The Development of New Strategies for the Divergent Synthesis of the Neoclerodane Furanoditerpenoid Natural Product Family

By

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ABSTRACT

The neoclerodane furanoditerpenoid family of natural products is a compelling target for a divergent total synthesis due to the complexity around their spirolactone-containing decalin core, the similarities between their functional groups, and biological activities that indicate a potential for future medicinal application. While being a relatively small molecule, the most structurally complex compound of the family, teucrin A, contains six stereocenters, five of which are contiguous. Our divergent synthesis route involves the stereo-controlled formation of a common decalin intermediate in four concise steps and 32% overall yield from commercially available starting materials. Additionally, desmethyl montanin A – an analog of montanin A missing its methyl group – can be produced from this key intermediate in one step and 95% yield, for a total of 30% yield over five steps. The dual-key step of this route consists of a Lewis acid-catalyzed Diels-Alder cycloaddition which stereo-selectively forms the spirolactone, followed by a gold-catalysed *6-exo-dig* cyclization of the Diels-Alder adduct to complete the decalin core. The complementarity of these two steps is the focus of the synthesis, with the remaining steps for the formation of select neoclerodane natural products consisting of simpler classical chemistry, highlighting the potential for the creation of a large “unnatural” product library for applications such as drug candidate screening. Progress has additionally been made toward teucrin A, setting a cornerstone for future advancements to be made on this project. This concise synthesis advocates for the Barriault group’s Diels-Alder/gold cyclization method of forming complex structural cores and will be applied to the total syntheses of other natural products in the future.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac = Acyl

BP = Biphenyl

Bu = Butyl

Bz = Benzyl

Cy = Cyclohexane

CYP3A = Cytochrome P450, family 3, subfamily A

DA = Diels-Alder

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE = Dichloroethane

DCM = Dichloromethane

DIPEA = N,N-Diisopropylethylamine

DMAP = 4-Dimethylaminopyridine

DMF = Dimethyl formamide

DMP = Dess-Martin periodinane

DMPS = Dimethylphenyl silyl

DMS = Dimethyl sulfide

DNA = Deoxyribonucleic Acid

D.r. = Diastereomeric ratio

EDG = Electron-donating group

E.e. = Enantiomeric excess

Eq. = equivalents

EWG = Electron-withdrawing group

FDA = Federal Drug Administration

FTIR = Fourier-transform infrared

Fur = Furanyl

GGPP = Geranyl geranyl pyrophosphate

h = hour

HMDS = Hexamethyldisilazane, AKA Bis(trimethylsilyl)amine

HOMO = Highest occupied molecular orbital

HPLC = High performance liquid chromatography

HRMS = High resolution mass spectrometry

HWE = Horner-Wadsworth-Emmons

IBX = 2-Iodoxybenzoic acid

IR = Infrared

LA = Lewis acid

LDA = Lithium diisopropylamide

LUMO = Lowest occupied molecular orbital

MCPBA = *meta*-Chloroperoxybenzoic acid

min = minute

NBS = N-bromo succinimide

NOESY = Nuclear Overhauser enhancement spectroscopy

O.n. = overnight

PCC = Pyridinium chlorochromate

PDC = pyridinium dichromate

Ph = Phenyl

Pyr = Pyridine

R.t. = room temperature

TBS = *tert*-butyldimethylsilyl

TDI = total daily intake

TES = Triethyl silyl

Tf = Triflate

THF = Tetrahydrofuran

TIPS = Triisopropyl silyl

TLC = Thin-layer chromatography

TMS = Trimethyl silyl

Ts = Tosyl

FORWARD: The Pursuit of Knowledge

Since the dawn of humanity, the pursuit of knowledge has been at the root of the human experience. The mysteries of the universe have intrigued mankind since they began to exist, and it has been the goal of humans to seek after the truths and meaning of life, our creation, and our existence. From a divine perspective outside of time, all knowledge and truth already exist, and everything to be known will eventually be discovered. The pursuit of scientists is to discover information about reality and apply the knowledge of natural properties for our own advancements and purposes. The term "science" comes from the Latin word *scientia* which translates to "knowledge". According to Merriam-Webster, the essential meaning of science is "*knowledge about or study of the natural world based on facts learned through experiments and observation".*[1] The emphasis in this definition is that the facts already exist and are learned through investigation.

Science is organized and explained through the compartmentalization of scientific information and data into models which are always changing and being modified to re-adapt to new knowledge acquired over time. John von Neumann, a mathematician and computer scientist from the early 20th century clarified the definition of science as such: "*1. Sciences do not try to explain, they hardly even try to interpret, they mainly make models. 2. Science is a construct which […] describes observed phenomena from a reasonably wide area".*[2] According to Encyclopedia Britannica, a scientific model is described as follows: *1. A representation of a real phenomenon difficult to observe directly. 2. Used to*

explain and predict the behaviour of real objects or systems 3. At best are approximations — not exact replicas. 4. Scientists constantly are working to improve and refine models".[3] As we see, the knowledge already exists around us in the natural world and remains simply to be discovered. In the aim of avoiding self-idolization and proceeding with humility, scientific discoveries cannot become a source of pride, nor can we feign that us scientists hold the unchallengeable gospel truth. Rather, we must acknowledge that our *sciencia* comes not from us, and that our models are not perfect replicas.

George Washington Carver was an American agrochemist from the 19th century, professor at Tuskegee University, and inventor who developed techniques for prevention of soil depletion that resulted from repeated planting of cotton. His success surpassed the racial divides of the time, and he received several awards, honours, and praises for his work. His findings allowed for the vast economic possibilities of impoverished farmers to expand into the production of peanuts, pecans, soybeans, and other produce.[4] Notably, while many scientists began to view science and religion as incompatible, Carver boldly claimed that his faith in Jesus was the only mechanism by which he could effectively pursue and perform the art of science, and that science is the knowledge of the proof of God's existence. Specifically, he refused to consider himself a scientific genius, and never took credit for his discoveries. Instead, he considered himself a vessel for divine inspiration and revelation, as he is quoted saying: "*[I] ask the Great Creator […] to permit me to speak to Him through the three Kingdoms of the world which He has created: the animal, mineral and vegetable Kingdoms".*[5] He has also made

strong statements in which he considers God and science inseparable: *"I never have to grope for methods: the method is revealed at the moment I am inspired to create something new"*, *"I am not interested in science or anything else that leaves God out of it"*, and *"I love to think of nature as wireless telegraph stations through which God speaks to us every day, every hour, and every moment of our lives".*[6] This all received strong disagreement from the scientific community, with an editorial in the New York times stating that Carver's juxtaposition of science and divine influence showed a *"complete lack of the scientific spirit".*[7]

Building on this perspective, science is merely the existing knowledge that is yet to be discovered, and our pursuit of knowledge is merely to uncover the already-fleshed-out handiwork of God. As written in Proverbs 2:1-6 (KJV), the psalmist David writes: *"My son, if thou wilt receive my words, and hide my commandments with thee; So that thou incline thine ear unto wisdom, and apply thine heart to understanding; Yea, if thou criest after knowledge, and liftest up thy voice for understanding; If thou seekest her as silver, and searchest for her as for hid treasures; Then shalt thou understand the fear of the Lord, and find the knowledge of God. For the Lord giveth wisdom: out of his mouth cometh knowledge and understanding."*

In other words, if we receive instruction from the Lord, tune our ears to the wisdom of the Lord, and seek after the knowledge of God, then we will find and receive His knowledge. Whether it is acknowledged or not, true wisdom and knowledge comes from the Lord, and this is an important reminder for scientists in pursuit of worldly knowledge.

This perspective applies as well to the total synthesis of natural products. Natural products already exist in nature and are already produced by plants and other organisms to a degree that is far more efficient than humans will probably ever accomplish in a lab. We can study the biosynthetic mechanisms, but in the end our approaches to synthesis seek to mimic the natural processes, or to be at most comparable to them. In the same way, all the chemical reactions we employ in the lab are exploiting the pre-existing properties of atoms and chemical compounds that we have discovered and now apply for our own uses. Every chemical law, process, and reactivity has already existed as an inherent attribute of every atom, and whether we can see their applications in nature or not, we simply discover their uses. For example, acetate protections we perform in the lab are copied directly from natural processes, while the inherent affinity of gold catalysts to alkynes is a property that has no known application in nature but can be exploited for synthetic uses. The question is: where did these properties come from, and why do they exist? Where we see a tailored use of chemical property in nature, and especially when we cannot see a use for the chemical property in nature, these properties come from God who wrote all the laws of nature upon the universe's Genesis. God knows everything before we do, has written it all out before time began, and it is up to us to receive divine knowledge through prayer and supplication. As stated in Isaiah 42:9: *"Behold, the former things have come to pass, and new things I now declare; before they spring forth I tell you of them,"* and Jeremiah 29:13: *"And ye shall seek me, and find me, when ye shall search for me with all your heart."*

As I moved forward completing my master's thesis, completed as much of the divergent synthesis as possible, and continue with my career, wherever I am led, I am simply mimicking the completed work of the Lord my God in my own workshop. In this way, everything I do glorifies Him, and everything I do is to glorify Him. This thesis is dedicated to my Lord and Saviour Jesus Christ, God the Son who dwelt among us in the flesh, to His atoning substitutionary sacrifice which saved me from eternal hell, to His mercy which permits me to be even sitting here alive to type these words, and His peace beyond understanding which gives me rest as I confront challenges, adversities, and lapses of weakness. As He spoke in Matthew 11:28: *"Come unto me, all ye that labour and are heavy laden, and I will give you rest."*

I pray that the Lord will speak through the words that I type here, and that the light of the Holy Spirit will shine through the work I performed in putting together this dissertation. Jesus states in Matthew 5:14-16: *"You are the light of the world. A city that is set on a hill cannot be hidden. Nor do they light a lamp and put it under a basket, but on a lampstand, and it gives light to all who are in the house. Let your light so shine before men, that they may see your good works and glorify your Father in heaven."* When readers will see the joy that it is in me in my conduct, actions, and work, I pray they will see where the joy in me is coming from, and that my declaration of such will answer to it. Finally, in Colossians 3:17: *"And whatever you do in word or deed, do all in the name of the Lord Jesus, giving thanks to God the Father through Him."* May God bless you as you read my thesis, and bless you as you go out, may you rest in Christ Jesus. Amen.

[1] Science definition & meaning. Merriam-Webster, https://www.merriam-webster.com/dictionary/science (accessed April 20, 2022).

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[7] Gilmore J. Man of science--and of God: George Washington Carver believed that providence guided his scientific investigations and that those investigations led to a better understanding of god and his handiwork. https://www.thefreelibrary.com/Man of science--and of God: George Washington Carver believed that...-a0112794990 (accessed April 20, 2022).

1. INTRODUCTION

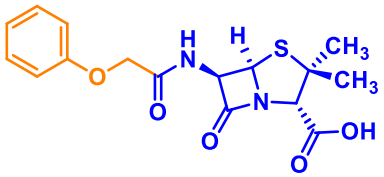
1.1 Natural products

There are many naturally occurring complex chemical compounds that plants and other organisms produce to fulfill certain biological roles – for example, to fight off bacteria – that have been discovered upon organism harvest and substance extraction. Many of these natural products have unknown biological roles and properties, and thus have yet to be applied in western medical settings. Throughout history, many biological extracts have been used as natural medicines, and while these naturopathic medicines may, in some cases, be labelled as pseudoscience, many natural extracts in fact contain biologically active natural products that have medicinal properties that do precisely as advertised. One example of this is the *Ginkgo biloba* extract that contains ginkgolides which are shown to have anti-platelet-activating, anti-apoptotic, anti-oxidative, neurotrophic, and neuro-immunomodulatory effects.[8]

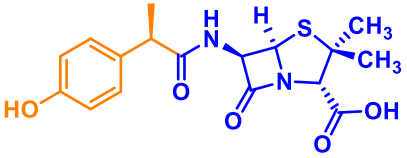
Natural products are of interest in many fields of science, namely for the pharmaceutical industry, in which many medicines are designed and developed by the inspiration of natural products whose biological roles serve as pharmaceuticals with medicinal properties. The role of synthetic and medicinal chemists in the pharmaceutical industry is to study the structure-activity relationship of natural products and modify their structures to make them more effective medicines.

Several examples of semi-synthetic pharmaceuticals can be listed. For instance, penicillin V is an antibiotic extracted from the fungus *P. chrysogenum,*[9] but

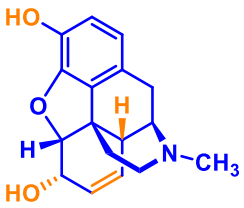
the most prescribed antibiotic is amoxicillin, a semi-synthetic derivative of penicillin V, and is the 23rd most prescribed medication, and the 1st most prescribed anti-biotic.[10] In **Scheme 1.1.i**, the fragments in blue are identical between penicillin V and Amoxicillin, while the structures in orange are modified between the two. Through structure-activity analysis, the portions in blue have been determined as essential for drug function, and the segments in orange have been modified for improvements to drug function, The same can be seen in the case of morphine, which is extracted from poppy, *P. somniferum,*[11] while the most prescribed opioid and the 49th most prescribed medication is the semi-synthetic derivative oxycodone.[10]



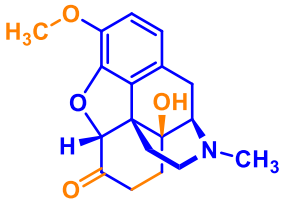
Penicillin V
(extracted from Fungus,
***P. chrysogenum*)**



Amoxicillin
(17th most prescribed medication,
1st most prescribed anti-biotic)



Morphine
(extracted from Poppy,
***P. somniferum*)**



Oxycodone
(48th most prescribed medication,
1st most prescribed opioid)

Scheme 1.1.i: Penicillin and morphine natural products, compared with semi-synthetic analogues and common pharmaceuticals amoxicillin and oxycodone. Identical structures are indicated in blue while differences in structure are indicated in orange.

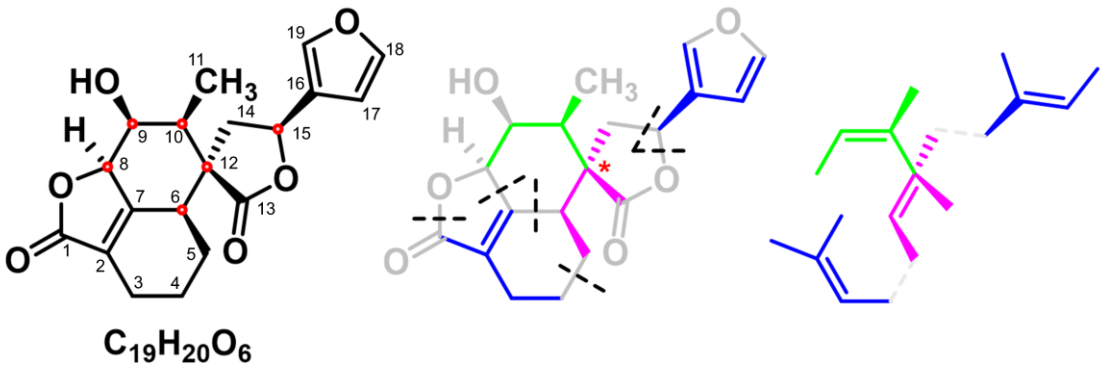
1.2 Total synthesis

Total synthesis is defined as the complete chemical synthesis of a complex molecule from simple commercially available precursors.[12] For very large compounds, total synthesis pathways may be much longer, more expensive, and smaller yielding than natural product extractions from the biological source. However, by developing total synthesis pathways, not only do synthetic chemists prove that synthetic pathways conducted in laboratories can match and contest with biosynthetic pathways, but in the process, the advances in synthetic chemistry necessary for these routes to be possible will add to the breadth of chemistry knowledge that will be essential for applications in the future, including for future total syntheses, and for the pharmaceutical and other chemical industries.

Within the fields of pharmaceutical science, synthetic organic chemistry, and chemical biology, efficient strategies to build collections of natural product-like frameworks with complexity and structural diversity from simple starting materials is heavily sought after, and it is the work of synthetic chemists working in total synthesis that elucidate these methods. While synthetic routes may never replace natural extractions when it comes to, for example, the mass-production of pharmaceuticals, all progress made in synthesizing never-before-made natural products, shortening synthesis routes, and improving yields all contribute to the advancement of organic chemistry. As such, the goal of total synthesis is not simply to replace existing natural product extraction methods, but to contribute to an ever-growing field of chemical synthesis in a variety of ways.

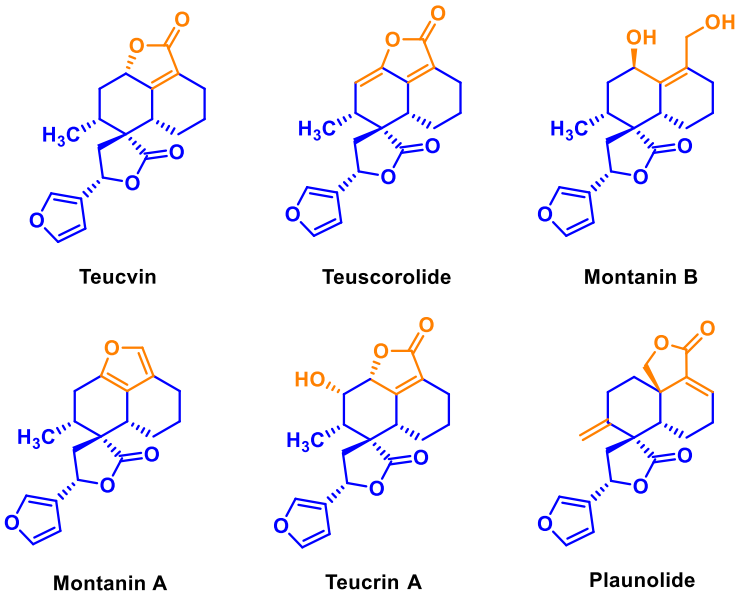
1.3 The neoclerodane furanoditerpenoid family

Clerodane diterpenoids are a large group of terpenes isolated from hundreds of plants, fungi, bacteria, and marine sponges, sharing their 20-carbon decalin core.[13] Within the categorization of clerodanes are specifications with respect to the relative stereochemistry of each molecule in the family. The *neo*-clerodanes have the same absolute stereochemistry of clerodin, the first clerodane discovered, while *ent-neo*-clerodanes are enantiomeric to clerodin.[14] More specifically, the furanoditerpenoid subfamily is contained within the broader classification of neoclerodane diterpenoids and consists of a vast number of compounds that contain a furanyl functionality and are found in germander plants for the most part within the *Teucrium* genus.[15] Their biosynthesis pathway has yet to be elucidated, but it is evident they come from the 20-carbon biosynthetic source of geranyl geranyl pyrophosphate (GGPP), derived from four C5 isoprene units joined head-to-tail. While certain molecules in the family have 20 carbons, most seem to have had a decarboxylation occur at some point in their biosynthesis due to their carbon count being 19 (**Scheme 1.3.i**).



Scheme 1.3.i: Proposed isoprene positioning for unelucidated teucrin A biosynthesis.

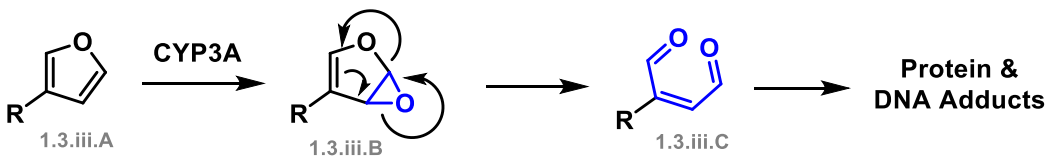
These neoclerodane furanoditerpenoids are a compelling target for a divergent total synthesis due to the complexity around their decalin core, including a common spiro γ-lactone containing a furanyl functionality, and the similarities between their functional groups, set apart mainly by the oxygenated functionalities localized on the opposite end of the decalin core to the spirolactone, identified in orange in **Scheme 1.3.ii**. As such, reaching a common intermediate through a concise synthesis that could diverge into the different members of the family on unique pathways is a feasible task. While being a relatively small molecule, the most structurally complex compound of the family, teucrin A, contains six stereocenters, five of which are contiguous. Of selected molecules, plaunolide is an exceptional example which contains a diterpene core. Its lactone is attached at a different decalin carbon and contains an *exo*-methylene rather than a methyl group, but apart from this, the main framework core is identical.



Scheme 1.3.ii: Non-exhaustive list of neoclerodane furanoditerpenoid natural product family. Structural similarities are indicated in blue, while differences are indicated in orange.

Various biological activities of these molecules indicate a potential for future medicinal application, including antifungal, antimicrobial, antitumoral, and antifeedant properties.[16] As a few examples, teucrin A – elucidated in 1973 by Popa and Reinbold and extracted from *Teucrium chamaedrys* – is an FDA-approved bitter flavoring agent used in the liquor industry and has antiseptic, anticholeretic, and ultimately hepatotoxic properties with an estimated tolerable daily intake (TDI) of 0.12 mg.[17] Plaunolide – extracted from *Croton stellatopilosus* – has anti-inflammatory properties and has potential for the treatment of ulcers.[18] Teuscorolide is isolated from the aerial part of *Teucrium scorodonia* plant, otherwise known as wood sage, whose extract has been used in herbal medicine for the treatment of skin and blood diseases, as well as fevers and colds.[19]

To explain the hepatoxicity of the neoclerodane furanoditerpenoids, the furan ring of the neoclerodane furanoditerpenoids is metabolized by CYP3A, as depicted in **Scheme 1.3.iii**. This forms an epoxide that induces a ring opening and affords a highly reactive conjugated α,β-unsaturated dial that leads to the formation of protein and DNA adducts.[20] While the hepatotoxicity has only been determined for teucrin A due to its FDA-approval process, it can be extrapolated that the other molecules of the family will also interact in this way with CYP3A due to the common furanyl moiety and will also have hepatotoxic properties if investigated.

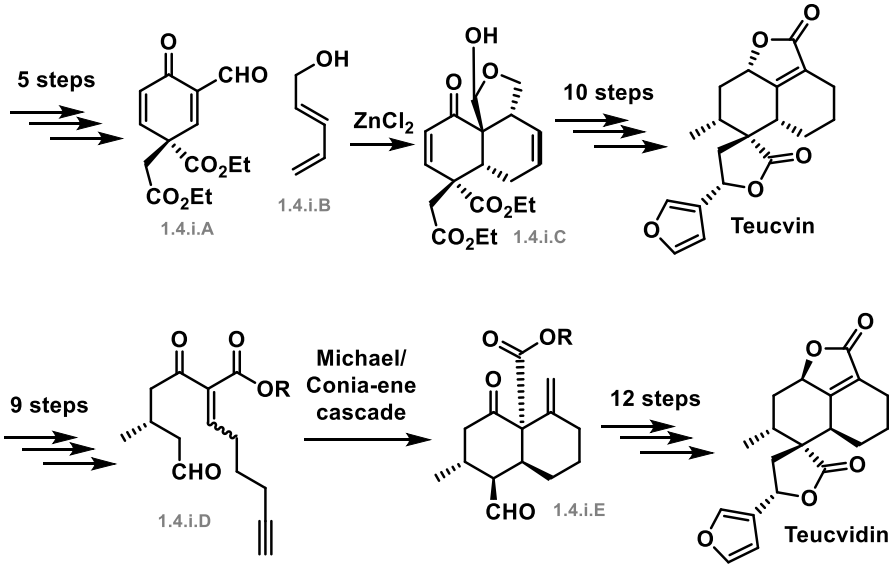


Scheme 1.3.iii: Metabolization of teucrin A by CYP3A, leading to hepatotoxic effects.

Montanin A contains a second furanyl moiety imbedded on the decalin core. It is isolated from the aerial portion of *Teucrium montanum* plant, and along with most of the other members of the neoclerodane furanoditerpenoid compounds, montanin A has undetermined biological activities and medicinal applications. Importantly, in its structural simplicity and distinguished semi-syntheses accomplished from montanin A to other members of the family in short oxidation sequences – namely teuscorolide and teucvin (see **Scheme 1.4.iii**) – is likely the biosynthetic precursor to other members of the family.[21]

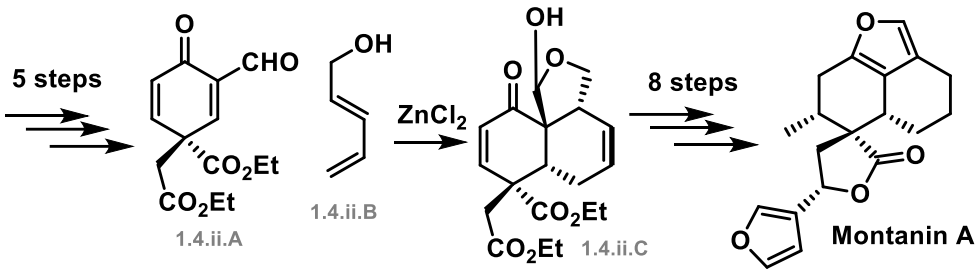
1.4 Literature precedent for neoclerodane synthesis

There are a few examples of neoclerodane furanoditerpenoid syntheses in the literature, including a 16-step synthesis of (±)-teucvin that was developed by the Liu group in 2003,[22] and a 22-step synthesis of (-)-teucvidin – a diastereomer to teucvin – that was published by the Lee group in 2012 (**Scheme 1.4.i**).[23]



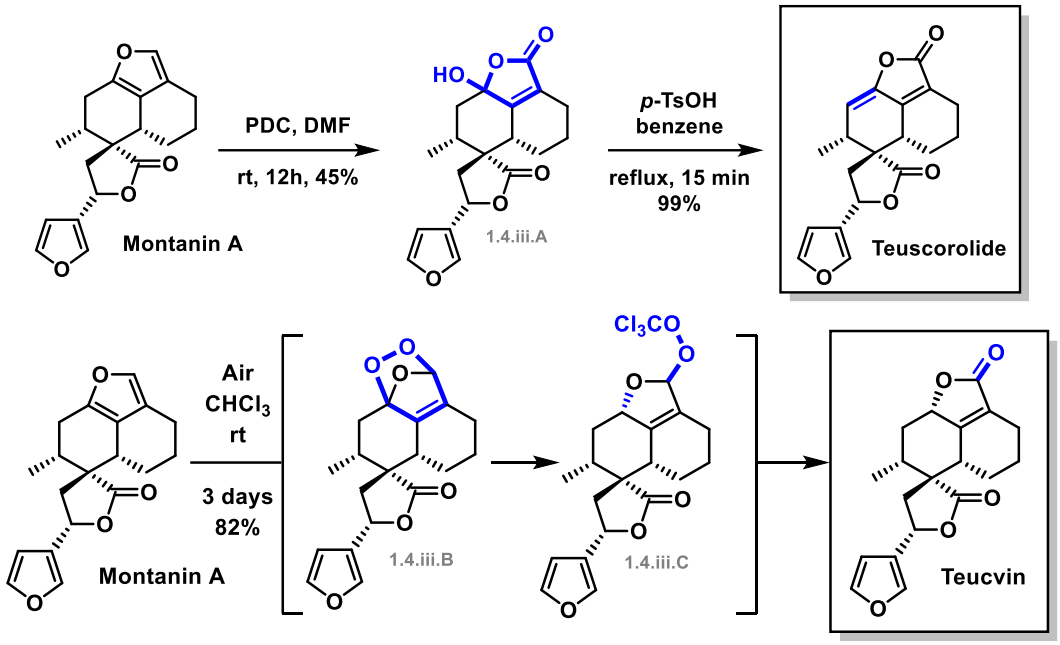
Scheme 1.4.i: Summary of teucvin synthesis by Liu and teucvidin synthesis by Lee.

Our ultimate interests in approach for the synthesis differs greatly from these featured syntheses. The following are two examples of relevant approaches. In 2008, the Liu group further published a 14-step synthesis of (±)-montanin (**Scheme 1.4.ii**), employing an advanced precursor **1.4.ii.C** prepared through a zinc-catalyzed Diels-Alder reaction.[24]



Scheme 1.4.ii: Summary of the total synthesis of (±)-montanin A by the Liu group.

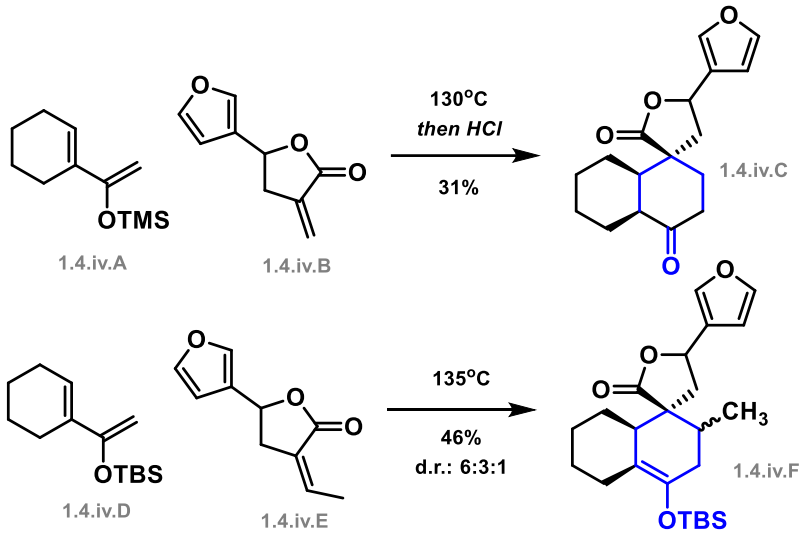
After a cursory inspection, one can argue that this synthesis is quite long and inefficient. The synthetic route already relies on a dienophile that takes five steps to make, from which nine steps are required to reach (±)-montanin A. However, one should note that they reported (±)-montanin A is converted to (±)-teuscorolide in two steps, via the oxidation of the fused-furan ring with PDC followed by the elimination of water in acidic conditions. In 2014, the same group reported a one-step transformation to (±)-teucvin from montanin A under open air conditions in $CHCl_3$ (**Scheme 1.4.iii**).[25] It becomes quite compelling that montanin A is a biosynthetic precursor to other molecules of the neoclerodane furanoditerpenoid family, as simple oxidation conditions lead to other natural products, some conditions of which have yet to be discovered: for example, montanin A to teucrin A in a short sequence.



Scheme 1.4.iii: Montanin A conversion to teuscorolide and teucvin.

In 2011, Ley *et al.* attempted to form the neoclerodane framework in the pursuit of a synthesis toward members of the natural product family.[26] Through retrosynthetic analysis, the group identified that the spirolactone in the decalin core could be a component of an electron-withdrawing dienophile for a feasible Diels-Alder approach. In aiming to form the *endo* adduct of the cycloaddition with a cyclohexadiene and the spirolactone dienophile with and without a methyl installed on the alkene, the stereochemistry of the decalin core could be set, affording a high degree of complexity in one step. As the *endo* product is sought after, the use of Lewis acids at low temperatures would likely be necessary to favor the *endo* product, unless an inherent *endo* selectivity of the reaction exists. As seen in **Scheme 1.4.iv**, although the dienophile is stable in acidic conditions, all cycloaddition attempts with Lewis acids were unsuccessful, and attempts were

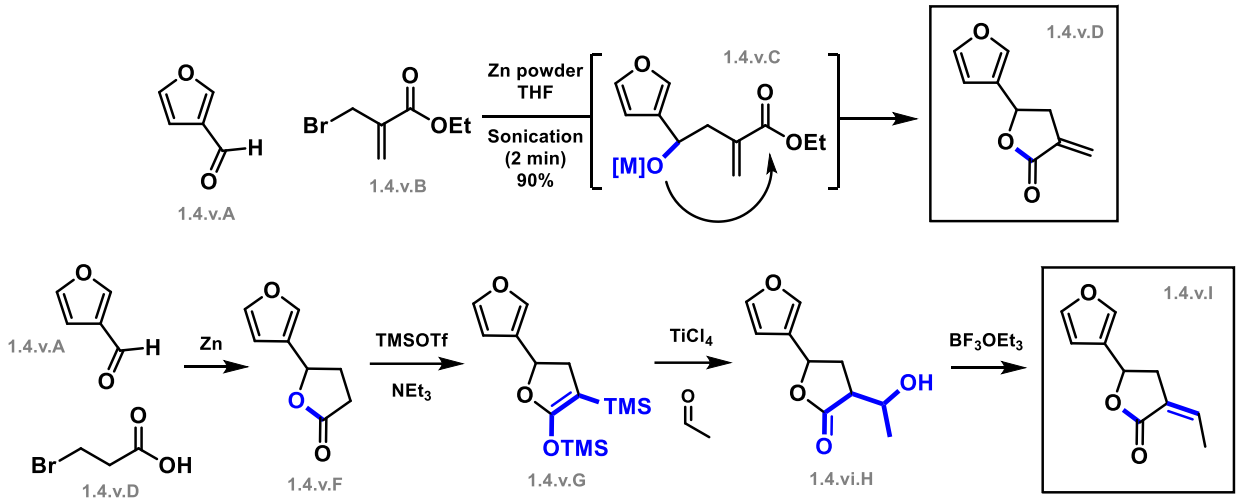
unsuccessful to increase yields and sufficiently for a viable total synthesis route. When a thermal Diels-Alder was performed at 130°C, a 31% yield was obtained with the disubstituted dienophile **1.4.iv.B**. When performing the cycloaddition with a dienophile containing the methyl group **1.4.iv.E**, the cycloadduct **1.4.iv.F** was generated in 46% yield as an inseparable mixture of diastereomers (6:3:1). The authors claim that the methyl group on the dienophile hindered the *endo* approach due to steric interactions at the transition state. As a result, the *exo* pathway becomes more competitive, leading to the formation of the undesired diastereomer.



Scheme 1.4.iv: Summary of Diels-Alder experimentation performed by the Ley group.

Given these results, Ley and co-workers concluded that the poor yields and lack of stereocontrol make this synthetic approach not viable for the total synthesis of Teucrin A or any molecule of the neoclerodane family. However, some valuable information can be pulled from this study.

Firstly, using their methods, the furanyl-containing dienophile can be synthesized in one step and the dienophile containing the methyl and 4 steps, (**Scheme 1.4.v**), but secondly, this work offers an indication that a viable synthesis of the neoclerodane core could use a 1,1-disubstituted dienophile such as **1.4.v.D** over **1.4.v.I**, but with the caveat of installing the methyl later in the synthesis. Finally, it seems that creating a highly substituted diene, in this case a multi-substituted cyclohexene, leads to an overly sterically encumbered transition state that does not result in a viable cycloaddition. As such, a simpler diene will be necessary.



Scheme 1.4.v: Synthesis of to dienophile candidates for the Diels-Alder reaction by Liu.

Another point of information that can be gathered from the work of the Liu group is that in contrast to the Ley group, who installed the furanyl group before the decalin formation, the group uses an oxidative cyclization–retro-cyclization process to install the furanyl moiety at the end of the synthesis. Depending on how difficult operations will be and how harsh conditions are in the end-game transformations of late-stage intermediates because of the furanyl reactivity, this approach may prove

to be useful. On the other hand, as the furanyl moiety remains stable in these oxidation conditions while the fused-furanyl reacts, this may not be a concern.

1.5 Overview of dual-key step reactions

To introduce the reactions involved in the dual-key step of this thesis's synthesis route, the following is a brief background into the Diels-Alder cycloaddition and gold(I)-catalyzed carbocyclizations.

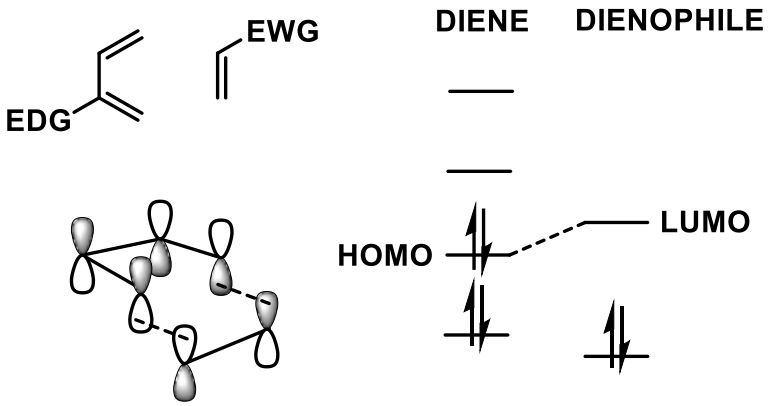
1.5.1 Overview of dual-key step reactions – Diels-Alder

The Diels-Alder is a thermally allowed concerted [4+2] cycloaddition between a conjugated diene and a substituted alkene forming a substituted cyclohexene adduct. The 1950 Nobel prize in chemistry was awarded to Otto Diels and Kurt Alder for this reaction that was first described in 1928.[27] Through its concerted mechanism, the Diels-Alder reaction allows for the regio- and stereo-controlled formation of two new carbon-carbon bonds. In the beginning, Diels-Alder reactions were conducted thermally, and more recently, Lewis acid catalysts have been used, allowing for cycloadditions at lower temperatures.

To this day, several applications of the Diels-Alder reaction have been reported in the literature, in industrial contexts, and remains the textbook example of pericyclic reactions. The first demonstration of the Diels-Alder cycloaddition in total synthesis was the Woodward synthesis of cholesterol in 1952, in which a hydroquinone was reacted with butadiene to yield the cis-bicyclene thermally.[28] From then, applications have been improved, using more selectively reactive starting

materials with respect to the electronics of the diene and dienophile and their molecular orbital energies.

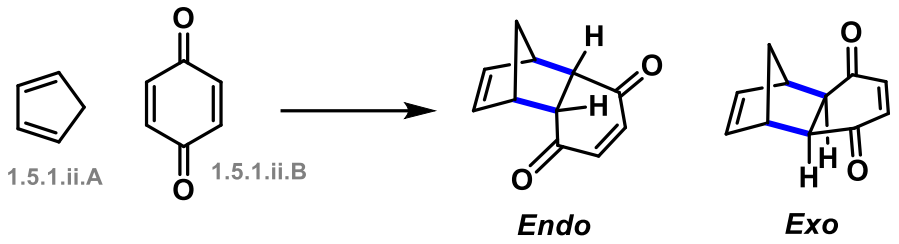
For a normal electron demand Diels-Alder (**Scheme 1.5.1.i**), an electron donating group – for instance, a silyl enol ether – on the diene which is rendered electron-rich, leads its π highest occupied molecular orbital (HOMO) to be nearer in energy to the π* lowest unoccupied molecular orbital (LUMO) of the dienophile, which is rendered electron-deficient by the presence of an electron-withdrawing group – for instance, an ester carbonyl. This is the more common type of Diels-Alder reaction and will be used for this project.



Scheme 1.5.1.i: Diagram for a basic Diels-Alder [4+2] cycloaddition, HOMO and LUMO interaction, where the energy gap is narrowed by EDGs and EWGs.

In terms of the Diels-Alder reaction outcome, two products are possible: the *endo* product and the *exo* product (**Scheme 1.5.1.ii**). The term *endo* indicates the diene is pointing in toward the alkene of the cyclohexene, while the term *exo* indicates the dienophile points away from the alkene of the cyclohexene. The *endo* adduct is generally the kinetic product in which favourable secondary orbital

interaction between the π-orbitals of the electron withdrawing group and the diene lowers the energy of the transition state, whereas the *exo* adduct is, in general, the thermodynamic product.



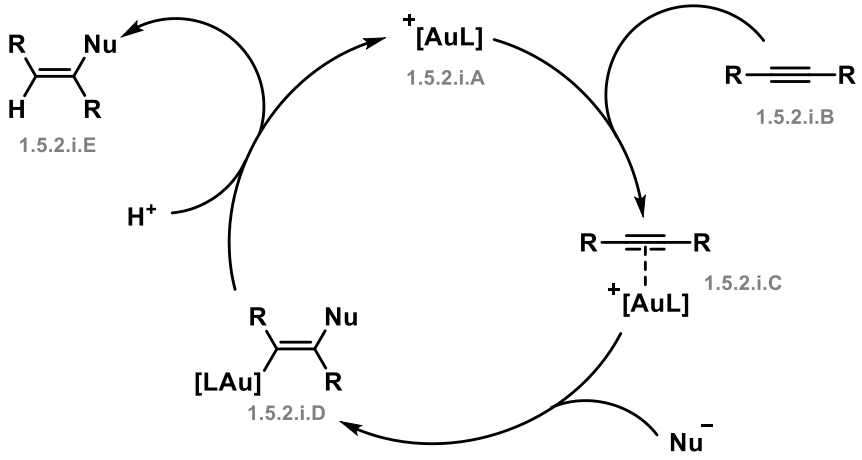
Scheme 1.5.1.ii: *Endo* and *exo* products of the Diels-Alder cycloaddition.

1.5.2 Overview of dual-key step reactions – Gold-catalyzed carbocyclization

Gold, while quite rare in its usage in organic chemistry, is a very useful transition metal in several chemical transformations due to inherent properties of the metal. It has been shown that gold catalysts are specific and more reactive than most other soft Lewis acid metals like mercury, copper, platinum, and palladium.[29] This is due to the greater Lewis acidity and backdonation ability of gold as compared to other metals of the same group as explained by the relativistic effect.[30] In summary, gold's electrons have an increased velocity to compensate for the larger nucleus –compared to the other soft Lewis acid metals – that exerts a strong electrostatic attraction, leading them to be closer to the nucleus, and resulting in a greater ionization energy. This leads to the contraction of the s and p orbitals of the gold atom, further shielding the 4f and 5d orbitals from the nucleus, which results in their expansion due to lesser nuclear attraction. The decreased size of the 6s orbital contributes to a low-lying LUMO which allows for greater Lewis acidity, and larger 5d

orbital increases the energy of the HOMO allowing the gold to stabilize positive charges though backdonation.

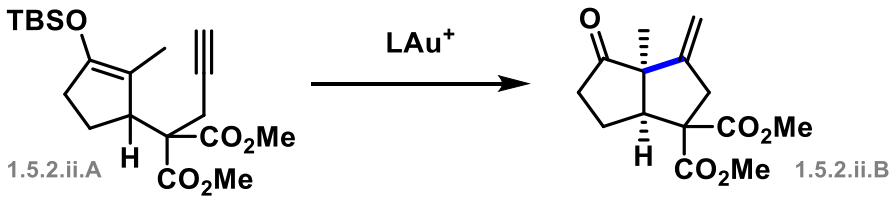
Carbon-carbon multiple bonds, namely alkynes and allenes, readily coordinate to gold(I) complexes, efficiently activating them for attack by a nucleophile. The cationic gold catalyst withdraws electron density from the π-rich multiple bond system, lowering its LUMO to decrease the energy gap between the HOMO of a nucleophile of choice. Upon addition of the nucleophile to the multiple bond system, the cationic gold catalyst is neutralized, and upon protodeauration – defined as the removal of gold from an organogold compound by a proton – the gold returns to its cationic state, producing the adduct and reforming the gold catalyst (**Scheme 1.5.2.i**).



Scheme 1.5.2.i: A cationic gold catalytic cycle.

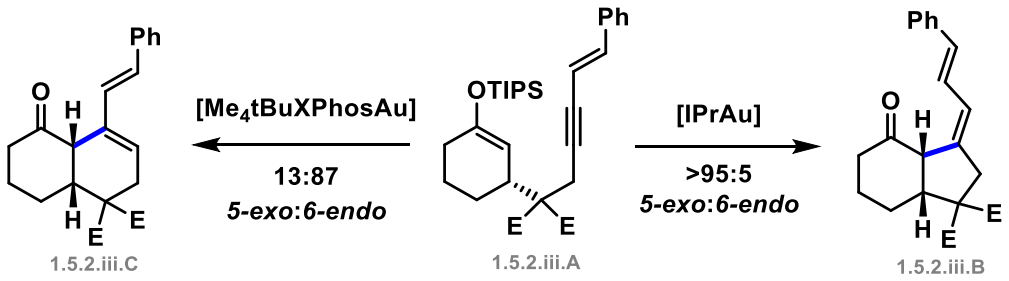
Gold(I) complexes have been used in a variety of synthetic applications in total syntheses and natural product core formation, as there are several examples in the literature of formation of complex carbocycles with quaternary stereocenters. Of

most relevance to the research conducted in the Barriault lab, methods of intramolecular additions of silyl enol ethers catalyzed by gold(I) onto alkynes are applied for the regio- and stereo-controlled formation of fused carbocycles, as seen in the work of the Toste group (**Scheme 1.5.2.ii**).[31] Since silyl enol ethers are readily accessed from ketones, this method is very reliable for the synthesis of carbocyclic frameworks.



Scheme 1.5.2.ii: Silyl enol ethers for intramolecular carbocyclizations by the Toste group.

These gold-catalyzed alkyne additions can lead to nucleophilic attacks on either of the carbons of the alkyne, resulting in either *5-exo-* or *6-endo-dig* products. Drawing inspiration from the work of Toste, Barriault and co-workers reported that the modulation of the steric and electronic properties of the ancillary ligand can lead to divergent selectivity for *5-exo-dig* and *6-endo-dig* processes.[32] σ-Donor ligands such as IPr lead to *5-exo-dig* cyclizations, while bulky phosphine ligands such as Me_4tBuXPhos shift the regioselectivity to yield the *6-endo-dig* products (**Scheme 1.5.2.iii**). The ability of gold complexes to form both *5-exo* and *6-endo-dig* cyclized products depending mainly on the ancillary ligands opens the possibility of modular divergent syntheses.

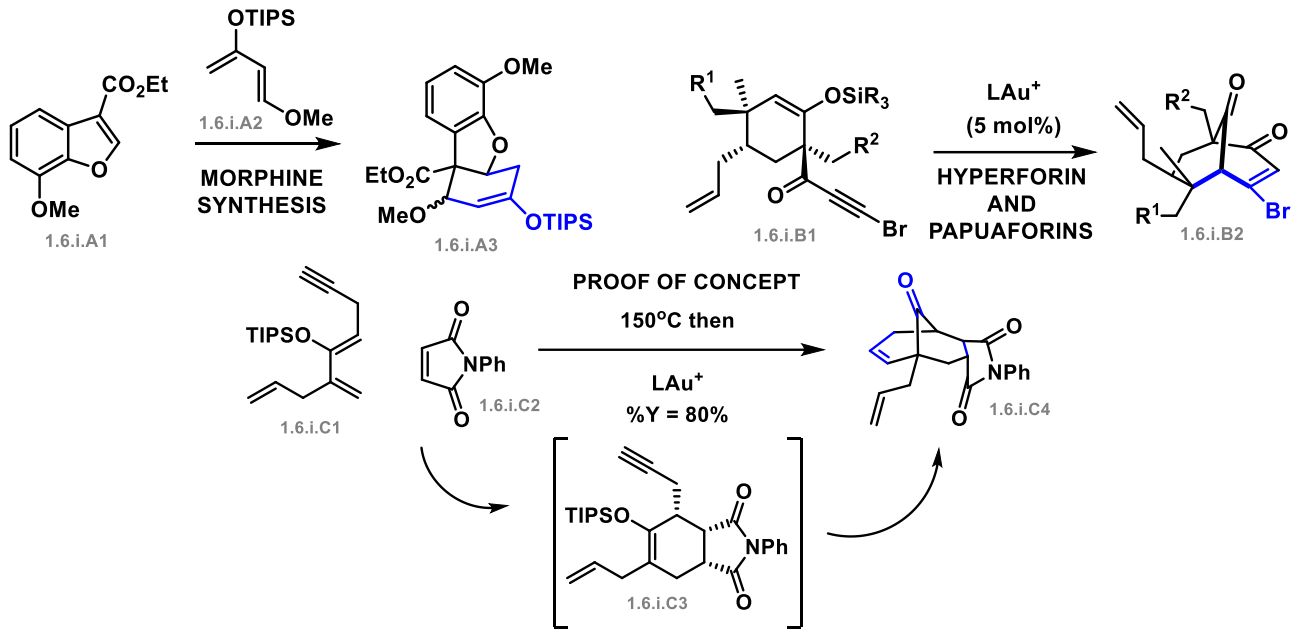


Scheme 1.5.2.iii: *Endo* and *exo* selectivity based on ligand of the gold complex.

1.6 Applications of Diels-Alder reaction and gold catalysis in synthesis

For the past decade, the Barriault group has been developing methods for rapidly constructing complex carbon skeletons involving Diels-Alder cycloadditions and gold(I)-catalyzed carbocyclizations and applying them in total syntheses. These Diels-Alder reactions have been conducted either thermally or using Lewis acids.

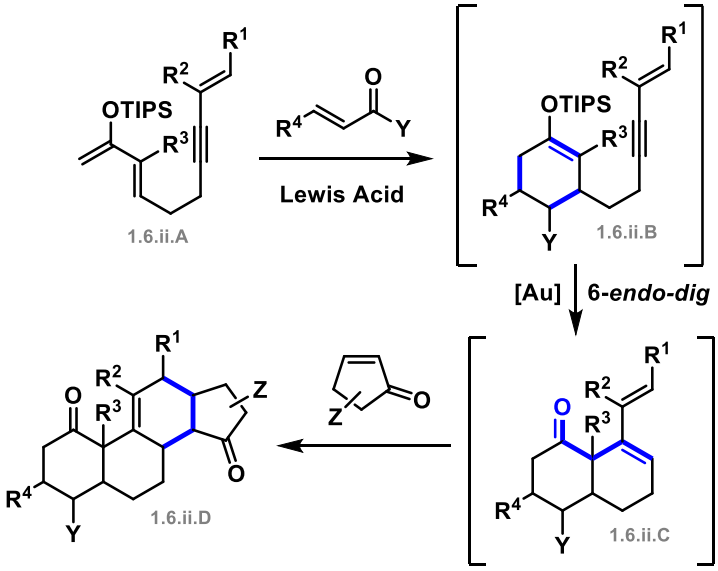
Many examples of these two reactions have been used by the Barriault group in total synthesis. As select examples depicted in **Scheme 1.6.i**, the nine-step formal synthesis of (±)-morphine in 2019 used a Diels-Alder reaction to rapidly construct the central scaffold of the molecule in the second step of the synthesis.[33] In 2018, the modular total synthesis of hyperforin, and papuaforins A, B, and C involved a gold(I)-catalyzed carbocyclization to form the central scaffold of the molecules.[34] In 2013, both the Diels-Alder and gold(I)-catalyzed carbocyclization were first combined into a single sequence in a proof-of-concept synthesis of bridged and fused carbocycles.[35]



Scheme 1.6.i - Diels-Alder cycloadditions and gold-catalyzed carbocyclizations in total syntheses and natural product-like scaffold syntheses from the Barriault group.

The complementarity of the two steps is that the Diels-Alder adduct contains the silyl enol ether necessary as the nucleophile for the following gold(I)-catalyzed carbocyclization. As such, the steps may be combined into a dual-key step for syntheses. This dual-key step has yet to be applied in a total synthesis route. In 2021, Barriault and co-workers reported a one-pot cascade sequence permitting the divergent synthesis of 6,6,5-tricyclic and 6,6,6,5-tetracyclic cores through ligand and reaction control.[36] The sequence begun with a Lewis acid-catalyzed Diels-Alder cycloaddition to form the first cyclohexene ring, whose adduct contains a silyl enol ether positioned for the following gold-catalyzed carbocyclization, forming the decalin core. This core contains an extra-cyclical diene that is used for the second Diels-Alder cycloaddition upon addition of the dienophile, forming the final ring of the system. Evidently, these transformations are highly useful in total syntheses, and

work in the Barriault lab seeks to demonstrate its robustness. The synthesis of compounds from the neoclerodane furanoditerpenoid families approached using the Diels-Alder / gold-catalyzed cyclization method as the dual-key step will be a showcase for the strategy's potential for concise, practical, and effective syntheses.



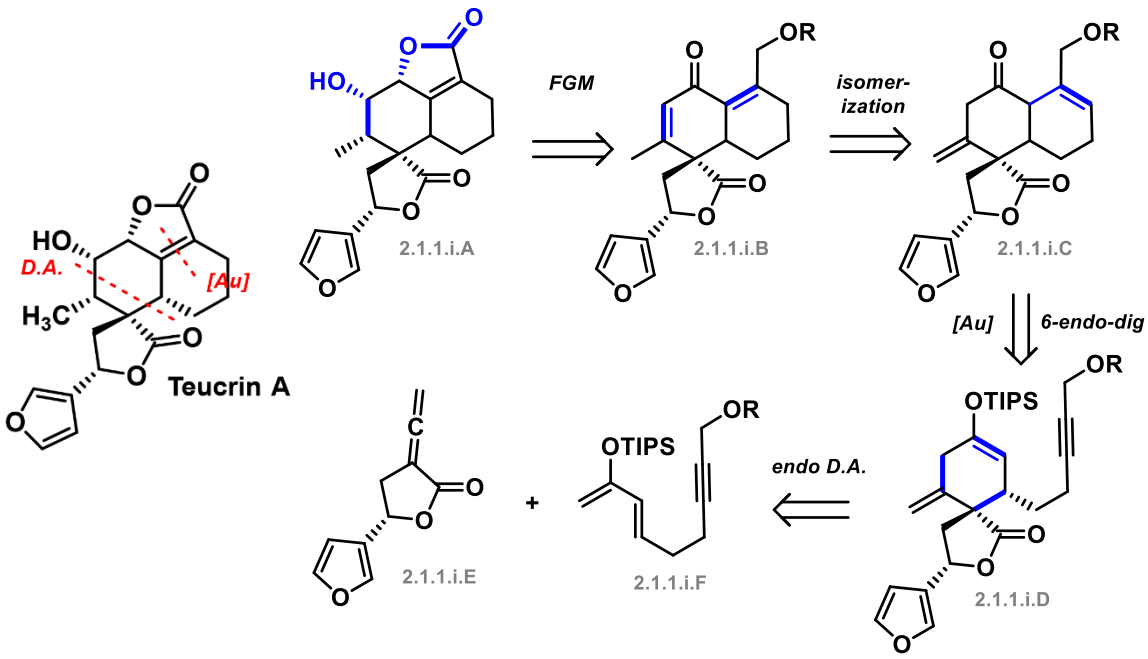
Scheme 1.6.ii: Targeted 6,6,6,5-tetracyclic core formation, one-pot involving two Diels-Alder cycloadditions and a gold-cyclized *6-endo-dig* carbocyclization.

2. THE SYNTHESIS: KEY INTERMEDIATE

2.1.1 Previous work: initial retrosynthetic analysis

Julie Brousseau – PhD graduate from the Barriault lab – began the synthesis project this thesis encompasses, and the following is a summary of the work she had completed before graduating and passing on the project to me.

The divergent total synthesis of the neoclerodane furanoditerpenoid family initiated as a total synthesis of teucrin A. To this point, there has not been a reported total synthesis of teucrin A in the literature. With the perspective of a Diels-Alder / gold-catalyzed *6-endo-dig* cyclization sequence, retrosynthetic analysis of possible bond disconnections led to the identification of a candidate dienophile and diene, as depicted in **Scheme 2.1.1.i**. The final structure of teucrin A could be derived through the functional group manipulations on an advanced intermediate **2.1.1.i.A**, which would result from the isomerization of the two resulting β,γ-double bonds of **2.1.1.i.C** to the thermodynamically favored α,β-unsaturated ketone system **2.1.1.i.B**. This decalin core would be synthesized through the Diels-Alder/*6-endo-dig* sequence from allene-containing dienophile **2.1.1.i.E** and alkyne-containing diene **2.1.1.i.F**. Notable aspects to this strategy include the use of an allene in the dienophile whose Diels-Alder adduct would contain a functionalizable *exo*-methylene at the position in which a methyl group is present in all neoclerodane furanoditerpenoids. Additionally, by including an oxygenated functionality on the diene's terminal end, a handle is already present in the adduct by which straight-forward oxidation and functional group manipulations could yield the natural products.

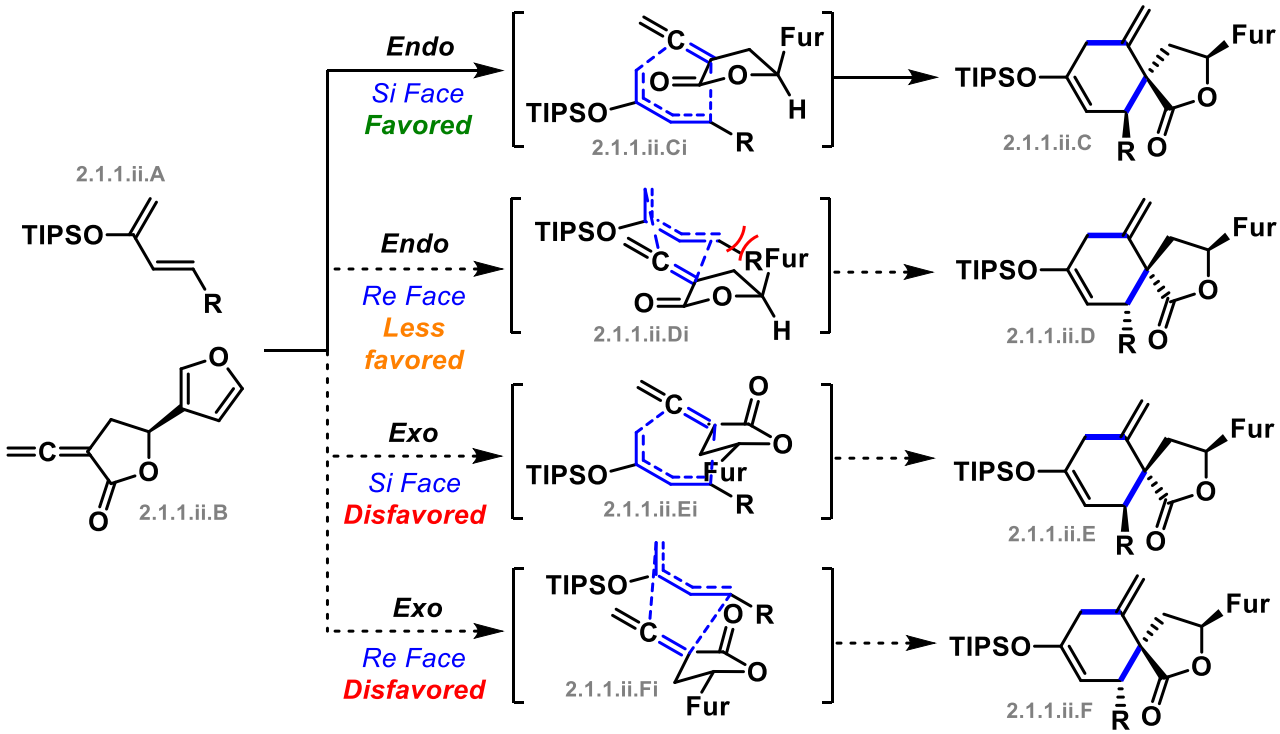


Scheme 2.1.1.i: Retrosynthetic analysis for teucrin A with Diels-Alder/gold(I) strategy.

While the starting intermediates of the Diels-Alder are highly functionalized, gold catalysts are remarkably chemoselective, and would presumably be able to accomplish the *6-endo-dig* while leaving the functional groups intact. Of note, for an enantioselective synthesis of a molecule in the neoclerodane family to be achieved, the dienophile must be enantiopure at the position of the furanyl moiety. With a racemic dienophile, the diastereomeric ratio of Diels-Alder products would not be altered, but the endpoint would be the racemic natural product.

The major point for setting the stereocenters of the structural core of the molecule is the Diels-Alder reaction. Due to the importance of this step, before carrying out investigations, an analysis of product outcomes had to be conducted. It was hypothesized that the presence of the furanyl group and its interactions with the linear chain and the R group of the diene would induce stereoselectivity in the Diels-

Alder reaction with the desired addition from the *si* face **2.1.1.ii.Ci** over the *re* face **2.1.1.ii.Di**, as depicted in **Scheme 2.1.1.ii**. The furanyl ring occupies space on one side of the dienophile, and thus favoring the approach of the diene on the opposite face. The use of Lewis acids and low temperatures would favour the *endo* products through the kinetic pathway, and as such, the two *endo* products would be the two products of the reaction, with the *si* face addition yielding the favoured product, and the *re* addition being the minor product.

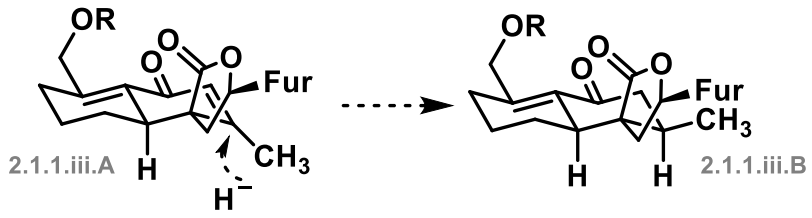


Scheme 2.1.1.ii: Possible outcomes for the Diels-Alder reaction and their transition states.

An important factor moving forward was that a highly substituted dienophile is involved in this potential reaction. As previously discussed, research from the Ley group has shown that the trisubstituted dienophile containing the methyl leads to issues with inseparable diastereomers, as there is no control over the stereochemistry of the methyl group.[26] In fact, it is known in the literature that due to

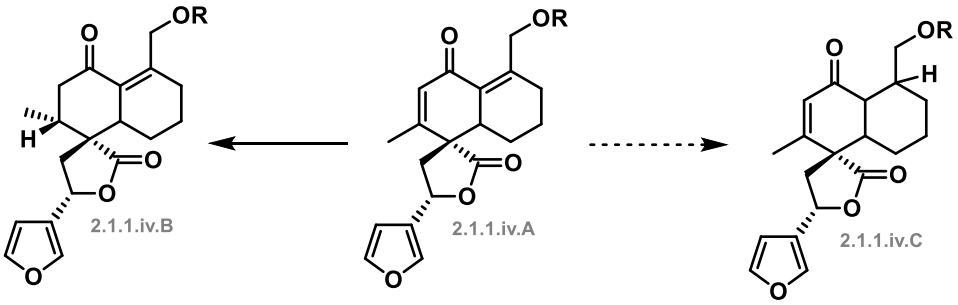
steric hindrance, trisubstituted dienophiles tend to undergo stepwise cycloadditions in the place of the concerted Diels-Alder.[37] As such, they require thermal conditions while Lewis acids are ineffective. The allene motif was potentially a workaround to the additional dienophile substitution by limiting the steric interactions during the C-C bond formations and would maintain the necessary functional handle for the later steps of the synthesis.

After the Diels-Alder and gold-catalyzed *6-endo-dig* cyclizations, the *exo*-methylene and alkene would be isomerized to the bis-α,β-unsaturated ketone system **2.1.1.i.B**, and the stereochemically correct methyl group could be yielded through the 1,4- hydride addition from the opposing side. As depicted in **Scheme 2.1.1.iii**, the hydride is hypothesized to add from the correct side, as the addition should proceed on the axial position through a chair-like transition state. On the flipside, the static positioning of the two hydrogen atoms (CH_2) on the bottom face of the spirolactone could be envisioned to take up the steric space where the hydride addition must occur, while the lactone carbonyl would not take up the same steric space, thus leading the addition to occur from the other side leading to the wrong diastereomer. The correct addition would thus depend on which kinetic pathway is favoured, whether the steric effects mentioned or the favourability of the chair-like vs. boat-like transition will contribute more significantly to the product distribution. Admittedly, due to the presence of 4 sp^2 C atoms in the ring, it is not likely that this decalin would sit in a chair conformation.



Scheme 2.1.1.iii: Predicted nucleophilic addition through chair-like transition state.

Additionally, between the two δ-positions in which the 1,4-addition of the hydride could occur, it is hypothesized that addition at the desired carbon will occur, leading to compound **2.1.1.iv.B**. Apart from the desired alkene being trisubstituted while the undesired alkene is tetrasubstituted, the cyclic torsion surrounding the undesired alkene could be envisioned to lead to misalignment of the π* orbital at the δ-position and the π-orbital of the carbonyl, leading the addition to be more difficult. This hypothesis is supported by previous experiments,[38] and through the crystal structure of an intermediate synthesized later in this project (**Section 2.6.5**).



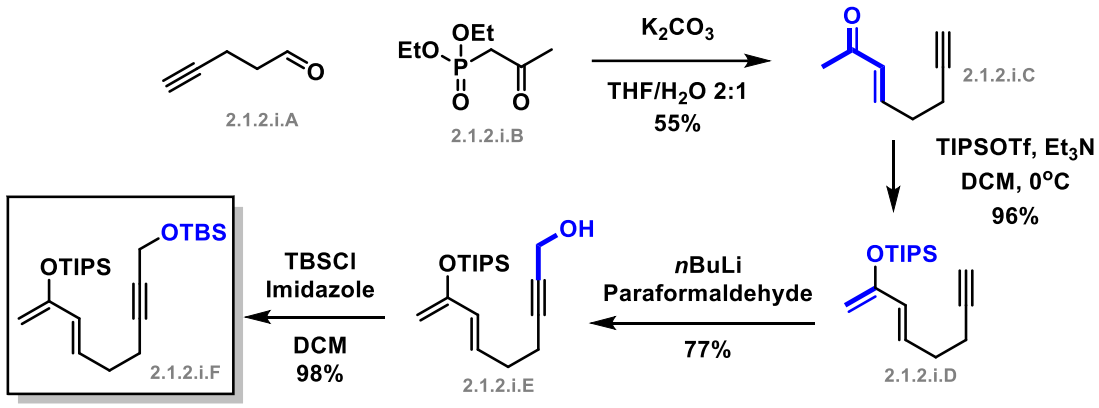
Scheme 2.1.1.iv: Both possible locations for the 1,4-nucleophilic hydride addition.

2.1.2 Previous work: first investigations

Several pathways were explored for the synthesis of the diene and the dienophile for the Diels-Alder reaction. To summarize all the attempts – as I never

conducted these reactions myself and dealt only with the final products prepared by Julie – the following are the winning routes.

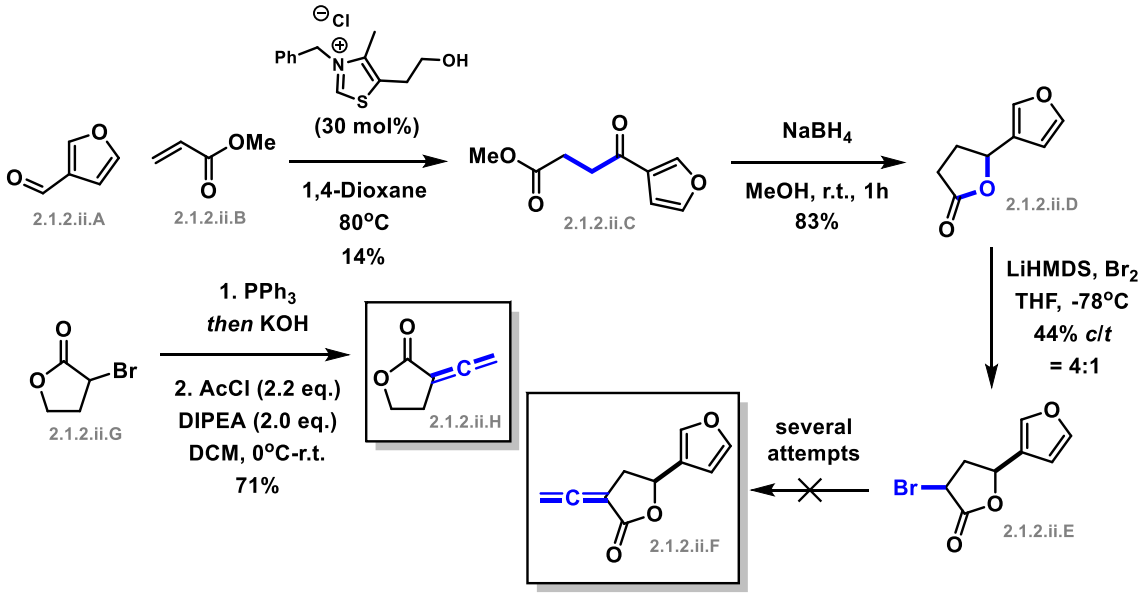
As laid out in **Scheme 2.1.2.i**, For the diene section, a Horner-Wadsworth-Emmons was performed on pentynal **2.1.2.i.A** (derived previously from pentynol) to yield the *E*-α,β-unsaturated ketone **2.1.2.i.C** in 55% yield. Following, the TIPS silyl enol ether **2.1.2.i.D** was formed in 96% yield to achieve the diene functionality, and the terminal alkyne was treated with *n*-BuLi and paraformaldehyde to give the propargylic alcohol **2.1.2.i.E** in 77% yield. The alcohol was converted to the corresponding silyl ether (TBS) **2.1.2.i.F** in 98% yield.



Scheme 2.1.2.i: Synthesis of the OTBS-containing diene in 40% total yield.

As laid out in **Scheme 2.1.2.ii**, issues were encountered in the final step of the synthesis of the furanyl-containing dienophile. The first step of this synthesis was a very poor yielding Stetter reaction that could not be improved, where furaldehyde **2.1.2.ii.A** performs a 1,4-addition onto methyl acrylate **2.1.2.ii.B** to afford compound **2.1.2.ii.C** in 14% yield. Following, a reduction of the ketone with $NaBH_4$ was performed to induce a lactonization to form the furanyl-containing lactone **2.1.2.ii.D**

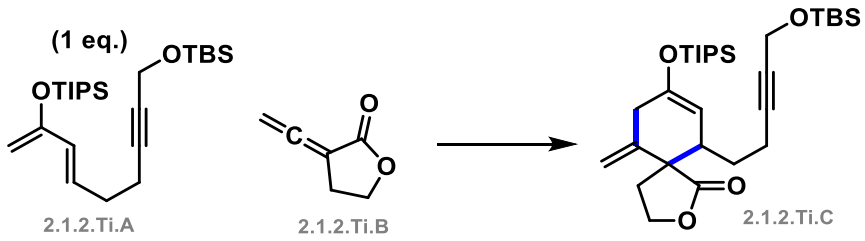
in 83% yield. An α-bromination was then performed to achieve substrate **2.1.2.ii.E** in 44% yield with a *cis/trans* ratio with respect to the stereocenter of the furanyl of 4:1. The final step to transform the bromine to the allene **2.1.2.ii.F** was unsuccessful after several attempts, and as such, a method for forming the furanyl-less allene-containing dienophile **2.1.2.ii.H** was developed in a two-step transformation starting from the commercially available α-bromo lactone **2.1.2.ii.G** in 71% yield. Clearly, this lack of success is due to incompatibility of the furanyl in the reaction conditions. The first Diels-Alder reaction were thus attempted with this substrate.



Scheme 2.1.2.ii: Unsuccessful synthesis of the desired allene-containing dienophile containing the furanyl, and synthesis of furanyl-less allene-containing dienophile.

As depicted in **Table 2.1.2.Ti**, the primary investigations into the Diels-Alder cycloaddition involved the allene-containing dienophile **2.1.2.Ti.B** and diene **2.1.2.Ti.A**. As shown in entry **1**, with the use of several Lewis Acids – Et_2AlCl, EtAl-sesquichloride, $AlCl_3$, $Gd(OTf)_3$, Tris(PhF_5)borane – run at -78°C in a variety of

solvents, no cycloaddition was accomplished, merely the hydrolysis of the silyl enol ether to its respective ketone. This varied scope of Lewis Acids indicates the inability for the catalyzed Diels-Alder reaction to proceed with the allene-containing dienophile, and as such, thermal Diels-Alder cycloadditions were attempted.



Entry	Dienophile	Additive	Temperature	Solvent	Yield / d.r.
1	2-3 eq.	L.A.*	-78°C	Several	0%
2	2 eq.	None	110°C	Toluene	27% d.r. = 3:1
3	5 eq.	None	110°C	Toluene	49% d.r.= 3:1

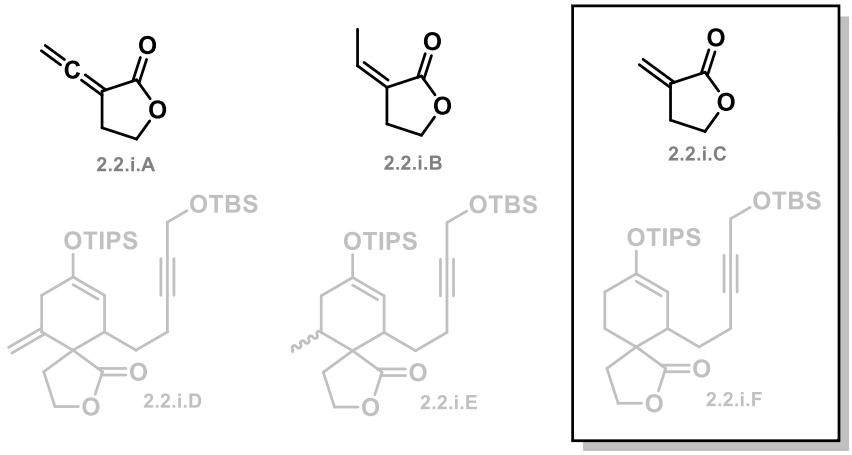
Table 2.1.2.Ti: Investigation of the Diels-Alder reaction with furanyl-less allene-containing dienophile. L.A. = Et_2AlCl, Sesquichloride, $AlCl_3$, $Gd(OTf)_3$, Tris(pentafluorophenyl)borane)

Performing the reaction at 110°C in toluene as in entry **2** led to a 27% yield of the desired product when 2.0 equivalents of the dienophile were used, and in entry **3** 49% yield of the product when 5.0 equivalents of the dienophile were used. In both cases, a 3:1 mixture of difficultly separable diastereomers (*endo* and *exo* products) were obtained. The identity of the major product was not determined as the NOESY of each diastereomer has similar signals. This could be a result of the cyclohexenes resting in a half-chair conformation. In the end, the yield of the thermal cycloaddition

remains poor even at the expense of five equivalents of dienophile used. Additionally, a mixture of *endo* and *exo* products was undesirable, and the lack of reactivity of the allene in the cycloaddition with Lewis Acids at low temperatures led to this route being an ineffective method to achieve the synthesis. One may suggest that the reason for this lack of is due to the reacting π-orbital of the allene possibly not being fully conjugated with the lactone carbonyl due to cyclic torsion, resulting in a higher LUMO, leading to a much more difficult cycloaddition. As such, the structure of the dienophile must be altered, and in this case, simplified.

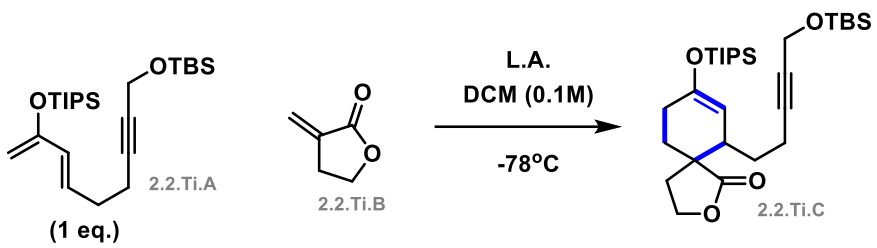
2.2 Continuing the Diels-Alder reaction investigation

The first task going forward was to determine which dienophile would be the smartest choice for the success of the Diels-Alder cycloaddition (**Scheme 2.2.i**). As we must abandon the allene substrate **2.2.i.A**, the following option is the dienophile **2.2.i.B** with the methyl group *syn* to the lactone carbonyl. The resulting *endo* Diels-Alder product would contain the methyl group with the correct stereochemistry. Once again, as we have seen from the work from the Ley group, the tri-substituted dienophile leads to uncontrolled stereochemistry of the methyl group in the product and a resulting inseparable mixture. Additionally, the furanyl group is not yet installed on this dienophile, which would further add diastereomers to the product profile. As a result, the optimal dienophile choice is commercially available **2.2.i.C**, where methyl installation is withheld until after the Diels-Alder cycloaddition to maximize the yield and selectivity of the Diels-Alder at the expense of additional steps to add the methyl group later in the synthesis route.



Scheme 2.2.i: Possible dienophiles and their respective Diels-Alder adducts.

To begin with entry **1** in **Table 2.2.Ti**, a thermal Diels-Alder reaction was performed to verify the success of the cycloaddition, resulting in an 18% yield with an undetermined diastereomeric ratio. Then, a short screening of Lewis acids was performed, with the reaction running for 30 min at -78°C followed by a quench with a saturated solution of $NaHCO_3$ in water. This was performed with the Lewis acids available at the time: Et_2AlCl, BF_3OEt_2, and $AlCl_3$. Et_2AlCl in entry **2** led to the highest yield of the initial screening of 15% in a 9.5:1 d.r., which is very poor considering 5.0 equivalents of the dienophile were used. Entry **3** used BF_3OEt_2 and found full degradation of the reagents, and no conversion occurred with $AlCl_3$ in entry **4**. Following with entry **5**, by increasing the equivalents of Et_2AlCl from 0.6 equivalents to 1.2 equivalents, the yield increased to 40% and a similar d.r. of 10:1.



Entry	Catalyst	Eq.	(2) Eq.	Time	Quench	Yield	d.r.
1	100°C	N/A	2	16 h	none	18%	n.d.
2	Et_2AlCl	0.6	5	30 min	$NaHCO_3$	15%	9.5:1
3	BF_3OEt_2	0.6	2	30 min	$NaHCO_3$	0% (degr.)	n/a
4	$AlEt_3$	1.0	2	30 min	$NaHCO_3$	0% (no conv.)	n/a
5	Et_2AlCl	1.2	2	30 min	$NaHCO_3$	40%	10:1
6	Et_2AlCl + 2,6-*t*BuPyr	1.2 2.0	2	30 min	$NaHCO_3$	0% (no conv.)	n/a
7	$EtAlCl_2$*	1.0	2	30 min	$NaHCO_3$	0% (degr.)	n/a
8	$EtAlCl_2$	1.0	2	30 min	NEt_3	55%	>20:1
9	$EtAlCl_2$	1.0	2	1 h	NEt_3	78%	>20:1
10	$EtAlCl_2$	1.0	2	3 h	NEt_3	20%	>20:1

Table 2.2.Ti: Screening conditions for the Diels-Alder reaction with the furanyl-less dienophile.

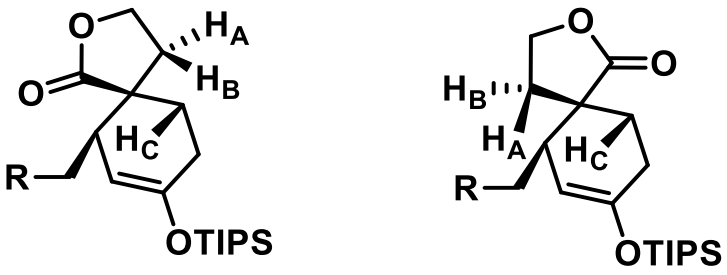
* = first scale-up attempt

A notable side product was the cycloaddition between the diene and its hydrolyzed α,β-unsaturated ketone counterpart, so to counter this, the bulky base 2,6-*t*butyl pyridine was added to the mixture to quench any proton in the mixture that would lead to the hydrolysis of the diene, while theoretically not complexing and deactivating the Lewis acid. The result was no conversion, implying that the Lewis acid was indeed quenched by the base. In the first attempted scale-up, $EtAlCl_2$ was then used as the Lewis acid which resulted in complete degradation of the products (entry **7**); however, an observation was made that the $NaHCO_3$ saturated solution in water froze upon addition to the DCM solution at -78˚C, meaning the reaction did not truly quench until the temperatures equilibrated to above 0˚C. This would lead to the Lewis acid reacting harshly to what would otherwise potentially be a successful reaction.

With the knowledge gain from entry **6** that nitrogen-containing bases can be used to quench the Lewis Acid, the quenching method was replaced with the addition of NEt_3, giving an impressive yield of 55% with a d.r. of >20:1, even with only 2.0 equivalents of the dienophile added (entry **8**). This is an improvement in both the yield and the diastereomeric ratio, and so investigations continued with $EtAlCl_2$ as the Lewis acid. From then on, the reaction time was increased from 30 minutes to 1 hour, improving the yield of 78% with the same >20:1 d.r. (entry **9**). When the reaction was stirred for 3 hours (entry **10**), the yield dropped to 20% while maintaining the d.r. (>20:1). In this case, running the reaction for more time than necessary leads to the hydrolysis of the product to its corresponding cyclohexanone. Left for future investigations was the hypothesis that an optimal time for running the

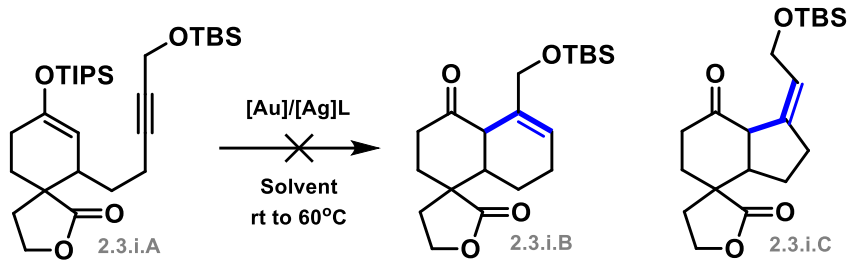
reaction between 1 hour and 3 hours would be achieved that would lead to the highest yield. For now, the goal was to determine if the gold-catalyzed cycloaddition was a feasible transformation, and so this was first pursued.

In terms of determining the identity of the major diastereomer, as with the previous instance, it was unsuccessful to distinguishing between the two products *via* NOESY. Preliminary computational model of the Diels-Alder adduct was compiled, and corroborated this conclusion, in that the protons of interest H_A and/or H_B (indistinguishable) are visible to H_C regardless of *exo* or *endo* products (**Scheme 2.2.ii**). As such, the identification of the major product needs to be delayed until the gold-catalyzed carbocyclization. By that point, the decalin core of the molecule would be rigidified, allowing for proper identification as well as through the formation of a crystal. Regardless, the stark >20:1 diastereomeric ratio in low temperature conditions indicates strongly that the favoured *endo* product was achieved as the major product.



Scheme 2.2.ii: Two indistinguishable Diels-Alder adducts by NOESY, demonstrating proton correlation between H_A or H_B to H_C in both adducts.

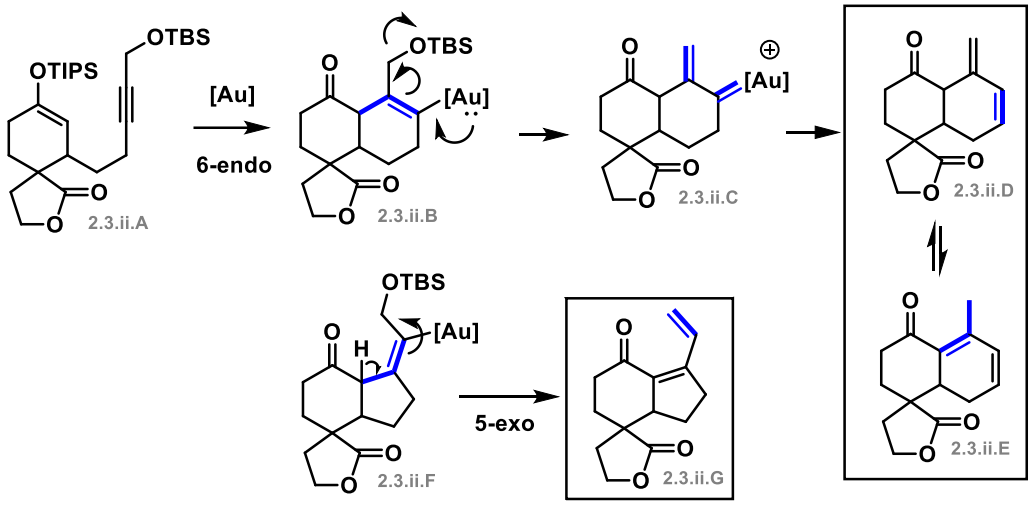
2.3 The first failure of the gold-catalyzed carbocyclization



Scheme 2.3.i: The desired products of the first gold-catalyzed carbocyclization attempted.

A very broad screening of conditions was performed to attempt to achieve the gold-catalyzed carbocyclization (**Scheme 2.3.i**) to either the *6-endo-dig* product or the *5-exo-dig* product. Several phosphine ligands on gold catalysts were screened, including VPhos, Me_4tBuXPhos, JackiePhos, JohnPhos, BrettPhos, CyJohnPhos, CataCXium, Cy-cBRIDP, XPhos, WangPhos, and IPr. For solvents, combinations of acetone:MeOH, acetone:DCM, DCM:MeOH, acetone, and wet DCM were screened, conditions previously explored in the Barriault group[39]. In all cases, product analysis led to the conclusion that the addition step of the *6-endo-dig* and *5-exo-dig* steps occurred correctly, but an unexpected product pathway occurred in which before protodeauration, it seems in the former case that the gold back-donates into the π-system, kicking out the OTBS group, followed by subsequent structural alterations before the eventual protodeauration, and in the later case, a mere isomerization kicks the OTBS group out. The final products were not completely characterized, but using HPLC to separate out the products, ^{13}C and ^{1}H NMRs were used to identify the loss of the OTBS group, the vinyl moiety of the *5-exo-dig* derivative **2.3.ii.G**, and the *exo*-methylene and methyl of the two *6-endo-dig* derivatives **2.3.ii.D** and **2.3.ii.E**. It was thought that the gold's back-donating properties could be avoided using silver

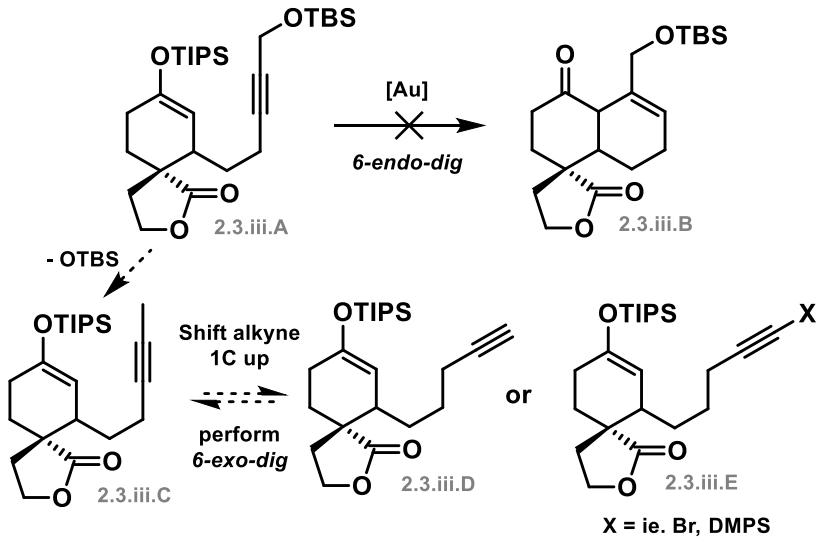
catalysts instead, but all attempts using several different silver complexes lead to the same product profile. In the end, it was concluded that it would be too difficult to avoid the loss of this OTBS group, and a clear overhaul of the reaction scheme needed to be thought out to achieve the synthesis. While it would be useful for there to be an functional handle present from the beginning of the synthesis, its immediate loss was unproductive.



Scheme 2.3.ii: Reaction products of the first gold-catalyzed carbocyclization attempted.

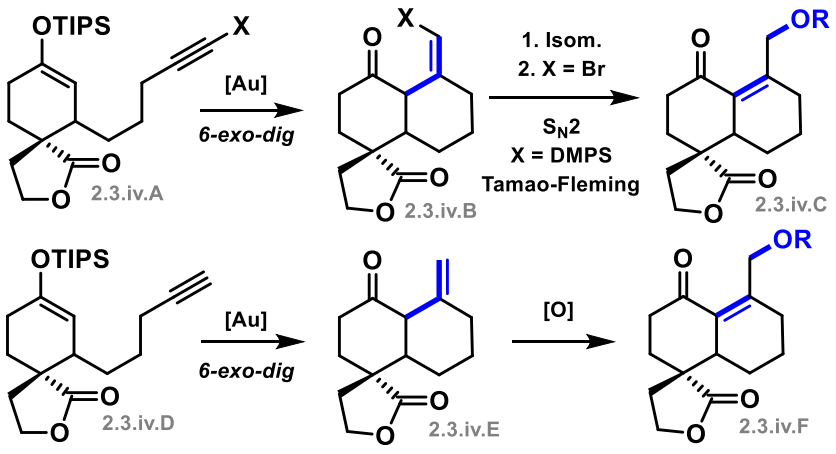
In conclusion, it was unsuccessful to design the molecule in such a way that a substrate could undergo a *6-endo-dig* cyclization while containing the propargyl alcohol moiety. In revising the strategy for the synthesis, the route was re-imagined around performing a *6-exo-dig* cyclization (**Scheme 2.3.iii**). This would involve removing the OTBS group from the start as in **2.3.iii.C** and shifting the alkyne up the structure by one position on the alkyl chain leading to a terminal alkyne **2.3.iii.D**. This new route is in fact more favorable in terms of *endo* vs. *exo* selectivity, as a *7-endo-dig* cyclization is much less favorable compared to the corresponding *6-exo-*

dig cyclization. Optionally, a bromine, DMPS, or other functional group could be installed on the terminal position of the alkyne **2.3.iii.E**, and further transformed after the cyclization[40].



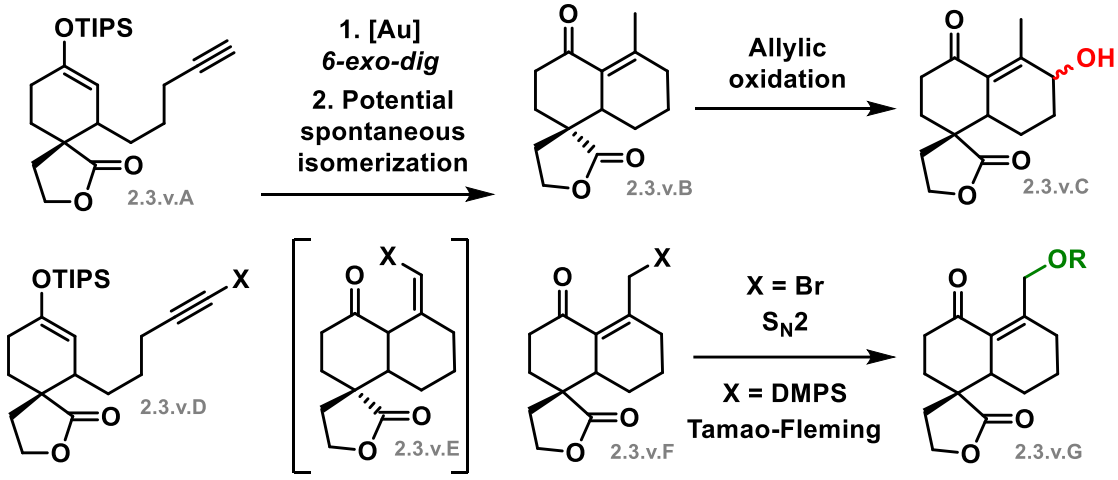
Scheme 2.3.iii: Plan for new strategy, rearranging the targeted Diels-Alder adduct.

Installing an oxygenated group directly to the end of the alkyne from the start of the synthesis would require the use of an electrophilic oxygen species (ie. peroxides) that are extremely reactive and would present an executional hazard. If the alkyne remains unfunctionalized at the terminal position, an oxidation will need to be performed after the cyclization (**Scheme 2.3.iv**). It is possible that directly after the *6-exo-dig* cyclization, an isomerization of the β,γ-unsaturated ketone to the α,β-unsaturated ketone will occur, making an oxidation difficult. If that is the case, the functionality at the end of the alkyne would prove to be useful.



Scheme 2.3.iv: Prospective transformations for the two alkyne functionalizations

The selectivity for a transformation at the allylic position on the un-functionalized substrate could be challenging (**Scheme 2.3.v**). As such, if the isomerization does occur spontaneously, then the substituted alkyne would offer a clearer route for the synthesis. Of course, an alternative oxidation that was yet discovered at this point in the route planning was, possible and was ultimately developed and implemented (see **Table 3.2.2.Ti**).

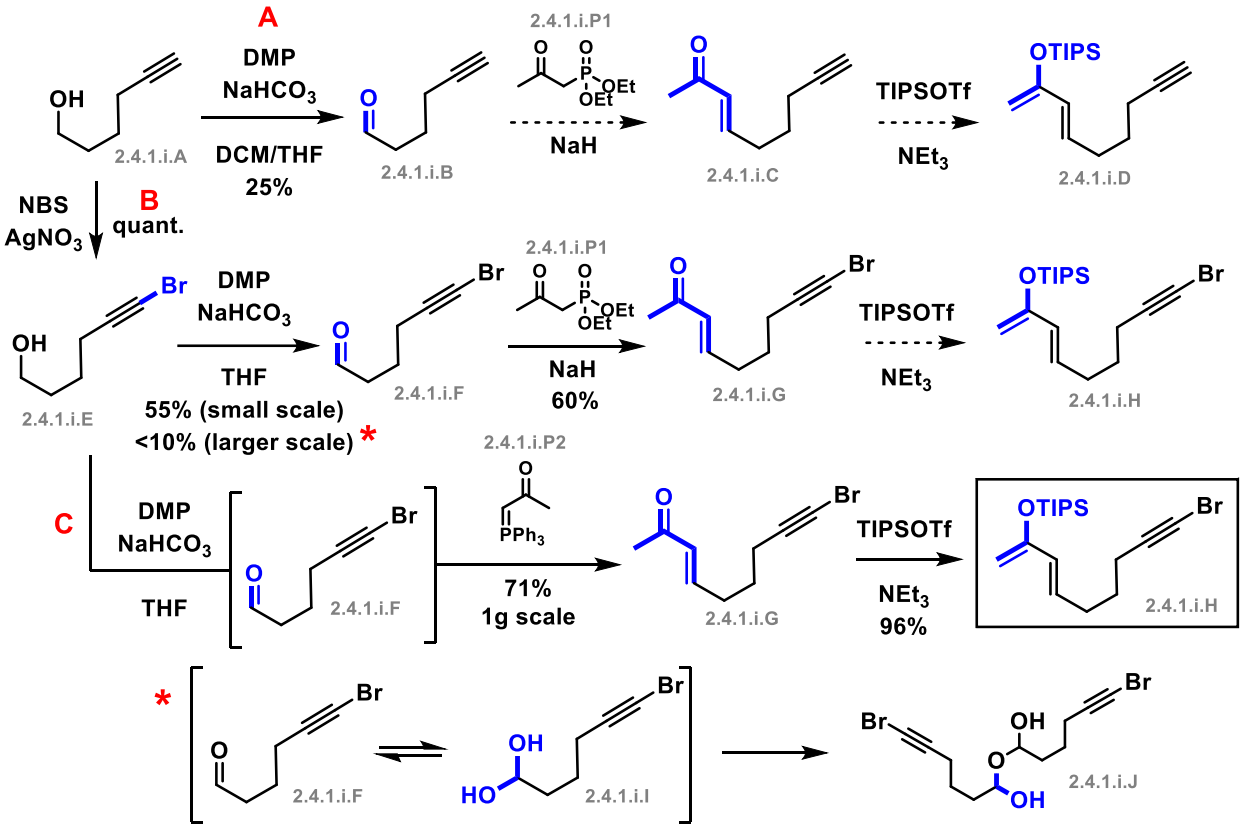


Scheme 2.3.v: Potential issues with regioselectivity involving an unsubstituted alkyne.

2.4.1 Investigating the *6-exo-dig* route – synthesis of diene and dienophile

To begin, the new diene and dienophile must be synthesized. For the diene (**Scheme 2.4.1.i**), a similar route could be used as in **Scheme 2.1.2.i**, starting with commercially available hexynol **2.4.1.i.A**. For the first route **A**, the three-step sequence would involve the oxidation of the hydroxyl to aldehyde **2.4.1.i.B**, followed by a Horner-Wadsworth-Emmons to yield the *E*-α,β-unsaturated ketone **2.4.1.i.C**, and finally, transformed to the silyl enol ether to yield the electron-rich diene **2.4.1.i.D**. The oxidation step was attempted with PCC[41], Parikh-Doering[42], and Dess-Martin[43] methods. The former two conditions led to multiple side products, and the yields were never determined. The DMP conditions was both the simplest reaction to set up due to DMP being an easily weighable solid, and the cleanest product profile leading to a near complete conversion to the aldehyde product with minimal side products. The main issue was that the aldehyde product is highly volatile, making its isolation extremely difficult. The highest isolated yield was 25% at a small scale.

The first idea of a solution to the volatility issue was to functionalize the alkyne as the first step of the scheme to increase the compound's molecular weight, as indicated in route **B**. With the use of NBS and $AgNO_3$[44], a quantitative yield of the brominated hexynol **2.4.1.i.E** was obtained at a 1-gram scale. This reaction was clean enough that the crude product could be used for the following DMP oxidation. While the isolated yield of product **2.4.1.i.F** was improved to 55% at a small scale, the aldehyde product was still very volatile, making its purification and isolation difficult. Especially at a larger scale, a portion of the product was lost.



Scheme 2.4.1.i: Synthesis of the new diene, issues encountered and main side product.

Additionally, a dimerization product **2.4.1.i.J** forms during the reaction and extraction process, in which the diol form **2.4.1.i.I** undergoes a nucleophilic attack on the aldehyde form. Either way, the following Horner-Wadsworth-Emmons (HWE) step was attempted with phosphonate **2.4.1.i.P1**[45]. Due to the nature of the volatile reagent, a sizeable portion of the reagent was lost in the process of setting up the reaction, as well as during the running time of the transformation. The dimerization product was also observed during the HWE reaction. As such, it seemed this reaction could not easily be carried out and purified as is. Since isolating the aldehyde was not feasible, and a one-pot reaction with the HWE was not possible due to the phosphonate needing to be prepared in a separate flask, the following

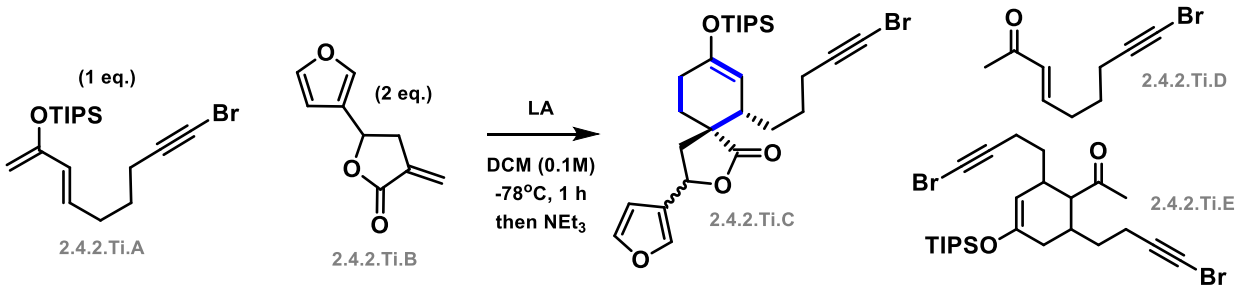
approach was to prepare the oxidation reaction and the phosphonate deprotonation in separate flasks, and transfer *via* canula the contents of one flask into the other. Both transfers *via* canula, the HWE preparation flask into the oxidation flask, and *vice versa*, were attempted at a small scale, but in the end, the reaction was quite messy and difficult to perform with a maximum yield of the HWE product 60% over the two steps. Especially once the scale would be increased, it was a concern that this reaction would prove to very irreproducible.

An alternative to the HWE was set on, indicated by route **C**, simply performing a Wittig reaction with commercially available phosphonium **2.4.1.i.P2** that was present in the laboratory, an easily weighable and handleable solid. The transformation worked successfully, obtaining a 71% yield of **2.4.1.i.G** from the start of the route at a 1 g scale. While the bromine addition was now seemingly unnecessary due to the molecular weight and volatility problem now being solved, the functionality was maintained due to the reaction's quantitative yield, and that after the prospective gold-catalyzed carbocyclization, the oxidation state would already be set. The final step involved the formation of the silyl enol ether **2.4.1.i.H**, achieving the diene in 96% isolated yield. This diene is acid sensitive and must be isolated in a basic column. For the synthesis of the dienophile, the method in **Scheme 1.4.iv** from the Ley group was used, synthesized in 90% yield.[26]

2.4.2 Investigating the *6-exo-dig* route – Diels-Alder

In the presence of a Lewis acid at -78°C and stirred for 1 hour followed by a quench with NEt_3, both Lewis acids Et_2AlCl in entry **1** and $EtAlCl_2$ in entry **2** were

surveyed (**Table 2.4.2.Ti**). One could suggest that a decrease in yield could be expected given the bulkier furan-containing dienophile that would lead to a slower reaction speed, and while the previous reactions ran to completion in an hour, it was also expected that a longer reaction time would be necessary. At this point, the goal was to ensure the gold reaction would be possible, so re-optimization of the reaction was withheld for later. Entry **1** with Et_2AlCl resulted in a yield of 28% and a d.r. of 1.77:1.0 of *endo* products, and entry **2** $EtAlCl_2$ resulting in a yield of 39% and a d.r. of 2.35:1. The two major products differ at the position of the furanyl pointing up or down because of either the *Si* or *Re* face addition. The ratio between *endo* and *exo* products remained at the previously determined 9:1 and >20:1, rendering the minor *exo* products negligible. The new significant ratio at the differing furanyl stereocenter is of importance. As was the case previously, $EtAlCl_2$ is the preferred Lewis acid for the cycloaddition, both for the yield as well as the resulting diastereomeric ratio.



Entry	Catalyst	Yield	d.r. (endo/exo)
1	Et_2AlCl	28%	1.77:1.0
2	$EtAlCl_2$	39%	2.35:1.0

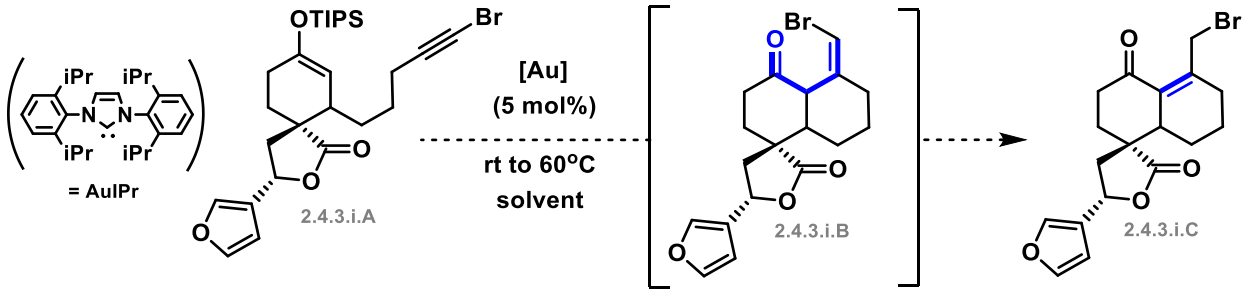
Table 2.4.2.Ti: Investigating the Diels-Alder reaction with the new diene.

In setting up the reaction in the same way as before, more hydrolysis of the diene generating **2.4.2.Ti.D** was observed, and the resulting Diels-Alder adduct **2.4.2.Ti.E** between the diene **2.4.2.Ti.A** and its hydrolyzed form was a major side product. Presumably, this was due to the slower reaction speed giving opportunity for the Lewis acid to cause hydrolysis of the diene. A simple troubleshooting involving a new bottle of dry DCM and a new bottle of the two Lewis acids did not improve the d.r. or reaction yields. One may suggest this difference in reaction success is possibly due to the presence of the furyl group rendering the cycloaddition more difficult, whether through conferring a conformational bias or through coordination with the Lewis Acid. Optimizations – including time sensitivity and careful preparation of the starting materials – needed to be performed, but at this point, the goal was to provide a decent amount of product to conduct investigations for the gold-catalyzed carbocyclization.

While the two major adducts proved to be difficult to separate by column chromatography, one of the products elutes slightly faster, and thus a small portion of the mixture could be isolated as a pure sample which could be used for investigations with the gold catalyzation. Presumably, the two diastereomers would be more easily separable following the carbocyclization. As in the previous case, the identity of the pure sample could not be confirmed, concerning the *endo* vs. *exo* products, in addition to the correct stereochemistry for the furanyl moiety.

2.4.3 Investigating the *6-exo-dig* route – gold-catalyzed carbocyclization

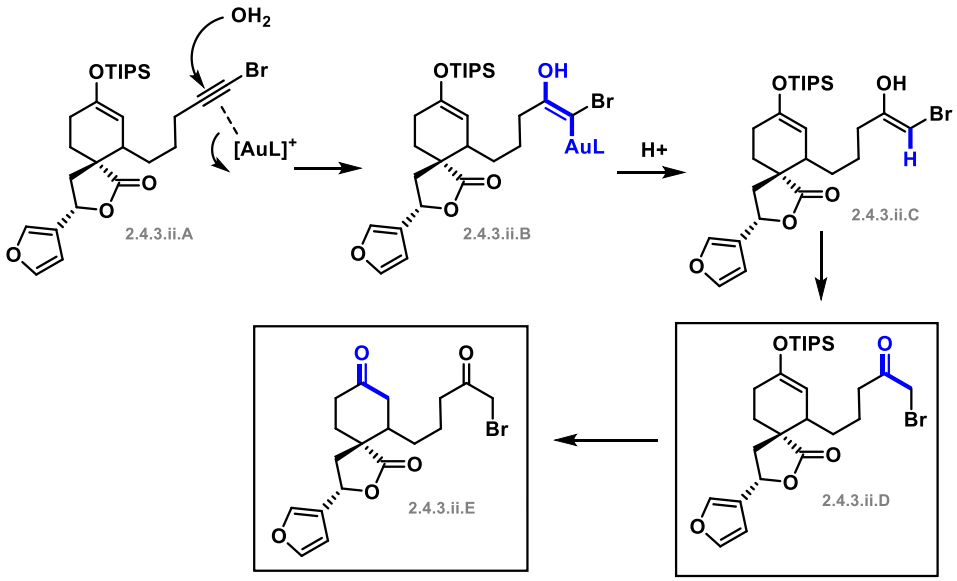
Previous studies in the Barriault lab have elucidated that the IPr ligand in gold-catalyzed carbocyclizations was particularly selective for the *5-exo-dig* product over the *6-endo-dig* product.[32] Presumably, the same selectivity for the *exo* product would be seen between the *6-exo-dig* and *7-endo-dig* products, and to a greater degree because a 7-membered ring forms much more slowly. As such, IPrAu was the go-to gold complex for the preliminary investigation (**Scheme 2.4.3.i**). The adduct **2.4.3.i.B** was expected to isomerize to the α,β-unsaturated ketone **2.4.3.i.B**, which would be favored due to the steric clash between the bromine and the ketone, in addition to the stability of the resulting conjugated system.



Scheme 2.4.3.i: Gold-catalyzed carbocyclization on brominated substrate.

By TLC analysis, the reaction looked successful, as two products were shown with a very strong conversion, assumed to be the *6-exo-dig* and *7-endo-dig* products. However, one product converted to the other over time. As depicted in **Scheme 2.4.3.i**, the product later identified as **2.4.3.i.D** converted to product **2.4.3.i.E**, indicating that this conclusion was not the case. The carbocyclization did not happen, and instead, water or methanol adds into the activated alkyne to yield **2.4.3.i.B**. Following protodeauration to **2.4.3.i.C**, the tautomerized product **2.4.3.i.D**

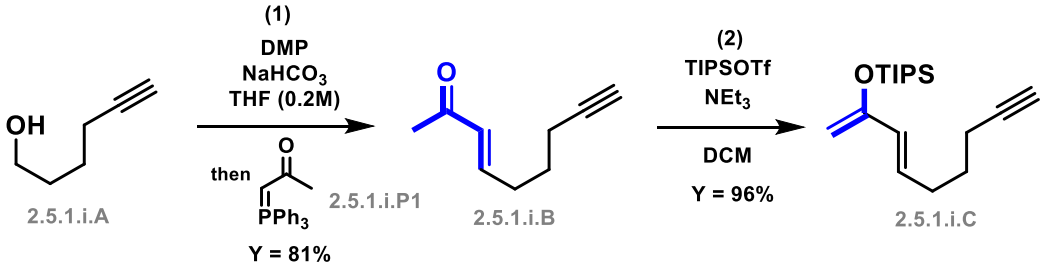
was obtained. After a hydrolysis of the OTIPS group, ketone product **2.4.3.i.E** appeared more and more over time. Some of the gold complexes previously used in section **2.3** were attempted for this transformation, all leading to the same product profile. When the reaction was attempted in a solvent system excluding methanol, the same product profile was observed. When attempted in dry DCM, no conversion was observed, indicating that the presence of water pushes this undesired product pathway forward. It seemed that the reaction would not move forward simply due to the presence of the bromine group. Whether it is due to the bromine's electronic effect on the electrophilicity of the activated alkyne, or the steric clash between the bromine and ketone in the product that disfavors the transformation, it became clear that this transformation is unfruitful. Additionally, a literature example of a gold-catalyzed carbocyclization of a bromoalkyne with a silyl enol ether could not be found. Moving forward, the investigations continued with the unsubstituted alkyne to test if the bromine indeed disallowed the transformation.



Scheme 2.4.3.ii: Mechanism for the undesired pathway of the gold-catalyzed reaction.

2.5.1 The winning *6-exo-dig* route – diene synthesis and Diels-Alder

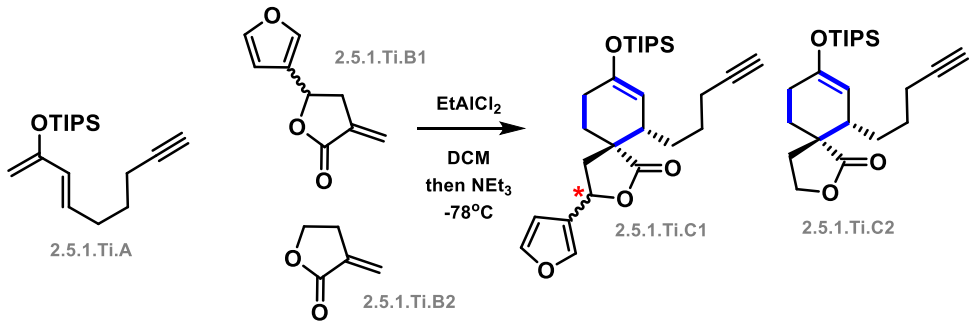
The route involving the unsubstituted alkyne diene (**Scheme 2.5.1.i**) is in fact the winning route for the synthesis, leading to the successful gold-catalyzed carbocyclization. Omitting the bromination, the yield of the DMP oxidation and Wittig homologation one-pot transformation improved from 71% to 81% to yield **2.5.1.i.B**. This reaction has been performed up to a 2 g scale, with the only inconvenience at this larger scale being dealing with the PPh_3O by-product of the reaction during purification. Following, the formation of the silyl enol ether **2.5.1.i.C** proceeded very efficiently in 96% yield in a short 10-minute reaction time. Proceeding from this concise two-step process was the optimization for the Diels-Alder cycloaddition.



Scheme 2.5.1.i: Concise route for the formation of the unsubstituted diene.

Previously, it was noted that the Diels-Alder cycloaddition involving the furanyl-less dienophile **2.5.1.Ti.B2** performed better than the cycloaddition involving the furanyl-containing dienophile **2.5.1.Ti.B1**. In this investigation, it was important to compare the two dienophiles to ensure that the reaction yields remained consistent. Additionally, it was noted that a longer reaction time would be necessary to push forward the reaction with the furanyl-containing dienophile. In **Table 2.5.1.Ti**, a 1-hour reaction time and a 90-minute reaction time for the furanyl-containing

dienophile were compared in entries **1** and **2**, of which the yields were 31%, and an improved 43%. These yields are still lower than those determined in previous investigations with the furan-less dienophile which had a yield of 78% (**Table 2.2.Ti**, entry **9**), and upon repeating this reaction with the furan-less dienophile in entry **3** for a 90 minute run-time rather than 1 hour, the yield obtained was 71%.



Entry	Dienophile	Time	Yield	d.r. at Furanyl
1	B1	1 h	31%	n.d.
2	B1	90 m	43%	n.d.
3	B2	90 m	71%	N/A
4	B1*	90 m	60%	n.d.
5	B1**	90 m	81%	2.5:1
6	B1 (2.5eq)	90 m	80%	2.5:1

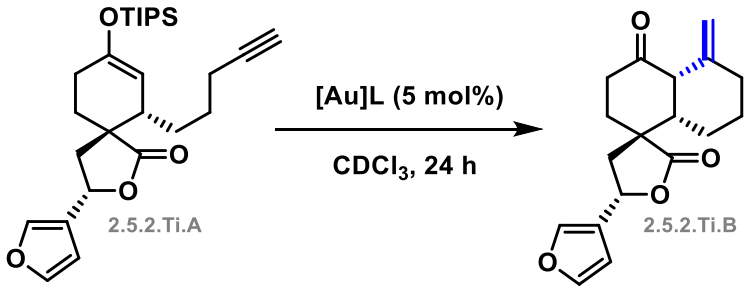
Table 2.5.1.Ti: Screening for the Diels-Alder cycloaddition of the winning route.

* indicates the diene was prepared the night before and stored in the freezer overnight.

** indicates the diene was prepared on the same day of the Diels-Alder reaction.

An NMR of the diene was taken, and no apparent degradation was observed. At this point, the improvement to 43% in entry **2** seemed sufficient to carry forward to the gold-catalyzed carbocyclization, but in the batch-up process, an unintended and important observation was noted: with a more freshly batched diene as used in entry **4**, the reaction yield increased to 60%. Surprisingly, it seemed the stability of the diene waned over time before the point by which it could be noticed in an NMR spectrum. Following this, entry **5** was carried out, in which the diene was prepared and purified on the same day that the Diels-Alder reaction was performed, showing a vast improvement to 81% yield, nearly doubling the yield from entry **2**. Additionally, as the yield was now desirable, the d.r. for entry **5** was recorded via crude ^{1}H NMR as 2.50:1, which was also an improvement over the previous entries. An additional modification that could be attempted to further increase the yield of the reaction would be to increase the equivalents of the dienophile; however, the preparation of this reagent is relatively costly, and so increasing the addition past 2 equivalents would be wasteful. Entry **6** was attempted with 2.5 equivalents of the diene rather than 2.0 equivalents, and no improvement of the reaction yield was observed. Additionally, reactions using DCE and THF as solvents were attempted with the conditions of entry **5**, but no formation of the desired product was observed, demonstrating DCM as the solvent of choice. With this, the final conditions were determined for this transformation as in entry **5**, and the route was pushed forward.

2.5.2 The winning *6-exo-dig* route – gold-catalyzed carbocyclization



Entry	Catalyst (5 mol%)	Temperature	Yield (%)
1	JohnPhosAu	r.t.	0
2	VPhosAu	r.t.	0
3	IPrAu	r.t.	trace
4	RuPhosAu	r.t.	trace
5	BPAu	r.t.	~10-20
6	BPAu	60°C	**58**

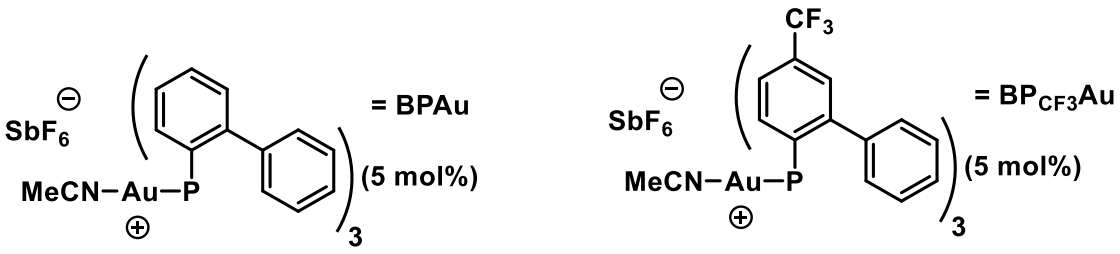
Table 2.5.2.Ti: Initial screening of the gold-catalyzed carbocyclization.

To begin investigations into the gold-catalyzed carbocyclization, a catalyst screening in $CDCl_3$ was performed (entries **1** to **4**). If no isomerization occurs, the desired product was anticipated to be easily identifiable by the two peaks of the *exo*-methylene moiety, expected to be found around 4.5-5.0 ppm. At room temperature in an overnight reaction, there was very little conversion. The use of IPr and RuPhos

ligands resulted in trace amounts of a product seemingly containing *exo*-methylene peaks, while the other complexes bore no conversion at all. The identity of the major product was not yet fully characterized due to its trace quantities, and before repeating the experiment at a higher temperature, a new bulky gold-complex developed in-house by Karim Muratov in the Gagosz group was suggested as a candidate for this transformation. A small portion was donated for testing (entry **5**).

To our surprise, the conversion shown by the BPAu catalyst was much greater than other entries, with a product yield hovering around 10-20%. Entry **6** was then conducted running the reaction at 60°C overnight, leading to an isolated yield of 58%. Surprisingly, the best complex thus far for this reaction was not a commercially available ligand, rather this novel catalyst that was developed in-house.

2.6.1 Gold rush – synthesis of the gold catalysts



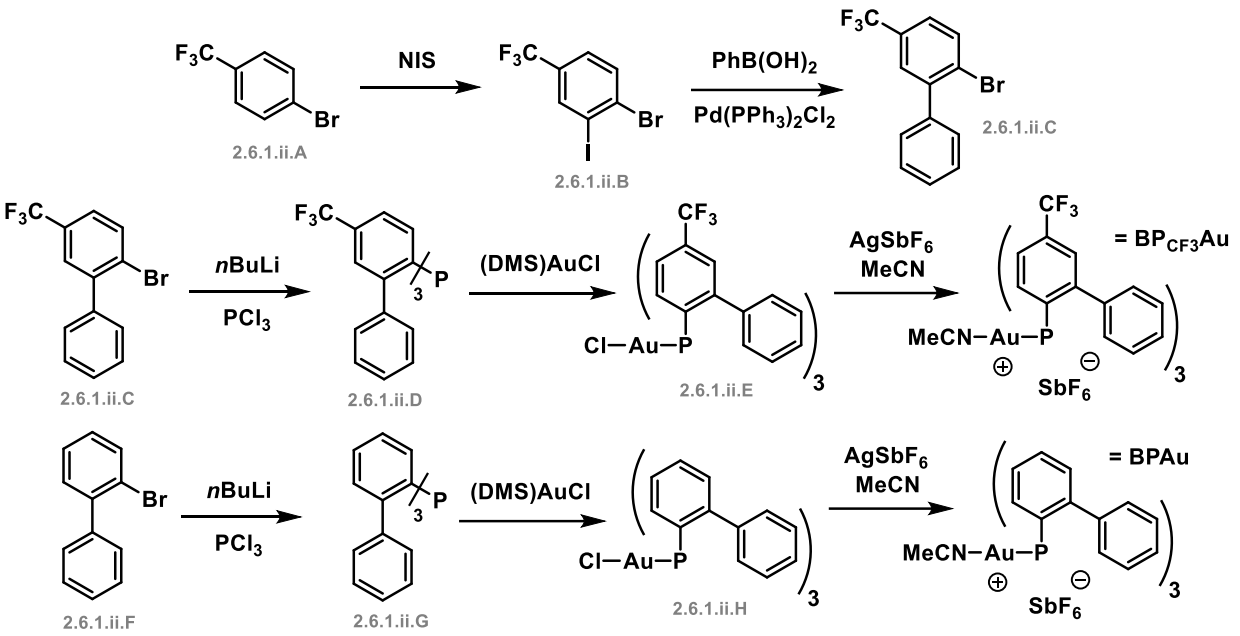
Scheme 2.6.1.i: Structures of the BPAu and $BP_{CF3}Au$ catalysts, as developed by Karim.

The proposed explanation for the success of BPAu (**Scheme 2.6.1.**i) is that the ligand takes up the steric space necessary for the long alkyl chain to be positioned in proximity to the silyl enol ether nucleophile to facilitate the carbocyclization. Otherwise, the conformational strain necessary for the *6-exo-dig* is

unfavorable, even with other complexes used. Karim had additionally prepared a version of this catalyst containing a CF_3 group on the *para* position of each biphenyl (named BP_{CF3}) rendering the ligand more electron withdrawing, thus pulling electron density from the gold, and activating the alkyne more strongly.

The BP and BP_{CF3} ligands are easily accessible (**Scheme 2.6.1.ii**). Bromo-biphenyl **2.6.1.ii.F** is commercially available, and the CF_3-containing bromo-biphenyl **2.6.1.ii.C** can be quickly synthesized in two steps: electrophilic iodine *ortho*-addition on CF_3-bromo-benzene **2.6.1.ii.A** with NIS, followed by Suzuki coupling with phenylboronic acid to install the phenyl group. The iodine addition did not require purification, and was easily performed at scale, of which the highest scale performed was 2g-scale.

From these two substrates, a lithium-halogen exchange and triple-addition onto PCl_3 was performed to yield the BP ligand and BP_{CF3} phosphate ligands **2.6.1.ii.D** and **2.6.1.ii.G**, followed by a complexation onto (DMS)AuCl to form the gold complexes **2.6.1.ii.E** and **2.6.1.ii.H**. Finally, an overnight counterion exchange with $AgSbF_6$ was performed, and after celite filtration to remove silver particle contaminants, the final bench-stable gold catalysts were yielded with a SbF_6 counterion. Overall, BPAu was prepared over 3 steps, and BP_{CF3}Au over 5 steps.



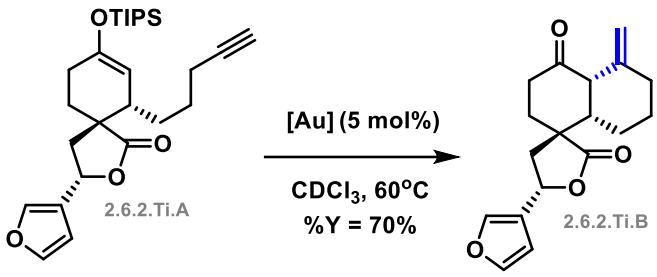
Scheme 2.6.1.ii: Synthesis routes for BPAu and $BP_{CF3}Au$.

2.6.2 Gold rush – testing the gold catalyst

It became clear that the gold-catalyzed carbocyclization needed to be run at a higher temperature for it to proceed. The following experiments in **Table 2.6.2.i** were carried out by Karim at 60°C in $CDCl_3$, monitored by ^1H NMR at the 6-hour and 24-hour timepoints, and the conversion and yield for each entry were recorded. JohnPhos, XPhos, IPr, and BP_{CF3} were the ligands screened. In all cases, a higher conversion translated to a higher yield, and after the full 24 hours, the conversion had plateaued to the final reaction results.

Entries **1** and **2** involving JohnPhosAu and XPhosAu showed very similar results, consisting of a poor 30-31% yield, despite 63-66% conversion. In entry **3**, IPrAu, which had shown trace amounts of product at room temperature in the

previous experiment (**Table 2.5.2.i**, entry **3**), demonstrated the highest yield of 42% in Entry **3.2**, but still notably less than BPAu which had a yield of 58%.



Entry	Catalyst (5 mol%)	Time	Conversion (%)	Yield (%)
1.1	JohnPhosAu	6 h	48	20
1.2	JohnPhosAu	24 h	63	30
2.1	XPhosAu	6 h	34	26
2.2	XPhosAu	24 h	66	31
3.1	IPrAu	6 h	56	30
3.2	IPrAu	24 h	73	42
4.1	$BP_{CF3}Au$	6 h	51	47
4.2	$BP_{CF3}Au$	24 h	**91**	**70**

Table 2.6.2.Ti: Karim's NMR-monitored gold catalyst screening.

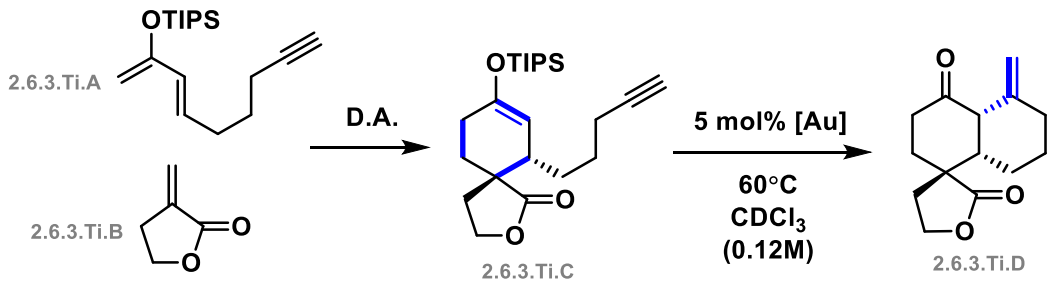
Finally, in entry **4**, the new catalyst $BP_{CF3}Au$ demonstrated a vastly improved conversion and yield. After 24 hours with entry **4.2**, 91% conversion was observed

with a final yield of 70%. It is evident that the electron withdrawing CF_3 group on the ligand positively impacts the yield of the carbocyclization through more strongly activating the alkyne upon gold complexation. Karim had been developing these gold complexes to perform difficult cyclizations like 6-carbon cyclizations and up, the logic being that the steric space the bulky ligand takes up leads to a restricted reactive space, similar to the concept of a biological enzyme's catalytic pocket. These findings support this hypothesis. It became clear that the BP-type catalyst worked best for this specific reaction, but following this finding, the question remained as to the catalyst's utility for similar transformations of other substrates.

2.6.3 Gold rush – determining scope

If the catalyst is broadly more effective than commercial gold complexes for *6-exo-dig* carbocyclizations, then this finding has incredible potential in organic synthesis. If the combination of this synthesis route's particular substrate is one of the few cases in which this catalyst happens to be more efficient, then it remains a useful finding only for this project. This may also offer indications to what route and structural components must be chosen to maximize the yield of the total synthesis. To begin, as in **Table 2.6.3.Ti**, the Diels-Alder adduct **2.6.3.Ti.C** was prepared for a catalyst screening monitored by NMR between the two highest yielding catalysts (IPrAu and $BP_{CF3}Au$). This was done in order to test the effectiveness of the gold complex on a less bulky substrate and examine if the steric contribution of the furanyl group is necessary for a high yielding carbocyclization. Similarly, the product formation is identified by the two distinct *exo*-methylene peaks that appear at 4.93 and 4.69 ppm, and disappearance of starting material by its distinct silyl enol ether

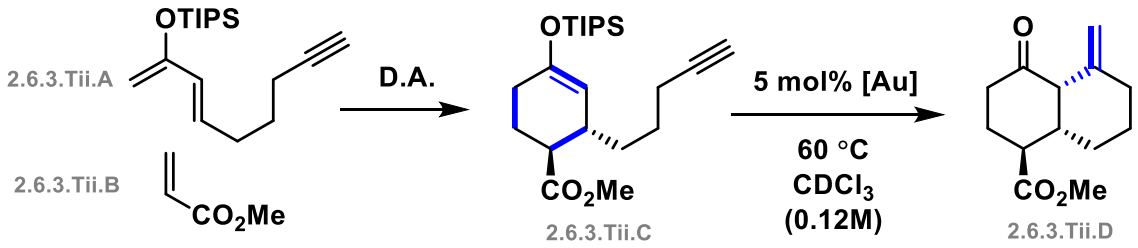
doublet peak at 4.89 ppm, though the products were never fully characterized. As seen in entry **1.2**, $BP_{CF3}Au$ only resulted in a yield of 35% in the same conditions as compared to the original 70% (**Table 2.6.2.Ti**), which is only a marginal improvement over entry **2.2** with IPrAu with a yield of 30%, which decreased from a previous 42%. Surprisingly, the mere exclusion of the furanyl group halved the yield of the reaction. This served as evidence that the steric space the furanyl group takes up is essential to position the gold complex, the alkyne chain, and the silyl enol ether to enable the carbocyclization to occur. The implication is that it is not a viable option to install the furanyl at the end of the synthesis to prevent potential furanyl reactivity issues later in the synthesis, as the furanyl is necessary for the gold-catalyzed carbocyclization.



Entry	Catalyst (5 mol%)	Time	Conversion (%)	Yield (%)
1.1	$BP_{CF3}Au$	6 h	45	25
1.2	$BP_{CF3}Au$	24 h	68	35
2.1	IPrAu	6 h	45	23
2.2	IPrAu	24 h	59	30

Table 2.6.3.Ti: Karim's NMR-monitored gold catalyst screening, furanyl-less substrate.

To further investigate the impact of the substrate complexity on the reaction success in **Table 2.6.3.Tii**, the simple Diels-Alder adduct **2.6.3.Tii.C** was readily prepared through the cycloaddition of diene **2.6.3.Tii.A** and methyl acrylate. The resulting substrate has the least amount of steric influence possible from the portion of the molecule that is seemingly contributing to the reaction success. Likewise, the product formation was identified by the two distinct *exo*-methylene peaks that appear at 4.96 and 4.72 ppm, and disappearance of starting material by its distinct silyl enol ether doublet peak at 4.93 ppm, though again, the products were never fully characterized. Continuing the same trend, the yield decreased to 20% for both catalysts as seen in entries **1.2** and **2.2**. In the end, the reaction outcome was virtually indistinguishable between $BP_{CF3}Au$ and IPrAu, and in conclusion, the positive outcome of $BP_{CF3}Au$ is specific to this route's substrate.



Entry	Catalyst (5 mol%)	Time	Conversion (%)	Yield (%)
1.1	$BP_{CF3}Au$	6 h	44	19
1.2	$BP_{CF3}Au$	24 h	63	20
2.1	IPrAu	6 h	43	19
2.2	IPrAu	24 h	49	20

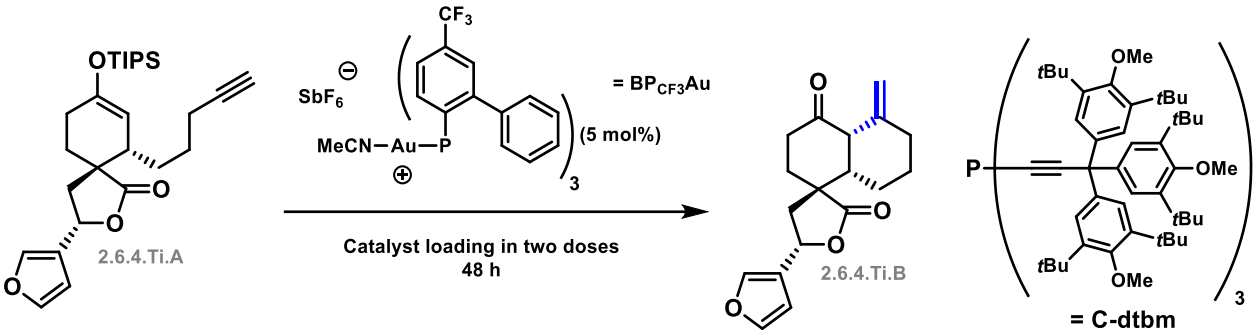
Table 2.6.3.Tii: Karim's NMR-monitored screening, spirolactone-less substrate.

2.6.4 Gold rush – scaling up the carbocyclization

Up to this point, the successful carbocyclization had been carried out only at very small scales (20 mg) with a maximum yield of 70% of the desired product, and only performed in $CDCl_3$. For a total synthesis, the reaction must be scaled up, and additionally, an alternative solvent to $CDCl_3$ must be found, as scaling up with this deuterated solvent would be unnecessarily expensive. Further, it is understandable that as the *6-exo-dig* transformation is already slow, reaction completion may require longer reaction times at larger scales. After some preliminary trials, it was determined that the addition of 5 mol% of catalyst loading in two portions gave the best results: after an overnight reaction with 2.5 mol% of catalyst, a second portion of 2.5 mol% was added and stirred for another overnight period. The investigations proceeded as shown in **Table 2.6.4.Ti**.

The main issue with scaling up with $CHCl_3$ instead of $CDCl_3$ is that chloroform is normally available commercially with ethanol as a stabilizer, which could evidently impact the gold complex and the reaction. If this is the case, an alternative solvent must be found. Additionally, having to run the reaction at 60°C now excludes common solvents like DCM and acetone that are normally used for these gold-catalyzed carbocyclization reactions. For an initial screening, ethanol-stabilized chloroform, DCE, and PhCl were compared to determine their effectiveness at carrying out the reaction (entries **1-3**). As predicted, the presence of ethanol in the reaction mixture leads to a complete degradation of the reagents, without any formation of the desired product (entry **1**). With DCE, an unidentified product was the

major product of the reaction, and the desired *6-exo-dig* product was obtained as the minor product in 30% yield (entry **2**).



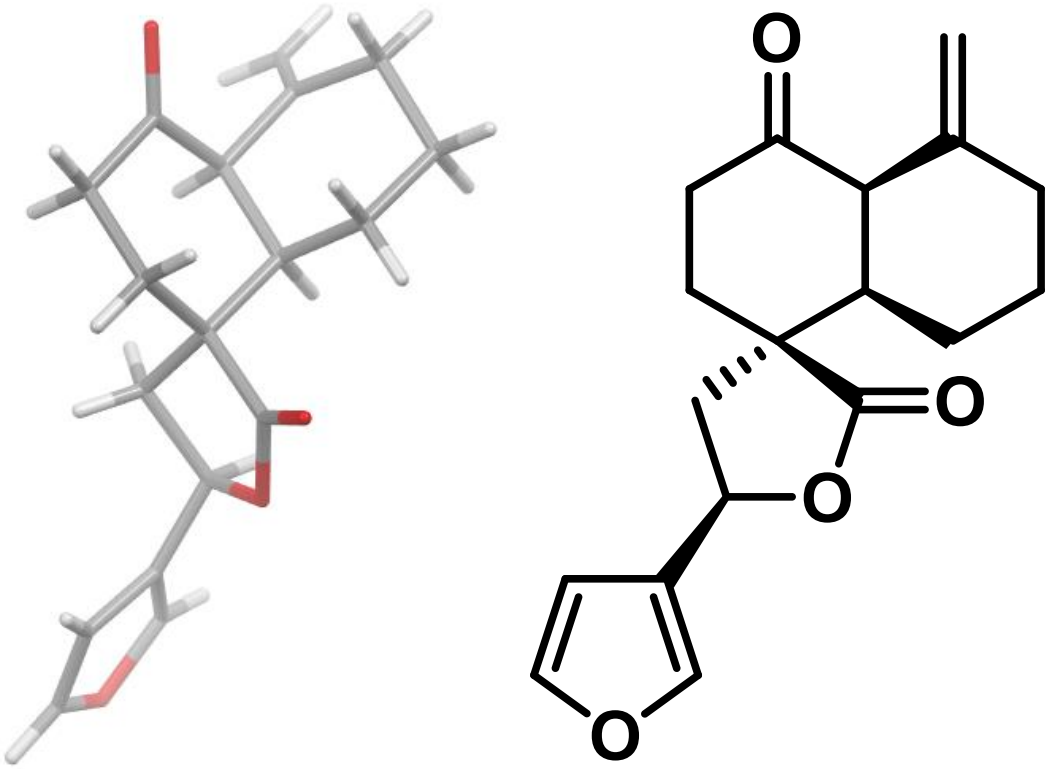
Entry	Catalyst (5 mol%)	Temperature	Solvent	Yield (%)
1	$BP_{CF3}Au$	60°C	$CHCl_3$ (ethanol)	0
2	$BP_{CF3}Au$	60°C	DCE	~30
3	$BP_{CF3}Au$	110°C	PhCl	46
4	$BP_{CF3}Au$	60°C	$CHCl_3$ (amylene)	**70**
5	C-btmsAu	60°C	$CHCl_3$ (amylene)	~20*

Table 2.6.4.Ti: Solvent screening for the scale-up of the gold-catalyzed carbocyclization.

In the case of PhCl, the reaction was carried out at higher temperature leading to side products forming, with an isolated yield of 46%. Performing the reaction using commercially available chloroform stabilized with amylene instead of ethanol gave the desired product with 70% yield (entry **4**). This reaction was performed at 600 mg at the largest, limited by the amount of substrate available at one given time, but the reaction could feasibly be carried out at a multi-gram scale.

Finally, as shown in entry **5**, the gold(I)-cyclization using bulky catalyst C-btmsAu[46] led to the formation of around 20% of the product overnight, as observed by TLC analysis; however, further reaction time led to degradation of the product, indicating that the instability of this large gold complex cannot withstand the long reaction times and high reaction temperatures required for this transformation. In the end, the key intermediate is achieved in 4 steps and a total yield of 32%.

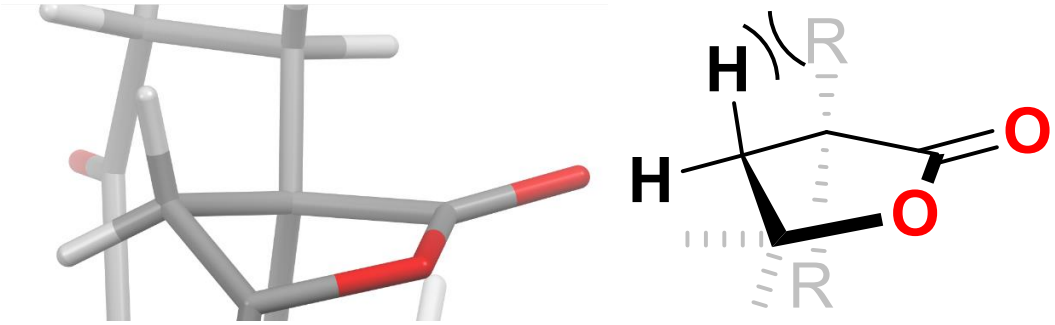
2.6.5 Gold Rush – examining the crystal structure of the key intermediate



Scheme 2.6.5.i: Crystal structure of the key intermediate carbocyclization product.

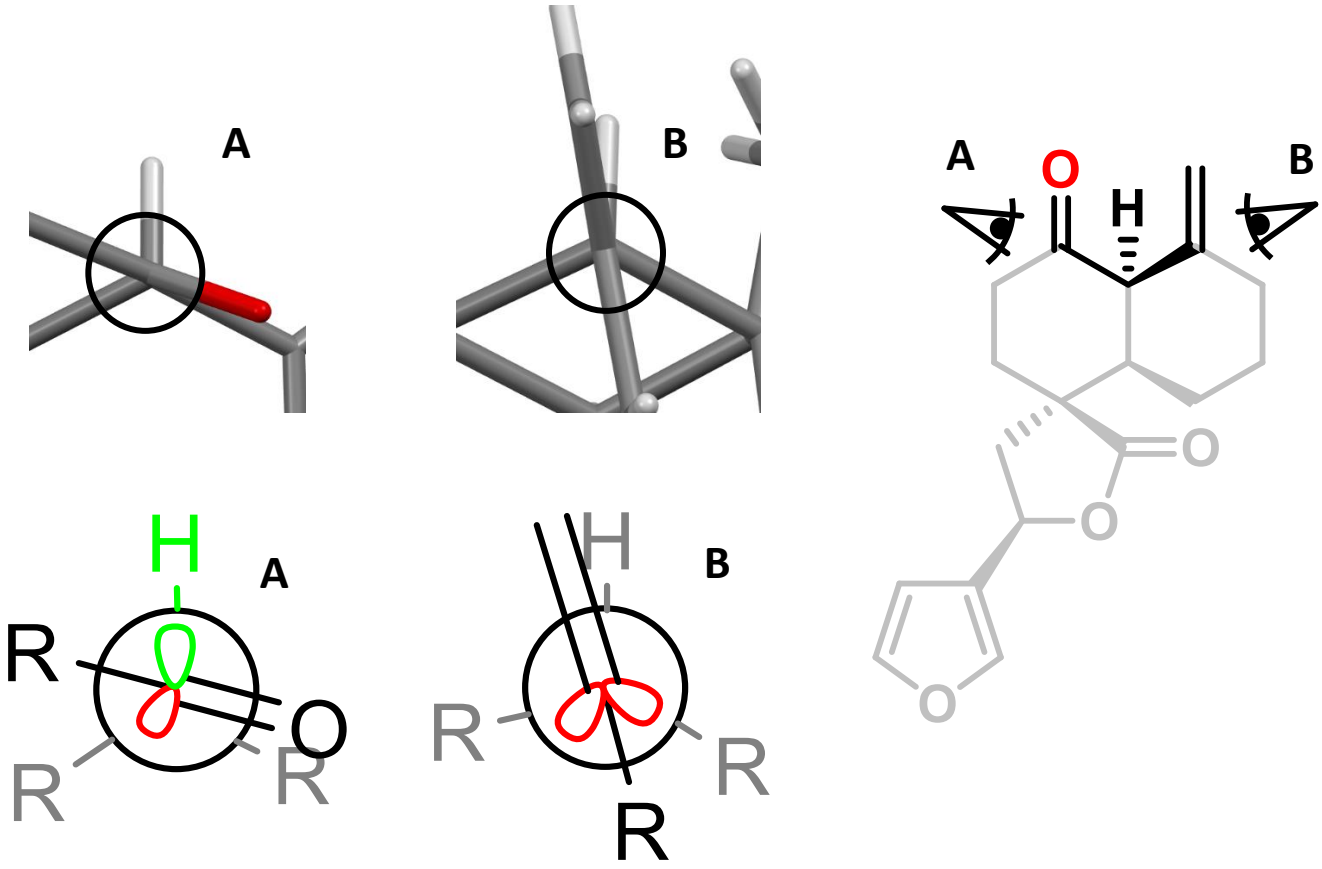
With the dual key step of the synthesis route established, the structure of the major diastereomer was confirmed (the opposite enantiomer as drawn up to this point), and was analyzed through X-ray crystallography (**Scheme 2.6.5.i**). Interesting

structural properties can be observed from the crystal structure that can advise us on route strategies and reaction decisions going forward. In **Scheme 2.6.5.ii**, it can be seen that the CH_2 protons on the spirolactone take up more steric space on the structure as compared to carbonyl oxygen. This gives credence to the hypothesis that a 1,4-addition of methyl at the position next to the spirocenter would occur on the desired side of the molecule.



Scheme 2.6.5.ii: CH_2 lactone protons take up more steric space than carbonyl.

In **Scheme 2.6.5.iii**, the *exo*-methylene is not in orbital alignment with the α-proton and carbonyl, implying that the *exo*-methylene is notably stable and resistant to isomerization to the α,β-unsaturated ketone. This should give more leniency when it comes to performing transformations in the end game of the synthesis without fear of unintentionally isomerizing the exo-methylene. This was further corroborated in future investigations, where potentially unstable intermediates (ie. Epoxides) did not spontaneously collapse but were able to be purified and handled readily. The Newman projections depict the angles surrounding the CH-carbonyl bond and the CH-*exo*-methylene bond. Antibonding orbitals that do not overlap are displayed in red, while the antibonding orbital that overlaps with the proton is depicted in green.

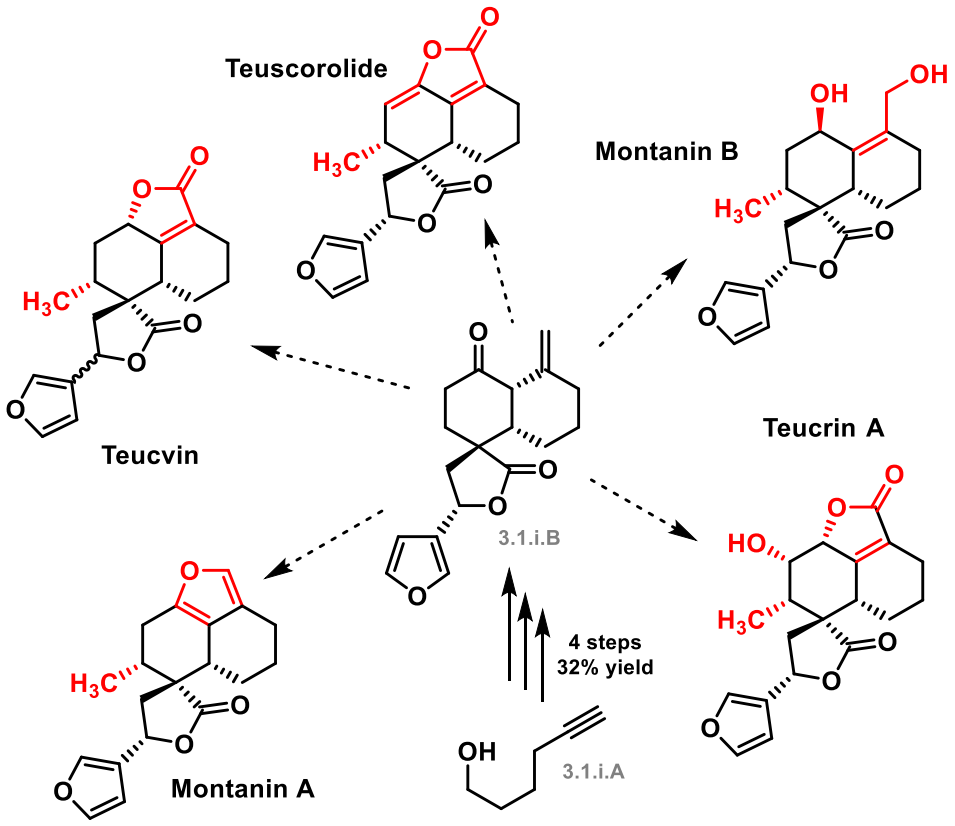


Scheme 2.6.5.iii: Newman projections indicating orbital overlap (green) of the α-proton to carbonyl antibonding orbital (A), but not to the *exo*-methylene antibonding orbital (B).

3. SYNTHESIS: ENDGAME PROGRESS

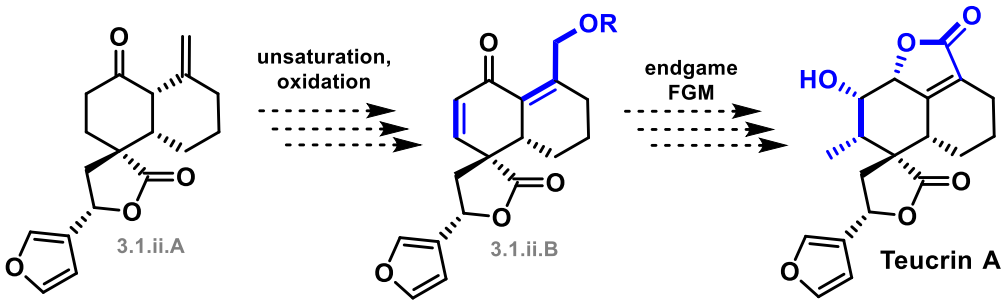
3.1 Divergent synthesis from the key intermediate

With the synthesis of the key intermediate in 4 steps and a total yield of 32%, including the correct setting of all stereocenters of the molecule core, the foundation has been set for the divergent synthesis of molecules in the neoclerodane furanoditerpenoid family. Analyzing the structure of select members of the family, the key differences are the installation of a methyl group on the decalin core α- to the spirolactone, and various oxidations on the upper face of the molecule. A route to each natural product could be feasibly envisioned.



Scheme 3.1.i: Prospective divergent scheme to several neoclerodane natural products.

Most of the functional handles are installed in the structure, however an important missing handle is required to install the methyl group. As previously discussed, a handle at this position, nor the methyl group itself could be present prior to the formation of the decalin core due to the inability for the Diels-Alder reaction to be carried out. In addition, further functionalization must be performed, namely the shifting of the *exo*-methylene and installation of an oxygenated group at the γ-position of the conjugated system. This may allow for a stable intermediate **3.1.ii.B** that can be used to diverge to some of the molecules in the natural product family. Not all the molecules in the natural product family will necessitate this second intermediate, but all selected natural products will require the installation of the methyl group through, most likely, a 1,4-addition to the α,β-unsaturation.



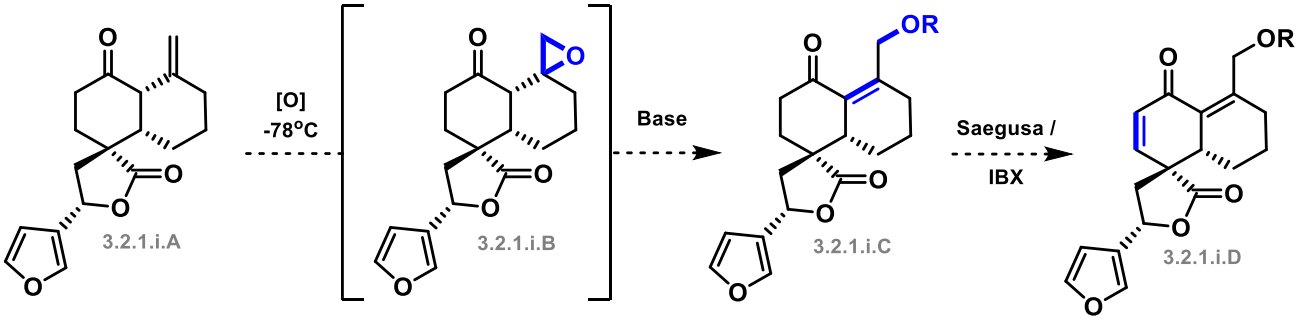
Scheme 3.1.ii: Proposed intermediate pathway of the divergent synthesis.

3.2.1 Oxidation investigation – initial plan

The oxidation route was first investigated over concerns about the isomerization of the *exo*-methylene to an α,β-unsaturated ketone. Additionally, full functionalization at this position could aid in the later formation of the α,β-unsaturated ketone necessary for the installation of the methyl group, as there would

be no issue selecting between the two α-protons. For the 1,4-addition, while there would be two δ-positions as seen in **3.2.1.i.D**, the desired alkene is disubstituted while the undesired alkene is tetrasubstituted, rendering the favourability very clear.

The proposed route as in **Scheme 3.2.1.i** to the second intermediate involves three distinct transformations: first, the epoxidation of the *exo*-methylene to form the epoxide **3.2.1.i.B**, that is then opened with a base which will afford **3.2.1.i.C** containing the α,β-unsaturation as well as the oxidation at the γ-position, then finally formation of the α,β-unsaturated ketone **3.2.1.i.D** through either a Saegusa oxidation or comparable method such as IBX oxidation.



Scheme 3.2.1.i: Proposed approach for the initial investigations into the oxidation route.

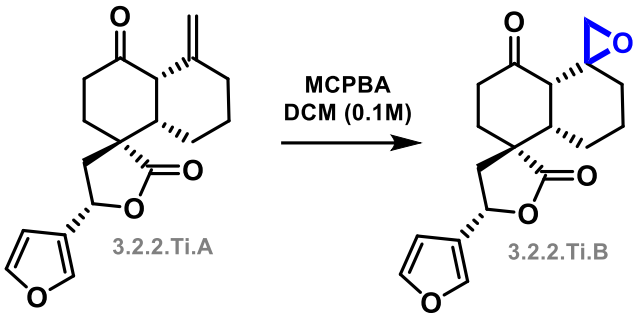
3.2.2 Oxidation investigation – epoxidation

The key concern for the oxidation route would be the conditions for the epoxidation step, that if too harsh may oxidize the furanyl group. The proposed solution to this problem would be to run the epoxidation at a low temperature to make preservation of the furanyl aromaticity more favoured than its oxidative transformation. Additionally, initial investigations are carried out with less than one equivalent of the oxidant to ensure that after epoxidation, no oxidation occurs on the

furanyl, and ideally, the final conditions must contain exactly 1.0 equivalent of the oxidant. A quenching reagent may also be added to neutralize any remaining oxidant, however if one equivalent of the oxidant is used, this may not be necessary.

MCPBA was chosen as the oxidant for this transformation[47], and to begin investigations, a screening of temperatures is carried out (**Table 3.2.2.Ti**). This screening must begin as low as reasonably possible to avoid overoxidation of the molecule. It is understood beforehand that certain of the screened conditions may lead to no conversion as the temperature would be too low, but this is part of the screening process. The initial conditions for the epoxidation as laid out in entry **1** consisted of 0.75 equivalents of MCPBA at -78°C. After running the reaction for 5 hours, no conversion occurs. Evidently, -78°C is too low of a temperature for MCPBA to react with any functional group on the molecule. In entry **2**, the reaction is run at -41°C with 0.75 equivalents of MCPBA, and again, after 5 hours, no conversion occurs. In entry **3**, no conversion occurs even in an excess of MCPBA at -78°C, as 1.5 equivalents are added to the reaction mixture. From this point, it is understood that at some unknown temperature above -41°C, a minimum temperature exists in which the reaction would proceed before oxidizing the furanyl. Instead of individually screening each imaginable convenient temperature to run the reaction at, which would be quite time consuming, the reaction in entry **4** was prepared with 1.5 equivalents of MCPBA at -78°C and run overnight in the dry ice bath. If the epoxidation is faster than oxidation of the furan ring, and one equivalent of MCPBA is used, as the reaction temperature would eventually warm up to room temperature, the epoxidation would proceed first, and all the MCPBA would have

been consumed, thus avoiding over-oxidation of the furan ring. Pleasingly, the desired product was obtained in 68% yield along with little over-oxidized product. The reaction was repeated with exactly 1.0 equivalent of MCPBA leading to a yield of 96%, with negligible side product or starting material observed (entry **5**). The quenching step was omitted as it was not necessary to reduce the excess of MCPBA.

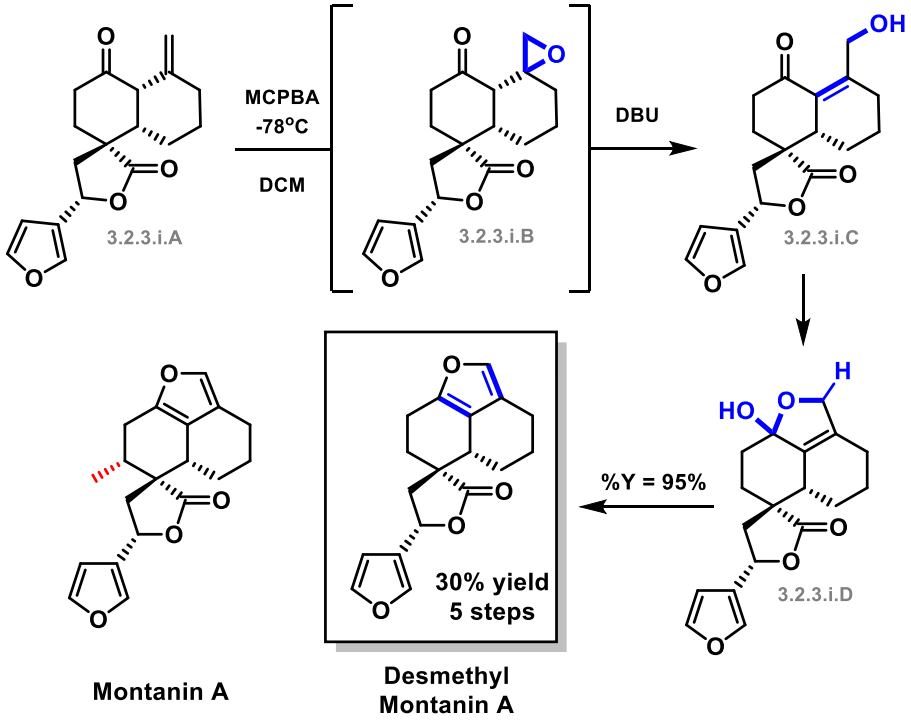


Entry	MCPBA Eq.	Time	Temperature	Quench	Yield (%)
1	0.75	5 h	-78°C	$Na_2S_2O_3$	0
2	0.75	5 h	-41°C	$Na_2S_2O_3$	0
3	1.5	5 h	-78°C	$Na_2S_2O_3$	0
4	1.5	o.n.	-78°C to r.t.	$Na_2S_2O_3$	68
5	1.0	o.n.	-78°C to r.t.	No quench	96

Table 3.2.2.Ti: Screening and optimization for the epoxidation step.

3.2.3 Oxidation investigation – epoxide opening, desmethyl montanin A

The opening of the epoxide with a base is a seemingly simple reaction, and in fact it occurred correctly. DBU was the base of choice, and upon addition to the epoxidation reaction mixture in one pot, nearly quantitatively deprotonated the α-proton, opening the epoxide. However, upon isolating the sole product of the reaction, the identity was unexpected, but in the end a blessing for the synthesis.

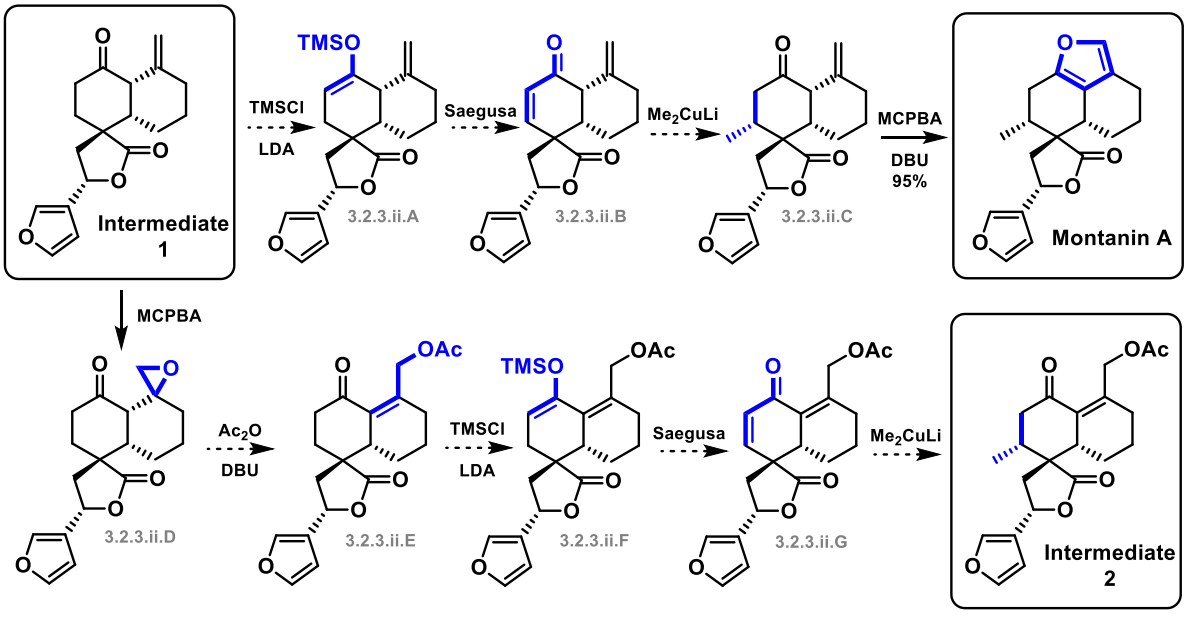


Scheme 3.2.3.i: Reaction scheme of epoxide opening to desmethyl montanin A.

As was predictably evident but overlooked, the freely opened hydroxyl **3.2.3.i.C** was not stable in this form. The hydroxyl added onto the ketone forming a 5-membered lactol **3.2.3.i.D**, then subsequently with the elimination of water, the system aromatized to the fused-furanyl. While this was initially seen as a setback for

the synthesis because the goal at this point was primarily to reach teucrin A through this strategy, upon a re-examination of the structure of the product and of other members of the neoclerodane furanoditerpenoid family, it was realized that desmethyl montanin A – an analog of montanin A missing its methyl group – was achieved in a 95% yield from the key intermediate. With this, the total synthesis of desmethyl montanin A was accomplished in 30% total yield over five steps.

To conclude the total synthesis of montanin A, a method to install the methyl group must occur before the formation of the fused-furan, as the handle for the 1,4-addition is only present with the α,β-unsaturated ketone. The order of the reactions was proposed to be: the formation of the α,β-unsaturated ketone, the methyl 1,4-addition, then the epoxidation and opening. The completion of this transformation is crucial as montanin A is a precursor to other natural products, but the acetylation of the hydroxyl upon epoxide opening was first investigated (**Scheme 3.2.3.ii**).

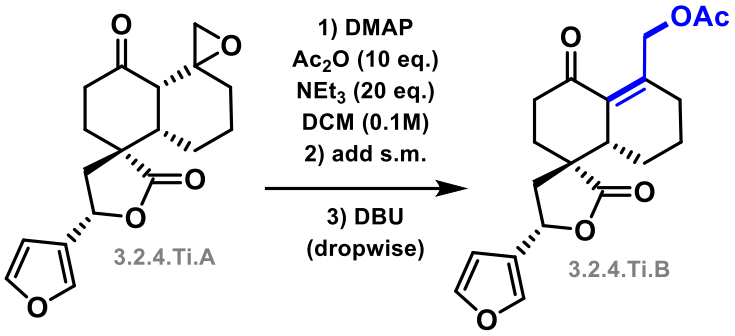


Scheme 3.2.3.ii: Prospective routes to the synthesis of montanin A and intermediate 2.

3.2.4 Oxidation investigation – Epoxide opening, acetylation

A method must be developed by which the epoxide can be opened and capped with an acetate prior to lactolization. The transformation's success depends on the competition between intramolecular lactol formation and intermolecular acetylation, where the equivalents of reagents will matter greatly. Investigations began by performing a DMAP-catalyzed acetylation[48], and specifically, determining how stable the epoxide was in the presence of the basic reaction. DBU effectively opened the epoxide in the previous reaction, however it remained uncertain whether or not DMAP or NEt_3 would be strong enough bases to open the epoxide.

As depicted in **Table 3.2.4.Ti**, beginning with entry **1**, the mixture of 1.0 equivalent of DMAP, 10 equivalents of Ac_2O, and 20 equivalents of NEt_3 in DCM was prepared prior to addition of the epoxide at -10°C. Upon addition of the epoxide and a running time over several hours, no conversion was observed. This confirmed that the basic mixture was not sufficient to open the epoxide at -10°C. Following this, the reaction was carried out at a slightly higher temperature of 0°C, and again, no conversion was observed (entry **2**). The reaction shown in entry **3** was carried out at room temperature and allowed to react overnight, and even so, no conversion was observed. At this point, it was safe to conclude no risk of epoxide opening prior to the addition of DBU. The reaction was then carried out by first preparing the activated acetylating reagent, then epoxide addition, then a dropwise addition of DBU followed (entry **4**). A 27% yield of the desired product was observed, indicating that the intermolecular acetylation can compete with the intramolecular lactol formation, even with only one equivalent of the DMAP-activated acetylation agent.



Entry	DMAP	DBU	Order	Temp.	Yield (%)
1	1.0	N/A	1,2	-10°C	0
2	1.0	N/A	1,2	0°C	0
3	1.0	N/A	1,2	r.t.	0
4	1.0	1.0	1,2,3	r.t.	25
5	3.0	1.0	1,2,3	r.t.	57
6	3.0	1.0	1,3,2	r.t.	0

Table 3.2.4.Ti: Screening for the epoxide opening and acetylation.

As only one equivalent of the activated acetylating agent was prepared, the following entry **5** involved tripling the equivalents to determine if an increase in yield could be attained, and indeed the yield improved to 57%. From then on, it was clear that an ever increasing equivalency of the DMAP would be necessary for the success of the reaction to favor the intermolecular acetylation over the intramolecular lactol formation. As shown in entry **6**, the order of addition was changed where the DMAP-catalyzed acetylating agent would be prepared, then

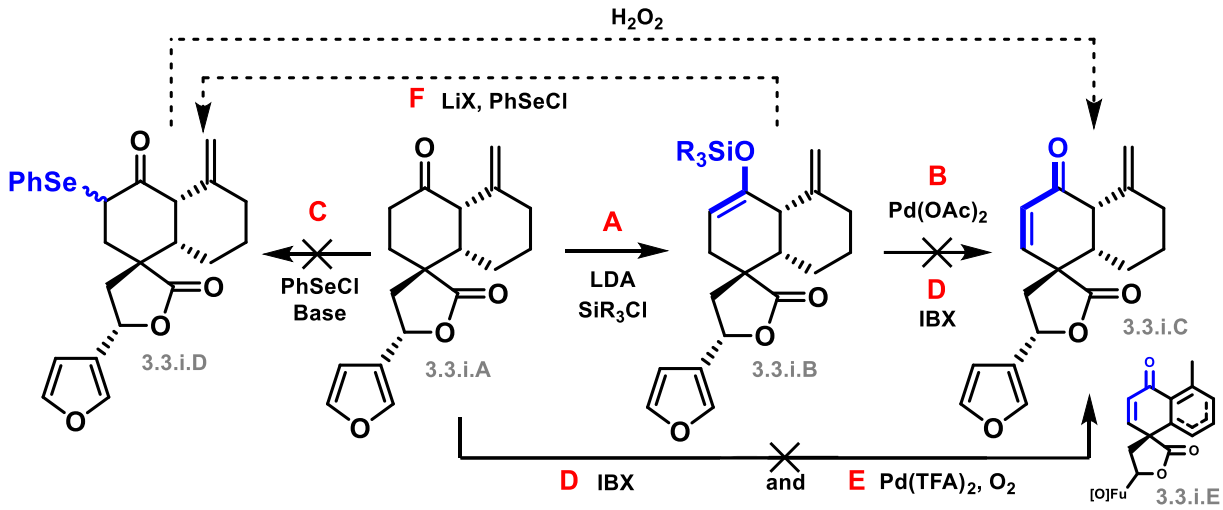
DBU added, then the epoxide added dropwise. In this way, instead of the ratio of the epoxide to the activated acetic anhydride being 1:3, it would be magnitudes higher – as one drop of the epoxide will be in the mixture with 3 equivalents of the acetylating agent – and the reaction should proceed vastly in favor of the acetylation. Sadly, in flipping the order of addition, no conversion occurred. For an unknown reason, the addition of the DBU to the Ac_2O and DMAP mixture rendered the DBU unable to deprotonate the α-proton, perhaps due to the DBU being acetylated, or that it complexes with the DMAP-catalyzed acetylating agent in some way. An additional portion of DBU added to the mixture following the addition of all the epoxide leads to product conversion; however, this defeats the purpose of the initial plan of inverting the order of addition to favor the acetylation. As such, this method is unsuccessful.

Moving forward, it seemed the solution would be to increase the equivalents of Ac_2O and DMAP to a point of heightened reaction yield while not being wasteful with reagents, though this has yet to be investigated further. At this point in the project, the focus was shifted to completing the synthesis of montanin A for it to be used as a precursor for the total syntheses of other natural products in the family. Namely, the methyl installation preceding oxidation needed to be established.

3.3 α,β-unsaturation of the key intermediate

The formation of an α,β-unsaturated ketone from a saturated ketone is, in theory, a very simple transformation. It commonly involves the Saegusa oxidation, a two-step process involving the formation of a silyl enol ether – which can be formed

selectively through kinetic or thermal control by the choice of base and temperature – and subsequent oxidation using $Pd(OAc)_2$[49].



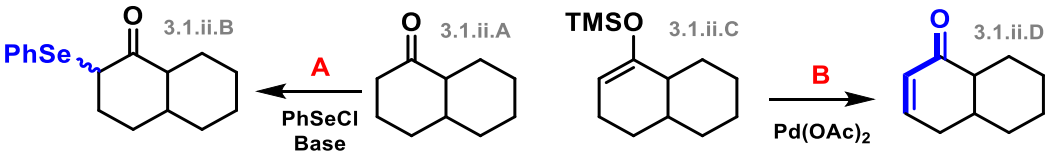
Scheme 3.3.i: Investigations into the α,β-unsaturation of the ketone.

As depicted in **Scheme 3.3.i** by step **A**, deprotonation of **3.3.i.A** using LDA at the least hindered position, then addition of TMS-chloride gave the corresponding silyl enol ether **3.3.i.B** (R = TMS) in 60% yield and was a generally stable intermediate. While not entirely optimized, a few other bases were screened, including LiHMDS which works, and KHMDS and NaHMDS which did not work. Using larger silyl agents such as TESCl and TIPSCl would result in more stable products, however the yields decreased. In general, it seems the silylating agent has difficulty entering the necessary steric space for the transformation. The following step **B** involves oxidation of the silyl enol ether to the α,β-unsaturated ketone with $Pd(OAc)_2$, but this transformation did not proceed. Several variations of the conditions were attempted, and even when heated, the extent of conversion observed was reversion of the silyl enol ether **3.3.i.B** back to the ketone **3.3.i.A**. In some cases, a small portion of the *exo*-methylene that isomerized to the α,β-

unsaturated ketone was observed, and in one instance, the product of TIPS-addition to the 2- and 5-positions of the furanyl was observed when 5.0 equivalents of TIPSCl were used. As such, the solution is not as simple as increasing the equivalents of the silyl reagent. In all cases, no α,β-unsaturation product **3.3.i.C** was observed. Likely, the quaternary center is too close to the reaction site.

Following, route **C** envisioned the installation of a selenide group at the α-position to yield **3.3.i.D**, which could be oxidized by H_2O_2 to the selenoxide and eliminated to afford the α,β-unsaturated ketone **3.3.i.C**[50]. With several modifications to the conditions, including raising the temperature up to 0°C anticipating some selenide addition on wrong α-position, it was never successfully installed. Either the starting material was entirely recovered, or some of the *exo*-methylene isomerized to the α,β-unsaturated ketone. Following, route **D** using IBX was attempted to directly install the α,β-unsaturation from the ketone, as well as to convert the silyl enol ether to the α,β-unsaturated ketone[51]; however, the reaction outcome was the oxidation of the furanyl, with the ketone remaining untouched, or the silyl ether hydrolyzed with some of the *exo*-methylene isomerized. Route **E**, involving $Pd(TFA)_2$ in an O_2 atmosphere, was the only reaction that led to the α,β-unsaturation of the ketone[52], but the conditions led to the overoxidation of the starting material presumably to a molecule like **3.3.i.E**. Namely, the α,β-unsaturated ketone was achieved, but the alkanes of the decalin core were oxidized to alkenes, the *exo*-methylene was entirely isomerized, and the furanyl group was also oxidized as observed through NMR analysis.

Another option would be to attempt route **F**, in which the silyl enol ether that was successfully formed performs a lithium exchange to afford the selenide addition at the α-position, but on top of being a 4-step transformation to simply add a methyl group, since the selenide addition still did not occur at 0°C, this transformation seems both inefficient and not feasible. In the end, all attempts to install this functionality were met with failures. Since none of these conditions worked, as in **Scheme 3.3.ii**, a simple model substrate **3.3.ii.A** – missing the spirolactone, *exo*-methylene, and furanyl – was used to determine if an operational inadequacy in reaction set-up prevented reaction success, or if it was indeed an issue with the substrate that prevented the reactions moving forward. If the reactions work not on the readily functionalizable model substrate, the reason must be operational errors, but if the reactions do work successfully with the model substrate, it can be concluded that the spirolactone and/or furanyl impede the reactions.



Scheme 3.3.ii: Investigations of the α,β-unsaturation using a model substrate. Products were observed by crude ^{1}H NMR and HRMS.

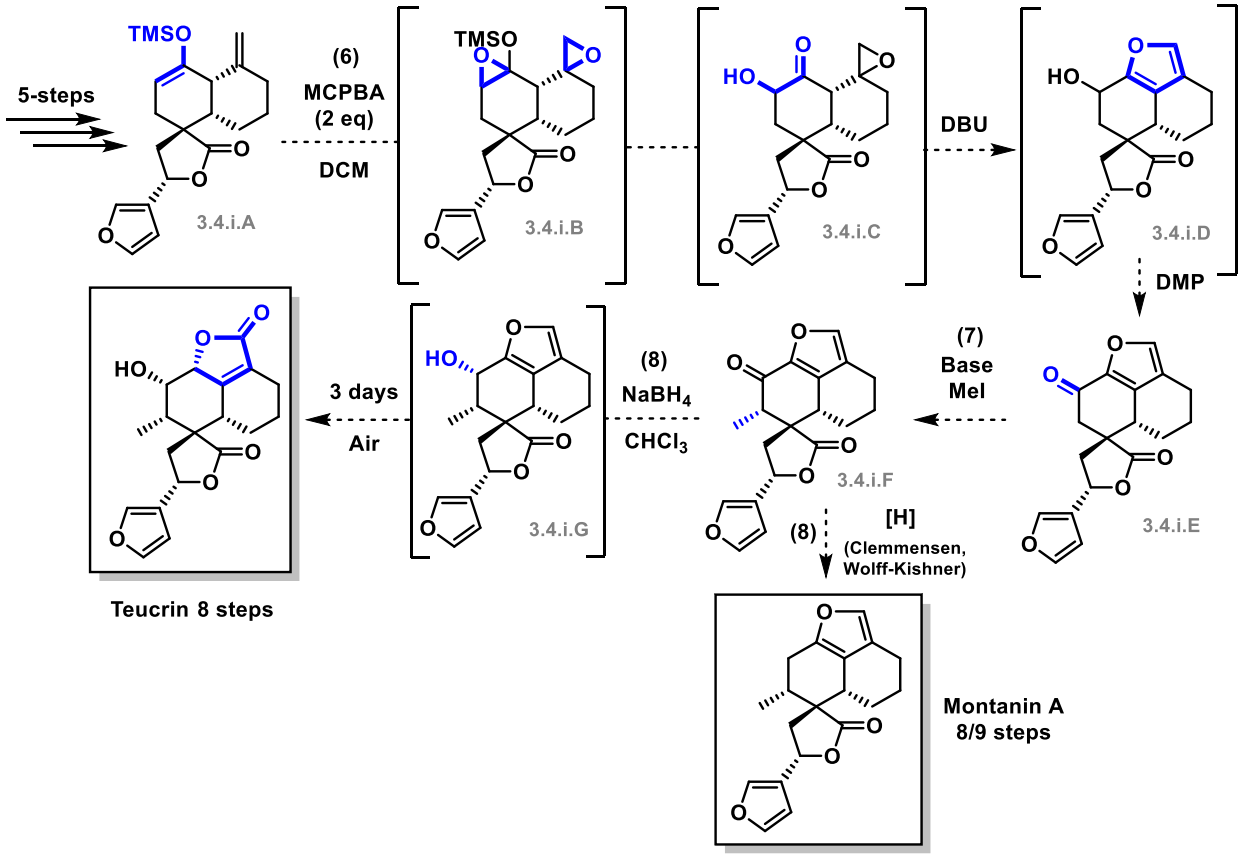
In both cases, the reactions proceeded successfully with the model substrate: the selenide was successfully added to the α-position of the ketone to yield **3.1.II.B** as in route **A**, and the silyl enol ether was transformed to the α,β-unsaturated ketone **3.1.II.D** as in route **B** upon the use of $Pd(OAc)_2$ as an oxidant. The selenide addition was confirmed by HRMS, and both products were observed by crude ^{1}H. Both these

reactions did not work on the synthesis substrate, leading to the conclusion that due to the presence of the spirolactone and/or furanyl, the functionalization necessary to perform the 1,4-addition of methyl is not possible. As previously determined, the Diels-Alder was deemed unable to proceed if a methyl group is present on the diene, and the gold-catalyzed carbocyclization was deemed unable to proceed if the spirolactone and furanyl moiety are not present, so as it stands, this approach was deemed not feasible.

3.4 Bis-epoxidation route for teucrin A and montanin A

The following proposed route, as depicted in **Scheme 3.4.i,** demonstrates a potential for a new strategy toward teucrin A and montanin A, employing a different approach to installing the problematic methyl group, *via* Rubottom Oxidation[53]. Similarly to before, the epoxidation and fused-furanyl formation step with DBU would be performed, however the starting intermediate would be the silyl enol ether **3.4.i.A**, and two equivalents of MCPBA would be used. As such, one can envisage that a bis-epoxidation of the *exo*-methylene and the silyl enol ether would yield the bis-epoxide **3.4.i.B**, and along the course of the overnight reaction, the OTMS group would collapse to open the unstable epoxide to form the α-hydroxyl ketone **3.4.i.C**. The hydroxyl stereochemistry should be a mixture, but this could be mediated in a later step. In the same reaction medium, DBU would be added to open the remaining epoxide to form the fused-furanyl **3.4.i.D**. Following this, the hydroxyl group could be oxidized to the ketone using DMP, yielding **3.4.i.E**, resolving the stereochemical mixture. If possible, this oxidation step could be performed one-pot. As there would be many reagents present in the reaction mixture, it would need to

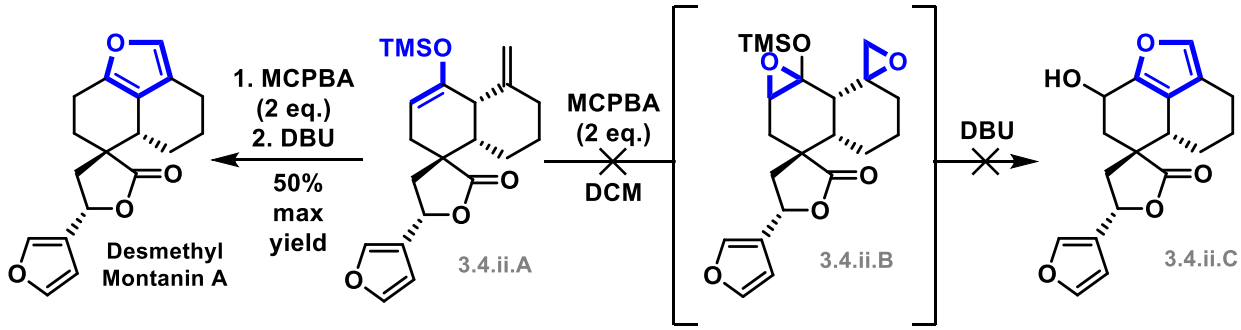
be determined whether the DMP could oxidize the hydroxyl to the ketone successfully in one-pot. Otherwise, a purification and separate step would be necessary.



Scheme 3.4.i: Proposed route for the synthesis of montanin A and teucrin A, notably through the bis-epoxidation of silyl enol ether starting intermediate.

The methyl group could then be installed through the enolate attack onto methyl iodide to yield **3.4.i.F**, by which the methyl group should be installed with the correct stereochemistry, as previously discussed (section **2.6.5**). From this point, to afford montanin A, either a Clemmensen reaction or Wolff-Kishner sequence could be performed to eliminate the ketone and yield montanin A in 8 or 9 steps respectively[54]. Concerns regarding the stability of the furanyl in the acidic conditions

of the Clemmensen reaction arise but should be investigated as a step could be saved over the Wolff-Kishner reduction. Alternatively, modifications to the Wolff-Kishner reaction that proceed in one step could be explored. To afford teucrin A, a reduction with $NaBH_4$ in chloroform could be performed to yield **3.4.i.G**, likely resulting in the correct stereochemistry of the hydroxyl group due to the methyl group blocking reduction from the bottom face. Finally, allowing the reaction mixture to continue stirring in the chloroform exposed to air would lead to the oxidation of the fused-furanyl to yield teucrin A in 8 steps, as seen from the work described in scheme **1.4.iii**.[25] This would prove to be a very efficient route, greatly improving the previous step-counts found in the literature. With this, investigations began into the initial bis-epoxidation step *via* Rubottom oxidation (**Scheme 3.4.ii**).



Scheme 3.4.ii: Unfruitful attempts to form the hydroxylated product through a bis-epoxidation *via* Rubottom oxidation. Desmethyl montanin A is the only relevant product.

As previously discussed in section **3.3**, the larger the silyl group (ie. TIPSCl, TESCl), the poorer the conversion. As such, TMSCl is used, and as with before, the highest yield achieved thus far was 60%. While **3.4.ii.A** would be the least stable

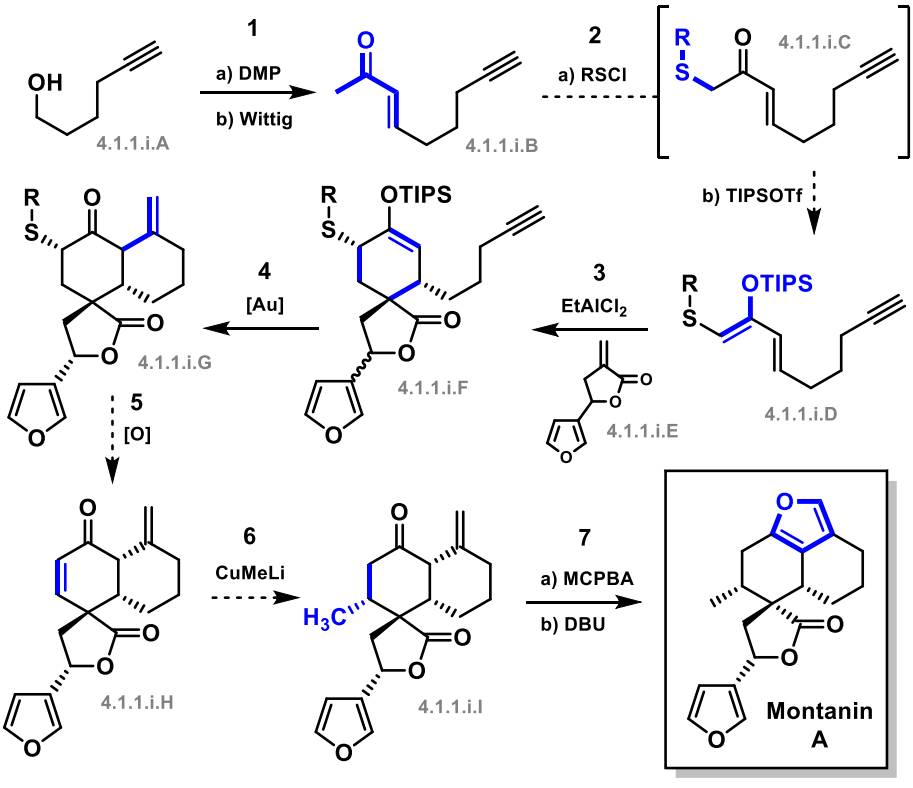
product formed, it has the highest yield and seems to be the only viable intermediate for this strategy. Optimizations of this step are to be explored in the future.

Regrettably, all attempts to accomplish this transformation were unfruitful. In every case, the hydroxylated product **3.4.ii.C** was not observed, indicating that the product **3.4.ii.B** with the epoxide on the silyl enol ether never formed. Theoretically, the silyl enol ether should be more reactive, and the epoxide should have formed there first. In reality, the second equivalent of MCPBA oxidized the furanyl group, and so the maximum yield for this method is effectively 50% for desmethyl montanin A, with the remainder being over-oxidized material. The initial thought was that the acid by-product of the MCPBA, or some acid present in the MCPBA, was de-silylating the starting material. As an attempted remedy, $NaHCO_3$ was added to the reaction mixture prior to the addition of MCPBA, but still, the epoxide did not form on the silyl enol ether. Either the insolubility of $NaHCO_3$ in DCM led to it not effectively quenching any acid during the process of the reaction, or the MCPBA simply is unable to enter the steric space to perform the epoxidation. A scope of organic bases could be explored as an alternative to $NaHCO_3$, as well as other epoxidation agents that could be used. Since the methodology with MCPBA was already established, and these future step ideas require a re-optimization of the epoxidation step, this new approach could not be attempted given time restraints. As such, this was the final venture of the project.

4. CONCLUSION

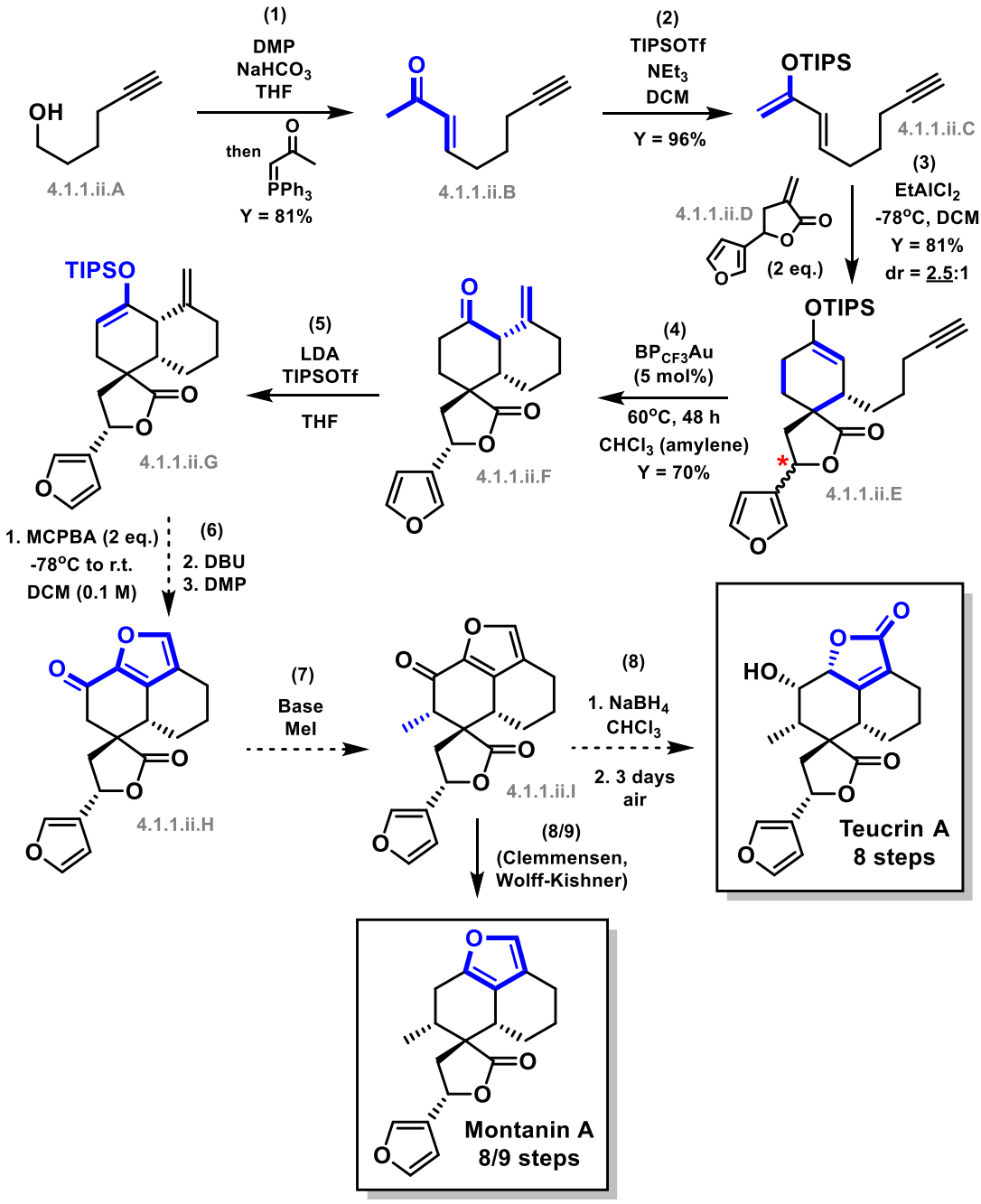
4.1.1 Future Steps – Methyl installation, montanin A and teucrin A

Since the Diels-Alder reaction only proceeded successfully without the presence of a methyl group on the dienophile, the gold-catalyzed carbocyclization only proceeded successfully in the presence of the spirolactone and furanyl, and the methyl installation strategies did not proceed with the spirolactone and furanyl present, our route is restricted moving forward with the necessary functionalizations. The following inclusion of sulfonium α-addition and sulfoxide elimination would not involve a step-count increase but would lead to a potentially successful methyl addition, albeit a likely less successful Diels-Alder (**Scheme 4.1.1.i**)[55].



Scheme 4.1.1.i: New proposed route for the total synthesis of montanin A

The first step would proceed as before, with the one-pot DMP oxidation and Wittig homologation to yield the *E*-α,β-unsaturated ketone **4.1.1.i.B**. For the following step, before the formation of the silyl enol ether to produce the diene, a sulfide would be installed at the α-position of the ketone **4.1.1.i.C**. In the same pot, the silyl enol ether **4.1.1.i.D** could be formed. The following Diels-Alder reaction may be impacted in terms of steric influence as there would be a new group on the bonding carbon of the diene, or electronics since the presence of the electronegative sulfur may impact the electron density of the diene. Additionally, a mixture of diastereomers of **4.1.1.i.F** with respect to the position of the sulfide would form. This ultimately matters not, as this group would be reduced and eliminated after the gold-catalyzed carbocyclization, and so the mixture of diastereomers could be carried through. The gold-catalyzed carbocyclization would proceed as before to yield the key intermediate **4.1.1.i.F**, and afterwards, the oxidation of the sulfide to the sulfone followed by its elimination with a base will form the α,β-unsaturated ketone **4.1.1.i.H**. A careful selection of base will be necessary here to ensure the isomerization of the *exo*-methylene does not occur; however, the proton at the β-position required to eliminate the sulfone should be sufficiently more acidic than the α-position involved in the *exo*-methylene isomerization. Following, this, the methyl addition with CuMeLi should proceed with a 1,4-addition on the carbonyl side of the spirolactone to yield **4.1.1.i.I** as previously discussed (section **2.6.5**) due to the greater steric space of the CH_2 protons on the spirolactone as compared to the carbonyl. Finally, the one-pot epoxidation and opening should proceed successfully as previously observed, leading to a 7-step synthesis of montanin A, the shortest yet.

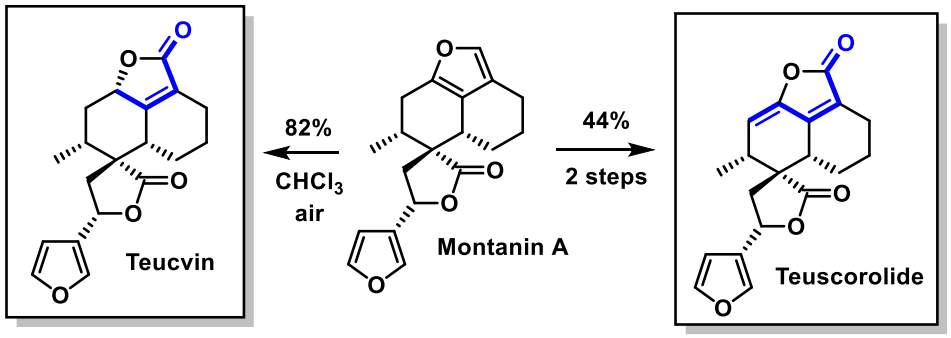


Scheme 4.1.1.ii: Proposed route for teucrin A and montanin A syntheses.

Additionally, as in **Scheme 4.1.1.ii**, the route investigated in section **3.4** could be further pursued, as it has the potential for a very succinct synthesis once the bis-epoxidation step is accomplished.

4.1.2 Future steps – Formal or total syntheses of teuscorolide and teucvin

As previously discussed, work out of the Liu group has demonstrated a 2-step transformation from montanin A to teuscorolide through the oxidation of the furanyl with PDC followed by elimination of water,[24] and montanin A has been shown by the same group to convert to teucvin in one step under open air conditions in $CHCl_3$.[25] As such, with the completed total synthesis of montanin A, a formal synthesis of these two other molecules in the divergent synthesis would be accomplished (**Scheme 4.1.2.i**). The oxidation step for teuscorolide has quite a poor yield of 45%, so ideally this could be improved upon, leading the potential of the shortest total synthesis of teuscorolide. From montanin A as a precursor, syntheses of other neoclerodane furanoditerpenoids like teucrin A can be envisioned (section **4.1.3**).

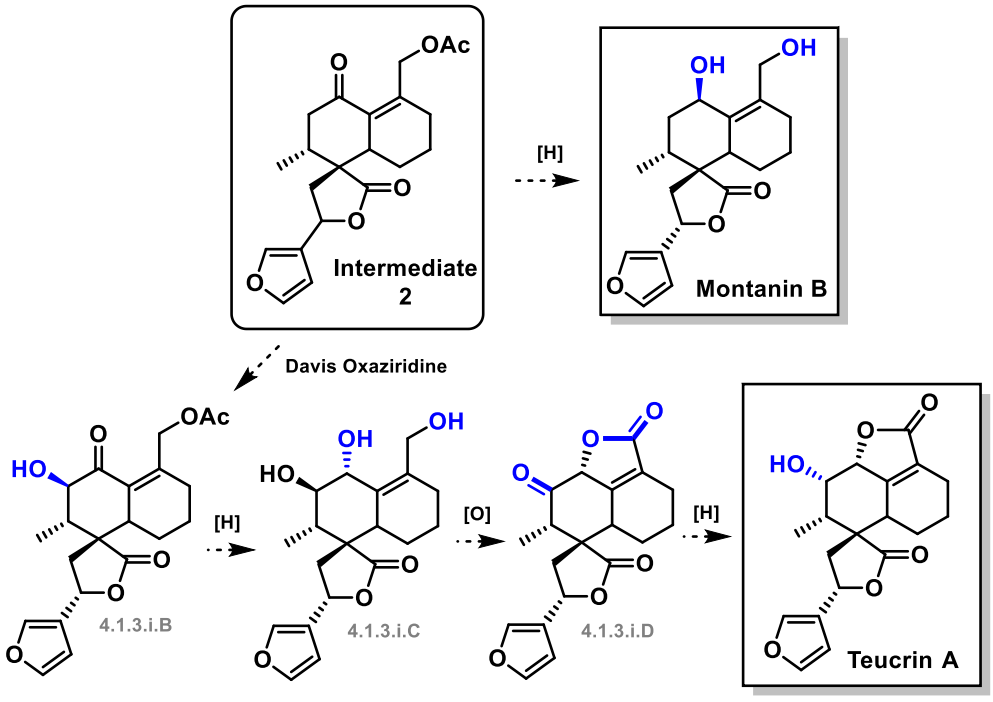


Scheme 4.1.2.i: Transformation from montanin A to teucvin and teuscorolide by Liu *et al*.

4.1.3 Future Steps – Syntheses of teucrin A and montanin B

Once the α,β-unsaturated ketone and 1,4-methyl addition steps are accomplished, Intermediate 2 will be synthesized in a total of 8 steps (**Scheme 4.1.3.i**). This intermediate contains the opened epoxide capped with an acetate group, and methyl group installed at the δ-position of the ketone, and can be used to

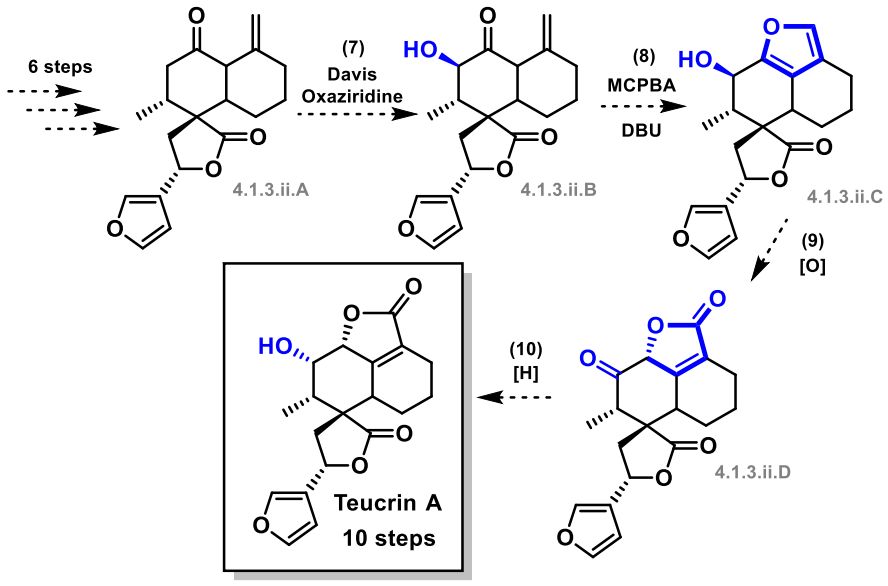
synthesize montanin B and teucrin A. For the 9-step total synthesis of montanin B, one additional step should be required, involving a reduction of the ketone to the hydroxyl and simultaneous reduction of the OAc group to the hydroxyl. Reduction conditions will need to be screened to ensure the correct stereoisomer is formed. Teucrin A initially requires an α-hydroxylation to **4.1.3.i.B** using a reagent such as Davis oxaziridine. While the stereochemistry of this hydroxyl would likely be incorrect due to the presence of the methyl group, the proceeding steps as follows would render the stereochemistry at this step irrelevant: directed reduction to yield **4.1.3.i.C** with the correct stereochemistry, followed by oxidation conditions to form the lactone and simultaneous hydroxyl oxidation to the ketone, and finally, the reduction of this ketone to the hydroxyl to yield teucrin A in 12 steps. In the final reduction step, the hydride will likely add *anti* to the methyl, resulting in the *syn*-hydroxyl as required.



Scheme 4.1.3.i: Divergent synthesis from intermediate 2 to montanin B and teucrin A.

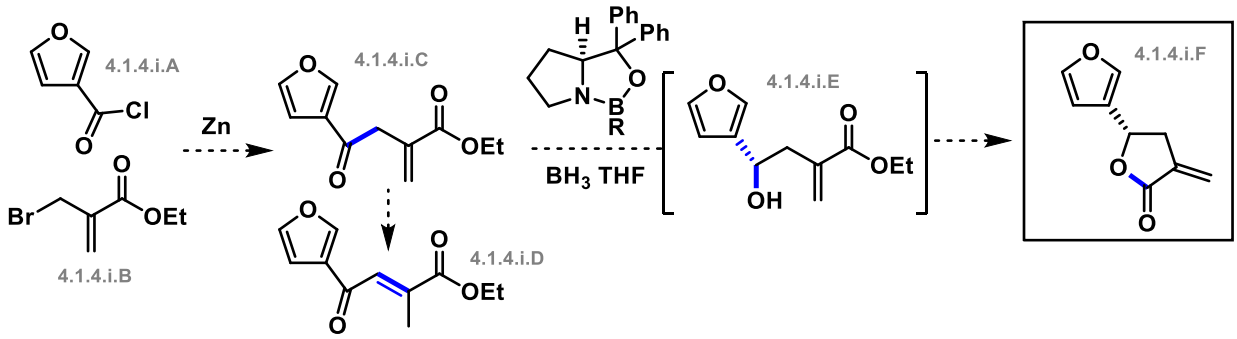
Four steps are necessary to achieve the complex core of the key intermediate, but eight additional steps from that point to finalize the synthesis of teucrin A, making this route quite step-heavy for a small number of seemingly simple functional group installations. Additionally, the final reduction-oxidation-reduction sequence is very inefficient.

A notable alternative can be inspired by the montanin A to teucvin oxidation with chloroform in air as depicted in **Scheme 4.1.2.i**: since teucvin and shares a similar structure to teucrin A, simply missing an α-hydroxyl that could be installed before the ketone and *exo*-methylene moieties are converted to the lactone, the synthesis could be shorted to ten steps instead of the twelve steps required when going through Intermediate 2. Even still, a shorter synthesis may be possible.



Scheme 4.1.3.ii: Alternative synthesis route to teucrin A.

4.1.4 Future steps – Enantiopure dienophile and enantioselective synthesis

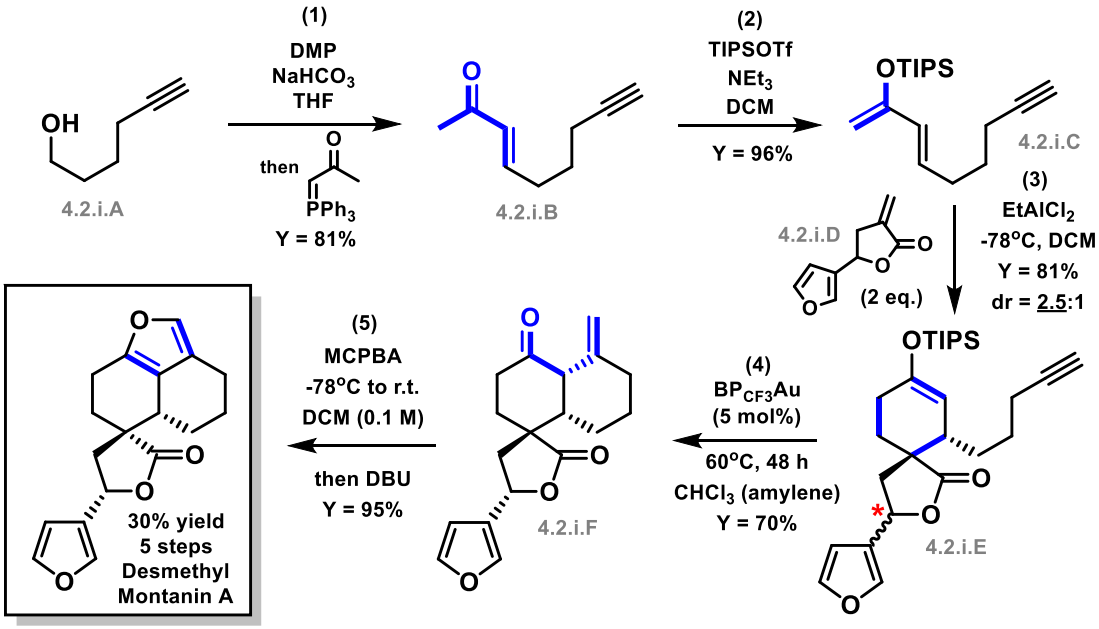


Scheme 4.1.4.i: Prospective route for the synthesis of an enantiopure dienophile.

To this point, the synthesis has been racemic because a racemic mixture of the dienophile was used. Rendering the dienophile enantiopure would lead the synthesis to be enantiospecific. Since the Diels-Alder reaction occurs on step 3, the dienophile synthesis needs to be a maximum of two steps long to not extend the length of the total synthesis. The dienophile has been synthesized in one step using the Reformatsky reaction from the Ley group that completes in two minutes in a sonicator, making it a very convenient transformation.[26] Using the same transformation (**Scheme 4.1.4.i**), a slight modification to the starting material from the furanocarbaldehyde to its acyl chloride analog **4.1.4.i.A** would lead to **4.1.4.i.C** by which a ketone rather than a hydroxyl is present, which previously would spontaneously lactonize. A stereo-controlled reduction of the ketone using conditions such as the Corey-Bakshi-Shibata reduction would form the correct hydroxyl stereoisomer, leading to lactonization of the desired enantiomer[56]. A major concern would be the highly favoured isomerization of the *exo*-methylene to the conjugated system between both the ketone and the ester. Care must be taken to ensure the work up, purification, and reduction step proceeds without isomerization.

4.2 Conclusion – In summary

A novel strategy has been developed for the divergent synthesis of the neoclerodane furanoditerpenoid natural product family, via a Diels-Alder / gold-catalyzed carbocyclization dual key step, producing a key decalin intermediate in 32% yield over four steps. The total synthesis of desmethyl montanin A was achieved in an additional step, with a 30% overall yield over five steps, and progress has been made into endgame functionalizations toward the synthesis of other molecules in the family. Future steps of the project will include re-arranging the synthesis to permit the methyl installation required to complete the montanin A total synthesis, finalizing the oxidation steps for each of the selected neoclerodane furanoditerpenoid total syntheses, and achieving enantiospecific syntheses through developing an enantiopure dienophile required for the Diels-Alder cycloaddition.



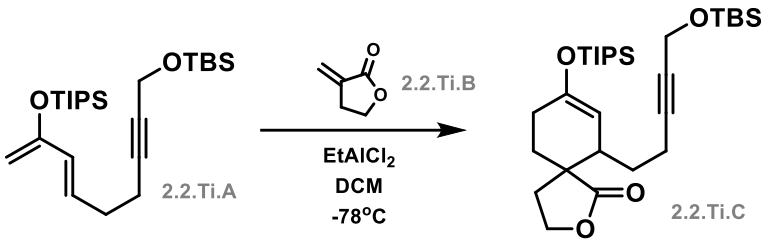
Scheme 4.2.i: Total synthesis of desmethyl montanin A in 5 steps and 30% overall yield.

5A. EXPERIMENTAL

A1. GENERAL INFORMATION

All reactions were performed under argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum unless otherwise indicated. All commercial reagents were used without purification unless otherwise noted. When no temperature is mentioned, the step was performed at room temperature. Anhydrous solvents were obtained by storing them over 4 Å molecular sieves. Reactions were monitored by thin layer chromatography (TLC) analysis using aluminum plates pre-coated (250 μm thickness) with ultra-pure silica gel (60 Å, SiliCycle). Thin layer chromatography plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Flash chromatographies were carried out on 230-400 mesh silica gel. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz or Bruker AMX 600 MHz instrument. NMR samples were dissolved in deuterated chloroform and chemical shifts are reported in ppm, referenced to residual un-deuterated chloroform. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments (101 MHz or 151 MHz). IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Concept - Magnetic sector Electron impact mass spectrometer (EI) and a Waters Synapt G1, HRes and Ion Mobility, Time of Flight Mass Spectrometer (ESI) at the University of Ottawa Mass Spectrum Centre. Melting points were recorded in triplicate using an Gallenkamp melting point apparatus.

A2. PROCEDURES AND CHARACTERIZATION

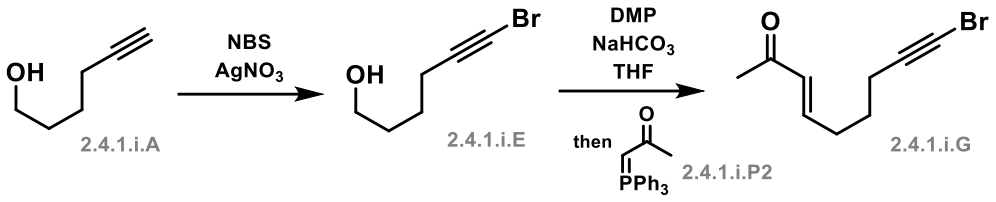


6-(5-((tert-butyldimethylsilyl)oxy)pent-3-yn-1-yl)-8-((triisopropylsilyl)oxy)-2 oxaspiro[4.5]dec-7-en-1-one:

Compound 2.2.Ti.C

To a solution of diene **2.2.Ti.A** (250 mg, 0.59 mmol) in 2.96 mL of dry DCM at room temperature was added dienophile **2.2.Ti.B** (116 mg, 1.18 mmol) The mixture was brought to -78°C and $EtAlCl_2$ solution in hexanes (590 µL, 0.59 mmol) was added dropwisely, and stirred for 1 h. To the mixture, NEt_3 (3 mL) was added at -78°C, the resulting reaction mixture was stirred for 1 min then brought to room temperature. Saturated $NaHCO_3$ in water (6 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (30 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 20% ethyl acetate/hexanes to isolate the title compound as a yellow oil (248 mg, 20:1 d.r., 78% yield). **IR** (neat, cm^{-1}): 2930, 2864, 1770, 1739, 1668, 1463, 1373, 1239, 1196, 1168, 1075. **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.88 (dd, J = 5.2, 1.3 Hz, 1H), 4.33 – 4.26 (m, 4H), 2.45 – 2.29 (m, 2H), 2.28 – 2.02 (m, 6H), 1.76 (dddd, J = 13.5, 9.1, 6.9, 4.4 Hz, 1H), 1.59 – 1.45 (m, 2H), 1.24 – 1.08 (m, 4H), 1.07 (d, J = 6.5 Hz, 18H), 0.90 (s, 8H), 0.10 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 179.8, 150.5, 103.0, 84.2, 79.4, 65.0, 51.9, 44.2, 36.9, 34.8, 31.3,

26.9, 26.6, 25.8, 18.0, 17.9, 16.6, 12.6, -5.1. **HRMS** (EI) m/z calculated for $C_{29}H_{52}O_4Si_2$ (M^+) 520.3404, found 520.3416.

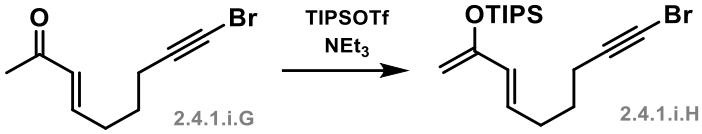


(E)-9-bromonon-3-en-8-yn-2-one

Compound 2.4.1.i.G

NBS is recrystallized by addition to ~90°C water, cooling in an ice bath, collecting white crystals through filtration, then drying in vacuo. A solution of **2.4.1.i.A** (1 g, 10.19 mmol), NBS (2 g, 11.21 mmol) and $AgNO_3$ (173 mg, 1.02 mmol) in 100 mL of acetone is prepared and stirred at room temperature for 1 h. The mixture is then filtered through celite, concentrated in vacuo, then resuspended in hexanes and concentrated in vacuo. To the crude mixture, 50 mL of THF and $NaHCO_3$ (1.28 g, 15.29 mmol) was added, then DMP (4.75 g, 11.12 mmol) was added, and the resulting reaction mixture was stirred at room temperature for 1 h. Phosphorane **2.4.1.i.P2** (6.48 g, 20.38 mmol) was slowly added, and stirred for 1 h. $NaHCO_3$ (50 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (250 mL total). The combined organic fractions were washed with brine (250 mL), then dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 20% ethyl acetate/hexanes to isolate the title compound as a yellow oil (1.56 g, 71% yield over two steps). **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.78 (dt, J = 16.0, 6.9 Hz, 1H), 6.10 (dt, J = 16.0, 1.5 Hz, 1H), 2.34 (qd, J = 7.0, 1.5 Hz, 2H), 2.25 (t, J = 6.9 Hz, 2H),

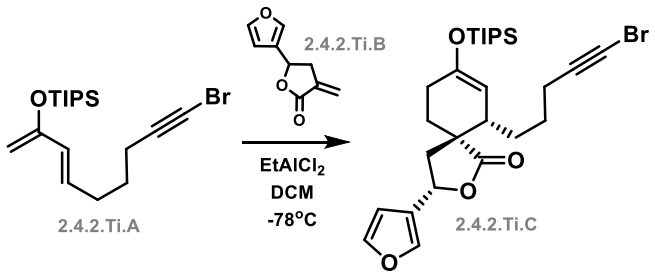
2.24 (s, 3H), 1.69 (dd, J = 7.7, 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 198.5, 146.8, 131.8, 79.2, 38.8, 31.3, 26.9, 26.6, 19.2. **HRMS** (EI) m/z calculated for $C_9H_{11}BrO$-H (M^+-H) 212.9915, found 212.9930.



(E)-((9-bromonona-1,3-dien-8-yn-2-yl)oxy)triisopropylsilane

Compound 2.4.1.i.H

To a solution of enone **2.4.1.i.G** (1.00 g, 4.65 mmol) in triethylamine (1.42mL, 19.4 mmol) in 10 mL of dry THF at 0°C, TIPSOTf (1.43 mL, 5.12 mmol) was added, and the resulting reaction mixture was stirred for 10 min. Saturated $NaHCO_3$ in water (10 mL) was added, layers separated, and the aqueous fraction was extracted 3 times with EtOAc (30 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 1% NEt_3/hexanes to isolate the title compound as a yellow oil (1.77 g, 93% yield). Immediately continue to the next step for highest yield. **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.02 (dt, J = 15.1, 6.9 Hz, 1H), 5.89 (dt, J = 15.2, 1.3 Hz, 1H), 4.20 (d, J = 18.9 Hz, 2H), 2.25 – 2.16 (m, 4H), 1.63 (p, J = 7.2 Hz, 2H), 1.29 – 1.17 (m, 3H), 1.10 (d, J = 7.1 Hz, 17H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 155.1, 129.9, 128.9, 93.3, 80.0, 31.0, 27.8, 19.1, 18.1, 12.8. **HRMS** (EI) m/z calculated for $C_{18}H_{31}BrOSi$+H (M^++H) 371.1405, found 371.1257.

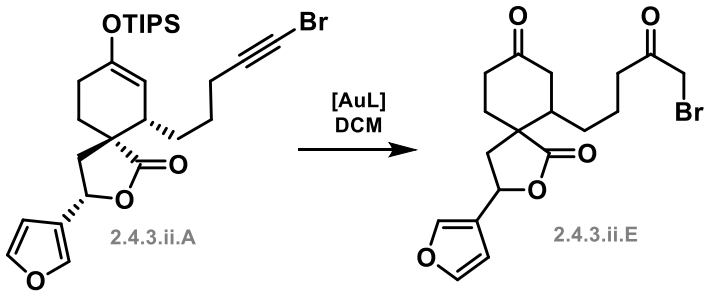


(3S,5S,6S)-6-(5-bromopent-4-yn-1-yl)-3-(furan-3-yl)-8-((triisopropylsilyl)oxy)-2-Oxaspiro[4.5]dec-7-en-1-one

Compound 2.4.2.Ti.C

To a solution of diene **2.4.2.i.A** (200 mg, 0.34 mmol) in 2.96 mL of dry DCM at room temperature, dienophile **2.4.2.i.B** (116 mg, 1.18 mmol) was added. The mixture was brought to -78°C and $EtAlCl_2$ solution in hexanes (590 µL, 0.59 mmol) was added dropwisely, and the resulting reaction mixture was stirred for 1 h. NEt_3 (3 mL) was added to the mixture at -78°C, the reaction mixture was stirred for 1 min, then brought to room temperature. $NaHCO_3$ (6 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (30 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 20% ethyl acetate/hexanes to isolate the title compound as a yellow oil (248 mg, 20:1 d.r., 39% yield). **IR** (neat, cm^{-1}): 2941, 2864, 1762, 1664, 1457, 1368, 1214, 1159. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.48 (dt, J = 1.7, 0.8 Hz, 1H), 7.43 (t, J = 1.7 Hz, 1H), 6.41 (dd, J = 1.9, 0.9 Hz, 1H), 5.48 (dd, J = 10.6, 5.7 Hz, 1H), 4.91 (dd, J = 5.5, 1.4 Hz, 1H), 2.57 – 2.51 (m, 2H), 2.32 (p, J = 4.2 Hz, 1H), 2.28 – 2.17 (m, 3H), 2.17 – 2.11 (m, 1H), 2.05 (dd, J = 12.8, 10.6, 1H), 1.71 – 1.63 (m, 2H), 1.62 – 1.55 (m, 1H), 1.53 – 1.41 (m, 2H), 1.22 – 1.11 (m, 3H), 1.08 (d, J = 6.3 Hz, 18H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 179.1, 150.3, 143.9, 140.0, 124.0,

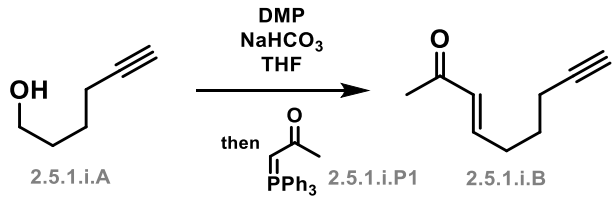
108.3, 103.6, 79.8, 71.4, 46.7, 42.4, 38.3, 32.6, 26.8, 26.6, 26.3, 19.9, 18.0, 17.9, 12.6. **HRMS** (EI) m/z calculated for $C_{27}H_{39}BrO_4Si$ (M^+) 534.1801, found 534.1829.



6-(5-bromo-4-oxopentyl)-3-(furan-3-yl)-2-oxaspiro[4.5]decane-1,8-dione

Compound 2.4.3.ii.E

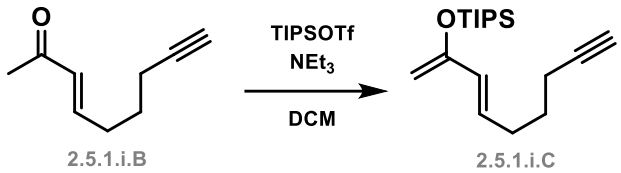
To a solution of Diels-Alder adduct **2.4.3.ii.A** (30 mg, 0.056 mmol) in 1 mL of DCM at room temperature, AuiPrSBF$_6$ (3.0 mg, 0.0039 mmol) was added, and the resulting reaction mixture was stirred overnight. The mixture was filtered through celite and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 30% ethyl acetate/hexanes to isolate the title compound as a yellow oil (13.9 mg, 66% yield). **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.48 (dt, J = 1.7, 0.9 Hz, 1H), 7.45 (t, J = 1.8 Hz, 1H), 6.40 (dd, J = 2.0, 0.9 Hz, 1H), 5.50 (t, J = 8.0 Hz, 1H), 3.87 (s, 2H), 2.99 – 2.92 (m, 1H), 2.76 (dd, J = 13.7, 7.9 Hz, 1H), 2.73 – 2.70 (m, 1H), 2.69 (d, J = 6.7 Hz, 1H), 2.49 (ddd, J = 14.7, 4.7, 1.6 Hz, 1H), 2.33 – 2.24 (m, 2H), 2.19 (dd, J = 13.7, 8.1 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.90 (ddd, J = 15.5, 11.2, 5.7 Hz, 1H), 1.76 – 1.72 (m, 1H), 1.65 – 1.58 (m, 1H), 1.58 – 1.50 (m, 1H), 1.34 – 1.26 (m, 1H), 1.25 (t, J = 7.2 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 209.3, 201.5, 177.8, 144.3, 139.7, 124.9, 108.1, 71.9, 46.0, 43.8, 41.9, 41.8, 39.1, 37.4, 35.2, 34.0, 30.0, 21.0. **HRMS** (EI) m/z calculated for $C_{18}H_{21}BrO_5$ (M^+) 396.0572, found 396.0542.



(E)-non-3-en-8-yn-2-one

Compound 2.5.1.i.B

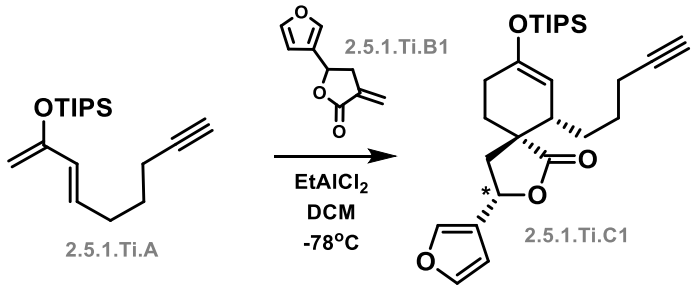
To a solution of **2.5.1.i.A** (2.00 g, 20.38 mmol), $NaHCO_3$ (9.50 g, 22.42 mmol) in 200 mL of dry DCM at room temperature, Dess-Martin periodinane (12.96 g, 30.56 mmol) was added, and the resulting reaction mixture was stirred for 1.5 h. To the mixture was slowly added phosphorane **2.5.1.i.P1** (12.98 g, 40.76 mmol) and stirred for 1.5 h. Saturated $NaHCO_3$ in water (200 mL) was added, layers separated, and the aqueous fraction was extracted 3 times with EtOAc (600 mL total). The combined organic fractions were washed with brine (800 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 20% ethyl acetate/hexanes to isolate the title compound as a yellow oil (2.25 g, 81% yield). **IR** (neat, cm^{-1}): 3287, 2941, 1670, 1625, 1430, 1359, 1251. **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.78 (dt, J = 16.0, 6.9 Hz, 1H), 6.10 (dt, J = 16.0, 1.6 Hz, 1H), 2.39 – 2.32 (m, 2H), 2.24 (s, 3H), 2.23 (td, J = 7.0, 2.6 Hz, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.70 (p, J= 7.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 198.5, 146.7, 131.8, 83.4, 69.1, 31.2, 26.9, 26.7, 17.9. **HRMS** (EI) m/z calculated for $C_9H_{12}O$-H (M^+-1H) 135.0810, found 135.0815.



(E)-triisopropyl(nona-1,3-dien-8-yn-2-yloxy)silane

Compound 2.5.1.i.C

To a solution of enone **2.5.1.i.B** (1.00 g, 4.65 mmol) and triethylamine (1.42 mL, 19.40 mmol) in 10 mL of dry THF at 0°C, TIPSOTf (1.43 mL, 5.12 mmol) was added, and the reaction mixture was stirred for 10 min. Saturated $NaHCO_3$ in water (100 mL) was added, layers separated, and the aqueous fraction was extracted 3 times with EtOAc (300 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 1% NEt_3/hexanes to isolate the title compound as a yellow oil (2.08 g, 96% yield). Immediately, continue to the next step for highest yield. **IR** (neat, cm^{-1}): 3300, 2940, 2866, 1589, 1464, 1372. **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.03 (dt, J = 15.1, 6.9 Hz, 1H), 5.90 (dt, J = 15.2, 1.3 Hz, 1H), 4.20 (d, J = 19.5 Hz, 2H), 2.31 – 2.13 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.64 (p, J = 7.2 Hz, 2H), 1.29 – 1.18 (m, 3H), 1.10 (d, J = 7.2 Hz, 18H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 155.2, 130.1, 128.8, 93.3, 84.2, 68.4, 31.0, 28.0, 18.1, 17.9, 12.8. **HRMS** (EI) m/z calculated for $C_{18}H_{32}OSi$ (M^+) 292.2222, found 292.2211.

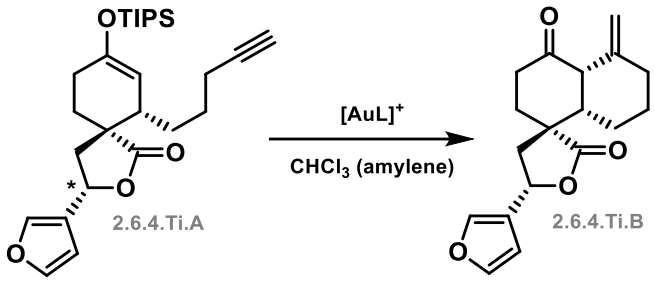


(3S,5S,6S)-3-(furan-3-yl)-6-(pent-4-yn-1-yl)-8-((triisopropylsilyl)oxy)-2-Oxaspiro[4.5]dec-7-en-1-one

Compound 2.5.1.Ti.C1

A solution of diene **2.5.1.Ti.A** (1.45 g, 5.95 mmol) and dienophile **2.5.1.Ti.B** (1.63 g, 9.91 mmol) was prepared in 50 mL of dry DCM at room temperature. The mixture was brought to -78°C and $EtAlCl_2$ solution in hexanes (4.95 mL, 4.95 mmol) was added dropwisely, and the resulting reaction mixture was stirred for 1.5 h. To the mixture was added NEt_3 (30 mL) at -78°C, stirred for 1 min, then brought to room temperature. $NaHCO_3$ (50 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (250 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 1% triethylamine/hexanes to isolate the title compound as a mixture of diastereomers as a yellow oil (1.83 g, 2.5:1 d.r., 81% yield). The following step is performed with the mixture of difficultly separable diastereomers as isolation is only entirely possible after the following transformation. The following analyses are from the cleanest possible column purification fractions. The 2.5:1 d.r. was determined through the crude NMR and comparison between the peak at 4.92 of the desired diastereomer and the peak at 4.83 from the undesired diastereomer. **IR** (neat, cm^{-1}): 3306, 2939, 2863, 1763, 1669, 1461, 1375. **^{1}H NMR (desired diastereomer)** (400 MHz, Chloroform-d) δ 7.47 (dt, J = 1.6, 0.8 Hz, 1H), 7.43 (t, J = 1.7 Hz, 1H), 6.41 (dd, J = 1.9, 0.9 Hz, 1H), 5.48 (dd, J = 10.5, 5.7 Hz, 1H), 4.92 (dt, J = 5.5, 1.2 Hz, 1H), 2.54 (dd, J = 12.7, 5.8 Hz, 1H), 2.32 (dd, J = 9.6, 5.0 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.19 (dd, J = 7.1, 2.5 Hz, 2H), 2.14 (dt, J = 7.0, 1.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.04 (dd, J = 12.7, 10.6

Hz, 1H), 1.94 (t, J = 2.6 Hz, 1H), 1.73 – 1.64 (m, 2H), 1.58 (ddt, J = 13.3, 5.8, 1.8 Hz, 1H), 1.49 (ddt, J = 11.1, 8.2, 3.2 Hz, 2H), 1.21 – 1.11 (m, 3H), 1.08 (d, J = 6.3 Hz, 18H). **^{1}H NMR (undesired diastereomer)** (400 MHz, Chloroform-d) δ 7.43 (s, 1H), 7.43 (s, 1H), 6.38 (dd, J = 1.8, 1.0 Hz, 1H), 5.48 – 5.41 (m, 1H), 4.83 (dt, J = 4.3, 1.3 Hz, 1H), 2.42 – 2.32 (m, 2H), 2.34 – 2.22 (m, 2H), 2.19 (dd, J = 13.3, 7.0 Hz, 1H), 2.17 – 2.11 (m, 2H), 2.11 – 2.05 (m, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.80 – 1.58 (m, 2H), 1.52 – 1.26 (m, 2H), 1.26 – 1.11 (m, 3H), 1.10 – 1.07 (m, 18H). **^{13}C NMR (desired diastereomer)** (101 MHz, Chloroform-d) δ 179.1, 150.3, 143.9, 140.0, 124.1, 108.4, 103.7, 84.1, 71.4, 68.5, 46.7, 42.5, 38.4, 32.6, 26.9, 26.7, 26.6, 18.6, 18.0, 12.6. **^{13}C NMR (undesired diastereomer)** (101 MHz, Chloroform-d) δ 179.0, 150.2, 143.8, 139.9, 124.0, 108.3, 103.6, 83.9, 71.3, 68.5, 46.6, 42.3, 38.2, 32.4, 26.8, 26.6, 26.4, 18.5, 17.9, 12.5. **HRMS** (EI) m/z calculated for $C_{27}H_{40}O_4Si$ (M^+) 456.2696, found 456.2674.

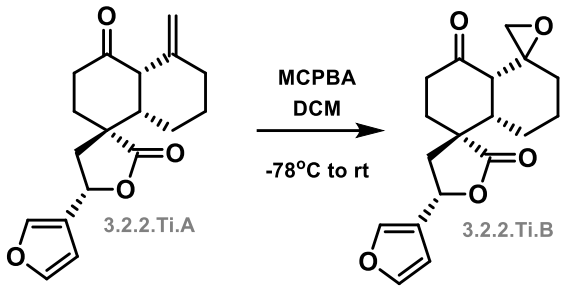


(3S,4a'S,5S,8a'S)-5-(furan-3-yl)-5'-methylenedecahydro-2H,4'H-spiro[furan-3,1'-naphthalene]-2,4'-dione

Compound 2.6.4.Ti.B

To a solution of adduct **2.6.4.Ti.A** diastereomer mixture (500 mg, 1.09 mmol) in 5 mL of $CHCl_3$ (stabilized by amylene) at 60°C, the first dosage of $AuBPCF_3$ (32.1 mg, 0.27 mmol) was added, and the resulting reaction mixture was stirred overnight. The

following day, a second dosage of the same amount was added to a total of 5 mol% catalyst loading, and the resulting reaction mixture was stirred overnight. The mixture was filtered through celite and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 40% ethyl acetate/hexanes to isolate the title compound as a white solid (164 mg, 70% yield). **IR** (neat, cm^{-1}): 2925, 2858, 1757, 1707, 1653, 1506, 1442, 1333, 1313. **^{1}H NMR (desired diastereomer)** (600 MHz, Chloroform-d) δ 7.52 (d, J = 1.2 Hz, 1H), 7.45 (t, J = 1.8 Hz, 1H), 6.44 – 6.44 (m, 1H), 5.54 (dd, J = 10.6, 5.7 Hz, 1H), 4.93 (t, J = 1.9 Hz, 1H), 4.70 (d, J = 1.7 Hz, 1H), 3.37 (d, J = 5.2 Hz, 1H), 3.02 (dd, J = 13.0, 5.7 Hz, 1H), 2.55 (td, J = 14.3, 4.8 Hz, 1H), 2.47 (ddd, J = 14.7, 4.7, 2.4 Hz, 1H), 2.34 – 2.24 (m, 3H), 2.24 – 2.18 (m, 2H), 1.90 – 1.85 (m, 2H), 1.82 (ddt, J = 14.1, 6.3, 2.3 Hz, 1H), 1.30 (qd, J = 13.5, 13.0, 3.6 Hz, 1H), 1.24 – 1.17 (m, 1H). **^{1}H NMR (undesired diastereomer)** (400 MHz, Chloroform-d) δ 7.49 (dt, J = 1.9, 1.0 Hz, 1H), 7.46 (t, J = 1.7 Hz, 1H), 6.44 (dd, J = 1.9, 0.9 Hz, 1H), 5.60 – 5.46 (t, 1H), 4.88 (q, J = 1.5 Hz, 1H), 4.67 – 4.50 (m, 1H), 3.14 (dd, J = 4.9, 1.7 Hz, 1H), 2.93 (dd, J = 13.0, 7.2 Hz, 1H), 2.59 – 2.30 (m, 5H), 2.26 – 2.16 (m, 2H), 2.12 – 1.81 (m, 3H), 1.29 – 1.03 (m, 2H). **^{13}C NMR (desired diastereomer)** (151 MHz, Chloroform-d) δ 207.6 (C), 177.1 (C), 144.8 (CH), 144.1 (C), 140.2 (CH), 123.4 (C), 112.6 (CH_2), 108.2 (CH), 71.1 (CH), 56.2 (CH), 48.3 (C), 44.7 (CH), 41.3 (CH_2), 38.1 (CH_2), 31.8 (CH_2), 30.5 (CH_2), 26.4 (CH_2), 25.3 (CH_2). **^{13}C NMR (undesired diastereomer)** (101 MHz, Chloroform-d) δ 207.6 (C), 177.7 (C), 150.0 (CH), 144.3 (C), 139.6 (CH), 124.5 (C), 112.2 (CH_2), 108.1 (CH), 70.9 (CH), 56.9 (CH), 49.3 (C), 46.8 (CH), 40.7 (CH_2), 37.5 (CH_2), 31.8 (CH_2), 28.2 (CH_2), 26.5 (CH_2), 24.2 (CH_2). **MP**: 147-148°C. **HRMS** (EI) m/z calculated for $C_{18}H_{20}O_4$ (M^+) 300.1362, found 300.1391.

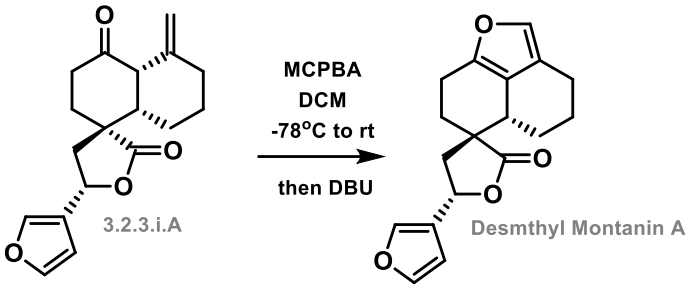


(3S,4a'S,5S,5'S,8a'S)-5-(furan-3-yl)octahydro-2H-dispiro[furan-3,1'-naphthalene-5',2''-oxirane]-2,4'(4a'H)-dione

Compound 3.2.2.Ti.B

To a solution of cycloadduct **3.2.2.Ti.A** (40 mg, 0.13 mmol) in 1.3 mL of dry DCM in a dry ice/acetone bath at a temperature of -78°C, exactly 1.0 equivalent of MCPBA (23.0 mg, 0.13 mmol) was added. The resulting reaction mixture was stirred overnight, allowing the bath to warm up to room temperature overnight. $Na_2S_2O_3$ (1.3 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (10 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 60% ethyl acetate/hexanes to isolate the title compound as a white solid (40.4 mg, 96% yield). **IR** (neat, cm^{-1}): 2936, 2860, 1772, 1714, 1506, 1444, 1404, 1308. **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.52 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.46 (t, *J* = 1.8 Hz, 1H), 6.43 (dd, *J* = 2.0, 0.9 Hz, 1H), 5.58 (dd, *J* = 10.6, 5.6 Hz, 1H), 2.90 (dd, *J* = 13.0, 5.7 Hz, 1H), 2.84 (d, *J* = 4.1 Hz, 1H), 2.64 (d, *J* = 4.1 Hz, 1H), 2.61 – 2.51 (m, 2H), 2.48 (ddd, *J* = 14.7, 4.7, 2.3 Hz, 1H), 2.30 – 2.19 (m, 4H), 2.12 (td, *J* = 14.1, 4.8 Hz, 1H), 1.92 (ddq, *J* = 12.9, 3.5, 1.7 Hz, 1H), 1.84 (ddq, *J* = 14.2, 6.5, 2.6 Hz, 1H), 1.54 (qt, *J* = 13.6, 3.8 Hz, 1H), 1.31 – 1.22 (m, 1H), 1.19 (ddq, *J* = 14.1, 3.8, 1.8 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 207.2 (C), 177.0 (C), 144.2 (CH), 140.2 (CH), 123.4 (C), 108.1 (CH), 71.3 (CH), 57.3

(C), 55.2 (C), 54.3 (CH_2), 48.2 (C), 42.0 (CH), 41.4 (CH_2), 38.1 (CH_2), 30.5 (CH_2), 29.7 (CH_2), 24.6 (CH_2), 22.8 (CH_2). **MP**: 160-161°C. **HRMS** (ESI+) m/z calculated for $C_{18}H_{20}O_5$+Na (M^++Na) 339.1208, found 339.1230.

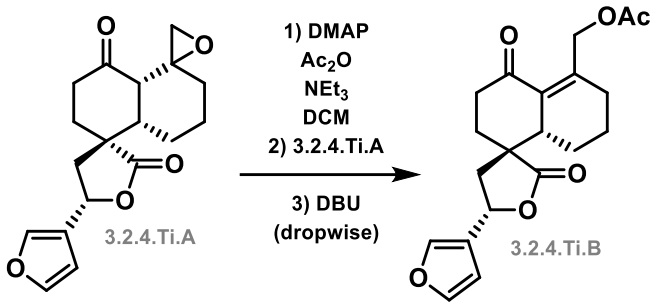


(3S,5S,5a'S)-5-(furan-3-yl)-3',4,4',5,5',5a',7',8'-octahydro-2H-spiro[furan-3,6'-naphtho[1,8-bc]furan]-2-one

Desmethyl montanin A

To a solution of cycloadduct **3.2.3.i.A** (9.8 mg, 0.033 mmol) in DCM (1 mL), MCPBA (5.63 mg, 0.033 mmol) was added at -78°C. The resulting reaction mixture was stirred overnight, allowing the bath to warm up to room temperature overnight. Following, DBU (4.87 µL, 0.033 mmol) was added to the solution for 10 min. $NaHCO_3$ (1 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with DCM (5 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 30% ethyl acetate/hexanes to isolate the title compound as a white solid. (9.2 mg, 95% yield). **IR** (neat, cm^{-1}): 2936, 2863, 1752, 1507, 1448, 1336, 1156, 1019. **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.47 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.07 (t, J = 1.4 Hz, 1H), 6.41 (dd, 1H), 5.45 (t, J = 8.0 Hz, 1H), 3.07 (dddd, J = 17.3, 10.3, 6.9, 2.6 Hz, 1H), 2.77 (d, 1H), 2.69 (dtt, J = 16.1, 10.6, 5.7 Hz, 3H), 2.45 (td, J = 17.0, 14.7, 5.7 Hz,

1H), 2.26 (dd, J = 13.3, 8.4 Hz, 1H), 2.15 (ttd, J = 14.0, 6.9, 6.5, 2.7 Hz, 2H), 2.11 – 2.04 (m, 2H), 1.69 – 1.59 (m, 1H), 1.29 – 1.19 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 176.3 (C), 147.7 (C), 144.1 (CH), 139.6 (CH), 136.5 (CH), 125.4 (C), 119.8 (C), 117.2 (C), 108.2 (CH), 71.6 (CH), 45.4 (C), 42.9 (CH_2), 41.7 (CH), 34.1 (CH_2), 25.4 (CH_2), 23.6 (CH_2), 21.3 (CH_2), 19.1 (CH_2). **MP**: 94-95°C. **HRMS** (EI) m/z calculated for $C_{18}H_{18}O_4$ (M^+) 298.1205, found 298.1186.

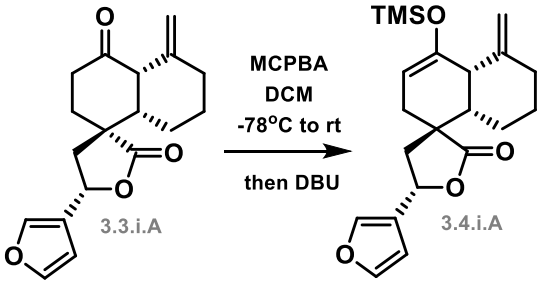


((3S,5S,8a'S)-5-(furan-3-yl)-2,4'-dioxo-3',4,4',5,6',7',8',8a'-octahydro-2H,2'H-spiro[furan-3,1'-naphthalen]-5'-yl)methyl acetate

Compound 3.2.4.Ti.B

To a solution of epoxide **3.2.4.Ti.A** (8 mg, 0.025 mmol) in 500 µL of dry DCM at room temperature was added DMAP (9.3 µL, 0.076 mmol), Ac_2O (23.9 µL, 0.25 mmol), and NEt_3 (70.7 µL, 0.51 mmol), and stirred at 0°C. DBU (3.8 µL, 0.025 mmol) was added dropwise, and the mixture was set to stir at 0°C for 3 h. $NaHCO_3$ (6 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (2.5 mL total). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel with 40% ethyl acetate/hexanes to isolate the title compound as a white solid (5.2 mg, 57% yield). **IR** (neat, cm^{-1}): 2918, 2853, 1757, 1715, 1675, 1613, 1506, 1445, 1366. **^{1}H NMR** (600

MHz, Chloroform-d) δ 7.48 (dt, J = 1.6, 0.9 Hz, 1H), 7.45 (td, J = 1.7, 0.4 Hz, 1H), 6.40 (ddd, J = 1.9, 0.9, 0.4 Hz, 1H), 5.50 – 5.44 (m, 1H), 4.87 – 4.83 (m, 2H), 3.19 (ddd, J = 16.2, 13.1, 6.9 Hz, 1H), 2.74 (dd, J = 13.7, 8.0 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.44 (ddd, J = 16.2, 5.3, 2.9 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.22 – 2.17 (m, 2H), 2.17 – 2.12 (m, 1H), 2.07 (s, 3H), 2.07 – 2.00 (m, 1H), 1.95 – 1.88 (m, 1H), 1.54 – 1.46 (m, 1H), 1.46 – 1.39 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 201.5 (C), 177.2 (C), 170.8 (C), 144.8 (C), 144.3 (CH), 139.7 (CH), 133.7 (C), 125.1 (C), 108.1 (CH), 71.9 (CH), 65.4 (CH_2), 47.1 (C), 45.9 (CH), 42.5 (CH_2), 37.5 (CH_2), 34.4 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 20.9 (CH_3), 20.8 (CH_2). **MP**: 140-141°C. **HRMS** (EI) m/z calculated for $C_{20}H_{22}O_6$ (M^+) 358.1416, found 358.1406.



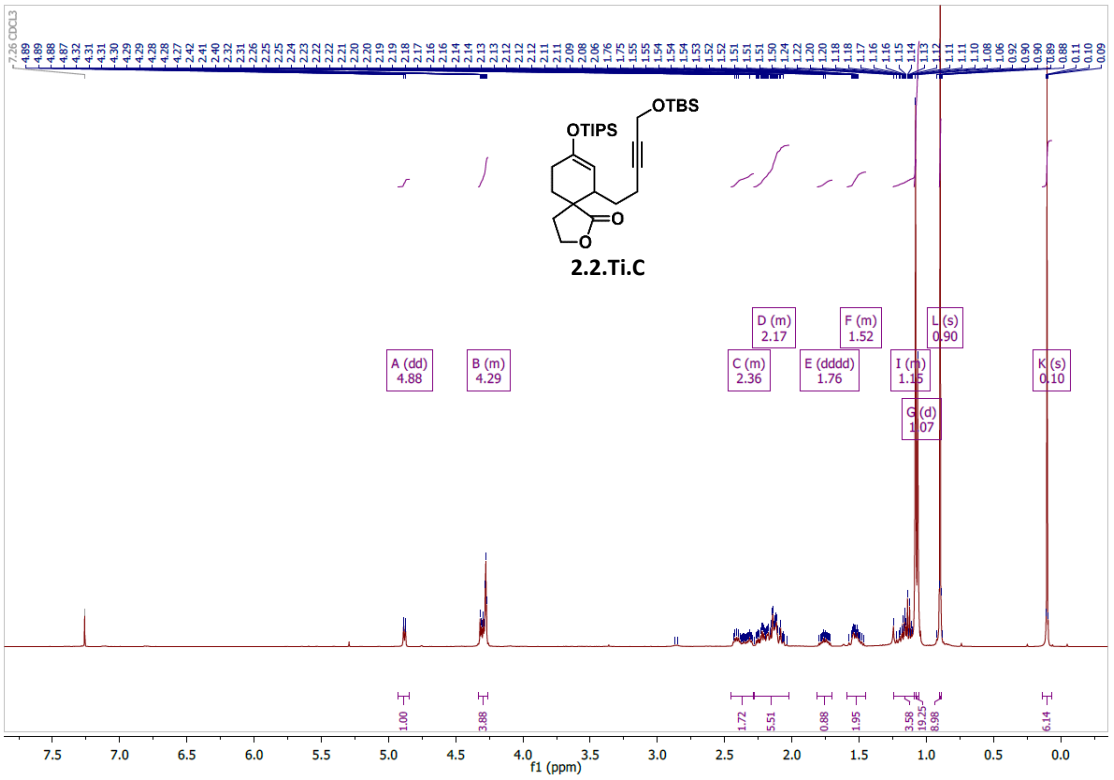
(3S,5S,8a'S)-5-(furan-3-yl)-5'-methylene-4'-((trimethylsilyl)oxy)-4,4a',5,5',6',7',8',8a'-octahydro-2H,2'H-spiro[furan-3,1'-naphthalen]-2-one

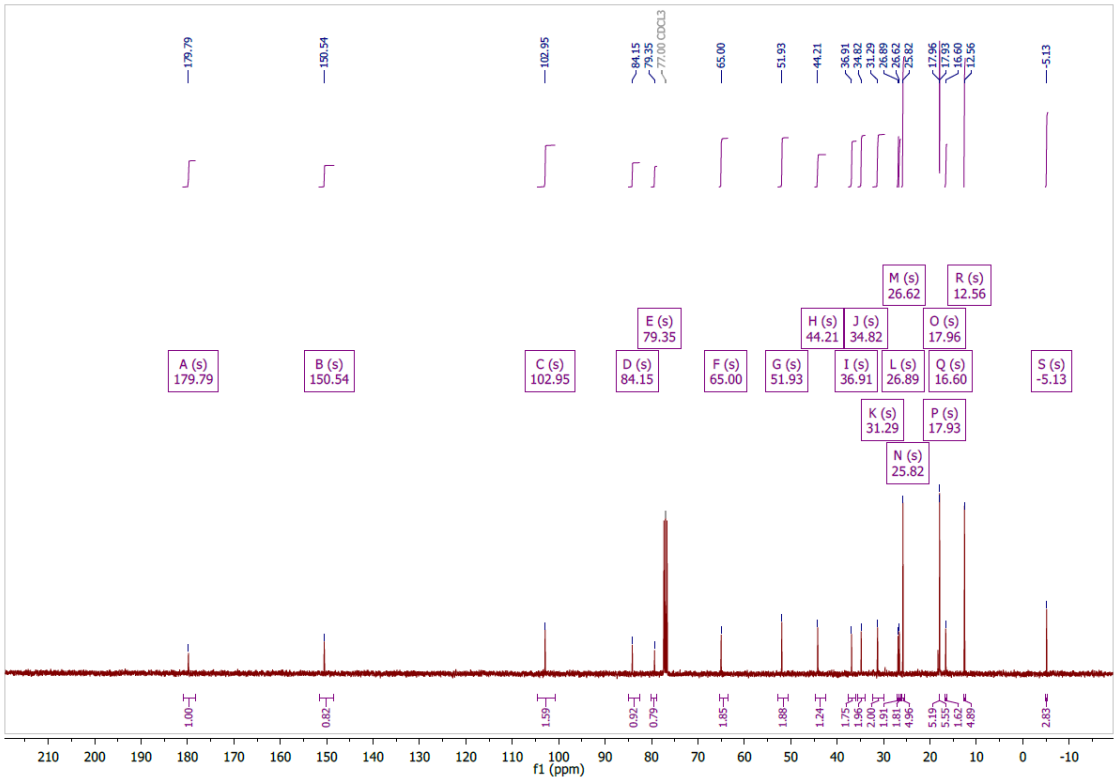
Compound 3.4.i.A

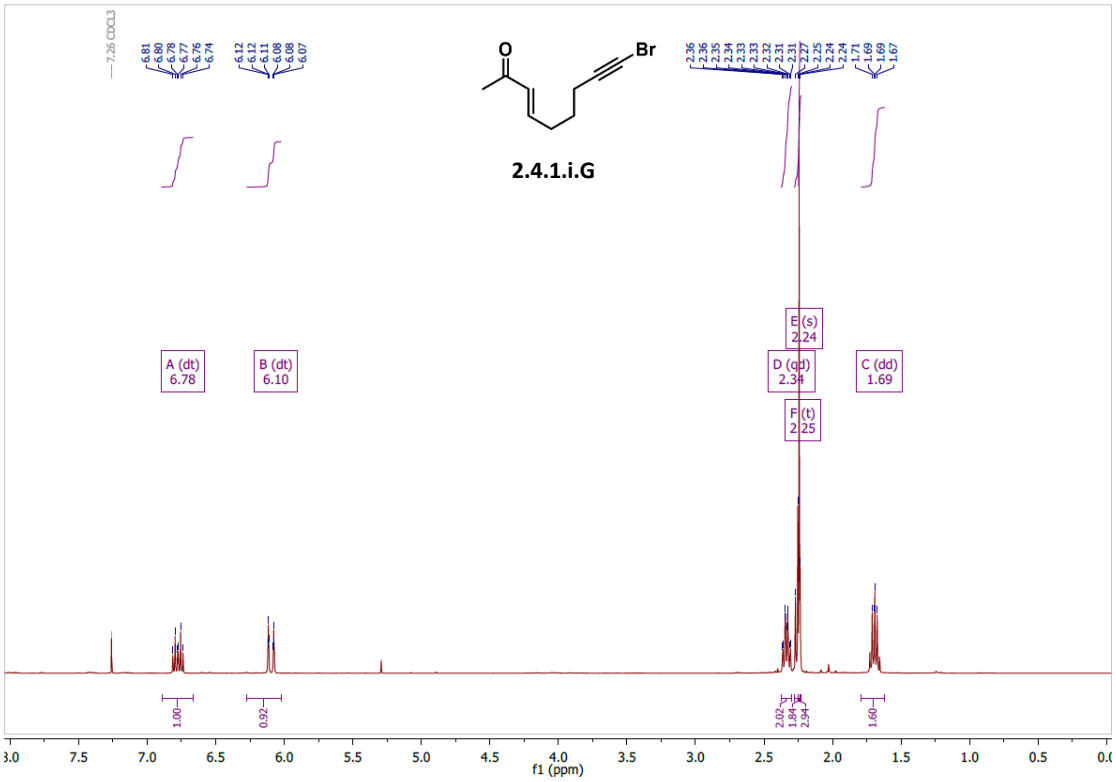
To a solution of cycloadduct **3.3.i.A** (64.7 mg, 0.22 mmol) in 2.2 mL of dry THF at -78°C was added LDA solution in THF (1.19 mL, 2.37 mmol) and stirred for 30 min. TMSCl (33 µL, 0.26 mmol) was added at -78°C, and stirred for 30 min. $NaHCO_3$ (3 mL) was added, layers separated, and the aqueous fraction was extracted 5 times with EtOAc (15 mL total). The combined organic fractions were dried with Na_2SO_4 and

concentrated in vacuo. The crude mixture was chromatographed on silica gel with 1% triethylamine/hexanes to isolate the title compound as a yellow oil (134 mg, 60% yield). **IR** (neat, cm^{-1}): 2919, 2850, 1685, 1570, 1413, 1299, 1258, 1184. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.49 (dt, J = 1.6, 0.8 Hz, 1H), 7.43 (t, J = 1.8 Hz, 1H), 6.42 (dd, J = 1.9, 0.9 Hz, 1H), 5.42 (dd, J = 10.2, 5.9 Hz, 1H), 4.85 (d, J = 2.0 Hz, 1H), 4.82 (dt, J = 5.5, 2.3 Hz, 1H), 4.77 – 4.73 (m, 1H), 3.13 (s, 1H), 2.92 (ddd, J = 17.5, 4.0, 2.3 Hz, 1H), 2.71 (dd, J = 13.2, 5.9 Hz, 1H), 2.19 (d, J = 13.2 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.89 (ddd, J = 12.9, 9.6, 3.6 Hz, 4H), 1.51 (td, J = 12.8, 9.4 Hz, 1H), 1.27 – 1.17 (m, 2H), 0.15 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 178.5, 147.8, 147.7, 144.0, 140.0, 124.1, 112.0, 108.4, 101.1, 70.8, 47.0, 46.3, 41.8, 39.7, 32.3, 30.6, 26.8, 23.6, 0.1. **HRMS** (EI) m/z calculated for $C_{21}H_{28}O_4Si$ (M^+) 372.1757, found 372.1762.

5B. SUPPLEMENTARY MATERIAL: SPECTRA



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B (dt)
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C (dd)
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D (qd)
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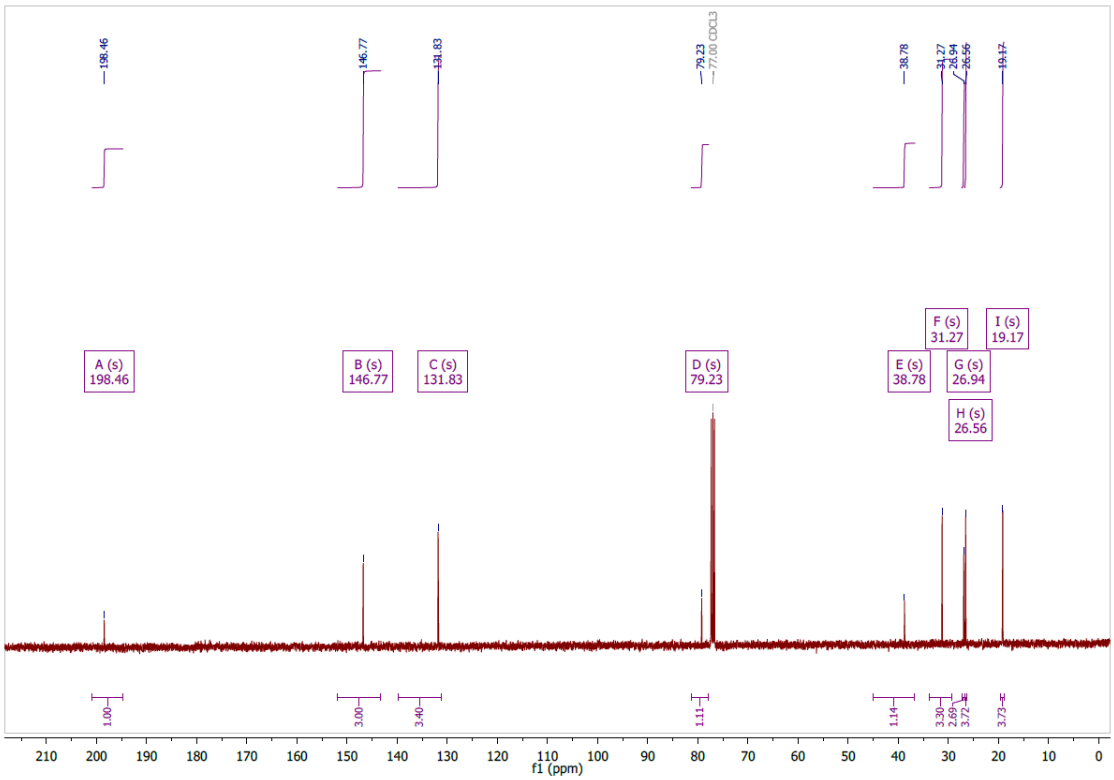
E (s)
2.24
F (t)
2.25
f1 (ppm)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B (s)
146.77
C (s)
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D (s)
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E (s)
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F (s)
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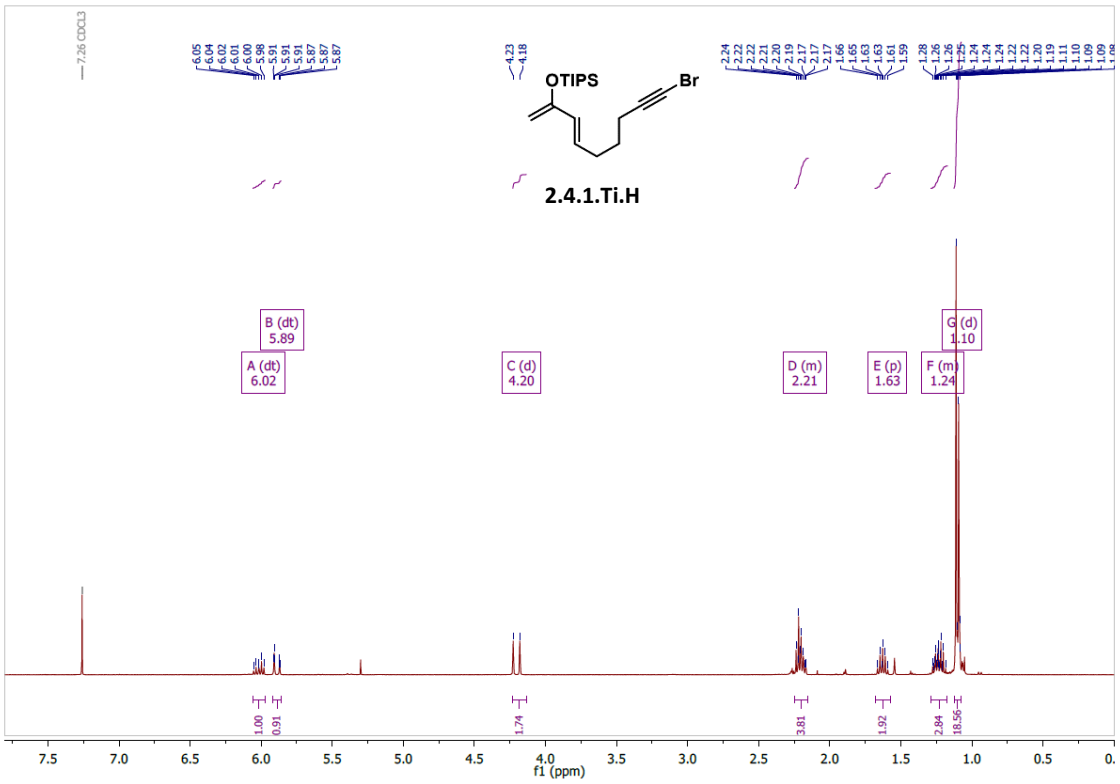
G (s)
26.94
H (s)
26.56
I (s)
19.17
f1 (ppm)


OTIPS
Br
2.4.1.Ti.H
B (dt) 5.89
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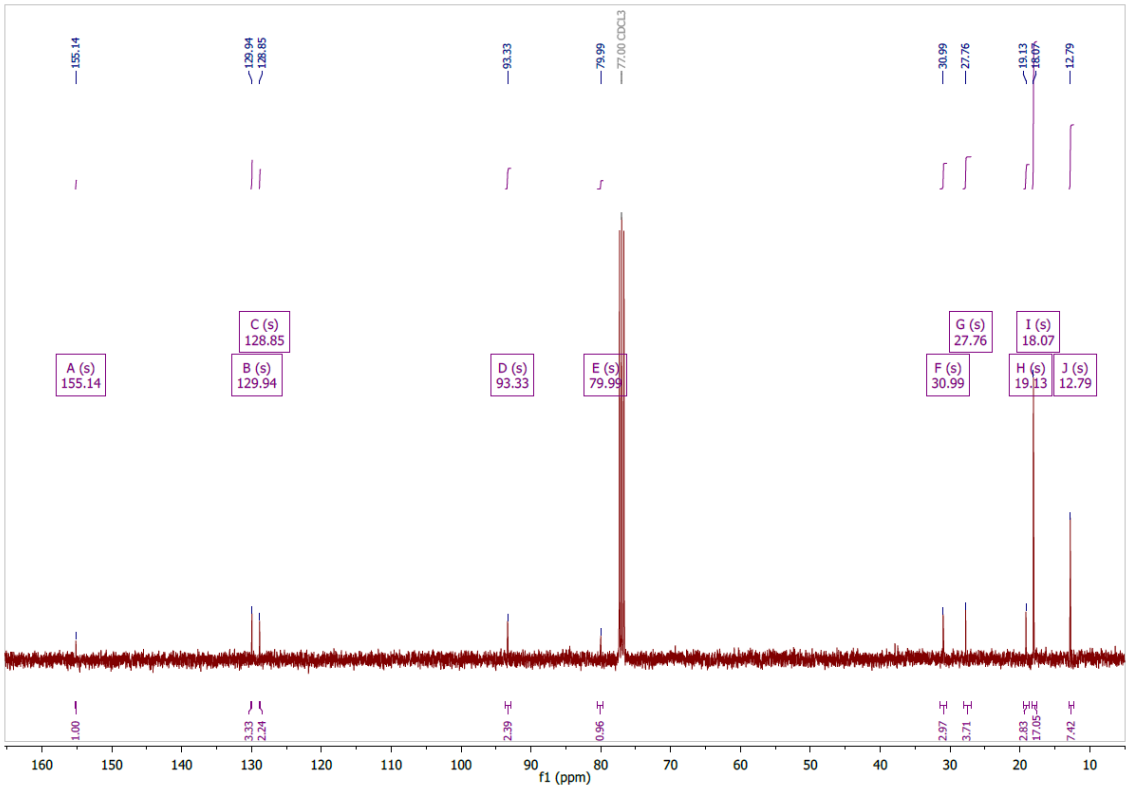
C (d) 4.20
D (m) 2.21
E (p) 1.63
F (m) 1.24
G (d) 1.10
f1 (ppm)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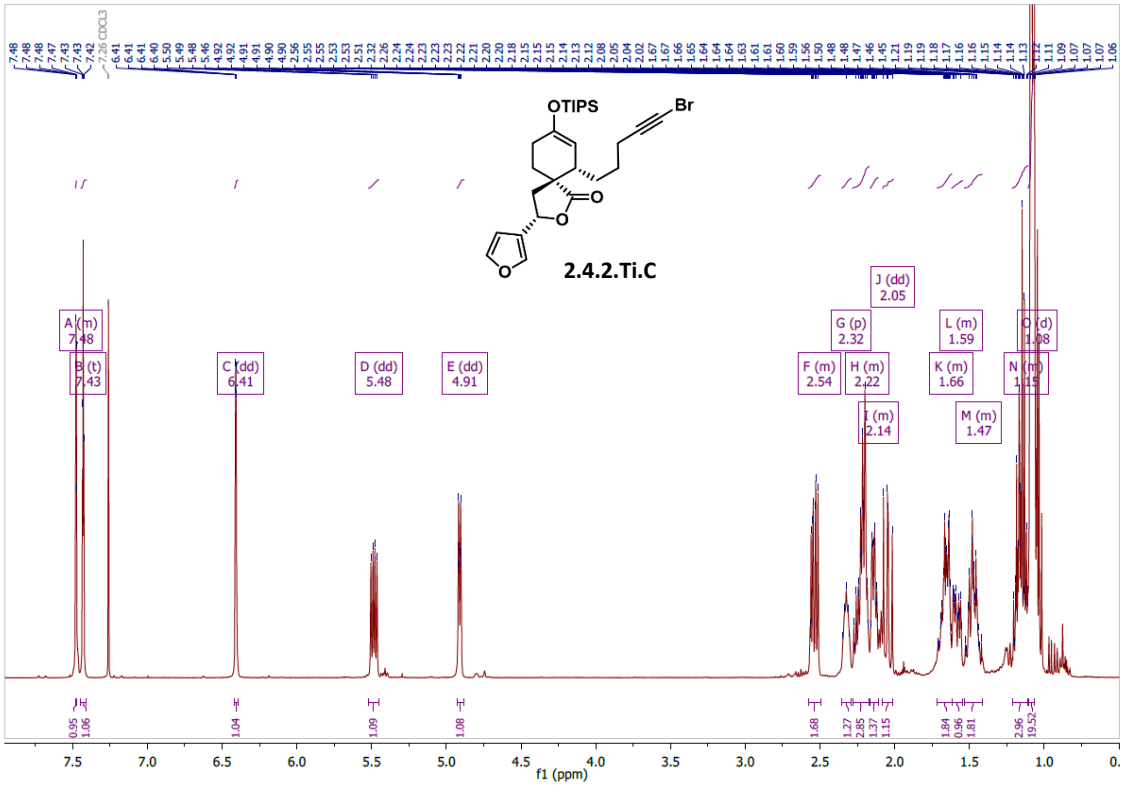
J (s) 12.79
f1 (ppm)


OTIPS
Br
O
O
O
2.4.2.Ti.C
A (m) 7.48
B (t) 7.43
C (dd) 6.41
D (dd) 5.48
E (dd) 4.91
F (m) 2.54
G (p) 2.32
H (m) 2.22
I (m) 2.14
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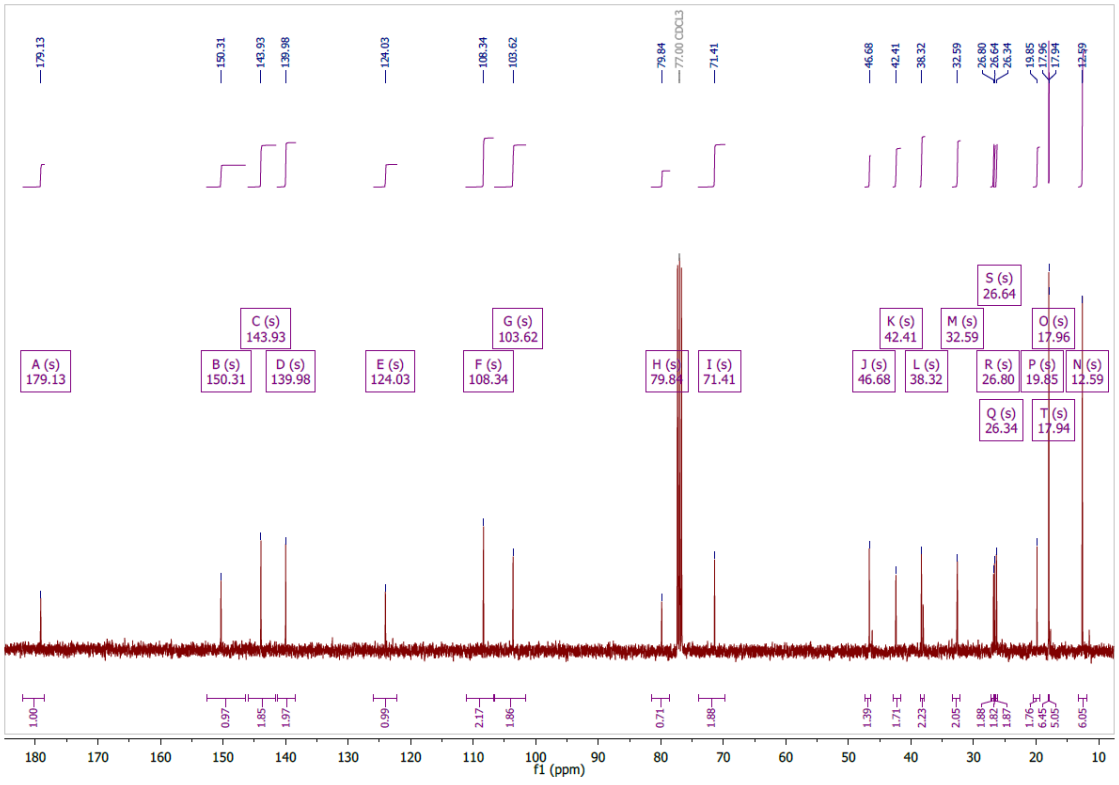
L (m) 1.59
M (m) 1.47
N (m) 1.19
O (d) 1.08
f1 (ppm)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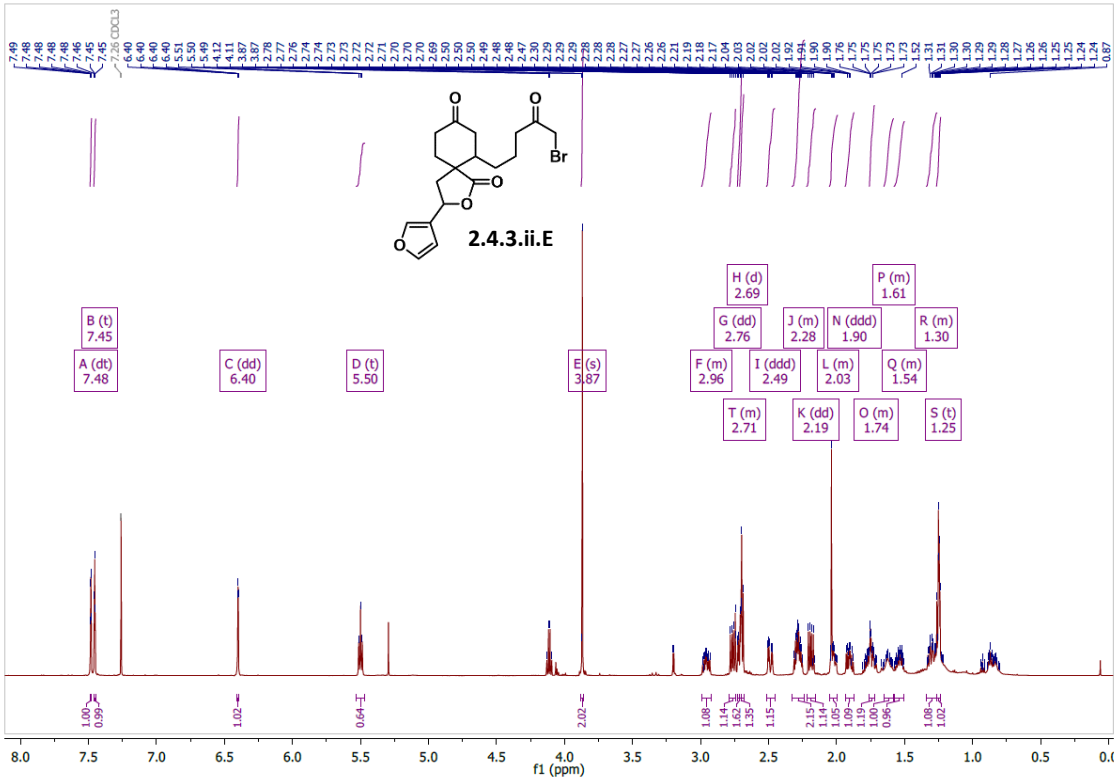
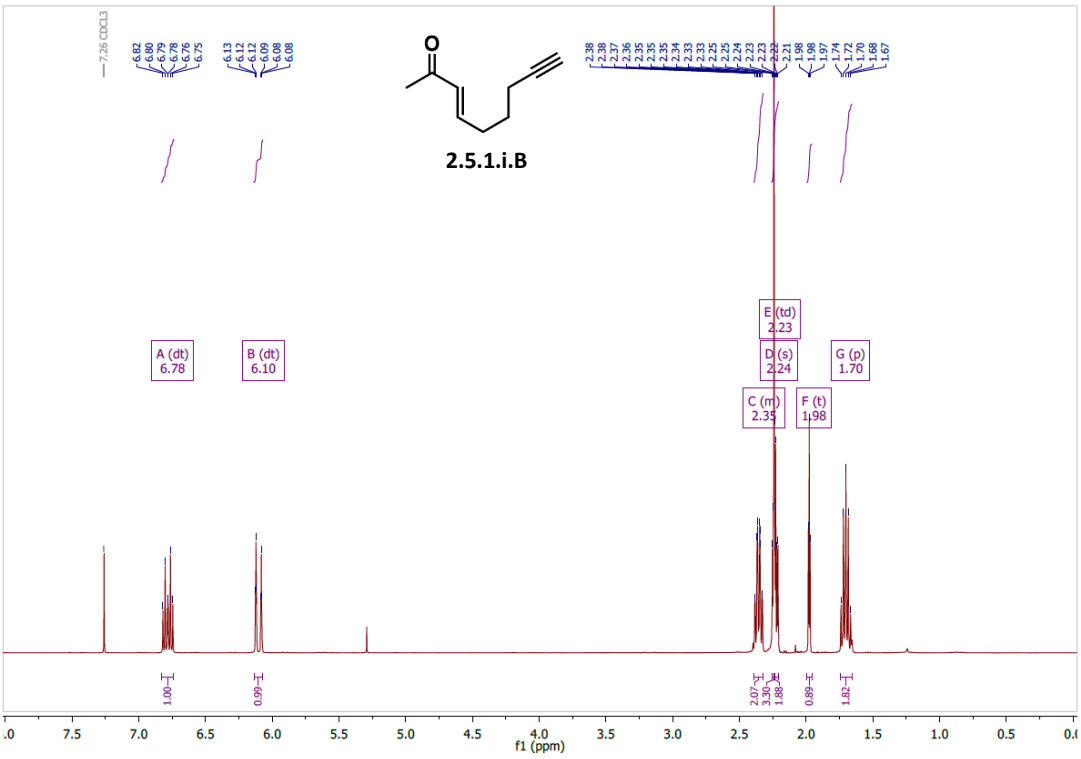
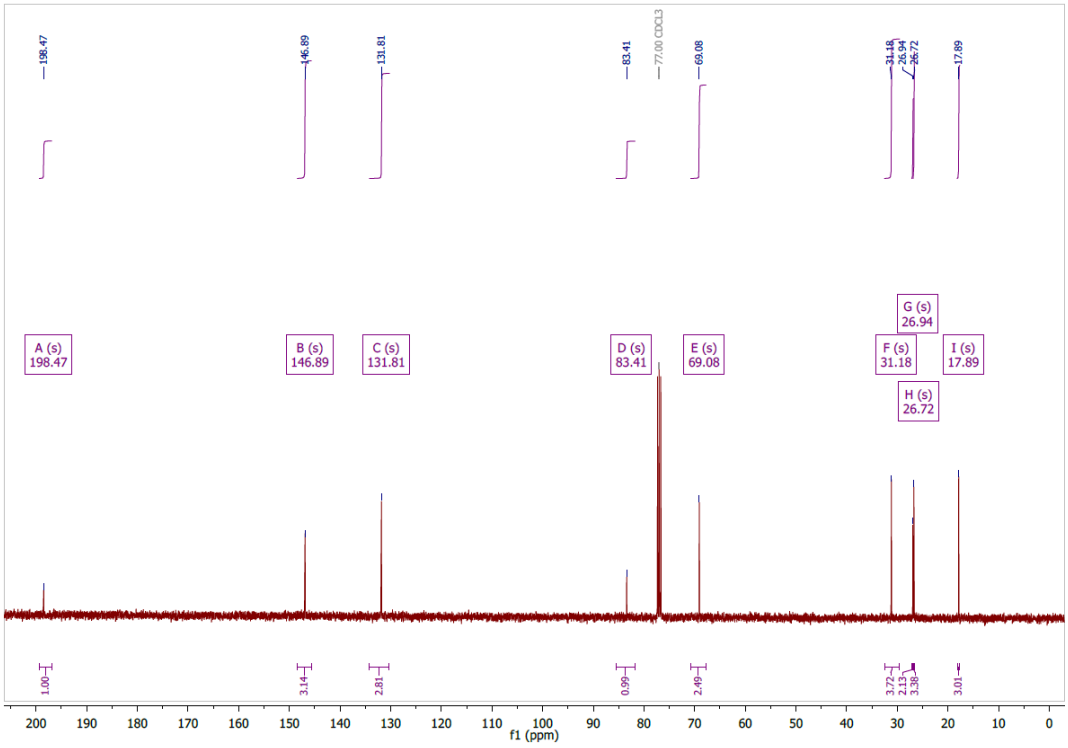
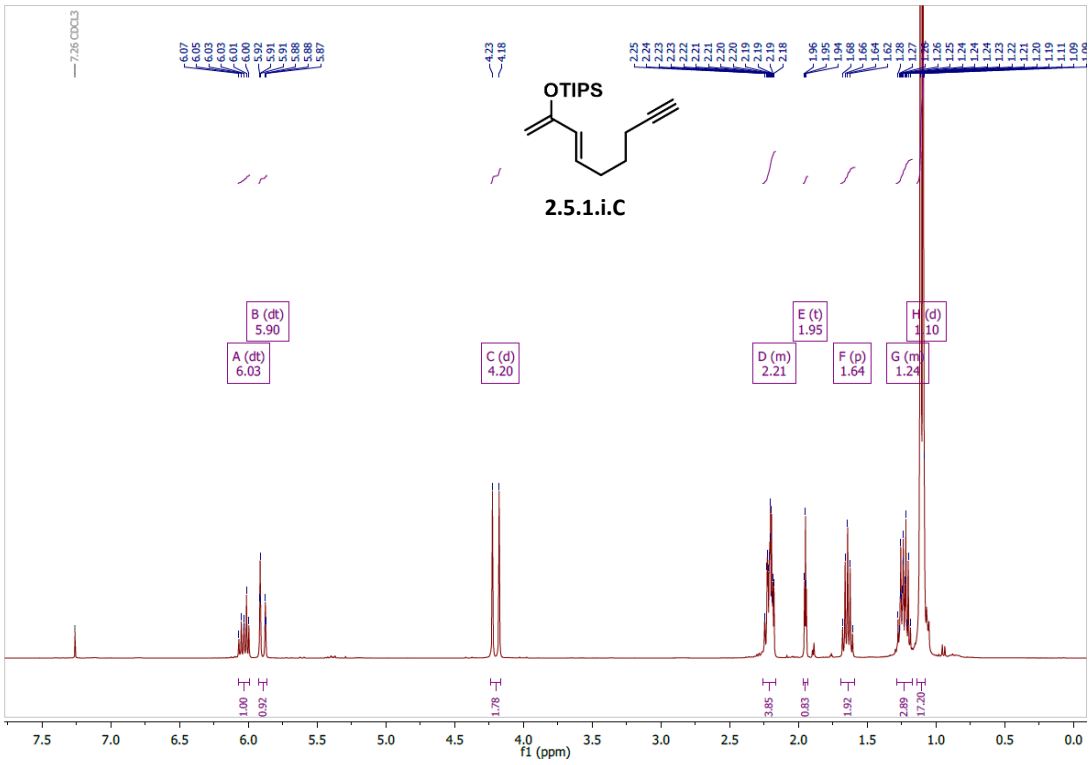
D (s) 139.98
E (s) 124.03
F (s) 108.34
G (s) 103.62
H (s) 79.84
I (s) 71.41
J (s) 46.68
K (s) 42.41
L (s) 38.32
M (s) 32.59
N (s) 12.59
O (s) 17.96
P (s) 19.85
Q (s) 26.34
R (s) 26.80
S (s) 26.64
T (s) 17.94
f1 (ppm)

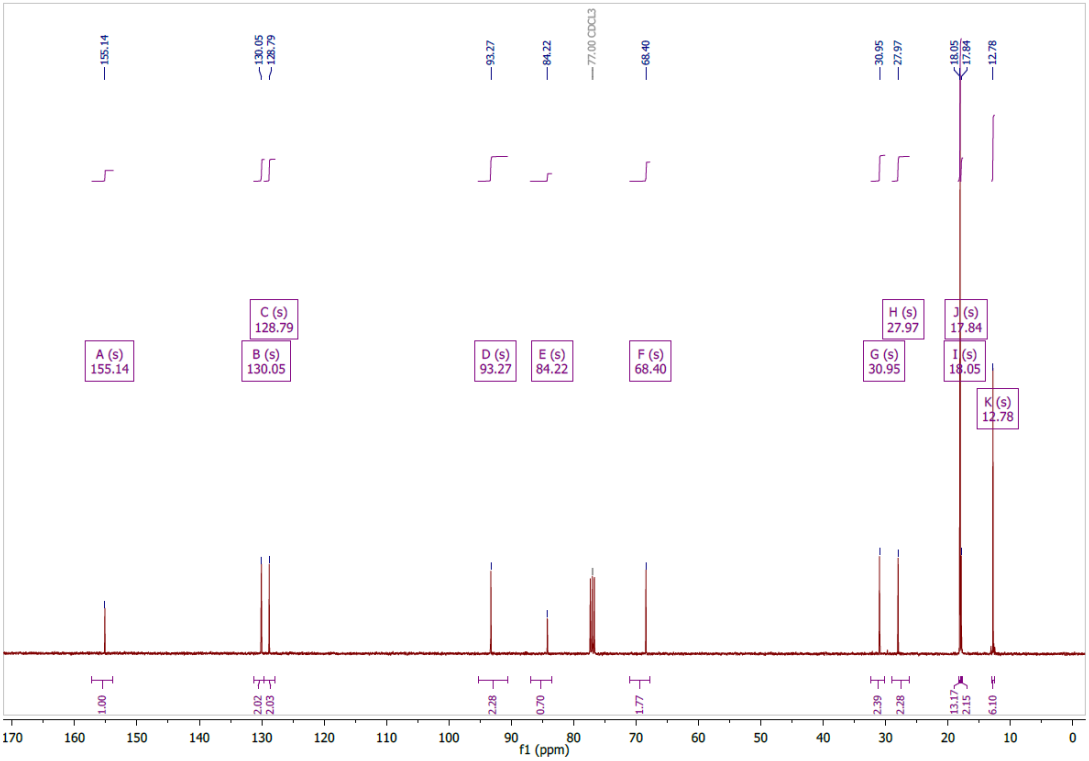

2.4.3.ii.E
A (dt) 7.48
B (t) 7.45
C (dd) 6.40
D (t) 5.50
E (s) 3.87
F (m) 2.96
G (dd) 2.76
H (d) 2.69
I (ddd) 2.49
J (m) 2.28
K (dd) 2.19
L (m) 2.03
N (ddd) 1.90
O (m) 1.74
P (m) 1.61
Q (m) 1.54
R (m) 1.30
S (t) 1.25
T (m) 2.71
f1 (ppm)

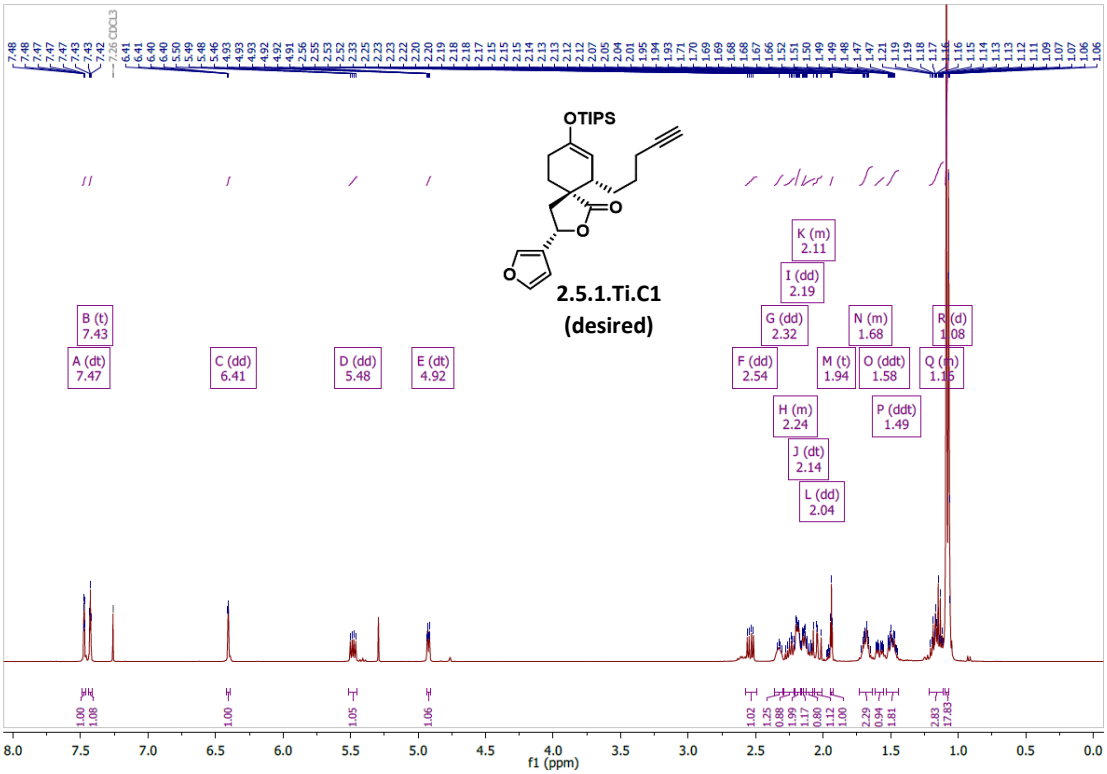

A (s) 209.30
B (s) 201.49
C (s) 177.80
D (s) 144.28
E (s) 139.70
F (s) 124.88
G (s) 108.06
H (s) 71.93
I (s) 46.01
J (s) 43.82
K (s) 41.90
L (s) 41.82
M (s) 39.12
N (s) 37.44
O (s) 35.20
P (s) 34.02
Q (s) 30.00
R (s) 20.97
f1 (ppm)

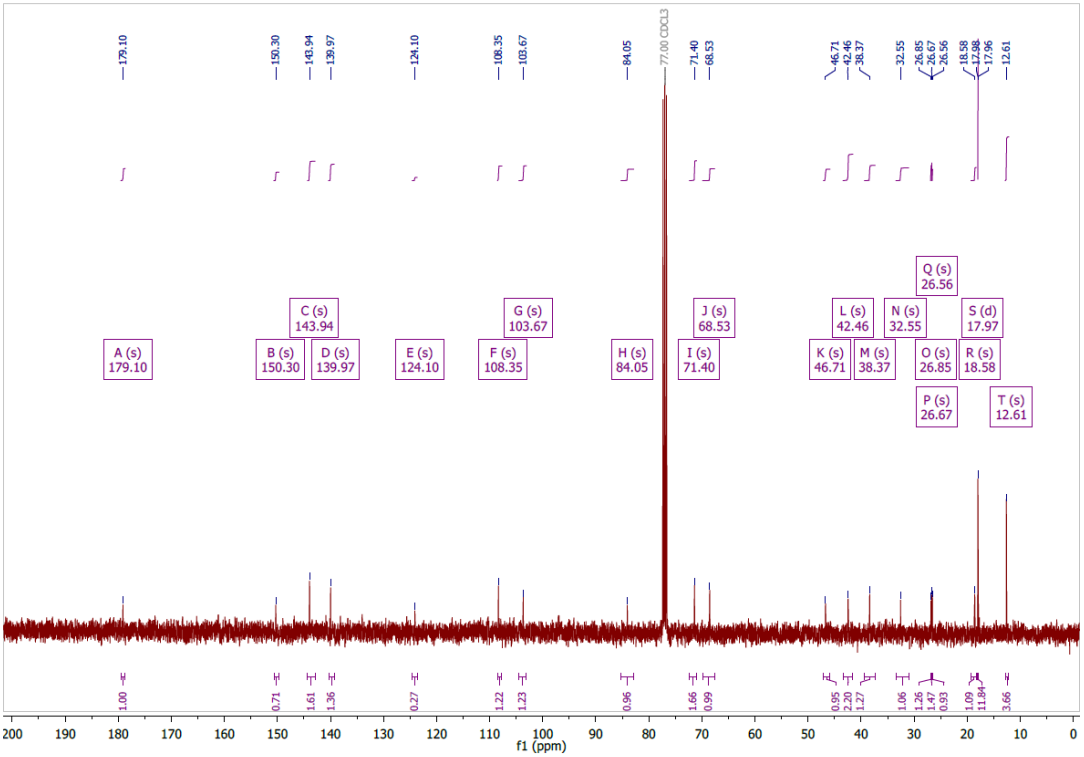

2.5.1.i.B
A (dt) 6.78
B (dt) 6.10
E (td) 2.23
D (s) 2.24
G (p) 1.70
C (m) 2.35
F (t) 1.98
f1 (ppm)

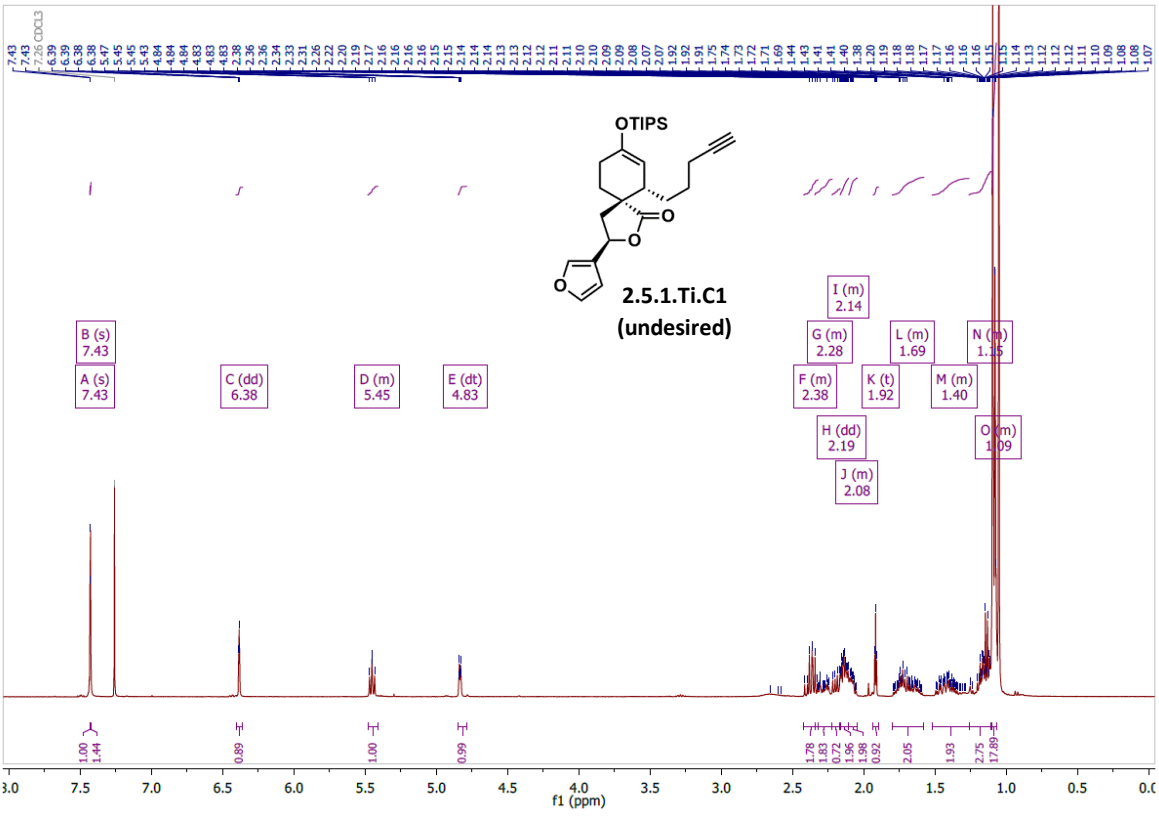

A (s) 198.47
B (s) 146.89
C (s) 131.81
D (s) 83.41
E (s) 69.08
G (s) 26.94
F (s) 31.18
I (s) 17.89
H (s) 26.72
f1 (ppm)

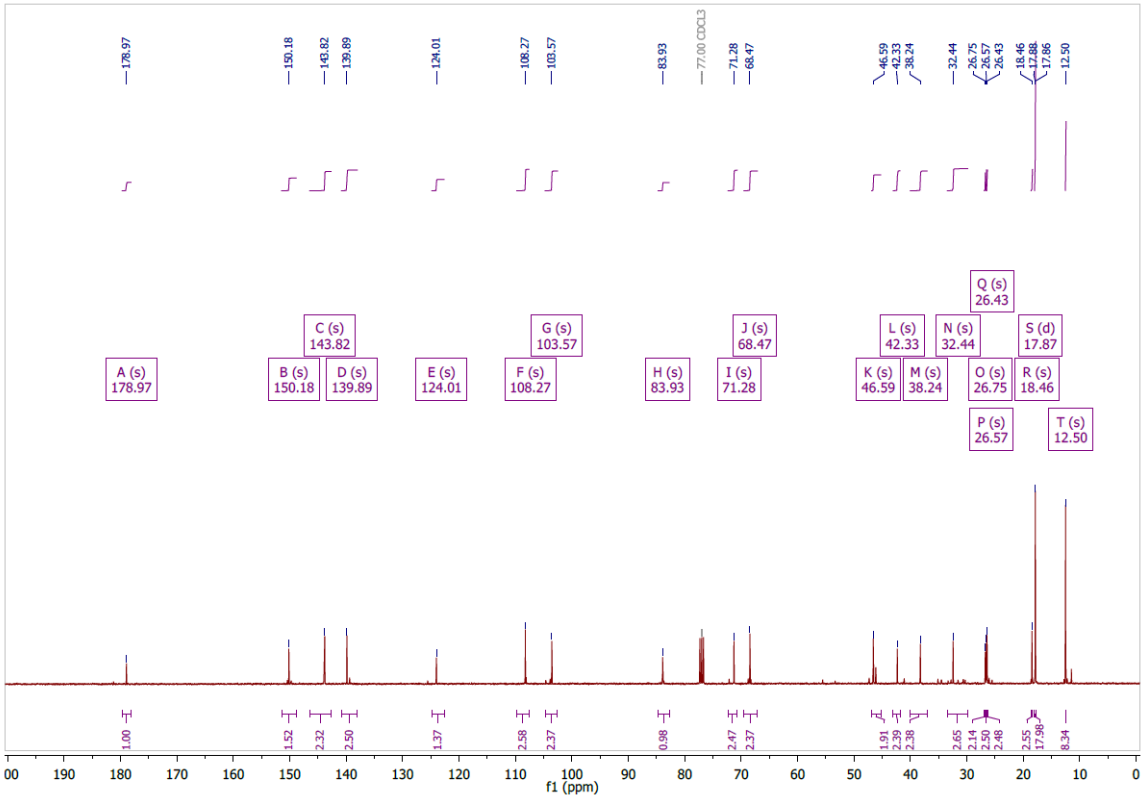

OTIPS
2.5.1.i.C
B (dt) 5.90
A (dt) 6.03
C (d) 4.20
E (t) 1.95
D (m) 2.21
F (p) 1.64
G (m) 1.24
H (d) 1.10
f1 (ppm)

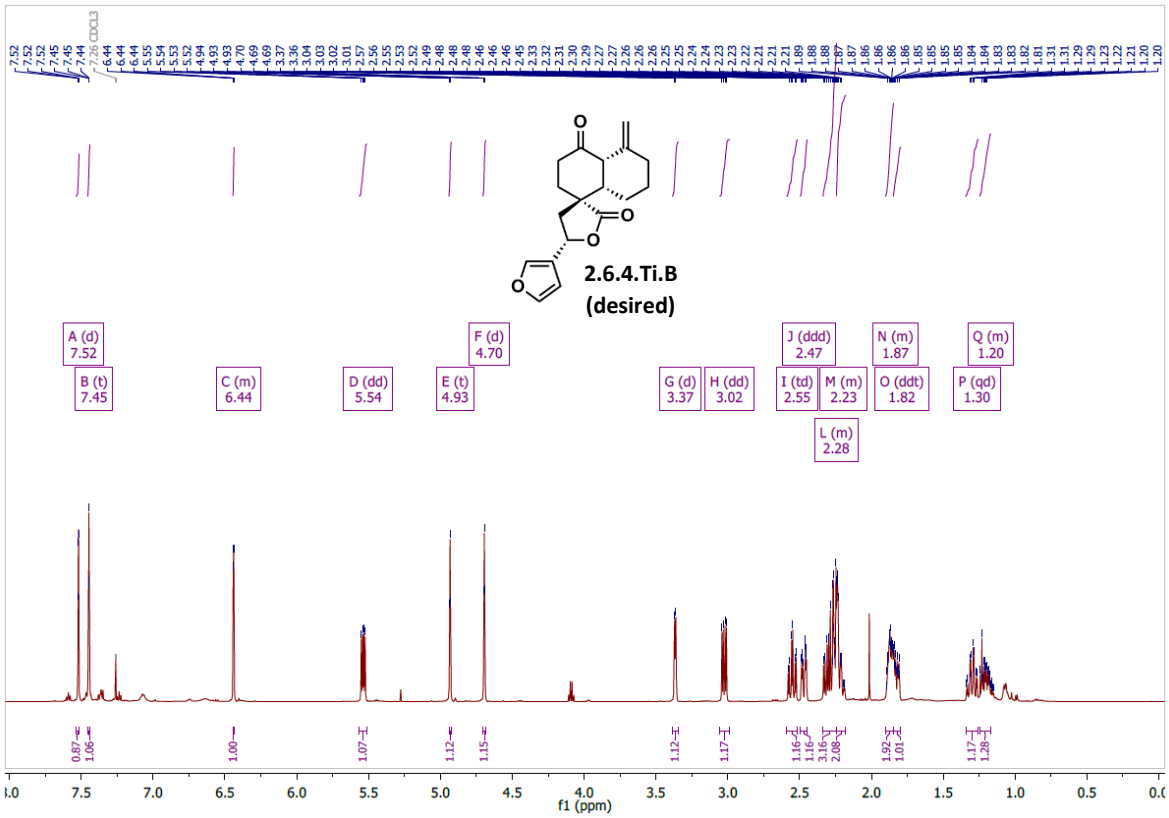

A (s) 155.14
C (s) 128.79
B (s) 130.05
D (s) 93.27
E (s) 84.22
F (s) 68.40
H (s) 27.97
G (s) 30.95
J (s) 17.84
I (s) 18.05
K (s) 12.78
f1 (ppm)

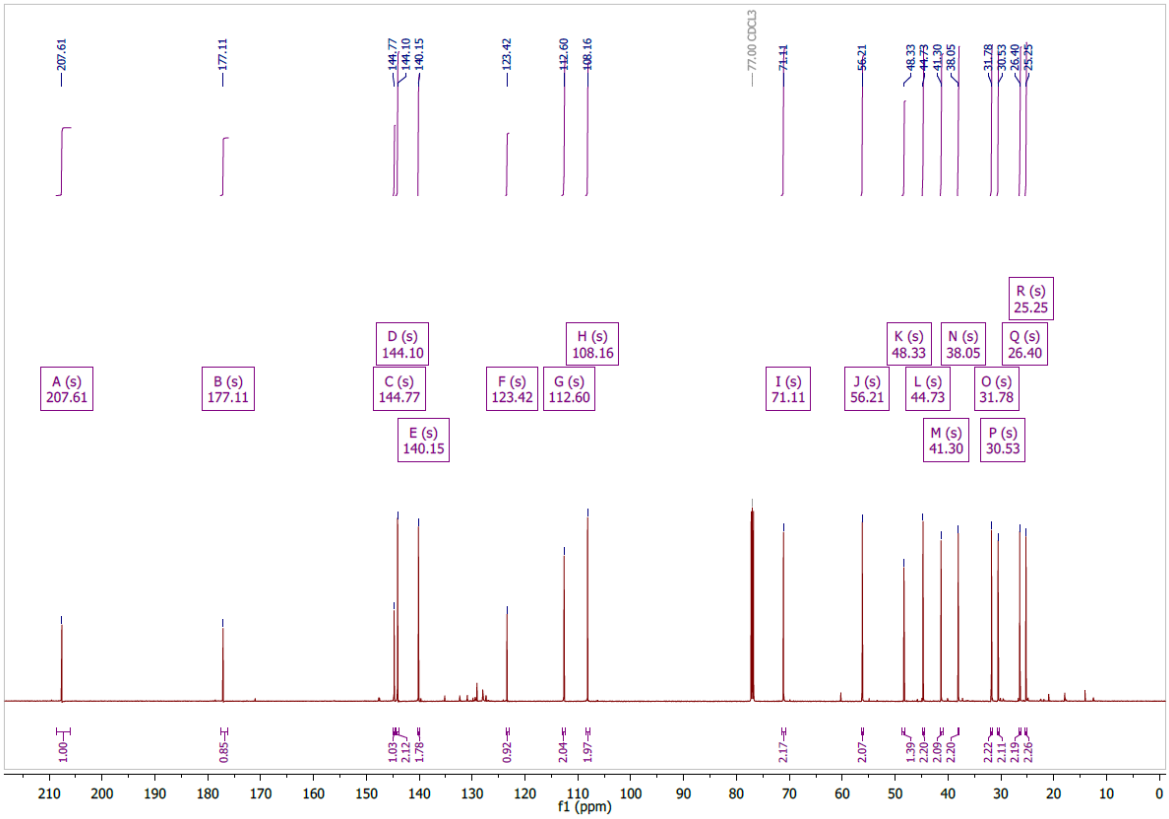

OTIPS
2.5.1.Ti.C1
(desired)
B (t) 7.43
A (dt) 7.47
C (dd) 6.41
D (dd) 5.48
E (dt) 4.92
K (m) 2.11
I (dd) 2.19
G (dd) 2.32
N (m) 1.68
R (d) 1.08
F (dd) 2.54
M (t) 1.94
O (ddt) 1.58
Q (m) 1.15
H (m) 2.24
P (ddt) 1.49
J (dt) 2.14
L (dd) 2.04
f1 (ppm)

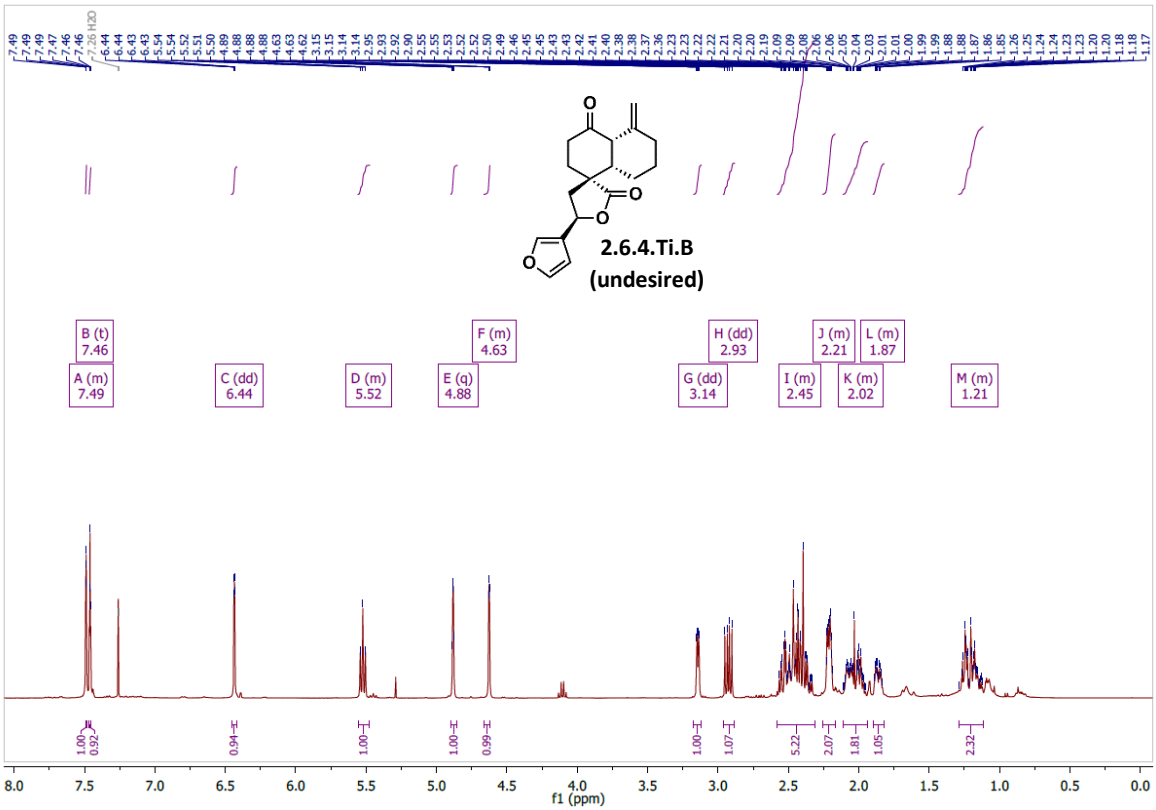

A (s) 179.10
B (s) 150.30
C (s) 143.94
D (s) 139.97
E (s) 124.10
F (s) 108.35
G (s) 103.67
H (s) 84.05
I (s) 71.40
J (s) 68.53
K (s) 46.71
L (s) 42.46
M (s) 38.37
N (s) 32.55
O (s) 26.85
P (s) 26.67
Q (s) 26.56
R (s) 18.58
S (d) 17.97
T (s) 12.61
f1 (ppm)

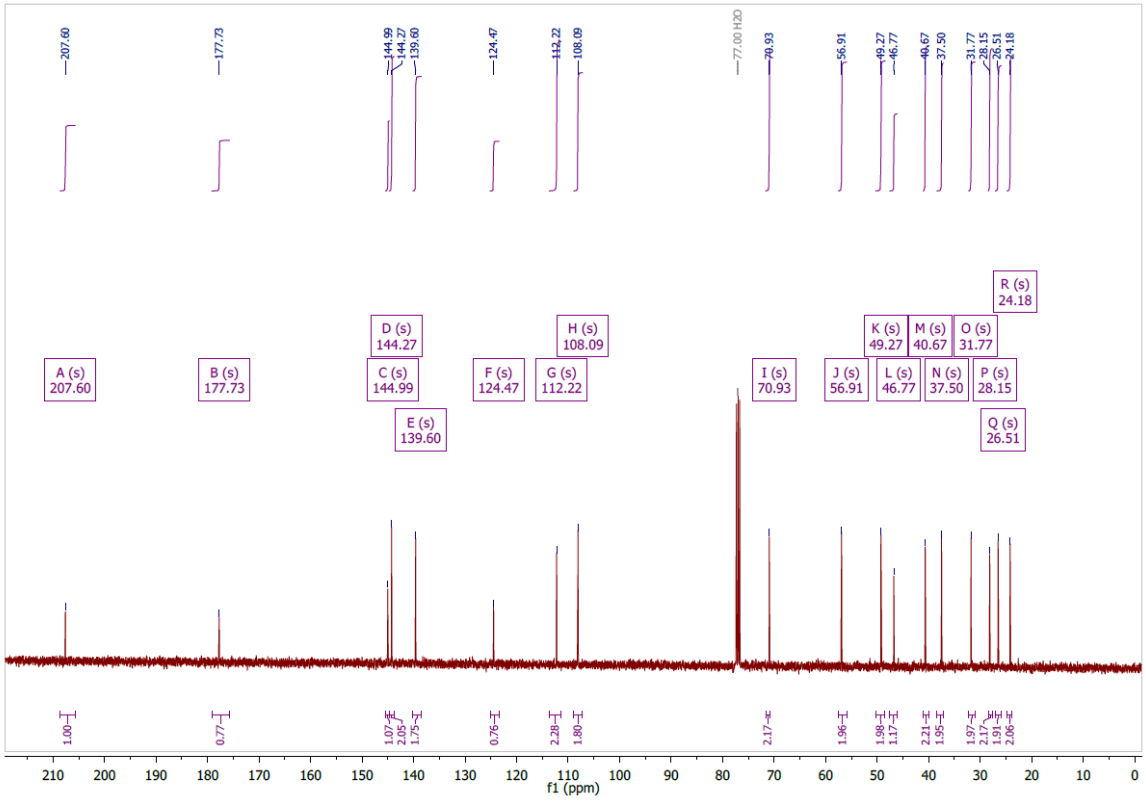

OTIPS
2.5.1.Ti.C1
(undesired)
B (s) 7.43
A (s) 7.43
C (dd) 6.38
D (m) 5.45
E (dt) 4.83
I (m) 2.14
G (m) 2.28
L (m) 1.69
N (m) 1.15
F (m) 2.38
K (t) 1.92
M (m) 1.40
H (dd) 2.19
O (m) 1.09
J (m) 2.08
f1 (ppm)

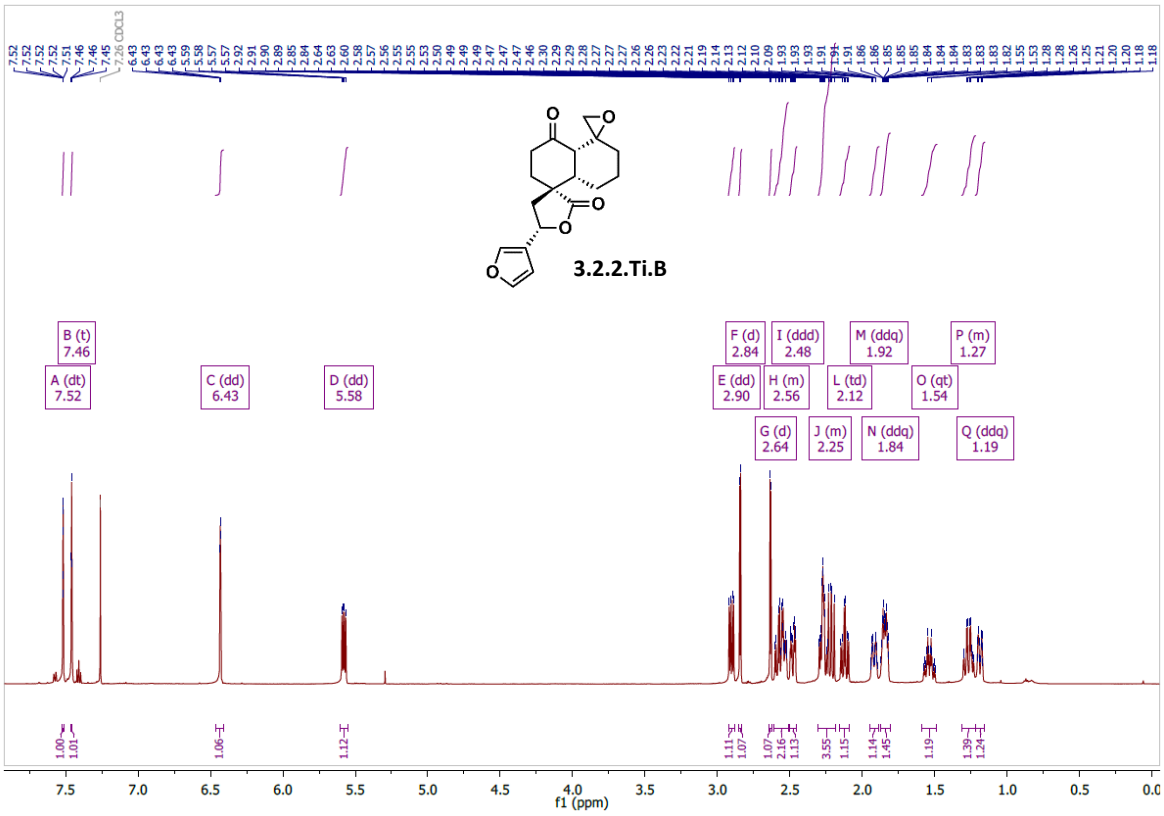

A (s) 178.97
B (s) 150.18
C (s) 143.82
D (s) 139.89
E (s) 124.01
F (s) 108.27
G (s) 103.57
H (s) 83.93
I (s) 71.28
J (s) 68.47
K (s) 46.59
L (s) 42.33
M (s) 38.24
N (s) 32.44
O (s) 26.75
P (s) 26.57
Q (s) 26.43
R (s) 18.46
S (d) 17.87
T (s) 12.50
f1 (ppm)

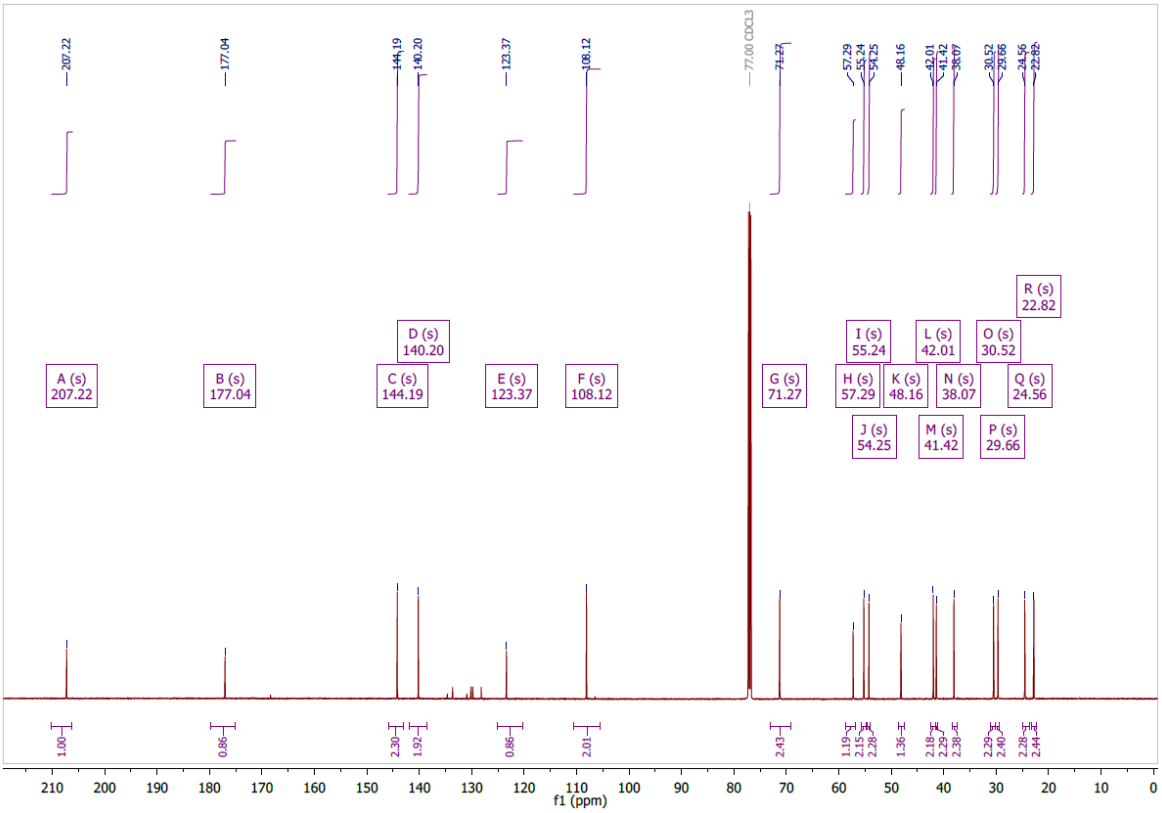

2.6.4.Ti.B
(desired)
A (d) 7.52
B (t) 7.45
C (m) 6.44
D (dd) 5.54
E (t) 4.93
F (d) 4.70
G (d) 3.37
H (dd) 3.02
I (td) 2.55
J (ddd) 2.47
M (m) 2.23
L (m) 2.28
O (ddt) 1.82
N (m) 1.87
P (qd) 1.30
Q (m) 1.20
f1 (ppm)

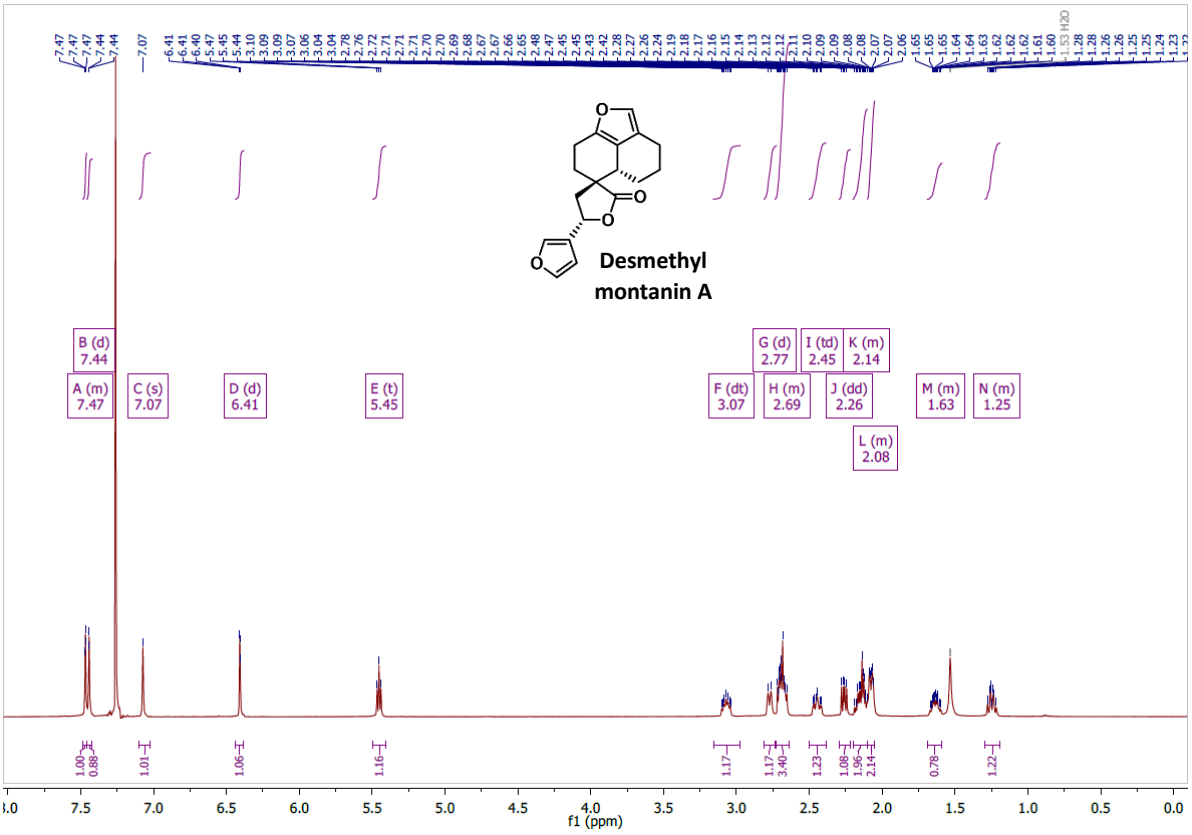

A (s) 207.61
B (s) 177.11
C (s) 144.77
D (s) 144.10
E (s) 140.15
F (s) 123.42
G (s) 112.60
H (s) 108.16
I (s) 71.11
J (s) 56.21
K (s) 48.33
L (s) 44.73
M (s) 41.30
N (s) 38.05
O (s) 31.78
P (s) 30.53
Q (s) 26.40
R (s) 25.25
f1 (ppm)

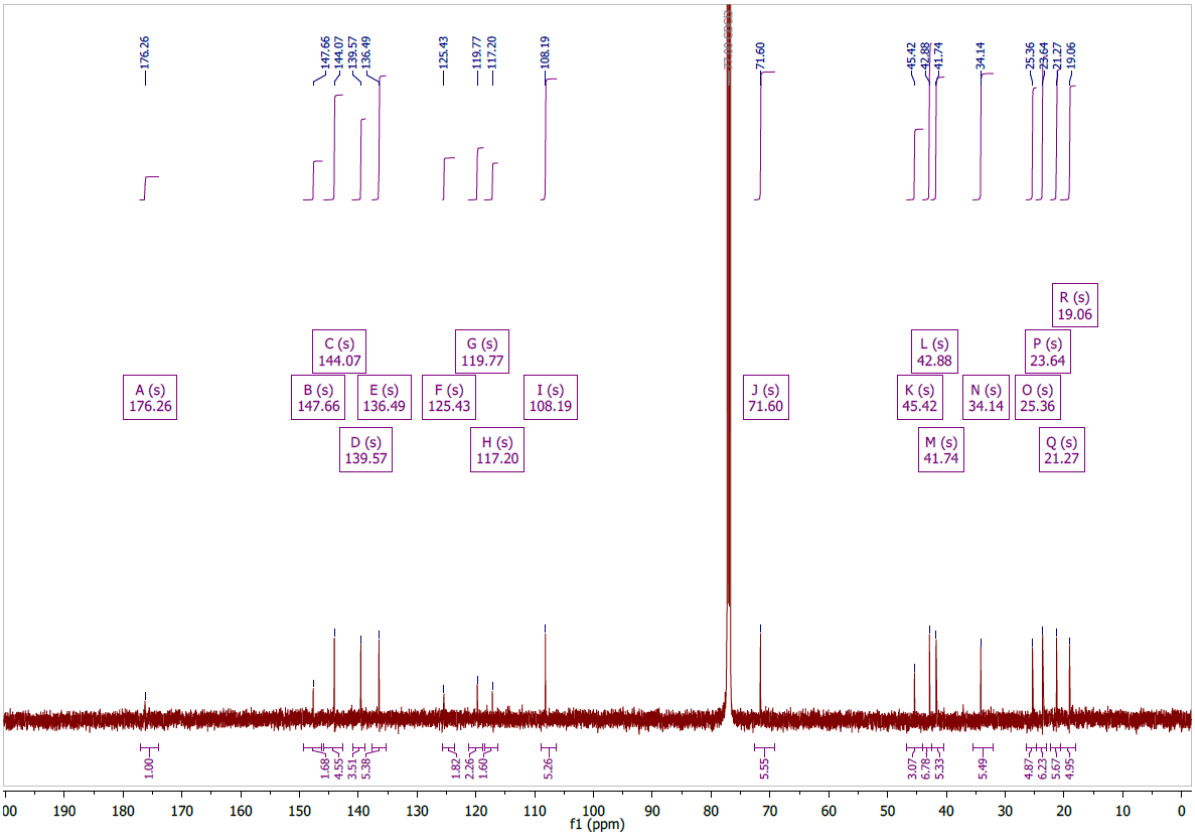

2.6.4.Ti.B
(undesired)
B (t) 7.46
A (m) 7.49
C (dd) 6.44
D (m) 5.52
F (m) 4.63
E (q) 4.88
H (dd) 2.93
G (dd) 3.14
J (m) 2.21
I (m) 2.45
L (m) 1.87
K (m) 2.02
M (m) 1.21
f1 (ppm)

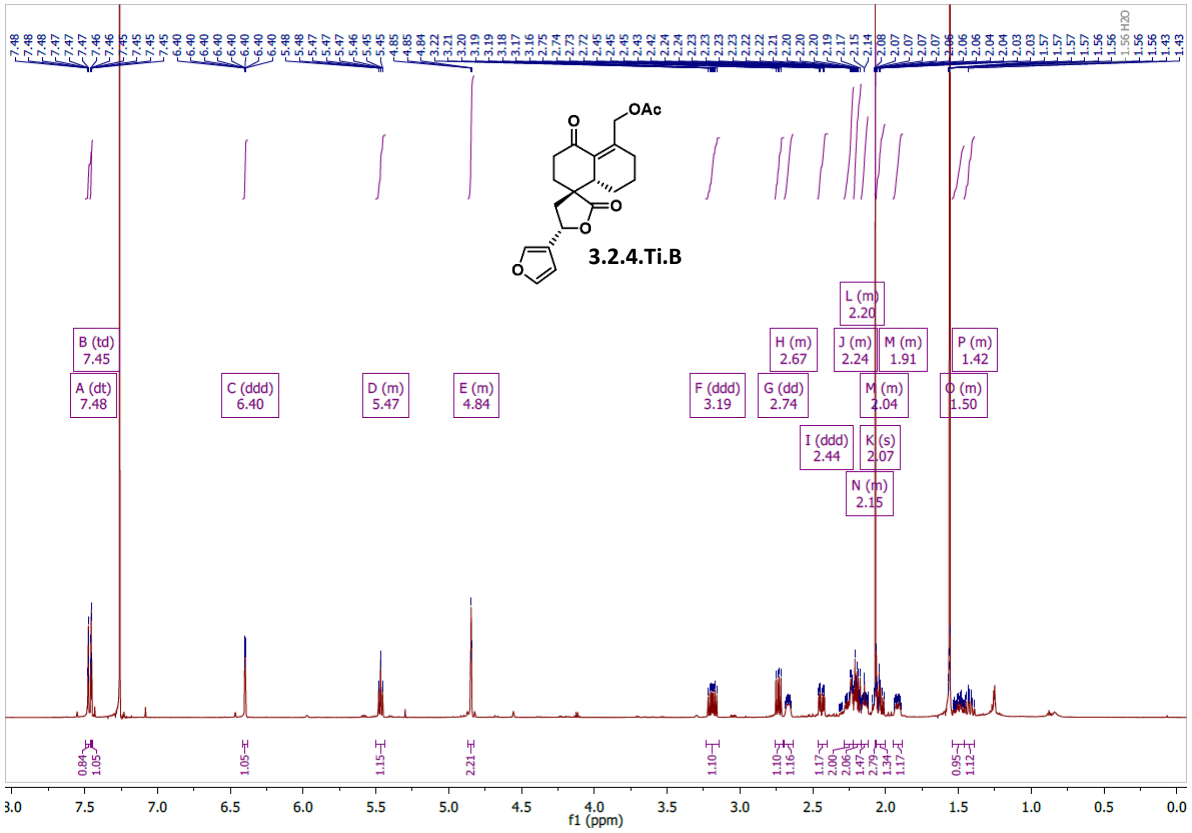

A (s) 207.60
B (s) 177.73
C (s) 144.99
D (s) 144.27
E (s) 139.60
F (s) 124.47
G (s) 112.22
H (s) 108.09
I (s) 70.93
J (s) 56.91
K (s) 49.27
L (s) 46.77
M (s) 40.67
N (s) 37.50
O (s) 31.77
P (s) 28.15
Q (s) 26.51
R (s) 24.18
f1 (ppm)

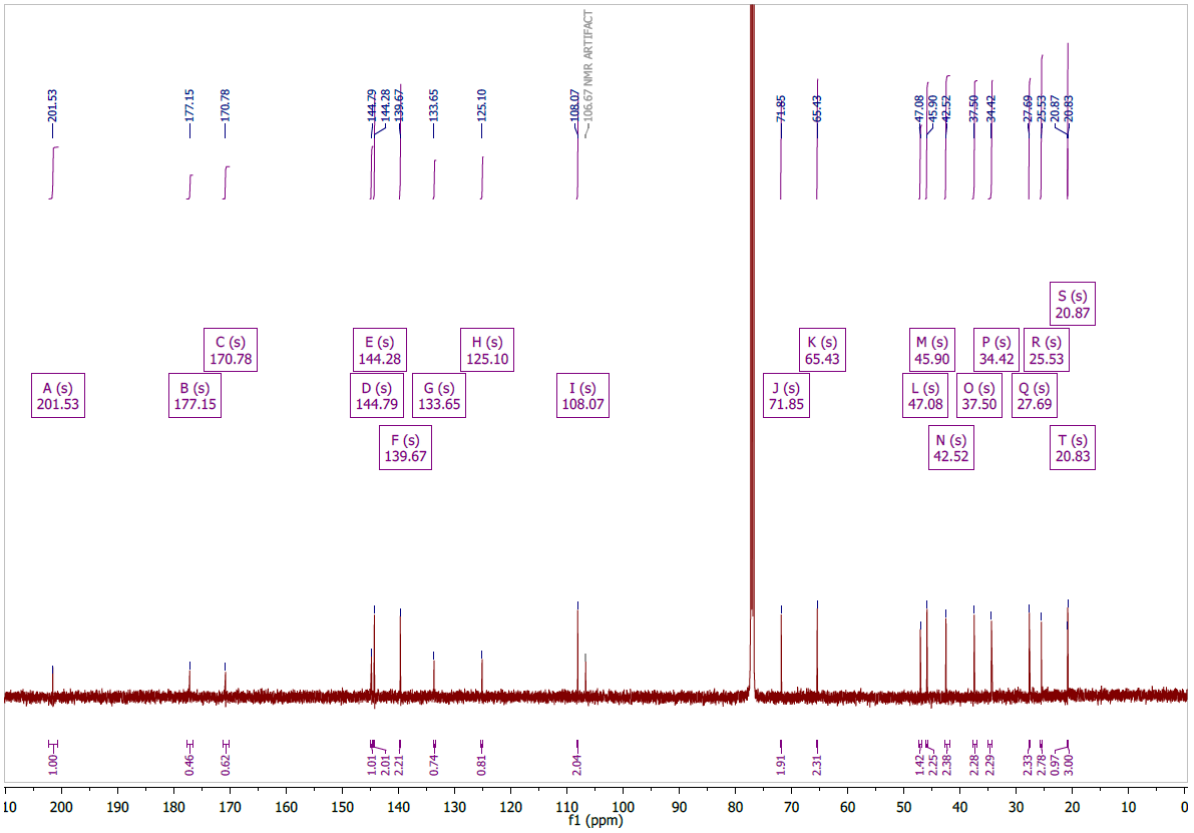

3.2.2.Ti.B
B (t) 7.46
A (dt) 7.52
C (dd) 6.43
D (dd) 5.58
F (d) 2.84
I (ddd) 2.48
M (ddq) 1.92
P (m) 1.27
E (dd) 2.90
H (m) 2.56
L (td) 2.12
O (qt) 1.54
G (d) 2.64
J (m) 2.25
N (ddq) 1.84
Q (ddq) 1.19
f1 (ppm)

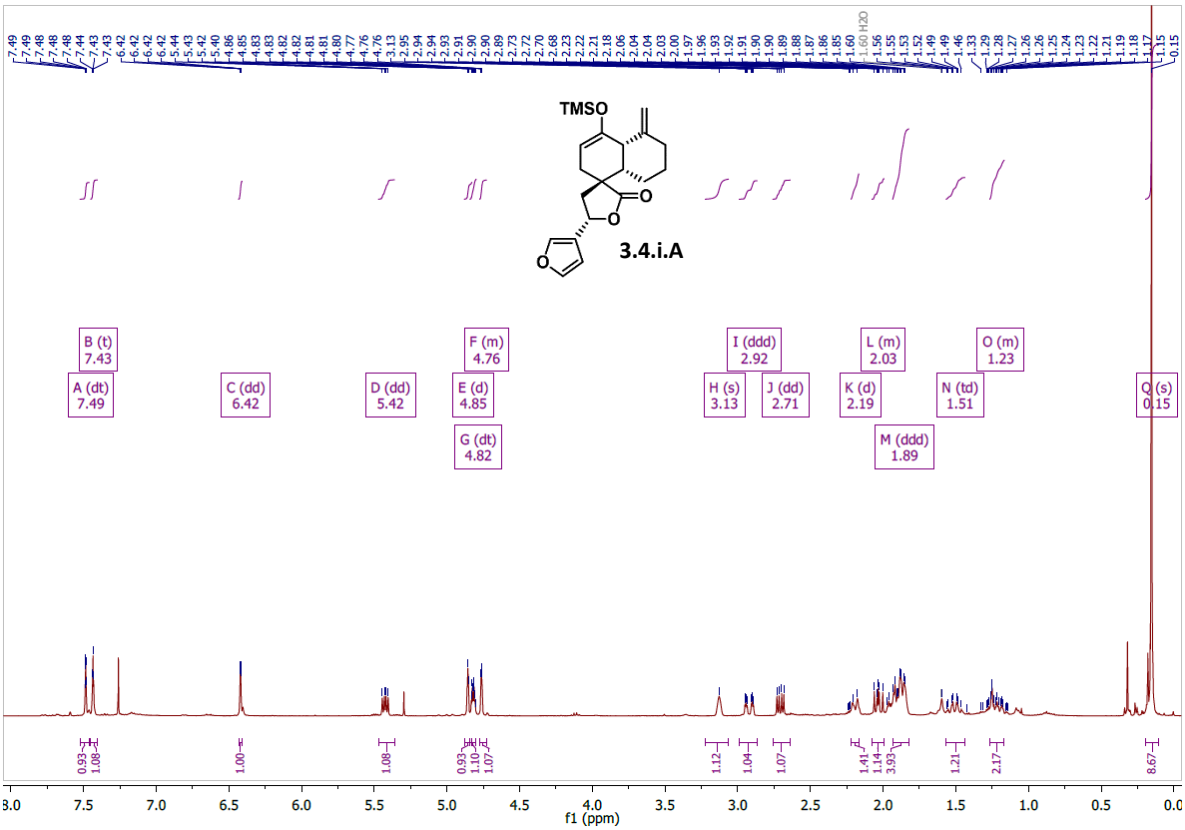

A (s) 207.22
B (s) 177.04
C (s) 144.19
D (s) 140.20
E (s) 123.37
F (s) 108.12
G (s) 71.27
H (s) 57.29
I (s) 55.24
J (s) 54.25
K (s) 48.16
L (s) 42.01
M (s) 41.42
N (s) 38.07
O (s) 30.52
P (s) 29.66
Q (s) 24.56
R (s) 22.82
f1 (ppm)

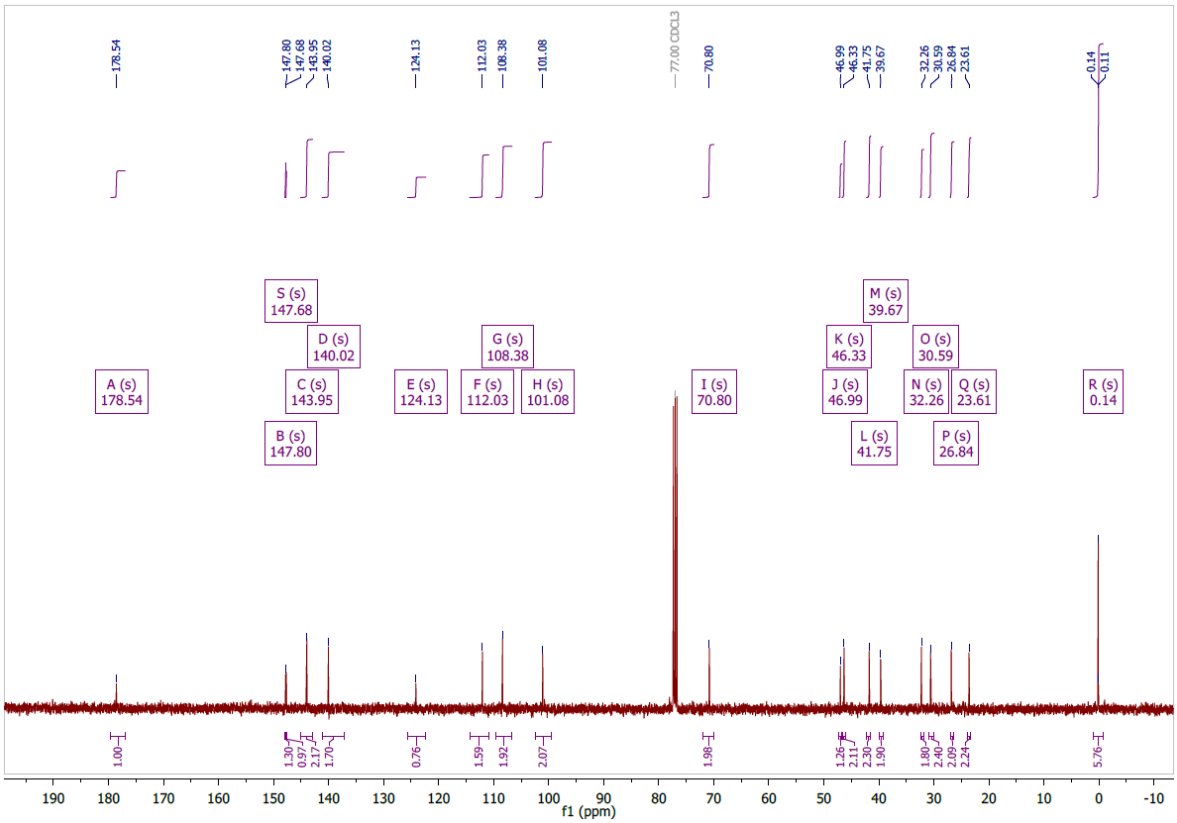

Desmethyl
montanin A
B (d) 7.44
A (m) 7.47
C (s) 7.07
D (d) 6.41
E (t) 5.45
G (d) 2.77
I (td) 2.45
K (m) 2.14
F (dt) 3.07
H (m) 2.69
J (dd) 2.26
L (m) 2.08
M (m) 1.63
N (m) 1.25
f1 (ppm)


A (s) 176.26
B (s) 147.66
C (s) 144.07
D (s) 139.57
E (s) 136.49
F (s) 125.43
G (s) 119.77
H (s) 117.20
I (s) 108.19
J (s) 71.60
K (s) 45.42
L (s) 42.88
M (s) 41.74
N (s) 34.14
O (s) 25.36
P (s) 23.64
Q (s) 21.27
R (s) 19.06
f1 (ppm)


OAc
O
O
O
O
3.2.4.Ti.B
B (td) 7.45
A (dt) 7.48
C (ddd) 6.40
D (m) 5.47
E (m) 4.84
F (ddd) 3.19
G (dd) 2.74
H (m) 2.67
I (ddd) 2.44
J (m) 2.24
K (s) 2.07
L (m) 2.20
M (m) 2.04
M (m) 1.91
N (m) 2.15
O (m) 1.50
P (m) 1.42
f1 (ppm)


A (s) 201.53
B (s) 177.15
C (s) 170.78
D (s) 144.79
E (s) 144.28
F (s) 139.67
G (s) 133.65
H (s) 125.10
I (s) 108.07
J (s) 71.85
K (s) 65.43
L (s) 47.08
M (s) 45.90
N (s) 42.52
O (s) 37.50
P (s) 34.42
Q (s) 27.69
R (s) 25.53
S (s) 20.87
T (s) 20.83
f1 (ppm)


TMSO
O
O
O
3.4.i.A
B (t) 7.43
A (dt) 7.49
C (dd) 6.42
D (dd) 5.42
F (m) 4.76
E (d) 4.85
G (dt) 4.82
I (ddd) 2.92
H (s) 3.13
J (dd) 2.71
L (m) 2.03
K (d) 2.19
M (ddd) 1.89
O (m) 1.23
N (td) 1.51
Q (s) 0.15
f1 (ppm)


S (s) 147.68
D (s) 140.02
C (s) 143.95
B (s) 147.80
A (s) 178.54
E (s) 124.13
G (s) 108.38
F (s) 112.03
H (s) 101.08
I (s) 70.80
M (s) 39.67
K (s) 46.33
O (s) 30.59
J (s) 46.99
N (s) 32.26
Q (s) 23.61
L (s) 41.75
P (s) 26.84
R (s) 0.14
f1 (ppm)

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