THE UNIVERSITY OF CHICAGO

SYNTHETIC STUDIES TOWARD *ENT*-KAURENE NATURAL PRODUCTS: AN APPLICATION OF CARBON–CARBON BOND ACTIVATION IN SYNTHESIS

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To my mom and dad. Thank you for everything you have given and taught me over the years.

This would not have been possible without you.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
Ac	acetate
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	di-tert-butyl dicarbonate
bod	bicyclo[2.2.2]octane-2,5-diene
BRSM	based on recovered starting material
Bu	butyl
Cb	N,N-diisopropylcarbamoyl
CBS	Corey–Bakshi–Shibata
C–C	carbon–carbon
C–H	carbon–hydrogen
CHP	cumene hydroperoxide
C–M	carbon–metal
C–N	carbon–nitrogen
C–O	carbon–oxygen
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	N,N′-Dicyclohexylcarbodiimide

DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DPEN	1,2-diphenylethylenediamine
dpm	dipropylene glycol methyl ether
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalence
ESI	electron spray ionization
esp	tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
g	gram
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz

L	liter
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	molarity
mg	milligram
MHz	megahertz
IMes	1,3-dimesitylimidazol-2-ylidene
mL	milliliter
m.p.	melting point
MS	molecular sieves
Ms	methanesulfonyl
N	Normality
n	normal
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
o	ortho
obs.	observed
o/n	over night
OTf	trifluoromethanesulfonate
p	para

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
(R)-DTBM-segphos	(R)-(−)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
ref.	reference
Rf	retention factor
r.f.	reflux
r.t.	room temperature
s	sec
SDS	sodium dioctyl phsophate
s.m.	starting material
SPS	solvent purification system
t	tert
TBAC	tetra-n-butylammonium chloride
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBS	*tert*-butylsilyl
TBTH	tertbutyltin hydride
TEA	triethylamine

temp.	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THP	tetrahydropyran
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TM	transition metal
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	trimethylsilyl
tol	toluene
Ts	toluenesulfonyl
µ	micro
VCP	vinylcyclopropane

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ABSTRACT

Recent work in the area of transition metal catalyzed carbon–carbon (C–C) σ-bond activation has allowed for new strategic bond disconnection. Toward this end, the Dong lab has developed a Rh(I)-catalyzed C–C bond activation/olefin insertion strategy to access highly polycyclic scaffolds found in natural products. Of specific interest are the *ent*-kaurenes eriocalyxin B and isodonal. Herein, we disclose our synthetic efforts toward the family through a C–C activation method. Other key steps in the synthesis include a tandem Birch reduction propargylation reaction as well as a carbon–oxygen bond cleavage / lactonization sequence.

CHAPTER 1

CARBON–CARBON BOND ACTIVATION STRATEGY IN SYNTHESIS

1.1 Introduction

The efficient construction of natural products and biologically activity compounds continue to intrigue and challenge synthetic chemist. Recent work in the area of transition metal (TM) catalyzed carbon–carbon (C−C) σ-bond activation has allowed for new strategic bond disconnection.[1] These novel approaches often reduce the number of required synthetic steps as well as improve atom economy when compared to classical methods. In 2015, Murakami and Ishida summarized the extent of C−C bond activation toward the synthesis of natural products and biologically active compounds.[2] This introductory chapter serves to highlight the work in recent years (2015-2020) toward the development of novel C–C bond activation strategies with a focus on their application in natural product and biologically active compound synthesis.

1.2 C–C Bond Activation by Oxidative Addition

A common strategy toward C–C activation is the oxidative addition of a TM into a C−C σ-bond. The process results in two reactive carbon–metal (C–M) bonds. Subsequent functionalization of the newly reactive C–M bonds is achieved through the migratory insertion of an unsaturated unit or cross-coupling reactions. This approach often relies on ring strain release of three- or four-membered rings. However, recent work is capable of expanding the scope of C–C activation by oxidative addition toward unstrained five-membered rings as well as acyclic ketones. Our first section highlights the oxidative addition strategy of C–C bond activation and its application in synthesis.

1.2.1 Oxidative Addition Into Cyclopropane

In 2010, the Yu group reported a novel [3 + 2 + 1] cycloaddition of 1-yne/1-ene vinylcyclopropane (VCP).[3] The reaction is homologous to the Pauson–Khand reaction, and is an efficient alternative to bicyclic cyclohexanone and cyclohexenone derivatives. The additional vinyl group stabilizes the initial C–C activated π-allyl rhodium species allowing for more mild reaction conditions compared to previous reports from the Narasaka group using simple cyclopropane starting materials.[4] Mechanistically, C–C activation of VCP **1** gives π-allyl rhodium species **2** (Figure 1.1). Migratory insertion of the tethered unsaturated united followed by carbon monoxide (CO) insertion gives 7-membered rhodacycle **4**. Reductive elimination and CO ligand exchange gives the desired [3+2+1] cycloadduct **6**. In recent years, the approach has been applied toward the synthesis of (±)-galanthamine, (−)-clovan-2,9-dione, and ent-1α-hydroxykauran-12-one.

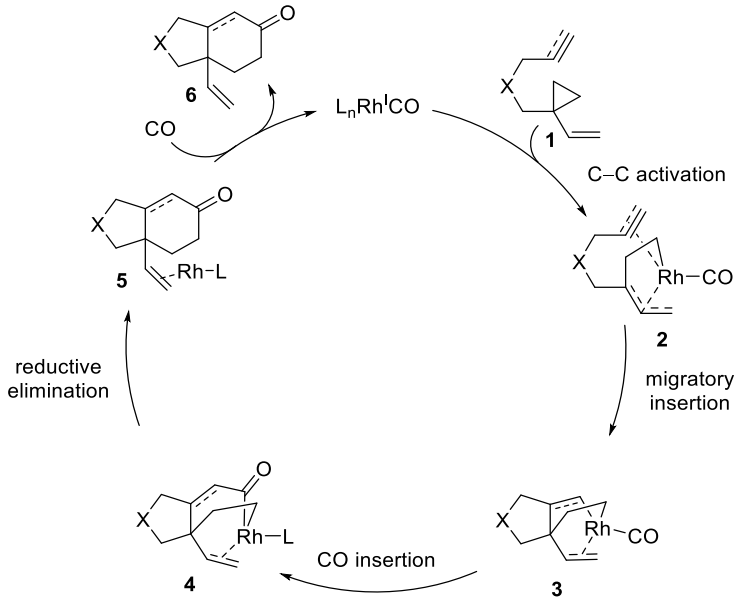
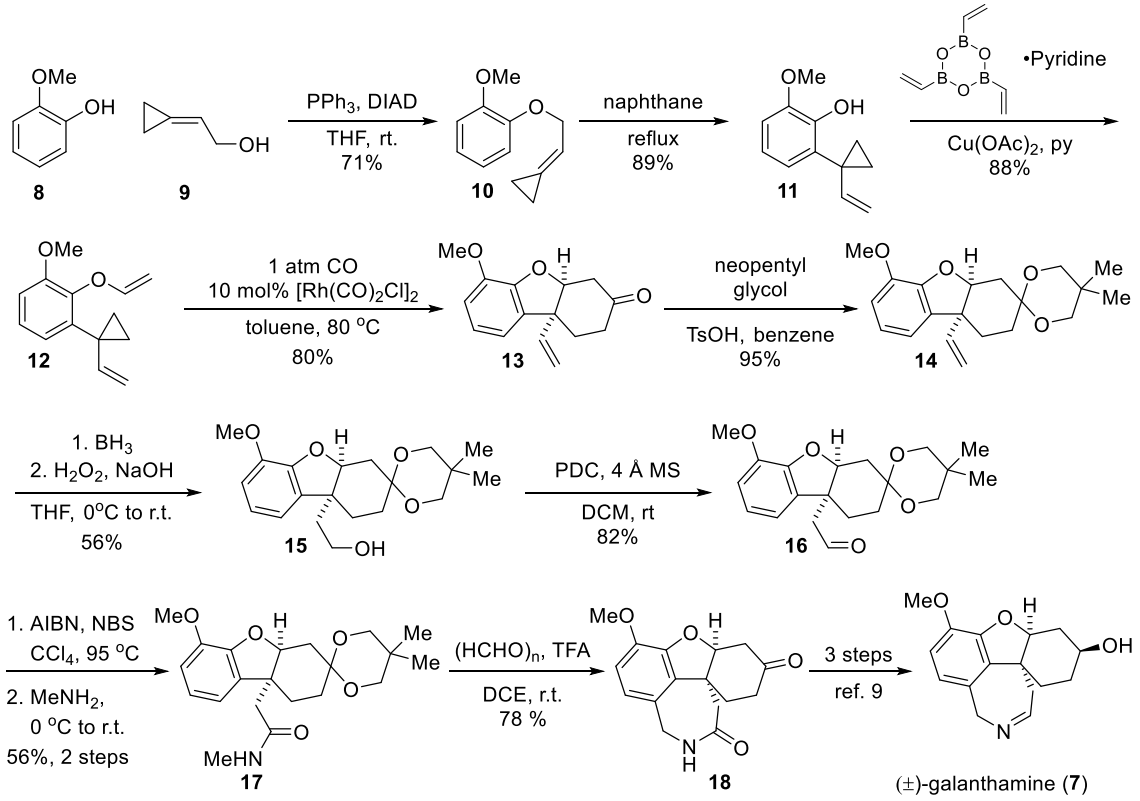


Figure 1.1 C–C Activation of Vinylcyclopropane

1.2.2 Formal Synthesis of (±)-Galanthamine

Galanthamine (**7**) belongs to the Amaryllidaceae family of natural products, with representative members including morphine and codeine.[5] Galanthamine is a reversible and competitive acetylcholine esterase inhibitor,[6] and has found use toward the treatment of Alzheimer's disease.[7] In 2015, the Yu group envisioned the construction the *cis*-hydrodibenzofuran motif of (±)-Galanthamine (**7**) by their [3+2+1] cycloaddition of 1-ene vinylcyclopropane.[8] In a forward manner, the Mitsunobu reaction between phenol **8** and allylic alcohol **9** afforded ether **10** (Scheme 1.1). A Claisen rearrangement followed by copper (Cu) catalyzed vinylation gave 1-ene-vinylcyclopropane **12**, setting the stage for the key [3+2+1] reaction via C–C activation. Treatment of **12** with rhodium carbonyl chloride $[Rh(CO)_2Cl]_2$ under CO atmosphere afforded the desired *cis*-hydrodibenzofuran motif **13**. After carbonyl protection, the terminal alkene was converted into the corresponding aldehyde **16** via hydroboration and oxidations. Aldehyde **16** was oxidized to acyl bromide and treated with methylamine gas to obtain amide **17**. The final step to complete the formal synthesis entailed a Picket-Spengler reaction with paraformaldehyde to furnish the lactam **18**, a known intermediate in the synthesis of (±)-galanthamine.[9]

Scheme 1.1 Formal Synthesis of (±)-Galanthamine

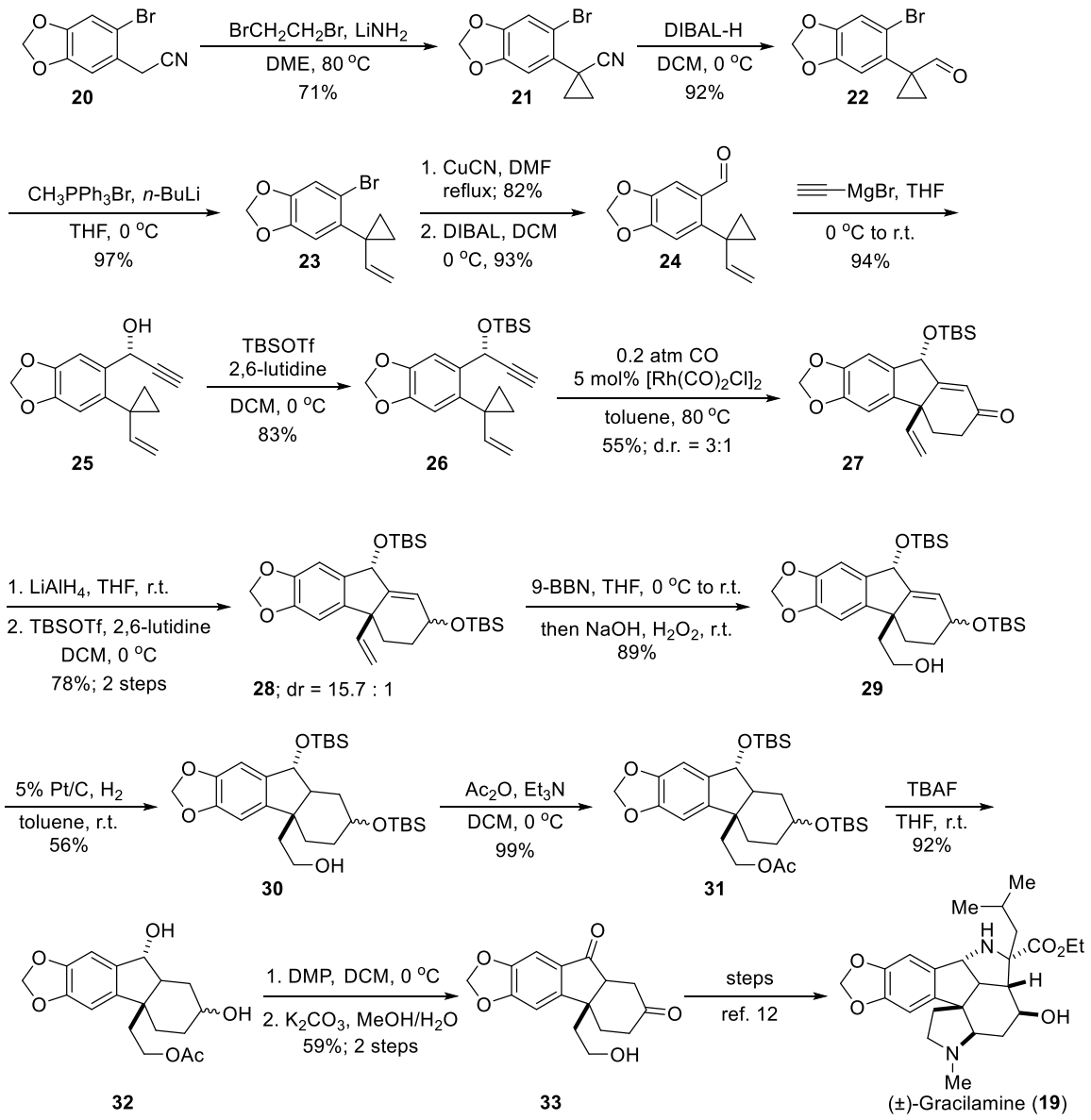


1.2.3 Synthesis of Gracilamine

Gracilamine (**19**) was isolated from *Galanthus gracilis* and also belongs to the Amaryllidaceae alkaloid family.[10] Of structural interest, gracilamine (**19**) contains a novel pentacyclic ring. In a similar fashion toward the synthesis of galanthamine (**7**), the core tricycle of **19** is envisioned from a rhodium (Rh) catalyzed [3+2+1] (Scheme 1.2).[11] The synthesis began with known bromide **20**. Cyclopropanation and cyanide reduction gave cyclopropane aldehyde **22**. The Wittig olefination resulted in vinyl cyclopropane **23**. Treatment of intermediate **8** with copper cyanide (CuCN) gave benzonitrile motif and reduction resulted in intermediate **24**. Gringard addition with ethynyl magnesium bromide resulted in **25**. Subsequent protection set up for the key C–C bond activation. The Rh(I)-catalyzed [3+2+1] proceeded smoothly to give [5.6] ring-fused product **27** in a diastereomeric ratio of 3:1. Attempts of 1,4 reduction were unsuccessful.

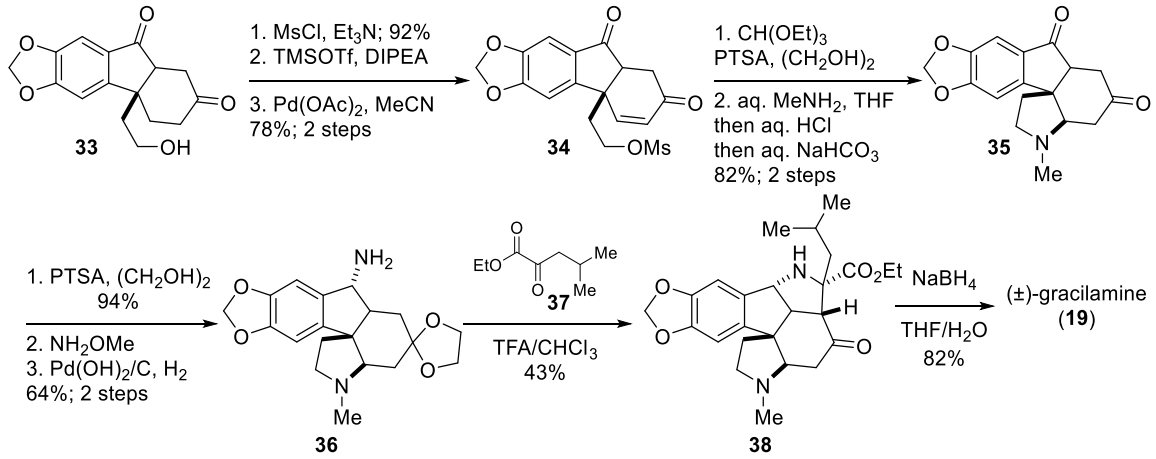
The authors finally settled for 1,2 reduction and subsequent protection to **28**. Hydroboration / oxidation of the terminal olefin gave intermediate **29**. Hydrogenation with platinum/carbon and hydrogen gas affording compound **30**. Acetylation of the primary alcohol followed by global silyl deprotection gave diol **32**. Oxidation of **32** with Dess–Martin periodinane gave the corresponding carbonyls. Acyl hydrolysis resulted in intermediate **33**, a known intermediate of Gao's synthesis toward (±)-gracilamine.[12]

Scheme 1.2 Formal Synthesis of (±)-Gracilamine



The completion of (±)-gracilamine (**19**) consisted of a mesylation and Saequesas-Ito oxidation to give enone **34** and the corresponding regio-isomer (Scheme 1.3).[12] Carbonyl protection allowed for sequential amination and 1,4-addition to **35**. Selective carbonyl protection and reductive amination gave amine **36** allowing for a Mannich addition with ester **37** to furnish the core **38**. Ketone reduction then gave (±)-gracilamine (**19**).

Scheme 1.3 Completion of (±)-Gracilamine

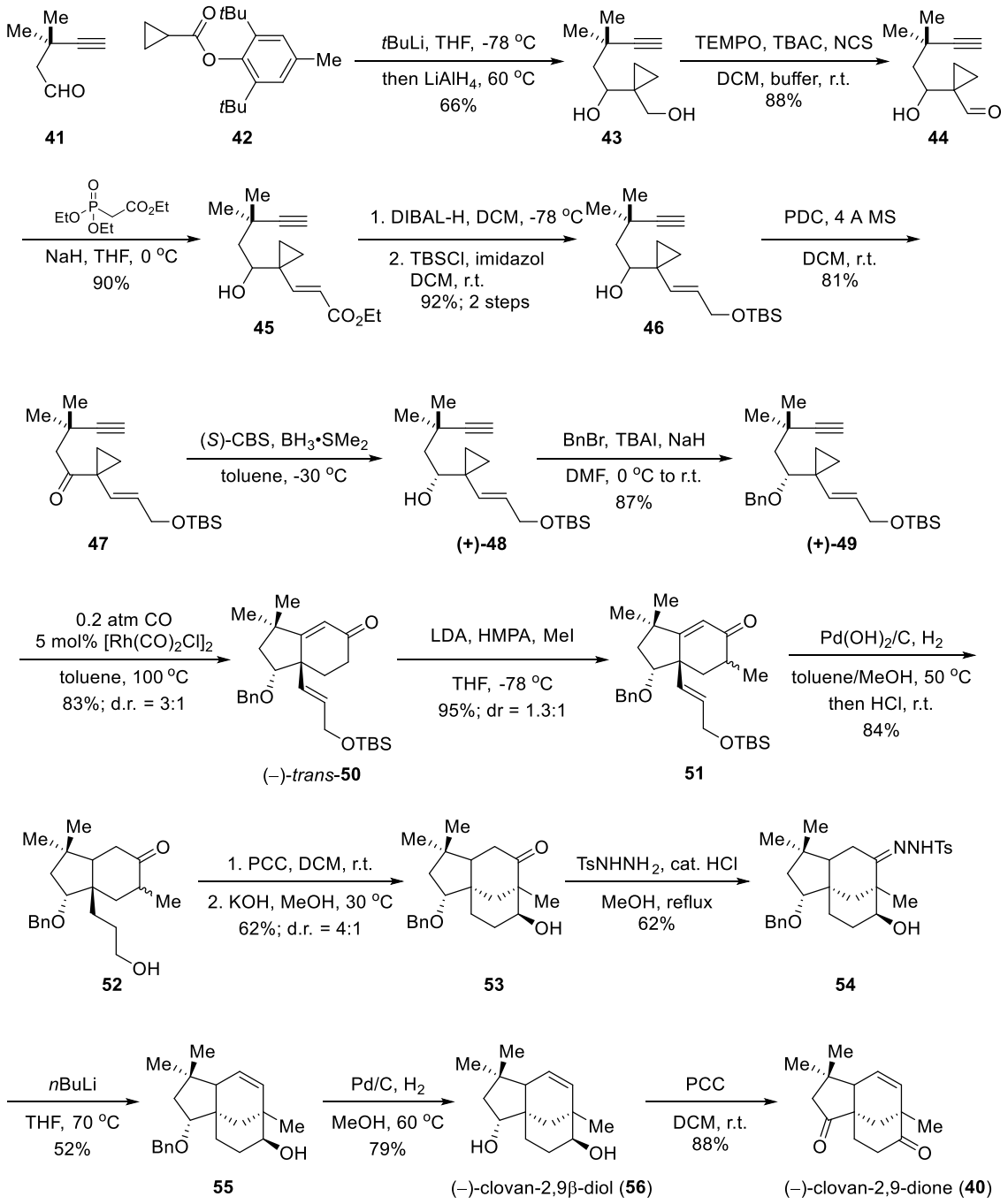


1.2.4 Synthesis of Clovan-2,9-dione

Clovan-2,9-dione (**40**) was isolated from the gorgonian coral *Rumphella antipathies* and exhibits an inhibitory effect in the production of superoxide anion and elastase released by human neutrophils.[13] Clovane-type natural products contain a tricycle [6.3.1.0] dodecane skeleton. In 2017, the Yu group constructed the [5.6.6] ring system of (−)-clovan-2,9-dione (**40**) using the Rh-catalyzed [3+2+1] cycloaddition of 1-yne-vinylcyclopropane with CO.[14] The synthesis begins with the intermolecular aldol condensation of known aldehyde **41** with ester **42** (Scheme 1.4). Global reduction gives diol **43**. Selective oxidation of the primary alcohol followed by Horner-Wadsworth-Emmons olefination yields E-vinyl cyclopropane **45**. Ester reduction and selective alcohol protection gives intermediate (±)-**46**. An enantioselective synthesis can be realized by oxidation and asymmetric Corey-Bakshi-Shibata reduction to (+)-**48**. Alcohol

protection furnishes the [3+2+1] cycloaddition precursor (+)-**49**. Treatment of (+)-**49** with $[Rh(CO)_2Cl]_2$ under CO atmosphere gave the desired gave the desired cycloaddition adduct (−)-*trans*-**50**. α-ketone methylation results in an inconsequential mixture of diastereomers **51**. One pot hydrogenation with Pearlman's catalyst and silyl deprotection yields intermediate **52**. Primary alcohol oxidation to the corresponding aldehyde set the stage for an intermolecular aldol reaction, resulting in a 4:1 mixture of diastereomers **53**. With the core scaffold constructed, the completion of (−)-clovan-2,9-dione (**40**) required standard functional group manipulation. Carbonyl reduction through a Shapiro reaction / hydrogenation sequence yields the natural product (-)-clovan-2,9b-diol (**56**) and global oxidation with pyridinium chlorochromate finished the synthesis of (−)-clovan-2,9-dione (**40**).

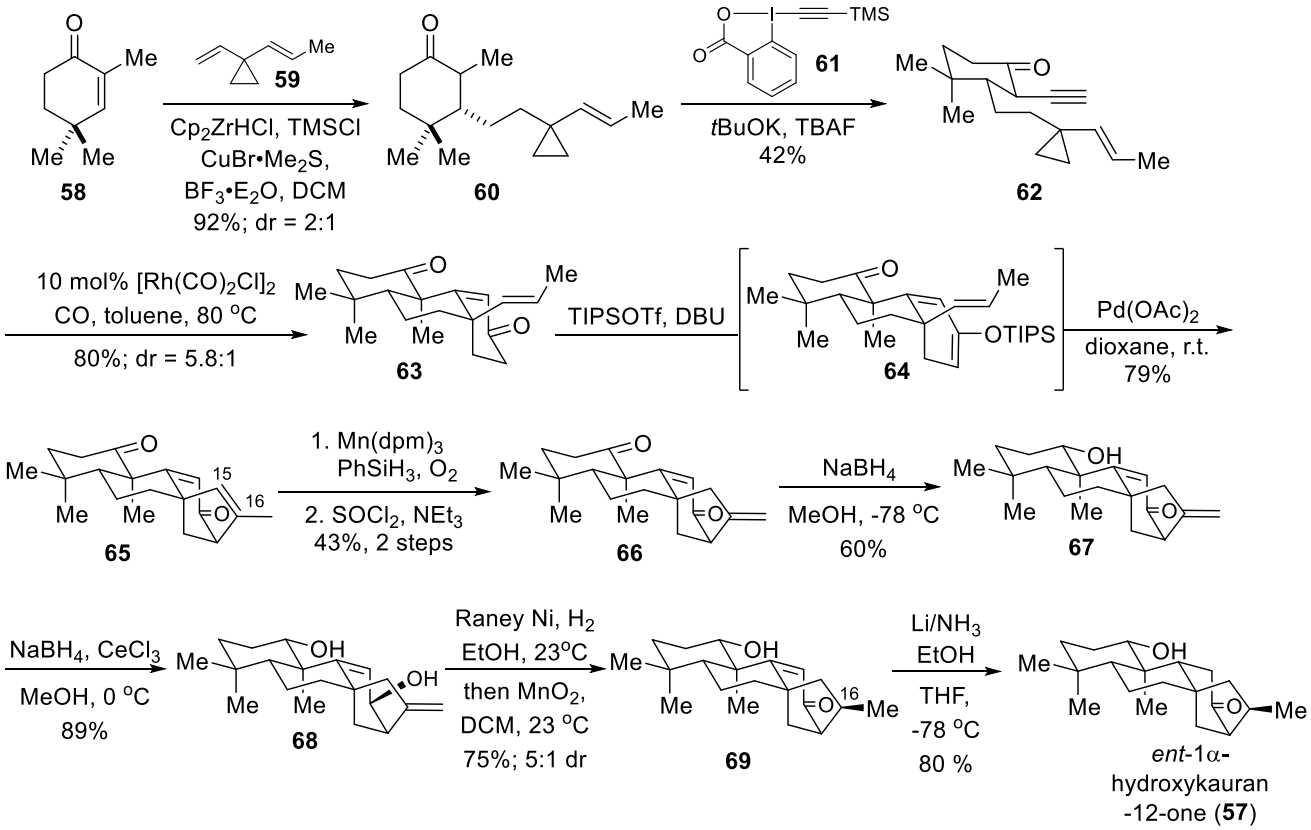
Scheme 1.4 Synthesis of (-)-Clovan-2,9-dione



1.2.5 Synthesis of *Ent*-1α-hydroxykauran-12-one

Ent-kaurene diterpenoids consist of a [6.6.6] tricyclic scaffold and contain a challenging [3.2.1] bicyclic moiety.[15] These natural products isolated for the *Isodon* genus exhibit many promising biological activities, such as anticancer, antifungal, and antiviral activities. In 2020, The Lei group envisioned that the core tetracyclic scaffold of *ent*-1α-hydroxykauran-12-one (**57**) could be constructed by the C–C activation of 1-yne-vinylcyclopropane (Scheme 1.5).[16] The synthesis began with Michael addition of VCP **59** on to enone **58** to obtain **60**. Subsequent alkynylation with **61** gave 1-yne-vinylcyclopropane **62**. The following key [3+2+1] cycloaddition via C–C activation proceeded in good yield to access tricyclic scaffold **63**, setting the stage for a palladium mediated cycloalkenylation. *In situ* generation of silyl enol ether **64** and treatment with palladium (II) acetate gave the desired [3.2.1] bicyclic moiety **65**. With the core structure of *ent*-kaurene diterpenoids in hand, various redox manipulations accessed a few of the *ent*-kaurene diterpenoid natural products. For example, isomerization of the C_{15}–C_{16} alkene to the terminal position proceeded via Mukaiyama hydration and dehydration to yield **66**. Ketone reductions then gave **68**. Hydroxyl directed reduction with Raney Ni provided the desired C_{16} stereochemistry followed by one pot allylic oxidation furnished **69**. **S**elective 1,4 reduction gave the first total synthesis of ent-1α-hydroxykauran-12-one **57**.

Scheme 1.5 Synthesis of *Ent*-1a-hydroxykauran-12-one



1.2.6 Oxidative Addition into Four-Membered Rings

In recent years, the Dong group as well as others has explored the scope four-membered ring compounds for C–C activation. A general mechanism is presented in Figure 1.2. Oxidative addition into the distal C–C bond of four-membered rings such as **70** gives the kinetically favored rhodacycle **71**. A decarbonylation / CO reinsertion sequence activates the proximal C–C bond activated rhodacycle **73**. Migratory insertion of a tethered unsaturated united followed by reductive elimination gives fused products such as **75**. In recent years the method has found use toward the synthesis of biologically active heterocycles as well as natural products.

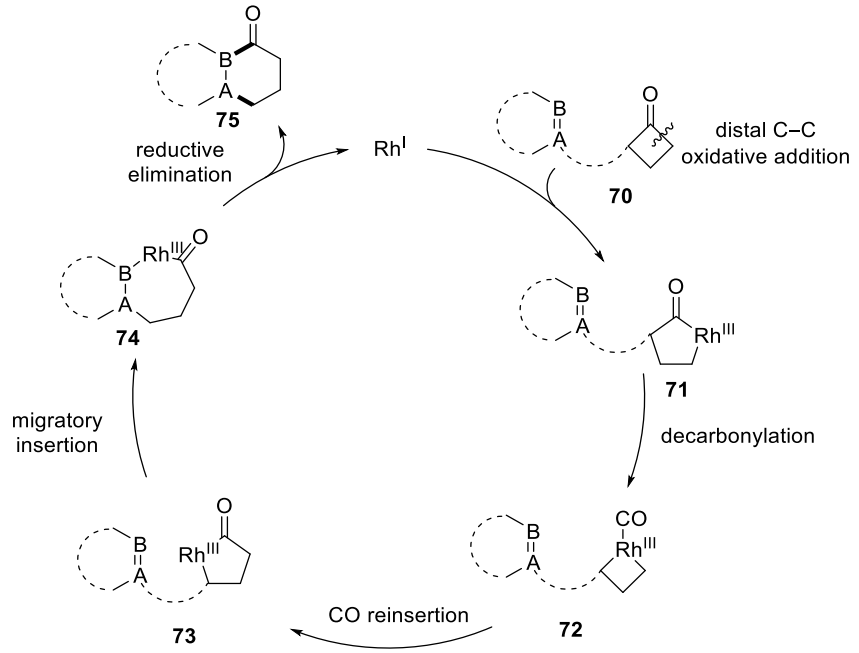


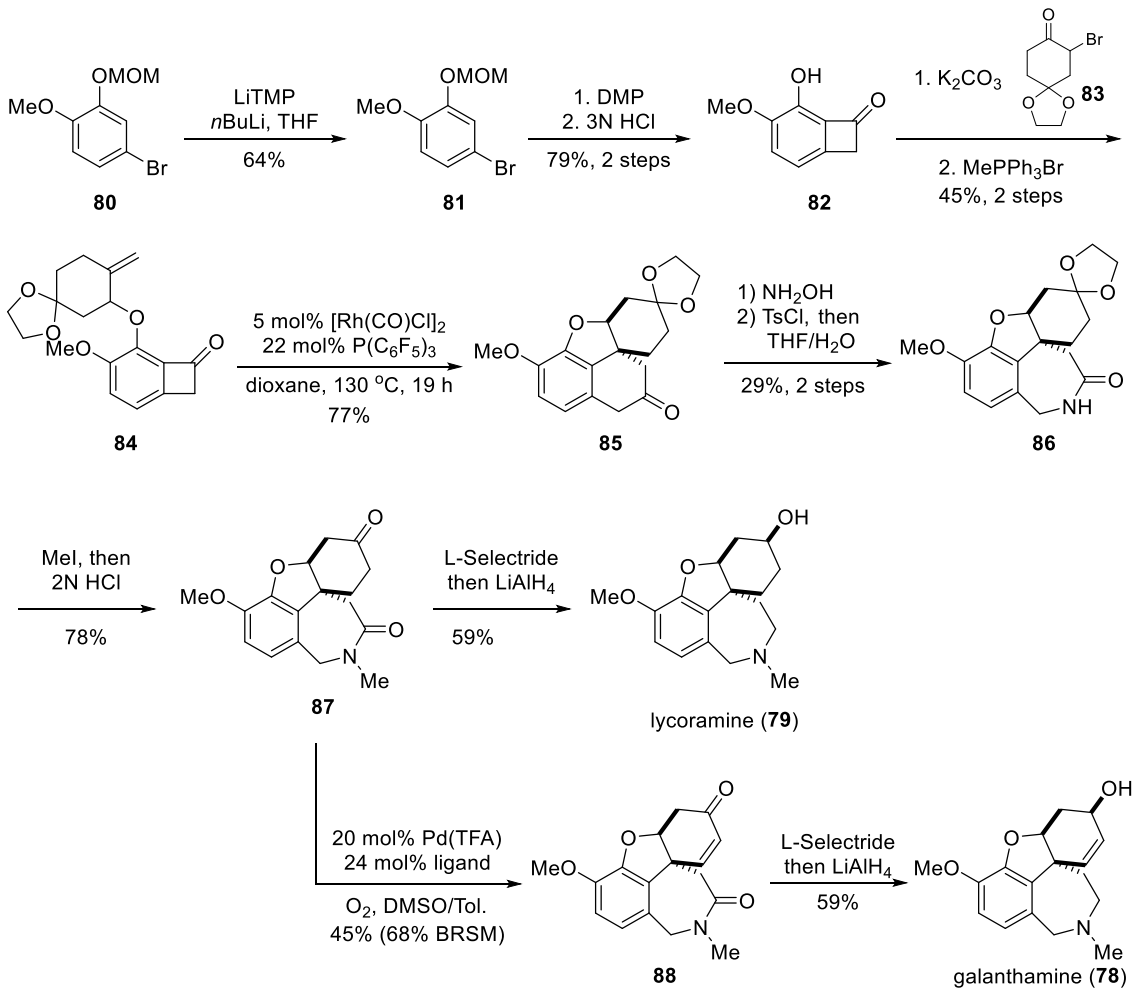
Figure 1.2 General C–C Activation Mechanism for Four-Membered Rings

1.2.7 Synthesis of Galanthamine and Lycoramine

Galanthamine (**78**) and lycoramine (**79**) belong to the Amaryllidaceae alkaloid family.[17] These natural products have been isolated from *Narcissus daffodil*[18] and exhibit neuron-protective activities.[19] Specifically, galanthamine (**78**) has found to decelerate the progression of Alzheimer diseases. The core tetracycle of the family was envisioned from a rhodium catalyzed C–C activation and late stage palladium carbon–hydrogen (C–H) functionalization.[20] The synthesis began with a [2+2] cycloaddition between benzyne precursor **80** and *in-situ* generated lithium enolate (Scheme 1.6). Oxidation and deprotection gave benzocyclobutenone **82**. Coupling with known alkyl bromide **83** followed by Wittig olefination gave C–C activation precursor **84**. The key C–C activation proceeded smoothly in the presence of $[Rh(CO)Cl]_2$ and $P(C_6F_5)_3$ to give tetracycle **85** in 77% yield on gram scale. A Beckman rearrangement furnaced lactam **86**. N-methylation followed by ketal deprotection gave the divergent ketone intermediate **87**. Diastereoselective ketone reduction with L-selectride followed by lactam reduction with lithium

aluminum hydride gave lycoramine (**79**). A palladium mediated oxidation of divergent intermediate **87** followed by similar reduction sequence yielded galanthamine (**78**).

Scheme 1.6 Synthesis of Galanthamine and Lycoramine

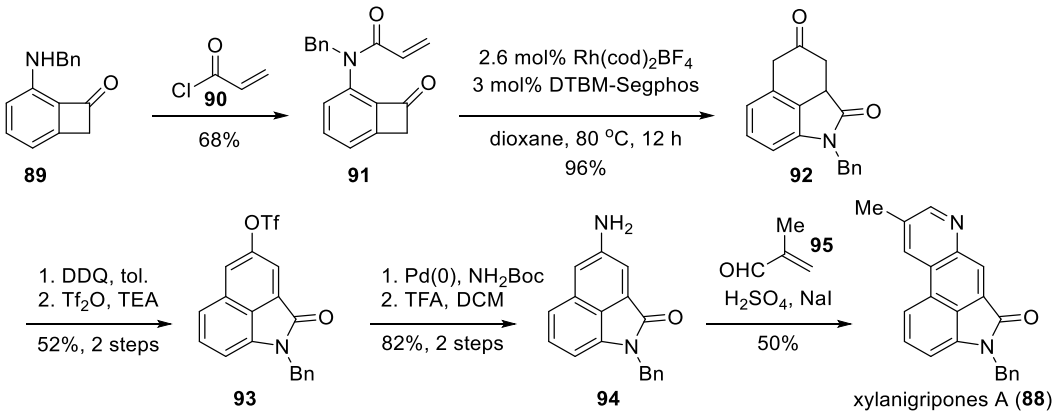


1.2.8 Synthesis of Xylanigripones A

Xylanigripones A (**88**) is an ergot alkaloid isolated from the fungus *Xylaria nigripes*.[21] To access the 3,4-polyfused oxindole ring system of xylanigripones A, an enantioselective Rh-catalyzed carboacylation of acrylic amides based on C–C activation was developed.[22] Initially, the acrylic amide **91** was accessed from amide formation between **89** and acryloyl chloride **90** (Scheme 1.7). The key C–C activation with Rh(I) gave an inconsequential mixture of tricyclic oxindole **92** in high yield. Oxidation by DDQ followed by triflation provided aryl triflate **93**. Buchwald-Hartwig

coupling followed by removal of the Boc protecting group gave naphthaylamine **94**. A one pot acid promoted annulation / benzyl deprotection completes the synthesis of xylanigripones A (**88**).

Scheme 1.7 Synthesis of Xylanigripones A

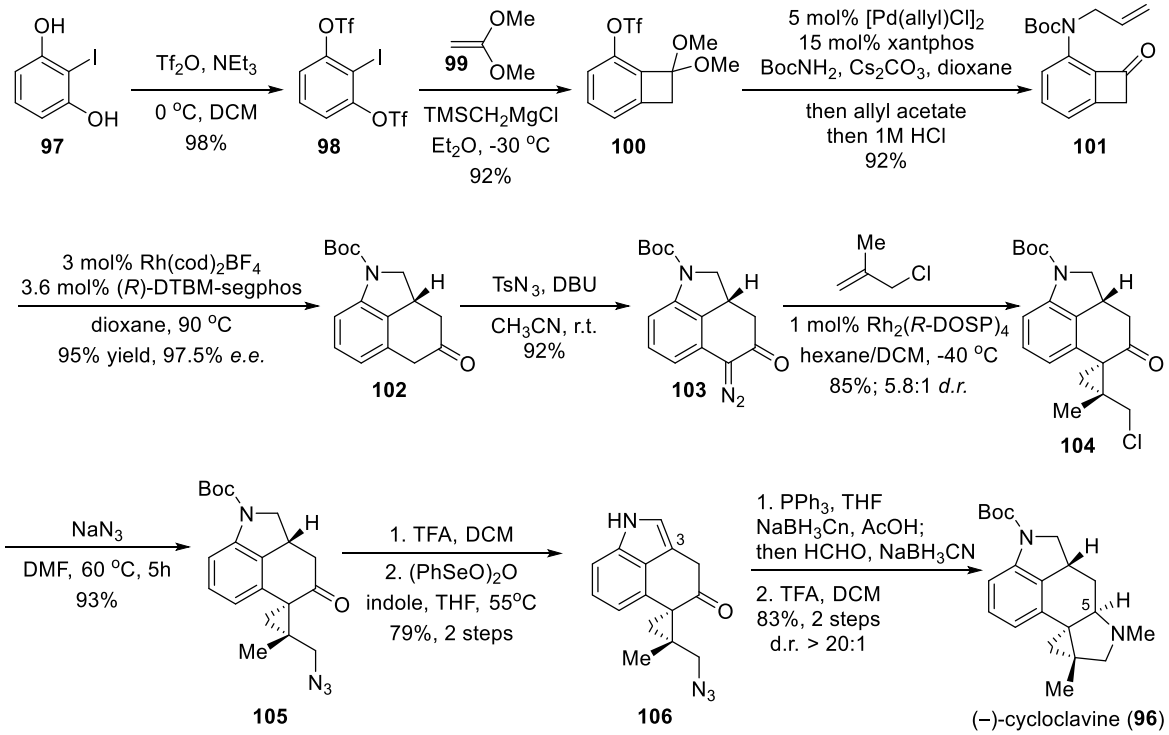


1.2.9 Synthesis of (–)-Cycloclavine

Isolated from *Ipomoea hildebrandtii*[23] and *Aspergillus japonicas*,[24] cycloclavine (**96**) is another member of the ergot alkaloid family with promising insecticidal and antiparasitic properties.[25] Key steps in the synthesis include a tandem carbon–nitrogen (C–N) bond coupling/allylic alkylation, an enantioselective Rh-catalyzed carboacylation, and a diastereoselective cyclopropanation.[26] In a forward manner, triflation of 2-iodoresorcinol (**97**) followed by [2+2] cycloaddition gave benzocyclobutane **100** (Scheme 1.8). The tandem C–N bond coupling/allylic alkylation sequence proceeded smoothly to give benzocyclobutenone **101** after acidic workup. Under the previously successfully Rh-catalyzed carboacylation conditions for the ether-linked substrates, poor yield and enantioselectivity was observed. A less bulky and more electron deficient catalytic system was found to be more efficient in overcoming the increased bulkiness and rigidity of a nitrogen linkage. Treatment of **101** with cationic rhodium in the presence of chiral phosphine ligand gave tetracycle **102** in high yield and enantioselectivity. The next

challenging step was an asymmetric cyclopropanation. Diazo-transfer gave intermediate **103**. Optimized conditions employed chiral Rh_2(*R*)-DOSP to give the desired diastereomer **104**. Control experiments with racemic catalyst show the reaction is substrate controlled, an example of matched/mis-matched case. With cyclopropane **104** in hand the completion of cycloclavine (**96**) was near. Displacement of chloride with sodium azide gave **105**. Boc-deprotection and dehydrogenation gave indole motif **106**. This dehydrogenation at C_3 was found to be crucial to install the correct stereochemistry at C_5 in the following aza-Wittig reduction/reductive amination sequence to yield the (–)-cycloclavine (**96**).

Scheme 1.8 Synthesis of (–)-Cycloclavine



1.2.10 Synthesis of the Proposed Structure of Cycloinumakiol and Structural Revision

The first synthesis of the proposed structure of cycloinumakiol (**107**) was enabled by C–C activation.[27] Cycloinumakiol was isolated from *podocarpus latifolius* and belongs to the inumakiol family of diterpenes.[28] The proposed structure of cycloinumakiol featured an unusual

oxidation and etherification of C_{20} resulting in a tetracyclic ring skeleton, an uncommon motif of the tricyclic inumakiol-family (Figure 1.3).

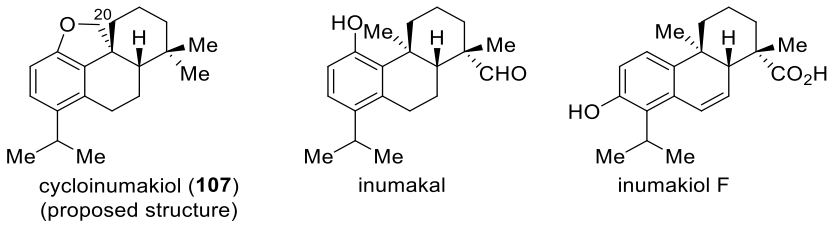
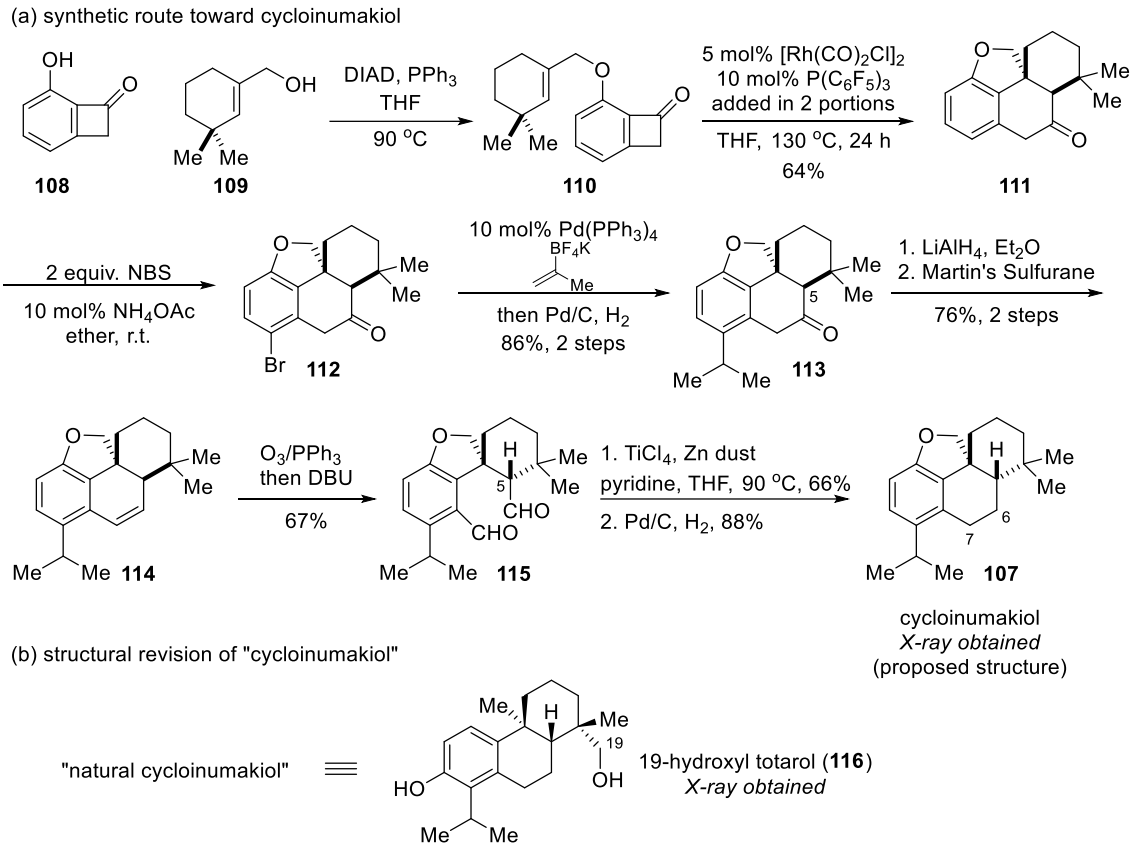


Figure 1.3 Representative Inumakiol-Family Diterpenes

The synthesis of proposed cycloinumakiol (**107**) began with the Mitsunobu coupling of benzocyclobutenone **108** and allylic alcohol **109** to give C–C activation precursor **110** (Scheme 1.9). Previously successful Rh(I)/phosphine ligand combination were found to be unsuccessful with the sterically hindered trisubstitued olefin. The combination of electron deficient $[Rh(CO)_2Cl]_2$ with π-acidic tris(perfluorophenyl)phosphine $[P(C_6F_5)_3]$ was found to be optimal for the challenging substrate. Electrophilic aromatic substitution followed by Suzuki cross-coupling and hydrogenation completed the carbon scaffold **113**. However, direct epimerization at C_5 was unsuccessful and a four step epimerization was necessary. Carbonyl reduction followed by dehydration with Martin's sulfurane gave styrene motif **114**. Oxidative cleavage and epimerization gave the desired stereochemistry at C_5. A McMurry coupling reinstalled the C_6–C_7 bond and hydrogenation completed the proposed structure of cycloinumakiol (**107**). The synthetic structure was unambiguously confirmed by X-ray crystallography, but did not match the spectroscopic data of natural cycloinumakiol. The structure of natural cycloinumakiol was later elucidated by x-ray crystallography to be 19-hydroxy totarol (**116**).

Scheme 1.9 Synthesis of the Proposed Structure of Cycloinumakiol (a) synthetic route toward proposed cycloinumakiol and (b) structural revision of "cycloinumakiol"

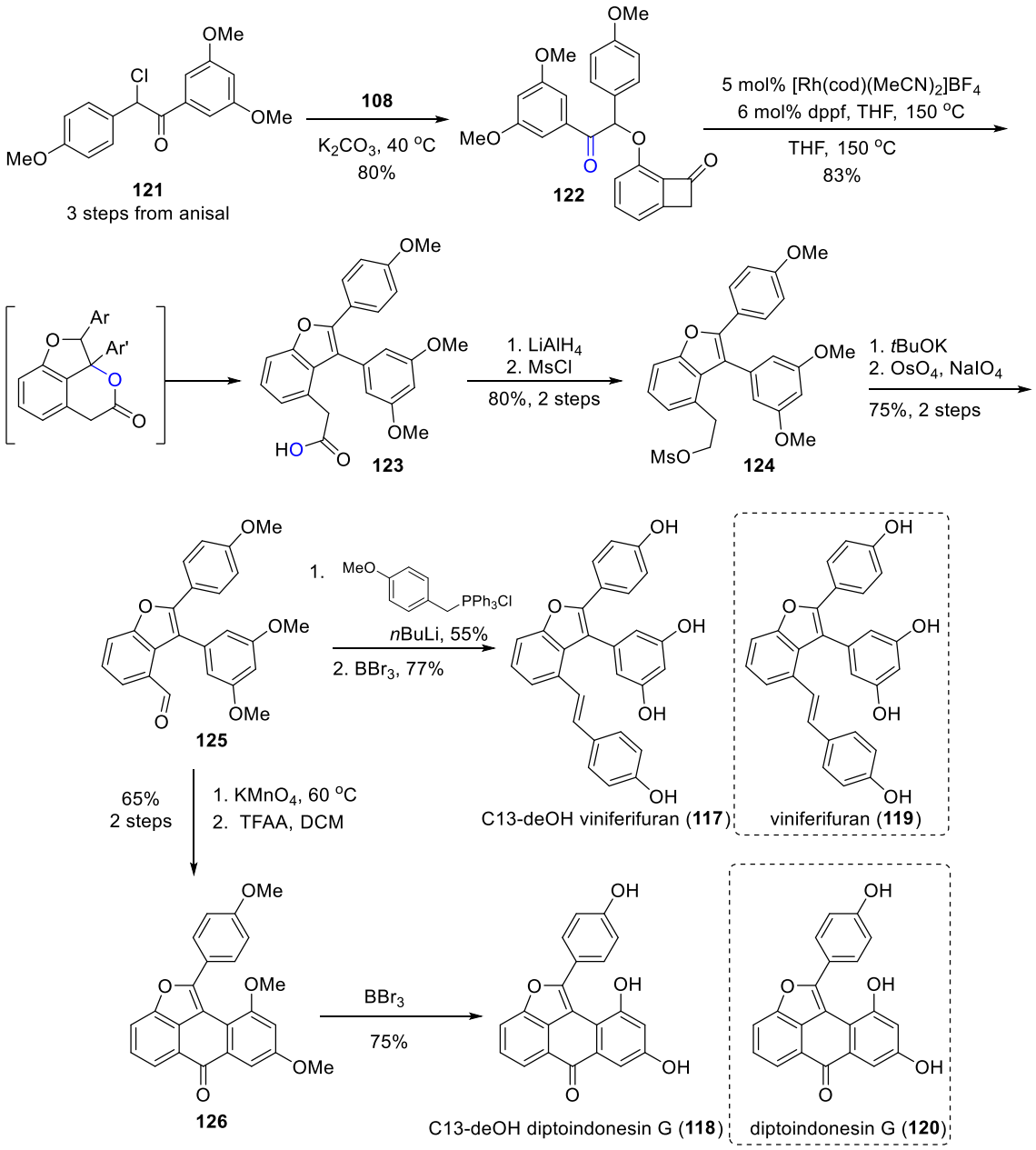


1.2.11. Synthesis of C_{13}-deOH-Viniferifuran and C_{13}-deOH-Diptoindonesin G

A novel carboacylation/aromatization cascade of carbonyls triggered by C–C activation was developed to access substituted benzofuran scaffolds.[29] The method was used to synthesize two members of the oligostilbene family: C_{13}-deOH-viniferifuran (**117**) and C_{13}-deOH-diptoindonesin G (**118**) (Scheme 1.10). Viniferifuran (**119**) was isolated from *Vitis vinifera*, fluoresces a light-blue color under ultraviolet light,[30] and acts as anti-inflammatory agent by inhibition of tyrosine-protein kinase SYK.[31] Diptoindonesin G (**120**) was isolated from *Hopea mengarawan* and shows an anti-proliferation effect in murine leukemia cells.[32] The synthesis of both natural products began with the coupling of acyloinchloride **121** with **108**. Treatment of **122**

with Rh(I) precatalyst in the presence of phosphine ligand gave the substituted benzofuran **123**. Conversion of the resulting carboxylic acid employing standard functional group manipulations gave divergent intermediate benzaldehyde **125**. A Wittig olefination followed by global methyl deprotection gave C_{13}-deOH-viniferifuran (**117**). The completion of C_{13}-deOH-diptoindonesin G (**118**) required an oxidative aromatization of divergent intermediate **125** followed by a similar global demethylation.

Scheme 1.10 Synthesis of C13-deOH-Viniferifuran and C13-deOH-Diptoindonesin G

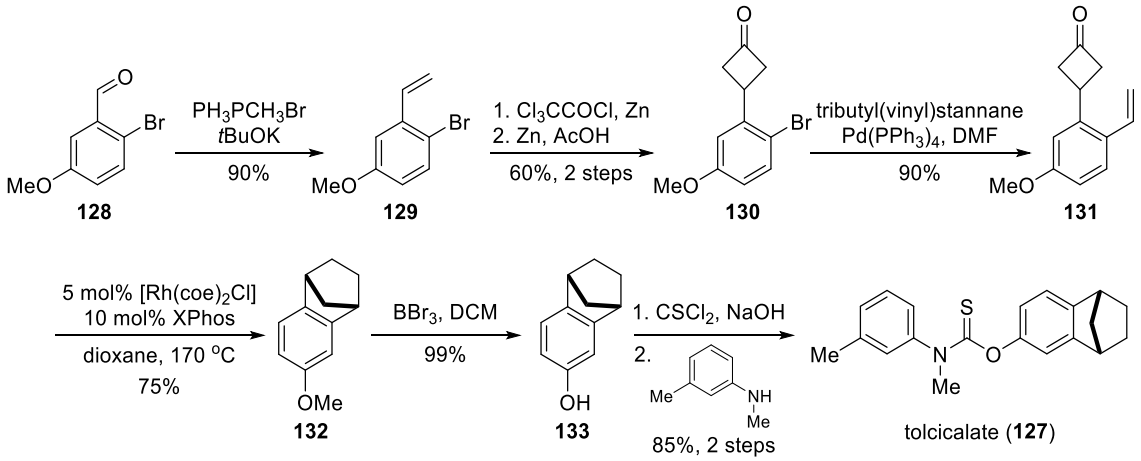


1.2.12 Synthesis of Tolcicalate

Tolcicalate (**127**) is used as an antifungal drug in its racemic form and exhibits a saturated, non-oxygenated [2.2.1] bridged bicycle that would be difficult to construct with conventional methods.[33] An ideal approach would be a [3+2] cycloaddition between inactivated cyclopropanes and olefins, a method that has remained elusive. A synthetic equivalent is a proposed [4+2-1]

between cyclobutanone and olefins. The challenge is overcoming the established [4+2] reaction. With arene tethers, such as the one found in tolcicalate (**127**), it was found that the competing [4+2] product was formed in equal amount compared to the [4+2-1] product.[34] The CO concentration was reduced by choosing a larger reaction vessel (i.e. increasing the head space), thus accelerating the decarbonylative pathway. The successful development of this method has been applied to the synthesis of tolcicalate (**127**). Beginning from aldehyde **128**, Wittig olefination gave styrene **129** (Scheme 1.11). A [2+2] reaction with *in situ* generated dichloroketene gave cyclobutenone **130** after reduction. Stille coupling installed the desired alkene and set the stage for the key [4+2-1]. Treatment of **131** with Rh(I) resulted in the desired C–C activation and formation of bridged cyclopentane **132**. The completion of tolcicalate (**127**) then required demethylation and thiocarboamate formation.

Scheme 1.11 Synthesis of Tolcicalate



1.2.13 Approach Toward N-Heterocycles

The prior strategy was also extended to nitrogen tethered substrates to access [3.2.1] bridged heterocycles (Figure 1.4).[34] During the reaction optimization, it was found that the use of bulky monodentate ligands is crucial to prevent saturation of the metal center and allow for olefin coordination. The method is fairly tolerable of cyclobutanones with various substituents at the C_3

position, including a hydrogen substituent that is known to undergo facile β-hydrogen elimination. The method does suffer when sterically hindered olefins are used as coupling partners; the competing cyclopropane side products are obtained. Nevertheless, a 1,1-disubstitued alkene gave the desired product in modest yield. The pharmaceutical sector has an interest for stereochemically rich N-heterocycles.[35]

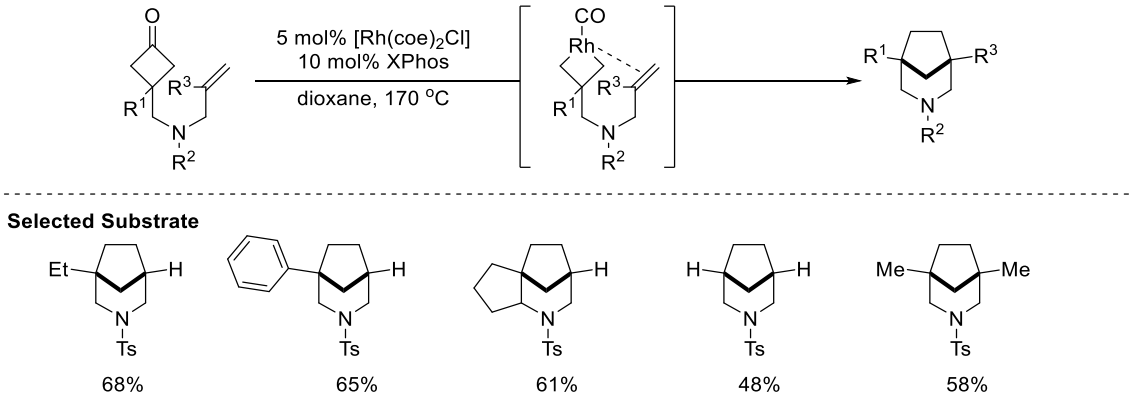


Figure 1.4 [4+2–1] Approach Toward Bridged N-Heterocycles

In addition, a [4+2] reaction enabled by C–C activation of cyclobutanone was developed to access [6.5.6] or [5.6] polycyclic carbo- and heterocycles (Figure 1.5).[36] The challenge of the proposed method is suppression of the competing decarbonylation pathway. In the work it was found that the use of electron-rich, less bulky PMe_2Ph ligand was crucial. Also of notable importance is a 1.6:1 phosphine ligand:rhodium metal ratio. The authors reason that the active catalytic species likely contains only one phosphine ligand, whereas increasing the ligand:metal ratio results in the inactive *trans*-$Rh(CO)(L)_2Cl$ species. With optimal conditions, the authors report a wide substrate scope. Of primary importance is the use of both arene or nitrogen linkers. The method is complementary to prior [3+2+1] cycloaddition with cyclopropanes.[37]

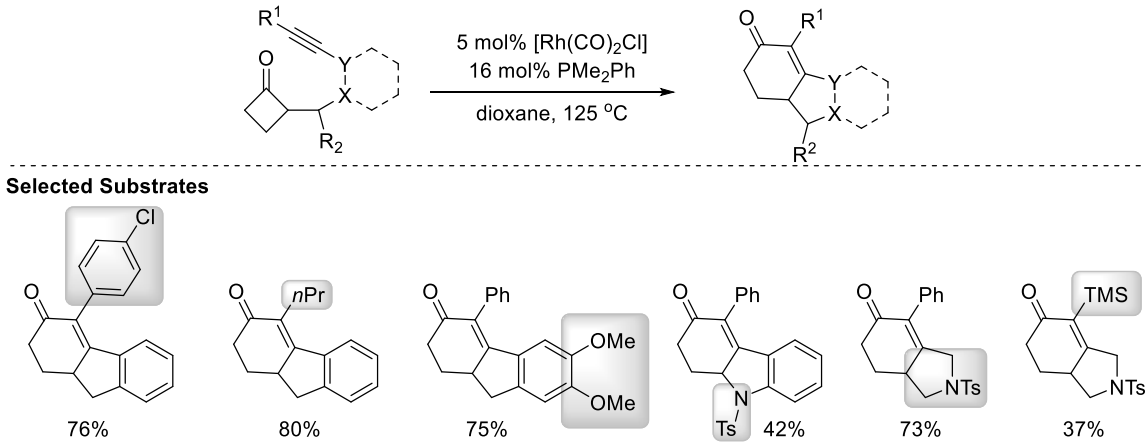


Figure 1.5 [4+2] Approach Toward N-Heterocycles via C–C Activation

One year later, an enantioselective variant of the method was developed based on kinetic resolution (Figure 1.6).[38] The inherent difficulty of the proposed reaction is catalyst differentiation of an enantiomeric pair (intermolecular recognition) over different π faces, i.e. alkene/alkynes or ketones (intramolecular recognition). In the work it was found that highly reactive cationic rhodium, generated *in situ*, at room temperature resulted in kinetic resolution of the asymmetric starting material with a selectivity factor up to 785. The origin of selectivity was elucidated by density functional theory calculations and is attributed to *N*-tosyl coordination to rhodium during C–C oxidative addition: in the transition state the (*S*) substrate has minimal steric interaction with the (*R*)-DTBM-segphos ligand and allows for this coordination whereas the (*R*) substrate cannot fit into the active pocket. The *N*-tosyl coordination also results in direct proximal C–C cleavage. Of notable interest, the reaction is suitable for both alkene and alkyne insertion partners as well as can tolerate variations of the *N*-sulfonyl protecting group and free alcohol functional groups. The constructed enantioenriched [5.6] bicycles can be conveniently transformed with no loss in enantioselectivity showcasing the practicality of the method toward complex natural products and biologically active compounds (Figure 1.7).

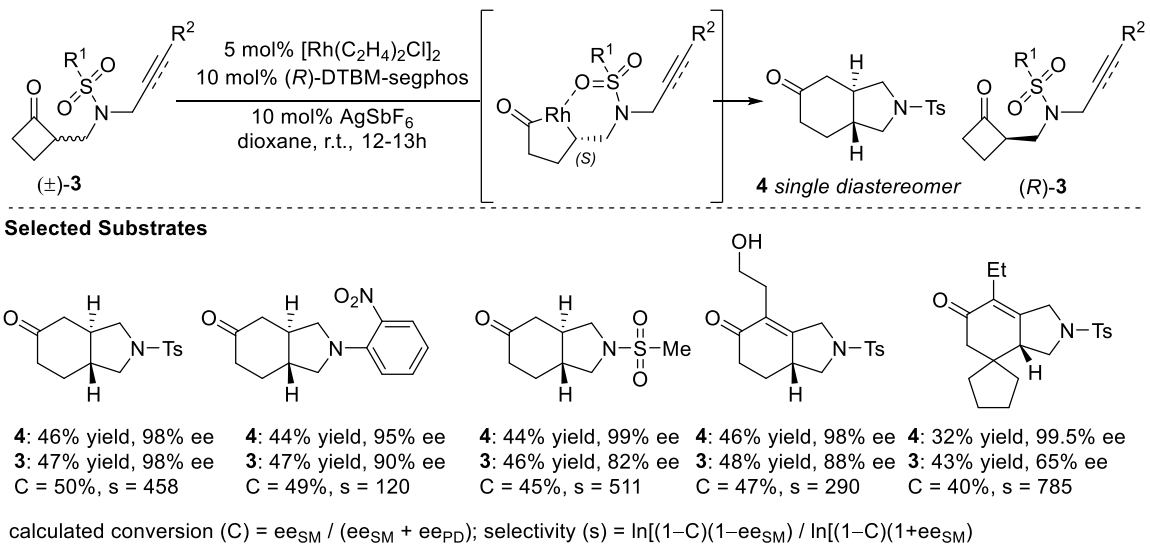


Figure 1.6 Enantioselective Synthesis of N-Heterocycles via Kinetic Resolution

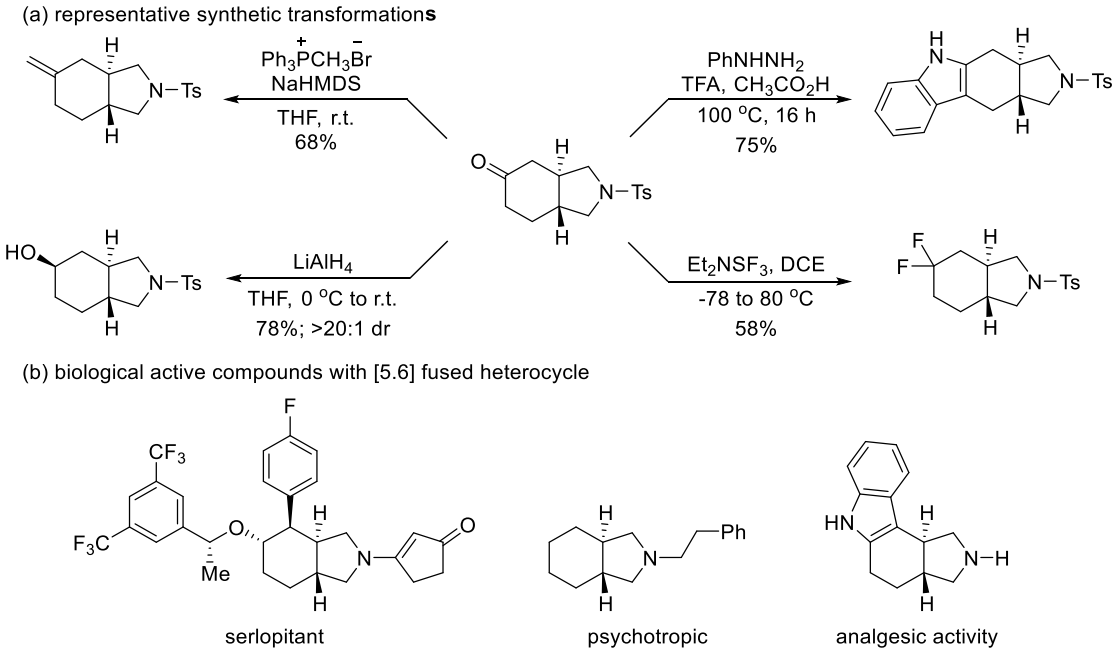


Figure 1.7 Synthetic Application of N-Heterocycles. (a) representative synthetic transformations and (b) biological active compounds with [5.6] fused heterocycle.

1.2.14 Oxidative Addition into Unstrained C–C Bonds

Compared to C–C activation of strained three and four membered rings, the activation of unstrained C–C bonds such is much more challenging. The difficulty comes from the reversible

C–C activation step; the C–C reductive elimination of unstrained systems is thermodynamically favored. In recent years, the Dong group has reported efficient methods for the tandem C–C activation / functionalization of unstrained C–C bonds. The key to the success is relying on an *in situ* directing group strategy as well as the tandem functionalization to overcome the thermodynamic sink. The method has found use toward the construction of common natural product motifs as well as has been applied toward the synthesis of serrulatane and amphilectane diterpene natural products.

1.2.15 Synthesis of α-Tetralone Motif

4-substituted α-tetralone is an versatile building block in terpene synthesis: it is a known intermediate for accessing erogorgiaene[39], (*R*)-ar-himachalene[40], and (–)-heliophenanthrone (Figure 1.8).[41] While the synthesis of simple α-tetralone may seem trivial, the preparation of enantioenriched C_4 substituted α-tetralone can require up to six steps.[40]

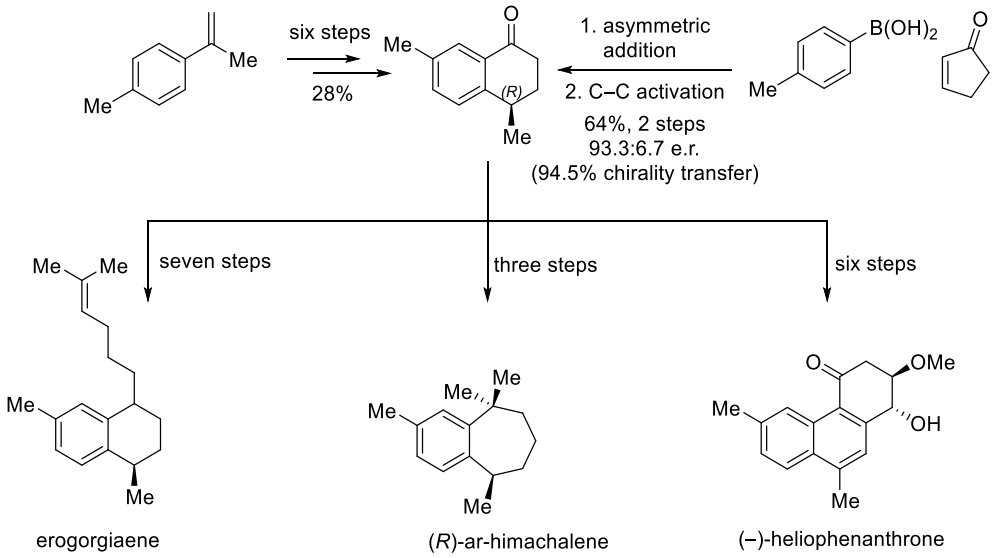


Figure 1.8 α-Tetralone in Natural Product Synthesis

To address this challenge, a ring expansion method through C–C activation of cyclopentanone was envisioned (Figure 1.9).[42] To overcome this thermodynamic sink of unstrained C–C

activation, a tandem sp^2 C–H functionalized was envision. Under the optimized conditions, with *in situ* installed directing group, the favored proximal C–C activation of 3-substituted cyclopentanone was followed by tandem sp^2 C–H functionalization/arylation to access α-tetralone motifs, greatly shortening the synthesis toward 4-substituted α-tetralone (Figure 1.8). Of note, suitable substrates include aryl boronic esters that are primed for subsequent functionalization as well as 3,4-disubstituted and ring-fused cyclopentanones (Figure 1.9). In both case the relative configuration of the starting material is preserved during the reaction.

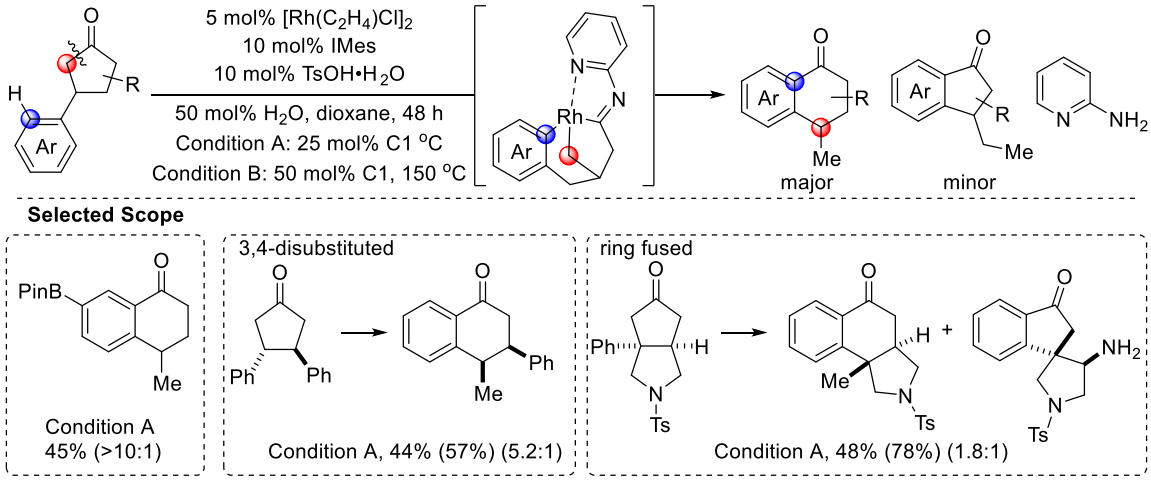
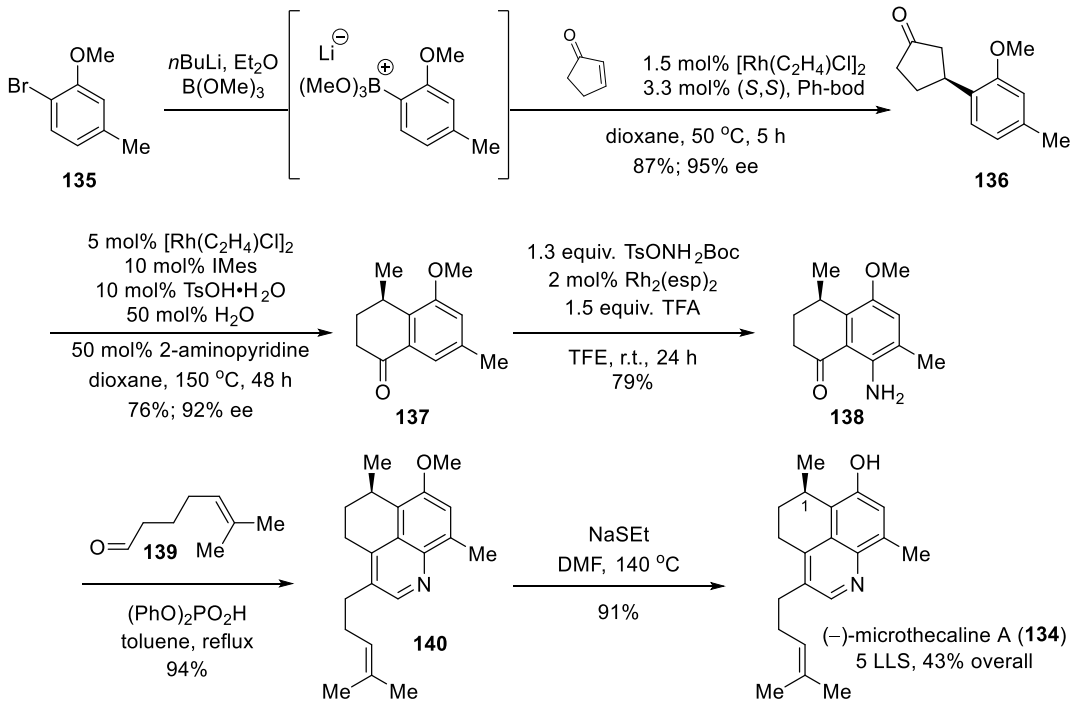


Figure 1.9 α-tetralone Construction via Unstrained C–C Bond Activation

The method was applied toward the synthesis of serrulatane and amphilectane diterpene natural products. (–)-Microthecaline A (**133**) was isolated from the roots of a Australian desert plan *Eremophila microtheca* and exhibits antimalarial activity against *Plasmodium falciparum*.[43] The construction of the C_1 stereocenter was envisioned via tandem C–C activation/arylation of cyclopentanone.[44] In a forward manner, asymmetric conjugate addition of *in situ* generated arylborate salt gave enantioenriched C_3 substituted cyclopentanone **136** (Scheme 1.12). The following key tandem C–C activation/arylation gave α-tetralone **137** with minimal stereochemical erosion. The installation of the C_5 nitrogen moiety presented itself as the next

challenge in the synthesis. Toward this end, directed arene C–H amination conditions were examined. After optimization it was found that rhodium catalyzed amination gave the desired aniline **138**. It should be noted that this is the first example of C–H amination in which the substrate contains an unprotected ketone functionality. With aniline **138** in hand, the quinoline ring was constructed by the Friedlander condensation with aldehyde **139**. Demethylation gave (–)-microthecaline A (**134**) in 5 longest linear steps with a 43% overall yield, a drastic improvement over the previously reported racemic synthesis in 15 steps with a 5% overall yield.[45]

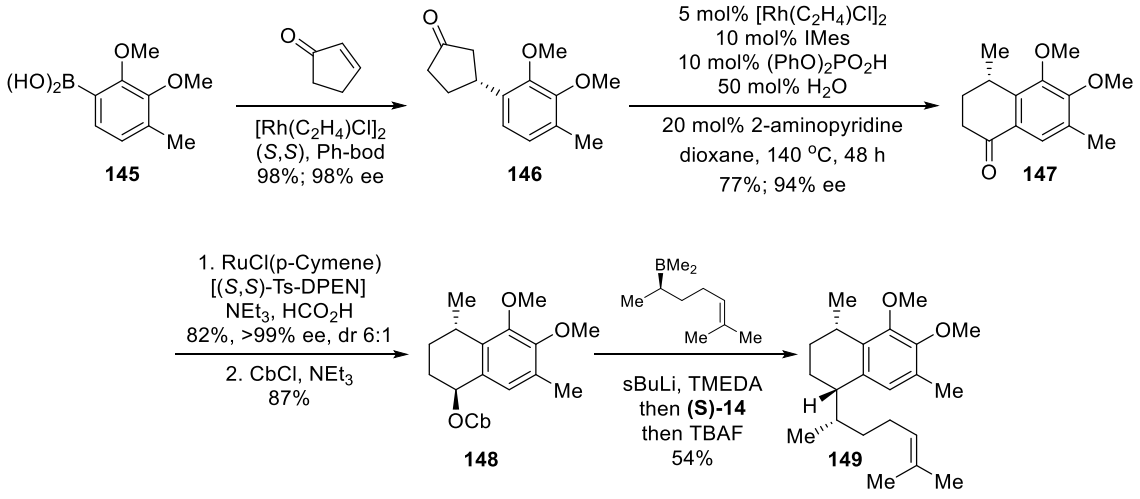
Scheme 1.12 Synthesis of (–)-Microthecaline A



With the success of (–)-microthecaline A (**134**), the authors turned toward the synthesis of (+)-seco-pseudopteroxazole (**141**), another serrulatane type natural product, as well as three amphilectane diterpenes (**142-144**) (Scheme 1.14). Compared to (–)-microthecaline A (**134**), the proposed targets contain an oxygenated C_7. The electron rich aryl group could destabilize the

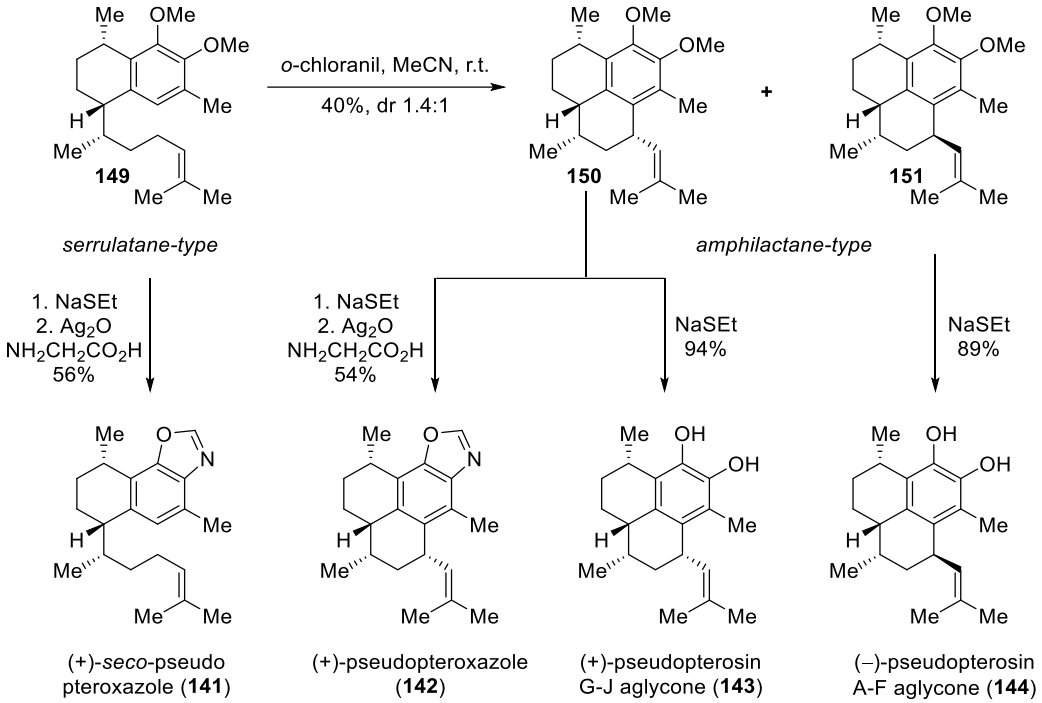
aryl-Rh intermediate during the C–H activation, making the tandem unstrained C–C activation/functionalization more challenging. The synthesis began with a similar Rh-catalyzed asymmetric 1,4-addition to cyclopentenone to give intermediate **146** (Scheme 1.13). As expected, under the standard C–C activation condition's low conversion of **146** to the desired α-tetralone **147** resulted. Changing the acid cocatalyst from TsOH to $(PhO)_2PO_2H$ resulted in 77% desired **147**. The authors proposed that the new acid cocatalyst promoted the C–H arene metalation step. Subsequent reduction and alcohol functionalization gave carbamate **148**. Lithiation-borylation afforded divergent serrulantane intermediate **149**.

Scheme 1.13 Construction of Divergent Serrulantane Intermediate



Divergent intermediate **149** was easily converted to (+)-seco-pseudopteroxazole (**141**) after demethylation and a one-pot oxidative oxazole formation (Scheme 1.14). To access amphilactane-type natural products, an oxidative C–C bond formation was envisioned. Treatement of **149** with *o*-chloranil afforded the desired tricyclic scaffolds. In a similar demethylation and a one-pot oxidative oxazole formation sequence, three amphilactane type natural products were constructed: (+)-pseudopteroxazole (**142**), (+)-pseudopterosin G-J aglycone (**143**), and (-)-pseudopterosin A-F aglycone (**144**).

Scheme 1.14 Completion of (+)-Seco-Pseudopteroxazole and Amphilectane Diterpenes



1.2.16 Synthesis of Chromanes

With the success of the tandem intramolecular unstrained C–C activation/functionalization, an intramolecular variant presented itself as the next key challenge. Recent work employs a tandem Suzuki–Miyaura cross coupling with the newly activated unstrained C–C bond.[46] Reaction conditions are similar to the previously reported conditions with one important additive: it was found that ethyl crotonate acts as a π acid to promote the reductive elimination step. Under the optimized conditions, simple ketones are cross-coupled with arylboronic acid derivatives (Figure 1.10 a). In general, electron-rich arylboronates are most suitable. 3-substituted cyclopentanones unexpectedly result in C–C activation of the more sterically hindered bond. Impressively, acyclic ketones such as acetone are suitable substrates. Indanones were also found as suitable substrates and the method was used to access functionalized chromanes; a common motif in natural products and biologically active compounds (Figure 1-10 b and c).[47]

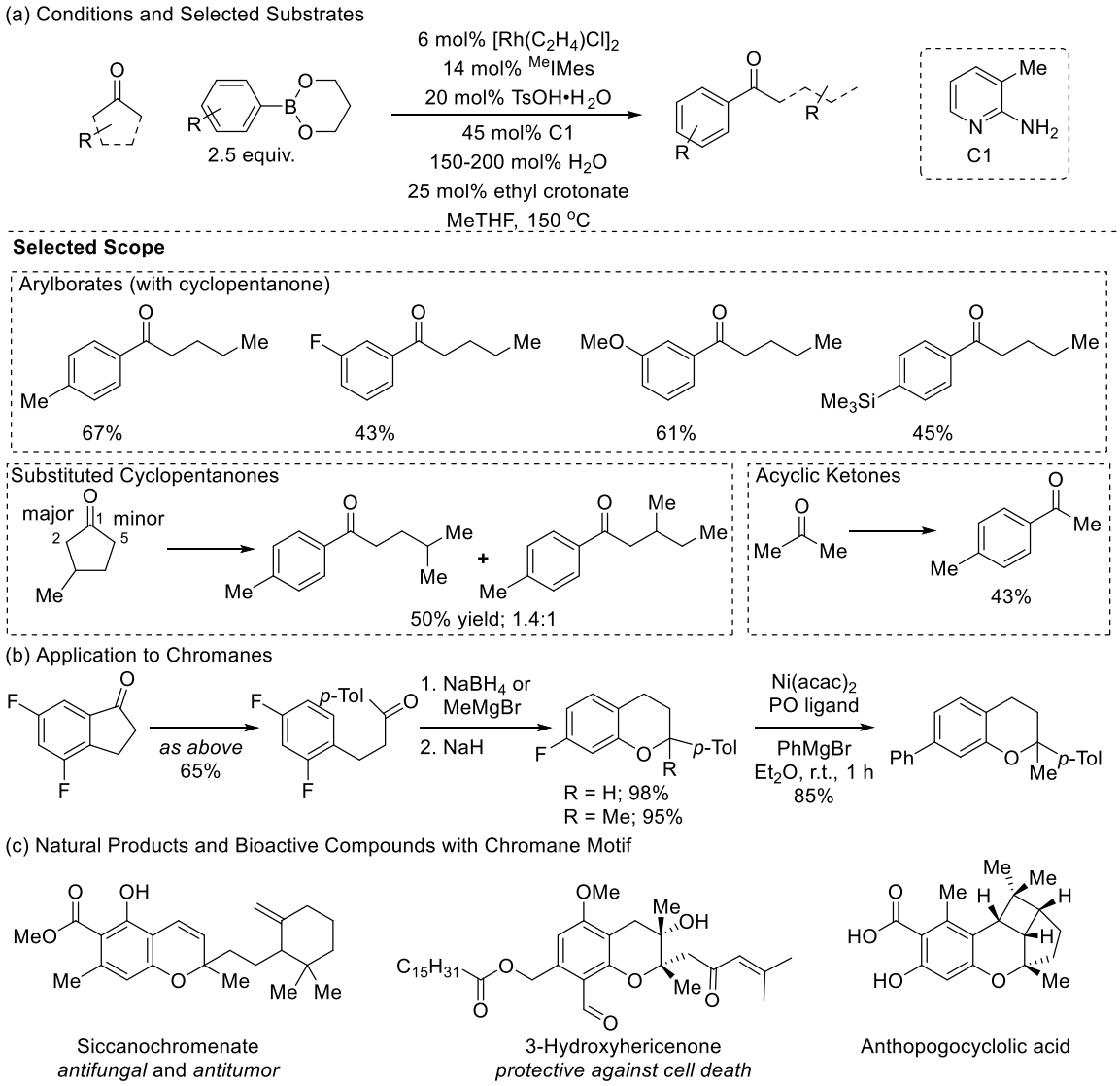


Figure 1.10 Suzuki-Miyaura Coupling of Simple Ketones. a) optimized conditions and selected substrate scope, b) method application toward chromanes, and c) chromanes in natural products and bioactive compounds.

1.2.17 Synthesis of Benzocycloheptanes

Benzocycloheptanes are a common motif found in biologically active small molecules.[48] The typical approach to these compounds relies on the functionalization of benzocycloheptenones. However, the synthesis of benzocycloheptenones is often non-trivial (Figure 1.11). Similar to the previous work in unstrained C–C activation, a tandem ethylene insertion into the activated C–C

bond of indanone was developed.[49] Under the optimized conditions, a two-carbon homologation results in benzocycloheptenone intermediates in route to the synthesis of pharmaceutical agents.

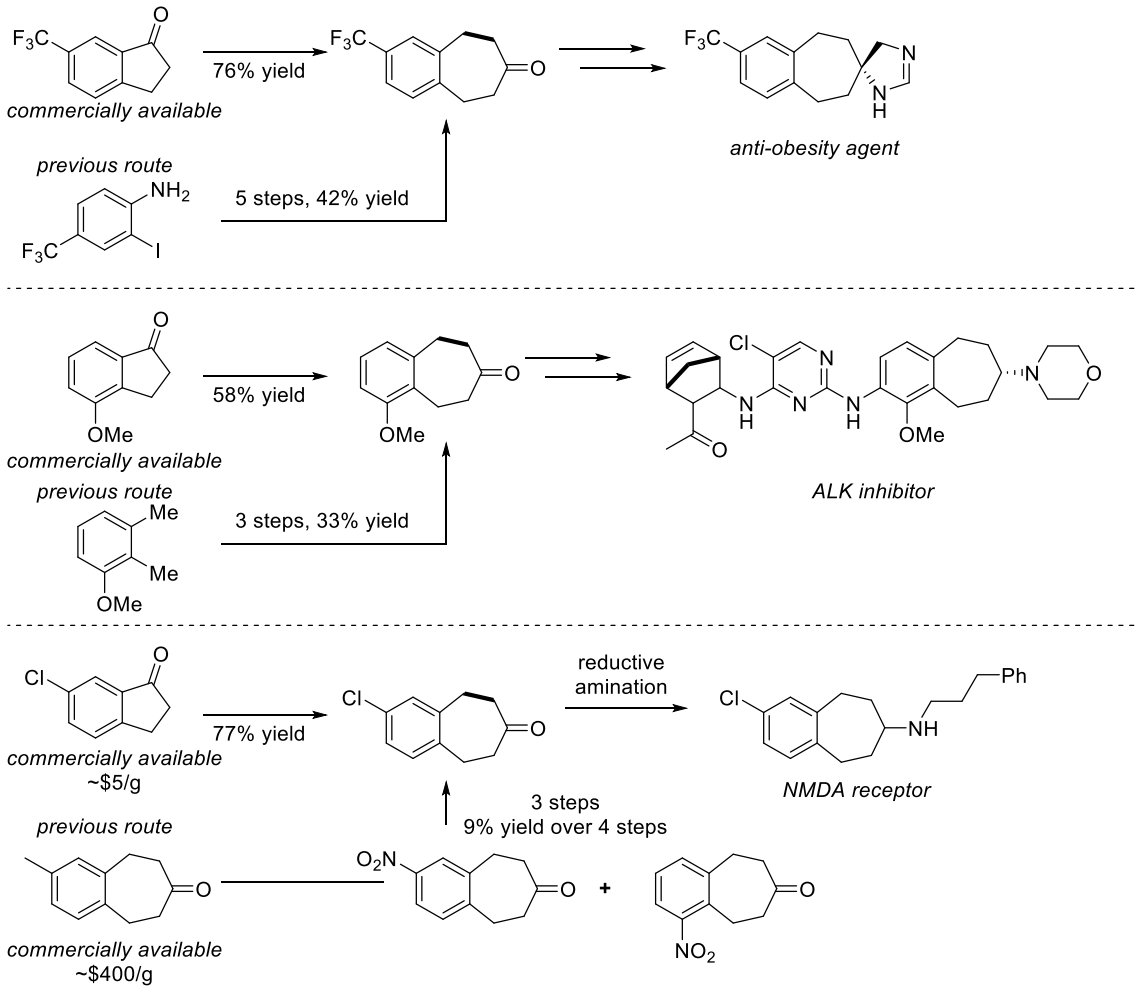


Figure 1.11 Two-Carbon Homologation of Indanone via C–C Activation

1.3 C–C Bond Activation by β-Carbon Elimination

Besides C–C activation by metal oxidative additoin, β-carbon elimination of strained ring systems may also activate C–C bonds. C–C activation by β-carbon elimination has been recently used to access [3.2.2] bicyclic scaffolds as well as substituted carvone derivatives. The later has been applied to the efficient synthesis of Xishacorene B.

1.3.1 Construction of [3.2.2] Bicyclic Scaffolds

[3.2.2] Bicyclic scaffolds are commonly found in natural products and bioactive compounds (Figure 1.12). However, their construction by classical methods is not facile. A novel [4+2] coupling enabled by C–C activation of cyclobutanones provides rapid access to the [3.2.2] bicyclic scaffold.[50] Under the optimized conditions a variety of 1,1,3-trisubstituted and 1,3-disbustituted allenes can be tolerated. Nitrogen or carbon linkers are both viable in the reaction giving either functionalized heterocycles or carbocycles, respectively. An enantioselective variant of the reaction was also developed using chiral phosphoramidite.

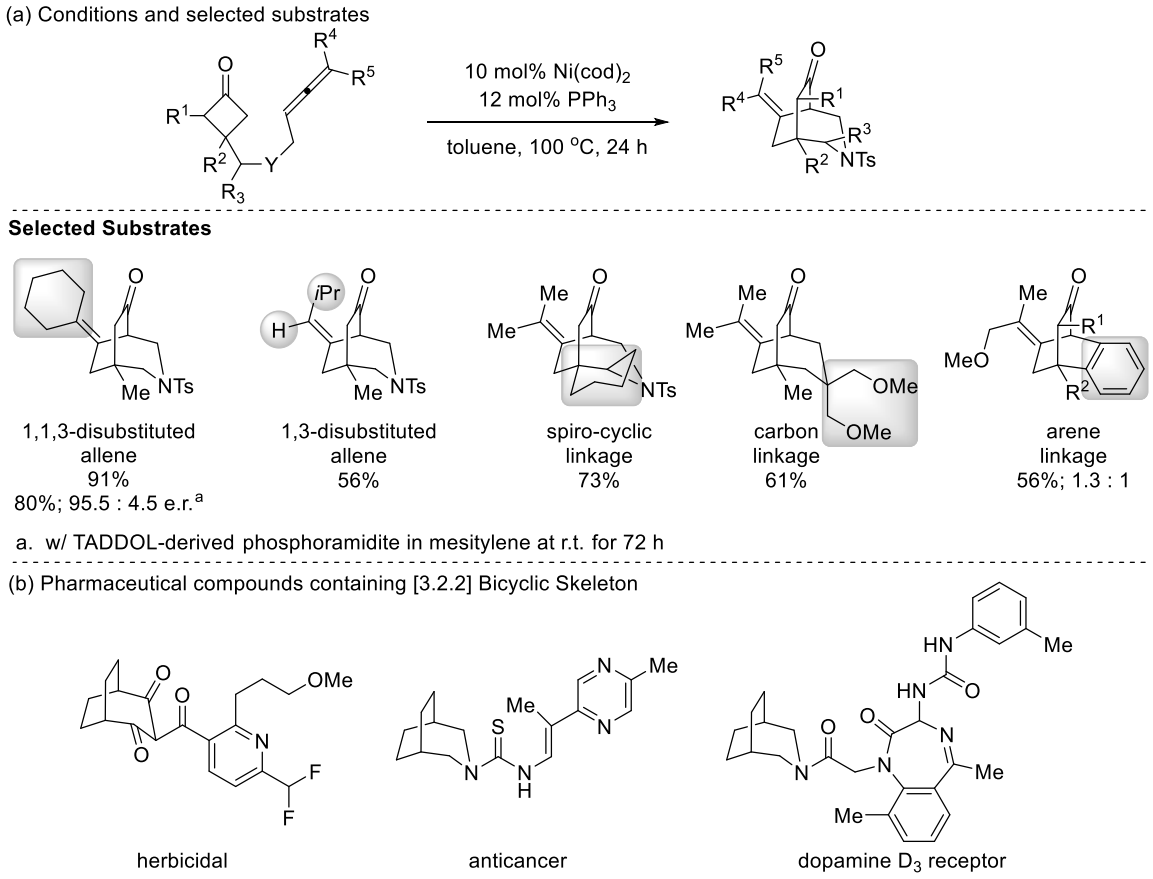


Figure 1.12 [3.2.2] Bicyclic Scaffold Construction via C–C Activation (a) conditions and selected substrates (b) pharmaceutical compounds containing [3.2.2] bicyclic skeleton.

The [4+2] coupling is proposed to proceed through the cyclometallation of nickel (0) into cyclobutanone **152** to give metallocycle **153** (Figure 1.13). β-carbon elimination activates the C–C bond. Reductive elimination from **154** gives [3.2.2] bicyclic scaffolds **155**.

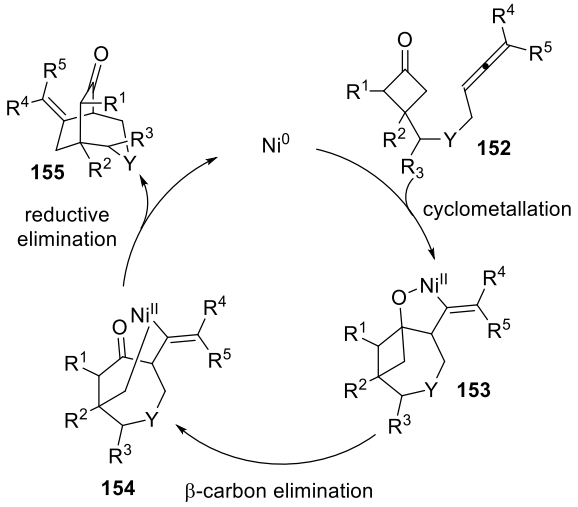


Figure 1.13 Mechanism of [4+2] Reaction by C–C Activation/β-C Elimination

1.3.2 Synthesis of Xishacorene B

In recent years, the Sarpong group has developed a novel C–C activation activation/coupling strategy of carvone. The mechanism is proposed to begin with the oxidative addition of palladium into an alkyl halide species (Figure 1.14). Ligand exchange with benzocyclobutanol derived carvone **156** gives palladium alkoxide species **157**. β-carbon elimination gives a newly reactive C–M bond. Following reductive elimination of **158**, enantioenriched substituted carvone derivates **159** are obtained. The method has been applied to the synthesis of xishacorene B (**160**).[51]

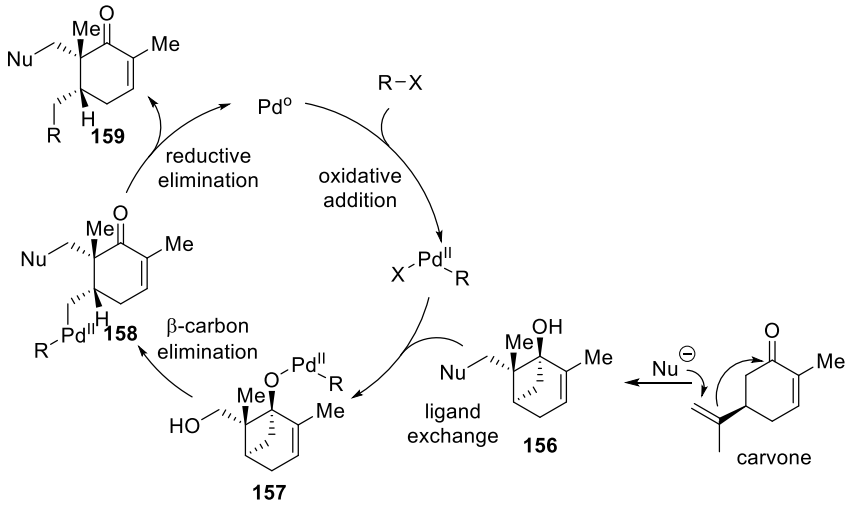
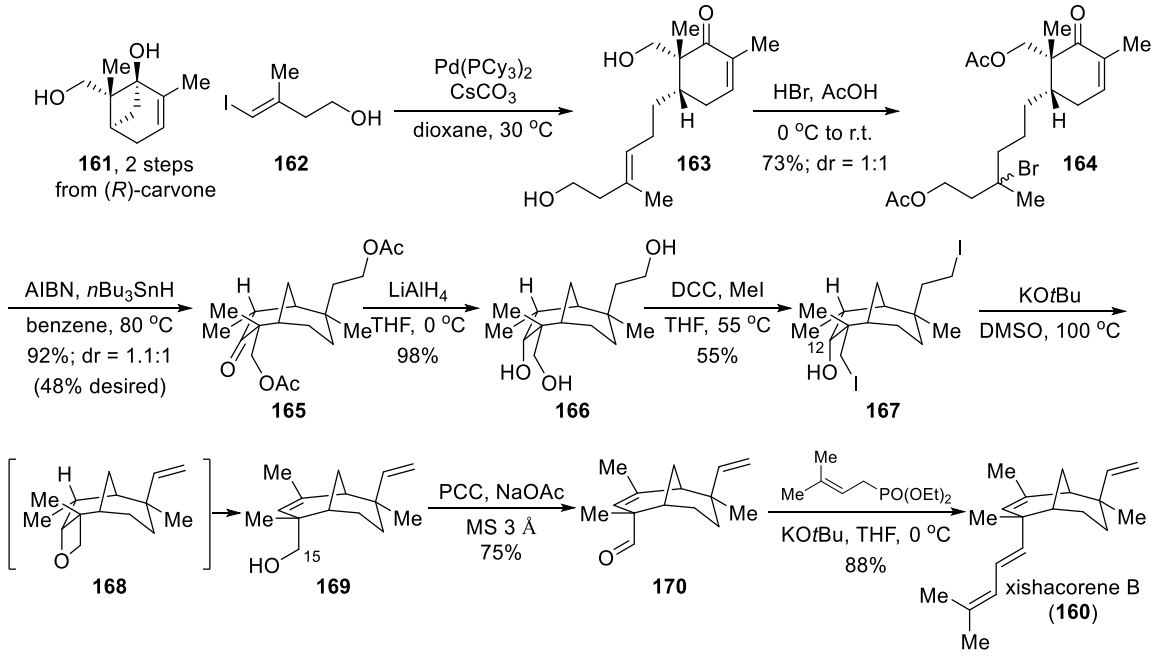


Figure 1.14 C–C Activation/Coupling Strategy of Carvone

Xishacorene B (**160**) is a diterpene isolated from the soft coral *Sinularia polydactyal*. It belongs two a new family of diterpenes which exhibit activity as promoters of concanavalin A-induced T-lymphocyte proliferation. Xishacorene B (**160**) exhibits an unusual bicyclo [3.3.1] framework which is expected to be accessed through a hydrogen atom transfer reaction. The precursor for the reaction is expected to arise from a C–C activation/coupling sequence of carvone derivative **161**. In a forward manner treatment of known cyclobutanol **161**[52] with $Pd(PCy_3)_2$ in the presence of known vinyl iodide **162**[53] gave coupled product **163** via C–C activation. The next key step in the synthesis is a hydrogen atom transfer reaction to construct the bicyclo [3.3.1] framework. After protection of the primary alcohol and alkene hydrobromination, treatment of **164** with AIBN and nBu$_3$SnH gave desired bicycle **165**. Completion of the synthesis of xishacorene B (**160**) now required standard functional group transformations. Global reduction with $LiAlH_4$ gave triol **166**. Conversion of the primary alcohols to diiodide **167** set up for elimination with potassium *tert*-butoxide. It is presumed that the elimination of the C_{12} alcohol proceeds through the four membered ring **168** to give **169**. Oxidation of the resulting C_{15} alcohol followed by a Horner-Wadsworth-Emmons reaction completes the synthesis of xishacorene B (**160**).

Scheme 1.15 Synthesis of Xishacorene B



1.4 Conclusion and Outlook

C–C bond activation strategies offer an innovative approach toward the synthesis of natural products and biologically active small molecules. The methods often allow straightforward bond construction, thus shortening the number of synthetic steps. With the continued development of novel C–C bond activation methodologies, one may expect facile construction of previously inaccessible targets. This introductory chapter served to summarize the recent utility of C–C bond activation strategies in synthesis and played as an opening act to my graduate work toward the synthesis of *ent*-kauranoid natural products via a C–C bond activation strategy.

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CHAPTER 2

A C–C BOND ACTIVATION STRATEGY TOWARD THE *ENT*-KAURENE CORE

2.1 Introduction

The development of selective and catalytic methodologies that allow access to biologically active compounds from relatively simple feedstock is of paramount interest. Toward this end, the Dong lab has developed a Rh(I)-catalyzed carbon–carbon (C–C) activation/olefin insertion strategy (Figure 2.1).[1] When using benzocyclobutenone, 'proximal' C–C bond activation followed by migratory insertion and reductive elimination of a tethered olefin results in highly polycyclic scaffolds. Herein, we propose to employ this C–C activation/olefin insertion method toward the synthesis of *ent*-kauranene natural products.[2]

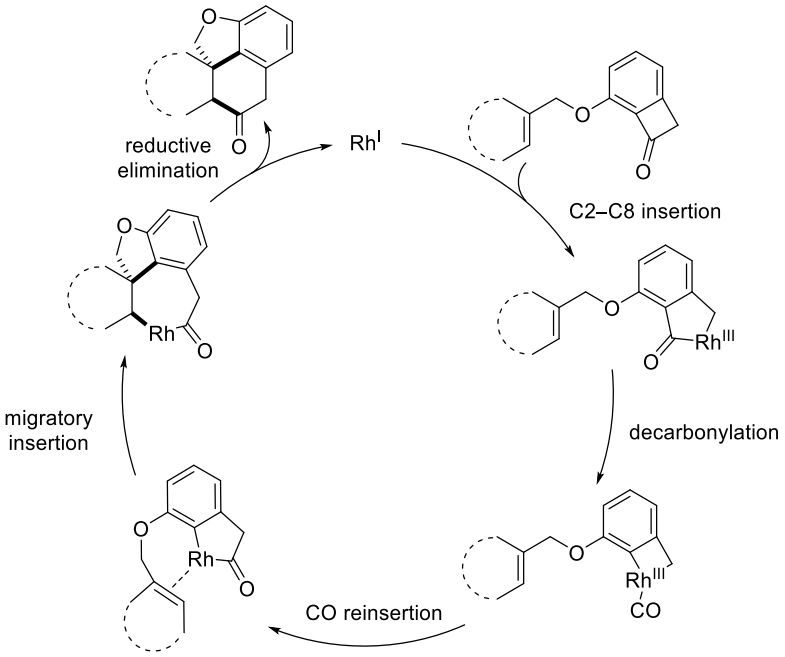


Figure 2.1 C–C Activation Strategy Toward Highly Polycyclic Scaffolds.

More than 600 e*nt*-kaurenes have been isolated from the genus *Isodon*.[2a] *Isodon Lamiaceae* has been used to treat cancer and inflammation in traditional Chinese medicine. E*nt*-kaurenes are

tetracyclic C_{20}-diterpenoids consisting of a perhydro-phenanthrene and a cyclopentane ring. Many *ent*-kaurenes exhibit highly oxidized motifs, attributing to their biological activity and making late stage derivatization challenging.[3] Biosynthetically, *ent*-kaurenes are derived from geranylgeranyl diphosphate (Figure 2.2).[2a] Initial cationic cyclization induced by (–)-copalyl diphosphate synthase gives *ent*-copalyl diphosphate. Further cyclization by *ent*-kaurene synthase gives the tertiary *ent*-primarenyl cation. Subsequent cation rearrangements install the exocyclic pentane ring in the *ent*-kaurenyl cation. Finally, deprotonation gives the *ent*-kaurane scaffold.

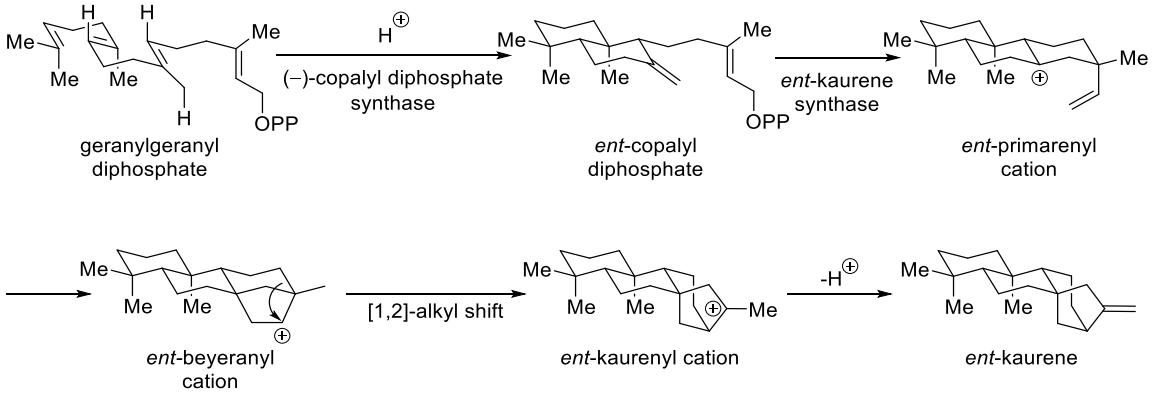


Figure 2.2 Biosynthesis of *Ent*-Kaurene

Within the *ent*-kaurane family, eriocalyxin B has paramount interest due to its diverse anti-cancer properties. Since its isolation, eriocalyxin B's mode of activation toward colon, breast, leukemia, pancreatic, and other carcinogenic cell lines has been elucidated.[4] To highlight eriocalyxin B's bioactivity, a comparison of its toxicity toward pancreatic endocarcenoma cell lines versus camptothecin, a current chemotherapeutic, was made (Figure 2.3).[5] While both eriocalyxin B and camptothecin exhibit high toxicity toward a number of pancreatic endocarcenoma cells, LC_{50} = 0.73-1.4 µM and LC_{50} = 0.75-1.7 µM respectively, eriocalyxin B

was found to be much less toxic toward healthy human liver cells (WRL68) with an LC_{50} > 3.58 µM when compared to camptothecin with LC_{50} = 1.9 µM.

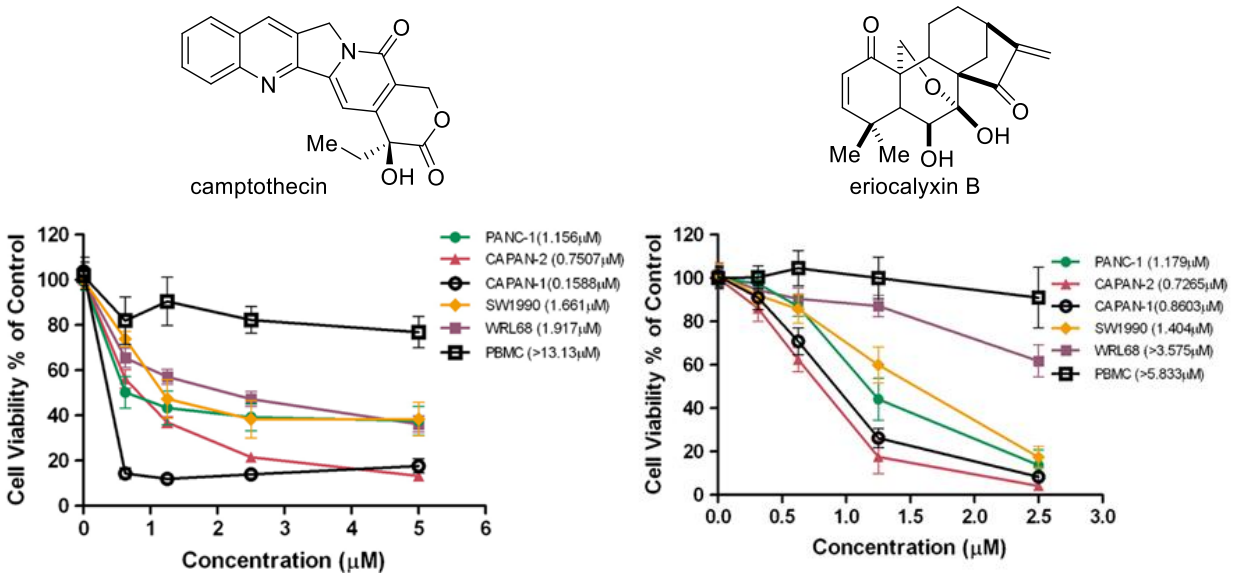


Figure 2.3 Cytotoxic Effects of Campothecin and Eriocalyxin B.[5] Human pancreatic adenocarcinoma cell lines (PANC-1, CAPAN-2, CAPAN-1, SW1990), normal human liver cell line (WRL68) and human peripheral blood mononuclear cells (PMBC).

Eriocalyxin B is of synthetic interest due to its poly-bridged/fused ring scaffold and highly oxidized functionalities which attribute toward its unique bioactivity (Figure 2.4).[6] Compared to other *ent*-kaurenes, eriocalyxin B contains a highly oxidized A-ring and lacks a C_{11}-oxygen functionality. In addition, the free Michael acceptor of the exocyclic pentane ring is proposed to attribute to eriocalyxin B's unique bioactivity. Together with these challenging structural features and its unique bioactivity, eriocalyxin B presents itself as an intriguing synthetic target.

Retrosynthetically, eriocalyxin B (**1**) is envision from late stage oxidations of hemiketal **2** (Figure 2.4). We plan to install C_6–C_7 bond via the McMurry coupling of **3**.[7] Spirocycle **3** is the key motif of C_{10}-spirolactone *ent*-kaurene such as isodonal (**4**). *Ent*-kaurene motif **3** is proposed from the carbon–oxygen (C–O) bond cleavage of the enol ether functionality in **5**. A tandem

birch reduction/propargylation from **6** is envisioned to access **5**.[8] Methyl benzoate **6** is proposed from the tetracyclic scaffold **7** which in turn may be constructed via a C–C bond activation/alkene insertion strategy from **8**.

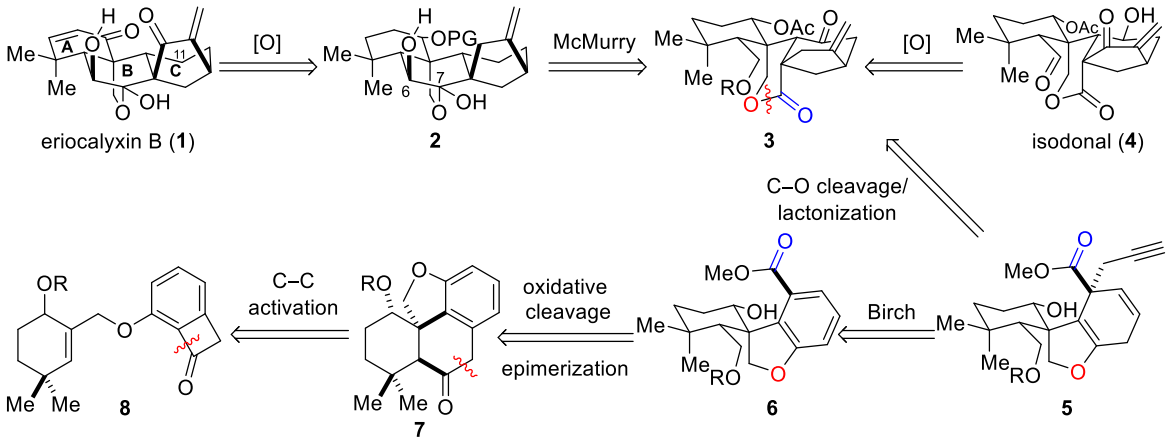


Figure 2.4 Retrosynthetic Analysis of Eriocalyxin B and Isodonal

2.2 Results and Discussion

The C–C activation precursor **8** was envision from the Mitsunobu coupling of relatively simply diol **9** and known benzocyclobutenone **10** (Scheme 2.1).[9] Diol **9** could be accessed in two steps from commercially available 4,4-dimethyl-2-cyclohexen-1-one: first the Morita-Balyis-Hillman[10] reaction followed by Luche Reduction. However, under standard Mistunobu conditions a mixture, of inseparable regioisomers was obtained. At lower temperatures, the undesired regioisomer was greatly favored (Table 2.1). We propose that the 1,3-diol forms a pentacoordinate, dialkoxyphosphorane intermediate resulting in the mixture of diastereomers.[11]

Scheme 2.1 Mitsunobu Coupling Between Diol **9** and Benzocyclobutenone **10**

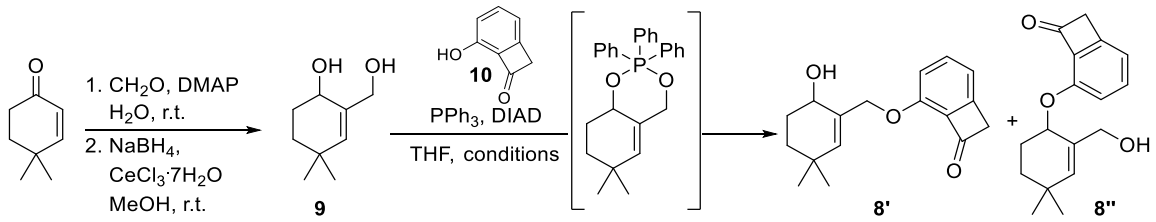


Table 2.1 Mitsunobu Coupling Between Diol **9** and Benzocyclobutenone **10**

entry	temp (ºC)	time (h)	ratio 8':8''	combined yield (%)
1	60	12	1:1.7	48
2	0 to 60	12	1:5	64
3	0 to rt	12	0:1	43

A minor route modification involving protecting group manipulations to access pure C–C activation precursor **8** was implemented (Scheme 2.2). The same Morita-Balyis-Hillman[10] reaction followed by acetate protection gave allyl acetate **11**. A similar Luche Reduction and silyl protection gave **12**.[12] In our hands, Tsuji-Trost palladium catalyzed cross coupling between **12** and **10** was unsuccessful.[13] We then settled for acetate deprotection to **13** in order to set up for our originally proposed Mitsunobu approach. Gratifyingly under standard conditions the desired product **8** was obtained, albeit in a low yield (Table 2.2, entry 1). After some optimization, it was found that premixing the reaction at 0 ºC with an excess of allylic alcohol, triphenylphosphine, and diisopropyl azodicarboxylate before heating to 60 ºC could give a modest 64% yield (Table 2.2, entry 4). The necessity for premixing at low temperatures may be attributed to competing initial deprotonation of either allylic alcohol or phenol motif by diisopropyl azodicarboxylate. The optimized Mitsunobu conditions are highly scalable giving access to decagram quantity of precursor **8**.

Scheme 2.2 Mitsunobu Coupling Between Allylic Alcohol **13** and Benzocyclobutenone **10**.

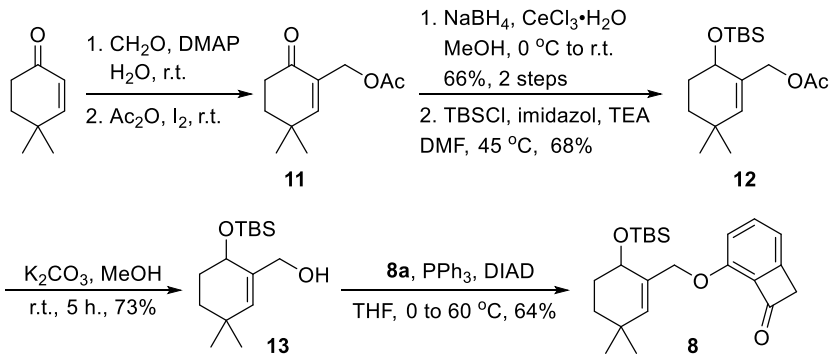
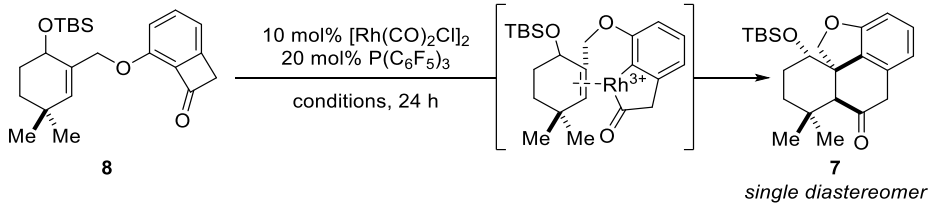


Table 2.2 Mitsunobu Coupling Between Allylic Alcohol **13** and Benzocyclobutenone **10**.

entry	equiv. 13	equiv. PPh_3	equiv. DIAD	temp (°C)	time (h)	yield (%)
1	1	1	1	60	12	32
2	1	2	2	60	12	26
3	1.1	1.1	1.1	60	18	4
4	1.5	1.5	1.5	0 to 60	4	64
5	1.5	1.5	1.5	0 to r.t.	12	33

With **8** in hand, we set out to attempt the key C–C activation/olefin insertion strategy. Beginning with previously reported conditions,[9b] delightfully we were able to obtain trace desired tetracycle as a single diastereomer (Table 2.3, entry 1). Lower concentration in tetrahydrofuran gave reduced yields (entry 2 and 3). Higher temperatures slightly increased the yield to 15% (entry 6). Changing to dioxane solvent resulted in modest improvement, however with poor reproducibility (entry 8). It was found that lower concentrations gave a slight decrease in yield, but with consistent results (entry 9).

Table 2.3 Preliminary C–C Activation/Alkene Insertion Attempts

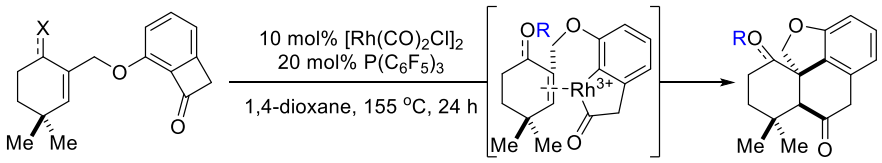


entry	concentration (M)	temperature (°C)	solvent	yield
1	0.2	130	THF	10
2	0.1	130	THF	>5
3	0.05	130	THF	>5
4	0.2	120	THF	0
5	0.2	140	THF	12
6	0.2	155	THF	15
7	0.2	155	MeTHF	0
8[a]	0.2	155	1,4-dioxane	26
9	0.05	155	1,4-dioxane	23

a. poor reproducibility

In attempts to improve the yield of the key step, we first looked at different alcohol protecting groups (Table 2.4). Previous reports have only shown tertbutyl-silyl (TBS) protecting group.[14] Similarly in our hands, the original TBS group gave the highest yield (entry 1). We also looked at the free alcohol (entry 5) and the corresponding free or protected carbonyl (entry 6 and 7), however in either case no desired product was obtained.

Table 2.4 Protecting Group Modification for C–C Activation/Alkene Insertion Strategy



entry	R	yield (%)	recovered s.m. (%)
1	TBSO	20	20
2	TIPSO	<5	50
3	PMBO	<10	50
4	THPO	<5	30
5	HO	0	0
6	O	0	0
7	1,2-ethanediol	0	20

We next turned our attention toward metal precatalysts that have found prior success in C–C activation/alkene insertions (Table 2.5).[1, 9b, 15] It was found that only Rh(I) precatalyst could give any desired product. Cation rhodium as well as ruthenium, nickel, or cobalt precatalyst were all unsuccessful in giving any desired product.

Table 2.5 Metal Precatalyst Screening for C–C Activation/Alkene Insertion Strategy

entry	precatalyst	yield (%)	recovered s.m. (%)
1	$[Rh(CO)_2Cl]_2$	15	20
2[a]	$[Rh(COD)Cl]_2$	15	71
3[a]	$[Rh(COD)_2]BF_4$	0	35
4	$RhCl(PPh_3)_3$	0	73
5	$Ru_3(CO)_{12}$	0	58
6	$Ni(COD)_2$	0	100
7[b]	$Co_2(CO)_8$	0	91

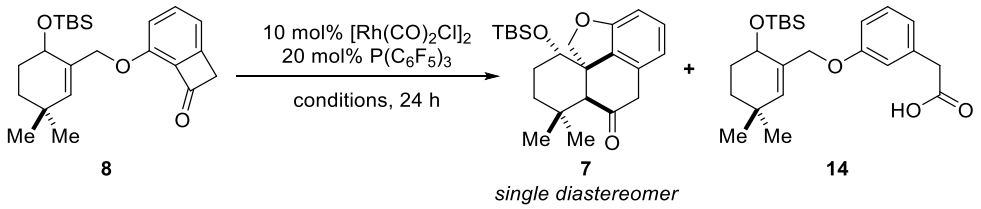
conditions: 20 mol% metal, 20 mol% $P(C_6F_5)_3$, 0.05 M dioxane, 155 °C, 24h. a. without ligand. b. 1 equiveillance of $Co_2(CO)_8$ was used.

At this time, carboxylic acid **14** was identified as a major deleterious side product. In other words, the C–C activation is proceeding smoothly, but the migratory insertion is challenging.[16] In attempts to improve alkene migratory insertion, a variety of ligands and additives were

explored (Table 2.6). Not too surprisingly, bidentate phosphine (entry 1) or electron rich phosphine (entry 2 and 3) ligands failed to convert the starting material. Only electron deficient ligands such as tris[3,5-bis(trifluoromethyl)phenyl]phosphine (entry 4) or triethyl phosphite[17] (entry 5) could give any desired product, but not as efficiently as the standard $P(C_6F_5)_3$ (entry 6). Z-type ligands such as triphenyl boron were also unsuccessful (entry 7). Quite serendipitously however, no added ligand gave a modest 49% yield of the desired tetracycle (entry 8). In other words, carbon monoxide as a very electron withdrawing and sterically unhindered ligand is optimal for the challenging trisubstituted olefin with neighboring gem-dimethyl and silyl ether functionalities.

Under the current optimal conditions of no added ligand, still 36% of acid **14** is obtained. The source of acid formation was envisioned from either adventitious water or hydrolysis of an intermediate acyl chloride upon isolation; the acyl chloride may form from migratory insertion of hydrochloric acid formed from the $[Rh(CO)_2Cl]_2$ precatalyst. Desiccants such as molecular sieves (entry 9) or proton scavengers such as pyridine (entry 10) however gave diminished yields of the desired product. A control experiment with no $[Rh(CO)_2Cl]_2$ precatalyst containing ethyl vinyl ether was conducted to rule out any possible thermal retro [2+2] decomposition of benzocyclobutenone.[18] In the control, quantitative starting material was recovered.

Table 2.6 Ligand and Additive Screening for C–C Activation/Alkene Insertion Strategy



entry	ligand	additive	yield (%)	acid (%)	recovered s.m. (%)
1	dppp	-	0	0	>90
2	PPh_3	-	0	0	>90
3	PCy_3	-	0	0	>90
4	Tris[3,5-bis(trifluoromethyl) phenyl]phosphine	-	>5	>5	40
5	triethyl phosphite	-	>5	>5	68
6	$P(C_6F_5)_3$	-	20	50	15
7	BPh_3	-	0	9	23
8	none	-	49	36	13
9	none	molecular sieves	3	16	49
10	none	pyridine	11	23	0
11	none	$ZnCl_2$	0	0	0
12[a]	none	ethyl vinyl ehter	0	0	100

conditions: 10 mol% $[Rh(CO)_2Cl]_2$, 20 mol% ligand, 0.05 M dioxane, 155 ^oC, 24h.

a. without $[Rh(CO)_2Cl]_2$

2.3 Conclusion

The core tetracyclic scaffold of *ent*-kaurene natural products was accessed by a C–C bond activation/olefin insertion strategy. The method gave a single diastereomer, highlighting the feasibility of an enantioselective synthesis; asymmetric reduction of **11** with either Corey-Bakshi-Shibata catalysis[19] or Noyori conditions[20] would set the stage. Other successes in the early stages include overcoming the regioselectivity problems in our Mitsunobu reaction. Addressing this issue allows for access to large quantities of C–C bond activation precursor **8**. Intermediate **8** can be converted into a modest yield of tetracycle **7** as a single diastereomer allowing us to explore later stages in our synthesis toward *ent*-kaurenes.

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CHAPTER 3

FIRST GENERATION APPROACH TO *ENT*-KAURENE MOTIF

3.1 Introduction With the successful construction of the core tetracyclic scaffold **7**, we turned our attentions toward the construction of key *ent*-kauranoid motif **3** (Figure 3.1). Oxidative cleavage and epimerization are envisioned to access intermediate **6**.[1] The quarternary stereocenter may be installed through a tandem Birch reduction/propargylation sequence.[2] We hypothesized that the diastereoselectivity for the reaction may be controlled by changing the C_1- and C_6-alcohol protecting groups; a bulky C_6 motif is envision to block *si*-face approached of the propargyl electrophile. Pending the success of a tandem Birch reduction/propargylation, C–O bond cleavage by hydrolysis of compound **5**'s enol ether motif and lactonizations is proposed to access the spirolactone **15**. Reductive radical cyclization will complete the *ent*-kauranoid motif **3**. With these goals and challenges in mind, we set out toward the synthesis of **3**.[3]

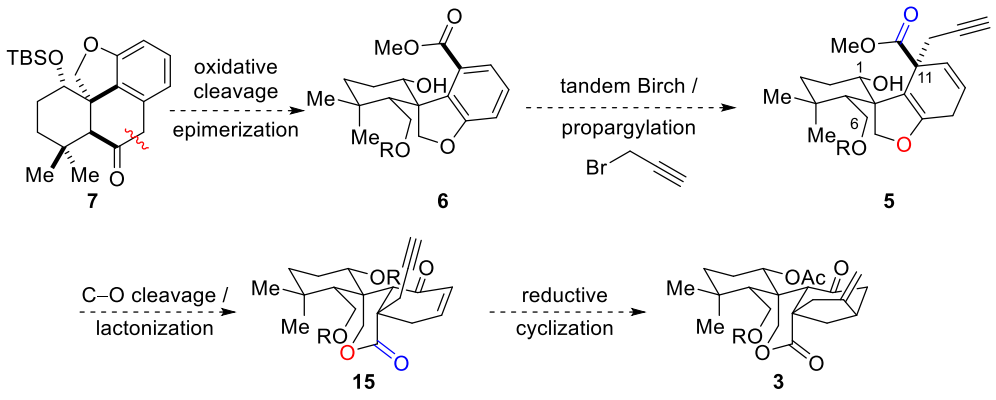
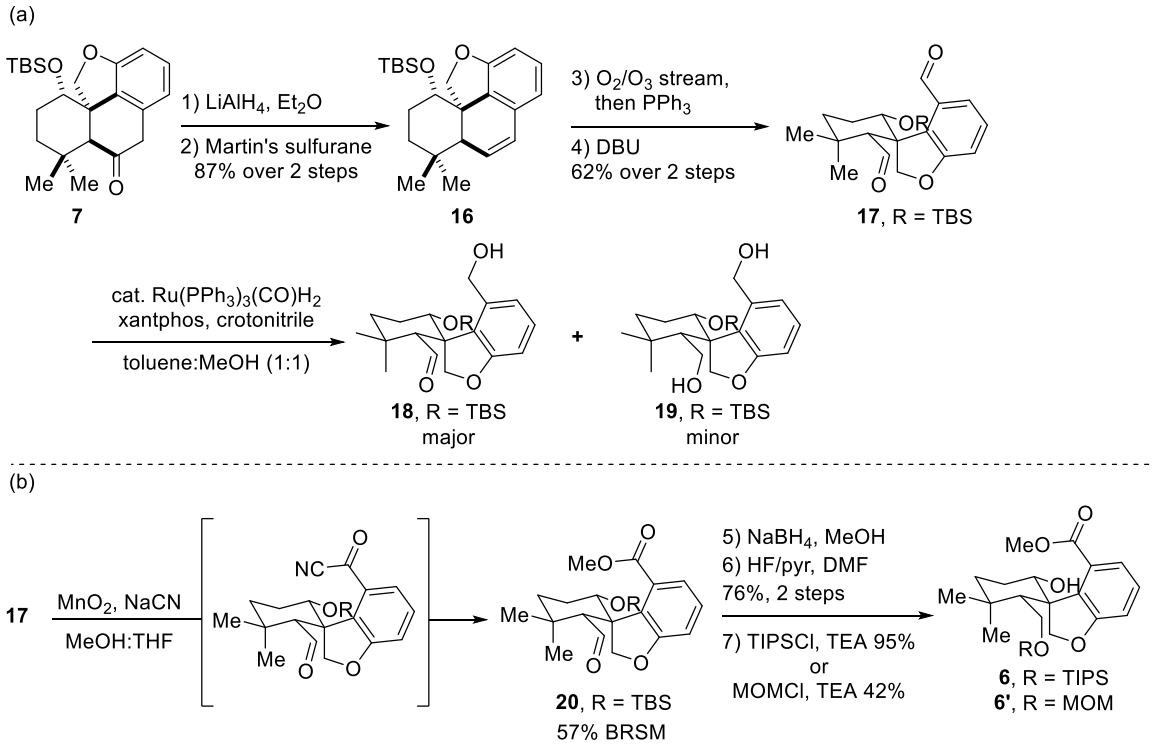


Figure 3.1 Proposed Route Toward *Ent*-Kauranoid Motif **3**

3.2 Results and Discussion The next task presented in the synthesis was the construction of a suitable tandem Birch reduction/propargylation precursor **6**. Carbonyl reduction of tetracycle **7** followed by dehydration with Martin's sulfurane gave styrene **16** (Scheme 3.1 a).[4] Oxidative

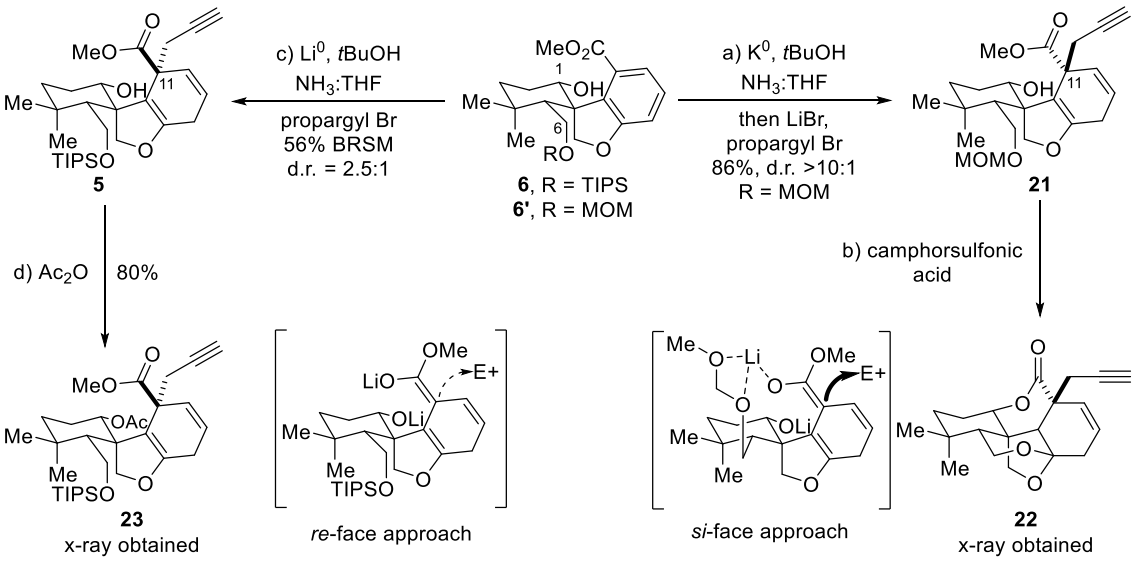
cleavage of **16** with ozone and epimerization gave dialdehyde **17**.[1] From **17**, we envisioned selective benzaldehyde oxidation to obtain a suitable Birch reduction precursor. Initial attempts at selective oxidation employed ruthenium transfer hydrogenation conditions.[5] Under the conditions, only reduction products **18** and **19** were observed. While undesired products, the reaction showed that in the case of dialdehyde **17**, the benzaldehyde is the most reactive carbonyl. After a short survey of literature conditions, we found that treatment of **17** with NaCN and MeOH in the presence of MnO_2 gave our desired methyl benzoate **20** (Scheme 3.2 b).[6] Three standard functional group manipulations then allowed us to access suitable Birch reduction substrates **6** and **6'**.

Scheme 3.1 Synthesis of Suitable Birch Reduction Precursors



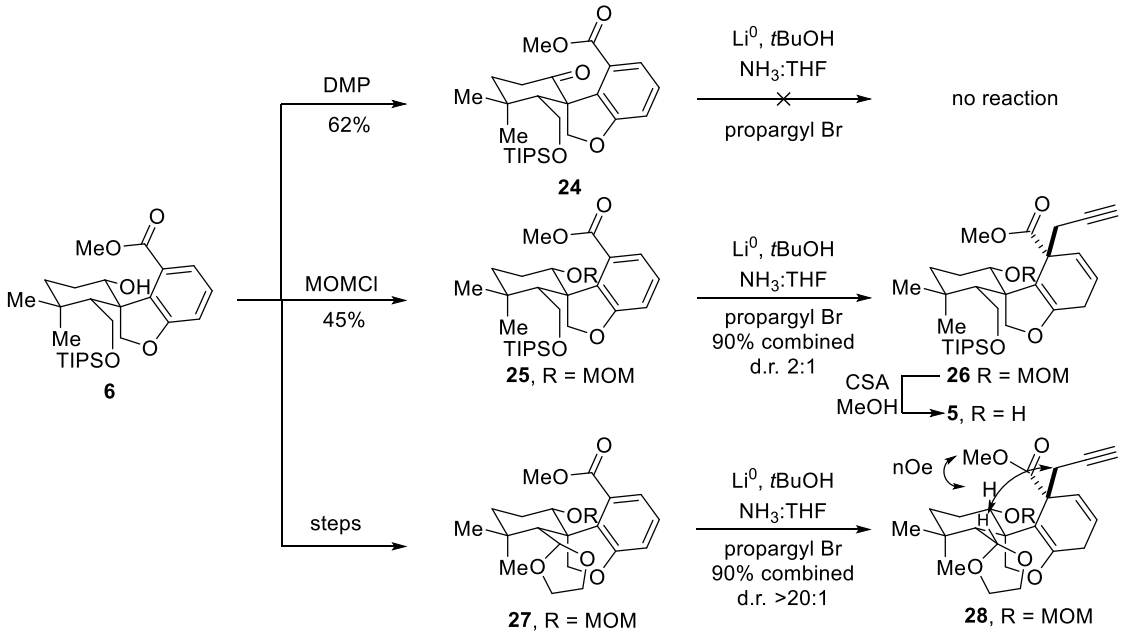
As previously mentioned, we proposed diastereoselective control in the tandem Birch reduction / propargylation sequence by modification of the C_1- and C_6-alcohol protecting groups. The first attempts employed substate **6'** featuring a free C_1-alcohol functionality and a C_6-methoxymethyl acetal (MOM) (Scheme 3.2). After some optimization, tandem Birch reduction / propargylation gave high yield and diastereoselectivity. The structure was originally proposed to be the desired diastereomer based on the assumption of a sterically hindered *si*-face. Hydrolysis of enol ether **21** under acidic conditions gave cage compound **22**; the structure of which was unambiguously confirmed by x-ray crystallography and revealing the incorrect C_{11}-stereochemistry. We now propose the undesired diastereomer arises from the chelation of C_6-MOM ether to the intermediate lithium enolate. This chelation renders the *si*-face less sterically hindered for propargyl bromide approach. On the basis of our hypothesis, the chelating C_6-MOM ether was exchanged for the non-chelating silyl ether **6**. Under slightly modified tandem Birch / propargylation conditions, a 2.5:1 diastereomeric mixture was obtained. The major diastereomer was confirmed to be the desired product **5** after acetate protection and x-ray crystallography of **23**.

Scheme 3.2 Chelation Effect of C_6 Alcohol Protecting Group in Birch Reduction



We attributed the low conversion and diastereoselectivity of **6** in the tandem Birch reduction / propargylation sequence due to the formation of a C_1-lithium alkoxide in close proximity to the aromatic ring. Oxidation of the secondary C_1-alcohol to the corresponding ketone or protection would prevent lithium alkoxide formation (Scheme 3.3). However, under our Birch reduction conditions, no reaction was observed with oxidized substrate **24** and the undesired diastereomer **25** predominated with the C_1-MOM ether. We also envisioned increasing the steric bulk of the *si*-face by converting the protected C_6-alcohol to a protected ketone; the change would effectively move the protecting group one carbon atom closer to the aromatic ring. However, the undesired diastereomer **28** was greatly favored (>20:1 dr) when substrate **27** was subjected to our standard Birch reduction / propargylation conditions.

Scheme 3.3 C_1 Effects in Birch Reduction / Propargylation



With conditions to obtain a modest yield of desired **23**, we focused our efforts in the next key step. We originally proposed C–O bond cleavage and subsequent lactonization via hydrolysis of the enol ether motif to obtain spirolactone **29** (Figure 3.2 a). However, under standard aqueous Brønsted acid induced enol ether hydrolysis conditions the stable intramolecular ketal **30** was obtained (Figure 3.2 b). Ketal **30** was resistant to further hydrolysis as well as thiol exchange. Attempting C–O cleavage with Lewis acids under mild conditions gave no conversion of **23**. Under more forcing conditions, substrate decomposition was typically observed. It was only with BCl_3 that an isolatable compound, alkyl chloride **31**, was obtained. It is now apparent that the C–O bond cleavage of this [5,6]-fused dihydrofuran with a spirocyclic motif will not be facile.

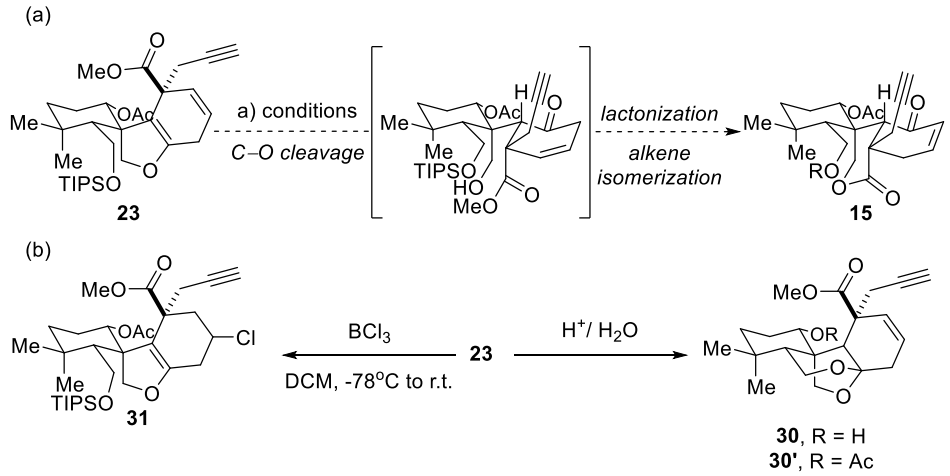


Figure 3.2 Acidic Attempts of C–O Bond Cleavage and Lactonization. (a) proposed reaction and (b) products obtained.

To overcome the inherent stability of the dihydrofuran **23**, we envisioned installing the exocyclic cyclopentane motif prior to C–O cleavage (Figure 3.3 a). It was hypothesized that the bridged 5-membered ring may impart additional stain on the C ring allowing for C–O bond cleavage. In order to install the D-ring, the C_{10}–C_9 alkene needs to be isomerized to the C_9–C_8 position. However, all attempts at alkene isomerization resulted in selective reactivity of the terminal alkyne (Figure 3.3 b). Metal catalyzed hydride walking[7] gave the corresponding carbonyl **32** whereas strong base induced isomerization gave the corresponding allene **33**.

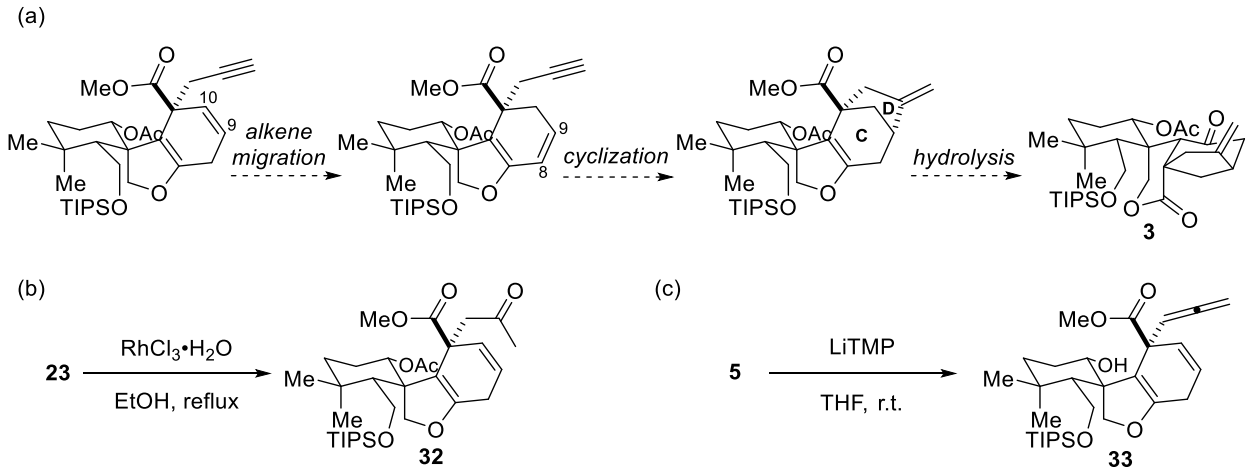
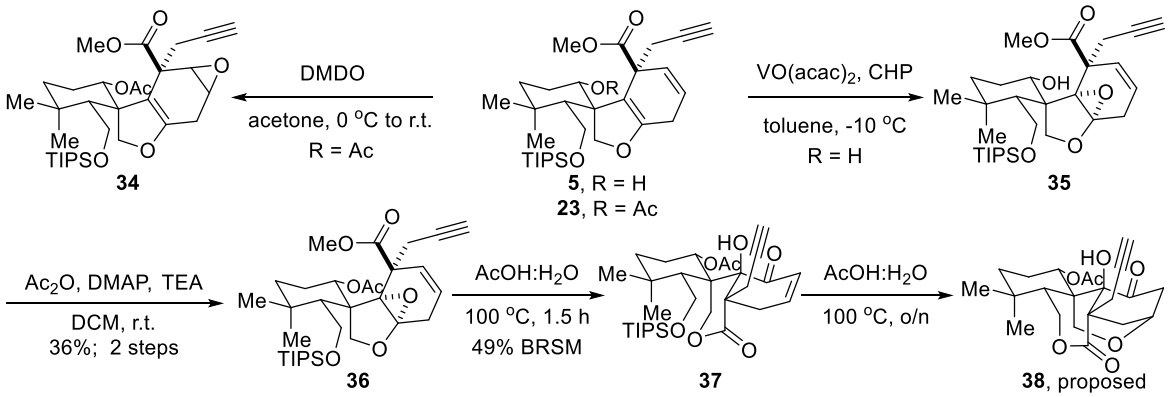


Figure 3.3 Proposed Modified Synthetic Route (a) proposed alkene migration and (b)/(c) products obtained

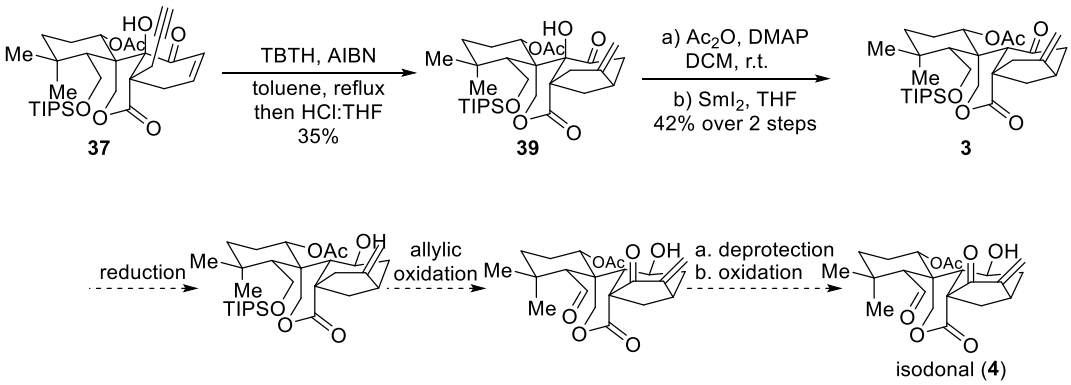
We next proposed prior oxidation of the enol ether motif to create a more liable C–O bond. Under Mukiayama hydration conditions however, ketone **32** was again obtained.[8] Attempting epoxidation of the more electron rich enol ether motif with dimethyldioxirane (DMDO)[9] gave selective epoxidation of the less sterically hindered *Z*-alkene (Scheme 3.4). Gratifyingly, directed epoxidation with $VO(acac)_2$ and cumene hydrogen peroxide gave the desired epoxidized **35**.[10] C–O cleavage of **35** was unsuccessful and it was found that prior protection of the C_1-alcohol as acetate **36** was necessary. Treatment of **36** with aqueous acid resulted in the desired C–O cleavage and lactonization to desired spirolactone **37**. To the best of our knowledge, it is the second example of [5.6] dihydrofuran ring opening by prior epoxidation in synthesis.[11] The added benefit of our directed epoxidation is diastereoselective control of the resulting C_{12}-stereocenter after C–O bond cleavage. While the trans-decalin motif is favored, in similar systems only a modest diastereomeric ratio was obtained.[2] Additionally, it should be noted that careful control of reaction time is necessary to prevent silyl deprotection and intramolecular transesterification to proposed product **38**.

Scheme 3.4 C–O Cleavage and Lactonization Enabled by Prior Epoxidation



With spirolactone **37** in hand, three simple transformation were needed to reach the *ent*-kauranoid motif **3** (Scheme 3.5). Reductive radical cyclization proceeded smoothly to install the exocyclic pentane motif **39**.[3] A two-step α-carbonyl deoxygenation was required due to the prior epoxidation. Acetate protection and treatment with SmI_2 gave **3**.[12] *Ent*-kauranoid motif **3** is expected to give access to isodonal (**4**) in four redox–manipulation steps whereas a key McMurry coupling is yet required for the completion of eriocalyxin B (**1**) (Figure 2.4).

Scheme 3.5 Completion of *Ent*-Kauranoid Motif and Proposed Synthesis of Isodonal



3.3 Conclusion The spirocyclic *ent*-kauranoid motif **3** of *ent*-kauranoid natural products has been accessed from core tetracycle **7**. The C_{11}-quartenary stereocenter was installed by a tandem Birch reduction/propargylation sequence. The diastereoselectivity of the reaction could be control by altering the steric hinderance about the *re*- and *si*-face of the carbonyl functionality. With modest yield of the desired diastereomer obtained, a challenging C–O bond cleavage of a [5.6] dihydrofuran revealed itself. It was found that prior epoxidation of the enol ether was necessary to induced the C–O cleavage. The final C–C bond of *ent*-kaurene motif **3** was installed by reductive radical cyclization. With an established route toward **3**, the synthesis of *ent*-kaurene natural products such as isodonal (**4**) and eriocalyxin B (**1**) is expected.

3.4 References

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CHAPTER 4

SECOND GENERATION APPROACH BASED ON CONFORMATIONAL ANALYSIS

4.1 Introduction The *ent*-kauranoid motif **3** has been accessed in our first-generation approach. However, there exists two limitations in the current route: 1) poor diastereoselectivity in our tandem Birch reduction/propargylation and 2) the necessity for prior epoxidation to induce C–O bond cleavage. In our second-generation strategy, we propose overcoming these two short comings by taking advantage of conformational analysis. Herein we propose changing the C_5-stereocenter to improve diastereoselectivity in the Birch reduction and eliminate the need for prior epoxidation.

In our first-generation strategy, poor diastereoselectivity was observed in the tandem Birch reduction/propargylation to construct the C_{11}-quarternary center. We attributed this to the equatorial C_6-protected alcohol positioned far away from the reactive C_{11}-enolate intermediate (Figure 4.1 a). In the model, changing the C_5-stereocenter to place the C_6-protected alcohol in the axial position results in a more sterically congested C_{11}-*si*-face (Figure 4.1 b). To support our hypothesis, density functional theory calculations were conducted to optimize the ground state geometry of the reactive C_{11}-enolate intermediate during the Birch reduction/propargylation sequence.[1] The calculations approximate the lithium enolate as a simple enol and the C_6-silyl protecting group as a *tert*-butyl. The calculations support our hypothesis in which the now axial C_6-group is in much closer proximity to C_{11}-*si*-face when compared to the equatorial C_6-substrate from our first-generation strategy. It is proposed that this conformational change will result in higher diastereoselectivity during our tandem Birch reduction/propargylation.

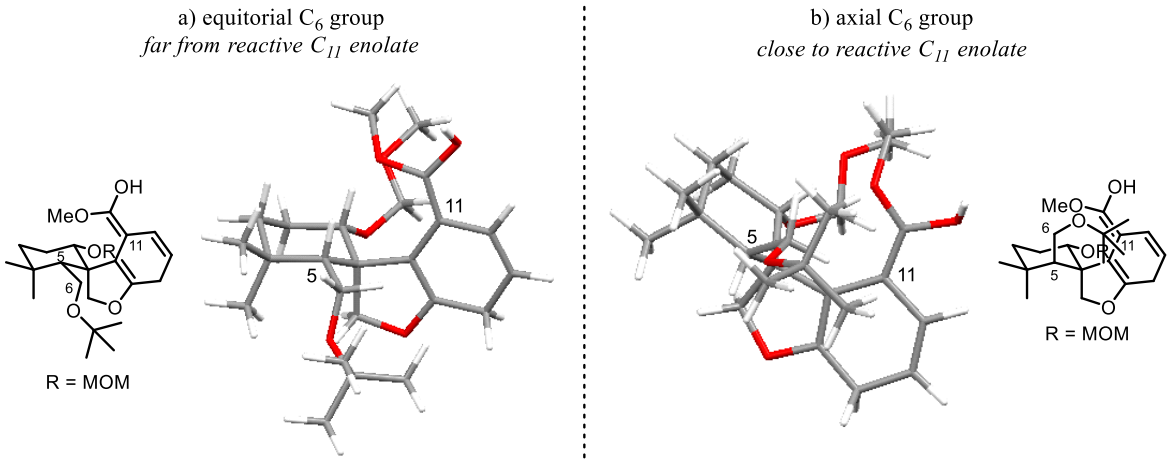


Figure 4.1 DFT Calculations of Birch Intermediate C_{11}-Enolate.[1] a) equatorial C_6-group from our first-generation and b) axial C_6-group in our proposed approach.

Pending the success of a highly diastereoselective tandem Birch reduction/propargylation from **41**, the C_5-epimer substrate **42** is also proposed to hinder the formation of an intermolecular ketal similar to **30** from our first-generation strategy. The approach is envisioned to allow direct C–O bond cleavage/lactonization to spirocycle **43** without the need for prior epoxidation (Figure 4.2). The synthesis of a C_5-epimer is feasible due to our highly diastereoselective C–C bond activation/unsaturated motif insertion strategy to access tetracycle **7**.

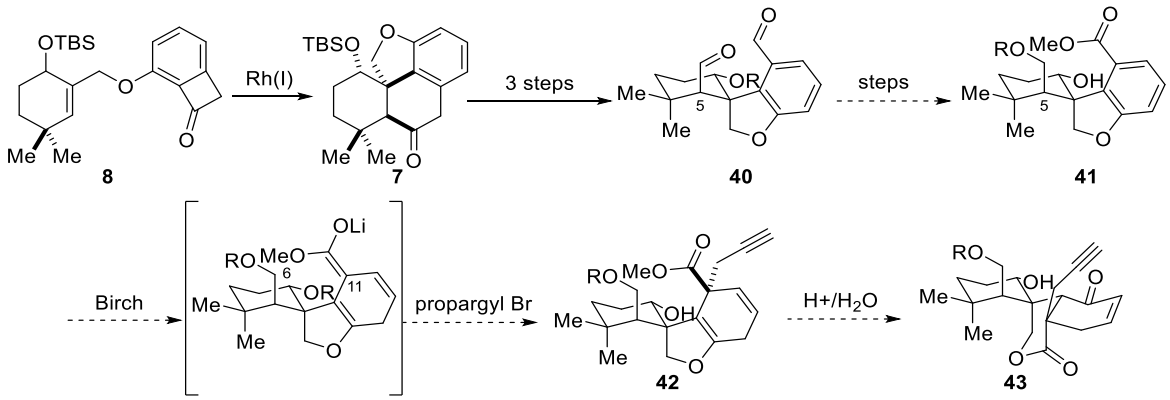
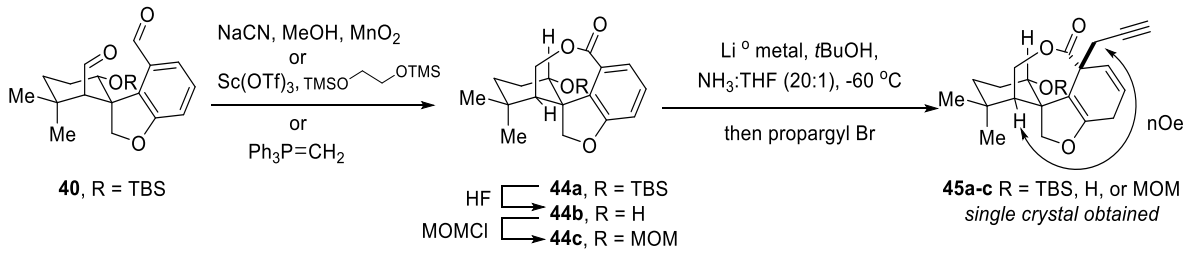


Figure 4.2 Proposed Second-Generation Synthetic Route

4.2 Results and Discussion Initial efforts toward a suitable C_5-epimer Birch precursor employed our previously successful selective benzaldehyde oxidation conditions (Scheme 4.1).[2] However, an unexpected intramolecular Cannizzaro reaction occurred to obtain lactone **44a**.[3] Other attempts to differentiate the two aldehydes (i.e. selective protection) also resulted in **40**. While unexpected, this Cannizzaro reaction allowed an efficient intramolecular oxidation state transfer to give a suitable Birch reduction substrate with an electron withdrawing group at the C_{11}-position. From here, we hoped that the [5,6,7]-fused tricycle would allow for a concave/convex argument in our tandem Birch reduction/propargylation. However, it was found that the propargyl electrophile solely approached from the undesired *si*-face to give **45**.

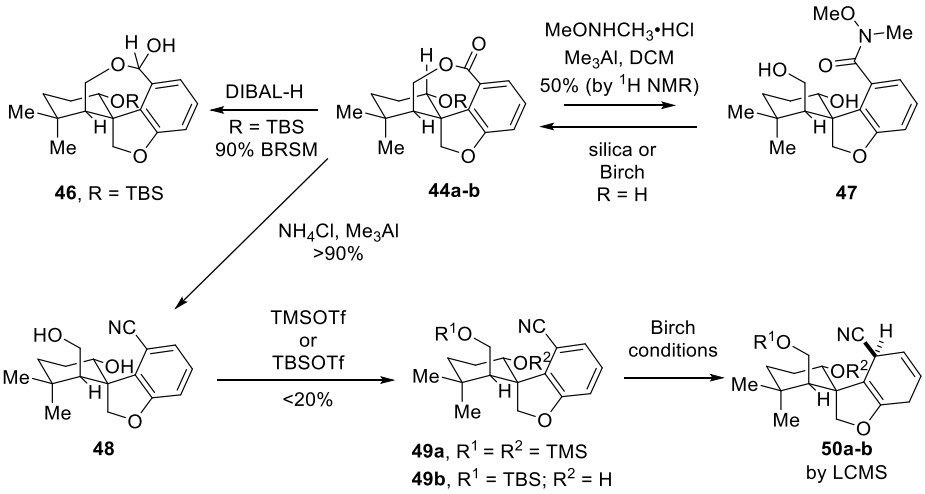
Scheme 4.1 Unexpected Cannizzaro Reaction



We next ventured to open the lactone **44** (Scheme 4.2). DIBAL-H reduction resulted in the isolation of hemiacetal **46**. Treatment with dimethylaluminum amide gave an unstable benzamide motif **47** which readily recyclized back to **44** upon isolation or under Birch reduction conditions.[4] After screening, we found that the lactone **44** could be opened to benzonitrile **48** and isolated without extensive purification. Conditions to protect the resulting free C_6-alcohol primarily resulted primarily in re-lactonization, but allowed for trace isolation of **49a-b**. However, benzonitriles **49a-b** failed to give any desired product under our standard tandem birch reduction/alkylation conditions; primarily re-lactonization was observed with trace reduction product observed by liquid chromatography–mass spectrometry. The poor reactivity of substrates

49a-b can be attributed to the reduced nucleophilicity of the intermediate nitrile anion when compared to the corresponding ester enolate.

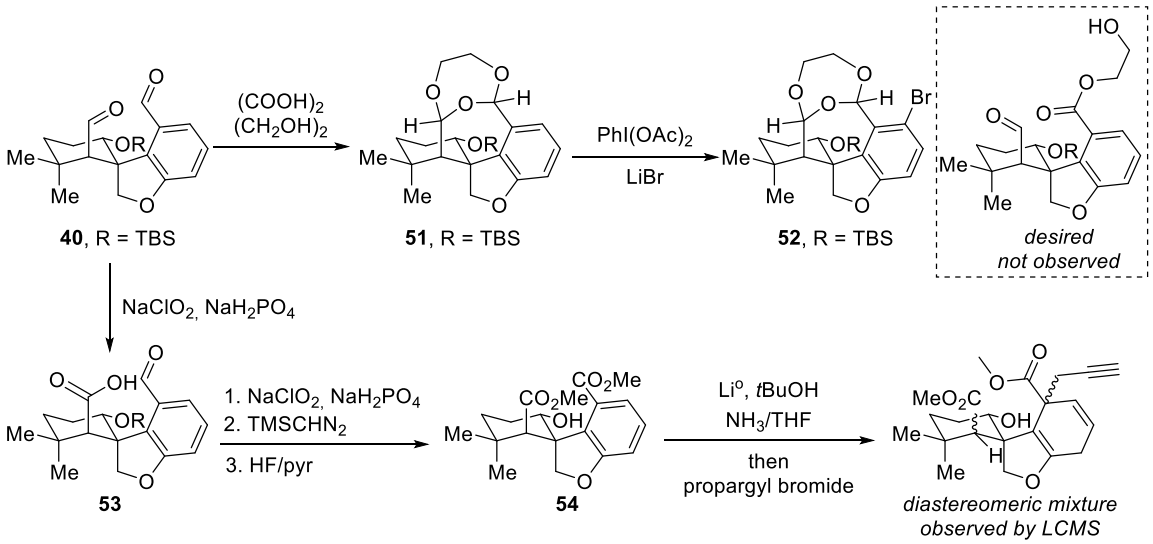
Scheme 4.2 Opening Lactone **44**



We then turned our attentions toward alternative benzylic oxidations to access a suitable Birch reduction substrate. During our earlier attempts at selective acetal installation, we found that under mild conditions the glycol bridge **51** could be obtained (Scheme 4.3).[5] We envisioned selective benzylic oxidation to the corresponding glycol ester.[6] However, only electrophilic aromatic substitution products such as **52** were obtained. Previous transfer hydrogenation conditions indicated that the benzaldehyde is the most reactive carbonyl in substrates similar to **40** (see Chapter 3). Attempting to exploit this reactivity, a selective Pinnick oxidation was envisioned. However, the aliphatic aldehyde was preferentially oxidized to give **53**. We then settled for global oxidation followed by esterification and silyl deprotection to **54**. Diester **54** is a suitable Birch reduction precursor with a C_{11}-electron withdrawing group and an axial C_6-substituent. However, under our standard Birch reduction conditions, a mixture of diastereomers was obtained presumably due to the readily epimerizable C_5-position. We did think about

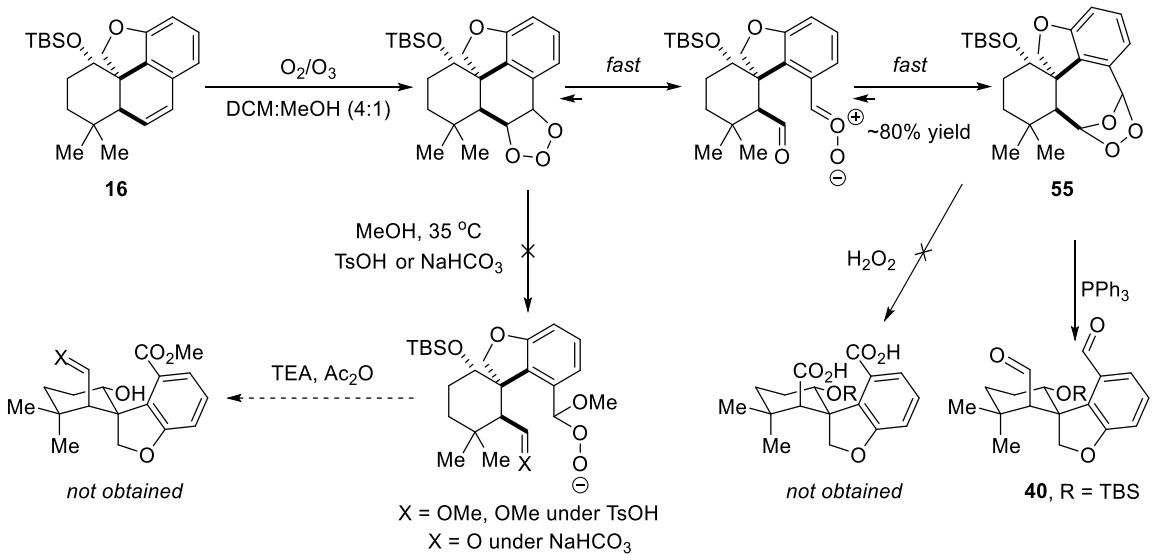
selective single hydride reduction of the aliphatic C_6-carbonyl, however under a variety of single hydride reducing conditions (DIBAL-H, $LiBHEt_3$, or Et_2OAlH_2) no reaction took place. The poor reactivity is attributed to sterics.

Scheme 4.3 Alternative Benzylic Oxidation Approach



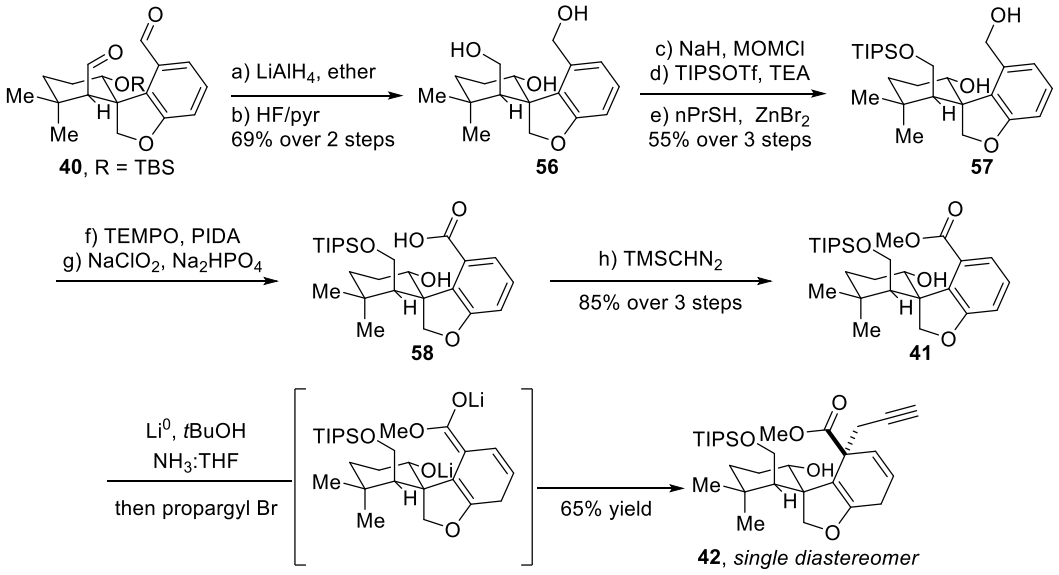
In another attempt to differentiate the two aldehydes of **40**, we took a step back and looked at the ozonolysis of **16** (Scheme 4.4). We envisioned differentiation through the Schreiber modification.[7] In the Schreiber modification of ozonolysis, the intermediate ozonide is expected to condense with solvent methanol. The regioselectivity for methanol attack is primarily controlled by sterics.[8] After decomposition of the intermediate hydroperoxy hemiacetal with acetic anhydride, the corresponding methyl benzoate is expected. However, in our hands only the intermediate trioxolane **55** was obtained upon isolation. Intermediate **55** was found to be resistant to oxidative conditions. The structure of trioxolane **55** was confirmed upon treatment of the isolated compound with triphenyl phosphine to obtain the previously characterized dialdehyde **40**. The spectroscopic data is also consistent with a similarly reported diterpenoidal ozonide in the literature.[9]

Scheme 4.4 Schreiber Modification of Ozonolysis



We finally settled for a redox manipulation strategy to obtain a suitable Birch reduction precursor (Scheme 4.5). Global reduction and silyl deprotection of **40** gave triol **56**. Selective benzylic alcohol protection with chloromethyl methyl ether (MOM-Cl) allowed for subsequent functional group transformations to obtain intermediate **57**. Primary alcohol oxidation with (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) followed by Pinnick oxidation gave benzylic acid **58**. Treatment with $TMSCHN_2$ gave desired **41**.[10] Methyl benzoate **41** is our originally proposed precursor (Figure 4.2) featuring an axial C_6-protected alcohol and a C_{11}-Birch reduction stable electron withdrawing group. Gratifyingly, under our standard birch reduction/propargylation conditions the desired product **42** could be obtained as a single diastereomer in a modest 65% yield. The success of the approach can be attributed to conformational analysis at the C_5 position. Now with a scalable route to **42**, we turn our attention toward C–O bond cleavage and lactonization.

Scheme 4.5 Redox Manipulation and Diastereoselective Birch Reduction/Propargylation



We initially proposed that the C_5-epimer **42** would prevent ketal formation and allow for direct C–O bond cleavage (Figure 4.3 a). However, under acidic conditions the 7-membered lactone **60** was obtained (Figure 4.3 b). Even with careful control of acid equivalence (1.2 equiv. methanolic HCl), silyl deprotection and lactonization dominated. We then attempted our previously successful directed epoxidation with vanadium. However, under the standard conditions rearomatized product **41** was observed, presumably through a hydrogen atom extraction pathway.[11] We also thought about cleaving the C–O bond with Lewis acids. When **59** was treated with trimethylsilyl iodide (TMSI), the intermolecular ketal **61** formed as a cis-decalin. Ketal **61** was also obtained from **59** with excess acid in methanol.

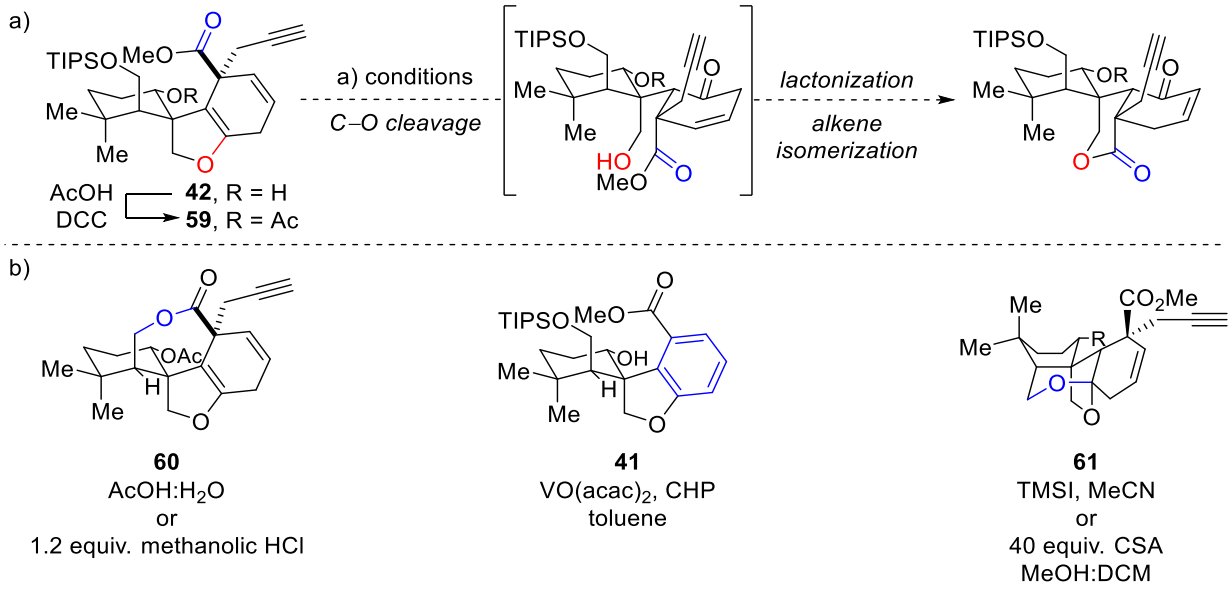
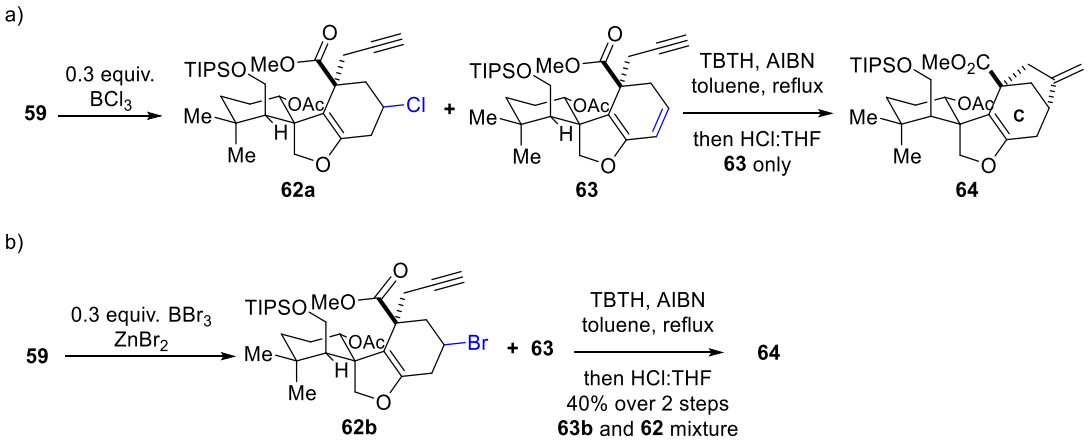


Figure 4.3 Attempted C–O Bond Cleavage and Lactonization of **42** and **49** a) proposed reaction and b) observed products

Unexpectedly, the 1,3-diene **63** and alkyl chloride **62a** were obtained when enol ether **59** was treated with BCl_3, presumably through an oxonium intermediate. While an unexpected product, **63** is a C_8-C_9 alkene isomerized product proposed in Figure 3.2. Reductive radical cyclization of **63** installed the exocyclic cylclopentane motif **64** (Scheme 4.6). The alkyl chloride **62a** was unreactive under reductive radical cyclization conditions. The alkyl bromide **62b** was proposed to allow for a convergent synthesis and thus overall higher yield to **64**. After some optimization, it was found that treatment of **59** with catalytic BBr_3 and 1.5 equiv. $ZnBr_2$ could give a mixture of **63** and bromide isomers **62b**. The product mixture was treated with tributyltin hydride (TBTH) and azobisisobutyronitrile (AIBN) to converge both intermediates to the same desired bridged structure **64**. As previously mentioned in chapter 3 (Figure 3.2), we propose that the exocyclic cyclopentane motif may impart additional strain on the C-ring allowing for C–O bond cleavage (Figure 4.5).

Scheme 4.6 Construction of Exocyclic Cyclopentane Motif a) initial observation and b) convergent approach with alkyl bromide.



We now envisioned C–O bond cleavage of **64** to obtained spirolactone **65** (Figure 4.5). Acid induced enol ether hydrolysis however resulted in a similar undesired ketal **66**. Attempting selective silyl deprotection, proposed to be followed by primary alcohol oxidation, gave lactone **67**. We next thought about exploiting the more electron rich double bond enol ether motif over the terminal alkene. Dimethyldioxirane (DMDO) epoxidation or hydroselenation with phenylselenyl chloride[12] preferred to react with the terminal alkene to give products **68** and **69**, respectively. On the other hand, hydrobromination with N-Bromosuccinimide (NBS) gave a mixture of allyl bromides **70a-b**, via an intermediate oxyallyl cation, and tentative hemiacetal **71**. In addition, Lewis acids such as $PdCl(MeCN)_2$ also appear to effectively activate the electron rich enol ether to give the tentative hydrolyzed products **72** and **73**.[13] While not yet fully characterized, we a reasonably certain of the structures **70-73** which exhibit the desired C–O bond hydrolysis as well as unexpected tendency for C_6-oxidation. These observations taken together may hold the key to induce C–O bond cleavage/lactonization

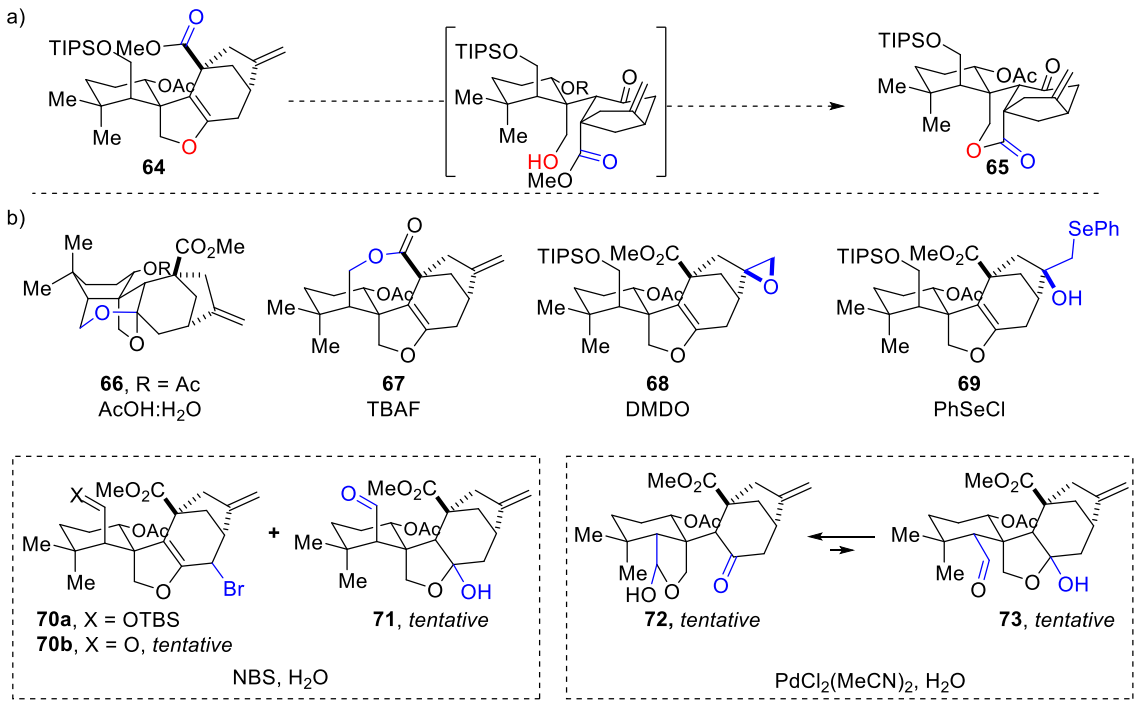


Figure 4.4 Attempted C–O Bond Cleavage and Lactonization of **64** a) proposed reaction and b) observed products

In Fujita's synthesis of enmein, it was found that a similar 5-membered ring intermediate would undergo base induced intramolecular transesterification to, in their case, the undesired 6-membered lactone **75** (Figure 4.6).[14] On this basis, it should stand to reason that the isomeric structures **72-73** will undergo a similar esterification to give the desired spirolactone **76**. Isodonal (**4**) is a few oxidation state manipulations away whereas a key McMurray coupling is yet required for the synthesis of eriocalyxin B (**1**).

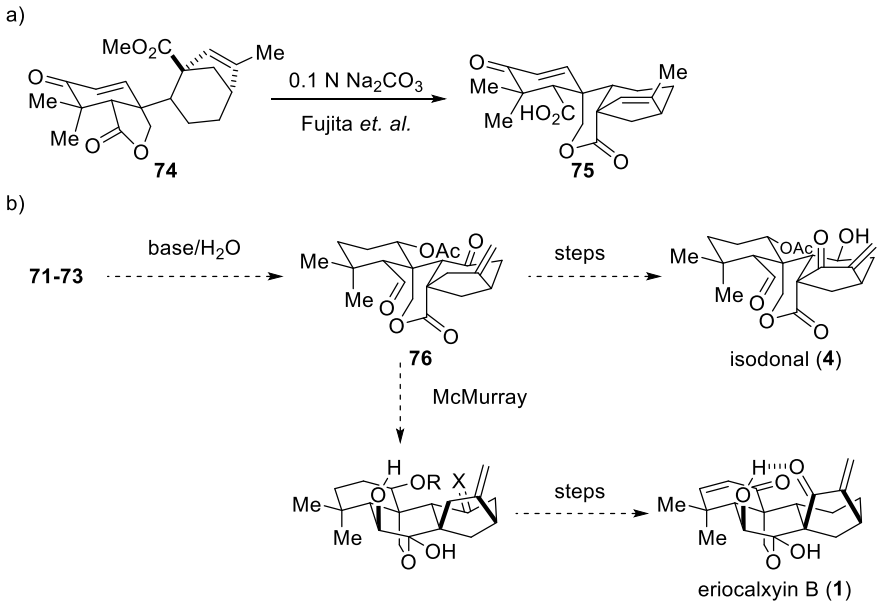


Figure 4.5 Proposed Completion of *Ent*-Kaurenes a) Fujita's observations in route toward enmein and b) proposed route toward Isodonal and Eriocalyxin B

4.3 Conclusion A second-generation strategy has been developed to overcome the limitation in our prior approach. By taking advantage of conformational analysis, the quarternary C_{11}-stereocenter was constructed as a single diastereomer as opposed to our previously observed 2.5:1 d.r. While successful in the tandem Birch reduction/propargylation, the C_5-stereochemical change did not allow for the proposed direct C–O bond cleavage. However, at this time it appears the axial C_6-substituent renders the enol ether motif more reactive as well as exhibits an unexpected tendency for oxidation. Further work in the lab aims to exploit this reactivity to obtain *ent*-kaurene motif **76** in route toward isodonal (**4**) and eriocalyxin B (**1**).

4.4 References

1. I would like to thank Mr. Cooper Taylor for preforming density functional theory calculations. DFT optimizations were performed through Gaussian 09 on the Midway2 Cluster at the University of Chicago's Research Computing Center. Ground state geometry optimizations and free energies (kcal/mol) were determined using the B3LYP/cc-pVDZ level of theory in the gas phase at 298K. All ground state structures display no imaginary frequencies..

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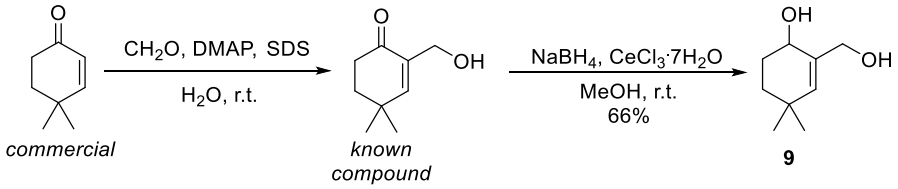
CHAPTER 5

SUPPORTING INFORMATION

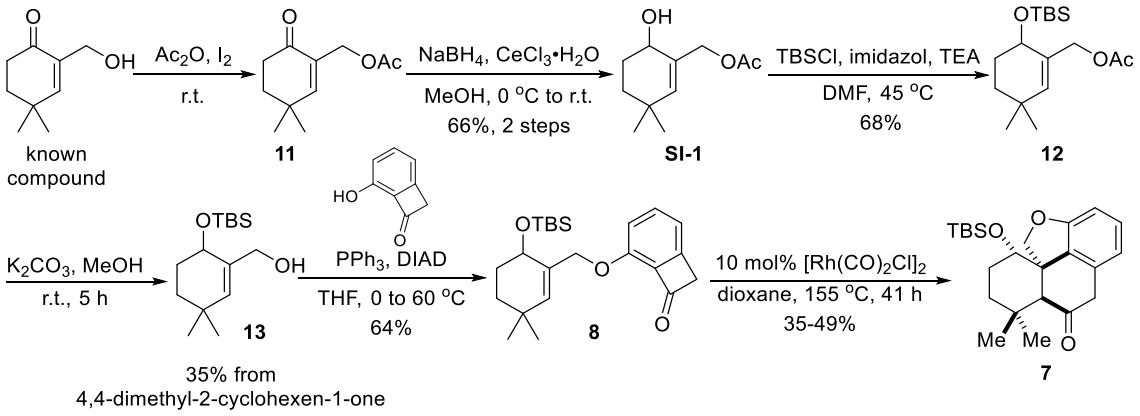
5.1 Experimental



2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone. A modified quench procedure from the previous report[1] was found to give higher yields on large scale. To a 1 L flask was added water (241 mL), 4,4-dimethyl-2-cyclohexen-1-one (30 g, 242 mmol), sodium dioctyl phosphate (0.1 equiv., 6.97 g, 24.2 mmol), and 4-dimethylaminopyridine (1 equiv., 29.5 g, 242 mmol). The reaction was stirred at room temperature for 15 minutes before formalin (241 mL) was slowly added. The reaction was stirred for 45 minutes before quenching with pH = 7 phosphate buffer (0.5 M) and extracting three times with ethyl acetate (3 x 200 mL). The combined organics were washed with water (200 mL), washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone as a colorless oil. The spectroscopic data is consistent with the previous report.

Compound 9 In a 1 L flask, 2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (24.7 g, 160 mmol) and $CeCl_3 \cdot 7H_2O$ (1 equiv., 59.7 g, 160 mmol) was dissolved in methanol (0.65 M, 250 mL). At 0 ^oC with stirring, $NaBH_4$ (1 equiv, 6.1 g, 160 mmol) was slowly added to minimized hydrogen evolution. Upon completion of addition, the reaction was warmed to room temperature allowed to stir for 30 minutes. The resulting solution was carefully quenched with water and

extracted three times (3 x 100 mL) with ethyl acetate. The combined organics were washed with water (200 mL), washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography and diol **9** was collected as a clear oil in 66% yield. Rf = 0.17 (2:5 EtOAc : Hexanes); m.p. = n/a; HRMS (ESI) obs. = 156.1146, ref. = 156.115 for $C_9H_{16}O_2$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 4.27 (t, *J* = 5.0 Hz, 1H), 4.18 (q, *J* = 12.0 Hz, 2H), 1.89 (dddd, *J* = 13.6, 10.2, 4.9, 3.3 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.60 (ddd, *J* = 13.5, 10.1, 3.2 Hz, 1H), 1.41 (ddd, *J* = 13.4, 7.9, 4.0 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.05, 155.67, 137.14, 135.51, 65.71, 65.12, 32.68, 31.71, 29.41, 28.60, 28.25, 27.57; IR (film) ν_{max} 698.38, 749.30, 865.37, 885.57, 897.64, 923.13, 938.66, 966.06, 999.08, 1038.42, 1071.15, 1123.52, 1142.23, 1181.77, 1228.88, 1274.96, 1360.43, 1453.47, 1664.37, 1719.39, 2864.23, 2954.76, 3346.27 cm^{-1}.



Compound SI-1. To a solution of 2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (63 g, 408.5 mmol) in acetic anhydride (1.0 equiv., 38.6 mL, 408.5 mmol), was added iodine (0.05 equiv, 5.2 g, 20.4 mmol). The reaction was stirred at 0 ^{0}C until consumption of the starting material by TLC. The reaction was quenched with saturated aqueous sodium thiosulfate (25 mL) and organics were extracted with ethyl acetate (3 x 25 mL). The combined organics were washed

once with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude residue was passed over a silica plug and used without further purification in the next step.

In a 1 L flask, crude allylic acetate (61.9 g, 315 mmol) from the previous step and $CeCl_3 \cdot 7H_2O$ (1 equiv., 117.6 g, 315 mmol) was dissolved in methanol (0.4 M, 77 mL). At 0 ^oC with stirring, $NaBH_4$ (1 equiv., 12 g, 315 mmol) was slowly added to minimized hydrogen evolution. Upon completion of addition, the reaction was warmed to room temperature allowed to stir for 30 minutes. The resulting solution was carefully quenched with water and extracted three times (3 x 150 mL) with ethyl acetate. The combined organics were washed with water (200 mL), washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography and **SI-1** was collected as a clear oil (66% over 2 steps). Rf = 0.43 (1:1 EtOAc:Hexanes); m.p. = n/a; HRMS (ESI) obs. = 198.1259, ref. = 198.1256 for $C_{11}H_{18}O_3$; ^1H NMR (400 MHz, z) δ 5.57 (s, 1H), 4.82 (dd, *J* = 12.2, 0.6 Hz, 1H), 4.40 (d, *J* = 12.2 Hz, 1H), 4.09 (q, *J* = 5.2 Hz, 1H), 2.09 (s, 3H), 1.93 – 1.83 (m, 1H), 1.79 – 1.70 (m, 1H), 1.60 (s, 1H), 1.63 – 1.55 (burried, 1H), 1.42 (dddd, *J* = 13.4, 7.9, 3.3, 0.6 Hz, 1H), 1.03 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.30, 140.22, 132.31, 66.41, 64.81, 32.61, 32.12, 29.35, 28.58, 28.19, 21.00; IR (film) ν_{max} 606.16, 646.82, 734.86, 876.11, 899.02, 915.95, 963.60, 1000.68, 1038.60, 1072.03, 1144.00, 1183.66, 1241.00, 1361.65, 1455.02, 1732.25, 2865.32, 2955.93, 3435.68 cm^{-1}.

Compound 12 To a 100 mL flask was added **SI-1** (15.1 g, 76 mmol) in DMF (2M, 38 mL). *Tert*-butyldimethylsilyl chloride (1.5 equiv., 17.2 g, 114 mmol), imidazol (2 equiv., 10.4 g, 152 mmol) and triethylamine (1.2 equiv, 12.6 mL, 91 mmol) was sequentially added. The viscous reaction mixture was heated to 45 ^oC on an oil bath and allowed to stir over night. The resulting solution was quenched with water (20 mL), extracted three times with ethyl acetate (3 x 20 mL),

washed with brine (20 mL), dried over MgSO4, concentrated under vacuum, and used without further purification. Rf = 0.70 (1:4 EtOAc:Hexanes); m.p. = n/a; HRMS (ESI) obs. = 312.2123, ref. = 312.2121 for $C_{17}H_{32}O_3Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (s, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.38 (d, *J* = 12.2 Hz, 1H), 4.19 (t, *J* = 5.7 Hz, 1H), 2.06 (s, 3H), 1.82 (dddd, *J* = 13.5, 8.3, 5.0, 3.1 Hz, 1H), 1.71 – 1.62 (m, 1H), 1.57 (ddd, *J* = 11.8, 8.3, 4.0 Hz, 1H), 1.38 (ddd, *J* = 13.1, 9.8, 3.0 Hz, 1H), 1.01 (s, 3H), 0.96 (s, 3H), 0.88 (s, 10H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 170.98, 138.99, 133.12, 66.30, 66.11, 33.52, 32.18, 29.88, 29.22, 29.18, 25.95, 21.25, 18.17, -4.15, -4.86. IR (film) ν_{max} 592.12, 604.36, 673.65, 774.72, 813.74, 856.95, 836.11, 887.00, 942.24, 965.30, 983.99, 1015.03, 1082.91,1251.83, 1361.04, 1463.02, 1471.61, 1746.20, 2857.49, 2895.23, 2955.86 cm $^{-1}$.

Compound 13 To a vial charged with crude material the previous step was added from MeOH (0.5M, 150 mL) and K_2CO_3 (1.2 equiv., 12.6 g, 91 mmol). The reaction was stirred at room temperature for 5 hours. The resulting solution was quenched with water (100 mL) and extracted three times with ethyl acetate (3 x 100 mL). Organics were washed with brine (100 mL), dried over $MgSO_4$, concentrated, and used purified via silica gel column chromatography. Compound **13** was obtained in 35% yield over five steps from 4,4-dimethyl-2-cyclohexen-1-one. Rf = 0.46 (1:4 EtOAc:Hexanes); m.p. = n/a; HRMS (ESI) obs. = 270.2022, ref. = 270.2015 for $C_{15}H_{30}O_2Si$; 1H NMR (500 MHz, $CDCl_3$) δ 5.48 – 5.41 (m, 1H), 4.32 – 4.27 (m, 1H), 4.12 (dd, J = 11.9, 3.0 Hz, 1H), 3.97 (dd, J = 11.9, 8.7 Hz, 1H), 2.23 (dd, J = 8.7, 3.0 Hz, 1H), 1.82 (dddd, J = 12.6, 7.2, 5.2, 3.1 Hz, 1H), 1.69 (dddd, J = 13.0, 10.8, 7.7, 3.0 Hz, 1H), 1.58 – 1.53 (burried, 1H), 1.41 – 1.34 (m, 1H), 1.03 (d, J = 3.4 Hz, 3H), 0.96 (s, 3H), 0.92 – 0.89 (m, 9H), 0.13 (s, 3H), 0.11 (s, 3H). 13C NMR (126 MHz, $CDCl_3$) δ 137.35, 136.87, 69.66, 65.98, 34.21, 32.10, 30.22, 29.91, 29.00, 26.03, 25.98, 25.98, 25.97, 25.80, 18.12, -3.97, -4.73, -4.74. IR (film) ν_{max} 673.65, 774.59,

835.48, 889.53, 938.53, 1004.93, 1080.60, 1182.80, 1252.89, 1360.73, 1471.47, 2857.44, 2955.47, 3354.79 cm^{-1}.

Compound 8 To a solution of **13** (1.5 equiv., 11.1 g, 40.9 mmol), benozocyclobutenone **10** (1 equiv., 3.7 g, 27.3 mmol), and PPh_3 (1.5 equiv., 10.7 g, 40.9 mmol) at 0 ^oC in THF (0.2M, 205 mL) in a pressure vessel was added DIAD (1.5 equiv., 8.1 mL, 40.9 mmol) drop wise. The reaction was capped and stir at 0 ^oC for 2 hours before being warmed to room then heating at 60 ^oC on an oil bath overnight. Upon completion, the reaction was cooled to room temperature, quenched with saturated aqueous NH_4Cl solution, extracted with diethyl ether (3 x 100 mL), washed with brine (100 mL), dried over $MgSO_4$ and concentrated. To the crude oil residue was added 100 mL 1:5 ether:hexane resulting in white triphenylphosphine solid. The triphenylphosphine was filtered off and rinsed with 20 mL 1:5 ether:hexane. The filtrate was concentrated and purified via silica gel column chromatography to give **8** as a colorless oil.

Rf = 0.5 (1:9 Et_2O:Hexanes); m.p. = n/a; HRMS (ESI) obs. = 386.2279, ref. = 386.2277 for $C_{23}H_{34}O_3Si$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.00 (d, *J* = 7.1 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 4.99 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.33 (t, *J* = 5.6 Hz, 1H), 3.90 (s, 2H), 1.84 (tdd, *J* = 8.3, 5.0, 3.1 Hz, 1H), 1.74 – 1.64 (m, 1H), 1.64 – 1.55 (m, 1H), 1.39 (ddd, *J* = 12.9, 9.6, 3.0 Hz, 1H), 1.03 (s, 3H), 0.94 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.85, 152.53, 150.64, 139.02, 137.60, 133.52, 132.72, 116.32, 114.92, 77.48, 77.16, 76.84, 73.72, 65.89, 51.23, 33.49, 32.17, 29.87, 29.22, 29.11, 25.94, 18.11, -4.24, -4.83; IR (film) ν_{max} 778, 836, 1047, 1270, 1469, 1569, 1603, 1766, 2856, 2928, 2954 cm^{-1}.

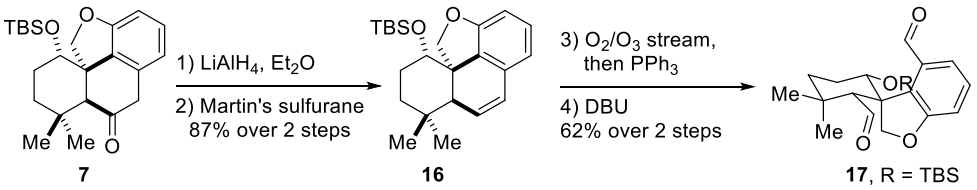
Compound 7

gram scale: To a flame dry 300 mL pressure was added **8** (3.88 mmol, 1.5 g). The vessel was transferred into a nitrogen filled glove box and 1,4-dioxane (0.05M, 77.6 mL) (distilled and degased) was added followed by $[Rh(CO)_2Cl]_2$ (0.10 equiv., 0.388 mmol, 150.8 mg). The reaction was sealed with a teflon screw cap and PTFE o-ring, removed from the glove box, and heated to 155 ^oC on a pre-heated oil bath for 41 hours. Upon completion, the reaction was cooled to room temperature, filtered over a pad of silica, concentrated, and purified via silica gel column chromatography to give 35% yield of **7** as a white solid.

milligram scale: In a nitrogent filled glove box to a flame dried 2 mL vial charged with **8** (0.0259 mmol, 10 mg) was added a fresh stock solution of $[Rh(CO)_2Cl]_2$ (0.10 equiv., 2.6µm, 1.01 mg) in dioxane (0.05 M, 0.518 mL). The vial was sealed with a PTFE cap, removed from the glove box, and heated to 155 ^oC on a pre-heated oil bath for 41 h. Upon completiong the reaction was ran through a celite plug, concentrated, and purified via silica column chromatography to give up to 51% yield of **7** as a white solid.

Rf = 0.5 (1:9 Et_2O:Hexanes); m.p. = 158.2-160.7 ^oC; HRMS (ESI) obs. = 386.2274, ref. = 386.2277 for $C_{23}H_{34}O_3Si$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.7 Hz, 1H), 6.60 (dd, *J* = 7.4, 6.9 Hz, 2H), 5.02 (d, *J* = 8.7 Hz, 1H), 4.38 (d, *J* = 8.5 Hz, 1H), 3.65 (d, *J* = 20.6 Hz, 1H), 3.53 (d, *J* = 20.3 Hz, 1H), 3.49 (dd, *J* = 10.9, 4.5 Hz, 1H), 2.55 (d, *J* = 2.0 Hz, 1H), 2.09 (dd, *J* = 16.1, 11.4 Hz, 1H), 1.77 (d, *J* = 15.8 Hz, 1H), 1.69 (d, *J* = 2.9 Hz, 1H), 1.29 (s, 1H), 1.26 (s, 3H), 0.91 (s, 3H), -0.25 (s, 3H), -0.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.20, 159.59, 130.79, 129.90, 129.28, 118.28, 107.38, 100.11, 78.45, 77.42, 77.16, 76.91, 73.57, 62.73, 53.52, 43.40, 33.76, 33.29, 29.29, 29.12, 28.97, 25.64, 17.85, -5.02, -6.10, -6.11. IR (film) ν_{max} 758.74, 777.85,

837.90, 1094.61, 1252.06, 1467.92, 1626.18, 1697.99, 2856.75, 2926.39, 2955.01, 3438.81 cm $^{-1}$.



Compound 16 To a solution of **7** (1.0 g, 2.6 mmol) in ether (0.03 M, 86 mL) at 0 ^{o}C was slowly added $LiAlH_4$ (2 equiv., 197 mg, 5.2 mmol). After the initial violent reaction, the solution was removed from the ice bath and allowed to warm to room temperature. After 20 minutes the reaction was cooled to 0 ^{o}C and carefully quenched with saturated aqueouse Rochelle salt and extracted with diethyl ether (3 x 50 mL). The combined organics were washed with water (100 mL), washed with brine (100 mL), dried over MgSO4, concentrated under vacuum, and collected as a light yellow solid. The diastereomeric mixture was used without further purification in the next step.

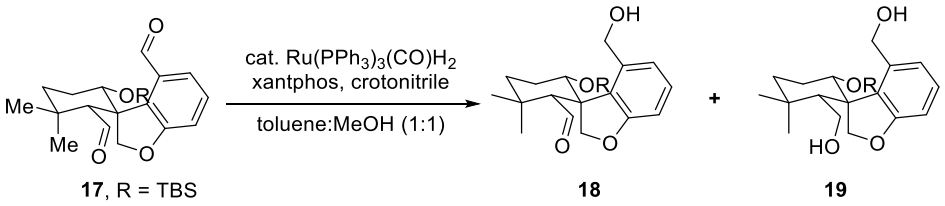
To a flame dry pressure vessel was added crude material from the previous step and transferred to a N_2 filled box. DCM (from SPS) (0.03M, 86 mL) was added followed by Martin's sulfurane (1.2 equiv., 2.1 g, 0.36 mmol). The pressure vessel was sealed, removed from box, and stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO4, concentrated under vacuum, and purified via silica gel column chromatography to give pure **16** as a white solid (87% over 2 steps).

Rf = 0.8 (1:4 Et_2O:Hexanes); m.p. = 100.2-102.0 ^{o}C; HRMS (ESI) obs. = 370.2335, ref. = 370.2328 for $C_{23}H_{34}O_2Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (t, *J* = 7.7 Hz, 1H), 6.58 (dd, *J* =

16.3, 7.7 Hz, 2H), 6.50 (dd, *J* = 9.8, 3.2 Hz, 1H), 5.94 (dd, *J* = 9.8, 2.1 Hz, 1H), 5.04 (d, *J* = 8.4 Hz, 1H), 4.27 (d, *J* = 8.4 Hz, 1H), 3.91 (dd, *J* = 11.4, 4.8 Hz, 1H), 1.72 – 1.61 (m, 1H), 1.56 (burried, 2H), 1.38 – 1.31 (m, 1H), 1.07 (s, 3H), 0.92 (s, 3H), 0.75 (s, 10H), -0.26 (s, 3H), -0.66 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.76, 131.34, 131.22, 129.13, 128.79, 126.37, 115.76, 108.55, 80.24, 69.96, 52.63, 49.57, 35.07, 32.58, 28.95, 28.15, 27.17, 25.75, 17.88, -4.92, -6.19. IR (film) ν_{max} 727.07, 775.23, 796.51, 820.76, 836.09, 874.66, 891.40, 899.28, 940.18, 1050.97, 1062.47, 1091.71, 1106.91, 1253.54, 1384.21, 1463.50, 1571.06, 1630.29, 2855.29, 2932.86, 2990.74 cm $^{-1}$.

Compound 17 To a round bottom flask was added **16** (963.6 mg, 2.6 mmol) in DCM (0.02 M, 130 mL). The solution was cooled to -78 ^{o}C and a stream of O_2/O_3 was bubbled through until a light blue color (~10 minutes). The reaction was placed under N_2 atmosphere and PPh_3 (10 equiv, 6.8 g, 26 mmol) in DCM (50 mL) was slowly added via syringe. The reaction was stirred at -78 ^{o}C for 30 minutes before removing from the dry ice / acetone bath and warming to room temperature. The reaction was stirred at room temperature for 2 hours. Upon completion, the reaction was directly concentrated under vacuum. The crude residue was disolved in toluene (0.02 M, 130 mL) and 1,8 diazabicyclo[5.4.0]undec-7-ene (1.2 equiv, 467 µL, 3.12 mmol) was added. The reaction was placed under N_2 atmosphere and heated to reflux overnight. Upon completion the reaction was cooled to room temperature and directly concentrated under vacuum. The crude product was purified via silica gel column chromatography to give **17** as a white solid (62% over 2 steps). Rf = 0.58 (1:5 ethyl acetate:hexanes); m.p. = 129.3-132.1 ^{o}C; HRMS (ESI) obs. = 402.2226, ref. = 370.2328 for $C_{23}H_{34}O_4Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 9.66 (d, *J* = 1.3 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.01 – 6.96 (m, 1H), 4.87 (d, *J* = 8.5 Hz, 1H), 4.61 (d, *J* = 8.5 Hz, 1H), 4.39 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.77 (d, *J* = 1.3 Hz, 1H), 1.80

– 1.65 (m, 2H), 1.63 – 1.52 (buried, 1H), 1.41 (dt, *J* = 13.4, 3.3 Hz, 1H), 1.23 (s, 3H), 0.99 (s, 3H), 0.63 (s, 10H), -0.14 (s, 3H), -0.66 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.62, 194.20, 162.61, 132.17, 129.38, 129.29, 115.88, 73.66, 72.22, 60.07, 55.46, 39.27, 33.92, 31.28, 28.78, 25.57, 22.18, 17.75, -4.18, -5.68. IR (film) ν_{max} 782.59, 836.32, 845.25, 880.70, 1088.83, 1204.49, 1259.9, 144886, 1470.86, 1683.02, 1717.13, 2341.79, 2359.64, 2852.34, 2891.65, 2924.53 cm $^{-1}$.



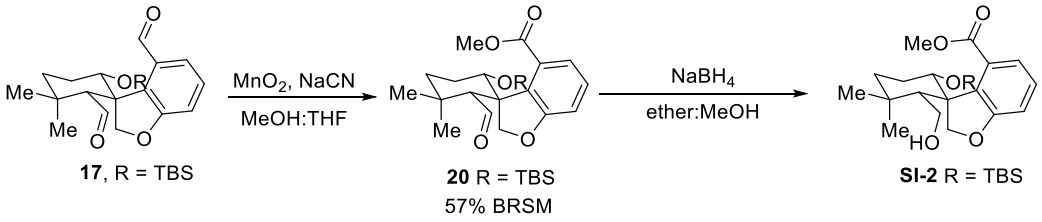
17, R = TBS **18** **19**

Compound 18 and 19 In a nitrogen filled box, a solution of $Ru(PPh_3)_3(CO)H_2$ (1.75 mg) and xantphos (1.1 mg) in toluene (750 µL) was prepared. The vial was sealed and the reaction was refluxed at 110 ^{o}C for 1 h. To a separate 2 mL vial in a N_2 box was added **17** (3.0 mg, 7.5 µmol) and a solution of crotonitrile (1.5 equiv., µmol 11.3) in MeOH was added (0.075M solution). The freshly prepared ruthenium catalyst in toluene was added (0.05 equiv., .38 µmol). The reaction was sealed and heated to 110 ^{o}C. Upon completion the reaction was cooled to room temperature, filtered over celite, and purified via silica prep-TLC. After 1 day, compound **18** was isolated as the major product. After 2 days, compound **19** was isolated as the sole product.

18: Rf = 0.43 (3:7 ethyl acetate:hexanes); LRMS obs. = 387.2 ($M^+ - H_2O$), ref. = 404.2 for $C_{23}H_{36}O_4Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (d, *J* = 4.0 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.87 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.68 (d, *J* = 9.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.96 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.98 (d, *J* = 4.0 Hz, 1H), 1.78 – 1.68 (m, 2H), 1.48 (dd, *J* = 7.7, 4.2 Hz, 2H), 1.26 (s, 2H), 1.12 (s, 3H),

1.09 (s, 3H), 0.66 (s, 9H), -0.12 (s, 3H), -0.60 (s, 3H); IR (film) $\nu_{max.}$ 775.57, 836.16, 1104.86, 1254.99, 1448.47, 146.57, 1470.91, 1719.71, 2855.07, 2927.70, 3417.13 cm $^{-1}$.

19: Rf = 0.14 (3:7 ethyl acetate:hexanes); m.p. = n/a; HRMS (ESI) obs. = 406.2539, ref. = 406.2535 for $C_{23}H_{38}O_4Si$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.62 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 8.9 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.20 (bs, 1H), 4.02 (d, *J* = 8.9 Hz, 1H), 3.86 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.58 (qd, *J* = 11.2, 3.2 Hz, 2H), 2.82 (bs, 1H), 2.03 (t, *J* = 3.4 Hz, 1H), 1.73 – 1.51 (m, 2H), 1.49 – 1.38 (m, 2H), 1.05 (s, 3H), 0.76 (s, 3H), 0.63 (s, 9H), -0.15 (s, 3H), -0.65 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.32, 136.81, 129.23, 129.04, 123.78, 109.46, 75.68, 72.78, 61.56, 60.97, 58.13, 55.33, 39.25, 33.99, 31.61, 28.95, 25.56, 21.34, 17.69, -4.38, -5.90. IR (film) ν_{max} 735.04, 775.50, 835.64, 853.56, 909.83, 992.99, 1016.05, 1040.12, 1105.67, 1254.43, 1448.60, 1471.45, 1586.16, 2855.98, 2893.69, 2934.5, 3312.56 cm $^{-1}$.

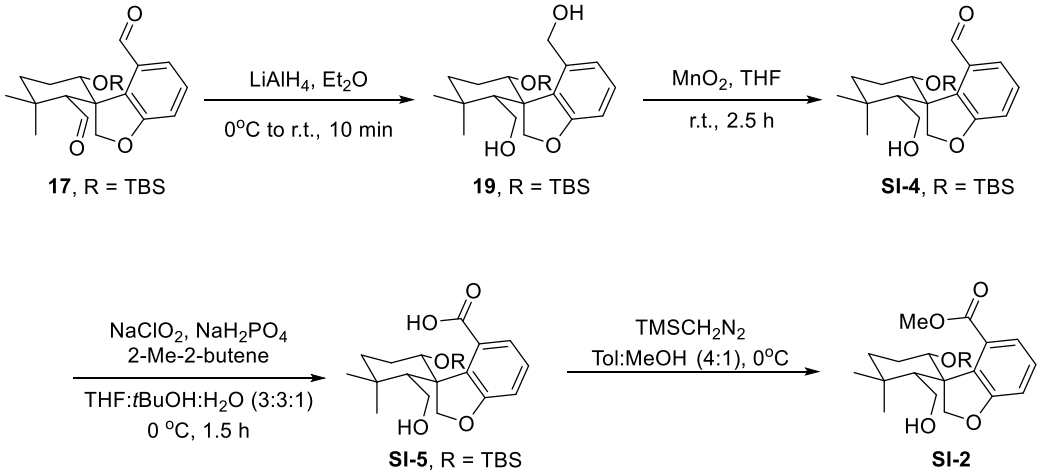


Compound 20 To a flame dried 5 mL round bottom flask was added **17** (10 mg, 0.025 mol), MnO_2 (24 equiv, 153.4mg, 0.60 mmol), and NaCN (2 equiv, 2.45 mg, 0.05 mmol). Dry MeOH (10 equiv, 10.1 µL, 0.25 mmol) in THF (0.05M, 500 µL) was added. The reaction was refluxed (80 ^{o}C) under N2 atmosphere for 36 h. Upon completition the reaction was cooled to room temperature, filtered through a pad of celite, and directly concentrated. The crude product was purified via silica gel column chromatography to give the desired product **20** (49% yield, 57% BRSM). Rf = 0.50 (1:4 Et_2O:hexanes); LRMS obs. = 433.2 (M+H), ref. = 432.2 for $C_{24}H_{36}O_5Si$;

(500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.88 (d, *J* = 8.5 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.58 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.75 (d, *J* = 1.7 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.61 (dd, *J* = 22.4, 12.7 Hz, 2H), 1.39 (d, *J* = 13.1 Hz, 1H), 1.19 (s, 3H), 1.01 (s, 3H), 0.65 (s, 11H), -0.11 (s, 3H), -0.61 (s, 3H).

Compound SI-2: To a solution **20** (2.5 mg, 5.8 µL) in ether:methanol (1.5 mL) at 0°C was added $NaBH_4$ (2 equiv, 0.5 mg). After 5 minutes, the reaction was quenched with water (1 mL), extracted with ethyl acetate (5 x 1 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to give crude desired product **SI-2** as a colorless oil. Rf = 0.27 (1:4 ethyl acetate:hexanes); m.p. = n/a; HRMS (ESI) obs. = 434.2493, ref. = 434.2489 for $C_{24}H_{38}O_5Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.15 (dd, *J* = 10.4, 5.3 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.77 (d, *J* = 8.7 Hz, 1H), 4.57 – 4.49 (m, 1H), 4.25 (d, *J* = 8.6 Hz, 1H), 3.93 – 3.87 (m, 3H), 3.66 – 3.55 (m, 2H), 2.49 (t, *J* = 3.9 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.53 – 1.50 (m, 1H), 1.38 (dd, *J* = 9.8, 3.5 Hz, 1H), 1.07 (s, 3H), 1.03 (dd, *J* = 6.9, 4.9 Hz, 1H), 0.80 (s, 3H), 0.65 (s, 9H), -0.10 (s, 3H), -0.58 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.41, 162.06, 132.15, 129.00, 128.67, 122.39, 113.31, 77.41, 77.16, 76.91, 73.63, 73.47, 62.48, 58.45, 52.33, 51.77, 39.24, 33.67, 31.91, 29.06, 25.64, 21.61, 17.76, -4.29, -5.83. IR (film) ν_{max} 752.87, 775.11, 836.28, 908.01, 1022.27, 1097.71, 1260.94, 1443.63, 1471.65, 1580.91, 1723.16, 2855.31, 2951.38, 3542.03 cm $^{-1}$.

Due to scalability issues and health concerns using super stoichiometric NaCN for direct benzaldehyde oxidation, an alternative route to compound **SI-2** was developed. While requiring more steps, the overall yield is actually higher than the direct oxidation conditions.



Compound 19 To a solution of **17** (778 mg, 1.93 mmol) in ether (0.03 M, 68 mL) at 0 °C was slowly added $LiAlH_4$ (2 equiv., 154 mg, 4.06 mmol). Once the initial violent reaction slowed, the reaction was removed from the ice bath and warmed to room temperature and stirred for 15 minutes. Upon completion, the reaction was again cooled to 0 °C and carefully quenched with saturated aqueous Rochelle's salt (20 mL). The crude product was extracted with ethyl acetate (3 x 50 mL), washed with water (100 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to obtain crude **19** as an amorphous white solid. Consistent with previous spectra and used without further purification.

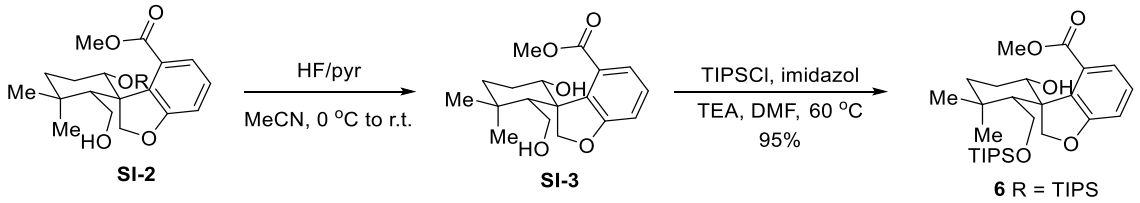
Compound SI-4 To crude **9** (~1.93 mmol) from the previous step in THF (0.02 M, 100 mL) was added MnO_2 (20 equiv., 38.65 mmol, 3.36 g). The reaction was stirred at room temperature for 2.5 hours. Upon completion, the reaction was filtered over a pad of silica with diethyl ether and the filtrate was concentrated under vacuum to obtain **SI-4** as a white solid. **SI-4** was used without further purification in the next step. Rf = 0.33 (3:7 ethyl acetate:hexanes); m.p. = 132.8 – 134.1;

HRMS (ESI) obs. = 404.2386, ref. = 404.2383 for $C_{23}H_{36}O_4Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.94 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.79 (d, *J* = 8.7 Hz, 1H), 4.41 (dd, *J* = 11.1, 4.7 Hz, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.64 (ddd, *J* = 11.4, 5.8, 3.9 Hz, 1H), 3.57 (dt, *J* = 11.7, 4.4 Hz, 1H), 2.65 (t, *J* = 4.1 Hz, 1H), 1.66 (dddd, *J* = 23.5, 16.6, 9.1, 3.1 Hz, 2H), 1.57 – 1.46 (m, 1H), 1.39 (qd, *J* = 6.6, 2.8 Hz, 1H), 1.07 (s, 3H), 0.82 (d, *J* = 7.9 Hz, 3H), 0.65 – 0.56 (m, 9H), -0.09 – -0.17 (m, 3H), -0.59 – -0.67 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.09, 162.27, 134.17, 133.30, 129.10, 127.57, 115.52, 73.50, 73.42, 62.49, 58.47, 51.69, 39.14, 33.64, 31.80, 29.06, 25.57, 21.67, 17.71, -4.12, -5.64. . IR (film) ν_{max} 747.33, 782.67, 806.06, 959.67, 1094.09, 1261.75, 1462.54, 1448.13, 1691.46, 2341.50, 2359.85, 2851.64, 2925.61, 2958.00, 2995.77, 3539.21 cm $^{-}$1.

Compound SI-5 To crude **SI-4** (~1.93 mmol) from the previous step in THF:*t*BuOH:H_2O (3:3:1, 0.01 M, 193 mL) at 0 ^{o}C was added sequentially 2-Me-2-butene (20 equiv., 4.1 mL, 38.6 mmol), $NaClO_2$ (8 equiv., 1.4 g, 15.4 mmol) and $NaH_2PO_4 \cdot H_2O$ (8 equiv, 2.1 g, 15.4 mmol). The reaction was stirred at 0 ^{o}C for 1.5 hours. Upon completion, the mixture was partition with brine (50 mL) and ethyl acetate (50 mL). Organics were extracted with ethyl acetate (3 x 100 mL), washed with water (150 mL), washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced vacuum to give **23** as a white solid. **23** was used in the next step without further purification. Rf = 0.18 (3:2 ethyl acetate:hexanes); m.p. = 173.9 – 175.4; HRMS (ESI) obs. = 420.2331, ref. = 420.2332 for $C_{23}H_{36}O_5Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.80 (d, *J* = 8.7 Hz, 1H), 4.56 – 4.52 (m, 1H), 4.26 (d, *J* = 8.7 Hz, 1H), 3.69 (ddd, *J* = 16.2, 11.6, 4.0 Hz, 2H), 2.70 – 2.62 (m, 1H), 1.71 – 1.63 (m, 1H), 1.61 – 1.47 (m, 2H), 1.43 – 1.33 (m, 1H), 1.07 (s, 3H), 0.78 (s, 3H), 0.65 (s, 9H), -0.10 (s, 3H), -0.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.08, 132.30,

128.79, 123.11, 113.88, 73.47, 73.40, 62.58, 58.51, 50.74, 39.01, 33.60, 31.61, 28.94, 25.63, 21.58, 17.73, -4.33, -5.82. IR (film) ν_{max} 738.57, 777.07, 834.95, 878.62, 907.38, 1100.04, 1257.93, 1442.51, 1470.95, 1581.75, 1698.68, 2855.11, 2927.27, 3376.23 cm $^{-1}$.

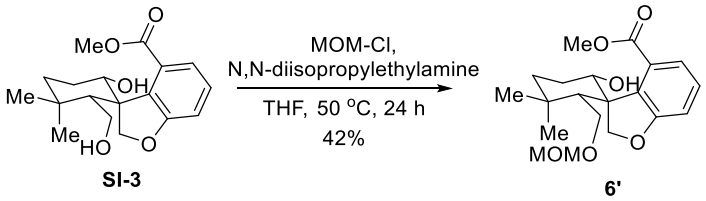
Compound SI-2 To crude **SI-5** (~1.93 mmol) from the previous step in toluene:MeOH (4:1, 0.01 M, 193 mL) at 0 ^{o}C was added $TMSCH_2N_2$ (2 M in hexanes, 1.5 equiv., 1.5 mL, 2.89 mmol). The colorless solution became pale yellow. The reaction was quenched by adding acetic acid until the solution returned colorless. The reaction was directly concentrated to give **SI-2** as a colorless oil. **SI-2** was used without further purification in the next step. Consistent with previous spectra.



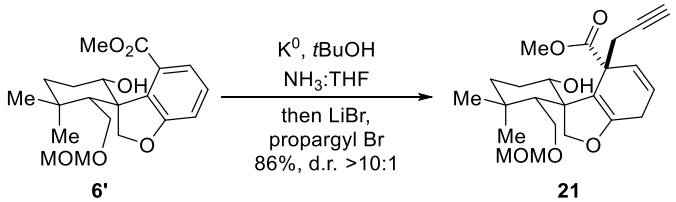
Compound SI-3 To crude **SI-2** (~1.93 mmol) from the previous step in acetonitrile (0.1 M, 19 mL) at 0 ^{o}C was added HF/pyridine (20 equiv, 3.47 mL, 38.6 mmol). The reaction was allowed to warm to room temperature overnight. Upon completion, the reaction was quenched with water (5 mL) and extracted with diethyl ether (5 x 5 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified via silica gel column chromatography to give **SI-3** as an amporphous solid. 76% yield from compound **20** (i.e. 5 steps). Rf = 0.13 (3:7 ethyl acetate:hexanes); m.p. = n/a; HRMS (ESI) obs. = 320.1629, ref. = 320.1624 for $C_{18}H_{24}O_5$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 4.73 (d, *J* = 9.1 Hz, 1H), 4.56 – 4.48 (m, 1H), 4.34 (d, *J* = 9.1

Hz, 1H), 3.91 (s, 3H), 3.63 (qd, *J* = 11.9, 4.0 Hz, 2H), 2.52 (t, *J* = 4.0 Hz, 1H), 1.80 (ddd, *J* = 7.9, 6.1, 3.0 Hz, 1H), 1.62 – 1.48 (burried, 2H), 1.48 – 1.40 (m, 1H), 1.09 (s, 3H), 0.82 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.17, 161.66, 129.34, 129.25, 122.95, 113.67, 73.31, 73.16, 62.22, 58.26, 52.54, 51.48, 39.22, 33.78, 31.95, 27.15, 21.74. IR (film) ν_{max} 733.38, 753.96, 809.35, 910.06, 1011.73, 1263.68, 1442.76 1579.15, 1721.29, 2249.73, 2950.95, 3435.45 cm $^{-1}$.

Compound 6 To a solution of **SI-2** (467 mg, 1.46 mmol,) in DMF (0.5M, 2.9 mL) was sequentially added TIPSCl (1.2 equiv., 375 μL, 1.75 mmol,), imidazol (2 equiv., 199 mg, 2.92 mmol,), and triethyl amine (1.2 equiv., 244 μL, 1.75 mmol,). The vial was sealed and heated to 60 ^{o}C overnight. Upon completion, the reaction was cooled to room temperature and quenched with aqueous saturated NH_4Cl (3 mL). The crude product was extracted with ethyl acetate (3 x 5 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated, and purified via silica gel column chromatographyy to obtain the desired product as a light-yellow oil in 95% yield. Rf = 0.5 (1:1 ethyl acetate:hexanes) . Rf = 0.27 (1:4 ethyl acetate:hexanes); m.p. = n/a; LRMS obs. = 477.3 (M+H) ref. = 476.3 for $C_{27}H_{44}O_5Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.71 (d, *J* = 8.7 Hz, 1H), 4.69 (burried, 1H), 4.53 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 3.68 (ddd, *J* = 13.8, 10.7, 3.8 Hz, 2H), 2.54 (dd, *J* = 4.4, 3.1 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.58 (dd, *J* = 14.3, 5.9 Hz, 2H), 1.44 – 1.39 (m, 1H), 1.29 (d, *J* = 3.4 Hz, 1H), 1.08 (s, 3H), 0.90 (s, 3H), 0.88 – 0.83 (m, 21H). ^{1}H NMR (500 MHz, C_6D_6) δ 7.50 (dt, *J* = 8.9, 4.4 Hz, 1H), 6.93 – 6.87 (m, 2H), 4.88-4.84 (burried, 1H), 4.85 (d, *J* = 8.6 Hz, 1H), 4.56 (d, *J* = 8.6 Hz, 1H), 3.79 (ddd, *J* = 13.6, 10.7, 3.8 Hz, 3H), 3.50 (s, 4H), 2.86 (dd, *J* = 4.6, 3.0 Hz, 1H), 1.64 (ddt, *J* = 29.1, 13.3, 3.2 Hz, 2H), 1.53 – 1.38 (m, 1H), 1.22 (dt, *J* = 6.5, 4.6 Hz, 1H), 1.16 (s, 3H), 1.02 (s, 2H), 0.98 – 0.95 (m, 21H), 0.76 (s, 3H).

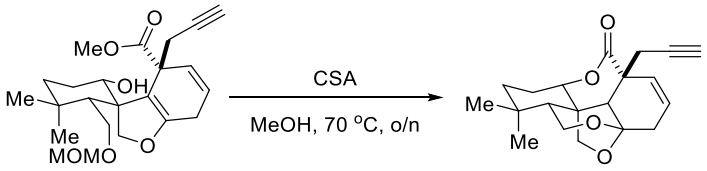


Compound 6'. To a flame dry round bottom flask was added a solution of **SI-3** (30 mg, 0.09 mmol) and KI (2 equiv., 31.2mg, 0.19 mmol) in THF (0.02 M, 5 mL) and placed under nitrogen atmosphere. MOM-Cl (8 equiv., 57 µL, 0.75 mmol) was added followed by N,N-diisopropylethylamine (10 equiv., 163.7 µL, 0.94 mmol). The reaction was heated under reflux at 50 °C for 24 hours. Upon completion the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 5 mL). The combined organics were wased with brine (10 mL), washed with water (10 mL), dried over $MgSO_4$, filtered, concentrated and purified via silica gel column chromatography to give **6'** (42%). Rf = 0.48 (2:3 ethyl acetate:hexanes); LRMS obs. = 392.1 ($M+H_2O$) and 303.1 (M – OMOM) ref. = 364.2 for $C_{20}H_{28}O_6$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.92 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.75 (d, *J* = 9.0 Hz, 1H), 4.71 (dd, *J* = 11.0, 4.7 Hz, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 1H), 4.13 (d, *J* = 6.6 Hz, 1H), 3.88 (s, 3H), 3.40 (ddd, *J* = 40.2, 10.5, 3.8 Hz, 2H), 2.99 (s, 3H), 2.65 (t, *J* = 3.7 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.65 – 1.52 (burried, 2H), 1.47 – 1.41 (m, 1H), 1.03 (s, 3H), 0.82 (s, 3H).



Compound 21 To a 10 mL Schlenk tube charged with **6'** (0.0145 mmol, 5.3 mg) and *t*BuOH (1 equiv., 0.0145 mmol, 1.4 µL) in THF (0.125 mL) at -78 °C was condensed NH_3 via a balloon

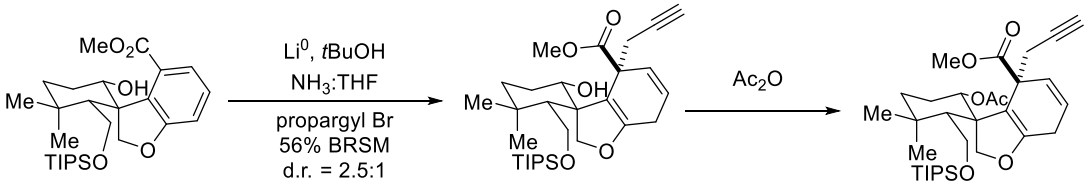
(~2.5 mL). While under a strong positive nitrogen flow, K metal chunks were slowly added to the reaction until a deep blue color is maintain for 15 minutes, at which time TLC shows complete consumption of the starting material. Then LiBr solid (10 equiv, 0.145 mmol, 12.6 mg) was added to the still blue reaction and stirred for 30 minutes at -78 ^{o}C. Then isoprene was slowly added via syringe until blue color disappeared to yellow. Then propargyl bromide solution (9.28 M in toluene, 10 equiv., 15.6 µL) in 0.1 mL THF was added to the reaction via syringe. The reaction was stirred for 10 minutes then carefully quenched with saturated aqueous NH_4Cl (2 mL). The reaction was slowly warmed to room temperature to evaporate NH_3. The crude reaction mixture was extracted with ethyl acetate (3 x 2 mL) , washed with brine (5 mL), dried over MgSO4, filtered, concentrated, and purified via silica column to give **21** with >10:1 d.r. in 86% combined yield. Rf =0.33 (1:9 Et_2O:DCM) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dt, *J* = 9.8, 3.4 Hz, 1H), 5.72 (dt, *J* = 9.7, 2.0 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H), 3.70 (d, *J* = 4.1 Hz, 2H), 3.37 (s, 3H), 3.26 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.98 (dd, *J* = 16.8, 2.6 Hz, 1H), 2.87 – 2.83 (burried, 1H), 2.84 – 2.83 (burried, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.89 (t, *J* = 4.1 Hz, 1H), 1.74 – 1.67 (m, 1H), 1.52 – 1.42 (m, 1H), 1.37 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.33 – 1.22 (burried, 1H), 1.03 (s, 3H), 0.82 (s, 3H).



21 **22**

Compound 22 To a 2 mL vial was added **21** (9 mg, 0.022 mmol) in anhydrous methanol (0.2 M, 100 µL). Camphorsulfonic acid (20 equiv., 103 mg, 0.445 mmol) was added and the vial was sealed with a PTFE cap. The reactio was heated to 70 ^{o}C on an oil bath overnight. Upon

completion the reaction was slowly added to 0 °C pH = 7 phosphate buffer (0.5M, 5 mL). The mixture was extracted ethyl acetate (3 x 5 mL), washed with pH = 7 phosphate buffer (0.5M, 5 mL), washed with brine (5 mL), dried over MgSO4, filtered, concentrated, and purified by silica column to give a white solid which was recrystallized from methanol to give crystals for x-ray. Rf =0.36 (3:7 ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 10.3, 2.8, 1.1 Hz, 1H), 5.84 (dddd, *J* = 10.3, 6.1, 2.2, 0.5 Hz, 1H), 4.57 (dd, *J* = 11.7, 4.3 Hz, 1H), 4.36 (d, *J* = 9.7 Hz, 1H), 3.99 (d, *J* = 8.3 Hz, 2H), 3.74 (dd, *J* = 9.8, 1.3 Hz, 1H), 2.64 (dd, *J* = 16.4, 2.6 Hz, 1H), 2.50 (dd, *J* = 16.5, 2.6 Hz, 1H), 2.39 (s, 1H), 2.34 (d, *J* = 6.1 Hz, 1H), 2.31 (t, *J* = 2.5 Hz, 1H), 2.11 – 2.09 (m, 1H), 1.98 – 1.88 (m, 2H), 1.61 (dd, *J* = 10.7, 3.6 Hz, 1H), 1.56 (s, 1H), 1.52 – 1.41 (m, 2H), 1.03 (s, 3H), 1.00 (s, 3H); IR (film) ν_{max} 651.03, 724.92, 836.08, 1016.56, 1029.93, 1080.64, 1125.23, 1191.10, 1206.37, 1267.64, 1344.10, 1371.20, 1429.04, 1459.64, 1732.16, 2955.10, 3278.10 cm $^{-1}$.



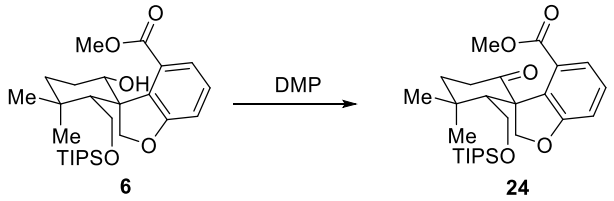
6 **5** **23**
x-ray obtained

Compound 5 To a flame dry 50 mL schlek tube was added birch precurosur **6** (0.052 mmol, 25 mg) in THF (0.1M) and *t*BuOH (0.26 mmol, 24.7 μL). Reaction mixture cooled to -78 °C and NH3 (0.006 M, ~8.5 mL) was condensed via balloons. With strong positive N_2 flow, Li metal was added in portions (0.131 mmol, ~0.9 mg cut into 3 pieces). (Li metal was added in portions; after each Li chunk was added waited until deep blue color disappeared to a light-yellow color, ~20-30 minutes, before the next chunk was added.) After the last portion of Li metal was added, the reaction was warmed to -65 °C until the blue solution turned light-yellow, ~1.5 hours.

Reaction cooled back to -78 oC and propargyl Br (0.52 mmol, 8.5 M in Tol; 1:8.5 in THF, 61.2 μL) was added. The reaction was allowed to slowly warm to -40 ^{o}C via cryo-cool for 1.5 hours and the yellow solution turned colorless. The reaction was then cooled to -78 ^{o}C and solid NH_4Cl was added. The reaction was allowed to warm to room temperature over night to evaporate NH_3. The crude residue was partition in water (20 mL) and ethyl acetate (20 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (20 mL), dried over MgSO4, filtered, concentrate under vacuum, and purified via silica column chromatography to give 10 mg (37%) of the desired product as a light-yellow oil. Rf = 0.48 (1:4 ethyl acetate : hexane) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 9.7, 4.0, 2.9 Hz, 1H), 5.61 (ddd, *J* = 9.8, 2.5, 1.6 Hz, 1H), 4.76 (d, *J* = 8.7 Hz, 1H), 4.43 (d, *J* = 8.7 Hz, 1H), 3.95 (ddd, *J* = 14.1, 10.8, 3.7 Hz, 2H), 3.84 – 3.78 (m, 1H), 3.67 (s, 3H), 3.17 (dd, *J* = 17.4, 2.6 Hz, 1H), 2.89 (dt, *J* = 22.0, 2.7 Hz, 1H), 2.71 (ddd, *J* = 22.0, 4.0, 1.6 Hz, 1H), 2.57 (dd, *J* = 17.5, 2.6 Hz, 1H), 2.50 (d, *J* = 1.6 Hz, 1H), 2.05 (q, *J* = 2.3 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.56 – 1.52 (m, 1H), 1.47 – 1.36 (m, 1H), 1.35 – 1.22 (m, 3H), 1.08 – 1.03 (m, 27H). ^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (ddd, *J* = 9.8, 4.0, 2.8 Hz, 1H), 5.52 (ddd, *J* = 9.8, 2.5, 1.5 Hz, 1H), 4.88 (d, *J* = 8.6 Hz, 1H), 4.75 (d, *J* = 8.6 Hz, 1H), 4.14 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.02 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.99 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.33 (s, 3H), 3.18 (dd, *J* = 17.3, 2.6 Hz, 1H), 2.82 (dt, *J* = 21.9, 2.7 Hz, 1H), 2.70 (ddd, *J* = 21.9, 4.0, 1.5 Hz, 1H), 2.53 (d, *J* = 1.5 Hz, 1H), 2.50 (dd, *J* = 17.3, 2.6 Hz, 1H), 1.82 (ddd, *J* = 13.2, 7.8, 3.5 Hz, 1H), 1.54 (t, *J* = 2.6 Hz, 1H), 1.53 – 1.42 (m, 1H), 1.28 – 1.25 (m, 1H), 1.22 – 1.19 (m, 1H), 1.19 – 1.14 (m, 21H), 1.13 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H).

Compound 23 To a solution of **5** (0.041 mmol, 21.4 mg) in DCM (0.1M, 0.410 mL) was sequentially added Ac_2O (10 equiv., 0.41 mmol, 38.8 μL), triethyl amine (5 equiv., 0.205 mmol, 28.5 μL) and 4-dimethylaminopyridine (1 equiv., 0.041 mmol, 5 mg). The reaction was heated to

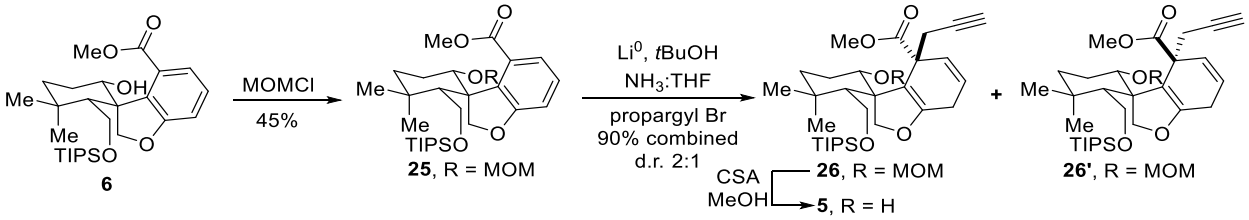
45 °C for 1 day. The reaction was quenched with aqueous NH_4Cl, extracted 3x with ethyl acetate, washed 1x with brine, dried over MgSO4, concentrated and purified via silica column to give the desired product as a white solid (21 mg, 92%). Recrystallization from methanol gave white crystals for x-ray. Rf = 0.62 (1:4 ethyl acetate : hexane) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (d, *J* = 8.9 Hz, 1H), 5.83 (d, *J* = 9.4 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.75 (d, *J* = 8.8 Hz, 1H), 4.42 (d, *J* = 8.7 Hz, 1H), 3.96 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.87 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.68 (s, 3H), 2.84 (d, *J* = 21.7 Hz, 1H), 2.68 (dd, *J* = 16.9, 2.5 Hz, 2H), 2.68 – 2.64 (m, 1H), 2.55 (dd, *J* = 16.8, 2.3 Hz, 1H), 2.44 (s, 1H), 2.06 (s, 3H), 1.96 (d, *J* = 9.1 Hz, 1H), 1.85 (s, 1H), 1.69 – 1.53 (burried, 1H), 1.36 – 1.30 (burried, 1H), 1.05 (t, *J* = 5.4 Hz, 27H).



6 **24**

Compound 24 To a 2 mL vial was added **6** (23.8 mg, 0.05 mmol) in DCM (0.1 M, 500 µL). $NaHCO_3$ (3 equiv., 12.6 mg, 0.15 mmol) and Dess-Martin periodinane (3 equiv., 63.6 mg, 0.15 mmol) was added. The vial was sealed with a PTFE cap and gently heated to 35 °C for 2 hours. Upon completion the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica gel column chromatography to give **25** (62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.26 (dd, *J* = 8.8, 0.5 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.47 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.80 (dt, *J* = 17.9, 5.0 Hz, 1H), 2.46 (ddd, *J* = 17.9, 11.2, 5.8 Hz, 1H), 2.37 (dd, *J* = 6.5, 3.0 Hz,

1H), 2.14 (ddd, *J* = 13.5, 11.3, 4.9 Hz, 1H), 1.56 (dt, *J* = 13.5, 5.5 Hz, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 0.86 (dd, *J* = 14.9, 5.9 Hz, 21H).



Compound 25 To a 2 mL vial charged with **6** (47.6 mg, 0.1 mmol) in DMF (0.1 M, 0.1 mL) at 0 ^{o}C was sequentially added KI (10 equiv., 83 mg, 1 mmol), triethylamine (5 equiv., 35 µL, 0.5 mmol) and MOMCl (10 equiv., 38 µL, 1 mmol). The reaction was allowed to slowly warm to room temperature over 2 hours. Upon completion, the reaction was quenched with saturated aqeuous NH_4Cl (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica gel column chromatography to give **25** (45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.71 (d, *J* = 8.7 Hz, 1H), 4.69 (dd, *J* = 10.5, 5.5 Hz, 1H), 4.46 (d, *J* = 8.7 Hz, 1H), 4.39 (d, *J* = 6.8 Hz, 1H), 4.14 (d, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 3.71 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.61 (dd, *J* = 10.7, 2.8 Hz, 1H), 2.82 (s, 3H), 2.60 (dd, *J* = 4.6, 2.8 Hz, 1H), 1.86 (td, *J* = 8.4, 4.9 Hz, 1H), 1.58 – 1.53 (buried, 2H), 1.44 – 1.38 (m, 1H), 1.08 (s, 3H), 0.89 (s, 3H), 0.88 – 0.82 (m, 21H).

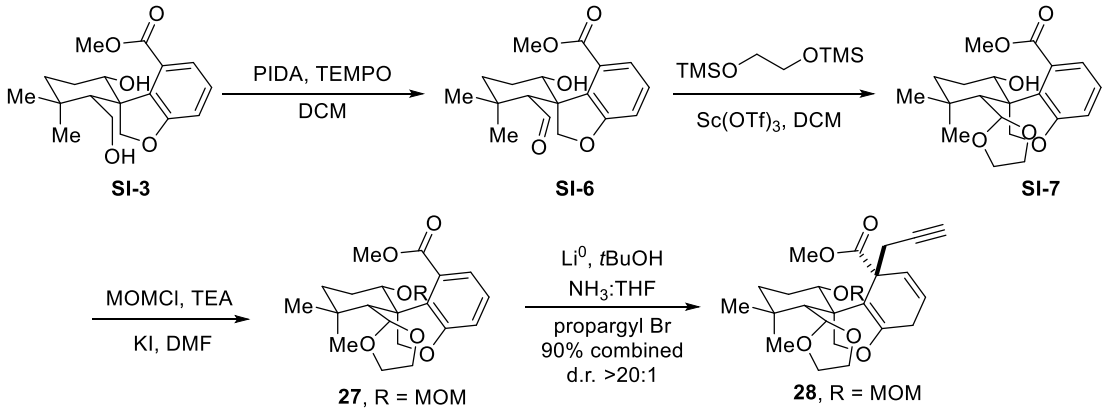
Compound 26 and **26'**. Standard Birch reduction / propargylation conditions as above.

26 ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dt, *J* = 9.9, 2.0 Hz, 1H), 5.89 (dt, *J* = 9.9, 3.4 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 4.38 (d, *J* = 8.9 Hz, 1H), 3.99 (d, *J* = 8.9 Hz, 1H), 3.92 – 3.89 (m, 2H), 3.73 (s, 3H), 3.36 – 3.30 (m, 2H), 3.29 (s, 3H), 2.78 (ddd, *J* = 5.2, 3.4, 2.1 Hz, 2H), 2.47 (dd, *J* = 16.0, 2.6 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.98

(dd, *J* = 4.9, 2.9 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.51 – 1.44 (m, 1H), 1.32 (dt, *J* = 13.7, 3.5 Hz, 2H), 1.25 (s, 5H), 1.06 (s, 25H), 0.87 (d, *J* = 3.2 Hz, 3H).

26' ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dt, *J* = 9.8, 1.9 Hz, 1H), 5.89 (ddd, *J* = 9.8, 3.8, 2.9 Hz, 1H), 4.77 (s, 2H), 4.61 (d, *J* = 8.5 Hz, 1H), 4.41 (t, *J* = 9.1 Hz, 1H), 3.89 (qd, *J* = 10.8, 4.2 Hz, 2H), 3.74 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.69 (s, 3H), 3.35 (s, 3H), 2.95 (dd, *J* = 16.3, 2.6 Hz, 1H), 2.83 (dt, *J* = 21.9, 2.6 Hz, 1H), 2.70 (ddd, *J* = 21.9, 3.9, 1.5 Hz, 1H), 2.46 (dd, *J* = 16.3, 2.6 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.54 (s, 9H), 1.46 – 1.40 (m, 1H), 1.34 – 1.28 (m, 2H), 1.17 (dd, *J* = 4.9, 3.3 Hz, 1H), 1.05 (s, 27H).

Compound 5 To a solution of **26** (2 mg, 3.6 µmol) in THF:MeOH (1:1, 0.036 M, 0.1 mL) was added camphorsulfonic acid (10 equiv., 8.4 mg, 0.036 mmol) and stirred at 35 °C until full conversion of the starting material by TLC. Upon completion the reaction was quenched with saturated aqeuous $NaHCO_3$ (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to give **5**. The spectral data is consistent as previously reported.



Compound SI-7 To a flame dry schlenk tube was added **S1-3** (16 mg, 0.05 mmol) in DCM (0.1 M, 0.5 mL) and cooled to 0 °C. Then (diacetoxyiodo)benzene (1.2 equiv., 19.3 mg, 0.06 mmol)

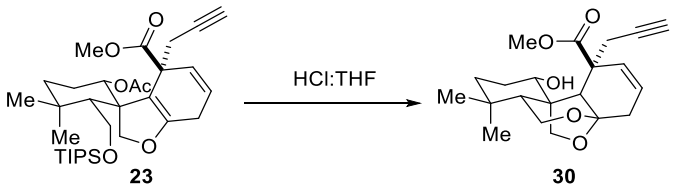
and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.5 equiv., 3.9 mg, 0.025 mmol) was added. The reaction was sealed with a rubber septum and stirred under N_2 and allowed to slowly warm to room temperature. Upon full conversion of the starting material by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with 10% aqueous $Na_2S_2O_3$ (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to obtain crude **SI-6** which was used in the next step without further purification.

Crude **SI-6** from the previous step was dissolved in DCM (0.1 M) and cooled to 0 ^oC. 1,2-bis(trimethylsilyloxy)ethane (10 equiv) and $Sc(OTf)_3$ (0.1 equiv.) was added and the reaction was allowed to slowly warm to room temperature over 3 hours. Upon completion the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to obtain crude **SI-7** which was used in the next step without further purification. Rf = 0.36 (3:7 diethyl ether:hexane) ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.82 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.90 (d, *J* = 1.0 Hz, 1H), 4.82 (d, *J* = 7.8 Hz, 1H), 4.71 (d, *J* = 7.8 Hz, 2H), 4.68 (dd, *J* = 14.2, 8.5 Hz, 2H), 3.88 (s, 3H), 3.64 (s, 1H), 3.52 – 3.46 (m, 2H), 3.42 (tdd, *J* = 7.4, 6.0, 4.1 Hz, 1H), 3.18 – 3.12 (m, 1H), 3.12 – 3.04 (m, 2H), 3.03 (d, *J* = 0.7 Hz, 1H), 1.71 – 1.49 (buried, 3H), 1.39 – 1.32 (m, 1H), 1.03 (s, 3H), 0.92 (s, 3H).

Compound 27 Procedure same as previously reported ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.86 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.94 (d, *J* = 8.1 Hz, 1H), 4.92 (d, *J* = 1.0 Hz, 1H), 4.69 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.69 (d, *J* = 8.1 Hz, 1H), 4.35 (d, *J* = 6.8 Hz, 1H), 4.13 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.53 – 3.47 (m, 1H), 3.41 (ddd, *J* = 13.0,

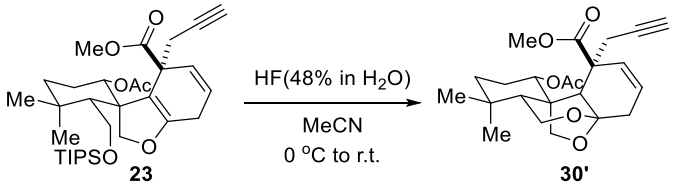
8.7, 5.2 Hz, 1H), 3.15 – 3.12 (m, 1H), 3.11 (buried, 1H), 3.09 (ddd, *J* = 6.9, 5.4, 2.1 Hz, 1H), 2.84 (s, 3H), 1.89 – 1.81 (m, 1H), 1.69 – 1.60 (m, 2H), 1.46 – 1.38 (m, 1H), 1.05 (s, 3H), 0.95 (s, 3H).

Compound 28 Standard Birch reduction / propargylation conditions. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 – 5.90 (m, 1H), 5.84 (ddd, *J* = 10.0, 2.4, 1.9 Hz, 1H), 5.24 (s, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 9.1 Hz, 1H), 4.45 (d, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 9.0 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.91 (ddd, *J* = 13.1, 7.5, 4.2 Hz, 1H), 3.79 (ddd, *J* = 13.7, 11.2, 5.0 Hz, 2H), 3.75 (s, 3H), 3.28 (s, 3H), 3.11 (dd, *J* = 11.2, 5.4 Hz, 1H), 2.99 (dd, *J* = 16.8, 2.4 Hz, 1H), 2.84 (dt, *J* = 22.0, 2.7 Hz, 1H), 2.75 – 2.67 (m, 1H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.78 (s, 1H), 1.57 (s, 1H), 1.21 – 1.16 (m, 2H), 1.06 (s, 3H), 1.01 (s, 3H).

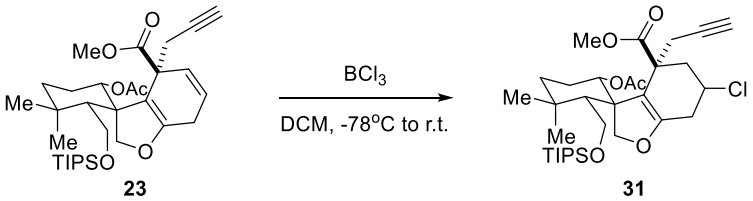


Compound 30 To a solution of **23** (0.002 mmol, 1 mg) in THF (0.02 M, 0.1 mL) at 0 °C was added HCl (12M, 0.05 mL). The reaction was stirred for 10 minutes at 0 °C before being removed from the ice bath and warming to room temperature. Upon consumption of the starting material by TLC, ~15 min., the reaction was carefully added into a cooled solution of pH = 7 phosphate buffer (0.05M). The mixture was then extracted with ethyl acetate (5 x 0.5 mL), washed with saturated aqueous $NaHCO_3$ (2 mL), washed with brine (2 mL), dried over $MgSO_4$, filtered, concentrated, and purified via silica column. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 9.7, 3.0 Hz, 1H), 5.90 (ddd, *J* = 9.7, 6.4, 2.2 Hz, 1H), 4.16 (d, *J* = 8.7 Hz, 1H), 4.07 (dd, *J* = 8.7, 1.2 Hz, 1H), 3.88 (d, *J* = 3.0 Hz, 1H), 3.86 (s, 1H), 3.85 (s, 3H), 3.58 (dd, *J* = 16.6, 2.5 Hz, 1H), 3.50 (dd, *J* = 8.3, 3.4 Hz, 1H), 3.06 (d, *J* = 5.4 Hz, 1H), 2.66 (ddd, *J* = 18.8, 3.4, 2.2 Hz, 1H),

2.58 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.51 (dd, *J* = 18.8, 6.3 Hz, 1H), 2.26 (s, 1H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.68 (dt, *J* = 11.3, 4.1 Hz, 1H), 1.48 – 1.44 (m, 1H), 1.39 (dt, *J* = 13.4, 3.3 Hz, 1H), 1.35 – 1.29 (m, 1H), 0.93 (s, 3H), 0.90 (s, 3H).

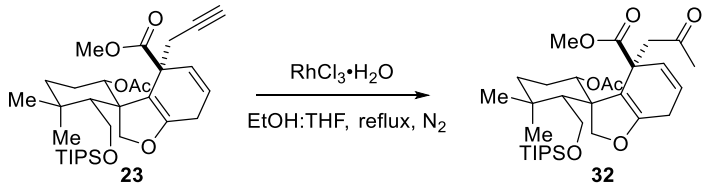


Compound 30' To a PTFE container with **23** (3.5 mg, 7 µg) in water (10 µL) at 0 °C was added HF_{aq} in acetonitrile (0.3M, 50 µL). The reaction was stirred for two days before an additonal portion of HF (48% in H_2O, 4 equiv., 1 µL) was added. Upon consumption of the starting material by TLC, the reactio was partition between water (1 mL) and diethyl ether (1 mL). Organics were extracted with ether (5 x 1 mL), washed with saturated aqueous $NaHCO_3$ (3 ml), washed with brine (3 mL), dried over $MgSO_4$, and purified via prep-TLC to obtain acetal. ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 2H), 4.60 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.27 (d, *J* = 8.7 Hz, 1H), 4.00 (d, *J* = 8.7 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 2H), 3.26 (dd, *J* = 16.3, 2.2 Hz, 1H), 2.73 (dd, *J* = 16.3, 2.4 Hz, 1H), 2.53 (s, 1H), 2.35 (t, *J* = 7.5 Hz, 1H), 2.14 (s, 3H), 2.03 – 1.95 (m, 1H), 1.69 (t, *J* = 8.6 Hz, 1H), 1.63 (dd, *J* = 15.8, 8.1 Hz, 1H), 1.41 (dt, *J* = 24.5, 11.1 Hz, 2H), 0.95 (s, 3H), 0.94 (s, 3H).



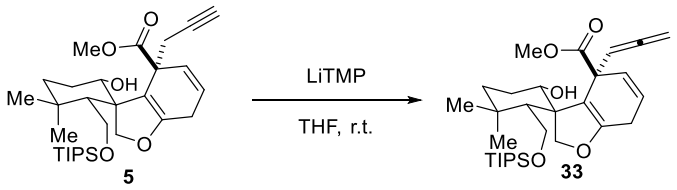
Compound 31 To a solution of **23** (5 mg, 8.9 µmol) in DCM (0.05 M, 180 µL) at -78 °C under nitrogen was added BCl_3 (1M in hexanes, 2.5 equiv., 10.7 µL, 10.7 µmol). The reaction was

allowed to slowly warm to room temperature overnight. Upon completion, the reaction was quenched with water (0.5 mL) and extracted with ethyl acetate (5 x 0.5 mL). The combined organics were washed with brine (2 mL), dried over $MgSO_4$, filtered, concentrated and purified via silica gel column chromatography to give alkyl chloride. LCMS obs. = 595.3 (M+H) ref. = 594.3 for $C_{32}H_{51}ClO_6Si$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 8.9 Hz, 1H), 4.88 (tdd, *J* = 8.1, 6.1, 3.1 Hz, 1H), 4.81 (dd, *J* = 11.3, 4.9 Hz, 1H), 4.43 (d, *J* = 9.0 Hz, 1H), 3.91 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.69 (s, 3H), 3.67 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.17 (dd, *J* = 15.8, 2.5 Hz, 1H), 2.83 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.71 (dd, *J* = 16.1, 5.4 Hz, 1H), 2.37 (dd, *J* = 11.5, 1.5 Hz, 1H), 2.37 (dd, *J* = 18.1, 2.6 Hz, 2H), 2.02 (s, 3H), 1.87 – 1.79 (m, 1H), 1.74 (dd, *J* = 13.4, 11.9 Hz, 1H), 1.35 – 1.30 (m, 2H), 1.08 (s, 3H), 1.07 – 1.02 (m, 21H); IR (film) ν_{max} 680.44, 728.89, 807.69, 838.64, 882.99, 999.23, 1046.56, 1070.11, 1102.23, 1242.82, 1367.43, 1463.16, 1720.00, 1734.93, 2065.81, 2853.10, 2923.91 cm $^{-1}$.

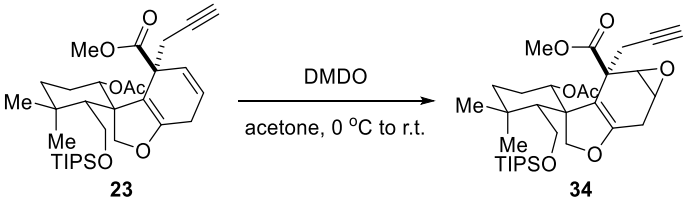


Compound 32 To a 5 mL "all-in-one" fused reflux aparatus was added a solution of **23** (3 mg, 5 μmmol) in ethanol:THF (1:1, 0.01 M, 300 μL) and added $RhCl_3 \cdot H_2O$ (0.40 equiv., 2 μmmol, 0.5 mg). The reaction was placed under N_2 and heated to 70 ^{o}C overnight. Upon completion the reaction was cooled to roomtemperature and filtered over a pad of celite. The crude product was purified via prep-TLC. LCMS obs. = 577.3 (M+H) ref. = 576.3 for $C_{32}H_{52}O_7Si$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 9.9, 2.0 Hz, 1H), 5.72 (ddd, *J* = 10.0, 3.9, 3.1 Hz, 1H), 5.00 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.85 (d, *J* = 8.7 Hz, 1H), 4.39 (d, *J* = 8.7 Hz, 1H), 3.90 (qd, *J* = 11.1, 4.6 Hz, 2H), 3.66 (s, 3H), 3.42 (d, *J* = 17.8 Hz, 1H), 2.72 – 2.67 (m, 2H), 2.29 (d, *J* = 17.8 Hz, 1H), 2.07

(s, 3H), 2.01 (s, 3H), 1.98 – 1.91 (m, 1H), 1.35 – 1.29 (m, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.04 (s, 21H).

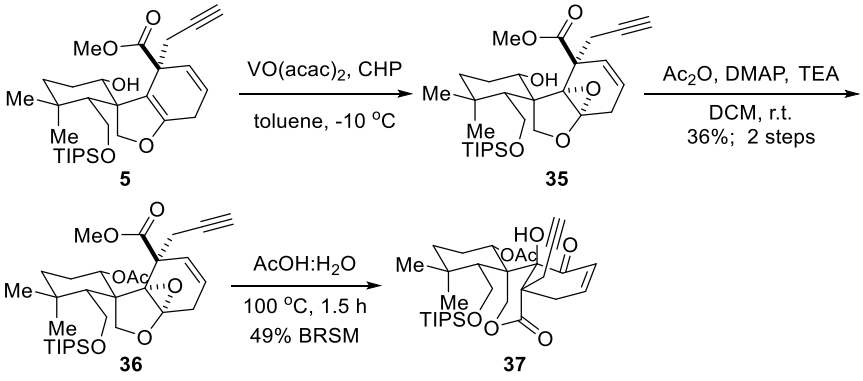


Compound 33 To a solution of **5** (8 mg, 0.016 mmol) in toluene (75 µL) at 0 °C was added freshly prepared LiTMP in ether (0.5M in ether, 5 equiv., 200 µL). The reaction was gradually warmed to room temperature then heated to 100 °C. Upon consumption of the starting material by TLC, the reaction was cooled to room temperature and quenched with water (0.5 mL). Organics were extracted with ether (5 x 0.5 mL), washed with brine (2 mL), dried over $MgSO_4$, filtered, concentrated and purified via silica gel column chromatography. LCMS obs. = 517.3 (M+H) ref. = 516.3 for $C_{30}H_{48}O_5Si$; ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (t, *J* = 6.8 Hz, 1H), 5.86 (dt, *J* = 9.7, 3.4 Hz, 1H), 5.86 (dd, *J* = 8.3, 4.6 Hz, 1H), 5.59 (dd, *J* = 6.9, 5.0 Hz, 1H), 4.87 (dd, *J* = 11.4, 6.8 Hz, 1H), 4.81 (dd, *J* = 11.2, 6.5 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.35 (d, *J* = 8.6 Hz, 1H), 3.94 (qd, *J* = 10.8, 3.6 Hz, 2H), 3.89 – 3.84 (m, 1H), 2.84 – 2.77 (m, 1H), 2.73 (ddd, *J* = 22.1, 3.8, 1.9 Hz, 1H), 1.93 (d, *J* = 2.1 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.47 – 1.40 (m, 1H), 1.32 (t, *J* = 3.9 Hz, 1H), 1.20 (t, *J* = 3.6 Hz, 1H), 1.06 (s, 27H).



Compound 34 In a 2 mL vial to a solution of **23** (5 mg, 9 µmol) in acetone (50 µ) at 0 °C was added DMDO (0.045 M in acetone, 1.2 equiv., 240 µL, 10.8 9 µmol). (DMDO was prepared as

reported by Taber, D. F. and coworkers.[2]) The reaction was sealed with a PTFE cap and allowed to slowly warm to room temperature overnight. Upon completion, the reaction was directly concentrated under vacuum and purified via silica gel column chromatography. LCMS obs. = 575.3 (M+H) ref. = 574.3 for $C_{32}H_{50}O_7Si$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 9.0 Hz, 1H), 4.72 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 3.99 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, *J* = 11.5, 2.1 Hz, 2H), 3.46 (dd, *J* = 5.1, 3.0 Hz, 1H), 3.15 (dd, *J* = 15.4, 2.5 Hz, 1H), 2.74 (dd, *J* = 15.4, 2.5 Hz, 1H), 2.57 (dt, *J* = 18.4, 10.3 Hz, 2H), 2.05 – 2.03 (burried, 1H), 1.77 – 1.69 (m, 1H), 1.64 – 1.58 (m, 1H), 1.31 (dd, *J* = 8.2, 3.5 Hz, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 1.05 (s, 21H).



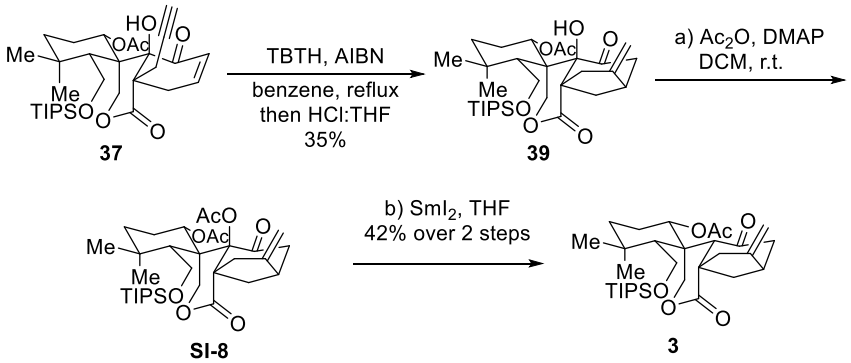
Compound 35: To a flame dry 10 mL schlenk tube was added **5** (0.039 mmol, 20 mg) in toluene (0.1 M, 390 µL). $VO(acac)_2$ (0.25 equiv., 0.01 mmol, 2.7 mg; recrystallized from acetone) was added and the suspension was stirred at room temperature under N_2 in the dark for 1 hour until $VO(acac)_2$ dissolved. The mixture was cooled to 0 °C and cumene hydroperoxide (6.0 equiv., 34.3 µL, 0.234 mmol) was added via syringe. The reaction was stirred at 0 °C under nitrogen in the dark for 24 hours; the reaction changed from deep brown color to yellow. Upon completion, the extraction was quenched with 10% $Na_2S_2O_3$ (1 mL), extracted with ether (5 x 1 mL), washed with 10% $Na_2S_2O_3$ (3 mL), washed with brine (3 mL), dried over Na_2SO_4, filtered and

concentrated under vacuum to give a 2:1 mixture of desired product and rearomatized birch precursor. Due to the instability of the epoxide product, the crude mixture was used without further purification. (Trace epoxide can be isolated via prep-TLC for analysis, but with significant loss of product.) Rf = 0.37 (1:4 ether : hexane) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 10.5, 2.3 Hz, 1H), 5.64 (ddd, *J* = 10.5, 4.2, 3.0 Hz, 1H), 4.40 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 3.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 1H), 3.60 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.30 (dd, *J* = 16.1, 2.6 Hz, 1H), 2.79 (ddd, *J* = 19.2, 4.2, 2.2 Hz, 1H), 2.68 (dt, *J* = 19.2, 2.8 Hz, 1H), 2.60 (dd, *J* = 16.1, 2.6 Hz, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.70 (dq, *J* = 7.8, 3.5 Hz, 1H), 1.53 (ddd, *J* = 10.2, 3.4, 1.3 Hz, 1H), 1.11 – 1.07 (m, 21H), 1.00 (s, 3H).

Compound 36: In a 4 mL vial to a crude material from the previous step (~0.039 mmol) in DCM (0.1 M, 390 μL) was added triethyl amine (5 equiv., 0.195 mmol, 27.2 μL), 4-dimethylaminopyridine (1 equiv., 0.039 mmol, 4.8 mg), and acetic anhydride (4.5 equiv., 0.176 mmol, 16.6 μL). The vial was capped and the reaction was heated to 45 ^{o}C overnight. The extraction was quenched with saturated aqueous NH_4Cl (1 mL) and organics were extracted with ether (5 x 1 mL). The combined organics were washed with brine (2 mL), dried over Na2SO4, filtered and concentrated under vacuum to give a 2:1 mixture of desired product and aromatized product. Due to the instability of the epoxide product, the crude mixture was used without further purification. (Trace epoxide can be isolated via prep-TLC for analysis, but with significant loss of product.) Rf = 0.42 (3:7 ether:hexane) LCMS obs. = 575.3 (M+H) ref. = 574.3 for $C_{32}H_{50}O_7Si$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 10.5, 2.3 Hz, 1H), 5.62 (ddd, *J* = 10.5, 4.2, 3.1 Hz, 1H), 5.43 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.99 (d, *J* = 8.6 Hz, 1H), 3.92 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.87 (d, *J* = 10.7 Hz, 1H), 3.63 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.05 (dd, *J* = 16.0, 2.6 Hz,

1H), 2.75 (ddd, *J* = 19.0, 4.2, 2.2 Hz, 1H), 2.66 (dt, *J* = 19.1, 2.8 Hz, 1H), 2.40 (dd, *J* = 16.0, 2.6 Hz, 1H), 2.09 (s, 3H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.61 – 1.58 (m, 1H), 1.42 (dt, *J* = 8.1, 3.5 Hz, 2H), 1.16 (s, 3H), 1.08 (d, *J* = 3.7 Hz, 21H), 1.03 (s, 3H). IR (film) ν_{max} 682.06, 732.93, 803.97, 883.98, 985.17, 1024.30, 1102.24, 1200.00, 1220.07, 1242.68, 1369.01, 1462.17, 1739.78, 2866.67, 2946.24, 3310.61 cm $^{-1}$.

Compound 37: To a 2 mL vial was added epoxide (2 mg, 3.5 μmol) in DCM. The solvent was removed via vacuum. To the vial charged with epoxide was added AcOH:H_2O:EtOH (3:1:1) (8 mM, 435 μL). The reaction was heated in an oil bath at 90 ^{o}C for 3 hours. The reaction was cooled to r.t. The reaction was partition in ether (1 mL) and water (1 mL). Organics were extracted with ether (5 x 1 mL), washed with water (1 mL), washed with $NaHCO_3$ (1 mL), washed with brine (1 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica column. Rf = 0.28 (2:3 ethyl acetate:hexane) LCMS: 561.3 (M+H) ref. = 560.3 for $C_{31}H_{48}O_7Si$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 10.1, 4.2 Hz, 1H), 6.15 (dt, *J* = 10.1, 1.9 Hz, 1H), 5.76 (s, 1H), 4.96 (dd, *J* = 8.4, 3.9 Hz, 1H), 4.85 (d, *J* = 12.1 Hz, 1H), 4.72 (d, *J* = 12.1 Hz, 1H), 3.91 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.9, 2.9 Hz, 1H), 3.30 (ddd, *J* = 20.2, 4.0, 2.3 Hz, 1H), 2.92 (dd, *J* = 4.4, 1.8 Hz, 1H), 2.87 (dd, *J* = 5.4, 2.7 Hz, 2H), 2.06 – 2.03 (m, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.99 (s, 3H), 1.69 – 1.61 (m, 1H), 1.43 (d, *J* = 5.9 Hz, 2H), 1.16 (dd, *J* = 9.3, 3.6 Hz, 1H), 1.12 (s, 3H), 1.10 (d, *J* = 4.8 Hz, 21H), 0.97 (s, 3H).

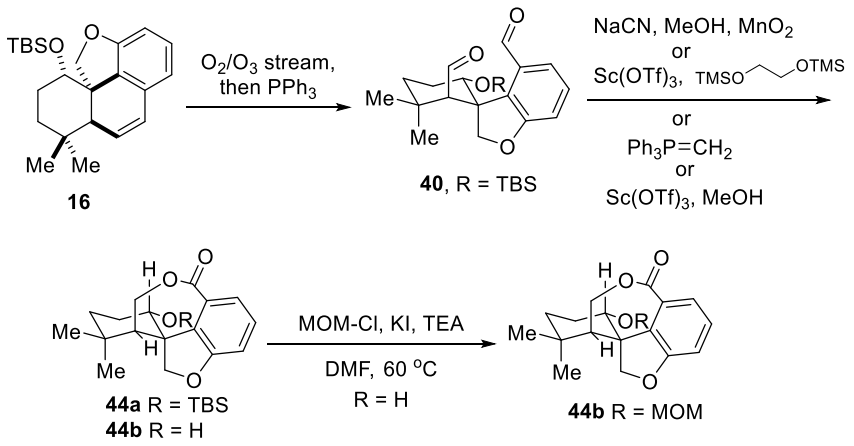


Compound 39: Substrate (2 mg, 0.0036 mmol) was added to a 2 mL vial and transferred into a nitrogen glove box. A stock solution of nBu_3SnH (2.5 equiv., 2.4 μL, 0.0089 mmol) and AIBN (0.5 equiv., 0.3 mg, 0.0018 mmol, 0.5 equiv.) in benzene (360 μL, 0.01M) was prepared and added to the reaction. The vial was sealed with a PTFE cap, removed from the glove box, and heated on a preheated oil bath for 2 hours. Upon completion, the reaction was cooled to room temperature and benzene was directly removed under vacuum. To the crude residue was added a solution of CuCl (0.5 equiv.) and 1N HCl (2 equiv.) in DMF (0.05M). The reaction was stirred at room temperature for 2 hours. Upon completion, the reaction was then diluted with water (1 mL), extracted with ether (5 x 1 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica column to give the desired product. R_f = 0.40 (2:3 ethyl acetate:hexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.30 – 5.24 (m, 1H), 4.90 (d, *J* = 20.7 Hz, 2H), 4.77 (dd, *J* = 28.5, 12.1 Hz, 2H), 3.89 (d, *J* = 17.2 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.39 (d, *J* = 16.0 Hz, 1H), 2.94 (t, *J* = 5.9 Hz, 1H), 2.71 – 2.60 (m, 2H), 2.59 – 2.45 (m, 2H), 2.36 (t, *J* = 7.7 Hz, 1H), 2.02 (s, 3H), 1.88 – 1.79 (m, 1H), 1.65 (burried, *J* = 9.6 Hz, 2H), 1.46 (burried, *J* = 9.3 Hz, 1H), 1.25 (s, 21H), 1.12 (s, 3H), 1.04 (s, 3H).

Compound SI-8: To a 4 ml vial was added substrate (2.5 mg, 0.0044 mmol), DCM (44 μL, 0.1M), DMAP (2.7 mg, 0.022 mmol, 5 equiv), Ac_2O (13.6 μL, 0.133 mmol, 30 equiv.), and TEA (9.2 μL, 0.066 mmol, 15 equiv.). The vial was sealed with a PTFE cap and heated to 55 ºC for 24 hours. The reaction was cooled to room temperature, diluted with ether (1 mL) and quenched with saturated NH_4Cl (1 mL). The organics extracted with ether (5 x 1 mL) washed with brine (5 mL), dried over Na2SO4, filtered, concentrated under vacuum, and passed through a plug of silica with ether. The filtrate was concentrated under vacuum to give acylated product and used in the next step without further purification. Rf = 0.28 (2:3 ethyl acetate:hexane) ^{1}H NMR (500

MHz, C_6D_6) δ 5.90 (s, 1H), 5.41 (t, *J* = 2.9 Hz, 1H), 4.12 (dd, *J* = 12.5, 6.8 Hz, 1H), 3.88 (d, *J* = 12.2 Hz, 1H), 3.77 (d, *J* = 8.2 Hz, 1H), 3.68 (d, *J* = 8.3 Hz, 1H), 3.21 (s, 1H), 2.21 (dt, *J* = 13.8, 2.5 Hz, 1H), 2.16 (ddd, *J* = 14.9, 4.0, 2.6 Hz, 1H), 2.13 – 2.07 (m, 1H), 2.02 (dt, *J* = 5.6, 3.0 Hz, 1H), 1.87 (d, *J* = 10.4 Hz, 1H), 1.82 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.60 (s, 3H), 1.59 (d, *J* = 1.5 Hz, 3H)1.53 (d, *J* = 6.8 Hz, 1H), 1.42 – 1.34 (burried, 3H), 1.34 (s, 3H), 0.74 (s, 3H).

Compound 3: The crude material from the previous step (0.0044 mmol) was added to a schlenk tube and backfilled with nitrogen. The reaction was cooled to -78 ^oC and SmI_2 (0.1 M in THF, 10 equiv.) was added and stirred until the purple solution turned yellow (~5 minutes). The reaction was quenched with 10% Na_2SO_4 (1 mL) and warmed to room temperature. The solution was extracted with ether (1 mL x 5). The combined organics were washed with 10% Na_2SO_4 (1 mL), washed with water (1 mL), washed with brine (1 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica column to give the desired product in 42% yield over 2 steps. Rf = 0.40 (2:3 ethyl acetate:hexane) LCMS obs. = 547.0 (M+H) ref. = 546.3 for $C_{31}H_{50}O_6Si$ ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (dd, *J* = 10.8, 4.4 Hz, 1H), 5.13 (s, 1H), 4.96 (s, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 4.27 (d, *J* = 12.7 Hz, 1H), 3.93 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.88 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.77 (s, 1H), 3.06 (dd, *J* = 6.8, 2.6 Hz, 1H), 2.93 (t, *J* = 4.9 Hz, 1H), 2.89 (d, *J* = 15.5 Hz, 1H), 2.58 (dd, *J* = 10.9, 4.7 Hz, 1H), 2.55 (d, *J* = 5.6 Hz, 1H), 2.52 (dd, *J* = 10.8, 5.1 Hz, 1H), 2.01 (dd, *J* = 5.9, 3.4 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.68 – 1.59 (m, 2H), 1.11 (s, 3H), 1.07 – 1.05 (m, 21H), 1.04 (s, 3H).



Compound 40: To a round bottom flask was added **16** (963.6 mg, 2.6 mmol) in DCM (0.02 M, 130 mL). The solution was cooled to -78 °C and a stream of O_2/O_3 was bubbled through until a light blue color (~10 minutes). The reaction was placed under N_2 atmosphere and PPh_3 (10 equiv, 6.8 g, 26 mmol) in DCM (50 mL) was slowly added via syringe. The reaction was stirred at -78 °C for 30 minutes before removing from the dry ice / acetone bath and warming to room temperature. The reaction was stirred at room temperature for 2 hours. Upon completion, the reaction was directly concentrated under vacuum and purified via silica gel column chromatography. Rf = 0.35 (1:4 diethyl ether:hexanes), m.p. = 111.2 – 117.7 °C; HRMS (ESI) obs. = 402.2225 ref. = 402.2226 for $C_{23}H_{34}O_4Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 9.74 (d, *J* = 6.3 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.35 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.52 (d, *J* = 8.3 Hz, 1H), 2.42 (dd, *J* = 6.1, 1.2 Hz, 1H), 2.12 (td, *J* = 13.9, 3.0 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.68 – 1.53 (m, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.60 (s, 10H), -0.02 (s, 3H), -0.45 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 194.47, 162.52, 135.32, 129.68, 116.40, 77.58, 69.56, 69.16, 57.71, 35.26, 32.83, 30.31, 30.26, 29.62, 25.69, 17.95, -5.01. IR (film) ν_{max} 743.05, 776.70, 836.10, 1085.62, 1109.31, 1256.90, 1447.76, 1471.49, 1697.30, 1716.56, 2856.82, 2928.92, 2955.06

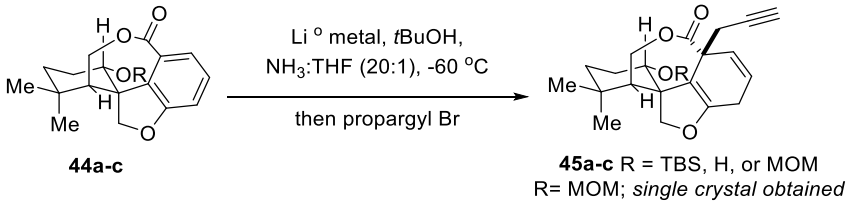
Compound 44a and 44b: To a 4 mL vial charged with **33** (40.3 mg, 0.1 mmol) was added MeOH (0.1 M, 1 mL) and $Sc(OTf)_3$ (0.5 equiv., 0.05 mmol, 24.5 mg). The reaction was heated to 60 ^oC for 20 minutes to obtain **44a**. Heating over night gives silyl deprotected product **44b**. Upon completion, the reaction was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with diethyl ether (3 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica gel column chromatography.

Compound 44a Rf = 0.5 (3:7 ethyl acetate:hexanes) ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 13H), 6.92 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.16 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 13.4 Hz, 1H), 4.35 (dd, *J* = 13.5, 5.5 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 3.74 (dd, *J* = 10.5, 5.7 Hz, 1H), 1.93 (dd, *J* = 5.4, 1.5 Hz, 1H), 1.67 (tdd, *J* = 12.8, 9.6, 3.0 Hz, 4H), 1.13 (s, 3H), 0.99 (s, 3H), 0.66 (s, 9H), -0.15 (s, 3H), -0.69 (s, 3H).

Compound 44b Rf = 0.15 (3:7 ethyl acetate:hexanes) ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.13 (d, *J* = 8.7 Hz, 1H), 4.54 (d, *J* = 13.5 Hz, 1H), 4.37 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.36 (d, *J* = 13.3 Hz, 1H), 3.82 (dd, *J* = 11.0, 5.3 Hz, 1H), 1.96 (dd, *J* = 5.4, 1.5 Hz, 1H), 1.83 – 1.77 (m, 1H), 1.76 – 1.62 (m, 2H), 1.50 – 1.44 (m, 1H), 1.16 (s, 3H), 1.00 (s, 3H).

Compound 44c To a flame dry 2 mL vial was added **xx** (5.8mg, 0.02 mmol) in DMF (0.1 M, 200 µL). KI (10 equiv, 33.2 mg, 0.2 mmol), triethyl amine (5 equiv., 13.9 µL, 0.1 mmol) and MOM-Cl (10 equiv., 15.2 µL, 0.2 mmol) was sequentially added. The vial was sealed with a PTFE cap and heated to 30 ^oC for 6 hours at which time TLC showed ~30% conversion. An additional portion of MOM-Cl (10 equiv., 15.2 µL, 0.2 mmol) was added and the reaction was heated to 65 ^oC for 2 days. The reaction was then cooled to room temperature and quenched with

saturated aqueous NH_4Cl (1 mL). Organics were extracted with diethyl ether (4 x 1 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica gel column chromatography to give 65% of the desired product. Rf = 0.23 (3:7 ethyl acetate:hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.31 – 7.27 (m, 1H), 6.98 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.10 (d, *J* = 8.7 Hz, 1H), 4.54 (d, *J* = 13.5 Hz, 1H), 4.39 (d, *J* = 6.9 Hz, 1H), 4.38 (dd, *J* = 13.5, 5.5 Hz, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 4.03 (d, *J* = 6.9 Hz, 1H), 3.75 (dd, *J* = 11.3, 5.3 Hz, 1H), 2.74 (s, 3H), 1.94 (d, *J* = 4.0 Hz, 1H), 1.91 (dd, *J* = 8.5, 4.7 Hz, 1H), 1.70 (ddd, *J* = 23.2, 16.6, 3.4 Hz, 2H), 1.63 – 1.59 (m, 2H), 1.50 – 1.44 (m, 1H), 1.15 (s, 3H), 1.01 (s, 3H).



44a-c

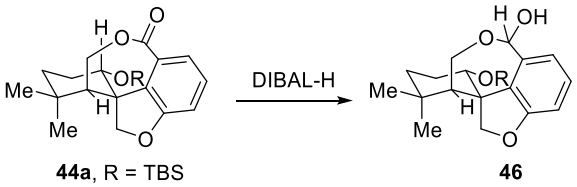
45a-c R = TBS, H, or MOM
R= MOM; *single crystal obtained*

Compounds 45a-c: Representative procedure with substrate **44b** is given. To a 10 mL Schlenk tube charged with **44b** (11.5 mg, 0.04 mmol) and *t*BuOH (5 equiv., 19 μL, 0.2 mmol) in THF (0.1 M, 400 μL) at -78 °C was condensed NH_3 via a balloon (~6.5 mL). While under a strong positive nitrogen flow, Li metal chunks (3-5 equiv.) were added to the reaction until a deep blue color is maintain for 15 minutes, at which time TLC shows complete consumption of the starting material. Then propargyl bromide solution (9.28 M in toluene, 10 equiv., 47 μL) in THF (400 μL) was added to the reaction via syringe. The reaction was stirred for 1.5 hours then carefully quenched with saturated aqueous NH_4Cl (5 mL). The reaction was slowly warmed to room temperature to evaporate NH_3. Organics were extracted with ethyl acetate (3 x 5 mL), washed with brine (15mL), dried over MgSO4, filtered, concentrated, and purified via silica column to give **45b**.

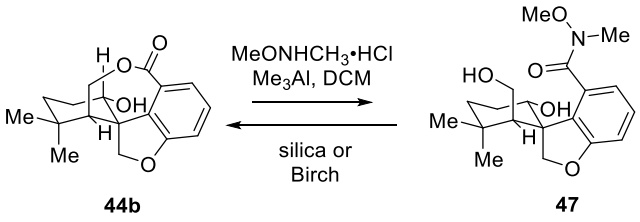
45a ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (ddd, *J* = 9.5, 2.9, 1.0 Hz, 1H), 5.80 (ddd, *J* = 9.5, 4.7, 2.4 Hz, 1H), 4.85 (d, *J* = 8.3 Hz, 1H), 4.80 (dd, *J* = 14.5, 8.4 Hz, 1H), 4.47 (dd, *J* = 14.6, 2.3 Hz, 1H), 4.03 (d, *J* = 8.3 Hz, 1H), 3.75 – 3.69 (m, 1H), 3.55 – 3.51 (m, 1H), 2.96 (dd, *J* = 17.7, 2.7 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.71 (ddd, *J* = 21.8, 4.7, 1.0 Hz, 1H), 2.56 (dd, *J* = 17.7, 2.7 Hz, 1H), 2.17 (dd, *J* = 3.5, 1.9 Hz, 1H), 1.96 (dt, *J* = 8.3, 2.3 Hz, 1H), 1.72 – 1.65 (m, 2H), 1.65 – 1.58 (m, 2H), 0.96 (s, 3H), 0.96 (s, 3H), 0.79 (s, 9H), -0.05 (s, 3H), -0.19 (s, 3H).

45b ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (ddd, *J* = 9.8, 5.4, 1.9 Hz, 1H), 6.10 (dd, *J* = 9.8, 2.9 Hz, 1H), 4.85 (d, *J* = 8.8 Hz, 1H), 4.72 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.64 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.17 (dd, *J* = 18.0, 2.8 Hz, 1H), 2.96 (dd, *J* = 18.0, 5.4 Hz, 1H), 2.70 (dt, *J* = 18.0, 2.4 Hz, 1H), 2.62 (ddd, *J* = 18.3, 4.7, 2.1 Hz, 1H), 2.16 (t, *J* = 2.7 Hz, 1H), 1.84 – 1.72 (m, 2H), 1.65 (buried, 1H), 1.31 (ddd, *J* = 10.1, 4.7, 2.1 Hz, 2H), 1.04 (d, *J* = 5.6 Hz, 3H), 0.93 (s, 3H).

45c ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (ddd, *J* = 9.4, 3.0, 0.8 Hz, 1H), 5.86 (ddd, *J* = 9.4, 4.8, 2.3 Hz, 1H), 4.84 (d, *J* = 8.7 Hz, 1H), 4.82 (dd, *J* = 14.3, 7.6 Hz, 2H), 4.51 (dd, *J* = 14.4, 1.3 Hz, 1H), 4.31 (dd, *J* = 32.8, 6.6 Hz, 2H), 4.05 (d, *J* = 8.7 Hz, 1H), 3.49 (dd, *J* = 11.2, 5.5 Hz, 1H), 3.23 (s, 3H), 2.97 (dd, *J* = 17.7, 2.7 Hz, 1H), 2.88 (ddd, *J* = 21.8, 2.9, 2.4 Hz, 1H), 2.16 (t, *J* = 2.7 Hz, 1H), 1.89 (d, *J* = 7.6 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.72 (ddd, *J* = 24.7, 13.6, 3.6 Hz, 1H), 1.37 – 1.30 (m, 1H), 1.01 (s, 3H), 0.97 (s, 3H).

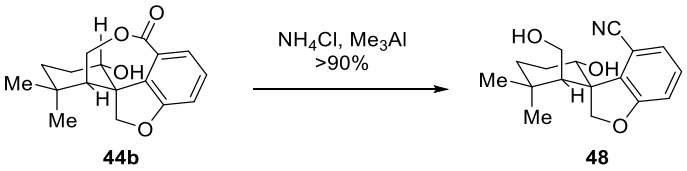


Compound 46: To a flame dry 10 mL schlenk tube was added **44a** (10.1 mg, 0.025 mmol) in toluene (0.05 M, 0.5 mL). The solution was cooled to -78 ^{o}C and DIBAL-H (1 M in hexanes, 1 equiv., 25 µL, 0.025 mmol) was added via syringe. The reaction was allowed to slowly warm to room temperature over night. Upon completion the reaction was carefully quenched with saturated aqueous Rochelle's salt (1 mL). Organics were extracted with diethyl ether (5 x 1 ml), washed with brine, dried over Na_2SO_4, filtered, concentrated under vacuum and purified via prep-TLC. Rf = 0.39 (1:4 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.69 – 6.66 (m, 1H), 6.22 (s, 1H), 5.04 (d, *J* = 8.2 Hz, 1H), 4.22 (dd, *J* = 10.1, 6.2 Hz, 1H), 4.19 (d, *J* = 8.2 Hz, 1H), 4.14 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.93 (d, *J* = 13.7 Hz, 1H), 2.84 (s, 1H), 1.84 (d, *J* = 5.3 Hz, 1H), 1.70 – 1.61 (m, 3H), 1.37 – 1.30 (m, 1H), 1.04 (s, 3H), 0.95 (s, 3H), 0.69 (s, 9H), -0.16 (s, 3H), -0.66 (s, 3H).



Compound 47 to a flame dry Schlenk tube was added N,O-dimethylhydroxylamine (10 equiv, 34.1 mg, 0.35 mmol) and cooled to 0 ^{o}C. Under nitrogen atmosphere, trimethyl aluminum (2 M in hexanes, 10 equiv, 175 µL, 0.35 mmol) was added. Once methane evolution slowed, the reaction was removed from the ice bath and warmed to room temperature. Then **44b** (0.035 mmol, 10.1 mg) in DCM (0.1 M, 350 µL) was added via syringe. The reaction was stirred at

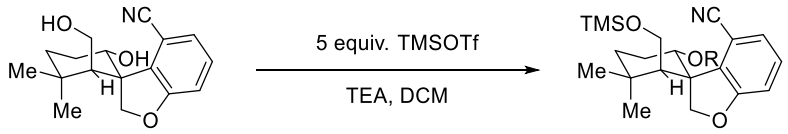
room temperature for 3 hours. Upon completion the reaction was carefully quenched with saturated aqueous $NaHCO_3$ (1 mL) and organics were extracted with ethyl acetate (5 x 1 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Crude ^1H NMR shows a 1:1 ratio of starting material and desired product. Attempts at further purification by silica gel column chromatography resulted in re-lactonization of the desired amide back to the starting material. The peaks corresponding to the desired product are reported and the crude ^1H NMR is provided along with an overlay of the starting material for further clarification. Rf = 0.3 (1:1 ethyl acetate:hexane); LCMS obs. = 350.2 (M+H) ref. = 349.2 for $C_{19}H_{27}NO_5$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 4.73 (dd, *J* = 25.5, 8.3 Hz, 2H), 3.65 (s, 3H), 3.64 – 3.60 (buried, 2H), 3.36 (s, 3H), 1.92 – 1.85 (m, 1H), 1.83 – 1.77 (m, 1H), 1.76 – 1.62 (buried, 2H), 1.16 (s, 3H), 1.00 (s, 3H).



44b **48**

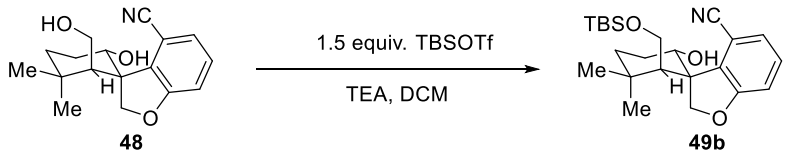
Compound 48: To a flame dry flask was added NH_4Cl (10 equiv, 26.7mg, 0.5 mmol) and placed under nitrogen. Reaction vessel cooled to 0 ^oC and trimethyl aluminum (2 M in hexanes, 10 equiv, 250 µL, 0.5 mmol) was added. Once methane evolution stopped, the reaction was warmed to room temperature and **xx** (14.4mg, 0.05 mmol) in toluene:DCM (1:1, 0.05 M, 1 mL) was added via syringe. The reaction was heated to 120 ^oC under a reflux condenser for two days. Upon completion, the reaction was cooled to room temperature and carefully quenched with saturated aqueous $NaHCO_3$ (1 mL). Organics were extracted with ether (5 x 1 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The title compound

was characterized and used in the next step without further purification; it partially decomposes on silica gel column chromatography. Rf = 0.09 (1:1 ethyl acetate:hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 2H), 6.93 (dd, *J* = 8.0, 0.6 Hz, 1H), 5.11 (d, *J* = 8.6 Hz, 1H), 4.38 (d, *J* = 13.6 Hz, 1H), 4.32 (d, *J* = 8.6 Hz, 1H), 4.19 (dd, *J* = 13.6, 5.5 Hz, 1H), 4.19 (dd, *J* = 13.6, 5.5 Hz, 1H), 3.91 (dd, *J* = 10.9, 5.4 Hz, 1H), 1.85 (d, *J* = 5.4 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.73 – 1.60 (m, 2H), 1.48 – 1.42 (m, 1H), 1.12 (s, 3H), 0.98 (s, 3H).

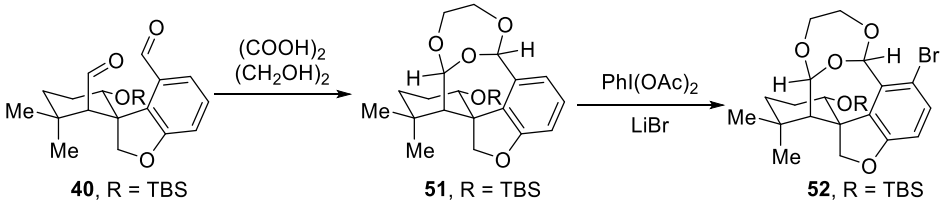


48 **49a**, R = TMS

Compound 49a To a flame dry flask was added xx (14.4 mg, 0.05 mmol) in DCM:TEA (1:1, 0.1 M, 0.5 mL). The solution was cooled to 0 °C and TMSOTf (5 equiv., 45.2 µL, 0.25 mmol) was added via syringe. The reaction was stirred for 30 minutes. Upon completion, the reaction was quenched with saturated $NaHCO_3$ (1 mL). Organics were extracted with diethyl ether (5 x 1 mL), washed with brine, dried over Na_2SO_4, filtered, concentrated and purified via silica gel column chromatography. ^{1}H NMR (500 MHz, C_6D_6) δ 6.94 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.70 (t, *J* = 7.9 Hz, 1H), 5.34 (dd, *J* = 10.9, 5.6 Hz, 1H), 4.96 (d, *J* = 8.2 Hz, 1H), 4.66 (d, *J* = 8.2 Hz, 1H), 3.82 (dd, *J* = 10.7, 3.7 Hz, 1H), 3.57 (dd, *J* = 11.0, 3.9 Hz, 1H), 1.93 (dq, *J* = 13.2, 5.3 Hz, 1H), 1.80 (d, *J* = 7.8 Hz, 1H), 1.75 (dd, *J* = 17.2, 7.4 Hz, 1H), 1.48 – 1.39 (m, 2H), 1.12 (s, 3H), 1.04 (s, 3H), 0.40 (s, 9H), 0.27 (s, 9H).



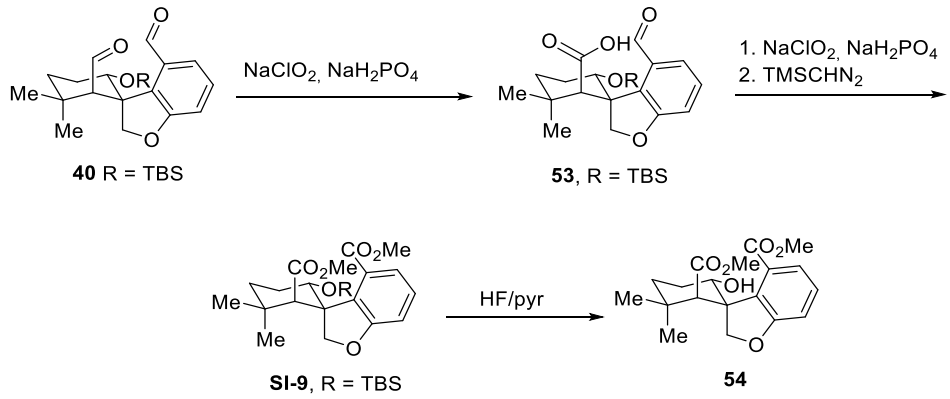
Compound 49b To a flame dry flask was added xx (14.4 mg, 0.05 mmol) in DCM:TEA (1:1, 0.1 M, 0.5 mL). The solution was cooled to 0 °C and TBSOTf (1.5 equiv., 17 µL, 0.075 mmol) was added via syringe. The reaction was stirred for 30 minutes. Upon completion, the reaction was quenched with saturated $NaHCO_3$ (1 mL). Organics were extracted with diethyl ether (5 x 1 mL), washed with brine, dried over Na_2SO_4, filtered, concentrated and purified via silica gel column chromatography. Rf = 0.36 (3:7 ethyl acetate:hexanes) LCMS obs. = 402.2 (M+H) ref. = 401.2 for $C_{23}H_{35}NO_3Si$ ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H), 6.99 (dd, *J* = 7.7, 1.1 Hz, 1H), 4.93 (dd, *J* = 10.4, 6.3 Hz, 1H), 4.70 (q, *J* = 8.4 Hz, 1H), 3.78 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.68 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.02 (dt, *J* = 12.4, 4.1 Hz, 1H), 1.88 (t, *J* = 5.5 Hz, 1H), 1.73 – 1.42 (burried, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 0.74 (d, *J* = 1.4 Hz, 99H), -0.12 (s, 3H), -0.20 (s, 3H).



Compound 51: To a 2 mL vial was added **40** (4.0 mg, 0.01 mmol) and ethylene glycol (10 equiv., 5.6 µL, 0.1 mmol). Oxalic acid (1 equiv., 0.9 mg, 0.01 mmol) in acetonitrile (0.1 M, 100 µL) was added followed by Na_2SO_4. The reaction was stirred at room temperature overnight. Upon completion the reaction was quenched with water (0.5 mL) and extracted with diethyl ether (5 x 0.5 mL). The combined organics were directly filtered over Na_2SO_4 and concentrated to give the title compound. The product was characterized and used in the next step without

further purification. Rf = 0.50 (1:4 diethyl ether:hexanes) LCMS obs. = 447.2 (M+H) ref. = 446.2 for $C_{25}H_{38}O_5Si$; ^{1}H NMR (400 MHz, C_6D_6) δ 7.01 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.65 (s, 1H), 5.24 (s, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.52 (dd, *J* = 11.1, 5.5 Hz, 1H), 4.05 (d, *J* = 8.3 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.51 (tt, *J* = 5.9, 3.0 Hz, 1H), 3.42 (ddd, *J* = 12.4, 2.2, 1.2 Hz, 1H), 3.37 (dt, *J* = 12.3, 1.3 Hz, 1H), 2.18 (d, *J* = 2.2 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.60 – 1.47 (m, 1H), 1.05 (ddd, *J* = 14.5, 7.4, 4.2 Hz, 1H), 0.89 (s, 9H), 0.86 (s, 3H), 0.60 (s, 3H), -0.14 (s, 3H), -0.52 (s, 3H).

Compound 52: To **51** (4.5 mg, 0.01 mmol) in THF (75 µL) was added a solution of LiBr (0.5 equiv., 0.43 mg, 0.005 mmol) in water (25 µL). Then (diacetoxyiodo)benzene (1.25 equiv., 4 mg, 0.0125 mmol) was added. The reaction was stirred at room temperature for 18 hours. Upon completion, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and saturated aqueous $NaHCO_3$ (0.5 mL). Organics were extracted with diethyl ether (6 x 1 mL), washed with water (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. Characterization was obtained without further purification. Rf = 0.55 (1:4 diethyl ether:hexanes) LCMS obs. = 524.9 and 526.9 (M+H) ref. = 524.1 and 526.1 for $C_{25}H_{38}O_5Si$ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 1H), 6.53 (dd, *J* = 8.5, 0.6 Hz, 1H), 6.20 (s, 1H), 5.25 (s, 1H), 4.94 (t, *J* = 9.7 Hz, 1H), 4.28 (dd, *J* = 10.3, 5.6 Hz, 1H), 4.19 (d, *J* = 8.2 Hz, 1H), 3.98 – 3.93 (m, 1H), 3.77 – 3.73 (m, 1H), 3.72 (dd, *J* = 12.3, 1.8 Hz, 1H), 3.63 (dd, *J* = 7.3, 5.7 Hz, 1H), 2.21 (d, *J* = 2.0 Hz, 1H), 1.72 – 1.53 (buried, 4H), 1.09 (s, 3H), 0.98 (s, 3H), 0.69 (s, 9H), -0.13 (s, 3H), -0.62 (s, 3H).



40 R = TBS

53, R = TBS

SI-9, R = TBS

54

Compound 53 To a solution of **40** (4.0 mg, 0.01 mmol) in THF:*t*BuOH (1:1, 430 µL) was added 2-Me-2-butene (5 equiv., 5.3 µL, 0.05 mmol). The reaction was cooled to 0 °C and a solution of $NaClO_2$ (1.1 equiv., 1.0 mg, 0.011 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.1 equiv., 1.5 mg, 0.011 mmol) in water (71µL) was slowly added. The reaction was loosely capped and allowed to slowly warm to room temperature overnight. Upon completion the reaction was partition between water (1 mL) and ethyl acetate (1 mL). Organics were extracted with ethyl acetate (5 x 1 mL), washed with water (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. Crude ^1H NMR indicated a 3:2 mixture of starting material and the undesired aliphatic aldehyde oxidized product. The peaks of the title compound are given and the crude ^1H NMR is reported as well as an overlay with the starting material for clarity. Rf = 0.32 (1:4 diethyl ether:hexane w/ 1% AcOH) LCMS obs. = 419.2 (M+H) ref. = 418.2 for $C_{23}H_{34}O_5Si$ ^1H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.41 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.23 (s, 1H), 7.00 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.17 (dd, *J* = 11.7, 4.4 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.68 (d, *J* = 8.4 Hz, 1H), 2.81 (s, 1H), 1.73 – 1.54 (buried, 4H), 1.43 (s, 3H), 1.05 (s, 3H), 0.63 (s, 9H), 0.08 (s, 3H), -0.10 (s, 3H).

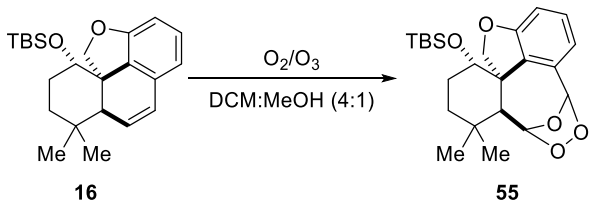
Compound SI-9 To a solution of **40** (4.0 mg, 0.01 mmol) in THF:*t*BuOH (1:1, 180 µL) was added 2-Me-2-butene (50 equiv., 53 µL, 0.5 mmol). The reaction was cooled to 0 °C and a solution of $NaClO_2$ (10 equiv., 9 mg, 0.1 mmol) and $NaH_2PO_4 \cdot H_2O$ (10 equiv., 14 mg, 0.1

mmol) in water (29µL) was slowly added. The reaction was loosely capped. The reaction was removed from the ice bath allowed to warm to room temperature and stirred for 4 hours. Upon completion the reaction was partition between water (1 mL) and ethyl acetate (1 mL). Organics were extracted with ethyl acetate (5 x 1 mL), washed with water (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated, and used without further purification.

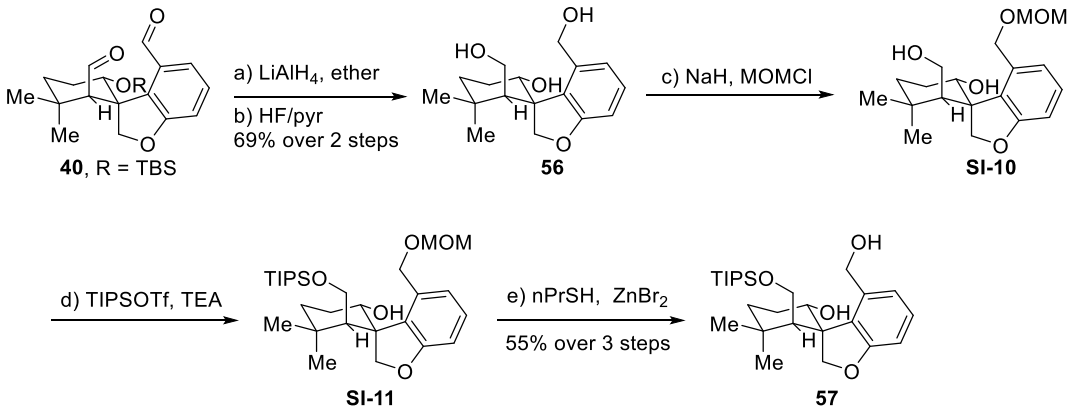
The crude material from the previous step was dissolved in toluene:methanol (4:1, 0.01 M, 1 mL) and cooled to 0 ^{0}C. $TMSCH_2N_2$ (2 M in hexanes, 4 equiv., 20 µL) was added and the reaction was allowed to slowly warm to room temperature. Upon consumption of the starting material by TLC, the now light-yellow solution was quenched with acetic acid until a clear solution. The reaction was directly concentrated under vacuum and purified via silica gel column chromatography to give the diester **SI-9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.38 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 1H), 4.51 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.44 (s, 3H), 2.67 (d, *J* = 1.6 Hz, 1H), 2.11 (td, *J* = 13.9, 3.4 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.47 – 1.40 (m, 1H), 1.30 – 1.22 (m, 2H), 1.20 (s, 3H), 0.87 (s, 3H), 0.69 (s, 9H), 0.13 (s, 3H), -0.22 (s, 3H).

Compound 54: To a solution of **SI-9** (4.6 mg, 0.01 mmol) in acetonitrile (0.1 M, 100 µL) at 0 ^{o}C was added HF/pyridine (10 equiv., 9 µL, 0.1 mmol). The reaction was stirred for 15 minutes before removing from the ice bath and stirring at room temperature overnight. Upon completion the reaction was quenched with water (0.5 mL) and extracted with diethyl ether (5 x 0.5 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated and used without further purification. Rf = 0.16 (1:4 diethyl ether:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.10 (dd, *J* = 12.6, 3.9 Hz, 1H), 4.74 (d,

J = 8.7 Hz, 1H), 4.69 (d, *J* = 8.7 Hz, 1H), 3.96 (s, 3H), 3.35 (s, 3H), 2.64 (d, *J* = 1.5 Hz, 1H), 2.01 (td, *J* = 13.7, 3.7 Hz, 1H), 1.93 (dq, *J* = 13.0, 3.7 Hz, 1H), 1.52 (dd, *J* = 13.1, 3.2 Hz, 1H), 1.43 (s, 1H), 1.28 (s, 3H), 0.88 (s, 3H).



Compound 55: To a solution of **16** (7.4 mg, 0.02 mmol) and $NaHCO_3$ (4 equiv., 8 mg, 0.08 mmol) in DCM:MeOH (4:1, 0.05 M, 0.4 mL) at -78 °C was bubbled O_2/O_3 stream until a light blue solution (~5-10 minutes). Nitrogen gas was sparged through the solution until the blue solution became colorless. The reaction was removed from the dry ice/acetone bath and warmed to room temperature. The crude reaction mixture was filtered over a cotton and directly concentrated under vacuum to give the product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.8 Hz, 1H), 6.77 – 6.68 (m, 2H), 6.46 (s, 1H), 5.70 (s, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.35 – 4.28 (m, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 2.08 (d, *J* = 2.0 Hz, 1H), 1.70 (d, *J* = 2.8 Hz, 3H), 1.44 – 1.40 (m, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.72 (s, 9H), -0.19 (s, 3H), -0.73 (s, 3H).



Compound 56: To a solution of dialdehyde **40** (4.0 mmol, 1.6 gram) in ether (200 mL) at 0 ^{o}C was slowly added $LiAlH_4$ (16 mmol). After the initial violent reaction subsided, the solution was removed from the ice water bath and warmed to room temperature. The reaction was monitored by TLC until the consumption of dialdehyde **j** (~20 minutes). The solution was cooled back to 0 ^{o}C and carefully quenched with saturated aqueous Rochelle's (50 mL) salt. The crude reaction mixture was extracted with ethyl acetate (3 x 50 mL), washed with water (100 mL), washed with brine (100 mL), dried over Na2SO4, filtered, and concentrated under vacuum to give crude diol as an amorphous solid which was used without further purification in the next step.

To a solution of crude diol (4.0 mmol) from the previous step in acetonitrile (0.1 M, 40 mL) in a PTFE container at room temperature was HF/pyridine (5 equiv, 20 mmol, 1.8 mL). The reaction was allowed to stir over night at which point exhibits ~50% conversion by TLC. An additional portion of HF/pyridine (5 equiv., 20 mmol, 1.8 mL) was added and the reaction was stirred for 12 hours at room temperature. The reaction was then quenched with water, extracted diethyl ether (5 x 25 mL), washed with saturated $NaHCO_3$ (100 mL), washed with water (100 mL), washed with brine (100 mL), dried over Na2SO4, filtered, concentrated, and purified via flash silica column to give triol **56** as an amorphous solid in 75% yield over 2 steps. Trituration with DCM results in a white solid triol **56**. Rf = 0.2 (1:1 ethyl acetate:hexanes) HRMS (ESI) obs. = 292.1672 ref = 292.1675 for $C_{17}H_{24}O_4$; m.p. = 153.0-156.5 ^{o}C.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.7 Hz, 1H), 6.83 (dd, *J* = 7.7, 1.8 Hz, 2H), 5.38 (d, *J* = 11.5 Hz, 1H), 4.82 (dd, *J* = 11.3, 4.8 Hz, 1H), 4.69 (dd, *J* = 45.7, 8.3 Hz, 2H), 4.58 (d, *J* = 11.4 Hz, 1H), 3.68 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.37 (d, *J* = 9.7 Hz, 1H), 1.96 (t, *J* = 9.9 Hz, 1H), 1.88 (d, *J* = 15.2 Hz, 1H), 1.72 (s, 1H), 1.54 – 1.48 (m, 2H), 1.28 (s, 3H), 1.17 (s, 3H). triol **l** is not very soluble in $CDCl_3$. To obtain a suitable ^{13}C NMR spectrum MeOD was used as solvent; for comparison the ^{1}H NMR in

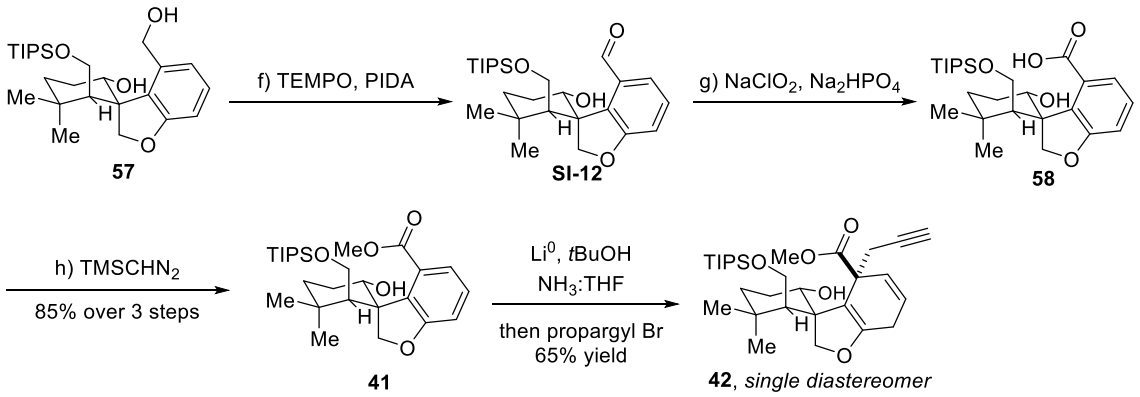
MeOD is also given. ^{1}H NMR (500 MHz, MeOD) δ 7.10 (s, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 4.77 (dd, *J* = 11.9, 4.6 Hz, 1H), 4.73 (d, *J* = 8.3 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 8.3 Hz, 1H), 3.59 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.27 (d, *J* = 3.0 Hz, 1H, buried in H2O peak), 2.02 (td, *J* = 13.0, 4.3 Hz, 1H), 1.85 (dq, *J* = 13.0, 4.3 Hz, 1H), 1.57 (s, 1H), 1.55 – 1.48 (m, 1H), 1.41 (dt, *J* = 13.3, 3.4 Hz, 1H), 1.28 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 162.66, 140.72, 130.34, 129.66, 123.72, 110.94, 76.91, 69.85, 63.81, 62.36, 61.07, 52.38, 37.81, 35.06, 33.48, 31.34, 29.71. IR (film) ν_{mas} 748.56, 775.88, 807.46, 977.57, 997.48, 1021.09, 1041.91, 1062.46, 1103.59, 1161.32, 1242.21, 1341.95, 1368.91, 1397.39, 1444.18, 1580.11, 1745.38, 2888.50, 2932.25, 2984.12, 3259.05.

Compound SI-10: To a solution of triol **56** (3.9 mmol, 1.1 gram) in DMF (39 mL) at 0 ^{o}C was added sodium hydride (60% in oil, 3.0 mmol, 447 mg). MOMCl (purified by passing directly over a basic alumina plug) was added (4.26 mmol, 323.6 μL) by directly submerging the syringe needle into the solution. The solution was stirred at 0 ^{o}C for 30 minutes at which time TLC shows ~80% conversion (the reaction is stopped to prevent decomposition). The reaction is carefully quenched with saturated NH_4Cl, extracted with diethyl ether (5 x 20 mL), washed with water (50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via silica column to give MOM protected product **m** as an amorphous solid in 63% yield. Rf = 0.16 (1:4 ethyl acetate:hexanes); HRMS obs. = 336.1946 ref = 336.1937 for $C_{19}H_{28}O_5$; m.p. = n/a.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, 1H), 6.86 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 4.75 – 4.69 (m, 4H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 3.68 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.40 (s, 3H), 3.39 – 3.37 (m, 1H), 1.98 – 1.86 (m, 2H), 1.71 (d, *J* = 2.6 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.27 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.97, 135.31, 129.30, 129.17, 124.02, 111.09, 95.82,

68.52, 67.99, 62.79, 60.10, 56.03, 36.99, 34.25, 33.09, 30.36, 27.99. IR (film) ν_{mas} = 442.61, 497.67, 546.87, 564.12, 597.40, 651.37, 703.30, 741.64, 777.25, 798.04, 922.63, 1017.15, 1042.13, 1097.29, 1150.13, 1211.45, 1246.02, 1314.05, 1336.33, 1363.72, 1387.38, 1441.17, 1465.37, 1582.08, 1609.66, 2825.78, 2944.86, 3065.48, 3462.56 cm $^{-1}$.

SI-11 (bab-10-138 and bab-10-151): To a solution of **SI-10** (3.0 mmol, 1 gram) in DCM (15 mL) at 0 oC was added triethylamine (15 mL). TIPSOTf (6.0 mmol, 1.6 mL) was added and the reaction was stirred at 0 ^{o}C for 30 minutes. The reaction was halted by inverse quench: the reaction mixture was poured into saturated $NaHCO_3$ at 0 ^{o}C. The aqueous layer was extracted with diethyl ether (3 x 20 mL), washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica column to give **n** as a colorless oil in 92% yield. Rf = 0.47 (1:4 ethyl acetate:hexanes) HRMS (ESI) obs. = 492.3268 ref. = 492.3271 for $C_{28}H_{48}O_5Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.79 (dd, *J* = 7.6, 0.9 Hz, 1H), 4.80 (d, *J* = 10.7 Hz, 1H), 4.69 (dd, *J* = 17.5, 6.7 Hz, 3H), 4.66 (dd, *J* = 26.4, 8.2 Hz, 3H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.34 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.73 (dd, *J* = 9.9, 9.0 Hz, 1H), 3.44 (dd, *J* = 10.1, 2.9 Hz, 1H), 3.40 (s, 3H), 2.01 – 1.95 (m, 1H), 1.92 (dd, *J* = 8.8, 2.7 Hz, 1H), 1.71 – 1.61 (m, 1H), 1.52 (dddd, *J* = 14.6, 10.9, 10.4, 5.9 Hz, 3H), 1.26 (s, 4H), 1.16 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 9H), 0.82 (s, 9H), 0.81 – 0.74 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.02, 134.11, 129.25, 129.14, 124.22, 111.48, 95.94, 77.37, 69.18, 67.89, 62.99, 59.39, 56.16, 53.42, 36.20, 34.02, 33.43, 29.43, 27.39, 18.13, 18.03, 17.85, 12.46, 11.94 IR (film) ν_{max} = 657.49, 680.77, 747.13, 777.22, 803.33, 838.62, 882.57, 920.22, 1013.93, 1040.89, 1062.33, 1100.63, 1151.27, 1211.09, 1248.99, 1294.75, 1317.01, 1365.12, 1382.57, 1443.11, 1463.97, 1582.82, 2865.64, 2891.11, 2942.33, 3504.60 cm $^{-1}$.

Compound 57 (bab-10-143 and bab-10-151): To a solution of **SI-11** (2.14 mmol, 1.06 gram) in DCM (21 mL) was added nPrSH (6.42 mmol, 489 μL). $ZnBr_2$ (2.36 mmol, 531.5 mg) was added and the reaction was stirred at room temperature for 45 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting solids were removed by vacuum filtration. The biphasic filtrate was extracted with diethyl ether (3 x 20 mL), washed with water (30 mL), washed with brine (30 mL), dried over Na_2SO_4, filtered, and purified by silica column to give **o** as a white solid in 76% yield. Rf = 0.18 (1:4 ethyl acetate:hexanes) HRMS (ESI) obs. = 448.3012 ref. = 448.3009 for $C_{26}H_{44}O_4Si$; m.p. = 124.1-125.5 ºC; ^{1}H NMR (400 MHz, CDCl3) δ 7.14 (t, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.77 (dd, *J* = 7.5, 0.8 Hz, 1H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.65 (dd, *J* = 53.3, 8.3 Hz, 2H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.40 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.46 (dd, *J* = 10.0, 2.7 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.91 (dd, *J* = 8.9, 2.5 Hz, 1H), 1.73 – 1.45 (m, 4H), 1.27 (s, 3H), 1.16 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 9H), 0.82 (d, *J* = 5.8 Hz, 9H), 0.76 (ddd, *J* = 11.4, 7.6, 3.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.93, 137.32, 129.48, 128.71, 123.32, 111.46, 76.98, 68.52, 65.46, 62.96, 59.18, 53.24, 36.14, 34.02, 33.39, 29.72, 27.98, 18.11, 18.01, 11.93, 0.14. IR (film) ν_{max} = 657.16, 682.36, 746.15, 774.89, 807.23, 838.65, 882.50, 920.36, 995.23, 1021.65, 1060.65, 1102.47, 1161.82, 1208.50, 1247.31, 1315.05, 1363.54, 1383.42, 1443.16, 1463.26, 1581.75, 2865.79, 2890.73, 2942.43, 3320.31 cm^{-1}.



Compound SI-12: To a solution of **57** (1.63 mmol, 730 mg) in DCM (0.03 M, 54 mL) was added (diacetoxyiodo)benzene (1.1 equiv., 1.79 mmol, 577.5 mg) followed by TEMPO (0.3 equiv., 0.49 mmol, 76.4 mg). The reaction was stirred at room temperature overnight. Upon completion, the reaction was quenched with saturated aqueous Na_2S_2O (30 mL) and extracted with ether (3 x 30 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and purified by silica gel column chromatography to give **SI-12** as a colorless oil in 92% yield. Rf = 0.28 (ethyl acetate:hexanes) HRMS (ESI) obs. = 446.2859 ref. = 446.2852 for $C_{26}H_{42}O_4Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.39 – 7.32 (m, 2H), 7.07 (dd, *J* = 7.4, 1.8 Hz, 1H), 5.08 (dd, *J* = 10.6, 6.6 Hz, 1H), 4.70 (q, *J* = 8.4 Hz, 2H), 3.70 (dd, *J* = 10.6, 8.0 Hz, 1H), 3.39 (dd, *J* = 10.6, 4.2 Hz, 1H), 2.01 (dq, *J* = 13.6, 6.7 Hz, 1H), 1.95 (dd, *J* = 7.9, 4.2 Hz, 1H), 1.59 (buried, 2zH), 1.49 (ddt, *J* = 13.8, 10.8, 6.9 Hz, 1H), 1.21 (s, 3H), 1.15 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 9H), 0.80 (d, *J* = 6.2 Hz, 9H), 0.79 – 0.72 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.55, 162.74, 136.01, 130.40, 129.26, 127.25, 116.62, 78.51, 67.12, 62.57, 59.37, 55.56, 36.09, 34.02, 33.52, 29.85, 28.17, 27.21, 18.08, 17.99, 11.90; IR (film) ν_{max} = 656.12, 683.54, 743.21, 787.54, 839.20, 882.48, 919.87, 996.03, 1014.38, 1058.61, 1099.68, 1161.75, 1177.08, 1205.65, 1251.58, 1322.05, 1365.55, 1407.94, 1445.51, 1463.86, 1576.36, 1601.84, 1699.17, 2741.60, 2865.40, 2942.21, 3454.23.

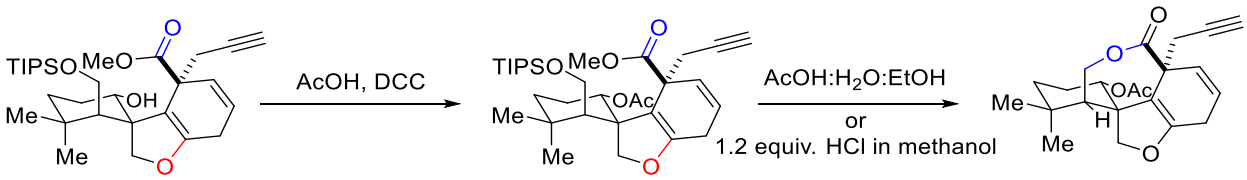
Compound 41: To a solution of **SI-12** (1.58 mmol, 703.7 mg) in THF:*t*BuOH:H_2O (3:3:1, 0.01 M 158 mL) was sequentially added 2-Me-2-butene (20 equiv., 31.6 mmol, 3.35 mL), $NaClO_2$ (8 equiv., 12.64 mmol, 1.14 gram), and $NaH_2PO_4 \cdot H_2O$ (8 equiv., 12.64 mmol, 1.74 gram). The reaction was allowed to stir at room temperature overnight. The mixture was partitioned with brine and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). Organics were washed with water (200 mL), with brine (200 mL), dried over Na_2SO_4, filtered, concentrated, and used without further purification.

The crude material from the previous step was dissolved in Toluene:MeOH (4:1, 158 mL) and cooled to 0 ^oC. $TMSCHN_2$ (2M in hexanes, 2 equiv., 3.16 mmol, 1.58 mL) was slowly added and the colorless solution became light-yellow. The reaction was removed from the ice bath and warmed to room temperature. After stirring for 10 minutes, the reaction was cooled to 0 ^oC and carefully quenched with a few drops of AcOH until the light-yellow solution became colorless. The crude mixture was directly concentrated under vacuum and the resulting oil was purified by silica gel column chromatography to give **41** as a white solid in 80% yield over 2 steps. Rf = 0.46 (1:4 ethyl acetate:hexanes) HRMS (ESI) obs. = 476.2958 ref. = 479.2958 for $C_{27}H_{44}O_5Si$ m.p. = 69.8-71.2 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.03 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.75 (dd, *J* = 24.7, 8.3 Hz, 2H), 4.61 (dd, *J* = 10.7, 6.7 Hz, 1H), 3.97 (s, 3H), 3.66 (t, *J* = 10.0 Hz, 1H), 3.36 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.20 (bs, 1H), 2.15 – 2.02 (m, 1H), 1.95 (dd, *J* = 9.8, 3.3 Hz, 1H), 1.74 – 1.50 (m, 3H), 1.28 (s, 3H), 1.20 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 9H), 0.96 – 0.87 (m, 3H), 0.87 (d, *J* = 5.0 Hz, 9H). ^1H NMR (500 MHz, C_6D_6) δ 7.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 4.88 (d, *J* = 8.3 Hz, 1H), 4.80 (ddd, *J* = 10.8, 6.6, 4.3 Hz, 1H), 4.65 (d, *J* = 8.3 Hz, 1H), 3.79 (t, *J* = 10.0 Hz, 1H), 3.52 (dd, *J* = 10.3, 3.3 Hz, 1H), 3.42 (s, 3H), 3.07 (d, *J* = 4.4 Hz, 1H), 2.07 (dd, *J* = 9.8, 3.3 Hz, 1H), 1.99 (dq, *J* =

14.1, 7.2 Hz, 1H), 1.48 (ddt, *J* = 13.7, 10.8, 6.9 Hz, 1H), 1.39 – 1.27 (m, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.00 (d, *J* = 6.4 Hz, 9H), 0.94 (d, *J* = 5.2 Hz, 9H), 0.92 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.68, 162.28, 131.10, 129.00, 128.81, 122.05, 114.26, 77.57, 66.30, 62.82, 59.88, 53.27, 52.87, 36.29, 34.07, 34.06, 28.17, 26.67, 18.09, 17.95, 11.82. IR (film) ν_{max} = 682.54, 751.11, 808.98, 882.21, 1014.60, 1070.11, 1100.36, 1141.41, 1202.85, 1267.53, 1315.87, 1384.42, 1438.42, 1462.82, 1720.28, 2865.11, 2942.48.

Compound 42: To a flame dry 10 mL Schlenk tube was added **41** (0.05 mmol, 23.8 mg) in THF (0.1 M, 0.5 mL). *t*BuOH (5 equiv., 0.25 mmol, 23.7 μL) was added. The Schlenk tube was sealed with a rubber septum and cooled to -78 °C. NH_3 (~8 mL) was condensed inside via a balloon. Under positive N_2 pressure, small lithium metal chunks (10 equiv., 3.5 mg cut into 4 pieces) were added resulting in a deep blue solution (additional lithium pieces (~0.5) mg were added if necessary to maintain a deep blue solution). The mixture was warmed to -65 °C with a MeOH:H_2O/dry ice bath. The reaction was allowed to stir for 45 minutes. Propargyl bromide (8.5 M in toluene, 0.5 mmol, 58.8 μL) in 500 μL of THF was added via syringe. The deep blue solution turned yellow and the reaction was allowed to slowly warm to -40 °C over the course of 2~3 hours; the solutions becomes progressively darker yellow over time. The rubber septum was removed and the reaction was removed from the MeOH:H_2O/dry ice bath to allow the evaporation of NH_3 gas. The reaction was then partitioned in water (5 mL) and organics were extracted with diethyl ether (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via TEA treated silica gel column chromatography to give **42** as a white solid in 62% yield as a single diastereomer. Rf = 0.21 (1:4 Et_2O:Hex); ^{1}H NMR (500 MHz, C_6D_6) δ 5.62 (dt, *J* = 9.7, 1.9 Hz, 1H), 5.55 (dt, *J* = 9.7, 3.3 Hz, 1H), 5.01 (d, *J* = 8.5 Hz, 1H), 4.50 – 4.44 (m, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 4.02

(dd, *J* = 11.2, 2.9 Hz, 1H), 3.72 (dt, *J* = 14.5, 7.3 Hz, 1H), 3.34 (s, 3H), 3.21 (d, *J* = 2.4 Hz, 2H), 2.75 (dd, *J* = 3.2, 2.0 Hz, 2H), 2.26 (s, 1H), 2.00 – 1.91 (m, 1H), 1.87 – 1.81 (m, 1H), 1.78 – 1.70 (m, 1H), 1.68 (dd, *J* = 3.3, 1.9 Hz, 1H), 1.65 – 1.52 (m, 1H), 1.37 – 1.27 (m, 3H), 1.17 (s, 22H), 1.03 (s, 3H), 0.99 (s, 3H). 2D COSY and NOE experiments are also provided. ^{13}C NMR (126 MHz, C_6D_6) δ 174.07, 158.28, 131.13, 123.76, 81.86, 79.38, 72.03, 68.33, 64.28, 56.82, 53.33, 52.26, 36.26, 34.14, 33.08, 30.50, 30.22, 29.64, 28.45, 27.92, 26.39, 18.64, 18.61, 12.94.



42 **59** **60**

Compound 59: To a solution of 42 (0.027 mmol, 13.9 mg) in DCM (0.1 M, 270 µL) was sequentially added DMAP (4 equiv., 0.108 mmol, 13.2 mg), AcOH (8.6 equiv., 0.23 mmol, 13.3 µL) and N,N′-dicyclohexylcarbodiimide (5 equiv., 0.14 mmol, 27.8 mg). The reaction was allowed to stir at room temperature for 1.5 hours. The resulting white solid was filtered out of solution with a cotton plug. The filtrate was quenched with saturated aqueous $NaHCO_3$, and organics were extracted with diethyl ether (5 x 1 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated, and purified by TEA treated silica gel column chromatography to give **59** as a white solid in 74% yield. Rf = 0.08 (1:4 Et_2O:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 9.8, 3.5 Hz, 1H), 5.74 (dt, *J* = 9.8, 2.0 Hz, 1H), 5.59 (t, *J* = 5.6 Hz, 1H), 4.39 (d, *J* = 8.5 Hz, 1H), 4.22 (d, *J* = 8.5 Hz, 1H), 3.71 (d, *J* = 3.3 Hz, 1H), 3.69 (s, 3H), 3.58 (dd, *J* = 10.3, 9.1 Hz, 1H), 2.82 (ddd, *J* = 22.1, 3.3, 2.3 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.66 (dd, *J* = 16.9, 2.6 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.06 (s, 3H), 1.99 – 1.94 (m, 2H), 1.64 – 1.56 (m, 2H), 1.31 (dt, *J* = 12.5, 6.0 Hz, 1H), 1.13 (s, 3H), 1.05 (d, *J* = 3.9 Hz, 21H), 0.88 (s, 3H).

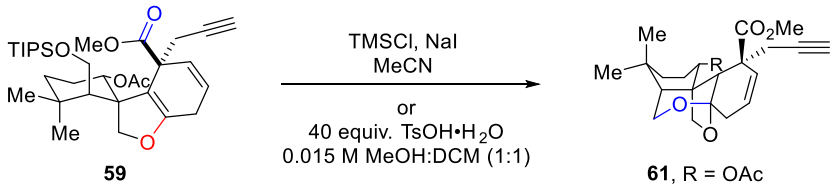
^{1}H NMR (500 MHz, C_6D_6) δ 5.92 (t, *J* = 5.9 Hz, 1H), 5.81 (dt, *J* = 9.8, 2.0 Hz, 1H), 5.57 (dt, *J* = 9.8, 3.4 Hz, 1H), 4.56 (d, *J* = 8.5 Hz, 1H), 4.32 (d, *J* = 8.5 Hz, 1H), 3.93 (dd, *J* = 10.4, 3.1 Hz, 1H), 3.76 (dd, *J* = 10.3, 9.4 Hz, 1H), 3.39 (d, *J* = 3.2 Hz, 3H), 2.82 (qd, *J* = 16.9, 2.6 Hz, 2H), 2.72 (dd, *J* = 3.4, 2.1 Hz, 2H), 2.33 – 2.21 (m, 2H), 2.19 (dd, *J* = 9.3, 3.1 Hz, 1H), 1.74 (t, *J* = 2.6 Hz, 1H), 1.70 (d, *J* = 3.5 Hz, 3H), 1.61 – 1.44 (m, 3H), 1.24 – 1.14 (m, 21H). ^{13}C NMR (101 MHz, C_6D_6) δ 173.46, 169.35, 158.18, 131.16, 123.15, 107.60, 82.58, 80.51, 72.43, 71.87, 63.50, 56.51, 56.27, 52.59, 52.18, 36.06, 34.73, 33.49, 31.13, 26.58, 25.95, 24.23, 20.93, 18.50, 18.29, 18.26, 12.38, 12.15, 1.42.

Compound 60

Procedure A: To a 2 mL vial was added **59** (5.6 mg, 0.01 mmol) and dissolved in AcOH:H_2O:EtOH (3:1:1, 0.01 M, 1 mL). The vial was sealed with a PTFE cap and heated to 100 ^{o}C for overnight. Upon completion, the reaction was cooled to room temperature and quenched with water (1 mL). Organics were extracted with diethyl ether (5 x 1 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum, and purified via TEA treated silica gel column chromatography to give **60**. Rf = 0.54 (3:7 ethyl acetate:hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 9.7, 3.4, 2.4 Hz, 1H), 5.94 – 5.90 (m, 1H), 5.01 (dd, *J* = 10.2, 6.0 Hz, 1H), 4.80 (d, *J* = 8.6 Hz, 1H), 4.52 (dd, *J* = 13.4, 3.0 Hz, 1H), 4.43 (dd, *J* = 13.4, 4.8 Hz, 1H), 4.18 (d, *J* = 8.6 Hz, 1H), 3.08 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.89 (dt, *J* = 4.7, 2.1 Hz, 1H), 2.73 (ddd, *J* = 4.8, 3.3, 1.0 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.05 (s, 3H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.93 – 1.90 (m, 1H), 1.55 – 1.51 (buried, 1H), 1.49 – 1.45 (m, 2H), 1.11 (s, 3H), 1.07 (s, 3H).

Procedure B: to a flame dry 2 mL vial was added **xx** (1 μM, 0.6 mg) in benzene. Benzene solvent was removed by directly attaching the vial to high vacuum with swirling. The remaining material

was dissolved in DCM (0.05 M, 24 µL). A 0.1 M solution of methanolic HCl was prepared from methanol and acetyl chloride. The freshly prepared methanolic HCl was added to the reaction (1 equiv., 12 µL) and stirred at room temperature overnight. Upon completing the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and organics were extracted with diethyl ether (5 x 0.5 mL) The combined organics were directly filtered over Na_2SO_4 and concentrated under vacuum. Crude ^{1}H NMR shows a 1:1.8 ratio of **60** to starting material **59**.

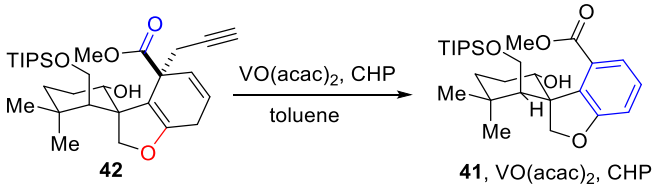


Compound 61

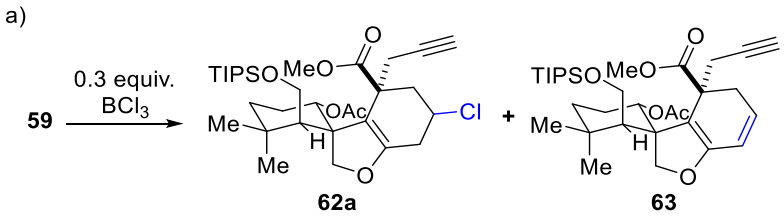
Procedure A: To a flame dry Schlenk tube was added **59** (1 mg, 2 µmol) in MeCN (50 µL) followed by NaI (5 equiv., 0.01 mmol, 1.5 mg) and placed under N_2 atmosphere. The reaction was cooled to 0 ^{o}C before TMSCl (1.2 equiv., 2.4 µmol) in MeCN (50 µL) was added via syringe. The reaction was stirred at 0^{o}C before quenching with 1:1 saturated aqueous $NaHCO_3$: saturated aqueous $Na_2S_2O_3$ (1 mL). The organics were extracted with diethyl ether (5 x 0.5 mL), and directly filtered over a silica:Na_2SO_4 plug. The filtrate was concentrated under vacuum to give **61**.

Procedure B: To a solution of **xx** (1 mg, 3 µmol) in MeOH:DCM (1:1, 200 µL) was added $TsOH{\cdot}H_2O$ (40 equiv., 23 mg, 0.12 mmol). The reaction was heated to 45 ^{o}C overnight. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and organics were extracted with diethyl ether (5 x 0.5 mL). The combined organics were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to give **61**. Rf = 0.47 (3:7 ethyl acetate:hexane) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 10.0, 3.0, 1.5 Hz, 1H), 5.83

(ddd, *J* = 10.0, 5.4, 2.5 Hz, 1H), 5.53 – 5.51 (m, 1H), 4.00 (dd, *J* = 12.6, 6.6 Hz, 1H), 3.87 (d, *J* = 12.8 Hz, 1H), 3.85 (s, 3H), 3.84 (d, *J* = 9.3 Hz, 1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.18 (dd, *J* = 15.5, 2.5 Hz, 1H), 2.68 (dt, *J* = 19.5, 2.8 Hz, 1H), 2.54 (dd, *J* = 15.5, 2.6 Hz, 1H), 2.45 (ddd, *J* = 19.6, 5.4, 1.5 Hz, 1H), 2.04 (s, 3H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.75 – 1.70 (m, 1H), 1.64 (d, *J* = 6.5 Hz, 1H), 1.50 – 1.44 (m, 2H), 1.43 (s, 1H), 1.09 (s, 3H), 0.94 (s, 3H).



Compound 41 Procedure is the same as above. Matches the previous spectral data.

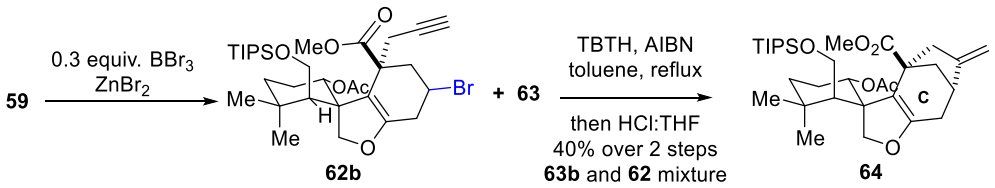


Compound 62a and 63: To a flame dry Schlenk tube was added **59** (3 mg, 5.4 µmol) in DCM (0.01 M, 0.5 mL). The solution was cooled to -78 °C and BCl_3 (1.2 equiv., 0.1 M in DCM, 64 µL, 6.4 µmol) was added via syringe. The reaction was transferred to an ice water batch and stirred for 2 hours. Upon completion the reaction was quenched with water (1 mL). The organics were extracted with diethyl ether (5 x 1 mL) and directly filtered over a pad of Na_2SO_4. The filtrate was concentrated under vacuum and the crude product was purified via TEA treated silical gel column chromatography.

62a: Rf = 0.37 (1:4 diethyl ether:hexane); LRMS obs. = 595.3 (M+H) ref. = 594.3 for $C_{32}H_{51}ClO_6Si$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (t, *J* = 8.2 Hz, 1H), 4.43 (d, *J* = 8.1 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 3.75 (s, 3H), 3.73 – 3.63 (m, 2H), 3.44 – 3.37 (m, 2H), 2.90 – 2.81 (m, 2H), 2.78 (t, *J* = 5.7 Hz, 1H), 2.44 (dd, *J* = 17.1, 10.4 Hz, 2H), 2.35 (t, *J* =

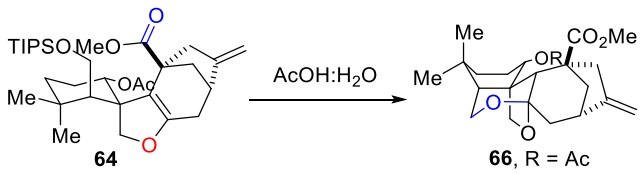
7.5 Hz, 2H), 2.21 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.06 (dd, *J* = 3.2, 1.8 Hz, 2H), 2.04 (s, 3H), 1.73 – 1.50 (buried, 2H), 1.15 (s, 3H), 1.07 (td, *J* = 7.8, 4.1 Hz, 21H), 1.03 (s, 3H).

63: Rf = 0.37 (1:4 diethyl ether:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (ddd, *J* = 9.6, 5.6, 2.5 Hz, 1H), 5.96 (dd, *J* = 9.8, 2.8 Hz, 1H), 5.39 (t, *J* = 8.5 Hz, 1H), 4.44 (d, *J* = 8.2 Hz, 1H), 4.37 (d, *J* = 8.3 Hz, 1H), 3.73 (s, 3H), 3.70 (dd, *J* = 8.6, 4.0 Hz, 2H), 3.42 (dd, *J* = 11.4, 9.7 Hz, 1H), 2.87 (d, *J* = 18.0 Hz, 1H), 2.80 (dd, *J* = 18.4, 5.5 Hz, 1H), 2.70 (d, *J* = 16.6 Hz, 1H), 2.50 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.06 (s, 3H), 1.99 (dd, *J* = 11.6, 3.6 Hz, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.68 – 1.57 (m, 3H), 1.39 (ddd, *J* = 10.7, 8.2, 2.0 Hz, 1H), 1.16 (s, 3H), 1.12 (m, 3H), 1.09 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 9H), 1.01 (d, *J* = 6.9 Hz, 9H).



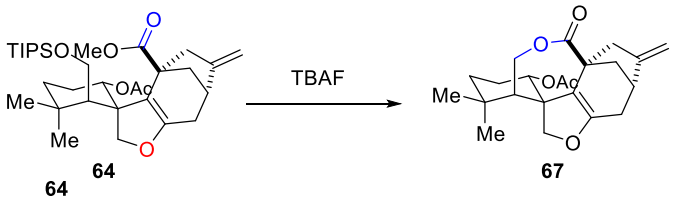
Compound 64 To a flame dry Schlenk tube was added $ZnBr_2$ (1.5 equiv., 9.8 mg, 0.0435 mmol). The reaction was sealed with a rubber septum and backfilled with N2 three times. **59** (16.3 mg, 0.029 mmol) in dry benzene (0.58 mL) was added to the reaction via syringe and cooled to -78 ^{o}C. The benzene solution froze solid. Then BBr_3 (0.01 M in DCM, 0.3 equiv., 0.875 mL) was added via syringe. The reaction was removed from the dry ice / acetone bath and allowed to warm to room temperature over 1 hour. Upon completion, the reaction was cooled to 0 ^{o}C and quenched with water (1 mL). Organics were extracted with diethyl ether (5 x 1 mL), washed with brine (5 mL), dried over Na_2SO_4 and filtered over a silica plug with diethyl ether. By crude ^{1}H NMR the crude material contained **63** (comparison pure material above) and by LCMS contained two bromide isotopes. The crude mixture was used without further purification in the next step.

The crude material from the previous step was charged to 4 mL vial and transferred to a N2 box. To the reaction vial was added a solution of tributytin hydride (w/ 0.05% BHT stabilizer, 2.5 equiv., 0.73 mmol, 19.5 μL) and azobisisobutyronitrile (0.5 equiv., 0.0145 mmol, 2.4) in toluene (taken from SPS). The vial was sealed with a PTFE cap, removed from the N2 box, and heated to reflux for 18 hours. Upon completion, the crude reaction mixture was directly concentrated and redissolved in THF (1 mL). The solution was cooled to 0 ^{0}C and treated with 6M HCl (500 μL) for 1.5 hours. The reaction was then quenched with water and organics were extracted with ether (6 x 1 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), washed with brine (5 mL), dried over Na_2SO_4, concentrated under vacuum and purified via TEA treated silica gel column chromatography to give **64**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (q, *J* = 8.7 Hz, 1H), 5.01 (s, 2H), 4.87 (s, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.59 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.46 (d, *J* = 9.6 Hz, 1H), 3.00 (bs, 1H), 2.92 (d, *J* = 15.8 Hz, 1H), 2.52 (d, *J* = 15.7 Hz, 1H), 2.47 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.24 (dd, *J* = 11.7, 5.8 Hz, 1H), 2.10 – 1.00 (buried, 3H) 1.67 – 1.59 (m, 1H), 1.14 (s, 3H), 1.08 (s, 3H), 1.06 (buried, 21H).

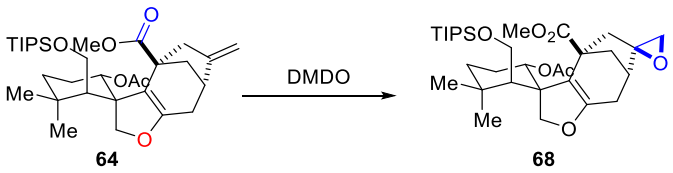


Compound 66 To a 2 mL was charged **64** in DCM. Solvent was removed by gently blowing N_2 over the vial. Then AcOH:H_2O (4:1, 0.1 mL) was added to the reaction vial and allowed to stir at room temperature for 10 days. Upon completion the reaction was diluted with water (1 mL) and extracted with diethyl ether (5 x 1 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and purified via TEA silica gel column chromatography. Rf = 0.40 (3:7 ethyl acetate:hexanes); LRMS obs. = 405.3 ref. = 404.2 for $C_{23}H_{32}O_6$; ^{1}H NMR (500 MHz, $CDCl_3$) δ

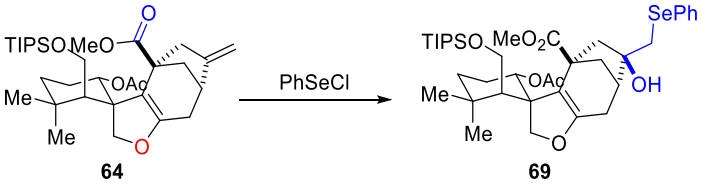
5.22 (t, *J* = 2.8 Hz, 1H), 4.88 (s, 1H), 4.84 (s, 1H), 3.98 (dd, *J* = 12.5, 6.7 Hz, 2H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.86 (d, *J* = 12.6 Hz, 1H), 3.82 (d, *J* = 9.0 Hz, 1H), 3.80 (d, *J* = 1.7 Hz, 1H), 3.78 (d, *J* = 2.0 Hz, 1H), 3.07 (s, 1H), 2.84 (dt, *J* = 17.9, 2.7 Hz, 1H), 2.75 (dd, *J* = 3.8, 0.5 Hz, 1H), 2.70 (d, *J* = 18.1 Hz, 1H), 2.11 (ddd, *J* = 13.5, 3.1, 1.3 Hz, 1H), 2.04 (d, *J* = 4.0 Hz, 1H), 2.02 (s, 3H), 2.01 (d, *J* = 2.3 Hz, 1H), 1.90 – 1.87 (m, 2H), 1.85 (dd, *J* = 13.6, 3.7 Hz, 1H), 1.72 – 1.66 (m, 2H), 1.63 (d, *J* = 6.7 Hz, 1H), 1.48 – 1.44 (m, 1H), 1.43 (s, 3H), 1.42 – 1.40 (m, 1H), 1.20 (s, 3H), 0.94 (s, 3H). COSY spectrum also provided.



Compound 67 To a PTFE container was added **xx** (1 mg, 1.8 µmol) in benzene. Solvent removed by high vacuum with swirling. The reaction vessel was cooled to 0 ^{o}C and TBAF (1 M in THF, 30 µL) was added. The vial was removed from the ice bath and allowed to warm to room temperature. The reaction was stirred for 4 hours. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The organics were extracted with diethyl ether (5 x 0.5 mL) and directly filtered over a plug of Na_2SO_4. The filtrate was concentrated under vacuum to give crude **67**. Rf = 0.4 (1:1 diethyl ether:hexane). A crude ^{1}H NMR spectrum is provided indicating loss of TIPS and the methyl ester. The DHF ring still installed [4.69 ppm (d, *J* = 8.7 Hz, 1H) and 3.92 ppm (d, *J* = 8.9 Hz, 1H)]. Other characterizing peaks such as the terminal olefins [4.84 ppm (bs, 2H)] can also be identified and are labeled in the provided spectrum.

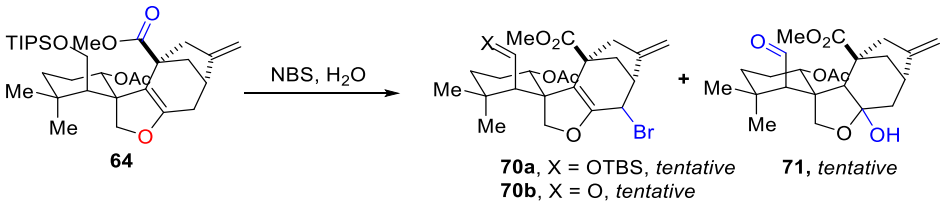


Compound 68 To a solution of **xx** (1 mg, 1.8 µmol) in acetone (50 µL) at 0 °C was added DMDO (0.083 M in acetone, 25 µL). The solution was allowed to slowly warm to room temperature over 4 hours. Upon completion the reaction was directly concentrated to give a **68**. The crude product contains ~15% birch precursor **41** carried over from prior steps. The desired product peaks are given. Rf = 0.13 (3:7 diethyl ether:hexane) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (t, *J* = 8.6 Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.29 (d, *J* = 8.1 Hz, 1H), 3.68 (s, 3H), 3.56 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 2.89 (d, *J* = 4.4 Hz, 1H), 2.81 (d, *J* = 4.4 Hz, 1H), 2.60 (dd, *J* = 13.8, 2.2 Hz, 1H), 2.52 (dd, *J* = 11.8, 5.4 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.42 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.17 – 2.12 (m, 1H), 2.06 (ddd, *J* = 11.6, 10.7, 4.8 Hz, 4H), 2.00 (s, 3H), 1.67 – 1.59 (m, 2H), 1.42 – 1.33 (m, 1H), 1.29 – 1.22 (m, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.06 (t, *J* = 6.4 Hz, 21H).



Compound 69 To a solution of **64** (1 mg, 1.8 µmol) in MeCN:H_2O (4:1, 100 µL) was added PhSeCl (1.5 equiv, 0.5 mg, 2.7 µmol). The reaction was stirred at room temperature for 24 hours. Upon completion the reaction was quenched with $NaHCO_3$ (0.5 mL). Organics were extracted with diethyl ether (5 x 0.5 mL), washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give crude **69**. LRMS obs. = 734.9 ref. = 734.3 for $C_{38}H_{58}O_7SeSi$. There is too little material to clearly resolve the aliphatic region in the proton spectrum, however all other defining peaks are cleanly assigned; the terminal olefin signals are not present. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.58 – 7.54 (m, 3H), 5.16 (t, *J* = 8.5 Hz, 1H), 5.06 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 8.1 Hz, 1H), 4.31 (d, *J* = 8.2 Hz, 1H), 3.68 (s, 3H), 2.96 (d, *J* = 14.3 Hz, 1H), 2.86 (d, *J* = 11.4 Hz, 1H), 2.65 (s, 1H), 2.53 – 2.47 (m, 3H), 2.30 (d, *J* = 18.3 Hz, 1H), 2.14 (d, *J* = 11.4 Hz, 1H), 2.05 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.07 (t, *J* = 6.5 Hz, 21H).

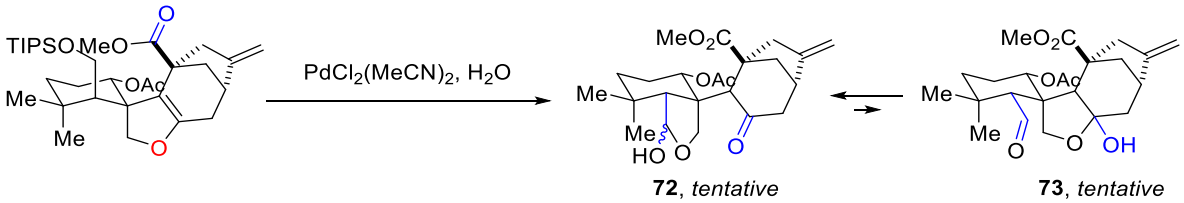


Compound 70a, 70b and 71: To a 2 mL vial charged with **64** (4 mg, 4.5 µmol) was added HFIP:H_2O (4:1, 0.016 M, 280 µL). NBS (1.5 equiv., 1.2 mg, 6.7 µmol) was added and the reaction was stirred in the dark for 1 hour. Upon completion the reaction was quenched with aqueous 10% $Na_2S_2O_3$ (0.5 mL) and extracted with diethyl ether (5 x 0.5 mL). The combined organics were washed with brine (2 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and purified via TEA treated silica gel column.

70a: Rf = 0.43 (3:7 diethyl ether:hexanes); LRMS obs. = 579.0 and 581.0 (M-H_2O) ref. = 596.2 and 598.2 for $C_{29}H_{45}BrO_6Si$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (t, *J* = 8.8 Hz, 1H), 5.20 (s, 1H), 5.03 (s, 1H), 4.47 (d, *J* = 8.2 Hz, 1H), 4.44 (s, 1H), 4.37 (d, *J* = 8.1 Hz, 1H), 3.71 (s, 3H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.24 (s, 1H), 2.78 (d, *J* = 15.7 Hz, 1H), 2.55 (d, *J* = 16.2 Hz, 1H), 2.47 (ddd, *J* = 11.4, 10.8, 6.2 Hz, 2H), 2.21 (dd, *J* = 12.2, 5.5 Hz, 1H), 2.15 (d, *J* = 12.0 Hz, 1H), 1.41 – 1.33 (m, 2H), 1.25 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.12 – 1.03 (buried, 21H). COSY provided

70b: Rf = 0.31 (3:7 ethyl acetate:hexanes); Due to poor reaction selectivity and the small scale, only modestly pure sample could be obtained. Characterizing peaks are labeled in the provided ^{1}H NMR spectrum.

71: Rf = 0.11 (3:7 ethyl acetate:hexanes); LCMS = 421.2 (M+H) ref. = 420.2 for $C_{23}H_{32}O_7$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, *J* = 6.1 Hz, 1H), 5.30 (dd, *J* = 7.9, 3.2 Hz, 1H), 4.97 (s, 1H), 4.89 (s, 1H), 3.96 (dd, *J* = 19.2, 8.7 Hz, 4H), 3.72 (s, 3H), 3.10 (d, *J* = 18.1 Hz, 1H), 2.82 (d, *J* = 17.9 Hz, 1H), 2.75 (s, 1H), 2.43 (d, *J* = 6.0 Hz, 1H), 2.10 (s, 1H), 2.09 – 2.04 (d, *J* = 6.2 Hz, 2H), 2.05 (s, 3H), 2.04 – 2.01 (m, 1H), 1.96 – 1.85 (m, 1H), 1.69 (dd, *J* = 11.1, 5.0 Hz, 1H), 1.60 (d, *J* = 8.4 Hz, 1H), 1.51 – 1.45 (m, 2H), 1.55 (buried, 3H), 1.43 (s, 3H). COSY provided



Compound 72 and 73: To a 2 mL vial charged with **64** (1 mg, 2 µmol) in MeCN:H_2O was added $PdCl_2$(MeCN). The reaction was heated to 100 ^{o}C and stirred overnight. Upon completion the reaction was directly filtered over a pad of silica with diethyl ether and concentrated under vacuum. Attempted isolation of the two spots by silica gel column chromatography revealed a complex diastereomeric mixture that also appears to be in equilibrium. Due to poor reaction selectivity and the small scale, only modestly pure samples and ^{1}H NMR spectrum could be obtained. Characterizing peaks are discussed and the crude ^{1}H NMR spectrum are given.

72:

Neither of the tentative structures show DHF peaks between the range of 5.0 – 4.0 ppm and both show a singlet for 1H at 3.03 and 2.94 ppm corresponding to the tertiary α-carbonyl position. The more polar compound shows a singlet at 9.85 ppm (d, J = 5.0 Hz, 1H) corresponding to an aldehyde next to one proton. Together with these promising peaks and mass observed [LRMS obs. = 379.0 (M-Ac), 405.0 (M-H_2O), and 439.0 (M+H_2O), ref. = 420.2 for $C_{23}H_{32}O_7$], which suggest of DHF ring cleavage and silyl group deprotection followed by C_6 oxidation, we propose tentative structures **72** and **73**. The crude ^{1}H NMR spectrum are provided.

References

1. Porzelle, A.; Williams, C. M.; Schwartz, B. D.; Gentle, I. R., Evaluating the Baylis-Hillman Reaction of Cyclic Enones Using Surfactants in Water. *Synlett* **2005,** *2005* (19), 2923-2926.

2. Taber*, D. F.; DeMatteo, P. W.; Hassan, R. A., Simplified preparation of dimethyldioxirane (DMDO). *Organic Syntheses* **2003,** *90*, 350-357.

5.2 NMR Spectra

Figure SI.1 ^{1}H NMR spectrum of **9** in $CDCl_3$

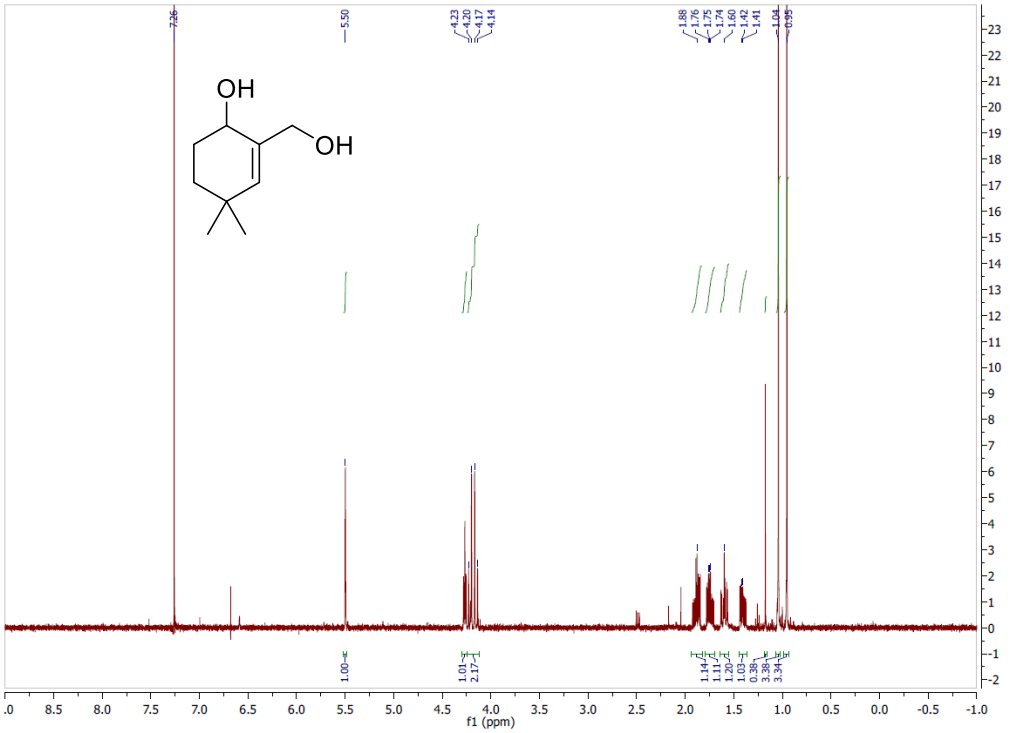


Figure SI.2 ^{13}C NMR spectrum of **9** in $CDCl_3$

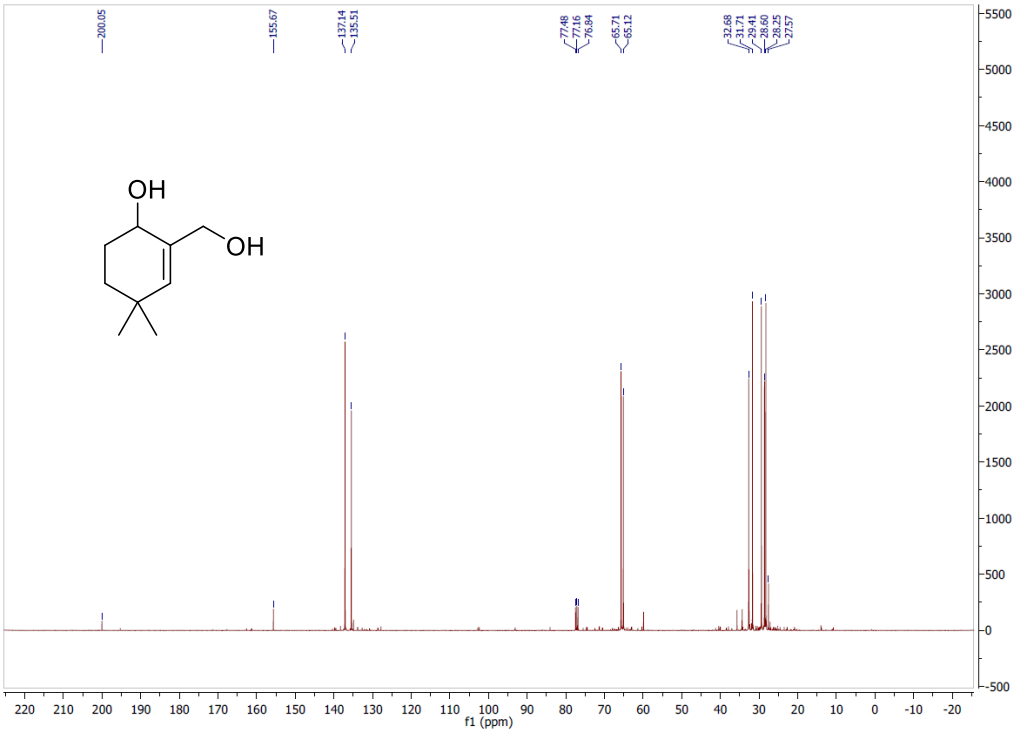


Figure SI.3 ^{1}H NMR spectrum of **SI-1** in $CDCl_3$

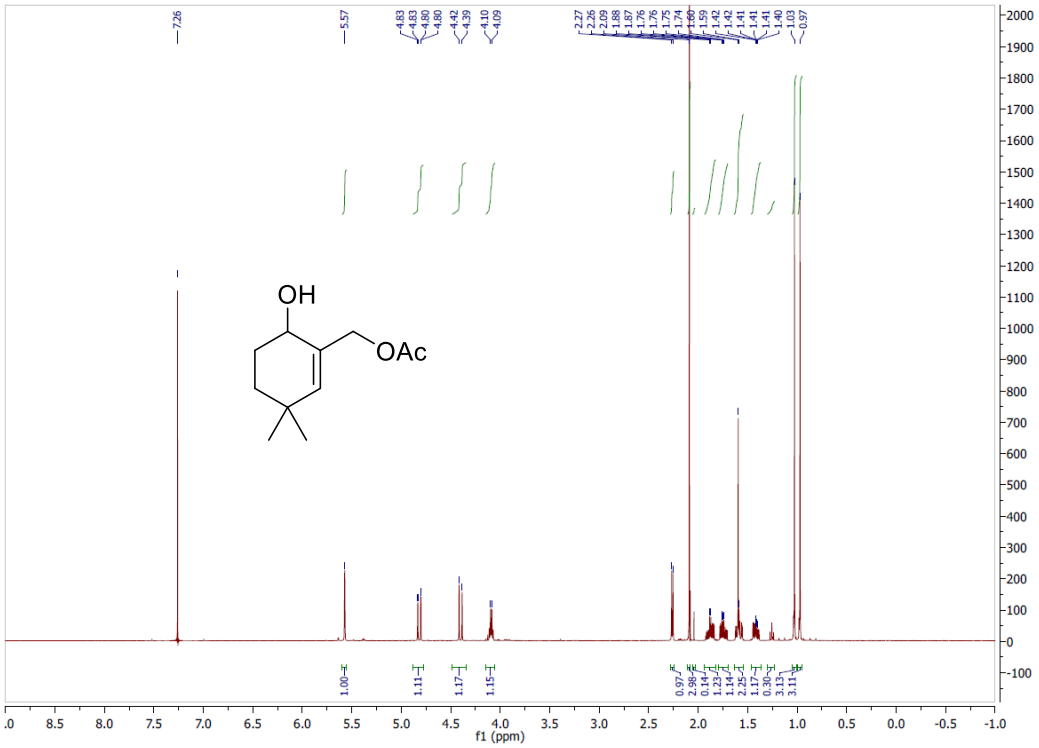


Figure SI.4 ^{13}C NMR spectrum of **SI-1** in $CDCl_3$

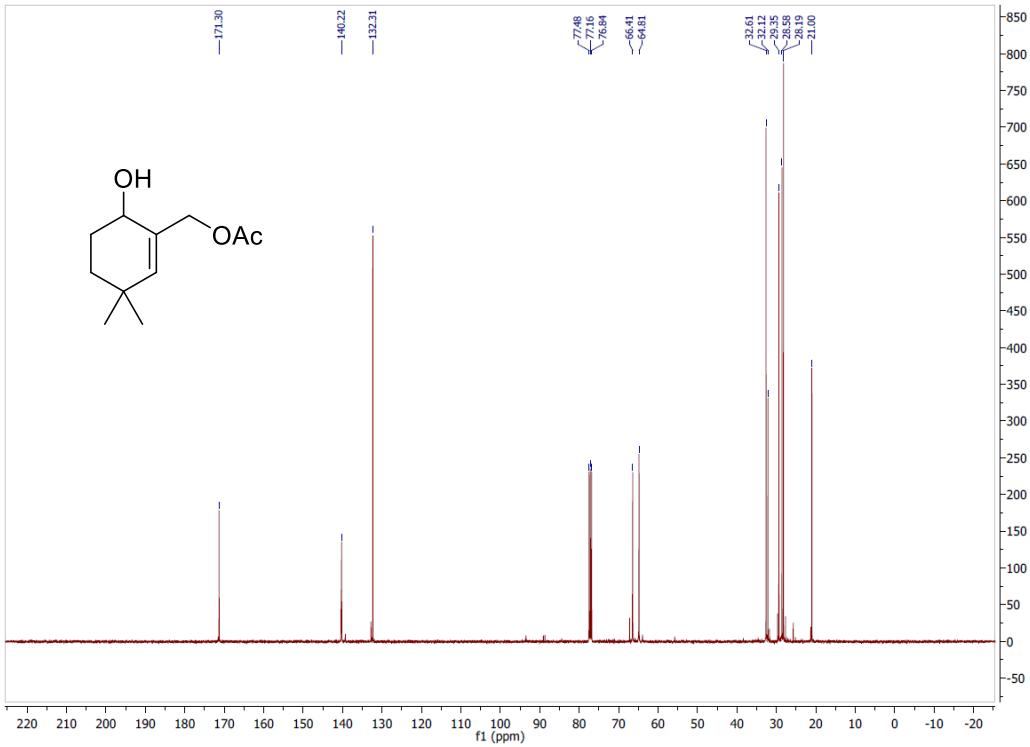


Figure SI.5 ^{1}H NMR spectrum of **12** in $CDCl_3$

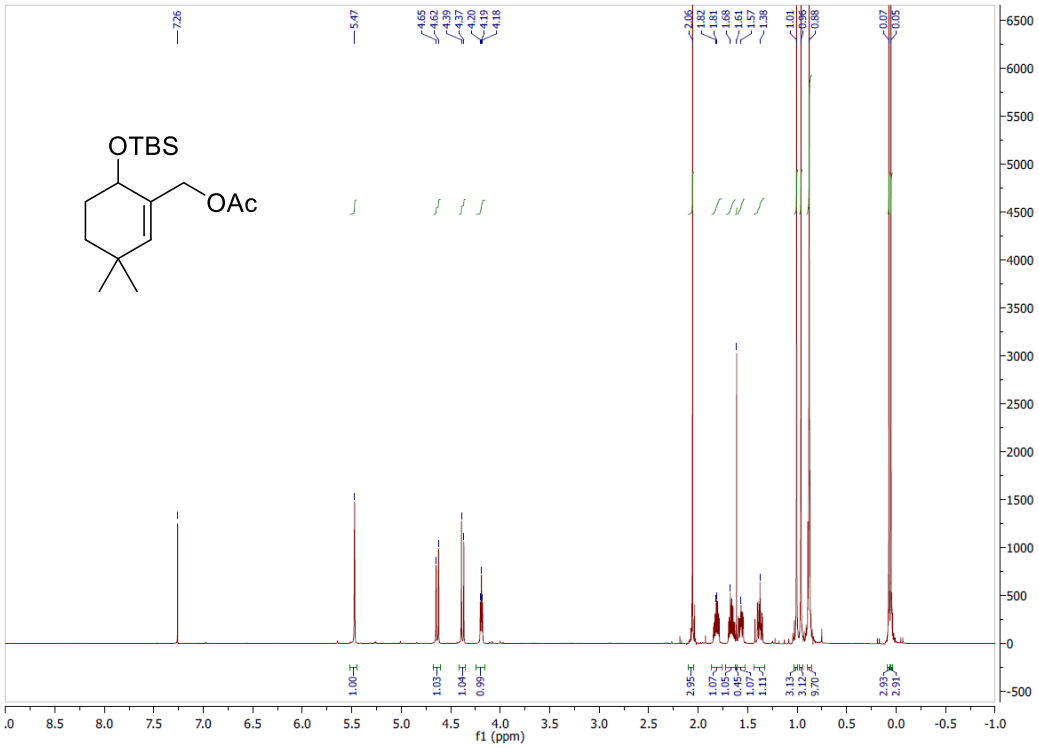


Figure SI.6 ^{13}C NMR spectrum of **12** in $CDCl_3$

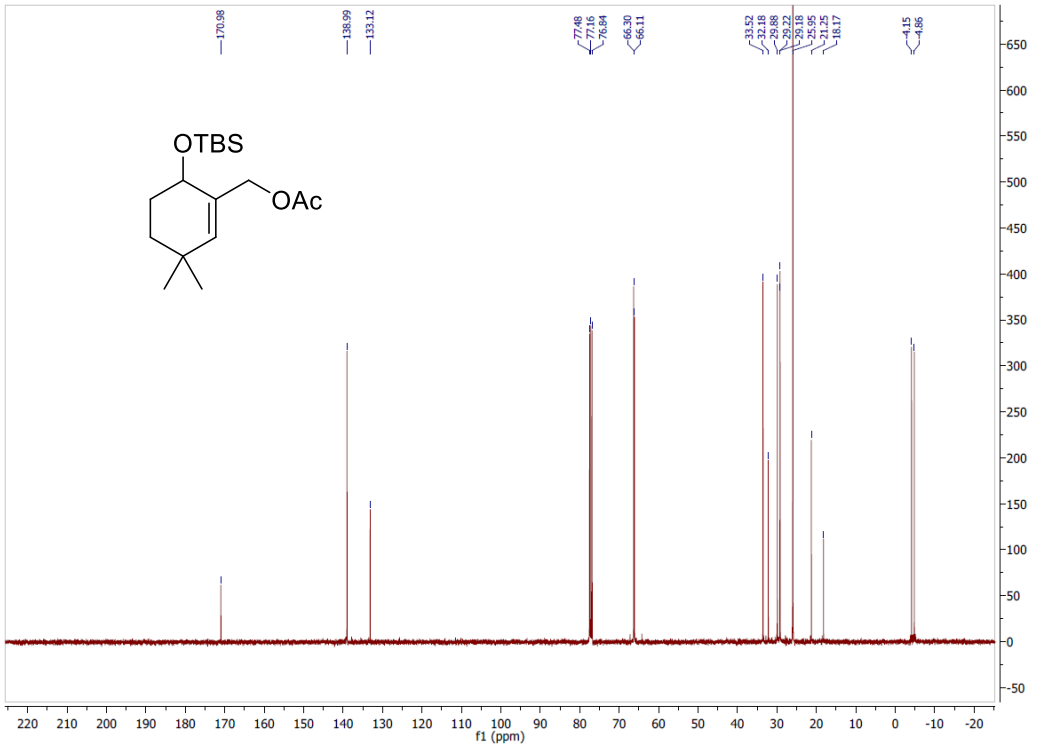


Figure SI.7 ^{1}H NMR spectrum of **13** in $CDCl_3$

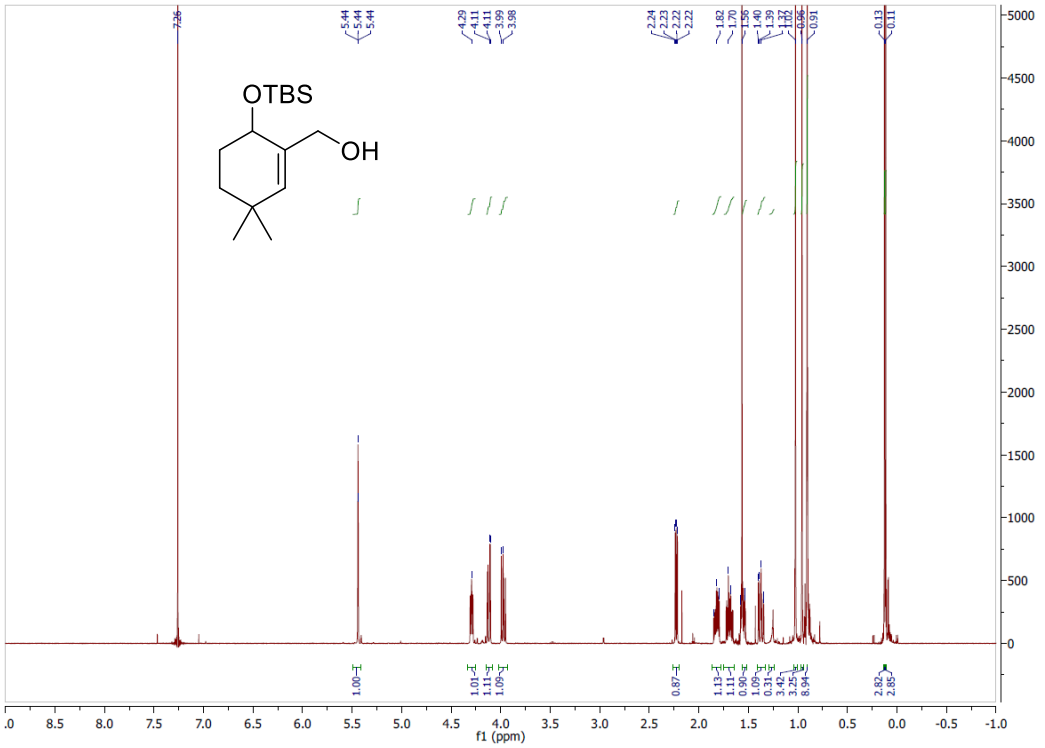


Figure SI.8 ^{13}C NMR spectrum of **13** in $CDCl_3$

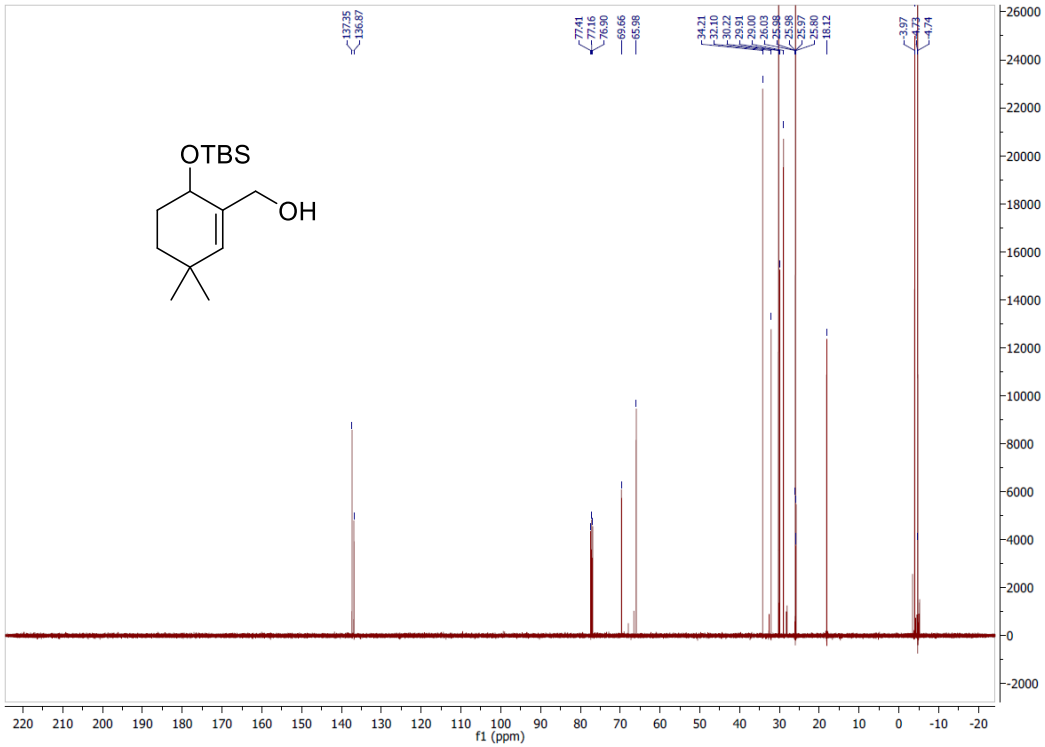


Figure SI.9 ^{1}H NMR spectrum of **8** in $CDCl_3$

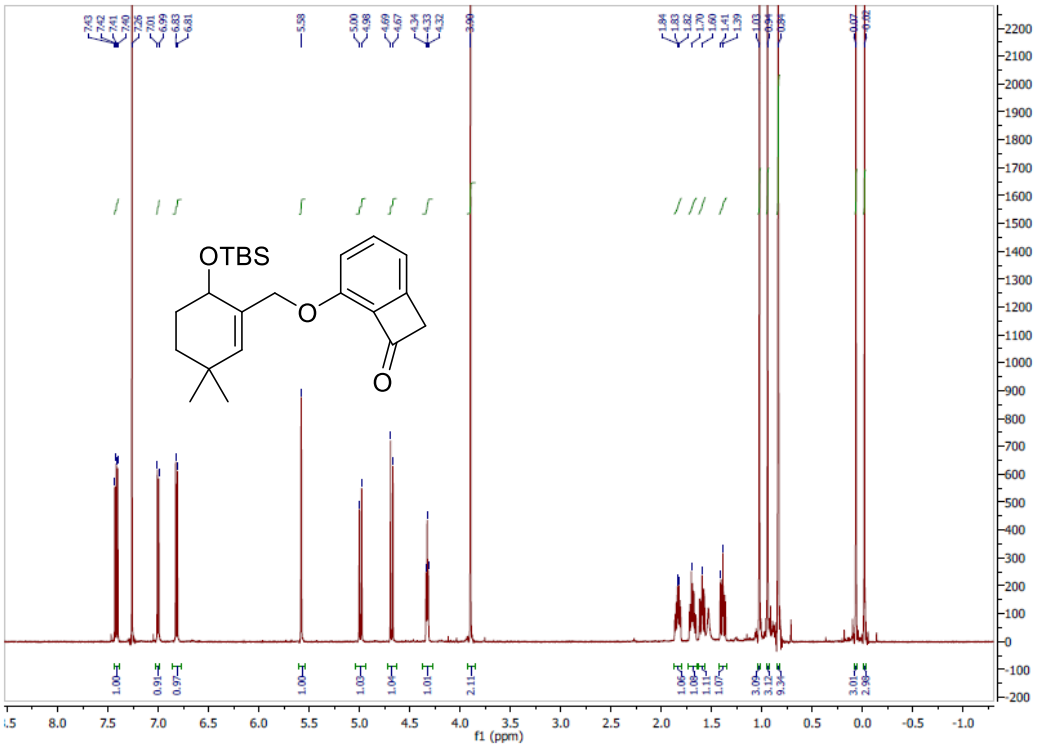


Figure SI.10 ^{13}C NMR spectrum of **8** in $CDCl_3$

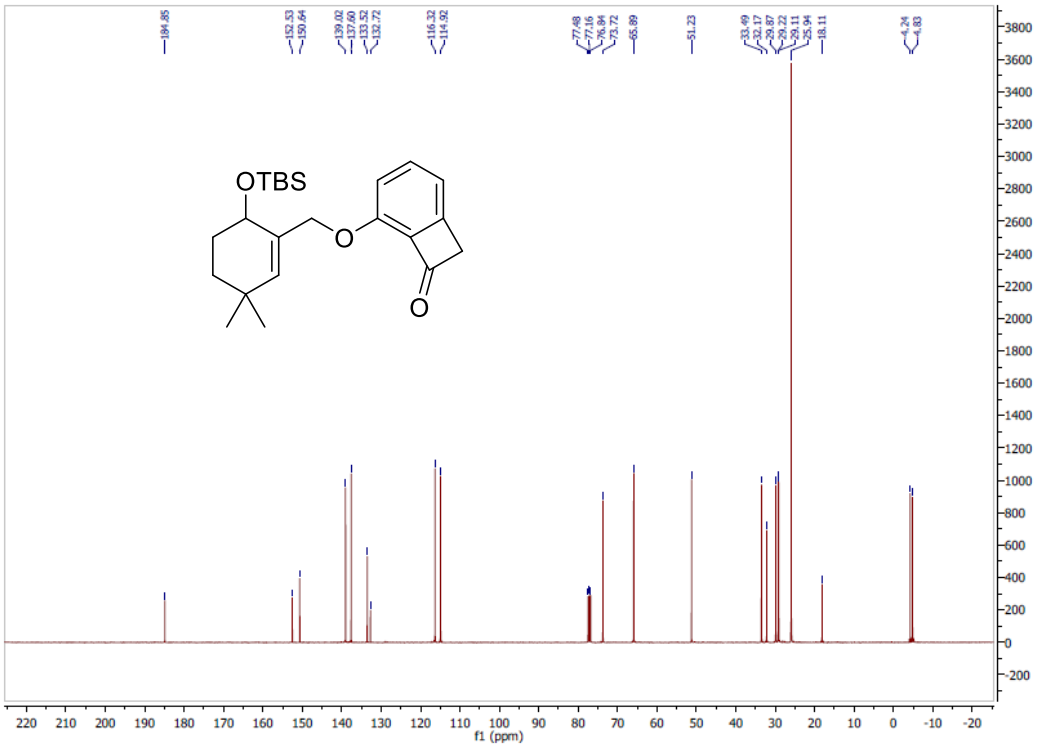


Figure SI.11 ^{1}H NMR spectrum of **7** in $CDCl_3$

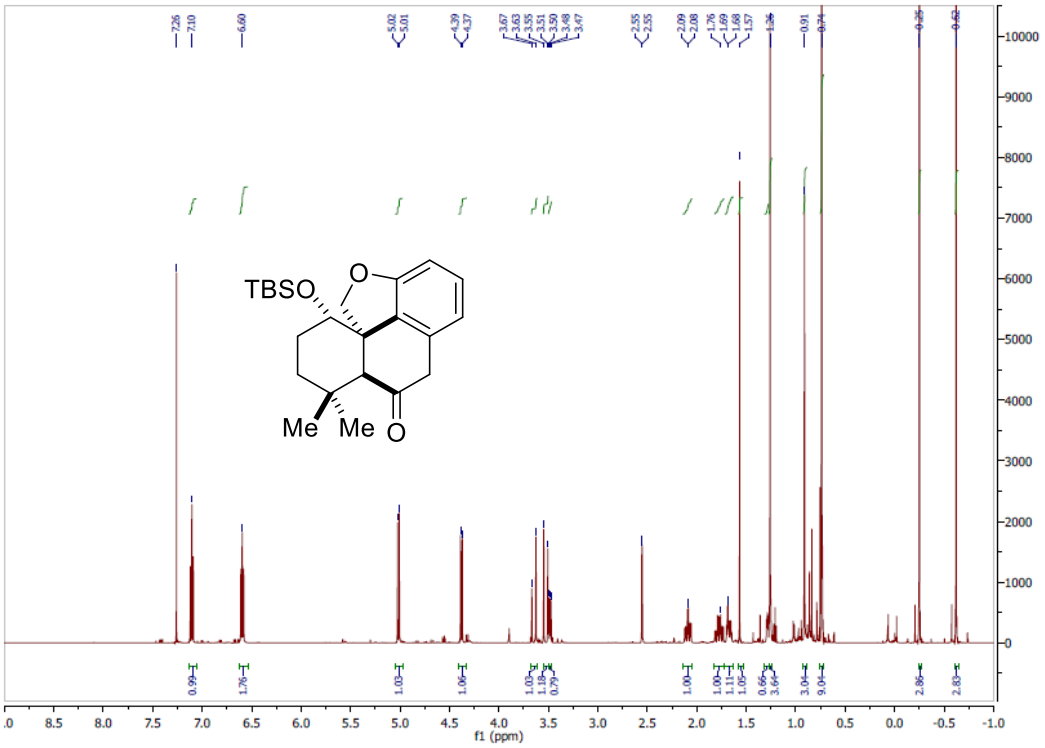


Figure SI.12 ^{13}C NMR spectrum of **7** in $CDCl_3$

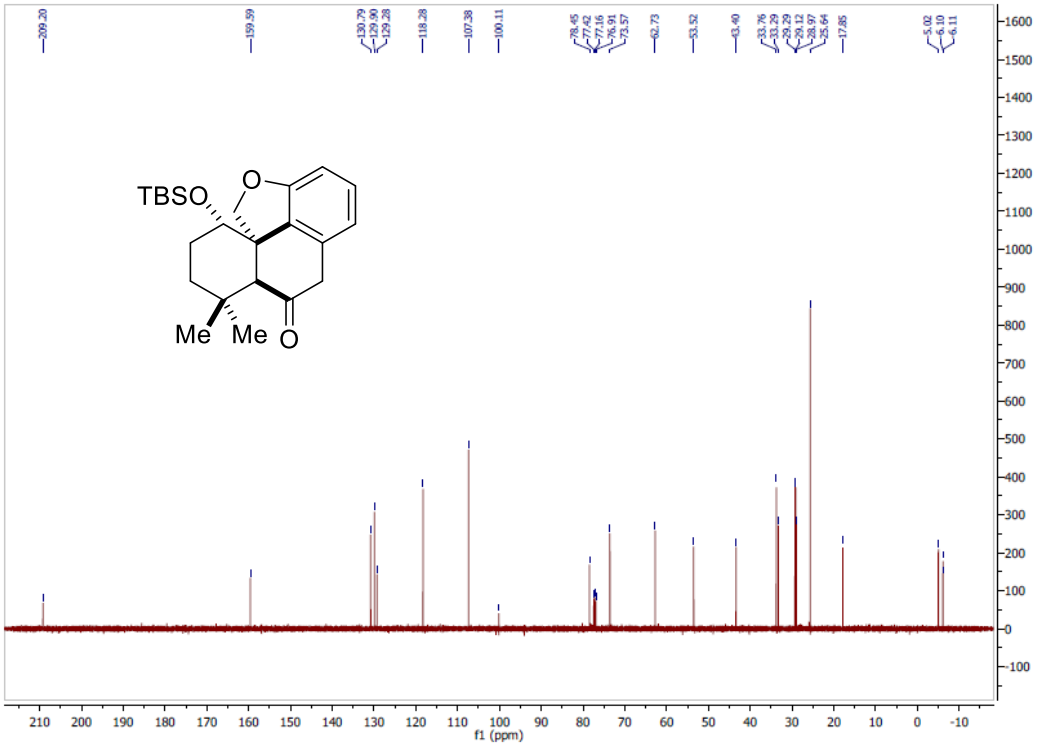


Figure SI.13 ^{1}H NMR spectrum of **16** in $CDCl_3$

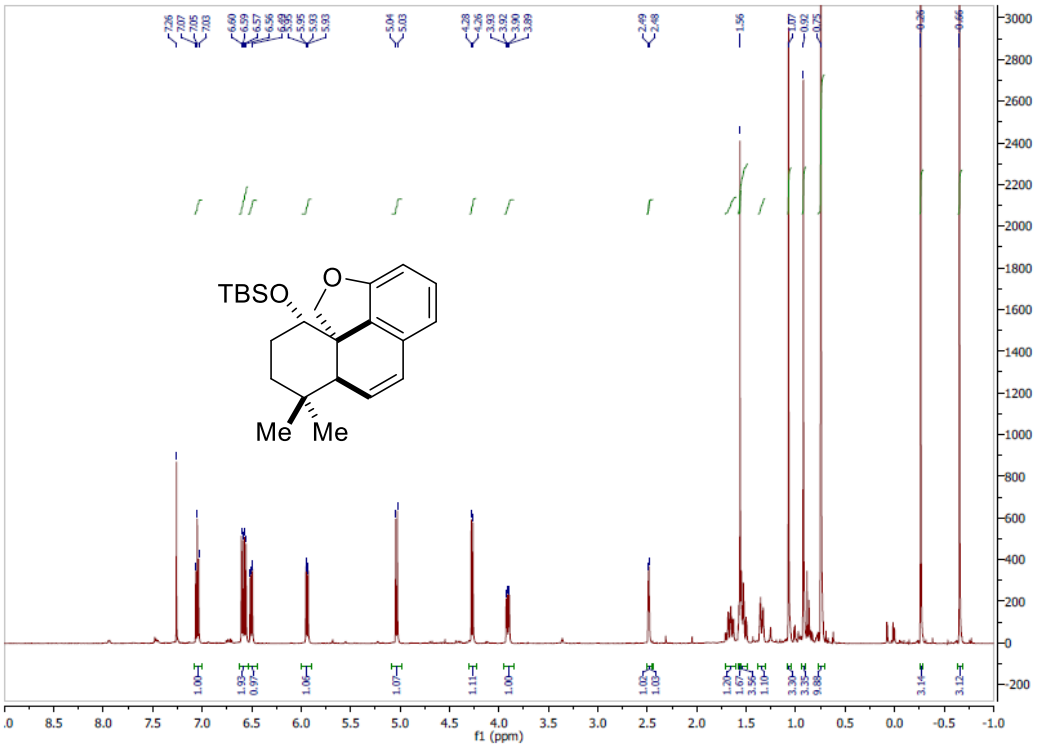


Figure SI.14 ^{13}C NMR spectrum of **16** in $CDCl_3$

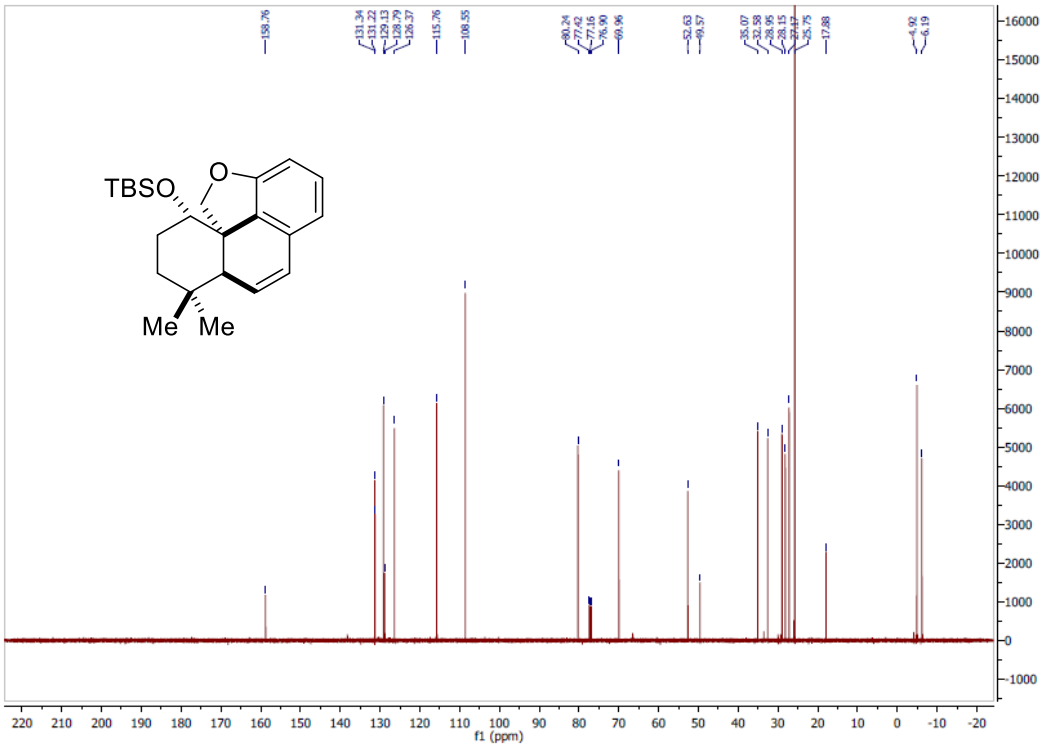


Figure SI.15 ^{1}H NMR spectrum of **17** in $CDCl_3$

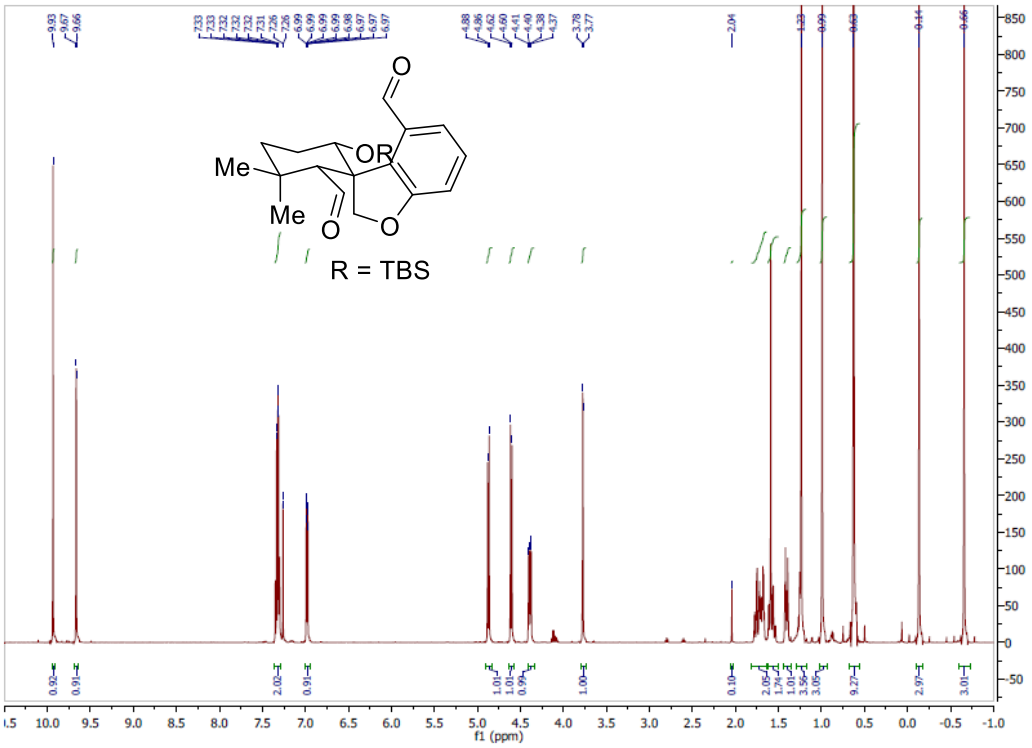


Figure SI.16 ^{13}C NMR spectrum of **17** in $CDCl_3$

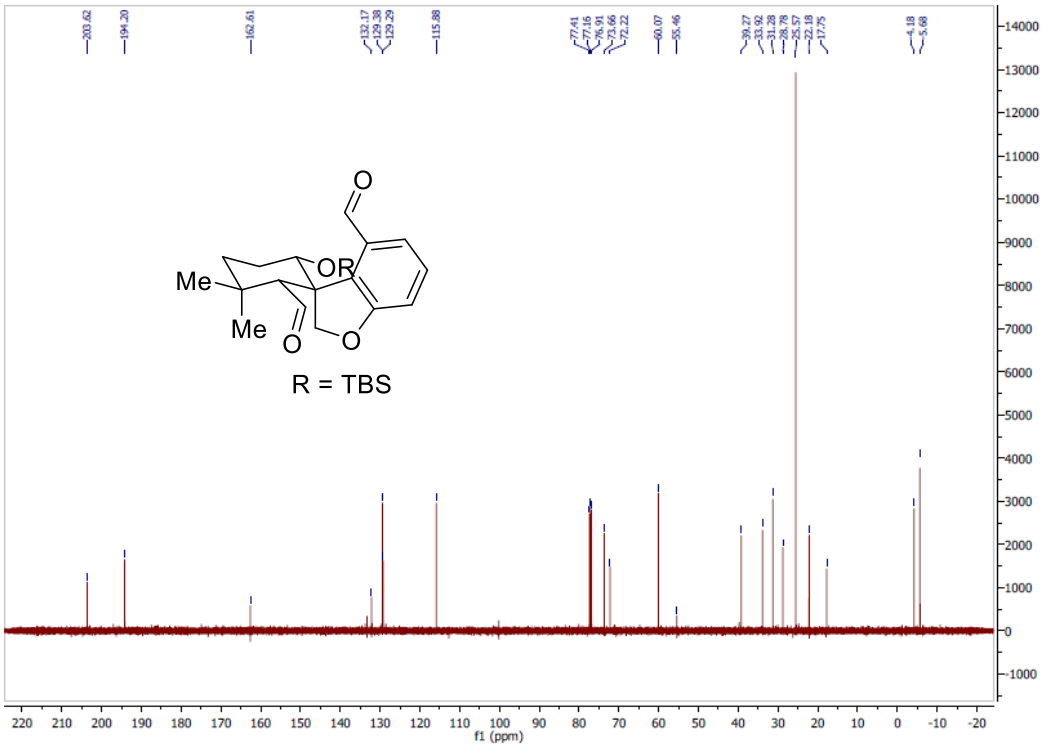


Figure SI.17 ^{1}H NMR spectrum of **18** in $CDCl_3$

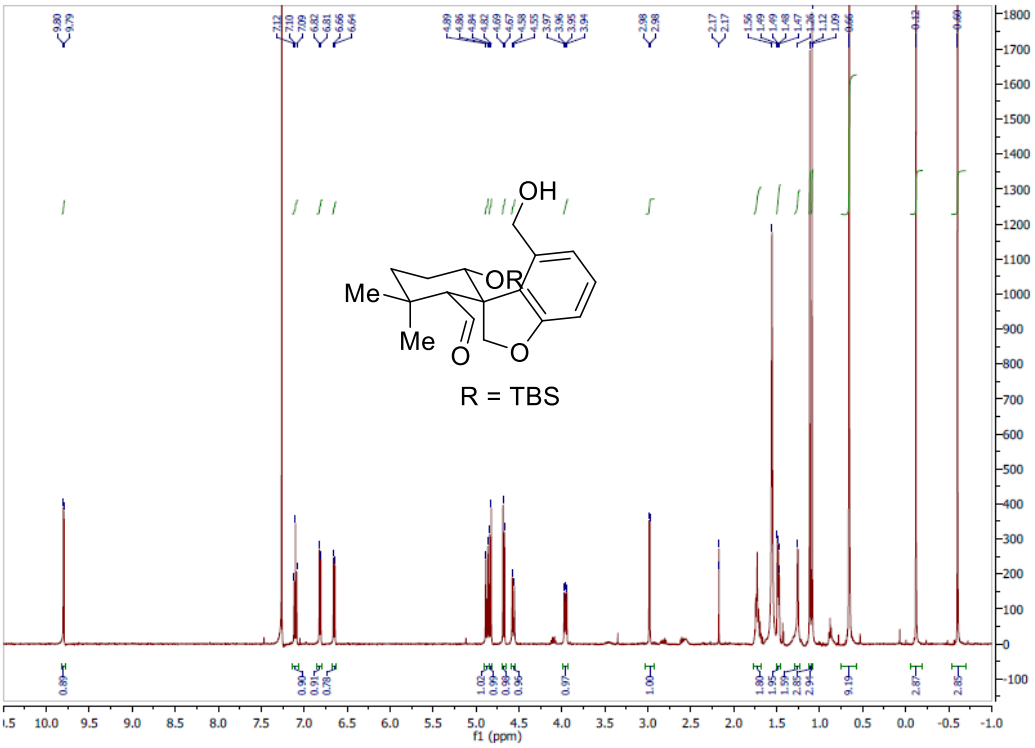


Figure SI.18 ^{1}H NMR spectrum of **19** in $CDCl_3$

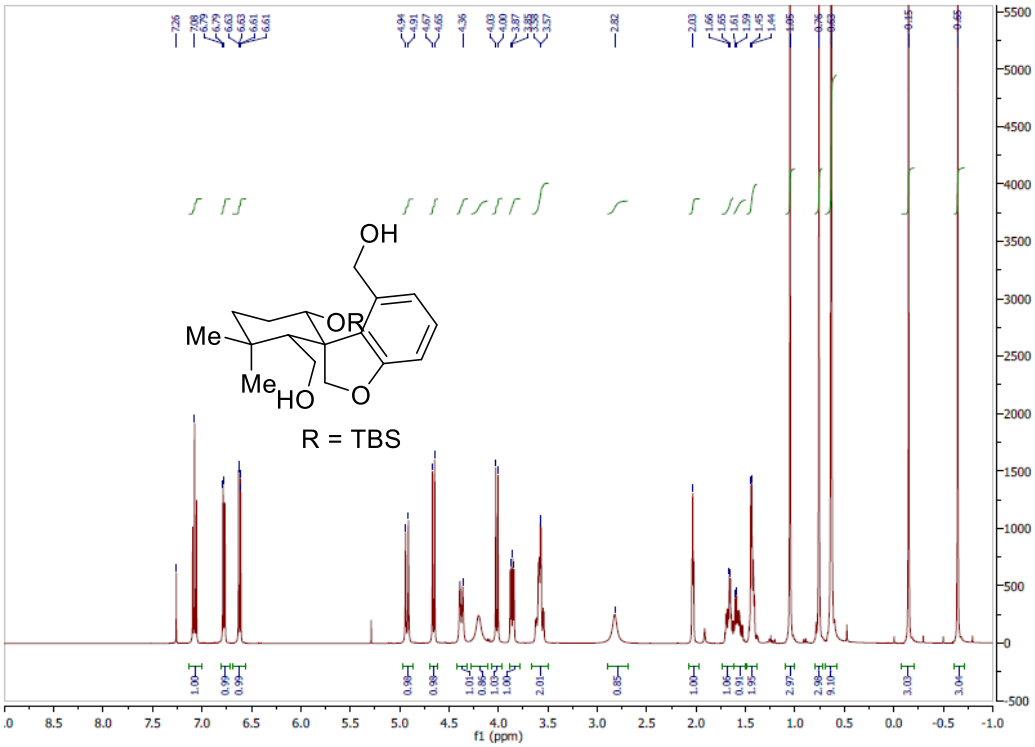


Figure SI.19 ^{13}C NMR spectrum of **19** in $CDCl_3$

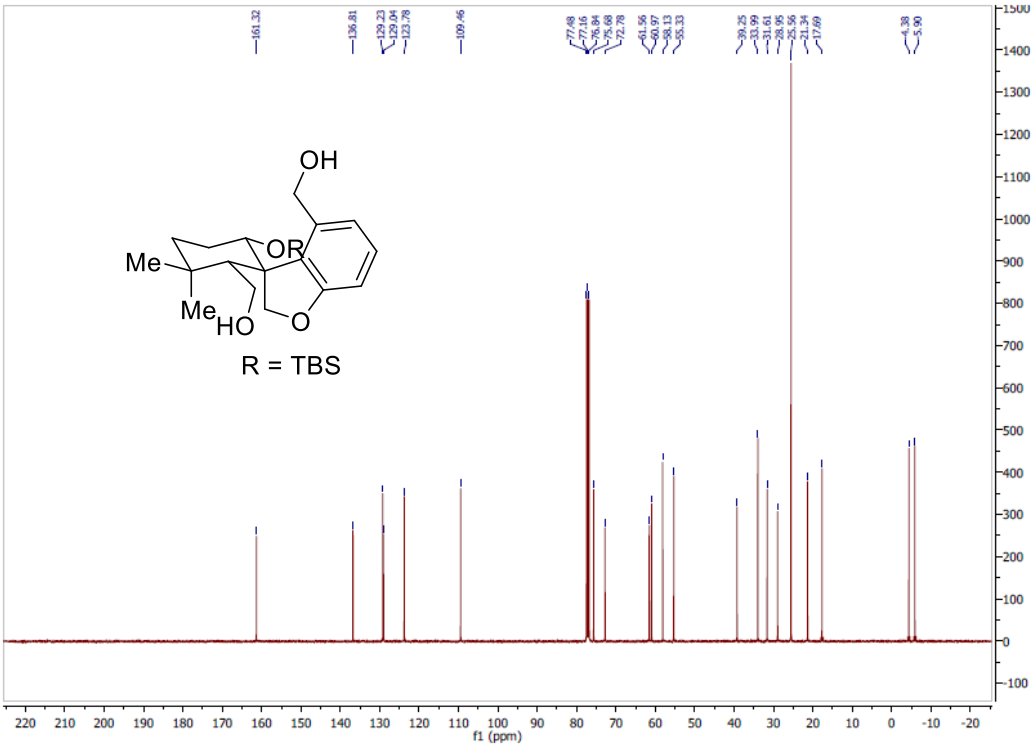


Figure SI.20 ^{1}H NMR spectrum of **20** in $CDCl_3$

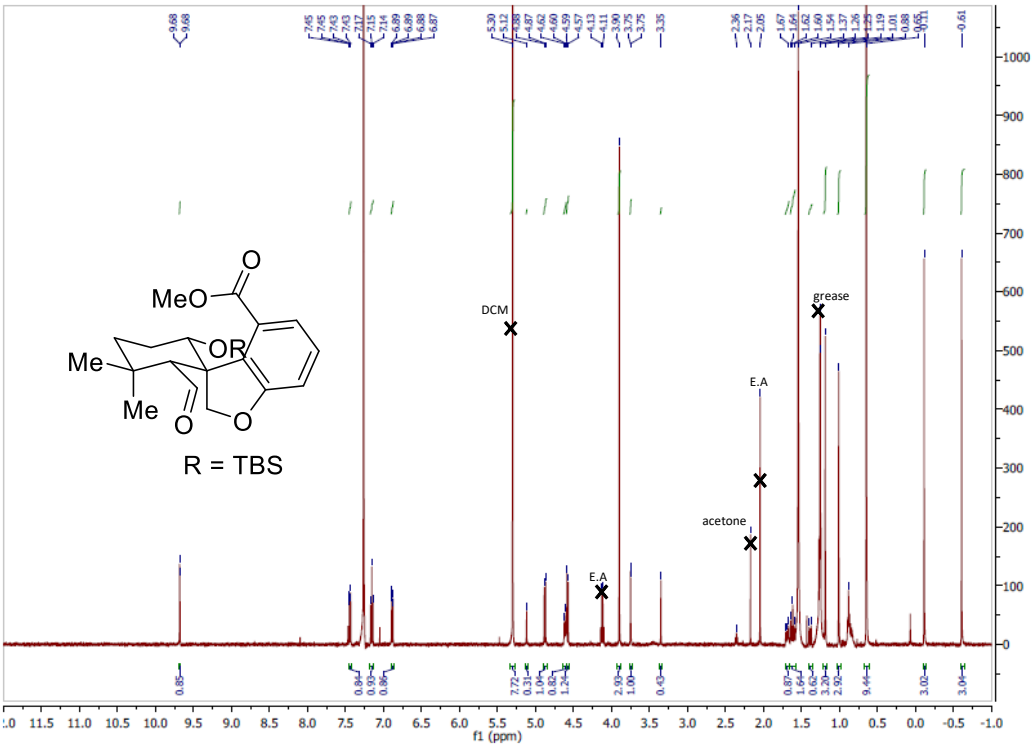


Figure SI.21 ^{1}H NMR spectrum of **SI-2** in $CDCl_3$

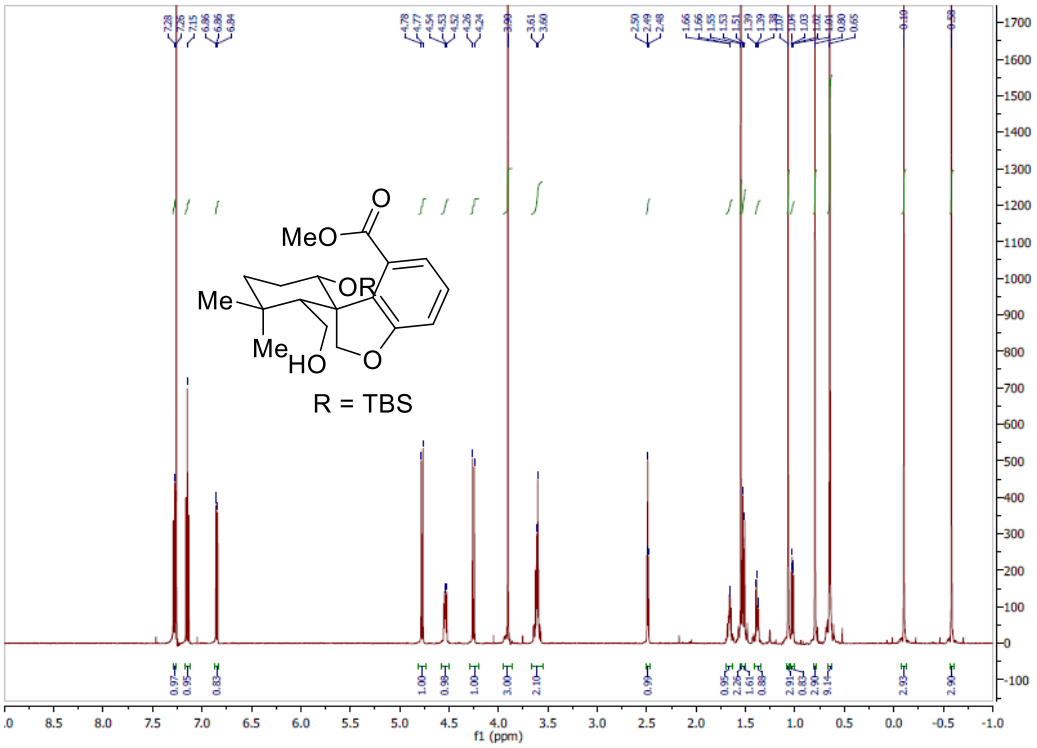


Figure SI.22 ^{13}C NMR spectrum of **SI-2** in $CDCl_3$

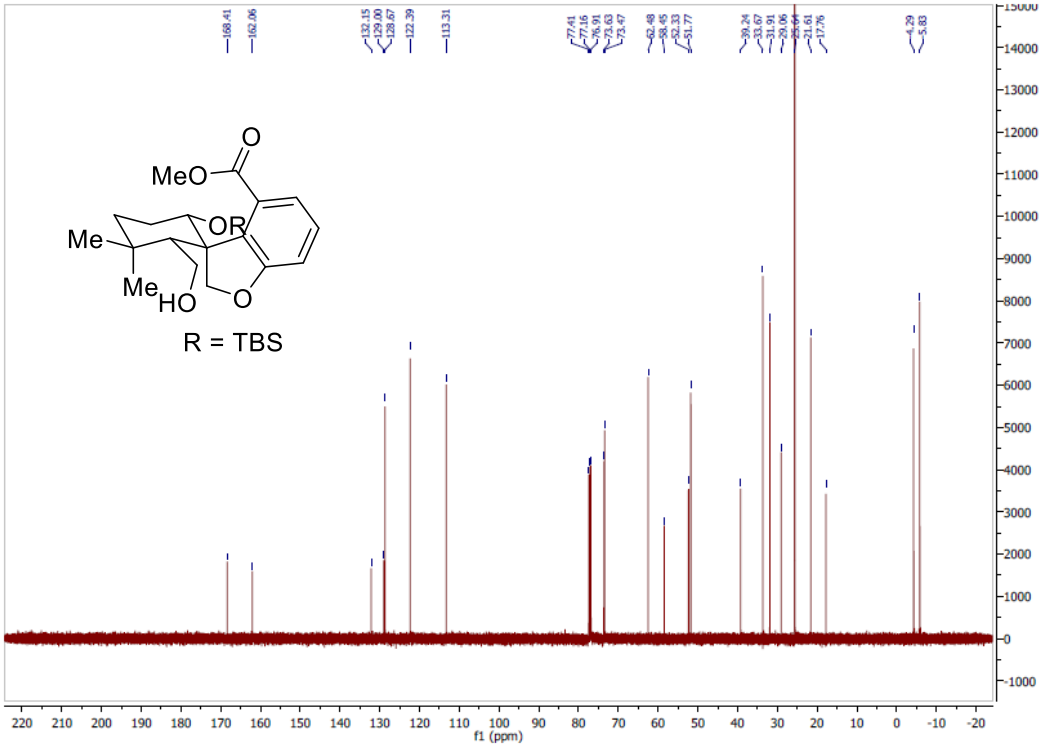


Figure SI.23 ^{1}H NMR spectrum of **SI-4** in $CDCl_3$

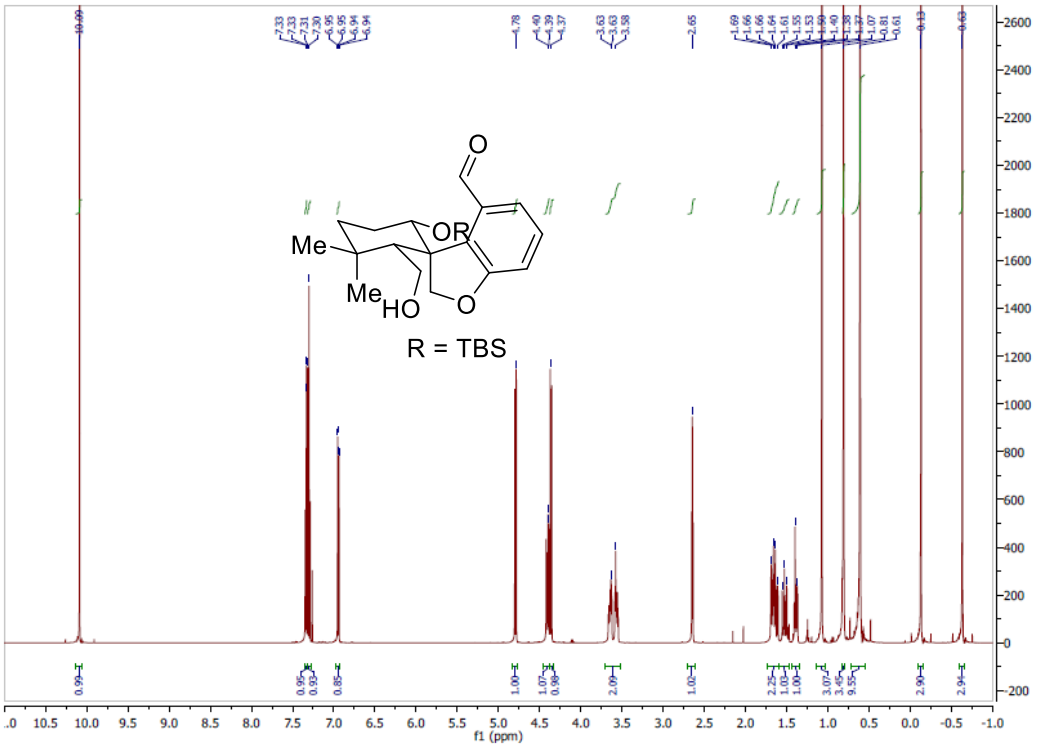


Figure SI.24 ^{13}C NMR spectrum of **SI-4** in $CDCl_3$

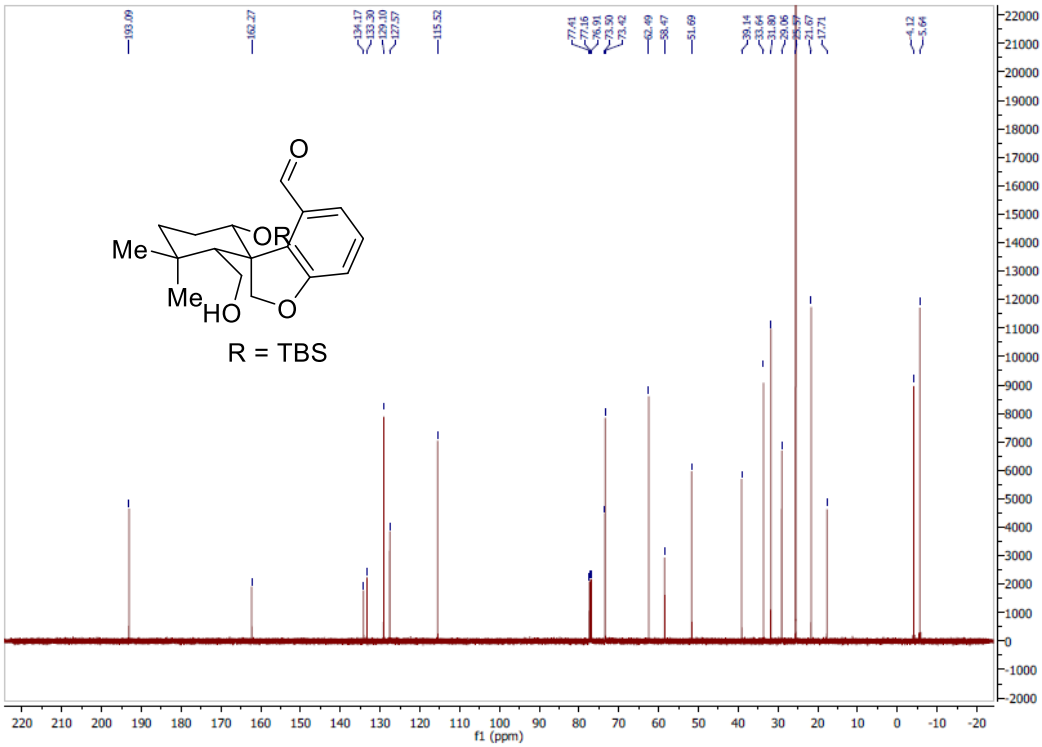


Figure SI.25 ^{1}H NMR spectrum of **SI-5** in $CDCl_3$

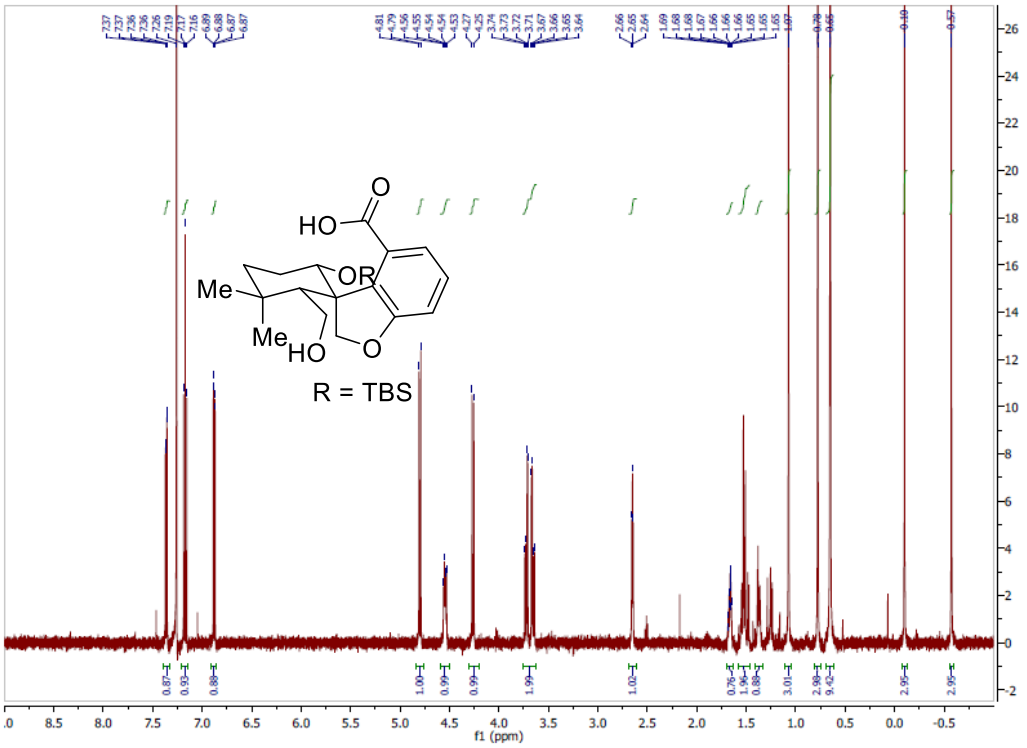


Figure SI.26 ^{13}C NMR spectrum of **SI-5** in $CDCl_3$

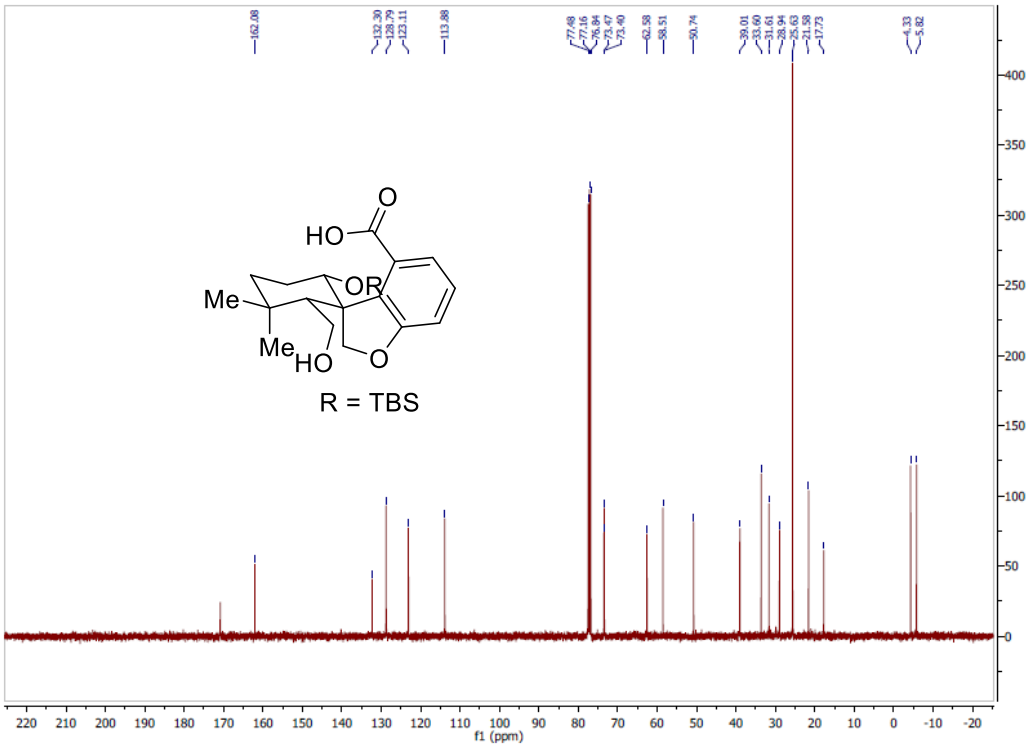


Figure SI.27 ^{1}H NMR spectrum of **SI-3** in $CDCl_3$

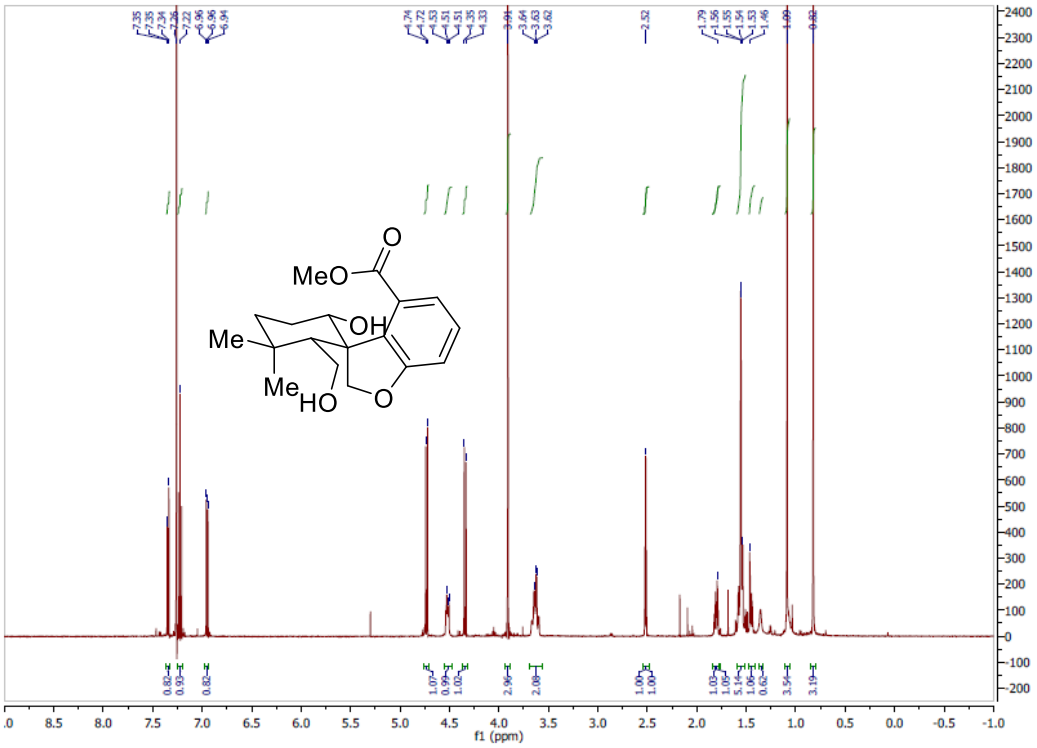


Figure SI.28 ^{13}C NMR spectrum of **SI-3** in $CDCl_3$

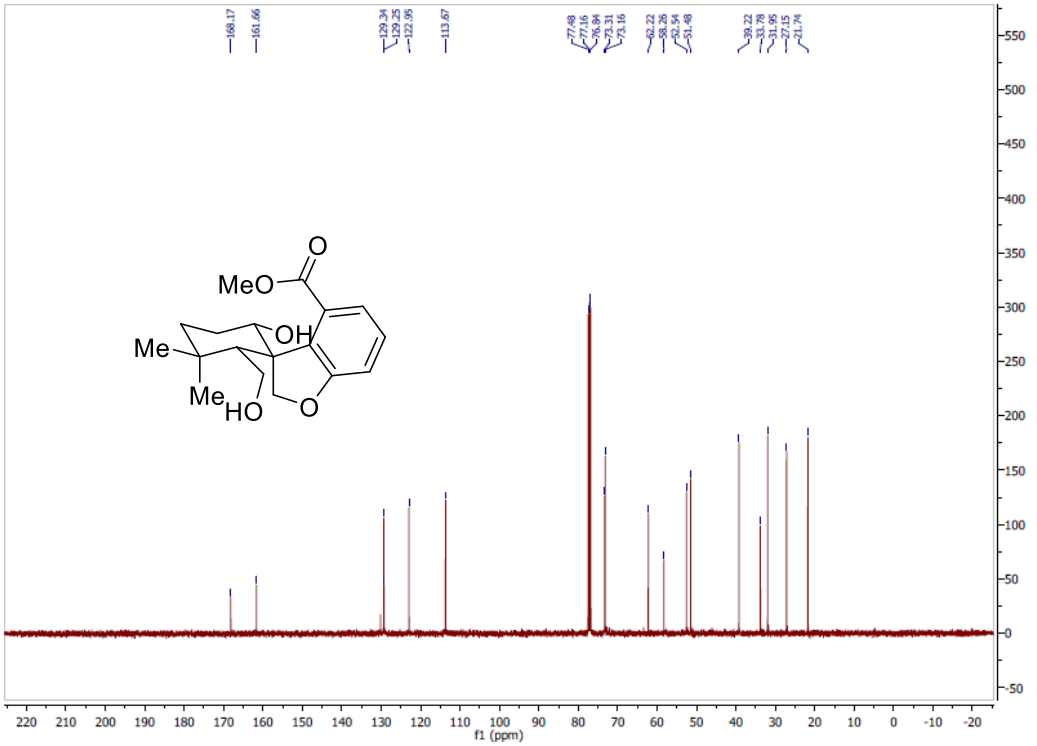


Figure SI.29 ^{1}H NMR spectrum of **6** in $CDCl_3$

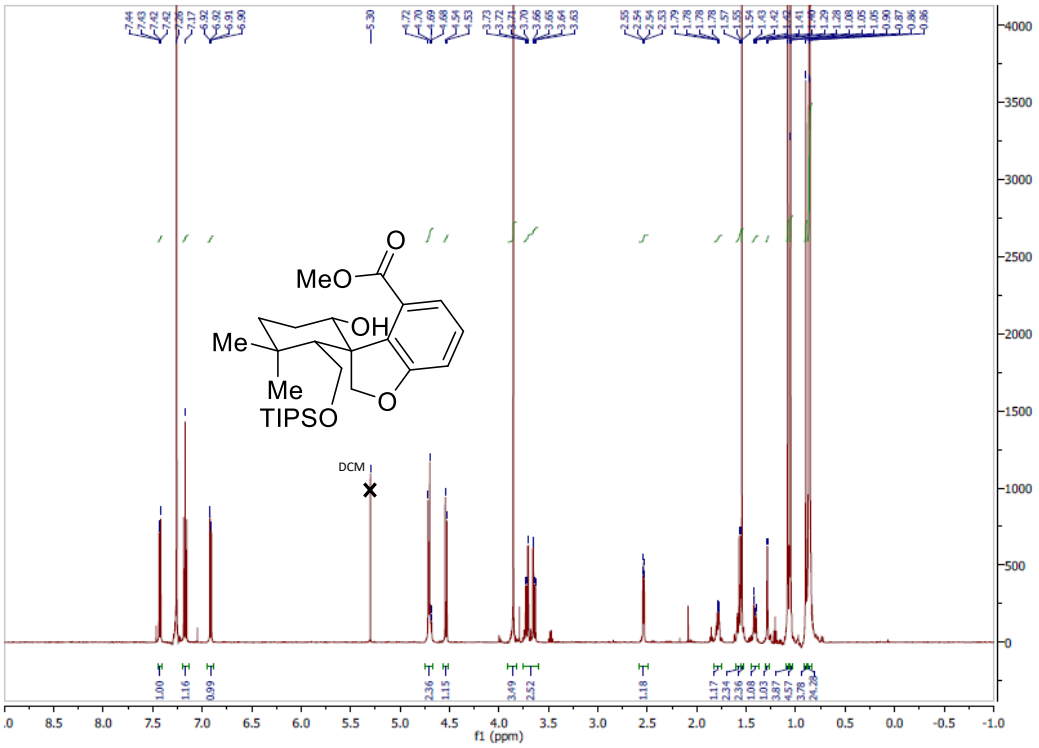


Figure SI.30 ^{1}H NMR spectrum of **6** in C_6D_6

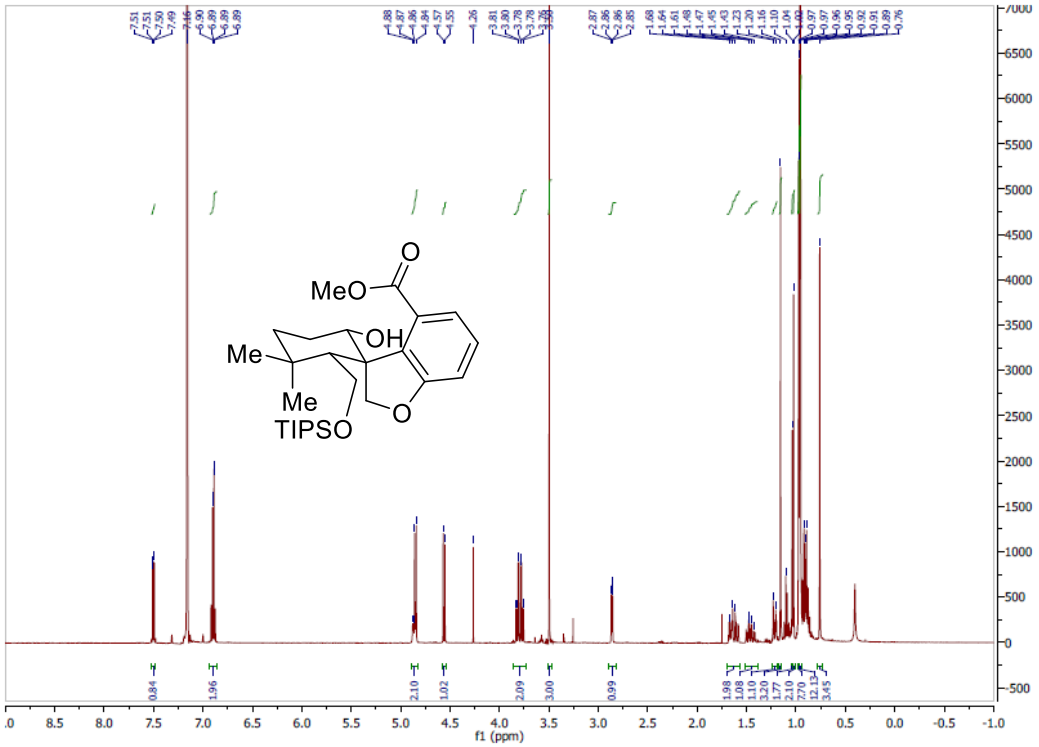


Figure SI.31 ^{1}H NMR spectrum of **6'** in $CDCl_3$

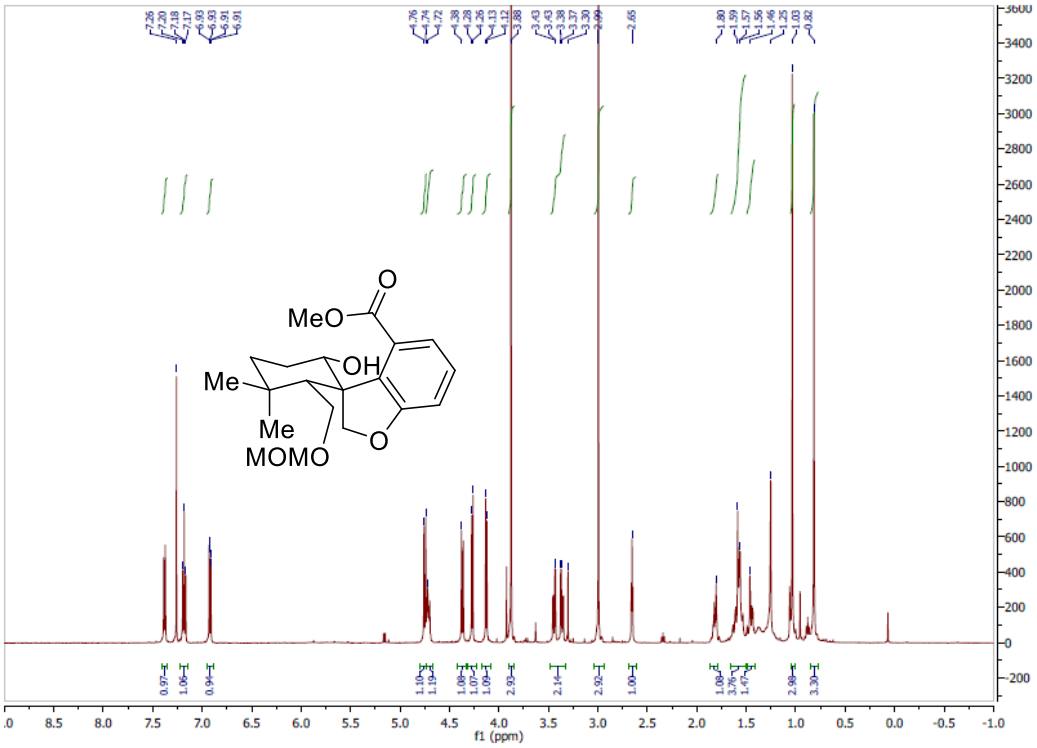


Figure SI.32 ^{1}H NMR spectrum of **21** in $CDCl_3$

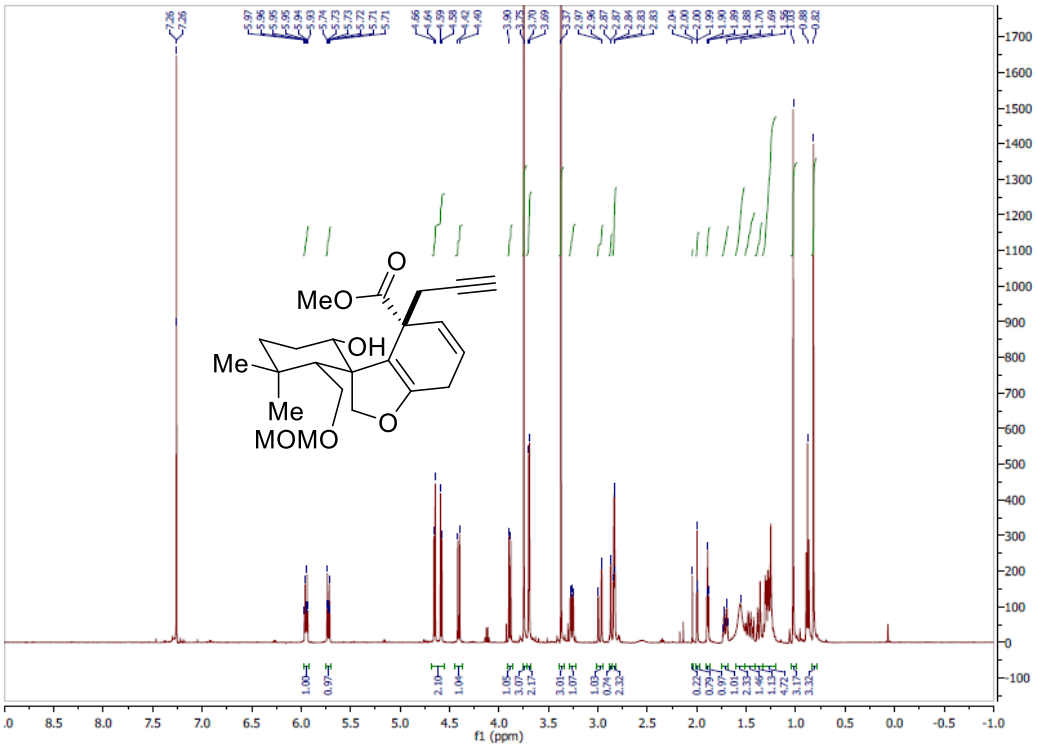


Figure SI.33 ^{1}H NMR spectrum of **22** in $CDCl_3$

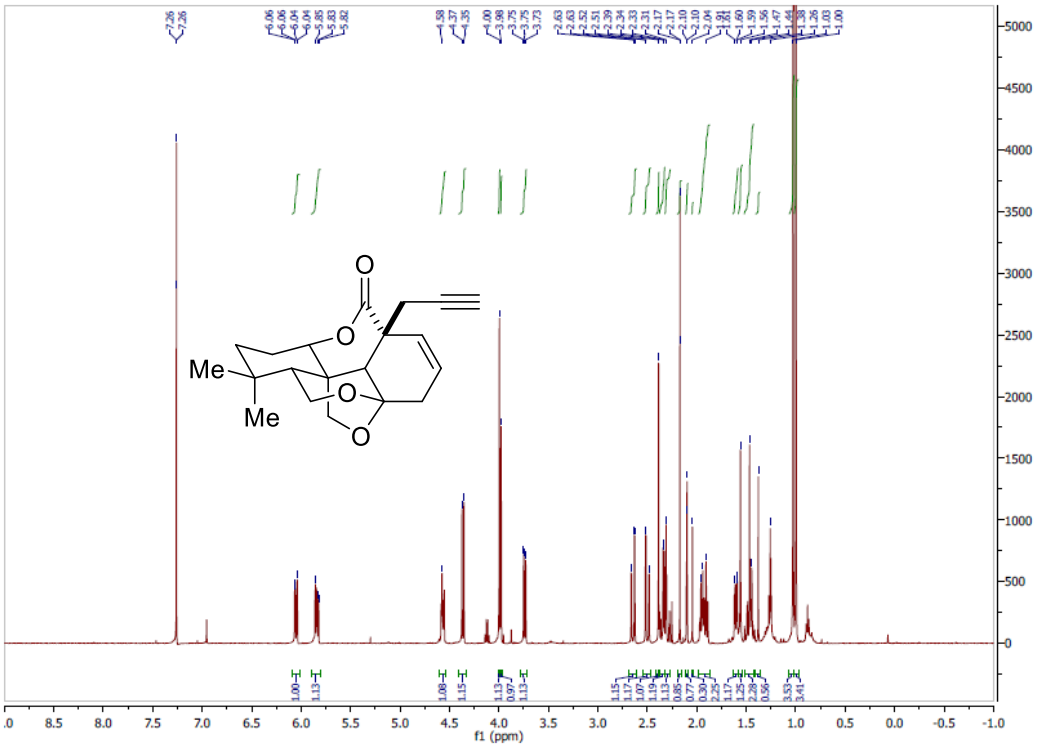


Figure SI.34 ^{1}H NMR spectrum of **5** in $CDCl_3$

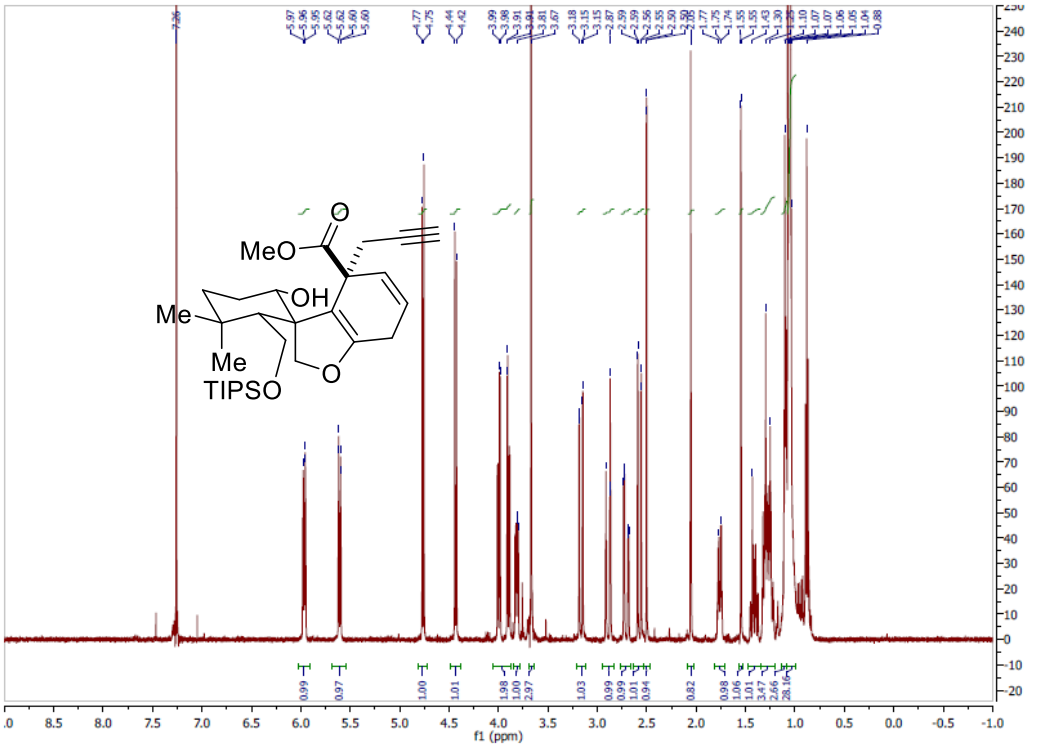


Figure SI.35 ^{1}H NMR spectrum of **5** in C_6D_6

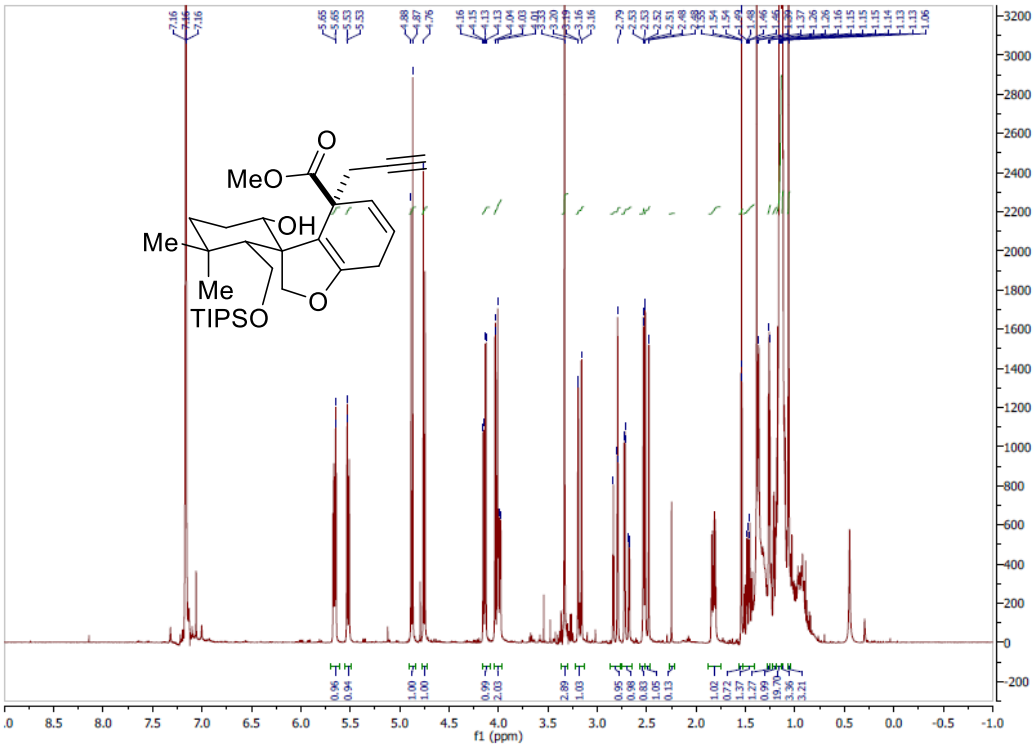


Figure SI.36 ^{1}H NMR spectrum of **23** in $CDCl_3$

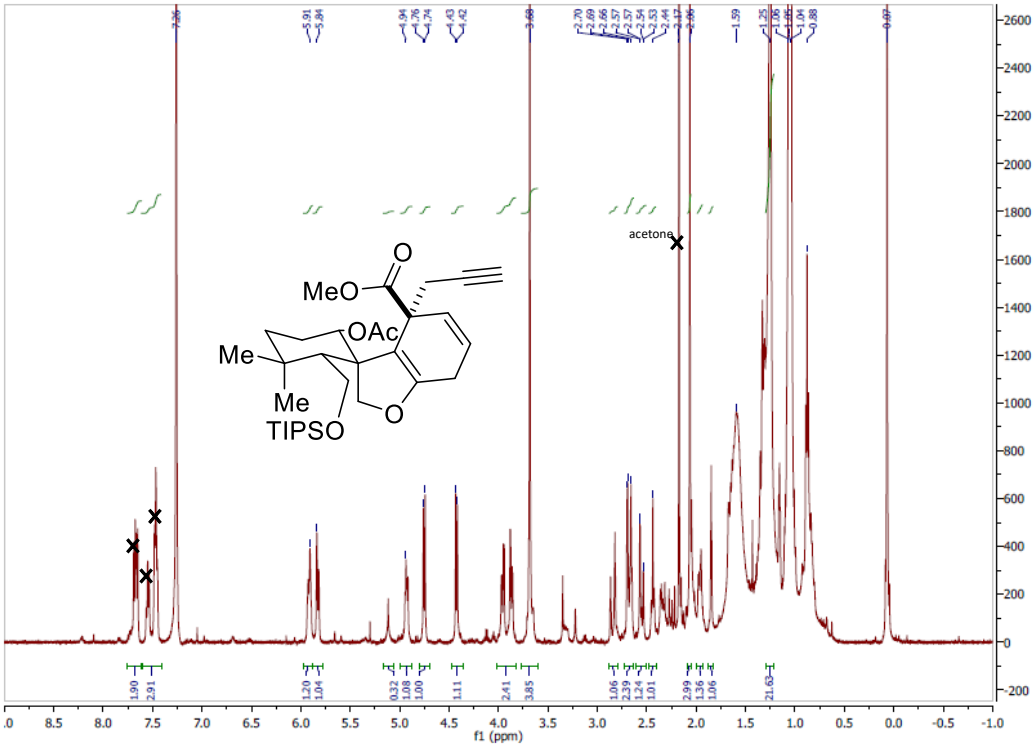


Figure SI.37 ^{1}H NMR spectrum of **24** in $CDCl_3$

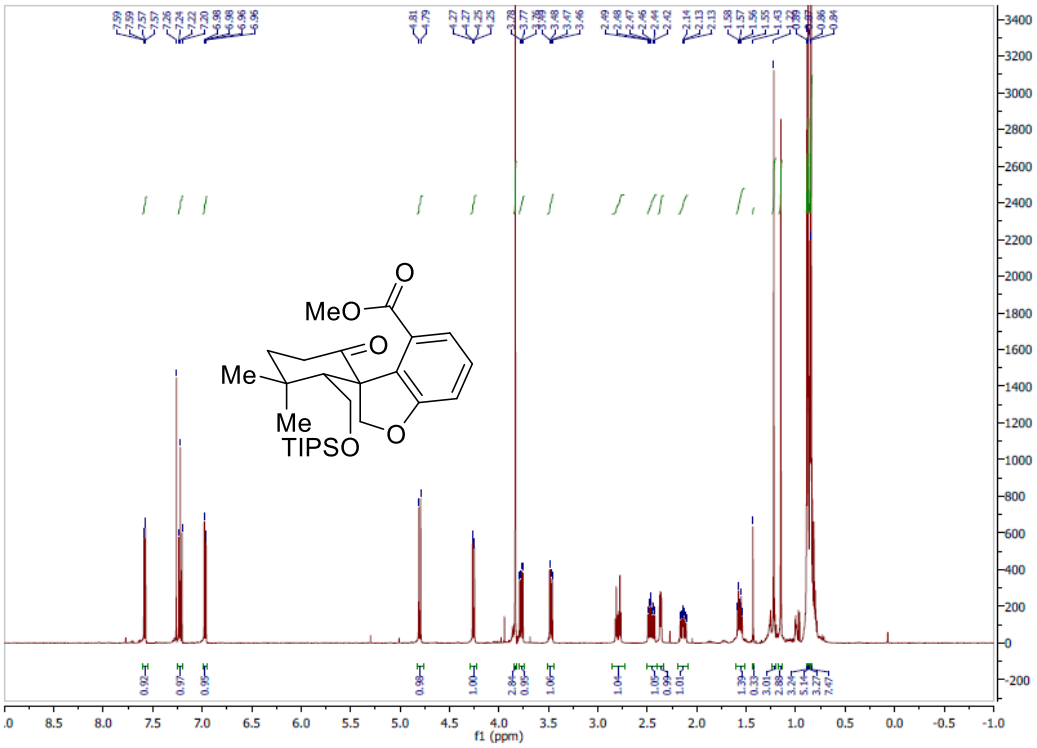


Figure SI.38 ^{1}H NMR spectrum of **25** in $CDCl_3$

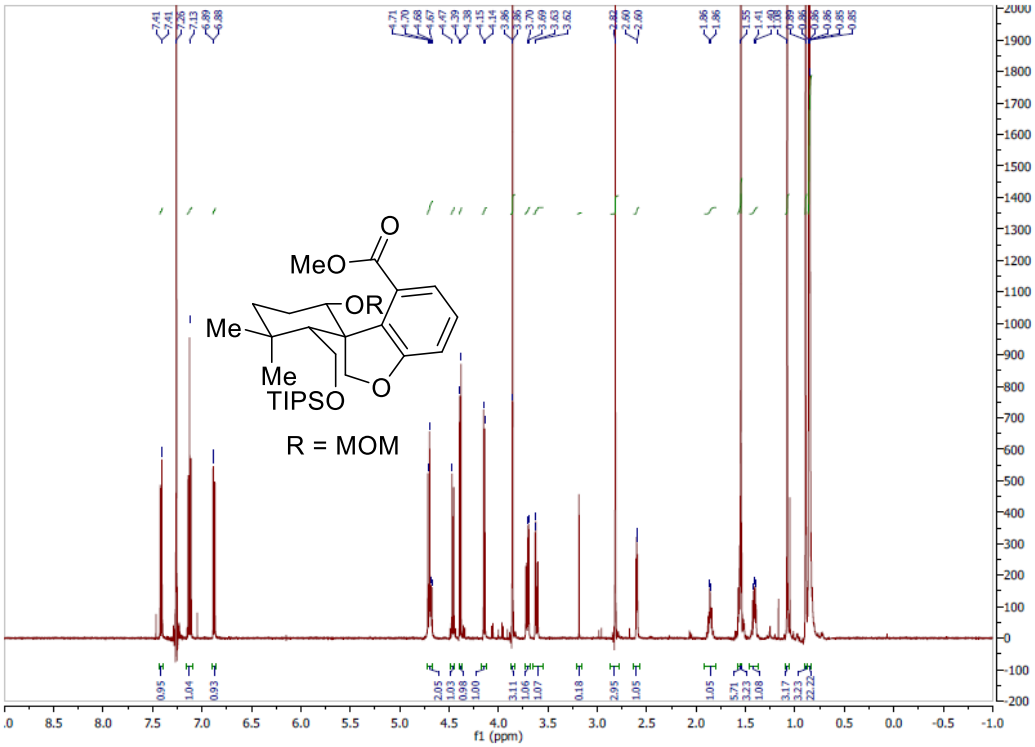


Figure SI.39 ^{1}H NMR spectrum of **26** in $CDCl_3$

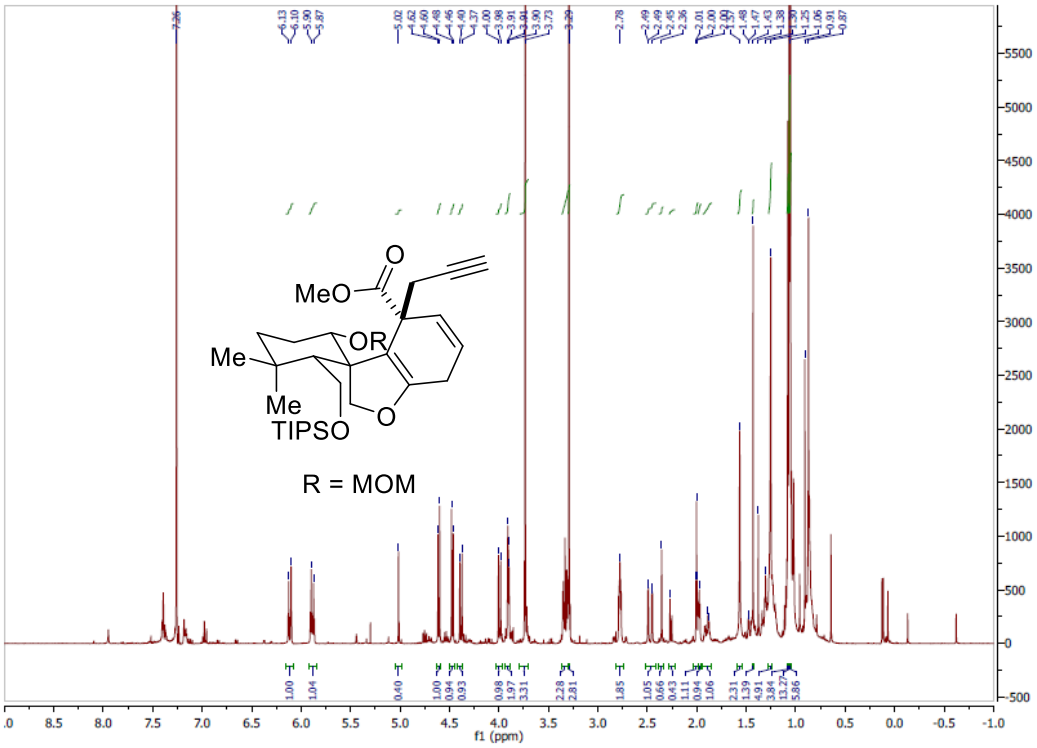


Figure SI.40 ^{1}H NMR spectrum of **26'** in $CDCl_3$

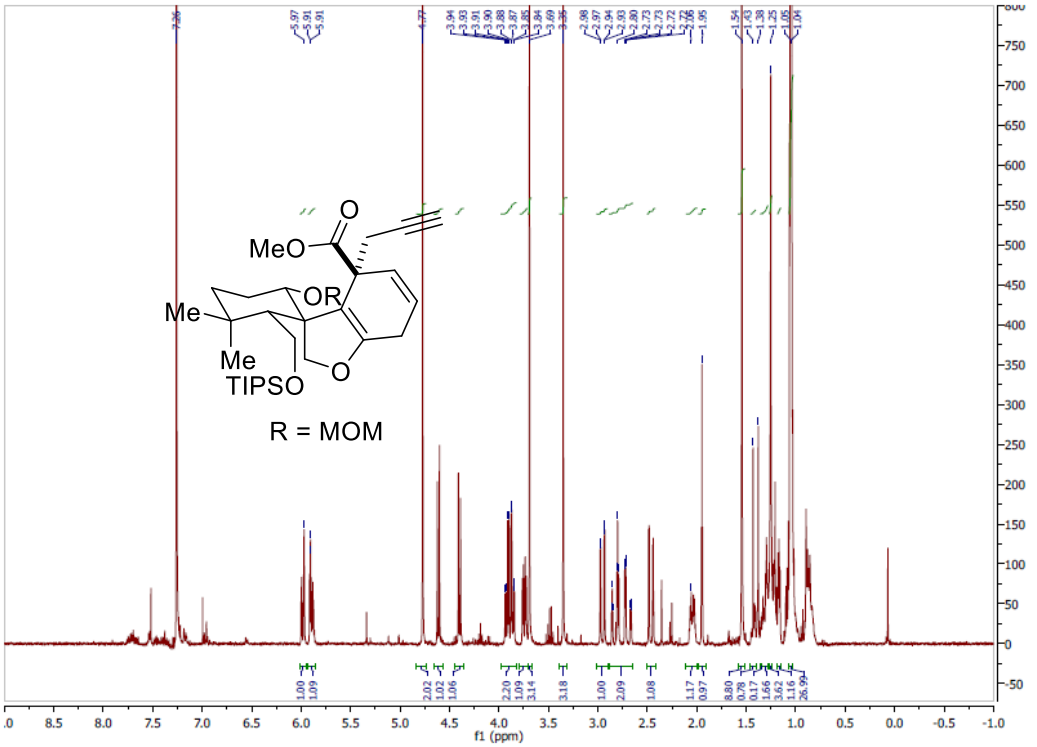


Figure SI.41 ^{1}H NMR spectrum of **SI-7** in $CDCl_3$

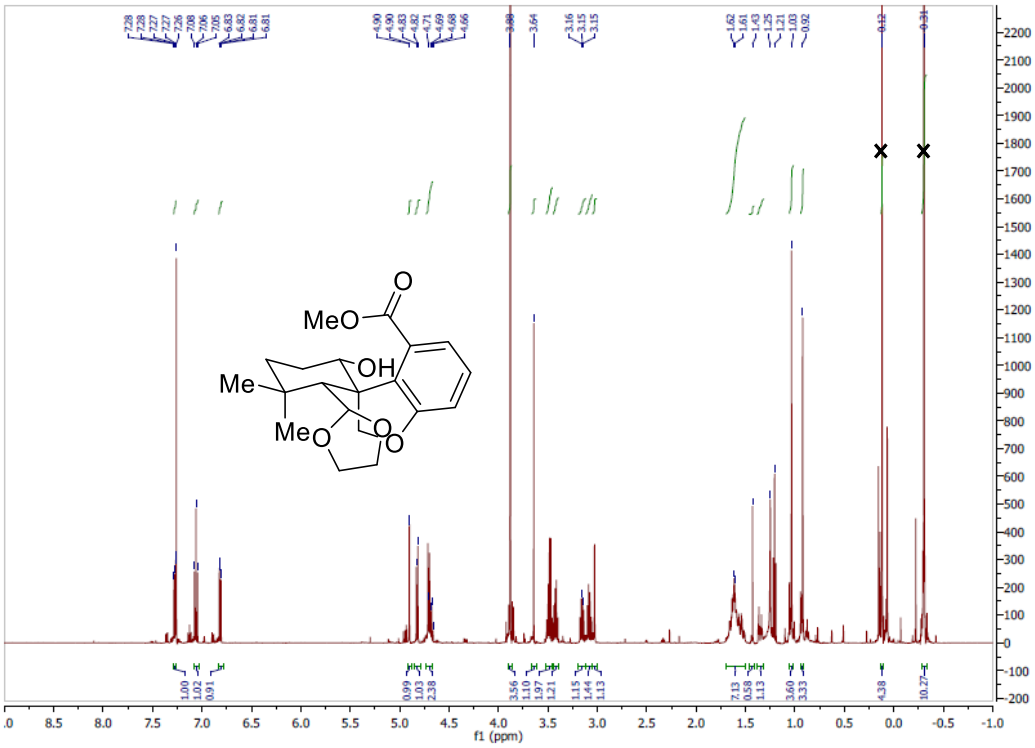


Figure SI.42 ^{1}H NMR spectrum of **27** in $CDCl_3$

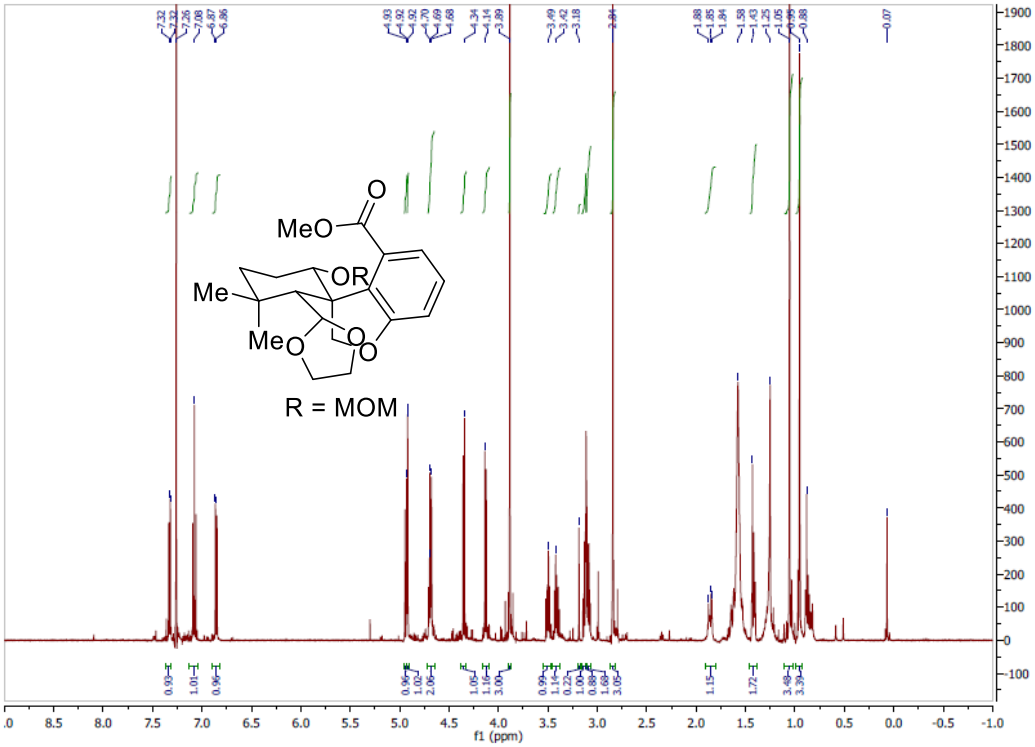


Figure SI.43 ^{1}H NMR spectrum of **28** in $CDCl_3$

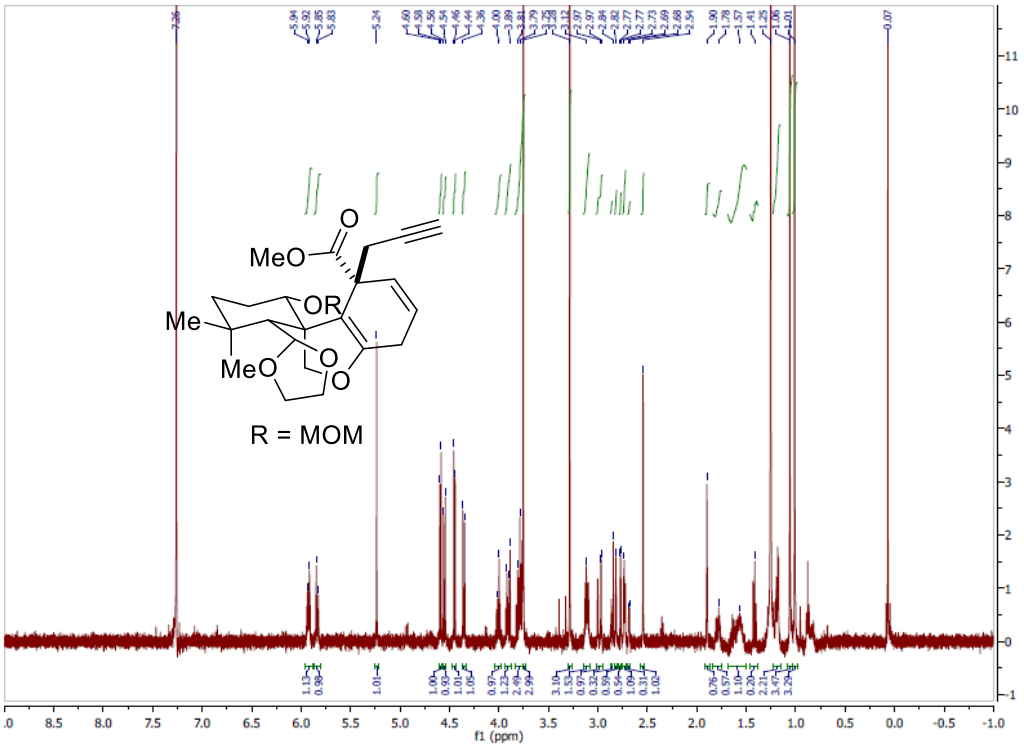


Figure SI.44 nOe spectrum of **28** in $CDCl_3$

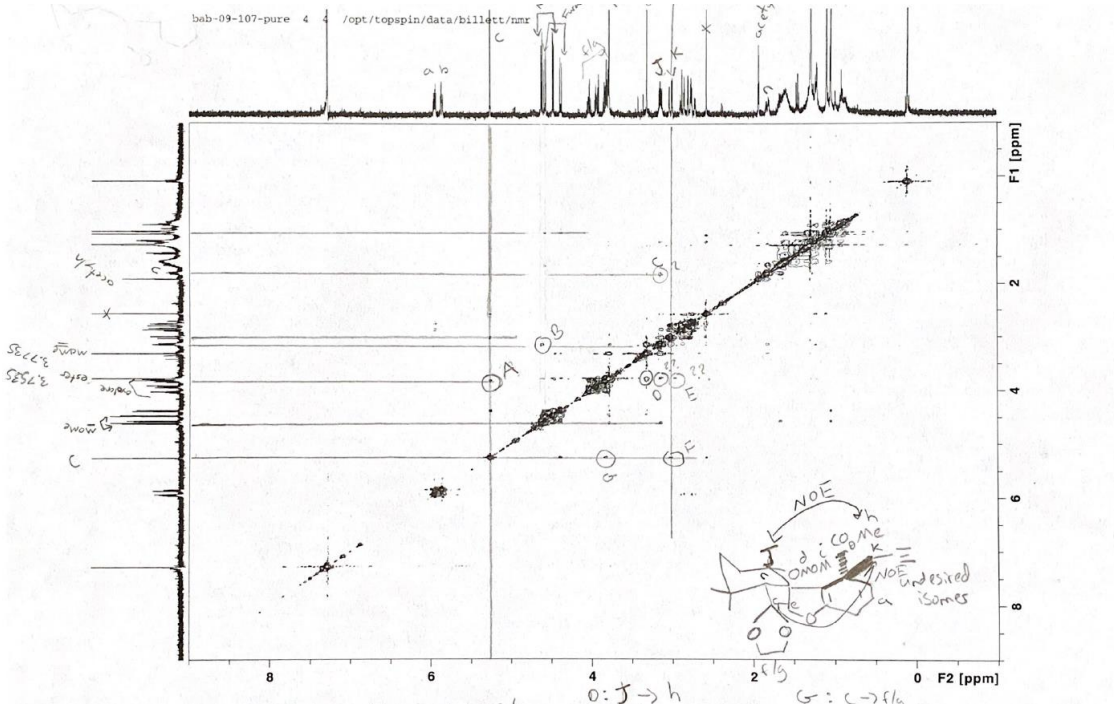


Figure SI.45 ^{1}H NMR spectrum of **30** in $CDCl_3$

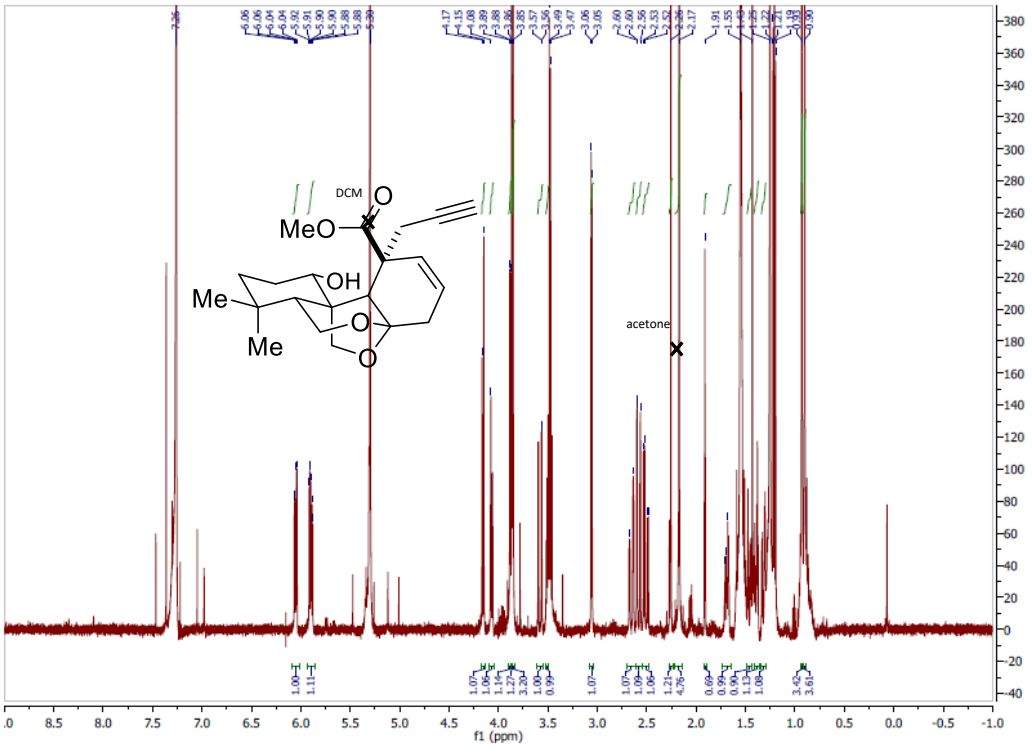


Figure SI.46 ^{1}H NMR spectrum of **30'** in $CDCl_3$

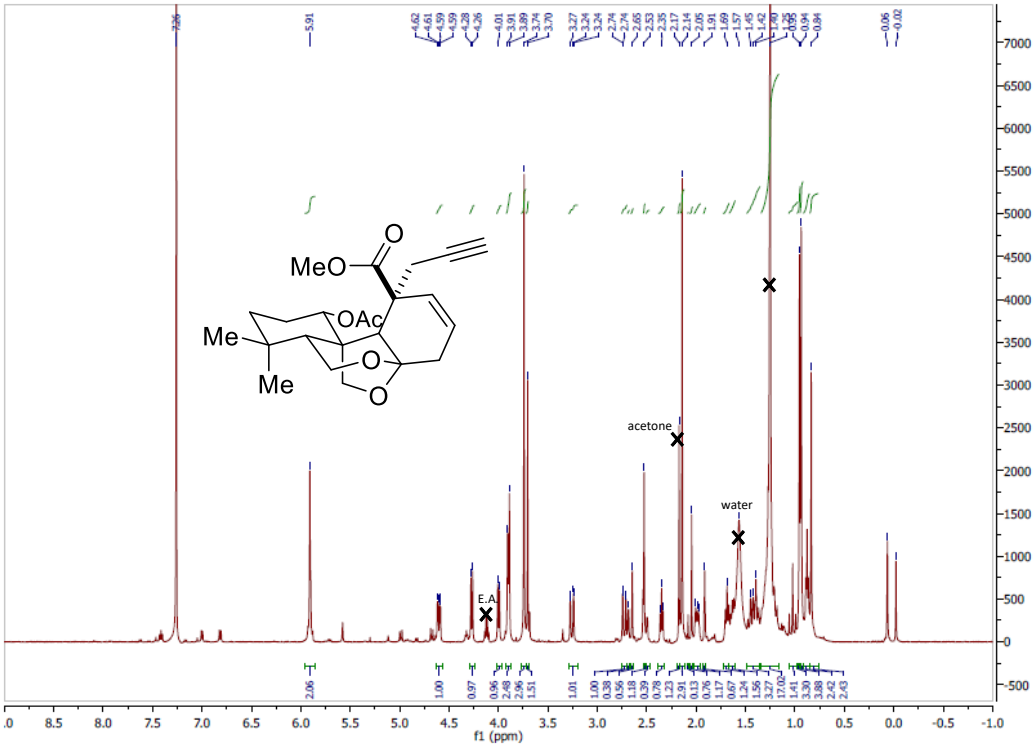


Figure SI.47 ^{1}H NMR spectrum of **31** in $CDCl_3$

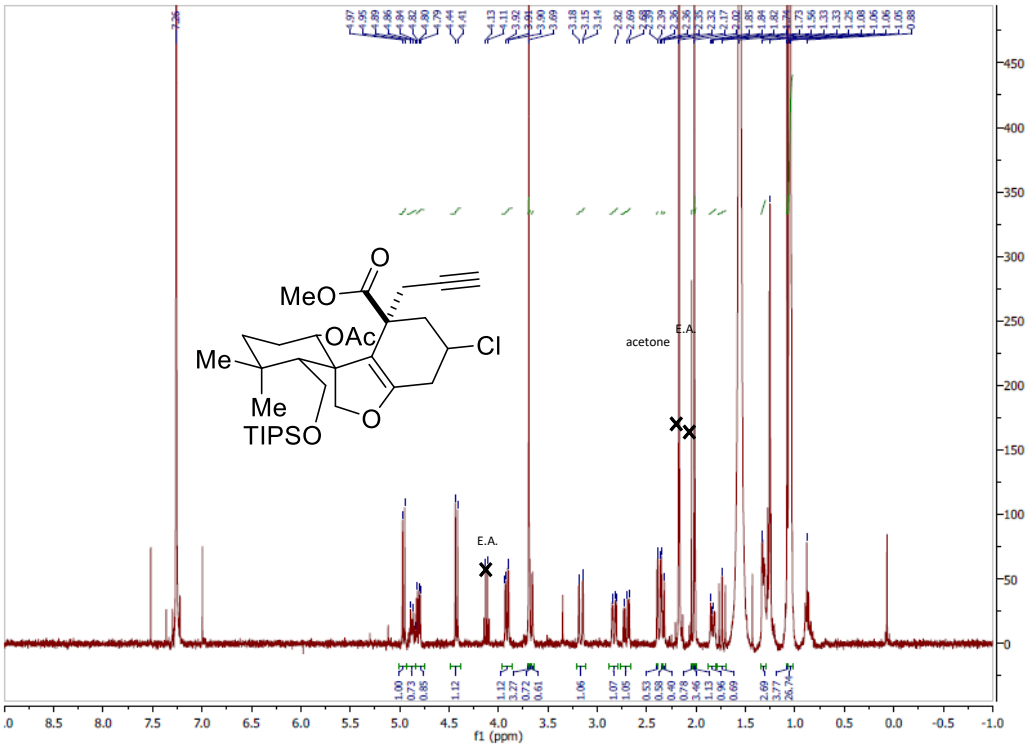


Figure SI.48 ^{1}H NMR spectrum of **32** in $CDCl_3$

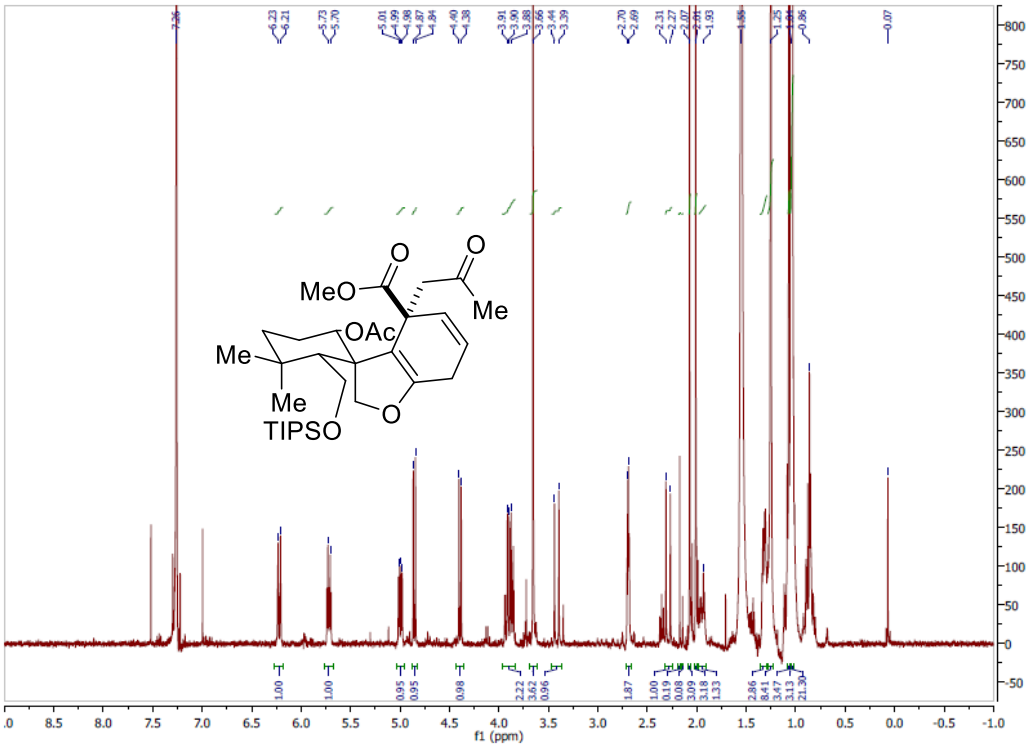


Figure SI.49 ^{1}H NMR spectrum of **33** in $CDCl_3$

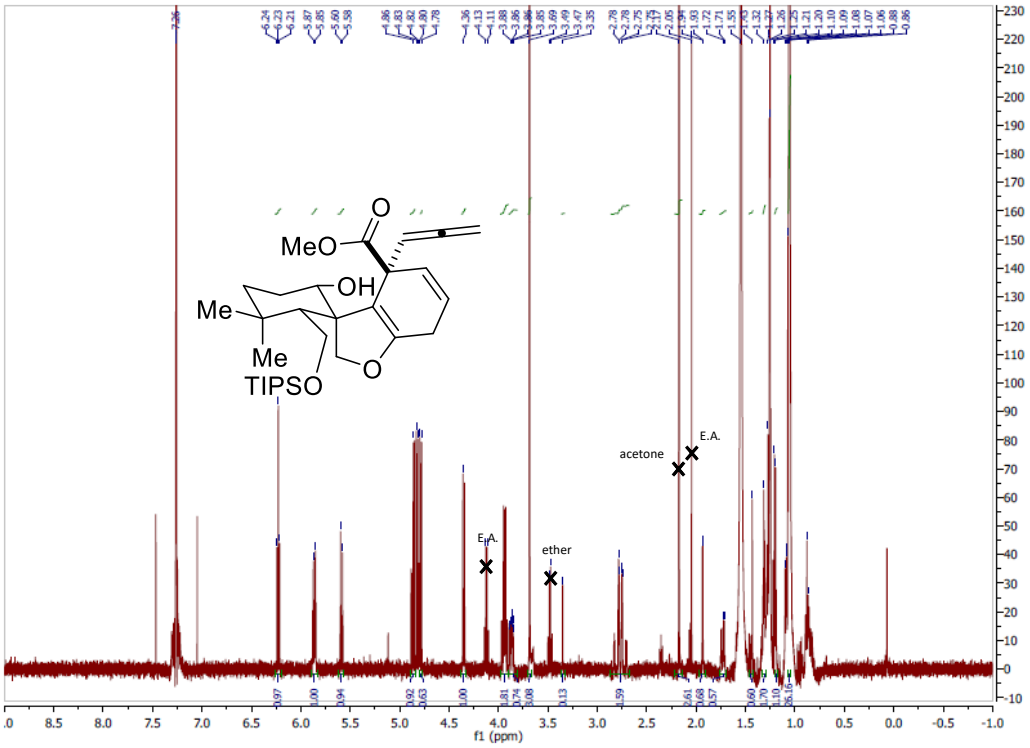


Figure SI.50 ^{1}H NMR spectrum of **34** in $CDCl_3$

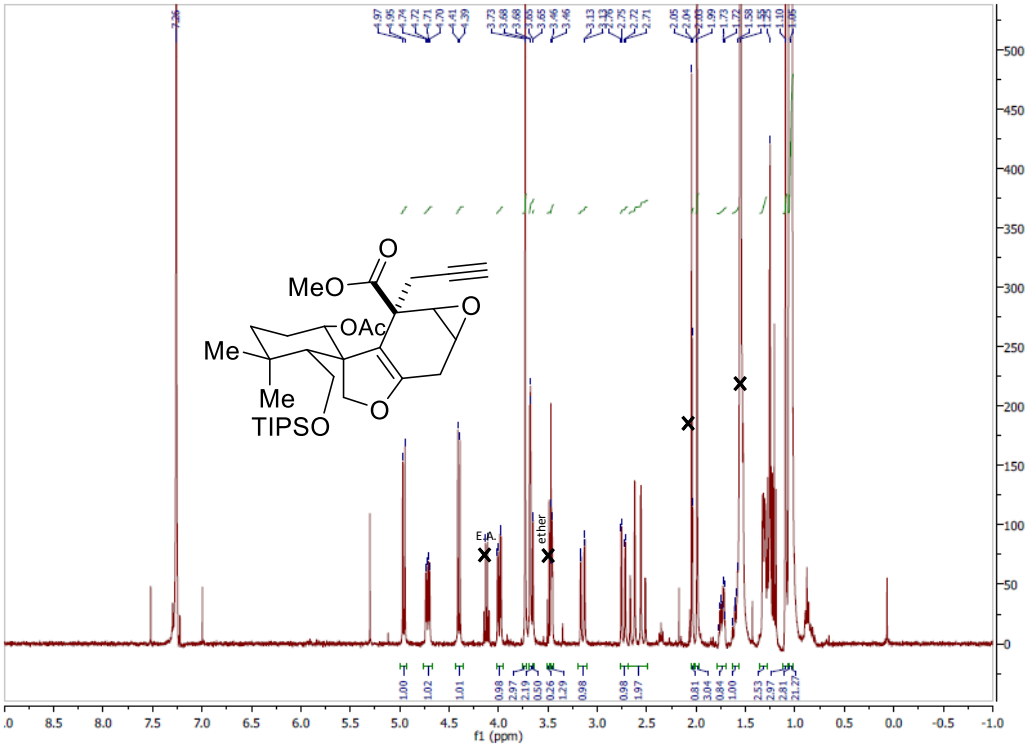


Figure SI.51 ^{1}H NMR spectrum of **35** in $CDCl_3$

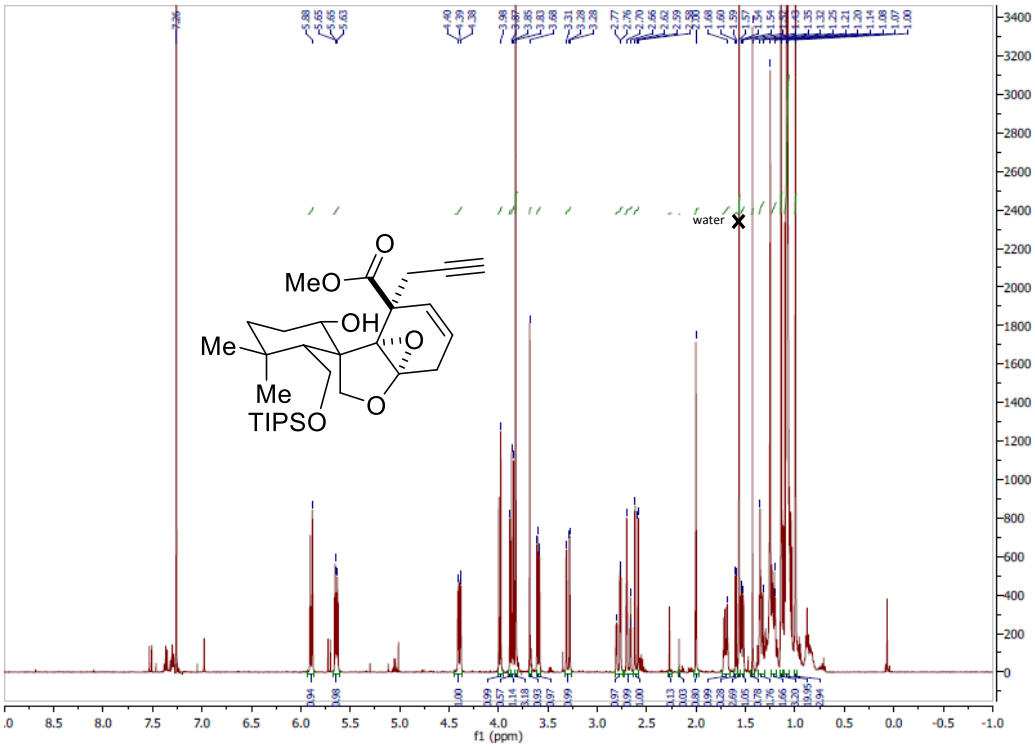


Figure SI.52 ^{1}H NMR spectrum of **36** in $CDCl_3$

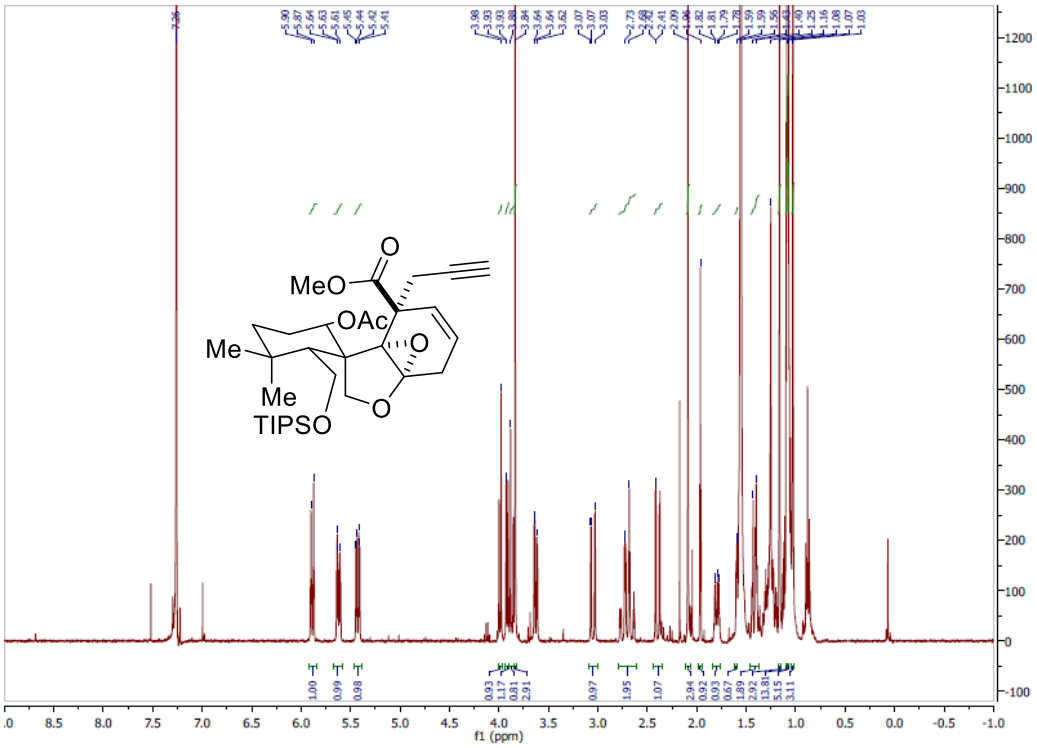


Figure SI.53 ^{1}H NMR spectrum of **37** in $CDCl_3$

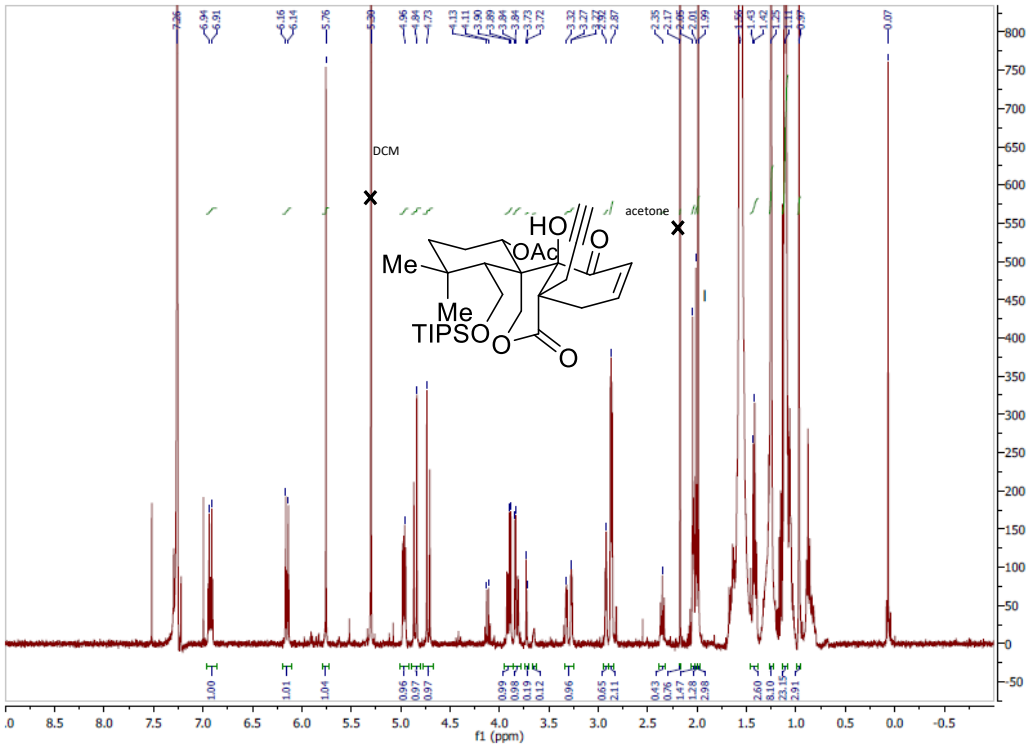


Figure SI.54 ^{1}H NMR spectrum of **39** in $CDCl_3$

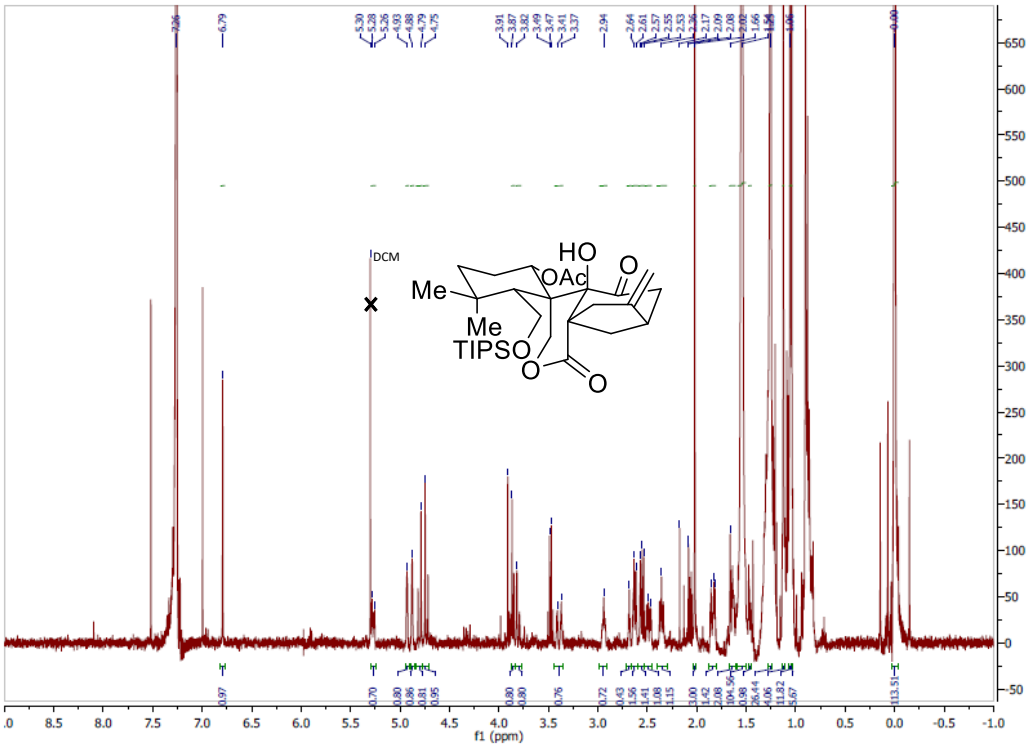


Figure SI.55 ^{1}H NMR spectrum of **SI-8** in C_6D_6

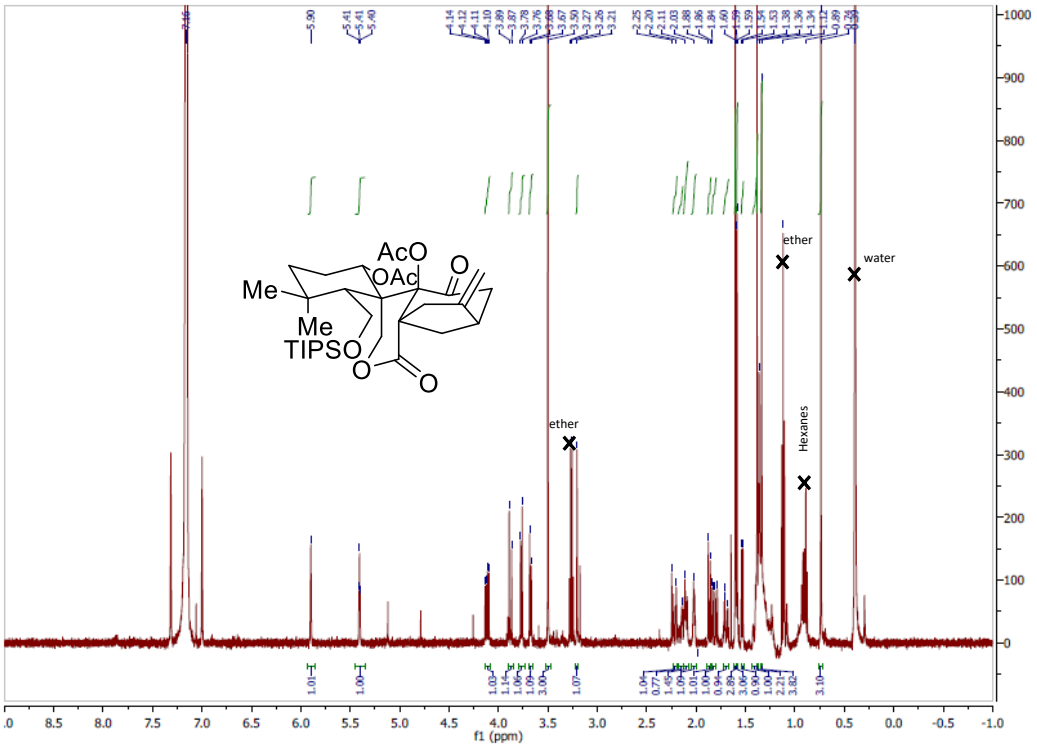


Figure SI.56 ^{1}H NMR spectrum of **3** in C_6D_6

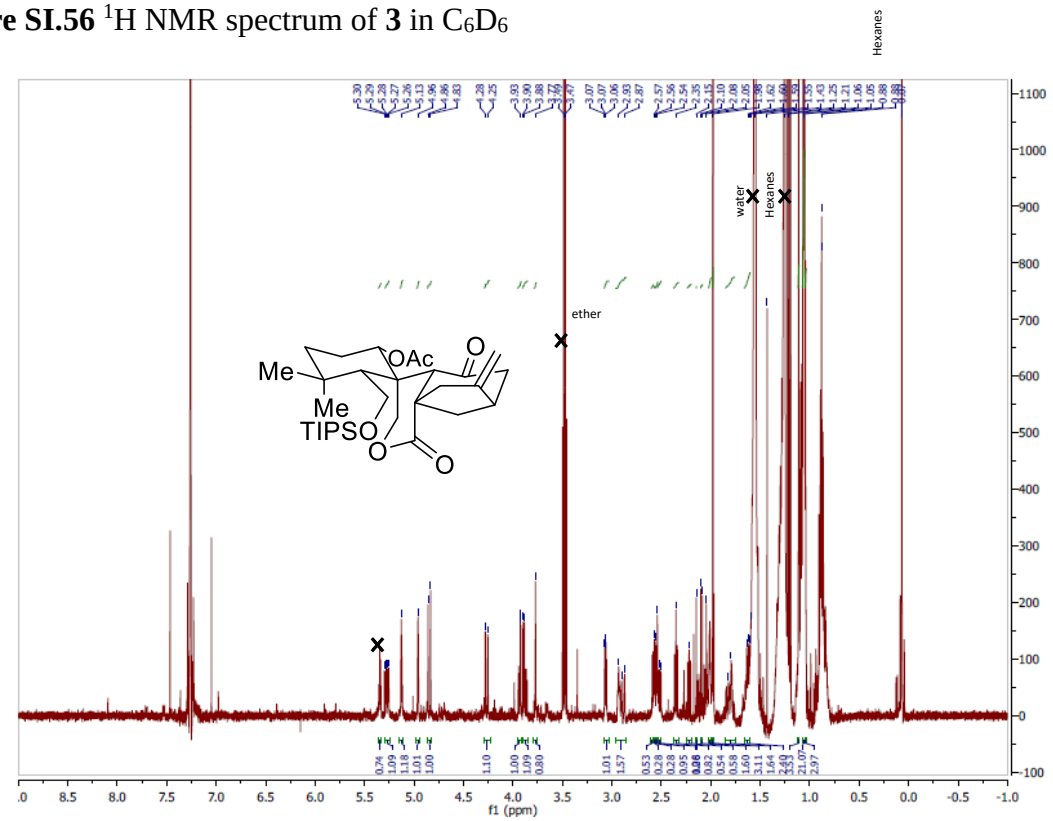


Figure SI.57 ^{1}H NMR spectrum of **40** in $CDCl_3$

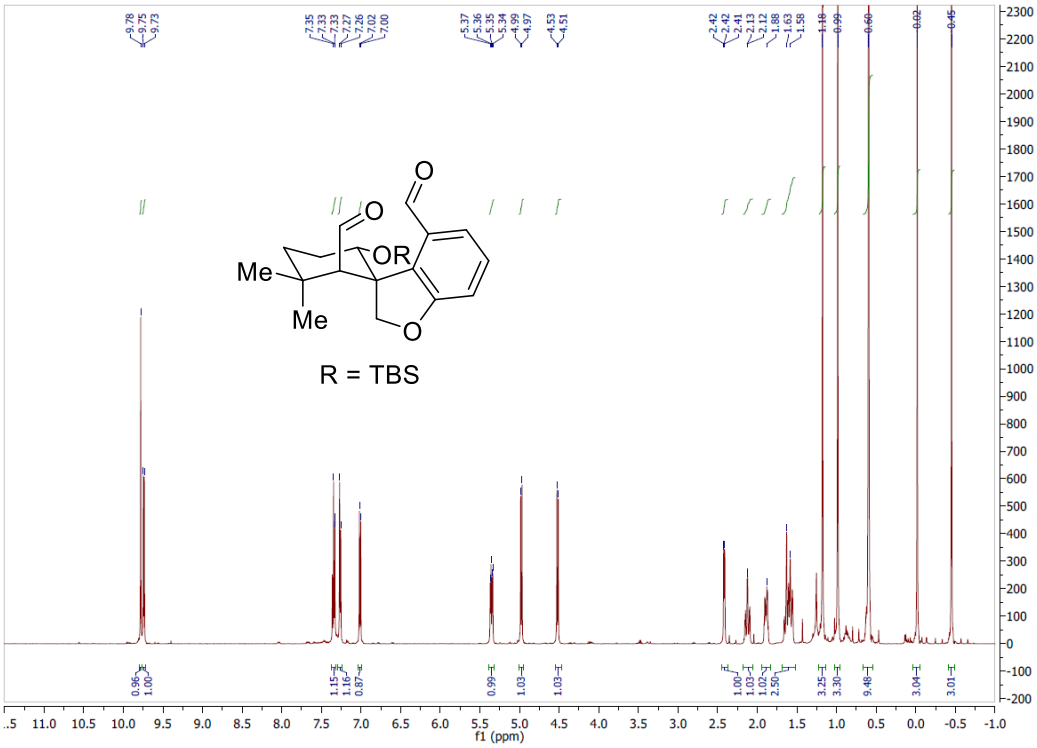


Figure SI.58 ^{13}C NMR spectrum of **40** in $CDCl_3$

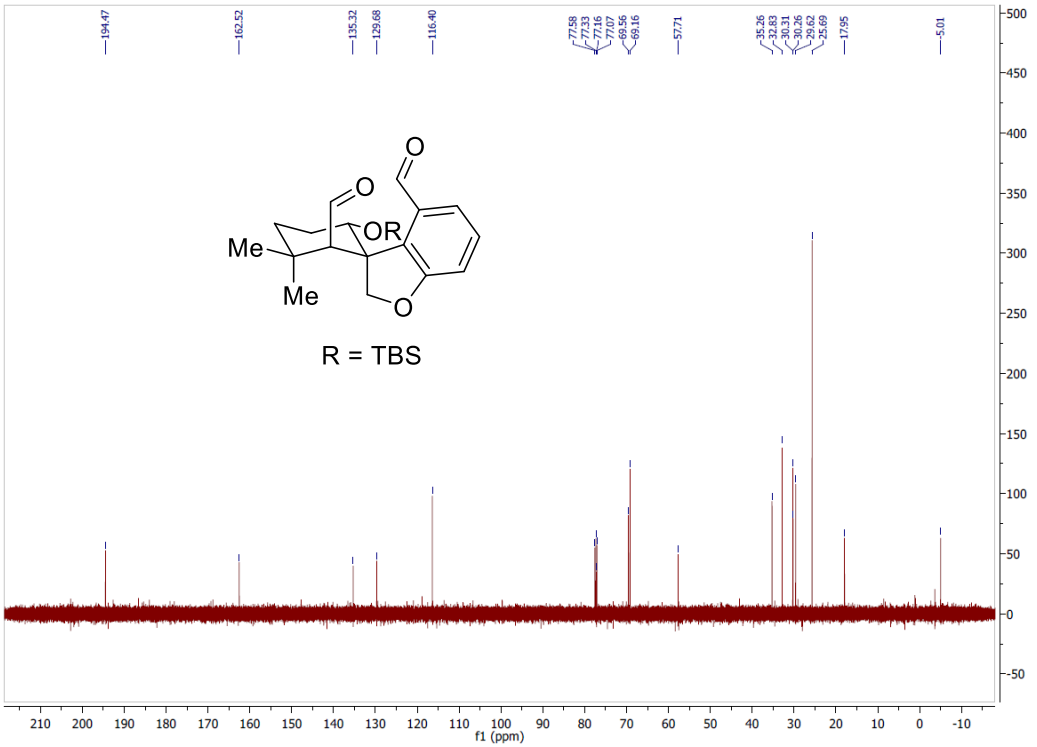


Figure SI.59 ^{1}H NMR spectrum of **44a** in $CDCl_3$

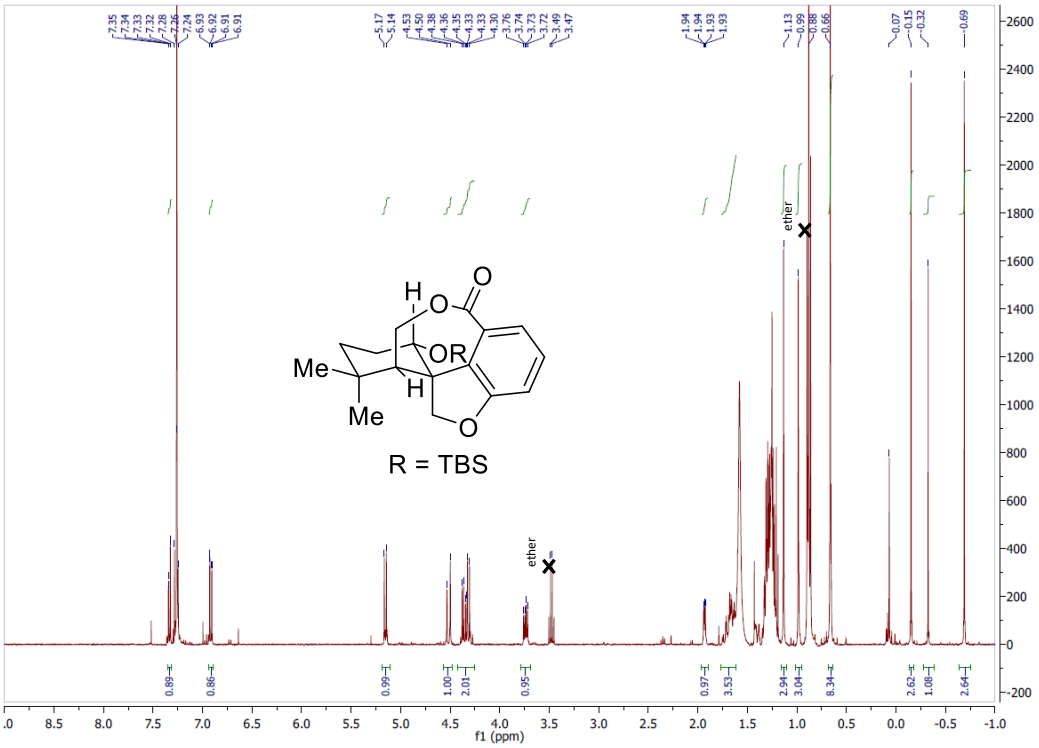


Figure SI.60 ^{1}H NMR spectrum of **44b** in $CDCl_3$

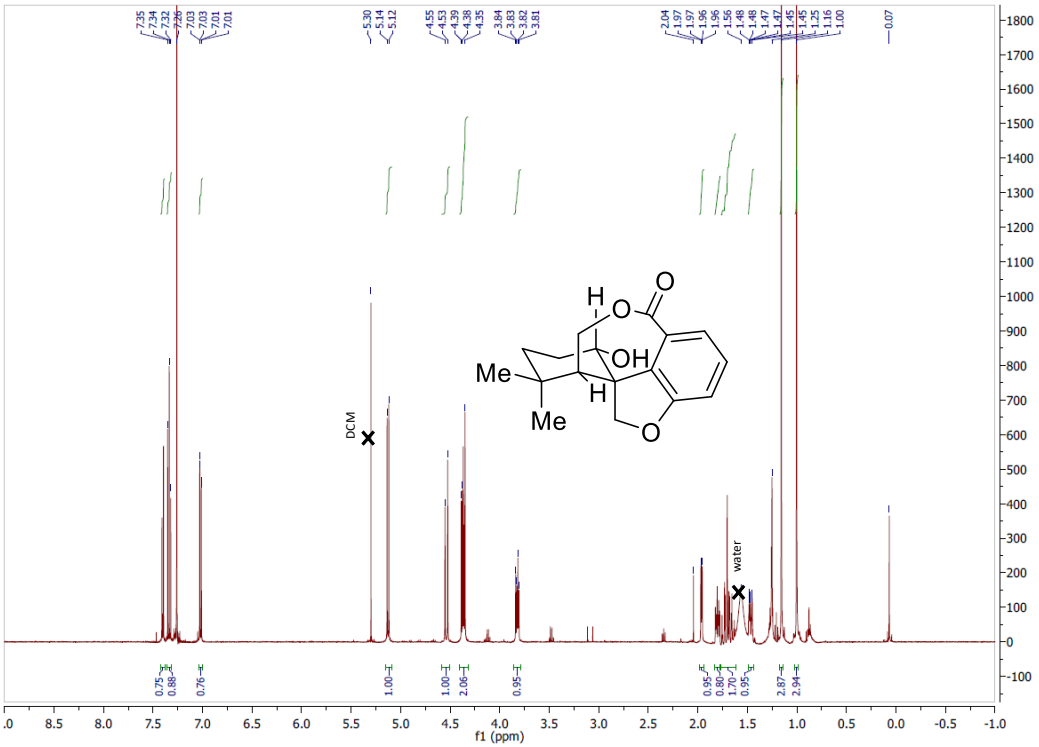


Figure SI.61 ^{1}H NMR spectrum of **44c** in $CDCl_3$

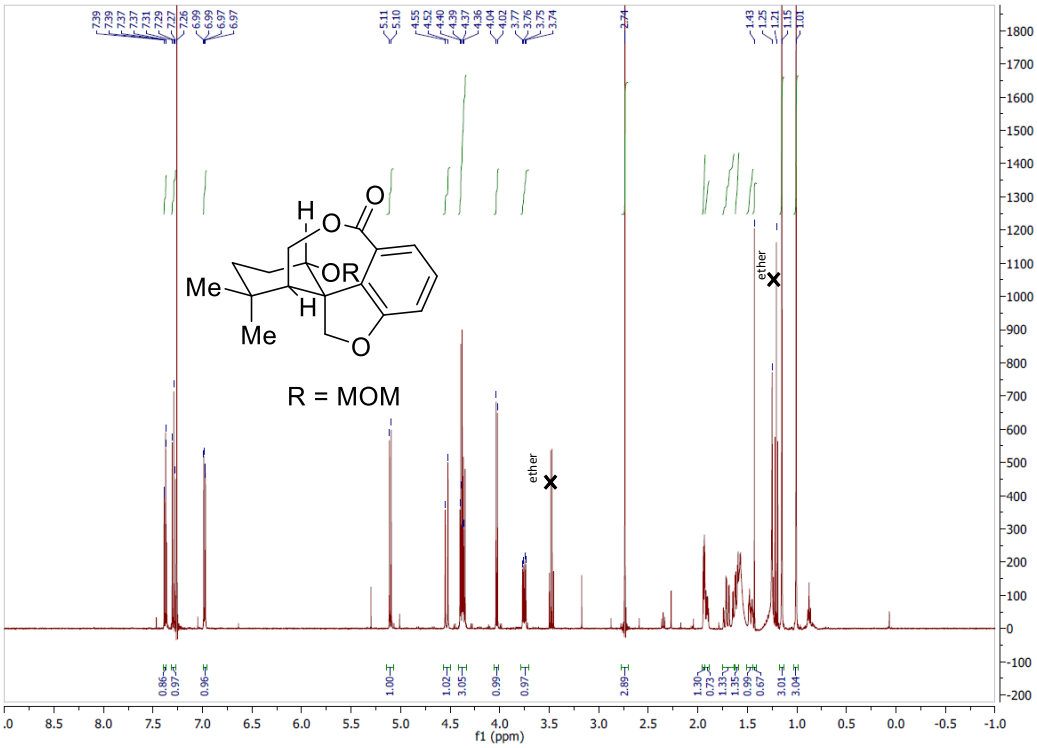


Figure SI.62 ^{1}H NMR spectrum of **45a** in $CDCl_3$

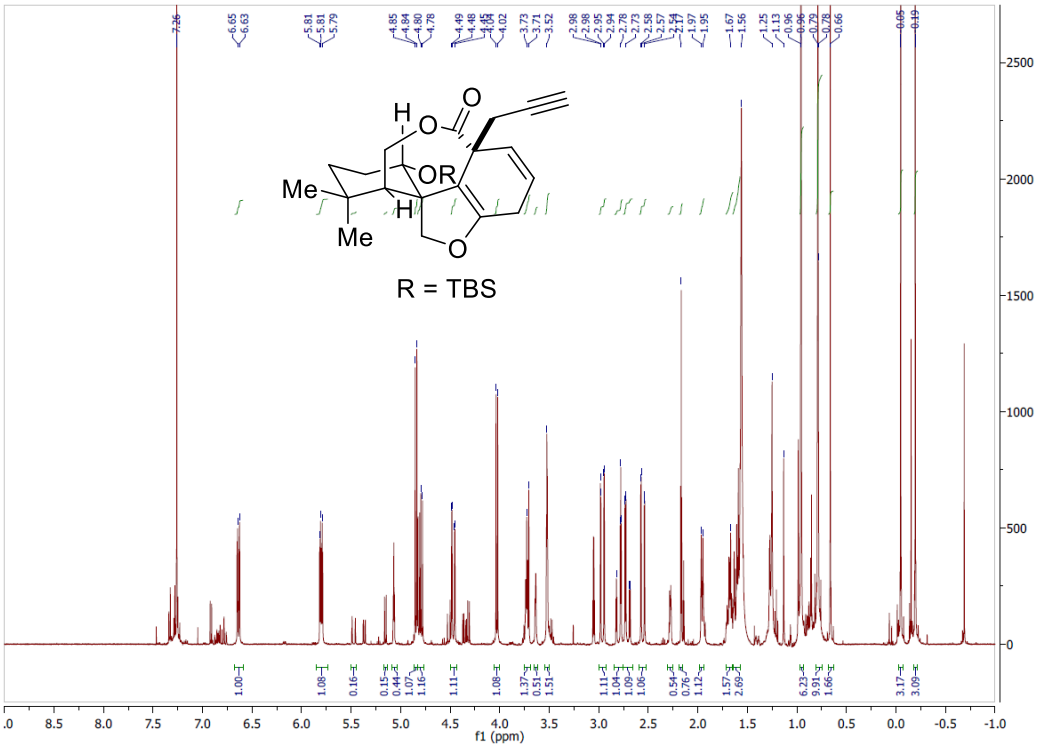


Figure SI.63 nOe spectrum of **45a** in $CDCl_3$

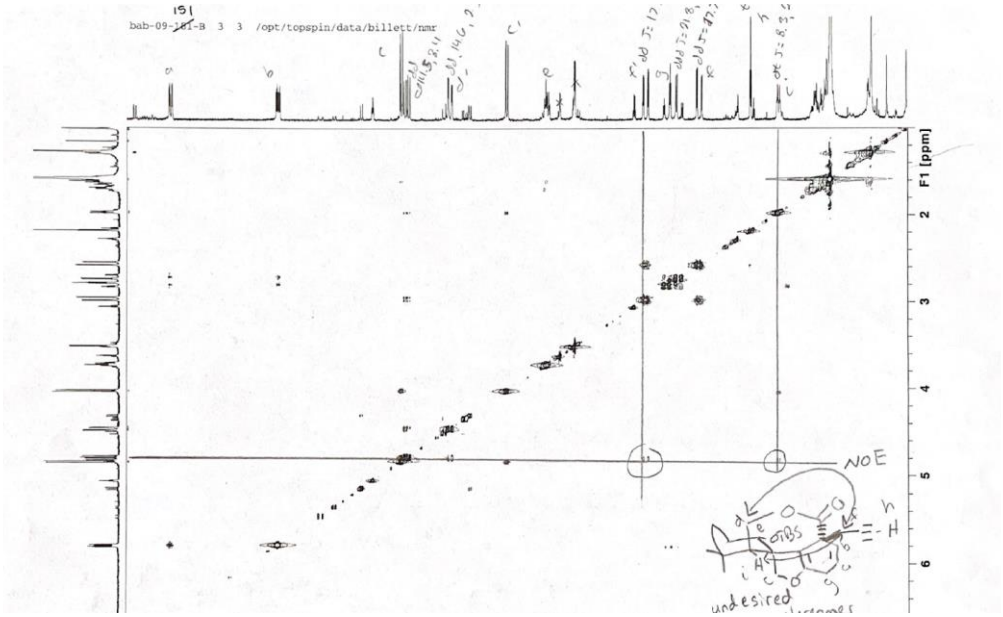


Figure SI.64 ^{1}H NMR spectrum of **45b** in $CDCl_3$

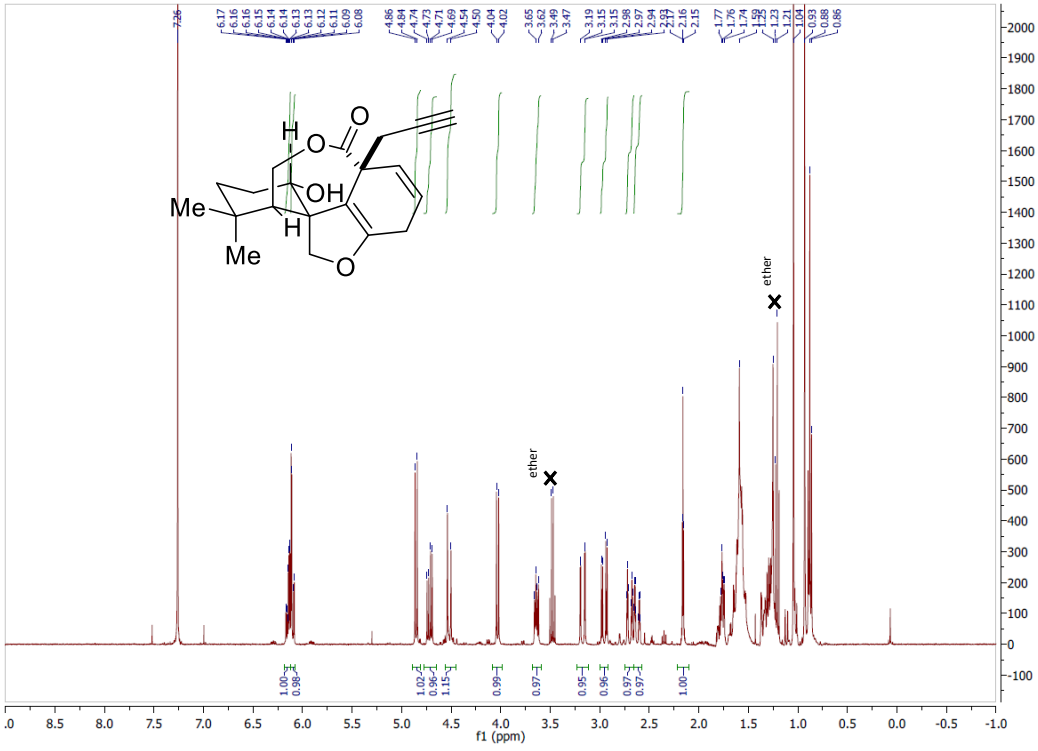


Figure SI.65 nOe spectrum of **45b** in $CDCl_3$

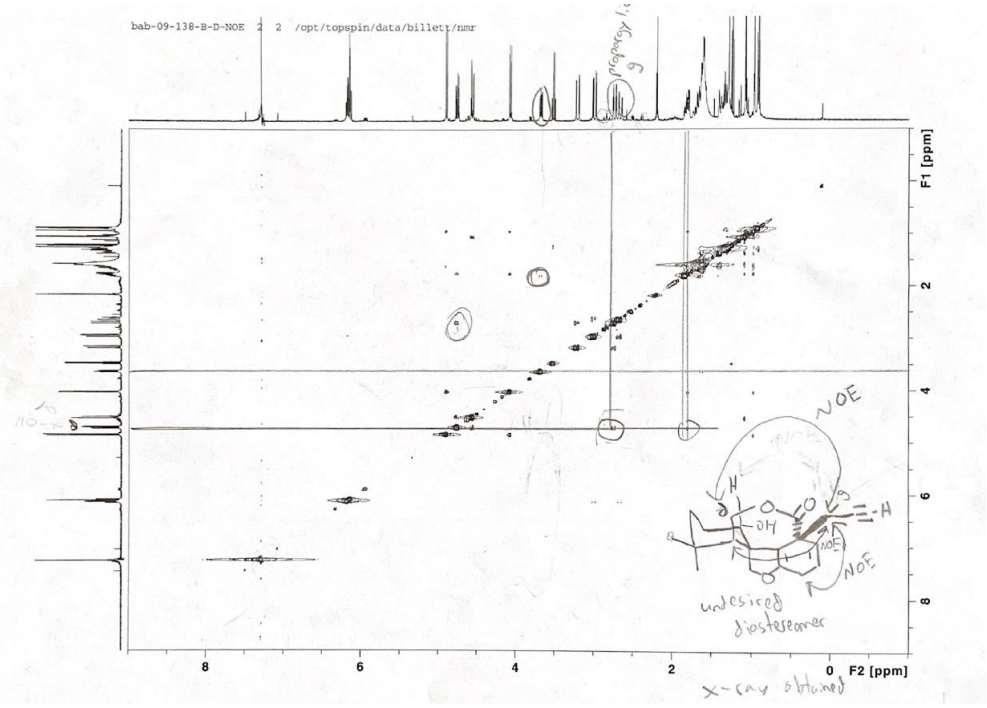


Figure SI.66 ^1H NMR spectrum of **45c** in $CDCl_3$

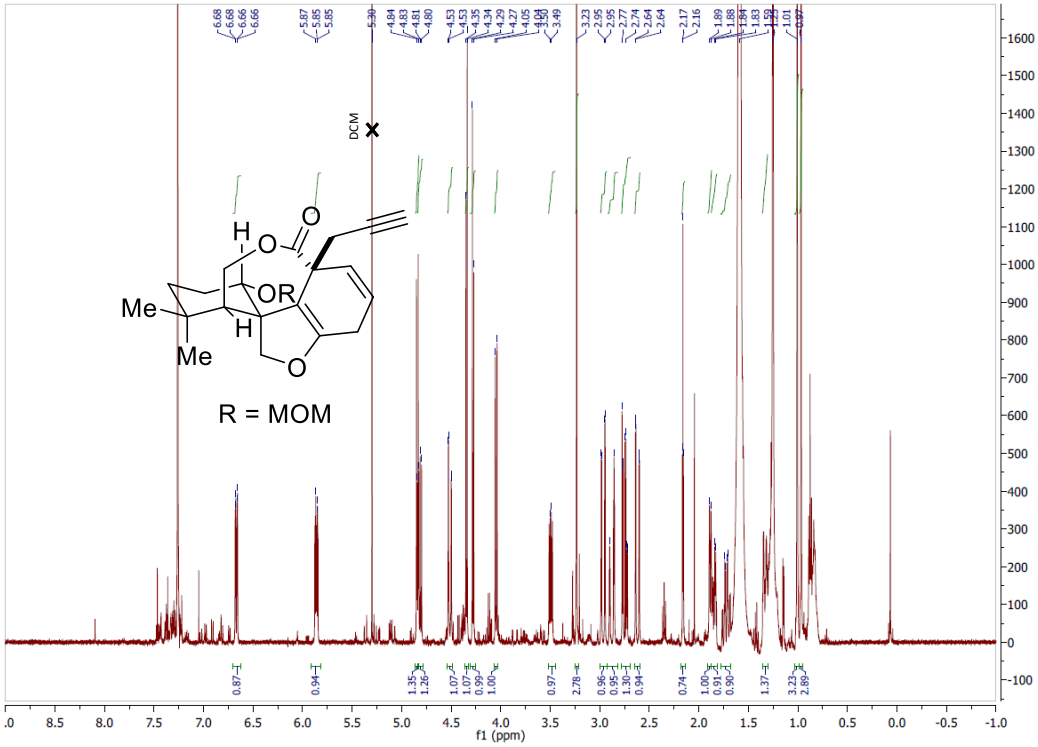


Figure SI.67 nOe spectrum of **45c** in $CDCl_3$

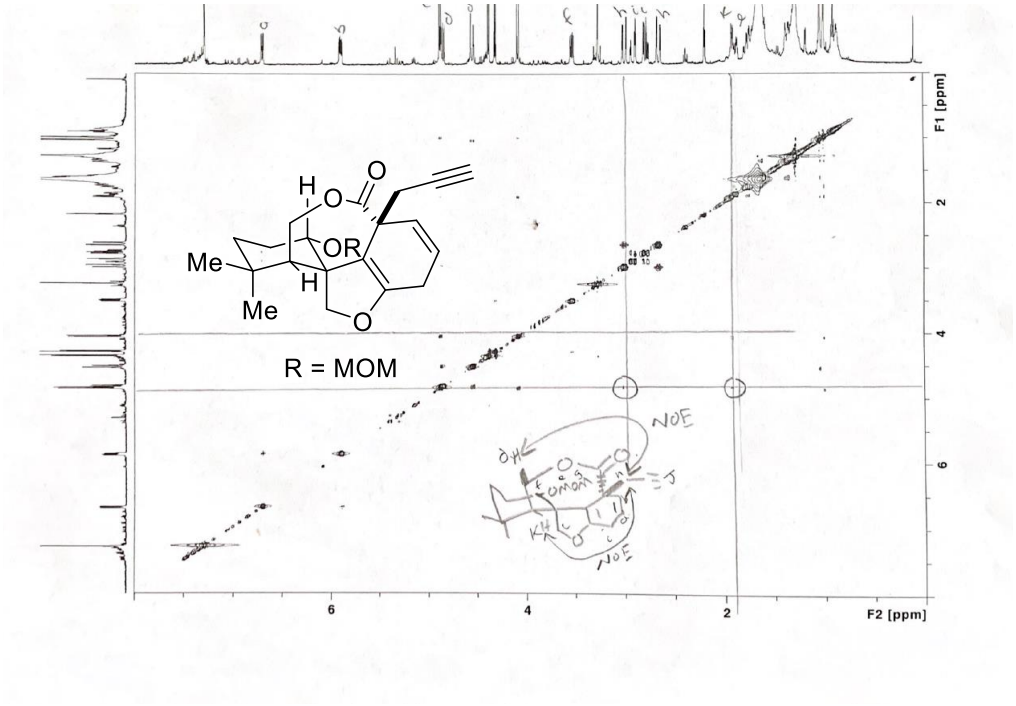


Figure SI.68 ^1H NMR spectrum of **46** in $CDCl_3$

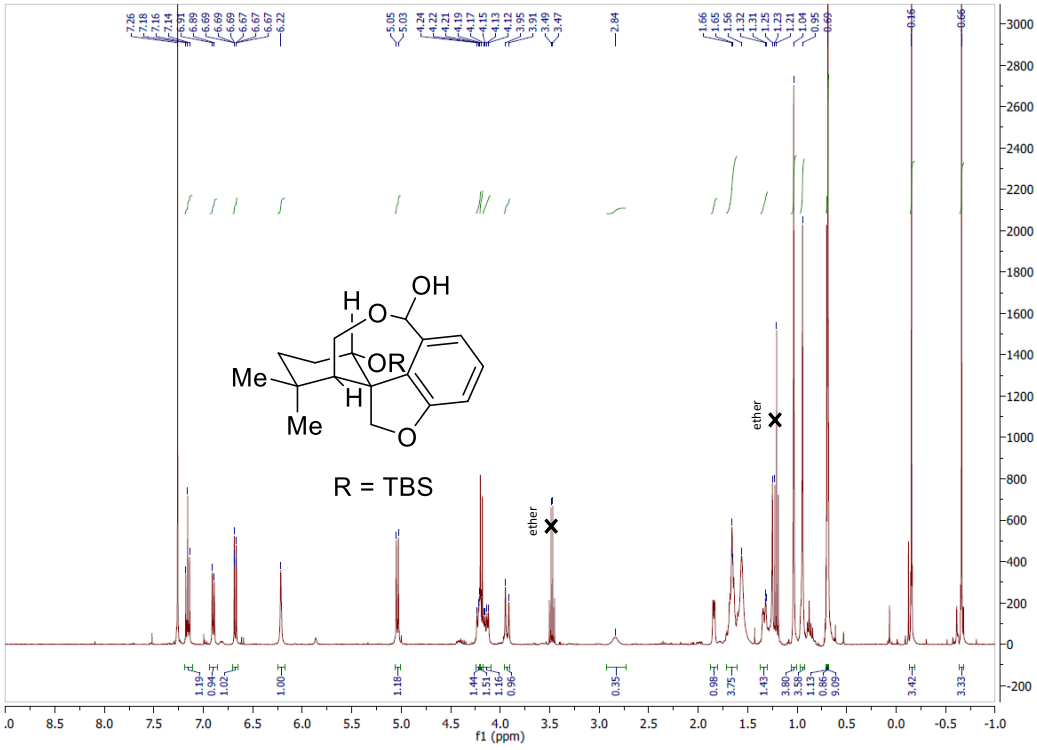


Figure SI.69 ^{1}H NMR spectrum of **47** in $CDCl_3$. Contains **44b** impurity

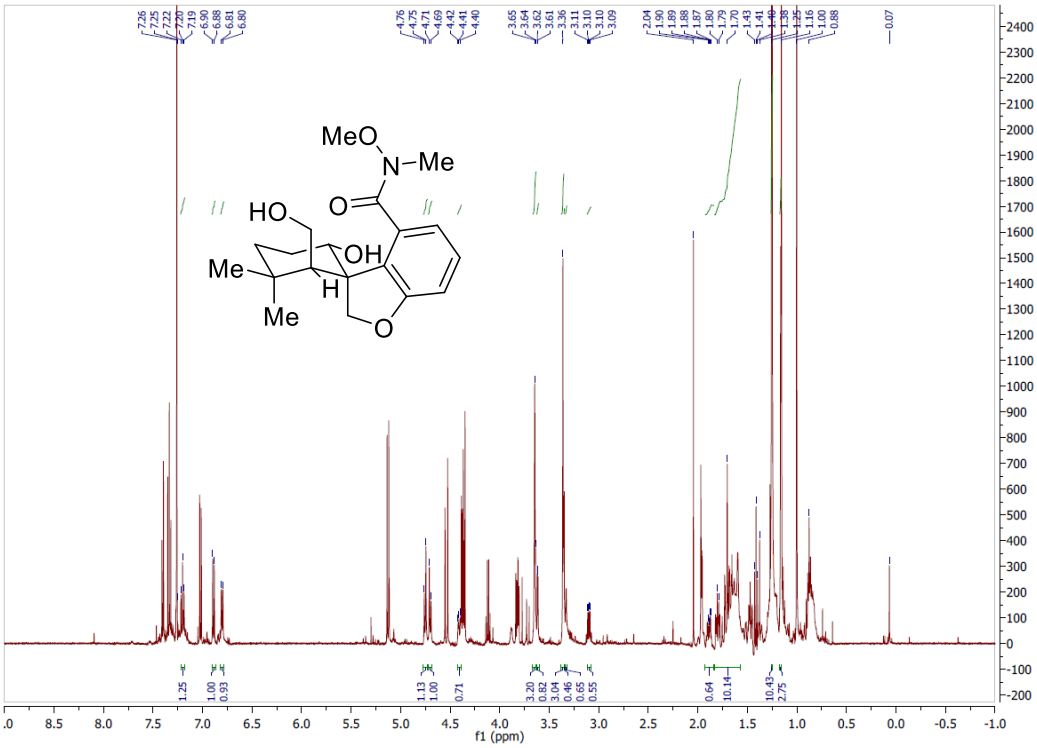


Figure SI.70 ^{1}H NMR spectrum overlay of **47** and **44b** in $CDCl_3$

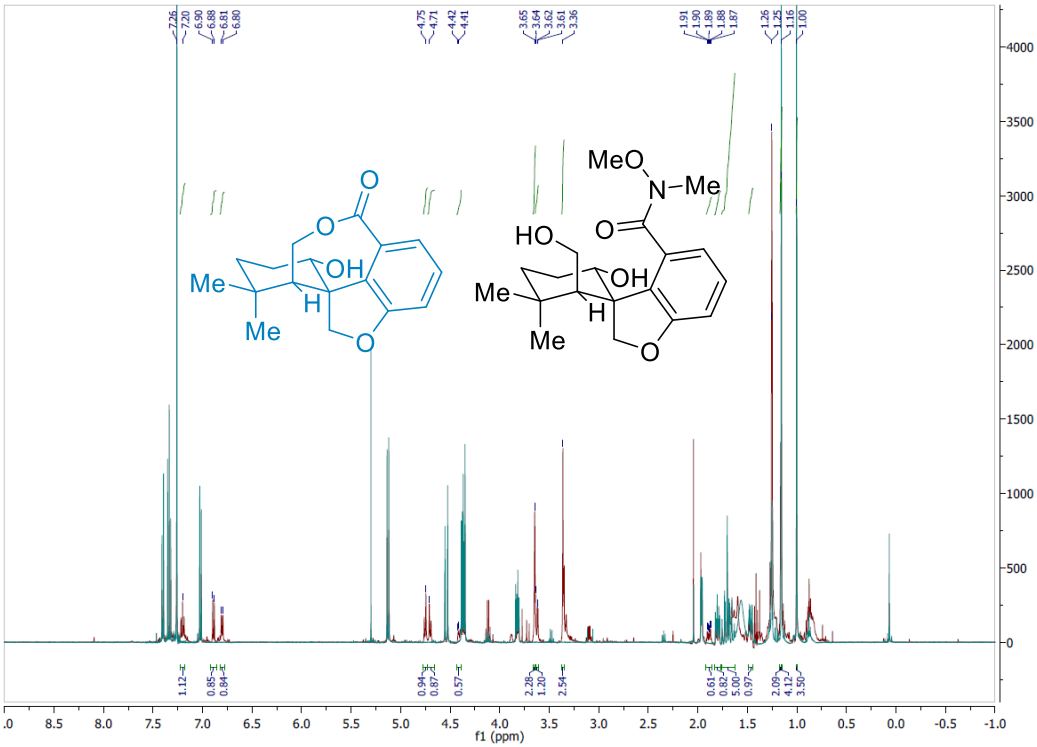


Figure SI.71 ^{1}H NMR spectrum of **48** in $CDCl_3$

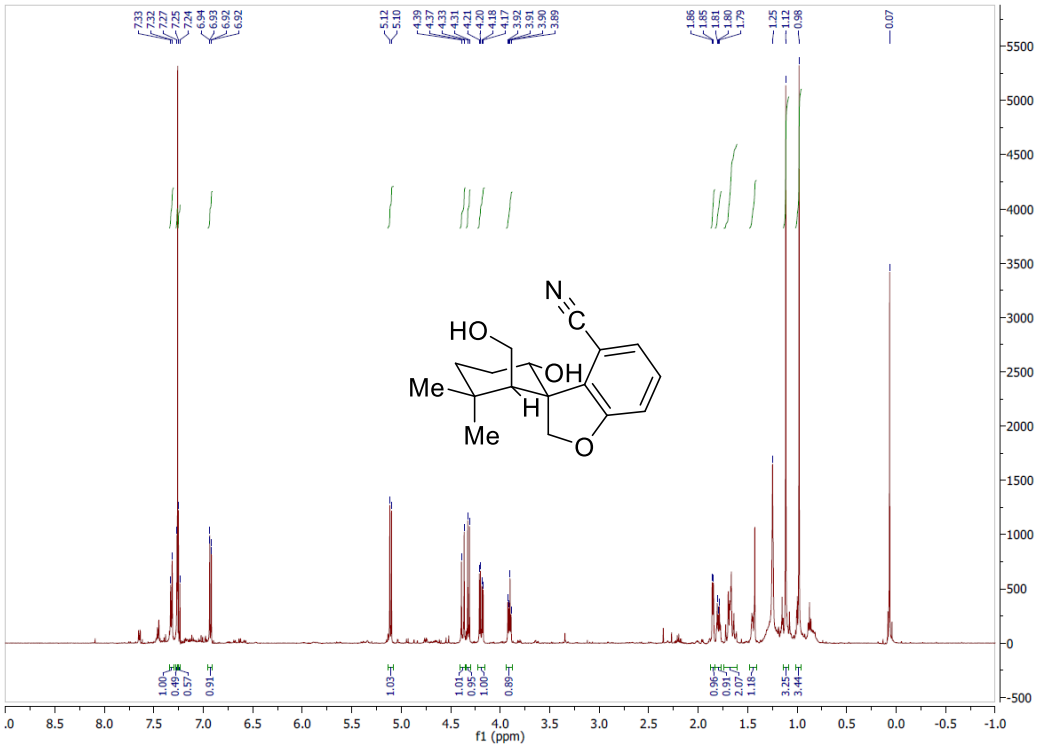


Figure SI.72 ^{1}H NMR spectrum of **49a** in $CDCl_3$

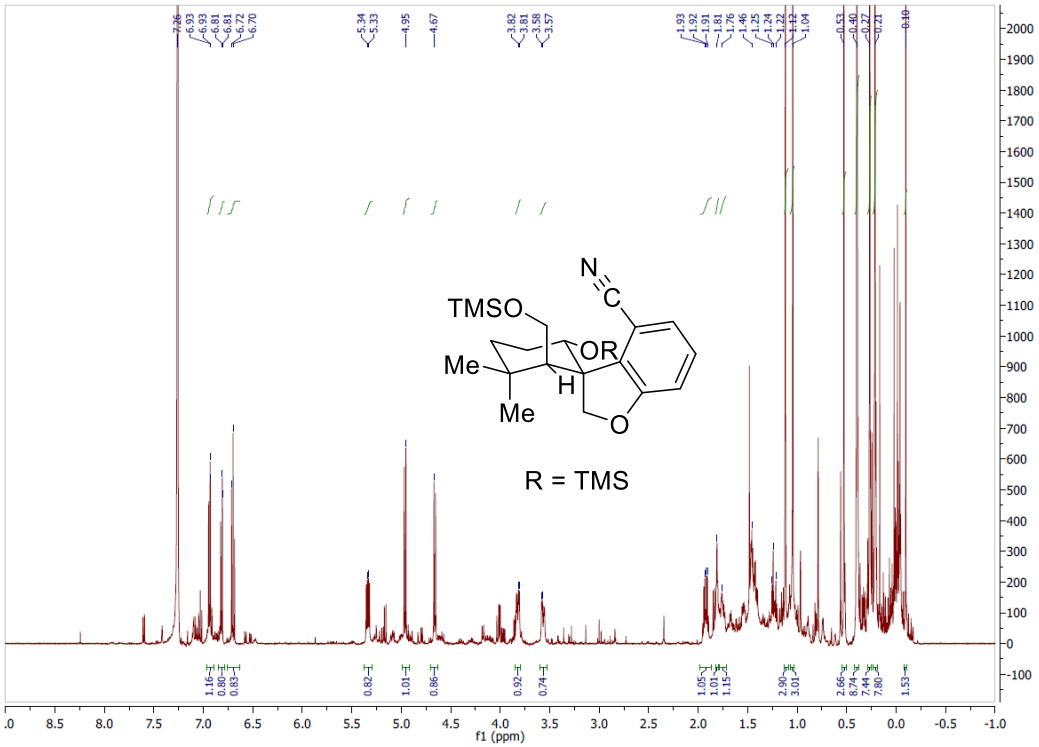


Figure SI.73 ^{1}H NMR spectrum of **49b** in $CDCl_3$

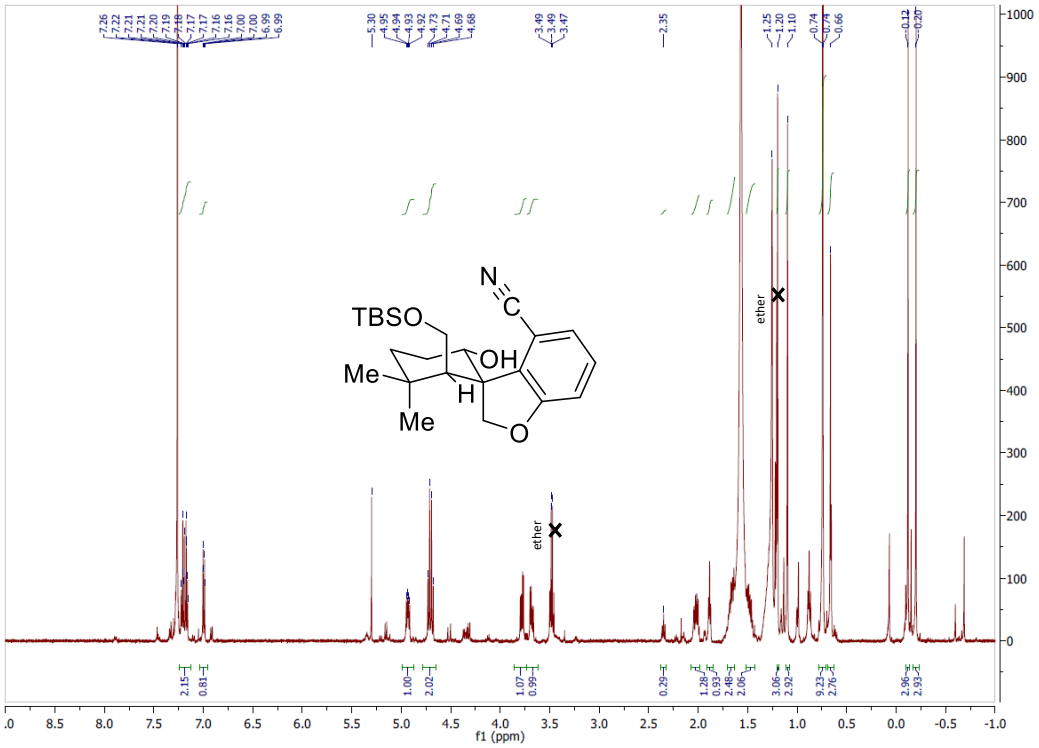


Figure SI.74 ^{1}H NMR spectrum of **51** in $CDCl_3$

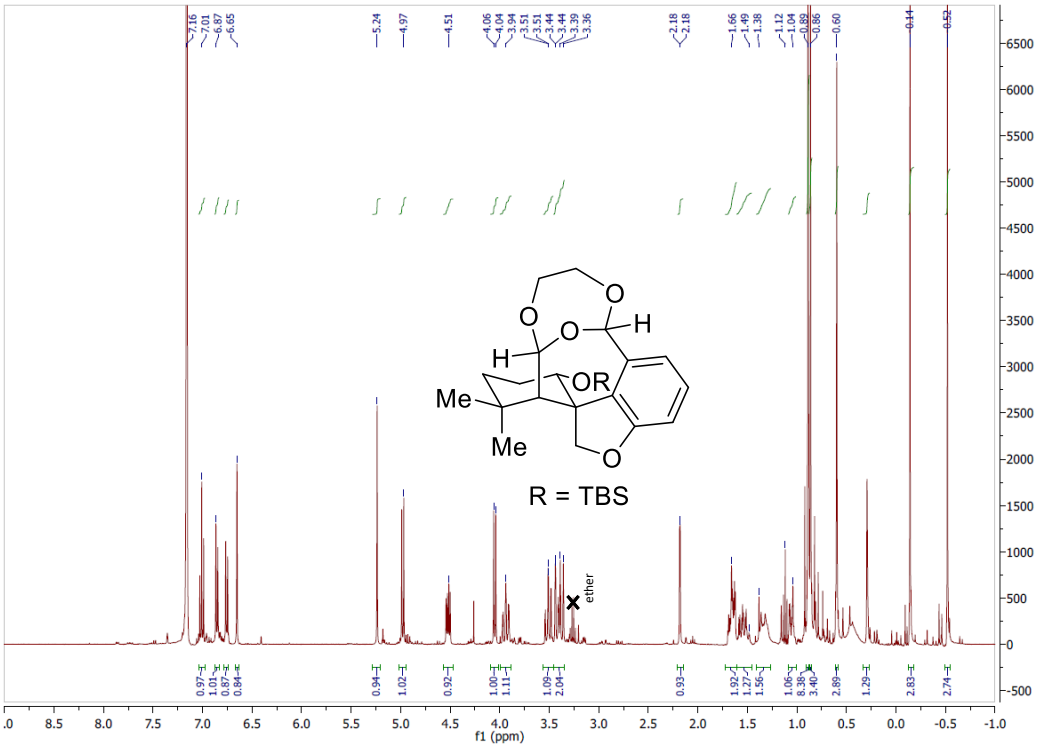


Figure SI.75 ^{1}H NMR spectrum of **52** in $CDCl_3$

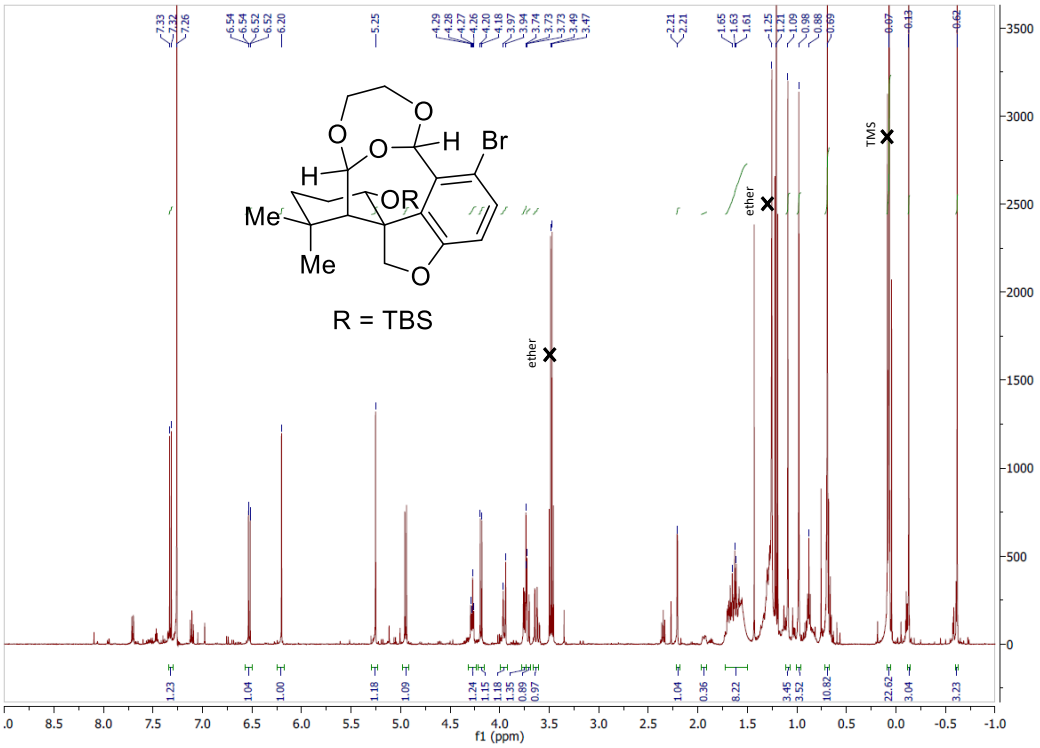


Figure SI.76 ^{1}H NMR spectrum of **53** in $CDCl_3$. Contains **40** impurity

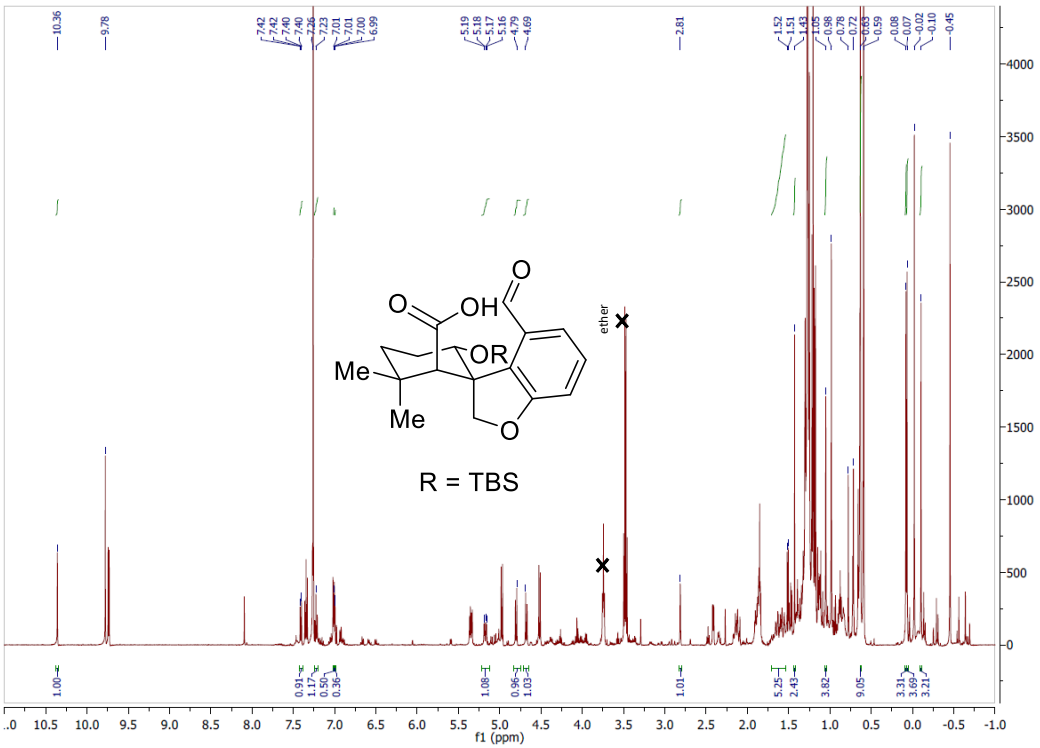


Figure SI.77 ^{1}H NMR spectrum overlay of **53** and **46** in $CDCl_3$

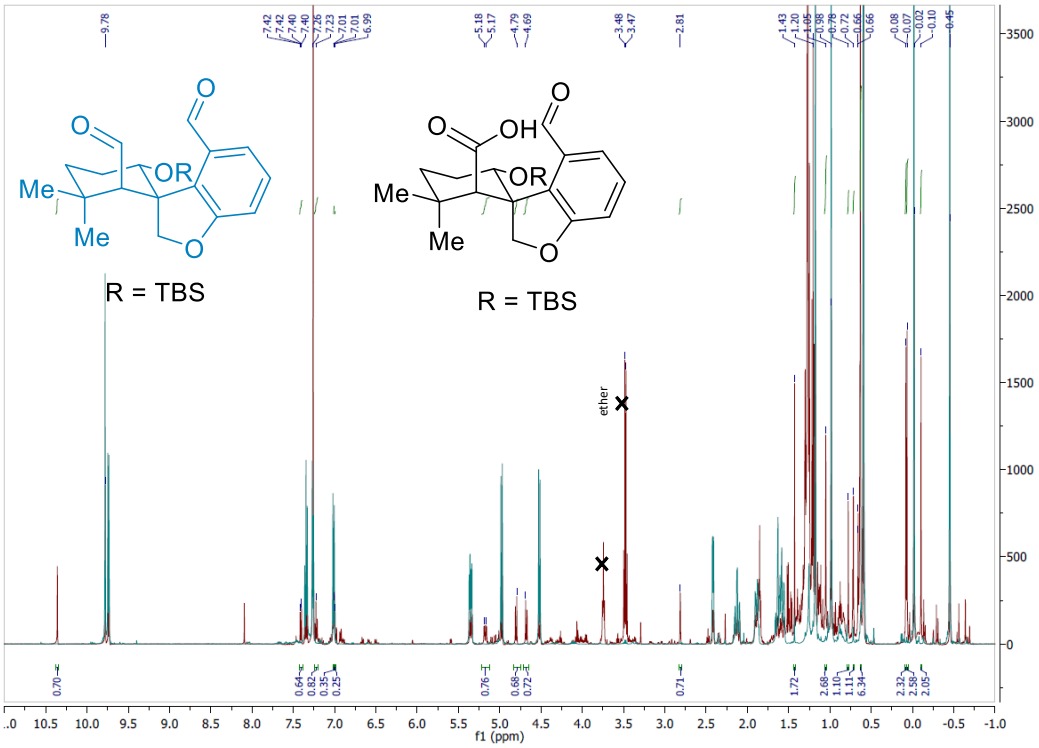


Figure SI.78 ^{1}H NMR spectrum of **SI-9** in $CDCl_3$

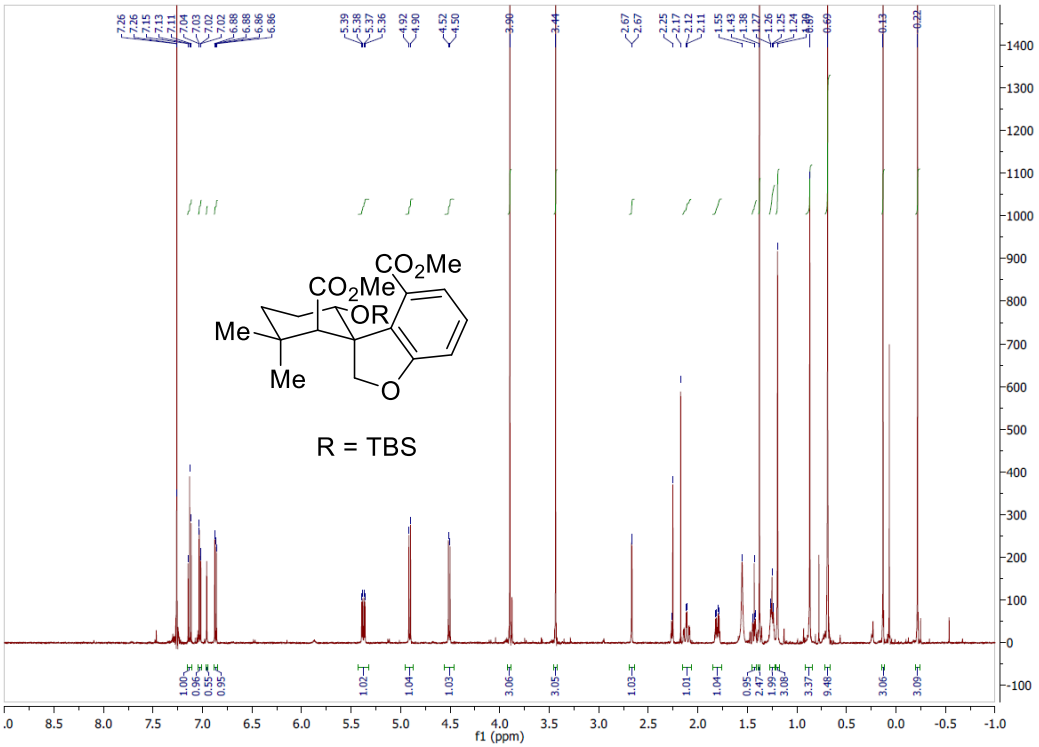


Figure SI.79 ^{1}H NMR spectrum of **54** in $CDCl_3$

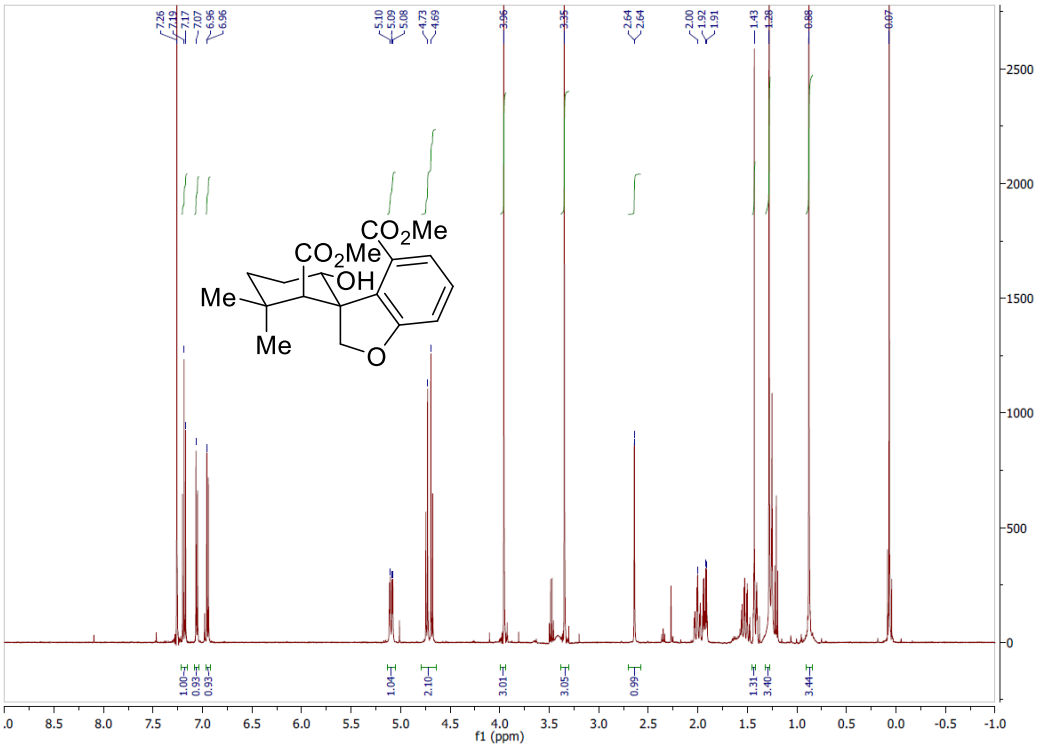


Figure SI.80 ^{1}H NMR spectrum of **55** in $CDCl_3$

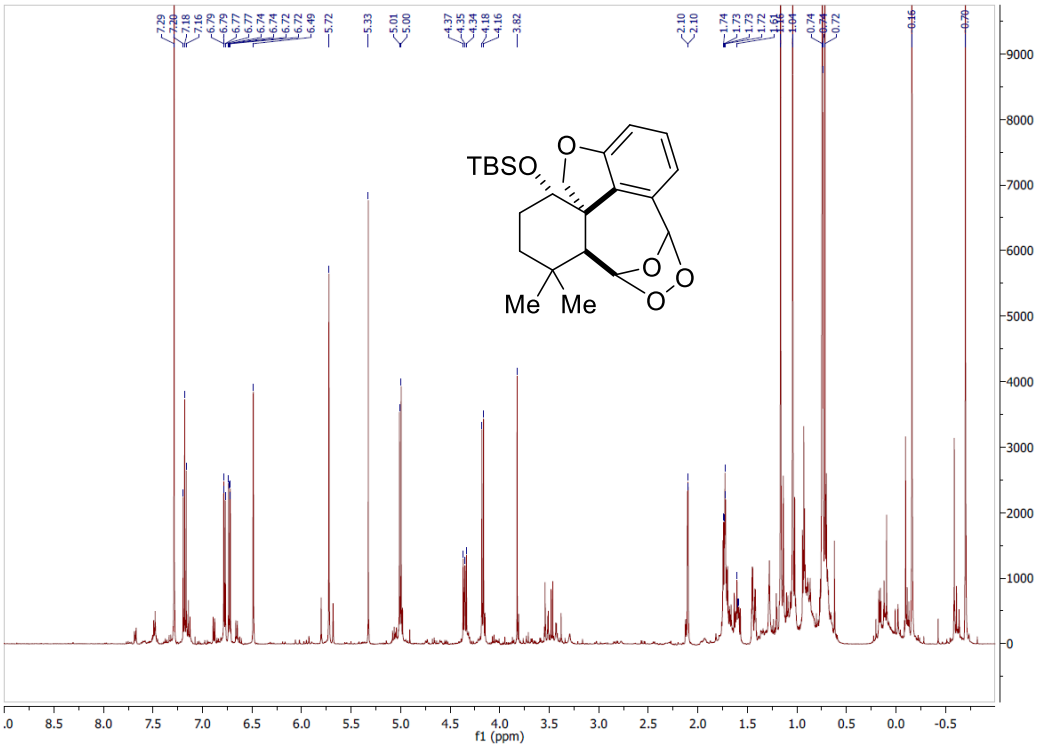


Figure SI.81 ^{1}H NMR spectrum of **56** in $CDCl_3$

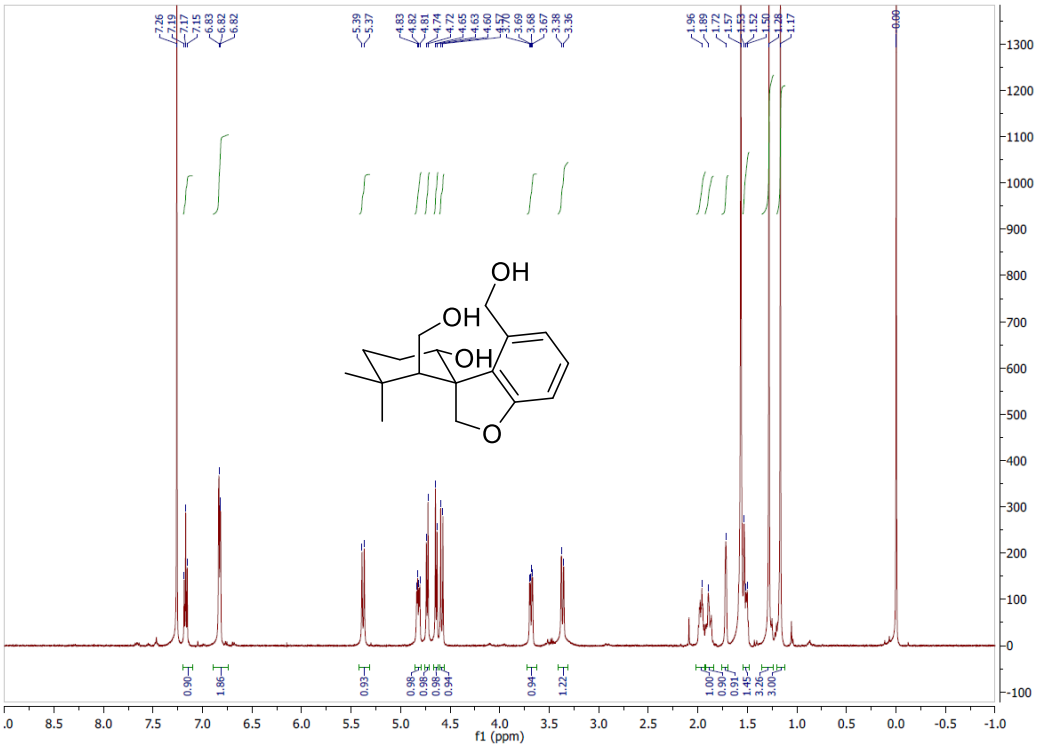


Figure SI.82 ^{1}H NMR spectrum of **56** in MeOD

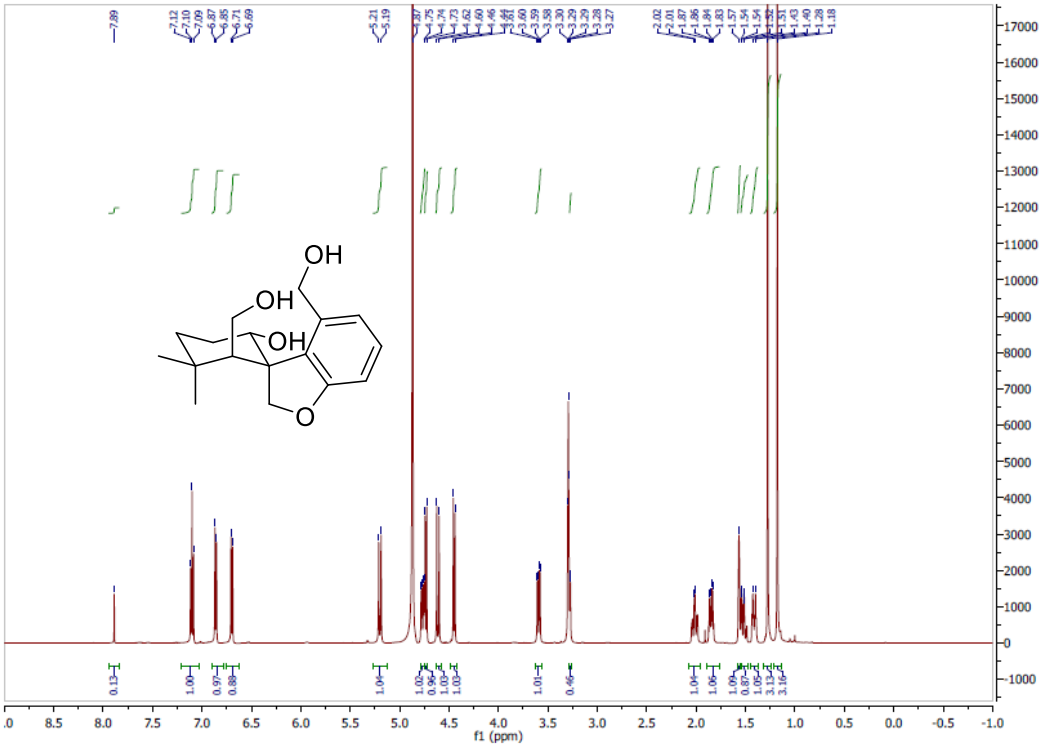


Figure SI.83 ^{13}C NMR spectrum of **56** in MeOD

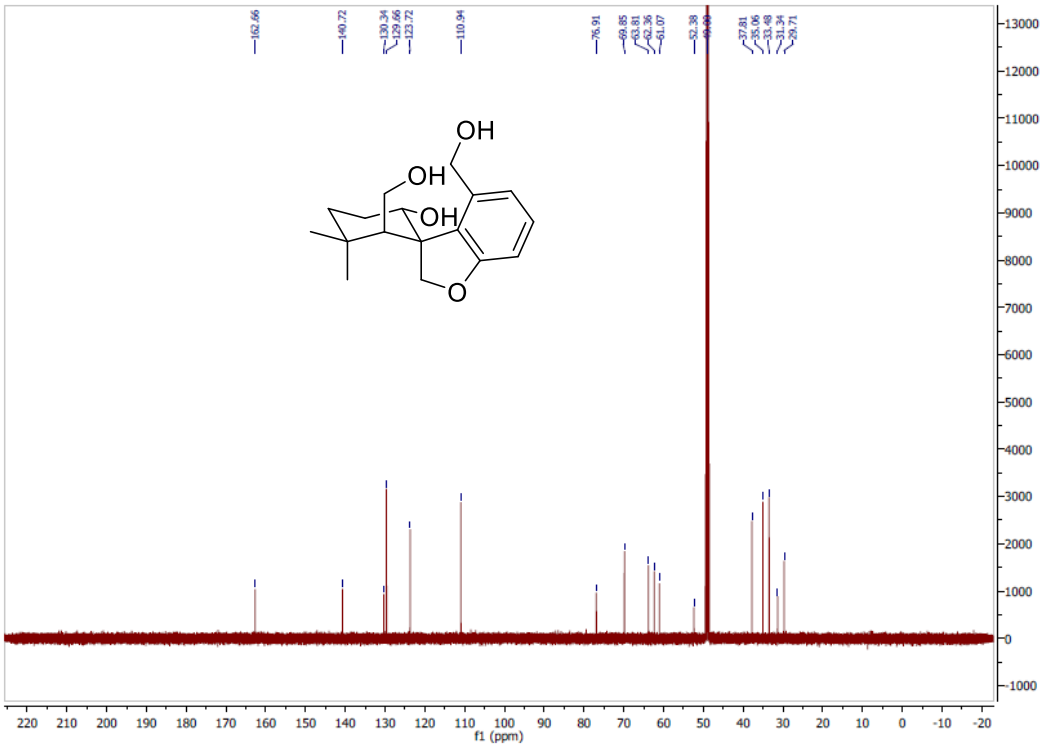


Figure SI.84 ^{1}H NMR spectrum of **SI-10** in $CDCl_3$

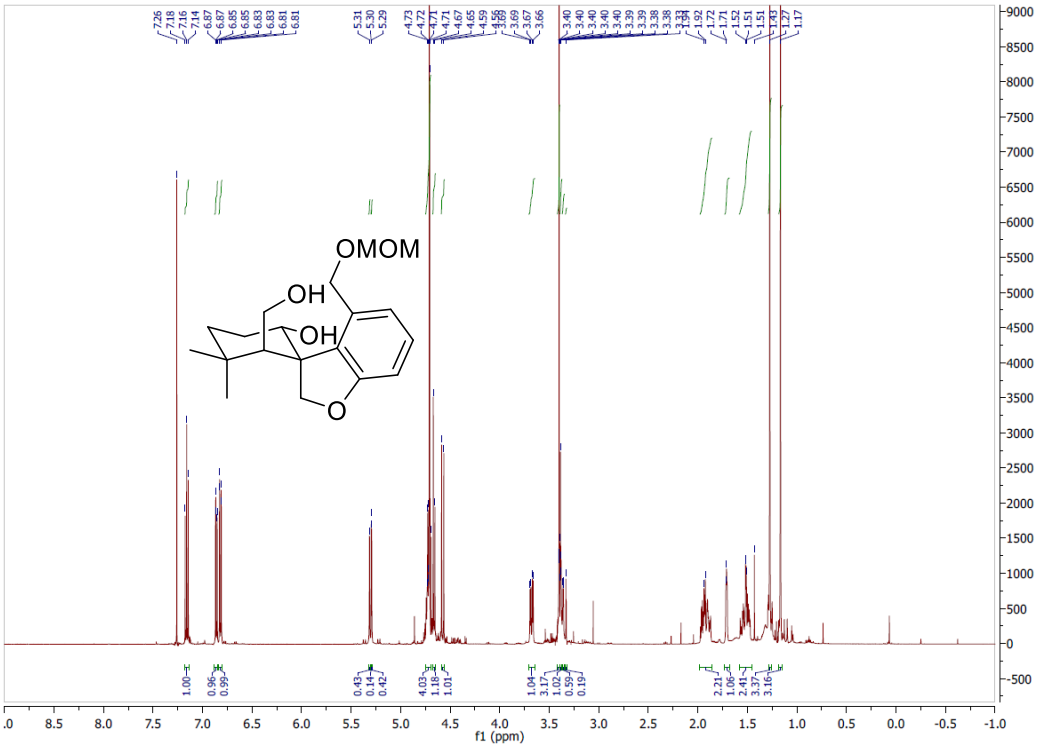


Figure SI.85 ^{13}C NMR spectrum of **SI-10** in $CDCl_3$

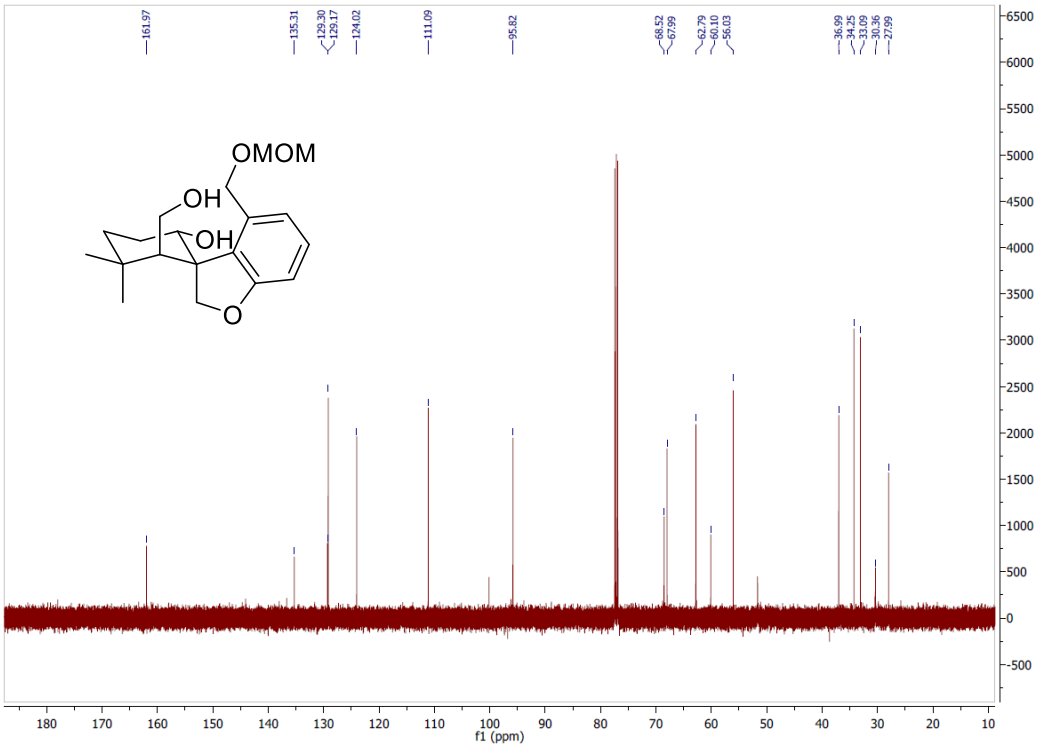


Figure SI.86 ^{1}H NMR spectrum of **SI-11** in $CDCl_3$

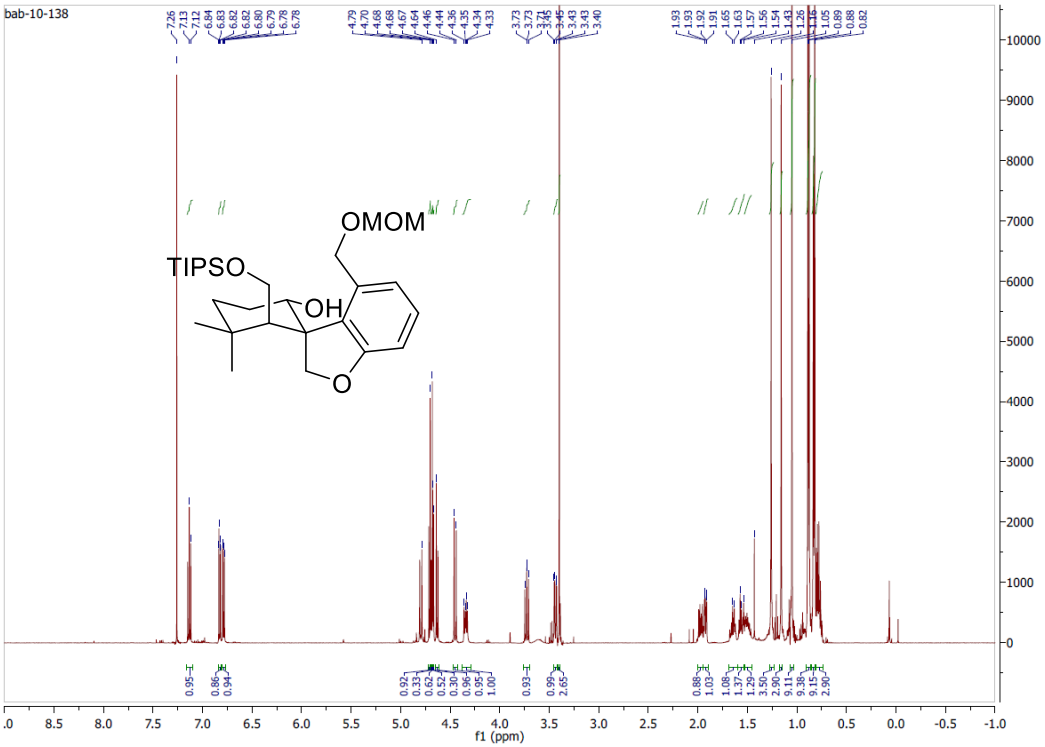


Figure SI.87 ^{13}C NMR spectrum of **SI-11** in $CDCl_3$

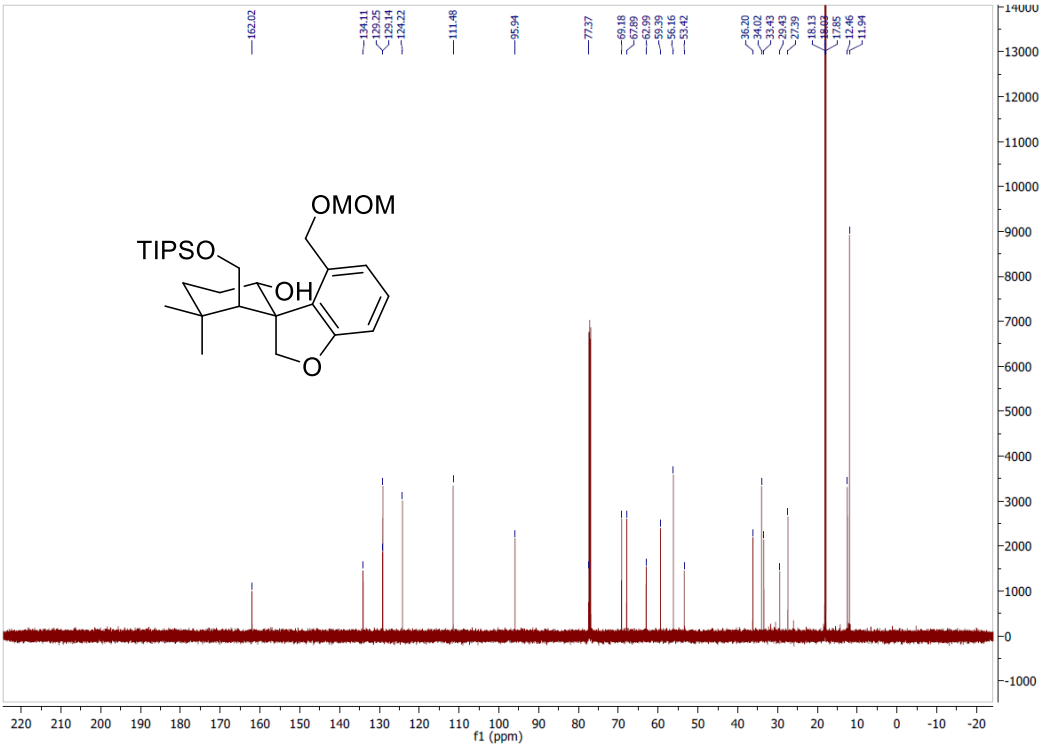


Figure SI.88 ^{1}H NMR spectrum of **57** in $CDCl_3$

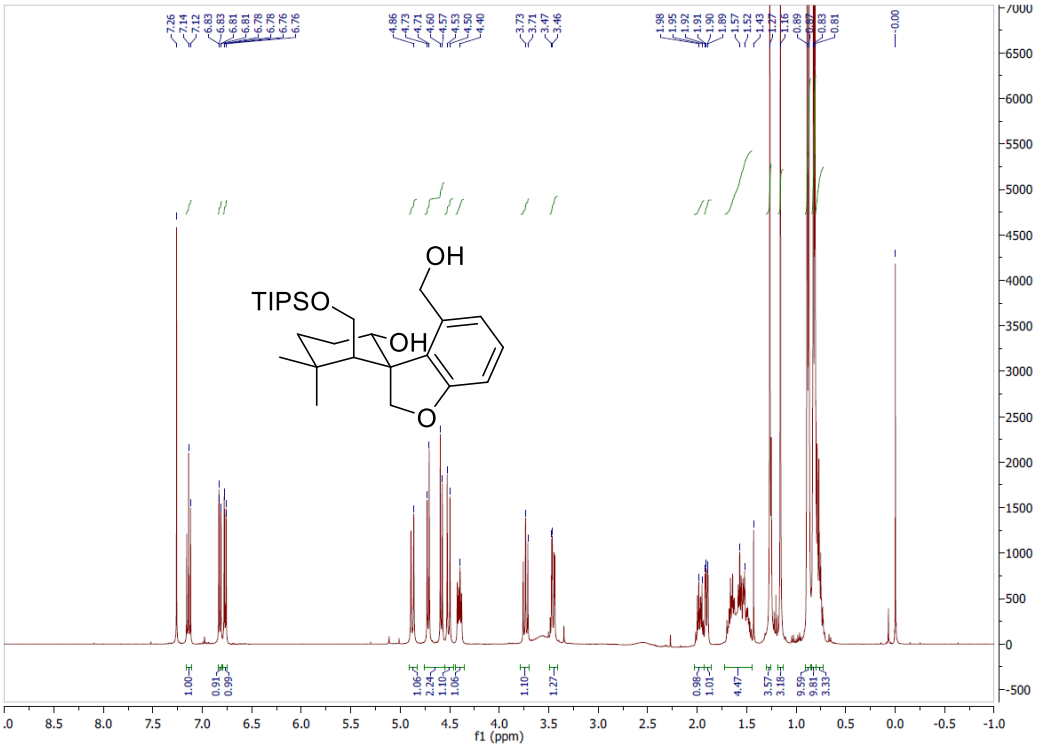


Figure SI.89 ^{13}C NMR spectrum of **57** in $CDCl_3$

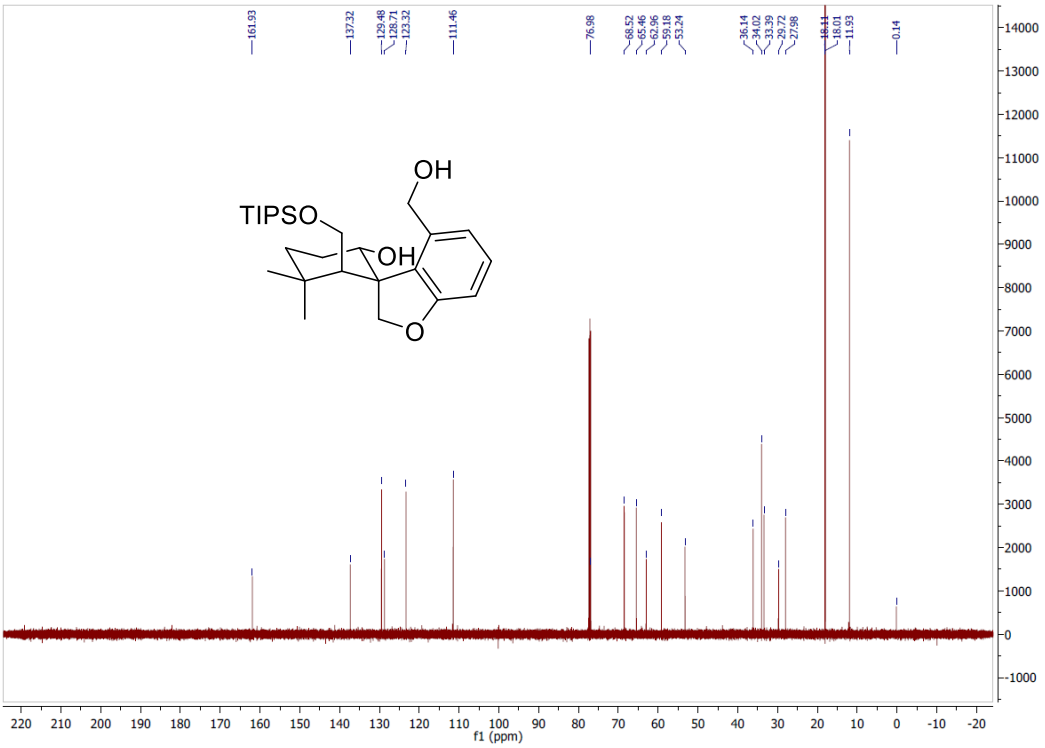


Figure SI.90 ^{1}H NMR spectrum of **SI-12** in $CDCl_3$

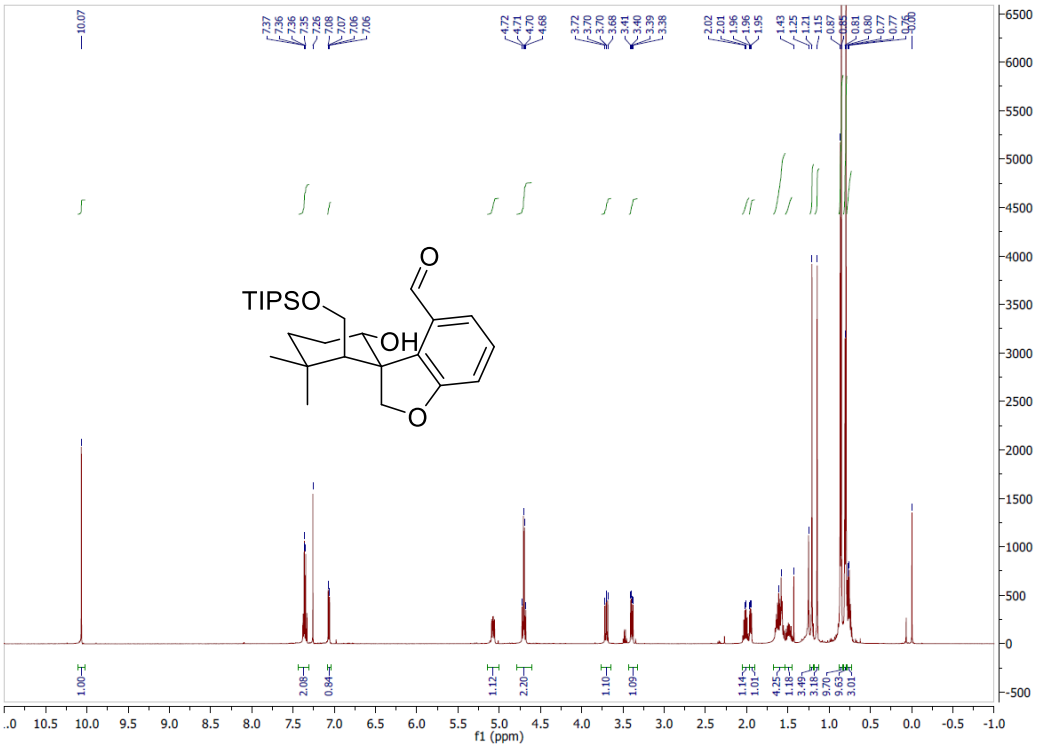


Figure SI.91 ^{13}C NMR spectrum of **SI-12** in $CDCl_3$

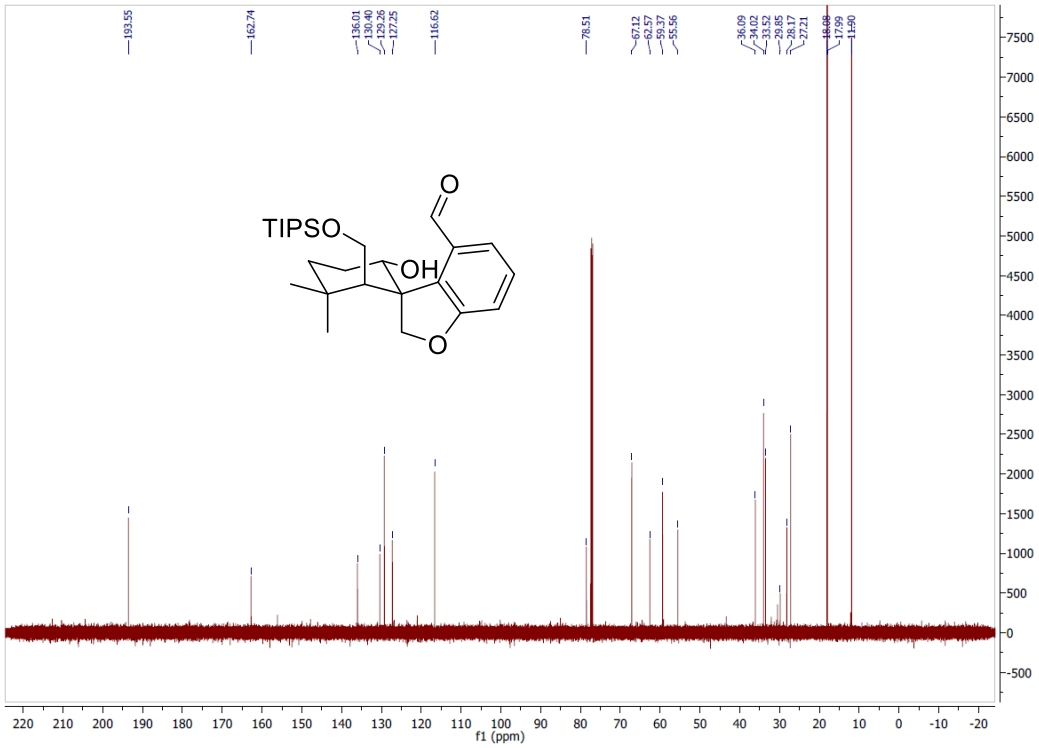


Figure SI.92 ^{1}H NMR spectrum of **41** in $CDCl_3$

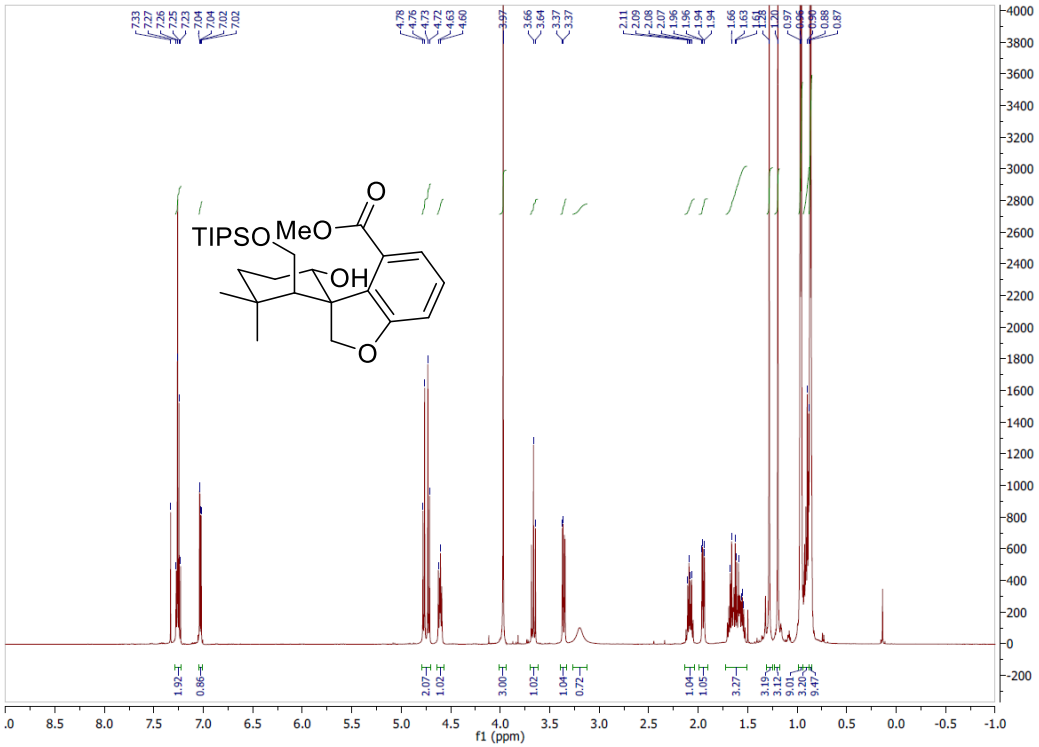


Figure SI.93 ^{1}H NMR spectrum of **41** in C_6D_6

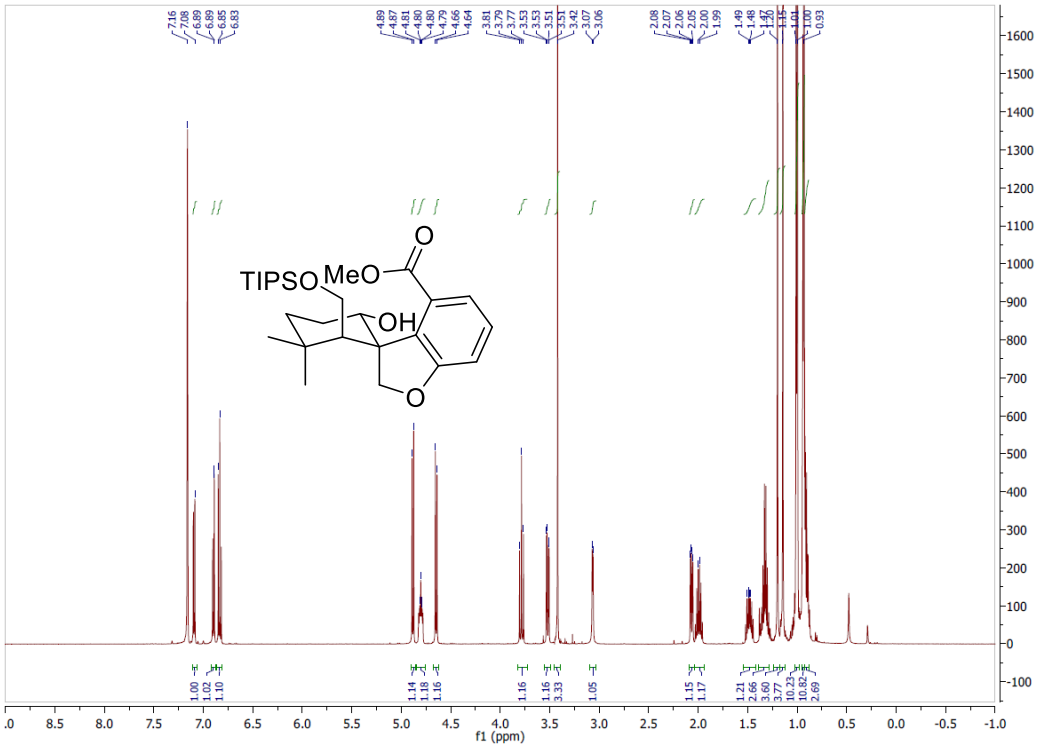


Figure SI.94 ^{13}C NMR spectrum of **41** in $CDCl_3$

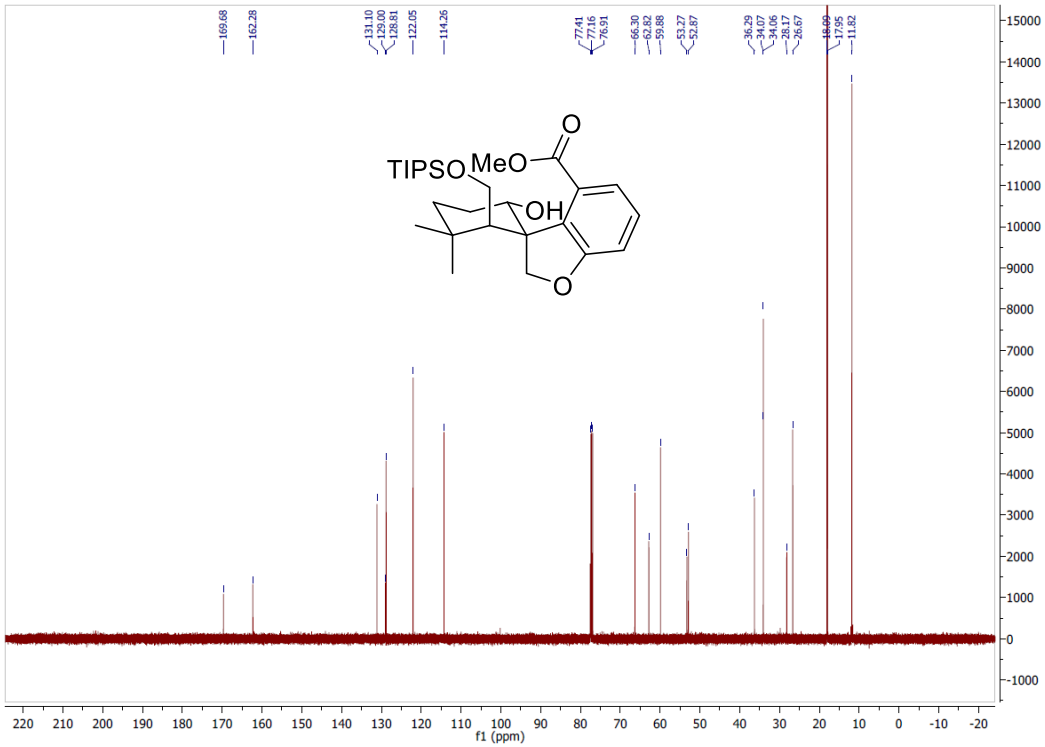


Figure SI.95 ^{1}H NMR spectrum of **42** in C_6D_6

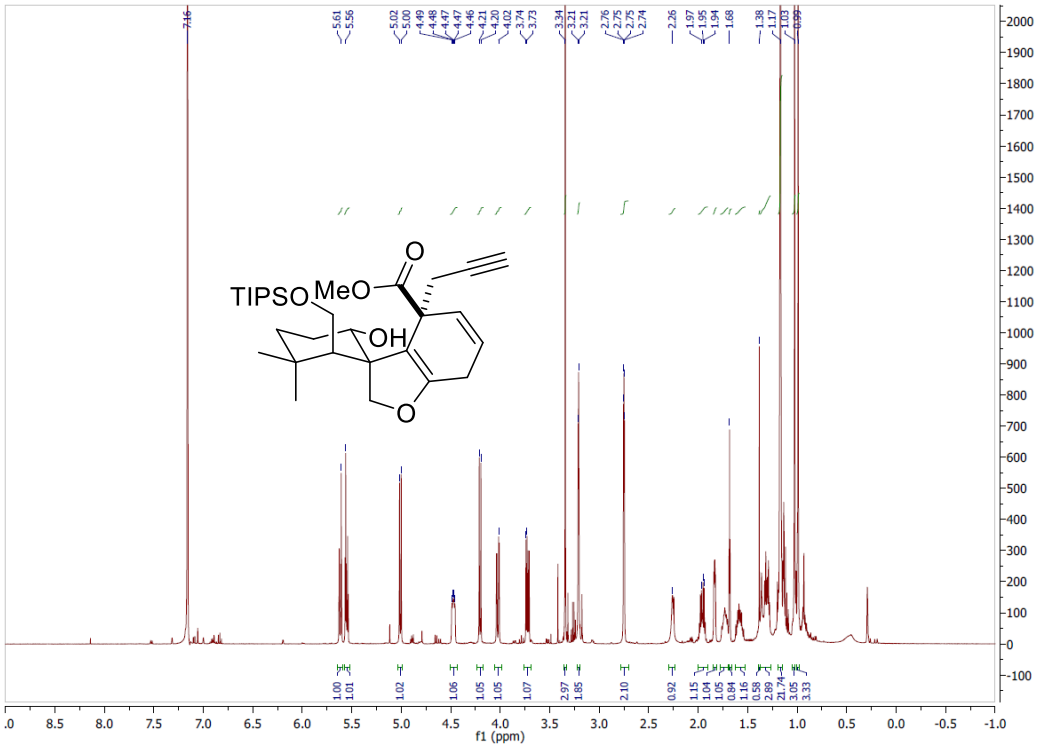


Figure SI.96 ^{13}C NMR spectrum of **41** in C_6D_6

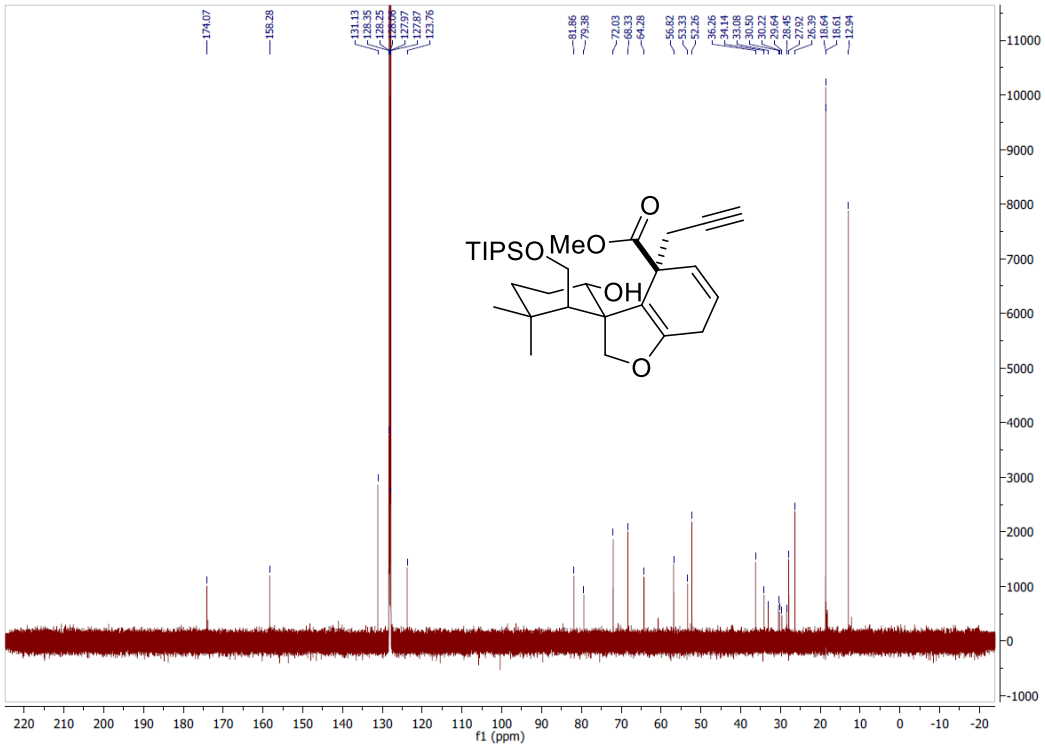


Figure SI.97 COSY spectrum of **41** in C_6D_6

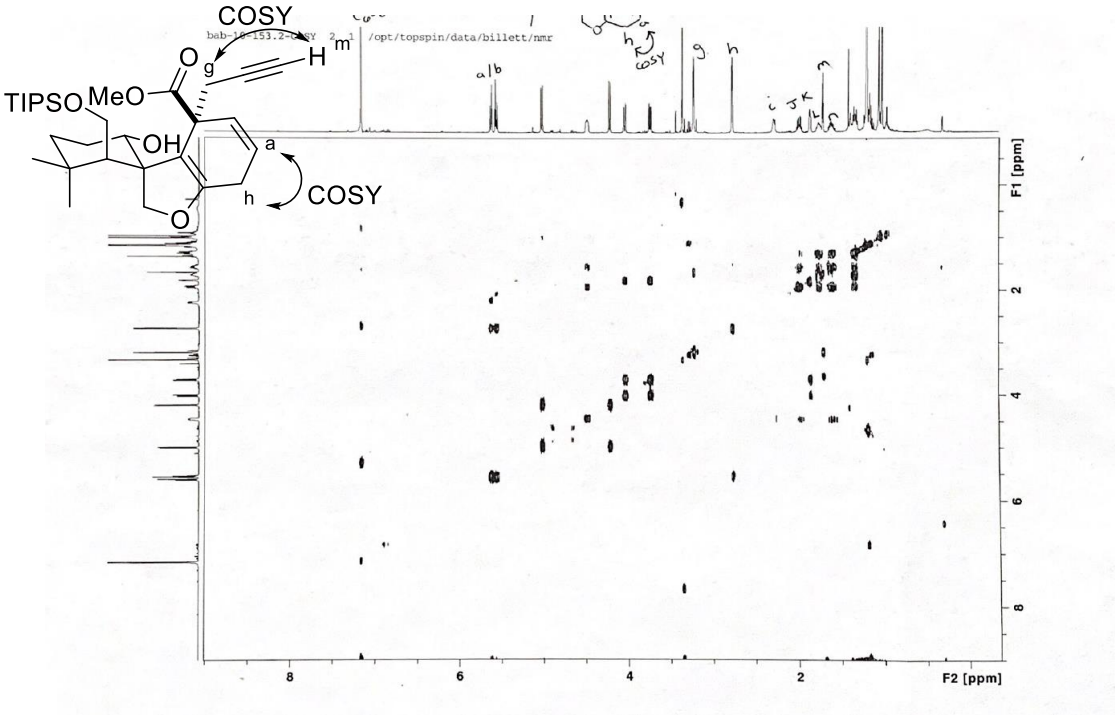


Figure SI.98 Expanded COSY spectrum of **41** in C_6D_6

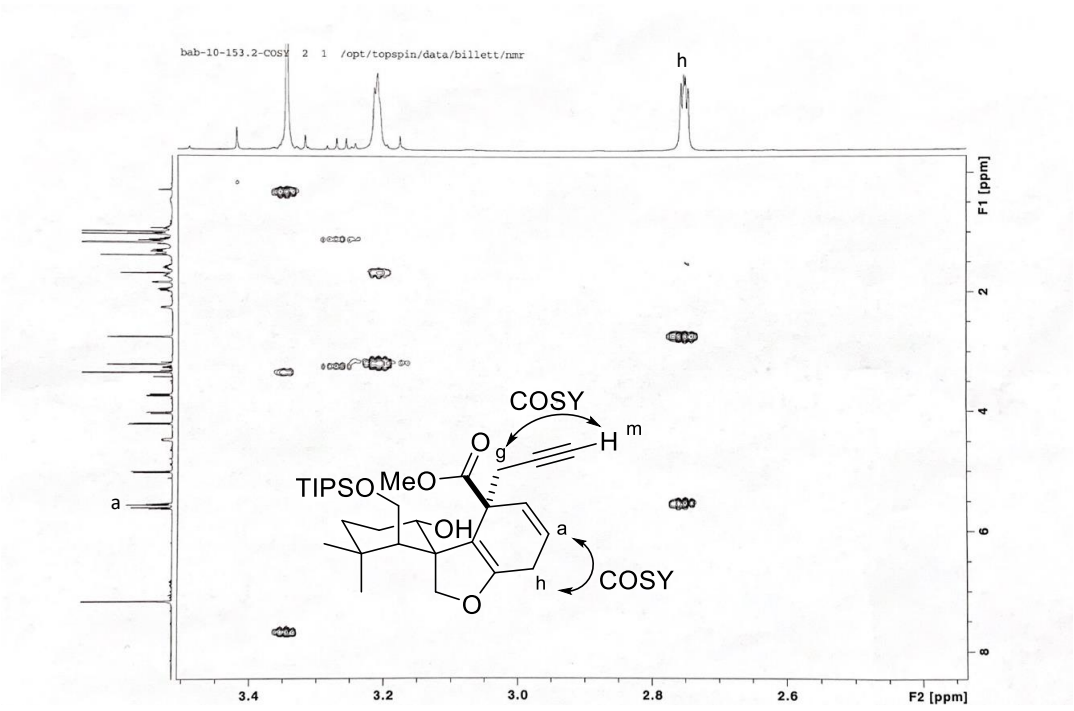


Figure SI.99 nOe spectrum of **41** in C_6D_6

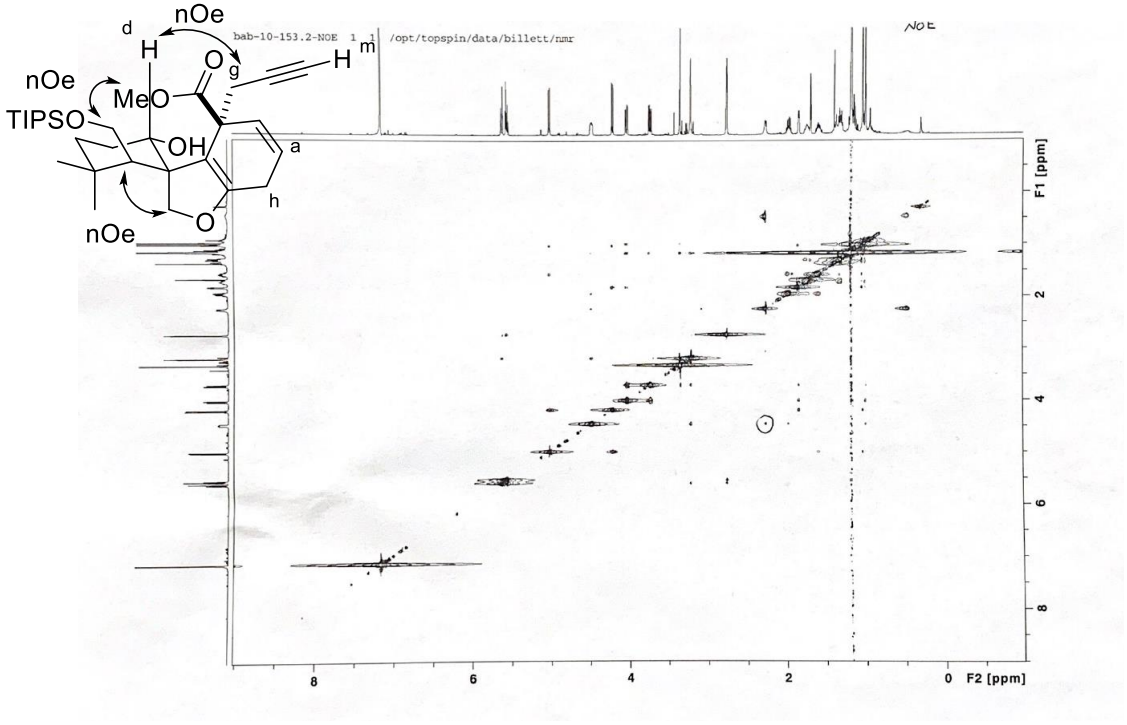


Figure SI.100 Expanded nOe spectrum of **41** in C_6D_6

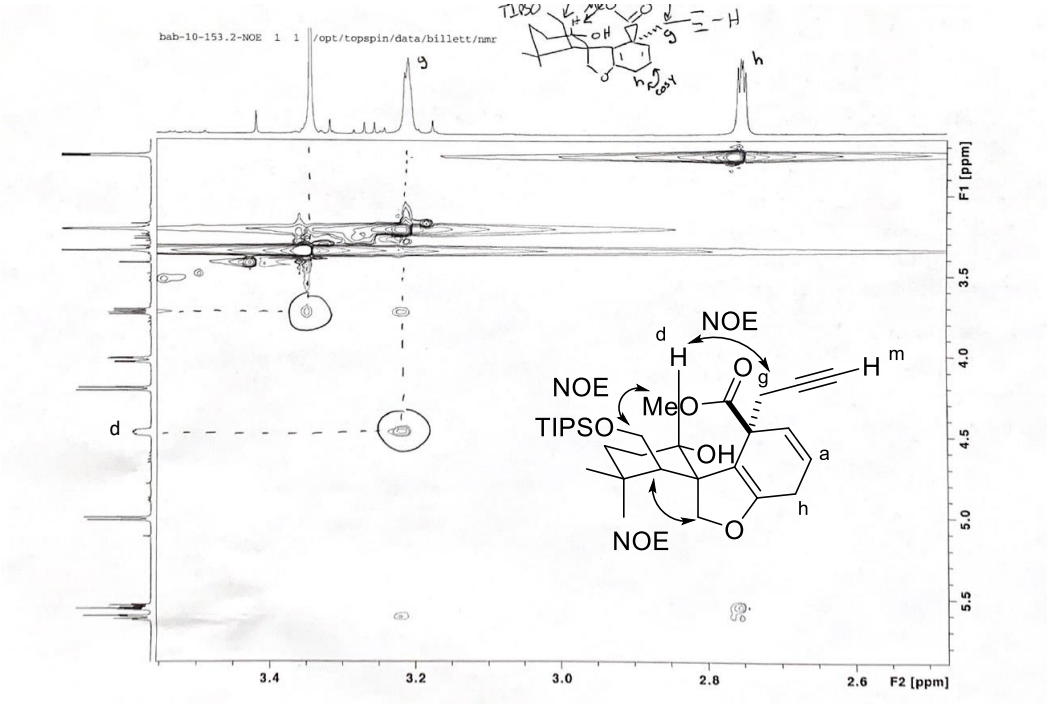


Figure SI.101 ^{1}H NMR spectrum of **59** in $CDCl_3$

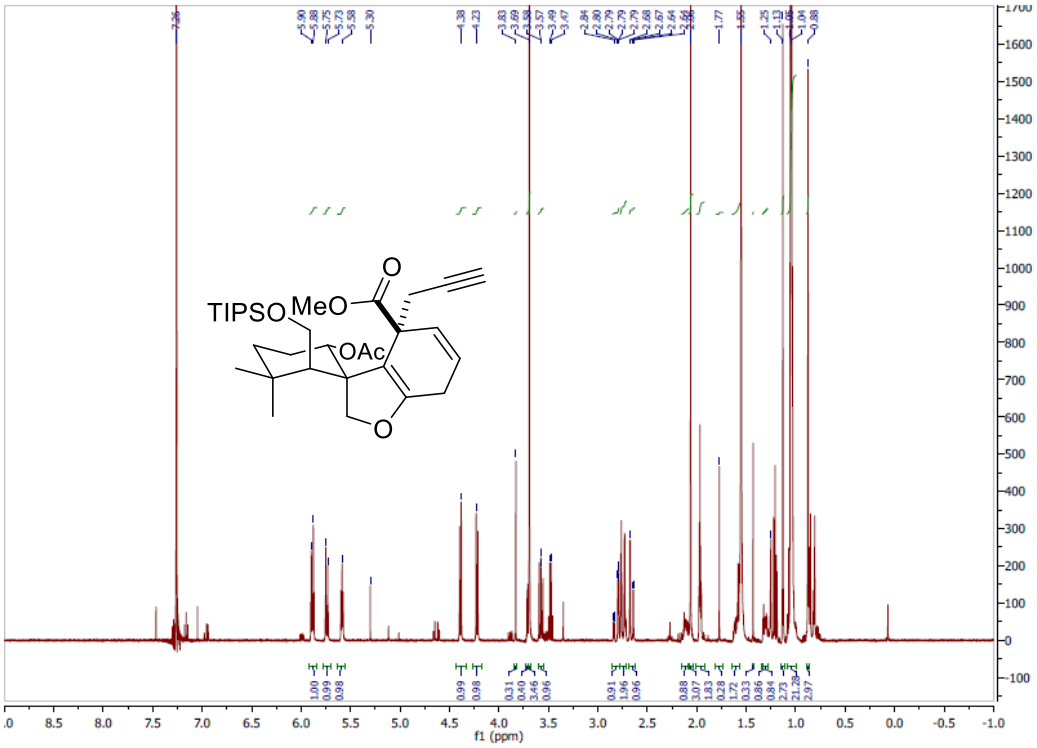


Figure SI.102 ^{1}H NMR spectrum of **59** in C_6D_6

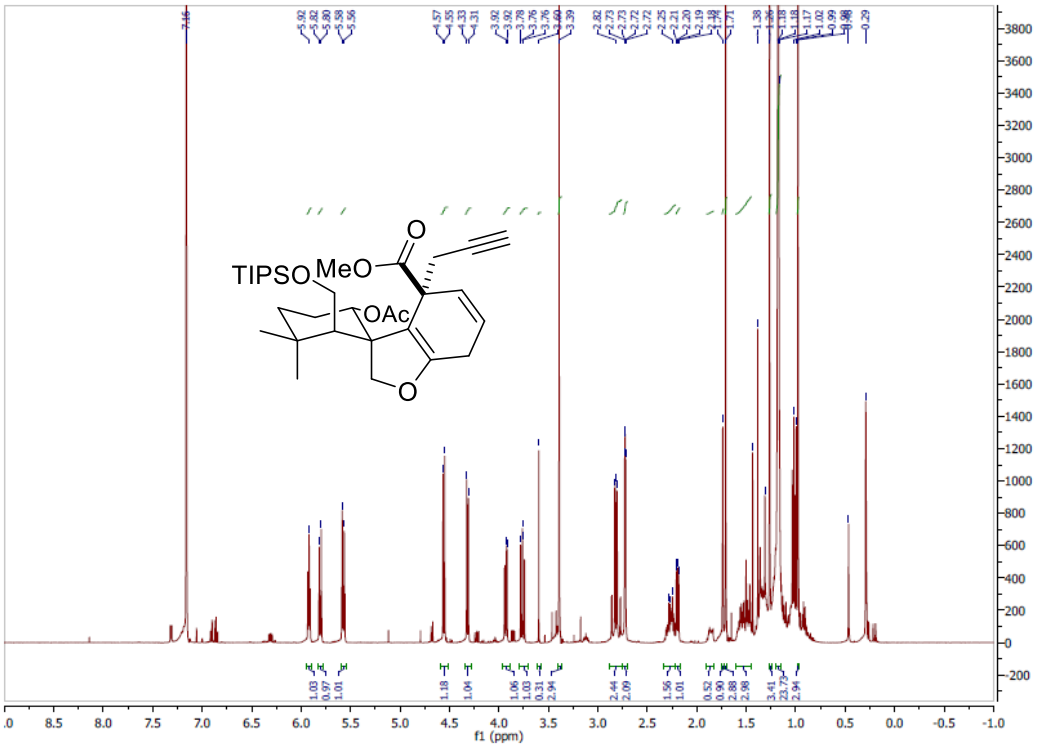


Figure SI.103 COSY spectrum of **59** in C_6D_6

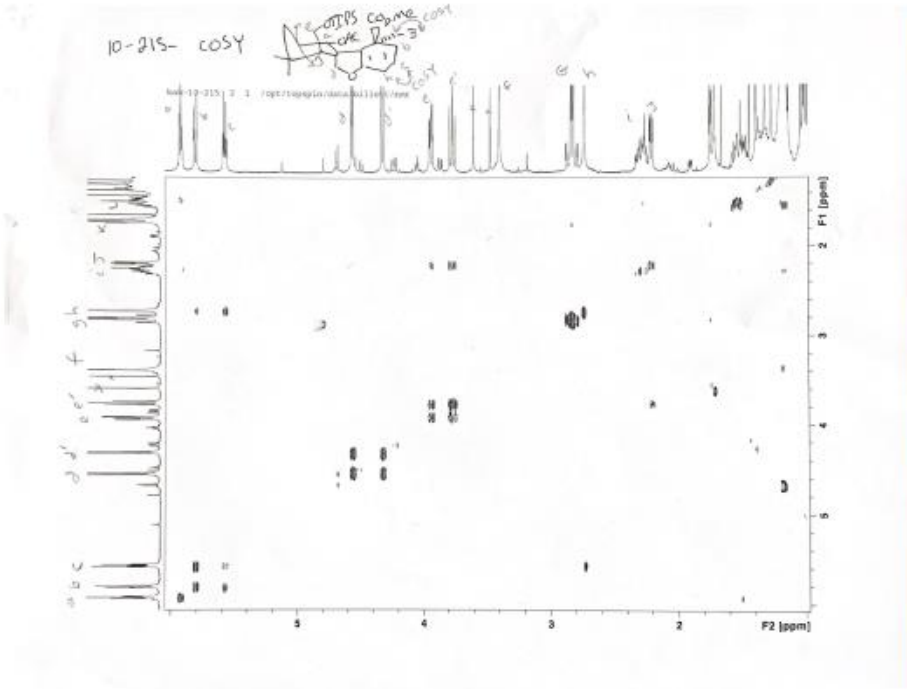


Figure SI.104 ^{13}C NMR spectrum of **59** in C_6D_6

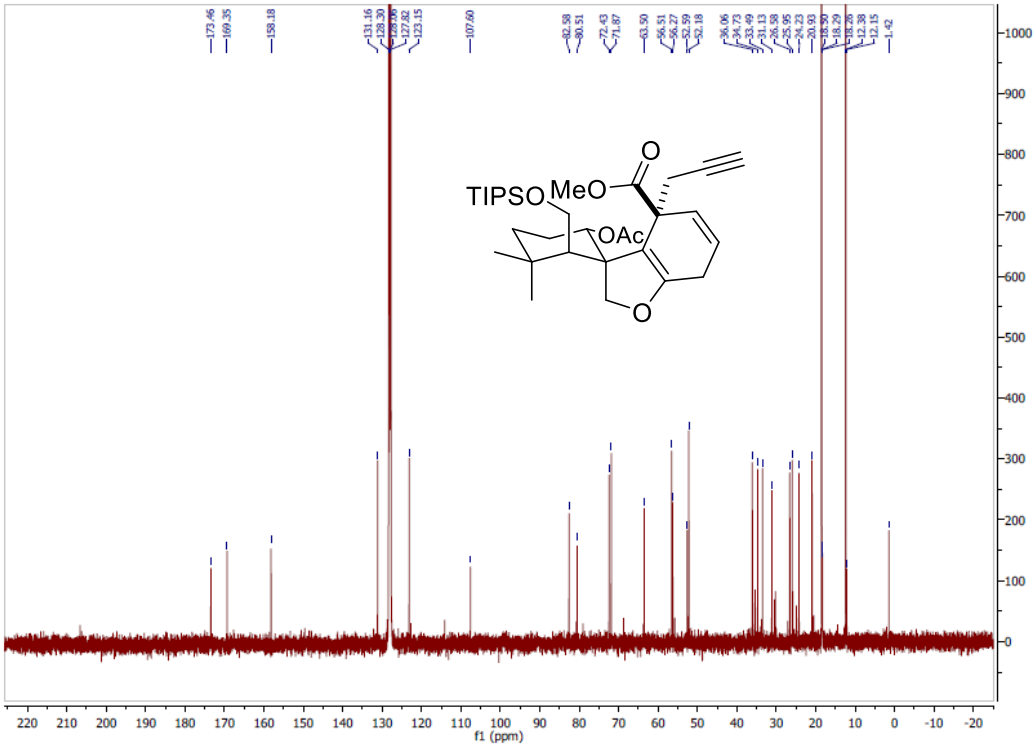


Figure SI.105 ^{1}H NMR spectrum of **60** in $CDCl_3$

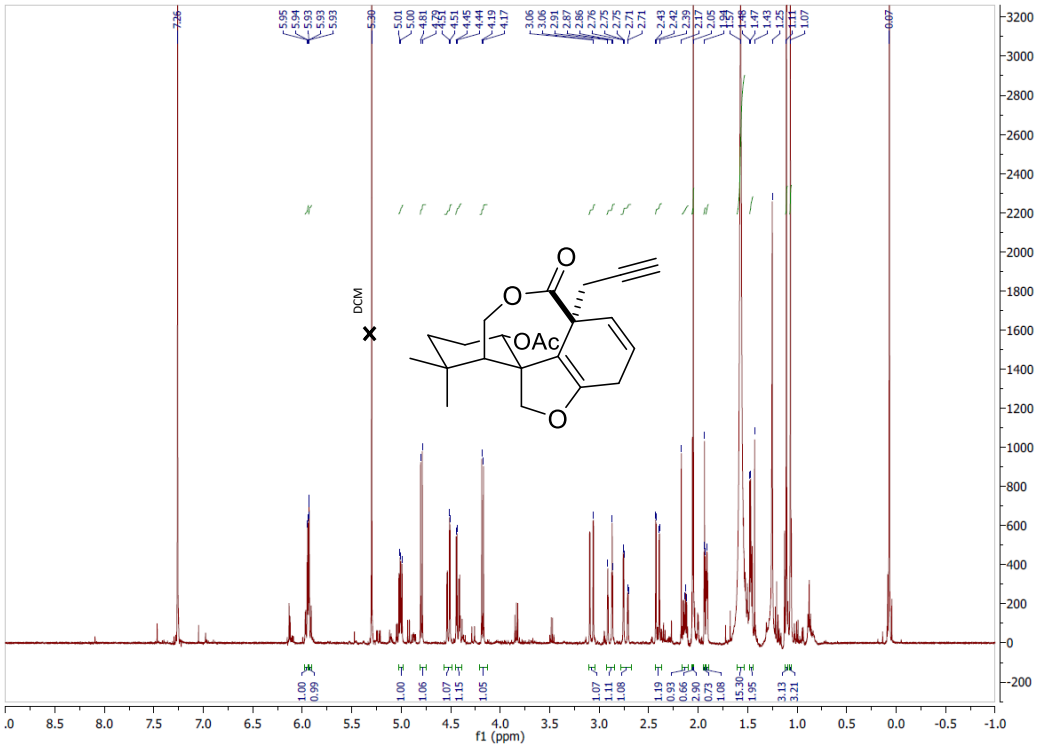


Figure SI.106 ^{1}H NMR spectrum of **61** in $CDCl_3$

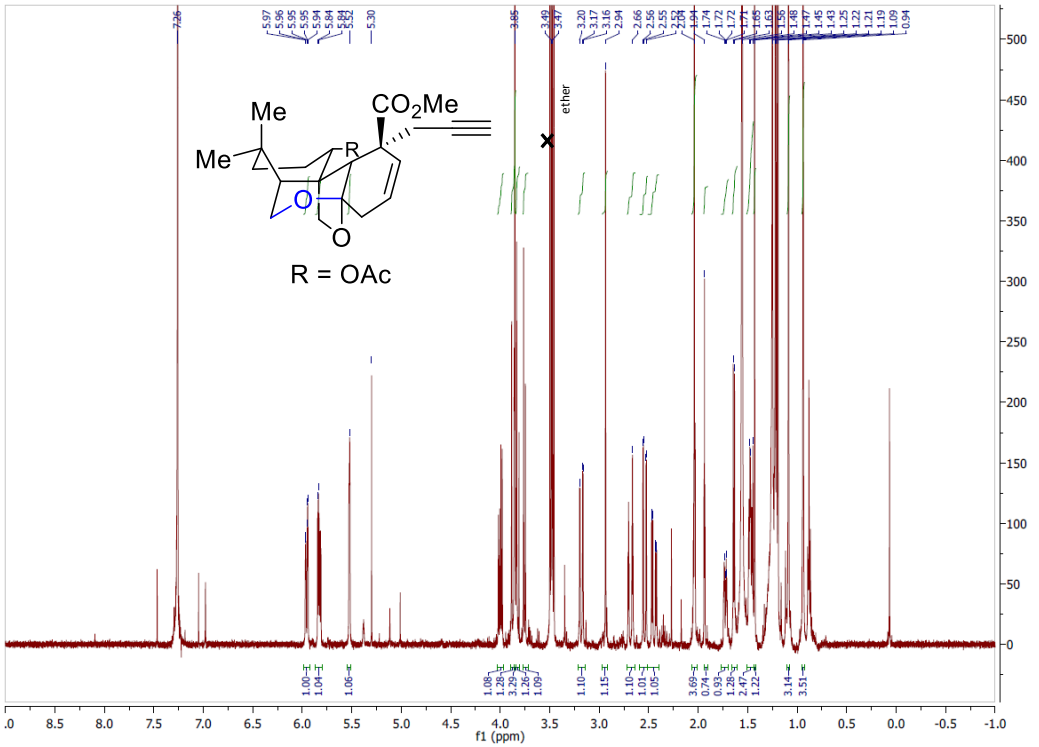


Figure SI.107 ^{1}H NMR spectrum of **62a** in $CDCl_3$

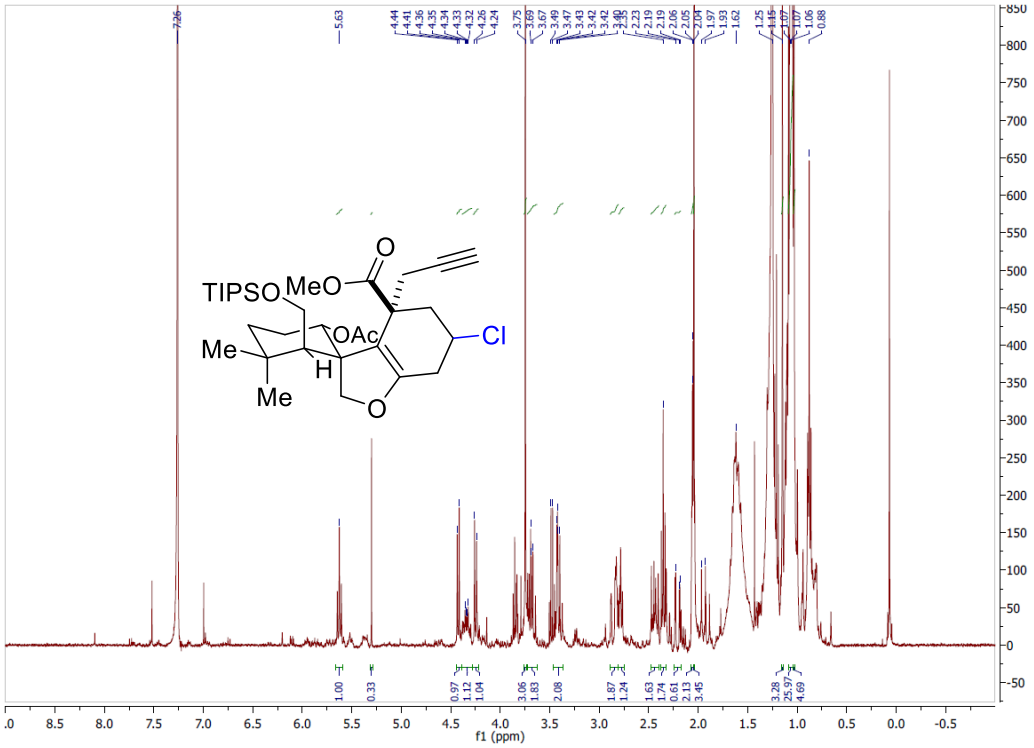


Figure SI.108 ^{1}H NMR spectrum of **63** in $CDCl_3$

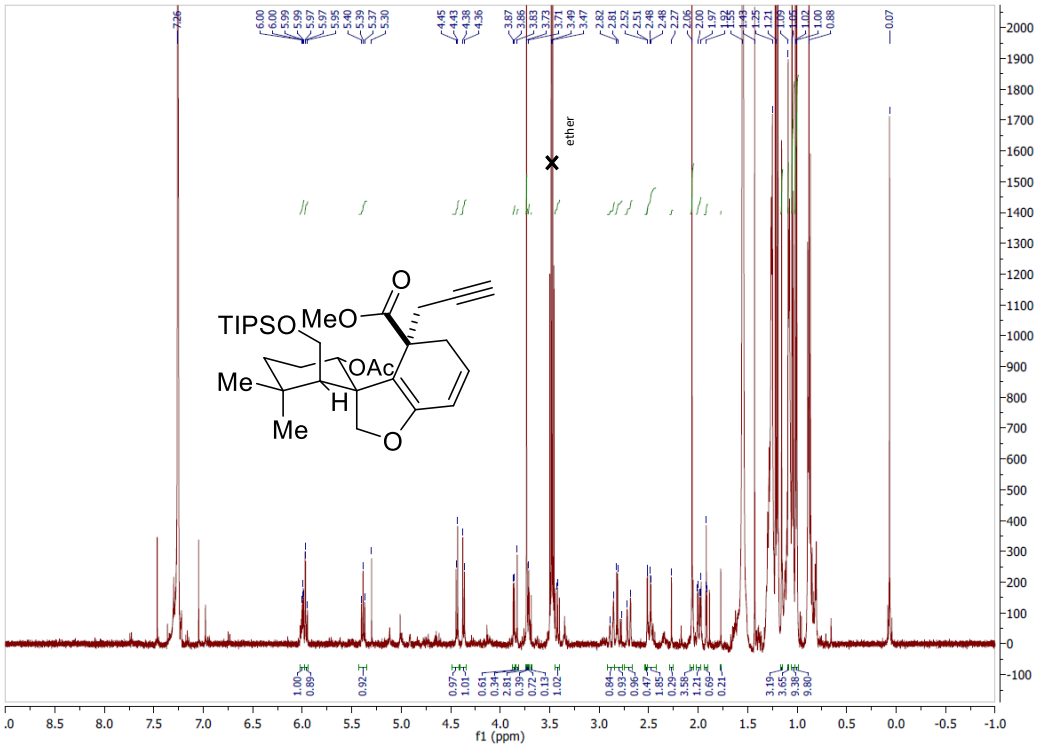


Figure SI.109 ^{1}H NMR spectrum of **64** in $CDCl_3$

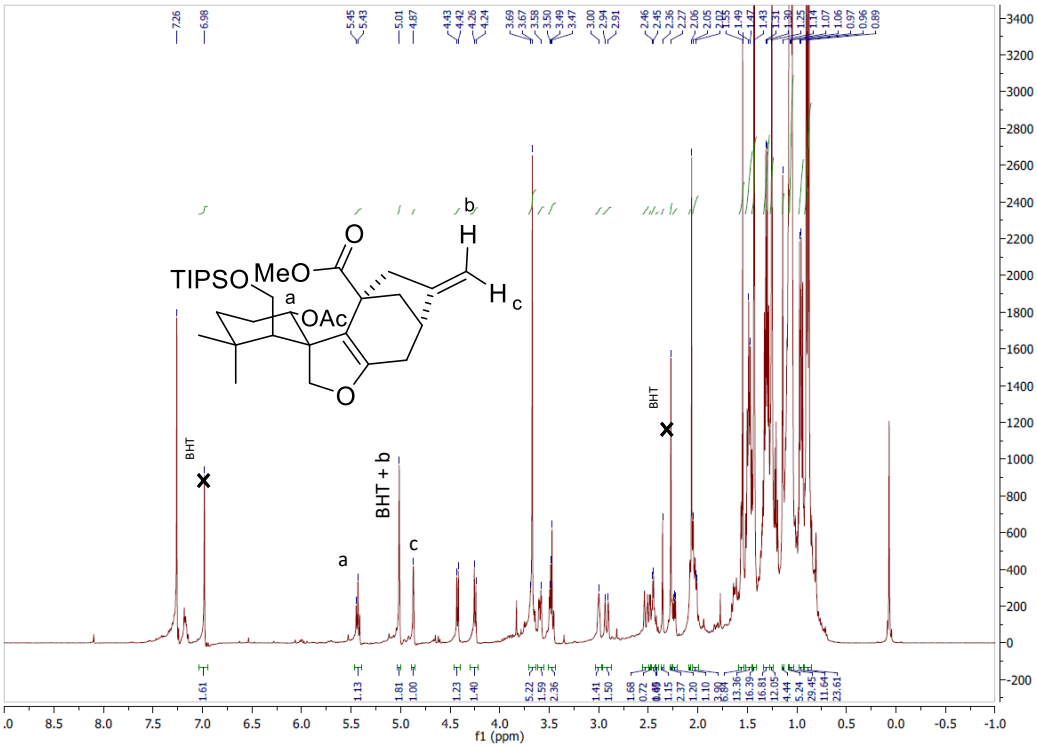


Figure SI.110 ^{1}H NMR spectrum of **66** in $CDCl_3$

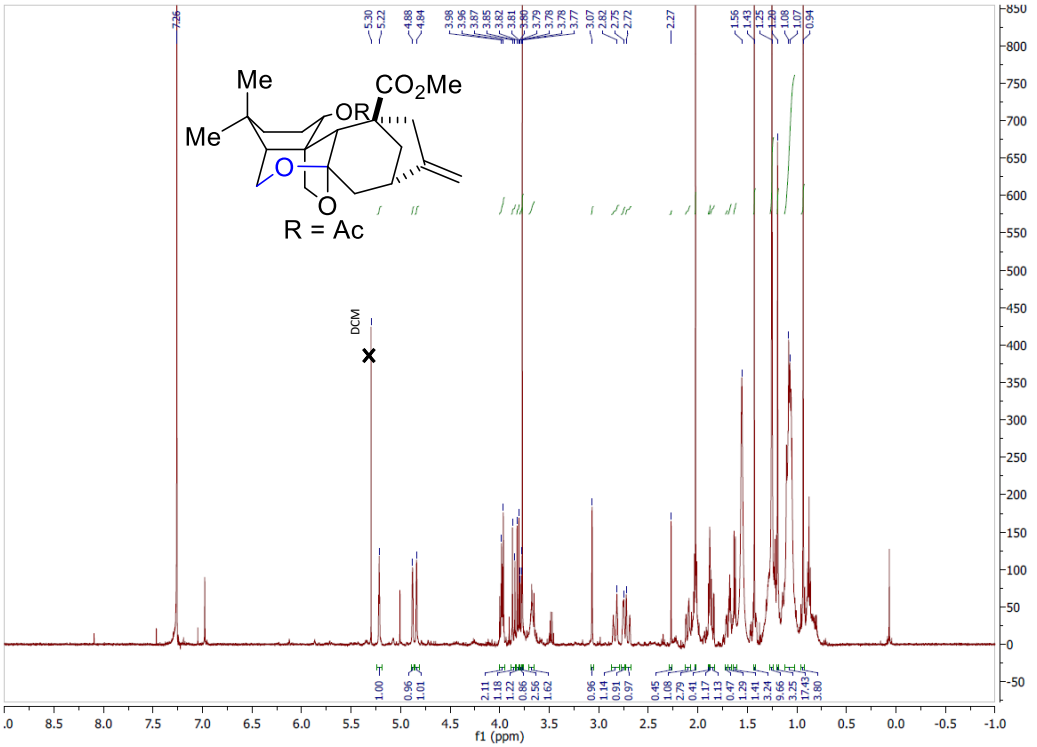


Figure SI.111 COSY spectrum of **66** in $CDCl_3$

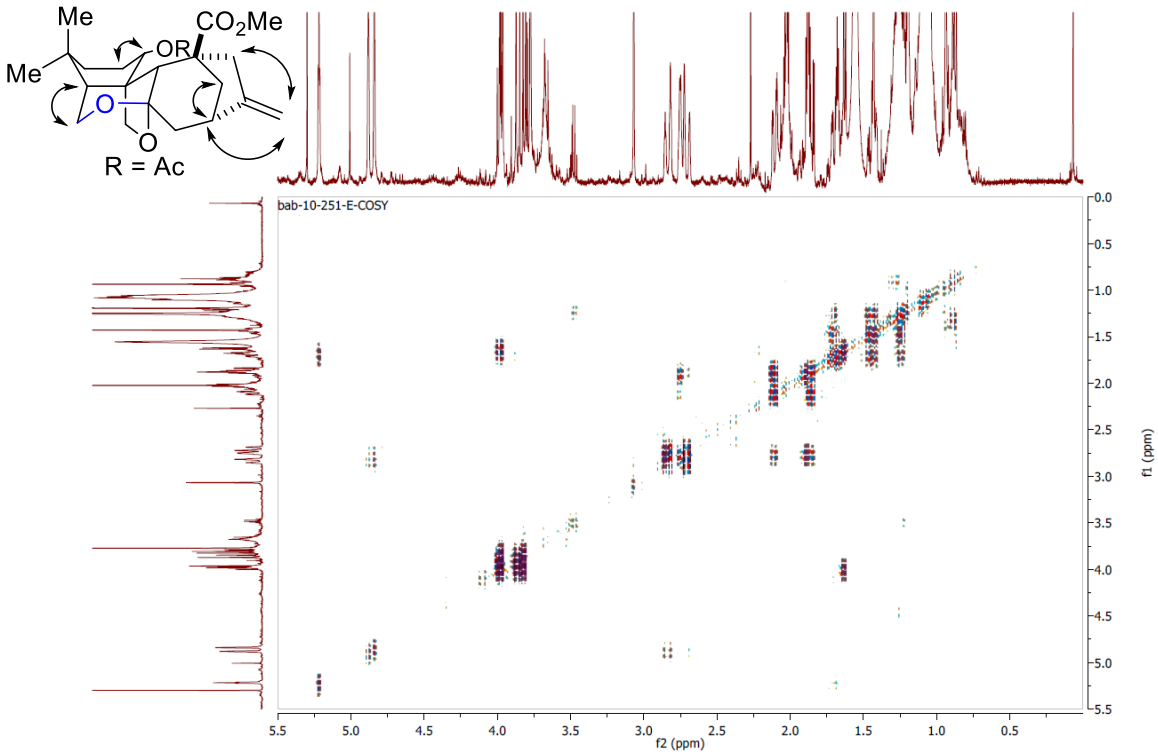


Figure SI.112 crude ^{1}H NMR spectrum of **67** in $CDCl_3$

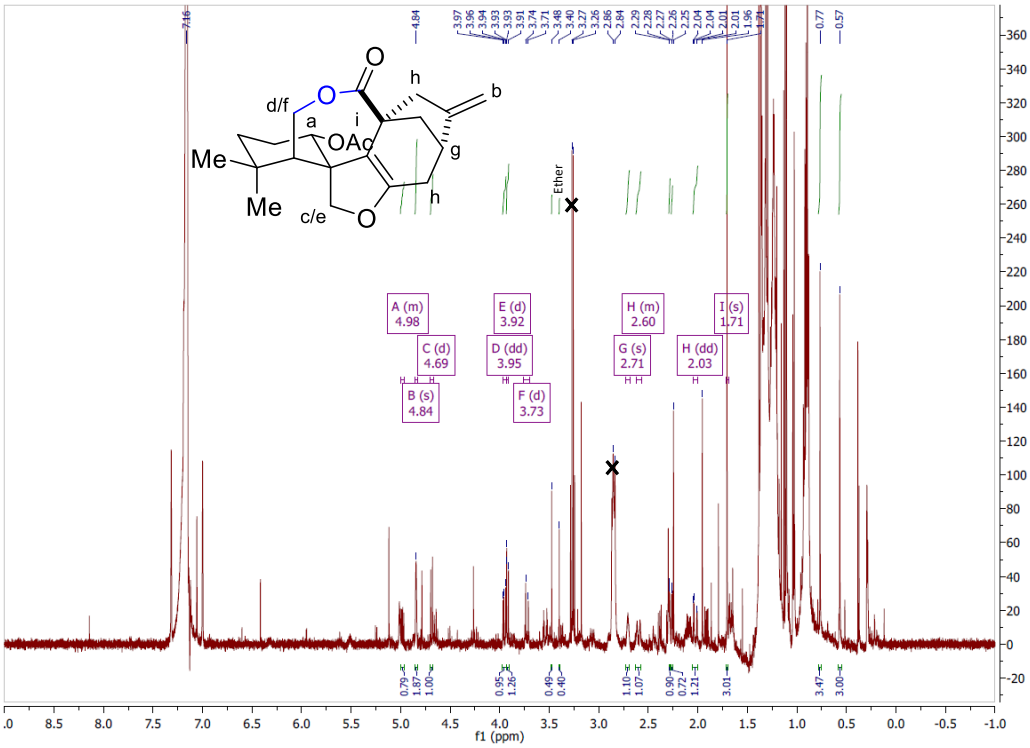


Figure SI.113 Expanded crude ^{1}H NMR spectrum of **67** in $CDCl_3$

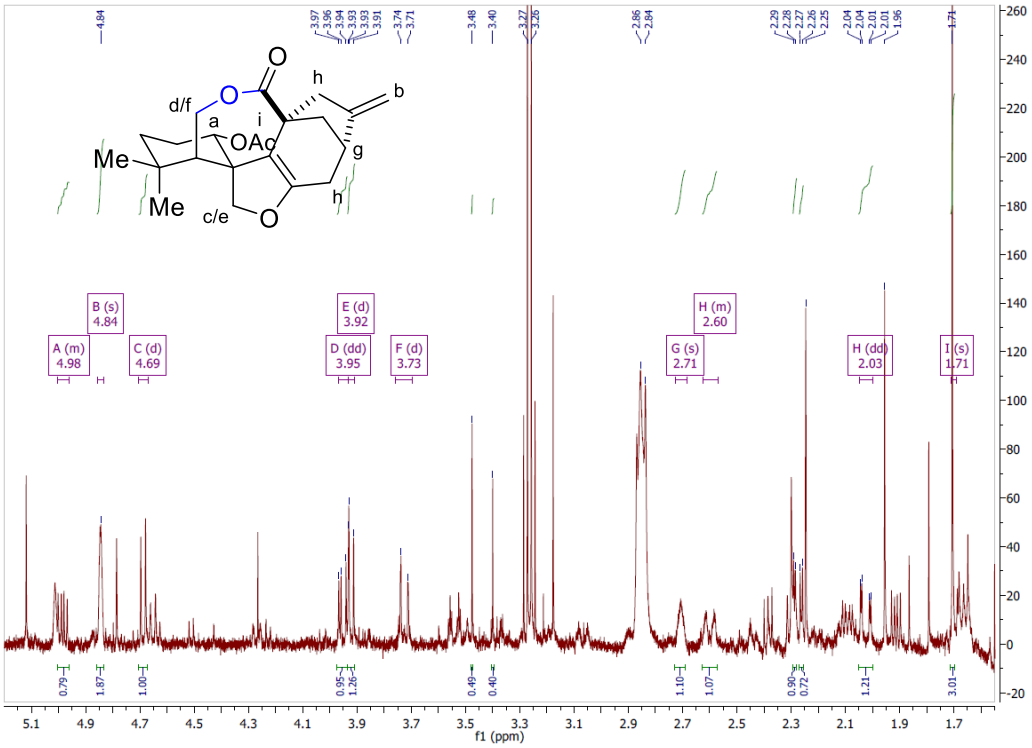


Figure SI.114 ^{1}H NMR spectrum of **68** in $CDCl_3$

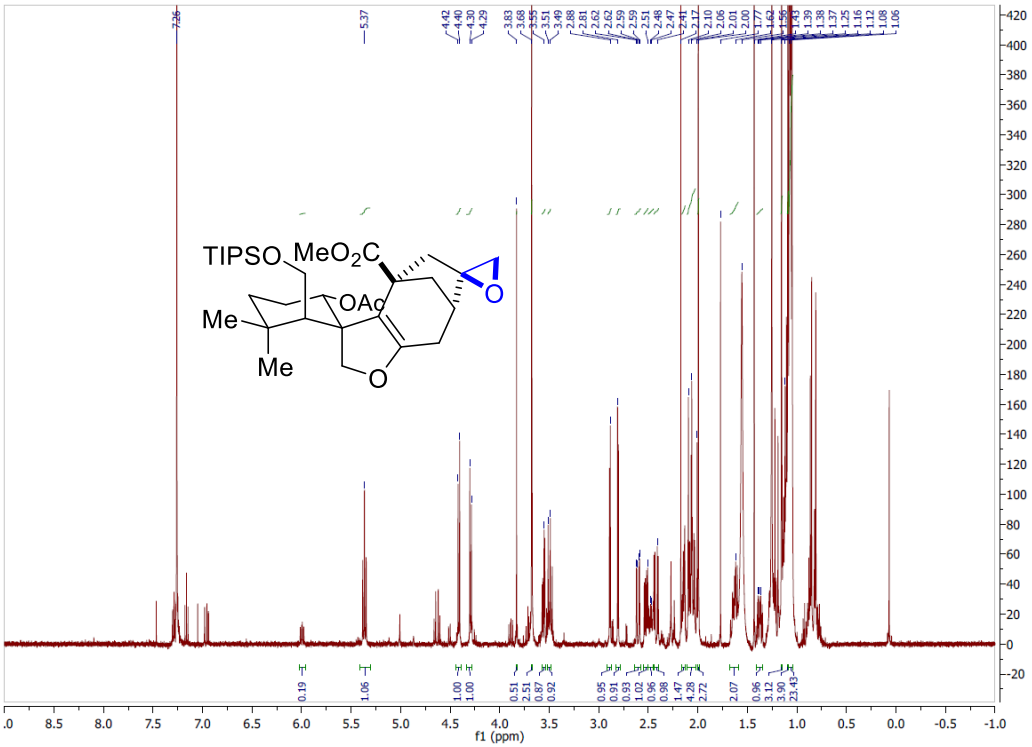


Figure SI.115 ^{1}H NMR spectrum of **69** in $CDCl_3$

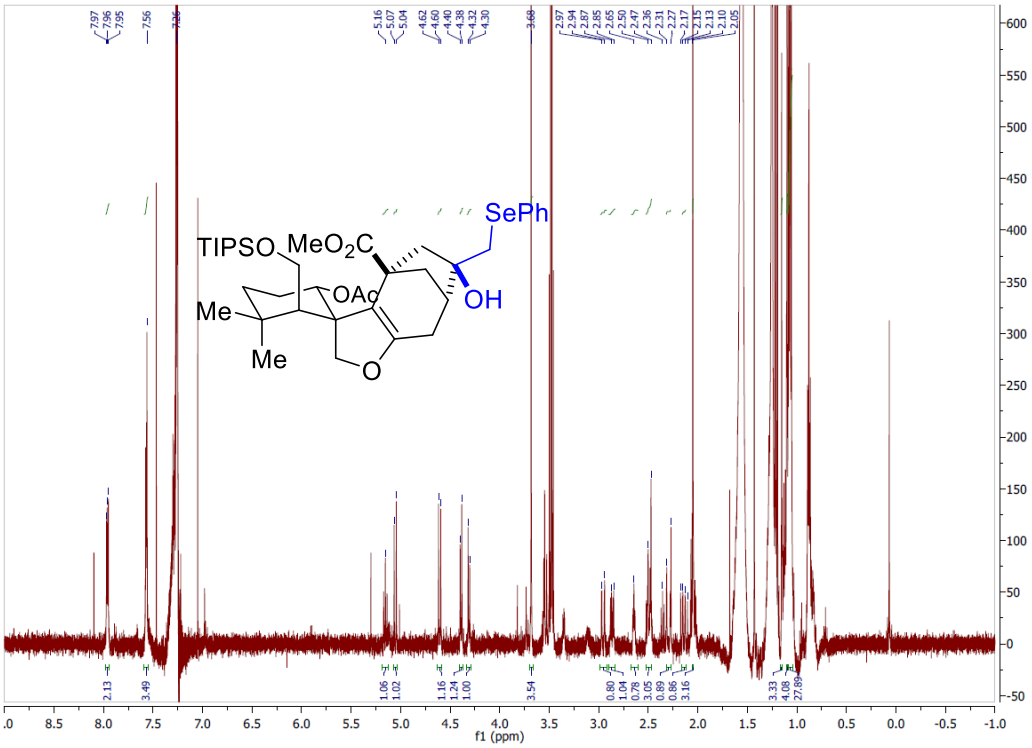


Figure SI.116 Expanded ^{1}H NMR spectrum of **69** in $CDCl_3$

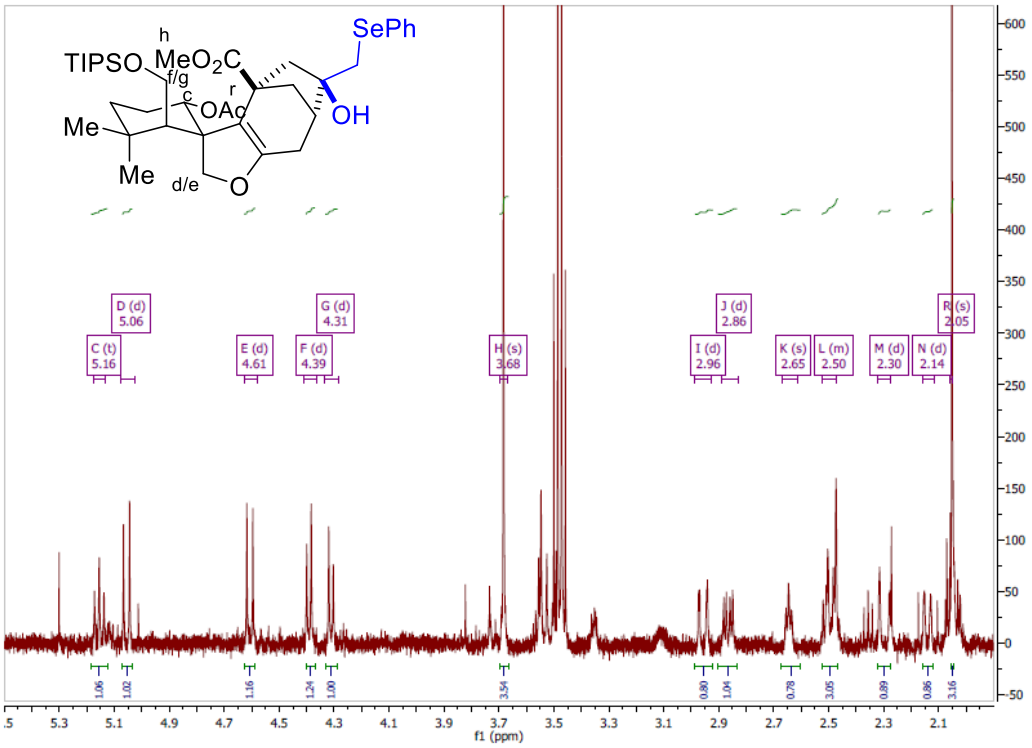


Figure SI.117 ^{1}H NMR spectrum of **70a** in $CDCl_3$

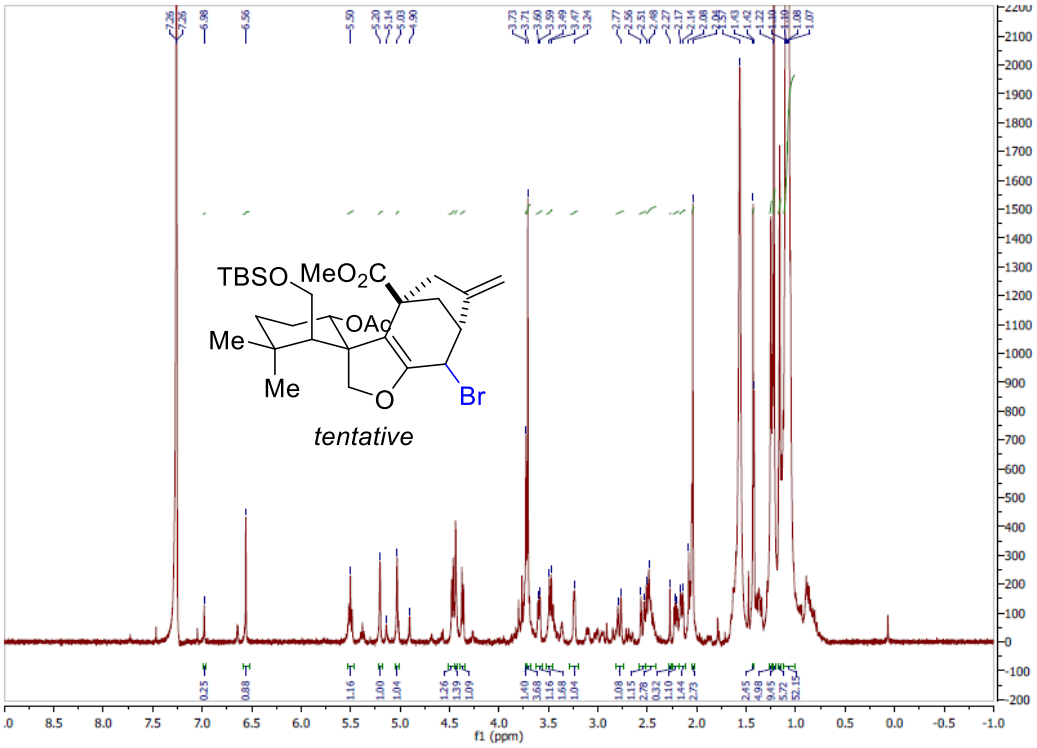


Figure SI.118 Expanded ^{1}H NMR spectrum of **70a** in $CDCl_3$

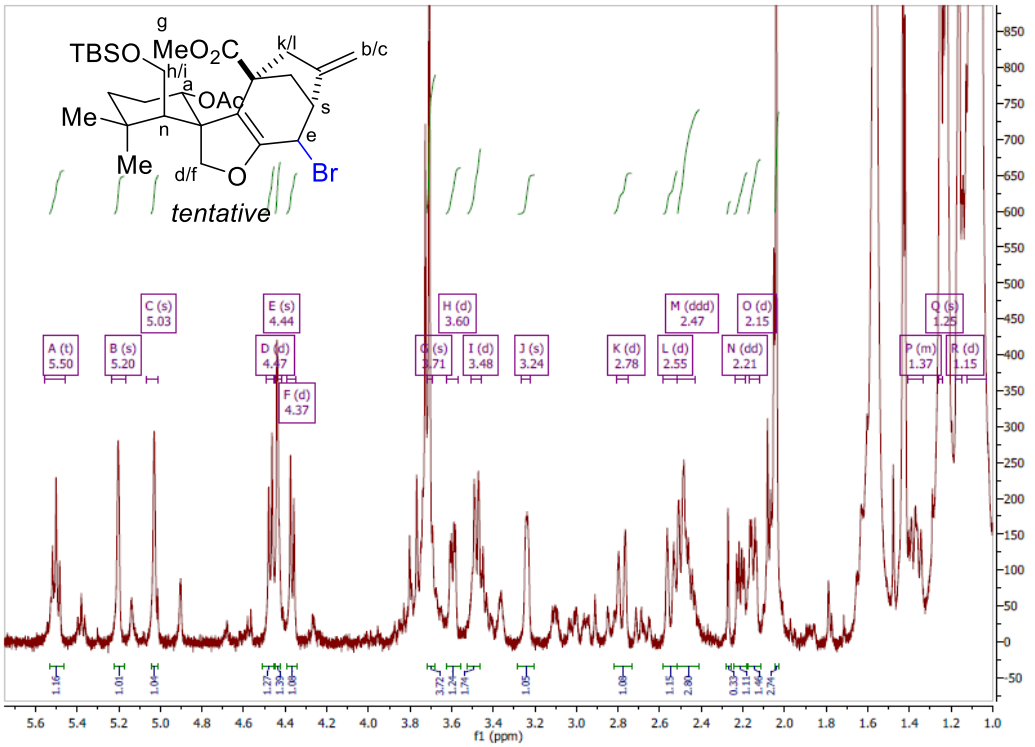


Figure SI.119 COSY spectrum of **70a** in $CDCl_3$

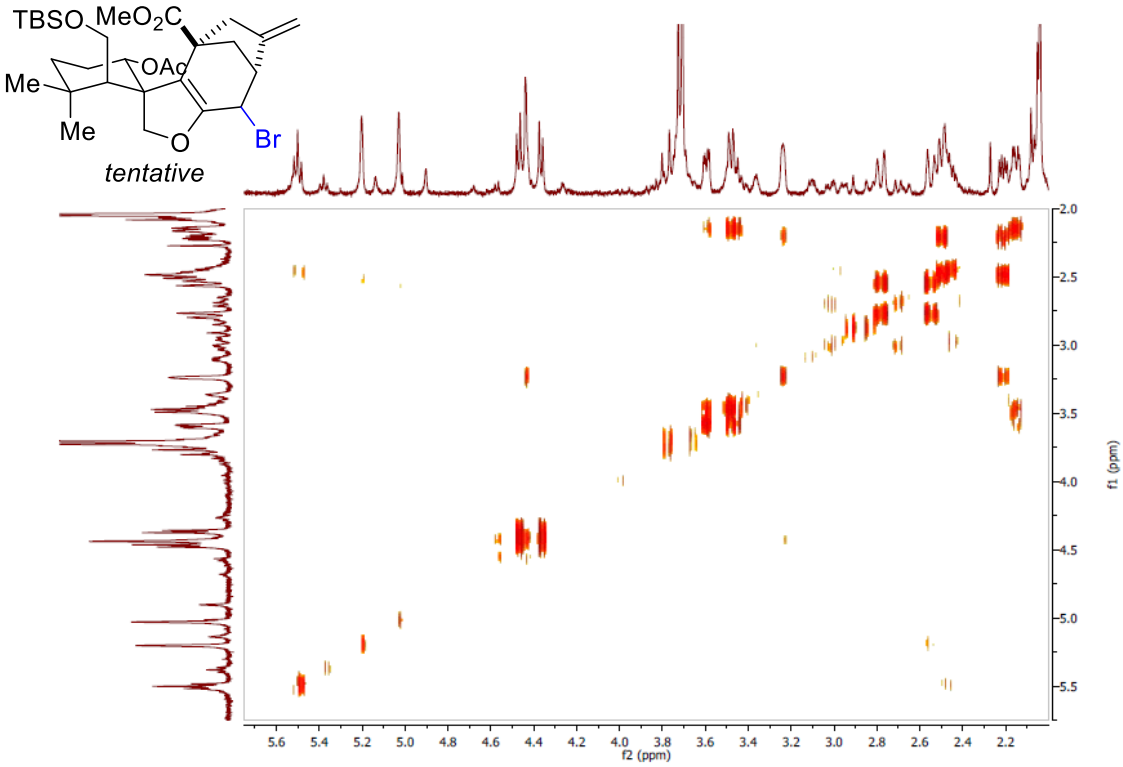


Figure SI.120 Crude ^1H NMR spectrum of **70b** in $CDCl_3$

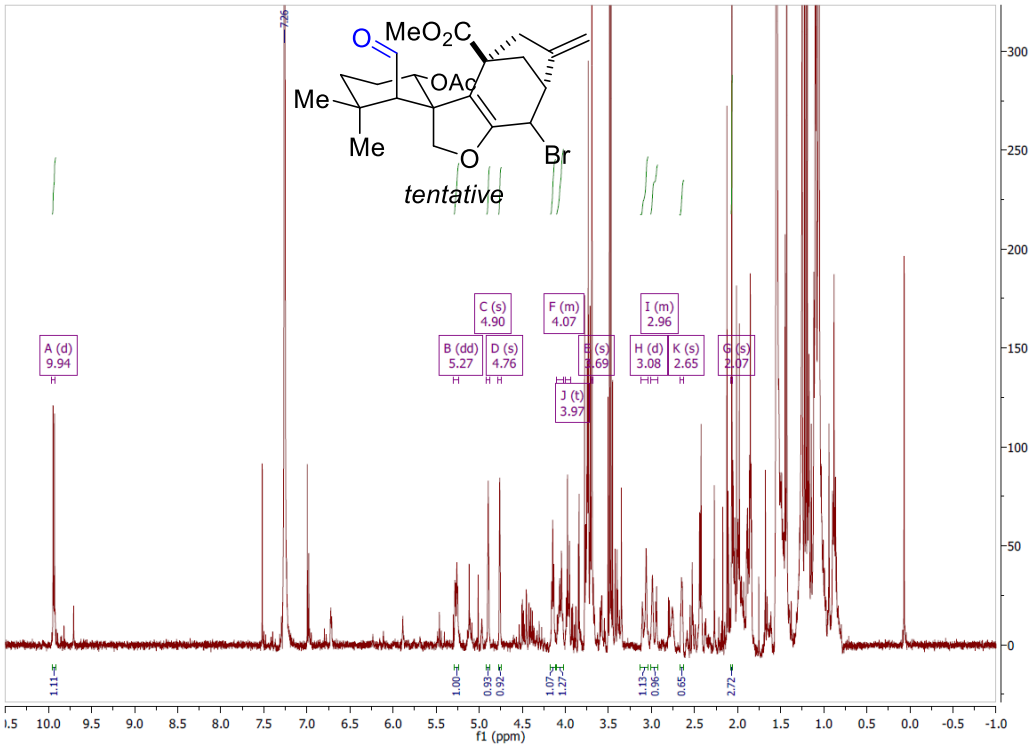


Figure SI.121 Expanded crude ^{1}H NMR spectrum of **70b** in $CDCl_3$

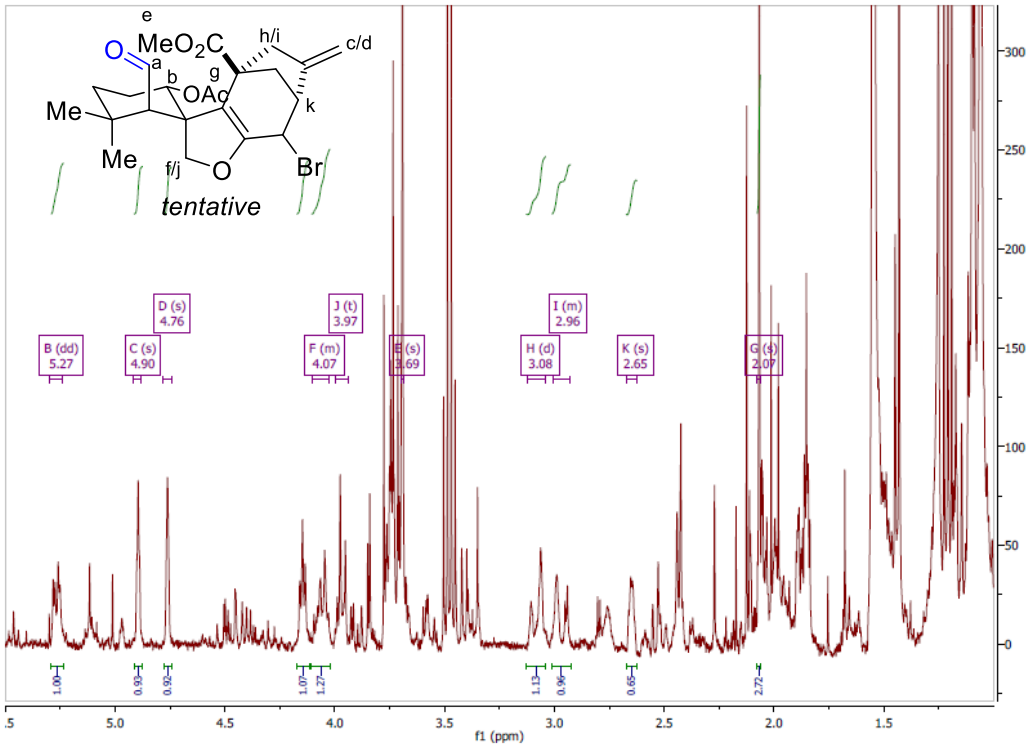


Figure SI.122 ^{1}H NMR spectrum of **71** in $CDCl_3$

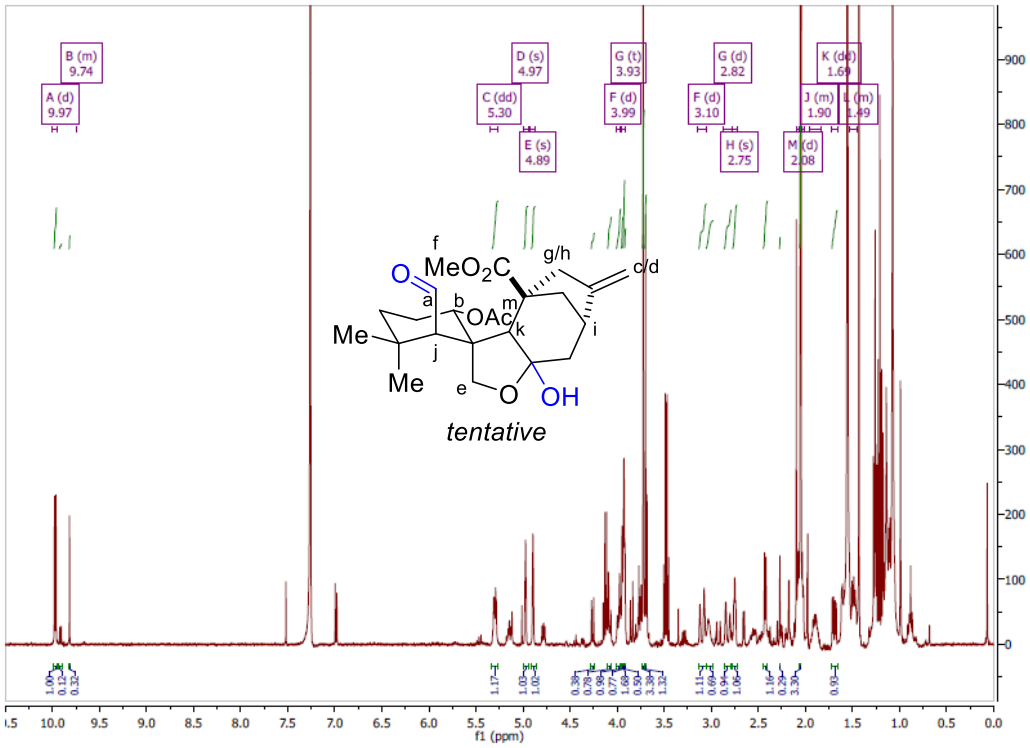


Figure SI.123 Expanded ^{1}H NMR spectrum of **71** in $CDCl_3$

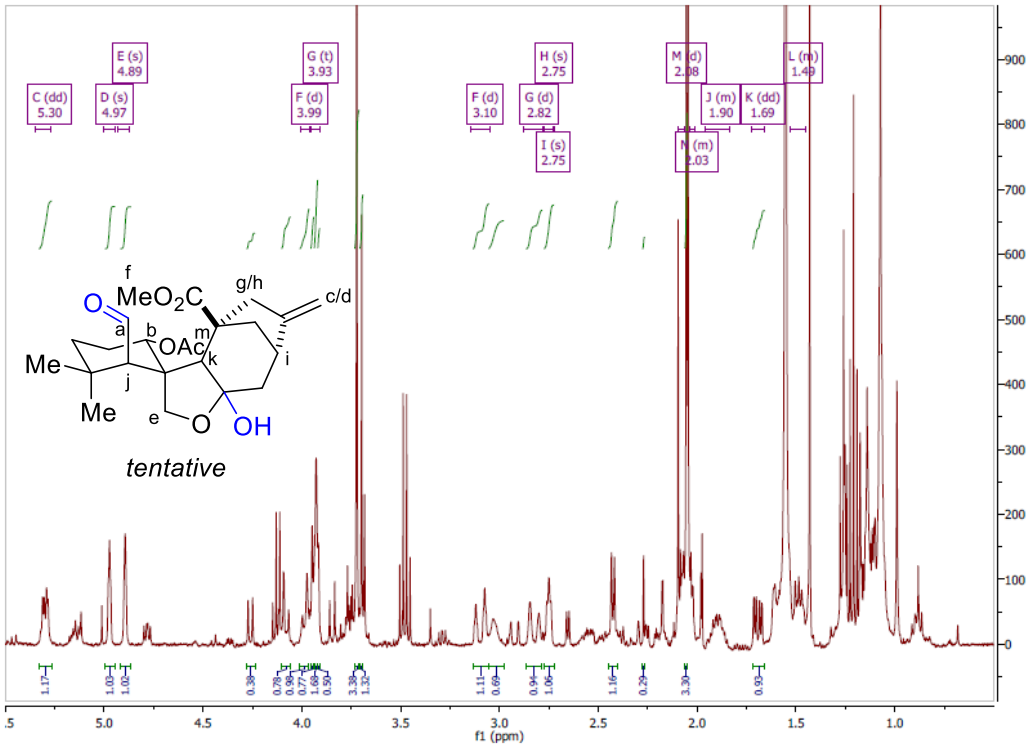


Figure SI.124 COSY spectrum of **71** in $CDCl_3$

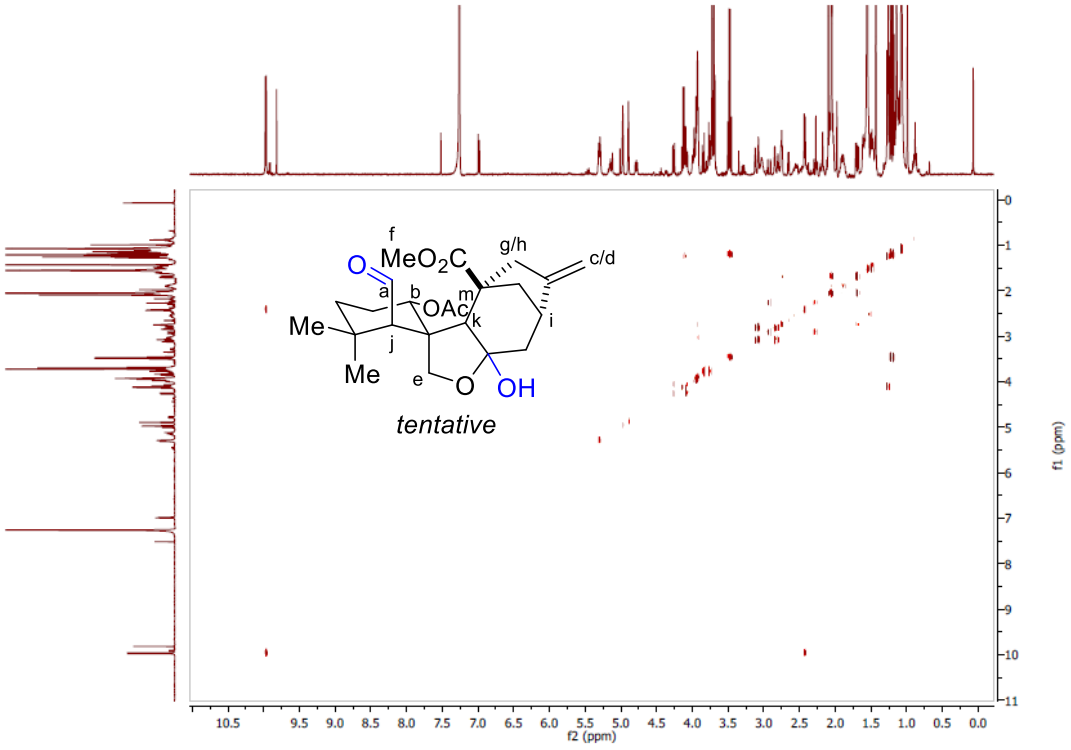


Figure SI.125 Expanded COSY spectrum of **71** in $CDCl_3$

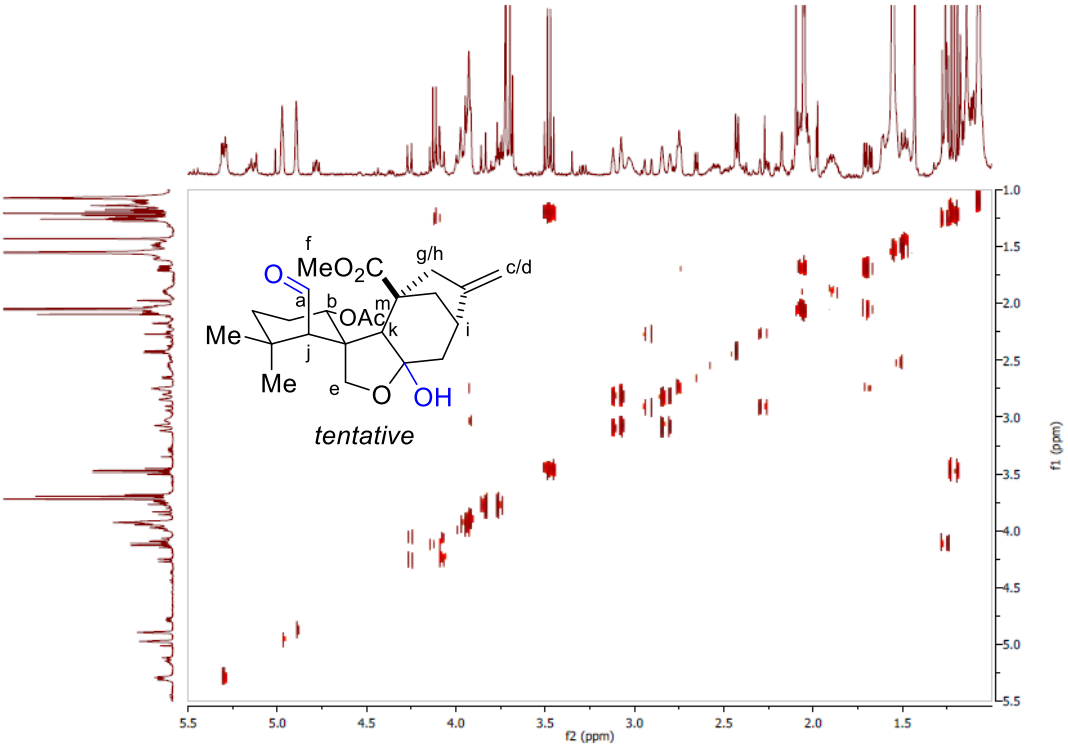


Figure SI.126 Expanded 2 COSY spectrum of **71** in $CDCl_3$

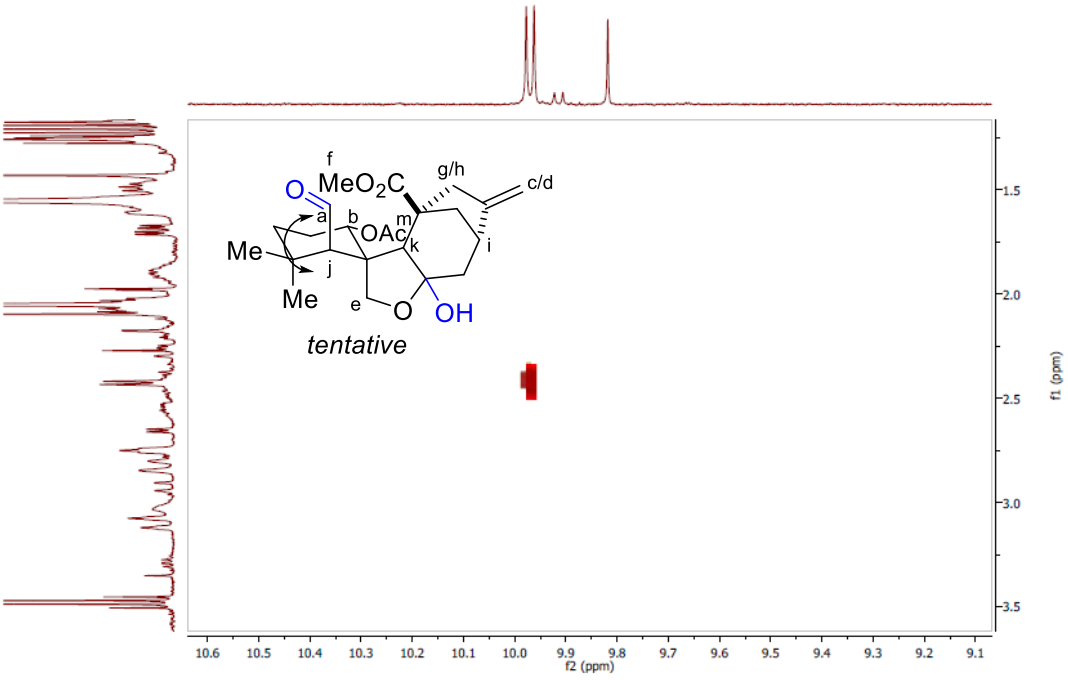


Figure SI.127 Crude ^{1}H NMR spectrum of **72** in $CDCl_3$

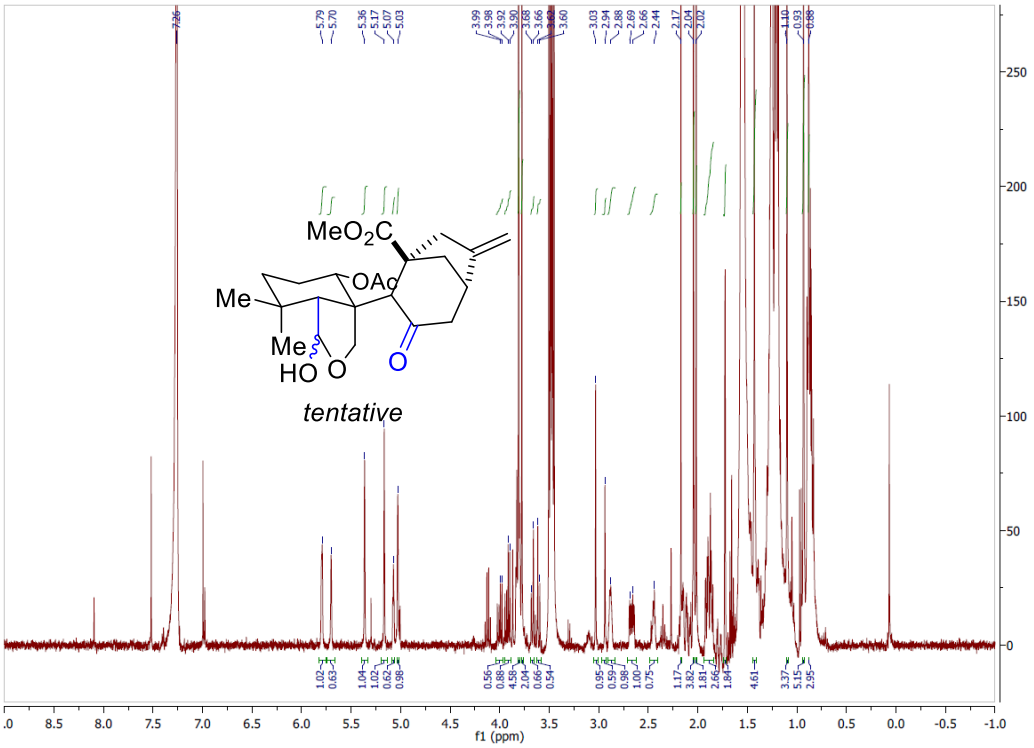


Figure SI.128 Expanded crude ^{1}H NMR spectrum of **72** in $CDCl_3$

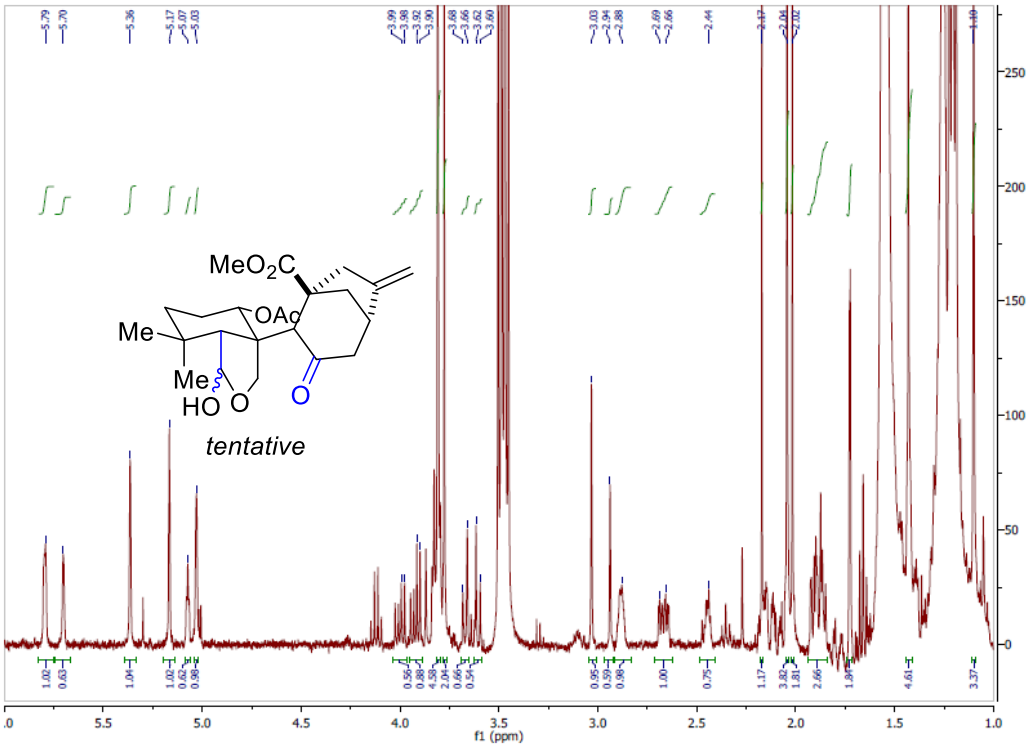


Figure SI.129 Crude ^{1}H NMR spectrum of **73** in $CDCl_3$

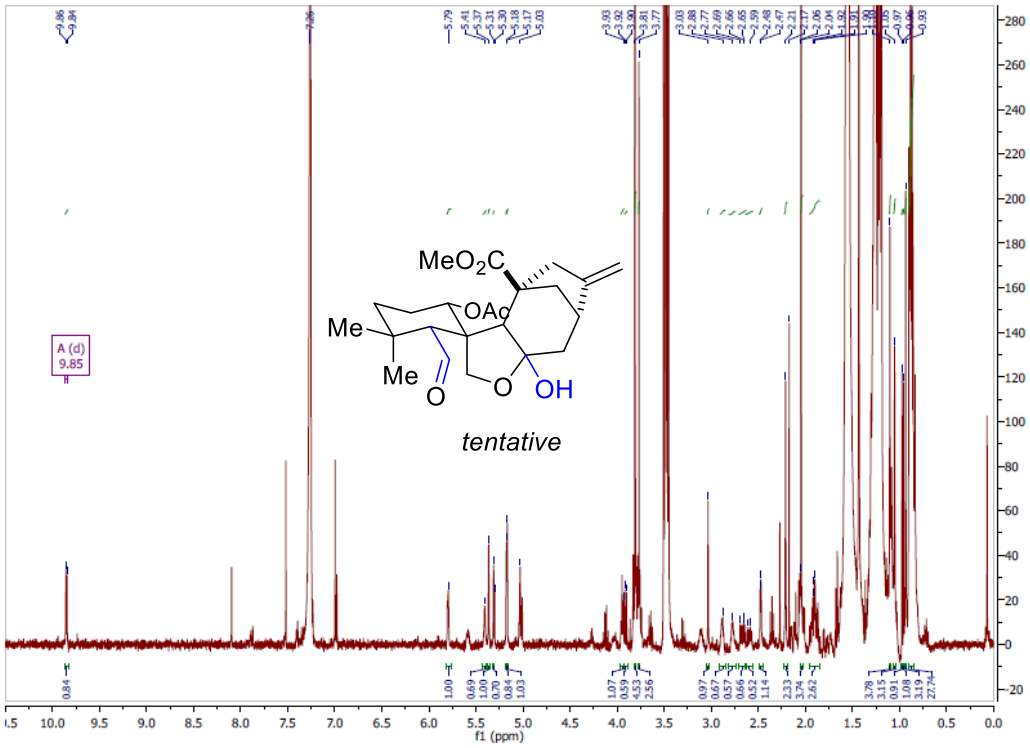
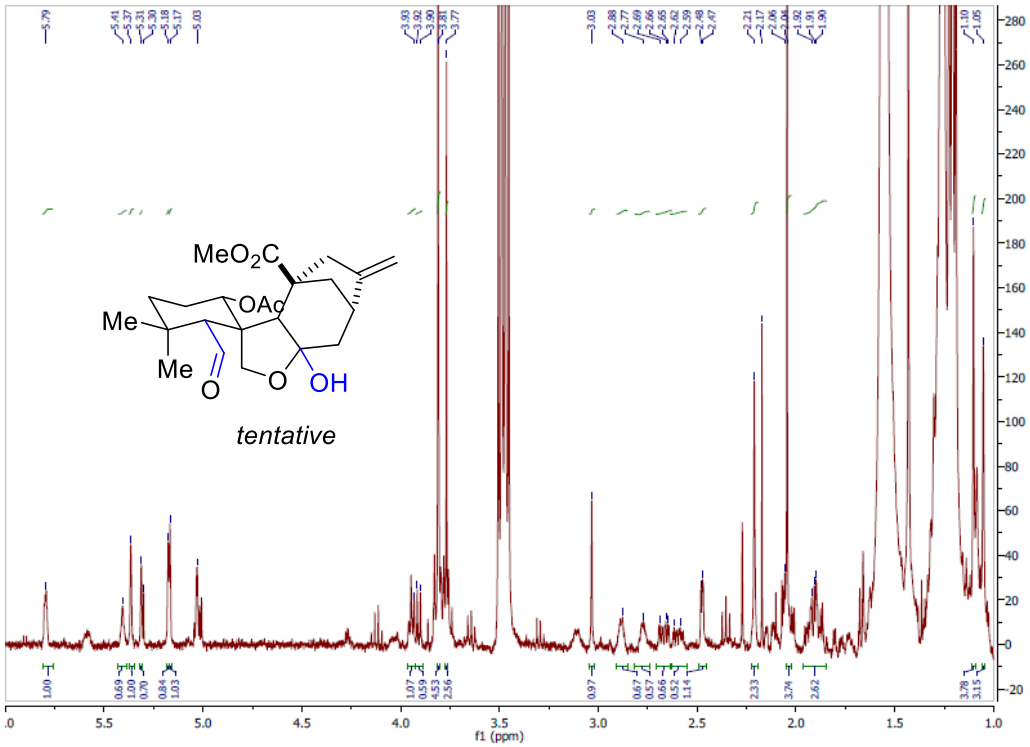
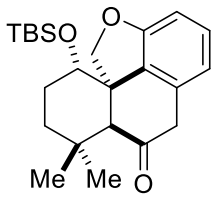


Figure SI.130 Expanded crude ^{1}H NMR spectrum of **73** in $CDCl_3$



5.3 X-Ray Crystallography



Bond precision:	C-C = 0.0030 A		Wavelength=0.71073
Cell:	a=6.6572(4)	b=13.7301(8)	c=18.1576(11)
	alpha=78.303(2)	beta=80.093(2)	gamma=88.093(2)
Temperature:	100 K		

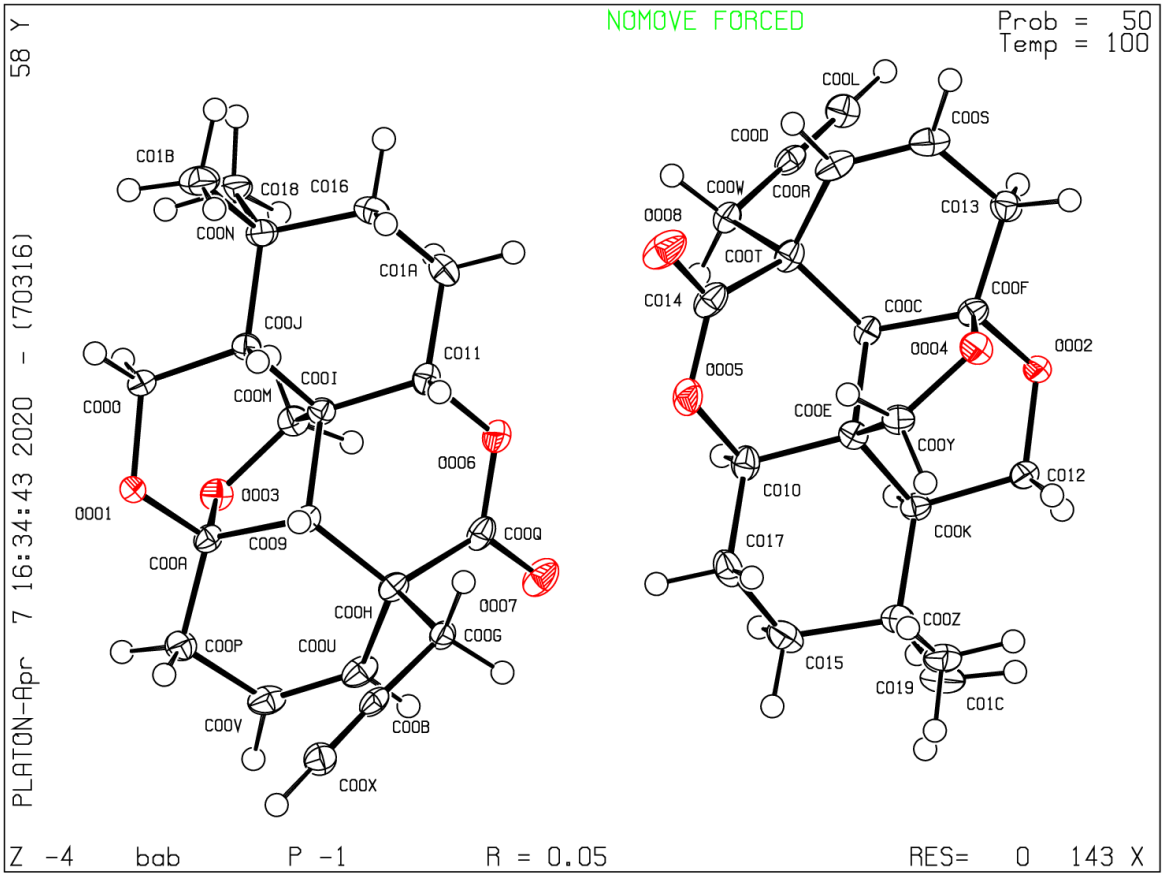
Volume	1600.98(17)
Space group	P -1
Hall group	-P 1
Moiety formula	C20 H24 O4
Sum formula	C20 H24 O4
Mr	328.39
Dx,g cm-3	1.362
Z	4
Mu (mm-1)	0.094
F000	704.0
F000'	704.36
h,k,lmax	8,16,22
Nref	6362
Tmin,Tmax	0.997,0.997
Tmin'	0.993

Correction method= # Reported T Limits: Tmin=0.705 Tmax=0.745
AbsCorr = MULTI-SCAN

Data completeness= 0.997 Theta(max)= 26.091

R(reflections)= 0.0483(4505) wR2(reflections)= 0.1166(6342)

S = 1.013 Npar= 437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Temp = 100
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C016
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C01A
O00J
C011
O00I
O00M
O000
O006
O001
O003
O00Q
O009
O00A
O007
O00H
O00G
O00P
O00U
O00V
O00B
O00X
C00L
O00D
O00S
O00W
O00R
C013
O008
O00T
O00F
C014
O00C
O004
O002
O005
O00E
O00Y
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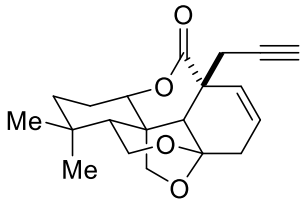
O00Z
C015
C019
C01C
Z -4 bab P -1 R = 0.05 RES= 0 143 X



Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=6.6572(4) b=13.7301(8) c=18.1576(11)
alpha=78.303(2) beta=80.093(2) gamma=88.093(2)

Temperature: 100 K

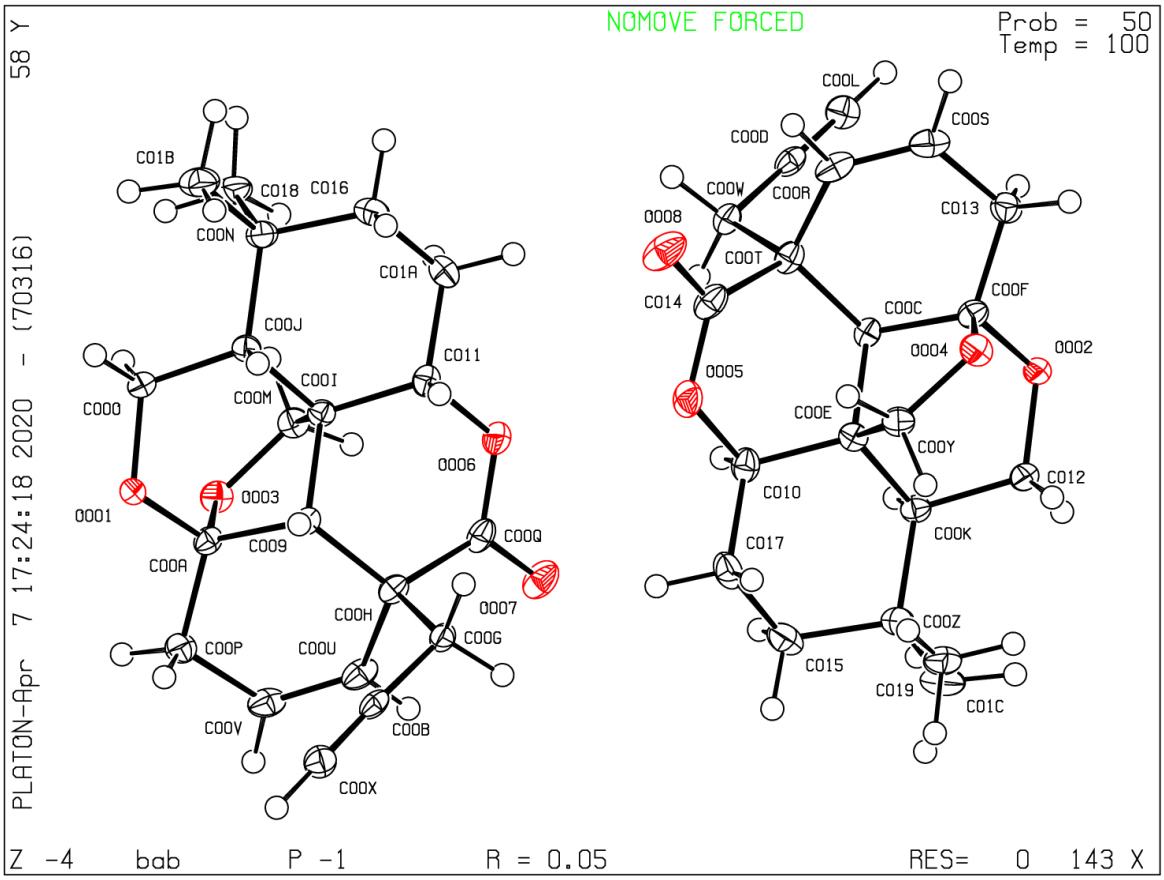
Volume	1600.98(17)
Space group	P -1
Hall group	-P 1
Moiety formula	C20 H24 O4
Sum formula	C20 H24 O4
Mr	328.39
Dx,g cm-3	1.362
Z	4
Mu (mm-1)	0.094
F000	704.0
F000'	704.36
h,k,lmax	8,16,22
Nref	6362
Tmin,Tmax	0.997,0.997
Tmin'	0.993

Correction method= # Reported T Limits: Tmin=0.705 Tmax=0.745
AbsCorr = MULTI-SCAN

Data completeness= 0.997 Theta(max)= 26.091

R(reflections)= 0.0483(4505) wR2(reflections)= 0.1166(6342)

S = 1.013 Npar= 437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C00I
C00O
C00M
O006
O003
O001
C009
C00Q
C00A
C00H
O007
C00P
C00U
C00G
C00V
C00B
C00X
C00L
C00D
C00S
C00W
C00R
C013
O008
C00T
C014
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O002
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C00E
C00Y
C012
C010
C00K
C017
C00Z
C015
C019
C01C
Z -4
bab
P -1
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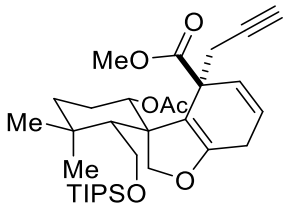


Bond precision: C-C = 0.0023 A Wavelength=0.71073

Cell: a=15.5101(12) b=8.6602(7) c=23.4017(18)
alpha=90 beta=101.177(2) gamma=90

Temperature: 100 K

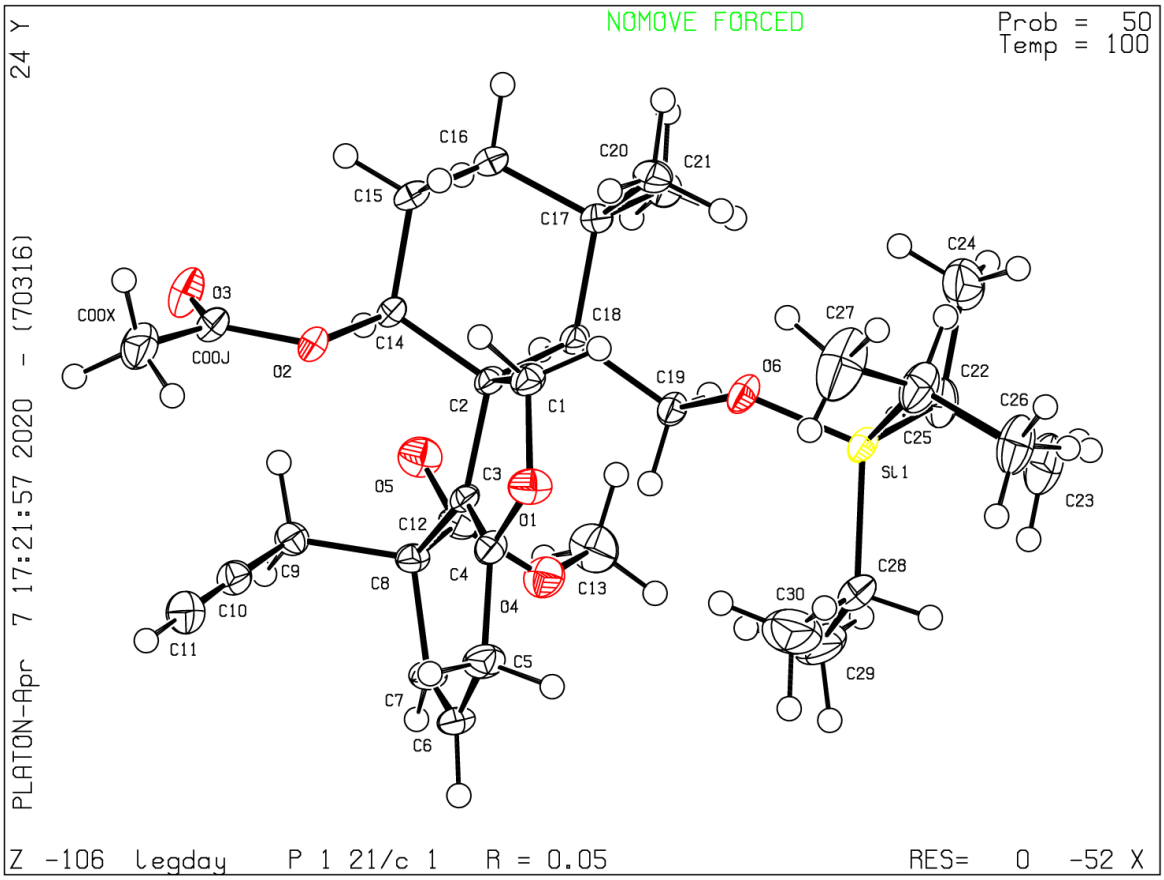
Volume	3083.7(4)
Space group	P 21/c
Hall group	-P 2ybc
Moiety formula	C32 H50 O6 Si
Sum formula	C32 H50 O6 Si
Mr	558.81
Dx,g cm-3	1.204
Z	4
Mu (mm-1)	0.117
F000	1216.0
F000'	1216.87
h,k,lmax	20,11,30
Nref	7141
Tmin,Tmax	0.977,0.977
Tmin'	0.977

Correction method= # Reported T Limits: Tmin=0.531 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 0.998 Theta(max)= 27.575

R(reflections)= 0.0478(5644) wR2(reflections)= 0.1288(7130)

S = 1.042 Npar= 362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Temp = 100
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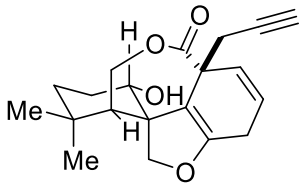
C21
C15
C17
C24
O3
COOX
COOJ
O2
C14
C18
C27
C22
C19
O6
C2
C1
C26
C25
SL1
C23
O5
C3
O1
C12
C9
C8
C4
C13
C28
C10
O4
C30
C11
C5
C29
C7
C6



Bond precision: C-C = 0.0102 A Wavelength=0.71073

Cell: a=13.482(2) b=13.911(2) c=18.092(3)

alpha=90 beta=95.662(5) gamma=90

Temperature: 100 K

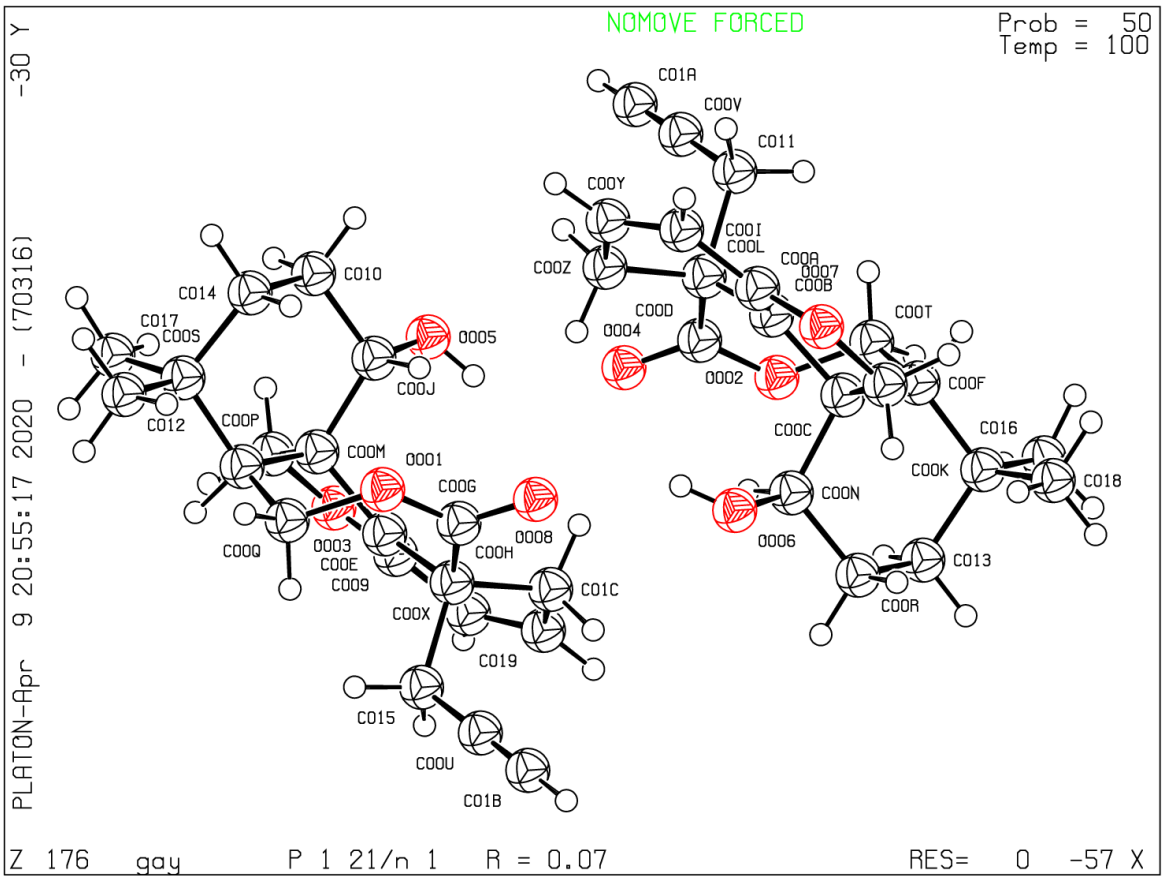
Volume	3376.6(9)
Space group	P 21/n
Hall group	-P 2yn
Moiety formula	C20 H24 O4
Sum formula	C20 H24 O4
Mr	328.39
Dx,g cm-3	1.292
Z	8
Mu (mm-1)	0.089
F000	1408.0
F000'	1408.71
h,k,lmax	11,12,15
Nref	2345
Tmin,Tmax	
Tmin'	

Correction method= # Reported T Limits: Tmin=0.595 Tmax=0.744
AbsCorr = MULTI-SCAN

Data completeness= 0.998 Theta(max)= 18.067

R(reflections)= 0.0674(1530) wR2(reflections)= 0.1780(2340)

S = 1.021 Npar= 199



Acknowledgement

I would like to thank Dr. Ki-Young Yoon for preforming X-ray crystallography experiments and calculations.