SYNTHESIS AND MANIPULATION OF CARBASUGARS AND COMPLEX NATURAL PRODUCT SCAFFOLDS

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SYNTHESIS AND MANIPULATION OF CARBASUGARS AND COMPLEX NATURAL PRODUCT SCAFFOLDS

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My doctoral studies have focused on the construction of natural products and diversification of complex natural product scaffolds. A specific natural product with interesting bioactivity, sch202596, an antagonist for the galinin receptor, contains two moieties that formed the basis for my graduate studies: a carbasugar and a spirocoumaranone (dienone). Work, therefore, focused on two areas: (1) asymmetric regio-resolution of allylic oxides for the synthesis and incorporation of carbasugars; and (2) asymmetric hypervalent iodide oxidative spirocyclization. A system was developed in which a racemic allylic oxide underwent a Tsuji-Trost allylation to yield four different enantioenriched regioisomers which were carried onto four different carbasugar natural products: streptol, MK7607, cyathiformine B and polyporapyranone G. This method, termed allylic oxide regio resolution (AORR), allowed for the control of product distribution through prudent ligand and protecting group selection. Additionally, AORR allowed for the incorporation of carbasugars into phenolic natural product scaffolds. Rubiyunnanin B, a glycosidic macrocyclic peptide with an interesting bioactivity profile was one particular natural product scaffold which could be subjected to AORR. A short synthesis of the rubiyunnanin B aglycone was developed and ^{1}H NMR analysis was used to determine the overall structure of the core. The second area of research resulted in the synthesis of arnottin II through hypervalent iodine mediated oxidative spirocyclization.

BIOGRAPHICAL SKETCH

Matthew Moschitto was born in Andover, Massachusetts in 1988. He obtained his B.Sc. at Bates College in Lewiston, Maine in 2011 with a major in chemistry and minor in Spanish. Soon after, he began his graduate career at Cornell University in the laboratory of Chad Lewis where he worked on the total synthesis of carbasugar natural products. Matt was a NIH Chemical Biology Interface training grant recipient in 2012 and was awarded a Simon Baker Scholarship award in 2015. Starting in April of 2016, he will take up a position as a post-doctoral researcher in the laboratory of Richard Silverman at Northwestern University. An avid traveler, Matt has spent time in various countries as well as having kayaked and hiked various national parks. In his free time in Ithaca, he has spent time skiing and playing hockey. Upon completion of his graduate studies, he will take time travelling in Patagonia.

ACKNOWLEDGMENTS

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LIST OF ABBREVIATIONS

Ac: acetyl
APCI: atmospheric pressure chemical ionization
AIBN: azobisisobutyronitrile
rac: racemic
AORR: allylic oxide regio resolution
BINAP: (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bn: benzyl
Boc: *tert*-butoxycarbonyl
Bu: butyl
CAN: ceric ammonium nitrate
Cbz: carboxybenzyl
COSY: correlated spectroscopy
DART: direct analysis in real time
dba: dibenzylideneacetone
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM: dichloromethane
DEA: diethylamine
DFT: density function theory
DIB: diacetoxyiodobenzene or bis(acetoxy)iodobenzene
$(DHQ)_2$-PHAL: hydroquinine 1,4-phthalazinediyl diether
DMAP: 4-dimethylaminopyridine
DMF: dimethylformamide
DMP: Dess-Martin periodinane
DMSO: dimethylsulfoxide
dppf: bis(diphenylphosphino)ferrocene
dr: diastereomeric ratio
DYKAT: dynamic kinetic asymmetric transformation
ee: enantiomeric excess
EI: electron impact
er: enantiomeric ratio
ESI: electrospray ionization
Et: ethyl
GALR: galinin receptor
HATU: (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
DIBAL-H: diisoproylaluminium hydride
HMBC: heteronuclear multiple bond correlation
HMDS: hexamethyldisilazide
HPLC: high-pressure liquid chromatography
HSQC: heteronuclear single quantum coherence
IC_{50}: half maximal inhibitory concentration
^{i}Pr: isopropyl
IR: infrared spectroscopy

K_i: inhibition constant, binding constant
LCMS: liquid chromatography mass spectrometer
LDA: lithium diisopropylamide
M.p.: melting point
m-CPBA: *meta*-chloroperoxybenzoic acid
Me: methyl
men: menthol
MOM: methoxymethyl
NADH: nicotinamide adenosine dinucleotide
nap: naphthyl
NBS: N-bromosuccinimide
NMR: nuclear magnetic resonance
nOe: nuclear Overhauser effect
NOESY: nuclear Overhauser effect spectroscopy
NP: natural product
Nu: nucleophile
Ph: phenyl
PIFA: bis(trifluoroacetoxy)iodobenzene
pin: pinacol
PMP: paramethoxyphenyl
ppm: parts per million
py: pyridine
R_f: retention factor
ROSEY: rotating frame nuclear Overhauser effect spectroscopy
SGLT: sodium-glucose co-transporter
SM: starting material
TBAF: tetrabutylammonium fluoride
TBS: *tert*-butyldimethylsilyl
t-Bu: *tert*-butyl
TEMPO: (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES: triethylsilyl
Tf: trifluoromethylsulfonyl
TFA: trifluoroacetic acid
TFAA: trifluoroacetic anhydride
THF: tetrahydrofuran
TLC: thin layer chromatography
TML: Trost modular ligand
Ts: toluenesulfonyl
Tyr: tyrosine
Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

CHAPTER 1

INTRODUCTION: CARBASUGARS, RESOLUTION AND TSUJI TROST ALLYLATION

The total synthesis and semisynthesis of natural products is an important area of organic chemistry. Since 1980, 10% of all approved pharmaceutical compounds are classified as natural products, while 22% are derived from natural products but are semisynthetically modified through medical chemistry screens.[1] These numbers increase to 12 and 25% when looking at anticancer drugs.[1] Isolation of sufficient quantities of natural products often requires large amounts of the starting biological material and tedious, low yielding purifications. Synthesis, therefore, strives to provide access to these materials in a straightforward and high yielding manner. The ability to use synthesis to further diversify complex scaffolds only augments the number of potentially useful compounds. Improving methods for obtaining such compounds serves to further our investigations into treating disease.

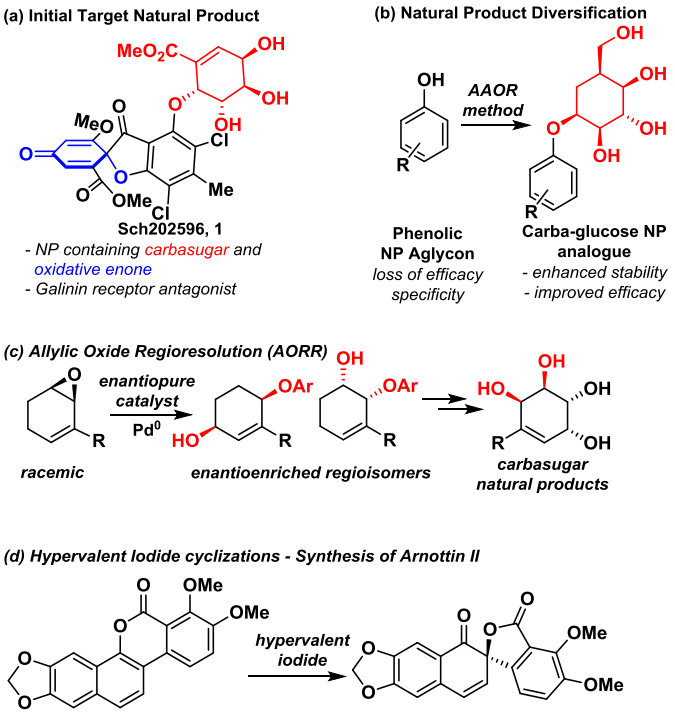


Figure 1.1: Summary of research undertaken

One specific compound that caught our attention was a spirocoumaranone called sch202596. Sch202596 contained two important, yet synthetically challenging features: a cyclitol or carbasugar (Scheme 1.1a, in red) as well as a spirocoumaranone or dienone (in blue).[2] Work, therefore, was split into multiple areas: (1) Allylic oxide regio resolution for the synthesis of natural product carbasugars (Figure 1.1c)[3]; (2) diversification of natural product scaffolds and the synthesis of rubiyunnanin B;[3b] and (3) hypervalent iodine mediated spirocyclizations and the synthesis of arnottin II.[4]

1.1: Carbohydrates and carbasugars

Carbohydrates are ubiquitous throughout Nature. They play an important role in localization of glycoconjugates and natural products through binding to carbohydrate specific receptors.[5] Binding these receptors can often cause signaling pathways to be activated or deactivated leading to, in extreme cases, cancers and various diseases. Nature, however, has mechanisms by which deglycosylation can occur through scission of the glycosidic bond targeting the conjugate for destruction.[6] Conversely, glycomimetic binding can lead to irreversible inhibition of glycosidase enzymes which in turn can lead to loss of glycoconjugate function.

Carbohydrates are also found on numerous natural products where they serve to enhance binding to a target or protect the aglycone from oxidative damage.[7] The aglycone can either be an ordinary alcohol or a phenol. The phenolic glycosidic bond is inherently less stable due to the lability of a phenol. Phenolic glycosidic natural product phenols are found in many forms: most commonly they are found on quinones and flavonoids (Figure 1.2). These compounds usually lack bioactivity and are mainly used as flavoring additives. A second class of natural phenolic glycosides is the tyrosine or phenylglycinol bound polypeptides such as vancomycin, arlyomycin A, cycloaspeptide G, and rubiyunnanin B. A third class of phenolic glycosides is polyphenolic, or highly substituted methoxy phenol compounds such as calicheamicin γ_1^I and phlorzin.

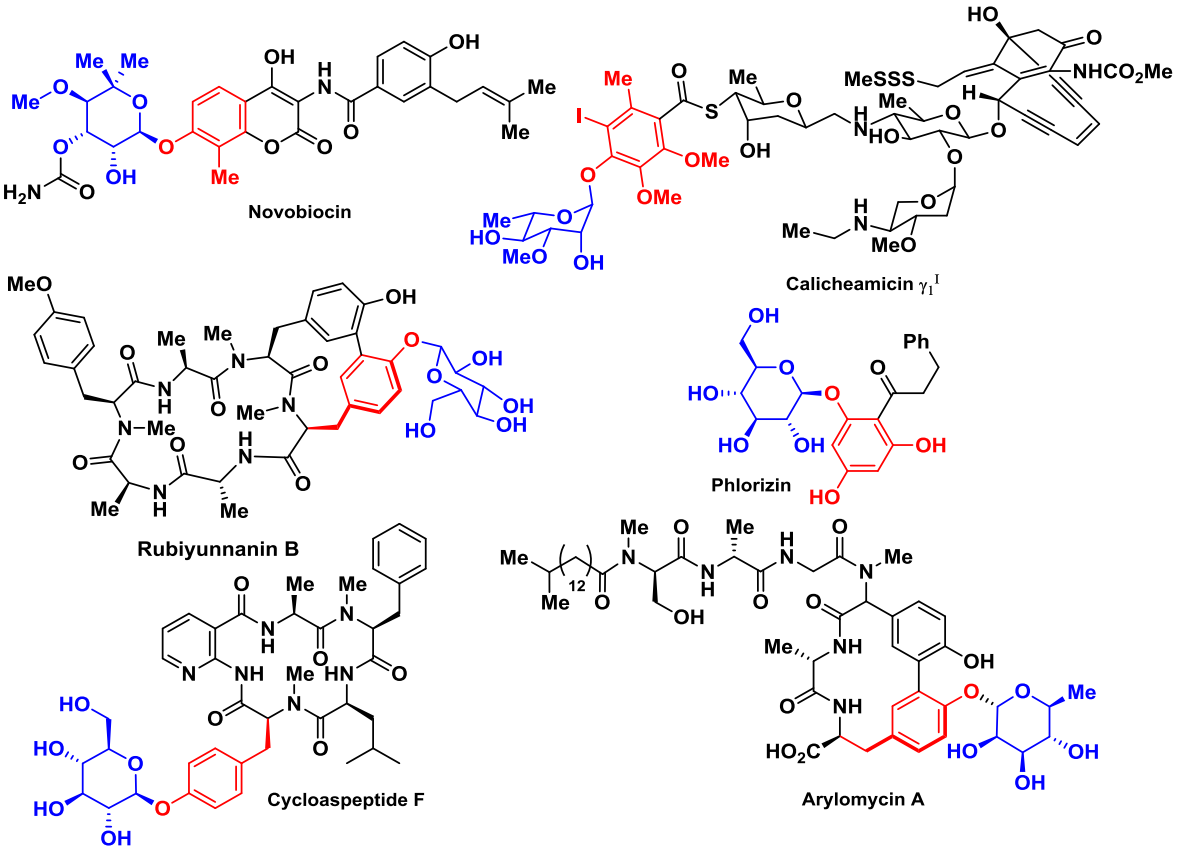


Figure 1.2: Natural product containing carbohydrates

Owing to the instability of the glycosidic bond and the nucleofugality of the phenol, phenolic glycosides are prone to hydrolysis. Half lives for phenolic glycosides have been calculated to be on the time scale of minutes to hours *in vivo*.[8] When deglycosylation occurs, there can be a loss of specificity or efficacy, which could result from a decrease in uptake, increased excretion or decreased binding to a specific active site. [9] Non-degradable sugars or glycomimetics have therefore become an important area of study, often restoring the function of the natural product.

Two forms of glycomimetics are possible, both focusing on increasing the stability of the glycosidic bond. Other possible forms of glycomimetics where amino sugars are incorporated are not discussed in this overview. One option is a carbon-bound glycomimetic in which the oxygen on the leaving entity is removed, and a carbon-carbon bond is forged (Figure 1.3a). This renders the carbohydrate more stable due to the strength of the carbon-carbon bond. These moieties can be naturally occurring (as is the case with aspalathin) or synthetic (as is the case with dapagliflozin, a

Bristol-Meyers Squib (BMS) marketed pharmaceutical that treats type II diabetes). Dapagliflozin possesses a half life of 17 hours compared to the parent phenolic glycoside **1.3** whose half life is 15 minutes (most likely due to loss of carbohydrate).[9]

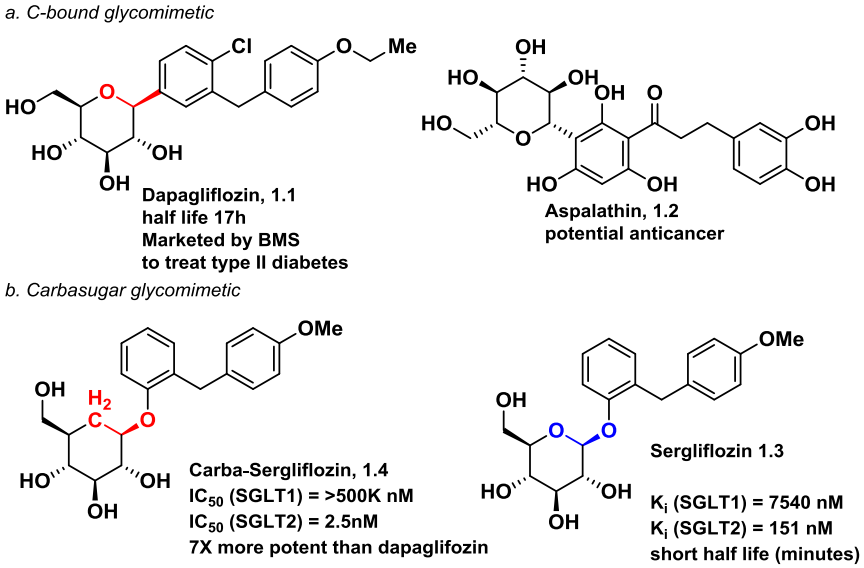


Figure 1.3: Glycomimetics and structure activity relationship

A second way to form a stable glycomimetic is to replace endocyclic oxygen of the carbohydrate with a methylene (Scheme 3.3b). These compounds, called carbocycles or carbasugars, are resistant to enzymatic degradation due to a lack of anomeric assistance in breaking the glycosidic bond.[10] Although some carbasugars are found in Nature, many have been developed synthetically as glycosidase inhibitors. Unlike dapagliflozin, the overall structure of a carbasugar is not altered with respect to the parent glycoside. In one study, Shing and co-workers noted that compound **1.3**, tested for use in treating type II diabetes, showed decreased efficacy and selectivity in binding towards a kidney specific sodium glucose cotransporter (SGLT2) versus a sodium glucose cotransporter found in other tissues (SGLT1).[9] Metabolic instability was considered one of the main factors for the compound being abandoned in clinical trials. The carbohydrate was replaced with the corresponding carbasugar (compound **1.4**) resulting in a drastic increase in binding, selectivity and efficacy towards SGLT2 (**1.4** was noted to be 17 times more potent than dapagliflozin). The authors

postulate that this is a result of the overall structure of the molecule remaining intact with only a minor change to the carbohydrate.

Naturally occurring monomeric carba-pyranoses are rare. Carba-galactopyranose (**1.5**) is the only carba-pyranose found in Nature (isolated from *Streptomyces* broth), and its bioactivity is unknown.[10] Natural carbasugars are more prevalent in the polyhydroxylcyclohexene derived form. These compounds possess a wide array of bioactivities including herbicidal (streptol and MK7607) to anti-tumor (pericosine, gabosine families).

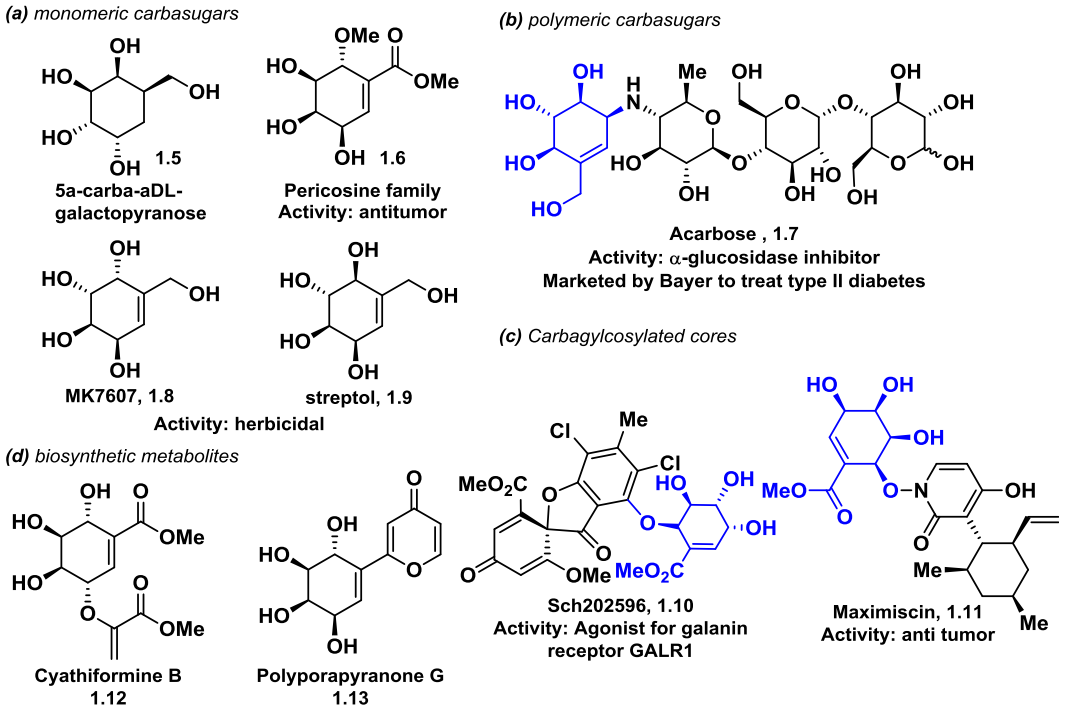
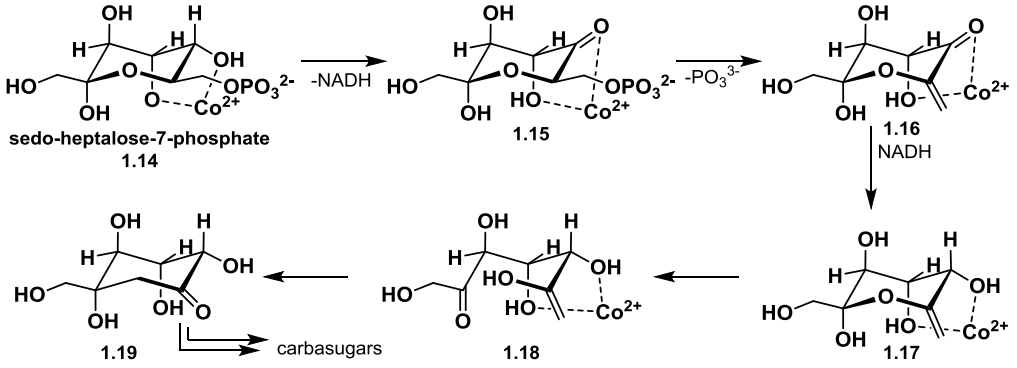


Figure 1.4: Natural product carbasugars

Natural carbasugars can also be found appended onto the core of natural products. In most cases the carbasugar bound is shikimate derived. Examples include sch202596 and maximscin, both of which possess interesting anti-cancer activity (Figure 1.4c). The third type of natural carbasugars is carbasugar polymers or carbasugar-polysaccharide polymers including validamycin A, acarviosine and acarbose (**1.7**), an important carbasugar containing molecule which is used in the treatment of type II diabetes.[10] Finally, carbasugar containing compounds can be found as

biosynthetic precursors or metabolites of biological pathways (Figure 1.4d). An example of this is cyathiformine B, a metabolite derived from the shikimic acid pathway.

The biosynthesis of carbocyclic compounds is represented by two major pathways: the shikimate pathway and the pentose phosphate pathway. The shikimate pathway is responsible for the synthesis of the majority of aromatic amino acids found in Nature. Shikimic acid is synthesized from phosphoenolpyruvate and erythrose-4-phosphate by a multistep aldol and cyclization sequence. The majority of shikimate bound natural products like sch202596 is formed from the shikimic acid pathway; however, most carbasugars are actually isolated from the pentose phosphate pathway.[10] Most carbasugars are derived from sedo-heptulose-7-phosphate (**1.14**), a key intermediate in the pentose phosphate pathway. Cyclization is proposed to be catalyzed by dehydroquinate synthase enzymes (cobalt containing enzymes) to yield compounds similar to **1.19** (Scheme 1.1).[11] From here, epimerization and other modifications can yield the majority of carbasugars.



Scheme 1.1: Biosynthesis of carbasugars[11]

To date over 140 carbasugars have been synthesized. In the carbapyranose family almost all possible epimers have been synthesized including, in some cases, both enantiomers of each carbapyranose. Limiting carbasugars to only the polyhydroxylcyclohexene containing compounds still leaves over 40 separate syntheses, most of which are unique and tailored for a particular carbasugar (Figure 1.5). The majority of syntheses originate from the chiral pool including a vast number of syntheses which start from carbohydrates, tartrates or shikimic and quinic acid.[12] The latter two compounds are natural cyclitols. In these syntheses only one enantiomer of the carbasugar

is accessible, and each synthesis is specific to the carbasugar of interest. Another class of syntheses involves the enzymatic dihydroxylation of arenes as perfected by Boyd and Hudlicky.[13] In these

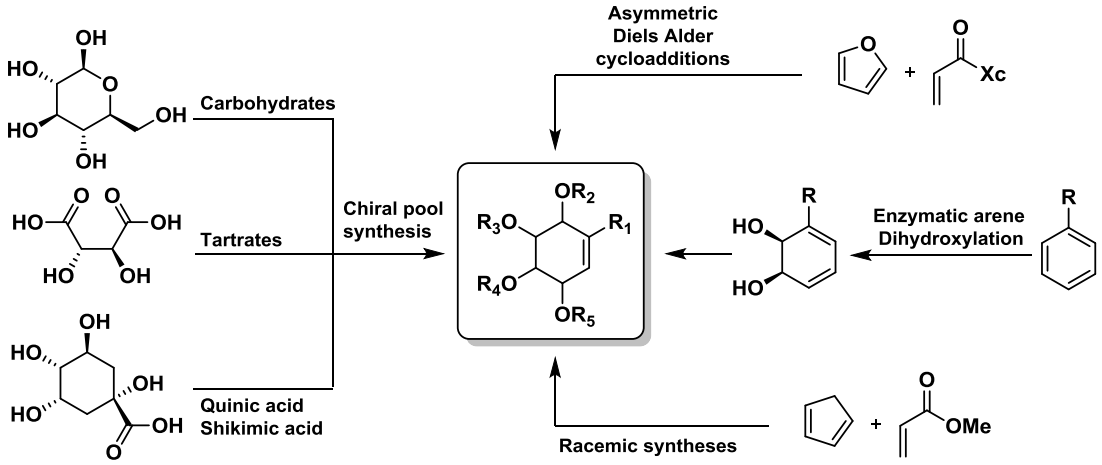
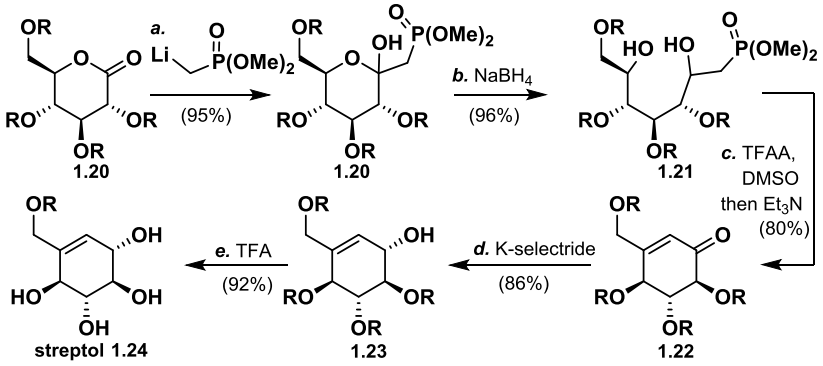


Figure 1.5: Summary of synthesis of carbasugars

cases as well, only a single enantiomer is accessible from the enzymatic dihydroxylation. The final method for the synthesis of carbasugars is through Diels-Alder cycloadditions.[4] Although many of these syntheses are racemic, asymmetric routes do provide access to both enantiomers of a particular carbasugar, but the enantiodetermining step, the Diels-Alder cycloaddition occurs early in the synthesis and is therefore not divergent.

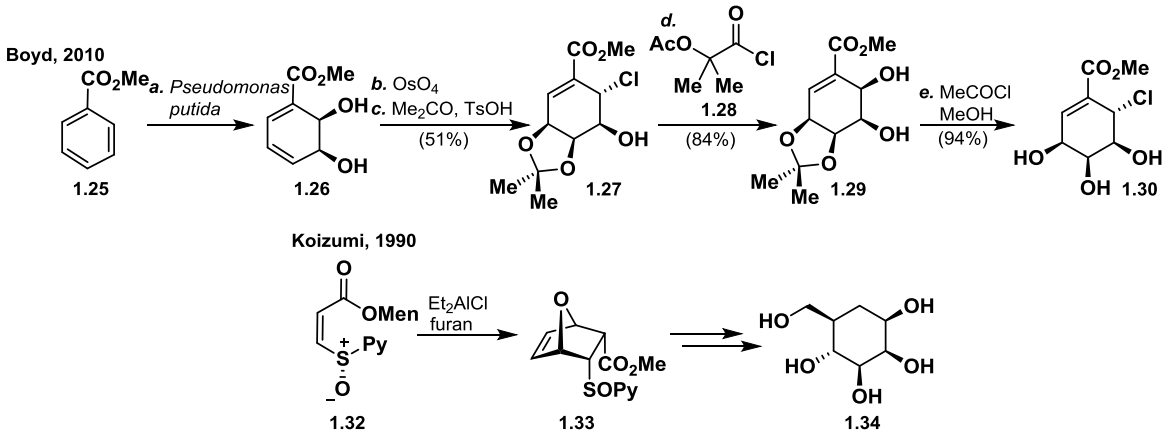


Scheme 1.2: Shing's synthesis of streptol from chiral pool[12a]

Like Nature, the majority of syntheses from carbohydrates involve the elongation of the open chain hexose to a heptose followed by ring closure. Whereas Nature performs this ring closure through intramolecular aldol reactions, many syntheses involve intramolecular Wittig olefinations or ring closing metathesis.[10] The carbasugar found on **1.4**, for example, was synthesized from D-

glucose (Scheme 1.2).[12a] Gluconolactone is exposed to lithiated methyldimethylphosphonate and then subsequently reduced to yield **1.21**. Upon oxidation, Wittig olefination with formaldehyde yields the enol pyruvate. Selective reduction of **1.22** and deprotection yields streptol, a polyhydroxycyclohexene based carbasugar.

Boyd, Donahue and Hüdlicky have pioneered the use of enzymes to perform the dihydroxylation of olefins resulting in a single enantiomer of product isolated (Scheme 1.3). Boyd, using Donahue's procedure dihydroxylates methyl benzoate to yield diene **1.26** as a single



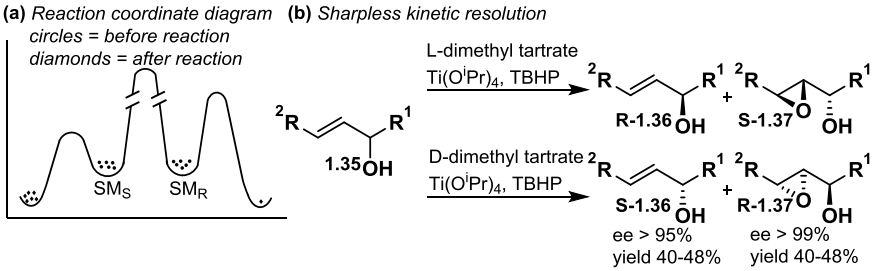
Scheme 1.3: Enzymatic dihydroxylation13a and asymmetric Diels-Alder cycloaddition14a for the synthesis of carbasugars

enantiomer.[13a] A directed dihydroxylation followed by protection yields the oxidation state necessary for the pericosine family. Minor tailoring steps including the introduction of a chloride with acid chloride **1.28** yields pericosine A (**1.30**). A final example of for the formation of an enantiopure carbasugar involves the use of asymmetric Diels-Alder cycloadditions. Koizumi and coworkers synthesized chiral sulfonate **1.32**. This undergoes a Diels-Alder cycloaddition to yield bicyclic compound **1.33** (*endo* and *exo* isomers are obtained and separated) which is desulphenylated and transformed into carba-mannopyranose **1.34** in ten steps. In the former two cases, a single enantiomer is obtainable whereas in the latter case, the enantiodetermining step occurs at step one of twelve. With this in mind we set out to develop a system that would provide late stage access to all enantiomers of carbasugar stereoarrays using asymmetric catalysis for use in the synthesis of carbasugar natural products.

1.2: Resolution of racemic mixtures

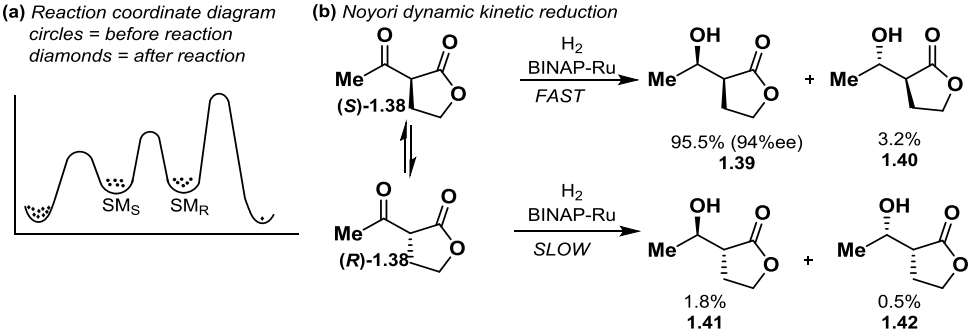
Asymmetric catalysis is a powerful method for the installation of chiral stereocenters. In most cases, asymmetric catalysis involves the introduction of a stereocenter from achiral material. An alternative method for obtaining enantioenriched material would be through resolution of enantiomers. The earliest involves the diastereomeric salt formation. Catalysis, however, offered increases opportunities for resolution including kinetic resolution, parallel kinetic resolution and dynamic kinetic resolution.

Kinetic resolution is a process by which two enantiomers react with a chiral catalyst at different rates (Scheme 1.4a), resulting in enantioenrichment of both the product and remaining starting material. [15] The selectivity of a catalyst in a kinetic resolution ultimately controls the enantioenrichment. A kinetic resolution must proceed to complete (50%) conversion for high enantiomeric ratios to be obtained. Conversely a high selectivity factor by a catalyst for one enantiomer over another can allow for incomplete conversions of a starting material. A drawback of a kinetic resolution however, is that only a maximum of 50% of the material is ultimately carried forward. Many examples of kinetic resolution have been demonstrated in the literature with pioneering work performed by Jacobsen, Kagan and Sharpless.[16] Sharpless developed the kinetic resolution of allylic alcohols using tartrate esters and $Ti(O^iPr)_4$ (Scheme 14.b) in whcih a D-tartrate-titanium complex reacts with one enantiomer of the allylic alcohol to epoxidize the olefin while the other enantiomer does not react. [17] Kinetic resolutions have also been demonstrated to work in many other reactions including Jacobsen's hydrolytic kinetic resolution of epoxides using Co(salen) complexes.[16]



Scheme 1.4: Kinetic resolution[17]

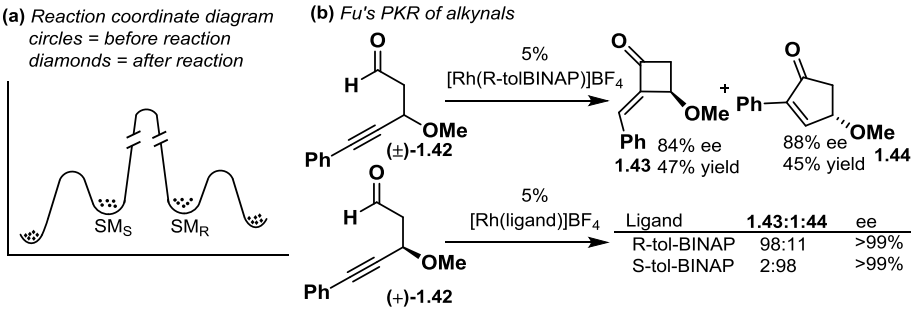
While a kinetic resolution usually results in only one enantioenriched product whose enantioselectivity is tied to the selectivity of the catalyst and conversion, parallel kinetic resolution and dynamic kinetic resolution offer the ability to obtain multiple enantioenriched product regardless of conversion.[15b] In a dynamic kinetic resolution, the enantiomers of the starting material are interconvertible, yet one enantiomer will react with a chiral catalyst at a faster rate thus resulting in an increased amount of a single enantioenriched product. A powerful example of a dynamic kinetic resolution is the reduction of substituted ketoesters such as **1.38** using BINAP-ruthenium complexes as demonstrated by Noyori.[18] In this reaction, the two enantiomers of the starting material interconvert on a fast time scale, yet one reduction proceeds at a faster rate than the other funneling material to one enantioenriched product, **1.39**, in 95.5% yield. The benefit of a dynamic kinetic resolution is complete conversion of a starting material to a single product can be obtained whereas in a kinetic resolution only a 50% maximum yield is possible.



Scheme 1.5: Dynamic kinetic resolution[18]

In parallel kinetic resolution each enantiomer reacts at a similar rate to give two different products (Scheme 1.5a). One of these products is enantioenriched while the other can be either enantioenriched or achiral.[19,10] Two types of parallel kinetic resolution can occur. In one, a racemic starting material reacts with a chiral catalyst to give two different products which can be structurally different yet enantioenriched (or one product is enantioenriched while the other is achiral). Since both enantiomers react at similar rates, conversion does not affect the enantioselectivity of the product. Fu and co-workers demonstrated a parallel kinetic resolution of 4-alkynals using BINAP-rhodium complexes (Scheme 1.5b).[20] In this reaction racemic **1.42** is exposed to chiral BINAP-Rh

to yield two different enantioenriched products, **1.43** and **1.44** in high ee and near 50% yield. These two products arise from two different insertions across the alkyne as dictated by the chirality of the ligand. If enantiopure starting material **(+)-1.42** is used along with *R*-BINAP, **1.43** is the major product. Switching the catalyst enantiomer switches the product distribution.



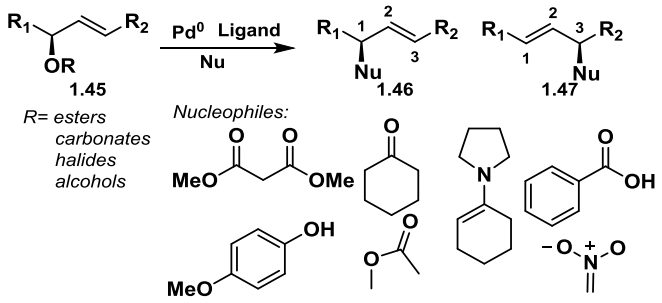
Scheme 1.6: Parallel kinetic resolution[20]

When the two products obtained from a parallel kinetic resolution contain the same functional group but at different locations, this is termed a regiodivergent parallel kinetic resolution. We, throughout the rest of this study, refer to this process as a *regio-resolution*. We define it as a subset of parallel kinetic resolution where each enantiomer of a starting material reacts with a chiral catalyst in the presence of a resolving agent to yield two regioisomeric enantioenriched compounds which are separable. Control of which compound is isolated can be obtained by catalyst selection. Given our interest in trying to obtain multiple carbasugar frameworks from a divergent synthesis, we decided to explore reactions that allowed for regio-resolution.

1.3:Tsuji Trost allylation

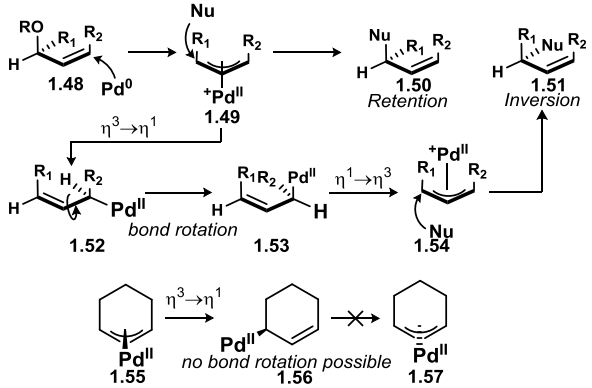
Upon examination of carbasugar skeletons, a trend of *syn*- or *anti*-1,2 and 1,4-cyclohexenediol motifs is discovered. We looked to employ a reaction that would allow us to introduce stereogenic hydroxyl groups while at the same time, allowing for regio-resolution. We believed this could be achieved using the Tsuji-Trost allylation. The Tsuji-Trost allylation consists of the palladium catalyzed substitution of allylic leaving groups with nucleophiles (Scheme 1.7).[21] Functional leaving groups include alcohols, acids, carbonates or halides while the nucleophile scope is limited to soft nucleophiles including carboxylic acids, malonates, enolates, enamines, phenols

and phthalimides. Overall, the products obtained, **1.46** and **1.47**, retain the stereochemistry from the starting material, **1.45**. Selectivity of additions is dictated by steric and electronic factors with electronic factors favoring addition at the more substituted position and steric parameters dictating addition at the less hindered position.



Scheme 1.7: Overview of Tsuji-Trost allylation

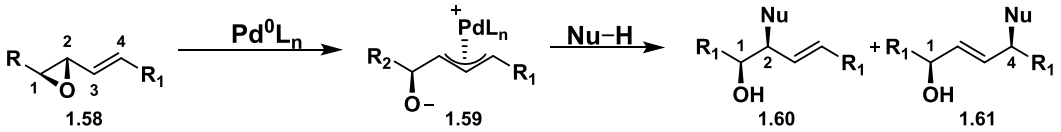
Mechanistically, for linear compounds such as **1.48**, palladium adds to the opposite face of the leaving group resulting in π-allyl complex **1.49**. A nucleophile can then add to the π allyl to form an overall retention product (**1.50**). In linear compounds, if complex **1.49** is destabilized due to factors such as $A^{1,3}$ or $A^{1,2}$ strain, a η^3-η^1 isomerization can occur. After bond rotation of complex **1.52**, η^1-η^3 isomerization occurs to result in a new π-allyl (**1.54**) which then undergoes nucleophilic addition to yield the inversion product **1.51**.



Scheme 1.8: Mechanism of Tsuji-Trost allylation

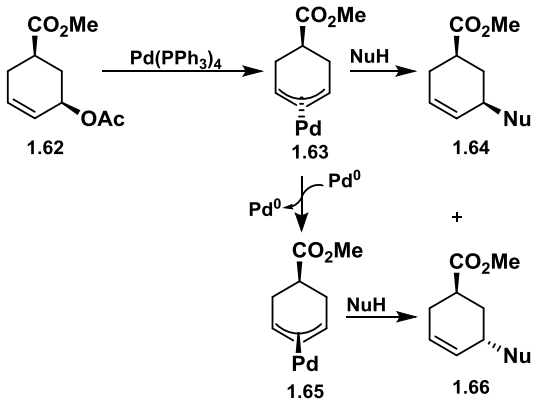
This reaction can be expanded to include the use of allylic epoxides and aziridines.[22] Unlike with allylic carbonates, the intermediate π-allyl complex contains a proximal stereocenter. Thus, allylations with epoxides result in two possible regioisomeric products: 1,2 or 1,4 addition with

respect to the alkoxide (**1.60** and **1.61**). The selectivity of the addition is determined by both steric and electronic effects but also can be affected by the nucleophile. Steric factors dictate that the nucleophile will add to the least hindered position while electronic factors favor nucleophile addition to the more electron deficient position. In the proposed mechanism, upon formation of the π-allyl, an alkoxide is formed and is protonated, in most cases, by the nucleophile leading to directed addition of the nucleophile to the two position of the π-allyl. Separately, when nucleophiles that bind to the newly formed alkoxide are employed like $TMSN_3$[23] or $B(OPh)_3$,[24] additions exclusively occur at the 2-position.



Scheme 1.9: Allylic oxides in Tsuji-Trost allylation

While the above isomerization is possible with acyclic allylic species, cyclic allylic species are unable to isomerize through the η^3-η^1-η^3 pathway. Up until this point, the molecules which have been discussed have not contained additional stereocenters. With the introduction of proximal stereocenters, no longer is the reaction under enantiomeric control. It has been observed that when a π-allyl is located proximal to a stereocenter, the inversion (rather than retention) product can be obtained. Backväll noted this trend and postulated that this π-allyl inversion was triggered by the attack of exogenous Pd^0 on a destabilized Pd-π-allyl resulting in an inversion of the product distribution.[25] In his study he employed allylic acetate **1.62** and noted that both retention and inversion products were obtained. By increasing the loading of palladium, he is able to determine, by ^{31}P HMR, that two π-allyl species (**1.63** and **1.65**) are forming and interconvert.



Scheme 1.10: Bäckvall's study into π-allyl isomerization[25a]

The introduction of asymmetric variants of the Tsuji-Trost allylation led to the synthesis of a series of Trost Modular Ligands (TML).[26] TMLs consist of a chiral diamine backbone amide linked to triarylphosphines. The three most common TMLs used are compound **1.67**, **1.68** and **1.69** which differ mainly in their bite angles (Figure 1.6a). The overall solution state structure of the TML-Pd-allyl complex is difficult to discern mainly due to oligomers and multiple species in solution.[27] Most inferences about the structure have been done through modeling or NMR analysis by Guy Lloyd-Jones. The palladium is known to bind to two phosphines during the reaction.[28] As to whether this is intermolecular or intramolecular depends on the concentration of the reaction and the π-allyl compound. Trost originally developed the wall and flap model for the TML (Figure 1.6b).[29] In this model, which was developed through DFT studies and observed reaction results, the palladium-π-allyl sits in the pocket of the ligand beneath the diamine backbone. The four pendant phenyl groups orient themselves in a C_2 symmetric manner such that two occupy a "wall" and block access to the pocket, while two occupy a "flap" and provide access to the pocket.

More recent work by Lloyd-Jones, however, has provided a second mechanism for TML selectivity.[27] By using deuterated TMLs and computation, Lloyd-Jones developed a different three-dimensional model for the TML series (Figure 1.6c). In this model, which is applicable for both cyclic and acyclic allylic carbonates, no phenyl ring actually reaches past the plane of the allyl

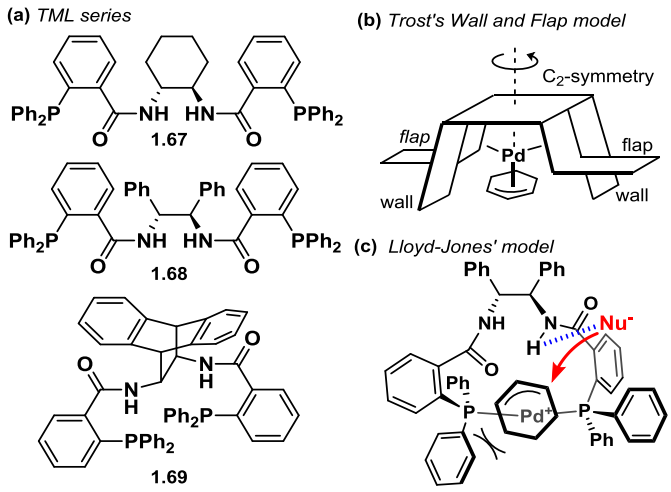
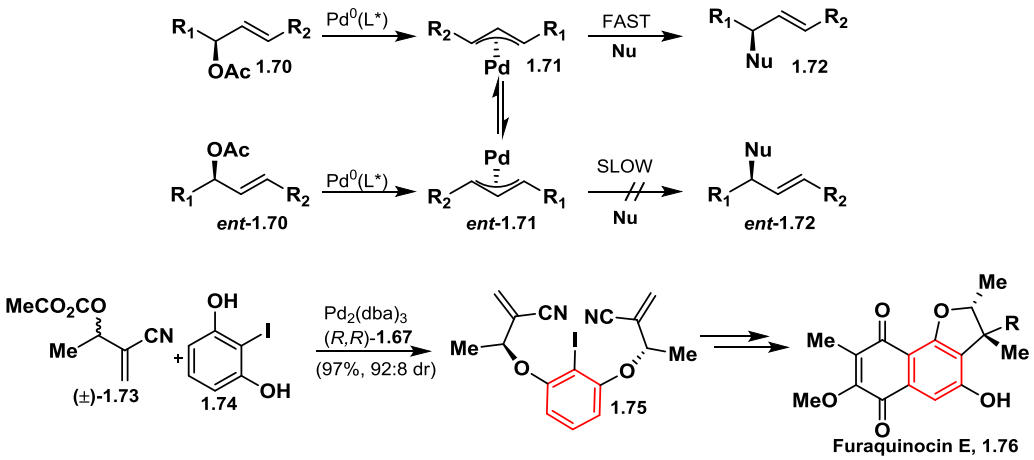


Figure 1.6: Model for TML series[27,29]

moiety. Instead, the allyl group is positioned in such a way that it is oriented towards the amide backbone. The amide N-H plays a critical role in assisting in ionizing the allylic carbonate and directing the incoming nucleophile to the π-allyl. The ligand itself adopts a more twisted conformation which imparts selectivity, which Lloyd-Jones describes as a "torqueselectivity" of the ligand towards the allyl compound. This results in one position being slightly more above the plane of the palladium and accessible to the amide directed attack of the incoming nucleophile. This mechanism, however, has not been necessarily extended to allylic epoxides. Though work by Lloyd-Jones has provided an alternative mechanism, Trost's "wall and flap" model still provides a powerful method of explanation for almost *all* asymmetric allylations and is still presented as a valid mechanism for recent results.

The ability for a linear allylic carbonate to proceed through η^3-η^1-η^3 isomerization allows for the conversion of a racemic starting material into an enantioenriched product through the use of chiral ligands. This process is called dynamic kinetic asymmetric transformation (DYKAT) and has been employed numerous times by Trost to obtain enantioenriched products.[30] In DYKAT, a racemic allylic acetate/carbonate reacts with a chiral palladium source. The intermediate π-allyl species, **1.71** and *ent*-**1.71,** interconvert through η^3-η^1-η^3 isomerization. Only **1.71** further reacts to form product due an increased rate of reaction catalyzed by the chiral ligand. This method has been

exploited many times by Trost in several total syntheses including during the total synthesis of Furaquinocin E (Scheme 1.11).[31] The stereocenter required for the molecule is introduced through a DKYAT of compound **1.73** and ligand **1.68**. Trost is able to obtain product **1.75** in a 92:8 dr which is further to the natural product.

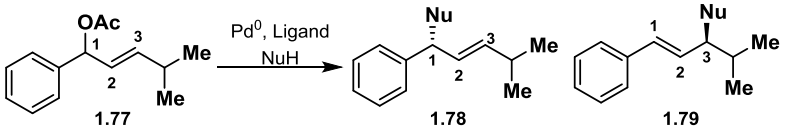


Scheme 1.11: Dynamic kinetic asymmetric transformation

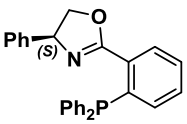
Regiodivergent parallel kinetic resolutions or regio-resolutions are also possible with the Tsuji-Trost allylation. Pfaltz and co-workers showed that racemic allylic acetates like **1.77** react with Pd^0 and malonates with **1.80** as a ligand to give two enantioenriched products with addition at the 1 position and the 3 position.[32] If they employ a chiral starting allylic acetate, they are able to obtain mostly **1.78** in high yield. Switching the enantiomer of the ligand yields a switch to yield *ent*-**1.79.**

The ability to obtain multiple different stereoisomers from a single intermediate is highly advantageous. If the divergent step in the synthesis falls in the latter half of the synthetic route, the utility and versatility of a particular method is augmented. This approach could be applied to the synthesis of carbasugars, a class of compounds that posses interesting structures and biological activities. Currently the synthesis of carbasugars is limited to mostly unique, linear routes from chiral starting materials. A divergent synthesis would allow efficient access to multiple forms of

Table 1.1: Pfaltz regiodivergent parallel kinetic resolution



1.77 1.78 1.79



(S)-1.80

SM	Ligand	**1.78** yield (%ee)	*ent*-**1.78** yield (%ee)	**1.79** yield (%ee)	*ent*-**1.79** yield (%ee)
rac	(*S*)-**1.80**	55(83)	–	–	45(99.5)
(*R*)	(*S*)-**1.80**	97(99.5)	–	3.0(64)	–
(*R*)	(*R*)-**1.80**	–	9.0(46)	–	91(99.5)

carbasugars from a single intermediate. This could be accomplished through a parallel kinetic resolution allowing the late stage isolation of multiple enantiopure compounds. The array of stereogenic hydroxyls found on carbasugars could be introduced through a Tsuji-Trost allylation. The use of the Tsuji-Trost allylation tolerates a parallel kinetic resolution as well as the isolation of multiple regioisomers and is controlled by an enantiopure ligand. With all these topics previously discussed we looked to develop a new method for the synthesis of enantiopure carbasugars.

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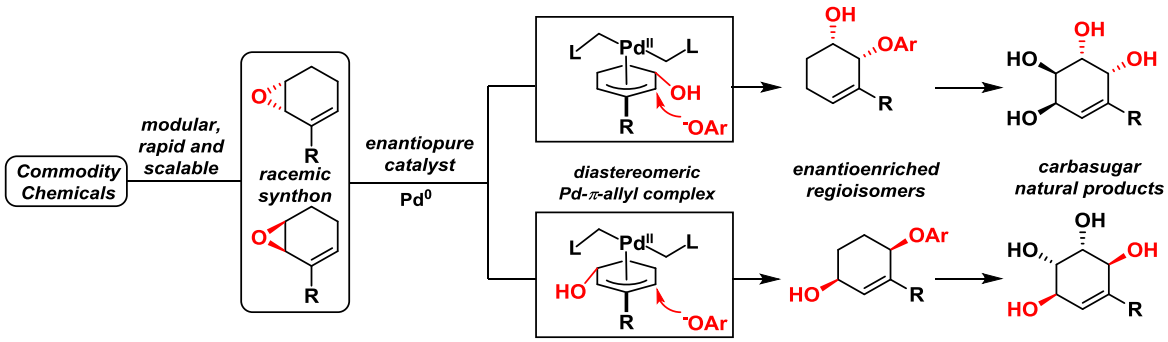
CHAPTER 2

ALLYLIC OXIDE REGIO RESOLUTION FOR THE SYNTHESIS OF CARBASUGARS

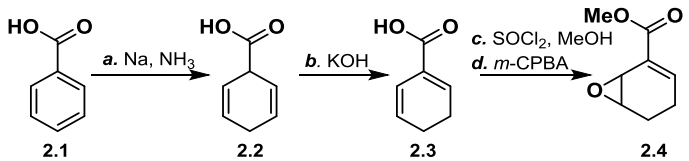
As previously discussed in Chapter 1, the stereoarrays of over 140 natural and unnatural carbasugars have been derived from the chiral pool, arene enzymatic dihydroxylation, or asymmetric Diels–Alder reactions. In all cases, carbasugar synthesis is target specific with the intent to access a single enantiomer. There exists no single method for accessing both enantiomers and the various carbasugar stereoarrays from a common intermediate. If the contiguous array of stereocenters found on carbasugars could be formed from a single racemic precursor with stereocontrol, the synthesis of carbasugars would be improved. The stereogenic array of hydroxyls found on carbasugars could be derived from a single precursor, an allylic oxide, through the use of a Tsuji-Trost allylation (Scheme 2.1). If we could control the addition modes of the nucleophile through ligand and steric effects, multiple enantioenriched products could be obtained and furthered to natural product carbasugars.



Scheme 2.1: Allylic oxide regio-resolution: synthesis of carbasugars

2.1: Initial and model studies towards allylic oxide regio resolution

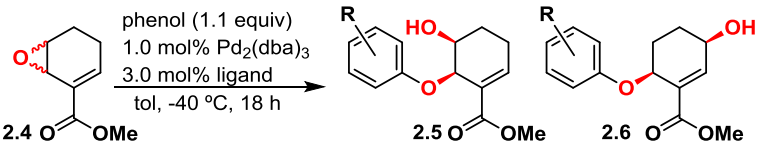
We began our investigation using allylic oxide **2.4** as a model compound. Oxide **2.4** was synthesized according to prior literature in four steps from benzoic acid as outlined in Scheme 2.2.[1]



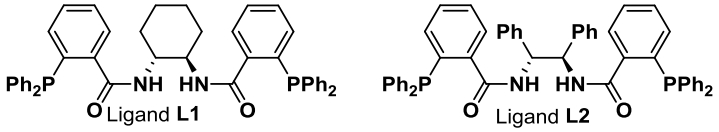
Scheme 2.2: Synthesis of oxide 2.4

Exposure of **2.4** to $Pd_2(dba)_3$, TML **L2**[2] and *p*-Me-PhOH resulted in two products. ^{1}H NMR analysis of coupling constants and COSY confirmed the structures of the 1,2 and 1,4 nucleophilic addition products, **2.5** and **2.6**, respectively. The 1,2 product (**2.5**) was isolated in a 32% yield in 87:13 er, while the 1,4 product (**2.6**) was obtained in 47% yield with a 96:4 (Table 2.1, entry 4). The starting oxide, isolated in minute amounts, was racemic indicating that regio-resolution was occurring, and that each enantiomer of the oxide was directly converting into a unique product. Cyclohexyl TML **L1** yielded 1,2 and 1,4 products albeit with reduced enantioenriched products and yields. BINAP proved to be ineffectual.

Table 2.1: Initial AORR results



entry	oxide **2.4**	ligand	phenol	**2.4** er	**2.5** er	**2.6** er	% yield (**2.4**:**2.5**:**2.6**)
1	(±)	PPh_3	**R** = *p*-Me	–	–	–	20:15:50
2	(±)	(*R*)-BINAP	**R** = *p*-Me	–	–	–	n. d.
3	(±)	(*R*,*R*)-**L1**	**R** = *p*-Me	40:60	22:78	10:90	35:29:24
4	(±)	(*R*,*R*)-**L2**	**R** = *p*-Me	57:43	96:4	93:7	2:39:34
5	(+)[a]	(*S*,*S*)-**L2**	**R** = *p*-Me	92:8	**98:2**	32:68	31:**34**:**4**
6	(–)[b]	(*S*,*S*)-**L2**	**R** = *p*-Me	10:90	24:76	**96:4**	28:**8**:**37**
7	(±)	(*S*,*S*)-**L2**	**R** = *p*-OMe	56:44	85:15	95:5	1:48:35

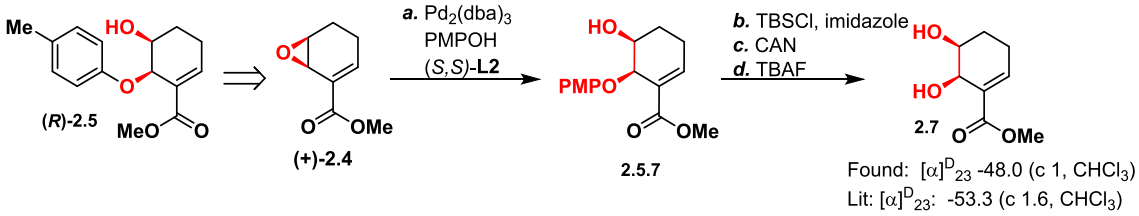


[a]Enantiomeric ratio of 92:8 favoring the (+)-**2.4** isomer. [b]Enantiomeric ratio of 10:90 favoring the (–)-**2.4** isomer.

To test for regio-resolution, we synthesized enantiopure oxide **2.4** (employing Jacobsen's Mn asymmetric epoxidation conditions[3]) and exposed it to standard conditions. Oxide (+)-**2.4** (90:10 er favoring + enantiomer) reacted with (*S*,*S*,)-**L2** to favor mainly 1,2 product formation in 41% yield (Table 2.1, entry 5). Switching the catalyst enantiomer to (*R*,*R*)-**L2** resulted in a

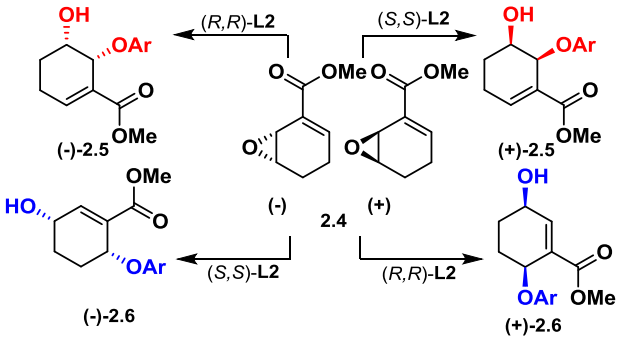
population shift favoring the 1,2 product in 37% yield (entry 6). In each case, enantiopurity increased for the major product while enantiopurity of the minor product decreased. Switching the enantiomer of the oxide from (+) to (-) also resulted in population inversion.

From the results shown (Table 2.1, entries 4-6), a model was developed. The absolute stereochemistry of the 1,2-addition product derived from the conditions in Table 2.1 (entry 7) was determined by comparison to a known compound, **2.7**.[4] Acylation and deprotection of **2.5.7** yielded known compound (*5R-6S*)-Methyl-5,6-dihydroxycyclohex-1-ene carboxylate (**2.7**) (Scheme 2.3). Combined with the data in Table 1.1 (entry 5), the 1,2-product must be derived from the (+) enantiomer of (±)-**2.4**. This allows for a model of selectivity to be created (Scheme 2.4) which matches oxide and ligand to specific enantioenriched product. From this model, we believed that (-)-**2.4** or similar oxides would react to give 1,4 products ((-)-**2.6** type) when (*R,R*)-**L2** is used and 1,2 products ((-)-**2.5** type) with (*S,S*)-**L2**. The converse would be true with (+)-**2.4** or similar oxides.



Scheme 2.3: Proof of stereochemistry

Additionally, given this model and our racemic studies, we can predict the ratio of the products that would be obtained from a specific starting enantiomeric ratio of an oxide. This can be demonstrated using our 90:10 enantioenriched oxide (Scheme 2.5a) A solution of (+)-**2.4** in 92:8 e.r. can react in two ways with the palladium complex. The 92% portion (+)-**2.4** will react, according to the model, when (*S,S*)-**L2** is utilized, to favor 1,2-addition in a 96:4 enantiomeric ratio (as per the data in Table 2.1, entry 4). Thus, the 92% portion (+)-**2.4** will react to form 88.32% (*R*)-**2.5**, and 3.68% of (*S*)-**2.6**. The 8% of the stock of (–)-**2.4** will react, favoring the 1,4-addition, to form 0.56% and 7.44% of (*S*)-**2.5** and (*R*)-**2.6** (derived from the enantiomeric ratio of **2.6** with (±)-**2.4**). Combining these numbers for both **2.5** and **2.6** provides the predicted enantiomeric ratio.



Scheme 2.4: AORR selectivity model

Additionally, the ratio of **2.5**:**2.6** can be predicted. The result shows excellent agreement between predicted and observed data (Table 2.2 and Table 2.1, entry 5). The calculations can be repeated employing a stock of 90:10 (-)-**2.4** (Scheme 2.5b). Excellent agreement is observed between the predicted and observed enantiomeric ratio of **2.6** and in the predicted and observed ratio of **2.5** and **2.6**. The increased enantiomeric ratio of **2.5** does not agree with the predicted to the same extent as observed before; we are unable, at this time, to explain this increase in enantiomeric ratio.

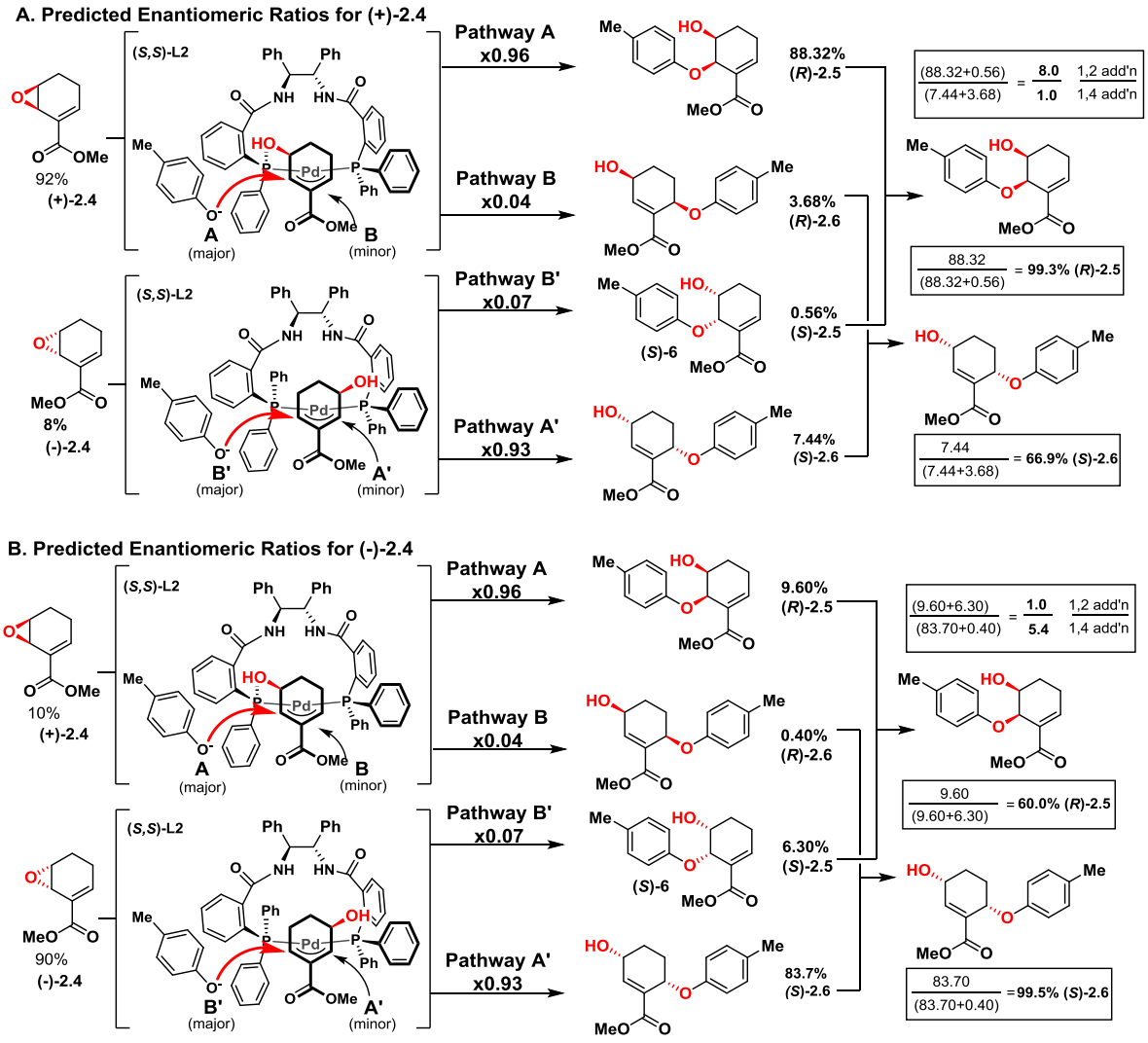
Table 2.2: Predicted and observed product and enantiomeric ratios

	92:8 er (+)-**2.4** epoxide			10:90 er (-)-**2.4** epoxide		
	2.5 er	**2.6** er	ratio **2.5**:**2.6**	**2.5** er	**2.6** er	ratio **2.5**:**2.6**
Predicted	99:1	33:67	8.0:1.0	60:40	1:99	1.0:5.4
Observed	98:2	32:68	8.5:1.0	76:24	4:96	1.0:4.6

Two aspects of note are: first, (±)-**2.4** reacts under normal conditions to yield a 1:1.14 ratio of **2.5**:**2.6**; these calculations do not take this into account and assume the ratio is 1:1. Second, the model does not take into account the epoxide degradation. Results from each enantiomeric run (Table 2.1, entry 5 and 6), show substantial recovery of isolated **2.4**. Thus from this, only the predicted ratio of **2.5**:**2.6** can be determined. Work is ongoing to understand the increased degradation when employing enantiopure epoxides.

Mechanistically we believe these results can be explained using Trost's wall and flap model for the Trost Modular Ligand.[5] As discussed in Chapter 1.3, Trost showed that the TML adopts a conformation where certain quadrants are blocked by the pendant phenyl groups on the phosphine. Placing the (+)-oxide in the pocket of the ligand results in the newly protonated alkoxide being placed away from the ligand in an open quadrant (**A**, Scheme 2.5). The four position has now

become blocked by a wall of the ligand leaving the two position of the π-allyl open for *pro-R* nucleophilic attack. The oxide enantiomer, (-)-**A** resides in the pocket in an opposite manner resulting a blocked two position and *pro-S* nucleophilic attack of the four position (**B**, Scheme 2.6).



Scheme 2.5: Allylic oxide regio resolution predictive model

Additionally, the ester linkage is critical to the regiodivergence. When 1,3 cyclohexadiene oxide (**2.8**) is used as the substrate, only 1,4 addition (**2.9**) is noted with no enantioinduction (Scheme 2.7). Conversely, when the ester is shifted from the 3 position to the 4 position (compound **2.11**), no nucleophilic addition is observed whatsoever as β-hydride elimination product (**2.14**) is solely observed.

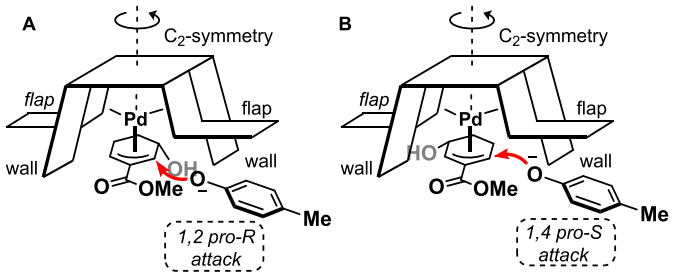
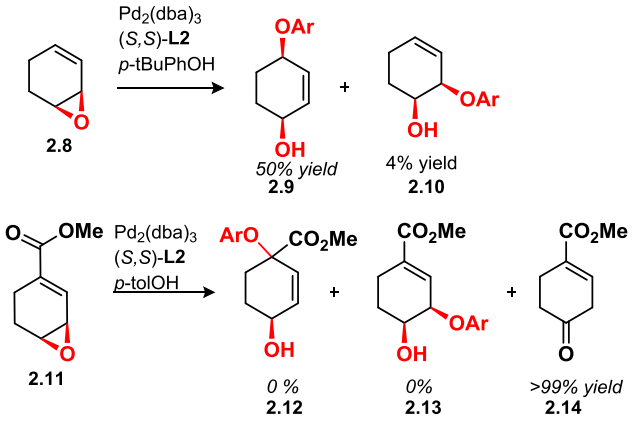


Figure 2.1: Wall and Flap model for enantioinduction[5]

There are a few possibilities concerning the role of the ester. Given that steric parameters ultimately dictate product distribution, the ester might allow nucleophilic addition to occur at two positions which have a similar steric environment. This addition could also be accelerated through a hydrogen bond between the incoming nucleophile and ester.[6] Separately, it is possible that the ester serves to orient the π-allyl in the pocket of the ligand in such a way that the aforementioned wall and flap model controls the addition.[7] This orientation could be achieved through a hydrogen bond to the amide N-H. Ultimately, more investigation would need to be carried out including various 2D NMR experiments.

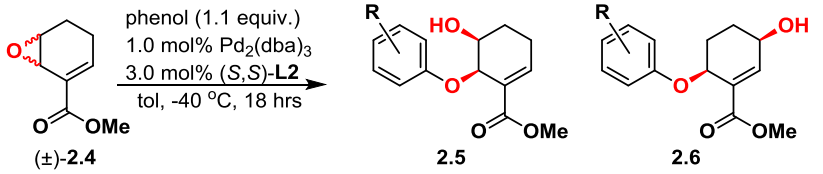


Scheme 2.6: Alternative epoxide reactivity

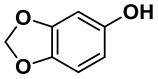
The utility of the AORR approach was expanded to include numerous phenols. Native phenol provided useful enantioinduction (Table 2.3, entry 1, 98:2 er for 1,2-addition, 91:9 for 1,4-addition) in a combined yield of 58%. Alkyl substitution (entries 2, 3) proved similar in stereoinduction. Other phenol donors such as electron donating substituents were similarly well tolerated (entries 4 and 5) with the Boc protected aniline providing lower conversion. 4-Nitrophenol

provided the highest enantioinduction (97:3 and 98:2 for 1,2- and 1,4-addition respectively, entry 6) albeit with low yield and degradation upon standing. This is most likely due to the lack of nucleophilicity of 4-nitrophenol. Sterically larger arenes, including *ortho* and *meta* substituted phenols (entry 7 and 8, respectively) resulted in similar high enantioinduction and yield. AORR was also tolerant to both 1- and 2-naphthol albeit with reduced enantioinduction (entries 9 and 10). Sesamol also provided high enantioinduction for both addition modes (entry 11). Nucleophiles containing bromide functionality also proceeded with no evidence of dehalogenation (entry 12). In all cases, the absence of palladium did not result in any conversion.

Table 2.3: Scope of regiodivergence



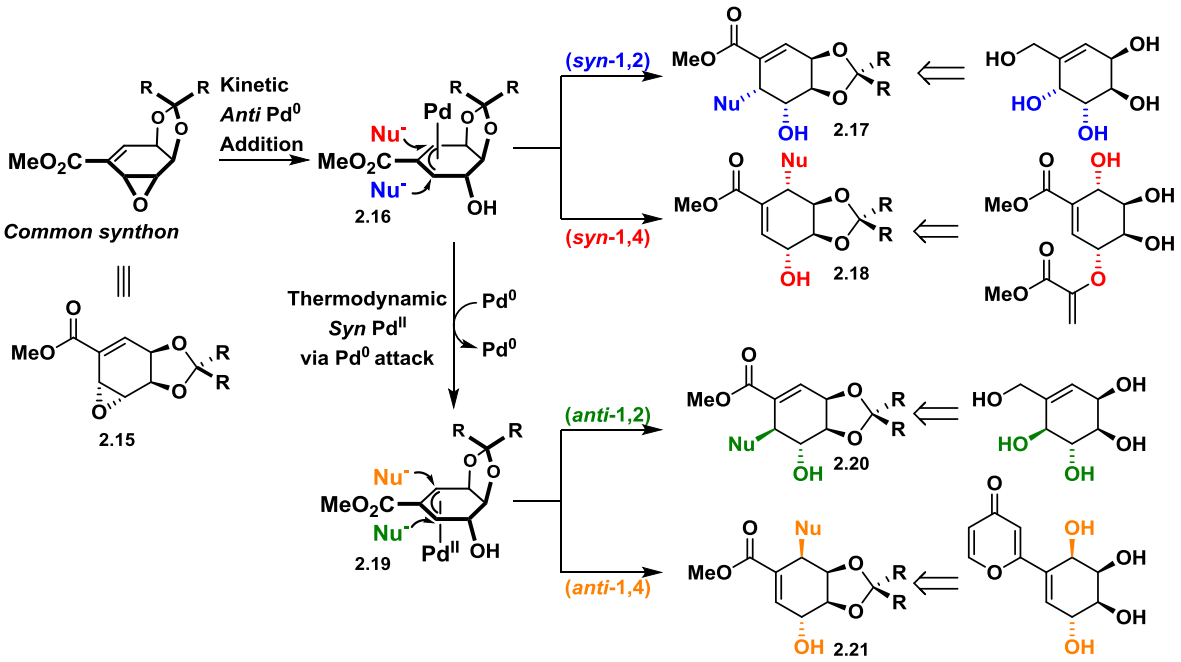
(±)-**2.4** **2.5** **2.6**

entry	phenol	**2.4** er[a]	**2.5** er[b]	**2.6** er[b]	% yield[c] (**2.4**:**2.5**:**2.6**)
1	**R** = H	-	98:2	91:9	0:31:27
2	**R** = *p*-Me	57:43	96:4	93:7	2:39:34
3	**R** = *p*-*t*Bu	52:48	96:4	91:9	24:28:34
4	**R** = *p*-OMe	56:44	85:15	95:5	1:48:35
5	**R** = *p*-NHBoc	51:49	90:10	84:16	29:21:23
6	**R** = *p*-NO_2	50:50	97:3	98:2	64:4:4
7	**R** = 2,4-dimethyl	68:32	94:6	84:16	8:31:34
8	**R** = 3,5-dimethyl	52:48	90:10	91:9	23:31:34
9	**R** = 2-nap	-	84:16	84:16	0:33:33
10	**R** = 1-nap	-	80:20	88:12	0:35:38
11		-	90:10	95:5	0:29:23

2.2: AORR of complex oxides: synthesis of carbasugars

Having verified that AORR is indeed feasible with our model substrate, we looked to increase the oxidation of the cyclohexadiene oxide to incorporate the prerequisite diol functionality. Cyclohexadiene oxides containing diol functionality have been synthesized previous by Usami and Campbell.[8] There exist, however, only one report by Hüdlicky and coworkers of the use of a sterically crowded cyclohexadiene oxide in a palladium catalyzed allylic substation reaction.[9] We

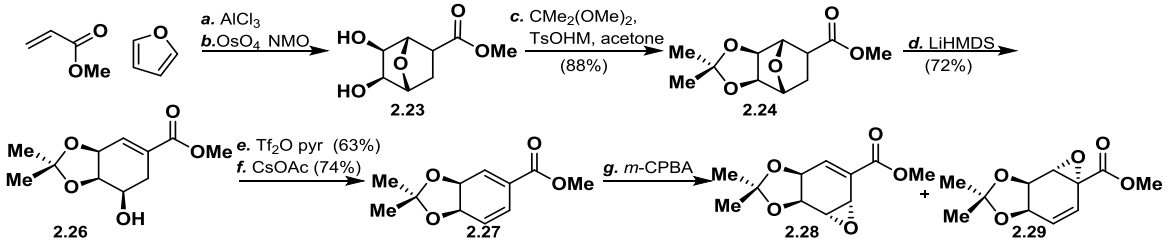
envisioned racemic compound **2.15** as our target allylic oxide. In order to obtain sufficient quantities of oxide **2.15**, a combination of steps laid out by Usami and Campbell were adapted to be performed on gram scale from easily obtainable starting materials.



Scheme 2.7: Regio-resolution of complex oxide for synthesis of natural product carbasugars

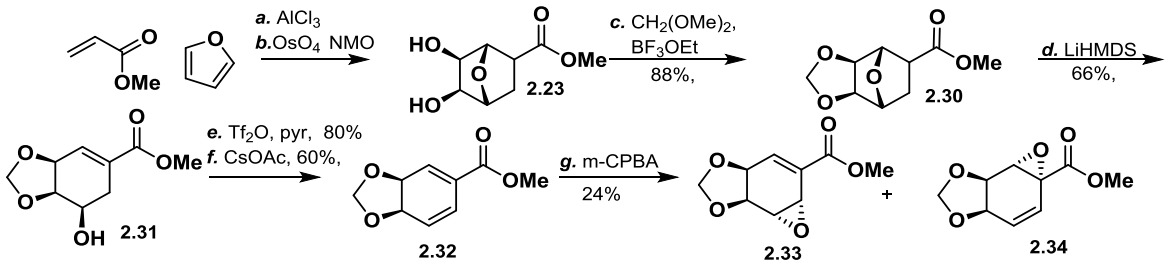
From racemic oxide (**2.15**), we envisioned that *syn*-1,2 and 1,4 addition modes could occur leading to two enantioenriched regioisomers (**2.17** and **2.18**) which could be furthered to two distinct natural products (Scheme 2.7). Literature, however, indicated that chiral, sterically condensed allylic oxides can invert to a more stable palladium complex.[10] We surmised that after palladium addition yielding allyl complex **2.16**, inversion could occur resulting in *syn*- palladium complex **2.19**. This could then proceed through normal nucleophilic addition to give *s*-1,2 and 1,4 products (**2.20** and **2.21**, respectively). Thus, by ligand and possible protecting group control, we could have access to both enantiomers of four possible carbasugar stereoarrays.

2.2.1: Synthesis of allylic oxide



Scheme 2.8: Synthesis of acetonide protected oxide

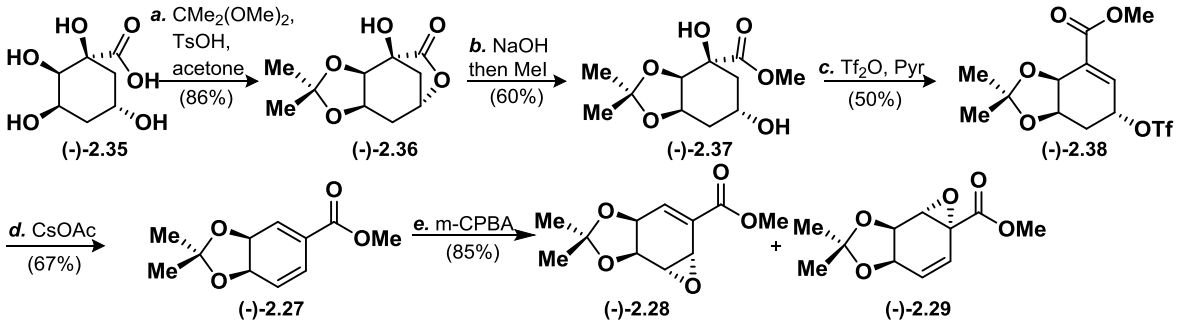
The synthesis of acetonide epoxide **2.28** began with a 50g scale aluminum trichloride catalyzed Diels-Alder cycloaddition of methyl acrylate and furan, two inexpensive commodity chemicals, resulting in a mixture of *endo* and *exo* cycloadducts **2.23** (Scheme 2.9).[11] Dihydroxylation, catalyzed by osmium tetraoxide resulted in large quantities of diol **2.23** which was protected with dimethoxypropane followed by the opening of the bridge ether with LiHMDS. Triflation and elimination of **2.26** were achieved through exposure to Tf_2O and CsOAc yielding pure diene **2.27**, which was unstable to silica gel chromatography and therefore used directly in the next step. Epoxidation was carried out with *m*-CPBA resulting in a mixture of oxides **2.28** and **2.29** in 63:37 ratio. During the course of these investigations, Usami published new conditions for this epoxidation using TFDO generated *in situ* which yields solely oxide **2.28** in fair yield; we were able to replicate these conditions in similar yields for later synthesis of oxide **2.28**.[12]



Scheme 2.9: Synthesis of dioxolane protected epoxide

During the course of our studies it was necessary to obtain different allylic oxides. Dioxolane protected oxide was obtained in a similar manner to oxide **2.28** as shown in Scheme 2.10. The dioxolane was introduced by exposing diol **2.23** to dimethoxymethane and $BF_3{\cdot}OEt_2$.

Enantiopure oxide (-)-**2.28** was obtained from quinic acid as outlined in Scheme 2.11. Both reaction sequences proceeded on gram scale.

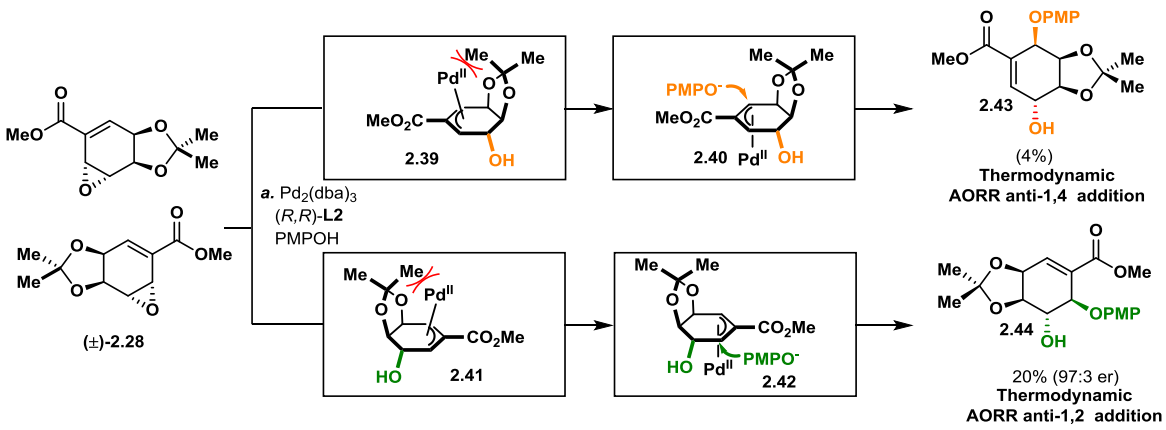


Scheme 2.10: Synthesis of enantioenriched acetonide oxide

2.2.2: AORR of complex oxides

Exposure of acetonide protected oxide **2.28** to $Pd_2(dba)_3$, (*S*,*S*)-**L2** and PMPOH resulted in both 1,2 and 1,4 addition products (Scheme 2.12, **2.43** and **2.44**, respectively). The 1,2 product (**2.44**) was isolated in a 20% yield and 97:3 er while the 1,4 product (**2.43**)was isolated in only 4% yield. Analysis of ^{1}H NMR and 2D nOe spectrometry indicated *trans* addition products. The steric bulk of the acetonide protecting group forced isomerization of the allyl species to the *anti*-palladium allyl complex **2.40**. The low 1,4 yield could be due to the steric hindrance of the acetonide at the 4 position. Oxide **2.28** was recovered in 66% yield with minor enantioenrichment. β-hydride elimination product was also observed.

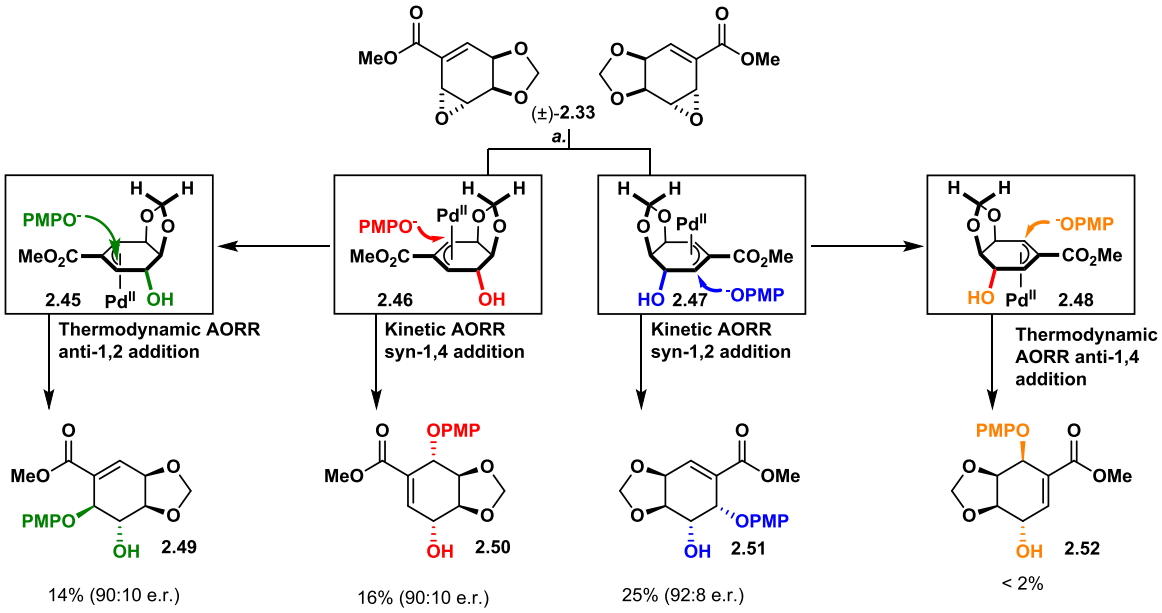
We surmised that the increased bulk of the acetonide protecting group could result in a destabilization of our kinetic π-allyl intermediate. By reducing the bulk of the acetonide to a dioxolane, *syn*-addition products might be possible. Dioxolane epoxide **2.33** was synthesized and exposed to $Pd_2(dba)_3$, (*S*,*S*)-**L2** and PMPOH (Scheme 2.13). *Syn*-1,2 and 1,4 addition products (**2.51** and **2.50**) were obtained along with *anti*-1,2 addition product (**2.49**). The *syn*-1,2 product was isolated in 25% yield with a 92:8 er presumably from intermediate **2.45**. The *anti*-1,2 and *syn*-1,4 products (**2.49** and **2.50**, respectively), which would be derived from the same intermediate **2.46**, were isolated in 16 and 14% respectively with enantiomeric ratios of 90:10 (for both). Traces of



Reagents and Conditions: a) $[Pd_2(dba)_3]$ (7.5 mol%), (*R,R*)-**L2** (22.5 mol%), *p*-$MeOC_6H_4OH$ (1.2 equiv), PhMe, 23°C, 96 h (4.0% **2.43**, 20% **2.44** (e.r. 97:3), 60% **2.28.**

Scheme 2.11: Acetonide derived AORR: isolation of thermodynamic products

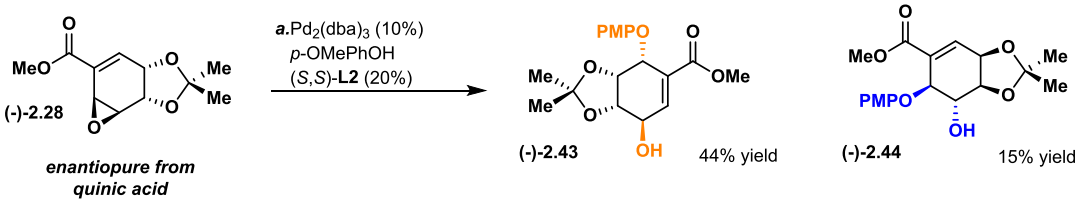
anti-1,4 product **2.52** were detected in the ^{1}H NMR of the crude reaction mixture. The remaining mass balance consisted of β-hydride elimination. The overall reduced yield of the combined three products could be explained by the constraints upon the system imposed by the bulky dioxolane. In terms of this transformation's utility, the production of three enantiomeric products from racemic starting materials outweighs the reduced yield of said products.



Reagents and Conditions: a) $[Pd_2(dba)_3]$ (10 mol%), (*R,R*)-**L2** (30 mol%), *p*-$MeOC_6H_4OH$ (1.2 equiv), PhMe, 23°C, 48 h (14% **2.49** (e.r. 90:10), 16% **2.50** (e.r. 90:10), 25% **2.51** (e.r. 92:8))

Scheme 2.12: Dioxolane protected AORR: kinetic and thermodynamic products

Although three out of the four possible stereoisomers could be obtained from our system, the *anti*-1,4 product (**2.52**) was not isolatable when dioxolane oxide **2.33** was employed and was only isolated in an unusable 4% when the acetonide oxide **2.28** was employed. To allay this reduced yield, we returned to our previously developed model. Oxide (-)-**2.28** can be synthesized enantiopure from quinic acid. If our model held true (and our complex oxides behaved similarly both in reactivity and optical rotation to our model oxides), the 1,4 addition product could be isolated enantioenriched using (*S,S*)-**L2** from (-)-**2.28**. Exposing oxide **(-)-2.28** to (*S,S*)-**L2** under standard condition resulted in an increased yield of 44% of the *anti*-1,4 product **2.43** as a single enantiomer with a 15% yield of 1,2 addition (Scheme2.14). It is worth noting that a switch in the enantiomer of the catalyst also shifted the population to favor the *anti*-1,2 addition.



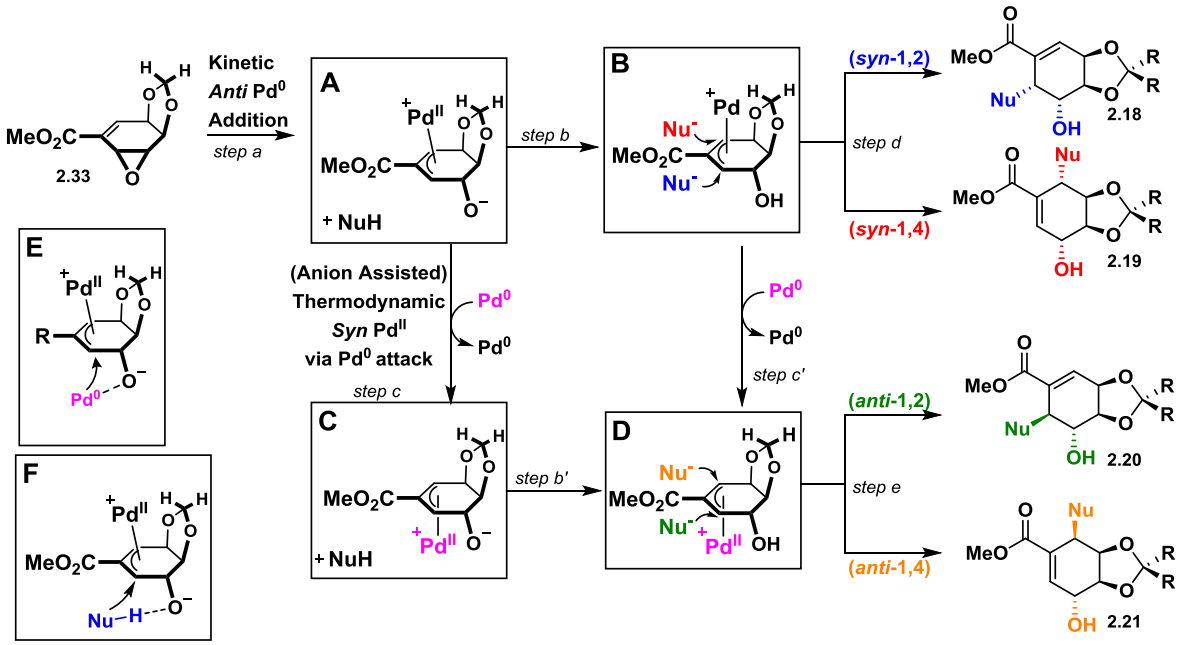
Reagents and Conditions: a) $[Pd_2(dba)_3]$ (10 mol%), (*S,S*)-**L2** (20 mol%), *p*-$MeOC_6H_4OH$ (1.2 equiv), PhMe, 23°C, 48 h, 44% **2.43,** 15% **2.44**;

Scheme 2.13: Enantiopure augmentation

2.2.3: Mechanistic insight

Multiple mechanisms can be put forth for the generation of both *syn* and *anti* addition products. Though more concrete studies to determine the exact mechanism were planned, time constraints forced their delay. The mechanism put forth, however, is based on previous work mainly by Bäckvall and co-workers along with some introductory mechanistic studies. It is possible for multiple mechanisms to be at work under different circumstances. The three possible mechanisms discussed for the isolation of both *anti* and *syn* products are: (1) nucleophilic isomerization of the Pd-π-allyl by exogenous Pd^0 attack; (2) direct oxidative addition to the allylic oxide and subsequent nucleophilic attack; and (3) attack of the nucleophile to the palladium center proceeded by reductive elimination.

Bäckvall and co-workers have done previous studies into the isomerization of Pd-π-allyl complexes (see Chapter 1.3).[10] By changing the equivalency of the palladium involved in the reaction coupled with ^{31}P NMR spectroscopy, they concluded that Pd-π-allyl species in cyclic molecules containing stereocenters are susceptible to isomerization by exogenous palladium. The case of the dioxolane epoxide **2.33** is examined first (Scheme 2.14). In this case normal *anti*-palladium addition (step *a*) to the allylic oxide occurs first resulting in kinetic π-allyl complex **A** (we call this intermediate and the products formed from it kinetic because it is the intermediate formed first and thus under kinetic control). At this point multiple pathways are possible. A deprotonation event must take place for nucleophilic attack to occur.[13] This deprotonation could be concomitant with nucleophilic attack in a direct manner as depicted in **F,** or it could be intramolecular (step *b*). Addition to both positions (1,2 and 1,4 addition) favors the latter case as directed deprotonation should favor 1,2 addition. Normal nucleophilic addition (step *d*) to the π-allyl (**D**) at the 2 or 4 position results in the standard *syn*-1,2 and 1,4 addition products. However, if Pd addition (step *a*) to the allylic oxide is slow (which is reasonable considering the steric congestion of the system, the consistent isolation of starting material and previous literature) then exogenous palladium would exist in the system. π-Allyl isomerization then occurs (step *c*) to yield **C** which is followed by nucleophile deprotonation (step *b*') and attack (step *e*). It is possible that the newly formed alkoxide could help direct palladium to the open face of the π-allyl as seen in **E**.[14] Alternatively, deprotonation could occur followed by isomerization (step *b* then *c'*) to yield **D**. One aspect that cannot be overlooked is an argument that given the nucleophile is present in stoichiometric amounts compared to the minute amount of catalytic palladium, the likelihood of nucleophile attack occurring before palladium attack and isomerization is higher; however, if one assumes the active nucleophile to reside in the deprotonated form (seen in **B** or **D**) only a catalytic amount (given that the newly formed alkoxide is the base) actually exists rendering both palladium and nucleophile to be present in similar quantities. Upon isomerization of the π-allyl to a thermodynamic intermediate, normal



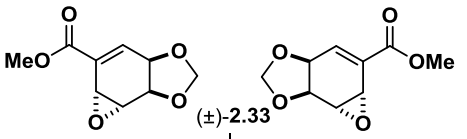
Scheme 2.14: Possible mechanism for isolation of *syn* and *anti* products

addition of the nucleophile can occur resulting in *anti* products. By increasing the steric bulk of the protecting group from a dioxolane to an acetonide, intermediate **A** becomes less stable due to an increased allyl-palladium bond distance due to steric decompression. The rate of isomerization could increase due to this weaker π interaction between the metal and allyl unit. It is also possible that in this case more exogenous palladium is present due to a slower rate of palladium addition to the allylic oxide precursor. Although more investigations are needed, a few experiments do shed light on this mechanism.

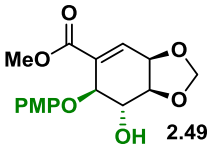
In the course of attempting to increase the yield of the products from AORR, we synthesized known and novel TML sets. Three ligand sets with different diamine backbones and thus different bite angles were used in this reaction (Table 2.3). The cyclohexyl and diphenyl backbones (**L1** and **L2**) behave similarly with near identical *syn*:*anti* ratios. Differences were noted in the increased yield of the *anti*-1,4 protect with the cyclohexyl ligand. **L1** however suffered from decreased enantiomeric ratios. Anden derived ligand **L3**[15] increased the overall yield of the reaction, while reducing overall enantiomeric ratios and completely shutting down the *anti* 1,2 pathway, thus

favoring higher production of *syn* products. Separately, an election rich ligand was envisioned resulting derived from tris-(2-furyl)phosphine. Synthesis was complete in three steps outlined in

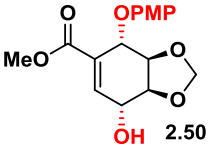
Table 2.4: AORR ligand screen



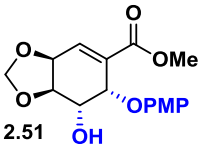
anti-1,2 addition



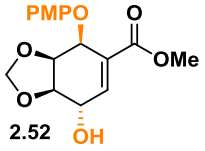
syn-1,4 addition



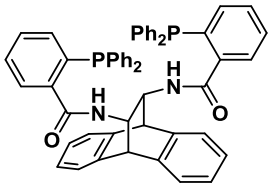
syn-1,2 addition

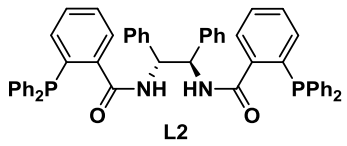


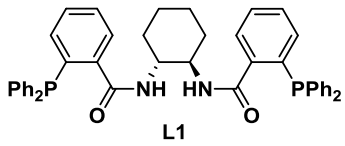
anti-1,4 addition

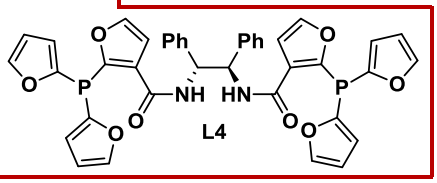


entry	ligand	anti-1,2 (yield, er)	syn-1,4 (yield, er)	syn-1,2 (yield, er)	anti-1,4 (yield er)	total yield	ratio syn:anti
1	**L1**	14%, 90:10	16%, 90:10	25%, 92:8	< 2%	55%	41:14
2	**L2**	12%, 98:2	21%, 69:31	17%, 86:14	7%, 84:16	57%	38:19
3	**L3**	0%	14%, 83:17	55%, 80:20	11%, 96:4	80%	69:11
4	**L4**	**43%, 98:2**	2%, 53:47	14%, 84:16	**28%, 66:34**	87%	16:71

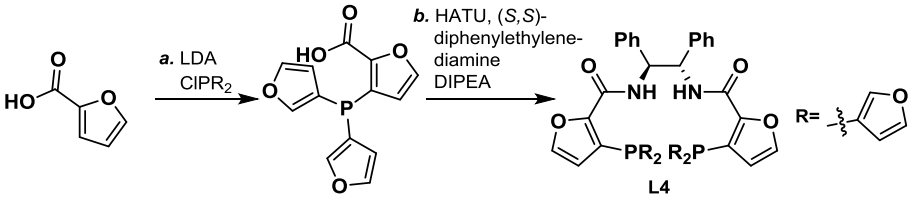








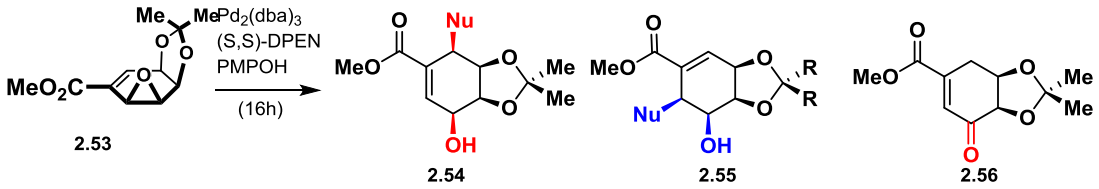
Scheme 2.6. Surprisingly, exposure of this ligand to standard conditions resulted in an inversion of the *syn*:*anti* population favoring the *anti* products. Unfortunately, enantiomeric ratios decreased with this ligand probably due to its smaller size. By increasing the electron density on the phosphine the palladium in turn has become more nucleophilic resulting in an increased rate of isomerization and more *anti* products.



Scheme 2.15: Synthesis of L4

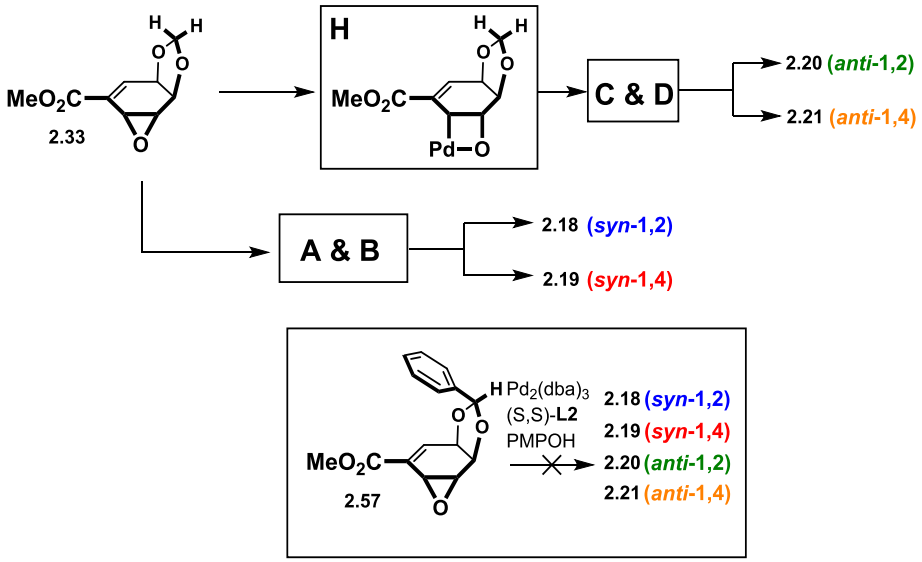
We hoped to expand the scope of the oxides used to include an all *syn* oxide, **2.53** which was prepared in two steps from diene **2.27**.[12] Exposure of this oxide under standard conditions resulted in

near racemic products. By switching the solvent to THF, we were able to obtain enantioenriched 1,2 product and enantioenriched β-hydride elimination products (**2.55** and **2.56**). The reaction was complete in 16 hours rather than the 48 required for the *trans* oxides **2.28** and **2.33**, and no *anti* products were obtained. In this system, palladium addition should occur rapidly to the open face of the allylic oxide while nucleophilic addition should be retarded. *Anti* addition products should not form due to a rapid addition of palladium to the allylic oxide and stable palladium π-allyl species.



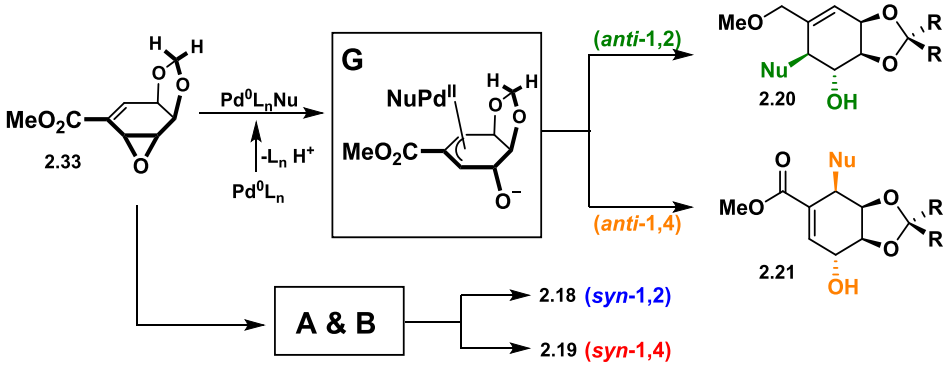
Scheme 2.16: All-*syn* oxide regio-resolution

The second possible mechanism would involve the direct oxidative addition of the palladium to the epoxide resulting in the formation of *syn*-π-allyl species (**H**, Scheme 2.18). Reports of palladium addition to epoxides are limited.[16] Mechanistic studies have shown that the palladium catalyzed rearrangement of epoxides to ketones proceeds through an S_N2 like mechanism rather than an oxidative addition to the C-O bond.[16] In rhodium catalyzed allylic alkylations, rhodium is thought to oxidatively add to the epoxide followed by nucleophilic attack of the rhodium-π-allyl resulting in *anti*-addition products (it is worth noting that in these cases only $[Rh(CO)_2Cl]_2$ promotes *anti* addition).[17,18] Additionally, with bicyclic allylic ethers (which operate in a similar manner to allylic oxides) rhodium leads to *anti* addition products due to oxidative addition into the bridge ether[19] while palladium yields *syn* products proceeding through normal addition and π-allyl formation.[20] Data from this work seems to indicate that the oxidative addition mechanism is unlikely due to the appearance of *syn* products when dioxolane epoxide **2.33** is used (although multiple congruent pathways may be operative). Additionally when epoxide **2.57** with a phenyl group positioned opposite the epoxide was exposed to standard conditions, no reaction occurred. If oxidative addition were to occur then oxide should have been consumed.



Scheme 2.17: Alternative mechanism: oxidative addition to oxide

The third mechanism consists of normal palladium-π-allyl formation followed by nucleophilic attack onto the palladium center and subsequent reductive elimination. In Tsuji-Trost allylations, soft nucleophiles add to the allyl resulting in net retention of the stereocenter whereas hard nucleophiles tend to add to the metal center and then proceed through reductive elimination.[21] Phenols, however, are considered soft nucleophiles and thus would seem to limit the possibility of this mechanism. If this mechanism was operative, oxide **2.33** (Scheme 2.17) should have yielded *anti* addition product via a similar mechanism due to the hindered approach of the nucleophile *syn* to the acetonide, yet only *syn* products were isolated.



Scheme 2.18: Alternative mechanism: palladium reductive elimination

Mechanism one seems to be preferred given the data obtained and literature precedence. More studies could be performed to help elucidate the structure of the intermediates along with molecular modeling. The ability to use ligands to control the *syn* or *anti* nucleophilic addition will only increase the utility of the reaction.

2.3: Synthesis of Carbasugars

The four stereoarrays obtained from AORR were furthered to four different natural products (Figure 2.2). Streptol and MK7606 are fully reduced pentahydroxycyclohexenols with herbicidal activity. Cyathiformine B is a shikimate-type cyclohexene carboxylate with an enol pyruvate side chain. Finally, polyporapyranone G is a pyranone containing cyclohexenol. The latter two natural products have no known bioactivity.

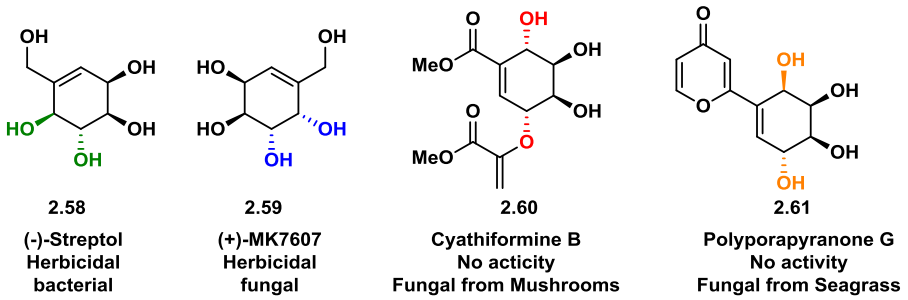
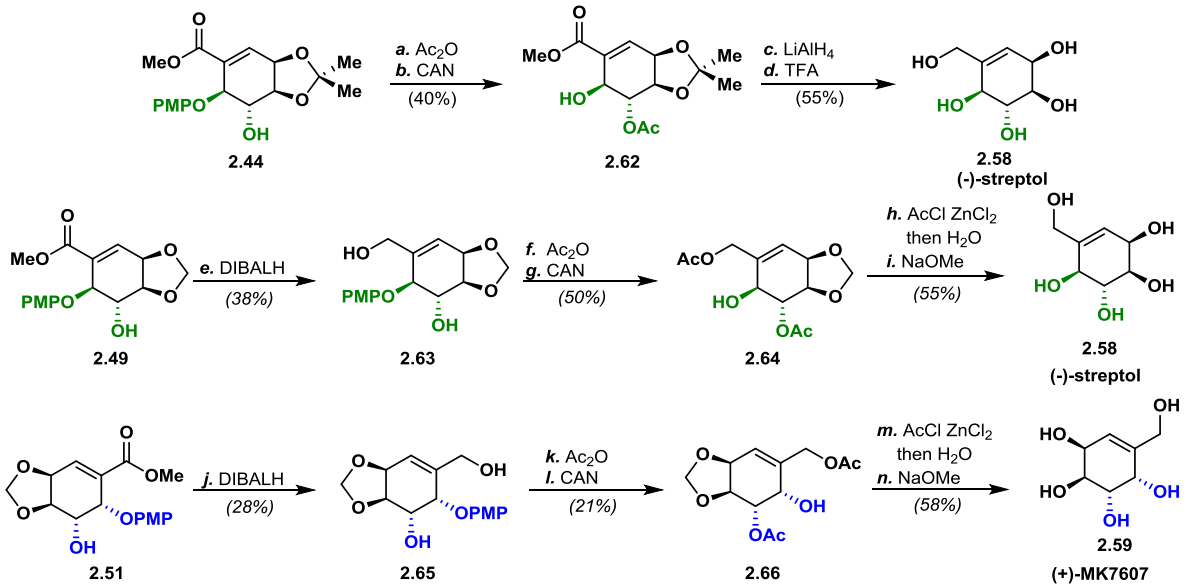


Figure 2.2: Carbasugar natural product targets

Streptol and its C-6 epimer MK7607 are cyclohexenol based bacterial metabolites. Streptol and MK7607 are one of a few monomeric carbasugars that possess bioactivity. Streptol exhibits herbicidal activity as a plant growth inhibitor and has been synthesized four times in as little as nine steps from chiral starting materials.[22,23] The 1,2 *anti* addition product **2.44** contains the stereoarray found in streptol. Three steps had to be accomplished to obtain streptol from **2.44**: reduction, oxidative deprotection, and a deprotection of the dioxolane or acetonide (Scheme 2.21). The order in which these steps were carried out varied depending on the protecting group. In the case of streptol, the acetonide protected 1,2 product **2.44** was acylated and the *p*-methoxyphenyl group cleaved with ceric ammonium nitrate (40% yield over two steps). It was necessary to protect the free alcohol due to quinone ketal formation derived from the attack of the proximal hydroxyl group on the oxidative

p-methoxyphenol intermediate. Lithium aluminum hydride reduction of the ester afforded a tetraol (lithium aluminum hydride was used in this case due to the ability to precipitate aluminium salts containing the water soluble tetraol). TFA deprotection followed by purification via DOWEX ion exchange resin afforded streptol in 55% yield over two steps.

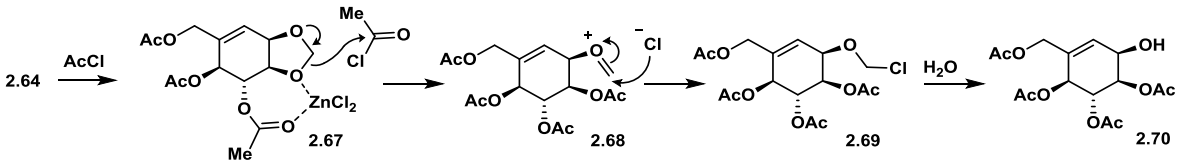


Reagents and Conditions: a) Ac_2O, $^{i}PrNEt$, DMAP, CH_2Cl_2; b) CAN (2.1 equiv), 3:1 MeCN:H_2O, 0 ^{o}C, 0.2 h, 40% (two stesps); c) $LiAlH_4$ (4.2 equiv), THF, 0 ^{o}C; d) TFA, MeOH, 55% (two stps); e) DIBAlH (3.5 equiv), CH_2Cl_2, 0.3 h, 38%; f) Ac_2O (3.0 equiv), DIPEA, DMAP,CH_2Cl_2, 0.3 h; g) CAN (2.2 equiv), MeCN/H_2O 4:1, 0.20 h, 49% (two steps); h) 1) AcCl, then $ZnCl_2$ (0.1 equiv), 0 to 23 ^{o}C; 2) H_2O, THF, 0.3 h; i) NaOMe (1 equiv), MeOH, 16 h, 55% (two steps); j) DIBAlH (3.5 equiv), CH_2Cl_2, 0.3 h, 28%; k) Ac_2O (3 equiv), DIPEA, DMAP, CH_2Cl_2, 0.3 h; l) CAN (2.2 equiv), MeCN/H_2O 4:1, 0.20 h, 21% (two steps); m) 1) AcCl, then $ZnCl_2$ (0.1 equiv), 0 to 23 ^{o}C; 2) H_2O, THF, 0.3 h; n) NaOMe (1 equiv), MeOH, 16 h, 57% (two steps).

Scheme 2.19: Total synthesis of streptol and MK6707

For the dioxolane containing intermediate **2.49**, it was necessary to change the order of steps. Due to complications with the lithium aluminum hydride reduction (over reduction of dioxolane, enoate and purification problems), the order in which the reduction and deprotection were switched. **2.49** was reduced with DIBAL-H in 38% yield to afford **2.63**. The reaction was sensitive to solvent as both the reaction solvent and DIBAL-H solution had to be composed of dichloromethane. Use of other solvents such as THF and toluene resulted in loss of *p* methoxyphenol. Protection and ceric ammonium nitrate deprotection yielded dioxane precursor **2.64** in 50% yield (two steps). Deprotection of the dioxolane proved difficult. Many different conditions were attempted including concentrated HCl, TMSOTF and TESOTF with 2,2'-bipyrdine and acetyl

bromide; however in all cases, no reaction occurred.[24] Ultimately acetyl chloride with catalytic $ZnCl_2$ afforded tetraacetyl-streptol (^{1}H NMR indicated that there were various patterns of acylation) which was then deprotected using methanolic sodium methoxide.[25] Purification of the final compound was achieved by passing through DOWEX 2WD resin to yield streptol in 55% yield (from **2.64**). Mechanistically, this deprotection is thought to occur by coordination of dioxolane oxygen to zinc (**2.67**) and rupture of the five membered ring followed by chloride attack at the oxonium (**2.68**). The corresponding chloromethyl ether is then trapped with water to yield the free hydroxyl (**2.70**) after loss of formaldehyde.

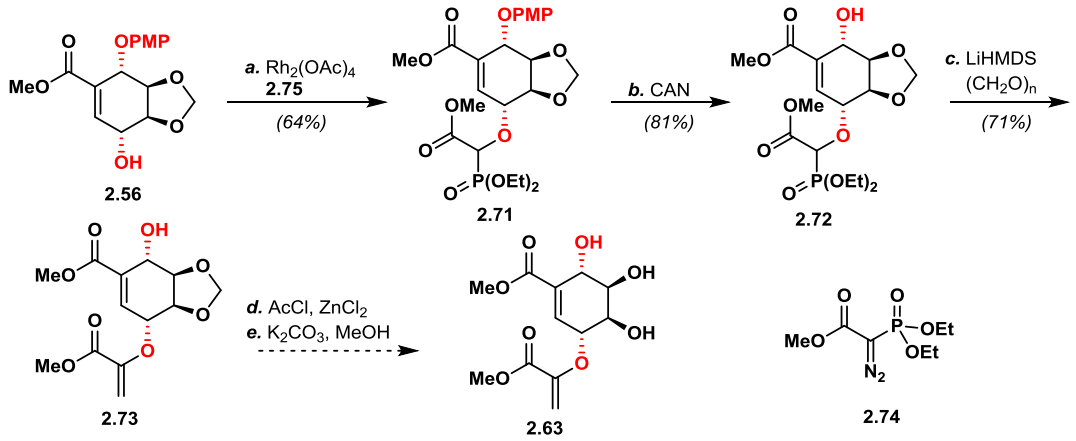


Scheme 2.20: Mechanism of dioxolane deprotection

MK7607, the C6 epimer of streptol, is also a fungal metabolite from *Curvularia eragrostidis* which possess herbicidal activity and contains the stereoarray present on the *syn*-1,2 addition product (**2.51**).[26] Four total syntheses of MK7607 have been reported, ranging from 11-16 steps starting from chiral materials.[27] The synthesis of MK7607from **2.51** proved to be identical to that of the synthesis of streptol. Reduction with DIBAL-H in dichloromethane (28% yield), acetyl protection, ceric ammonium nitrate deprotection (21% yield over two steps), and zinc chloride catalyzed deprotection (58% yield) proved uneventful to yield MK7607. The total step count to both streptol and MK7607 was 11 steps.

Cyathiformine B is a metabolite found on the chorismic acid pathway and was isolated from *Clitocybe cyanthiformis*, a mushroom.[28] The molecule has only been synthesized once in four steps from chorismic acid.[29] The *syn*-1,4 product (**2.56**) contains the stereoarray necessary for cyathiformine B. The steps required include installation of an enol pyruvate side chain and final deprotection. Enol pyruvates are known to be unstable moieties especially under acid conditions.[30] The enol pyruvate side chain was installed through diazophosphomalonate insertion into *syn*-1,4

addition product **2.56** in 64% yield. This was followed by oxidative cleavage of the *p*-methoxyphenyl group in 81% yield with surprisingly little degradation of the phosphomalonate. Horner-Wadsworth-Emmons olefination produced **2.63** in 71% yield. Deprotection of the dioxolane proved difficult under the previous $ZnCl_2$ conditions due to cleavage of the enol pyruvate. Cyathiformine B was ultimately obtained in low yield but was not reproducible.

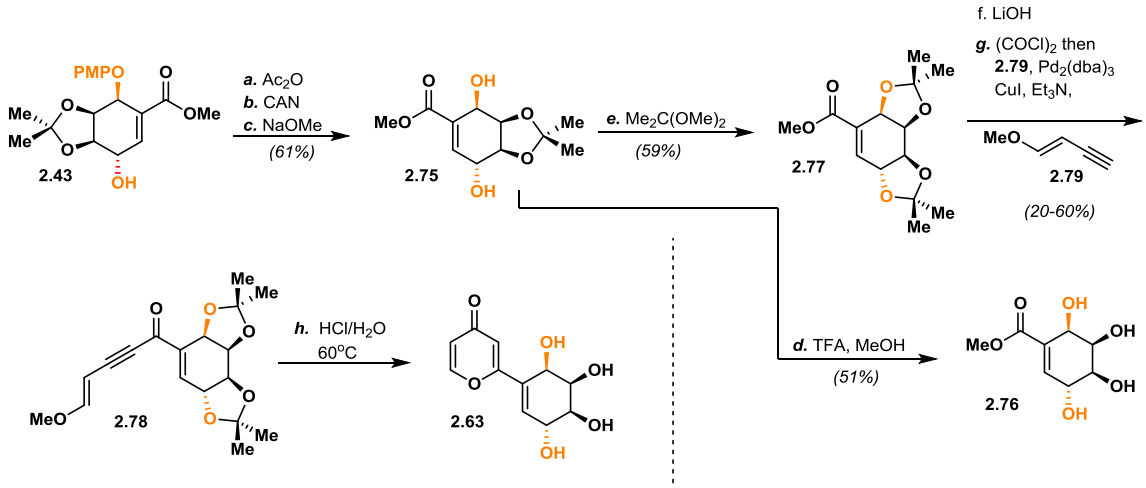


Reagents and Conditions: a) $[Rh_2(OAc)_4]$, **2.74**, CH_2Cl_2, 5 h, reflux, 64%; b) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 81%; c) LiHMDS, CH_2O, THF, 2 h, -78 °C, 71%.

Scheme 2.21: Total synthesis of cyathiformine B

Finally, the 1,4 *anti* product contained the stereoarray found on polyporapyranone G, a fungal metabolite isolated from sea grass.[31] There currently are no reported syntheses of polyporapyranone G. Acetyl protection, ceric ammonium nitrate deprotection and deacylation with methanolic sodium methoxide yielded diol **2.75** in 61% yield. Exposure to dimethoxypropane and TsOH resulted in a protecting group rearrangement and bis(acetonide) species **2.77**. Saponification of **2.75** followed by careful exposure to oxalyl chloride afforded the acid chloride which was used without further purification. Sonogashira coupling of the terminal enyne **2.79**[32] to the acyl chloride was accomplished with $Pd_2(dba)_3$ and CuI. This reaction resulted in variable yields ranging from 20-60%. The resulting enyne was unstable over long periods of time; however was stable to rapid silica gel chromatography. Although $Pd(PPh_3)_4$ also accomplished this coupling, $Pd_2(dba)_3$ was used due to ease of removal of dibenzylideneacetone as compared to triphenylphosphine. The final step of the synthesis was the acidic hydration of enyne **2.78**.[33] Ultimately, rather harsh conditions of 4M HCl at

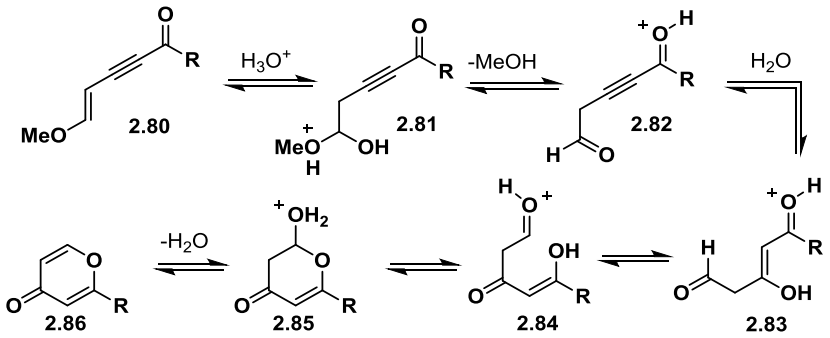
60°C were needed to effect the cyclization. Upon analysis of the ^{1}H NMR spectra of the crude reaction mixture, two products were isolated, one matching the structure of polyporapyranone G (we were unable to determine the other structure). Polyporapyranone G could be isolated through preparatory HPLC to yield enough material to match to literature data.



Reagents and Conditions: a) Ac_2O (3 equiv), DIPEA, DMAP, CH_2Cl_2, 0.3 h; b) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 63%; c) NaOMe, MeOH, 0.1 h, 23 °C, 98%; d) TFA, MeOH, 40°C, 7 h, 51%. e) $Me_2C(OMe)_2$, Me_2CO, TsOH (cat.), Na_2SO_4, 1 h, 59%. f) 1) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C, 2h; 2) **2.79** (5 equiv.), $Pd_2(dba)_3$ (5 mol %), CuI (10 mol %), Et_3N (3 equiv.), toluene, 0 to 23 °C, 1h, 42%; h) 4M HCl/H_2O, 60 °C.

Scheme 2.22: Total synthesis of Polyporapyranone G

The final hydration step is an interesting transformation. Work initially done by Crimmins and co-workers found this cyclization to be a facile method for creating γ-pyrones.[33] Their conditions, however, did not require the heat and level of acidity that we ultimately needed to obtain cyclization. It was noted that the acetonide protecting groups deprotected quickly upon exposure to acid. It is possible that the tetraol product interfered with the cyclization due to hydrogen bonding networks and solvation. Attempts to cyclize the structure using other methods such as K_2CO_3 and MeOH were ineffectual. Mechanistically this cyclization occurs through water attack into the β position of the alkyne. This is then followed by protonation and hydration of the enol ether resulting in a terminal aldehyde (**2.83**). Compound **2.84** is then able to proceed through a 6-endo-trig attack of the aldehyde which then dehydrates to form the γ-pyrone (**2.82**).



Scheme 2.23: Mechanism of pyranone formation

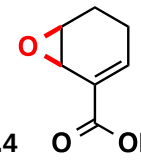
In conclusion, we developed a method by which a racemic allylic oxide could be diverged into four different enantioenriched regioisomers. These regioisomers were then furthered to four different natural products, streptol, MK7607, cyathiformine B and polyporapyranone G. The strength of this method was the ability to control product distribution through ligand and protecting group selection. Prudent ligand selection allowed access to both enantiomers of a specific carbasugar while diol protecting group selection controlled whether normal *syn* addition products or *anti* addition products were obtained. Yields of a specific product could be increased by the use of enantiopure starting material and ligand selection. After analyzing the scope of this method with simple epoxides and a myriad of phenols, we looked to further the utility to include complex phenols and the addition to carbasugars to natural product scaffolds (Chapter 3).

2.4: Experimental:

Methyl 1,3-cyclohexadiene-2-carboxylate was prepared according to literature procedures.[1] The diene carboxylate (2.01 g, 14.5 mmol, 1.0 equiv.) was exposed to *m*-CPBA (3.38 g, 19.6 mmols, 1.3 equiv.) in DCM (140 mL) at 0 °C for 6 h. The reaction was then poured into 100.0 mL of a cooled 1 M solution of NaOH, extracted with DCM (3 x 50.0 mL) and dried over Na_2SO_4. Flash column chromatography of the crude oil (9:1 hexanes/EtOAc, v/v) resulted in 1.36 g (61% yield) of a volatile colorless oil.

Enantioenriched epoxide (+)-**2.4** was prepared using the corresponding [*N*,*N*'-bis(3,5-di-tertbutylsalicylidene)-1,2cyclohexane- diaminato]manganese(III) chloride complex according to

literature procedure.[34] To a buffered solution of 0.05 M Na_2HPO_4 and bleach (10 mL, 0.55 M in NaOCl) was added methyl 1,3-cyclohexadiene-2-carboxylate **2.3** (400.0 mg, 2.89 mmol, 1.0 equiv.) and *R,R* [*N,N*'-bis(3,5-di-tertbutylsalicylidene)-1,2cyclohexane-diaminato] manganese(III) chloride (185.0 mg, 0.289 mmol, 0.1 equiv.) in DCM (4.0 mL). The reaction was stirred for 18 hours under air after which the layers were separated. The aqueous layer was extracted with DCM (10.0 mL), and the combined organic layers were washed with brine (10.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (9.5:1 hexanes/EtOAc) yielded (80.3 mg, 0.519 mmol) enantioenriched (+)-**2.4** as a yellow oil. Analysis by chiral GC indicated (+)-**2.4** ($[\alpha]_D^{20.0}$ +31.9 (*c* 1.00, $CHCl_3$) was obtained in a 90:10 enantiomeric ratio.



2.4

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (m, 1H), 3.92 (m, 1H), 3.79 (s, 3H), 3.59 (m, 1H), 2.31 (m, 1H), 2.20 (m, 1H), 1.61 (m, 1H), 1.27 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 143.0, 127.6, 54.2, 51.5, 45.8, 20.5, 19.7; **IR** (neat) ν = 2932, 2857, 1715, 1641, 1268 cm^{-1}; **TLC** R_f = 0.60 (9:1 hexanes/EtOAc v/v); **HRMS** (ES^+) calc'd for $C_8H_{10}O_3$ 154.0630; found 154.0625.

Addition of phenols into oxide 2.4

General Procedure A: 42.9 mg (0.278 mmol, 1.0 equiv.) of racemic epoxide **2.4** was dissolved in 2.0 mL of toluene in a flame-dried vial outfitted with a septum followed by the addition of 17.0 mg (0.157 mmol, 0.56 equiv.) of *p*-cresol. The resulting solution was degassed with argon and cooled to -40 °C. In a separate vial, 2.4 mg (1 mol%) of $Pd_2(dba)_3$ and 6.6 mg (3 mol%) of DPEN-ligand **L2**[2] was dissolved in 1.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 6 h before an additional 15.2 mg (0.142 mmol, 0.51 equiv.) of *p*-cresol was added and the solution purged with argon. The reaction was stirred for an additional 12 h at -40 °C before it was quenched with an

aqueous NH_4Cl solution, extracted with ether (2 x 1.5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by column chromatography (9:1 hexanes/EtOAc) to give 28.1 mg of 1,2-product **2.5b** (32% yield) and 25.0 g (47% yield) of 1,4-product **2.6b** as white solids. The recovered epoxide **2.4** (2%) was recovered in 57:43 enantiomeric ratio.

Methyl (5S, 6R)-5-hydroxy-6-O-(phenoxy)-cyclohex-1-enecarboxylate (2.5a)

$[\alpha]_D^{20.0}$ -127.7 (*c* 1.00, $CHCl_3$); M.p. 63 – 66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.20 – 7.15 (m, 2H), 7.15 – 7.12 (m, 1H), 7.02 – 6.91 (m, 1H), 5.28 (d, *J* = 3.7 Hz, 1H), 3.92 (dt, *J* = 11.5, 3.8 Hz, 1H), 3.61 (s, 3H), 2.54 (m, 1H), 2.39 – 2.26 (m, 1H), 2.10 – 1.93 (m, 1H), 1.93 – 1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.7, 144.1, 129.6, 122.0, 117.4, 115.9, 73.2, 69.6, 51.9, 25.4, 25.3; IR (film, cm^{-1}) 3435, 2950, 2360, 1710, 1595, 1490, 1250, 1227, 750; TLC R_f = 0.37 (7:3 hexanes:EtOAc v/v); HPLC 97:3 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:methanol. Retention times: R_T= 8.0 min, 10.7 min; HRMS (EI^+) *m/z* Calc'd for $C_{14}H_{16}O_4$ 248.1049, found 248.1047.

Methyl (3R, 6S)-3-hydroxy-6-O-(phenoxy)-cyclohex-1-enecarboxylate (2.6a)

$[\alpha]_D^{20.0}$ -20.8 (*c* 0.50, $CHCl_3$); M.p. 36 – 39 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.12 (t, *J* = 1.8 Hz, 1H), 7.04 – 6.95 (m, 3H), 5.14 (br s, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 3.75 (s, 3H), 2.24 – 2.14 (m, 1H), 2.05 – 1.96 (m, 1H), 1.91 – 1.77 (m, 1H), 1.61 (tt, *J* = 14.2, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.0, 145.8, 130.6, 129.7, 121.7, 117.0, 68.2, 67.9, 52.2, 26.5, 25.4; IR (film, cm^{-1}) 3403, 2950, 2358, 1718, 1490, 1250, 1226, 751; TLC R_f = 0.25 (7:3 hexanes:EtOAc v/v); HPLC 95:5 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T= 5.9 min, 6.6 min; HRMS (EI^+) *m/z* Calc'd for $C_{14}H_{16}O_4$ 248.1049, found 248.1055.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-methylphenoxy)-cyclohex-1-enecarboxylate (2.5b): $[\alpha]_D^{20.0}$ -112.4 (*c* 1.00, $CHCl_3$); **M.p.** 88–90 °C **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.14 (dd, *J* = 4.8, 3.0 Hz, 1H), 7.09 – 7.01 (m, 4H), 5.20 (d, *J* = 3.8 Hz, 1H), 3.88 (ddt, *J* = 11.4, 9.2, 3.7 Hz, 1H), 3.61 (s, 3H), 2.59 – 2.46 (m, 1H), 2.35 – 2.25 (m, 1H), 2.28 (s, 3H), 2.14 (d, *J* = 9.2 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.90 – 1.80 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 157.5, 143.9, 131.3, 129.9, 129.4, 117.2, 73.4, 69.4, 51.8*, 51.8*, 25.2, 20.6; **IR** (film, cm^{-1}) 3450, 3312, 2219, 1698, 506, 1221, 983, 796, 734; **TLC** R_f = 0.32 (7:3 hexanes/EtOAc v/v); **HPLC** 96:4 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes/isopropanol. Retention times: R_T= 7.6 min, 9.6 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{18}O_4$ 262.1205, found 262.1200. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-methylphenoxy)-cyclohex-1-enecarboxylate (2.6b): $[\alpha]_D^{20.0}$ -12.1 (*c* 1.00, $CHCl_3$); **M.p.** 94–98 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.14 – 7.06 (m, 3H), 6.95 – 6.88 (m, 2H), 5.07 (br s, 1H), 4.36 – 4.28 (m, 1H), 3.76 (s, 3H), 2.29 (s, 3H), 2.21 – 2.14 (m, 1H), 2.04 – 1.96 (m, 1H), 1.92 – 1.77 (m, 1H), 1.57 (dt, *J* = 3.5 Hz, 14.2 Hz 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.4, 155.9, 145.8, 131.0, 130.6, 130.1, 117.1, 68.6, 67.8, 52.1, 26.4, 25.3, 20.7; **IR** (film, cm^{-1}) 3175, 2954, 1713, 1508, 1251, 1226, 1025, 960, 812; **TLC** R_f = 0.21 (7:3 hexanes/EtOAc v/v); **HPLC** 93:7 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes/isopropanol. Retention times: R_T= 5.7 min, 8.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{18}O_4$ 262.1205, found 262.1202.

1,2-product **2.5c** (21.9 mg, 28%, 96:4 e.r.) and 1,4-product **2.6c** (26.9 mg, 34%, 91:9 e.r.) were isolated following general procedure A with recovered epoxide **2.4** (9.5 mg, 24%, 52:48 e.r.). Analytical standards used for the characterization of **2.5c** and **2.6c** were prepared from a separate trial giving enantiomeric ratios of 96:4 and 91:9 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-*tert*-butylphenoxy)-cyclohex-1-enecarboxylate (2.5c)

$[\alpha]_D^{20.0}$ -92.4 (*c* 1.00, $CHCl_3$); M.p. 53 – 56 °C; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.35 – 7.24 (m, 2H), 7.15 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.11 – 7.03 (m, 2H), 5.26 (d, *J* = 3.8 Hz, 1H), 3.90 (dt, *J* = 11.2, 3.7 Hz, 1H), 3.61 (s, 3H), 2.61 – 2.46 (m, 1H), 2.39 – 2.23 (m, 1H), 2.15 – 1.90 (m, 1H), 1.91 – 1.79 (m,

1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 157.3, 144.7, 144.0, 129.4, 126.4, 116.7, 73.1, 69.5, 51.9, 34.3, 31.6, 25.4, 25.3; IR (film, cm^{-1}) 3435, 2953, 2358, 1716, 1509, 1220, 1043; TLC R_f = 0.42 (7:3 hexanes:EtOAc v/v); HPLC 96:4 e.r, Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol. Retention times: R_T= 6.7 min, 7.2 min; HRMS (EI^+) *m/z* Calc'd for $C_{18}H_{24}O_4$ 304.1675, found 304.1661.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-*tert*-butylphenoxy)-cyclohex-1-enecarboxylate (2.6c)

$[\alpha]_D^{20.0}$ -10.1 (*c* 0.75, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 – 7.27 (m, 2H), 7.11 (br s, 1H), 6.96 – 6.91 (m, 2H), 5.11 (br s, 1H), 4.37 – 4.28 (m, 1H), 3.75 (s, 3H), 2.24 – 2.15 (m, 1H), 2.03 – 1.95 (m, 1H), 1.88 – 1.77 (m, 1H), 1.58 (tt, *J* = 14.2, 3.4 Hz, 1H), 1.29 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 155.7, 145.8, 144.3, 130.7, 126.4, 116.3, 68.0, 67.9, 52.2*, 52.2*, 34.3, 31.7, 26.5, 25.3; **IR** (film, cm^{-1}) 3399, 2952, 2867, 2359, 1718, 1508, 1250, 1225, 1030, 757; TLC R_f = 0.29 (7:3 hexanes:EtOAc v/v); **HPLC** 91:9 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T= 4.6 min, 6.0 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{18}H_{24}O_4$ 304.1675, found 304.1673. * denotes presumed rotamers in a 1:1 ratio.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-methoxyphenoxy)-cyclohex-1-enecarboxylate (2.5d):

$[\alpha]_D^{20.0}$ -114.9 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.14 (dd, *J* = 4.6, 3.1 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.84 – 6.78 (m, 2H), 5.11 (d, *J* = 3.7 Hz, 1H), 3.89 (dt, *J* = 11.3, 3.8 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 2.61 – 2.46 (m, 1H), 2.39 – 2.22 (m, 1H), 2.06 – 1.95 (m, 1H), 1.91 – 1.81 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.6, 154.8, 153.6, 143.9, 129.4, 118.9, 117.6, 114.5, 74.4, 69.4, 55.7, 51.8, 25.3; **IR** (film, cm^{-1}) 3481, 3004, 2950, 2834, 2359, 1709, 1500, 1211, 748; **TLC** R_f = 0.21 (7:3 hexanes/EtOAc v/v); **HPLC** 92:8 e.r., Chiral HPLC eluting at 1.25 mL/min with 99% hexanes/isopropanol for 20.00 minutes then a gradient from 1% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 29.2 min, 31.7 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{18}O_5$ 278.1154, found 278.1152.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-methoxyphenoxy)-cyclohex-1-enecarboxylate (2.6d):

$[\alpha]_D^{20.0}$ +15.5 (*c* 1.00, $CHCl_3$)[†]; **M.p.** 49–54 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.09 (dd, *J* = 1.8 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.86 – 6.81 (m, 2H), 4.97 (br s, 1H), 4.36 – 4.28 (m, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 2.20 – 2.11 (m, 1H), 2.02 (d, *J* = 18.7 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.55 (tt, *J* = 14.2, 3.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 166.4, 154.7, 152.1, 145.8, 130.6, 118.9, 114.7, 69.9, 67.8, 55.7, 52.1, 26.3, 25.2; **IR** (film, cm^{-1}) 3285, 2953, 2869, 1713, 1505, 1252, 1218, 1032, 826, 724; **TLC** R_f = 0.15 (7:3 hexanes/EtOAc v/v); **HPLC** 94:6 e.r., Chiral HPLC eluting at 1.00 mL/min with 90% hexanes/isopropanol. Retention times: R_T= 8.7 min, 14.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{18}O_5$ 278.1154, found 278.1167. [†]Analytical standard was obtained as the enantiomer of **2.6b** from the (*R,R)*-**L2** ligand.

1,2-product **2.5e** (20.7 mg, 21%, 90:10 e.r.) and 1,4-product **2.6e** (22.3 mg, 23%, 84:16 e.r.) were isolated following general procedure A with recovered epoxide **2.4** (12.1 mg, 29%, 51:49 e.r.). Analytical standards used for the characterization of **2.5e** and **2.6e** were prepared from a separate trial giving enantiomeric ratios of 94:6 and 89:11 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-N-Bocphenoxy)-cyclohex-1-enecarboxylate (2.5e)

$[\alpha]_D^{20.0}$ -92.4 (*c* 0.50, $CHCl_3$); M.p. 134 – 136 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.27 – 7.23 (m, 2H), 7.15 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.35 (s, 1H), 5.15 (d, *J* = 3.6 Hz, 1H), 3.88 (ddt, *J* = 12.2, 8.5, 3.8 Hz, 1H), 3.61 (s, 3H), 2.58 – 2.47 (m, 1H), 2.37 – 2.24 (m, 1H), 2.03 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H), 1.50 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.6, 155.6, 153.2, 144.1, 132.7, 129.3, 120.2, 118.1, 80.5, 73.9, 69.5, 51.9, 28.5, 25.4, 25.3; **IR** (film, cm^{-1}) 3481, 3358, 2974, 2921, 1720, 1695, 1511, 1210, 1150; **TLC** R_f = 0.13 (7:3 hexanes:EtOAc v/v); **HPLC** 94:6 e.r., Chiral HPLC eluting at 1.00 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 33.1 min, 35.5 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{19}H_{25}O_6N$ 363.1682, found 363.1686.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-N-Bocphenoxy)-cyclohex-1-enecarboxylate (2.6e)

$[\alpha]_D^{20.0}$ -19.8 (*c* 0.50, $CHCl_3$); M.p. 61 – 65 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28 – 7.23 (m, 2H), 7.10 (dd, *J* = 1.9, 1.6 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.37 (s, 1H), 5.01 (t, *J* = 3.0 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.74 (s, 3H), 2.18 – 2.09 (m, 1H), 2.02 – 1.94 (m, 1H), 1.81 (tdd, *J* = 13.0, 10.4, 2.9 Hz, 1H), 1.58 (tt, *J* = 14.5, 3.0 Hz, 1H), 1.49 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 154.1, 153.2, 145.8, 132.5, 130.6, 120.7, 118.0, 80.5, 69.2*, 69.2*, 67.9, 52.2*, 52.2*, 28.5, 26.5, 25.3; **IR** (film, cm^{-1}) 3342, 2950, 1702, 1509, 1254, 1220, 1160; **TLC** R_f = 0.12 (7:3 hexanes:EtOAc v/v); **HPLC** 89:11 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 31.9 min, 34.0 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{19}H_{25}O_6N$ 363.1682, found 363.1688. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2.5f** (3.2 mg, 4%, 97:3 e.r.) and 1,4-product **2.6f** (2.9 mg, 4%, 98:2 e.r.) were isolated following general procedure A with recovered epoxide **12.4** (27.6 mg, 64%, 50:50 e.r.). Analytical standards used for the characterization of **2.5f** and **2.6f** were prepared from a separate trial giving enantiomeric ratios of 98:2 and 98:2 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-nitrophenoxy)-cyclohex-1-enecarboxylate (2.5f)

$[\alpha]_D^{20.0}$ -108.2 (*c* 0.50, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.22 – 8.17 (m, 2H), 7.26 – 7.21 (m, 3H), 5.44 (d, *J* = 3.7 Hz, 1H), 3.96 (ddt, *J* = 12.0, 8.0, 3.8 Hz, 1H), 3.66 (s, 3H), 2.58 (dtd, *J* = 20.3, 5.4, 2.3 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.05 – 1.87 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.1, 165.0, 145.1, 141.9, 128.2, 125.9, 116.7, 73.1, 69.8, 52.1*, 52.1*, 25.7, 25.2; **IR** (film, cm^{-1}) 3458, 2952, 1710, 1590, 1509, 1493, 1330, 1250; **TLC** R_f = 0.12 (7:3 hexanes:EtOAc v/v); **HPLC** 98:2 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 35.9 min, 38.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{14}H_{15}NO_6$ 239.0899, found 239.0898. * denotes presumed rotamers in a 1:1 ratio

Methyl (3R, 6S)-3-hydroxy-6-O-(4-nitrophenoxy)-cyclohex-1-enecarboxylate (2.6f)

$[\alpha]_D^{20.0}$ +37.5 (*c* 0.50, $CHCl_3$) [†]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 – 8.17 (m, 2H), 7.18 (dd, *J* = 2.2, 1.4 Hz, 1H), 7.06 – 7.00 (m, 2H), 5.28 (s, 1H), 4.38 (s, 1H), 3.74 (s, 3H), 2.21 – 2.13 (m, 1H), 2.10 – 2.02 (m, 1H), 1.88 – 1.69 (m, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 165.9, 163.2, 146.7, 141.8, 129.4, 126.2, 115.9, 68.5, 67.6, 52.3, 26.4, 25.6; **IR** (film, cm^{-1}) 3391, 2950, 1708, 1438, 1255, 1041, 756; **TLC** R_f = 0.09 (7:3 hexanes:EtOAc v/v); **HPLC** 98:2 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol for 20.00 minutes then a gradient from 5% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 31.9 min, 34.0 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{14}H_{15}NO_6$ 239.0899, found 239.0895. [†]Analytical standard was obtained as the enantiomer of **2.5f** from the (*R*,*R*)-**L2**.

1,2-product **2.5g** (23.4 mg, 31%, 96:4 e.r.) and 1,4-product **2.6g** (25.8 mg, 34%, 84:16 e.r.) were isolated following general procedure A with recovered epoxide **2.4** (0.4 mg, 1%, 68:32 e.r.). Analytical standards used for the characterization of **2.5g** and **2.6g** were prepared from a separate trial giving enantiomeric ratios of 85:15 and 90:10 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(2,4-dimethylphenoxy)-cyclohex-1-enecarboxylate (2.5g)

$[\alpha]_D^{20.0}$ -106.6 (*c* 0.75, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.19 – 7.11 (m, 2H), 7.00 – 6.89 (m, 2H), 5.20 (d, *J* = 3.7 Hz, 1H), 3.89 (ddt, *J* = 12.0, 8.0, 3.7 Hz, 1H), 3.57 (s, 3H), 2.62 – 2.47 (m, 1H), 2.41 – 2.31 (m, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 2.07 – 1.96 (m, 1H), 1.93 – 1.83 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.7, 155.6, 143.8, 131.5, 131.0, 129.8, 127.7, 127.3, 115.7, 73.6, 69.6, 51.8, 25.4, 25.4, 20.7, 16.6; **IR** (film, cm^{-1}) 3434, 2949, 1716, 1489, 1250, 1217, 1042; TLC R_f = 0.50 (7:3 hexanes:EtOAc v/v); **HPLC** 85:15 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T= 3.7 min, 4.2 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{16}H_{20}O_4$ 276.1362, found 276.1357.

Methyl (3R, 6S)-3-hydroxy-6-O-(2,4-dimethylphenoxy)-cyclohex-1-enecarboxylate (2.6g)

$[\alpha]_D^{20.0}$ -19.4 (*c* 0.50, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.10 (dd, *J* = 2.2, 1.3 Hz, 1H), 7.03 – 6.92 (m, 3H), 5.09 (br s, 1H), 4.39 – 4.27 (m, 1H), 3.74 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H), 2.13 –

2.06 (m, 1H), 2.05 – 1.96 (m, 1H), 1.93 – 1.78 (m, 1H), 1.65 – 1.58 (dt, *J* = 13.9, 3.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.4, 154.1, 145.3, 131.5, 130.8, 130.4, 128.0, 127.1, 114.3, 68.7, 67.8, 52.0, 26.6, 25.6, 20.5, 16.5; **IR** (film, cm^{-1}) 3415, 2949, 1719, 1499, 1250, 1219, 1032; **TLC** R_f = 0.40 (7:3 hexanes:EtOAc v/v); **HPLC** 90:10 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:methanol. Retention times: R_T= 4.2 min, 5.0 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{16}H_{20}O_4$ 276.1362, found 276.1367.

1,2-product **2.5h** (21.5 mg, 31%, 90:10 e.r.) and 1,4-product **2.6h** (24.5 mg, 34%, 91:9 e.r.) were isolated following general procedure A with recovered epoxide **2.4** (9.2 mg, 23%, 52:48 e.r.). Analytical standards used for the characterization of **2.5h** and **2.6h** were prepared from a separate trial giving enantiomeric ratios of 90:10 and 92:8 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(3,5-dimethylphenoxy)-cyclohex-1-enecarboxylate (2.5h)

$[\alpha]_D^{20.0}$ -93.3 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.15 (dd, *J* = 4.7, 3.0 Hz, 1H), 6.77 (s, 2H), 6.63 (s, 1H), 5.26 (d, *J* = 3.7 Hz, 1H), 3.90 (ddt, *J* = 12.3, 8.2, 3.7 Hz, 1H), 3.64 (s, 3H), 2.53 (dtd, *J* = 20.0, 5.2, 3.0 Hz, 1H), 2.33 (dddd, *J* = 9.7, 6.4, 3.1, 1.1 Hz, 1H), 2.28 (s, 6H), 2.02 – 1.92 (m, 1H), 1.90 – 1.82 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.6, 159.6, 143.9, 139.3, 129.4, 123.8, 114.9, 72.8, 69.5, 51.9*, 51.9*, 25.4, 25.2, 21.6; **IR** (film, cm^{-1}) 3434, 2949, 1714, 1590, 1293, 1246, 1150, 1039, 755; **TLC** R_f = 0.53 (7:3 hexanes:EtOAc v/v); **HPLC** 90:10 e.r., Chiral HPLC eluting at 1.25 mL/min with 97% hexanes:methanol. Retention times: R_T= 6.0 min, 6.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{16}H_{20}O_4$ 276.1362, found 276.1352. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(3,5-dimethylphenoxy)-cyclohex-1-enecarboxylate (2.6h)

$[\alpha]_D^{20.0}$ -14.0 (*c* 0.75, $CHCl_3$); M.p. 93 – 95 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.10 (dd, *J* = 2.2, 1.4 Hz, 1H), 6.63 (s, 3H), 5.11 (br s, 1H), 4.37 – 4.28 (m, 1H), 3.76 (s, 3H), 2.28 (s, 6H), 2.18 (ddt, *J* = 14.5, 4.0, 2.6 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.86 – 1.78 (m, 1H), 1.58 (dt, *J* = 14.0, 3.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.4, 158.0, 145.7, 139.4, 130.7, 123.4, 114.6, 67.9, 67.8, 52.2, 26.6,

25.3, 21.6; **IR** (film, cm^{-1}) 3408, 2949, 1717, 1590, 1292, 1252, 1150, 1031; TLC R_f = 0.29 (7:3 hexanes:EtOAc v/v); **HPLC** 92:8 e.r., Chiral HPLC eluting at 1.25 mL/min with 90% hexanes:isopropanol. Retention times: R_T= 3.6 min, 4.2 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{16}H_{20}O_4$ 276.1362, found 276.1370.

1,2-product **2.5i** (25.8, 33%, 84:16 e.r.) and 1,4-product **2.6i** (25.7 mg, 33%, 84:16 e.r.) were isolated following general procedure A with no recovered epoxide **2.4.** Analytical standards used for the characterization of **2.5i** and **2.6i** were prepared from a separate trial giving enantiomeric ratios of 89:11 and 97:3 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(2-naphthoxy)-cyclohex-1-enecarboxylate (2.5i)

$[\alpha]_D^{20.0}$ -124.3 (*c* 2.00, $CHCl_3$); M.p. 82 – 86 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.78 – 7.74 (m, 3H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.8, 1.3, 1H), 7.34 (ddd, *J* = 8.2, 6.8, 1.2, 1H), 7.30 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.19 (dd, *J* = 4.8, 3.0 Hz, 1H), 5.44 (d, *J* = 3.6 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.58 (s, 3H), 2.62 – 2.50 (m, 1H), 2.40 – 2.27 (m, 1H), 2.07 – 1.97 (m, 1H), 1.94 – 1.85 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 157.5, 144.2, 134.6, 129.6, 129.5, 129.2, 127.7, 127.2, 126.4, 124.1, 119.7, 111.4, 73.2, 69.6, 51.9, 25.4, 25.4; **IR** (film, cm^{-1}) 3431, 3055, 2949, 1709, 1250, 1212, 1041, 747; **TLC** R_f = 0.29 (7:3 hexanes:EtOAc v/v); **HPLC** 89:11 e.r., Chiral HPLC eluting at 1.25 mL/min with 99% hexanes:isopropanol then a gradient of 1% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 26.2 min, 29.9 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{18}H_{18}O_4$ 298.1205, found 298.1215.

Methyl (3R, 6S)-3-hydroxy-6-O-(2-naphthoxy)-cyclohex-1-enecarboxylate (2.6i)

$[\alpha]_D^{20.0}$ -5.7 (*c* 0.50, $CHCl_3$); M.p. 63 – 66 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 – 7.71 (m, 3H), 7.44 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.34 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.31 (d, *J* = 2.5 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (dd, *J* = 2.2, 1.4 Hz, 1H), 5.30 (t, *J* = 2.9 Hz, 1H), 4.36 (dddd, *J* = 10.5, 6.1, 2.2, 1.1 Hz, 1H), 3.75 (s, 3H), 2.32 – 2.25 (m, 1H), 2.07 – 1.98 (m, 1H), 1.94 – 1.81 (m, 1H), 1.67 (tt, *J* = 14.2, 3.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 155.8, 146.0, 134.6,

130.5, 129.7, 129.5, 127.8, 127.0, 126.4, 124.0, 120.0, 109.9, 68.1*, 68.1*, 67.9, 52.2*, 52.2*, 26.6, 25.2; **IR** (film, cm^{-1}) 3420, 2949, 2359, 1717, 1250, 1214, 1031, 748; **TLC** R_f = 0.18 (7:3 hexanes:EtOAc v/v); **HPLC** 97:3 e.r., Chiral HPLC eluting at 1.25 mL/min with 99% hexanes:isopropanol then a gradient from 1% to 30% isopropanol in hexanes from 20.01 to 40.00 minutes. Retention times: R_T= 31.0 min, 31.5 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{18}H_{18}O_4$ 298.1205, found 298.1194. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2.5j** (27.3 mg, 35%, 80:20 e.r.) and 1,4-product **2.6j** (29.8 mg, 38%, 88:12 e.r.) were isolated following general procedure A with no recovered epoxide **2.4**. Analytical standards used for the characterization of **2.5j** and **2.6j** were prepared from a separate trial giving enantiomeric ratios of 80:20 and 90:10 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(1-naphthoxy)-cyclohex-1-enecarboxylate (2.5j)

$[\alpha]_D^{20.0}$ -123.2 (*c* 0.50, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.19 – 8.13 (m, 1H), 7.83 – 7.77 (m, 1H), 7.49 – 7.39 (m, 5H), 7.24 (dd, *J* = 4.9, 2.9 Hz, 1H), 5.52 (d, *J* = 3.7 Hz, 1H), 3.99 (ddt, *J* = 11.7, 9.8, 3.7 Hz, 1H), 3.44 (s, 3H), 2.69 – 2.58 (m, 1H), 2.47 – 2.33 (m, 1H), 2.21 – 2.09 (m, 1H), 2.01 – 1.93 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 155.3, 144.1*, 144.0*, 134.6, 129.3, 127.6*, 127.6*, 126.5, 126.2*, 126.1*, [126.0, 126.0, 126.0, 125.9] – single carbon signal, 125.3*, 125.3*, 121.8*, 121.8*, 121.4*, 121.3*, 109.3, 73.8*, 73.7*, 69.6, 51.7*, 51.6*, 25.5, 25.4; **IR** (film, cm^{-1}) 3390, 2951, 1709, 1395, 1246, 1235, 1091, 1042, 770; **TLC** R_f = 0.28 (7:3 hexanes:EtOAc v/v); **HPLC** 80:20 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:methanol. Retention times: R_T= 10.7 min, 15.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{18}H_{18}O_4$ 298.1205, found 298.1201. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(1-naphthoxy)-cyclohex-1-enecarboxylate (2.6j)

$[\alpha]_D^{20.0}$ +67.0 (*c* 1.00, $CHCl_3$); M.p. 132 – 135 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.25 – 8.18 (m, 1H), 7.82 – 7.77 (m, 1H), 7.50 – 7.35 (m, 4H), 7.20 (dd, *J* = 2.2, 1.3 Hz, 1H), 7.08 (d, *J* = 7.4, 1H), 5.41 (t, *J* = 3.0 Hz, 1H), 4.42 – 4.35 (m, 1H), 3.70 (s, 3H), 2.30 – 2.22 (m, 1H), 2.07 – 1.87 (m, 2H),

1.68 (dt, *J* = 14.0, 3.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 153.9, 146.0, 134.8, 130.6, 127.6, 126.8, 126.4, 126.0, 125.3, 122.4, 120.9, 107.3, 68.2, 67.9, 52.2*, 52.2*, 26.9, 25.5; **IR** (film, cm^{-1}) 3244, 3052, 2950, 2359, 1717, 1256, 1234, 771; **TLC** R_f = 0.19 (7:3 hexanes:EtOAc v/v); **HPLC** 90:10 e.r., Chiral HPLC eluting at 1.0 mL/min with 98% hexanes:methanol. Retention times: R_T= 7.9 min, 11.6 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{18}H_{18}O_4$ 298.1205, found 298.1207. * denotes presumed rotamers in a 1:1 ratio.

1,2-product **2.5k** (23.1 mg, 29%, 90:10 e.r.) and 1,4-product **2.6k** (18.5 mg, 23%, 95:5 e.r.) were isolated following general procedure A with no recovered epoxide **2.4**. Analytical standards used for the characterization of **2.5k** and **2.6k** were prepared from a separate trial giving enantiomeric ratios of 92:8 and 95:5 respectively.

Methyl (5S, 6R)-5-hydroxy-6-O-(1,3-benzodioxol-5-yl)-cyclohex-1-enecarboxylate (2.5k)

$[\alpha]_D^{20.0}$ +104.4 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.14 (dd, *J* = 4.7, 3.0 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 5.08 (d, *J* = 3.7 Hz, 1H), 3.87 (ddt, *J* = 11.5, 9.2, 3.8 Hz, 1H), 3.65 (s, 3H), 2.52 (dtd, *J* = 20.1, 5.3, 2.8 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.02 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 155.0, 148.2, 144.0, 142.6, 129.3, 109.9, 108.0, 101.4, 100.8, 74.8, 69.6, 51.9*, 51.9*, 25.4, 25.3; **IR** (film, cm^{-1}) 3446, 2950, 2360, 1710, 1480, 1242, 1175, 1035, 746; **TLC** R_f = 0.20 (7:3 hexanes:EtOAc v/v); **HPLC** 92:8 e.r., Chiral HPLC eluting at 1.0 mL/min with 95% hexanes:isopropanol. Retention times: R_T= 20.4 min, 23.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{16}O_6$ 292.0947, found 292.0952.

Methyl (3R, 6S)-3-hydroxy-6-O-(1,3-benzodioxol-5-yl)-cyclohex-1-enecarboxylate (2.6k)

$[\alpha]_D^{20.0}$ -16.7 (*c* 0.75, $CHCl_3$); M.p. 70 – 73 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.09 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.92 (dd, *J* = 1.43, 1.41 Hz, 2H), 4.93 (t, *J* = 2.8 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.78 (s, 3H), 2.21 – 2.10 (m, 1H), 2.04 – 1.97 (m, 1H), 1.91 – 1.76 (m, 1H), 1.54 (tt, *J* = 14.4, 3.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4,

153.4, 148.3, 145.8, 142.6, 130.6, 109.8, 108.2, 101.3, 101.0, 70.2, 67.9, 52.2*, 52.2*, 26.5, 25.2; **IR** (film, cm^{-1}) 3408, 2950, 1715, 1482, 1254, 1177, 1033; **TLC** R_f = 0.14 (7:3 hexanes:EtOAc v/v); **HPLC** 95:5 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes:isopropanol. Retention times: R_T= 8.9 min, 12.4 min; **HRMS** (EI^+) *m/z* Calc'd for $C_{15}H_{16}O_6$ 292.0947, found 292.0935. * denotes presumed rotamers in a 1:1 ratio.

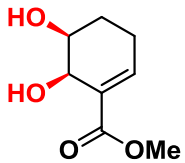
(*5R-6S*)-Methyl-5,6-dihydroxycyclohex-1-ene carboxylate (2.7): To a solution of **2.5b** (129.0 mg, 0.464 mmol, 1.0 equiv., 78:22 e.r.) in dichloromethane (4.5 mL) was added DMAP (5.0 mg, 0.041 mmol, 0.09 equiv.), imidazole (63.1 mg, 0.464 mmol, 1.0 equiv.), and TBSCl (140.0 mg, 0.183 mmol, 1.0 equiv.). Upon completion, the reaction was concentrated *in vacuo* and purified via flash chromatography (2:1 hexanes/EtOAc, v/v) to yield 167.6 mg (43% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 (m, 1H), 7.10 (m, 2H), 6.60 (m, 2H), 5.03 (d, *J* = 2.9 Hz, 1H), 3.81 (dt, *J* = 11.9, 3.5 Hz, 1H), 3.75 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.51 (m, 1H), 2.3 (m, 1H), 2.18 (m, 1H), 1.68 (m, 1H), 0.71 (s, 9H), -0.01 (s, 3H), -0.14 (s, 3H).

The protected alcohol above (167.6 mg, 0.427 mmol, 1.0 equiv.) was suspended in 1.0 mL MeCN and 1.0 mL H_2O. The reaction was cooled to 0 °C and ceric ammonium nitrate (538.4 mg, 0.982 mmol, 2.3 equiv.) was added in one portion. The reaction was stirred at 0 °C for 5 minutes and then passed through a plug of silica (eluting with EtOAc) and concentrated. The residue was purified by flash chromatography (1:1 hexanes/EtOAc, v/v) to yield 40.0 mg of product (33 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 4.8, 2.9 Hz, 1H), 4.45 (d, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 7.76 (m, 1H) 2.81 (d, *J* = 1.6 Hz, 1H), 2.41 (dtd, *J* = 20.1, 5.4, 2.2 Hz, 1H), 2.30 – 2.11 (m, 1H), 1.97 – 1.77 (m, 1H), 1.62 (m, 1H), 0.92 (s, 9H), 0.11 (s, 6H).

To the alcohol above (40 mg, 0.140 mmol, 1.0 equiv.) in THF (1.0 mL), was added TBAF (14.0 μL, 0.14 mmol, 1.0 equiv, 1M in THF) at 0 °C. The reaction was warmed to 23 °C and stirred. Upon completion, the reaction was concentrated and purified by flash chromatography (1:1

hexanes/EtOAc, v/v) to yield 11.0 mg (45% yield) of **2.7** as a colorless oil and compared to authentic spectra of the known compound.[4]

Methyl (*5S*, *6R*)-5,6-dihydroxycyclohex-1-enecarboxylate (2.7)



2.7

[α]$_D^{20.0}$ -48.0 (*c* 1, $CHCl_3$, 78:22 e.r.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 3.9 Hz, 1H), 4.53 (bs, 1H), 3.84 (m, 1H), 3.53 (d, *J* = 3.0 Hz, 1H), 2.43 (m, 1H), 2.21 (m, 1H), 1.85 (m, 1H), 1.70 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.34, 143.34, 129.90, 67.72, 65.37, 51.81, 24.79, 23.95; **TLC** R_f = 0.10 (1:1 hexanes/EtOAc v/v).

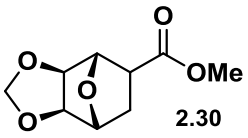
Literature (*Org. Biomol. Chem.* **2009**, 7, 2619)[9]: **[α]$_D^{20.0}$** -52.9 (c 2.9, >99:1 e.r.); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.02 (dd, J = 4.4, *J* = 3.3 Hz, 1H), 4.46 (d, *J* = 3.1 Hz, 1H), 4.05 (s, 1H), 3.70 (m, 4H), 3.52 (s, OH), 2.42-2.30 (m, 1H), 2.21-2.09 (m, 1H), 1.18-1.61 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2, 143.3, 130.4, 68.5, 64.8, 51.8, 24.7, 24.2; **TLC:** R_f = 0.29 (1:1 hexanes/EtOAc v/v).

Diol **2.9** was synthesized according to modified literature procedures.[5]

A flamed dried round bottom flask was charged with methyl acrylate (70.0 mL) and cooled to -20 °C. $AlCl_3$ (3.5 g) was then added portionwise followed by the dropwise addition of furan (60 mL). Once the addition was complete (0.5 h), the reaction was warmed to 23 °C and stirred for 5 h. Water (20 mL) was added and the layers separated and the organic layer was concentrated. The red oil was diluted with CH_2Cl_2, dried over Na_2SO_4 and concentrated to yield a red oil which was used without further purification.

The red oil (57.0 g) from above was dissolved in 1.5 L of acetone and 140.0 mL of water. NMO (112.6 g total weight of solution, 50% in water) was added followed by the addition of OsO_4 (12.0 mL, 185 mmol, 0.5mol%, 0.15 M in CH_2Cl_2). The reaction was stirred for 48 hours or until starting material disappeared. Sodium sulfite (20.0 g) was then added to the reaction and stirred for 0.5 h before the solvent was removed under reduced pressure. The resulting oil was dissolved in a

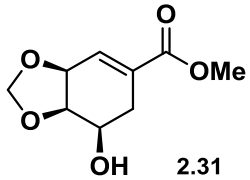
minimal amount (ca. 15 mL) of EtOAc and cooled to 0 °C. The precipitate was collected and washed with Et_2O. This procedure was repeated to yield 40.0 g of diol whose spectra agreed with known data.[5]



2.30

The diol above **(**7.0 g, 37.5 mmol) was dissolved in a solution of $CH_2(OMe)_2$ (60.0 mL) and CH_2Cl_2 (65.0 mL) and was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (18.0 mL, 0.106mol, 3 equiv) in CH_2Cl_2 (65.0 mL) was added dropwise via an addition funnel over 0.5 h. The reaction was then stirred for 0.5 h at 0°C and then diluted with water (20.0 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to yield a black oil which was purified by flash chromatography (1:1 EtOAc/hexanes, v/v) to yield 6.67 g (33.1 mmol, 88% yield) as a mixture of endo and exo isomers of **2.30** (the isomers can be separated using flash chromatography [2:1 hexanes/EtOAc, v/v]).

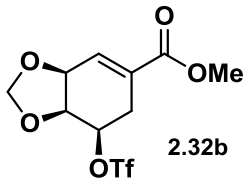
Endo (major) Isomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.06 (d, *J* = 1.0 Hz, 1H), 4.77 (d, *J* = 1.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 1H), 4.22 (s, 2H), 3.69 (s, 3H), 2.95 (dt, *J* = 11.3, 5.5 Hz, 1H), 1.90 (dddd, *J* = 12.6, 11.4, 6.0, 1.1 Hz, 1H), 1.72 (ddd, *J* = 13.1, 5.2, 1.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.9, 97.0, 81.9, 81.0, 80.2, 79.4, 52.3, 43.3, 27.6; **IR** (film, cm^{-1}) 2955, 1729, 1200, 1048; **TLC** R_f = 0.80 (2:1 EtOAc/hexanes, v/v); **HRMS** (DART) *m/z* calc for $C_9H_{12}O_5$ $(M+H)^+$: 201.0757, found 201.0752.



2.31

A solution of HMDS (8.5 mL, 39.0 mmol, 1.2 equiv.) in dry THF (150.0 mL) is cooled to -78 °C and *n*-BuLi (23.3 mL, 37.3 mmol, 1.1eq, 1.6M in hexanes) is added slowly. The reaction is stirred for 20 minutes at -78 °C before **2.30** (6.70 g, 33.9 mmol) in THF (50.0 mL) is added via cannula in one portion. After stirring for 20 minutes the flask is allowed to warm to 0 °C where it is promptly quenched with water (10.0 mL) and extracted with EtOAc (2 x 20.0 mL). Drying over Na_2SO_4, concentration *in vacuo* and flash chromatography (1:1 hexanes/EtOAc, v/v) yielded an amber oil (6.2 g, 31 mmol, 91%).

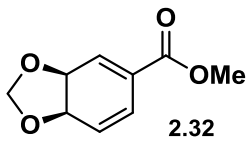
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 1H), 4.96 (s, 1H), 4.95 (s, 1H), 4.72 (bs, 1H), 4.22 (dd, *J* = 6.2, 2.7 Hz, 1H), 3.93 (m, 1H), 3.73 (s, 3H), 2.72 (d, *J* = 6.2 Hz, 1H), 2.61 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.41 (dd, *J* = 16.9, 9.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 132.9, 131.3, 95.0, 75.6, 72.7, 67.1, 52.2, 27.9; **IR** (film, cm^{-1}) 3452, 2952, 1713, 1436, 1241, 1049, 728; **TLC** R_f = 0.45 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* calc for $C_9H_{12}O_5$ $(M+H)^+$: 201.0757, found 201.0753.



2.32b

2.31 (9.553g, 47.7 mmol) is dissolved in CH_2Cl_2 (230.0 mL) and cooled to 0 °C. Pyridine (7.60 mL, 95.5 mmol, 2 equiv.) is added followed by the dropwise addition of Tf_2O (9.60 mL, 57.3 mmol, 1.1 equiv) in CH_2Cl_2 (25.0 mL). The reaction is stirred at 0°C for 20 minutes and then rapidly washed with 1M HCl (2 x 10 mL), dried over Na_2SO_4 and concentrated. Purification via flash chromatography (1:1 hexanes/EtOAc, v/v) yields unstable triflate (12.4 g, 38.5 mmol, 80% yield) as a pale oil.

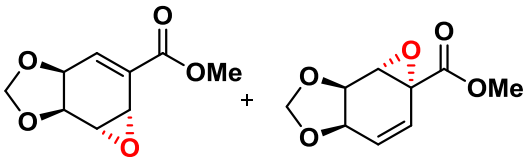
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (m, 1H), 5.16 (ddd, *J* = 8.2, 5.0, 2.6 Hz, 1H), 5.06 (s, 1H), 5.05 (s, 1H), 4.84 (m, 1H), 4.39 (dd, *J* = 5.7, 2.3 Hz, 1H), 3.80 (s, 3H), 2.91 (ddt, *J* = 17.0, 8.7, 2.2 Hz, 1H), 2.82 (dd, *J* = 17.1, 5.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.5, 133.0, 129.6, 122.4, 119.8, 117.3, 114.8, 95.9, 82.8, 73.1, 72.9, 52.7, 25.9; **IR** (film, cm^{-1}) 2957, 1719, 1657, 1409, 1268, 1141, 913; **TLC** R_f = 0.75 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* calc for $C_{10}H_{11}F_3O_7S$: 333.0150 $(M+H)^+$, found 333.0241.



2.32

Triflate, **2.32b** (2.80 g, 8.6 mmol) is dissolved in DMF (40.0 mL) and anhydrous CsOAc (1.73 g, 10.1 mmol, 1.05 equiv.) is added in one portion. The reaction is stirred for 1.75 h. Saturated $NaHCO_3$ (50.0 mL) is added carefully and the organic layer is extracted with Et_2O (2 x 50.0 mL) and washed (2 x 100.0 mL) with brine. Drying over Na_2SO_4 and concentration under reduced pressure yields unstable diene **2.32** as white needles which were sufficiently pure for the next step. Analytical samples were purified by flash chromatography (5:1 Et_2O/pentane, v/v) to yield a white powder.

M.p. 55-57 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 3.8 Hz, 1H), 6.55 (d, *J* = 10.0 Hz, 1H), 6.03 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 4.72 (dd, *J* = 9.3, 3.8 Hz, 1H), 4.55 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.87 (s, 3H); **^{13}CNMR** (126 MHz, $CDCl_3$) δ 165.6, 132.0, 127.7, 124.6, 122.9, 91.0, 69.9, 69.6, 52.2; **IR** (film, cm^{-1}) 2851, 1717, 1441, 1250, 1089; **HRMS** (DART) *m/z* calc for $C_9H_{10}O_4$: 183.0652 $(M+H)^+$, found 183.0649.



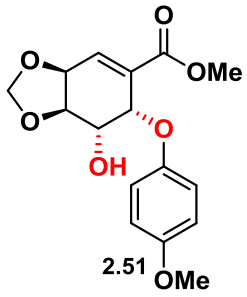
2.33 **2.34**

To a flame dried round bottom flask was added crude diene **2.33** (2.5 g, 13.7 mmol) in CH_2Cl_2 (60.0 mL). *m*-CPBA (3.50 g, 15.1 mmol, 1.1 equiv., 75%) in CH_2Cl_2 (40.0 mL) was then added dropwise and the reaction heated to 40 °C for 18 h. The reaction was cooled and washed with saturated sodium thiosulfate (30.0 mL) and saturated sodium bicarbonate (2 x 30.0 mL), dried over Na_2SO_4 and concentrated. The oil obtained was purified by flash chromatography (9:1 hexanes/EtOAc, v/v) to yield 1.30 g (6.54 mmol, 24% yield) of a 2:1 ratio of inseparable epoxides.

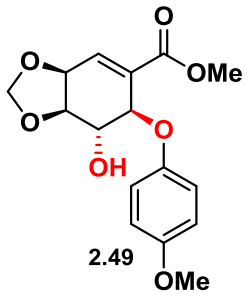
Based on analysis of the ^{1}H NMR and literature precedence, the ^{1}H NMR for both **2.33** and **2.34** can be determined, the ^{13}C NMR however is a mixture of the two compounds and is consistent with literature[2,3]: **^{1}H NMR (2.34)** (500 MHz, $CDCl_3$) δ 6. 76 (bs, 1H), 4.96 (s, 1H), 4.90z (m, 1H), 4.60 (m, 2H), 3.94 (dd, *J* = 3.9, 1.7 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 3.7, 1.5 Hz, 1H); **^{1}H NMR (2.33)** (500 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 10.6, 1.6 Hz, 1H), 5.80 (dd, *J* = 10.5, 2.6 Hz, 1H), 4.96 (s, 1H), 4.86 (s, 1H), 4.60 (m, 1H), 4.52 (m, 1H), 3.89 (d, *J* = 1.8 Hz, 1H), 3.78 (s, 3H); **^{13}C NMR (2.33 & 2.34)** (75 MHz, $CDCl_3$) δ 168.7, 165.2, 137.7, 129.7, 129.4, 124.4, 95.3, 94.7, 70.4, 70.4, 70.1, 69.9, 55.0, 53.1, 52.4, 51.6, 49.3, 45.9; **TLC** R_f = 0.40 (4:1 hexanes/EtOAc, v/v).

Kinetic Addition of *p*-OMePhOH:1.07 g (5.43 mmol, 1.0 equiv.) of a mixture containing racemic epoxide **2.33** and **2.34** (2:1 by ^{1}H NMR respectively) was dissolved in 24.0 mL of toluene in a flame-dried round bottom flask outfitted with a septum followed by the addition of 826.6 mg (6.66 mmol, 1.2 equiv.) of *p*-methoxyphenol. The resulting solution was thoroughly degassed with argon. In a separate round bottom flask, 248.9 mg (5 mol%) of $Pd_2(dba)_3$ and 651.1 mg (15 mol%) of

DPEN-ligand **5**[3] was dissolved in 12.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then added to the epoxide solution via syringe. The reaction was allowed to stir for 18 hours before an additional 249.3 mg (5 mol%) $Pd_2(dba)_3$ and 649.1 mg (15 mol%) of **L2**[3] dissolved and degassed in 12.0 mL of toluene was added. (0.174 mmol, 0.6 equiv.) of phenol was added and the solution purged with argon. The reaction was stirred for an additional 12 hours at room temperature before being concentrated. The crude oil was then purified by column chromatography (4:4:1 DCM/hexanes/EtOAc) to give 169.0 mg of 1,4-product **2.50** (14% yield) and a mixture of 1,2-products **2.49** and **2.51** as a pale yellow oil. The 1,2-products where then separated by column chromatography (95:5 CH_2Cl_2/ether) to give 185.5 mg of *syn*-1,2-product **2.51** (16% yield) and 254.8 mg of *anti*-1,2-product **2.49** (22% yield) as pale yellow oils.

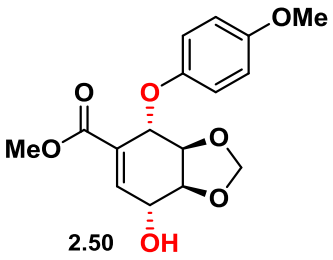


$[\alpha]_D^{20.0}$ +96.6 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$ δ 7.05 – 6.99 (m, 3H), 6.84 – 6.78 (m, 2H), 5.23 (d, *J* = 3.2 Hz, 1H), 5.12 (s, 1H), 5.01 (s, 1H), 4.85 (dd, *J* = 7.0, 3.1 Hz, 1H), 4.53 (dd, *J* = 7.7, 7.2 Hz, 1H), 3.92 (dd, *J* = 7.8, 3.3 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 155.0, 152.3, 137.6, 132.1, 118.9, 114.5, 94.8, 75.9, 74.6, 73.1, 70.7, 55.6, 52.3; **IR** (film, cm^{-1}) 3445, 2951, 1721, 1504, 1253, 1211, 1078, 1033; **TLC** R_f = 0.17 (9:1 DCM/Ether v/v); **HPLC** 90:10 e.r., Chiral HPLC eluting at 1.25 mL/min with 95% hexanes/methanol. Retention times: R_T= 58.6 min, 62.9 min; **HRMS** (ESI) *m/z* Calc'd for $C_{16}H_{18}O_7Na$ $(M+Na)^+$ 345.09447, found 345.09426.



$[\alpha]_D^{20.0}$ +11.8 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.10 – 7.03 (m, 2H), 6.91 (d, *J* = 3.8 Hz, 1H), 6.88 – 6.80 (m, 2H), 5.13 (s, 1H), 5.07 (s, 1H), 4.97 (d, *J* = 4.3 Hz, 1H), 4.80 (dd, *J* = 6.4, 3.8 Hz, 1H), 4.34 (dd, *J* = 4.8, 4.7 Hz, 1H), 4.27 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H); **^{13}C**

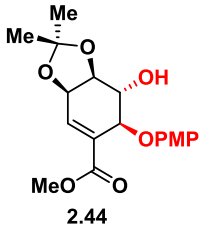
NMR (100 MHz, $CDCl_3$) δ 166.0, 155.0, 152.6, 134.2, 132.5, 119.1, 114.7, 94.8, 75.1, 75.0, 70.8, 68.0, 55.8, 52.3; **IR** (film, cm^{-1}) 3465, 2954, 1719, 1505, 1246, 1214, 104, 1033; **TLC** R_f = 0.28 (9:1 DCM/Ether v/v); **HPLC** 94:6 e.r., Chiral HPLC eluting at 1.00 mL/min with 90% hexanes/isopropanol. Retention times: R_T= 15.6 min, 21.9 min; **HRMS** (ESI) *m/z* Calc'd for $C_{16}H_{18}O_7Na$ $(M+Na)^+$ 345.09447, found 345.0933.



$[\alpha]_D^{20.0}$ +44.5 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 6.4 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.88 – 6.80 (m, 2H), 5.38 (d, *J* = 1.9 Hz, 1H), 4.96 (s, 1H), 4.67 (s, 1H), 4.65 (dd, *J* = 6.9, 2.2 Hz, 1H), 4.55 (d, *J* = 7.0 Hz, 1H), 4.51 – 4.44 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.7, 155.5, 150.5, 143.7, 132.7, 118.5, 114.9, 94.2, 77.2, 74.7, 64.8, 55.7, 52.4; **IR** (film, cm^{-1}) 3490, 2948, 1719, 1505, 1246, 1211, 1089, 1032; **TLC** R_f = 0.27 (7:3 hexanes/EtOAc v/v); **HPLC** 89:11 e.r., Chiral HPLC eluting at 1.00 mL/min with 90% hexanes/isopropanol. Retention times: R_T= 21.4 min, 26.5 min; **HRMS** (ESI) *m/z* Calc'd for $C_{16}H_{18}O_7Na$ $(M+Na)^+$: 345.09447, found 345.09420.

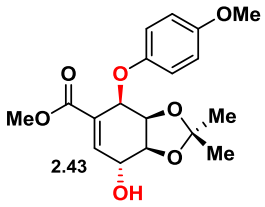
Preparation of (-)-2.43 – from racemic oxide: 876.0 mg (3.87 mmol) of a racemic mixture of **2.28** and **2.28b** (68:32 respectively) was dissolved in 30 mL of toluene with 368.8 mg (2.97 mmol, 1.2 equiv. with respect to epoxide **2.28**) of *p*-methoxyphenol and degassed with argon, then cooled to 0 °C. In a separate flask, 122.6 mg (5 mol%) $Pd_2(dba)_3$ was added to a solution of 312.1 mg (15 mol%) ligand in 15 mL of toluene and degassed with argon until the purple solution became yellow. The solution was then cooled to 0 °C. The Pd solution was then added to the epoxide solution and the resulting yellow solution was warmed to room temperature. After 72 h, an additional 5.0 mL toluene solution containing 63.0 mg (2.5 mol%) $Pd_2(dba)_3$ and 157.6 mg (7.5 mol%) ligand, was added. After an additional 24 h, the reaction was purified by column chromatography (4:1 hexanes/EtOAc v/v) using silica that was previously deactivated with triethylamine to give 183.1 mg

of 1,2-addition product **(-)-2.44** (20% yield) and 22.8 mg (3%) of 1,4-addition product **2.43**. Both products were isolated as pale yellow oils. The recovered epoxide (**2.28** and **2.28b**, 63%) was obtained in 64:36 and 51:49 enantiomeric ratio respectively.



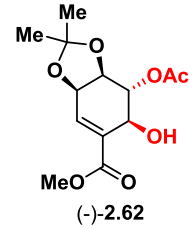
2.44

$[\alpha]_D^{20.0}$ -20.2 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 9.0 Hz, 2H), 6.85 (dd, *J* = 3.8, 1.1 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 4.94 (dd, *J* = 5.3, 1.0 Hz, 1H), 4.75 (ddd, *J* = 6.2, 3.8, 1.1 Hz, 1H), 4.29 (td, *J* = 6.2, 0.7 Hz, 1H), 4.22 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 1.52 – 1.49 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4*, 165.8*, 154.4*, 152.8*, 134.3*, 134.2*, 131.9, 118.2, 114.3, 110.8, 75.8*, 75.7*, 70.8*, 70.7*, 70.0, 55.5*, 55.4*, 51.9*, 51.8*, 27.7, 25.8; **IR** (film, cm^{-1}) 3451, 2967, 2933, 1720, 1504, 1250, 1030; **TLC** R_f = 0.53 (1:1 hexanes/EtOAc v/v); **HPLC** 97:3 e.r., Chiral HPLC eluting at 1.0 mL/min with 90% hexanes/isopropanol. Retention times: R_T= 9.6 min, 22.6 min; **HRMS** (DART) *m/z* Calc'd for $C_{14}H_{16}O_4$ $(M+H)^+$ 350.1366, found 350.1369. *denotes presumed rotamers in a 1:1 ratio.



2.43

$[\alpha]_D^{20.0}$ -141.1 (*c* 1.00, $CHCl_3$); **M.p.** 55–58 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.03 – 6.99 (m, 3H), 6.83 – 6.77 (m, 2H), 5.20 (d, *J* = 3.2 Hz, 1H), 4.97 (dd, *J* = 6.8, 3.1 Hz, 1H), 4.56 (dd, *J* = 7.7, 6.8 Hz, 1H), 3.92 (ddd, *J* = 7.6, 6.1, 3.2 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 165.68, 155.10, 152.43, 138.34, 131.39, 119.02, 114.57, 110.28, 76.18, 74.73, 72.73, 72.01, 55.71, 52.35, 27.66, 25.29; **IR** (film, cm^{-1}) 3340, 2934, 1720, 1505, 1211, 1054; **TLC** R_f = 0.23 (7:3 hexanes/EtOAc v/v); **HRMS** (DART) *m/z* Calc'd for $C_{18}H_{23}O_7$: 351.1444 $(M+H)^+$, found 351.1441.



(-)-2.62

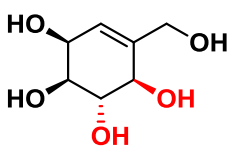
Preparations of 2.43 from (-)-2.28 – enantiopure augmentation: 244.9 mg (0.99 mmol, 1 equiv) of a mixture containing enantiopure epoxide **2.28** and **2.28b** (68:32 respectively) was dissolved in 6.0 mL of toluene. 161.5 mg (1.30 mmol, 1.3 equiv.) of *p*-methoxyphenol was added and the resulting pale yellow solution

was degassed thoroughly with argon. In a separate flask, 50.2 mg (5 mol%) of $Pd_2(dba)_3$ and 129.4 mg (15 mol%) ligand were added to 4.0 mL of toluene and degassed with argon until the purple solution became yellow. Once yellow, the solution was added via syringe at room temperature to the reaction containing the epoxide. The reaction stirred under inert atmosphere for 24 h before an additional 50.1 (5 mol%) mg $Pd_2(dba)_3$ and 130.3 mg (15% mol) ligand dissolved in 4.0 mL of toluene was added. The reaction stirred for an additional 12 hours before being concentrated to give a yellow oil. The reaction was then purified by column chromatography (4:1 hexanes/EtOAc) to give 112.3 mg (44% yield) of trans-1,4-product **2.44** and 38.0 mg (15% yield) of trans-1,2-product **2.43** with no recovered starting material.

Preparation of streptol from 2.44: To a flame dried round bottom flask was added **(-)-2.44** (135.5 mg, 0.386 mmol, 1.0 equiv., 96:4 e.r.), diisopropylethylamine (134.0 μL, 0.77 mmol, 2.0 equiv.), DMAP (2.00 mg), and acetic anhydride (730.0 μL, 0.77 mmol, 2.0 equiv.) in dichloromethane (2.0 mL). The reaction was stirred for 30 minutes until completion and then passed through a plug of silica gel (eluting with 1:1 hexanes/EtOAc, v/v) to obtain 122.0 mg acetylated product which was used without further purification.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 9.1 Hz, 2H), 6.98 (m, 1H), 6.82 (d, *J* = 9.1 Hz, 2H), 5.56 (dd, *J* = 4.7, 3.7 Hz, 1H), 4.97 (d, J = 3.53 Hz, 1H), 4.76 (ddd, *J* = 6.0, 3.6, 0.9 Hz, 1H), 4.33 (t, *J* = 5.3 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 1.98 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H).

The acetylated product (61.1 mg, 0.312 mmol, 1 equiv.) was dissolved in 1.60 mL MeCN:H_2O (3:1) and cooled to 0 °C open to air. Ceric ammonium nitrate (358.3 mg, 0.653 mmol, 2.1 equiv.) was added in one portion and the reaction stirred for 20 minutes. Upon completion, water (2 mL) was added and the solution was extracted with chloroform (2 x 5 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:1 dichloromethane/EtOAc, v/v) to yield 43.0 mg (40% yield from (-)-**2.44**) of **2.62** as a yellow oil.



2.58
(-)-streptol

[α] $^{20.0}_{D}$ +8.33 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.85 (d, *J* = 3.4 Hz, 1H), 5.44 (dd, *J* = 5.1, 3.9 Hz, 1H), 4.69 (dd, *J* = 5.3, 3.4 Hz, 1H), 4.45 (dd, *J* = 8.9, 3.9 Hz, 1H), 4.36 (t, *J* = 5.1 Hz, 1H), 3.79 (s, 3H), 3.28 (d, *J* = 8.9 Hz, 1H), 2.04 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.6, 166.3, 135.4, 131.6, 111.4, 732.0, 71.4, 70.4, 64.7, 52.4, 28.0, 26.3, 21.0. **IR** (film, cm^{-1}) 3517, 2987, 1720,1372, 1210, 1024; **TLC** R_f = 0.5 (3:1 CH_2Cl_2/EtOAc, v/v); **HRMS** (ESI^+) *m/z* Calc'd for $C_{14}H_{16}O_4$ 287.1131, found 287.1125.

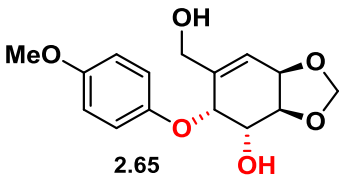
(-)-streptol (2.58). To a flame dried round bottom flask was added 43.0 mg of **2.62** (0.150 mmol, 1 equiv.) under argon. The reaction was cooled to 0 °C and $LiAlH_4$ (24.0 mg, 0.631 mmol, 4.2 equiv.) was added in three portions. The reaction was allowed to stir at 0 °C for 45 minutes until complete. 25.0 µL water was then added followed sequentially by 25 µL of 1M NaOH and 75.0 µL of water. The solution was allowed to stir for 5 minutes. The solid was filtered off and washed with 3 mL of THF. The filtrates were combined and concentrated to yield the reduced triol (30.0 mg) that was used without further purification.

The triol was dissolved in 0.70 mL MeOH and 10.0 µL of TFA was added. The reaction was stirred for 2 hours at 40 °C, diluted with 1 mL of toluene and concentrated to yield 14.6 mg (55% yield from **19**) of streptol (**2.58**) as a colorless solid.

[α] $^{20.0}_{D}$ -70.6 (c 0.17, H_2O); **^{1}H NMR** (500 MHz D_2O) δ 5.84 (dd, *J* = 5.5, 1.7 Hz, 1H), 4.27 (t, *J* = 4.8 Hz, 1H), 4.23 (d, *J* = 14.2 Hz, 1H), 4.14 (d, *J* = 14.1 Hz, 1H), 4.07 (d, *J* = 7.6 Hz, 1H), 3.69 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.57 (dd, *J* = 10.7, 4.2 Hz, 1H). **^{13}C NMR** (126 MHz, D_2O) δ 142.1, 122.1, 72.5, 72.2, 70.6, 66.1, 61.2. **IR** (film, cm^{-1}) 3298, 2906, 1671, 1374, 1008, 878, 824. **HRMS** (ESI^+) *m/z* Calc'd for $C_7H_{12}O_5Na$, 199.0582, found 199.0581.

Preparation of streptol and Mk6707 from dioxolane: 2.51 (70.0 mg, 0.217 mmol) was dissolved in dichloromethane (1.0 mL) and cooled to -78 °C under argon. DIBAl-H (700 µL, 0.694

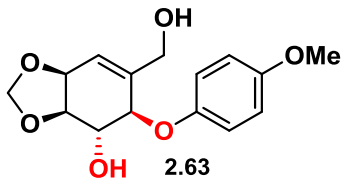
mmol, 3.2 equiv., 1M in CH_2Cl_2) was added dropwise over 5 minutes. The reaction was stirred for 0.5 h at -78 °C and quenched with methanol. The reaction was warmed to room temperature and 2.0 mL of a 1:1 solution of 30% sodium potassium tartrate and a 30% aqueous ethanolamine were added and stirred for 1 h. The now clear solution was extracted with hot EtOAc (5 x 2.0 mL), washed with cold 1M HCl (1.0 mL), dried over Na_2SO_4 and concentrated. Flash chromatography (1:1 hexanes/EtOAc, v/v) yielded 20.0 mg (0.068 mmol, 28% yield) of **2.65**.



2.65

$[\alpha]_D^{20.0}$ +45.5 (*c* 1.00, $CHCl_3$); **M.p.** 109-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 5.92 (d, *J* = 3.5 Hz, 1H), 5.04 (s, 1H), 4.96 (s, 1H), 4.85 (d, *J* = 3.4 Hz, 1H), 4.72 (t, *J* = 5.0 Hz, 1H), 4.37 (t, *J* = 6.2 Hz, 1H), 4.23 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.18 (d, *J* = 6.4 Hz, 1H), 3.77 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.3, 152.1, 140.0, 122.1, 118.6, 115.0, 94.6, 76.0, 75.5, 72.4, 69.5, 63.9, 55.8; **IR** (film, cm^{-1}) 3330, 1608, 1214, 1184, 811; **TLC** R_f = 0.20 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* calc for $C_{15}H_{22}NO_6$ $(M+NH_4)^+$ 312.1447, found 312.1432.

2.48 (55.0 mg, 0.171 mmol) was converted to **2.63** (19.0 mg, 0.065mmol, 38 % yield) in the same manner as above.

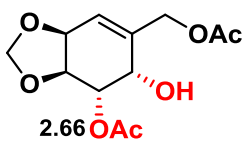


2.63

$[\alpha]_D^{20.0}$ -42.0 (*c* 1.00, $CHCl_3$); **M.p.** 109–112 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.03 (m, 2H), 6.83 (m, 2H), 5.98 (dq, *J* = 3.3, 1.5 Hz, 1H), 5.22 (s, 1H), 5.03 (s, 1H), 4.75 (ddd, *J* = 8.4, 2.3, 1.2 Hz, 1H), 4.51 (ddd, *J* = 6.9, 3.6, 1.5 Hz, 1H), 4.27 (m, 2H), 4.24 (dd, *J* = 8.6, 6.8 Hz, 1H), 3.96 (td, *J* = 8.5, 2.6 Hz, 1H), 3.77 (s, 3H), 3.48 (s, 1H), 2.56 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9, 153.5, 143.1, 119.7, 117.6, 115.0, 95.4, 79.7, 76.8, 72.9, 72.5, 62.8, 55.8; **IR** (film, cm^{-1}) 3310, 33239, 2926, 1506, 1210; **TLC** R_f = 0.30 (2:1 EtOAc/hexanes, v/v); **HRMS:** (DART) *m/z* calc for $C_{15}H_{22}NO_6$ $(M+NH_4^+)$ 312.1447, found 312.1437.

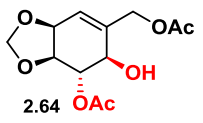
2.65 10.0mg, 0.034mmol) was dissolved in 0.30mL CH_2Cl_2. $^{i}Pr_2NEt$ (17.0 µL, 0.102 mmol, 3 equiv.), DMAP (2.0 mg) and Ac_2O (10 µg, 0.102 mmol, 3equiv.) was added and stirred for 0.5 h. The reaction was diluted with saturated sodium bicarbonate solution (1.0 mL) and extracted with EtOAc (2 x 2.0 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated to yield diacetate that was used without further purification.

The diacetate from above (11.5 mg, 0.030 mmol) was dissolved in 4:1 MeCN/H_2O (0.15 mL) and cooled to 0 °C. To this was added ceric ammonium nitrate (36.6 mg, 0.067 mmol, 2.2 equiv.) and the reaction stirred for 15 minutes. The solution was washed with saturated sodium bicarbonate (1.0 mL) and extracted with EtOAc (2 x 2.0 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc to 1:1 hexanes/EtOAc, v/v) yielded 2.0 mg (0.007 mmol, 21% yield over two steps) of **2.66**.



$[\alpha]_D^{20.0}$: +52.5 (*c* 0.20, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.10 (m, 1H), 5.09 (s, 1H), 4.96 (s, 1H), 4.68 (q, *J* = 13.6 Hz, 2H), 4.60 (m, 1H), 4.48 (dd, *J* = 8.1, 6.5 Hz, 1H), 4.38 (t, *J* = 3.8 Hz, 1H), 2.17 (s, 3H), 2.11 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ^{13}170.9, 170.7, 137.6, 124.4, 94.8, 77.4, 72.9, 72.6, 66.0, 64.7, 21.3, 21.0; **IR** (film, cm^{-1}) 3229, 1615, 1505, 1230; **TLC** R_f = 0.33 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* calc for $C_{12}H_{27}O_7$ $(M+H)^+$: 273.0974, found 273.0964.

2.63 (20.0 mg, 0.068 mmol) was converted to **2.64** (9.0 mg, 0.033 mmol, 48.5 % yield) in the same manner as above.

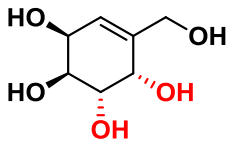


$[\alpha]_D^{20.0}$: -2.5 (*c* 0.90, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.17 (m, 1H), 5.15 (s, 1H), 5.01 (s, 1H), 4.83 (d, *J* = 13.7 Hz, 1H), 4.65 (d, *J* = 13.7 Hz, 1H), 4.54 (m, 1H), 4.25 (t, *J* = 6.8 Hz, 1H), 4.15 (d, *J* = 6.9 Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.3, 170.9, 139.2, 121.1, 95.2, 74.1, 72.9, 72.4, 68.3, 63.8, 21.2,

21.0; **IR** (film, cm^{-1}) 3466, 2922, 1738, 1227, 1040; **TLC** R_f = 0.39 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* calc for $C_{12}H_{27}O_7$ $(M+H)^+$: 273.0974, found 273.0964.

A round bottom flask was charged with **2.66** (5.8 mg, 0.021 mmol) under argon and cooled to 0 °C. Freshly distilled AcCl (0.25 mL) was then added and the solution stirred for 10 minutes at 0 °C. Anhydrous $ZnCl_2$ (ca 1 mg,) was added and the reaction stirred at 0 °C for 0.3 h before being warmed to room temperature and stirred for an additional 0.3 h. Disappearance of nonpolar (high R_f) compound by TLC indicated completion of reaction. The solution was diluted with 1.0 mL THF and concentrated to a third of its volume. Water (0.5 mL) was then added and stirred for 10 minutes. The reaction is then extracted with EtOAc (2 x 3.0 mL), dried over Na_2SO_4 and concentrated. The material is passed through a plug of silica gel (1:1 hexanes/EtOAc, v/v) to yield MK7607-tetracetate (5.5 mg, 0.015 mmol, 70% yield). **^{1}H-NMR (**400 MHz, $CDCl_3$) δ 6.04 (d, *J* = 4.8 Hz, 1H), 5.74 (d, *J* = 4.2 Hz, 1H), 5.50 (dd, *J* = 10.4, 4.2 Hz, 1H), 5.34 (dd, *J* = 10.5, 4.3 Hz, 1H), 4.58 (d, *J* = 13.8 Hz, 1H), 4.56 (m, 1H) 4.50 (d, *J* = 13.8 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H).

The above tetraacetate (5.5 mg, 0.15 mmol) was dissolved in anhydrous methanol (0.10 mL) and cooled to 0 °C. NaOMe in MeOH (15 µL, 0.15 mmol, 1equiv., 1M solution, freshly prepared from Na and MeOH is then added. The reaction was warmed and stirred at room temperature for 12 h. Water (0.1 mL) was added followed by DOWEX 50X2-200 (washed with methanol) until the pH of the solution was 2. After filtration, the solution was concentrated to yield 1.50 mg (0.0085 mmol, 57% yield) of MK7607 (**2.59**).

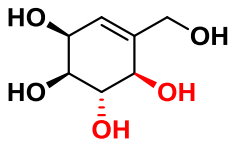


2.59
(+)-MK7607

$[\alpha]_D^{20.0}$ +41.3 (*c* 0.15, H_2O); **^{1}H NMR** (500 MHz D_2O) δ 5.85 (dt, *J* = 5.0, 1.6 Hz, 1H), 4.31 (ddd, *J* = 5.1, 3.2, 2.0 Hz, 1H), 4.24 (d, *J* = 3.6 Hz, 1H), 4.14 (s, 2H), 3.88 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.85 (dd, *J* = 10.4, 3.7 Hz, 1H); **^{13}C NMR** (126 MHz, D_2O) δ 142.2, 126.0, 70.6, 70.3, 68.6, 68.0, 64.0; **IR** (film, cm^{-1}) 3316, 2946,

2833, 1651, 1447, 1258, 1010; **HRMS** (DART) *m/z* calc for $C_7H_{12}O_5$: 177.0763 $(M+H)^+$, found 177.0758.

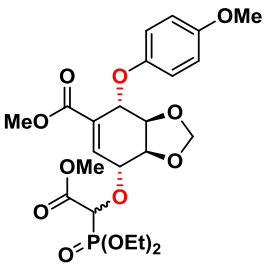
2.64 (9.0 mg, 0.033 mmol) was converted to streptol (**2.58**) (3.1 mg, 0.018 mmol, 55% yield) in the same manner as above.



2.58
(-)-streptol

$[\alpha]_D^{20.0}$ -24.0 (c 0.1, H_2O); **^{1}H NMR** (500 MHz D_2O) δ 5.84 (dd, *J* = 5.5, 1.7 Hz, 1H), 4.27 (t, *J* = 4.8 Hz, 1H), 4.23 (d, *J* = 14.2 Hz, 1H), 4.14 (d, *J* = 14.1 Hz, 1H), 4.07 (d, *J* = 7.6 Hz, 1H), 3.69 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.57 (dd, *J* = 10.7, 4.2 Hz, 1H); **^{13}C NMR** (126 MHz, D_2O) δ 142.1, 122.1, 72.5, 72.2, 70.6, 66.1, 61.2; **IR** (film, cm^{-1}) 3298, 2906, 1671, 1374, 1008, 878, 824; **HRMS** (ESI^+) *m/z* calc for $C_7H_{12}O_5Na$ $(M+Na)^+$, 199.0582, found 199.0581.

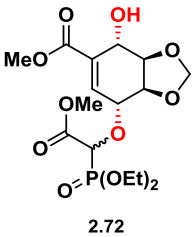
Preparation of Cyathiformine B: 26.3 mg (0.082 mmol, 1 equiv.) of **22** was dissolved in 1.0 mL of DCM. To the clear colorless solution was added a catalytic amount (0.8 mg) of $Rh_2(OAc)_4$ turning the solution a pale green. The solution was heated to 85 °C and a separate solution containing 35.2 mg (0.149 mmol, 1.8 equiv.) of diazophosphate, **23** in 1.5 mL of DCM was added dropwise over 10 minutes. The reaction continued at reflux for 3 h before cooling to room temperature. The reaction was then concentrated and purified by column (2:1 then 1:1 hexanes/EtOAc, v/v) to give 27.9 mg (64%) of a clear colorless oil as a mixture of diastereomers and 3.8 mg (14%) recovered starting material.



2.71

$[\alpha]_D^{20.0}$ -12.3 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.08 (d, *J* = 3.7 Hz, 1H), 7.04 – 6.97 (m, 5H), 6.86 – 6.80 (m, 4H), 5.23 – 5.20 (m, 2H), 5.04 (s, 2H), 4.89 (d, *J* = 19.7 Hz, 1H), 4.82 (d, *J* = 6.3 Hz, 2H), 4.71 (d, *J* = 18.6 Hz, 1H), 4.51 (dd, *J* = 6.2, 4.0 Hz, 1H), 4.47 – 4.41 (dd, *J* = 6.2, 4.2 Hz, 1H), 4.35 (td, *J* = 4.0, 1.1 Hz, 1H), 4.32 – 4.28 (m, 2H), 4.28 – 4.18 (m, 9H), 3.83 (d, *J* = 2.6 Hz, 5H), 3.78 – 3.74 (m, 18H), 1.37 – 1.31 (m, 12H);

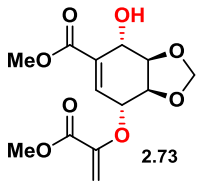
^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 167.9, 165.5, 165.4, 155.0, 151.8, 151.7, 137.6, 137.0, 131.5, 130.8, 118.0, 117.9, 114.8, 94.3, 76.2, 75.9, 75.0, 74.7, 71.3, 71.2, 64.1, 55.8, 53.0, 52.3, 16.6; **IR** (film, cm^{-1}) 2953, 1725, 1506, 1260, 1214, 1024; **TLC** R_f = 0.11, 0.19 (1:2 hexanes/EtOAc, v/v); **HPLC** 86:14 e.r.; **HRMS** (DART) *m/z* Calc'd for $C_{23}H_{32}O_{12}P$ $(M+H)^+$: 531.1626, found 531.1603. Characterization performed on a 1:1 mixture of inseparable diastereomers.



2.72

39.0 mg (0.074 mmol, 1 equiv.) of **2.71** was dissolved in 4.0 mL of 4:1 CH_3CN/H_2O v/v solution. The solution was cooled to 0 °C and ceric ammonium nitrate (88.9 mg, 0.162 mmol, 2.2 equiv.) was added in a single portion. After 5 minutes the solutions had become orange the starting material had been consumed by this time. The reaction was diluted with water and the organics extracted with EtOAc (3 x 7.0 mL). The extracts were dried with Na_2SO_4, filtered, and concentrated. Purification by column (2:1 EtOAc/hexanes, v/v) gave 23.6 mg (76%) of **2.72** as a red oil.

$[\alpha]_D^{20.0}$ -17.8 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.09 (t, *J* = 4.2 Hz, 3H), 5.01 (s, 1H), 4.98 (s, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.70 – 4.63 (m, 2H), 4.57 (d, *J* = 19.0 Hz, 1H), 4.45 (dd, *J* = 7.1, 3.8 Hz, 1H), 4.42 – 4.36 (m, 3H), 4.36 – 4.28 (m, 3H), 4.26 – 4.15 (m, 8H), 3.86 – 3.80 (m, 12H), 1.37 – 1.29 (m, 12H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 168.8, 167.8, 167.3, 165.9, 137.7, 137.3, 136.4, 134.9, 94.4, 94.3, 79.0, 78.9, 76.0, 75.8, 75.7, 75.6, 75.1, 75.0, 66.0, 65.6, 64.1, 64.0, 53.2, 53.1, 52.6, 16.6, 16.5; **IR** (film, cm^{-1}) 3481, 2912, 1723, 1253, 1092, 1021, 980; **TLC** R_f = 0.29 (EtOAc); **HPLC** 87:13 e.r.; **HRMS** (DART) *m/z* Calc'd for $C_{16}H_{19}O_{11}P$ $(M+H)^+$: 425.1207, found 425.1188. Characterization performed on a 1:1 mixture of inseparable diastereomers.

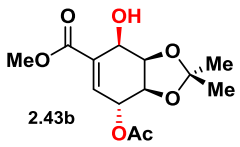


2.73

71.2 mg (0.168 mmol, 1.0 equiv.) of **2.72** was dissolved in 4.0 mL of anhydrous THF and cooled to -78 °C under argon to give a pale yellow solution. Fresh LiHMDS, prepared from the addition of 225.0 µL *n*-BuLi to 75.0 µL of HMDS in 4.0 mL of THF at -78 °C, was add slowly turning the solution brown. The reaction stirred for 0.5 h at -78 °C before the dropwise addition of a 9.0 mL solution of THF containing freshly cracked *p*-

formaldehyde (711.1 mg, 100 equiv.). After stirring at bath temp for 0.3 h, the reaction was transferred to a bath at 0 °C and allowed to stir for 0.5 h, upon which it was quenched with 8.0 mL of a saturated NH_4Cl. The product was extracted in EtOAc (3 x 10.0 mL) and dried with Na_2SO_4. The crude product was filtered though a pad of celite then purified by column (1:1 EtOAc/hexanes, v/v) to give 36.1 mg (71%) of product **2.73** as a yellow oil.

$[\alpha]_D^{20.0}$ -39.9 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.14 (d, *J* = 4.6 Hz, 1H), 5.60 (d, *J* = 3.2 Hz, 1H), 5.04 (s, 1H), 4.93 (d, *J* = 3.3 Hz, 1H), 4.82 (dd, *J* = 4.6, 3.1 Hz, 1H), 4.79 – 4.73 (m, 2H), 4.53 – 4.44 (m, 2H), 3.82 (s, *3*H), 3.80 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 165.8, 163.1, 148.6, 136.8, 136.3, 98.2, 94.4, 78.4, 74.8, 71.4, 65.2, 52.9, 52.6; **IR** (film, cm^{-1}) 3477, 2923, 1721, 1438, 1255, 1168, 1091, 1032; **TLC** R_f = 0.77 (EtOAc); **HPLC** 87:13 e.r.; **HRMS** (DART) *m/z* Calc'd for $C_{13}H_{17}O_8$ $(M+H)^+$: 301.0918, found 301.0903.

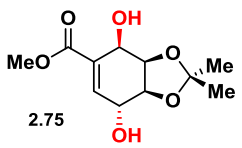


Preparation of Polyporapyranone G and tetraol 2.76: 214.6 mg (0.613 mmol, 1 equiv) of **2.43** was dissolved in 10 mL of anhydrous CH_2Cl_2. 200 µL (2.12 mol, 3.5 equiv) was added followed by 330 µL (1.89mmol, 3.0 equiv) of diisopropylethylamine and 1 mg (cat.) of DMAP. The reaction stirred for 1 h at room temperature before TLC showed consumption of starting material. The reaction was then washed with 2.0 mL of 1M HCl and organic layer separated then dried with $MgSO_4$. Filtration and concentration yielded the crude acetate which was used without further purification. **^{1}H NMR** ($CHCl_3$, 300 MHz) δ 7.15 (d, *J* = 3.3 Hz, 1H), 7.04 – 7.98 (m, 2H), 6.83 – 6.76 (m, 2H), 5.42 (d, *J* = 2.9 Hz, 1H), 5.02 (dd, *J* = 6.7, 3.4 Hz, 1H), 4.91 – 4.77 (m, 2H), 3.78 (d, *J* = 0.6 Hz, 3H), 3.76 (s, 3H), 1.79 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H).

The crude acetate was dissolved in a 10.5 mL of 4:1 CH_3CN/H_2O (v/v) solution. The solution was cooled to 0 °C and 760.0 mg (1.39 mmol, ca 2.1 equiv.) of ceric ammonium nitrate was added in a single portion. After 5 minutes, TLC showed consumption of the starting material. The

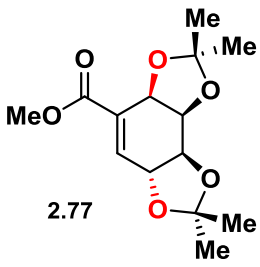
resulting yellow solution was diluted with 10.0 mL of water and the organics extracted with EtOAc (3 x 10.0 mL). The extracts were combined and dried with Na_2SO_4. Filtration and concentration gave the crude product which was purified by column (7:3 hexanes/EtOAc v/v) yielding 78.3 mg (45% over 2 steps) of **2.43b** as a yellow oil.

$[\alpha]_D^{20.0}$ -96.3 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.01 (d, *J* = 3.5 Hz, 1H), 5.02 (dd, *J* = 8.6, 3.4 Hz, 1H), 4.85 (dd, *J* = 6.5, 3.6 Hz, 1H), 4.81 (d, *J* = 3.4 Hz, 1H), 4.56 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.80 (s, 3H), 2.16 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 170.5, 165.8, 136.6, 132.7, 110.5, 73.4, 72.7, 72.3, 64.3, 52.5, 27.6, 25.6, 21.2; **IR** (film, cm^{-1}) 3371, 3072, 2987, 1722, 1237, 1062, 853; **TLC** R_f = 0.29 (7:3 hexanes/EtOAc v/v); **HRMS** (DART) *m/z* Calc'd for $C_{13}H_{19}O_7$ $(M+H)^+$: 287.1125, found 287.1119.



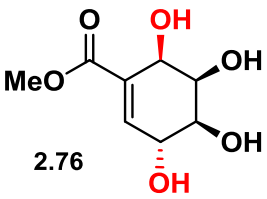
29.0 mg (0.101 mmol, 1 equiv.) of **2.43b** was dissolved in 1.0 mL of anhydrous MeOH under argon and cooled to 0 °C to give a yellow solution. In a separate flask, 7.1 mg (0.309 mmol, 3 equiv.) of sodium metal was added to 1 mL of anhydrous MeOH under argon. This solution was then added dropwise to the solution containing the starting material causing it to brown. After 5 minutes, all the starting material had been consumed and the reaction was acidified to pH = 3 using 1M HCl causing the solution to lighten in color. The product was the extracted with EtOAc (3 x 3 mL) and dried with Na_2SO_4. Filtration and concentration gave 19.7 mg (80%) of the diol (**2.75**) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.91 (d, *J* = 3.5 Hz, 1H), 4.79 (ddd, *J* = 6.0, 3.4, 0.8 Hz, 1H), 4.66 (d, *J* = 3.6 Hz, 1H), 4.43 (t, *J* = 6.2 Hz, 1H), 4.05 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.81 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H).

The crude diol **2.75** was then dissolved in 2.5 mL of anhydrous acetone and 2.5 mL 2,2-dimethoxypropane to give a yellow solution. 900.0 mg (6.34 mmol, excess) of Na_2SO_4 was added and a catalytic amount of *p*-TsOH. The reaction was heated to reflux under N_2 for 1 hour. Once the



starting material was consumed by TLC, the reaction was cooled and washed with a saturated $NaHCO_3$ solution. The product was extracted with DCM (3 x 3.0 mL) and dried with Na_2SO_4. Filtration and concentration gave 17.8 mg (78%) of the product as a yellow oil. No further purification was necessary.

$[\alpha]_D^{20.0}$ +26.8 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 6.72 – 6.70 (m, 1H), 4.96 (d, *J* = 5.6Hz, 1H), 4.69 – 4.64 (m, 2H), 4.58 (ddd, *J* = 4.9, 2.9, 1.3 Hz, 1H), 3.82 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.5, 136.8, 129.1, 109.8, 109.3, 73.6, 72.4, 70.7, 69.2, 52.4, 28.0, 27.7, 26.4, 26.0; **IR** (film, cm^{-1}) 2986, 2934, 1726, 1247, 1059, 851; **TLC** R_f = 0.80 (1:1 hexanes/EtOAc v/v); **HRMS** $[M+H]^+$ *m/z* Calc'd for $C_{15}H_{18}O_5$ 285.1333, found 285.1326.



5.4 mg (0.022 mmol, 1 equiv.) of the crude diol **2.75** was dissolved in 0.5 mL of methanol and 100 µL of water. Trifluoroacetic acid (15 µL, 10 equiv.) was then added. The resulting solution was heated to 40 °C. Once the starting material was consumed by TLC (approx. 7 h), the reaction was diluted with toluene and concentrated to dryness. The resulting film was washed with ether (3 x 1.0 mL) and then dried under vacuum to yield 2.3 mg (51%) of **2.76** as an off-white foam.

$[\alpha]_D^{20.0}$ -193.0 (*c* 0.10, CH_3OH); **^{1}H NMR** (D_2O, 400 MHz) δ 7.00 (d, *J* = 4.9 Hz, 1H), 4.71 (d, *J* = 4.0 Hz, 1H), 4.51 (t, *J* = 4.6 Hz, 1H), 3.98 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.92 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (CD_3OD, 125 MHz) δ 167.9, 139.5, 132.0, 68.2, 67.7, 65.5, 65.5, 52.6; **IR** (film, cm^{-1}) 3285, 2948, 2837, 1651, 1405, 1010; **TLC** (reverse phase) R_f = 0.89 (9:1 H_2O/MeCN v/v); **HRMS** (DART) *m/z* Calc'd for $C_8H_{13}O_6$ $(M+H)^+$: 205.0707, found 205.0709.

Table 2.5: Comparison of natural and synthetic samples

Natural **Streptol**	Current synthesis of **Streptol**
^{1}H NMR (D_2O, 400MHz) [22]	
3.61 (dd *J* = 11, 4 Hz)	3.57 (dd, *J* = 10.7, 4.2 Hz)
3.73 (dd *J* =11, 8 Hz)	3.69 (dd, *J* = 10.7, 7.8 Hz)
4.11 (dq *J* = 8, 1 Hz)	4.07 (d, *J* = 7.6 Hz)
4.17 (d *J* = 14 Hz)	4.14 (d, *J* = 14.1 Hz)
4.26 (dq *J* = 14, 1 Hz)	4.23 (d, *J* = 14.2 Hz)
4.33 (dd *J* = 5, 4 Hz)	4.27 (t, *J* = 4.8 Hz)
5.88 (dq *J* = 5, 1 Hz)	5.84 (dd, *J* = 5.5, 1.7 Hz)
^{13}C NMR (D_2O, 100MHz) [7]	
62.0	62.0
66.0	66.0
71.2	71.2
72.7	72.7
73.0	73.0
122.8	122.8
142.8	142.8
Optical Rotation[8], $[\alpha]_D^{20.0}$	
+88.1 (*c* 0.3, H_2O)	-70.6 (c 0.17, H_2O)

Natural **MK7607**	Current synthesis of **MK7607**
^{1}H NMR (D_2O, 400MHz) [26]	
3.86(dd, *J* = 3.6, 10.2, 1H)	3.85 (dd, *J* = 10.4, 3.7 Hz, 1H)
3.89(dd, *J* = 3.6, 10.2, 1H)	3.88 (dd, *J* = 10.4, 3.9 Hz, 1H)
4.16 (s, 2H)	4.14 (bs, 2H)
4.25(d, *J* = 3.6, 1H)	4.24 (d, *J* = 3.6 Hz, 1H)
4.32(dd, *J* = 4.2, 4.2, 1H)	4.31 (ddd, *J* = 5.1, 3.2, 2.0 Hz, 1H)
5. 85(d, *J* = 4.9. 1H).	5.85 (dt, *J* = 5.0, 1.6 Hz, 1H)
^{13}C NMR (D_2O, 100MHz) [7]	
63.0	64.0
67.0	68.0
67.6	68.6
69.3	70.3
69.6	70.6
125.1	126.0
142.2	142.2
Optical Rotation[8], $[\alpha]_D^{20.0}$	
+210 degree (c 1.0, H_2O)	+41.3 (*c* 0.15, H_2O)

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CHAPTER 3

ADDITION OF CARBASUGARS TO COMPLEX PHENOLS AND TOTAL SYNTHESIS OF RUBIYUNNANIN B

As discussed in Chapter 1, the addition of carbasugars onto biologically important scaffolds could lead to enhanced bioactivities. Due to the decrease in efficacy and specificity upon loss of glycoside, forging complex scaffold-carbasugar bonds is of importance. Furthermore, numerous natural products contain carbasugars such as sch202596 and maximiscin. Up until this point, the phenols tested in the allylic oxide regio resolution (AORR) consisted of small, achiral and relatively unhindered molecules. To test the applicability of AORR, we sought to expand its phenol scope to include complex, chiral natural product scaffolds.

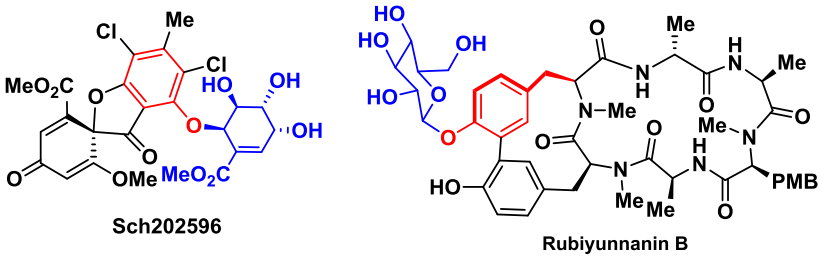
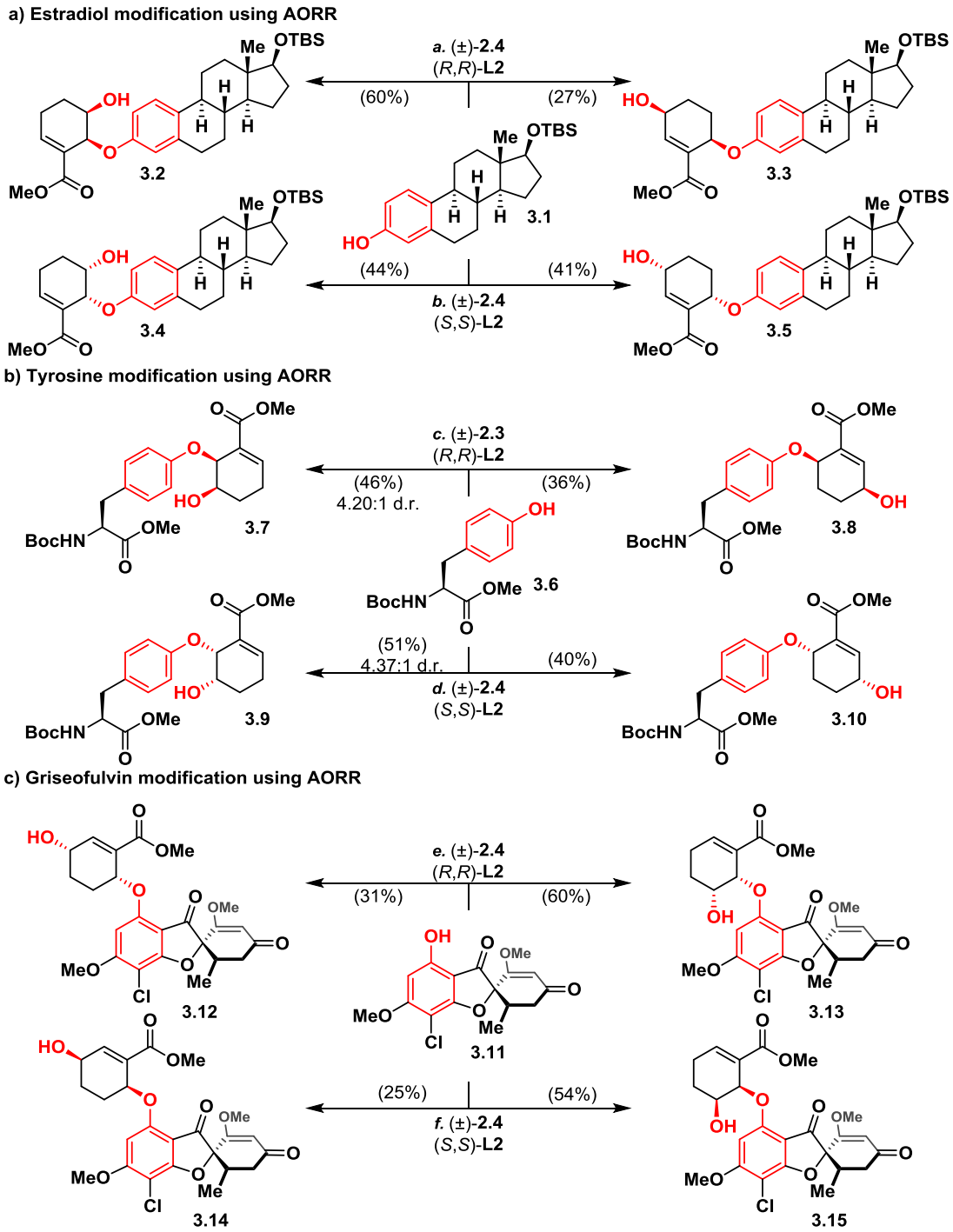


Figure 3.1: Carbasugar or glucose containing natural products

3.1: Model complex phenol addition

We began our studies by choosing a set of chiral phenols to test in the AORR with our model epoxide (**2.4**). Protected estradiol[1] (**3.1**) was chosen as a model for a large, chiral phenol. **3.1** reacted smoothly with oxide **2.4** in the presence of (*R,R*)-**L2** to yield both 1,2 and 1,4 products in 60 and 27% yield, respectively (**3.2** and **3.3**) as single diastereomers. Switching the enantiomer of the ligand yielded a 44 and 41% yield of the diastereomeric 1,2 and 1,4 products, **3.4** and **3.5,** respectively. Given the number of glycosylated tyrosine based natural products, Boc-tyrosine-OMe was chosen as our next model compound. Boc-tyrosine-OMe (**3.6**) yielded 1,2 and 1,4 products in 46 and 36% yield, respectively, when reacted with (*R,R*)-**L2** under standard reactions conditions.



Reagents and conditions: (a) 5.0 mol % $Pd_2(dba)_3$, 15.0 mol % (*R,R*)-**L2**, toluene, **2.4** (1.4 equiv), -40 °C, 96 h; (b) 5.0 mol % $Pd_2(dba)_3$, 15.0 mol % (*S,S*)-**L2**, toluene, **2.4** (1.4 equiv), -40 °C, 96 h; (c) 1.0 mol % $Pd_2(dba)_3$, 3.0 mol % (*R,R*)-**L2**, toluene, **2.4** (1 equiv), -40 °C, 72 h; (d) 1.0 mol % $Pd_2(dba)_3$, 3.0 mol % (*S,S*)-**L2**, toluene, **2.4** (1.1 equiv), -40 °C, 72 h; (e) 5.0 mol % $Pd_2(dba)_3$, 15.0 mol % (*R,R*)-**L2**, toluene, **2.3** (1.8 equiv), -40 °C, 18 h; (f) 5.0 mol % $Pd_2(dba)_3$, 15.0 mol % (*S,S*)-**L2**, toluene, **2.4** (1.8 equiv), -40 °C, 18 h.

Scheme 3.1: AORR of complex phenols

Although the 1,4 product (**3.8**) was isolated as a single diastereomer, the 1,2 product (**3.7**) was isolated as a 4.20:1 mixture of diastereomers. The 4.20:1 diastereoselectivity could be a result of the distant chirality of the tyrosine with respect to the reaction center or deleterious coordination of the palladium to the carbonate causing perturbations to the ligand-palladium structure.[2] The same trend was observed when the ligand was switched to (*S,S*)-**L2**. 1,4 Product (**3.10**) was isolated as a single diastereomer whereas the 1,2 product (**3.9**) was isolated in a 4.37:1 ratio of diastereomers. Lastly, in an effort towards the synthesis of sch202596, we sought to use a phenol with similar steric parameters. Demethylated griseofulvin[3] (**3.11**) was obtainable in large quantities and served as a suitable model phenol. **3.9** was added to epoxide **2.4** to yield 31% 1,4 addition product **3.12** and 60% 1,2 addition product **3.13**. These products were inseparable by silica gel chromatography and resulted in partial degradation of each material (usually producing the starting material griseofulvin). Ultimately florisil chromatography reduced degradation, and the two products were isolated as a mixture. For analytical purposes, they were separated by preparatory HPLC. The use of (*R,R*)-**L2** resulted in opposite diastereomers of the 1,2 and 1,4 products in 54 and 25% yield, respectively. Having verified that AORR worked with complex, chiral and hindered phenols, we attempted to expand the reaction to involve more complex epoxides. Initial trials showed that compounds such as griseofulvin or geodin could be added into more complex epoxides. The selectivity of this reaction is currently being evaluated.

3.2: Synthesis of rubiyunnanin B and analogues

Having shown that it is possible to append small and large phenols onto allylic oxides, we looked to apply AORR to synthesize carbasugar analogues of natural product aglycones. We looked specifically for natural products which show a loss of efficacy upon loss of glycoside. Rubiyunnanin B is one such natural product. Rubiyunnanin B is part of a class of hexapeptidic compounds isolated from the *rubiacae* family (Scheme 3.3). All compounds from this family contain a hexapeptide composed of two alanine amino acids (one of which is D-alanine), three modified tyrosine residues,

two of which form a fused tyrosine dimer and a third amino acid which is usually an alanine in most cases (rubiyunnanin A and B), although other amino acids such as glutamic acid (rubiyunnanin D, **3.18**) are known. The tyrosine dimer can either be formed from a carbon-oxygen bond as is the case in deoxybouvardin (**3.19**) and rubiyunnanin C (**3.21**), a carbon-carbon bond as in rubiyunnanin B (**3.16**), or a fused dihydrobenzofuran dimer (C-C and C-O bond formations) as is the case in rubiyunnanin A (**3.18**).[5] In all rubiyunnanin molecules (except rubiyunnanin A), the tyrosine dimer forms a 12 member macrocycle with an internal *cis*-amide (**3.16**, Figure 3.2 inset).

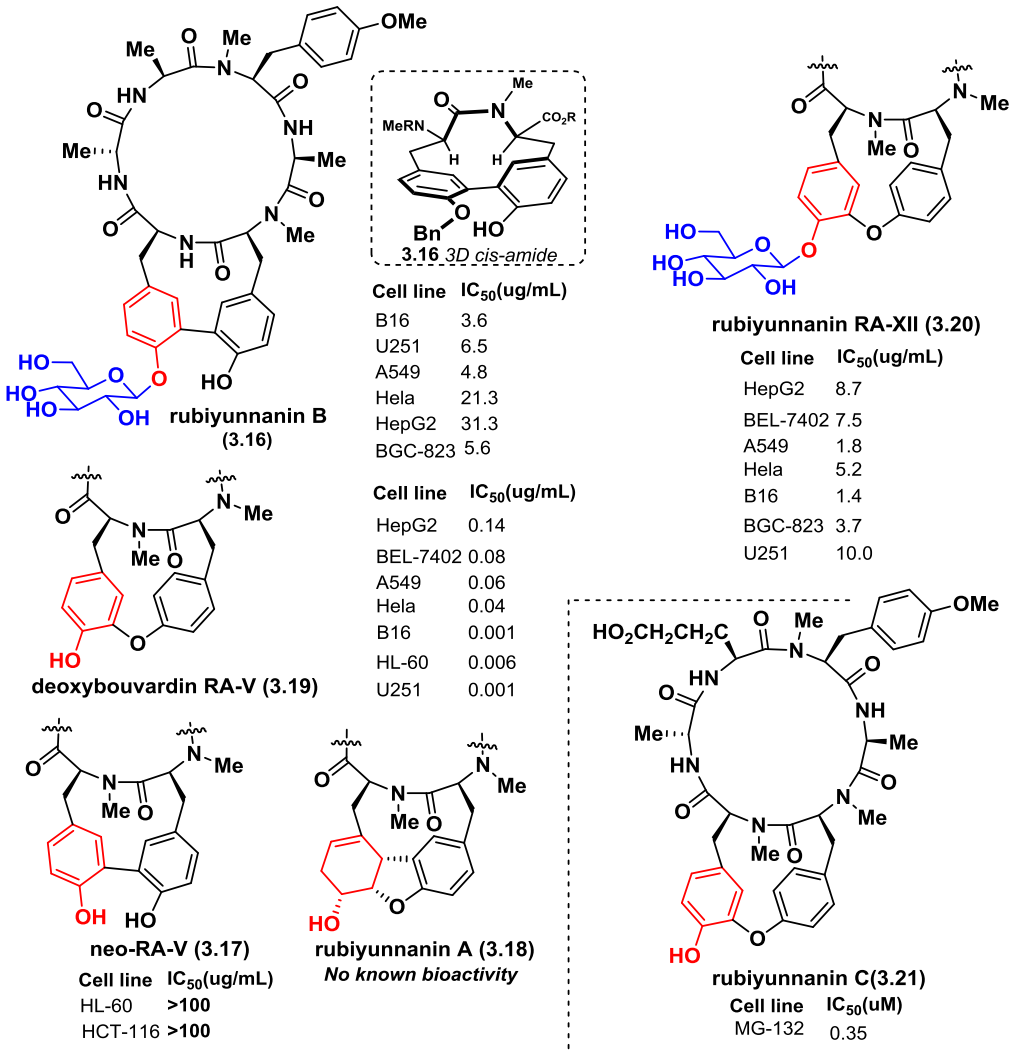
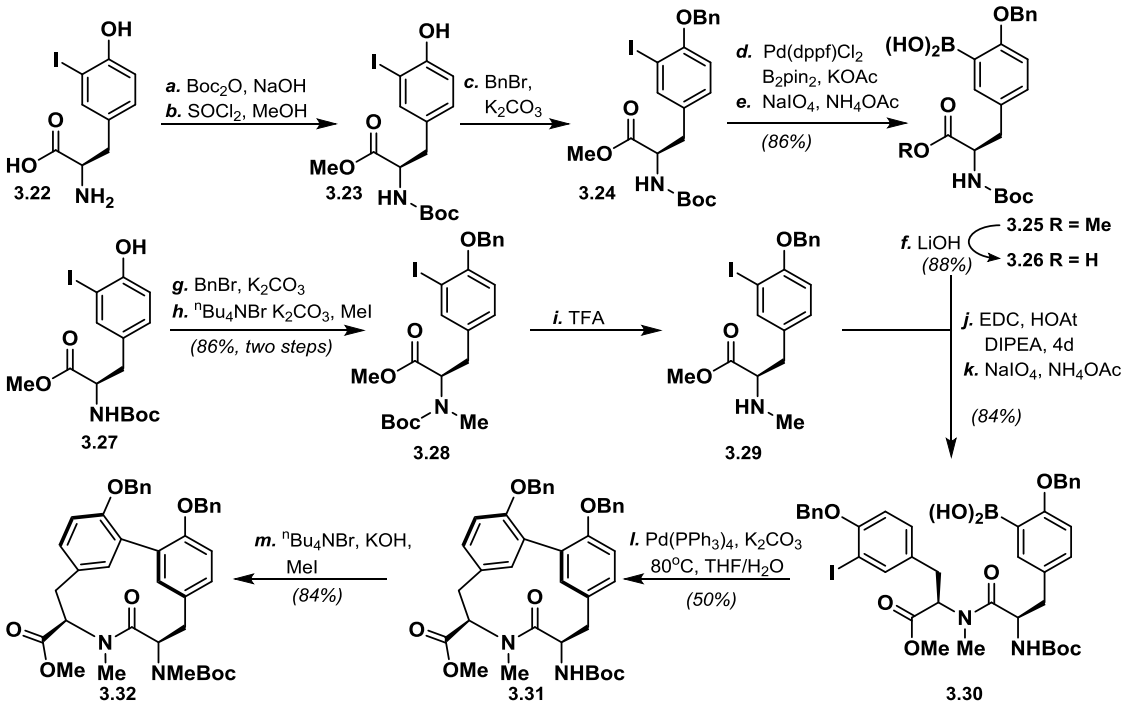


Figure 3.2: Bioactivities of the rubiyunnanin family

Bioactivities of the rubiyunnanins differ with minor structural changes. Deoxybouvardin (**3.19**) exhibits IC_{50} concentrations between 0.001 and 0.014 μg/mL against various cancer cell lines;

however, the glycosylated version, RA-XII (**3.20**) exhibits IC_{50} values substantially higher between 1.8 and 10 μg/mL.[5a] Conversely, rubiyunnanin B (**3.16**) possesses a glycosylated tyrosine and IC_{50} values between 3.6 and 31 μg/mL while the aglycone (**3.17**) does not possess antitumor bioactivity (IC_{50} > 100 μg/mL).[4, 5b] Given that past studies have shown that instability of a carbohydrate can lead to decreased efficacy, we thought rubiyunnanin B to be an ideal study for the preparation of carbasugar analogues.

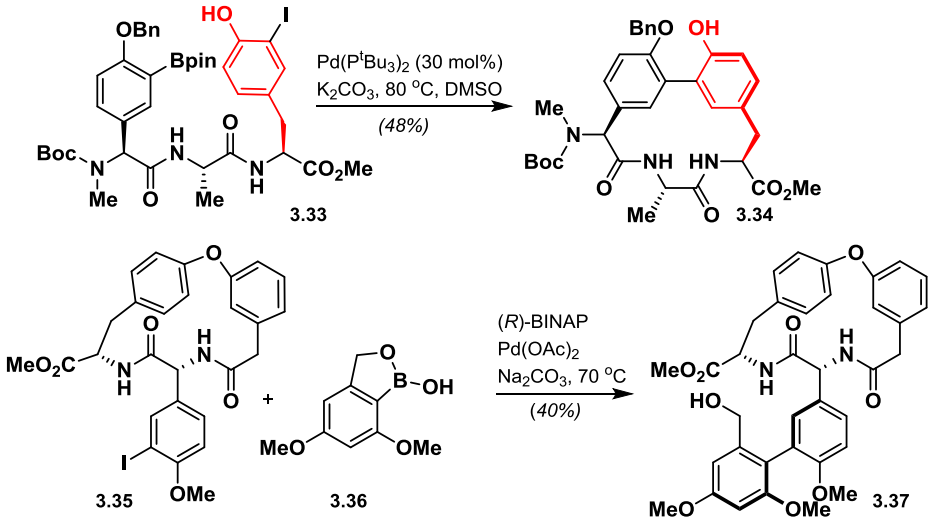


Scheme 3.2: Previous synthesis of *neo*-RA-V by Takeya.[5b]

3.2.1: Previous synthesis of rubiyunnanin B type molecules

Although no synthesis of rubiyunnanin B exist in literature, *neo*-RA-V has been prepared by the group of Takeya.[5b] Their critical bond formation steps include a Suzuki dityrosine coupling, amide bond formation, and methylation of their amides. The late stage transformations of their synthesis are carried out on small (<10mg) scale and require many preparatory purifications. They advance 3-iodotyrosine to Boc-3I-tyrosine(OBn)-OMe rapidly. At this point, they methylate the amide using phase transfer catalysis and perform a Miyaura borylation. They convert the bis(pinicolato)boronic ester, **3.25** to the boronic acid and saponify the methyl ester to yield **3.26**.

Separately, they couple deprotected Boc-3I-tyrosine-OMe (**3.29**) to their boronic acid over 96 hours (10 mg scale) to yield boronic acid **3.30**. Suzuki coupling of the two tyrosine pieces yields the fused 12 member cycle **3.31** which is isolated as two isomers whose structures could not be differentiated by NMR spectroscopy. One compound is isolated in 50% yield while the other is isolated in 15% yield. The minor compound can be converted to the major compound by heating in toluene at 80 °C. It is presumed by the authors that these two compounds are atropisomers with *cis/trans* amide bond isomerization on the NMR timescale. They, however, have little evidence for this assertion, and the two compounds could be explained as locked rotamers of the *cis/trans* amide compound with atropisomers that interconvert on the NMR timescale. They finish the synthesis of the molecule by methylation of the remaining amide nitrogen using phase transfer catalysis to afford **3.32**. After macrocyclization, they deprotect the benzyl ethers to obtain *neo*-RA-V (**3.17**).

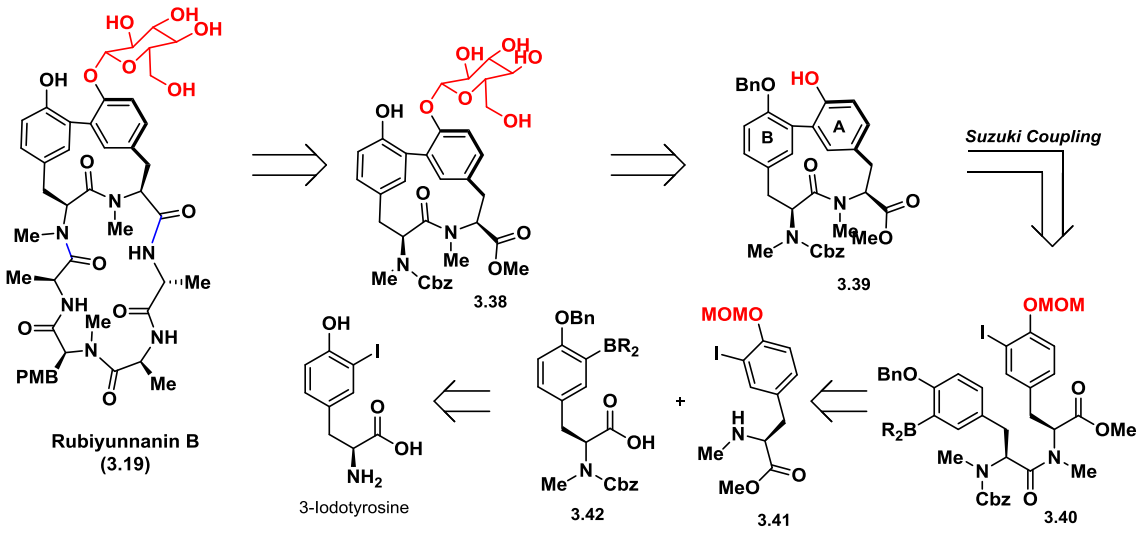


Scheme 3.3: Peptidic biaryl couplings in synthesis[6,7]

For tyrosine containing molecules, the key steps often involves a Suzuki coupling between an aryl iodide and a boronic acid or ester, yet due to the strain and steric hindrance, yields of dityrosine couplings are often low. A few natural products beyond rubiyunnanin B contain a dityrosinyl or a tyrosinyl-phenylglycinol bond including arlyomycin and vancomycin. Arylomycin contains a tyrosine-alanine-phenylglycinol macrocycle, and the coupling of the two aryl groups is

accomplished in 50% yield using $Pd(^tBu_3)_4$ (Scheme 3.3a).[6] It is worth noting in the arlyomycin synthesis that the phenylglycinol is coupled unprotected to limit the amount of epimerization of the tyrosine α proton. To reduce protolysis, the authors employed bulky, electron rich phosphines. In Nicolaou's synthesis of vancomycin, the carbon-carbon bond is forged through a Suzuki coupling involving **3.35** and **3.36**.[7] In this case the coupling is not intermolecular, and the hindered *ortho* coupling results in low reactivity. Hutton has shown that coupling dityrosine pieces when not intramolecular can result in higher yields.[8] By employing sterically hindered palladium ligands and a free phenol, reaction time decreases, although yield also tends to decrease due to increased protolysis.

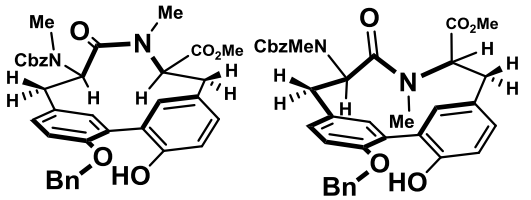
3.2.2: Synthesis of rubiyunnanin B



Scheme 3.4: Retrosynthesis of Rubiyunnanin B

We looked to optimize the previous synthesis and the carbon-carbon bond formation as well as identify the three dimensional structure of the two compounds obtained from the Suzuki coupling. Rubiyunnanin B will be obtained after a final macrocyclization and hydrogenolysis of the benzyl carbamate and benzyl ether (chosen due to the acid sensitivity of the glycoside). Similar to previous work, we will form the dityrosine dimer using a Suzuki coupling of an aryl iodide and aryl bis(pinicolato)boronic ester **3.40**. To avoid late stage N-methylation, both amino acids will be methylated prior to coupling. The B-ring tyrosine containing the Bpin will be installed through a

similar Miyaura coupling from 3-iodotyrosine derivative. The A-ring tyrosine will be protected with an acid sensitive monomethyl methyl ether (MOM) group and also derived from 3-iodotyrosine. We were also interested in trying to determine the overall structure of the coupled product. If previous work is indicative, two possible conformers are possible each of which could contain atropisomers (Figure 3.3). In depth NMR experiments would be used to determine reaction products.

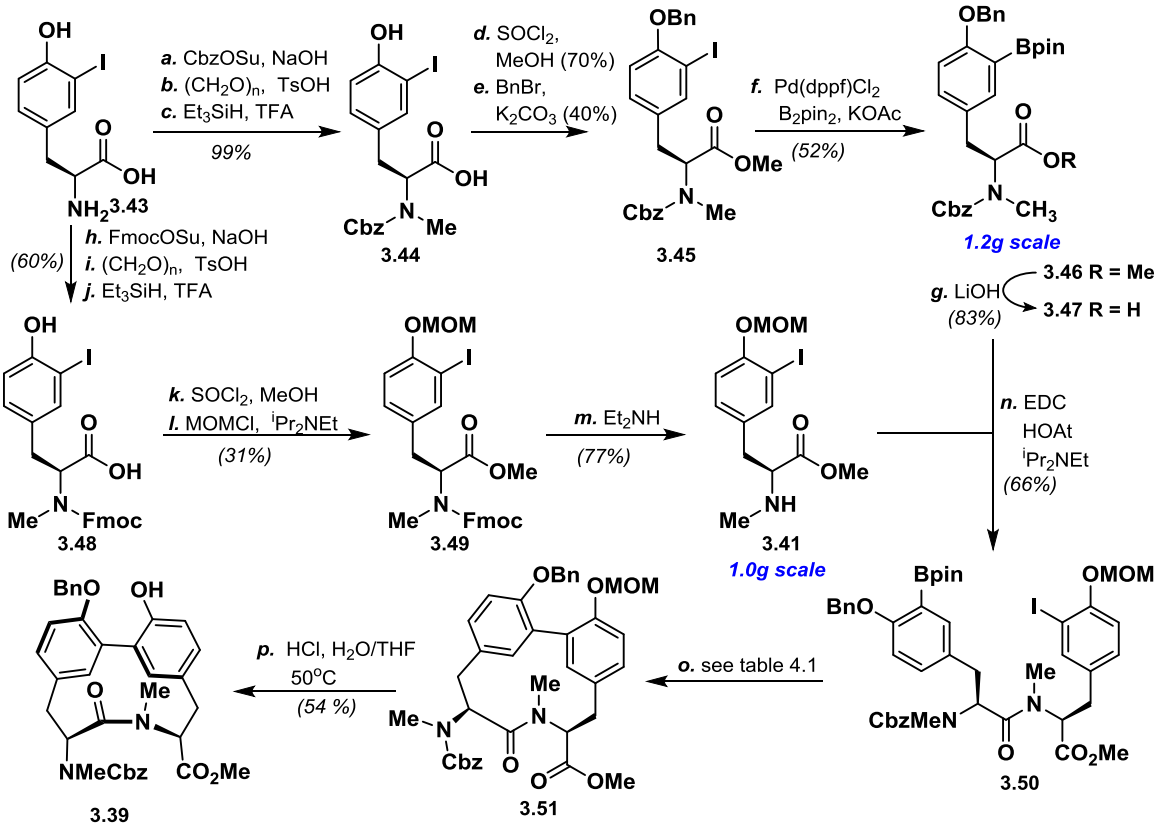


cis-**3.39** *trans*-**3.39**

Figure 3.3: Possible isomers of coupled dityrosine product

The synthesis of the B-ring tyrosine of rubiyunnanin B began with benzyl chloroformate protection of 3-iodotyrosoine (Scheme 3.5). A two step N methylation procedure yielded known CbzNMe-3I-tyrosine-OH (**3.44**). Esterification and benzyl protection afforded **3.45** which was converted to Bpin compound **3.46** in 52% yield using the Miyaura borylation protocol.[5b] Construction of the A ring of rubiyunnanin B started from FmocNMe-3I-tyrosine-OH (**3.43**, synthesized in the same manner), which was esterified and protected as the monomethoxy ether (31% yield). Deprotection of **3.49** proceeded cleanly with diethylamine in 77% yield. Coupling of acid **3.47** and amine **3.41** was accomplished with EDC and HOAt to yield **3.50** in 66% yield. **3.50** was unstable to silica gel chromatography yet was sufficiently pure to be used in the next step.

Initial attempts at the Suzuki coupling of **3.50** employing conditions used in the synthesis of arlyomycin ($Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, DMSO, 80 °C) yielded **3.51** in modest yield (Table 3.1, entry 1). After purification by silica gel chromatography, LC/MS indicated two peaks whose *m/z* corresponded to **3.51**. ^{1}H NMR at 23 °C indicated multiple compounds with broadening in all peaks similar to what Takeya reported in the synthesis of *neo*-RA-V (Figure 3.5).[5c] ^{1}H NMR at -40 °C showed a defined set of two peaks (Figure 3.4).

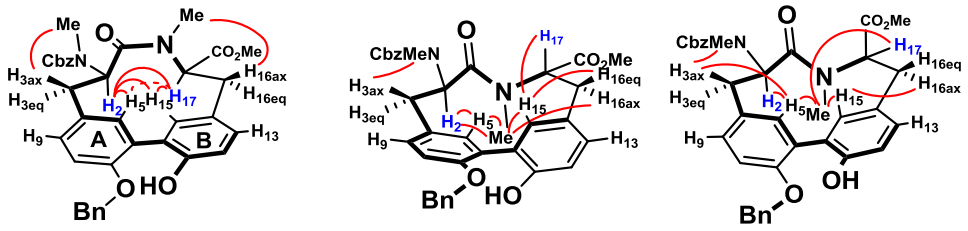


Reagents and conditions: a) CbzOSu, 1M NaOH/dioxane (1:1), 2 h; b) $(CH_2O)_n$, TsOH (0.1 equiv.), C_6H_6:DMF (25:1), 100 °C, 2h; c) Et_3SiH (3 equiv.), TFA:CH_2Cl_2 (1:1) 0 °C to 23 °C, 3h, 99% (three steps); d) $SOCl_2$, MeOH, 80 °C, 2h, 70%; e) BnBr, K_2CO_3, DMF, 50 °C, 12h, 40%; f) Pd(dppf)Cl_2·CH_2Cl_2 (5 mol%), B_2pin_2 (1.3 equiv.), K_2CO_3, DMSO, 80 °C, 52%; g) LiOH (2 eqiv.), THF:H_2O,MeOH (3:1:1), 0 °C, 2h; h) FmocOSu, 1M NaOH/dioxane (1:1), 2 h; i) $(CH_2O)_n$, TsOH (0.1 equiv.), C_6H_6:DMF (25:1), 100 °C, 2h; j) Et_3SiH (3 equiv.), TFA:CH_2Cl_2 (1:1) 0 °C to 23 °C, 3h, 60% (three steps); k) $SOCl_2$, MeOH, 80 °C, 2h; l) MOMCl, $^iPr_2NEt$, 31% (two steps); m) Et_2NH (20 equiv.), CH_2Cl_2, 77%; n) EDC (1.3 equiv), HOAt (1.5 equiv), **3.41** (1.3 equiv.), $^iPr_2NEt$ (2.1 equiv.), 0 °C to 23 °C, 48h, 66%; p) 4M HCl:THF (1:2), 50 °C, 3h, 54%.

Scheme 3.5: Synthesis of rubiyunnanin B

This material was then exposed to 4M HCl at 50 °C for 2 hours to deprotect the monomethoxy ether in yields ranging from 23 to 54%. The resulting deprotected material was purified to yield three distinct species by LC/MS whose *m/z* matched that of **3.39**. Analysis of ^1H NMR showed two major sets of compounds, each of which exchanged with a second rotameric compound. ROESY data indicated that **3.39a** showed a nOe correlation between α protons (Figure 3.4, H_2 and H_{17}). Additional nOe correlations were observed between an axial β-proton (H_{2ax}) and the Cbz N-methyl as well as between an axial β proton (H_{16ax}) and the internal N-methyl. This indicates an internal *cis*-amide as is expected with the rubiyunnanin compounds. Furthermore, ring

A is twisted above the biaryl plane while ring B is below. α -Proton H_2 has strong nOe correlations with both internal aryl protons (H_5 and H_{15}) whereas α-proton H_{17} shows a strong correlation to the ring B aryl proton (H_{15}) and a weak correlation to the A ring aryl proton (H_5. Strong three bond COSY correlations between β protons H_{2eq}, H_{16eq}, and H_{16ax} and aryl protons (and weak COSY correlations between H_{2eq} and aryl protons) confirm the orientation of the rings as per the Karplus equation for benzylic protons.[12] We therefore believe that **3.39a** (more specifically *P-cis*-**3.39a**) is oriented in a manner shown in Figure 3.4.



P-cis-**3.39a**
$J_{2ax,1}$ = 9.0 Hz
$J_{16ax,17}$ = 11.5 Hz
strong COSY: H_5 - H_{3eq}
H_{13} - H_{16eq}
H_{13} - H_{16ax}
weak COSY: H_5 - H_{3ax}

M-trans-**3.39b**
$J_{2ax,1}$ = 9.0 Hz
$J_{16ax,17}$ = 12.0 Hz
strong COSY: H_5 - H_{3eq}
H_{13} - H_{16eq}
weak COSY: H_5 - H_{3ax}
H_{13} - H_{16ax}

P-trans-**3.39a**
$J_{2ax,1}$ = 11.4 Hz
$J_{16ax,17}$ = 5.92 Hz
strong COSY: H_5 - H_{2ax}
weak COSY: H_{15} - H_{16ax}
no COSY: H_{15} - $H1_{6eq}$
H_5 - $H2_{eq}$

Figure 3.4: Important correlations of molecule 3.39

P-cis-**3.39a** exchanges with a second compound, *P-cis*-**3.39arot** as evidenced by exchange peaks present in ROESY data. This compound contains identical correlations, including between each α proton and between the α proton and the aryl ring, as well as an identical pattern in three bond COSY couplings. This second compound therefore cannot be an atropisomer or *trans*-amide isomer but rather rotamers at the Cbz N-methyl, although no correlations could confirm this.

The second isomeric compound isolated was determined to be the H_{17} epimer of *P-cis*-**3.39a**. This compound (**3.39b**) contains a *trans*-amide. Strong nOe correlations are seen between the internal N methyl and protons H_2, H_{16ax}, $H_{5,}$ and H_{15}. The epimerized α proton H_{17} correlates only with H_{15}. Large coupling constants (J = 12.0 Hz) between H_{17} and H_{16ax} also support this conformation. This data is also supported by three bond COSY correlations which indicate that only one proton (H_{2ax}) is perpendicular to the aryl ring. It is most likely that ring B in this compound is

above the biaryl plane whereas ring A is canted below the plane. We therefore believe this compound, *M-trans*-**3.39b** is oriented as seen in Figure 3.4.

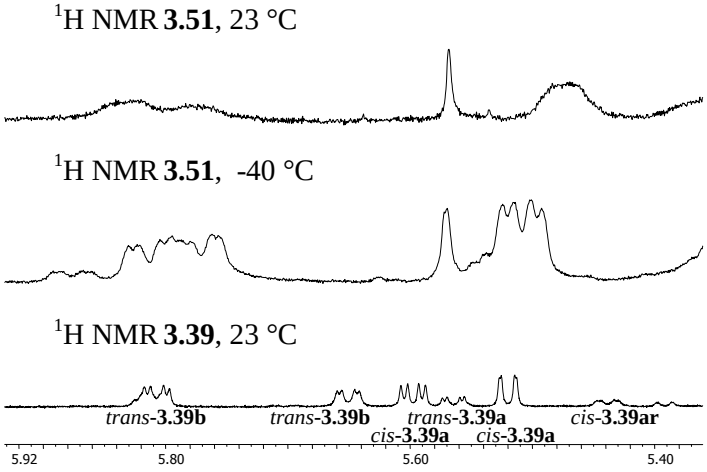


Figure 3.5: ^{1}H NMR comparison of coupled products

^{1}H NMR indicated a third compound was formed in this reaction. This compound was separated from *P-cis*-**3.39a** and *M-trans*-**3.39b** by preparatory TLC, and its structure determined to be *P-trans*-**3.39a**. This compound was present in small quantities when Pd(dppf)Cl_2·CH_2Cl_2 (15 mol%) was used at a ratio of 42:44:4 (*P-cis*-**3.39a**: *M-trans*-**3.39b**: *P-trans*-**3.39a**) but increased to 23:34:44 when catalyst loading of Pd(dppf)Cl_2·CH_2Cl_2 were increased (Table 3.1, entry 2). No nOe was observed between α protons H_2 and H_{17} indicating a *trans* isomer. H_2 showed correlations to an axial β proton (H_{3ax}), α proton H_2 and the internal N-methyl. This indicated that the B ring is slight canted above the biaryl plane. The A ring aryl proton H_{15} has correlations with axial β proton H_{16ax} and with the internal N-methyl. It does not show a correlation with H_{17} indicating that the A ring is canted below the biaryl plane. H_{17} retains the same stereochemistry as *P-cis*-**3.39a** which is supported by the smaller coupling constants β protons H_{16}. The position of the rings is also supported by long range three bond COSY couplings.

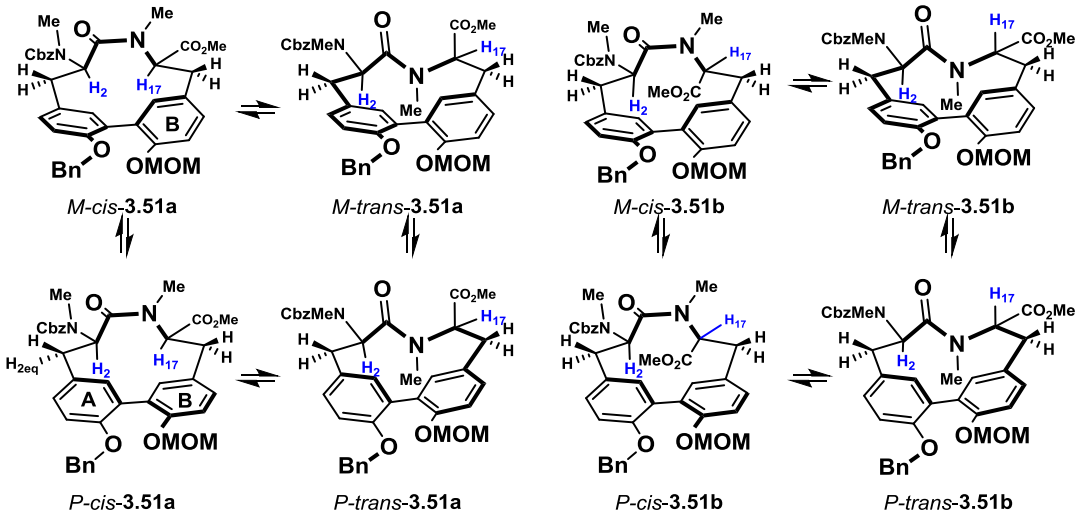
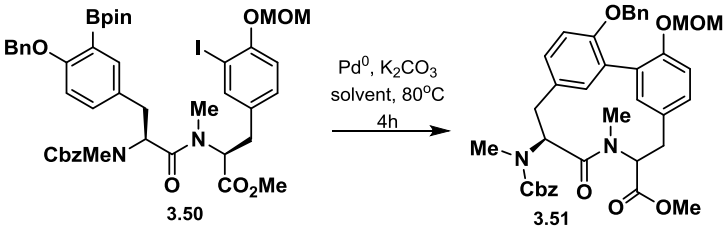


Figure 3.6: Possible conformations of 3.51

Broad signals in **3.51** could be a result of isomerization between possibly eight different compounds and their eight Cbz N-methyl rotamers. Given that it is possible for atropisomerism to exist, **3.51a** could consist of both atropisomers and *cis/trans* isomers resulting in four different compounds *P-cis*-**3.51a,** *M-cis*-**3.51a**, *P-trans*-**3.51a**, and *M-trans*-**3.51a.** If epimerization has occurred it is also possible for 4 more compounds to be observed: *P-cis*-**3.51b,** *M-cis*-**3.51b**, *P-trans*-**3.51b**, and *M-trans*-**3.51b.** Exchange between each set, due to either atropisomerism or *cis/trans* amide exchange, would lead to broadening. Deprotection of the material, however, results in only

Table 3.1: Suzuki coupling of dityrosine



entry	catalyst (eq)	solvent	scale	yield[a]	ratio **3.39**[b]
1	$Pd(dppf)Cl_2$-DCM (0.15)	DMSO	200mg	34%	46:41:13
2	$Pd(dppf)Cl_2$-DCM (0.3)	DMSO	100mg	18%	46:22:35
3	$Pd(PPh_3)_4$ (0.15)	THF:H_2O (6:1)	200mg	15%	73:24:4
4	$Pd(P^tBu_3)_2$ (0.15)	DMSO	200mg	13%	90:10:0
5	Xphos Pd G2 (0.1)	THF:H_2O(1:1)[c]	100mg	<5%	>99:1:0

[a] isolated yields after column; [b] ratio: (*cis*-**3:39a:***trans*-**3.39b**:*trans*-**3.39a)** determined by LC/MS analysis and ^1H NMR analysis of **3.39;** [c] 0.5M K_3PO_4 solution was used as base instead of K_2CO_3 at 40°C for 30 minutes.

two **3.39a** compounds *P-cis*-and *M-trans*-**3.39b.** Decreasing the size of a group in the *ortho* position of an atropisomeric compound should encourage more rotational freedom which would result in broadening of peaks; this, however, was not seen. The lack of broadening could be explained by a critical hydrogen bond between the now free phenol and the benzyl ether, thus stabilizing the atropisomer isolated. Rubiyunnanin B would be able to adopt the same critical hydrogen bond, thus stabilizing the ring.

Increasing the rate of reaction should decrease epimerization (assuming that epimerization of the molecule is happening before coupling due to harsh conditions). Increasing the loading of $Pd(dppf)_2 \cdot CH_2Cl_2$ decreased epimerization but also resulted in a decreased yield; reaction time did not change. A more electron rich phosphine, $Pd(P^tBu_3)_2$ resulted in almost a 90:10:0 ratio of epimers favoring *P-cis*-**3.39a**, however, in a combined yield of only 13% (Table 3.1, entry 4). Changing solvent and catalyst to $Pd(PPh_3)_4$ in THF:water reduced epimerization but also resulted in low yield. Mild Suzuki conditions pioneered by the Buchwald group involving the use of Xphos Pd G2, resulted in >99:1 ratio of epimers and completion of the reaction in 30 minutes at 40 °C; however, with yields between 5 and 10%.[13] Optimization of the reaction conditions by removing silica gel chromatography of **3.51** and directly exposing the crude reaction mixture to 4M HCl at 50 ^oC for 30 minutes resulted in a increase in yield to 56% over two steps (Scheme 3.8).

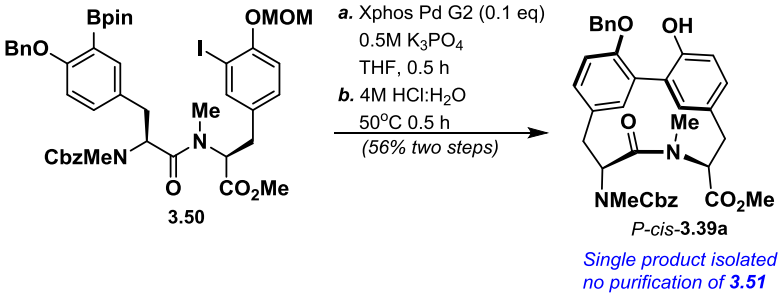


Figure 3.7: Optimized cross coupling and deprotection

The final steps involve the incorporation of the glycoside. Using trichloroacetimidate sugar **3.42**, **3.38** was obtained as a single diastereomer as evidenced by LC/MS data. Work is ongoing at this time to isolate and characterize this molecule. Due to time constraints, the synthesis was

terminated at this point. The remaining steps would involve the saponification of the acid followed by peptide coupling of the tetrapeptide. Global hydrogenolysis would cleave both the benzyl group and benzylchloroformate. A final peptide coupling would yield rubiyunnanin B.

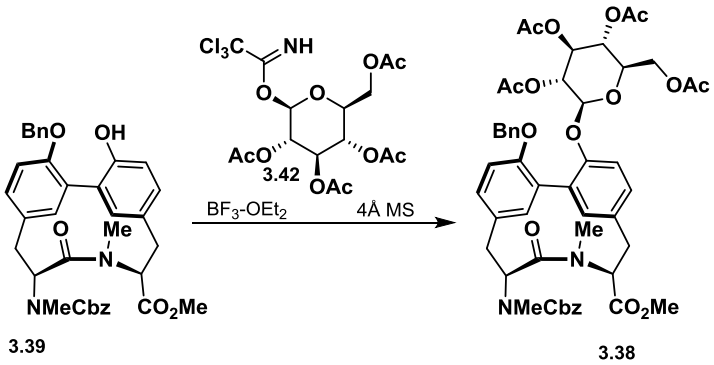


Figure 3.8: Glycosylation of aglycone

3.3: Conclusions from Chapters 1, 2 and 3

We have shown up until this point that AORR is capable of producing small molecule carbasugars and have now expanded it to include the addition of more complex chiral scaffolds to carbasugars. This should open new areas for possible biological screening of unique, chiral natural product cores. The hope is that this method can be further generalized to allow for the isolation of more carbasugar stereoarrays. A drawback is that one must select the protecting group (early in the synthesis of the oxide) in order to choose between a *syn* or *trans* addition. Data presented in Table 2.4, has shown that the development of new ligands that are electronically different, could control the *syn/anti* addition distribution. Furthermore, the yields of these reactions would need to be increased for this method to become more applicable. We also looked to understand the mechanism of this reaction. From the data presented, we believe *anti* addition products are obtained from a palladium-π-allyl inversion. More mechanistic studies would help elucidate this mechanism.

This method allows rapid access to an array of different natural products which could open new frontiers in medicinal chemistry screening. Glycosidic natural products are relative well studied in literature; however, it remains to be seen exactly how they behave *in situ* due to difficulties in the isolation of any complex (mainly due to the instability of glycosidic bonds). Natural products such

as rubiyunnanin B which lose bioactivity upon loss of carbohydrate are interesting examples. Thus, we targeted the synthesis of rubiyunnanin B. Ultimately we developed a rapid synthesis to obtain a single isomer of the core of rubiyunnanin B. More steps would need to be taken to complete the synthesis of the natural product and obtain its carbasugar variant.

3.4: Experimental

Allylic-Oxide Regio Resolution of Estradiol: 17-O-*tert*butyldimethylsilylestradiol (**3.1**) was prepared according to literature procedures using a bis-TBS protection followed by selective removal of the phenolic silane.[2] In addition to the discussed use of the (*S,S*)-**L2**, (*R,R*)-**L2** was also used and the results are included below. Products are a single diastereomer unless otherwise noted.

In a flame-dried flask outfitted with a septum, racemic epoxide **2.4** (68.0 mg, 0.44 mmol, 1.4 equiv) was dissolved in 6.5 mL of toluene followed by 17-O-*tert*butyldimethylsilylestradiol **7** (120.0 mg, 0.31 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (14.7 mg, 5.0 mol%) and (*R,R*)-**L2** (36.7 mg, 15.0 mol%) were dissolved in 4.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. After 96 hours at -40 °C, the reaction was concentrated to a volume of 2.0 mL and then purified by flash chromatography (9:1, hexanes:EtOAc v/v) to yield **3.2** (101.5 mg, 60%) and **3.3** (46.9 mg, 27%), both as white solids and single diastereomers. The epoxide (**2.4**, 22%) was recovered in 93:7 enantiomeric ratio.

Methyl (5R, 6S)-5-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-cyclohex-1-enecarboxylate (3.2): $[\alpha]_D^{20.0}$ -97.3 (*c* 1.00, $CHCl_3$); **M.p.** 38 – 42 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 4.6, 3.1 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 5.25 (d, *J* = 3.7 Hz, 1H), 3.91 (dt, *J* = 11.3, 3.7 Hz, 1H), 3.66 (s, 3H), 3.64 (t, *J* = 7.7 Hz, 1H), 2.88-2.77 (m, 1H), 2.57-2.48 (m, 1H), 2.37-2.22 (m, 2H), 2.21 – 2.11 (m, 1H), 2.11-1.79 (m, 6H), 1.66 – 1.63 (m, 1H), 1.55-1.03 (m, 7H), 0.89 (s, 9H), 0.73 (s, 3H), 0.03 (s, 3H), 0.02 (s,

3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6, 157.3, 143.8, 138.1, 134.1, 129.4, 126.4, 117.2, 114.2, 81.9, 72.7, 69.4, 51.9, 49.8, 44.3, 43.7, 38.9, 37.3, 31.1, 29.9, 27.4, 26.5, 26.0, 25.4, 25.2, 23.4, 18.2, 11.5, -4.3, -4.6; IR (film, cm^{-1}) 3433, 2926, 2854, 1717, 1495, 1246, 1094, 834, 773; **TLC** R_f = 0.57 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{32}H_{48}SiO_5$ 540.3271, found 540.3263.

Methyl (3S, 6R)-3-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-cyclohex-1-enecarboxylate (3.3): $[\alpha]_D^{20.0}$ -25.6 (*c* 1.00, $CHCl_3$); **M.p.** 43 – 47°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 1H), 7.10 (dd, *J* = 2.2, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.09 (br s, 1H), 4.32 (dddd, *J* = 10.6, 6.1, 2.1, 1.0 Hz, 1H), 3.76 (s, 3H), 3.64 (t, *J* = 7.9 Hz, 1H), 2.89 – 2.78 (m, 1H), 2.34 – 2.10 (m, 3H), 2.04-1.76 (m, 5H), 1.71-1.03 (m, 10H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 155.7, 145.9, 138.3, 133.9, 130.6, 126.5, 117.1, 114.1, 81.9, 68.0*, 68.0*, 67.8, 52.2*, 52.2*, 49.8, 44.3, 43.7, 39.0, 37.3, 31.1, 20.0, 27.4, 26.5, 26.5, 26.0, 25.3, 23.4, 18.3, 11.5, -4.3, -4.7; **IR** (film, cm^{-1}) 3389, 2926, 2853, 1719, 1496, 1247, 1094, 834, 773; **TLC** R_f = 0.43 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{32}H_{48}SiO_5$ 540.3271, found 540.3263. * denotes presumed rotamers in a 1:1 ratio.

In a flame-dried flask outfitted with a septum, racemic epoxide **2.4** (121.6 mg, 0.788 mmol, 1.4 equiv) was dissolved in 7.0 mL of toluene followed by 17-O-*tert*butyldimethylsilylestradiol **7** (208.1 mg, 0.539 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (26.2 mg, 5.0 mol%) and (*S*,*S*)-**L2** (67.0 mg, 15.0 mol%) were dissolved in 4.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. After 96 hours at -40 °C, the reaction was concentrated to a volume of 2.0 mL and then purified by flash chromatography (9:1, hexanes:EtOAc, (v/v) to yield **3.4** (127.9 mg, 44%) and **3.5** (119.2 mg, 41%) both as white solids and single diastereomers. The epoxide (**2.4**, 18%) was recovered in 66:34 enantiomeric ratio.

Methyl (5S, 6R)-5-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-cyclohex-1-enecarboxylate (3.4): $[\alpha]_D^{20.0}$ -28.0 (*c* 1.00, $CHCl_3$); **M.p**. 56 – 60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 4.6, 3.1 Hz, 1H), 6.94 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 5.25 (d, *J* = 3.7 Hz, 1H), 3.91 (ddt, *J* = 11.3, 9.1, 3.7 Hz, 1H), 3.65 (s, 3H), 3.64 (t, *J* = 8.5 Hz, 1H), 2.86-2.79 (m, 1H), 2.58 – 2.47 (m, 1H), 2.37-2.23 (m, 2H), 2.20 – 2.11 (m, 1H), 2.06-1.80 (m, 6H), 1.71-1.59 (m, 1H), 1.54-1.07 (m, 7H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 157.3, 143.8, 138.0, 134.0, 129.4, 126.3, 117.0, 114.3, 81.8, 72.7, 69.4, 51.8*, 51.8*, 49.7, 44.2, 43.6, 38.9, 37.2, 31.0, 29.9, 27.4, 26.4, 25.9, 25.2, 25.1, 23.3, 18.2, 11.4, -4.4, -4.7; **IR** (film, cm^{-1}) 3435, 2928, 2855, 1719, 1496, 1246, 1095, 834, 774; **TLC** R_f = 0.57 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{32}H_{48}SiO_5$ 540.3271, found 540.3264. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(17-O-*tert*butyldimethylsilylestradiol)-cyclohex-1-enecarboxylate (3.5): $[\alpha]_D^{20.0}$ +27.5 (*c* 0.50, $CHCl_3$); **M.p.** 64 – 69 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.10 (dd, *J* = 2.4, 1.3 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 5.09 (br s, 1H), 4.34 – 4.30 (m, 1H), 3.75 (s, 3H), 3.64 (t, *J* = 8.0 Hz, 1H), 2.88 – 2.77 (m, 1 H), 2.32 – 2.11 (m, 3H), 2.04 – 1.76 (m, 5H), 1.74 – 1.03 (m, 10H), 0.89 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 155.6, 146.1, 138.2, 133.8, 130.5, 126.5, 116.9, 114.3, 81.9, 68.0, 67.7, 52.2, 49.8, 44.3, 43.7, 39.0, 37.3, 31.1, 30.0, 27.4, 26.5, 26.3, 26.0, 25.3, 23.4, 18.2, 11.5, -4.3, -4.7; **IR** (film, cm^{-1}) 3410, 2928, 2855, 1720, 1496, 1247, 1095, 834, 773; **TLC** R_f = 0.43 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{32}H_{48}SiO_5$ 540.3271, found 540.3268.

Allylic-Oxide Regio Resolution of Tyrosine

In addition to the discussed use of (*S*,*S*)-**L2**, (*R*,*R*)-**L2** was also tested and the results are shown below. Products are shown to be a single diastereomer unless otherwise noted. In flame dried flask outfitted with a septum, racemic epoxide **2.4** (264.7 mg, 1.71 mmol, 1.05 equiv.) was dissolved

in 12.0 mL of toluene followed by the addition of Boc-L-Tyr-OMe **3.6** (482.5 mg, 1.63 mmol, 1.0 equiv.). The resulting solution was degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (12.4 mg, 1.0 mol%) and (*R*,*R*)-**L2** (34.2 mg, 3.0 mol%) of was dissolved in 1.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 72 hours before being worked up as in general procedure A. The reaction was purified by flash chromatography (7:3 hexanes:EtOAc v/v) to yield 664.3 mg of an inseparable mixture of **3.7** and **3.8** and 0.8 mg of recovered oxide (59:41 e.r.). Analytical standards of **3.7** and **3.8** were purified by preparatory HPLC (90:10 to 1:99 water:acetonitrile v/v) and yields **3.7** (45% yield, 4.37 d.r. as determined by ^{1}H NMR) and **3.8** (36% yield as a single diastereomer) as determined by ^{1}H NMR analysis of the homogenous mixture.

Methyl (5S, 6R)-5-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate (3.7): Note: The following data are for the major diastereomer isolated (4.37:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.08 – 7.00 (m, 4H), 5.23 (d, *J* = 3.7 Hz, 1H), 4.95 (br d, *J* = 8.1 Hz, 1H), 4.56 – 4.50 (m, 1H), 3.90 (dt, *J* = 11.2, 3.8 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.07 – 2.95 (m, 2H), 2.58 – 2.48 (m, 1H), 2.38 – 2.25 (m, 1H), 2.04 – 1.84 (m, 2H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 166.5, 158.8, 155.2, 144.1, 130.6, 130.4 129.3, 117.5, 80.1, 73.3, 69.5, 54.6, 52.3, 51.8, 37.6, 28.4, 25.4, 23.5. Optical rotation, IR, and HRMS were not obtained due to mixture of diastereomers. * denotes presumed rotamers in a 1:1 ratio.

Methyl (3R, 6S)-3-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate (3.8)

$[\alpha]_D^{20.0}$ +36.4 (*c* 1.00, $CHCl_3$); **M.p.** 38–42 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 1.6 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.94 – 6.88 (m, 2H), 5.07 (t, *J* = 2.8 Hz, 1H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.53 (dt, *J* = 8.7, 6.0 Hz, 1H), 4.36 – 4.26 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.01 (tt, *J* = 14.1, 6.8 Hz, 2H), 2.17 – 2.09 (m, 1H), 2.00 – 1.92 (m, 1H), 1.80 (tdd, *J* = 12.9, 10.3, 2.7 Hz, 1H), 1.57 (tt, *J* = 14.3, 3.2 Hz, 1H), 1.41 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 166.4, 157.1, 155.3, 145.8,

130.5, 128.9, 128.6, 117.1, 80.1, 68.3, 67.9, 54.6, 52.4*, 52.4*, 52.2*, 52.2*, 37.6, 28.5, 26.5, 25.3; **IR** (film, cm^{-1}) 3370, 2951, 1718, 1508, 1255, 1167, 1031; **TLC** R_f = 0.17 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{23}H_{31}O_8N$ 449.2049, found 449.2056. * denotes presumed rotamers in a 1:1 ratio.

In a flame-dried flask outfitted with a septum, racemic epoxide **2.4** (301.0 mg, 1.02 mmol, 1.0 equiv.) was dissolved in 12.0 mL of toluene followed by the addition of Boc-L-Tyr-OMe **3.6** (562.1 mg, 1.0 mmol, 0.98 equiv.). The resulting solution was degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (14.5 mg, 1.0 mol%) and (*S*,*S*)-**L2** (39.3 mg, 3.0 mol%) was dissolved in 6.0 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was allowed to stir for 72 hours before being worked up as in general procedure A. The reaction was purified by flash chromatography (7:3 hexanes:EtOAc v/v) to yield 712.0 mg of an inseparable mixture of **3.9** and **3.10** and 43.4 mg of recovered oxide (53:47 e.r.). Analytical standards of **3.9** and **3.10** were purified by preparatory HPLC (90:10 to 1:99 water:acetonitrile v/v) and yields **3.9** (51% yield, 4.20 d.r. as determined by ^{1}H NMR) and **3.10** (40% yield as a single diastereomer) as determined by ^{1}H NMR analysis of the homogenous mixture.

Methyl (5R, 6S)-5-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate (3.9)

Note: The following data are for the major diastereomer isolated (4.20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.08 – 6.99 (m, 4H), 5.22 (d, *J* = 3.6 Hz, 1H), 5.00 – 4.96 (m, 1H), 4.55 – 4.50 (m, 1H), 3.89 (dt, *J* = 11.4, 3.7 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.06 – 2.96 (m, 2H), 2.57 – 2.48 (m, 1H), 2.36 – 2.27 (m, 1H), 2.02 – 1.93 (m, 1H), 1.89 – 1.80 (m, 1H), 1.41 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 166.5, 158.8, 155.2, 144.1, 130.7, 130.4, 129.3, 117.5, 80.1, 73.3, 69.5, 54.6, 52.4, 51.9, 37.6, 28.4, 25.4, 25.3. Optical rotation, IR, and HRMS were not obtained due to mixture of diastereomers.

Methyl (3S, 6R)-3-hydroxy-6-O-(Boc-L-Tyr-OMe)-cyclohex-1-enecarboxylate (3.10)

$[\alpha]_D^{20.0}$ +10.2 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 1.7 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.95 – 6.90 (m, 2H), 5.10 (t, *J* = 2.9 Hz, 1H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.54 (q, *J* = 6.7 Hz, 1H), 4.40 – 4.27 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.02 (qd, *J* = 14.0, 5.9 Hz, 2H), 2.19 – 2.13 (m, 1H), 2.04 – 1.96 (m, 1H), 1.87 – 1.73 (m, 1H), 1.59 (tt, *J* = 14.2, 3.2 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 166.4, 157.1, 155.3, 146.2, 130.5, 130.2, 129.0, 117.0, 80.1, 68.3, 67.7, 54.6, 52.3*, 52.3*, 52.2*, 52.1*, 37.5, 28.4, 26.3, 25.3; **IR** (film, cm^{-1}) 3369, 2951, 1718, 1508, 1256, 1167, 1031; **TLC** R_f = 0.17 (7:3 hexanes:EtOAc v/v). **HRMS** (EI^+) *m/z* Calc'd for $C_{23}H_{31}O_8N$ 449.2049, found 449.2042. * denotes presumed rotamers in a 1:1 ratio.

Allylic-Oxide Regio Resolution of Griseofulvin

4-des-methyl-griseofulvin **3.11** was prepared by the demethylation of griseofulvin following a literature procedure.[3] In addition to the discussed use of (*S*,*S*)-**L2**, (*R*,*R*)-**L2** was also tested and the results are shown below. Products are shown to be a single diastereomer unless otherwise noted.

In flame-dried flask outfitted with a septum, racemic epoxide **2.4** (81.2 mg, 0.527 mmol, 1.8 equiv.) was dissolved in 1.3 mL of toluene followed by the addition of 4-des-methyl-griseofulvin **3.11** (99.5 mg, 0.294 mmol, 1.0 equiv.). The resulting solution was thoroughly degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (17.1 mg, 5.0 mol%) and (*R*,*R*)-**L2** (39.9 mg, 15.0 mol%) was dissolved in 0.6 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was continued at -40 °C and monitored by ^{1}H NMR until total consumption of the starting phenol was observed (approx. 18 hours). The reaction was then concentrated to dryness and was purified by flash chromatography (100% DCM, then 95:5 DCM:MeOH v/v) using Florisil as the stationary phase to yield 132.4 mg of a mixture containing **3.12** (60% yield), **3.13** (31% yield), and 9.0 mg of recovered phenol **3.11** (9%). Degradation of the products on Florisil is suspected to regenerate griseofulvin **3.11**. Similar

degradation, but to a much greater extent, was observed when using silica as the stationary phase. Analytical standards of **3.12** and **3.13** could be separated from one another and purified by a silica column (5:1 toluene/acetone v/v) then preparatory HPLC (80:20 to 35:65 water:acetonitrile v/v over 35 minutes) to remove **3.11**. Both products were isolated as white solids.

Methyl (5R, 6S)-5-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-enecarboxylate (3.12)

$[\alpha]_D^{20.0}$ +366.6 (*c* 1.00, $CHCl_3$); **M.p**. 90 – 92 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30 (dd, *J* = 4.9, 2.7 Hz, 1H), 7.18 (s, 1H), 5.55 (s, 1H), 5.24 (d, *J* = 3.4 Hz, 1H), 4.05 (s, 3H), 3.79 (dt, *J* = 12.0, 3.8 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.93 (dd, *J* = 16.2, 13.3 Hz, 1H), 2.82 (ddd, *J* = 13.4, 6.7, 4.3 Hz, 1H), 2.59 (dt, *J* = 20.4, 5.3 Hz, 1H), 2.48 – 2.30 (m, 2H), 2.24 – 2.09 (m, 1H), 2.00 – 1.89 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.9, 194.2, 170.8, 169.0, 166.7, 165.2, 158.6, 146.8, 127.9, 106.9, 105.2, 98.5, 97.2, 91.1, 77.3, 69.3, 57.4, 56.9, 52.2, 40.2, 36.6, 25.8, 24.6, 14.5; **IR** (film, cm^{-1}) 3457, 2949, 1709, 1611, 1584, 1224, 1210, 753; **TLC** R_f = 0.28 (1:4 acetone:toluene v/v); **HRMS** (DART) *m/z* Calc'd for $C_{24}H_{26}ClO_9$ $(M+H)^+$: 493.1260, found 493.1269.

Methyl (3S, 6R)-3-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-enecarboxylate (3.13)

$[\alpha]_D^{20.0}$ +298.9 (*c* 1.00, $CHCl_3$); **M.p.** 126 – 128 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.18 (d, *J* = 1.3 Hz, 1H), 6.55 (s, 1H), 5.52 (s, 1H), 5.35 (br s, 1H), 4.33 (ddd, *J* = 9.2, 6.2, 2.0 Hz, 1H), 4.02 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 2.95 (dd, *J* = 16.5, 13.4 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.60 (br s, 1H), 2.39 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.18 – 1.92 (m, 3H), 1.71 (tt, *J* = 13.7, 3.5 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.1, 192.3, 171.1, 169.3, 166.2, 164.6, 156.7, 147.7, 129.0, 106.6, 105.0, 97.8, 93.9, 90.7, 70.9, 67.5, 57.2, 56.8, 52.2, 40.1, 36.7, 27.0, 26.5, 14.3; **IR** (film, cm^{-1}) 3399, 2950, 1711, 1611, 1585, 1357, 1224, 751; **TLC** R_f = 0.17 (1:4 acetone:toluene v/v); **HRMS** (DART) *m/z* Calc'd for $C_{24}H_{26}ClO_9$ $(M+H)^+$: 493.1260, found 493.1268.

In flame dried flask outfitted with a septum, racemic epoxide **2.4** (81.2 mg, 0.527 mmol, 1.8 equiv.) was dissolved in 1.3 mL of toluene followed by the addition of 4-des-methyl-griseofulvin

3.11 (99.5 mg, 0.294 mmol, 1.0 equiv.). The resulting solution was thoroughly degassed with argon and cooled to -40 °C. In a separate flask, $Pd_2(dba)_3$ (16.7 mg, 5.0 mol%) of and (*S*,*S*)-**L2** (38.9 mg, 15.0 mol%) was dissolved in 0.6 mL of toluene. The resulting purple solution was degassed and stirred at room temperature until it became yellow (approx. 10 min.). The solution was then cooled to -40 °C and added to the epoxide solution via syringe. The reaction was continued at -40 °C and monitored by ^{1}H NMR until total consumption of the starting phenol was observed (approx. 18 hours). The reaction was then concentrated to dryness and purified by flash chromatography (100% DCM, then 95:5 DCM/MeOH, v/v) using Florisil as the stationary phase to yield 132.4 mg of a mixture containing **3.14 (**54% yield), **3.15** (25% yield), and 6.2 mg of recovered phenol **3.11** (6%). Degradation of the products on Florisil is suspected to regenerate griseofulvin **3.11**. Similar degradation, but to a much greater extent, was observed when using silica as the stationary phase. Analytical standards of **3.14** and **3.15** could be separated from one another and purified by a silica column (5:1 toluene/acetone, v/v) then preparatory HPLC (80:20 to 35:65 water:acetonitrile v/v over 35 minutes) to remove **3.11**. Both products were isolated as white solids.

Methyl (5S, 6R)-5-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-enecarboxylate (3.14)

$[\alpha]_D^{20.0}$ +61.0 (*c* 1.00, $CHCl_3$); **M.p.** 196 – 198 °C; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.32 – 7.27 (m, 1H), 7.20 (s, 1H), 5.53 (s, 1H), 5.23 (d, *J* = 3.8 Hz, 1H), 4.05 (s, 3H), 3.81 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 3.05 (dd, *J* = 16.5, 13.5 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.64 – 2.52 (m, 1H), 2.50 – 2.28 (m, 2H), 2.23 – 2.09 (m, 1H), 2.04 – 1.91 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.9, 194.7, 170.7, 169.1, 166.7, 165.3, 158.8, 146.8, 128.0, 107.2, 104.9, 98.6, 97.8, 90.9, 77.7, 69.3, 57.5, 56.8, 52.2, 40.2, 36.6, 25.8, 24.7, 14.4; **IR** (film, cm^{-1}) 3468, 2949, 1709, 1611, 1224, 1046, 753; **TLC** R_f = 0.26 (1:4 acetone/toluene v/v); **HRMS** (DART) *m/z* Calc'd for $C_{24}H_{26}ClO_9$ $(M+H)^+$: 493.1260, found 493.1268.

Methyl (3R, 6S)-3-hydroxy-6-O-(4-des-methyl-griseofulvin)-cyclohex-1-enecarboxylate (3.15)

$[\alpha]_D^{20.0}$ +96.9 (*c* 1.00, $CHCl_3$); **M.p.** 102 – 104 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.15 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.53 (s, 1H), 5.51 (s, 1H), 5.34 (d, *J* = 3.2 Hz, 1H), 4.33 (ddd, *J* = 10.3, 6.2, 2.6 Hz, 1H), 4.01 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 3.04 – 2.93 (m, 1H), 2.87 – 2.78 (m, 1H), 2.47 – 2.35 (m, 2H), 2.20 – 1.94 (m, 2H), 1.73 (tt, *J* = 13.9, 3.6 Hz, 1H), 0.94 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.0, 192.3, 171.1, 169.4, 166.2, 164.6, 156.6, 147.5, 129.1, 106.7, 104.8, 97.9, 94.2, 90.7, 71.0, 67.5, 57.2, 56.8, 52.2, 40.1, 36.6, 27.1, 26.5, 14.4; **IR** (film, cm^{-1}) 3400, 2940, 1712, 1612, 1357, 1177, 750; **TLC** R_f = 0.17 (1:4 acetone:toluene v/v); **HRMbS** (DART) *m/z* Calc'd for $C_{24}H_{26}ClO_9$ $(M+H)^+$: 493.1260, found 493.1272.

Total synthesis of rubiyunannin B aglycone

Synthesis of 3-iodotyrosine: 3-Iodotyrosine was synthesized according to a modified literature procedure.[9] In a 3L three neck round bottom flask, 12.00 g (66.23 mmol) of tyrosine was dissolved in 600 mL concentrated NH_4OH and cooled to 0 °C. 16.75g (66.23 mmol, 1.0 eq) of I_2 was dissolved in 150 mL of absolute ethanol and placed in an addition funnel. The addition funnel was placed above a *plastic* conical funnel with in turn was positioned above the three neck flask (during the course of the addition of the iodine, a small amount nitrogen triiodide (touch explosive) will form on the tip of the dropping apparatus. For safety, having the nitrogen triiodide form on the plastic funnel rather than a glass addition funnel reduces hazards should a small explosion occur). Iodine was added dropwise slowly over the course of 2 hours at 0 °C. Upon completion of the addition, the reaction is stirred for 1 hour before the reaction was concentrated to a slurry. The slurry was suspended in 150 mL of water and the solution was brought to a pH of 5 with concentrated HCl. The solid was filtered and suspended in acetone at 0 °C for 1 hour. Filtration of the solid yielded 9-12 g of 3-iodotyrosine.

FmocMeN-3I-tyrosine-OH (3.48): FmocMeN-3I-tyrosine-OH was synthesized according to modified literature procedure.[10] Fmoc-3I-Tyrosine-OH (12.00 g, 22.795 mmol) was dissolved in

110.0 mL of benzene and 4.00 mL of DMF. Paraformaldehyde (4.10 g, 0.136 mol, 6 eq.) and TsOH (390 mg, 2.28 mmol, 0.10 eq.) were added, and the reaction heated to 100 °C for 2 hours. Upon cooling, the reaction was diluted with EtOAc (100 mL), washed with saturated sodium bicarbonate (100 mL), dried over Na_2SO_4 and concentrated to yield a crude oil. The crude oil (*ca*. 8.20 g, 15.15 mmol) was dissolved in 6.00 mL of TFA and 6.00 mL of CH_2Cl_2. The reaction was cooled to 0 °C and Et_3SiH (7.26 mL, 45.44 mmol, 3 eq.) was added. The flask was allowed to warm to room temperature and stirred for 4 hours. After concentration the oil was azeotroped with hexanes (3 x 50 mL) to remove excess TFA to yield 7.50 g (13.80 mmol, 60 % yield) of FmocMeN-3I-tyrosine-OH whose spectra matched literature spectra.

FmocMeN-3I-tyrosine(OMOM)-OMe (3.49): FmocMeN-3I-tyrosine-OH (7.50 g,13.80 mmol) was dissolved in MeOH (70 mL). $SOCl_2$ (2.00 mL, 27.60 mmol, 2.0 eq.) was added dropwise, and the reaction was heated to 50 °C for 2 hours. Cooling and concentration under reduced pressure yielded crude FmocMeN-3I-tyrosine-OMe which is used without further purification. FmocMeN-3I-Tyrosine-OMe (7.60 g, 13.80 mmol) was dissolved in CH_2Cl_2 (80 mL) and DIPEA (4.20 mL, 24.220 mmol, 1.7 eq) was added. The reaction was cooled to 0 °C and MOMCl (1.47 mL, 19.38 mmol, 1.4 eq) is added dropwise under argon. The reaction was stirred for 2 hours before DIPEA (2.00 mL, 12.11 mmol, 0.85 eq) and MOMCl (0.73 mL, 9.65 mmol, 0.7 eq) were added again. The reaction was stirred for another 2 hours and the procedure was repeated until TLC and LC/MS indicated no starting material. The reaction was quenched by the addition of 1M HCl (20 mL) and the layers separated. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield crude **3.49** which was purified by flash chromatography (4:1 hexanes/EtOAc, v/v) to yield 3.00 g (4.98 mmol, 31 % yield) of FmocMeN-3I-tyrosine(OMOM)-OMe as a translucent oil.

$\mathbf{[\alpha]_D^{20.0}}$ = -40.3 (*c* 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$, 1.5:1 mixture of rotamers) δ 7.87 – 7.20 (m, 9H), 7.20 – 6.73 (m, 2H), 5.18 and 5.13 (s, 2H), 5.00 – 4.13 (m, 4H), 3.76 and 3.63 (s, 3H), 3.84 – 3.24 (m, 1H), 2.84 and 2.80 (s, 3H), 3.11 – 2.51 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$,

mixture of rotamers) δ 171.2, 170.7, 156.5, 155.9, 155.0, 154.9, 144.0, 143.8, 141.3, 141.2, 139.7, 139.5, 132.5, 132.4, 129.8, 129.7, 127.7, 127.1, 125.1, 124.6, 120.0, 120.0, 114.8, 114.8, 95.0 (br), 87.1, 87.0, 67.8, 67.4, 60.2, 60.1, 56.4, 56.3, 52.4, 52.4, 47.2, 47.1, 33.7, 33.6, 32.1, 31.8. **IR** 3023, 2950, 1707, 1654,1222. **HRMS (**DART$^+$) calc'd for $C_{28}H_{29}INO_6$: 602.1040, found 602.1033. **TLC** R_f = 0.35 (2:1 hexanes/EtOAc, v/v)

HMeN-3I-tyrosine(OMOM)-OMe (3.41): FmocMeN-3I-tyrosine(OMOM)-OMe (1.20 g, 2.00 mmol) was dissolved in CH_2Cl_2 (10.0 mL), and diethylamine (4.12 mL, 40.0 mmol, 20 eq.) was added. The reaction was stirred overnight and then concentrated. Flash chromatography (3:1 hexanes/EtOAc, v/v then EtOAc, then 9:1 EtOAc/MeOH, v/v) yielded 560.0 mg (1.47 mmol, 74 % yield) of HMeN-3I-tyrosine(OMOM)-OMe.

$[\alpha]_D^{20.0}$ = +9.30 (*c* 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (t, *J* = 1.6 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.19 (s, 2H), 3.68 (s, 3H), 3.49 (s, 3H), 3.38 (td, *J* = 6.7, 1.2 Hz, 1H), 2.84 (dd, *J* = 6.7, 3.2 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.6, 154.9, 139.9, 132.6, 130.2, 114.7, 95.0, 87.2, 64.4, 56.4, 51.7, 38.0, 34.7. **IR** (cm^{-1}) 3337, 2970, 1732, 1487, 1150, 984. **HRMS** (DART$^+$) calc'd for $C_{13}H_{19}INO_4$: 380.0359, found: 380.0352. **TLC:** R_f = 0.2 (1:1 hexanes/EtOAc, v/v)

CbzMeN-3I-tyrosine-OH (3.44): CbzMeN-3I-tyrosine-OH was synthesized according to a modified literature procedure in the same manner as FmocMeN-3I-tyrosine-OH. Spectral data matched literature.[11]

CbzMeN-3I-tyrsoine(OBn)-OMe (3.45): CbzMeN-3I-tyrosine-OH (2.50 g, 5.49 mmol) was dissolved in MeOH (28.0 mL), and $SOCl_2$ (0.84 mL, 11.5 mmol, 2.1 eq.) was added dropwise. The reaction was heated at 50 °C for 2 hours before cooling and concentration under reduced pressure. The crude CbzMeN-3I-tyrosine-OMe (2.10 g, 4.475 mmol) was dissolved in DMF (22.0 mL), and K_2CO_3 (1.30 g, 9.40 mmol, 2.1 eq.) was added followed by the addition of BnBr (0.69 mL, 5.82 mmol, 1.3 eq). The reaction was heated to 50 °C and stirred overnight under argon. The reaction

was cooled, diluted with H_2O (50 mL) and extracted (3 x 50 mL) with EtOAc. The EtOAc was washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated to yield a crude oil which was purified by flash chromatography (4:1 hexanes/EtOAc, v/v) to yield **3.45** (1.20 g, 2.145 mmol, 50 % yield) as a translucent oil.

$[\alpha]_D^{20.0}$ = -35.3 (*c* 1.00, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, isolated as a 1.20:1 mixture of rotamers) δ 7.71 – 7.53 (m, 1H), 7.55 – 7.20 (m, 10H), 7.13 (dd, *J* = 8.4, 2.2 Hz) and , 7.03 (dd, *J* = 8.3, 2.1 Hz) 1H, 6.77 and 6.73 (d, *J* = 8.4 Hz) 1H, 5.14, 5.12, 5.04 and 3.78 (s, 4H), 4.96 and 4.81 (dd, *J* = 10.6, 5.0 Hz) 1H, 3.78 and 3.70 (s, 3H), 3.30 – 3.17 and 3.31 – 3.16 (m, 2H), 3.02 and 3.01 (s, 3H). **^{13}C NMR** ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 171.2, 171.0, 156.6, 156.1, 156.1, 155.8, 139.8, 136.6, 136.5, 136.5, 136.2, 129.9, 129.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.9, 127.6, 127.0, 112.6, 112.5, 86.8, 86.6, 70.8, 67.6, 67.4, 65.3, 60.6, 60.3, 52.4, 33.9, 33.6, 32.1, 31.8. . **IR** (cm^{-1}) 3031, 2359, 1698, 1740, 1482, 734. **HRMS** ($DART^+$) calc'd for $C_{26}H_{27}INO_5$, found 560.0934. **TLC** R_f = 0.4 (2:1 hexanes/EtOAc, v/v)

CbzMeN-3Bpin-tyrsoine(OBn)-OMe (3.46): CbzMeN-3I-tyrsoine(OBn)-OMe (1.10 g, 2.05 mmol) was added to DMSO (10.0 mL) and degassed with argon and sonication. B_2pin_2 (676.80 mg, 2.67 mmol, 1.3 eq), KOAc (603.65 g, 6.15 mmol, 3 eq.) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (83.72 mg, 0.10 mmol, 0.05 eq) was then added. The reaction was heated at 80 °C for 12 hours. Upon cooling, the reaction was diluted with H_2O (30 mL) and extracted (3 x 30 mL) with EtOAc. The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield a black oil which was purified by flash chromatography (5:1 hexanes/EtOAc, v/v) to yield CbzMeN-3Bpin-tyrsoine(OBn)-OMe (900 mg, 1.609 mmol, 52 % yield) as a clear oil.

$[\alpha]_D^{20.0}$ = -31.8 (*c* 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$, isolated as a 1.10:1 mixture of rotamers) δ 7.73 – 7.48 (m, 3H), 7.46 – 7.07 (m, 9H), 6.82 (t, *J* = 8.9 Hz, 1H), 5.20 – 5.00 (m, 4H), 4.95 and 4.78 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.73 and 3.66 (s, 3H), 3.35 – 3.19 (m, 1H), 3.10 – 2.89 (m, 1H), 2.85 and 2.83 (s, 3H), 1.37 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers) δ

171.7, 171.4, 162.3, 162.2, 156.6, 156.0, 137.7, 137.7, 137.3, 137.2, 136.8, 136.5, 133.0, 132.8, 129.9, 129.0, 128.9, 128.5, 128.2, 127.9, 127.6, 127.4, 126.8, 112.2, 112.2, 83.6, 70.0, 70.0, 67.4, 67.3, 60.9, 60.5, 52.3, 34.4, 34.1, 32.4, 31.9, 25.0. . **IR** (cm^{-1}) 2977, 1742, 1702, 1605, 1141, 750. **HRMS** ($DART^{+}$) calc'd for $C_{32}H39BNO_7$ 560.2820, found 560.2815. **TLC** R_f= 0.14 (4:1 hexanes/EtOAc, v/v)

Dityrosine 3.45: CbzMeN-3Bpin-tyrsoine(OBn)-OMe (220.00 mg, 0.40 mmol) was dissolved in THF:MeOH:H_2O (3.20 mL, 3:1:1 ratio) and cooled to 0 °C. $LiOH{\cdot}H_2O$ (37.30 mg, 0.79 mmol, 2.0 eq.) was added and the reaction is stirred at 0 °C for 2 hours. Upon completion, the solution was carefully acidified to pH 2 by the addition of 1 M HCl (10 mL) and extracted with EtOAc (2 x 10 mL). After drying over Na_2SO_4, the solution was concentrated to yield CbzMeN-3Bpin-tyrsoine(OBn)-OH (180.0 mg, 0.33 mmol, 83 % yield) which was used in the next reaction without purification.

CbzMeN-3Bpin-tyrsoine(OBn)-OH (220 mg, 0.40 mmol) was dissolved in THF (2.00 mL), and EDC (100.50 mg, 0.52 mmol, 1.3 eq.) and HOAt (82.30 mg, 0.61 mmol, 1.5 eq) were added at 0 °C. The reaction was stirred for 5 minutes before HNMe-3I-tyrosine(OMOM)-OMe (200.00 mg, 0.524 mmol, 1.3 eq) in 0.50 mL of THF and DIPEA (0.14 mL, 0.85 mmol, 2.1 eq.) was added. The reaction was allowed to warm to room temperature and stirred under argon for 48 hours. Upon completion, the reaction was diluted with EtOAc (10 mL), washed with 1M HCl (2 x 10 mL) and saturated sodium bicarbonate solution (10 mL). The solution was dried over Na_2SO_4 and concentrated *in vacuo* to yield 230mg (0.254 mmol, 63 % yield) of **3.50** as an unstable white solid, yet sufficiently pure to be used in the next step.

Dityorsine *P-cis*-**3.39a**: **3.50** (20 mg, 0.03 mmol) was dissolved in 0.2 mL THF and 0.2 mL of 0.5M K_3PO_4 solution. The reaction was degassed by sparging with argon over sonication for 15 minutes. Xphos Pd G2 was added and the reaction heat at 40 °C for 30 minutes. The reaction was cooled and diluted with 1.0 mL 1M HCl. The aqueous layer was extracted with EtOAc (2 x 3.00 mL), and the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The

material could be purified at this point by flash chromatography (3:1 hexanes/EtOAc, v/v) but was used next step without purification. **HRMS** (DART$^+$) calc'd for $C_{38}H_{41}N_2O_8$ 653.2863, found 653.2858. **TLC** R_f= 0.67 (1:1 hexanes/EtOAc, v/v). Crude **3.50** was dissolved in THF (0.2 mL) and 4M HCl (0.1 mL) was added. The reaction was heated at 50 °C for 30 minutes and then cooled. Concentration and purification by flash chromatography (3:1 hexanes/EtOAc, v/v) yielded **3.39** **(**8.50 mg, 0.014 mmol, 56% yield) as a single diastereomer.

P-cis-**3.39a: $[\alpha]_D^{20.0}$** = -21.9 (*c* .85, $CDCl_3$) **^{1}H NMR**: (600 MHz, $CDCl_3$) δ 7.35 – 7.40 (m, 10H), 7.06 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 5.60 (dd, *J* = 11.6, 4.4 Hz, 1H), 5.52 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.24 (d, *J* = 11.6 Hz, 1H), 5.16 (d, *J* = 11.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.12 (m, 1H), 3.61 (dd, *J* = 16.3, 4.5 Hz, 3H), 3.60 (s, 3H), 3.06 (dd, *J* = 16.8, 11.6 Hz, 1H), 2.98 (s, 3H)2.70 (s, 3H), 2.45 (dd, *J* = 14.8, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers): 29.67, 29.77, 32.65, 32.65, 34.74, 34.74, 52.50, 56.66, 60.64, 67.85, 67.85, 71.04, 71.04, 110.99, 115.64, 126.01, 127.58, 127.65, 128.33, 128.43, 128.60, 128.97, 129.51, 131.28, 136.06, 136.36, 139.85, 140.66, 152.33, 153.63, 156.15, 171.26, 172.13, 127.5, 127.5, 128.5. **IR** (cm^{-1}) 3339, 2926, 2850, 1741, 1694, 1650, 1217, 735. **HRMS** (DART$^+$) calc'd for $C_{36}H_{37}N_2O_7$ 609.2601, found 609.2593. **TLC** R_f = 0.56 (1:1 hexanes/EtOAc, v/v)

M-trans-**3.39b: ^{1}H NMR** (600 MHz, CDC_3) δ 7.41–7.30 (m, 10H), 7.11 (m, 1H), 7.05 (dd, *J* = 9.23, 1.78 , 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.62 (bs, 2H), 5.81 (dd, *J* = 10.8, 4.0 Hz, 1H), 5.65 (dd, *J* = 12.2, 3.6 Hz, 1H), 5.23 (d, *J* = 11.8 Hz, 1H), 5.20 (m, 1H), 5.17 (m, 1H), 5.16 (m, 1H), 3.76 (*s*, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.08 (m, 1H), 3.01 (s, 3H), 2.96 (s, 3H), 2.82 (m, 1H). **^{13}C NMR:** see Table 3.3.

P-trans-**3.39a**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (m, 10H), 7.08 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.77 (s, 1H), 5.56 (dd, *J* = 11.4, 3.2 Hz, 1H), 5.17 (m, 4H), 3.91 (t, *J* = 5.9 Hz, 1H), 3.66 (s, 3H) 3.51 (dd, *J* = 15.2, 11.4 Hz, 1H), 3.41 (dd, *J* = 15.6, 5.4 Hz, 1H), 3.13 (dd, *J* = 15.6, 6.5 Hz, 1H), 3.02 (s, 3H), 2.99 (s, 3H), 2.73 (dd, *J* = 15.2, 3.1 Hz, 1H).

Table 3.2: NMR shifts and key correlations for *cis*-3.39a

Number	^{1}H δ	^{13}C	J	key nOe	COSY
1	--	172.13	--		
2	5.52	56.66	10, 1.2	5, 17	3
3ax	4.12	34.74	m	18	2, 3eq, 9 (wk)
3eq	2.45	34.74	14.8, 1,4		2, 3ax, 9
4	--	131.28			
5	6.74	140.66	2.6		
6	6.80	110.99	8.2		
7	--	153.63	--		
8	--	128.97	--		
9	7.06	128.60	8.1, 2.6	2, 17, 32	3 ax, 3eq (wk)
10	--	128.33	--		
11	--	152.33	--		
12	6.77	115.64	8.2		
13	7.04	129.51	8.2, 2.4		16ax, 16eq
14	--	126.01	--		
15	6.83	139.85	2.8	17	
16ax	3.06	32.65	16.8, 11.6	32	17, 16eq, 13
16eq	3.61	32.65	16.3, 4.5	17	17, 16ax, 13
17	5.60	60.64	11.6, 4.4	2, 5, 15, 16eq	16
18	2.98	29.77	*s*	3ax	
19	--	156.15	--		
20a	5.04	67.85	12.5		
20b	5.12	67.85	12.5		
21	--	136.36	--		
22	7.38-7.41	127.5-128.5	*m*		
23	7.38-7.41	127.5-128.5	*m*		
24	7.38-7.41	127.5-128.5	*m*		
25a	5.16	71.04	11.5		
25b	5.24	71.04	11.5		
26	--	136.06	--		
27	7.39	127.58	*m*		
28	7.38	128.43	*m*		
29	7.41	127.65	*m*		
30	--	171.26	--		
31	3.60	52.50	*s*		
32	2.70	29.67	*s*	16ax	

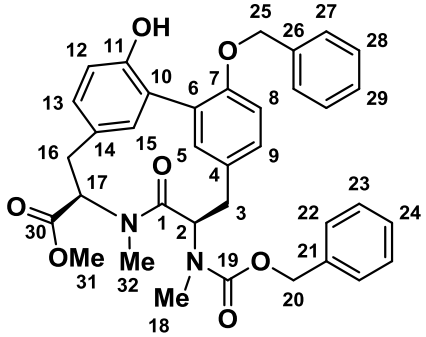
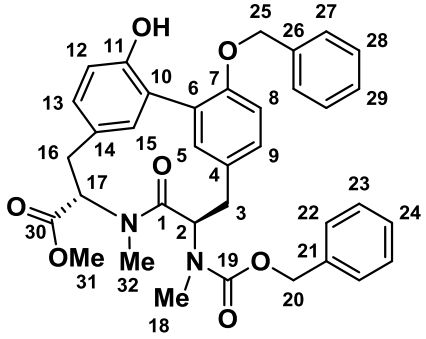


Table 3.3: NMR shifts and key correlations for *trans*-3.39b

Number	^{1}H δ	^{13}C δ	J (Hz)	key nOe	COSY
1	--	171.62	--		
2	5.65	55.17	12.2, 3.6	5, 32	3ax, 3eq
3ax	3.56	32.46	m	18	2, 9
3eq	2.80	32.46	m		2, 9
4	--	130.22	--		
5	7.12	128.54	m	2, 32	
6	6.91	112.04	8.3		
7	--	152.81	--		
8	--	128.08	--		
9	6.62	138.18	*bs*		3eq, 3ax
10	--	126.70	--		
11	--	152.57	--		
12	6.79	115.64	8.5		
13	7.06	128.97	9.2, 1.8		16eq, 16ax
14	--	126.72	--		
15	6.62	136.78	*s*	16eq, 17, 32	
16ax	3.08	30.85	*m*	32	13, 17
16eq	3.51	30.85	*m*	15, 17	13, 17
17	5.81	55.69	10.8, 4.0	15, 16eq	
18	3.01	29.81	*s*	3ax	
19	--	156.02	--		
20a	5.16	67.96	*m*		
20b	5.21	67.96	*m*		
21	--	136.41	--		
22	7.38	128.52	*m*		
23	7.37	128.55	*m*		
24	7.37	128.5	*m*		
25a	5.17	71.36	11.8		
25b	5.23	71.36	11.8		
26	--	135.77	--		
27	7.40	127.55	*m*		
28	7.40	128.73	*m*		
29	7.39	128.81	*m*		
30	--	171.48	--		
31	3.76	52.56	*s*		
32	2.96	30.32	*s*	2,5,15,16ax,17	



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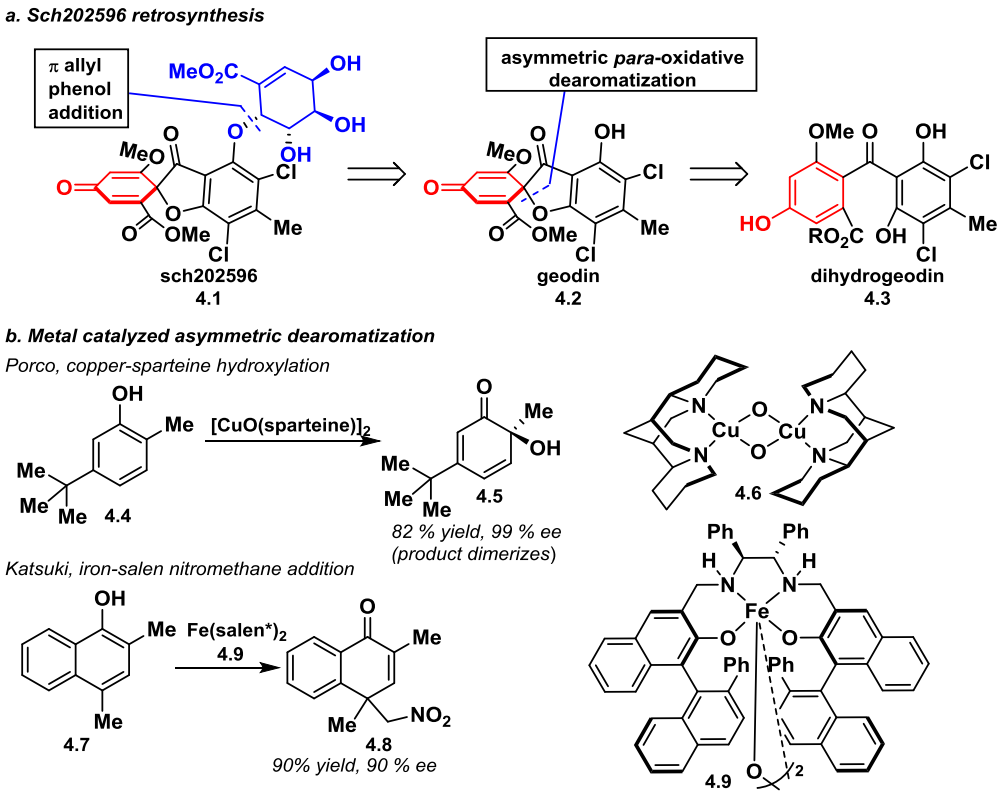
CHAPTER 4

HYPERVALENT IODINE CYCLIZATIONS: SYNTHESIS OF ARNOTTIN I AND II

As previously commented upon, sch202596 contains two important moieties: a carbasugar and a spirocoumaranone (Scheme 4.1a). The installation of the carbasugar has already been addressed (Chapter 2). The second moiety of interest is the dienone found on the precursor, geodin (**4.2**), derived in Nature from the corresponding phenolic compound **4.3**. The oxidation of **4.3** is catalyzed by the enzyme cytochrome p450 to obtain a single enantiomer of **4.2**. Methods for the installation of asymmetric oxidative dearomatization products are limited;[1] however, organometallic catalysis has provided some useful transformations in this area (Scheme 4.1b).



Scheme 4.1: Oxidative dearomatization of phenols

Porco and co-workers have hydroxylated phenols using copper-sparteine-oxo specie **4.6**[2] while Katsuki has been able to perform oxidative dearomatization-additions of naphthols using iron-oxo species such as **4.9**.[3] A final area of asymmetric oxidative cyclizations and the focus of this study employs chiral hypervalent iodide reagents.

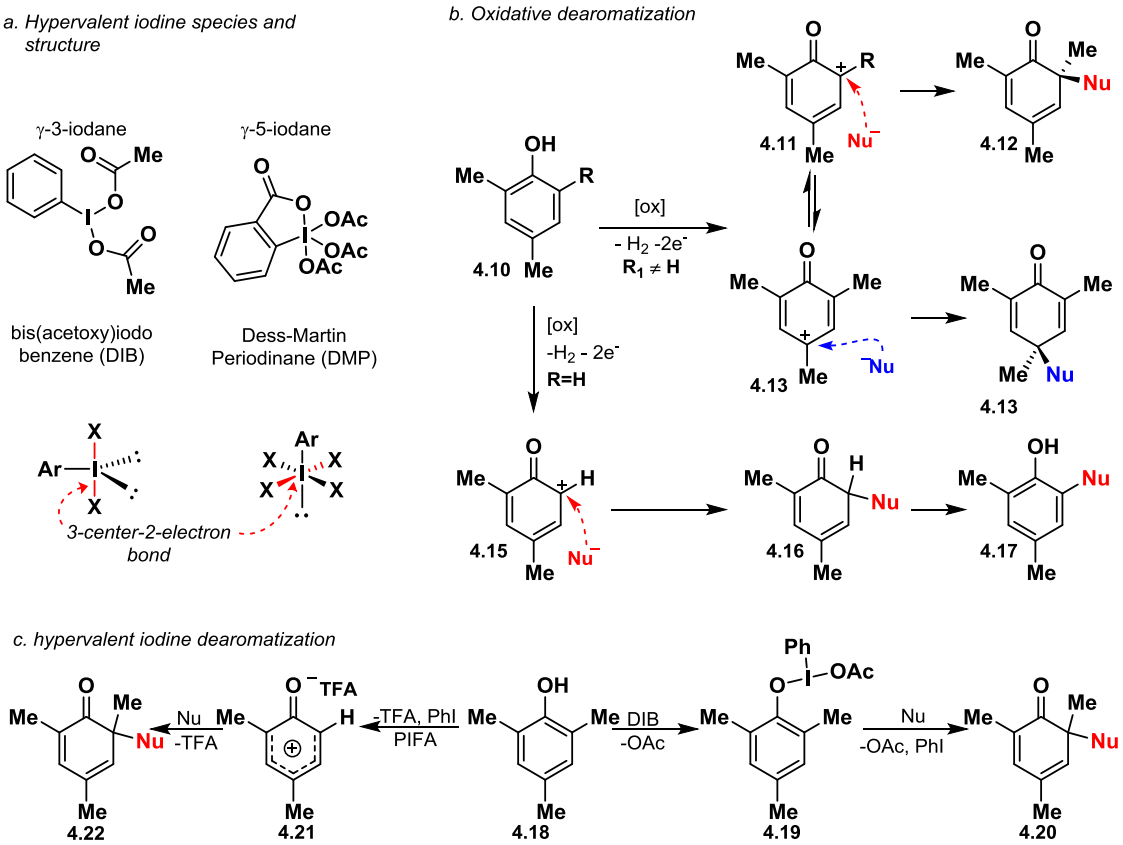
4.1: Overview of hypervalent iodine and asymmetric oxidative cyclizations

Hypervalent iodide has recently become an important oxidant for chemical transformations.[4] It is relatively non-toxic and made from inexpensive precursors. Hypervalent iodine species are found in either an oxidation state of +3, such as in $PhI(OAc)_2$, +5 (DMP) or +7 ($NaIO_4$) (Scheme 4.2a). For compounds in the +3 oxidation state (or γ-3-iodanes), the iodine is bound through a normal σ bond to an aryl group. Two ligands occupy apical positions at an angle of 180°, and the ligand-iodine-ligand bond is considered 3-center-2 electron bond, in that two electrons are shared between the two ligand-iodide bonds.[5] Stability of the 3-center-2-electron bond is achieved through electronically deficient ligands, thus making the iodine electron deficient and an excellent oxidant.

Hypervalent iodine compounds have been employed in numerous oxidations. $PhI(OAc)_2$ (DIB) is employed as an oxidant in conjunction with TEMPO for the oxidation of alcohols[6] or as a terminal oxidant in palladium catalyzed oxidations.[7] Hypervalent iodine compounds can also perform the oxidation of phenol to dienones.

One type of phenolic oxidation is an oxidative dearomatization-nucleophilic addition reaction (Scheme 4.2b).[8] Two forms of oxidative dearomatization exist depending on the substitution of the phenol. Upon binding to the oxidant, the *ortho* and *para* position becomes electrophilic. If the *ortho* or *para* position is unsubstituted (**4.15**) then nucleophilic attack will occur followed by rearomatization to give substituted aryl compounds like **4.17**; however, if the *ortho* or *para* position are substituted, nucleophilic attack will occur resulting in dearomatization of the starting phenol and introduction of a stereocenter (**4.12** or **4.13**). *Ortho* and *para* selectivity derives

from numerous factors, such as sterics and electronic parameters as well as nucleophile choice (due to hydrogen bonding with the nucleophile).[8]



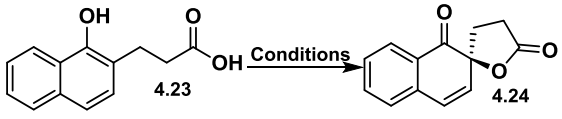
Scheme 4.2: Hypervalent iodine mediated oxidative dearomatization

Mechanistically, hypervalent iodine catalyzed oxidative dearomatizations are thought to proceed via a ligand exchange reaction where the phenol displaces an apical ligand (**4.19**) and is oxidized (Scheme 4.2c). Depending on the electron withdrawing capability of the ligand, it is possible for ionization to occur first resulting in a cationic allyl species **4.21** which is then trapped by a nucleophile.[9] Bis(trifluoroacetoxy)iodobenzene (PIFA) is thought to act through the latter mechanism whereas DIB reacts through the former.

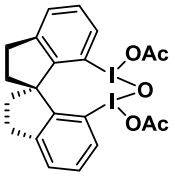
The generation of a stereocenter also allows for asymmetric variants of this oxidation. Few examples of asymmetric hypervalent iodine oxidations exist. Kita demonstrated in 2009 that chiral hypervalent iodine species such as **4.25** can be employed in the oxidative dearomatization of 1-

naphthols.[10] Enantiomeric excesses of 65% were obtained employing chiral species **4.25** (Table 4.1, entry 1). Ishihara expanded upon this reaction with a new hypervalent iodine species **4.26**.[11] He was able to cyclize **4.23** using catalytic **4.26** and *m*-CPBA as a terminal oxidant to yield **4.24** in 55% yield and 92% ee (Table 4.1, entry 3). We looked to expand the use of chiral hypervalent iodine species with the ultimate goal of the synthesis of geodin through an (unprecedented) *para* asymmetric oxidative cyclization.

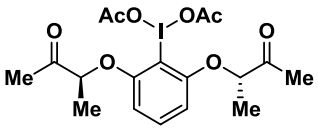
Table 4.1: Asymmetric hypervalent iodine examples



Entry	catalyst (mol %)	% yield	% ee	additives
1	**4.25** (55)	72	66	
2	**4.25** (15)	70	65	mCPBA (1.3eq)
3	**4.26** (15)	55	92	mCPBA (1.3eq)



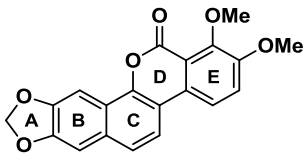
4.25



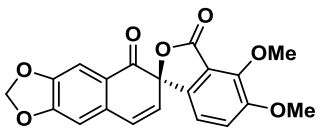
4.26

4.2: Previous synthesis of Arnottin II

Before attempting the synthesis of geodin, we sought to synthesize a natural product containing an *ortho* subsisted oxidative dearomatization. Arnottin II is one such compound. The arnottins (I and II) are coumarin-type natural products isolated from the bark of the *xanthoxylkum arnottianum Maxim* (rutaceae) and are surmised to possess antibiotic properties (Figure 4.1).[12] Syntheses of these interesting metabolites have been reported after the initial isolation and structural determination.[13] Arnottin I is not thought to be the biosynthetic precursor to arnottin II but rather a branch metabolite. There have been numerous syntheses of arnottin I whereas only one reported synthesis of arnottin II.



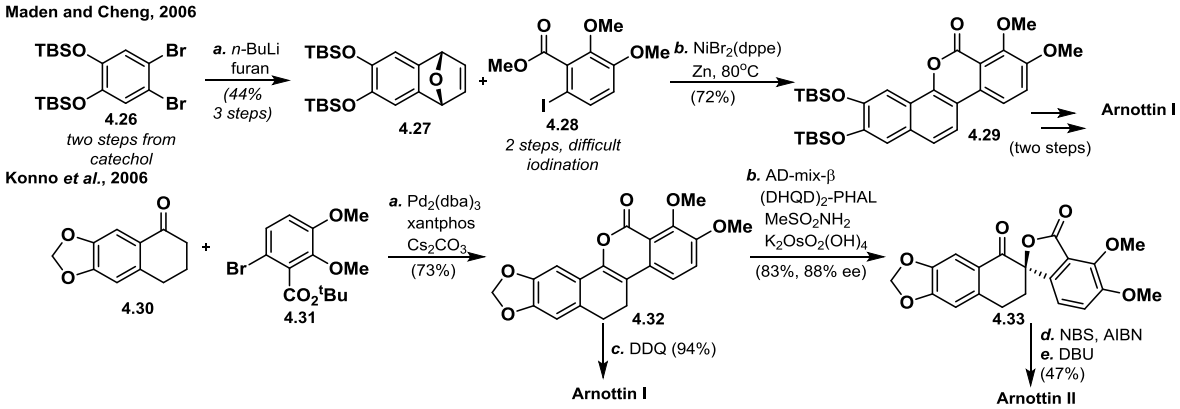
Arnottin I



Arnottin II

Figure 4.1: Arnottin I and II

Syntheses of arnottin I usually forge the C and D rings simultaneously through a coupling reaction. Madan and coworkers form the C ring through a benzyne-furan [4+2] cycloaddition followed by tandem Ni catalyzed Heck-lactonization reaction (Scheme 4.3a).[14] Though expedient, the reaction requires a change in protection groups and the use of aryl iodide **4.28**. The aryl iodide is difficult to procure requiring stoichiometric amounts of toxic thallium trifluoroacetate. A second synthesis of arnottin I and arnottin II attempted by Konno and co-workers relies on construction of the D ring through an enol-Heck-lactonization cascade (Scheme 4.3b).[15] This procedure, though elegant, requires 6,7-dimethoxy-1-tetralone (**4.30**, $40/g) as starting material and results in dihydro-arnottin-I (**4.32**, converted in a single step to arnottin I). The only synthesis of arnottin II employs a Sharpless dihydroxylation of **4.32** to afford dihydro-arnottin II, **4.33** in 83% yield and 88% ee (crystallized to 93% ee) which is converted to arnottin II in two steps. We therefore thought that oxidative cyclization of arnottin I acid would be a rapid method of the synthesis for arnottin II.

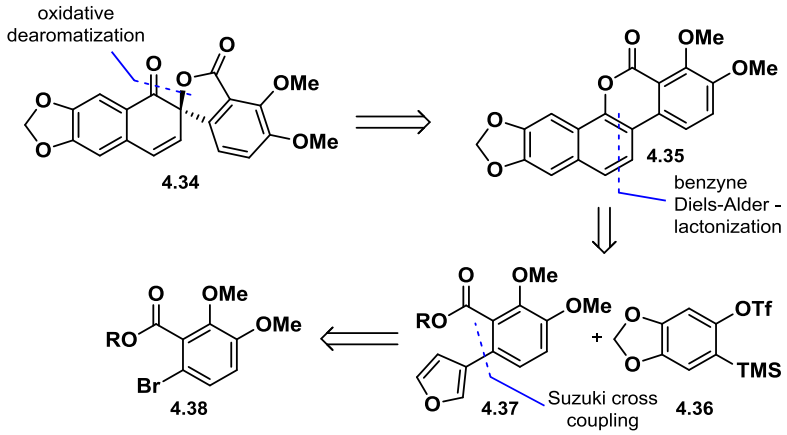


Scheme 4.3 Previous synthesis of arnottin I and arnottin II by Madan and Konno

4.3: Synthesis of arnottin I and II

Tandem oxidative dearomatization and spirocyclization[1,8] is capable of converting simple benzocoumarins to chiral spirocyclic lactones which are found in several natural product families. The direct conversion of arnottin I to arnottin II using this method has not yet been reported. Recent advances have allowed for asymmetric hypervalent iodide oxidative dearomatization;[10,11] however,

few examples exist within total synthesis. In order to study and expand upon current methods for hypervalent iodine mediated spirocyclization, a short and concise synthesis of the arnottins was pursued. The preparation of arnottin I utilized a benzyne cycloaddition, hydrolysis, and oxidative spirocyclization to arnottin II to provide large quantities of the metabolites for testing (Scheme 4.4).

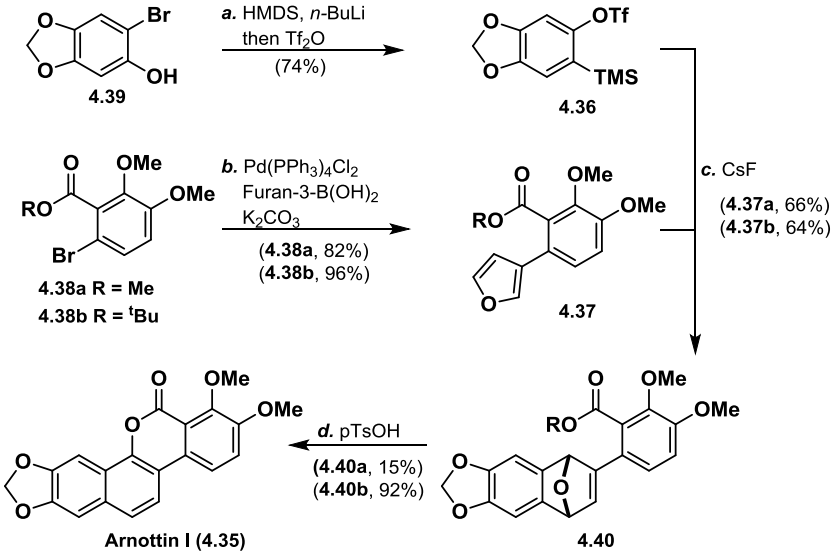


Scheme 4.4: Retrosynthesis of arnottin I and II

A convergent synthetic path to arnottin I was planned using a benzyne cycloaddition with a 3-furyl benzoate, followed by lactone formation (Scheme 4.4). Bis-lithiation of 6-bromosesamol[16] followed by trimethylsilyl chloride quench and triflation using under Mori's procedure[17] afforded benzyne precursor **4.36** in 74% overall yield on 5 gram scale. The furyl coupling partner was prepared from readily available dimethoxybenzoic acid and converted to either the methyl (**4.38a**) or *tert*-butyl bromoester (**4.38b**) in 2 steps.[15] The bromoester (**4.38**) was cross-coupled under Suzuki's condition with commercially available 3-furylboronic acid in 82 and 96% yield for the methyl and *tert*-butyl ester, respectively. The benzyne-mediated cycloaddition proceeded with slow generation of excess (1.4eq) benzyne from seasamol-silyltriflate using weakly soluble CsF in acetonitrile. The *in-situ* cycloaddition produced the arnottin I bridged ether (rac-**4.40a**, rac-**4.40b**) in 66 and 64% yield, respectively.

Unsaturated bicyclic ethers, such as **4.40**, can be converted to naphthols under a variety of conditions including Bronsted acids,[18] ruthenium,[19] rhodium,[20] and aluminum complexes.[21] The naphthol regioisomer produced is less predictable and was unknown for structure **4.40** at the onset of

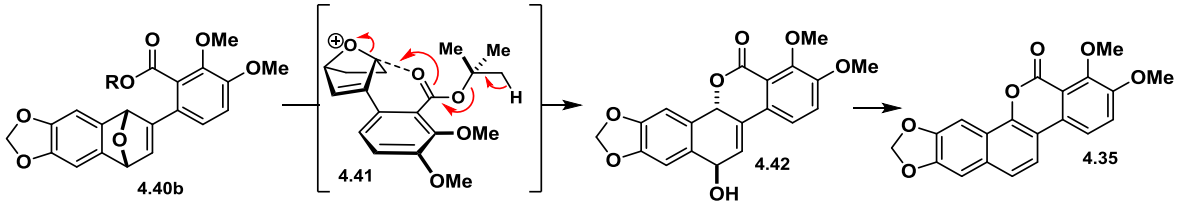
these studies. For the transformation of esters *rac*-**4.40a** and *rac*-**4.40b** to **4.35**, several conditions were attempted: Lewis acids such as BF_3-etherate or $Sc(OTf)_3$ gave complex mixtures and nucleophiles such as NaI and NaBr resulted in degradation. Bronsted acids were effective



Scheme 4.5: Synthesis of arnottin I

with HCl and TsOH both providing arnottin I for *rac*-**4.40a** and *rac*-**4.40b** in differing yield. Exposure of methyl ester *rac*-**4.40a** to TsOH in methanol led to non-regiospecific naphthol formation resulting in both arnottin I (15%) and the 4-naphthol derivative.[22] Identical reaction conditions were attempted with *tert*-butyl ester *rac*-**4.40b** and surprisingly led to clean conversion of arnottin I in 92% yield with no 4-napthol derivative observed. The synthetically prepared arnottin I displayed spectroscopic and physical properties identical to the natural product.[12] The disparity in reaction yield between *rac*-**4.40a** and *rac*-**4.40b** to arnottin I and the absent 4-naphthol derivative in the *rac*-**4.40b** reaction suggests the mechanism follows different paths for each ester employed. The methyl ester (*rac*-**4.40a**) produced both arnottin I and the 4-naphthol derivative suggesting naphthol formation occurred with little specificity. The resultant 1-naphthol produced arnottin I whereas the 4-naphthol was incapable of cyclization. The *tert*-butyl ester (*rac*-**4.40b**) cleanly afforded arnottin I suggesting the ester is deprotected prior to naphthol formation. One plausible mechanism is the weakening of a *tert*-butyl ester proton due to carbonyl lone-pair donation into the C-O σ* of the

bicycle, resulting in loss of isobutylene and carboxylate promoted rupture of the allylic ether as shown by intermediate **4.41** (Scheme 4.6). The resultant benzylic alcohol (**4.42**) is quickly dehydrated to arnottin I. Furthermore, *in situ* ^{1}H NMR, showed no *tert*-butanol formation during the course of the reaction discouraging the phenol formation and lactonization scenario. Isobutylene was not observed, however, the volatility would make detection difficult. The fortuitous sequence afforded large quantities of arnottin I and allowed the study of conversion to arnottin II.

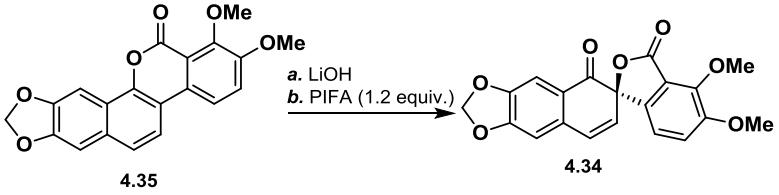


Scheme 4.6: Rupture of bridged furan 4.40

Saponification of arnottin I required immediate exposure to spirocyclization conditions due to competitive recyclization and recovery of arnottin I in acid. Careful hydrolysis of arnottin I was followed by protonation of the carboxylate to a pH of 2-3, which reduced the conversion to arnottin I and retained solubility for the spirocyclization studies. The saponified phenol acid was immediately exposed to different hypervalent iodine conditions to affect the spirocyclization. The highly reactive bis(trifluoroacetoxy)iodobenzene (PIFA) was necessary to form racemic arnottin II in DCM with cesium carbonate as an additive in 23% yield (Table 4.2, entry 1). Given that Kita noted substantial increases in yield using fluorinated solvents[18] trifluoroethanol and hexafluoroisopropanol were also investigated. Trifluoroethanol (TFE, entry 2, 25%) was inferior as compared to hexafluoroisopropanol (HFIP, entry 3, 40%) as solvent. Blends of DCM and HFIP (entry 4, 28%) did not offer enhanced yields. An intensely colored intermediate was formed over the first twenty minutes of the reaction and persisted throughout the duration of the reaction. Two possible intermediates could exist; a ligand exchanged trapped γ3-iodane **4.43**, or a dissociated cationic complex **4.44**.[8] We reasoned the breakdown of the mixed hypervalent intermediate could occur through liberation of the weaker carboxylate donor using a nucleophilic donor. DMAP (entry 5) was added to the reaction, but did not increase the yield substantially as compared to its absence (entry

3). Perchlorate salts, known to increase yields involving nucleophilic addition to phenoxenium radical cations,[15] also did not improve the reaction and had noted degradation (entry 6). Slow addition of PIFA over one hour provided a boost in yield and generated arnottin II in 56% overall yield over the two steps (entry 7).

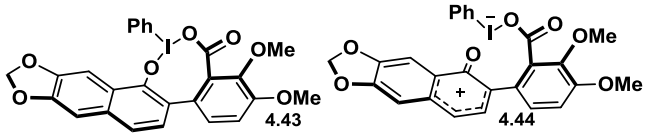
Table 4.2: Hypervalent iodine cyclization conditions



4.35 4.34

entry	solvent	additive	time (h)	temp (°C)	yield[a] (%)
1	DCM	Cs_2CO_3	4	-40	23
2	TFE	–	4	-20	25
3	HFIP	–	12	0	40
4	DCM/HFIP	–	12	0	28
5	HFIP	Et_3N, DMAP	12	0	35
6[b]	HFIP/MeCN	$MgClO_4$	12	0	25
7[b]	HFIP	–	12	0	56

[a]Yield refers to isolated yields following silica gel chromatography. [b]Syringe pump addition of PIFA over one hour.



4.43 4.44

Figure 4.2: Possible hypervalent intermediates

Attempts at asymmetric spirocyclization using chiral hypervalent iodine using Ishihara's catalyst and conditions (catalytic iodide, 1.1eq *m*-CPBA) resulted in the isolation of starting Arnottin I. Similarly when preoxidized chiral reagent **4.26-I(OAc)$_2$** was used only Arnottin I was isolated back. Further investigations were planned into this reaction but were later abandoned due to a shift in focus.

4.4:Experimental

***tert*-Butyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (4.37b):** 1.43 g (4.50 mmol, 1.0 eq.) of *tert*-butyl 6-bromo-2,3-dimethoxybenzoate (**4.38b**),[14] 750.0 mg (6.76 mmol, 1.5 eq.) of furan-3-boronic acid, and 1.865 g (13.50 mmol, 3.0 eq.) of K_2CO_3 were dissolved in DMF (30.0 mL). The resulting solution was degassed under argon for 10 minutes. 253.0 mg of $Pd(PPh_3)_2Cl_2$ (1.06 mmol, 8 mol%) and H_2O (10.0 mL) were then added to the reaction flask, and this solution was stirred at 90 °C for 4 hours. The reaction mixture was run through a Celite plug, diluted with toluene (10.0 mL), and concentrated *en vacuo*. This product was purified by column chromatography (3:1 hexanes/EtOAc, v/v) and dried under vacuum to yield 1.32 g of methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**4.37b**, 96% yield) as a white solid. mp 46-48 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.89 (d, *J* = 1.9 Hz, 6H), 3.83 (s, 3H); δ **^{13}C NMR** (101 MHz, CDCl3) δ 167.0, 151.8, 145.8, 142.8*, 142.7*, 139.7*, 139.6*, 130.4, 124.8, 123.7, 122.5, 113.1, 111.2*, 111.1*, 82.3, 61.5, 56.0, 28.1; **IR** (neat, cm^{-1}) 2973, 2935, 1715, 1482, 1291, 1265, 1059, 1029, 795; **TLC** R_f = 0.60 (3:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* Calc'd for $C_{17}H_{21}O_5$ $(M^+H)^+$: 305.1389, found 305.1375. *denotes rotamers.

Methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (4.37a): 2.00g (18.0 mmol) of methyl 6-bromo-2,3-dimethoxybenzoate (**4.38a**) yielded 3.53g (12.5 mmol, 82% yield) of 6-(furan-3-yl)-2,3-dimethoxybenzoate (**4.37a**) according to the above procedure. m.p. 43-45 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.3, 151.6, 145.9, 143.0, 139.1, 128.3, 124.5, 123.8, 122.6, 113.6, 110.3, 61.5, 55.8, 52.3; **IR** (neat, cm^{-1}) 804, 1258, 1723; **TLC** R_f = 0.4 (2:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* Calc'd for $C_{14}H_{14}O_5$ $(M^+H)^+$: 262.0841, found 262.0838

***tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (4.40b):** 335.0 mg (1.036 mmol, 1.4 eq.) of 6-trimethylsilyl)benzo[d][1,3]dioxol-5-yl-

trifluoromethanesulfonate (**4.36**)[17] and 225.0 mg (0.74 mmol, 1.0 eq.) of *tert*-butyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**4.37b**) were dissolved with acetonitrile (10.0 mL) in a flame-dried flask. The solution was charged with argon, then 337.0 mg (2.22 mmol, 3.0 eq.) of CsF was added and the reaction mixture was let stir at 23 °C for 24 hours. The solution was diluted with water (30.0 mL) and extracted with ethyl acetate (3 x 15.0 mL). The combined organic layers were washed with water (30.0 mL) and brine (30.0 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by column chromatography (3:1 hexanes/EtOAc, v/v) to yield 201.6 mg of *tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**4.40b**, 64% yield) as an off-white solid. m.p. 150 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.5 Hz, 1H), 6.94 (dd, *J* = 1.4, 0.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.83 (t, *J* = 0.5 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.79 (t, *J* = 0.8 Hz, 1H), 5.73 (dt, *J* = 1.8, 0.8 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 1.49 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7, 153.3, 152.6, 146.2, 144.8, 144.4, 143.4, 143.0, 136.7, 129.7, 122.9, 122.1, 112.6, 104.0, 103.7, 101.3, 85.0, 84.0, 82.4, 61.5, 56.1, 28.1; **IR** (neat, cm^{-1}) 2973, 2935, 1715, 1482, 1292, 1265, 1142, 1059, 1029, 795; **TLC** Rf = 0.31 (3:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* Calc'd for $C_{20}H_{17}O_7$ $(M\text{-}C_4H_8)^+$: 369.0974, found 369.0960.

Methyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (4.40a): 780.0 mg (2.23mmol) of methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**4.37a**) yielded 375.0 mg (0.98mmol, 66% yield) of methyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**4.40a**) as per the above procedure. m.p. 56-58 °C (decomp); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.6 Hz, 1H), 6.93 (m, 2H), 6.81 (m, 2H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 5.75 (t, *J* = 0.8 Hz, 1H), 5.71 (dt, *J* = 1.8, 0.8 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 153.5, 152.4, 146.3, 144.7, 144.3, 143.1, 142.6, 136.5, 127.6, 123.4, 122.0, 113.1, 103.9, 103.5, 101.2, 84.9, 83.9, 61.6, 56.0, 52.5; **IR** (neat, cm^{-1}) 2941, 1724, 1460, 1254, 1035; **TLC** Rf = 0.5 (2:1 hexanes/EtOAc v/v); **HRMS** (DART) *m/z* Calc'd for C21H19O7 $(M^+H)^+$: 383.1131, found 383.1129.

Arnottin I (4.35): 150.0 mg (0.354 mmol, 1.0 eq.) of *tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**4.40b**) was added to a flame-dried round-bottomed flask and dissolved in anhydrous MeOH (5 mL). 15.2 mg (0.0884 mmol, 0.25 eq.) of *p*-toluenesulfonic acid was then added to this solution and stirred at 50 °C under nitrogen atmosphere for 24 hours. The reaction mixture was then cooled to 0 °C and filtered, and the off-white solid was washed with cold MeOH. This product was dried under vacuum to yield 113.4 mg of arnottin I (**4.35**, 92% yield). m.p. >250 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9 Hz, 1H), 7.85 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.14 (s, 1H), 6.10 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7, 153.2, 152.5, 146.1, 144.8, 144.4, 143.4, 142.9, 136.6, 129.6, 122.8, 122.1, 112.6, 103.9, 103.6, 101.3, 85.0, 83.9, 82.3, 61.5, 56.0, 28.0; **IR** (neat, cm^{-1}) 3010, 2943, 1734, 1489, 1463, 1276, 1122, 1039, 821; **TLC** R_f = 0.50 (1:1 hexanes/EtOAc, v/v); **HRMS** (DART) *m/z* Calc'd for $C_{20}H_{15}O_6$ $(M^+H)^+$: 351.0869, found 351.0855

Arnottin II (4.34): Arnottin I (**4.35**, 12.0 mg, 0.035 mmol) was suspended in 0.5 mL of THF: MeOH:H_2O (3:1:1, v/v/v) and 7.0 mg, (0.17 mmol, 5.0 eq.) of $LiOH{\cdot}H_2O$ was added. The reaction was heated at 50 °C for 2 hours over which time the solution became red. The flask was cooled to 0 °C and 1M HCl was added dropwise until the solution turned yellow-orange indicating a pH of 2-3. The solution was extracted with Et2O (2 x 1.0 mL), dried over Na_2SO_4 and concentrated at 23 °C yielding an unstable yellow-orange solid. The flask was cooled to 0 °C and HFIP (0.50 mL) was added. PIFA (17.0 mg, 0.041 mmol, 1.1 eq.) in 0.50 mL of HFIP was added over 1 hour at 0 °C via syringe pump and then the reaction was stirred at 23 °C. After 12 hours the reaction was quenched with 1M HCl (1.0 mL), extracted with CH_2Cl_2 (2 x 1.0 mL), dried over Na_2SO_4 and concentrated. Flash chromatography (2:1 hexanes/EtOAc, v/v) yielded arnottin II (**4.34**, 7.0 mg, 0.02 mmol, 56% yield) as an off yellow solid. m.p. 206-208 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.78 (t, *J* = 4.1 Hz, 2H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.09 (m, 4H), 4.17 (d, *J* = 0.8 Hz, 3H), 3.86 (s, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.1, 167.6, 154.1, 153.6, 149.1, 148.6, 139.2,

134.6, 130.3, 128.4, 123.2, 119.2, 117.4, 115.6, 108.1, 107.7, 102.6, 84.5, 62.8, 57.0; **IR** (neat, cm^{-1}) 1682, 1770, 2853, 2921; **TLC** R_f = 0.45 (1:1 hexanes/EtOAc v/v); **HRMS** (DART) *m/z* Calc'd for $C_{20}H_{15}O_7$ $(M^+H)^+$: 367.0818, found 367.0811.

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22. The 4-naphthol derivative was observed by ^{1}H NMR.

APPENDIX 1

SPECTRA AND SUPPLEMENTAL DATA

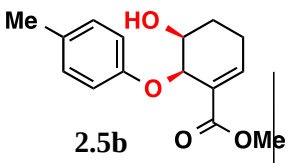
5.1: General Procedures

Where appropriate, reactions were carried out under an inert atmosphere of argon or nitrogen with dry solvents, using anhydrous conditions unless otherwise stated. Dry toluene, dichloromethane (DCM), and triethylamine (Et_3N), were obtained by passing the previously degassed solvents through activated alumina columns. Tetrahydrofuran (THF) was distilled from the blue solutions of sodium benzophenone ketal before use. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material. Flash column chromatography was performed using Silicycle Silica Gel 60 Å (40-53 μm). Analytical thin-layer chromatography (TLC) was performed using Merck Silica Gel 60 Å F-254 precoated plates (0.25 mm thickness). Reverse phase analytical thin-layer chromatography (RTLC) was performed using Merck Silica Gel 60 Å RP-18 WF_{254} precoated plates (0.25 mm thickness. Infrared spectra were obtained on a ThermoNicolet iS10 FT-IR spectrometer. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Analytical normal phase HPLC was performed on a Hewlett-Packard 1050 Series chromatograph equipped with a single wavelength detector (230 nm) using a Chiralpak AD-RH column (5 μm, 4.6 x 150 mm, 20 °C). Analytical GC was performed on a Shimadzu GC-2010 chromatograph equipped with a FID detector using a J+W Scientific column (5 μm, 30 m x 0.250 mm). Low-resolution mass spectra (LRMS) were recorded on an Agilent LC/MSD 1100 TOF mass spectrometer by electrospray (ES) or atmospheric-pressure chemical ionization (ACPI) time of flight experiment. High-resolution mass spectra were obtained at the Mass Spectrometry Facility at the University of Illinois Urbana-Champaign, on an Agilent 6890N Network GC System with a JEOL JMS-GCmate II Mass Spectrometer (magnetic sector)

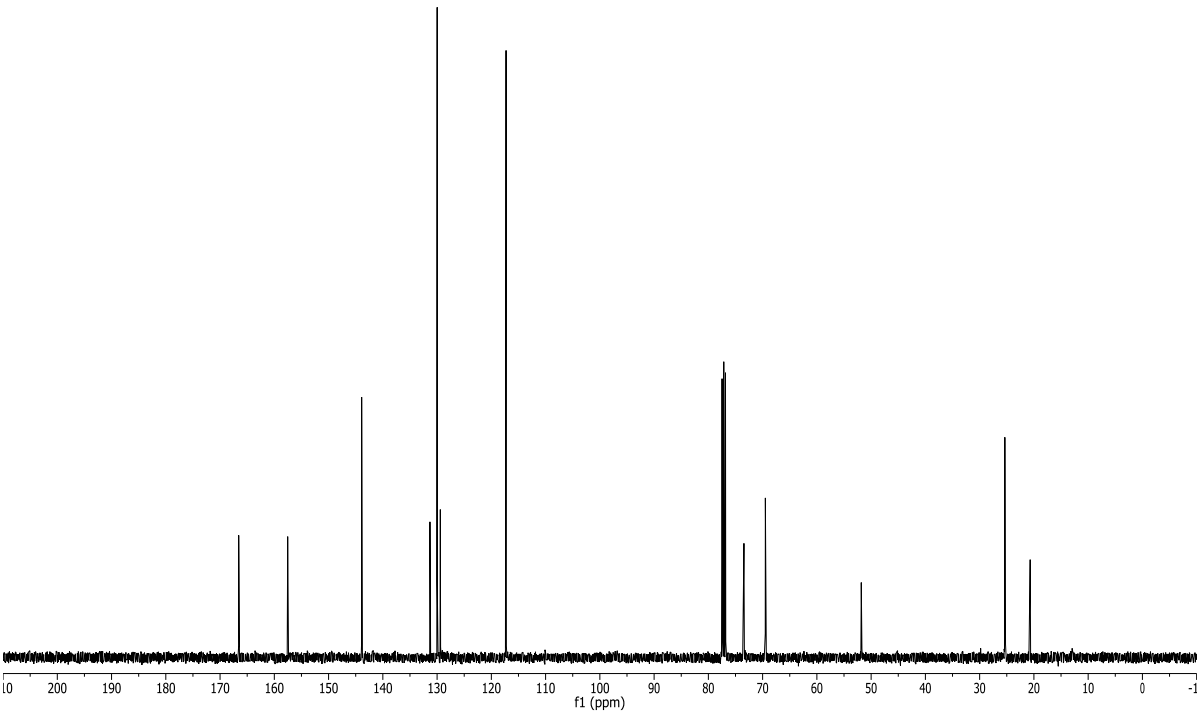
using electron impact experiments, or on an Exactive Plus Orbitrap Mass Spectrometer with a DART SVP ion source from Ion Sense. The method of ionization is given in parentheses. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at the sodium D line (path length 1 dm, corrected to 20.0 °C).

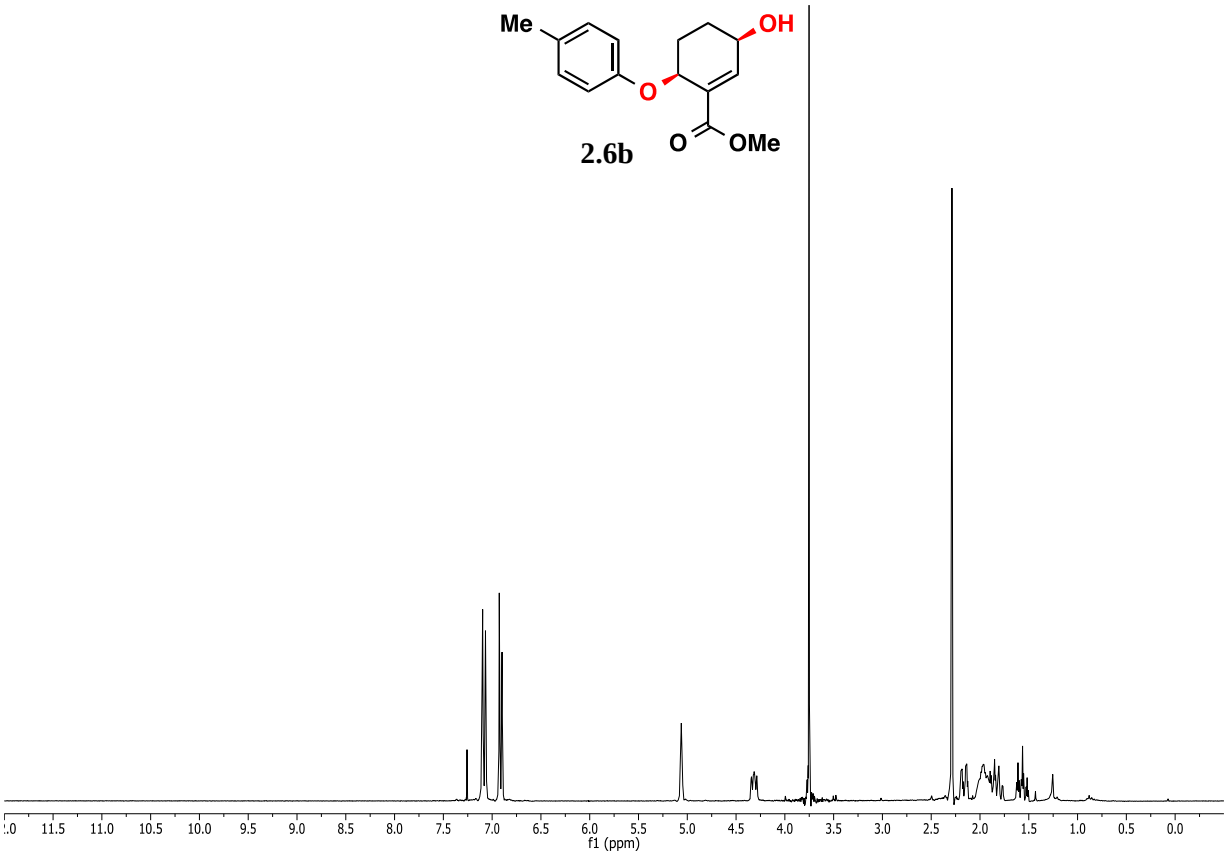
^{1}H and ^{13}C NMR data follows for each compound discussed in Chapters 2-4. Proton NMR spectra were recorded on either a Mercury 300, Varian 400, or 500 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (δ 0.0). Data is reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on a Varian 400 or 500 (100 MHz) spectrometer with proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to deuterated chloroform (δ 77.16). NMR data was collected at 25 °C.

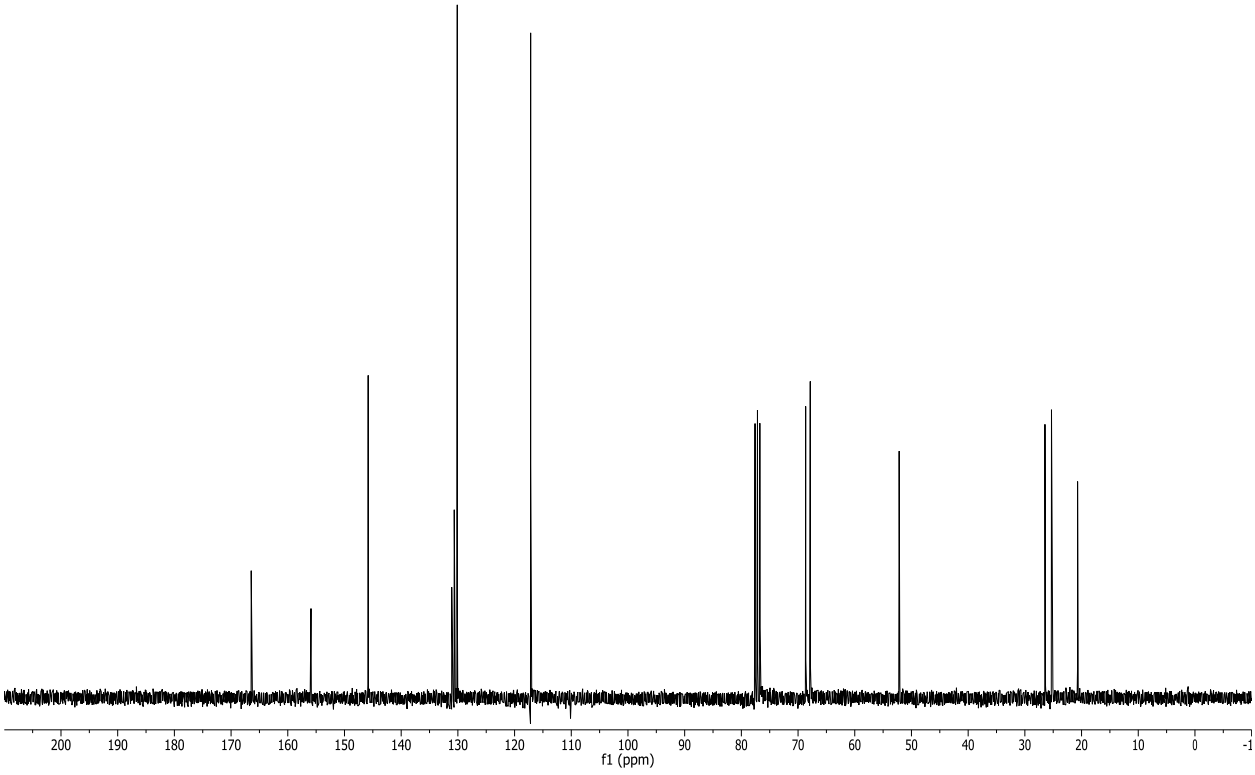
5.2: Chapter 2 spectra

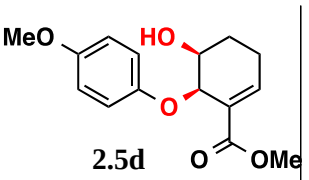


2.5b

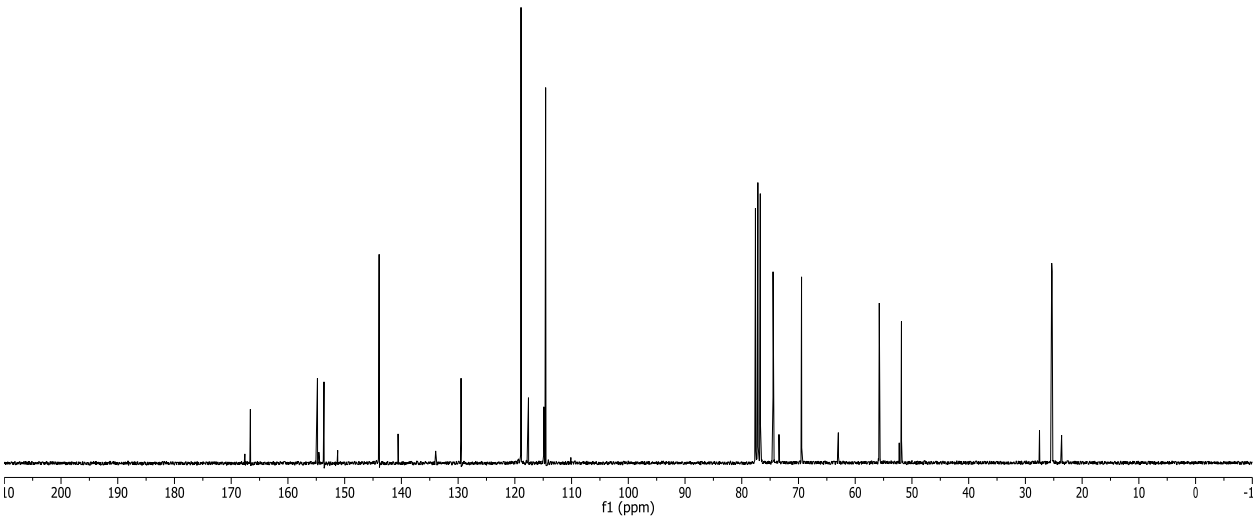


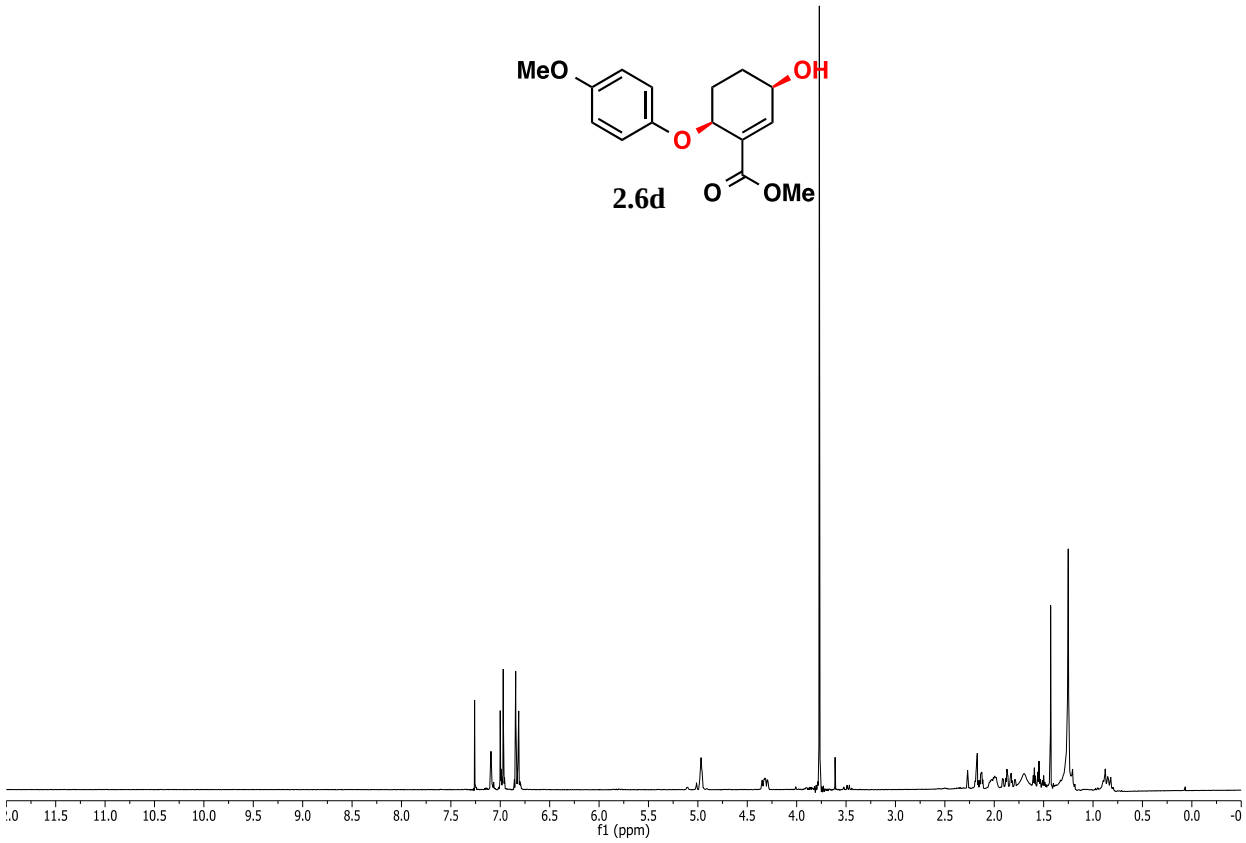

Me
O
OH
O
OMe
2.6b
f1 (ppm)

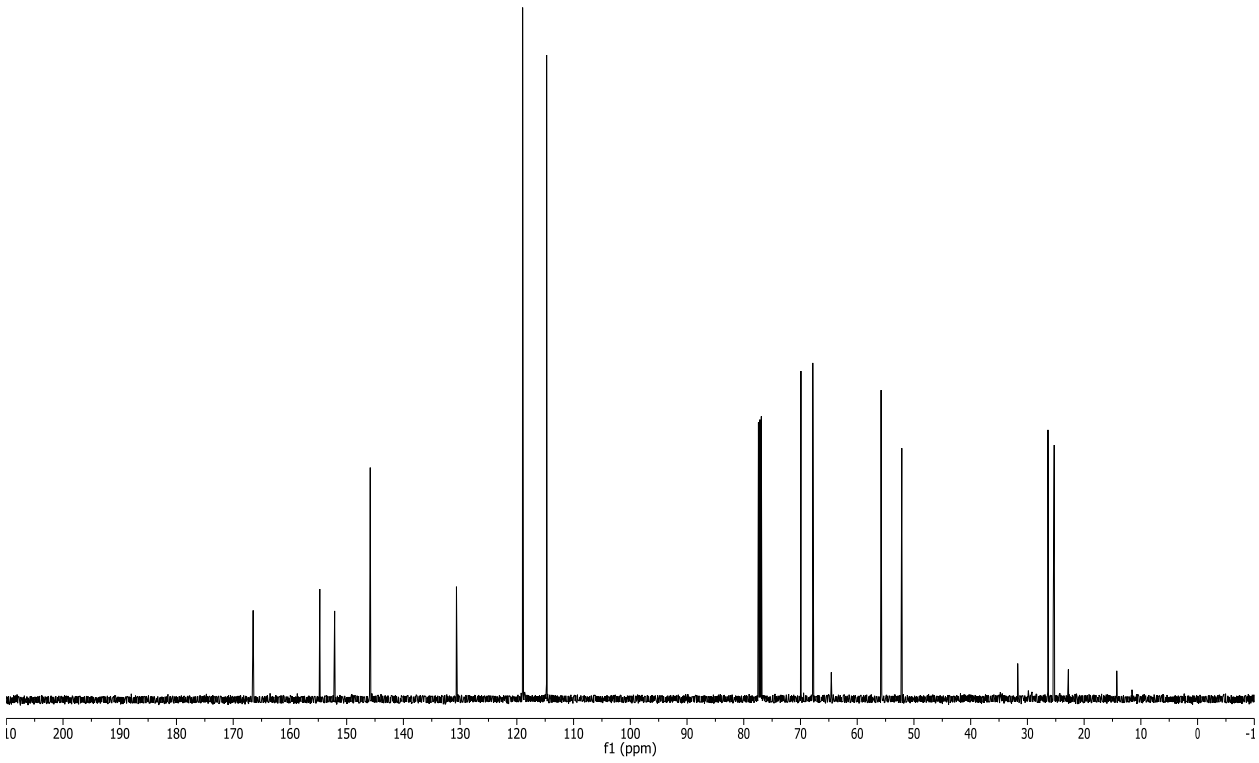

f1 (ppm)

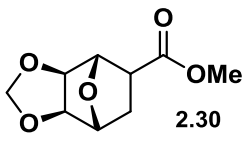


2.5d

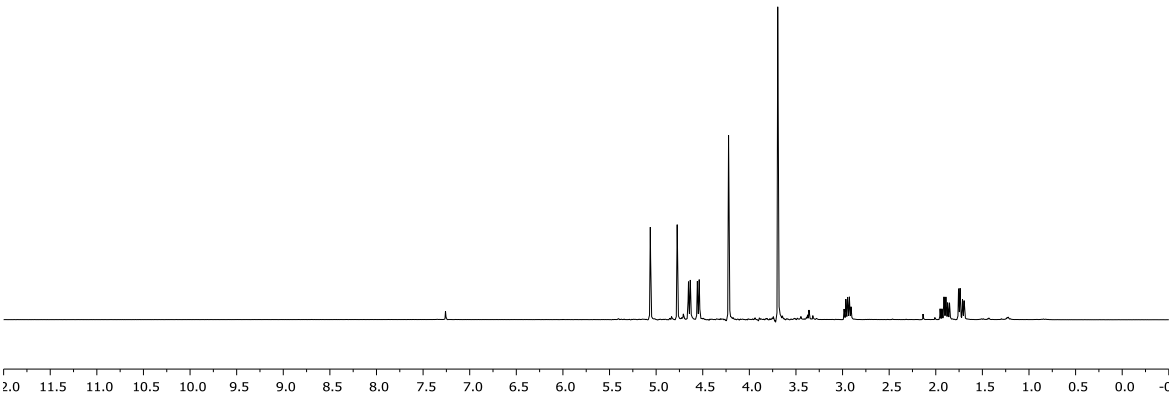



MeO
OH
O
O
OMe
2.6d
f1 (ppm)


f1 (ppm)


O
O
OMe
O
O

2.30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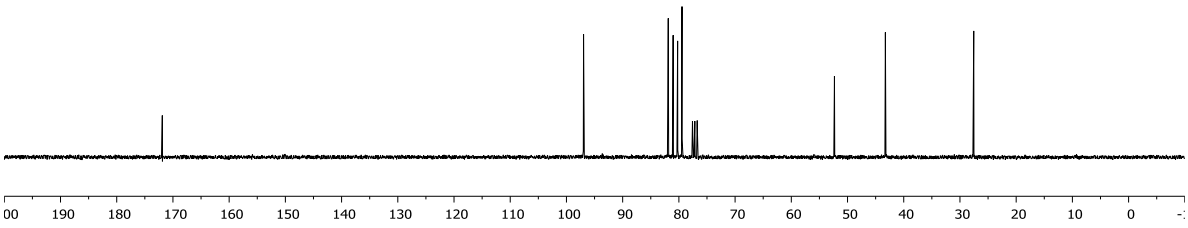
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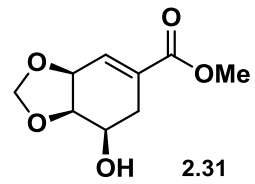
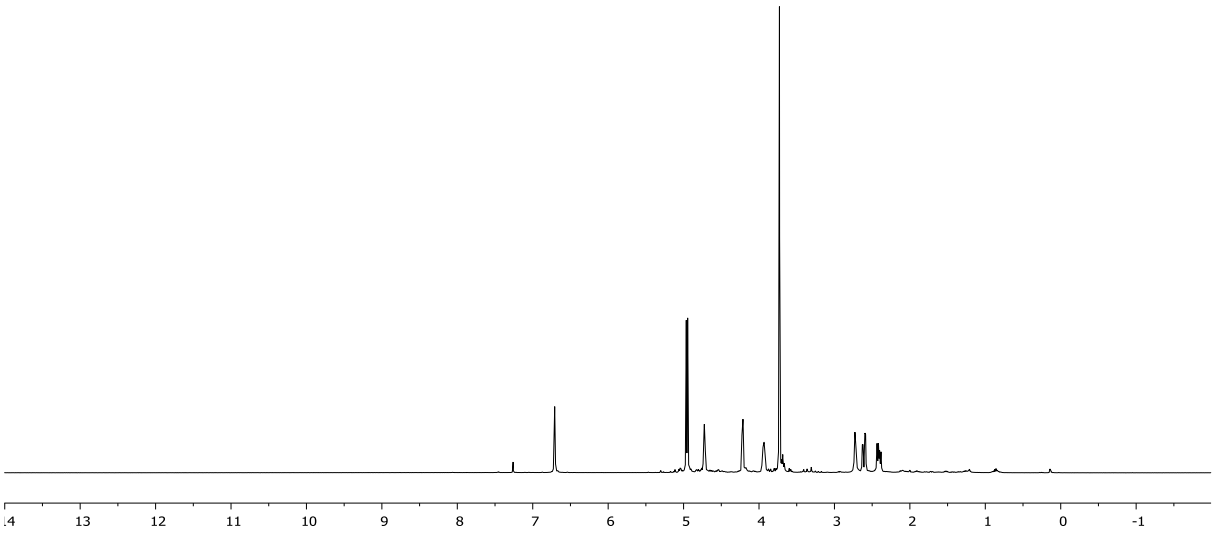

O
O
OMe
O
OH

2.31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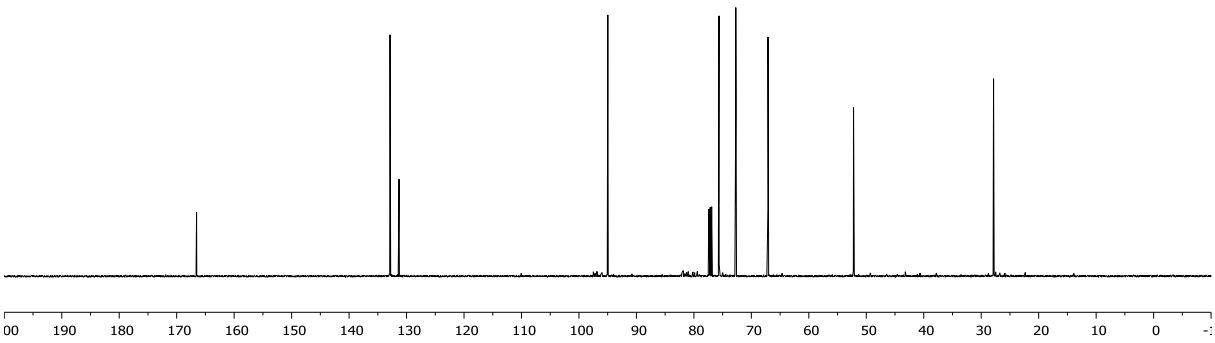
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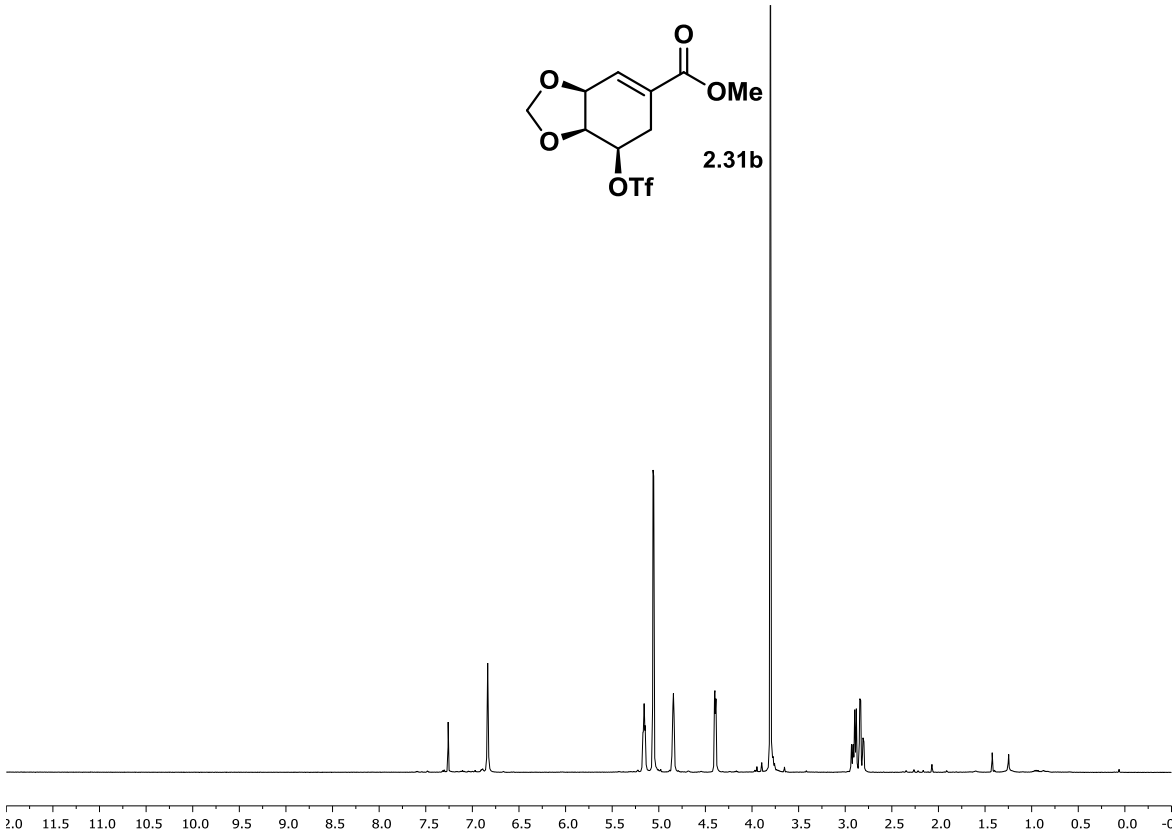
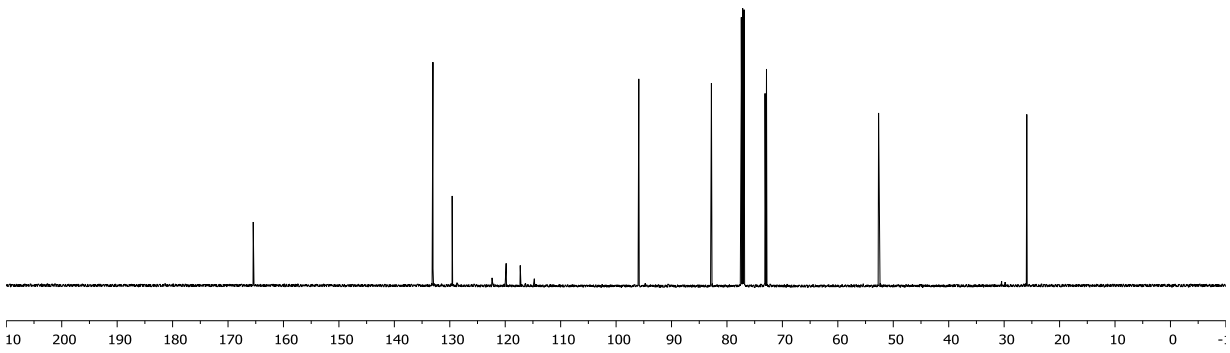

O
OMe
O
O
2.31b
OTf
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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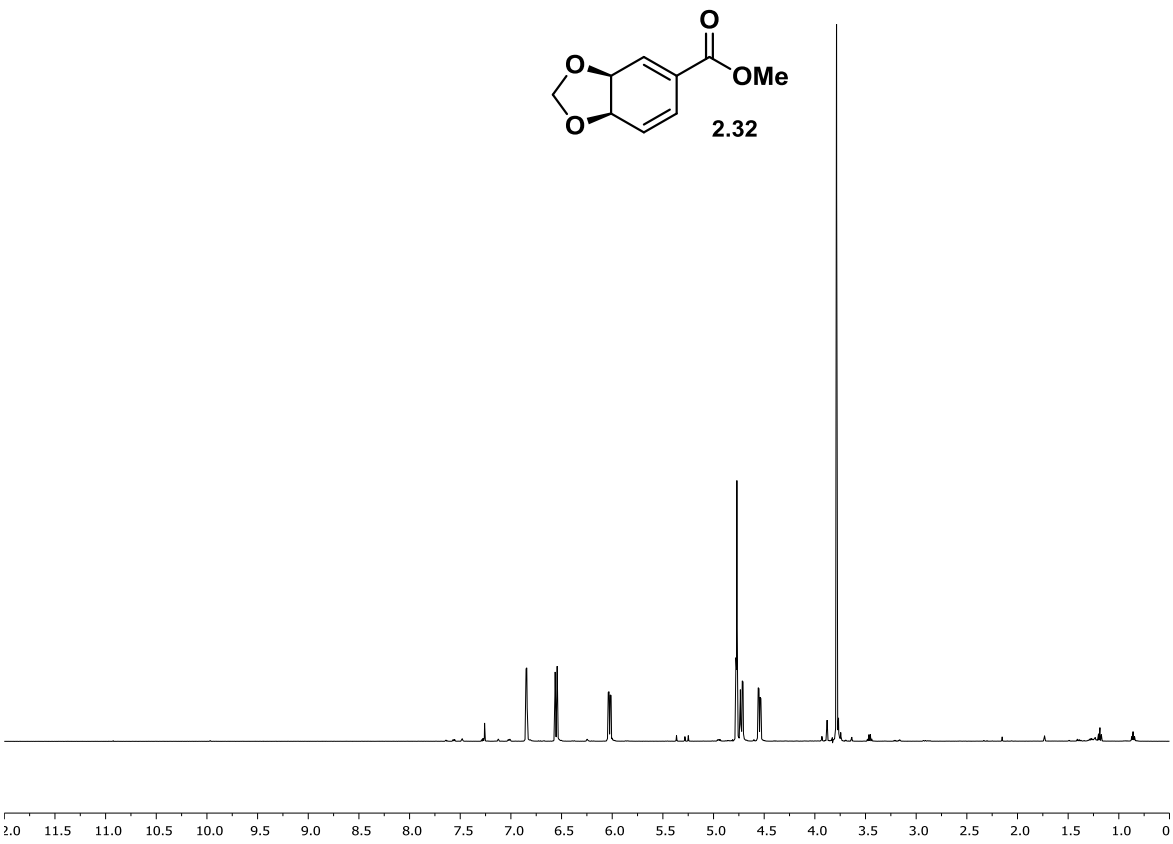
O
O
OMe
O
2.32
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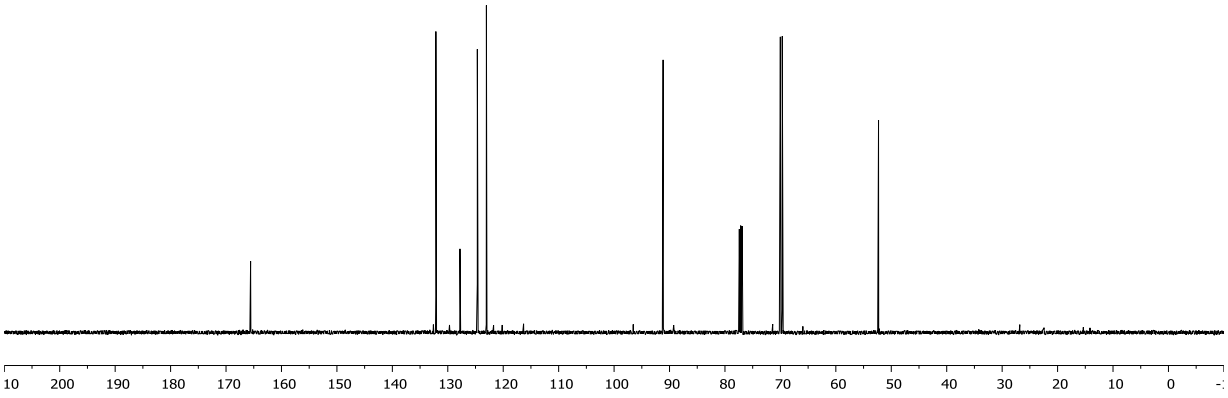
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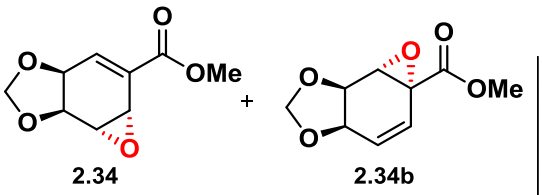
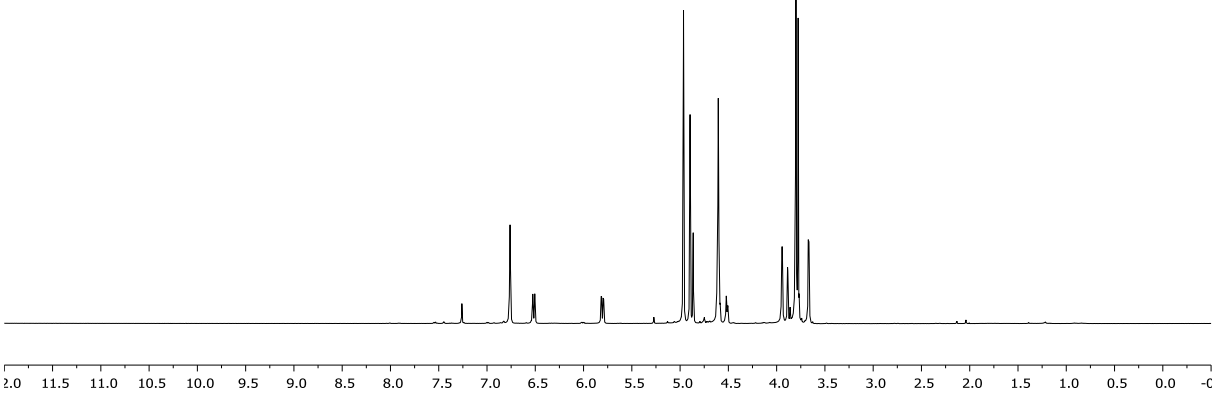
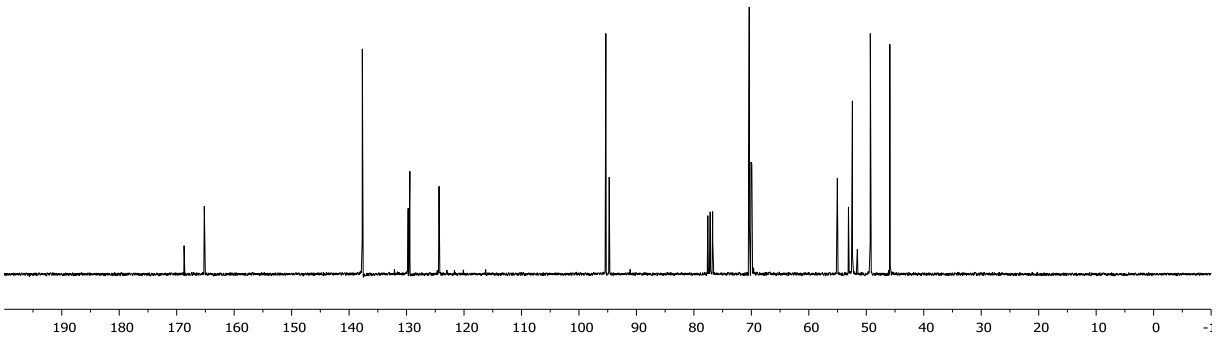

O
OMe
O
O
O
+
O
O
OMe
O
O

2.34 2.34b


11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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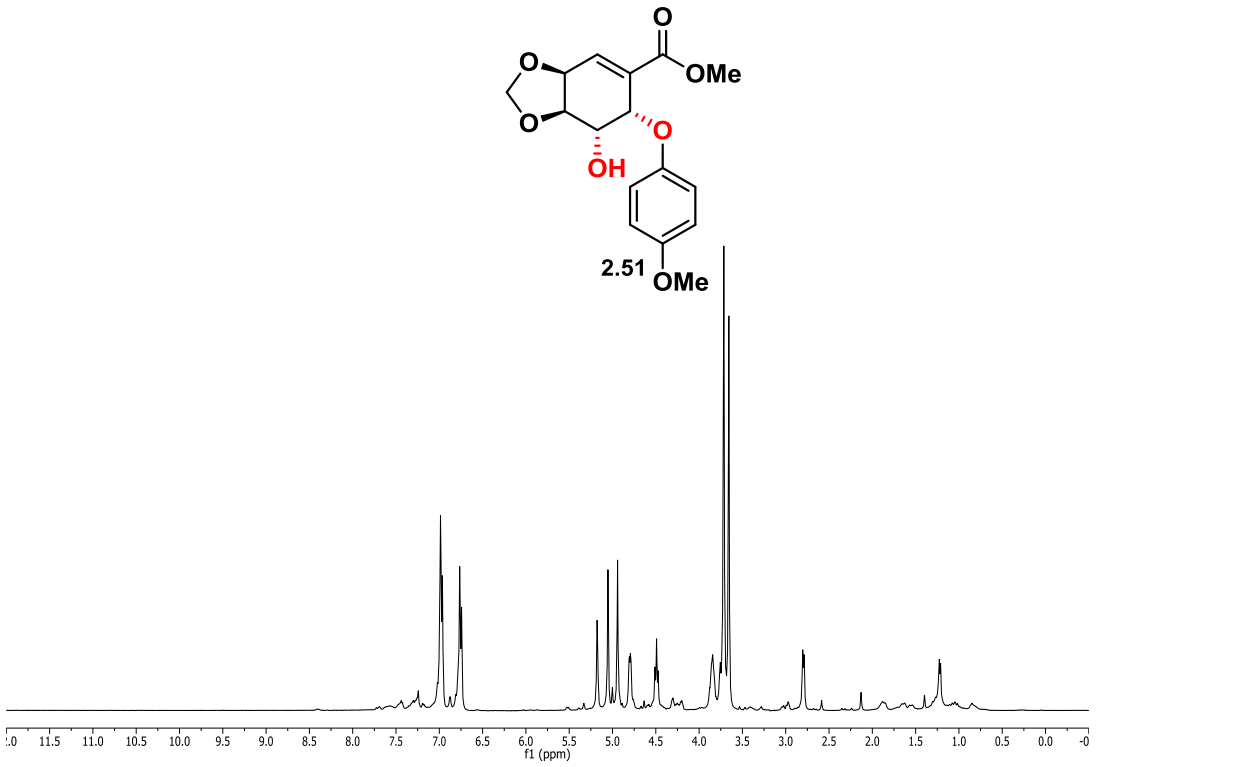
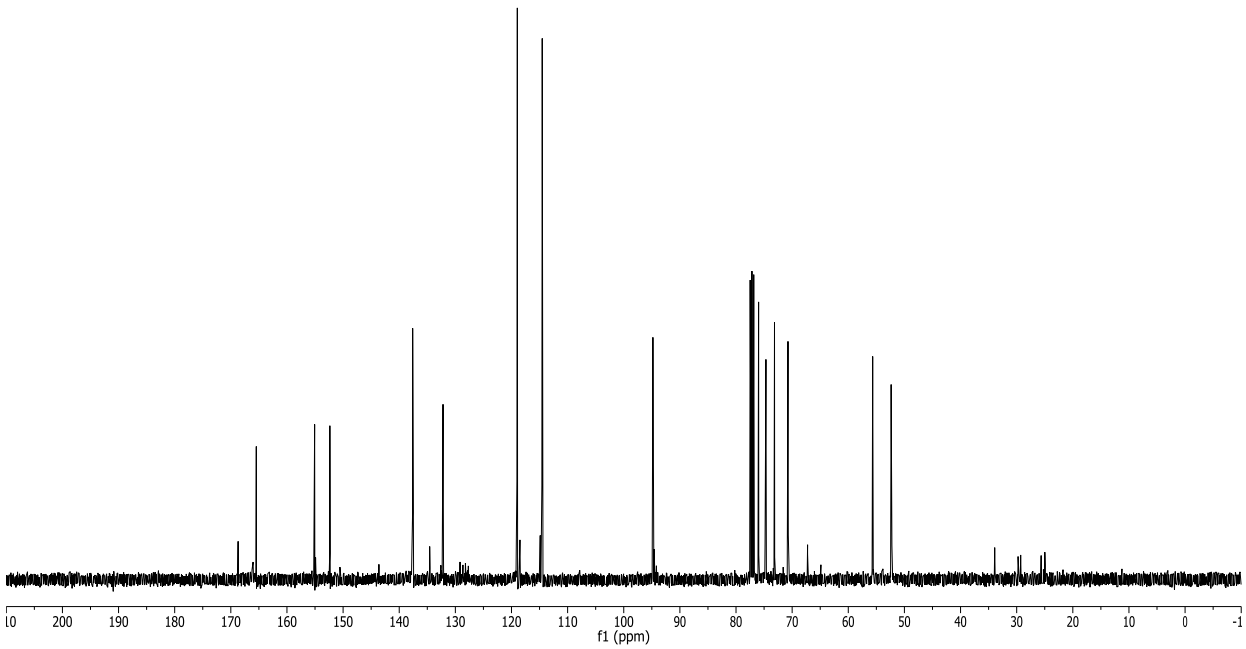
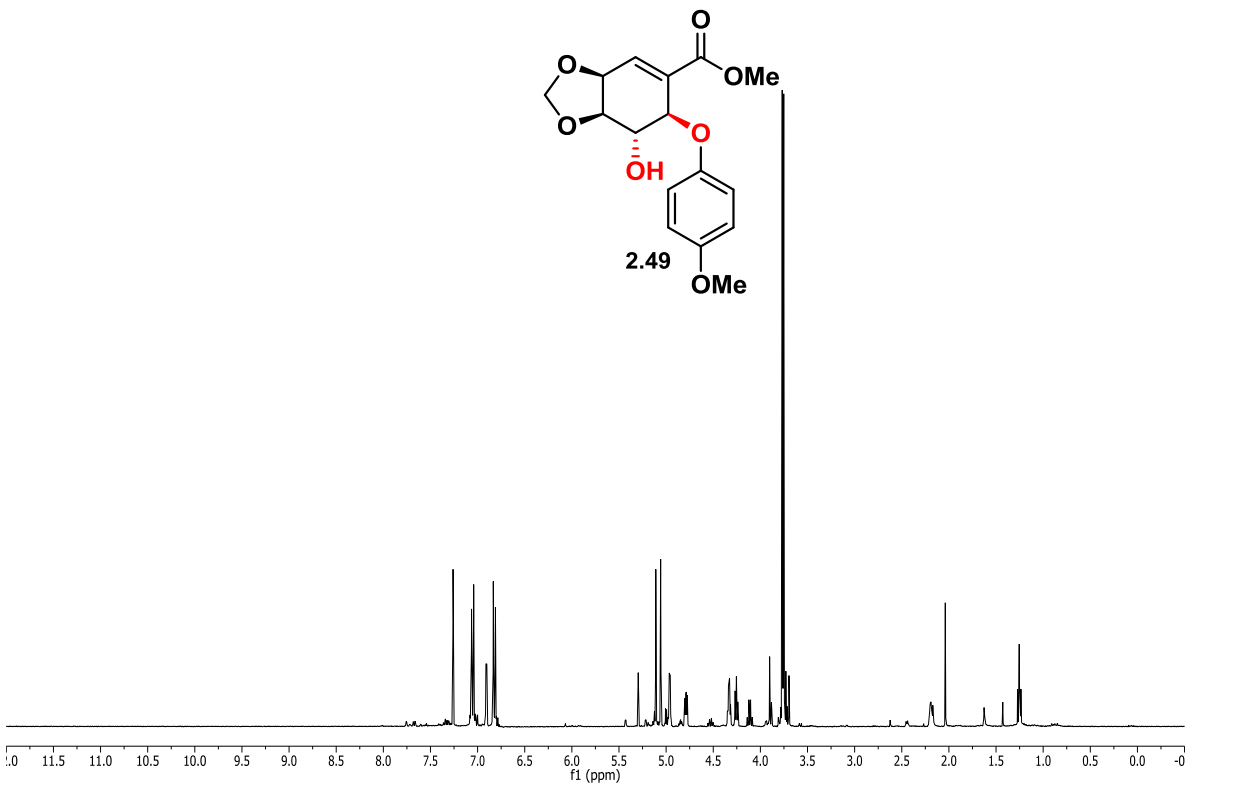
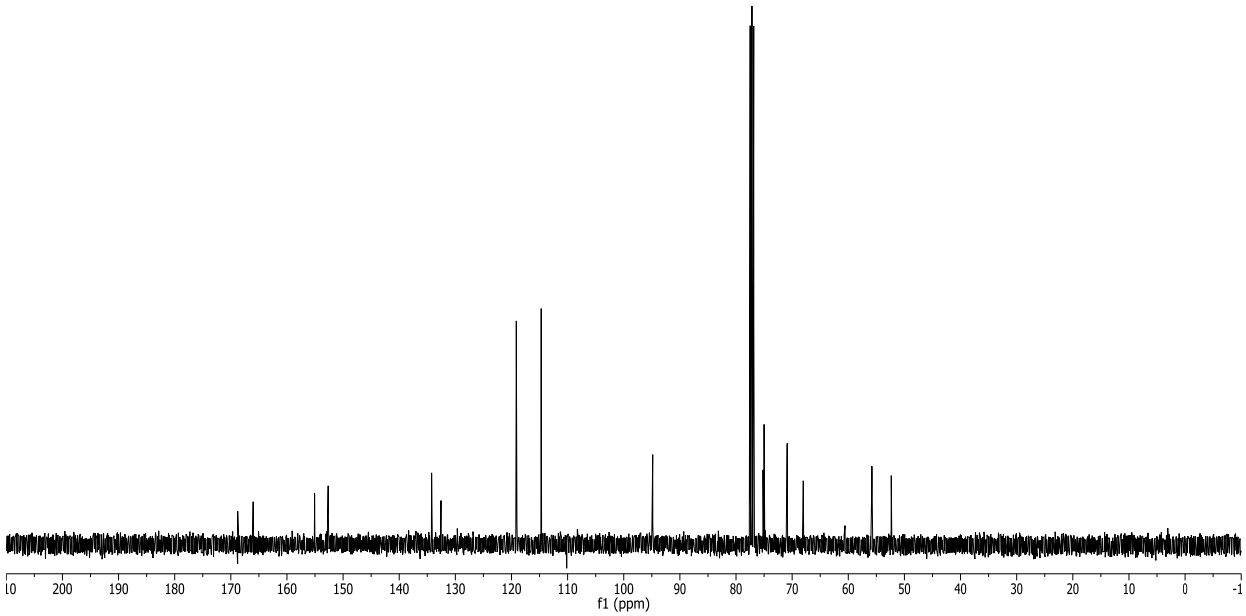
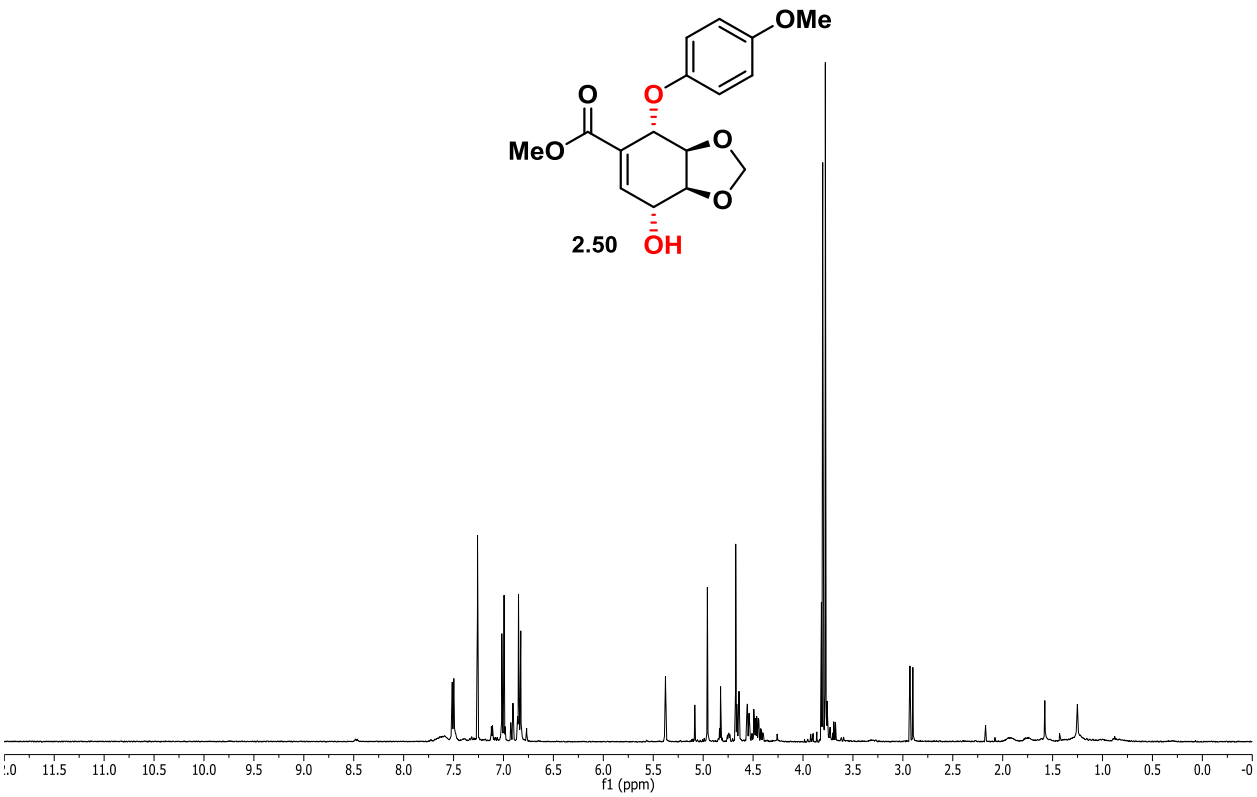
30
20
10
0

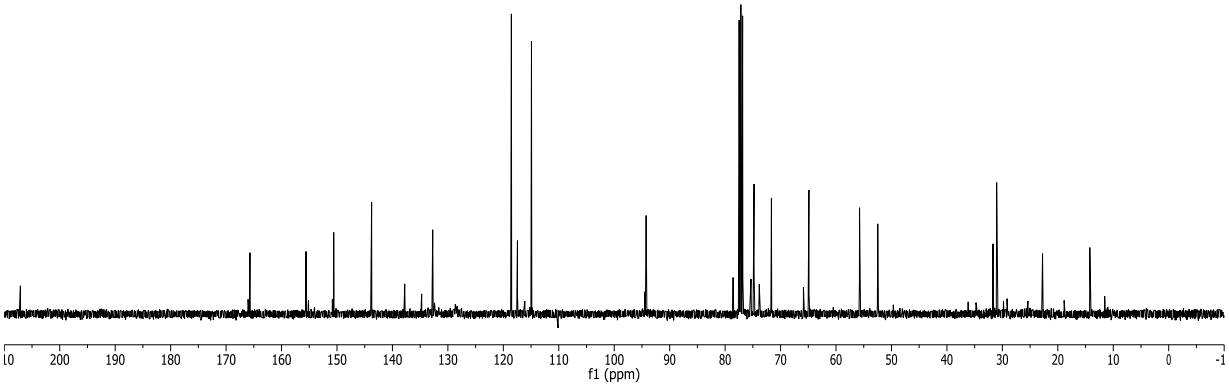

O
OMe
O
O
O
OH
2.51
OMe
f1 (ppm)

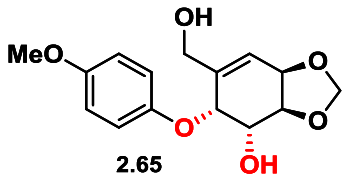

f1 (ppm)


O
OMe
O
O
O
OH
2.49
OMe
f1 (ppm)

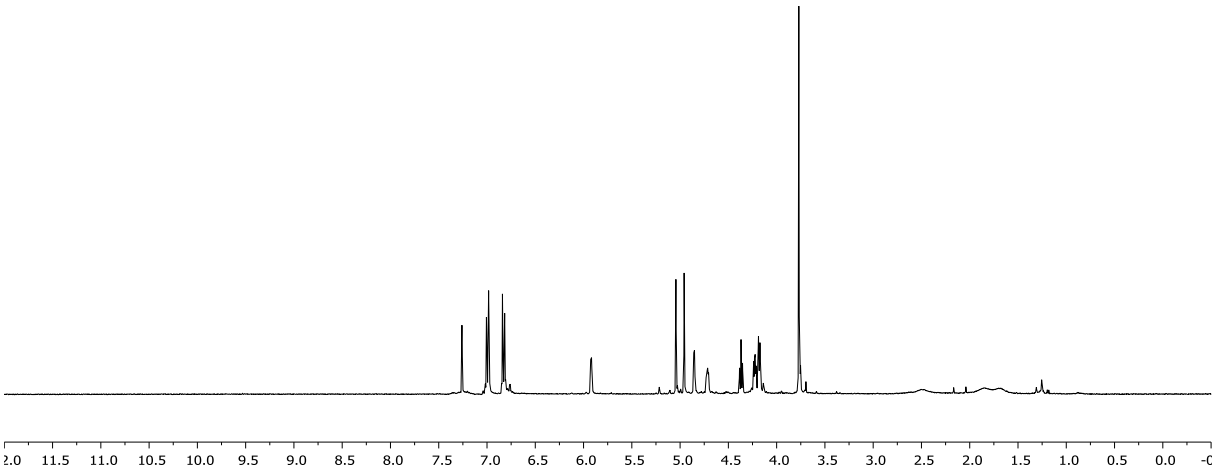

f1 (ppm)

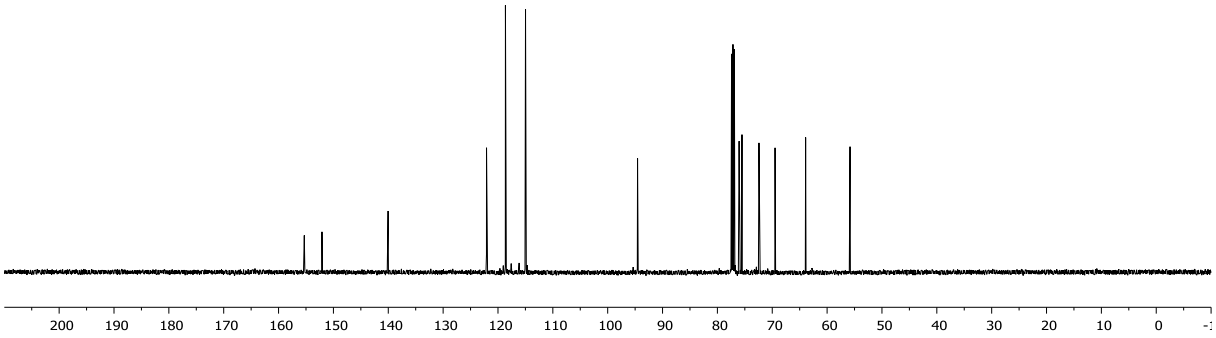

OMe
O
O
MeO
O
O
2.50
OH
f1 (ppm)


f1 (ppm)


OH
MeO
O
O
O
OH

2.65


11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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180
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150
140
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120
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100
90
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50
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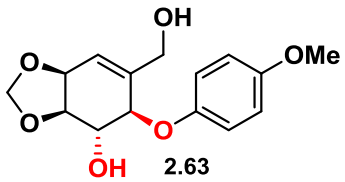
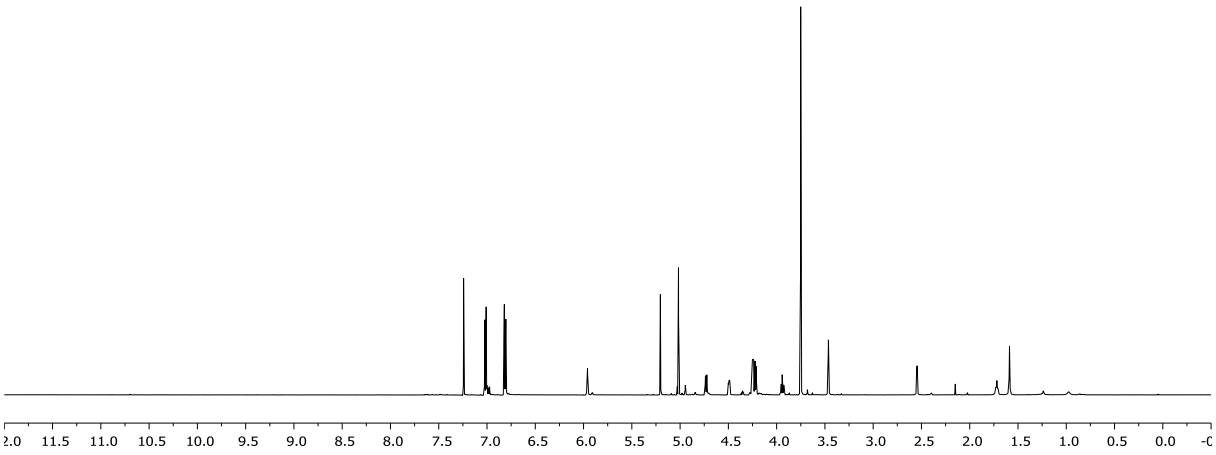
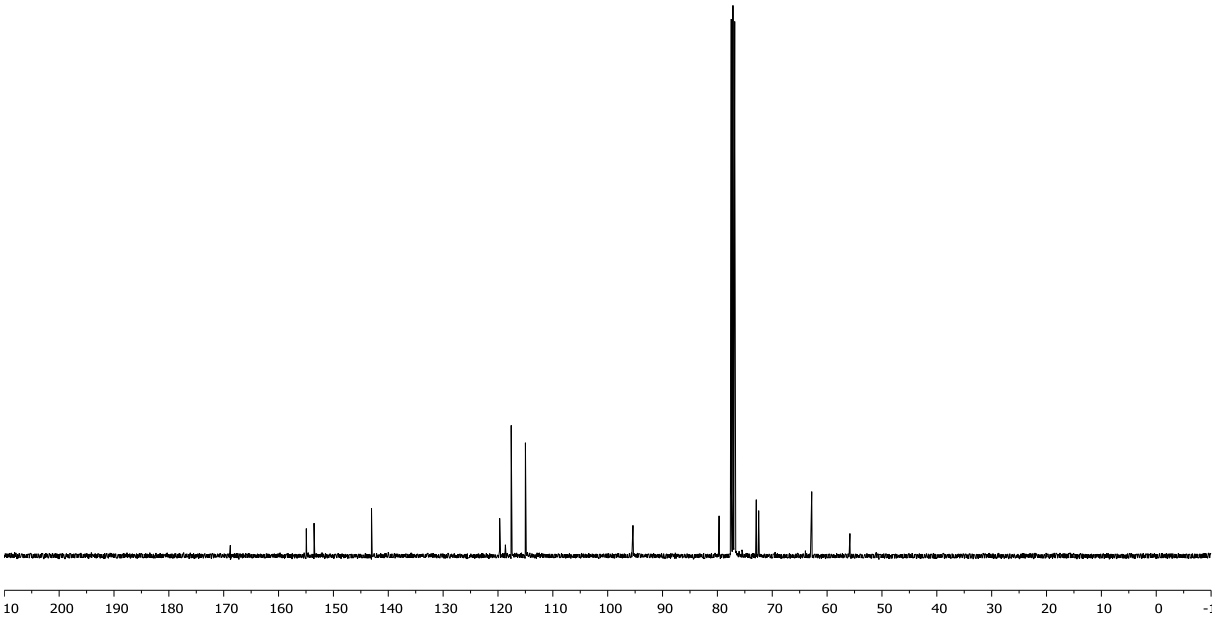
30
20
10
0


OH
OMe
O
O
O
OH

2.63


2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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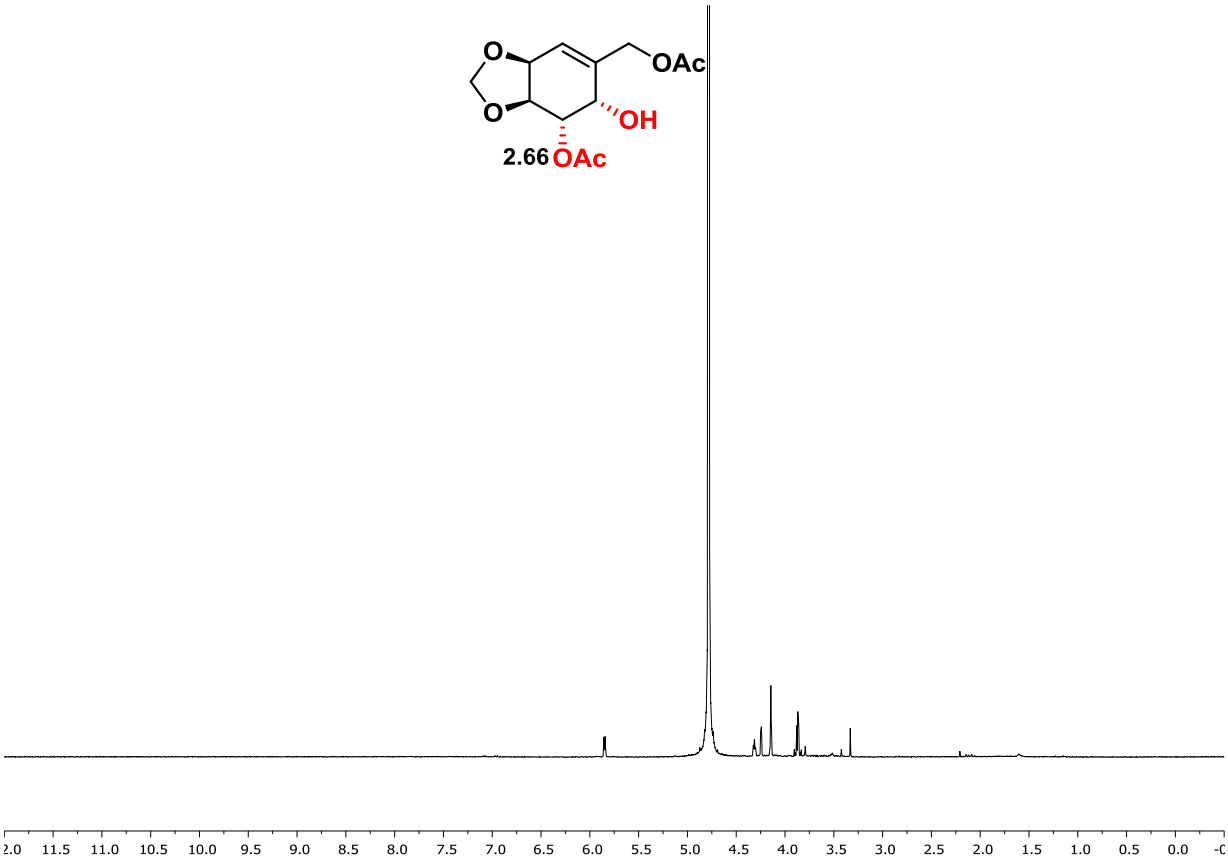
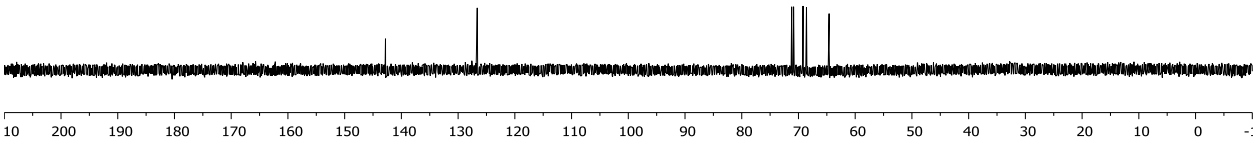

O
O
OAc
OH
2.66
OAc
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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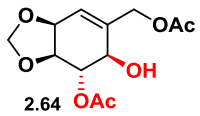
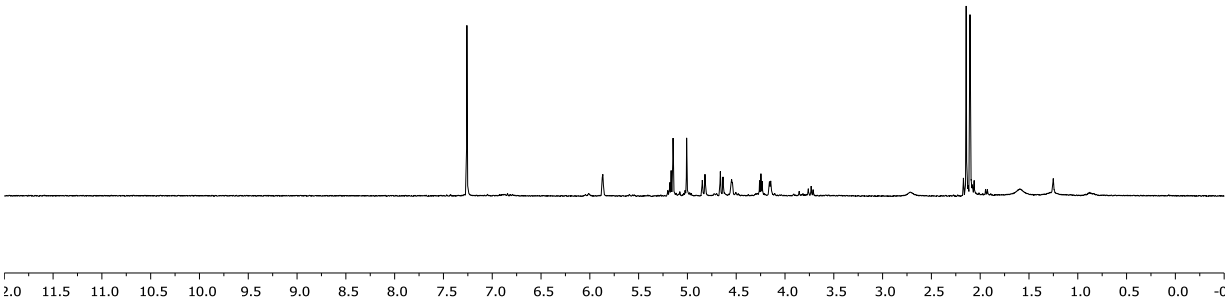

O
O
OAc
OH
OAc

2.64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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
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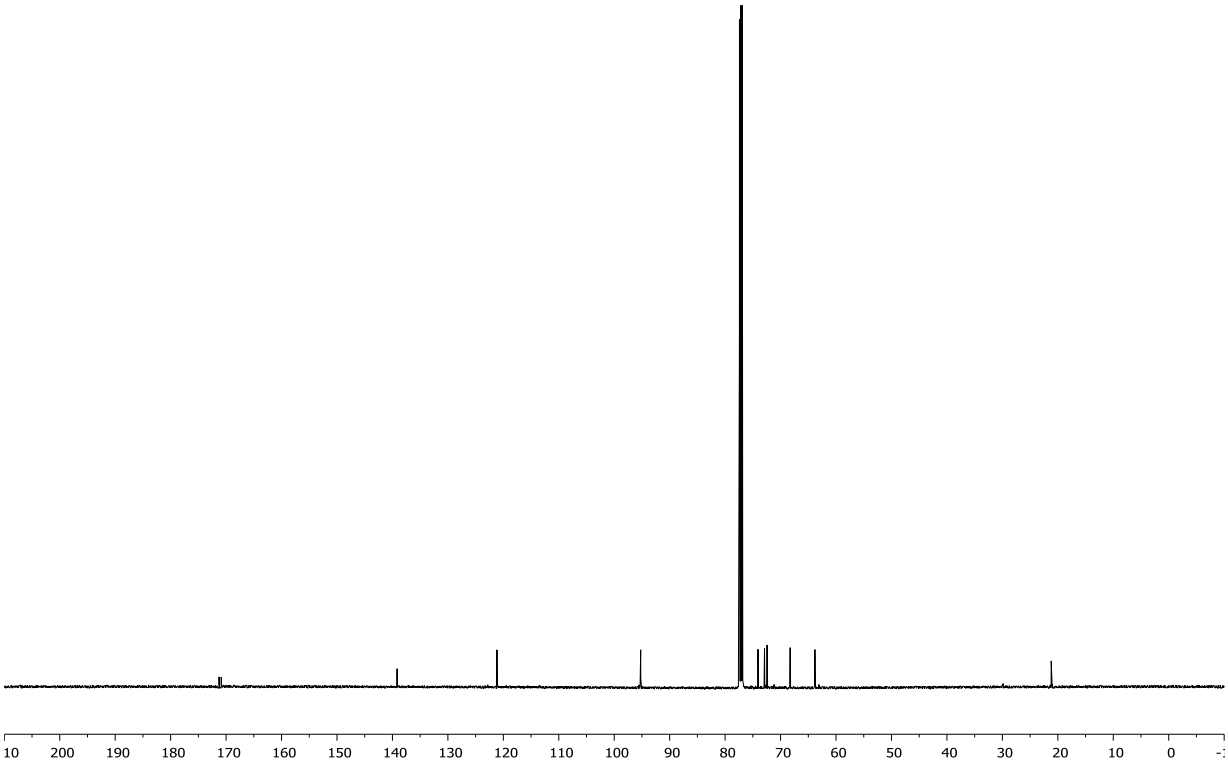
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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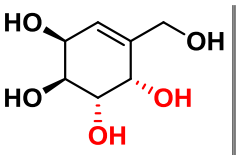
30
20
10
0


HO
OH
HO
OH
OH

2.58
MK7607

11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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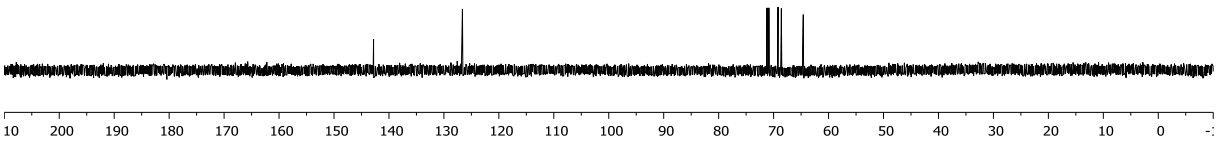
2.0
1.5
1.0
0.5
0.0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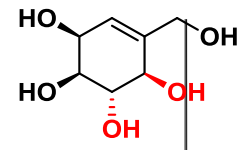
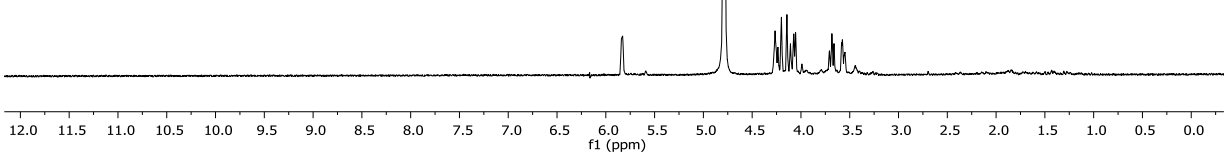
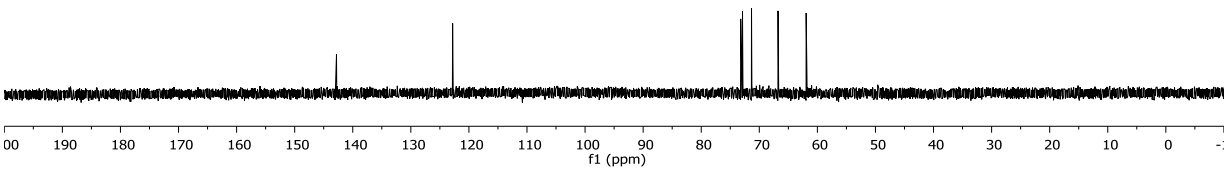
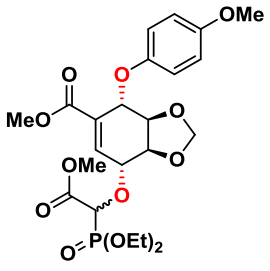
30
20
10
0



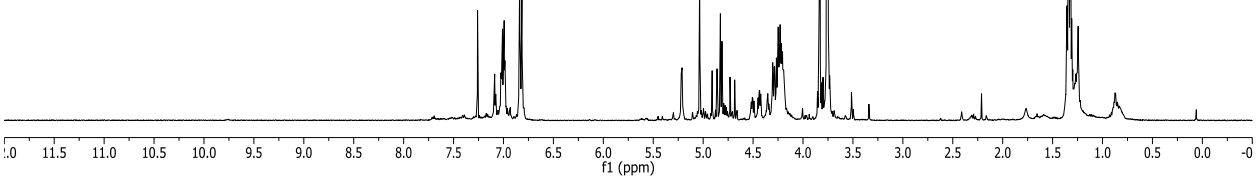
2.58
(-)-streptol

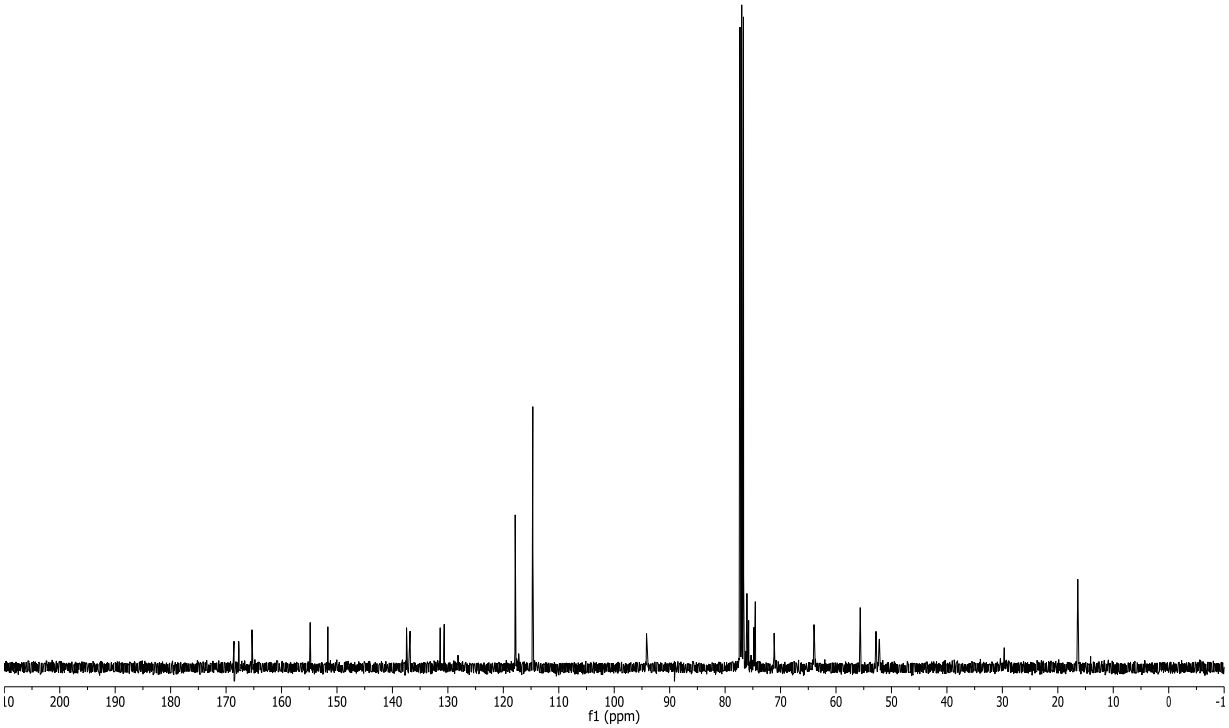





OMe
O
MeO
O
O
OMe
O
O
O
P(OEt)2

2.71


11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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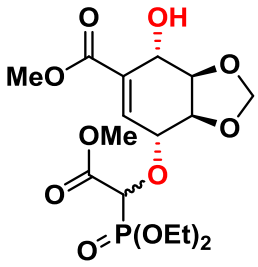
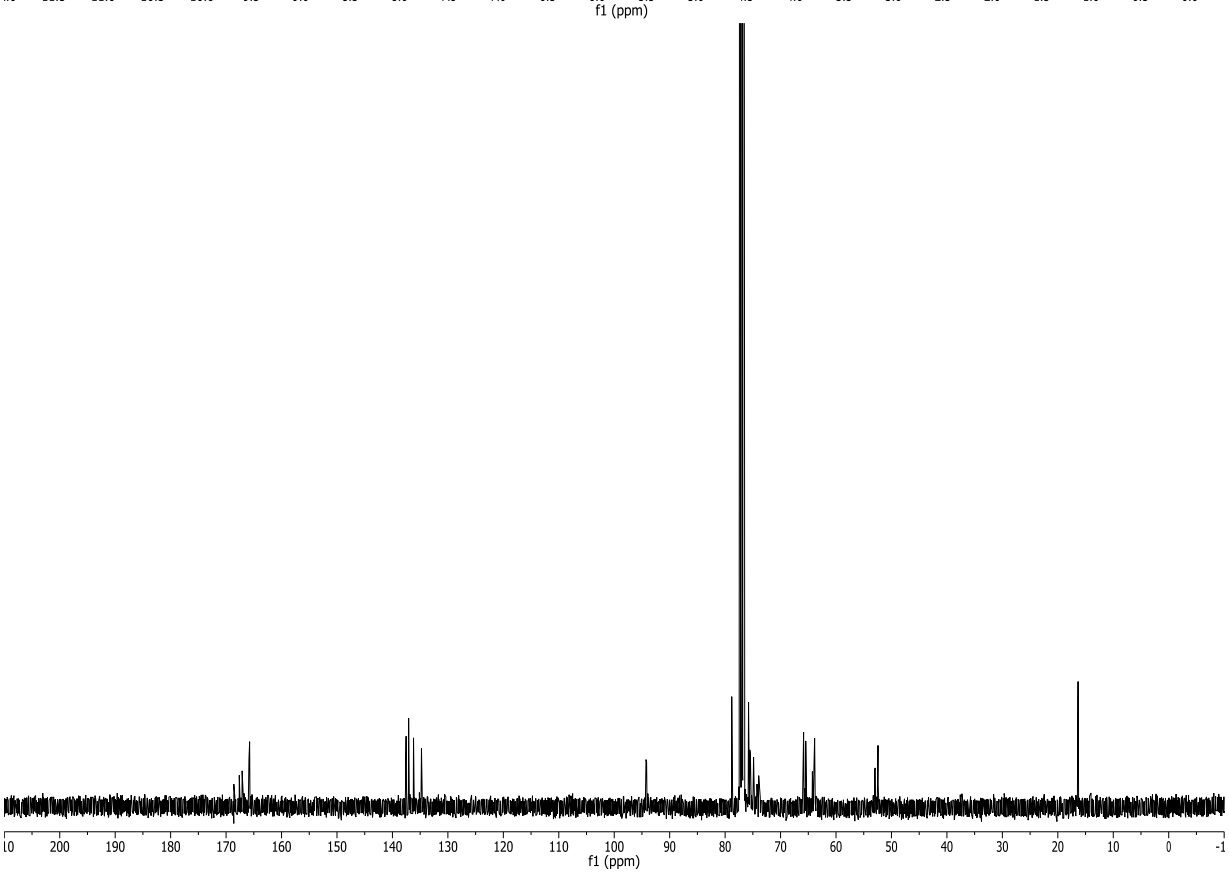
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OH
MeO
O
O
OMe
O
O
O
P(OEt)2

2.72

11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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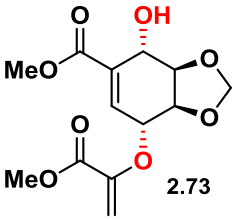
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OH
MeO
O
O
O
MeO
O

2.73

11.5
11.0
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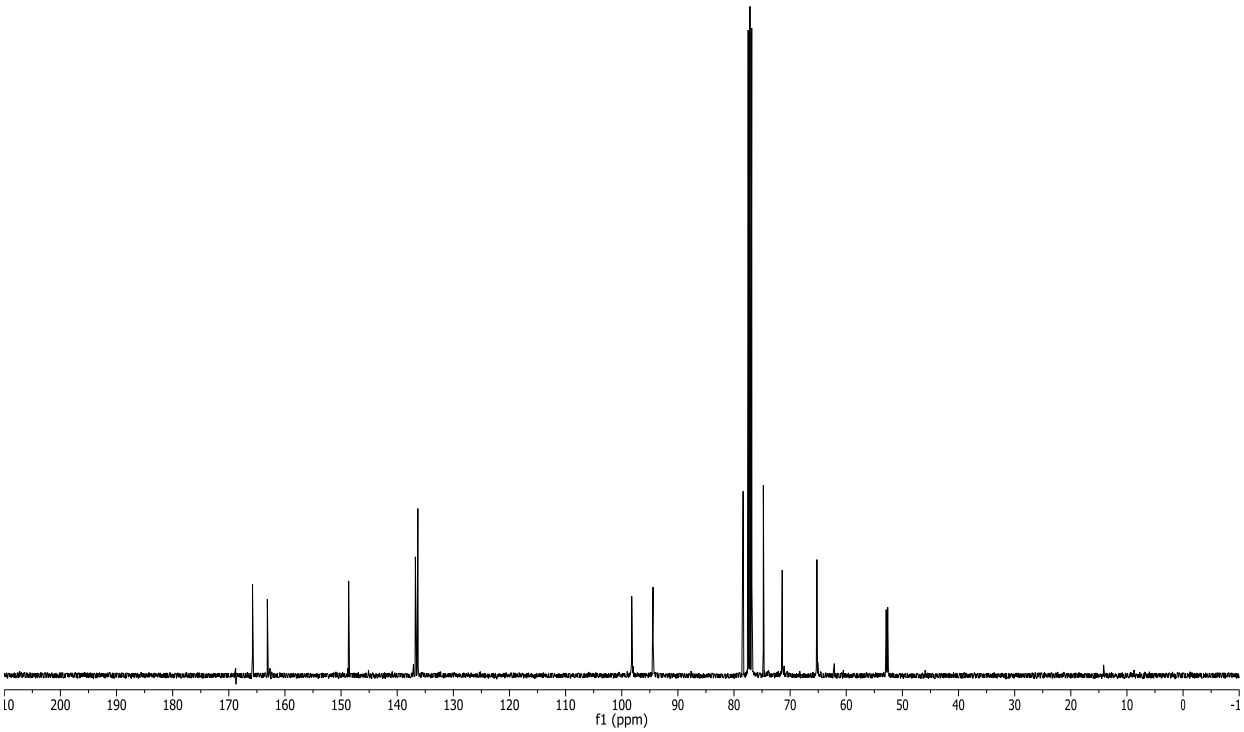
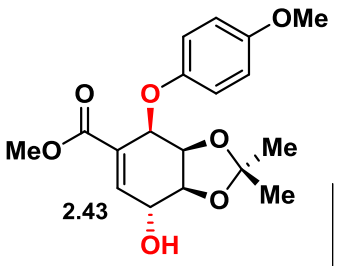
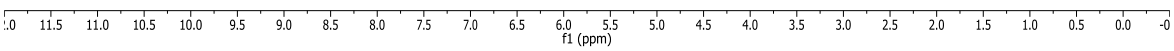
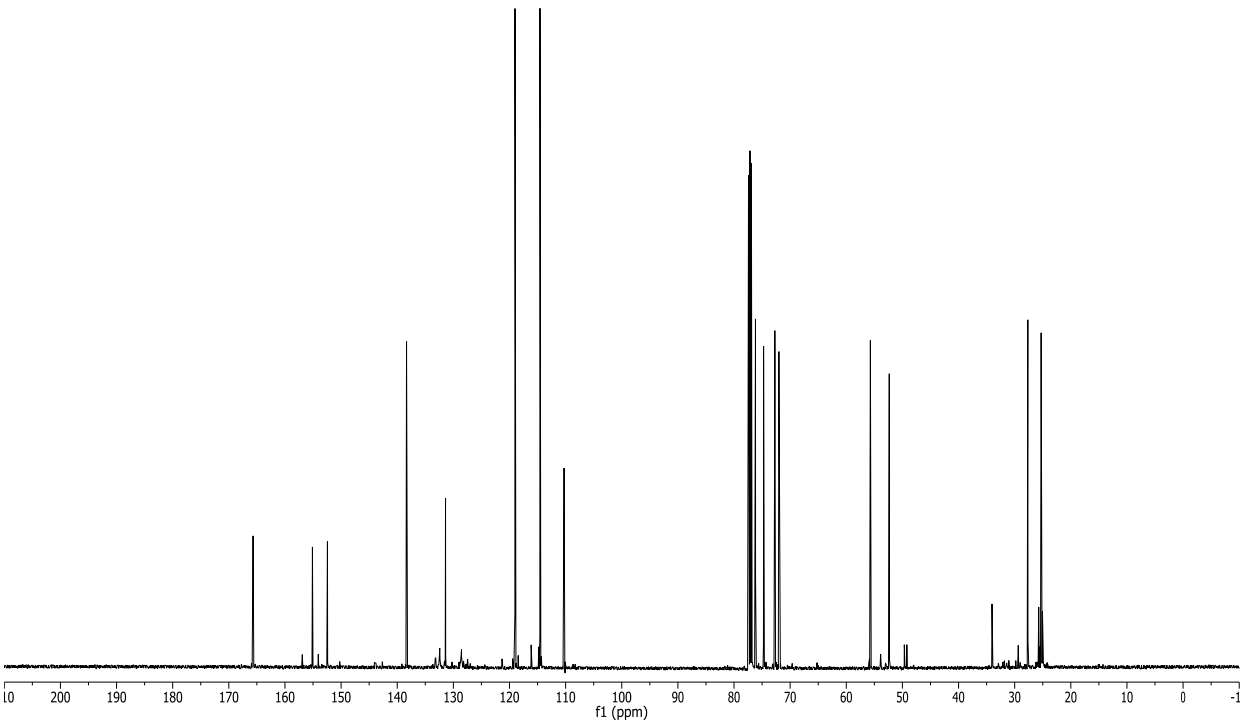
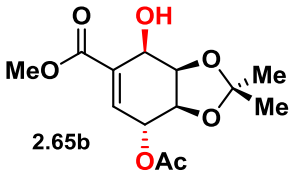
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

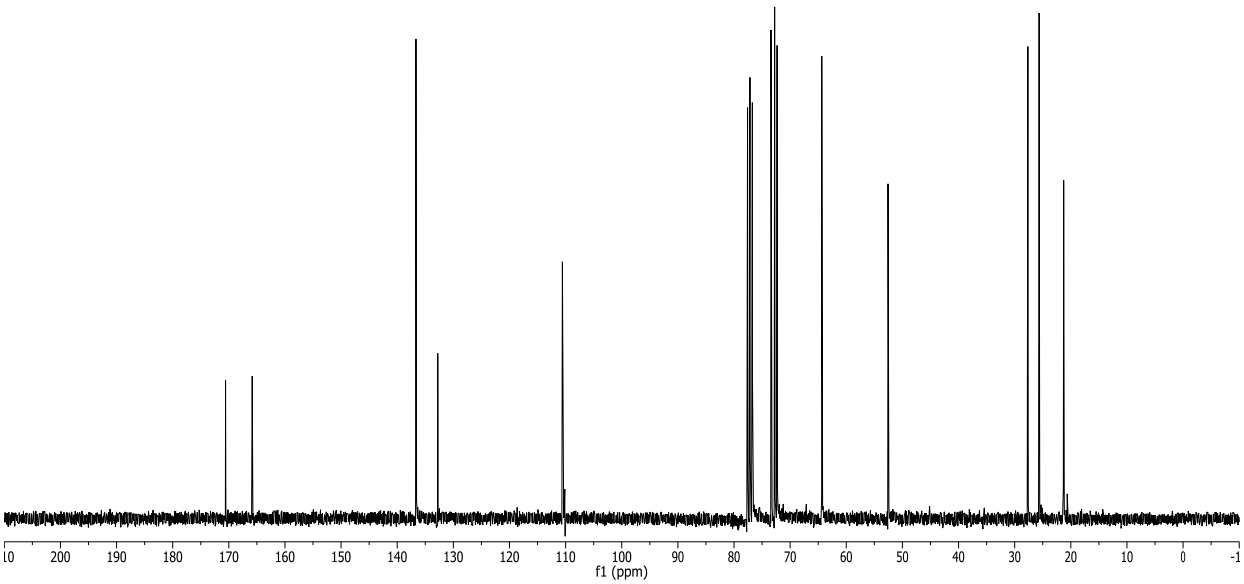

OMe
O
O
MeO
O
Me
Me
O
2.43
OH

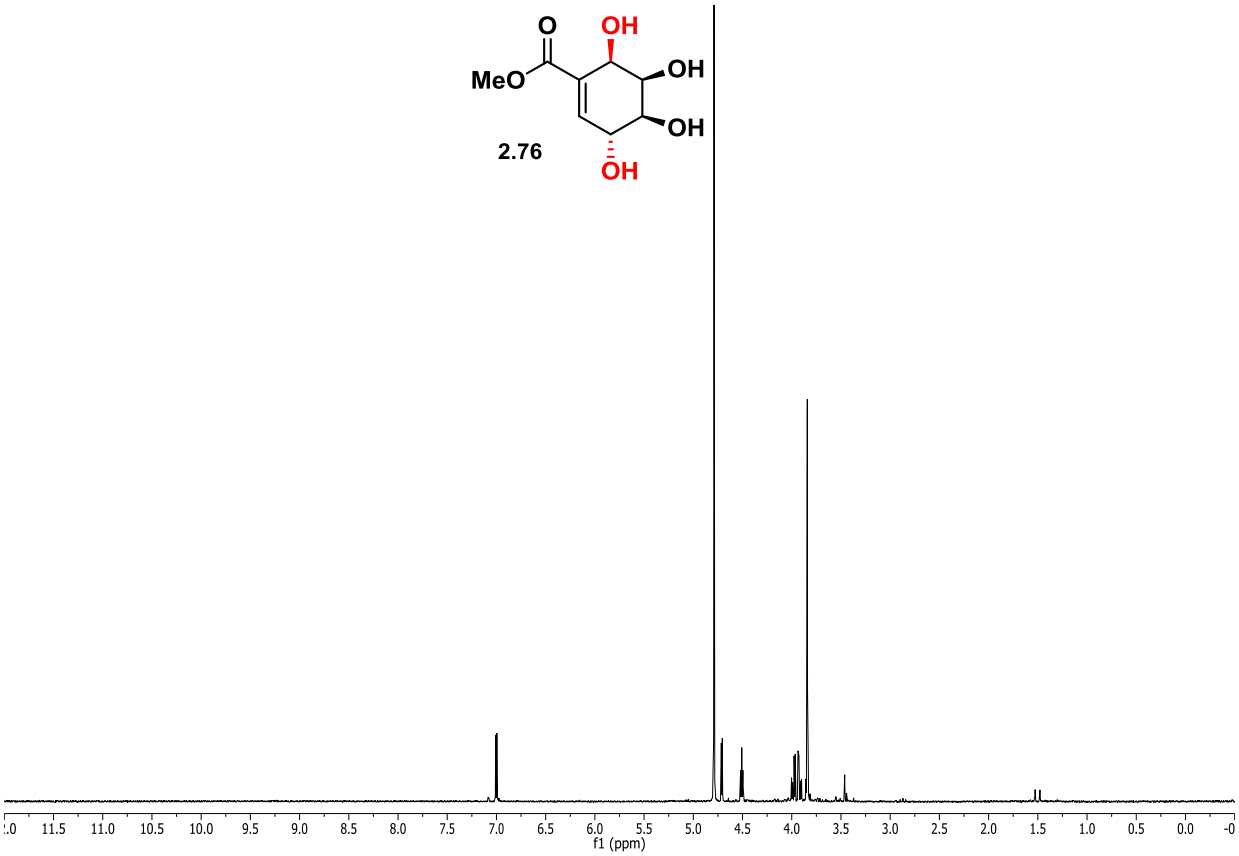

f1 (ppm)

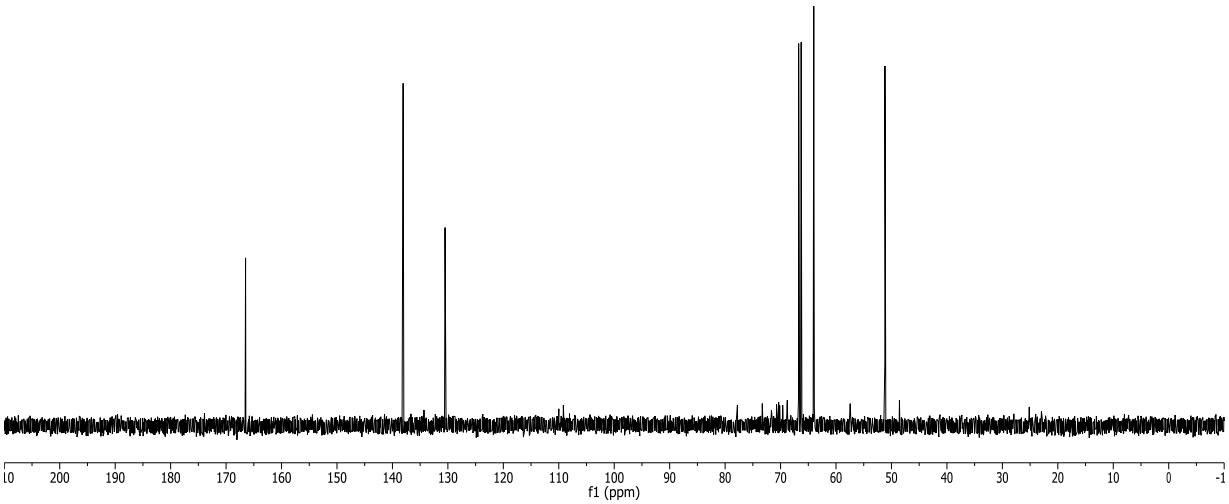

f1 (ppm)

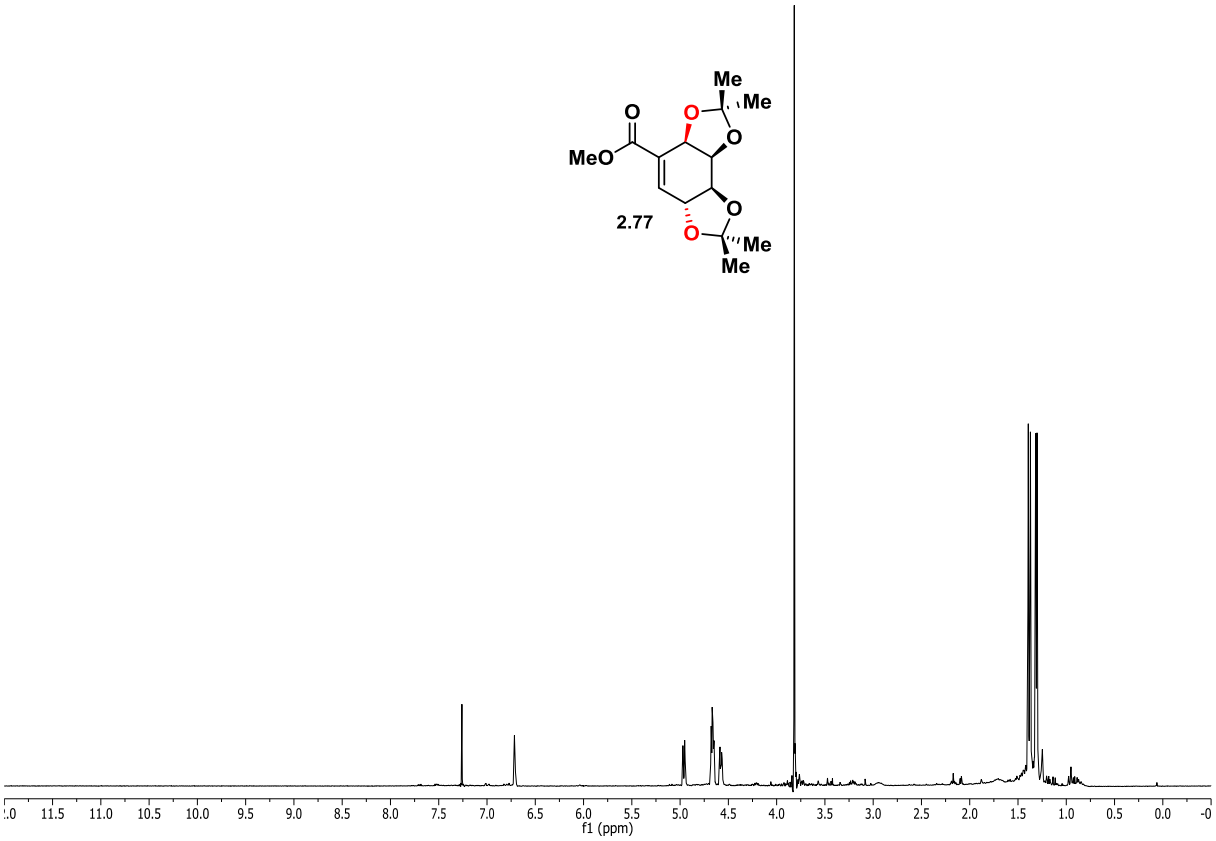

O
OH
MeO
O
Me
Me
O
2.65b
OAc

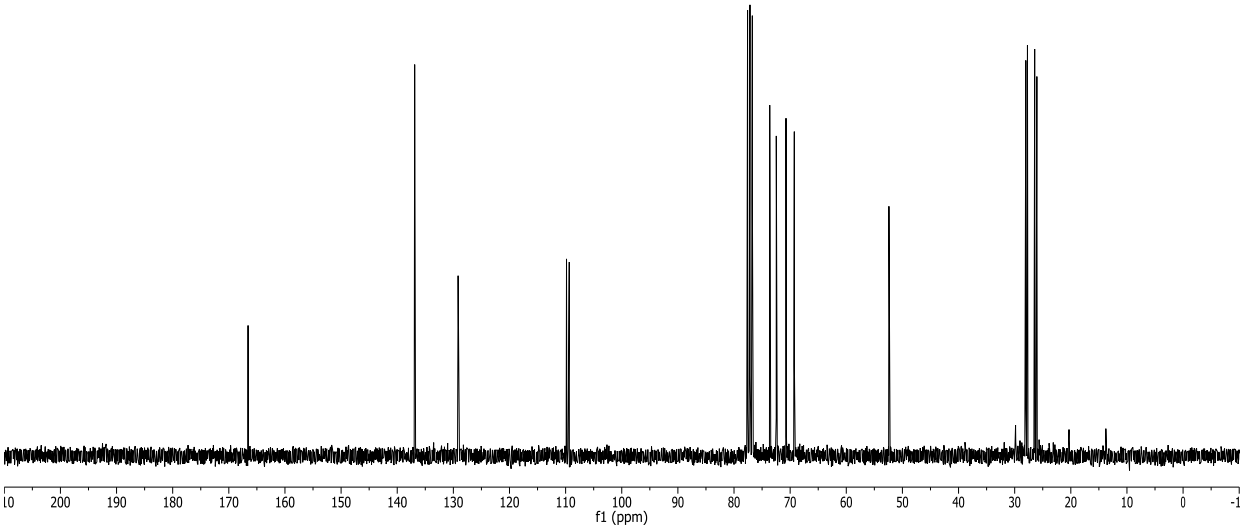
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

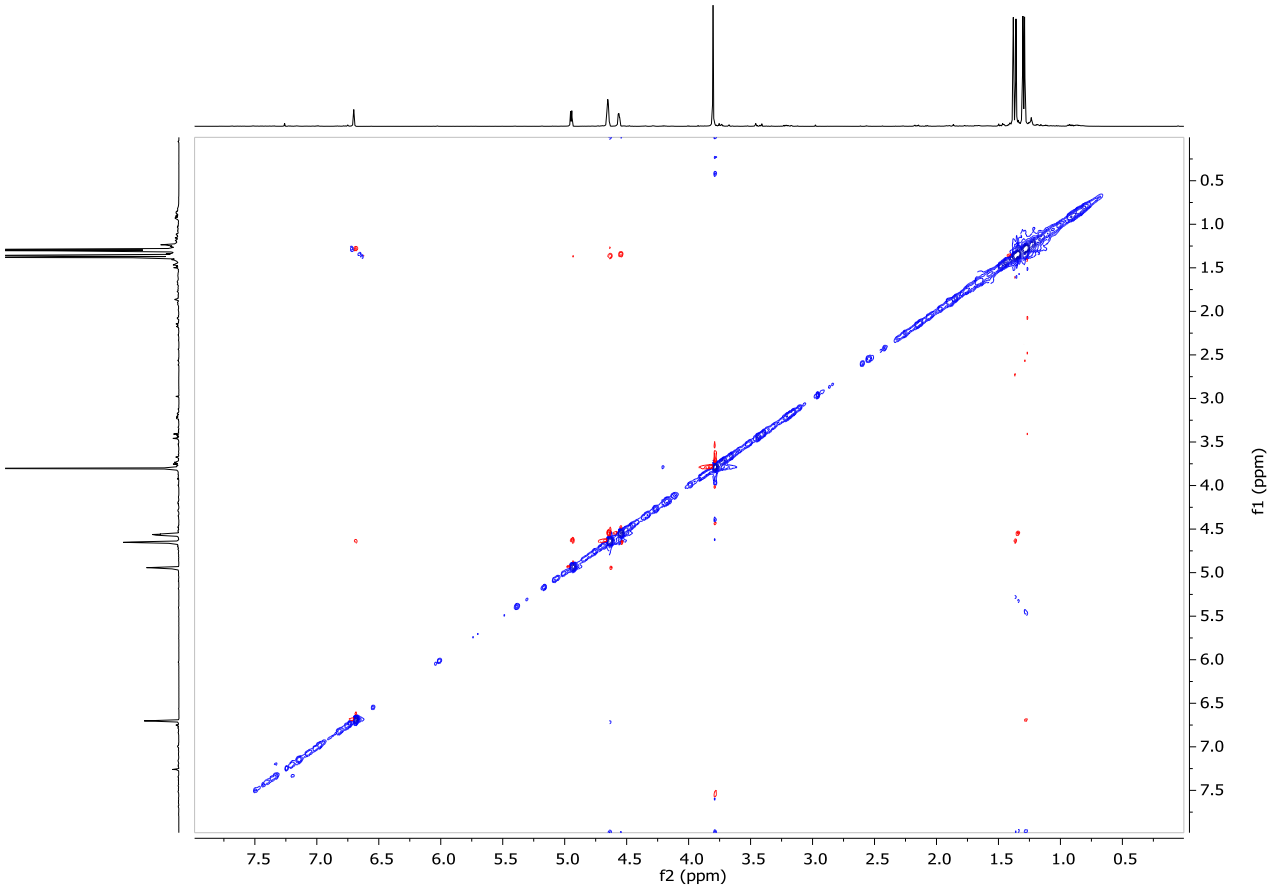

O
OH
MeO
OH
OH
2.76
f1 (ppm)

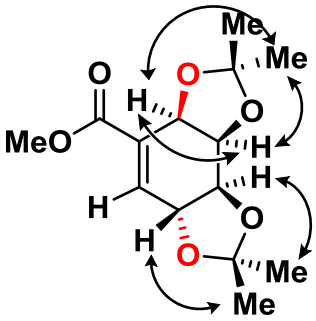

f1 (ppm)


Me
Me
O
O
MeO
O
O
2.77
O
Me
Me
f1 (ppm)


f1 (ppm)

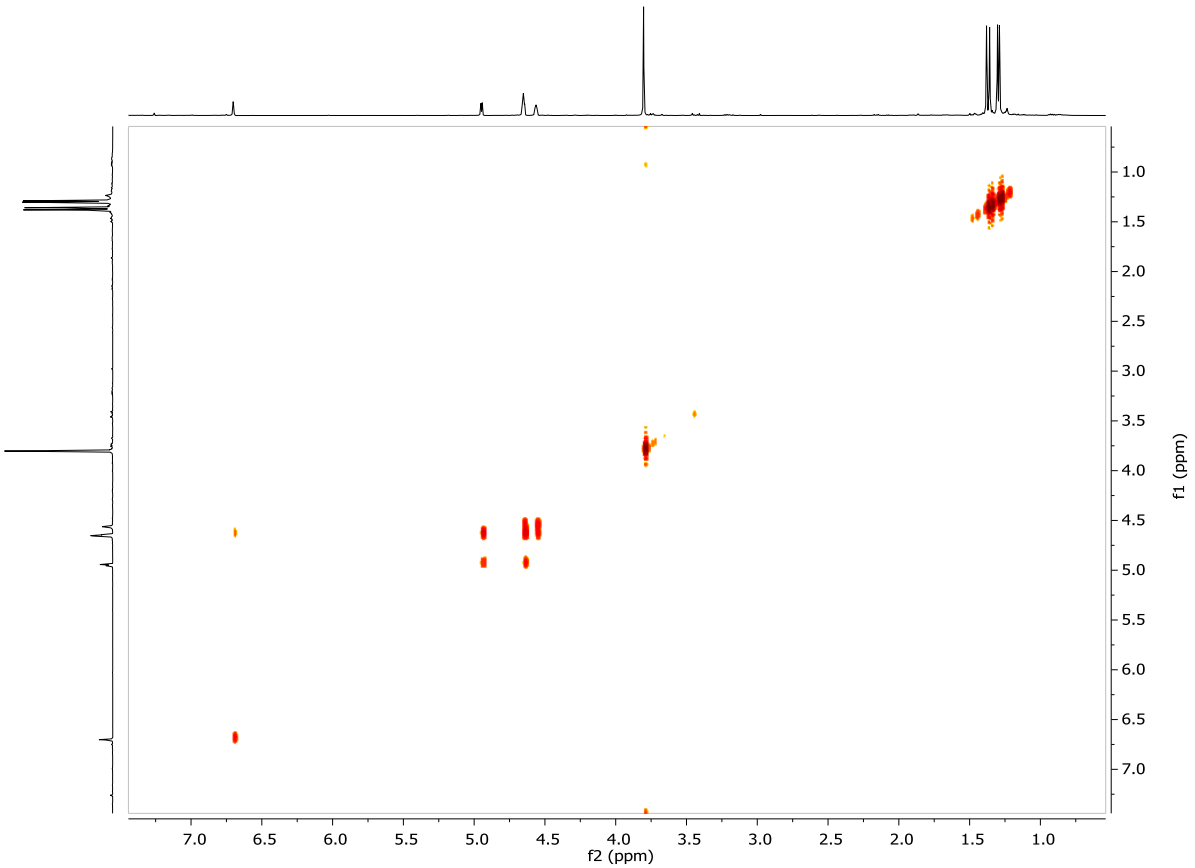
NOESY of compound **2.77**

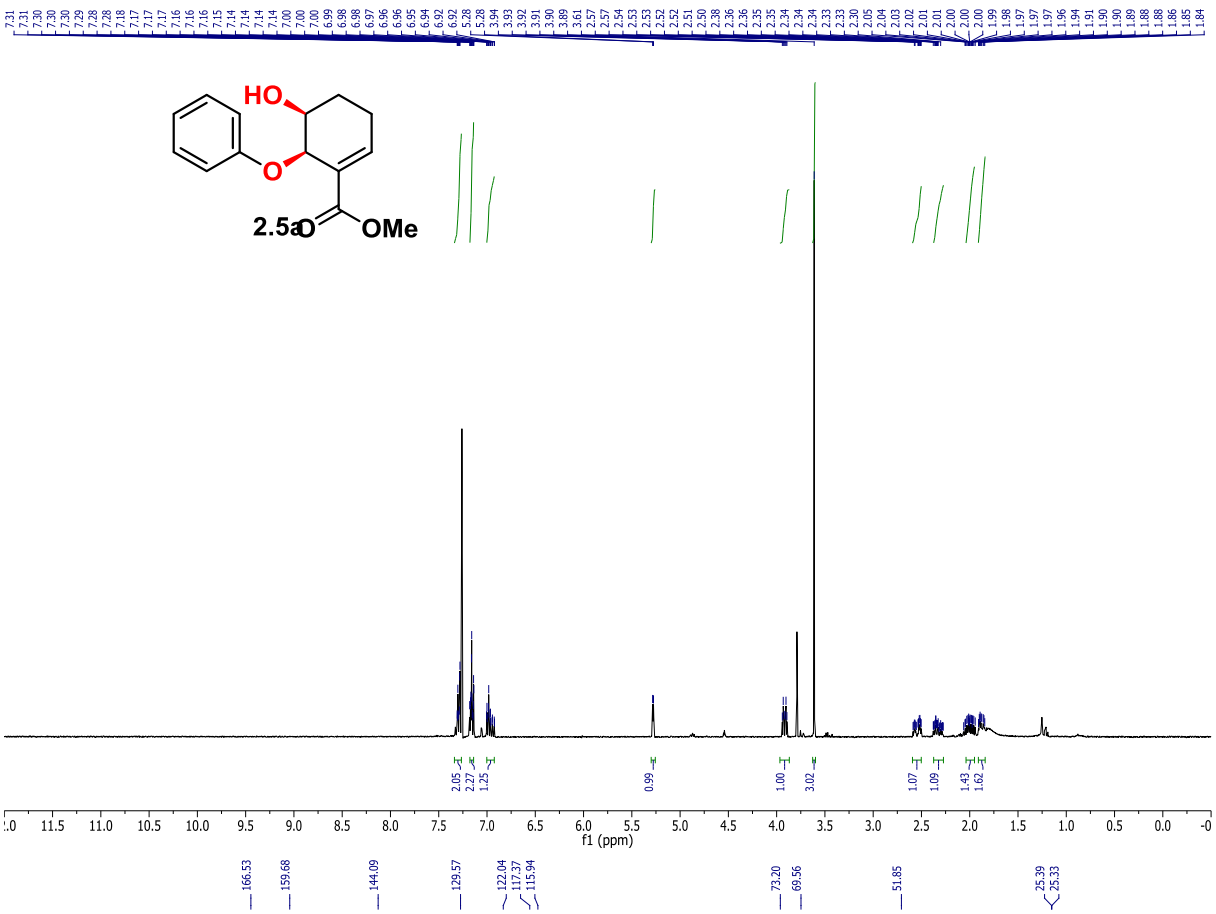


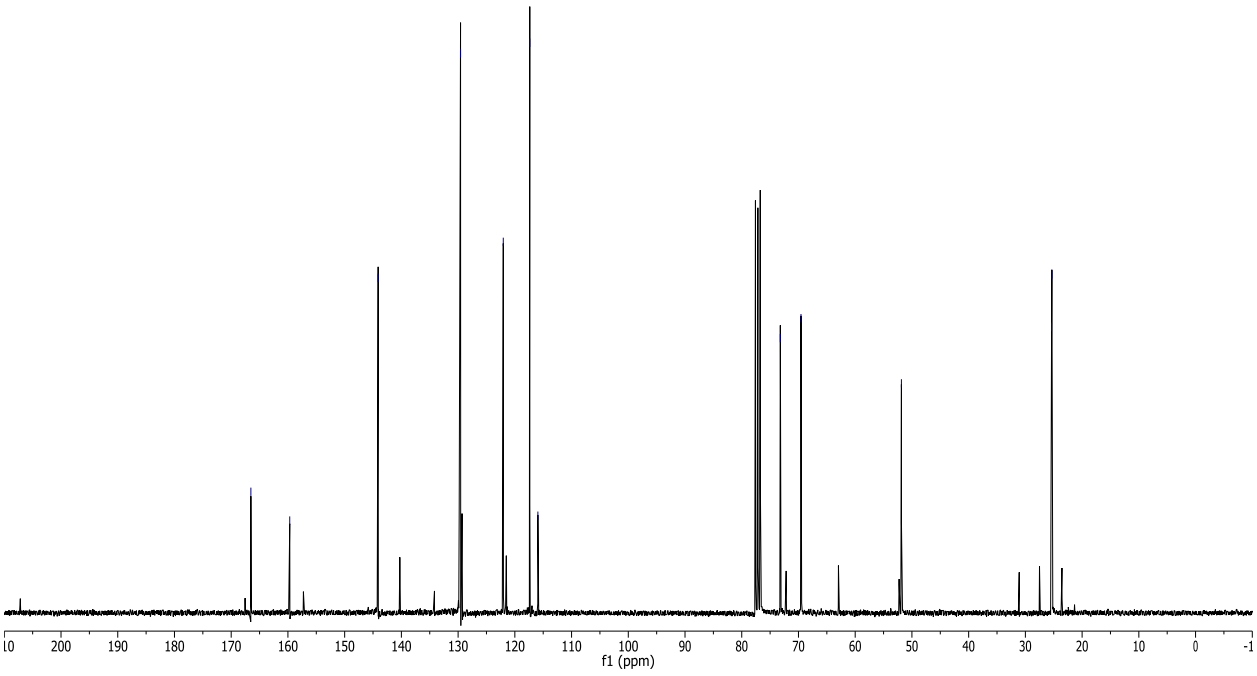


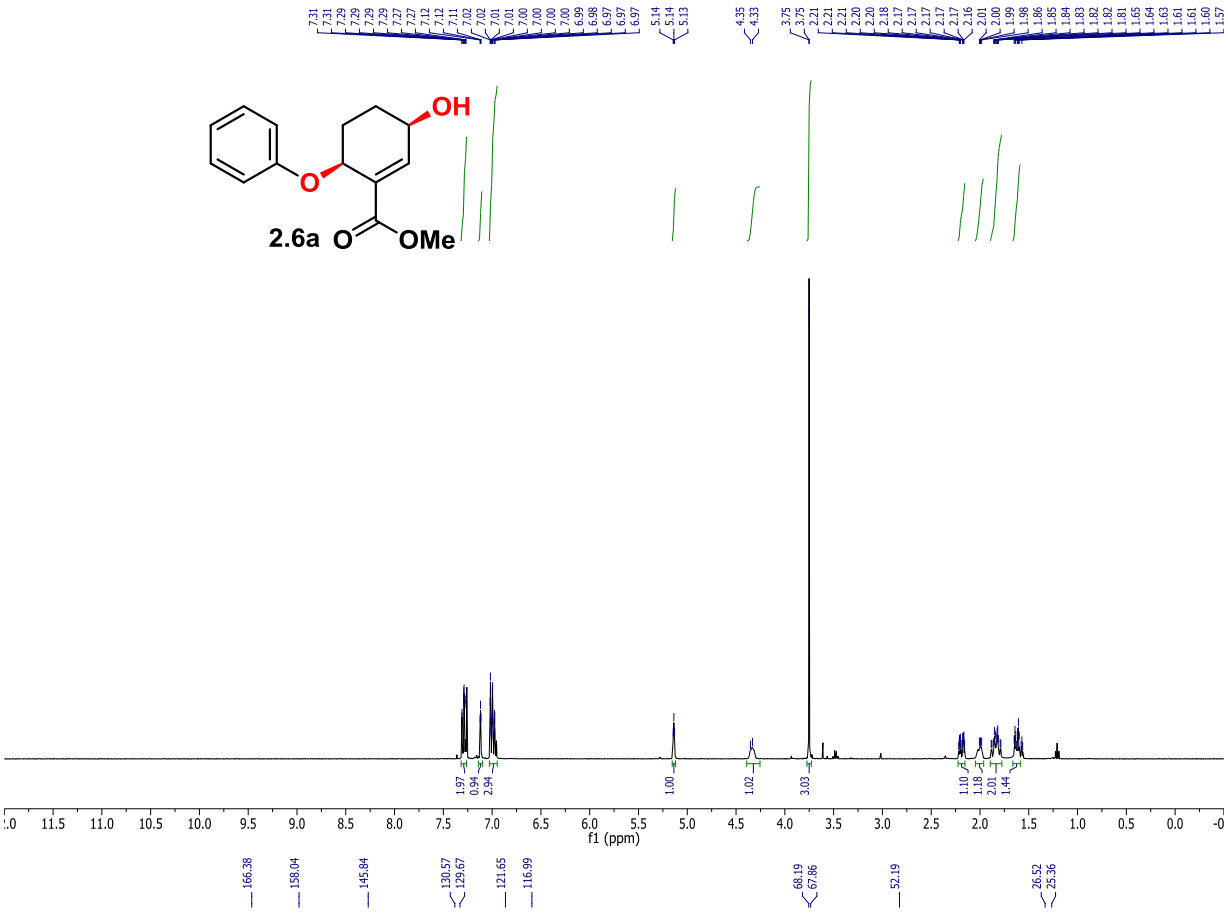
2.77 - NOE

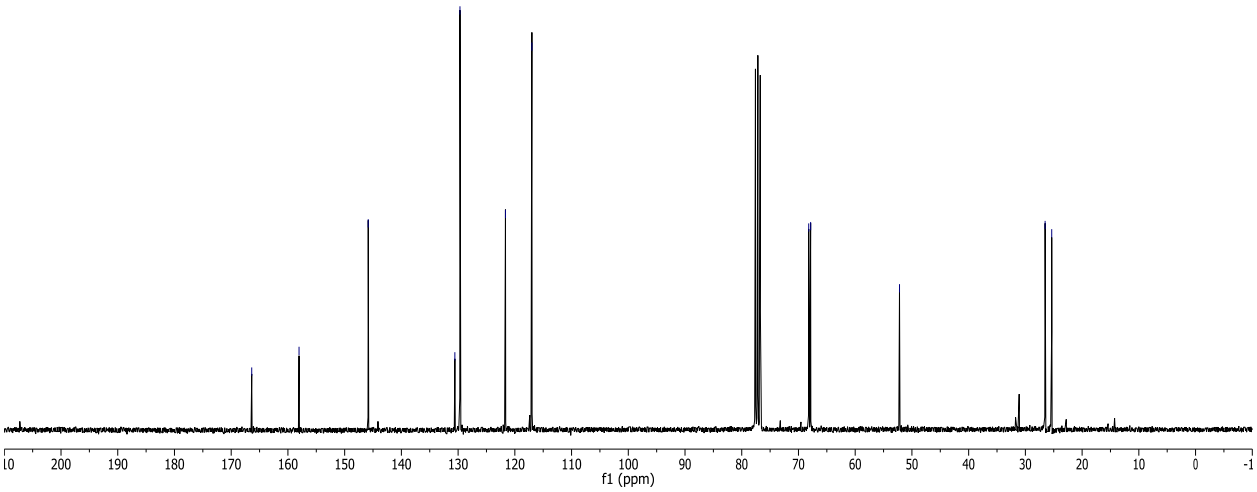
COSY of compound **2.77**

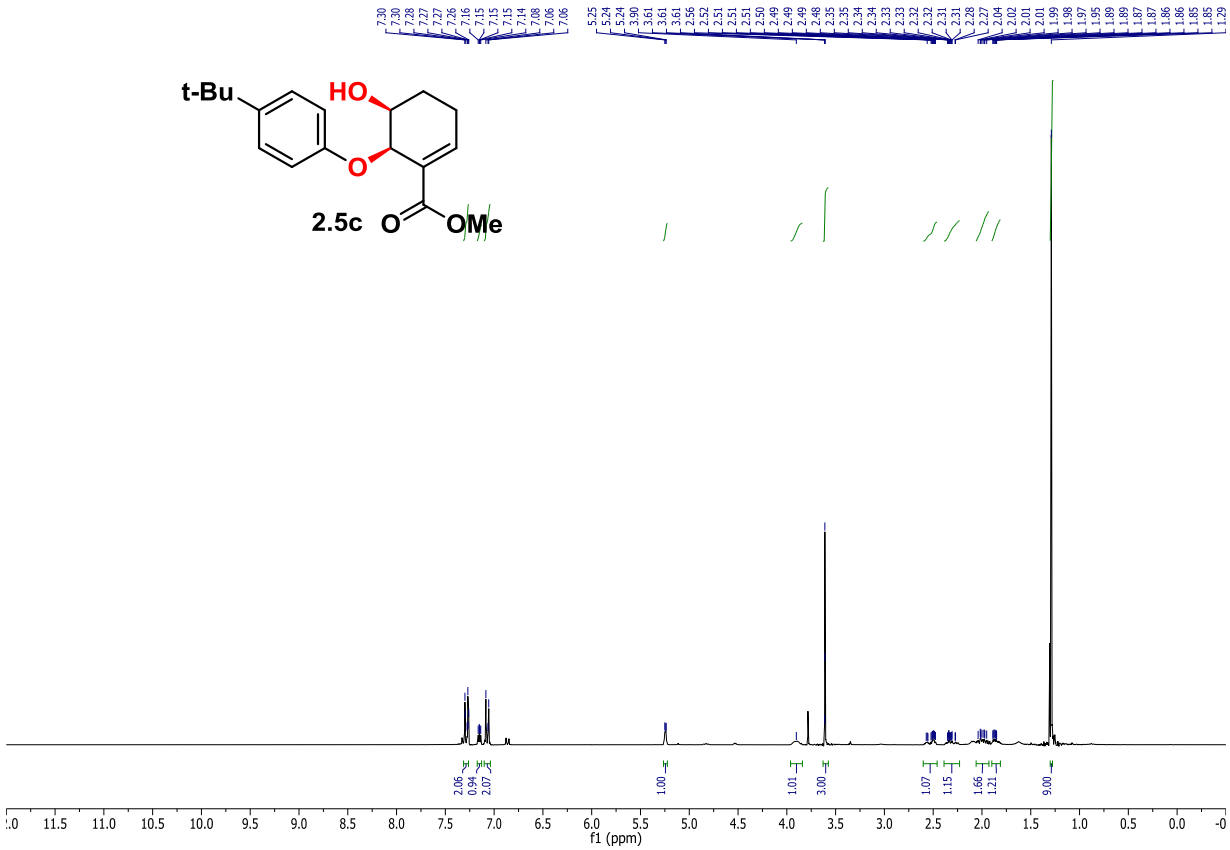


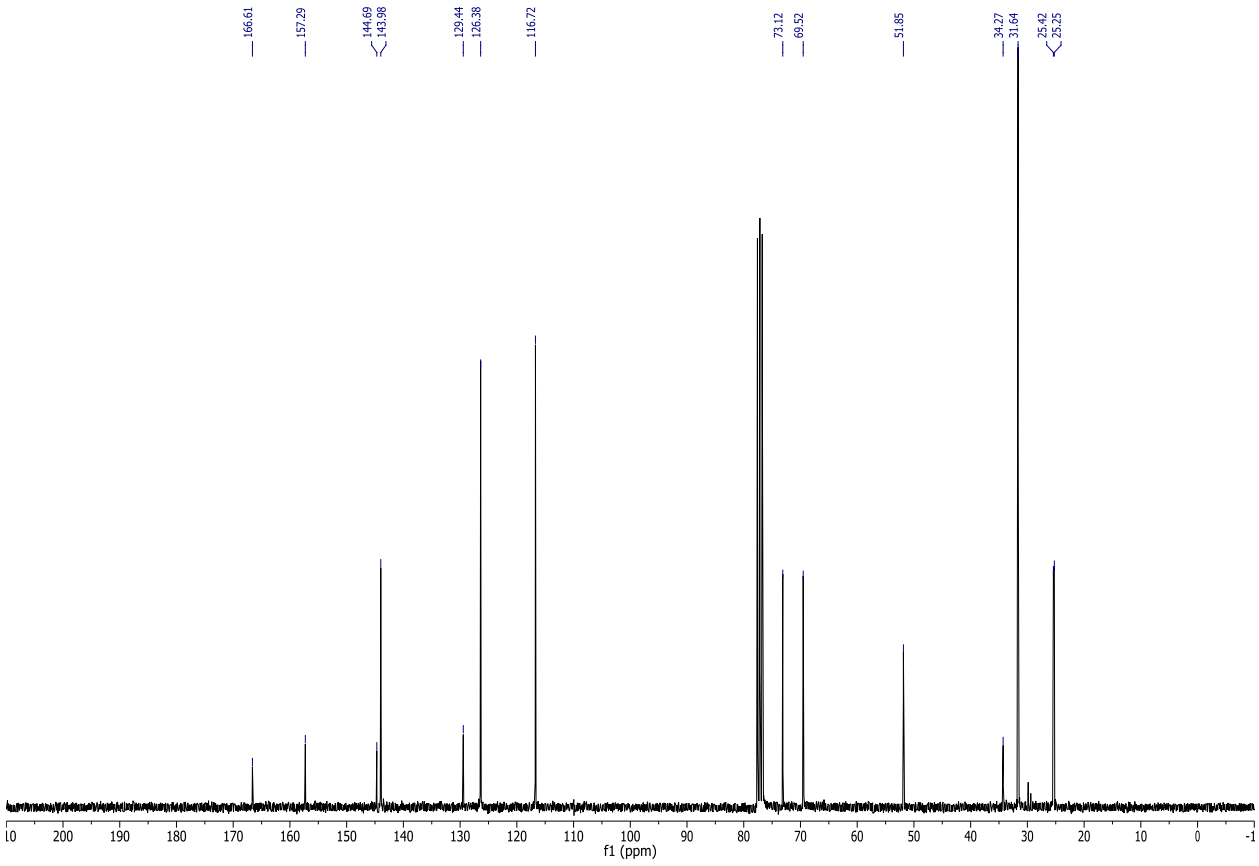

HO
O
O
OMe
2.5a
f1 (ppm)

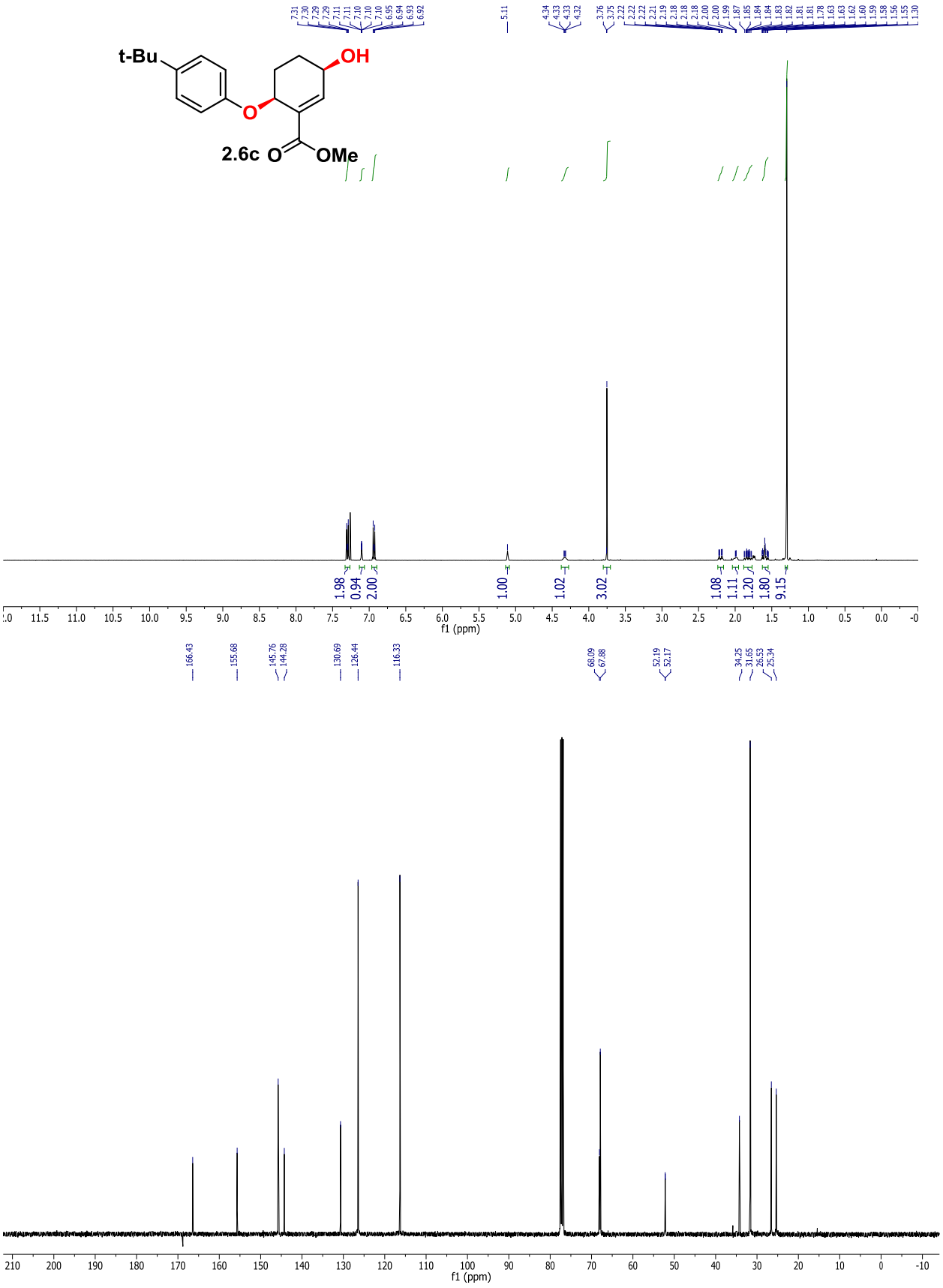

f1 (ppm)

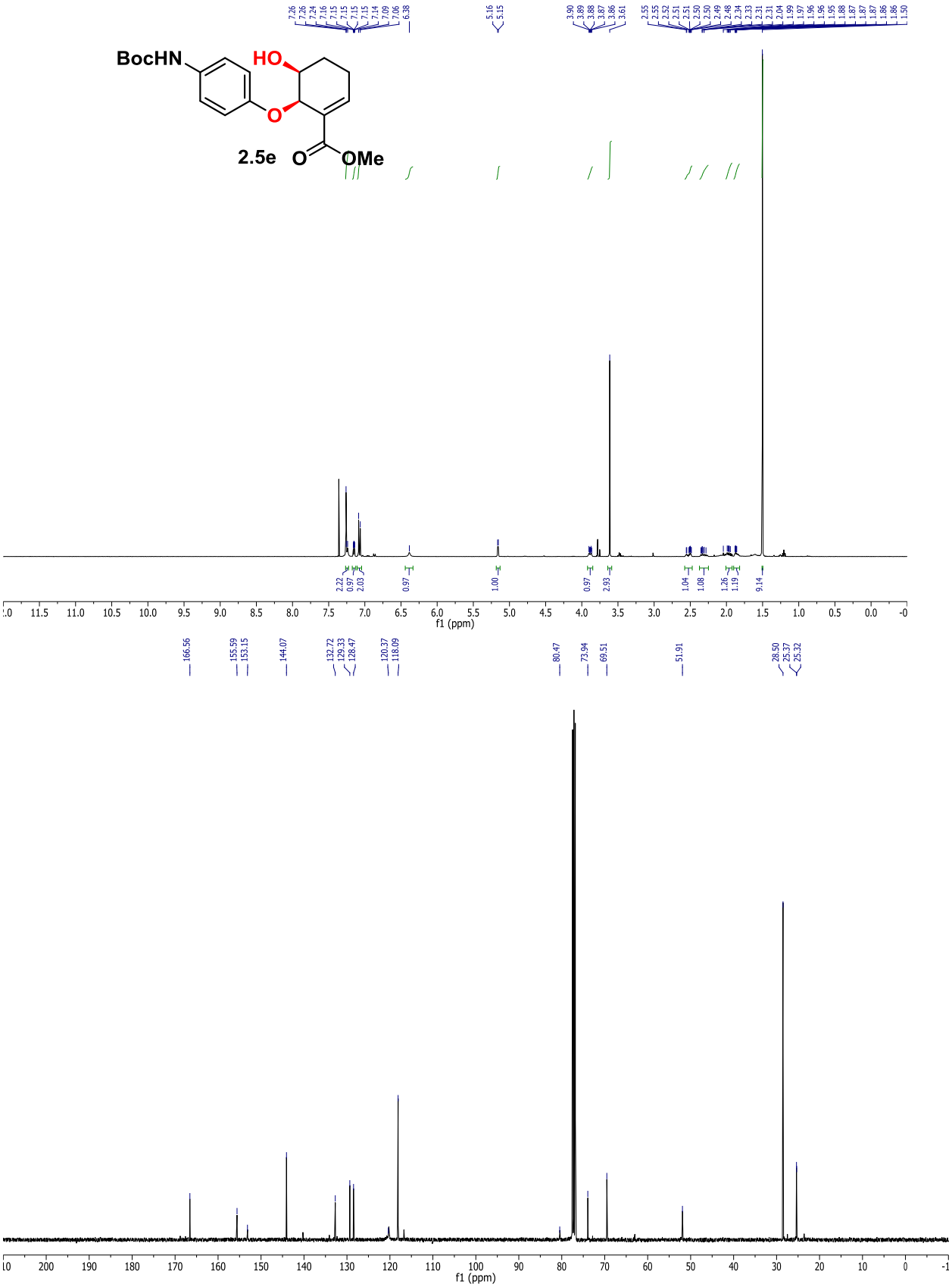

OH
O
2.6a O
OMe
f1 (ppm)

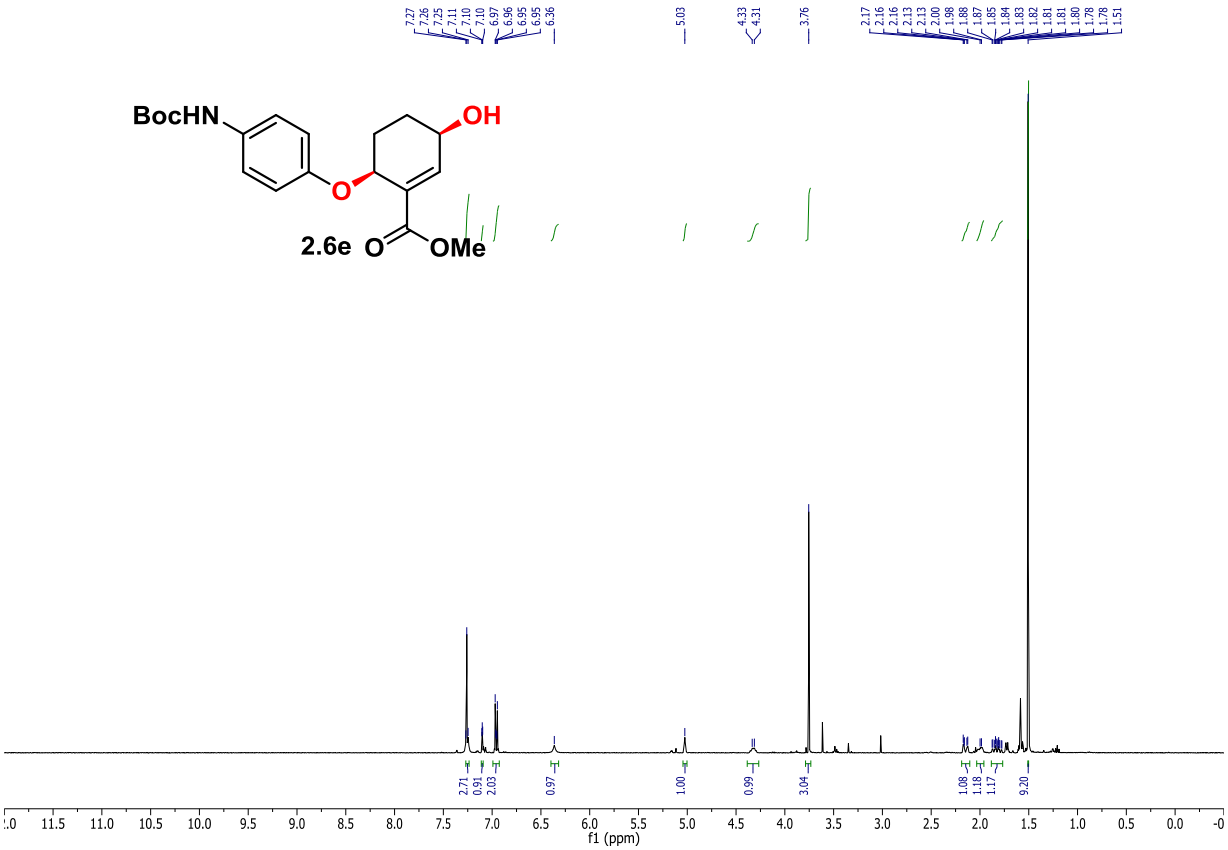

f1 (ppm)

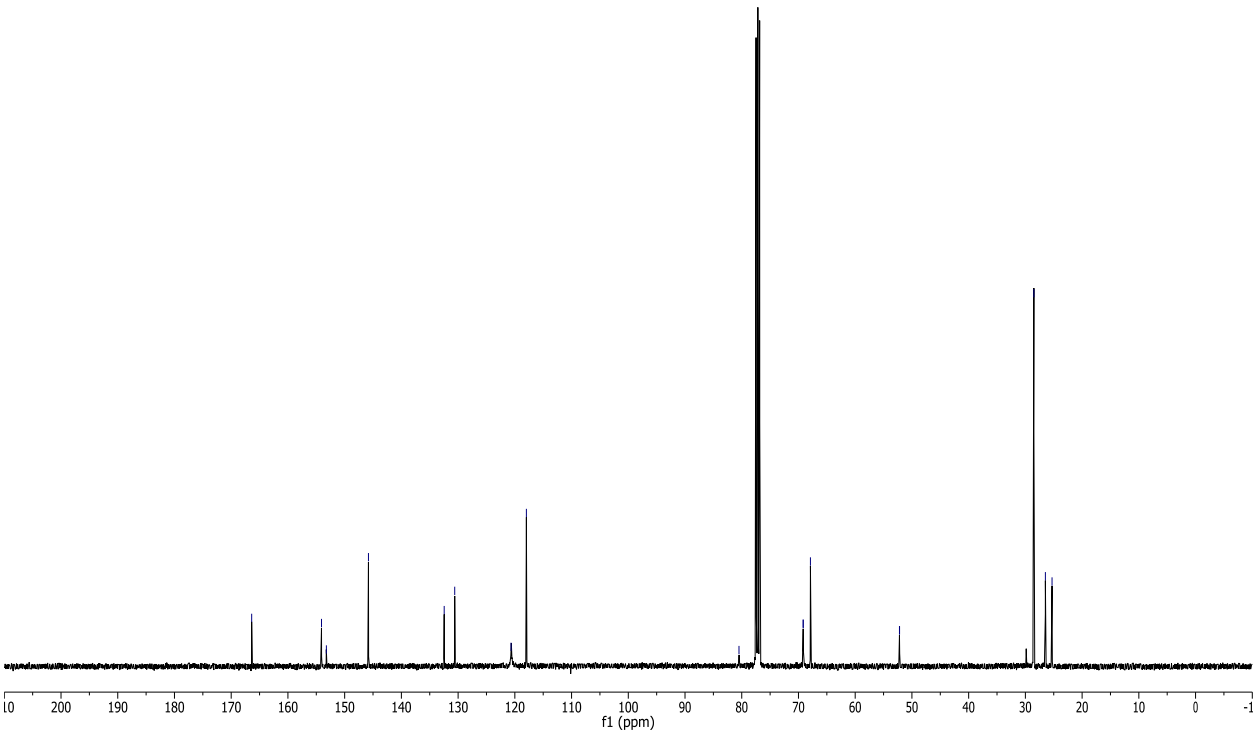

t-Bu
HO
O
2.5c
O
OMe
f1 (ppm)

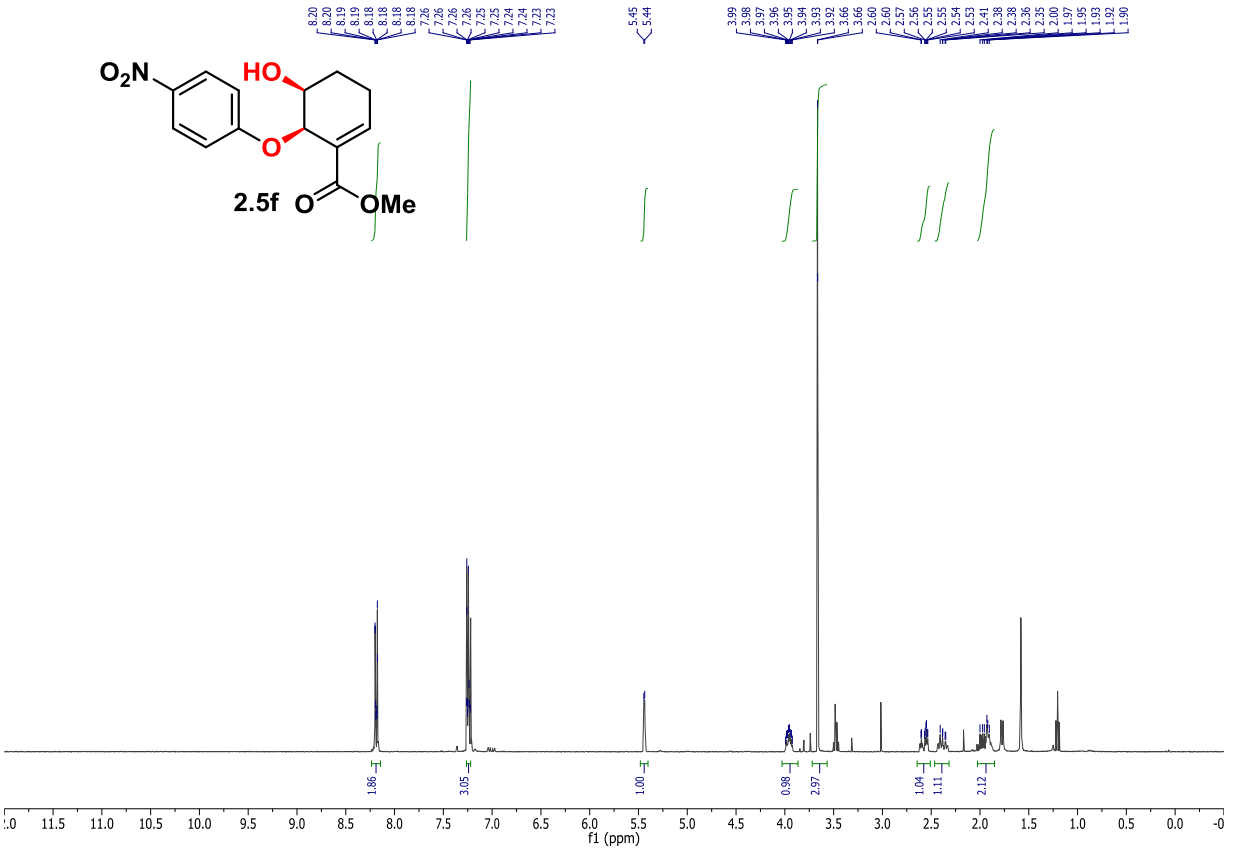

166.61
157.29
144.69
143.98
129.44
126.38
116.72
73.12
69.52
51.85
34.27
31.64
25.42
25.25
f1 (ppm)

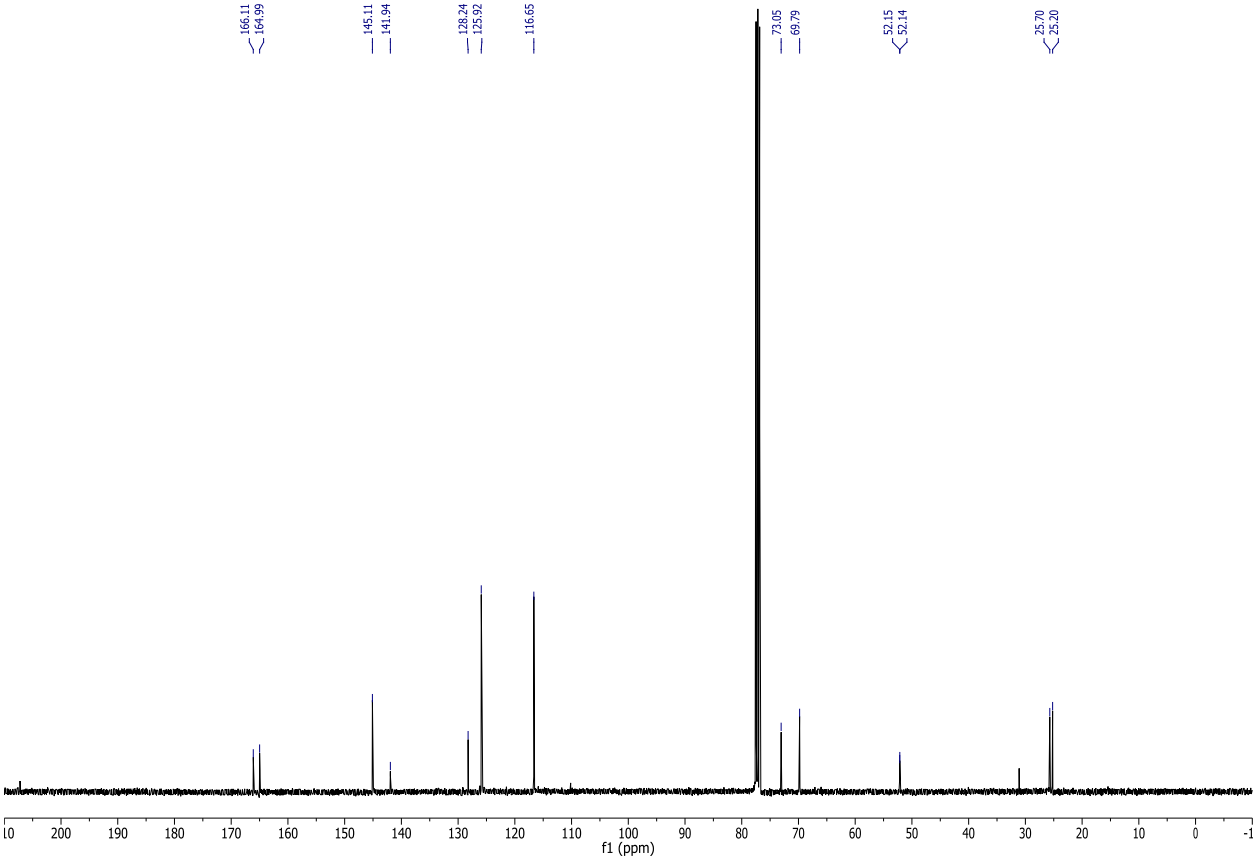

t-Bu
OH
O
2.6c O
OMe
f1 (ppm)
f1 (ppm)

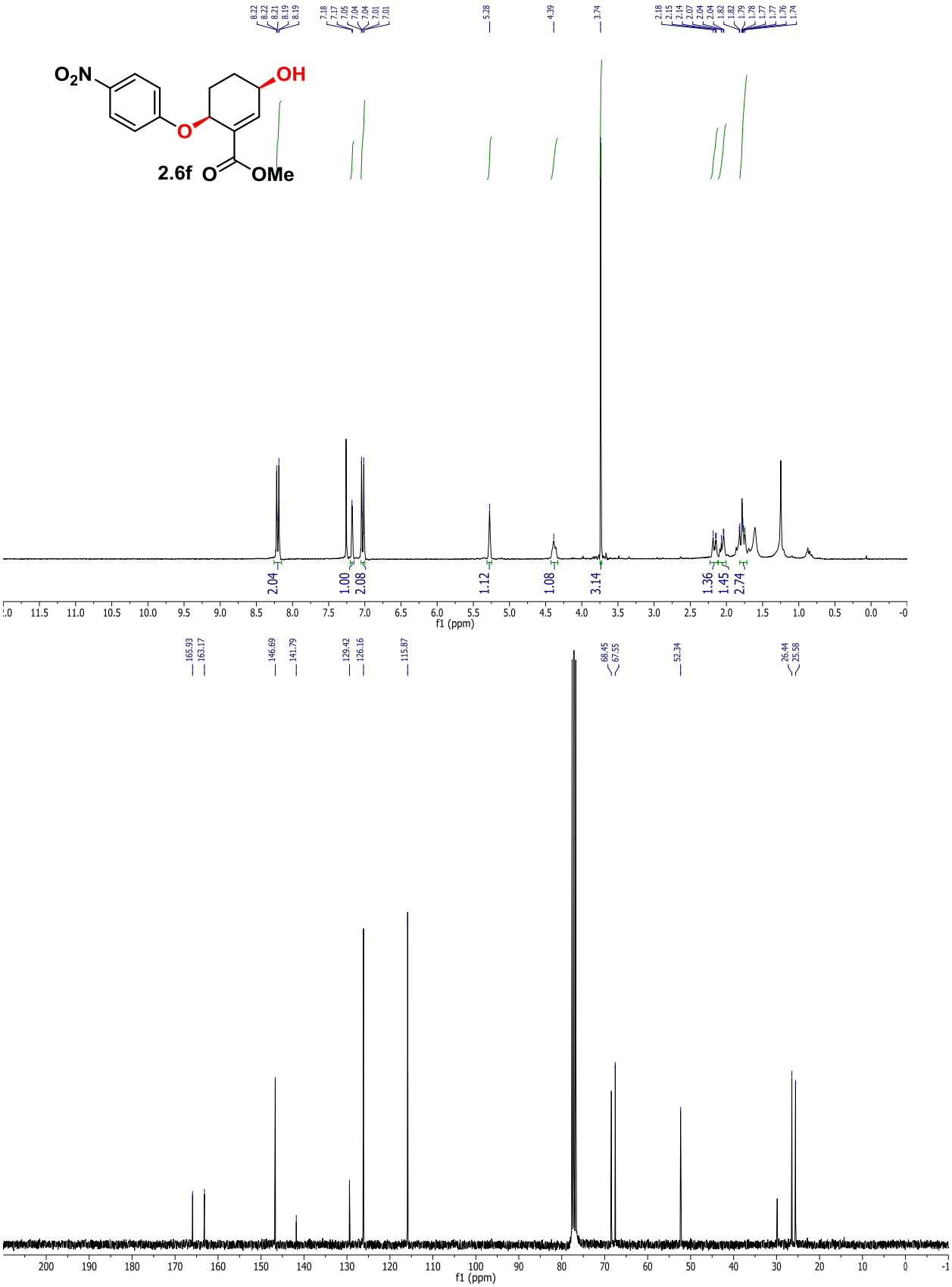

BocHN
HO
O
2.5e
O
OMe
f1 (ppm)
f1 (ppm)

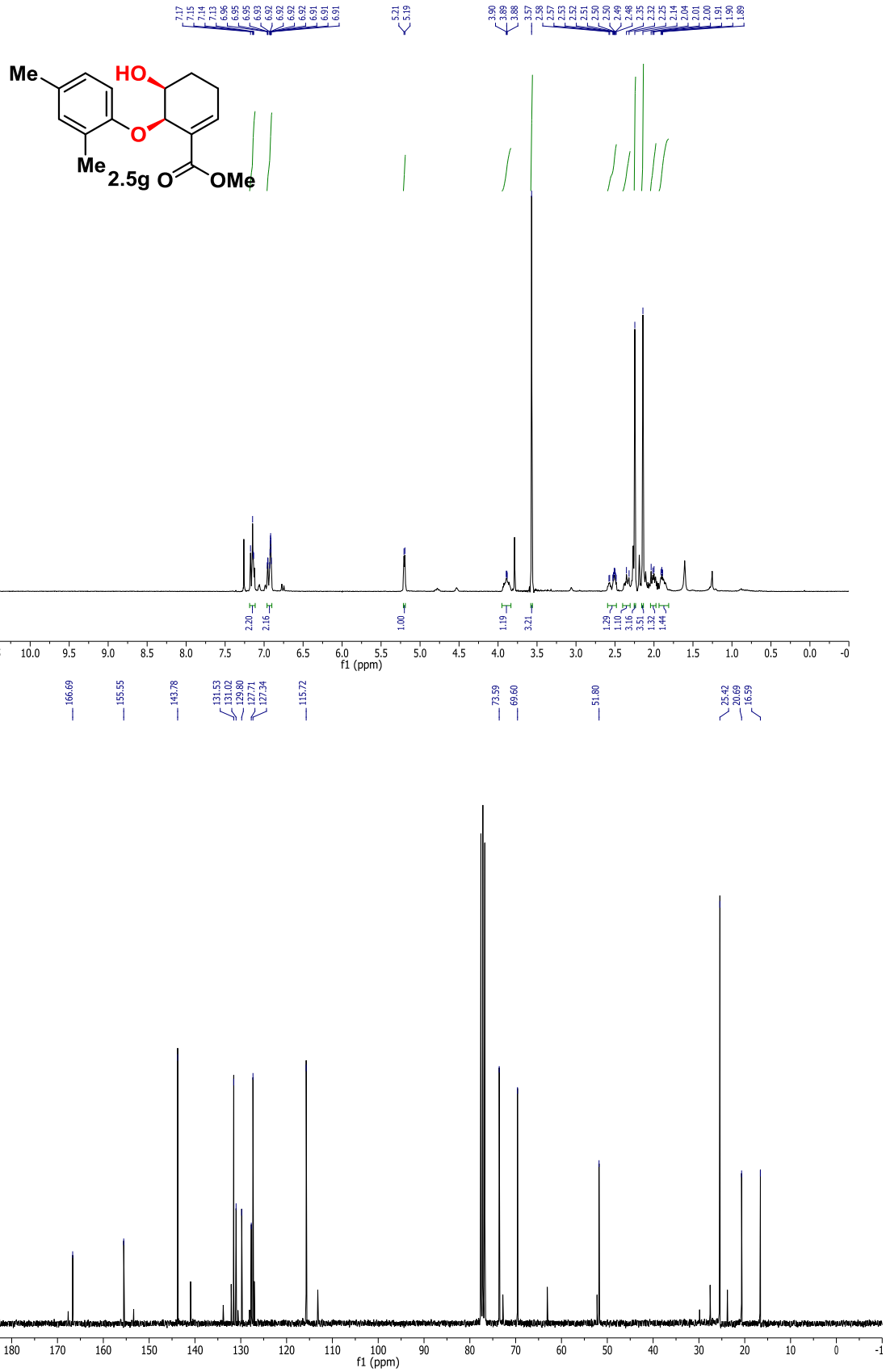

BocHN
OH
O
2.6e O
OMe
f1 (ppm)

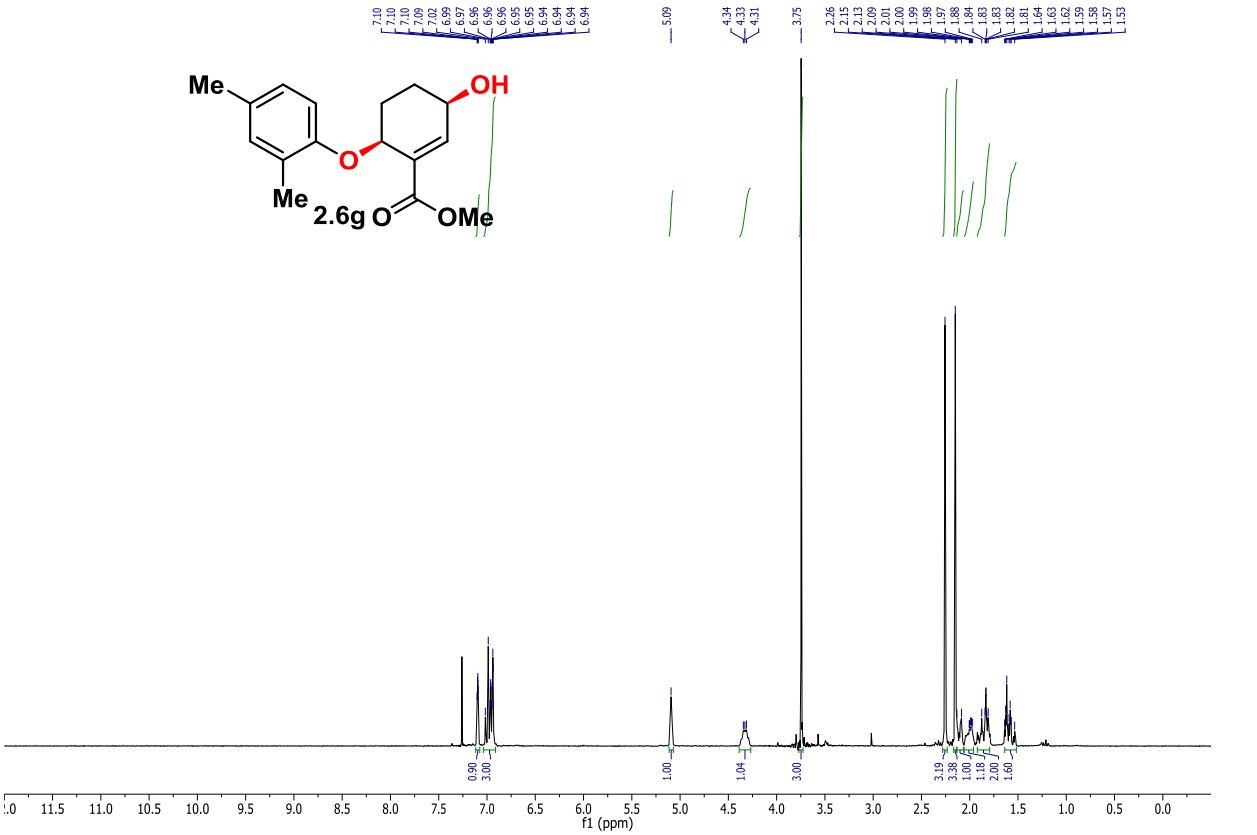

f1 (ppm)

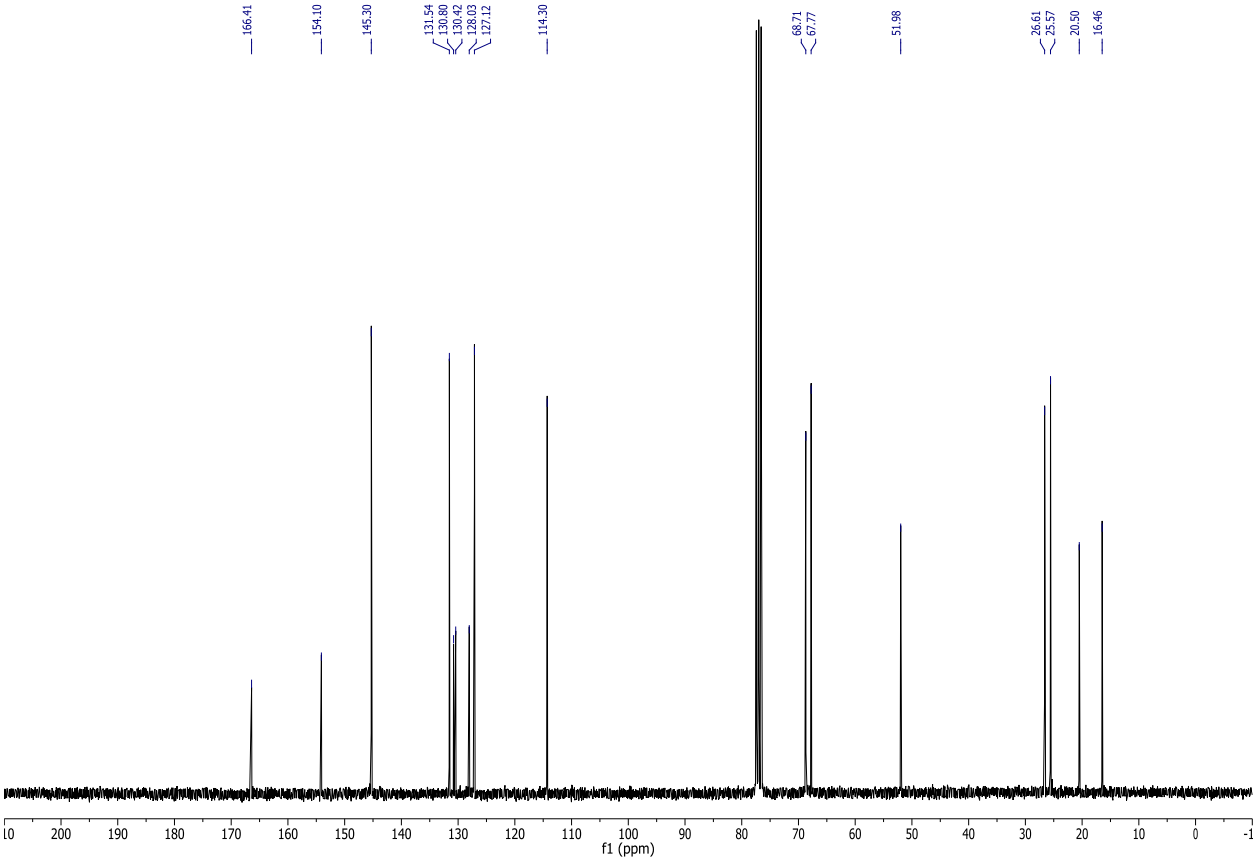

O2N
HO
O
2.5f
O
OMe
f1 (ppm)

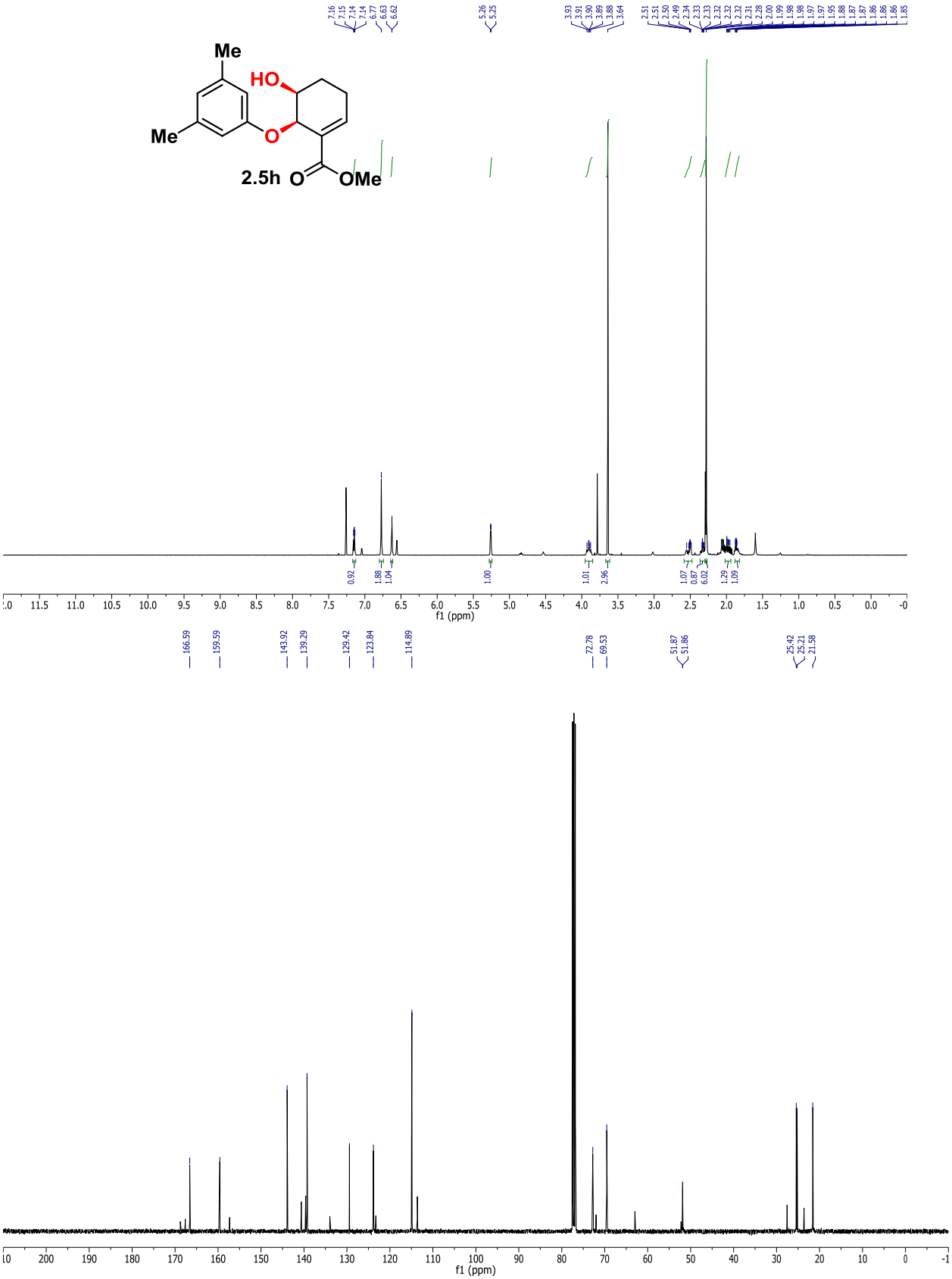

f1 (ppm)

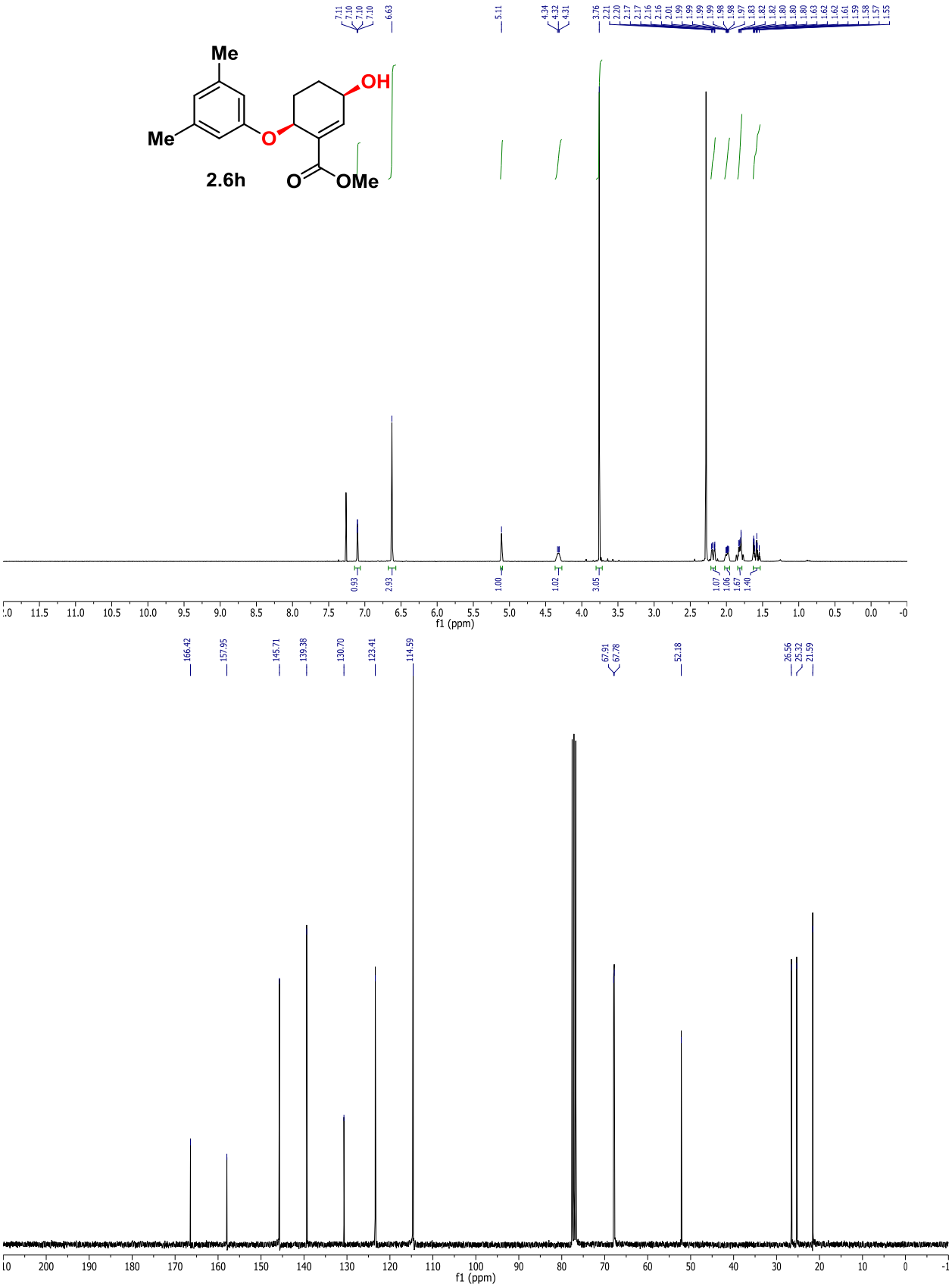

O2N
OH
O
2.6f O
OMe
f1 (ppm)
f1 (ppm)

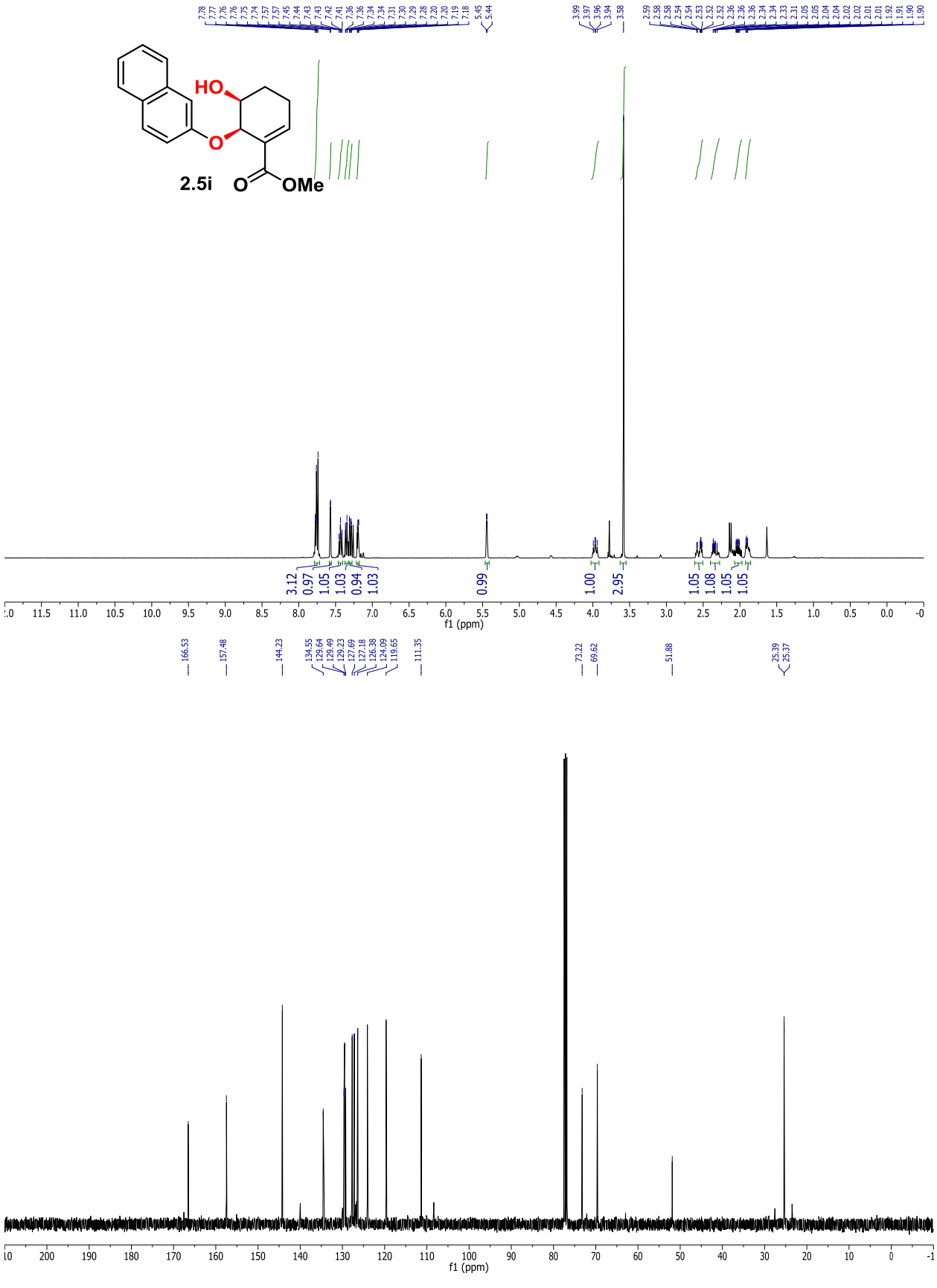

Me
HO
O
Me
2.5g O
OMe
f1 (ppm)
f1 (ppm)

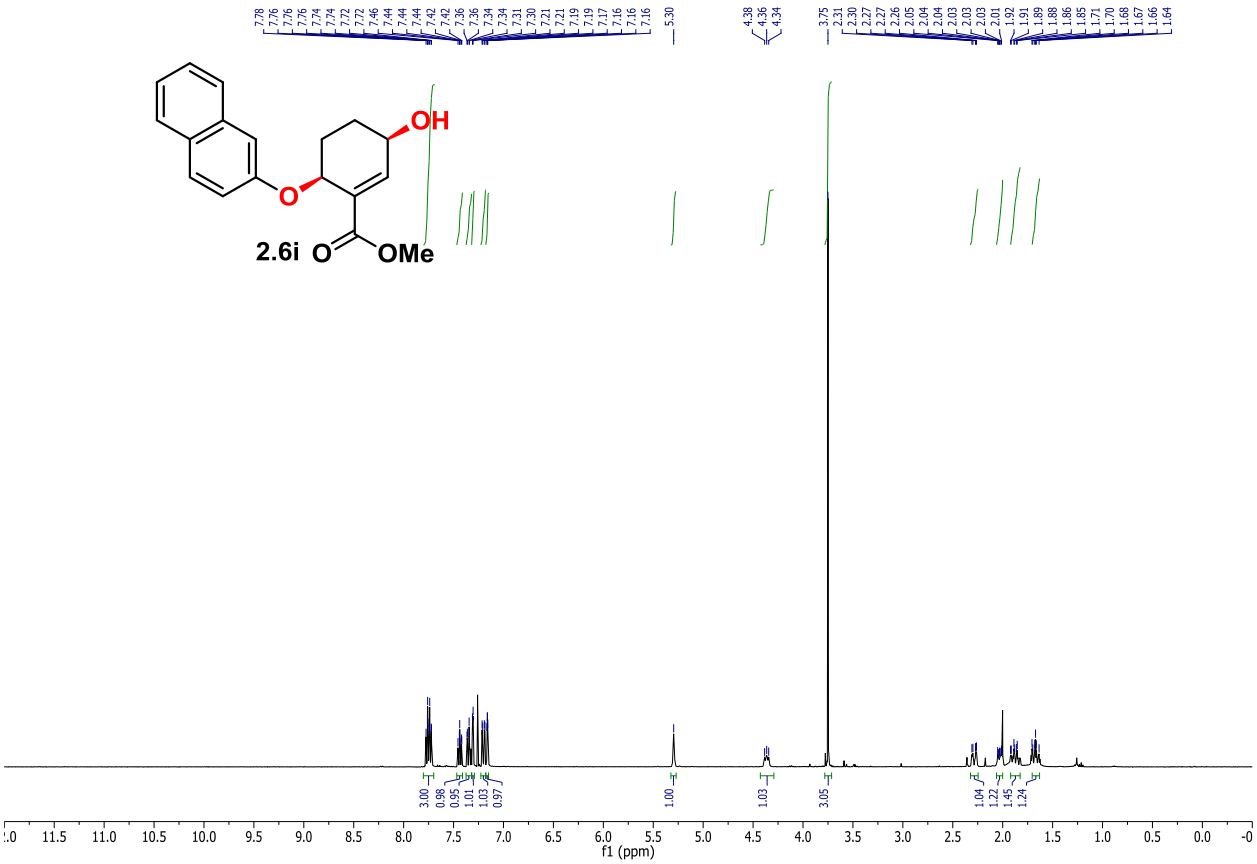

Me
OH
O
Me
2.6g O
OMe
f1 (ppm)

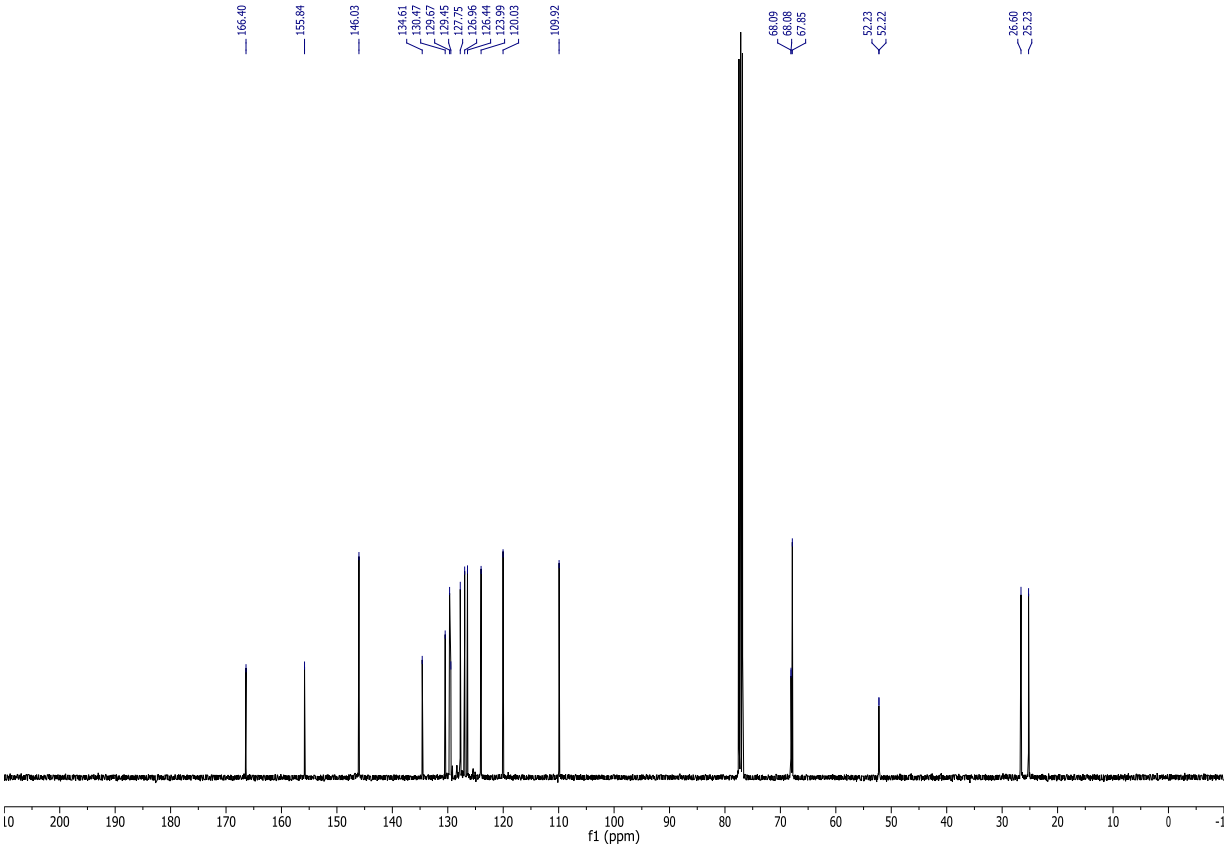

f1 (ppm)

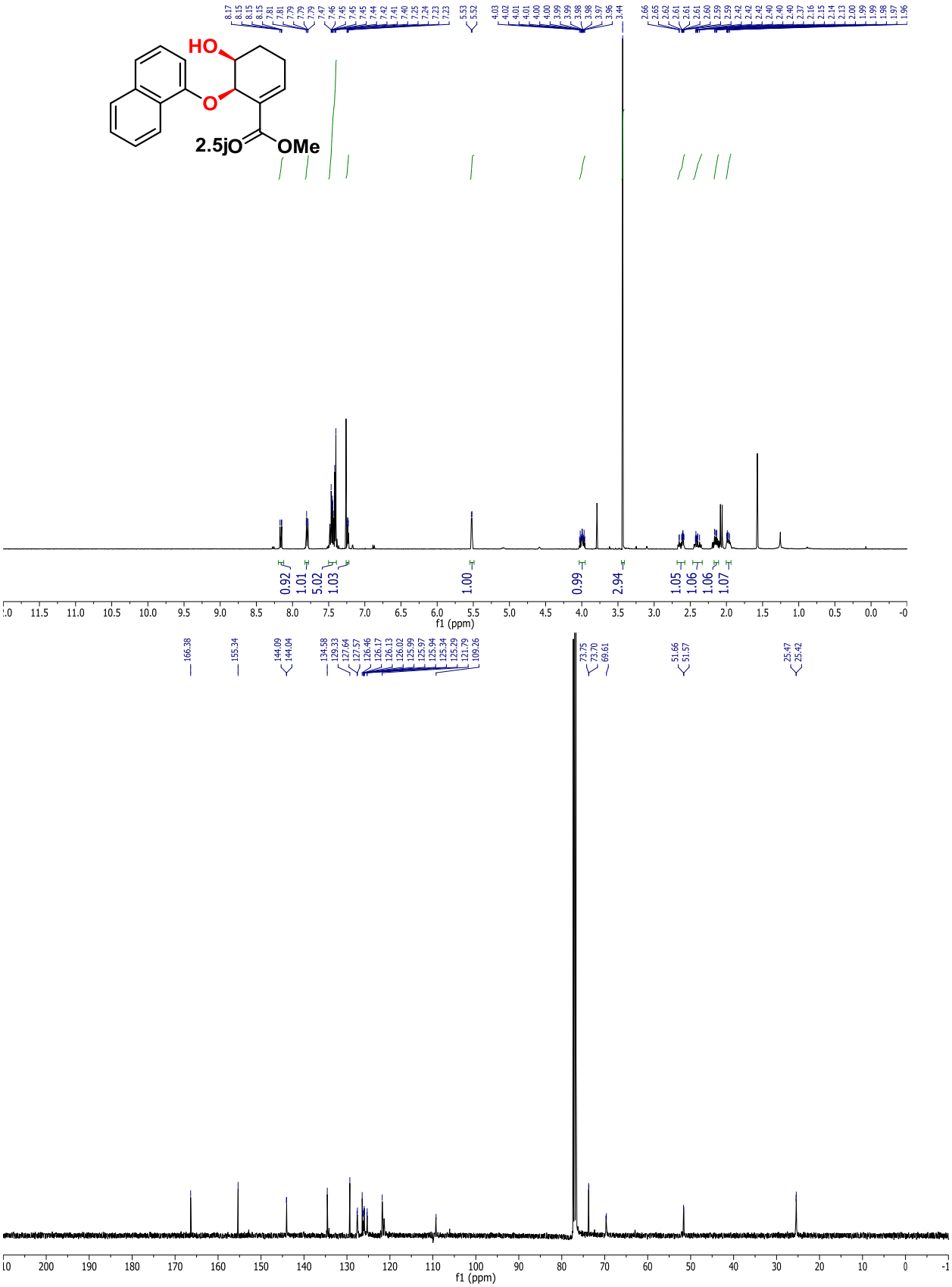

Me
HO
Me
O
2.5h O
OMe
f1 (ppm)
f1 (ppm)

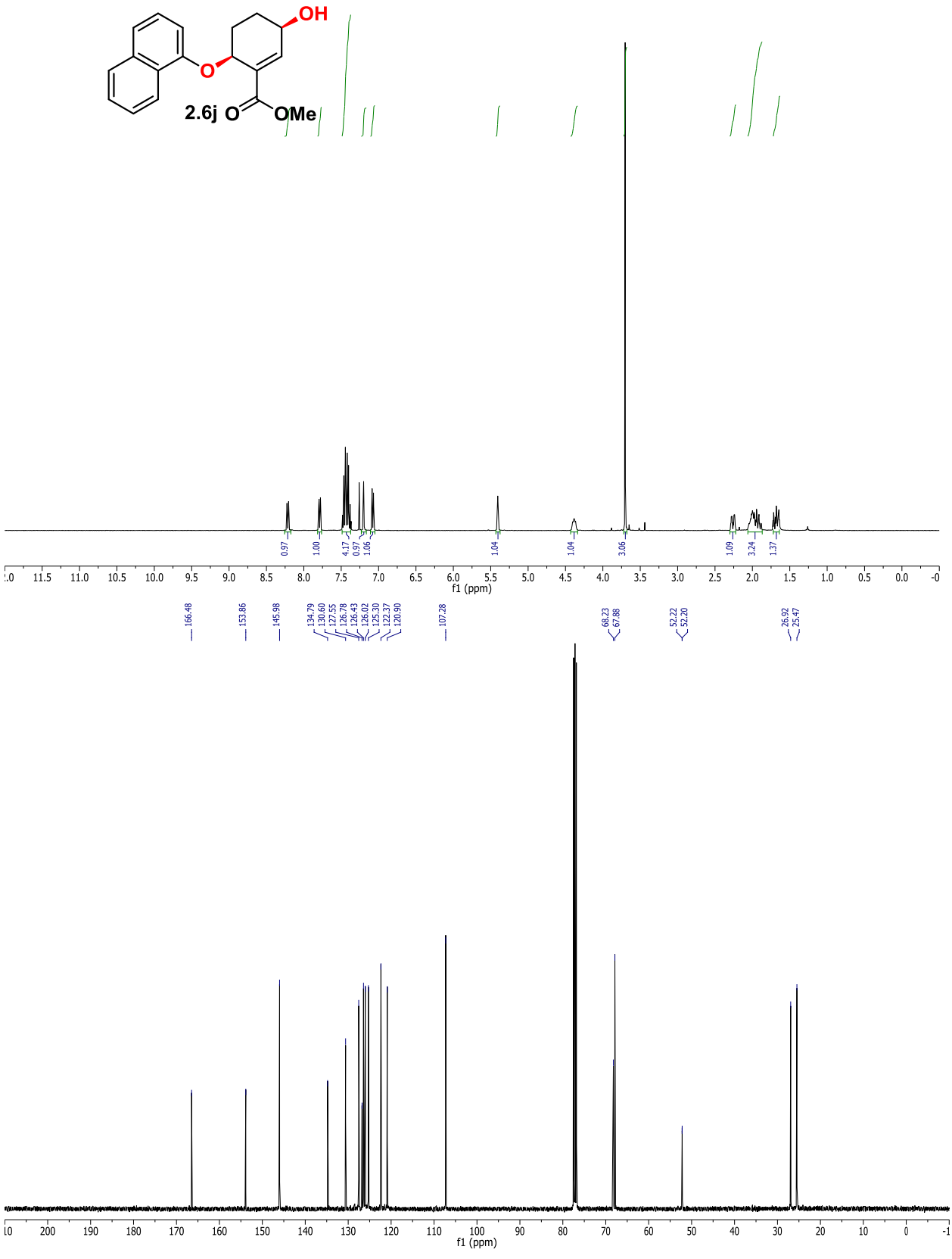

Me
OH
Me
O
O
OMe
2.6h
f1 (ppm)
f1 (ppm)

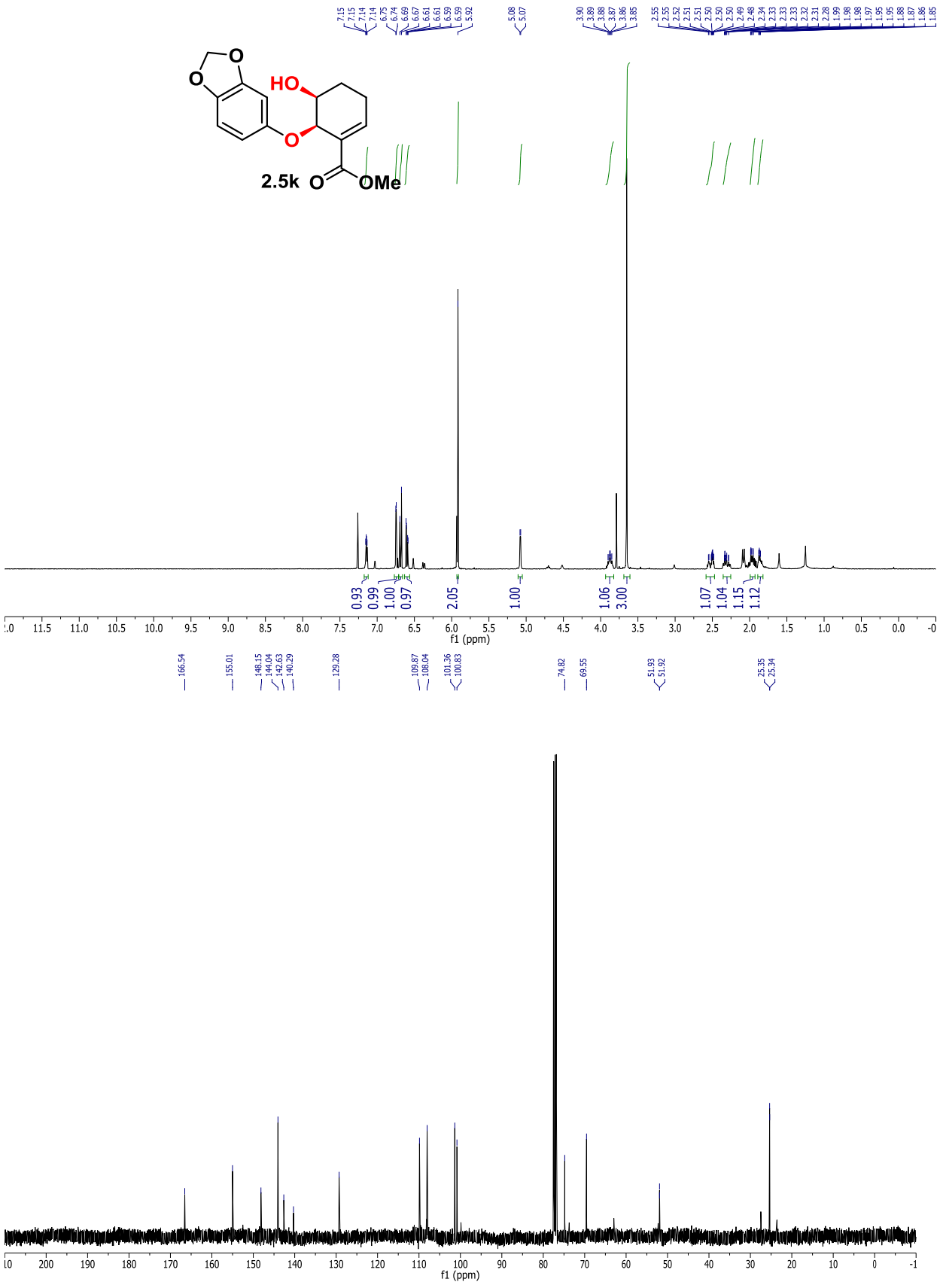

HO
O
O
OMe
2.5i
f1 (ppm)
f1 (ppm)

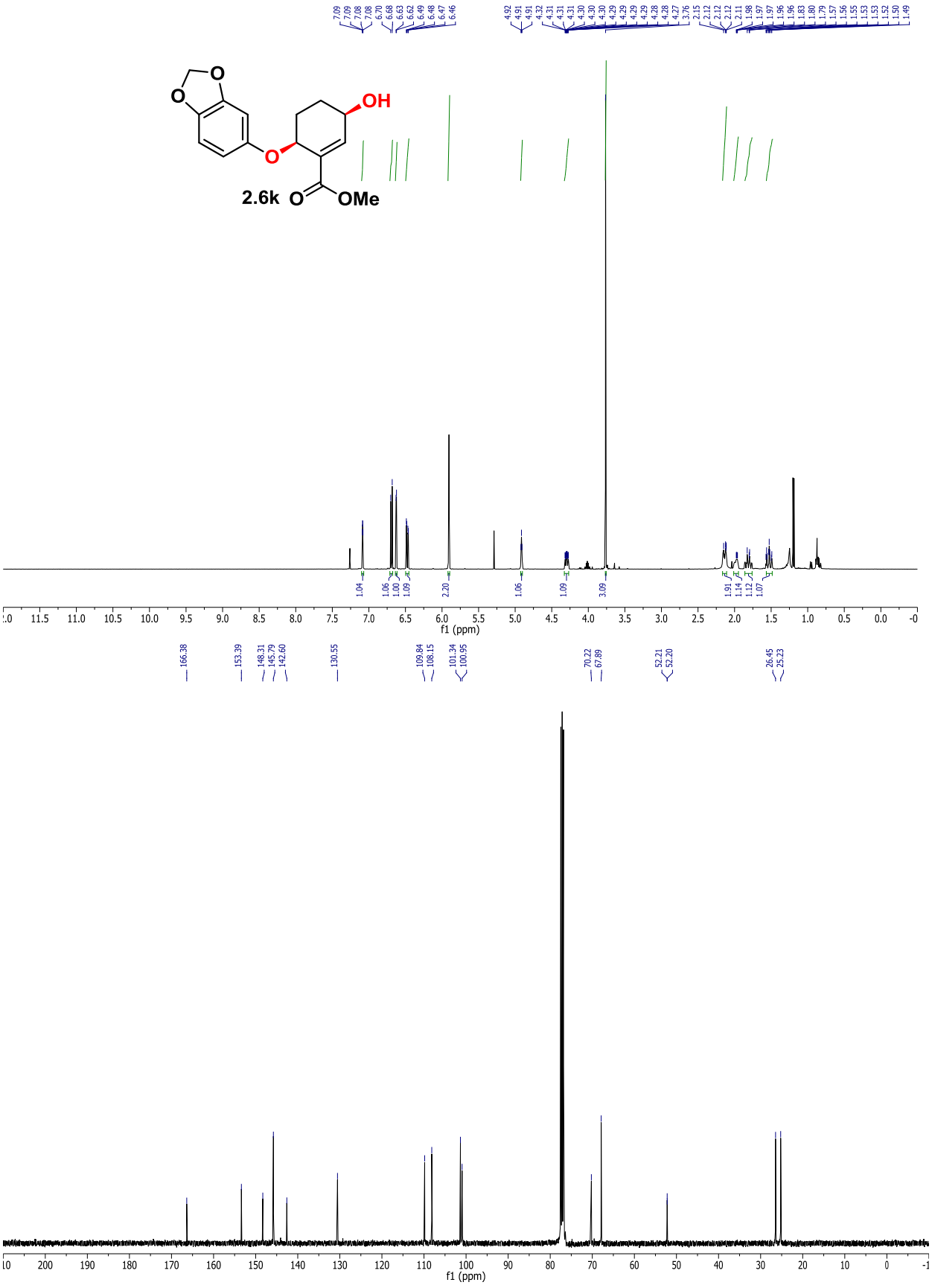

OH
O
2.6i O
OMe
f1 (ppm)


f1 (ppm)

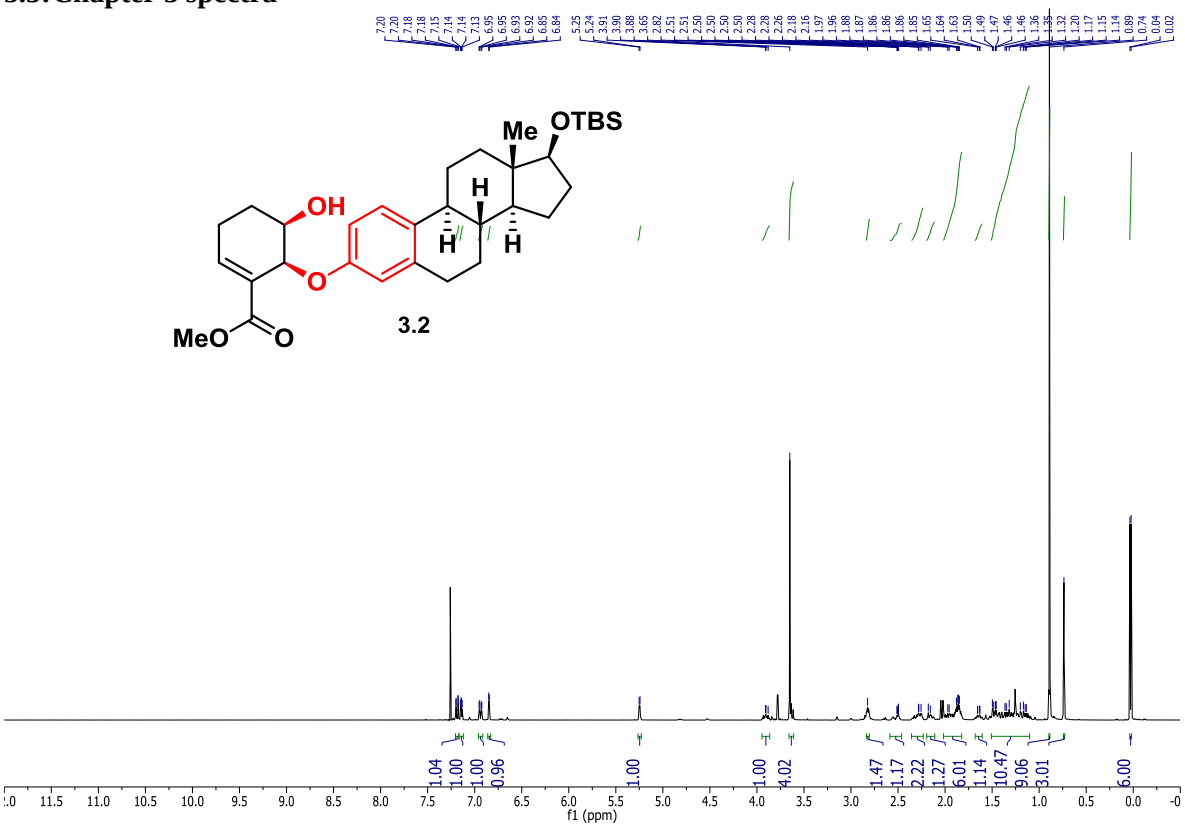

HO
O
2.5jO
OMe
f1 (ppm)
f1 (ppm)

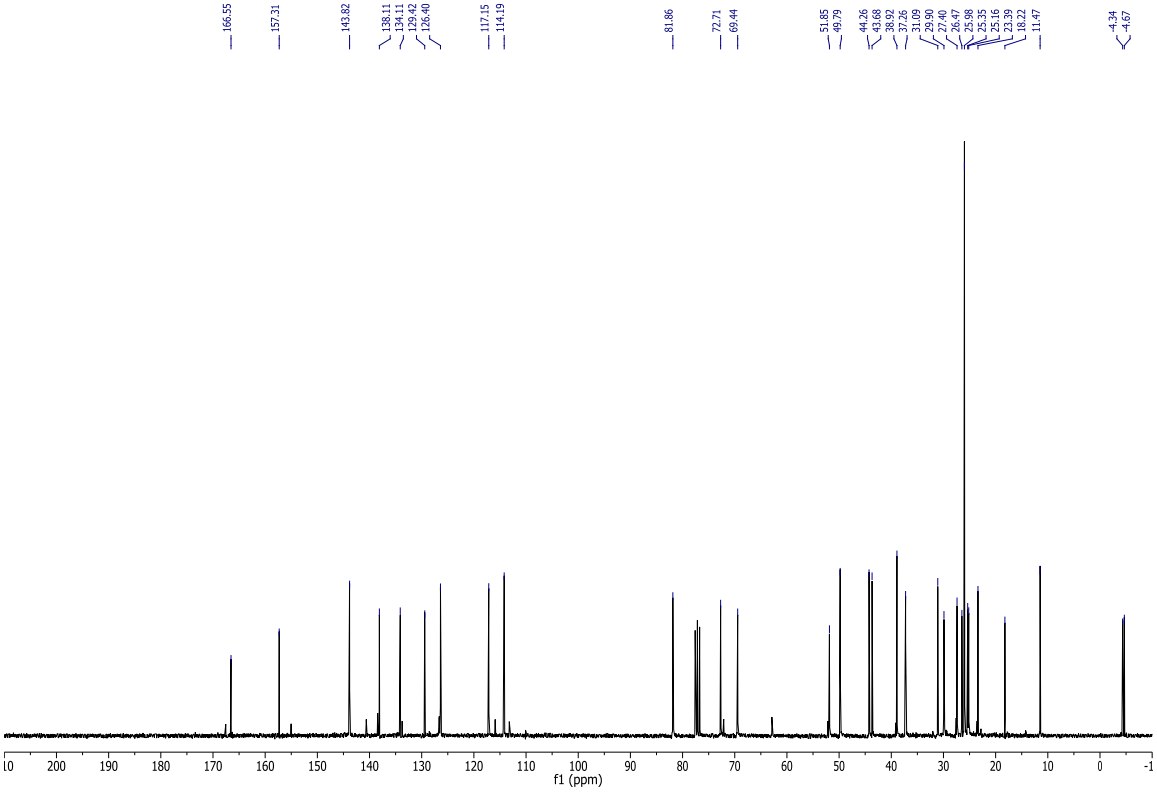

OH
O
2.6j O
OMe
0.97
1.00
4.17
0.97
1.06
1.04
1.04
3.06
1.09
3.24
1.37
f1 (ppm)
166.48
153.86
145.98
134.79
130.60
127.55
126.78
126.43
126.02
125.30
122.37
120.90
107.28
68.23
67.88
52.22
52.20
26.92
25.47
f1 (ppm)

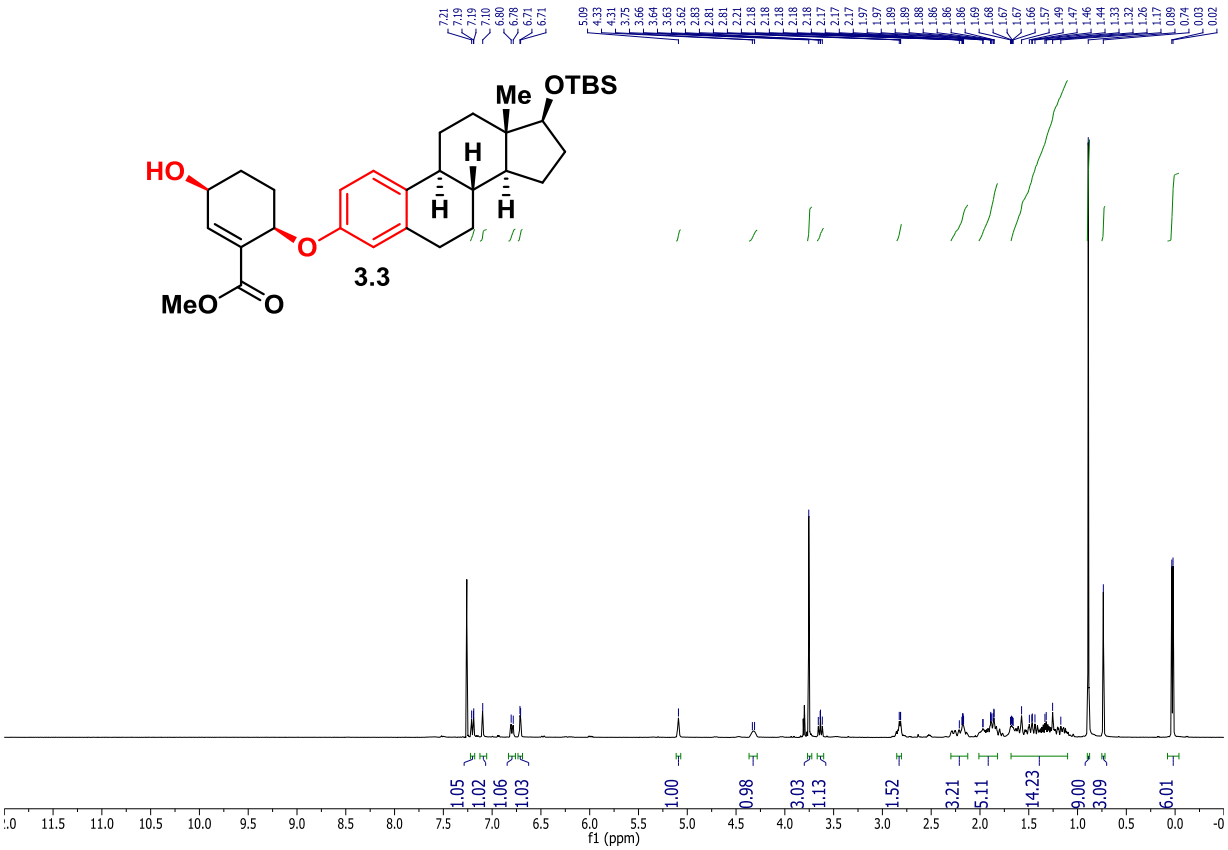

HO
O
O
O
2.5k O
OMe
f1 (ppm)
f1 (ppm)

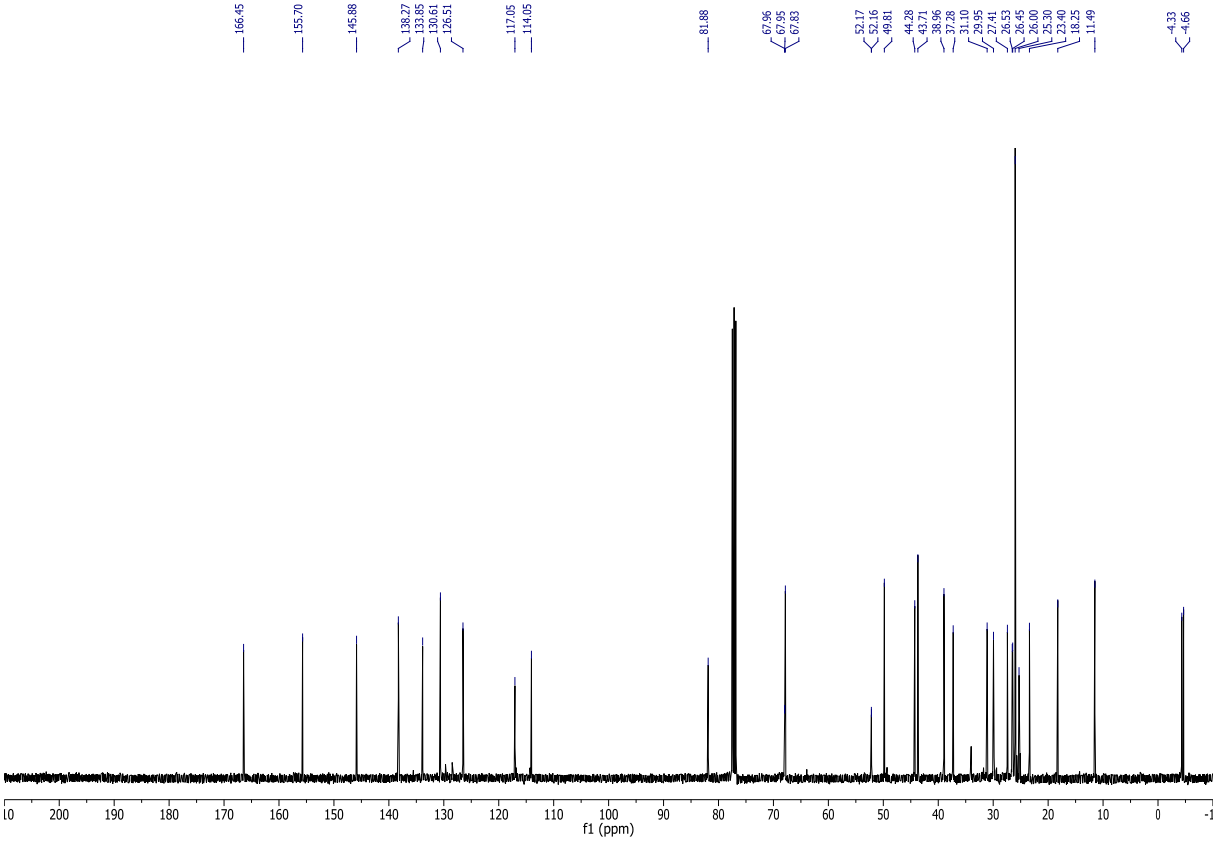

OH
O
O
O
2.6k O
OMe
f1 (ppm)
f1 (ppm)

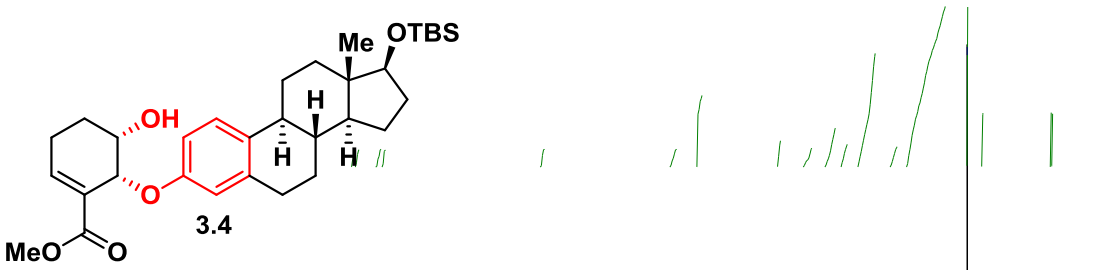
5.3: Chapter 3 spectra





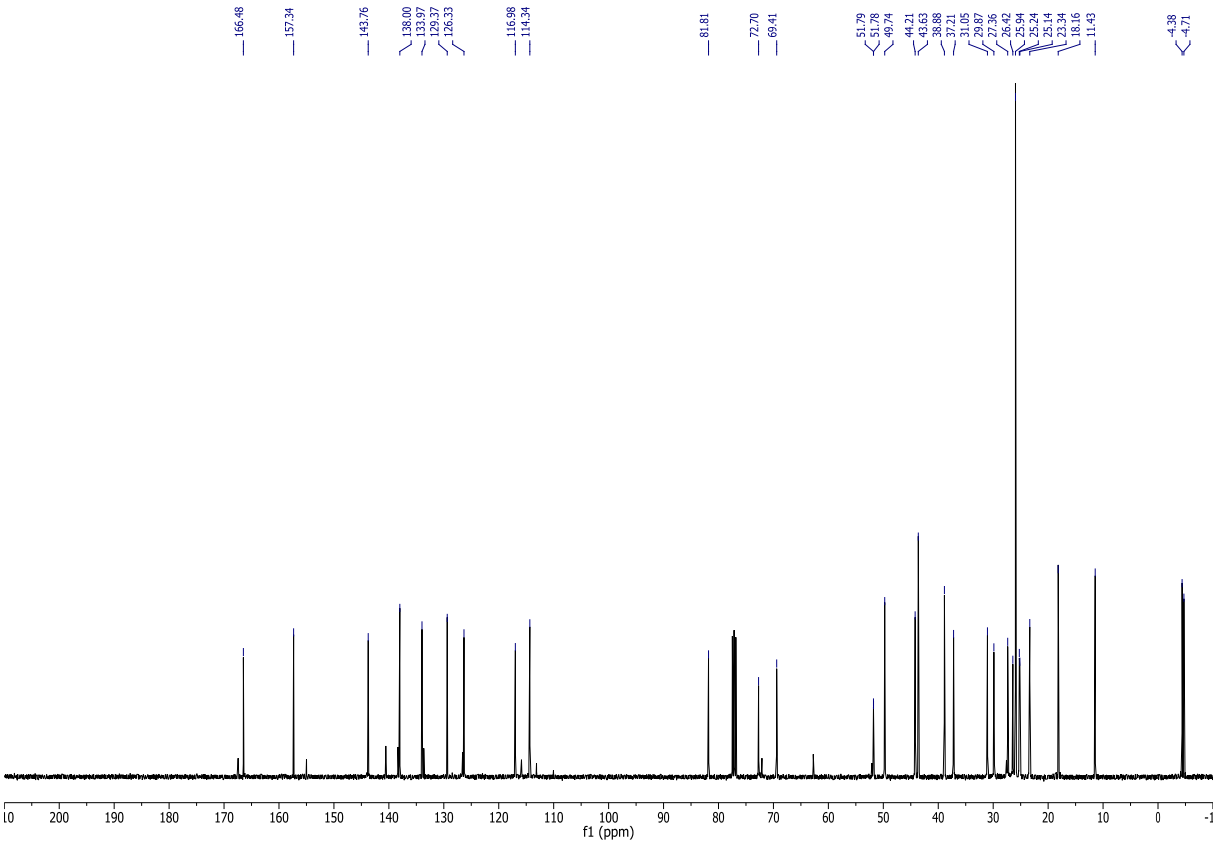

HO
Me
OTBS
H
H
H
O
MeO
O
3.3
f1 (ppm)

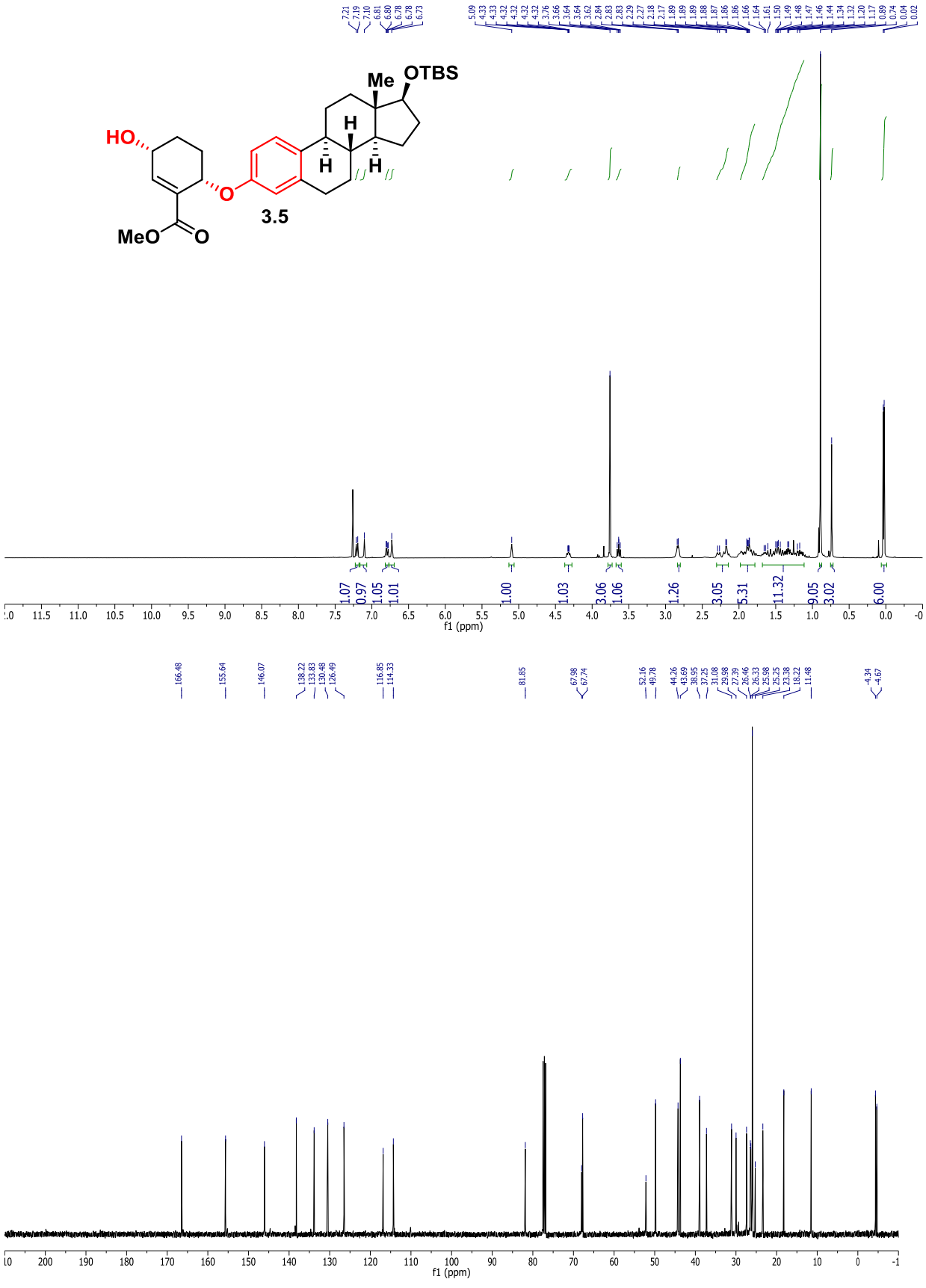

f1 (ppm)

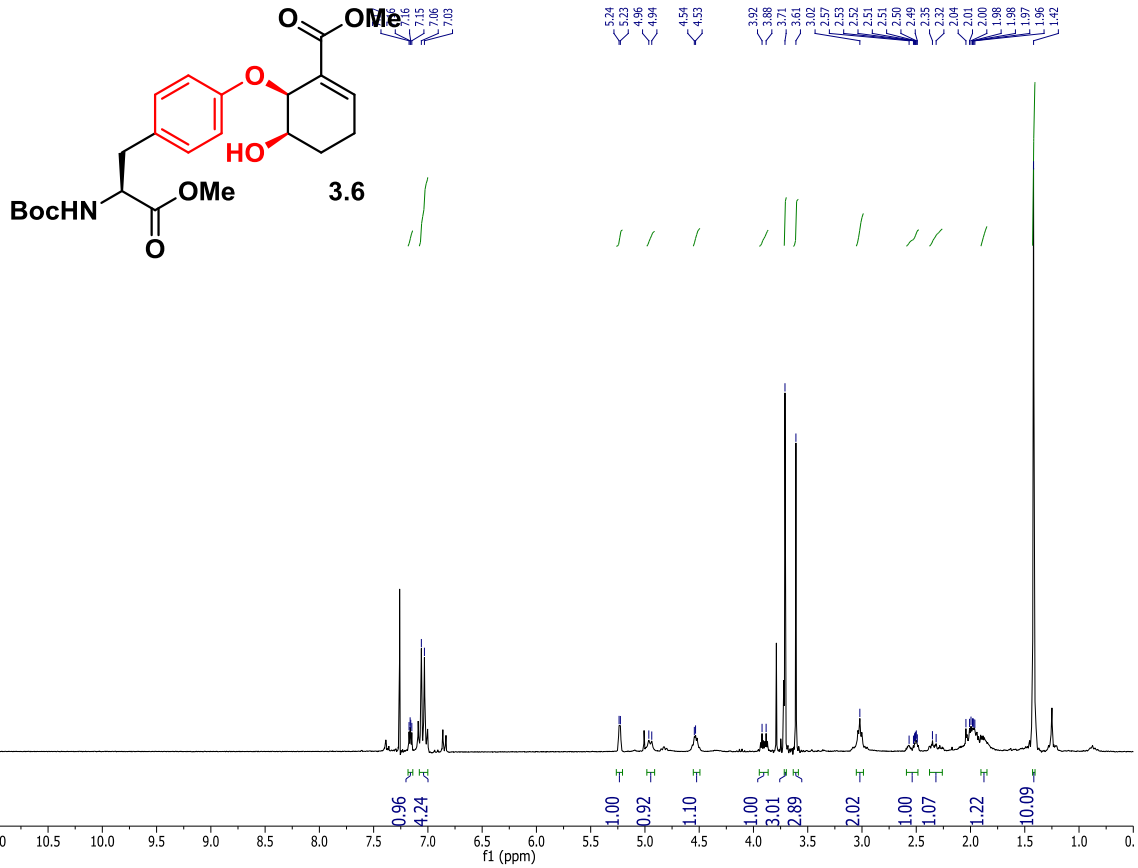


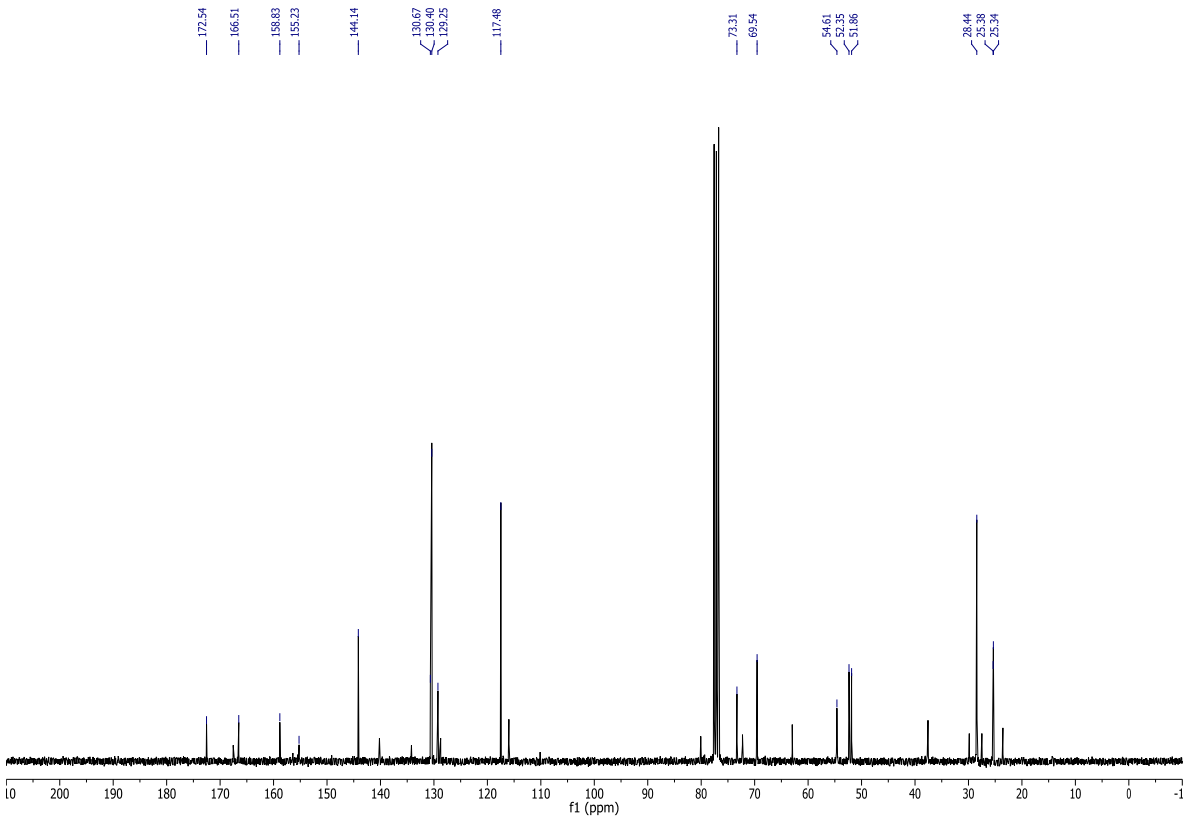
Me
OTBS
H
OH
H
H
O
MeO
O
3.4

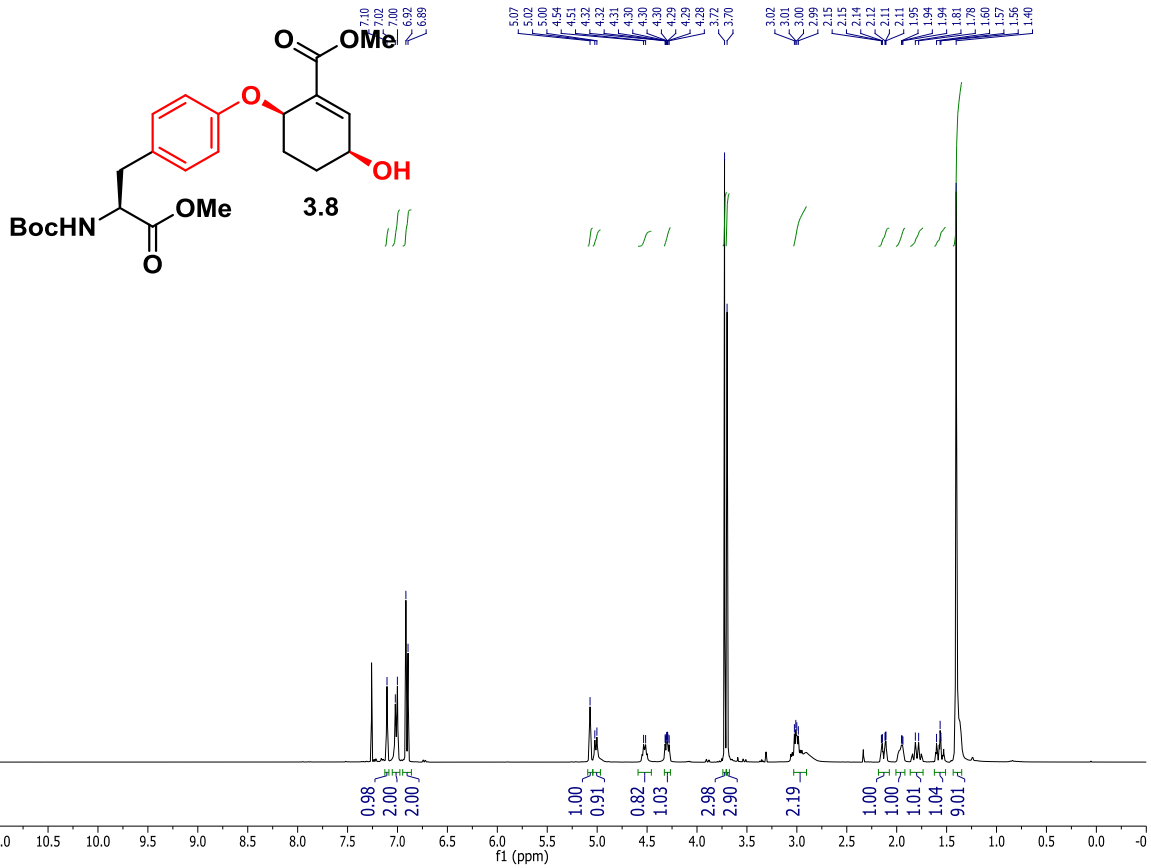
1.01
0.98
1.01
0.97
1.00
1.00
4.05
1.49
1.07
2.21
1.29
6.43
1.15
9.09
9.05
3.05
3.08
3.02
f1 (ppm)

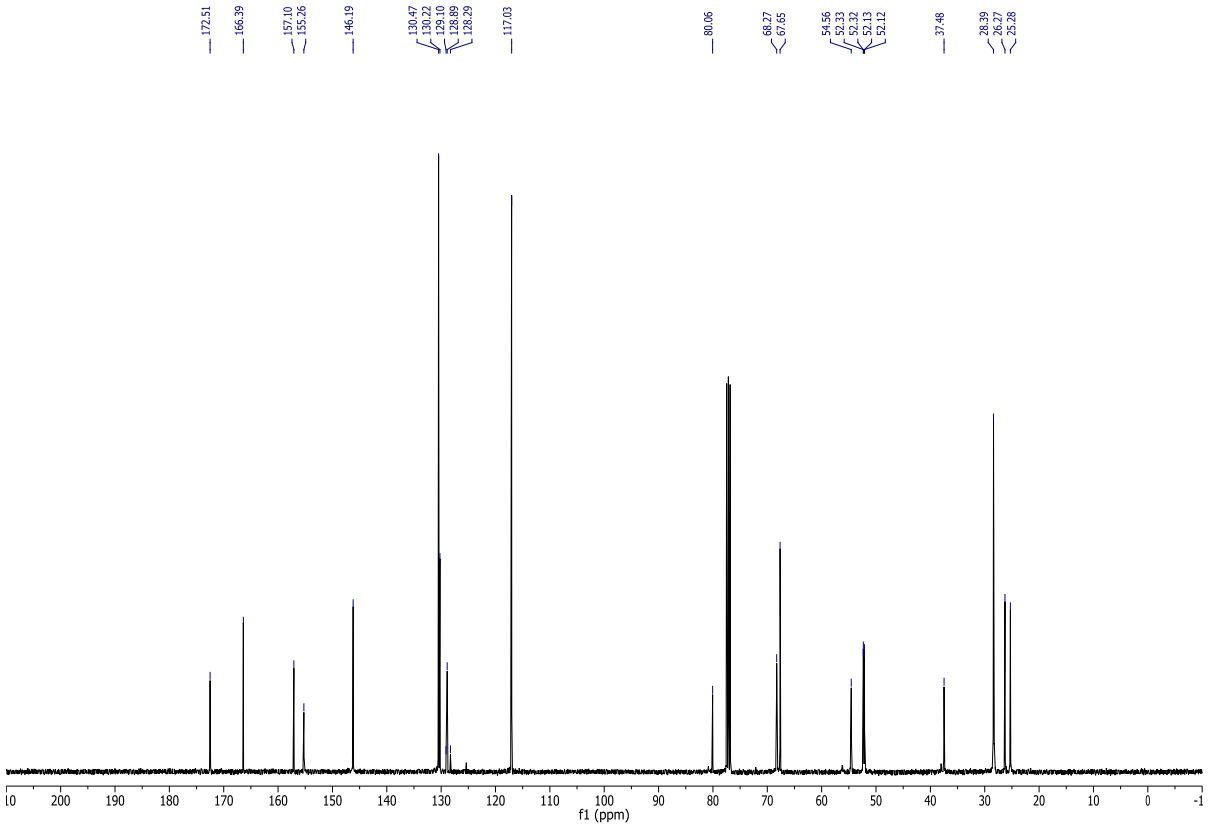

166.48
157.34
143.76
138.00
133.97
129.37
126.33
116.98
114.34
81.81
72.70
69.41
51.79
51.78
49.74
44.21
43.63
38.88
37.21
31.05
29.87
27.36
26.42
25.94
25.24
25.14
23.34
18.16
11.43
-4.38
-4.71
f1 (ppm)

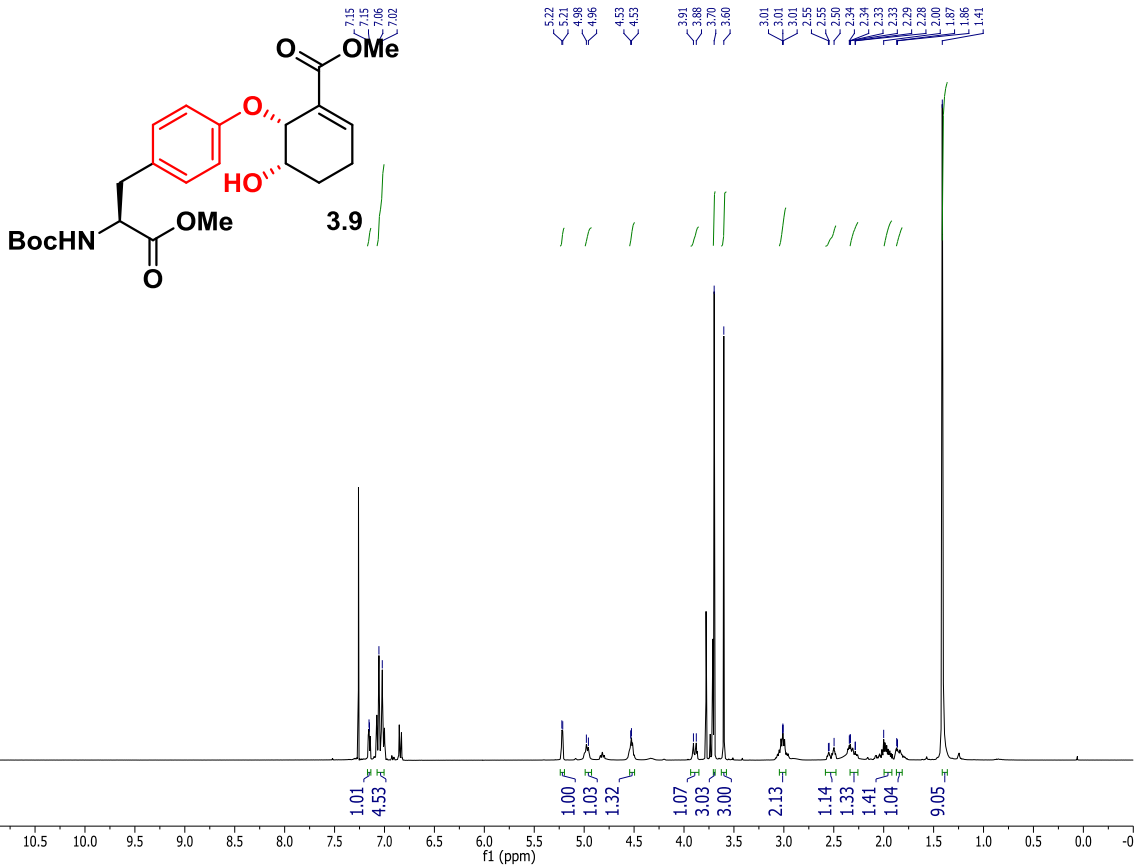

HO
Me
OTBS
H
H
H
O
MeO
O
3.5
f1 (ppm)
f1 (ppm)

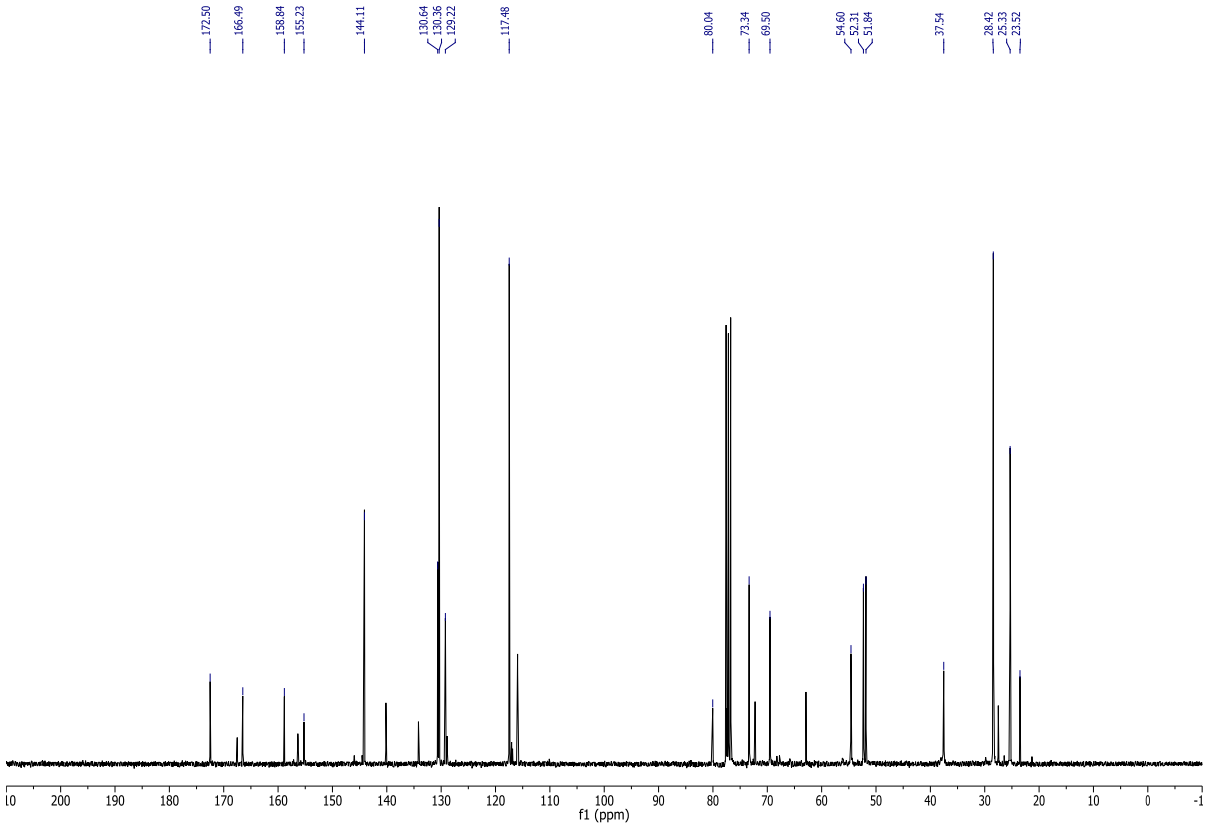

O
OMe
O
HO
BocHN
OMe
O
3.6
f1 (ppm)

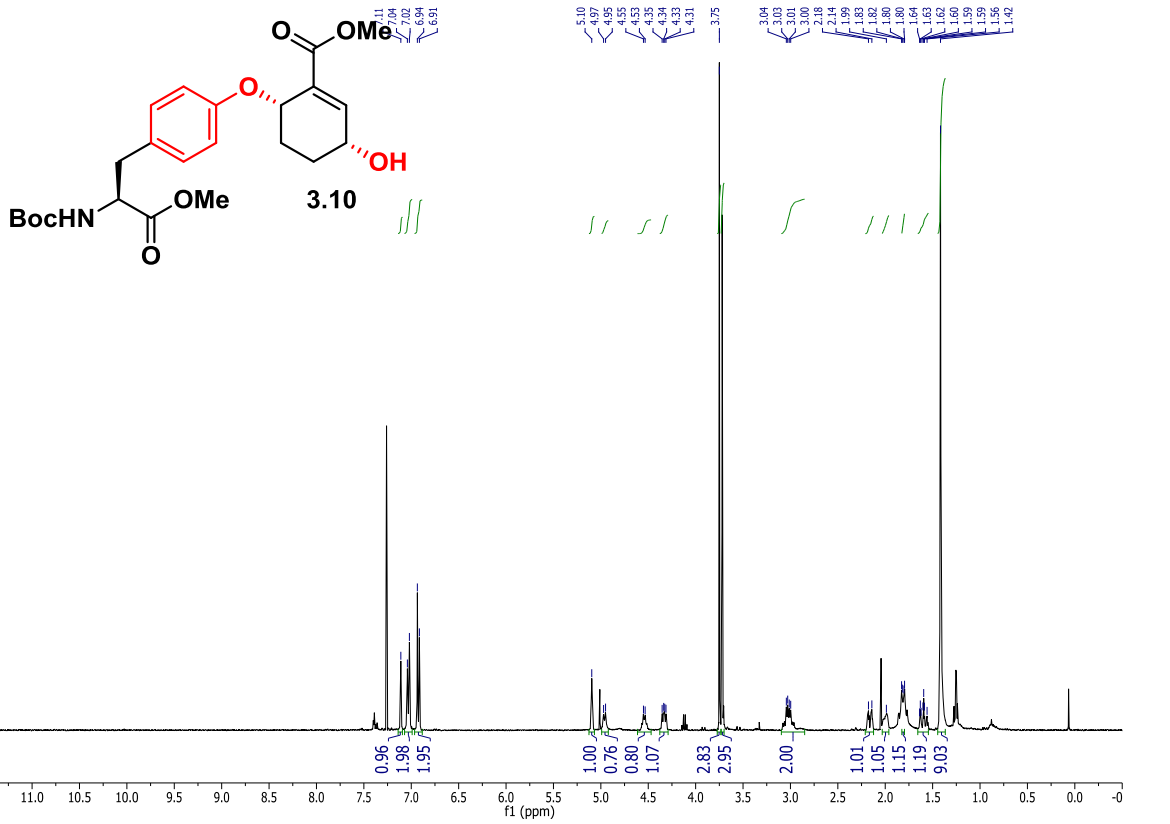

f1 (ppm)

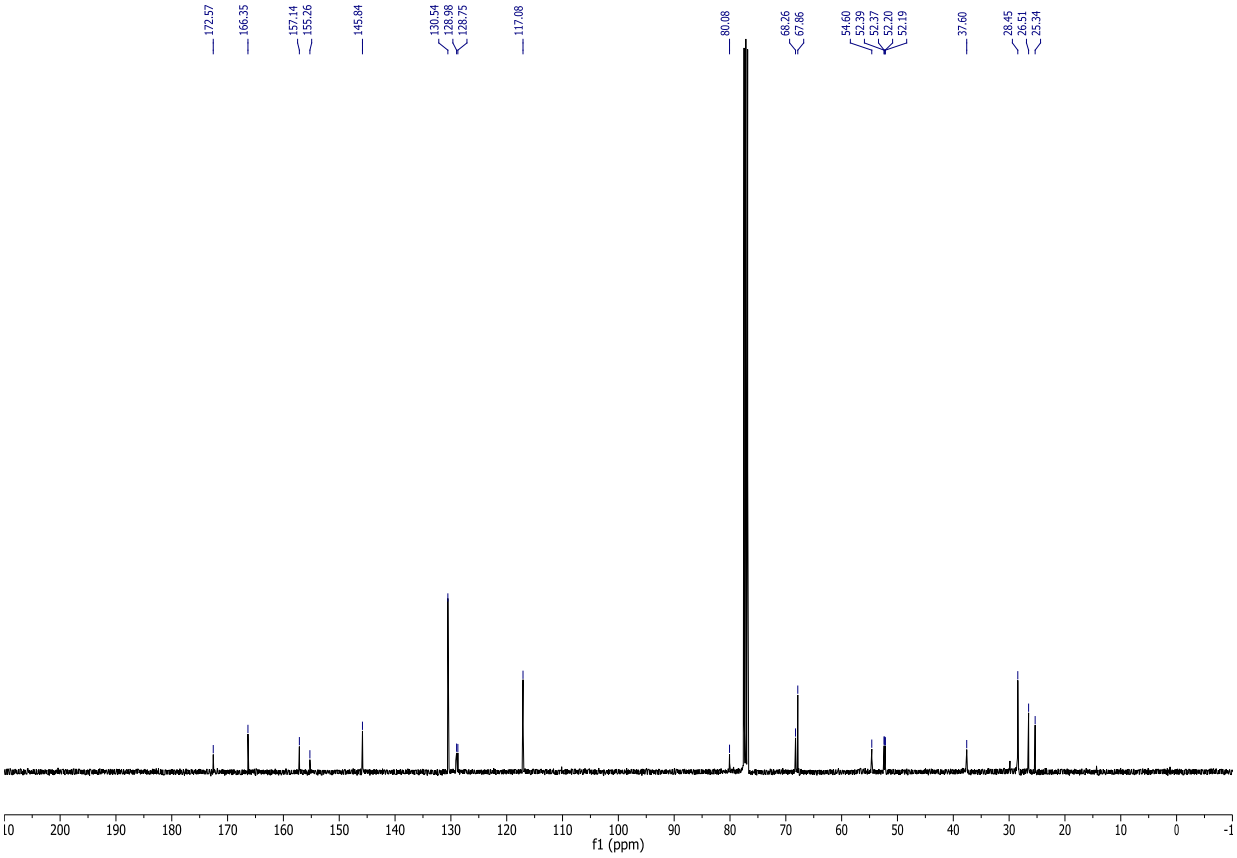

OMe
O
OH
BocHN
OMe
O
3.8
f1 (ppm)

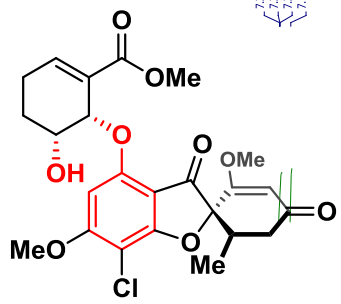

f1 (ppm)


O
OMe
O
HO
BocHN
OMe
O
3.9
f1 (ppm)

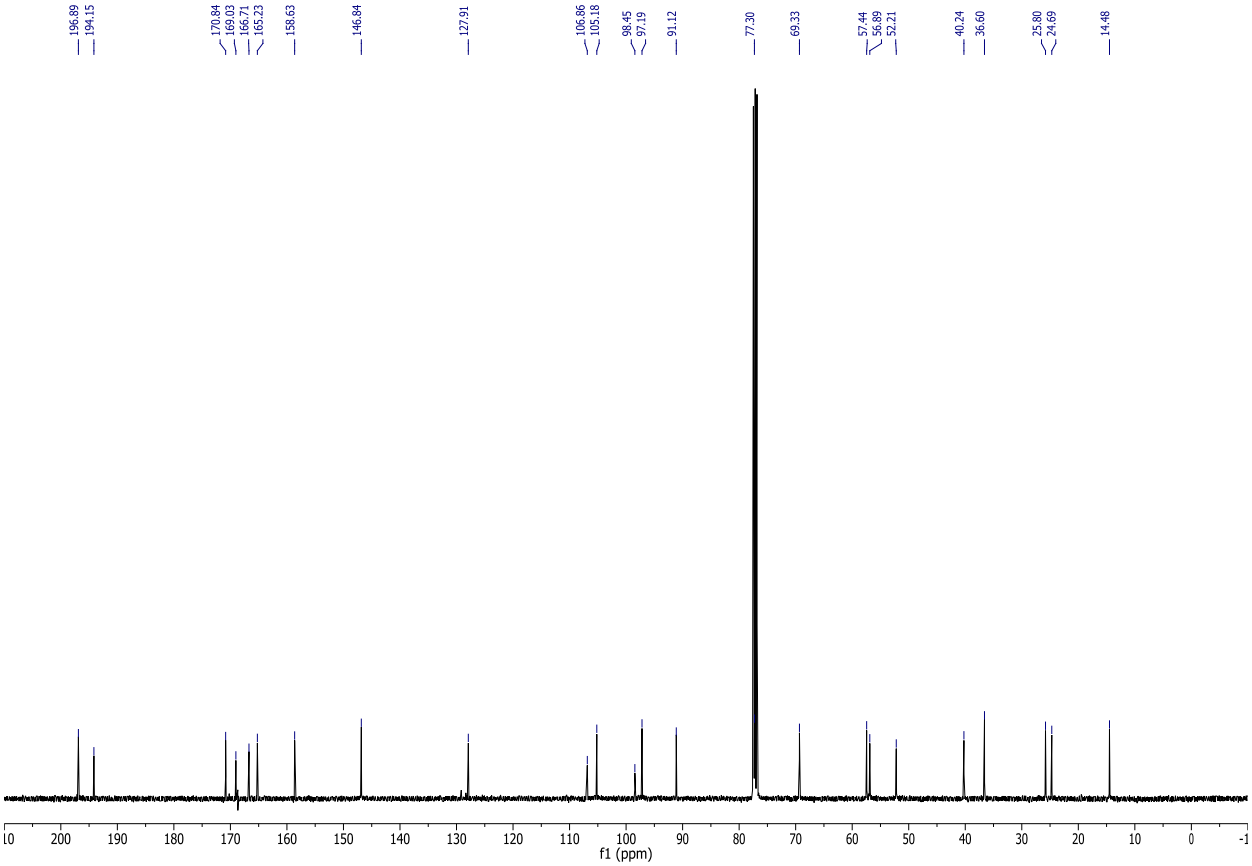

f1 (ppm)

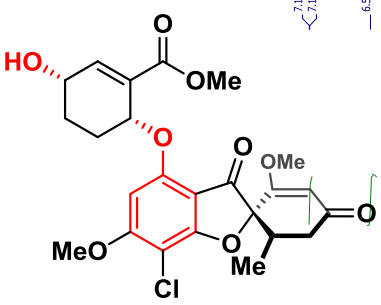

O
OMe
O
OH
BocHN
OMe
O
3.10
f1 (ppm)


f1 (ppm)

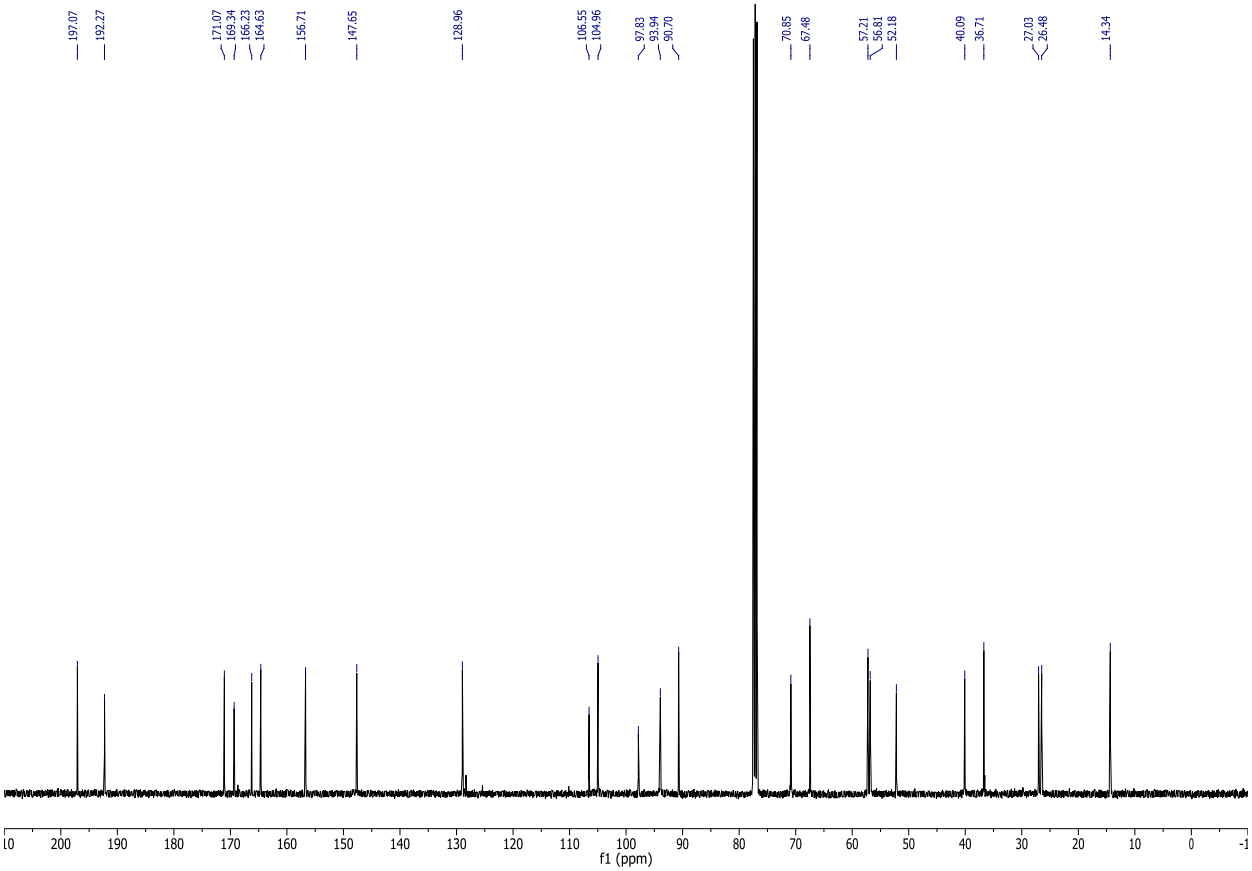


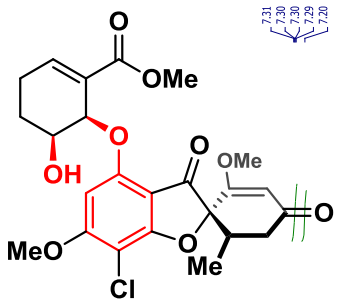
3.13





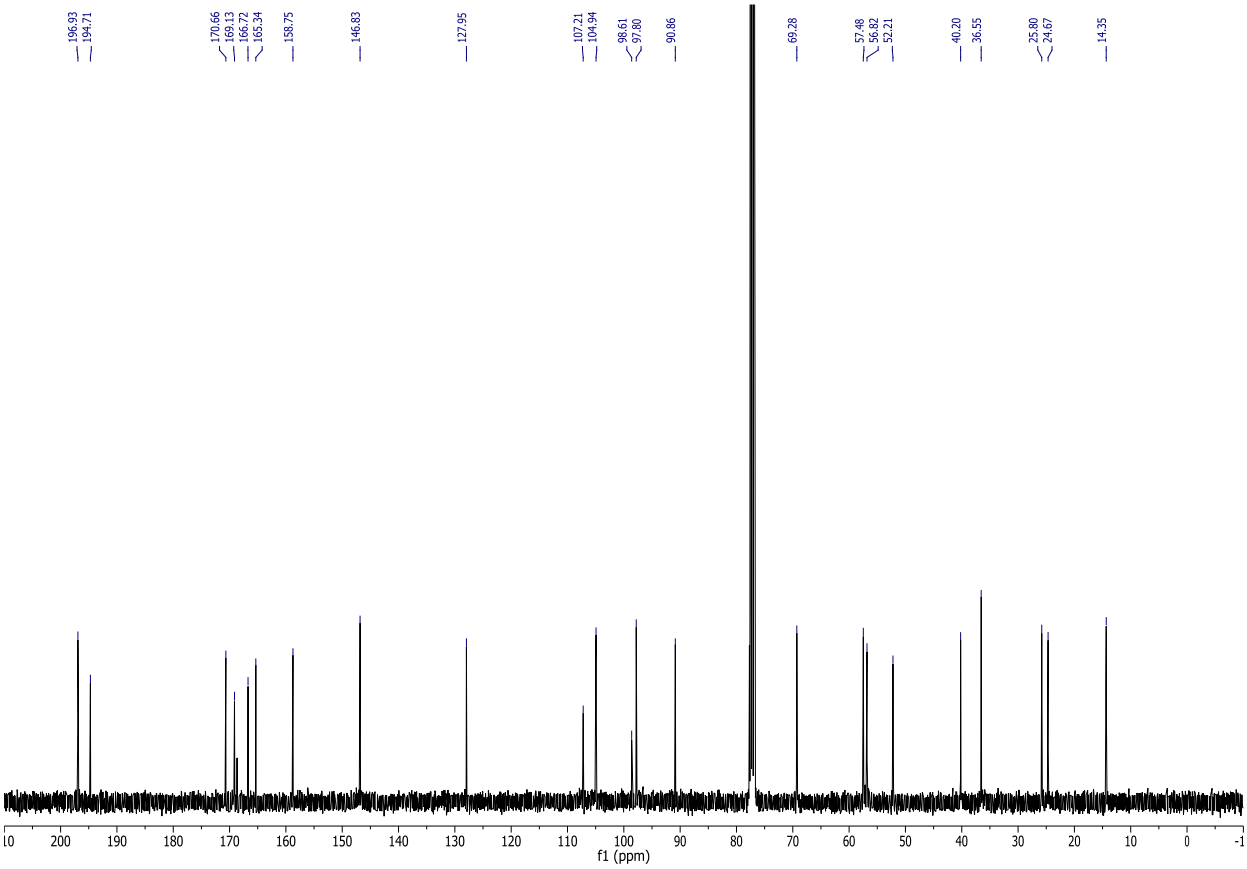
3.12

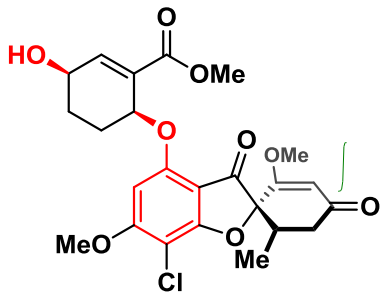



O
OMe
O
OH
O
OMe
O
MeO
O
Me
Cl

3.15

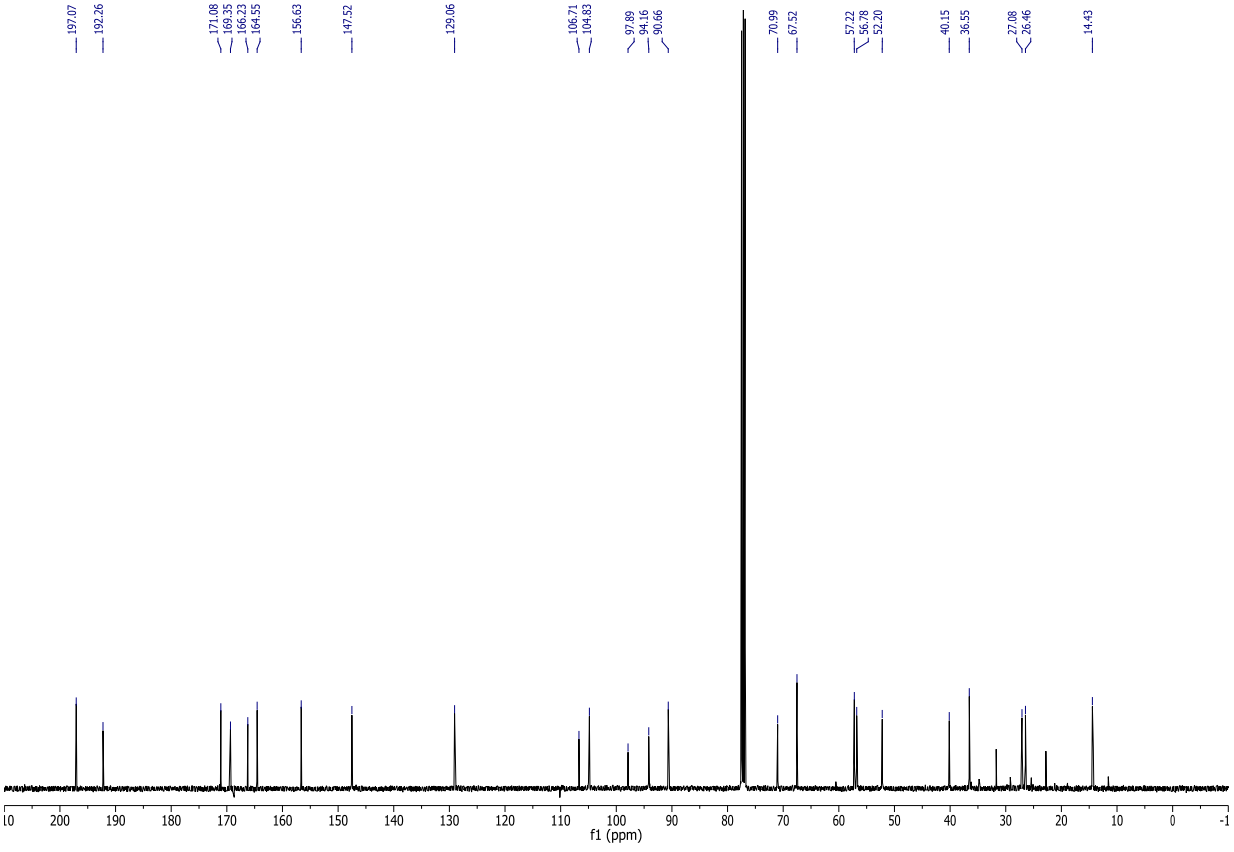
7.31
7.30
7.30
7.29
7.29
7.20
5.53
5.24
5.23
4.05
3.83
3.79
3.74
3.60
3.05
3.04
3.00
2.89
2.89
2.87
2.61
2.56
2.55
2.53
2.47
2.45
2.41
2.40
2.19
2.17
2.15
2.01
1.99
0.95
0.93
1.10
0.97
0.96
1.00
3.08
1.06
3.03
3.09
1.08
1.12
1.14
2.16
1.09
1.10
3.04
f1 (ppm)


196.93
194.71
170.66
169.13
166.72
165.34
158.75
146.83
127.95
107.21
104.94
98.61
97.80
90.86
69.28
57.48
56.82
52.21
40.20
36.55
25.80
24.67
14.35
f1 (ppm)

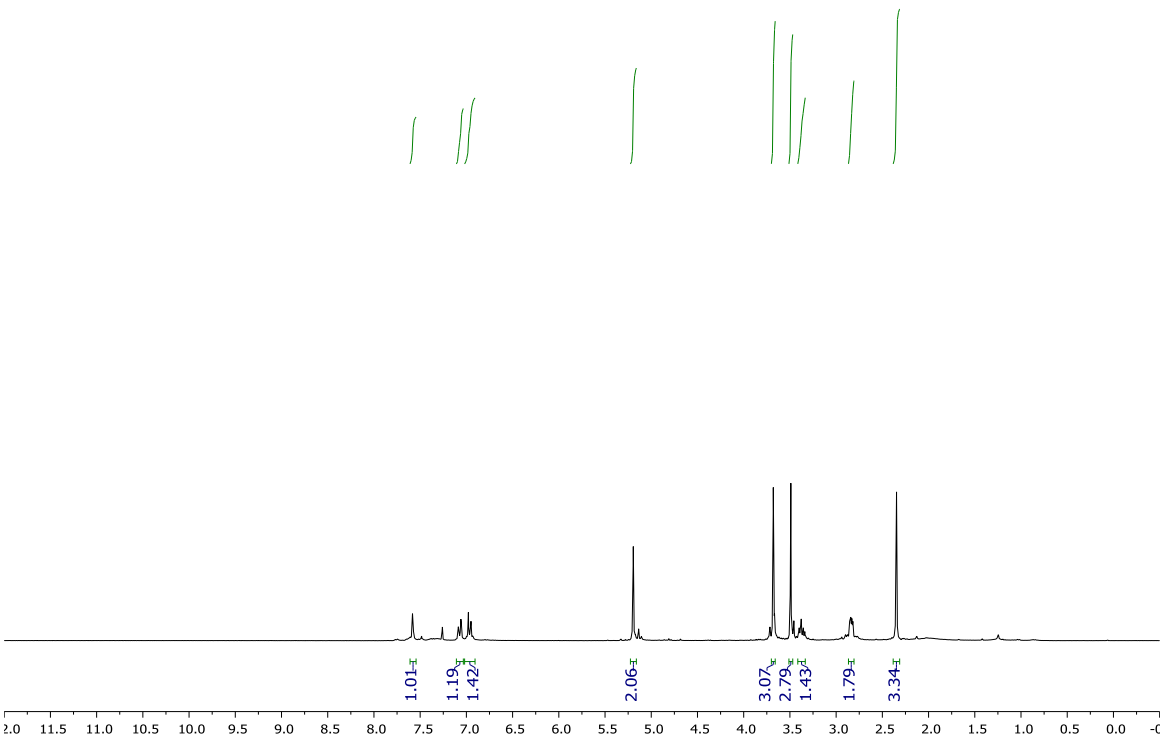

HO
O
OMe
O
O
OMe
O
MeO
O
Me
Cl

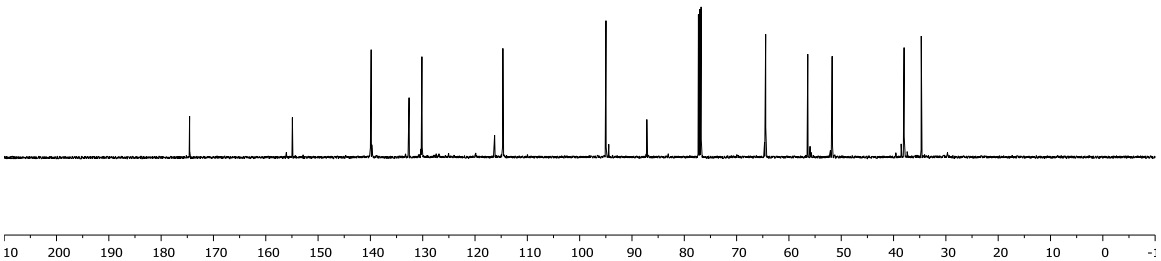
3.14

7.17
7.17
7.16
6.53
5.51
5.35
4.34
4.02
3.70
3.60
2.99
2.99
2.95
2.85
2.84
2.83
2.43
2.42
2.39
2.38
2.13
2.06
2.06
2.05
2.04
2.02
1.76
1.74
1.73
1.72
1.69
0.95
0.93
0.99
1.00
1.00
1.00
0.99
3.03
3.01
3.05
1.00
1.04
1.18
3.34
1.04
3.02
f1 (ppm)

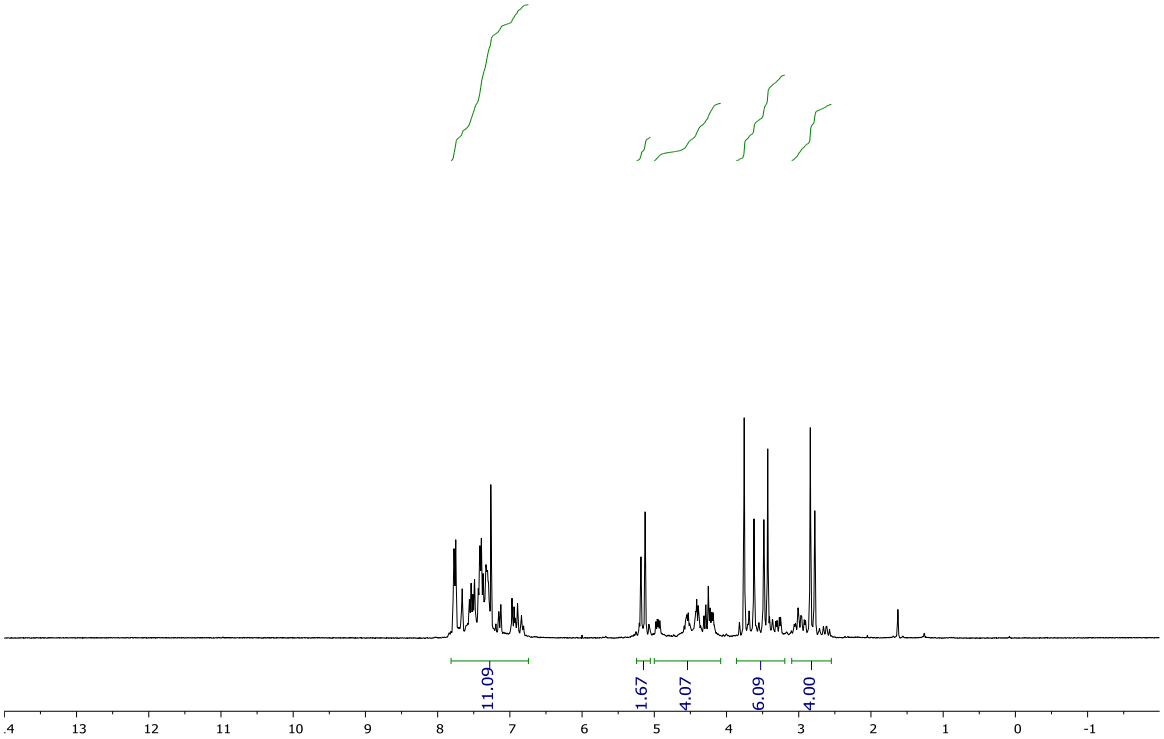

197.07
192.26
171.08
169.35
166.23
164.55
156.63
147.52
129.06
106.71
104.83
97.89
94.16
90.66
70.99
67.52
57.22
56.78
52.20
40.15
36.55
27.08
26.46
14.43
f1 (ppm)

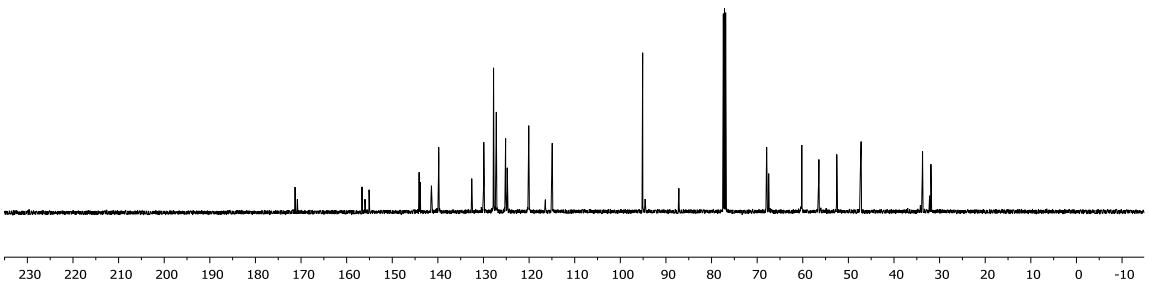
MeHN-3I-Tyrosine(OMOM)-OMe: (**3.49**):



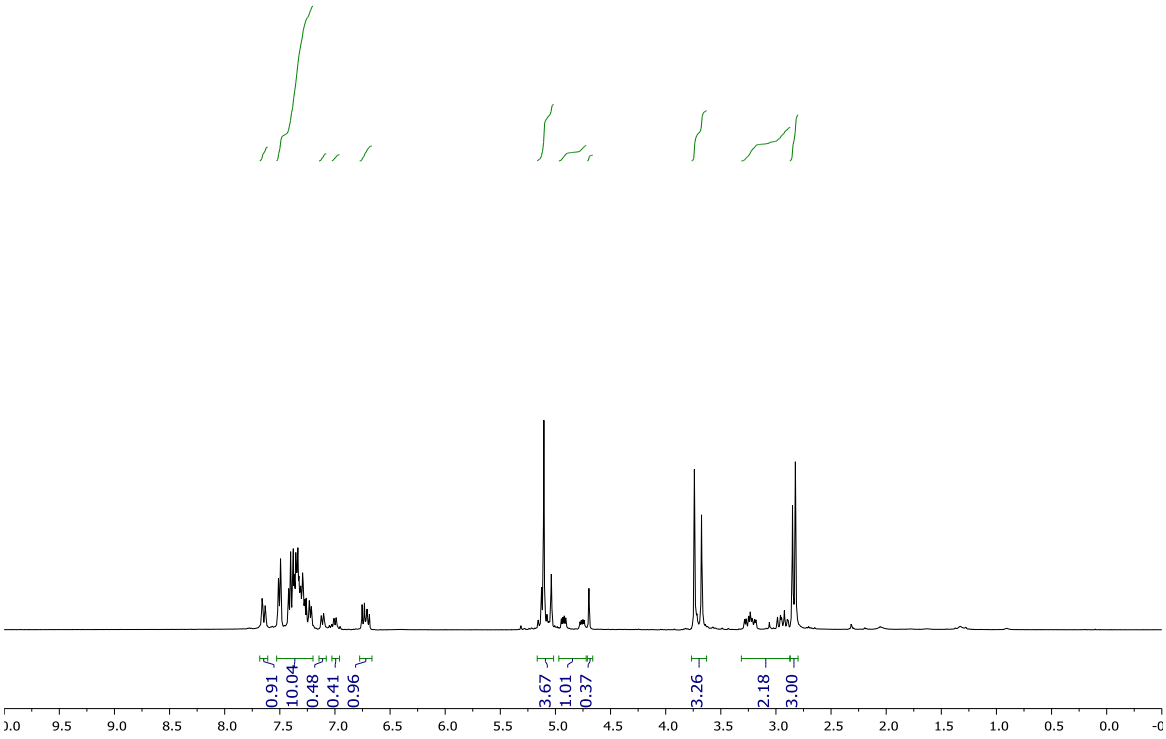


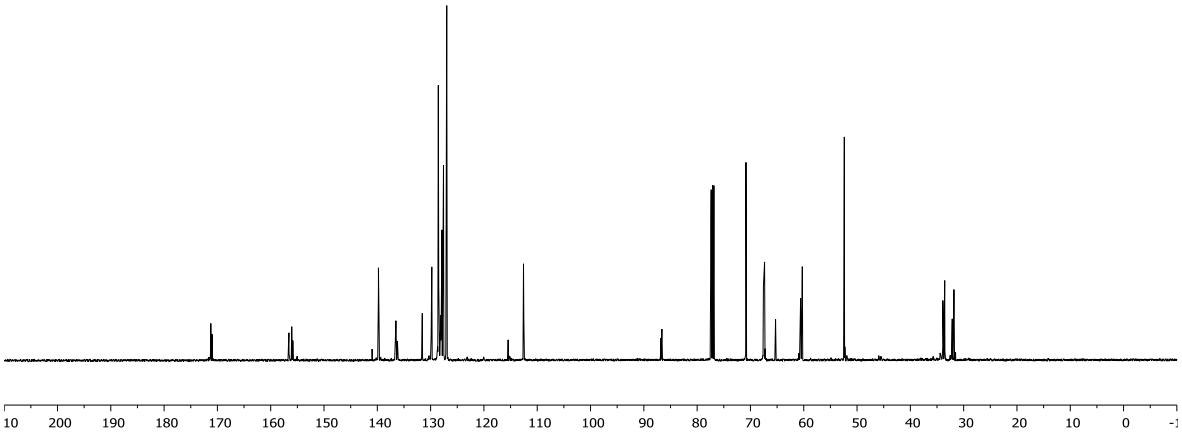
FmocMeN-3I-tyrosine-OMe (**3.49**):



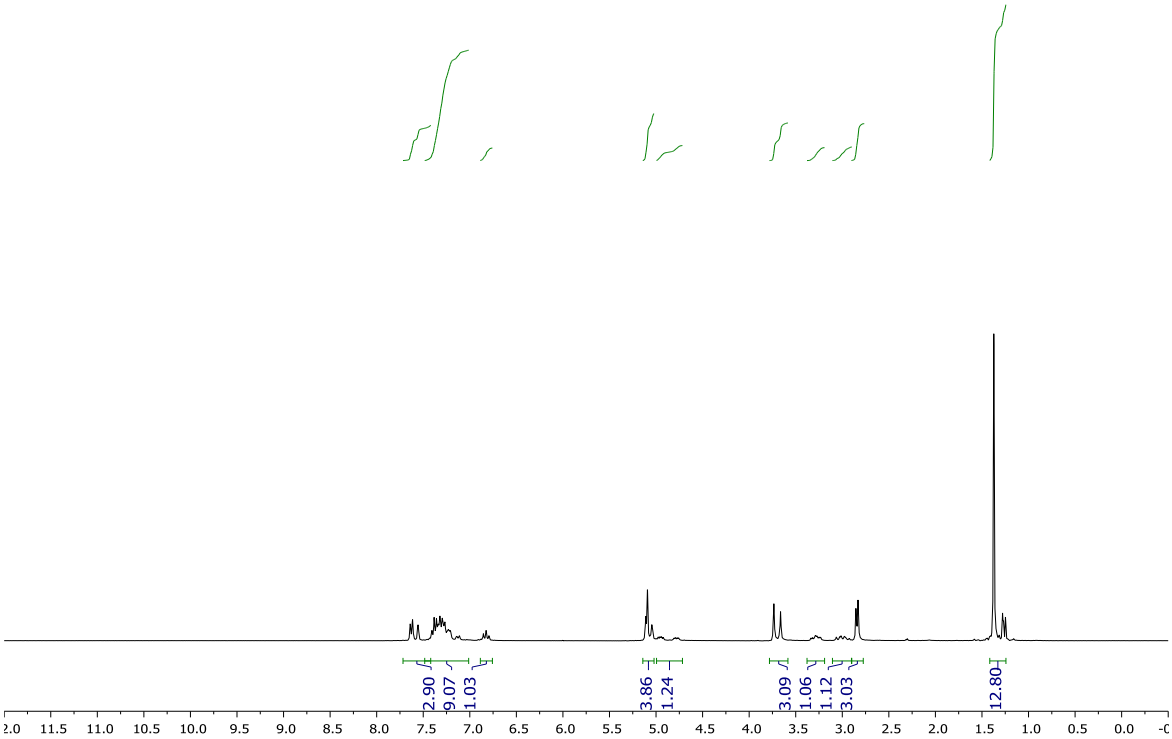


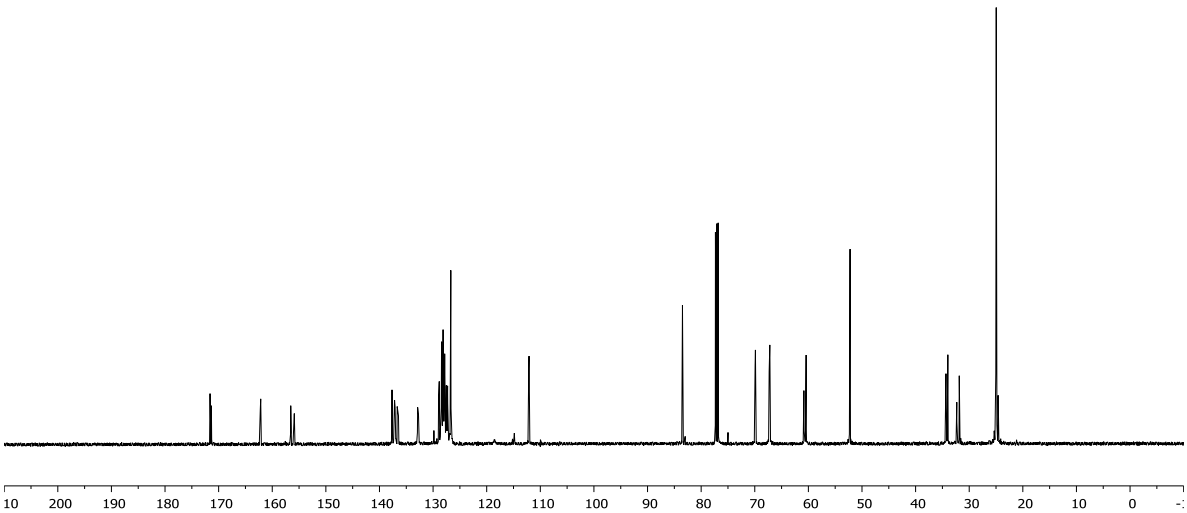
CbzMeN-3I-Tyrosine(OBn)-OMe (**3.45**)



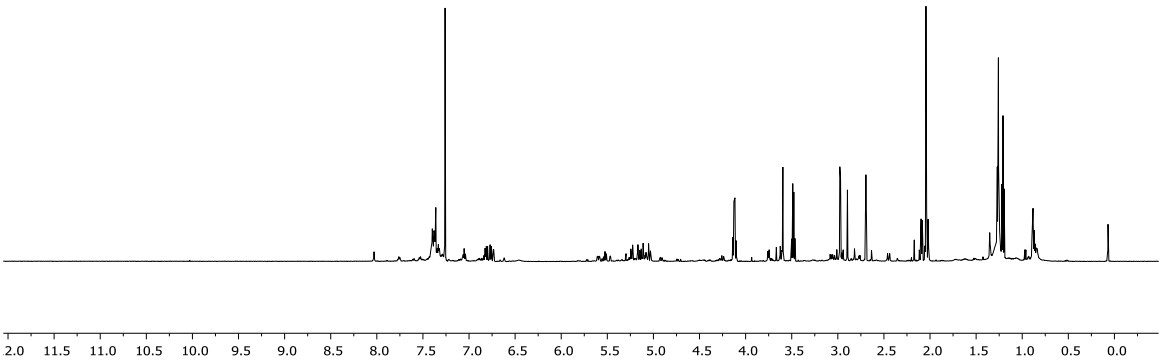


CbzMeN-3Bpin –tyrosine(OBn)-OMe (**3.46**)

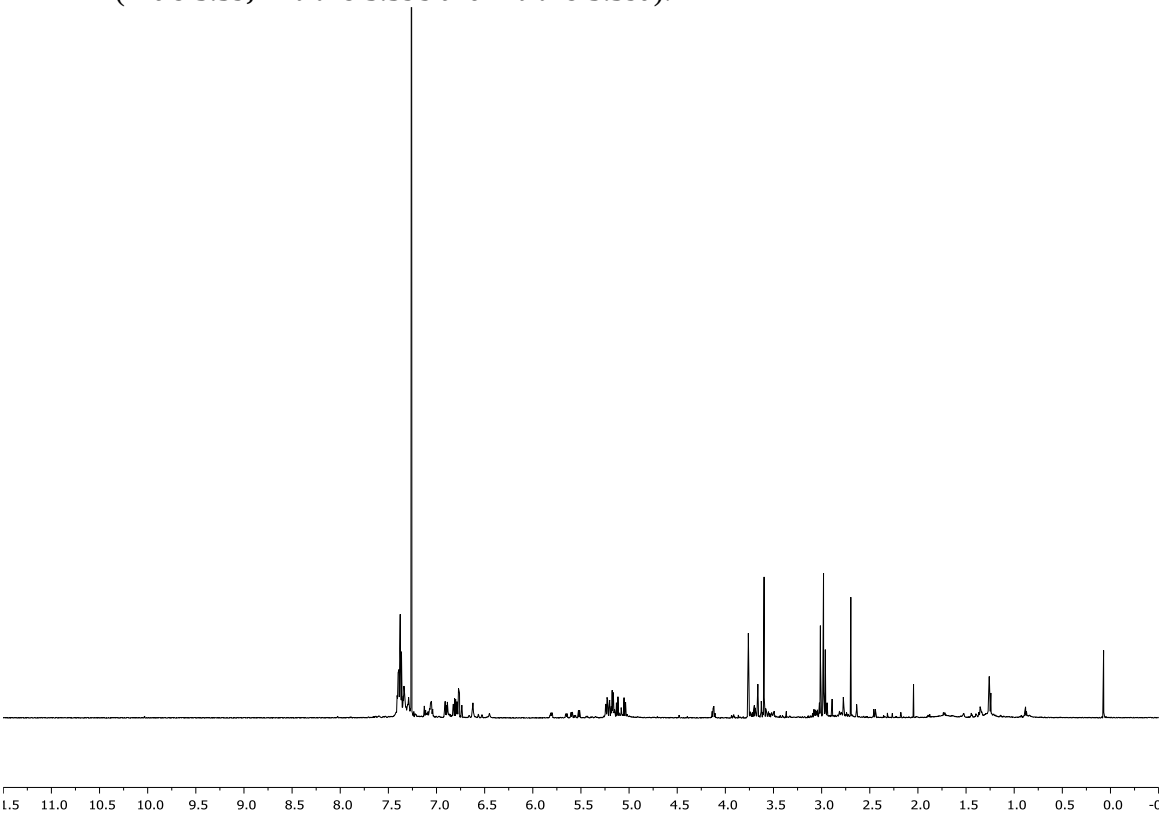




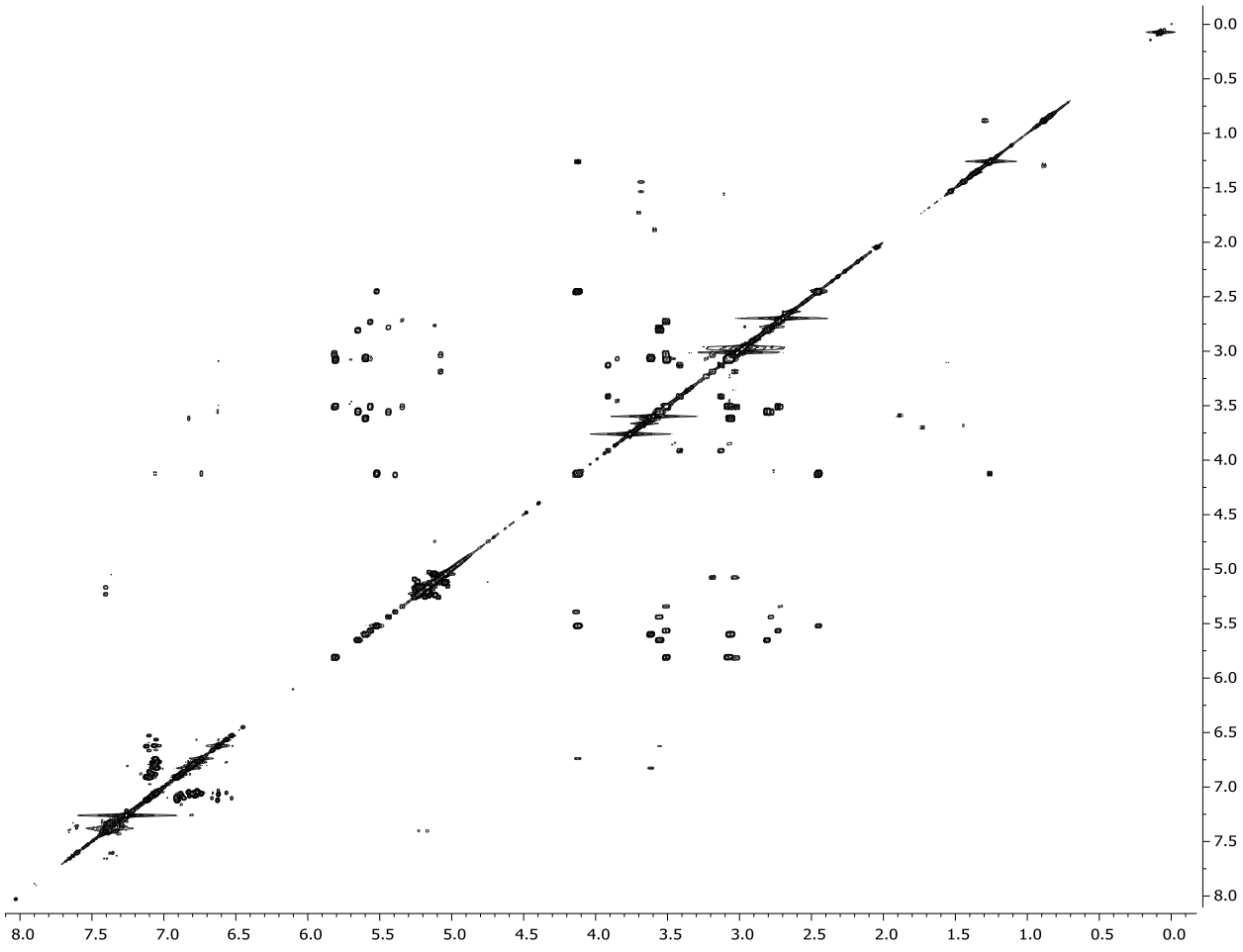
^{1}H NMR (*P-cis*-**3.39a**):



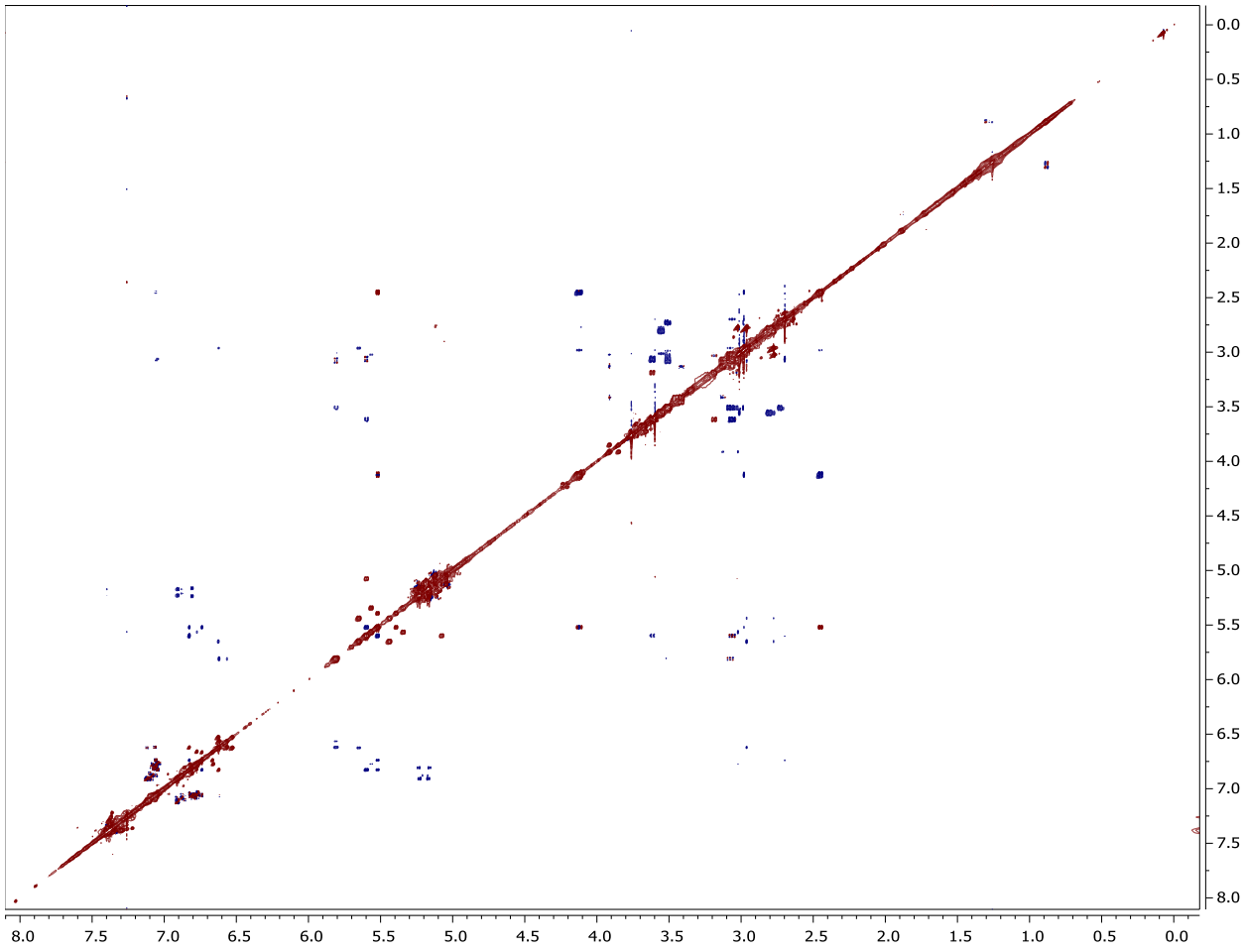
^{1}H NMR (*P-cis*-**3.39,** *M-trans*-**3.39b** and *P-trans*-**3.39a**):



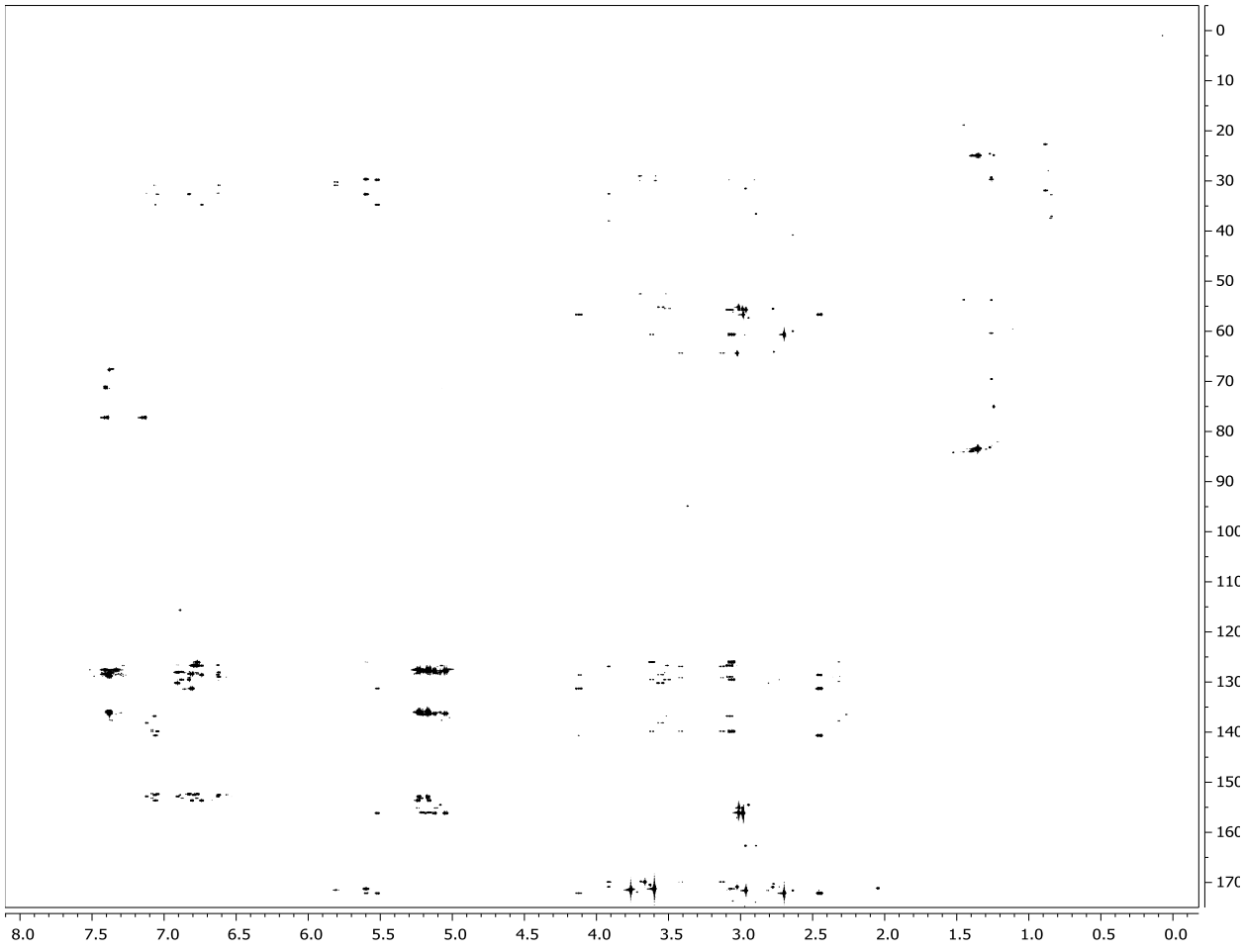
COSY (*P-cis*-**3.39,** *M-trans*-**3.39b** and *P-trans*-**3.39a**):



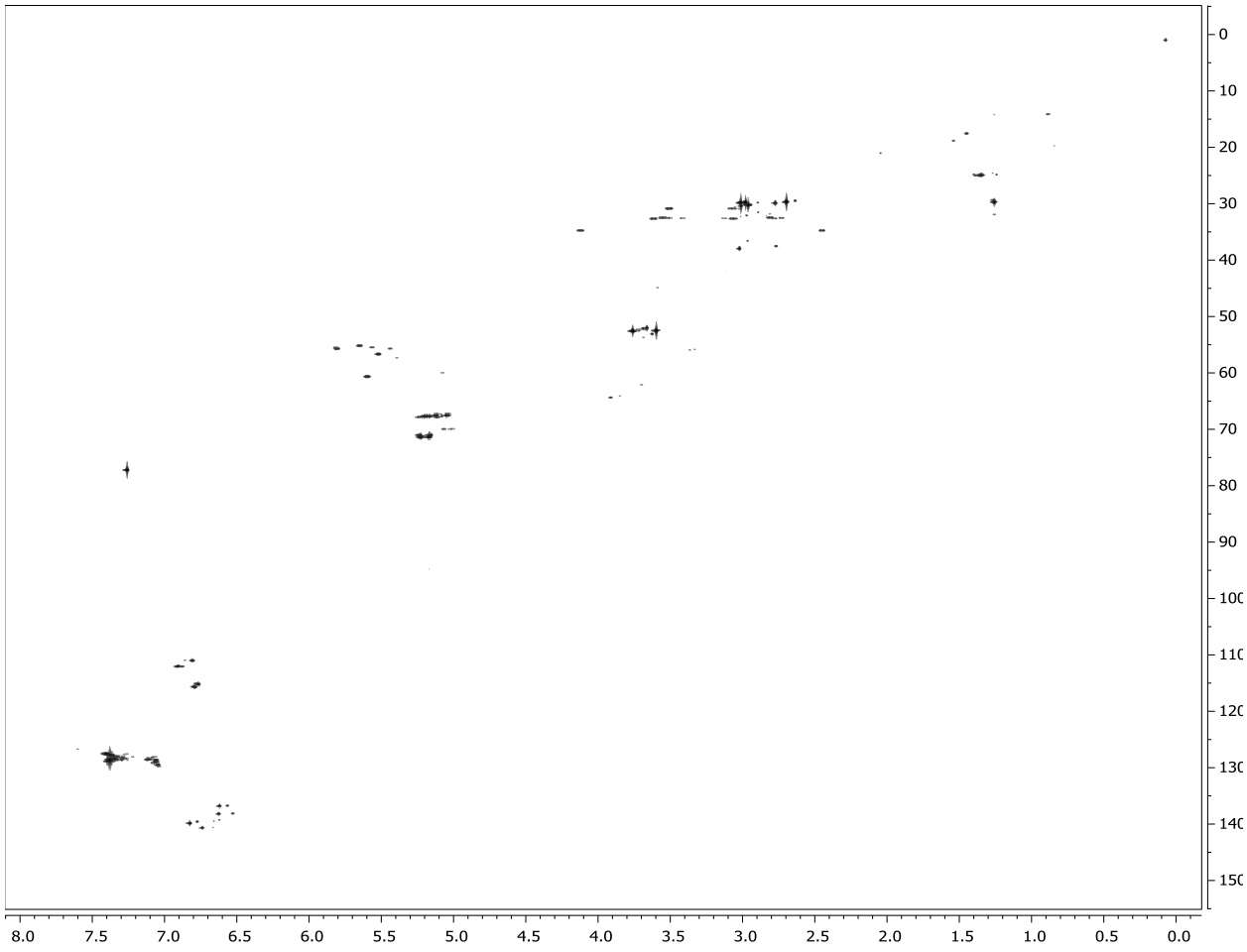
ROESY (*P-cis*-**3.39,** *M-trans*-**3.349** and *P-trans*-**3.39a**):



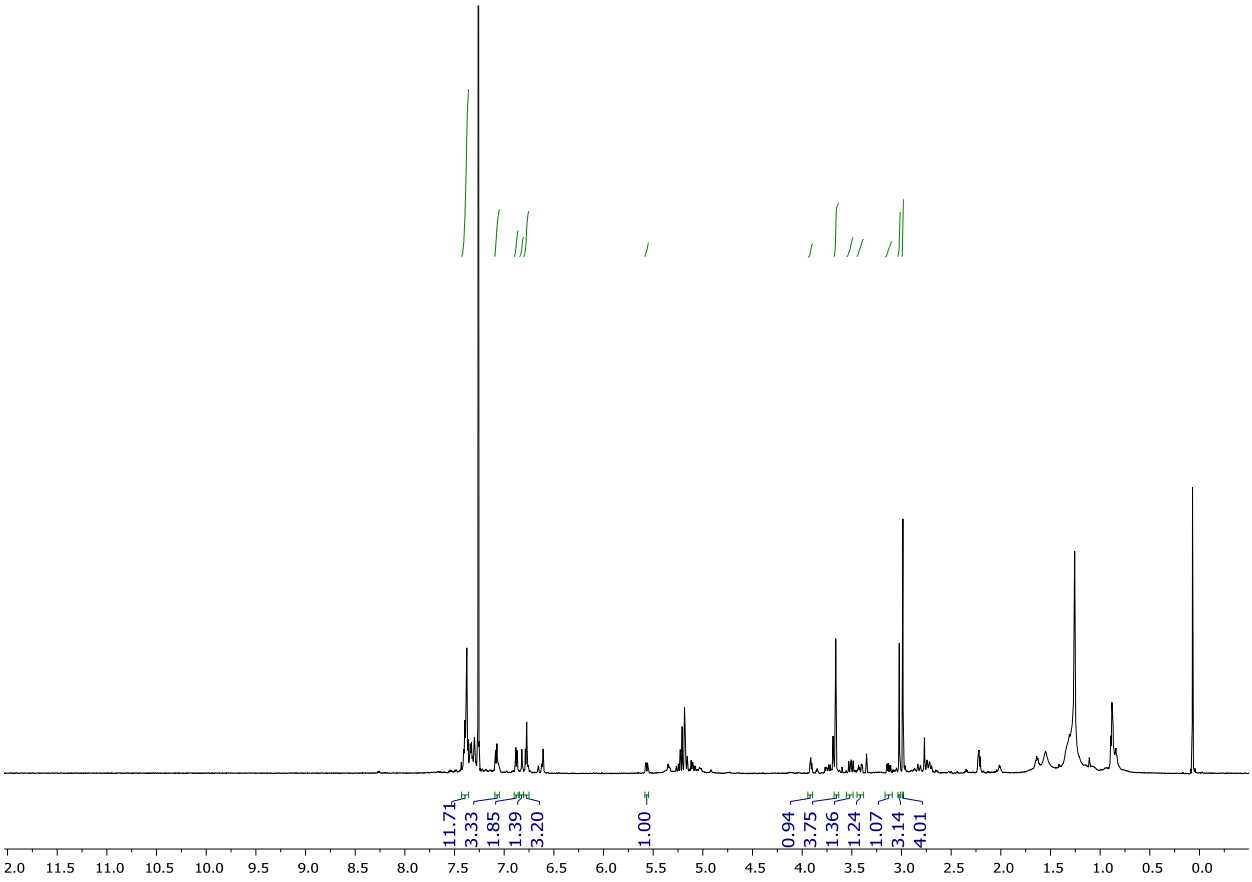
HMBC (*P-cis*-**3.39,** *M-trans*-**3.349** and *P-trans*-**3.39a**):



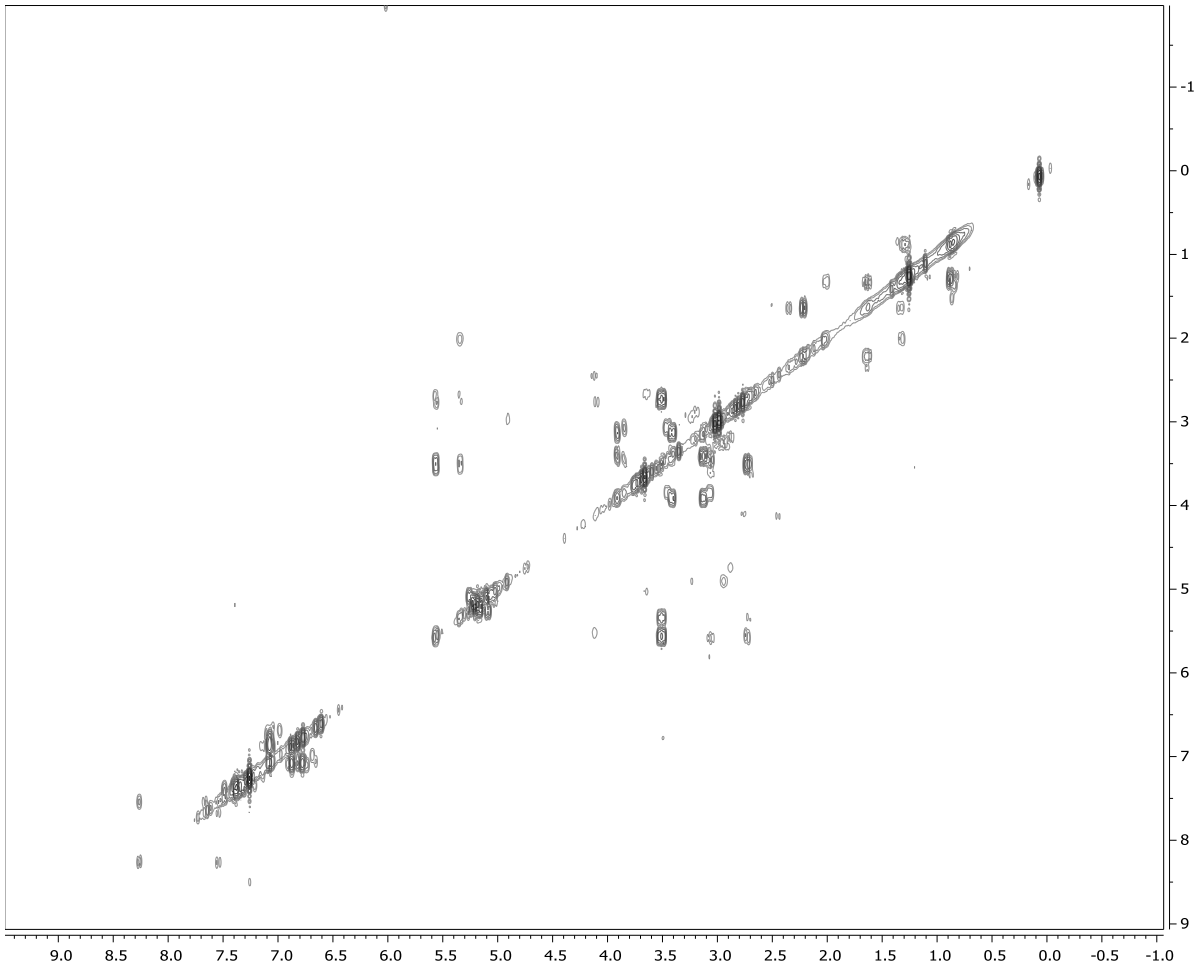
HSQC (*P-cis*-**3.39,** *M-trans*-**3.349** and *P-trans*-**3.39a**):



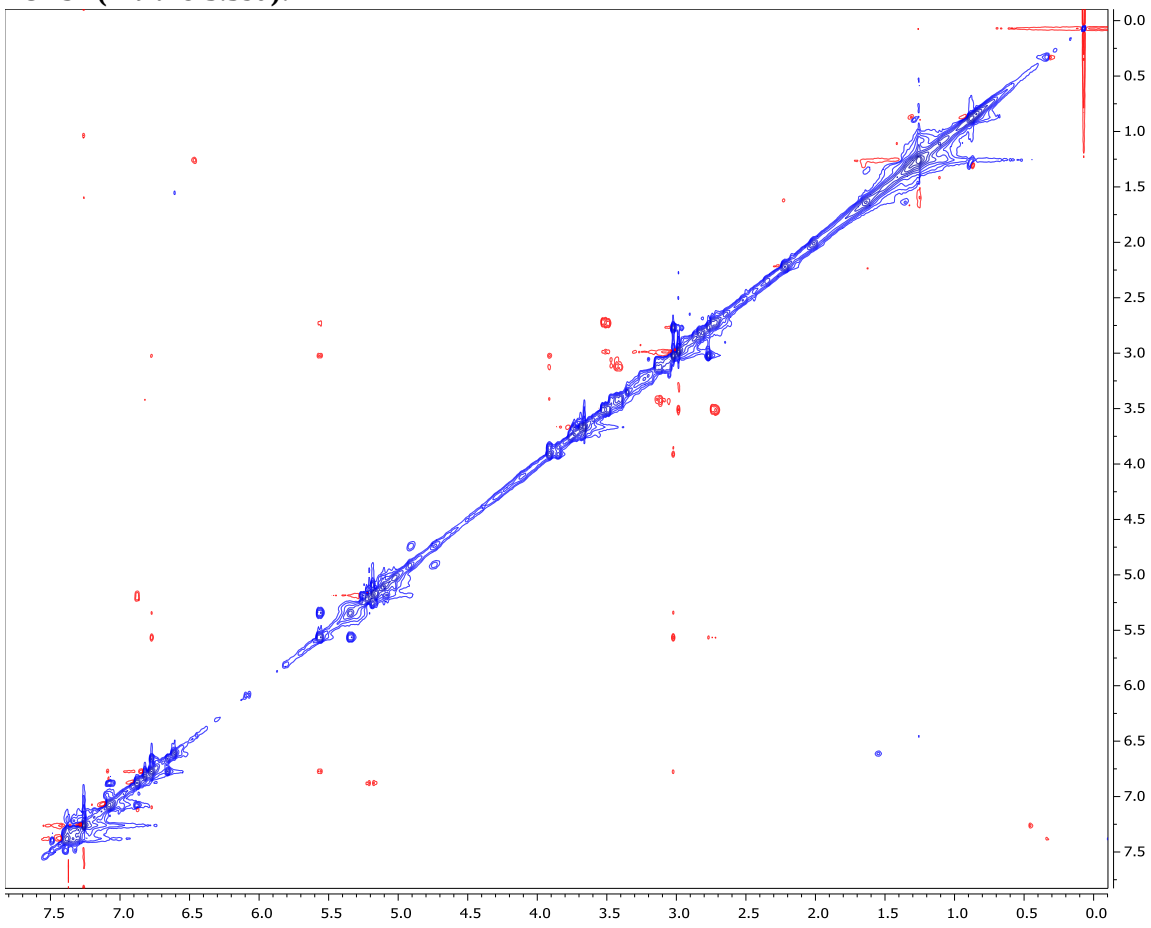
^{1}H NMR (*P-trans*-**3.39a**)



COSY (*P-trans*-**3.39a)**:

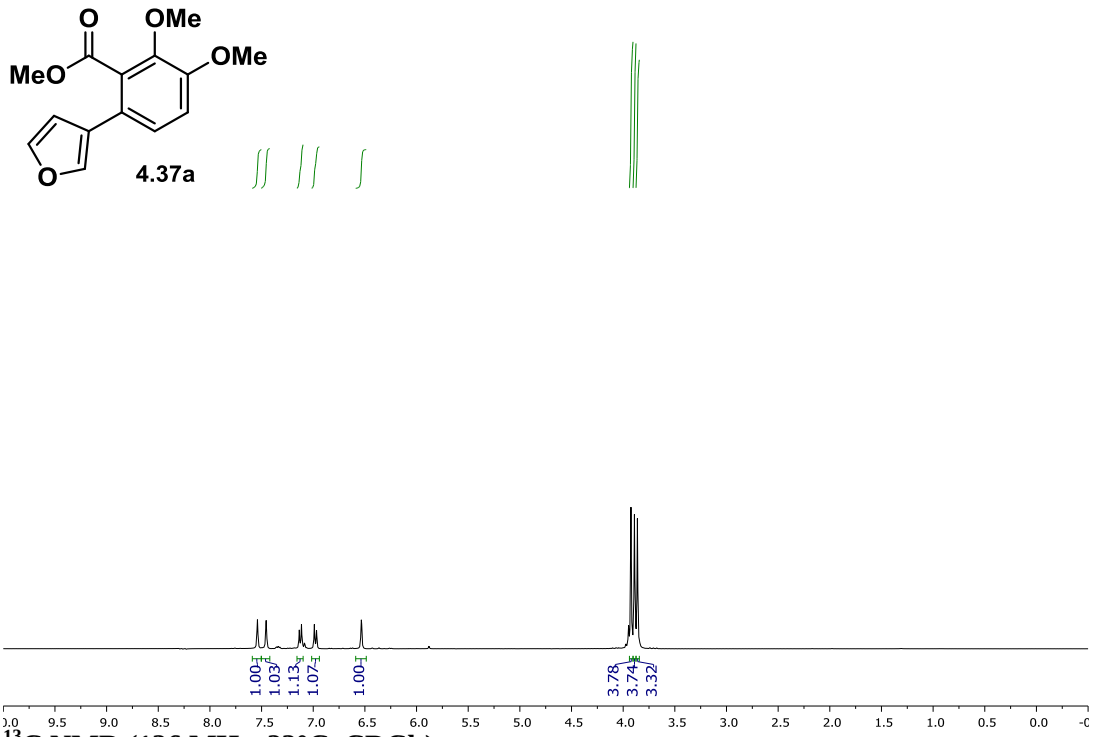


ROESY(*P-trans*-**3.39a):**

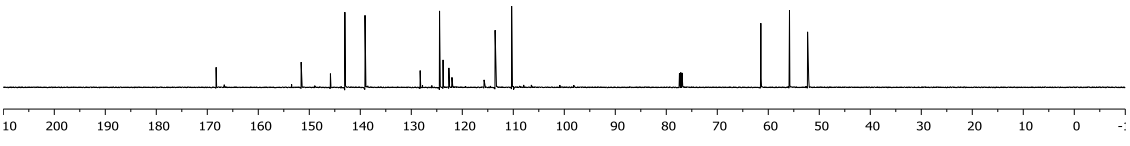


5.4: Chapter 4 spectra

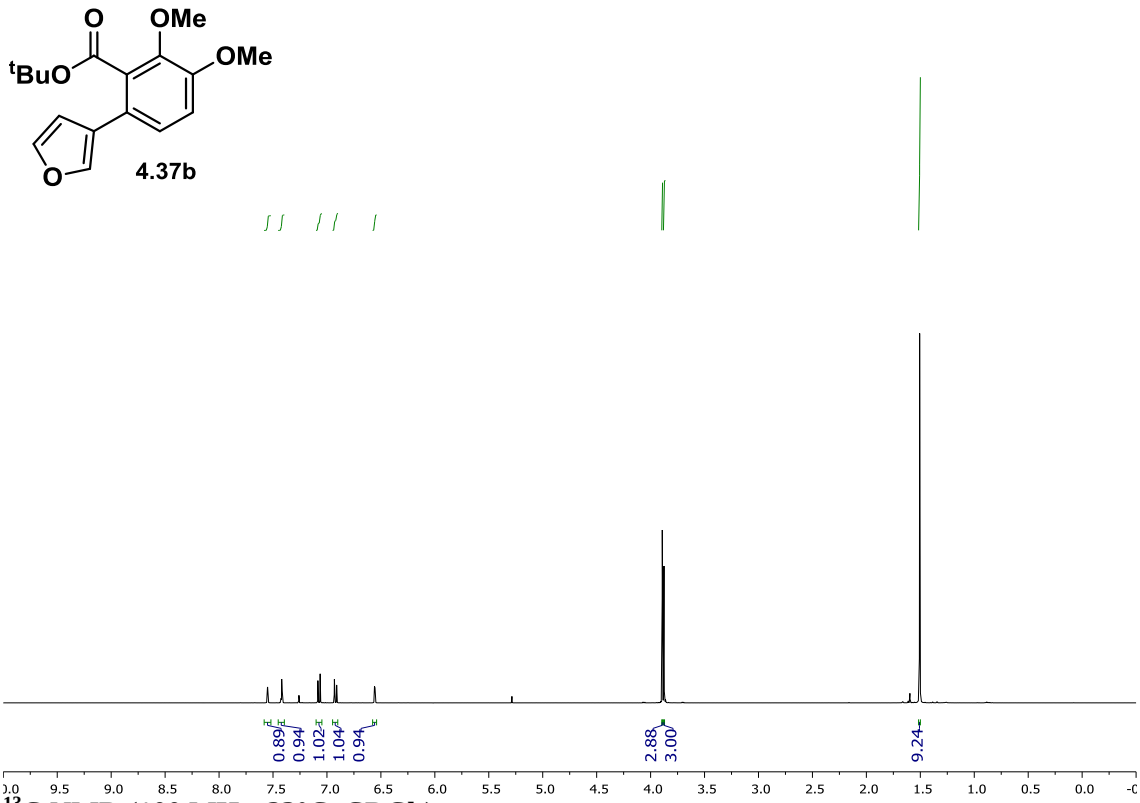
^{1}H NMR (400 MHz, 23°C, $CDCl_3$)



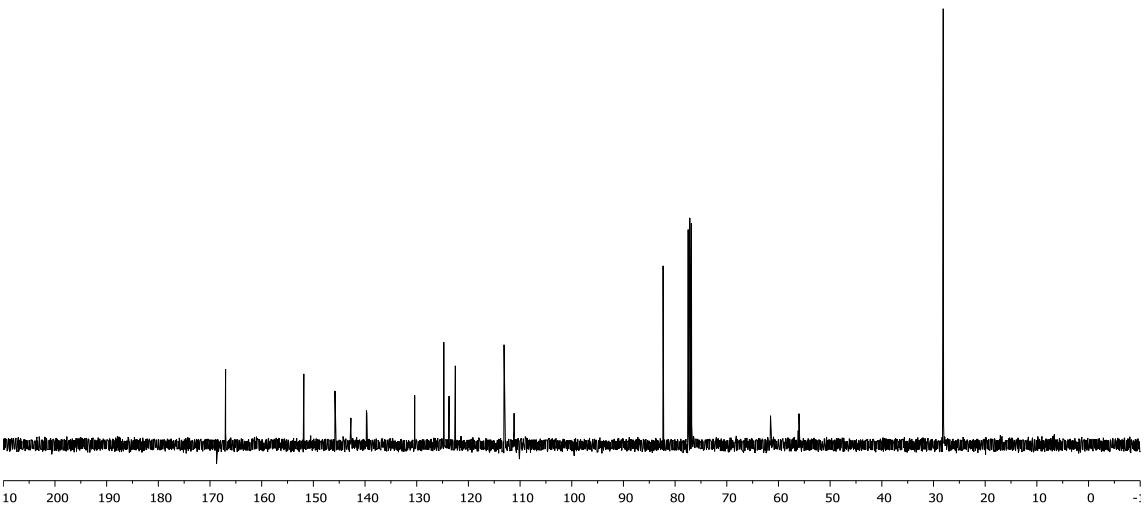
^{13}C NMR (126 MHz, 23°C, $CDCl_3$)



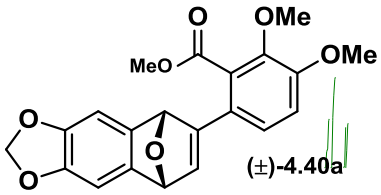
^{1}H NMR (400 MHz, 23°C, $CDCl_3$)

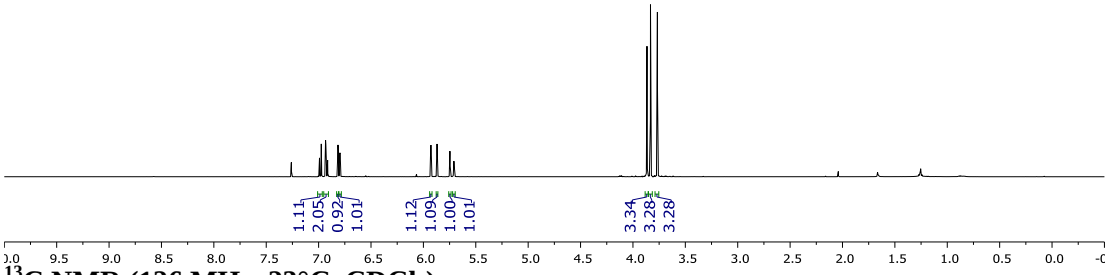


^{13}C NMR (100 MHz, 23°C, $CDCl_3$)

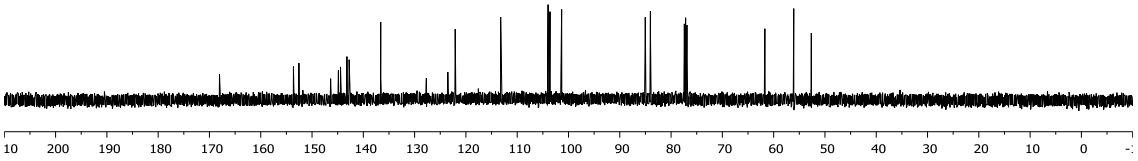


^{1}H NMR (500 MHz, 23°C, $CDCl_3$)

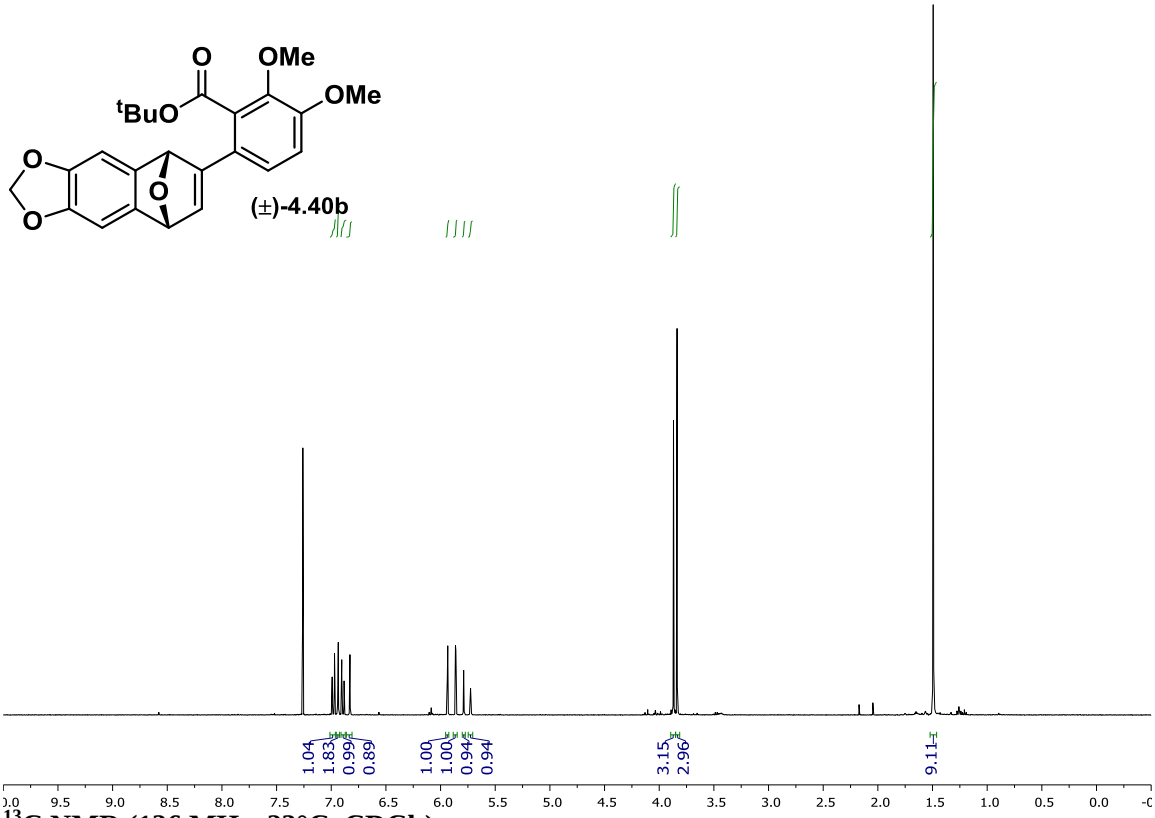




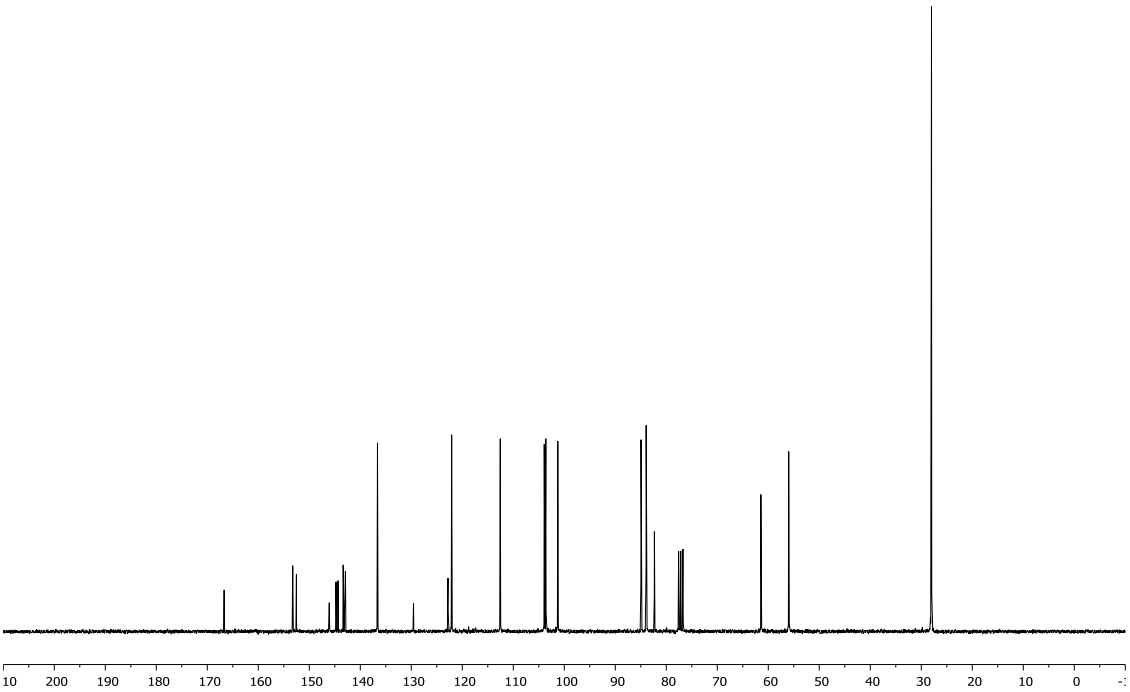
^{13}C NMR (126 MHz, 23°C, $CDCl_3$)



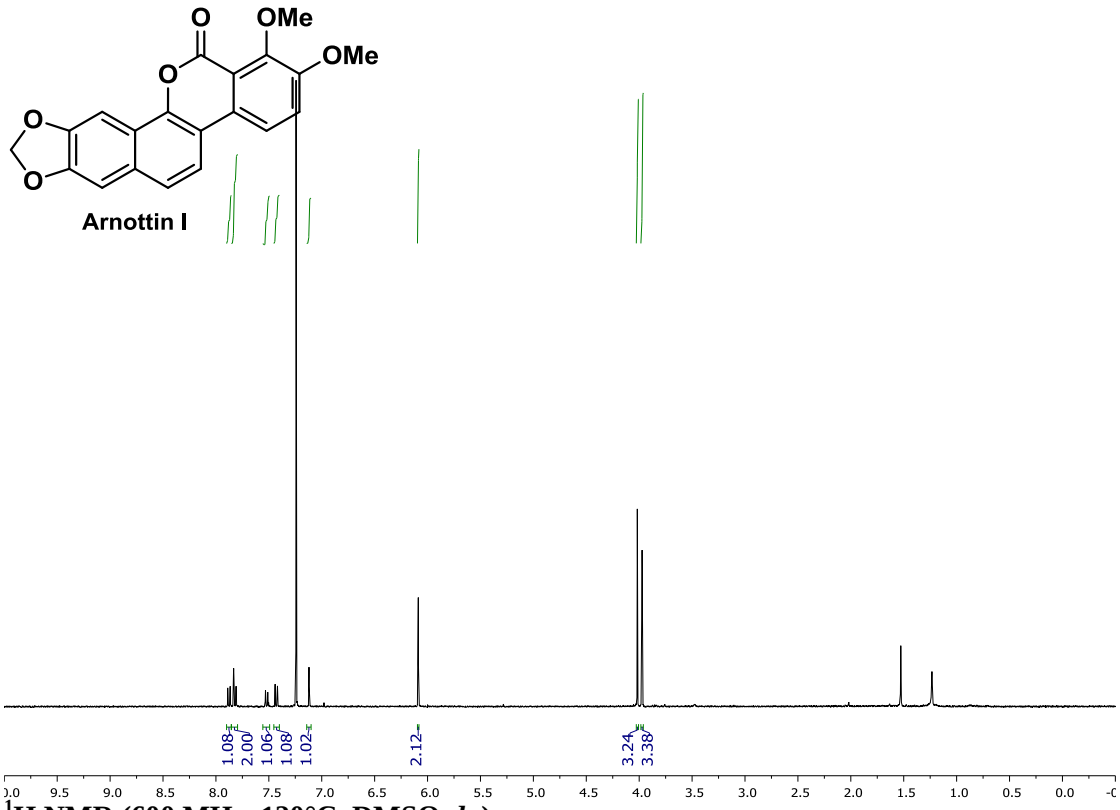
^{1}H NMR (400 MHz, 23°C, $CDCl_3$)



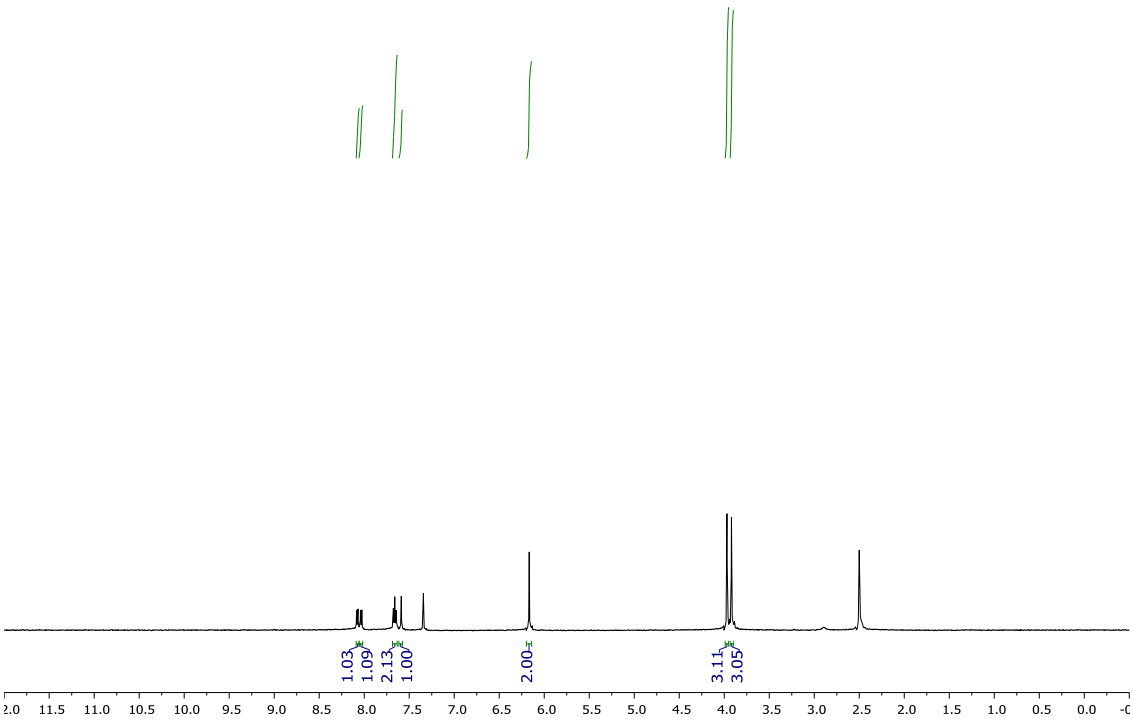
^{13}C NMR (126 MHz, 23°C, $CDCl_3$)



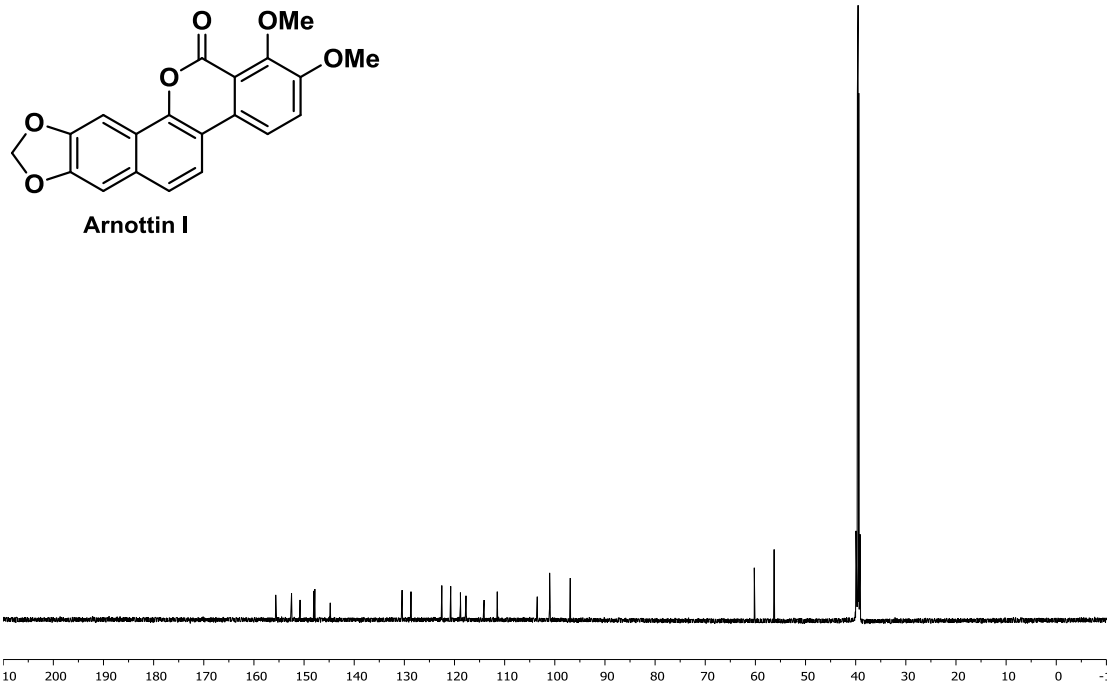
^{1}H NMR (400 MHz, 23°C, $CDCl_3$)



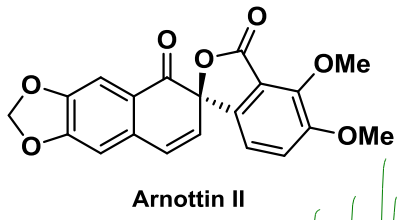
^{1}H NMR (600 MHz, 120°C, DMSO-d_6)



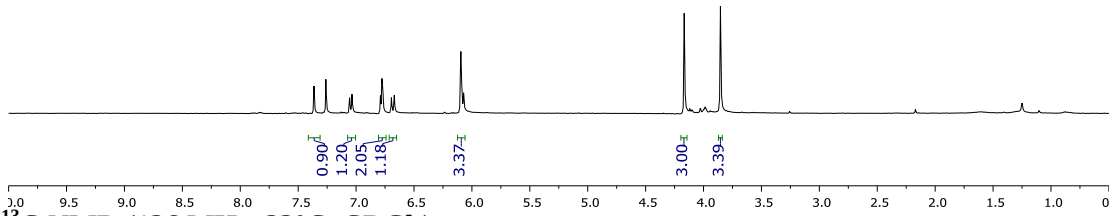
^{13}C NMR (150 MHz, 120 °C, DMSO-d_6)



^{1}H NMR (400 MHz, 23°C, $CDCl_3$)



Arnottin II



^{13}C NMR (126 MHz, 23°C, $CDCl_3$)