benzylpiperidine gave **29**. The hydrogenation of **29** furnished the free amine **31**, which was treated with isocyanates to get the final urea analogue **32**.



Scheme 7: *Reagents and conditions:* (a) benzyl chloroformate, Na_2CO_3, CH_2Cl_2, rt, 12 h, 85% ; (b) $(COCl_2)_2$, DMSO, CH_2Cl_2, -78 °C, Et_3N, 1 h, 86%; (c) $NaBH(OAc)_3$, MeOH, 0-rt ^oC, 6 h, 78% ; (d) H_2, Pd/C, MeOH, rt, 12 h, 89%; (e) RHNCOOPh, THF, 0-rt ^oC, 5 h, 80%.

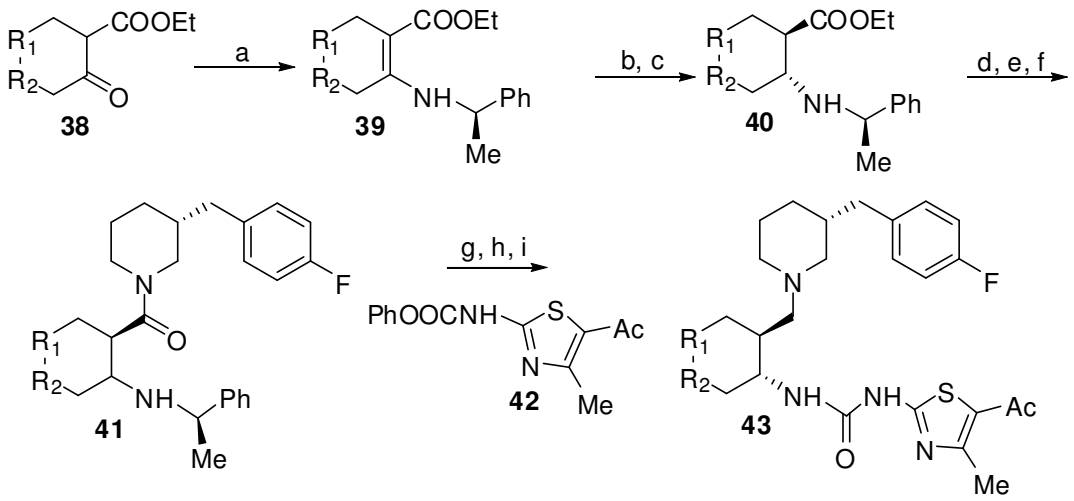
Lucca, D. G. V. and coworkers synthesized the another 3-benzylpiperidine fragment from commercially available N-benzyl-3-piperidone **33** as shown in Scheme 8. First, the benzyl group was converted to N-Boc-3-piperidone **34** by a catalytic hydrogenolysis, followed by acylation with di-tert-butyl dicarbonate. A Wittig reaction with 4-fluoro-benzylphosphonium chloride and *n*-butyllithium was performed, gave the olefin **35** followed by a catalytic hydrogenation to afford Boc-protected 3-(4-fluorobenzyl)piperidine **36**. This compound was initially resolved by a preparative chiral HPLC and gave the required (*S*)-(+)-isomer. However, a practical large-scale resolution method was developed, which uses (*R*)-(-)-mandelic acid. Thus, **36** was deprotected gave the free amine 3-(4-fluorobenzyl)piperidine, which was resolved by the formation of a diastereomeric salt to selectively crystallize the (*S*)-(+)-3-(4-fluorobenzyl)piperidine mandelic acid salt (98% ee after two recrystallizations) **37**.



Scheme 8: *Reagents and conditions:* (a) Reagents and conditions: H_2, Pd/C, MeOH, rt, 12 h, 90%; (b) $(Boc)_2O$, $NaHCO_3$, (aq)/THF, rt, 12 h 92%; (c) (4-F-benzyl)$P(Ph)_3Cl$, BuLi, THF, 0-rt ^oC, 75%; (d) 4N HCl, Na_2CO_3, dioxane, rt, 8 h, 78%; (e) (*R*)-(-)-mandelic acid, AcCN, recrystallize; (f) NaOH (aq), ether, rt, 12 h, 87%.

2.5 Pruitt, J. R. *et al.* (2007)[20]

Pruitt, J. R. and co-workers synthesized the analogues of 3-benzylpiperidine. Since 2-amino-4-methyl-5-acetylthiazole is commercially available, they chose this aromatic group for SAR exploration of the central region of the molecule. The compounds were prepared from *β*-ketoesters **38**, as shown in Scheme 9. Condensation of **38** with (*R*)-(+)-*α*-methylbenzylamine provided the corresponding vinylogous carbamates **39**. They proved that reduction of the *β*-aminoesters **40** to be sensitive to the structure of the starting material, as they had summarized in the literature.[20] Standard reduction using sodium triacetoxyborohydride proceded with fair to good selectivity in the piperidine cases, providing mostly the expected but undesired cis relative stereochemistry. In this manner they had discussed some other methods for the reduction. Saponification of the esters and coupling with (*S*)-(+)-3-(4-fluorobenzyl)piperidine provided the amide intermediates **41**. Reductive removal of the benzylic chiral auxiliary was followed by amide reduction with borane, and urea formation by reaction with the phenoxycarbonylaminothiazole **42**. (In the case of the tetrahydrothiophene derivative, oxidation to the sulfone was performed prior to the reductive debenzylation.) Finally, deprotection of boc removal, followed by standard nitrogen derivatization reactions (alkylation, reductive alkylation, acylation), provided the analogs of 3-benzylpiperidine.



Scheme 9: *Reagents and conditions*: (a) (*R*)-(+)-*α*-methylbenzylamine, p-TsOH, benzene, reflux, 76%; (b) $NaBH(OAc)_3$, HOAc, CH_3CN, 0 ^oC, 84% (c) K_2CO_3, EtOH, reflux, 7-22%; (d) LiOH or NaOH, H_2O-THF, rt, 6 h, 87%; (e) (*S*)-(+)-3-(4-fluorobenzyl)piperidine, BOP, Et_3N, CH_2Cl_2, rt (60-100% for 2 steps); (f) Oxone, MeOH, H_2O, acetone, rt, 72%; (g) $Pd(OH)_2$ (20% on carbon), H_2 (60 psi), EtOH, rt; (h) BH_3, THF, rt, then AcOH; (i) **42**, CH_3CN, rt (12-42% for 3 steps).

3. Present work:

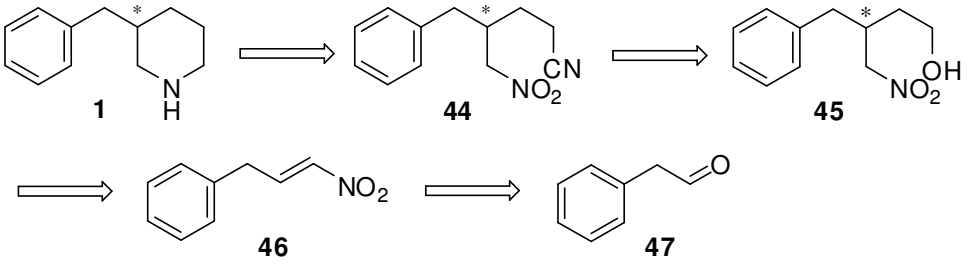
3.1 Objective:

Various methods for the synthesis of 3-Benzylpiperidine **1** and their derivatives have been documented in the literature. Most of these approaches employed chiral pool starting materials or multisteps to get the target compound **1**. As part of our program dealing with the asymmetric synthesis of alkaloids we were interested in the development of a convenient method for the preparation of enantiomerically pure 3-substituted benzyl piperidines. Although several methods[27] exist for the asymmetric synthesis of 3-Benzyl piperidines.[28] We wish to develop a short and efficient general method for the preparation of 3-substituted benzyl piperidines compounds.

3.2 Retro synthetic approach:

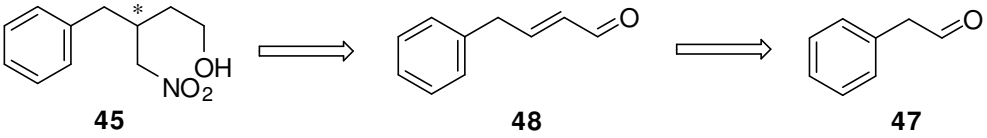
The retrosynthesis of 3-benzylpiperidine **1** is outlined in Scheme 10. The 3-benzylpiperidine **1** could be effectively constructed from the nitrocyanide **44** by using DIBAL-H reduction followed

by acid hydrolysis and subsequently intramolecular reductive amination of the amine group with aldehyde using Zn/acetic acid. The nitrocyanide **44** in turn could be prepared by converting the free hydroxyl group of nitroalcohol **45** into its toluenesulfonate derivative followed by treatment with NaCN. The nitroalcohol **45** could be prepared from the nitroalkene **46** by the Michael addition using acetaldehyde followed by the reduction of the resulting aldehyde. The nitroalkene **46** in turn could be easily synthesized from the phenylacetaldehyde **47** by the attack of the nitromethane followed by dehydration using Et_3N as the base.



Scheme 10: Retrosynthesis of 3-benzylpiperidine using Michael addition of unsaturated nitro alkene.

In another retrosyntetic plan, the nitroalcohol **45** derivative could also be synthesized from unsaturated aldehyde **48** by the Michael addition using nitromethane followed by the reduction of the resulting aldehyde (Scheme 11). The unsaturated aldehydes could be synthesized from the phenyl acetaldehyde **47** by wittig reaction followed by DIBAL-H reduction.

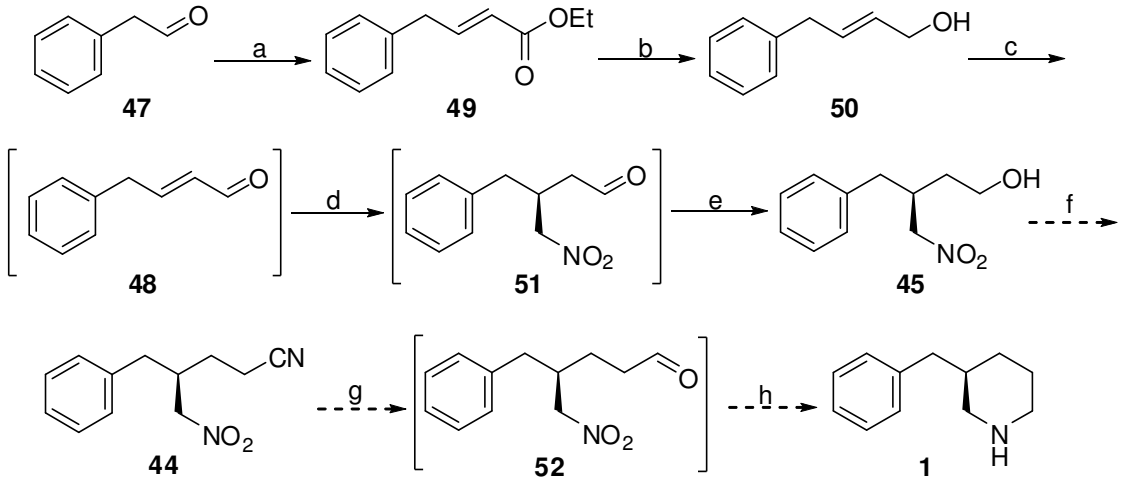


Scheme 11: Retrosynthesis of 3-benzylpiperidine using Michael addition of unsaturated aldehyde.

4. Result and Discussion:

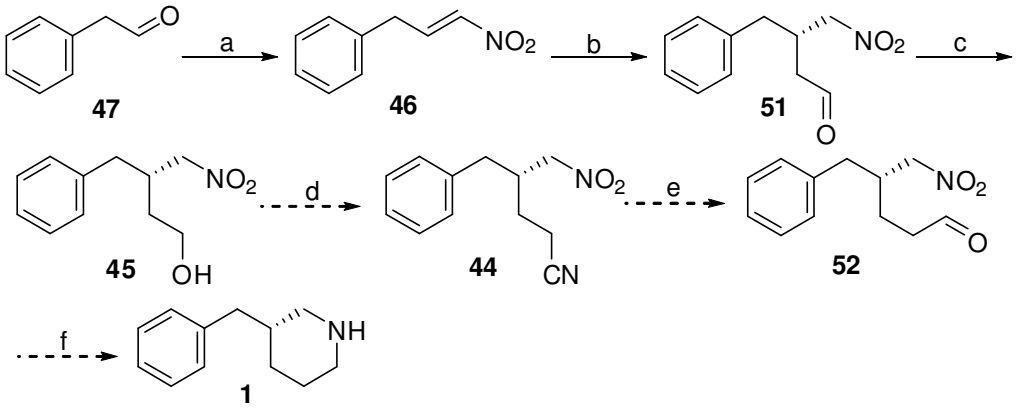
The synthesis has been designed herein for 3-benzylpiperidine **1** using the commercially available phenylacetaldehyde **47** as shown in Scheme 12. The phenylacetaldehyde **47** under wittig olfenation conditions gave ester **49** in the 95% yield. The ^{1}H NMR indicates aromatic protons at 7.33-7.16 (m, 5H), trans olfenic protons adjacent to ester at 7.10 (d, J = 16.2 Hz, 1H),

olefinic protons at 5.81 (d, *J* = 16.0 Hz, 1H), methyl protons of ester at 4.17 (q, *J* = 8.48 Hz, 2H), methylene protons adjacent to aromatic ring at 3.52 (d, *J* = 5.48 Hz, 2H), methylene protons of ester at 1.27 (t, *J* = 4.56 Hz, 2H). The ^{13}C NMR indicates carboxlylic carbon at 166.3, olefinic carbon at 147.2, aromatic carbons at 137.5, 128.8, 128.6, olefinic carbon adjacent to ester group at 122.3, methylene carbon of ester group at 60.2, methylene carbon adjacent to benzene ring at 38.4, methyl carbon of ester at 14.2. With pure ester in hand, we then subjected it to the DIBAL-H reduction to afford the alcohol **50** in the 85% yield. The proton ^{1}H NMR indicates aromatic protons at 7.36-7.17 (m, 5H), olefinic protons at 5.88-5.81 (m, 1H) and 5.71-5.65 (m, 1H), methylene protons adjacent to hydroxyl group at 4.10 (d, *J* = 5.04 Hz, 2H), methylene protons adjacent to benzene ring at 3.38 (d, *J* = 6.88 Hz, 2H), proton of hydroxyl group at 1.72 (br s, 1H). The ^{13}C NMR indicates aromatic carbons at 139.9, 128.5, 128.4, 126.1, olefinic carbons at 131.5 and 130.2, methylene carbon adjacent to aromatic ring at 38.5, methylene carbon attached to hydroxyl group at 63.4. IR peaks of alcohol **50** shows OH stretching at υ 3338.4, =C-H stretching at 3026.2, C=C stretching at 1493.1, *trans* =C-H bending at 969.0, C-H bending at 696.621 cm^{-1}. The alcohol **50** under Swern conditions furnished conjugated aldehyde which was observed unstable. Then we subsequent treated this conjugated aldehyde under Michael addition conditions using diphenylprolinol silyl ether as the catalyst for the synthesis of nitroaldehyde **51**, which on subsequent treatment with $NaBH_4$ was expected to give nitroalcohol **45**, but the reaction did not work good due to the unstability of the aldehyde. Therefore, we need some alternative approach to make the stable aldehyde.



Scheme 12: *Reagents and conditions*: (a) PH_3P=CHOOEt, dry THF, rt, 24 h, 95%; (b) DIBAL-H, dry CH_2Cl_2, 0-rt °C, 2 h, 85%; (c) $(COCl_2)_2$, DMSO, CH_2Cl_2, -78 °C, Et_3N, 1 h; (d) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, $PhCO_2H$, MeOH, 24 h; (e) $NaBH_4$, MeOH, 0 ^oC, 15 min; (f) (i) TsCl, Et_3N, CH_2Cl_2, rt (ii) NaCN, DMF; (g) DIBAL-H; (h) Zn/AcOH, H_2O.

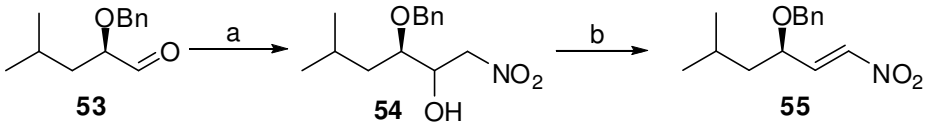
To overcome this problem, another Scheme was designed for 3-Benzylpiperidine **1** which was designed from the commercially available phenylacetaldehyde as shown in the Scheme 12. The base catalyzed condensation of phenylacetaldehyde **47** with nitromethane furnished the nitroalkene **46**. Then asymmetric Michael addition of acetaldehyde with nitroalkene **46** in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether **6** in a sealed tube was carried out to afford the nitroaldehyde adduct **51**, which on subsequent reduction with $NaBH_4$ could deliver the nitroalcohol derivative, but again the reaction did not work good for the synthesis of desired intermediate. The free hydroxyl group of **45** could be converted into its toluenesulfonate derivative which on subsequent treatment with NaCN in dry DMF could furnish the cyano compound **44**. Compound **44** could be subjected to reduction using DIBAL-H at -78 ^oC followed by acid hydrolysis to furnish the nitroaldehyde **52**, followed by intramolecular reductive amination using Zn-acetic acid will expected to give the target compound 3-benzyl piperidine **1**.



Scheme 13: *Reagents and conditions*: (a) i) CH_3NO_2, NaOH, MsCl, NEt_3, rt, 2h, 80%; (b) (i) acetaldehyde, (*R*)-diphenylprolinol silyl ether, 1,4-dioxane, 4 ^oC to rt, 18 h; (c) $NaBH_4$, MeOH, 0 ^oC, 15 min; (d) (i) TsCl, Et_3N, CH_2Cl_2; (ii) NaCN , DMF; (e) DIBAL-H, HCl; (f) Zn/Acetic acid.

An another approach, we have tried to synthesize intermediate **55**, which is core unit of the various biologically active compounds starting from stable aldehyde **53** and then converted into

55. This reaction also proves that intermediate **46** could be synthesized. The proton ^{1}H NMR indicates aromatic aromatic protons at 7.40-7.29 (m, 5H), olefinic protons at 7.22-7.17 (m, 1H) and 7.14-7.11 (m, 1H), benzylic protons at 4.60 (d, *J* = 11.48 Hz, 1H) and 4.43 (d, *J* = 11.44 Hz, 1H), methine protons adjacent to *o*-benzyl at 4.14 (m, 1H), methine protons of isopropyl group at 1.81 (m, 1H), methylene protons adjacent to isopropyl group at 1.66 (m, 1H) and terminal methyl protons at 0.92 (d, *J* = 6.88 Hz, 3H) and at 0.85 (d, *J* = 6.88 Hz, 3H). The ^{13}C NMR indicates aromatic carbons at 139.6, 128.5, 128.0, 127.8, olefinic carbons at 142.5 and 137.2, methine carbon adjacent to *o*-benzyl group at 73.6, benzylic carbon at 71.7, methylene carbon adjacent to isopropyl group at 43.8, methine carbon of isopropyl group at 24.3, methyl carbons at 23.0 and 22.0. IR peaks of the Nitroalkene **55** shows C-H stretching at 2957.6, C=C stretching at 1650.0, =N-O symmteric at 1525.1 and 1349, =C-H bending at 729.2, C-H bending at 697.1 cm^{-1}



53 **54** **55**

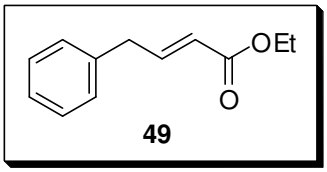
Scheme 14: *Reagents and conditions*: (a) CH_3NO_2, NaOH, 0 ^{o}C-rt, 1 h; (b) MsCl, Et_3N, rt, 1 h, 82%.

5. Conclusion:

In conclusion, an efficient enantioselective synthesis of 3-Benzylpiperidine **1** has been attempted from phenylacetaldehyde **47** employing Michael addition reaction as the key step. The merits of this synthetic approach are high yielding reaction steps. Presently, we are in the process of optimizing various reaction conditions to get the stable aldehyde and work is in progress in this direction.

6. Experimental section:

6.1 (*E*)-ethyl 4-phenylbut-2-enoate (49):



49

To the solution of (etoxycarboxylmetylene)triphenylphosphorane (3.48g, 9.98 mmol) in dry THF (15 mL) was added dropwise a solution of the phenylacetaldehyde (1g, 8.322 mmol) in dry THF (10 mL). The reaction mixture was stirred for 24 h at room tempetrature, it was then concentrated and purified by silica gel column chromatography using (EtOAc /Hexane 1:99) as eluent to afford the α, β-unsaturated olefin as a transparent liquid.

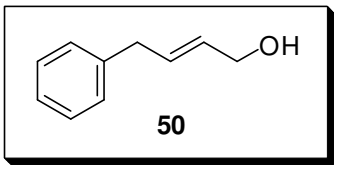
Yield: 1.5g, 95%.

Mol. Formula: $C_{12}H_{14}O_2$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.16 (m, 5H), 7.10 (m, 1H), 5.81 (d, *J* = 12.0 Hz, 1H), 4.17 (q, *J* = 8.48 Hz, 2H), 3.52 (d, *J* = 5.48 Hz, 2H), 1.27 (t, *J* = 4.56 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 147.2, 137.4, 128.8, 128.6, 122.3, 60.2, 38.4, 14.2.

6.2 (*E*)-4-phenylbut-2-en-1-ol (50):



50

To a solution of ester (500 mg, 2.63 mmol) **49** in dry DCM at 0 °C was added dropwise DIBAL-H (3.9 mL, 3.945 mmol). The reaction mixture was allowed to warm at room temperature over 2 h. To quench the reaction mixture methanol (6 mL) was added dropwise at 0 °C and the mixture becomes waxy solid. Then 2N HCl (10mL) was added dropwise, then organic phase was separated and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated purified by silica gel column chromatography using (EtOAc /Hexane 1:9) as eluent to furnish alcohol alcohol **50** as transparent liquid.

Yield: 330 mg, 85%.

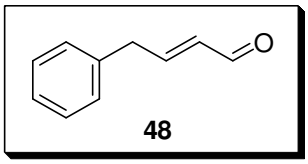
Mol. Formula: $C_{10}H_{12}O$

1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.17 (m, 5H), 5.88-5.81 (m, 1H), 5.72-5.65 (m, 1H), 4.10 (d, *J* = 5.04 Hz, 2H), 3.38 (d, *J* = 6.88 Hz, 2H), 1.72 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 131.5, 130.2, 128.5, 128.4, 126.1, 38.5, 63.4.

IR (CH_2Cl_2) ν: 2957.6, 2253.9, 1650.0, 1525.1, 1349.8, 1090.4, 907.9, 729.2.

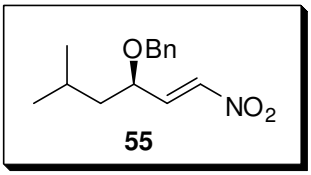
6.3 (*E*)-4-phenylbut-2-enal (48):



48

To a solution of Oxalyl chloride (0.43 mL, 5.067 mmol) in dry CH_2Cl_2 (10 mL) at -78 ^oC was added dropwise DMSO (0.77 mL, 10.47mmol) in CH_2Cl_2 (10 mL) over 15 min .The reaction mixture was stirred for 30 min and a solution of alcohol **50** (0.5g, 3.378 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -78 °C and then Et_3N (2.06 mL, 14.806 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 1 hr. The reaction mixture was poured into saturated solution of $NaHCO_3$ (20 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used for the next step without further purification.

6.4 (*R*, *E*)-((5-methyl-1-nitrohex-1-en-3-yloxy)methyl)benzene (55):



55

To a solution of aldehyde **53** (1g, 4.84 mmol) in MeOH was added CH_3NO_2 (0.66 mL, 5.332 mmol), aq. NaOH(0.238g, 5.808 mmol), MeOH (0.5ml) at 0 °C. The above solution was then stirred for 2 h. The reaction was then quenched with water, extracted with ethylacetate, concentrated *in vacuo* and used as such for the next step without further purification.

To a solution of above crude in DCM (10ml) was added Et_3N (0.10 mL, 0.729 mmol,), MsCl (0.04 ml, 0.583 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 2

h. The reaction was quenched with water, extracted with DCM, dried and concentrated purified by silica gel column chromatography using (EtOAc /Hexane 1:9) as eluent to furnish nitroalkene.

Yield: 960 mg, 80%.

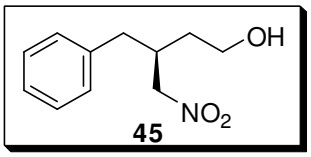
Mol. Formula: $C_{14}H_{19}NO_3$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 7.22-7.17 (m, 1H), 7.14-7.11 (m, 1H), 4.60 (d, *J* = 11.48 Hz, 1H), 4.43 (d, *J* = 11.44 Hz, 1H), 4.16-4.12 (m, 1H), 1.86-1.76 (m, 1H), 1.69-1.62 (m, 1H),1.42-1.35 (m, 1H), 0.92 (d, *J* = 6.88 Hz, 3H), 0.85 (d, *J* = 6.88 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 137.2, 139.6, 128.5, 128.0, 127.8, 73.6, 71.7, 43.8, 24.3, 23.0, 22.0.

IR (CH_2Cl_2) ν: 338.4, 3026.2, 2920.4, 1493.1, 1453.0, 969.0, 696.6.

6.5 (3-benzyl-4-nitrobutan-1-ol) (45):



45

To a 1,4-dioxane (2.0 mL) solution of (*S*)-diphenyltrimethylsiloxymethyl pyrrolidine (265 mg, 0.81 mmol, 10 mol%) and nitroalkene 12 (1.2 g, 8.05 mmol) was added phenylacetaldehyde (4.5 mL, 80.5 mmol) in a sealed tube at 4 °C. The reaction mixture was stirred at room temperature for 18 h and then quenched with 1 N HCl (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) washed with brine, dried over anhydrous Na_2SO_4, concentrated in *vacuo*, and used as such for the next step without further purification.

To the above crude product were added MeOH (15 mL), $NaBH_4$ (228 mg, 6.01 mmol) and the reaction mixture stirred for 15 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 3:7 v/v) as eluent to afford the nitro alcohol.

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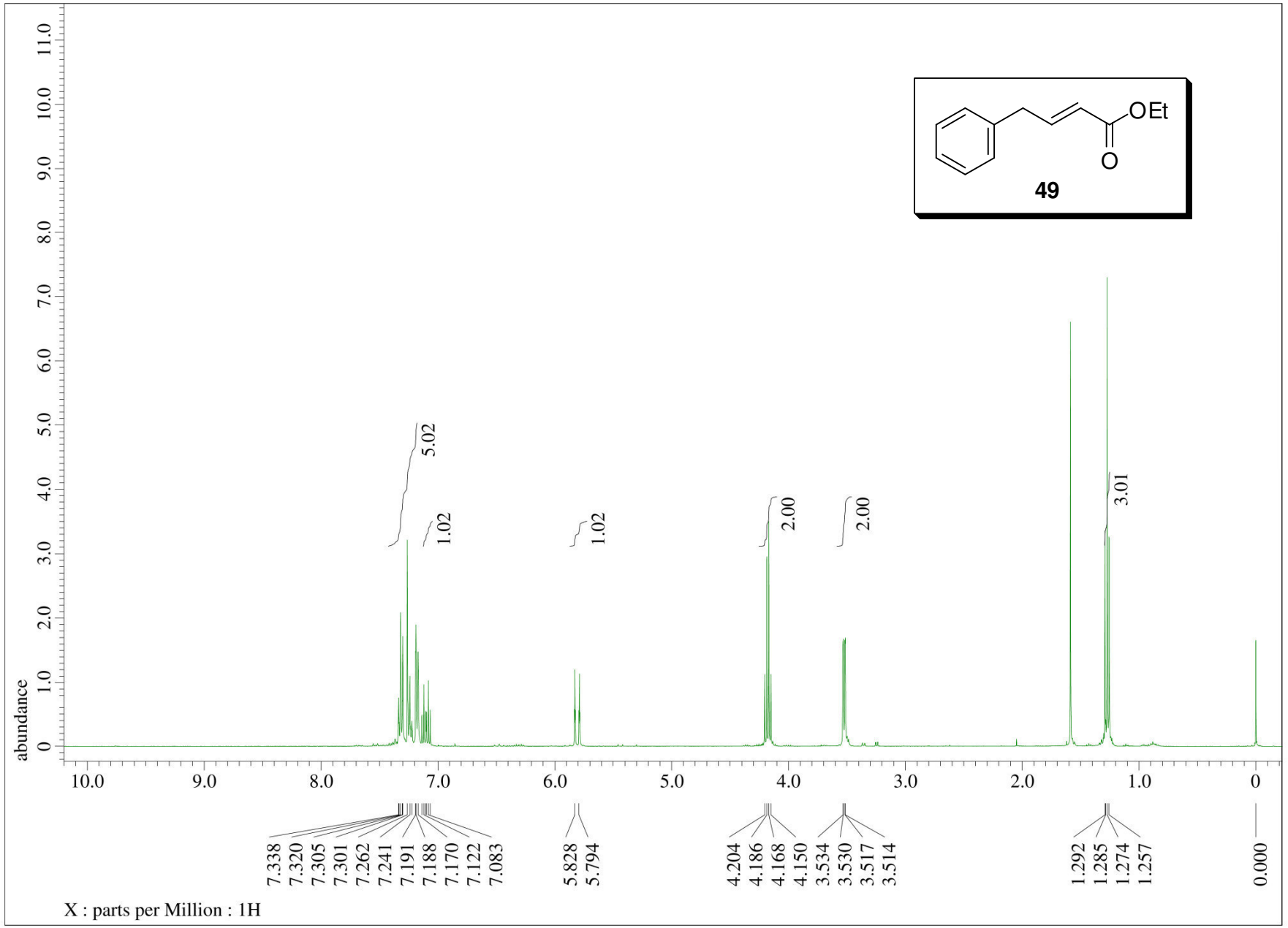
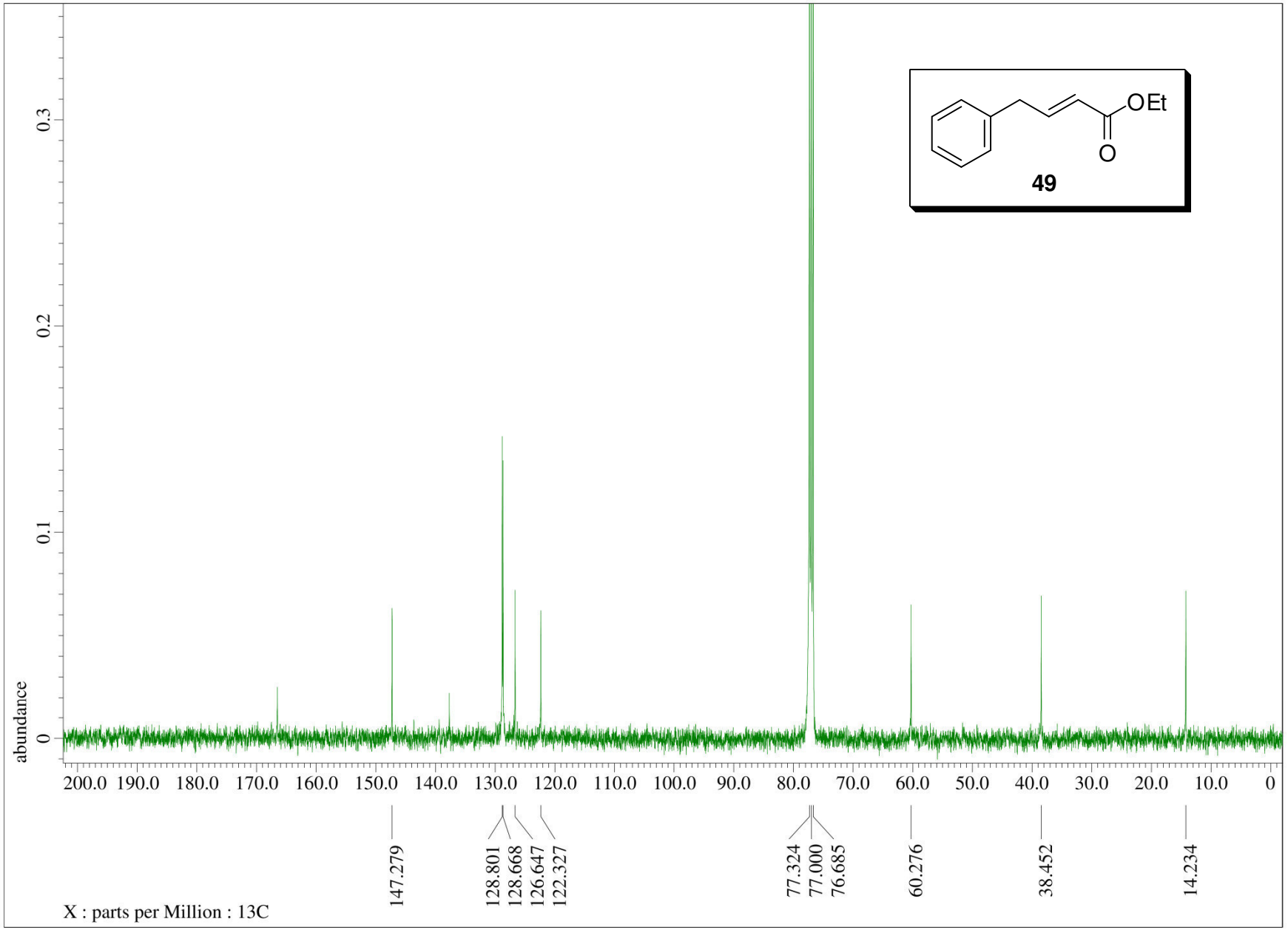
8. **SPECTRA:**

1. ^{1}H, ^{13}C NMR spectra of **49**
2. ^{1}H, ^{13}C NMR and IR spectra of **50**
3. ^{1}H, ^{13}C NMR and IR spectra of **55**

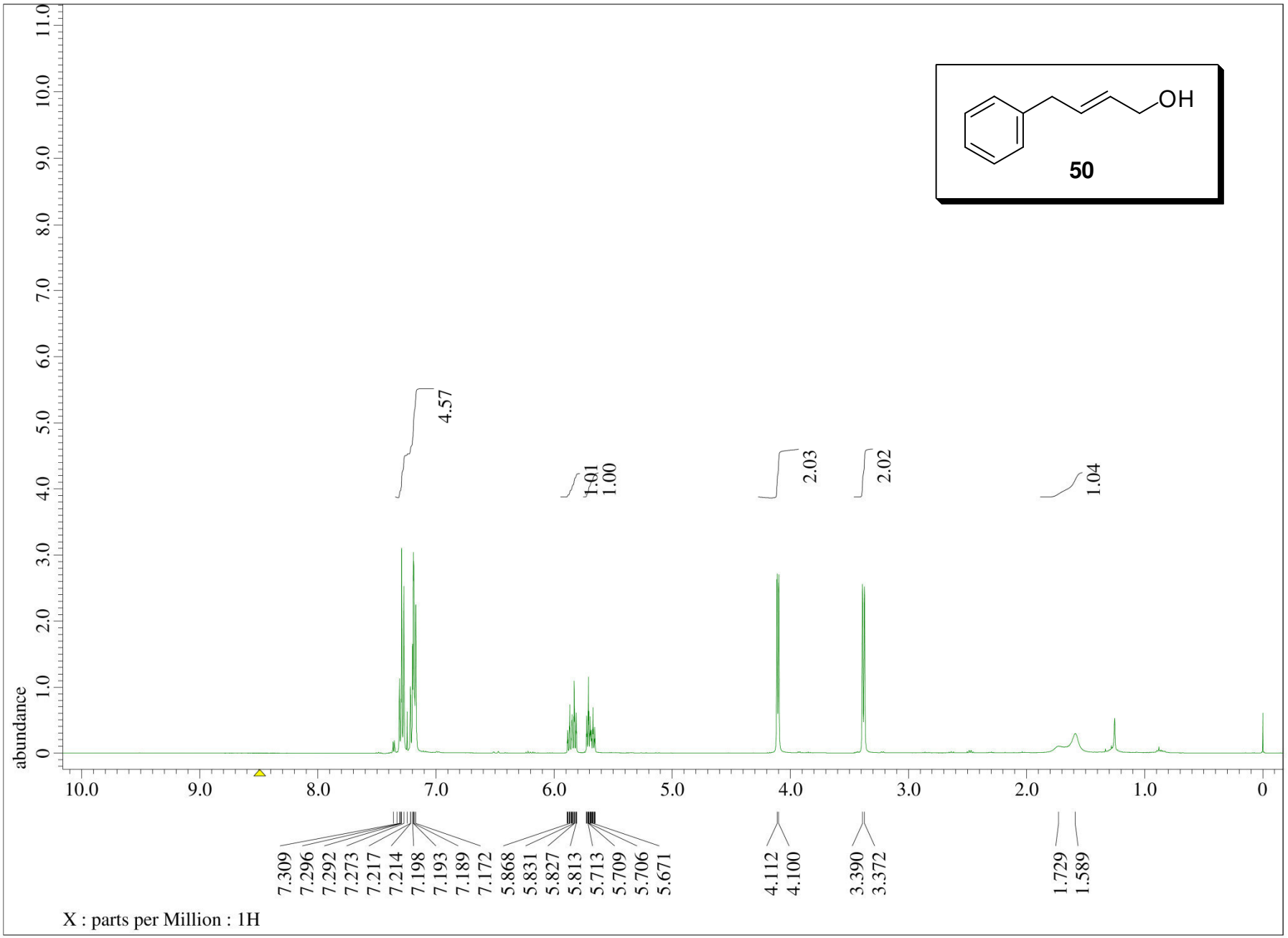
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



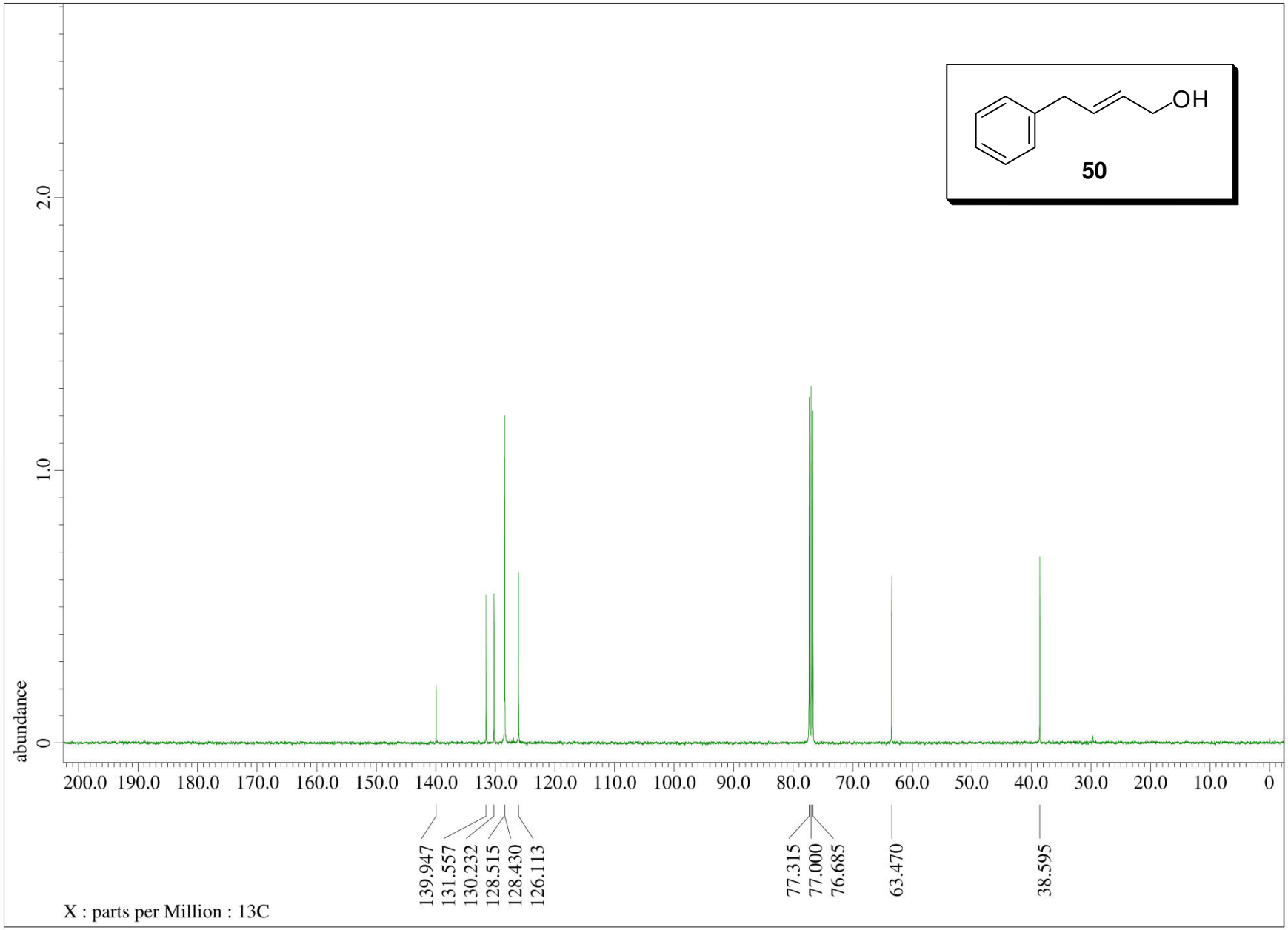
^{13}C NMR (100 MHz, $CDCl_3$/TMS)



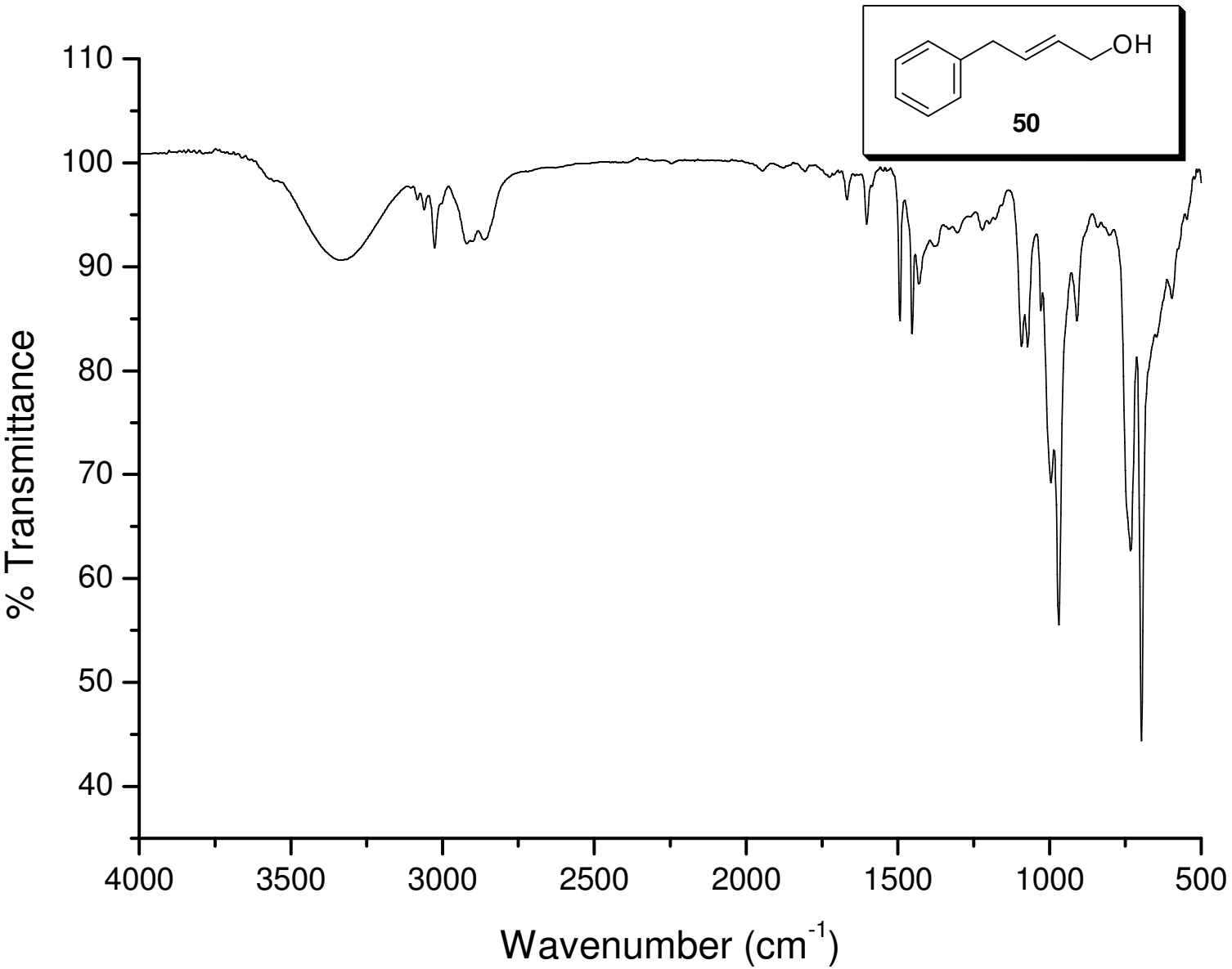
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



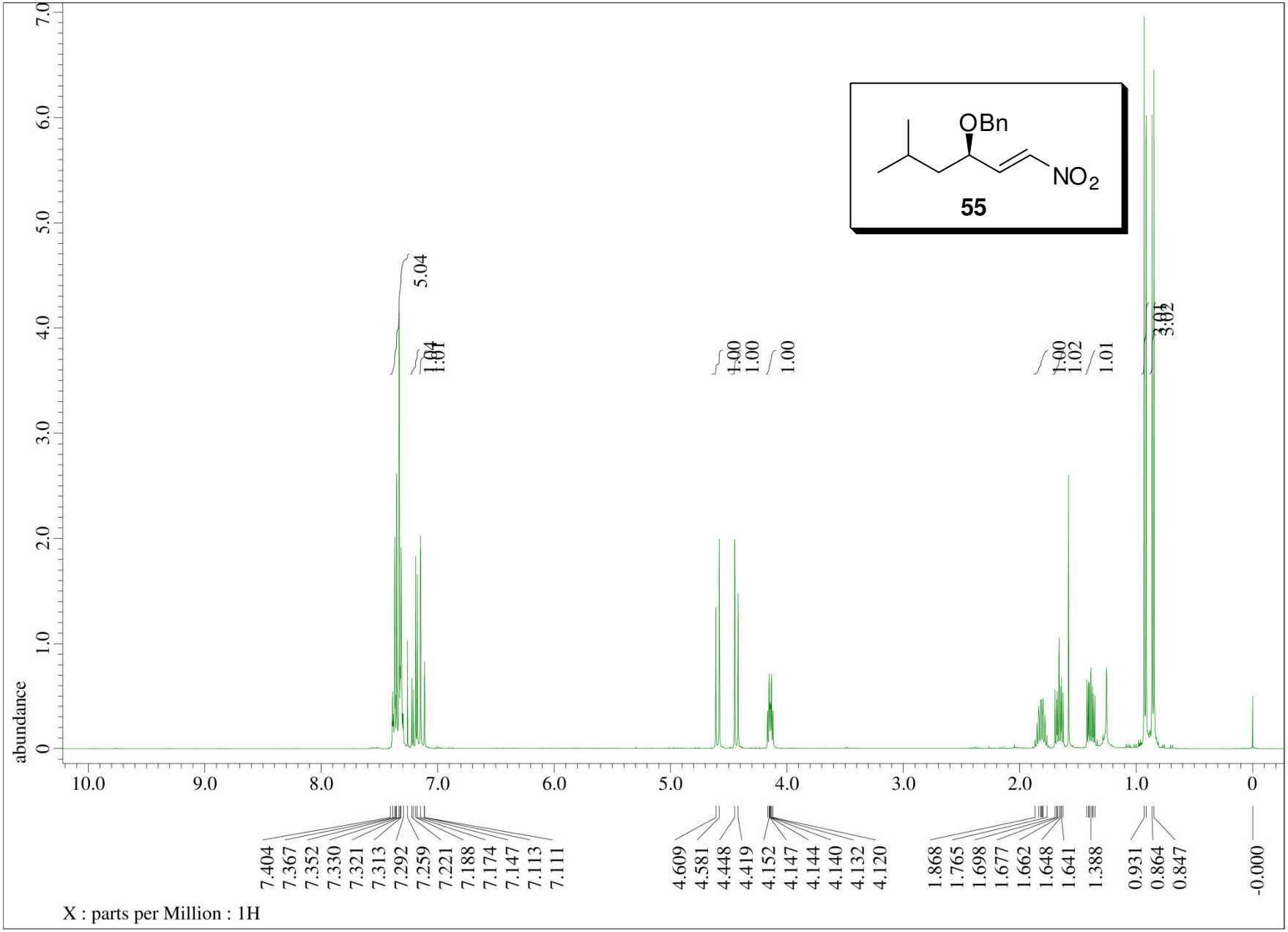
^{13}C NMR (100 MHz, $CDCl_3$/TMS)



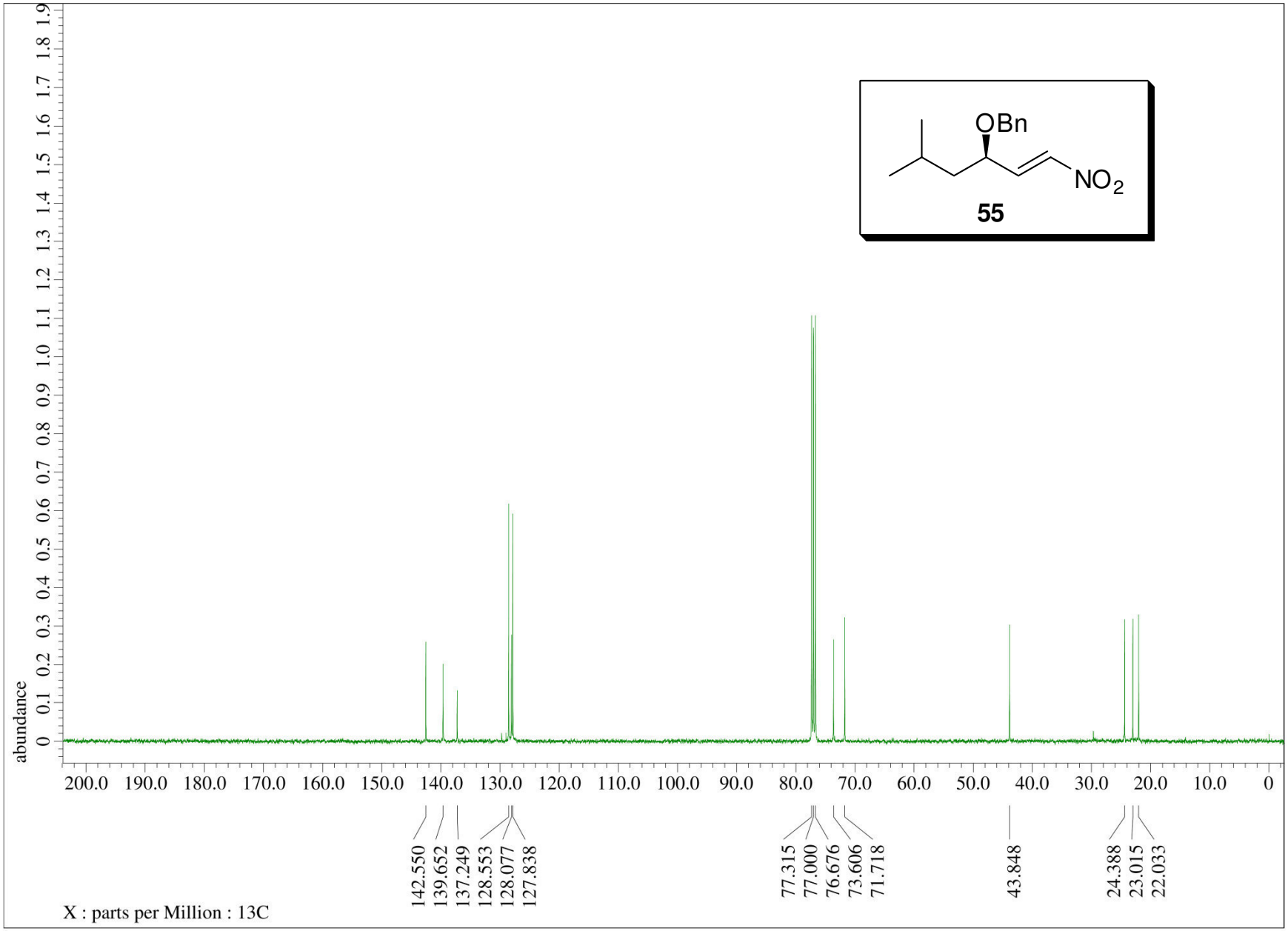
IR spectra of **50**



^{1}H NMR (400 MHz, $CDCl_3$/TMS)



^{13}C NMR (100 MHz, $CDCl_3$/TMS)



IR spectra of **55**