Cost Efficient, Scalable Asymmetric Synthesis of Bronze Birch Borer Kairomone (5S,7S)-7-Methyl-1,6-dioxaspiro[4.5]decane

By

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Abstract

With the increased use of birch trees, specifically non-native birches in parks, and beautification projects, an increase of infestations by the bronze birch borer (*Agrilus anxius)* has occurred. While reactive measures are available to try to remediate infested trees, a proactive strategy is not as widely available. (5S,7S)-7-Methyl-1,6-dioxaspiro[4.5]decane (5S,7S-conophthorin) has been identified as a possible kairomone that attracts bronze birch borers to susceptible trees. These susceptible trees include Eurasian varieties and stressed native North American species. While synthesized in the past, a scalable, cost efficient synthesis of this kairomone will likely enable its production industrially, and help allow for mass detection/trapping strategies of the pest to be implemented before infestations occur.

Dedication

Dedicated to my parents Tammy and Dwayne Atwood, and my wife Alyson.

Acknowledgements

There are so many people to acknowledge. First, the MaGee group, past and present students. I want to single out Muhammad as he has been a great teacher and friend throughout the ups and downs. I also want to thank Dave as he was always there to answer my questions as well as Peter Silk, and Peter Mayo for introducing me to this project. I cannot thank my wife Alyson, and our family enough for all the support they have shown over the years. An acknowledgement must also be made to the funding body that made this research possible.

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List of Symbols, Nomenclature or Abbreviations

BBB	Bronze birch borer
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
BMS	Borane dimethyl sulfide
BuLi	n-Butyllithium
BY	Baker's yeast
CAD	Canadian dollar
C_n	Carbon chain of length n
Conc	Concentrated
d	Doublet (spectra)
D	Dextrorotatory, refers to a compound's stereochemistry relative to glyceraldehyde
DCM	Dichloromethane
DDT	Dichlorodiphenyltrichloroethane
DHP	3,4-dihydro-2H-pyran
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EAB	Emerald ash borer
e.e.	Enantiomeric excess
Et_2O	Diethylether
EtOAc	Ethyl acetate
FTIR	Fourier transformed infrared
GDP	Gross Domestic Product

GSOB	Golden spotted oak borer
h	Hour (time)
J	Coupling constant
L	Levorotatory, refers to a compound's stereochemistry relative to glyceraldehyde
LAH	Lithium aluminum hydride
m	Multiplet (spectra)
MeCN	Acetonitrile
MeOH	Methanol
NADH	Nicotinamide adenine dinucleotide
NMR	Nuclear magnetic resonance
nr	No reaction
PG	Protecting group
PPh_3	Triphenylphosphine
PPL	porcupine pancreas lipase
ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
quint	Quintet
R	Latin; *Rectus* = right, refers to stereochemistry about an atom
Rf	Retention factor
rt	Room temperature
S	Latin; *Sinister* = left, refers to stereochemistry about an atom
s	Singlet (spectra)

t	Triplet (spectra)
TBS	t-butyldimethylsilyl group
THF	Tetrahydrofuran
THP	Tetrahydropyranyl ether group
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosyl group
Z	German; *zusammen* = together, refers to stereochemistry about a double bond
σ	Greek; *sigma* , refers to a type of chemical bond
*	anti-bonding

Chapter One

Introduction

Canada's Forestry Industry

Canada's forests are one of the most important natural resources in the country. They provide habitat for a large portion of Canada's diverse flora, and fauna. The forestry industry also employed 210,000 people nationally as of 2017. In the same year the forestry industry in Canada accounted for approximately $24.6 billion of GDP, and nearly 7% of all exports were from the forestry sector.[1] A newly developing portion of Canada's forestry industry is the pulp extraction from birch trees, a species that is underused in the industry.[2] The protection and preservation of birch trees is a top priority for the growth and prosperity of the forestry industry.

Beautification projects

In recent years many municipalities, and towns have been improving their parks, and downtowns with extensive landscaping, providing more outdoor shaded areas. Many times, birch trees are chosen for these projects as they provide good shade, while also having unique bark. These trees are typically called ornamental trees. These projects provide not only outdoor spaces, but also increase property value. Keeping these trees can therefore be an important part of a town or city's management responsibilities. While pesticides are the typical management strategy, in parks, downtowns, or city centers, pesticides can prove dangerous to the public, and in many places have been banned.[3] Consequently, other mitigating, and detection strategies are needed to ensure the safety of ornamental birches.

Bronze birch borer

The bronze birch borer (BBB), Figure 1, is a metallic looking beetle endemic to North America.[4] It is 7-12 mm in length and subsists off tree foliage as an adult. The damage done to birch trees is typically reserved for exotic birches, but stress on native North America species can result in infestation.

Figure 1: Photograph of Bronze Birch Borer.[5]

Due to the co-evolution of native North American birch species, and BBB, a natural resistance has formed. This is not so for Eurasian birches that are typically used as ornamental trees; BBB poses a threat to ornamental Eurasian birch species in North America.[6]

Depending upon the host and the local climate, the life cycle of BBB can vary between one and two-year cycles, and the number of instars can also vary, as shown in Figure 2. BBBs with a more robust host, and cooler climates tends to favor a biennial cycle.[4,7]

To date no pheromones have been identified that are associated with BBB reproduction; males actively seek out possible mates on host trees.[8] Once a mate is found,

and eggs ready, they are oviposited on the host tree by the female, usually in the cracks, and crevasses of the tree. Two weeks later, the eggs hatch and give way to neonates that bore into the host tree where they feed off phloem and xylem of the tree. In more extreme cases, like during an infestation, this can severely restrict the transportation of important compounds and water within the tree often called girdling.[9] In more northern climates adults emerge from these trees in late June to early July, but in warmer climates like the southern United States adults emerge as early as May.[4,7]

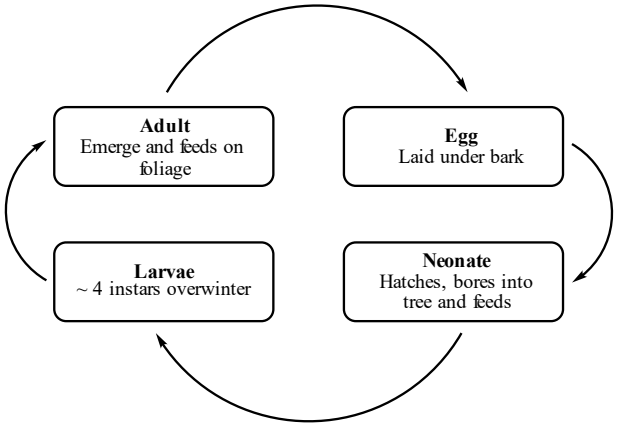


Figure 2: Life cycle of BBB.

Adult BBB live for two to five weeks, and subsist off foliage until reaching sexual maturity, where the cycle continues.[4,10,11] The amount of de-foliation is not considered to significantly damage the tree, whereas branch girdling as a result of boring is.[4,11]

Enemies to BBB include woodpeckers, and various parasitic species. Some of such parasites have been looked at as a possible natural control measure due to the specificity of the targeted pest.[12]

BBB Infestation

A long history of birch tree die-off has been associated with both, stress events, such as drought, and BBB outbreaks,[13] Figure 3. Recent large outbreaks include a 105 million die-off of birch trees in the Great Lakes region in 1988. This was determined to be due to cohort senescence, as well as other stressing events like drought, and elevated temperatures that lead to the massive infestation.[14] Events such as wildfires can clear a large area, providing ideal conditions for new tree growth. As these new trees grow, and then age into senescence they as a group become susceptible to infestations, and lead to large BBB epidemics.[13]

Figure 3: Birch tree girdling from BBB infestation.[15]

North America has seen large BBB outbreaks in the past. A much larger concern comes when looking at Canadian exports to Eurasian countries. If any forestry products are exported to Europe, or Asia with BBB present it could result in BBB's entrance into these regions. Not only would this be potentially devastating for those regions, but for the Canadian forest industry as well as this would undoubtedly result in a ban of Canadian forest products in these markets. This scenario would be very similar to the *Agrilus planipennis*, Emerald Ash Borer (EAB) introduction to North America in 2002.[16] Up to 99% of ash trees in infested areas are killed in Canada due to EAB. The possible devastating effect makes BBB control strategies very important for maintaining native Eurasian birch population, and Canada's forestry exports.

BBB Chemical control

The use of chemicals to control BBB has been used in the past. Dichlorodiphenyltrichloroethane (**1**, DDT) was the first insecticide used to control BBB populations, Figure 4; however, due to its negative ecological impact other chemicals have been developed as effective agents against BBB. One of such is Emamectin benzoate (**2**), Figure 4.[13,17] Systemic insecticides, which include **2**, use the tree to distribute the active compound and have shown to effectively control BBB. It also gives the ability to target BBB larvae that are oviposited under the bark but is disadvantaged by being environmentally toxic.

Along with insecticides, bark sprays such as chlorpyrifos (**3**), lindane (**4**), and bifenthrin (**5**) have been employed as a preventative measure to varying degrees of success, Figure 4.[13] However, the use of these bark sprays are limited due to the tendency toward toxicity and negative environmental impacts.[18,19]

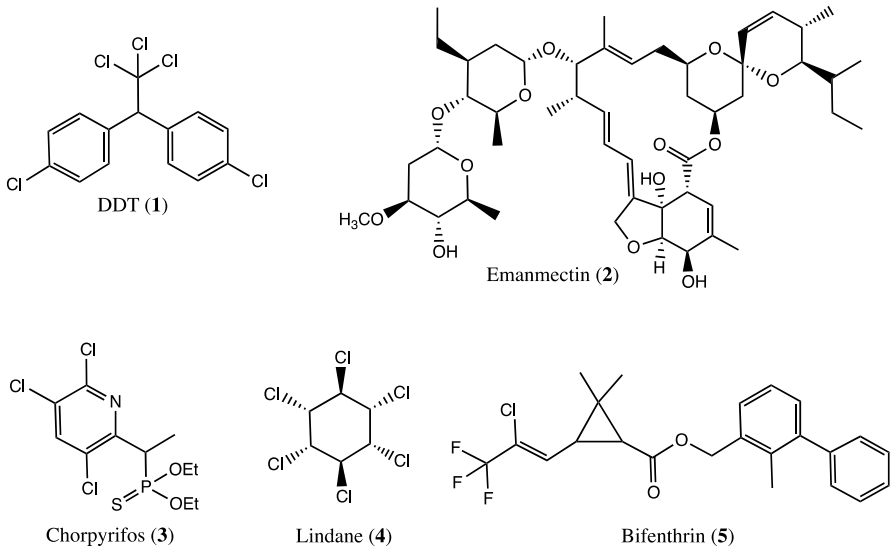


Figure 4: Molecular structures of insecticides used against BBB.

These protective sprays, and insecticides must be applied correctly to produce the required effect, including the time of year, and where on the tree it is applied.[13]

BBB Biological control

Other control methods have been implemented for pestilent insects. The use of sex pheromones has been used to confuse and disrupt normal reproductive activity, and in turn reduce the overall pest population.[20,21] For insect pests with known, or easy to produce sex pheromones, this is a plausible strategy that can help control a population. With the lack of a known sex pheromone, BBB does not have this control handle, therefore other measures must be used.

Natural enemies do exist for BBB and may be able to be utilized in biological control, as have been proposed for EAB, and Goldspotted Oak Borer (GSOB). [12] The use of parasites of BBB may be able to control population and spread and can prevent most of the harm that comes about when using toxic insecticides. However, they can become a

problem if the parasite used is not specific for that species, or perhaps other unintended consequences arise.

In conjunction with insecticide spraying, which is becoming increasingly unpopular due to public pressure, trapping can provide a way to determine problem areas and allow them to be specifically addressed before a more serious measure is required.[22,23] With BBB's lack of a known sex pheromone, a trapping/monitoring and targeted spraying method is the most plausible course of chemical control. While a sex pheromone is not known for BBB, certain compounds have been shown to be effective at attracting BBB and may be appropriate for the use in a pheromone trapping strategy.[8,24] Although pheromones of the target organism are typically used, there is evidence that suggests that these can be substituted by kairomones, which are compounds that are produced from a separate organism but still elicit a similar attractiveness.[25]

The use of a pheromone, or kairomone in a trap is an attractive idea, as it provides a way to reduce the amount of potentially toxic insecticides used to control a species. In a community setting such as a park, this can be very valuable. The use of various kairomones in a trap bait can lead to an increase in catch rate and increase the length of usefulness in the field.[26] Of the potential attractants, (5S,7S)-conophthorin, (**S)-6**, and (3Z)-hexenol, **7** have been proposed to do just this,[24] Figure 5.

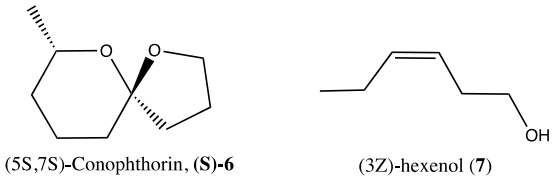


Figure 5: Molecular structure of BBB kairomone (5S,7S)-conophthorin and (3Z)-hexenol.

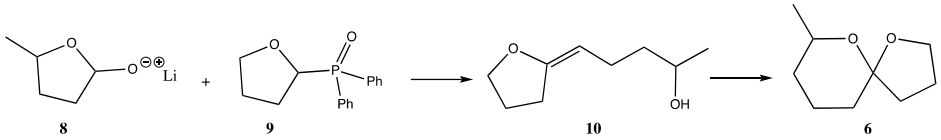
(S)-6 has a wide use in this field, displaying an antennal response from over 10 different bark beetle species, and other insect species.[27,28] It has also shown to produce behavioral responses in sawyer beetles.[29]

BBB Attractant Synthesis

Past synthesis of (5S,7S)-conophthorin

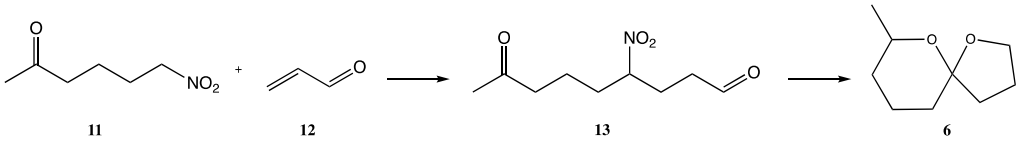
To date, six syntheses of **6** have been reported. Two of these routes produce racemic **6**.[30,31] Three others report the (**S**)-**6** enantiomer and one has been used to produce either racemic **6** or (**S**)-**6** alone depending upon the stereochemistry of the starting materials.[32–34]

One of the first syntheses of spiroketal compounds employed Wittig, or Horner-Wittig olefinations to construct oxygen containing ring **10**, with an exocyclic double bond extending to a secondary, or terminal hydroxyl group. Acid then catalyzed the final cyclization resulting in spiroketal **6**,[31,35] Scheme 1.



Scheme 1: Formation of conophthorin via Wittig olefination.

Conophthorin has been synthesized via Wittig, or Horner-Wittig olefinations, as well as by dicarbonyl nitro alkane **13**. Both syntheses used acid catalysis to produce the final spiroketal product **6**,[30,31] Scheme 2.



Scheme 2: Formation of conophthorin via dicarbonyl nitro alkane intermediates.

One novel route uses a hetero-Diels–Alder strategy between tetrahydrofuran ring **8** and methyl vinyl ketone **12**, Figure 6.[36] The result is a spiroketal-alkene **16** with the double bond positioned adjacent to the dihydropyranyl ether oxygen. Although not done by the researchers, a hydrogenation can be envisioned to give **6**.

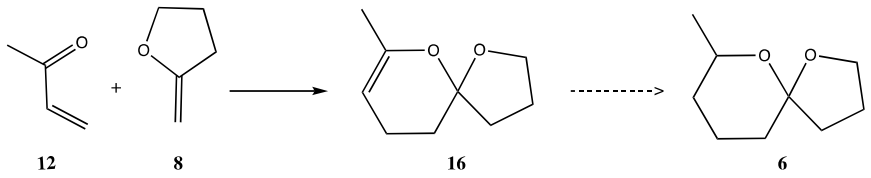


Figure 6: Hetero-Diels–Alder of 2-methylenetetrahydrofuran **8** and methyl vinyl ketone **12**.

Much of the earlier syntheses of spiroketal compounds implemented keto-diol **17** as the reactant in the spiroketalization step,[36] Figure 7. The spiroketalization step typically used acid as a catalyst and produced two acetals with one diastereoisomer predominating. As the acetalization reaction is under thermodynamic control, this suggests that the main product is also the thermodynamic product. Although the origin of the effect is still not clear, the most common argument includes the favorable oxygen orientation leading to the ability of the nonbonding oxygen orbital to donate into the σ^* orbital of the C-O bond, known as the anomeric effect,[36] Figure 8.

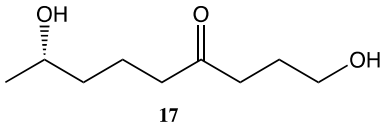


Figure 7: Keto-diol intermediate required for (5S,7S)-conophthorin synthesis.

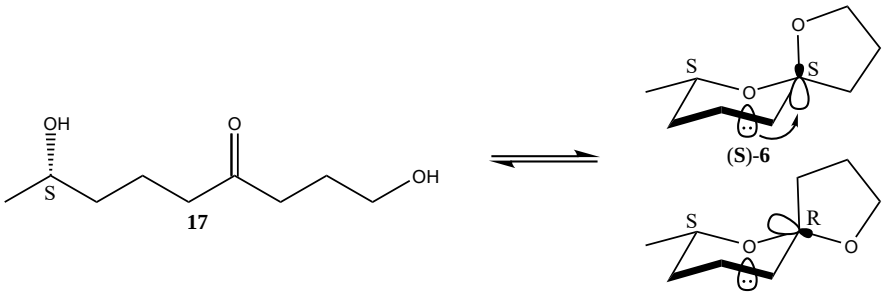
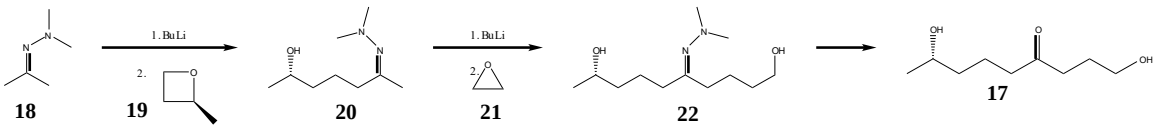


Figure 8: Proposed anomeric hyperconjugation.

The result of this thermodynamically favorable orientation of oxygens with respect to the anomeric carbon in the final spiroketal product (**S**)-**6**, is that the outcome of the reaction is one diasteroisomer is predominantly produced. Due to this anomeric effect, in order to synthesize optically pure compound, the only stereochemistry that needs to be controlled, either by "purchasing" or synthesizing it in the synthesis of (**S**)-**6** is the secondary alcohol.

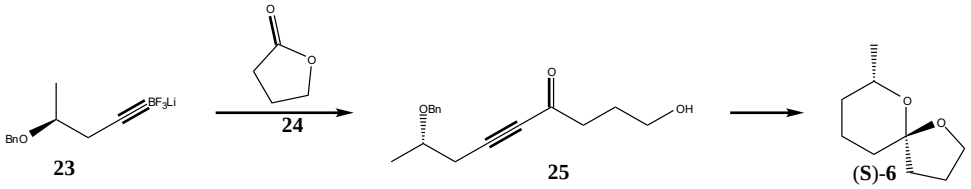
The preparation of alkyne intermediates has been performed successfully and also use an acid/base catalyzed spiroketalization.[37] Scheme 4. This route has the advantage of being able to take advantage of the chiral pool.

The use of chiral epoxides has been used as a source of this needed stereochemistry, but these tend to be expensive and require harsh conditions to alkylate the ring.[38] Previous work has used lithium nucleophiles conducted at temperatures below -70 °C,[24,39] Scheme 3.



Scheme 3: The use of chiral epoxides and oxetanes in the synthesis of conophthorin.

Lactone **24** has also been used in a similar manner to epoxides and oxetanes in other routes to (**S**)-**6**, Scheme 4. In order to make the route asymmetric, this necessitates the use of a chiral secondary alcohol for the remaining six-carbon unit required for the keto-diol intermediate **17**. This acylation, much like the opening of epoxides and oxetanes, relied on strong carbon nucleophiles, and were performed at -78 °C.



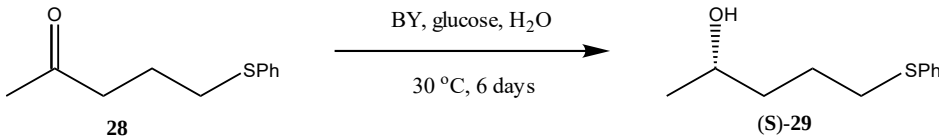
Scheme 4: Lactone opening in the synthesis of (5S,7S)-conophthorin.

Other researchers have used chiral resolution methods to access the stereochemistry. Specifically, lipase resolution of 1,3-butanediol **26**,[32] Scheme 5. This enantioenriched diol was then chain extended via Wittig olefination to afford the nine-carbon keto-diol **17** required for spiroketalization. This method of preparing the stereocenter resulted in 91% e.e. but required the use of mercury salts later in the synthesis to remove the 1,2-ethanedithiol ketone protecting group.

Scheme 5: Lipase resolution of 1,3-butanediol.

Asymmetric reductions have been used to prepare the chiral center which has been extended to other spiroketals of differing ring sizes. For example, 4-(phenylthio)-2-butanone, and its five-carbon chain analog **28** were used as starting materials in baker's

yeast reductions, resulting in asymmetric 4-(phenylthio)-2-butanol and 5-(phenylthio)-2-pentanol (**S**)-**29** respectively with high optical purity,[33] Scheme 6.

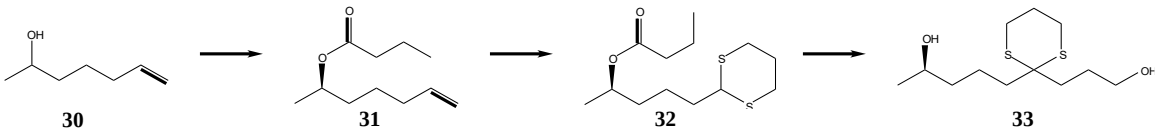


28 (**S**)-**29**

Scheme 6: Baker's yeast reduction to produce 5-(phenylthio)-2-pentanol.

With the asymmetric phenylthio-alcohol **29** generated, production of spiroketal (**S**)-**6** product required five steps, four of which were performed at temperatures lower than -40 °C, making these series of reactions unsuitable for large scale use.

Other researchers used porcine pancreatic lipase (PPL) to resolve 6-heptene-2-ol **30**,[34] Scheme 7. The resulting product **31** was treated with ozone, 1,2-ethanedithiol, followed by deprotonation of the afforded dithiane via lithium base to couple the remaining needed side of the keto-diol intermediate. This, however, does not fall in the same category as the other lithium-based approaches due to the temperature that the reaction was performed at. Typically, as seen in previous routes, reactions utilizing carbon nucleophiles or strong lithium bases were run at -78 °C to avoid possible side reactions resulting in decreased yields.[40] In the example noted above, the dithiane was deprotonated at -10 °C in this case with good yields, which provided a way to use this chemistry for larger scale reactions. Unfortunately, while the dithiane strategy is useful for larger scale reactions, the use of ozone in this route is not favorable on large scale reactions due to explosion hazards.



30 **31** **32** **33**

Scheme 7: Use of PPL resolution of 6-heptene-2-ol in the synthesis of (5R,7R)-conophthorin (**R**)-**6**.

The retrosynthetic possibilities of conophthorin are quite limited as the number of synthetic handles are few. Ultimately the retrosynthetic choices revolve around how to install the alcohol stereochemistry and where to excise the alkane. Typically, the scission is done on either side of the carbonyl, with a coupling reaction of some type required to install the remaining half of the keto-diol intermediate.[35]

Justification of study

Previous syntheses of (5S,7S)-conophthorin, **6**, while useful in an academic laboratory setting, would be challenging for larger scale synthesis;many of the previous routes disregarded the use of more "green" and safe reagents that are more suitable for commercialization.[32,33,39,41] The use of liquid ammonia in chiral epoxide ring opening/alkylation requires specific equipment, low temperatures, and uses a highly reactive metal. Use of 1,2-ethanedithiol, a ketone protecting group, results in the use of toxic mercury salts and is also not an acceptable route to the target, nor is the use of alkyl lithium nucleophiles due to the temperature that is typically required. Where the temperature is acceptable for larger scale lithium-based reactions the step-up to install the dithiane used in the lithium nucleophile reaction uses ozone to cleave an alkene to produce an aldehyde. Ozone is typically avoided in larger reactions due to explosion concerns.

A representative area may provide some insight into the required quantity of conophthorin needed for an infestation in a single season. Looking at a park such as Odell Park in Fredericton, New Brunswick, and assuming 25 m buffer space between traps, and a 0.50 mg/day release rate, approximately 50 g would be required to serve the area in a 116 day season.[24,42] When thinking about more than one park in more than one city the quantities start to exceed the scope of current routes.

Ultimately, no current synthesis of (5S,7S)-conophthorin adequately meets the requirements to be scaled up to an adequate size to service a forest that has been infested; after extensive search, no commercial sources were found for (5S,7S)-conophthorin.

Objectives

This study set out to develop a safe, efficient synthetic route to (5S,7S)-conophthorin utilizing cheap starting materials. Two strategies to (5S, 7S)-conophthorin were envisioned:

1) Beginning the route with the stereochemistry of the secondary alcohol already installed. The advantage in this case is the absence of an asymmetric reaction to induce chirality and would take advantage of the chiral pool.
2) The second approach would be to introduce the chiral alcohol asymmetrically. This route would need to employ very cheap starting materials and reagents to induce the stereochemistry.

The culmination of these approaches produced three routes, two of which used the chiral pool strategy, and the other producing the required stereochemistry within the route. The first two routes required thirteen and eleven steps, respectively, while the route where

the stereochemistry was introduced required eight. What follows is a description of the efforts to develop each of them.

Chapter Two

Results and Discussion

Synthetic strategy

An evaluation of the keto-diol conophthorin intermediate **17** is a good starting point to understand the restrictions produced by its simplicity. The final acidic cyclization is well known, and we can, for now, ignore it and focus on the disconnections of the straight chain keto-diol **17**.

The disconnection (s) must be done in a way that enables the easy integration, or production of stereochemistry at the secondary hydroxyl, Figure 9.

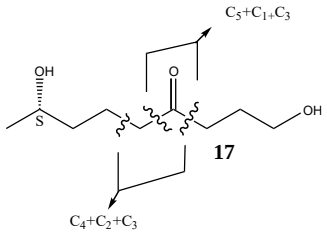


Figure 9: Useful retrosynthetic disconnections of conophthorin keto-diol intermediate.

The other complication comes about when looking for synthetic handles to afford a coupling reaction between the carbon chains. While there are coupling reactions that can allow one carbon adjacent to a ketone, these reactions, like a Wittig, or Horner-Wittig olefinations, typically produce much waste via phosphorus products and should be avoided if possible but are not unusable as coupling reactions.

The first synthetic strategy attempted utilized two disconnections to generate three units of four-, two-, and three-carbons in length, denoted $C_4 + C_2 + C_3$. The stereochemistry needed for conophthorin resides on the C_4 chain meaning that an (S)-2-butanol derivative would most likely be the next retrosynthetic step, Figure 10.

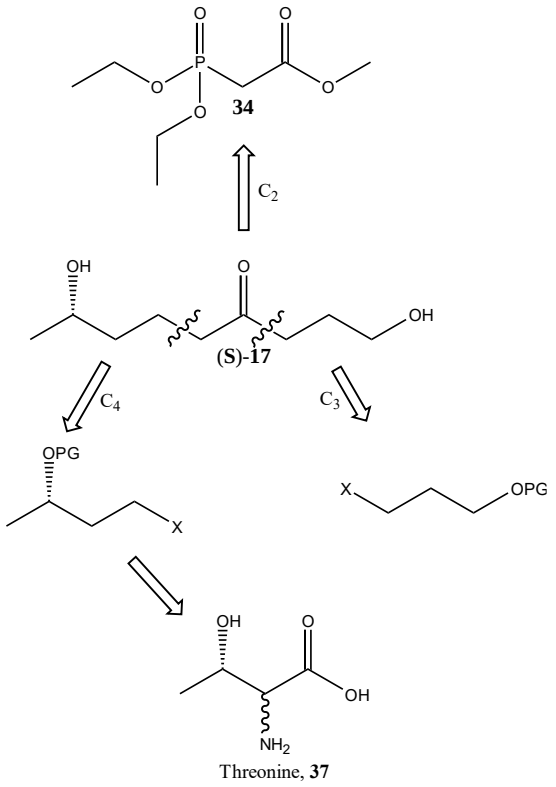


Figure 10: Retrosynthetic analysis of $C_4 + C_2 + C_3$ disconnection of conophthorin keto-diol.

It is possible to envision a route to the keto-diol derivative which starts with a four-carbon chain where the requisite stereochemistry can be accessed from the chiral pool, and eventually extended to a six-carbon chain. A coupling reaction with a three-carbon chain would give the nine-carbon unit needed. Common chiral pool compounds include sugars, terpenes, and amino acids. Threonine, a member of the latter category, was utilized in the first route.

The second and third routes utilized were developed after a failing of the first. The same coupling reaction was used to generate the final nine-carbon chain and a similar $C_5 + C_1 + C_3$ disconnection of the alkane backbone was done but used significantly different processes to introduce the requisite stereochemistry, Figure 11.

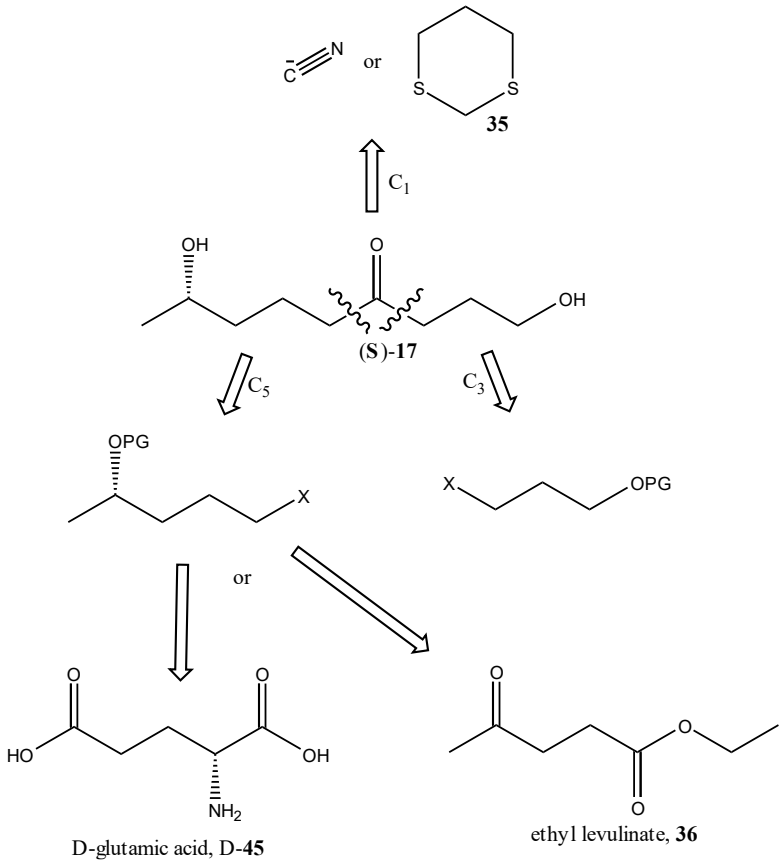
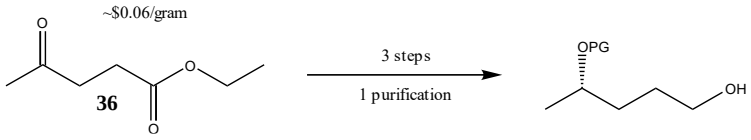


Figure 11: Retrosynthetic analysis of a $C_5 + C_1 + C_3$ disconnection of conophthorin keto-diol.

The second route was developed with the same idea in mind as the firsttilizing the amino acid chiral pool in a similar manner, but with a shortened synthesis. The use of a diazotization reaction on glutamic acid produces the correct functionalization. This route also gives control of what stereoisomer is in the final keto-diol intermediate by changing the starting material. Natural, and unnatural stereoisomers of glutamic acid are available from a multitude of vendors. The unnatural isomer of glutamic acid is required to give the correct final stereochemistry, and while, more expensive than the natural isomer, this route is still an improvement to existing asymmetric syntheses of conophthorin.

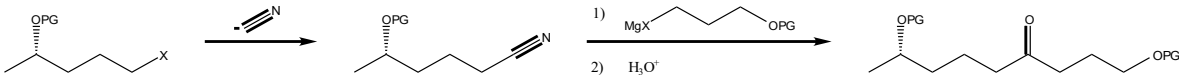
The third route utilizes an extremely cheap starting material, ethyl levulinate, as a source of C_5, Scheme 8. A process was developed to effectively install the stereochemistry via a baker's yeast reduction, protect the afforded asymmetric secondary hydroxyl group, and reduce the ester functionality to setup the coupling reaction in moderate yield without any purification between steps. This makes the route significantly more economical and is easily amenable to larger scale reactions.



Scheme 8: Yeast reduction to (S)-1,4-pentanediol derivative.

The coupling of the $C_5 + C_1 + C_3$ units is a key step in the synthesis of conophthorin using routes two and three. Two interesting couplings were investigated.

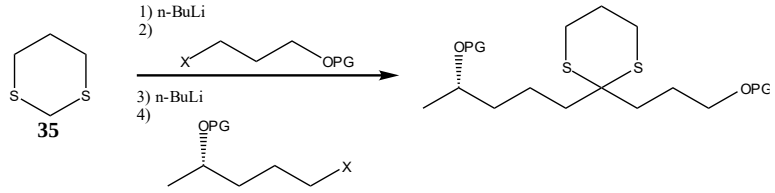
The first coupling utilized a protected bromopropanol as a Grignard reagent. The $C_5 + C_1$ side of the keto-diol intermediate was produced via a one-carbon homologation reaction between the (S)-1,4-pentanediol derivative, and a cyanide ion, Scheme 9. The product, being a nitrile, could then be reacted with the Grignard reagent, and upon acid hydrolysis of the resulting imine, a ketone would be produced. This is very similar to work that has been done on similar spiroketals.[41]



Scheme 9: Coupling of $C_5 + C_1$, followed by Grignard with a C_3 unit and hydrolysis.

The second coupling, like the first, has been used for these keto-diol type compounds before and gives very good yield,[34] Scheme 10. The coupling, using 1,3-dithiane **35**, is typically done in two steps, involving two separate deprotonations of the

sulfur containing ring, and two purification steps. After the second deprotonation and coupling **17** can be obtained after deprotection of the 1,3-dithiane ring and THP ethers.



Scheme 10: General 1,3-dithiane $C_5 + C_1 + C_3$ coupling.

Preparation of C_6 via threonine

The first strategy to synthesize (**S**)-**6** was envisioned from the $C_4 + C_2 + C_3$ disconnection of the keto-diol intermediate (**S**)-**17** and started with the amino acid threonine as the source of C_4, Figure 12. The starting material is a point of attention as this is where the required stereochemistry of the final product is derived.

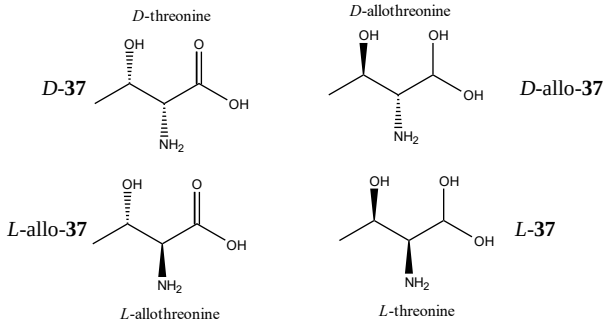
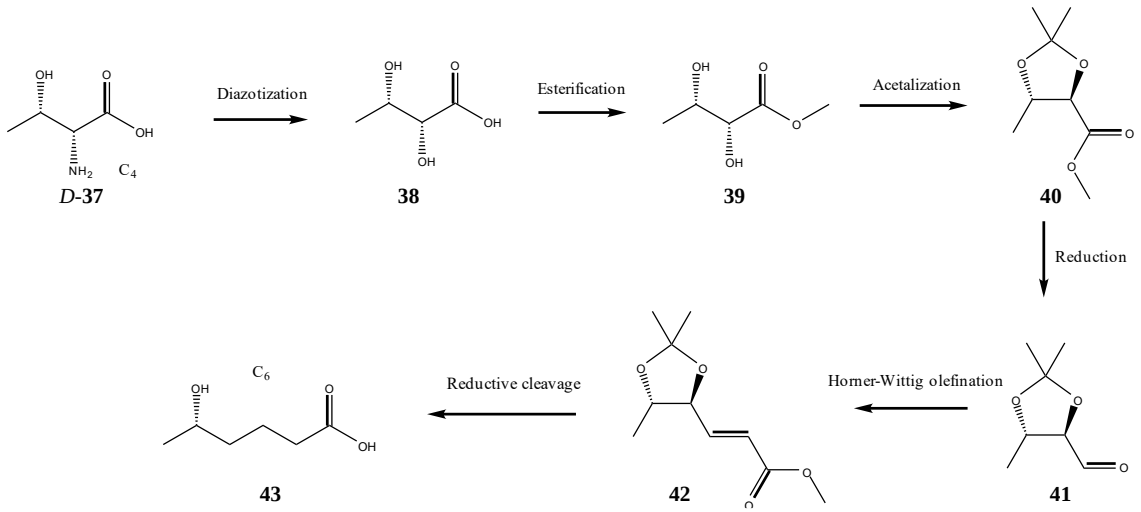


Figure 12: The four stereoisomers of threonine, **37**.

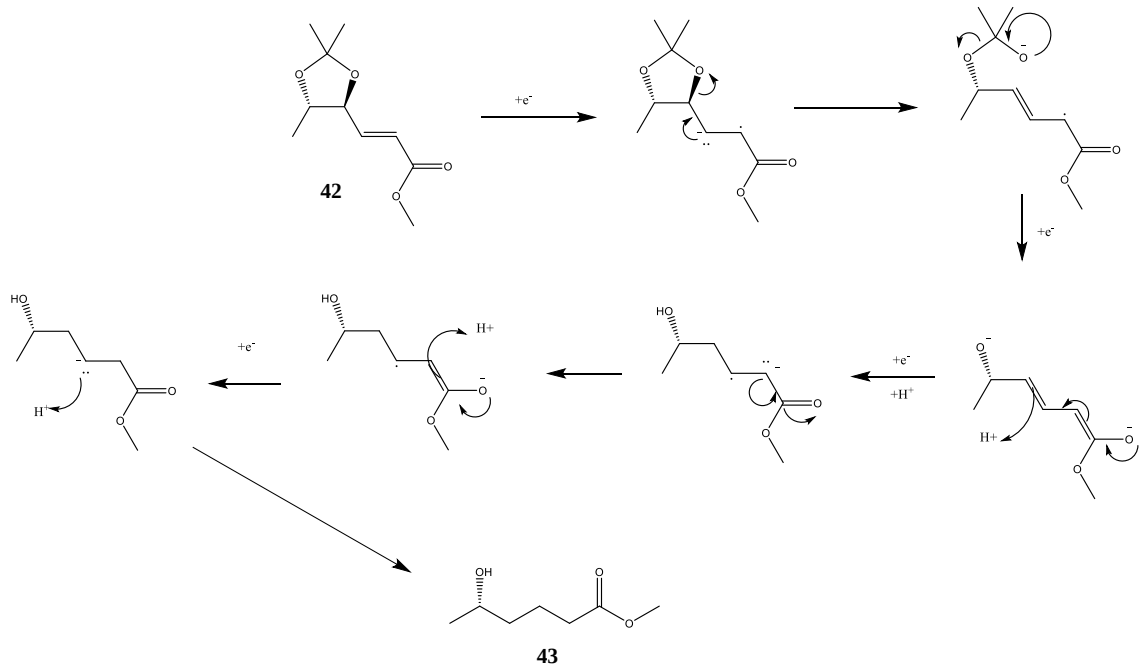
Threonine has four different stereoisomers due to the two stereocenters it possesses. Typically, these isomers are denoted via the *D*/*L* nomenclature. This is the designation of a stereoisomer in relation to the dextrorotatory or levorotatory enantiomer of glyceraldehyde. The “allo” included in the other two isomers translates to “other” in Greek. Ultimately *D*-threonine, *D*-**37**, or *L*-allothreonine, *L*-allo-**37** provides the S stereocenter at the secondary hydroxyl required for conophthorin. *D*-**37**, the enantiomer

of natural threonine *L*-**37**, is the most commonly available stereoisomer of threonine with a secondary alcohol in the "S" configuration and was used for this synthetic endeavour.

A sequence was envisioned in which after a diazotization reaction and following solvolysis, esterification, diol protection and reduction of the ester, aldehyde **41** was produced, Scheme 11. Following Horner-Wittig olefination to provide α, β–unsaturated acetonide ester **42**, reductive elimination using the relatively environmentally benign metal magnesium would then generate 5-hydroxy-hexanoate ester **43**.[43] The stereochemistry of the hydroxyl group produced in the diazotization reaction is of little consequense in this scheme, as it will be sacrificed to affect the reductive cleavage to produce **43**, Scheme 12. A reduction, Grignard or other suitable addition, and oxidation will afford keto-diol **17**.

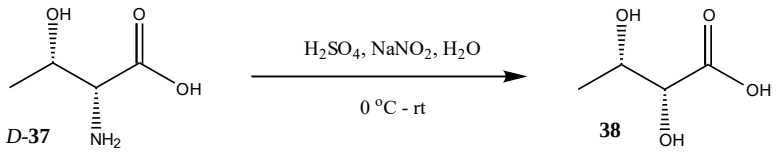


Scheme 11: Route to synthesize C_6 from threonine *D*-**37**.



Scheme 12: Proposed mechanism of the reductive cleavage of **42** using magnesium and MeOH.

Ideally, the initial diazotization of *D*-**37** to the dihydroxy acid **38** would be as smooth as reported, this unfortunately was not the case, Scheme 13.[44] After slow addition of the nitrite solution into a sulfuric acid-threonine solution at 0 °C over 1 h, a blue, bubble producing solution was noted. With subsequent overnight stirring at room temperature a sample was taken from the crude reaction mix and ^{1}H NMR (DMSO) spectra were taken. This was compared to the starting threonine *D*-**37**. No peaks of interest were noted aside from the starting material.



Scheme 13: Diazotization of threonine *D*-**37**.

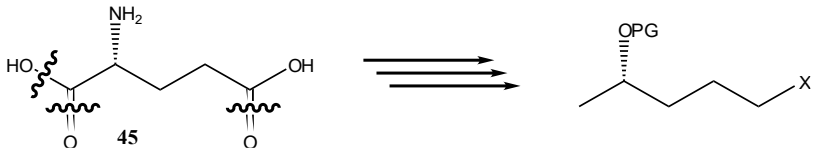
This crude material was resubjected to two subsequent diazotization reactions with the thought that multiple runs of this reaction may produce some product that could be confirmed via ^{1}H NMR. No reported peaks for the product, **38** were found in the crude reaction sample which appeared to be a mixture of starting material and a large portion of side reactions. These side reactions were noted via multiple doublets appearing in the 1.10 ppm to 0.90 ppm range indicating that there were multiple terminal methyl protons in different chemical environments. No doublet was noted at 0.91 ppm from **38**'s terminal methyl group.[45]

As not to completely abandon the idea of amino acid chiral pool as a starting point another scheme was devised starting with glutamic acid, having a five-carbon chain, Scheme 14.

Preparation of C_6 via glutamic acid

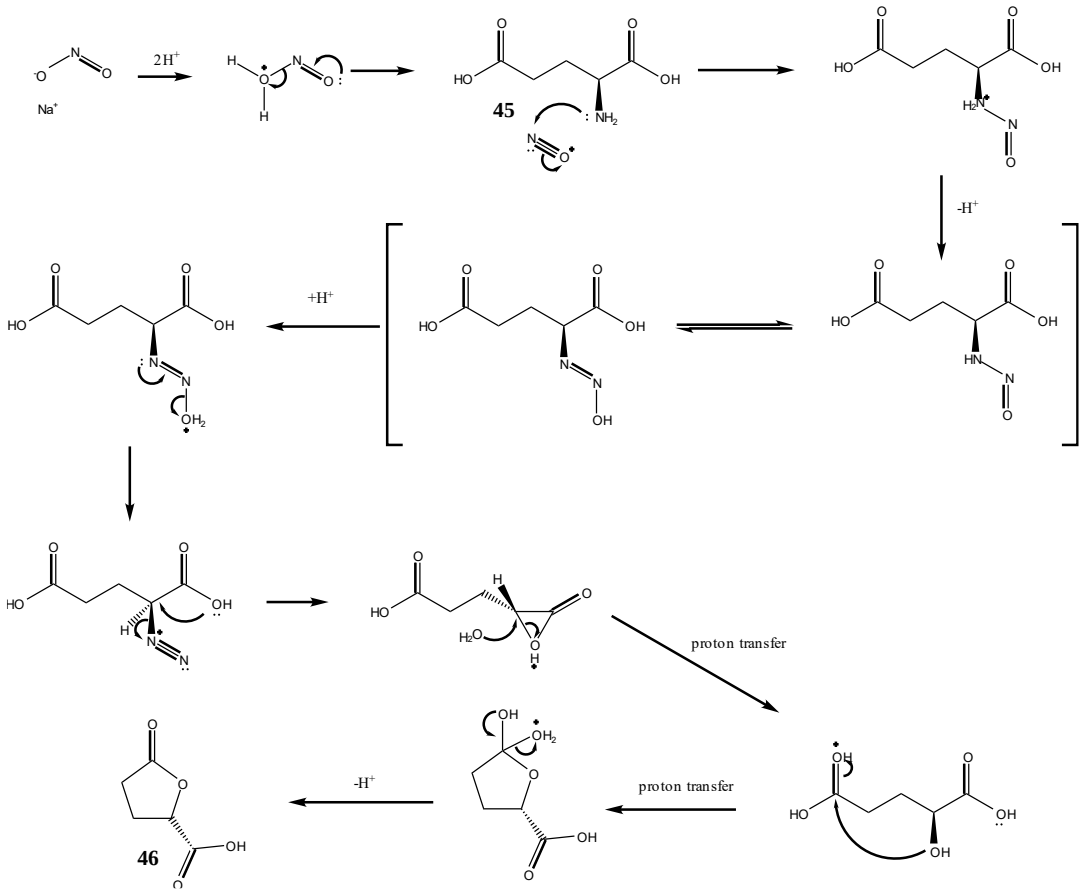
A second route, designed after the failure of the first, departs from the previous attempt by the difference in the starting materials chain length. The Horner-Wittig coupling reaction using a four-carbon chain will not provide the correct position of the resulting carbonyl for a five-carbon chain if the same C_2 coupling is used. This led to the investigation of more cost effective, and relatively benign coupling reactions.

A Grignard reaction was envisioned as a suitable process to couple the C_5 chain, following extension to the C_6 chain via a homologation reaction with sodium cyanide. The C_3 chain required for the Grignard reaction could be provided by the commonly available 3-bromopropanol, **44**.



Scheme 14: Forward look from glutamic acid to C_5 1,4-pentanol derivative.

The 1,4-pentandiol derivative required to setup the one-carbon homologation reaction could be arrived at via a diazotization reaction of glutamic acid giving lactone acid, **46**, Scheme 15. Selective reduction of the acid would produce lactone alcohol, **47**. Tosylation would provide **48**, and exhaustive reduction would generate diol **49**. A selective acetylation of primary alcohols can be done using mild conditions.[46] This leaves the mono acetylated product **50** with a free secondary hydroxyl group which can be protected using TBSCl giving **51**. A deacetylation can be done giving mono protected diol, **52**. The now open primary hydroxyl group can be converted into a leaving group; tosylation gives protected tosylate, **53**, or an Appel reaction would give iodide, **54**. This sets up a homologation reaction with a cyanide salt to produce the C_6 chain nitrile, **55**.



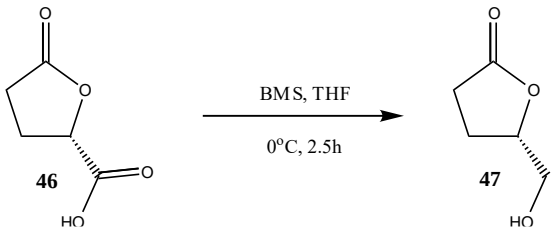
Scheme 15: Mechanism and stereochemical outcome of a diazotization reaction with glutamic acid **45**.

The diazotization reaction of glutamic acid **45** follows in an analogous way as the reaction with threonine *D*-**37**. However, unlike the previous route, our interest does now turn to the stereochemical outcome of the diazotization reaction as the afforded stereogenic carbon is also present in (**S**)-**6**. It is proposed that, via an interesting interaction of the carboxylic acid oxygen and generated diazonium group, this reaction retains the stereochemical configuration of its starting amino acid via an oxiranium ion intermediate.[47]This allows a way to install the required secondary hydroxyl group without inverting the stereochemistry at the attached carbon.

For the case of our target molecule the natural stereoisomer of glutamic acid was chosen as a starting material which would produce (**R**)-**6** as it was already available in our inventory. Once the route was deliniated the sequence would be repeated using the unnatural amino acid.

Unlike the reaction with threonine *D*-**37**, the reference followed for this diazonium reaction used HCl as an acid source.[48] Other than the acid used the only difference in procedure was the concentration of the reaction. In any event, the reaction proceeded as described, but with one slight modification. The crystallization of the afforded lactone acid, **46** was done differently than reported as a -30 °C freezer was not available at the time so, in its place, multiple batches were harvested after reducing the solvent volume and leaving in a lab fridge at approximately 0 °C. Further harvests were combined and recrystallized from a minimum of hot chloroform. These crystallizations produced beautiful white needle-like crystals that were dried via desiccation and were found to match literature ^{1}H and ^{13}C NMR spectra but had an elevated melting point.[48] This difference in melting point could be explained by the addition of desiccation; if there was water present in the literature sample a depression in melting point would be expected. A broadening of melting point would also be expected but was not seen. This method also produced a much better yield than the reference.

With lactone acid **46** characterized and pure, the selective acid reduction was attempted using borane-dimethylsulfide (BMS) complex, Scheme 16.



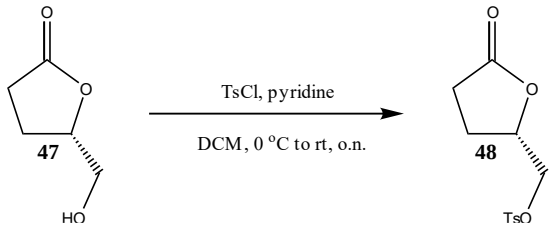
Scheme 16: Selective reduction of lactone acid **46**.

The first attempt was run at room temperature following a standard literature protocol.[48] This resulted in a compound being visualized on TLC (1:1, hex:EtOAc, stain: $KMnO_4$) on the baseline along with the product lactone alcohol **47**. This indicated that the starting material had been converted to a much more polar compound. It was proposed that **46** had been over reduced into a di, or triol and a change in conditions may be required to obtain a useful yield.

Attempt two tries to prevent the proposed over reduction by cooling the reaction to 0 °C in an ice bath and slowing the addition time of BMS from 20 min to 1 h. This was sufficient to produce alcohol, **47** in a 76% yield after purification and showed no highly polar products. The original reference utilized reaction temperatures of -78 °C and resulted in a 93% yield, which while better, was not feasible if a significant scale was used; a 76% yield was adequate. The mechanism of this reaction is not fully understood but has been studied; the selectivity is thought to be achieved via the competing production of an alkane, in the case of ester and lactone functionalities, and the production of diatomic hydrogen in the case of carboxylic acids. The production of hydrogen being faster comparatively leads to the selectivity.[49]

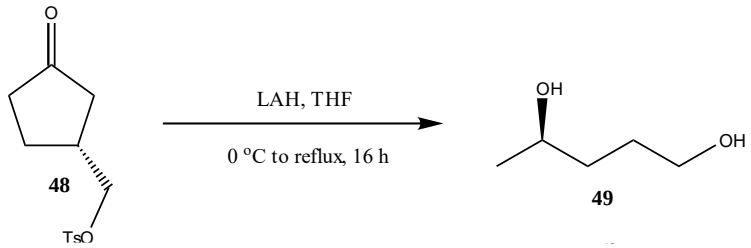
With successful formation of alcohol **47**, the next step in the route was tosylation, which proceeded smoothly and produced **48** as a white solid, Scheme 17. Extra acid

washings were added to the procedure as some TsCl was present in the ^{1}H NMR of crude **48**.



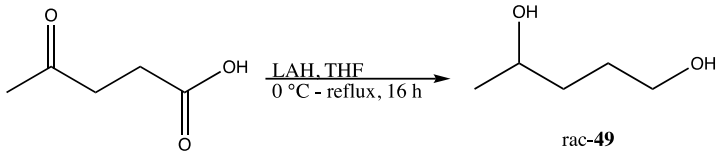
Scheme 17: Tosylation of lactone alcohol **47**.

The exhaustive reduction of the afforded lactone tosylate **48** using LAH in refluxing THF gave diol **49** as a clear colourless oil in good yield, Scheme 18. An "anhydrous workup" was done to avoid any problems with **49** possibly being stuck in the aqueous phase of an extraction due to the high polarity of the diol.



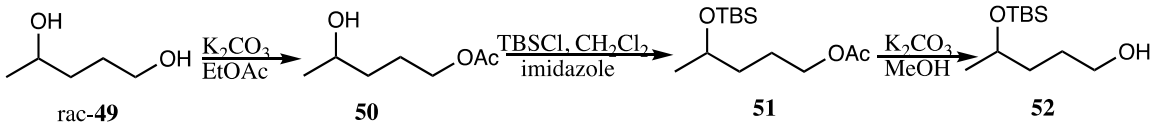
Scheme 18: Exhaustive reduction of lactone tosylate **48**.

Given that there was much exploration to be done, it was decided to generate the racemic diol such that it could be used to probe further reactions, thus conserving the more "expensive" (**R)-49** until such time that the route was clearly delineated. To this end, an exhaustive reduction of levulinic acid using LAH gave the desired racemic diol rac-**49** in good yield, Scheme 19.



Scheme 19: Exhaustive reduction of levulinic acid to give rac-**49**.

Diol **49** was selectively acetylated using K_2CO_3 as base, and ethyl acetate as solvent, and acetate source.[46] No change to the acetylation procedure was needed to give a good yield but a dilution with Et_2O was included to ensure adequate filtering of the salts produced, Scheme 20. This acylation effectively blocks the primary alcohol to enable the protection of the unaffected secondary alcohol. A portion of the crude mixture of **50** was purified and ^{1}H NMR was taken to ensure mono acylation. Protection using TBSCl gave TBS-acetate **51** which was immediately deacylated to give **52**. All reactions proceeded in good yields as **52** was produced in 70% overall yield from rac-**49**.

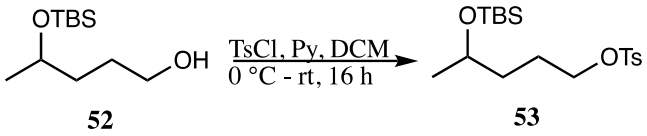


Scheme 20: Acetylation-protection-deacetylation of diol **49**.

Ideally selective tosylation of diol **49** would have been preferable as this would have eliminated the need for the protecting group "dance" noted above. However, all attempts only resulted in poor yields.

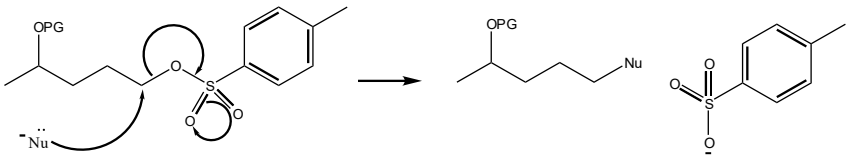
With selectively protected alcohol **52** constructed, tosylation of **52** to genereate **53** was undertaken, Scheme 21. Once tlc indicated complete consumption of **52**, the reaction mixture was quenched with aq. NH_4Cl, washed with aq. $NaHCO_3$, extracted and concentrated to provide the crude product. Surprisingly this was found not to be bench

stable and decomposed into a green-black tarry solution, upon sitting on the benchtop over a matter of hours.



Scheme 21: Attempted tosylation of protected diol **52**.

Since there appeared to be no decomposition occurring in the basic conditions of the reaction flask the culprit was believed to be the acid used to quench the reaction, or perhaps residual tosyl chloride. Attempts to address this decomposition included: use of $CuSO_4$ in place of NH_4Cl to neutralize the pyridine via complexation, minimizing the amount of concentration of solvent after work-up, and only using an equimolar amount of tosyl chloride relative to alcohol. Unfortunately, all these attempts failed.

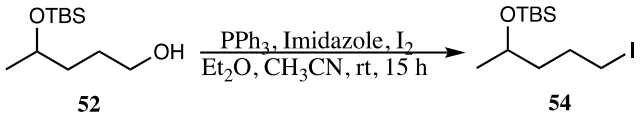


Scheme 22: Proposed decomposition of pentandiol tosylate derivatives.

It should be noted that a purified product was obtained in one attempt, but during overnight storage in the fridge the same decomposition was noted. A final attempt employed the $CuSO_4$ wash, along with an aq. $NaHCO_3$ wash of fractions after purification via flash chromatography. The idea was that a small amount of acetic acid or HCl may be produced during chromatography via the reaction of silica gel with ethyl acetate or excess tosyl chloride. This slightly extended the lifetime of **53** but ultimately led to the same green-black tar. A ^1H NMR of the resulting tar showed peaks for TsOH which differed from equivalent peaks in **53** and those of TsCl. This suggested that some nucleophilic

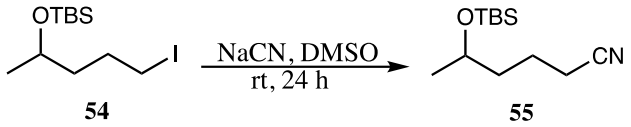
attack was taking place to produce the TsOH and the green-black tar, Scheme 22. In any event, another reaction was needed to avoid the unstable **53**. Some alternatives to possibly avoid these problems, while not attempted, include adding NaCN after the consumption of **52** before the workup of the reaction, or a direct conversion of alcohol **52** to nitrile **55** using N-tosyl imidazole in refluxing DMF.[50] This is work that should be explored in the future.

As an alternative to trying to access the tosylate, an Appel reaction was used to install the required leaving group to enable the following one-carbon homologation. This reaction, instead of installing a tosylate group, replaced the alcohol with an iodide in a single step, Scheme 23. This reaction was first attempted using THF as a solvent, following a reference which employed the same reaction on the same substrate.[51] These conditions were found to be inadequate to affect the change to the product, iodide **54**. The typical solvent of DCM gave low yield as well. A commonly used solvent system in our group was employed to try to solve the lack of reactivity; a mixture of Et_2O and MeCN in a 3:1 ratio was suitable to get a good yield of **54**. The downside was the large amount of material needed to enable the reaction; triphenyl phosphine and imidazole were both required in at least molar equivalents and typically used in much higher equivalents. If eventually this route is to be used for the large scale synthesis of conophthorin then an alternative to this would be required. Although not investigated, a method recently developed by Porter would solve this challenge.[52] Regardless, this did, however, give a stable substrate for work on the one-carbon homologation.



Scheme 23: Appel reaction of **52**.

From iodide **54,** the one-carbon homologation with sodium cyanide was attempted in DMSO and uneventfully gave the nitrile **55**, Scheme 24, as a clear colourless oil in good yield providing the C_6 chain required.

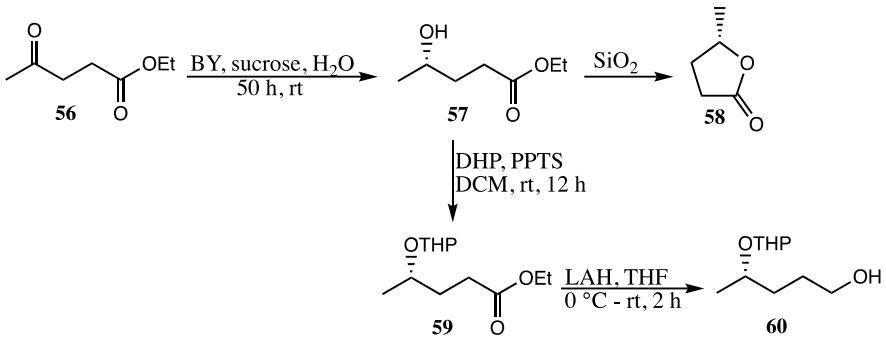


Scheme 24: Homologation of iodide **54**.

Preparation of C_6 via ethyl levulinate

With C_6, in the form of nitrile **55** prepared starting from glutamic acid **45** another route was envisioned which intersected the afore mentioned route. This route, unlike the previous one installs the correct stereochemistry for the final (**S**)-**6** product and does so in a cost-effective manner.

Using the knowledge from the preparation of rac-**49**, ethyl levulinate **56** was used as a starting point, as it could easily afford **49** in an enantioenriched manner. A known selective asymmetric reduction could be employed to reduce the ketone to the required alcohol using baker's yeast, Scheme 25.[53] A full reduction using LAH was also done by the researcher to give **49** asymmetrically.



Scheme 25: Baker's yeast reduction of keto-diol **56** and conversion to alcohol **60**.

The first attempt at isolating alcohol-ester **57** was unsuccessful due to the complications noted by the method's original authors; **57** was cyclizing on the SiO_2 column during purification to give lactone **58**. While not done by the researchers, a protection step can be envisioned to prevent the lactonization as well as avoid the acylation-protection-deacylation reactions that the previous route starting from glutamic acid **45** described. This would give THP-ester **59**. Unfortunately, **59** was not isolable via chromatography either due to the other compounds produced by the yeast coeluting. To circumvent this problem, upon protection of alcohol **57**, it was immediately subjected to reduction using LAH to give THP-alcohol **60** after purification.

Optimization of this process was undertaken and the results are presented in Table 1. Control of fermentation time, temperature, and THP protection conditions allowed the yield to increase to 45% over the three aforementioned steps with no purification between steps. No further optimization was attempted after obtaining a 45% yield due to the researchers of the original paper claiming the maximum yield obtained from the yeast reduction being 47-60%. Namely, if it is assumed a maximum of 60% yield from the yeast reduction was obtained, then the THP protection and LAH reduction steps proceeded in an 80% overall yield, this was deemed more than acceptable.

Ethyl Levulinate (g)	Yeast Reduction Temperature (°C)	Yeast Reduction Time (h)	DHP (eq)	Yield of **60** (%)
3.26	-	50	1.5	22
3.26	30-34	50	1.5	38
3.26	30-34	72	1.5	32
3.88	**30-34**	**50**	**2**	**45**

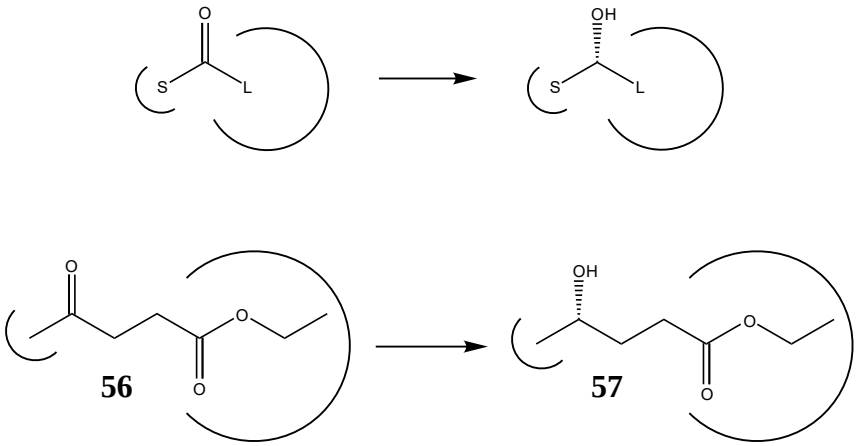
Table 1: Optimization of production of THP-alcohol **60**.

Initially the yield of **60** from **56** was too low to rationalize the use of this route at just 22%. While not done by the researchers a constant temperature was employed to ensure the full activity of the yeast in solution for the entire reaction. This did show promise as the yield saw an increase from 22% to 38%. An increased fermentation time was attempted at 72 h but showed no increase in yield of **60**. Visualization of remaining **59** on tlc, while not easily done due to cyclization and resulting streaking, led me to believe that the THP protection step was not going to completion. It was possible some of the yeast by-products may have been also reacting with the DHP and thus consuming it. An increase to two equivalents of DHP adequately protected the alcohol and gave an acceptable yield of 45%.

The use of organisms to effect organic transformations is not a new concept and has been used since the early days of humans, producing bread, beer, and other alcoholic beverages. The earliest use of baker's yeast to perform a reduction, other than for

foodstuffs, was a reduction of the aldehyde functionality of furfural to give the alcohol, furfuryl alcohol.[54]

Reductions of ketones, such as **56** follows a rule based on the size of the substituents of the given keto ester, Scheme 26.[55] This rule stems from the geometry of the active site of the oxo-reductase enzyme which is present and participates in the reduction. By holding the substrate in a specific manner, NADH, the reducing agent, can only deliver the reducing hydride to one side of the substrate. To predict the stereochemical outcome of **57** we must rank the size of the substituents flanking the soon to be reduced carbonyl. In the case of **56**, the two substituents of interest were a methyl group, and the carbon chain that extends and terminates at the ester functionality. This orientation of substituents provides a reducing hydride, from NADH, in a fashion that produces the stereocenter with the "S" stereochemical configuration.

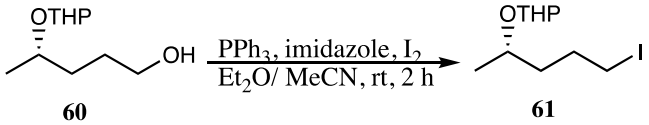


Scheme 26: Baker's yeast reduction rules applied to keto-ester **56**.

Isopropanol has been proposed and used as an additive to these keto-ester reductions using baker's yeast.[56] One trial was run using this approach: 5 mL portions were added every 24 h using the optimized conditions. The idea was to try and extend the

life of the co-enzyme NADH used by the baker's yeast's oxo-reductase to affect the asymmetric reduction. It is proposed that the consumed NADH, now NAD^+, may be able to be regenerated via the pentose-phosphate pathway if sufficient carbohydrates are freely available. This pathway is used by the yeast to produce NADH and five-carbon sugars that, further down the metabolic pathway, provides the backbone of nucleotides that are ultimately used to produce the organism's genetic material. The use of isopropanol for this purpose proved to not increase yield or provide any advantage over not using isopropanol; no further improvements were pursued. While other substrates such as 5-oxo-hexanoates were envisioned to be a more direct route to C_6 via baker's yeast reduction, no known method gives adequate yield or e.e.[57–60]

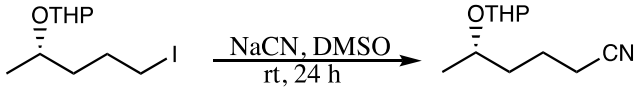
With an optimized method to generate THP-alcohol **60**, an Appel reaction, analogous to that performed on **52**, was done. This proceeded smoothly and gave an 82% yield of the THP-iodide **61**, Scheme 27.



60 **61**

Scheme 27: Appel reaction on THP-alcohol **60**.

The one-carbon homologation of **61** to nitrile **62** proceeded analogously to the conversion of **54** to **55**, giving a clear, slightly yellow oil in good yield, Scheme 28.



61 **62**

Scheme 28: Homologation reaction on THP-iodide **61**.

Interestingly, but not consequently, these compounds, **61** and **62,** were a mixture of diastereoisomers and found to be in a 60:40 mixture, Figure 13. The exact reasons as to why a 50:50 mixture is not observed could be due to the anomeric effect about the THP ether.

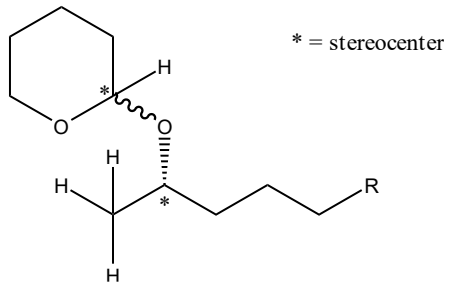
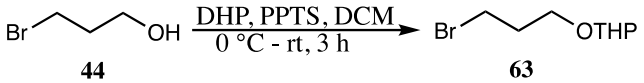


Figure 13: Position of stereocenters and hydrogens whose chemical shift is affected potentially by the anomeric effect in **61** and **62**.

Coupling of C_6 and C_3

With C_6, in the form of nitrile **55** and **61**, the other side of the keto-diol intermediate, C_3, needed to be constructed, Scheme 29. Synthesis of C_3 involved a simple protection of commercially available 3-bromo-1-propanol **44**, as its THP-ether. As seen in previous routes, this proceeded uneventfully to give **63** as a clear colorless oil in excellent yield.

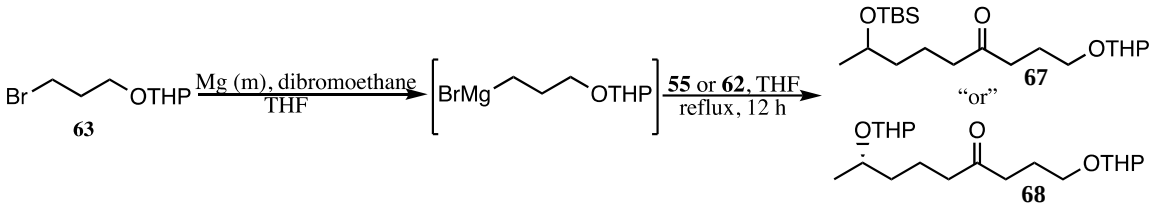


44 **63**

Scheme 29: THP protection to THP-bromide **63**.

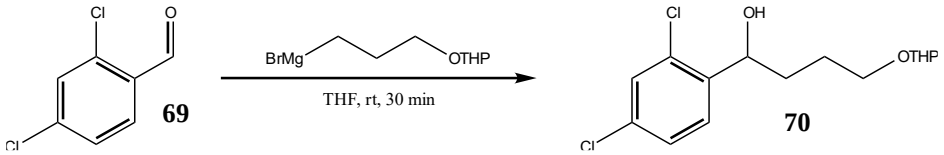
Initial attempts at the Grignard coupling involved activation of an excess (3 eq.) of magnesium strips with 1,2-dibromoethane (0.1 eq) in THF, Scheme 30. This formed a light brown solution and produced heat that, once cooled, was ready for addition of **63**.

The addition of the bromoalkanes produced a grey or near black solution and was stirred until it was noted that no more magnesium was consumed. To this solution was added nitrile **55** or **62** in THF and the mixture was heated at reflux overnight. Upon quenching and hydrolysis, no protected keto-diol was obtained from these trials regardless of protecting groups used; the starting nitrile material was recovered.



Scheme 30: Attempted coupling of bromide **63** with nitrile **55** or **62**.

It was proposed that the Grignard reagent may be the problem. A simple test was performed which included the same preparation of the Grignard reagent but 2,4-dichlorobenzaldehyde **69** was used as the electrophile, Scheme 31. This reaction was monitored via tlc and showed no starting material present after just 30 minutes of reaction time at rt. This eliminated the Grignard reagent as the problem in the reaction.



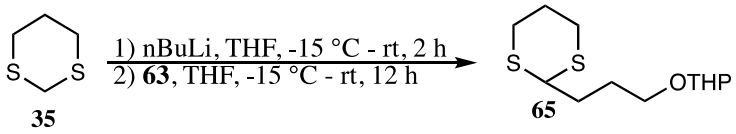
Scheme 31: Test reaction of Grignard reagent produced from THP-bromide **63**.

Reactivity problems have been noted in the literature for reactions of Grignard reagents with nitriles.[61] The addition of Cu(I) salts have been used in the past to increase the reactivity, effectively producing a higher order cuprate *in situ*. To explore this possibility, 0.1 equivilent of Cu(I)I was added after the addition of **55** or **62** and produced

a black suspension that unfortunately did not produce any coupling with the nitrile. No further investigations using the nitrile coupling strategy were pursued.

With failure of the Grignard coupling strategy, an alternative pathway was sought. Given that the two coupling substrates generated both contained halides, it was felt that utilizing dithiane chemistry may prove useful. There was precedent for this strategy in a previous synthesis of conophthorin.[34] However, unlike that synthesis, we wanted to explore whether the coupling could be performed at more convenient temperatures (e.g. above -20 °C) and if the deprotection could be accomplished without the use of toxic mercury salts.

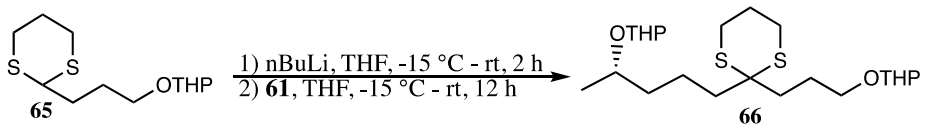
To this end, coupling of **35** and **63** was attempted using n-BuLi as base in THF at -15 °C and to our satisfaction the desired product, **65**, was produced as a clear colourless oil in good yield, Scheme 32.[34]



35 **65**

Scheme 32: First alkylation of the dithiane ring.

With a successful first alkylation accomplished at a temperature amenable to large scale, there was excitement to see if the second alkylation would proceed as efficiently. Consequently, the second coupling was undertaken in a similar manner but using **61** as the electrophile. The coupled THP-dithiane, **66**, was obtained as a clear colourless viscous oil in an excellent 88% yield, Scheme 33.

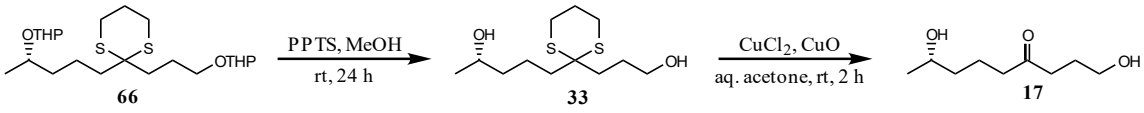


Scheme 33: Second alkylation of the 1,3-dithiane ring.

With the full carbon backbone in place, a decision to the order of deprotection was now at hand. In principle, it should make no difference as to whether the alcohols were liberated first or the ketone. However, it was felt that since the THP protecting groups are usually removed under acidic conditions, then perhaps if the ketone were freed up first, this would allow for the THP protecting groups to be removed and cyclization to the acetal could be accomplished in a single step.

With this in mind, a test was done looking at deprotecting the dithiane ring first using $CuCl_2$ and CuO in aq. acetone.[62] Unfortunately, this resulted in a number of compounds, as evidenced by tlc and ^{1}H-NMR. Given this result, it was decided to abandon this approach.

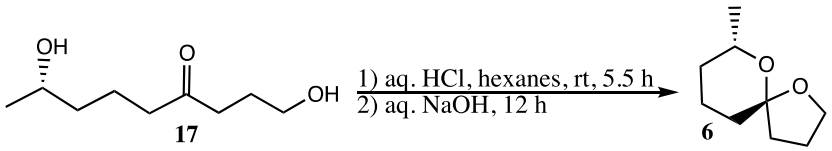
Pivoting, the THP protecting groups were first removed in a straightforward manner by subjection of **66** to mild acid hydrolysis in alcoholic solvent to give diol **33** in an excellent 83% yield, Scheme 34. Treatment of diol **33** to Cu catalyzed deprotection efficiently generated keto-diol **17** which was taken onto the next step without purification.[62]



Scheme 34: Deprotection of THP-dithiane **66** to keto-diol **17**.

With enatioenriched keto-diol **17** in hand, what remained was acid catalyzed cyclization.[24] Following literature precedent, keto-diol **17** was subjected to a biphasic

mixture of aqueous HCl and hexane for 5.5 h to yield (5S,7S)-conophthorin, **(S)-6** in 42% yield after SiO_2 chromatography over two steps, Scheme 35. With this success, synthesis of **(S)-6** occurred in 8 steps from ethyl levulinate **56** with an overall yield of 9%.



Scheme 35: Cyclization of keto-diol **17**.

While a yield of 9% should leave much to be desired, a comparison to other syntheses of **6** is a better way to judge this synthesis. A route used recently, for a BBB trapping project, started at a chiral epoxide which was chain extended via a lithium nucleophile.[24,34] This route originally gave **6** in a 14% yield starting from (S)-Propylene oxide and utilized harsh conditions that are not in line with a large-scale synthesis.

To gain perspective on the scalability and economics of the route developed, a scenario can be envisioned where a park needs to monitor for BBB. If a park similar to Odell Park in Fredericton, New Brunswick requires 50 g of **6** over a typical season then a initial baker's yeast fermentation of approximately 500 g of ethyl levulinate **36** is required. The cost of 500 g of **36** from a reputable chemical seller, such as Sigma-Aldrich, is approximately $200 CAD. The same analysis done to the synthesis above results in 134 g of (S)-Propylene oxide being required. From the same seller, 134 g of (S)-Propylene oxide is approximately $3,700 CAD.

While 500 g of ethyl levulinate, **36**, would require a fermentation volume of over 100 L, this is easily handled by modern industrial or pilot scale bioreactors.

Chapter Three

Conclusion and Future Studies

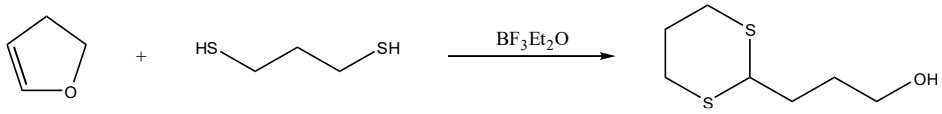
The ultimate goal of this study was to develop a quick, relatively safe, and cost-effective route to the BBB kairomone (5S,7S)-conophthorin **6**. The main steps in this work were the induction of stereochemistry via a baker's yeast reduction of ethyl levulinate, and the carbon-carbon coupling reactions. The asymmetric reduction, done via the yeast reduction, was combined with a THP-protection, and LAH reduction to give the protected diol, C_5, directly. This series of reactions was optimized to give adequate yields of C_5. The carbon-carbon coupling reaction which initially was planned to be a Grignard coupling of C_6 and C_3, unfortunately, due to the lack of reactivity between the two reactants, did not work. A second method was chosen to take its place. The dithiane chemistry that was used for the carbon-carbon coupling, while much more expensive than the original idea, provided a path to couple C_5, C_1, and C_3 in a fashion that was acceptable in its yield and ease of use.

A second route to the protected diol C_5 was also devised and started from the chiral pool chemical glutamic acid. While this route was also acceptable it required protection, and deprotection steps that the former route did not, ultimately translating into a longer synthetic pathway. However, this route, starting from glutamic acid, does allow for the synthesis of (5R,7R)-conophthorin depending upon the stereoisomer of glutamic acid used as the starting material.

The final route, starting with ethyl levulinate, and ending at (5S,7S)-conophthorin **(S)-6** provided a 9% yield over all steps.

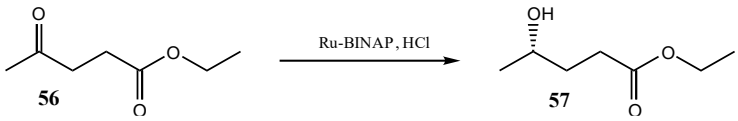
Future Studies

The Grignard coupling that was proposed, coupling C_6 and C_3, would have been an extremely cheap coupling method to produce the nine-carbon chain required for the keto-diol intermediate, and target, **6**. If this reaction were to be successfully applied to this study, a significant amount of time and money would be removed from the route, adding to its usability. Provided that the Grignard coupling is not feasible for this work, a simpler method to produce THP-dithiane **65** is known that uses 2,3-dihydrofuran, 1,3-propanedithiol and BF_3Et_2O giving the dithiane-alcohol which can then be protected to give **65**, Scheme 36.[34] This method to produce **65** avoids the need for two anionic reactions to couple C_5, C_1, and C_3, and instead couples C_5 and C_4 directly. It also avoids using 1,3-dithiane **35**, which is the priciest reagent in the series of reactions. The five member analogue of **35**, 1,3-dithiolane, could also be used in a similar manner to **35**, but at a slightly reduced cost.



Scheme 36: Alternative route to dithiane derivatives.

Future considerations should also include the use of better yielding reactions for the induction of stereochemistry to ethyl levulinate as a maximum yield of 45% leaves much to be desired. A possible alternative may be the use of ruthenium BINAP catalyzed enantioselective hydrogenation which has been used with ethyl levulinate as a substrate in the past, Scheme 37.[63]



Scheme 37: Alternative asymmetric reduction of **56**.

This could nearly double the yield of the asymmetric reduction step and may be more amenable to larger scale reactions depending upon the price of the chemicals used and ability to recover the chiral ligand, Ru-BINAP. Another possible way to increase the overall yield would be to start at the six-carbon analog of ethyl levulinate and use other bioenzymatic methods such as extracted enzymes to afford the asymmetric reduction.[57–60]Although an oxidation reaction would be required to obtain the required ketone functionality from the nucleophilic addition to the six-carbon analogue, this may still be an economic route. Unfortunately no adequate baker's yeast transformation is known in the literature.

Chapter Four

Experimental Methods

General experimental conditions

Unless stated otherwise, all reactions were performed in oven-dried glassware and carried out under an inert argon atmosphere. All temperatures that were recorded were relative to external bath temperatures. Reagents, which were sensitive to air, were transferred using rubber septa by syringes. Solvents were removed via a Büchi rotary-evaporator and a bath temperature of 45 °C.

Reagents and solvents

All commercial reagents were obtained from various commercial suppliers and used without any further purification. Reaction solvents were obtained from a Grubbs column solvent purification system. Distilled water was used for all work-up procedures.

Chromatography

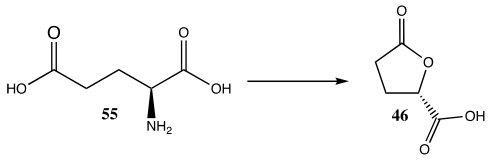
Reactions were monitored via thin-layer chromatography using Merck silica gel 60 F_{254} 0.25 mm thickness plates. Visualizing agent on tlc was either a short wave UV light or by immersing the plate in a solution of potassium permanganate or phosphomolybdic acid and then heating it on a hot plate. Purification was done by either flash column chromatography on Merck silica gel (230-400 mesh) or by using preparative thin-layer plates (0.5 mm) with the indicted eluent. Solvents for separations were used without any further purification.

Physical data

All nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded either on a Varian Inova 300 MHz instrument or an Agilent 400 MR DD2 400 MHz instrument at 25 °C. Deuterated chloroform containing tetramethylsilane (TMS) as an internal standard was used as solvent. Chemical shifts are reported in parts per million (ppm) and referenced to TMS or residual NMR solvent. All proton-proton coupling constants are reported in Hertz (Hz). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, number of protons, coupling constant in Hz). Multiplicity is designated using abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), and ^{13}C NMR as: chemical shift (number of carbons). Fourier transformed infrared spectra (FT-IR) were recorded on Perkin-Elmer 727B infrared spectrometer. Samples were prepared either by putting the neat compound on a 32 mm diameter KBr window, or dissolving the compound in CH_2Cl_2, adding a drop or two on the KBr window followed by air evaporation of the solvent.

Preparation of compounds

Synthesis of (S)-5-oxotetrahydrofuran-2-carboxylic acid, **46**[48]

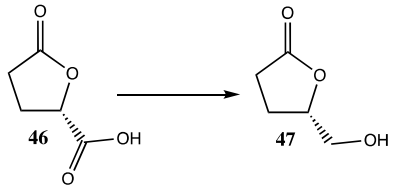


The compound was prepared following the procedure by Charette except with slight modifications.[47] L-Glutamic acid **45** (14.7 g, 99.9 mmol) was dissolved in water (50 mL), along with conc. hydrochloric acid (21 mL, 11.65 M, 244.7 mmol). The solution was cooled to 0 °C in an ice bath and sodium nitrite (10.50 g, 152.2 mmol) dissolved in water (50 mL) was added dropwise over 1.5 h during which time the solution took on a blue colour with production of bubbles. After addition, the reaction mixture was allowed to warm to rt and stir overnight. The mixture was concentrated in vacuo to give a pale yellow oil which was then taken up in nearly boiling acetone (200 mL), and filtered while hot. Filtered material was washed with hot acetone (1 x 200 mL). The filtrate was concentrated in vacuo and taken up in hot chloroform (340 mL) where it was stirred over $MgSO_4$ for 3 h in a 50 °C water bath. The mixture was filtered, washed with hot chloroform and the solution reduced to 75 mL, where a seed crystal was added, and the solution cooled to 0 °C and left overnight. The resulting needle-like white crystals were filtered off and washed with ice cold chloroform. A second and third crop of crystals were harvested in the same manner. Crops two and three were combined and recrystalized in a minimum amount of hot chloroform. The combined material was dried via vacuum desiccation ($CaSO_4$) for 24 h, to give white needle-like crystals.

Yield: 9.85 g, 76%.

m.p.:	80 – 82 °C
^{1}H NMR (400 MHz, $CDCl_3$):	δ 6.86 (bs, 1H), 5.00 (m, 1H), 2.60 (m, 3H), 2.41 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 176.2, 174.3, 75.2, 26.7, 25.8.
FT-IR (neat, cm $^{-1}$):	3448, 1781, 1638, 1420, 1245, 1186, 1068

Synthesis of (S)-5-(hydroxymethyl)dihydrofuran-2(3H)-one, **47**[48]



The compound was prepared following the procedure by Charette except with slight modifications.[48] Lactone acid **46** (0.51 g, 3.93 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Borane dimethyl sulfide (2.2 mL, 2 M, 4.40 mmol) was added dropwise over 1 h, warmed to rt, and stirred for an additional 2.5 h where a cloudy mixture was noted. To the reaction mixture was added methanol (2 mL), and the resulting mixture was concentrated in vacuo. The crude product was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (1:1, Rf = 0.37) to give a clear colourless liquid.

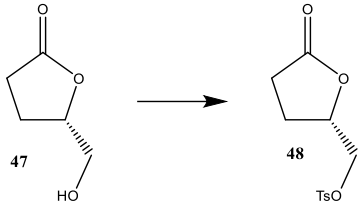
Yield: 0.34 g, 76%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (m, 1H), 3.85 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.61 (dd, *J* = 12.5, 4.6 Hz, 1H), 3.42 (bs), 2.53 (m, 2H), 2.23 (m, 1H), 2.11 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 80.9, 63.9, 28.6, 23.0.

FT-IR (neat, cm $^{-1}$): 3523, 2922, 2874, 1736, 1464, 913, 885, 835, 804, 736.

Synthesis of (S)-(5-oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate, **48**[48]



The compound was prepared following the procedure by Charette except with slight modifications. To lactone-alcohol **47** (0.682 g, 5.87 mmol) and pyridine (0.55 mL, 6.83 mmol) in DCM (10 mL) was added p-tolenesulfonyl chloride (1.65 g, 8.46 mmol) in DCM (7 mL) at 0 °C. The solution was allowed to warm and stirred at rt overnight. To the reaction mixture was added water (10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layer was successively washed with HCl (0.5 M, 3 x 10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The washed organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting crude yellow oil was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (1:1, Rf = 0.29) to give a white powder.

Yield: 1.38 g, 87%

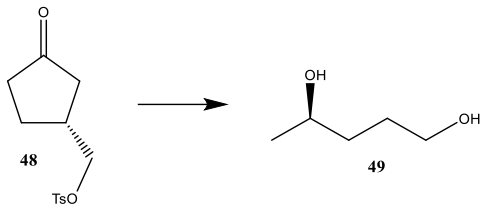
m.p.: 78 – 81 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.69 (m, 1H), 4.17 (m, 2H), 2.55 (m, 5H), 2.35 (m, 1H), 2.12 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 145.4, 132.2, 130.0, 127.9, 76.4, 69.9, 27.8, 23.5, 21.6.

FT-IR (neat, cm $^{-1}$): 2957, 1774, 1598, 1451, 1356, 1294, 1177, 1096, 1072, 975, 944, 816, 667, 569, 555, 528.

Synthesis of (R)-pentane-1,4-diol, **49**[48]



The compound was prepared following the procedure by Charette except with slight modifications. To a suspension of LAH (0.75 g, 19.77 mmol) in THF (15 mL) cooled to 0 °C was added lactone-tosylate **48** (1.29 g, 5.05 mmol) in THF (20 mL) dropwise. After complete addition, the ice bath was removed, and the reaction mixture was then heated at reflux for 20 h. The reaction mixture was cooled to 0 °C, diluted with Et_2O (10 mL) and then quenched by slow dropwise addition of water (0.75 mL), followed by NaOH (0.75 mL, 15% w/w), and finally, water (2.25 mL) once more. The mixture was warmed to rt and stirred for 15 min which resulted in a fine white suspension being formed. To this was then added $MgSO_4$ and stirring continued for 15 min, where the solution was filtered through a plug of celite and concentrated. The crude clear oil was purified via SiO_2 column chromatography eluting with EtOAc/MeOH (9:1, Rf = 0.58) to give a colourless oil.

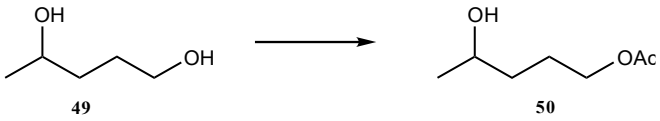
Yield: 0.40 g, 77%

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (m, 1H), 3.65 (m, 2H), 2.90 (bs, 2H), 1.58 (m, 4H), 1.19 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 67.9, 62.8, 36.2, 29.0, 23.5.

FT-IR (neat, cm $^{-1}$): 3353, 2968, 2938, 2876, 1655, 1377, 1135, 1057, 1011.

Synthesis of 4-hydroxypentyl acetate, **50**[64]



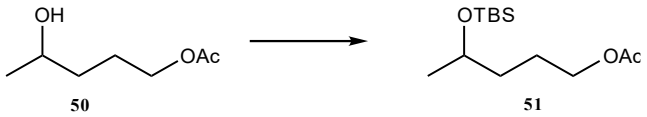
49 **50**

To diol **49** (0.61 g, 5.82 mmol) in EtOAc (6.0 mL) was added potassium carbonate (0.80 g, 5.82 mmol). This suspension was heated at reflux for 2 h, cooled to rt, diluted with Et_2O (3 mL), filtered through celite, and concentrated to give a colourless oil. A portion of the crude oil was purified via SiO_2 column chromatography eluting with neat EtOAc (Rf = 0.32) to give a clear colourless oil. The remaining was taken into the next step without further purification.

Yield: 0.723 g, 85%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (t, *J* = 6.6 Hz, 2H), 3.82 (m, 1H), 2.04 (s, 3H), 1.64 (m, 5H), 1.20 (d, *J* = 6.2 Hz, 3H).

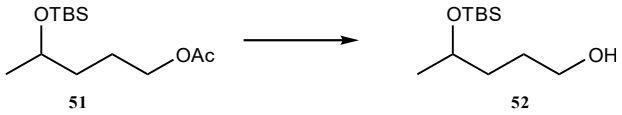
Synthesis of 4-((tert-butyldimethylsilyl)oxy)pentyl acetate, **51**[65]



50 **51**

Acetate **50** (1.30 g, 8.89 mmol) was dissolved in DCM (20 mL). Imidazole (0.91 g, 13.31 mmol) and TBSCl in toluene (3.7 mL, 50% w/w, d = 0.87) were then added and the solution was allowed to stir overnight at rt. The solution was poured into water (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 ml). The combined organic layer was washed with brine (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a pale yellow oil. Hexanes/EtOAc (9:1, Rf = 0.35). This was taken into the next step without further purification.

Synthesis of 4-((tert-butyldimethylsilyl)oxy)pentan-1-ol, **52**[66]



51 **52**

To TBS-acetate **51** (1.85 g, 7.12 mmol) in MeOH (13 mL) was added potassium carbonate (1.03 g, 7.47 mmol). The solution was stirred at rt for 2 h at which time it was quenched by addition of sat. NH_4Cl (10 mL), and then diluted with water (10 mL). The mixture was then extracted with EtOAc (3 x 20 mL). The combined extracts was then washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a slightly yellow liquid. The crude product was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (5:1, Rf = 0.25) to give a clear colourless oil.

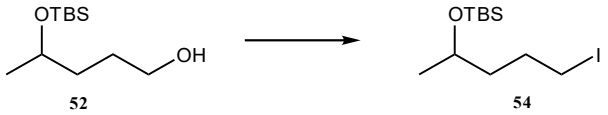
Yield: 1.32 g, 82% over two steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (m, 1H), 3.61 (m, 2H), 2.23 (bs, 1H), 1.66-1.46 (m, 4H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 68.4, 63.0, 36.0, 28.5, 25.8, 18.1, -4.5, -4.8.

FT-IR (neat, cm $^{-1}$): 3325, 2929, 2859, 1473, 1463, 1374, 1256, 1139, 1100, 1051, 939, 837, 774, 664.

Synthesis of 4-((tert-butyldimethylsilyl)oxy)-1-iodopentane, **54**[67]



52 **54**

Triphenyphosphine (1.53 g, 5.84 mmol) and imidazole (0.411 g, 6.04 mmol) were dissolved in Et_2O/MeCN (3:1, 20 mL) and then iodine (1.48 g, 5.84 mmol) was added portion-wise over one minute producing a yellow suspension. After stirring for 10 min, TBS-alcohol **52** (1.22 g, 5.56 mmol) in Et_2O/MeCN (3:1, 10 mL) was added and the solution was stirred for 15 h. The reaction was diluted with hexanes (20 mL) and filtered through a plug of celite. The filtrate was washed with brine, and dried ($MgSO_4$) and concentrated to give a yellow liquid which was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (30:1, Rf = 0.30) to give a clear colourless oil.

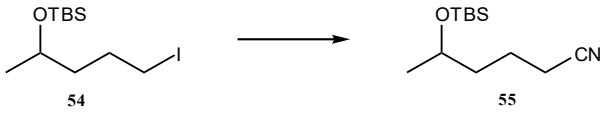
Yield: 1.29 g, 71%

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (m, 1H), 3.20 (m, 2H), 1.94 (m, 2H), 1.55 (m, 2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 67.6, 40.3, 29.9, 25.9, 23.8, 18.1, 7.3, -4.4, -4.8

FT-IR (neat, cm $^{-1}$): 2858, 1472, 1462, 1407, 1374, 1257, 1230, 1176, 1129, 1091, 1048, 939, 904, 889, 826, 808, 773, 711, 663, 598, 573, 506, 436

Synthesis of 5-((tert-butyldimethylsilyl)oxy)hexanenitrile, **55**[68]



54 **55**

To THP-iodide **54** (1.28 g, 3.91 mmol) in DMSO (11 mL) was added sodium cyanide (0.25 g, 5.16 mmol). The solution was stirred at rt for 24 h where it then was poured into water (150 mL) and extracted with Et_2O (3 x 20 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil which was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (10:1, Rf = 0.63) to give a clear colourless oil.

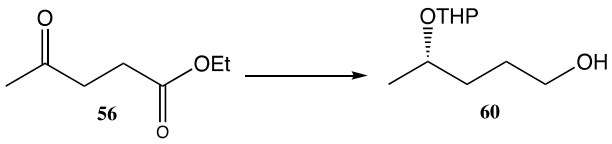
Yield: 0.65 g, 73%

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.83-1.48 (m, 4H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 2.9 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 67.6, 38.8, 25.8, 23.7, 21.7, 18.0, 17.3, -4.3, -4.8

FT-IR (neat, cm $^{-1}$): 1473, 1463, 1375, 1257, 1138, 1096, 1026, 837, 807, 776

Synthesis of (4S)-4-((tetrahydro-2H-pyran-2-yl)oxy)pentan-1-ol, **60**[53]



The compound was prepared following the procedure by Jacobs except with slight modifications. To water (800 mL) was added dry active yeast (Fleischmann traditional, 100 g). This was stirred for 10 min and then sucrose (25.0 g) was added and allowed to stir for an additional 10 min. To this was added ethyl levulinate **56** (3.88 g). This heterogenous slurry was stirred at 30-34 °C with an attached bubbler for 50 h. The reaction mixture was filtered through celite giving a yellow solution which was extracted with Et_2O (5 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil which was of sufficient purity to use in the next step.

The oil was taken up in DCM (80 mL) and dihydropyran (4.53 g, 53.83 mmol, 2 eq) and PPTS (0.726 g, mmol, 0.1 eq) were added. The solution was stirred at 0°C for 3 h, then allowed gradually to warm to rt and stir overnight. The solution was quenched by addition of sat. Na_2CO_3 (30 mL) and then extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil which was of sufficient purity for use in the next step.

The yellow oil was taken up in THF (30 mL) and slowly added to a stirring suspension of LAH (4.10 g, 107.7 mmol, 4 eq) in THF (100 mL) at 0 °C. After complete addition, the solution was allowed to stir for 2 h at rt where the reaction was cooled to 0°C, and an additional amount of Et_2O (40 mL) was added. Following this, water (4 mL)

was added slowly dropwise, then aq. NaOH (15%, 4 mL), and finally again, water (12 mL). This solution was allowed to stir until a white suspension was produced (ca. 10-20 min). $MgSO_4$ was added and after stirring for 15 min the mixture was filtered through celite and washed with Et_2O. The filtrate was concentrated in vacuo to give the product as a yellow oil which was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (1:1, R_f = 0.33) to give a clear pale yellow oil.

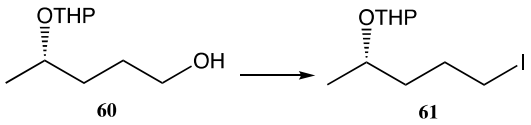
Yield: 2.27 g, 45%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (m, 1H), 3.84 (m, 2H), 3.62 (m, 2H), 3.47 (m, 1H), 2.17 (bs, 1H), 1.66 (m, 10H), 1.23 (d, *J* = 6.3 Hz, 1.5H), 1.12 (d, *J* = 6.1 Hz, 1.5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.7, 96.1, 73.9, 71.1, 62.96, 62.91, 62.8, 62.7, 33.9, 32.8, 31.2, 31.1, 28.7, 28.5, 25.40, 25.37, 21.4, 20.0, 19.9, 19.1.

FT-IR (neat, cm $^{-1}$): 3324, 2854, 1441, 1380, 1136, 1022, 870, 812.

Synthesis of (4S)-4-((tetrahydro-2H-pyran-2-yl)oxy)-1-iodopentane, **61**[69]



Triphenylphosphine (1.82 g, 6.95 mmol), and imidazole (0.50 g, 7.32 mmol) were dissolved in Et_2O/MeCN (3:1, 20 mL) and then iodine (1.790 g, 7.05 mmol) was added portion-wise over one minute resulting in a yellow suspension. After stirring for 10 min, THP-alcohol **60** (1.25 g, 6.63 mmol) was added dropwise over 2 minutes as a solution in Et_2O/MeCN (3:1, 10 mL). This was stirred for 2 h, then sodium thiosulfate solution (2%, 15 mL) was added, the layers separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with brine and dried ($MgSO_4$). The suspension was filtered, and concentrated in vacuo to give a clear colourless liquid. The crude material was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (10:1, Rf = 0.45) to give a clear colourless oil.

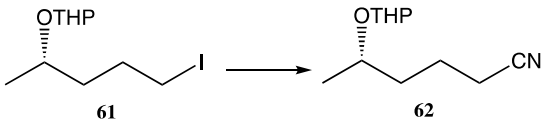
Yield: 1.63 g, 82%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 (m, 0.5H), 4.62 (m, 0.5H), 3.95-3.70 (m, 2H), 3.48 (m, 1H), 3.20 (m, 2H), 2.08-1.43 (m, 10H), 1.23 (d, *J* = 6.3 Hz, 1.5H), 1.11 (d, *J* = 6.1 Hz, 1.5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.8, 95.8, 73.0, 70.0, 62.8, 62.7, 38.1, 37.2, 31.1, 29.8, 29.4, 25.5, 25.4, 21.5, 20.0, 19.9, 19.2, 7.3, 7.0.

FT-IR (neat, cm $^{-1}$): 2937, 2868, 1452, 1440, 1375, 1232, 1201, 1173, 1133, 1077, 1023, 995, 870, 814, 727, 597.

Synthesis of (5S)-5-((tetrahydro-2H-pyran-2-yl)oxy)hexanenitrile **62**



61 **62**

To THP-iodide **61** (1.55 g, 5.20 mmol) in DMSO (14 mL) was added sodium cyanide (0.331 g, 6.76 mmol). After stirring at rt for 24 h the mixture was poured into water (200 mL) and extracted with Et_2O (3 x 20 mL). The combined extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil which was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (5:1, Rf = 0.25) to give a clear colourless oil.

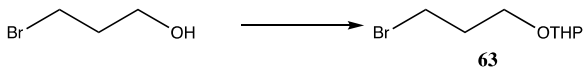
Yield: 0.798 g, 78%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61 (m, 0.7H), 4.55 (m, 0.3H), 3.94-3.66 (m, 2H), 3.53-3.34 (m, 1H), 2.38 (m 2H), 1.91-1.41 (m, 10H), 1.24 (d, *J* = 6.3 Hz, 1.5H), 1.12 (d, *J* = 6.1 Hz, 1.5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 119.9, 119.6, 99.0, 98.9, 96.2, 73.3, 70.0, 67.0 63.1, 62.9, 62.4, 36.0, 35.4, 31.2, 31.1, 30.7, 28.9, 25.5, 25.4, 25.38, 25.2, 21.8, 21.5, 21.4, 20.1, 20.0, 19.6, 19.2, 17.3, 17.1, 17.0.

FT-IR (neat, cm $^{-1}$): 2943, 2870, 1454, 1441, 1379, 1353, 1342, 1261, 1200, 1136, 1120, 1076, 1032, 1023, 1004, 904, 870, 812

Synthesis of 3-bromo-1--((tetrahydro-2H-pyran-2-yl)oxy)propane. **63**[70]



63

To a 100 mL RBF was added 3-bromo-1-propanol (4.04 g, 29.07 mmol) and DCM (60 mL). The solution was cooled to 0 °C and dihydropyran (2.93 g, 34.88 mmol) and PPTS (0.736 g, 2.93 mmol) were added. The solution was stirred at this temperature for 3 h and then allowed to gradually warm to rt and stir overnight. To this was added sat. Na_2CO_3 (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude product as a yellow oil which was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (4:1, R_f = 0.55) to give a clear colourless oil.

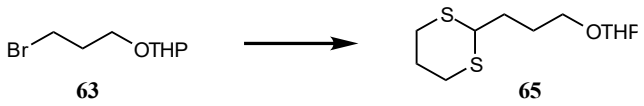
Yield: 5.97 g, 92%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (m, 1H), 3.85 (m, 2H), 3.50 (m, 4H), 2.11 (quint, *J* = 6.3 Hz, 2H), 1.90-1.43 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.8, 64.8, 62.2, 32.9, 30.6 30.5, 25.4, 19.4.

FT-IR (neat, cm $^{-1}$): 2944, 2872, 1441, 1352, 1258, 1201, 1134, 1119, 1034, 870, 816, 564.

Synthesis of 2-(4-(cyclohexyloxy)butyl)-1,3-dithiane **65**[71]



63 **65**

To 1,3-dithiane, **35** (0.596 g, 4.93 mmol) in THF (10 mL) at -15 °C was added n-BuLi in hexanes (2.0 mL, 4.93 mmol, 2.5 M). This was allowed to stir for 2 h at this temperature and then THP-bromide, **63** (1.00 g, 4.48 mmol) in THF (5 mL) was added. The solution was stirred and gradually allowed to warm to rt over 2 h and then stir overnight. To the reaction mixture was added ether (10 mL) and sat. NH_4Cl (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a clear colourless oil. The residue was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (8:1, Rf = 0.30) to give a clear colourless oil.

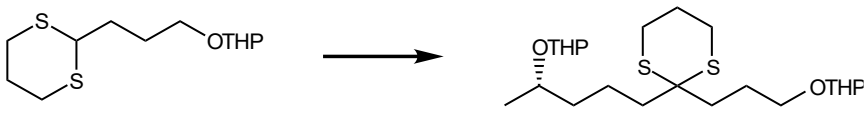
Yield: 0.94 g, 80%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (m, 1H), 4.06 (t, *J* = 6.6 Hz, 1H), 3.84 (m, 3.74 (m, 1H), 3.49 (m, 1H), 3.40 (m, 1H), 2.85 (m, 4H), 2.10 (m, 1H), 1.91-1.75 (m, 6H), 1.68 (m, 1H), 1.61-1.45 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.6, 66.6, 62.1, 47.3, 32.3, 30.6, 30.3, 26.8, 25.9, 25.4, 19.4.

FT-IR (neat, cm $^{-1}$): 2941, 2866, 2659, 1450, 1441, 1423, 1352, 1322, 1275, 1200, 1136, 1121, 1076, 1034, 986, 905, 868, 814, 775, 664

Synthesis of (8S)-4-(1,3-dithian-2-yl)-1,8-di-(tetrahydro-2H-pyran-2-yl)oxy)nonane, **66**



65 **66**

To a 25 mL RBF was added THP-dithiane **65** (0.509 g, 1.94 mmol) in THF (5 mL) and the solution was cooled to -15 °C. n-BuLi (0.8 mL, 2.5 M, 2.00 mmol) was added dropwise over 1 min, after complete addition, the solution was stirred for 2 h at -15 °C. Then THP-iodide **61** (0.516 g, 1.73 mmol) in THF (2 mL) was added dropwise over 2 min. After complete addition, the solution was allowed to gradually warm to rt and stir overnight. Saturated NH_4Cl (10 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (35 mL), dried ($MgSO_4$), filtered and concentrated to give a clear yellow oil. This was purified via SiO_2 column chromatography eluting with hexanes/EtOAc (8:1, R_f = 0.14) to give a clear colourless oil.

Yield: 0.674 g, 88%

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (m, 0.5H), 4.63 (m, 0.5H), 4.58 (m, 1H), 3.96-3.67 (m, 4H), 3.49 (m, 2H), 3.41 (dt, *J* = 9.7, 6.1 Hz, 1H), 2.80 (m, 4H), 2.03-1.33 (m, 24H), 1.23 (d, *J* = 6.3 Hz, 1.5H), 1.11 (d, *J* = 6.1 Hz, 1.5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.84, 98.83, 98.7, 98.65, 95.7, 73.8, 72.77, 70.8, 67.2, 67.18, 69.2, 62.6, 62.3, 62.22, 62.20, 53.1, 53.06, 38.5, 38.4, 37.5, 36.64, 36.63, 31.23, 31.22,

	30.7, 26.0, 25.6, 25.5, 25.48, 25.47, 24.7, 24.66, 21.7, 20.2, 20.1, 19.9, 19.8, 19.54, 19.53, 19.1.
FT-IR (neat, cm $^{-1}$):	2852, 2737, 2656, 1465, 1351, 1322, 1275, 1260, 1199, 981, 904, 868, 814, 679.

Synthesis of (S)-5-(2-(3-hydroxypropyl)-1,3-dithian-2-yl)pentan-2-ol, **33**[34]

To THP-dithiane **66** (0.422 g, 0.975 mmol) in MeOH (15 mL) was added PPTS (0.05 g, 0.2 mmol, 0.2 eq). This was stirred at rt for 24 h, sat. $NaHCO_3$ (10 mL) was added and stirred for 10 min. The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic layers were dried with $MgSO_4$, filtered and solvent evaporated. The residue was purified via SiO_2 column chromatography eluting with neat EtOAc (Rf = 0.37) to give a viscous clear colourless oil.

Yield: 0.213 g, 83%

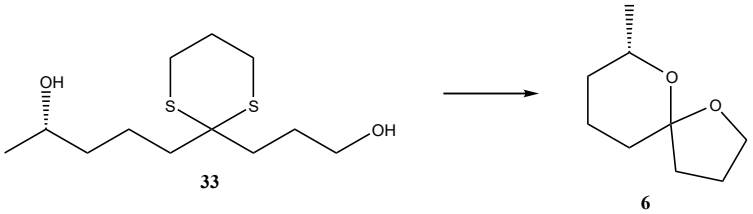
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (m, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.81 (m, 4H), 2.03-1.81 (m, 6H), 1.75-1.41 (m, 8H), 1.20 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 67.8, 62.8, 53.0, 39.2, 38.3, 34.4, 27.6, 26.0, 25.4, 23.6, 20.3.

FT-IR (neat, cm $^{-1}$): 3365, 2945, 1780, 1454, 1421,1375, 1275, 1238, 1182, 1134, 1062, 935, 907, 752

$[\alpha]_D^{20}$ -14.9° (c 0.93, $CHCl_3$).

Synthesis of (5S,7S)-conophthorin, **6**[34]



33 **6**

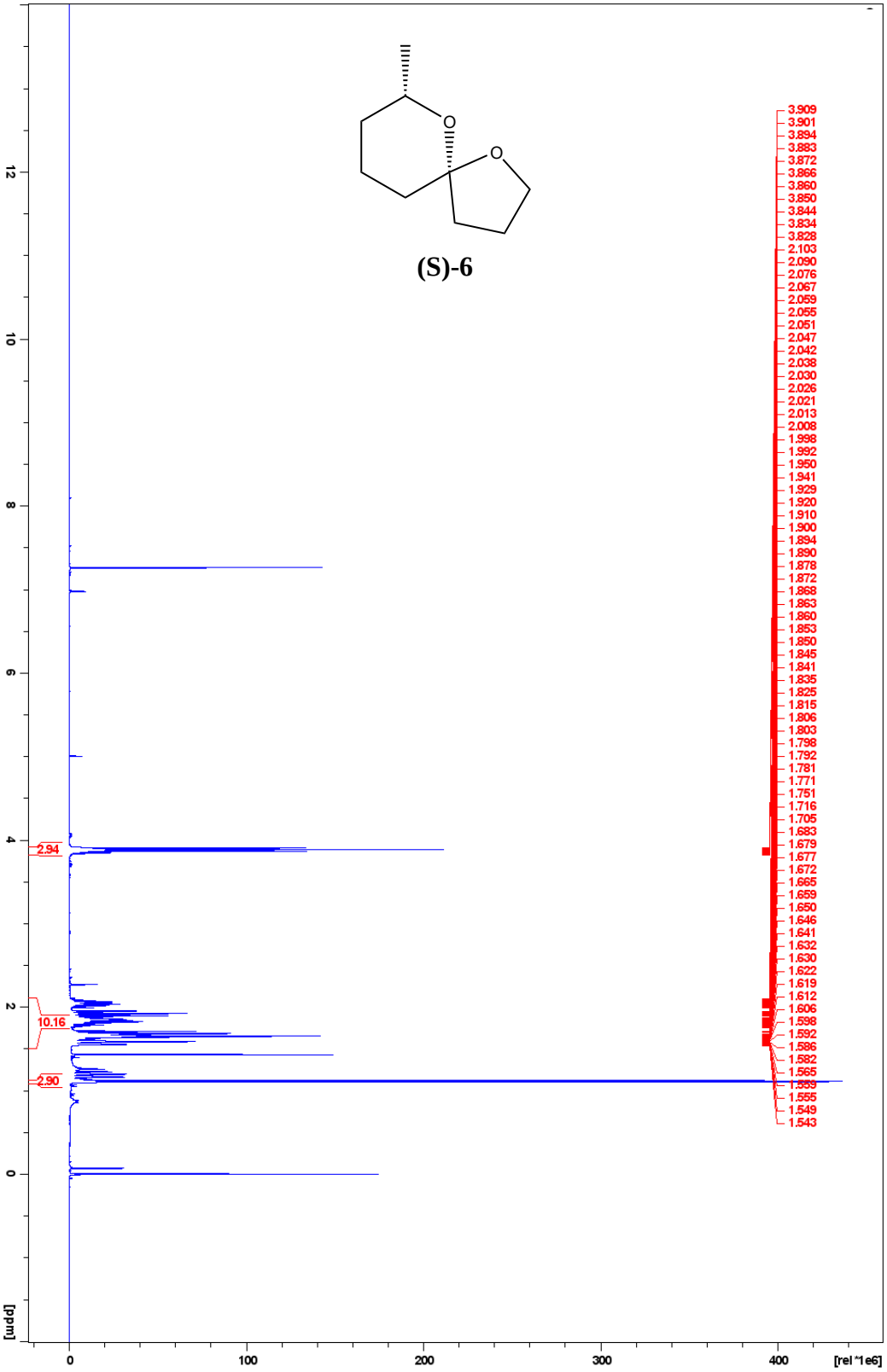
The compound was prepared following the procedure by Jacobs except with slight modifications. To dithiane **33** (0.19 g, 0.72 mmol) in aq. acetone (99:1, 5 mL) was added $CuCl_2$ (0.19 g, 1.4 mmol, 2 eq) and CuO (0.23 g, 2.9 mmol, 4 eq) where a dark red suspension was produced. After 30 min of stirring a colour change to dark green was noted, with a final change, after 1 h, to brown. This was stirred for a total of 2 h at rt. After stirring, the mixture was filtered through celite and washed with Et_2O. The combined filtrate and washings were concentrated in vacuo, diluted with Et_2O and washed with Na_2CO_3 (5% solution). The Na_2CO_3 solution was then extracted with Et_2O (3 x 15 mL) and all organic phases were combined, dried ($MgSO_4$) and filtered. This solution was concentrated in vacuo to give crude keto diol **17** as a clear colourless oil. To the crude **17** was added Et_2O/hex (1:3, 20 mL) and HCl (6 M, 1 mL) and the mixture was stirred at rt for 5.5 h. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were stirred with NaOH (10 mL, 20 wt.%) for 12 h. The layers were again separated and the aqueous layer was extracted with Et_2O (2 x 15mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at 52 mmHg and 22 °C. The oily residue was purified via column chromatography eluting Et_2O/hex (1:4, Rf = 0.90) to give the title compound (5S,7S)-conophthorin **6** as a clear colourless oil.

Yield: 0.043 g, 42%

^{1}H NMR (400 MHz, $CDCl_3$):	δ 3.88 (m, 3H), 2.10-1.52 (m, 10H), 1.11 (d, J = 6.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 106.0, 66.8, 66.4, 38.0, 32.8, 32.6, 23.8, 22.0, 20.4.
FT-IR (neat, cm $^{-1}$):	3426, 2937, 2860, 1726, 1460, 1379, 1273, 1121, 1075, 1032, 904, 870, 814, 756.
$[\alpha]_D^{23}$	-75.4° (c 2.49, n-pentane).

Appendix A

^{1}H NMR spectra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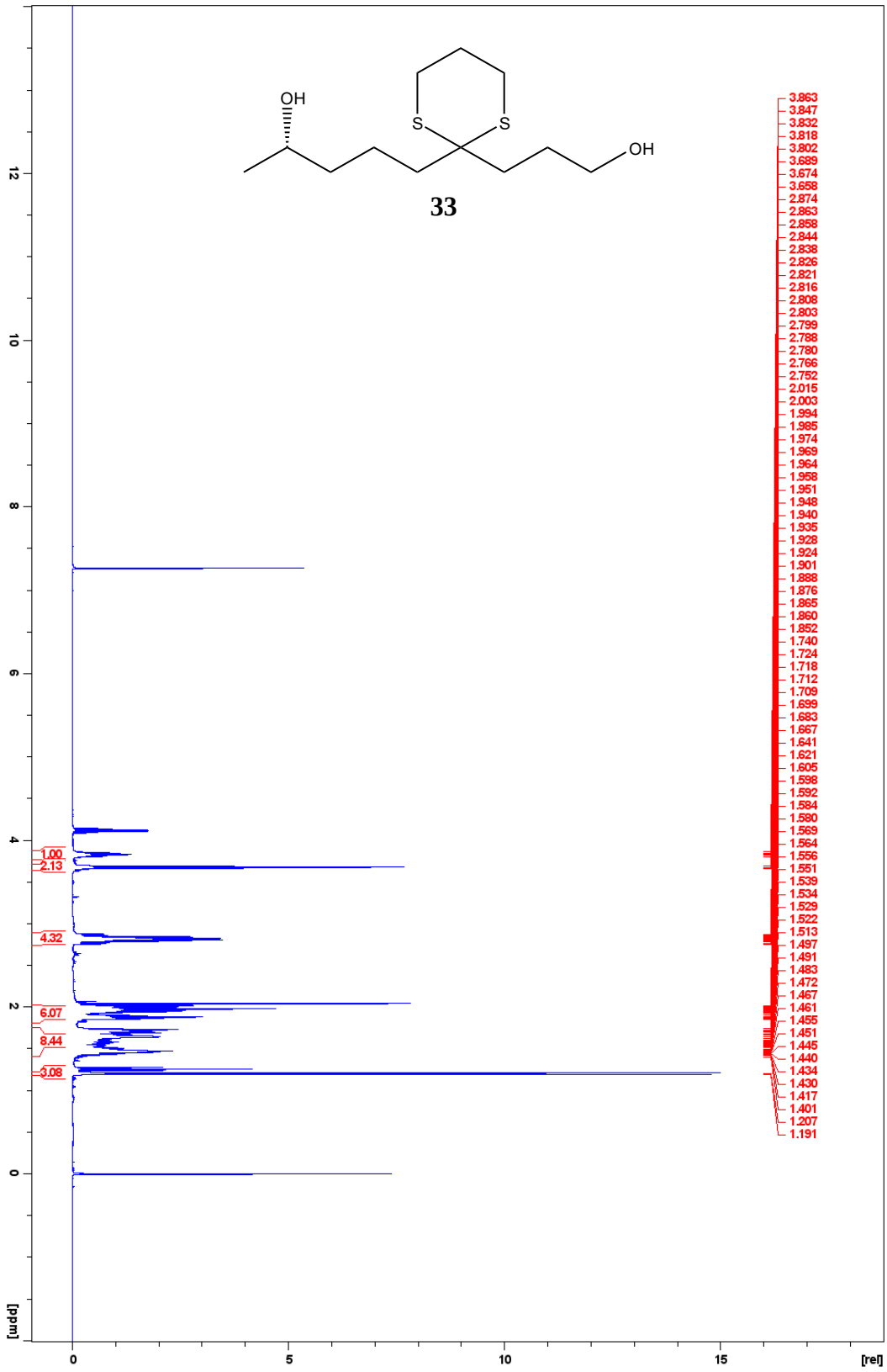
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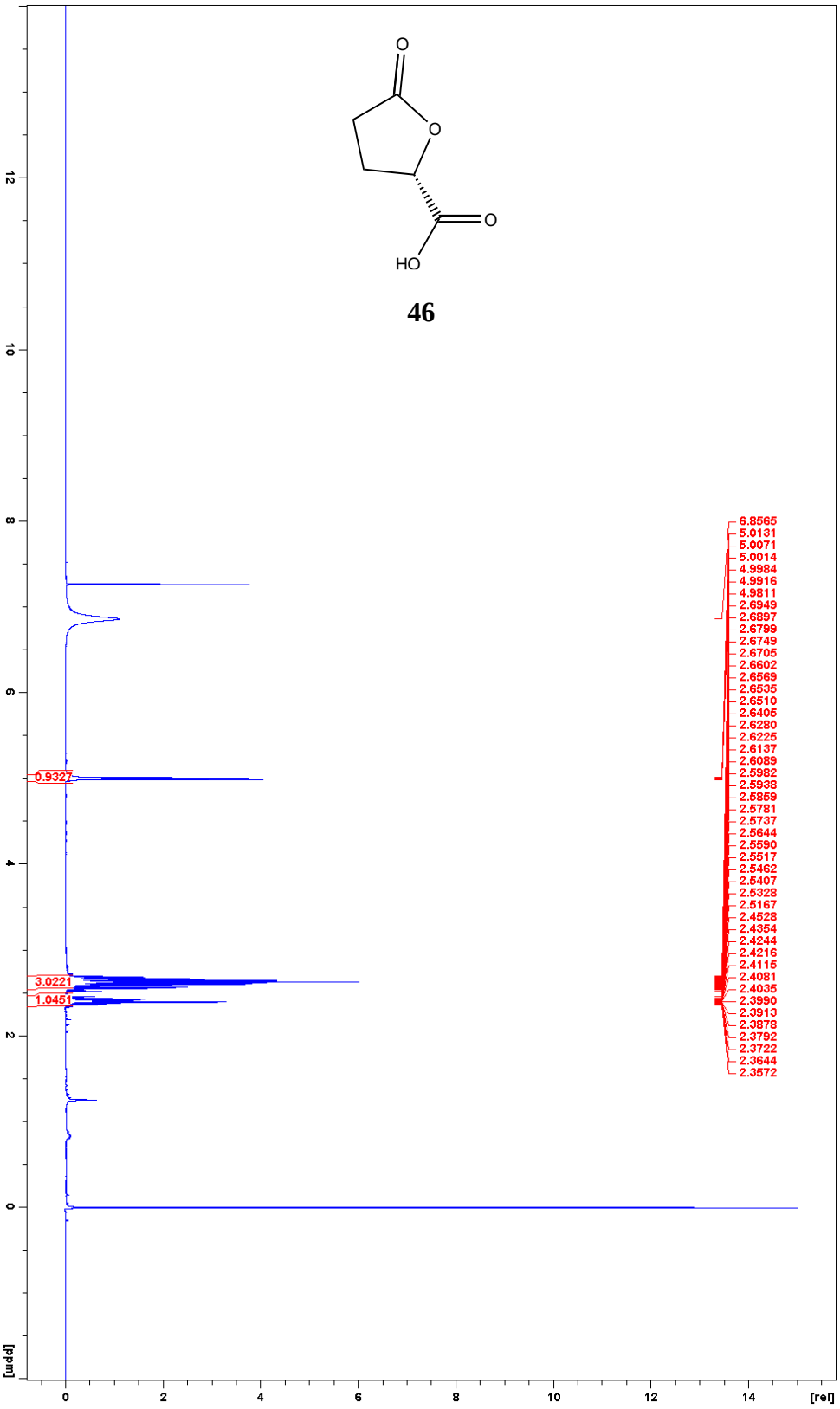
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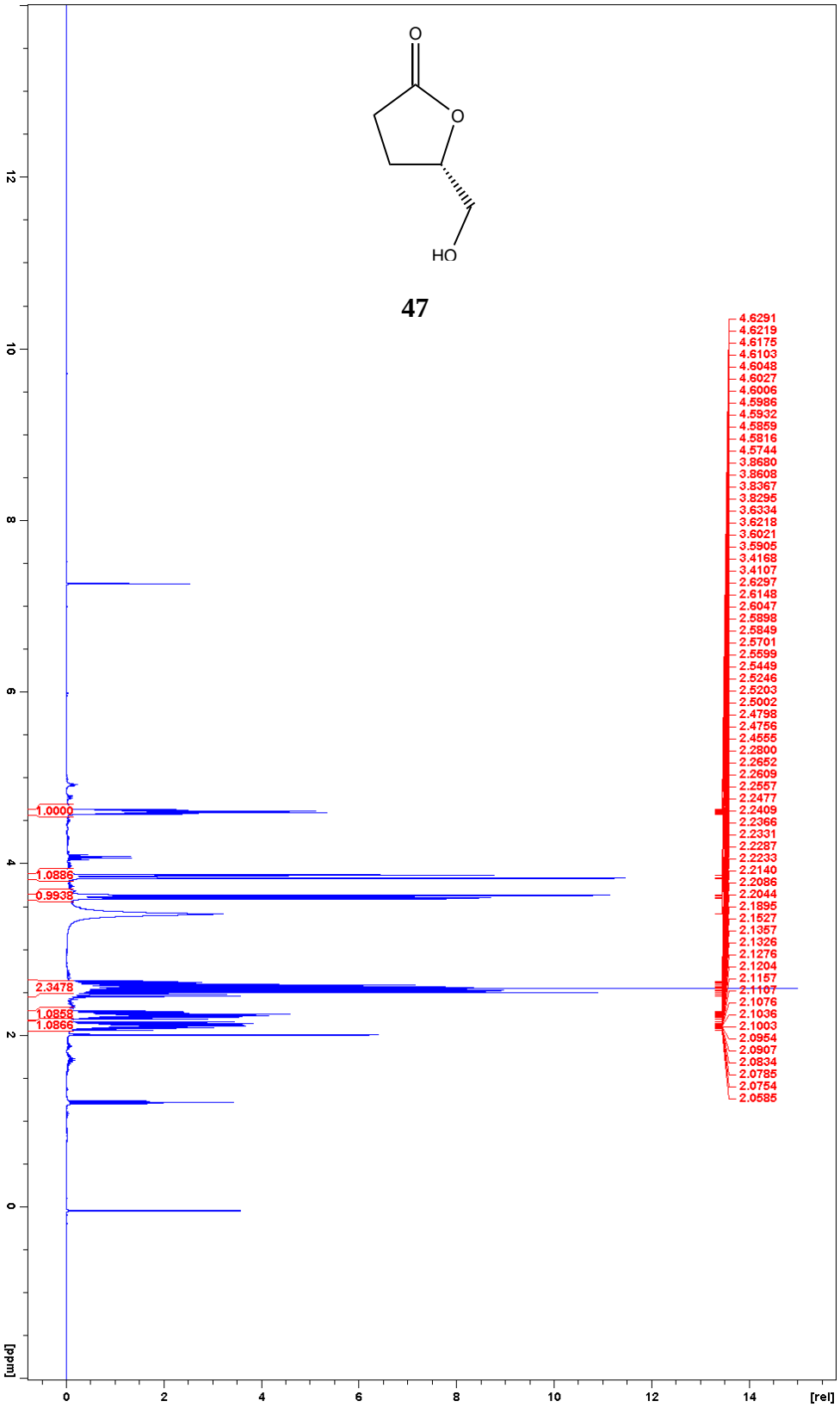
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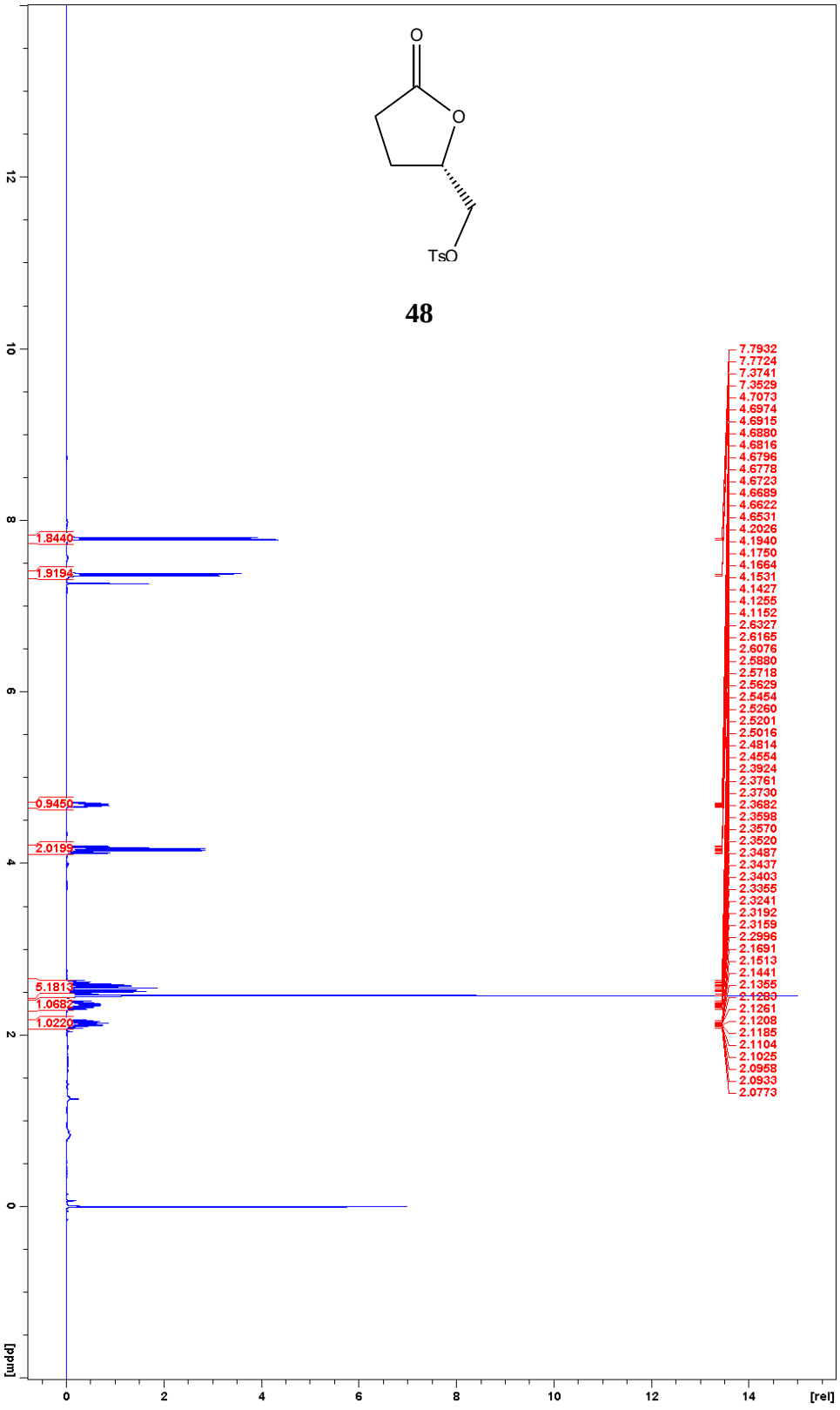
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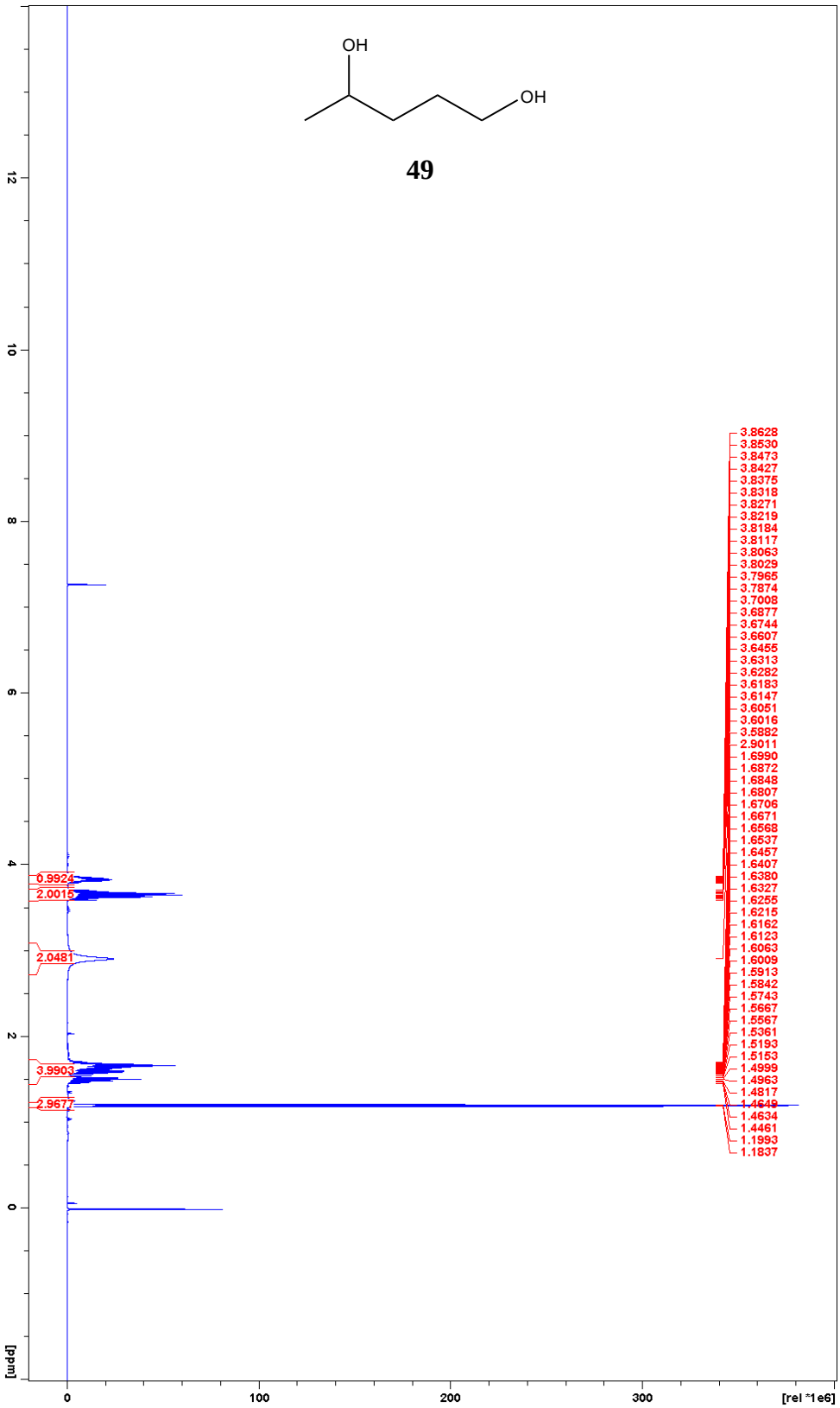
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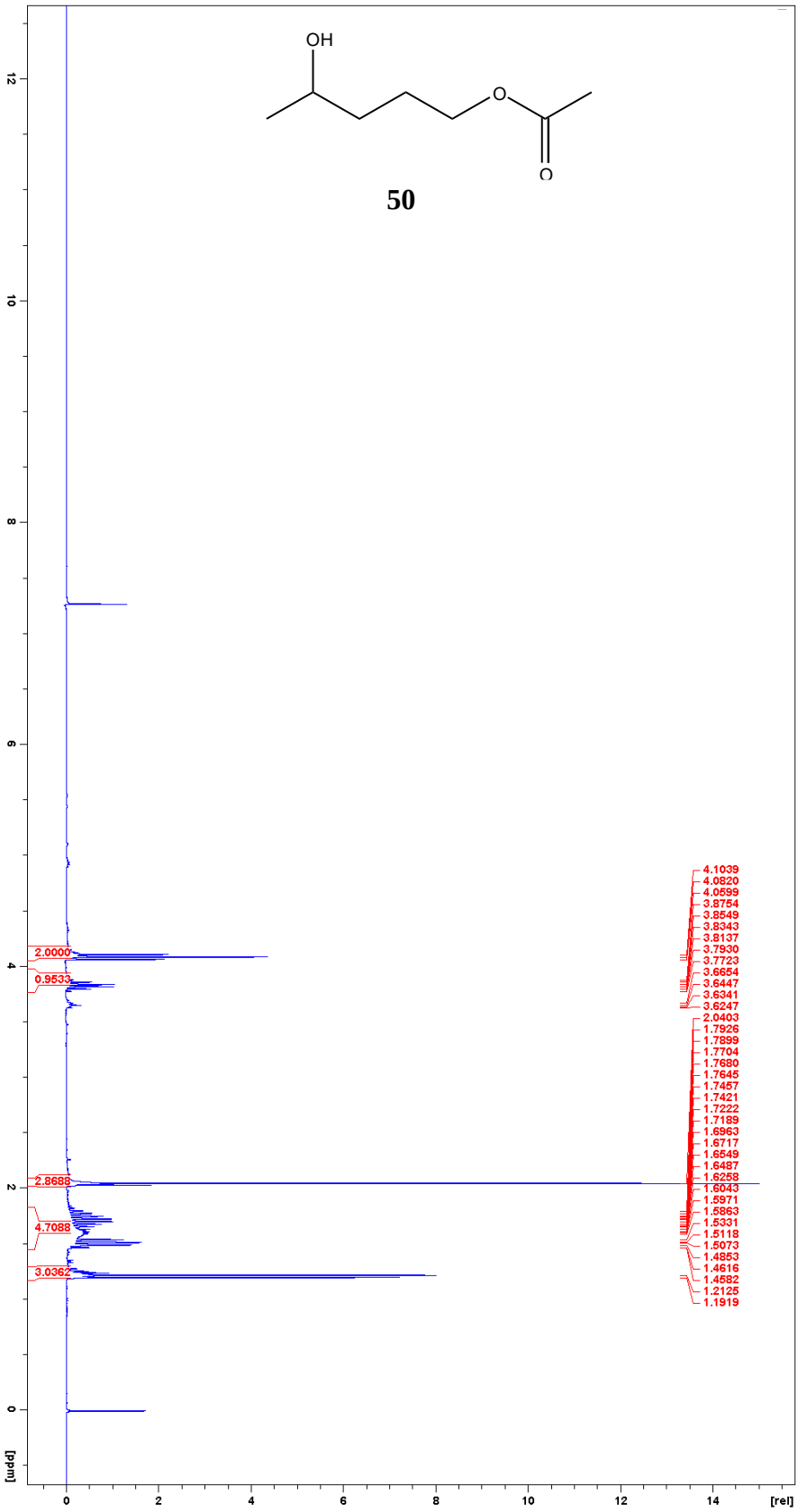
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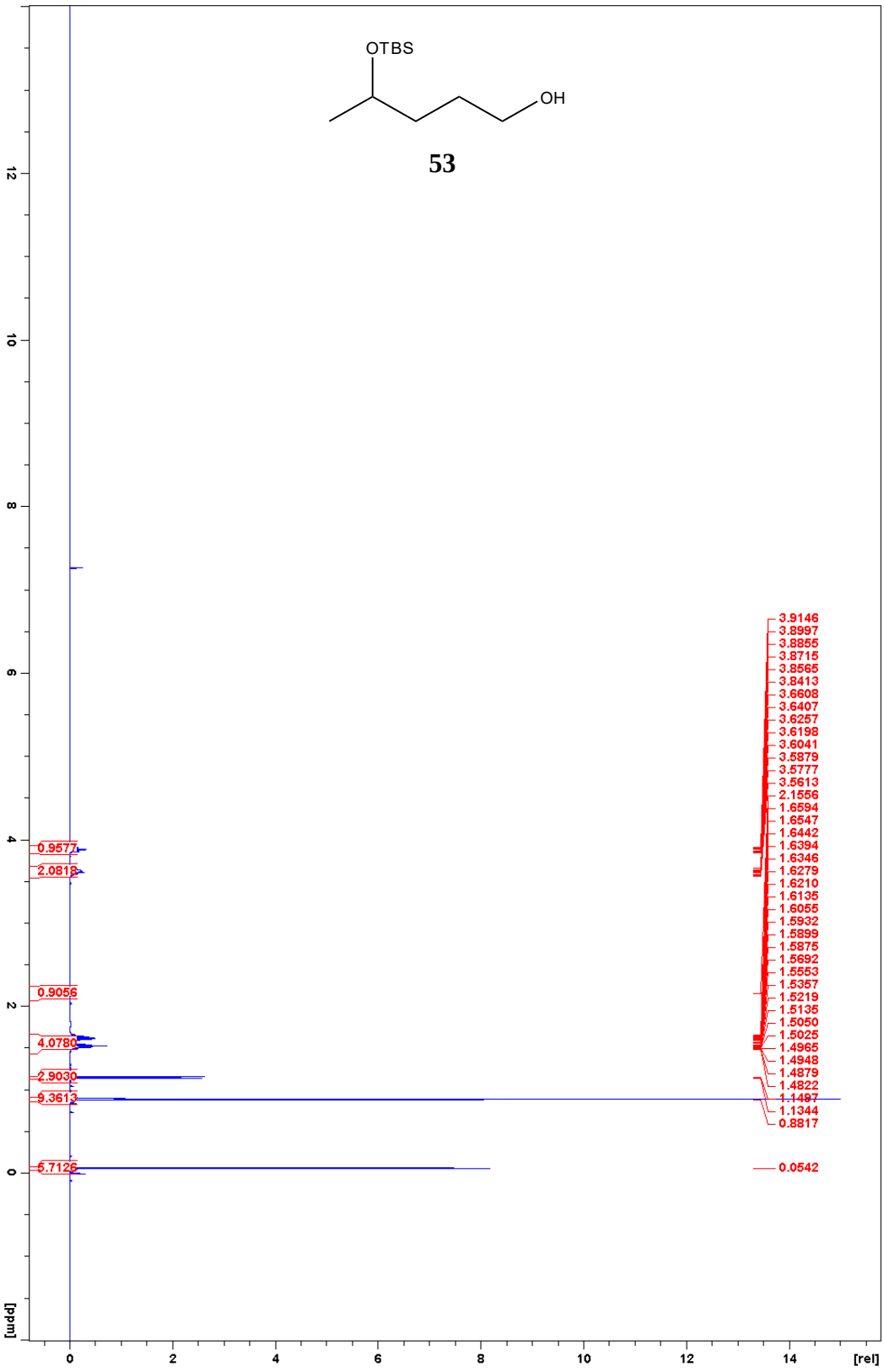
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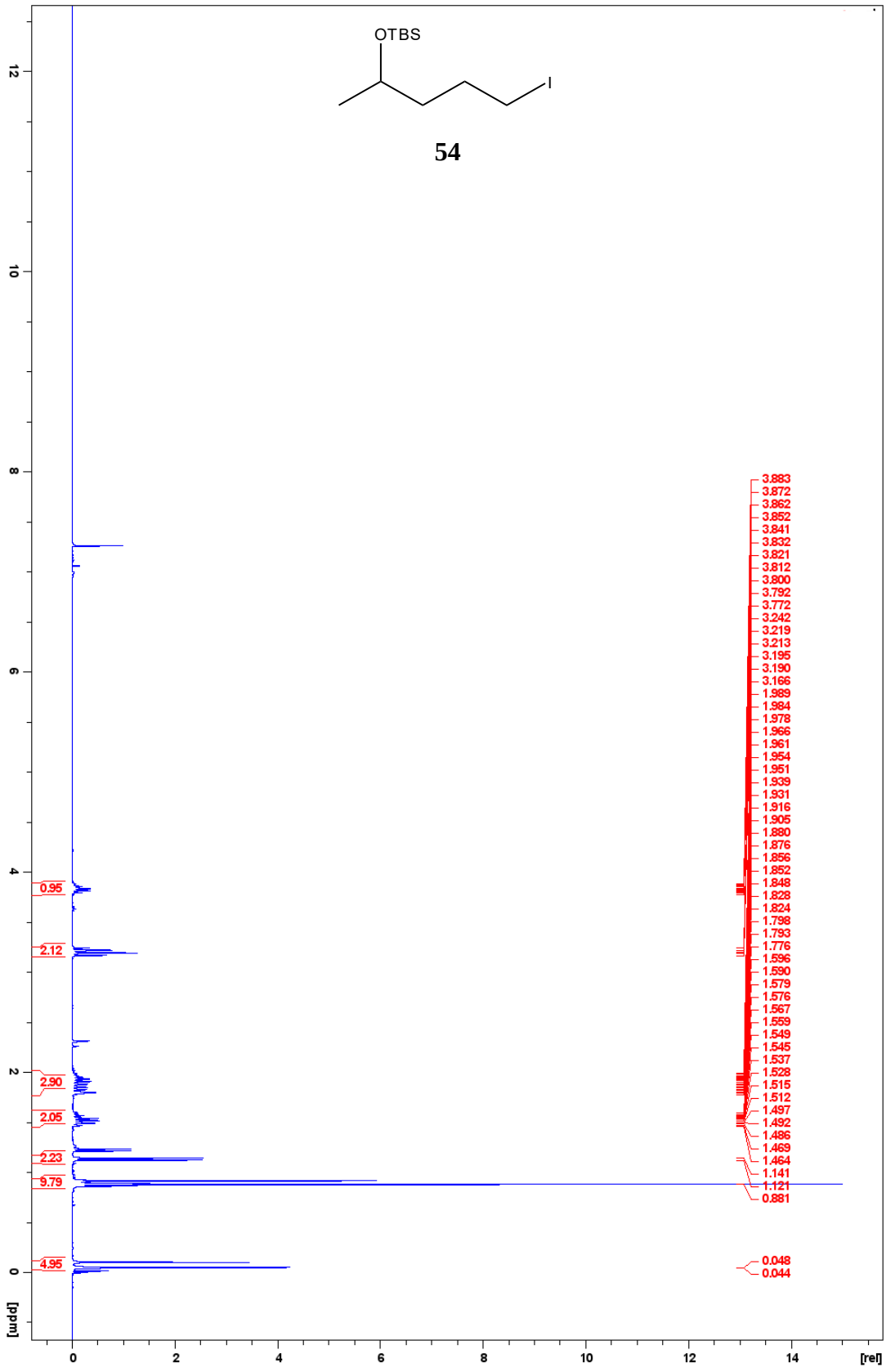
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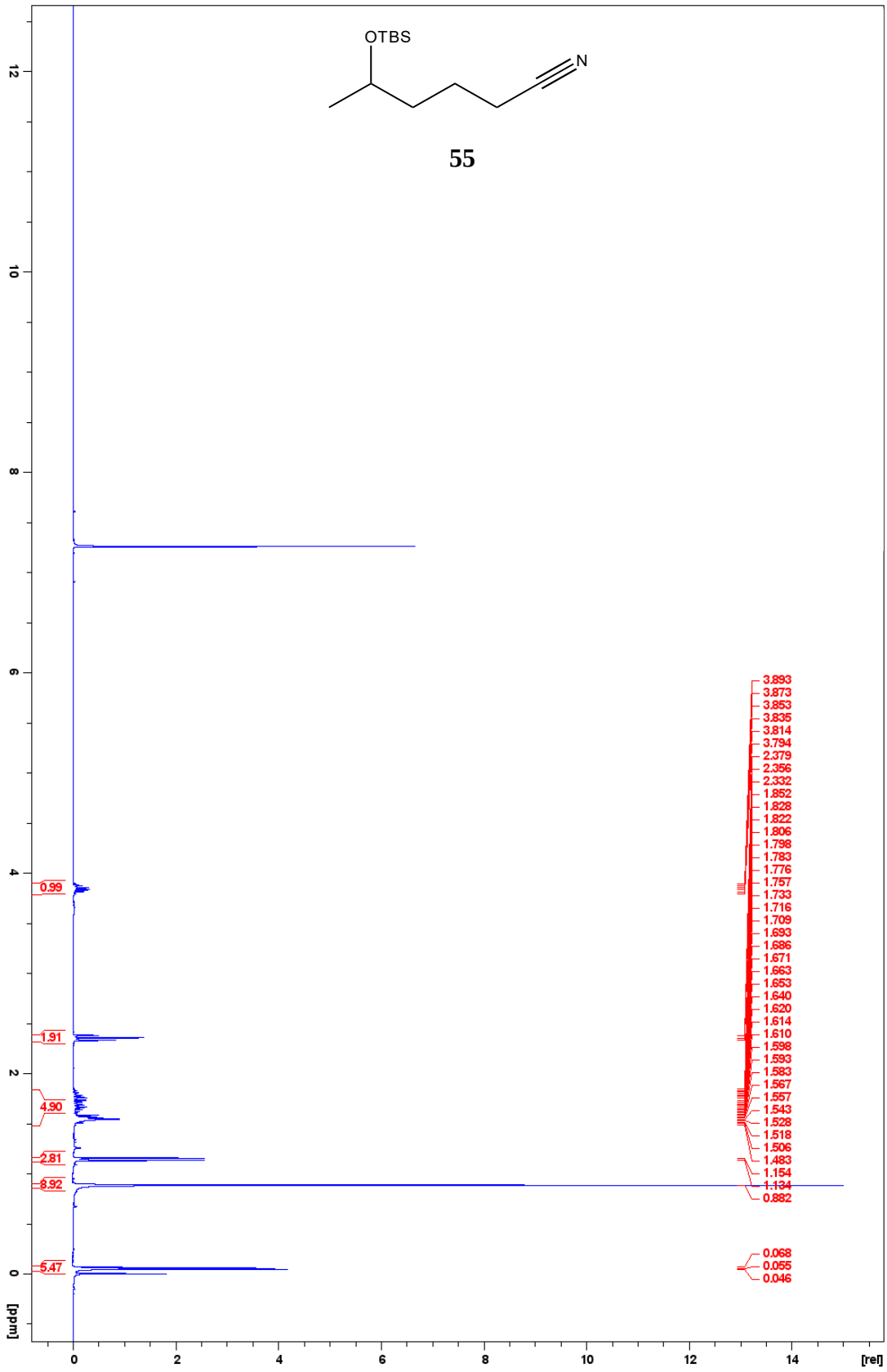
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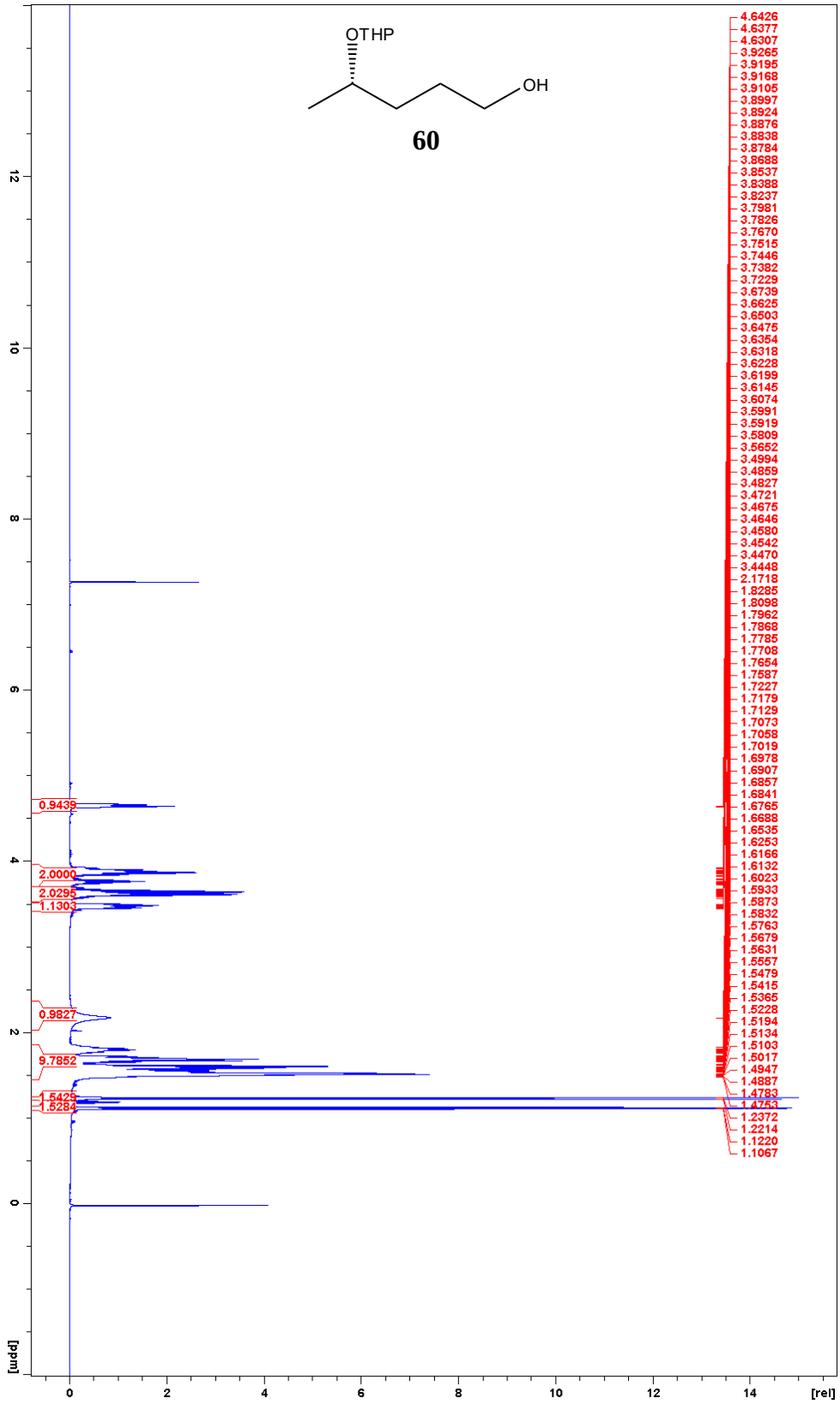
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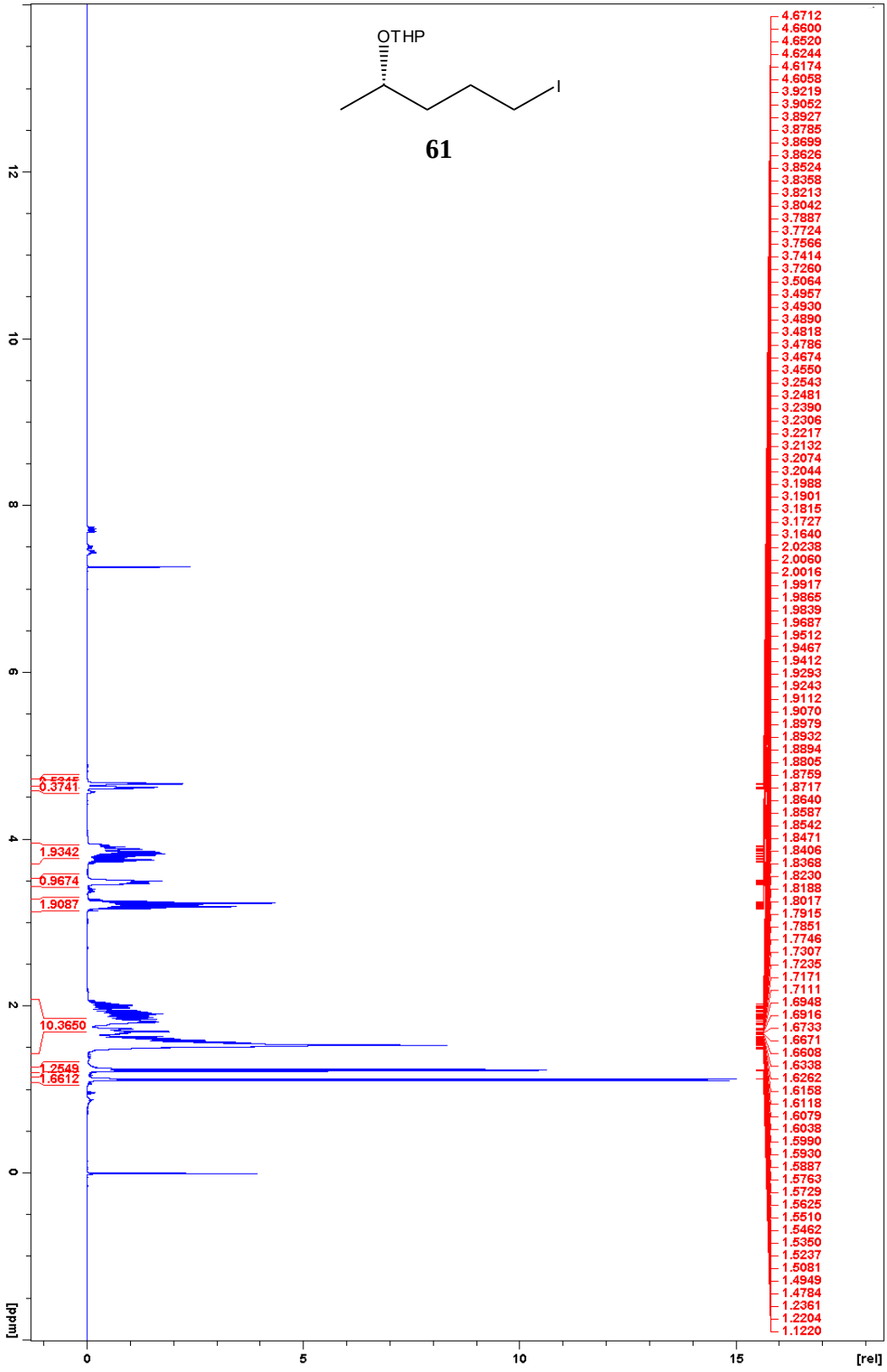
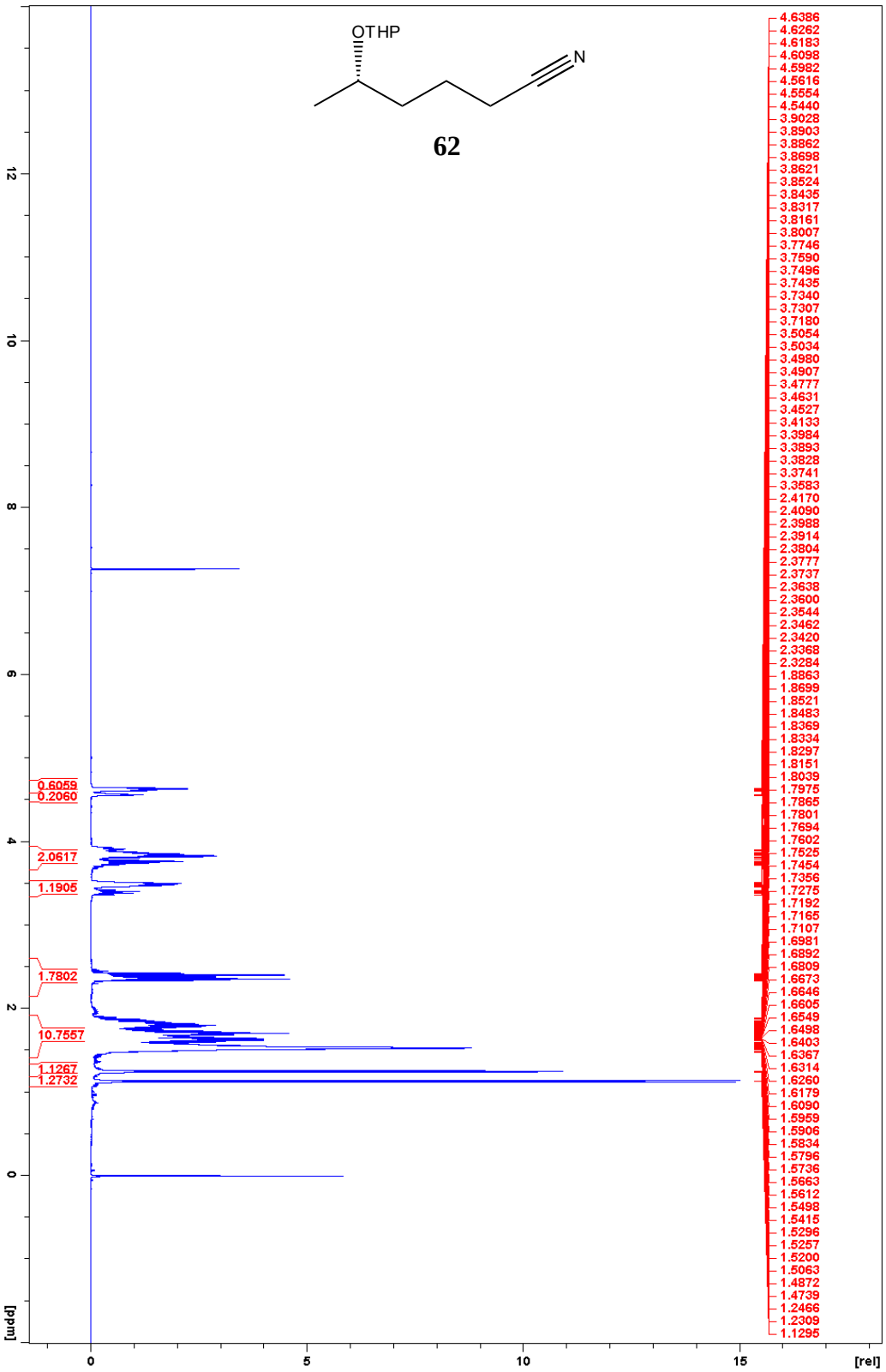
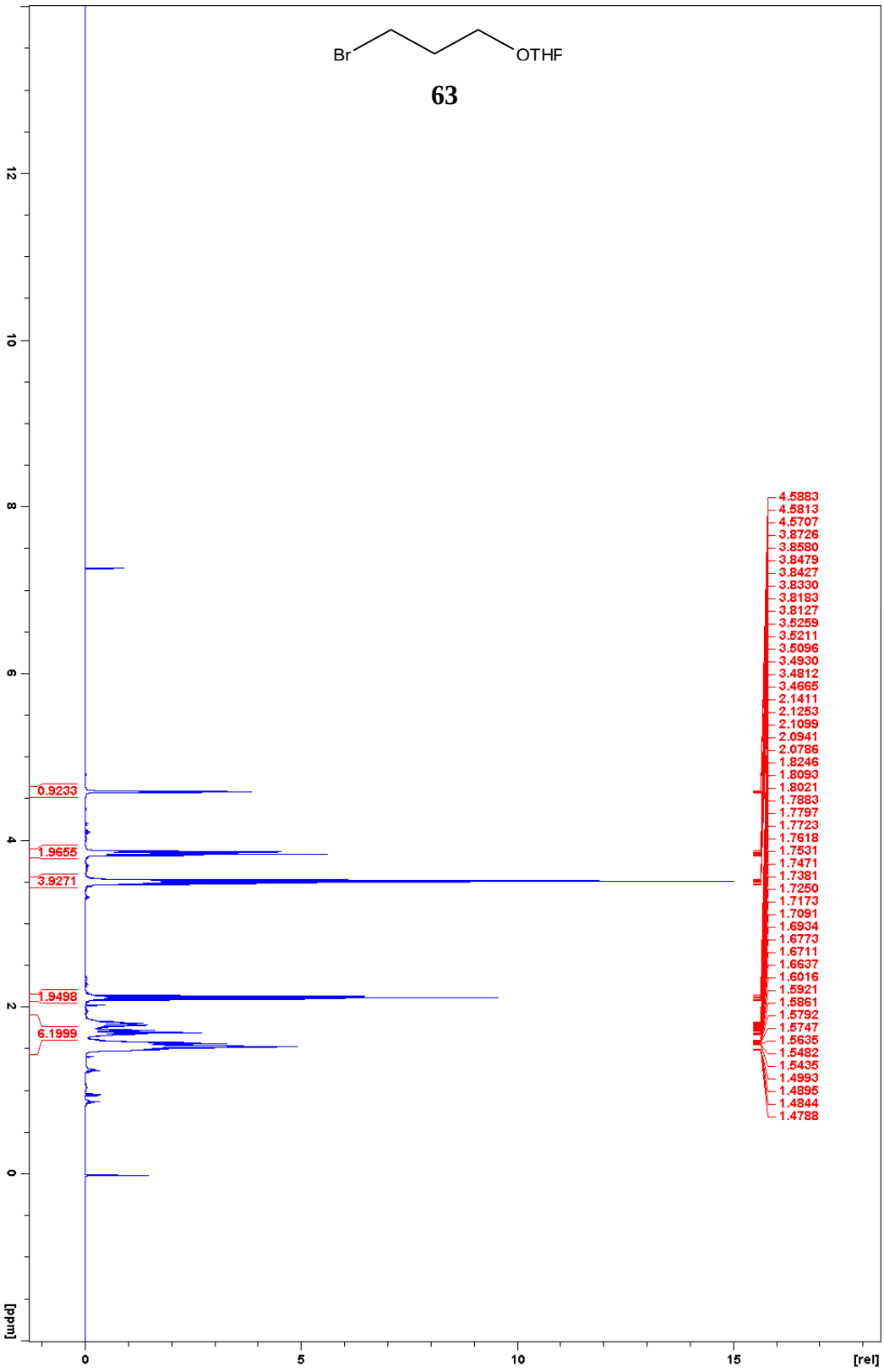
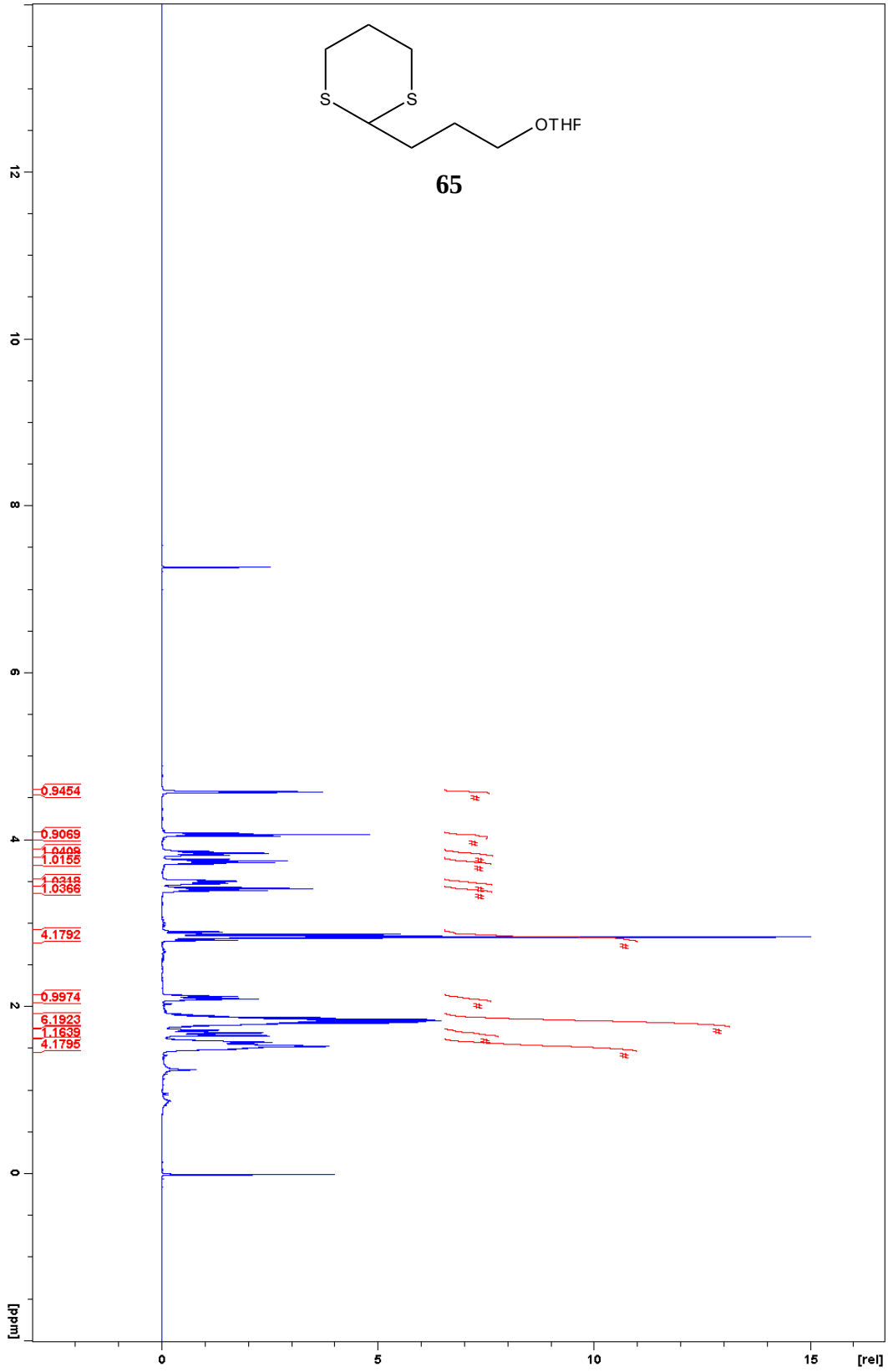
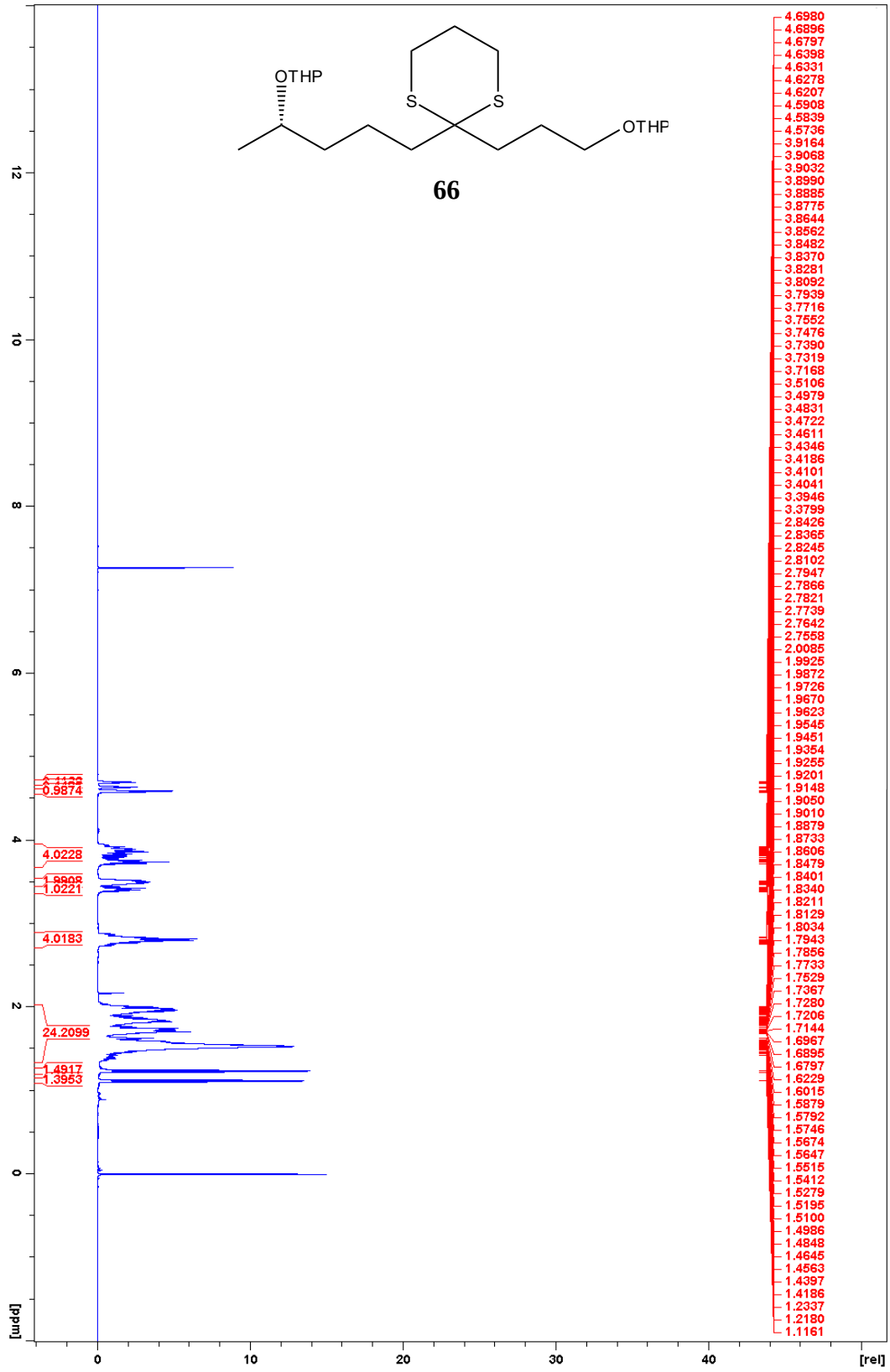
3.7981
3.7826
3.7670
3.7515
3.7446
3.7382
3.7229
3.6739
3.6625
3.6503
3.6475
3.6354
3.6318
3.6228
3.6199
3.6145
3.6074
3.5991
3.5919
3.5809
3.5652
3.4994
3.4859
3.4827
3.4721
3.4675
3.4646
3.4580
3.4542
3.4470
3.4448
2.1718
1.8285
1.8098
1.7962
1.7868
1.7785
1.7708
1.7654
1.7587
1.7227
1.7179
1.7129
1.7073
1.7058
1.7019
1.6978
1.6907
1.6857
1.6841
1.6765
1.6688
1.6535
1.6253
1.6166
1.6132
1.6023
1.5933
1.5873
1.5832
1.5763
1.5679
1.5631
1.5557
1.5479
1.5415
1.5365
1.5228
1.5194
1.5134
1.5103
1.5017
1.4947
1.4887
1.4783
1.4753
1.2372
1.2214
1.1220
1.1067
0.9439
2.0000
2.0295
1.1303
0.9827
9.7852
1.5429
1.5284
[ppm]
[rel]


OTHP
I
61
0.3741
1.9342
0.9674
1.9087
10.3650
1.2549
1.6612
[ppm]
[rel]


OTHP
N
62
0.6059
0.2060
2.0617
1.1905
1.7802
10.7557
1.1267
1.2732
[ppm]
[rel]

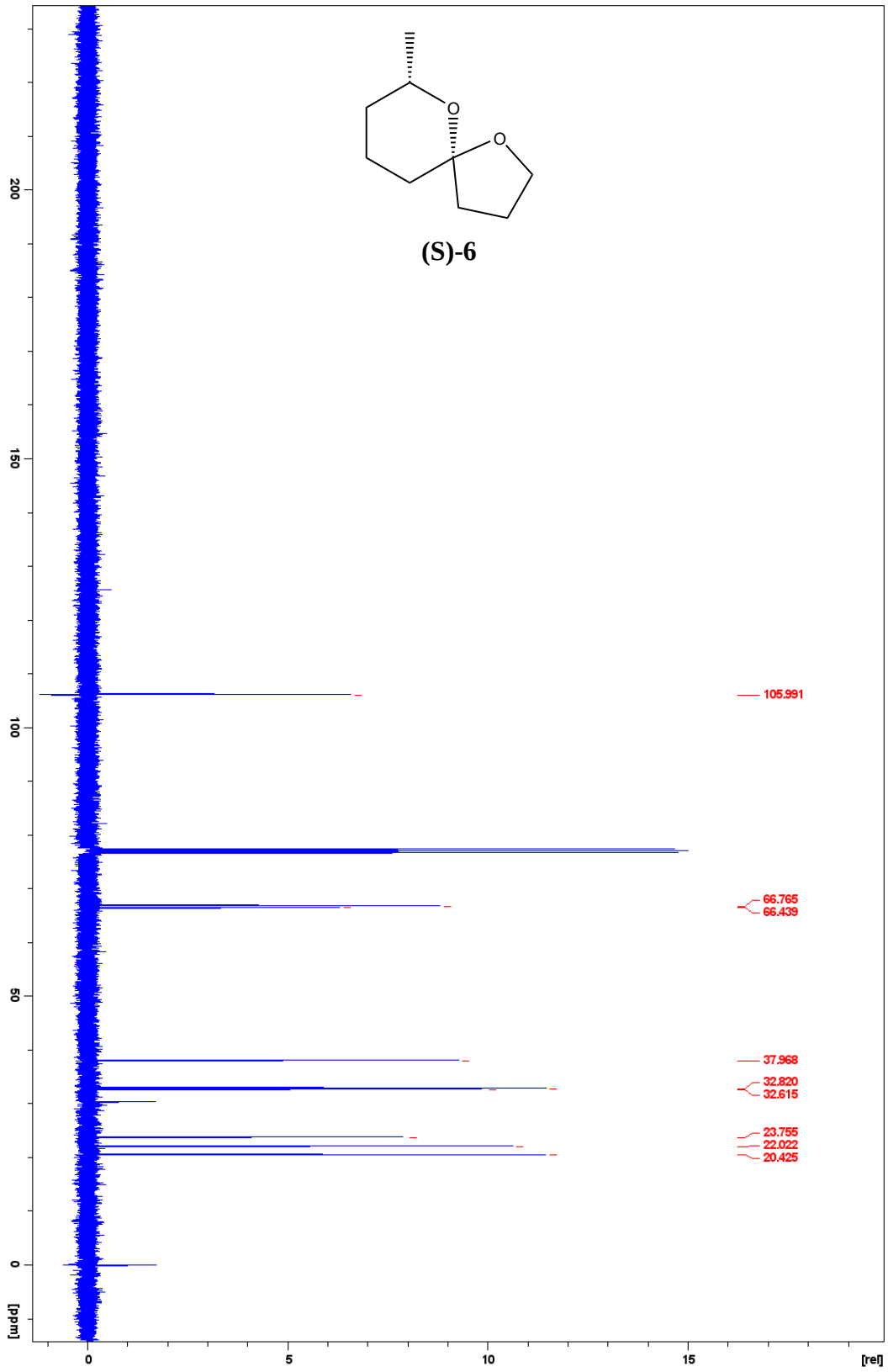

Br
OTHP
63
0.9233
1.9655
3.9271
1.9498
6.1999
4.5883
4.5813
4.5707
3.8726
3.8580
3.8479
3.8427
3.8330
3.8183
3.8127
3.5259
3.5211
3.5096
3.4930
3.4812
3.4665
2.1411
2.1253
2.1099
2.0941
2.0786
1.8246
1.8093
1.8021
1.7883
1.7797
1.7723
1.7618
1.7531
1.7471
1.7381
1.7250
1.7173
1.7091
1.6934
1.6773
1.6711
1.6637
1.6016
1.5921
1.5861
1.5792
1.5747
1.5635
1.5482
1.5435
1.4993
1.4895
1.4844
1.4788
[ppm]
[rel]


S
S
OTHF
65
0.9454
0.9069
1.0408
1.0158
1.0318
1.0366
4.1792
0.9974
6.1923
1.1639
4.1795
[ppm]
[rel]

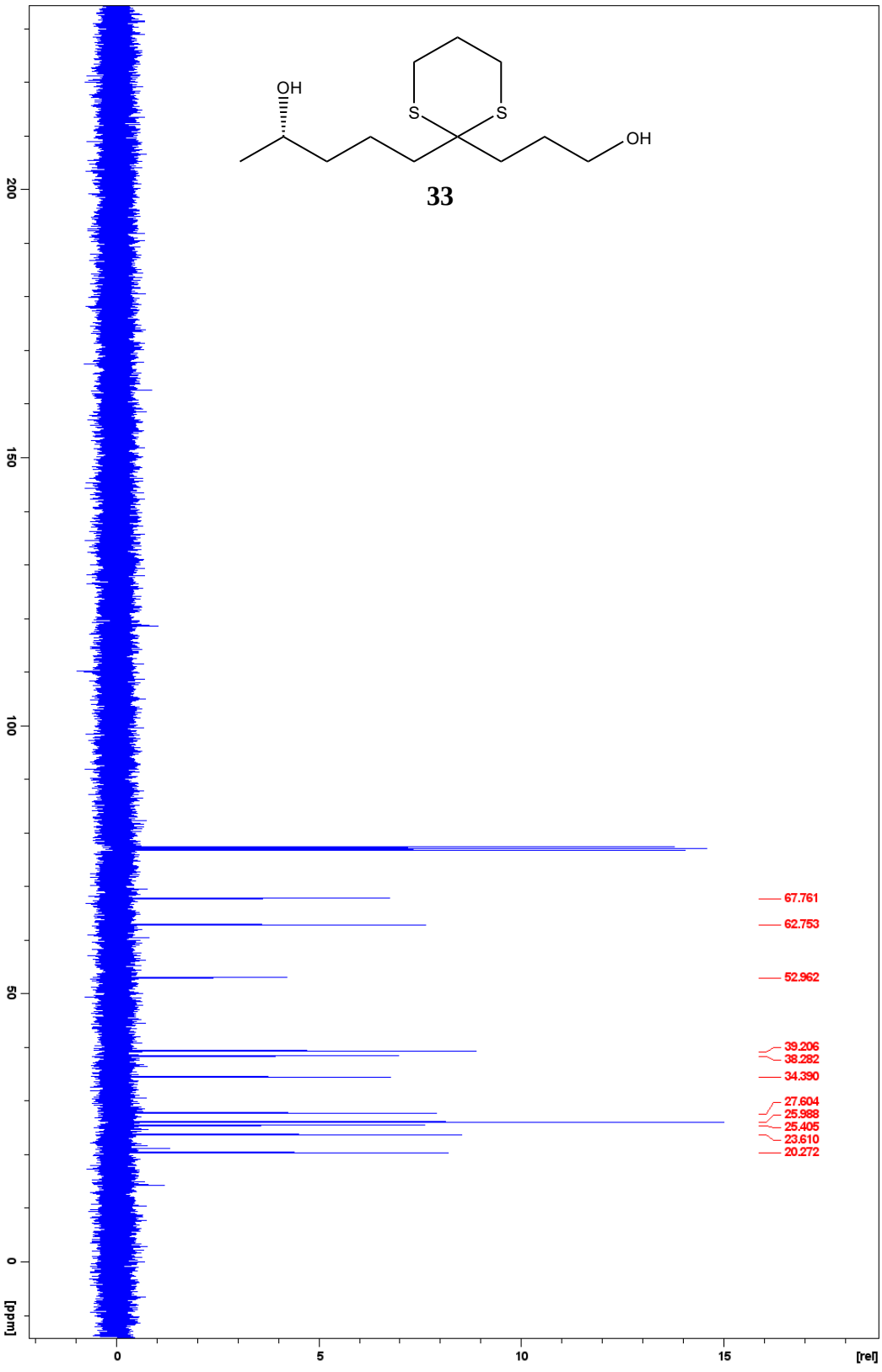

OTHP
S
S
OTHP
66
4.6980
4.6896
4.6797
4.6398
4.6331
4.6278
4.6207
4.5908
4.5839
4.5736
3.9164
3.9068
3.9032
3.8990
3.8885
3.8775
3.8644
3.8562
3.8482
3.8370
3.8281
3.8092
3.7939
3.7716
3.7552
3.7476
3.7390
3.7319
3.7168
3.5106
3.4979
3.4831
3.4722
3.4611
3.4346
3.4186
3.4101
3.4041
3.3946
3.3799
2.8426
2.8365
2.8245
2.8102
2.7947
2.7866
2.7821
2.7739
2.7642
2.7558
2.0085
1.9925
1.9872
1.9726
1.9670
1.9623
1.9545
1.9451
1.9354
1.9255
1.9201
1.9148
1.9050
1.9010
1.8879
1.8733
1.8606
1.8479
1.8401
1.8340
1.8211
1.8129
1.8034
1.7943
1.7856
1.7733
1.7529
1.7367
1.7280
1.7206
1.7144
1.6967
1.6895
1.6797
1.6229
1.6015
1.5879
1.5792
1.5746
1.5674
1.5647
1.5515
1.5412
1.5279
1.5195
1.5100
1.4986
1.4848
1.4645
1.4563
1.4397
1.4186
1.2337
1.2180
1.1161
0.9874
4.0228
1.0221
4.0183
24.2099
1.4917
1.3953
[ppm]
[rel]

Appendix B

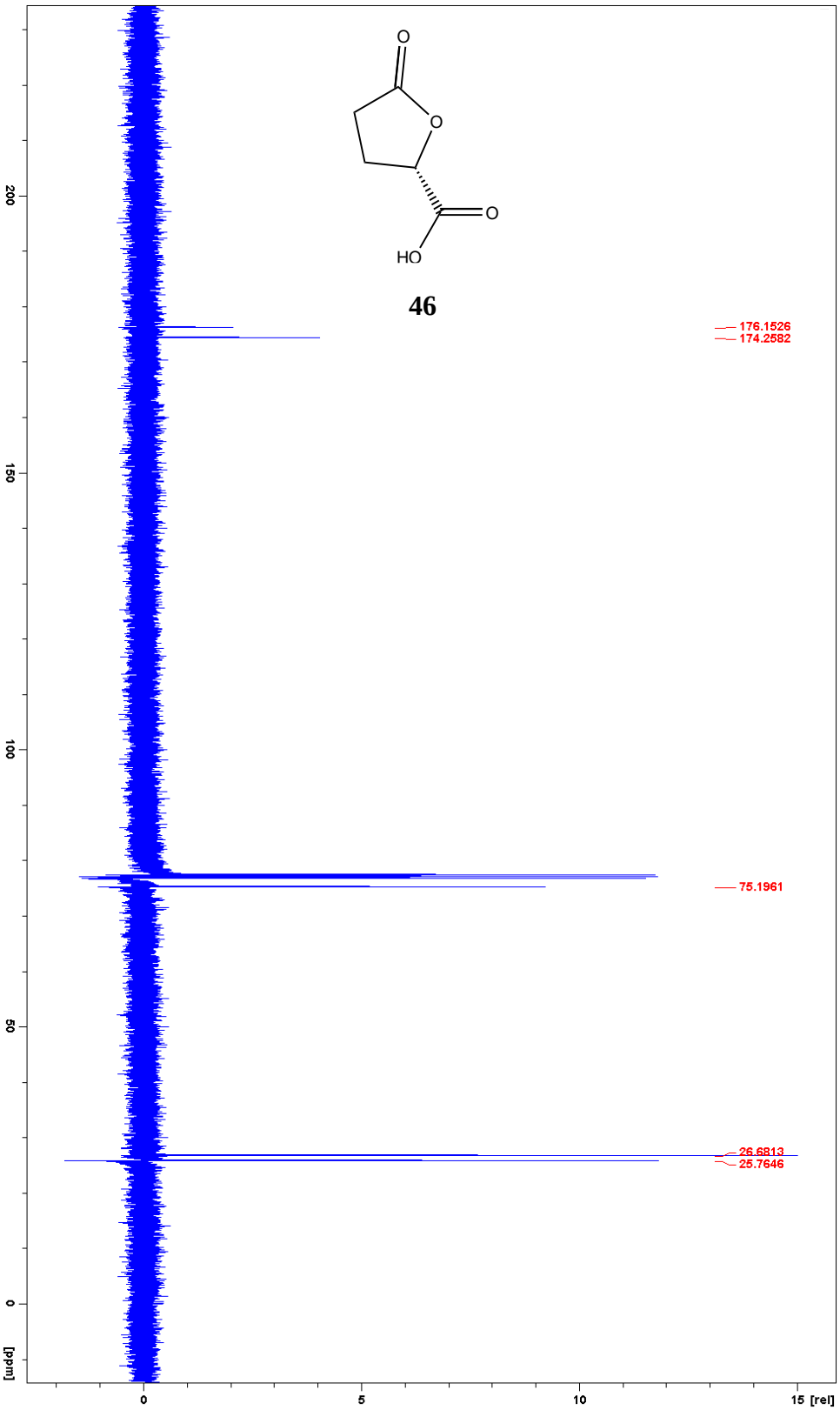
^{13}C NMR


O
O
200
150
100
50
0
[ppm]
0
5
10
15
[rel]
105.991
66.765
66.439
37.968
32.820
32.615
23.755
22.022
20.425

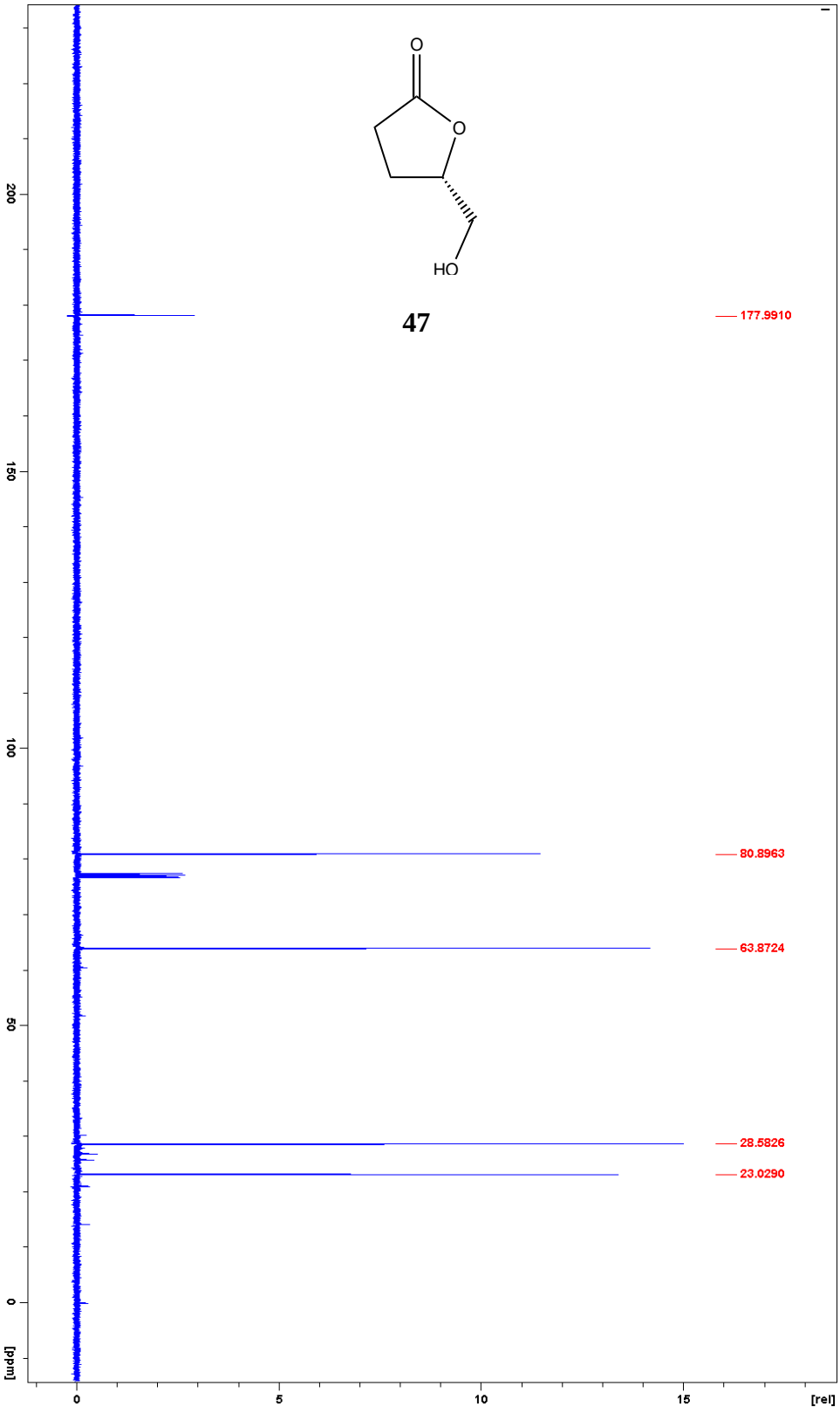
(S)-6

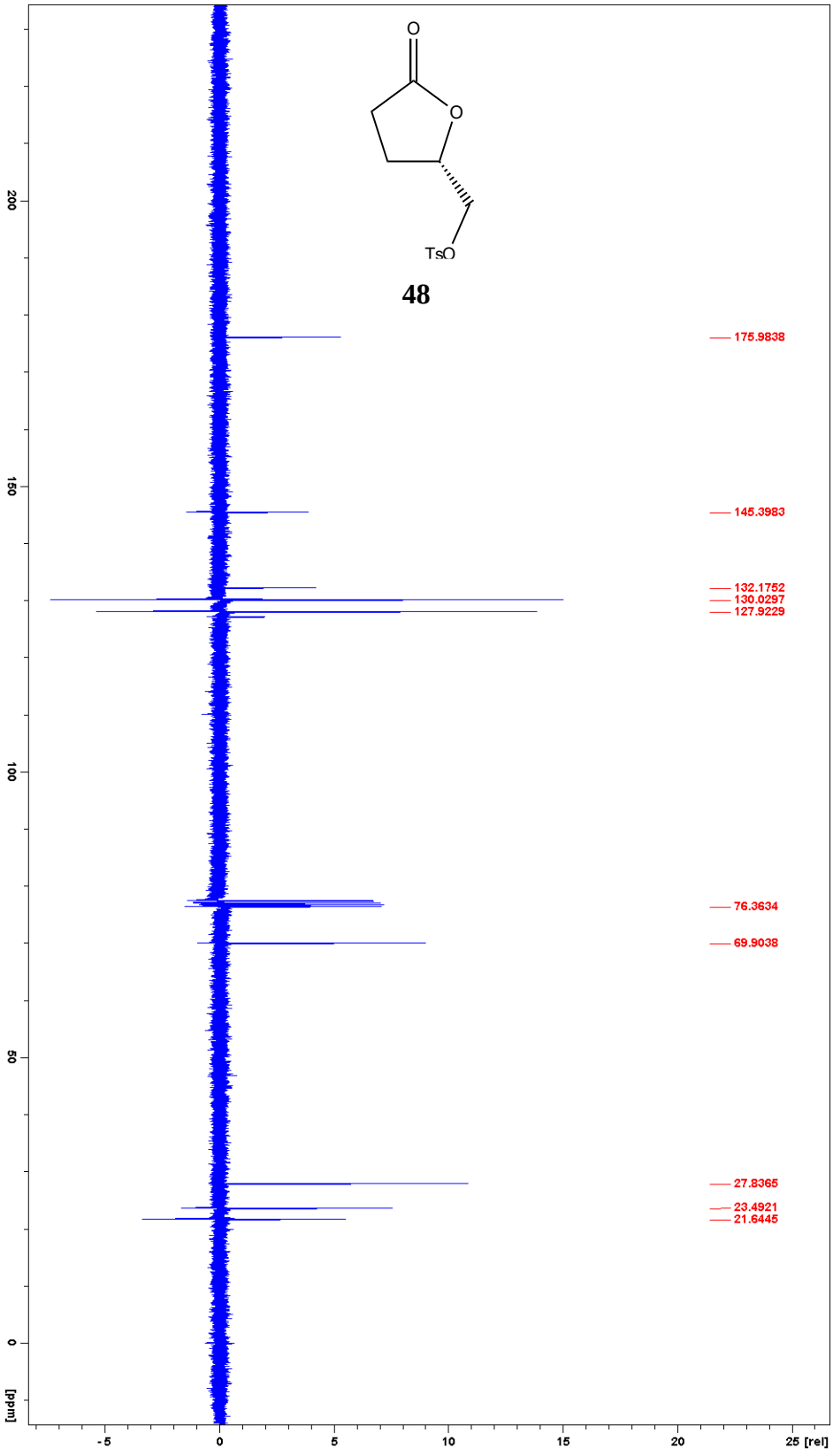

OH
S
S
OH
200
150
100
50
0
[ppm]
0
5
10
15
[rel]
67.761
62.753
52.962
39.206
38.282
34.390
27.604
25.988
25.405
23.610
20.272

33

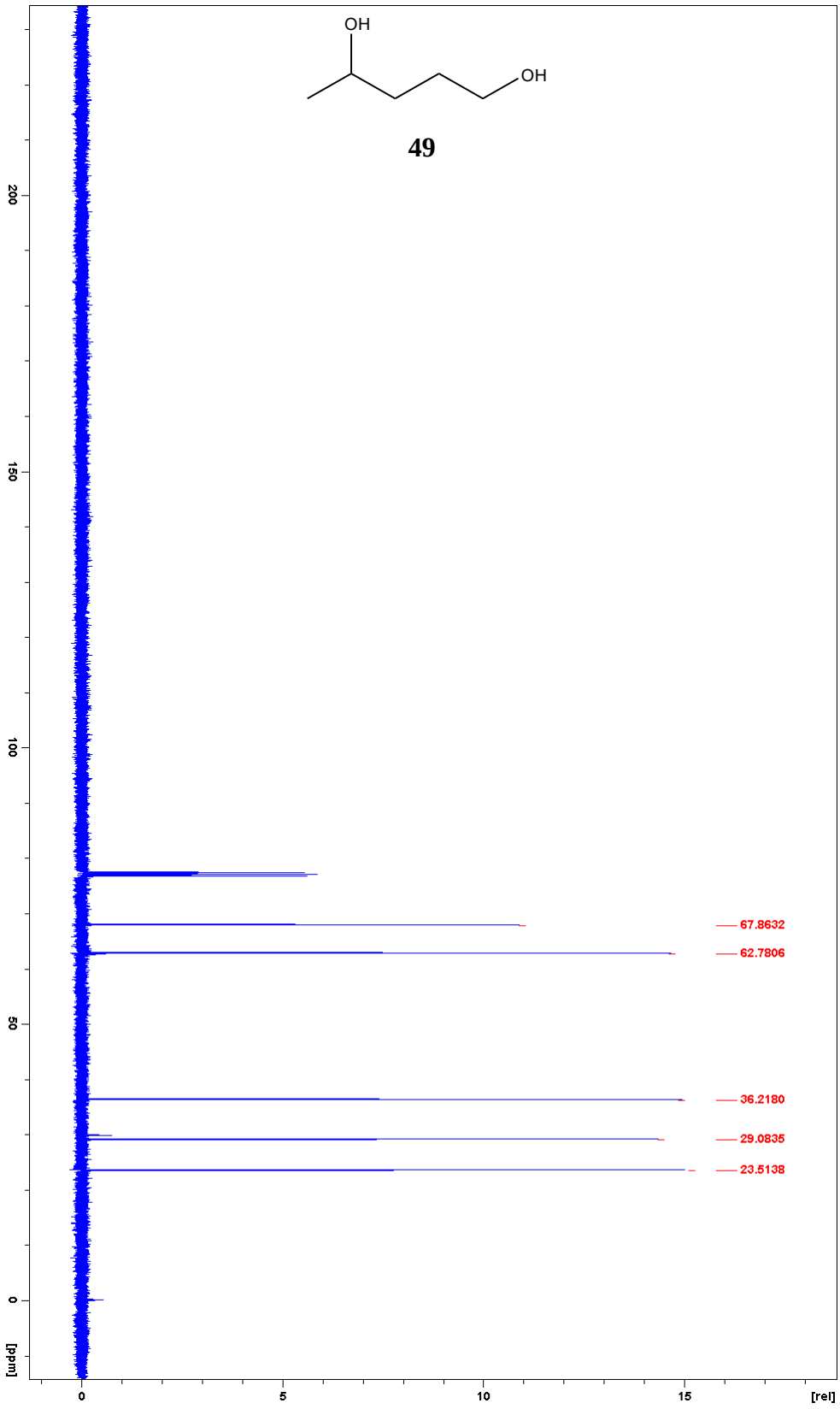

O
O
O
HO
200
150
100
50
0
[ppm]
176.1526
174.2582
75.1961
26.6813
25.7646
0
5
10
15 [rel]

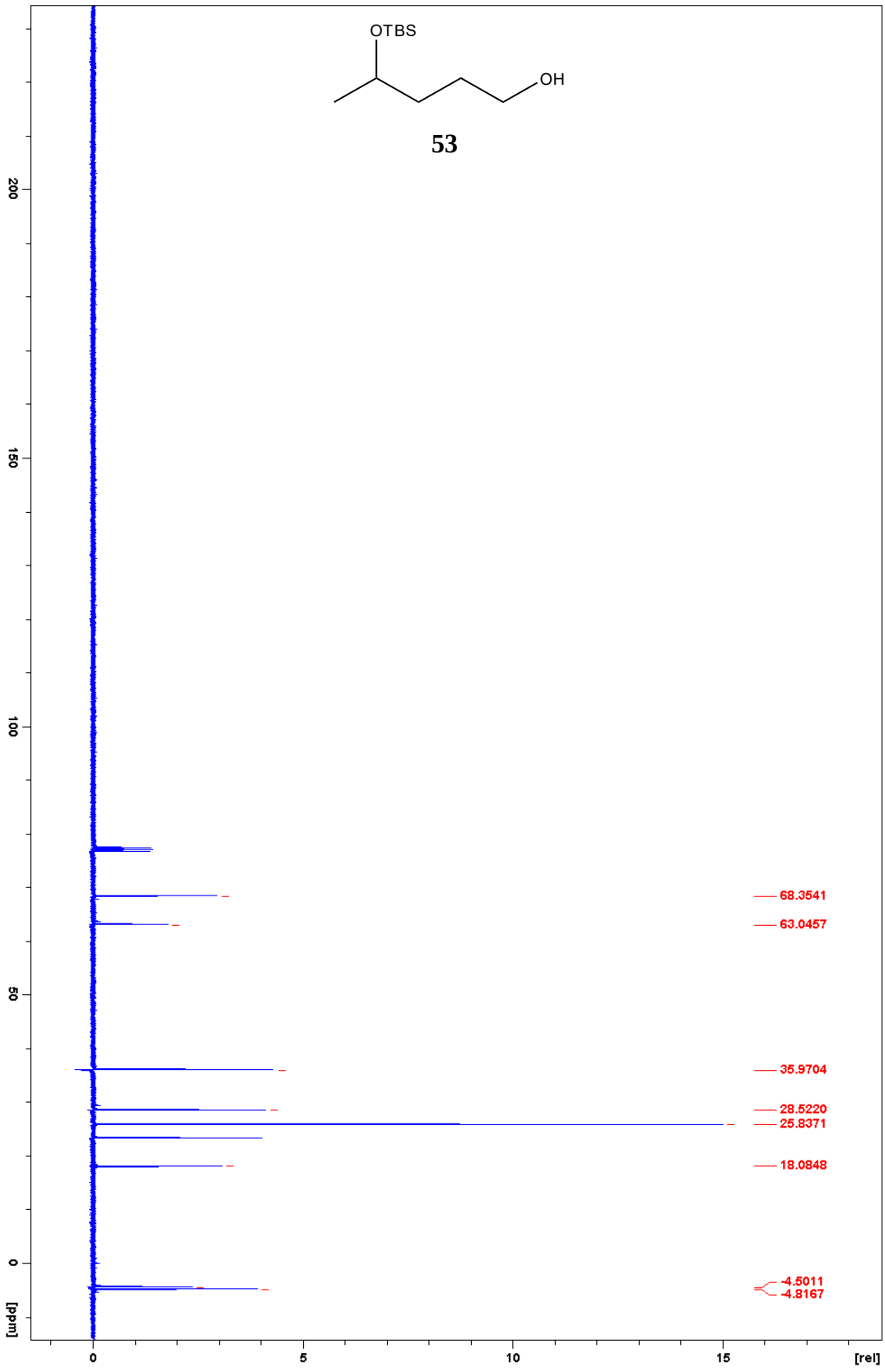
46


O
O
HO
47
177.9910
80.8963
63.8724
28.5826
23.0290
200
150
100
50
0
[ppm]
0
5
10
15
[rel]

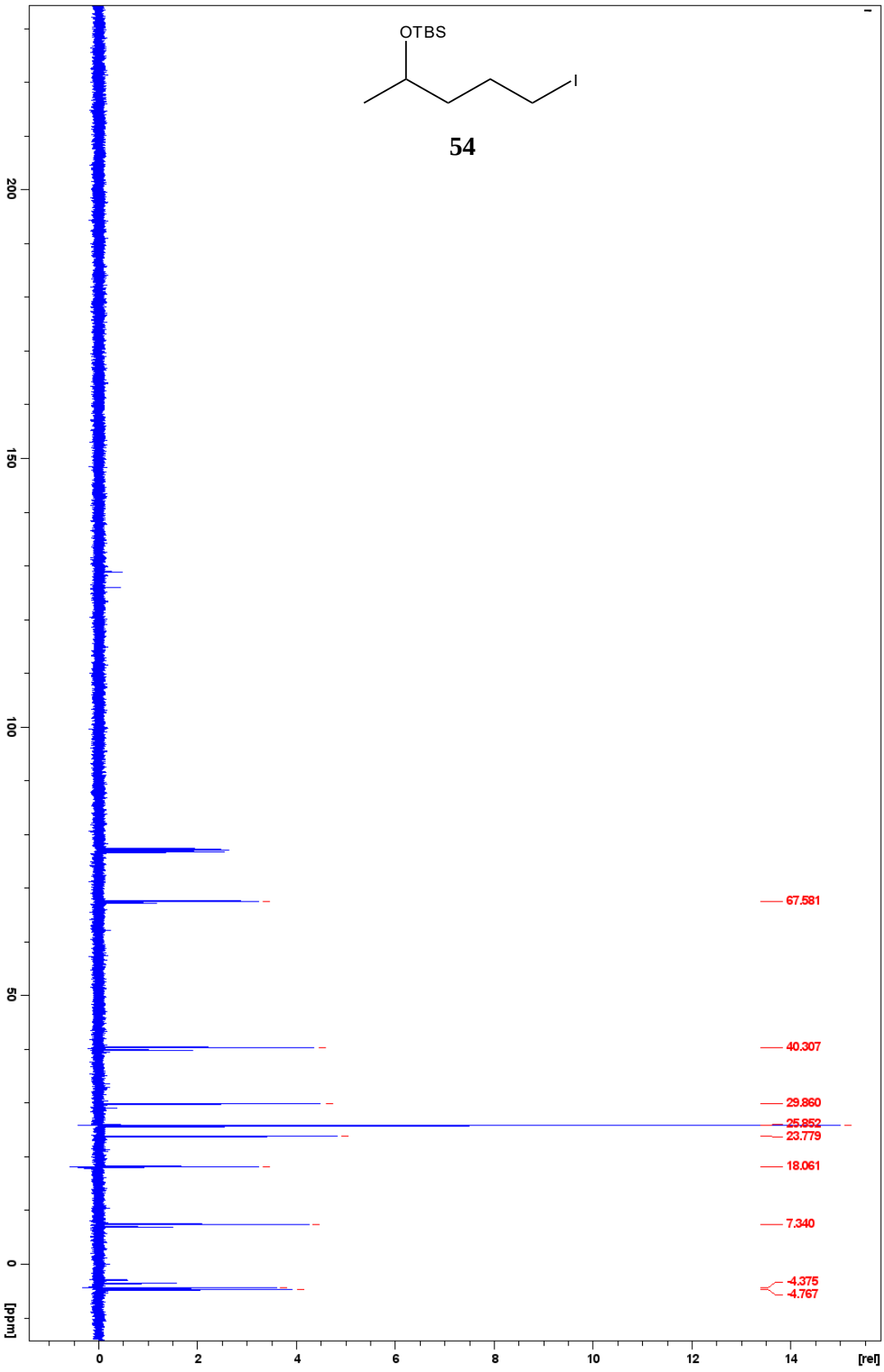

O
O
TsO
175.9838
145.3983
132.1752
130.0297
127.9229
76.3634
69.9038
27.8365
23.4921
21.6445
200
150
100
50
0
[ppm]
-5
0
5
10
15
20
25 [rel]

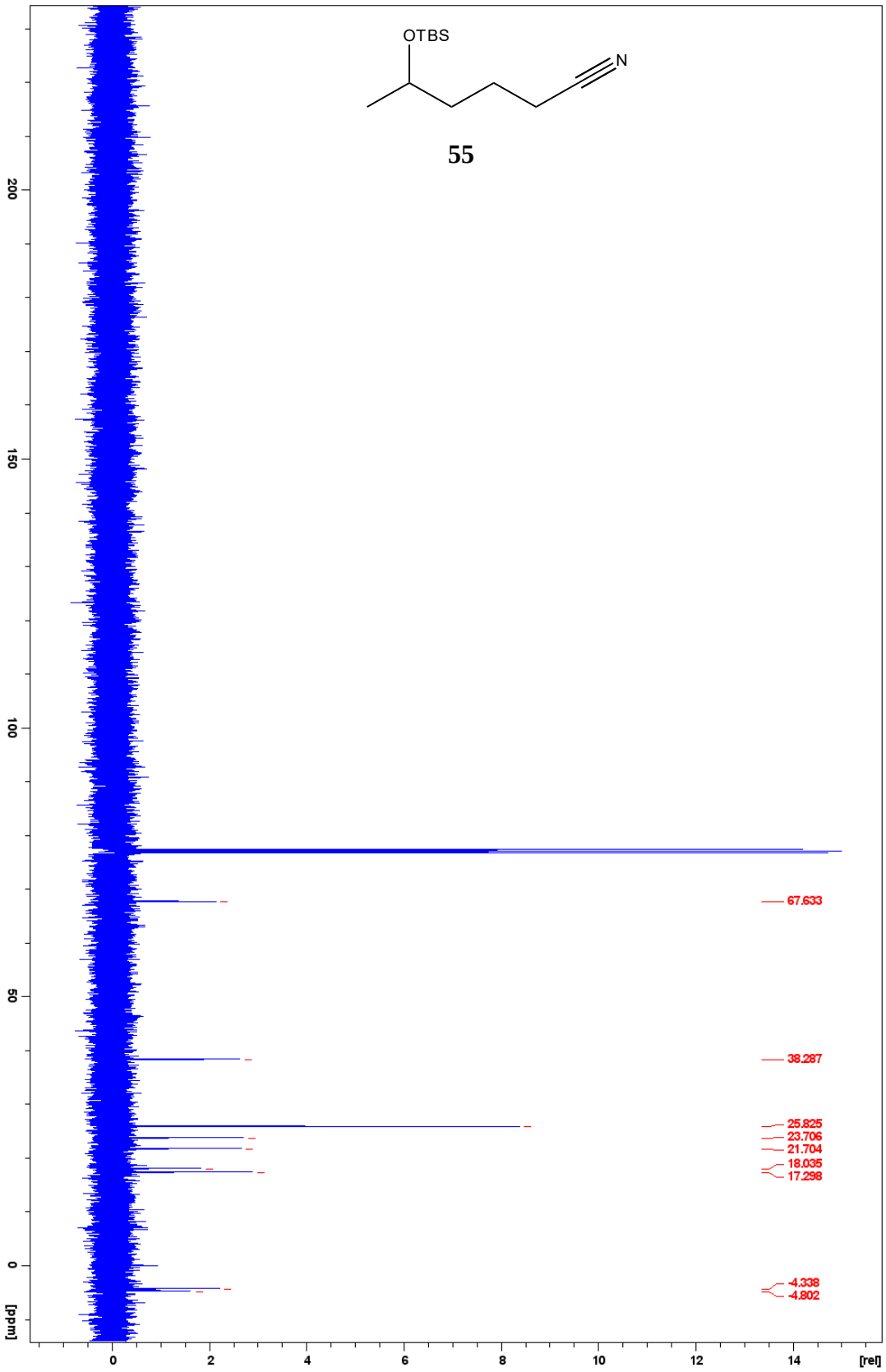
48


OH
OH
49
200
150
100
50
0
[ppm]
67.8632
62.7806
36.2180
29.0835
23.5138
0
5
10
15
[rel]

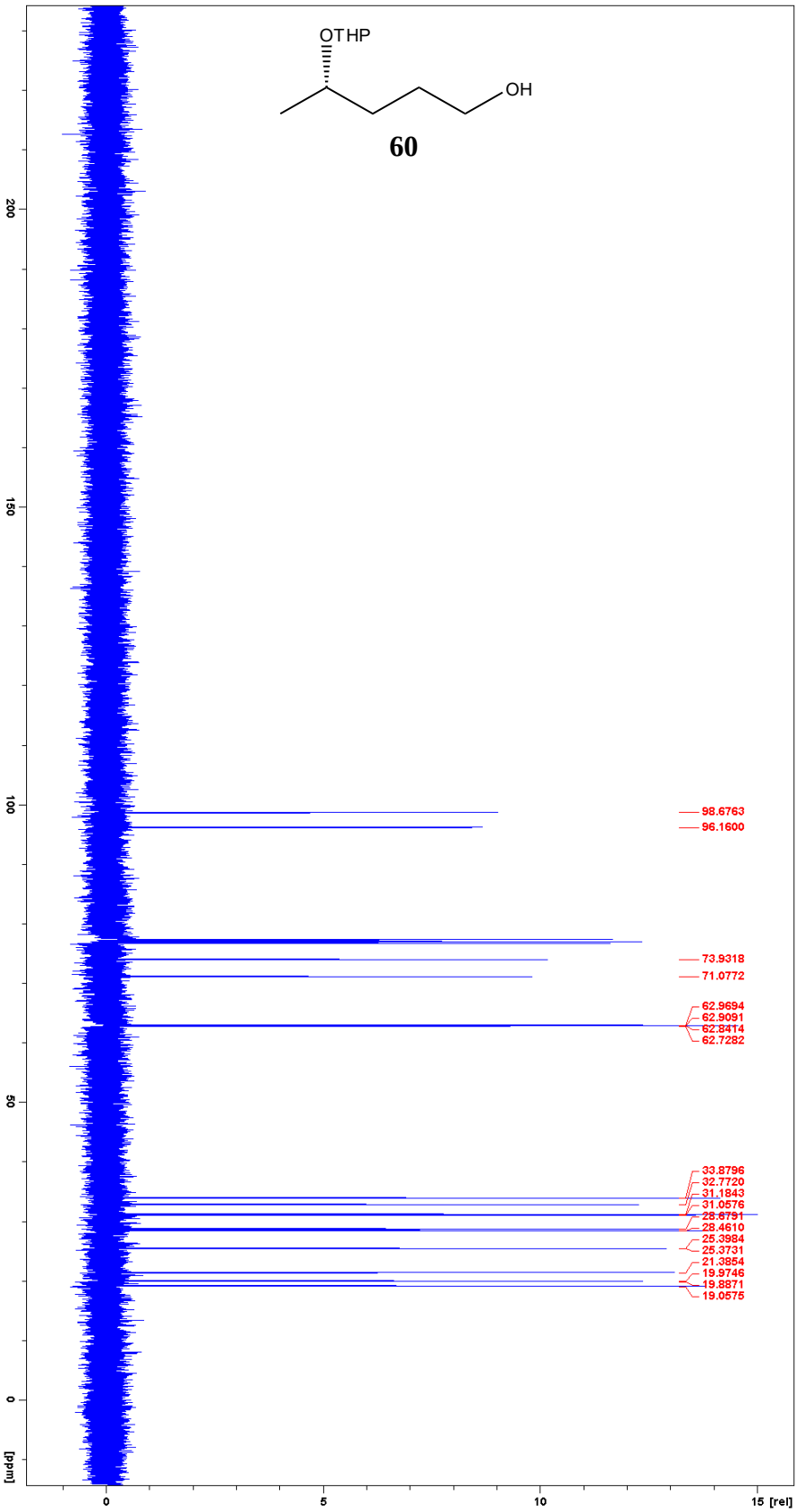

OTBS
OH
68.3541
63.0457
35.9704
28.5220
25.8371
18.0848
-4.5011
-4.8167
200
150
100
50
0
[ppm]
0
5
10
15
[rel]

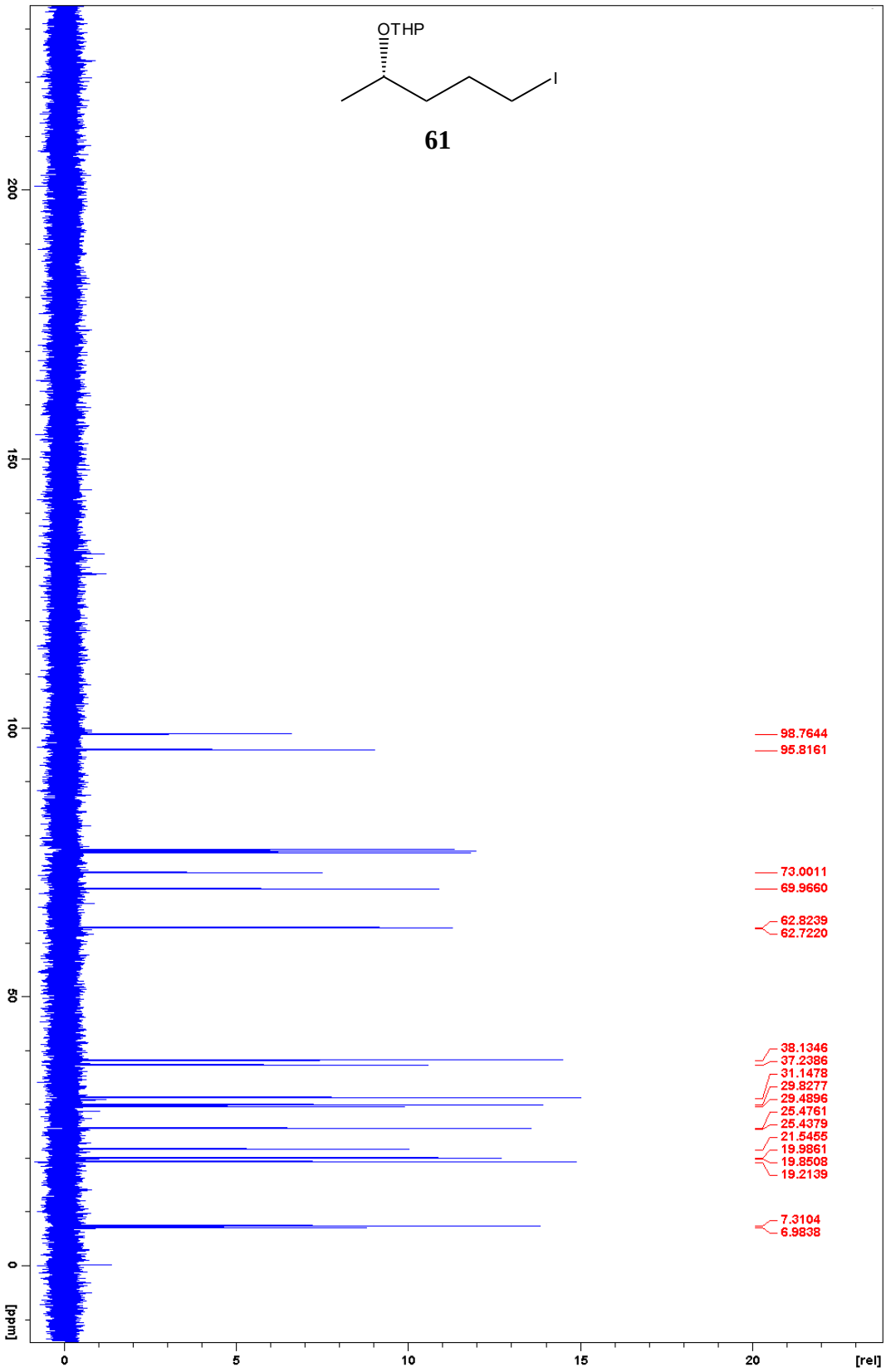
53

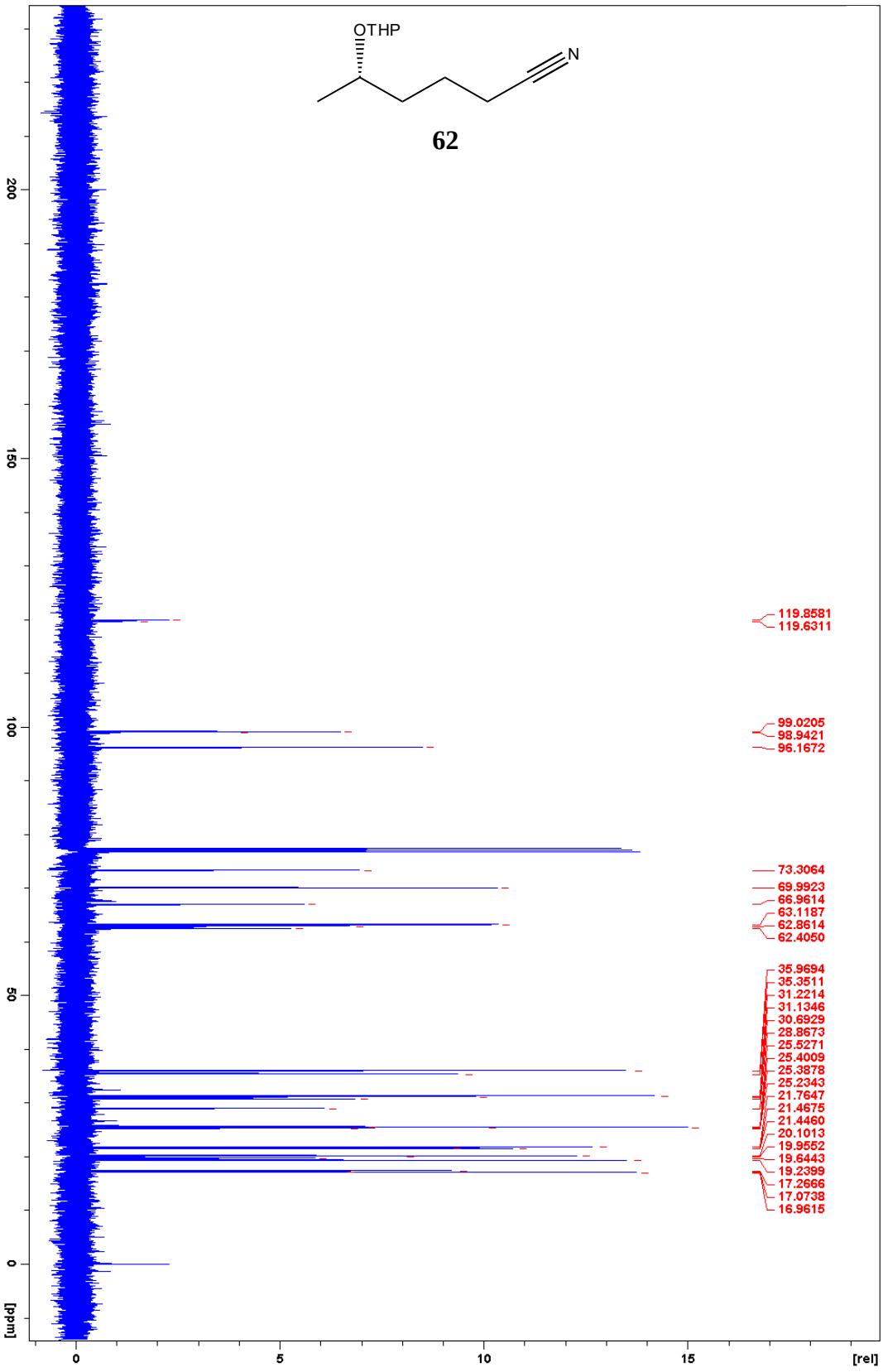

OTBS
I
54
200
150
100
50
0
[ppm]
0
2
4
6
8
10
12
14
[rel]
67.581
40.307
29.860
25.852
23.779
18.061
7.340
4.375
4.767

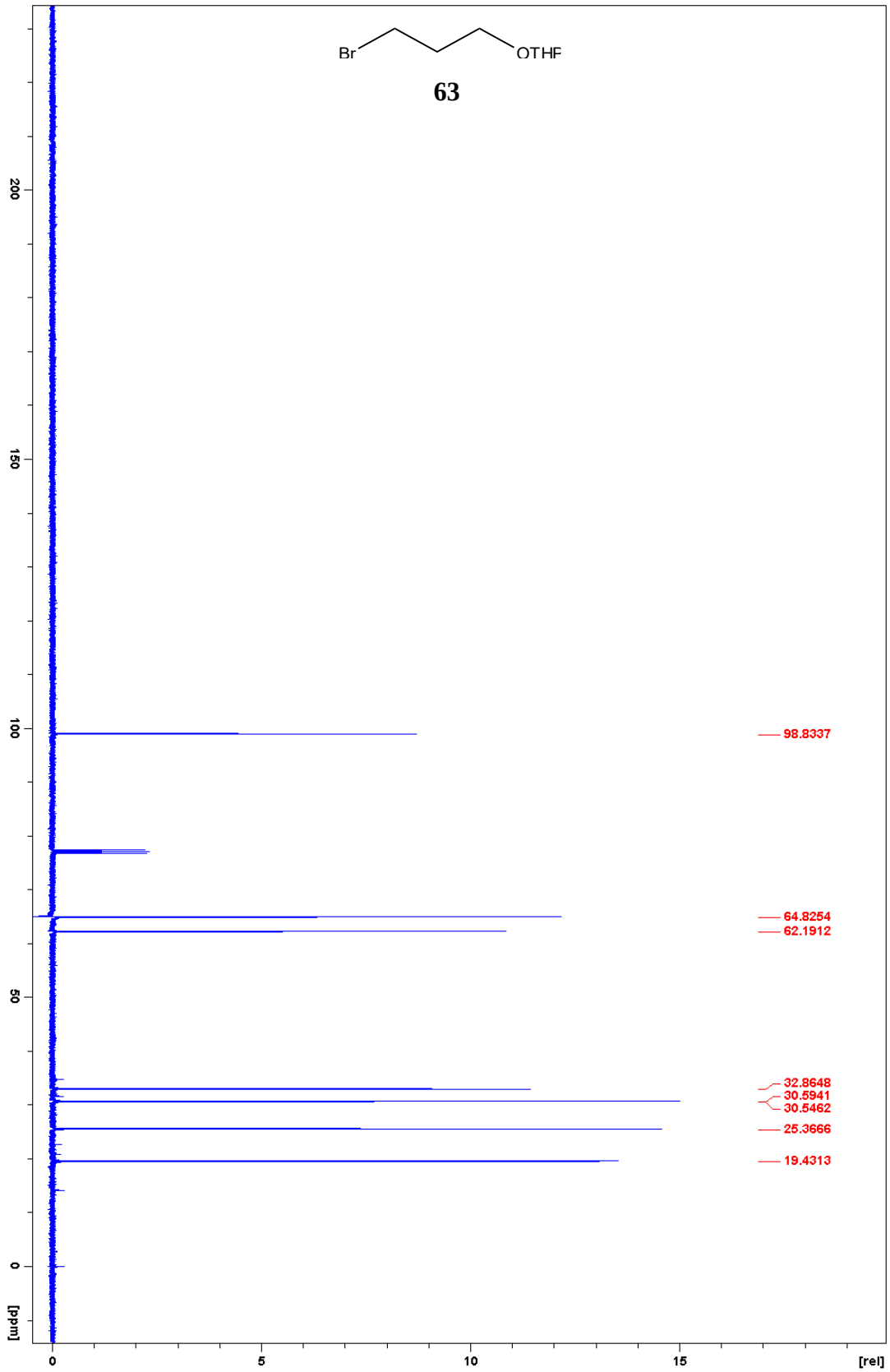

OTBS
N
67.633
38.287
25.825
23.706
21.704
18.035
17.298
-4.338
-4.802
200
150
100
50
0
[ppm]
0
2
4
6
8
10
12
14
[rel]

55

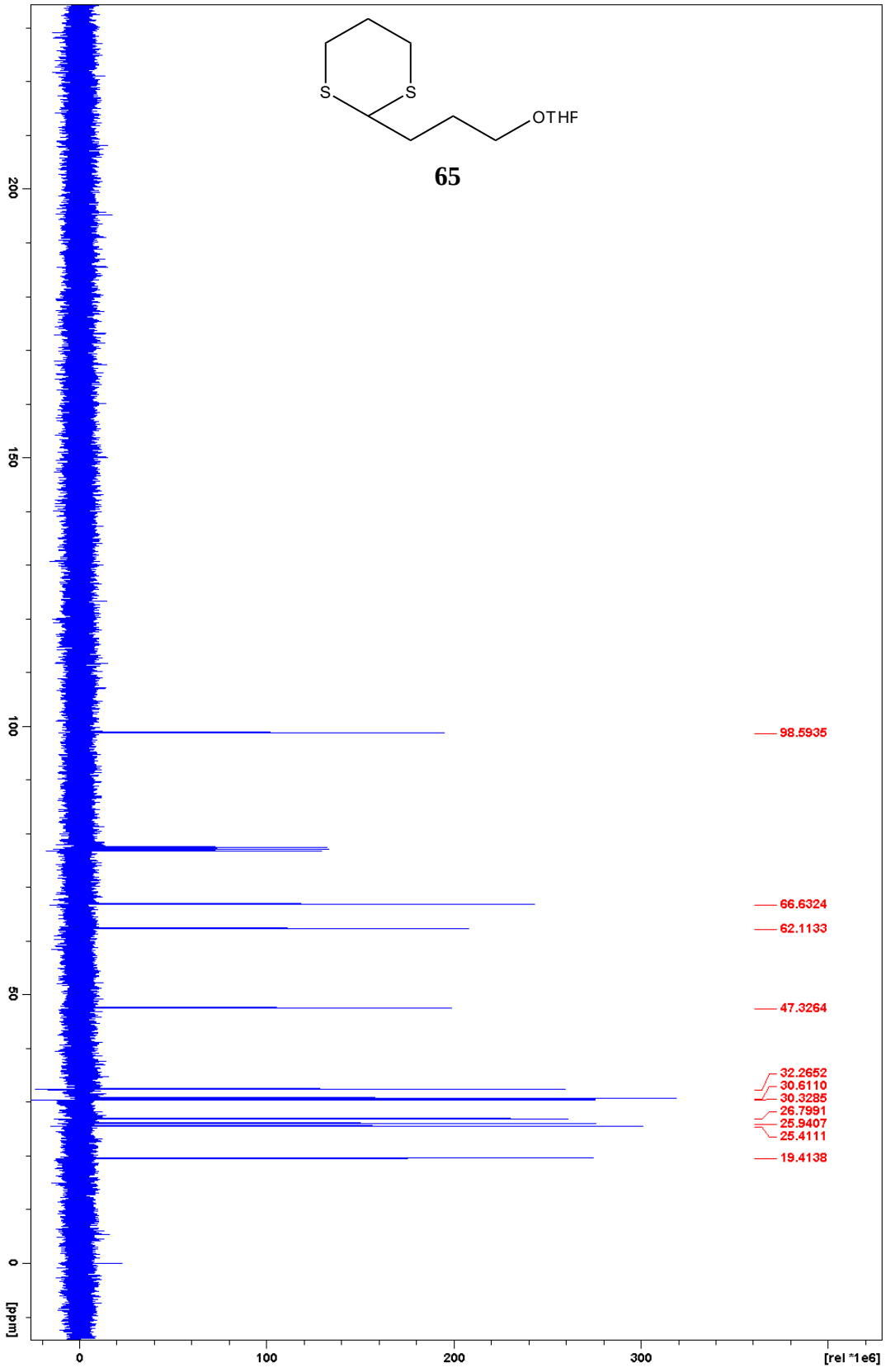

OTHP
OH
60
200
150
100
50
0
[ppm]
0
5
10
15 [rel]
98.6763
96.1600
73.9318
71.0772
62.9694
62.9091
62.8414
62.7282
33.8796
32.7720
31.1843
31.0576
28.6791
28.4610
25.3984
25.3731
21.3854
19.9746
19.8871
19.0575


OTHP
I
61
200
150
100
50
0
[ppm]
0
5
10
15
20
[rel]
98.7644
95.8161
73.0011
69.9660
62.8239
62.7220
38.1346
37.2386
31.1478
29.8277
29.4896
25.4761
25.4379
21.5455
19.9861
19.8508
19.2139
7.3104
6.9838

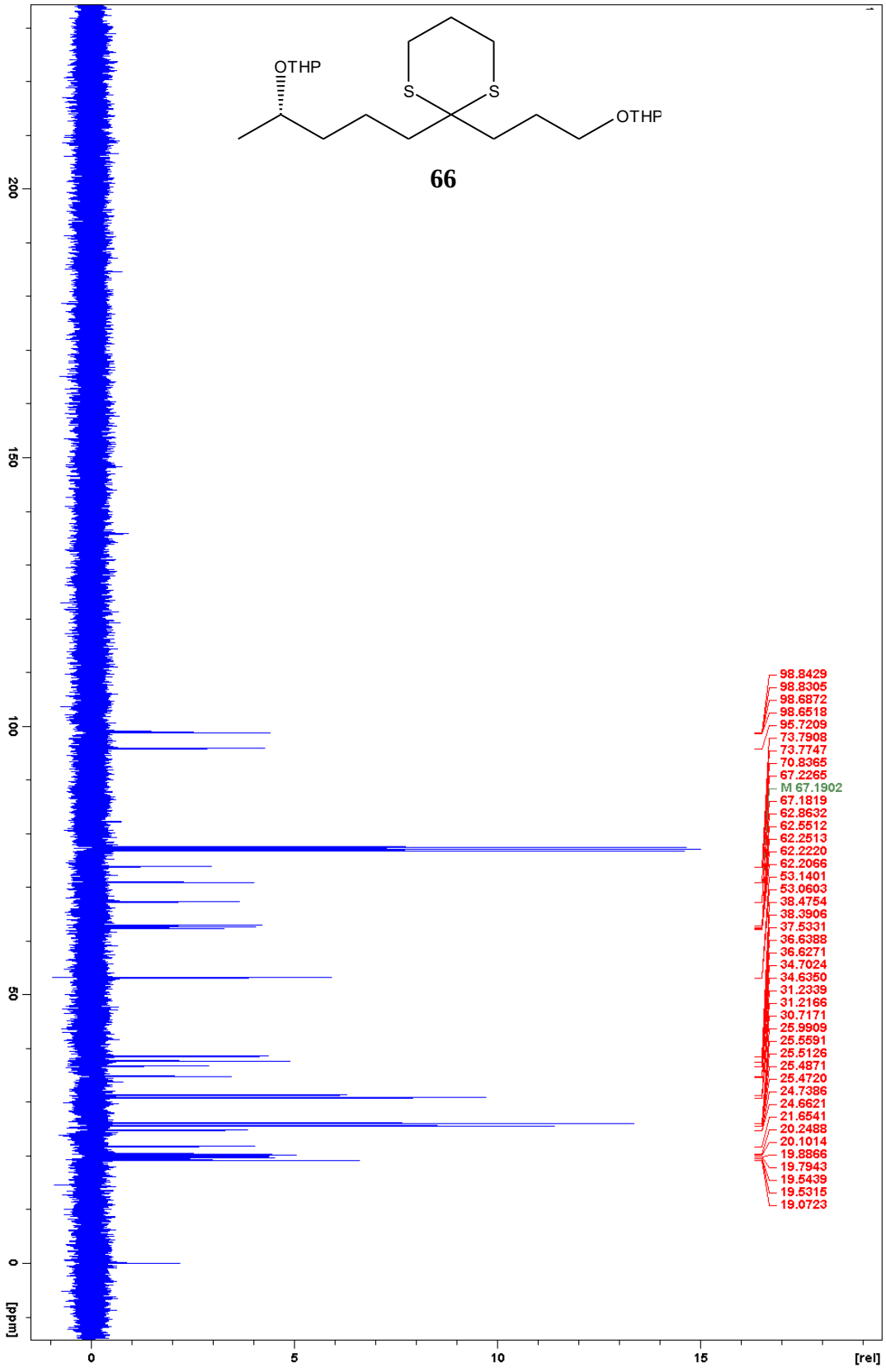

OTHP
N
62
119.8581
119.6311
99.0205
98.9421
96.1672
73.3064
69.9923
66.9614
63.1187
62.8614
62.4050
35.9694
35.3511
31.2214
31.1346
30.6929
28.8673
25.5271
25.4009
25.3878
25.2343
21.7647
21.4675
21.4460
20.1013
19.9552
19.6443
19.2399
17.2666
17.0738
16.9615
200
150
100
50
0
[ppm]
0
5
10
15
[rel]


Br
OTHP
98.8337
64.8254
62.1912
32.8648
30.5941
30.5462
25.3666
19.4313
200
150
100
50
0
[ppm]
0
5
10
15
[rel]

63


S
S
OTHP
98.5935
66.6324
62.1133
47.3264
32.2652
30.6110
30.3285
26.7991
25.9407
25.4111
19.4138
200
150
100
50
0
[ppm]
0
100
200
300
[rel *1e6]

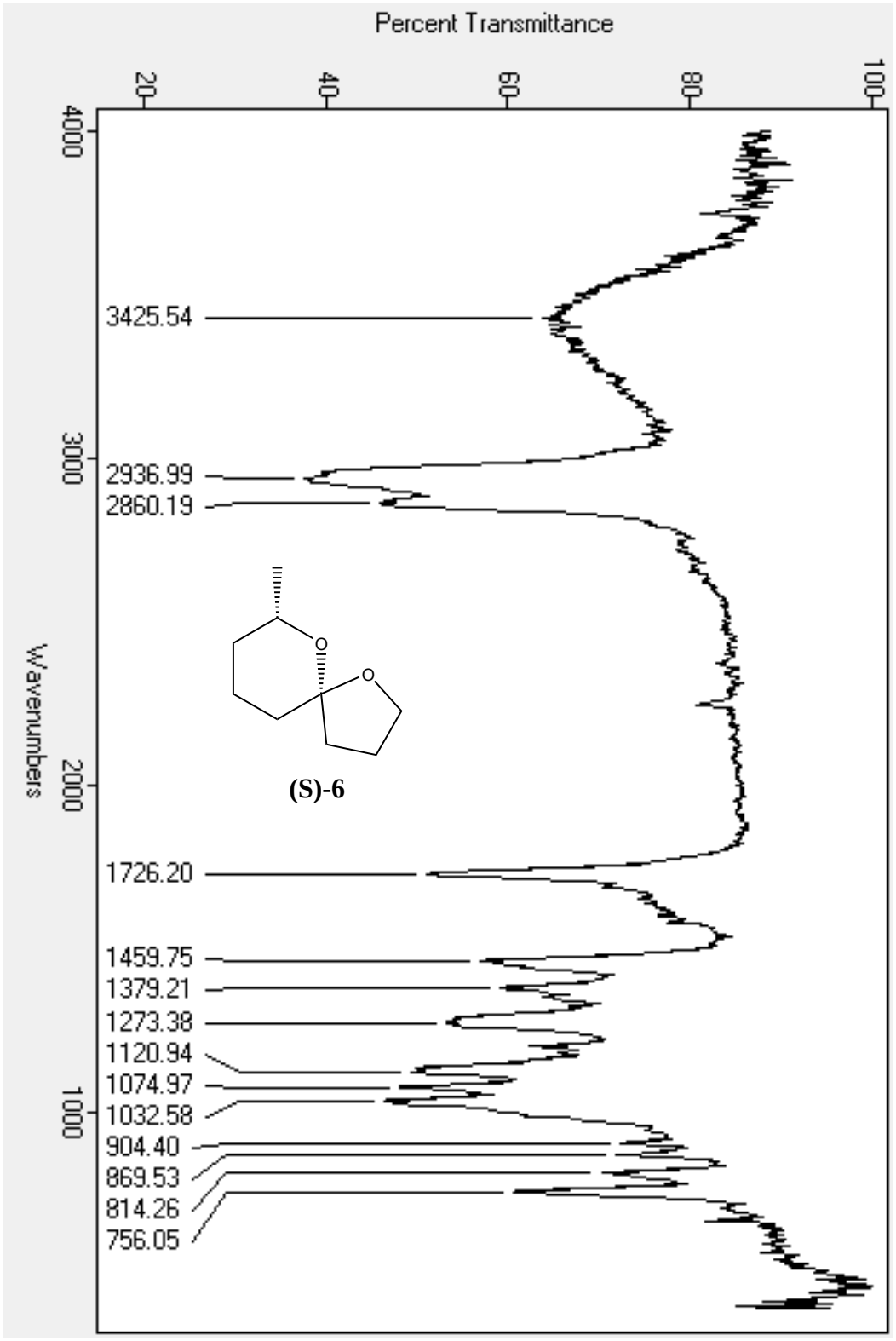
65


OTHP
S
S
OTHP
200
150
100
50
0
[ppm]
0
5
10
15
[rel]
98.8429
98.8305
98.6872
98.6518
95.7209
73.7908
73.7747
70.8365
67.2265
M 67.1902
67.1819
62.8632
62.5512
62.2513
62.2220
62.2066
53.1401
53.0603
38.4754
38.3906
37.5331
36.6388
36.6271
34.7024
34.6350
31.2339
31.2166
30.7171
25.9909
25.5591
25.5126
25.4871
25.4720
24.7386
24.6621
21.6541
20.2488
20.1014
19.8866
19.7943
19.5439
19.5315
19.0723

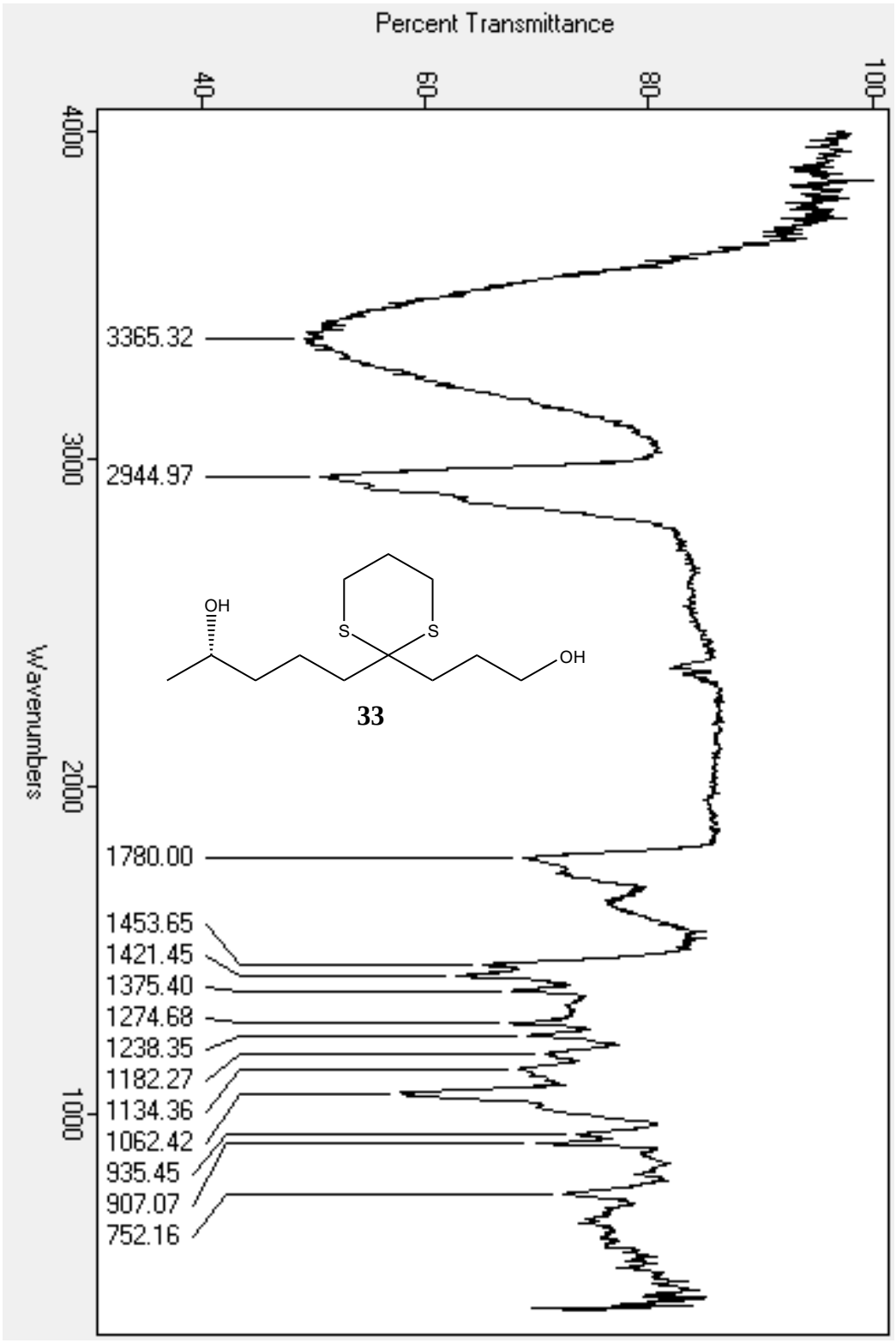
66

Appendix C

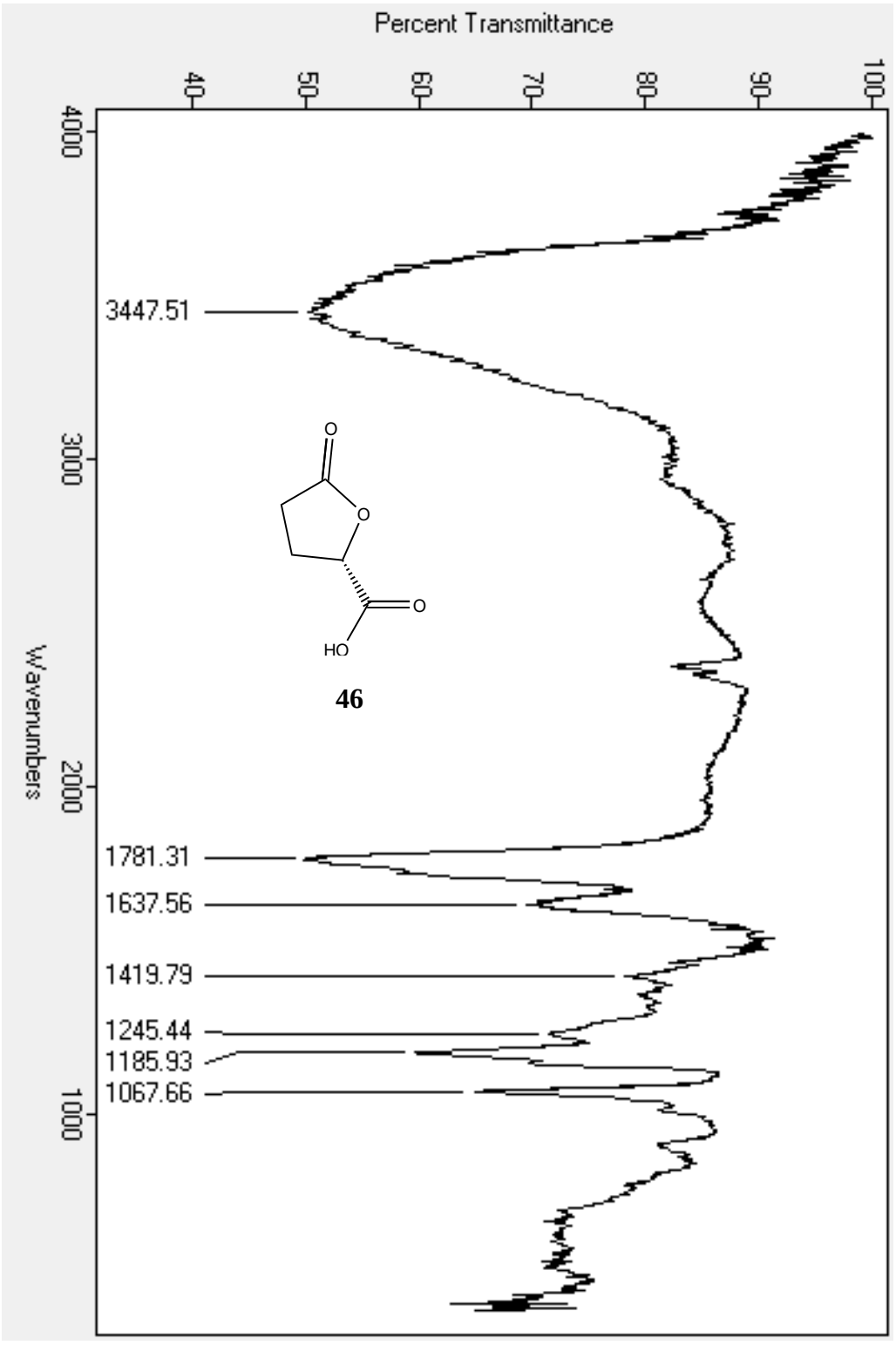
FTIR Spectra


Percent Transmittance
20
40
60
80
100
4000
3000
2000
1000
Wavenumbers
3425.54
2936.99
2860.19
1726.20
1459.75
1379.21
1273.38
1120.94
1074.97
1032.58
904.40
869.53
814.26
756.05
O
O

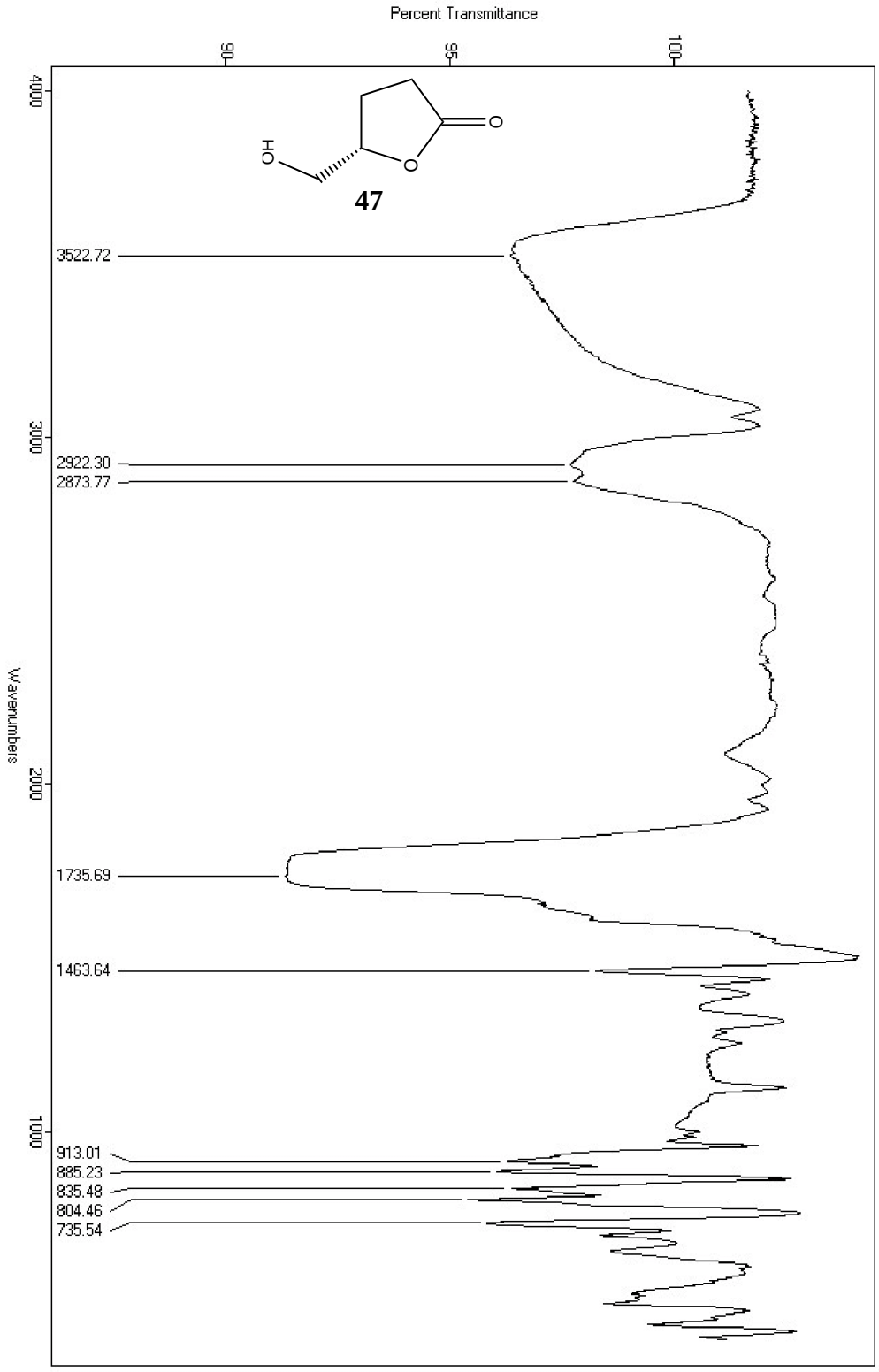
(S)-6

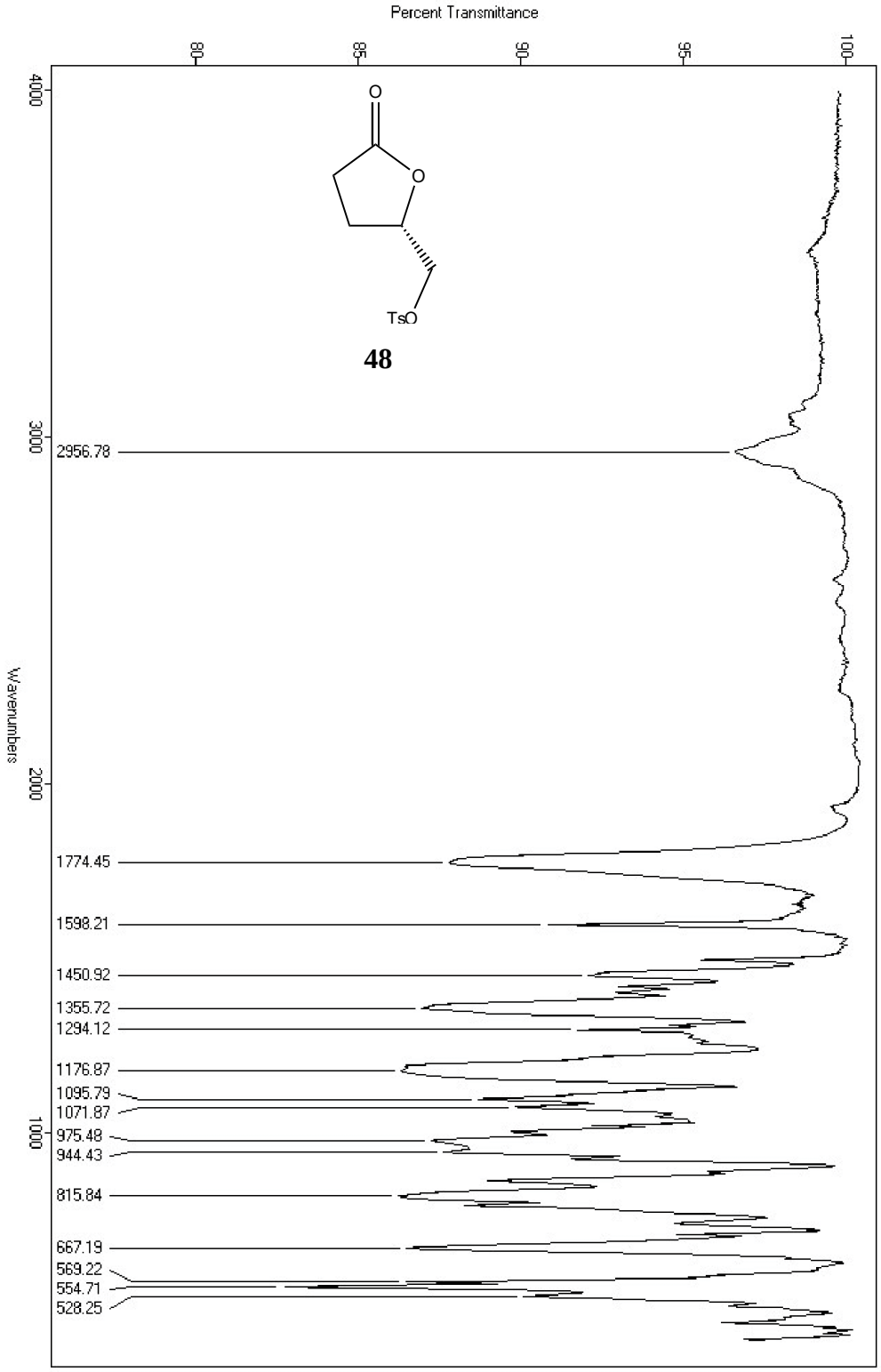

Percent Transmittance
40
60
80
100
4000
3000
2000
1000
Wavenumbers
3365.32
2944.97
1780.00
1453.65
1421.45
1375.40
1274.68
1238.35
1182.27
1134.36
1062.42
935.45
907.07
752.16
OH
S
S
OH

33


Percent Transmittance
40
50
60
70
80
90
100
4000
3000
2000
1000
W/avenumbers
3447.51
1781.31
1637.56
1419.79
1245.44
1185.93
1067.66
O
O
O
HO

46


Percent Transmittance
90
95
100
4000
3000
2000
1000
W/avenumbers
HO
O
O
47
3522.72
2922.30
2873.77
1735.69
1463.64
913.01
885.23
835.48
804.46
735.54


Percent Transmittance
80
85
90
95
100
4000
3000
2000
1000
Wavenumbers
O
O
TsO
2956.78
1774.45
1598.21
1450.92
1355.72
1294.12
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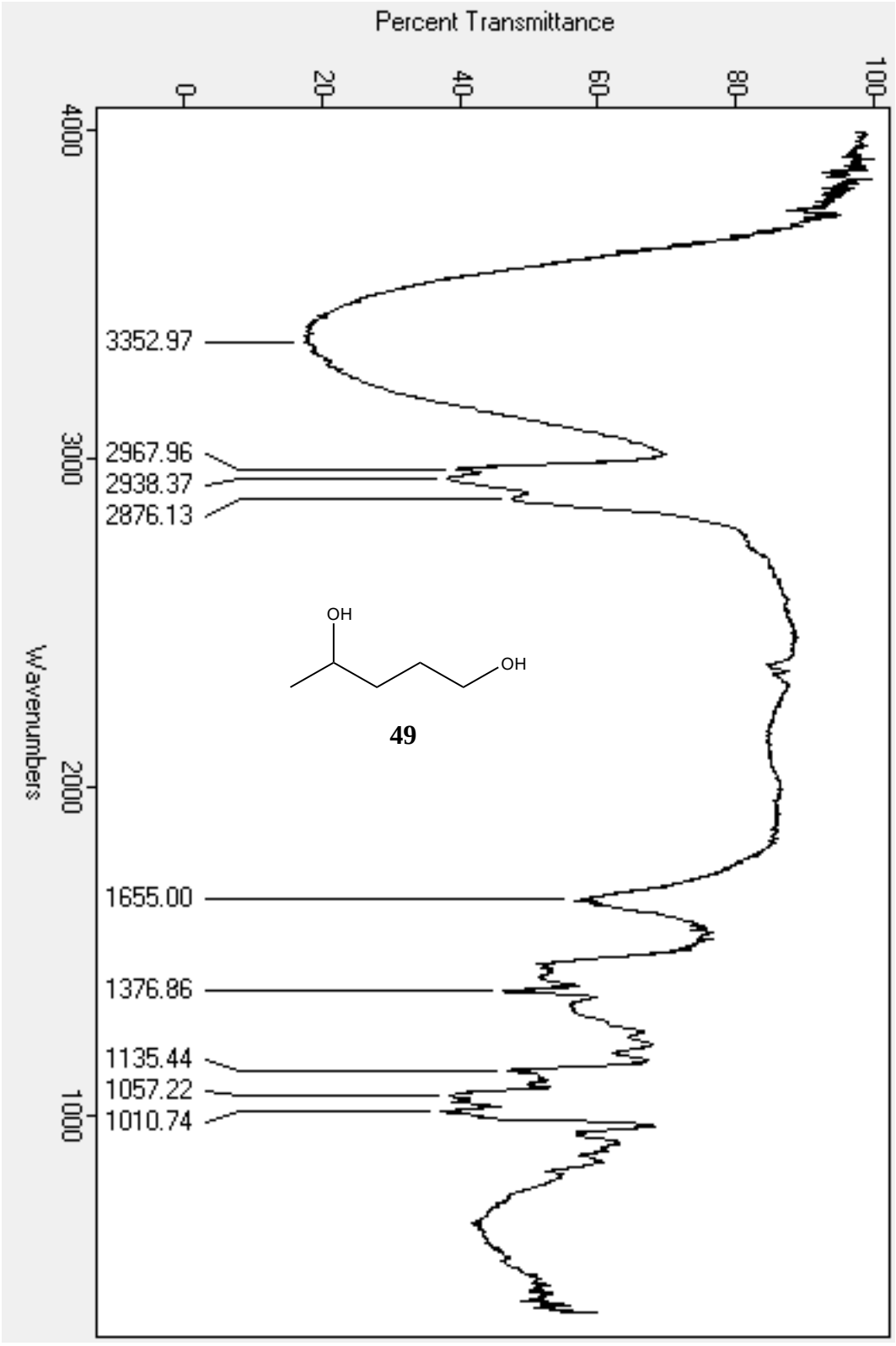
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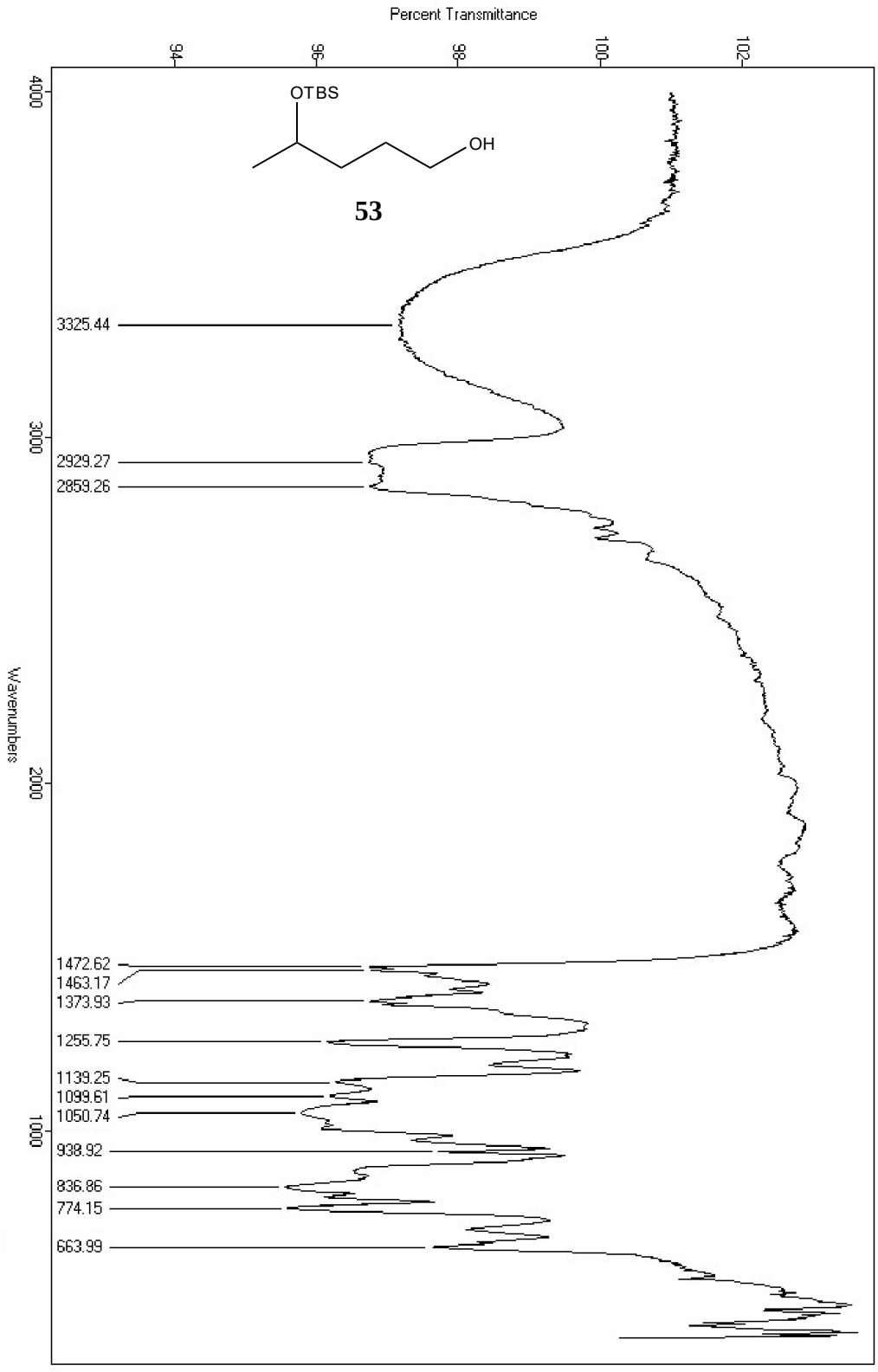
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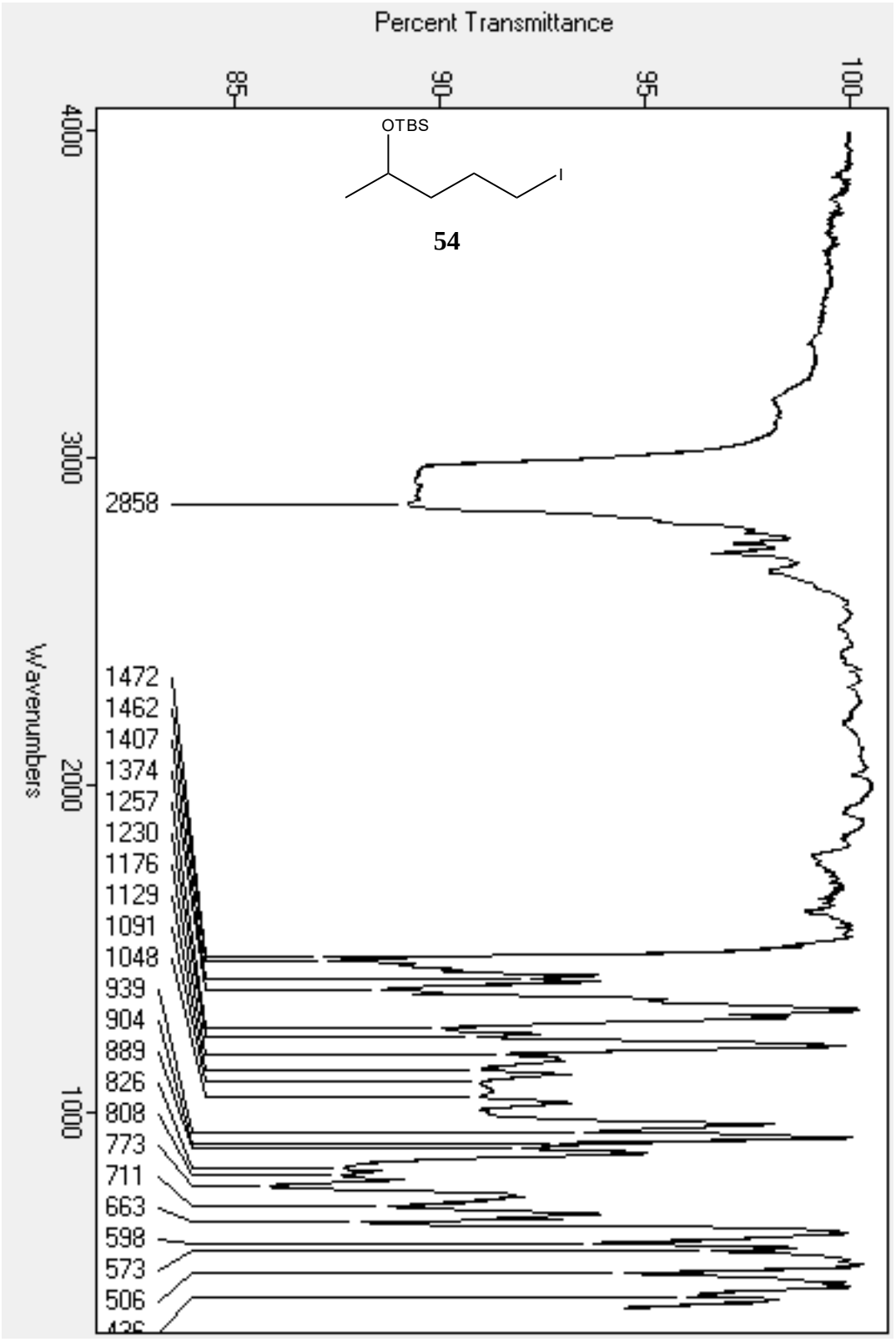
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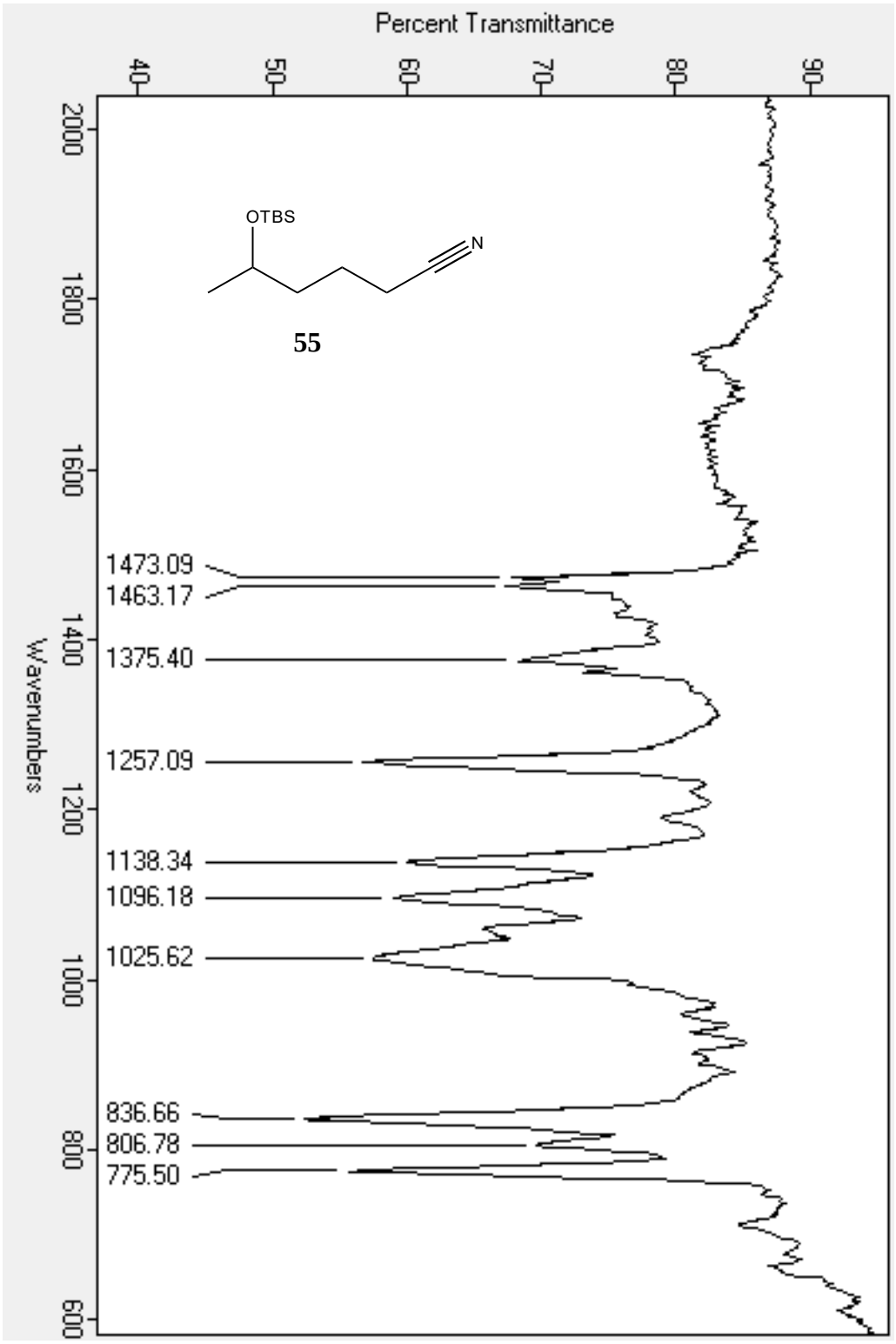
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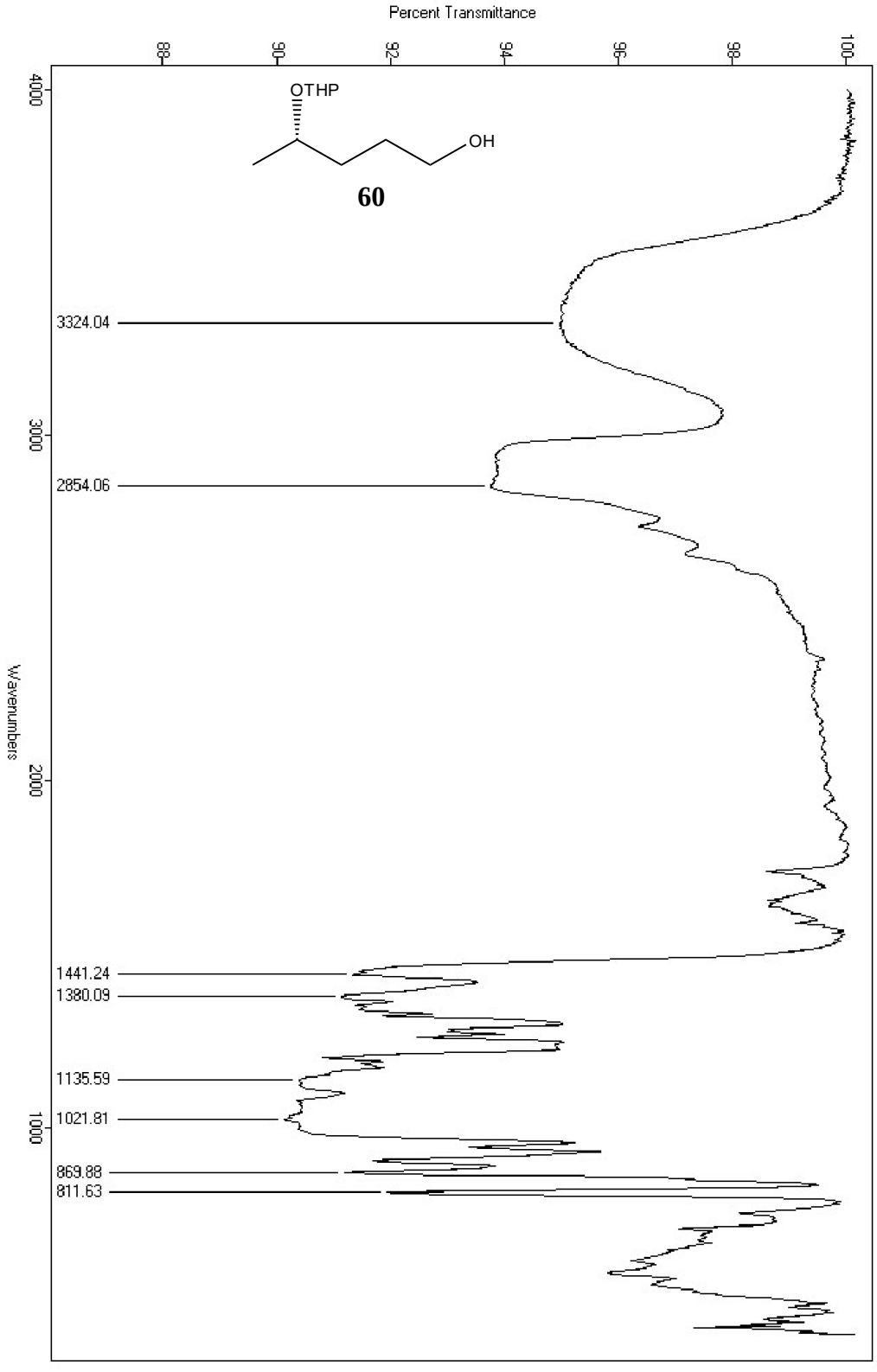
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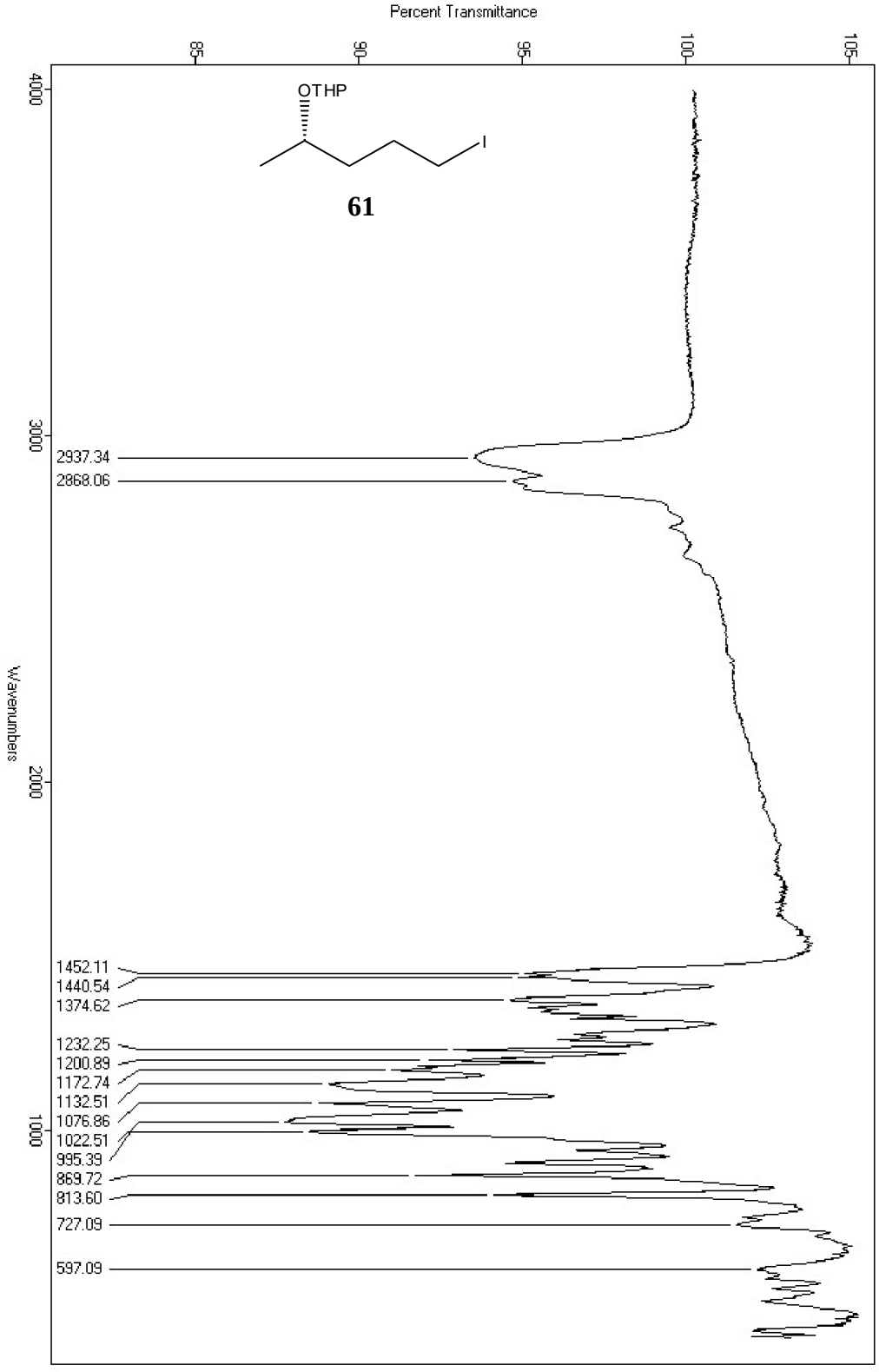
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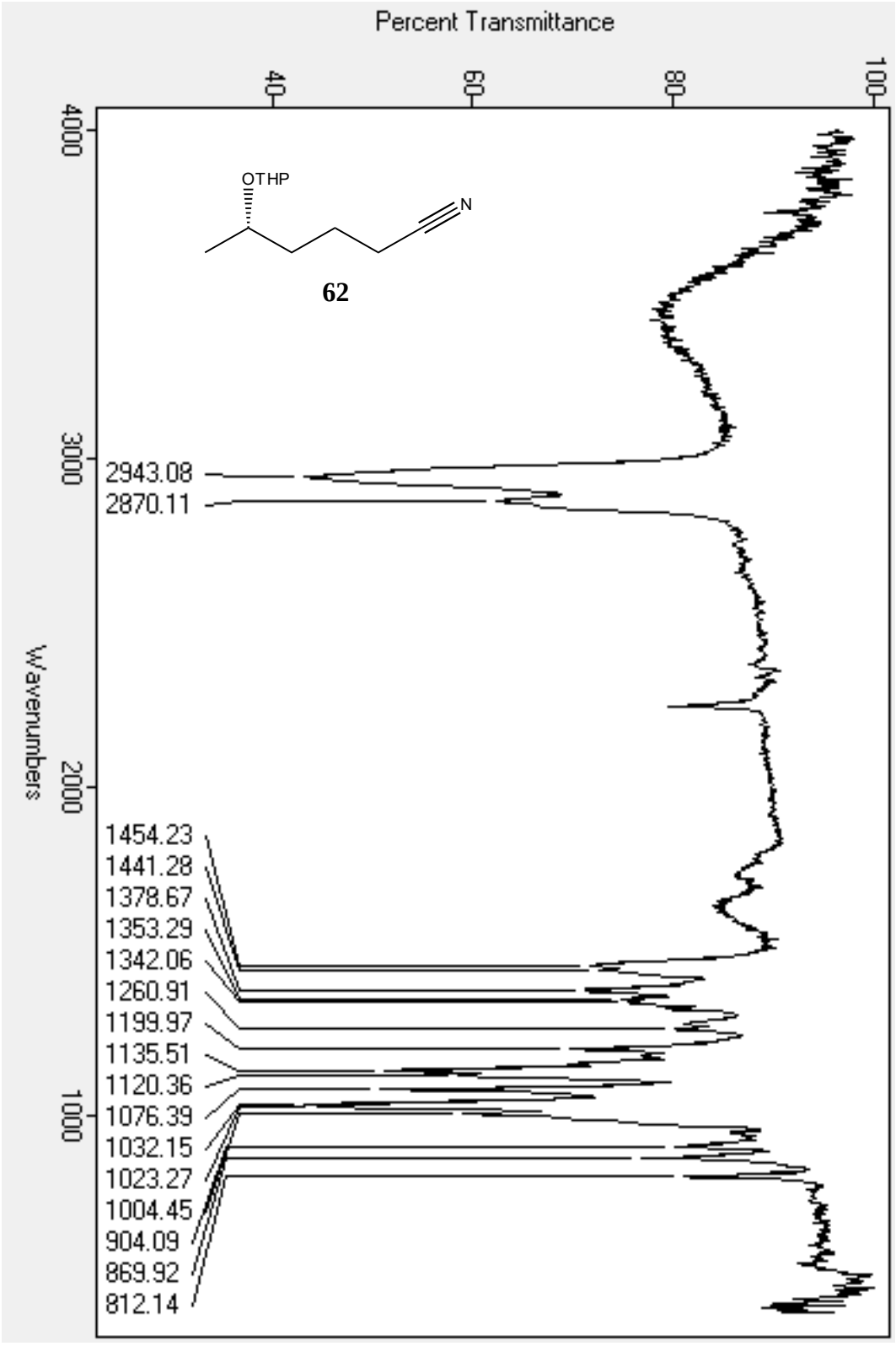
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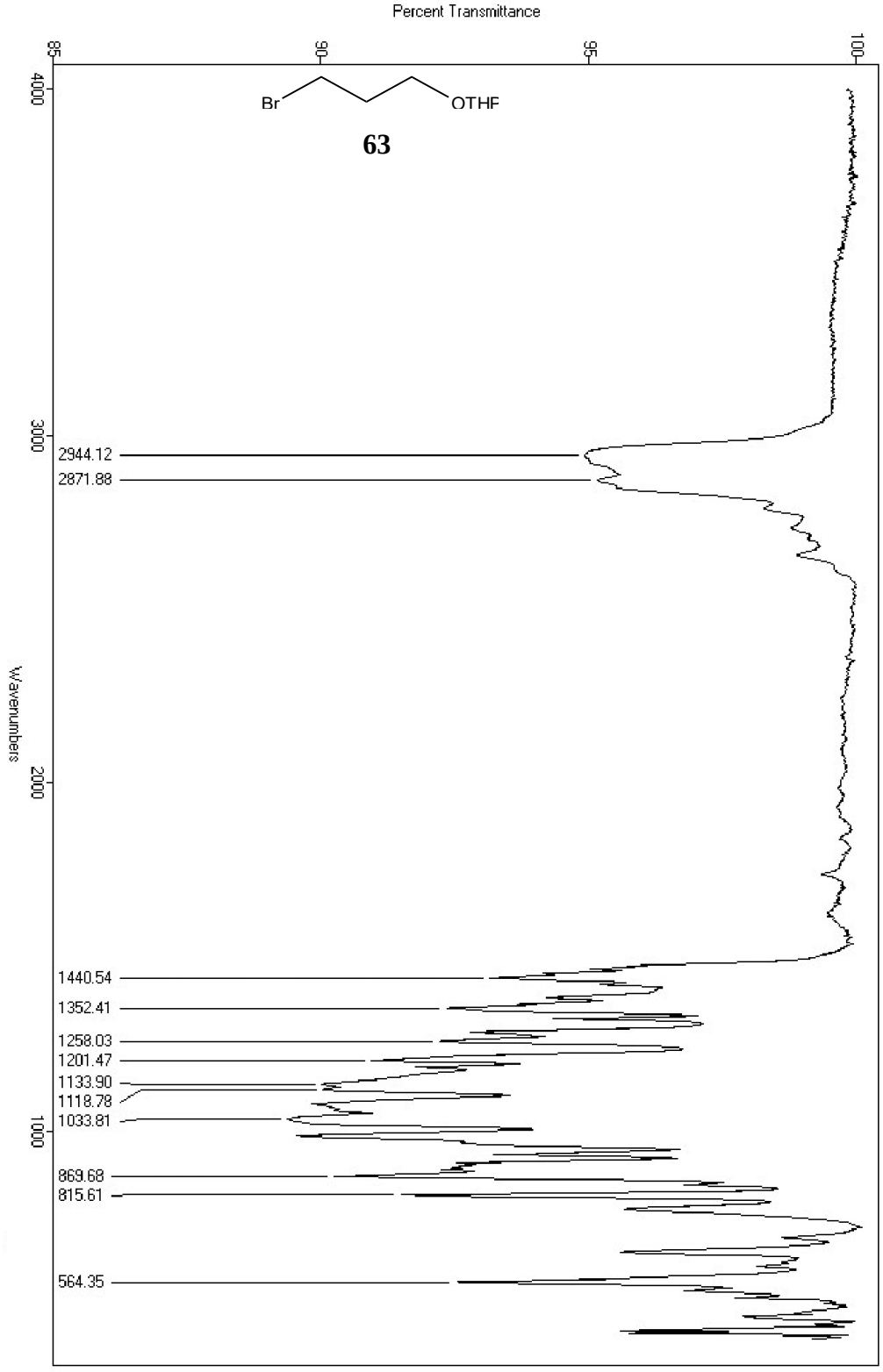
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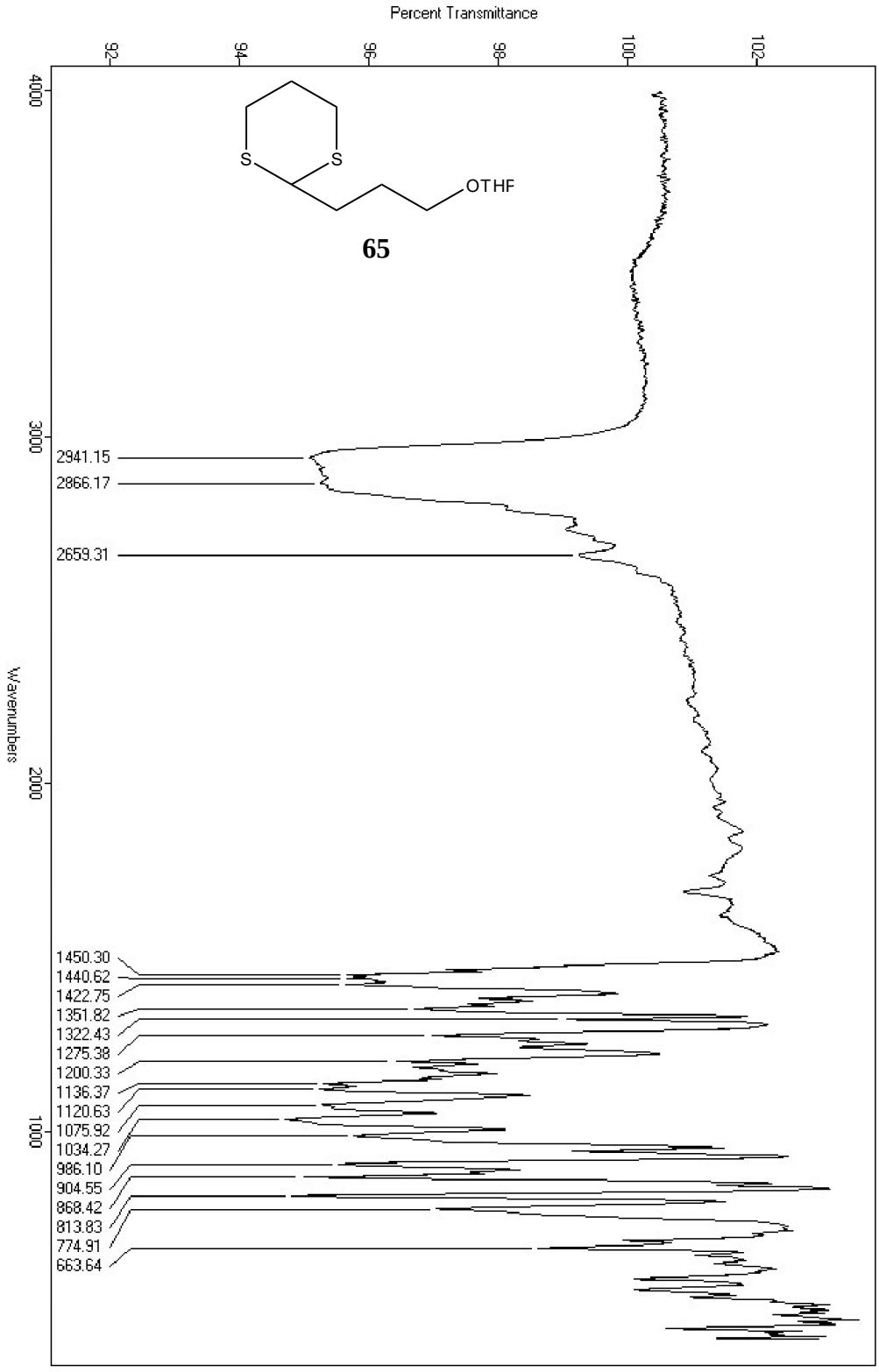
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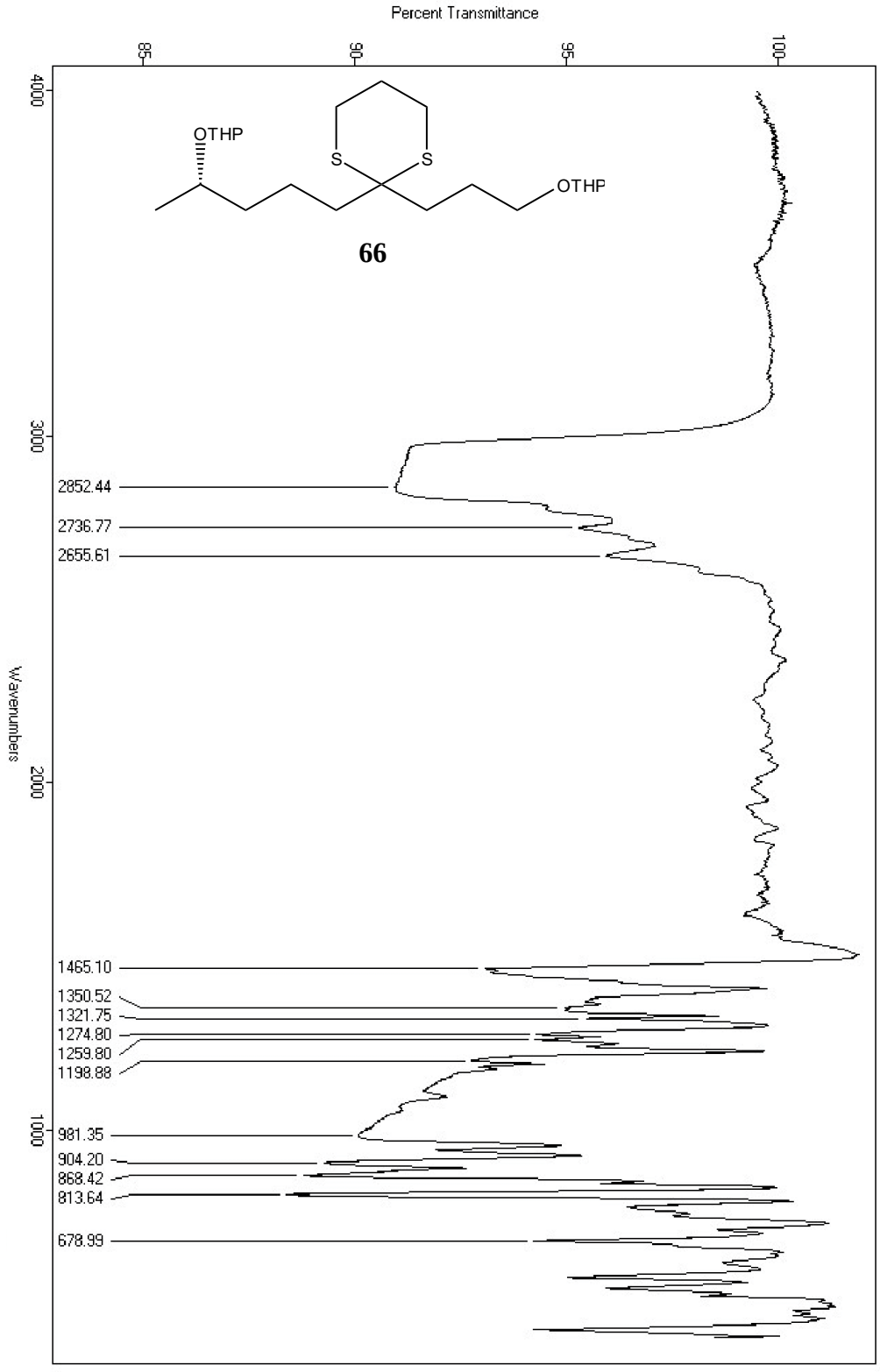
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References

(1) Government of Canada. How does the forest industry contribute to the economy? | Natural Resources Canada http://www.nrcan.gc.ca/forests/report/economy/16517 (accessed Apr 7, 2020).

(2) Government of Canada. Producing Forest Products From Birch Trees | Natural Resources Canada https://www.nrcan.gc.ca/simply-science/20297/producing-forest-products-birch-trees/20327 (accessed Apr 7, 2020).

(3) Appleby, J. E.; Randell, R.; Rachesky, S. Chemical Control of the Bronze Birch Borer. *Journal of Economic Entomology* **1973**; Vol. 66. https://doi.org/10.1093/jee/66.1.258.

(4) Barter, G. W. Studies of the Bronze Birch Borer, Agrilus Anxius Gory, in New Brunswick. *The Canadian Entomologist* **1957**, *89* (1), 12–36. https://doi.org/10.4039/Ent8912-1.

(5) 002551.jpg (3594×2322) https://tidcf.nrcan.gc.ca/images_web/imfc/insectes/large/002551.jpg (accessed Dec 7, 2020).

(6) Nielsen, D. G.; Muilenburg, V. L.; Herms, D. A. Interspecific Variation in Resistance of Asian, European, and North American Birches (Betula Spp.) to Bronze Birch Borer (Coleoptera: Buprestidae) . *Environmental Entomology* **2011**, *40* (3), 648–653. https://doi.org/10.1603/en10227.

(7) Carlson, R. W.; Knight, F. B. Biology, Taxonomy, and Evolution of Four Sympatric Agrilus Beetles (Coleoptera: Buprestidae). In *Contributions of the American Entomological Institute*; **1969**; Vol. 4, p 104.

(8) Akers, R. C.; Nielsen, D. G. Mating Behavior of the Bronze Birch Borer, (Coleoptera: Buprestidae). *Journal of Entomological Science* **1992**, *27* (1), 44–49. https://doi.org/10.18474/0749-8004-27.1.44.

(9) Barter, G. W. Survival and Development of the Bronze Poplar Borer Agrilus Liragus Barter & Brown (Coleoptera: Buprestidae). *The Canadian Entomologist* **1965**, *97* (10), 1063–1068. https://doi.org/10.4039/Ent971063-10.

(10) Akers, R. C.; Nielsen, D. G. Spatial Emergence Pattern of Bronze Birch Borer, (Coleoptera: Buprestidae) from European White Birch. *Journal of Entomological Science* **1990**, *25* (1), 150–157. https://doi.org/10.18474/0749-8004-25.1.150.

(11) Anderson, R. F. The Relation Between Host Condition and Attacks by the Bronzed Birch Borer. *Journal of Economic Entomology* **1944**, *37* (5), 588–596. https://doi.org/10.1093/jee/37.5.588.

(12) Taylor, P. B.; Duan, J. J.; Fuester, R. W.; Hoddle, M.; van Driesche, R. Parasitoid Guilds of Agrilus Woodborers (Coleoptera: Buprestidae): Their Diversity and Potential for Use in Biological Control. *Psyche (London)* **2011**, *2012*, 1–10. https://doi.org/10.1155/2012/813929.

(13) Muilenburg, V. L.; Herms, D. A. A Review of Bronze Birch Borer (Coleoptera: Buprestidae) Life History, Ecology, and Management.

Environmental Entomology **2012**, *41* (6), 1372–1385. https://doi.org/10.1603/EN12238.

(14) Jones, E. A.; Reed, D. D.; Mroz, G. D.; Liechty, H. O.; Cattelino, P. J. Climate Stress as a Precursor to Forest Decline: Paper Birch in Northern Michigan, 1985-1990. *Canadian Journal of Forest Research* **1993**, *23* (2), 229–233. https://doi.org/10.1139/x93-030.

(15) BBBhab2.jpg (432×576) https://extension.entm.purdue.edu/publications/E-50/E50graphics/BBBhab2.jpg (accessed Dec 7, 2020).

(16) Emerald ash borer | Natural Resources Canada https://www.nrcan.gc.ca/our-natural-resources/forests-forestry/wildland-fires-insects-disturban/top-forest-insects-diseases-cana/emerald-ash-borer/13377 (accessed Apr 21, 2020).

(17) Yen, T. H.; Lin, J. L. Acute Poisoning with Emamectin Benzoate. *Journal of Toxicology - Clinical Toxicology* **2004**, *42* (5), 657–661. https://doi.org/10.1081/CLT-200026968.

(18) Dai, P.-L.; Wang, Q.; Sun, J.-H.; Liu, F.; Wang, X.; Wu, Y.-Y.; Zhou, T. Effects of Sublethal Concentrations of Bifenthrin and Deltamethrin on Fecundity, Growth, and Development of the Honeybee *Apis Mellifera Ligustica*. *Environmental Toxicology and Chemistry* **2010**, *29* (3), 644–649. https://doi.org/10.1002/etc.67.

(19) Rauh, V. A.; Perera, F. P.; Horton, M. K.; Whyatt, R. M.; Bansal, R.; Hao, X.; Liu, J.; Barr, D. B.; Slotkin, T. A.; Peterson, B. S. Brain Anomalies in Children Exposed Prenatally to a Common Organophosphate Pesticide.

Proceedings of the National Academy of Sciences of the United States of America **2012**, *109* (20), 7871–7876. https://doi.org/10.1073/pnas.1203396109.

(20) Shorey, H. H.; Kaae, R. S.; Gaston, L. K.; Mclaughlin, J. R. Sex Pheromones of Lepidoptera. XXX. Disruption of Sex Pheromone Communication in Trichoplusia Ni as a Possible Means of Mating Control. *Environmental Entomology* **1972**, *1* (5), 641–645. https://doi.org/10.1093/ee/1.5.641.

(21) Vick, K. W.; Coffelt, J. A.; Sullivan, M. A. Disruption of Pheromone Communication in the Angoumois Grain Moth with Synthetic Female Sex Pheromone. *Environmental Entomology* **1978**, *7* (4), 528–531. https://doi.org/10.1093/ee/7.4.528.

(22) Trumble, J. T.; Baker, T. C. Flight Phenology and Pheromone Trapping of Spodoptera Exigua (Hübner) (Lepidoptera: Noctuidae) in Southern Coastal California. *Environmental Entomology* **1984**, *13* (5), 1278–1282. https://doi.org/10.1093/ee/13.5.1278.

(23) Hallett, R. H.; Oehlschlager, A. C.; Borden, J. H. Pheromone Trapping Protocols for the Asian Palm Weevil, Rhynchophorus Ferrugineus (Coleoptera: Curculionidae). *International Journal of Pest Management* **1999**, *45* (3), 231–237. https://doi.org/10.1080/096708799227842.

(24) Silk, P. J.; Ryall, K. L.; Grant, G.; Roscoe, L. E.; Mayo, P.; Williams, M.; Leclair, G.; Kimoto, T.; Williams, D.; Rutledge, C. Tree Girdling and Host Tree Volatiles Provides a Useful Trap for Bronze Birch Borer Agrilus

Anxius Gory (Coleoptera: Buprestidae). *Forestry* **2020**, *93* (2), 265–272. https://doi.org/10.1093/forestry/cpz021.

(25) Miller, D. R. Ethanol and (-)-α-Pinene: Attractant Kairomones for Some Large Wood-Boring Beetles in Southeastern USA. *Journal of Chemical Ecology* **2006**, *32* (4), 779–794. https://doi.org/10.1007/s10886-006-9037-8.

(26) Weber, D. C.; Leskey, T. C.; Walsh, G. C.; Khrimian, A. Synergy of Aggregation Pheromone with Methyl (E,E,Z)-2,4,6-Decatrienoate in Attraction of Halyomorpha Halys (Hemiptera: Pentatomidae). *Journal of Economic Entomology* **2014**, *107* (3), 1061–1068. https://doi.org/10.1603/EC13502.

(27) Zhang, Q. H.; Tolasch, T.; Schlyter, F.; Francke, W. *Enantiospecific Antennal Response of Bark Beetles to Spiroacetal (E)-Conophthorin*; **2002**; Vol. 28. https://doi.org/10.1023/A:1020569303433.

(28) Beck, J. J.; Mahoney, N. E.; Cook, D.; Gee, W. S. Generation of the Volatile Spiroketals Conophthorin and Chalcogran by Fungal Spores on Polyunsaturated Fatty Acids Common to Almonds and Pistachios. *Journal of Agricultural and Food Chemistry* **2012**, *60* (48), 11869–11876. https://doi.org/10.1021/jf304157q.

(29) Morewood, W. D.; Simmonds, K. E.; Gries, R.; Allison, J. D.; Borden, J. H. Disruption by Conophthorin of the Kairomonal Response of Sawyer Beetles to Bark Beetle Pheromones. *Journal of Chemical Ecology* **2003**, *29* (9), 2115–2129. https://doi.org/10.1023/A:1025690519818.

(30) Rosini, G.; Ballini, R.; Marolta, E. Functionalized Nitroalkanes in Synthesis of 1,6-Dioxaspiro[4.5]Decane Components of Paravespula Vulgaris Pheromone. *Tetrahedron* **1989**, *45* (18), 5935–5942.

(31) Ley, S. v.; Lygo, B.; Organ, H. M.; Wonnacott, A. Wittig and Horner-Wittig Coupling Reactions of 2-Substituted Cyclic Ethers and Their Application to Spiroketal Synthesis. *Tetrahedron* **1985**, *41* (18), 3825–3836. https://doi.org/10.1016/S0040-4020(01)91403-6.

(32) Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Tamayo, J. A.; Martos, A. Lipase Mediated Resolution of 1,3-Butanediol Derivatives: Chiral Building Blocks for Pheromone Enantiosynthesis. Part 3. *Tetrahedron Asymmetry* **2001**, *12* (2), 293–300. https://doi.org/10.1016/S0957-4166(01)00038-6.

(33) Hong Liu and Theodore Cohen. S-(+)-5-(Phenylthio)-2-Pentanol and S-(+)-4-(Phenylthio)-2-Butanol: Readily Prepared, Useful Additions to the Chirality Pool. Highly Enantioselective Syntheses of Naturally Occurring Spiroketal Pheromones. *J. Org. Chem.* **1995**, *60* (46), 2022–2025. https://doi.org/https://doi.org/10.1016/j.tetlet.2005.09.085.

(34) Ramaswamy, S.; Oehlschlager, A. C. Chemico-Enzymatic Syntheses of Racemic and Chiral Isomers of 7- Methyl-1,6-Dioxaspiro[4.5]Decane. *Tetrahedron* **1991**, *47* (7), 1157–1162. https://doi.org/10.1016/S0040-4020(01)86372-9.

(35) Wonnacott, A. New Methods for Spiroketal Synthesis; Thesis. *Imperial College London*, **1986**.

(36) Perron, F.; Albizati, K. F. Chemistry of Spiroketals. *Chemical Reviews* **1989**, *89* (7), 1617–1661. https://doi.org/10.1021/cr00097a015.

(37) Doubsky, J.; Streinz, L.; ˇaman, D. S.; Zedník, J.; Koutek, B. Alkynyltrifluoroborates as Versatile Tools in Organic Synthesis: A New Route to Spiroketals. *Tetrahedron Letters* **2000**, *5* (26), 4909–4911. https://doi.org/10.1021/ol047987k.

(38) Enders, D.; Dahmen, W.; Dederichs, E.; Gatzweiler, W.; Weuster, P. Synthesis of Spiroacetal Pheromones via Metalated Hydrazones. *Synthesis (Germany)* **1990**, *1990* (11), 1013–1018. https://doi.org/10.1055/s-1990-27080.

(39) Jacobson, R.; Taylor, R. J.; Smith, L. R.; Williams, H. J. Naturally Occurring Spirocyclic Ketals from Lactones. 3. *Journal of Organic Chemistry* **1982**, *47* (16), 3140–3142. https://doi.org/10.1021/jo00137a020.

(40) Stanetty, P.; Roller, H.; Mihovilovic, M. Directed Ortho-Lithiation of Phenylcarbamic Acid 1,1-Dimethylethyl Ester (N-Boc-Aniline). Revision and Improvements. *Journal of Organic Chemistry* **1992**, *57* (25), 6833–6837. https://doi.org/10.1021/jo00051a030.

(41) Perkins, M. v.; Kitching, W.; König, W. A.; Drew, R. A. I. An (S)-(+)-Lactic Acid Route to (2S,6R,8S)-2,8 Dimethyl-1,7-Dioxaspiro[5,5]Undecane and (2S,6R,8S)-2-Ethyl-8-Methyl-1,7-Dioxaspiro[5,5]Undecane and Demonstration of Their Presence in the Rectal Glandular Secretion of Bactrocera Nigrotibialis(Perkins). *Journal of*

the Chemical Society, Perkin Transactions 1 **1990**, No. 9, 2501–2506. https://doi.org/10.1039/P19900002501.

(42) Miller, D. R.; Dodds, K. J.; Hoebeke, E. R.; Poland, T. M.; Willhite, E. A. Variation in Effects of Conophthorin on Catches of Ambrosia Beetles (Coleoptera: Curculionidae: Scolytinae) in Ethanol-Baited Traps in the United States. *Journal of Economic Entomology* **2015**, *108* (1), 183–191. https://doi.org/10.1093/jee/tou043.

(43) Bringmann, G.; Lang, G.; Michel, M.; Heubes, M. Stereochemical Assignment of the Fungal Metabolite Xestodecalactone A by Total Synthesis. *Tetrahedron Letters* **2004**, *45* (13), 2829–2831. https://doi.org/10.1016/j.tetlet.2004.02.005.

(44) Cohen-Arazi, N.; Katzhendler, J.; Kolitz, M.; Domb, A. J. Preparation of New α-Hydroxy Acids Derived from Amino Acids and Their Corresponding Polyesters. *Macromolecules* **2008**, *41* (20), 7259–7263. https://doi.org/10.1021/ma8012477.

(45) Kolitz, M.; Cohen-Arazi, N.; Hagag, I.; Katzhendler, J.; Domb, A. J. Biodegradable Polyesters Derived from Amino Acids. *Macromolecules* **2009**, *42*, 4520–4530. https://doi.org/10.1021/ma900464g.

(46) Mallesha, N.; Rao, S. P.; Suhas, R.; Gowda, D. C. A Green Method for Selective Acetylation of Primary Alcohols Using Ethyl Acetate and Solid Potassium Carbonate. *Journal of Chemical Research* **2011**, *35* (9), 536–539. https://doi.org/10.3184/174751911X13155057300536.

(47) Stuhr-Hansen, N.; Padrah, S.; Strømgaard, K. Facile Synthesis of α-Hydroxy Carboxylic Acids from the Corresponding α-Amino Acids. *Tetrahedron Letters* **2014**, *55* (30), 4149–4151. https://doi.org/10.1016/j.tetlet.2014.05.090.

(48) Bonnaventure, I.; Charette, A. B. Probing the Importance of the Hemilabile Site of Bis(Phosphine) Monoxide Ligands in the Copper-Catalyzed Addition of Diethylzinc to N-Phosphinoylimines: Discovery of New Effective Chiral Ligands. *Journal of Organic Chemistry* **2008**, *73* (16), 6330–6340. https://doi.org/10.1021/jo800969x.

(49) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. A Revised Mechanism for Chemoselective Reduction of Esters with Borane-Dimethyl Sulfide Complex and Catalytic Sodium Tetrahydroborate Directed by Adjacent Hydroxyl Group. *Tetrahedron* **1992**, *48* (20), 4067–4086. https://doi.org/10.1016/S0040-4020(01)92187-8.

(50) Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A. A Simple One-Pot Procedure for the Direct Conversion of Alcohols into Alkyl Nitriles Using TsIm. *Tetrahedron Letters* **2007**, *48* (38), 6779–6784. https://doi.org/10.1016/j.tetlet.2007.07.091.

(51) Jayasundera, K. P.; Brodie, S. J.; Taylor, C. M. Synthesis of a Transition-State Analog for the Hydrolysis of the Zearalenone Lactone. *Tetrahedron* **2007**, *63* (40), 10077–10082. https://doi.org/10.1016/j.tet.2007.07.042.

(52) Ellwood, A. R.; Porter, M. J. Selective Conversion of Alcohols into Alkyl Iodides Using a Thioiminium Salt. *Journal of Organic Chemistry* **2009**, *74* (20), 7982–7985. https://doi.org/10.1021/jo901415n.

(53) Jacobs, H.; Berryman, K.; Jones, J.; Gopalan, A.; Aravamudan, &. Bakers' Yeast Reductions of Alkyl Levulinates: Synthesis of (R)-(+) and (S)-(-)4-Methylbutyrolactones. *Synthetic Communications* **1990**, *20* (7), 999–1010. https://doi.org/10.1080/00397919008052803.

(54) Csuk, R.; Glänzer, B. I. Baker's Yeast Mediated Transformations in Organic Chemistry. *Chemical Reviews* **1991**, *91* (1), 49–97. https://doi.org/10.1021/cr00001a004.

(55) Prelog, V. Specification of the Stereospecificity of Some Oxido-Reductases by Diamond Lattice Sections. *Pure and Applied Chemistry* **1964**, *9* (1), 119–130. https://doi.org/10.1351/pac196409010119.

(56) Ojha, P.; Sharma, A.; Verma, P. S.; Sharma, I. K. Green Chemical Methods for the Reduction of Keto Esters. *International Journal of ChemTech Research* **2011**; Vol. 3 (2), 917-927.

(57) Nanduri, V. B.; Hanson, R. L.; Goswami, A.; Wasylyk, J. M.; LaPorte, T. L.; Katipally, K.; Chung, H. J.; Patel, R. N. Biochemical Approaches to the Synthesis of Ethyl 5-(S)-Hydroxyhexanoate and 5-(S)-Hydroxyhexanenitrile. *Enzyme and Microbial Technology* **2001**, *28* (7–8), 632–636. https://doi.org/10.1016/S0141-0229(01)00318-0.

(58) Díaz-Rodríguez, A.; Borzeĭcka, W.; Lavandera, I.; Gotor, V. Stereodivergent Preparation of Valuable γ- Or δ-Hydroxy Esters and

Lactones through One-Pot Cascade or Tandem Chemoenzymatic Protocols. *ACS Catalysis* **2014**, *4* (2), 386–393. https://doi.org/10.1021/cs4010024.

(59) Gong, X. M.; Zheng, G. W.; Liu, Y. Y.; Xu, J. H. Identification of a Robust Carbonyl Reductase for Diastereoselectively Building Syn-3,5-Dihydroxy Hexanoate: A Bulky Side Chain of Atorvastatin. *Organic Process Research and Development* **2017**, *21* (9), 1349–1354. https://doi.org/10.1021/acs.oprd.7b00194.

(60) HEIDLAS, J.; ENGEL, K. -H; TRESSL, R. Purification and Characterization of Two Oxidoreductases Involved in the Enantioselective Reduction of 3-oxo, 4-oxo and 5-oxo Esters in Baker's Yeast. *European Journal of Biochemistry* **1988**, *172* (3), 633–639. https://doi.org/10.1111/j.1432-1033.1988.tb13936.x.

(61) Weiberth, F. J.; Hall, S. S. Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines. *Journal of Organic Chemistry* **1987**, *52* (17), 3901–3904. https://doi.org/10.1021/jo00226a033.

(62) Burghardt, T. E. Developments in the Deprotection of Thioacetals. *Journal of Sulfur Chemistry*. **2005**, pp 411–427. https://doi.org/10.1080/17415990500195198.

(63) Starodubtseva, E. v; Turova, O. v; Vinogradov, M. G.; Gorshkova, L. S.; Ferapontov, V. A. Enantioselective Hydrogenation of Levulinic Acid Esters in the Presence of the RuII-BINAP-HCl Catalytic System. *Russian*

Chemical Bulletin **2005**, *54* (10), 2374–2378. https://doi.org/10.1007/s11172-006-0125-2.

(64) Figadére, B.; Chaboche, C.; Franck, X.; Peyrat, J. F.; Cavé, A. Carbonyl Reduction of Functionalized Aldehydes and Ketones by Tri-n-Butyltin Hydride and SiO2. *Journal of Organic Chemistry*. **1994**, pp 7138–7141. https://doi.org/10.1021/jo00102a048.

(65) Brimble, M. A.; Funnell, C. J.; Gorsuch, S.; Sidford, M. Synthesis of a Spiroacetal Intermediate for the Synthesis of the Anti-Helicobacter Pylori Agent CJ-12, 954. *Arkivoc* **2001**, *2001* (1), 74–87. https://doi.org/10.3998/ark.5550190.0002.106.

(66) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. Synthesis of β-Resorcylic Macrolides via Organopalladium Chemistry. Application to the Total Synthesis of (S)-Zearalenone. *Journal of Organic Chemistry.* **1991**, *56* (8), 2883–2894. https://doi.org/10.1021/jo00008a053.

(67) Jayasundera, K. P.; Brodie, S. J.; Taylor, C. M. Synthesis of a Transition-State Analog for the Hydrolysis of the Zearalenone Lactone. *Tetrahedron* **2007**, *63* (40), 10077–10082. https://doi.org/10.1016/j.tet.2007.07.042.

(68) Lüthy, C.; Konstantin, P.; Untch, K. G. Total Synthesis of Dl-19-Hydroxyprostaglandin E1 and Dl-13-Cis-15-Epi-19-Hydroxyprostaglandin E1. *Journal of the American Chemical Society.* **1978**, *100* (19), 6211–6217. https://doi.org/10.1021/ja00487a043.

(69) Kitahara, T.; Koseki, K.; Mori, K. The Synthesis and the Absolute Configuration of Phoracantholide I and J; the Defensive Secretion of the

Eucarypt Longicorn, Phoracantha Synonyma. *Agricultural and Biological Chemistry.* **1983**, *47* (2), 389–393. https://doi.org/10.1080/00021369.1983.10865622.

(70) Capson, T. L.; Thompson, M. D.; Dixit, V. M.; Gaughan, R. G.; Dale Poulter, C. Synthesis of Ammonium Analogues of Carbocationic Intermediates in the Conversion of Presqualene Diphosphate to Squalene. *Journal of Organic Chemistry.* **1988**, *53* (25), 5903–5908. https://doi.org/10.1021/jo00260a019.

(71) Yoneda, N.; Fukata, Y.; Asano, K.; Matsubara, S. Asymmetric Synthesis of Spiroketals with Aminothiourea Catalysts. *Angewandte Chemie* **2015**, *127* (51), 15717–15720. https://doi.org/10.1002/ange.201508405.

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