L-Proline Catalyzed Asymmetric Synthesis of Serotonin Norepinephrine Reuptake Inhibitors

Thesis submitted in partial fulfillment of the requirements

For the award of the degree of

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In

Chemistry

Submitted By:

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Under the guidance of

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to the

School of Chemistry and Biochemistry

Thapar University

Patiala-147004 (Punjab)

INDIA

2014

Certificate

This is to certify that the project entitled **"L-Proline Catalyzed Asymmetric Synthesis of Serotonin Norepinephrine Reuptake Inhibitors"** being submitted by **Ms. Avneet Kaur** in the partial fulfillment of requirement for the award of the degree of Masters of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonified work carried under the supervision of Dr. Satyendra Kumar Pandey and no part of this project has been submitted for award of any other degree by me.

18.07.2014

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School of Chemistry and Biochemistry,

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Thapar University, Patiala.

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled "**L-Proline Catalyzed Asymmetric Synthesis of Serotonin Norepinephrine Reuptake Inhibitors"** in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of January to July 2013, 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 recognition.

Patiala

Date: 18.07.2014

Avneet Kaur

Avneet Kaur

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

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I am obliged to Mr. Yuvraj Garg without whom I would not have been able to complete my dissertation. My sincere thanks to the research scholars of the chemistry department for their help and valuable suggestions. I am grateful to all laboratory staff for their cooperation during the period of my assignment, which helped me in completing this task through various stages. In my daily work I have been blessed with a friendly and cheerful group of research scholars Ms. Suraksha, Mr. Lalit Mehta, and Mr. Akul Sen Gupta.

I would like to express my heartiest thanks to my dear friend Ramandeep Kaur for her support and wishes for the successful completion of this project.

Lastly, I thank almighty, my beloved family for their constant encouragement and blessings without which this project would not be possible.

Avneet Kaur

LIST OF CONTENT

ABSTRACT

An enantio- and diastereo selective synthesis of SNRIs (Serotonin Norepinephrine Reuptake inhibitors) compound **7** and **8** has been attempted employing protection of amine group, Swern oxidation and L- Proline catalyzed asymmetric cross aldol reaction as the key steps. These SNRIs compounds are potent inhibitors of serotonin (5-HT) and norepinephrine (NE) reuptake. Beside being used widely as an antidepressants, these can also be used to treat various disorders, such as depression, neuropathic pain,anxiety disorders, obsessive-compulsive disorder (OCD), and attention deficit hyperactivity disorder (ADHD). They show balanced activity at both the transporters and minimizes the drug-drug interactions.The merit of this synthesis is high yielding reaction steps as asymmetric catalyst.

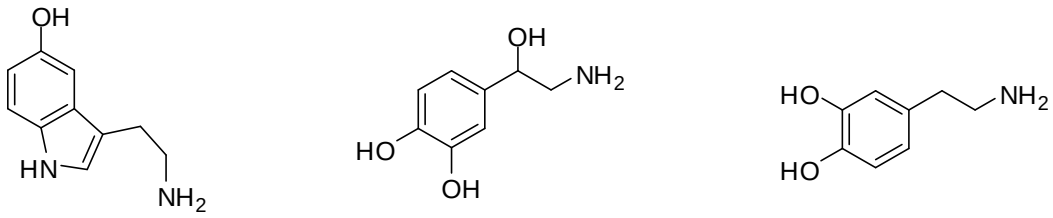
Keywords: Swern oxidation, Protection of amine group, Deprotection of amine group, L-Proline catalysed asymmetric aldol reaction.

L-Proline Catalyzed Asymmetric Synthesis of Serotonin Norepinephrine Reuptake Inhibitors

1. Introduction

In today's complex life, people have been suffering from various mental disorders out of which depression is the most common disorder. It is a chronic and recurring illness that is affecting up to 20% of the population across the globe.[1-3] It is the fourth leading cause of diseases or disability worldwide and is expected to rise to second by 2020.[4] The most widely accepted basis for depression is malfunctioning of serotonin **1**, norepinephrine **2** and dopamine **3** neurotransmitters. The neurotransmitters, serotonin and norepinephrine are known as mood modifiers and help in relieving symptoms of depression. The basic strategy for treating mental disorders including depression, generalized anxiety disorder, and several chronic pain conditions is manipulating the levels of the neurotransmitters serotonin (5-Hydroxytryptamine, 5-HT) and norepinephrine (noradrenalin, NE) in central nervous system. Antidepressants manipulate this level by inhibiting the action of corresponding reuptake transporters SERT (serotonin transporter) and NET (norepinephrine transporter).

Monoamine reuptake inhibitors are established class of drugs that has shown great potential for the treatment of number of central nervous system disorders, especially major depressive disorder. These drugs act as a reuptake inhibitor of one or more of the three major monoamine neurotransmitters namely, serotonin, norepinephrine, and dopamine by blocking the action of one or more of the respective monoamine transporters (MATs). Many monoamine transporter inhibitors have been used clinically for treating CNS-related diseases like, atomoxetine, an effective selective norepinephrine reuptake inhibitor (sNRI) for attention deficit hyperactivity disorder (ADHD).[5]

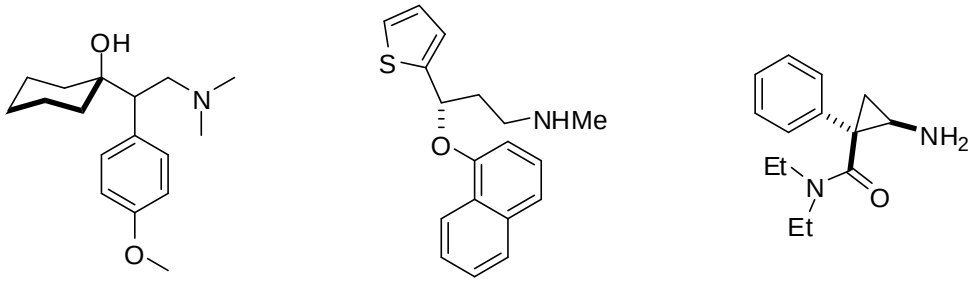


1 **2** **3**

Figure 1. Structure of the neurotransmitters present in human body.

Serotonin norepinephrine reuptake inhibitors (SNRIs), the dual action inhibitors are one of the monoamine reuptake inhibitors. SNRIs are potent inhibitors of serotonin (5-HT) and norepinephrine (NE) reuptake. This dual pharmacology mechanism can be used to

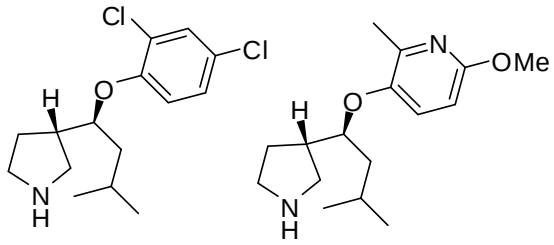
treat various disorders, such as depression,[6-7]neuropathic pain,[8] anxiety disorders, obsessive-compulsive disorder (OCD), and attention deficit hyperactivity disorder (ADHD). It show balanced activity at both the transporters and minimizes the drug-drug interactions. They offer the prospective for superior anti-depressant activity[9] as compared to selective serotonin reuptake inhibitors (SSRIs). Amine containing compounds are rich source of reuptake inhibitors having variety in their activity. Dual reuptake inhibitors, Venlafaxine **4,** Duloxetine **5** and Milanacipran **6** with an amine and aryl group have shown their efficacy as anti-depressants and have proven to be safe and effective drugs.



4 **5** **6**

Figure 2. Structure of some commercially available SNRIs drugs.

In order to improve the shortcomings of SSRIs, there has been a large interest in developing various combinations with serotonin inhibitors. Herein we designed a new approach for the enantio- and diastereo selective synthesis of compounds **7** and **8,** the serotonin norepinephrine reuptake inhibitors through L-Proline catalysed asymmetric cross aldol reaction.



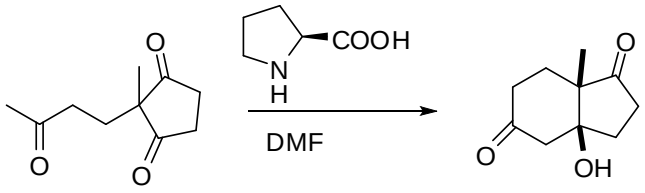
7 **8**

Figure 3. Structures of serotonin norepinephrine reuptake inhibitors **7** and **8**.

1.1 Proline as a Universal Asymmetric Organocatalyst

Aldol reaction is one of the most powerful methods for the construction of carbon–carbon bond in organic synthesis. This atom economical process couples two carbonyl partners to give both self and cross aldol β-hydroxyketones and β-hydroxyaldehydes. Besides suffering from selectivity, notably chemo- and regioselectivity problems, a major challenge is to perform aldol reaction asymmetrically. Although, chiral auxiliaries have been used widely to carry out asymmetric aldol reactions,[10-12] some success has also been achieved using asymmetric catalyst. In order to have more atom economical approach, upcoming challenge is to find a compound that will catalyze the direct aldol addition without prior stoichiometric formation of the nucleophile and to do so asymmetrically. One remarkable molecule, the amino acid Proline, turns out to be a key component in all of the catalytic strategies such as enantioselective catalysis, heterogeneous and homogeneous catalysis, acid and base catalysis, and biocatalysis. Being an effective organocatalyst, proline has paved a new way to several powerful asymmetric transformations, such as aldol, Mannich and Michael addition reactions.

The first proline catalysed direct asymmetric intramolecular aldol reaction was the Hajos–Parrish–Eder–Sauer–Wiechert cyclization, discovered in 1971.[13-15] It is an enol-endo aldolization althogh enol-exo cyclizations are also possible using proline catalysis as shown in scheme **1**.



9 **10**

Scheme 1: Hajos-Parrish-Eder-Sauer-Wiechert reaction.

Over the last three decades, seminal research from the laboratories of Evans,[16-19] Heathcock,[20-24] Masamune[25-28] and Mukaiyama[29-32] has established the aldol reaction as the principal chemical reaction for the stereoselective construction of complex polyol archtitecture. Recently, studies by Barbas,[33-34] List,[35-37] Shibasaki,[38-41] and Trost[42-43] have outlined the first examples of enantioselective direct aldol reactions, an important class of metal or proline catalyzed transformations that do not require the pregeneration of enolates or enolate equivalents.

Nucleophilic activity of proline is mainly due to its pyrroline part which forms iminium ions and enamines with carbonyl compounds. The mechanism of the proline-catalyzed aldol reaction as shown in Figure 4 is similar to that of a class I aldolase enzyme in nature. The intermolecular aldol condensation proceeds through enamine formation which is the rate determining step, followed by carbonyl addition to form iminium ion. The hydrolysis of iminium ion formed gives the aldol product. Due to its diverse catalytic activity, amino acid proline will open future opportunities to form products with high regio, diastereo and enantioselectivities

Significant features of this reaction are the following:

1. Proline is nontoxic, biodegradable, cheap, and readily available in both enantiomeric forms.
2. The reaction can be performed at room temperature or low temperature, eliminates the requirement of heating and refluxing.
3. No prior modification in carbonyl substrates such as deprotonation or pregeneration of enolates or enolate equivalents.
4. Being water soluble, catalyst can be readily removed by aqueous extraction.
5. Proline has two functional groups (carboxylic acid and an amine group) so it can act both as acid or base and can also facilitate chemical transformations in concert.

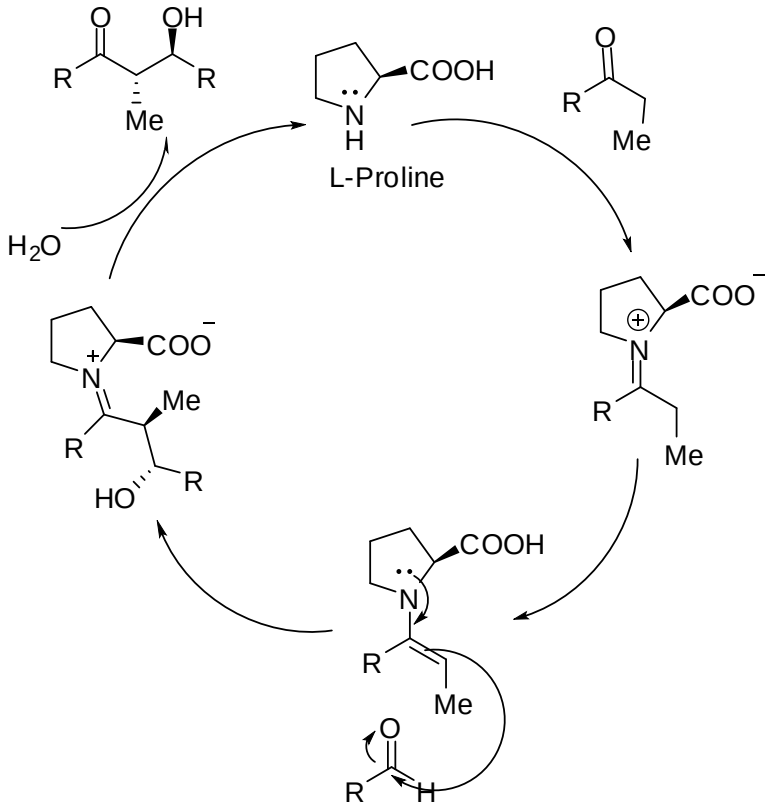
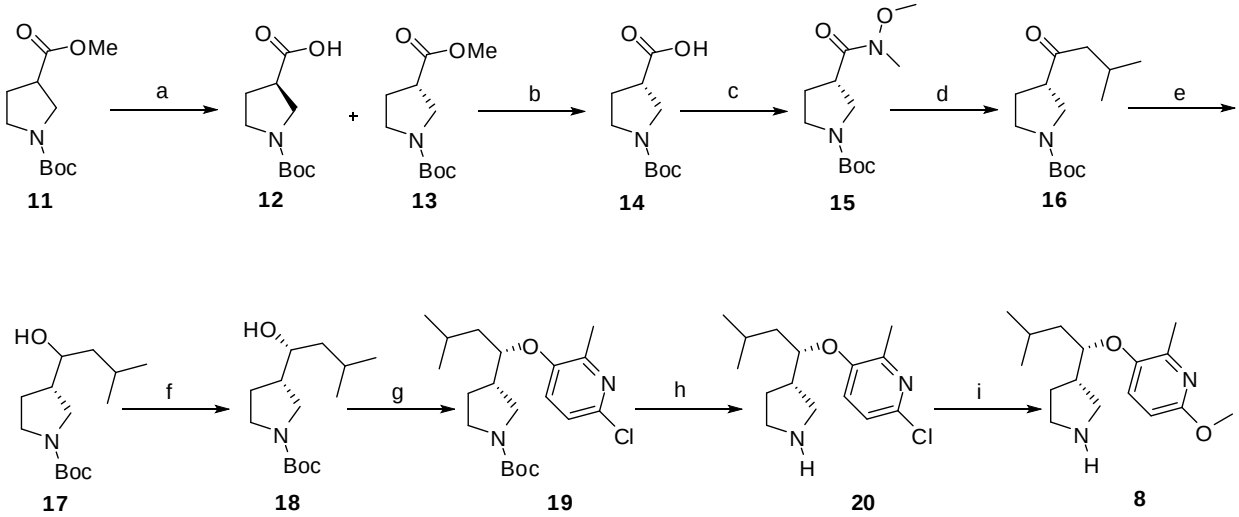


Figure 4. Mechanism of proline catalysed asymmetric aldol reaction.

2. Review of literature

2.1 Johansson, A. M. *et al.* (2013)[44]

Johansson, A. M. and co workers discovered a series of 3-substituted pyrrolidines, exemplified by compound **8** .They prepared the key intermediate **11** on the kilogram scale.[45] Racemic mixture of **11** was resolved to give the (*R*)-methyl carboxylic acid **12** and (*S*)-methyl ester **13.** The ester **13** undergoes hydrolysis followed by standard organic conversion afforded Weinreb amide **15**. Weinreb amide **15** on treatment with isobutylmagnesium chloride furnished ketone **16**, which on reduction afforded alcohol derivatives **17**. The resulting diastereoisomeric alcohols were then separated using flash chromatography to give pure intermediate (S,S)-**18**. 2-methyl-6-chloro-pyridine was introduced *via* standard synthetic strategy to give **19** which on Boc deprotection gave **20** followed by methoxide addition furnished the desired compound **8** in 9 steps (Scheme 2).

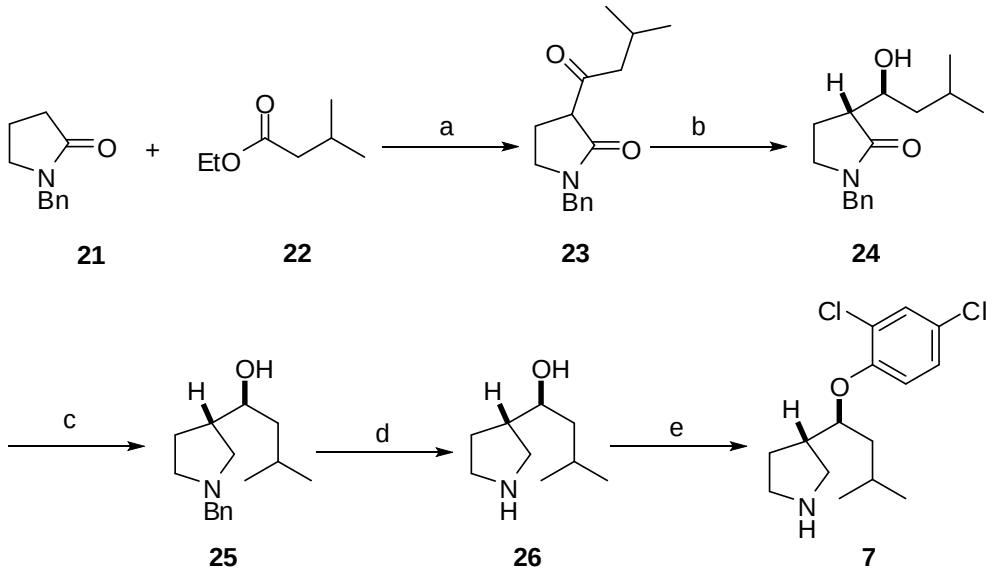


Scheme 2: *Reagents and conditions*: (a) i) lipase AS, buffer phosphate, K_2CO_3, **2**- 55%, and **3**- 43%, 98% ee; (b) LiOH, THF, 74%; (c) *N*,*O*-dimethylhydroxyl-amine, HCl, CDI, DCM, (92%); (d) *i*-BuMgCl, THF, (94%); (e) $NaBH_4$, MeOH, 98%; (f) flash chromatography biotage 150 M, heptane/IPA 95:5, 45%, 96% de; (g) NaH, 6-chloro-3-fluoro-2-methyl-pyridine, DMA, 87%; (h) TFA, anisole, (quantitative yield); (i) NaOMe, DMSO, 90%.

2.2 Magnus, N. A. *et al.* (2013)[46]

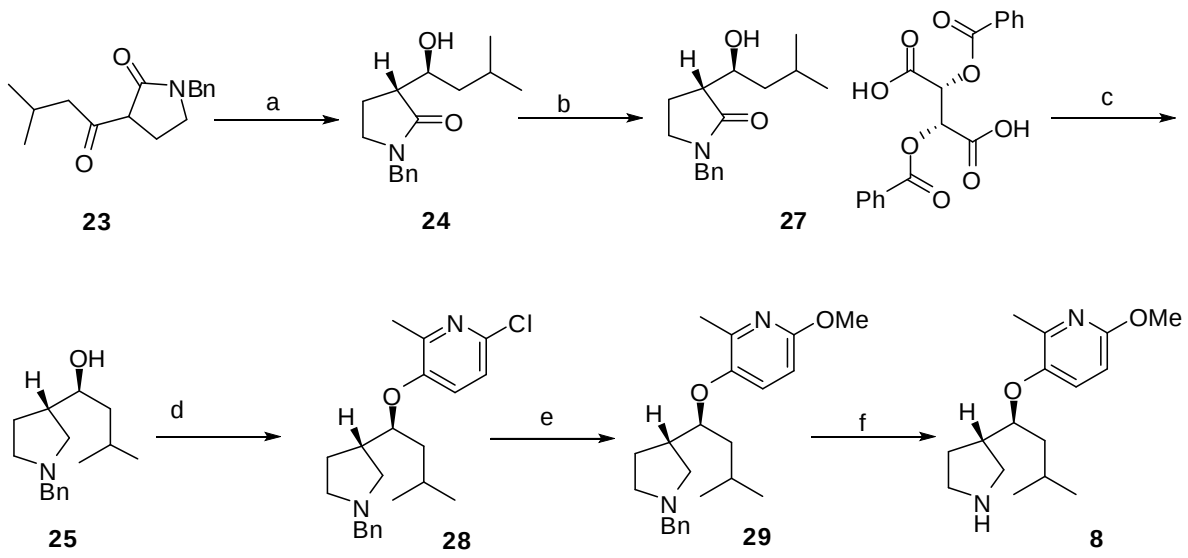
Nicholas A. Magnus and co workers prepared SNRIs **7** and **8**, based on a dynamic kinetic resolution (DKR) accompanied by enantio- and diastereoselective hydrogenation of a

β-keto-γ-lactam. They combined *N*-benzyl-γ-lactam **21** with ethyl isovalerate **22** and added the mixture to LDA at −10 to 5°C, leading to precipitation of enolate**,** which undergo an acidic workup to give β-keto-γ-lactam **23** as oil. Diastereoselective hydrogenation of **23** afforded (±)-**24** as a solid. Reduction of (±)-**24** led to (±)-**25**, removal of protecting group furnished (±)-**26.** The alcohol (±)-**26** under a SNAr reaction furnished (±)-**7** as an oil, which was then purified with 81% overall yield (Scheme 3).



Scheme 3: *Reagents and conditions:* (a) i) LDA, 2-MeTHF, -10-5^{o}C, ii) heptanes, iii) aq.10% citric acid, MTBE; (b) i) $RuCl_2(PPh_3)_3$, H_2 (350 psi), MeOH, 50^{o}C; ii) Silica bond ® TAAcONa, CH_3CN; iii) MTBE/heptanes; (c) Vitride®, PhMe, 0-22^{o}C; (d) $Pd(OH)_2/C/H_2$, EtOH, 23^{o}C; (e) 2,4-dichloro-1-fluorobenzene, ^{t}BuOK/NMP, 4-22^{o}C; (f) i) L-DTTA, EtOH/EtOAc, 50-22^{o}C, ii) re-crystallization, EtOH/EtOAc.

They prepared pyrrolidinyl ether **8** starting from *β*-keto-*γ*-lactam **23** which under hydrogenation condition afforded **24**. Reduction of **24** afforded pyrrolidine **25** oil which was purified via a crystalline diastereomeric salt **27**. Pyrrolidine **25** on treatment with t-BuOK and 6-chloro-3-fluoro-2-methylpyridine afforded the SNAr adduct **28**. The methoxy moiety was installed on chloride **28** followed by hydrogenation afforded the target compound **8** (Scheme 4).



Scheme 4: *Reagents and conditions:* (a) $Ru(OAc)_2$[(*S*)-tol-BINAP], IPA/35% HCl/LiCl, H_2 (85-90 psi), 65^{o}C; (b) i) Vitride, PhMe, 0-22^{o}C, ii) (*L*)-DBTA/MeOAc, 22-50^{0}C; (c) Aq. $NaHCO_3$, TEA/MTBE, 22^{o}C; (d) *t*-BuOK, 6-chloro-3-fluoro-2-methylpyridine, DMF, 22^{o}C; (e) MeOK, DMSO, 100^{o}C; (f) H_2/Pd-C, EtOH, 60^{o}C.

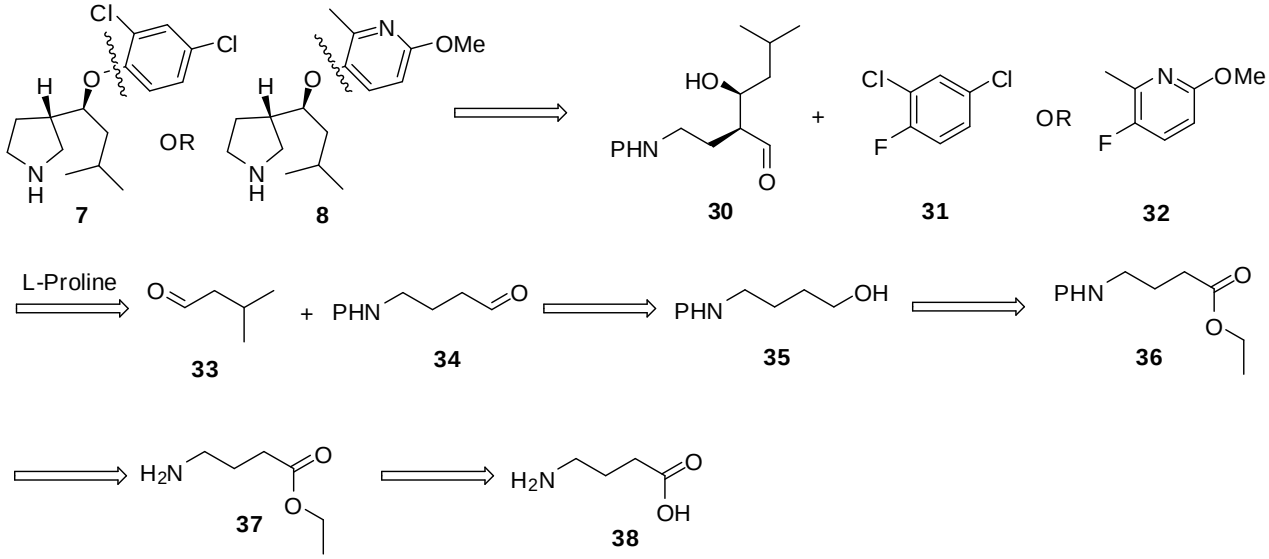
3 Present work

3.1 Objective:

In the literature, so far only two approaches have been reported for SNRIs **7** and **8**, recently by Nicholas, A. M. *et al*.[46] The original routes used to prepare compounds **7** and **8** had been achieved in multisteps featuring a 1, 3- dipolar cycloaddition, manipulation of protecting groups and enzyme resolution. Johansson, A.M. *et al*. discovered the synthesis of SNRIs**7** and **8** in overall 9 steps. As part of our research program aimed at developing enantio- and diastero selective synthesis, we became interested to develop a new and highly efficient synthetic approach for SNRIs **7** and **8** employing Swern oxidation and asymmetric aldol reaction as the key steps.

3.2 Retrosynthetic Approach:

The reterosynthetic approach for SNRIs **7** and **8** is outlined in Scheme 5. The pyrrolidine ring system could be effectively prepared from protected *β*-hydroxyaminoaldehyde **30** using reductive amination, followed by coupling with aromatic compounds **31** and **32** could afford **7** and **8** respectively. *β*-Hydroxyaminoaldehyde **30** was visualized as a synthetic intermediate which could be synthesized from L-proline catalysed asymmetric cross aldol reaction of isovaleraldehyde **33** and **34**. The amino aldehyde **34** could be obtained from oxidation of alcohol **35** which could be obtained from the reduction of ester **36**. The intermediate **36** could be easily prepared from amino ester **37** which in turn could be obtained from esterification of cheaply available 4-aminobutyric acid **38** (Scheme 5).

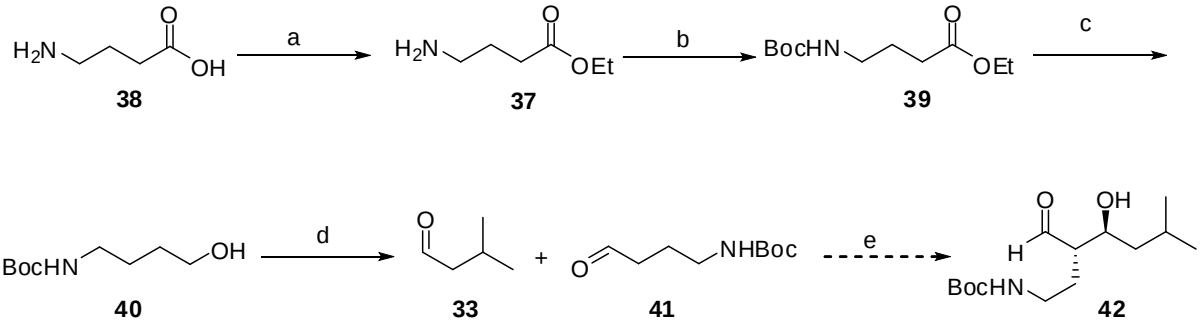


Scheme 5: Reterosynthesis of compound **7** and **8**.

4. Result and discussion:

The synthesis started from the commercially and cheaply available starting material 4-aminobutanoic acid **38** as shown in Scheme 6. 4-aminobutanoic acid was subjected to esterification under acidic condition to give **37**. Amino group protection of **37** with $(Boc)_2O$ led to compound **39** in 94 % yield, which on subsequent treatement with $LiAlH_4$ afforded **40** in 80% yield**.** The ^1H NMR spectrum of **39** indicates NH proton at 4.72 (broad, one proton), methylene protons of ester at 4.068 (quartet, *J*=6.8, two protons), methylene protons adjacent to amine at 3.09 (multiplet, *J*=6.4, two protons), aliphatic methylene protons adjacent to carbonyl at 2.28 (triplet, *J*=7.32, two protons), methylene protons at 1.75 (multiplet, two

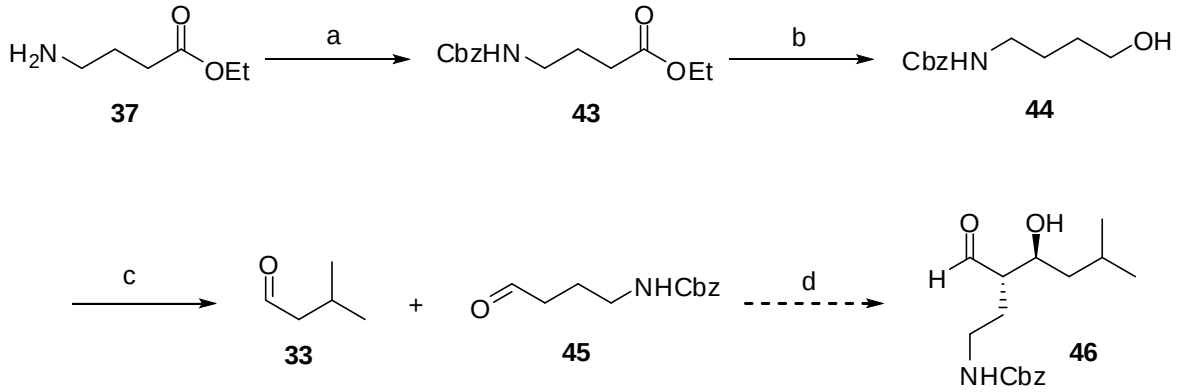
protons), Boc group at 1.37 (singlet, nine protons), methyl protons of ester at 1.19 (triplet, *J*=7.36, three protons). The ^{1}H NMR spectrum of **40** indicates NH proton at 4.84 (broad, one proton), methylene protons adjacent to hydroxyl group at 3.57 (triplet, *J*=5.96, two protons), methylene protons adjacent to NH group at 3.07 (doublet, *J*=5.96, two protons), hydroxyl proton at 2.68 (broad, one proton), aliphatic methylene protons at 1.50 (multiplet, *J*= 2.76, four protons), Boc group at 1.37 (singlet, nine protons). Alcohol **40** is converted into aldehyde **41** using Dess-Martin-periodinane (DMP). The resulting protected **41** was then under asymmetric cross aldol reaction with isovaleraldehyde **33** using L-proline as a catalyst did not gave the desired product *β*-hydroxyaminoaldehyde **42** (Scheme 6). However, we have attempted various reaction conditions to achieve the compound **42**, as depicted in the table 1, but the reaction did not work, and recovered the starting material (SM). The reaction did not work may be because of unstability of aldehyde **41**. Therefore, we need some alternative approach with a suitable protecting group to make aldehyde **41.**



Scheme 6: *Reagents and conditions*: (a) EtOH, H_2SO_4, reflux, overnight; (b) di-*tert*-butyldicarbonate, $NaHCO_3$, THF/H_2O (1:1), rt, 20 h, 94%; c) $LiAlH_4$, THF, 0^{o}C to rt, 3h, 80%; (d) DMP, DCM, 0^{o}C to rt.

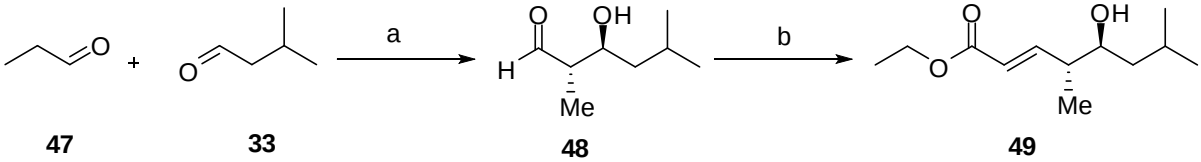
To overcome this problem, another scheme was designed to prepare Cbz protected *β*-hydroxyaminoaldehyde **46** as shown in Scheme 7. Cbz protection of **37** led to formation of Cbz protected ester **43** which on subsequent reduction with $LiAlH_4$ afforded alcohol **44**. Swern oxidation of alcohol **44** furnished aldehyde **45** in 92% yield. The ^{1}H NMR spectrum of **45** indicates aromatic protons at 7.29 (multiplet, five protons), methylene protons adjacent to -NH group at 5.44 (multiplet, one proton), methylene protons adjacent to aromatic ring at 5.11 (multiplet, two protons), NH proton at 4.64 (broad, one proton), methylene proton adjacent to NH group at 3.55 (multiplet, *J*=8.24, one proton), methylene proton adjacent to aldehyde at 3.29 (multiplet, *J*=7.36, one proton), methylene proton adjacent to aldehyde at 2.1 (multiplet, one proton), aliphatic methylene protons at 1.82 (multiplet, three protons).

The resulting protected aldehyde **45** was then on treatment with proline catalyzed asymmetric cross aldol reaction with isovaleraldehyde **33** could give Cbz protected *β*-hydroxyaminoaldehyde **46** (Scheme **7**). However, the reaction was messy and did not give the desired intermediate **46**.



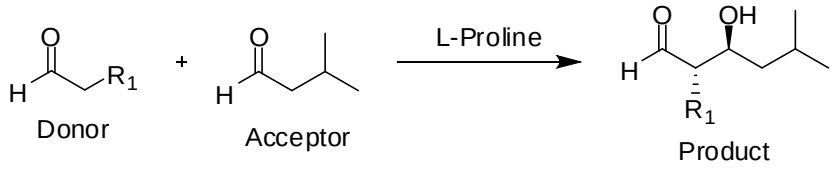
Scheme 7: *Reagents and conditions*: (a) $NaHCO_3$, benzylchloroformate, H_2O, 20 h; (b) $LiAlH_4$, anhydrous THF, 0^oC to rt, 3h; (c) Oxalyl chloride, dry CH_2Cl_2, DMSO, -78^oC, Et_3N, -60^oC , 1h; (d) L-Proline, DMF, 4^oC,24 h.

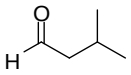
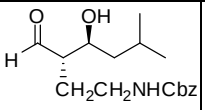
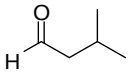
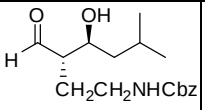
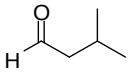
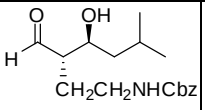
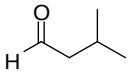
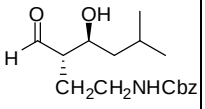
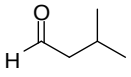
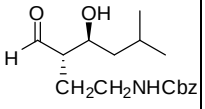
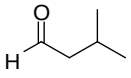
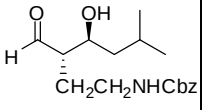
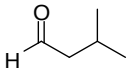
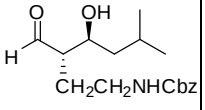
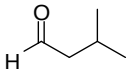
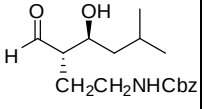
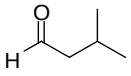
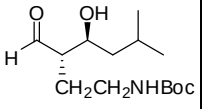
A known standard L-proline catalysed asymmetric model reaction for the conformation of aldol reaction of propanal (donor) and isovaleraldehyde (acceptor) has been successfully demonstrated.[47] Due to unstability of aldehyde **48**, it was converted into stable Wittig product **49** (Scheme 8). The ^1H NMR spectrum of **49** indicates olefinic proton at 6.96 (doublet of doublet, *J*=8.24,7.76, one proton) and at 5.86 (doublet, one proton), methylene protons of ester at 4.2 (quartet , *J*=6.88, two protons), methine proton adjacent to hydroxyl group at 3.64 (multiplet, one proton), methine proton adjacent to double bond at 2.38 (multiplet, one proton), methane proton at 1.78 (multiplet, one proton), hydroxyl group at 1.57 (broad, one proton), methyl protons of ester and methylene protons at 1.21-1.43 (multiplet, five protons), aliphatic methyl protons at 1.07-1.12 (multiplet, *J*=6.84, three protons), two methyl groups at 0.92 (doublet of doublet, *J*=6.4, six protons).

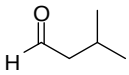
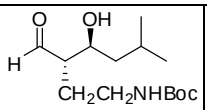
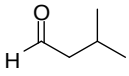
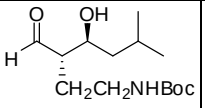
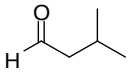
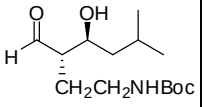
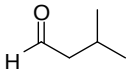
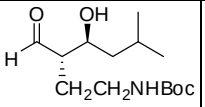
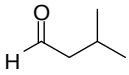
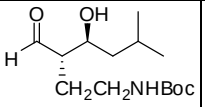
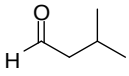
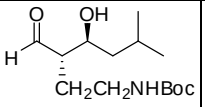
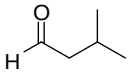
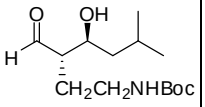
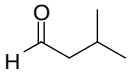
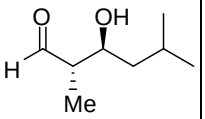


Scheme 8: *Reagents and conditions:* (a) L-Proline, DMF, 4^oC, 24 h; (b) PPh_3=CHCOOEt, dry THF, rt, overnight, 72% (over the two steps).

Table 1. Optimisation of L-proline catalysed asymmetric cross aldol reaction.

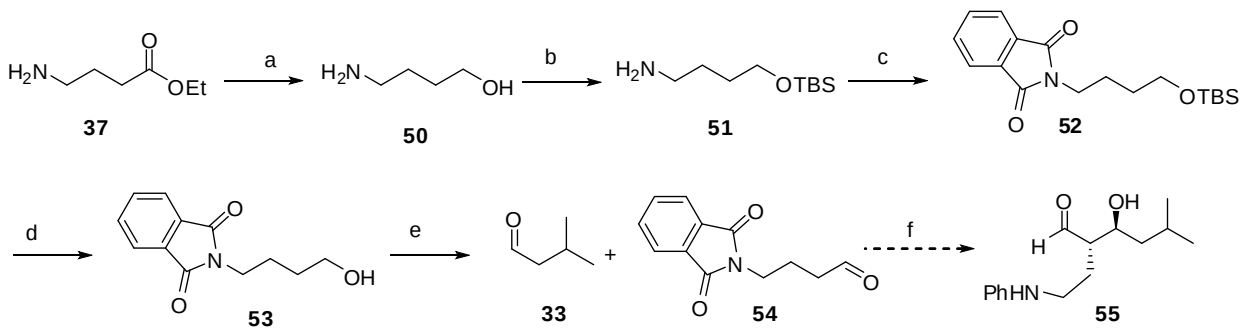


Entry	**R_1**	**R_2**	**Product**	**Solvent**	**Catalyst mole %**	**Temp. (^oC)**	**Result (% yield)**
1	CH_2CH_2NHCbz			CH_3CN	10	4	No Reaction
2	CH_2CH_2NHCbz			CH_3CN	20	4	No Reaction
3	CH_2CH_2NHCbz			CH_3CN	10	25	No Reaction
4	CH_2CH_2NHCbz			CH_3CN	20	25	No Reaction
5	CH_2CH_2NHCbz			DMF	10	4	No Reaction
6	CH_2CH_2NHCbz			DMF	20	4	No Reaction
7	CH_2CH_2NHCbz			DMF	10	25	No Reaction
8	CH_2CH_2NHCbz			DMF	20	25	No Reaction
9	CH_2CH_2NHBoc			CH_3CN	10	4	Messy Reaction

10	CH_2CH_2NHBoc			CH_3CN	20	4	Messy Reaction
11	CH_2CH_2NHBoc			CH_3CN	10	25	Messy Reaction
12	CH_2CH_2NHBoc			CH_3CN	20	25	Messy Reaction
13	CH_2CH_2NHBoc			DMF	10	4	Messy Reaction
14	CH_2CH_2NHBoc			DMF	20	4	Messy Reaction
15	CH_2CH_2NHBoc			DMF	10	25	Messy Reaction
16	CH_2CH_2NHBoc			DMF	20	25	Messy Reaction
17	Me			DMF	10	4	72

5. Future Prospective:

To overcome the problems related with clean reaction in cross aldol reaction, we now fully protected the free amino group. Therefore we designed phthalimide protected *β*-hydroxyaminoaldehyde **55** which could be prepared from the intermediate **37**. We have successfully achieved first three steps, reduction, TBS protection of hydroxyl group and phthalaminde protection. We are hopeful of achieving our target compound SNRIs compound **7** and **8** using this strategy as the amine group is now fully protected.



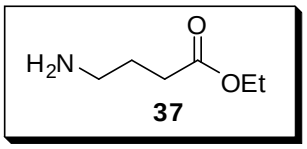
Scheme 9: *Reagents and conditions :* (a) LAH,THF, 0^{o}C to rt; (b) Imidazole, TBS-Cl, DCM, 0^{o}C to rt; (c) Phthalic anhydride, Et_3N, toluene, reflux, 100^{o}C; (d) PTSA, THF, 0^{o}C to rt; (e) Oxalyl chloride, dry CH_2Cl_2, DMSO, -78^{o}C, Et_3N, -60^{o}C , 1h; (f) L-Proline, DMF, 4^{o}C, 24h.

6. Conclusion

In conclusion, an enantio- and diastereo selective synthesis of SNRIs **7** and **8** has been attempted employing Swern oxidation and asymmetric cross aldol reaction as the key steps. The merit of this synthesis is high yielding reaction steps as asymmetric catalyst. The synthetic strategy described has significant potential for further extension to optimize the different reaction conditions to achieve the target compounds.

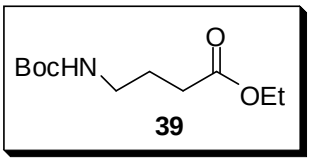
7. Experimental section

7.1 Ethyl 4-aminobutanoate (37):



To a solution of 4-aminobutyric acid **38** (5g, 48.5 mmol) in ethanol (75 ml) was added H_2SO_4 (5ml) at room temperature. The reaction mixture was then refluxed overnight. The reaction mixture was quenched with addition of saturated $NaHCO_3$ solution, filtered and evaporated ethanol on water bath. The aqueous phase was extracted with EtOAc (3× 50 ml). It was then dried over Na_2SO_4, concentrated and used as such for the next step without purification.

7.2 Ethyl 4-(*tert*-butoxycarbonylamino)butanoate (39):



39

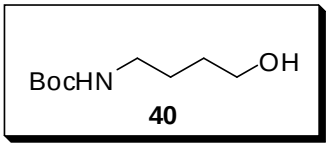
A solution of **37** (1g, 7.6 mmol) in THF/H_2O (1:1) was added $NaHCO_3$ (2g, 22.8 mmol) followed by addition of a solution of di-*tert*-butyldicarbonate (2g, 9.1 mmol) and stirred for 20 hours. After 20 hours the reaction mixture was diluted with distilled H_2O and then extracted with EtOAc (3× 20 ml). The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (EtOAc/hexane, 1:4) to afford **39** as yellow oil.

Yield: 1.65 g, 94%.

Mol.Formula: $C_{11}H_{21}NO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J*= 7.36 Hz, 3H), δ 1.37 (s, 9H), δ 1.75 (m, 2H), δ 2.28 (t, *J*= 7.32,2H), δ 3.09 (d, *J*= 6.4, 2H), δ 4.068 (q, *J*=6.8, 2H), δ 4.72 (br,1H).

7.3 *tert*-Butyl 4-hydroxybutylcarbamate (40):



40

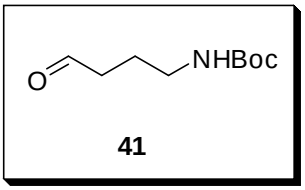
To a stirred suspension of $LiAlH_4$ (196mg, 5.184 mmol) in anhydrous THF (5ml) was added a solution of **39** (1g, 4.32 mmol) in THF (5ml) dropwise at 0^{o}C under nitrogen atmosphere. The mixture was then stirred for one hour at 0^{o}C and for 2 hours at room temperature. The reaction mixture was then quenched with 10% NaOH and extracted with ethyl acetate (3×50ml). the organic layer was then dried (Na_2SO_4, concentrated and purified by silica gel chromatography (EtOAc /hexane, 3:7) to afford **40** as pale yellow oil.

Yield: 650 mg, 80%.

Mol.Formula: $C_9H_{19}NO_3$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), δ 1.50 (m, *J*= 2.76 Hz, 4H), δ 2.68 (s, 1H), δ 3.07 (d, *J*= 5.96, 2H), δ 3.57 (t, *J*= 5.96, 2H), δ 4.84 (br,1H).

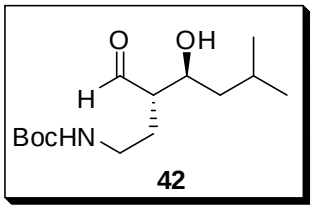
7.4 *tert*-Butyl 4-oxobutylcarbamate (41):



41

To a solution of **40** (500mg, 2.65 mmol) in dry DCM (7 ml) was added Dess-Martin-periodinane (1.4g, 3.3 mmol) at 0^oC. The resulting solution was warmed to room temperature and stirred for 1 hour with addition of 3 ml DCM twice every 15 minutes. The resulting solution was then diluted with diethylether and quenched by addition of saturated solution of $Na_2S_2O_3$ and $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4, concentrated in vacuo and used as such for the next step without purification.

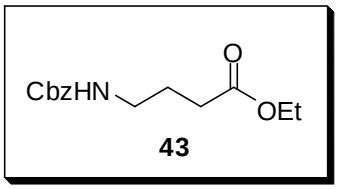
7.5 *tert*-butyl (*3S.4S*)-3-formyl-4-hydroxy-6-methylheptylcarbamate (42):



42

A solution of isovaleraldehyde **33** (475 mg, 5.5 mmol) in DMF (5 ml) precooled to 4^oC was added slowly over the course of 1 hour to a stirring suspension of **41** (1.03 g, 5.5 mmol), L-proline (65 mg, 0.55 mmol) and DMF (5 ml) at 4^oC. After 24 hours resulting solution was diluted with diethylether and washed with H_2O. The combined aqueous layer was back extracted with 3 portions of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo.

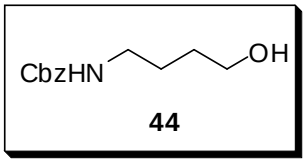
7.6 Ethyl 4-(2-oxo-2-phenylethylideneamino)butanoate (43):



43

To a solution of **37** (200mg, 1,526 mmol) in H_2O (10 ml) was added $NaHCO_3$ (512mg, 6.106 mmol) followed by addition of a solution of benzylchloroformate (313 mg, 1.831 mmol) and stirred for 20 hours. After 20 hours the reaction mixture was diluted with distilled H_2O and then extracted with EtOAc (3× 20 ml). The organic layer was separated, dried (Na_2SO_4), concentrated and used as such for the next step without purification.

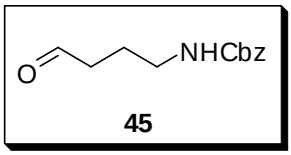
7.7 Benzyl 4-hydroxybutylcarbamate (44):



44

To a stirred suspension of $LiAlH_4$ (200 mg, 5.03 mmol) in anhydrous THF (5ml) was added a solution of **43** (1.4 g, 4.2 mmol) in THF (5ml) dropwise at 0^oC under nitrogen atmosphere. The mixture was then stirred for one hour at 0^oC and for 2 hours at room temperature. The reaction mixture was then quenched with 10% NaOH and extracted with ethyl acetate (3×50ml). The organic layer was then dried (Na_2SO_4), concentrated and used as such for the next step without purification.

7.8 Benzyl 4-oxobutylcarbamate (45):



45

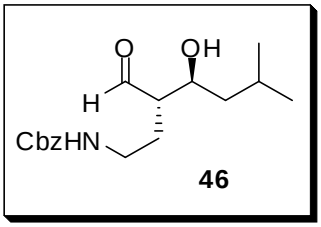
To a solution of oxalyl chloride (2.6g, 20.1 mmol) in dry CH_2Cl_2 (20 ml) at -78^oC was added dropwise dry DMSO (3.24g, 41.5 mmol) in CH_2Cl_2 (5 ml). After 30 min, alcohol **44** (2.75g, 13.4 mmol) in CH_2Cl_2 (10ml) was added over 10 min giving copious white precipitate. After stirring for 1 hour at -78^oC the reaction was brought to -60^oC and Et_3N (6g, 59 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (50 ml) and CH_2Cl_2 .The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated and purified (EtoAc/hexane, 1:4) afford aldehyde **45** as pale yellow oil.

Yield: 2.5g, 92%.

Mol.Formula: $C_{12}H_{15}NO_3$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76-1.85 (m, 3H), δ 1.97-2.1 (m, 1H), δ 3.23-3.33 (m, *J*= 7.36 Hz , 1H), δ 3.50-3.57 (m, *J*=8.24 Hz ,1H), δ 4.64 (br, 1H), δ 4.99-5.18 (m, 2H), δ 5.44-5.49 (m, 1H), δ 7.24-7.34 (m, 5H)

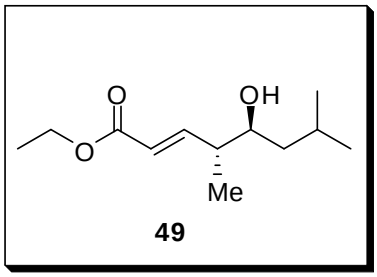
7.9(*2S,3S)*-3-hydroxy-5-methyl-2-(2-(2-oxo-2-phenylethylideneamino)ethyl)hexanal (46):



46

A solution of isovaleraldehyde (475 mg, 5.5 mmol) in DMF (5 ml) precooled to 4^{o}C was added slowly over the course of 1 hour to a stirring suspension of **46** (1.12 g, 5.5 mmol), L-proline (65 mg, 0.55 mmol) and DMF (5 ml) at 4^{o}C. After 24 hours resulting solution was diluted with diethylether and washed with H_2O. The combined aqueous layer was back extracted with 3 portions of DCM. The organic layer were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo (please see the table 1).

7.10 (*4R,5S,E*)-ethyl 5-hydroxy-4,7-dimethyloct-2-enoate (49):



49

i) **Aldol reaction**: A solution of isovaleraldehyde **33** (740 mg, 8.62 mmol) in DMF (5 ml) precooled to 4^{o}C was added slowly over the course of 1 hour to a stirring suspension of propanal (1g, 17.24 mmol), L-proline (200 mg, 1.724mmol) and DMF (5 ml) at 4^{o}C. After 24 hours resulting solution was diluted with diethylether and washed with H_2O. The combined aqueous layer was back extracted with 3 portions of DCM. The organic layer were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo .

(ii) **Wittig reaction**: A solution of wittig reagent (PPh_3=CHCOOEt) (6.75g, 19.367 mmol) in THF (10ml) was made to stir for 10 min. After that a solution of **48** (1.862g, 12.911 mmol) in THF (10ml) was added to wittig solution. The reaction mixture was then stirred overnight at room temperature. The reaction mixture was concentrated and purified using silica gel column chromatography (EtOAc/hexane, 1:4) afford yellow oil **49.**

Yield: 2 g, 72% (over 2 steps).

Mol.Formula: $C_{12}H_{22}O_3$

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (dd, *J*= 6.4, 6.88 Hz, 6H), δ 1.07-1.12 (m, *J*= 6.84, 3H), δ 1.21-1.43 (m, 5H), δ 1.57 (s,1H), δ 1.78 (m, 1H), δ 2.38 (m,1H), δ 3.64 (m,1H), δ 4.2 (q, *J*= 6.88 Hz, 2H), δ 5.86 (d, 1H), δ 6.96 (dd, *J*= 8.24,7.76 Hz,1H).

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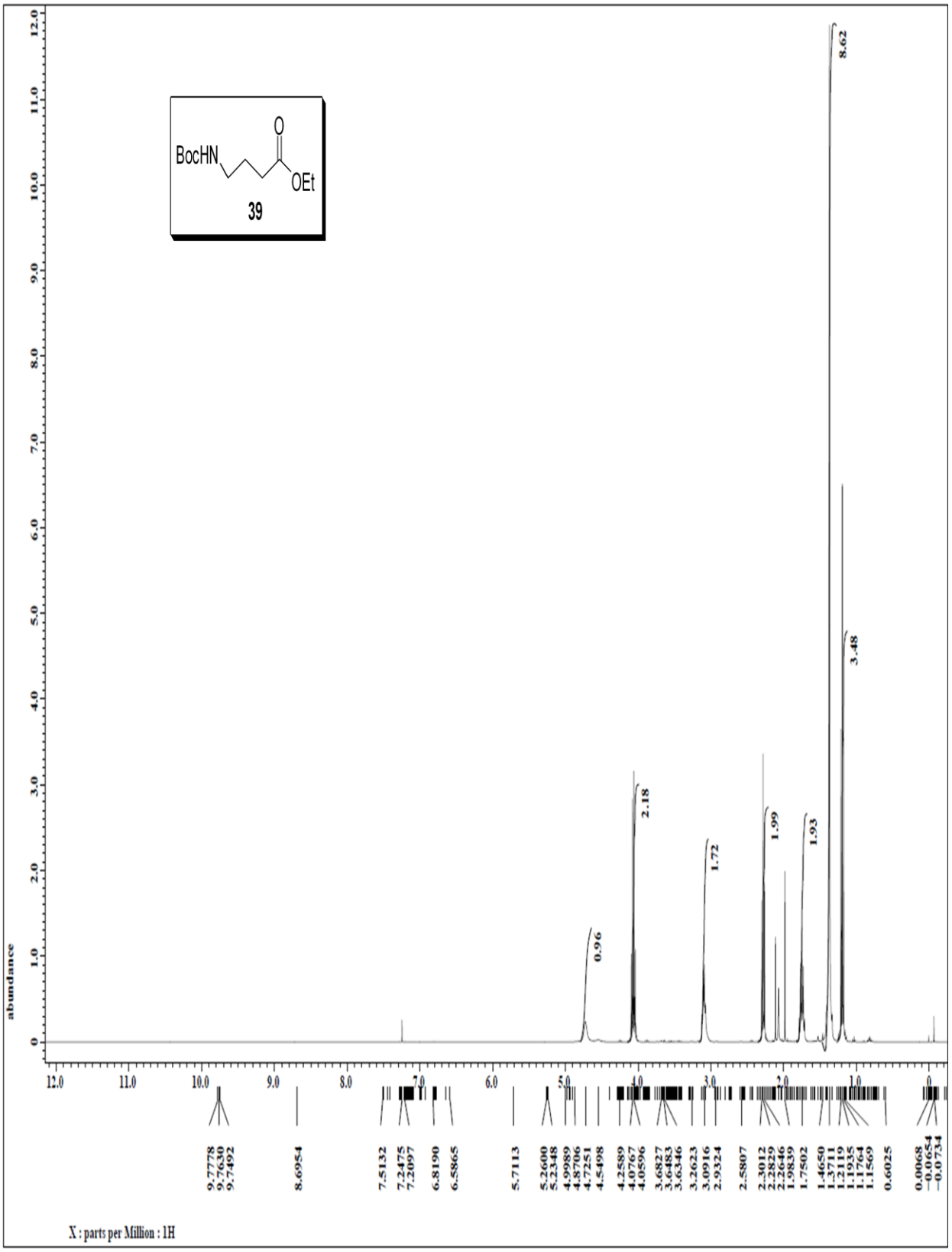
9. SPECTRA:

1. ^{1}H NMR spectra of **39.**
2. ^{1}H NMR spectra of **40**.
3. ^{1}H NMR spectra of **45**.
4. ^{1}H NMR spectra of **49**.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6.0
5.0
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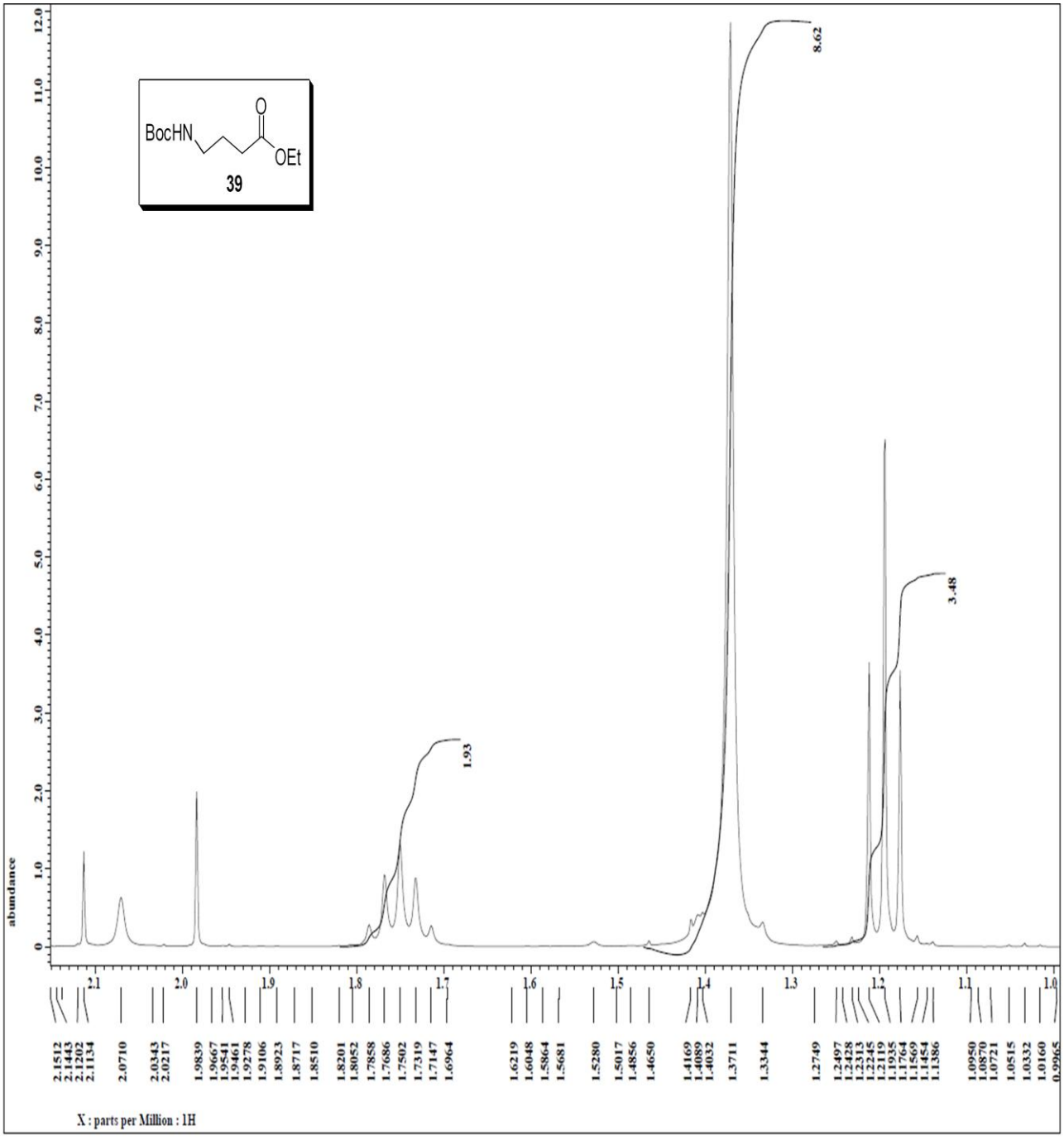
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abundance
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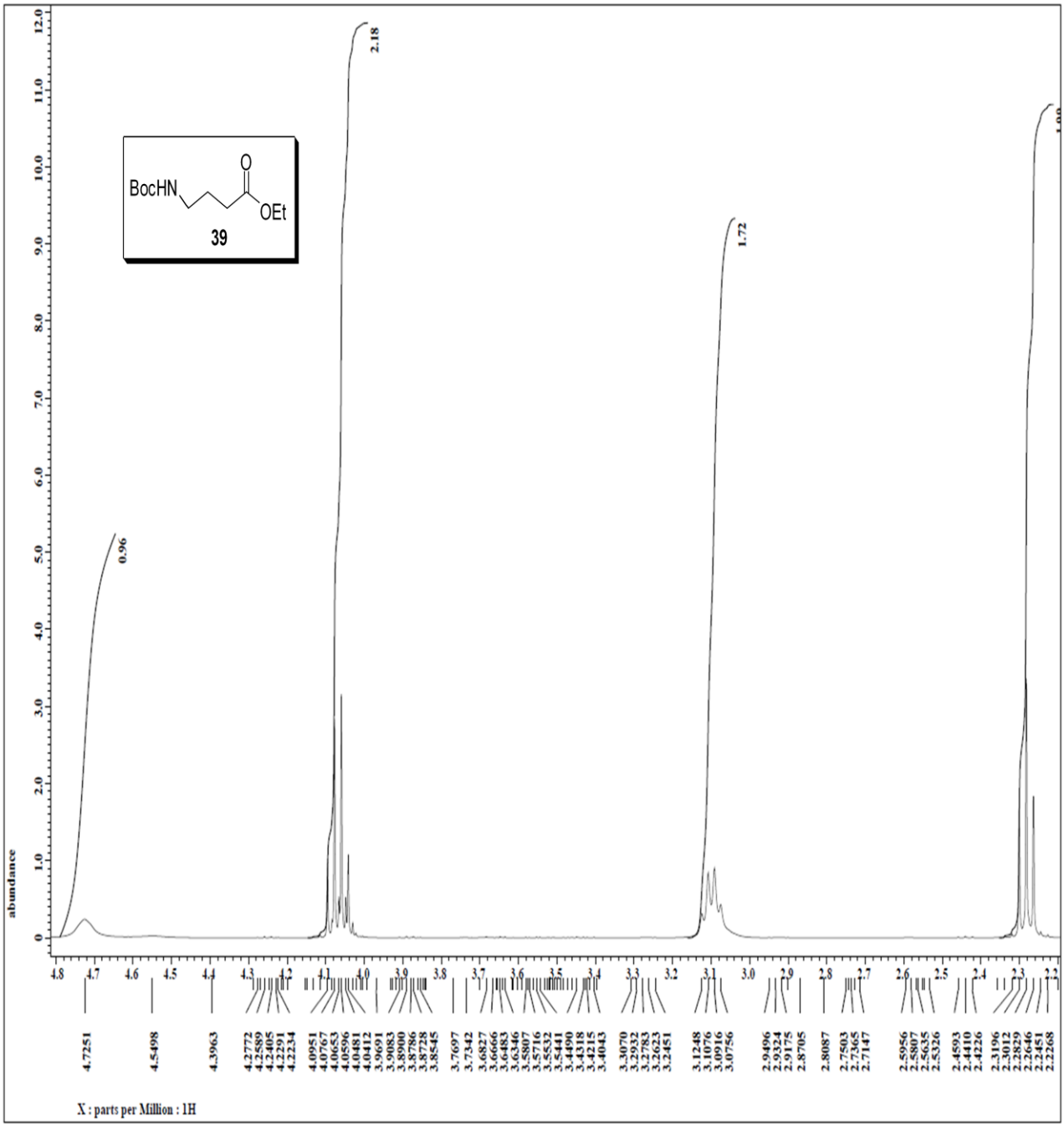
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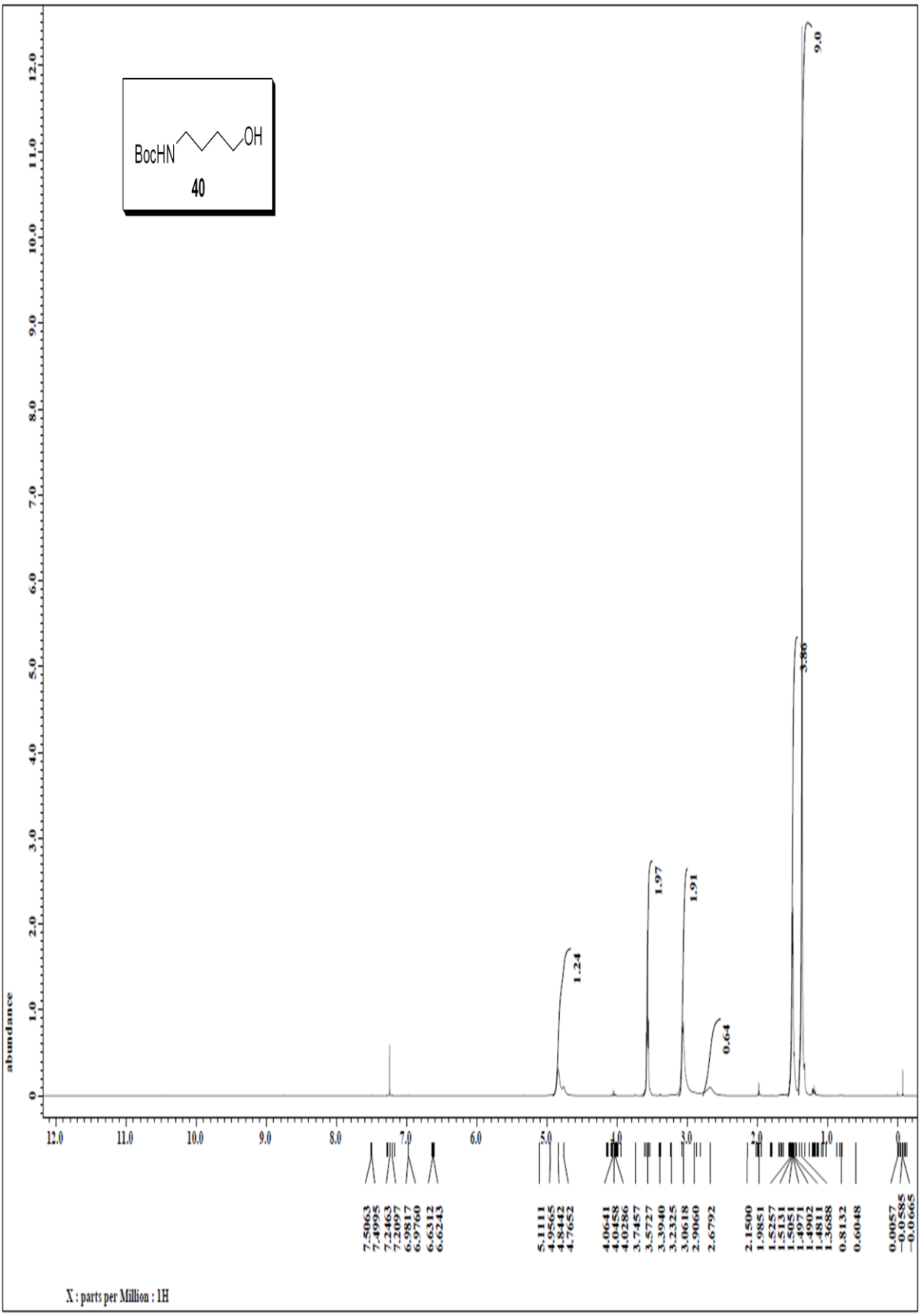
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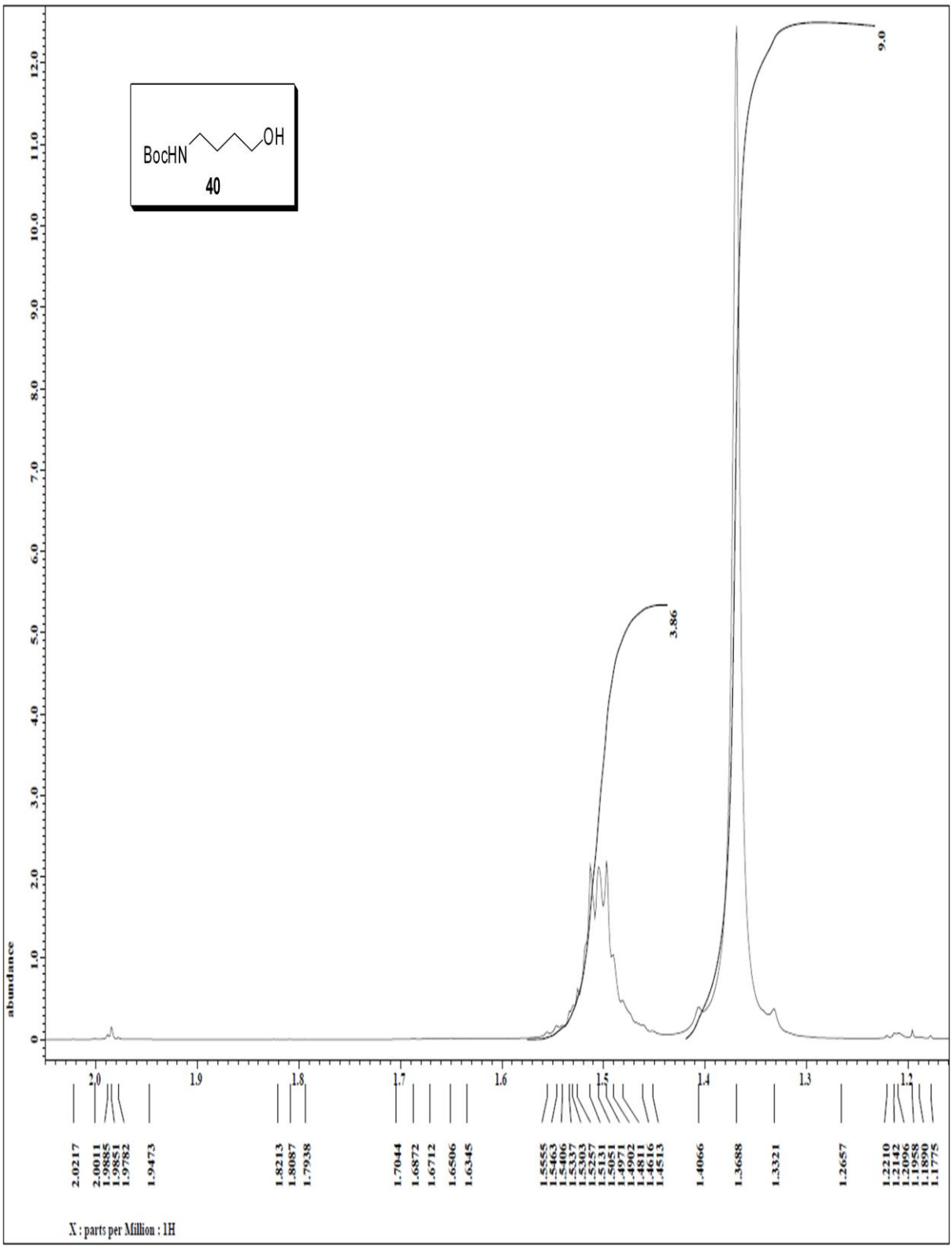
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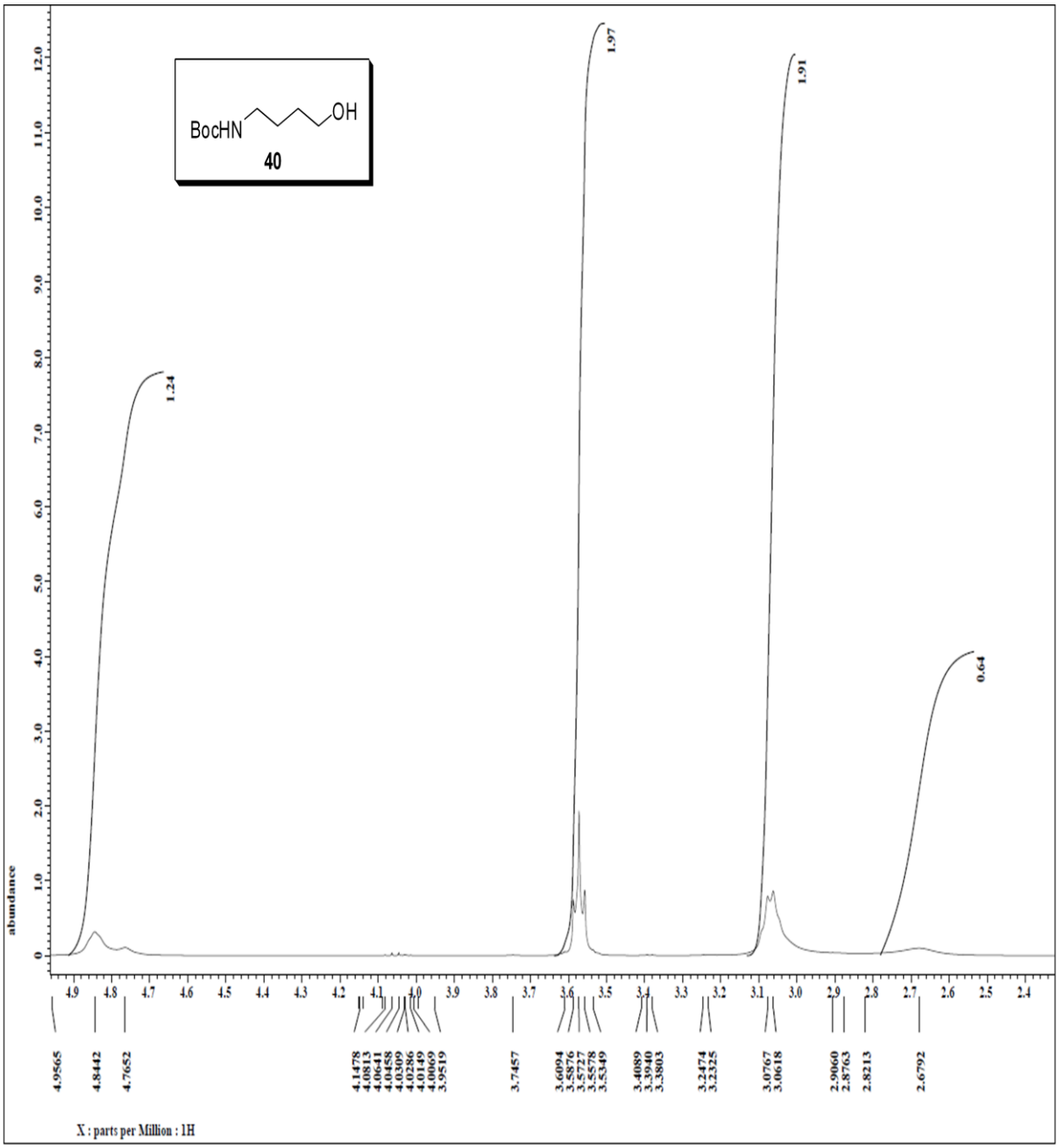
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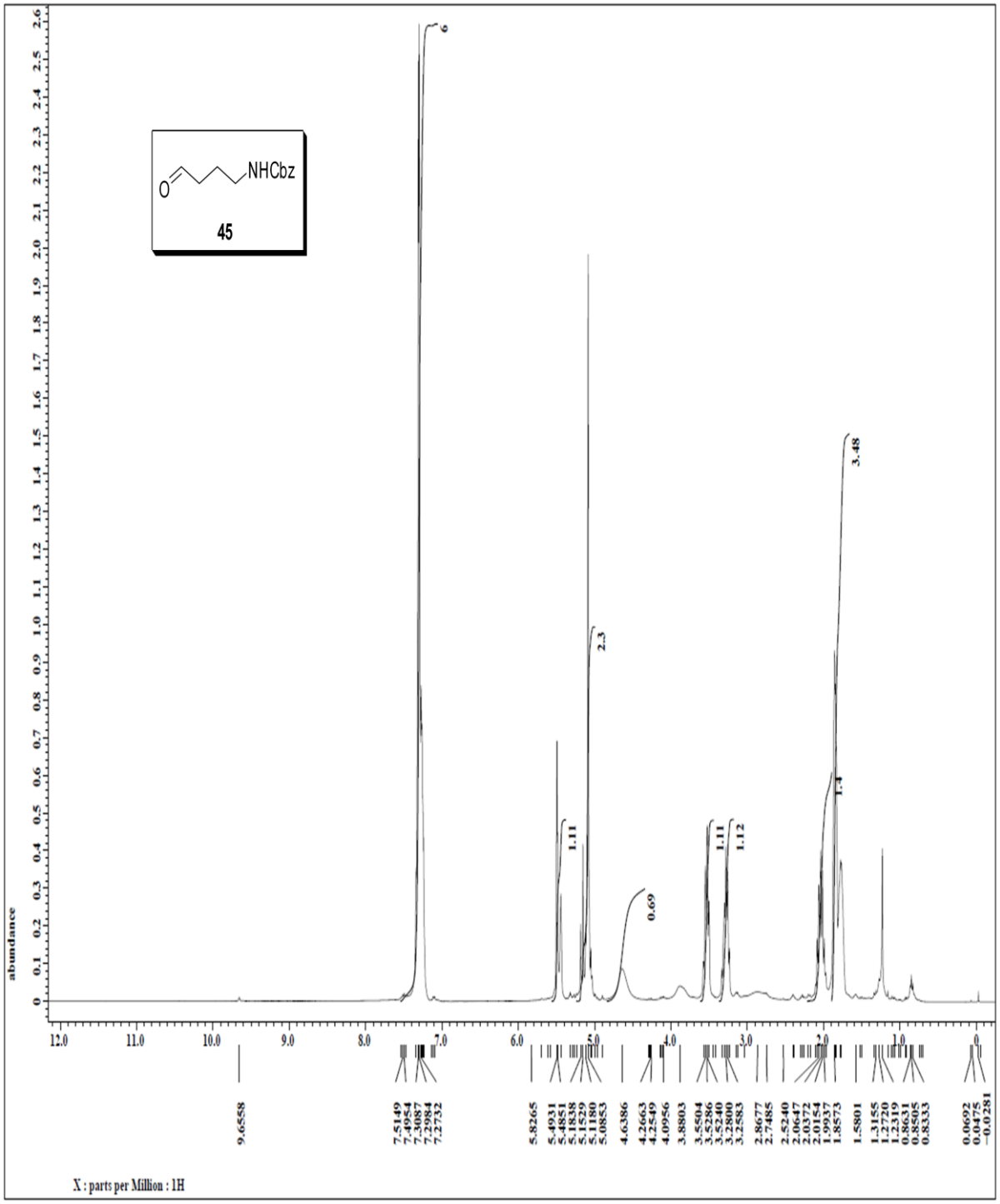
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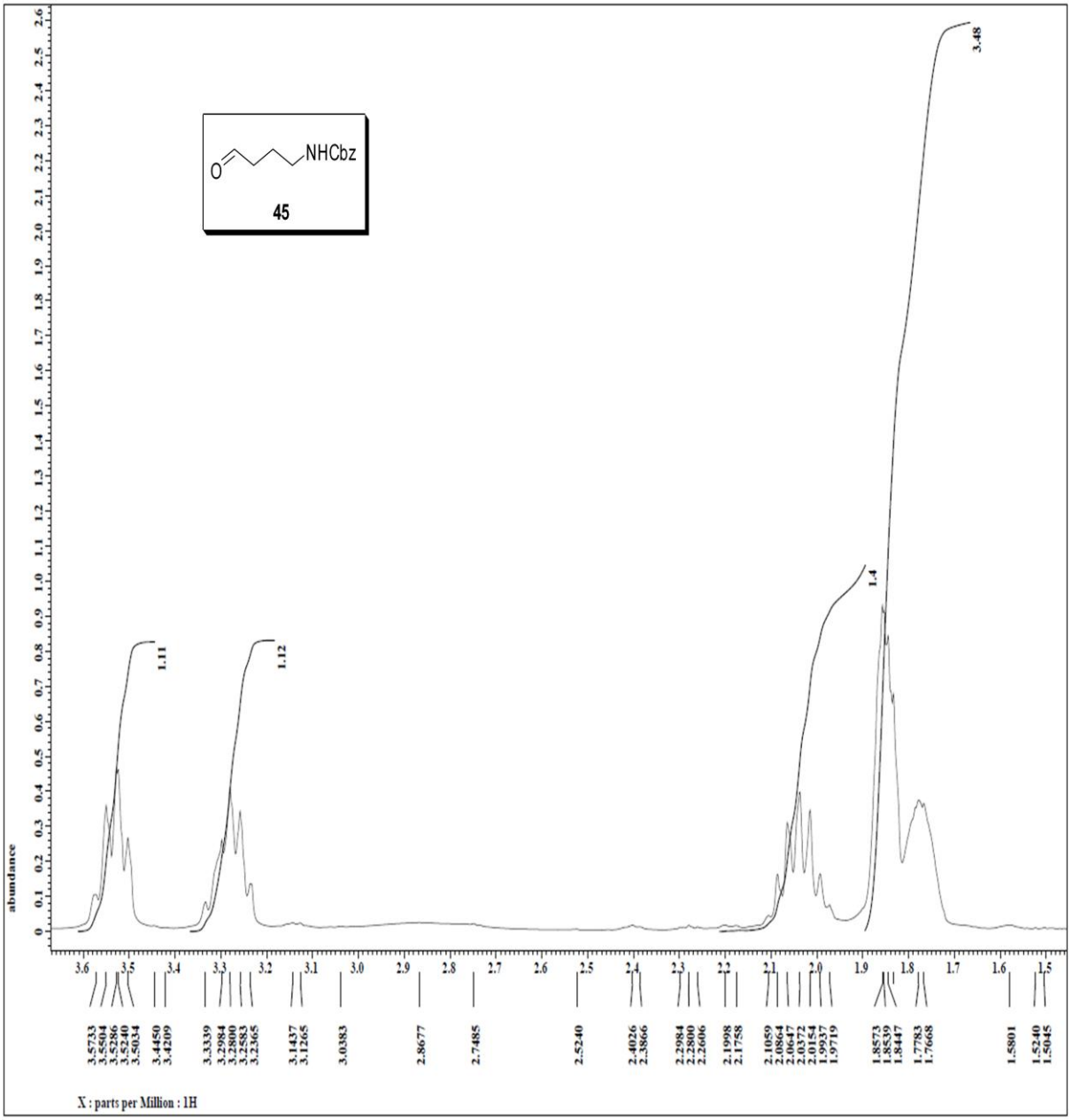
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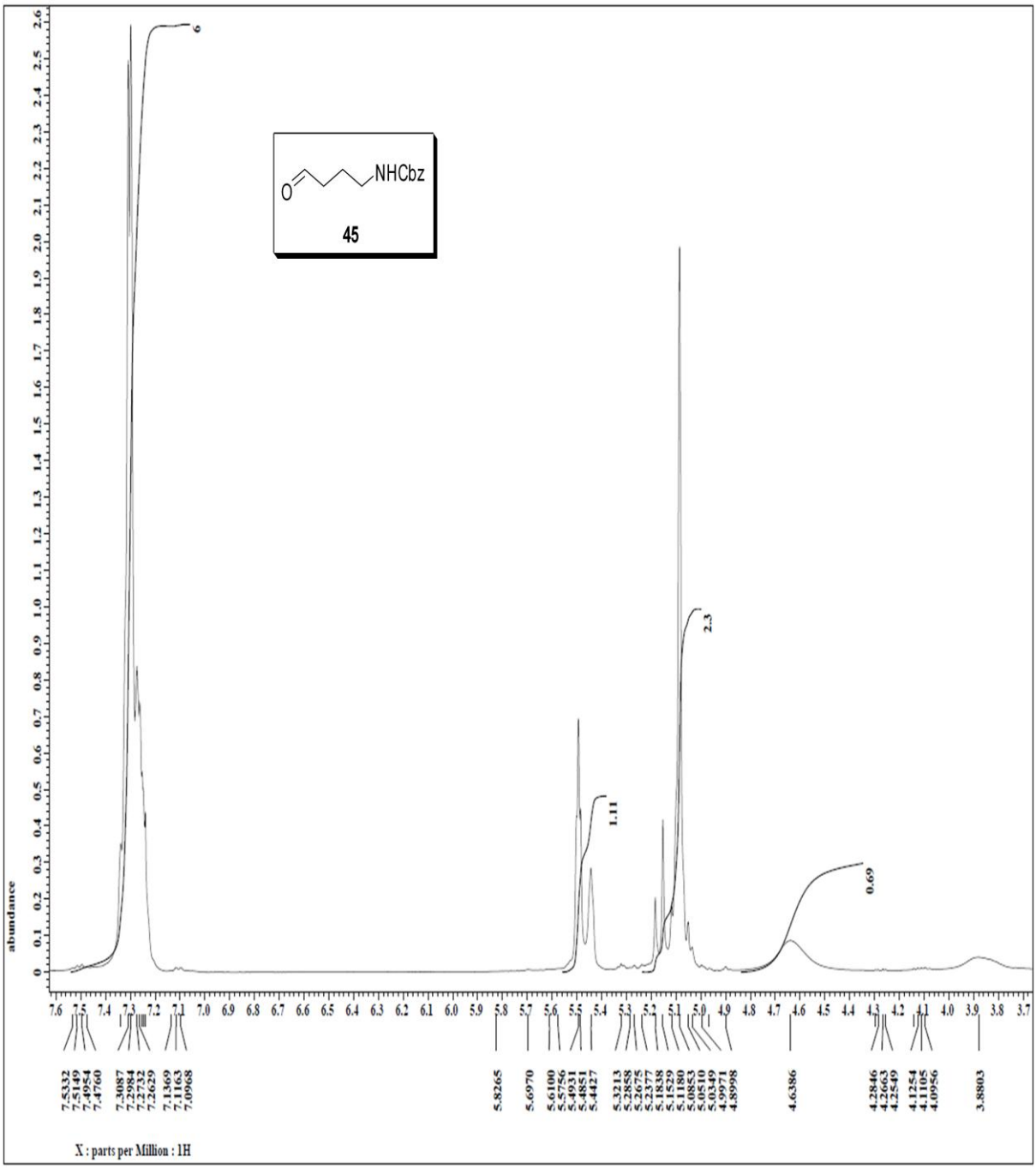
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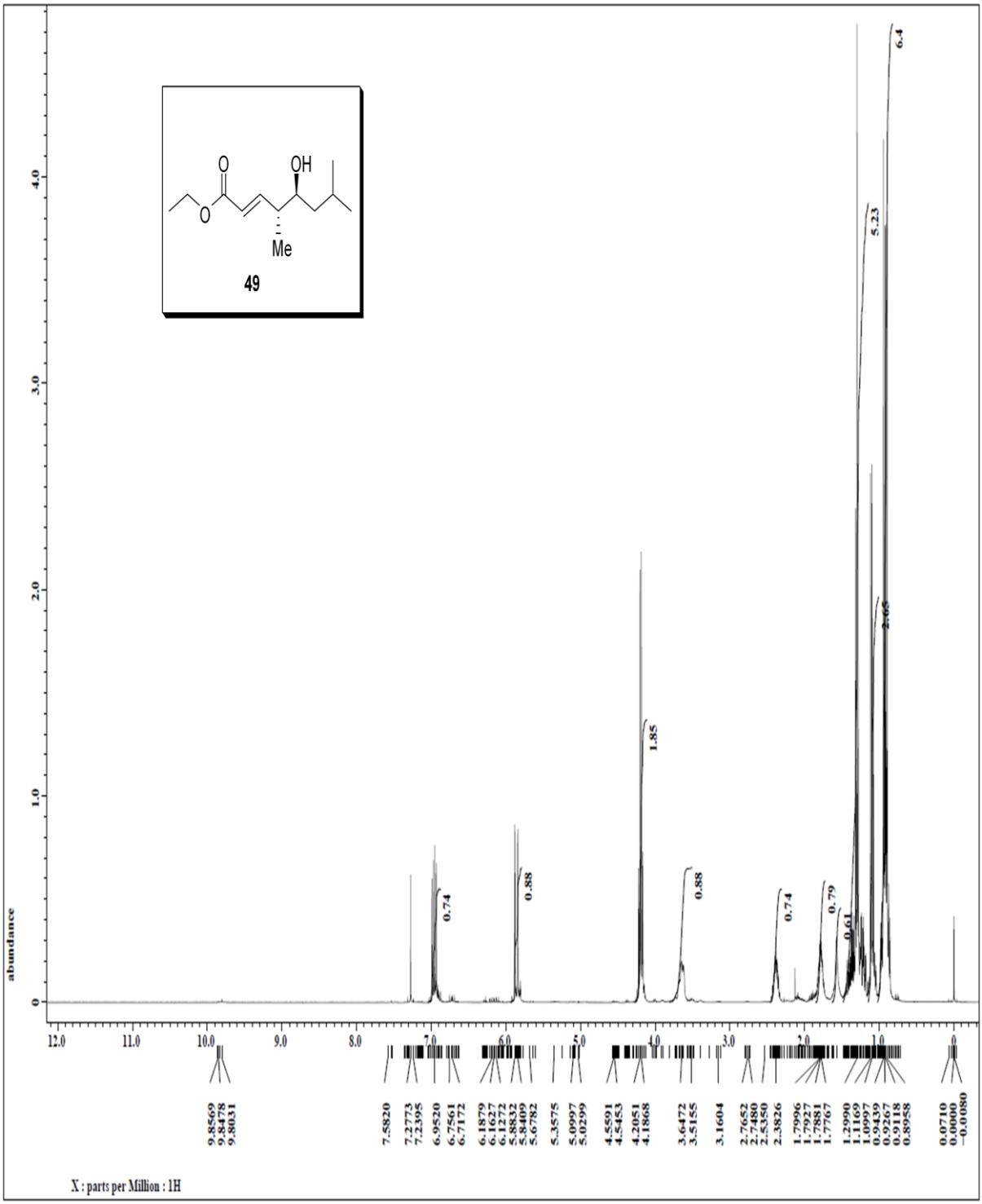
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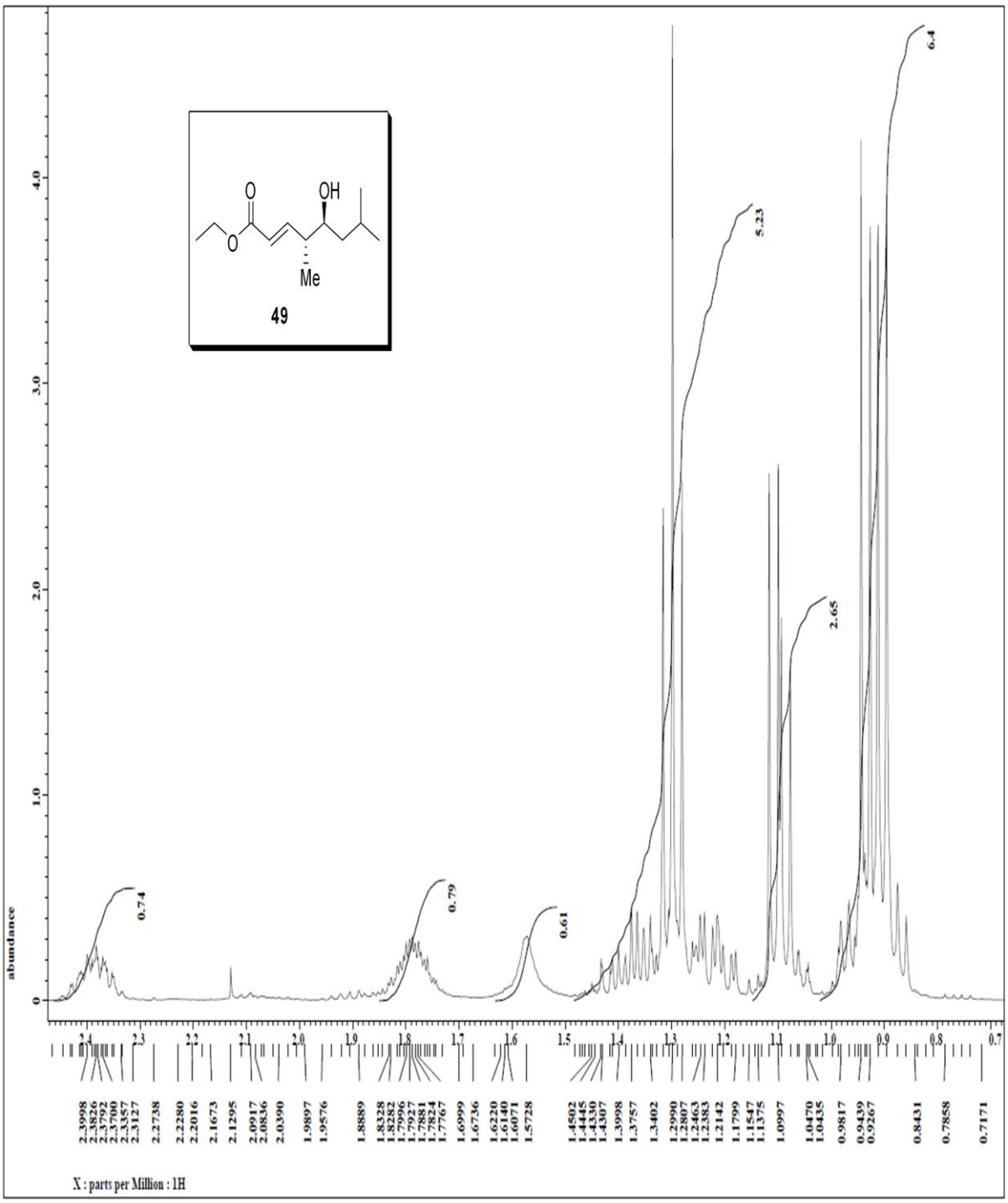
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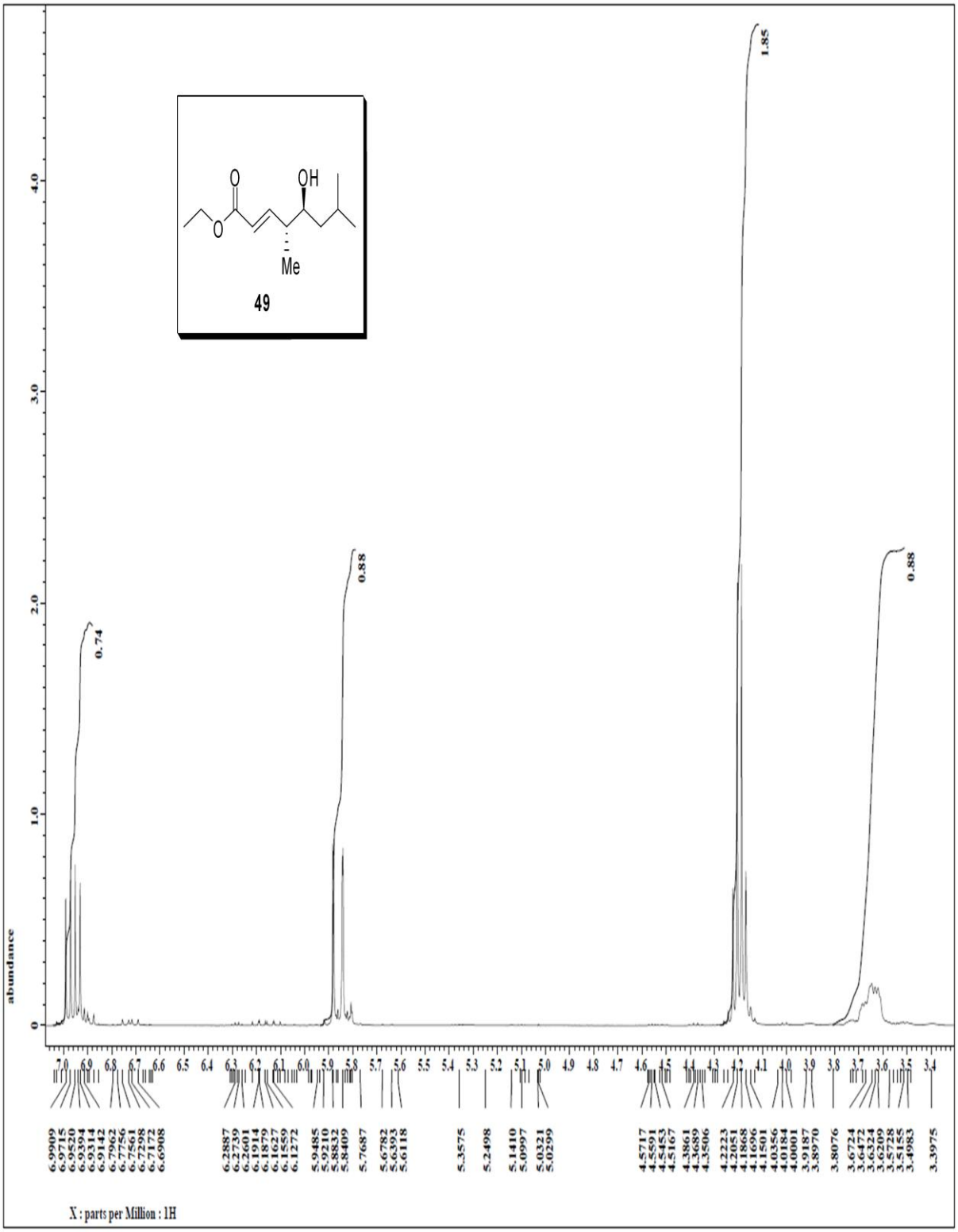
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