An Enantioselective Approach Towards the Total Synthesis of (-)-Heliotridane.

Thesis submitted in partial fulfilment of the requirements

For the award of the degree of

Masters of Science

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

2017

Certificate

This is to certify that the project entitled "***An Enantioselective Approach Towards the Total Synthesis of (-)-Heliotridane***" being submitted by Miss Amanpreet Kaur in the partial fulfilment of requirement for the award of the degree of Masters of Science in the School of Chemistry and Biochemistry, Thapar university, Patiala, is an original 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.

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Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled. "*An Enantioselective Approach Towards the Total Synthesis of (-)-Heliotridane*" in partial fulfilment 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 2017, 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.

Amanpreet Kaur

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Date: 13/7/17

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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Acknowledgement

This dissertation would not have been possible without the guidance and help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study.

First, and foremost, my gratitude to Dr. Satyendra Kumar Pandey, for his advice, supervision and crucial contribution which made him a backbone of this project work and so to this dissertation. The blessing, help and guidance given by him time to time shall carry me a long way in the journey of life on which I am about to embark.

A special word of appreciation for helpful and encouraging attitude of Dr. Amjad Ali. Head, School of Chemistry and Biochemistry for providing the necessary facilities.

My great sense of gratitude to Miss Amanpreet Kaur for her support and guidance throughout the research work. I am highly thankful to all my lab mates especially, Suraksha, Anju, Yuvraj Garg, Ramandeep Kaur and Ajay for providing helpful and cheerful environment during my project work.

I deeply appreciate the love, wishes and cooperation provided by Pooja Sharma and Bimal Kumar for the successful completion of this project. Words are not enough to express my feelings about my immense gratitude that I owe to my family (Mr. Parminder Singh and Mrs. Iqbal Kaur) and my brother (Mr. Harmanpreet Singh) for their blessings and moral support. I would like to express my heartiest thanks to my dear friend Kamaljeet Kaur for her support and wishes for the successful completion of this project. Last but not the least I am thankful to all the persons who helped me directly or indirectly during the tenure of my project work.

Above all, I am grateful to GOD, Almighty who sustain this amazing world and without whose grace and blessings anybody can ever succeed.

Amanpreet Kaur

LIST OF CONTENT

An Enantioselective Approach Towards the Total Synthesis of (-)-Heliotridane

1. Introduction

Pyrrolizidine alkaloids has gained great importance in recent years due to their significant biological activities like glycosidases inhibitors[1,2] and many other therapeutic uses. Pyrrolizidine alkaloids has the potential to be used as drugs for the treatment of cancer, viral infection and diabetes.[3] Necine bases are the main components of the biologically active pyrrolizidine alkaloids.[4] Australine **1** which has been isolated from *Castanospermum australe*[5] has the potential to act as an inhibitor for some glycoprotein-processing enzyme[6], fungal amyloglucosidase and shows anti-HIV activity.[7] (±)-Curassanecine **2** was isolated from glaucous fleshy herb *Heliotropium curassavicum*[8] and has similar physiological properties.[9]

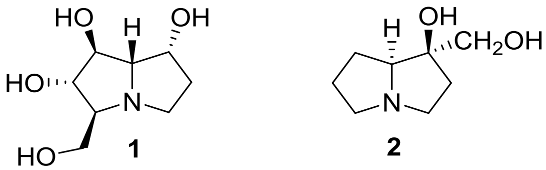

Figure 1. Structure of glycoprotein-processing enzyme inhibitors.

(-)-Isoretronecanol **3** isolated from *Planchonella*, *Heliotropium* and *Hammarbya species* and many other pyrrolizidine alkaloid derivatives like (-)-Petasinecine **4**, (-)-Rosmarinecine **5**, Isotussilagine **6**, Tussilagine **7** and Hastanecine **8** which has been isolated from natural plants possess promising pharmacological properties like as an insecticidal and fungicidal.[10]

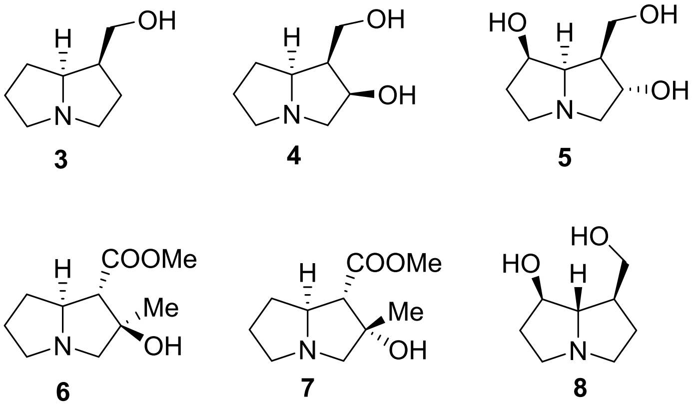

Figure 2. Structure of some naturally isolated pyrrolizidine alkaloids.

Optically active trifluorinated heliotridane **9** has very important role in medicinal and agricultural chemistry.[11] Fluorinated organic compounds are biologically more active then non fluorinated analogues this is because the bond strength of C-F bond (485 KJ mol^{-1}) is greater than C-H bond (416 KJ mol^{-1}) so fluorinated organic compounds are metabolically more stable. Fluorinated pyrollizidine alkaloids have increased membrane permeability, lipophilicity and they bind to the target molecule more strongly.[12]

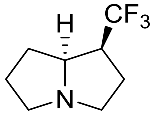

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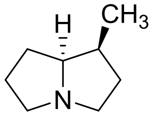
Figure 3. Structure of biologically active trifluorinated heliotridane.

The isolation of heliotridane **10** and pseudoheliotridane **11** has been done from many plant sources. Pseudoheliotridane **11** has been isolated from *Trachelanthus korolkovi*.[13] Heliotridane **10** has been isolated as the degradation product of variety of alkaloids found in *Heliotrofiiuna, Erechtites, Senecio, Crotalaria* and *Trichodesma genera*[14] have promising pharmacological properties like anticancer, antimitotic, immunostimulatory, cytotoxic.[15] In 1937, Men'shikov[16] and co-workers synthesized heliotridane **10** for the first time and characterized it as its picrate salt. Later Prelog and Zalan[17] in 1944 synthesized heliotridane **10** in five steps starting from γ-phenoxy-α-methylbutyronitrile and γ-ethoxypropyl bromide.



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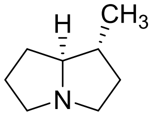

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Figure 4. Structure of Heliotridane and Pseudoheliotridane

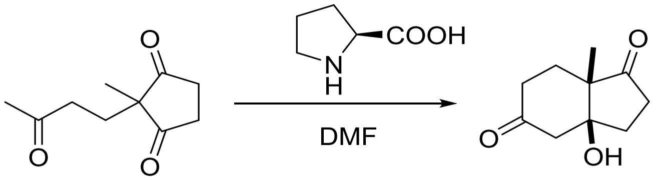
Due to the shortage of natural resources available for the isolation of pyrrolizidine alkaloids, and structural diversity among pyrrolizidine alkaloids, they attracted the researchers to synthesize these pyrrolizidine alkaloids and their related compounds in the laboratory. The main aim of our research programme was to synthesize pyrrolizidine alkaloid (-)-heliotridane **10** because of its unique structure and attractive biological properties.

1.1 L-Proline catalyzed asymmetric aldol reaction

Aldol reaction results in the formation of new C-C bonds. It involves the reaction between the two same carbonyl compound (self aldol condensation) or between two different carbonyl compounds (crossed aldol condensation) which results in the formation of a new *β*-hydroxy carbonyl compound, the product of the reaction is referred as aldol. The aldol product once formed can loose the water molecule to form *α, β*-unsaturated carbonyl compounds.

To perform aldol reaction asymmetrically is the major task, although this problem has been sligtly overcome by using asymmetric catalyst. One remarkable molecule that can overcome the upcoming challenge to catalyze direct aldol addition asymmetrically is Proline. Proline is a cyclic, pyrrolidine based, secondary amino acid which plays a very important role in various catalytic strategies such as homogeneous and heterogeneous catalysis, enantioselective catalysis, acid-base catalysis, and biocatalysis. Proline plays a crucial role in various powerful asymmetric transformations such as Mannich, aldol and Micheal reactions[18].

Hajos-Parrish-Eder-Sawer-Wiechert cyclization was the first Proline catalyzed direct asymmetric intramolecular aldol reaction discovered in 1971[19-20] as shown in Scheme 1.



Scheme 1: Hajos-Parrish-Eder-Sawer-Wiechert reaction

Recently, studies by Shibasaki,[21-22] Barbas[23-24] and Trost[25-26] have summarized the examples of Proline catalyzed enantioselective direct Aldol reaction in which the pre-generation of enolates is not required. The mechanism of Proline catalyzed asymmetric aldol reaction is shown in Figure 5. Firstly, there is the formation of enamine which is the slowest and the rate determining step, followed by the formation of iminium ion by the addition of the carbonyl compound. Aldol product is formed by the hydrolysis of iminium ion.

Amino acid Proline results in the formation of products with high enantio-, diastereo- and regioselectivities.

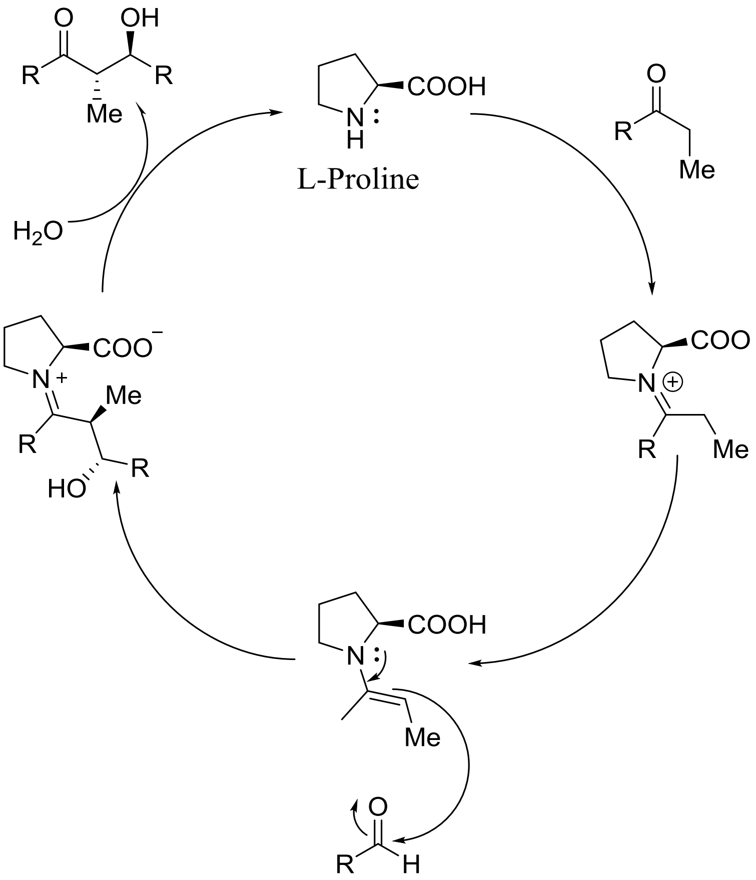


Figure 5. Mechanism of proline catalyzed asymmetric aldol reaction.

Significant features of Proline catalyzed asymmetric aldol reaction are:

1. Proline is cheap, biodegradable and its both enantiomeric forms are readily available.

2. Protonation or pre-generation of enolates in carbonyl substrates is not required.

3. Due to the presence of bifunctional groups (amine group and carboxylic group) it can act both as a base or as a acid.

4. Heating or refluxing is not required as the reaction can be carried out at room temperature.

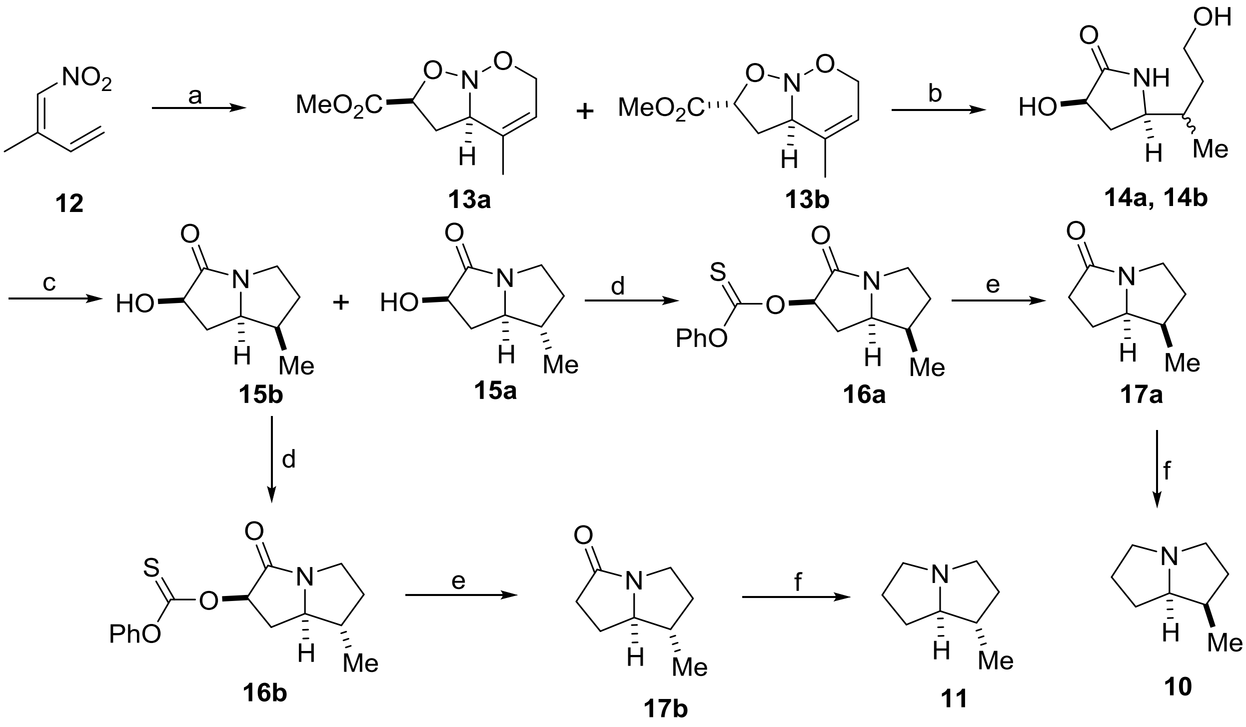
5. Aqueous extraction helps in the easy recovery of the catalyst as the Proline amino acid is highly water soluble.

2. Review of literature:

2.1 Koc, E. *et al.* (2017)[14]

Koc and co-workers synthesized heliotridane **10** and pseudoheliotridane **11** in six steps starting from an acyclic nitrodiene **12**. The starting material **12** was synthesized from isoprene in four steps by a known procedure.[27]

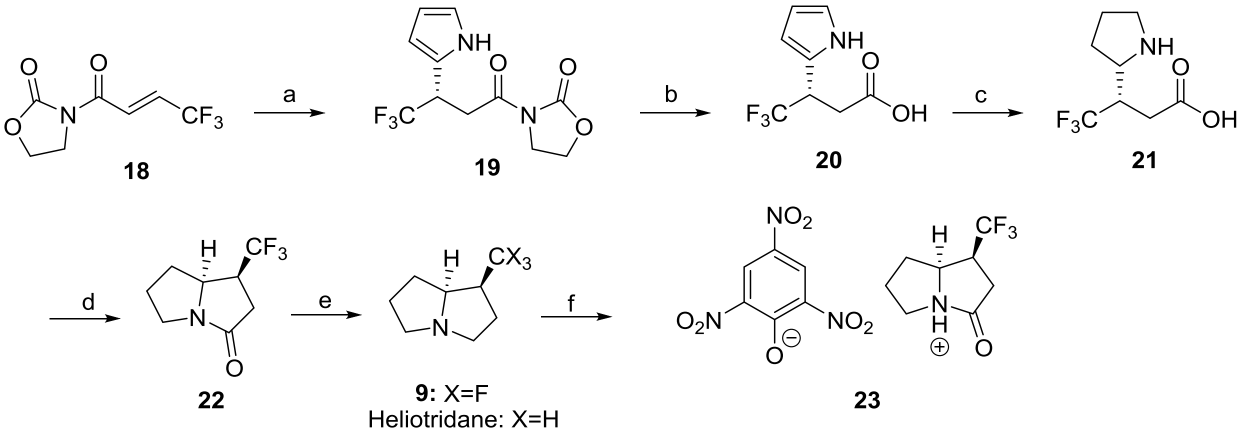
On heating **12** with methyl acrylate in the presence of hydroquinone monomethyl ether (MeHQ) and $NaHCO_3$ furnished **13a** and **13b** diastereoisomers. Hydrogenation of **13b** with raney Ni in the presence of H_2 produced isomeric mixture of the lactam alcohol **14a** and **14b**. Mitsunobu reaction of **14** in the presence of ADDP and tri-*n*-butylphosphine furnished pyrrolizidinones **15a** and **15b** in 90% yield. **15a** and **15b** were converted to separable thionocarbonates **16a** and **16b** by using phenylchlorothionocarbonate and 4-DMAP. Treatment of **16a** and **16b** with AIBN and tributyltin hydride gave lactams **17a** and **17b** respectively. **17a** and **17b** undergo reduction in the presence of LAH to produce heliotridane **10** (24%) and pseudoheliotridane **11** (7%), respectively.



Scheme 1: *Reagent and conditions*: (a) Methyl acrylate, MeHQ, $NaHCO_3$, DCE, 90 ^{o}C, 18 h, 81%; (b) Raney Ni, H_2, MeOH, 200 psi, rt, 18 h, 83%; (c) ADDP, Bu_3P, THF, 0 ^{o}C to rt, 24 h, 90%; (d) Phenyl chlorothionoformate, DMAP, CH_3CN, rt, 2.5 h; (e) AIBN, Bu_3SnH, benzene, reflux, 2.5 h, 83%; (f) $LiAlH_4$, THF, 65 ^{o}C, sealed tube, 6.5 h.

2.2 Huang, Y. *et al.* (2010)[28]

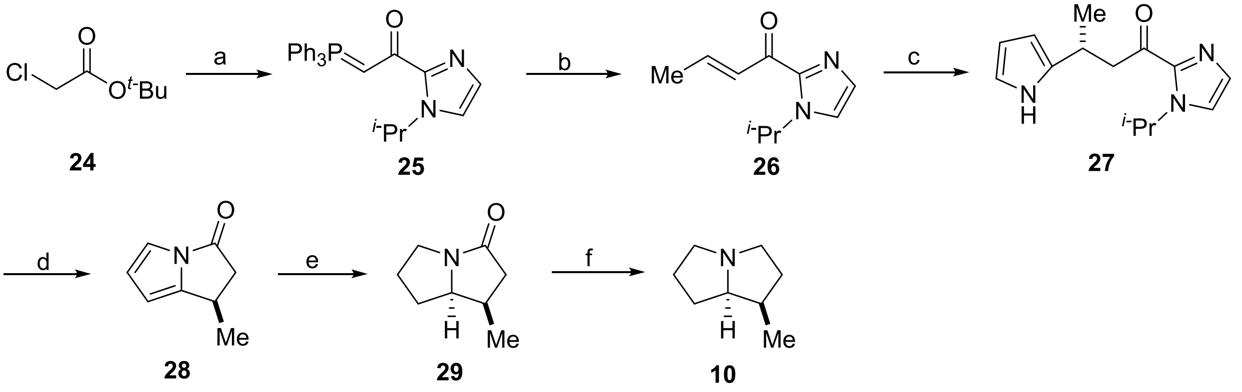
Huang and co-workers used Friedel-crafts reaction to synthesize optically active trifluorinated heliotridane. They explored the reactivity of **18** as the nucleophilic acceptor, on reacting **18** with unprotected pyrrole in the presence of (*R*,*R*)-4,6-dibenzofurandiyl-2,2-*bis*(4-phenyloxazoline) as a catalyst obtained the product **19** in 97% yield. By the action of NaOH in THF carboxylic acid **20** was obtained from the Friedl craft reaction adduct **19** in 80% yield. Carboxylic acid **20** was reduced to 2-pyrrolidine carboxylic acid **21** in the presence of H_2, and rhodium as a catalyst. Cyclised product **22** was obtained from **21** on heating under reflux in the presence of *tris*(1,3-dihydro-2-oxobenzoxazolin-3-yl) phosphine oxide, then, **22** was reduced in the presence of $LiAlH_4$ to produce volatile trifluorinated heliotridane **9** which was isolated as its picrate **23.**



Scheme 2: *Reagent and conditions:* (a) (*R*,*R*)-4,6-dibenzofurandiyl-2,2-bis(4-phenyloxazoline), $Zn(NTf_2)_2$, 4A^{o} MS, CH_2Cl_2, -75 ^{o}C, 24 h, 97%; (b) i) 1N NaOH, THF, rt, 1 h, ii) 1N HCl, 80%; (c) H_2 (10 atm), 5% Rh-Al_2O_3, EtOH, rt, 24 h; (d) *tris*(1,3-dihydro-2-oxobenzoxazolin-3-yl) phosphine oxide, Et_3N, CH_3CN, reflux, 80 ^{o}C, 6 h, 30%; (e) $LiAlH_4$, Et_2O, 35 ^{o}C, 6 h, 54%; (f) picric acid, Et_2O, rt, 1 h, 35%.

2.3 Evans, D. A. *et al.* (2006)[29]

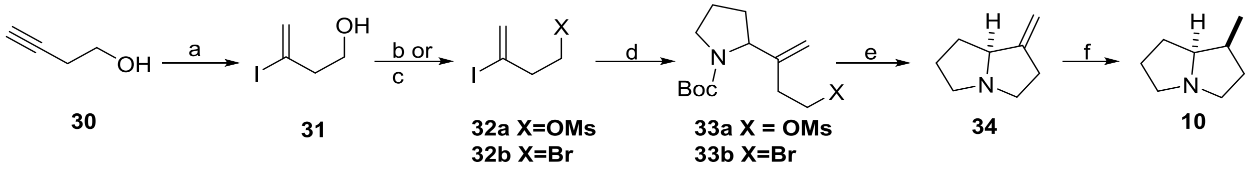
Evans and co-workers used 2-acyl imidazole cleavage and cyclization for the synthesis of heliotridane **10**. *α, β*-unsaturated 2-acyl imidazole **26** was obtained in two steps. Firstly, wittig reagent **25** was prepared starting from *tert*-butyl chloro-acetate **24**. On reacting **25** with acetaldehyde via Wittig olefination reaction they obtained **26** in good yields. The compound **26** on reaction with pyrrole in the presence of *bis*(oxazolinyl) pyridine-scandium (iii) triflate complex furnished **27** (99%). Imidazole cleavage of **27** occurs in the absence of an external nucleophile, internal acylation of pyrrole nitrogen took place to give 2, 3-dihydro-1*H*-pyrrolizine **28**. Reduction of **28** in the presence of H_2, and rhodium as a catalyst produce **29** which further on reduction in the presence of LAH furnished heliotridane **10** in 97% yield.



Scheme 3: *Reagent and conditions:* (a) i)1-*iso*-propyl-1*H*-imidazole, THF, dry ice/acetone bath, 30 min, *n*-BuLi; ii) PPh_3, benzene, reflux, 15 h; (b) CH_3CHO, benzene, rt to reflux, 15-18 h; (c) 5 mol% of bis(oxazolinyl) pyridine-scandium (III) triflate complex, CH_3CN, pyrrole, $4A^o$ MS, -40 ^oC, 16 h, 91%; (d) CH_3CN, MeOTf, Hunig's base, rt, 2 h, 99%; (e) H_2 (1 atm), 5% Rh-Al_2O_3, rt, 19 h; (f) i) $LiAlH_4$, 65 ^oC, 6.5 h; ii) $Na_2SO_4.10H_2O$, rt, 12.5 h, 97%.

2.4 Dieter, R. K. *et al.* (2002)[30]

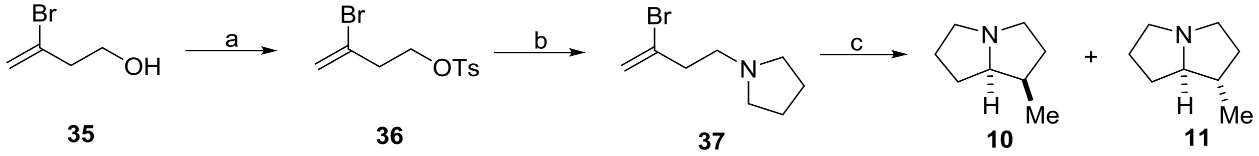
Dieter, R. K. and co-workers used *α*-(*N*-carbamoyl) alkylcuprate chemistry for the synthesis of Heliotridane **10**. They proposed synthesis of heliotridane **10** from alkynyl alcohol **30.** Firstly, alkynyl alcohol **30** was treated with HI prepared in situ forming hydroxyl vinyl iodide **31** which is then converted into mesyl **32a** and bromide **32b** derivatives. N-Boc protected pyrrolidinyl cuprate intermediate generated by the addition of CuCN.2LiCl was successfully converted to vinylation product **33a** and **33b**, which on N-Boc deprotection and cyclisation in the presence TMSOTf produced **34**. Reduction of **34** in the presence of H_2, Pd/C afforded heliotridane **10**.



Scheme 4: *Reagent and conditions:* (a) MeSiCl, NaI, CH_3CN, H_2O, 25 ^{o}C; (b) i) MsCl, Et_3N, CH_2Cl_2, -40 ^{o}C; ii) $NaHCO_3$, Et_2O; (c) LiBr, DMF, reflux, 1 h; (d) i) N-Boc protected pyrrolidine, *sec*-BuLi, THF, TMEDA, -78 ^{o}C, 1.25 h; ii) CuCN.2LiCl, -78 ^{o}C, 1 h; (e) TMSOTf, CH_2Cl_2, under Ar, -20 to 25 ^{o}C, 12 h, 92%; (f) H_2, Pd/C (10%), CH_2Cl_2, 12 h, 99%.

2.5 Robertson, J. *et al.* (1996)[31]

Robertson, J. and co-workers prepared heliotridane **10** and pseudoheliotridane **11** by 5-exo-trig cyclisation of **37** which is prepared from alcohol **35** in two steps. Firstly the alcohol **35** undergo tosylation to give **36** followed by substitution with pyrrolidine to yield **37**. Further, compound **37** undergo 5-exo-trig cyclisation to furnish heliotridane **10** and pseudoheliotridane **11** in good yields.



Scheme 5: *Reagent and conditions:* (a) TsCl, pyridine, rt, 74%; (b) pyrrolidine, PhH, reflux, 59%; (c) Bu_3SnH, AIBN, PhH, reflux, 3 h, then PhSH, rt, 67%.

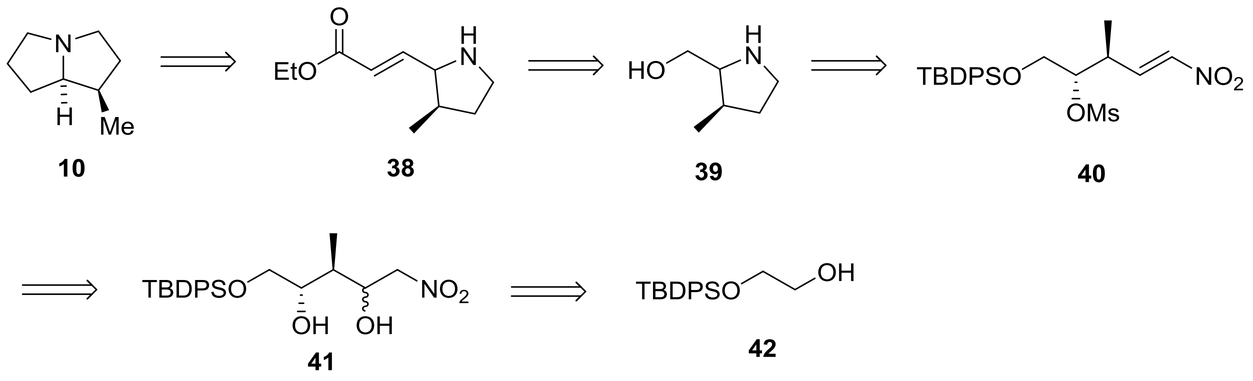
3. Present work

3.1 Objective:

Various synthetic routes for the synthesis of (-)-heliotridane **10** have been reported in literature. Despite the existence of efficient chemistry routes, synthesis of (-)-heliotridane **10** requires cost effective strategy, strong stereochemical approach and reduction in total number of steps leading to high yields. Herein, we wish to report efficient and short synthetic approach for the synthesis of (-)-heliotridane **10** using Swern oxidation, the remarkable catalytic activity of L-proline in the stereoselective formation of cross aldol product and Henry reaction as the key steps.

3.2 Retro synthetic approach:

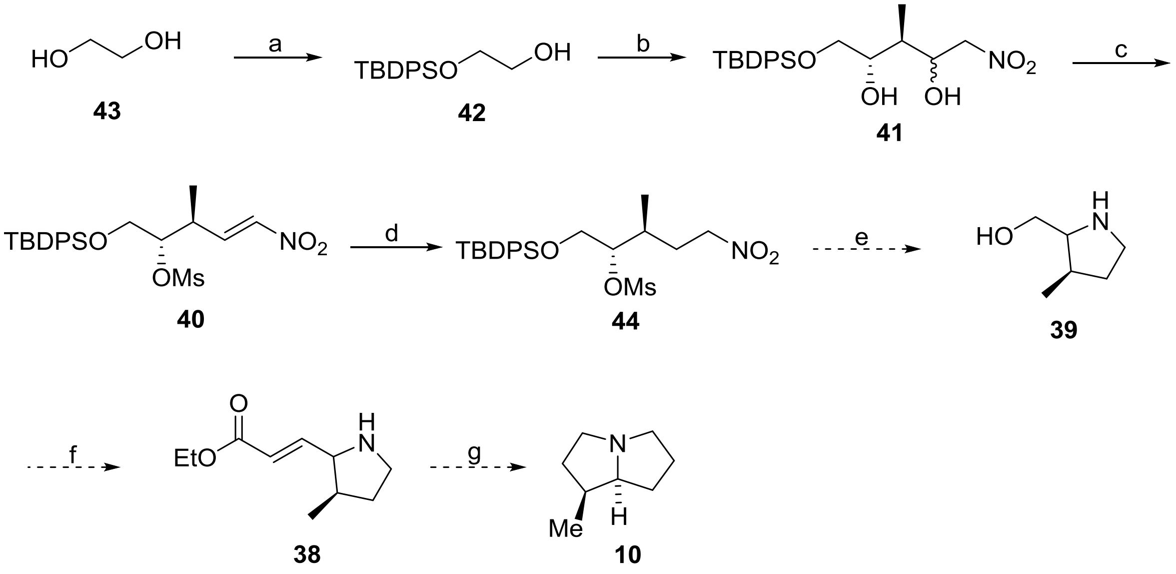
The retrosynthesis of (-)-heliotridane **10** is shown in Scheme 6. (-)-Heliotridane **10** could be efficiently prepared from pyrrolidine acrylate **38** through reduction followed by cyclisation. Pyrrolidine acrylate **38** could be synthesized from pyrrolidine alcohol **39** via oxidation followed Wittig olefination. Compound **39** could be easily accessed from **40** by reduction followed by cyclisation of the resultant amine. The *α, β*-unsaturated nitroalkene **40** could be obtained from diastereoisomeric nitro alcohol **41** through *O*-mesylation and dehydration of alcohol. The diol **41** could be obtained from the aldehyde of silyl protected alcohol **42** via L-proline catalysed cross aldol coupling with propionaldehyde, followed by Henry reaction of resultant aldehyde.



Scheme 6: Retrosynthetic approach for the synthesis of (-)-heliotridane.

4. Results and discussion

The synthetic sequence for the synthesis of (-)-heliotridane **10** was initiated from commercially available ethylene glycol **43** as shown in Scheme 7. Ethylene glycol **43** on treatment with DIPEA and TBDPSCl furnished *tert*-butyldiphenyl silyl monoprotected alcohol **42** with 96% yield. With the pure **42** in hand, we subjected it to Swern oxidation with oxalyl chloride, DMSO and Et_3N in DCM to furnish TBDPS protected aldehyde as an intermediate, which without further purification, was subjected to asymmetric cross aldol reaction with propionaldehyde in the presence of L-Proline to give cross aldol aldehyde intermediate which again without further purification, was exposed to Henry reaction in the presence of nitromethane, aqueous NaOH to furnish nitroalcohol **41** as a nonseparable mixture of diasteroisomers. Nitroalcohol **41** was then subjected to dehydration in the presence of Et_3N, MsCl to obtain *α, β*-unsaturated monosilylated nitroalkene **40** with 87% yield. With the pure olefin **40** in hand, it was subjected to hydrogenation in the presence of $Pd(OH)_2$ in MeOH to yield nitroderivative **44** in 92% yield.

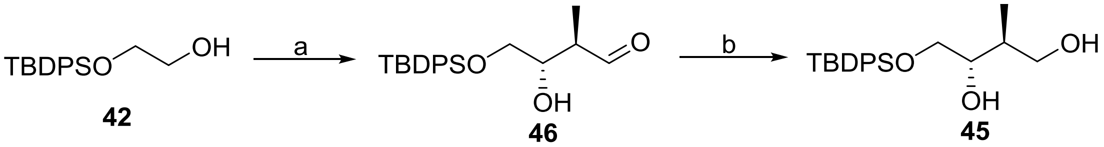


Scheme 7: *Reagent and conditions*: (a) TBDPSCl, DIPEA, DMF, rt, 24 h, 96%; (b) (i) Oxalyl chloride, DMSO, Et_3N, DCM, -78 ^oC to rt, 1 h, (ii) propionaldehyde, L-Proline, dioxane, 4 ^oC, 48 h, (iii) CH_3NO_2, *aq*. NaOH, MeOH, 0 ^oC to rt, 1 h, 85%; (c) MsCl, Et_3N, DCM, 1.5 h, 0 ^oC to rt, 87%; (d) $Pd(OH)_2$, MeOH, 12 h; (e) (i) Zn, AcOH, CH_2Cl_2, (ii) TBAF, THF; (f) (i) Oxalyl chloride, DMSO, Et_3N, DCM, -78 ^oC to rt, (ii) triphenylphosphine (Wittig reagent), THF, rt; (g) (i) $LiAlH_4$, THF; (ii) MsCl, Et_3N, DCM, 0 ^oC to rt.

In the ^{1}H NMR of **42** aromatic protons were found resonating at δ 7.68-7.66 (m, 4H), 7.44-7.37 (m, 6H). A triplet corresponding to methylene proton adjacent to TBDPSO was found resonating at δ 3.76 (t, J = 4.4 Hz, 2H), a multiplet due to the methylene proton adjacent to OH group gave a signal at δ 3.68-3.67 (m, 2H) while a singlet corresponding to hydroxyl proton was observed at δ 2.154 and a sharp singlet found at δ 1.07 (s, 9H) corresponding to the *tert*-butyl's methyl proton. In the ^{13}C-NMR spectrum the aromatic carbons of diphenyl group were observed resonating at δ 135.5, 129.7, 127.7. Two methylene carbon were resonating at δ 64.9, 63.6, while signals at δ 26.8 and 19.2 corresponds to the carbons of *tert*-butyl group.

In the ^{1}H NMR spectrum of **40** aromatic protons were observed at δ 7.65-7.61 (m, 4H), 7.47-7.40 (m, 6H). The alkene proton were found resonating δ 7.17-7.12 (m, 1H), δ 6.92 (d, J = 13.6 Hz, 1H) confirming the formation of the product. A quartet was observed at δ 4.70-4.66 (q, J = 5.2 , 10.4 Hz, 1H) due to the proton adjacent to methyl sufonate group. Two multiplets found resonating at δ 3.84-3.83 (m, 1H), 3.71-3.68 (m, 1H) corresponds to the two protons adjacent to TBDPSO. A sharp singlet of methyl proton of methanesulfonate was observed at δ 2.97 (s, 3H). A multiplet due to proton adjacent to methyl group was observed at δ 1.28-1.25 (m, 1H). A doublet was observed due to methyl proton at δ 1.22-1.21 (d, J = 6.8 Hz, 3H). A sharp singlet was observed due to *tert*-butyl's methyl proton at δ 1.06 (s, 9H). In the ^{13}C-NMR spectrum the characteristic peaks are observed at δ 141.2, 135.5, 128.0, 83.5, 63.1, 38.6, 35.2, 26.7, 19.1, 14.5 ppm.

In the ^{1}H NMR spectrum of **44** the ten aromatic protons showed their characteristic peaks at their respective positions. The absence of olefinic protons showed the formation of the product. The signals due to methanesulfonate group, methylene protons and *tert*-butyl group of TBDPSO were found resonating at their respective positions. The characteristic peaks in ^{13}C- NMR were observed at δ 135.5, 127.9, 86.2, 73.3, 63.3, 38.6, 31.7, 29.0, 26.7, 19.1, 15.4 ppm.



Scheme 8: *Reagents and conditions*: (a) (i) Oxalyl chloride, DMSO, Et_3N, DCM, -78 ^{o}C to rt, 1 h, (ii) propionaldehyde, L-Proline, dioxane, 4 ^{o}C, 48 h; (b) $NaBH_4$, MeOH, 0 ^{o}C, 30 min.

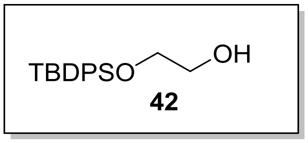
The formation of the cross aldol product (unstable intermediate) **46** was confirmed by the ^{1}H, ^{13}C- NMR spectrum of the corresponding alcohol **45** formed by the reduction of cross aldol product. In the ^{1}H NMR spectrum of **45** aromatic protons were observed in the region δ 7.67-7.65 (m, 4H), 7.46-7.37 (m, 6H). A multiplet due to hydroxyl protons were observed at δ 3.95-3.71 (m, 1H), 3.06-3.00 (m, 1H). A multiplet due to methylene proton adjacent to TBDPSO and hydroxyl group were observed at δ 3.67-3.57 (m, 4H). A multiplet due to the proton adjacent to methyl group appeared at δ 1.81-1.74 (m, 1H). A sharp singlet due to *tert*-butyl group protons of TBDPSO group at δ 1.07 (s, 9H). A doublet was observed due to methyl group at δ 0.75 (d, J = 6.88 Hz, 3H).

5. Conclusion

In conclusion we have attempted to develop a concise, systematic synthetic approach for the synthesis of (-)-heliotridane **10** that involves the McMillan's coupling showing the catalytic activity of L-Proline, Henry reaction and dehydration reaction as the key steps. The advantage of our approach for the synthesis of (-)-heliotridane **10** was to provide cost effective and high yielding method. The protocol for the synthesis of (-)-heliotridane **10** has reached to the synthesis of **44** and the rest of the work is in progress and will be reported in due course of time.

6. Experimental section

6.1. 2-((*tert*-butyldiphenylsilyl)oxy)ethan-1-ol, 42



42

To a stirred solution of DMF (50 mL) were added DIPEA (29.85 mL, 173.24 mmol), ethylene glycol **43** (1.074 mL, 17.30 mmol) and TBDPSCl (5 mL, 18.19 mmol) sequentially at room temperature. The reaction mixture was stirred for 24 h and after completion, the reaction mixture was quenched with cold water (20 mL). The aqueous layer was extracted with EtOAc (30 mL×3) washed with 1N HCl solution (30 mL×2) and finally with the saturated solution of $NaHCO_3$ (30 mL×2). The organic extract was washed with brine and dried over Na_2SO_4 and evaporated in *vacuo* to give yellowish liquid, which was purified by silica gel column chromatography with hexane-EtOAc (9.5:0.5) to obtain **42**.

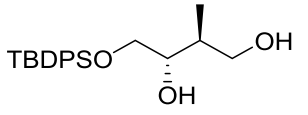
Yield: 5 g, 96%.

Mol. Formula: $C_{18}H_{24}O_2Si$

^{1}H NMR (400 Hz, $CDCl_3$): δ 7.68-7.66 (m, 4H), 7.44-7.37 (m, 6H), 3.76 (t, J = 4.4 Hz, 2H), 3.68-3.67 (m, 2H), 2.15 (s, 1H), 1.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 129.7, 127.7, 64.9, 63.6, 26.8, 19.2.

6.2. (*2S, 3S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutane-1,3-diol, 45



45

To the stirred solution of oxalyl chloride (2.07 mL, 23.97 mmol) in DCM (35 mL) at -78 °C was added DMSO (3.5 mL, 49.54 mmol) dissolved in DCM (35 mL). The reaction mixture was stirred for 30 minutes and the temperature of the reaction mixture was maintained at -78 °C. After 30 minutes of stirring, dropwise addition of compound **42** (4.8 g, 15.98 mmol) dissolved in DCM (35 mL) to the reaction mixture was carried out maintained at -78 °C. The solution was again stirred for additional 30 minutes at -78 °C followed by the addition of Et_3N (9.7 mL, 70.31 mmol) dissolved in DCM (35 mL). The resulting solution was continued to stir for 1 h at room temperature. After the completion of the reaction, the solution was diluted with water (30 mL). The aqueous layer was extracted with DCM (30 mL×3), washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to furnish light yellowish aldehyde which was used without further purification as such for the next step.

To the stirred solution of above aldehyde (4.2 g, 14.07 mmol) taken in dioxane (15 mL) was added L-Proline (0.16 g, 1.40 mmol). The temperature of the reaction mixture was maintained at 4 °C. The solution of propionaldehyde (4.90 mL, 70.38 mmol) in dioxane (15 mL) was added dropwise over the course of 24 h at 4 °C, after the complete addition the resulting solution was stirred for additional 24 h. The reaction mixture was quenched with water (30 mL) after completion as monitored by TLC. The aqueous layer was extracted with EtOAc (20 mL×3). The extract was finally washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give viscous intermediate aldehyde which was used as such for the next step.

To the stirred solution of above aldehyde (500 mg, 1.40 mmol) in MeOH (10 mL) was added $NaBH_4$ (106 mg, 2.80 mmol). The reaction mixture was stirred for 30 min at 0 ^{o}C. On completion of reaction as monitored by TLC, the reaction was quenched with the saturated solution of NH_4Cl, extracted with EtOAc (15 mL×3), dried over Na_2SO_4, concentrated in *vacuo* and purified by silica gel column chromatography with hexane-EtOAc (9:1) to obtain **45.**

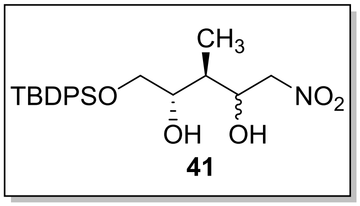
Yield: 475 mg, 95%.

Mol. Formula: $C_{21}H_{30}O_3Si$.

^{1}H NMR (400 Hz, $CDCl_3$): δ 7.67-7.65 (m, 4H), 7.46- 7.37 (m, 6H), 3.95-3.71 (m, 1H), 3.67-3.57 (m, 4H), 3.06-3.00 (m, 1H), 3.00 (d, *J* = 2.76 Hz, 1H), 1.81-1.74 (m, 1H), 1.07 (s, 9H), 0.75 (d, *J* = 6.88 Hz, 3H).

^{13}C NMR (100 MHz. $CDCl_3$): δ 135.4, 132.8, 129.9, 127.8, 77.1, 67.4, 66.3, 37.0, 26.8, 19.2, 13.4.

6.3. (*2S, 3S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-5-nitropentane-2,4-diol, 41



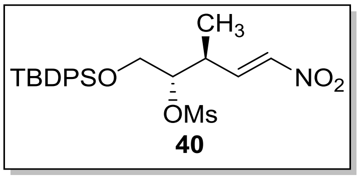
41

To the stirred solution of aldehyde (3.5 g, 9.816 mmol) (obtained from the cross aldol reaction) in MeOH (30 mL) were added nitromethane (0.5 mL, 10.79 mmol) and aqueous solution of NaOH (471 mg, 11.77 mmol) sequentially at 0 ^{o}C. The resulting solution was stirred for 1 h at room temperature, and quenched with water (20 mL) after the completion of the reaction. Aqueous layer was extracted with EtOAc (20 mL×3) washed with brine, dried over anhydrous Na_2SO_4, concentrated in *vacuo*, purified by silica gel column chromatography hexane-EtOAc (9:1) to obtain nitroalcohol **41** as a light yellowish liquid.

Yield: 3.4 g, 85%.

Mol. Formula: $C_{22}H_{31}NO_5Si$.

6.4.(*2S,3S,E)*-1-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-5-nitropent-4-en-2-yl methanesulfonate, 40



40

To the stirred solution of nitroalcohol **41** (3 g, 7.18 mmol) in DCM (25 mL) was added NEt_3 (3.02 mL, 21.55 mmol), MsCl (3.02 mL, 21.55 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature. After completion, the reaction mixture was quenched with water (20 mL) and the aqueous layer was extracted with DCM (30 mL×3), washed with brine, dried over anhydrous Na_2SO_4, concentrated in *vacuo*, purified by silica gel chromatography hexane-EtOAc (9:1) to obtain **40** as colourless liquid.

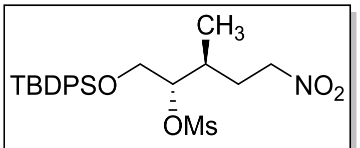
Yield: 3 g, 87%.

Mol. Formula: $C_{23}H_{31}NO_6SSi$.

^{1}H NMR (400 Hz, $CDCl_3$): δ 7.65-7.61 (m, 4H), 7.47-7.40 (m, 6H), 7.17-7.12 (m, 1H), 6.92 (d, J = 13.6 Hz, 1H), 4.70-4.66 (q, J = 5.2, 10.4 Hz, 1H), 3.84-3.83 (m, 1H), 3.71-3.68 (m, 1H), 2.97 (s, 3H), 1.28-1.25 (m, 1H), 1.22-1.21 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (100 MHz. $CDCl_3$): δ 141.2, 135.5, 128.0, 83.5, 63.1, 38.6, 35.2, 26.7, 19.1, 14.5.

6.5. (*2S,3S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-5-nitropentan-2-yl methanesulfonate, 44.



44

To the stirred solution of compound **40** (2.5 g) in MeOH (40 mL) was added catalytic amount of Pd(OH)$_2$. The reaction mixture was stirred for 12 h under the atmosphere of H$_2$. After the completion of the reaction, the reaction mixture was filtered over the celite bed and eluted with the solution of DCM-MeOH (9:1). The filterate was concentrated in *vacuo* and purified by silica gel column chromatography hexane-EtOAc (9:1) to give **44** as a colorless liquid.

Yield: 2.3 g, 92%.

Mol. Formula: $C_{23}H_{33}NO_6SSi$.

^{1}H NMR (400 Hz, CDCl$_3$): δ 7.67-7.62 (m, 4H), 7.46-7.39 (m, 6H), 4.58-4.54 (q, J = 3.6 Hz, 5.2 Hz, 1H), 4.43-4.34 (m, 2H), 3.90-3.76 (m, 2H), 2.98 (s, 3H), 2.23-2.18 (m, 2H), 1.29-1.25 (m, 1H), 1.06 (s, 9H), 0.98 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz. CDCl$_3$): δ 135.5, 127.9, 86.2, 73.3, 63.3, 38.6, 31.7, 29.0, 26.7, 19.1, 15.4.

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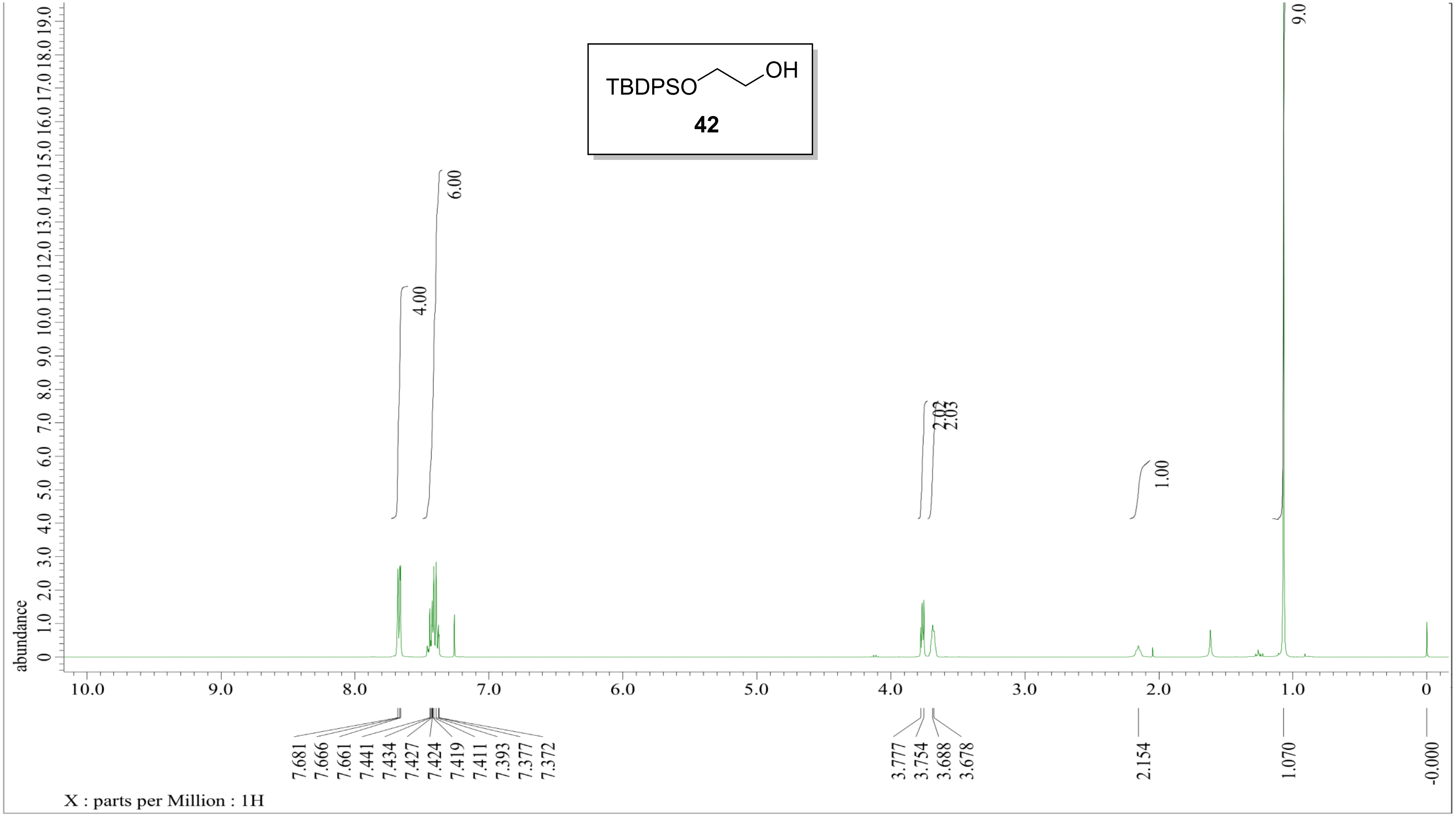
^{1}H-NMR spectrum of 42



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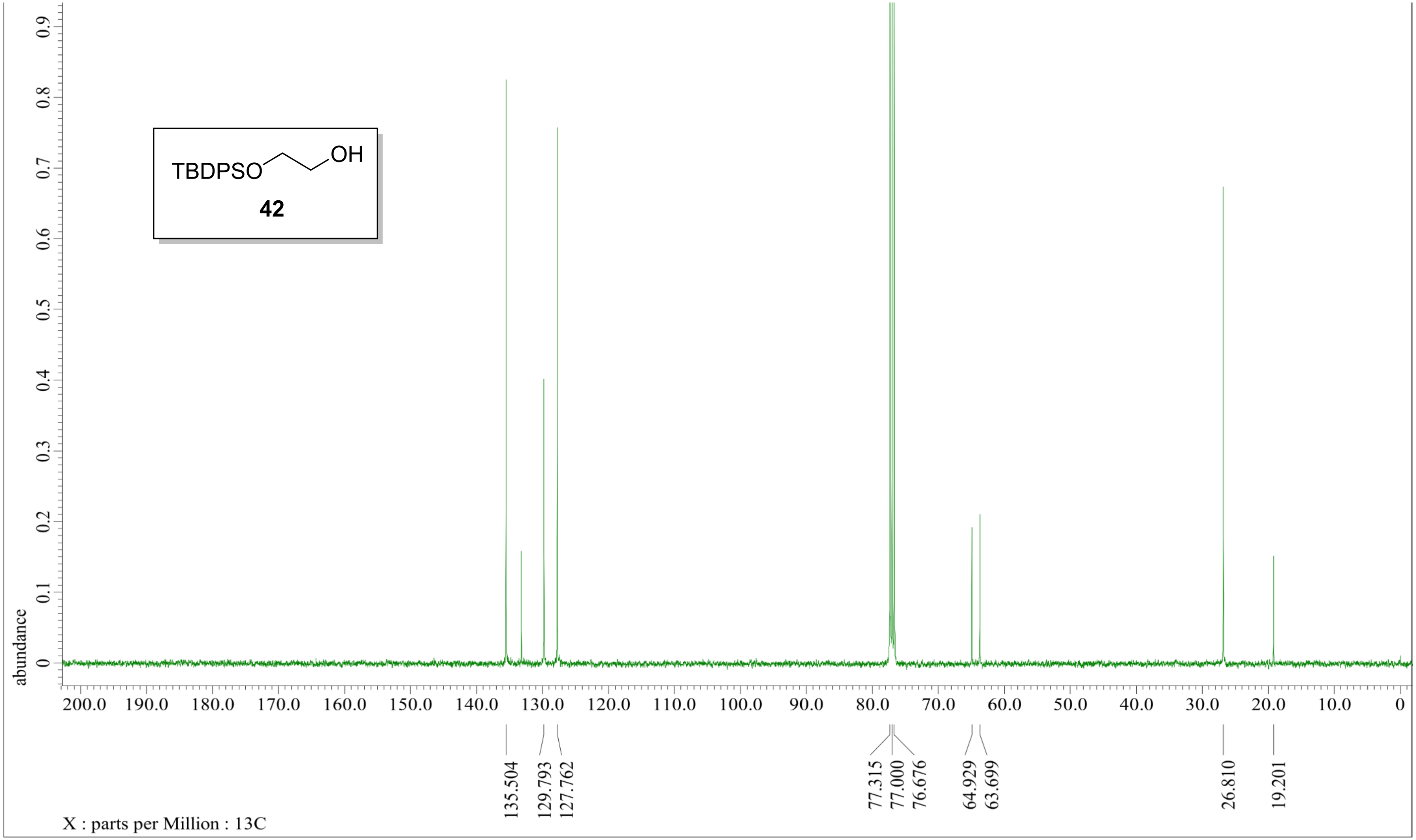

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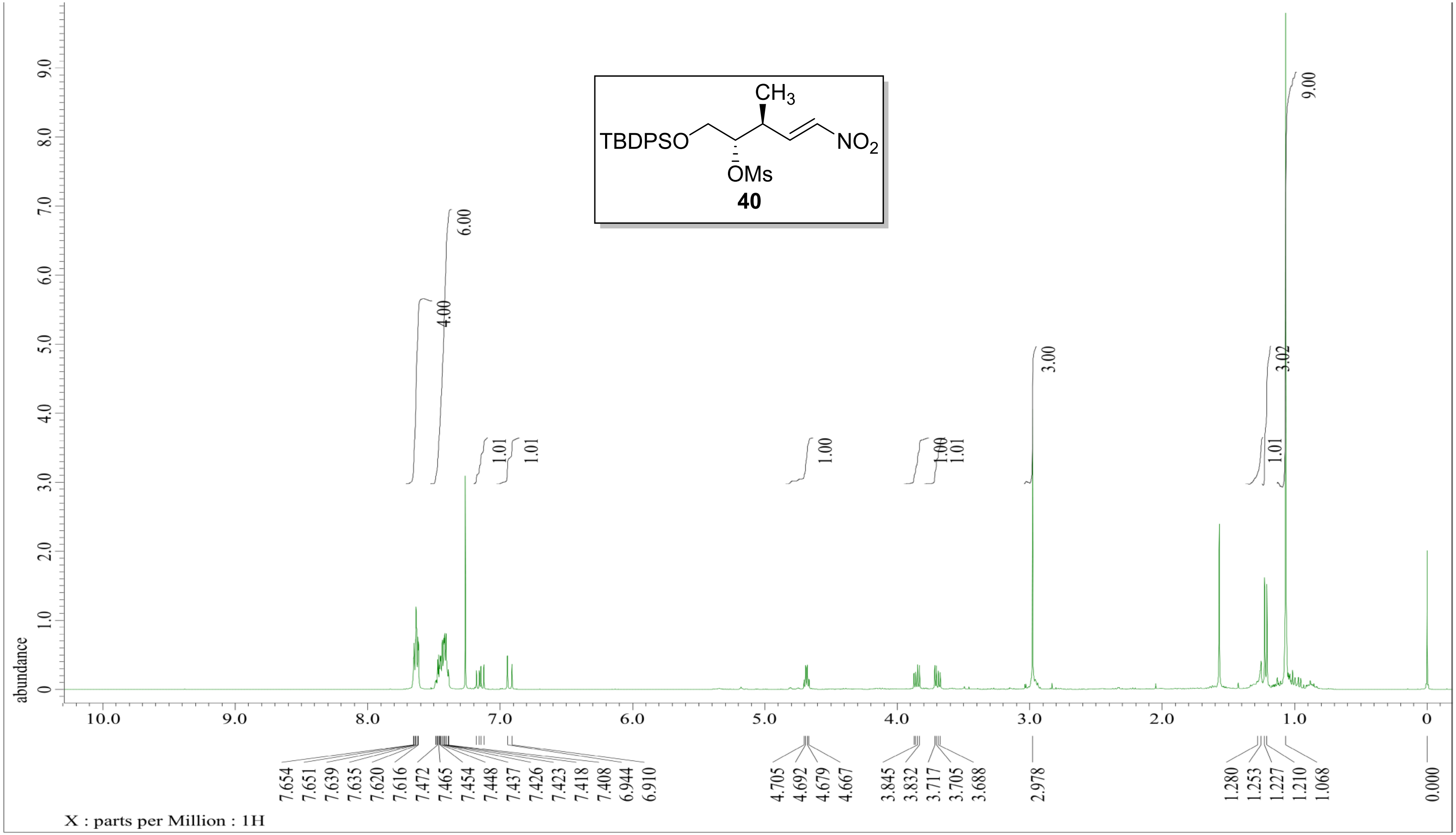

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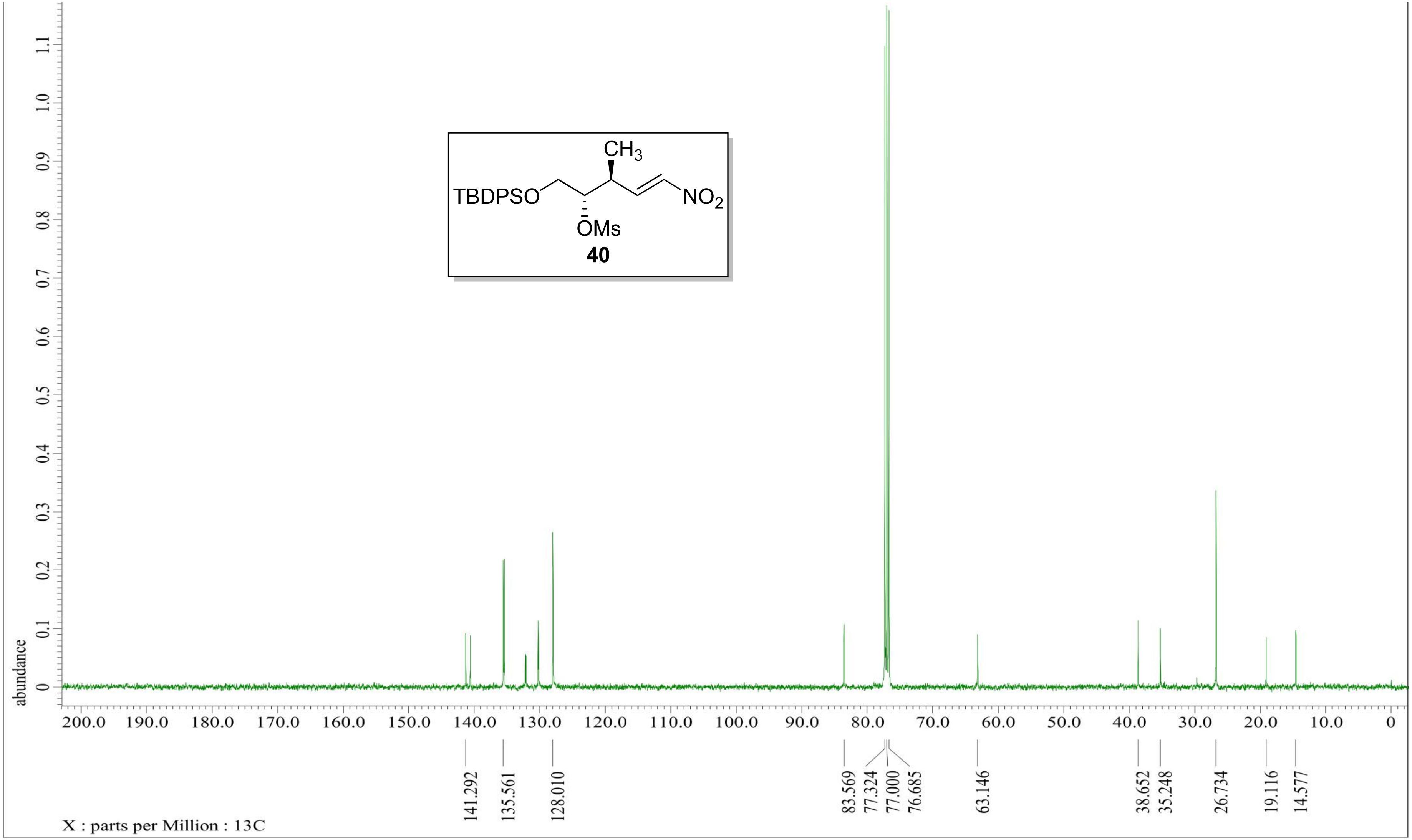

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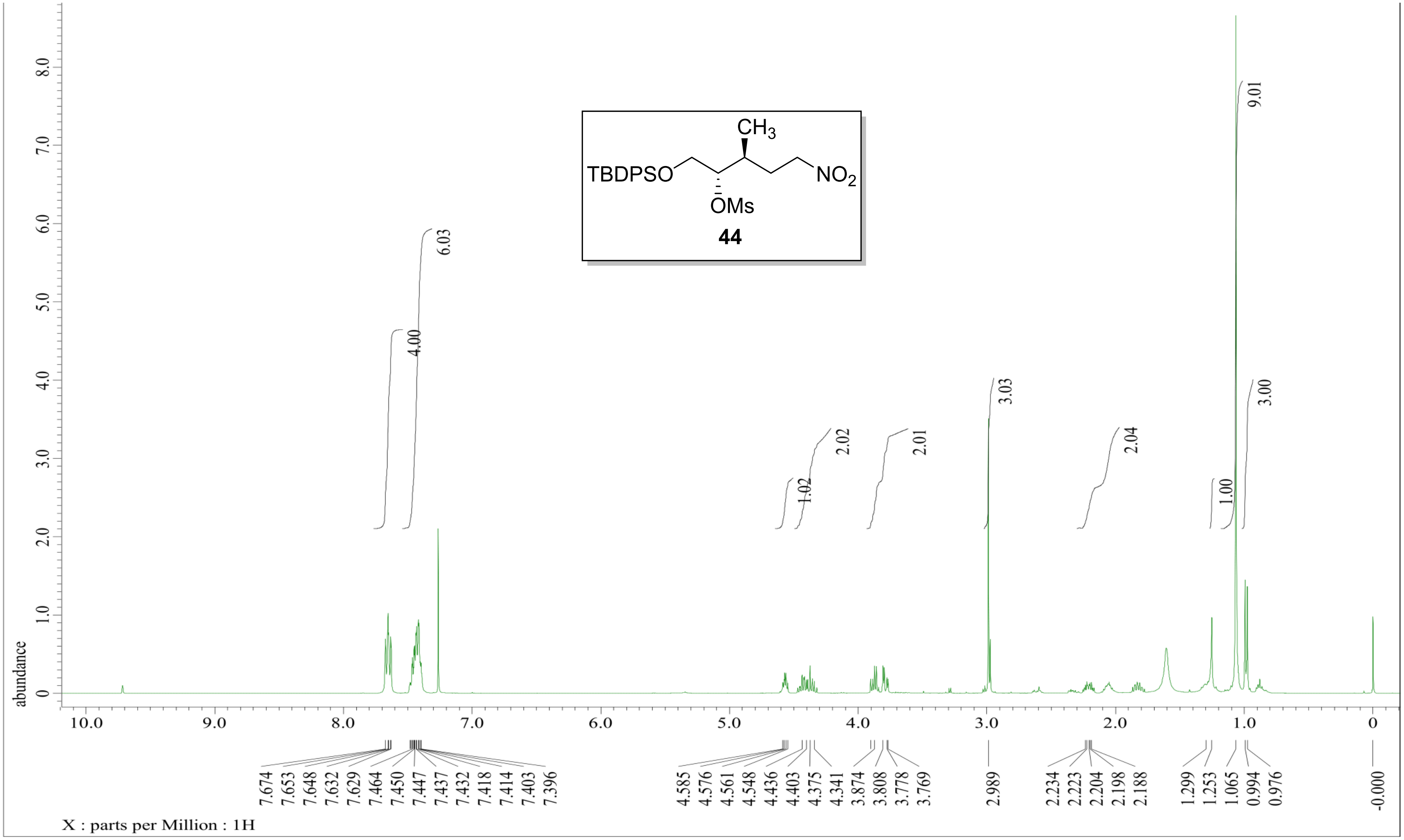

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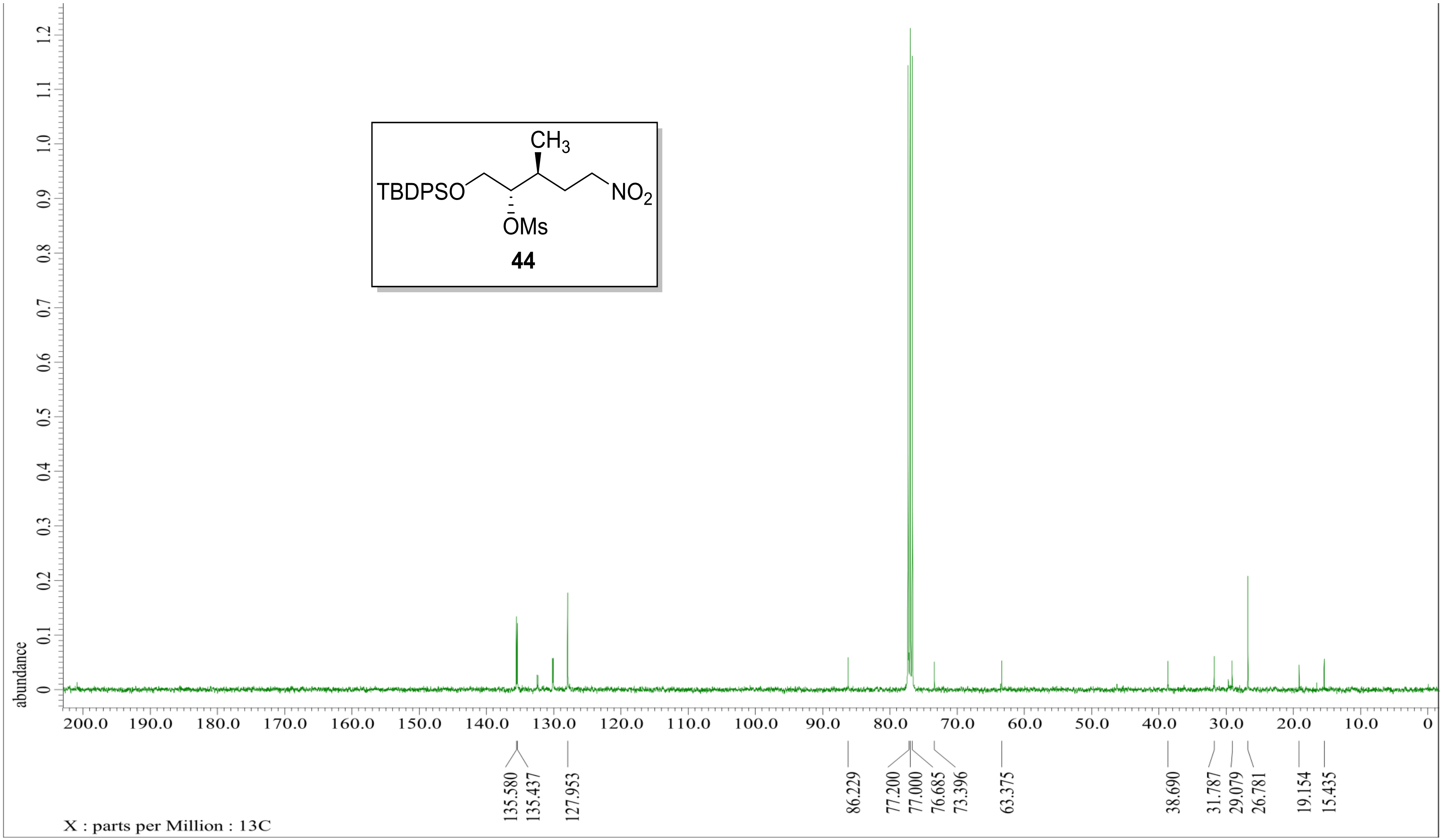

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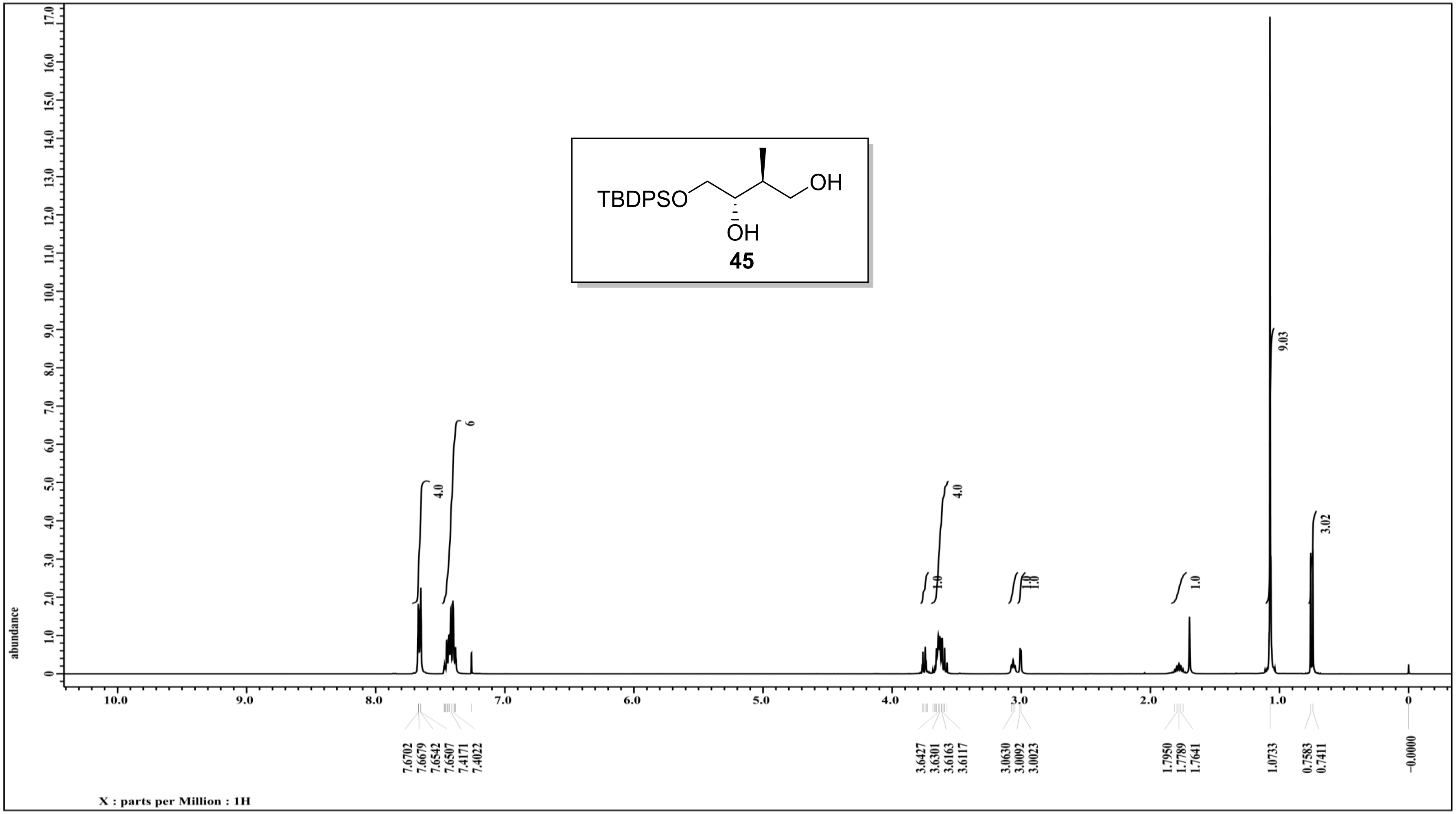

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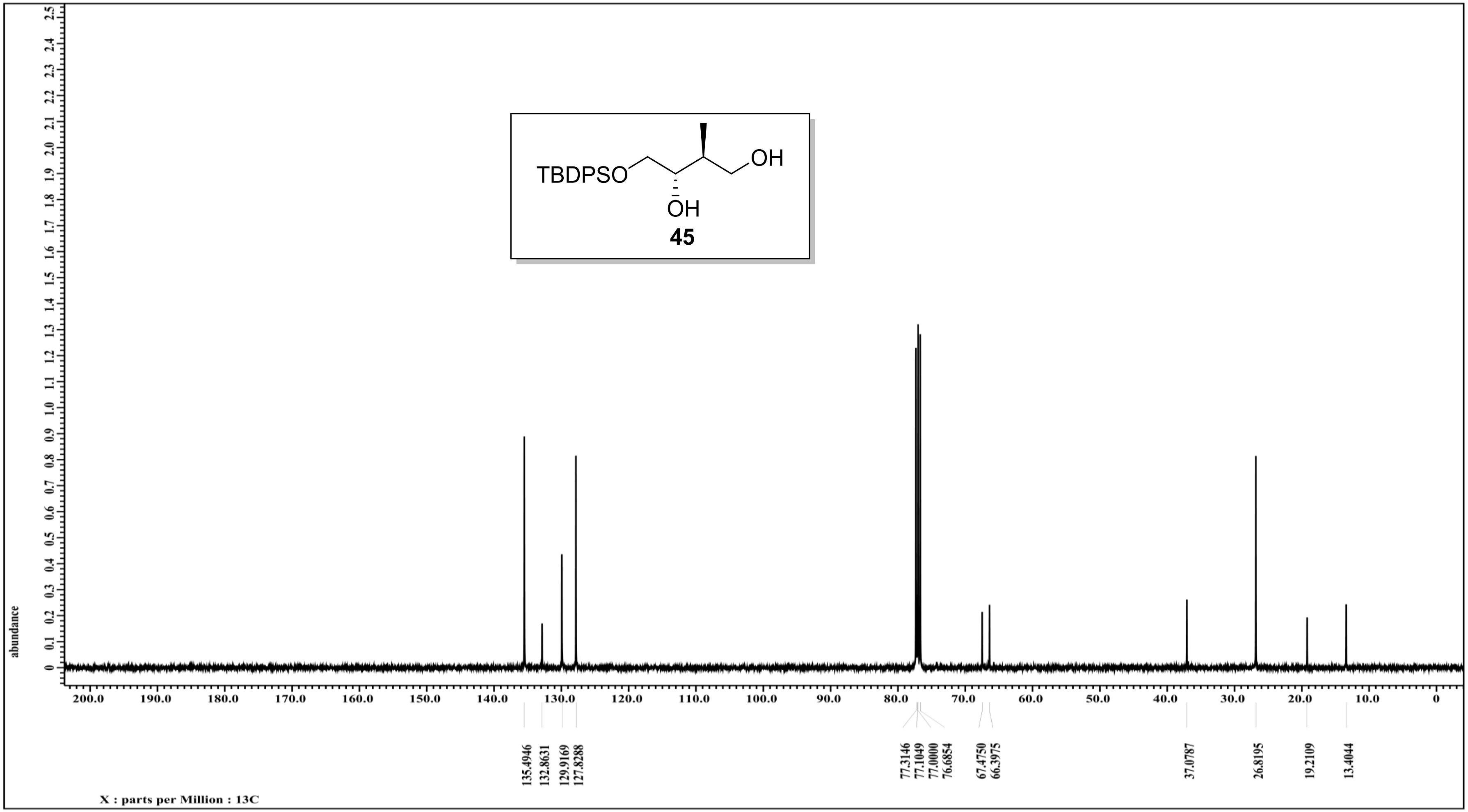

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