Synthetic studies towards Berkeley lactone I & Ilyoresorcy I

DILEEP PALADUGU

Roll No. 17069

A dissertation submitted for the partial fulfillment of BS-MS dual degree in Chemical Science

Indian Institute of Science Education and Research, Berhampur

May 2022

Dedicated to my beloved parents

Certificate of Examination

This is to certify that the dissertation titled "Synthetic studies towards Berkeley lactone I & Ilyoresorcy I" submitted by Mr. Dileep Paladugu (Reg. No.MS17069) for the partial fulfillment of the BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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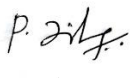
(Thesis Supervisor)

25/05/2022

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. Thirupathi Barla at the Indian Institute of Science Education and Research, Berhampur. This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.



Dileep Paladugu

Dated: May 25, 2022

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

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UNDERTAKING

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Acknowledgement

I am overwhelmed with immense pleasure in all humbleness to express my rich gratitude and respect for my teacher and guide ***Dr. Thirupathi Barla***, Assistant professor, Department of Chemical Science, Indian Institute of Science Education and Research, Berhampur. First and foremost, I would like to thank him for providing me with this wonderful project opportunity. He has enlightened me with the finer skills of synthetic chemistry through his methods. I am forever indebted to him for the helping hand he has always held out for me. His support has been crucial in my career which helped me take up every task that I have come across, with confidence. It would have been impossible to achieve this goal without his constant support and encouragement. I consider myself fortunate to be associated with him who has helped me in taking a decisive step in my career.

I would like to express my deepest thanks to ***Dr. Gurupada Hazra*** and ***Mr. Sudip Mandal*** for the guidance and unconditional help they have provided throughout the entirety of my project work. They have been there to assist me whenever I faced difficulties. I am indeed fortunate to have worked with them and to have learned chemistry through their methods.

I pay rich tribute to my senior lab mate ***Ms. Gitanjali Mishra*** for her help and encouragement. She has helped me refine my methods for the betterment of my project work. I am thankful for her assistance in every aspect throughout this period.

I am deeply obliged to my fellow lab mates ***Ms. Shilpa Mary Paul*** *and* ***Mr. Arunava Patra*** at Natural Product Synthesis and Catalysis Laboratory, for their cheerful company and lending assistance whenever needed.

My sincere thanks to all the faculties, scientific staff, and non-teaching staff of the department of chemical sciences at IISER Berhampur for their support and encouragement through the course of this work.

I extend my gratitude to the Central Advanced Instrumentation Facility division, ***Dr. Balaram Mohapatra, Mr. Pratap Chandra Behera, Mr. Sunil Kumar P.S***., and **Mr. Suman Sinha**, for their excellent service and cooperation during my research work.

I am forever indebted to my beloved parents ***Vijaya Kumar- Dhanalakshmi*** and my brother ***Rakesh*** for the affection and care they have bestowed upon me throughout my life. Without their constant support and encouragement, it would have been impossible to reach this point in my life.

As much as my graduate program has been a personal pursuit, the story would not have been completed without the efforts, help, and company of my co-workers, friends, and well-wishers who have been an integral part of this saga for the last five years. My heartfelt thanks and deep sense of appreciation to all the people mentioned here and others whose names I might have omitted unwittingly.

Dileep Paladugu

General Remark

1. Nuclear Magnetic Resonance spectra were recorded on Bruker AVANCE NEO Ascend 400 & 700 MHz FT-NMR spectrometer. Selected data are reported as follows. Chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, b = broadened, dd = doublet by doublet, dt = doublet by triplet and td = triplet by doublet), coupling constants (*J* in Hz) and assignments.
2. HRMS were taken using Quadruple-TOF (Q-TOF) micro MS system using electrospray ionization (ESI) technique.
3. Melting points were recorded on the Esico International melting point apparatus and are uncorrected.
4. All evaporations were carried out under reduced pressure on Heidolph and Buchi rotary evaporators at below 40 °C.
5. Room temperature = 25-35°C.
6. All solvents and reagents were purified and dried by standard techniques.
7. All the reactions were monitored by analytical thin-layer chromatography (TLC) using e-Merck silica gel plates ($60F_{254}$). Visualization was accomplished with UV light (256 mm), iodine and dipping in 2% phosphomolybdic acid in 15% aq. H_2SO_4 or 2.75% p-anisaldehyde in 3% H_2SO_4 or a-naphthol in 5% H_2SO_4 in EtOH or ninhydrin in methanol and acetic acid followed by heating.
8. All non-aqueous reactions were carried out under a nitrogen (N_2)/argon atmosphere using dry, freshly distilled solvents unless otherwise noted.
9. Optical rotations were measured only for pure compounds and not for mixtures using sodium (589, D line; Anton Paar MCP 200 system) lamp and are reported as follows: $[\alpha]\ D^{25}$ (c = g/100 mL, solvent).

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List of abbreviations

PMB = *p*-Methoxybenzyl

RCM = Ring-closing metathesis

ESI-MS = Electron spray ionization – Mass spectroscopy

HRMS=High-resolution mass spectrometry

DCM = Dichloromethane

DMSO = Dimethyl sulfoxide

THF = Tetrahydrofuran

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DMF = Dimethyl form amide

DMAP = Dimethyl amino pyridine

LDA = Lithium Diisopropylamide

TLC = Thin layer chromatography

PMBOH= 4-Methoxybenzyl alcohol

2,2-DMP=2,2-Dimethoxypropane

CSA=Camphor sulfonic acid

TBSCl=tert-Butyldimethylsilyl chloride

DIBAL-H=Diisobutylaluminium hydride

BnOH=Benzyl alcohol

DIAD=Diisopropyl azodicarboxylate

NHPI=N-Hydroxyphthalimide

DIC=N, N′-Diisopropylcarbodiimide

RALs= Resorcylic acid lactones

Abstract

Natural products are chemical compounds that are usually produced by microorganisms, animals and plants, etc., are displayed a wide range of biological activities. Historically, natural products have played an important role in the development of pharmaceutical drugs, bioactive molecules, pesticides, nutritional, cosmetic, and healthcare products, etc. Typically, these compounds have been isolated in minute quantities from the natural sources, which hampers their complete biological study. Chemical synthesis of natural products is a common, and still prominent, method of obtaining these natural products from inexpensive and readily available starting ingredients. This thesis describes the synthetic studies towards two important natural products, Berkeley lactone I and Ilyoresorcy I by utilizing cutting-edge reactions such as Wittig reaction, Mitsunobu Reaction, Stille coupling, Pinnick oxidation, Swern oxidation, Sharpless asymmetric dihydroxylation, decarboxylative cross coupling, DIBAL-H reduction, LDA coupling, Vilsmeier–Haack reaction etc.

Chapter 1: Synthetic studies towards Berkeley lactone I

1.1 Introduction

Macrolides are a group of natural products isolated from various strains of *Streptomyces* bacteria or fungi, having a macrolide ring structure linked to one or more sugars. They constitute a class of polyketides and exhibit pertinent and promising biological activities. They are characterized by the presence of a macrocyclic lactone, sometimes a keto group, a neutral sugar either linked to amino sugar or a lactone ring in the core structure as shown in Figure **1**.

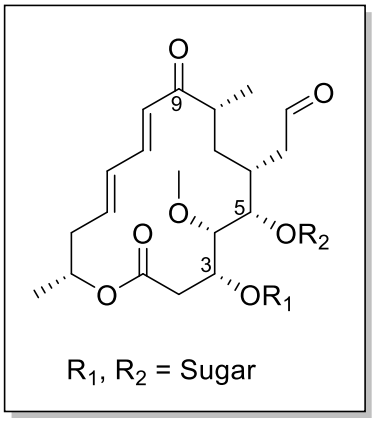


Figure 1: General structure of macrolide antibiotics

The chemistry of macrolide antibiotics originated with the isolation of pikromycin (**Figure 2**) by Brockmann and Henkel in 1950.[1] Soon after, the discovery of erythromycin (**Figure 2**) in 1952 stood as a prominent point of research interest, owing to its antibiotic properties.[2] Several macrolides were discovered from various bacteria and fungi after the breakthrough discovery of erythromycin. There are many criteria for the classification of compounds of this type but natural macrolides usually consist of 14- 15- or 16-membered macrocyclic lactone rings and differ from each other by the type and number of sugar moieties attached as well as by their various modes of binding to the aglycone part. Recently, renewed interest in the synthesis of 16-membered macrolide derivatives has been evoked by their interesting biological properties, relatively good gastric tolerance, and the low tendency for producing allergy and induce resistance. A brief insight into some of the 16-membered biologically potent macrolide antibiotics discovered over the years is discussed in the following sections.

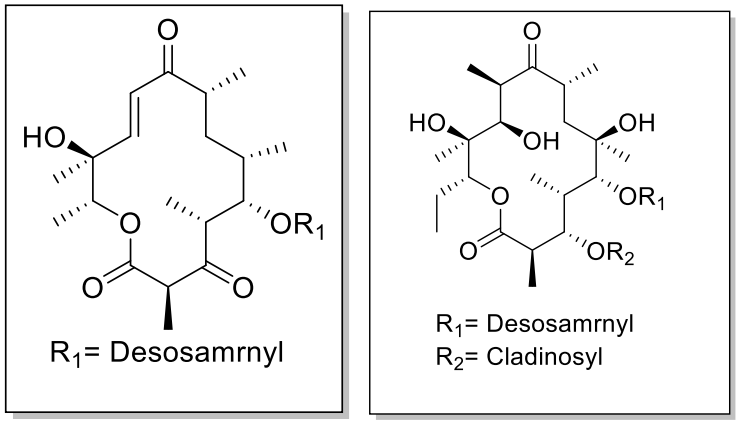


Figure 2: Pikromycin & Erythromycin

Carbomycin the very first 16-membered macrolide antibiotic was discovered from *Streptomyces halstedii*.[3] It was originally reported by Fred W. Tanner Jr. of Pfizer (**Figure 3**).[4] It showed activity in reducing the growth of gram-positive bacteria related to some Mycoplasma strains.[5] It is a mild antibiotic that is used in combination with other antibiotic medications.

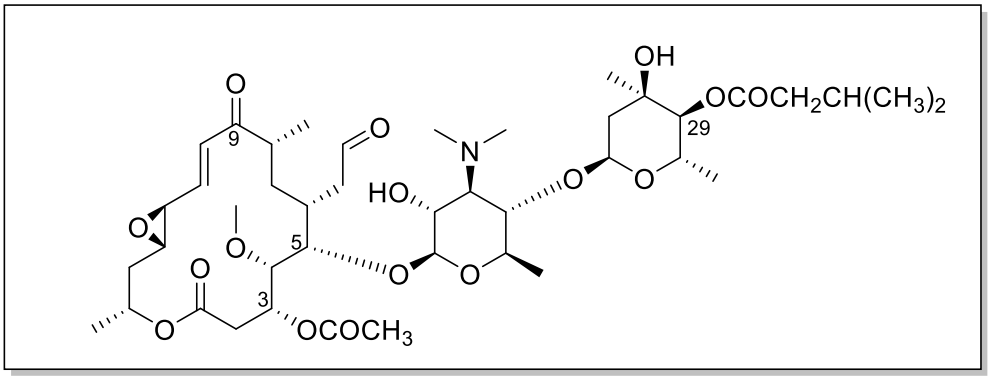


Figure 3: Carbomycin

Leucomycins were isolated from *Streptomyces kitasatoensis*.[6] These natural products contain a 16-membered aglycone, sugar attached to a mycaminose-mycarose disaccharide (**Figure 4**). The substituents in the aglycone at position C-3 and the mycarose moiety at position C-29 distinguish leucomycins structurally. All of these natural products were observed to exhibit antibacterial activities[7-10] against gram-positive bacteria and erythromycin-resistant bacteria like *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Hence, they gained great attention in the field of medicinal chemistry.

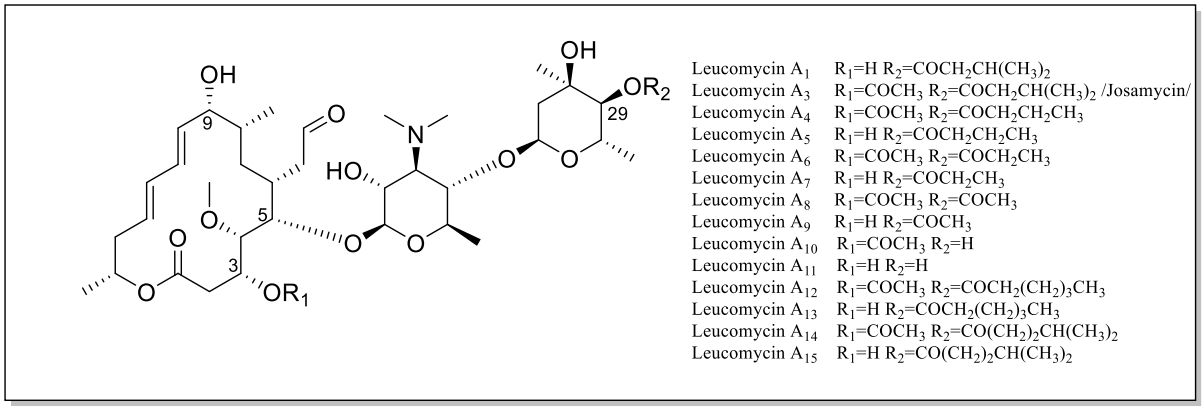


Figure 4: Leucomycins

Spiramycin produced by *Streptomyces ambofaciens*[11] is a mixture of 16-membered macrolide antibiotics[13-14] and a disaccharide mycaminose-mycarose moiety connected to the C-5 atom, similar to leucomycins, but unlike them, there is an additional sugar-forosamine at the C-9 position (**Figure 5**). They used to treat toxoplasmosis, as well as other soft tissue infections and antibacterial activity against gram-positive and gram-negative strains of *Staphylococcus albus*.[12]

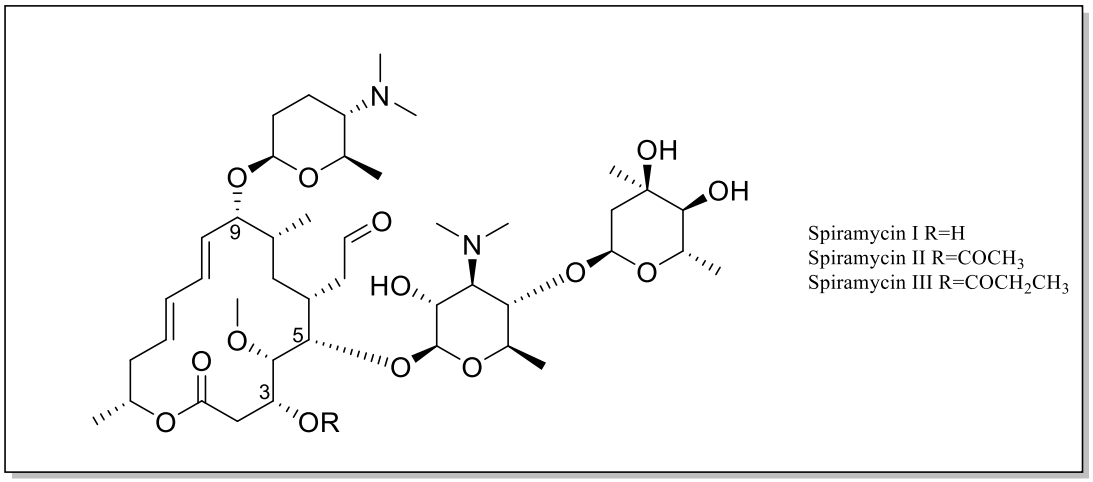


Figure 5: Spiramycin

Midecamycins are macrolide antibiotic produced by *Streptomyces mycarofaciens*.[15] They contain a 16-membered macrolide with a propionyl group at the C-3-position and a disaccharide moiety at the C-5-position, similar to leucomycins (**Figure 6**). They exhibited antibacterial activity against gram-positive and gram-negative strains of *Staphylococcus albus*.[16,17]

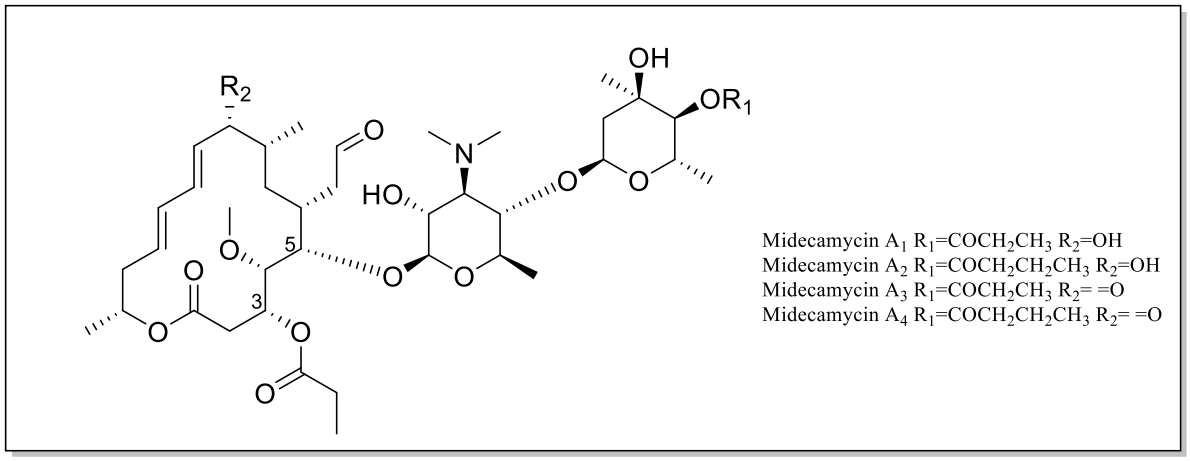


Figure 6: Midecamycin

Tylosin was first identified from *Streptomyces fradiae* and is still commercially manufactured by fermentation.[18] Tylosin A contains a 16-membered polyketide macrocyclic ring (**Figure 7**) known as a tylactone.[19] This macrolide has *β-D*-mycaminose and *α-L*-mycarose in disaccharide form coupled at C-5 of the tylactone scaffold, and a neutral *β -D*-mycinose sugar is added at position C-23. Tylosin D varies from tylosin A in that it has a $–CH_2OH$ group linked to position 6 of the tylactone rather than a $-CH_2CHO$ group. It is used as a feed additive,[5] antibiotic[20] in European countries.

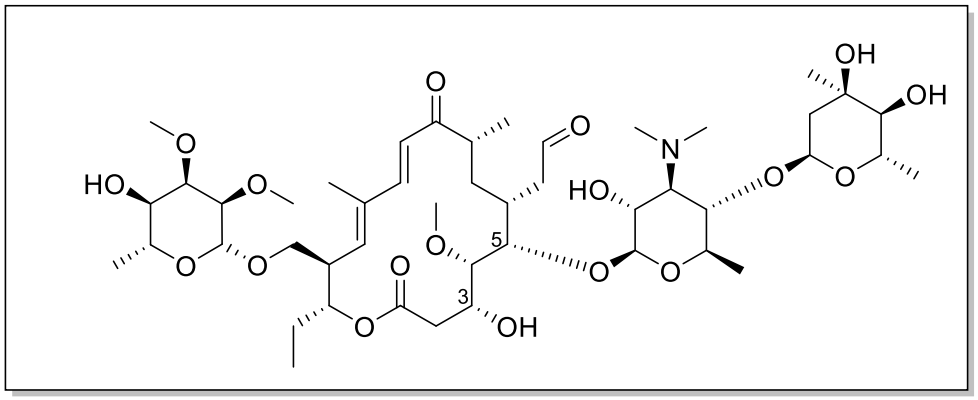


Figure 7: Tylosin

Andrea A. Stierle *et al* found 11 novel macrolides in the fermentation *of Penicillium fuscum and P. camembertii/clavigerum*, named Berkeley lactones. The fungus was established as pure cultures from a single sample of surface water from Berkeley Pit Lake in the United States. These 11 new macrolides include eight Berkeley lactones A-H (**Figure 8**) and three other known antibiotic macrolides A26771B, patulin, and citrinin.[21] Subsequently, complete

structural elucidation of these newly isolated macrolides was carried out and relative and absolute configurations were assigned.

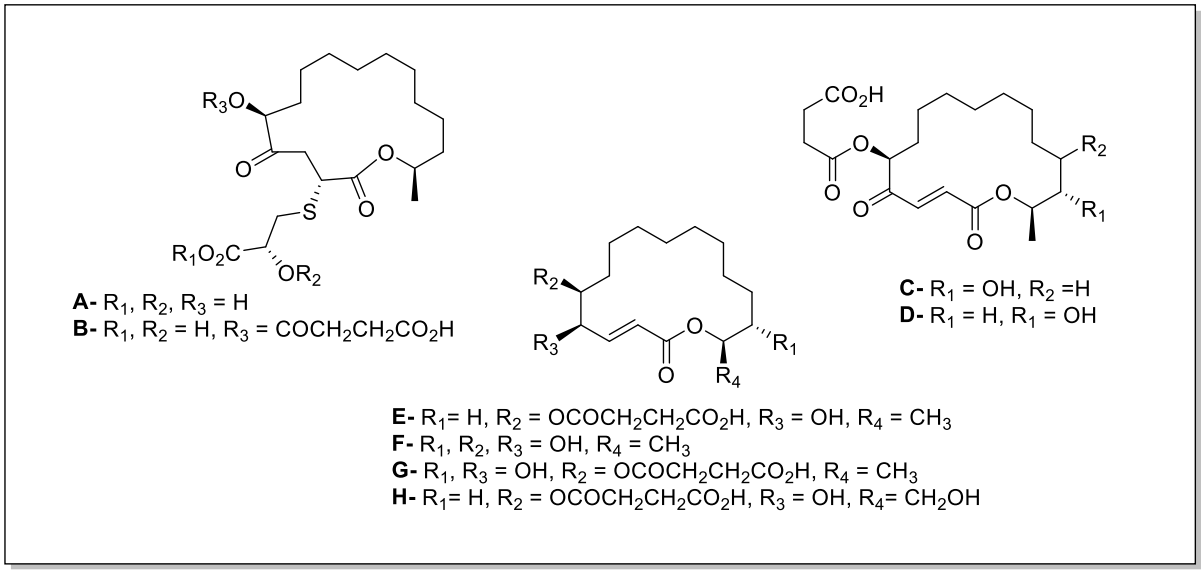


Figure 8: Berkeley lactones A-H

In line with the above-mentioned macrolides, Berkeley lactone A showed activity against a variety of multidrug-resistant *Staphylococcus aureus and Bacillus anthracis* bacteria. The antibiotic activity was also found for A26771B, which is connected to Berkeley lactones.[21]

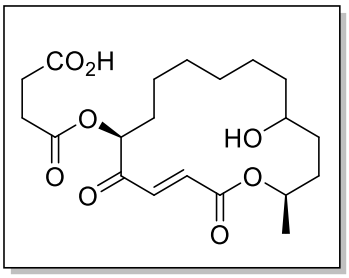
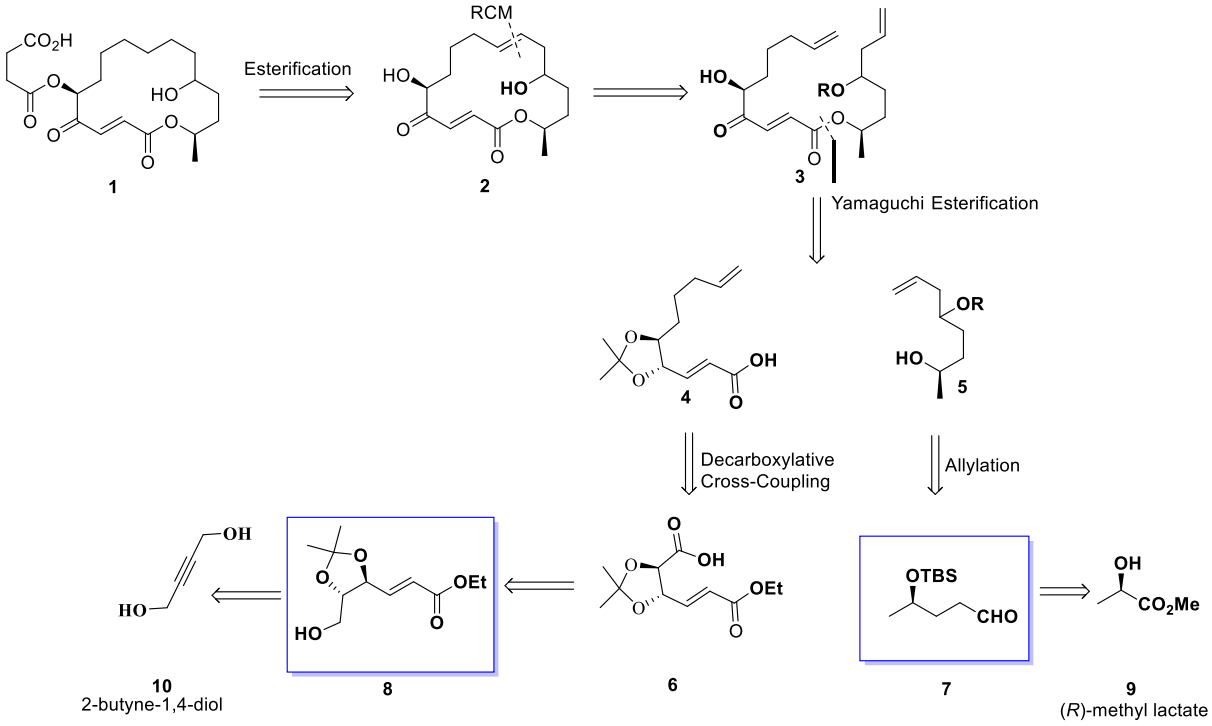


Figure 9: Berkeley lactone I

In addition to these Berkeley lactones, 11 new macrolides were discovered by the same group Andrea A. Stierle *et al*[22] from *Penicillium turbatum Westling (ATCC 28797)* and named Berkeley lactones (I-O). Five Berkeley lactones I-M, two Berkeley lactones N-O, and Citreohybriddional, as well as the known compound A26771B, Berkeley lactone E, and gliovictin, are among the 11 novel macrolides. Subsequently, complete structural elucidation of these newly isolated Berkeley lactones was carried out and relative and absolute configurations were assigned to all except Berkeley lactone I. The potential action of these novel compounds was tested against a variety of bacteria as well as two Candida species. Berkeley Lactone I (**Figure 9**) was found to be effective against four multidrug-resistant strains of *Staphylococcus aureus*.

1.1 Present work

Berkeley lactone I, a 16 membered macrolide attracted our attention to synthesize chemically and thereby its structural assignment by total synthesis starting from commercially available starting materials. The following sections describe its retrosynthetic analysis and synthetic studies toward Berkeley lactone I.



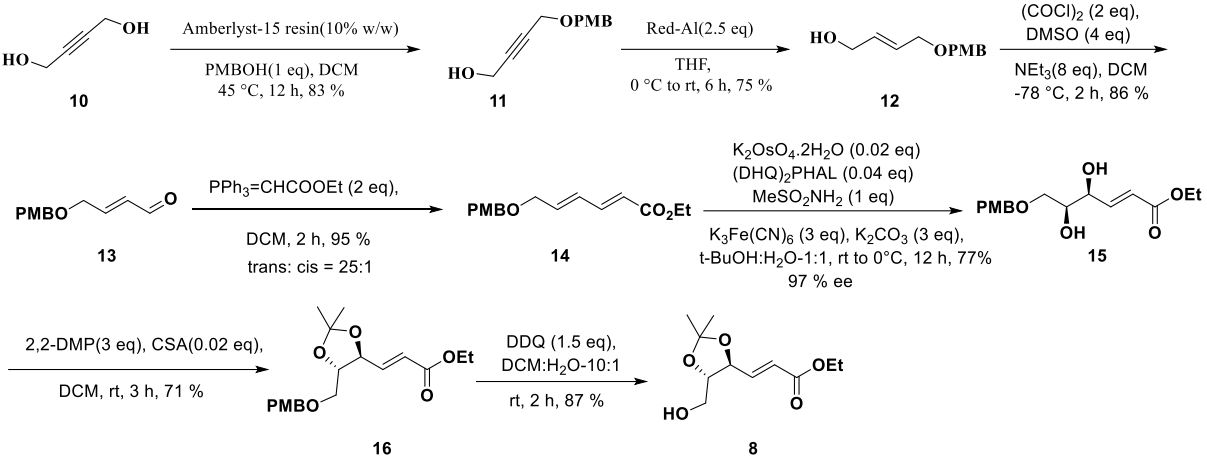
Scheme1: Retrosynthetic analysis of Berkeley lactone I

As per retrosynthetic analysis, the proposed Berkeleylactone I (**1**) could be prepared from the macrocyclic compound **2** by esterification. Compound **2** could be synthesized by Yamaguchi esterification of **4** and **5**, followed by the ring-closing metathesis (RCM) of compound **3** using Grubb's catalyst. Compound **4** could be achieved via decarboxylative cross-coupling of compound **6,** in turn, could be prepared from commercially available 2-butyne-1,4-diol **10.** Alcohol compound **5** could be synthesized from commercially available (*R*)-methyl lactate **9**.

Synthesis of the aliphatic fragment 8:

Synthesis of the fragment **8** was initiated from commercially available 2-butyne-1,4-diol **10**. The primary hydroxy of diol **10** was selectively protected as its PMB ether with Amberlyst-15 resin and 4-methoxy benzyl alcohol to obtain the mono-protected compound **11** in 83% yield.[23] The presence of two doublets at δ 7.30 (d, *J* = 8.4 Hz, 2H) and δ 6.90 (d, *J* = 8.4 Hz,

2H), one singlet at δ 3.82 (s, 3H), for PMB group in ^{1}H NMR spectrum indicated the formation of the product. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z 229.0838 [M + Na] $^{+}$ in HRMS spectrum further confirmed this transformation.



Scheme 2: Synthesis of the compound **8**

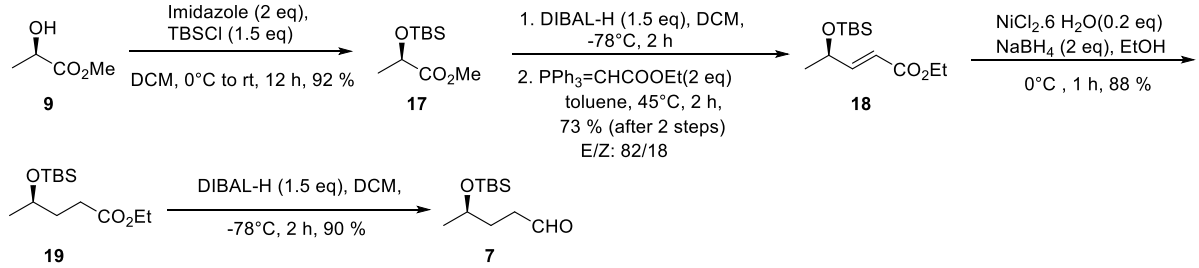
Reduction of PMB-protected alkyne **11** with Red-Al afforded trans alkene **12** in 75% yield.[23] ^{1}H NMR spectrum of compound **12** revealed a signal at 5.96 – 5.73 ppm, as multiplet for two double bond protons indicating the compound formation. ^{13}C NMR revealed two new peaks at δ 129.42 and 127.75 ppm for olefinic carbons as additional support for the product formation. A peak at *m/z* 231.0995 [M + Na]$^{+}$ in HRMS spectrum further confirmed this. Following Swern oxidation conditions, compound **12** was converted to its corresponding aldehyde **13** in an 86% yield.[23] The product formation was confirmed by ^{1}H NMR spectrum, which showed a signal corresponding to aldehyde proton at δ 9.6 ppm indicating the compound formation, ^{13}C NMR spectrum revealed resonance peak at δ 193.29 ppm for aldehyde carbonyl carbon was in the favour of the product formation. The HRMS spectrum showed a peak at *m/z* 229.0942 [M + Na] $^{+}$ finally confirmed this transformation. Aldehyde **13** was subjected to Wittig reaction with Ph_3P=CH(COOEt) in CH_2Cl_2 at ambient temperature furnished an unsaturated ester **14** in 95% yield[24] as the required compound as a major isomer (trans: cis = 25:1). ^{1}H NMR spectrum of compound **14** revealed a signal at δ 6.99-6.82 ppm, as a multiplet for two double bond protons and the loss of δ 9.6 ppm peak indicating the compound formation. ^{13}C NMR spectrum was in full agreement with the assigned structure. IR absorption spectrum revealed a peak at 1709cm^{-1} which unambiguously proved the presence of ester. The HRMS spectrum showed a peak at *m/z* 299.1264 [M + Na]$^{+}$ finally confirming the product formation. Then the unsaturated ester **14** was subjected to Sharpless asymmetric dihydroxylation with AD mix-α (2% K_2OsO_4, 4% $(DHQ)_2$-PHAL) produced a diol compound **15** in 77% yield[24] (97% ee was measured by chiral

HPLC). The structure was confirmed by its ^{1}H NMR study, which revealed the absence of olefinic proton peaks whereas the presence of new peaks was due to alcohol protons at δ 3.00 and 2.79 ppm was in support of this transformation. ^{13}C NMR spectrum also revealed the disappearance of olefin carbon signals and it was in full agreement with the product which supported the product formation. IR absorption spectrum revealed a broad peak at 3312 cm^{-1} which unambiguously proved the presence of alcohol. The HRMS spectrum showed a peak at *m*/*z* 333.1298 [M + Na]$^{+}$ finally confirming the product formation. Diol compound **15** was protected as its acetonide by using 2,2- dimethoxypropane, in presence of the catalytic amount of camphor sulfonic acid (CSA) and it produced the required compound **16** in 71% yield.[24] The product was characterized by its ^{1}H NMR study which showed a new peak at δ 1.48 ppm, absence of δ 3.00 and 2.79 ppm corresponding to hydroxy proton indicating the product formation. The HRMS spectrum showed a peak at *m*/*z* 373.1617 [M + Na]$^{+}$ finally confirming the product formation. ^{13}C NMR spectrum was in full agreement with the assigned structure. A PMB ether present in compound **16** was deprotected by using DDQ, which smoothly afforded primary alcohol **8** in an excellent 87% yield.[24] In the absence of two doublets at δ 7.30 (d, *J* = 8.4 Hz, 2H) and δ 6.90 (d, *J* = 8.4 Hz, 2H), one singlet at δ 3.82 (s, 3H), for PMB group and presence of δ 2.21-2.01 ppm for hydroxy proton in ^{1}H NMR spectrum indicated the formation of the product. ^{13}C NMR spectrum was in full agreement with the assigned structure. IR absorption showed the characteristic band at 3478 cm^{-1} for hydroxy functionality was also supported by this conversion. The HRMS spectrum showed a peak at *m*/*z* 253.1065 [M + Na]$^{+}$ finally confirming the product formation (**Scheme 2**).

Synthesis of the aliphatic fragment 7:

Our synthesis of the aliphatic aldehyde fragment **13** is depicted in **Scheme 3**. Silyl ether protection of (*R*)-methyl lactate **9** was achieved successfully by treating **9** with imidazole and tert-butylchlorodimethylsilane in CH_2Cl_2 with excellent yield 92%.[25] The presence of 0.92 (d, *J* = 2.7 Hz, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm for TBS group in ^{1}H NMR spectrum indicated the formation of the product. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z 241.1245 [M + Na] $^{+}$ in HRMS spectrum further confirmed this transformation. Thus, the reduction of ester **17** to the aldehyde by using DIBAL-H in CH_2Cl_2, followed by the treatment with the two-carbon ylide, ethoxycarbonyl methylene triphenylphosphorane (Ph_3P=CHCOOEt), gave *α,β*-unsaturated ester **18** in 73% yield[26] (***E/Z*** = 82:18). ^{1}H NMR spectrum of compound **18** revealed a signal at δ 6.94 and 6.00 ppm for two double bond protons indicating the compound formation. ^{13}C NMR spectrum was in full agreement with the

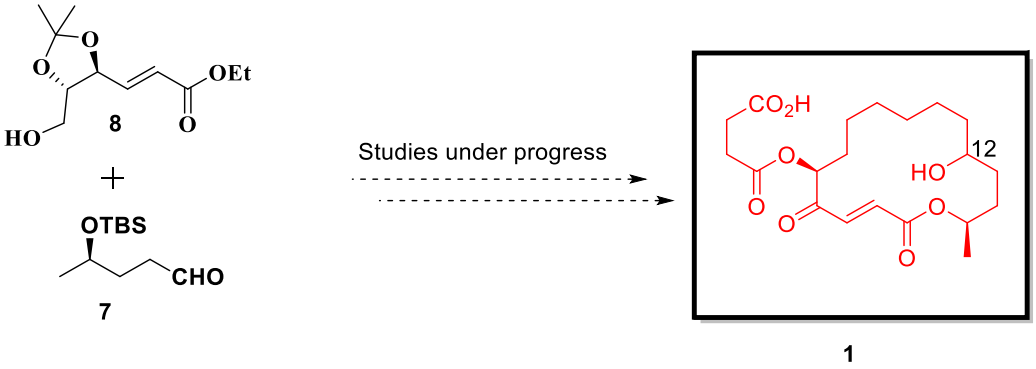
assigned structure. IR absorption spectrum revealed a peak at 1719 cm^{-1} which unambiguously proved the presence of ester functionality. A peak at m/z 281.1535 $[M + Na]^+$ in HRMS spectrum further confirmed this transformation.



Scheme 3: Synthesis of the compound **7**

Reduction of the double bond in compound **18** using $NaBH_4$ in the presence of $NiCl_2 \cdot H_2O$ gave the saturated ester **19** an 88% yield.[27] The structure was confirmed by its ^1H NMR study, which revealed the absence of olefinic proton signals at δ 6.94 and 6.00 ppm was in support of this transformation. ^{13}C NMR spectrum also revealed the disappearance of olefin carbon signals subsequently the product spectrum was in full agreement with the product which supported the product formation. The HRMS spectrum showed a peak at *m/z* 283.1702 $[M + Na]^+$ finally confirming this transformation. Further reduction of ester **19** with DIBAL-H in CH_2Cl_2 gave aldehyde **7** in a 90% yield.[27] The appearance of the peak δ 9.8 ppm in ^1H NMR showed the formation of aldehyde functionality. ^{13}C NMR spectrum revealed resonance peak at δ 202.75 ppm for aldehyde carbonyl carbon was in the favour of the product formation. IR absorption spectrum showed a sharp peak at 1726 cm^{-1} for ester carbonyl provided additional proof in the favour of the product (**Scheme 3**).

1.2 Conclusion

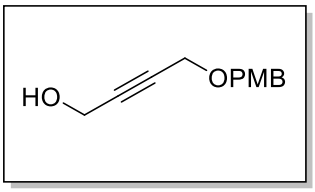


Scheme 4: Future scope

Studies are under progress by utilizing the key fragments **8** and **7** and achieve the natural product in our laboratory. The proposed scheme would be utilizing, decarboxylative cross-coupling, Yamaguchi esterification, and Ring Closing-Metathesis (RCM) to accomplish the natural product.

1.4 Experimental Section

1.4.1 4-((4-methoxybenzyl)oxy)but-2-yn-1-ol **11**



To a stirred solution of butyne-1,4-diol **10** (10.0 g, 116 mmol, 1 equiv.) and a catalytic amount of Amberlyst-15 resin (1.0 g, 10% w/w) in anhydrous CH_2Cl_2 (100 mL) was added 4-methoxybenzyl alcohol (14.5 ml, 116 mmol, 1 equiv.) dropwise at room temperature and heated to reflux at 45 °C for overnight (12 h). After completion of the reaction (monitored by TLC), it was filtered through a pad of Celite. The filtrate was washed with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain a brown oil, which on purification by silica gel column chromatography (ethyl acetate/hexane = 3: 7) afforded **11** (21 g, 83%) as a colourless liquid.

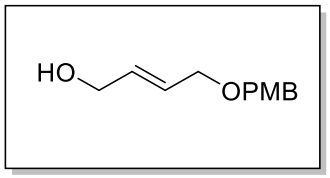
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 4.33 (s, 2H), 4.19 (s, 2H), 3.82 (s, 3H), 2.13 (b, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.4, 129.7,129.3, 113.8, 84.8, 81.7, 71.3, 57.0, 55.3, 51.0 ppm

IR (neat) **:** ν_{max} 3385, 2933, 2837, 1611, 1511, 1246, 1174, 1120, 1027, 818 cm^{-1}

HRMS (ESI-TOF) **:** m/z $[M + Na]^+$: 229.0838.

1.4.2 (E)-4-((4-methoxybenzyl) oxy) but-2-en-1-ol **12**



To a solution of compound **11** (20 g, 97 mmol, 1equiv.) in anhydrous THF (240 mL), was added Red-Al (70 mL, 243 mmol, 2.5 equiv., 70% in toluene) at 0 °C and allowed to stir at room temperature for 6 h. After complete consumption of the starting material (monitored by TLC), it was quenched with a saturated solution of sodium potassium tartrate (100 mL) at 0 °C and diluted with ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (42× 75 mL). The combined organic layers were washed with brine (2× 100 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 3: 7) to furnish the desired compound **12** (15 g, 75%) as a colourless liquid.

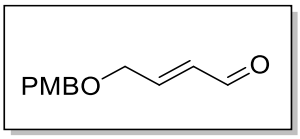
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.96 – 5.73 (m, 2H), 4.47 (s, 2H), 4.14 (dd, *J* = 3.6, 2.5 Hz, 2H), 4.01 (t, *J* = 6.1 Hz, 2H), 3.81 (d, *J* = 1.1 Hz, 3H), 2.21 (b, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.2, 132.3, 130.2, 129.4, 127.7, 113.8, 71.9, 69.8, 62.8, 55.2 ppm.

IR (neat) **:** ν_{max} 3383, 2933, 2908, 2853, 2837, 1611,1585, 1511, 1462, 1359, 1301, 1244, 1173, 1090, 1031, 969, 816, 756, 576, 515 cm^{-1}

HRMS (ESI-TOF) **:**m/z $[M + Na]^+$: 231.0995.

1.4.3 (E)-4-((4-methoxybenzyl) oxy) but-2-enal **13**



To a stirred solution of oxalyl chloride (4.1 mL, 48.07 mmol, 2 equiv.) in CH_2Cl_2 (40 mL), was added DMSO (6.8 mL, 96.15 mmol, 4 equiv.) at −78 °C. After 20 min, alcohol **12** (5 g, 24.04 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was added to the reaction mixture and stirred at −78 °C for 45 min. Then triethylamine (26.7 mL, 192.3 mmol, 8 equiv.) was added to the reaction mixture and stirred at the same temperature for a further 45 min. After completion of the reaction (monitored by TLC), it was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layer was washed with water (30 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated, evaporated to dryness, and then purified by silica gel column chromatography (ethyl acetate/hexane = 1: 4) to obtain the desired product **13** (4.2 g, 86%) as a colourless liquid.

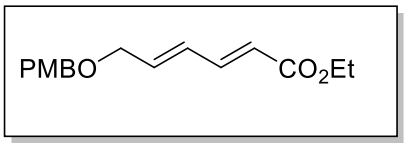
^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.59 (d, *J* = 7.9 Hz, 1H), 7.30 (s, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.89 – 6.82 (m, 1H), 6.59 – 6.16 (m, 1H), 4.54 (s, 2H), 4.27 (dd, *J* = 4.1, 1.9 Hz, 2H), 3.82 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 193.2, 159.4, 153.2, 131.8, 129.5,129.4 113.9, 72.7, 68.2, 55.2 ppm.

IR (neat) **:** ν_{max} 2907, 2836,2727, 1684, 1641, 1611, 1585, 1511, 1462, 1442, 1358, 1244, 1173, 1138, 1102, 1029, 966, 816, 757, 635, 567 cm^{-1}

HRMS (ESI-TOF) **:**m/z $[M+Na]^+$:229.0942.

1.4.4 Ethyl (2E,4E)-6-((4-methoxybenzyl) oxy) Hexa-2,4-dienoate **14**



To a stirred solution of **13** (3.5 g, 16.99 mmol, 1 equiv.) in CH_2Cl_2 (84 ml), Ylide $PPh_3{=}CH_2COOEt$ (11.8 g 33.9 mmol, 2 equiv.) was added and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and then purified by silica gel column chromatography (ethyl acetate/hexane = 1: 9) to obtain the desired product **14** (4.46 g, 95%) as a colourless oil.

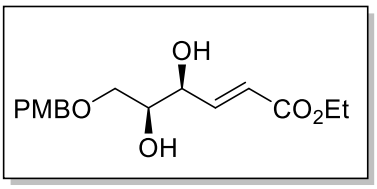
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.42 – 7.19 (m, 3H), 6.99 – 6.82 (m, 2H), 6.48 – 6.32 (m, 1H), 6.25 – 6.13 (m, 1H), 5.90 (d, *J* = 15.4 Hz, 1H), 4.50 (s, 2H), 4.34 – 4.18 (m, 2H), 4.14 (ddd, *J* = 6.7, 4.6, 1.3 Hz, 2H), 3.83 (s, 3H), 1.36 – 1.20 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.9, 159.3, 143.7, 138.7, 129.9,129.4, 129.2, 121.5, 113.8, 72.3, 69.3, 60.3, 55.2, 14.2 ppm.

IR (neat) **:** ν_{max} 1709, 1645, 1612, 1512 cm^{-1}

HRMS (ESI-TOF) **:**m/z $[M + Na]^+$: 299.1264.

1.4.5 Ethyl (4S,5S, E)-4,5-dihydroxy-6-((4-methoxybenzyl) oxy) hex-2-enoate **15**



To a 100 mL round bottom flask was added 1:1 t-butyl alcohol (15 mL)/H_2O (15 mL), $K_3Fe(CN)_6$ (6.8 g, 20.7 mmol), K_2CO_3 (2.8 g, 20.7 mmol), $CH_3SO_2NH_2$ (655 mg, 6.9 mmol), $(DHQ)_2$-PHAL (215 mg, 0.3 mmol, 4 mol %) and $K_2OsO_4.2H_2O$ (51 mg, 0.2 mmol, 2 mol %). The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. To this solution was added a solution of **14** (2.0 g, 6.9 mmol) in 2 mL of CH_2Cl_2 dropwise and stirred vigorously at 0 °C for 12 h. After completion of the reaction (monitored by TLC), saturated aqueous sodium sulfite was added to quench the reaction while stirring vigorously at 0 °C then the solution was warmed to room temperature. Ethyl acetate was added to the reaction mixture, and after the separation of the layers, the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with 2 M KOH and brine to remove the methane sulfonamide, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to furnish the desired compound **15** as a colourless solid (1.7 g, 77%, 97% ee by HPLC analysis [DAICEL CHIRALPAK@OJ-H (250×4.6mm, 5μm), hexanes/i-PrOH = 60/40, 1.0 mL/min, 254 nm]

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.36 – 7.15 (m, 2H), 7.07 – 6.68 (m, 3H), 6.14 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.50 (q, *J* = 11.3 Hz, 2H), 4.37 (qd, *J* = 4.5, 1.7 Hz, 1H), 4.26 – 4.15 (m, 2H), 3.82 (s, 3H), 3.80 – 3.71 (m, 1H), 3.69 – 3.53 (m, 2H), 3.00 (t, *J* = 13.2 Hz, 1H), 2.79 (d, *J* = 5.8 Hz, 1H), 1.32 (dt, *J* = 14.3, 7.3 Hz, 3H) ppm.

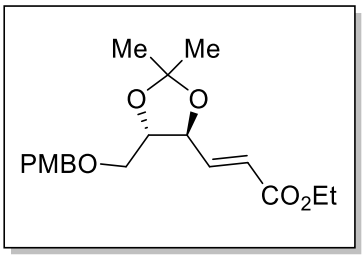
^{13}C NMR (100 MHz, $CDCl_3$) : δ166.2, 159.5, 146.1, 129.5, 129.4, 122.4, 113.8, 73.3, 72.1, 71.8, 71.1, 60.5, 55.2, 14.22 ppm.

IR (neat) **:** ν_{max} 3480, 3312, 2980, 2915, 2866, 1718, 1664, 1611, 1512, 1454, 1365, 1248, 1174 cm^{-1}

HRMS (ESI-TOF) : m/z $[M + Na]^+$: 333.1298.

M.P. **:**65-70°C

1.4.6 Ethyl (E)-3-((4S,5S)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate **16**



To the stirred solution of diol **15** (3.0 g, 9.3 mmol) in CH_2Cl_2 (90 mL), was added 2,2-DMP (3.4 mL, 27.7 mmol) and catalytic amount of *L*-(-)-camphor sulfonic acid (CSA, 43 mg, 0.18 mmol, 2 mol%) at room temperature and stirred for 3 h at room temperature. After completion of the reaction, the reaction mixture was quenched by the addition of an aqueous saturated $NaHCO_3$ solution at room temperature. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50mL). The combined CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in a vacuum. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to furnish the desired compound **16** colourless liquid (2.8 g, 83%).

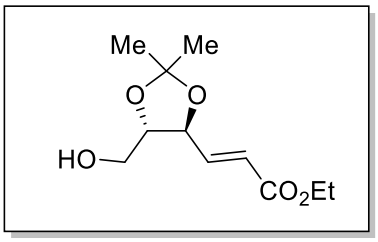
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.27 (d, *J* = 7.8 Hz, 2H), 7.09 – 6.66 (m, 3H), 6.10 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.54 (s, 2H), 4.41 (tdd, *J* = 18.0, 11.0, 6.9 Hz, 1H), 4.29 – 4.15 (m, 2H), 4.03 – 3.88 (m, 1H), 3.83 (s, 3H), 3.61 (d, *J* = 4.7 Hz, 2H), 1.48 (dd, *J* = 17.0, 5.2 Hz, 6H), 1.30 (q, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.0, 159.3, 144.0, 129.8, 129.3, 122.5, 113.8, 110.1, 79.6, 73.3, 68.9, 60.5, 55.2, 26.8, 14.2 ppm.

IR (neat) **:** ν_{max} 2985, 1718, 1661, 1612, 1586, 1512, 1463, 1369, 1300, 1245 cm^{-1}

HRMS (ESI-TOF) :m/z $[M + Na]^+$: 373.1617.

1.4.7 Ethyl (E)-3-((4S,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylate **8**



To a stirred solution of PMB-ether **16** (2.3 g, 6.3 mmol) in CH_2Cl_2 (40 mL) and water (4 mL) at room temperature, was added DDQ (2.1 g, 9.5 mmol) and allowed to stir for 2 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with a saturated $NaHCO_3$ solution. The organic compound was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to give a red coloured crude product which on purification by silica gel column chromatography (ethyl acetate/hexane = 3:7) afforded the desired primary alcohol **8** colourless liquid (1.6 mg, 94%).

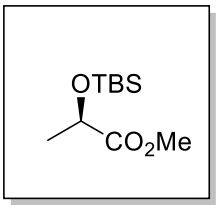
^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.91 (ddd, *J* = 15.6, 5.7, 1.9 Hz, 1H), 6.15 (ddd, *J* = 15.6, 2.1, 1.5 Hz, 1H), 4.53 (dddd, *J* = 7.1, 5.7, 2.7, 1.4 Hz, 1H), 4.22 (qd, *J* = 7.1, 2.3 Hz, 2H), 4.01 – 3.82 (m, 2H), 3.66 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.21 – 2.01 (m, 1H), 1.46 (dd, *J* = 7.2, 1.7 Hz, 6H), 1.41 – 1.20 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.9, 143.7, 122.9, 110.1, 80.7, 76.0, 60.7, 26.8, 14.1 ppm.

IR (neat) **:** ν_{max} 3478, 2985, 2936, 1717, 1660, 1460, 1370, 1301 cm^{-1}

HRMS (ESI-TOF) :m/z $[M + Na]^+$:253.1065.

1.4.8 Methyl (R)-2-((tert-butyldimethylsilyl) oxy) propanoate **17**



To the solution of methyl (*R*)-2-hydroxypropanoate **9** (10 g, 96 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (100 ml), was added imidazole (13 g, 192 mmol, 2 equiv.) and the reaction mixture was cooled to 0 °C. tert-butylchlorodimethylsilane (21.7 g, 144 mmol, 1.50 equiv.) was added slowly and the resulting reaction mixture was stirred overnight at room temperature. After complete consumption of the starting material (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (100 mL), H_2O (100 mL), and extracted with CH_2Cl_2 (200 mL x 3). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, and concentrated. The resulting residue was purified by flash chromatography (ethyl acetate/hexane = 1: 19) to afford the desired product as a colourless liquid **17** (19.2 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.34 (q, *J* = 6.7 Hz, 1H), 3.73 (s, 3H), 1.29 (t, *J* = 69.7 Hz, 3H), 0.92 (d, *J* = 2.7 Hz, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm.

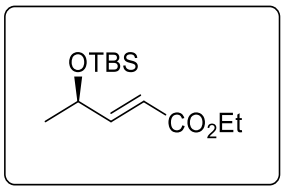
^{13}C NMR (100 MHz, $CDCl_3$) : δ 174.5, 68.3, 51.8, 25.6, 21.3, 18.2, –5.0, –5.3 ppm.

IR (neat) **:** ν_{max} 2953, 2930, 1758, 1739, 1462, 1252, 1142 cm^{-1}

HRMS (ESI-TOF) **:** $[M+Na]^+$:241.1245.

Specific Rotation : $[\alpha]_D^{27.3}$ +24.5 (*c* = 1, $CHCl_3$)

1.4.9 Ethyl (R, E)-4-((tert-butyldimethylsilyl) oxy) pent-2-enoate **18**



To a stirred solution of silyl ether **17** (1 g, 4.59 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL), was added DIBAL-H (25% M solution in toluene, 4 mL, 6.88 mmol, 1.5 equiv.) at –78 °C. The reaction mixture was stirred at the same temperature for an additional 90 mins. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with a saturated aqueous solution of potassium sodium tartrate (5 mL). The mixture was left to stir for 4 h until the organic and aqueous phases had completely separated. The organic phase was extracted with CH_2Cl_2 (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. A mixture of the above crude aldehyde (865 mg) and (ethoxy carbonyl methylene) triphenyl phosphorane (3.2 g, 9.19 mmol, 2 equiv.) in toluene (12 mL) was heated at reflux for 2 h 45 °C. The filtrate was concentrated and the resulting residue was purified by column chromatography (ethyl acetate/hexane = 1:19) to give *α, β*-unsaturated esters **18** (866 mg, 73%; *E/Z* = 82:18)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.94 (dd, *J* = 15.5, 4.1 Hz, 1H), 6.00 (dd, *J* = 15.5, 1.8 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.32 – 4.01 (m, 2H), 1.32 (dd, *J* = 7.1, 2.7 Hz, 3H), 1.30 – 1.23 (m, 3H), 0.97 – 0.91 (m, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm.

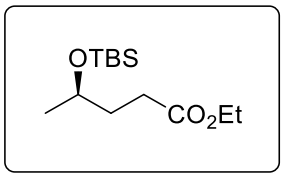
^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.8 (s), 151.9 (s), 118.9 (s), 67.7 (s), 60.2 (s), 25.8 (s), 23.5 (s), 18.2 (s), 14.2 (s) ppm.

IR (neat) : ν_{max} 2956, 2930, 2857, 1719, 1659, 1471, 1367, 1293, 1254, 1152 cm^{-1}

HRMS (ESI-TOF) **:** $[M+Na]^+$: 281.1535.

Specific Rotation : $[\alpha]_D^{28.8}$ –10.5 (*c* = 1, $CHCl_3$)

1.4.10 Ethyl (R)-4-((tert-butyldimethylsilyl) oxy) pentanoate **19**



To a solution of **18** (4 g, 15.47 mmol, 1.0 equiv.) in anhydrous EtOH (100 mL) at 0 °C, was added $NiCl_2 \bullet 6H_2O$ (0.74 g, 3.094 mmol, 0.2 equiv.). After 10 mins $NaBH_4$ (1.2 g, 30.95 mmol, 2 equiv.) was added portion-wise. The resulting mixture was stirred at the same temperature for 1 h. Upon completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the reaction mixture was passed through Celite and washed with ethyl acetate (50 ml). The reaction mixture was concentrated and purified by silica gel flash chromatography (ethyl acetate/hexane = 1:19) to give **19** as a colourless oil (3.53 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.14 (q, *J* = 7.1 Hz, 1H), 3.99 – 3.73 (m, 1H), 2.57 – 2.19 (m, 1H), 1.90 – 1.59 (m, 1H), 1.37 – 1.21 (m, 2H), 1.15 (d, *J* = 6.1 Hz, 2H), 0.90 (s, 5H), 0.06 (t, *J* = 4.6 Hz, 3H) ppm.

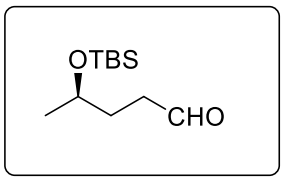
^{13}C NMR (100 MHz, $CDCl_3$) : δ 173.8, 67.4, 60.1, 34.3, 30.4, 25.8, 23.6, 18.0, 14.2, –4.4, –4.8 ppm.

IR (neat) : ν_{max} 2957, 2930, 2857, 1735, 1462, 1373, 1254 cm^{-1}

HRMS (ESI-TOF) : $[M+Na]^+$: 283.1702.

Specific Rotation : $[\alpha]_D^{29.4}$ –23.44 (*c* = 0.9, $CHCl_3$)

1.4.11 (R)-4-((tert-butyldimethylsilyl) oxy) pentanal **7**



To a solution of ester **19** (0.45 g, 1.73 mmol, 1.0 equiv.) in CH_2Cl_2 (8 mL), was added DIBAL-H (25% M solution in toluene, 1.5 mL, 2.6 mmol, 1.5 equiv.) dropwise at –78 °C and stirred for 2 h at the same temperature. The reaction mixture was then quenched with sat. aq potassium sodium tartrate (5 mL) and then allowed to stir vigorously for 1 h. The mixture was left to stir for 2 h until the organic and aqueous phases had completely separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with water (5 mL) and dried over Na_2SO_4. The reaction mixture was concentrated and purified by silica gel flash chromatography (ethyl acetate/hexane =1:19) to give **7** as a colourless liquid (340 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.80 (t, *J* = 1.7 Hz, 1H), 3.89 (dqd, *J* = 12.2, 6.1, 4.4 Hz, 1H), 2.51 (tt, *J* = 5.3, 3.0 Hz, 2H), 2.11 – 1.55 (m, 2H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.94 – 0. 87 (m, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 202.7, 67.4, 40.1, 31.6, 25.8, 23.6, 18.0, –4.3, –4.8 ppm.

IR (neat) : ν_{max} 2955, 2929, 2887, 2856, 2713, 1726, 1472, 1462, 1375, 1253 cm^{-1}

Specific Rotation : $[\alpha]_D^{29.4}$ –25.10 (*c* = 1, $CHCl_3$)

1.5 References

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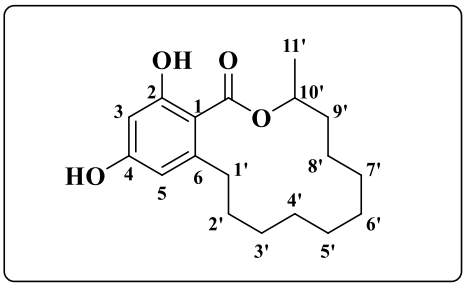
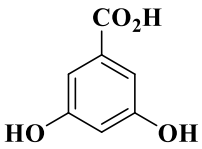
Chapter-2: Synthetic studies towards Ilyoresorcy I

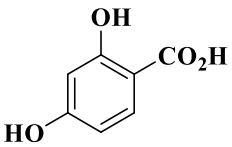
2.1 Introduction

Resorcylic acid lactones (RALs) are naturally occurring mycotoxins found in a variety of fungal strains. They are a type of polyketide that are usually produced by fungal metabolites & show interesting and promising biological properties. A resorcylic acid ring and a 14-membered lactone macrocycle with a methyl substituent at the C-10' position in the core structure distinguish them (**Figure 1**). The lactone moiety of most RALs is 14-membered, 12-membered, or 10-membered.[1] The isolation of radicicol from *Monocilliumnordinii* in 1953[2] was the first discovery of resorcylic acid lactones. Because of its antibacterial[3] and cytotoxic characteristics,[4] radicicol attracted great interest from many synthetic and medicinal chemists for study interest.

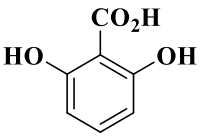




3,5-dihydroxybenzoic acid
(α-Reosrcylic acid)



2,4-dihydroxybenzoic acid
(β-Resorcylic acid)



2,6-dihydroxybenzoic acid
(γ-Resorcylic acid)

Figure 1: General structure of resorcylic acid lactones

For a long time after their discovery, the scientific community was only barely attracted towards RALs. Following the discovery of radicicol as a strong and specific inhibitor of Hsp90,[15] as well as hypothemycin and L-783,277 as kinase inhibitors,[16] general interest in RALs grew. Following the groundbreaking finding of radicicol, more than a hundred RALs were identified in diverse fungi. The following section provides a quick overview of some of the RALs that have captivated biologists and chemists alike throughout the years.

Hellwig et al. isolated pochonins A–F (**Figure 2**) from the clavicipitaceous hyphomycete *Pochonia chlamydosporia var. catenulata* strain P 0297 on a mission to uncover new antiviral chemicals for the treatment of HCV infection (Herpes Simplex Virus).[5]

Pochonins **A–B** shares an epoxide appendage and an enone moiety that appears to be responsible for their biological profiles. Pochonin **C** has a trans-chlorohydrin moiety with the *E*-enone moiety, whereas pochonin **D/E** is chlorohydrin-free. Pochonin **F** differs mostly in the aromatic substitution, and in the purest sense, it cannot be considered a RAL because the aromatic component differs from that of the RAL.

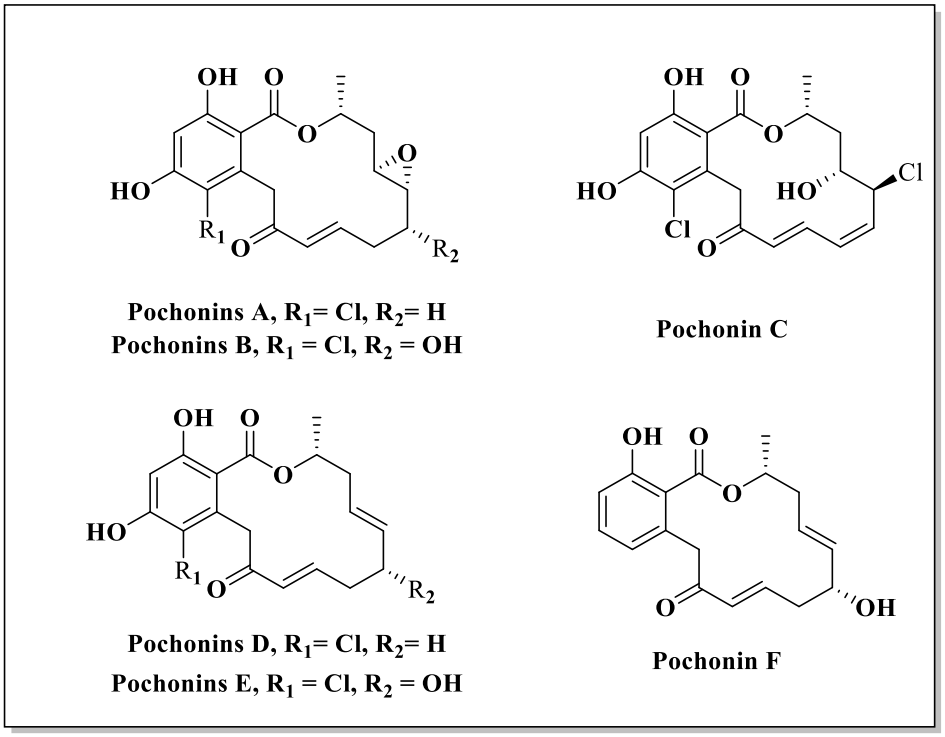


Figure 2: Pochonins A–F

Three novel *β*-resorcylic acid lactones have recently been identified from *Fusarium* sp. PSU-ES123[6], a seagrass-derived fungus. Seagrasses are marine plants that are a rich source of endophytic fungi capable of producing structurally interesting bioactive compounds like the antifeedants luteolin, apigenin, and luteolin 4'-glucuronide, as well as the antibacterial meroterpenoid nodosol and antimicrobial aspegillumarins A and B. The structures of 5' β -hydroxyzearalenone, 7' β -hydroxyzearalenone, and 9' α -hydroxyzearalenone (**Figure 3**) were well described by traditional spectroscopic techniques, and their absolute configurations were validated by advanced Mosher's method.

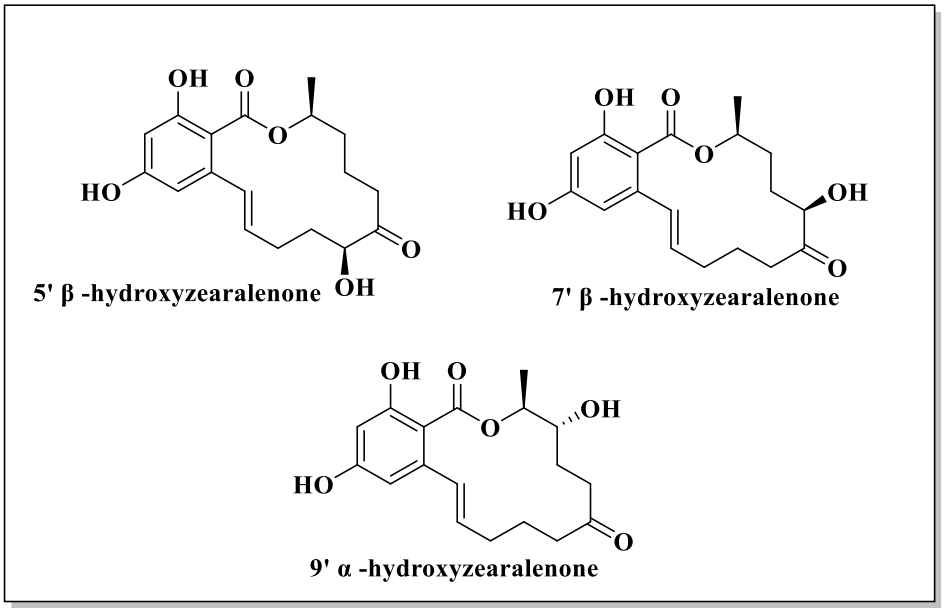


Figure 3: Hydroxyzearalenones

6 novels of 14-membered resorcylic acid lactones (RALs), known as hyalodendriellins A–F (**Figure 4**), were discovered from a *Hyalodendriella* sp. culture. Antinematodal, larvicidal, cytotoxic, antibacterial, and antifungal properties of all identified compounds were assessed. Caenorhabditis elegans and meloidogyne incognita showed moderate antinematodal activity against Hyalodendriellin A. Hyalodendriellin C had a larvicidal impact on the mosquito Aedes aegypti fourth-instar larvae.[7]

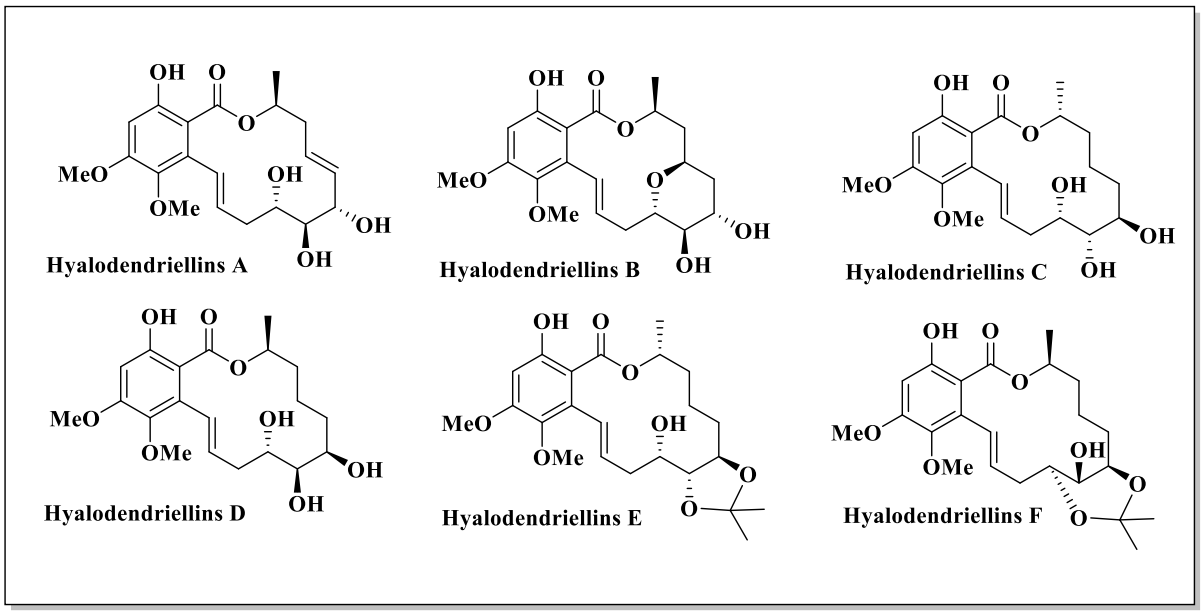


Figure 4: Hyalodendriellins A–F

RALs' biological effects are mostly determined by their capacity to inhibit Hsp90, as seen in radicicol, pochonins, and related compounds, or as selective kinase inhibitors, as seen in hyothemycin, LL-Z1640-2, and other similar compounds. These RALs were examined in depth because of their important biological features in comparison to other RAL classes with less striking properties. However, structure-activity relationship studies (SAR) conducted on these groups of chemicals have shown that they are helpful. Even though naturally occurring RALs provide significant information regarding biological activity during SARs research, their kind and structural changes are limited. As a result, analogue synthesis has shown to be useful in investigating the biological features of these compounds.[8] These compounds piqued the curiosity of synthetic chemists all around the world due to their intriguing structural variations and wide range of biological value. Synthesis of RALs has been accomplished with considerable success in the past and remains a demanding and fascinating endeavour today.

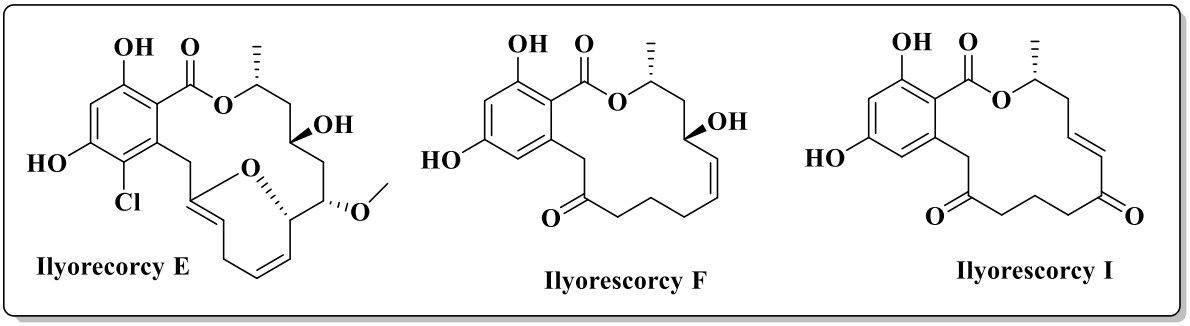
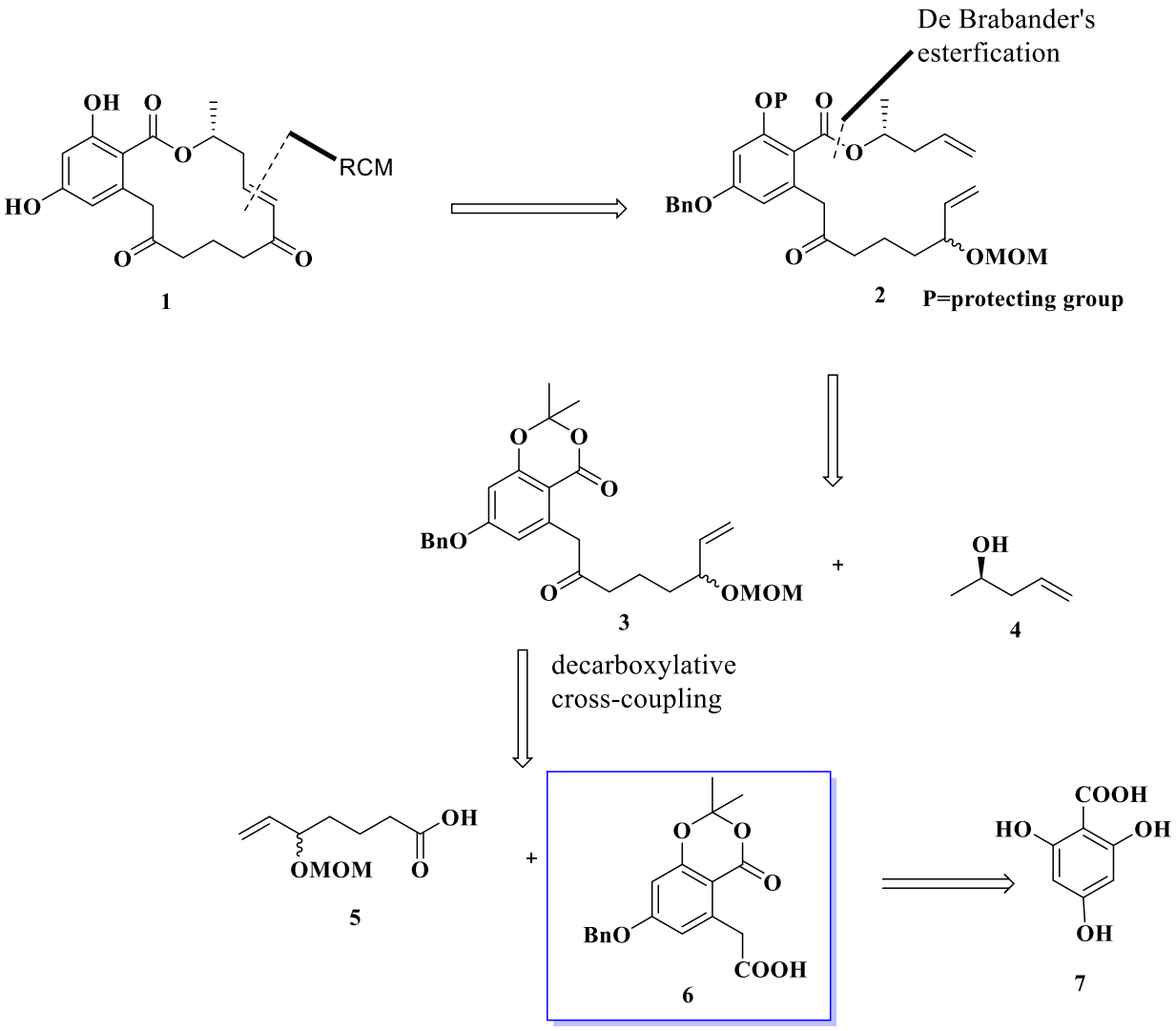


Figure 5: Ilyoresorcy E, F, and I

Zhou et al. recently found 12 novel RALs from the fermentation of the soil-derived fungus *Ilyonectria sp. sb65*, which they named Ilyoresorcy. [14] The fungus was discovered in the soil near the fibrous roots of Schisandra bicolour var in Xinning county, Hunan province, China. Three RAL_{16} (16 membered lactones), eight RAL_{14} (14 membered lactones), one 12 membered RAL_{12}, and five other RALs are among the 12 new RALs. The structural elucidation of these freshly separated RALs was then completed, with relative and absolute configurations ascribed. These novel compounds were tested against A549 human lung adenocarcinoma, 769-P human renal cell carcinoma, and HCT116 human colorectal cancer cell lines to see if they had any cytotoxic activity. Ilyoresorcy E, F, and I exhibited selective immunosuppressive effects toward the LPS-induced B-cell proliferation with IC_{50} values ranging from 5.5 to 21.9 μM (**Figure 5**).

2.2 Present work

Following the discovery and bioactivity studies of Ilyoresorcy I, as synthetic chemists, we have been interested in developing efficient synthetic techniques for the production of this molecule or its unique structural feature to verify its absolute configuration by chemical synthesis. We attempted to suggest an effective synthetic strategy for Ilyoresorcy I total synthesis using commercially accessible, low-cost starting materials (**Scheme 1& 6**). The sections that follow describe the steps taken to complete the entire synthesis of Ilyoresorcy I.

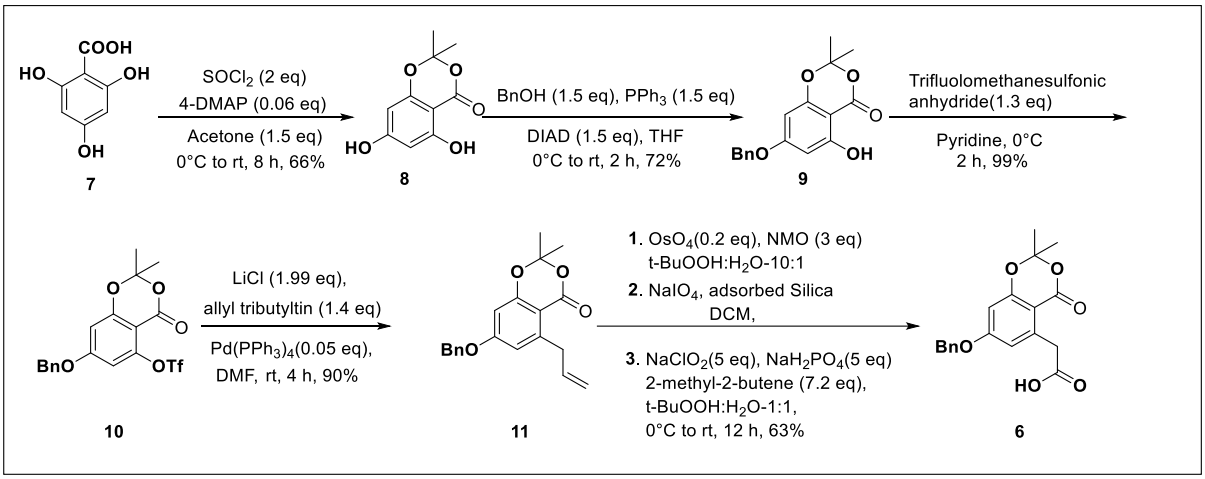


Scheme3: First retrosynthetic analysis of Ilyoresorcy I

As per our retrosynthetic analysis, we contemplated that the synthesis of Ilyoresorcy I (**1**) could be accomplished by the ring-closing metathesis (RCM) of compound **2** using Grubb's catalyst, followed by MOM ether & benzyl groups deprotection. The ester compound **2** could be

obtained by the De Brabander's esterification of **3** with the Allylic alcohol **4** which was available in our lab. The aromatic lactone fragment **3** could be obtained by the coupling of the aromatic fragment **6** with the aliphatic carboxylic acid **5,** which was available in our lab via decarboxylative cross-coupling. The aromatic fragment **6** could be synthesized from commercially available 2,4,6- trihydroxy benzoic acid **7**.

Synthesis of aromatic fragment 6

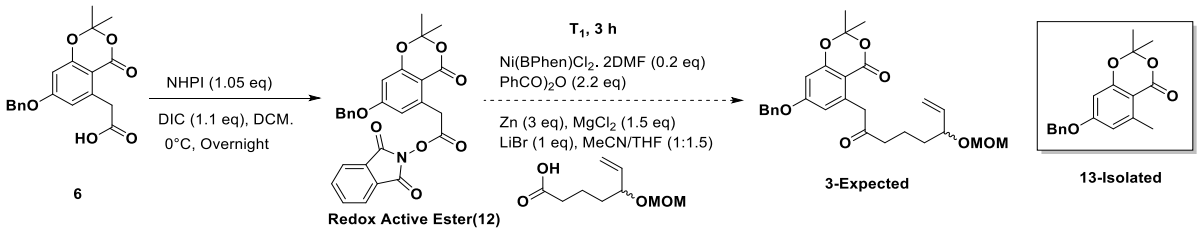


Scheme 4: Synthesis of the compound **6**

Synthesis of the carboxylic acid **6**, required for the decarboxylative cross-coupling, was synthesized from commercially available 2,4,6- trihydroxy benzoic acid. The reaction of 2,4,6-trihydroxy benzoic acid monohydrate **7** with $SOCl_2$, DMAP, and acetone gave the acetonide protected compound **8** in 66% yield.[17] The presence of singlet at δ 1.67 ppm for methyl groups of acetonide in ^{1}H NMR spectrum indicated the formation of the product. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z 211.0610 $[M + Na]^+$ in HRMS spectrum further confirmed this transformation. Selective protection of the phenolic group **8** as its benzyl ether following the Mitsunobo protocol (PPh_3, DIAD) afforded compound **9** in 72% yield.[18] The presence of multiplet at δ 7.46 – 7.35 & singlet at δ 5.09 ppm for the benzyl group and the loss of hydroxy proton in the ^{1}H NMR spectrum indicated the formation of the product. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z [M]: 301.1091 in HRMS spectrum further confirmed this transformation

The free hydroxyl group in **9** was converted to its triflate with trifluolomethanesulfonic anhydride in the presence of anhydrous pyridine to obtain compound **10** in 99% yield.[17] The absence of hydroxy proton at δ 10 ppm in the ^{1}H NMR spectrum indicated the formation of the

product. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z [M + H]$^{+}$: 433.0599 in HRMS spectrum further confirmed this transformation. Treatment of **10** with allyl stannane and LiCl in the presence of palladium catalyst under Stille coupling conditions furnished **11** in 90% yield.[17] The presence of alkene hydrogen peaks at δ 6.11 – 5.92 & 5.07 ppm confirmed the product formation. ^{13}C NMR spectra were in full accord with the assigned structure. A peak at m/z [M + H]$^{+}$ 325.1469 in HRMS spectrum further confirmed this transformation. Dihydroxylation of **11** with OsO_4 & NMO followed by oxidative cleavage with $NaIO_4$ awarded aldehyde in 93% yield. The presence of δ 9.79 ppm peak in crude ^{1}H NMR supported the formation of aldehyde. Further oxidation of the crude aldehyde under Pinnick oxidation conditions afforded the carboxylic acid **6** in 63% yield. This transformation was confirmed by the analysis of the compound, which showed all desired peaks on both ^{1}H and ^{13}C NMR. The absence of the aldehyde proton signal in the ^{1}H NMR spectrum indicated the loss of aldehyde functionality. Instead, the appearance of the peak δ174.38 ppm in ^{13}C NMR showed the formation of carboxylic acid functionality. IR absorption spectrum revealed a peak at 2918 & 1728 cm^{-1} which unambiguously proved the presence of carboxylic acid. The HRMS spectrum showed the desired peak at m/z 365.1050 [M + Na]$^{+}$ thus providing satisfactory proof of the product formation.



Scheme 3: Coupling of aromatic and aliphatic fragments **6** & **5**

Coupling of fragments 6 & 5

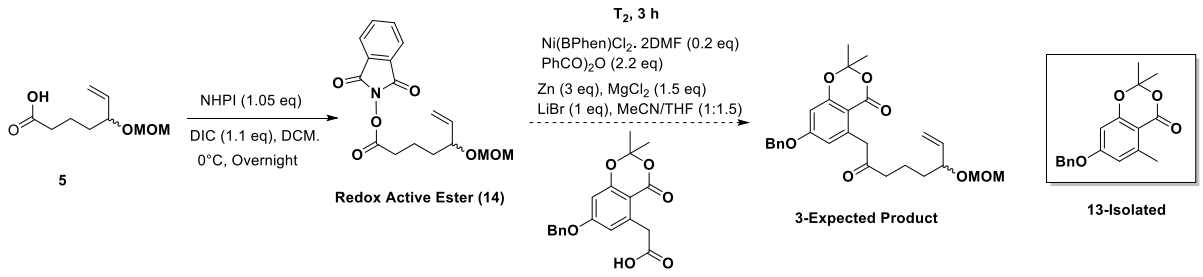
Having both the aromatic and aliphatic coupling partners **6 & 5** in hand, decarboxylative cross-coupling was carried out towards the construction of a macrocyclic framework under different conditions as shown in the (**Schemes 3, 4 & 5 and Table 1 & 2**). Accordingly, the formation of redox-active ester was achieved with NHPI & DIC, and ^{1}H NMR analysis revealed the characteristic protons of the redox-active ester which showed signals at δ 7.93 – 7.85 (m, 2H), 7.81 – 7.68 (m, 2H), 7.50 – 7.33 (m, 5H), 6.75 (s, 1H), 6.48 (d, *J* = 17.8 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 2H), 4.47 (s, 2H), 1.71 (s, 6H). indicating the compound formation. We began

immediately examining the cross-coupling of redox-active ester **12** with MOM-protected aliphatic carboxylic acid **5** as a test reaction.

S.No	Redox-Active Ester(**12**)formation	Temperature($\mathbf{T_1}$)	Observation
1	Redox-active ester was formed, purified (Column Chromatography), confirmed (^{1}H NMR), and used for the next step immediately.	27^o C	Expected product was not formed. Compound **13** was isolated and confirmed by ^{1}H NMR
2	Redox-active ester was formed, purified (Column Chromatography, confirmed (^{1}H NMR), and used for the next step immediately.	45 °C	Expected product was not formed. Compound **13** was isolated and confirmed by ^{1}H NMR

Table 2: Details of experiments executed for the coupling of compounds **6**, **5**

Using a catalytic system of Ni(Bphen)Cl_2•2DMF and $(PhCO)_2O$, Zn, $MgCl_2$, LiBr, MeCN/THF, we observed no cross-coupled product at room temperature (**Table 1 –Entry 1)**. Unfortunately, **13** was observed which was formed most probably by abstracting proton during reductive elimination in decarboxylative cross-coupling. Under the heating conditions also (**Table 1 – Entry 2**), the same proton abstracted product **13** was observed and confirmed by ^{1}H NMR. We next investigated the redox-active ester **14** (formed from an aliphatic carboxylic acid fragment **5** with NHPI & DIC) and **6** (**Scheme-4**). The desired product was not obtained and **13** was observed with & without heating conditions (**Table 2**).

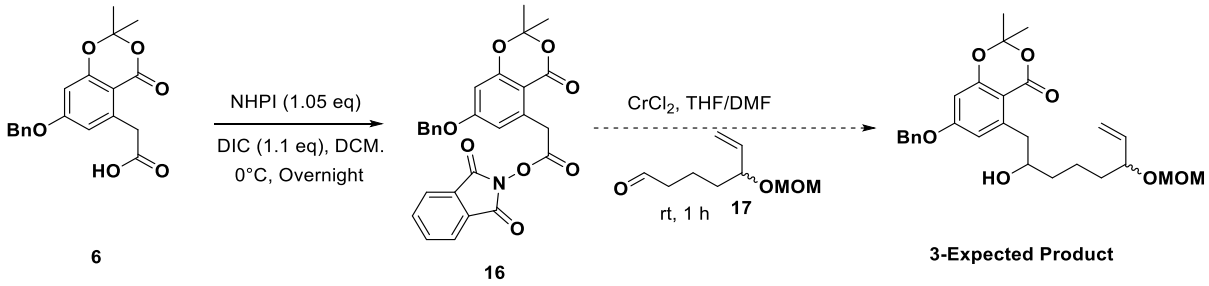


Scheme 4: Coupling of aliphatic and aromatic fragments **5** & **6**

S.No	Redox-Active Ester(**14)** Formation	Temperature($\mathbf{T_2}$)	Observation
1	Redox-active ester was formed and used for the next step immediately.	27 °C	Expected product was not formed. Compound **13** was isolated and confirmed by ^{1}H NMR
2	Redox-active ester was formed, and used for the next step immediately.	45 °C	Expected product was not formed. Compound **13** was isolated and confirmed by ^{1}H NMR

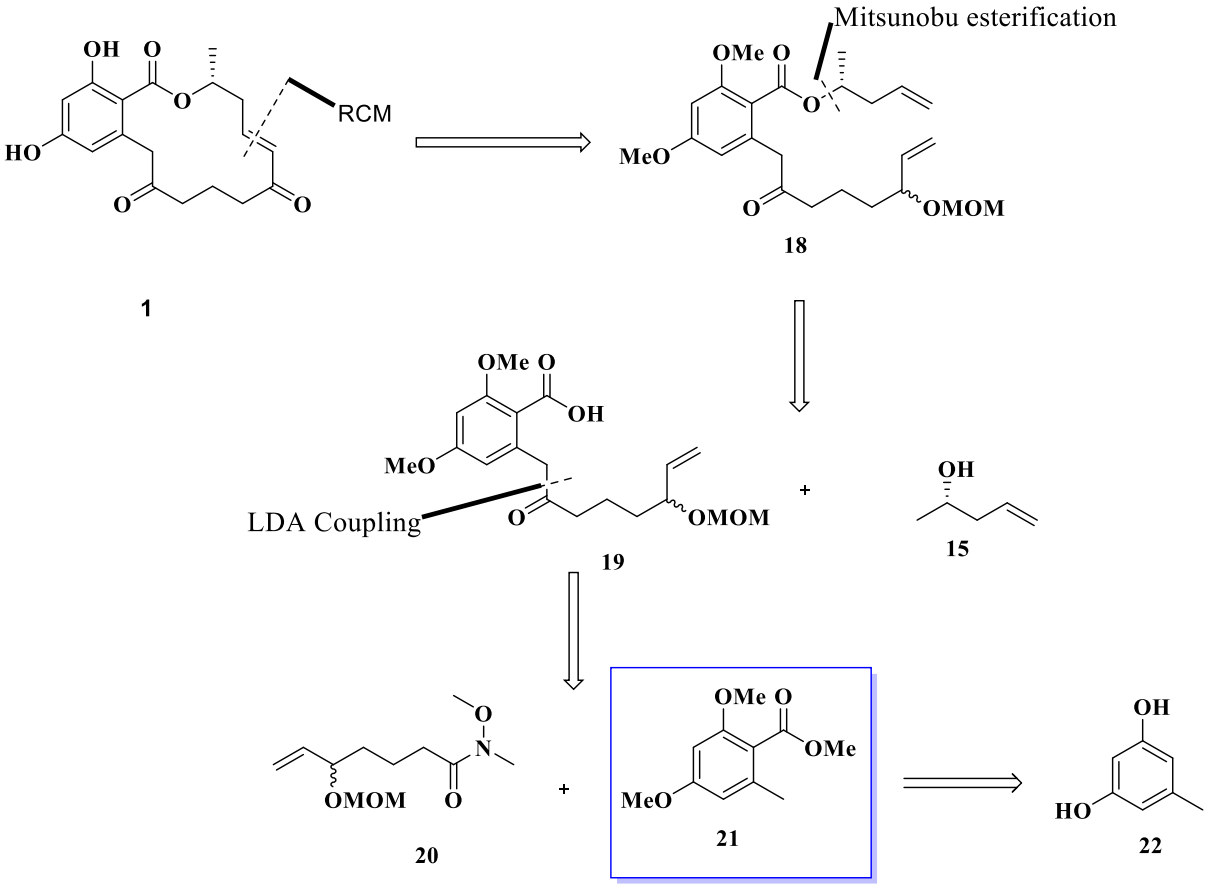
Table 2: Details of experiments executed for the coupling of compounds **5**, **6**

To circumvent this problem, we tried to optimize under decarboxylative Nozaki−Hiyama−Kishi(NHK) conditions. The reaction of redox-active ester **16** with aliphatic aldehyde fragment **17** (Which was available in our lab**)** in the presence of $CrCl_2$ left us with no product (**scheme 5**). Due to unsatisfactory results, we attempted to change the aromatic partner in our retrosynthetic plan and followed the new forward synthetic plan as shown in the (**Scheme 6**)



Scheme 5: Coupling of aromatic and aliphatic fragments **6** & **17**

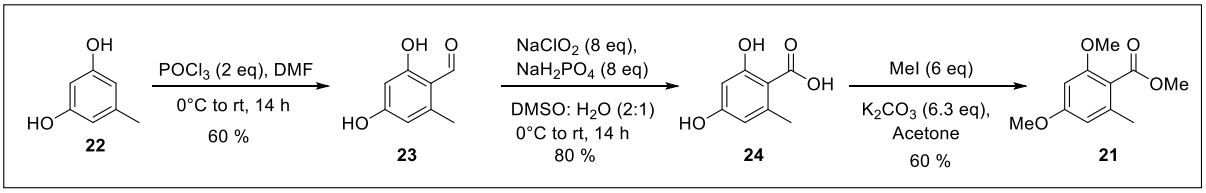
Modified Retrosynthetic Plan



Scheme 6: Modified retrosynthetic analysis of Ilyoresorcy I

As per our new retrosynthetic analysis, we contemplated that the synthesis of Ilyoresorcy I (**1**) could be accomplished by the ring-closing metathesis (RCM) of compound **18** using Grubb's second-generation catalyst, followed by MOM ether -deprotection and Methyl -deprotection. The ester compound **18** could be obtained by the Mitsunobu esterification of **19** with the Allylic alcohol **15** which was available in our lab. The ester compound **19** could be obtained by the coupling of the aromatic lactone fragment **21** with the aliphatic carboxylic acid **20** via benzylic lithiation of the compound **21**. The aromatic fragment **21** could be synthesized from commercially available orcinol **22**.

Synthesis of aromatic fragment 21

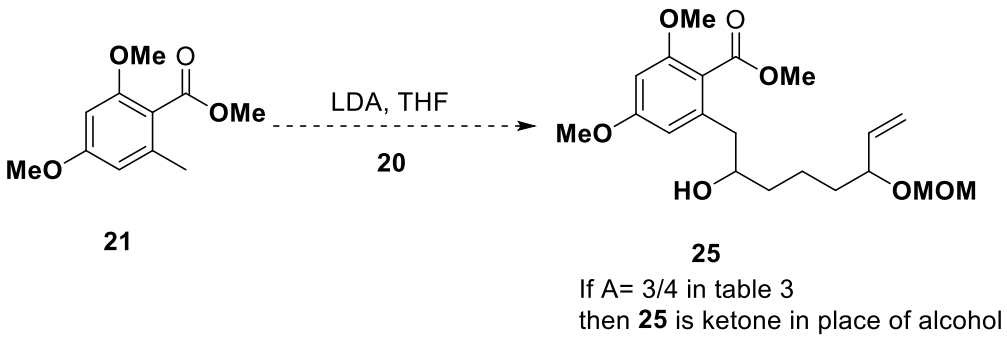


Scheme 7: Synthesis of the compound **21**

To evaluate the feasibility of our approach, we started our investigations with the synthesis of the aromatic ester **21** from the commercially available orcinol in three steps. Aldehyde insertion into orcinol was achieved smoothly by subjecting to the Vilsmeier-Haack reaction. Treatment of orcinol **22** with $POCl_3$ (2 equiv.) in DMF for 14 h furnished **23** as yellow solids in 60% yield.[19] The product formation was confirmed by ^{1}H NMR spectrum, which showed a signal corresponding to aldehyde proton at δ 10.12 ppm indicating the compound formation, ^{13}C NMR spectrum revealed resonance peak at δ 193.43 ppm for aldehyde carbonyl carbon was in the favour of the product formation. The HRMS spectrum showed a peak at m/z [M + H] $^+$: 153.0549 finally confirming this transformation. IR absorption spectrum revealed a peak at 1624.34 cm^{-1} which unambiguously proved the presence of an aldehyde.

Aldehyde **23** was oxidized to carboxylic acid **24** under Pinnick oxidation conditions by treating with $NaClO_2$ (8 equiv.) and NaH_2PO_4(8 equiv.) in DMSO: H_2O mixture for 14 h resulting in **24** as yellow solids in 80% yield.[19] The absence of δ 10.12 peak in the ^{1}H NMR spectrum & δ 193.43 in ^{13}C and the presence of δ 173.36 in ^{13}C showed the loss of aldehyde and the formation of carboxylic acid in **24**. The HRMS spectrum showed a peak at m/z [M-1]: 167.0336 finally confirming this transformation. IR absorption spectrum revealed a peak at 2943.12 and 1622.45 cm^{-1} which unambiguously proved the presence of an aldehyde. Methylation of three OH groups was achieved by methyl iodide which resulted in **21** yellow solids in 60% yield.[20] ^{1}H NMR analysis revealed the characteristic protons of the methyl group which showed signals at 3.88 (s, 3H), 3.80 (s, 6H) indicating the compound formation. ^{13}C NMR spectra were in full accord with the assigned structure. The HRMS spectrum showed the desired peak at m/z 211.0970 [M + H] $^+$ thus providing satisfactory proof of the product formation.

Coupling of fragments 21 & 20



Scheme 8: Coupling of aromatic and aliphatic fragments **21 & 20**

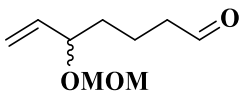
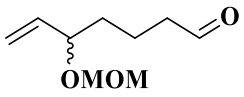
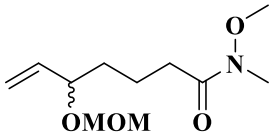
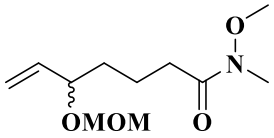
S.No.	**20**	LDA equivalents	Observations
1		1.1	Expected product was not formed. Starting material recovered
2		2.5	Expected product was not formed. Starting material recovered
3		1.1	Expected product was not formed. Starting material recovered
4		2	Expected product was not formed. Starting material recovered.

Table 3: Details of experiments executed for the coupling of compounds **21**, **20**

The stage was set for the crucial LDA coupling reaction between the aliphatic fragment **20** and the aromatic ester fragment **21**. (**Scheme 6**) Although this method is similar to substrates and is reasonably reported, the reaction was not as straightforward as we initially conceived. Several attempts were made to re-create the reported procedures but none were up to the mark. (**Table 3**) Consequently, we had to venture into trying an array of methods and conditions in our attempts to synthesize a compound **25**.

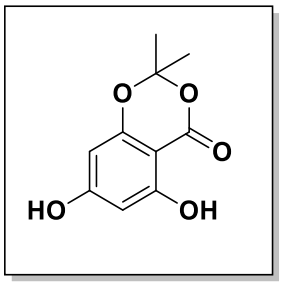
Few procedural changes were then introduced to try and achieve the product **25** formation. Initial attempts toward LDA coupling with the aliphatic aldehyde (**Table 3- Entry 1**) were unsuccessful. Increased LDA (**Table 3- Entry 2)** equivalents also left us with no product. Due to no conversion with an aldehyde in increased equivalents, the next coupling was tried with aliphatic Weinreb amide (**Table 3- Entry 3 & 4)**. Surprisingly, the MOM group, double bond hydrogens and one of the methyl groups hydrogens were absent in the ^{1}H NMR for (**Table 3- Entry 4**). Due to unsatisfactory results, we attempted to standardize the reaction by experimenting with an array of conditions and methods to try and improve the results. A concise picture of the experimental variations attempted is summarized in table **3.**

2.3 Conclusion

We have synthesized the key fragments **6, 21** to achieve Ilyoresorcy I and they were well characterized by spectral and analytical data such as ^{1}H NMR, ^{13}C NMR, HRMS and IR. However, we ended up with no product after several variations in aromatic coupling partners **21 & 6**. Because of the challenges in linking, more trials on modifying the aliphatic fragment are needed.

2.4 Experimental Section

2.4.1 5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3] dioxin-4-one **8**



To a solution of 2, 4, 6-trihydroxy benzoic acid **7** (2 g, 11.8 mmol, 1 equiv.), 4- dimethyl amino pyridine (87 mg, 0.71 mmol, 0.06 equiv.), and acetone (1.3 ml, 17.7 mmol, 1.5 equiv.), was added a solution of thionyl chloride (1.7 ml, 23.6 mmol, 2 equiv..) slowly at 0 °C and stirred for 1 h. At this point, the reaction mixture was purged with nitrogen to remove HCl. After 8 h of stirring at rt, the solvent was concentrated and the residue dissolved in a mixture of hexane-methylene chloride (l: l, v/v) and filtered through a pad of silica gel and then the filtrate was evaporated. To the residue was added hexane and the resultant solution cooled to 15 °C and allowed to stand overnight. The desired product was filtered and dried to obtain **8** as a white solid (1.5 g, 66%)

^{1}H NMR (400 MHz, DMSO-d_6) : δ 10.89 (s, 1H), 10.30 (s, 1H), 6.02 (s, 1H), 5.94 (d, *J* = 0.8 Hz, 1H), 1.67 (s, 6H) ppm.

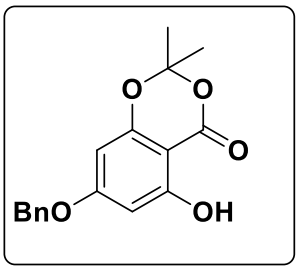
^{13}C NMR (100 MHz, DMSO-d_6) : δ 166.7, 163.9, 162.6, 157.3, 106.8, 97.7, 95.7, 92.2, 25.5 ppm.

IR (neat) : ν_{max} 3179, 2922, 2851, 1626, 1600, 1268, 1158, 1090 cm^{-1}

HRMS (ESI-TOF) :m/z $[M + H]^+$:211.0610

M.P. :200-210°C

2.4.2 7-(benzyloxy)-5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3] dioxin-4-one **9**



To a stirred solution of diol **8** (200 mg, 0.952 mmol, 1 equiv.) and benzyl alcohol (0.15 mL, 1.43 mmol, 1.5 equiv.) in THF (2 mL), was added triphenylphosphine (375 mg, 1.43 mmol, 1.5 equiv.), and DIAD (0.3 mL, 1.43 mmol, 1.5 equiv.) at 0 ºC and the mixture was warmed to rt over 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc(25 ml), washed thrice with water(3 × 5 ml) and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography over silica gel (EtOAc: Hex 1:19) to afford **9** (205 mg, 72 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 10.47 (s, 1H), 7.46 – 7.35 (m, 5H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.09 (s, 2H), 1.75 (s, 6H) ppm.

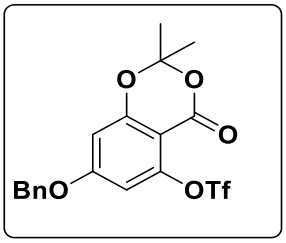
^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.7, 165.1, 163.1, 156.8, 135.6, 128.7, 128.4, 127.5, 106.9, 96.5, 95.3, 93.2, 70.4, 25.6 ppm.

IR (neat) : ν_{max} 3199, 2935, 1675, 1638, 1583, 1501, 1353, 1268, 1192, 1162, 1095, 1025, 713, 679 cm^{-1}

HRMS (ESI-TOF) :m/z [M]: 301.1091

M.P. :80-85°C

2.4.3 7-(benzyloxy)-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5 yl trifluoromethanesulfonate **10**



Trifluolomethanesulfonic anhydride (0.11 mL, 0.649 mmol, 1.3 equiv.) was successively added to a solution of compound **9** (150 mg, 0.499 mmol, 1 equiv.) in anhydrous pyridine (1.5 mL) and the mixture was stirred at 0 ºC for 2 h. The reaction was quenched with water (5 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford compound **10** (193 mg, 90%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.51 – 7.35 (m, 5H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 5.13 (d, *J* = 28.0 Hz, 2H), 1.76 (s, 6H) ppm.

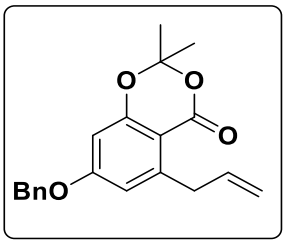
^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.6, 158.8, 157.0, 149.9, 134.6, 128.8, 127.6, 106.6, 105.8, 102.0, 101.2, 71.2, 25.5 ppm.

IR (neat) : ν_{max} 1739, 1626, 1579, 1424, 1283, 1218, 1195, 1158, 1137, 1052, 823, 731 cm^{-1}

HRMS (ESI-TOF) : m/z $[M + H]^+$: 433.0599

M.P. :80-90°C

2.4.4 5-allyl-7-(benzyloxy)-2,2-dimethyl-4H-benzo[d] [1,3] dioxin-4-one **11**



To a stirred solution of Triflate **10** (750 mg, 1.73 mmol, 1 equiv.) in anhydrous DMF (7.5 mL) were added LiCl (150 mg, 3.44 mmol, 1.99 equiv.), $Pd(PPh_3)_4$ (105 mg, 0.087 mmol, 0.05 equiv.) and allyl tributyltin (0.8 mL, 2.4 mmol, 1.4 equiv.) at room temperature. The resulting mixture was allowed to stir for another 4 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (25 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1: 9) to obtain **11** (506 mg, 90%) as a colourless liquid.

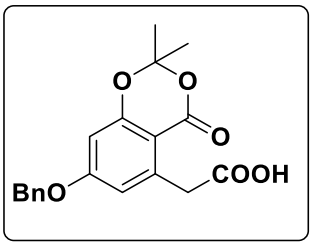
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.54 – 7.34 (m, 5H), 6.60 (s, 1H), 6.31 (d, *J* = 66.1 Hz, 1H), 6.11 – 5.92 (m, 1H), 5.07 (d, *J* = 10.3 Hz, 4H), 3.89 (t, *J* = 23.1 Hz, 2H), 1.69 (s, 6H) ppm.

^{13}C NMR (175 MHz, $CDCl_3$) : δ 164.0, 160.1, 159.0, 147.2, 136.4, 135.7, 116.4, 112.7, 105.0,100.3, 70.3, 38.4, 25.6 ppm.

IR (neat) : ν_{max} 2927, 1723, 1608, 1575, 1437, 1276, 1202, 1156, 1050 cm^{-1}

HRMS (ESI-TOF) :m/z $[M + H]^+$: 325.1469

2.4.5 2-(7-(benzyloxy)-2,2-dimethyl-4-oxo-4H-benzo[d][1,3] dioxin-5-yl) acetic acid **6**



To a solution of **11** in t-butanol & water (10:1), was added OsO_4 (1.6 ml, 0.2 equiv., 0.031 mmol) and NMO (in 50 % toluene, 0.22 ml, 3 equiv., 0.462 mmol) at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with sodium thiosulfite and diluted with ethyl acetate (5 ml). The layers were separated and the aqueous phase was extracted thoroughly with ethyl acetate (3 × 5 ml). The combined organic layers were washed with water (10 ml), dried over anhydrous Na_2SO_4, and concentrated. The crude product was used for the next step without purification.

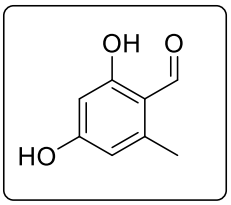
The crude (428 mg) was dissolved in CH_2Cl_2 (47 ml) and silica paste (230-400 mesh silica in $NaIO_4$, 3.3 g) was added and stirred for 1 hour. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (10 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was used for the next step without purification by checking only ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.79 (s, 1H), 7.63 – 7.33 (m, 5H), 6.51 (d, *J* = 12.1 Hz, 1H), 6.46 (d, *J* = 12.4 Hz, 1H), 5.15 (dd, *J* = 38.0, 25.8 Hz, 2H), 4.24 – 3.97 (m, 2H), 1.71 (s, 6H).

To a solution of crude aldehyde (397 mg, 1.22 mmol, 1 equiv.) in 6.6 ml, tertiary butyl alcohol was added 2-Methyl-2-Butene (1 ml, 8.8 mmol, 7.2 equiv.) at room temperature. NaH_2PO_4 (732 mg, 6.1 mmol, 5 equiv.) and $NaClO_2$ (552 mg, 6.1 mmol, 5 equiv.) were dissolved in 6.6 ml water and added to this mixture dropwise, at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (5 ml). The layers were separated and the aqueous phase was extracted thoroughly with ethyl acetate (3 × 5 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc: Hexane, 3:7) to afford the desired product as a yellow solid **6** (264 mg, 63 % yield).

^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.50 – 7.31 (m, 5H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.46 (t, *J* = 8.6 Hz, 1H), 5.09 (s, 2H), 4.34 – 3.44 (m, 2H), 1.71 (s, 6H) ppm.
^{13}C NMR (175 MHz, $CDCl_3$)	: δ174.3, 164.3, 161.4, 159.0, 139.3, 135.4,128.3, 114.6, 105.6, 101.6, 70.1, 60.4, 40.4, 25.5 ppm.
IR (neat)	: ν_{max} 2918, 1728, 1700, 1613, 1583, 1440, 1327, 1283, 1206, 1173, 1054, 1028, 969 cm^{-1}
HRMS (ESI-TOF)	:m/z $[M + Na]^+$: 365.1050
M.P.	: 145-150°C

2.4.6 2,4-dihydroxy-6-methylbenzaldehyde **23**



To a solution of $POCl_3$ (3 ml, 32.22 mmol, 2 equiv.) in dry DMF (10 ml) at 0 °C has added a solution of orcinol **22** (2 g, 16.11 mmol, 1 equiv.) in DMF (5 ml). The reaction mixture was stirred at room temperature for 14 h. Starting material conversion was monitored by work-up for a small amount of aliquot taken from the reaction mixture according to the below-described procedure. Following this, it was cooled down to 0 °C, and treated with ice-cold H_2O (25 ml), then with 10% NaOH solution to a pH of 10. The resulting solution was heated to reflux for 15 minutes and cooled down to 0 °C. The solution was then acidified to pH = 3 with concentrated HCl. The solids formed were filtered with what man filtration, washed with H_2O, and oven-dried at 100 °C to furnish the product as a yellow solid **23** (1.4g, 60% yield).

^{1}H NMR (400 MHz, Acetone-d_6) : δ 12.50 (s, 1H), 10.12 (s, 1H), 9.55 (s, 1H), 6.32 (s, 1H), 6.19 (s, 1H), 2.55 (s, 3H) ppm.

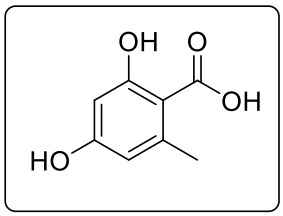
^{13}C NMR (100 MHz, Acetone-d_6) : δ 193.4, 165.8, 145.1, 111.7, 100.5, 17.2 ppm.

IR (neat) : ν_{max} 3080, 1622, 1585, 1455, 1269, 1203, 1164 cm^{-1}

HRMS (ESI-TOF) : m/z $[M + H]^+$: 153.0549

M.P. :180-190°C

2.4.7 2,4-dihydroxy-6-methyl benzoic acid **24**



To a solution of the **23** (1.8g, 11.8 mmol, 1 equiv.) and NaH_2PO_4 (12 g, 94.4 mmol, 8 equiv.) in DMSO (100 ml) and H_2O (25 ml) at 0 °C, was slowly added a solution of $NaClO_2$ (9.1 g, 94.4 mmol, 8 equiv.) in H_2O (25 ml). The mixture was allowed to stir at room temperature for 12 h. After complete conversion (monitored by TLC), saturated Na_2CO_3 solution was added (25 ml) and the reaction mixture was extracted with ethyl acetate (50 ml). The aqueous phase was acidified to pH = 1 with concentrated HCl and was extracted with ethyl acetate (3×25ml). This extracted layer was washed with brine (25 ml) and dried over anhydrous Na_2SO_4. and concentrated, evaporated to dryness, and then purified by silica gel column chromatography (ethyl acetate/hexane = 1: 1) to obtain the desired product **24** (1.65 g, 80 %) as a yellow solid.

^{1}H NMR (400 MHz, Acetone-d_6) : δ 6.31 (s, 1H), 6.22 (d, *J* = 20.1 Hz, 1H), 2.54 (s,3H) ppm.

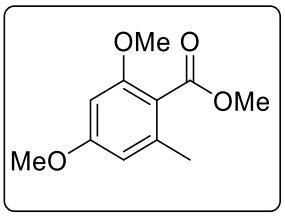
^{13}C NMR (100 MHz, Acetone-d_6) : δ 173.3, 166.3, 162.5, 144.1, 111.2, 100.7, 41.68, 23.4 ppm.

IR (neat) : ν_{max} 2943, 1622, 1503, 1456, 1359, 1259, 1211, 1174 cm-1

HRMS (ESI-TOF) : m/z [M-1] : 167.0336

M.P. :170-180°C

2.4.8 Methyl 2,4-dimethoxy-6-methyl benzoate **21**



To a suspension of K_2CO_3 (61 mg, 0.44 mmol, 6.3 equiv.) in acetone (20 mL) was added **24** (100 mg, 0.07 mmol) and MeI (0.026 ml, 0.42 mmol, 6 equiv.) was added and the reaction mixture was refluxed for 7 h. After complete conversion (monitored by TLC), the excess solvent was evaporated, the mixture was poured into H_2O, and the reaction mixture was extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with $NaHCO_3$ (10 mL) and brine (10 mL). dried over Na_2SO_4, and was concentrated on the rotatory evaporator and dried under a high vacuum. The crude product was purified by column chromatography over silica gel (EtOAc: Hex; 1:3) to afford **21** (68 mg, 60 %) as yellow liquid and turned into a white solid on cooling to 4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.31 (s, 2H), 3.88 (s, 3H), 3.80 (s, 6H), 2.28 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.3, 161.3, 158.2, 138.2, 116.3, 106.6, 96.1, 55.9, 55.3, 52.0, 19.9 ppm.

IR (neat) : ν_{max} 2949, 2929, 1722, 1603, 1586, 1326, 1262, 1200, 1155, 1092, 1050, 815 cm-1

HRMS (ESI-TOF) : m/z $[M + H]^+$: 211.0980

M.P. :40-50°C

2.5 References

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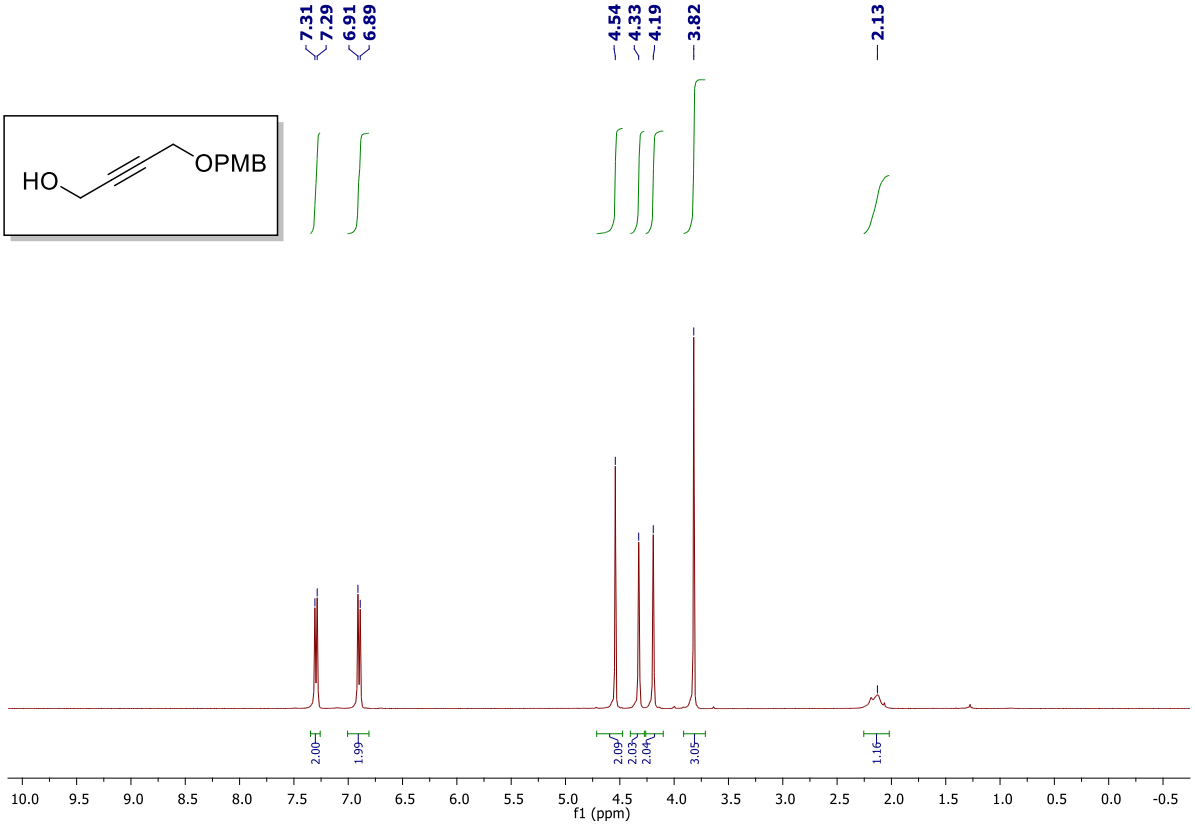
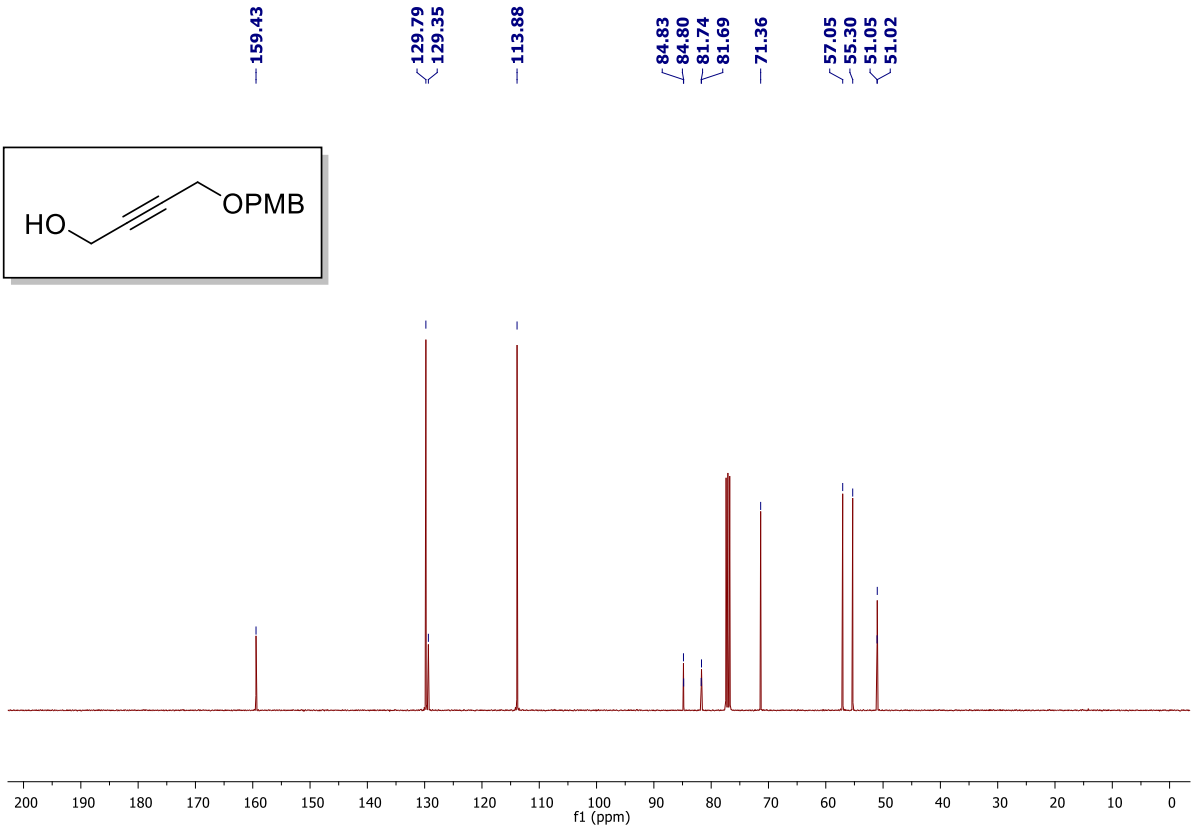
Chapter 1 Spectral data

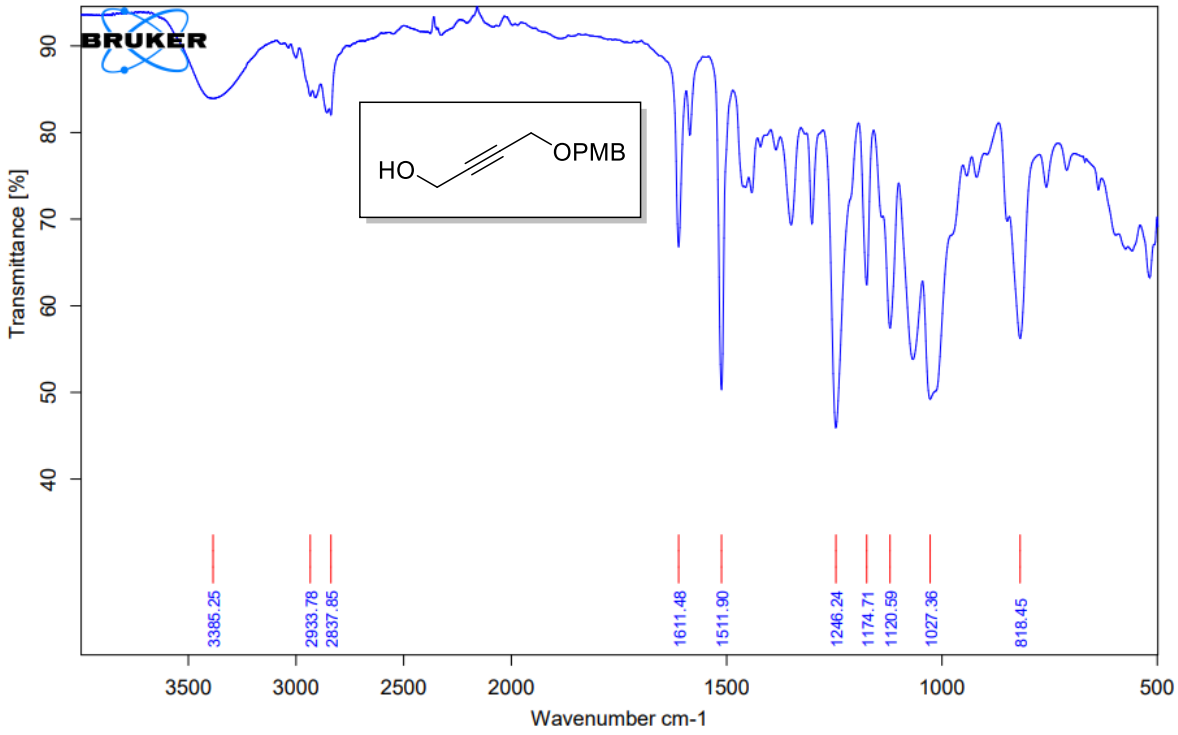
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 11



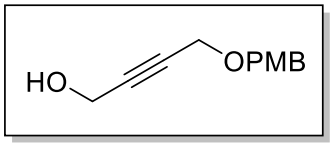
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 11



IR Spectrum of the compound 11



HRMS (ESI-TOF) spectrum of the compound 11



Elemental Composition Report **Page 1**

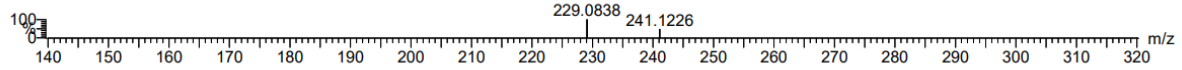
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Even Electron Ions
18 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 12-12 H: 14-14 O: 3-200 23Na: 0-1

TB
SM-234-3 5 (0.113) Cm (5:7)

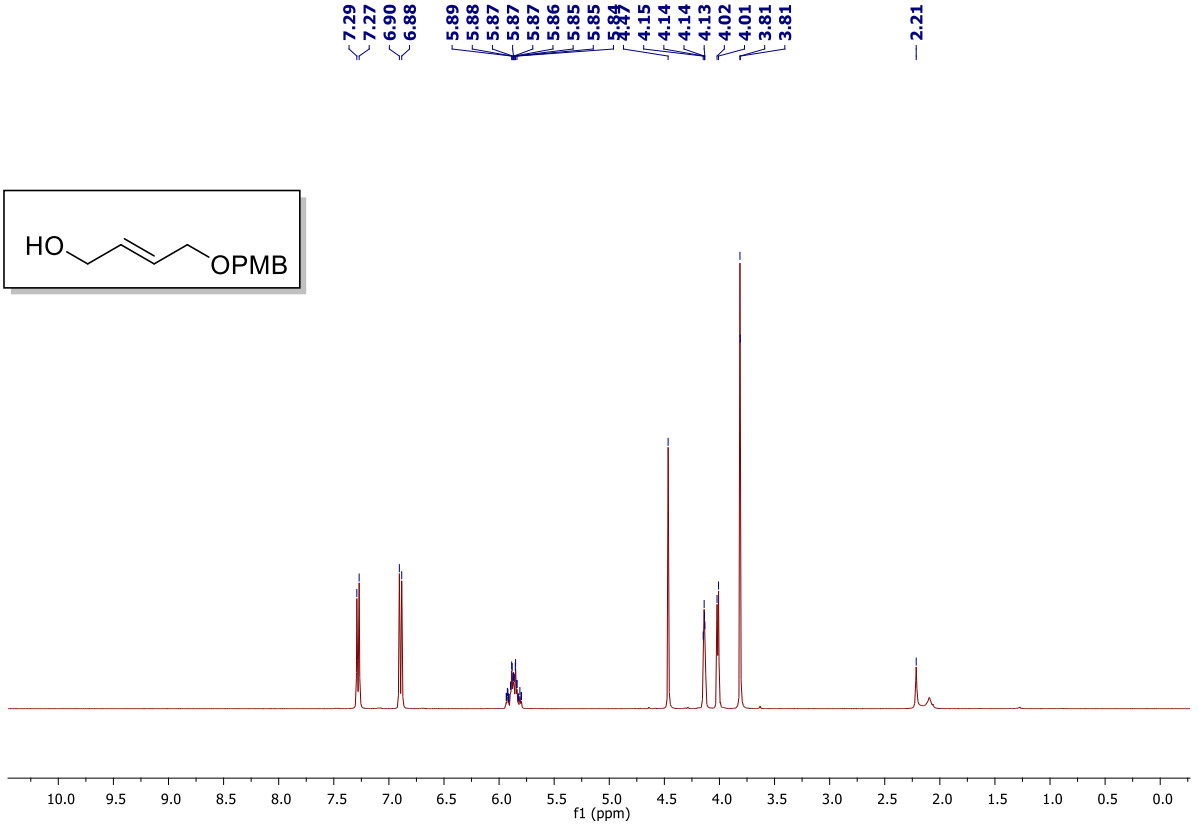
IISER Berhampur

1: TOF MS ES+
1.72e+006

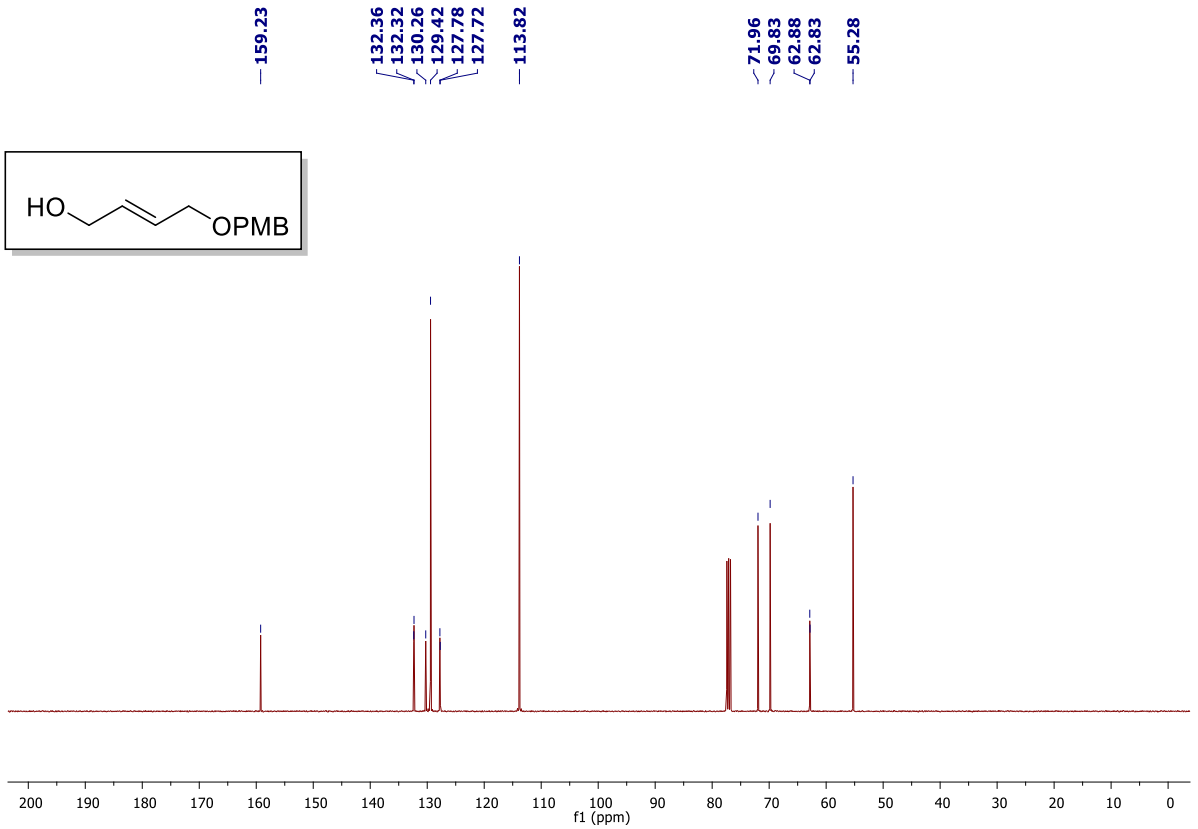


Minimum:				-1.5	
Maximum:		5.0	10.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
229.0838	229.0841	-0.3	-1.3	5.5	C12 H14 O3 23Na

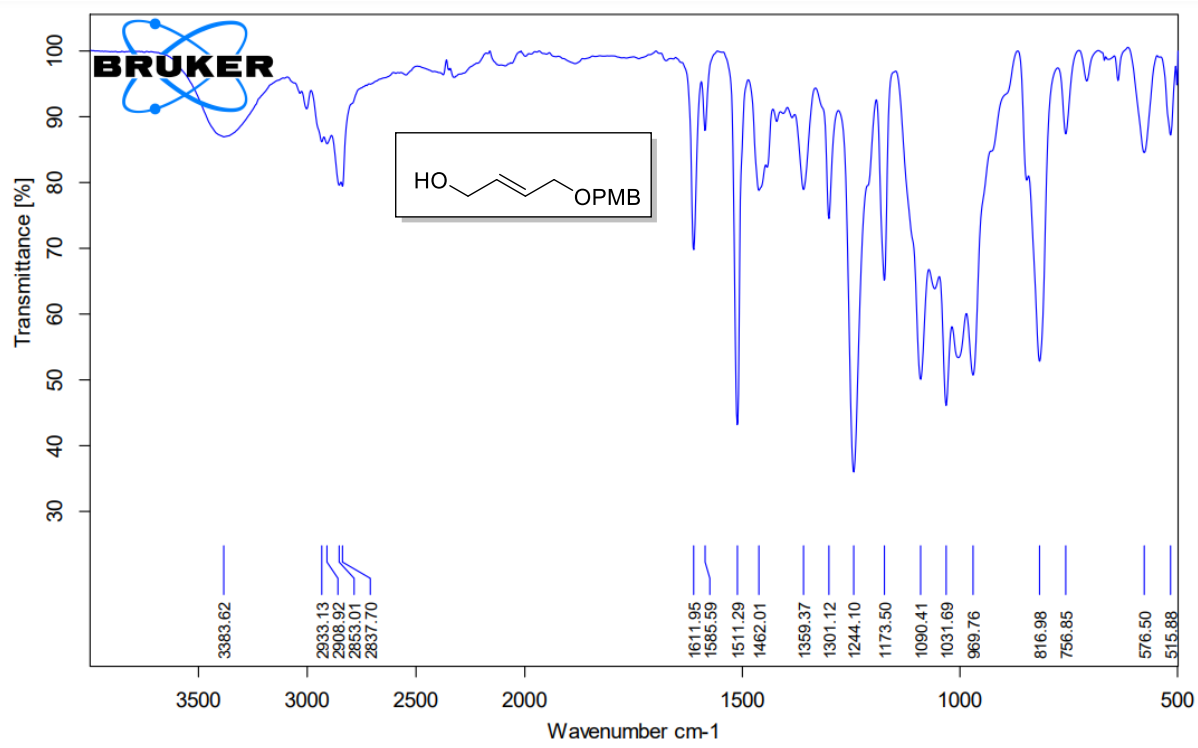
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 12



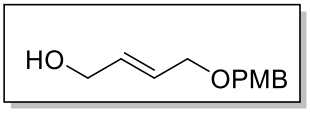
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 12



IR spectrum of the compound 12



HRMS (ESI-TOF) spectrum of the compound 12

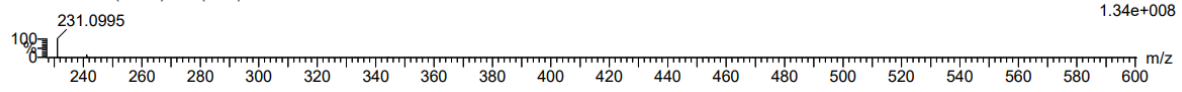


Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

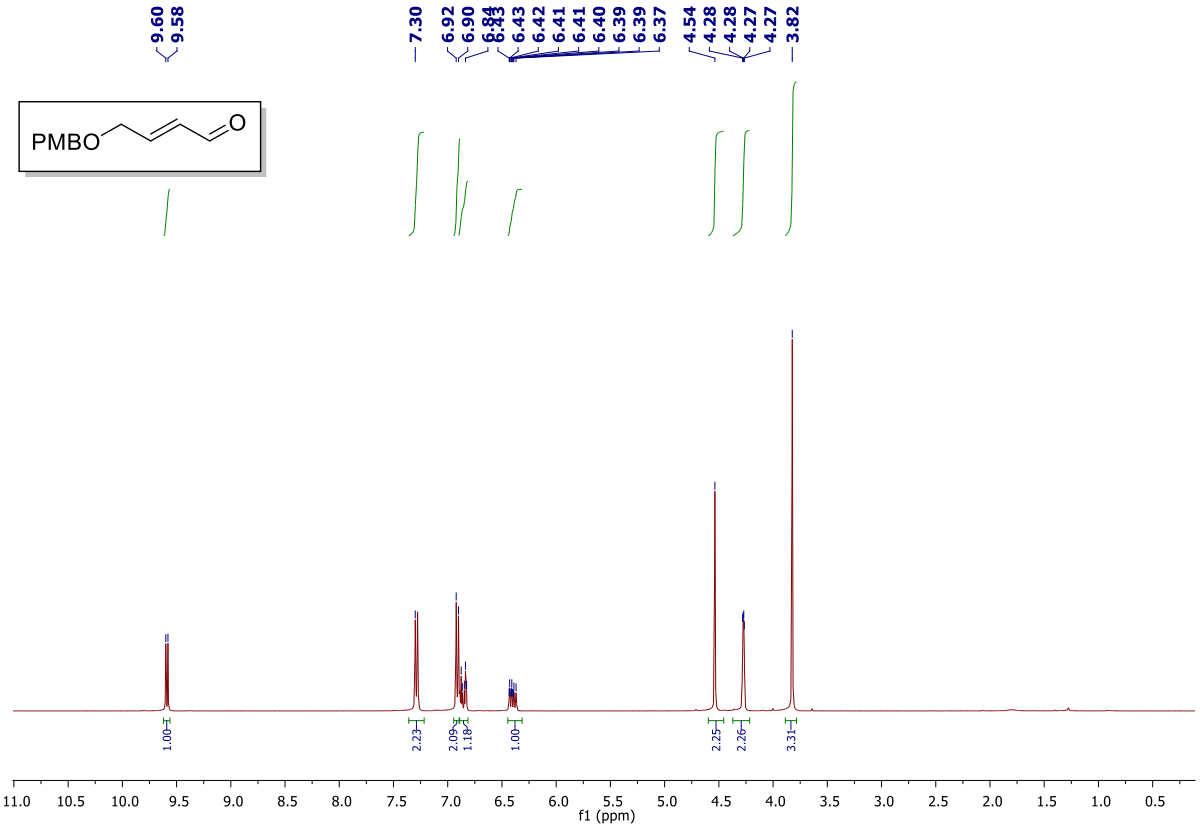
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-17 H: 10-23 O: 3-200 23Na: 0-1

TB
SM-236-ne 25 (0.485) Cm (5:53)
IISER Berhampur
1: TOF MS ES+
1.34e+008

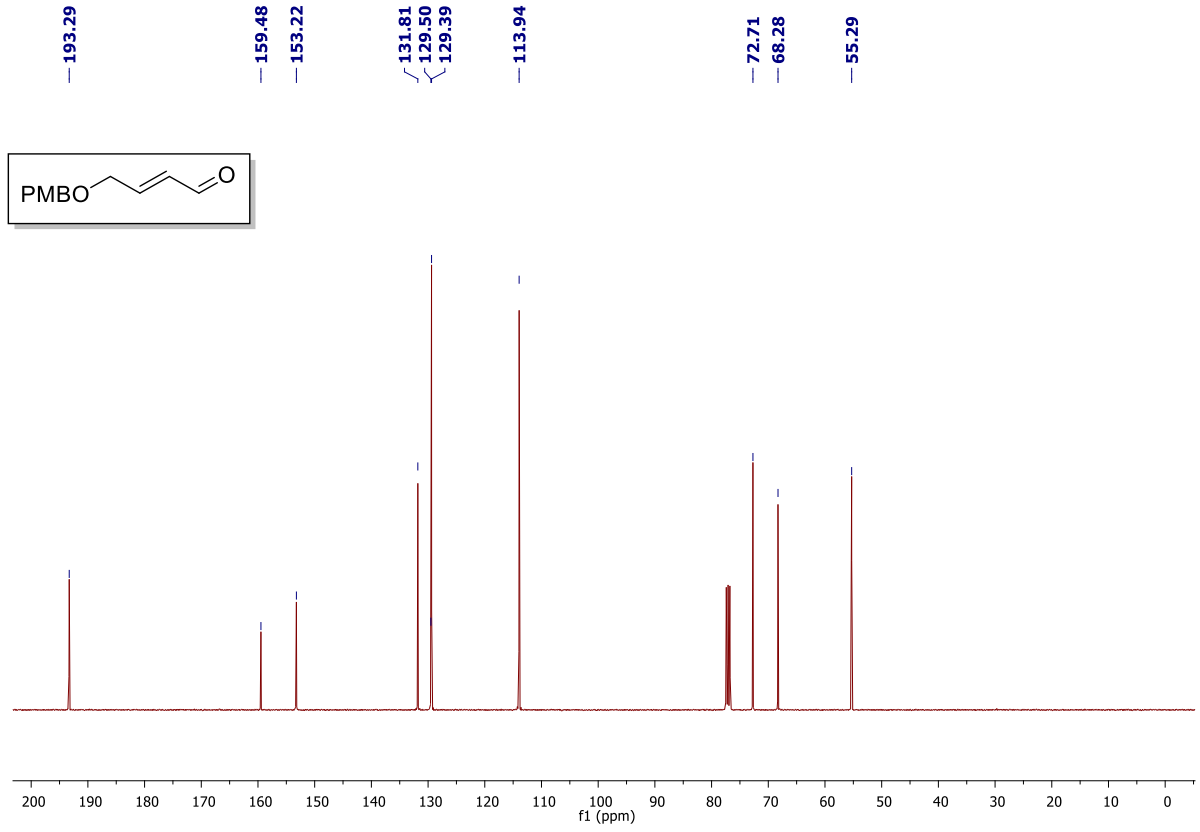


Minimum:				-1.5	
Maximum:		5.0	5.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
231.0995	231.0997	-0.2	-0.9	4.5	C12 H16 O3 23Na

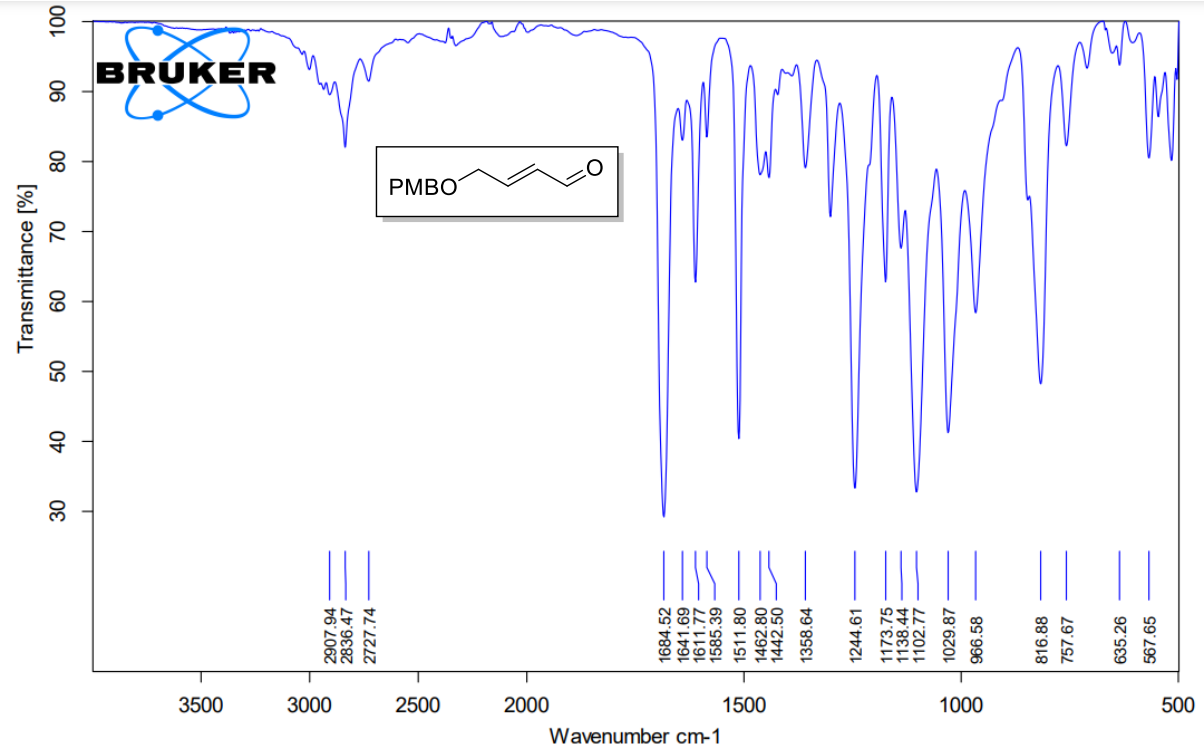
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 13



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 13

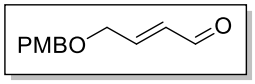


IR spectrum of the compound 13



HRMS (ESI-TOF) spectrum of the compound 13

Elemental Composition Report **Page 1**



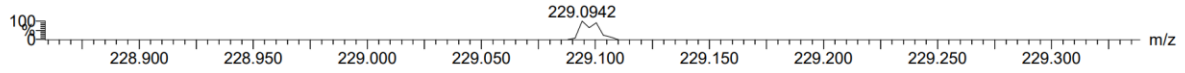
Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-23 H: 10-30 O: 2-200 23Na: 0-1

TB
SM-241-RE-1 24 (0.457)

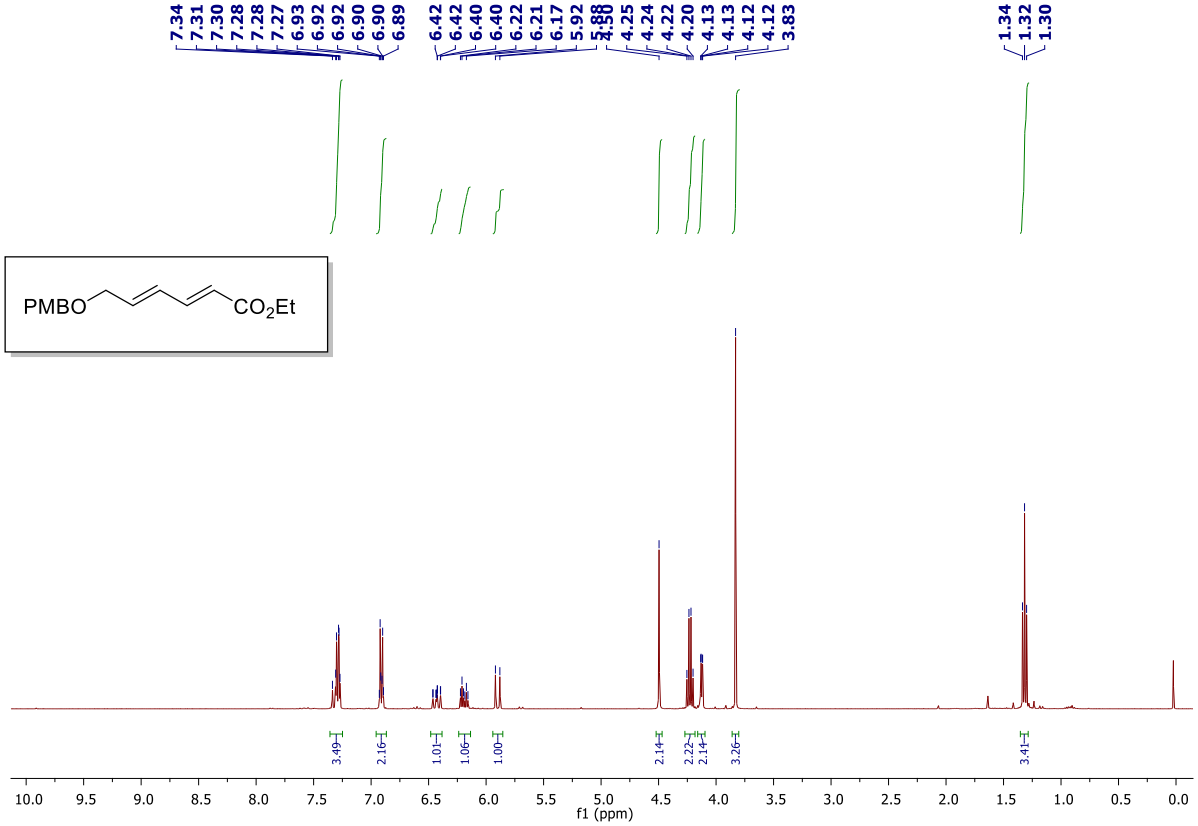
IISER Berhampur

1: TOF MS ES+
5.51e+002

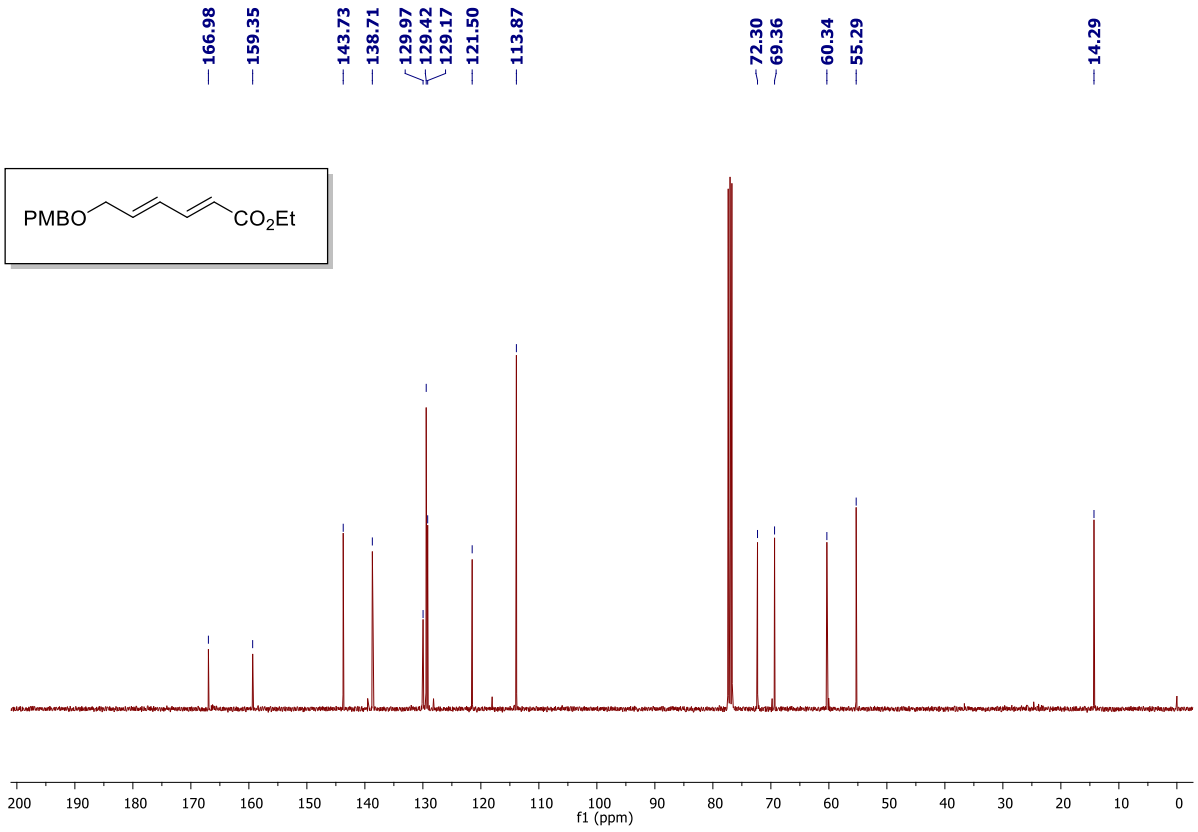


Minimum:				-1.5	
Maximum:		5.0	50.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
229.0942	229.0865	7.7	33.6	8.5	C14 H13 O3
	229.0841	10.1	44.1	5.5	C12 H14 O3 23Na

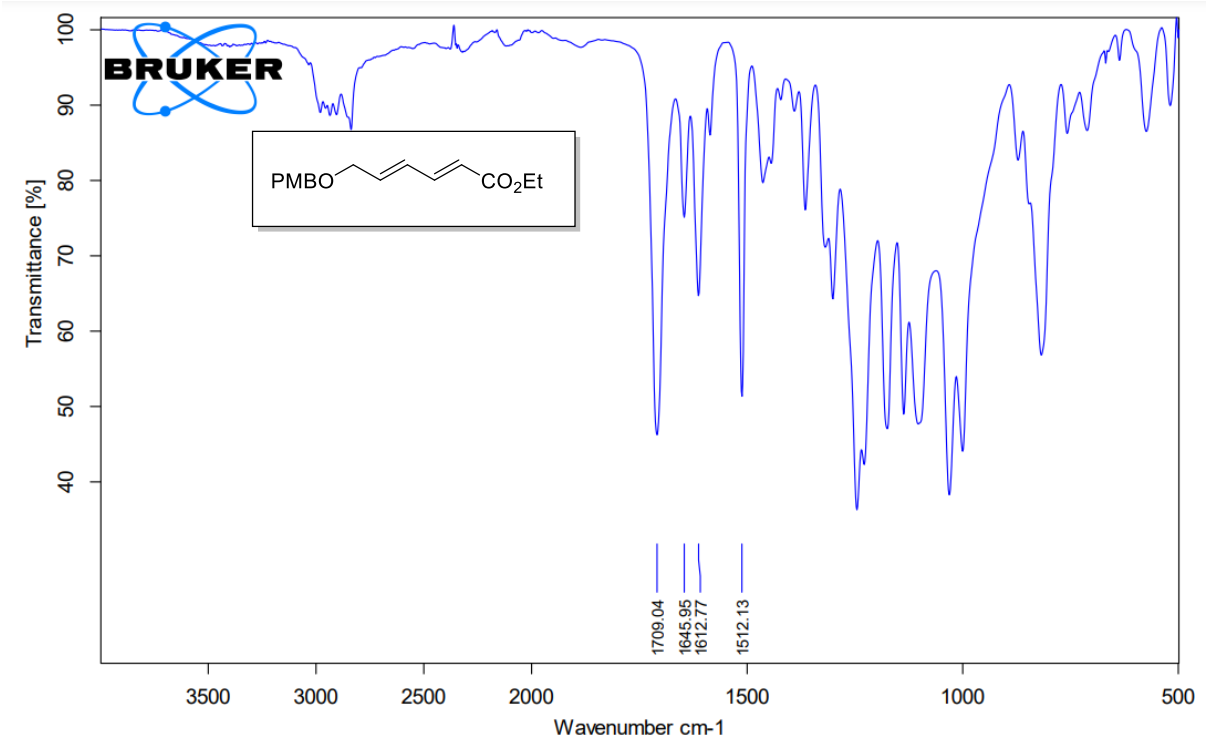
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 14



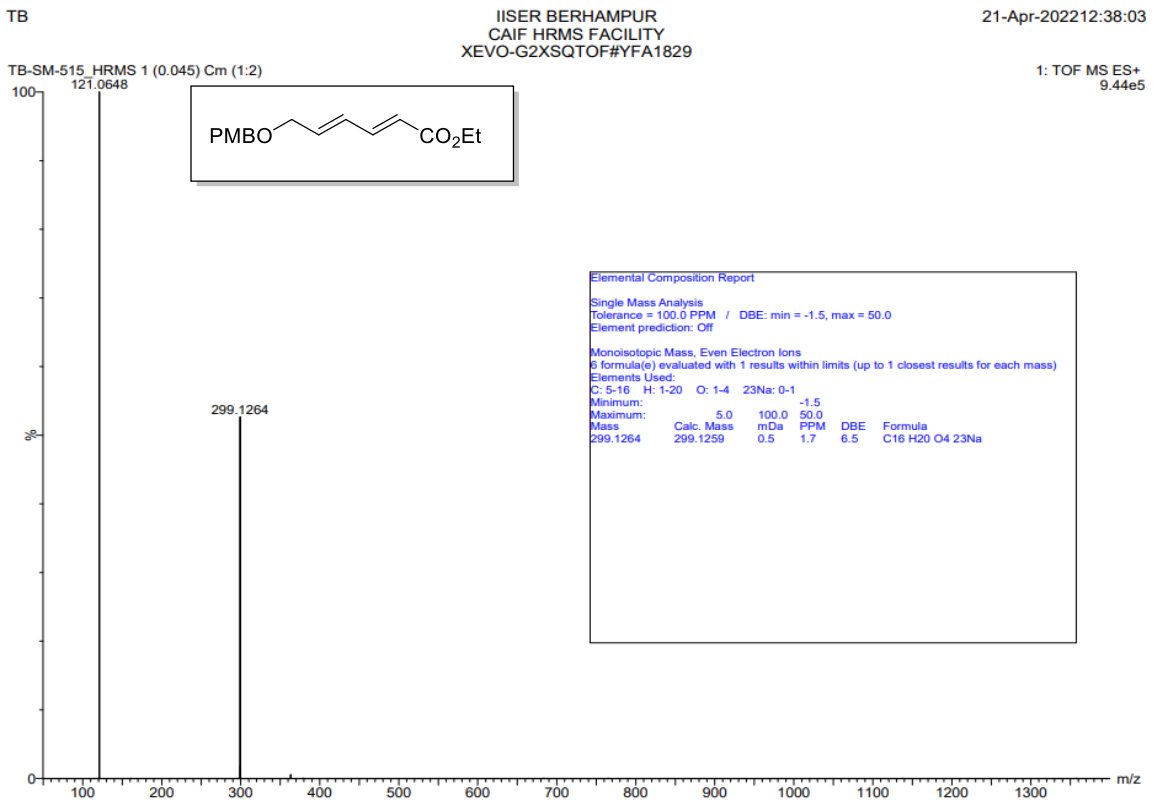
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 14



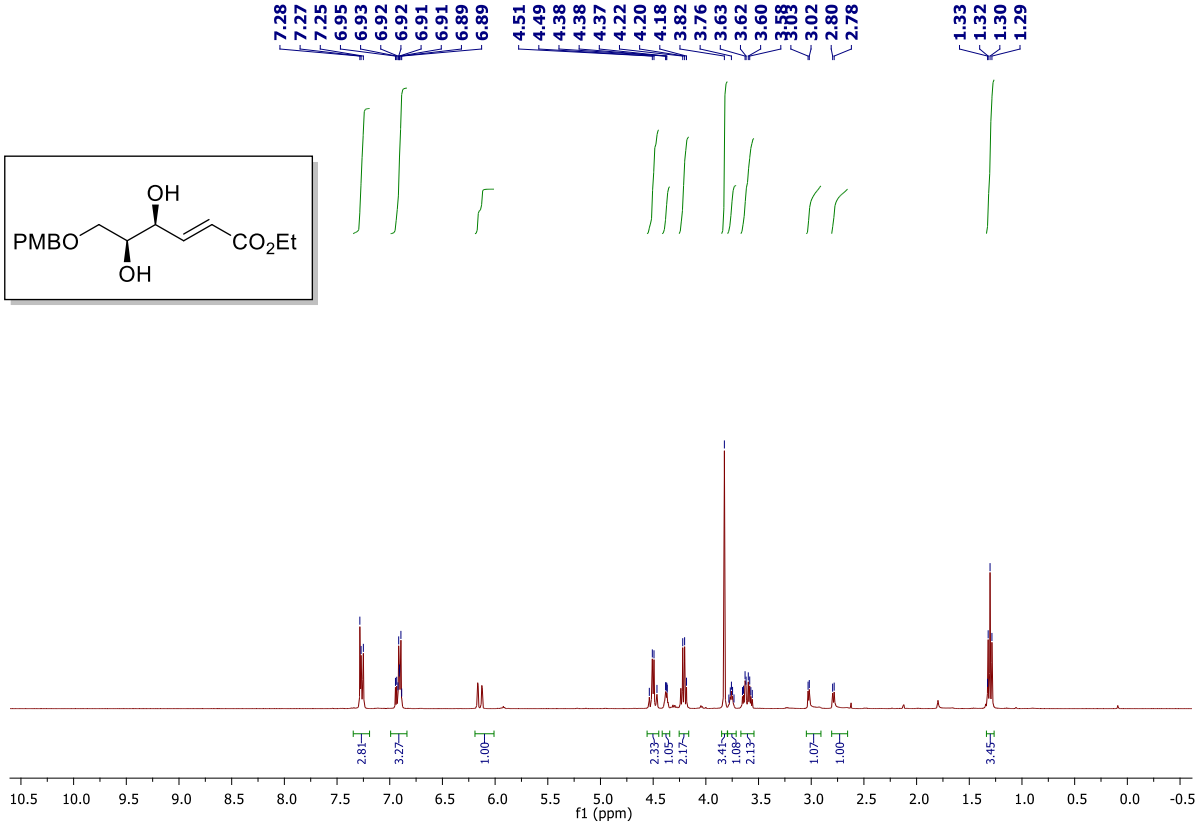
IR spectrum of the compound 14



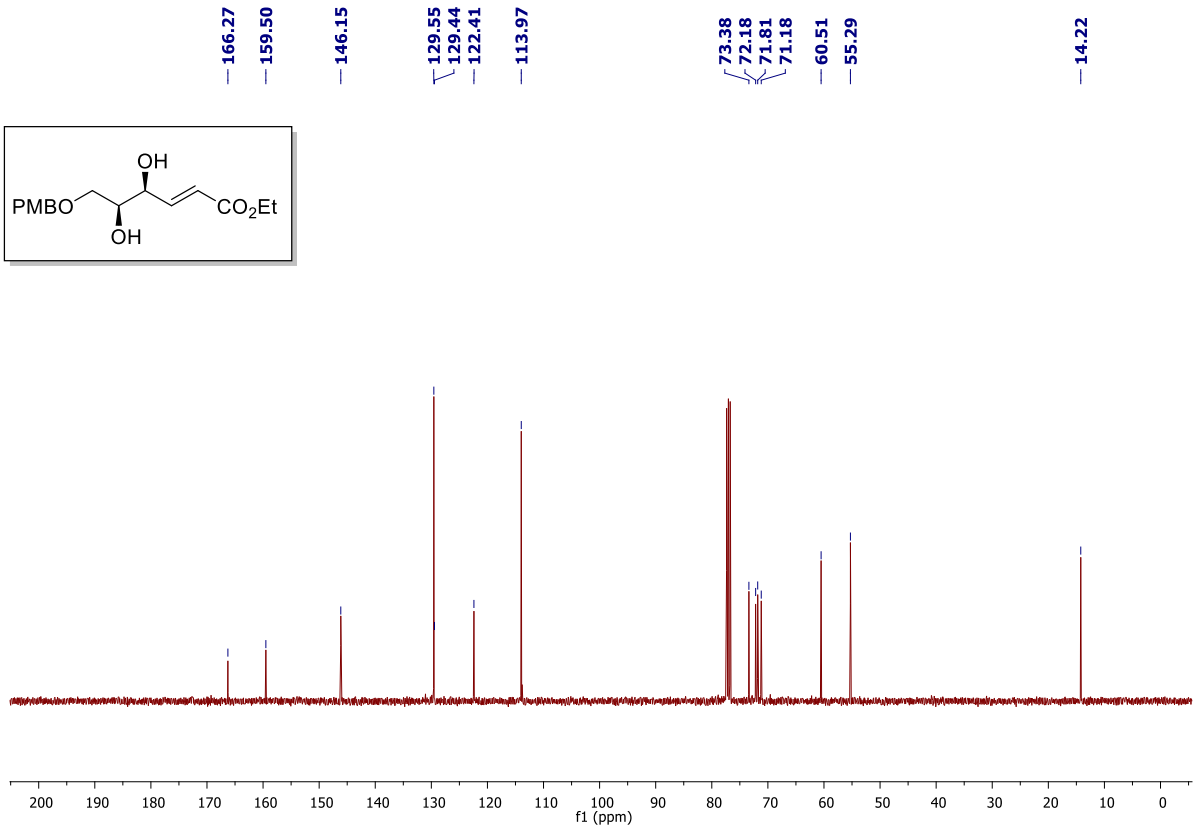
HRMS (ESI-TOF) spectrum of the compound 14



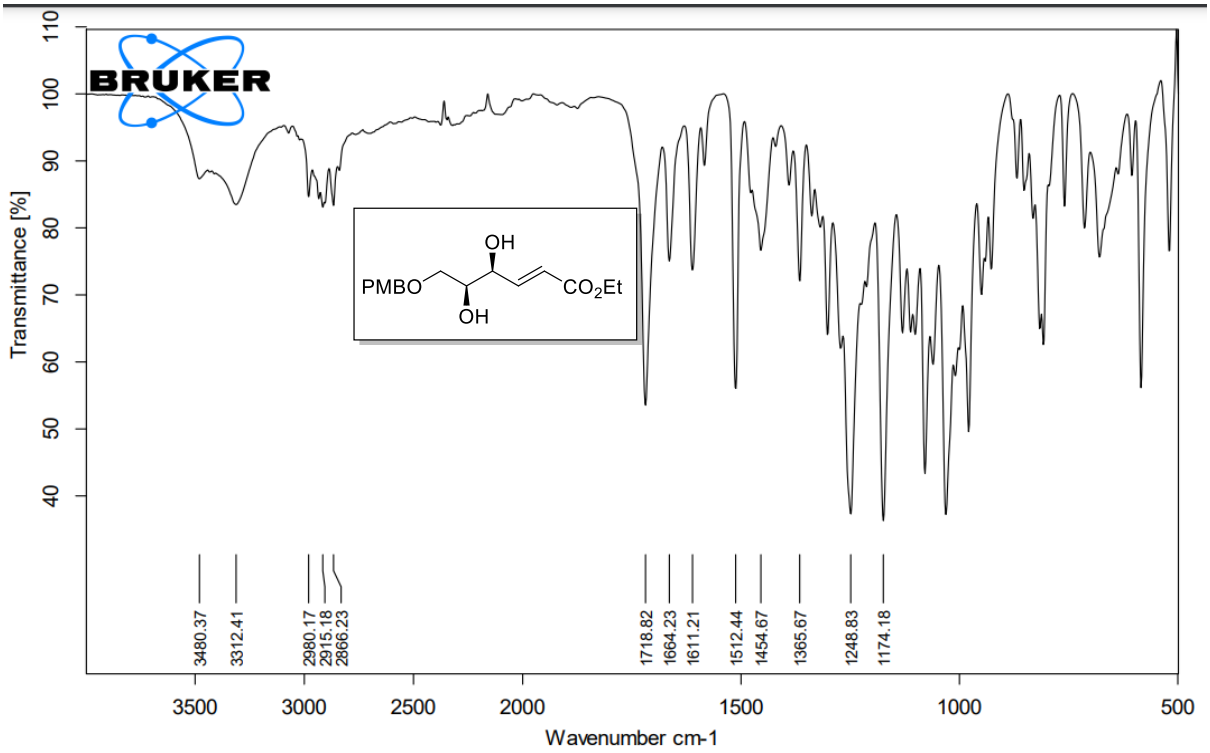
1H NMR (400 MHz, $CDCl_3$) spectrum of the compound 15



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 15

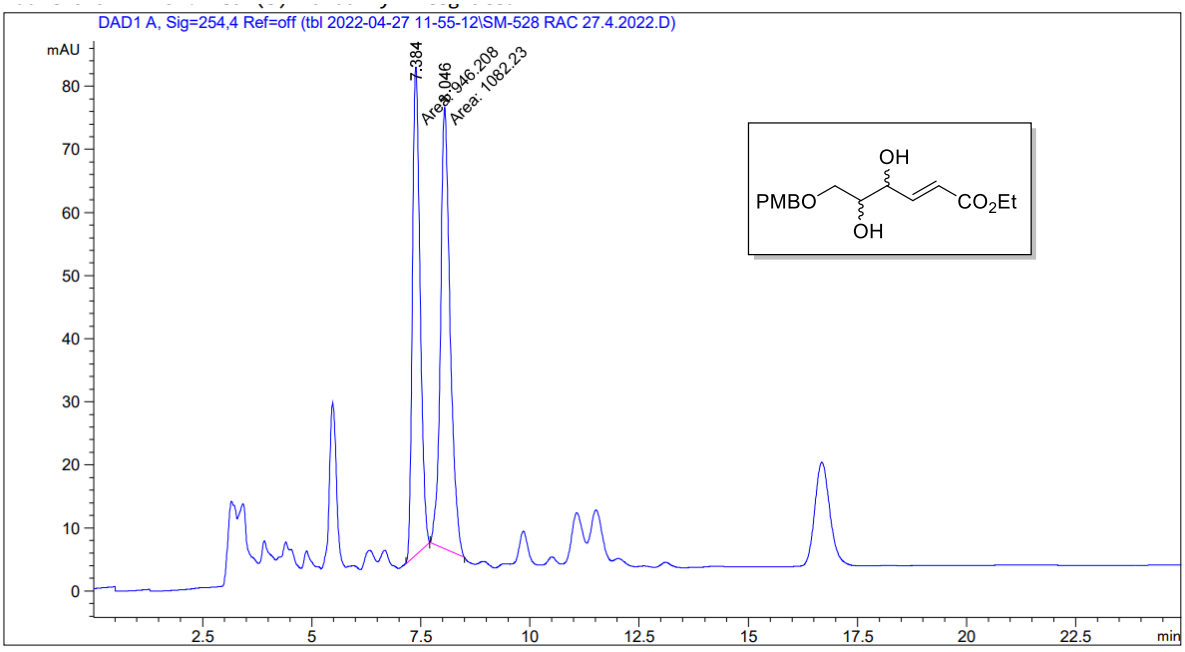


IR spectrum of the compound 15



Chiral HPLC: Enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALPAK@OJ-H (250×4.6mm, 5µm), hexanes/i-PrOH = 60/40, 1.0 mL/min, 254 nm), t_{major} = 8.3 min, t_{minor} =9.5 min; ee = 969%.

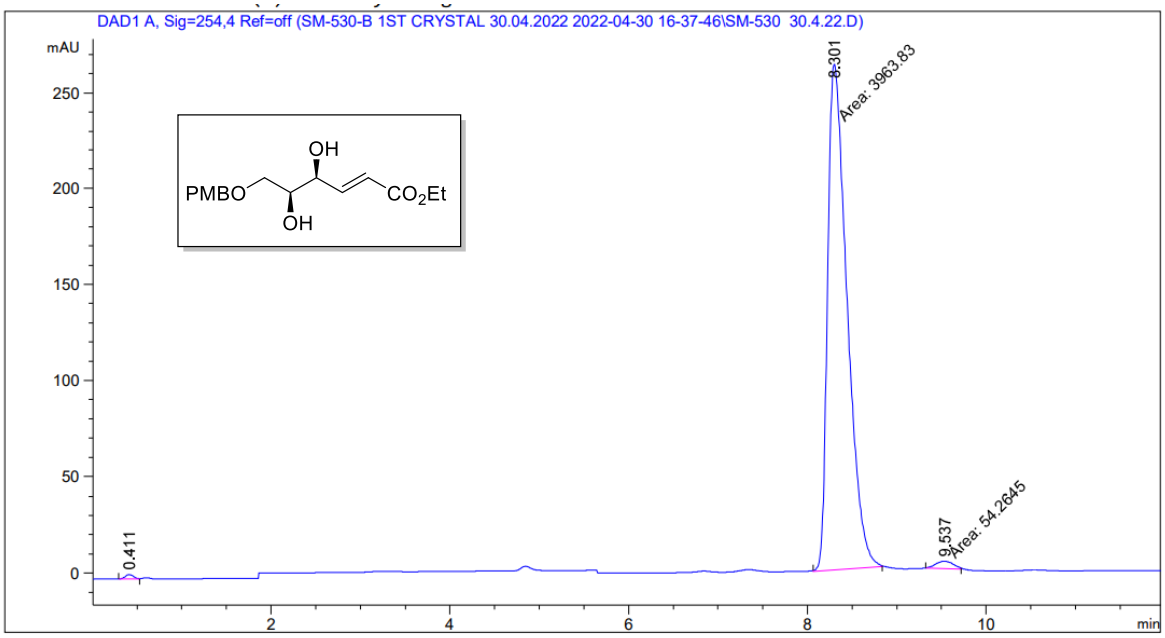
HPLC chromatogram of racemic compound 15



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.384	MM	0.2036	946.20770	77.44324	46.6470
2	8.046	MM	0.2577	1082.23499	69.99484	53.3530

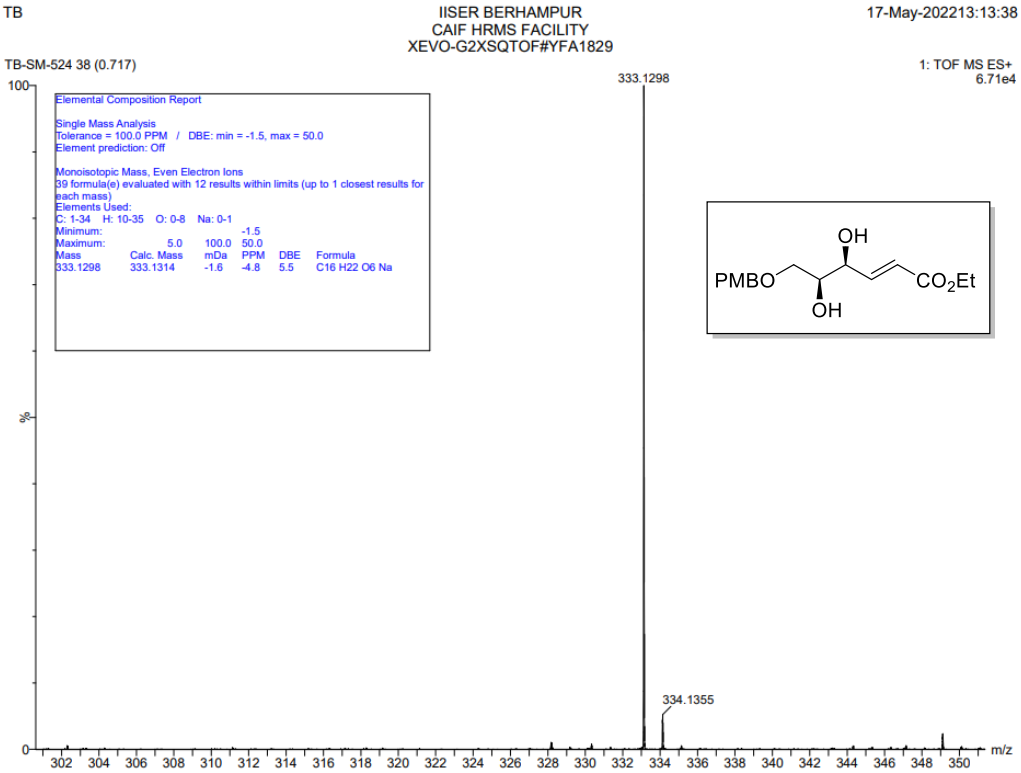
HPLC chromatogram of chiral compound 15



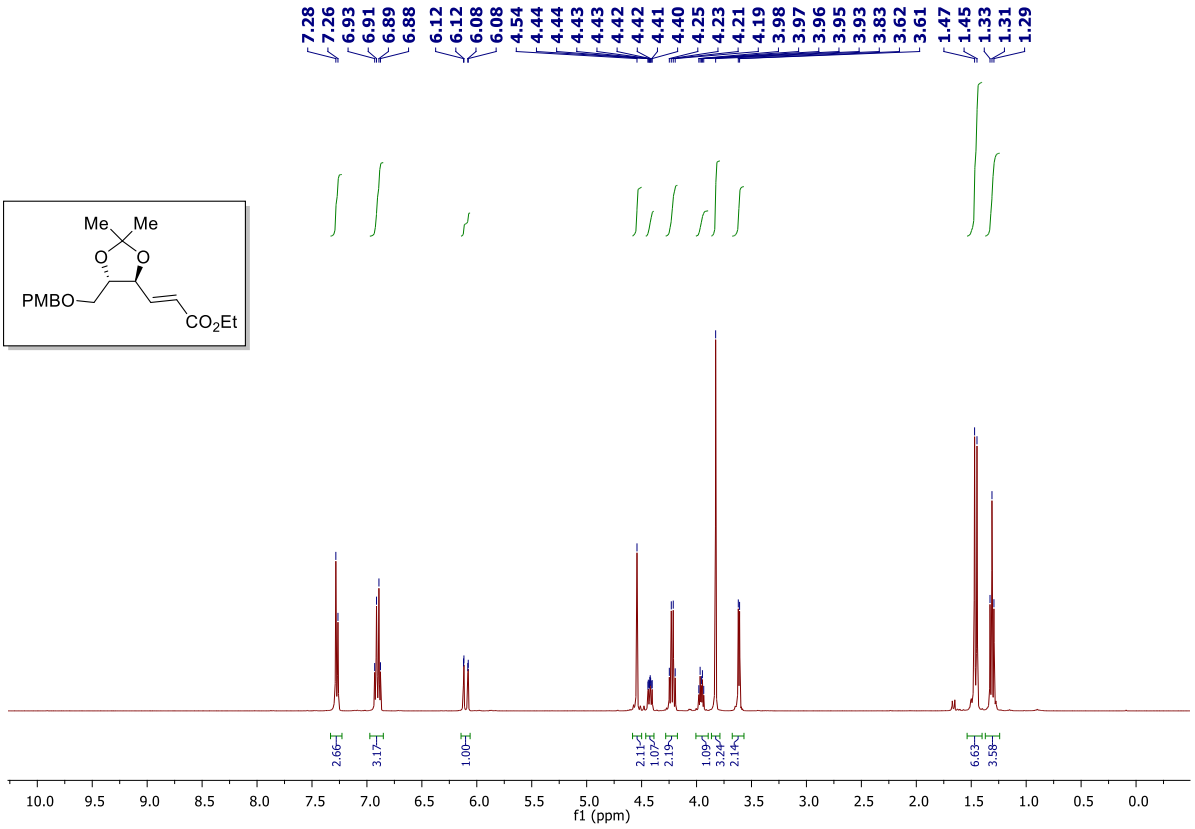
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.411	BV	0.1001	13.75674	2.16663	0.3412
2	8.301	MM	0.2508	3963.82544	263.46082	98.3129
3	9.537	MM	0.2290	54.26451	3.94880	1.3459

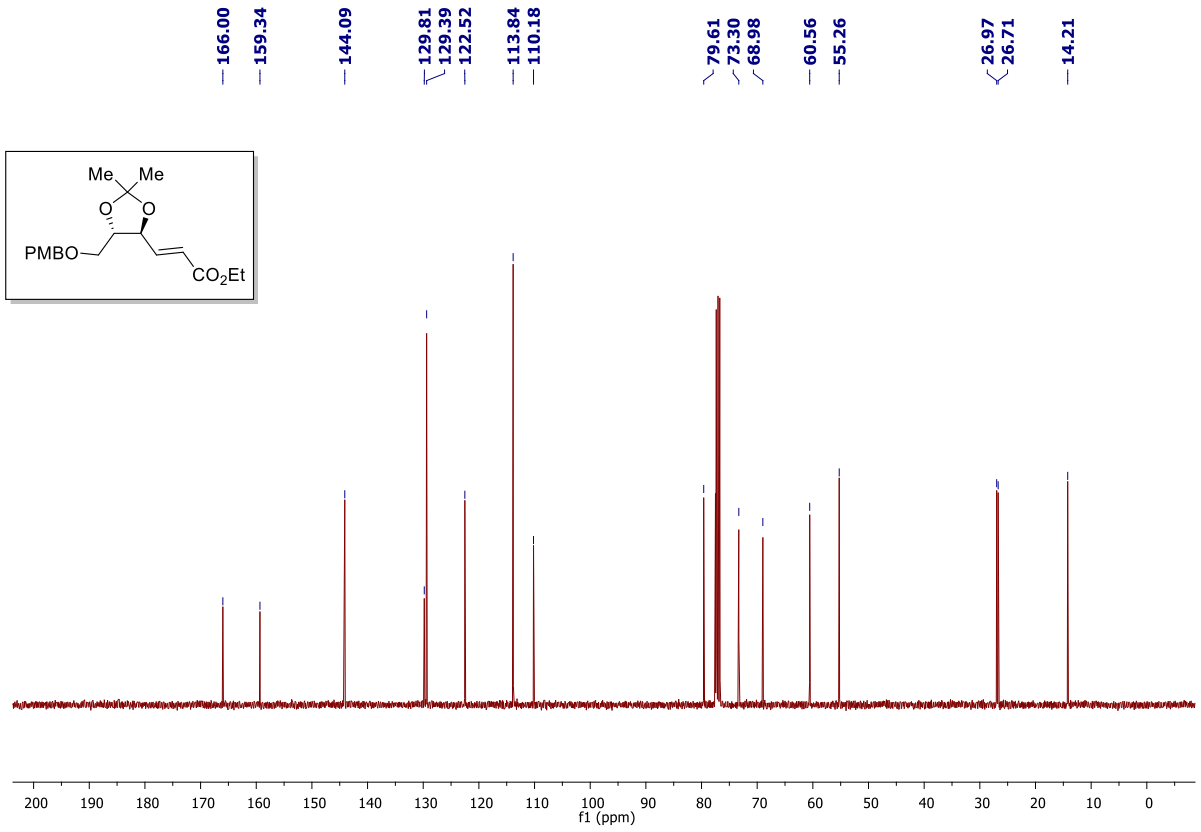
HRMS (ESI-TOF) spectrum of the compound 15



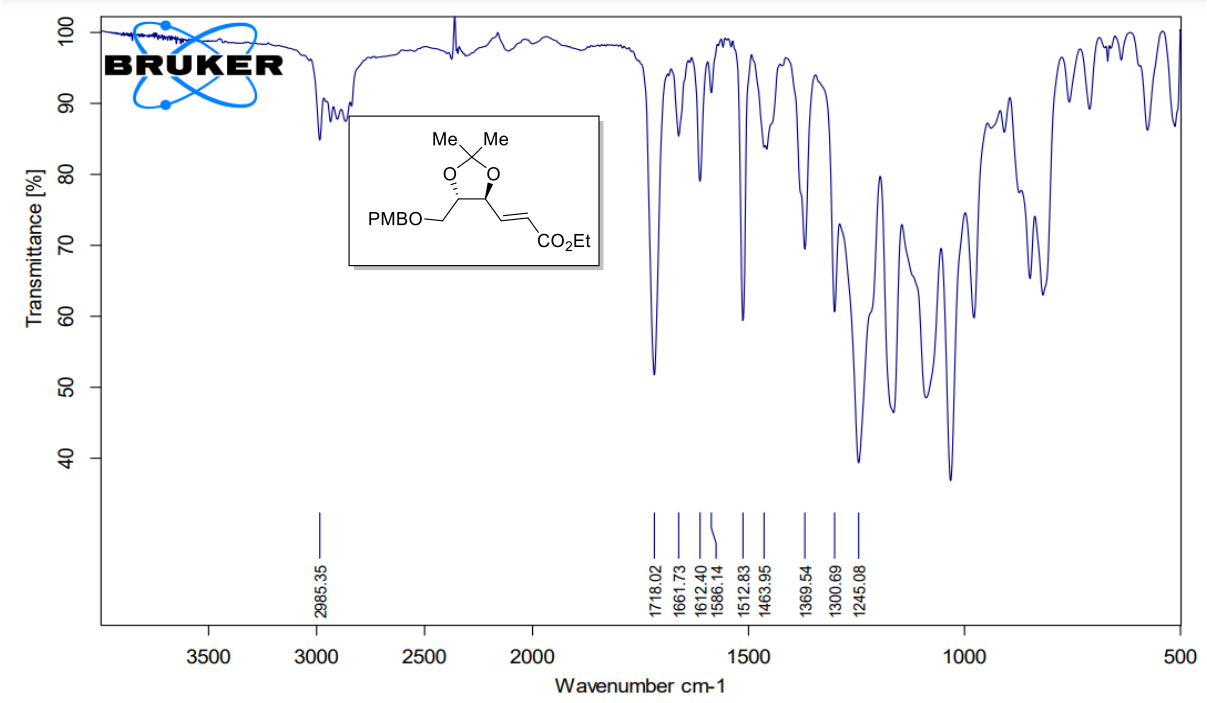
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 16



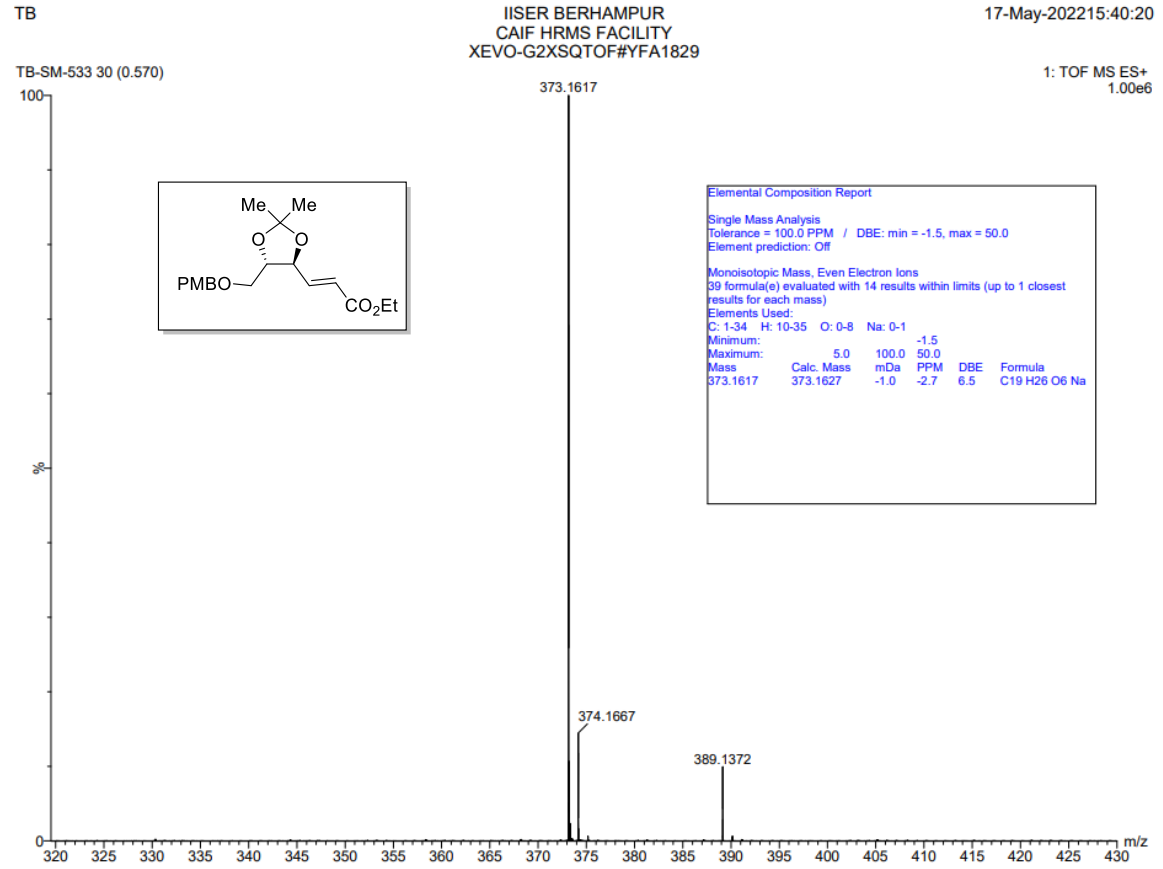
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 16



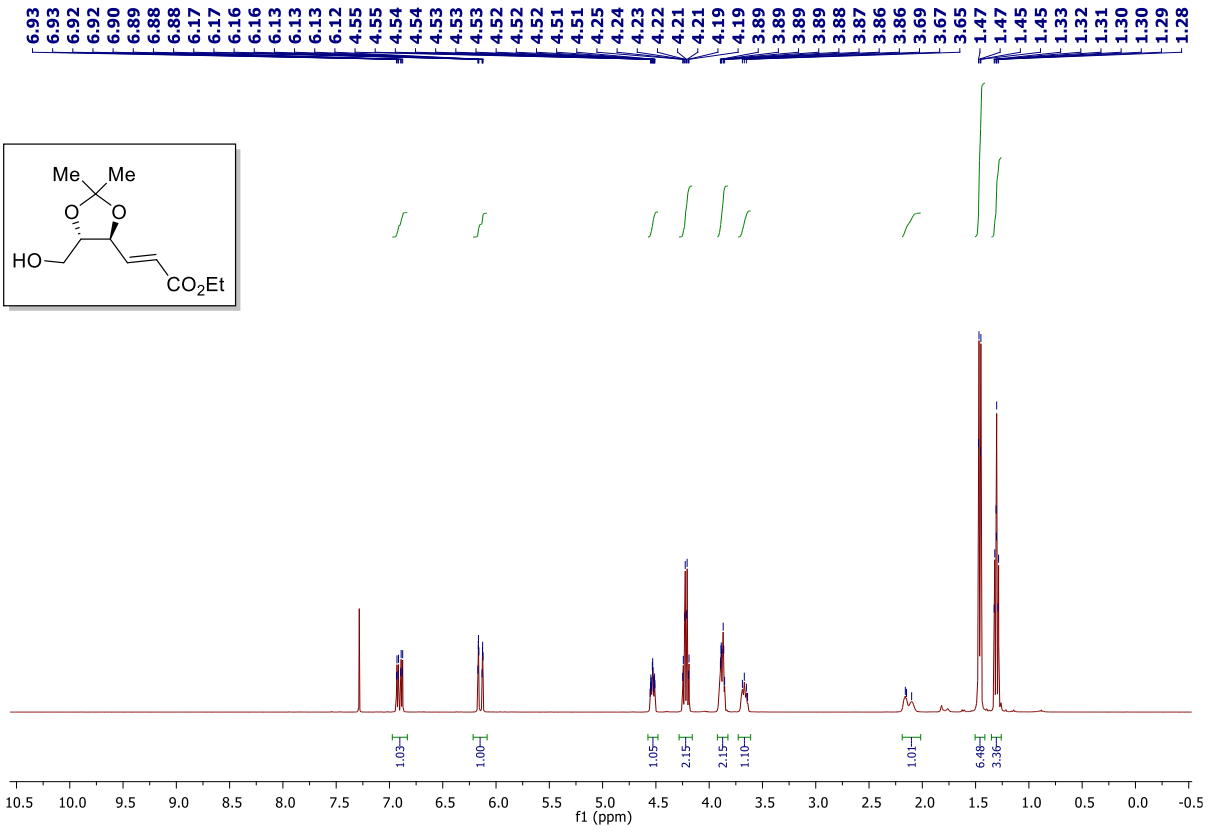
IR spectrum of the compound 16



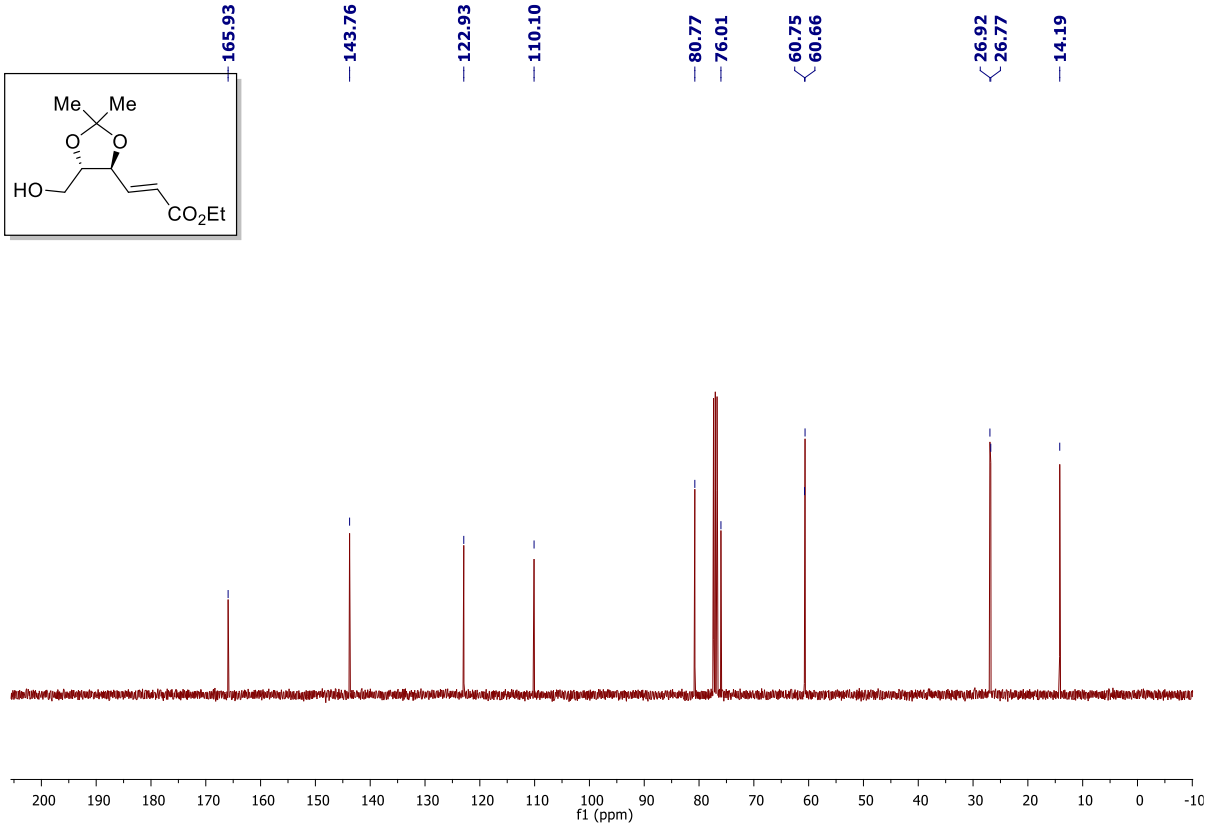
HRMS (ESI-TOF) spectrum of the compound 16



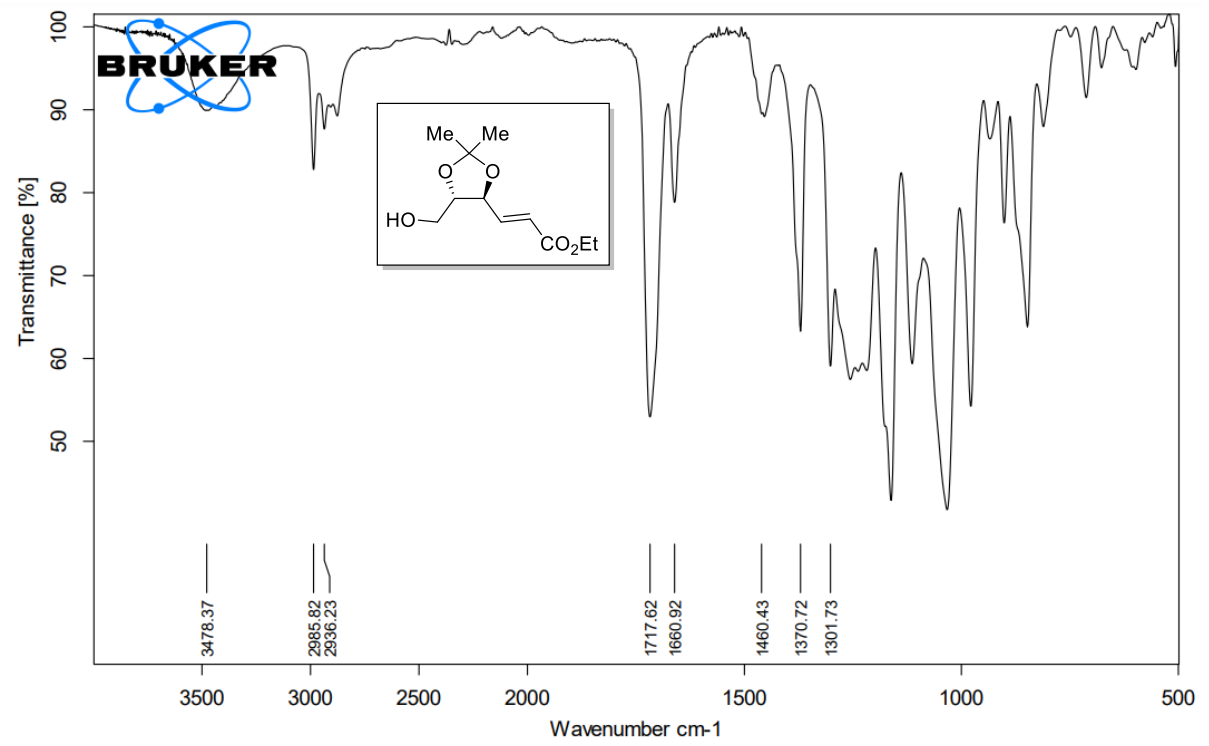
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 8



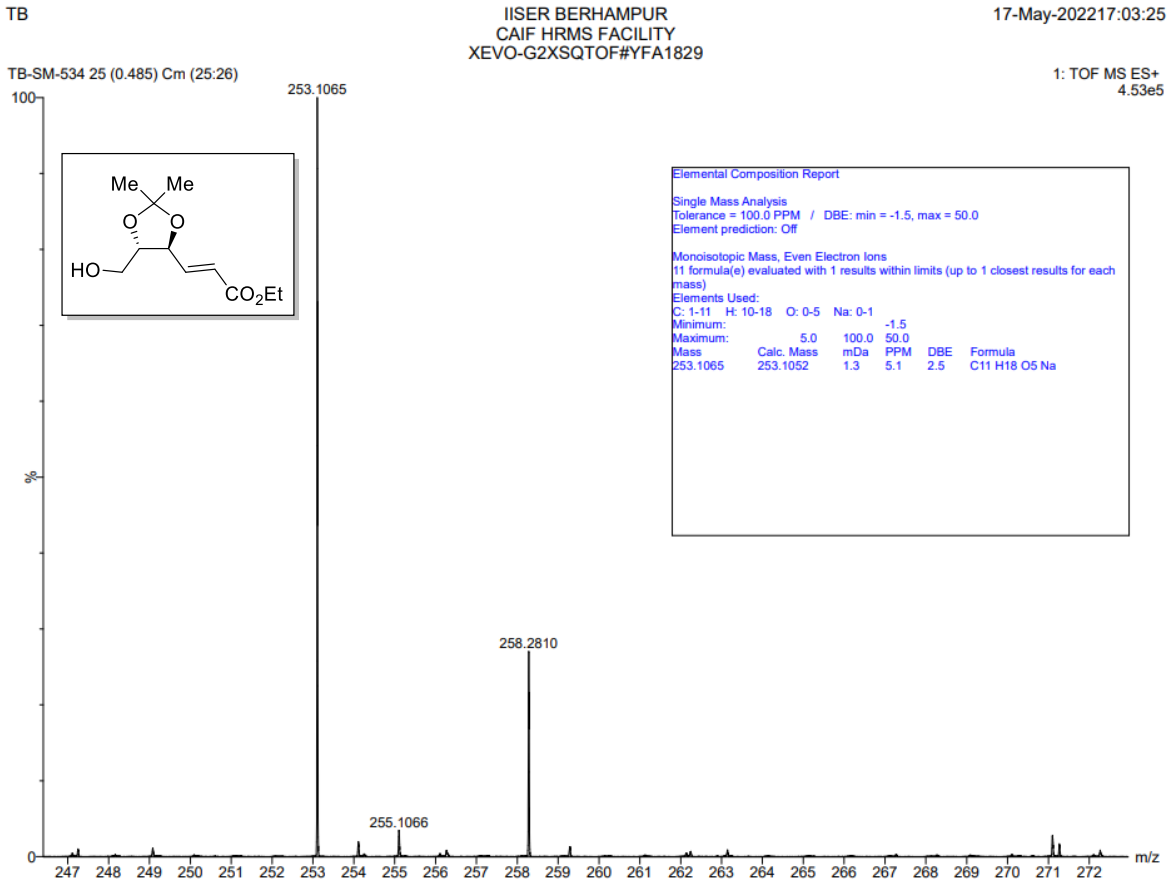
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 8



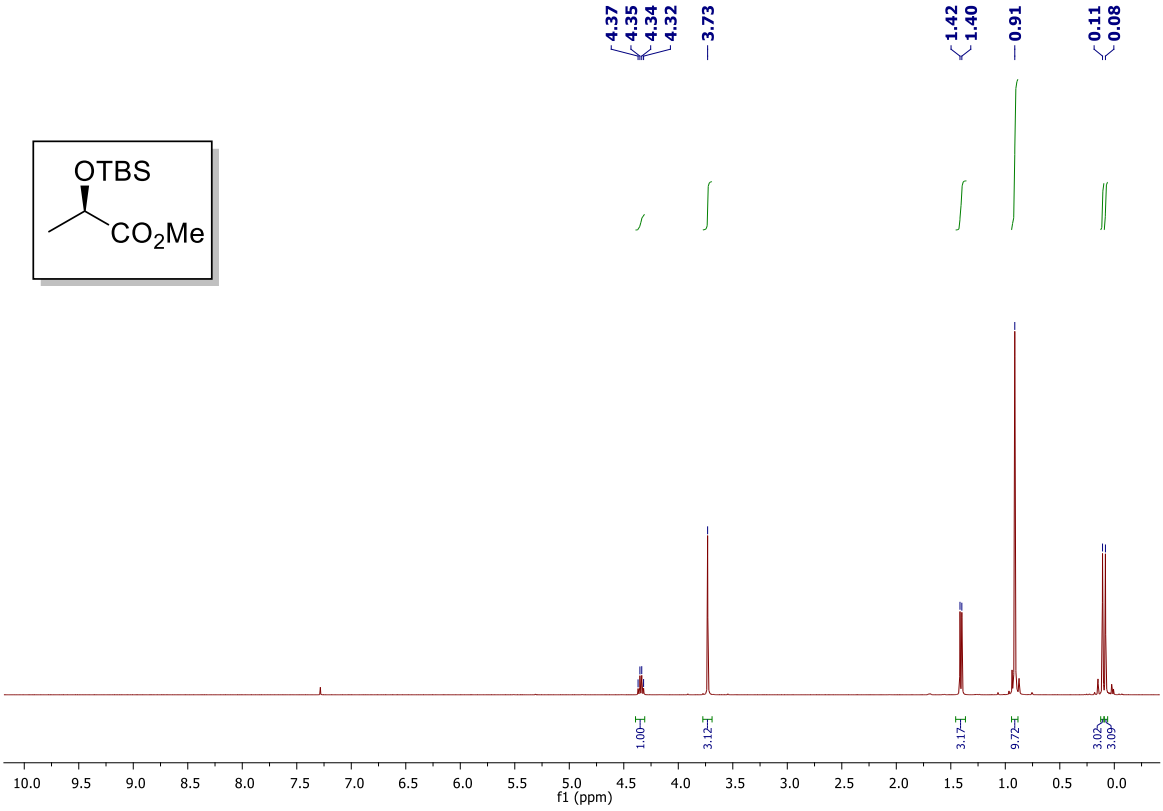
IR spectrum of the compound 8



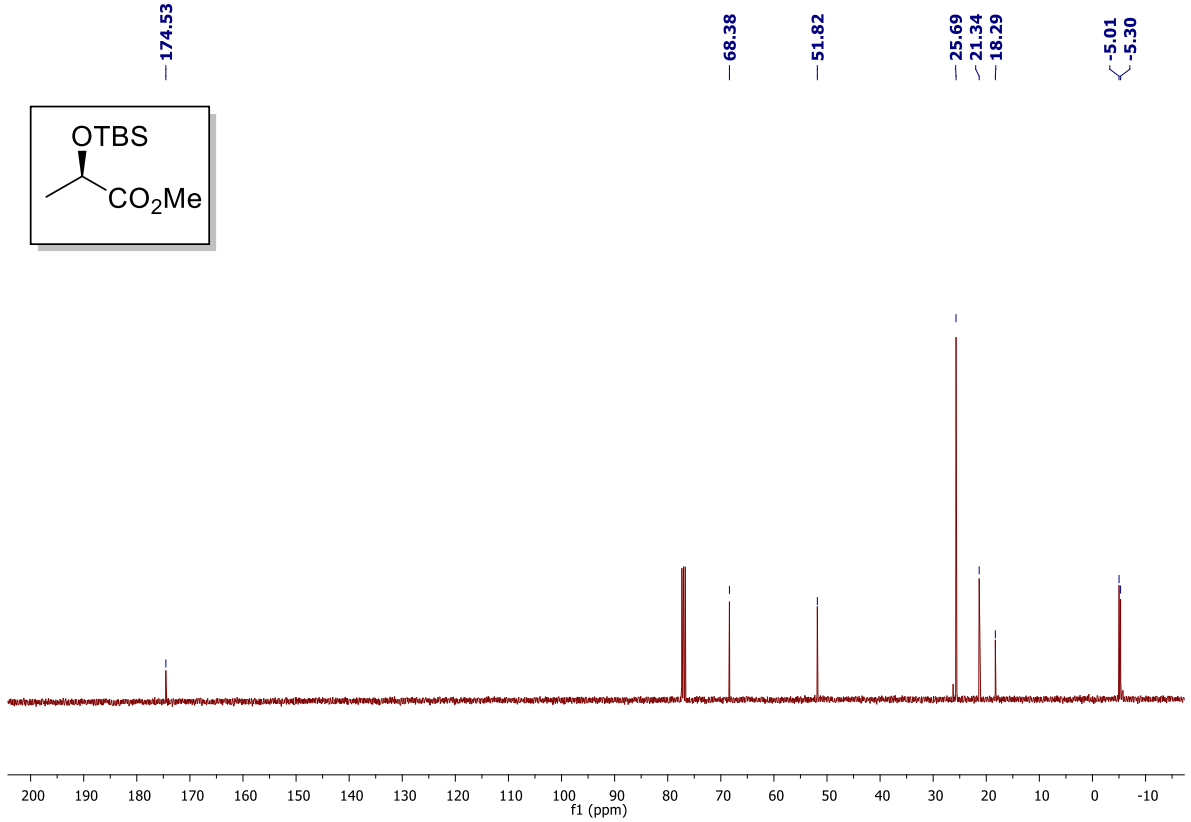
HRMS (ESI-TOF) spectrum of the compound 8



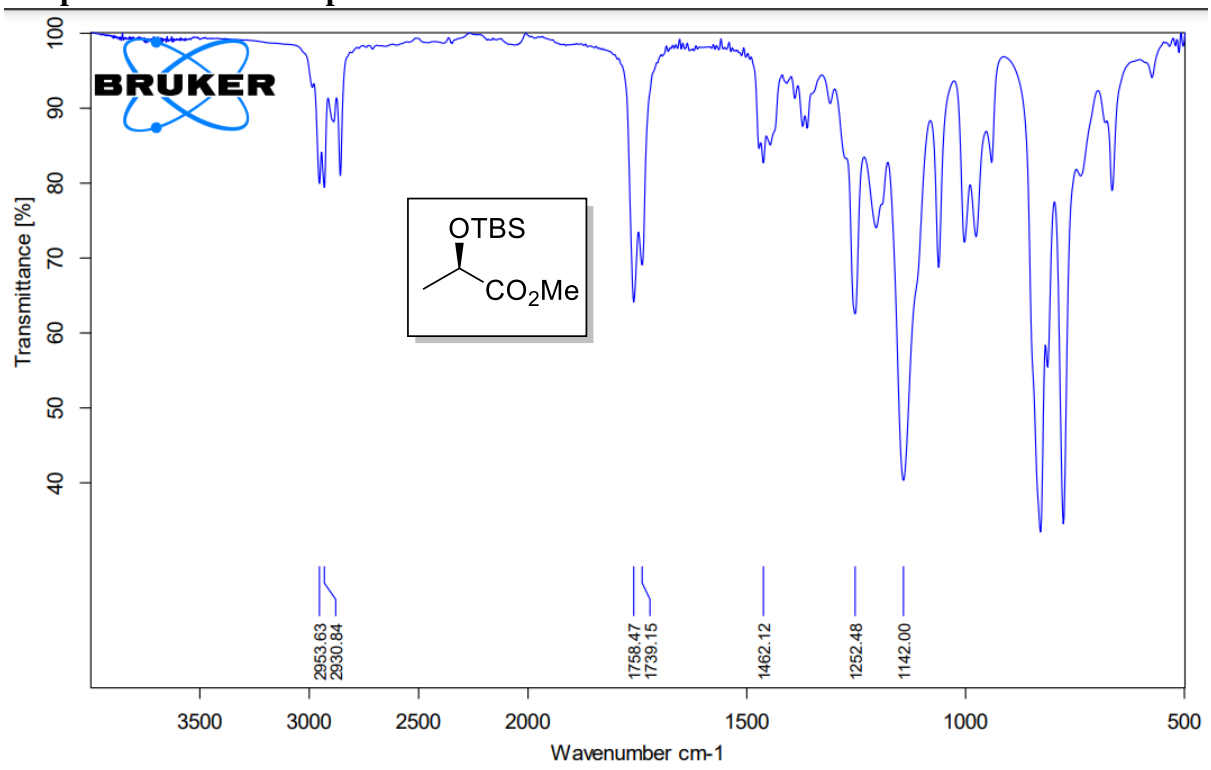
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 17



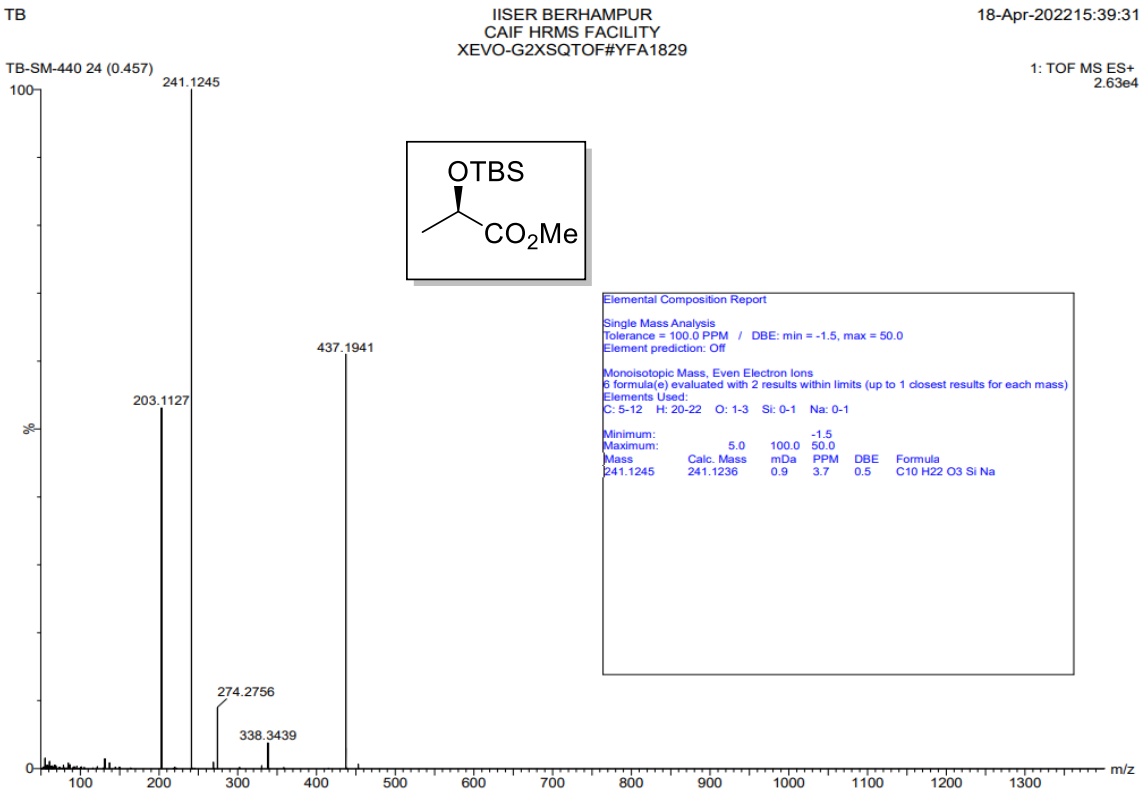
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 17



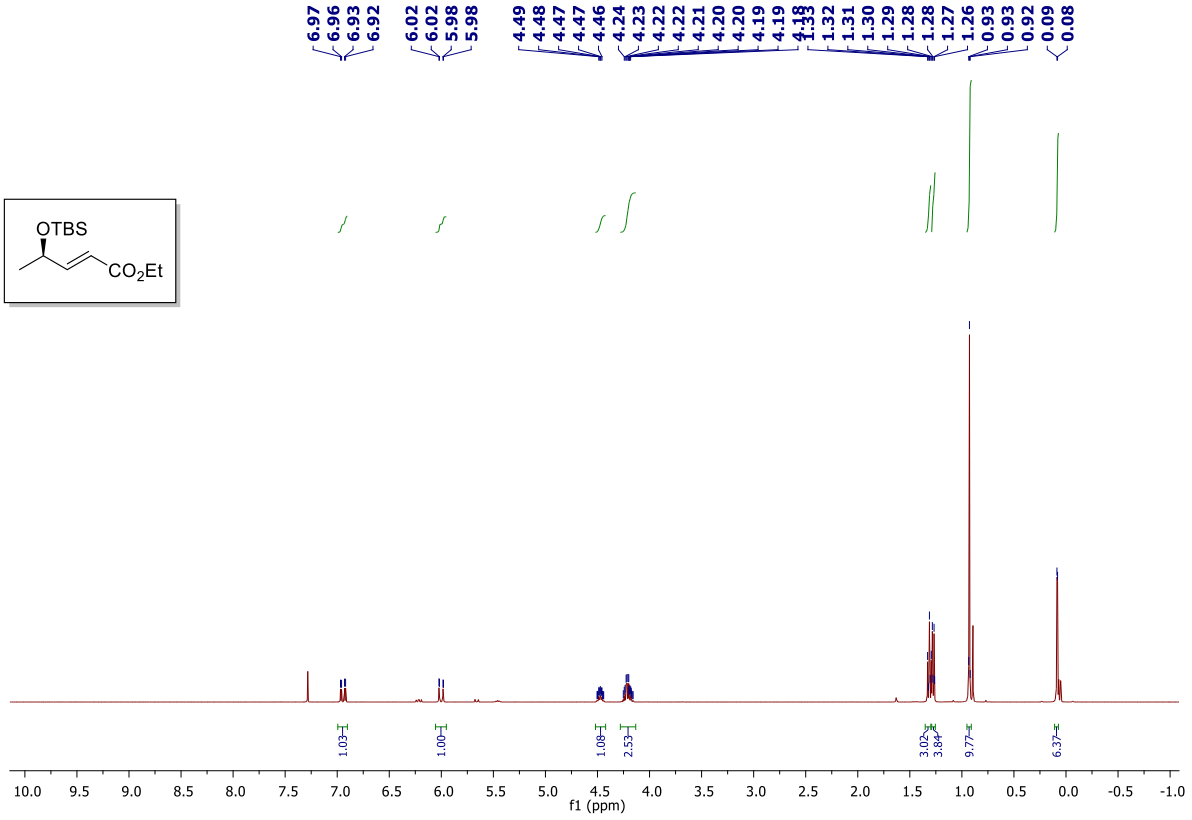
IR spectrum of the compound 17



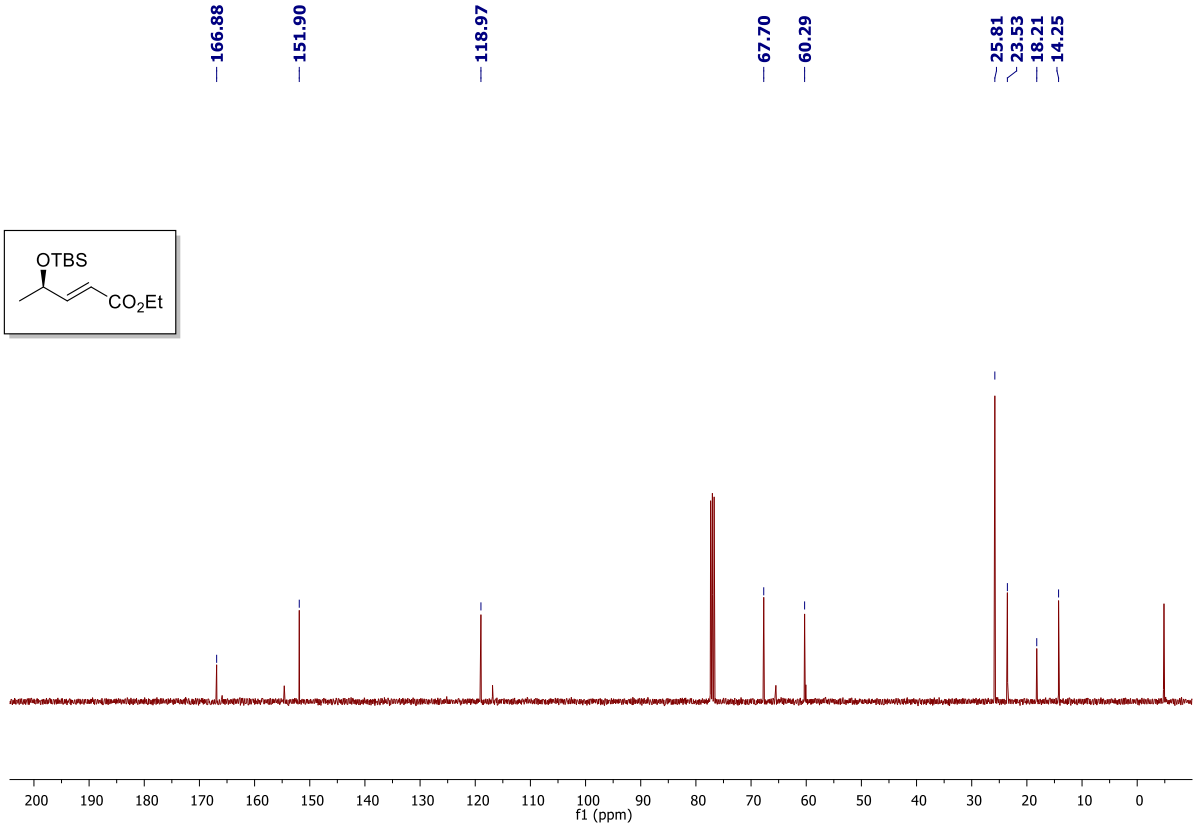
HRMS (ESI-TOF) spectrum of the compound 17



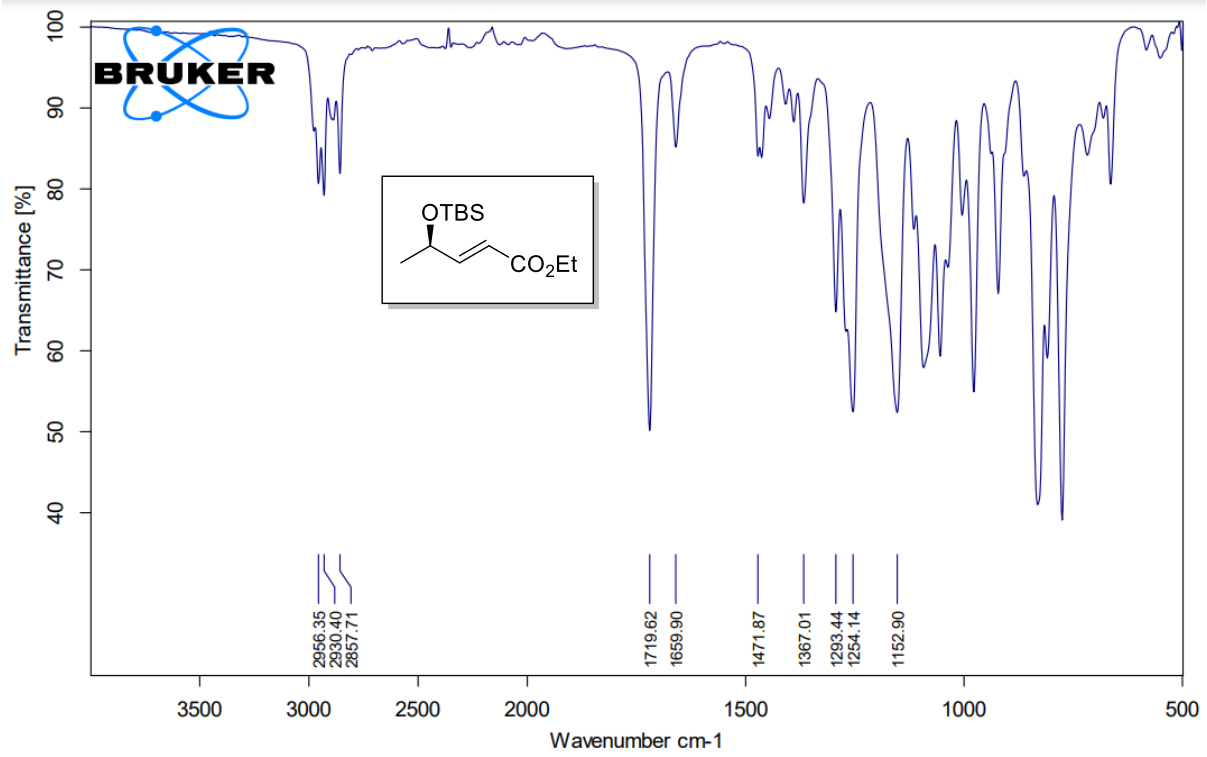
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound(Major) 18



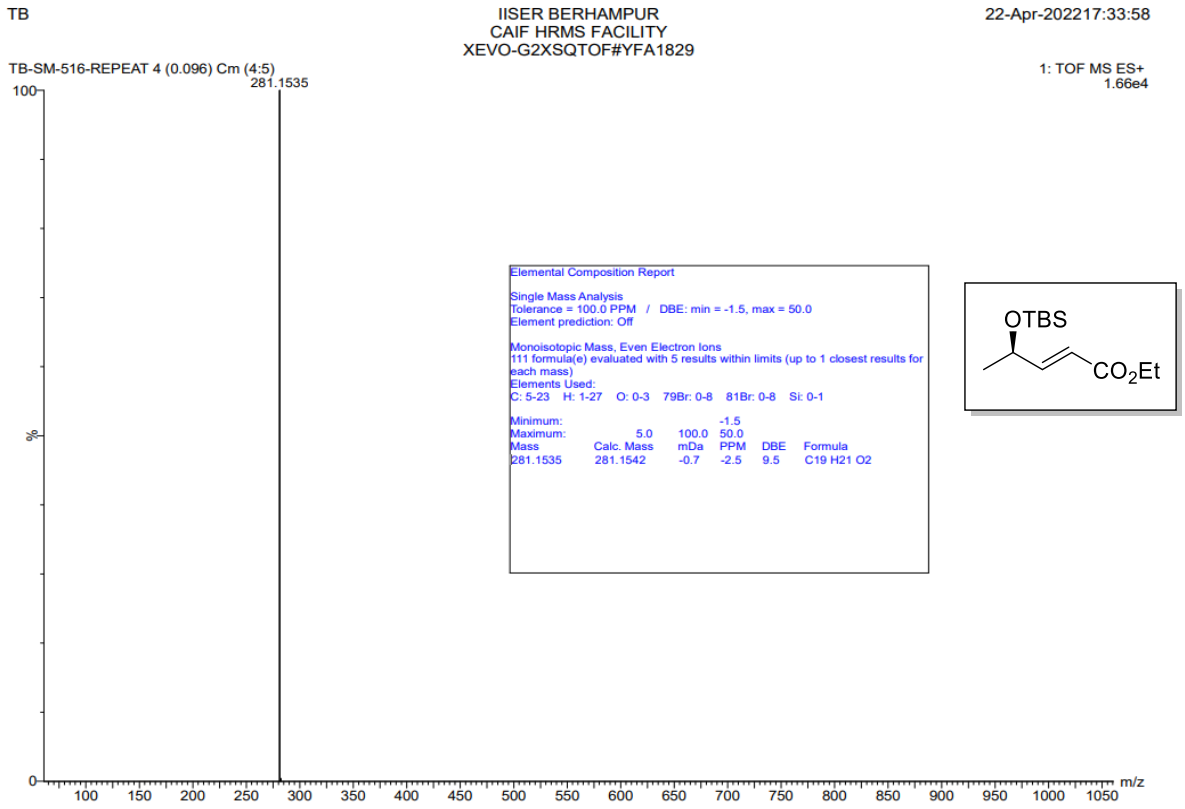
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound(Major) 18



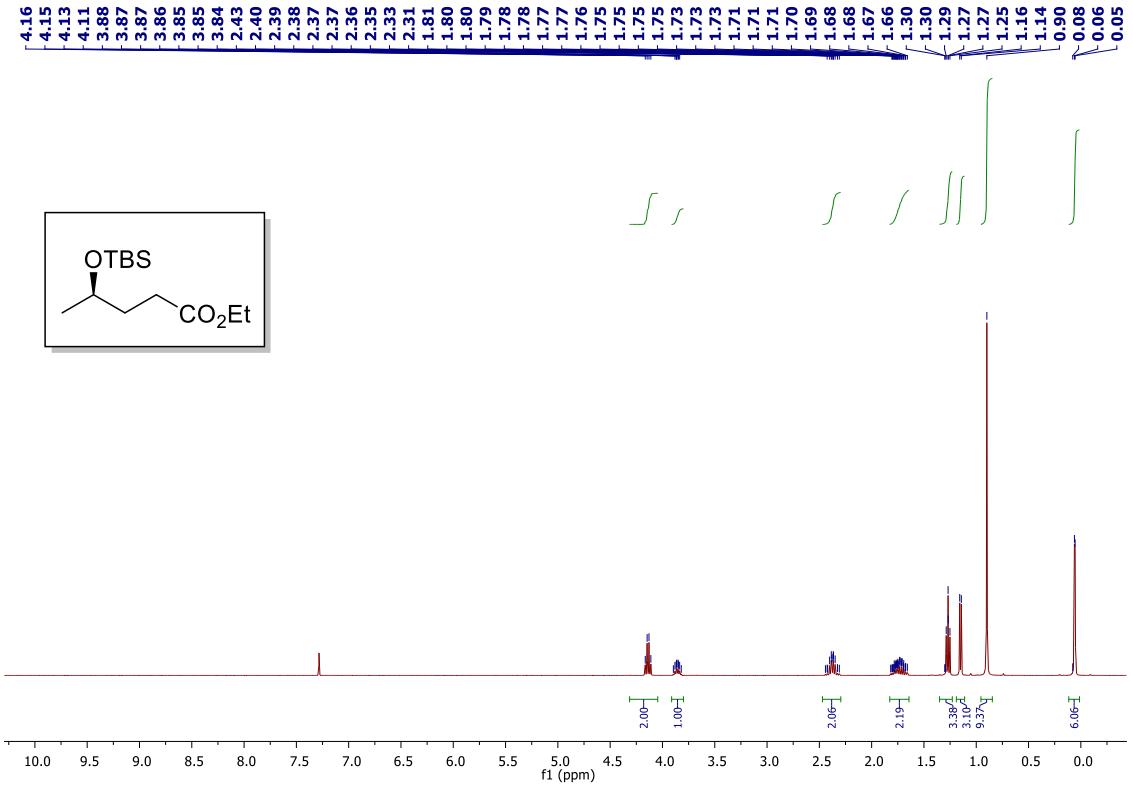
IR spectrum of the compound 18



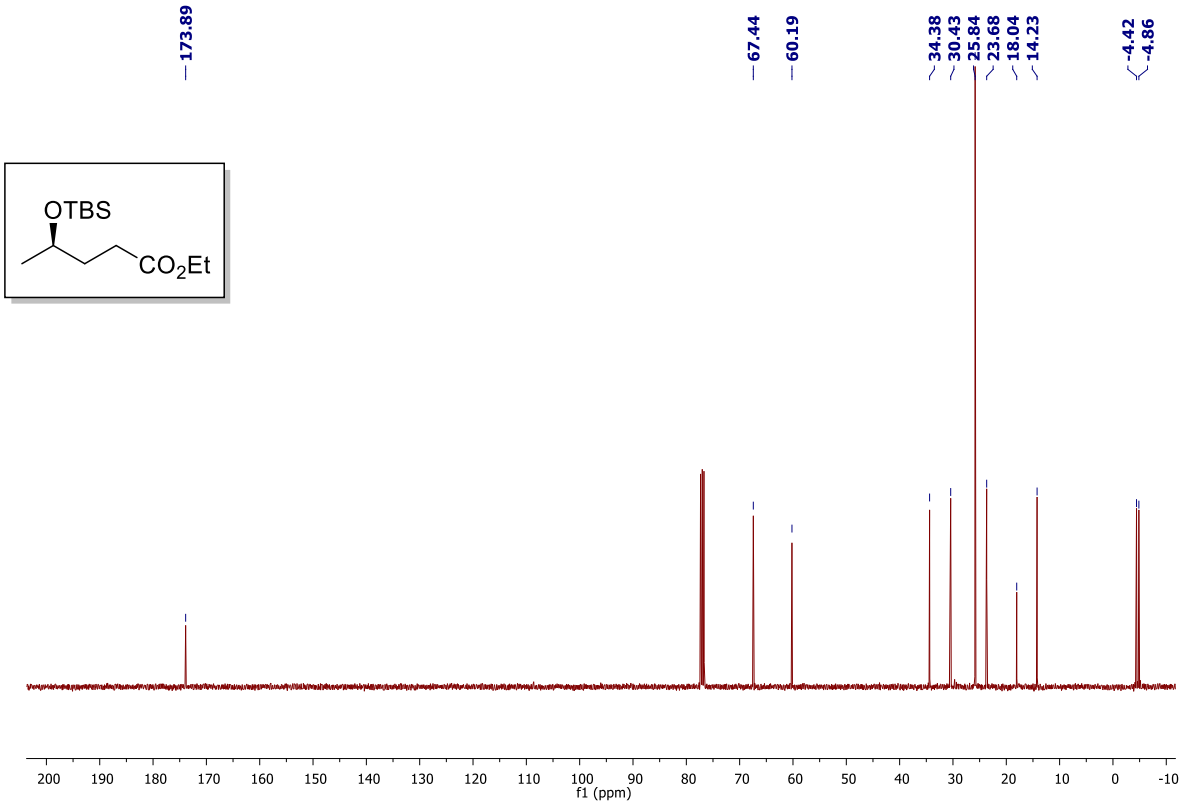
HRMS (ESI-TOF) spectrum of the compound 18



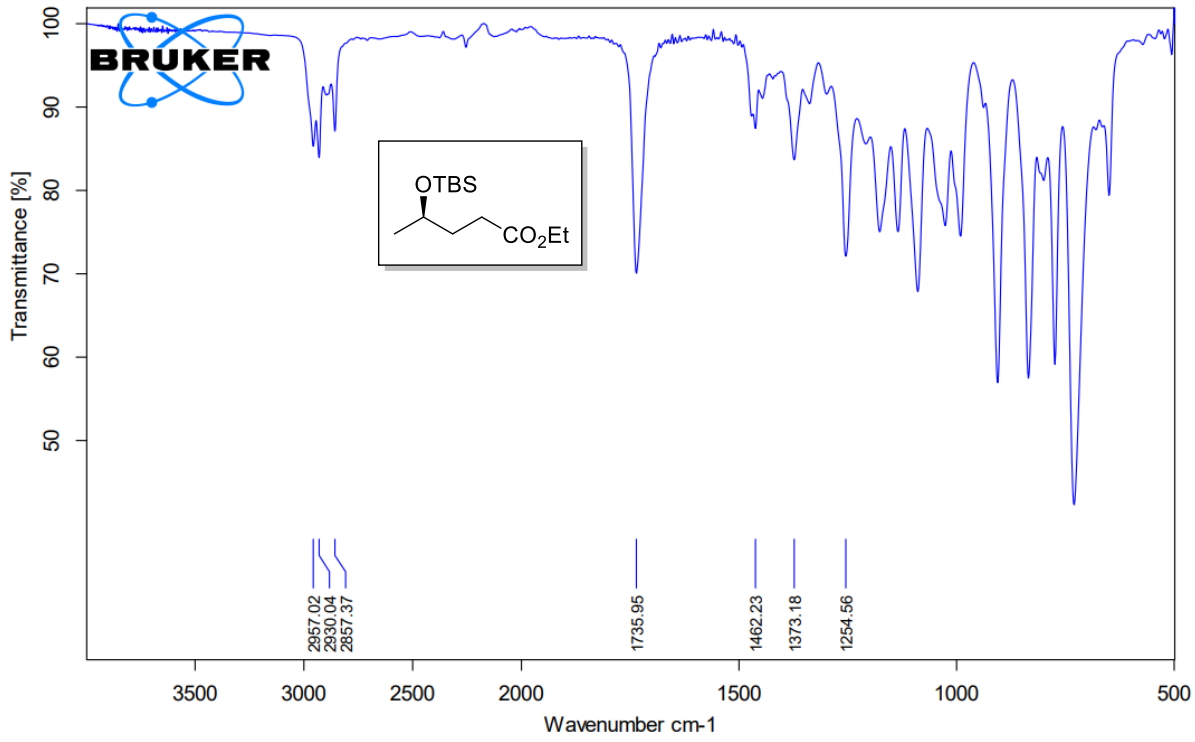
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 19



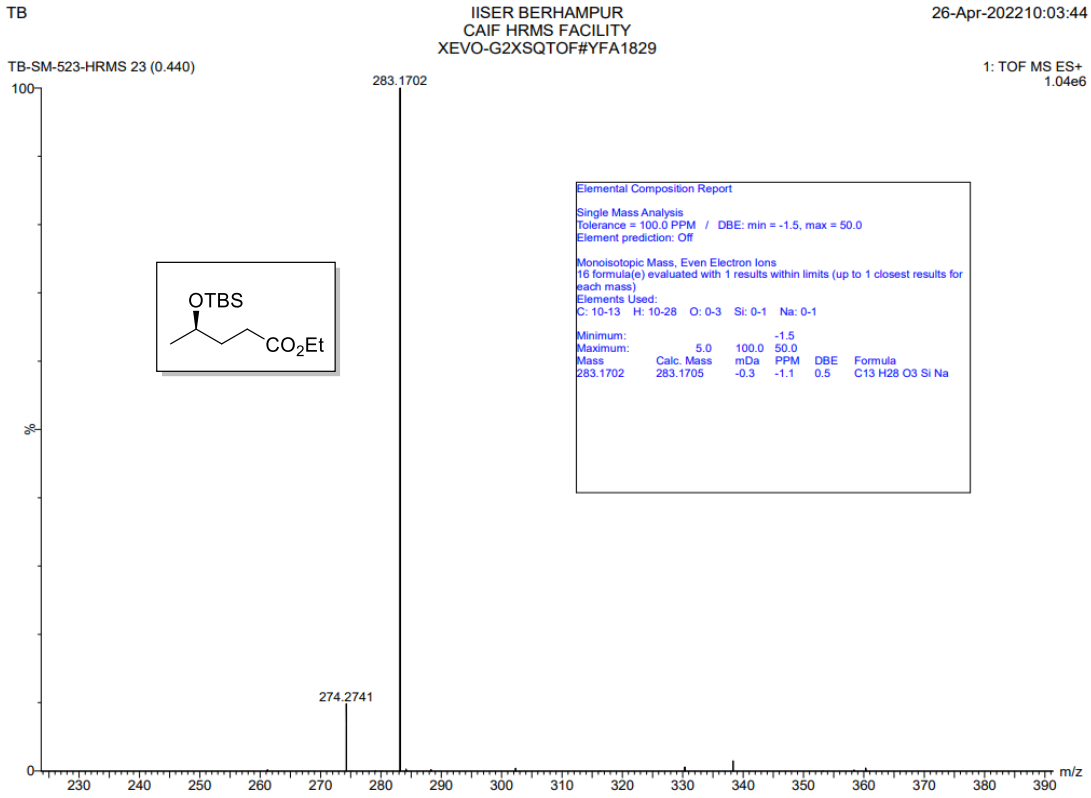
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 19



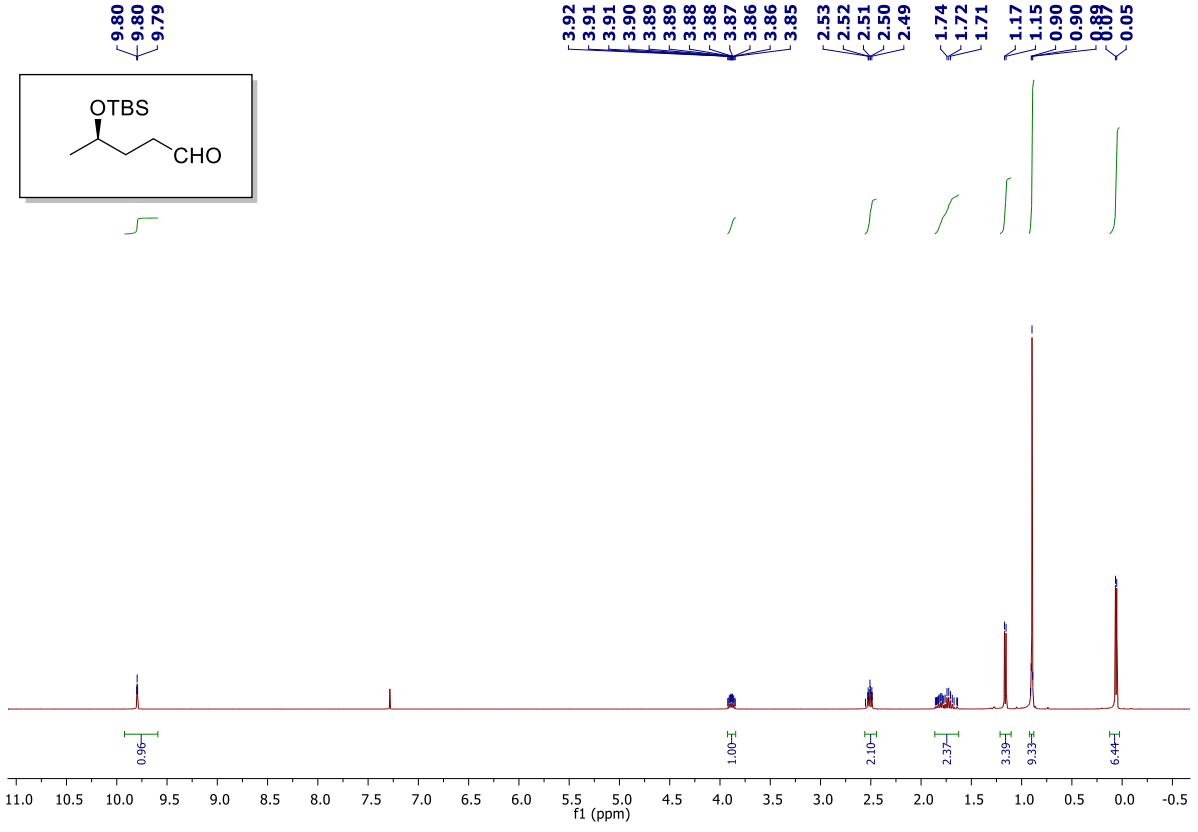
IR spectrum of the compound 19



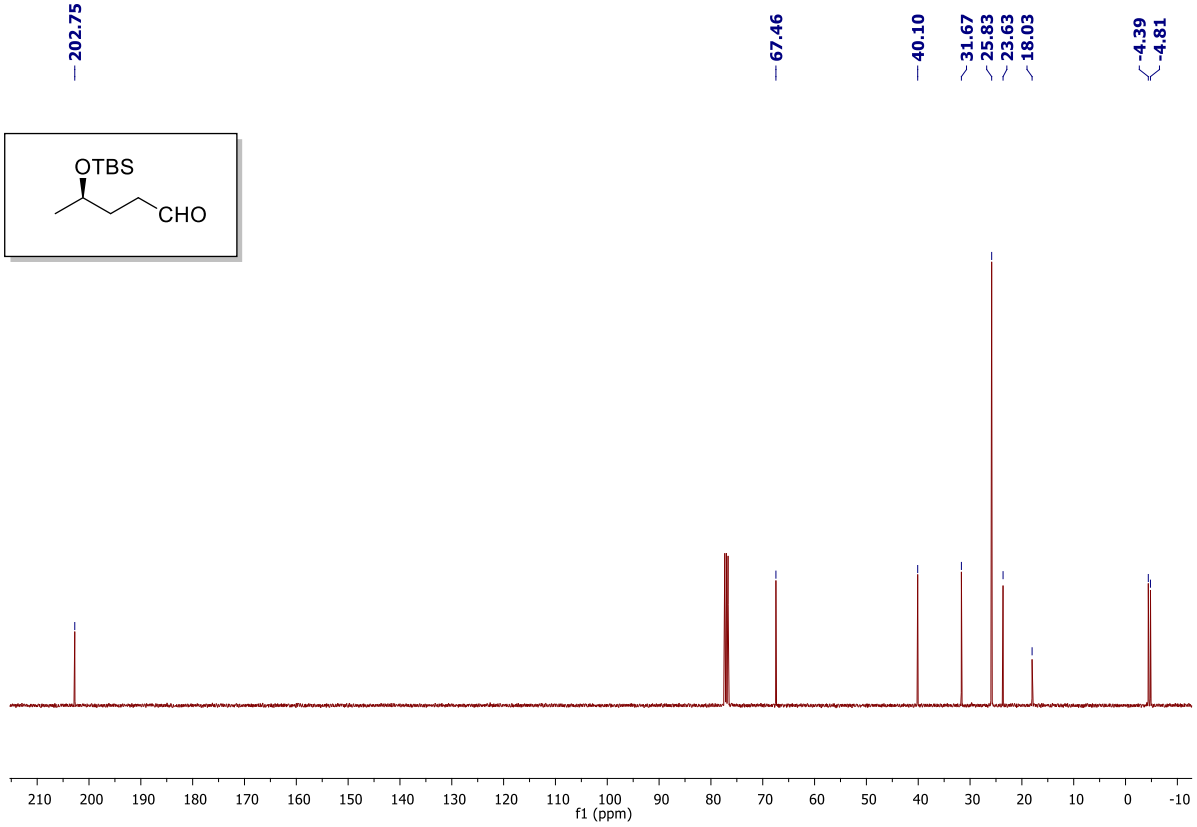
HRMS (ESI-TOF) spectrum of the compound 19



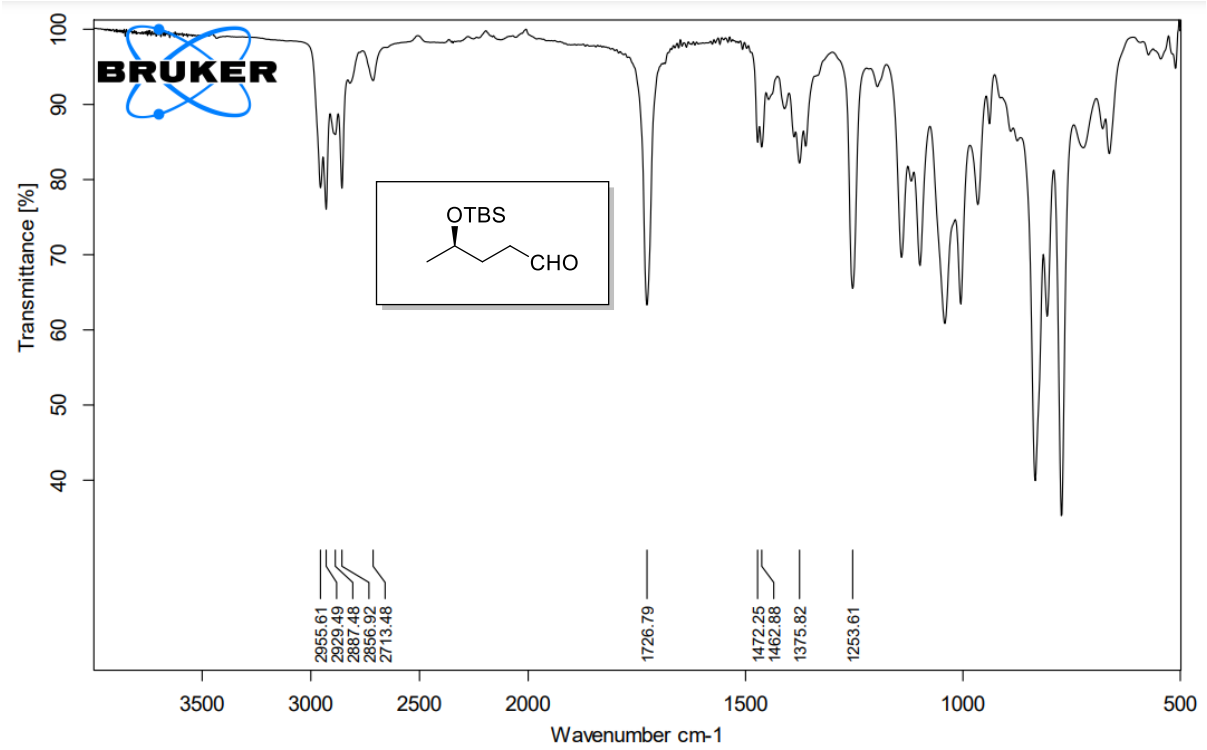
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 7



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 7

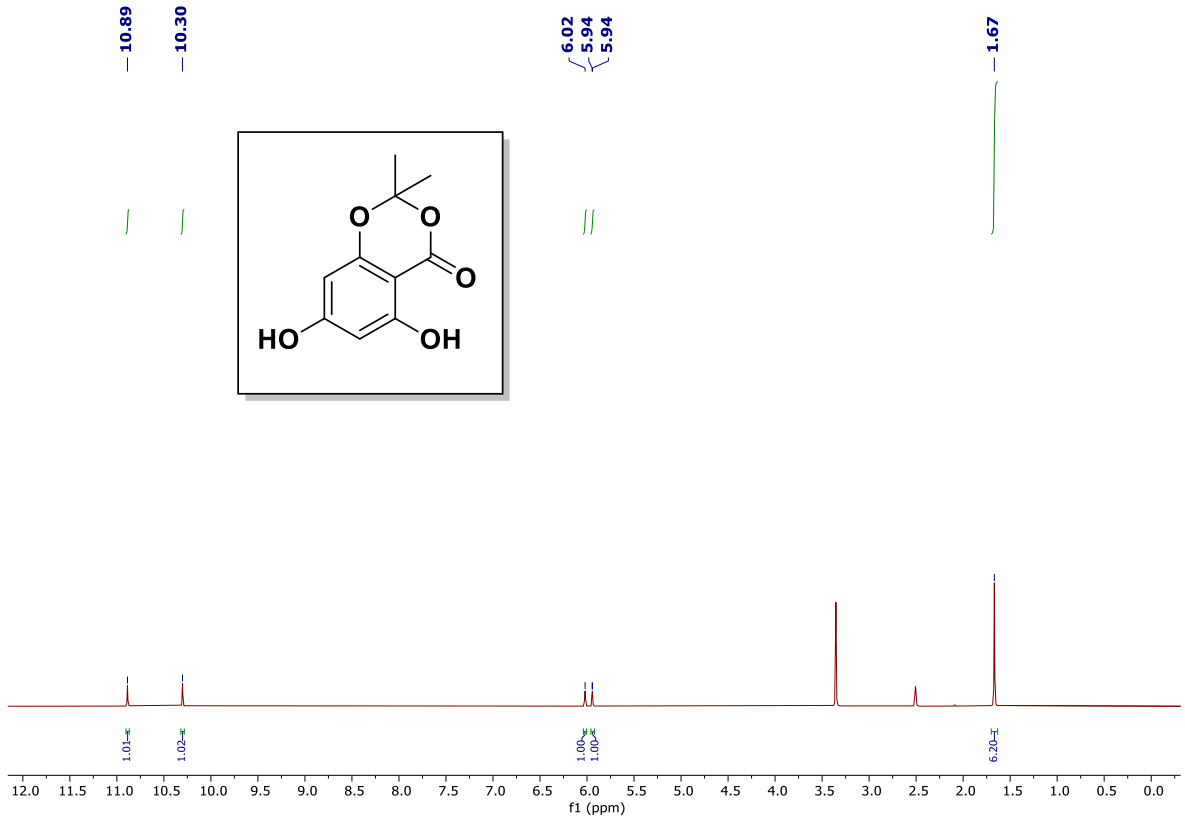


IR spectrum of the compound 7

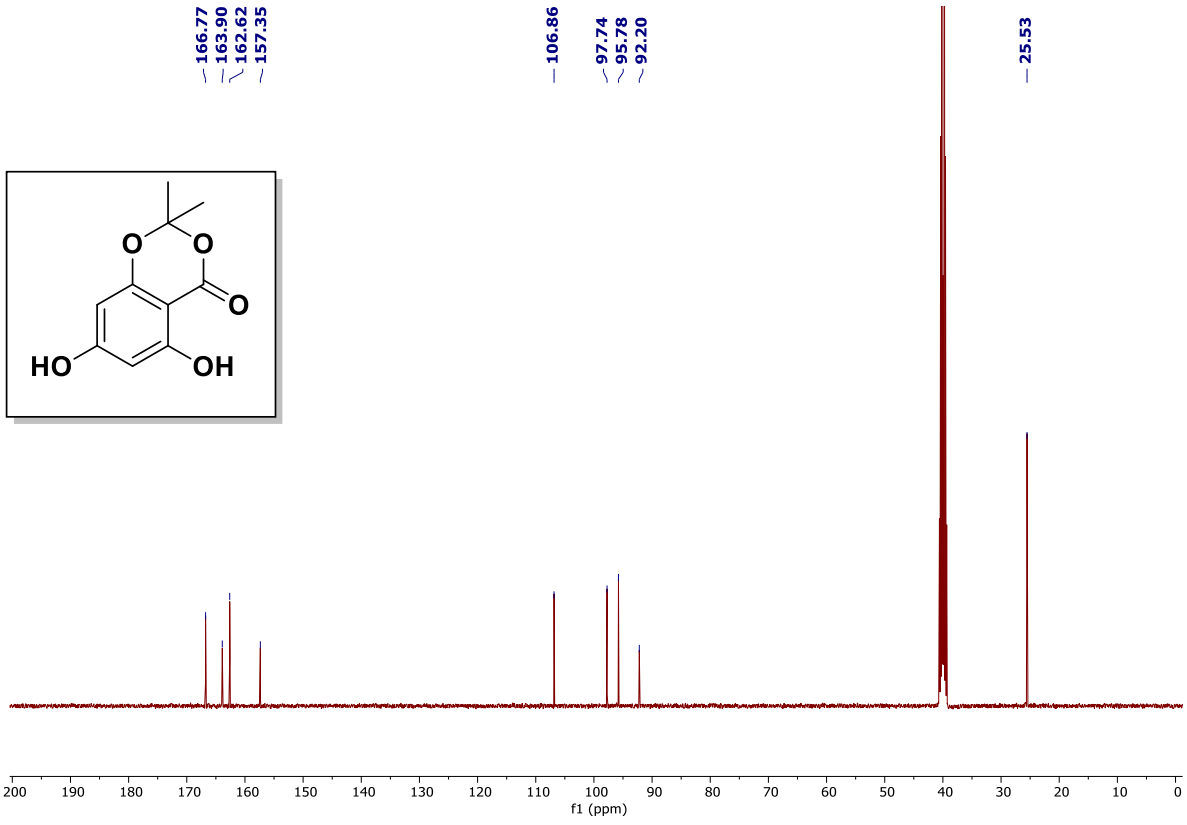


Chapter 2 Spectral data

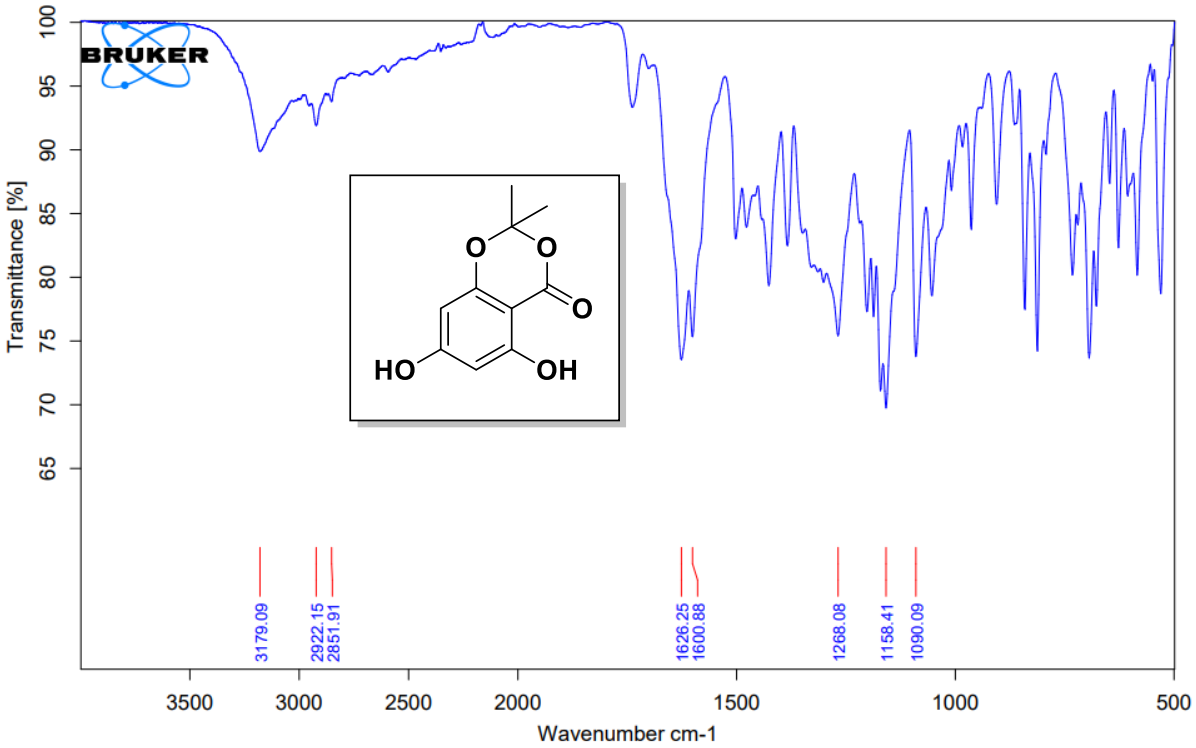
^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of the compound 8



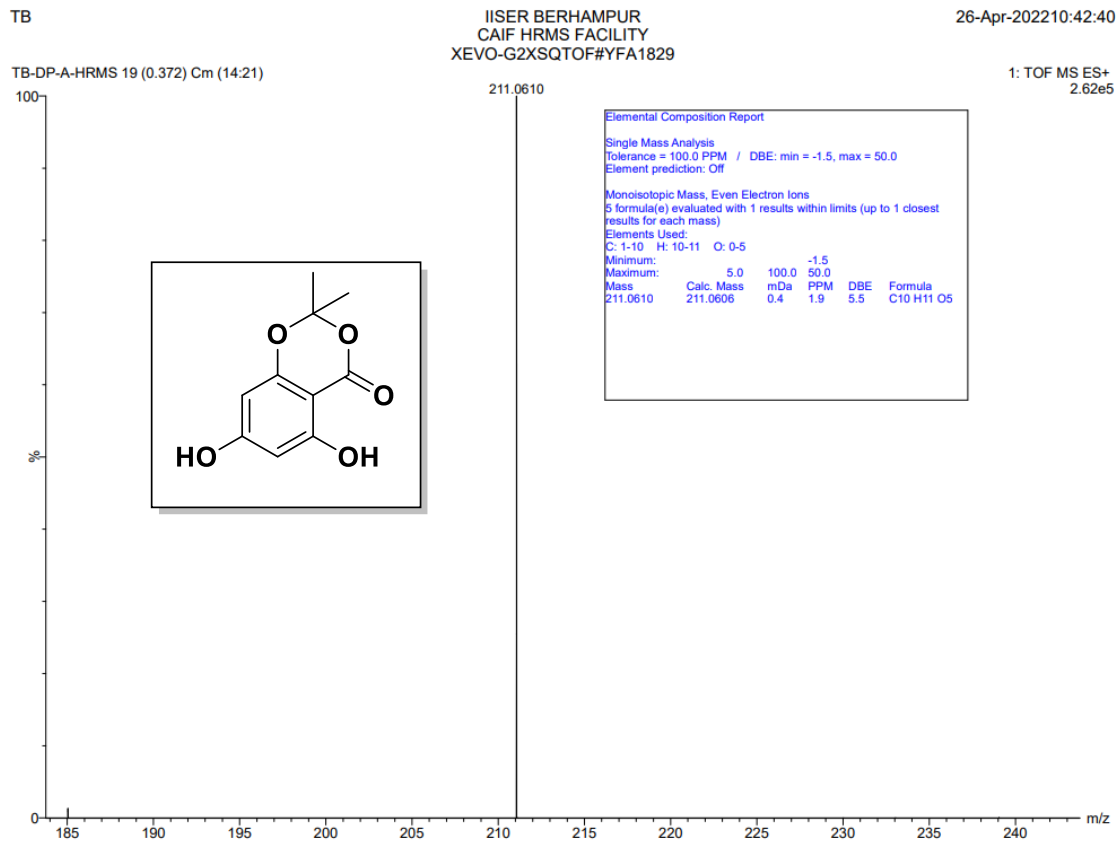
^{13}C NMR (100 MHz, DMSO-d$_6$) spectrum of the compound 8



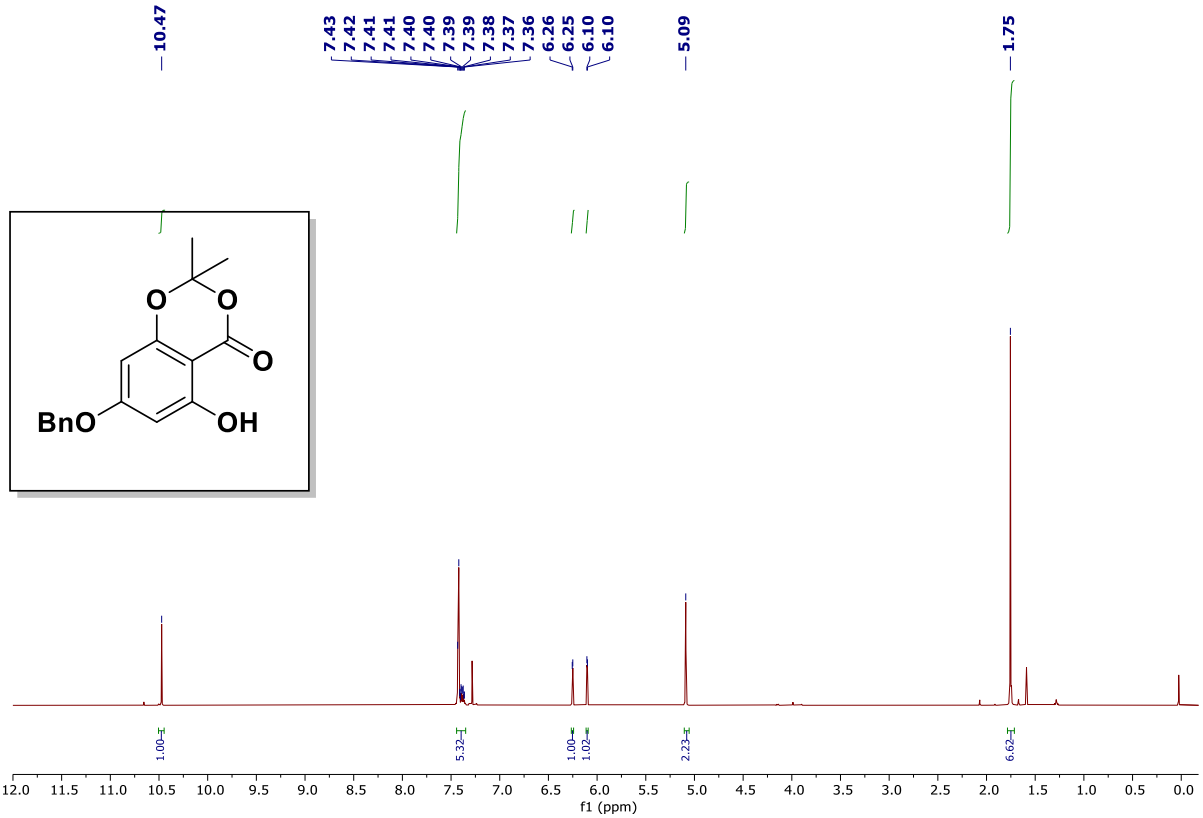
IR spectrum of the compound 8



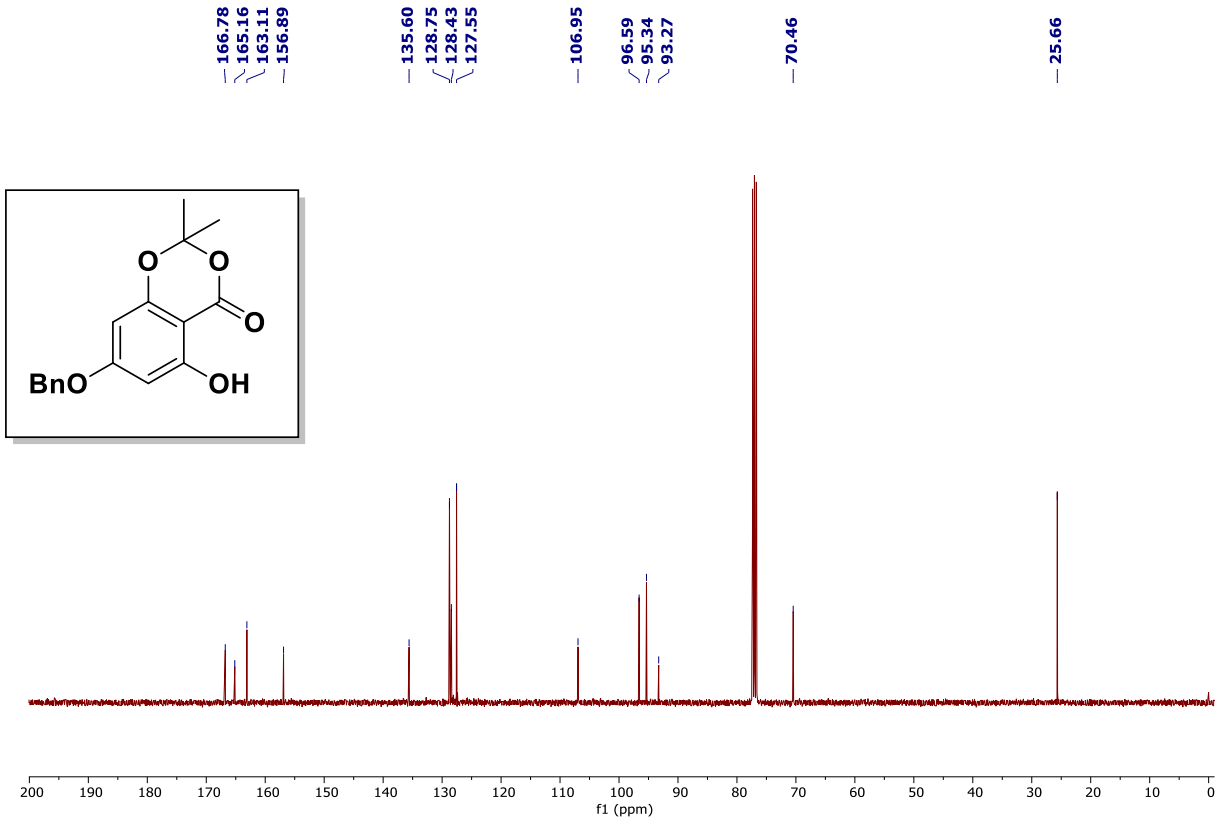
HRMS (ESI-TOF) spectrum of the compound 8



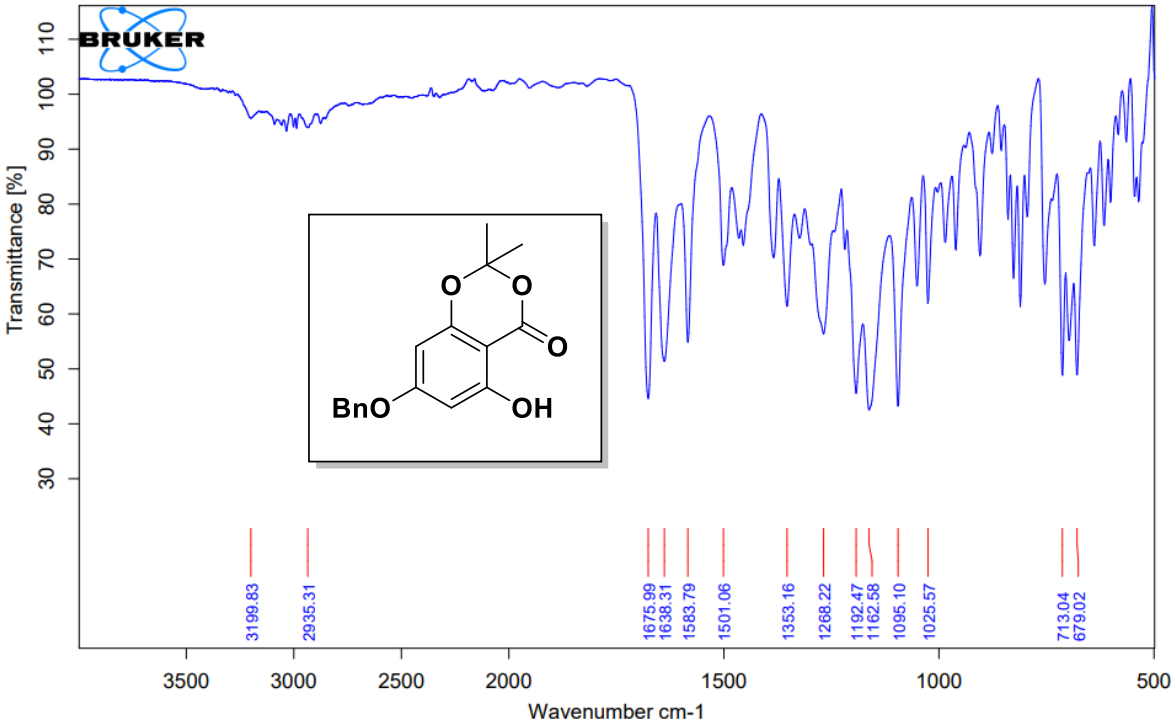
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 9



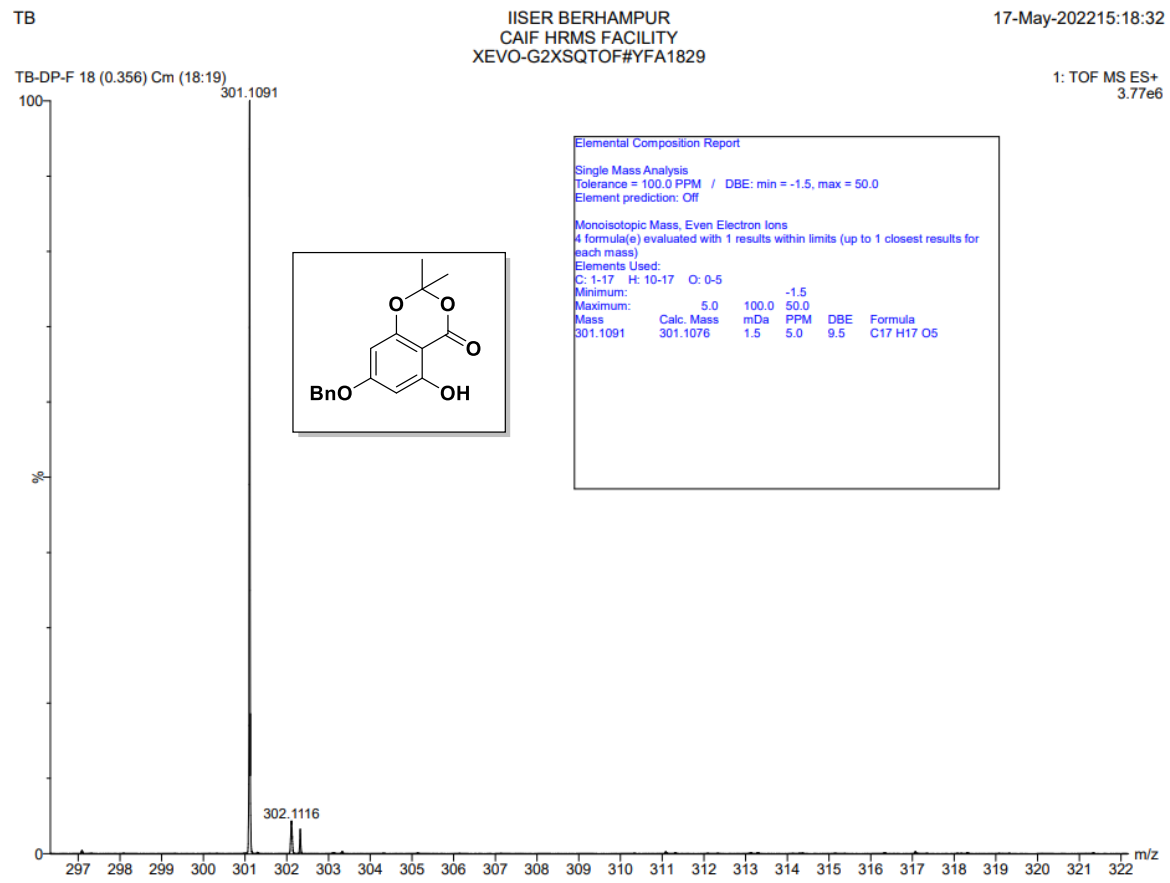
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 9



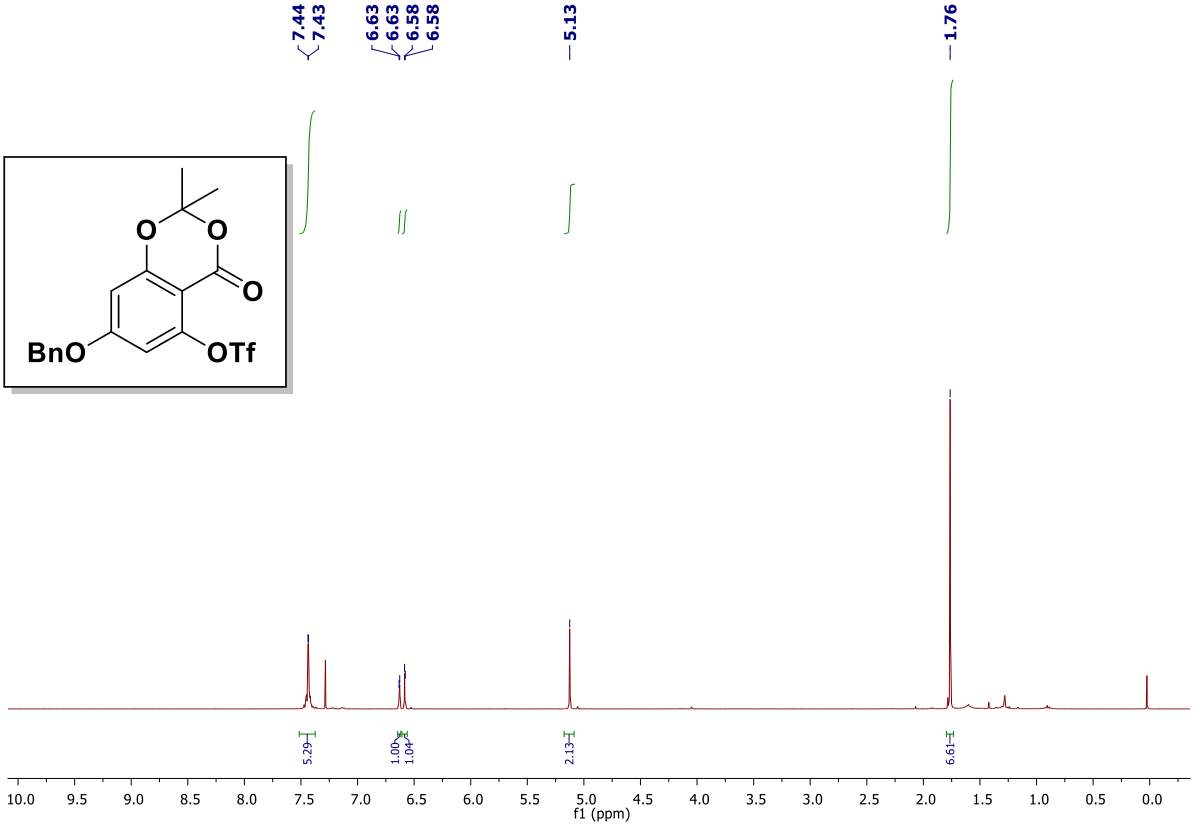
IR spectrum of the compound 9



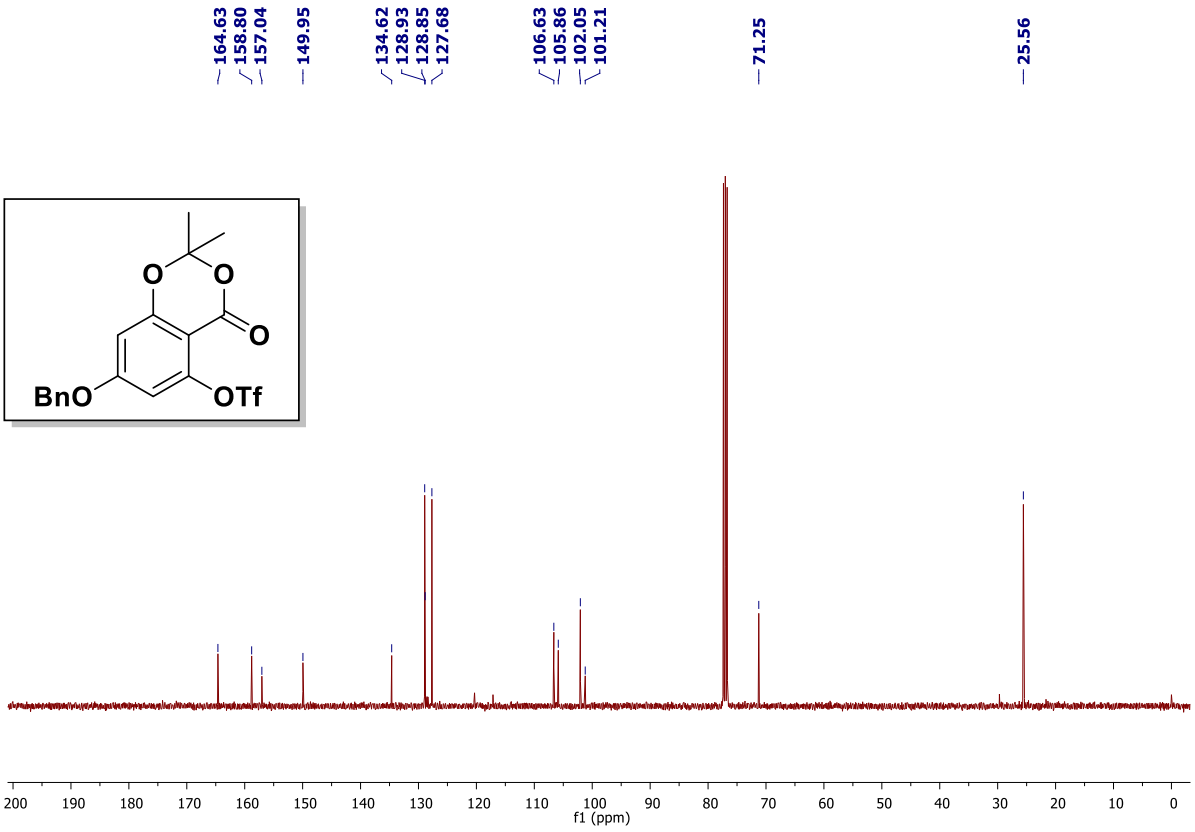
HRMS (ESI-TOF) spectrum of the compound 9



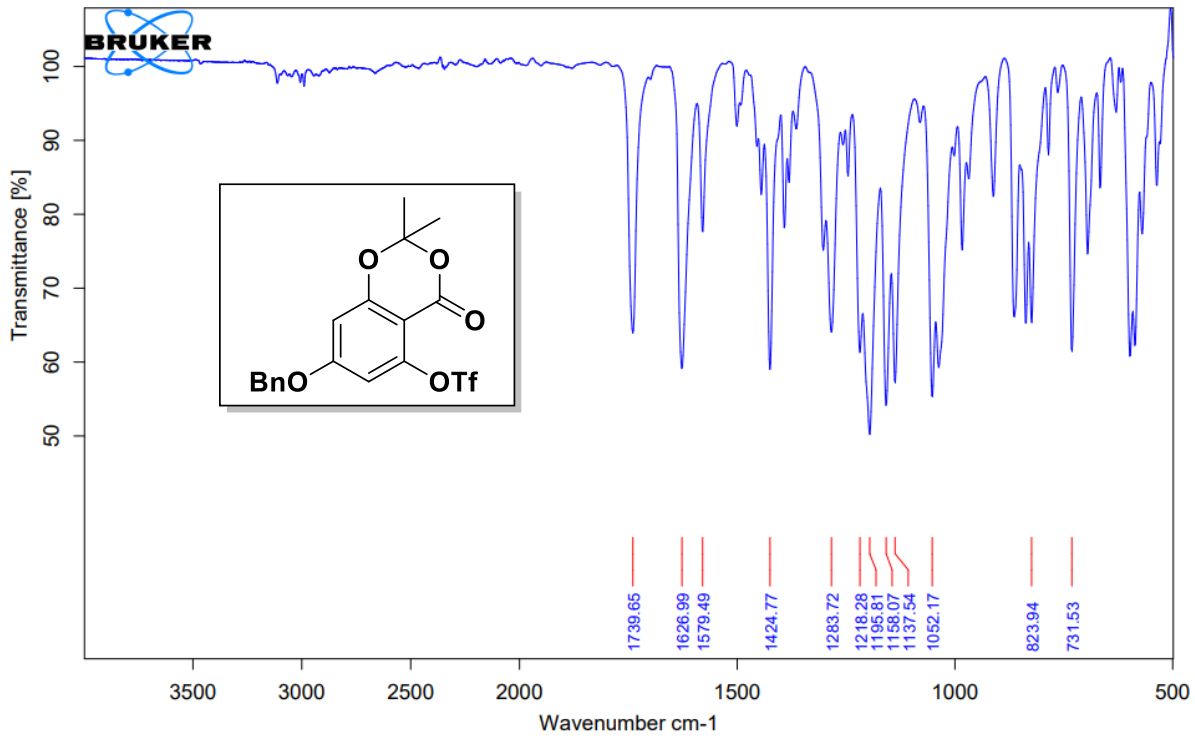
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 10



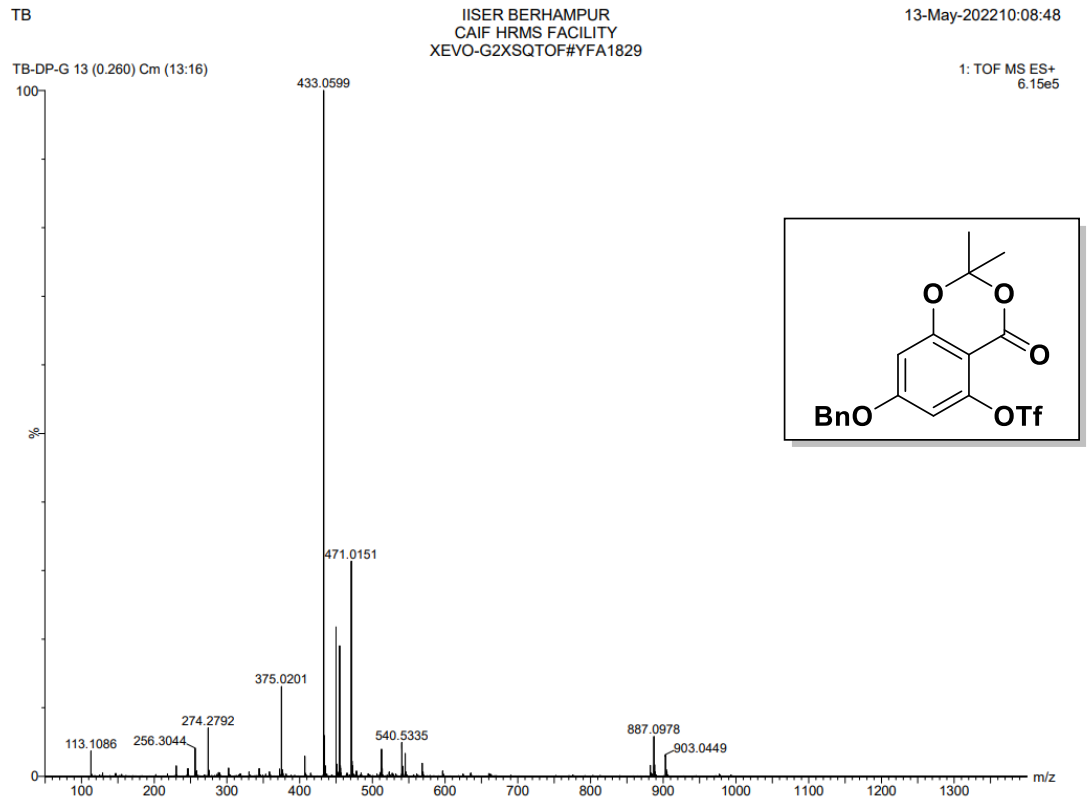
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 10



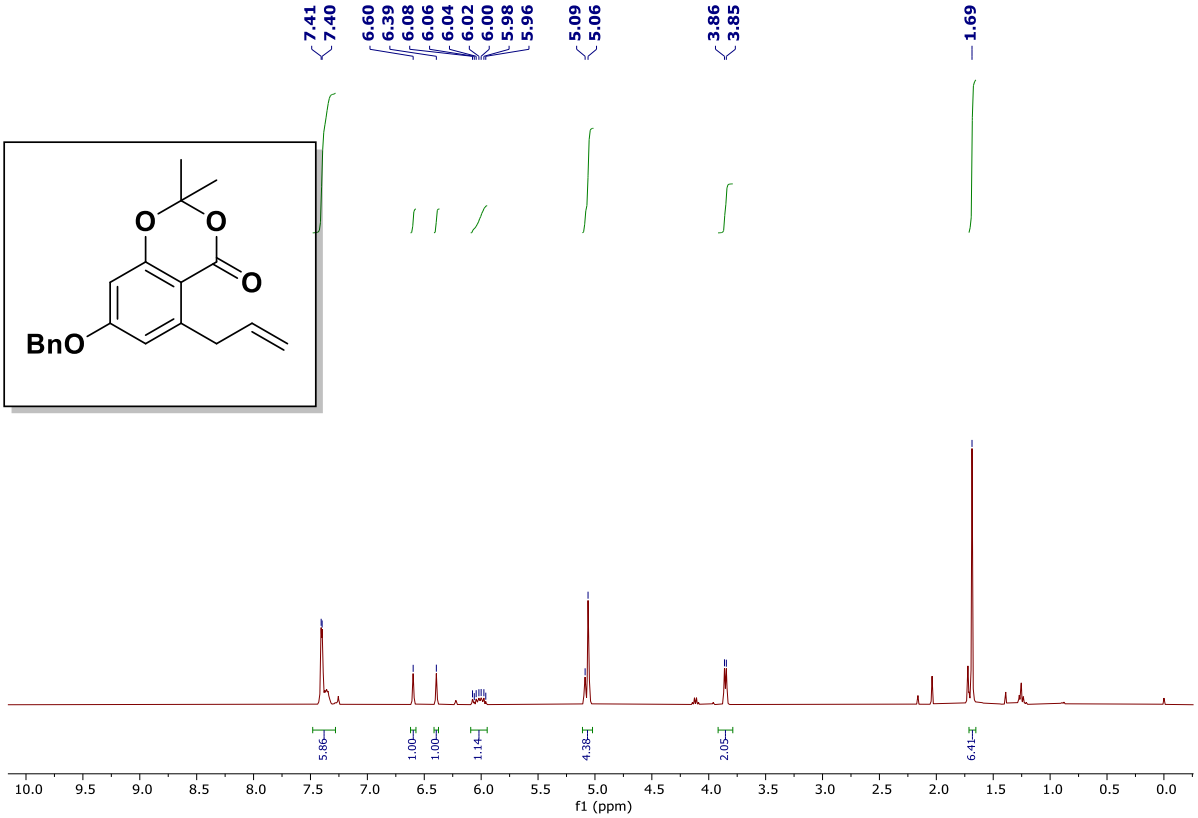
IR spectrum of the compound 10



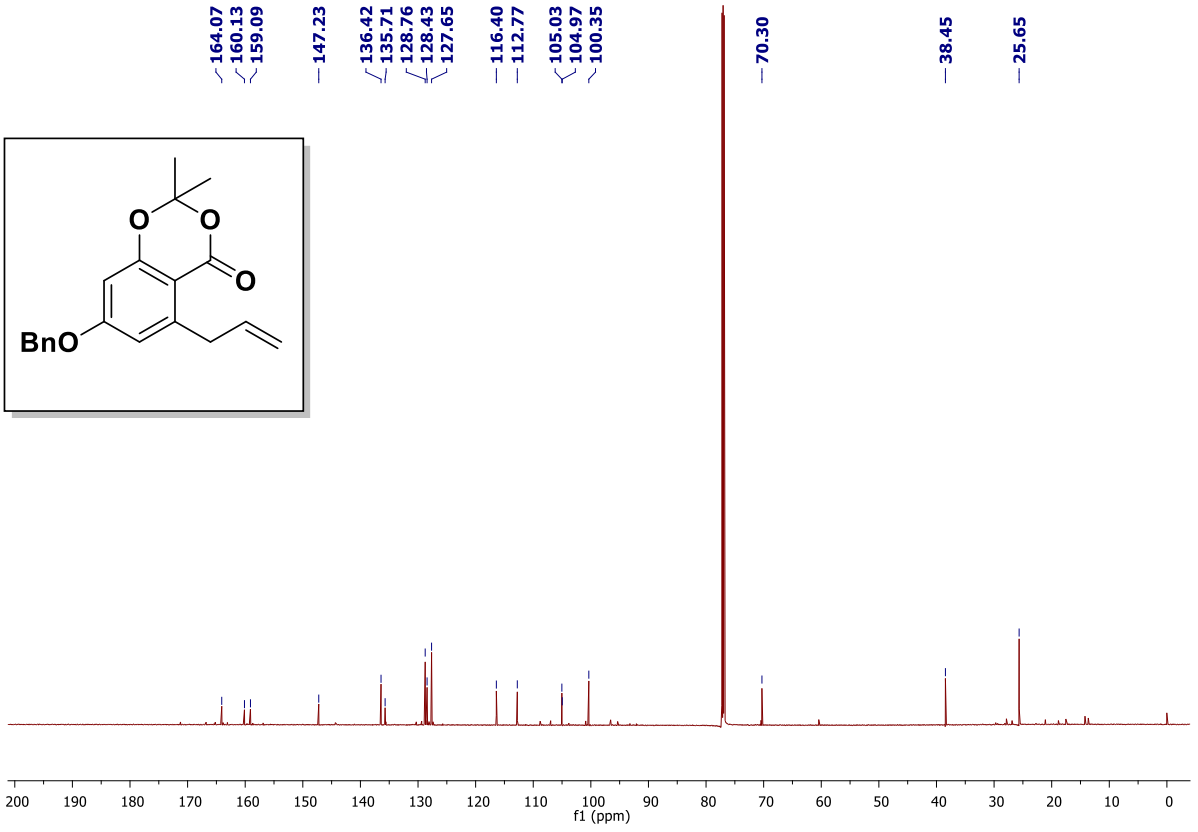
HRMS (ESI-TOF) spectrum of the compound 10



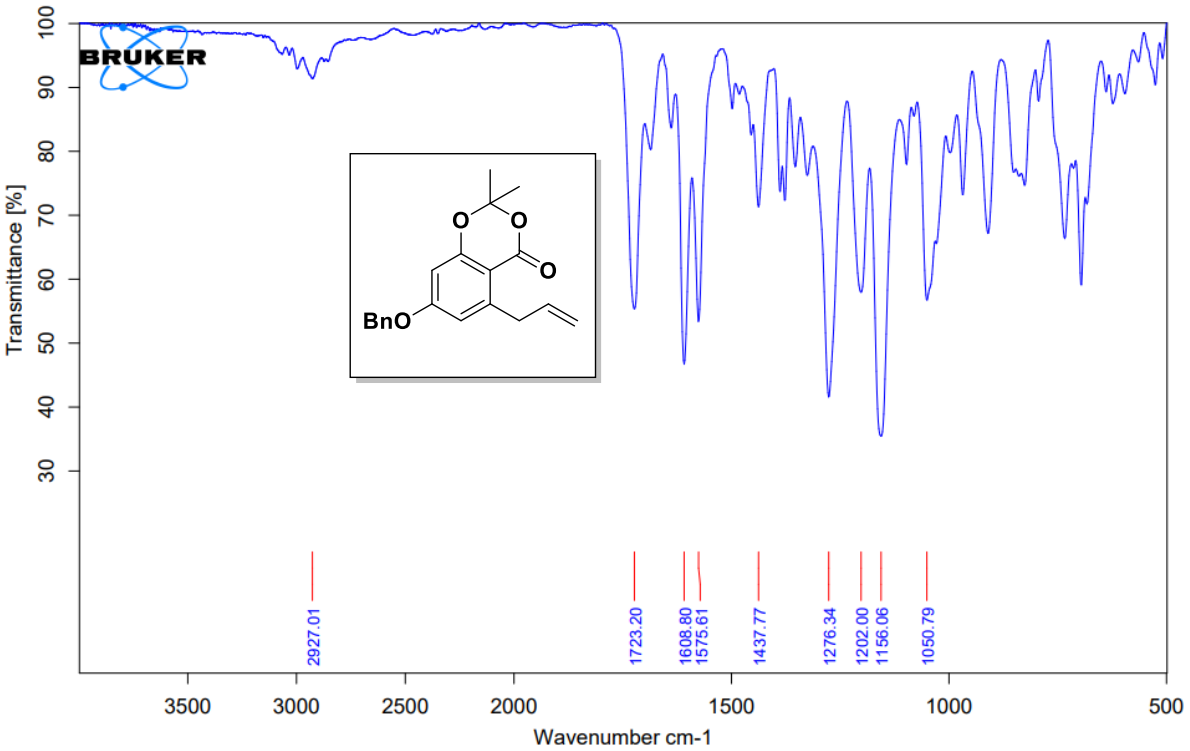
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 11



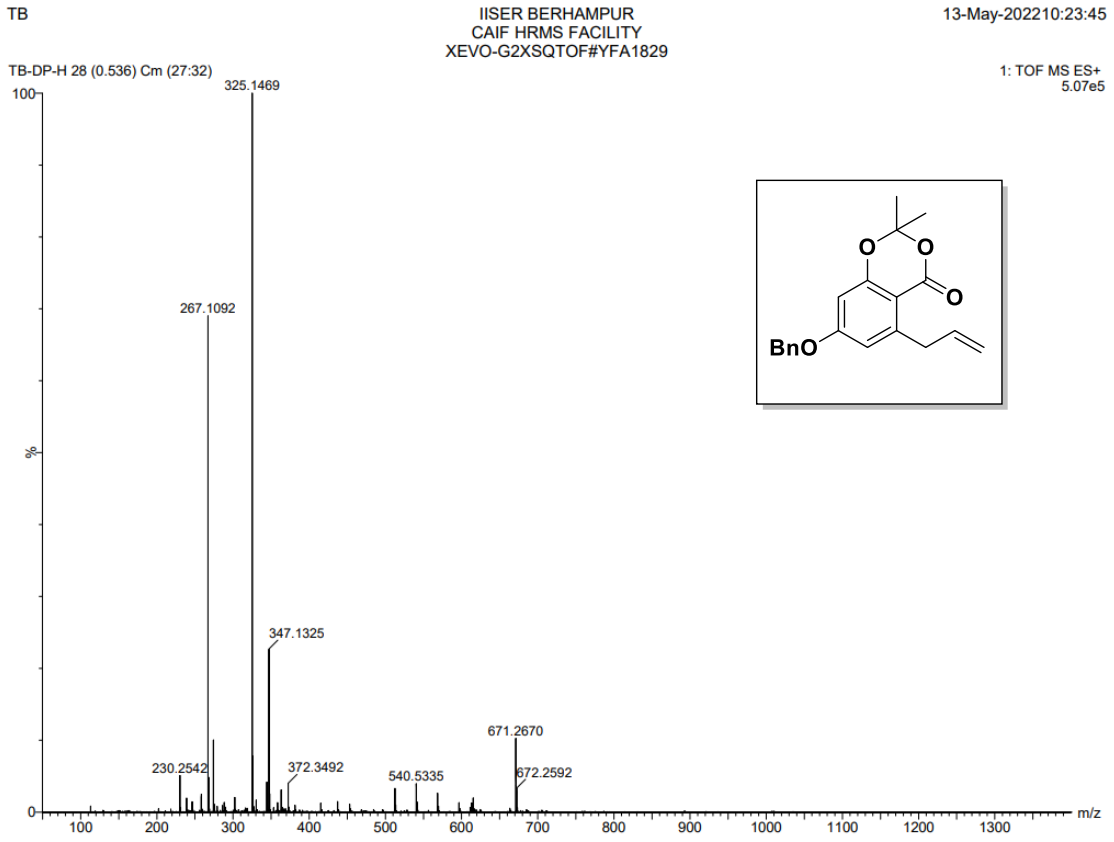
^{13}C NMR (175 MHz, $CDCl_3$) spectrum of the compound 11



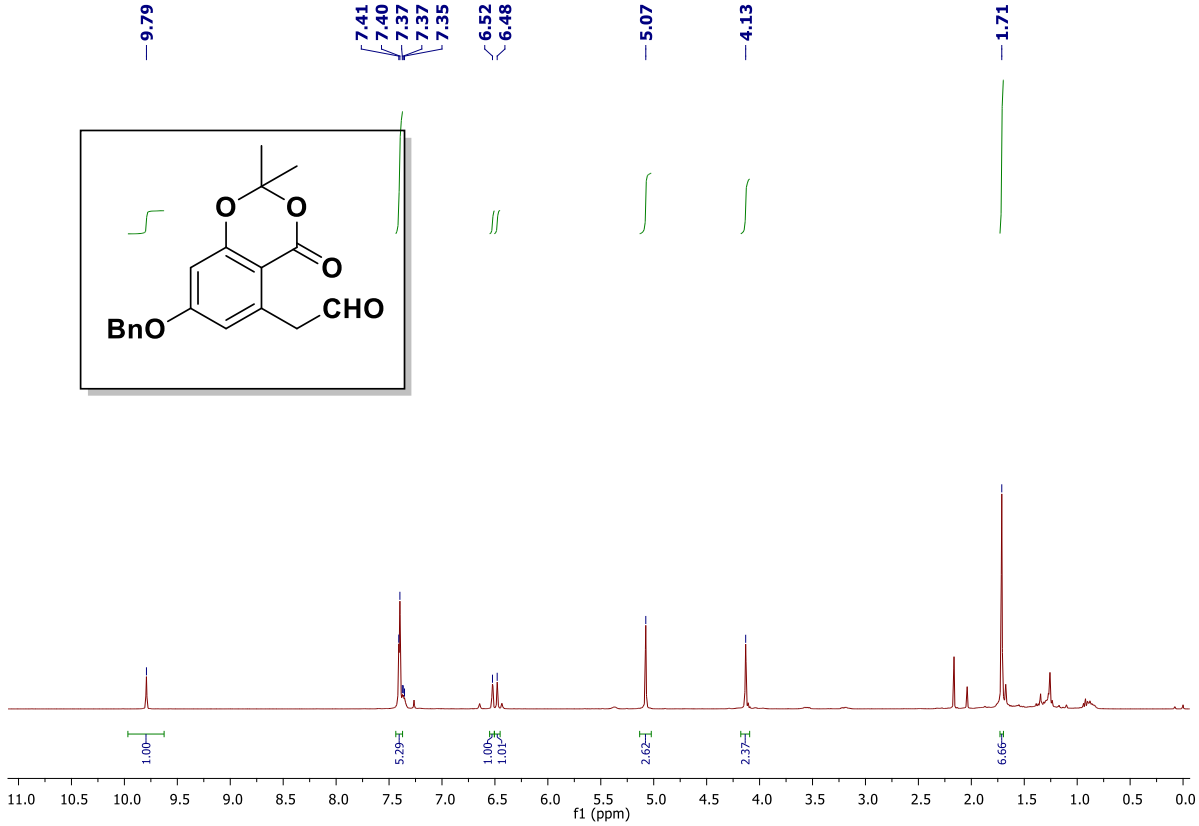
IR spectrum of the compound 11



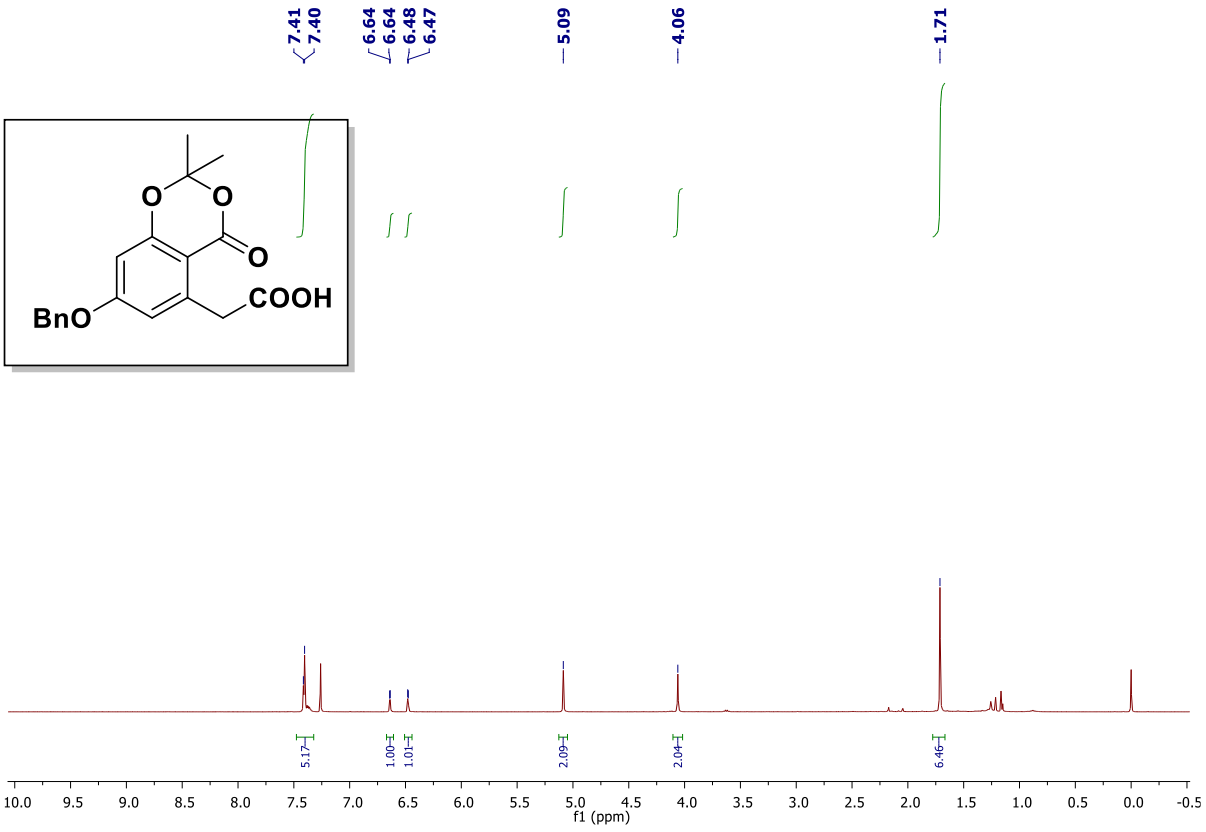
HRMS (ESI-TOF) spectrum of the compound 11



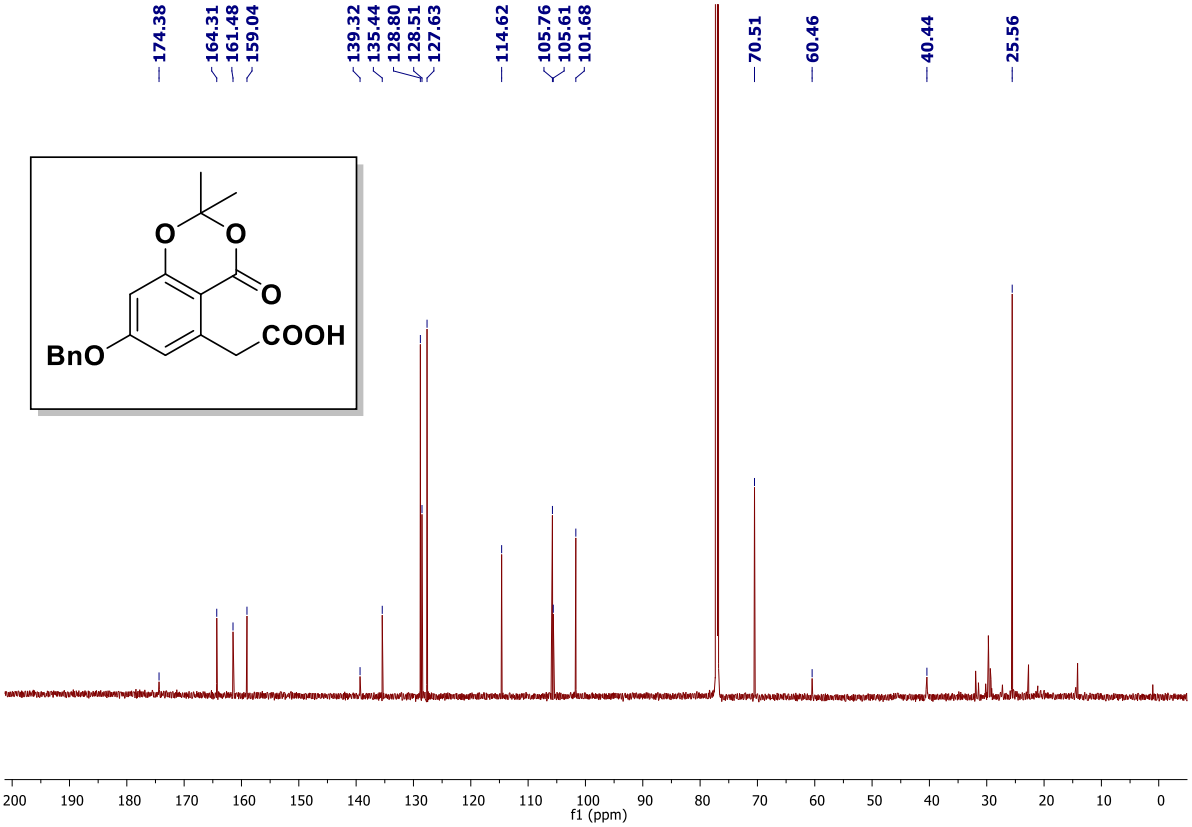
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 6 Intermediate (Crude)6



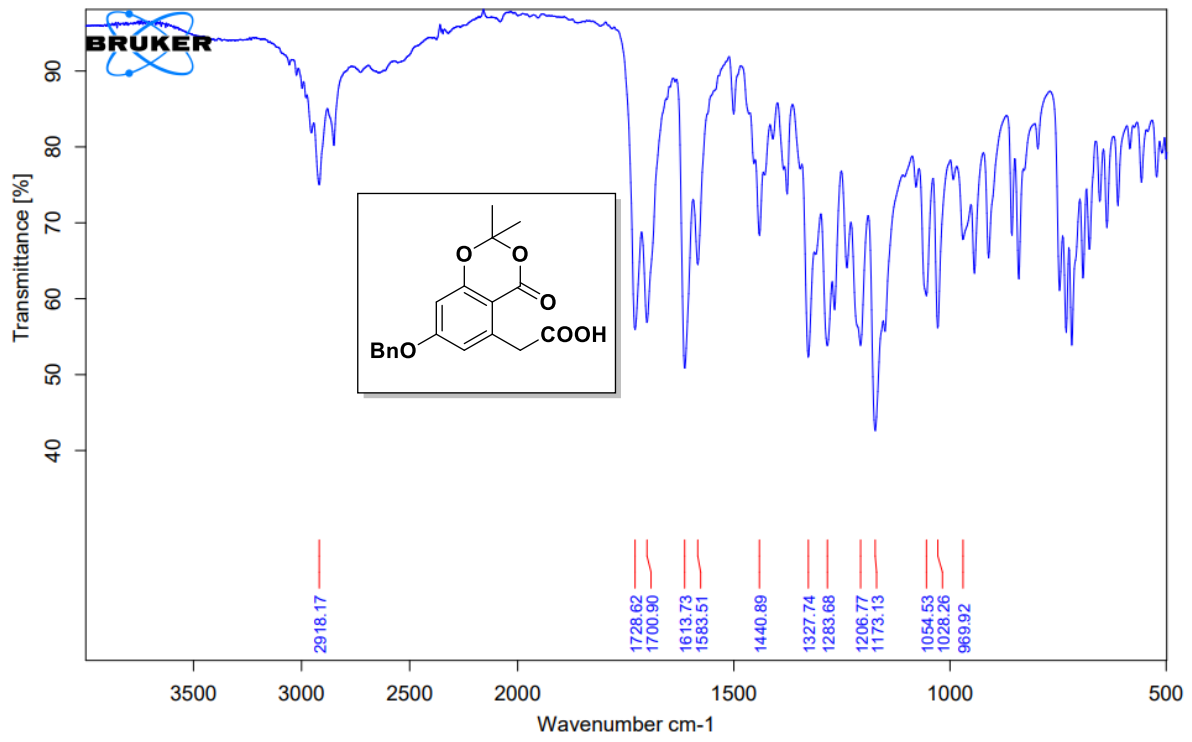
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 6



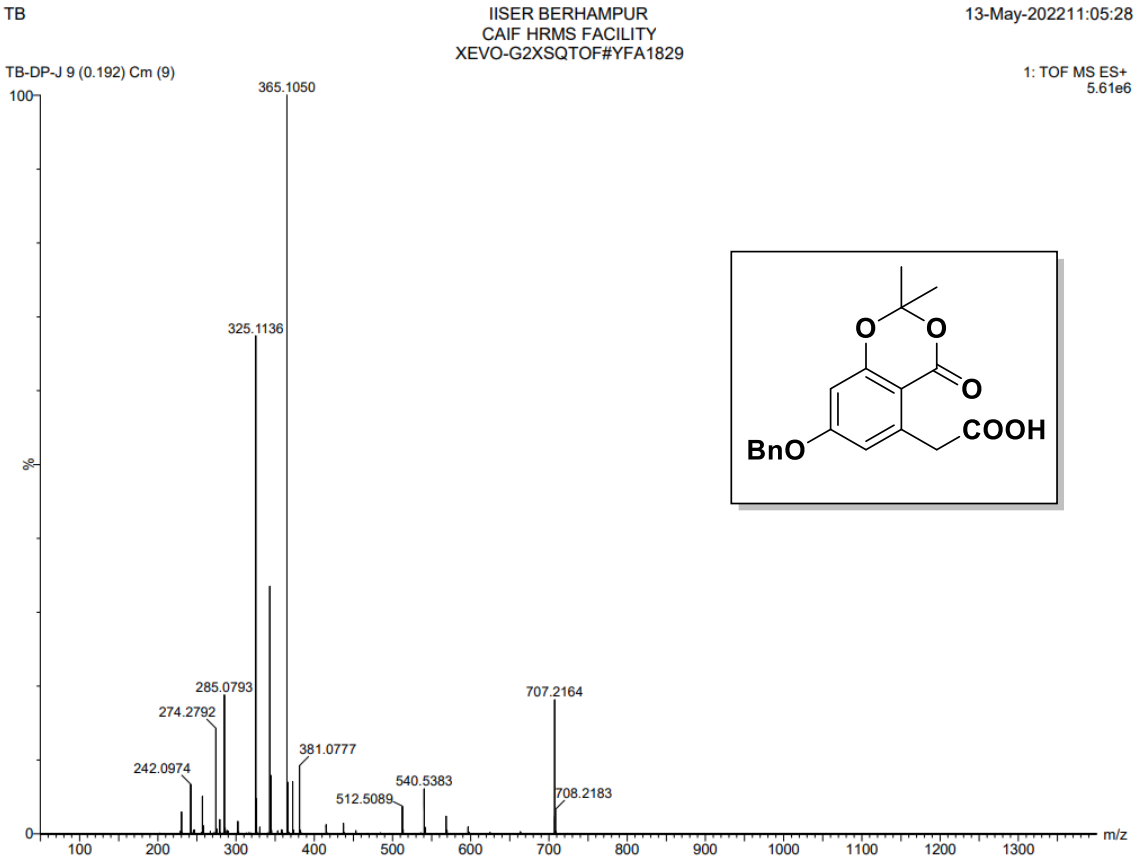
^{13}C NMR (175 MHz, $CDCl_3$) spectrum of the compound 6



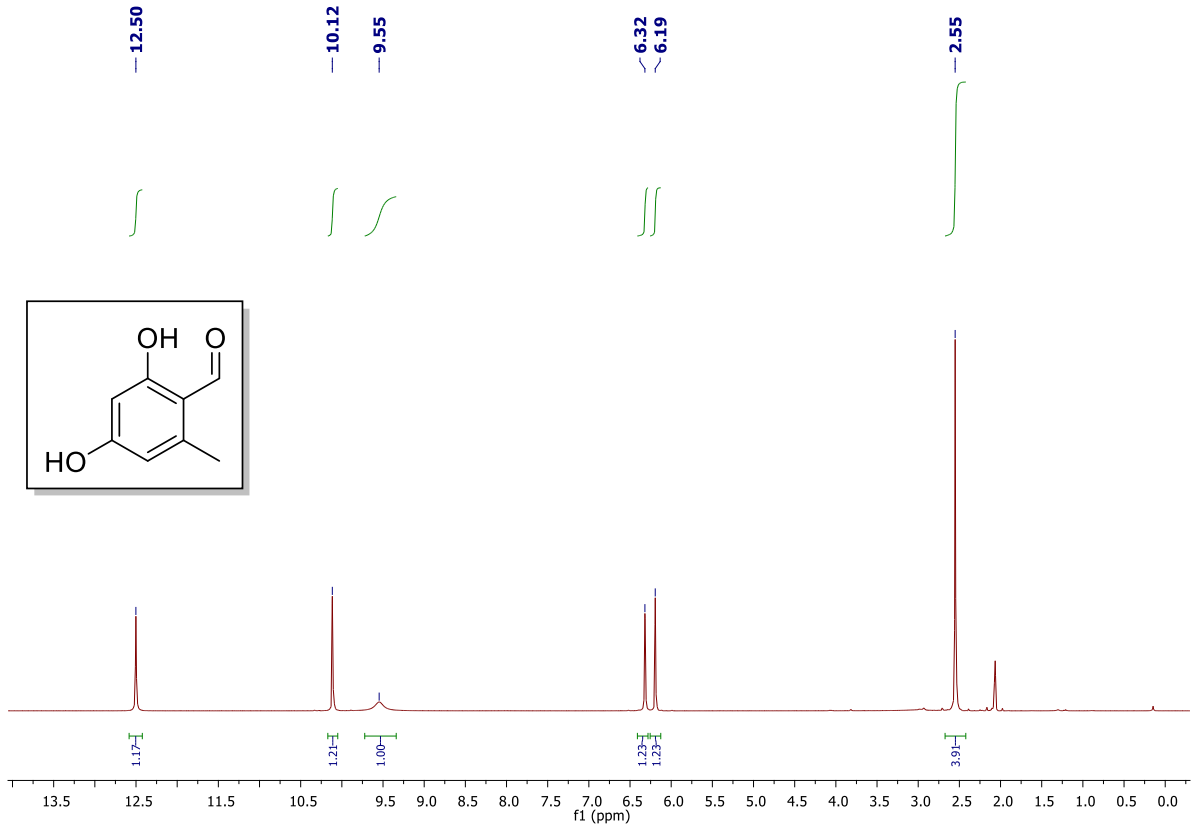
IR spectrum of the compound 6



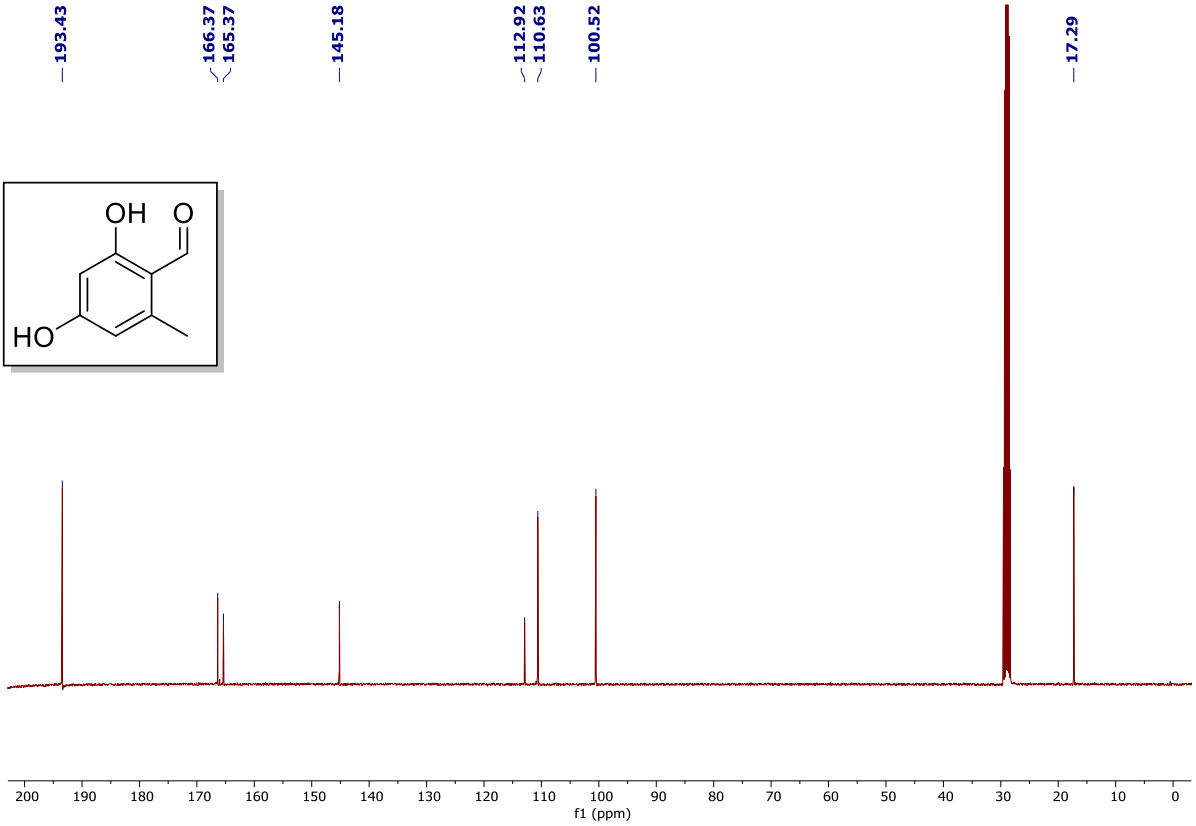
HRMS (ESI-TOF) spectrum of the compound 6



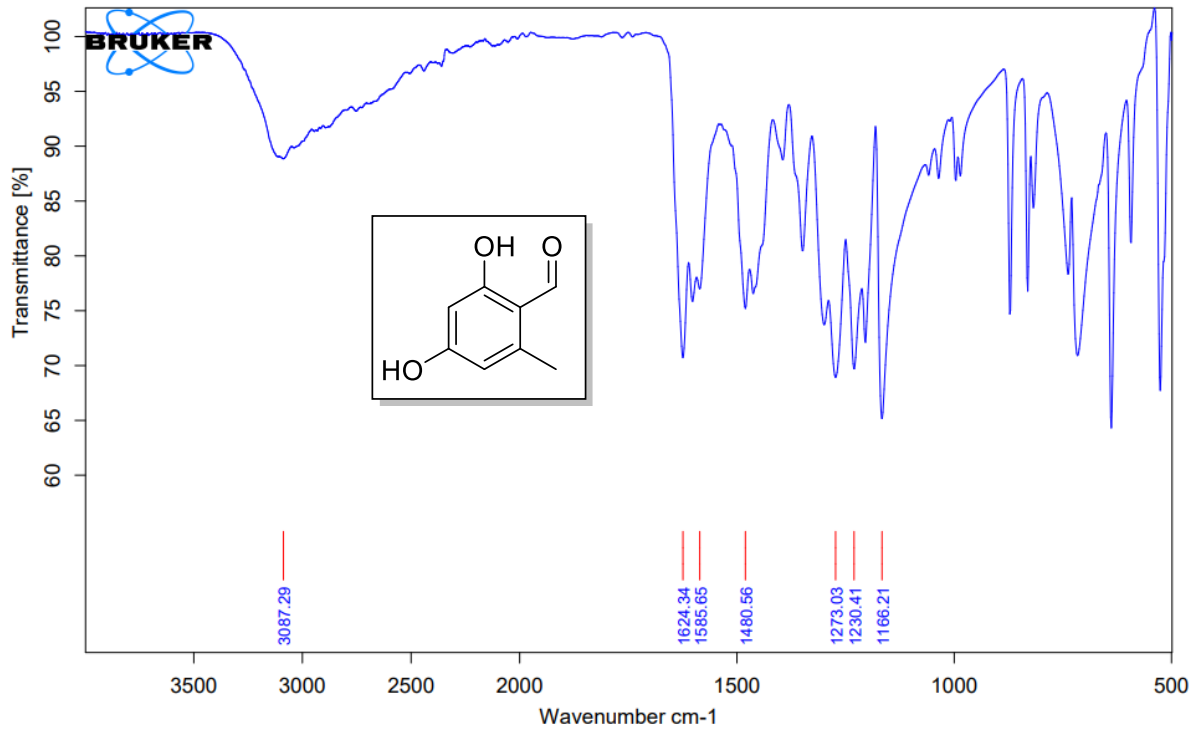
^{1}H NMR (400 MHz, Acetone) spectrum of the compound 23



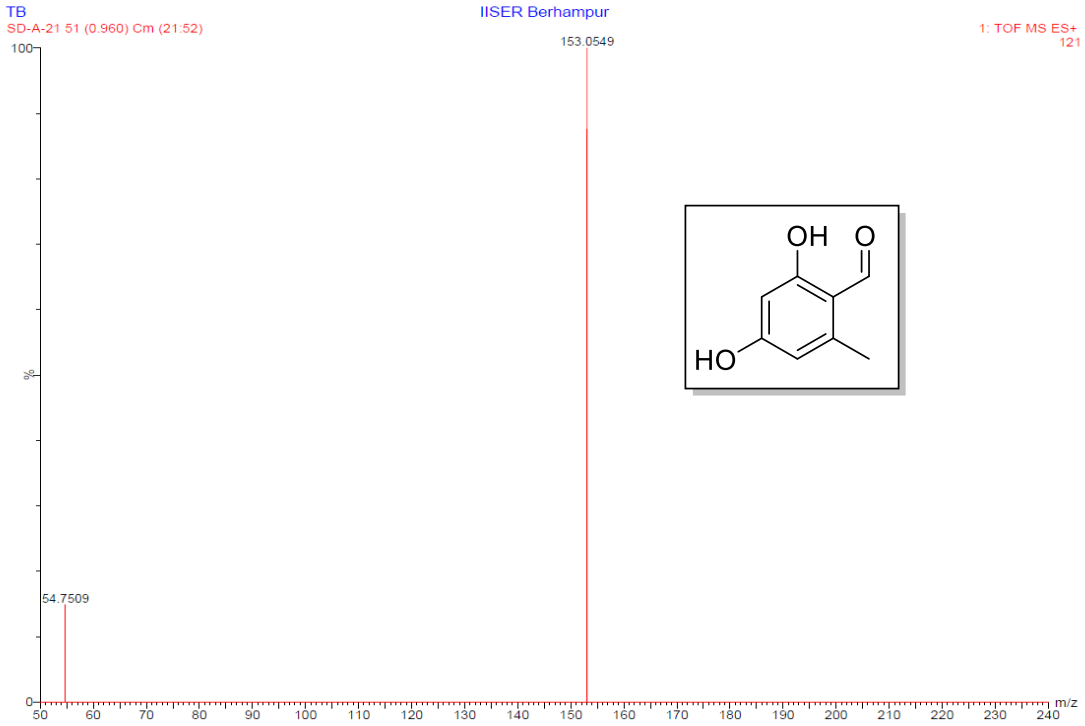
^{13}C NMR (100 MHz, Acetone) spectrum of the compound 23



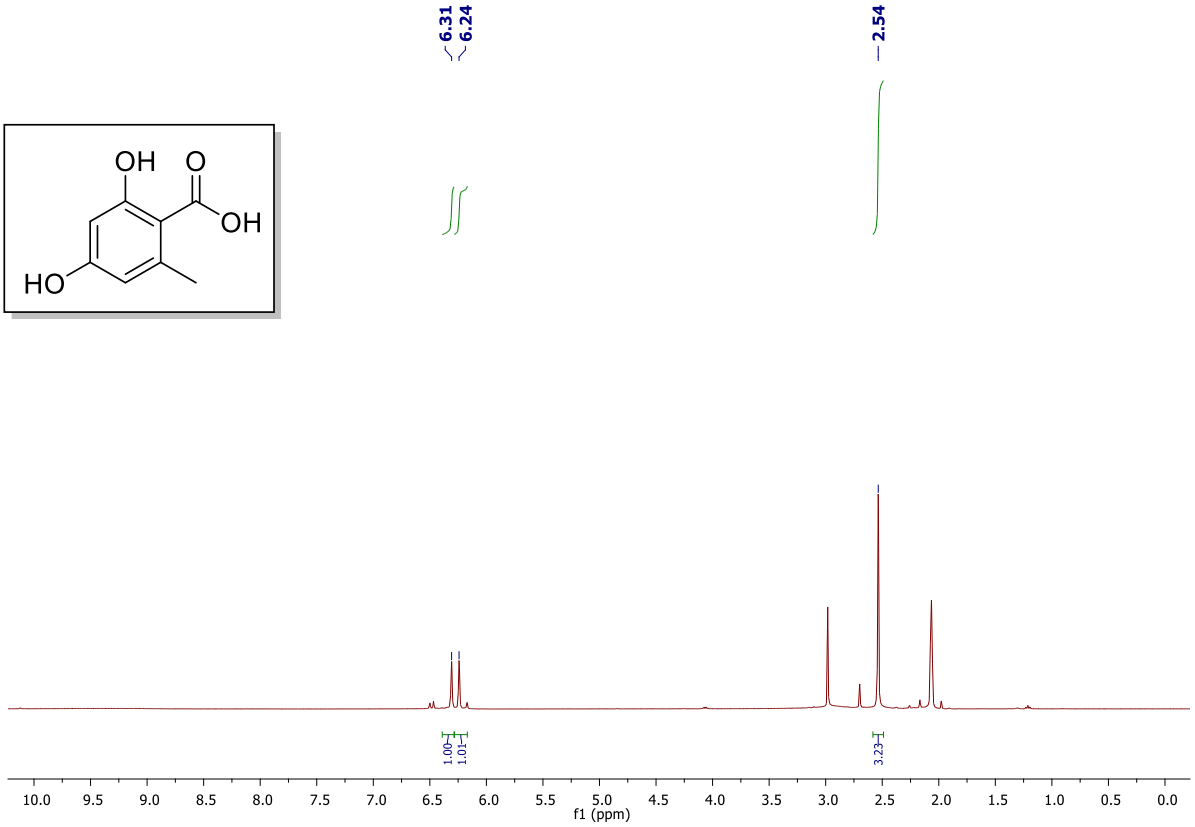
IR spectrum of the compound 23



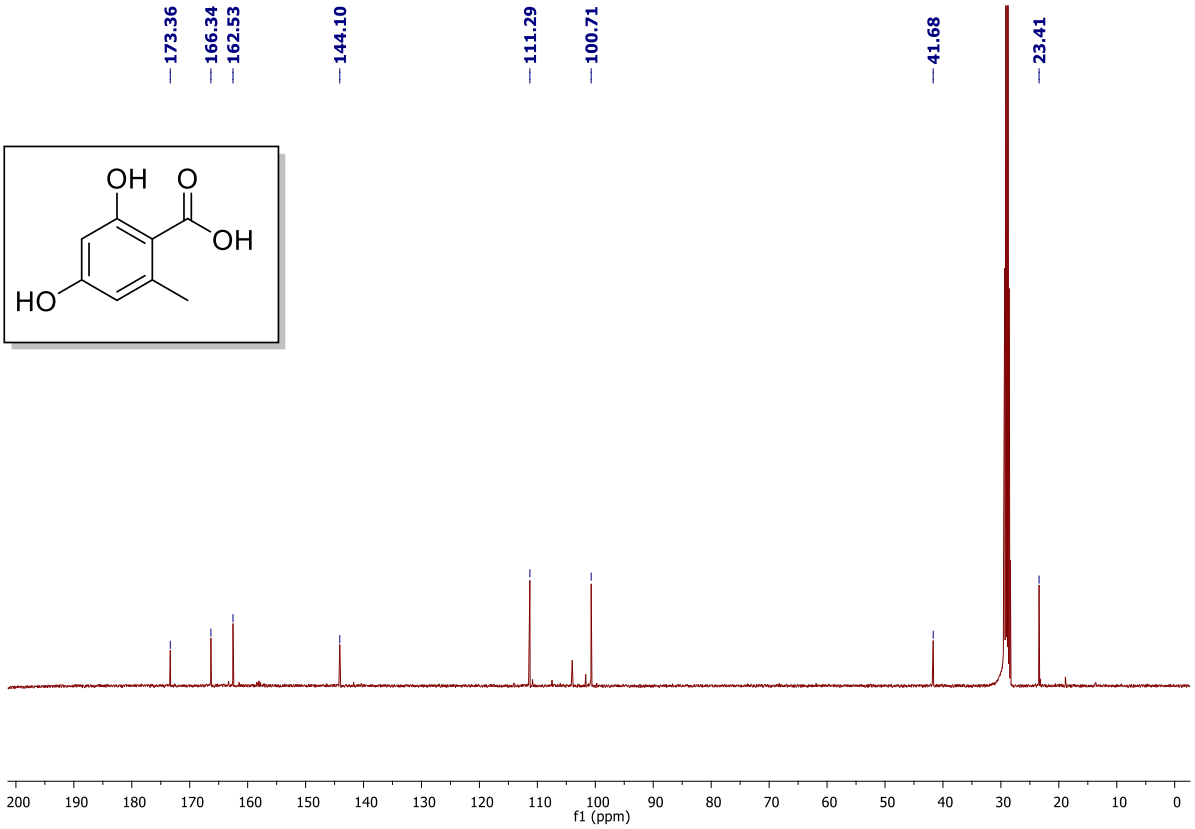
HRMS (ESI-TOF) spectrum of the compound 23



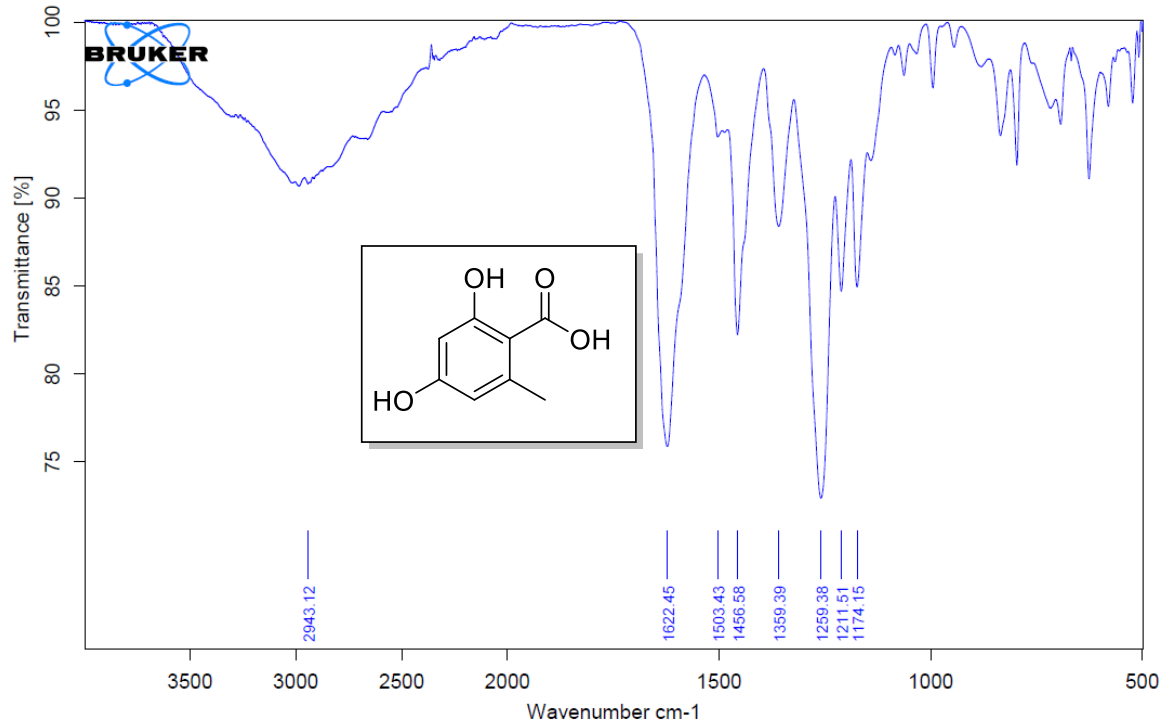
3.18 ^{1}H NMR (400 MHz, Acetone) spectrum of the compound 24



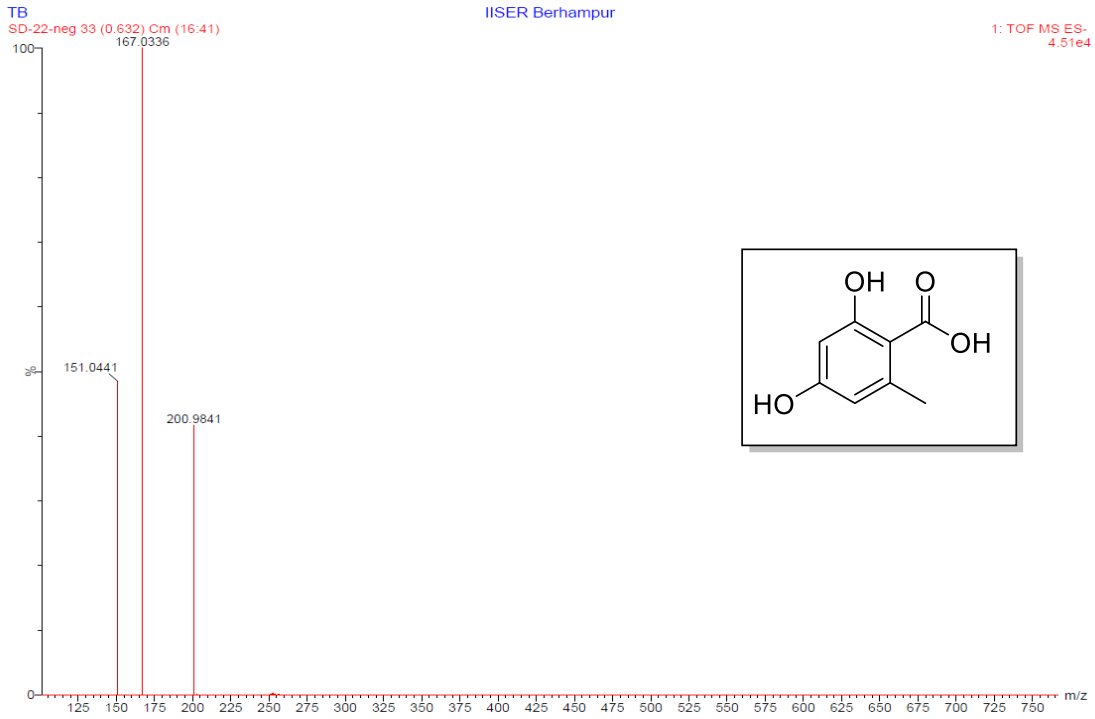
^{13}C NMR (100 MHz, Acetone) spectrum of the compound 24



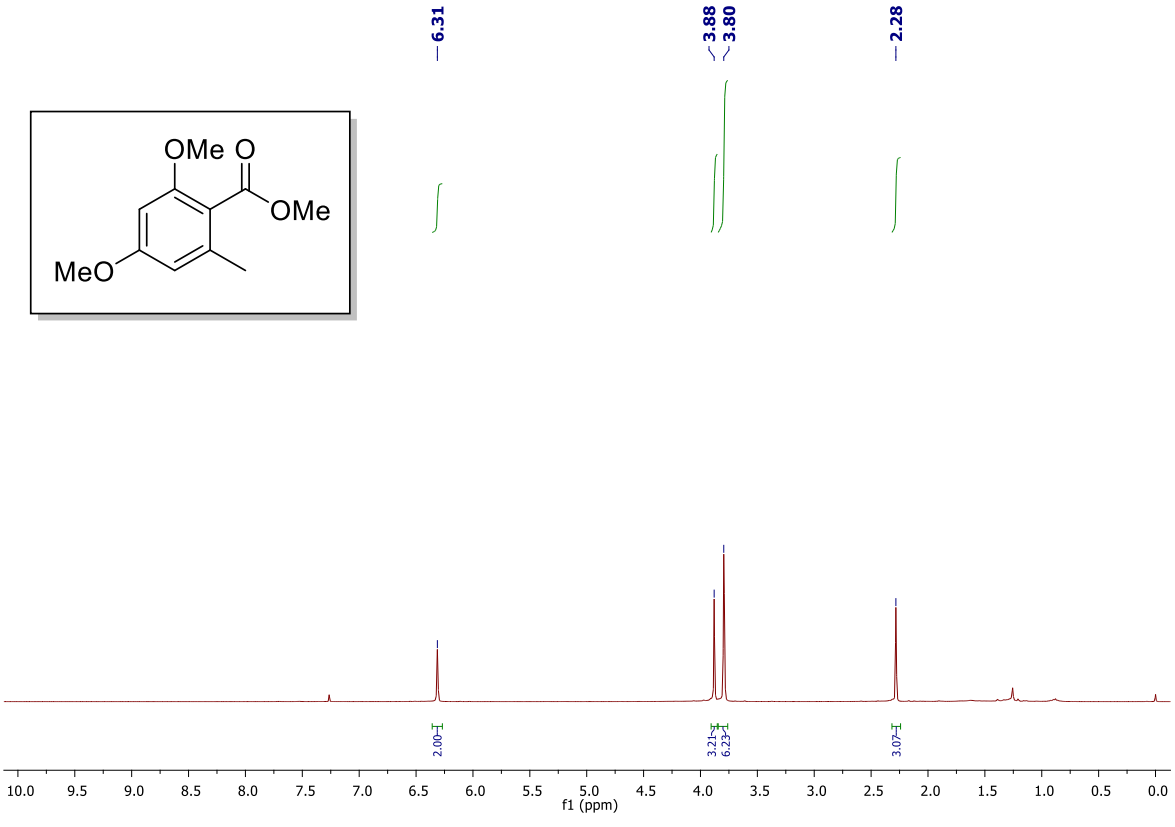
IR spectrum of the compound 24



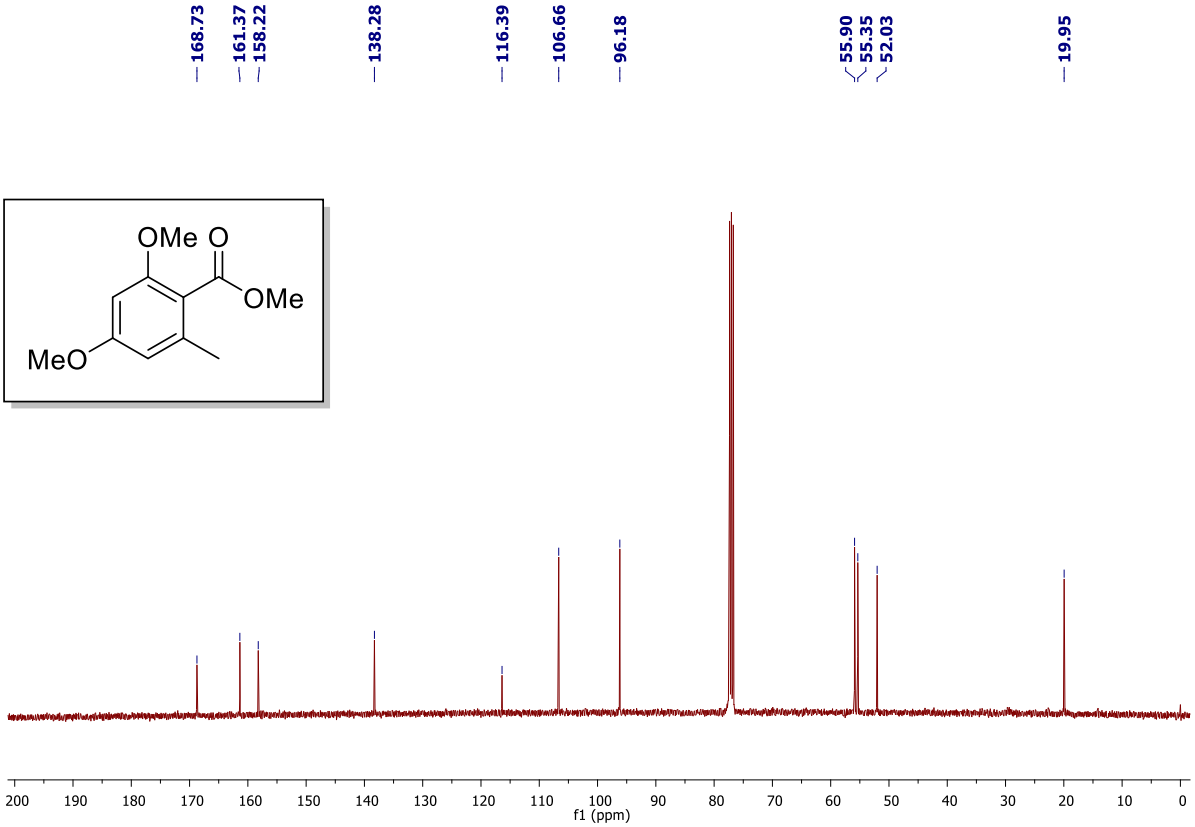
HRMS (ESI-TOF) spectrum of the compound 24



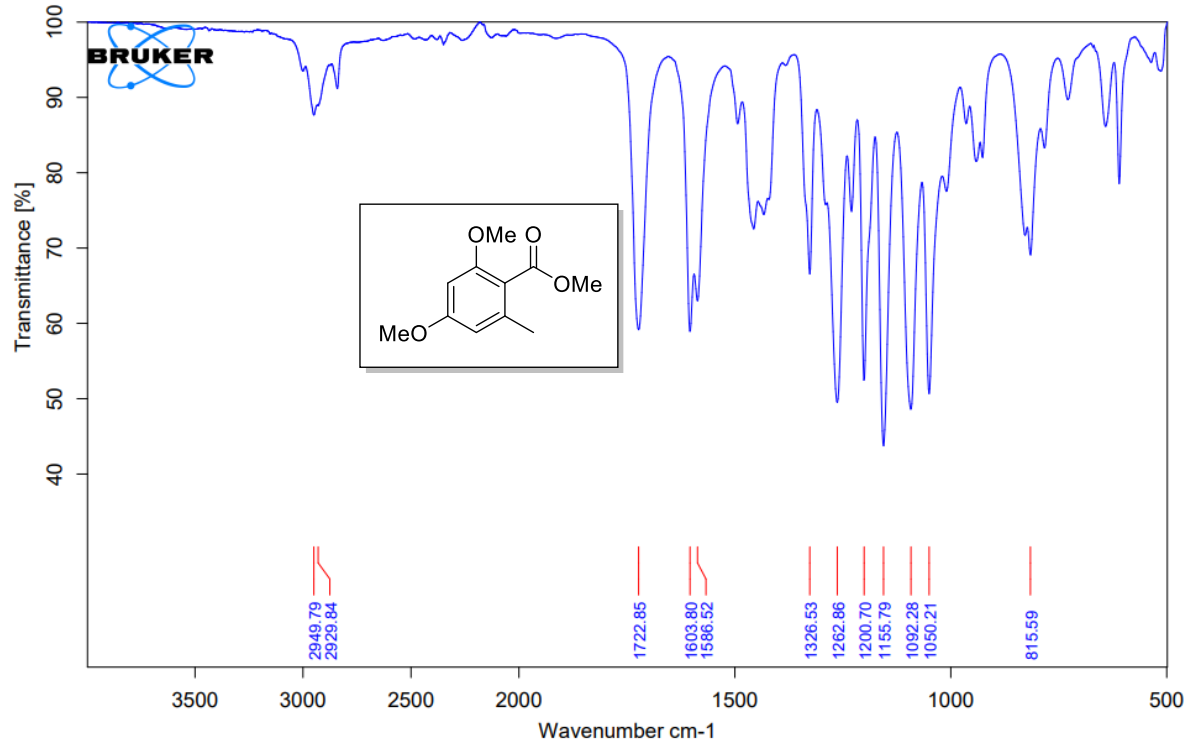
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound 21



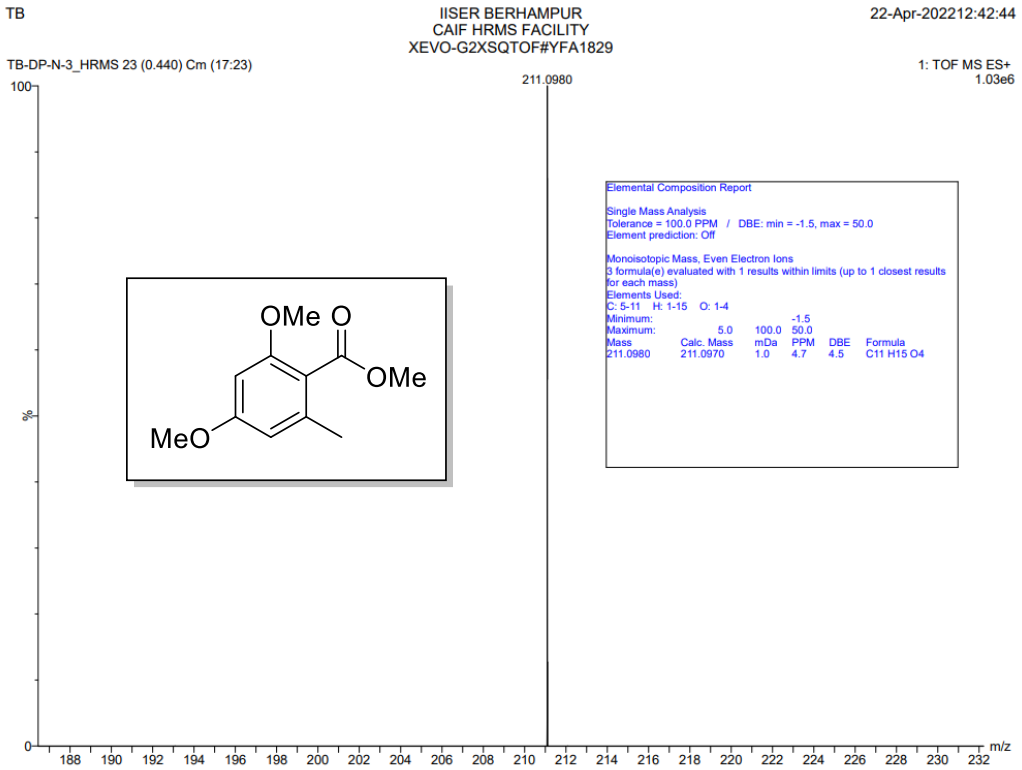
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound 21



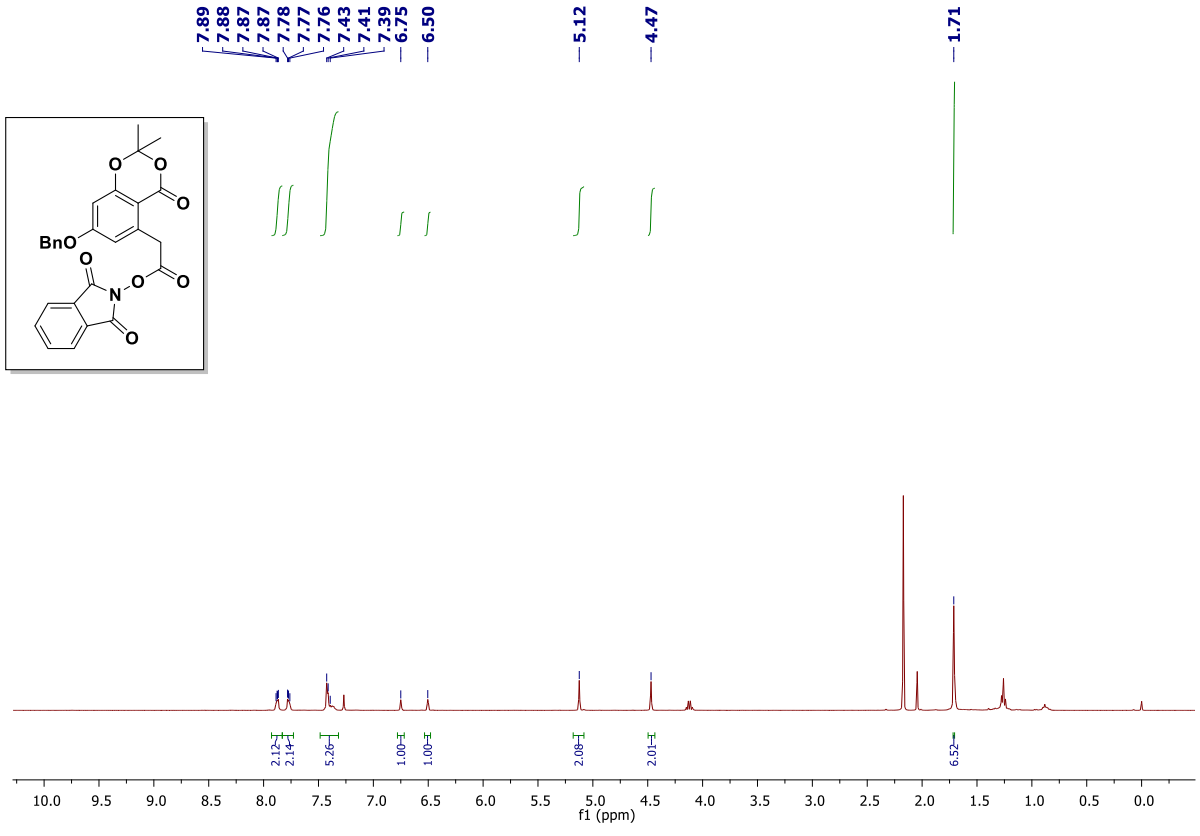
IR spectrum of the compound 21



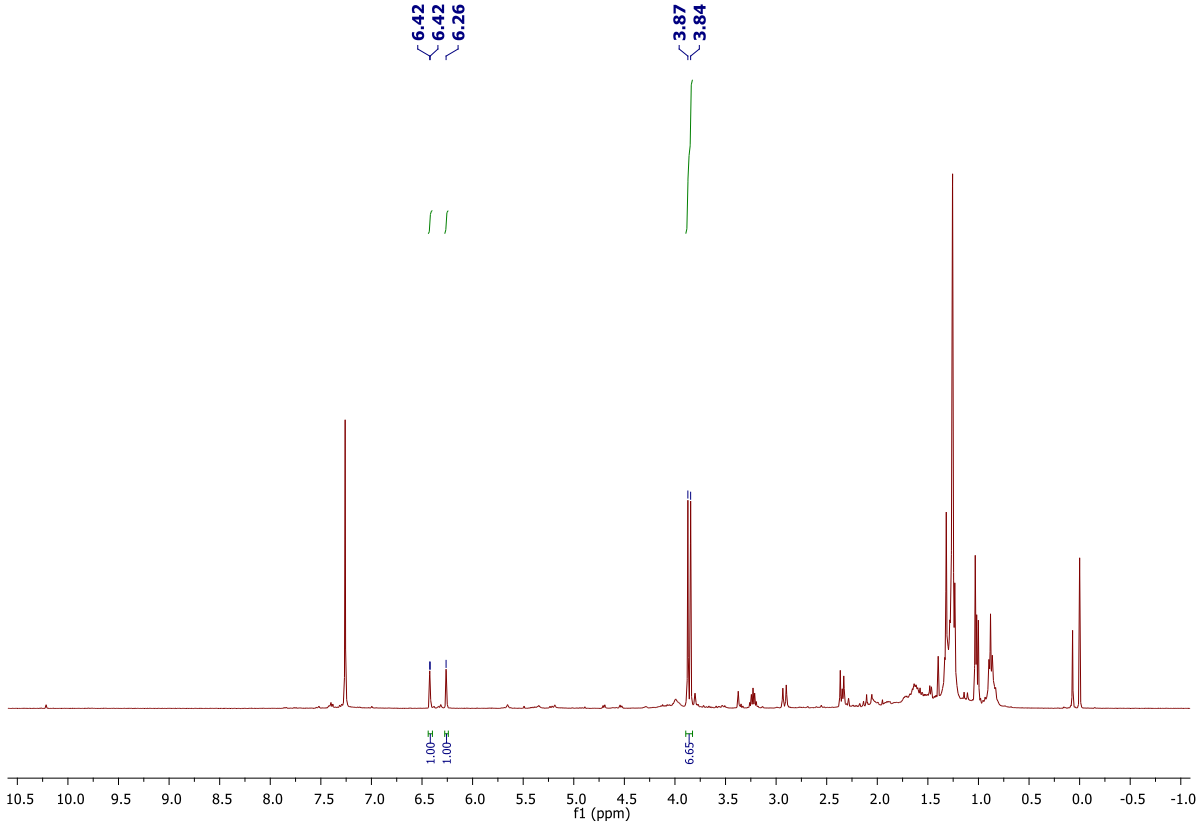
HRMS (ESI-TOF) spectrum of the compound 21



^{1}H NMR (400 MHz, $CDCl_3$) of Redox-active ester during decarboxylative cross coupling



^{1}H NMR (400 MHz, $CDCl_3$) of expected product 25-provided to show missing peaks



^{1}H NMR (400 MHz, $CDCl_3$) of proton abstracted compound during decarboxylative cross coupling