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A GENERAL SCAFFOLD FOR THE SYNTHESIS OF DYSIHERBAINE AND ITS ANALOGUES

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A GENERAL SCAFFOLD FOR THE SYNTHESIS OF DYSIHERBAINE AND ITS ANALOGUES

by

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Supervisor: Scott R. Gilbertson

Dysiherbaine **1** and a select number of structurally related compounds have been shown to have selective effects on ionotropic glutamate receptors (iGluRs). iGluRs are essential components in the central nervous system (CNS); playing an important role in memory and learning. They also play a role in a number of neurological disorders, including schizophrenia, epilepsy, Rasmussen's encephalitis and stroke; along with neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. This dissertation describes the synthesis of key molecule **4** and future directions for its use. The molecule will serve as the branch point for the synthesis of other analogues. We designed a 12 step route to this molecule that utilizes highly stereo- and regioselective reactions. The molecule **4** will provide dysiherbaine and a series of analogues without having to design a new total synthesis for each analogue. While there are a number of syntheses of dysiherbaine reported, they are not appropriate for the easy variation of the important C_8-amino C_9-alcohol pharmacophore. The molecule **4** has a double bond between the C_8 and C_9 position as

the key reactive functional group. The principal reactivity that will be used to synthesize derivatives of this molecule involves the double bond. Addition reactions of electrophilic reagents to the double bond are the most typical, and include hydroxylation, hydrogenation, halogenation, alkylation, amination, etc. This will be a unique and simple way to make dysiherbaine and analogues with just few steps from molecule **4**. Finally, this work will provide unique molecules that will enhance the understanding of the structure and function of ionotropic Glu receptors in the CNS.

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Chapter 1: General Introduction

I. GLUTAMATE & ITS RECEPTORS

L-Glutamate

L-Glutamate (Glu) is the major excitatory amino acid neurotransmitter in the mammalian central nervous system and is thought to play an important role in brain development through activation of Glu receptors.[1] Glu released into synapses is either reabsorbed directly into neurons by the ion-exchange system or is soaked-up by astrocytes (glial cells) which convert the glutamate into glutamine (a molecule which cannot cause excitotoxicity). Glutamine can then be safely transported back to neurons for re-conversion into glutamate. Excitotoxicity due to glutamate is a major destructive process seen in strokes and other forms of brain ischemia.[2] The ability to define the role of Glu came as a result of finding receptors for Glu and labeling them with various analogs. Glu receptors are divided into two groups. One is a ligand gated ion channel (ionotropic receptors) and the other is G-protein coupled receptor (metabotropic receptor).[3-5] The activation of Glu receptor is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity such as LTP (long term potentiation) and LTD (long term depression) which are thought to underlie learning and memory.[6] Additionally, Glu receptors are potential targets for therapies for CNS disorders such as epilepsy and Alzheimer's disease.[7]

Glutamate Receptors

Glu receptors are divided into two groups. One is a ligand gated ion channel (ionotropic receptor) and the other is a G-protein coupled receptor (metabotropic receptor). Ionotropic Glu receptors mediate excitatory synaptic transmission. In the pre-synaptic nerve terminal, an influx of calcium ions allows the release of Glu into the synaptic cleft which activates glutamate receptors on the post-synaptic nerve terminals. As a ligand gated ion channel, binding of Glu allows ions to pass through the channel, resulting in a depolarization that is propagated down to the axons.[8] Then the CNS becomes excited.

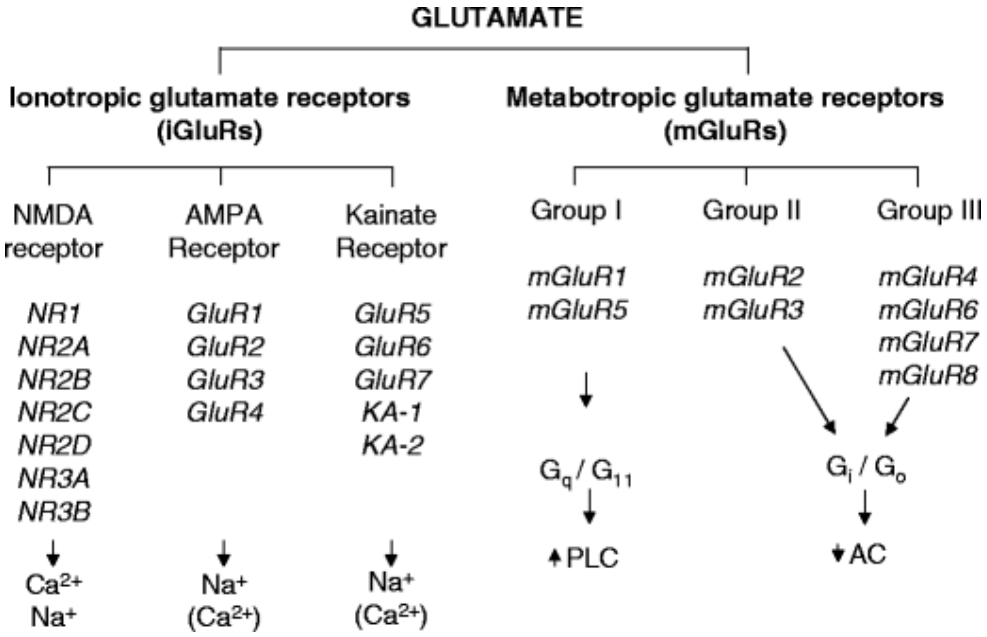


Figure 1.1: This figure is adopted and modified from ref 9 with permission. Classification of the ionotropic and metabotropic glutamate receptors.

Ionotropic Glu receptors are assemblies of homo- or heteromeric tetramers which are subdivided into three groups, NMDA (*N*-methyl-D-aspartic acid), AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and kainate, based on their selective agonists (Fig 1.1).[4, 5, 9]

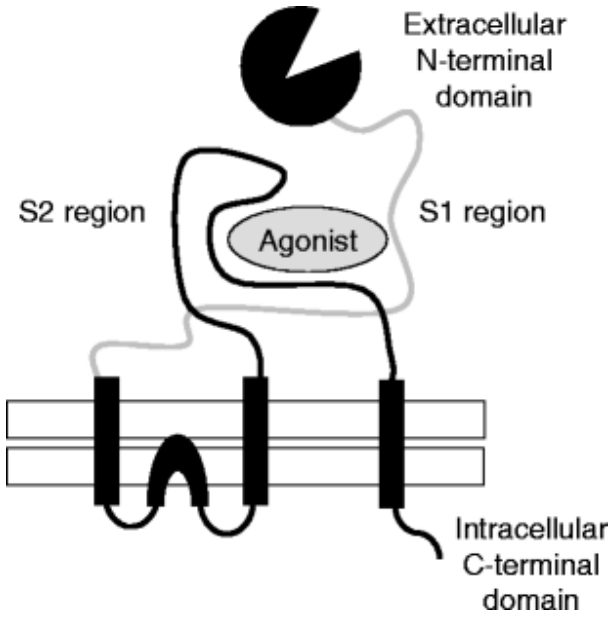


Figure 1.2: This figure is adopted and from ref 9 with permission. Schematic representation of an iGluR family member.

For ionotropic glutamate receptor subunits, there is an extracellular amino acid N-terminal domain which shows similar shape to the metabotropic glutamate receptor bi-lobed agonist binding domain. There are 4 domain segments in the membrane from the left to the right, M1, M2, M3 and M4 respectively. M2 domain forms a pore and has re-entrant loop, both ends facing to the cytoplasm so that it does not cross the membrane

unlike other 3 transmembrane domains (M1, M3 and M4). A large extracellar loop links the two transmembrane domains, M3 and M4, and M4 domain is connected an intracellular amino acid C-terminal domain. Agonist binding site in iGluRs is located in between S1 and S2 domain regions in the extracellular site (Fig 1.2).[9]

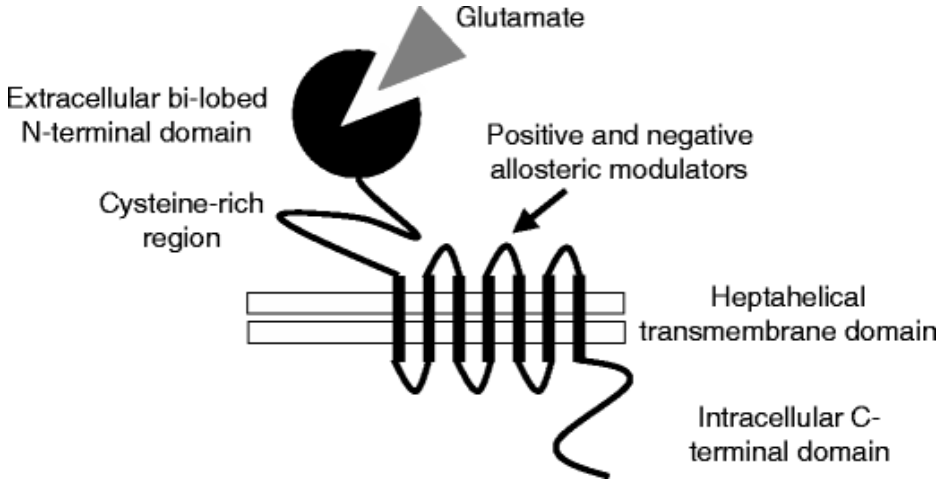


Figure 1.3: This figure is adopted and from ref 9 with permission. Schematic representation of an mGluR family member.

Metabotropic glutamate receptors are G-protein coupled receptors and eight members (mGluR1-8) are identified so far. They are divided into three groups based on the sequence homology, second messenger coupling and pharmacology. Group I contains mGluR1 and 5, group II has mGluR2 and 3, and group III includes mGluR4 and 6-8. Group I mGluR activate PLC (phospholipase C) via G_q/G_{11} and Group II and III are negatively coupled to AC (adenylyl cyclase) via G_i/G_o (Fig 1.1).[3, 9, 10] All mGluRs have large extracellular bi-lobed N-terminal domain which has glutamate binding site and the

N-terminal domain is linked to the 7-transmembrane domain via cystein rich region (Fig 1.3). Intracellular C-terminal domain regulates receptor signal which is from glutamate binding site through the transmembrane domains by interacting with proteins of its downstream. There two kinds of pharmacological ligands for mGluR, competitive and non-competitive. Competitive ligands will interact with bi-lobed N-terminal domain ligand binding site. As non-competitive ligands, positive and negative allosteric modulators bind to heptahelical transmembrane domain in extracellular site.[9, 11] Group I mGluRs are known to increase the activity of NMDA receptros.[12] On the other hand, Group II and III mGluRs tend to protect neurons from excitotoxicity, possibly by reducing the activity of NMDA receptors.[13] Metabotropic glutamate receptors are also thought to affect dopaminergic and adrenergic neurotransmission.

NMDA Receptors

NMDA receptors are composed of assemblies of NR1 subunits, NR2 (A-D) subunits, and NR3 (A & B) subunit. They are assembled as tetramers of glycine-binding NR1, glutamate-binding NR2 and/or glycine-binding NR3. Expression of subunits of NR1 and at least one NR2, or NR1 and both NR2 and NR3 is required to form functional channels.[9, 14] NMDA receptors require both glutamate and a co-agonist, glycine, to bind to allow the receptor to function.[15] NR1/NR2 receptors are gated by both glycine and glutamate but the NR1/NR3 receptors are gated by only glycine. Therefore, NR1/NR3 heteromeric receptors do not function as a glutamate receptor (NR1/NR3 heteromeric receptors have no Glu binding site).[16]

There is no ion flow through the NMDA receptors when they are at resting membrane potentials due to a voltage-dependent blockage of the channel by magnesium

ions. The blockage can be reversed by the activation of AMPA receptors that depolarizes the post-synaptic terminal resulting in the release of magnesium ion so that the NMDA receptors can be activated.[17] NMDA receptors have high permeability to calcium ions as well as being permeable to other cations compared to GluR2-containing AMPA receptors. GluR2 receptor has Q/R (glutamine/arginine) editing site and most GluR2 receptor is a GluR2(R) form which is not permeable to calcium ions..[18] Therefore, the activation of NMDA receptor causes a calcium influx into the post-synaptic cells and this is one of the reasons why NMDA receptor activation is thought to have a crucial role for LTP and LTD.[19]

AMPA Receptors

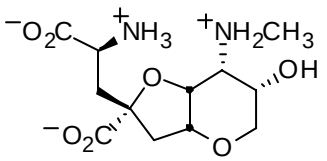
AMPA receptors are composed of subunits GluR1-4, products from separate genes. Like NMDA receptors, they are tetramers likely heteromeric. They also have an extracellular N-terminal and intracellular C-teminal and the ligand binding site is located between S1 and S2 region. Extreacellular domain S2 in the all AMPA receptors has splice variants called flip and flop to give further complexity to them. Small change in this region gives quite different desensitization kinetics to the AMPA receptors.[9, 20, 21] Almost all the native AMPA receptors are calcium ion impermeable and it is determined by the GluR2 subunit with the post-transcriptional editing of the mRNA. It is called Q/R (glutamine/arginine) editing site and located the pore loop M2 domain. GluR2(Q) is calcium ion permeable but GluR2(R) is not. Therefore, GluR2 is the most important subunit among those by governing calcium ion permeability which will affect AMPA receptor properties according to the composition of heteromeric receptors because GluR2 containing AMPA receptors will not allow calcium ion to pass the channel mostly.[22]

Kainate Receptors

Kainate receptors form both home or heteromeric tetramers from assemblies of GluR5-7 and KA1 and 2 and share many of the same structural characteristics as the NMDA and AMPA receptors. Calcium ion permeability is very slight in KA receptors but varies with their subunit composition because GluR5, 6 and 7 subunits also undergo alternative splicing and RNA editing similar to the AMPA receptor subunits. In addition, this explains reason why KA receptors have different pharmacologic and functional properties depending on their subunit composition.[9, 23]

II. DYSIHERBAINE AND ANALOGUES

Characterizing ionotropic Glu receptors is fundamental to assess their function in mammalian CNS processes such as learning and memory, and in CNS disorders including stroke, epilepsy and Alzheimer's disease. Selective ligands for Glu receptors are essential tools to facilitate the study of physiological and pathological processes in the mammalian CNS. However, the lack of selective ligands for these receptors, especially for kainate receptors, has made it difficult to do this. Therefore, finding a natural or novel synthetic selective iGlu receptor ligands is critical for the central nervous system research.[24]



dysiherbaine (DH)
1

Figure 1.4: Structure of dysiherbaine (**1**)

Dysiherbaine (**1**), (Fig 1.4) extracted from the Micronesian marine sponge *Dysidea herbacea*, is a neurotoxic excitatory amino acid, causing seizures upon injection into mice.[25] The structure is characterized by a *cis*-fused hexahydrofuro[3,2-b]pyran ring system containing a glutamic acid substructure.[26] Dysiherbaine is an agonist for AMPA and KA receptors. It showed more epileptogenic activity than DOM (domoate) or kainate, known KA receptor agonists, and has higher affinity (selectivity) for KA over AMPA receptors, but has almost no effect on NMDA receptors (Fig 1.5).[27] These results implicate that dysiherbaine potentially could be a good ligand for non-NMDA type ionotropic glutamate receptors.

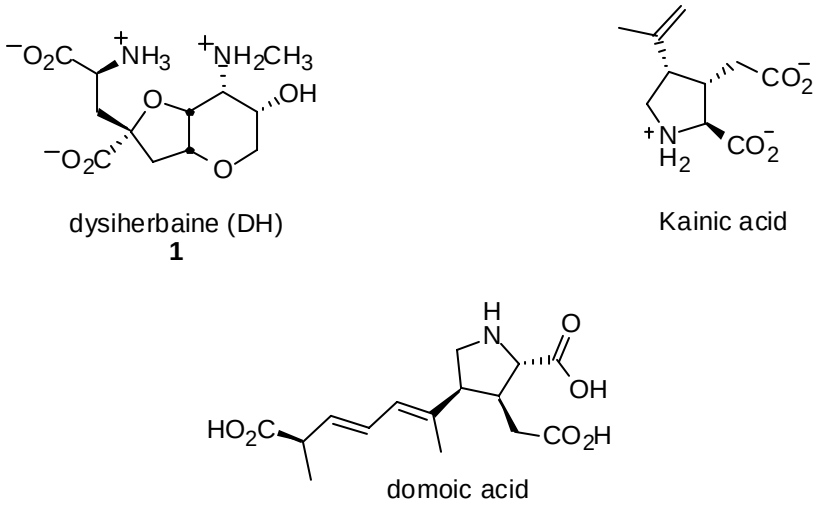


Figure 1.5: Structures of dysiherbaine (**1**) and representative KA receptor agonists.

For KA receptors, previous study has shown that dysiherbaine has high affinity for GluR5 and GluR6, but low affinity for KA2 subunits. This is one of the reasons why KA receptors show slightly different properties depending upon homomeric or heteromeric receptors.[28] Neodysiherbaine A (**2**), which is a minor extract from the same marine sponge, has different a functional group (-OH) at position C_8 from dysiherbaine and shows high affinity for KA2 but low affinity for GluR5 and GluR6 subunits. On the other hand, another analogue of dysiherbaine, MSVIII-19 (**3**) which has no functional groups on C_8 and C_9 positions, shows an antagonistic effect against KA receptors (MSVIII-19 was found to be a weak partial agonist later from Swanson's group) (Fig 1.6 & Table 1.1).[29, 30] These results reflect that small structural differences give rise to different pharmacologic properties and illustrate that the C_8-C_9 region of these molecules is an important pharmacophore.

Table 1.1: K_i values for DH (**1**) and related compounds for the displacement of [^{3}H]kainate from kainate receptor subunits.

	GluR5	*GluR6*	*KA2*
	*n*M	*n*M	μM
DH	0.5 ± 0.1	1.3 ± 0.1	4.3 ± 0.8
neoDH	7.7 ± 1.3	33 ± 9.0	0.6 ± 0.3
MSVIII-19	128 ± 21	> 100,000	> 100

Date in this table are adopted from ref 29 with permission. K_i values were calculated using the Cheng-Prusoff equation ($K_i = IC_{50}/(1 + [\text{radio-ligand}]/K_D)$). IC_{50} values were determined using a one-site competition fit using Prism 4 software. K_D values used were 73 *n*M, 13 *n*M, and 15 *n*M for GluR5, GluR6, and KA2 subunits, respectively. Values represent the mean ± S.E.M., n = 3.

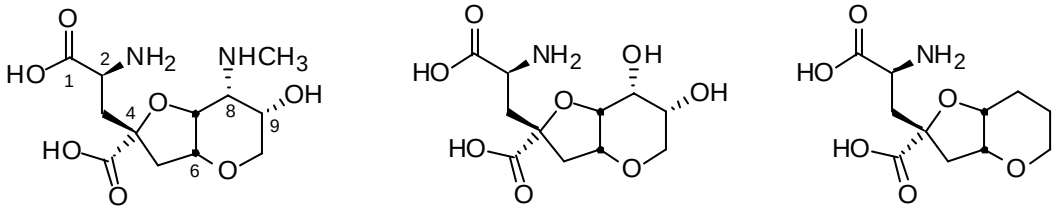


Figure 1.6: Structures of dysiherbaine (**1**) and its related compounds.

Previous studies have measured behavioral activity and affinities for KA and AMPA receptors with these five molecules, dysiherbaine (**1**), neodysiherbaine A **(2**) and their derivatives (Fig 1.7). 4-epiDH requires higher concentrations to induce the activity than DH. However, it showed similar behavioral profiles to DH despite its higher

concentration and structural change, notably, the seizure status lasted for as long as two days. 4-epi neoDH is also weak convulsant and its behavioral profile is similar to that induced by neoDH. 8,9-epineoDH is not convulsant at relatively high doses. In affinity studies, 4-epiDH is much more selective for KA over AMPA receptors like DH and this result shows C_4 stereochemistry may alter receptor selectivity between KA and AMPA.[26, 27]

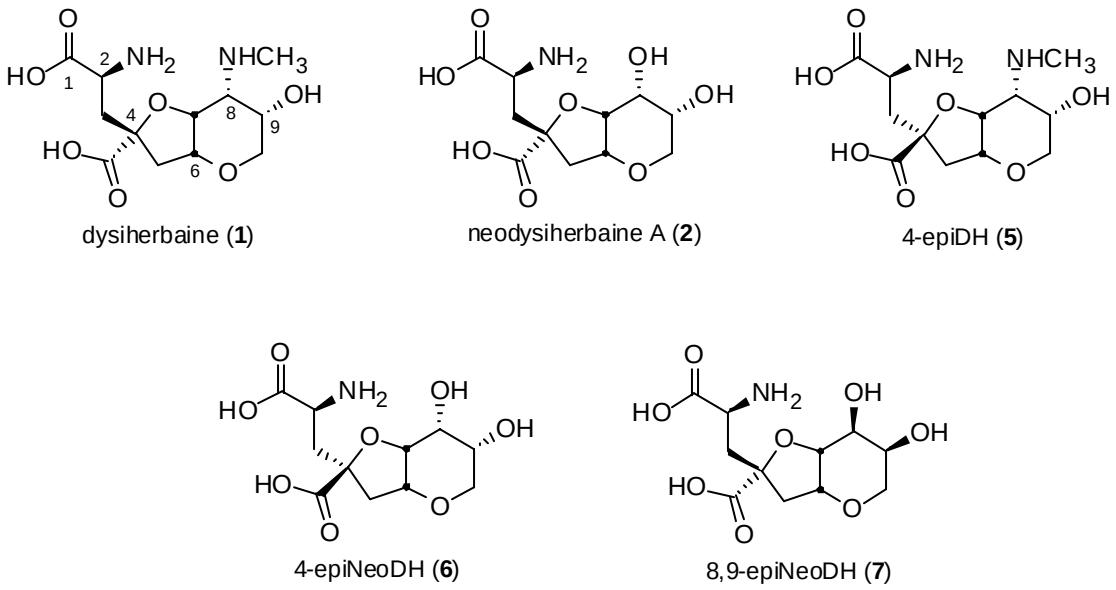
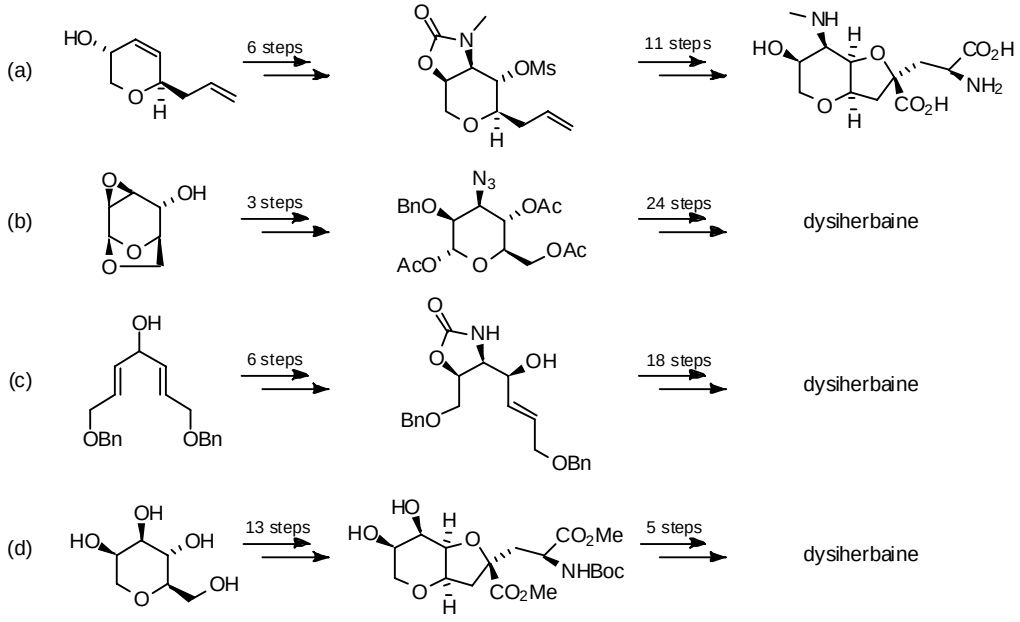


Figure 1.7: Structures of dysiherbaine (**1**) and its congeners.

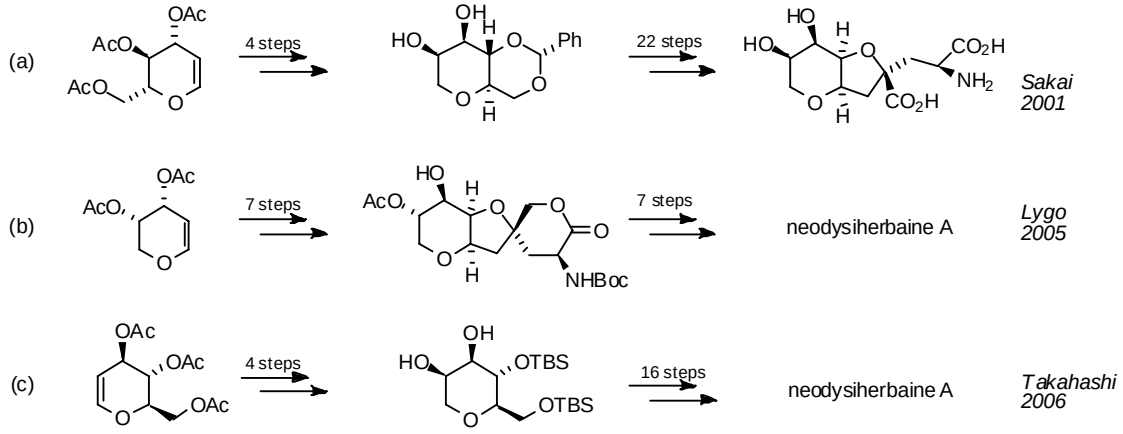
III. PREVIOUS TOTAL SYNTHESES OF DYSIHERBAINE & NEODYSIHERBAINE A

In terms of understanding and studying the structure and function of Glu receptors, especially KA receptors in the CNS, dysiherbaine and its known analogues are very useful molecules because of their unique pharmacological properties and selectivity for Glu receptors. However, their limited availability from natural sources delays further studies. Their novelty and low availability make them attractive targets for synthetic studies. There have been several reports of total syntheses of dysiherbaine (**1**) and neodysiherbaine A (**2**) described in the literature.[31-39] Simplified versions of seven synthetic routes for these molecules are presented in Scheme 1.1. One common feature of the each route for dysiherbaine is that the amino alcohol groups were installed just 3 or 6 steps from beginning of the routes (a), (b), and (c) (Scheme 1.1 (i)). In route (d), although the amino group was applied after 13 steps, dysiherbaine was made *via* neodysiherbaine A moiety which already had the diol group in the starting material. For neodysiherbaine A, the diol groups were generated just 4 or 7 steps into the synthesis (a), (b), and (c) (Scheme 1.1 (ii)). The incorporation of either the diol (neodysiherbaine A) or the amino alcohol (dysiherbaine) at an early stage renders probing the structure activity relationships of this important pharmacophore difficult since each new derivative will require a significant number of synthetic steps.

(i) Dysiherbaine

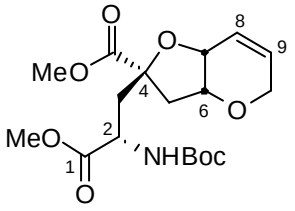


(ii) Neodysiherbaine A



Scheme 1.1: Previous total syntheses of dysiherbaine (**1**) and neodysiherbaine A (**2**).[31-37]

The ultimate goal of this project is the synthesis of dysiherbaine and its derivatives by a short, relatively cost-effective route that will allow for the synthesis of analogs at carbons 8 and 9. Our main target molecule is the olefin analogue (**4**) which has a carbon-carbon double bond between C_8 and C_9 (Fig 1.8). A double bond is a relatively selective site useful for adding variation. Once this molecule has been made, it will serve as the branch point for the rapid synthesis (few steps) of dysiherbaine and analogues thereof. This will play a pivotal role in developing agonists or antagonists for KA receptors that possess different selectivity than dysiherbaine and its known analogues.



4

Figure 1.8: Olefin analogue (**4**) as the main target.

Chapter 2: Synthesis of the Key Intermediate for Dysiherbaine & Its Analogues

I. TARGET MOLECULE 4

When developing the synthesis of a molecule there is no fixed synthetic route to a given structure. Hundreds of synthetic routes are possible for the synthesis of the same molecule. Each route has its own advantages and disadvantages. The ideal synthetic approach will have maximized desired features and minimized undesirable features. However what is defined as desirable in a synthetic route often depends on the purpose of the synthesis. In the case of our approach to dysiherbaine we believe our proposed route will maximize our access to potentially important analogues of dysiherbaine while also providing a short approach to the parent. The first goal is to synthesize the olefin analogue **4** (Fig 2.1). The target molecule **4** was chosen because it will give us dysiherbaine as well as serve as the branch point for the synthesis of other analogues. While there are a number of syntheses of dysiherbaine reported, they are not appropriate for the easy variation of the important C_8-amino C_9-alcohol pharmacophore. In every case, these approaches incorporate the pharmacophore very early in their respective routes. This effectively eliminates the potential for the easy systematic variation of this region of the molecule since each derivative would effectively require a new total synthesis (Scheme 1.1).

The molecule (**4**) has a double bond between the C_8 and C_9 position as the key reactive functional group. The principal reactivity that will be used to synthesize derivatives of this molecule involves the double bond. Addition reactions of electrophilic reagents to the double bond are the most typical, and include hydroxylation,

hydrogenation, halogenation, alkylation, amination, etc. This will provide a unique and simple way to make dysiherbaine and analogues with just few steps from molecule **4**.

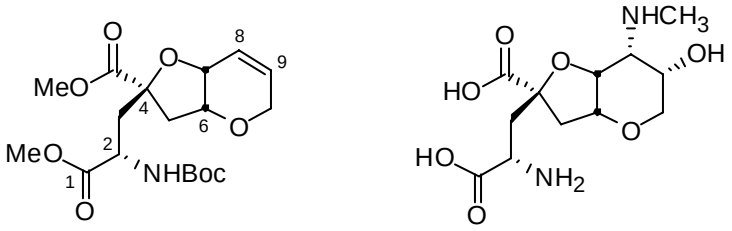
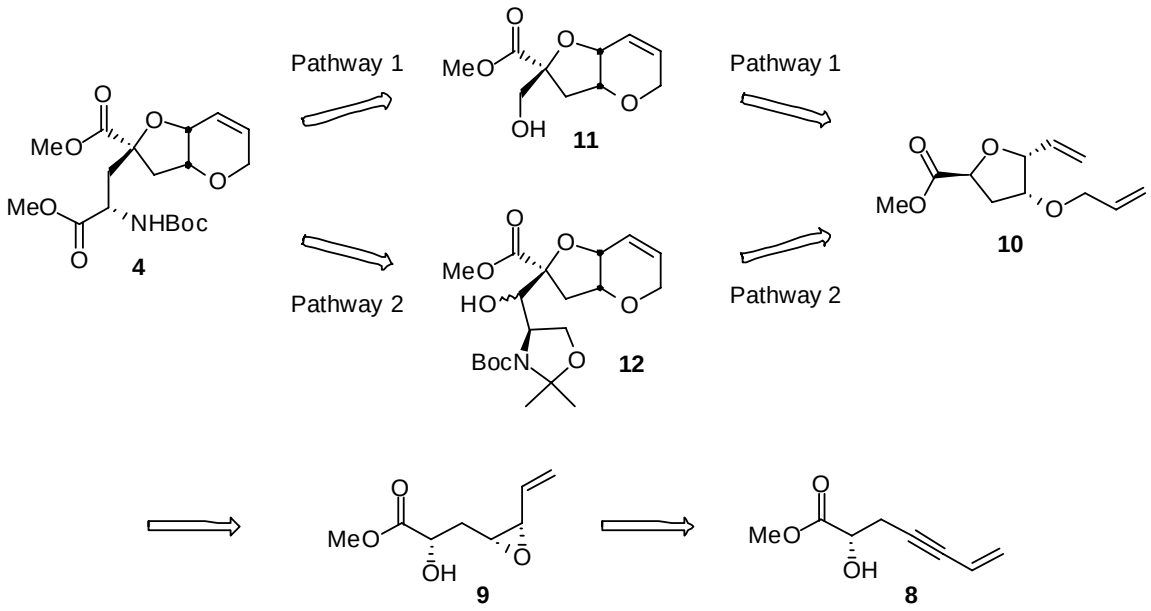


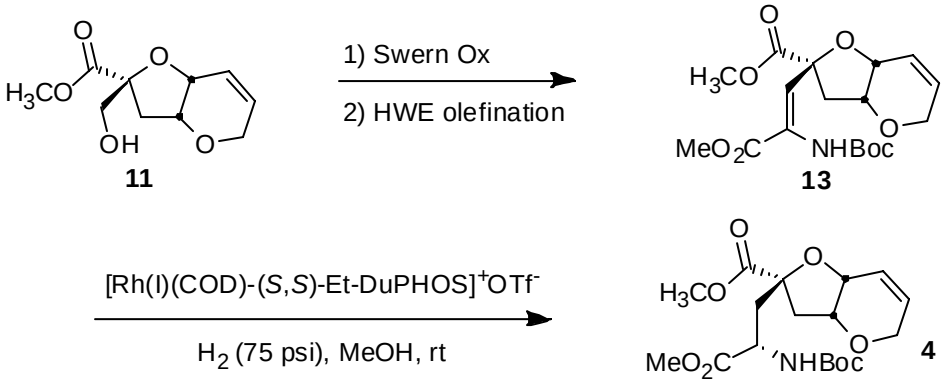
Figure 2.1: Target molecule **4** and dysiherbaine (**1**).

II. RETROSYNTHETIC ANALYSIS

Our retrosynthetic analysis of the target molecule **4** begins with two different pathways (Scheme 2.1). In pathway 1, the molecule **4** is formed by three consecutive reactions from molecule **11**, Swern oxidation, Horner-Wadsworth-Emmons olefination, and selective asymmetric hydrogenation (Scheme 2.2).

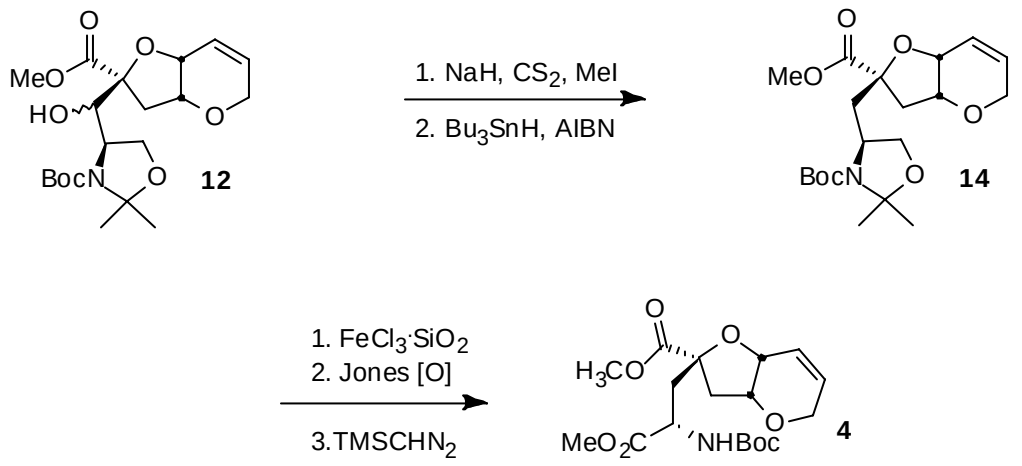


Scheme 2.1: Retrosynthetic analysis for target molecule **4**.



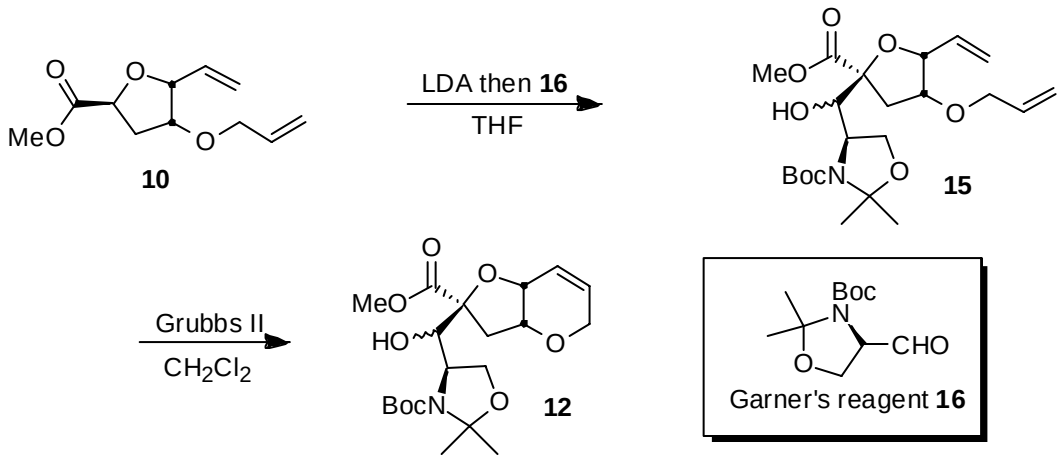
Scheme 2.2: Synthesis in pathway 1.

In pathway 2, the molecule **4** is formed by Barton-McCombie radical deoxygenation and Jones oxidation followed by esterification from bicyclic molecule **12** (Scheme 2.3). Compound **10** is a common intermediate for both of these pathways. Additionally both of these pathways form the required pyran ring via a metathesis reaction.

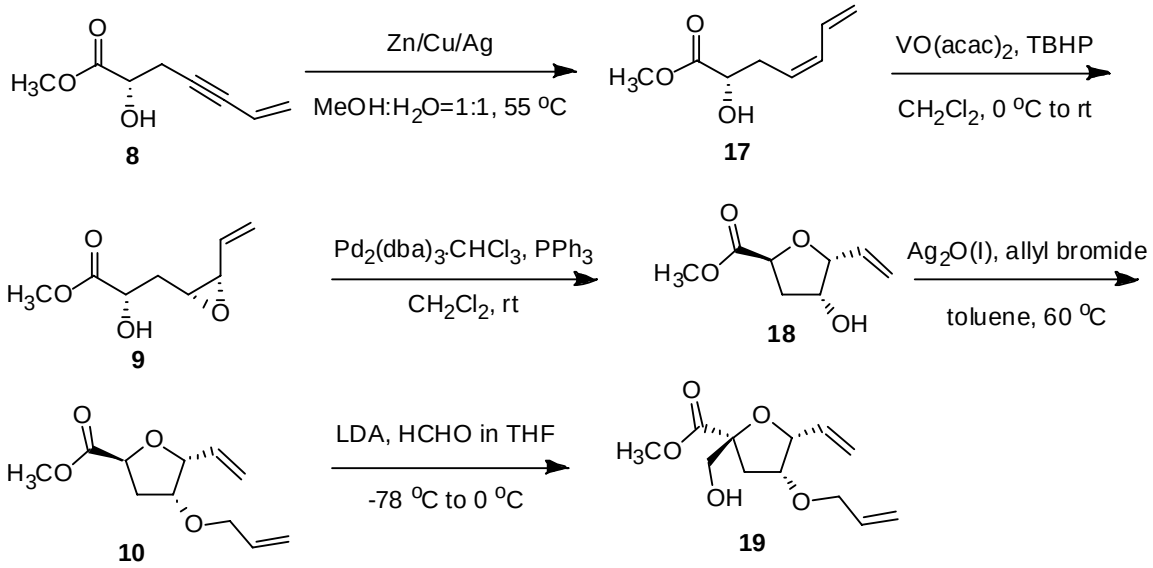


Scheme 2.3: Synthesis in pathway 2.

Addition of Garner's reagent and ring-closing metathesis from 5-membered ring **10** gives bicyclic molecule **12** (Scheme 2.4). Pathway 1 has been completed but pathway 2 has yet to be completed. Allylic ether **10** comes from regioselective epoxide opening and allylation of alcohol, respectively. By using Zn emulsion complex the triple bond of molecule **8** is reduced to *cis*-directed double bond to make homo allylic alcohol. Vanadium catalyzed epoxidation gives the epoxide **18** regio- and stereo-selectively (Scheme 2.5).



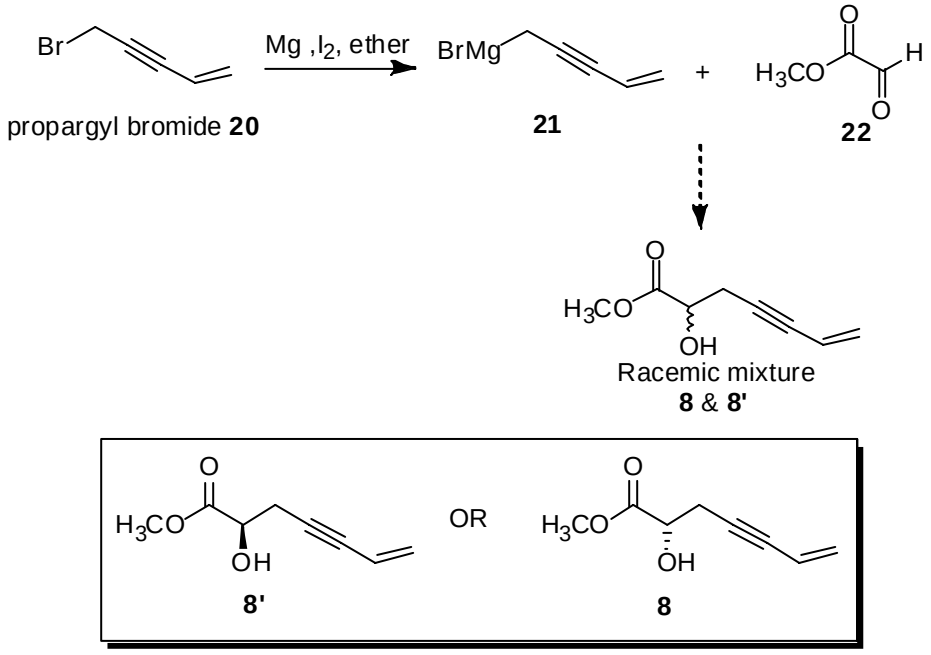
Scheme 2.4: Synthesis of **12** using Garner's reagent.



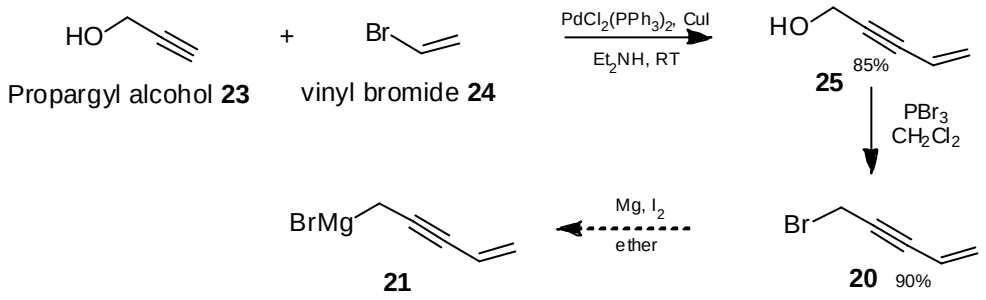
Scheme 2.5: Synthesis of **19** from molecule **8**.

III. SYNTHESIS OF ENYNE 8

Synthesis of enyne **8** was one of the most challenging steps. Our first route for this molecule was Grignard reaction using methyl glyoxalate (**22**) and propargylic bromide (**20**) (Scheme 2.6). The alcohol **25** was easily synthesized by Castro-Stephens coupling[40-43] of propargyl alcohol and vinyl bromide. Bromination of propargylic alcohol (**25**) gave the desired product **20** (Scheme 2.7).

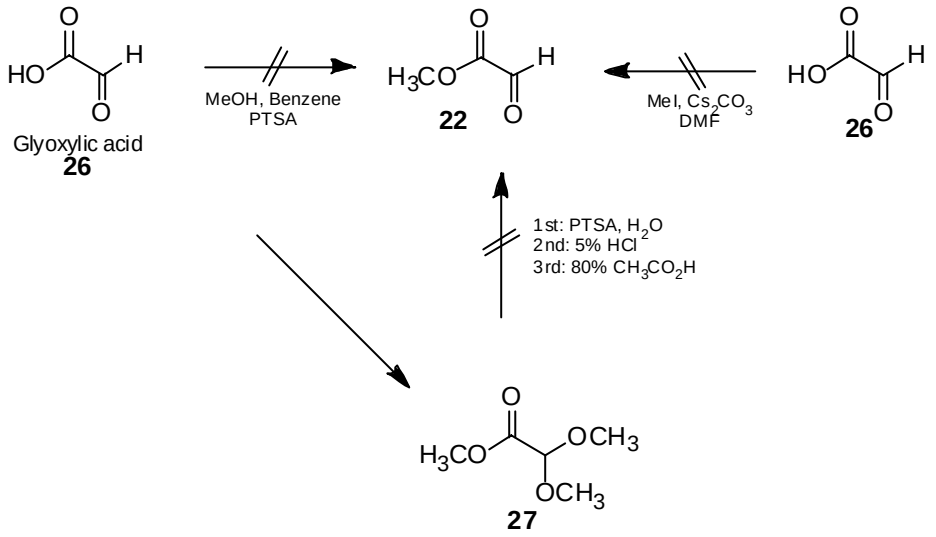


Scheme 2.6: First approach for the synthesis enyne **8** & **8'**.



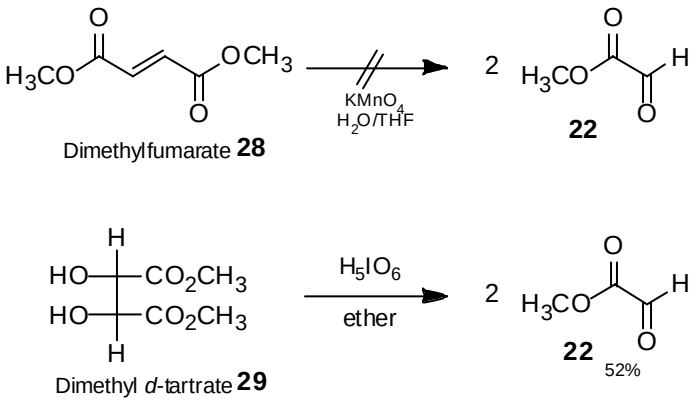
Scheme 2.7: Synthesis of alkyl bromide **20** for enyne.

Methylation of glyoxalate to form **22** was attempted by treatment of glyoxylic acid with methanol in benzene in presence of *p*-TSA. However, the dimethyl acetal **27** was formed by this procedure rather than the desired methylglyoxalate. The selective hydrolysis of **27** to methylglyoxalate (**22**) was attempted by three different reagents (PTSA, HCl and acetic acid). However we were not able to obtain glyoxalate (**22**). An alternative method, using methyl iodide and cesium carbonate was attempted but also failed. (Scheme 2.8).



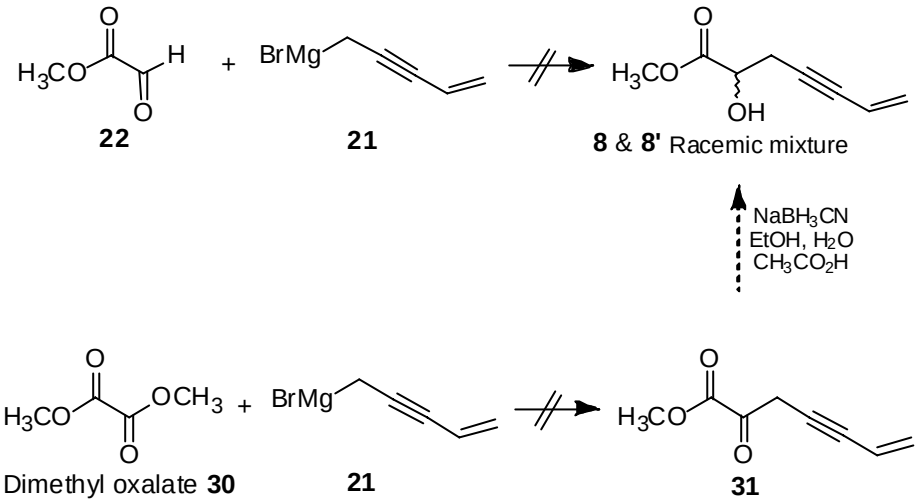
Scheme 2.8: Attempts for the synthesis of glyoxalate **22**.

Since esterification reactions were not successful, the oxidative cleavage of dimethylfumarate (**28**) and dimethyl *d*-tartrate (**29**) was attempted (Scheme 2.9).[44] While the cleavage of dimethylfumarate with potassium permanganate was not successful, the desired methylglyoxalate was successfully obtained, in 52% yield from dimethyl *d*-tartrate by using periodic acid.[45] With these two starting materials in hand, the Grignard reaction was performed to obtain enynes (**8 & 8'**). However this reaction did not provide the desired product (Scheme 2.10).

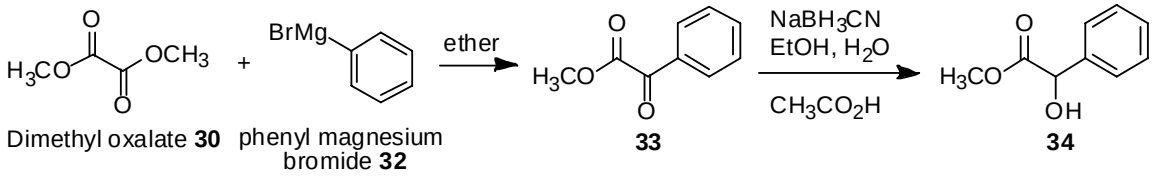


Scheme 2.9: Additional attempts for the synthesis of glyoxalate.

In the second approach, we replaced the starting glyoxalate with dimethyl oxalate (**30**) which would have produced α-keto ester **31**. The ketone group in molecule **31** would then be reduced to alcohols (**8 & 8'**) (Scheme 2.10). As a test reaction, we successfully made molecule **34** by Grignard reaction followed by reduction (Scheme 2.11). Our system, however, with dimethyl oxlalate and enyne magnesium bromide **21** gave no product and starting materials were recovered in the reaction (Scheme 2.10). Based on the results from the first and second routes, it was decided that the desired enyne magnesium bromide **21** was not generated in high yield.



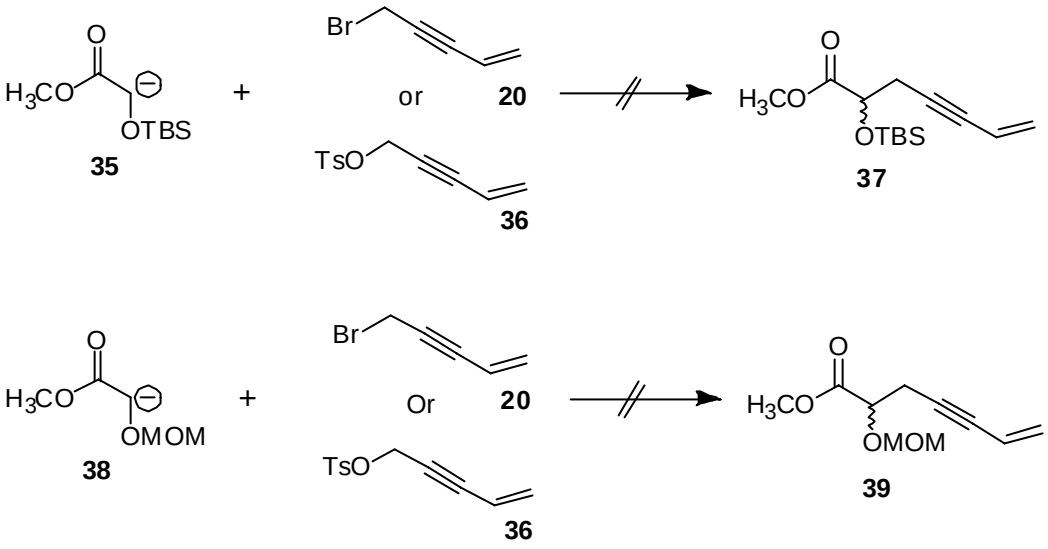
Scheme 2.10: Using of glyoxalate & dimethyl oxalate for Grignard reaction.



Scheme 2.11: Test reaction using dimethyl oxalate.

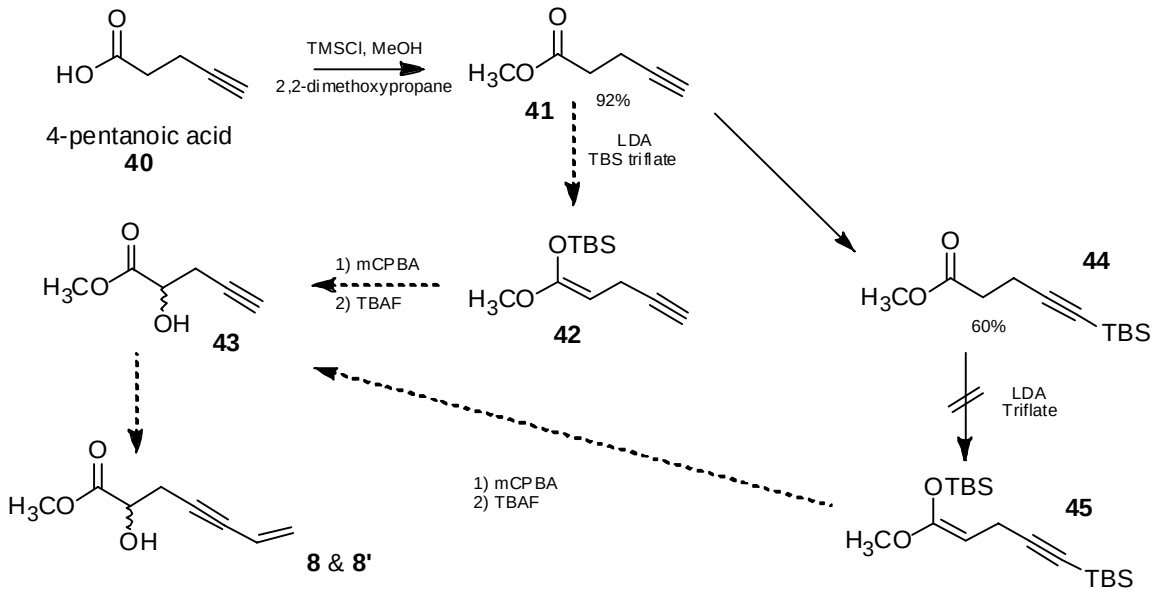
After failing in the first two routes it was decided to change the properties of the starting materials, from electrophile to nucleophile and nucleophile to electrophile. As the third route, we generated two different nucleophiles and electrophiles and performed four

different reactions two by two (Scheme 2.12). In these cases the desired molecules were once again not obtained.



Scheme 2.12: Sn2 reactions for the synthesis of enyne (**37** or **39**).

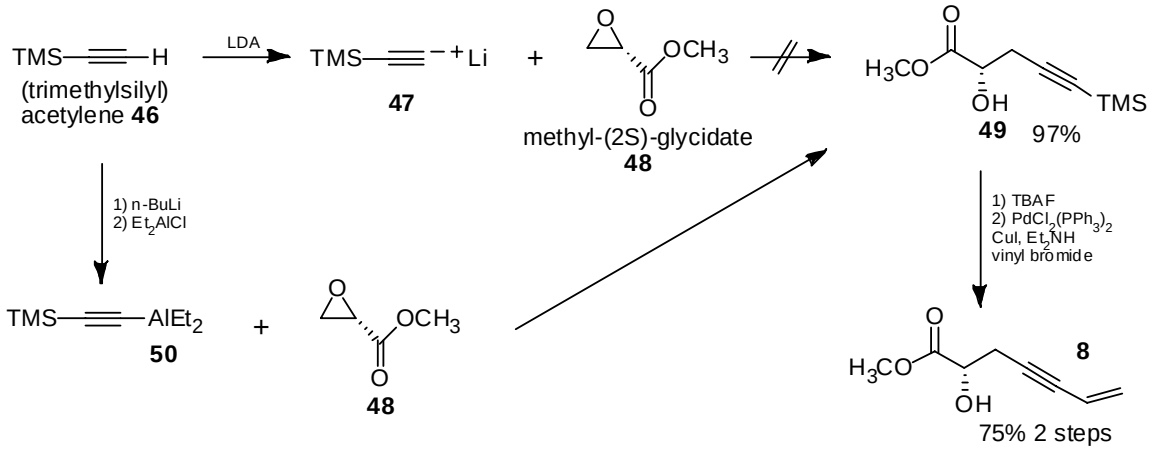
Next, the synthesis with using 4-pentanoic acid (**40**) was attempted. The plan was esterification, enolization followed by epoxidation and epoxide opening to obtain an intermediate (**43**) that would be used in a Castro-Stephens coupling (Scheme 2.13). Methylester **41** was obtained in 92% yield with methanol and TMSCl. Attempt to use LDA to form the necessary enolate resulted in the formation of **44**. Treatment of **44** with LDA followed by *tert*-butyldimethylsilyl triflate resulted in the recovery of unreacted starting material.



Scheme 2.13: Route using 4-pentanoic acid for the synthesis of enynes (**8** & **8'**).

The next attempt was the epoxide opening reaction using methyl glycidate (**48**) and (trimethylsilyl)acetylene anion (**47**) (Scheme 2.14). The acetylide anion (**47**) was generated with LDA and was combined with methyl-(2*S*)-glycidate (**48**). However, the reaction gave a mixture of products where the acetylide added to both the epoxide and the ester. Attempts to find regio-selective addition between the epoxide ring and carbonyl group lead to the preparation of alkynyl aluminum reagent which was reported to react in a similar fashion to cupurates.[46-49] After generation of the acetylide anion with n-BuLi and the anion was treated with diethyl aluminum chloride resulting in diethyl aluminum

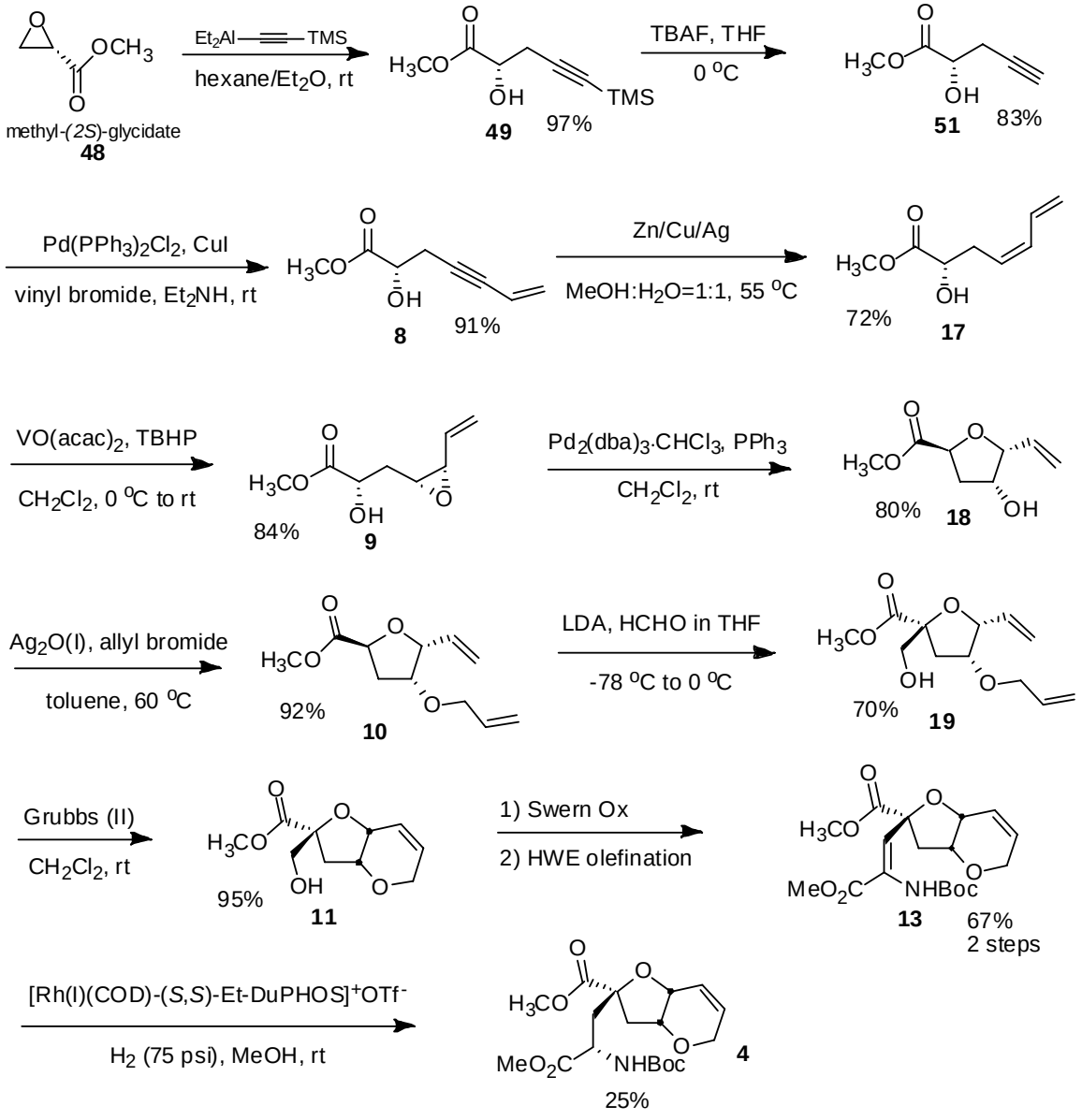
acetylene reagent **50**. This aluminum reagent gave molecule **49** when reacted with methyl glycidate in 91% yield. Finally, deprotection of the molecule **49** with TBAF followed by Castro-Stephens vinyl coupling gave molecule **8** (Scheme 2.14). Both enantiomers, methyl-2(*R*)-glycidate and methyl-2(*S*)-glycidate, are commercially available. In the initial reaction methyl-2(*S*)-glycidate was used. The chiral center from the epoxide opening will be used to direct the next diastereoselective step in this route, the epoxidation of the diene.



Scheme 2.14: Epoxide opening reaction for the synthesis of enyne **8**.

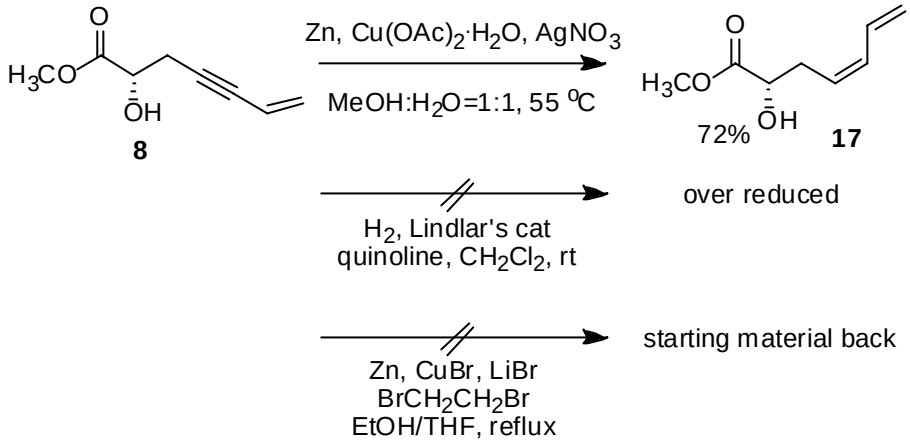
IV. SYNTHESIS OF TARGET MOLECULE

With the enyne **8** in hand, we continued the synthesis toward our target molecule. (Scheme 2.15).



Scheme 2.15: Forward synthesis of target molecule **4**.

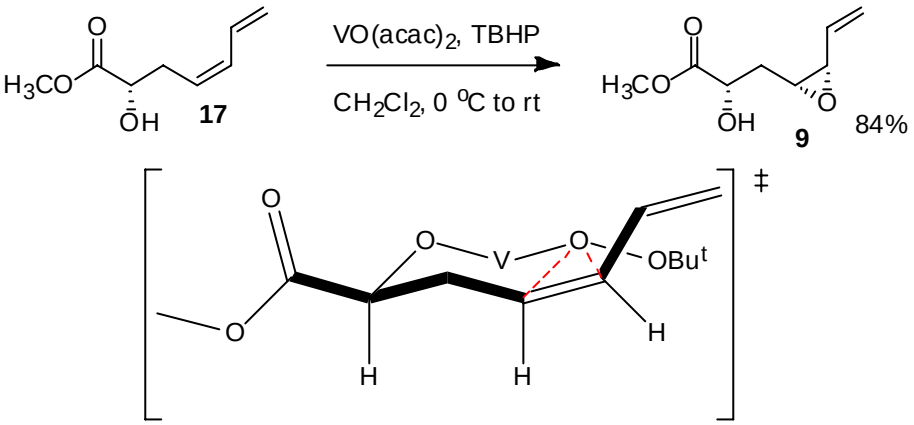
Initially, the necessary syn reduction of the alkyne to a *cis* diene **17** was attempted with Lindlar's catalyst. This system proved resistant to this reagent. Early in the reaction based on TLC the desired molecule appeared to form but was contaminated with the over reduced product (Scheme 2.16).



Scheme 2.16: *cis*-directed selective hydrogenation of enyne **8**.

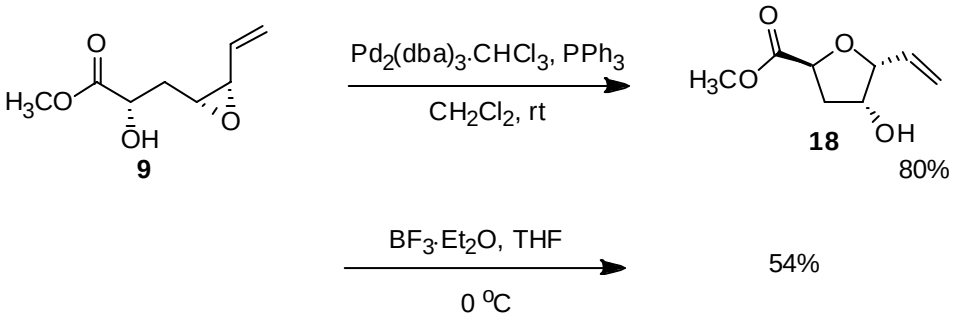
Attempts to control this reaction to provide the diene, by altering time, catalyst, or hydrogen gas pressure failed. Alternatively, other reducing conditions using an activated Zn complex (Scheme 2.16) succeeded. Among two different versions of this reaction attempted the second, with active Zn complex from Zn dust, copper(II) acetate monohydrate, and silver nitrate in methanol and water mixture gave the product **17** in 72% yield.[50] The proton coupling constant between the two olefinic protons proved that the reaction gave only the *cis*-directed double bond. Regio-, stereo-selective epoxidation of homo-allylic alcohol **17** was performed by using vanadium acetotoacetate with *tert*-butyl hydroperoxide in methylene chloride. This procedure gave a 10:1 mixture of the desired diastereomer **9** in 84% yield.[51-54] Based on the theoretical transition state, (*S*)-

configured homoallylic alcohol **17** will be coordinated with vanadium catalyst to afford desired the epoxide as a main diastereomer as described in Scheme 2.17.[51]



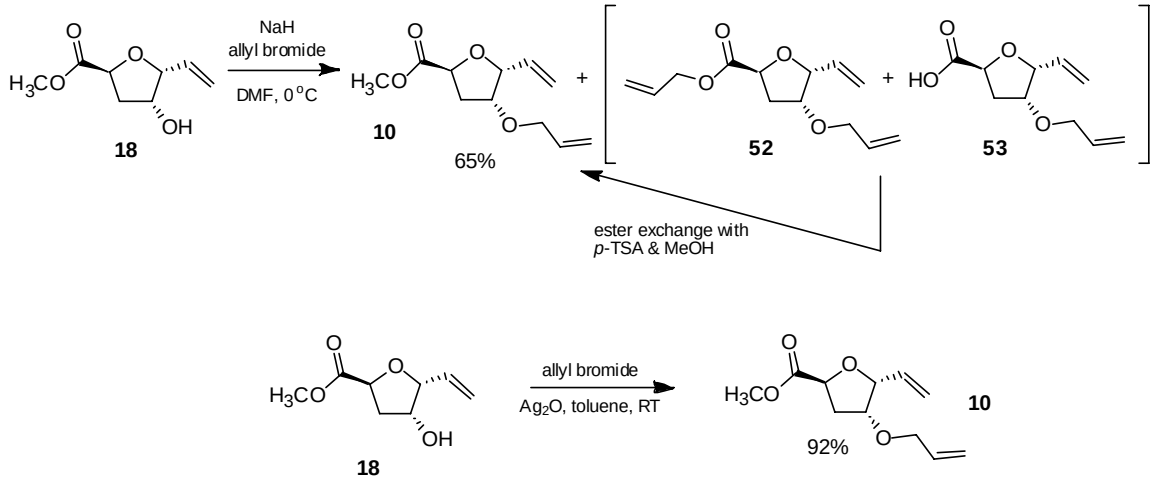
Scheme 2.17: Stereo and regio selective epoxidation and its transition state.

The next step was epoxide opening to form the 5-membered tetrahydrofuran **18**. This step required extensive optimization to find the best Lewis acid and reaction conditions. Eventually boron trifluroride etherate was found to be the best reagent.[55] However, the reaction yield was only modest (54%). An alternate procedure using palladium catalyst, in the presence of triphenyl phosphine in dichloromethane gave the desired furan ring **18** in 80% yield (Scheme 2.18).[56-58]



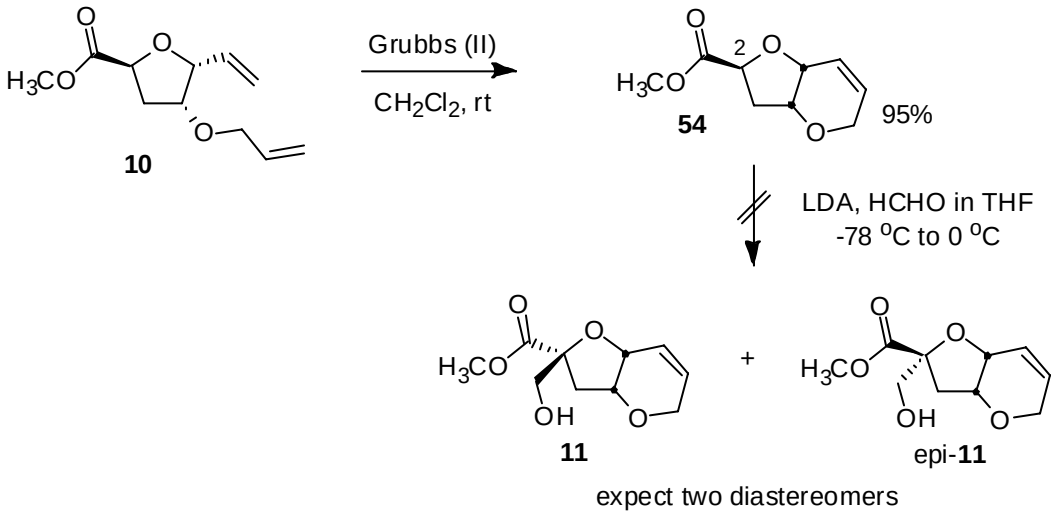
Scheme 2.18: Epoxide opening reactions.

Transformation of alcohol on the ring to allylic ether was performed with NaH and allyl bromide in DMF. Although this reaction gave the product (**10)**, it required the additional reaction of converting the allyl ether side products (**52** & **53**) to the desired ester **10** (total 65% yield). To avoid the formation of these side products an alternate approach with silver(I) oxide was used. This method with allyl bromide in toluene afforded the allylic ether **10** in good yield (92%) without side products (Scheme 2.19).[59, 60]



Scheme 2.19: Transformation of alcohol to allylic ether.

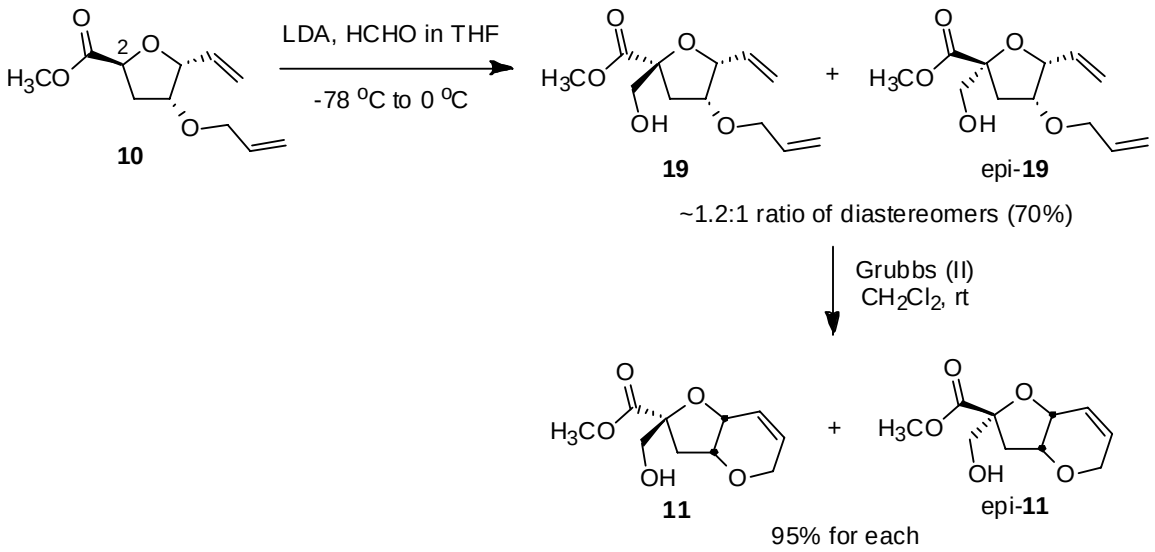
The next challenge was the generation of the quaternary center at the C_2 position of molecule **54** on the precursors (**11** & its epimer). Initially, a sequence was attempted that involved ring closing metathesis, with Grubbs(II) catalyst, followed by alkylation with LDA and formaldehyde solution in THF.[61, 62] However, this reaction gave the starting material back along with its epimer (Scheme 2.20). Based on formation of the epimer, it was clear that the necessary anion was generated but addition of formaldehyde did not occur.



Scheme 2.20: Attempt to generate quaternary carbon center.

The failure of the initial attempts on compound **54** lead to the development of alternate approach in which the formation of quaternary center is performed before the metathesis reaction. Deprotonation followed by reaction with formaldehyde generated the quaternary carbon center as about 1.2:1 ratio of diastereomers (epimers) in 70% yield (Scheme 2.21).[62] Although *R*-configured stereochemistry (molecule epi-**19**) is not the correct to provide dysiherbaine, this diastereomer is also required as a scaffold for

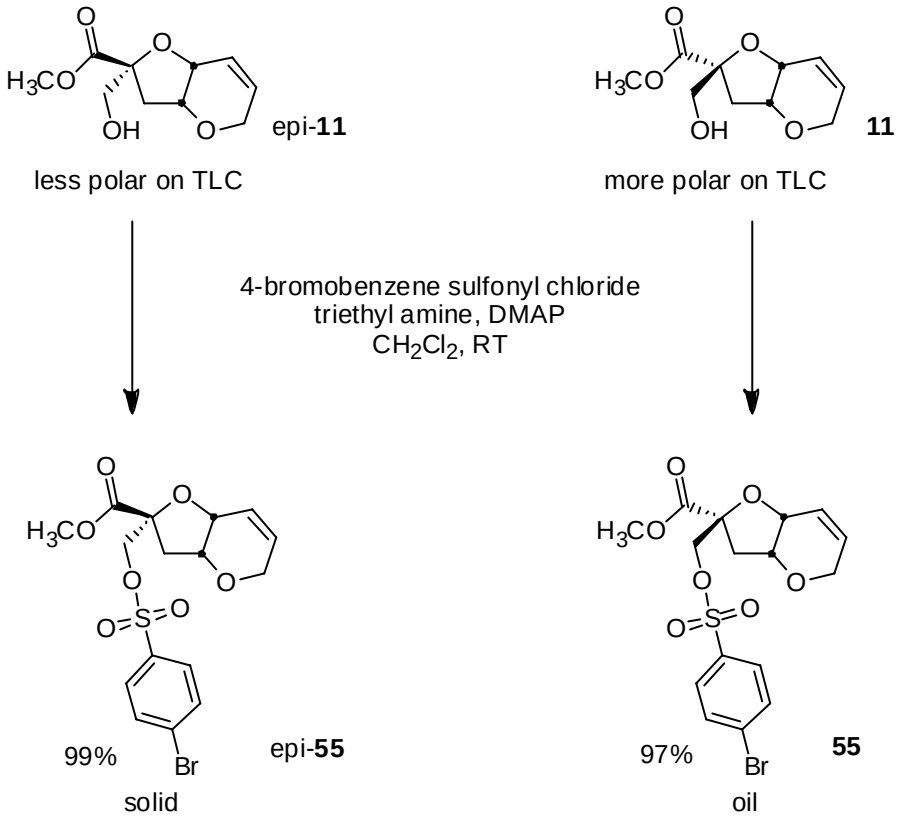
research on glutamate receptor ligands. In later versions of this synthesis we hope to better control the stereochemistry at C_2. Two diastereomers (**19** & epi-**19**) were separated and purified by silica gel column chromatography. Following this step they were subjected to ring closing metathesis with Grubbs(II) catalyst. The rings were closed successfully in good yields (95% for each diastereomer) (Scheme 2.21).[63-65]



Scheme 2.21: Alkylation of C_2 center and ring closing methathesis.

Before proceeding to the next step, the stereochemistry of these molecules was verified. Since two diastereomers (**11** & epi-**11**) are oily compounds, it was necessary to derivatize the molecules to obtain crystals for X-ray crystallography study. 4-bromo benzene sulfonyl group was attached at the alcohol group of each diastereomer. High quality crystals, suitable for X-ray diffraction were obtained from the less polar diastereomer while the polar diastereomer remained an oil (Scheme 2.22). Based on the

X-ray structure, it was determined that the less polar diastereomer has the structure assigned epi-**55.** (Scheme 2.22 & Fig 2.2).



Scheme 2.22: Preparation for X-ray crystallography.

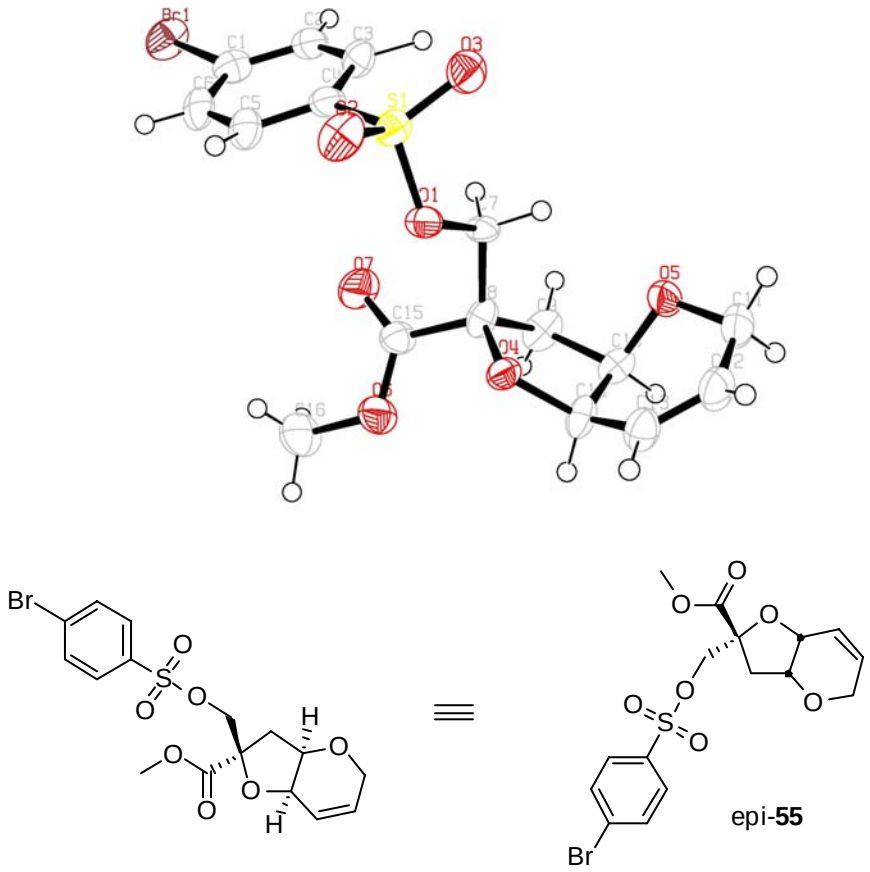
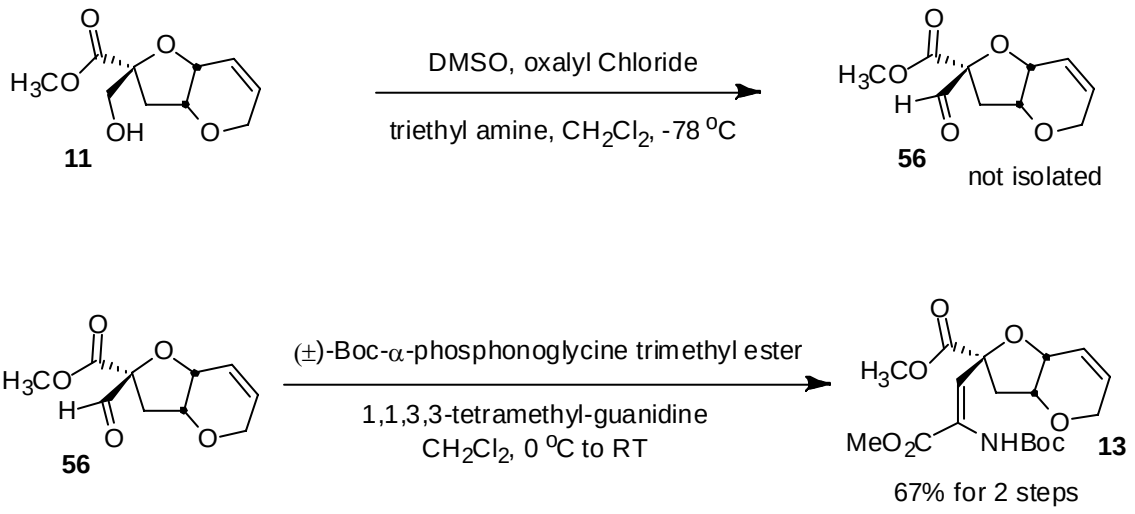


Figure 2.2: X-ray structure of molecule epi-**55**.

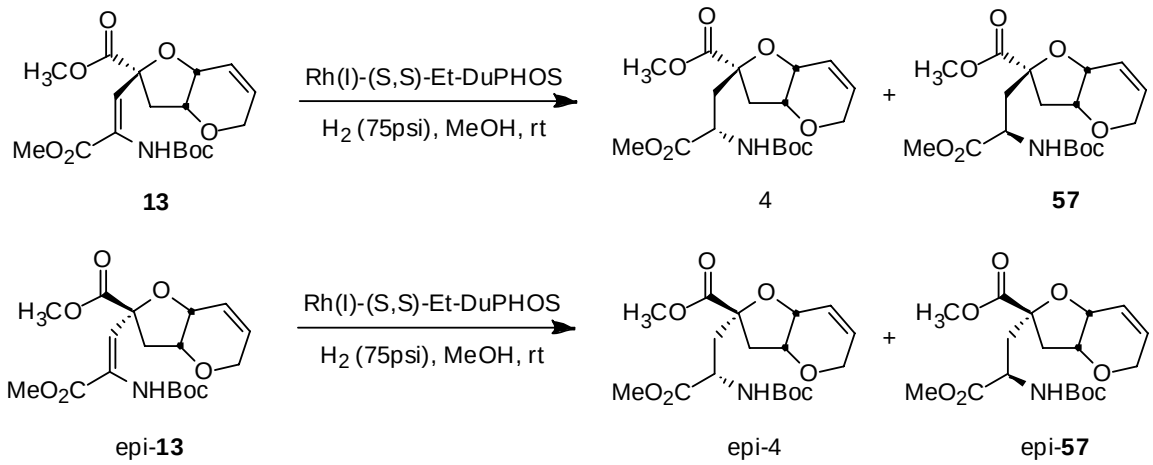
Swern oxidation[30, 66, 67] of the alcohol **11** provided the aldehyde **56** which then underwent a Horner-Wadsworth-Emmons olefination[30, 68] to introduce the amino acid moiety and provide **13** (Scheme 2.23). Oxidation was performed with DMSO, oxalylchloride, and triethyl amine in methylene chloride. This aldehyde was used for the next reaction without purification. Three different amine protected reagents were used in the HWE olefination, Boc, Cbz, and acetyl protected amine groups. Each protecting

group afforded the molecule with slightly different yields over the two steps (Boc: 67%, Cbz: 70%, Ac: 53%).



Scheme 2.23: Swern oxidation and HWE olefination.

Finally, selective asymmetric hydrogenation of the enamide in molecule **13** gave the desired target molecule (**4**) (Scheme 2.24). The reaction was attempted on the three different *N*-protected molecules in the presence of $[Rh^{I}(COD)$-(*S*,*S*)-EtDuPHOS$]^{+}OTf^{-}$ as a catalyst in THF under hydrogen (75psi) at room temperature. In all three cases the desired products were not obtained. Both double bonds were reduced. The reaction was then run in methanol under the same conditions. This approach provided the desired reduction product in moderate yield (Table 2.1).[30, 69] Although the last step required further optimization, the target molecule **4** is ready for application toward the synthesis of analogues as well as dysiherbaine itself.



Scheme 2.24: Selective asymmetric hydrogenation.

Table 2.1: Hydrogenation of molecule **13** with different *N*-protecting groups.

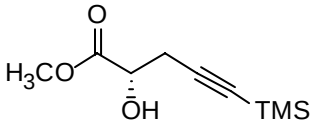
Protecting group	Yield (%)	Recovery of Starting material	Separation of diastereomer by column
Boc (**13**)	25%	50%	Yes (5:1)
Cbz	32%	50%	Yes (4:1)
Acetyl	52%	29%	No

In summary, a concise and stereoselective synthesis of target molecule **4** has been developed. Our synthesis requires 12 steps from commercially available methyl-2(*S*)-glycidate. The absolute configuration of the target molecule has been established by X-ray crystallography. The target molecule will permit variability at C_8 and C_9 by modification of the double bond.

V. EXPERIMENTAL SECTION

General procedures. Unless noted all chemicals were purchased from Aldrich Chemical Co. or Acros Chemicals and used without further purification. Anhydrous toluene and CH_2Cl_2 were obtained from a Pure Solv® solvent drying system by Innovative Technology. Anhydrous THF was obtained from distillation from sodium metal and benzophenone prior to usage. Reactions were monitored by TLC using Aldrich polyester silica gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed using silica gel (ICN Silitech 32-63 D, 60 Å). ^{1}H NMR spectra were recorded on a Varian Mercury 300 spectrometer (300 MHz) and are reported in parts per million (δ) relative to TMS. Coupling constants (J) are reported in Hertz. ^{13}C NMR spectra were obtained using a Varian Mercury 300 spectrometer (75 MHz) and are reported in parts per million (δ) relative to TMS. Mass spectra were recorded on Surveyor MSQ LC-MS from ThermoFinnigan. All reactions, unless otherwise noted, were carried out under N_2 in oven-dried glassware. Schlenk tubes were carefully washed with acid, thoroughly rinsed, and oven-dried prior to use.

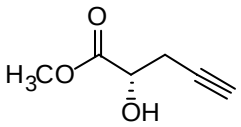
(*S*)-methyl 2-hydroxy-5-(trimethylsilyl)pent-4-ynoate (49)



(Trimethylsilyl)acetylene (1.2 g, 12.2 mmol) was added to 10 mL of hexane at 0 ℃ under N_2 atmosphere. *n*-Butyllithium (2.5 M in hexane, 4.9 mL, 12.2 mmol) was added to the acetylene solution at 0 ℃; sufficient dry Et_2O was added to dissolve the salts. This solution was stirred at 0 ℃ for 1.5 h to form the lithium acetylide. The lithium

acetylide solution was transferred *via cannula* under N_2 atmosphere to a dry reaction flask that contained Et_2AlCl (1 M in hexane, 12.2 mL, 12.2 mmol)), producing a white precipitate. This solution was then stirred for 3.5 h at room temperature; the precipitate was allowed to settle and the supernatant was transferred to a third dry reaction flask *via cannula*. Methyl-(*2S*)-glycidate (**48**) (0.5 g, 4.9 mmol) was added to the transferred supernatant at room temperature. After stirring at room temperature for 3.5 h, the reaction was cooled in an ice bath and quenched with 0.3 M HCl. The resulting solution was washed with 0.3 M HCl (20 mL) and water (20mL) and extracted with ethyl acetate (3 × 20 mL). The organic extract was dried over $MgSO_4$, followed by filtration and solvent removal to give dark yellow oil. After purification by flash chromatography, eluting with 1:3 EtOAc/hexane, 0.97 g (91%) of the hydroxyl pentynoate **49** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (dt, J = 7.2, 4.5 1H), 3.82 (s, 3H), 3.02 (d, J = 7.2 Hz, 1H), 2.73 (dd, J = 4.8, 2.1 Hz, 2H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 100.8, 88.4, 69.2, 52.9, 26.6, 0.3; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_9H_{16}O_3Si$: 223.0766, measured 223.0744.

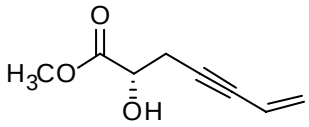
(*S*)-methyl 2-hydroxypent-4-ynoate (51)



Compound **49** (7.68 g, 38 mmol) was added to 200 mL of THF at 0 ℃ under N_2 atmosphere. TBAF (1 M in THF, 13.3 mL, 13.3 mmol) was dropped to the reaction at 0 ℃. After stirring at 0 ℃ for 1 h, solvent was removed *in vacuo*. The crude product was purified by flash chromatography, eluting with 3:4:2 EtOAc/hexane/CH_2Cl_2, 4.1 g (83%)

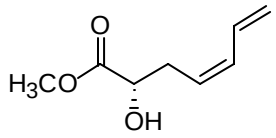
of the hydroxyl alkyne **51** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (dt, J = 6.6, 4.8 Hz, 1H), 3.78 (s, 3H), 3.25 (d, J = 6.6 Hz, 1H), 2.66 (ddd, J = 8.7, 5.1, 2.7 Hz, 2H), 2.05 (t, J = 2.4 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 78.9, 71.6, 69.1, 53.1, 25.1; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_6H_8O_3$: 151.0371, measured 151.0377.

(*S*)-methyl 2-hydroxyhept-6-en-4-ynoate (8)



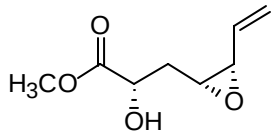
Compound **51** (11.1 g, 86 mmol) was added to a solution of 175 mL of diethylamine, dichlorobis(triphenylphosphine)-palladium(II) (300 mg, 0.43 mmol), and copper iodide (160 mg, 0.86 mmol) at room temperature under N_2 atmosphere. Excess (more than 2 eq. of vinyl bromide) of liquefied vinyl bromide was dropped into the reaction at room temperature. After stirring at room temperature for 15 h, solvent was removed *in vacuo*. The crude product was filtered through celite to remove the catalysts. Water was added and the mixture was extracted with ethyl acetate three times. The combined organic layer was concentrated *in vacuo* and purified by flash chromatography, eluting with 1:3 EtOAc/hexane, 12.2 g (91%) of the hydroxyl heptenynoate **8** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddt, J = 17.7, 10.8, 2.1 Hz, 1H), 5.56 (dd, J = 17.4, 2.4 Hz, 1H), 5.41 (dd, J = 11.1, 2.7 Hz, 1H), 4.33 (dt, J = 5.1, 4.8 Hz, 1H), 3.80 (s, 3H), 3.05 (d, J = 5.1, 1H), 2.80 (ddd, J = 9.0, 4.5, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 127.0, 117.1, 84.7, 82.4, 69.3, 53.1, 26.1; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_8H_{10}O_3$: 177.0528, measured 177.0521.

(*S*,*Z*)-methyl 2-hydroxyhepta-4,6-dienoate (17)



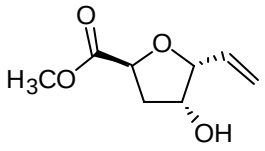
Zinc dust (19.8 g, 303 mmol) was treated with 50 mL of 3% HCl for 1-2 min, and then the liquid was decanted. This was repeated two more times, after which the zinc slurry was rinsed repeatedly with distilled water to remove traces of acid. A solution of copper(II) acetate monohydrate (1.69 g, 8.5 mmol) in 50 mL of distilled water was added slowly to the zinc slurry while cooling in an ice bath. The mixture was stirred for 10-15 min, and a solution of silver nitrate (1.86 g, 11.0 mmol) in 50 mL of distilled water was added likewise. The resulting mixture was filtered, and the active zinc reagent was suspended in a mixture of 50 mL of MeOH and 60 mL of distilled water. A solution of compound **8** (1.37 g, 8.8 mmol) in 10 mL of MeOH was added at once, and the mixture was stirred at 50-60 ℃ for 15 h under an N_2 atmosphere. Upon completion of the reaction by TLC, the unreacted Zn/Cu/Ag was filtered off and washed with 50 mL of MeOH and then with a mixture of 80 mL of MeOH and 10 mL of 10% HCl. The filtrate was extracted with CH_2Cl_2. The extract was dried with $MgSO_4$ and evaporated to give homoallylic alcohol **17** (1.37g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (ddd, J = 16.8, 10,6, 10.6 Hz, 1H), 6.12 (dd, J = 10.8, 10.8 Hz, 1H), 5.45 (dt, J = 10.8, 7.5 Hz, 1H), 5.20 (d, J = 16.8 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.28 (dd, J = 5.4, 5.1 Hz, 1H), 3.74 (s, 3H), 3.05 (s, 1H), 2.71-2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 132.7, 131.8, 125.5, 118.6, 70.5, 52,8, 32.9; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_8H_{12}O_3$: 179.0684, measured 179.0682.

(*S*)-methyl 2-hydroxy-3-((*2R,3S*)-3-vinyloxiran-2-yl)propanoate (9)



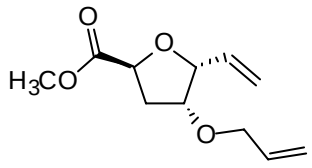
Compound **17** (3.48 g, 22.3 mmol) was added to the solution of 180 mL of dichloromethane and vanadyl(IV) acetylacetonate (0.12 g, 0.45 mmol) at 0 ℃ under N_2 atmosphere. *tert*-butyl hydroperoxide (5.5 M in decane, 6.1 mL, 33.5 mmol) was slowly dropped into the reaction mixture at 0 ℃. After stirring for 30 min at 0 ℃, the reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum, then diluted with ethyl acetate (200 mL) and washed two times with a saturated solution of $Na_2S_2O_3$ (100 mL). The aqueous layer is separated and washed one time with ethyl acetate (100 mL), the collected organic layers are washed one time with brine (200 ml), dried with $MgSO_4$, and concentrated under vacuum. The resulting crude product was purified by flash chromatography, eluting with 1:1 EtOAc/hexane, 3.24 g (84%) of the epoxide **9** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.1, 10.2, 6.6 Hz, 1H), 5.52 (d, J = 17.1 Hz, 1H), 5.38 (d, J = 10.5 Hz, 1H), 4.43- 4.37 (m, 1H), 3.80 (s, 3H), 3.49 (dd, J = 6.9, 4.2 Hz, 1H), 3.35, (dt, J = 6.9, 4.8 Hz, 1H), 2.87 (d, 5.7 Hz,1H), 2.01 (dd, J = 7.2, 3.9 Hz 1H), 1.91 (dd, J = 8.4, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 132.1, 120.9, 68.8, 57.4, 55.5, 53.0, 32.9; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_8H_{12}O_4$: 195.0633, measured 195.0629.

(*2S,4R,5R*)-methyl 4-hydroxy-5-vinyltetrahydrofuran-2-carboxylate (18)



To a stirred solution of epoxide **9** (4.20 g, 24.5 mmol) in 170 mL of dry dichloromethane was added $Pd_2(dba)_3 \cdot CHCl_3$ (1.01 g, 4 mol%) and PPh_3 (1.28g, 20 mol%) at room temperature under nitrogen atmosphere. After the mixture was stirred for 1 h, the solvent was removed *in vacuo*. The resulting crude product was purified by flash chromatography, eluting with 3:2 EtOAc/hexane, 3.00 g (71%) of the furan **18** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd, J = 17.1, 10.5, 6.0 Hz, 1H), 5.56 (d, J = 17.4 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H), 4.59 (dd, J = 9.9, 2.7 Hz, 1H), 4.44-4.41 (m, 1H), 4.26-4.21 (m, 1H), 3.79 (s, 3H), 2.76 (d, J = 8.7, 1H), 2.49 (ddd, J = 13.5, 9.6, 4.2 Hz, 1H), 2.30 (ddd, J = 13.8, 2.4, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 132.1, 120.9, 68.8, 57.4, 55.5, 53.0, 32.9; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_8H_{12}O_4$: 195.0633, measured 195.0627.

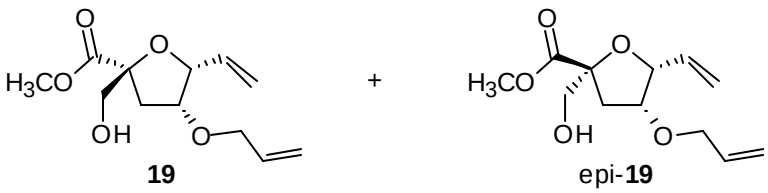
(*2S,4R,5R*)-methyl 4-(allyloxy)-5-vinyltetrahydrofuran-2-carboxylate (10)



To a stirred solution of furan **18** (0.44 g, 2.6 mmol) in 4.5 mL of dry toluene was added silver (I) oxide (1.79 g, 7.7 mmol) and allyl bromide (2.49g, 20.6 mmol) at room

temperature under nitrogen atmosphere. The mixture was stirred at about 60 ℃ for 24 h under an N_2 atmosphere. After the reaction mixture was filtered through celite and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography, eluting with 1:3 EtOAc/hexane, 0.5 g (92%) of the furanyl allyl ether **10** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (ddd, J = 17.4, 10.2, 7.8 Hz, 1H), 5.80 (ddt, J = 17.1, 10.2, 4.8 Hz, 1H), 5.38 (d, J = 17.1 Hz, 1H) 5.27 (d, J = 10.5, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.12 (d, J = 10.5, 1H), 4.52 (dd, J = 8.7, 4.2 Hz, 1H), 4.38 (dd, J = 7.8, 4.2 Hz, 1H), 4.04-3.84 (m, 3H), 3.73 (s, 3H), 2.48 (ddd, J = 13.5, 4.2, 3.3 Hz, 1H), 2.33 (ddd, 13.5, 8.7, 4.8 Hz,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 134.4, 134.2, 118.8, 116.6, 85.2, 79.2, 76.0, 70.3, 52.4, 36.2; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_{11}H_{16}O_4$: 235.0946, measured 235.0942.

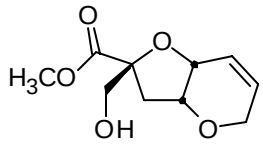
(*2S,4R,5R*)-methyl 4-(allyloxy)-2-(hydroxymethyl)-5-vinyltetrahydrofuran-2-carboxylate (19 & epi-19)



2.5 M n-BuLi (2.83 mL, 7.07 mmol) was added to the solution of diisopropyl amine (0.95 g, 9.42 mmol) and 10 mL dry THF at -78 ℃ and the mixture was stirred for 1 h at the same temperature under nitrogen atmosphere. To a stirred solution of allyl ether **10** (1.0 g, 4.71 mmol) in 5 mL dry THF was added freshly prepared LDA solution *via* cannula at -78 ℃ under nitrogen atmosphere. After stirring the reaction mixture for 1 h, freshly prepared formaldehyde solution (excess) was added slowly at the same

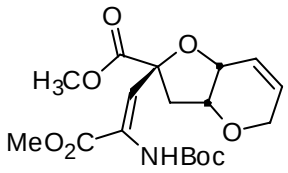
temperature and then the resulting solution was allowed to warm to 0 ℃ over 3 h. The reaction was quenched with sat. *aq* NH_4Cl (20 mL) at 0 ℃, and the mixture was extracted with ethyl acetate (15 mL) three times. The combined organic layers were dried (MgSO4) and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography, eluting with 3:2 EtOAc/hexane and the two diastereomers were separated, 439 mg (38%) of hydroxyl methyl furan **19** and 359 mg (31%) of hydroxyl methyl furan epi-**19** were obtained. Hydroxyl methyl furan **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (ddd, J = 17.4, 10.2, 8.1 Hz, 1H), 5.80 (ddt, J = 17.1, 10.2, 5.1 Hz, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.29 (d, J = 10.2 Hz, 1H), 5.23 (d, J = 17.4 Hz, 1H), 5.13 (d, J = 10.5 Hz, 1H), 4.48 (dd, J = 8.1, 3.9 Hz, 1H), 4.04-3.63 (m, 5H), 3.74 (s, 3H), 2.63 (dd, J = 13.5, 1.5 Hz, 1H), 2.18 (dd, J = 13.5, 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 134.4, 134.1, 119.1, 116.5, 86.7, 86.4, 80.1, 70.0, 66.4, 52.8, 37.7; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_{12}H_{18}O_5$: 265.1052, measured 265.1049; Hydroxyl methyl furan epi-**19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (ddd, J = 17.1, 10.2, 7.5 Hz, 1H), 5.84 (ddt, J = 17.1, 10.5, 5.4 Hz, 1H), 5.41 (d, J = 17.4 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.26 (d, J = 17.4 Hz, 1H), 5.17 (d, J = 10.2 Hz, 1H), 4.52 (dd, J = 7.5, 3.6 Hz, 1H), 4.07-3.82 (m, 5H), 3.77 (s, 3H), 2.54 (t, J = 6.6 Hz, 1H), 2.36 (d, J = 3.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 134.1, 133.2, 119.4, 117.2, 85.7, 85.3, 80.3, 70.6, 66.4, 52.8, 38.3; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_{12}H_{18}O_5$: 265.1052, measured 265.1048; Formaldehyde solution procedure: In a flame-dried flask a mixture of paraformaldehyde (2.0 g, 68 mmol, 1.0 equiv) and *p*-toluenesulfonic anhydride (328 mg, 0.1 mmol, 0.0015 equiv) in anhydrous THF (16.7 ml) was heated and slowly distilled using a microdistillation kit at such a rate that approximately one drop of distillate was collected every 10 sec. The distillate was collected at -78 ℃ under an anhydrous N_2 atmosphere to give THF solutions of formaldehyde having concentrations of ca. 2 M.

(*2S,3aR,7aR*)-methyl 2-(hydroxymethyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate (11)



Grubbs(II) catalyst (49 mg, 0.06 mmol) was added to the solution of compound **19** (348 mg, 1.44 mmol) and CH_2Cl_2 (200 mL) at room temperature under N_2 atmosphere. After stirring for 3 h at room temperature, solvent was removed *in vacuo*. The resulting crude product was purified by flash chromatography, eluting with 3:1 EtOAc/hexane, 293 mg (95%) of the furopyran **11** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06-6.05 (m, 2H), 4.21-4.18 (m, 1H), 4.08 (d, J = 3.0 Hz, 2H), 4.00 (t, J = 15.6 Hz, 2H), 3.81 (dd, J = 11.4, 6.6 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, J = 11.7, 6.9 Hz, 1H), 2.53 (d, J = 13.8 Hz, 1H), 2.32 (dd, J = 13.5, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 130.8, 122.4, 87.0, 75.5, 74.5, 66.5, 64.0, 52.7, 39.4; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_{10}H_{14}O_5$: 237.0739, measured 237.0738.

(*2S,3aR,7aR*)-methyl 2-((*Z*)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxoprop-1-enyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate (13)

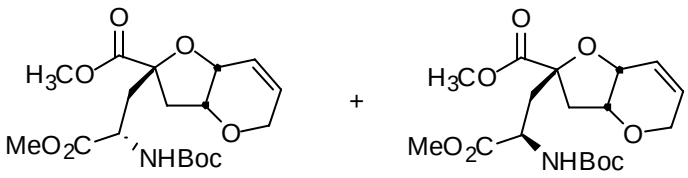


To a solution of DMSO (0.6 mL, 8.4 mmol) in 4 mL of CH_2Cl_2 at -78 ℃ was added oxalylchloride (0.55 mL, 6.3 mmol). The resultant mixture was stirred at -78 ℃ for

15 min, and then a solution of hydroxyl furopyran **11** (450 mg, 2.1 mmol) in CH_2Cl_2 (15 mL) was added to the reaction mixture. The reaction mixture was stirred at the same temperature for 45 min and then treated with triethylamine (1.75 mL, 12.6 mmol). The resultant mixture was allowed to warm to room temperature over 1 h and quenched with saturated aqueous NH_4Cl (15 mL). The mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude aldehyde as yellow oil.

To a stirred solution of the above aldehyde in CH_2Cl_2 (20 mL) at 0 ℃ were added $(MeO)_2P(O)CH(NHBoc)CO_2Me$ (1.87 g, 6.3 mmol) and *N*,*N*,*N*',*N*'-tetramethylguanidine (1.05 mL, 8.4 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography, eluting with 1:1 EtOAc/hexane, 540 mg (67%) of the furopyran enamide **13** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.08 (s, 2H), 5.91 (s, 1H), 4.23-3.90 (m, 4H), 3.78 (s, 3H), 3.72 (s, 3H), 2.95 (d, J = 13.8 Hz, 1H), 2.37 (dd, J = 14.1, 4.8 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 165.0, 152.8, 131.19, 131.12, 123.6, 122.1, 84.8, 81.3, 74.8, 74.0, 64.1, 53.2, 52.7, 28.4; HRMS- ESI: m/z $[M + Na]^+$ calculated for $C_{18}H_{25}NO_8$: 406.1478, measured 406.1471.

(*2R,3aR,7aR*)-methyl 2-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate (4)



4 epi-**4**

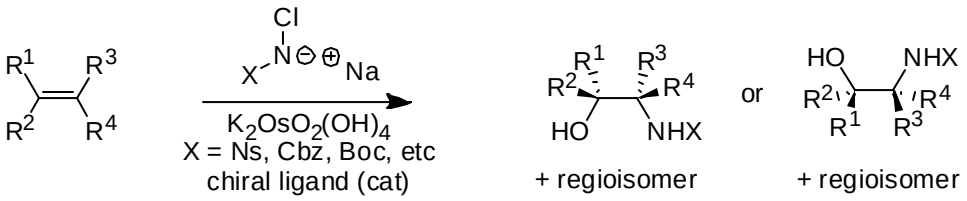
A degassed mixture of [Rh^{I}(COD)-(*S*,*S*)-EtDuPHOS]OTf (1.9 mg, 0.0026 mmol) and furopyran enamide **13** (50 mg, 0.13 mmol) in MeOH (3.0 mL) was placed in a hydrogenation bottle and pressurized with hydrogen to an initial pressure of 75 psi. The reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography, eluting with 1:1 EtOAc/hexane, 3 mg (5.4%, less polar on TLC) and 10 mg (20.0% , more polar on TLC) of the **4** & its epimer were obtained (50 % of starting material was recovered). Less polar on TLC ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 2H), 5.45 (d, J = 6, 1H), 4.32-4.34 (m, 1H), 4.14-3.95 (m, 4H), 3.74 (s, 3H), 3.72 (s, 3H), 2.63 (d, J = 14.1 Hz, 1H), 2.54 (dd, J = 14.4, 4.8 Hz, 1H), 2.27-2.21 (m, 2H), 1.44 (s, 9H); HRMS- ESI: m/z $[M + Na]^{+}$ calculated for $C_{18}H_{27}NO_8$: 408.1634, measured 408.1635.; More polar on TLC ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 2H), δ 5.15 (d, J = 7.5, 1H), 4.44-4.36 (m, 1H), 4.20-3.94 (m, 4H), 3.72 (s, 3H), 3.68 (s, 3H), 2.65 (d, J = 13.5 Hz, 1H), 2.38 (dd, J = 14.7, 9.3 Hz, 1H), 2.23 (d, J = 13.8, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 172.6, 130.4, 122.6 84.4, 80.1, 75.2, 73.9, 64.0, 52.69, 52.64, 51.0, 44.0, 39.4, 28.6; HRMS- ESI: m/z $[M + Na]^{+}$ calculated for $C_{18}H_{27}NO_8$: 408.1634, measured 408.1631.

Chapter 3: Future Directions for Dysiherbaine & Its Analogues

Previous studies illustrated that C_8 and C_9 centers are an important pharmacophore for dysiherbaine and its analogues. This is based on the observation that such analogues have shown different properties on Glu receptors according to groups on those carbons (Fig 1.10 & Table 1.4). To maximize the ability to modify this pharmacophore the target molecule **4,** which has a double bond between C_8 and C_9 carbon centers, was chosen. The selection of a double bond is important since it can be transformed to other moieties by a variety of reactions. With few steps, the target molecule **4** will be converted to dysiherbaine, neodysiherbaine, or a series of analogues. In this chapter, we will show examples of how molecule **4** can be utilized for these transformations.

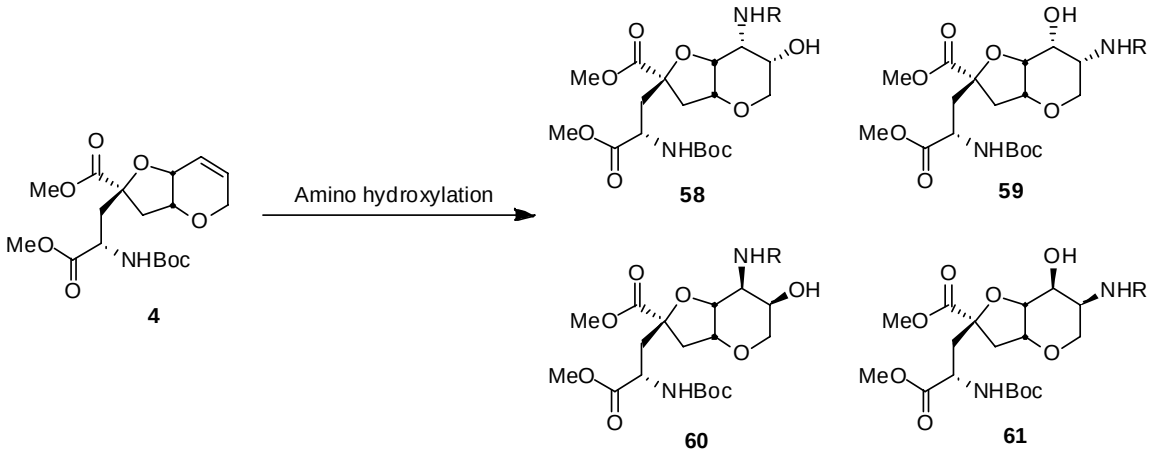
I. AMINOHYDROXYLATION: DYSIHERBAINE

Dysiherbaine has methyl amine group at C_8 and hydroxyl group at C_9. Sharpless asymmetric aminohydroxylation is one of reactions that will be attempted to synthesize dysiherbaine from the molecule **4.**[70, 71] In the case of aminohydroxylation, which uses an osmium catalyst, both stereoselectivity and regioselectivity of the products will have to be considered. There are four possible products from this reaction (Scheme 3.2). In Sharpless asymmetric aminohydroxylation (Scheme 3.1), the stereochemistry is controlled by using chiral ligands but the steric environment of molecule **4** may over ride the ligand and make it difficult to obtain the stereoselectivity found in dysiherbaine.



Scheme 3.1: Sharpless asymmetric aminohydroxylation.

From Sharpless asymmetric aminohydroxylation, four possible products can be obtained. Molecule **58** has correct regio- and stereo chemistry for dysiherbaine but it appears likely that molecules, **60** and its regio isomer **61,** will be the major products because of the concave shape of molecule **4**. Addition will be more rapid from the front face of the picture because molecule **4** has puckered shape and back side more hindered (Scheme 3.2 and Figure 3.1). A reaction protocol that will likely provide the natural stereochemistry at C_8 and C_9 centers is an application of the Woodward-Prevost reaction.[72]



Scheme 3.2: Possible products from amino hydroxylation.

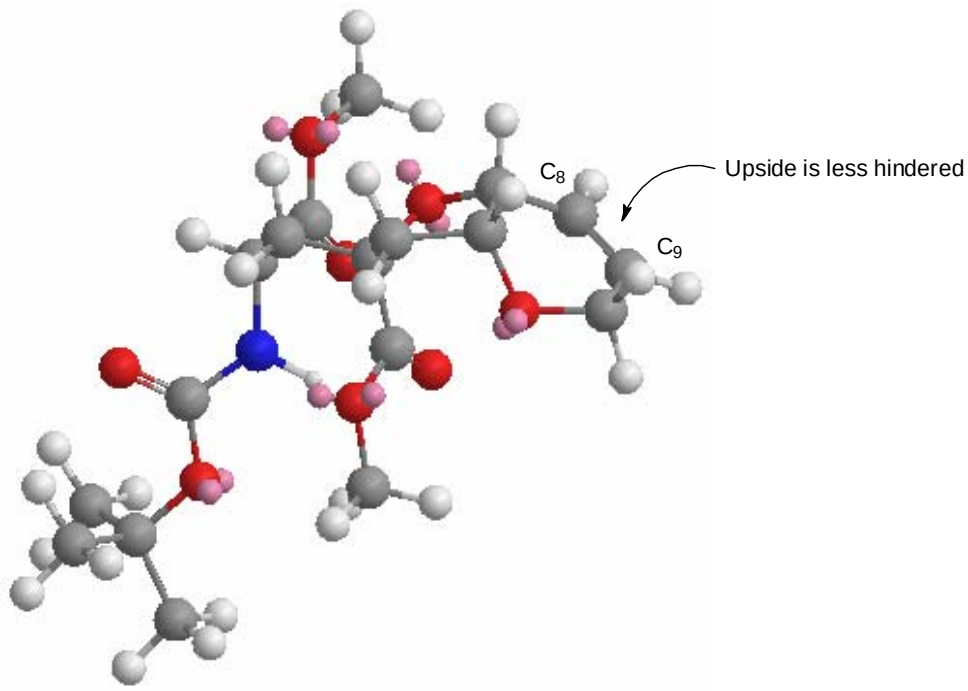
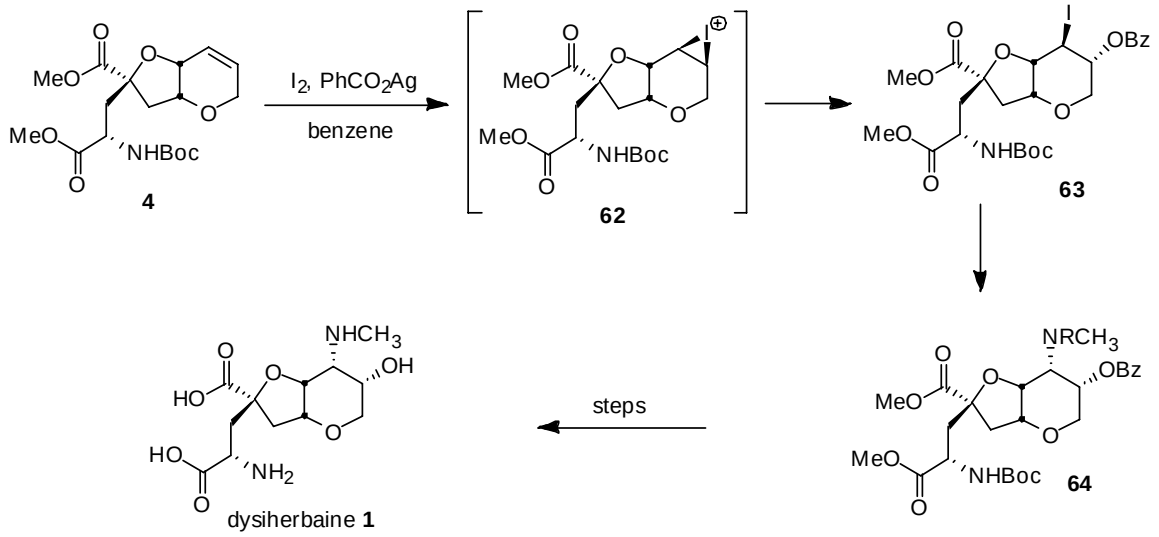


Figure 3.1: 3D picture of molecule **4**.

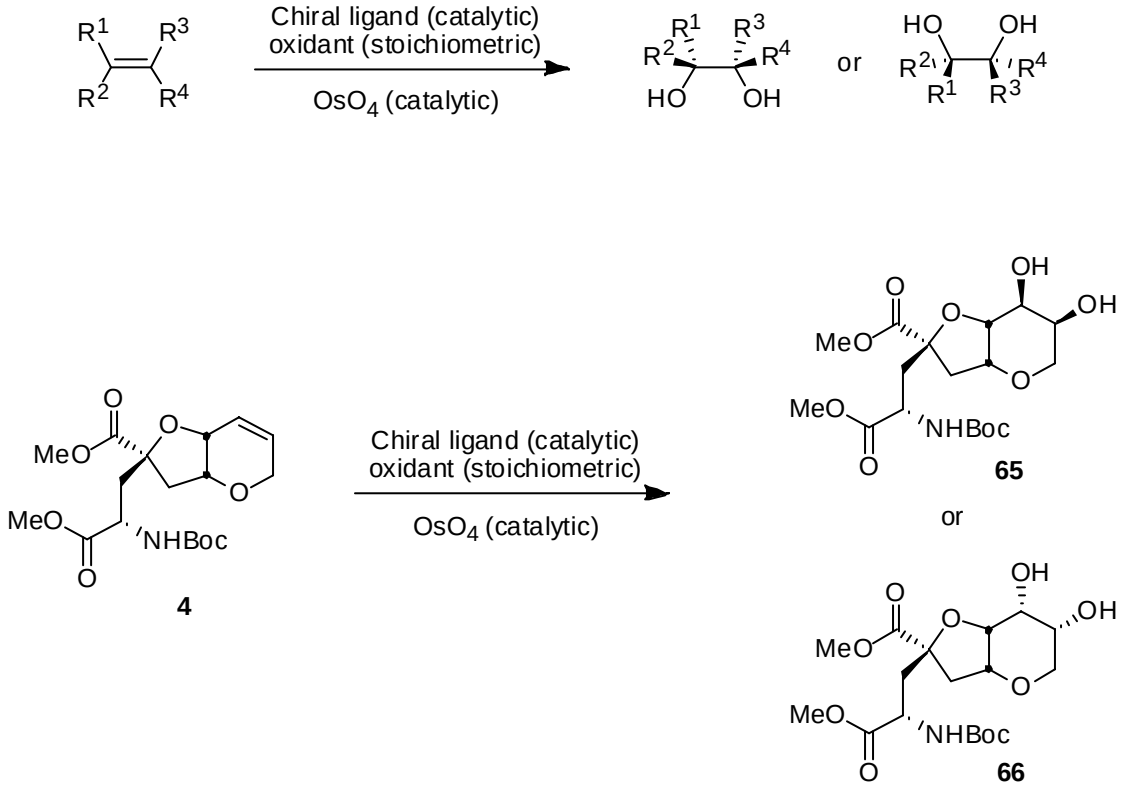
In this procedure, the first step is the reaction of the alkene with iodine to form the cyclic iodonium ion **62**. Next, the iodonium ion is opened by the silver benzoate to form corresponding *trans*-iodo benzoate **63.**[73] The iodine is then displaced by a protected amine, through Sn2 reaction to form molecule **64**. Additional deprotection and hydrolysis steps will provide dysiherbaine (Scheme 3.3). As with the Sharpless reaction, it is also possible that this reaction will provide the regioisomer where the amine has added to C_8 rather than C_9. While these regio chemical issues will complicate the synthesis of dysiherbaine we desire both sets of regioisomers for testing by our collaborators.



Scheme 3.3: Application of Woodward-Prevost reaction.

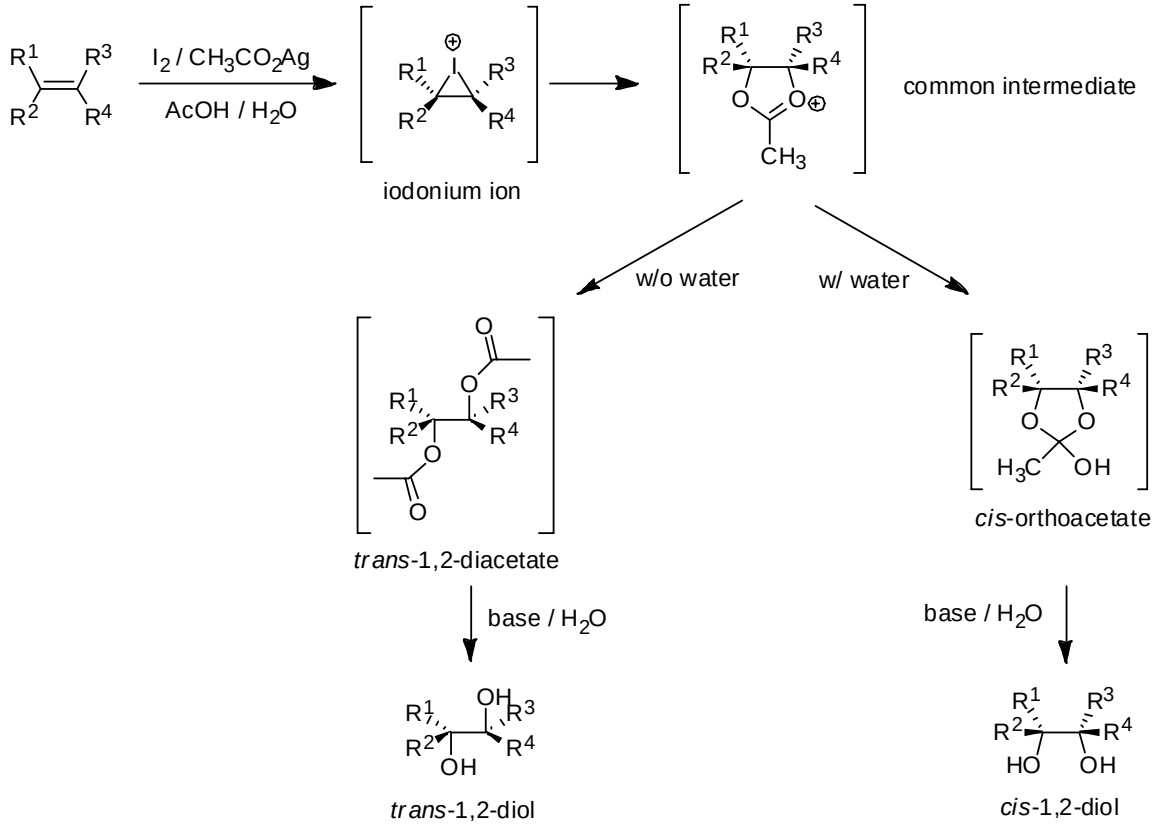
II. DIHYDROXYLATION: NEODYSIHERBAINE

Neodysiherbaine has hydroxyl groups at C_8 and C_9. The first attempt to install these functional groups will be with the Sharpless asymmetric dihydroxylation reaction using chiral ligands.[74, 75] In this case, however, it is not clear which stereochemistry will be obtained with chiral ligand because of the shape of molecule **4** as mentioned in previous section. It will be difficult to obtain molecule **66** by Sharpless asymmetric dihydroxylation even with the proper chiral ligand and molecule **65** is likely to be the major product. As with the stereochemistry of dysiherbaine not only is the natural product desired but also analogs with different stereochemistry will be useful.



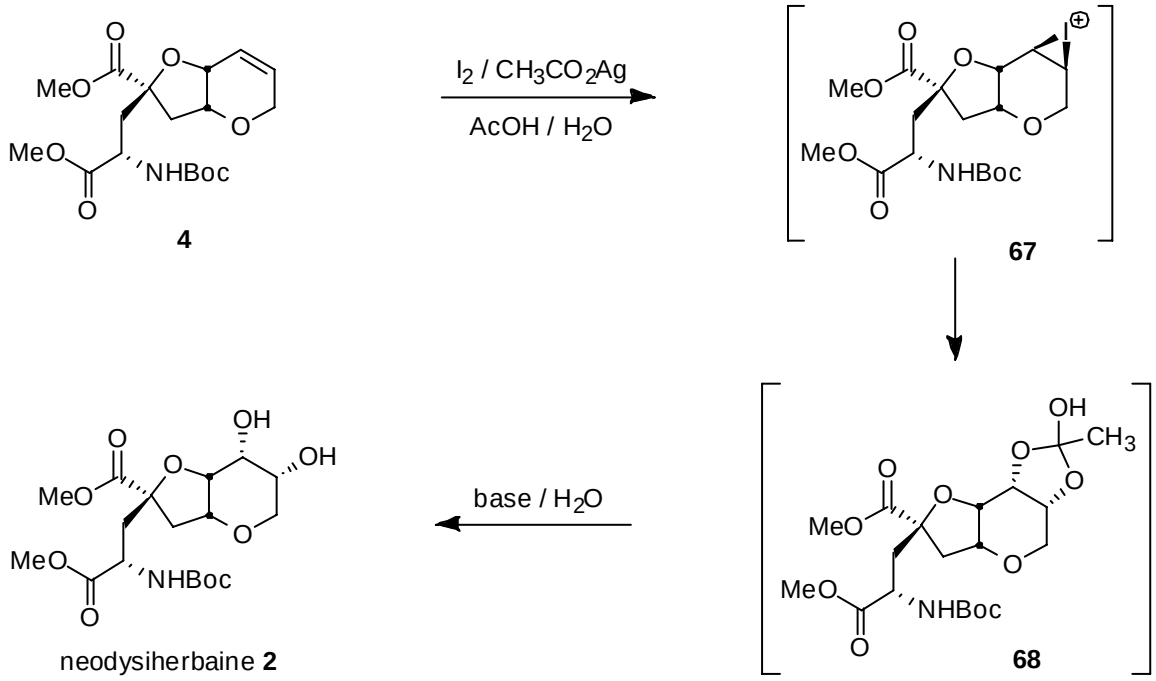
Scheme 3.4: Sharpless asymmetric dihydroxylation & application of molecule **4**.

One solution to the problem of obtaining the unnatural chemistry with the Sharpless reaction is the use of the Woodward-Prevost reaction. By using 1 equivalent of iodine, silver acetate and acetic acid/water, *cis*-orthoacetate will be formed through iodonium ion. In the absence of water, this reaction gives *trans*-1,2-diacetate. However, in the presence of water the common intermediate is converted to a *cis*-orthoacetate which is hydrolyzed to the corresponding *cis*-1,2-diol (Scheme 3.5).[76]



Scheme 3.5: Woodward-Prevost reaction (wet reaction).

From the molecule **4**, treating with 1 equivalent of iodine, silver acetate and acetic acid/water will give intermediate molecule **68** through molecule **67**. Hydrolysis will provide the diol, neodysiherbaine, stereospecifically (Scheme 3.6).



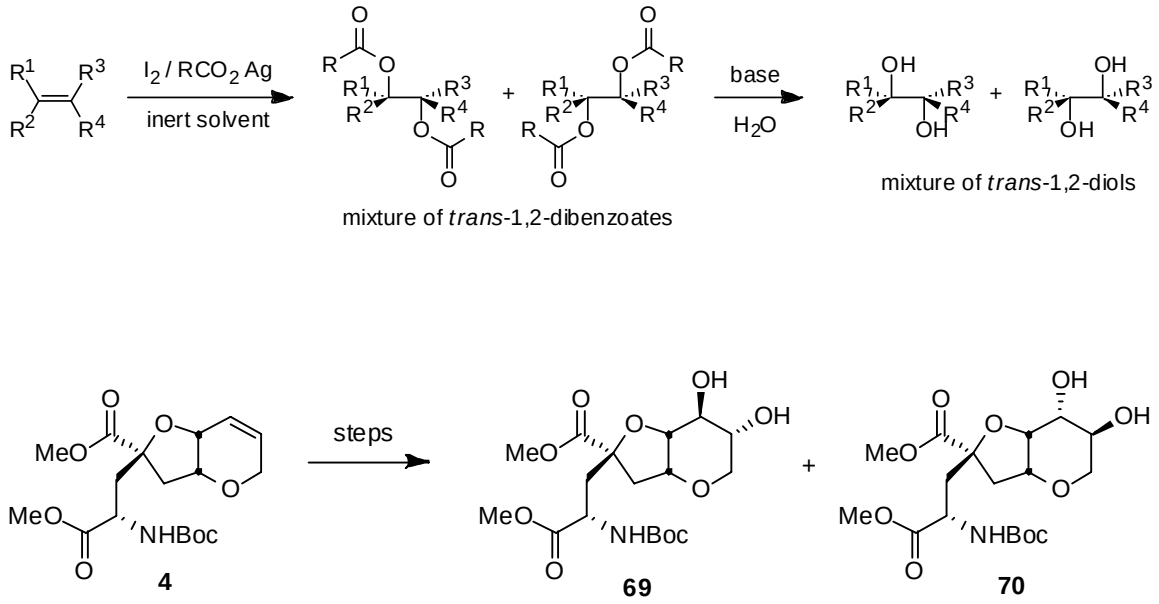
Scheme 3.6: Application of Woodward-Prevost reaction for neodysiherbaine.

III. EXTENDED TRANSFORMATION

Besides dysiherbaine and neodysiherbaine from the molecule **4**, it will be possible to introduce a variety of functional derivatives of dysiherbaine at the C_8 & C_9 pharmacophore. For example, *trans*-dihydroxy groups, monohydroxy, halo-hydroxy, monoamine, ring extension products, C_4 epimers and C_2 & C_4 epimers. The detail description of these transformations is introduced in the following sections.

Trans dihydroxy groups

The classic Prevost reaction is run using inert solvent instead of the acetic acid/water system in Woodward-Prevost version. This difference leads to *trans*-dihydroxy derivatives (Scheme 3.7) rather than *cis*.

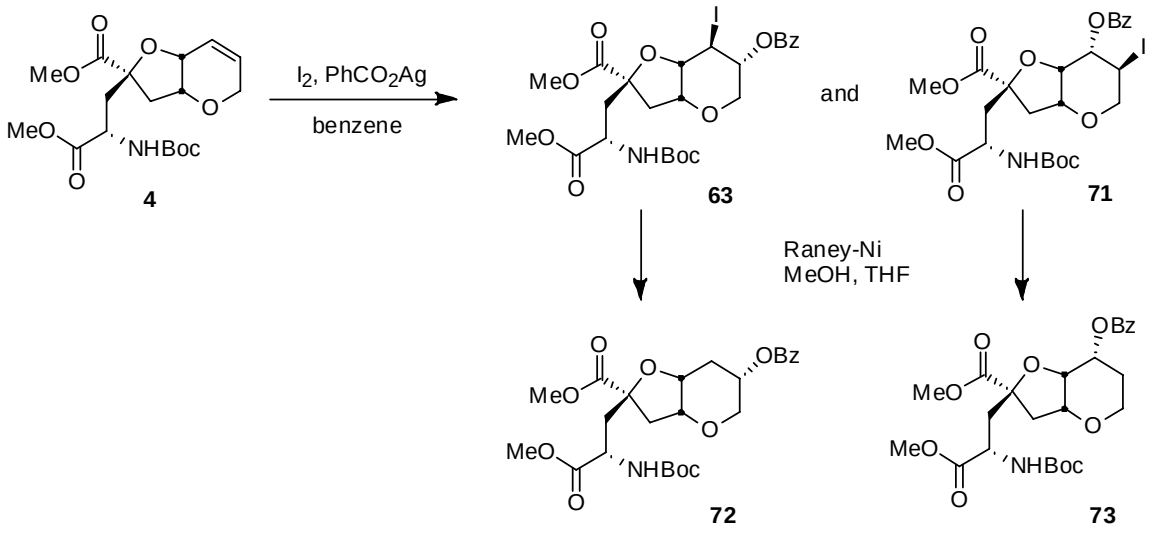


Scheme 3.7: Prevost reaction and its application for *trans*-diol derivatives.

Biological study has shown that neodysiherbaine with *trans* stereochemistry such as **69** have the highest affinity for GluR5-2a subunits and a derivative from of **70** had an affinity about 300-fold lower than neodysiherbaine for GluR5-2a subunits and was inactive at other subunits.[77]

Monohydroxy derivative

Molecule **4** can be subjected to Prevost reaction conditions followed by dehalogenation of molecule **63** and **71** with Raney nickel to obtain the monohydroxy derivatives.[73]



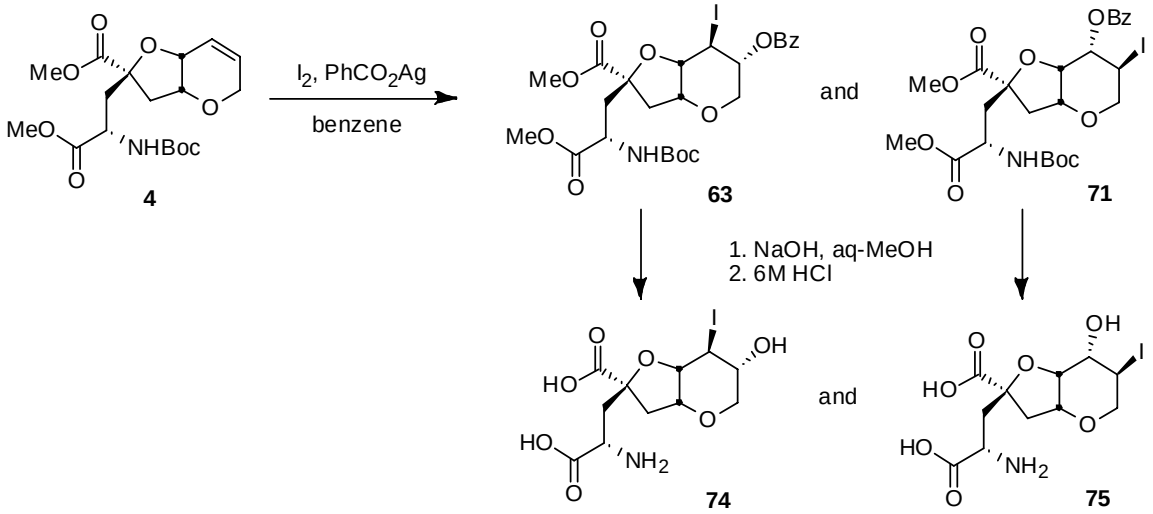
Scheme 3.8: Prevost and dehalogenation.

Two different iodo-benzoates (**63** & **71**) can be isolated from the Prevost reaction and iodide group in each molecule can be removed a Raney-Ni dehalogenation (Scheme 3.8). In addition, hydroboration could be a simple method for the mono-hydroxylation although it would potentially give four possible diastereomers. It has been shown that both derivatives from molecule **72** and **73** are KA receptor agonists. The alcohol from molecule **72** is considered as a full agonist, or a highly efficacious partial agonist, because it showed similar amplitude of currents elicited at a concentration of 100 μM from GluR5 receptors by saturating concentrations (10 mM) of glutamate in

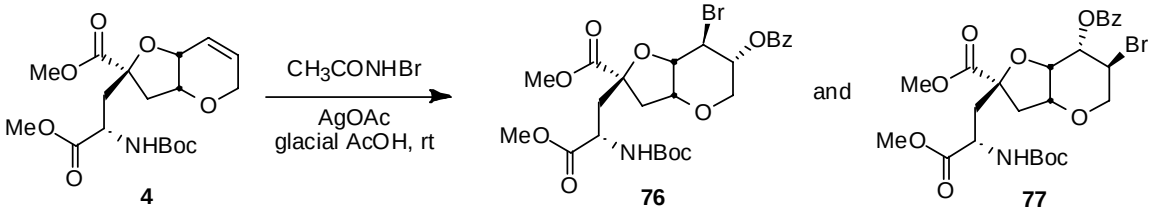
electrophysiology study. In contrast, the alcohol from molecule **73** is a very weak agonist that evoked only small currents from GluR5 receptors at high concentrations.[77]

Halo-hydroxy derivatives

We can stop the reaction in the first step which is described in Scheme 3.8 and deprotection and hydrolysis of molecule **63** and **71** will give iodo-hydroxy derivatives (Scheme 3.9). If we use *N*-bromo acetamide and silver acetate with molecule **4**, the reaction will give bromo-hydroxy derivatives (Scheme 3.10)[78].



Scheme 3.9: Iodo-hydroxy derivatives.

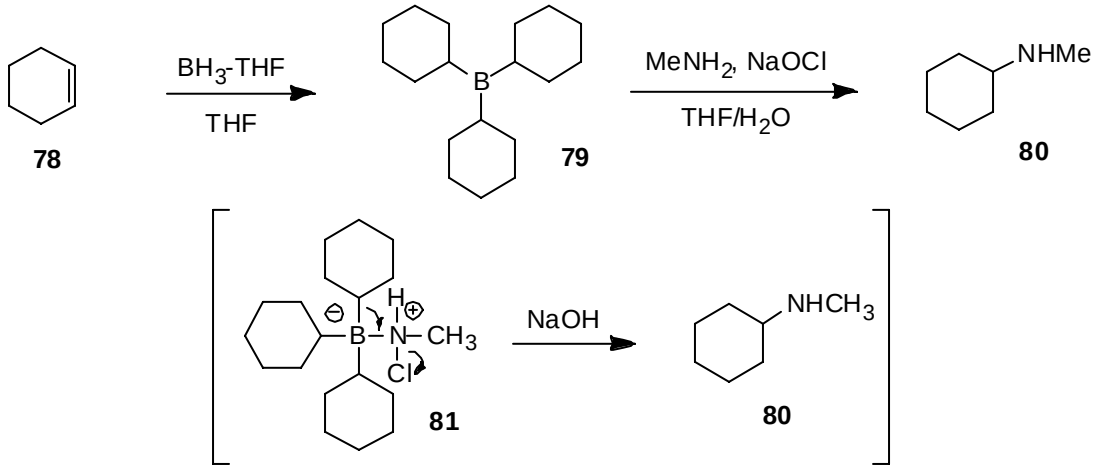


Scheme 3.10: For bromo-hydroxy derivatives.

There are more options for the synthesis of other halo-hydroxy derivatives. Epoxidation of the double bond followed by epoxide opening by nucleophilic halide will be the one of options to obtain similar products.

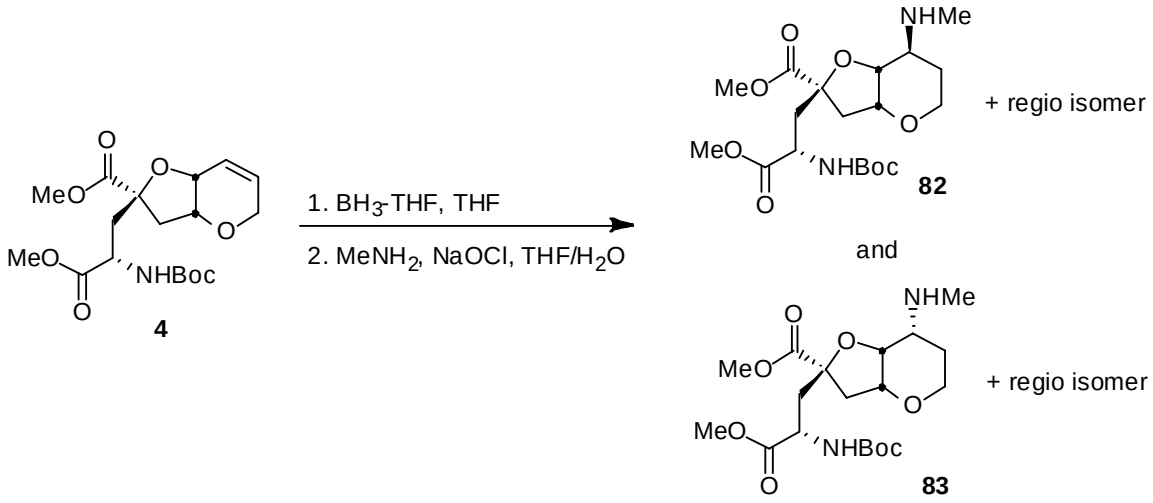
Mono-amino derivatives

The reaction of triakylborane (**79**) with alkylamine has been used to form dialkyl amines. For example, in Scheme 3.11, cyclohexene (**78**) is treated with borane-THF complex to give tricyclohexanyl borane (**79**) and *N*-chloro methyl amine from sodium hypochlorite with methyl amine reacts with tricyclohexanyl borane to produce methyl cyclohexanyl amine (**80**)[79].



Scheme 3.11: Synthesis of dialkyl amine.

This reaction sequence can be applied to molecule **4** to provide mono amino derivatives as described in Scheme 3.12. As with a number of the reactions above it is not certain which diastereomers will be formed in the reaction but each would be a new dysiherbaine derivative.

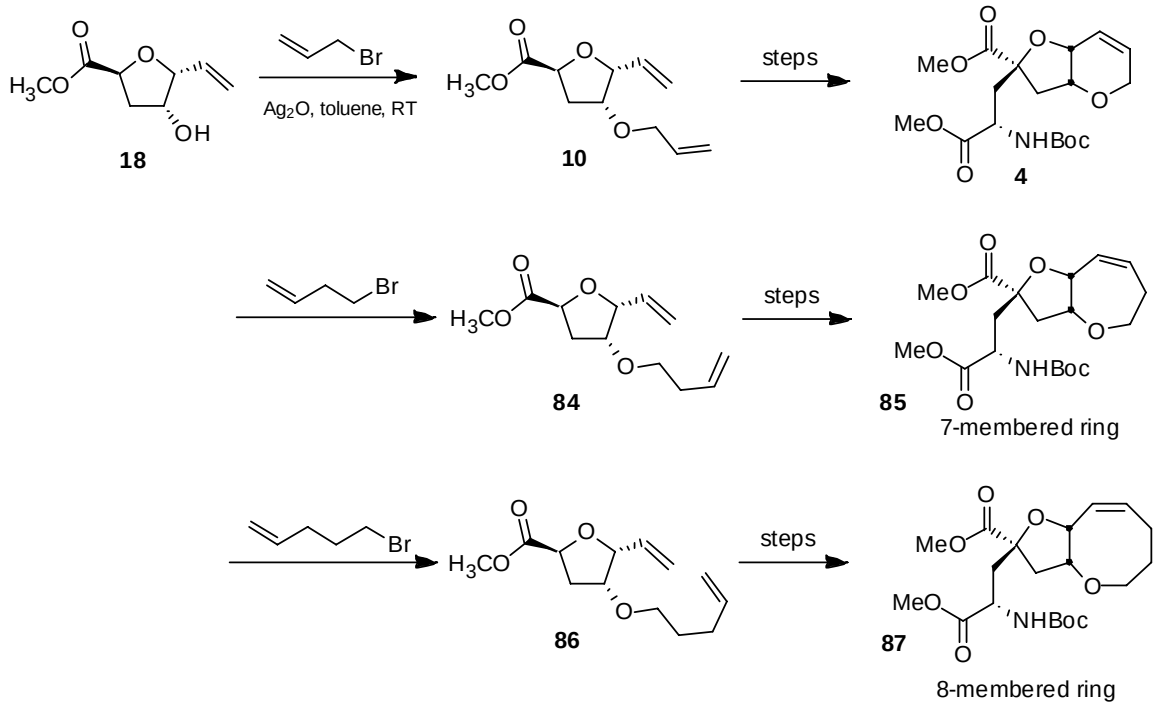


Scheme 3.12: Application of dialkyl amine synthesis (mono amino derivatives)

Ring extension

Reaction of molecule **18** with allyl bromide is the sequence that provides our target molecule **4** with a double bond in the 6-membered ring. Increasing the size of ring could be a good approach to derivatives. By increasing the ring size the molecule becomes more flexible and it will interact with glutamate receptors in a different manner than the dihydropyran derivatives. Reaction of 4-bromo-1-butene with molecule **18**, instead of allyl bromide, will give a precursor (**84**) that following reaction with Grubbs catalyst will provide a 7-membered ring system molecule **85**. Likewise 5-bromo-1-pentene will lead to an 8-membered ring **87**. Once the extended ring systems **85** and **87**

are obtained the double bond in each ring system can be fully functionalized in the same manner as described previously. This will provide two more sets of derivatives in addition to derivatives from molecule **4** (Scheme 3.13).



Scheme 3.13: Ring extension using with different alkyl bromides.

C_4 epimers

Molecule epi-**4** has opposite stereochemistry at the C_4 position from molecule **4** (Figure 3.2). The C_4 epimer was made in the alkylation of molecule **10**. In this reaction, two diastereomers, **19** and its epimer are obtained in 1:1 ratio. Fortunately they are easily separated through silica gel column chromatography. Following the procedure for the synthesis of molecule **4,** the epimer of **19** was converted to the epimer of **4** (epi-**4**)

(Scheme 3.14). This diastereomer (epi-**4**) will be modified in the same manner as is planned for **4**.

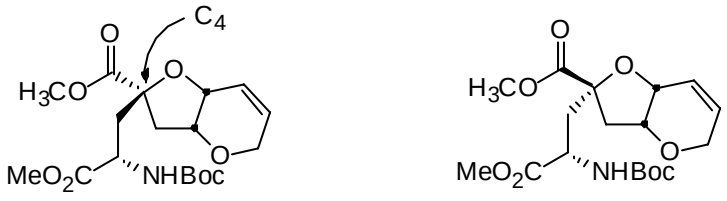
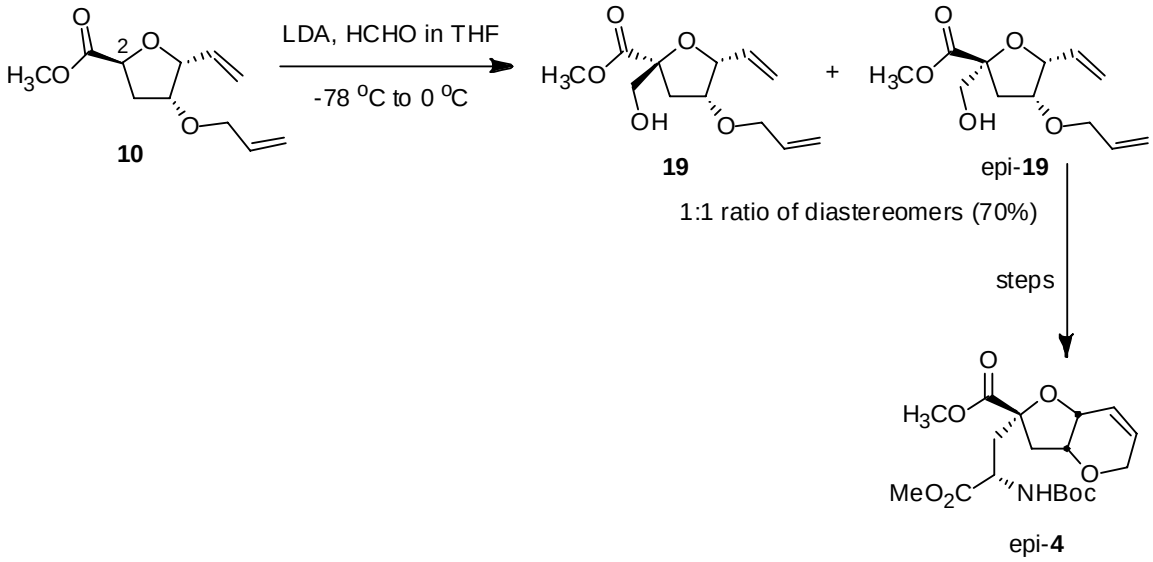


Figure 3.2: Molecule **4** and its C_4-epimer.

In previous studies, C_4 epimer of neodysiherbaine was found to have a novel pharmacological profile for the GluR5-2a subunit suggesting that other C_4 epimer analogs, in addition to epi-neodysiherbaine, could be good candidates for study with novel pharmacological properties especially in kainate receptor antagonism.[77]



Scheme 3.14: Synthesis of C_4-epimer of molecule **4**.

C_2 & C_4 epimer

C_2 & C_4 epimer has opposite stereochemistry at both the C_2 and C_4 positions of molecule **4** (Figure 3.3). In the selective hydrogenation step, reaction of molecule epi-**13** with $[Rh^I(COD)\text{-}(R,R)\text{-EtDuPHOS}]^+OTf^-$ as a catalyst instead of $[Rh^I(COD)\text{-}(S,S)\text{-EtDuPHOS}]^+OTf^-$ will give C_2 & C_4 epimer (molecule epi-**57**) of molecule **4** (Scheme 3.15). Again through the procedure worked out for the synthesis of **4** there are a series of novel analogs that will be accessible from this chemistry.

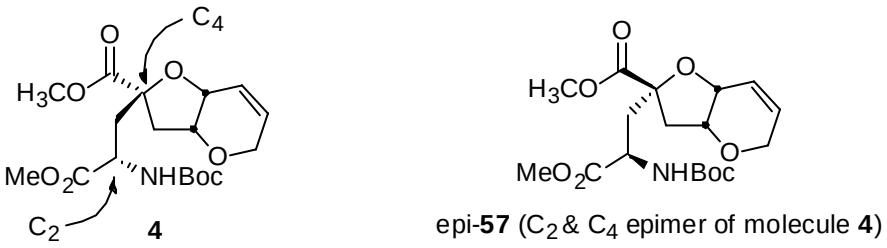
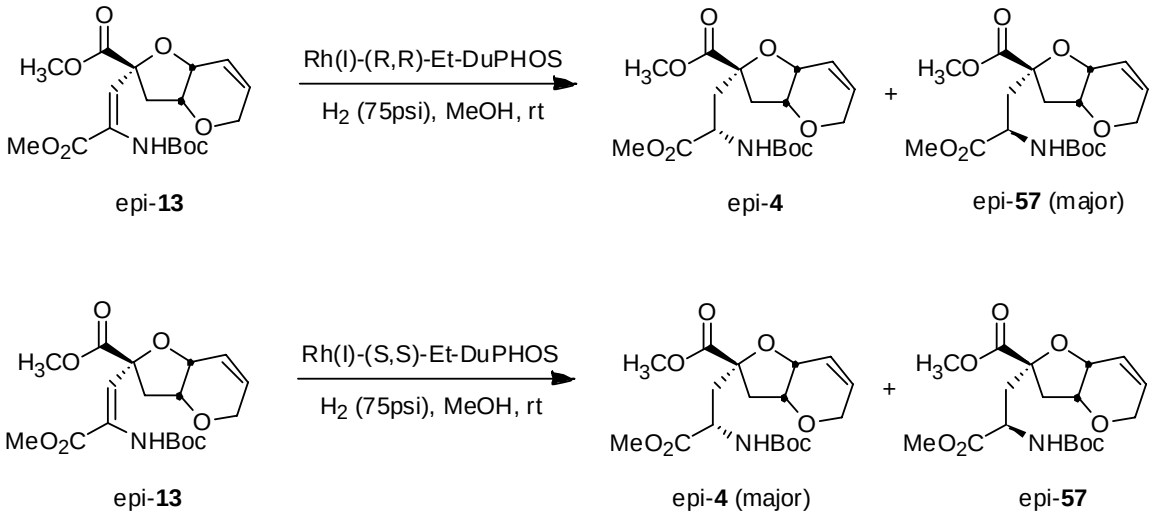


Figure 3.3: Molecule **4** and its C_2 & C_4 epimer.



Scheme 3.15: Synthesis of C_2 & C_4 epimer of molecule **4**.

C_2 & C_4 epimer of neodysiherbaine has shown different pharmacological properties than C_4 epimer in the previous study. It acts as GluR5-2a and GluR6-a selective antagonist and is the first compound to act as a functional selective antagonist for GluR5 and GluR6 containing receptors without concurrent activity on AMPA receptors. Swanson et. al. suggest that C_2 & C_4 epimer along with C_4 epimer of neodysiherbaine represent new templates for synthetic manipulation that could lead to novel pharmacological profiles of KA receptor antagonism[77].

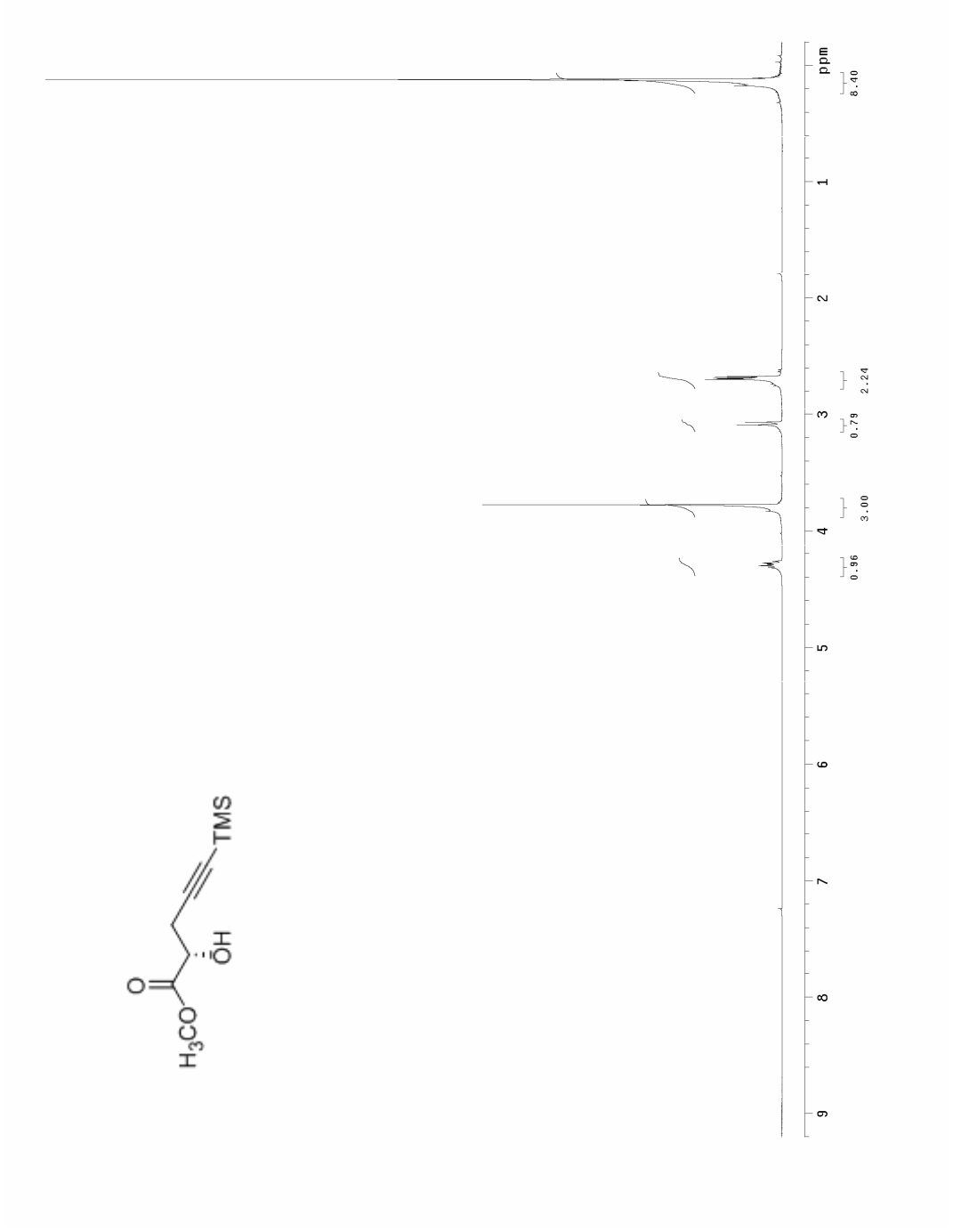
In summary, this chapter shows future directions for the synthesis of dysiherbaine, neodysiherbaine and their derivatives from molecule **4**. Through a series of reactions on the key double bond in molecule **4** a wide number of derivatives are accessible by only few steps. Some of the derivatives are already known and have been shown to have interesting pharmacological activities in comparison to dysiherbaine and neodysiherbaine. Along with known analogues, a range of novel derivatives will be made from molecule **4.** A number of them could possess different activity as Glu receptor ligand agonists or antagonists than known ligands.

Appendix A

Spectral Data: ^{1}H-NMR and ^{13}C-NMR

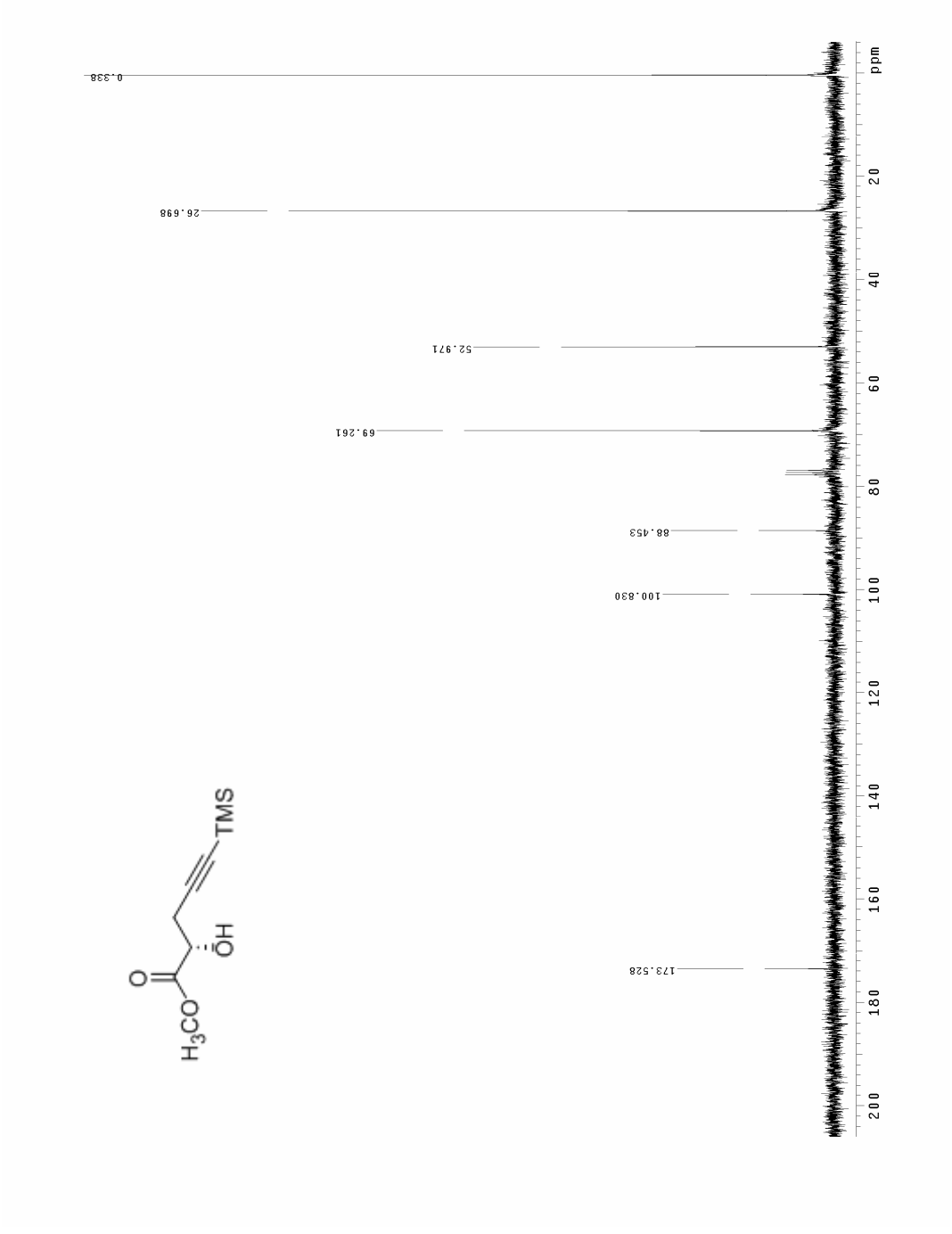
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxy-5-(trimethylsilyl)pent-4-ynoate **49**



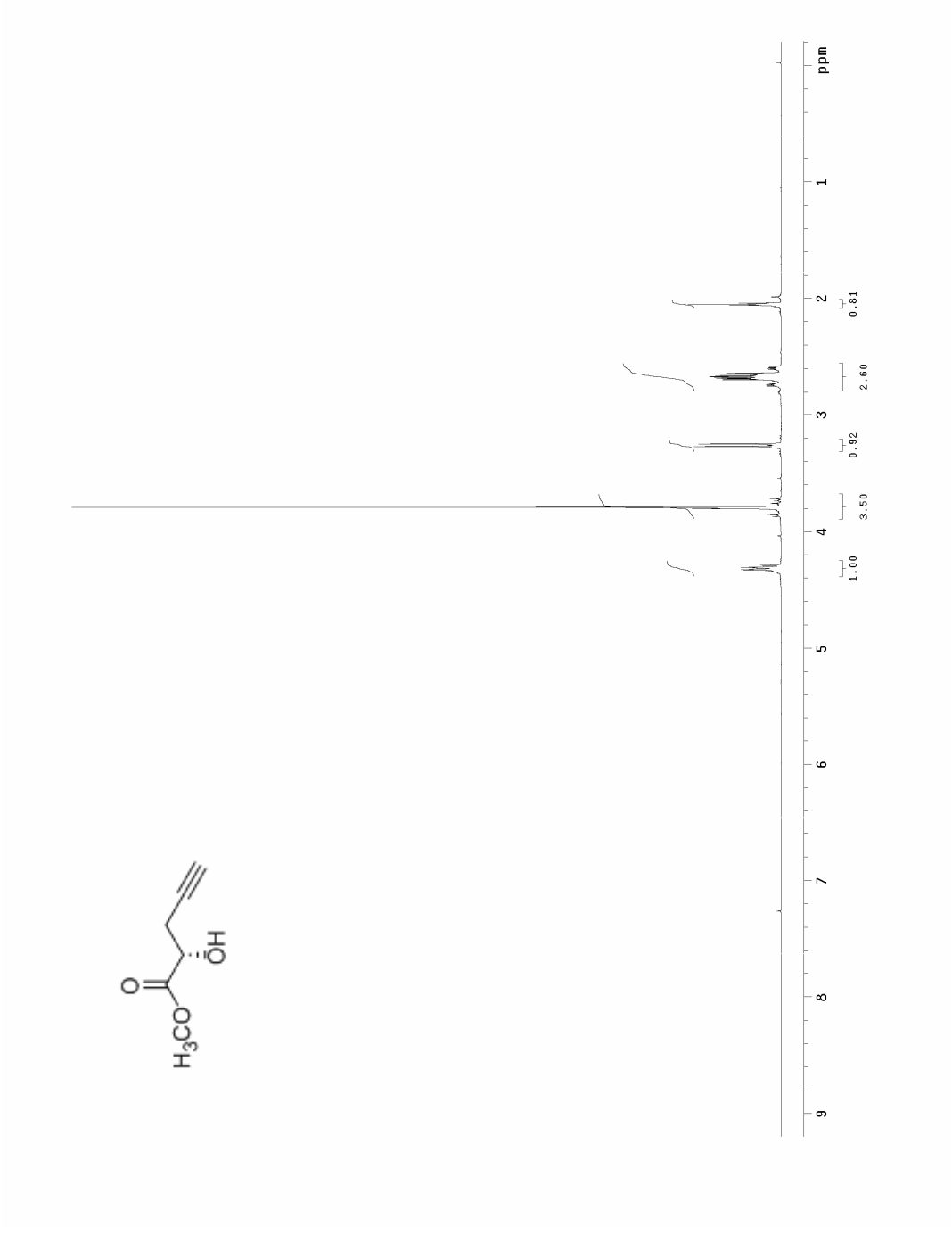
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxy-5-(trimethylsilyl)pent-4-ynoate **49**



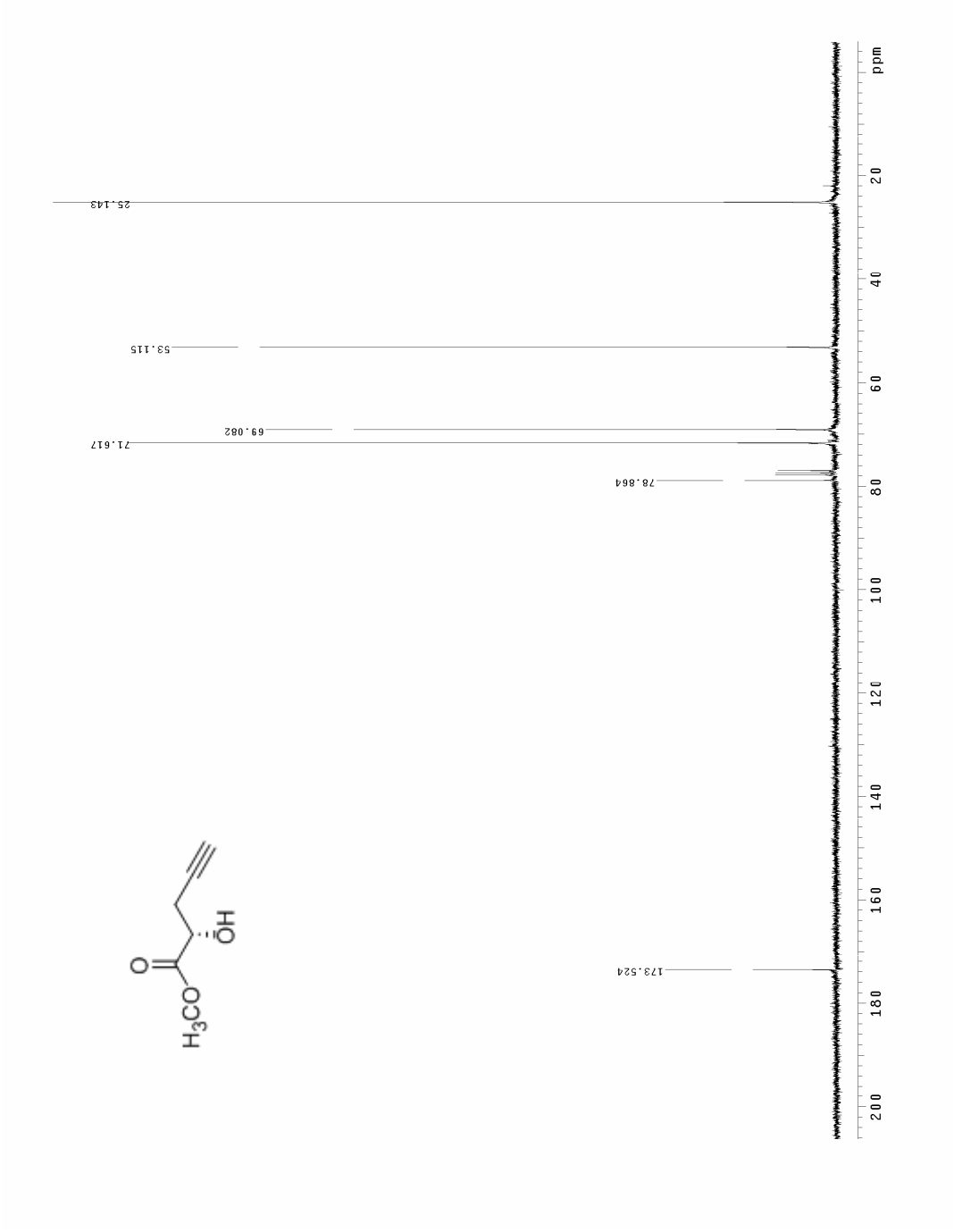
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxypent-4-ynoate **51**



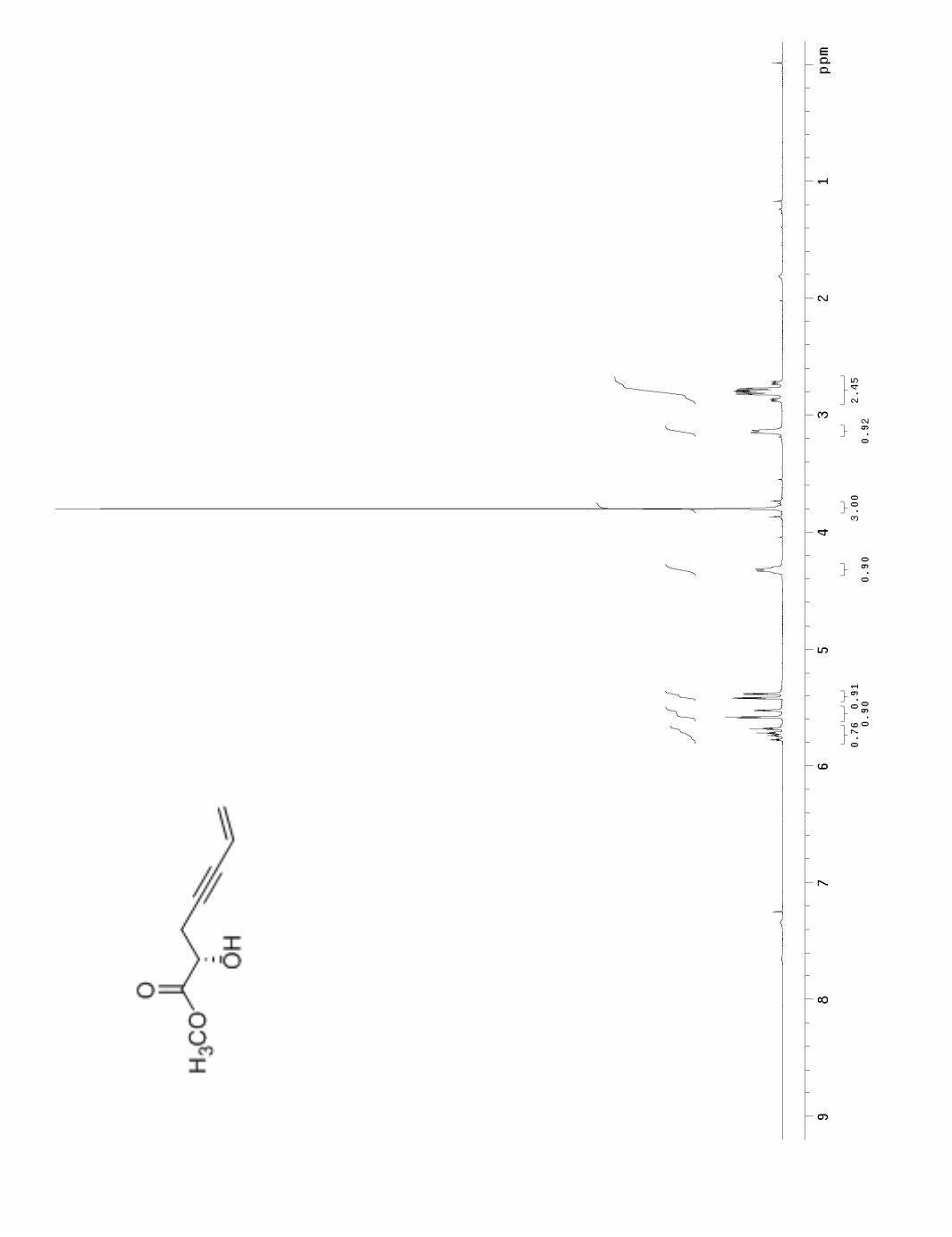
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxypent-4-ynoate **51**



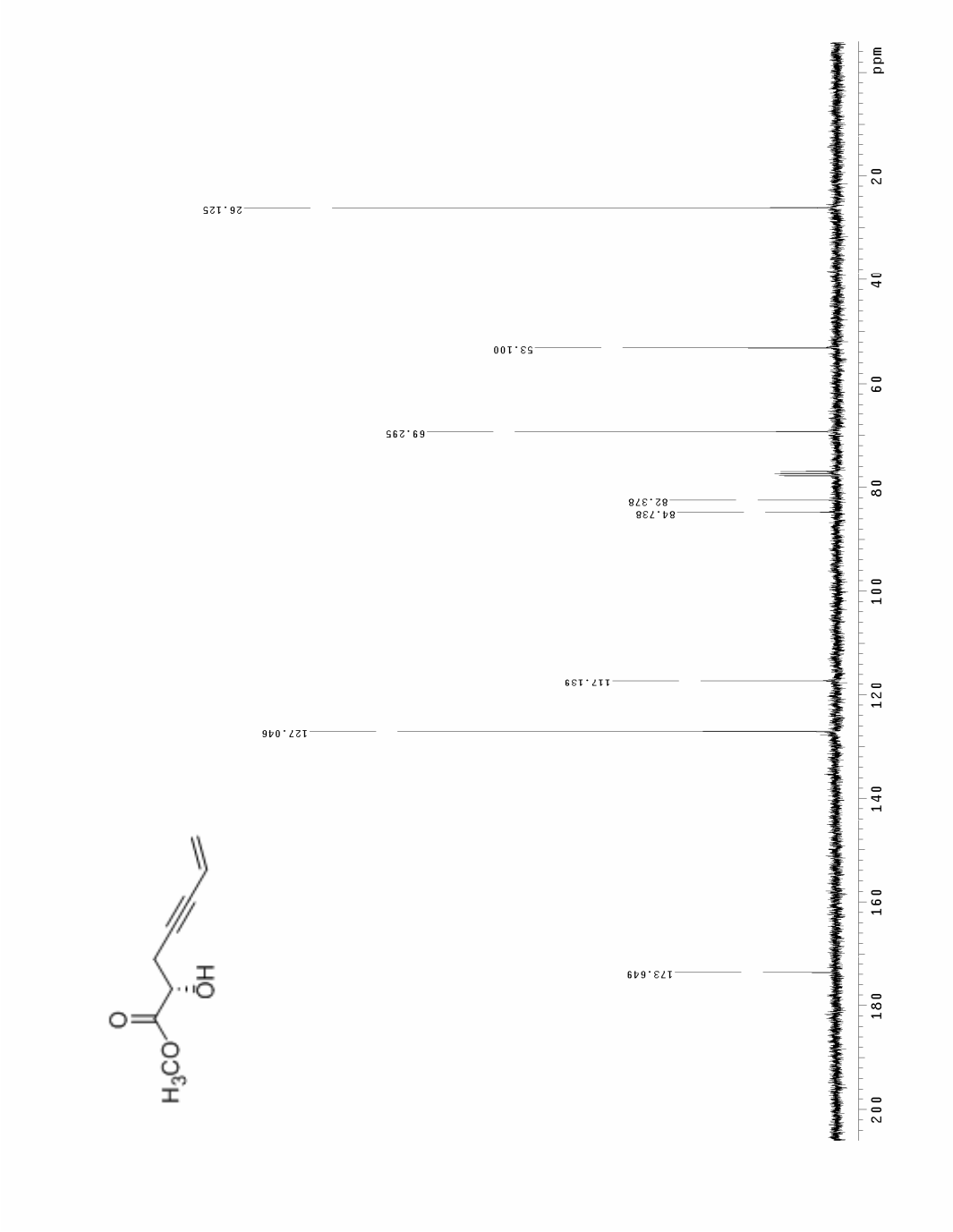
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxyhept-6-en-4-ynoate **8**



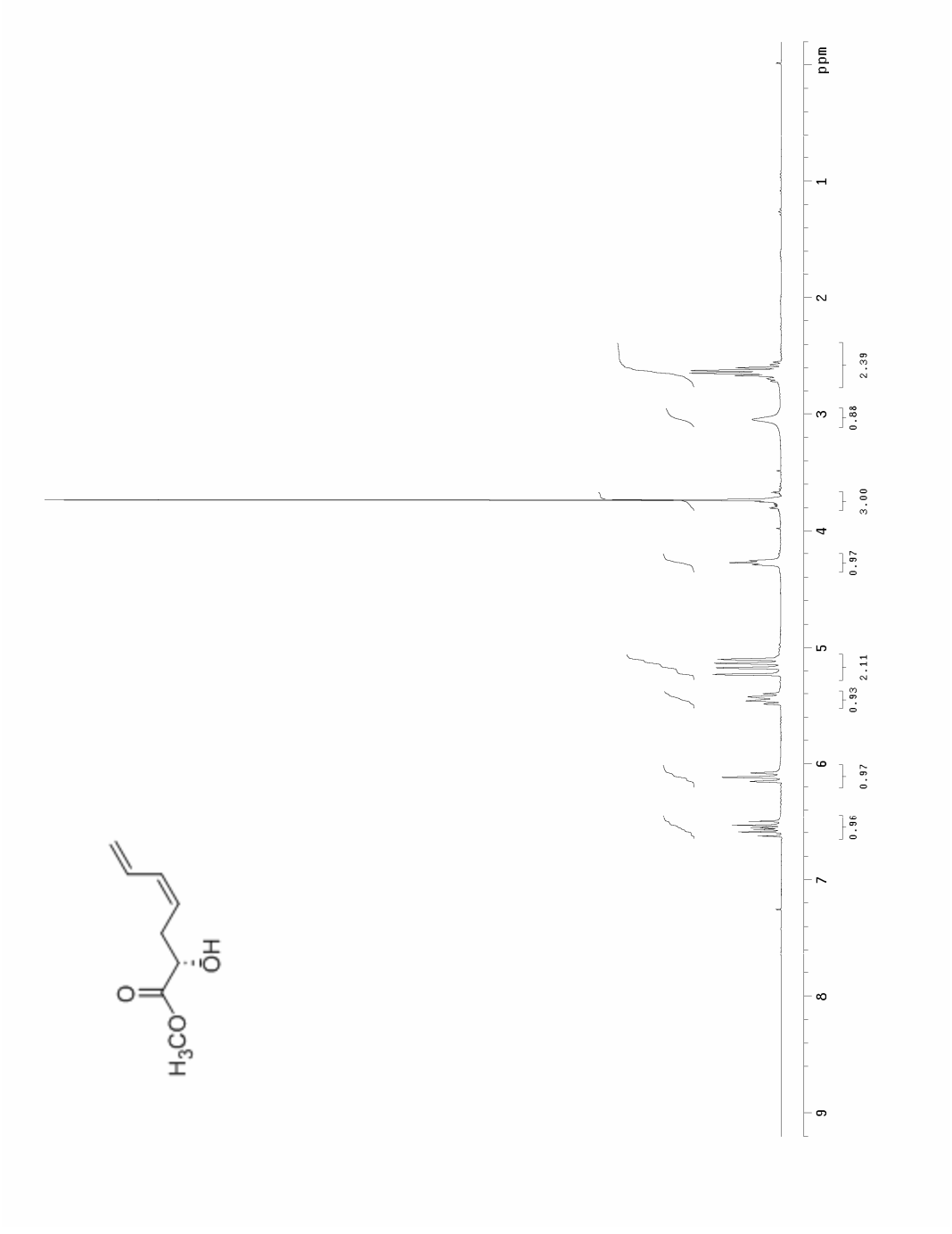
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxyhept-6-en-4-ynoate **8**



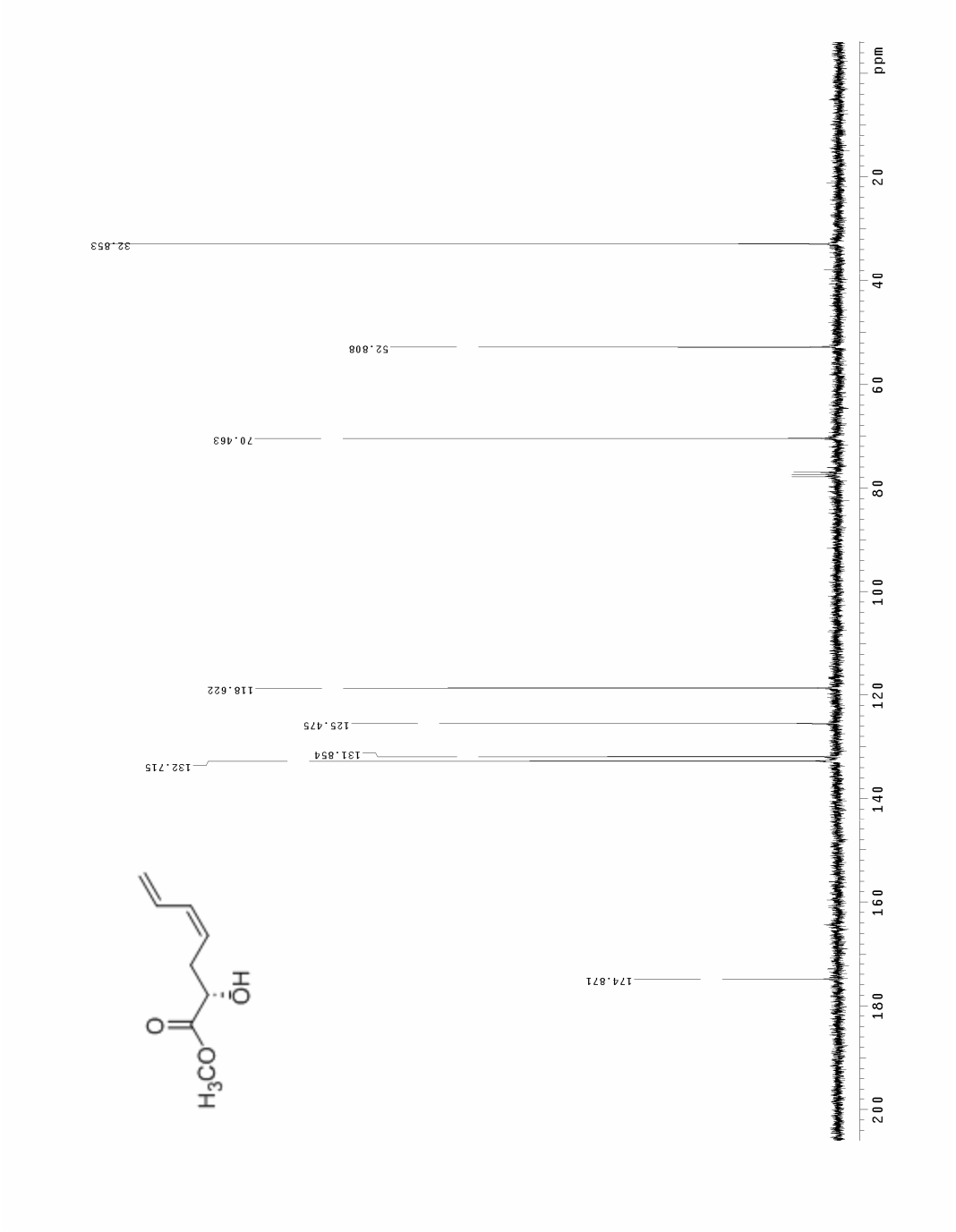
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*S,Z*)-methyl 2-hydroxyhepta-4,6-dienoate **17**



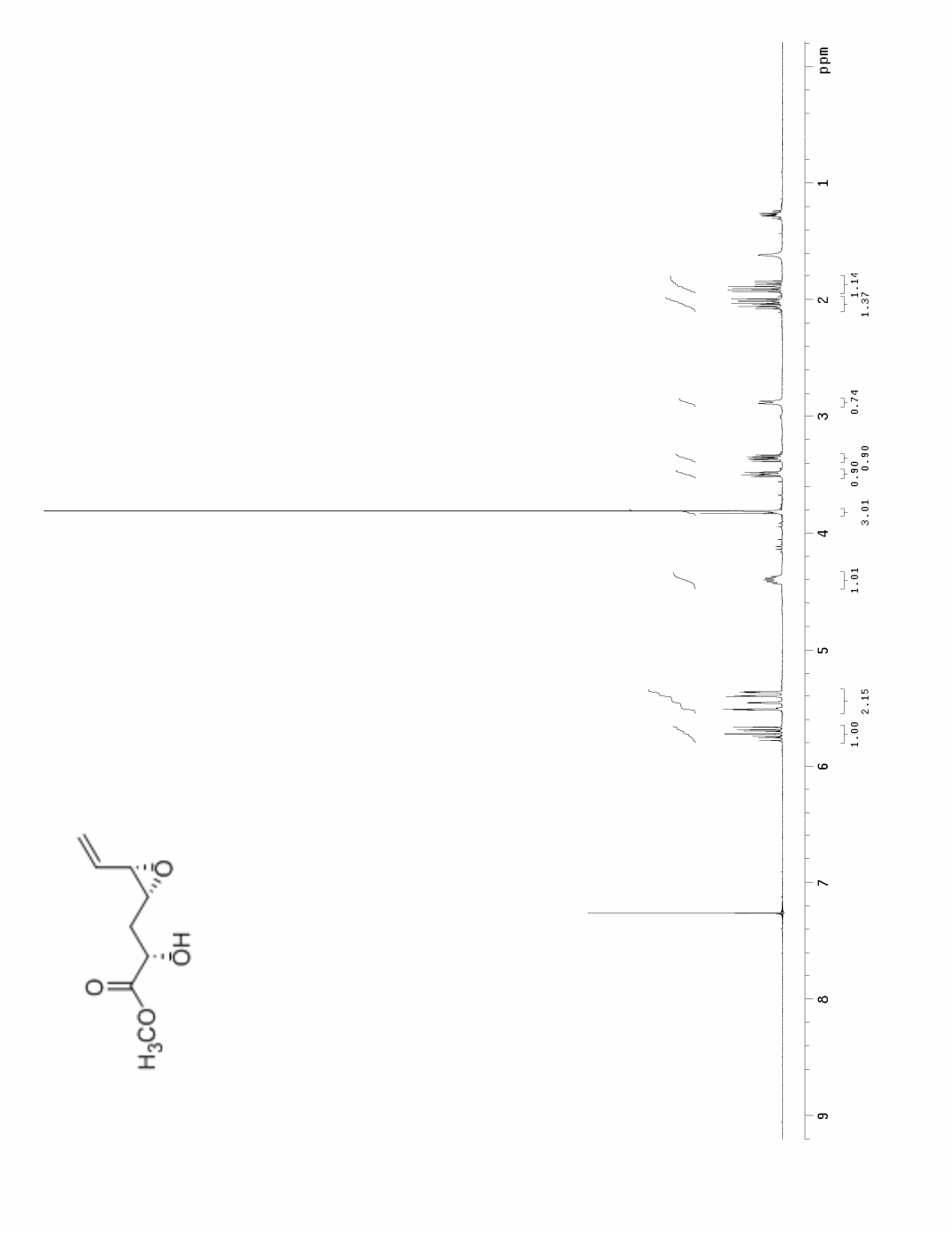
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*S,Z*)-methyl 2-hydroxyhepta-4,6-dienoate **17**



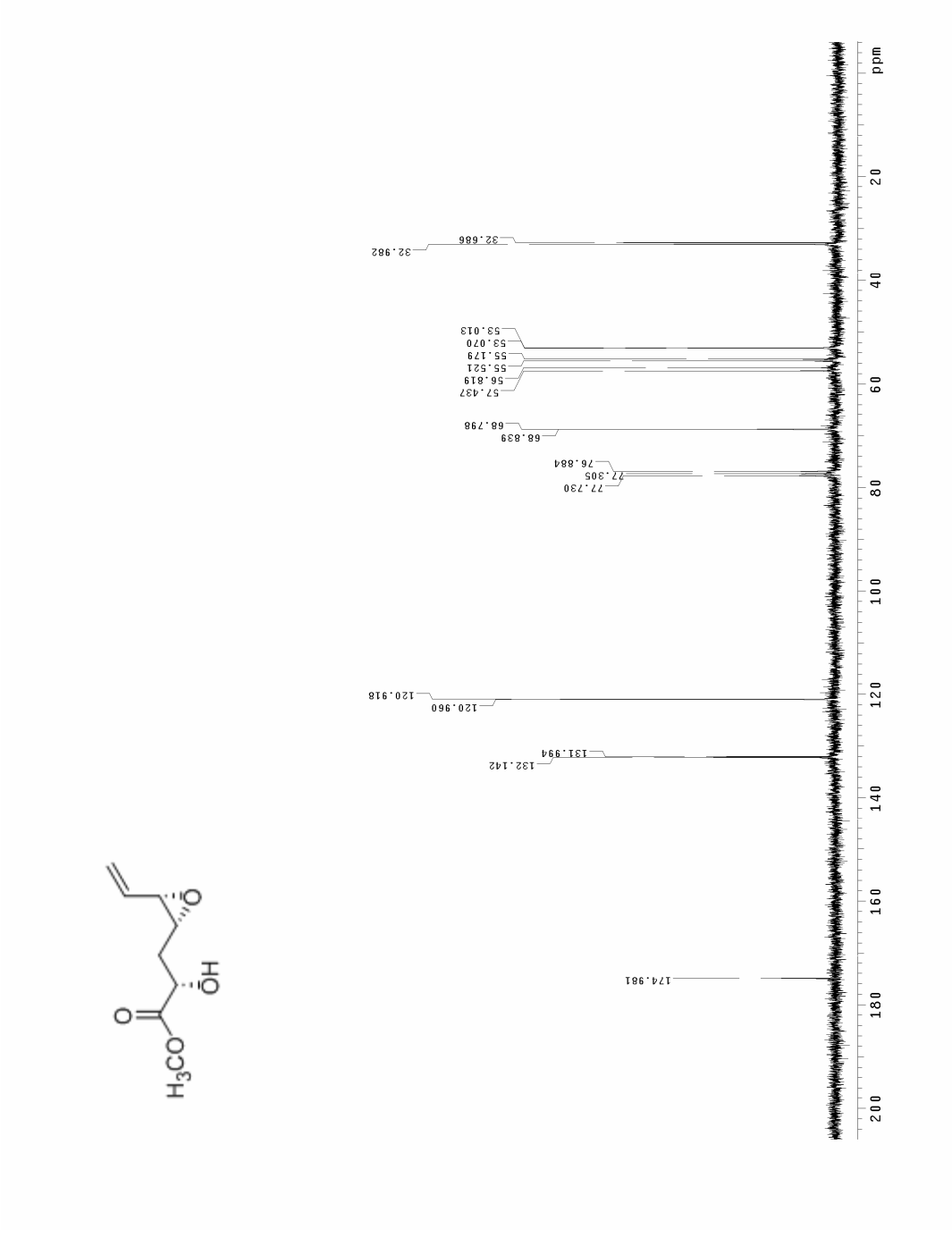
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxy-3-((*2R,3S*)-3-vinyloxiran-2-yl)propanoate **9**



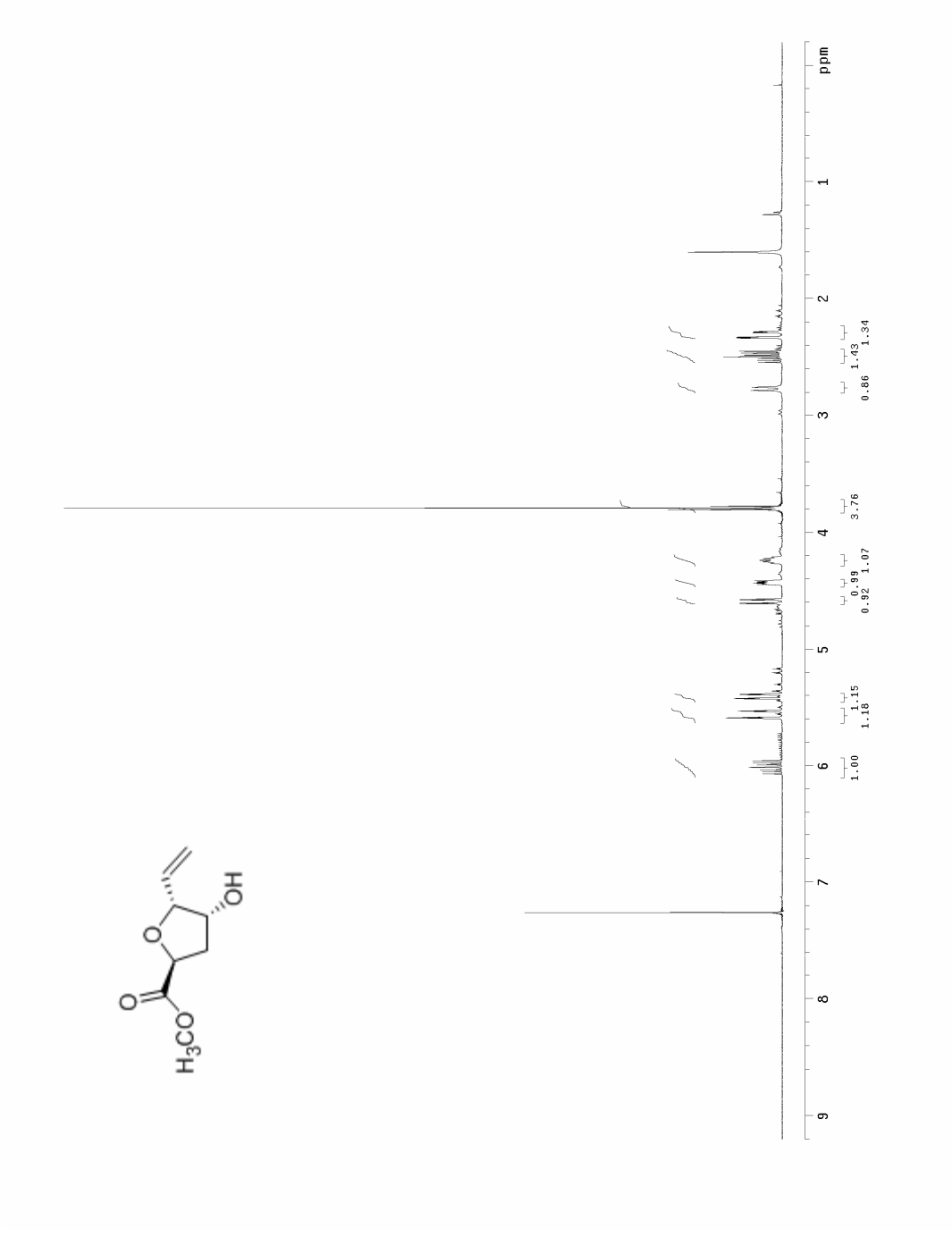
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*S*)-methyl 2-hydroxy-3-((*2R,3S*)-3-vinyloxiran-2-yl)propanoate **9**



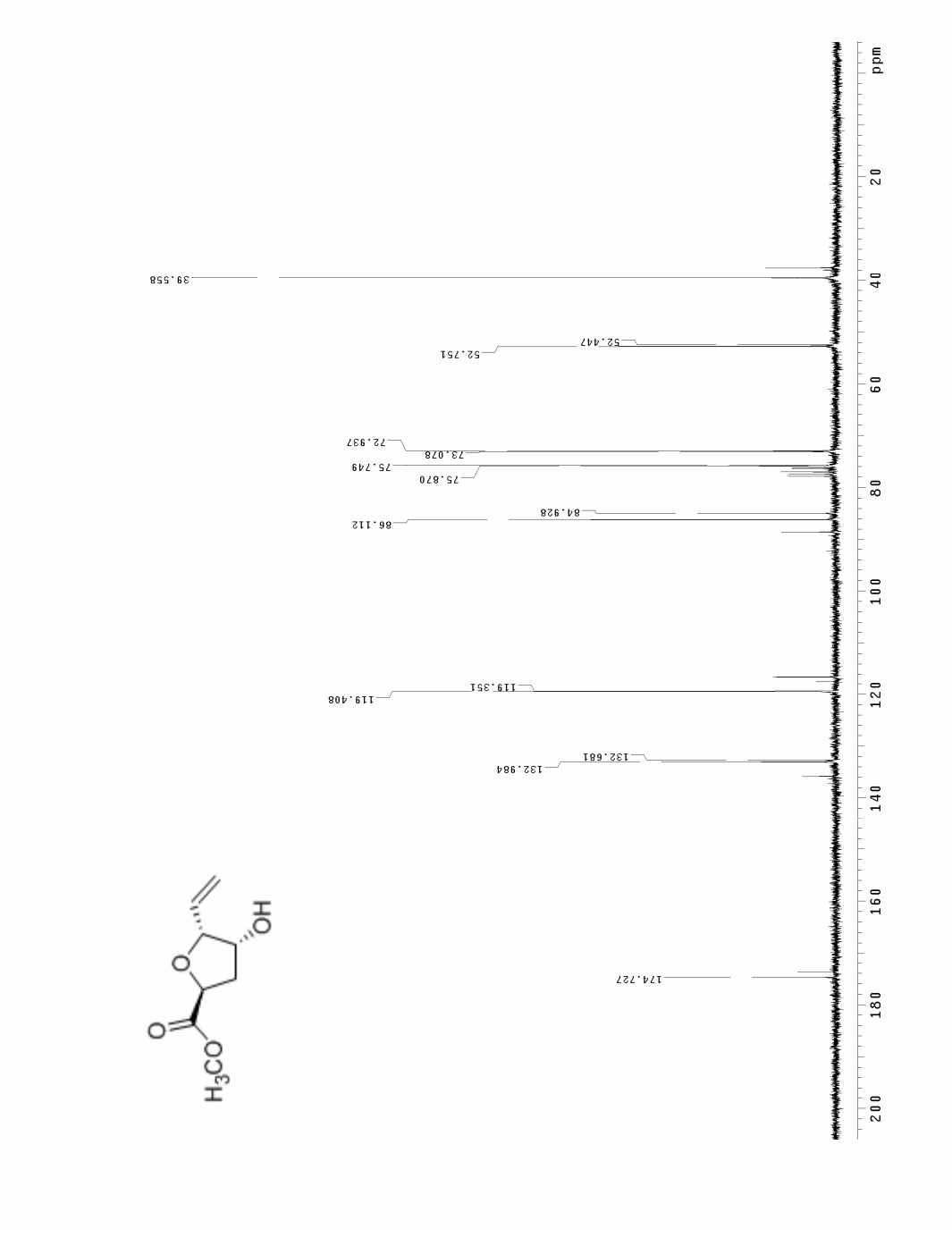
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-hydroxy-5-vinyltetrahydrofuran-2-carboxylate **18**



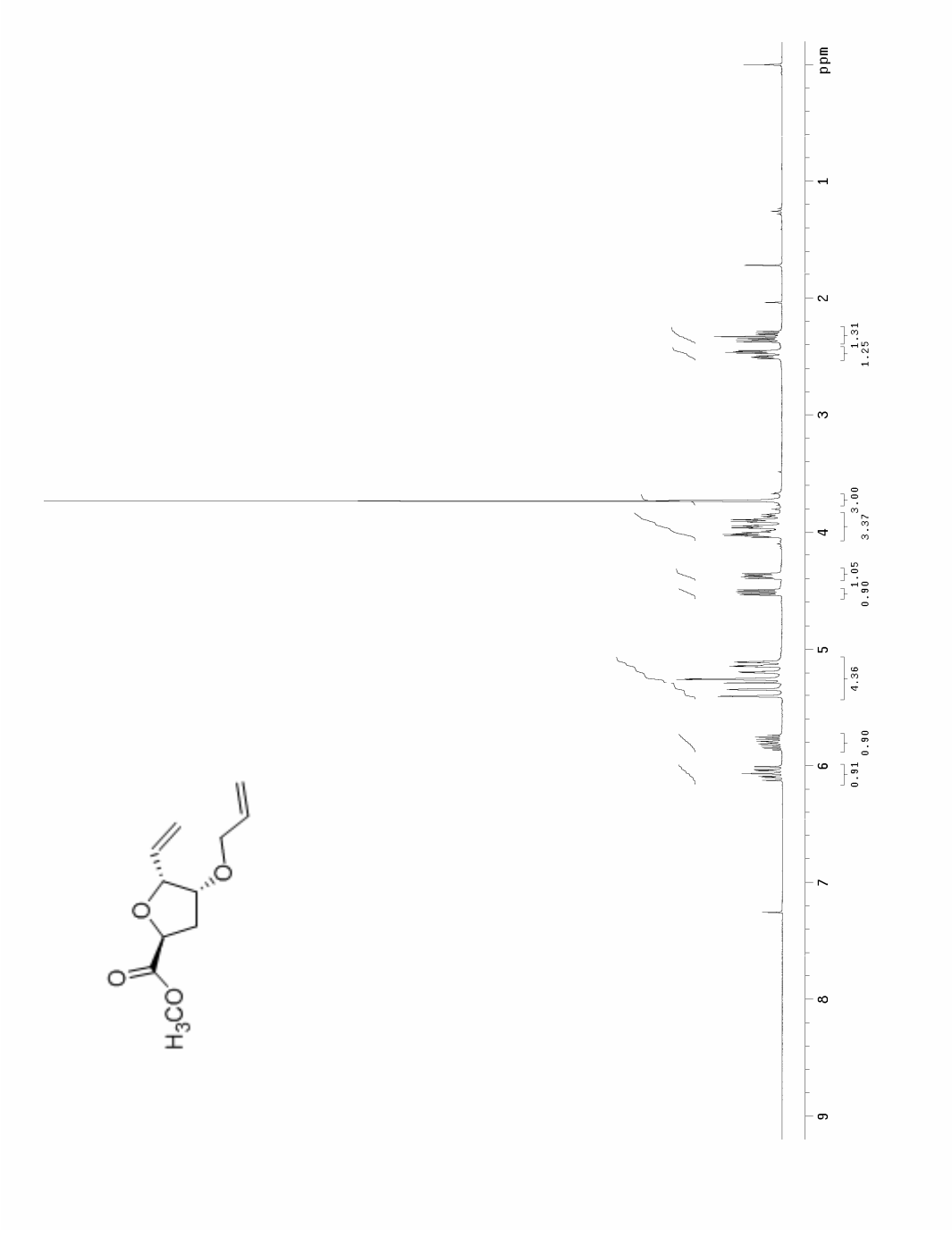
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-hydroxy-5-vinyltetrahydrofuran-2-carboxylate **18**



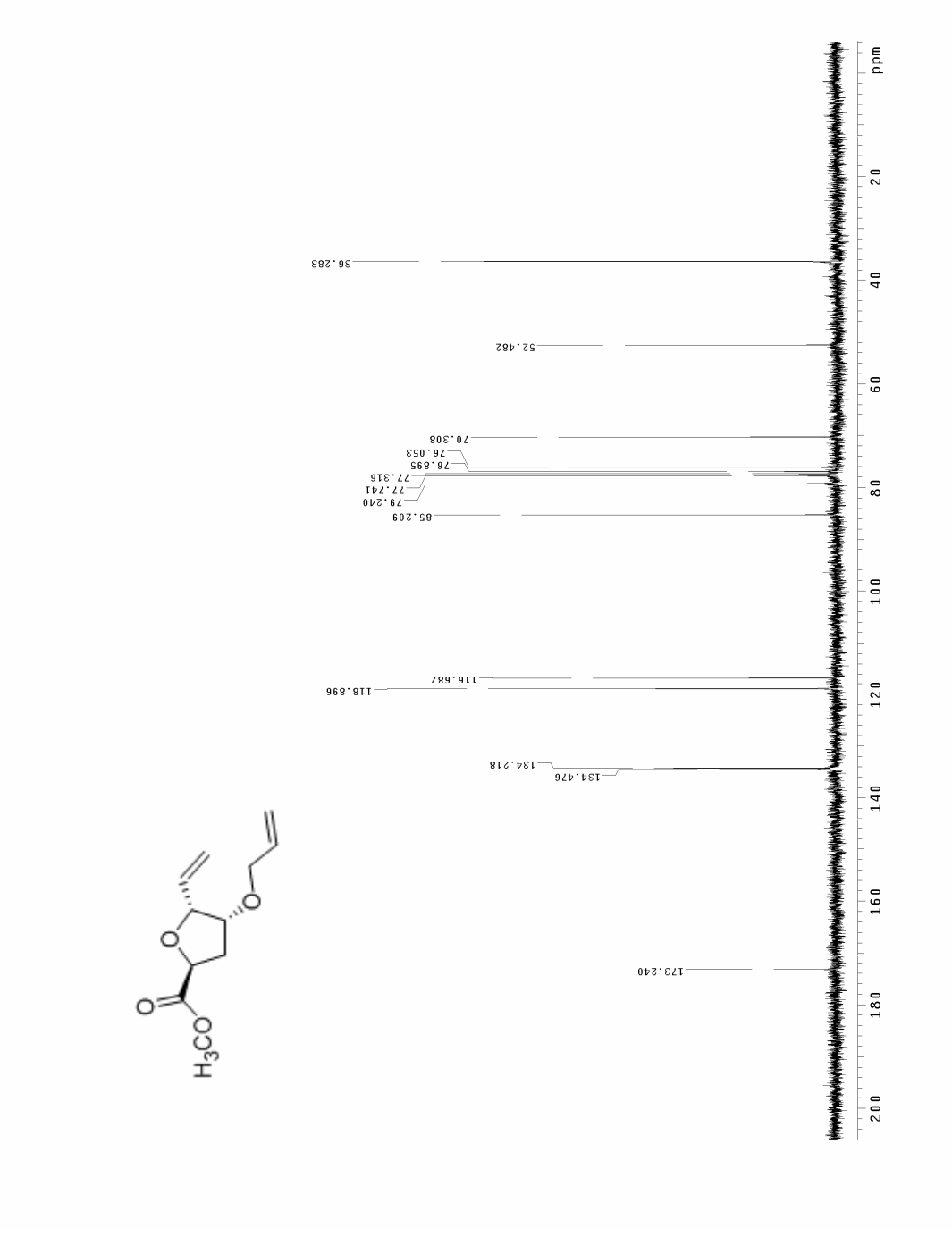
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-(allyloxy)-5-vinyltetrahydrofuran-2-carboxylate **10**



^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

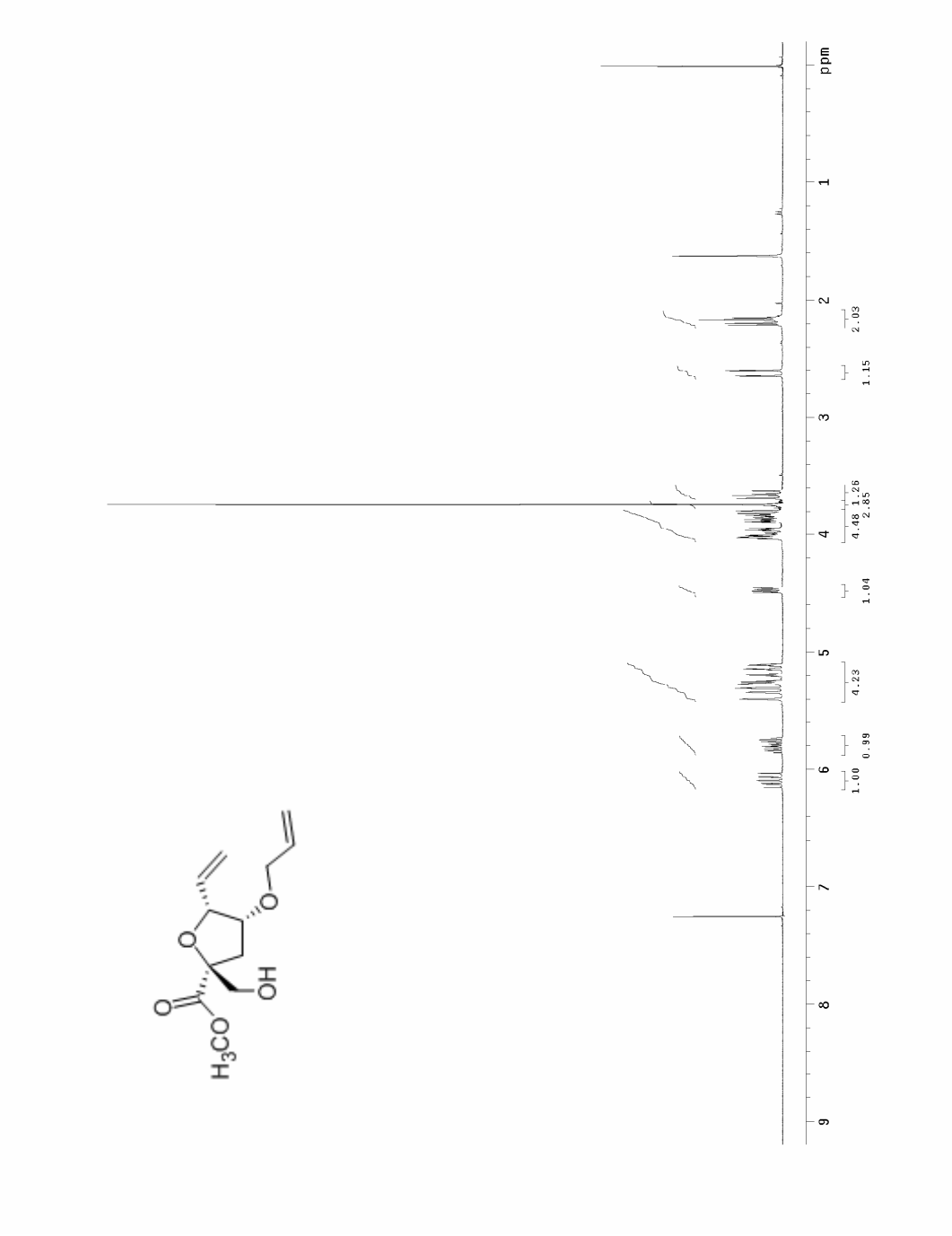
(*2S,4R,5R*)-methyl 4-(allyloxy)-5-vinyltetrahydrofuran-2-carboxylate **10**



^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-(allyloxy)-2-(hydroxymethyl)-5-vinyltetrahydrofuran-2-carboxylate

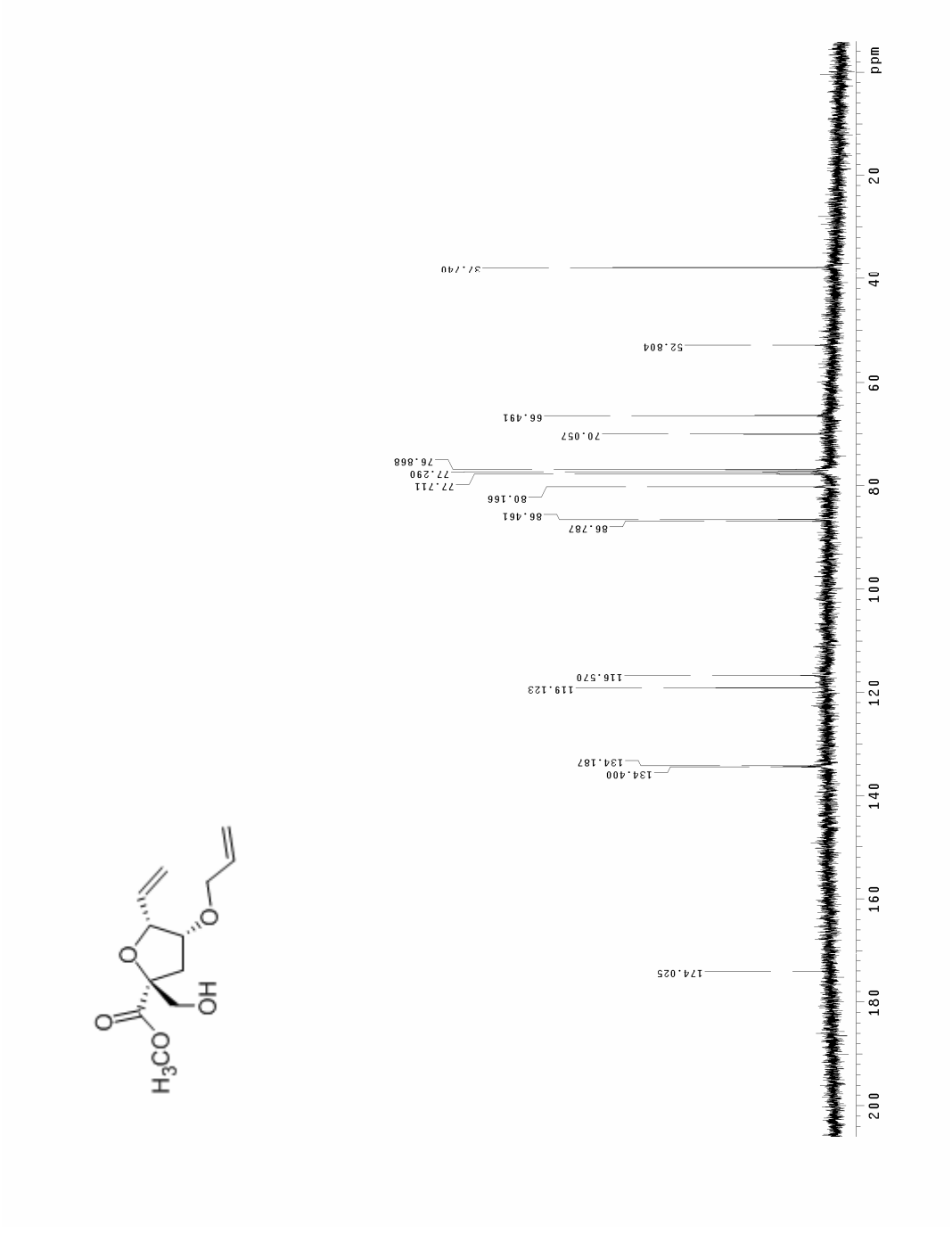
19



^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-(allyloxy)-2-(hydroxymethyl)-5-vinyltetrahydrofuran-2-carboxylate

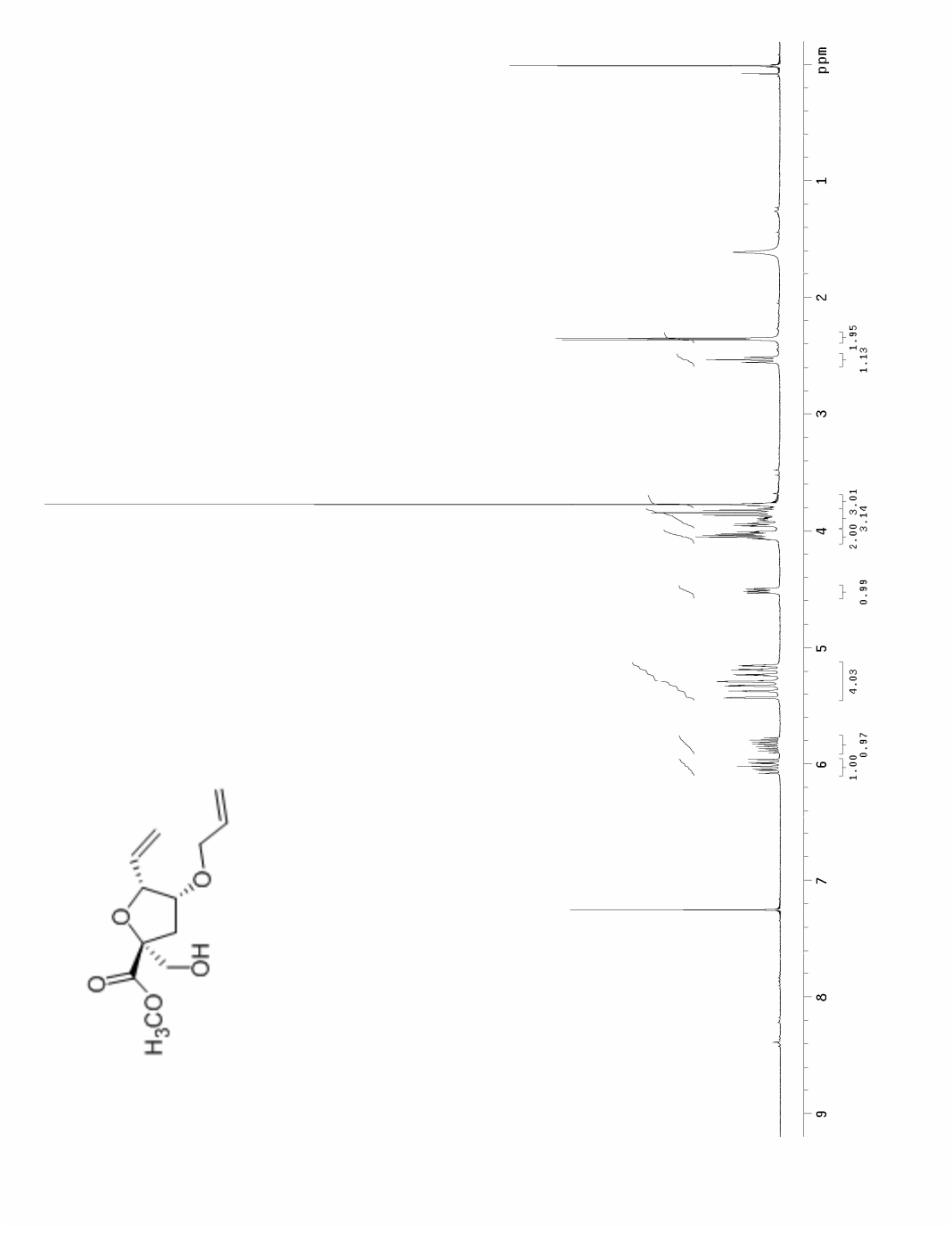
19



^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,4R,5R*)-methyl 4-(allyloxy)-2-(hydroxymethyl)-5-vinyltetrahydrofuran-2-carboxylate

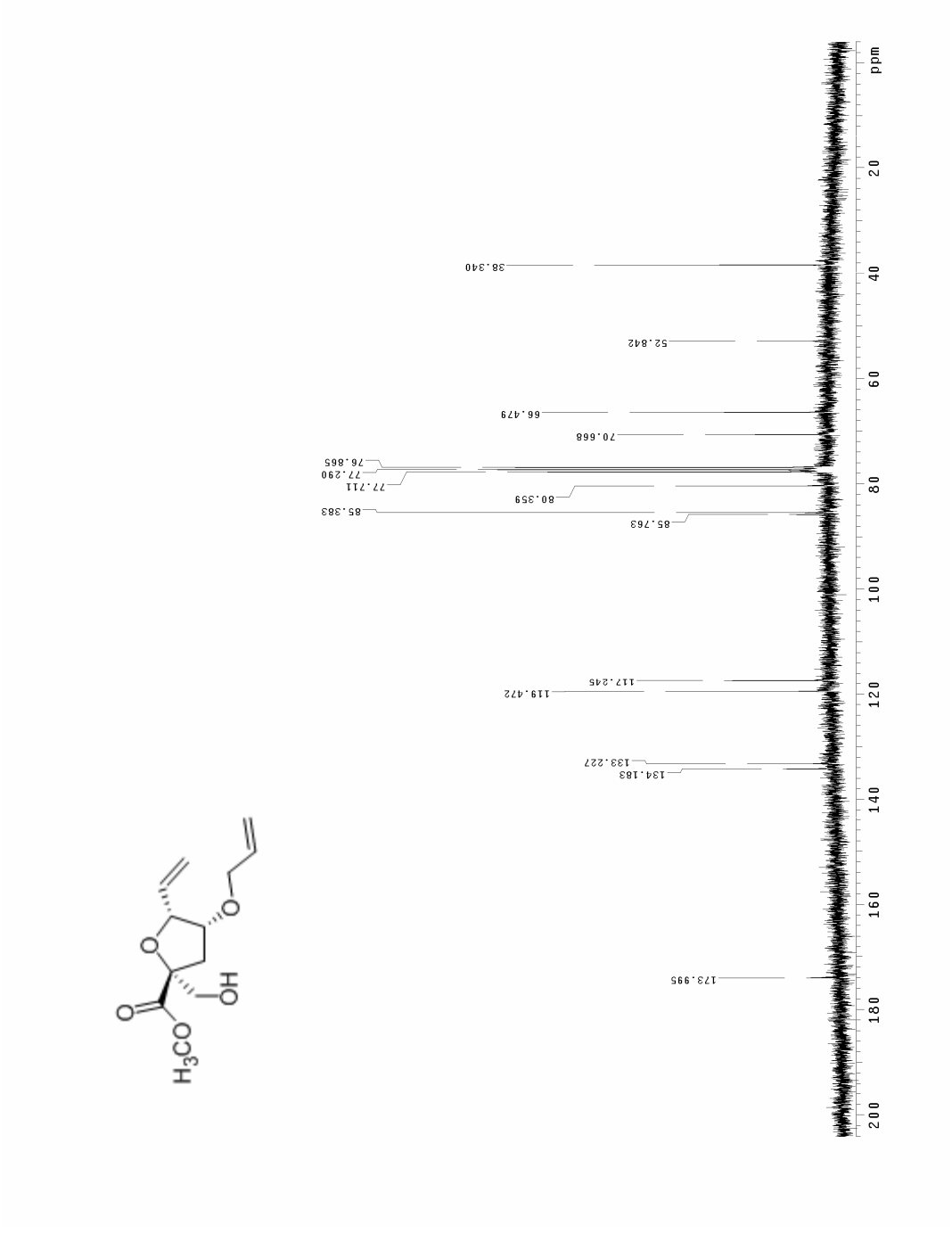
epi-19



^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

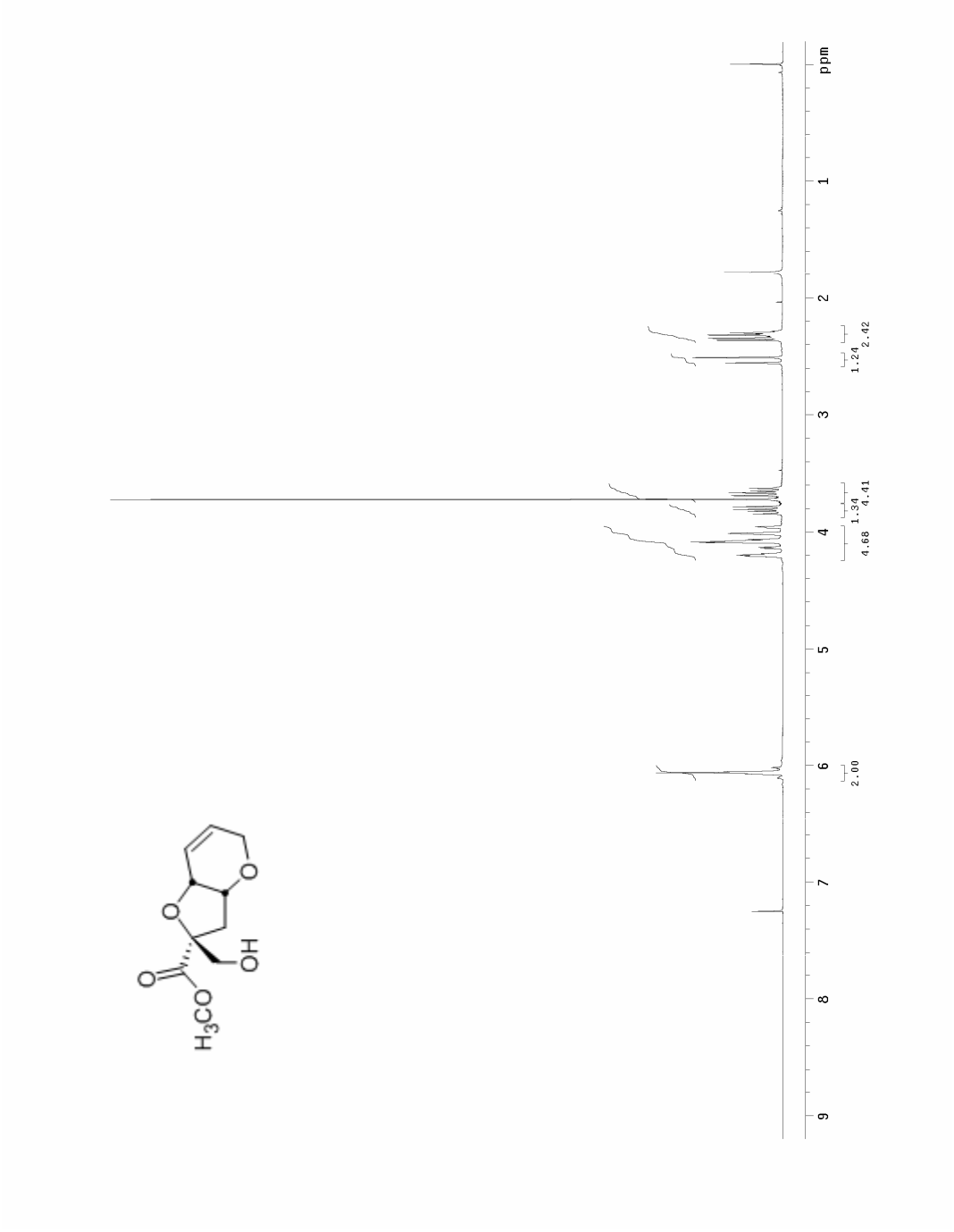
(*2S,4R,5R*)-methyl 4-(allyloxy)-2-(hydroxymethyl)-5-vinyltetrahydrofuran-2-carboxylate

epi-19



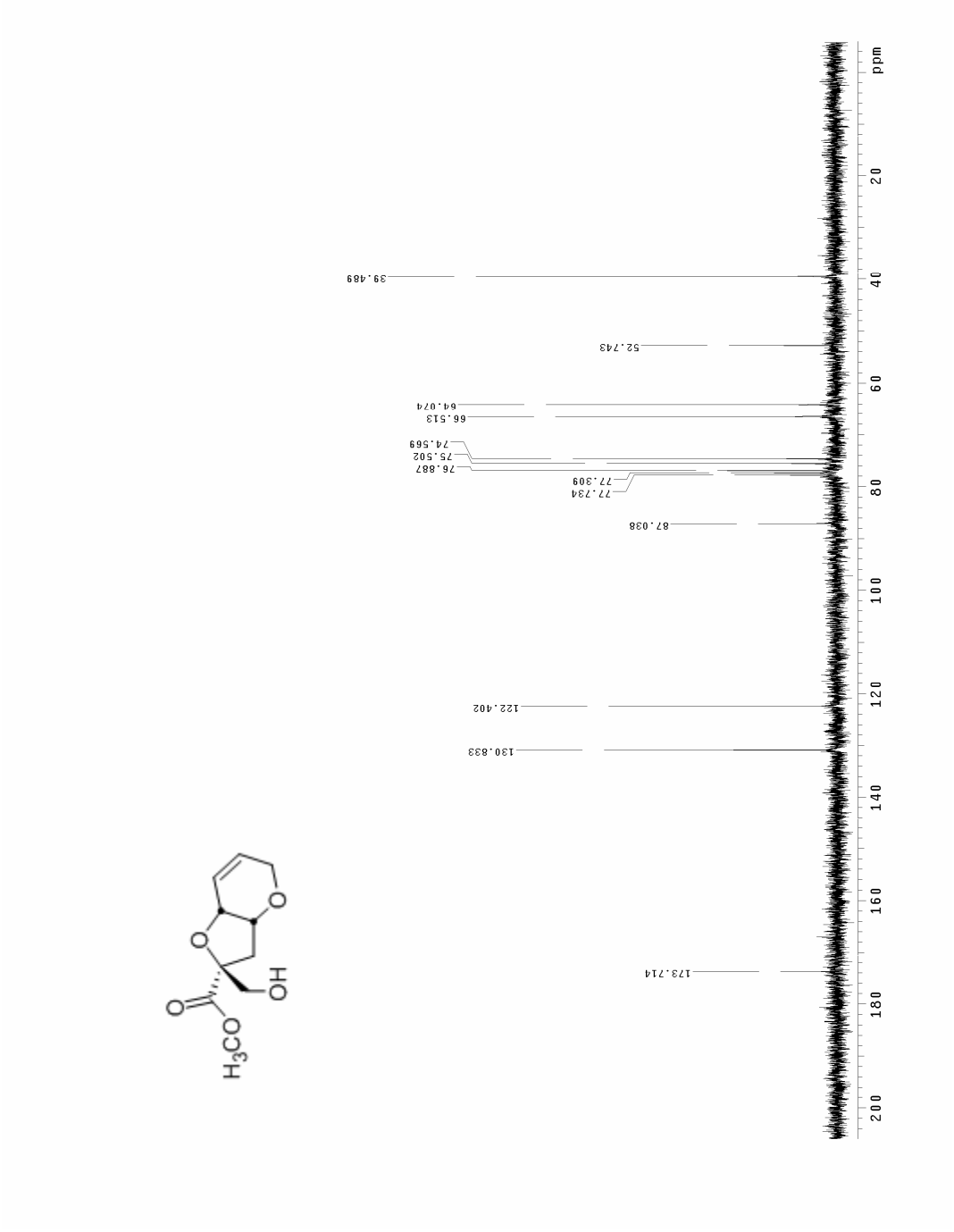
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-(hydroxymethyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **11**



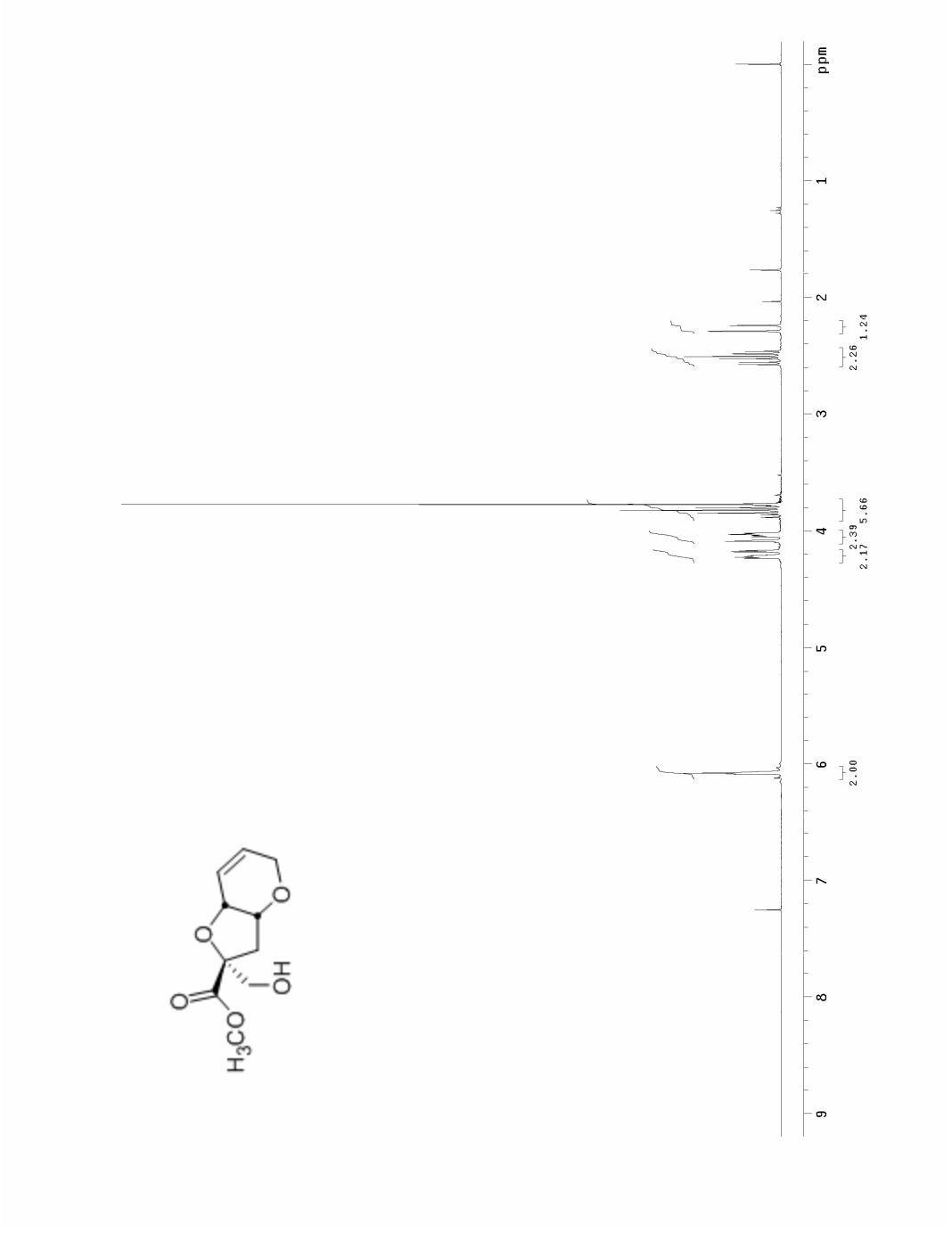
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-(hydroxymethyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **11**



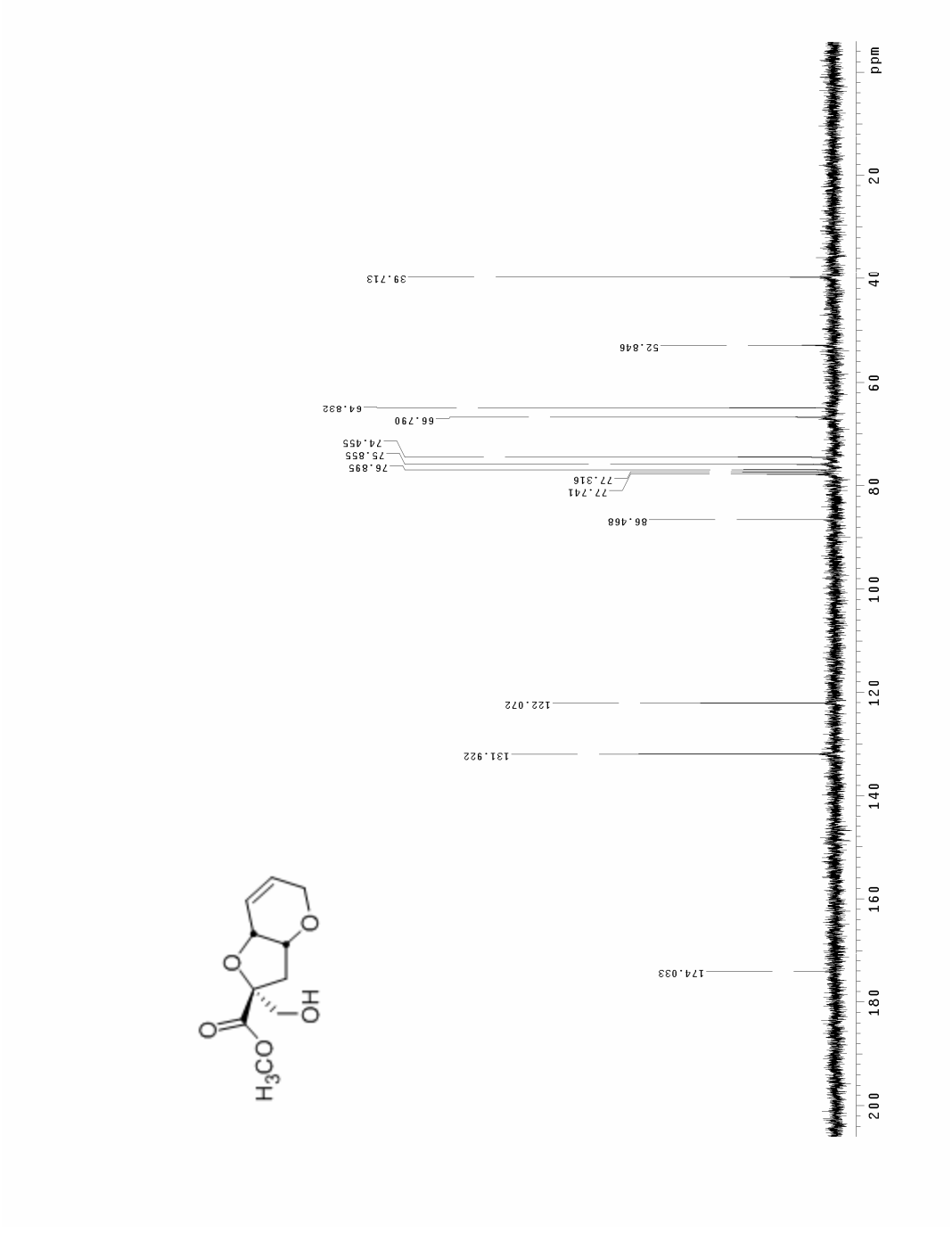
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-(hydroxymethyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **epi-11**



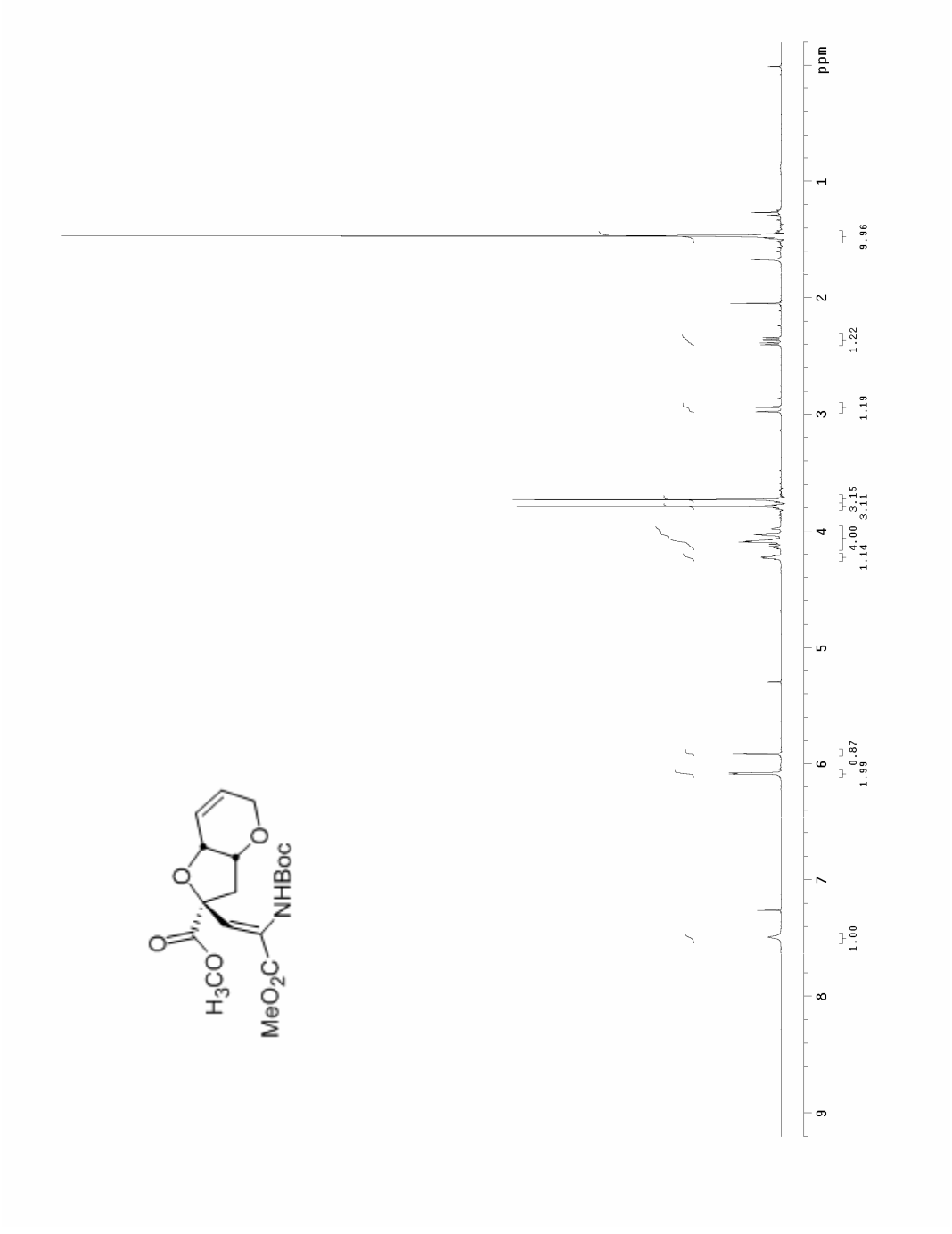
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-(hydroxymethyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **epi-11**



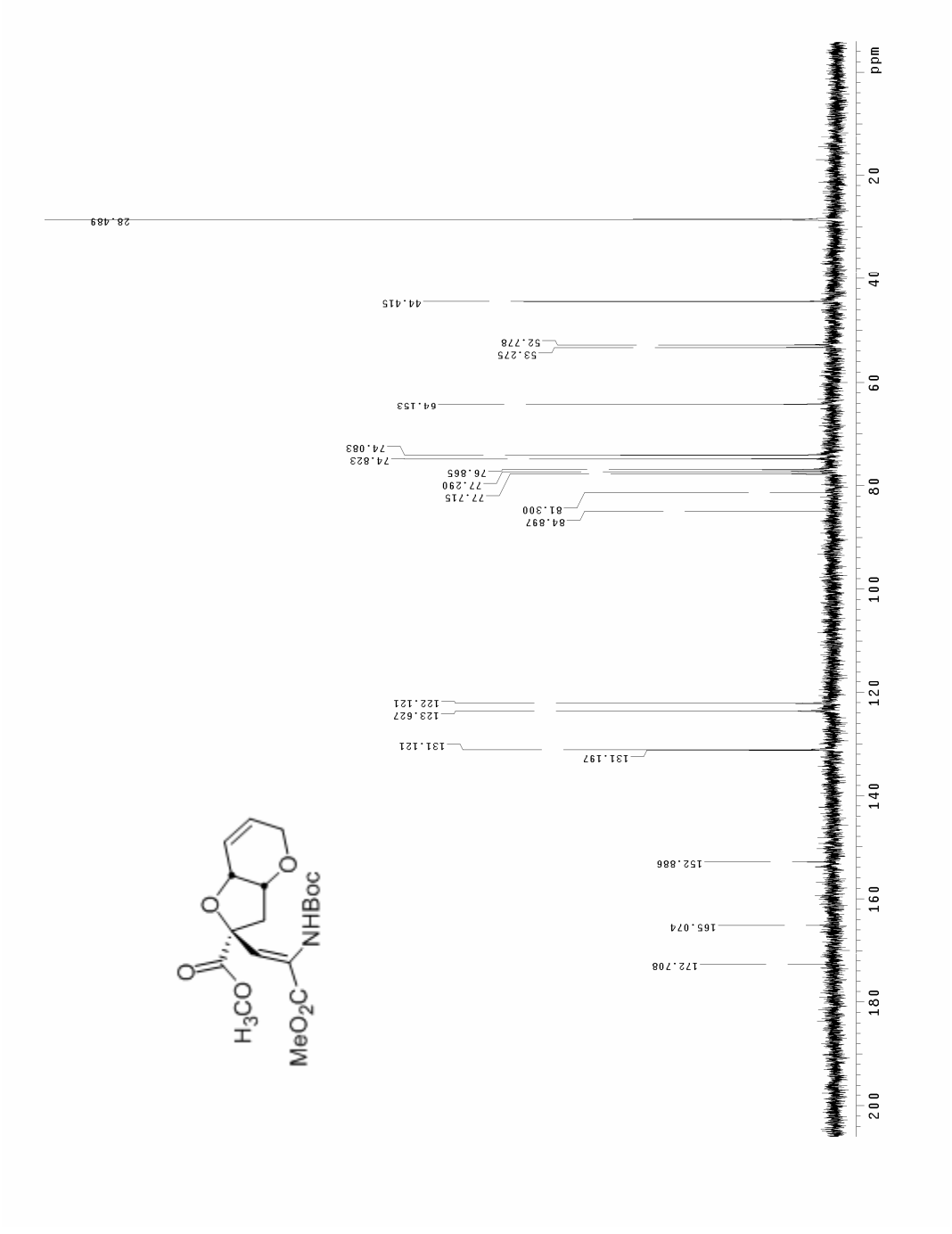
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-((*Z*)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxoprop-1-enyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **13**



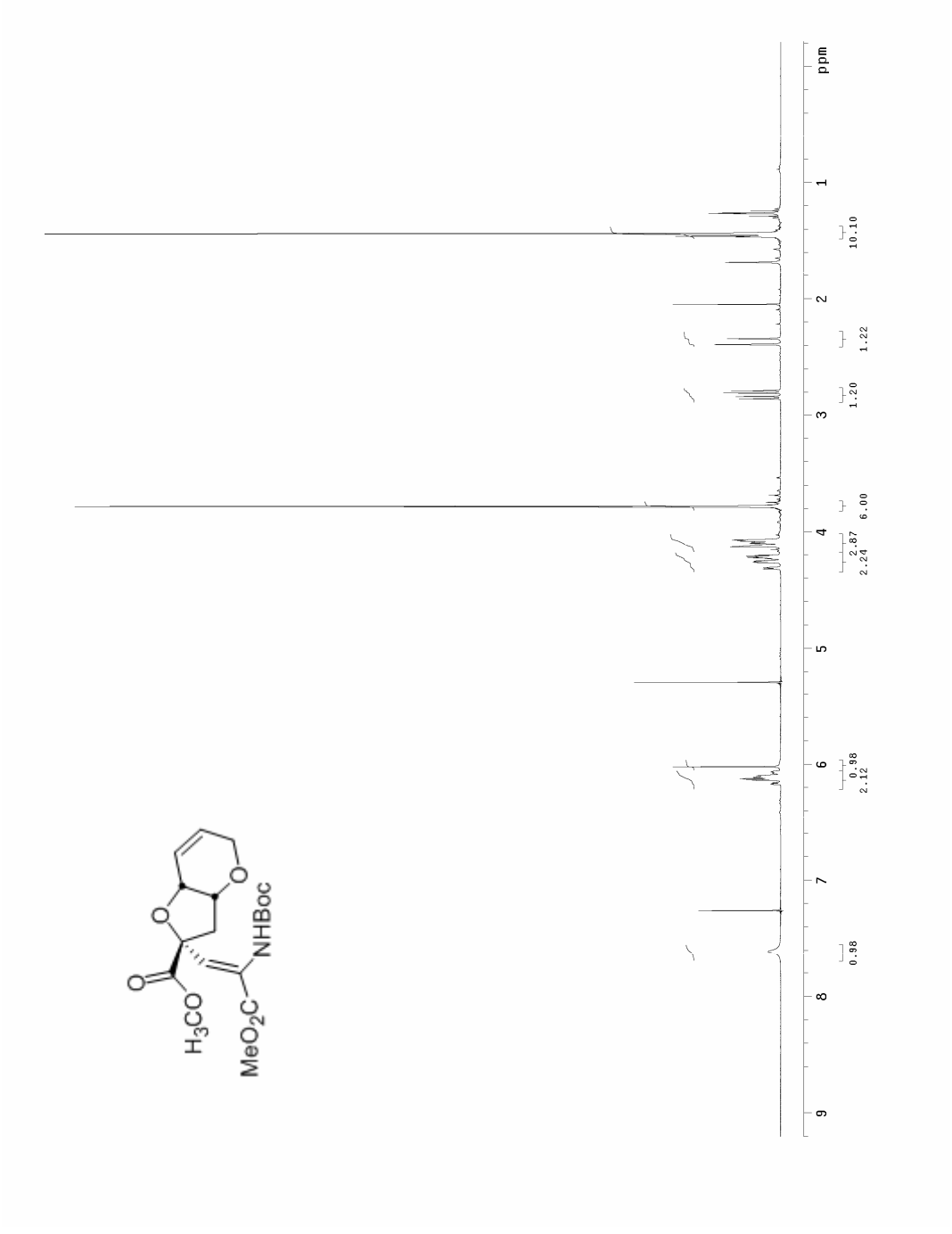
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-((*Z*)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxoprop-1-enyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **13**



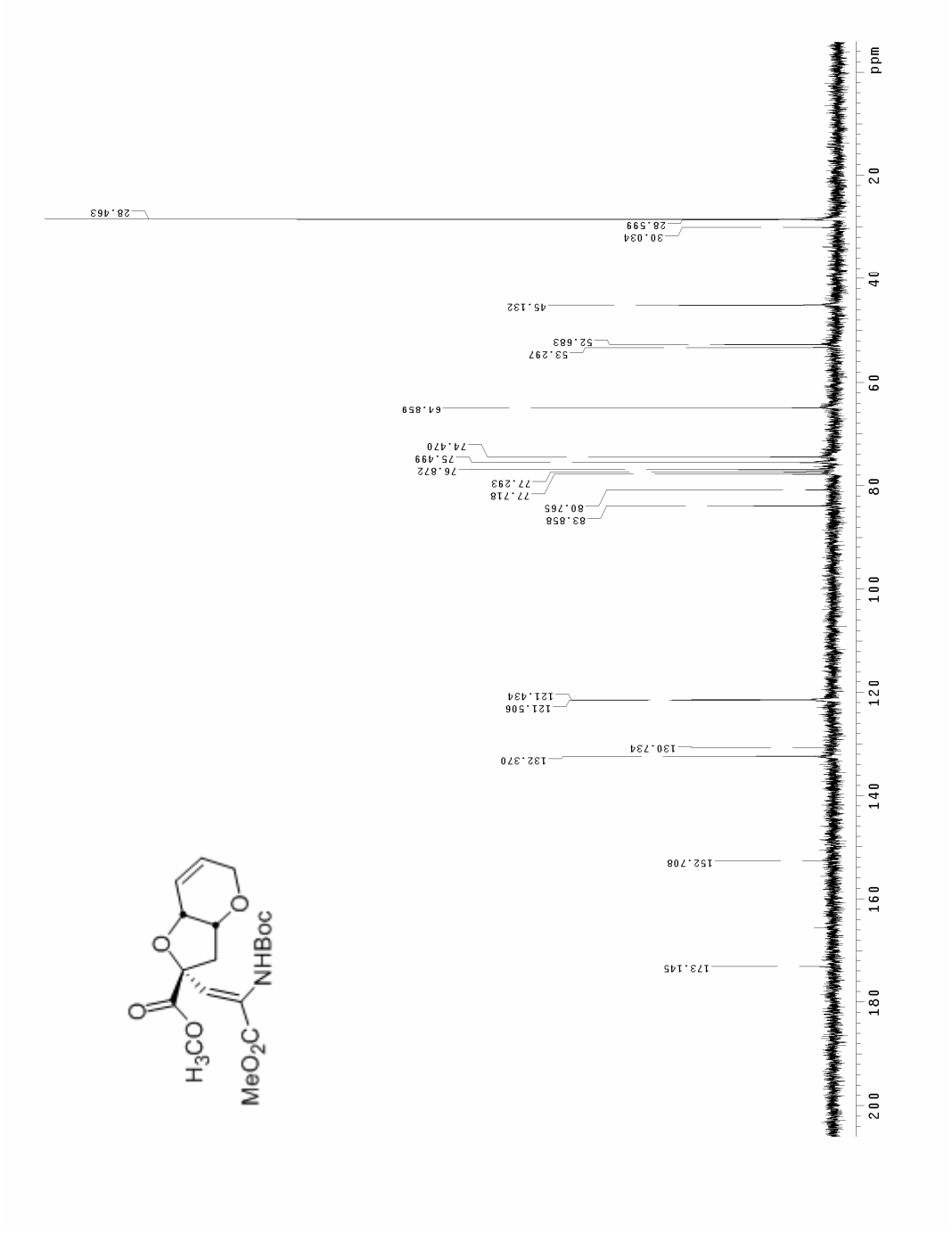
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2S,3aR,7aR*)-methyl 2-((*Z*)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxoprop-1-enyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **epi-13**



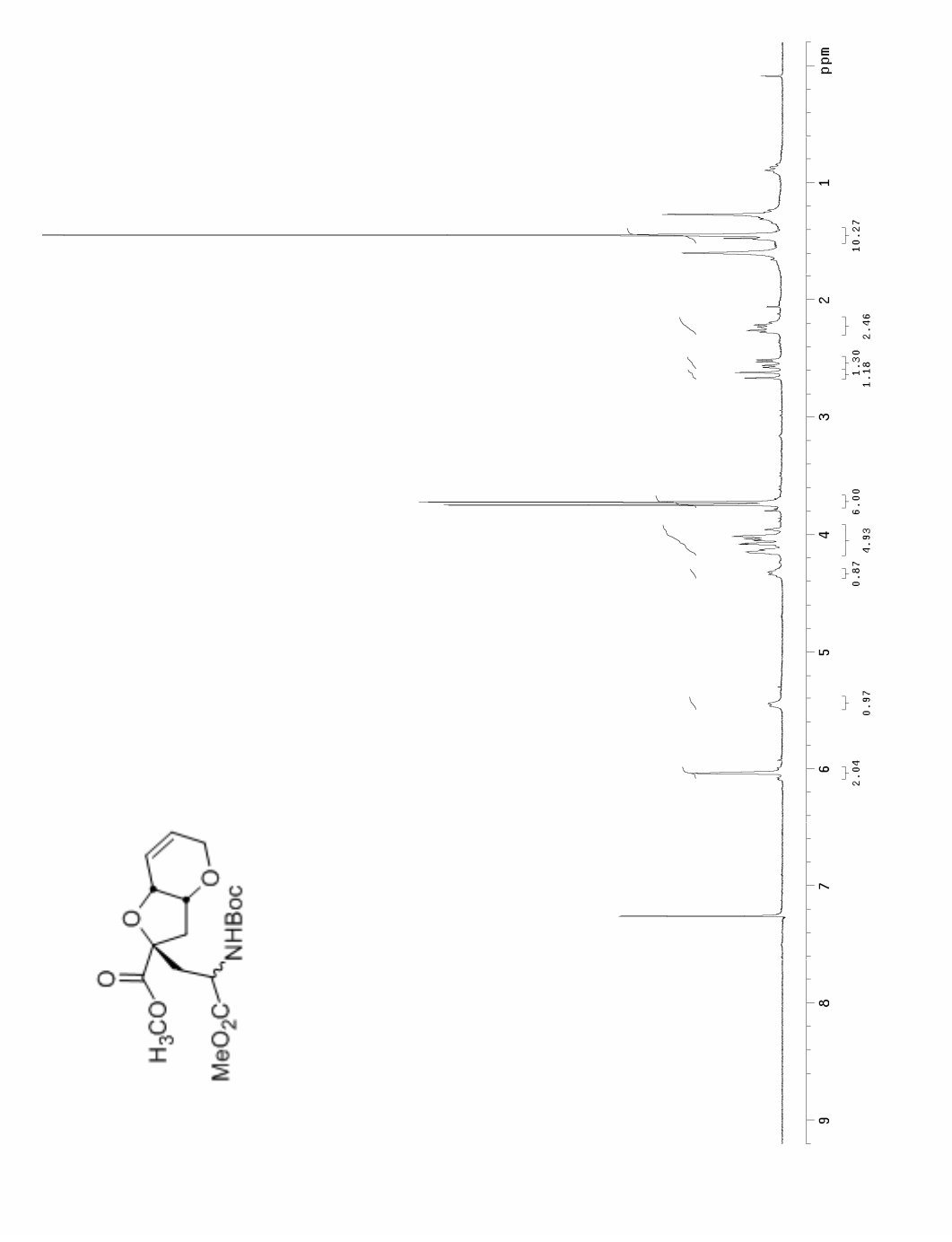
^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

((*2S,3aR,7aR*)-methyl 2-((*Z*)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxoprop-1-enyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **epi-13**



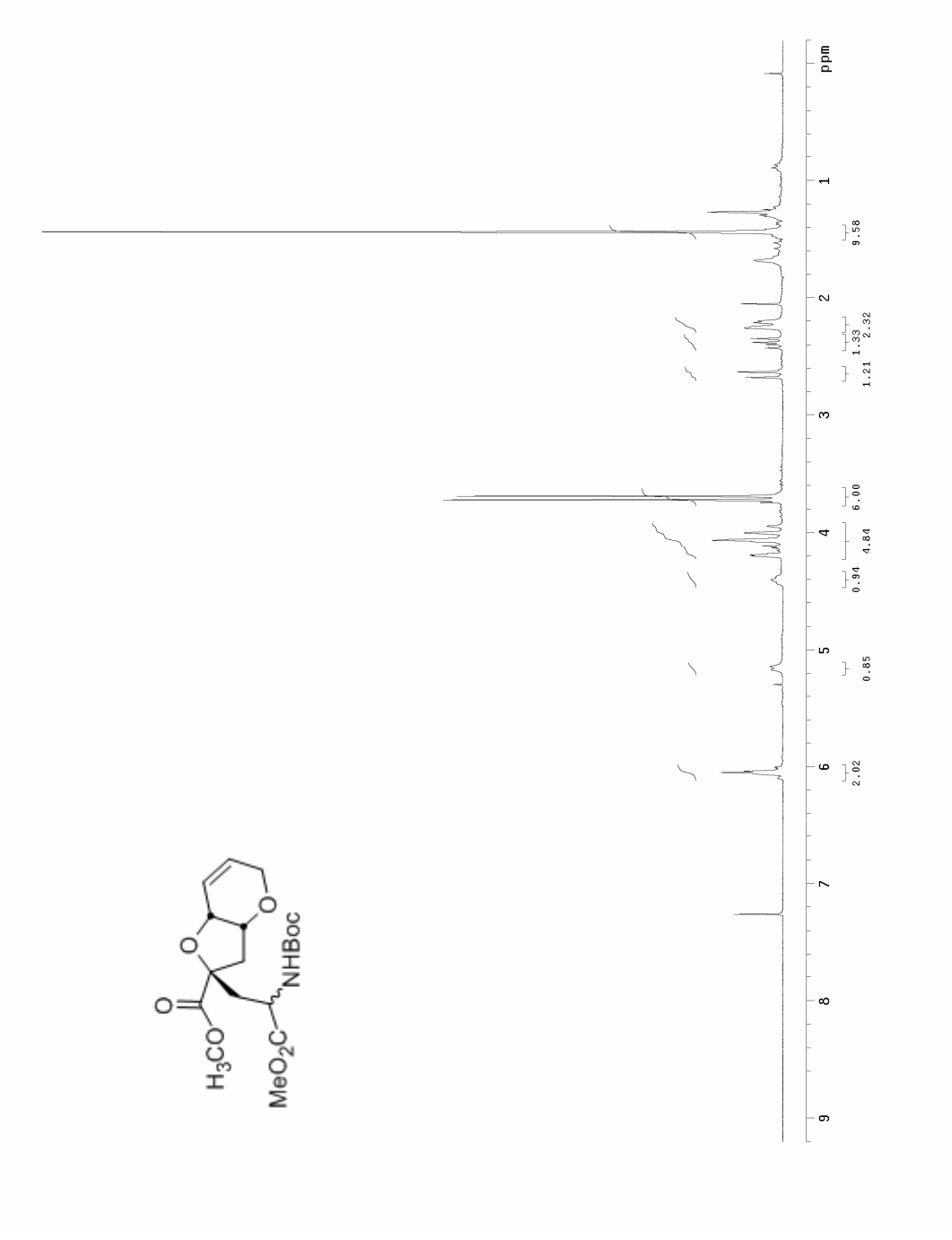
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2R,3aR,7aR*)-methyl 2-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **4** (Less polar on TLC)



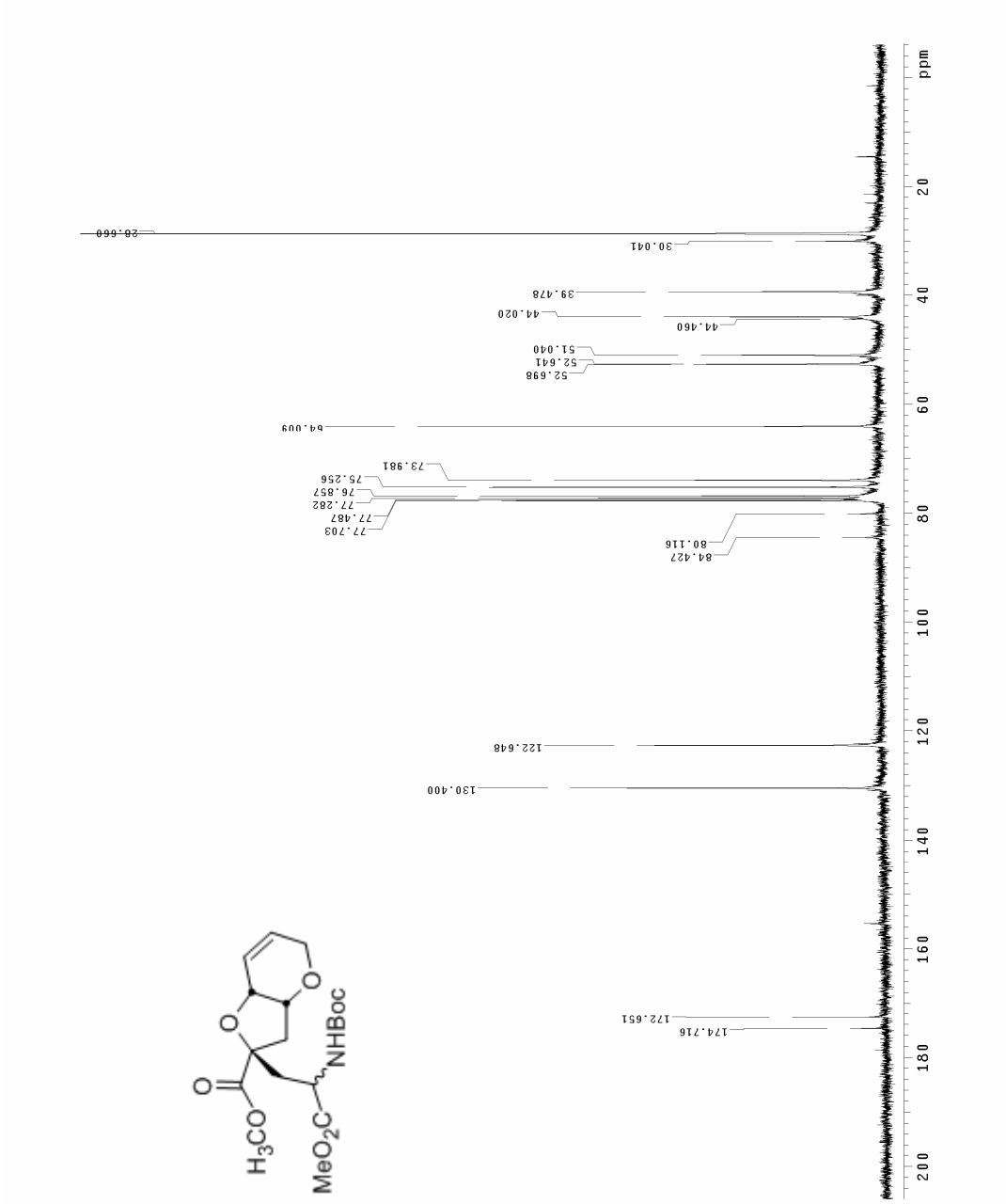
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

(*2R,3aR,7aR*)-methyl 2-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **4** (More polar on TLC)



^{13}C-NMR Spectrum (75 MHz, $CDCl_3$)

(*2R,3aR,7aR*)-methyl 2-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-carboxylate **4** (More polar on TLC)



Appendix B

X-ray Crystallography Data: Molecule epi-55

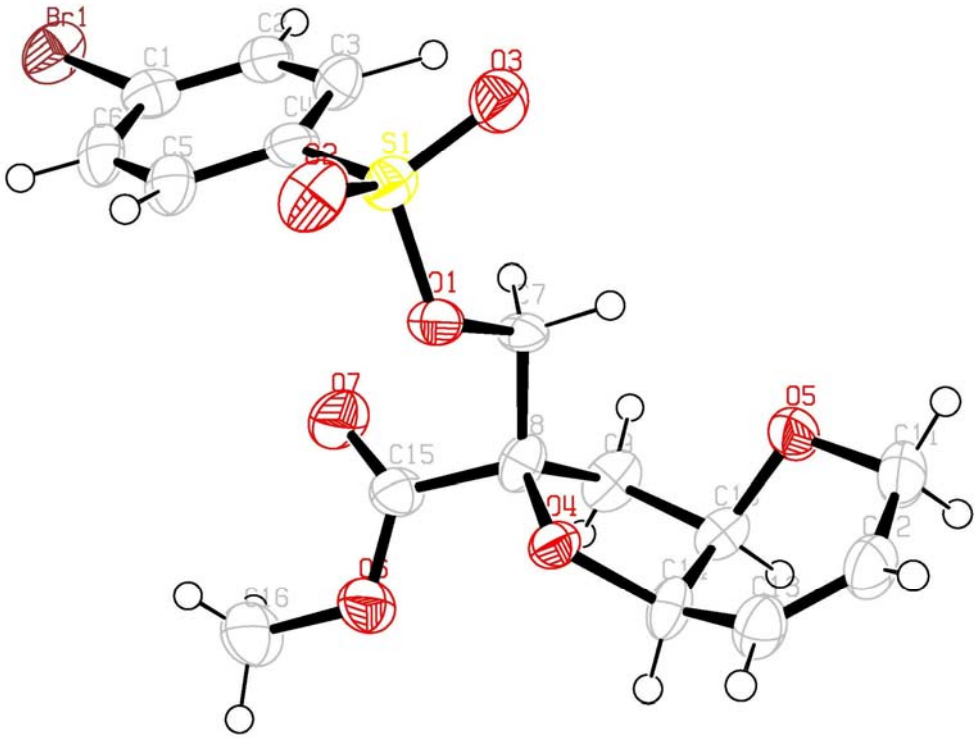


Table A. Crystal data and structure refinement for epi-**55**.

Identification code	**epi-33**	
Empirical formula	C16H17BrO7S	
Formula weight	433.27	
Temperature	110(2)K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 9.3562(2) Å	α = 90°
	b = 10.4754(2) Å	β = 115.2340(10) °
	c = 10.0316(2) Å	γ = 90°
Volume	889.37(3) $Å^3$	
Z	2	
Density (calculated)	1.618 Mg/m^3	
Absorption coefficient	4.576 mm^{-1}	
F(000)	440	
Crystal size	0.25 × 0.25 × 0.075 mm^3	
Theta range for data collection	4.33 to 66.92°	
Index ranges	-11<=h<=10, 0<=h<=12, 0<=h<=11	
Reflections collected	9781	
Independent reflections	1652 [R(int) = 0.0211]	
Completeness to theta = 66.92°	98.3%	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1652 / 1 / 256	
Goodness-of-fin on F^2	1.19	
Largest diff. peak and hole	0.502 and -0.642 e.$Å^{-3}$	

Table B. Atomic coordinates and equivalent isotropic displacement parameters for epi-**55**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	0.0967(9)	0.3843(9)	-0.0408(9)	0.0373(19)
C2	0.0961(10)	0.4793(9)	-0.1353(9)	0.0387(19)
C3	0.1100(9)	0.4479(8)	-0.2630(9)	0.0353(18)
C4	0.1207(10)	0.3203(9)	-0.2944(10)	0.0344(18)
C5	0.1159(10)	0.2244(9)	-0.2015(10)	0.0388(19)
C6	0.1068(10)	0.2572(9)	-0.0727(10)	0.039(2)
C7	-0.1473(8)	0.3505(7)	-0.6296(9)	0.0275(16)
C8	-0.3123(9)	0.2950(8)	-0.6974(8)	0.0331(17)
C9	-0.4343(10)	0.3978(9)	-0.7750(9)	0.041(2)
C10	-0.4623(10)	0.3841(9)	-0.9362(9)	0.0371(19)
C11	-0.3496(13)	0.4417(11)	-1.0988(9)	0.049(2)
C12	-0.3499(13)	0.3044(10)	-1.1372(10)	0.044(2)
C13	-0.3850(11)	0.2130(10)	-1.0671(9)	0.041(2)
C14	-0.4387(10)	0.2439(9)	-0.9497(9)	0.0361(19)
C15	-0.3460(10)	0.2335(9)	-0.5752(9)	0.0360(18)
C16	-0.4799(14)	0.0749(12)	-0.5074(12)	0.055(3)
Br1	0.09897(10)	0.42218(13)	0.14475(9)	0.0522(4)
O1	-0.0395(6)	0.2448(5)	-0.5697(6)	0.0337(12)
O2	0.2167(7)	0.1590(7)	-0.4349(7)	0.0456(15)
O3	0.1855(7)	0.3862(7)	-0.5115(7)	0.0443(15)
O4	-0.3218(6)	0.2013(5)	-0.8055(6)	0.0312(12)
O5	-0.3433(7)	0.4578(5)	-0.9552(6)	0.0383(14)
O6	-0.4420(8)	0.1344(7)	-0.6210(7)	0.0452(15)
O7	-0.2944(8)	0.2767(8)	-0.4523(6)	0.0537(18)
S1	0.1358(2)	0.27596(19)	-0.4578(2)	0.0336(5)

Table C. Bond lengths [Å] and angles [°] for epi-**55**.

C1-C2	1.373(13)
C1-C6	1.382(13)
C1-Br1	1.894(8)
C2-C3	1.382(13)
C2-H2	0.93
C3-C4	1.387(13)
C3-H3	1.16(9)
C4-C5	1.384(13)
C4-S1	1.766(9)
C5-C6	1.374(13)
C5-H5	1.01(7)
C6-H6	0.93
C7-O1	1.445(9)
C7-C8	1.513(10)
C7-H7A	1.08(10)
C7-H7B	0.99(16)
C8-O4	1.437(10)
C8-C9	1.530(12)
C8-C15	1.533(11)
C9-C10	1.530(11)
C9-H9A	0.97
C9-H9B	0.97
C10-O5	1.432(11)
C10-C14	1.500(13)
C10-H10	1.11(8)
C11-O5	1.427(10)
C11-C12	1.489(16)
C11-H11A	0.97

C11-H11B	0.97
C12-C13	1.309(14)
C12-H12	0.80(10)
C13-C14	1.499(12)
C13-H13	0.99(9)
C14-O4	1.462(9)
C14-H14	0.98
C15-O7	1.204(11)
C15-O6	1.321(11)
C16-O6	1.468(11)
C16-H16A	0.96
C16-H16B	0.96
C16-H16C	0.96
O1-S1	1.577(5)
O2-S1	1.407(7)
O3-S1	1.433(7)
C2-C1-C6	121.2(8)
C2-C1-Br1	121.5(7)
C6-C1-Br1	117.2(7)
C1-C2-C3	119.6(9)
C1-C2-H2	120.2
C3-C2-H2	120.2
C2-C3-C4	119.0(8)
C2-C3-H3	108(4)
C4-C3-H3	133(4)
C5-C4-C3	121.3(8)
C5-C4-S1	118.2(7)
C3-C4-S1	120.4(7)
C6-C5-C4	119.0(9)

C6-C5-H5	118(4)
C4-C5-H5	120(4)
C5-C6-C1	119.8(9)
C5-C6-H6	120.1
C1-C6-H6	120.1
O1-C7-C8	106.9(6)
O1-C7-H7A	102(5)
C8-C7-H7A	113(5)
O1-C7-H7B	118(8)
C8-C7-H7B	112(7)
H7A-C7-H7B	105(10)
O4-C8-C7	109.0(6)
O4-C8-C9	107.8(6)
C7-C8-C9	111.0(7)
O4-C8-C15	110.4(7)
C7-C8-C15	108.7(6)
C9-C8-C15	110.0(7)
C8-C9-C10	103.2(6)
C8-C9-H9A	111.1
C10-C9-H9A	111.1
C8-C9-H9B	111.1
C10-C9-H9B	111.1
H9A-C9-H9B	109.1
O5-C10-C14	111.3(7)
O5-C10-C9	107.3(7)
C14-C10-C9	102.8(7)
O5-C10-H10	103(4)
C14-C10-H10	121(5)
C9-C10-H10	111(4)
O5-C11-C12	111.7(8)

O5-C11-H11A	109.3
C12-C11-H11A	109.3
O5-C11-H11B	109.3
C12-C11-H11B	109.3
H11A-C11-H11B	107.9
C13-C12-C11	122.7(9)
C13-C12-H12	113(8)
C11-C12-H12	123(7)
C12-C13-C14	120.6(9)
C12-C13-H13	117(5)
C14-C13-H13	123(5)
O4-C14-C13	110.6(7)
O4-C14-C10	110.6(7)
C13-C14-C10	113.2(8)
O4-C14-H14	108.8
C13-C14-H14	108.8
C10-C14-H14	108.8
O7-C15-O6	124.6(8)
O7-C15-C8	122.1(8)
O6-C15-C8	113.2(7)
O6-C16-H16A	109.5
O6-C16-H16B	109.5
H16A-C16-H16B	109.5
O6-C16-H16C	109.5
H16A-C16-H16C	109.5
H16B-C16-H16C	109.5
C7-O1-S1	117.9(5)
C8-O4-C14	108.5(6)
C11-O5-C10	111.8(7)
C15-O6-C16	114.6(7)

O2-S1-O3	121.6(4)
O2-S1-O1	105.1(4)
O3-S1-O1	107.8(3)
O2-S1-C4	109.1(4)
O3-S1-C4	107.7(4)
O1-S1-C4	104.2(4)

Symmetry transformations used to generate equivalent atoms:

Table D. Anisotropic displacement parameters for epi-**55**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \ldots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	0.029(4)	0.049(5)	0.037(4)	-0.008(4)	0.017(3)	-0.001(3)
C2	0.034(4)	0.043(5)	0.034(4)	-0.004(4)	0.011(3)	-0.008(4)
C3	0.034(4)	0.034(5)	0.034(4)	0.003(4)	0.011(3)	0.008(3)
C4	0.031(4)	0.041(5)	0.028(4)	-0.006(4)	0.011(3)	-0.010(3)
C5	0.037(4)	0.037(5)	0.040(4)	0.008(4)	0.014(3)	0.010(3)
C6	0.032(4)	0.043(5)	0.042(4)	0.015(4)	0.014(4)	0.017(4)
C7	0.017(3)	0.023(4)	0.036(4)	0.002(3)	0.005(3)	0.000(3)
C8	0.036(4)	0.039(4)	0.025(4)	-0.001(3)	0.013(3)	0.009(4)
C9	0.038(4)	0.052(6)	0.035(4)	-0.007(4)	0.018(3)	0.013(4)
C10	0.033(4)	0.045(5)	0.028(4)	-0.004(3)	0.008(3)	0.002(4)
C11	0.066(6)	0.049(6)	0.031(4)	0.005(4)	0.020(4)	-0.006(5)
C12	0.059(5)	0.047(5)	0.029(4)	-0.003(4)	0.022(4)	-0.001(4)
C13	0.050(5)	0.044(5)	0.030(4)	-0.001(4)	0.018(4)	0.003(4)
C14	0.032(4)	0.046(5)	0.026(4)	0.010(3)	0.008(3)	0.013(4)
C15	0.034(4)	0.044(5)	0.034(4)	-0.004(4)	0.018(3)	-0.008(4)
C16	0.063(6)	0.065(6)	0.051(5)	-0.001(5)	0.037(5)	-0.013(6)
Br1	0.0466(5)	0.0782(8)	0.0359(5)	-0.0059(5)	0.0216(4)	0.0020(5)
O1	0.031(3)	0.035(3)	0.033(3)	-0.004(2)	0.012(2)	-0.008(2)
O2	0.038(3)	0.056(4)	0.042(3)	-0.001(3)	0.016(3)	0.014(3)
O3	0.040(3)	0.058(4)	0.039(3)	0.004(3)	0.021(3)	-0.001(3)
O4	0.032(3)	0.030(3)	0.027(3)	-0.003(2)	0.007(2)	-0.002(2)
O5	0.051(3)	0.031(3)	0.034(4)	-0.002(2)	0.019(2)	-0.007(2)
O6	0.055(4)	0.049(4)	0.039(3)	-0.006(3)	0.028(3)	-0.015(3)
O7	0.063(4)	0.072(5)	0.030(3)	-0.011(3)	0.024(3)	-0.016(4)
S1	0.0295(9)	0.0411(11)	0.0299(9)	-0.0013(8)	0.0122(7)	0.0002(8)

Table E. Torsion angles [°] for epi-**55**.

C6-C1-C2-C3	-1.7(12)
Br1-C1-C2-C3	173.7(6)
C1-C2-C3-C4	1.5(12)
C2-C3-C4-C5	0.7(13)
C2-C3-C4-S1	179.1(6)
C3-C4-C5-C6	-2.7(13)
S1-C4-C5-C6	178.9(7)
C4-C5-C6-C1	2.4(13)
C2-C1-C6-C5	-0.3(13)
Br1-C1-C6-C5	-175.8(6)
O1-C7-C8-O4	-56.8(8)
O1-C7-C8-C9	-175.3(6)
O1-C7-C8-C15	63.6(8)
O4-C8-C9-C10	-22.2(9)
C7-C8-C9-C10	97.1(8)
C15-C8-C9-C10	-142.6(7)
C8-C9-C10-O5	-85.4(8)
C8-C9-C10-C14	32.0(9)
O5-C11-C12-C13	17.8(15)
C11-C12-C13-C14	4.5(15)
C12-C13-C14-O4	-113.6(10)
C12-C13-C14-C10	6.0(13)
O5-C10-C14-O4	83.3(8)
C9-C10-C14-O4	-31.3(8)
O5-C10-C14-C13	-38.5(10)
C9-C10-C14-C13	-153.0(7)
O4-C8-C15-O7	153.9(8)
C7-C8-C15-O7	34.4(12)

C9-C8-C15-O7	-87.3(10)
O4-C8-C15-O6	-29.3(9)
C7-C8-C15-O6	-148.8(7)
C9-C8-C15-O6	89.6(9)
C8-C7-O1-S1	-164.8(5)
C7-C8-O4-C14	-117.5(7)
C9-C8-O4-C14	3.0(8)
C15-C8-O4-C14	123.2(7)
C13-C14-O4-C8	141.5(8)
C10-C14-O4-C8	18.1(9)
C12-C11-O5-C10	-51.3(11)
C14-C10-O5-C11	62.7(9)
C9-C10-O5-C11	174.4(7)
O7-C15-O6-C16	-1.9(13)
C8-C15-O6-C16	-178.6(8)
C7-O1-S1-O2	-172.1(6)
C7-O1-S1-O3	-41.0(6)
C7-O1-S1-O4	73.2(6)
C5-C4-S1-O2	-29.1(8)
C3-C4-S1-O2	152.4(7)
C5-C4-S1-O3	-163.1(7)
C3-C4-S1-O3	18.5(8)
C5-C4-S1-O1	82.7(7)
C3-C4-S1-O1	-95.8(7)

Symmetry transformations used to generate equivalent atoms:

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Vita

Chang Won Kang was born in Seoul, Republic of Korea on June 05, 1971 to Inhak Kang and Sungja Park. He is married to Hyesook Chon and has a daughter, Hannah. Chang Won majored in Chemistry and received his Bachelor of Science degree from Kwangwoon University in Korea. During his undergraduate studies, Chang Won became interested in organic chemistry and continued his scientific training at the Graduate School of Korea University in Korea. While at Korea University, Chang Won conducted research related to self assembled DNA-small molecule for DNA crystal and received his Master of Science degree in the area of organic chemistry. Chang Won continued his chemical biology (organic synthesis) at the University of Texas Medical Branch (UTMB) under the supervision of Dr. Scott R. Gilbertson and was involved in the total synthesis of dysiherbaine. His dissertation demonstrates synthesis of target molecule for dysiherbaine and its application for analogues.

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Summary of Dissertation

Dysiherbaine **1** and a select number of structurally related compounds have been shown to have selective effects on ionotropic glutamate receptors (iGluRs). iGluRs are essential components in the central nervous system (CNS); playing an important role in memory and learning. They also play a role in a number of neurological disorders, including schizophrenia, epilepsy, Rasmussen's encephalitis and stroke; along with neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. This dissertation describes the synthesis of key molecule **4** and future directions for its use. The molecule will serve as the branch point for the synthesis of other analogues. We designed a 12 step route to this molecule that utilizes highly stereo- and regioselective reactions. The molecule **4** will provide dysiherbaine and a series of analogues without having to design a new total synthesis for each analogue. While there are a number of syntheses of dysiherbaine reported, they are not appropriate for the easy variation of the important C_8-amino C_9-alcohol pharmacophore. The molecule (**4**) has a double bond between the C_8 and C_9 position as the key reactive functional group. The principal reactivity that will be used to synthesize derivatives of this molecule involves the double bond. Addition reactions of electrophilic reagents to the double bond are the most typical, and include hydroxylation, hydrogenation, halogenation, alkylation, amination, etc. This will be a unique and simple way to make dysiherbaine and analogues with just few steps

from molecule **4**. Finally, this work will provide unique molecules that will enhance the understanding of the structure and function of ionotropic Glu receptors in the CNS.

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