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Total Synthesis of Anticancer Agent Deoxypodophyllotoxin and Antiviral F4-4 Demonstrating the Utility of the Intramolecular Styryl Diels-Alder (ISDA) Reaction

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A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

Total Synthesis of Anticancer Agent Deoxypodophyllotoxin and Antiviral F4-4 Demonstrating the Utility of the Intramolecular Styryl Diels Alder (ISDA) Reaction

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The intramolecular styryl Diels – Alder (ISDA) reaction is a rare and unique [4+2] cycloaddition with potential in the syntheses of polycycles. Its utility is based on the formation of two rings and one stereocenter in a single step, making it an efficient method for the construction of lignan-type natural product targets. Detailed mechanistic studies with complex esters and the application to natural product synthesis has been limited due to drawbacks including the loss of aromaticity, producing slow reactivity, a potentially problematic thermal [1,3]-hydrogen shift, and electronic mismatch related to the substituents on the aryl functional groups. In this research, we found conditions that led to the successful application of the ISDA reaction on the total synthesis of the anticancer deoxypodophyllotoxin and the antiviral agent F4-4. Deoxypodophyllotoxin was synthesized in seven steps, which is a very concise synthesis for a complex lignan. Density functional theory was used to analyze the two components of the ISDA reaction, the [4+2] cycloaddition and the [1,3]-hydrogen shift. Several pathways were analyzed, and the rate determining step was determined to be the [4+2] cycloaddition. We also found that the [1,3]-hydrogen shift is assisted by di-*tert*-butylhydroxytoluene and is lower in energy than the [4+2] cycloaddition.

The two targets chosen for this research have important biological activities. Deoxypodophyllotoxin is known as a potent anticancer agent related to podophyllotoxin. Podophyllotoxin is a more abundant lignan which is the precursor of the FDA approved drugs etoposide and teniposide, used for the treatment of lung and testicular cancer. Other biological activities of deoxypodophyllotoxin have been found including antibacterial, antiviral, and anti-inflamatory activity. Also, it was recently discovered that F4-4 possesses antiviral activities against Herpes simplex viruses 1 (HSV-1), 2(HSV-2), and *H. zoster*. Since both deoxypodophyllotoxin and F4-4 are not available in large quantities from natural sources, chemical synthesis is important for continuing research and drug development of these compounds.

Keywords: Intramolecular Diels-Alder, styryl, lignan, deoxypodophyllotoxin, anticancer, antiviral

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LIST OF ABBREVIATIONS

BHT	2,6-Di-*tert*-butyl-4-methylphenol hydroxytoluene
Bn	Benzyl
n-BuLi	Butyllithium
CDI	Carbonyldiimidazole
COSY	Correlation Spectroscopy (NMR)
DA	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7ene
DCB	1,2-Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DCC	N,N-dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIAD	Diisopropyl azodicarboxilate
DIBAL-H	Diisobutylaluminum hydride
DMAS	Dimethylacetamide
DMF	Dimethylformamide
DPT	Deoxypodophyllotoxin
ED_{50}	Effective Dose
EDCI	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
Ghosez's reagent	1-Chloro-N,N,2-trimethyl-1-propenylamine
GC	Gas Chromatography
HOMO	Highest Occupied Molecular Orbital
HQ	Hydroquinone
IC_{50}	Half maximal inhibitory concentration
ID_{50}	Infectious Dose
IRC	Intrinsic Reaction Coordinate

ISDA	Intramolecular Styryl Diels-Alder
IR	Infrared Spectroscopy
LUMO	Lowest Unoccupied Molecular Orbital
MS	Mass Spectrometry
MW	Microwave
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
Ph	Phenyl
SMD	Solvation Model Density
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyl dimethylsilyl
THF	Tetrahydrofuran
$TMSCH_2N_2$	Trimethylsillyl diazomethane
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
UV	Ultraviolet spectroscopy

Chapter 1. Background

1.1. Intramolecular Styryl Diels-Alder Reaction

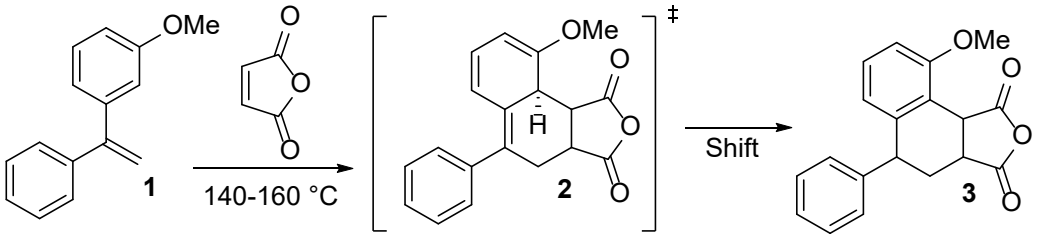
More than 100 years after its discovery,[1] the Diels-Alder (DA) reaction remains one of the most useful reactions for the construction of six-membered rings with high regio- and stereocontrol. Developments on the DA reaction include Lewis acid activation,[2] chiral organo-catalysis,[3] microwave activation,[4] and photoredox catalysis.[5]

The intramolecular styryl Diels-Alder (ISDA) reaction is a rare [4+2] cycloaddition with great promise for the construction of polycyclic compounds including, lignan-type natural products with important biological activity. The styryl functionality[6] is the diene portion of the reaction and the dienophile is conjugated to a carbonyl. The reaction involves two transition states; the [4+2] cycloaddition and a [1,3]-hydrogen shift.

Several drawbacks limit the study and application of this reaction to complex targets. These drawbacks include slow reactivity due to loss of aromaticity in the [4+2] cycloaddition step, and a potentially problematic [1,3]-hydrogen shift. When applied to the construction of lignan type compounds, an electronic mismatch is found with the substituents on the aryl functional groups. However, the ISDA reaction has potential to form the polycyclic cores of naturally occurring products with significant biological activities.[7]

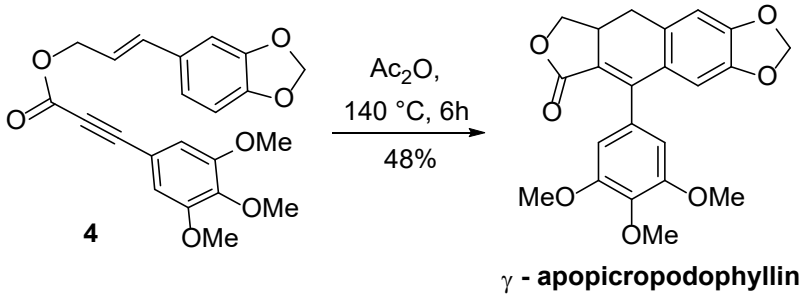
Limited examples of the successful use of this reaction has increased interest in the ISDA reaction and highlighted its utility in total synthesis.[8] The first example of the use of styryl functionality as a diene was reported by Wagner-Jauregg[9] using 1,1 -diarylethylene and maleic anhydride at high temperature (scheme 1). Even though the reaction was limited to highly

activated dienophiles and gave low yields, it showed the activity of styryl functional groups as dienes for the Diels-Alder reaction.



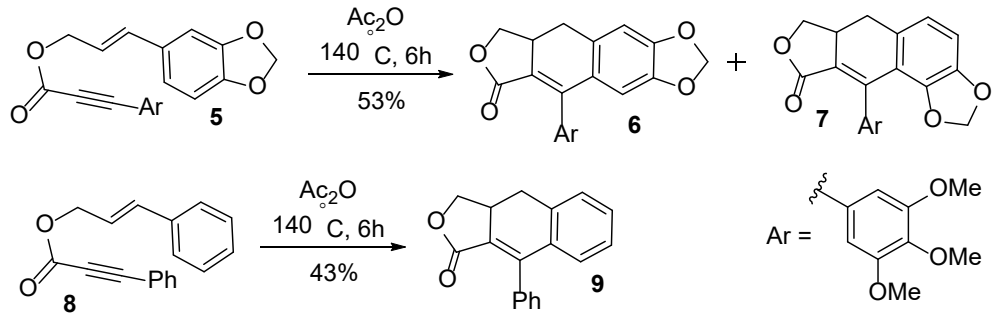
Scheme 1. Wagner-Jauregg styryl intermolecular reaction.

Based on this precedent, Klemm and coworkers pioneered research into the intramolecular styryl Diels-Alder reaction with the purpose of constructing the natural lignin *d,l*-apopicropodophyllin (scheme 2).[10] Refluxing of the electron rich ester **4** in acetic anhydride gave the corresponding natural product in moderate yield, (48%) proving the potential utility of the ISDA reaction for synthesis.



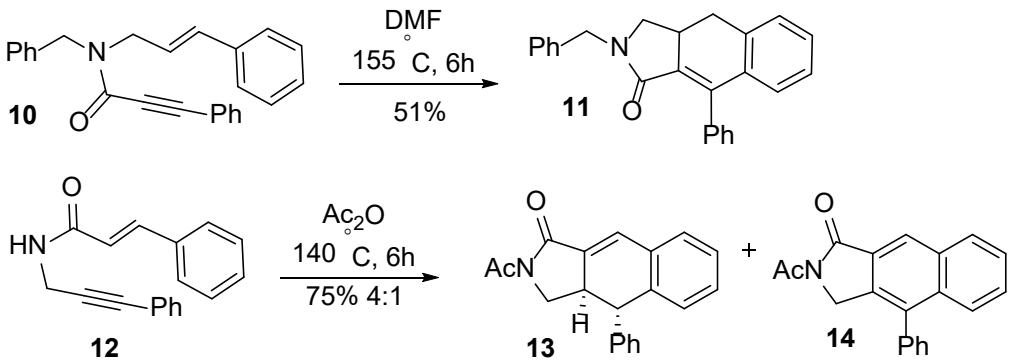
Scheme 2. Klemm synthesis of *d,l*-apopicropodophyllin.

Subsequent studies report the cyclization of several alkynyl-alkenyl esters[11] using acetic anhydride at high temperatures. Polycyclic lactones like **9** were obtained in moderate yields. Use of substituted esters, similar to **5,** gave mixtures of isomers isolated and characterized by NMR studies, where the major product is the linear polycycle. In scheme 3, the major product is **6** with 53% yield.



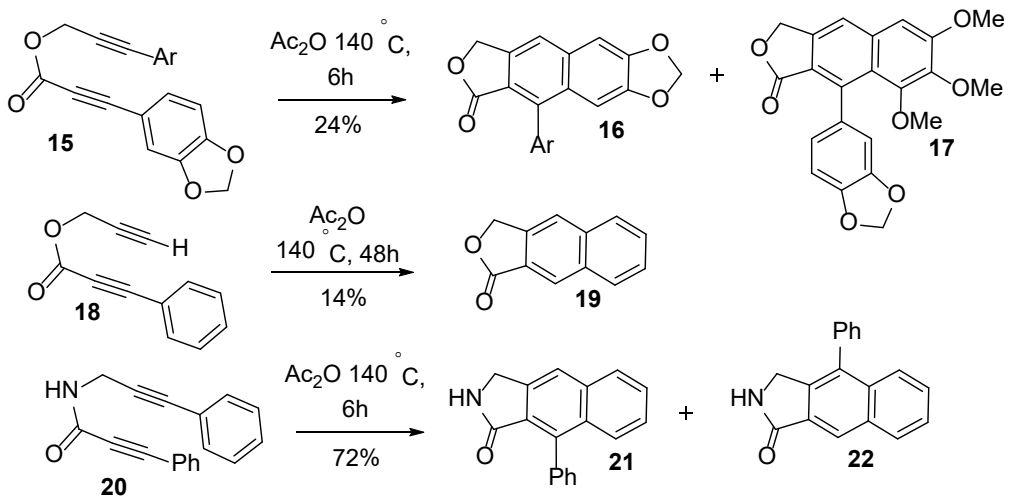
Scheme 3. Ester examples by Klemm.

Amides have also been employed as substrates for the ISDA reaction giving lactams as products.[12] Secondary amides are more effective in performing the ISDA reaction than esters or protected amides, as shown in scheme 4. Changing the solvent from acetic anhydride to DMF was also more efficient.



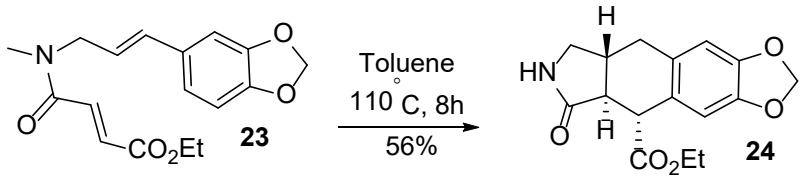
Scheme 4. Amide examples by Klemm.

Bis-alkynyl aryl conjugates were also used as dienes,[4,13] giving a mixture of naphthalene products in low to moderate yields (scheme 5). Ester **15** and amide **20** show such mixtures, in which either end of the ester or amide worked as the diene to form the mentioned mixture.



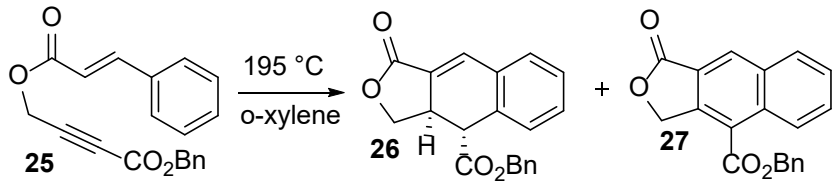
Scheme 5. Bis-alkynyl examples by Klemm.

These studies gave a better idea of the scope and possible applications of the ISDA reaction and sparked the curiosity of many scientists. In the early development of the ISDA reaction, Cox reported a different approach by activating the dienophile of tertiary amide **23** with a second carbonyl as shown in scheme 6. [14] This approach lowered the temperature of the reaction to 110 °C instead of 140 – 160 °C.



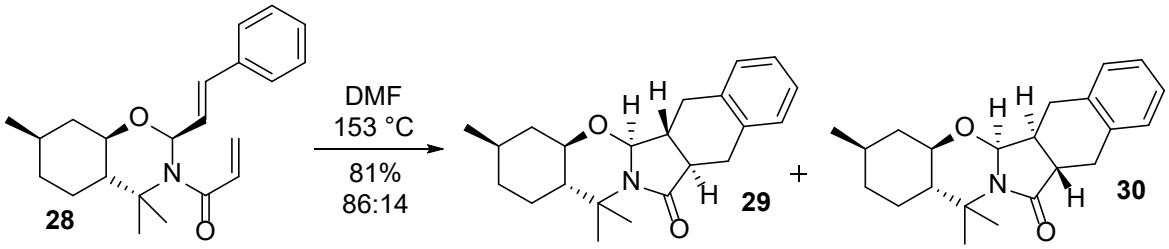
Scheme 6. Cox amide activated dienophile.

A similar approach was taken later by Chackalamannil and coworkers,[15] applying it to esters with an activated propargylic moiety **25**. High temperature was employed and mixtures of dihydro / naphthol type products were obtained.



Scheme 7. Activated propargylic ester.

Other activated dienophiles have been used along with fixed structures using a chiral auxiliary. Pedrosa and coworkers[16] used a menthol derivative as an auxiliary to construct benzo-cyclohexyl lactams. In this case an α,β-unsaturated amide was attached to a chiral template from amino menthol compound **28**. Restrictions in the cyclic structure and the presence of a chiral auxilary favor the ISDA reaction giving good yield and selectivity, as shown in scheme 8.

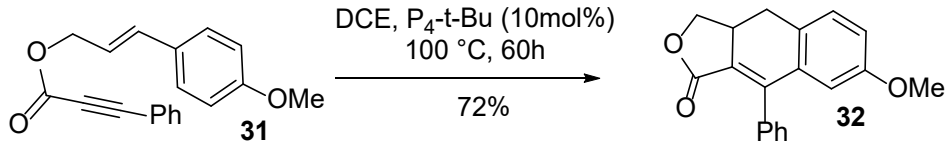


Scheme 8. Pedrosa's example of activated dienophile and chiral auxiliary.

These thermal conditions inspired the construction of core structures of several natural products. Klemm used his discoveries to construct the natural product *dl*-apopicropodophyllin, as shown in scheme 2.

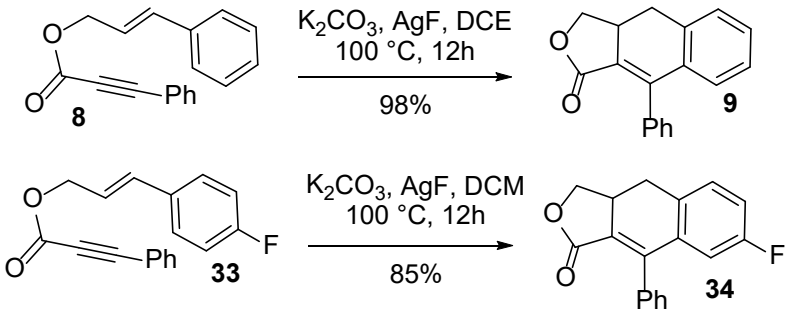
In an attempt to improve yields and stereoselectivity of the ISDA reaction, other conditions have been applied. These strategies involve Lewis acids and microwave conditions. Based on the hypothesis that the rate determining step of the ISDA reaction is the hydrogen shift, Lin and coworkers experimented with several bases including K_2CO_3, NaOEt, and DBU among

others.[17] They found that P_4-t-Bu phosphazene when applied in 10 mol% in DCE to simple esters (compound **31**), promoted ISDA reactions in good yields.



Scheme 9. Base promoted ISDA reaction.

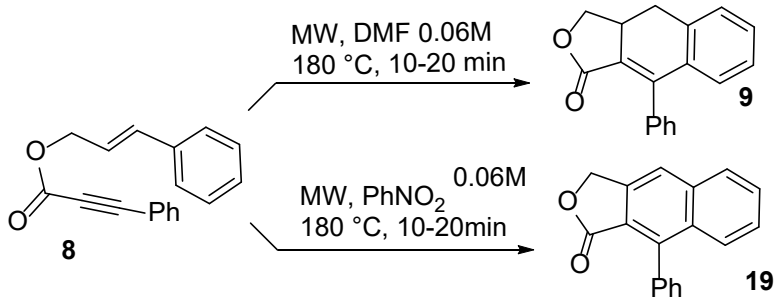
Later, an improved methodology combining K_2CO_3 and silver (I) fluoride in stoichiometric quantities was published.[18] In this study, unsubstituted styryl alkynyl esters were used as starting material. Because the coordination of the carbonyl and base promoted hydrogen shift, the conditions of the reaction are improved requires lower temperatures and shorter reaction times as illustrated in scheme 10.



Scheme 10. Lewis acid and base promoted ISDA reaction.

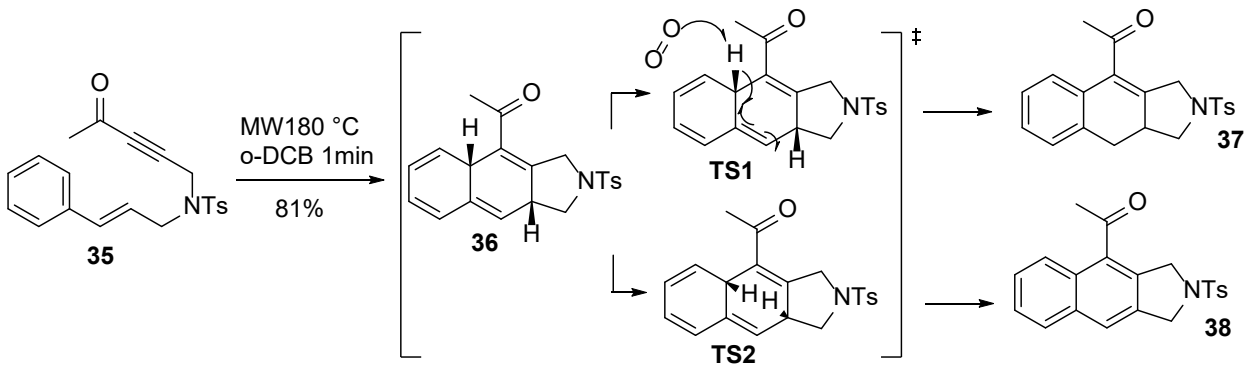
Microwave (MW) irradiation has also been used to obtain better yields and increase selectivity. Several solvents have been used for microwave ISDA reactions. Brummond and coworkers studied[19] the effects of solvent on unsubstituted styryl alkenyl esters to selectively form arylnaphthalene or aryldihydronaphthalene lactones. Experiments with DMF provided the aryldihydronaphthalene lactone **9** while experiments with $PhNO_2$ produced arylnaphthalene

lactone **19** with loss of hydrogen gas. The explanation of the selectivity may be based on the oxidative character of $PhNO_2$ known in heterocycle formations.[20]



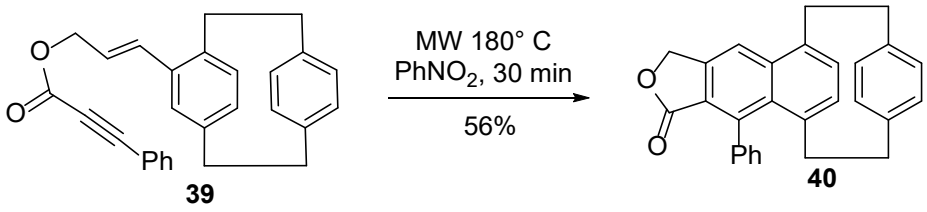
Scheme 11. Effect of DMF and $PhNO_2$ in MW ISDA reactions.

Subsequent studies by Brummond showed cyclization of methyl ketone styrenes using microwave conditions in dichlorobenzene.[21] In this study, it was concluded that the dihydronaphthalene product and the naphthalene product come from the same intermediate. The initial [4+2] cycloaddition is the same for both products. After the [4+2] cycloaddition, a radical mechanism with hydrogen abstraction and an allyl radical intermediate may be initiated by trace oxygen. This allyl radical abstracts a hydrogen atom from another [4+2] intermediate producing the dihydronaphthalene product **37**. Crossover experiments with deuterated substrates demonstrated this intermolecular hydrogen abstraction. Hydrogen loss can also happen after the [4+2] cycloaddition. This was demonstrated as hydrogen gas observed by NMR and GC analysis producing the naphthalene product **38**. Series of naphthols like **38** have been studied as fluorophores with potential application as biomarkers in cellular membranes and lipid dynamics.[22]



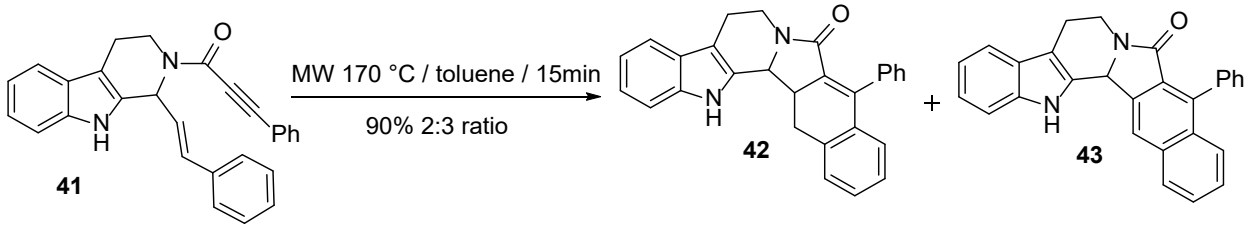
Scheme 12. ISDA proposed mechanism of dihydronaphthalene and naphthalene products.

More complicated fluorophores have been made using MW conditions for the ISDA reaction. Benedetti and his team[23] reported the formation of [2.2]paracyclophane naphthalenes by irradiating [2.2]paracyclophane esters (**39**) in the presence of nitro benzene at 180 °C for 30 min. Experiments with different substituents have been applied with yields ranging from 19 to 78%. It is expected that these unique structures will be applied as chemical probes and optical sensors.



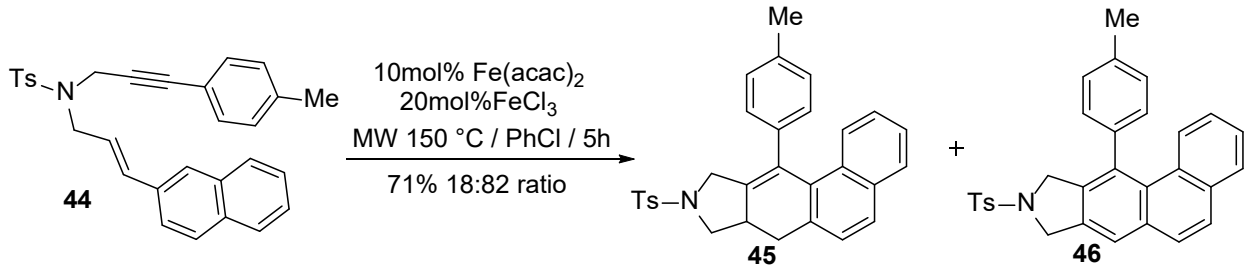
Scheme 13. Application of ISDA reaction in the synthesis of fluorophores.

Other microwave conditions for the ISDA reaction were also applied to the production of alkaloid type compounds with toluene as the solvent at high temperatures.[24] In this study, mixtures of **42** and **43** were produced. Addition of substituents in the ring resulted in poor selectivity giving mixtures of regioisomers that was impossible to quantified.



Scheme 14. ISDA reaction applied to alkaloid type compounds production.

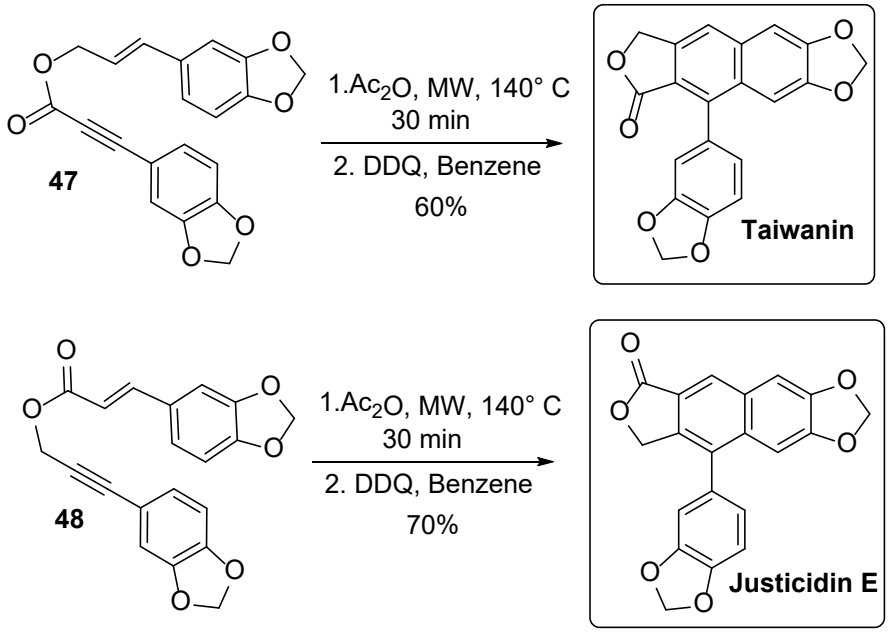
Catalysts have also been used in conjunction with MW conditions. Kang and coworkers[25] used Fe (II) and Fe (III) to produce naphthalene derivates. Use of ferric chloride slightly favored dihydronaphthalene compound **45**, while 10 mol% of $Fe(acac)_2$ in conjunction with 20 mol % of $FeCl_3$ increased the selectivity favoring the naphthalene product **46**. Density functional theory (DFT) was used to determine the mechanism. Iron coordinates the styryl diene lowering the energy of the lowest unoccupied molecular orbital (LUMO) in the transition state. This coordination favors the loss of hydrogen (H_2) leading to the naphthalene product. Kang and coworkers demonstrated that the coordinated state may exist in a boat-like conformation making the hydrogens closer and thus easier to lose H_2 in the process.



Scheme 15. MW and Iron catalyzed ISDA reaction.

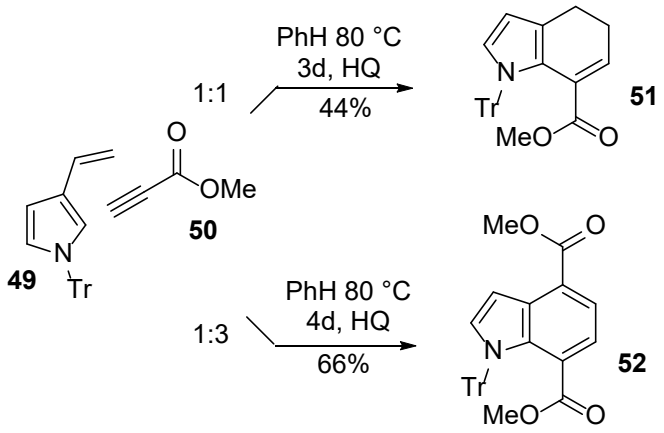
Microwave conditions proved to be effective in the synthesis of taiwanin and justicidin E, two natural products with biological activity.[26] In this case, acetic anhydride was used, taking a precedent from Klemm's early results, and applying microwave conditions. Thirty minutes

allowed for [4+2] cycloaddition and further oxidation with DDQ produced the naturally occurring compounds in good overall yields. Change in the position of the carbonyl is the difference between both products as shown in Scheme 16.



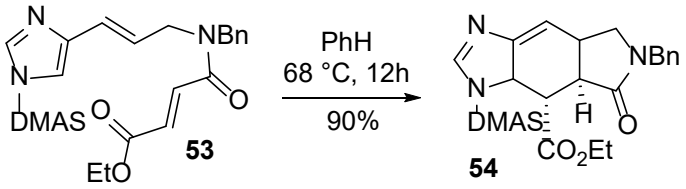
Scheme 16. Synthesis of taiwanin and justicidin E using ISDA MW conditions.

Conditions mentioned before have been applied to aromatic heterocycles. These substrates have been found to have utility as good dienes[27] and with direct application to total synthesis. The first intermolecular styryl-type Diels-Alder reaction study was performed by Jones and co-workers.[28] The reaction of one equivalent of 1-methyl-3-vinylpyrrole with one equivalent of methyl propiolate produced the Diels-Alder product **51**. Three equivalents of methyl propiolate led to the formation of a substituted benzopyrrole diester via a second Diels-Alder reaction and a retro Diels-Alder reaction with elimination of ethene. These early studies demonstrated that vinylpyrrole, vinylpyrrazole, thiophene and indoles can be good dienophiles for styryl-type Diels-Alder reactions.[29]



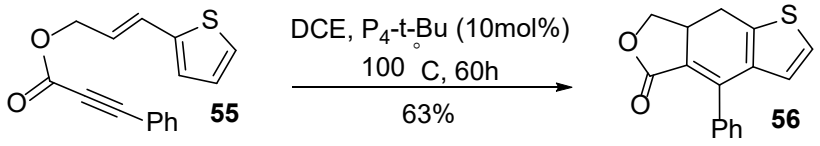
Scheme 17. Intermolecular styryl Diels-Alder reaction on heterocycles.

Additional examples of ISDA reactions have demonstrated the scope of this reaction on heterocycles. Lovely and coworkers demonstrated that a 4-vinylimidazole derivative from urocanic acid was suitable for ISDA reactions.[30] Activated substrates containing electron withdrawing groups close to the dienophile were found to be the best compounds for these reactions as shown in scheme 18. Compound **53** reacted at 68 °C over 12 hours resulting in impressively high yields (90%). Inactivated substrates required higher temperatures and longer times to give products in more moderate yields.



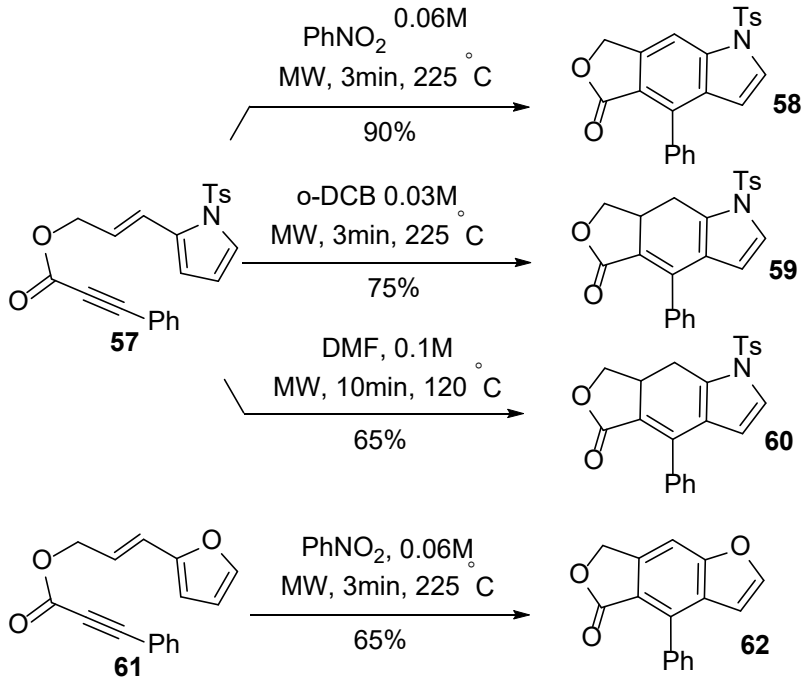
Scheme 18. Vinylimidazole ISDA reaction.

Similar conditions as for the styryl substrate were applied with heterocycles. Base conditions were employed with thiophene in an ISDA reaction.[17] Addition of the base in this case proved to be effective producing the desired Diels-Alder product **56** in moderate yield (Scheme 19). In contrast, other propiolic esters under thermal conditions gave poor yields.



Scheme 19. ISDA on heterocycles under basic conditions.

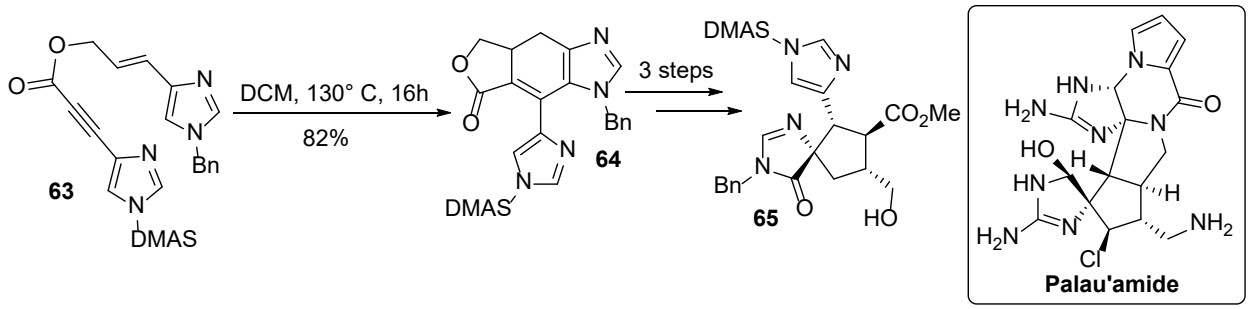
The application of microwave conditions on ISDA reactions with heterocycles is worth mentioning because of the interesting cores that can be formed. Brummond, in microwave studies, also used heterocycles.[19] As mentioned before (scheme 11), use of o-DCB as solvent favored conversion to a dihydro-product **59** (scheme 20). Using DMF favored the dihydro product **60**, as well. On the other hand, use of nitro benzene gave good yields of the benzopyrrole product **58**. This is also true when tethered furans are employed as substrates.[31]



Scheme 20. Solvent effects on ISDA reactions.

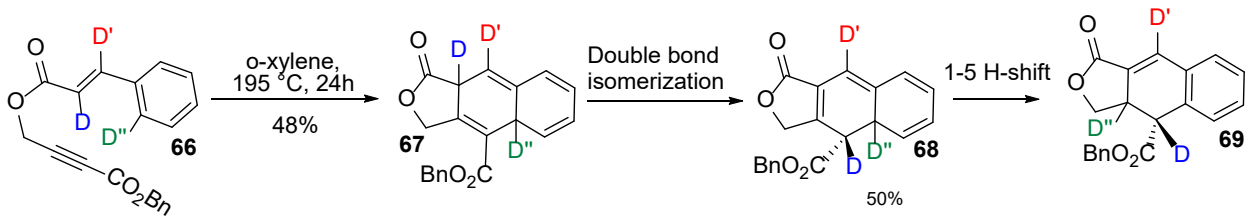
Lovely and coworkers applied ISDA reactions on heterocycles to construct a spiro cyclopentyl imidazole core leading to palau'amine.[32] They were able to achieve 82% yield of

product **65** by heating deoxygenated DCM to 130 °C in a sealed tube for 16h. Oxidative rearrangement gave the spiro structure contained in the natural product.



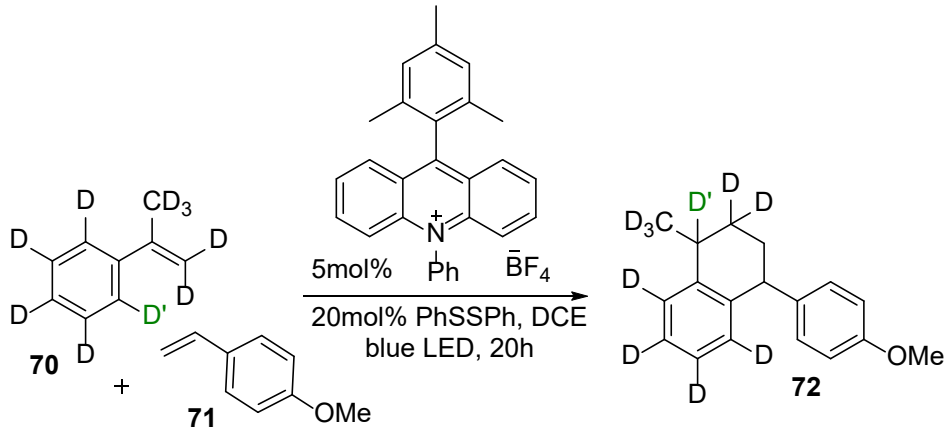
Scheme 21. ISDA reaction applied to heterocycles.

Very few mechanistic studies have been applied to the ISDA reaction, including Brummond, as mentioned before. These studies are a combination of experimentation with deuterium substrates and DFT calculations, which have focused on explaining the products resulting from [1,3]-hydrogen shifts or loss of H_2. Results may highlight alternatives for future development. Mechanistic studies were performed first by Chackalamannil and coworkers with deuterated substrates.[10, 33] The experiment was performed in o-xylene at 195 °C for one day. The mechanism is consistent with a [4+2] cycloaddition, a double bond isomerization and a [1,5]-Hydrogen shift. Analysis of substrates with deuterium in different positions led to the mechanism shown in Scheme 22. A [1,5]-hydrogen shift was demonstrated by the change in position of D" in green (Scheme 22). Also, it was expected that deuterium atom D in blue was lost in the reaction and NMR studies showed reincorporation of 50% of this deuterium after isomerization. Deuterium D' in red does not participate in the mechanism.



Scheme 22. Mechanistic studies with double bond isomerization and [1-5] H shift.

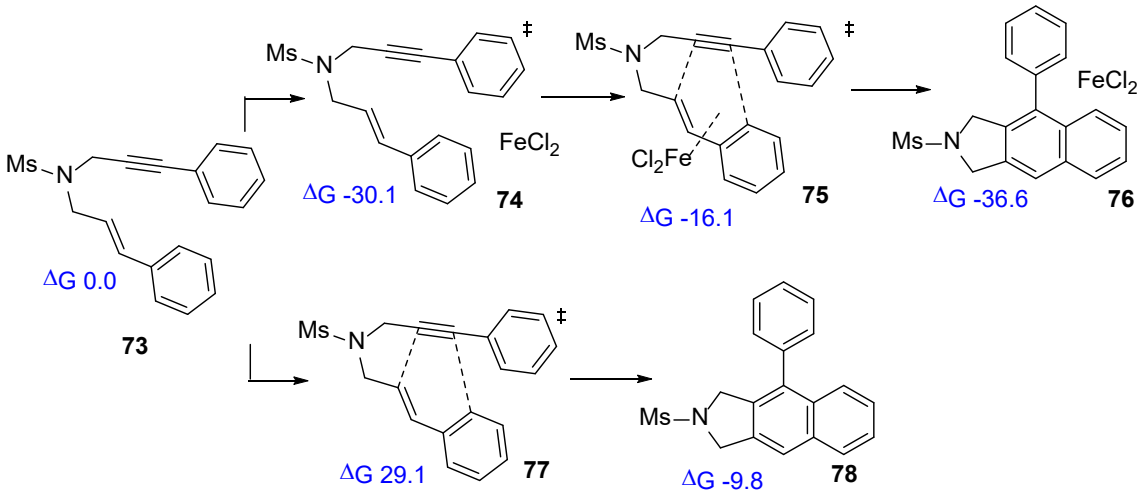
Deuterium studies on the intermolecular styryl Diels-Alder reaction by Huang are consistent with the labeling studies of Brummond in demonstrating a hydrogen shift.[34] Huang and coworkers applied their photoredox catalysis conditions (5 mol% acridinium catalyst, blue LED, 20h) obtain the fully deuterated methylstyrene and p-methoxystyrene to produce **72** (Scheme 23). The deuterium D' in green (Scheme 23) shifted position with 35% incorporation.



Scheme 23. Deuterium experiments for photoredox ISDA reaction

DFT calculations have been a useful tool to demonstrate and visualize transition states. In the study by Kang and coworkers[25] DFT calculations helped to identify the mechanism by which Fe (II) interacts with the diene. According to the results, iron (II) adopts a η^4-interaction with the styryl diene which lowers the energy from 29.1 kcal/mol (non-catalyzed ISDA reaction) to 14

kcal/mol (Scheme 24). This interaction explains the higher production of naphthalene product through the loss of hydrogen H_2.



Scheme 24. DFT calculation with sulfonamide.

Until recently there were no detailed mechanistic studies of the ISDA reaction including both transition steps and complex starting material. The work presented in this dissertation provides an analysis of the mechanism of the ISDA reaction combining the [4+2] cycloaddition step and the [1,3]-hydrogen shift necessary to explain the outcomes through DFT calculations. These mechanistic studies are necessary for future development and applications to total synthesis. This work also demonstrates the utility of the ISDA reaction in total synthesis of natural products by presenting the synthesis of the known anticancer deoxypodophyllotoxin and the application of the ISDA reaction in the construction of the antiviral agent F4-4.

1.2. Synthetic Targets

Much attention has been drawn to the synthesis of secondary metabolites, not only because of the structural diversity and the potential to discover new methodologies and reactions, but also for their biological activities.[35] Many secondary methabolites have proven to be potent

anticancer, antiviral or antimicrobial agents, among other activities.[36] Because of the scarcity of many of these compounds from natural sources, synthetic methodologies are often applied to obtain them in sufficient quantities for clinical trials. Synthesis of secondary metabolites gives control over functional groups and structure, which means that properties like solubility, bioavailability and target binding of a new therapeutic agent can be modified. The ISDA reaction is an efficient tool to synthesize polycyclic lignans, an important class of secondary methabolites.

Lignans are polyphenols, a class of secondary metabolites found in different species of plants.[7, 37] Even though the role of lignans in plants is unclear, it is believed that their production has an important link to defense mechanisms. Our attention has been focused on the synthesis of lignans deoxypodophyllotoxin (DPT) and F4-4.

1.2.1. Deoxypodophyllotoxin

DPT is a lignan secondary metabolite extracted from the plant *Anthriscus sylvestris* (232 mg/kg) and related in structure to podophyllotoxin, a more abundant natural product and precursor of the FDA approved drug etoposide and teniposide.[38] DPT has been isolated and studied for several years due to its potential as a less toxic and more potent anticancer agent (see biological activity).

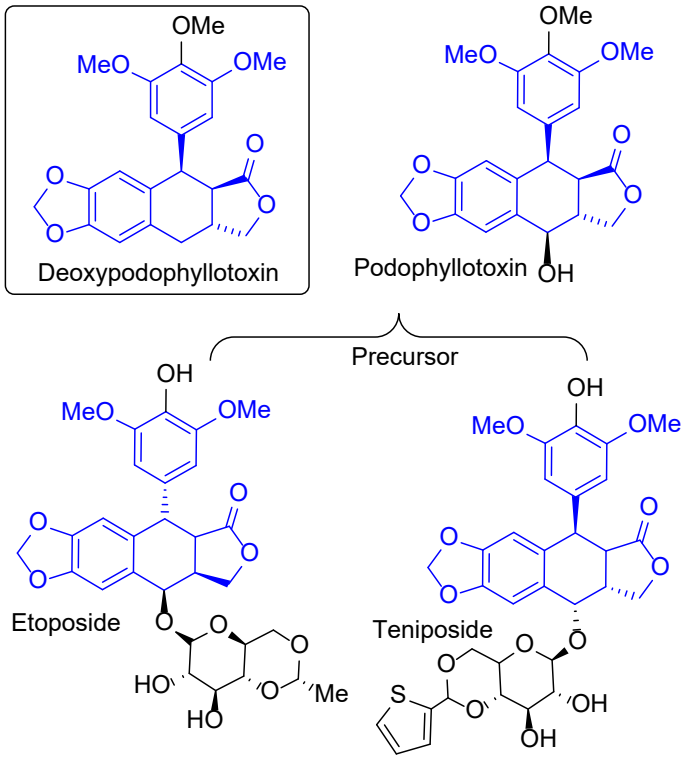


Figure 1. DPT and related anticancer agents

1.2.1.1. Isolation

DPT was isolated from the root of the plant *Anthriscus sylvestris* and related species in small quantities[39] (232 mg/kg of dry rhizomes).[40] The *Anthriscus sylvestris* plant is found in many different parts of the world and has been used in traditional medicine. For example, it has been used in Korea for the treatment of bronchitis.[41] Unfortunately, the plant has recently been listed as an endangered species in China and India.[42] Fortunately, the DPT compound has also been found in the Madagascar plant *Cleistanthus boivinianus*, though, in small quantities.[43] It has also been found that Aspergillus fumigatus, an endophytic fungi isolated from the twigs of *Juniperus communis*, produces DPT. Extraction of 2-4 μg of the compound required nine days of fermentation.

1.2.1.2. Biological Activity

The attention that DPT has received over time is due to its potential anticancer activity. As mentioned before (figure 1), DPT is closely related to the FDA approved drugs etoposide and teniposide commonly prescribed for treatment of lung and testicular cancer.[44] Although these two drugs and DPT are related in their structure, they have different mechanisms of action. In fact, the small structural changes in DPT make it a more potent anticancer agent, which is less toxic to normal cells due to differences in its mode of action.[45] While etoposide and teniposide are inhibitors of the topoisomerase II, DPT is known to inhibit tubulin polymerization.[46] Compared with podophyllotoxin, DPT showed enhanced inhibition of in vitro microtubule assembly (ID_{50} 0.5 nM tubulin-β vs 0.6 nM podophyllotoxin), which promotes apoptosis.[47] It also showed less toxicity to normal untransformed cells (IC_{50} 79 μM).[48] DPT has been evaluated in human cancer cell lines including HepG2, A549, HeLa and HCT-8, among others, and in normal cell lines WI-38.[47]

Other biological activities that have been found in DPT include antibacterial (tested against S. aureus, E. coli and H. pylori),[49] antiviral activity (Herpes virus types 1 and 2HSV-1,2 ED_{50} 4.0, 11 ng/mL vs acyclovir 50 ng/mL),[50] anti-inflamatory (COX-1,2: IC_{50} 10 nM),[51] anti-allergy (regulation of anaphylaxis reactions),[52] and even insecticidal activity[53], among others.

1.2.1.3. Synthetic Efforts

DPT is a highly valuable compound for its potential to become an effective treatment against not only cancer but several other illnesses as mentioned before. Several syntheses have been tested in order to improve its production and inspire posterior research and application as anticancer agent. These total syntheses range between 10 to 20 steps with most of them involving normal demand, Intermolecular Diels-Alder reactions (Figure 2).

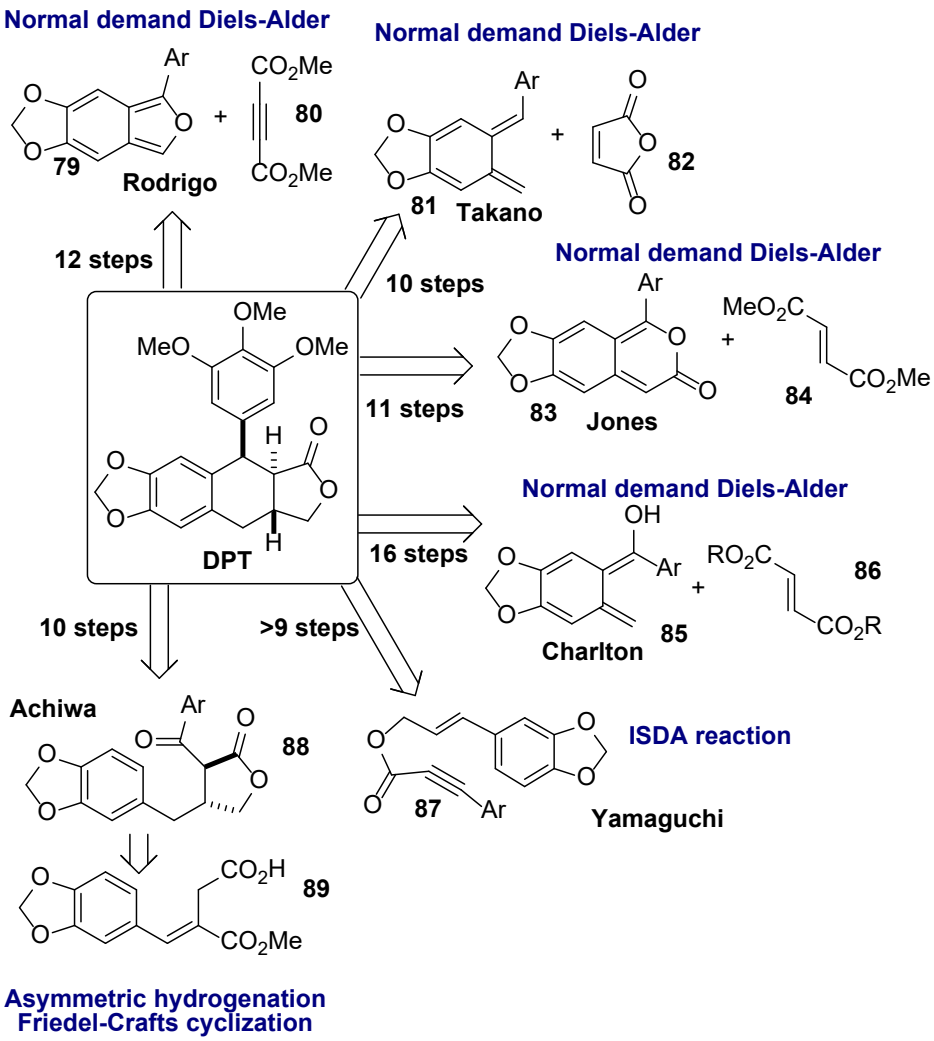


Figure 2. Synthesis strategies to produce DPT.

The first total synthesis of DPT was reported in 1980 by Rodrigo.[54] In this synthesis, a series of reductions and epimerizations were used. The key reaction of this synthetic design is an intermolecular, normal demand Diels-Alder reaction between benzofuran **79** and acetylenedicarboxylate, a highly activated dienophile, giving moderate yields of the cycloadduct. The racemic DPT was made in 12 steps. An approach with similar key step was taken by Jones,[55] who used benzopyrone **83** and dimethyl maleate **84**, which by decarboxylation gave a Diels-Alder product. Eleven steps were necessary to complete the synthesis.

In Takano's synthesis,[56] the diene of the key intermolecular Diels-Alder reaction was made *in situ* by elimination of a β-hydroxysilane in a benzyl equivalent of the Peterson reaction. This diene is reacted with maleic anhydride producing a lactone core structure of DPT. The synthesis is completed in 10 steps including opening of the lactone and a series of isomerizations. On the other hand, cyclobutene decomposition was used by Charlton[57] to make the diene for the intermolecular Diels-Alder reaction. Formation of the lactone was difficult in both syntheses generating poor yields.

The synthetic designed by Achiwa[58] was based on the introduction of chirality early in the synthesis by using an asymmetric hydrogenation with a rhodium catalyst, followed by a reductive lactonization. Friedel-Crafts cyclization was also used as one of the key reactions in the 10-step synthesis.

A synthesis of DPT using an ISDA reaction was developed by Yamaguchi[59] and coworkers based on Klemm's results. The ISDA reaction was performed in DMF at 145°C. Then, opening and closing of the lactone were necessary to finish the synthesis. The total synthesis required more than 9 steps and the beginning steps were not clearly characterized.

1.2.2. F4-4

F4-4 is a lignan extracted from the roots of the *Kalanchoe pinnata* plant native to the Pacific Islands. This plant has been used by indigenous people to treat asthma, mouth sores and leishmanial[60] conditions.

This lignan has a scaphopetalone like structure attached to a xylose sugar. It was recently discovered and published by the Brigham Young University (BYU) Department of Biology.[61]

1.2.2.1.Isolation

In a study by Cates and coworkers at BYU, 31 species of medicinal plants were selected to test antiviral activity.[62] It was discovered that the acetone extract of the roots of the *K. pinnata* plant had antiviral activity at concentrations lower than 0.1mg/mL. Further purification of the extract using HPLC revealed the structure of two compounds with antiviral activity KPB-100 and KPB-200. The compound KPB-100 was originally called F4-4, being the fourth fraction of their HPLC purification, and just 2mg /Kg have been isolated. The structure was determined by Dr. Burt in the Department of Chemistry at BYU using 2D NMR.[61]

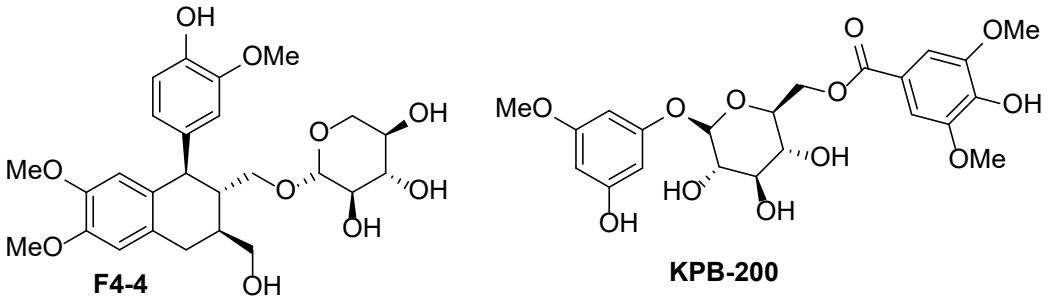


Figure 3. Antiviral compounds isolated from the *K. pinnata* plant.

1.2.2.2.Biological Activity

F4-4 has been tested as an antiviral against Herpes simplex viruses 1 (HSV-1), 2(HSV-2), and H. zoster (>5 μM). These viruses are responsible for cold-sores, sexually-transmitted diseases, and shingles. Infections by herpes viruses are counted among the most common contagious diseases in the world. Even though there is no cure for these illnesses, antiviral drugs are sought to control the production and replication of the virus, giving the patient better quality of life. For the most sensitive part of the population, immunosuppressed patients and newborns finding a treatment can be a matter of life and death. Therefore, the discovery of F4-4 as an antiviral is significant.

Because of the similarities between F4-4 and DPT, it has been hypothesized that F4-4 has other biological activities including anticancer activity. Unfortunately because of its scarcity in natural sources it has not been possible to check that hypothesis.

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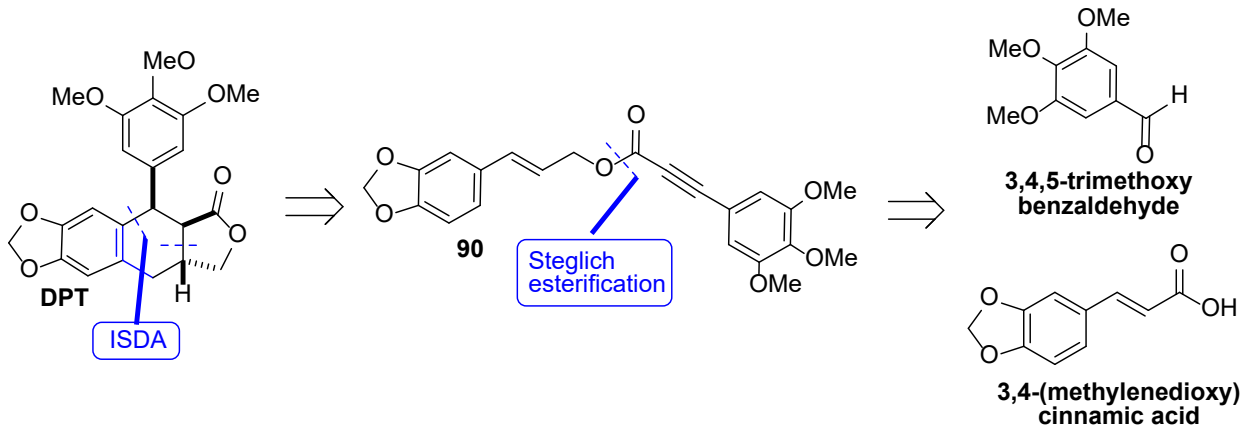
Chapter 2. Total Synthesis of Deoxypodophyllotoxin

2.1. Retrosynthetic Analysis

Reported total syntheses of DPT range between 10 to 20 steps. Our approach is a seven-step synthesis, which is short for a complex lignan like DPT. This is accomplished by forming two rings and a stereocenter in a single step using the ISDA reaction.

We envisioned constructing the core polycycle of DPT via an ISDA reaction of the electron-rich ester **90**. This ester has the necessary substituents to construct DPT. The ester is constructed starting from the readily available materials 3,4-methylenedioxy cinnamic acid and 3,4,5-trimethoxybenzaldehyde.[1]

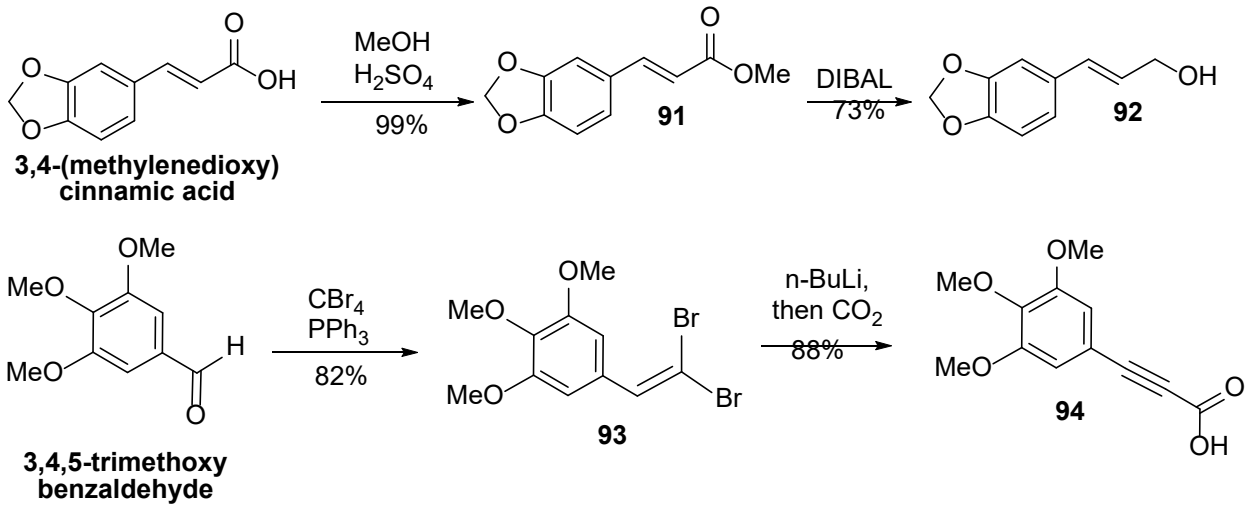


Scheme 25. Retrosynthetic analysis of DPT

2.2. Synthesis of Precursors

The beginning of our synthesis has two routes. First, Fisher esterification[2] and subsequent reduction[3] provided the cinnamic alcohol **92**. Second, a reaction with triphenyl phosphine and carbon tetrabromide converts the 3,4,5-trimethoxybenzaldehyde to the corresponding dibromo alkene **93**. This is then treated under Corey-Fuchs conditions,[4] trapping the acetylene anion with

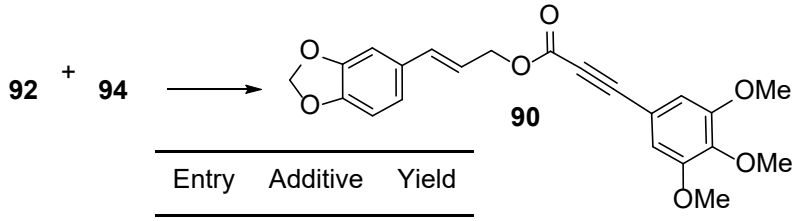
carbon dioxide to produce the alkyne acid **94**. These reactions were performed in high yields as shown in scheme 26.



Scheme 26. Synthesis DPT precursors.

Esterification of compound **92** and **94** proved to be surprisingly challenging. Steglich esterification[5] was first explored giving moderate yields of the desired ester **90** (61%). This yield is attributed to the difficult purification of the compound. A side product of the reaction is a urea like compound which co-elutes with the ester produced. In hopes of improving the purification and yield of this reaction, we used water-soluble EDCI for this reaction, but even lower yields were achieved (Table 1). Finally, the Mitsunobu[6] coupling of **92** and **94** proved to be reproducible and effective to access ester **90** in moderate yields (63%).

Table 1. Conditions for formation of ester **90**.

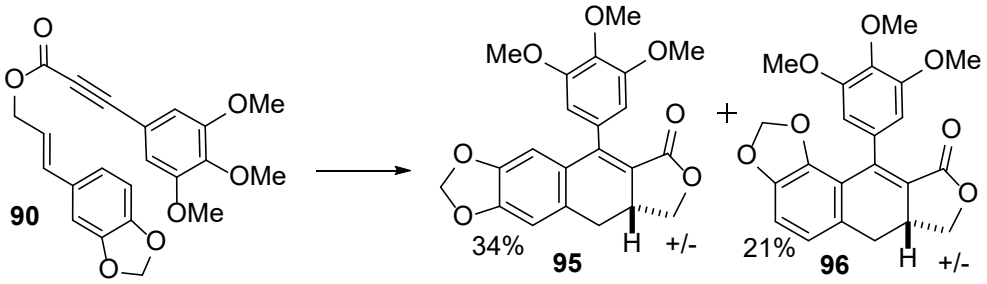


Entry	Additive	Yield
1	DCC DMAP	61%
2	EDCI DMAP	35%
3	DIAD PPh_3	63%

2.3. Applied ISDA Reaction

With the electron rich ester in hand, we proceeded to examine the ISDA reaction. First, the Klemm[7] thermal conditions were applied obtaining a 14% yield of the Diels-Alder adducts with some decomposition products (Table 2). Then, we considered other published conditions. For example, the use of silver (I) hexafluoroantimoniate and base[8] (entry 4) did not furnish the ISDA product, but decomposition was evident by TLC. The decomposition observed may be due to radical side reactions perhaps polymerization of the alkyne styryl ester. In fact, addition of the radical scavenger BHT, improved the yields of the reaction. Several solvents were also screened (DMF, acetonitrile, toluene, benzonitrile), resulting in the conclusion that benzonitrile gave higher yields of the product. Mixtures of solvents such as benzonitrile and acetonitrile did not improve the yields.

Table 2. Some conditions tested for the ISDA reaction on DPT.



Entry	Solvent	Additive	Conditions	Yield
1	DMF 0.01 M	-	160 °C/ 6h	14%
2	PhCN 0.02 M	BHT 20 mol%	160 °C /2h	39%
3	MeCN 0.1 M	BHT 1.5 eq	90 °C/ 8h	11%
4	Toluene 0.1 M	$AgSbF_6$ (1eq) / K_2CO_3 (2 eq)	100 °C/ 18h	-
5	PhCN 0.1 M	BHT 1.5 eq	160 °C/ 2h	56%
6	PhCN 0.02 M	BHT 1.5 eq	160 °C/ 2h	20%

In the analysis of the ISDA products, we isolated two isomers with 1.6:1 selectivity. X-ray crystal structures were obtained from pure samples confirming the conformation for both. In both crystals the cyclohexene ring adopts a half chair conformation avoiding torsional strain. We determined that the rotation of the styryl bond gave rise to both structures. At this point, we hypothesized that a radical mechanism could be responsible for the easy rotation of the bond. Later in chapter 4, an analysis with density functional theory (DFT) calculations showed this radical mechanism to be the highest in energy. Formation of isomers was not quantified by Klemm in earlier work, however we did not expect the formation of this isomer because of high steric interactions. This will also be explained with DFT calculations.

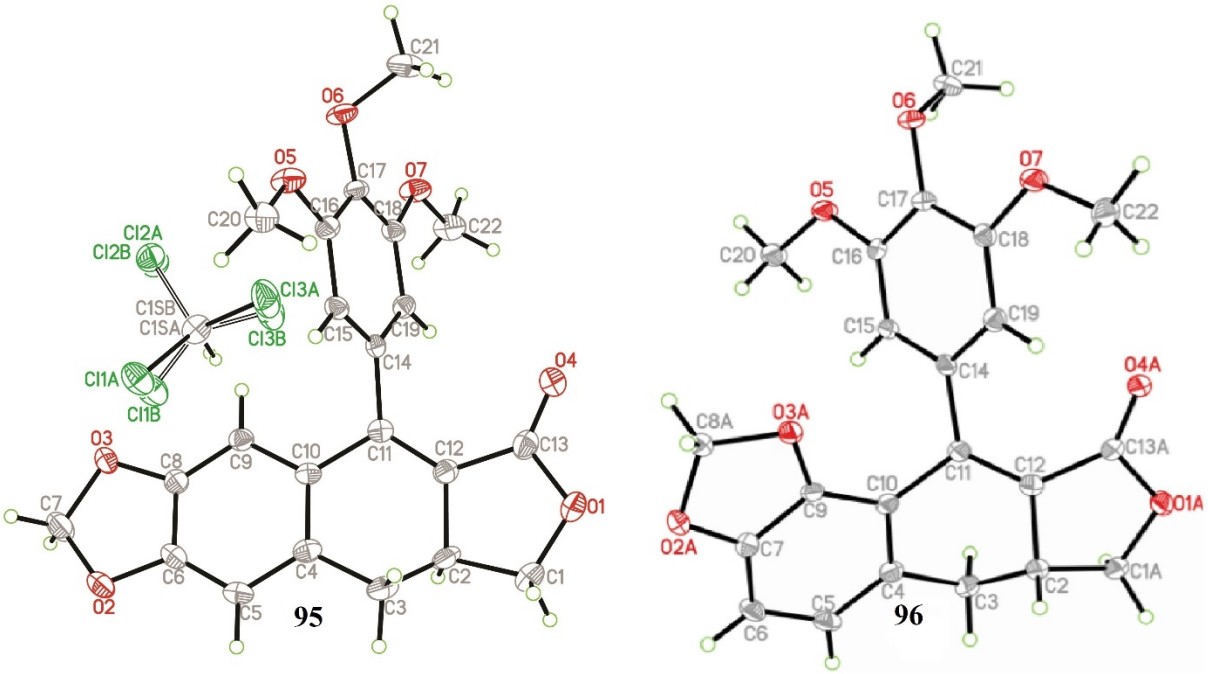
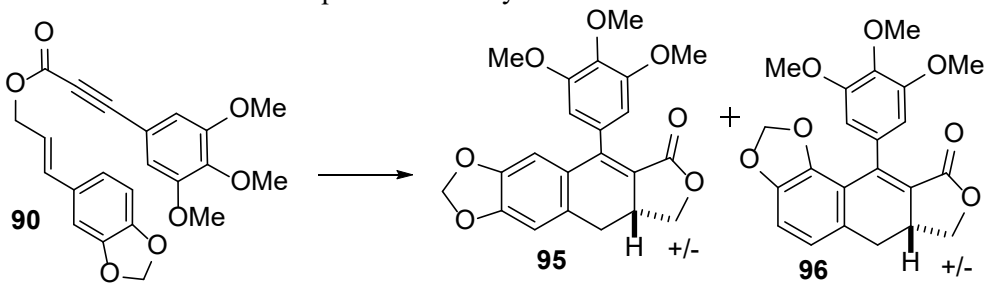
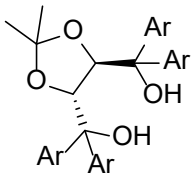


Figure 4. Crystal structures of ISDA cycloadducts **95** and **96**.

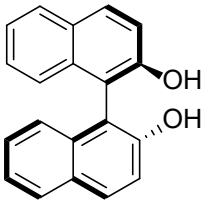
Successful application of the ISDA reaction encouraged us to test Lewis acids and organocatalysts for asymmetric ISDA reactions. We screened several metal catalysts under different conditions (Table 3). Evident decomposition was present in many of the reactions and no Diels-Alder product was produced. Applying BHT to the reaction did not have any favorable effect. Photocatalysis was also tested using $Ru^{II}(bpy)_3$ and methyl viologen as proposed by Yoon,[9] but after 48 hours only starting material was isolated (entry 2). Hydrogen bonding organocatalysts have also been proven successful in Diels – Alder reactions.[10] We tested Binol, Taddol and a urea-like compound, finding that Taddol was able to perform the reaction (entry 9). Even though the yields are low, Taddol has the potential to be developed as an organocatalyst for the ISDA reaction.

Table 3. Development of the asymmetric ISDA reaction.

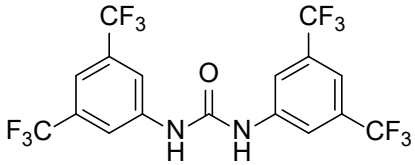




Taddol



R-Binol



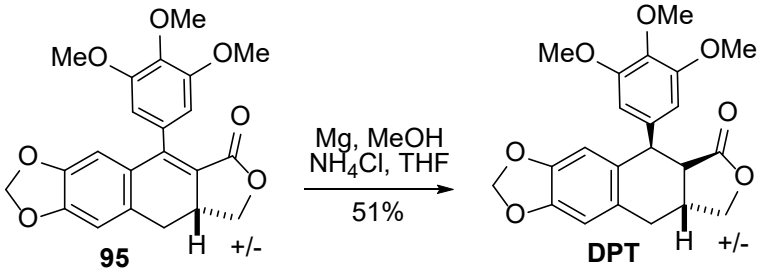
1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea

Entry	Catalyst	Additive	Conditions	Yield
1	$AgSbF_6$ (1)	K_2CO_3 (1)	100 °C/ 18h	NR
2	$Ru(bpy)_3(PF_6)$ (2mol%	$MV(PF_6)_2$ (15mol%)	rt /48h	NR
3	$TfN(Al(Me)Cl)_2$ (2)	-	0 °C/ 1h	decomp.
4	BF_3Et_2O (1.5)	BHT	-78 °C/ 1h	decomp.
5	$Cu(NTf_2)_2$ (5mol%)	-	rt / 2h	NR
6	$ZnCl_2$	BHT	-78 °C/ 2.5h	NR
7	$Sc(OTf)_3$	BHT	-78 °C / 2.5h	NR
8	$MgBr_2$ Et_2O	BHT	-78/2.5	NR
9	Taddol (1)		100 °C / 4h	13%
10	R- Binol (1)		100 °C / 8h	3%
11	Urea (1)		100 °C / 6h	NR

2.4. Completing the Synthesis

Reduction of the double bond of compound **95** gave DPT. Hydrogenation using Pd-based catalyst in high pressure, SmI_2, Na and Li metal with Birch (NH_3, THF) conditions proved to be ineffective in performing the reduction with many side products. Only Mg(0) in MeOH was

effective in giving the cis[11] reduction needed to complete the DPT synthesis (Scheme 27). This stereochemistry was proven by NMR including NOE studies, which are described in the experimental section. ^{1}H and ^{13}C NMR were directly compared to the NMR of the isolated product.[12]



Scheme 27. Reduction with Mg(0) in Methanol to produce DPT

2.5. References

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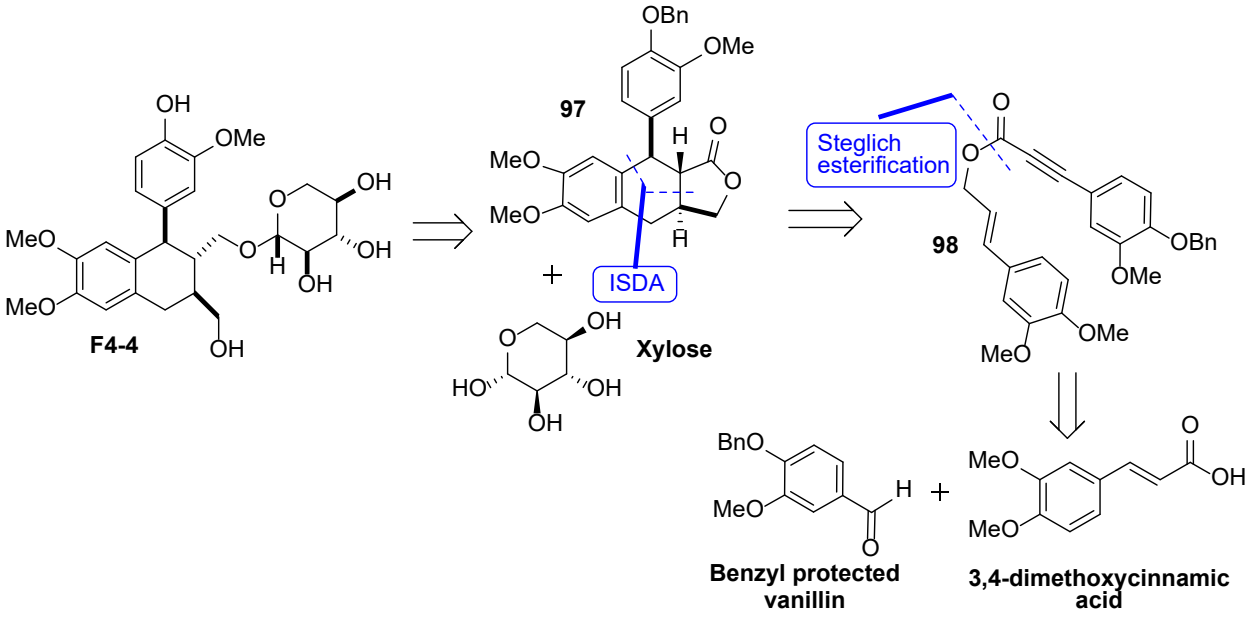
Chapter 3. The Total Synthesis of F4-4

3.1. Retrosynthetic Analysis

Our approach for the synthesis of F4-4 is a thirteen-step synthesis with the key ISDA reaction forming the scaphopetalone-like structure. The advantage of using the ISDA reaction is that the core is created together with a stereocenter in a single step. F4-4 could be constructed from the polycyclic lactone **97** and xylose. This polycyclic lactone is the result of the ISDA reaction of ester **98** which could be constructed from the 3,4-dimethoxycinnamic acid and benzyl protected vanillin, both commercially available.

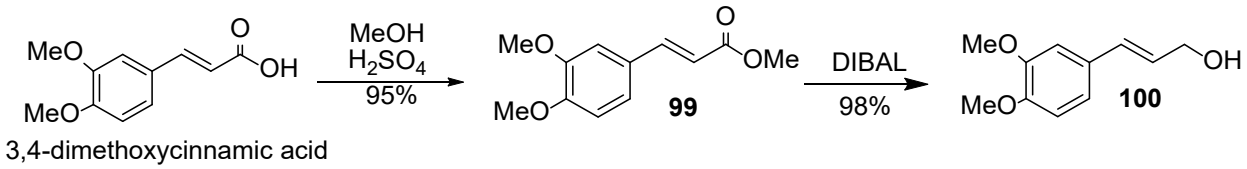


Scheme 28. Retrosynthetic analysis of F4-4.

3.2. Synthesis of Precursors

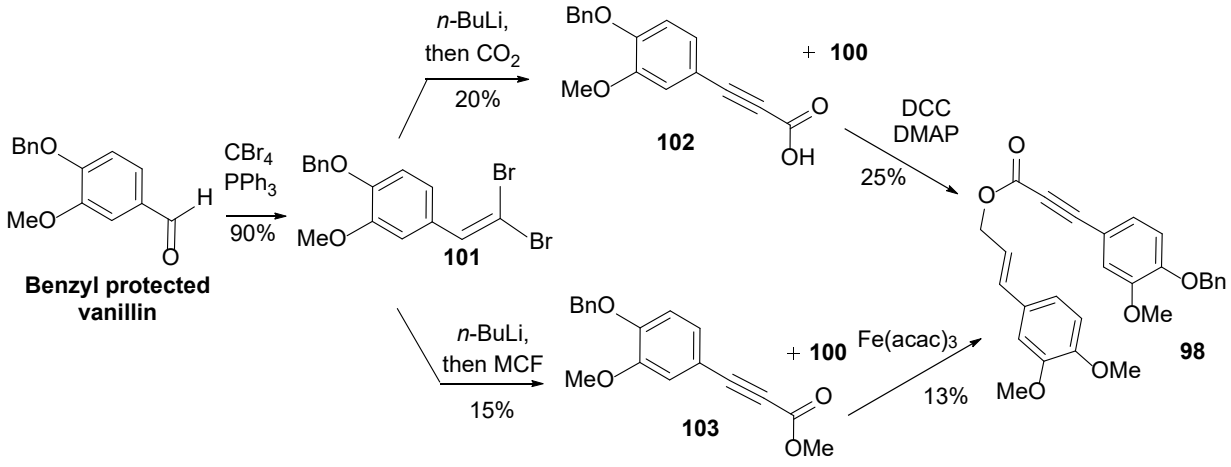
Our synthesis began with readily available 3,4-dimethoxycinnamic acid and benzyl protected vanillin which contain the substituents needed for the assembly of **F4-4**. 3,4-

Dimethoxycinnamic acid was subjected to Fischer esterification[1] giving the cinnamic ester **99** in 95% yield. Reduction[2] with DIBAL-H yielded the cinnamic alcohol **100** in 98% yield.



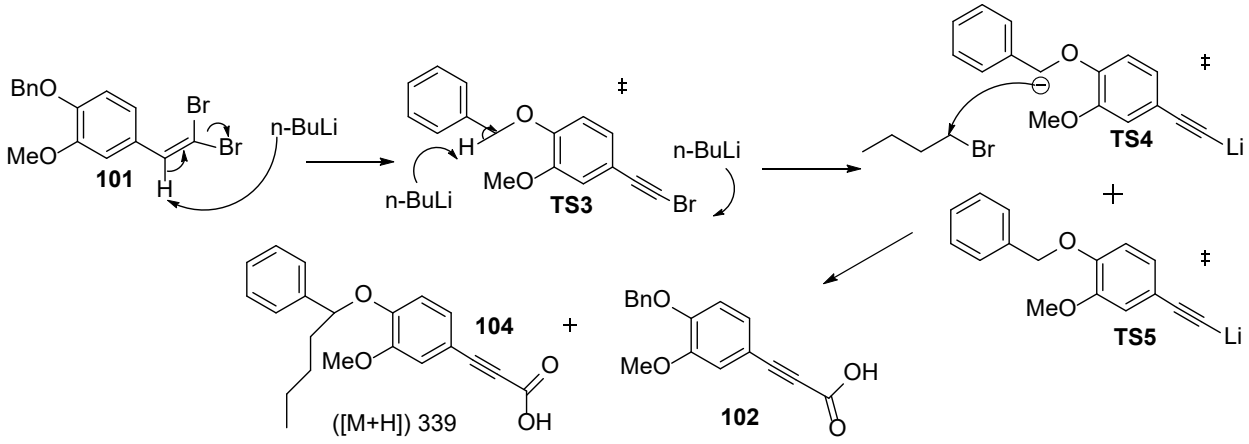
Scheme 29. Synthesis of cinnamic alcohol precursor **102**.

On the other hand, benzyl protected vanillin was converted to the corresponding dibromo compound **101**. This intermediate was reacted under Corey-Fuchs conditions,[3] trapping the acetylene anion with methyl chloroformate[4] to give the alkyne ester **103,** or with carbon dioxide to produce the alkyne acid **102**. This alkyne acid did not perform well under esterification (Steglich esterification[5], and variations with EDCI), meaning appearance of several UV active spots, low yields and difficult purification. Attempts of transesterifications with the alkyne ester **103** and $Fe(acac)_3$ gave[6] multiple UV active spots and low yields of the desired product.



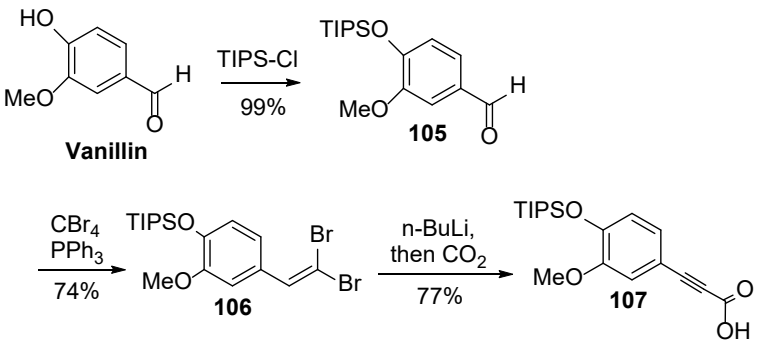
Scheme 30. Synthesis of benzyl protected ester **98**.

Because of the low yields and difficult purification of the esterification or transesterification, we decided to take a closer look at the Corey-Fuchs reaction and the products obtained. Looking at the acid formation, we found that low yields were due to the formation of two acids, one of them a butylated acid **104**. The proposed mechanism for this undesired side reaction is represented in Scheme 31. We discovered that the *n*-BuLi was not only reacting with the hydrogen closest to the dibromide, but also with the acidic hydrogens of the benzyl protecting group. This creates an anion which then attacks the primary halide formed in the reaction in a S_N2 fashion. ^1H NMR showed the peaks for the butylated acid as well as correlation of these peaks by COSY. A mass of MS m/z 339 ([M+H]) further proves the presence of this acid.



Scheme 31. Proposed mechanism for the formation of butylated acid **104**.

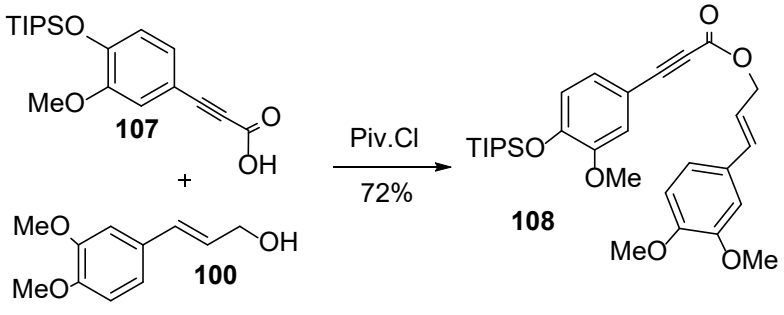
After analyzing the problem presented, trying purifications, and different reaction conditions, we decided to change the protecting group to a triisopropylsilyl (TIPS) group. We started by protecting vanillin with excellent yield (99%). Then this aldehyde was converted to the corresponding dibromoalkene **106**. Treatment under Corey-Fuchs conditions and trapping the acetylene anion with CO_2 produced the alkyne acid **107**.



Scheme 32. Synthesis of the acid precursor **107**.

With the precursors in hand, we focused on the production of the ester. At first, Steglich esterification[7] was explored giving the ester in moderate yields 61%. Purification by flash chromatography was difficult due to coelution of the product with the urea by-product, normally produced in the reaction. We tried changing the conditions and procedure[8] (entry 2, table 4), without improvement. Use of CDI[9] (entry 3, table 4) carbodiimide did not simplify the purification. In hopes of improving the yield and purification, we tested other esterification procedures as outlined in table 4. Use of pivaloyl chloride (entry 9) gave the best results and we obtained pure ester **108** in 72% yield, via a mixed anhydride procedure.[10]

Table 4. Esterification tested conditions.



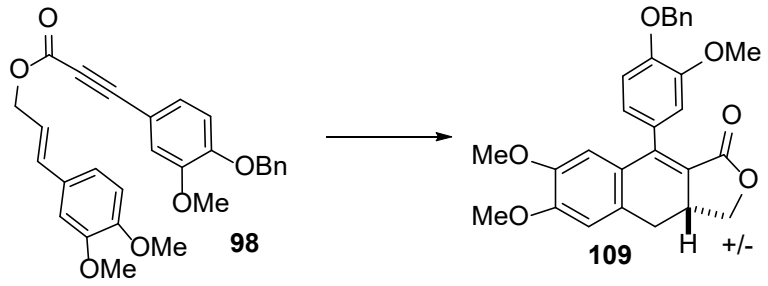
Entry	Esterification	Yield	Obs.
1	Steglich	61%	DCC, DMAP
2	Steglich	52%	Change in procedure, order of addition, etc.
3	Steglich	70%	DIC, impure ester
4	Mitsunobu[11]	47%	
5	Ghosez[10]	56%	
6	BOP-Cl[12]	0.6%	
7	CDI	5%	
8	Pivaloyl Cl	62%	Pivaloyl Cl 1.2eq
9	Pivaloyl Cl	72%	Pivaloyl Cl 1eq

3.3. Applied ISDA Reaction

Two different substrates were tested for F4-4 under the ISDA conditions. These substrates relate to the different protecting groups. We started with experiments on the benzyl protected ester. Some of the original conditions were tested (table 5) including Klemm's thermal conditions (entry 1),[13] silver catalyst and base (entry 3), photoredox catalysis (entry 4),[14] among others. Good insights came from these experiments. First, decomposition of starting material was evident by TLC with the original thermal conditions and Jiansheng's conditions.[15] These results indicated radical side reactions, including polymerization of the alkyne allyl ester, were

occurring. Second, polar solvents, specifically benzonitrile, increased the yields of the reactions. Third, addition of BHT, a radical scavenger, increased the rate of formation of the desired ISDA product.

Table 5. ISDA experiments for benzyl protected ester cyclization.



Entry	Solvent	Additive	Conditions	Yield and obs
1	DMF 0.01 M	-	170 °C/ 6h	24%
2	Toluene 0.1M	$AgBF_4$ (1eq)	115 °C/ 1h	decomp.
3	Toluene 0.1 M	$AgSbF_6$ (1eq) / K_2CO_3 (2 eq)	120 °C/ 24h	NR
4	CH_3CN 0.08 M	Ru^{II}(bpy) 3mol%	rt	NR
5	CH_3CN 0.05M	BHT 10mol%	80 °C/ 25h	21%
6	PhCN 0.02M	BHT 10mol%	130 °C/ 4h	44%
7	PhCN 0.1 M	BHT 1.5 eq	160 °C/ 2h	53%
8	PhCN 0.02 M	BHT 1.5 eq	160 °C/ 2h	30%

After obtaining the TIPS protected ester, testing was done with different conditions not only to the recently found conditions (PhCN and BHT), but also with original conditions and others that were mentioned in the background. Again, we found that benzonitrile and BHT were the best conditions for this substrate and we obtained an overall yield of 54%. A closer look of this reaction revealed the formation of two isomers. The dihydronaphthol **110** is the major

product (38%) and a naphthol **111** is formed as the minor product (16%). In the synthesis of DPT, the isomers formed due to rotation in the diene. In this case, rotation may give a very sterically hindered product which was not isolated. Loss of hydrogen H_2 gives naphthol **111.** Different solvents, as outlined in table 6 were tested including water which has been known to promote Diels-Alder reactions.[16]

As part of this studies, an X-ray crystal structure was obtained from a pure sample of **111** confirming the conformation of the minor product (Figure 5).

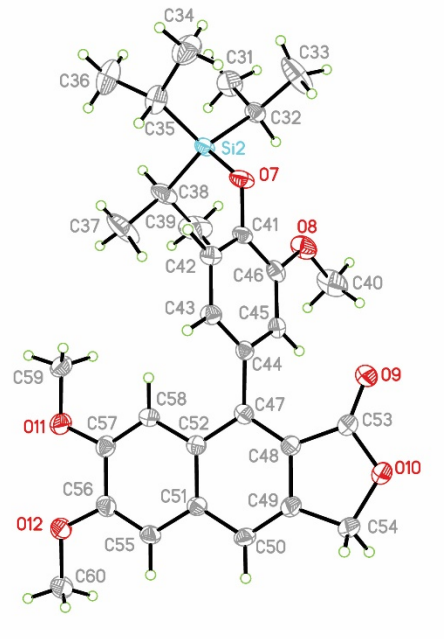
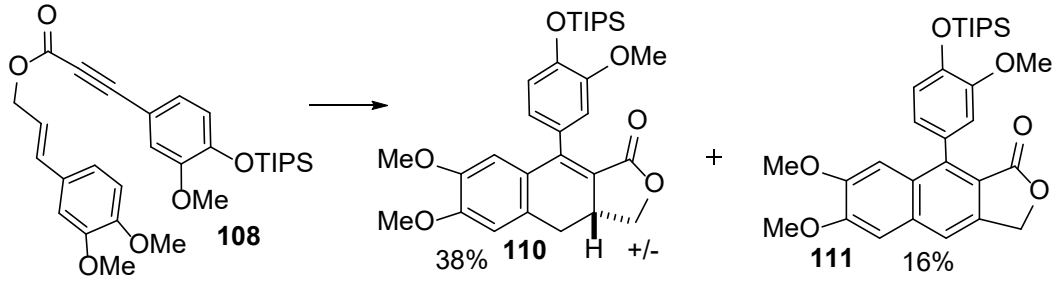


Figure 5. X-ray crystal structure of naphthol **111**.

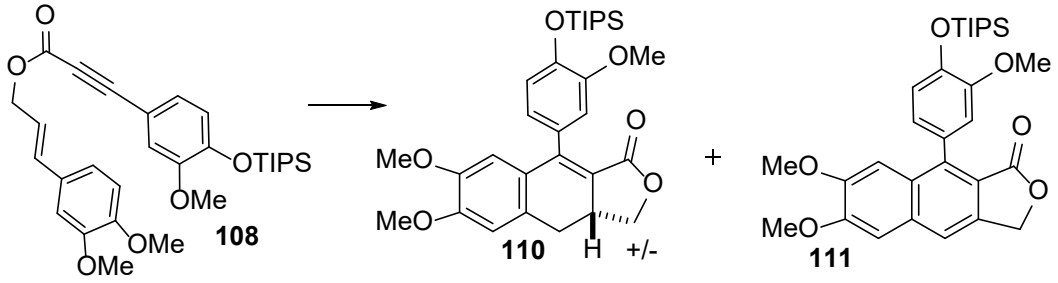
Table 6. Some of the experiments tested on TIPS protected ester.



Entry	Solvent	Additive	Conditions	Yield and obs
1	DMF 0.05M	-	145 °C/ 3h	5%
2	DMF 0.07M	-	145 °C°/3h	10%
2	DCE 0.1M	P_4-*t*-Bu 10mol%	90 °C/7h	1.4%
3	DCM 0.01M	Phosphoric acid 10mol%	rt / 72h	NR
4	H_2O 0.05M	BHT (1.5eq)	80 °C / 1h	13%
5	CH_3CN 0.05M	BHT (1.5eq)	80 °C/7h	5%
6	PhCN 0.02M	BHT (1.5eq)	145 °C/ 6h	54%
7	THF 0.02M	BHT (1.5 eq)	70 °C/ 55h	4%
8	dioxane	BHT (1.5 eq)	100 °C/ 8h	5%
9	trifluoro toluene 0.02M	BHT (1.5eq)	100 °C/ 6h	3.4%
10	acetic anhydride 0.05M	BHT (1.5eq)	130 °C/ 5h	NR
11	DMF 0.05M	Taddol 27mol%	100 °C/ 29h	12%

Microwave conditions were also explored for the ISDA reaction with substrate **108**.[17] These conditions gave poor results (Table 7). More experimentation with different solvents and additives may be needed.

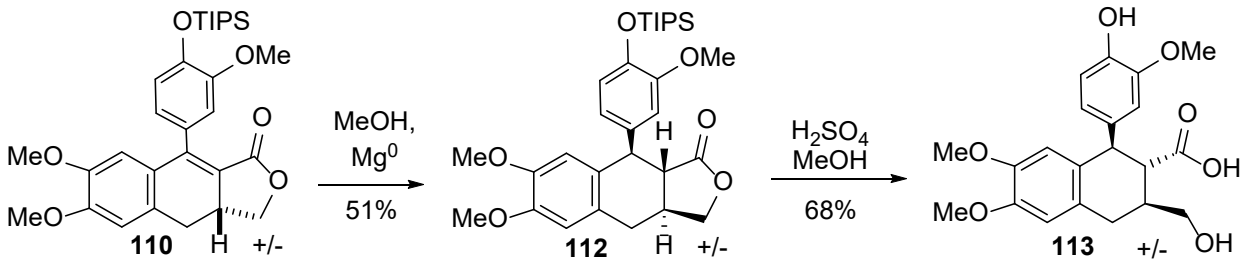
Table 7. MW conditions tested on TIPS protected ester.



Entry	Solvent	Additive	Conditions	Yield and obs
1	DMF 0.05M	-	130 °C/ 15min	5%
2	DMF 0.05M	BHT (1.5eq)	130 °C/ 20 min	13%
2	toluene 0.07 M	BHT (1.5eq)	130 °C/ 30 min	1.4%
3	Toluene 0.07M	-	130 °C / 30 min	1.5%
4	Trifluoro toluene 0.04M	-	130 °C / 1h	2%
5	Trifluoro toluene 0.04M	BHT (1.5eq)	130 °C / 1h	3%
6	PhCN 0.04M	-	130 °C / 1h	12%
7	PhCN 0.04M	BHT (1.5 eq)	130 °C / 1h	4%

3.4. Completing the Synthesis

After successful application of the ISDA reaction with our new found conditions we proceeded to reduce the double bond in compound **110**. Reduction with Red-Al[18] and L-selectride proved to be ineffective resulting in many side products. Only Mg(0) in MeOH was effective in giving the reduction needed[19] in 51% yield (Scheme 33).



Scheme 33. Reduction and opening of the lactone on F4-4.

We obtained an X-ray crystal structure of compound **112**, confirming the conformation of the reduced compound. The image shows the trans configuration needed and the half chair conformation adopted by the cyclohexane ring to avoid torsional strain.

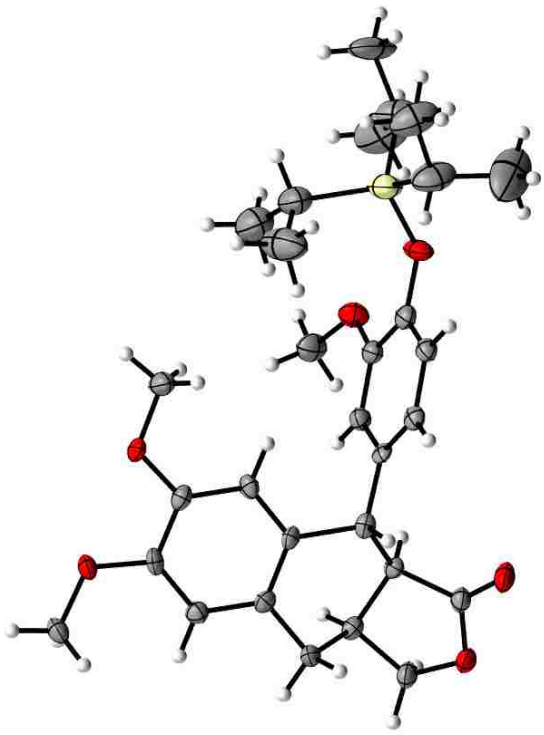


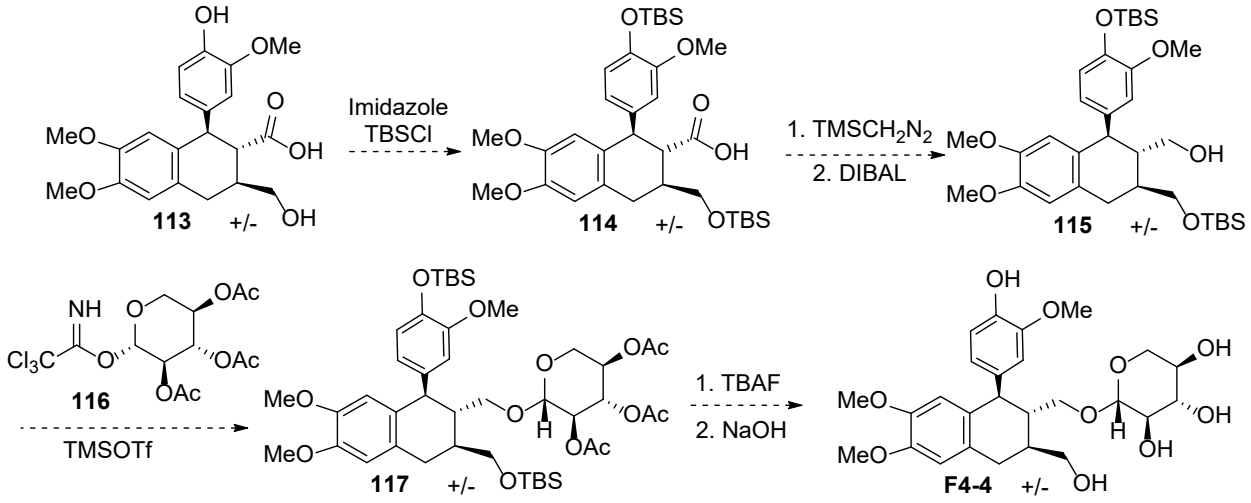
Figure 6. X-ray crystal structure of the reduction product **112**.

The reduction was followed by opening of the lactone. Basic conditions[20] (NaOH or KOH in ethanol or methanol) were ineffective. We have deduced that the lactone is being reformed again in these basic conditions. We then explored acid conditions[21] obtaining

compound **113** in moderate yields. These conditions removed the TIPS protecting group from the phenol, but protection of the alcohol is needed for the next steps, thus it does not affect the future work.

3.5. Future Work

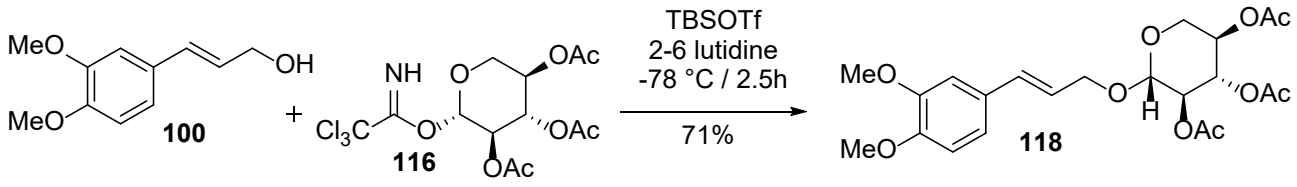
Five more steps are needed to finish the synthesis of F4-4, as noted in scheme 33. Protection of the phenol and alcohol is necessary for esterification on the acid. Trimethylsilyl diazomethane ($TMSCH_2N_2$) is used for the esterification[22] and subsequent reduction with DIBAL-H will produce the primary alcohol **115**. Schmidt glycosidation with acetyl alpha xylose trichloroacetimate gives compound **117**. Finally, deprotection with base and TBAF gives the **F4-4** product.



Scheme 34. Steps to complete synthesis of F4-4.

To make sure that glycosylation is possible we performed a model glycosidation of alcohol **100** with acetate protected xylose. At first, we explored bromine acetate protected xylose[23] without any favorable results. The Schmidt glycosidation[24] at -78 °C gave us the best result with alcohol **100**. In order to perform the reaction, we synthesized the trichloroacetimate compound **116** according to the work published by Lin[25] and coworkers. This is a known 3-step

synthesis starting from xylose. Xylose is first acetylated using acetic anhydride and anhydrous sodium acetate followed by selective deprotection on the anomeric carbon using hydrazine acetate and finally treatment with trichloroacetimidate.



Scheme 35. Schmidt glycosidation model experiment with alcohol **102**.

In conclusion, we have accomplished a synthesis of the core of F4-4 using a ISDA reaction. Four more steps are necessary to obtain F4-4.

3.6. References

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Chapter 4. Mechanistic Studies

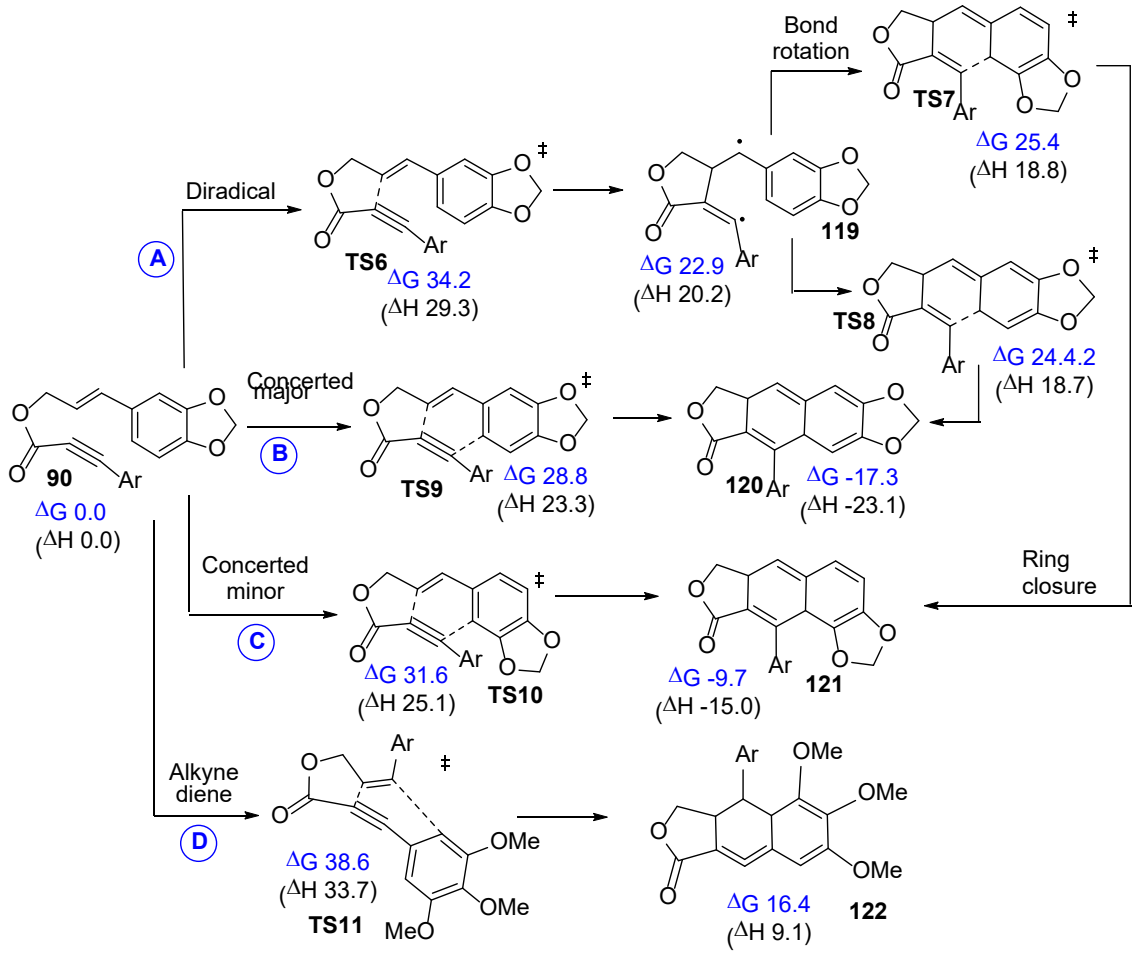
To better understand the ISDA reaction, knowing that it is impossible to observe the intermediates of this reaction, we turned to density functional theory (DFT) calculations. These calculations helped us to understand the mechanism of the [4+2] cycloaddition, and the [1,3]-hydrogen shift necessary for aromatization, together with the production of different isomers and identify the rate determining step of the reaction. This knowledge is vital for future development and application of the ISDA reaction. Calculations were performed in Gaussian 09[1] with M06-2X/6-31G(d,p) functional and an ultrafine integration grid.[2] The connection between starting material, intermediates and products was verified with intrinsic reaction coordinate (IRC). Local minimum and second order saddle point (transition state) searches were verified with frequency calculations. The free energies reported correspond to (U)M06-2X/def2TZVP//(U)M06-2X/6-31G(d,p). We used the SMD solvation model for benzonitrile.[3] Spin projections were performed on the open shell singlet radicals in order to remove triple spin wave contamination providing a better estimate for the open-shell singlet energy.[4] We examined possible pathways for both the [4+2] cycloaddition and the [1,3]-hydrogen shift completing the ISDA reaction of the substrate DPT.[5]

4.1. [4+2] Cycloaddition

First, we considered the styryl functionality as diene and the alkynyl part as dienophile, pathways A, B and C on Scheme 36. Formation of the isolated isomers could result from a diradical intermediate **119** (pathway A) with lactone formation. This radical intermediate is stabilized by delocalization on to the aryl group. Ring closure could happen at two different aryl positions generating the regioisomers **120** and **121**. IRC showed the connection of **TS6** to diradical intermediate **119** which later forms the cycloadducts that were isolated.

The concerted mechanisms for both isomers were also considered (pathways B and C). In this case rotation of the styryl bond would produce both regioisomers. The transition states showed a highly asynchronous relation with a difference of 0.8 Å in the partial C–C bond forming distances (formation of the two C-C bonds showed in **TS9** and **TS10**). This means that the second partial C – C bond has enough of a stabilizing effect to give a lower energy transition state in pathways B and C compared with **TS6** of pathway A (ΔG 28.8 for **TS9** vs ΔG 34.2 kcal/mol), (Scheme 36).

Due to high conjugation and electron rich character of the substrate, we also considered a pathway with the diene and dienophile reversed (pathway D, Scheme 36). In this pathway, the cycloadduct **122** has a highly strained allenyl type structure making this pathway higher in energy and not likely to operate.

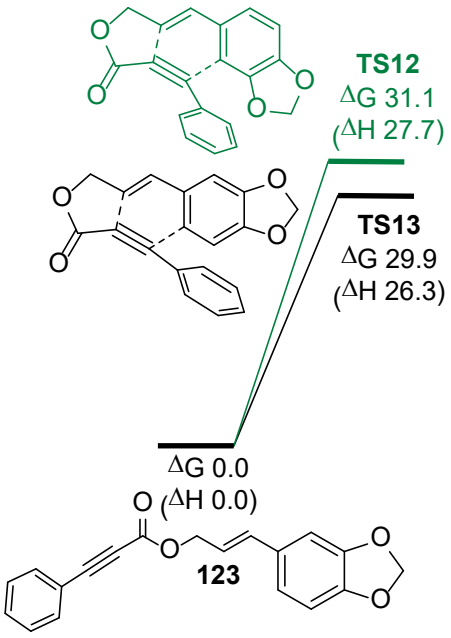


Scheme 36. [4+2] cycloaddition pathways calculated by DFT (kcal/mol).

We analyzed the difference between the transition states **TS9** and **TS10** compared with our experimental results. While the ΔΔH between these two transition states is only 1.8 kcal/mol, correlating with the experimental results, the ΔΔG of 2.8 kcal/mol overestimates the experimental. To obtain more accurate results, we performed thermochemical corrections at 433K (recalculation of pathways using experimental temperature) giving a ΔΔG between **TS9** and **TS10** of 1.9 kcal/mol which is closer to the experimental product ratio.

In an effort to better understand the selectivity for **120** over **121**, we performed calculations on the less sterically hindered starting material **123** (Scheme 36). Calculation of the

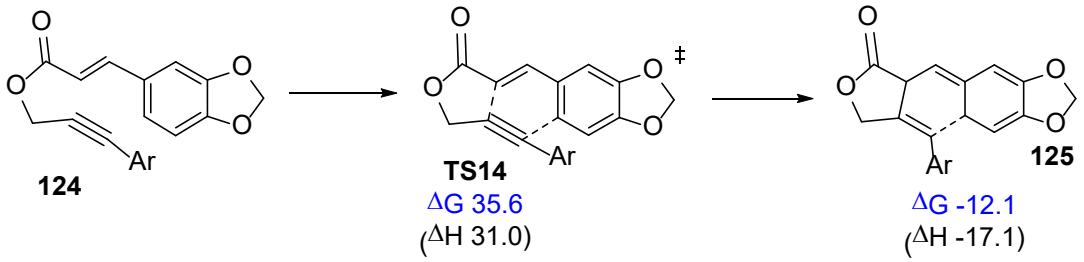
concerted mechanisms with this starting material gave a ΔΔG of 1.2 kcal/mol and ΔΔH 1.4 kcal/mol meaning that steric interactions affect the formation of the isomers. We hypothesized that bulky substituents would eliminate the formation of structures like cycloadduct **121**. This is confirmed by the ISDA reaction on F4-4 where the substituents on the aryl groups are bulkier and there was no evidence of an isomer similar to **121**, instead naphthol product was formed.



Scheme 37. Concerted mechanism with less hindered starting material.

Carbonyl groups have been known to be a significant accelerating factor in Diels-Alder reactions. Conjugation of a carbonyl with the dienophile withdraws electrons from the system and lowers the gap between the HOMO (highest occupied molecular orbital) and the LUMO (lowest unoccupied molecular orbital). To explore the relationship of the carbonyl in this specific example, we calculated concerted and stepwise single mechanisms with substrate **124** in which the carbonyl has been moved to be conjugated to the diene (Scheme 38). The ΔG of the concerted pathway is now 35.6 kcal/mol compared with **TS9** with an energy of 28.8 kcal/mol being raised almost 7 kcal/mol by the change of the carbonyl. This suggests that the position of

the carbonyl plays a more important role than the donation character of the aryl substituents in the system.

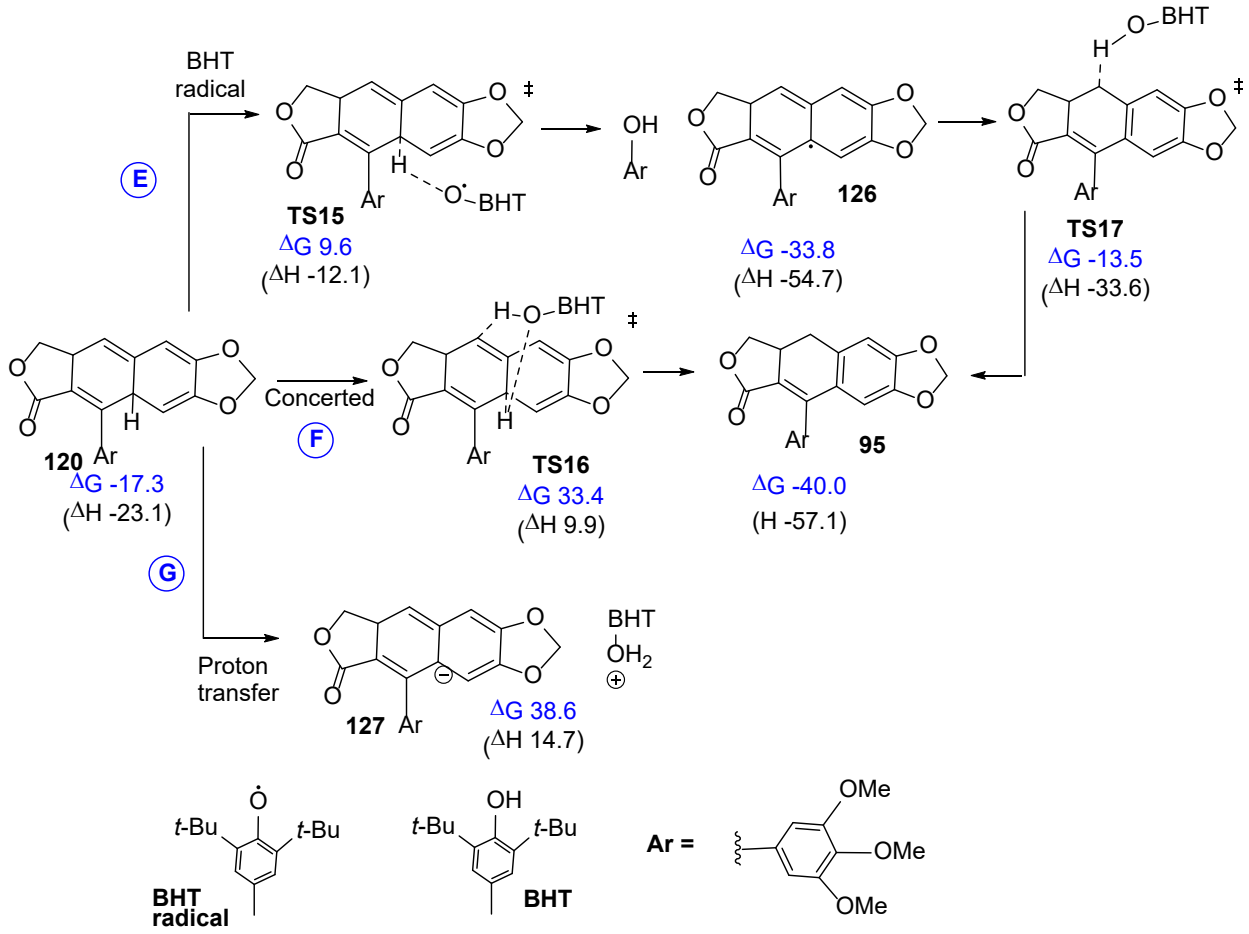


Scheme 38. Change of carbonyl DFT calculated.

4.2. [1,3]-Hydrogen Shift

In order to rearomatize the ring after the [4+2] cycloaddition, a [1,3]-hydrogen shift is necessary. Unimolecular hydrogen shift is unlikely. According to Hoffmann and Woodward rules,[6,7] the thermal [1,3]-hydrogen shift is suprafacial involving 4 electrons, which is not allowed. For this reason, we examined different pathways involving butylated hydroxytoluene (BHT). BHT was introduced in the reaction as a radical scavenger to prevent radical side reactions. It is well known that this compound reacts with trace amount of oxygen to produce radicals.[8] In fact, there are studies of the formation and stability of BHT radicals.[9] Therefore, it was expected that at least small quantities of BHT radicals would be present. We proposed that BHT radicals could assist with the [1,3]-hydrogen shift. To evaluate this hypothesis, we calculated three pathways shown in Scheme 39 (pathways E, F and G). These pathways were evaluated in both major and minor cycloadducts, finding similar results (see experimental details for supporting data on minor product). With these calculations we found that, effectively, the pathway E, using BHT radical is the lowest in energy having a barrier of 26.9 kcal/mol, being also lower than the concerted [4+2] cycloaddition. The concerted pathway F and the proton transfer pathway G proved to be higher in energy, even more than the [4+2] cycloaddition. Other

radical pathways (presence of oxygen) may be operative in this case but they were beyond the scope of this experiment.



Scheme 39. BHT assisted [1,3]-hydrogen shift.

We can conclude that the rate determining step for the ISDA reaction is the [4+2] cycloaddition, and focus should be given to this part of the reaction in order to improve yields and selectivity. The mechanism of this [4+2] cycloaddition is concerted, yet highly asynchronous, being lower in energy than the diradical mechanism. Small energy differences between the major and minor product found experimentally are controlled by steric interactions between the substituents. The [1,3]-hydrogen shift is assisted by BHT radical.

4.3. References and Notes

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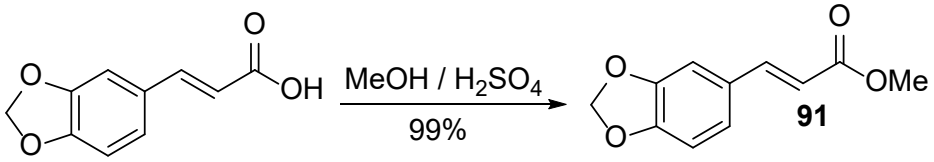
Chapter 5. Experimental Details and Data

5.1. General Methods and Materials

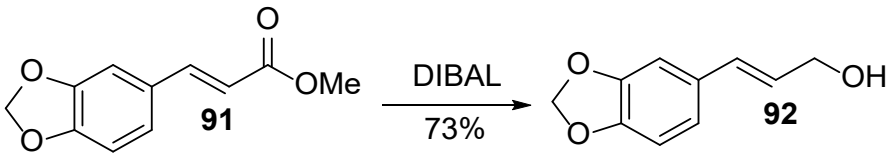
Sensitive reactions to air and water were performed in flame-dried or oven dried glassware under Argon. Air and moisture sensitive reagents were introduced via dry syringe. Solvents used in the reactions (THF, DCM, and toluene) were drawn from a pressurized dry solvent system. In this system, HPLC or similar grade solvent is flushed through activated alumina casks and stored under argon, thus keeping the solvent dry. Benzonitrile was used directly form the bottle. Triethylamine was distilled before use. Purification through flash chromatography was performed using 230 x 400 mesh silica gel. Thin-layer chromatography (TLC) was performed with glass pre-coated silica plates (silica gel 60 F_{254}, 0.255 mm) acquired from Merck. Spots on TLC plates were evident using UV_{254}. All ^{1}H and ^{13}C NMR were obtained with 500 MHz and 125 MHz using deuterated chloroform (7.27 ppm ^{1}H NMR, 77.36 ppm ^{13}C NMR) as reference with or without TMS (0.0 ppm). Signals for ^{1}H NMR are reported as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet).[1] Agilent multi-mode source mass spectrometer was used for all the mass spectral data.

5.2. Procedures from Chapter 2: DPT Synthesis



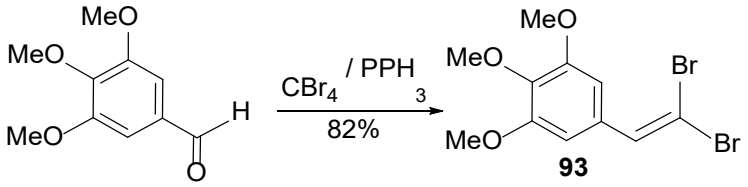
Methyl (E)-3-(benzo[d][1,3]dioxol-5-yl) acrylate 91. To a solution of 3,4-(Methylenedioxy) cinnamic acid (5.0 g, 25.9 mmol) in methanol (0.4 M, 65 ml) was added carefully and slowly concentrated H_2SO_4 (3.1 mL). The mixture was heated at reflux (65 °C) overnight. The reaction mixture was cooled to room temperature and the white precipitate (product) was filtrated. Solid

$NaHCO_3$ (6.1g) was slowly added to the solution. The solution was added to a separatory funnel containing methylene chloride and washed with water (3 x 50 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated. The resulting solid was crystallized with ethyl acetate and hexane (5.27 g, 99%) generating **91** as a white solid. Characterization data: **TLC R_f** 0.6; **mp** = 132-136 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) 3.78 (s, 3H), 5.99 (s, 2H), 6.26 (d, *J*= 15.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J*= 8Hz, 1H), 7.02 (s, 1H), 7.59 (d, *J*= 15.8, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 51.63, 101.56, 106.45, 108.53, 115.67, 124.45, 128.78, 144.55, 148.32, 149.61, 167.60; **IR** 1703, 1625 cm^{-1}; **MS** m/z calculated for $C_{11}H_{10}O_4$ 206.0579 found 206.0566, ([M+H]) 207.0639, ([M+Na]) 229.0449

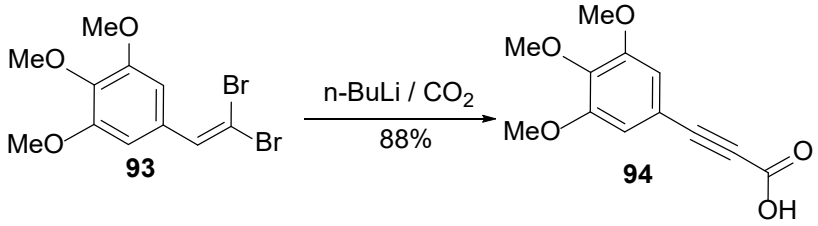


(E)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol 92. DIBAL-H (16 mL, 1.0M in heptane, 2.5 equiv.) was slowly added via syringe to a stirred solution of methyl (E)-3-(benzo[d][1,3]dioxol-5-yl) acrylate **91** (1.3 g, 6.31 mmol) in dry methylene chloride (0.1 M, 63 mL) cooled to 0 °C (ice water bath) under Argon gas. The mixture was allowed to warm to room temperature for 2h. Methanol (7 mL) was slowly added to the mixture, followed by aqueous HCl (1 M, 61 mL). The mixture was added to a separatory funnel containing water (10 mL). The aqueous layer was extracted with methylene chloride (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$). The dry organic layers were submitted to silica gel chromatography (50% EtOAc/hexanes) to obtain the desired alcohol **92** (73%, 800 mg) as a white solid. Characterization data: **TLC R_f** 0.4 (35% ethyl acetate/hexanes); **mp** = 75.8-78.1 °C; **^{1}H NMR** ($CDCl_3$, 500MHz) 4.29 (d, *J*= 4.1 Hz, 2H), 5.96 (s, 2H), 6.17-6.23 (obs m, 1H), 6.53 (d, J= 15.9,

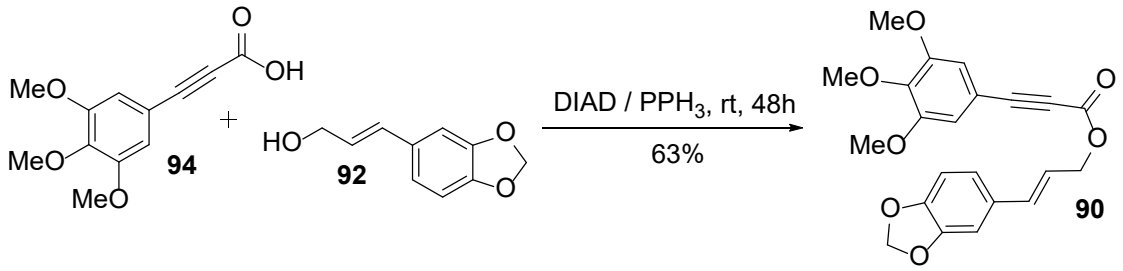
1H), 6.76 (d, J= 7.9, 1H), 6.81 (d, J= 7.9, 1H), 6.93 (s,1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 63.76, 101.09, 105.74, 108.30, 121.18, 126.67, 130.99, 131.11, 147.31, 148.02; **IR** 3264, 2888, 1445 cm^{-1}; **MS** m/z calculated for $C_{10}H_{10}O_3$ 178.0630 found 178.0629, ([M+Na]) 201.0521



5-(2,2-dibromovinyl)-1,2,3-trimethoxybenzene 93. To a solution of triphenylphosphine (3 equiv. 45.8 mmol, 12,03 g) in dry methylene chloride (0.3 M, 153 mL) cooled to 0 °C under Argon gas, was added carbon tetrabromide (1.5 equiv, 22.94 mmol, 7.60 g) and stirred at 0 °C for 15 min. To the solution, was added 3,4,5-trimethoxybenzaldehyde (3.0 g, 15.29 mmol) in dry methylenne chloride (2 M, 8 mL). The resulting mixture was stirred at rt overnight. The mixture was triturated with cold hexanes (45 mL) and filtered (paper cone) to remove excess triphenylphosphine. The filtrate was concentrated and subjected to silica gel chromatography (10% EtOAc/hexanes) to obtain the dibromo olefin product **93** (82%, 4.39 g) as a yellow solid. Characterization data: **TLC R_f** 0.6 (35% ethyl acetate/hexanes); **mp** = 57-60 °C; **^{1}H NMR** ($CDCl_3$, 500MHz) 3.85 (s, 6H), 3.86 (s, 3H), 6.78 (s, 2H), 7.39 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 56.14, 60.83, 88.76, 105.73, 130.54, 136.60, 138.29, 152.97; **IR** 3004, 2835, 1577 cm^{-1}; **MS** m/z calculated for $C_{11}H_{12}Br_2O_3$ 349.9153 found 349.9147, ([M+H]) 350.9229, ([M+Na]) 372. 9017.

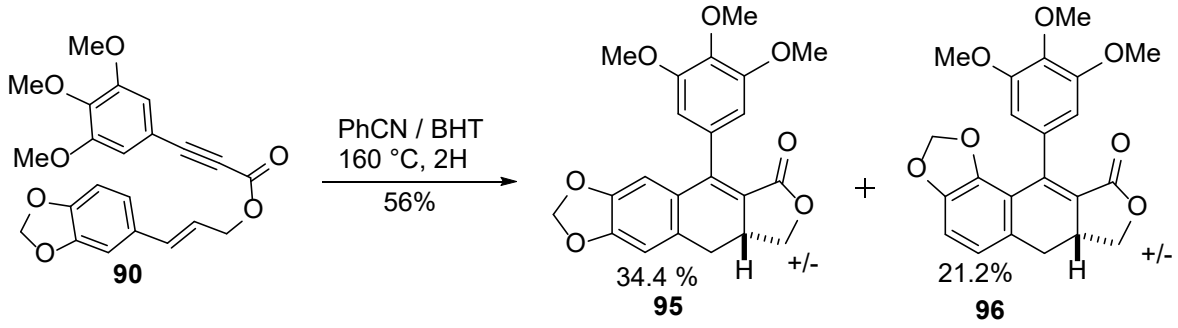


3-(3,4,5-trimethoxyphenyl) propiolic acid 94. To a solution of 5-(2,2-dibromovinyl)-1,2,3-trimethoxybenzene **93** (3.30 g, 9.43 mmol) in dry THF (0.6 M, 16.00 mL) under Argon gas cooled to -78 °C (dry ice / acetone bath) was added a solution of n-butyllithium (2.5 M, 1.9 equiv, 17.92 mmol, 7.16 mL) The dark brown solution was stirred for 20 min at -78 °C and solid carbon dioxide (crushed, 10 equiv, 120 mmol, 5.00 g – excess) was added at once. The mixture was gradually allowed to warm to rt stirring continuously. The mixture was poured into water in a separatory funnel and a 1:1 mixture of EtOAc/ hexanes (50 mL) was added. The aqueous part was acidified (pH 2 approximately) with HCl (6.0 N) and extracted with ethylacetate (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to access the desired propiolic acid **94** (88%, 1.95 g) as an orange solid. Characterization data: **TLC R_f** 0.10 (35% ethyl acetate /hexanes), **mp**= 137-142 °C, **^{1}H NMR** ($CDCl_3$, 500MHz) 3.86 (s, 6H), 3.89 (s, 3H), 6.85 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 56.26, 61.07, 79.44, 89.44, 110.64, 113.69, 141.23, 153.15, 158.35; **IR** 3472, 2951, 2213, 1704 cm^{-1}; **MS** m/z calculated for $C_{12}H_{12}O_5$ 236.0685, ([M+H]) 237.0741



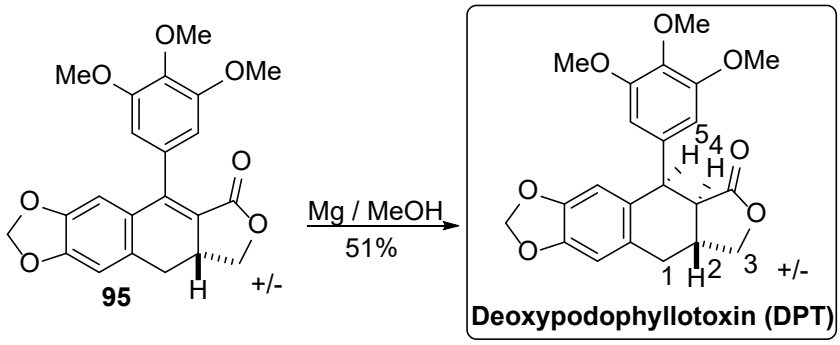
(E)-3-(benzo[d][1,3]dioxol-5-yl) allyl 3-(3,4,5-trimethoxyphenyl) propiolate 90. To a THF solution (0.2 M, 7 mL) of (E)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol **92** (1 equiv. 1.4 mmol, 0.25 g) and 3-(3,4,5-trimethoxyphenyl) propiolic acid **94** (1.2 equiv, 1.68 mmol, 0.4 g) was added diisopropyl azodicarboxylate (1.2 equiv, 1.68 mmol, 0.35 mL) at once. The solution was cooled to 0 °C and solid triphenylphosphine (1.2 equiv, 1.68 mmol, 0.44 g) was added along

with an additional 2 mL of THF. The solution was then warmed rt and stirred for 48 hr. The solution was concentrated and subjected to silica gel chromatography (30% ethyl acetate/hexanes) to yield the desired ester as a white solid **90** (63%, 357 mg). Characterization data: **TLC R_f** 0.46; **mp** = 128.0 -129.6 °C; **^{1}H NMR** ($CDCl_3$, 500MHz) 3.86 (s, 6H), 3.89 (s, 3H) 4.86 (d, *J*= 6.4 Hz, 2H), 6.14-6.20 (obs m, 1H), 6.64 (d, J= 15.9, 1H), 6.77 (d, J= 9, 1H), 6.85 (s, 2H), 6.86 (d, J= 1.1, 1H), 6.95 (s,1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 56.24, 61.03, 66.68, 87.02, 101.21, 105.86, 108.33, 110.38, 114.14, 120.13, 121.75, 130.39, 135.35, 153.16, 153.88; **IR** 2853, 2217, 1708, 1700 cm^{-1}; **MS** m/z calculated for $C_{22}H_{20}O_7$ 396.1209 found ([M+H]) 397.1278, ([M+Na]) 419.1105 .



(*dl*)-5-(3,4,5-trimethoxyphenyl)-8a,9-dihydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(8H)-one (major) 95. To a solution of (E)-3-(benzo[d][1,3]dioxol-5-yl)allyl 3-(3,4,5-trimethoxyphenyl)propiolate **90** (1 equiv, 0.1 g, 0.25 mmol) in benzonitrile (0.1 M, 2.5 mL) was added 2,6 di-t-butylhydroxytoluene (BHT, 1.5 equiv, 0.37 mmol, 0.08 g). The mixture was heated at reflux (160 °C) for 2h. The mixture was cooled to rt, diluted with hexane (5 mL) and subjected to radial chromatography (25% EtOAc /hexanes) to yield two Diels-Alder products (overall 56%, 55.1 mg) the major product **95** as white solid (34.4% yield, 34.1 mg) and the minor product **96** as a green solid (21.2% yield, 21mg). Characterization data for ***Major Diels-Alder*** product **95**: **TLC R_f** 0.12 (35% EtOAc/hexanes) **mp** = 240-242 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz)

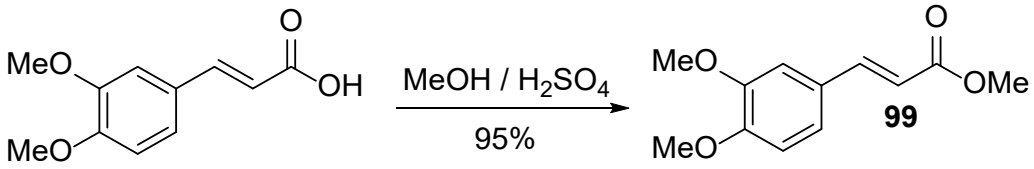
2.81 (obs t , *J*= 15.77 Hz, 1H), 2.95 (dd, *J*= 6.6, 8.32 Hz, 1H), 3.44-3.36 (m, 1H), 3.85 (s, 6H), 3.93 (s, 3H), 4.02 (obs t, *J*= 8.81 Hz, 1H), 4.71 (obs t, *J*= 8.81, 1H), 5.98 (s, 2H), 6.10 (s, 1H), 6.52 (s, 1H), 6.56 (s, 1H), 6.78 (s, 1H) **^{13}C NMR** ($CDCl_3$, 125 MHz) 33.33, 35.80, 56.16, 61.03, 67.95, 70.87, 101.84, 103.64, 107.22, 108.61, 109.49, 119.11, 119.90, 129.64, 130.74, 146.80, 147.28, 148.70, 152.96; **IR** cm^{-1} 2917, 1744; **MS** m/z calculated for $C_{22}H_{20}O_7$ 396.1209 found ([M+H]) 397.1288. ***Minor Diels-Alder*** product **96: TLC R$_f$** 0.14 (35% EtOAc/hexanes) **mp** = 194-197 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) 2.75 (obs t *J*= 15.04 Hz, 1H), 2.97 (dd, *J*=5.99, 8.55, 1H) 3.34-3.41 (m, 1H), 3.84 (s, 6H), 3.92 (s, 3H), 4.02 (obs t, J= 8.68, 1H), 4.69 (obs t, J= 8.93, 1H), 5.63 (s, 1H), 5.72 (s,1H), 6.62 (s, 2H), 6.75 (s, 1H), 6.76 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 33.52, 36.56, 56.20, 60.96, 70.59, 101.12, 109.12, 118.46, 120.40, 123.03, 129.04, 129.61, 144.36, 146.92, 147.78, 152.35, 167.90; **IR** cm^{-1} 1747; **MS** m/z calculated for $C_{22}H_{20}O_7$ 396.1209 found ([M+H]) 397.1199.



Deoxypodophyllotoxin (DPT) (5S,5aS,8aR)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one. To a solution of (R)-5-(3,4,5-trimethoxyphenyl)-8a,9-dihydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(8H)-one **95** (1 equiv. 0.02g, 0.038 mmol) in 1:1 MeOH (0.1M, 0.42 mL) and THF (0.1 M, 0.42 mL) at -15 °C (ethylenglycol-dry ice bath) was added freshly crushed Mg (30 equiv. 1.13 mmol, 0.03g) and ammonium chloride (2 equiv, 0.07 mmol, 0.004 g). The mixture was gradually allowed to warm

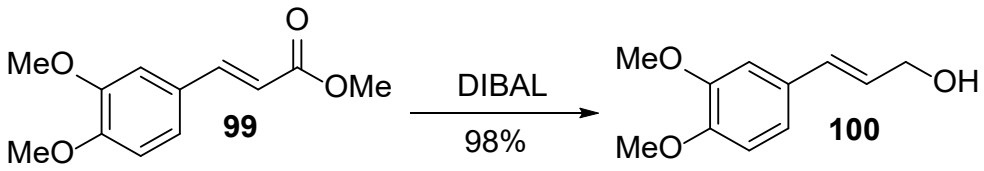
to rt stirring vigorously for 3 h. Saturated solution of NH_4Cl (7 mL) was added at -15 °C and allowed to warm to rt. The mixture was placed in a funnel extraction and washed with dichloromethane and water (3 x 20 mL). The combined organic phases were dried in $MgSO_4$, concentrated and crystalized in hot methanol obtaining white small precipitate of final product DPT (51.2% yield 7.7 mg). Characterization data: **TLC R_f** 0.10 (35% EtOAc/hexanes) ; **mp** = 199.0-200.5 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) 2.52 (dd, *J*= 9.9 ,5.38 Hz, 1H), 2.88 (dd, J= 9.05, 6.24 Hz, 1H), 3.0-3.09 (obs m, 1H), 3.35 (dd, *J* = 2.44, 7.1 Hz, 1H), 3.79 (s, 6H), 3.84 (s, 3H), 3.99 (dd, *J*= 2.6, 6.6 Hz 1H), 4.38 (d, J= 2.1 Hz, 1H), 4.46 (obs t, J= 8.31, 1H), 5.93 (s, 1H), 5.96 (s, 1H), 6.34 (s, 2H), 6.59 (s, 1H), 6.68 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) 32.04, 32.98, 45.31, 46.38, 56.19, 60.39, 60.86, 72.74, 100.99, 104.93, 108.80, 109.87, 128.27, 130.44, 138.20, 146.77, 146.87, 153.36, 178.39; **IR** 1757 cm^{-1}; **MS** m/z $C_{22}H_{22}O_7$ 398.1366 found 398.1346 ([M+H]) 399.1387 ([M+H]), ([M+NH4]) 416.1705. To further prove the stereochemistry of Hydrogens 4 and 5, we performed **1D NOESY** experiments. When H2 was irradiated, increments on H 3,4,1 were enhanced. On the other hand, when H4 was also irradiated increments on H 5,2 and 3 were enhanced. The fact that enhancement on H5 only occurs when H4 is irradiated demonstrates the cis configuration of the final product.

5.3. Procedures from Chapter 3: F4-4 Synthesis



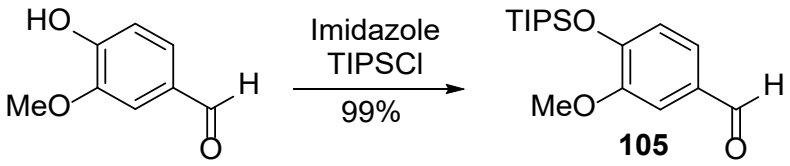
(E) – Methyl-3-(3,4-dimethoxyphenyl) acrylate 99. To a solution of cinnamic acid (8.0g, 38.4 mmol) in methanol (0.4M, 96ml) was added carefully and slowly concentrated H_2SO_4 (4.6 mL). The mixture was heated at reflux (65°C) overnight. The reaction mixture was cooled to rt and

solid $NaHCO_3$ (9.1g) was slowly added. The solution was added to a funnel extraction containing methylene chloride and washed with water (3 x 50 mL) and brine. The combined organic layers were dried ($MgSO_4$), concentrated and submitted to silica gel chromatography (4:1 hexanes/ethyl acetate to access the desired methyl ester **99** (8.1 g, 95%) as a pallid yellow solid. Characterization data: **TLC R_f** 0.5 (35% ethyl acetate/hexanes). Crystallization of the compound is also possible using ethyl acetate/hexanes; big crystals are produced but only 85% recovery. Characterization data: **mp**= 69-71° C; **^{1}H NMR** ($CDCl_3$, 500MHz) 3.67 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 6.20 (d, 1H), 6.72 (d, 1H), 6.92 (s, 1H). 6.96 (d, 1H), 7.51(d, 1H); **^{13}C NMR** ($CDCl_3$, 500MHz) 51.42, 55.70, 55.77, 109.54, 110.90, 115.32, 122.46, 127.21, 144.62, 149.07, 151.01, 167.44. **IR** 3001, 2950, 2838, 1712 cm^{-1}. **MS** m/z calculated for $C_{12}H_{14}O_4$ 222.0892 found 222.0924 ([M+H]) 223.0945, ([M+Na]) 245.0838.

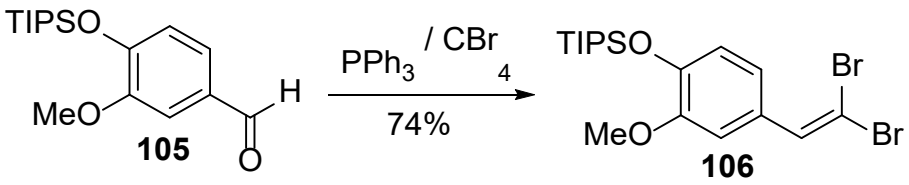


(E)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol 100. To a stirred solution of (E) – Methyl-3-(3,4-dimethoxyphenyl) acrylate **99** (5.0 g, 22.5 mmol) in dry methylene chloride (0.1 M, 225 mL) cooled to 0°C (ice water bath) under Argon gas was slowly added DIBAL-H (56 mL, 1,0 M in heptanes, 2.5 equiv.) via syringe. The mixture was allowed to warm to rt for 2h. To the mixture, was slowly added, methanol (24 mL) followed by aqueous HCl (1 M, 236mL). The mixture was added to a separatory funnel containing water (40mL). The aqueous layer was extracted with methylene chloride (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$). The dry organic layers were submitted to silica gel chromatography (50% EtOAc/hexanes) to obtain the desired alcohol **100** (98%, 4.3 g) as a white solid. Characterization data: **mp**= 78-80 °C; **TLC R_f**

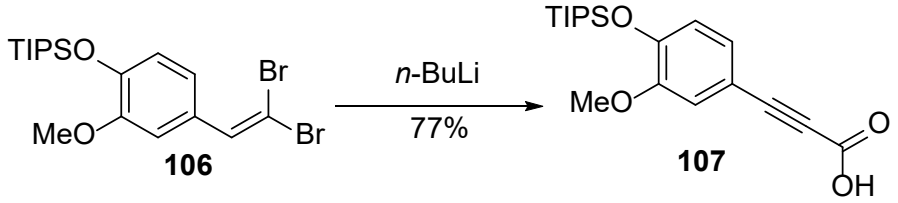
0.18 (35% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 500MHz) 3.89(s, 3H), 3.90 (s, 3H), 4.31 (d, 2H), 6.25 (m, 1H), 6.55 (d, 1H), 6.82 (d, 1H) 6.92 (d, 1H), 6.95 (s, 1H); **^{13}C NMR** ($CDCl_3$, 500MHz) 55.81, 55.92, 63.85, 108.81, 111.09, 119.69, 126.53, 129.72, 131.16, 148.91, 149.02. **IR** 3491, 2934, 2836 cm^{-1}. **MS** m/z calculated for $C_{11}H_{14}O_3$ 194.0943. ([M+H]) 195.1023



3-methoxy-4-((triisopropylsilyl)oxy)benzaldehyde 105. To a solution of vanillin (5.0 g, 32.89 mmol) in THF (0.8M, 41mL) was added imidazole (8.9 g, 131.57 mmol, 4 equiv) and stirred at room temperature for ten minutes. Then, TIPS chloride (triisopropylsilyl chloride, 9.16mL, 42.76 mmol, 1.3 equiv) was added and the reaction mixture was stirred overnight. 5 mL of water was added to the reaction and stirred for ten minutes. The reaction mixture was concentrated, and DCM was added. The mixture was added to a separatory funnel and extracted with 1M HCl and brine. The organic layer was dried under $MgSO_4$, concentrated and subjected to silica gel chromatography (10% EtOAc/hexanes) to obtain the desired protected aldehyde **105** (99%, 10 g) as a pale-yellow oil. Characterization data: **TLC R_f** 0.74 (35% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 500MHz) 1.09 (d, 18H), 1.27 (m, 3H), 3.86 (s, 3H), 6.97 (d, 1H), 7.34 (d, 1H), 7.36 (d, 1H), 7.39 (d, 1H), 9.84 (s, 1H); **^{13}C NMR** ($CDCl_3$, 500MHz) 12.91, 12.92, 12.95, 17.70, 17.73, 17.74, 17.75, 17.75, 17.76, 17.76, 17.77, 17.78, 17.79, 17.80, 17.82, 17.83, 17.84, 17.84, 17.85, 17.86, 17.87, 55.40, 110.04, 120.14, 126.18, 130.61, 151.57, 151.82, 190.95 cm^{-1}. **IR** 2944, 2866, 1698, 1593 cm^{-1}. **MS** m/z calculated for $C_{17}H_{28}O_3Si$ 308.1808, ([M+H]) 309.1875.

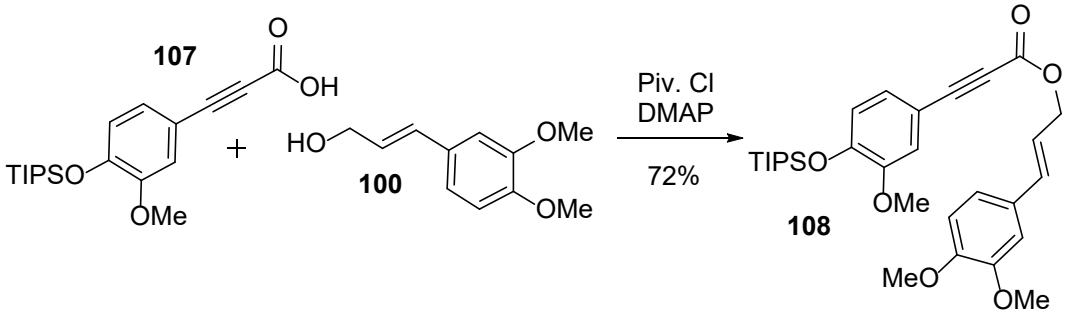


(4-(2,2-dibromovinyl)-2-methoxyphenoxy)triisopropylsilane 106. To a solution of triphenylphosphine (3 equiv. 97.40 mmol, 25.5 g) in dry methylene chloride (0.3 M, 324 mL) cooled to 0°C under Argon gas, was added carbon tetrabromide (1.5 equiv. 48.71 mmol, 16.12 g) and stirred at 0°C for 15 min. To the solution was added 3-methoxy-4-((triisopropylsilyl)oxy)benzaldehyde **105** (10.0 g, 32.47 mmol). The resulting mixture was stirred at rt overnight. The mixture was triturated with cold hexanes (120 mL) and filtered (paper cone) to remove excess triphenylphosphine. The filtrate was concentrated and subjected to silica gel chromatography (10% EtOAc/hexanes) to obtain dibromo olefin product **106** (74%, 11 g) as a yellow oil. Characterization data: **TLC R_f** 0.91. **^{1}H NMR** 1.12 (d, 18H), 1.28 (m, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 7.03 (dd, 1H), 7.20 (d, 1H), 7.42 (s, 1H). **^{13}C NMR** 12.50, 12.90, 13.30, 17.75, 17.80, 17.83, 17.85, 17.86, 17.89, 17.93, 17.94, 17.96, 17.99, 55.51, 86.88, 112.05, 120.17, 121.88, 128.42, 136.64, 146.16, 150.55. **IR** 2943, 2865, 1598, 1500 cm^{-1}. **MS** m/z calculated for $C_{18}H_{28}O_2Br_2Si$ 462.0225, ([M+H]) 463.0322.



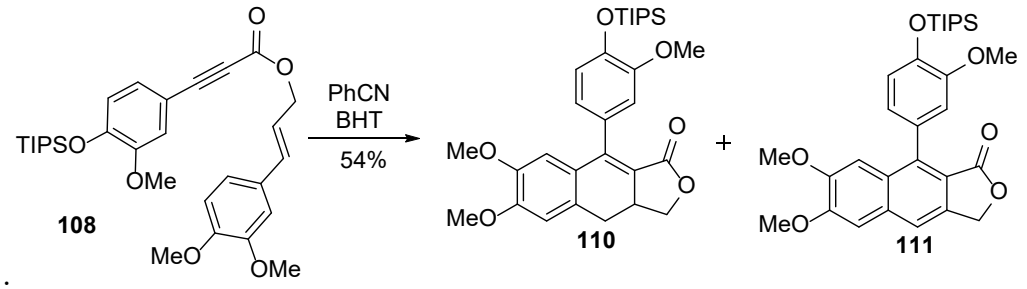
3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)propiolic acid 107. To a solution of (4-(2,2-dibromovinyl)-2-methoxyphenoxy)triisopropylsilane **106** (6.5 g, 14 mmol) in dry THF (0.6 M, 23 mL) under Argon gas cooled to -78°C (dry ice / acetone bath) was added a solution of n-

butyllithium (2.5 M, 1.9 equiv. 26.6 mmol, 10.6 mL). The yellow solution was stirred for 20 min at -78°C and solid carbon dioxide (crushed, 10 equiv. 140 mmol, 6 g – excess) was added at once. The mixture was gradually allowed to warm to room temperature stirring continuously. The mixture was acidified (pH 2 approximately) with HCl (6.0 N) and extracted with DCM (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. Crystallization with hot ethyl acetate / hexane accessed the desired propiolic acid **107** (77%, 3.7 g) as a yellow solid. Characterization data: **mp**= 105-111 °C; **TLC R_f** 0.06 (35% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 500MHz) 1.09 (d, 18H), 1.27 (m, 3H), 3.82 (s, 3H), 6.85 (d, 1H), 7.09 (d, 1H), 7.15 (dd, 1H); **^{13}C NMR** ($CDCl_3$, 500MHz) 12.86, 12.89, 17.80, 17.82, 17.84, 17.85, 17.85, 17.87, 55.50, 79.36, 90.49, 111.26, 111.53, 120.61, 127.48, 149.12, 150.83. **IR** 2941, 2211, 1676 cm^{-1}. **MS** m/z calculated for $C_{19}H_{28}O_4Si$ 348.17569 found 384.17992 ([M+H]) 349.1872, ([M+NH_4]) 366.21283, ([M+Na]) 371.16888.



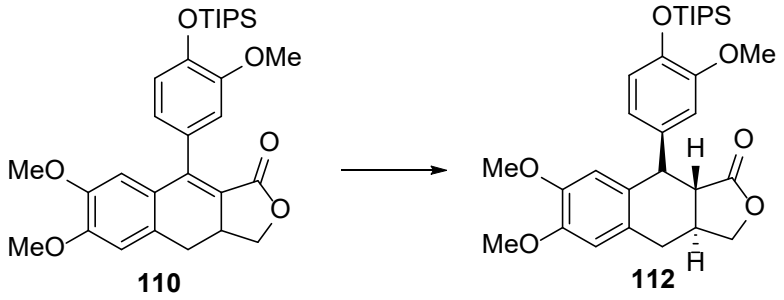
(E)-3-(3,4-dimethoxyphenyl)allyl 3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)propiolate 108. To a DCM solution (0.1 M, 46 mL) of 3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl) propiolic acid **107** (1 equiv. 4.6 mmol, 1.6 g) at room temperature was added triethylamine (2.4 equiv, 11.03mmol, 1.5mL) and pyvaloyl chloride (1 equiv. 4.6 mmol, 0.6mL) and stirred for 30 minutes. (E)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol **100** (1.6 equiv, 7.4 mmol, 1.4 g) and DMAP (0.1 equiv, 0.46 mmol, 60mg) were added at once and the orange solution was stirred for

6h. The mixture was extracted with water and DCM. The organic layer was dried with $MgSO_4$, filtrated, and concentrated. The yellow oil was subjected to silica gel chromatography (15% ethylacetate/hexanes) to yield the desired ester **108** (72%, 1.74 g) as a pale-yellow oil. Characterization data: **TLC R_f** 0.58. **^{1}H NMR** 1.09 (d, 18H),1.25 (m, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.88 (d, 2H), 6.22 (m, 1H), 6.67 (d, 1H), 6.84 (m, 2H), 6.96 (m, 2H), 7.06 (d, 1H), 7.12 (dd,1H). **^{13}C NMR** C: 12.87, 17.81, 55.82, 55.90, 66.59, 79.68, 87.86, 108.90, 111.04, 111.75, 116.33, 120.17, 120.20, 120.55, 127.01, 129.07, 135.27, 148.66, 149.06, 149.35, 150.77, 154.13. **IR** 3430, 2944, 2866, 2211, 1706 cm^{-1}; **MS** m/z calculated for $C_{30}H_{40}O_6Si$ 524.25942 found 524.26601 ([M+H]) 525.27298, ([M+Na]) 547.25334



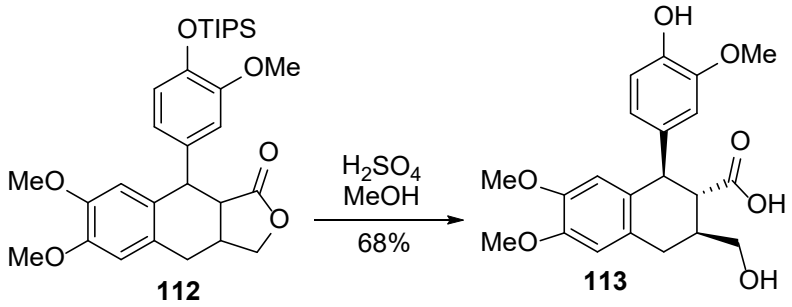
6,7-dimethoxy-9-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-3a,4-dihydronaphtho[2,3-c]furan-1(3H)-one 110. To a solution of (E)-3-(3,4-dimethoxyphenyl)allyl 3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)propiolate **108** (1 equiv, 120mg, 0.25 mmol) in benzonitrile (0.02 M, 12 mL) was added 2,6 di-t-butylhydroxytoluene (BHT 1.5, 0.36 mmol, 0.08 mg). The mixture was heated at reflux (145°C) for 6h. The mixture was cooled to room temperature, diluted with hexane (24 mL) and subjected to radial chromatography (20% EtOAc /hexanes radial chromatography) to yield two Diels – Alder products (54% overall yield). The desired dihydronaphthol (48 mg 38%) product as a yellow semisolid and the naphthol (20 mg 16%) as an orange oil. Characterization data: *dihydronaphthol product **110*** **TLC R_f** 0.25. **^{1}H NMR**. 1.12 (d,

18H), 1.29 (m, 3H), 2.81 (t, 1H), 2.94 (dd, 1H), 3.42 (m, 1H), 3.62 (s, 3H), 3.80 (s, 3H), 3.94 (s, 3H), 4.00 (t, 1H), 4.71 (t, 1H), 6.54 (s, 1H), 6.86 (m, 4H) **^{13}C NMR** 12.89, 17.87, 32.92, 35.90, 55.53, 55.58, 55.68, 56.08, 68.01, 70.97, 106.02, 111.04, 122.33, 114.21, 118.04, 119.04, 119.96, 120.40, 122.34, 127.45, 128.74, 129.13, 139.58, 145.90, 147.49, 147.54, 149.99, 168.41; **IR** 2965, 1769, 1758 cm^{-1} **MS** m/z calculated for $C_{30}H_{40}O_6Si$ 524.26635 found 524.26635 ([M+H]) 525.27364, ([M+Na]) 547.25557.*Naphthol product **111*** **TLC R$_f$** 0.36. **^{1}H NMR**. 1.16 (d, 18H), 1.32 (m, 3H), 3.29 (s, 3H), 5.34 (s, 2H), 6.76 (dd, 1H), 6.84 (d, 1H), 6.94 (d, 1H), 7.50 (d, 1H), 7.72 (d, 1H), 7.80 (s, 1H). **^{13}C NMR** 12.91, 17.83, 17.99, 18.01, 55.56, 56.03, 56.20, 56.71, 60.74, 67.33, 110.39, 113.37, 117.85, 119.09, 120.47, 120.98, 121.87, 124.46, 128.36, 131.23, 132.81, 140.42, 144.52, 149.71, 150.56; **IR** 2941, 1512 **; MS** m/z calculated for $C_{30}H_{38}O_6Si$ 522.24377 found 522.25052 ([M+H]) 523.25779, ([M+NH$_4$]) 540.28429, ([M+Na]) 545.23912.



6,7-dimethoxy-9-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one 112. To a solution of 6,7-dimethoxy-9-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-3a,4-dihydronaphtho[2,3-c]furan-1(3H)-one **110** (1 equiv. 190 mg, 0.36 mmol) in 1:1 MeOH (0.1 M, 3.6 mL) and THF (0.1 M, 3.6 mL) at -15°C (ethyleneglycol-dry ice bath) was added freshly crushed Mg (30 equiv, 10.8 mmol, 260mg) and ammonium chloride (2 equiv, 0.73 mmol, 39mg). The mixture was gradually allowed to warm to room temperature stirring vigorously for 3 h. A saturated solution of NH$_4$Cl (20 mL) was added

at -15°C and allowed to warm to rt. The mixture was placed in a funnel extraction and washed with dichloromethane and water (3 x 20 mL). The combined organic layers were dried in $MgSO_4$, filtrated and concentrated. The product was dissolved in hot ethanol refrigerated overnight giving the desired compound **112** as a white solid (51% 96mg). Characterization data: **mp** = 136 – 139 °C; **TLC R_f** 0.38; **^{1}H NMR**. 1.08 (d, 18H), 1.24 (m, 3H), 2.49 (d, 1H), 2.85 (dd, 1H), 3.01 (m, 1H), 3.33 (m, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 3.88 (s, 3H), 3.97 (m, 1H), 4.42 (m, 2H), 6.48 (d, 1H), 6.61 (s, 1H), 6.65 (s, 1H), 6.67 (s, 1H), 6.77 (d, 1H). **^{13}C NMR** 12.83, 17.88, 31.52, 31.90, 44.28, 44.57, 55.84, 72.87, 111.97, 112.56, 119.76, 120.28, 126.93, 129.69, 135.90, 144.18, 147.94, 150.92, 178.60; **IR** 2943, 2866, 1769, 1512 cm^{-1}; **MS** m/z calculated for $C_{30}H_{42}O_6Si$ 526.2751 ([M+H_2O]) 544.30890.



(1R,2S,3S)-1-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid 113. To a solution of 6,7-dimethoxy-9-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **112** (50 mg, 0.095 mmol) in MeOH (2 mL) was added 1 N solution of H_2SO_4 (0.1 mL) The mixture was heated to reflux (65 °C) and stirred for 24 h. After cooling to room temperature, the solvent was evaporated, and the residue was extracted with DCM and water. The combined organic layers were concentrated. The crude was purified by radial chromatography to afford **113** as a translucid oil. (25 mg, 68%) Characterization data: **TLC R_f** 0.04 **^{1}H NMR**. 2.51 (dd, 1H), 2.89

(dd, 1H), 3.03 (m, 1H), 3.32 (dd, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.95 (dd, 1H), 4.43 (t, 2H), 5.61 (s, 1H), 6.52 (d, 1H), 6.62 (s, 1H), 6.67 (d, 2H), 6.81 (d, 1H). **^{13}C NMR** 14.20, 31.44, 32.71, 44.41, 46.71, 55.94, 72.95, 110.44, 111.67, 112.60, 114.34, 120.24, 126.94, 129.30, 134.77, 144.29, 146.68, 148.00, 148.12. **IR** 3443, 2941, 2865, 1764 cm^{-1}; **MS** m/z calculated for $C_{21}H_{24}O_7$ 388.1522, ([M+H]) 389.17.

5.4. X-ray Crystallography Data from Chapter 2: DPT Synthesis

5.4.1. X-ray Crystallography Major Diels-Alder Product 95

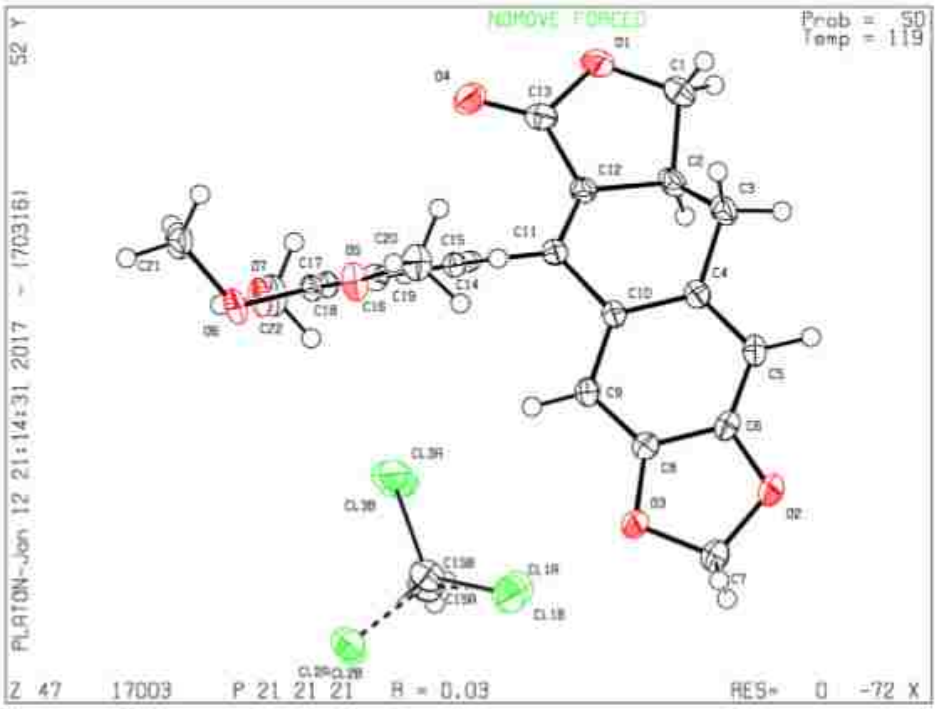


Figure 7. Crystal structure CIF file major product **95**.

Table 8. X-ray crystal data and structure refinement for Diels-Alder major product **95**.

Empirical formula	C23 H21 Cl3 O7	
Formula weight	515.75	
Temperature	119(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.0365(7) Å	a= 90°
b = 15.2618(16) Å	b= 90°.	
c = 20.961(2) Å	g = 90°.	

Volume	2251.0(4) $Å^3$
Z	4
Density (calculated)	1.522 Mg/m^3
Absorption coefficient	4.075 mm^{-1}
F(000)	1064
Crystal size	0.200 x 0.140 x 0.060 mm^3
Theta range for data collection	3.582 to 68.874°.
Index ranges	-8<=h<=7, -18<=k<=18, -24<=l<=25
Reflections collected	21020
Independent reflections	4145 [R(int) = 0.0783]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7531 and 0.5580
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4145 / 312 / 314
Goodness-of-fit on F^2	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0704
R indices (all data)	R1 = 0.0358, wR2 = 0.0720
Absolute structure parameter	-0.005(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.208 and -0.232 $e.Å^{-3}$

5.4.2. X-ray Crystallography Minor Diels-Alder Product 96

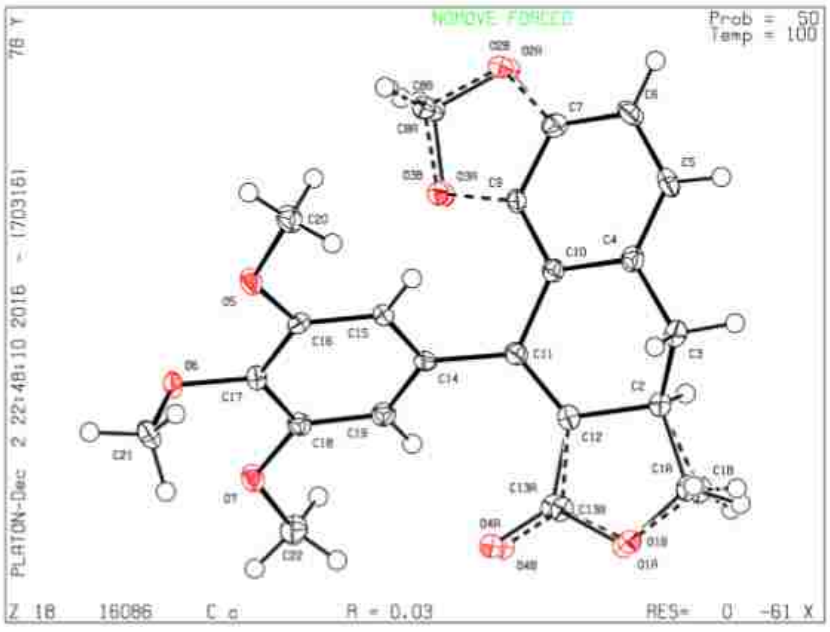


Figure 8. Crystal structure CIF file minor product **96**.

Table 9. X-ray crystal data and structure refinement for minor Diels-Alder product **96**.

Identification code	16086
Empirical formula	C22 H20 O7
Formula weight	396.38
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	a = 4.6806(2) Å a= 90°. b = 33.3839(11) Å b= 101.048(2)°. c = 11.9303(4) Å g = 90°.
Volume	1829.64(12) $Å^3$
Z	4
Density (calculated)	1.439 Mg/m^3
Absorption coefficient	0.900 mm^{-1}
F(000)	832
Crystal size	0.440 x 0.380 x 0.060 mm^3
Theta range for data collection	2.647 to 68.262°.
Index ranges	-5<=h<=5, -40<=k<=40, -14<=l<=14
Reflections collected	32497
Independent reflections	3245 [R(int) = 0.0398]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3245 / 449 / 288
Goodness-of-fit on F^2	0.830
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0832
R indices (all data)	R1 = 0.0263, wR2 = 0.0836
Absolute structure parameter	0.07(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.171 and -0.164 $e.Å^{-3}$

5.5. X-ray Crystallography Data for F4-4

5.5.1. X-ray Crystallography Minor Diels-Alder Product 111

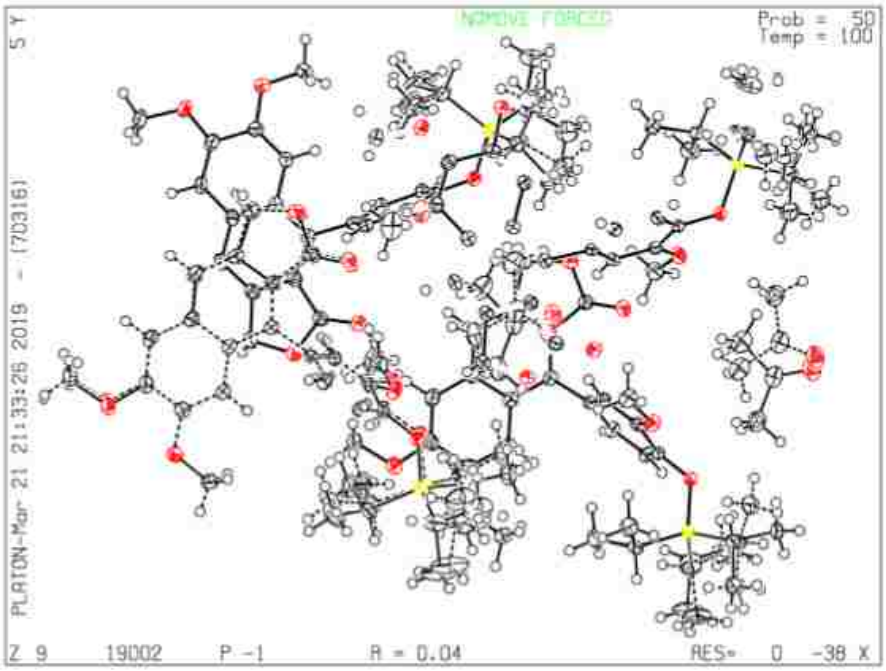


Figure 9. Crystal structure CIF file minor product **111**.

Table 10. X-ray crystal data and structure refinement for minor Diels-Alder product **111**.

Identification code	19002	
Empirical formula	C31.50 H41 O6.50 Si	
Formula weight	551.73	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 16.2889(3) Å	α= 108.8640(10)°.
	b = 17.6448(3) Å	β= 98.8680(10)°.
	c = 22.7265(4) Å	γ = 101.2560(10)°.
	c = 11.9303(4) Å	g = 90°.
Volume	5893.73(19) $Å^3$	
Z	8	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	1.059 mm^{-1}	
F(000)	2368	
Crystal size	0.125 x 0.075 x 0.035 mm^3	
Theta range for data collection	2.113 to 68.425°.	
Index ranges	-19<=h<=19, -21<=k<=21, -27<=l<=23	

Reflections collected	108339
Independent reflections	21570 [R(int) = 0.0631]3245
Completeness to theta = 67.679°	99.8 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	21570 / 4476 / 1686
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1029
R indices (all data)	R1 = 0.0567, wR2 = 0.1110
Extinction coefficient	n/a
Largest diff. peak and hole	0.521 and -0.335 e.Å^{-3}

5.6. Data and XYZ Coordinates from Chapter 4: Mechanistic Studies

5.6.1. Computational Assessment Generalities

Transition states and intermediates for different pathways of the ISDA reaction were calculated on substrate **90** of the DPT synthesis. First, Diels-Alder reaction mechanisms included diradical styryl, concerted styryl and alkyne as a diene. Second, BHT assisted mechanisms were calculated to include concerted and step-wise BHT assisted and stepwise radical pathway as outlined in chapter 4. M06-2X/6-31G(d,p) calculations were performed in Gaussian 09[2] with an ultrafine integration grid.[3] Frequency and intrinsic reaction coordinate (IRC) calculations were used to verify connections on the potential energy surfaces. For open shell species UM06-2X was used. Reported free energies correspond to (U)M06-2X/def2-TZVP//(U)M06-2X/6-31G(d,p) with the benzonitrile SMD solvation model.[4] Spin projection was calculated to remove triplet wave function contamination giving accurate open-shell singlet energies.[5]

5.6.2. XYZ Coordinates

5.6.2.1. XYZ Coordinates for first step [4+2] cycloaddition Diels-Alder

5.6.2.1.1. XYZ Coordinates for Diels-Alder reaction concerted and stepwise mechanisms

90 (SM)

M06-2X/6-31G(d,p)
Electronic Energy = -1376.29397929
Electronic and Zero-Point Energy = -1375.906992
Enthalpy = -1375.878684
Free Energy = -1375.970083
M06-2X/def2-TZVP
Electronic Energy = -1376.8316465

C	-2.0349320	-0.6256790	-0.8863220
C	-0.9065880	-0.9664760	-1.1618710
C	0.4498030	-1.3263080	-1.5302910
O	0.8272440	-2.4564000	-0.9263280
C	2.1864760	-2.8811140	-1.1864460
C	3.1549660	-2.1355500	-0.3247640
H	2.4107030	-2.7474640	-2.2469170
H	2.1767140	-3.9466840	-0.9469210
C	4.1207100	-1.3678170	-0.8388670
C	5.1496900	-0.6296240	-0.0866600
H	3.0351530	-2.2563770	0.7505490
H	4.1595870	-1.2495070	-1.9218540
C	5.4404660	-0.9078910	1.2539320
C	6.4129640	-0.1938190	1.9667560
C	7.0862220	0.7958680	1.2823690
C	6.8136030	1.0763570	-0.0543150
C	5.8609250	0.3855430	-0.7653110
H	4.9153330	-1.7127460	1.7577090
H	5.6547380	0. 6152760	-1.8055990
H	6.6352040	-0.4151150	3.0044620
O	1.1312350	-0.6816300	-2.2928980
C	8.5741570	2.2751170	0.5638980
H	9.5046450	1.7743100	0.2667590
H	8.7333130	3.3360800	0.7575320
O	7.5992170	2.1154170	-0.4664070
O	8.0512400	1.6475020	1.7359950
C	-3.3678370	-0.2307890	-0.5518320
C	-4.0929630	-0.9817530	0.3873780
C	-3.9340590	0.8917780	-1.1598520
C	-5.3939820	-0.6081680	0.7097380

H	-3.6339020	-1.8534580	0.8363710
C	-5.2305620	1.2680000	-0.8236470
H	-3.3813610	1.4786750	-1.8847340
C	-5.9703480	0.5319720	0.1103520
O	-6.1946910	-1.2866310	1.5623460
O	-7.2501780	0.9085450	0.3522760
O	-5.7904790	2.3439810	-1.4482670
C	-5.6537260	-2.4395950	2.1907580
H	-5.3706190	-3.1964400	1.4511710
H	-4.7842610	-2.1848060	2.8062650
H	-6.4451420	-2.8339040	2.8276740
C	-7.6082200	1.1595180	1.7149580
H	-7.9422140	0.2458000	2.2085680
H	-8.4241740	1.8843930	1.6880310
H	-6.7655110	1.5876800	2.2679480
C	-5.9625540	3.4783500	-0.6019280
H	-6.6278360	3.2550920	0.2375780
H	-6.4091520	4.2612300	-1.2165550
H	-4.9951900	3.8241760	-0.2199460

TS6

M06-2X/6-31G(d,p)
Electronic Energy = -1376.24186181
Electronic and Zero-Point Energy = -1375.856386
Enthalpy = -1375.829675
Free Energy = -1375.913334
M06-2X/def2-TZVP
Electronic Energy = -1376.7769487
$\langle S^2 \rangle = 0.347547$

O	4.4999640	-0.8799310	1.9785950
O	2.4605800	-1.7713350	2.5543210
O	-1.7415200	4.4570420	-3.2361980
O	-0.1869040	4.8131890	-1.6784510
O	-3.9229300	-2.2202550	0.2235480
O	-1.5504880	-3.3884710	0.4774490
O	0.6734770	-2.3035720	-0.5244750
C	-1.7772810	1.6174710	-1.9308450
C	-1.2732860	2.7454570	-1.6119730
C	3.6202470	1.2005310	0.9807020
H	4.5857690	1.6219120	0.7253690
C	3.5138860	-0.0167050	1.6189700
C	2.2723400	-0.5526230	1.9719010
C	1.0978530	0.0916010	1.6933920
H	0.1395850	-0.3459510	1.9547880

C	1.1640050	1.3436410	1.0100870
C	-0.5439860	-0.3489190	-1.3023870
H	0.3372440	0.1351090	-1.7029820
C	-1.7881770	0.3026140	-1.4035880
C	-2.9625230	-0.2968360	-0.9088320
H	-3.9081640	0.2205610	-1.0083410
C	-2.8734210	-1.5393640	-0.2896400
C	-1.6269020	-2.1843210	-0.1567940
C	-0.4688300	-1.5961910	-0.6818830
C	0.5393350	4.0608090	-0.6897790
H	0.9508010	4.7818410	0.0193170
H	1.3494630	3.5341130	-1.2003230
C	3.8642930	-1.8757870	2.7858830
H	4.2129930	-2.8641060	2.4842820
H	4.0795390	-1.6756970	3.8424970
C	1.8454220	-1.7801550	-1.1292570
H	1.7409000	-1.7427530	-2.2199580
H	2.0832570	-0.7788200	-0.7532110
H	2.6531360	-2.4641820	-0.8652300
C	-1.7866850	-4.4874790	-0.3994240
H	-1.0334980	-4.5178660	-1.1948570
H	-2.7862890	-4.4237990	-0.8431840
H	-1.7150570	-5.3953360	0.2020370
C	-5.2059980	-1.6292160	0.0924390
H	-5.2641970	-0.6790140	0.6349770
H	-5.4620200	-1.4632360	-0.9598050
H	-5.9110510	-2.3372250	0.5280110
C	-1.1219980	4.0590440	-2.2833510
C	-0.4507000	3.1049880	-0.0553570
H	-1.2966210	3.6450440	0.3810340
C	-0.0967360	1.9898200	0.7412630
H	-0.9414540	1.5325530	1.2533020
C	2.4289830	1.8763860	0.6881050
H	2.5118940	2.8551630	0.2354160

119

<u>M06-2X/6-31G(d,p)</u>
Electronic Energy = -1376.25825010
Electronic and Zero-Point Energy = -1375.872935
Enthalpy = -1375.845565
Free Energy = -1375.932613
<u>M06-2X/def2-TZVP</u>
Electronic Energy = -1376.793136
$\langle S^2 \rangle$ = 0.95778

C	1.6075490	-0.2503620	-1.2420290
C	2.7603360	0.3068680	-0.6319190
C	2.9414580	1.7059770	-0.5177110
C	1.9032740	2.6938850	-0.9044210
C	-0.2453420	1.9307510	0.3108440
C	0.7710080	2.7221400	0.1667380
C	1.1001260	3.8695900	1.0775080
O	2.1047400	4.5847960	0.5361470
O	0.6004500	4.1543460	2.1339330
C	2.3929020	4.1438300	-0.8050830
H	3.4678290	4.2442010	-0.9597890
H	1.8589070	4.7947990	-1.5022780
C	3.7445930	-0.5730110	-0.0755750
C	1.3829220	-1.6296720	-1.2913430
C	2.3494730	-2.4426280	-0.7358830
C	3.5088070	-1.9165420	-0.1499360
H	4.6349800	-0.1762050	0.4004870
H	0.4882110	-2.0444670	-1.7424410
H	0.8670890	0.4067240	-1.6839710
H	3.8116730	2.0699330	0.0235890
H	1.4751650	2.4885160	-1.8884360
C	-1.2783300	1.0125180	0.3329220
C	-1.0947190	-0.2402930	0.9805300
C	-2.5124310	1.3189790	-0.3017550
C	-2.1278370	-1.1656460	0.9746320
H	-0.1382860	-0.4585940	1.4387980
C	-3.5327550	0.3778890	-0.2920100
H	-2.6307510	2.2783950	-0.7885980
C	-3.3566870	-0.8592760	0.3569480
O	-2.0572800	-2.3990860	1.5240510
O	-4.3722650	-1.7658400	0.3840060
O	-4.7396910	0.5461120	-0.8785100
C	-0.8205050	-2.7747550	2.1085340
H	-0.0102470	-2.7529180	1.3697650
H	-0.5634510	-2.1227310	2.9507050
H	-0.9534520	-3.7943450	2.4703920
C	-4.3846210	-2.6159270	-0.7611830
H	-3.4615000	-3.2037360	-0.8179080
H	-5.2360870	-3.2889220	-0.6466210
H	-4.5038070	-2.0306880	-1.6795450
C	-4.9808470	1.7886850	-1.5195600
H	-4.2773200	1.9566450	-2.3426640
H	-5.9945080	1.7320640	-1.9162740
H	-4.9143210	2.6195800	-0.8083670
O	2.3601540	-3.7989810	-0.6190960
C	3.6864650	-4.1310530	-0.2022920

H	3.6448590	-4.9027030	0.5667790
H	4.2670670	-4.4590040	-1.0733130
O	4.2637550	-2.9448750	0.3397140

TS7

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25755691
Electronic and Zero-Point Energy = -1375.871952
Enthalpy = -1375.845795
Free Energy = -1375.926719
M06-2X/def2-TZVP
Electronic Energy = -1376.7913806
$<S^2>$ = 0.628379

C	-3.8733780	2.1753590	4.0665590
C	-2.4680760	2.0603090	3.8229290
C	-1.7282570	3.1822360	3.4378540
C	-0.4217060	3.0130470	2.7798760
C	-1.1008290	0.9930120	1.3326570
C	-0.5973370	2.1800090	1.4534910
C	-0.1112480	3.0510170	0.3388630
O	0.3324290	4.2198720	0.8300580
O	-0.0872620	2.8000770	-0.8383460
C	0.2110160	4.3140760	2.2607440
H	-0.4111770	5.1850290	2.4793630
H	1.2110640	4.4769370	2.6656330
C	-1.8683300	0.7546320	3.7840210
C	-4.6897720	1.0694890	4.2113590
C	-4.0792910	-0.1822680	4.1132240
C	-2.7139570	-0.3253360	3.9296140
H	-0.7944720	0.6157360	3.7650660
H	-5.7574380	1.1610600	4.3764390
H	-4.3069250	3.1705220	4.0927800
H	-2.2217970	4.1493930	3.3853790
H	0.2875250	2.4550400	3.4007030
C	-1.5104080	-0.2389560	0.8106040
C	-2.8916220	-0.5337890	0.7312540
C	-0.5451490	-1.2147160	0.4704660
C	-3.2918030	-1.7926040	0.2958760
H	-3.6107470	0.2196590	1.0295120
C	-0.9666390	-2.4719690	0.0501490
H	0.5057070	-0.9686730	0.5529240
C	-2.3384500	-2.7626200	-0.0564700
O	-4.5820790	-2.1979950	0.2091050
O	-2.7327230	-3.9924760	-0.4935060

O	-0.1369240	-3.4875540	-0.2804590
C	-5.5773570	-1.2955020	0.6658620
H	-5.4299190	-1.0404900	1.7226750
H	-5.5892960	-0.3770430	0.0691760
H	-6.5301440	-1.8122780	0.5502230
C	-3.0746880	-4.8799720	0.5681630
H	-3.9861680	-4.5476470	1.0771610
H	-3.2495390	-5.8592910	0.1187550
H	-2.2552060	-4.9554950	1.2921390
C	1.2563190	-3.2500650	-0.1649790
H	1.5360370	-3.0096860	0.8668680
H	1.7466540	-4.1761320	-0.4657240
H	1.5790460	-2.4386840	-0.8271100
O	-4.6556800	-1.4118940	4.2405530
C	-3.6411600	-2.3318120	3.8257270
H	-3.8164360	-2.6102740	2.7767040
H	-3.6507520	-3.2044310	4.4791380
O	-2.3925400	-1.6557470	3.9407520

TS8

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25799202
Electronic and Zero-Point Energy = -1375.871822
Enthalpy = -1375.845581
Free Energy = -1375.927877
M06-2X/def2-TZVP
Electronic Energy = -1376.7921198
$\langle S^2 \rangle = 0.645601$

C	-1.1640240	3.2334410	-1.9971910
C	-0.3554220	2.8746260	-3.1151470
C	1.0432400	2.8977410	-3.0223320
C	1.6962520	2.9889740	-1.7064420
C	0.1026270	1.3355230	-0.5235510
C	1.2926940	1.7395110	-0.8247240
C	2.5721570	1.0585450	-0.4496330
O	3.6177630	1.7362120	-0.9501890
O	2.7122280	0.0591550	0.2067430
C	3.2286130	2.8725760	-1.7431150
H	3.5988410	2.7047270	-2.7575750
H	3.7217270	3.7500470	-1.3218470
C	-0.9869600	2.3146730	-4.2803110
C	-2.5512780	3.0298200	-1.9809580
C	-3.1014480	2.4302810	-3.0881520
C	-2.3293060	2.0993620	-4.2213470

H	-0.3978470	2.0255780	-5.1440940
H	-3.1560400	3.2958940	-1.1212590
H	-0.7108600	3.7456880	-1.1566780
H	1.6317350	2.5551580	-3.8698990
H	1.3898150	3.8751560	-1.1415300
C	-1.0655660	0.6970640	-0.1123000
C	-1.8051320	-0.0475440	-1.0638940
C	-1.5591390	0.8728180	1.2027560
C	-3.0253380	-0.6032350	-0.6977890
H	-1.4192190	-0.1414650	-2.0719160
C	-2.7775120	0.3004790	1.5510780
H	-0.9763360	1.4420000	1.9153170
C	-3.5244400	-0.4232160	0.6039410
O	-3.8215850	-1.3156790	-1.5278570
O	-4.7439130	-0.9311380	0.9422000
O	-3.3399250	0.3805890	2.7797030
C	-3.3969420	-1.4504870	-2.8729240
H	-3.2536840	-0.4726850	-3.3482080
H	-2.4639720	-2.0213390	-2.9436450
H	-4.1910810	-1.9899960	-3.3895300
C	-4.6609380	-2.2232520	1.5367410
H	-4.0602650	-2.1946210	2.4525190
H	-5.6807000	-2.5242710	1.7837340
H	-4.2281370	-2.9468670	0.8367870
C	-2.6265710	1.1001060	3.7719450
H	-2.5021510	2.1514920	3.4892330
H	-3.2264540	1.0407090	4.6801350
H	-1.6427270	0.6551190	3.9577270
O	-4.3882580	2.0510080	-3.2984490
C	-4.4729140	1.7064100	-4.6834910
H	-5.0490410	0.7868570	-4.7949020
H	-4.9265680	2.5379400	-5.2362640
O	-3.1394370	1.4949110	-5.1415270

TS9

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25755124
Electronic and Zero-Point Energy = -1375.871246
Enthalpy = -1375.844691
Free Energy = -1375.927344
M06-2X/def2-TZVP
Electronic Energy = -1376.7920273

C	-0.5355510	-1.2154910	1.7345880
C	-0.2007760	0.0673350	1.2255460

C	1.0897550	0.5991680	1.4273010
C	2.1114380	-0.1832960	1.9845590
C	1.4444660	-2.3314570	0.4286180
C	2.3768530	-1.5980330	0.8469320
C	3.8549380	-1.5418790	0.7024530
O	4.4263370	-0.5397230	1.3806160
O	4.5178010	-2.3236940	0.0678270
C	3.5130530	0.3854490	2.0003510
H	3.5620060	1.3209910	1.4362580
H	3.8816270	0.5548720	3.0139140
C	-1.0935690	0.7128530	0.3043100
C	-1.7332960	-1.8686360	1.3851390
C	-2.5306950	-1.2391780	0.4668670
C	-2.2212240	0.0394650	-0.0471370
H	-0.8475800	1.6815610	-0.1178530
H	-1.9855940	-2.8463500	1.7800250
H	0.0717330	-1.6580380	2.5150500
H	1.3612510	1.4957940	0.8735260
H	1.8654320	-0.7936930	2.8534210
O	-3.6814230	-1.6785260	-0.1031580
O	-3.1813390	0.3899000	-0.9554120
C	0.5873270	-3.2773840	-0.1861130
C	-0.2461630	-2.8624870	-1.2401960
C	0.5219860	-4.5920090	0.3099560
C	-1.1425650	-3.7716620	-1.8005060
H	-0.1965940	-1.8347230	-1.5791230
C	-0.3769710	-5.4907330	-0.2631690
H	1.1749260	-4.8872650	1.1211070
C	-1.2216780	-5.0819480	-1.3073410
O	-0.5124010	-6.7832190	0.1146940
O	-2.1301860	-5.9568060	-1.8301850
O	-1.9940250	-3.4798750	-2.8110350
C	0.3200440	-7.2415430	1.1670380
H	1.3805980	-7.1578940	0.9040020
H	0.1316880	-6.6894900	2.0947220
H	0.0688710	-8.2916650	1.3173610
C	-1.6192710	-6.6769540	-2.9473320
H	-0.7430020	-7.2707440	-2.6633160
H	-2.4135460	-7.3452890	-3.2854190
H	-1.3493110	-5.9947800	-3.7616020
C	-2.0246320	-2.1370050	-3.2621500
H	-2.2636260	-1.4451380	-2.4460210
H	-1.0695800	-1.8427640	-3.7121070
H	-2.8086830	-2.0889290	-4.0184850
C	-4.2421450	-0.5435750	-0.7675270
H	-4.6398120	-0.8490960	-1.7355040

H	-5.0169370	-0.0980380	-0.1315640

TS10

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25543539
Electronic and Zero-Point Energy = -1375.868090
Enthalpy = -1375.841912
Free Energy = -1375.922957
M06-2X/def2-TZVP
Electronic Energy = -1376.7898299

C	-4.7996250	-3.9328280	-0.7198930
C	-5.5568280	-2.8249790	-1.2150960
C	-6.0271750	-1.8393170	-0.3258020
C	-5.6594080	-1.8572170	1.0323790
C	-3.0663830	-2.4236570	0.4967170
C	-3.8769640	-1.6687360	1.1002660
C	-3.7493490	-0.5245710	2.0433250
O	-4.9256460	-0.0716440	2.4920250
O	-2.7084580	-0.0454370	2.4170420
C	-6.0827750	-0.6784460	1.8877430
H	-6.5741450	0.0895770	1.2842530
H	-6.7456200	-0.9763830	2.7022310
C	-5.6310960	-2.5938030	-2.6210700
C	-4.1812500	-4.7358420	-1.6630660
C	-4.2554050	-4.4758790	-3.0161610
H	-6.1922420	-1.7311260	-2.9676070
H	-4.8214630	-4.2291280	0.3216260
H	-6.4346980	-0.9232560	-0.7483760
H	-5.7070400	-2.8193560	1.5436010
O	-3.5743830	-5.4294560	-3.7095220
C	-1.9231630	-3.1127430	0.0237660
C	-1.5817530	-3.0491610	-1.3401090
C	-1.1703830	-3.8936980	0.9224230
C	-0.4732490	-3.7623750	-1.7952720
H	-2.1877290	-2.4533580	-2.0120370
C	-0.0761290	-4.6124510	0.4471510
H	-1.4497550	-3.9164160	1.9679990
C	0.2665900	-4.5627370	-0.9134920
O	0.7232930	-5.3901000	1.2133090
O	1.3004790	-5.3182640	-1.3859070
O	-0.0571380	-3.7891500	-3.0844870
C	0.4042040	-5.4878460	2.5917090
H	0.4766600	-4.5137750	3.0882660
H	-0.6006420	-5.8987540	2.7393870

H	1.1380550	-6.1681140	3.0242050
C	2.5550140	-4.6472380	-1.3172830
H	2.8080100	-4.3994270	-0.2803580
H	3.3037380	-5.3328740	-1.7183780
H	2.5424020	-3.7312260	-1.9187870
C	-0.8237660	-3.0571070	-4.0272950
H	-1.8545930	-3.4284340	-4.0745210
H	-0.8317170	-1.9868570	-3.7931570
H	-0.3423990	-3.2107430	-4.9932840
C	-4.9918380	-3.4079780	-3.5347690
H	-5.0417650	-3.2283050	-4.6027580
O	-3.4439500	-5.8710170	-1.4567150
C	-2.8402140	-6.1566150	-2.7164950
H	-2.9100560	-7.2250610	-2.9236370
H	-1.7978840	-5.8131930	-2.7197860

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M06-2X/6-31G(d,p)
Electronic Energy = -1376.33752356
Electronic and Zero-Point Energy = -1375.946975
Enthalpy = -1375.920900
Free Energy = -1376.003084
M06-2X/def2-TZVP
Electronic Energy = -1376.8697393

C	1.7357470	-0.1110940	-0.8274440
C	3.1028860	0.3675120	-0.2993050
C	3.4009590	1.6758540	-0.2658220
C	2.4035670	2.7100790	-0.6750350
C	0.6428270	0.9262900	-0.5408920
C	0.9973800	2.2140220	-0.5134110
C	0.1550380	3.4030770	-0.2126760
O	0.9823440	4.4310250	0.0982080
O	-1.0409090	3.5409120	-0.2365510
C	2.3511600	3.9838520	0.1786390
H	2.5865930	3.7683300	1.2261470
H	2.9875740	4.7908120	-0.1844440
C	4.0871030	-0.6260880	0.1369350
C	1.3576270	-1.5177230	-0.4013950
C	2.3058490	-2.3154400	0.0802960
C	3.6770970	-1.8862260	0.3170870
H	5.0954280	-0.3085400	0.3795110
H	0.3516770	-1.8793570	-0.5757950
H	1.8272100	-0.1384190	-1.9288650
H	4.3861380	2.0022070	0.0600990

H	2.5609690	3.0053270	-1.7246300
C	-0.7562100	0.4660530	-0.3263130
C	-1.3348590	0.5842220	0.9367950
C	-1.4452520	-0.1337010	-1.3837400
C	-2.6322700	0.1066880	1.1421360
H	-0.7745880	1.0488270	1.7390370
C	-2.7414180	-0.6124990	-1.1737050
H	-0.9662630	-0.2278300	-2.3517370
C	-3.3414680	-0.4801290	0.0861800
O	-3.2924010	0.1590300	2.3227670
O	-4.6216410	-0.9151700	0.2818280
O	-3.4997540	-1.2160500	-2.1180410
C	-2.6270300	0.7753730	3.4130530
H	-1.7086270	0.2395110	3.6774360
H	-2.3875890	1.8216120	3.1928260
H	-3.3219370	0.7340050	4.2520580
C	-4.6789570	-2.2431020	0.7923370
H	-4.1404840	-2.3201290	1.7435830
H	-5.7331090	-2.4756460	0.9550690
H	-4.2567790	-2.9559450	0.0745570
C	-2.9317540	-1.3640700	-3.4087760
H	-2.0254340	-1.9796290	-3.3800900
H	-3.6869840	-1.8633350	-4.0161020
H	-2.6953340	-0.3908540	-3.8536530
O	2.2091440	-3.6189690	0.4684720
C	3.5335130	-4.0900430	0.6792560
H	3.5741820	-4.6603590	1.6080760
H	3.8537830	-4.6939870	-0.1767190
O	4.3762610	-2.9450330	0.7931230

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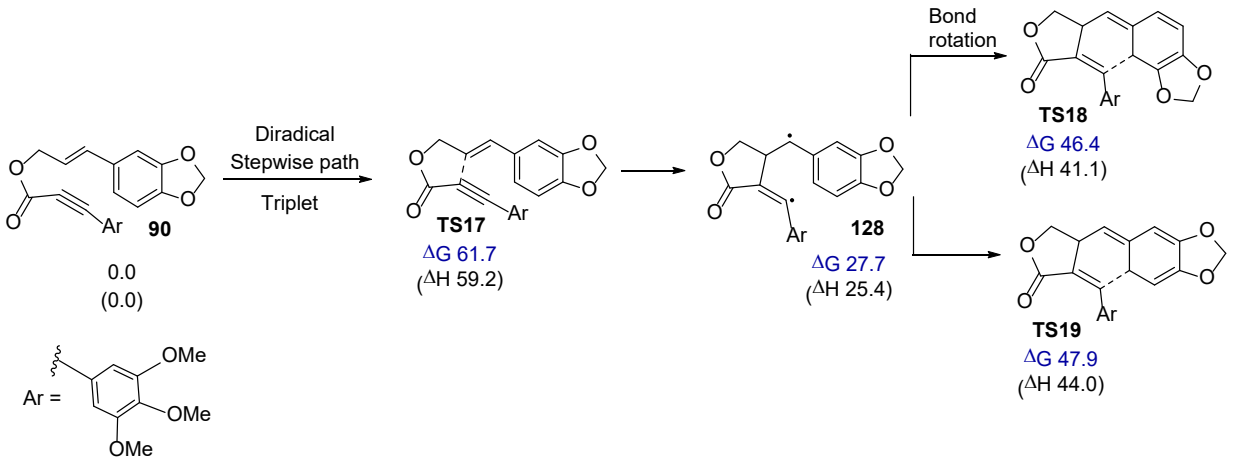
M06-2X/6-31G(d,p)
Electronic Energy = -1376.32471215
Electronic and Zero-Point Energy = -1375.934450
Enthalpy = -1375.908312
Free Energy = -1375.991289
M06-2X/def2-TZVP
Electronic Energy = -1376.8566532

C	-3.3294200	2.1680880	1.2417580
C	-3.0917760	1.0954450	0.2722410
C	-3.9328230	0.0545120	0.1633100
C	-3.5740910	-1.0958720	-0.7297740
C	-1.2031010	-0.3282670	-0.5831970
C	-2.0863550	-1.3231150	-0.6985170

C	-1.8493220	-2.7875370	-0.7009210
O	-3.0425610	-3.4101050	-0.5544080
O	-0.8242110	-3.4051420	-0.8349060
C	-4.1001710	-2.4696840	-0.2844360
H	-4.3059280	-2.4854710	0.7903920
H	-4.9846010	-2.7983390	-0.8298750
C	-1.8187450	1.0820260	-0.6052760
C	-2.4234860	3.1343240	1.4930080
C	-1.2043520	3.1153230	0.7212180
C	-0.9283600	2.2069040	-0.2175840
H	-2.1331600	1.2537260	-1.6499500
H	-2.5856570	3.9072910	2.2357520
H	-4.2591250	2.1234260	1.8012630
H	-4.8436010	0.0062430	0.7553980
H	-3.8933990	-0.8903410	-1.7634480
C	0.2528120	-0.5260370	-0.3593690
C	0.6672230	-1.0603410	0.8626530
C	1.1777250	-0.1476230	-1.3322470
C	2.0323990	-1.2186390	1.1139190
H	-0.0752600	-1.3448360	1.5984560
C	2.5416230	-0.3048570	-1.0762810
H	0.8319110	0.2840380	-2.2629260
C	2.9703500	-0.8535390	0.1399110
O	2.5512020	-1.7086020	2.2653060
O	4.3050490	-1.0291050	0.3743620
O	3.5285930	0.0451580	-1.9358280
C	1.6331700	-2.1017340	3.2716020
H	1.0279090	-1.2546320	3.6137040
H	0.9719610	-2.9008100	2.9178670
H	2.2339380	-2.4730750	4.1020930
C	4.8983260	0.0969370	1.0123760
H	4.4444860	0.2742840	1.9940870
H	5.9582510	-0.1303170	1.1418480
H	4.7935910	0.9965200	0.3946910
C	3.1373790	0.6810410	-3.1409360
H	2.5783230	1.6025370	-2.9411150
H	4.0592980	0.9257730	-3.6688250
H	2.5294660	0.0174780	-3.7661370
O	-0.2573680	4.1188490	0.7103290
C	0.7878270	3.5571210	-0.0778750
H	1.5042670	3.0421160	0.5821150
H	1.2684600	4.3353160	-0.6701500
O	0.1815290	2.5967260	-0.9359480

5.6.2.1.2. XYZ Coordinates for triplet states Diels-Alder mechanism

Triplet states for the diradical Diels-Alder mechanism were found being 32.9 kcal/mol higher in energy than the concerted mechanism.



Scheme 40. Energy surface. Triplet states Diels-Alder reaction stepwise mechanism.

Triplet **TS17**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.19565828
Electronic and Zero-Point Energy = -1375.812681
Enthalpy = -1375.785191
Free Energy = -1375.872601
M06-2X/def2-TZVP
Electronic Energy = -1376.7324715
$<S^2>$ = 2.028783

O	5.5651200	1.1412430	3.4209620
O	4.3683530	-0.7535220	2.9186850
O	-2.2148190	4.1912680	-2.6460600
O	-0.1323820	4.3689960	-1.9101990
O	-4.7303930	-2.3936690	-0.1218400
O	-2.7928460	-4.1790920	-0.4959660
O	-0.3914750	-3.4825230	-1.3992390
C	-1.6892260	1.2048540	-1.3580330
C	-1.3284880	2.3765140	-1.4272130
C	4.0290060	2.7437870	2.3289450
H	4.6032930	3.6310250	2.5704690
C	4.4420550	1.4899310	2.7347890

C	3.7077840	0.3369610	2.4275750
C	2.5436770	0.3783770	1.7132240
H	1.9853050	-0.5217710	1.4776400
C	2.0811410	1.6607970	1.2729640
C	-0.9811980	-1.1259030	-1.3945740
H	-0.0048830	-0.7970110	-1.7278600
C	-1.9865490	-0.1728130	-1.1620100
C	-3.2690730	-0.5499030	-0.7354210
H	-4.0230640	0.2102920	-0.5767100
C	-3.5396820	-1.9021630	-0.5290240
C	-2.5391440	-2.8642110	-0.7428700
C	-1.2683000	-2.4757650	-1.1951500
C	0.9015880	3.6725930	-1.1825750
H	1.6216560	4.4539280	-0.9147600
H	1.3949380	2.9546730	-1.8467370
C	5.3812890	-0.2307700	3.7763280
H	6.3126170	-0.7756520	3.6196330
H	5.0472230	-0.2925840	4.8194760
C	0.9190020	-3.1247540	-1.8102810
H	0.9065880	-2.6091110	-2.7767890
H	1.4086240	-2.4882680	-1.0641750
H	1.4709610	-4.0595640	-1.9065630
C	-3.4340070	-4.8380180	-1.5863090
H	-2.8034710	-4.8134300	-2.4819840
H	-4.4025240	-4.3761750	-1.8054090
H	-3.5883820	-5.8743060	-1.2811440
C	-5.7737390	-1.4610600	0.1159770
H	-5.5022310	-0.7560260	0.9093770
H	-6.0290560	-0.9073650	-0.7942350
H	-6.6354240	-2.0478640	0.4338890
C	-1.2855040	3.7064320	-2.0497030
C	0.3113980	2.9879580	0.0087250
H	-0.2665900	3.6290690	0.6771500
C	0.8786340	1.7440150	0.5301580
H	0.3369340	0.8176620	0.3401670
C	2.8415120	2.8152620	1.5985300
H	2.4819970	3.7874000	1.2757320

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M06-2X/6-31G(d,p)
Electronic Energy = -1376.25393310
Electronic and Zero-Point Energy = -1375.867995
Enthalpy = -1375.840677
Free Energy = -1375.928310
M06-2X/def2-TZVP

Electronic Energy = -1376.789164
$\langle S^2 \rangle$ = 2.061148

O	5.8690400	-2.2213400	0.9064170
O	4.3929000	-3.0055840	-0.6695090
O	-1.0643060	5.0481670	-0.5245720
O	1.1357520	4.6429720	-0.5847670
O	-4.1153960	-1.0243130	2.3033430
O	-4.1652090	-2.6471580	0.2063010
O	-2.9567230	-2.0340880	-2.0877220
C	-1.2904580	2.0885280	-0.1404600
C	-0.1923000	2.7999590	-0.1470340
C	4.7183340	-0.0712080	1.3231750
H	5.4264730	0.2947180	2.0579890
C	4.8743720	-1.3084290	0.7302240
C	3.9706050	-1.7837510	-0.2286550
C	2.8830500	-1.0613930	-0.6305350
H	2.1905570	-1.4408910	-1.3744650
C	2.6805760	0.2260740	-0.0340340
C	-2.0894940	0.0406370	-1.1740580
H	-1.5743740	0.3211980	-2.0839250
C	-2.0059380	0.8910180	-0.0441640
C	-2.6864050	0.5666750	1.1541370
H	-2.6237400	1.2435790	1.9966600
C	-3.4204600	-0.6119320	1.2208270
C	-3.4777160	-1.4765990	0.1117880
C	-2.8185230	-1.1383720	-1.0847530
C	2.0045730	3.4961170	-0.6210210
H	2.9367550	3.7631110	-0.1222620
H	2.2041110	3.2448370	-1.6672490
C	5.4257610	-3.4007460	0.2319000
H	6.2549370	-3.8342850	-0.3280080
H	5.0216720	-4.1085620	0.9661940
C	-2.3003980	-1.7412160	-3.3114380
H	-2.6711260	-0.8081360	-3.7494190
H	-1.2153710	-1.6736160	-3.1726740
H	-2.5275420	-2.5700880	-3.9816240
C	-5.4886920	-2.5600130	-0.3193040
H	-5.4683430	-2.3120430	-1.3857830
H	-6.0718450	-1.8067090	0.2221360
H	-5.9480890	-3.5403990	-0.1834280
C	-4.0924850	-0.1851680	3.4471130
H	-3.0741130	-0.0669290	3.8339130
H	-4.5147620	0.8015400	3.2264180
H	-4.7071980	-0.6816520	4.1979970
C	-0.1521510	4.2684390	-0.4368930

C	1.2420790	2.3520980	0.0883530
H	1.4502900	2.4186830	1.1640900
C	1.5613940	0.9922080	-0.4312470
H	0.9177380	0.5951520	-1.2115810
C	3.6133500	0.6881650	0.9320080
H	3.4710680	1.6647060	1.3834940

Triplet **TS18**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.23057859
Electronic and Zero-Point Energy = -1375.845358
Enthalpy = -1375.819056
Free Energy = -1375.901928
M06-2X/def2-TZVP
Electronic Energy = -1376.24525
$<S^2>$ = 2.038283

C	3.6837110	-0.0090550	0.8558180
C	3.0637490	0.6859820	-0.1817820
C	3.1741500	2.0941210	-0.3158260
C	2.1557620	2.8555490	-1.1074360
C	0.4013300	1.0766630	-0.6881300
C	0.7469820	2.3364900	-0.8985990
C	-0.1646870	3.5180490	-0.9078460
O	0.5926600	4.6385850	-0.8933100
O	-1.3677010	3.5588510	-0.9379980
C	1.9819930	4.3220040	-0.6817870
H	2.2049640	4.4512320	0.3825180
H	2.5766170	5.0218570	-1.2687680
C	2.1580220	-0.0192150	-1.0932210
C	3.4846100	-1.3998850	1.0890510
C	2.6426470	-2.0451680	0.2291590
C	2.0517350	-1.3840760	-0.8715760
H	2.0342410	0.3507230	-2.1086520
H	3.9791400	-1.9156990	1.9030800
H	4.3222140	0.5465100	1.5363400
H	3.9292920	2.6354230	0.2461300
H	2.3862200	2.8319040	-2.1857670
C	-0.7812740	0.3481790	-0.3178010
C	-1.4543410	0.6738140	0.8724760
C	-1.1976030	-0.7376710	-1.1041270
C	-2.5583370	-0.0835480	1.2602830
H	-1.1122190	1.5159170	1.4608360
C	-2.3027380	-1.4898990	-0.7069560
H	-0.6557000	-0.9749630	-2.0103550

C	-2.9749040	-1.1773320	0.4840260
O	-3.2983230	0.1488020	2.3702190
O	-4.0235720	-1.9470220	0.8943400
O	-2.7975150	-2.5455070	-1.3946170
C	-2.9346750	1.2631490	3.1691500
H	-1.9272570	1.1453360	3.5836390
H	-2.9855300	2.1969690	2.5979670
H	-3.6575730	1.2989590	3.9842660
C	-5.2888160	-1.4025500	0.5287130
H	-5.3830970	-1.3343690	-0.5610220
H	-6.0486580	-2.0840350	0.9153770
H	-5.4311070	-0.4108290	0.9712590
C	-2.1451600	-2.8920970	-2.6047100
H	-1.0954360	-3.1585500	-2.4328310
H	-2.6766110	-3.7597330	-2.9961120
H	-2.1939460	-2.0760280	-3.3344690
O	2.3316750	-3.3692620	0.1628440
C	1.3339950	-3.4815300	-0.8515580
H	1.5306220	-4.3609690	-1.4645530
H	0.3407690	-3.5220030	-0.3850430
O	1.4338080	-2.3085240	-1.6569370

Triplet **TS19**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.22417442
Electronic and Zero-Point Energy = -1375.839952
Enthalpy = -1375.813214
Free Energy = -1375.898368
M06-2X/def2-TZVP
Electronic Energy = -1376.7571903
$\langle S^2 \rangle$ = 2.028838

C	1.9782840	-0.0573640	-1.0542330
C	2.8325960	0.7312150	-0.1904060
C	3.0291030	2.1277550	-0.5203220
C	1.9923560	2.8711870	-1.2980150
C	0.2498240	1.0904070	-0.8281640
C	0.5905700	2.3368240	-1.1095910
C	-0.3341090	3.5065600	-1.1987180
O	0.4106680	4.6362400	-1.1608560
O	-1.5332140	3.5329210	-1.2988490
C	1.7857830	4.3316460	-0.8592590
H	1.9383680	4.4427020	0.2193500
H	2.4121140	5.0441050	-1.3958660
C	3.3635330	0.1793110	0.9726610

C	1.7730530	-1.4349690	-0.7838450
C	2.2814060	-1.9276950	0.4021820
C	3.0645580	-1.1572640	1.2461410
H	3.9739590	0.7692350	1.6479290
H	1.2340420	-2.0715310	-1.4755460
H	1.9211950	0.2477690	-2.0979520
H	3.9080540	2.6540190	-0.1611660
H	2.2350000	2.8769080	-2.3745930
C	-0.9564620	0.3894470	-0.4837400
C	-1.6078630	0.6833670	0.7265050
C	-1.4194160	-0.6416570	-1.3173080
C	-2.7420700	-0.0440950	1.0847420
H	-1.2269280	1.4798980	1.3532320
C	-2.5566390	-1.3610830	-0.9507910
H	-0.8992260	-0.8481050	-2.2446040
C	-3.2082200	-1.0793070	0.2596920
O	-3.4672820	0.1665920	2.2088110
O	-4.2887630	-1.8213710	0.6390010
O	-3.1079870	-2.3533610	-1.6869050
C	-3.0456370	1.2173230	3.0630610
H	-2.0378050	1.0349920	3.4524010
H	-3.0659470	2.1829920	2.5454810
H	-3.7542560	1.2362980	3.8912130
C	-5.5280790	-1.2211780	0.2741890
H	-5.6032690	-1.1115180	-0.8136500
H	-6.3182810	-1.8872960	0.6255680
H	-5.6424950	-0.2406140	0.7491800
C	-2.4741470	-2.6799650	-2.9122240
H	-1.4460220	-3.0238350	-2.7502860
H	-3.0590580	-3.4898550	-3.3486700
H	-2.4678970	-1.8271220	-3.6002610
O	2.1491610	-3.1835750	0.9292890
C	3.1052170	-3.2447100	1.9853000
H	2.6660800	-3.7390540	2.8520730
H	4.0055800	-3.7664150	1.6354950
O	3.4460450	-1.8973290	2.3244170

5.6.2.1.3. XYZ Coordinates for less hindered starting material

In order to explain the small energy difference between concerted mechanisms of two TS of the isomers (**TS9** and **TS10**), we performed calculations with a less hindered starting material (**123**). The energy difference between both isomers is 1.2 kcal/mol compared with 2.8 kcal/mol of the

original ester. This proves that steric interactions play an important role in defining the selectivity between **95** and **96** products.

123

M06-2X/6-31G(d,p)
Electronic Energy = -1032.86798347
Electronic and Zero-Point Energy = -1032.579389
Enthalpy = -1032.559200
Free Energy = -1032.631066
M06-2X/def2-TZVP
Electronic Energy = -1033.265456

C	4.0020330	0.1817940	-0.2801180
C	2.9431370	0.7298700	-0.4874690
C	1.6671910	1.3539120	-0.7878530
O	1.3470530	2.2628220	0.1365640
C	0.0572210	2.8994270	-0.0316000
C	-1.0401360	2.0208250	0.4787000
H	-0.0887560	3.1513990	-1.0841740
H	0.1411480	3.8170060	0.5547480
C	-2.0262060	1.5798080	-0.3084450
C	-3.1647600	0.7383150	0.0981220
H	-0.9934830	1.7576110	1.5338710
H	-1.9935370	1.8396860	-1.3666270
C	-3.5214700	0.5571340	1.4393030
C	-4.5894440	-0.2669680	1.8188340
C	-5.2880540	-0.8893420	0.8060850
C	-4.9523330	-0.7072560	-0.5327970
C	-3.9057770	0.0960950	-0.9198530
H	-2.9701720	1.0789590	2.2146860
H	-3.6493460	0.2252340	-1.9663890
H	-4.8595600	-0.4049660	2.8595360
O	1.0000880	1.0800710	-1.7579800
C	-6.8220120	-1.9018500	-0.4390660
H	-7.7100620	-1.2717490	-0.5753210
H	-7.0413590	-2.9515320	-0.6361070
O	-5.7842170	-1.4580840	-1.3135870
O	-6.3379370	-1.7559080	0.8973870
C	5.2514020	-0.4695600	-0.0264690
C	6.0015940	-0.1295200	1.1094240
C	5.7215530	-1.4520810	-0.9105440
H	5.6292140	0.6307190	1.7882080
H	5.1346000	-1.7086060	-1.7863340
C	6.9311360	-2.0868840	-0.6554900

H	7.2948020	-2.8468320	-1.3392920
C	7.6747290	-1.7483110	0.4749270
H	8.6186200	-2.2475020	0.6703420
C	7.2099090	-0.7707620	1.3543980
H	7.7897320	-0.5085110	2.2332500

TS12

M06-2X/6-31G(d,p)
Electronic Energy = -1032.82561461
Electronic and Zero-Point Energy = -1032.538312
Enthalpy = -1032.519412
Free Energy = -1032.585499
M06-2X/def2-TZVP
Electronic Energy = -1033.218481

C	-0.5282800	-1.2316740	1.7145980
C	-0.2056600	0.0627260	1.2297450
C	1.0865080	0.5955180	1.4219140
C	2.1156340	-0.1823550	1.9685540
C	1.4622890	-2.3305700	0.4062550
C	2.3905970	-1.5926450	0.8236810
C	3.8704830	-1.5356450	0.6960330
O	4.4340570	-0.5327600	1.3793830
O	4.5395790	-2.3171530	0.0679130
C	3.5133650	0.3941490	1.9854870
H	3.5597420	1.3248640	1.4131700
H	3.8762190	0.5745640	2.9992090
C	-1.1208950	0.7329100	0.3494660
C	-1.7381030	-1.8731570	1.3803770
C	-2.5644290	-1.2136480	0.5097490
C	-2.2631810	0.0753350	0.0161480
H	-0.8840930	1.7123270	-0.0525370
H	-1.9878010	-2.8554770	1.7647640
H	0.0947080	-1.6927700	2.4715850
H	1.3474440	1.5014450	0.8781760
H	1.8755180	-0.8026290	2.8321990
O	-3.7473760	-1.6229570	-0.0090020
O	-3.2558320	0.4637960	-0.8347010
C	0.6098230	-3.2823600	-0.2036170
C	-0.1249450	-2.9415060	-1.3575180
C	0.4354010	-4.5594480	0.3661090
H	-0.0101200	-1.9503460	-1.7861600
H	0.9923130	-4.8234620	1.2594970
C	-4.3050730	-0.4876780	-0.6776380
H	-4.6752700	-0.7910000	-1.6574730

H	-5.1031390	-0.0606040	-0.0592050
C	-0.9879550	-3.8663540	-1.9330580
H	-1.5433900	-3.5942340	-2.8254580
C	-1.1555630	-5.1292490	-1.3645540
H	-1.8388480	-5.8437360	-1.8118950
C	-0.4429550	-5.4663080	-0.2124880
H	-0.5690860	-6.4467280	0.2367690

TS13

M06-2X/6-31G(d,p)
Electronic Energy = -1032.82391029
Electronic and Zero-Point Energy = -1032.536857
Enthalpy = -1032.517941
Free Energy = -1032.584472
M06-2X/def2-TZVP
Electronic Energy = -1033.218481

C	-4.8495010	-3.9426390	-0.6808570
C	-5.5230840	-2.8042030	-1.2240150
C	-6.0009080	-1.7987440	-0.3615030
C	-5.6984490	-1.8309620	1.0120190
C	-3.1039680	-2.4769890	0.5490830
C	-3.9079450	-1.7154540	1.1524360
C	-3.7774880	-0.5919680	2.1197800
O	-4.9531650	-0.0968750	2.5241010
O	-2.7357680	-0.1598030	2.5450720
C	-6.1058410	-0.6369510	1.8518120
H	-6.5222500	0.1589840	1.2282140
H	-6.8273230	-0.9034080	2.6263610
C	-5.4945640	-2.5773700	-2.6322440
C	-4.2166580	-4.7814230	-1.5791710
C	-4.1788360	-4.5220590	-2.9340850
H	-5.9919330	-1.6929090	-3.0190500
H	-4.9458730	-4.2315140	0.3584290
H	-6.3481160	-0.8666310	-0.8026560
H	-5.8039320	-2.7898640	1.5204850
O	-3.5024910	-5.5122970	-3.5750630
C	-1.9727910	-3.1381560	0.0127020
C	-1.6247310	-2.9448550	-1.3408280
C	-1.1923190	-4.0079220	0.8019090
H	-2.2415980	-2.2972800	-1.9574070
H	-1.4630970	-4.1718240	1.8401290
C	-4.8315370	-3.4231270	-3.5000590
H	-4.8011470	-3.2436750	-4.5686680
O	-3.5634610	-5.9544910	-1.3177690

C	-2.8963690	-6.2882360	-2.5334530
H	-3.0333310	-7.3491340	-2.7472630
H	-1.8350290	-6.0240980	-2.4568890
C	-0.0813380	-4.6352430	0.2548450
H	0.5157660	-5.2977470	0.8740170
C	0.2818300	-4.4069040	-1.0745990
H	1.1597140	-4.8901860	-1.4913300
C	-0.4936390	-3.5594790	-1.8661020
H	-0.2251240	-3.3851020	-2.9038410

5.6.2.1.4. XYZ Coordinates for phenyl-alkyne pathway

Mechanism between phenyl-alkyne as diene and alkene as dienophile was also explored finding higher in energy than using the styryl group as diene. Starting material 92 was shown before.

TS11

M06-2X/6-31G(d,p)
Electronic Energy = -1376.24199741
Electronic and Zero-Point Energy = -1375.855529
Enthalpy = -1375.828941
Free Energy = -1375.912511
M06-2X/def2-TZVP
Electronic Energy = -1376.7757045

O	5.2694270	0.3473540	1.5379760
O	3.7935050	-0.9327280	2.7489060
O	-0.2561380	4.1574430	-2.9063280
O	0.0279510	4.4768800	-0.7220050
O	-4.1386000	-2.4295690	-0.8465130
O	-2.0608380	-3.6790480	0.1909190
O	0.5348490	-2.4711760	0.0377710
C	-1.2859770	1.3860590	-2.0050540
C	-0.8894400	2.4254470	-1.3643230
C	3.5796550	1.7451400	0.4106690
H	4.2845680	2.3250170	-0.1734720
C	4.0027610	0.7603710	1.2799390
C	3.1011100	-0.0143390	2.0148890
C	1.7465600	0.1599180	1.9171610
H	1.0519080	-0.4558990	2.4790280
C	1.2765490	1.1868320	1.0522210
C	-0.4274070	-0.6035930	-0.9942230
H	0.5742420	-0.2037350	-1.0787920
C	-1.5261570	0.0718130	-1.5576020

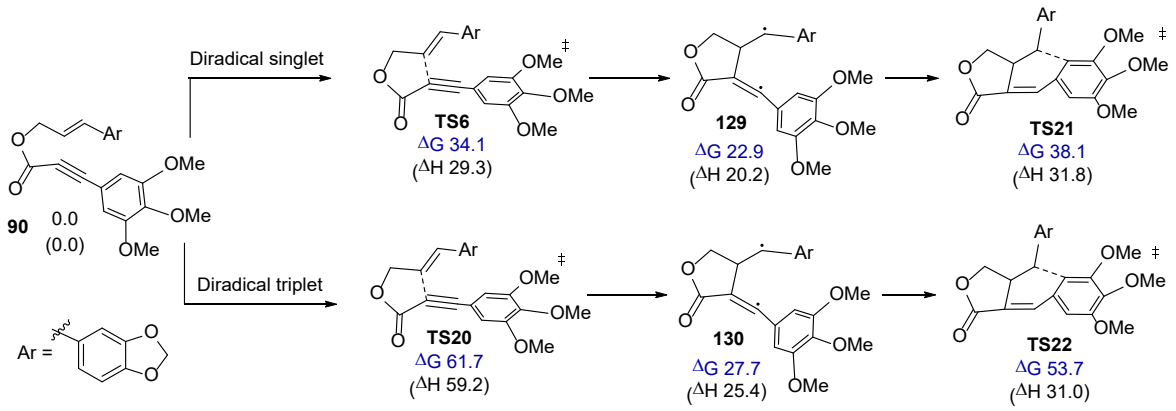
C	-2.8133350	-0.5205760	-1.5309120
H	-3.6517090	0.0115580	-1.9618460
C	-2.9685290	-1.7601070	-0.9375150
C	-1.8592690	-2.4476090	-0.3676120
C	-0.5960680	-1.8735740	-0.4155810
C	-0.2711020	3.8724550	0.5448090
H	-1.0105000	4.5055860	1.0397590
H	0.6489920	3.8708520	1.1307750
C	5.1644740	-0.5491330	2.6486760
H	5.7790010	-1.4300590	2.4635060
H	5.4694990	-0.0275490	3.5636360
C	0.4793860	-3.2547570	1.2275700
H	-0.2436090	-2.8466310	1.9397170
H	0.2218030	-4.2950410	1.0126180
H	1.4816060	-3.2119630	1.6598640
C	-2.0005450	-4.7348710	-0.7649930
H	-1.0236400	-4.7553370	-1.2629130
H	-2.7897190	-4.6264490	-1.5165950
H	-2.1467950	-5.6672310	-0.2164900
C	-5.2778130	-1.8240020	-1.4369260
H	-5.5139410	-0.8692060	-0.9541630
H	-5.1285170	-1.6607170	-2.5099300
H	-6.1027520	-2.5201730	-1.2861240
C	-0.3598360	3.7453880	-1.7789230
C	-0.8495150	2.4575490	0.3689370
H	-1.9065590	2.4235920	0.6269730
C	-0.1513320	1.3572400	0.9393710
H	-0.7509900	0.5920050	1.4244530
C	2.1996310	1.9471400	0.3081160
H	1.8427370	2.6946520	-0.3927710

122

M06-2X/6-31G(d,p)
Electronic Energy = -1376.28804177
Electronic and Zero-Point Energy = -1375.896909
Enthalpy = -1375.871352
Free Energy = -1375.951234
M06-2X/def2-TZVP
Electronic Energy = -1376.8184862

O	-3.5393010	-2.5611840	-1.3567760
O	-3.4004820	-2.2612880	0.9162230
O	5.7989360	0.0314700	-1.0284710
O	4.9787170	-1.3741460	0.5122810
O	-1.7728580	2.5263120	-1.5717290

O	-2.2353070	2.2936290	0.9632010
O	-0.0821560	1.1803630	2.6612490
C	2.8196660	0.9769810	-1.0098590
C	3.4033540	-0.1502970	-0.6272010
C	-1.2135500	-1.8737560	-1.8632810
H	-1.2809610	-2.0150270	-2.9360020
C	-2.2887720	-2.1113940	-1.0360980
C	-2.2016760	-1.9385270	0.3427870
C	-1.0442330	-1.5184950	0.9557330
H	-0.9936830	-1.3767510	2.0316660
C	0.0682520	-1.2531400	0.1307180
C	1.2692520	0.9199230	0.7811440
H	2.0676490	1.2386410	1.4559930
C	1.5579120	1.3332800	-0.6432710
C	0.5167700	1.8389090	-1.4583920
H	0.7042450	2.0092900	-2.5104440
C	-0.7107770	2.0849480	-0.8946540
C	-0.9972980	1.8962850	0.5285100
C	-0.0338870	1.3899690	1.3389820
C	3.7111610	-1.6006020	1.1632660
H	3.6596070	-0.9600970	2.0514870
H	3.6769370	-2.6470720	1.4674290
C	-4.3152680	-2.3631770	-0.1760830
H	-4.8841720	-1.4278620	-0.2642300
H	-4.9737830	-3.2186200	-0.0225150
C	-1.1884610	1.6333200	3.4434100
H	-1.3542690	2.7027810	3.3029490
H	-2.0985770	1.0804040	3.1993770
H	-0.9088040	1.4311170	4.4776040
C	-3.2610580	1.3329120	0.7154890
H	-3.2144440	0.5154160	1.4457050
H	-3.1818740	0.9196550	-0.2953780
H	-4.2144230	1.8548670	0.8191030
C	-1.6362160	2.7099600	-2.9775940
H	-0.8857550	3.4750340	-3.1983030
H	-1.3609630	1.7685480	-3.4642230
H	-2.6116860	3.0393520	-3.3327400
C	4.8460380	-0.4348660	-0.4554490
C	2.6276910	-1.2169160	0.1438780
H	2.4066300	-2.0847470	-0.4851690
C	1.3204520	-0.6881180	0.7692960
H	1.3078750	-0.9583520	1.8310390
C	-0.0279640	-1.4363370	-1.2490010
H	0.8317290	-1.2129930	-1.8751490



Scheme 41. Phenyl-alkyne singlet and triplet energies

Singlet **TS21**

<u>M06-2X/6-31G(d,p)</u>
Electronic Energy = -1376.24382041
Electronic and Zero-Point Energy = -1375.856851
Enthalpy = -1375.830837
Free Energy = -1375.912207
<u>M06-2X/def2-TZVP</u>
Electronic Energy = -1376.776997
$<S^2>$ = 0.128884

C	3.2681200	-2.7972750	-3.8443290
C	3.1953310	-2.4080930	-2.4923200
C	4.3345420	-1.7473210	-1.9134930
C	4.5967540	-1.5895880	-0.4800960
C	3.7586690	0.8011230	-0.2036710
C	3.7713550	-0.4273000	0.2452370
C	3.0839800	-1.0285830	1.4113300
O	3.3166970	-2.3575820	1.4455560
O	2.3945510	-0.4861320	2.2377210
C	4.2299560	-2.7918830	0.4259260
H	3.7527880	-3.6056190	-0.1217650
H	5.1241170	-3.1725880	0.9235370
C	1.9941210	-2.6286280	-1.7609960
C	2.2061990	-3.4242980	-4.5009440
C	1.0605920	-3.6358330	-3.7605530
C	0.9625050	-3.2410800	-2.4229910
H	1.8769120	-2.3101960	-0.7306060
H	2.2720090	-3.7245190	-5.5404490
H	4.1881810	-2.6045210	-4.3883830
H	5.1720350	-1.5794840	-2.5832900
H	5.6506040	-1.3393580	-0.3477760
C	4.2703710	1.1943820	-1.4526720

C	3.6574430	0.6006300	-2.5805890
C	5.4389060	1.9830070	-1.6152650
C	4.1743560	0.8288140	-3.8768210
H	2.6854060	0.1336570	-2.4934000
C	5.9496670	2.1656280	-2.8844480
H	5.9156710	2.4103080	-0.7424810
C	5.3228460	1.5852030	-4.0318270
O	3.4620890	0.2796930	-4.8902340
O	5.8619790	1.8329800	-5.2635220
O	7.0520560	2.8866290	-3.1743400
C	4.1446620	-0.1890420	-6.0510490
H	5.1077760	-0.6372650	-5.7896520
H	3.4936650	-0.9477770	-6.4905080
H	4.3072130	0.6123960	-6.7762360
C	5.4042450	3.0583860	-5.8310990
H	5.6776040	3.9083200	-5.1968160
H	5.8924150	3.1573900	-6.8023210
H	4.3165150	3.0419300	-5.9696240
C	7.7004350	3.5452210	-2.0969560
H	8.0865530	2.8254160	-1.3670540
H	8.5323040	4.0948110	-2.5371090
H	7.0232750	4.2456740	-1.5964050
O	-0.1150780	-4.1834270	-4.1589030
C	-0.9118820	-4.3117890	-2.9763890
H	-1.9146680	-3.9291070	-3.1707950
H	-0.9330390	-5.3631170	-2.6679950
O	-0.2876350	-3.5257070	-1.9611850

Triplet **TS22**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.22406565
Electronic and Zero-Point Energy = -1375.810865
Enthalpy = -1375.836428
Free Energy = -1375.891600
M06-2X/def2-TZVP
Electronic Energy = -1376.7546503
$\langle S^2 \rangle$ = 2.035487

C	3.4829800	-2.4915370	-3.5903730
C	2.9084700	-2.0374810	-2.3852010
C	3.7770180	-1.4808050	-1.3745830
C	3.3846710	-1.4104170	0.0771080
C	5.0385320	0.4634540	0.3966770
C	4.3046920	-0.5270260	0.9008290
C	4.4097270	-1.1237980	2.2466100

O	3.8344690	-2.3529220	2.2131320
O	4.8859130	-0.6678700	3.2568900
C	3.5454460	-2.7311370	0.8531230
H	2.6454080	-3.3463030	0.8570220
H	4.3898250	-3.3118390	0.4663970
C	1.4953110	-2.0734140	-2.2299050
C	2.7154420	-2.9933140	-4.6466080
C	1.3475420	-3.0088810	-4.4662310
C	0.7604410	-2.5570780	-3.2818880
H	1.0065380	-1.7317160	-1.3243450
H	3.1696700	-3.3536460	-5.5629760
H	4.5636450	-2.4520460	-3.6948360
H	4.8384380	-1.6690150	-1.5354240
H	2.3502750	-1.0617400	0.1840500
C	5.0322700	0.9495610	-0.9504350
C	3.8631120	0.6249100	-1.7018910
C	6.1855780	1.4263270	-1.5842240
C	3.8525620	0.8993880	-3.1054300
H	2.8933740	0.6648760	-1.2133970
C	6.1737660	1.6177830	-2.9604750
H	7.0771710	1.6126480	-0.9976900
C	5.0082140	1.3370870	-3.7354880
O	2.6445400	0.7086050	-3.6691510
O	5.0264070	1.6276660	-5.0716220
O	7.2207270	2.0824020	-3.6767580
C	2.4883860	0.5423740	-5.0746200
H	2.5954490	1.4909670	-5.6040240
H	3.1995980	-0.1868250	-5.4710130
H	1.4745120	0.1588950	-5.2066200
C	5.7682230	0.6988080	-5.8611260
H	5.3651640	-0.3153490	-5.7515640
H	5.6624130	1.0198620	-6.8988280
H	6.8253940	0.7021820	-5.5830170
C	8.4113480	2.3924650	-2.9688330
H	8.8188730	1.5053880	-2.4717840
H	9.1213680	2.7494530	-3.7145320
H	8.2373680	3.1792290	-2.2267390
O	0.3759900	-3.4710080	-5.3058940
C	-0.8523640	-3.0213960	-4.7338240
H	-1.1794720	-2.1082790	-5.2486090
H	-1.6003480	-3.8114310	-4.8039250
O	-0.5934240	-2.7262660	-3.3625250

5.6.2.1.5. XYZ Coordinates for carbonyl change

The effect of the position of the carbonyl was evaluated.

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M06-2X/6-31G(d,p)
Electronic Energy = -1376.30379703
Electronic and Zero-Point Energy = -1375.917019
Enthalpy = -1375.888660
Free Energy = -1375.979355
M06-2X/def2-TZVP
Electronic Energy = -1376.8413086

C	-2.5696360	1.1011920	0.4066990
C	-1.4776970	1.5880520	0.5880210
O	0.8481840	1.2719110	0.4811210
C	3.0970300	0.7130300	0.2574940
C	4.4020510	1.0150080	0.3291370
C	5.5367010	0.1516970	-0.0038510
H	2.7173250	-0.2482130	-0.0715620
H	4.6571450	2.0184640	0.6685700
C	5.3743730	-1.1687430	-0.4431940
C	6.4682130	-1.9816900	-0.7587730
C	7.7224880	-1.4243750	-0.6123520
C	7.8986390	-0.1135940	-0.1748320
C	6.8342360	0.6977300	0.1354920
H	4.3770760	-1.5834300	-0.5444400
H	6.9784050	1.7191900	0.4716150
H	6.3402400	-3.0011650	-1.1036700
C	9.9017230	-1.0614970	-0.3622670
H	10.7022710	-0.9300680	-1.0907770
H	10.2845460	-1.4342590	0.5951520
O	9.2309040	0.1822870	-0.1572610
O	8.9343230	-1.9826950	-0.8752630
C	-3.8679280	0.5250030	0.2001210
C	-4.4266420	-0.2967200	1.1931140
C	-4.5739980	0.7950660	-0.9725310
C	-5.6851420	-0.8598010	1.0005310
H	-3.8609690	-0.4943520	2.0949580
C	-5.8381400	0.2392120	-1.1561610
H	-4.1635390	1.4399220	-1.7415550
C	-6.4004690	-0.5977010	-0.1878070
O	-6.3030190	-1.6732800	1.8837740
O	-7.6325880	-1.1548570	-0.3195300
O	-6.5187720	0.5122110	-2.3109620

C	-5.6236640	-1.9481950	3.0980080
H	-4.6734540	-2.4635810	2.9178320
H	-5.4364710	-1.0304890	3.6667830
H	-6.2828300	-2.5988730	3.6725840
C	-7.8715090	-1.9092980	-1.5089470
H	-8.1921240	-1.2710530	-2.3365410
H	-8.6679190	-2.6150360	-1.2661030
H	-6.9749220	-2.4623460	-1.8060520
C	-7.6623150	1.3440800	-2.1141700
H	-8.1289090	1.4687420	-3.0923750
H	-8.3767200	0.8848650	-1.4229320
H	-7.3601720	2.3233860	-1.7263500
O	2.3446850	2.8571010	1.0276550
C	2.1034390	1.7359000	0.6327850
C	-0.1792950	2.2143620	0.8203580
H	-0.0745290	2.5096050	1.8691750
H	-0.0689350	3.1149650	0.2081750

TS14

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25454090
Electronic and Zero-Point Energy = -1375.868380
Enthalpy = -1375.841713
Free Energy = -1375.925077
M06-2X/def2-TZVP
Electronic Energy = -1376.785623

C	-0.8117960	-0.8124110	1.2171890
C	-1.2044870	0.3451230	0.4935840
C	-0.2442000	1.2991810	0.1028630
C	1.1213500	1.0235990	0.2537990
C	0.8437300	-1.5368110	-0.6415690
C	1.5251940	-0.4871770	-0.7308360
O	2.9351310	1.4211870	-1.2299870
C	-2.5395300	0.4294250	-0.0302870
C	-1.7072270	-1.8714230	1.4708090
C	-2.9512430	-1.7724090	0.9100120
C	-3.3632920	-0.6293840	0.1881760
H	-2.8526640	1.2924510	-0.6082430
H	-1.4080510	-2.7488610	2.0329960
H	0.1488460	-0.8296100	1.7182400
H	-0.5475920	2.0803060	-0.5902510
H	1.4823790	0.6129470	1.1980430
O	-3.9616370	-2.6788580	0.9193190
O	-4.6362950	-0.8342120	-0.2650360

C	0.2477630	-2.8221240	-0.7609170
C	-0.9822850	-2.9469740	-1.4295550
C	0.8488320	-3.9385450	-0.1521850
C	-1.6112590	-4.1900030	-1.4852030
H	-1.4368050	-2.0650950	-1.8644790
C	0.2176620	-5.1796920	-0.2288180
H	1.7978590	-3.8197260	0.3550930
C	-1.0216920	-5.3069080	-0.8761880
O	0.7168370	-6.3271950	0.2878090
O	-1.6553350	-6.5165800	-0.9033060
O	-2.8007640	-4.4177070	-2.0898830
C	1.9930010	-6.2611200	0.9015410
H	2.7541520	-5.8991950	0.2012440
H	1.9788060	-5.6169220	1.7878950
H	2.2366800	-7.2801390	1.2027530
C	-1.3187340	-7.2866240	-2.0529520
H	-0.2430990	-7.4946960	-2.0815680
H	-1.8659540	-8.2281880	-1.9772370
H	-1.6149800	-6.7682670	-2.9720040
C	-3.4669330	-3.2961920	-2.6427880
H	-3.6520750	-2.5243810	-1.8863860
H	-2.8938280	-2.8561620	-3.4671580
H	-4.4199020	-3.6648670	-3.0231520
C	-5.1111390	-1.9886350	0.4252720
H	-5.6536590	-2.6328650	-0.2676670
H	-5.7398800	-1.6811940	1.2696670
O	2.1010940	3.1886520	-0.1880540
C	2.0753120	1.9990910	-0.3751110
C	2.7492440	0.0163020	-1.4355320
H	2.6761040	-0.1502730	-2.5129330
H	3.6362600	-0.4983820	-1.0554500

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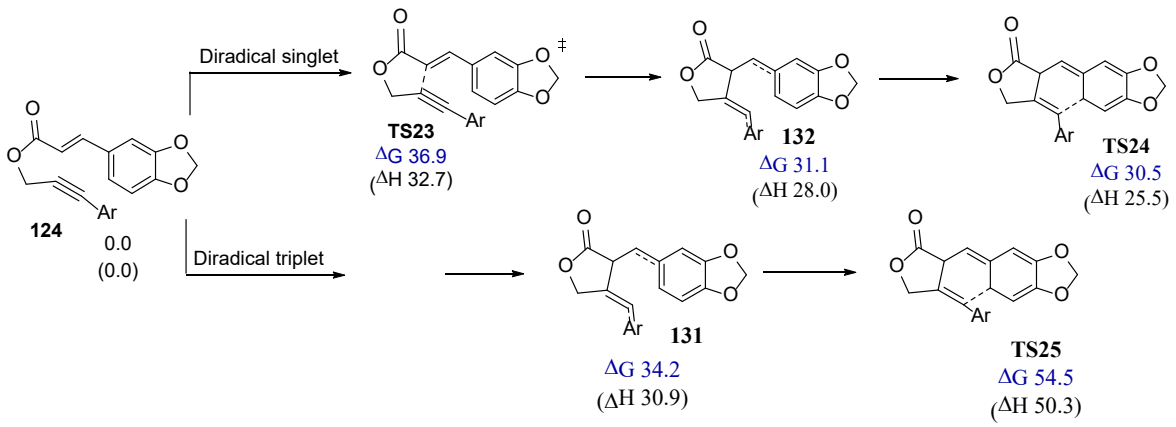
M06-2X/6-31G(d,p)
Electronic Energy = -1376.33703145
Electronic and Zero-Point Energy = -1375.946977
Enthalpy = -1375.920806
Free Energy = -1376.003604
M06-2X/def2-TZVP
Electronic Energy = -1376.8696118

C	-1.5736200	0.4443540	-0.8344600
C	-2.9989710	0.0978520	-0.3612190
C	-3.4440360	-1.1671680	-0.4094120
C	-2.5464730	-2.2698500	-0.8637470

C	-0.6125050	-0.7265240	-0.5840320
C	-1.0979530	-1.9651880	-0.6366020
O	-1.4979560	-4.1540060	0.0602910
C	-3.8782850	1.1704250	0.1113710
C	-1.0497620	1.7684330	-0.3101530
C	-1.9133140	2.6411800	0.1994130
C	-3.3319710	2.3620800	0.3769680
H	-4.9228930	0.9569640	0.3104320
H	-0.0030400	2.0167670	-0.4371710
H	-1.6392640	0.5585790	-1.9316900
H	-4.4619450	-1.4156300	-0.1212090
H	-2.7176660	-2.5039230	-1.9301620
C	0.8360760	-0.4674310	-0.3456350
C	1.4029180	-0.7936740	0.8874340
C	1.6105730	0.1016730	-1.3609020
C	2.7666840	-0.5676240	1.1026140
H	0.7759400	-1.2105090	1.6664380
C	2.9706970	0.3359580	-1.1401060
H	1.1467330	0.3567140	-2.3071100
C	3.5550360	-0.0177710	0.0844490
O	3.4161950	-0.8428190	2.2572700
O	4.8940410	0.1678830	0.2812290
O	3.8124750	0.8895070	-2.0435250
C	2.6633350	-1.4447750	3.2976190
H	1.8548440	-0.7889800	3.6391790
H	2.2417700	-2.4050680	2.9790720
H	3.3616550	-1.6126030	4.1175980
C	5.1977000	1.4512810	0.8176300
H	4.7325850	1.5849450	1.8009180
H	6.2829690	1.5035270	0.9226130
H	4.8601920	2.2462790	0.1429920
C	3.2675120	1.2531680	-3.3010390
H	2.4771140	2.0044810	-3.1932830
H	4.0909080	1.6779000	-3.8756190
H	2.8692100	0.3801240	-3.8300450
O	-1.6784200	3.8986450	0.6738430
C	-2.9468900	4.5119040	0.8604130
H	-2.9572720	5.0486330	1.8097280
H	-3.1652780	5.1797150	0.0195170
O	-3.9178400	3.4673850	0.8986360
C	-0.4297240	-3.2916860	-0.3927990
H	-0.0095410	-3.7212290	-1.3090950
H	0.3392540	-3.2717770	0.3806380
C	-2.7088210	-3.5934390	-0.1366080
O	-3.7266830	-4.1245910	0.2196410



Scheme 42. Change of carbonyl singlet and triplet states energies.

Singlet **TS23**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.24457964
Electronic and Zero-Point Energy = -1375.860139
Enthalpy = -1375.832981
Free Energy = -1375.916902
M06-2X/def2-TZVP
Electronic Energy = -1376.7796975
$<S^2>$ = 0.450226

O	4.9990470	-0.3595570	1.2630000
O	3.6741380	-0.6120030	3.1221360
O	0.2427180	4.6403190	-1.2655050
O	-4.4359750	-2.2771950	-0.4850340
O	-2.3116450	-3.7498700	0.1245150
O	0.1797350	-2.8157130	-0.1435770
C	-1.5091340	1.4977520	-1.5395790
C	-1.0443740	2.6387330	-1.2626430
C	3.4125630	1.0361920	-0.0220880
H	4.0409760	1.1451350	-0.8987410
C	3.8205740	0.2940980	1.0676520
C	3.0093850	0.1366610	2.1935780
C	1.7616530	0.6988000	2.2799660
H	1.1387960	0.5645720	3.1581800
C	1.3157720	1.4866970	1.1817850
C	-0.6331490	-0.6467750	-0.8700440
H	0.3578860	-0.2259720	-0.9786430
C	-1.7526980	0.1600700	-1.1582610
C	-3.0596930	-0.3531910	-1.0389360
H	-3.9034770	0.2812270	-1.2787860
C	-3.2359850	-1.6710360	-0.6271480

C	-2.1222860	-2.4748160	-0.3171930
C	-0.8237400	-1.9617270	-0.4508640
C	4.7984290	-1.1563590	2.4320360
H	4.5790750	-2.1897600	2.1341320
H	5.6823280	-1.1008930	3.0674380
C	1.5004760	-2.2983420	-0.2171020
H	1.7660150	-2.0259090	-1.2449770
H	1.6145980	-1.4239790	0.4335310
H	2.1595140	-3.0960520	0.1271710
C	-2.2217030	-4.7170750	-0.9193260
H	-1.2410880	-4.6756930	-1.4055070
H	-3.0077570	-4.5573070	-1.6658940
H	-2.3560440	-5.6961450	-0.4564940
C	-5.5893290	-1.5033100	-0.7730810
H	-5.6548460	-0.6263660	-0.1193010
H	-5.5995780	-1.1774770	-1.8191280
H	-6.4437410	-2.1545540	-0.5889710
C	-0.4966710	3.0968910	0.4182140
H	-1.4316420	3.5339750	0.7774080
C	0.0035960	2.0776370	1.2552720
H	-0.6719790	1.6636590	1.9984820
C	2.1491820	1.6326490	0.0541820
H	1.7921500	2.1904130	-0.8067520
C	-0.7828000	3.9346550	-1.9659150
H	-1.6849260	4.5547810	-1.9821290
H	-0.4365260	3.7719610	-2.9876330
C	0.4496350	4.2068420	-0.0102860
O	1.2857800	4.7201320	0.6844140

132 singlet intermediate

<u>M06-2X/6-31G(d,p)</u>
Electronic Energy = -1376.25555175
Electronic and Zero-Point Energy = -1375.870049
Enthalpy = -1375.842767
Free Energy = -1375.928484
<u>M06-2X/def2-TZVP</u>
Electronic Energy = -1376.7912302
$<S^2>$ = 0.985159

C	-1.5684400	1.0520140	-1.1499270
C	-2.3866500	1.0797960	0.0115080
C	-3.2034260	-0.0122020	0.3715610
C	-3.2194840	-1.2834770	-0.3840820
C	-0.7273350	-1.8566260	-0.1954720
C	-1.9698190	-2.2014910	-0.2856840

O	-3.9108250	-3.5034230	0.0340340
C	-2.3609090	2.2428060	0.8499980
C	-0.7283370	2.1132250	-1.4955270
C	-0.7330630	3.2135090	-0.6625630
C	-1.5377580	3.2689890	0.4843390
H	-2.9701750	2.2912770	1.7462550
H	-0.1003480	2.0777720	-2.3786800
H	-1.5893840	0.1801670	-1.7951230
H	-3.7832960	0.0401440	1.2874810
H	-3.3845520	-1.1091540	-1.4600460
C	0.5869730	-1.4432950	-0.0806670
C	1.1602170	-1.2573560	1.2073170
C	1.3624940	-1.1978200	-1.2477690
C	2.4788590	-0.8377850	1.3135300
H	0.5563060	-1.4545850	2.0837250
C	2.6788800	-0.7792550	-1.1175470
H	0.9097170	-1.3475680	-2.2198310
C	3.2415370	-0.5793820	0.1586980
O	3.1319500	-0.6428310	2.4825510
O	4.5235660	-0.1329170	0.2748030
O	3.5130450	-0.5331040	-2.1538030
C	2.4067730	-0.8900110	3.6760770
H	1.5347700	-0.2311660	3.7554940
H	2.0785570	-1.9338620	3.7340730
H	3.0930940	-0.6807310	4.4966670
C	5.4700810	-1.1919620	0.3994320
H	5.4682440	-1.8219240	-0.4972010
H	6.4515590	-0.7284880	0.5141430
H	5.2537990	-1.8063740	1.2802190
C	2.9914930	-0.7094200	-3.4603860
H	2.1495710	-0.0331050	-3.6481090
H	3.8050750	-0.4706440	-4.1454100
H	2.6702700	-1.7439930	-3.6264070
O	-0.0003760	4.3551890	-0.7576880
C	-0.5501070	5.2445020	0.2172360
H	0.2592290	5.7429920	0.7511460
H	-1.2089160	5.9661260	-0.2814790
O	-1.3094180	4.4521700	1.1281080
C	-2.5285340	-3.6144940	-0.3374310
H	-2.0368340	-4.2897300	0.3640840
H	-2.4732950	-4.0298310	-1.3484350
C	-4.3252320	-2.2240050	0.0659380
O	-5.4370240	-1.9244440	0.4114910

TS24 singlet

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25544583
Electronic and Zero-Point Energy = -1375.870694
Enthalpy = -1375.844140
Free Energy = -1375.926883
M06-2X/def2-TZVP
Electronic Energy = -1376.7898867
$<S^2>$ = 0.647912

C	2.3344390	-0.1707580	-0.7280230
C	2.9013270	0.8216930	0.1251940
C	3.1223780	2.1220130	-0.3429730
C	2.4748970	2.5628700	-1.5909750
C	0.2136510	1.4348820	-1.1517200
C	0.9011690	2.4669120	-1.5048170
O	1.5417420	4.6884400	-2.0558420
C	3.0828020	0.5191470	1.5208050
C	1.9148990	-1.4197400	-0.2473460
C	2.0392780	-1.6363430	1.1034070
C	2.6334760	-0.6864790	1.9617260
H	3.5046060	1.2550740	2.1969590
H	1.4750460	-2.1631520	-0.9027020
H	2.2928000	0.0093770	-1.7960150
H	3.5015770	2.8765010	0.3400920
H	2.7851360	1.9879940	-2.4738250
C	-0.7139650	0.4692390	-0.7548450
C	-0.8522490	0.1814940	0.6251510
C	-1.4245490	-0.2904800	-1.7146270
C	-1.6840060	-0.8557970	1.0298740
H	-0.2707900	0.7522680	1.3392750
C	-2.2712770	-1.3093060	-1.2891660
H	-1.3057870	-0.0572870	-2.7650840
C	-2.3941880	-1.6093180	0.0792910
O	-1.8651420	-1.2344780	2.3174850
O	-3.1838790	-2.6471250	0.4793680
O	-3.0204050	-2.0782660	-2.1132740
C	-1.0702540	-0.5883520	3.2964370
H	-0.0006050	-0.6994460	3.0797010
H	-1.3107730	0.4783450	3.3699090
H	-1.2988600	-1.0755140	4.2446990
C	-4.4912040	-2.2311310	0.8635730
H	-5.0204810	-1.7802040	0.0162230
H	-5.0265420	-3.1245610	1.1901990
H	-4.4457520	-1.5118120	1.6888870

C	-2.9097780	-1.8347070	-3.5053420
H	-1.8866480	-2.0028630	-3.8602870
H	-3.5802940	-2.5444080	-3.9901600
H	-3.2180780	-0.8141970	-3.7592810
O	1.6408580	-2.7101200	1.8327860
C	2.2194190	-2.5389030	3.1283750
H	1.4794150	-2.7809810	3.8920360
H	3.1115530	-3.1707330	3.2137460
O	2.5922580	-1.1670170	3.2407760
C	0.3934710	3.8478500	-1.8868530
H	-0.2395720	4.2830340	-1.1101810
H	-0.1555790	3.8261510	-2.8316730
C	2.7033730	4.0347310	-1.8787650
O	3.7621320	4.6015010	-1.9412200

131 triplet intermediate

M06-2X/6-31G(d,p)
Electronic Energy = -1376.25569284
Electronic and Zero-Point Energy = -1375.870551
Enthalpy = -1375.843294
Free Energy = -1375.928730
M06-2X/def2-TZVP
Electronic Energy = -1376.7893308
$\langle S^2 \rangle$ = 2.062719

O	-1.9855670	3.8555310	-0.8324740
O	-1.5158010	3.6825370	1.4080170
O	-3.3817810	-3.2890040	-1.1780830
O	4.5920830	-1.6792110	0.7083190
O	4.5186090	0.9357990	0.2443500
O	2.3187350	2.1613330	-0.6026290
C	-0.1100310	-2.0434590	-0.4524340
C	-1.2812810	-2.6024760	-0.3841120
C	-2.5761280	1.4781960	-1.1804040
H	-2.8060930	1.5697470	-2.2358670
C	-2.2038930	2.5731670	-0.4263160
C	-1.9139780	2.4617550	0.9381630
C	-1.9516270	1.2666860	1.6010800
H	-1.6885250	1.1908120	2.6508460
C	-2.2967550	0.1005230	0.8483890
C	1.0268940	0.1058050	-0.5035280
H	0.1011760	0.5781660	-0.8118780
C	1.0358290	-1.2935280	-0.2395980
C	2.2340490	-1.9299250	0.1872420
H	2.2221280	-2.9952250	0.3796820

C	3.3931060	-1.1808410	0.3280160
C	3.3835270	0.2036700	0.0686560
C	2.1992420	0.8348490	-0.3584430
C	-1.8345640	4.6104600	0.3718560
H	-1.0184550	5.3241340	0.2556960
H	-2.7819460	5.1117720	0.6065270
C	1.1263740	2.8785680	-0.8779720
H	0.6165950	2.4909290	-1.7673710
H	0.4487340	2.8399170	-0.0185220
H	1.4273160	3.9110400	-1.0588710
C	5.3294630	0.9901900	-0.9268670
H	4.7914380	1.4732970	-1.7500990
H	5.6413760	-0.0146760	-1.2324020
H	6.2114680	1.5814350	-0.6750040
C	4.6547430	-3.0642720	1.0059370
H	3.9908160	-3.3225390	1.8384370
H	4.3965650	-3.6736020	0.1326230
H	5.6872590	-3.2660620	1.2914600
C	-2.2921680	-2.4621220	0.7557350
H	-2.1603250	-3.2900970	1.4644400
C	-2.2446380	-1.1624310	1.4901810
H	-2.0422810	-1.1894530	2.5547170
C	-2.6222310	0.2455460	-0.5258830
H	-2.8984240	-0.6258810	-1.1099960
C	-3.6126360	-2.7552400	0.0382930
C	-1.9774110	-3.4144480	-1.4611750
H	-1.7102030	-4.4747650	-1.4136920
H	-1.7924020	-3.0345160	-2.4671430
O	-4.7252180	-2.5705420	0.4506900

Triplet **TS25**

M06-2X/6-31G(d,p)
Electronic Energy = -1376.22508782
Electronic and Zero-Point Energy = -1375.840558
Enthalpy = -1375.814042
Free Energy = -1375.897994
M06-2X/def2-TZVP
Electronic Energy = -1376.7570526
$\langle S^2 \rangle$ = 2.027695

C	2.3620940	-0.2133780	-0.6302930
C	2.9710460	0.8593060	0.1208610
C	3.1811780	2.1186350	-0.5614360
C	2.2542600	2.5376580	-1.6631820
C	0.5519280	0.7984880	-1.0261560

C	0.8563360	1.9755060	-1.5378650
O	0.6829610	4.2974520	-1.8062250
C	3.2362090	0.7096590	1.4803460
C	2.1605950	-1.4794680	-0.0277020
C	2.4183250	-1.5787060	1.3259900
C	2.9372590	-0.5253550	2.0597420
H	3.6427690	1.5251340	2.0689220
H	1.8046630	-2.3274420	-0.6012270
H	2.4889920	-0.1942730	-1.7105730
H	3.9230500	2.8275330	-0.2104460
H	2.6909540	2.3354030	-2.6586580
C	-0.6544720	0.0848560	-0.6926120
C	-0.7914790	-0.4163820	0.6118340
C	-1.6479350	-0.1497880	-1.6579700
C	-1.9251930	-1.1501810	0.9530700
H	-0.0074690	-0.2223510	1.3334740
C	-2.7908060	-0.8700640	-1.3025020
H	-1.5169030	0.2384970	-2.6607930
C	-2.9236590	-1.3881200	-0.0047030
O	-2.1524930	-1.6814160	2.1777840
O	-4.0176460	-2.1384600	0.3166220
O	-3.8242900	-1.1310960	-2.1370880
C	-1.1398030	-1.5010380	3.1558700
H	-0.1873600	-1.9363970	2.8282280
H	-0.9915080	-0.4400140	3.3869090
H	-1.4870730	-2.0195100	4.0497590
C	-5.0296200	-1.3857370	0.9787620
H	-5.3898500	-0.5705960	0.3407410
H	-5.8522070	-2.0731160	1.1846700
H	-4.6569350	-0.9736760	1.9227990
C	-3.7341080	-0.6240750	-3.4575490
H	-2.8703760	-1.0409880	-3.9877850
H	-4.6490010	-0.9333540	-3.9634460
H	-3.6695540	0.4699840	-3.4623060
O	2.2090620	-2.6493050	2.1559190
C	2.8838730	-2.3112060	3.3679700
H	2.2730430	-2.6011200	4.2230670
H	3.8653560	-2.8022870	3.3874530
O	3.0653010	-0.8938440	3.3672230
C	-0.0926590	3.0892480	-1.9272210
H	-0.9600850	3.1648470	-1.2678720
H	-0.4311670	3.0082510	-2.9653170
C	1.9926460	4.0412000	-1.6386560
O	2.8047200	4.9160460	-1.4961060

5.6.2.1.6. XYZ Coordinates for temperature correction

This temperature correction was performed on original ester **90** and, **TS9** and **TS10**, at 433 K which are the experimental conditions.

90
M06-2X/6-31G(d,p)
Temperature 433.15 K
Electronic Energy = -1376.29397929
Electronic and Zero-Point Energy = -1375.906992
Enthalpy = -1375.852818
Free Energy = -1376.016314
M06-2X/def2-TZVP
Electronic Energy = -1376.8316466

C	-2.0350140	-0.6259020	-0.8864270
C	-0.9066750	-0.9667420	-1.1620000
C	0.4497270	-1.3265730	-1.5304150
O	0.8272250	-2.4565470	-0.9261720
C	2.1864710	-2.8812170	-1.1861910
C	3.1549160	-2.1355210	-0.3245930
H	2.4107270	-2.7477150	-2.2466860
H	2.1767500	-3.9467660	-0.9465380
C	4.1206890	-1.3678660	-0.8387420
C	5.1496520	-0.6296030	-0.0865940
H	3.0350500	-2.2561870	0.7507410
H	4.1596210	-1.2497090	-1.9217500
C	5.4403900	-0.9077100	1.2540610
C	6.4128530	-0.1936010	1.9668350
C	7.0861950	0.7960120	1.2823280
C	6.8136020	1.0763220	-0.0543340
C	5.8609380	0.3854750	-0.7653320
H	4.9152110	-1.7125070	1.7579020
H	5.6547970	0.6150850	-1.8056460
H	6.6350640	-0.4147780	3.0045770
O	1.1310870	-0.6820610	-2.2931230
C	8.5741260	2.2752020	0.5637840
H	9.5046810	1.7744480	0.2667450
H	8.7332080	3.3362030	0.7573300
O	7.5992770	2.1153640	-0.4665560
O	8.0511950	1.6476680	1.7359280
C	-3.3678960	-0.2309630	-0.5519280
C	-4.0929970	-0.9817700	0.3874010
C	-3.9341020	0.8915860	-1.1600530
C	-5.3939880	-0.6081050	0.7098440

H	-3.6339470	-1.8534540	0.8364720
C	-5.2305440	1.2678490	-0.8237580
H	-3.3814170	1.4783550	-1.8850290
C	-5.9703180	0.5320320	0.1103350
O	-6.1946590	-1.2863810	1.5625440
O	-7.2501100	0.9087260	0.3523490
O	-5.7904800	2.3439040	-1.4484750
C	-5.6536750	-2.4392950	2.1911750
H	-5.3706720	-3.1962780	1.4516940
H	-4.7841700	-2.1844060	2.8065460
H	-6.4450690	-2.8334310	2.8282130
C	-7.6080360	1.1598070	1.7149880
H	-7.9421830	0.2461730	2.2086810
H	-8.4238860	1.8848270	1.6880860
H	-6.7652600	1.5878620	2.2679550
C	-5.9622570	3.4783020	-0.6022700
H	-6.6273750	3.2552350	0.2374500
H	-6.4089550	4.2611810	-1.2168640
H	-4.9947960	3.8241630	-0.2205210

TS9

M06-2X/6-31G(d,p)

Temperature 433.15 K

Electronic Energy = -1376.25752

Electronic and Zero-Point Energy = -1375.871060

Enthalpy = -1375.819229

Free Energy = -1375968726

M06-2X/def2-TZVP

Electronic Energy = -1376.4425601

C	-0.5516730	-1.2286690	1.7542540
C	-0.2179540	0.0592440	1.2578340
C	1.0725130	0.5899890	1.4641940
C	2.0939890	-0.1950490	2.0166530
C	1.4283420	-2.3318130	0.4404190
C	2.3609590	-1.6033130	0.8659100
C	3.8390170	-1.5445240	0.7245390
O	4.4092300	-0.5472990	1.4108620
O	4.5031870	-2.3214190	0.0851630
C	3.4953920	0.3735680	2.0361410
H	3.5440400	1.3125620	1.4777720
H	3.8639920	0.5368370	3.0507120
C	-1.1123940	0.7144720	0.3452520
C	-1.7518910	-1.8766240	1.4027690
C	-2.5533870	-1.2355160	0.4962670
C	-2.2430610	0.0468260	-0.0077500

H	-0.8662940	1.6868990	-0.0681990
H	-2.0043560	-2.8576690	1.7890930
H	0.0568690	-1.6791290	2.5291170
H	1.3435410	1.4911450	0.9175280
H	1.8480940	-0.8136650	2.8796880
O	-3.7095480	-1.6656190	-0.0700900
O	-3.2067320	0.4079610	-0.9079180
C	0.5798850	-3.2766320	-0.1889150
C	-0.2594480	-2.8531450	-1.2347810
C	0.5353160	-4.6020030	0.2796650
C	-1.1366320	-3.7660140	-1.8187640
H	-0.2270920	-1.8173790	-1.5509080
C	-0.3462030	-5.5037830	-0.3151540
H	1.1928920	-4.9036040	1.0847150
C	-1.1935120	-5.0880340	-1.3544080
O	-0.4607130	-6.8060130	0.0355700
O	-2.0822770	-5.9681180	-1.9017100
O	-1.9891240	-3.4677760	-2.8266670
C	0.3716750	-7.2701540	1.0854540
H	1.4326110	-7.1653400	0.8316250
H	0.1683850	-6.7373060	2.0211700
H	0.1357100	-8.3265020	1.2153340
C	-1.5477810	-6.6601020	-3.0258470
H	-0.6657320	-7.2455580	-2.7424790
H	-2.3277470	-7.3342300	-3.3850620
H	-1.2793940	-5.9589810	-3.8243890
C	-2.0561670	-2.1125990	-3.2353300
H	-2.3085430	-1.4532490	-2.3968690
H	-1.1109770	-1.7799140	-3.6792720
H	-2.8442830	-2.0609280	-3.9871870
C	-4.2697630	-0.5233040	-0.7223080
H	-4.6730790	-0.8196060	-1.6908790
H	-5.0399200	-0.0805380	-0.0788900

TS10

M06-2X/6-31G(d,p)

Temperature 433.15 K

Electronic Energy = -1376.25543587

Electronic and Zero-Point Energy = -1375.868086

Enthalpy = -1375.816653

Free Energy = -1375.964356

M06-2X/def2-TZVP

Electronic Energy = -1376.441796

C	-4.7998500	-3.9329580	-0.7208330
C	-5.5566100	-2.8247690	-1.2159580

C	-6.0272300	-1.8394030	-0.3264930
C	-5.6601030	-1.8578660	1.0318460
C	-3.0669580	-2.4243280	0.4968160
C	-3.8776770	-1.6696820	1.1005340
C	-3.7502990	-0.5260880	2.0443050
O	-4.9267150	-0.0732190	2.4927540
O	-2.7094930	-0.0473780	2.4188120
C	-6.0836490	-0.6792770	1.8873690
H	-6.5742760	0.0891690	1.2838120
H	-6.7472240	-0.9772750	2.7012390
C	-5.6301300	-2.5929940	-2.6218750
C	-4.1812520	-4.7357810	-1.6640290
C	-4.2548300	-4.4753320	-3.0170620
H	-6.1908380	-1.7299940	-2.9683220
H	-4.8221980	-4.2296520	0.3205660
H	-6.4344460	-0.9231200	-0.7488770
H	-5.7081300	-2.8201390	1.5427680
O	-3.5739370	-5.4289830	-3.7104790
C	-1.9234450	-3.1131020	0.0240850
C	-1.5818520	-3.0493570	-1.3397350
C	-1.1706070	-3.8939250	0.9228040
C	-0.4730890	-3.7622460	-1.7947780
H	-2.1879010	-2.4536720	-2.0117070
C	-0.0761510	-4.6124460	0.4476350
H	-1.4501370	-3.9167800	1.9683340
C	0.2667840	-4.5625300	-0.9129550
O	0.7232920	-5.3899970	1.2138700
O	1.3008520	-5.3178370	-1.3853240
O	-0.0568190	-3.7888660	-3.0839490
C	0.4037920	-5.4881910	2.5921430
H	0.4760090	-4.5142620	3.0890150
H	-0.6010590	-5.8992340	2.7394040
H	1.1375830	-6.1685150	3.0246540
C	2.5553120	-4.6467080	-1.3163730
H	2.8080890	-4.3989190	-0.2793960
H	3.3041690	-5.3322660	-1.7173530
H	2.5427700	-3.7306640	-1.9178370
C	-0.8231910	-3.0564680	-4.0266950
H	-1.8539960	-3.4278140	-4.0743570
H	-0.8312130	-1.9863120	-3.7921460
H	-0.3415630	-3.2097500	-4.9926110
C	-4.9906780	-3.4069880	-3.5355960
H	-5.0399770	-3.2268320	-4.6035320
O	-3.4444480	-5.8713360	-1.4578460
C	-2.8398170	-6.1560620	-2.7173820
H	-2.9087750	-7.2244590	-2.9249950

H	-1.7977110	-5.8118940	-2.7199680

5.6.2.2. XYZ Coordinates for second step [1,3]-hydrogen shift

5.6.2.2.1. [1,3]-Hydrogen shift major product

TS15

M06-2X/6-31G(d,p)
Electronic Energy = -2036.70180111
Electronic and Zero-Point Energy = -2035.967736
Enthalpy = -2035.923232
Free Energy = -2036.043632
M06-2X/def2-TZVP
Electronic Energy = -2037.4516837

C	0.2561010	-1.1449310	0.0136880
C	-0.3629750	-2.5111570	0.1707050
C	-0.0933510	-3.5153730	-0.6986600
C	0.7716290	-3.3086870	-1.8913500
C	1.4528130	-1.1019900	-0.8924180
C	1.6452740	-2.1007030	-1.7639490
C	2.8220230	-2.3364990	-2.6371450
O	2.8467700	-3.6582000	-2.9451010
O	3.6541840	-1.5733940	-3.0562470
C	1.8241500	-4.3758820	-2.2220360
H	1.4599190	-5.1768250	-2.8651460
H	2.2655560	-4.7973130	-1.3129400
C	-1.2604340	-2.7577630	1.2937840
C	0.3403010	-0.3471900	1.2536270
C	-0.5058080	-0.6458070	2.2577960
C	-1.3195170	-1.8350660	2.2704310
H	-1.8103080	-3.6910920	1.3472440
H	0.9802160	0.5240040	1.2980600
H	-0.5698600	-0.4250710	-0.6258950
H	-0.5684400	-4.4845080	-0.5629840
H	0.1319560	-3.1909400	-2.7837690
C	-4.3535210	-0.9518730	0.5100300
C	-2.5306910	0.3996250	-0.3219400
C	-3.5336880	0.8965870	1.8226560
C	-4.3052310	-0.2668010	1.7383850
H	-5.0753270	-1.7562350	0.4062110
H	-3.6326370	1.5085680	2.7138020
O	-1.5057390	0.4971070	-1.1265030
C	-5.1234540	-0.7366270	2.9062890
H	-5.2992510	0.0696930	3.6232270

H	-4.5998830	-1.5443320	3.4328810
H	-6.0907050	-1.1329840	2.5834180
C	-2.6810570	1.2950600	0.7971680
C	-2.0680640	2.7028490	0.7679690
C	-3.5254490	-0.6172280	-0.5482490
C	2.3474670	0.0855230	-0.8177380
C	3.5779820	0.0174950	-0.1728760
C	1.8849640	1.2933460	-1.3528110
C	4.3640850	1.1661710	-0.0758980
H	3.9470910	-0.9131890	0.2455570
C	2.6677940	2.4430290	-1.2440690
H	0.9131250	1.3237480	-1.8350820
C	3.9127320	2.3811310	-0.5934280
O	2.3252210	3.6570320	-1.7331280
O	4.6795030	3.5068960	-0.4740370
O	5.5984800	1.0859730	0.5056280
C	5.6866140	1.7457240	1.7674930
H	6.7007940	1.5816440	2.1353510
H	5.5030650	2.8186640	1.6648340
H	4.9709050	1.3151750	2.4777210
C	5.4652670	3.7568800	-1.6375160
H	6.1651410	2.9329370	-1.8163820
H	4.8262360	3.8925220	-2.5166480
H	6.0250830	4.6749290	-1.4508990
C	1.1343790	3.7317110	-2.5023310
H	1.1787570	3.0594080	-3.3664760
H	0.2519240	3.4910640	-1.8989370
H	1.0625310	4.7627250	-2.8489840
C	-1.6745390	-0.7012790	4.1764210
H	-1.2347600	-1.0002910	5.1312050
H	-2.5665900	-0.0851140	4.3209020
O	-2.0154130	-1.8692440	3.4315180
O	-0.7096150	0.0256080	3.4168680
C	-2.6153710	3.5733990	1.9053840
H	-2.2019350	4.5825530	1.8109340
H	-3.7070520	3.6517500	1.8736190
H	-2.3238870	3.1878730	2.8879940
C	-2.4745050	3.3583080	-0.5665750
H	-3.5644730	3.3808930	-0.6758830
H	-2.1074280	4.3902840	-0.6008440
H	-2.0541820	2.8108320	-1.4142600
C	-0.5387040	2.7101110	0.8738900
H	-0.2151080	2.3352050	1.8501250
H	-0.0937920	2.0971800	0.0905470
H	-0.1693860	3.7377500	0.7678160
C	-3.8664780	-0.0520200	-2.9507700

H	-2.9598620	0.5560440	-2.9911850
H	-4.7071880	0.5925720	-2.6719660
H	-4.0622200	-0.4499970	-3.9527120
C	-2.5314470	-2.0959740	-2.3913080
H	-2.6914320	-2.4248610	-3.4251510
H	-2.4582120	-2.9867090	-1.7608490
H	-1.5852790	-1.5532310	-2.3426280
C	-4.9790770	-2.0714040	-2.0277610
H	-4.9185270	-2.9514970	-1.3793950
H	-5.1080320	-2.4271840	-3.0549130
H	-5.8731120	-1.5019090	-1.7537150
C	-3.7096110	-1.2151420	-1.9507990

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M06-2X/6-31G(d,p)
Electronic Energy = -2036.77431973
Electronic and Zero-Point Energy = -2036.034064
Enthalpy = -2035.988793
Free Energy = -2036.110439
M06-2X/def2-TZVP
Electronic Energy = -2037.5265779

C	0.1544700	1.3150980	-0.9517400
C	-0.6322540	2.4815860	-1.2910660
C	-0.2810800	3.7446350	-0.8201270
C	0.8153920	3.9188010	0.1651990
C	1.3928210	1.4898320	-0.1969700
C	1.6967430	2.7153580	0.2828600
C	2.9884520	3.1917040	0.8248440
O	3.0216530	4.5436860	0.6777670
O	3.9044620	2.5905990	1.3268530
C	1.8760960	5.0077580	-0.0653400
H	1.5996030	5.9881480	0.3223340
H	2.1455380	5.0840940	-1.1239590
C	-1.7804310	2.3300940	-2.1451730
C	-0.2019660	0.0432790	-1.4432420
C	-1.3137970	-0.0494780	-2.2406990
C	-2.0833870	1.0795480	-2.5871440
H	-2.3759960	3.1944620	-2.4180370
H	0.3939540	-0.8307810	-1.2117720
H	-1.1373040	-0.6900520	2.7987800
H	-0.8824940	4.6049710	-1.0990830
H	0.3727200	4.1268820	1.1595660
C	-3.8807460	0.7996260	0.5673320
C	-2.3612380	-0.8938420	1.3215460

C	-3.8662220	-1.3440130	-0.4884000
C	-4.3871450	-0.0558850	-0.4105280
H	-4.2978550	1.7990160	0.6303710
H	-4.2764300	-2.0150370	-1.2356190
O	-1.3536410	-1.3516370	2.1330050
C	-5.4822200	0.4095490	-1.3365170
H	-5.6875670	-0.3359560	-2.1099030
H	-5.2071060	1.3437750	-1.8355140
H	-6.4146790	0.5899910	-0.7903130
C	-2.8459390	-1.7965090	0.3539980
C	-2.2887260	-3.2242090	0.2295980
C	-2.8831650	0.4119610	1.4640320
C	2.3240940	0.3313000	-0.0544710
C	3.4253370	0.2322220	-0.9028460
C	2.0463050	-0.6570540	0.8911900
C	4.2753050	-0.8720920	-0.7950420
H	3.6083880	1.0104730	-1.6338020
C	2.9053350	-1.7552460	1.0042670
H	1.1531130	-0.5815440	1.5023230
C	4.0269190	-1.8569710	0.1707250
O	2.7402100	-2.7710060	1.8838730
O	4.8824060	-2.9144610	0.3017570
O	5.3646110	-1.0803440	-1.5706480
C	5.6533480	-0.1032060	-2.5566870
H	6.5587670	-0.4417320	-3.0608700
H	4.8409960	-0.0219290	-3.2877400
H	5.8361980	0.8785370	-2.1056490
C	4.4795810	-4.0419760	-0.4687110
H	3.4910040	-4.3973930	-0.1557780
H	4.4575260	-3.7974590	-1.5368920
H	5.2171270	-4.8275850	-0.2942060
C	1.7272620	-2.6229060	2.8672970
H	1.8624870	-1.6955030	3.4365640
H	0.7253390	-2.6331420	2.4247400
H	1.8323430	-3.4757560	3.5384880
C	-2.9292020	-0.7067850	-3.6413620
H	-2.6921000	-0.8669030	-4.6980040
H	-3.8363330	-1.2424910	-3.3516420
O	-3.1008040	0.6899220	-3.3984840
O	-1.8327500	-1.1507680	-2.8398650
C	-3.0137190	-4.0207820	-0.8630120
H	-2.5701370	-5.0196650	-0.9273160
H	-4.0801880	-4.1424230	-0.6462350
H	-2.9078500	-3.5455010	-1.8436550
C	-2.4780050	-3.9912090	1.5510500
H	-3.5372910	-4.0182450	1.8292750

H	-2.1362730	-5.0250680	1.4285070
H	-1.9196180	-3.5394270	2.3714330
C	-0.8002020	-3.1874630	-0.1632360
H	-0.6965530	-2.8525500	-1.2006200
H	-0.2190030	-2.5180110	0.4741840
H	-0.3688490	-4.1930990	-0.0895790
C	-2.7681110	0.7700010	3.9650820
H	-2.3257660	-0.2124480	4.1581680
H	-3.8521660	0.6555530	4.0618880
H	-2.4230690	1.4434040	4.7564860
C	-0.9153390	1.6857140	2.4804210
H	-0.6522840	2.4451990	3.2245690
H	-0.7004070	2.0859910	1.4872090
H	-0.2346360	0.8441140	2.6454860
C	-3.1343030	2.7195660	2.5003030
H	-2.9134000	3.2334650	1.5582150
H	-2.7858420	3.3556830	3.3195490
H	-4.2190120	2.6172330	2.5968680
C	-2.4192770	1.3637890	2.5854230

TS17

M06-2X/6-31G(d,p)
Electronic Energy = -2036.73652488
Electronic and Zero-Point Energy = -2036.001570
Enthalpy = -2035.956743
Free Energy = -2036.079595
M06-2X/def2-TZVP
Electronic Energy = -2037.4872027

C	0.5626940	-1.3431210	1.8713840
C	-0.6016080	-2.0859720	2.2139420
C	-1.5794130	-1.5835050	3.1818720
C	-1.1044720	-0.4880320	4.0996330
C	0.8145830	-0.0426470	2.5264240
C	0.0029670	0.3403290	3.5282540
C	-0.0603570	1.6605840	4.2044680
O	-1.2712600	1.7544050	4.8085270
O	0.7539750	2.5444850	4.2819400
C	-2.0965790	0.6149480	4.4970520
H	-2.6896890	0.3848090	5.3818560
H	-2.7593680	0.8759360	3.6620280
C	-0.8934020	-3.3029440	1.5532770
C	1.4316520	-1.8088570	0.8617560
C	1.1183180	-2.9962000	0.2463600
C	-0.0217760	-3.7307210	0.5860900

H	-1.7821120	-3.8701320	1.8090030
H	2.3161080	-1.2529580	0.5759110
H	-2.6096480	-1.2207060	2.4181350
H	-2.1004900	-2.3935230	3.6971420
H	-0.7319910	-0.9464620	5.0309230
C	-6.5913060	0.6844740	2.0808720
C	-4.4654530	-0.3195860	1.4981400
C	-5.2405620	1.6763900	0.3605120
C	-6.3974450	1.6997990	1.1399780
H	-7.5081180	0.7061420	2.6597240
H	-5.1171330	2.4558740	-0.3831880
O	-3.5776870	-1.3023000	1.6231060
C	-7.4417200	2.7661180	0.9485820
H	-8.3097690	2.3695920	0.4094960
H	-7.0492520	3.6090730	0.3748110
H	-7.8041900	3.1411180	1.9103260
C	-4.2633320	0.6940470	0.5068150
C	-3.0197200	0.6961990	-0.3926570
C	-5.6670920	-0.3357200	2.2810100
C	1.8977230	0.8419060	2.0043800
C	1.5581140	1.9726930	1.2641940
C	3.2329840	0.5057450	2.2363030
C	2.5686380	2.7806410	0.7370040
H	0.5145330	2.2137560	1.1104900
C	4.2420630	1.3214240	1.7162350
H	3.4728310	-0.3806170	2.8121040
C	3.9122880	2.4640630	0.9734930
O	5.5679620	1.0952870	1.8692000
O	4.8997320	3.2711540	0.4839070
O	2.3475960	3.8834540	-0.0161140
C	0.9951410	4.2421910	-0.2487930
H	1.0211340	5.1418700	-0.8637370
H	0.4565140	3.4517140	-0.7852390
H	0.4739600	4.4609660	0.6902760
C	5.4058880	2.8195000	-0.7682140
H	5.8372750	1.8164660	-0.6764900
H	4.6159350	2.8100380	-1.5281130
H	6.1855780	3.5223200	-1.0679380
C	5.9488210	-0.0422940	2.6252030
H	5.5731070	0.0184230	3.6525790
H	5.5911100	-0.9687250	2.1617140
H	7.0388620	-0.0447330	2.6394640
C	1.1399030	-4.8985660	-0.9151450
H	0.9340820	-5.0726930	-1.9721520
H	1.7751760	-5.6849310	-0.4923940
O	-0.0922170	-4.8415210	-0.1908260

O	1.7826670	-3.6307170	-0.7539870
C	-3.0668790	1.8164140	-1.4395330
H	-2.1580830	1.7682250	-2.0480230
H	-3.9250400	1.7163300	-2.1123890
H	-3.1030290	2.8092050	-0.9796400
C	-2.8938030	-0.6359500	-1.1546910
H	-3.7929580	-0.8245220	-1.7514670
H	-2.0403890	-0.5850710	-1.8402790
H	-2.7458310	-1.4749620	-0.4744920
C	-1.7694480	0.9271640	0.4654180
H	-1.8077910	1.9097260	0.9526290
H	-1.6699360	0.1648480	1.2360390
H	-0.8701180	0.8888650	-0.1615970
C	-5.8680750	-2.8356650	2.6407530
H	-4.8702290	-3.0373620	2.2526170
H	-6.5838470	-2.9121470	1.8149250
H	-6.1231530	-3.6059680	3.3770250
C	-4.9544520	-1.3536870	4.4641950
H	-5.1540930	-2.1426700	5.1982580
H	-5.0438270	-0.3871160	4.9716490
H	-3.9290790	-1.4697120	4.1149000
C	-7.3608080	-1.3262170	3.9027650
H	-7.4919430	-0.3959520	4.4641070
H	-7.5188950	-2.1554360	4.5994060
H	-8.1396780	-1.3811450	3.1350980
C	-5.9535300	-1.4477830	3.3017210

TS16

M06-2X/6-31G(d,p)
Electronic Energy = -2037.297207
Electronic and Zero-Point Energy = -2036.548161
Enthalpy = -2036.503626
Free Energy = -2036.621663
M06-2X/def2-TZVP
Electronic Energy = -2038.050121

C	2.0954140	-1.2126350	-0.9767590
C	2.6701310	-2.3869470	-1.6564730
C	2.1294020	-2.8643260	-2.8312570
C	1.3206920	-1.9287020	-3.6830470
C	0.9029370	-0.6325210	-1.5486880
C	0.4932770	-1.0431550	-2.7857060
C	-0.7935780	-0.8077680	-3.4397150
O	-0.8822990	-1.6425140	-4.5199130
O	-1.6971390	-0.0424200	-3.1844350

C	0.2274270	-2.5569970	-4.5557020
H	-0.1002640	-3.5215320	-4.1450810
H	0.5139700	-2.6894540	-5.6006130
C	2.7479680	-0.6534850	0.1833840
C	3.8236890	-1.2962820	0.6881340
C	4.3143780	-2.5009430	0.1049220
H	2.3480980	0.2370250	0.6571570
H	0.9396540	-2.4729110	-0.0498670
H	2.5299560	-3.7755550	-3.2706300
H	1.9640180	-1.3131160	-4.3421620
C	0.0553150	0.2623770	-0.6987710
C	0.3834020	1.6089430	-0.5444720
C	-1.0271470	-0.2907120	-0.0118640
C	-0.3795830	2.4086290	0.3150210
H	1.2268740	2.0199070	-1.0869530
C	-1.7837950	0.5051760	0.8512120
H	-1.2869970	-1.3330910	-0.1604360
C	-1.4501370	1.8542080	1.0291780
O	-2.8463110	0.0612610	1.5645510
O	-2.1583310	2.6228640	1.9101530
O	-0.1578010	3.7258700	0.5358620
C	0.9473430	4.3188580	-0.1257140
H	0.9652130	5.3615570	0.1917950
H	1.8886820	3.8363370	0.1610350
H	0.8332480	4.2746740	-1.2145550
C	-3.2558860	3.2914140	1.2985650
H	-2.9094110	3.9831630	0.5223000
H	-3.9576340	2.5728420	0.8600730
H	-3.7625190	3.8549370	2.0844140
C	-3.1659100	-1.3166080	1.4481190
H	-3.4608670	-1.5732600	0.4236110
H	-2.3196830	-1.9447760	1.7524800
H	-4.0067670	-1.4925280	2.1202080
C	5.6809310	-1.8853340	1.7456910
H	6.5220520	-1.3276790	1.3127420
H	5.9293060	-2.2826720	2.7300680
O	5.3405150	-2.9640000	0.8713720
O	4.5402160	-1.0488430	1.8406400
C	-0.4742960	-3.9256260	0.8168810
C	-1.5858110	-4.5299430	0.2123440
C	-2.5855700	-4.9612320	1.0916560
H	-3.4772670	-5.4277910	0.6930990
C	-2.4820790	-4.8291420	2.4718160
C	-1.3176800	-4.2802610	3.0006010
H	-1.2308070	-4.2165010	4.0782490
C	-0.2659390	-3.8210070	2.2031540

C	0.9762510	-3.2026120	2.8667920
C	0.9938850	-3.4481490	4.3831600
H	0.9608970	-4.5154140	4.6236470
H	1.9274250	-3.0422600	4.7843000
H	0.1708170	-2.9450740	4.8975660
C	0.9237460	-1.6798140	2.6656660
H	0.8182480	-1.3817220	1.6211960
H	0.0666400	-1.2612720	3.2050270
H	1.8399150	-1.2185810	3.0504520
C	2.2795220	-3.8157480	2.3250150
H	3.1326310	-3.3032750	2.7831500
H	2.3336020	-4.8757960	2.5944510
H	2.3970150	-3.7403660	1.2463280
C	-3.6050670	-5.2586660	3.3763880
H	-3.2213790	-5.6899430	4.3044680
H	-4.2271260	-4.3983710	3.6468700
H	-4.2478340	-5.9945430	2.8880940
C	-1.7516560	-4.7524590	-1.3037050
C	-2.9908800	-5.6075950	-1.6079660
H	-2.9315460	-6.5959830	-1.1416550
H	-3.9146320	-5.1187400	-1.2872800
H	-3.0518740	-5.7474710	-2.6905390
C	-0.5454660	-5.5150870	-1.8970210
H	0.3461770	-4.9072460	-2.1076680
H	-0.8257220	-5.9158900	-2.8758470
H	-0.2500500	-6.3535750	-1.2598450
C	-1.9500420	-3.4020050	-2.0021630
H	-2.8188210	-2.8790680	-1.5885470
H	-1.0785700	-2.7518330	-1.8956420
H	-2.1185160	-3.5500080	-3.0737060
O	0.5832090	-3.4379800	-0.0432670
H	0.6187650	-3.7473810	-0.9814040
C	3.7723970	-3.0704540	-0.9960410
H	4.1826530	-3.9786640	-1.4253240

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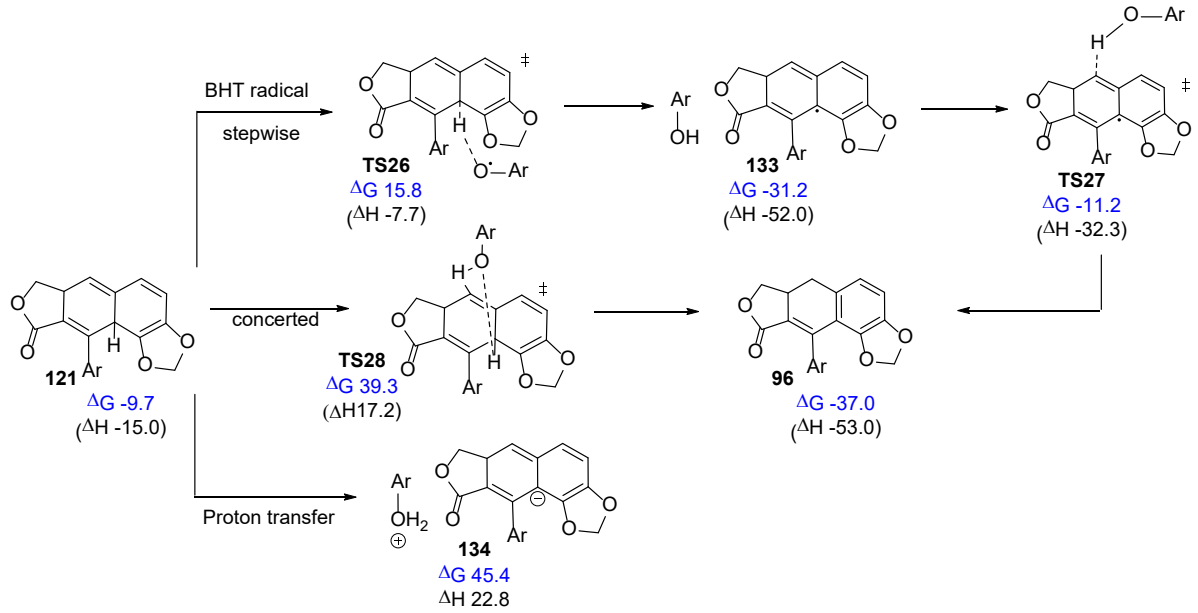
M06-2X/6-31G(d,p)
Electronic Energy = -2037.287997
Electronic and Zero-Point Energy = -2036.030069
Enthalpy = -2036.492381
Free Energy = -2036.609752
M06-2X/def2-TZVP
Electronic Energy = -2036.536983

C	-0.9568140	1.2553500	-1.1436110

C	-1.9755540	2.3025210	-1.3603640
C	-0.5992980	3.9534950	-0.1032140
C	0.3315870	1.6774970	-0.7434290
C	0.5374440	3.0071910	-0.3859610
C	1.7781260	3.7381440	-0.3249150
O	1.4858960	5.0795340	-0.1874560
O	2.9459840	3.3885440	-0.3769030
C	0.0807100	5.3007300	-0.3769090
H	-0.2276660	6.1044330	0.2956520
H	-0.0889740	5.6139350	-1.4167270
C	-1.2626390	-0.1172210	-1.4570130
C	-2.4644850	-0.4073910	-2.0009660
C	-3.4284260	0.6067810	-2.2820660
H	-0.5443020	-0.9043370	-1.2563950
H	1.0577790	-0.5274360	1.4661070
H	-0.8851160	3.9288020	0.9722020
C	1.4774230	0.7225180	-0.7097550
C	1.8309900	-0.0198550	-1.8320630
C	2.2172760	0.5901520	0.4866980
C	2.9399540	-0.8778600	-1.7836230
H	1.2574060	0.0906380	-2.7441720
C	3.3516610	-0.2413950	0.5151310
H	2.0490630	1.3190590	1.2734380
C	3.6917040	-1.0048310	-0.6078270
O	4.1548100	-0.3936510	1.5878420
O	4.7404260	-1.8748900	-0.5485280
O	3.3587650	-1.6343940	-2.8163980
C	2.5826440	-1.6110400	-4.0071630
H	3.0566850	-2.3172580	-4.6883940
H	1.5527060	-1.9291370	-3.8107290
H	2.5785330	-0.6149160	-4.4616870
C	5.9528970	-1.3151600	-1.0481750
H	5.8497680	-1.0388920	-2.1031370
H	6.2445160	-0.4337790	-0.4662520
H	6.7210350	-2.0841720	-0.9498200
C	3.9516200	0.4784410	2.6893520
H	4.0235140	1.5281060	2.3859730
H	2.9789390	0.3071960	3.1683490
H	4.7400500	0.2489320	3.4054660
C	-4.1386910	-1.3235890	-3.1276290
H	-3.8602550	-1.3581630	-4.1899340
H	-4.9532490	-2.0149380	-2.9077330
O	-4.5452460	0.0050480	-2.7977120
O	-3.0150570	-1.6328760	-2.3216190
C	-0.8809210	-1.2712100	1.7886670
C	-1.8127690	-0.2974620	2.1617590

C	-3.1002130	-0.5073260	1.6604180
H	-3.8811750	0.2126210	1.8746020
C	-3.4246180	-1.6131160	0.8745780
C	-2.4533390	-2.5778370	0.6245960
H	-2.7329830	-3.4413260	0.0353000
C	-1.1375530	-2.4446130	1.0784440
C	-0.0928030	-3.5525430	0.8585780
C	-0.6224820	-4.6103310	-0.1188530
H	-0.8458720	-4.1741630	-1.0988220
H	0.1443700	-5.3777690	-0.2560720
H	-1.5210520	-5.1071640	0.2568700
C	0.1756240	-4.2378790	2.2093490
H	0.5671220	-3.5334570	2.9498120
H	-0.7402360	-4.6839960	2.6093880
H	0.9182380	-5.0320530	2.0778910
C	1.2294620	-3.0043760	0.2832830
H	1.7486940	-3.7891210	-0.2755060
H	1.0543220	-2.1718280	-0.4061630
H	1.9158370	-2.6731190	1.0662940
C	-4.8068600	-1.7419700	0.2947520
H	-4.9473830	-2.7153160	-0.1803830
H	-5.5718190	-1.6181430	1.0671520
H	-4.9760890	-0.9655230	-0.4598600
C	-1.5215830	0.8449750	3.1557780
C	-2.6904640	1.8393080	3.1935330
H	-2.8656610	2.2829460	2.2076840
H	-3.6166760	1.3745350	3.5406790
H	-2.4452470	2.6444970	3.8912360
C	-0.2583450	1.6593690	2.8108570
H	0.6785650	1.2091020	3.1616100
H	-0.3095990	2.6276610	3.3171510
H	-0.1824490	1.8450090	1.7366420
C	-1.3812370	0.2297560	4.5606080
H	-2.3031160	-0.2798180	4.8553000
H	-0.5684400	-0.5052510	4.6345310
H	-1.1679730	1.0184070	5.2892340
O	0.5139290	-1.0705420	2.1567570
H	0.6313930	-0.6882800	3.0533460
C	-3.2228120	1.9133260	-2.0160450
H	-3.9811150	2.6620150	-2.2219950
C	-1.7593760	3.6013740	-0.9881120
H	-2.4951840	4.3637340	-1.2381140

5.6.2.2.2. [1,3]-Hydrogen shift minor product



Scheme 43. [1,3]-hydrogen shift of **123** to isolated product **98**.

TS26

M06-2X/6-31G(d,p)
Electronic Energy = -2036.69496851
Electronic and Zero-Point Energy = -2035.959901
Enthalpy = -2035.915838
Free Energy = -2036.033338
M06-2X/def2-TZVP
Electronic Energy = -2037.445226

C	0.2246620	-0.9339870	0.3126030
C	-0.5147300	-2.2317090	0.5841250
C	-0.2948370	-3.3433990	-0.1528990
C	0.6466160	-3.3575380	-1.3003540
C	1.3949720	-1.0384080	-0.6374780
C	1.5495790	-2.1632120	-1.3508170
C	2.6826160	-2.5729470	-2.2297960
O	2.6912230	-3.9306510	-2.2737920
O	3.4847660	-1.9224760	-2.8468100
C	1.6769510	-4.4859780	-1.4101390
H	1.2972700	-5.3931450	-1.8797610
H	2.1261880	-4.7231760	-0.4403430
C	-1.4253340	-2.3171210	1.7228010

C	0.4471990	-0.2519530	1.5898950
C	-0.3364470	-0.4550520	2.6872890
H	-2.1118580	-3.1579140	1.7524110
H	-0.5651570	-0.1999350	-0.2766870
H	-0.8527810	-4.2501250	0.0713290
H	0.0603080	-3.3807720	-2.2341390
C	-4.4631730	-1.1551020	0.1695600
C	-2.6731340	0.4032940	-0.3077550
C	-4.0276310	0.6645430	1.6832070
C	-4.6697770	-0.5512330	1.4211880
H	-5.0805270	-2.0106950	-0.0886960
H	-4.3072440	1.2035580	2.5833410
O	-1.5613680	0.6536810	-0.9450450
C	-5.6158450	-1.1626510	2.4171760
H	-6.4682860	-1.6344000	1.9195930
H	-5.9933950	-0.4171280	3.1217680
H	-5.1133050	-1.9431210	3.0018730
C	-3.0704960	1.1962490	0.8247460
C	-2.5364300	2.6253540	0.9961550
C	-3.5234230	-0.6783160	-0.7328550
C	2.2883360	0.1438300	-0.7744240
C	3.6547410	0.0318590	-0.5270920
C	1.7135050	1.3620720	-1.1467020
C	4.4686870	1.1573340	-0.6691090
H	4.0684260	-0.9233130	-0.2283990
C	2.5330940	2.4840670	-1.2921770
H	0.6432150	1.4226310	-1.3175500
C	3.9123100	2.3803340	-1.0668970
O	2.0951490	3.7145270	-1.6527370
O	4.7165370	3.4716530	-1.2408010
O	5.8043560	1.1718420	-0.4446750
C	6.4156730	-0.0607060	-0.1032990
H	7.4798440	0.1497450	0.0070060
H	6.0270080	-0.4541470	0.8427980
H	6.2745870	-0.8079650	-0.8925940
C	4.8347190	4.2567720	-0.0595710
H	3.8553530	4.6276600	0.2635530
H	5.2903440	3.6760190	0.7508220
H	5.4791660	5.1038310	-0.3022980
C	0.6962160	3.8728850	-1.8255080
H	0.3183470	3.2396600	-2.6369110
H	0.1572160	3.6425290	-0.9006590
H	0.5375940	4.9203780	-2.0841240
O	0.0193730	0.4031880	3.6871150
C	-3.3169100	3.3910140	2.0716480
H	-2.9537740	4.4231720	2.1092650

H	-4.3897650	3.4185990	1.8541650
H	-3.1784590	2.9566860	3.0670500
C	-2.7163950	3.3796860	-0.3348600
H	-3.7725170	3.4069480	-0.6257890
H	-2.3683980	4.4136070	-0.2272470
H	-2.1487560	2.9025170	-1.1370040
C	-1.0576170	2.6385660	1.3952430
H	-0.9328830	2.1684400	2.3752990
H	-0.4462430	2.1074920	0.6644280
H	-0.6972630	3.6721870	1.4708300
C	-3.5501640	0.0223130	-3.1267000
H	-2.7010660	0.6955190	-2.9934250
H	-4.4729900	0.5840300	-2.9440550
H	-3.5628380	-0.3210110	-4.1670860
C	-2.1580200	-1.9580690	-2.4708580
H	-2.1131420	-2.2139570	-3.5363300
H	-2.1397190	-2.8902250	-1.8986860
H	-1.2736780	-1.3685170	-2.2157160
C	-4.6255580	-2.1219090	-2.5010410
H	-4.5965170	-3.0395140	-1.9047090
H	-4.5725790	-2.4132450	-3.5552040
H	-5.5916640	-1.6337610	-2.3350990
C	-3.4521670	-1.1883880	-2.1790030
C	-1.3505930	-1.4508430	2.7660560
H	-1.9816590	-1.5298540	3.6440960
O	1.3451680	0.7290870	1.8416060
C	1.2359950	1.0015320	3.2445560
H	2.0830720	0.5356250	3.7625270
H	1.2045940	2.0797780	3.4074070

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<u>M06-2X/6-31G(d,p)</u>
Electronic Energy = -2036.76993653
Electronic and Zero-Point Energy = -2036.030069
Enthalpy = -2035.984720
Free Energy = -2036.106668
<u>M06-2X/def2-TZVP</u>
Electronic Energy = -2037.521851

C	-0.0784970	0.7726720	1.7370260
C	1.1493850	1.4818330	2.0542890
C	1.2776410	2.8387900	1.7294870
C	0.0838070	3.6201830	1.3047890
C	-1.0951770	1.4261590	0.9091480
C	-0.9729420	2.7510980	0.6898530

C	-1.6662250	3.5595120	-0.3413330
O	-0.9477560	4.6949810	-0.5375310
O	-2.6738630	3.3401850	-0.9647580
C	0.2782510	4.6899180	0.2170660
H	1.1035350	4.4367610	-0.4561670
H	0.4276440	5.6925480	0.6180670
C	2.2040390	0.8023660	2.7228800
C	-0.1622360	-0.5294390	2.1975820
C	0.8734500	-1.1405150	2.9105230
H	3.1202020	1.3510190	2.9214040
H	1.3083780	-0.2157550	-2.7252660
H	2.2049950	3.3578020	1.9539340
H	-0.3472660	4.1241210	2.1896830
C	4.1404940	0.6723010	-0.2913570
C	2.5107650	-0.7528120	-1.3176120
C	3.9428140	-1.6081880	0.4016440
C	4.5639460	-0.3652070	0.5312920
H	4.6239490	1.6365870	-0.1805250
H	4.2775860	-2.4141440	1.0464370
O	1.4870590	-0.9994350	-2.1947450
C	5.6325700	-0.1532630	1.5727390
H	6.4396630	-0.8861290	1.4746630
H	5.2225520	-0.2615440	2.5835750
H	6.0702940	0.8451540	1.4937300
C	2.9132760	-1.8392380	-0.5092240
C	2.2308670	-3.2125800	-0.6145170
C	3.1180910	0.5140860	-1.2367260
C	-2.1682620	0.6166540	0.2597840
C	-3.4565430	0.6648260	0.7888540
C	-1.8642420	-0.1733610	-0.8498980
C	-4.4660190	-0.0994790	0.1992220
H	-3.6573700	1.2886600	1.6514150
C	-2.8864070	-0.9107750	-1.4572650
H	-0.8451810	-0.2132620	-1.2220940
C	-4.1865150	-0.8702800	-0.9364470
O	-2.7331700	-1.6894460	-2.5551120
O	-5.1887090	-1.5722600	-1.5456510
O	-5.7469680	-0.1547060	0.6362950
C	-6.0797760	0.6333380	1.7666860
H	-7.1386470	0.4568130	1.9569980
H	-5.5004650	0.3354020	2.6479440
H	-5.9199720	1.6996180	1.5705320
C	-5.3163980	-2.8947160	-1.0353210
H	-4.3975270	-3.4689370	-1.2025730
H	-5.5464230	-2.8804280	0.0363010
H	-6.1393990	-3.3680160	-1.5743850

C	-1.4749810	-1.6544950	-3.2073880
H	-1.2064840	-0.6291160	-3.4921470
H	-0.6829590	-2.0777980	-2.5822500
H	-1.5853510	-2.2583010	-4.1090890
O	0.5148760	-2.4157970	3.2319980
C	2.8836670	-4.2411320	0.3182660
H	2.3624210	-5.1978090	0.2111920
H	3.9382170	-4.4062100	0.0731990
H	2.8140670	-3.9426430	1.3694180
C	2.3355630	-3.7743030	-2.0442220
H	3.3850290	-3.8568890	-2.3478270
H	1.8988090	-4.7786860	-2.0739060
H	1.8157720	-3.1521070	-2.7726550
C	0.7584300	-3.0897480	-0.1841390
H	0.7082490	-2.8823770	0.8879300
H	0.2338080	-2.2890990	-0.7079090
H	0.2301010	-4.0326240	-0.3704400
C	3.0305600	1.3542320	-3.6221030
H	2.5626070	0.4344830	-3.9880980
H	4.1114380	1.2353730	-3.7462180
H	2.6988720	2.1717790	-4.2708830
C	1.1945270	2.0113600	-1.9908990
H	0.9859890	2.9927550	-2.4308410
H	0.9367410	2.0438340	-0.9288150
H	0.4982120	1.3175840	-2.4752180
C	3.4509480	2.9665270	-1.7934850
H	3.2383140	3.2764580	-0.7641190
H	3.1279040	3.7686240	-2.4640290
H	4.5328650	2.8523280	-1.9072960
C	2.6956950	1.6796950	-2.1533240
O	-1.1847090	-1.4210130	2.0586250
C	-0.8821830	-2.4939250	2.9490270
H	-1.4485050	-2.3667650	3.8805790
H	-1.1075820	-3.4452780	2.4662140
C	2.0794990	-0.5084440	3.1641740
H	2.8795480	-1.0157470	3.6921250

TS27

M06-2X/6-31G(d,p)
Electronic Energy = -2036.73464166
Electronic and Zero-Point Energy = -2036.000323
Enthalpy = -2035.955706
Free Energy = -2036.077081
M06-2X/def2-TZVP
Electronic Energy = -2037.4842978

C	0.4922950	-1.4835250	1.8728460
C	-0.7302620	-2.1787900	2.1505280
C	-1.6794500	-1.6320060	3.1199700
C	-1.0962080	-0.6781690	4.1355630
C	0.7799470	-0.1915440	2.5263010
C	0.0146190	0.1643400	3.5763480
C	-0.0640690	1.4954320	4.2351620
O	-1.2218680	1.5485000	4.9381210
O	0.6961670	2.4297200	4.2168160
C	-2.0459170	0.3986820	4.6852090
H	-2.5315780	0.1209110	5.6213520
H	-2.8086080	0.6745390	3.9465750
C	-1.0507250	-3.3607980	1.4697680
C	1.3405240	-2.0952460	0.9630940
C	0.9986640	-3.2799750	0.3038550
H	-1.9920920	-3.8502170	1.7014030
H	-2.5998380	-1.0470750	2.3408530
H	-2.3140880	-2.4073940	3.5542200
H	-0.7045740	-1.2624980	4.9836910
C	-6.7209790	0.5251700	1.9891880
C	-4.4055430	0.0269970	1.4813930
C	-5.3779880	2.1566630	0.8511030
C	-6.6085470	1.7825900	1.3972440
H	-7.6831140	0.2514530	2.4066870
H	-5.3078830	3.1371590	0.3926700
O	-3.3910220	-0.8314920	1.4041580
C	-7.7845660	2.7187560	1.3290910
H	-8.6046150	2.3743340	1.9635420
H	-8.1633630	2.7973230	0.3038310
H	-7.5035030	3.7279730	1.6453780
C	-4.2675820	1.3204150	0.8759720
C	-2.9396140	1.7774590	0.2542750
C	-5.6564160	-0.3729880	2.0511720
C	1.8066600	0.6978670	1.9177650
C	1.6541780	1.0726290	0.5803820
C	2.9133480	1.1051350	2.6580560
C	2.6234650	1.8760730	-0.0195950
H	0.7925720	0.7222340	0.0222150
C	3.8905330	1.8983090	2.0511200
H	3.0029000	0.8013510	3.6929580
C	3.7424420	2.2939290	0.7156370
O	5.0130340	2.3367550	2.6696640
O	4.6840310	3.0964390	0.1362240
O	2.5808500	2.3016420	-1.3058430
C	1.4267930	1.9648850	-2.0565210

H	1.5631210	2.4124910	-3.0411630
H	1.3193520	0.8792370	-2.1659240
H	0.5215610	2.3759200	-1.5933490
C	5.6382410	2.3628500	-0.6248530
H	6.3443780	3.0876380	-1.0342920
H	6.1786870	1.6502730	0.0091060
H	5.1528950	1.8250970	-1.4468030
C	5.1577500	2.0166180	4.0428800
H	4.3236500	2.4122000	4.6338690
H	5.2317270	0.9343060	4.1985420
H	6.0848070	2.4898560	4.3677240
O	2.0217960	-3.6646580	-0.5031190
C	-3.0366400	3.1890060	-0.3383660
H	-2.0620080	3.4626300	-0.7551170
H	-3.7718870	3.2466180	-1.1475230
H	-3.2949390	3.9363490	0.4188410
C	-2.5130860	0.8316030	-0.8832090
H	-3.2808920	0.7957900	-1.6638550
H	-1.5881640	1.2031490	-1.3411560
H	-2.3409310	-0.1809830	-0.5163550
C	-1.8554590	1.8036070	1.3392190
H	-2.1515470	2.4453350	2.1780010
H	-1.6671050	0.7984050	1.7144220
H	-0.9152140	2.1950390	0.9334670
C	-5.3158520	-2.9051350	1.9362200
H	-4.2393330	-2.8598270	1.7783070
H	-5.8018040	-2.9277630	0.9543890
H	-5.5595170	-3.8405550	2.4517130
C	-5.0983940	-1.6466720	4.1154310
H	-5.1533450	-2.6106350	4.6345780
H	-5.5474220	-0.8831920	4.7599310
H	-4.0474770	-1.3933330	3.9783260
C	-7.3137420	-2.0150950	3.0748860
H	-7.7504250	-1.2880160	3.7655110
H	-7.3839550	-2.9978360	3.5512680
H	-7.9214040	-2.0386050	2.1642710
C	-5.8375350	-1.7200190	2.7691130
C	-0.1929170	-3.9358990	0.5284470
H	-0.4367820	-4.8572880	0.0126660
O	2.6052560	-1.7430630	0.5979260
C	2.9235590	-2.5581500	-0.5274970
H	3.9485120	-2.9185730	-0.4394320
H	2.7724560	-1.9837700	-1.4505390

TS28

M06-2X/6-31G(d,p)
Electronic Energy = -2037.284636
Electronic and Zero-Point Energy = -2036.535288
Enthalpy = -2036.490898
Free Energy = -2036.611329
M06-2X/def2-TZVP
Electronic Energy = -2038.0385328

C	1.9615780	-2.8195620	-2.2748770
C	0.6074320	-2.4912820	-2.8485330
C	0.4621980	-0.6587030	-1.0930400
C	0.0672940	-1.2087700	-2.2730130
C	-0.8015670	-0.6105580	-3.2957700
O	-0.5639850	-1.2548090	-4.4773180
O	-1.6115890	0.2859580	-3.2400360
C	0.5444910	-2.1660840	-4.3456290
H	0.3437600	-3.0296450	-4.9823260
H	1.4589330	-1.6620150	-4.6826210
H	0.5206580	-2.7382570	0.3049680
H	2.6424060	-3.4335350	-2.8597780
H	-0.1329580	-3.2916080	-2.6893990
C	-0.1870290	0.5826250	-0.5764680
C	0.4623070	1.8093380	-0.7065490
C	-1.4376240	0.4853600	0.0293530
C	-0.1593270	2.9635480	-0.2247650
H	1.4369070	1.8533510	-1.1789450
C	-2.0552120	1.6407440	0.5152450
H	-1.9207180	-0.4824030	0.1005700
C	-1.4101760	2.8787680	0.4025340
O	-3.2762530	1.6706050	1.1043500
O	-2.0005680	4.0073230	0.9017060
O	0.3603180	4.2125420	-0.3135230
C	1.6352160	4.3379940	-0.9184110
H	1.8785380	5.4005780	-0.8971660
H	2.3982720	3.7812270	-0.3618880
H	1.6219300	3.9919040	-1.9580560
C	-2.8319270	4.6552790	-0.0541100
H	-2.2580780	4.9440810	-0.9421180
H	-3.6636440	4.0071660	-0.3537170
H	-3.2289950	5.5527290	0.4246990
C	-3.9512150	0.4328100	1.2481420
H	-4.1462220	-0.0332110	0.2753450
H	-3.3803400	-0.2622740	1.8744830
H	-4.9004760	0.6584520	1.7347550

C	-0.5117120	-4.5747340	0.9117950
C	-1.6262190	-5.2092850	0.3380230
C	-2.3286050	-6.0718900	1.1794950
H	-3.1981600	-6.5961720	0.8010550
C	-1.9569240	-6.2890620	2.5048860
C	-0.8405000	-5.6284980	3.0035510
H	-0.5586180	-5.8123220	4.0328120
C	-0.0730350	-4.7492390	2.2296880
C	1.1336870	-4.0300930	2.8485330
C	1.4697090	-4.5799850	4.2421270
H	1.7120570	-5.6469410	4.2112260
H	2.3467010	-4.0455630	4.6186440
H	0.6586050	-4.4234540	4.9580680
C	0.7965790	-2.5397130	3.0226300
H	0.4200870	-2.0590530	2.1148150
H	0.0239380	-2.4159160	3.7879590
H	1.6903650	-1.9862960	3.3319470
C	2.3923840	-4.2250470	1.9893490
H	3.2600890	-3.8301480	2.5275060
H	2.5673730	-5.2877820	1.7925320
H	2.3655920	-3.6970790	1.0366070
C	-2.7606870	-7.2199210	3.3720360
H	-2.2852580	-7.3658110	4.3441740
H	-3.7652170	-6.8189490	3.5406360
H	-2.8771540	-8.1965990	2.8932830
C	-2.0532030	-5.0247910	-1.1254610
C	-3.3258470	-5.8211750	-1.4507760
H	-3.1820480	-6.8979960	-1.3234760
H	-4.1744020	-5.5040720	-0.8374850
H	-3.5850430	-5.6417460	-2.4984580
C	-0.9565790	-5.5915000	-2.0493910
H	0.0406110	-5.1683710	-1.8999490
H	-1.2261860	-5.4181570	-3.0964970
H	-0.8703190	-6.6714670	-1.8940730
C	-2.3896660	-3.5469780	-1.4054150
H	-3.2694040	-3.2562730	-0.8211340
H	-1.5851460	-2.8534050	-1.1624630
H	-2.6331640	-3.4186480	-2.4663800
O	0.2024630	-3.6690750	0.0310660
H	0.9136430	-4.0159410	-0.5739760
C	3.7929130	-2.4111000	-0.6662840
H	4.4301500	-3.0608250	-1.2590960
C	1.5839280	-1.2462910	-0.3865470
C	2.4364300	-2.1901090	-1.1427580
C	3.4369360	-0.9735440	1.2012770
C	2.1768920	-0.6765590	0.7735090

C	4.2869290	-1.8265270	0.4690170
H	5.3019400	-2.0168740	0.8045070
O	1.5740920	0.1583370	1.6783900
O	3.6634390	-0.3747850	2.4382250
C	2.6618010	0.6225090	2.4828010
H	3.0423750	1.5584010	2.0431550
H	2.3207640	0.7687110	3.5077710

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M06-2X/6-31G(d,p)
Electronic Energy = -2037.275499
Electronic and Zero-Point Energy = -2036.525193
Enthalpy = -2036.480068
Free Energy = -2036.611329
M06-2X/def2-TZVP
Electronic Energy = -2038.0313455

C	-0.0361860	0.9000070	-0.9638550
C	1.1531540	1.0707390	-1.8137430
C	1.3196230	-1.3867340	-1.9698020
C	-0.7707000	-0.3154550	-1.0627590
C	-0.1511910	-1.3916700	-1.6721430
C	-0.7104870	-2.6456620	-2.1529330
O	0.2725800	-3.3289060	-2.8281370
O	-1.8117500	-3.1466360	-2.0440650
C	1.4262950	-2.4994610	-3.0151790
H	2.3160920	-3.1249470	-2.9121890
H	1.3945110	-2.0785290	-4.0283790
C	-0.4439610	2.0549800	-0.2550020
C	0.1075940	3.2879360	-0.4444750
H	3.3338340	-2.5499490	1.8736860
H	1.9022720	-1.7189420	-1.0615600
C	-2.2043290	-0.3616880	-0.6536320
C	-3.0938440	0.5932250	-1.1552110
C	-2.6498450	-1.3503970	0.2238350
C	-4.4372360	0.5521000	-0.7804270
H	-2.7248600	1.3607530	-1.8255420
C	-3.9915360	-1.3850930	0.6083180
H	-1.9448980	-2.0873400	0.5863870
C	-4.8930370	-0.4443910	0.0936990
O	-4.5202970	-2.2927990	1.4678610
O	-6.2165080	-0.5083680	0.4334900
O	-5.3853850	1.4256200	-1.2057340
C	-4.9749270	2.4314710	-2.1143500
H	-5.8677780	3.0122600	-2.3480910

H	-4.2211950	3.0925300	-1.6704320
H	-4.5741960	1.9976870	-3.0375320
C	-6.5409760	0.3267370	1.5386290
H	-5.9785550	0.0304000	2.4318200
H	-6.3326570	1.3781200	1.3097900
H	-7.6090540	0.2037080	1.7292160
C	-3.6363420	-3.2651040	1.9952480
H	-3.1849110	-3.8712510	1.2009370
H	-2.8398630	-2.7998500	2.5888720
H	-4.2385010	-3.9060960	2.6397510
C	-1.5838120	3.5213780	0.9286300
H	-1.7692790	3.7514740	1.9780590
H	-2.4380340	3.8099360	0.2946610
O	-0.4147320	4.1857690	0.4834490
C	3.1690910	-0.6366530	1.1045410
C	2.0617280	-0.1817420	1.8188620
C	1.9625770	1.2119640	1.8921990
H	1.1220780	1.6639410	2.4066110
C	2.9068710	2.0552870	1.3084500
C	3.9650050	1.5038070	0.5841820
H	4.6716840	2.1803020	0.1184330
C	4.1380060	0.1230660	0.4498380
C	5.3281600	-0.4838560	-0.3152320
C	6.1286700	0.6178900	-1.0211380
H	6.5557720	1.3335830	-0.3130710
H	6.9571940	0.1553190	-1.5645660
H	5.5109310	1.1631210	-1.7425250
C	4.8686570	-1.4703190	-1.4066900
H	4.4823190	-2.4116280	-1.0094430
H	4.1052050	-1.0145590	-2.0451300
H	5.7272890	-1.7282670	-2.0346330
C	6.2727180	-1.1883050	0.6744340
H	7.1325360	-1.5919780	0.1296100
H	6.6452580	-0.4825950	1.4233720
H	5.7933860	-2.0205480	1.1964080
C	2.8044470	3.5454740	1.4878590
H	3.2633230	4.0747760	0.6492140
H	1.7622330	3.8631020	1.5739890
H	3.3291970	3.8503880	2.4004910
C	1.0708150	-1.0993260	2.5617290
C	-0.2070060	-0.3221310	2.9096370
H	-0.0130390	0.4942170	3.6102970
H	-0.6772960	0.0932380	2.0113820
H	-0.9144290	-1.0039000	3.3907760
C	1.7329680	-1.5564220	3.8729600
H	2.6582130	-2.1269620	3.7125040

H	1.0478190	-2.2049260	4.4283820
H	1.9876900	-0.6969590	4.4995680
C	0.6317970	-2.3353250	1.7432040
H	0.4502560	-2.0856130	0.6915220
H	1.3201440	-3.1860200	1.8121970
H	-0.3098630	-2.7129350	2.1528960
O	3.3601010	-2.0854650	1.0055930
H	2.7151130	-2.4967000	0.3723610
C	1.6494570	2.4176940	-2.0329720
H	2.4735290	2.5421010	-2.7309120
C	1.7222940	-0.0221410	-2.4224240
H	2.4914730	0.1020910	-3.1811990
O	-1.3556020	2.1234170	0.7777500
C	1.1548940	3.5058210	-1.3640930
H	1.5653560	4.5001900	-1.5107960

5.6.2.3. XYZ Coordinates for isolated products

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M06-2X/6-31G(d,p)
Electronic Energy = -2036.77847192
Electronic and Zero-Point Energy = -2036.039017
Enthalpy = -2035.993298
Free Energy = -2036.120914
M06-2X/def2-TZVP
Electronic Energy = -2037.5300616

C	-1.6764120	1.3639850	-0.2798180
C	-0.4085730	1.9468950	-0.0768690
C	0.7630890	1.0559440	0.2684590
C	0.6480180	-0.2457540	-0.5063590
C	-1.8249070	-0.1094780	-0.1751100
C	-0.7072030	-0.8572210	-0.2828350
C	-0.5257740	-2.3208340	-0.1241980
O	0.8045390	-2.5814260	-0.1114840
O	-1.3328660	-3.2111540	-0.0164570
C	1.5825950	-1.3709260	-0.0546330
H	1.9148940	-1.2247090	0.9800580
H	2.4544900	-1.5053810	-0.6984620
C	-0.2370880	3.3370390	-0.1550650
C	-2.7960270	2.1705680	-0.5878760
C	-2.5967380	3.5268660	-0.6645810
C	-1.3470090	4.1005640	-0.4458920
H	0.7361090	3.7905350	0.0009610
H	-3.7725930	1.7358710	-0.7667980

H	1.7124710	1.5620020	0.0658930
H	0.7396440	0.8281000	1.3446070
H	0.7859290	-0.0493870	-1.5791740
C	5.3525120	-1.7874390	1.3336430
C	4.6908000	0.2399860	0.1370940
C	5.4316990	-1.7385950	-1.1022100
C	5.5908800	-2.4430260	0.1054980
H	5.5255670	-2.3557010	2.2419320
H	5.6600910	-2.2660550	-2.0220720
O	4.2164710	1.3999180	0.1470630
C	6.0437510	-3.8706060	0.1072150
H	7.0318430	-3.9593820	0.5733620
H	6.1040360	-4.2748560	-0.9048780
H	5.3603430	-4.4922960	0.6949190
C	5.0082880	-0.4269750	-1.1367180
C	4.8436140	0.3362580	-2.4497470
C	4.9410890	-0.4774370	1.4002000
C	-3.1859730	-0.6755930	0.0290170
C	-3.9535310	-0.2339310	1.1116490
C	-3.6985410	-1.5992740	-0.8817440
C	-5.2417720	-0.7411090	1.2956110
H	-3.5412820	0.5004200	1.7934700
C	-4.9878500	-2.1032150	-0.6977220
H	-3.0871450	-1.9195390	-1.7152140
C	-5.7551150	-1.6887790	0.3989020
O	-5.5902640	-2.9926190	-1.5229860
O	-7.0032950	-2.2066400	0.5954560
O	-6.0740980	-0.3802820	2.3010250
C	-5.5988920	0.5940850	3.2145440
H	-6.4034350	0.7550340	3.9322510
H	-4.7067300	0.2424400	3.7448740
H	-5.3709570	1.5393010	2.7085290
C	-8.0073060	-1.4973660	-0.1235460
H	-8.0651440	-0.4560000	0.2134270
H	-7.8081310	-1.5225150	-1.2007990
H	-8.9571950	-1.9955490	0.0792470
C	-4.8345980	-3.4656050	-2.6260200
H	-4.5713710	-2.6508170	-3.3098960
H	-3.9207030	-3.9716090	-2.2946000
H	-5.4739130	-4.1795800	-3.1457060
C	-2.8288490	5.7356410	-0.7005260
H	-3.0056400	6.4472520	-1.5074400
H	-3.1775880	6.1246000	0.2640640
O	-1.4297030	5.4483050	-0.6139470
O	-3.4930130	4.5064690	-0.9898360
C	5.3240800	-0.4891660	-3.6490570

H	5.2048180	0.1057660	-4.5598990
H	6.3816720	-0.7591890	-3.5610550
H	4.7407010	-1.4068580	-3.7748330
C	5.6670580	1.6379110	-2.4186410
H	6.7263340	1.4221140	-2.2422640
H	5.5826680	2.1411060	-3.3879480
H	5.3139090	2.3152710	-1.6410470
C	3.3556820	0.6615840	-2.6730590
H	2.7747380	-0.2625070	-2.7695410
H	2.9491190	1.2521560	-1.8496210
H	3.2401400	1.2304620	-3.6025430
C	5.7185220	1.4663790	2.7673900
H	5.4804570	2.1787600	1.9764260
H	6.7599250	1.1470440	2.6522340
H	5.6249790	1.9733360	3.7339340
C	3.3187150	0.7268000	2.9194880
H	3.2259700	1.2360190	3.8854100
H	2.6294890	-0.1252040	2.9248460
H	3.0235760	1.4178510	2.1299040
C	5.1227460	-0.6492380	3.9209140
H	4.4663450	-1.5237250	3.9799920
H	5.0010350	-0.0793470	4.8473250
H	6.1599910	-0.9969840	3.8775310
C	4.7704180	0.2529230	2.7322570

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M06-2X/6-31G(d,p)
Electronic Energy = -2036.77382875
Electronic and Zero-Point Energy = -2036.034530
Enthalpy = -2035.988454
Free Energy = -2036.117841
M06-2X/def2-TZVP
Electronic Energy = -2037.5237183

C	-2.5591350	2.2369850	0.4361870
C	-2.1737450	3.3722830	1.2079500
C	-1.3529640	3.1306750	2.4533360
C	-0.3671210	2.0005440	2.1883210
C	-2.1673830	0.8738180	0.8665000
C	-1.1074080	0.7855600	1.6973850
C	-0.5322050	-0.4055890	2.3765770
O	0.3858180	0.0230790	3.2750650
O	-0.7632600	-1.5816630	2.2395600
C	0.3545410	1.4544780	3.4243650
H	-0.1948910	1.6883070	4.3428300

H	1.3834890	1.8018480	3.5212420
C	-2.5476710	4.6526100	0.8282810
C	-3.2816330	2.5030520	-0.7184180
C	-3.6453410	3.7998440	-1.0849230
H	-2.2422590	5.4923580	1.4450830
H	-0.8382760	4.0488600	2.7493810
H	-2.0100790	2.8349910	3.2836920
H	0.3647950	2.3199610	1.4330470
C	6.9295790	-1.0760300	0.2711850
C	5.0112310	0.0385020	-0.7583050
C	4.6908600	-1.9940640	0.5690730
C	6.0749000	-2.0601660	0.8144080
H	7.9897640	-1.1655110	0.4850820
H	4.0679180	-2.7687420	1.0034740
O	4.5384870	0.9703550	-1.4487680
C	6.6566810	-3.1744920	1.6290720
H	7.2374530	-3.8499020	0.9895910
H	5.8793130	-3.7585640	2.1252570
H	7.3451390	-2.7856070	2.3859480
C	4.1279320	-0.9916520	-0.1913310
C	2.6258020	-0.9232630	-0.4563680
C	6.4589510	-0.0404080	-0.5004270
C	-2.9789520	-0.2827510	0.4042170
C	-4.3648030	-0.2415270	0.5436680
C	-2.3643350	-1.3812680	-0.2030440
C	-5.1410380	-1.3067220	0.0917400
H	-4.8625260	0.6131580	0.9910470
C	-3.1362500	-2.4536970	-0.6442960
H	-1.2863580	-1.3941310	-0.3001180
C	-4.5353180	-2.4171740	-0.5035310
O	-2.6343640	-3.5785960	-1.2070030
O	-5.2747540	-3.4767940	-0.9487500
O	-6.4912620	-1.2427910	0.2869920
C	-7.3150770	-1.4548830	-0.8586620
H	-8.2688890	-0.9693030	-0.6431660
H	-6.8712890	-0.9950860	-1.7483830
H	-7.4828640	-2.5178460	-1.0502940
C	-5.7783040	-4.2862890	0.1120520
H	-4.9548480	-4.7232800	0.6879620
H	-6.4219450	-3.7040920	0.7811530
H	-6.3608860	-5.0845720	-0.3509720
C	-1.2227660	-3.7145660	-1.2134350
H	-0.7459030	-2.9491690	-1.8373370
H	-0.8176880	-3.6593670	-0.1963250
H	-1.0153500	-4.6984890	-1.6351570
O	-4.3026570	3.7657010	-2.2819580

C	1.8772880	-2.0852030	0.2052850
H	0.8079570	-1.9703920	0.0079390
H	2.1928900	-3.0565770	-0.1914940
H	2.0045780	-2.0916100	1.2926020
C	2.3515020	-0.9910340	-1.9705470
H	2.7403350	-1.9241240	-2.3926900
H	1.2691890	-0.9685700	-2.1436460
H	2.8066500	-0.1512730	-2.4967000
C	2.0448800	0.3832800	0.1170070
H	2.1759960	0.4186970	1.2051820
H	2.5168780	1.2610070	-0.3263080
H	0.9694100	0.4187900	-0.0960400
C	7.2949780	0.9866030	-2.6320810
H	6.2853070	1.2164190	-2.9736700
H	7.5809940	0.0011540	-3.0154430
H	7.9852660	1.7251200	-3.0543960
C	6.9988750	2.4155600	-0.5771490
H	7.6963650	3.1584610	-0.9797100
H	7.0608440	2.4540990	0.5158480
H	5.9865460	2.6850760	-0.8795050
C	8.8487770	0.7678070	-0.7088490
H	8.9970200	0.8052960	0.3753480
H	9.4737380	1.5460870	-1.1575370
H	9.2092520	-0.1996140	-1.0733900
C	7.3866340	1.0180810	-1.0950680
O	-3.6840140	1.6389220	-1.6934960
C	-3.3006590	4.8976880	-0.3337950
H	-3.5798650	5.9009020	-0.6346700
C	-4.5737130	2.3865420	-2.5214280
H	-4.3803810	2.1509460	-3.5682220
H	-5.6102890	2.1597850	-2.2393700

5.6.3.4. XYZ Coordinates for BHT radical (di-*t*-butylhydroxytoluene)

M06-2X/6-31G(d,p)
Electronic Energy = -660.3784899
Electronic and Zero-Point Energy = -660.031358
Enthalpy = -660.012589
Free Energy = -660.076182
M06-2X/def2-TZVP
Electronic Energy = -660.6033718
$\langle S^2 \rangle = 0.779868$

C	1.2179850	1.5484830	-0.0078990
C	0.0023560	-0.5770060	0.0014510
C	-1.2199030	1.5423720	-0.0073040

C	-0.0001360	2.2531860	-0.0096060
H	2.1328980	2.1312410	-0.0114250
H	-2.1360030	2.1242640	-0.0098320
O	0.0040670	-1.8292130	0.0059520
C	-0.0163930	3.7509420	0.0071440
H	-0.3508570	4.1164430	0.9855320
H	0.9743540	4.1658370	-0.1885280
H	-0.7185610	4.1436190	-0.7347720
C	-1.2678850	0.1684450	-0.0015910
C	-2.5882670	-0.6003550	-0.0001280
C	1.2690150	0.1713200	-0.0018810
C	2.5920000	-0.5924020	-0.0001070
C	-2.6819270	-1.4852780	-1.2571900
H	-1.8826910	-2.2267400	-1.2788560
H	-3.6453370	-2.0070240	-1.2648510
H	-2.6218240	-0.8757520	-2.1654400
C	-2.6841210	-1.4770520	1.2624490
H	-3.6473440	-1.9991220	1.2714800
H	-1.8847500	-2.2181090	1.2906140
H	-2.6261250	-0.8617840	2.1669430
C	-3.7932840	0.3476480	-0.0040610
H	-3.8106350	0.9902200	0.8823540
H	-3.8095250	0.9845250	-0.8945840
H	-4.7128050	-0.2457740	-0.0027220
C	2.6889420	-1.4775530	-1.2568660
H	3.6541030	-1.9960410	-1.2637440
H	1.8920870	-2.2215320	-1.2784740
H	2.6273090	-0.8685250	-2.1653380
C	2.6907060	-1.4682980	1.2629310
H	3.6557130	-1.9870440	1.2719830
H	2.6307630	-0.8527960	2.1671300
H	1.8937680	-2.2119170	1.2913580
C	3.7941270	0.3593880	-0.0041850
H	3.8087610	0.9959470	-0.8949380
H	3.8095810	1.0022150	0.8820560
H	4.7152890	-0.2314870	-0.0025110

5.6.3.5. XYZ Coordinates for BHT

M06-2X/6-31G(d,p)
Electronic Energy = -661.007866934
Electronic and Zero-Point Energy = -660.648001
Enthalpy = -660.628833
Free Energy = -660.692989
M06-2X/def2-TZVP
Electronic Energy = -661.2349528

C	-1.1962020	1.4773500	-0.0035490
C	0.0454370	-0.5722240	0.0025110
C	1.1858180	1.5491970	-0.0028180
C	-0.0348230	2.2313600	-0.0042590
H	-2.1461780	2.0046200	-0.0063300
H	2.0962400	2.1391680	-0.0044070
C	-0.0701490	3.7380220	0.0049300
H	-1.0901060	4.1099910	-0.1205240
H	0.3181200	4.1388360	0.9475670
H	0.5441840	4.1555570	-0.7991620
C	1.2630260	0.1610840	0.0003460
C	2.6260090	-0.5541650	-0.0004880
C	-1.2056230	0.0712460	0.0002220
C	-2.6105940	-0.5823120	-0.0004450
C	2.7854510	-1.4182200	1.2632970
H	2.0315770	-2.2034010	1.3201600
H	3.7752170	-1.8888130	1.2634220
H	2.7097010	-0.7978430	2.1631880
C	2.7815150	-1.4221500	-1.2621120
H	3.7708560	-1.8936260	-1.2634430
H	2.0267420	-2.2067980	-1.3147630
H	2.7039980	-0.8042640	-2.1635840
C	3.7885930	0.4481820	-0.0037630
H	3.7814580	1.0893950	0.8835480
H	4.7323040	-0.1065050	-0.0041440
H	3.7790480	1.0864260	-0.8931810
C	-2.6654110	-2.1189670	0.0047040
H	-3.7150740	-2.4266940	0.0038160
H	-2.2221280	-2.5623030	-0.8953470
H	-2.2256360	-2.5561420	0.9095520
C	-3.3700330	-0.1253690	-1.2594180
H	-4.3749860	-0.5612930	-1.2652220
H	-3.4780080	0.9612910	-1.3035790
H	-2.8509640	-0.4527840	-2.1662140
C	-3.3754540	-0.1167350	1.2521160
H	-3.4835080	0.9701640	1.2884880
H	-4.3804960	-0.5524900	1.2565460
H	-2.8603450	-0.4379920	2.1633640
O	0.1921230	-1.9297210	0.0052890
H	-0.6643490	-2.3645330	0.0102900

5.6.3.6. XYZ Coordinates for benzonitrile

M06-2X/6-31G(d,p)
Electronic Energy = -324367411264

Electronic and Zero-Point Energy = -324.267106
Enthalpy = -324.26011
Free Energy = -324.297348
M06-2X/def2-TZVP
Electronic Energy = -324.4881734

C	-2.0390060	-0.0001230	0.0002460
N	-3.1964120	0.0000580	-0.0000540
C	0.0889750	-1.2185440	-0.0000540
H	-0.4634940	-2.1520700	-0.0003270
C	1.4787470	-1.2102550	0.0000770
H	2.0219360	-2.1492520	0.0001790
C	2.1710940	0.0001000	0.0000200
H	3.2565080	0.0000630	0.0000470
C	1.4786590	1.2103280	-0.0000660
H	2.0216420	2.1494310	0.0001240
C	0.0888080	1.2184560	-0.0000080
H	-0.4636790	2.1519350	0.0000530
C	-0.6002820	-0.0000480	-0.0001640

5.7. References and Notes

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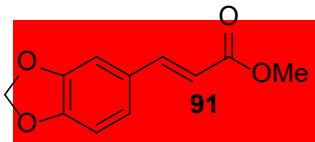
Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian 09, Revision B.01. Wallingford CT, **2009**.

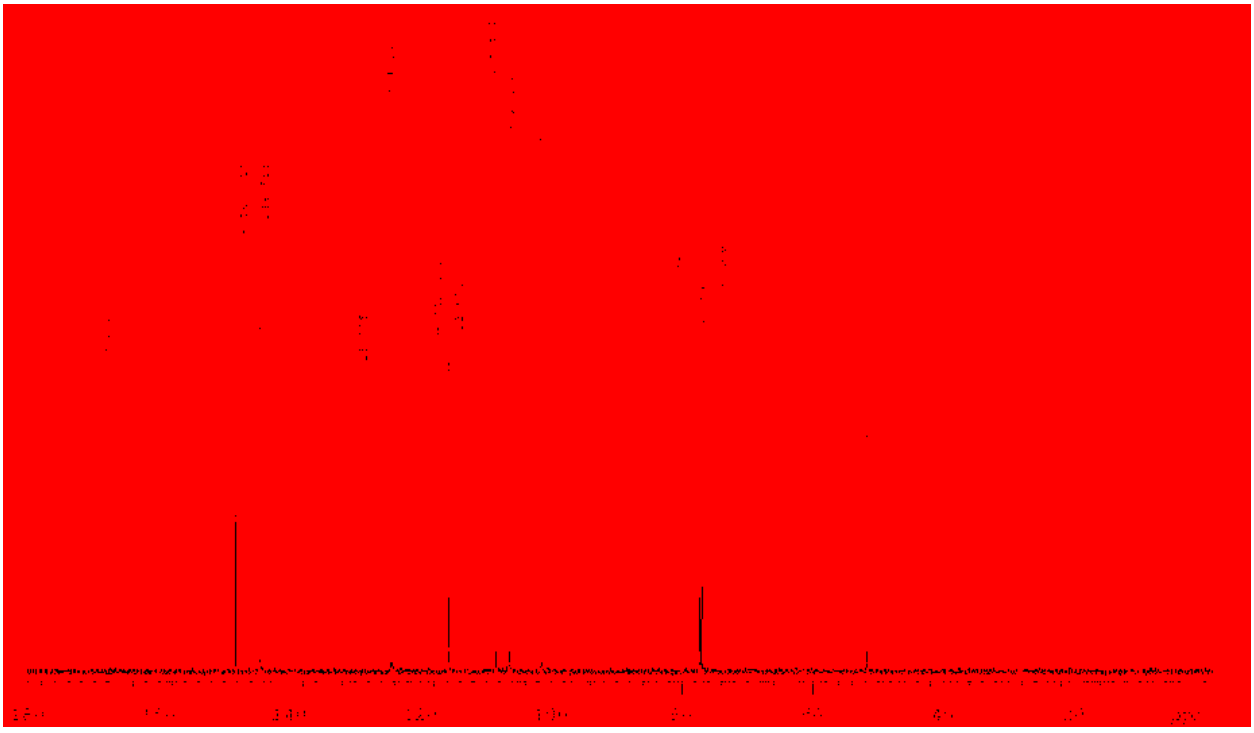
3. (a) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys* **2006,** *125*, 194101. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res* **2008,** *41*, 157–167. (c) Zhao, Y.; Truhlar, D. *Theor Chem Acc* **2008,** *120*, 215–241. (d) Jacquemin, D.; Perpète, E. A.; Ciofini, I.; Adamo, C.; Valero, R.; Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2010,** *6*, 2071–2085.
4. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009,** *113*, 6378–6396.
5. Ess, D. H.; Cook, T. C. *J. Phys. Chem. A* **2012,** *116*, 4922–4929.
6. def2-TZVP basis sets were downloaded from https://bse.pnl.gov/bse/portal (accessed January 1, 2016).

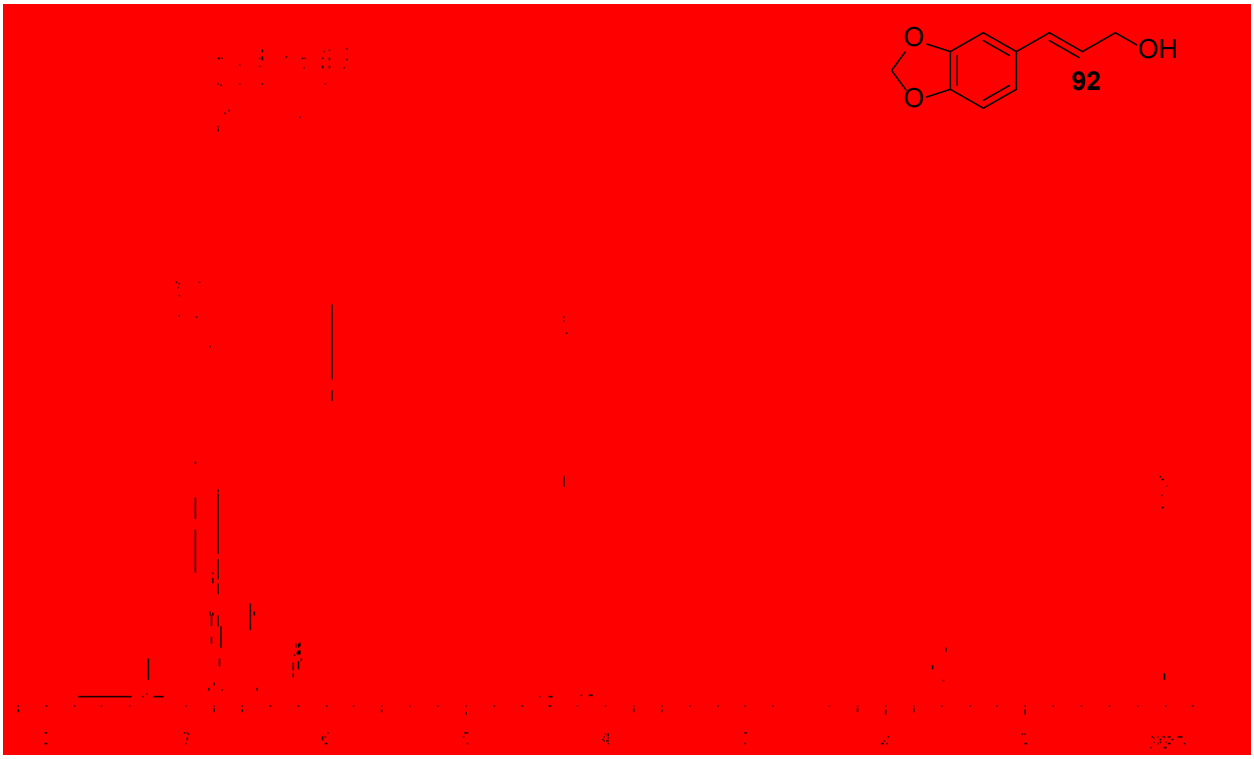
6. Selected NMR Spectra

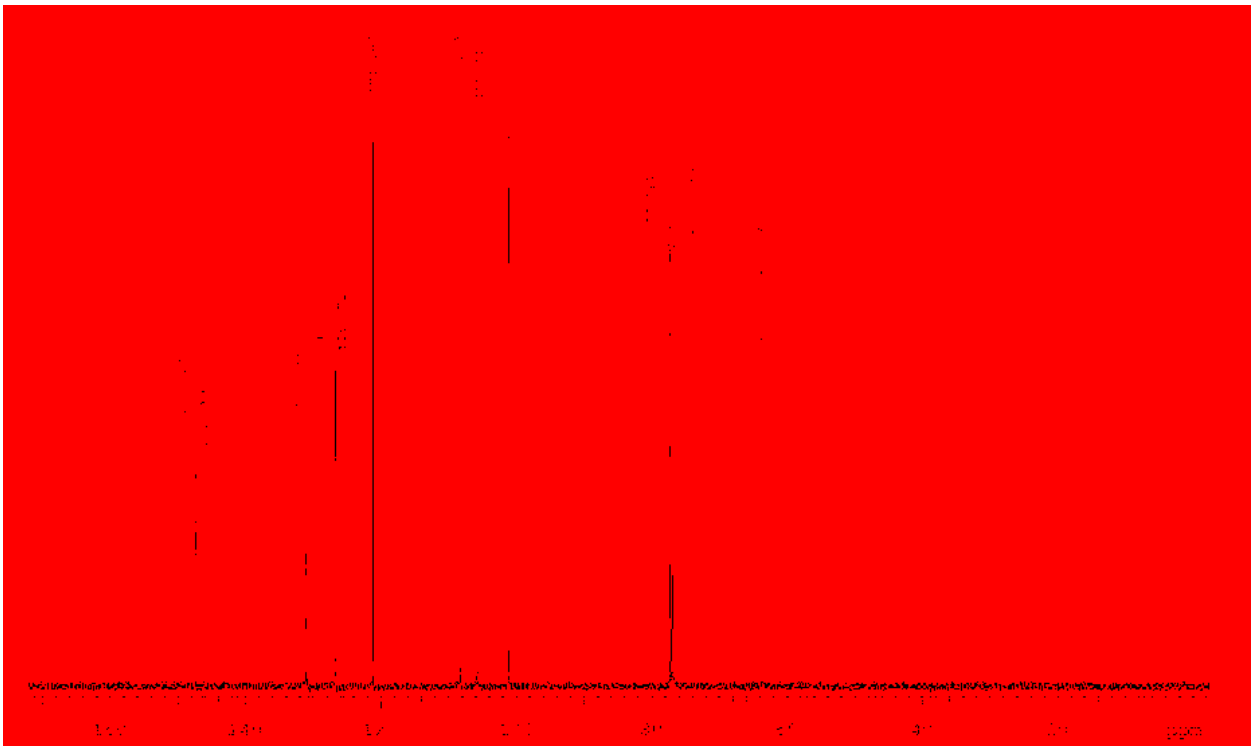
6.1. DPT Synthesis

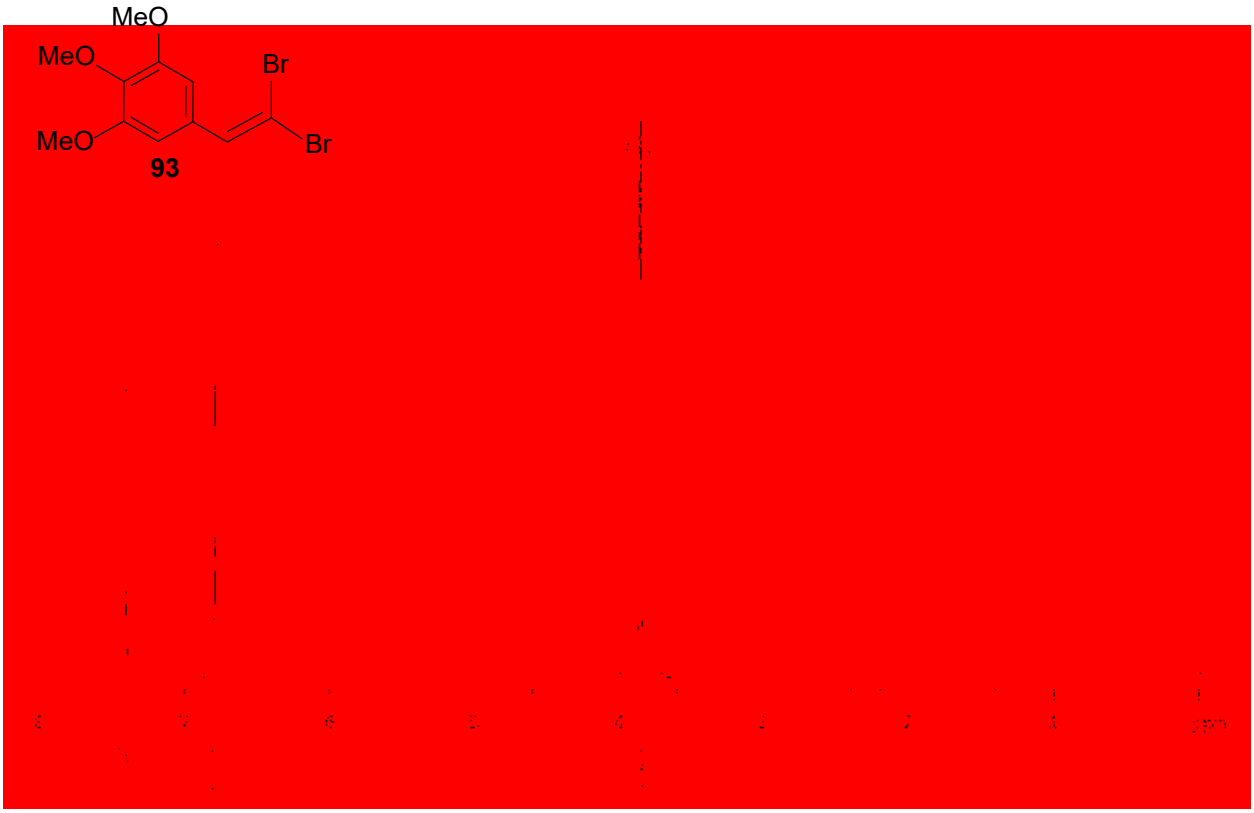


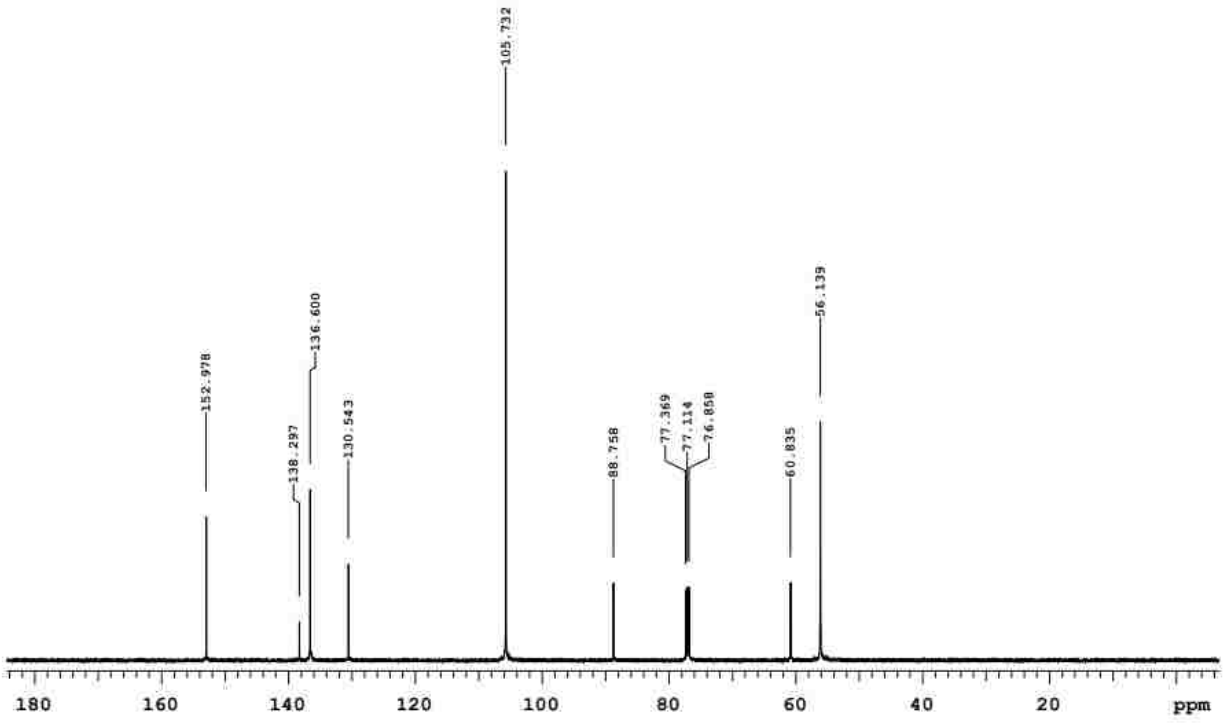
91

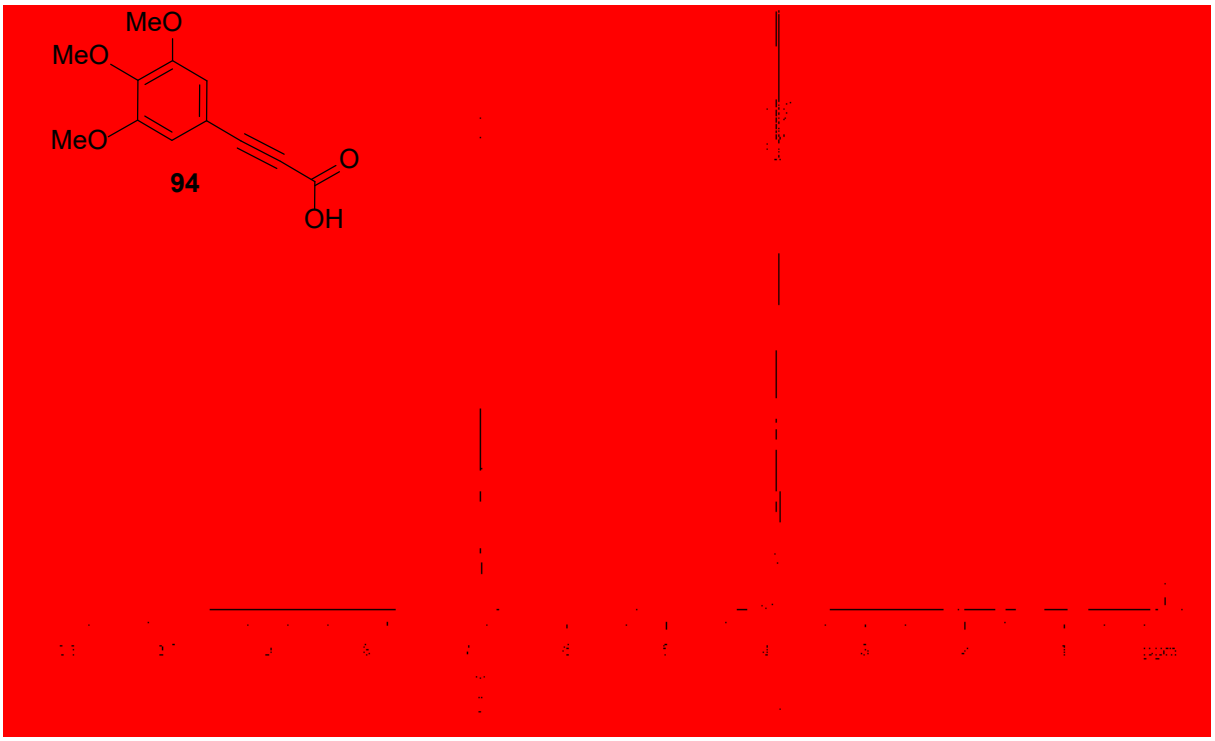


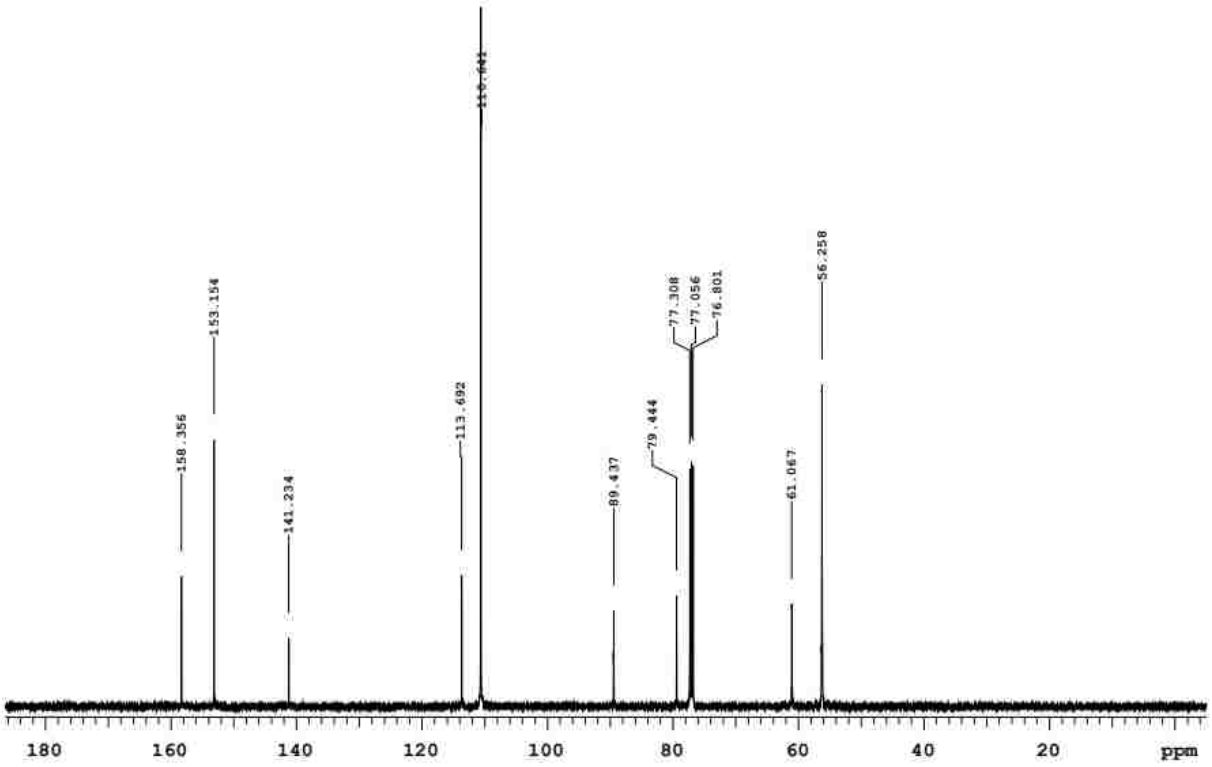

O
O
OH
92

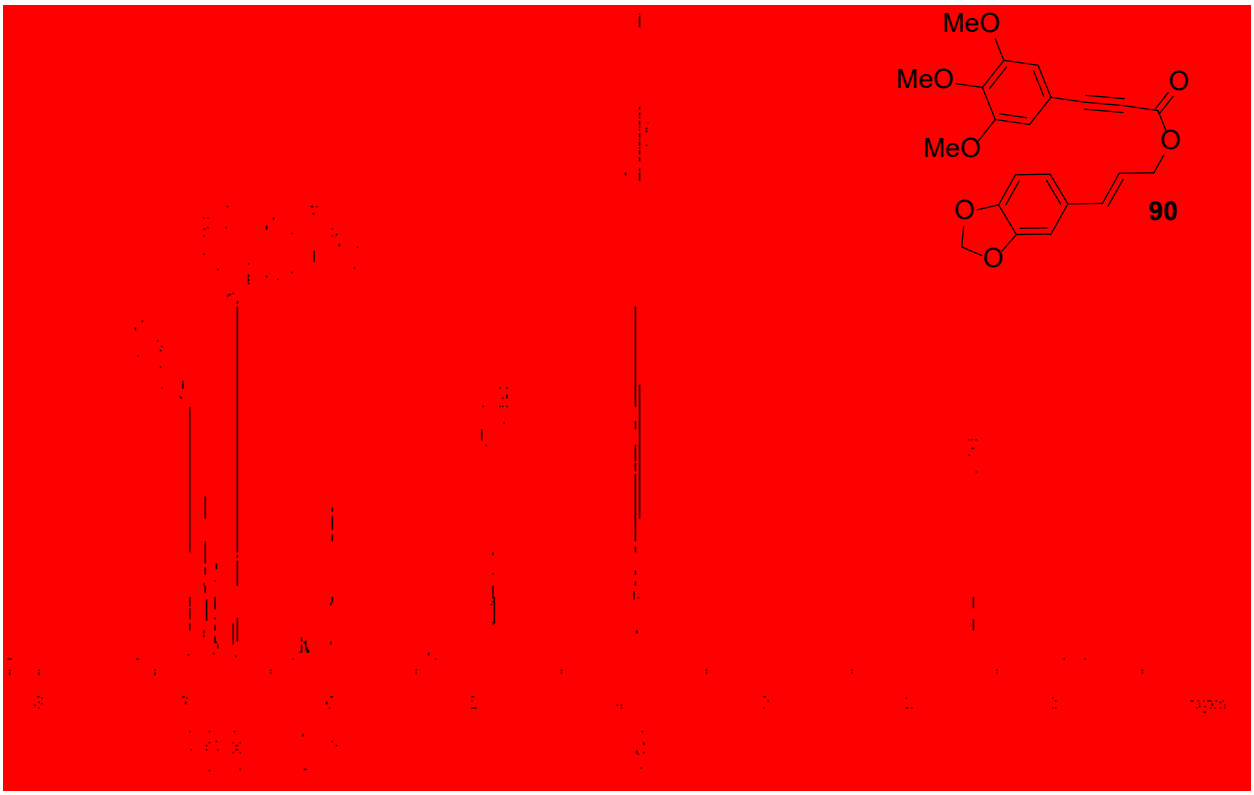


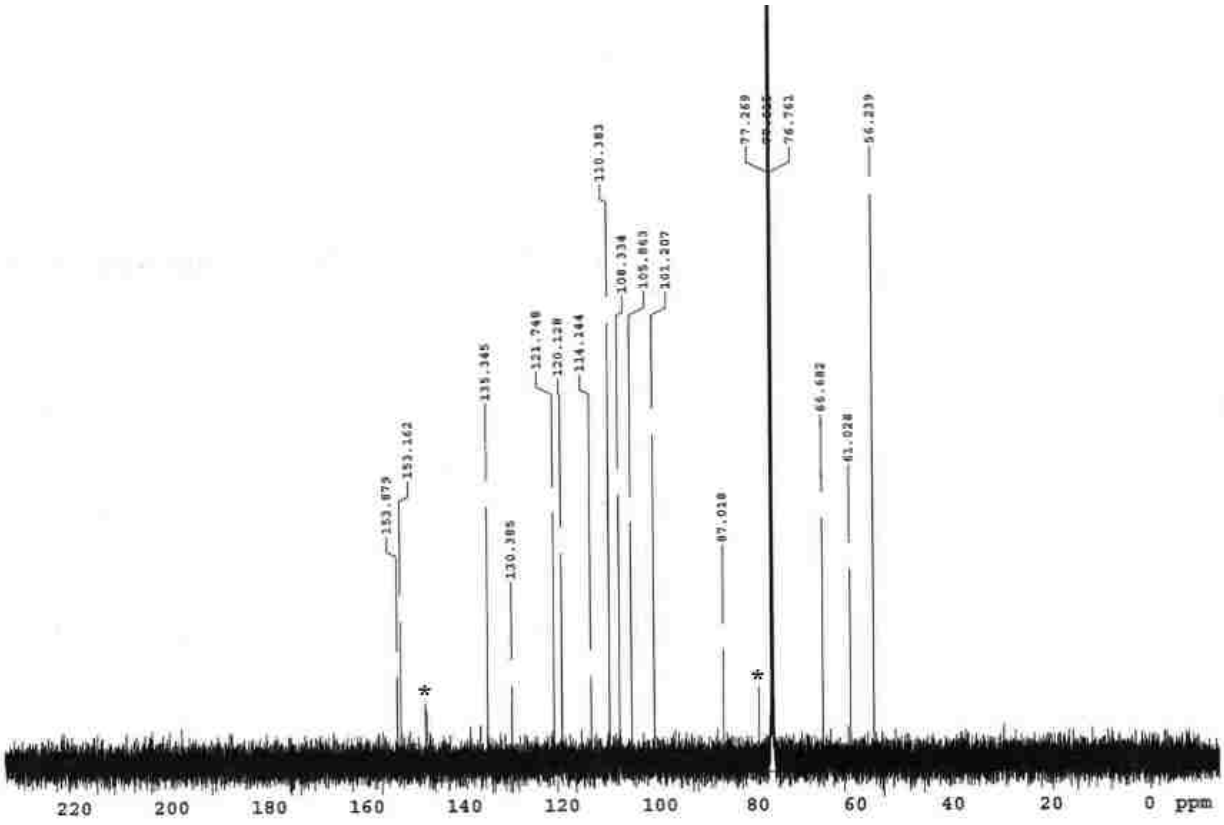

MeO
MeO
MeO
Br
Br
93


152.978
138.297
136.600
130.543
105.732
88.758
77.369
77.114
76.858
60.835
56.139
180
160
140
120
100
80
60
40
20
ppm


MeO
MeO
MeO
O
OH
94


158.356
153.154
141.234
113.692
110.641
89.437
79.444
77.308
77.056
76.801
61.067
56.258
180
160
140
120
100
80
60
40
20
ppm


MeO
MeO
MeO
O
O
O
O
90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135.345
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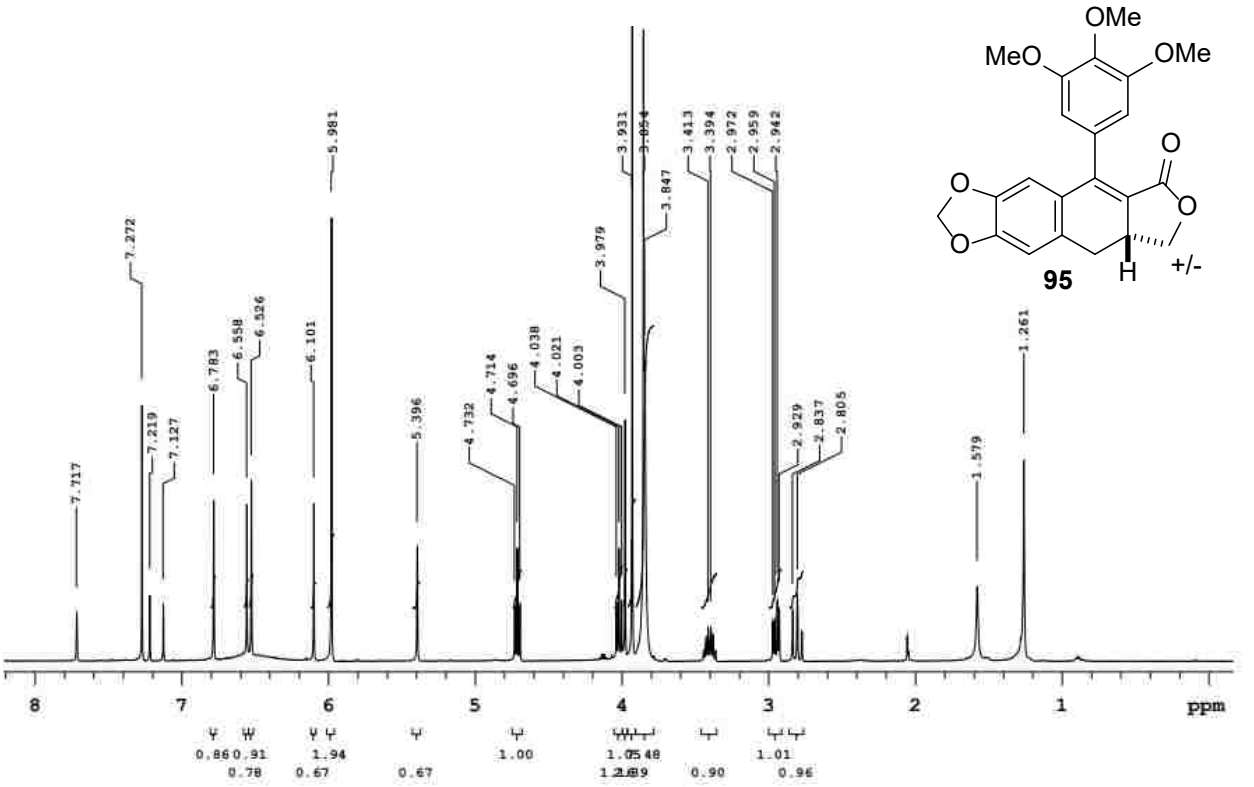
121.740
120.128
114.144
110.383
108.334
105.863
101.807
97.010
77.269
76.761
66.682
61.028
56.239
*
*
220
200
180
160
140
120
100
80
60
40
20
0
ppm

* Impurities


OMe
MeO
OMe
O
O
O
O
H
+/-
95
7.717
7.272
7.219
7.127
6.783
6.558
6.526
6.101
5.981
5.396
4.732
4.714
4.696
4.038
4.021
4.003
3.979
3.931
3.854
3.847
3.413
3.394
2.972
2.959
2.942
2.929
2.837
2.805
1.579
1.261
8
7
6
5
4
3
2
1
ppm
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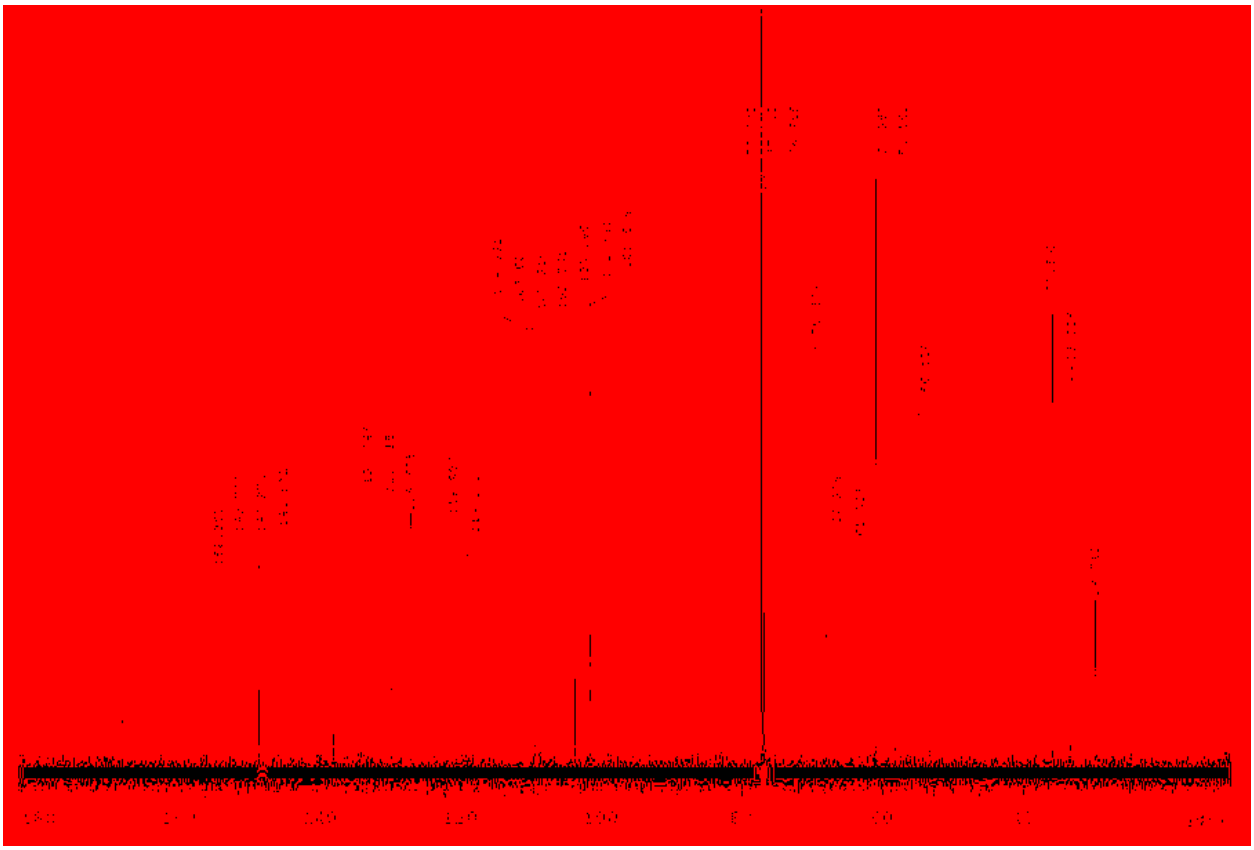
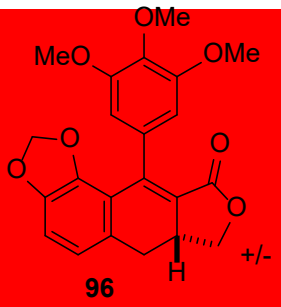
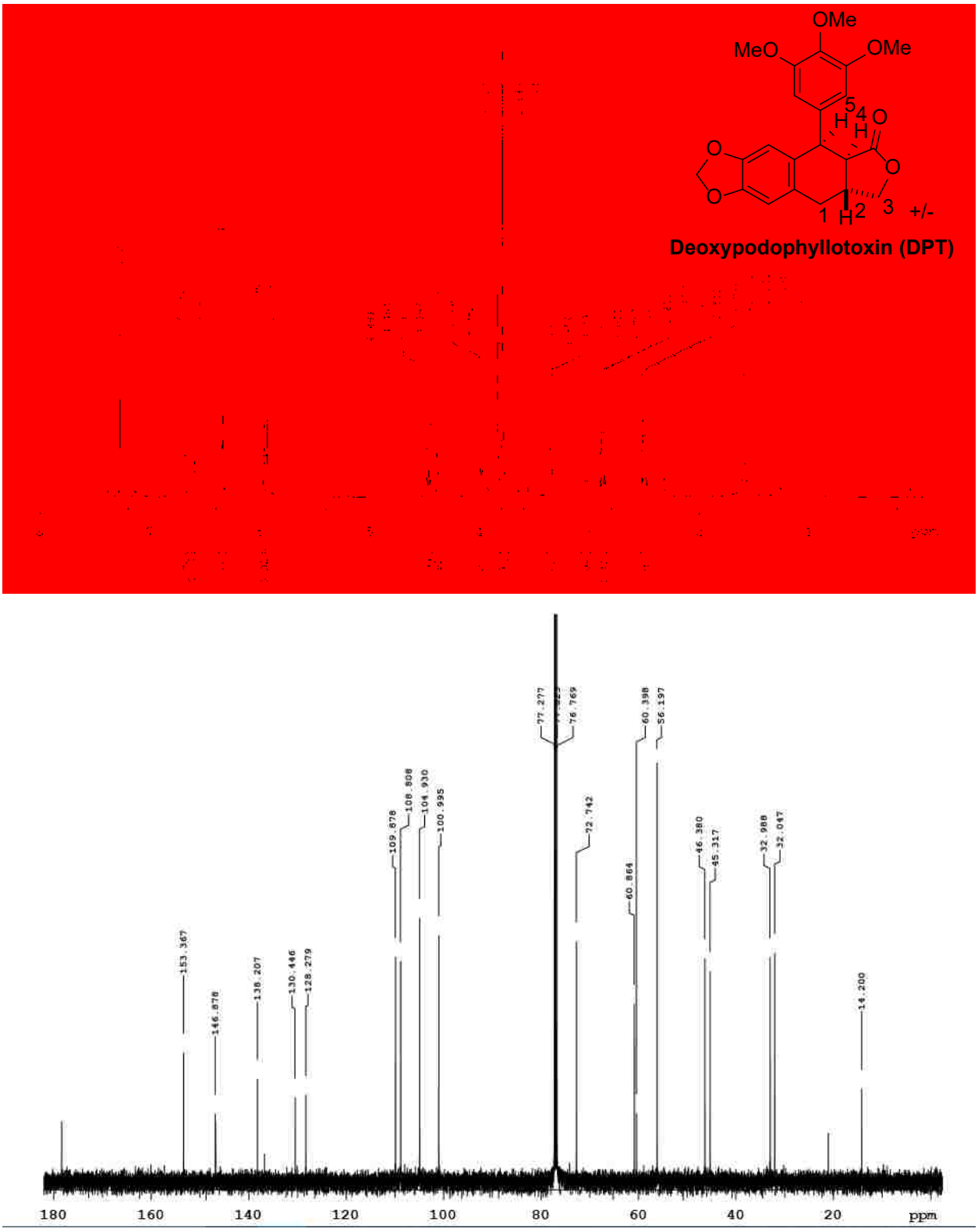
0.91
1.94
0.67
0.67
1.00
1.01
0.78
0.90
0.96

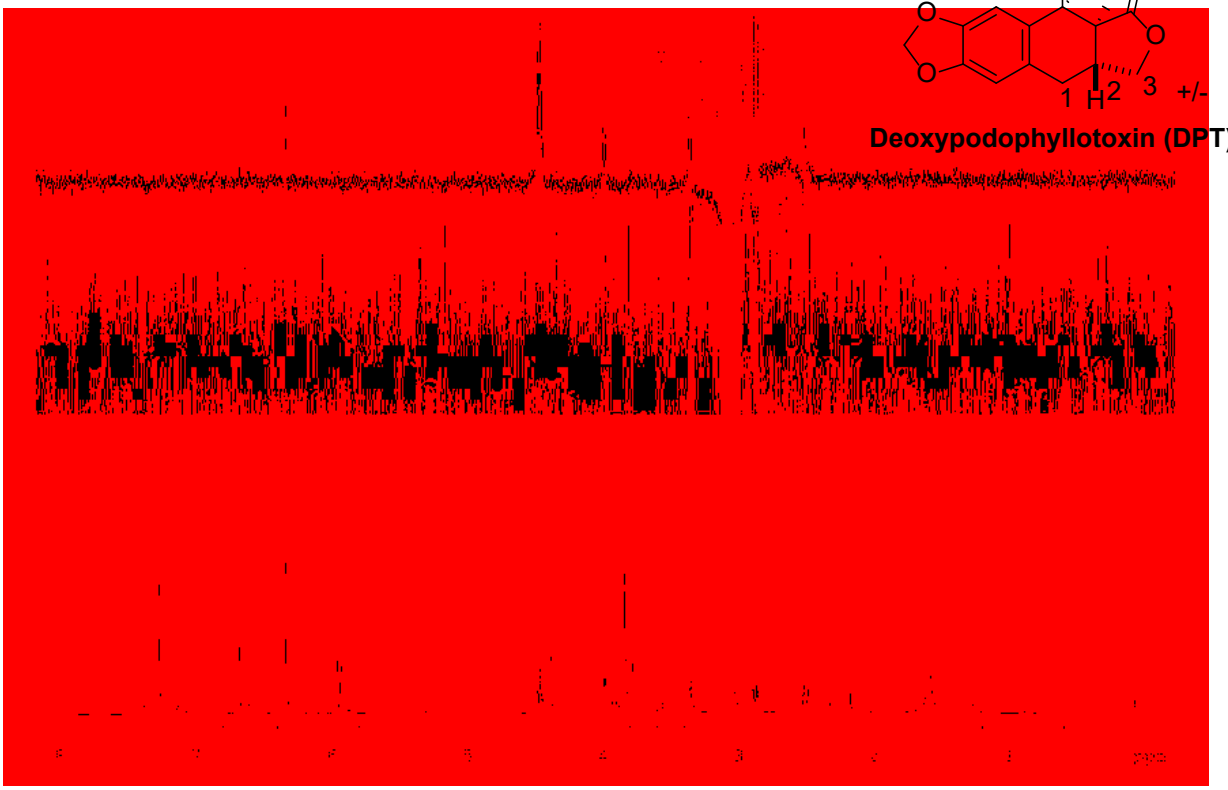


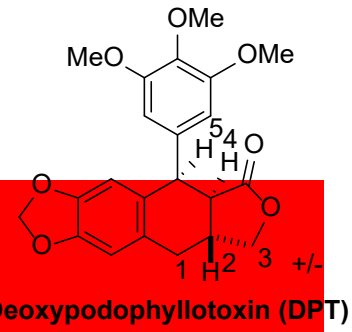


96


OMe
MeO
OMe
O
O
O
O
+/-
Deoxypodophyllotoxin (DPT)
153.367
146.878
138.207
130.446
128.279
109.878
108.808
104.930
100.995
77.277
76.769
72.742
60.864
60.398
56.197
46.380
45.317
32.988
32.047
14.200
180
160
140
120
100
80
60
40
20
ppm

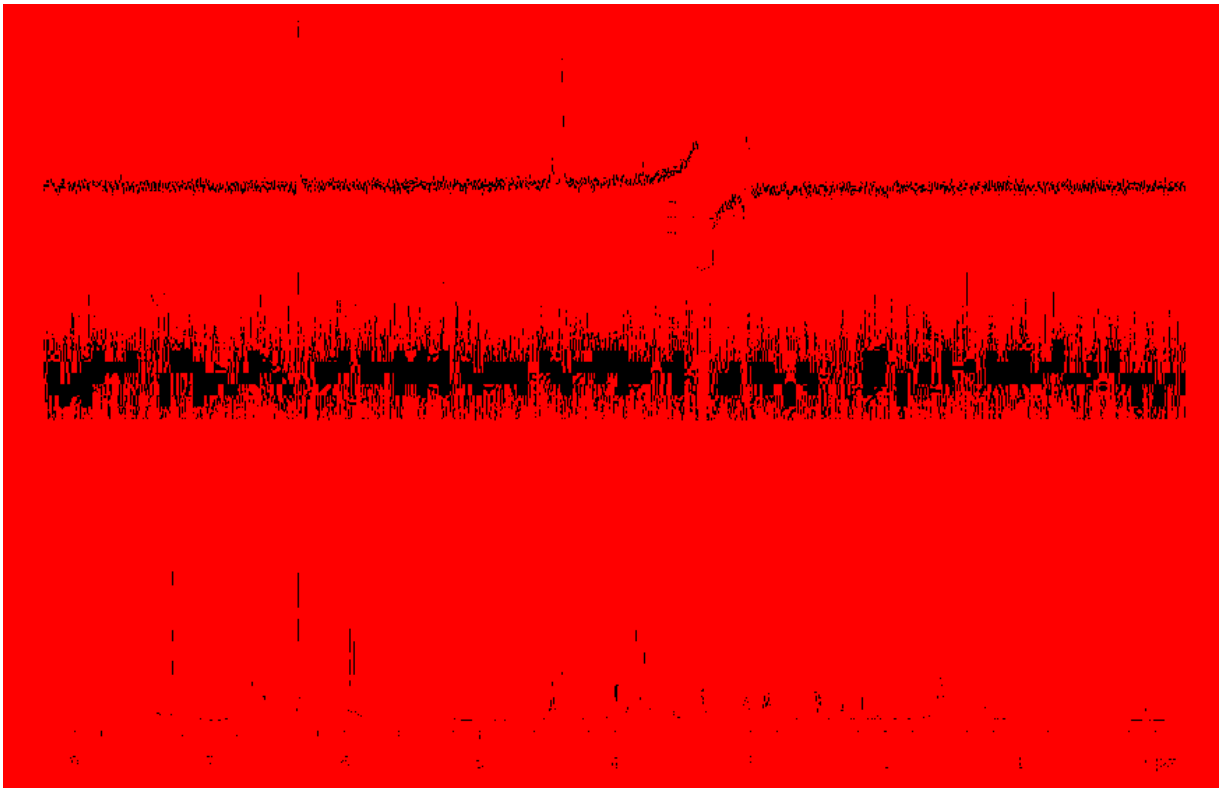
DPT NOESY H2

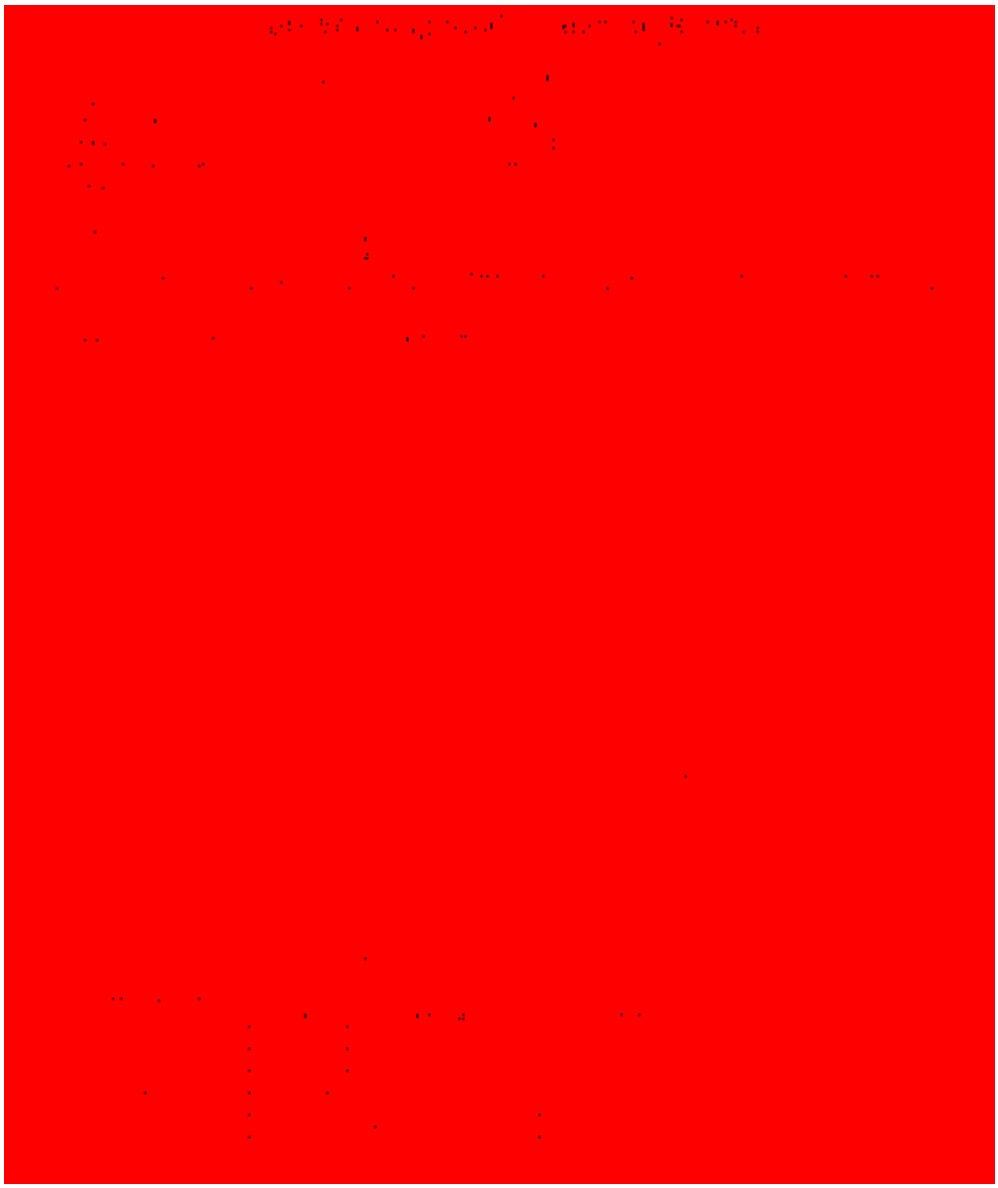




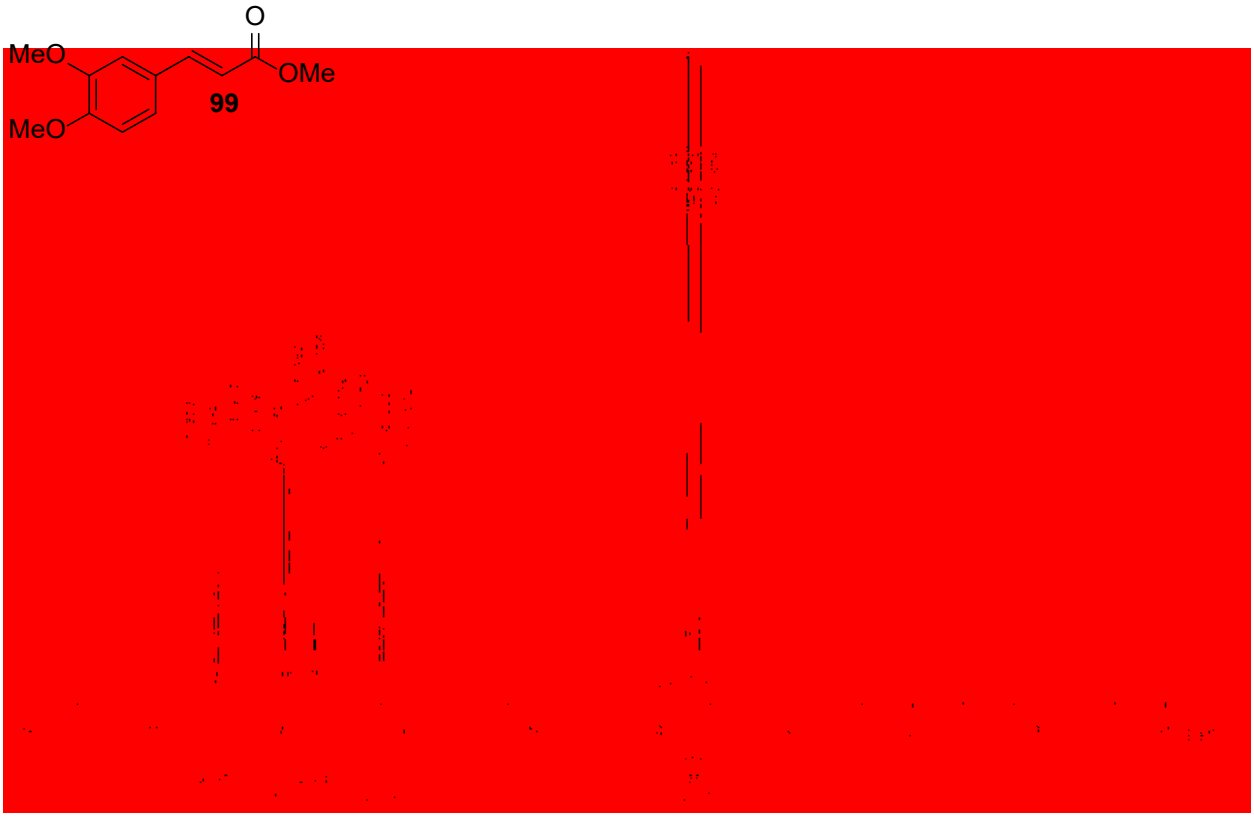
Deoxypodophyllotoxin (DPT)

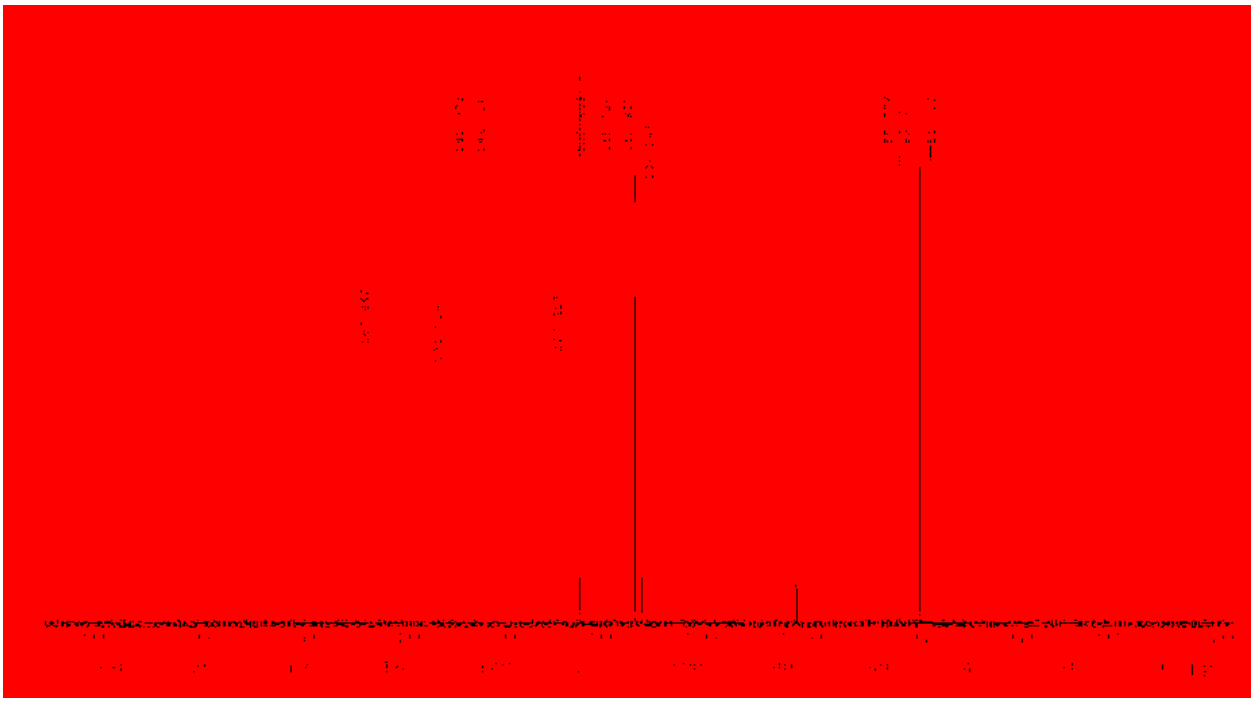
DPT NOESY H4

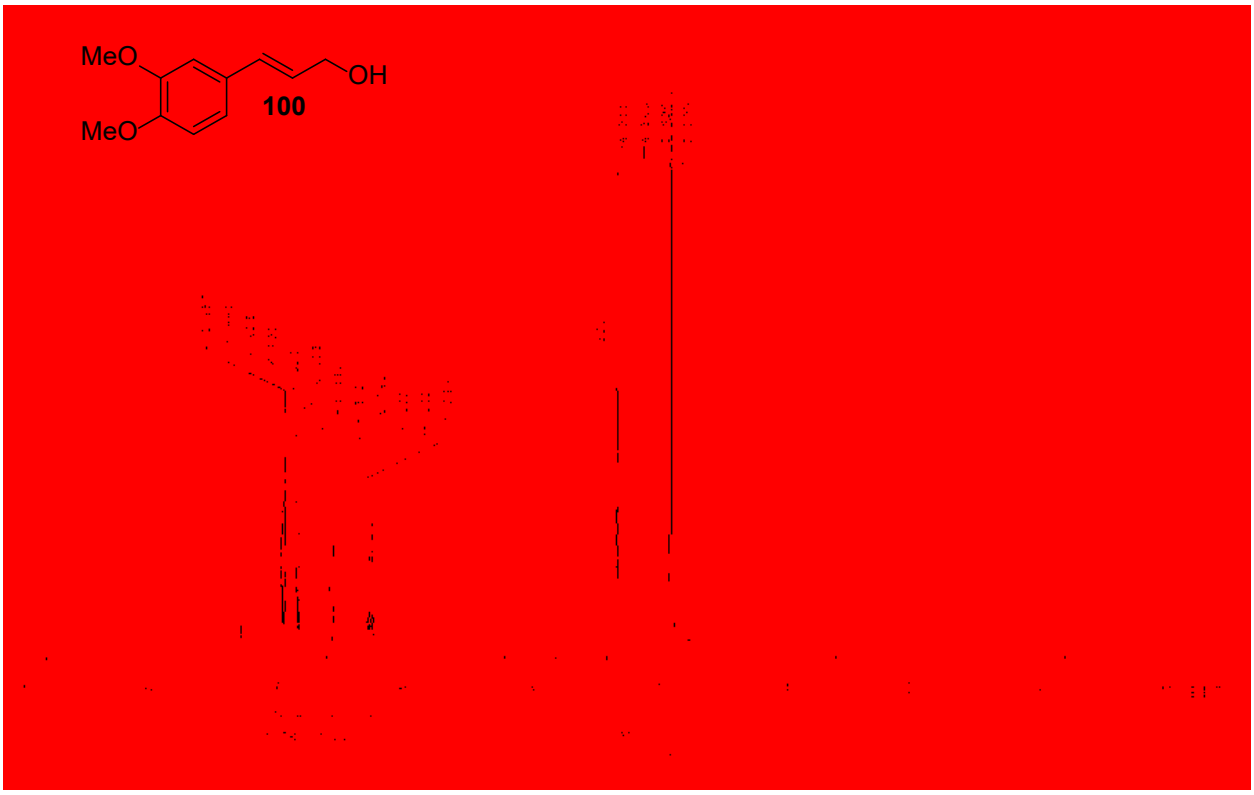




6.2. F4-4 Synthesis



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MeO
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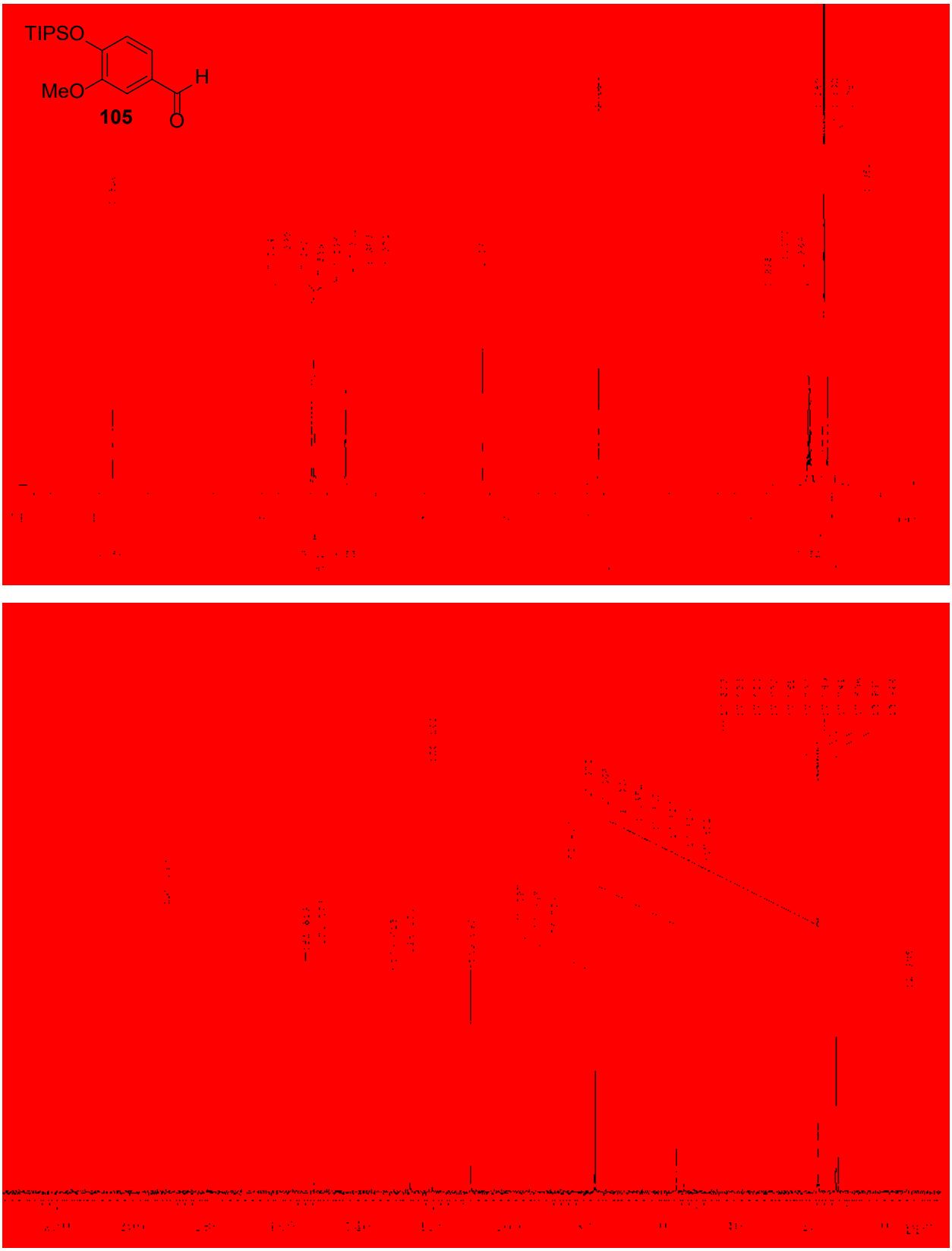
100


TIPSO
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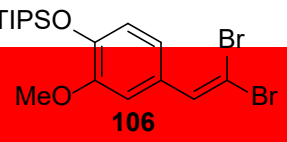
105



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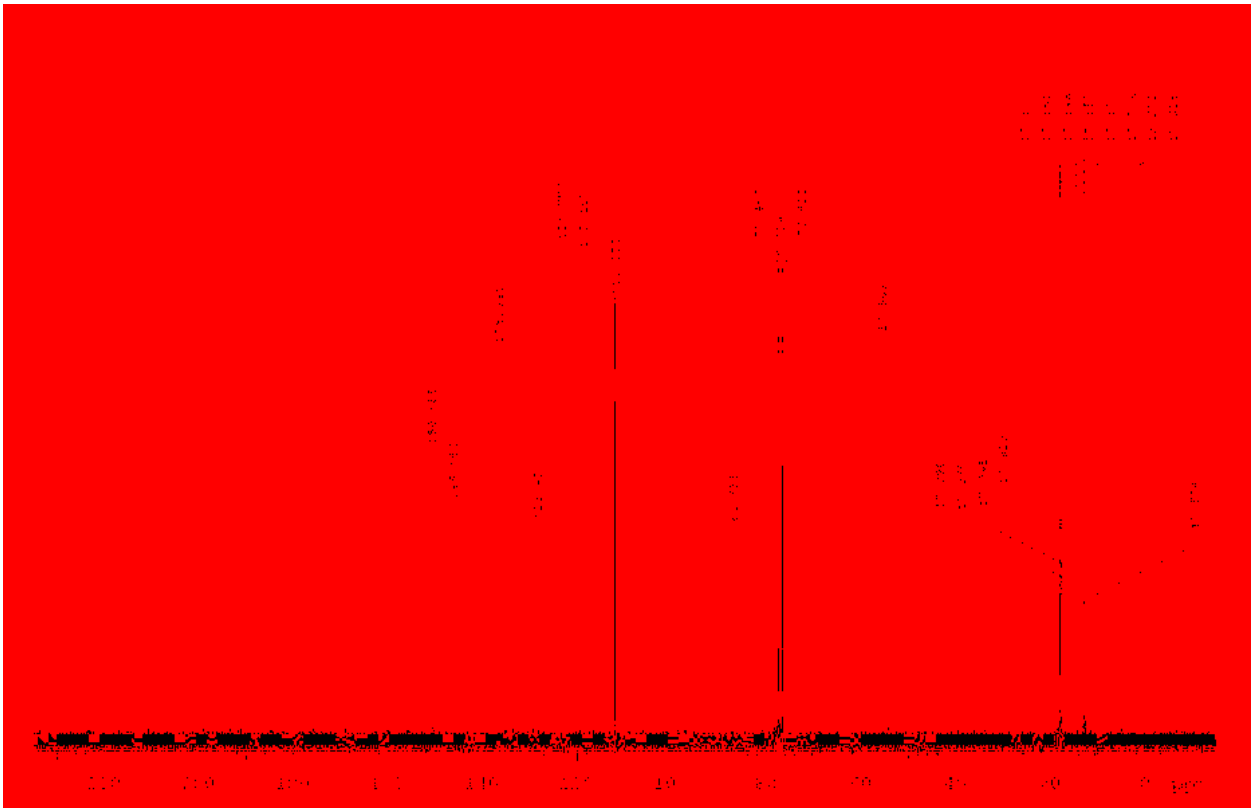

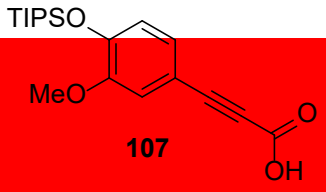

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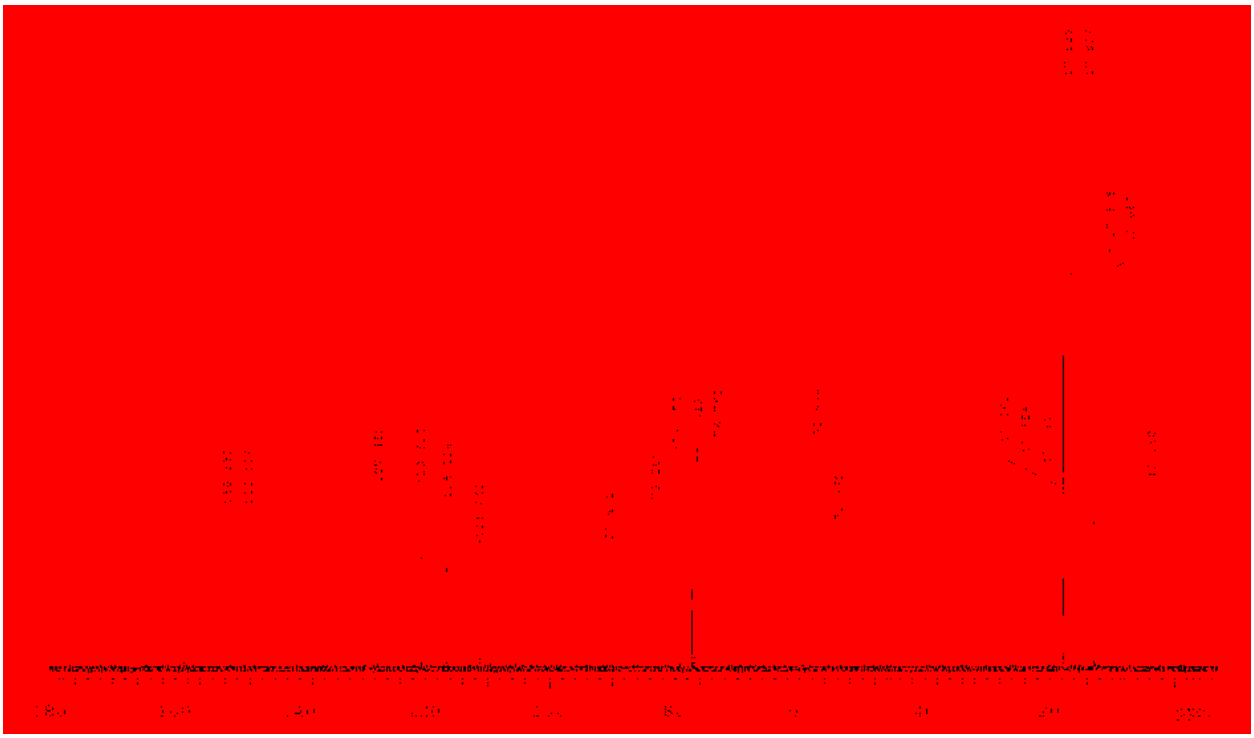

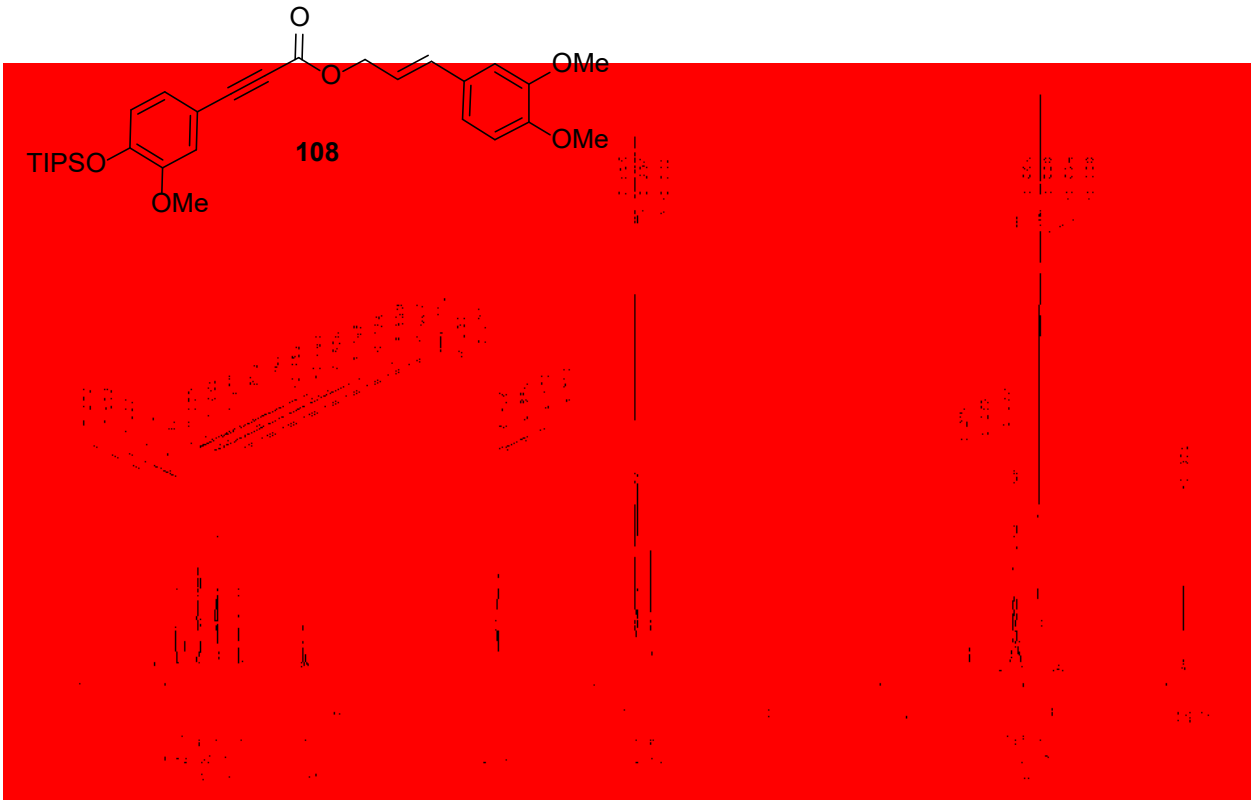
O
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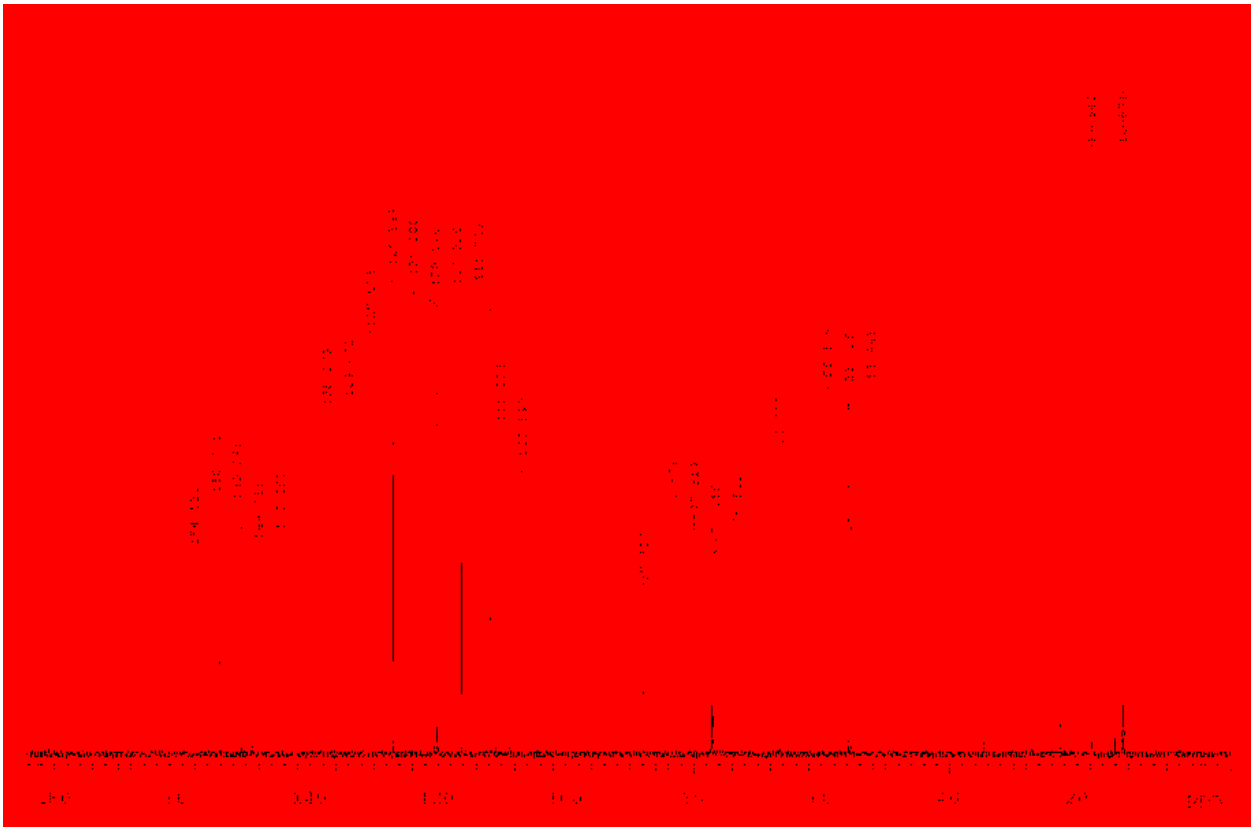

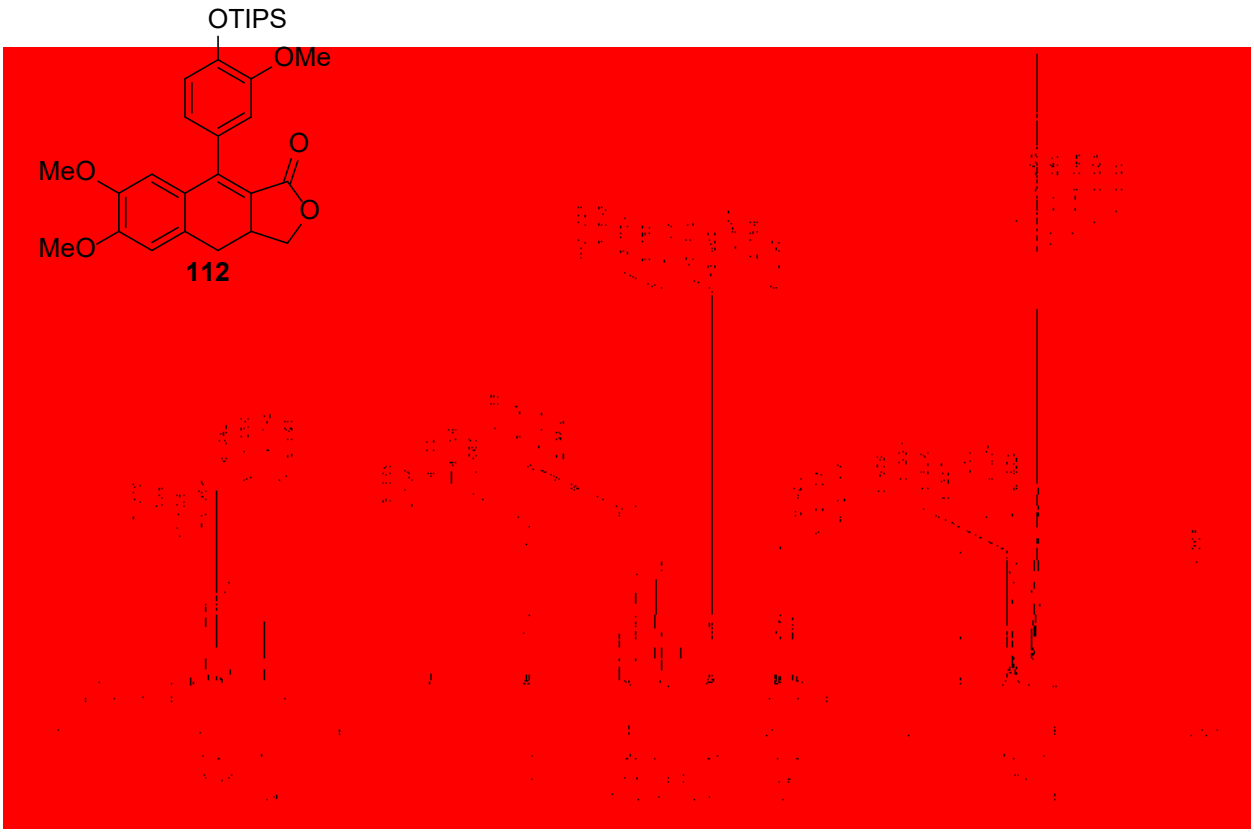

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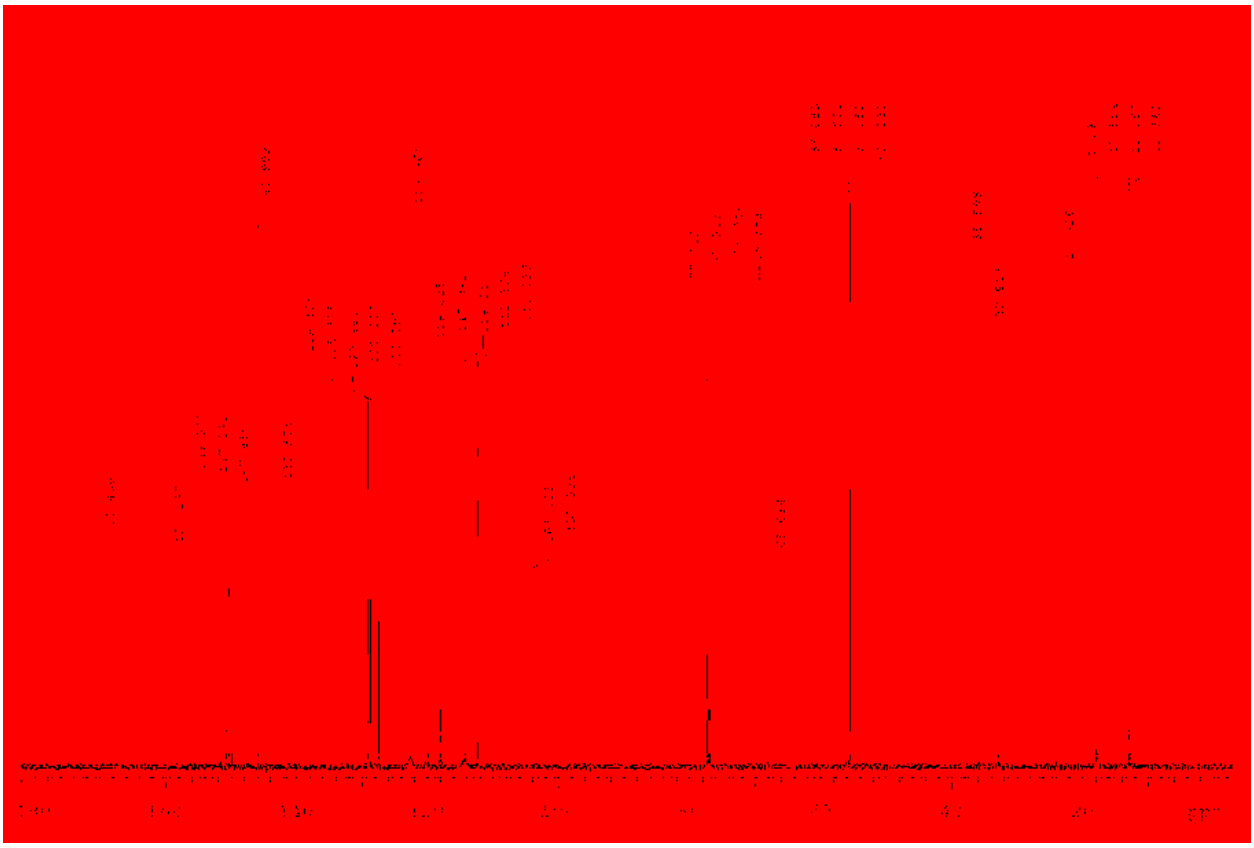

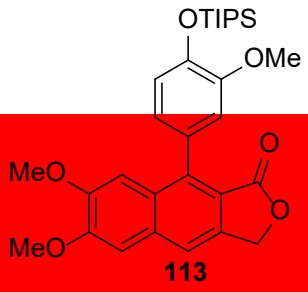

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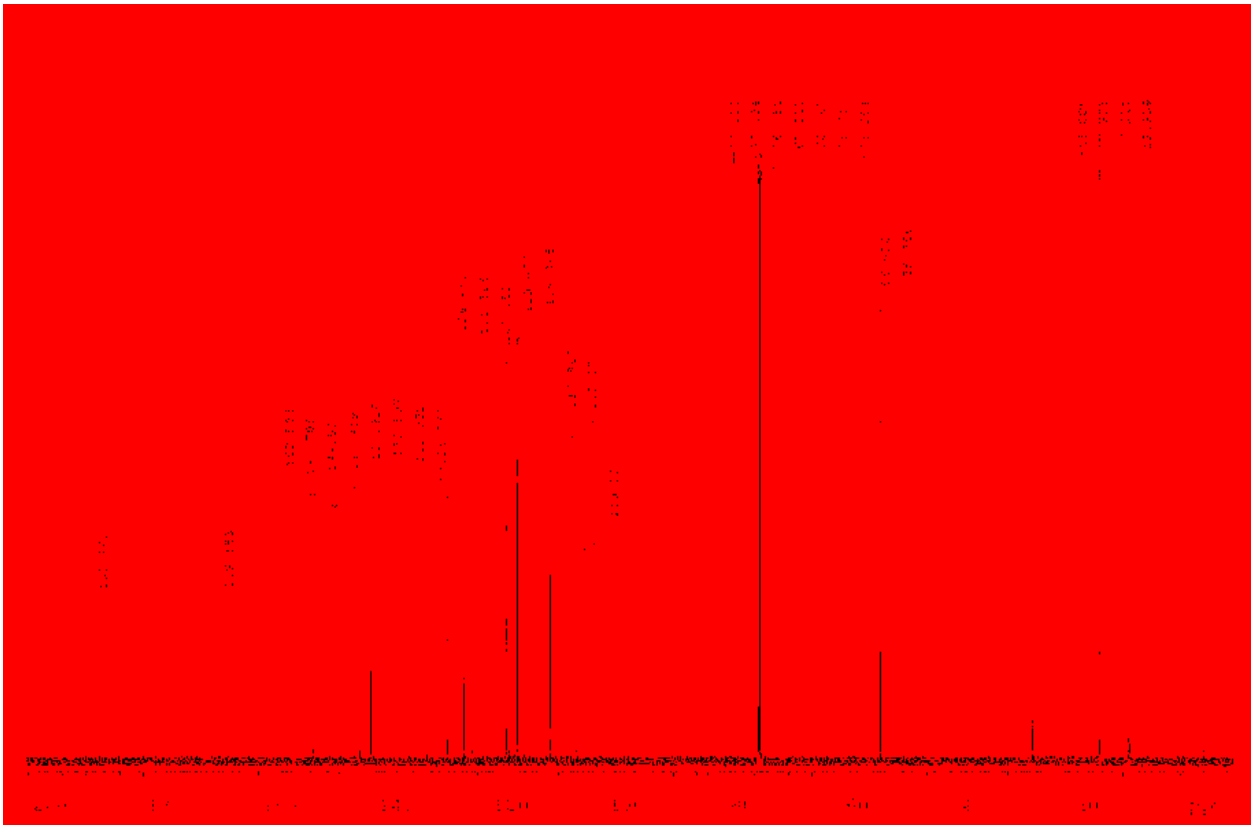

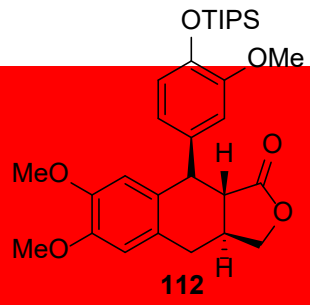

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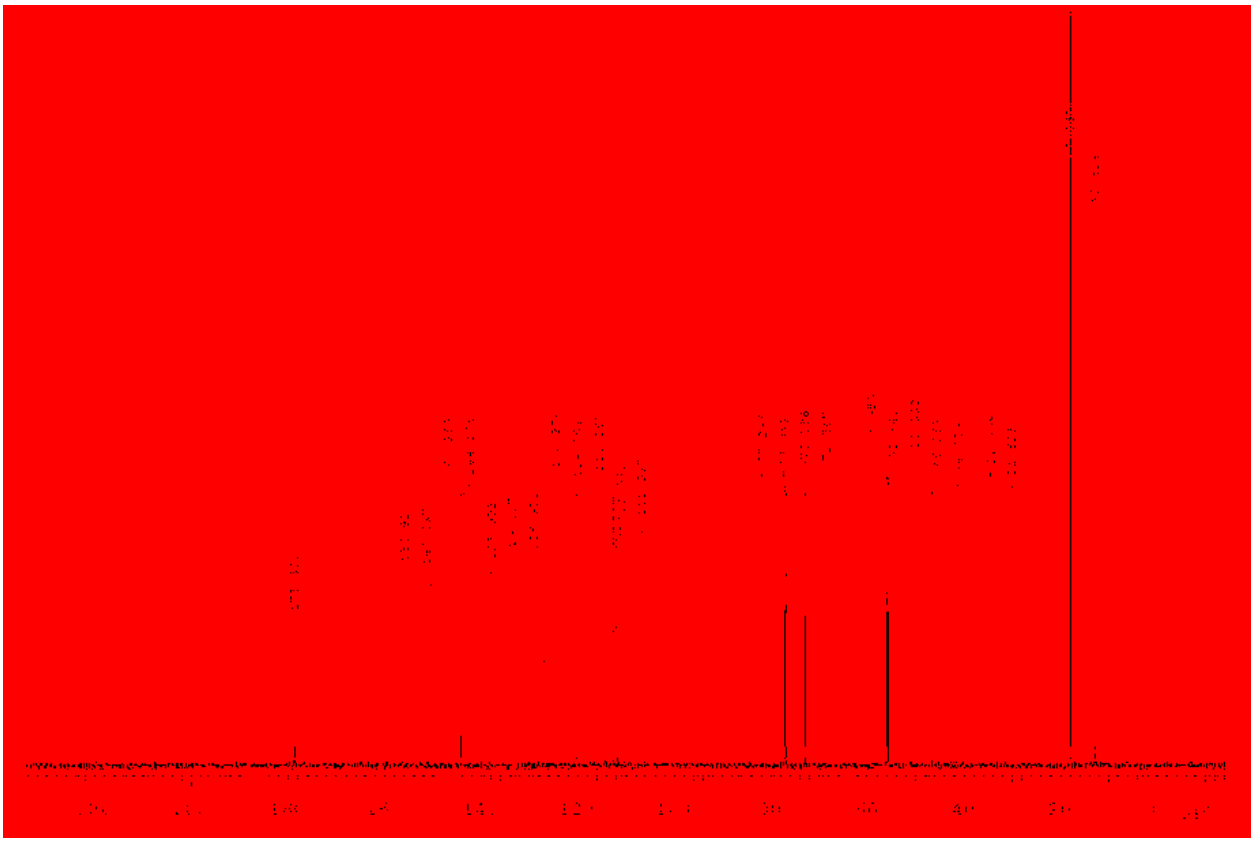

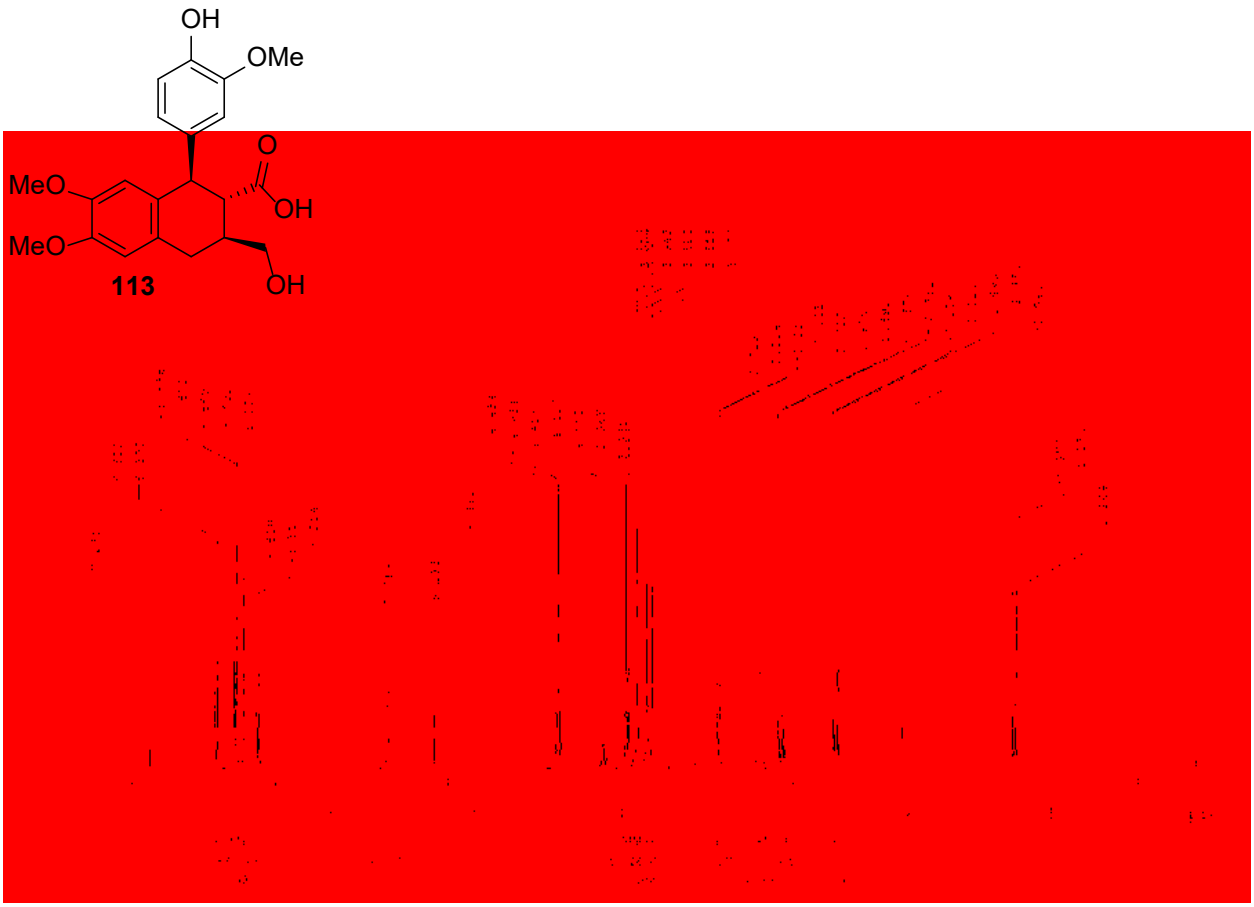

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