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Toward (–)-Enterocin: Evolution of a Serial C–H Functionalization Strategy

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 27/03/2018

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"Noble Odysseus, you ask about your sweet homecoming, but the god will make it a bitter journey. I think you will not escape the Earth-Shaker, who is angered at heart against you," **...** ***The Ghost of Teiresias, The Odyssey, Homer.***

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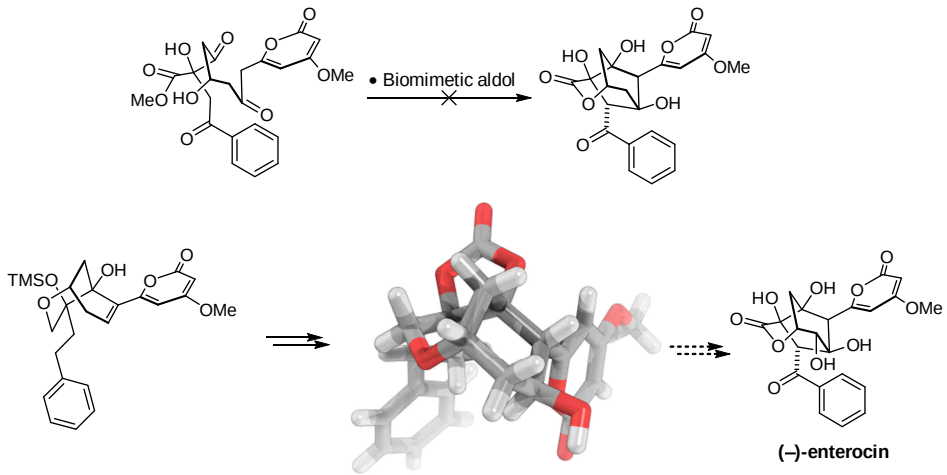
Abstract

Polyketides represent a major class of natural products with widely varied structural features and therapeutic properties. The antibiotic enterocin is a structurally unique polyketide isolated from several strains of *Streptomyces* microorganisms which features a compact, heavily oxidized oxa-protoadamantane core with seven contiguous sterocenters. Our initial investigations towards its total synthesis led us to question the feasibility of a bioinspired approach which inspired the design of a *de novo* strategy that relied on late-stage functionalization. The latter permitted the convergent assembly of its 2-oxabicyclo[3.3.1]nonane core by means of a cuprate Barbier reaction. Thereafter, further investigations to close the final cyclopentane ring of enterocin conclude this script.



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"*It's strange how a descent seen from below looks like a climb*" Goofy

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I also wish to mention an unaccountable amount of gratitude and love towards my wife Eva Morre: I told you it would have been fine, generally I am always right.

List of Abbreviations

Å	angstrom
Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
aq.	aqueous
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
br	broad (NMR spectroscopy, IR spectroscopy)
Bu	butyl
BQ	benzoquinone
°C	degree Celsius
cal	calorie(s)
CCDC	Cambridge Crystallographic Data Centre
CoA	coenzyme A
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
δ	chemical shift (NMR)
d	doublet (NMR spectroscopy)
D	dexter (“right”)
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$C_2H_4Cl_2$	1,2-dichloroethane
CH_2Cl_2	dichloromethane
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DIPT	diisopropyl D-tartrate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethyoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
E	opposite, *trans*
ee	enantiomeric excess
EI	electron impact ionization
ent	enantiomer
epi	epimer
eq	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
Et	ethyl
EWG	electron withdrawing group
FCC	Flash column chromatography
g	gram(s)
h	hour(s)
H•	Hydrogen radical
HG II	Hoveyda-Grubbs II catalyst
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
hv	irradiation
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
Hz	Hertz (frequency)
i	*iso*(mer)
IC_{50}	half maximal inhibitory concentration
imid	imidazole
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant (NMR)
k	kilo
L	liter(s)

L	laevus (“left”)
LEDs	Light-emitting diodes
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	molar
m	meter(s)
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m	*meta*
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mL	milliliter(s)
mmol	millimole(s)
MOM	methoxymethyl
MS	mass spectrometry
MS	molecular sieves
Ms	methanesulfonyl
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
NP(s)	Natural product(s)
Nu	nucleophile
p	*para* (isomer)
PG	protecting group
PHAL	phthalazine
Piv	pivaloyl
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *para*-toluene-sulfonate
p-TsOH	*para*-toluenesulfonic acid
pyr	pyridine
q	quartet (NMR spectroscopy)
R	undefined substituent
rac	racemic
RCM	ring-closing metathesis
R_f	retention factor
RT	room temperature
s	strong (IR spectroscopy)
s	singlet (NMR spectroscopy)
sat.	saturated
S.A.D.	Sharpless asymmetric dihydroxylation
S_N	nucleophilic substitution
T	temperature
t	time
t	tertiary
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydrogenperoxide
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet (irradiation)
w	weak (IR spectroscopy)
wt%	weight percent
Z	zusammen, “together”

Table of Contents

Abstract ..... **I**

Acknowledgement ..... **II**

List of Abbreviations ..... **IV**

1. Enterocin: General Introduction **3**

1.1. Isolation, Activity and Structure of the Enterocins 3

1.2. Biosynthesis and Enzymatic Total Synthesis 6

1.3. Previous Approaches 9

1.4. References 11

2. Biomimetic Approaches to (−)-Enterocin and (−)-Deoxyenterocin **12**

2.1. First Approach 12

2.2. Further Synthetic Studies on a Partially Cyclized Precursor 25

2.3. References 31

3. Late-Stage Oxidation Approaches Toward Enterocin **34**

3.1. Late-Stage Functionalization of Complex Scaffolds 34

3.1.1. Total Synthesis of Taxuyunnanine D 34

3.1.2. Total Synthesis of Majucin 36

3.1.3. Total Synthesis of Nigelladine A 38

3.2. Toward (−)-Enterocin: An Improved Cuprate Barbier Protocol to Overcome Strain and Sterical Hinderance 40

3.3. Second Generation Late-Stage Oxidation Approach Towards Enterocin 45

3.3. References 51

4. Conclusion and Outlook **55**

5. Summary **56**

6. Experimental Section **60**

6.1. General Experimental Details 60

6.2. Supporting Information for Chapter 2.1. 62

6.2.1. Experimental Procedures 61

6.2.2. References. 102
6.2.3. NMR Spectra for Chapter 2.1. 103
6.2.4. X-ray Crystallographic Data for Chapter 2.1. 145
6.3. Supporting Information for Chapter 2.2. 147
6.3.1. Experimental Procedures 147
6.3.2. NMR Spectra for Chapter 2.2. 156
6.4. Supporting Information for Chapter 3.2. 167
6.4.1. Experimental Procedures 167
6.4.2. Screening Tables 199
6.4.3. References. 206
6.4.4. NMR Spectra for Chapter 3.2. 207
6.4.5. X-ray Crystallographic Data for Chapter 3.2. 239
6.5. Supporting Information for Chapter 3.3. 242
6.5.1. Experimental Procedures 3.3. 242
6.5.2. References 262
6.5.3. NMR Spectra for Chapter 3.3. 263
6.5.4. X-ray Crystallographic Data for Chapter 3.3 281

1. Enterocin: General Introduction

1.1. Isolation, Activity and Structure of the Enterocins

In the late 1970s the Miyairi[1a] and Seto[1b] groups independently reported the isolation of a new polyketide natural product (NP) from terrestrial strains of *Streptomyces* which they respectively named enterocin (**1.1**) and vulgamycin (**Figure 1.1**).

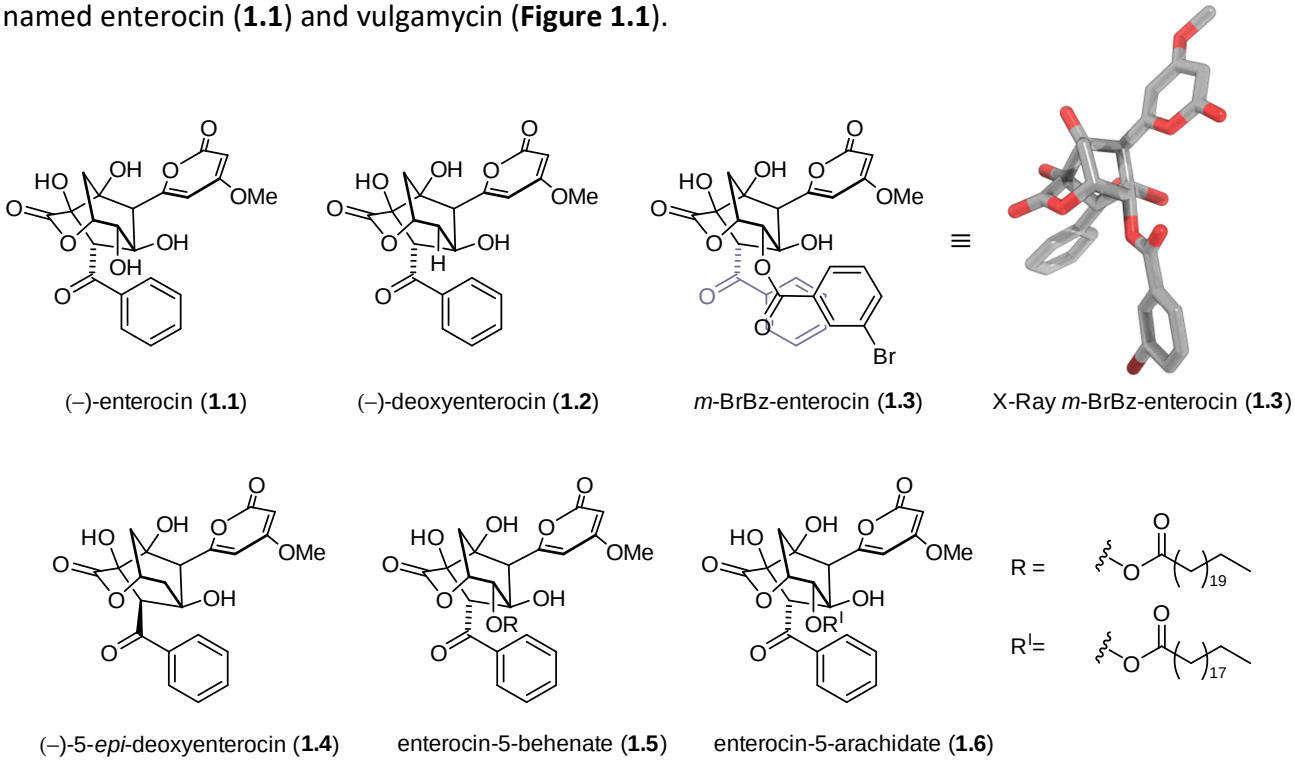


Figure 1.1 Structures of naturally occurring enterocins and X-ray structure of *m*-BrBz derivative of **1.3**.

The relative configuration of **1.1** was elucidated by NMR analysis,[1b] and later the absolute configuration was unequivocally determined by X-ray crystallographic analysis of a benzoylated derivative (**1.3**).[1c] In 1991[1d] another isolation of **1.1** from a different strain of *Steptomyces* was reported, and shortly thereafter Fenical *et al.*[1e] reisolated the same NP from a marine ascidian of the genus *Didemnum* together with sizable quantities of the closely related (−)-deoxyenterocin (**1.2**) and minor fractions of enterocin-5-behenate (**1.5**) and enterocin-5-arachidate (**1.6**). In this case the authors surmised a symbiotic relationship between the ascidians and microorganisms to explain the origin of the newly found NPs. Indeed in the same year, the Davidson group reported the isolation of a number of α-pyrone containing compounds (**1.4**, **1.5** and **1.6**) derived "*from a*

streptomycete cultured from shallow water marine sediments."[1f] Finally, in 2017, the group of Zhu[1g] published a study on *streptomyces* sp. OUCMDZ-3434, an endophytic microorganism, living in the tissues of another organism in symbiotic fashion that seemingly enhances the adaptability of this marine algae host. This endophyte produces both (−)-enterocin (**1.1**), of which 600 mg were isolated, and (−)-deoxyenterocin (**1.2**).

Structurally, all the enterocins possess a rigid oxa-protoadamantane[2] scaffold that is adorned with a diverse set of functional groups (**Figure 1.2**). This cage is a rare structural feature that is found only in a handful of biosynthetically unrelated compounds such as anisatinic acid (**1.7**),[3a] the trixanolides (**1.8**)[3b] and a few from the annotinolides series (**1.9** and **1.10**).[3c] Enterocin's seven contiguous stereocenters are constituents of the cage, four of which are hydroxylated positions while the other two are attached to a benzoyl unit and an α-pyrone unit. The secondary alcohol is acylated with fatty acids residues in the case of **1.5** and **1.6**, while it is not present in **1.2** may have consequences with regards to the biogenesis of these NPs.

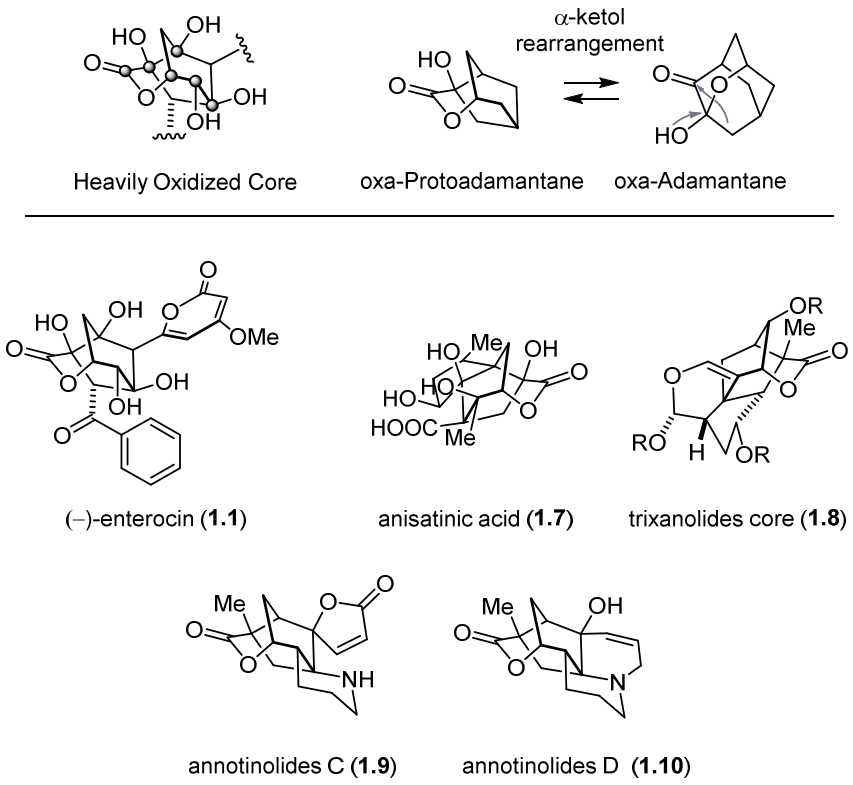


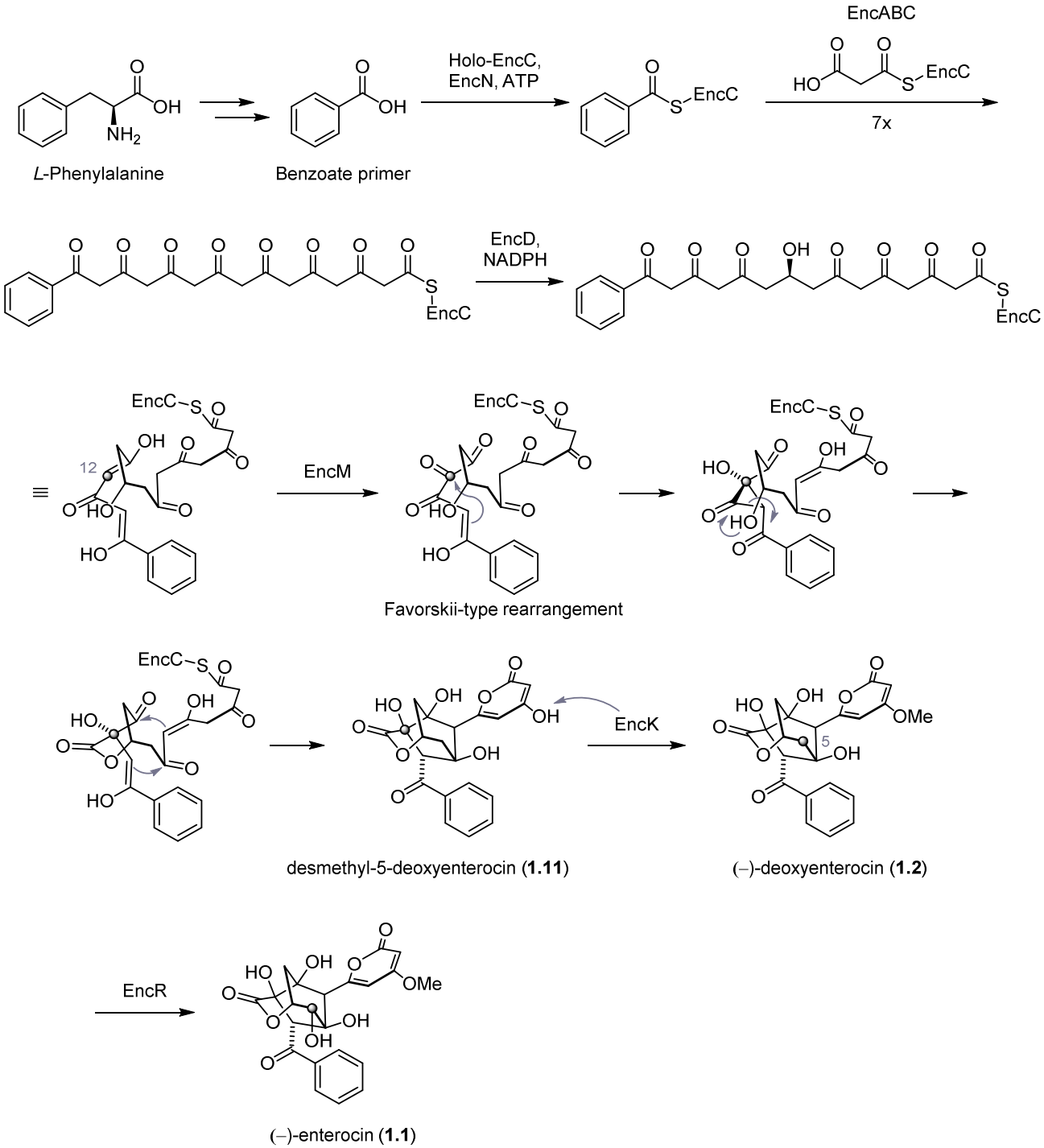
Figure 1.2 Oxa-protoadamane structural motif in natural products.

The early reports of **1.1** mention its bacteriostatic activity against gram-positive and gram-negative bacteria such as *Escherichia coli*, *Staphylococcus* and *Corynebacterium*.[1a] Later on, in 1991,

industrial researchers disclosed that enterocin showed herbicidal activity when applied post-emergence to the cultivation of maize, cotton and barley.[1d] During the course of their studies they discovered that this antibiotic is targeting an isoleucine-dependent pathway. Of late, deoxyenterocin has been evaluated through a CPE inhibition assy to be active against influenza A (H1N1) virus.[1g]

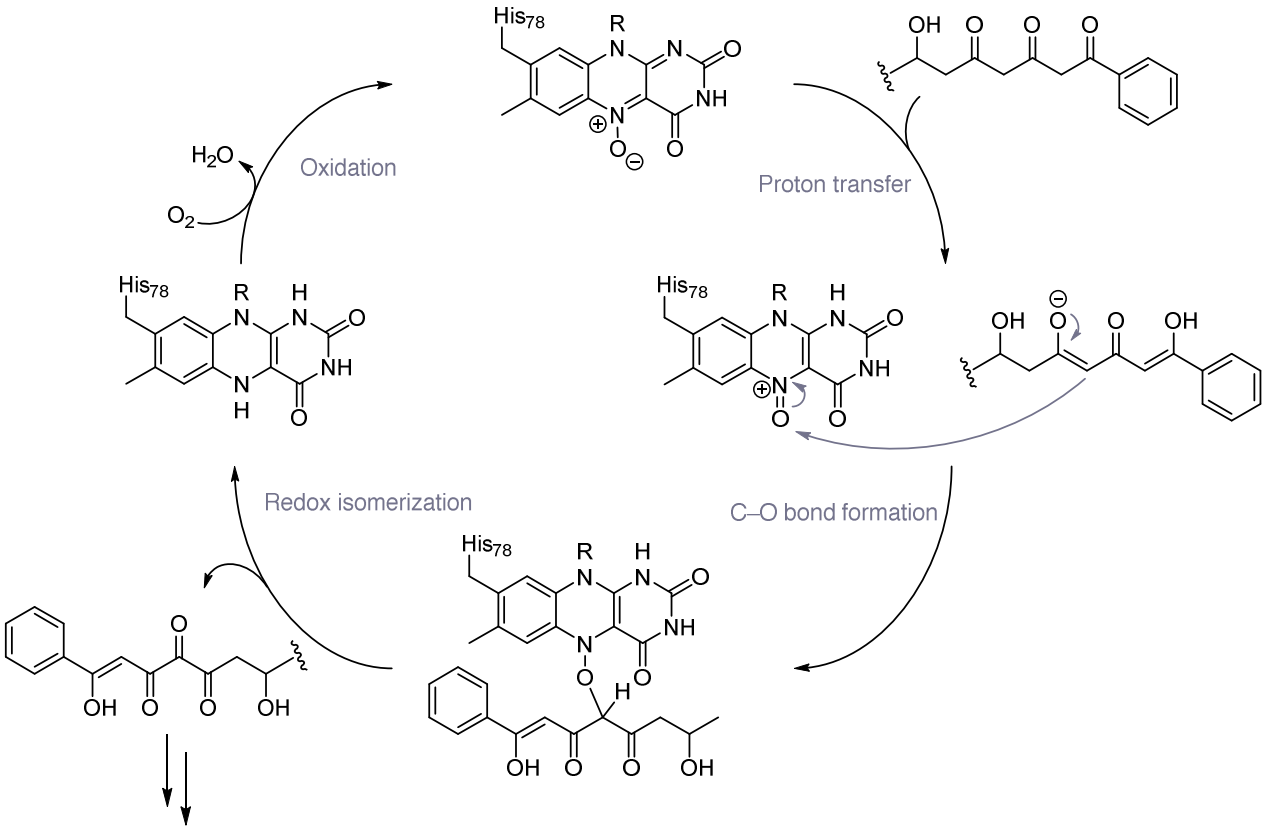
1.2. Biosynthesis and Enzymatic Total Synthesis

The biosynthesis of the enterocins was studied extensively in a series of publications by the Moore group, culminating in the enzymatic total synthesis of **1.1** (**Scheme 1.1**) and the elucidation of a highly unusual mechanism in its biosynthesis. [4]



Scheme 1.1 Overview of enterocin's biosynthetic pathway.

A benzoate unit, derived from *L*-phenylalanine, functions as the primer that undergoes elongation by a ketosynthase chain-length-factor heterodimer (EncABC), which adds seven molecules of malonyl coenzyme A to provide an octaketide. Subsequent NADPH-dependent reductase EncD reduces it to a dihydrooctaketide which, instead of following the typical type II polyketide pathway that forms aromatic ring systems, is oxidized by a rare oxygenase, EncM (**Scheme 1.2**). This flavoprotein cofactor enacts a sequential oxidation at C_{12} to form a trione which undergoes a Favorskii-type rearrangement. Therefore, EncM acts as a "Favorskiiase" enzyme. As a result, the benzylketone enolate forms a cyclopropanone intermediate that is ruptured intramolecularly by the only hydroxyl available to yield a reactive lactone. It is probable that this enzyme also mediates the subsequent aldol reactions that close the tricyclic core as well as the pyrone condensation to give desmethyl-5-enterocin intermediate **1.11**. A putative methyltransferase (EncK) completes the biosynthesis of natural **1.2** whereas **1.1** is formed after a final cytochrome P450 hydroxylase (EncR) installs the C_5 secondary alcohol.

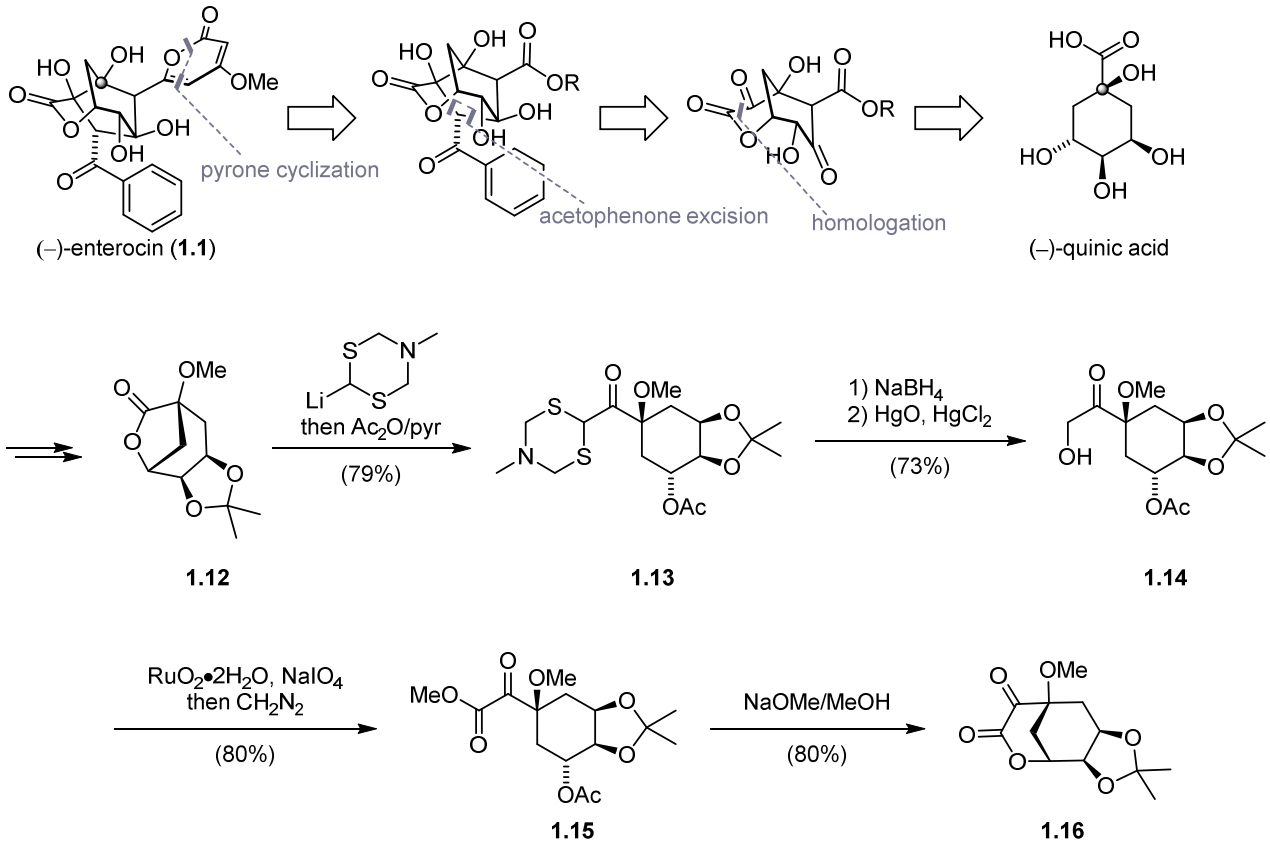


Scheme 1.2 Moore's proposed EncM oxidative mechanism.

The mechanism of the flavin cofactor of EncM has also been investigated in depth. The EncM enzyme, whose structure was elucidated by X-ray crystallography, consists of a homodimer which is covalently linked to a flavin cofactor by a histidine residue (**Scheme 1.2**). This resides in an L-shaped tunnel where the dihydroctaketide can be accommodated in an elongated conformation to avoid uncatalyzed aldol condensation reactions that result in aromatic structures. Structural analysis of this ligand-binding tunnel revealed that the (*R*)-configuration of the hydroxyl group is pivotal for the enzyme's substrate recognition and for the "*spatial and temporal control of the EncM catalyzed reaction.*"[4] Mechanistically, Moore and coworkers propose that the flavin-*N*-oxide undergoes a proton transfer with the substrate and subsequent tautomerization of the resulting *N*-hydroxylamine to an *O*-electrophilic oxoammonium ion. Subsequent C−O bond formation with the newly formed enolate could then proceed through a direct nucleophilic attack (mechanistic possibilities are reported in the original publication)[4c] followed by a redox isomerization to yield a triketide whose fate has been previously described. The reduced flavin cofactor is finally oxidized by oxygen to close the catalytic cycle.

1.3. Previous Approaches to (−)-Enterocin

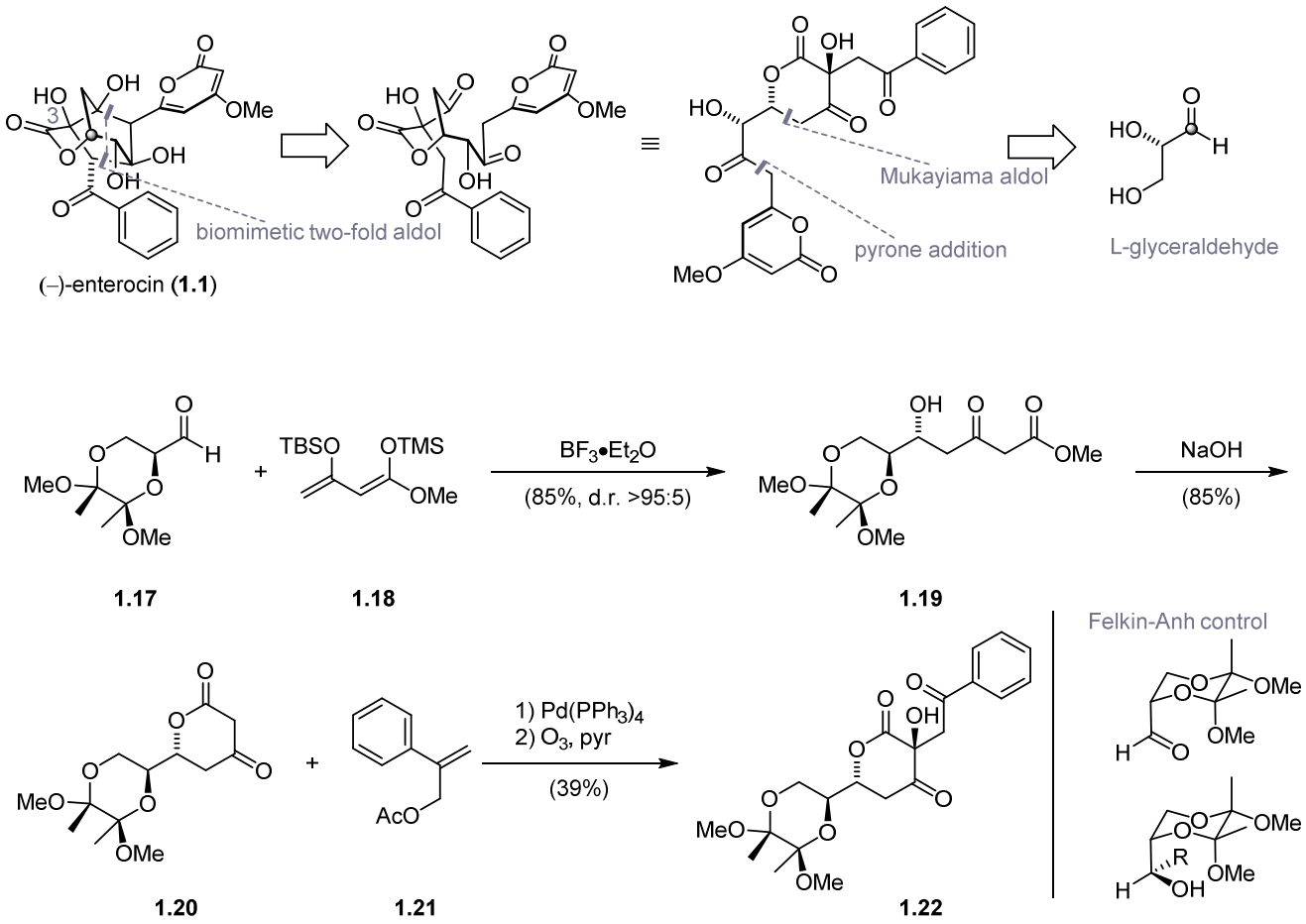
The first reported approach towards the total synthesis of (−)-enterocin (**1.1**) was conducted by Khuong-Huu and commenced from (−)-quinic acid (**Scheme 1.3**), which already contains the cyclohexane ring with two correctly positioned hydroxyls.[5] Although only briefly discussed, α-ketolactone **1.16** is key intermediate in their retrosynthetic analysis. This lactone was accessed by elaboration of quinic acid to lactone **1.12** followed by one homologation to **1.13**. This was then treated with a lithiated *N*-methyl-dihydrodithiazine, a more easily hydrolyzable analog of dithiane, and acetylated to compound **1.13**. Subsequent reduction/deprotection yielded an hydroxyaldehyde which readily tautomerized to ketone **1.14**. Eventually, oxidation by RuO_4 and base-catalyzed lactonization advanced the synthesis to bicyclic compound **1.16**. Despite the interesting strategy no further studies were disclosed.



Scheme 1.3 First report by Khuong-Huu of an approach to the synthesis of **1.1**.

The second attempt to synthesize enterocin was based on a biomimetic disconnection relying on the two-fold aldol reactions which were previously discussed.[6] Unraveling of this substrate resulted in a densely functionalized β-ketolactone which was traced back to *L*-glyceraldehyde

(**Scheme 1.4**). In the forward sense, vinylogous addition of silyl ketene acetal **1.18** to Ley's protected aldehyde (**1.17**) delivered Mukaiyama aldol product **1.19** with good yield and excellent d.r. Lactonization to **1.20** and subsequent palladium-catalyzed allylation with **1.21** provided an exomethylene-containing substrate that was ozonolyzed to **1.22**. Serendipitously, this oxidation also introduced the requisite C_3 tertiary alcohol of **1.1**. The reported route ends at this point, probably due to the high reactivity of the ring which is known, at least in biosynthetic studies, to be prone to hydrolytic ring-opening or retro-Claisen reactions in alcoholic solvents.



Scheme 1. 4 Approach by Bach *et al.* to the synthesis of **1.1**.

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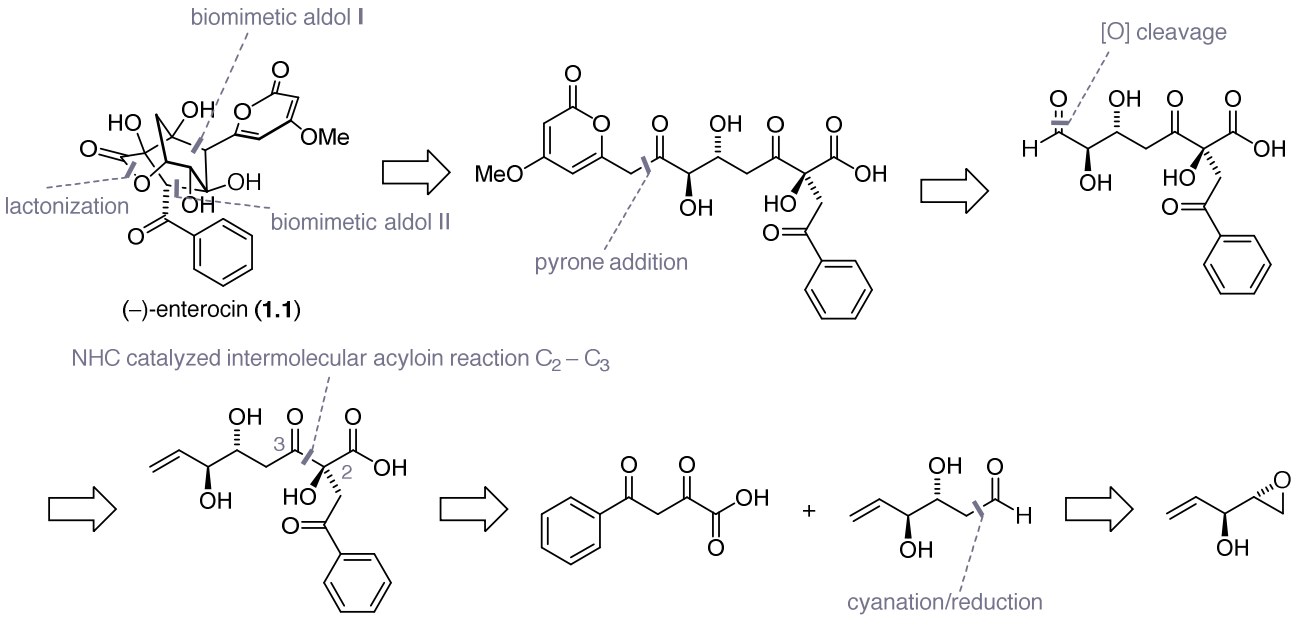
2. Biomimetic Approaches to the Enterocins

2.1. First Approach

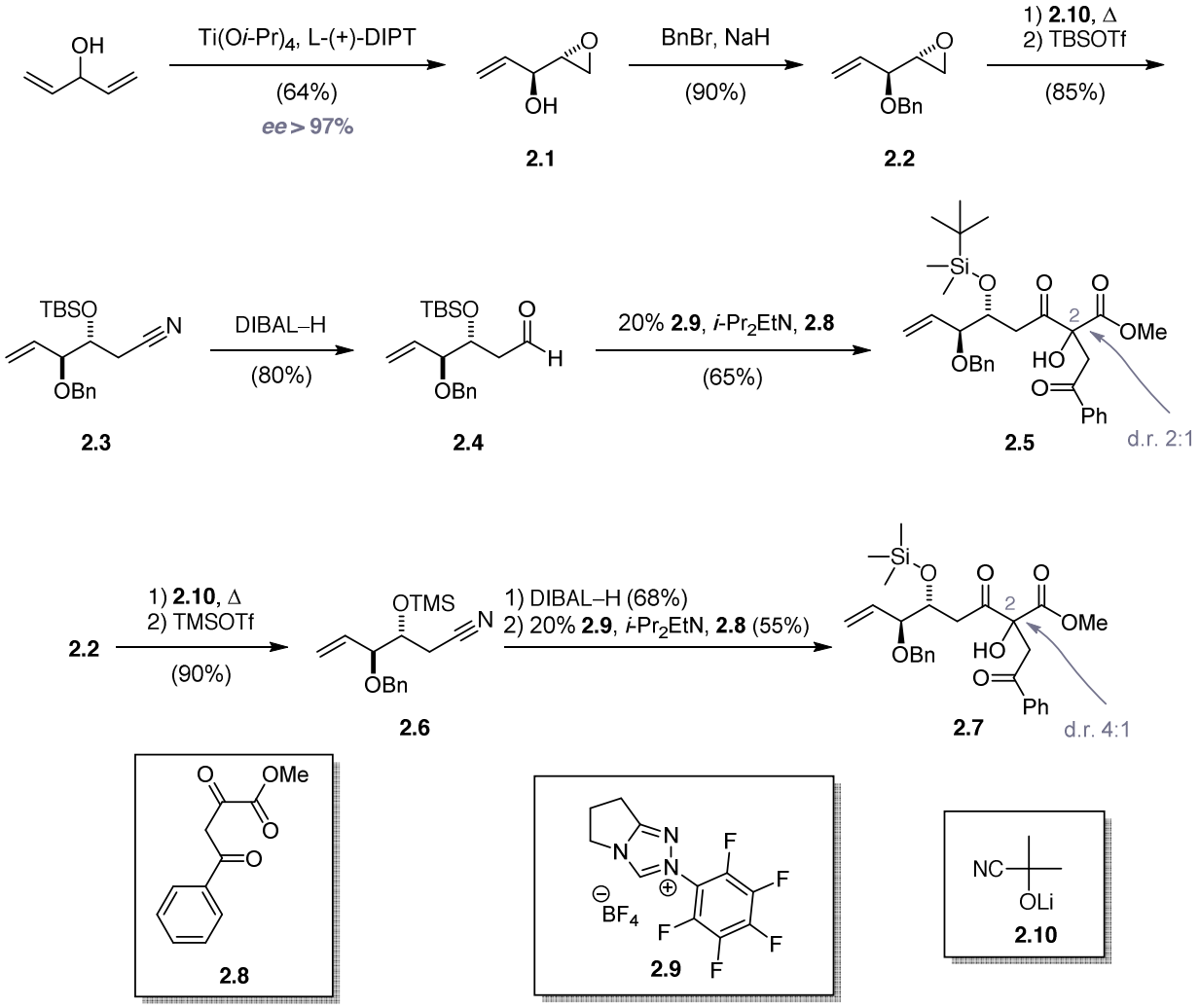
Inspired by the biosynthesis of **1.1**, we decided to develop a retrosynthesis of enterocin that relied on two aldol reactions to compose the bicyclo[3.2.1]octane carbon core. Disconnection of these bonds of enterocin unraveled a linear, fully functionalized, polyketide-like structure (**Scheme 2.1**). We sought to assemble this biomimetic precursor by the addition of a pyrone segment onto an aldehyde, which in turn could arise from the oxidative cleavage of a terminal olefin. The resulting chiral triketide fragment was envisioned to be constructed using an unusual intermolecular acyloin reaction which, to the best of our knowledge, is unreported in the setting of complex natural product synthesis. Such disconnection at $C_2 - C_3$ simplified the preparation of this linear precursor to known compounds.



Scheme 2.1 Retrosynthetic analysis comprising of the two biomimetic aldol reactions and an intermolecular acyloin reaction.

The synthesis started with Sharpless epoxidation of divinyl carbinol followed by benzyl protection (**2.1**),[1] providing epoxide **2.2** (**Scheme 2.2**) on multigram scale with excellent *ee*. We then were faced with a seemingly straightforward cyanation of **2.2**, but soon found that reported methods to

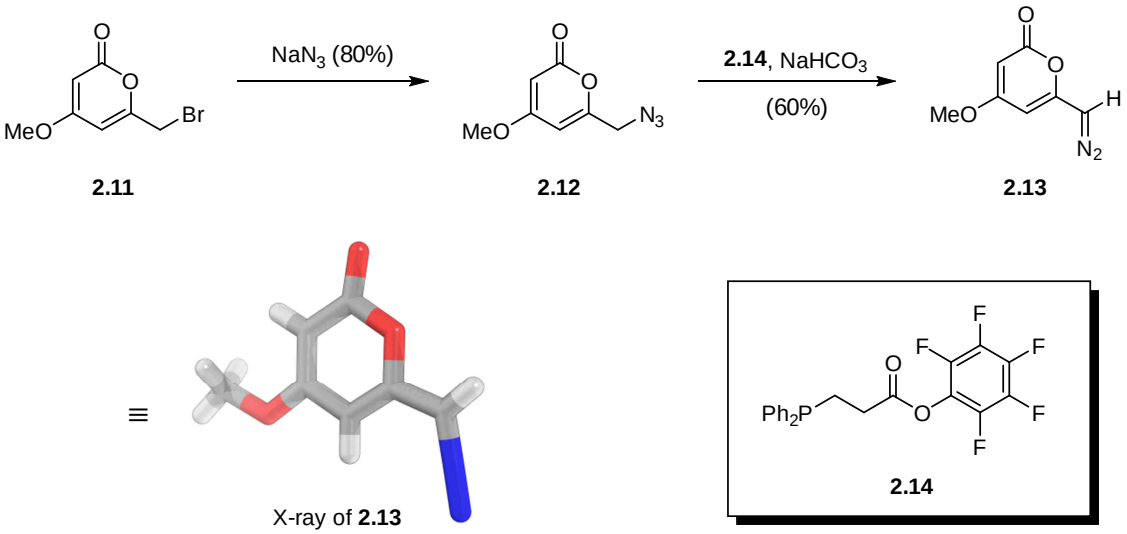
implement such a ring-opening were cumbersome on larger scales, requiring excess amounts of KCN, long reaction times, and moderate regioselectivity. Instead, we employed lithium cyanohydrin **2.10** as an air stable LiCN source,[2] which delivered perfect regioselectivity and further allowed the direct silylation of the crude mixture to afford nitrile **2.3**, which was then reduced to aldehyde **2.4** using DIBAL–H.



Scheme 2.2 Construction of the central aldehyde and key NHC-mediated acyloin reaction.

With this intermediate in hand, we were ready to explore the intermolecular acyloin fragment coupling.[3] Using precatalyst **2.9**, product **2.5** could indeed be obtained, albeit in 15% yield, wherein significant mass balance is attributed to dimerization of **2.4**. After calibrating the reaction stoichiometry, we were able to isolate **2.5** as a 2:1 mixture of diastereomers at C_2. Starting from epoxide **2.2** we analogously prepared the corresponding TMS-protected aldehyde through

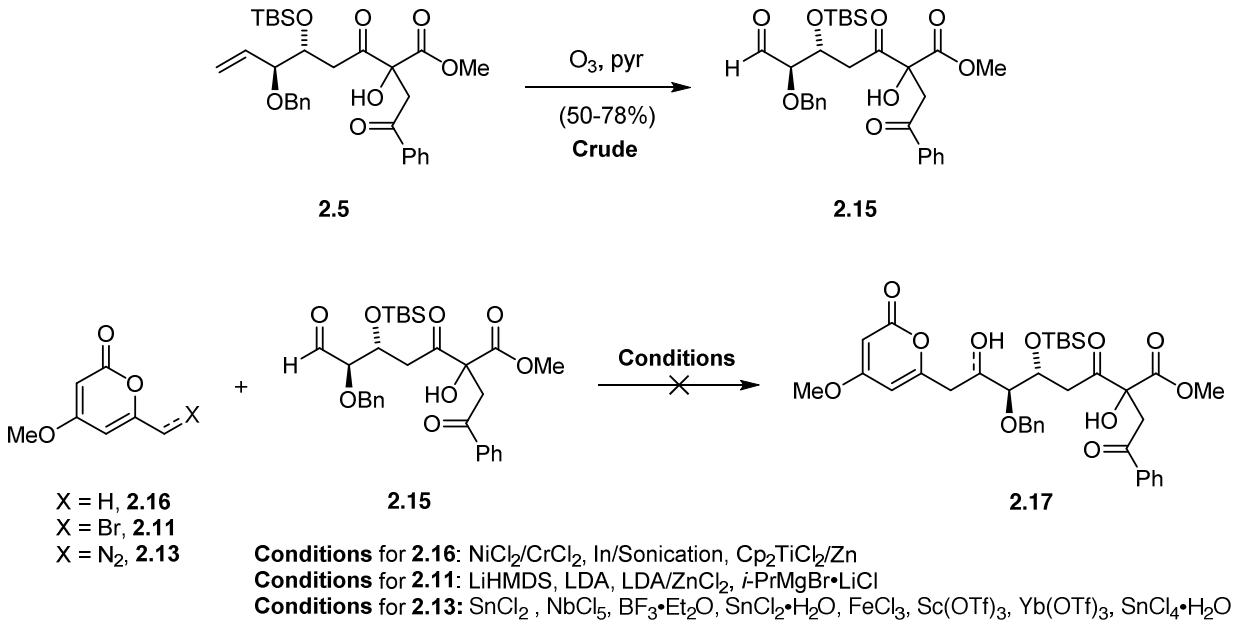
cyanation/protection (**2.6**) and then DIBAL-H reduction. Interestingly, TMS-protected analogue **2.7** could be obtained in comparable yield with an improved 4:1 diastereomeric ratio. Although the assignment of the C_2 configuration was not possible, these results suggest that stereocontrol may be imparted by either a chiral catalyst or by introduction of a chiral auxiliary on ester **2.8**.[4]



Scheme 2.3 Preparation and X-ray of diazopyrone **2.13**.

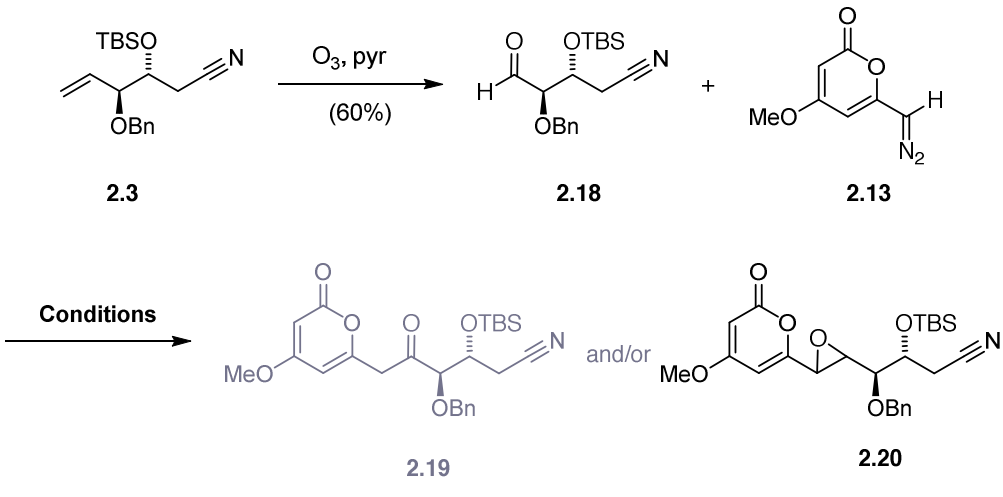
We realized that the addition of the pyrone fragment provided an opportunity to develop uncharted chemistry. In analogy to carbonyl chemistry we became interested in adapting unreported diazo-pyrone **2.13** to Roskamp chemistry (**Scheme 2.3**).[5] Since treatment of known bromide **2.11**[6] with Fukuyama's *N*,*N*'-Ditosylhydrazine[7] did not deliver the corresponding diazo compound, we prepared azide **2.12** which was conveniently transformed into **2.13** employing phosphine **2.14**, as developed by Raines.[8] We reasoned that this diazo compound might exhibit the reactivity of a vinylogous diazoester and potentially undergo a formal C–H insertion with an aldehyde.

We then proceeded to oxidize the terminal alkene of **2.5** to the corresponding aldehyde by means of a pyridine-catalyzed reductive ozonolysis (**Scheme 2.4**).[9] This mild method permitted us access to crude tetracarbonyl **2.15**, which slowly decomposed at ambient conditions, and was therefore used directly in screening trials.



Scheme 2.4 Attemped of pyrone fragment addition.

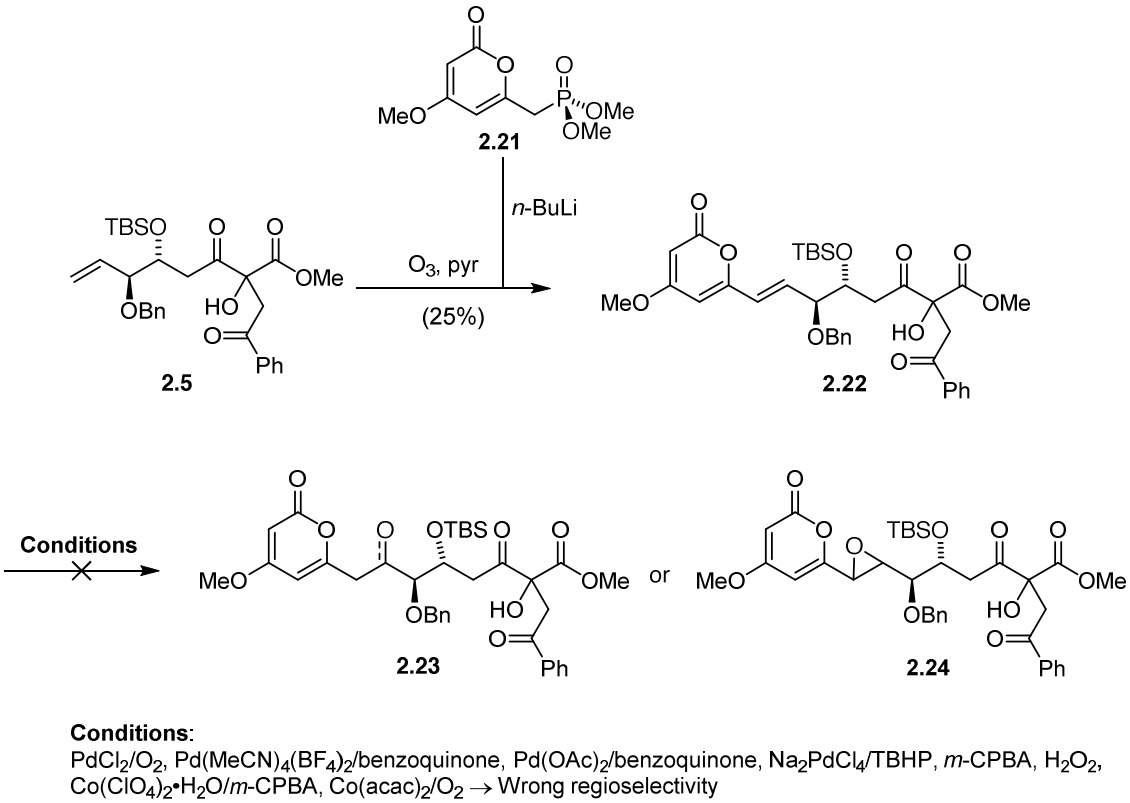
To execute a vinylogous Roskamp, we employed several Lewis acids with diazo-pyrone **2.13** to no avail (**Scheme 2.4**). Under the assumption that the host of Lewis basic sites hampered the desired pathway, we turned to a 1,2-addition/oxidation sequence. Metallation of pyrone **2.16**, Lewis-acid mediated reactions, direct use of bromo-pyrone **2.11** under Nozaki-Hiyama-Kishi conditions, indium sonication or catalytic Reformatsky[10] conditions unanimously failed to deliver **2.17**. We deemed that the dense oxidation surrounding the tertiary alcohol might be liable in coordination to a Lewis acid. Therefore, we attempted the same chemistry on a simpler substrate, namely nitrile **2.18** (**Scheme 2.5**).



Scheme 2.5 Attemped of pyrone fragment addition onto compound **2.18**.

Unfortunately, the host of conditions attempted was ineffective, delivering at best traces of epoxide **2.20**.

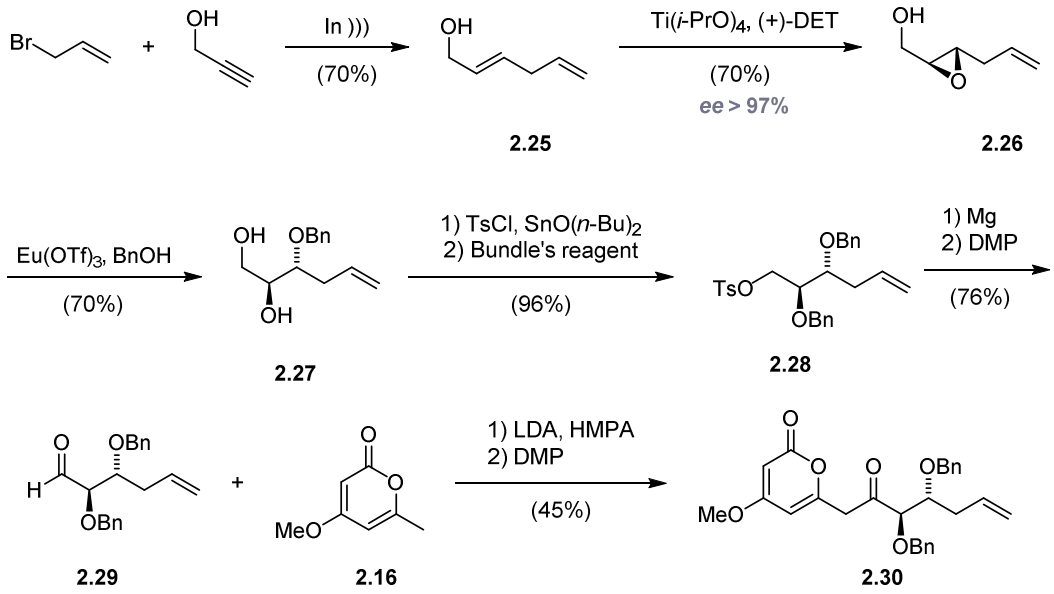
A final attempt to couple the pyrone fragment was made by treating phosphonate **2.21**[11] with *n*-BuLi and directly adding the ozonolysis mixture to the resulting stabilized anion (**Scheme 2.6**). This one-pot protocol yielded the desired product **2.22** in moderate amounts and with complete (*E*)-selectivity. For the first time, we were able to isolate the fully elaborated carbon chain of enterocin. As attempts to hydrate **2.22** were unsuccessful, the linear biomimetic precursor was assembled through an inverted order of events wherein the pyrone was first added to a less functionalized central fragment followed by acyloin coupling, which was deemed chemoselective enough to avoid unwanted side-reactions.



Scheme 2.6 HWE olefination of the pyrone fragment and unsuccessful functionalization.

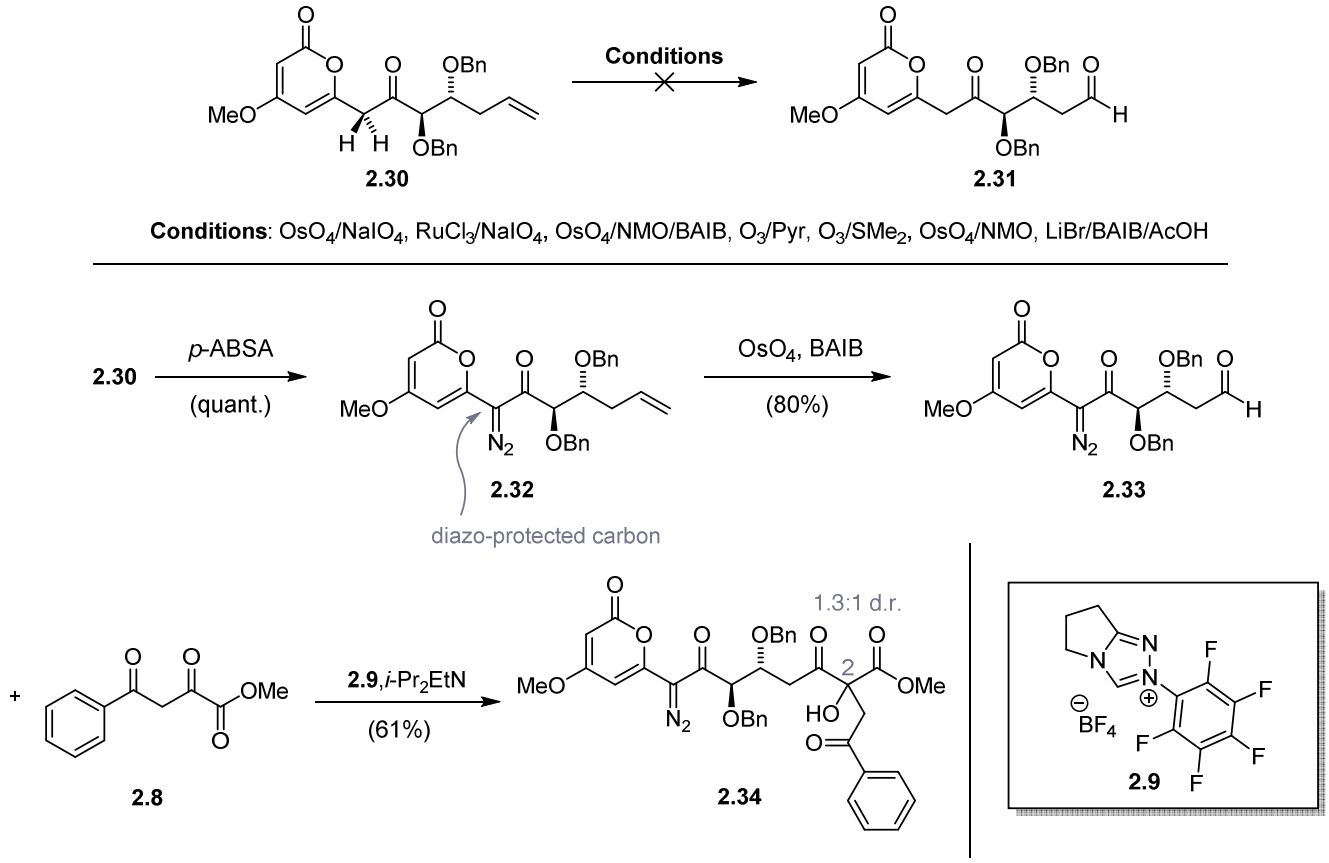
We commenced with an (*E*)-selective synthesis of skipped diene **2.25**[12] by means of a carboindination reaction under sonication (**Scheme 2.7**).[13] This allylic alcohol was readily converted to chiral epoxide **2.26** under Sharpless conditions with excellent *ee*.[12] The configuration of the epoxide was then used to set the *anti*-diol by employing a mixture of $Eu(OTf)_3$/BnOH that

delivered primary alcohol **2.27** in good yield and in 20:1 d.r.[14] Use of the less expensive $La(OTf)_3$ was also possible, albeit with a lower diasteromeric ratio (10:1 d.r.). A reliable tosylation/benzylation sequence afforded **2.28**, which was then reductively deprotected with metallic Mg and oxidized to provide aldehyde **2.29** in gram quantities. Benzylic lithiation of pyrones is reported to be troublesome due to the *ortho*-directing effects on the ring, normally translating to low yields and the formation of isomeric products.[15] We realized these problems could be somewhat mitigated using Et_2O as the solvent, which delivered ketone **2.30**, after oxidation, in moderate yet reliable yields.



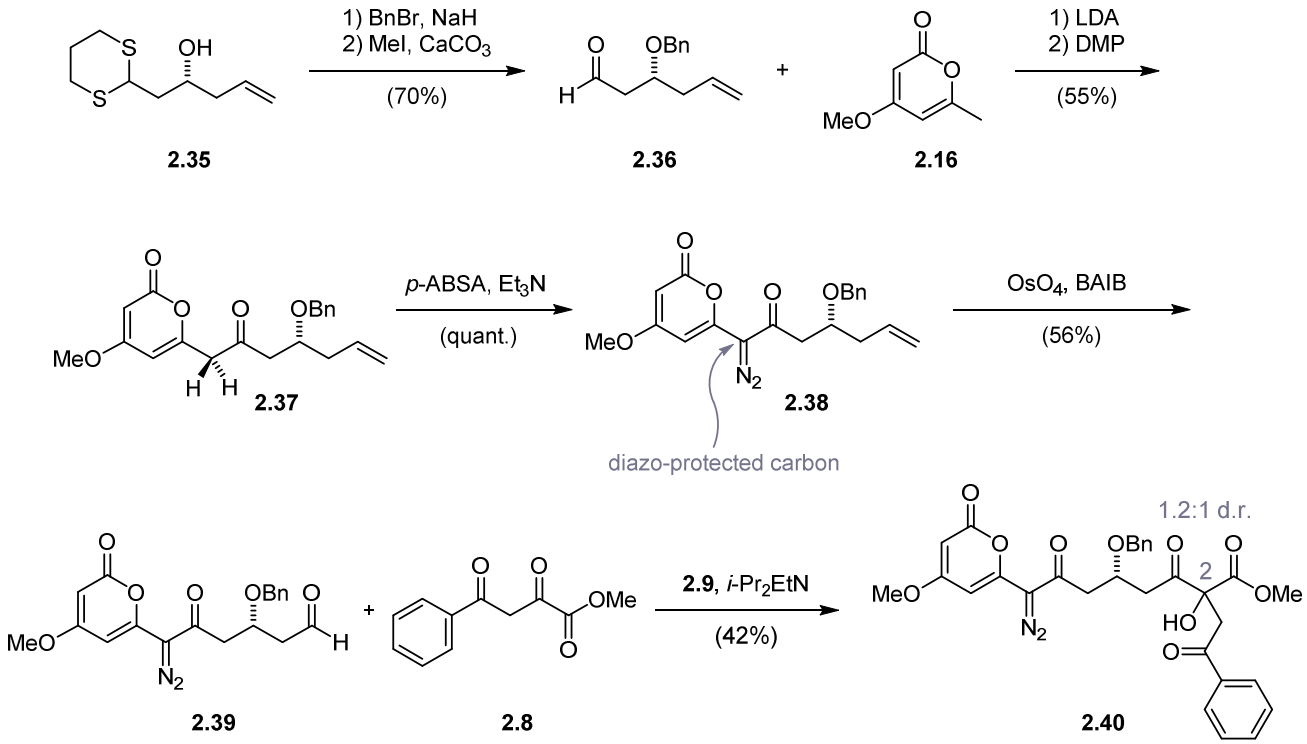
Scheme 2.7 *De novo* construction of terminal alkene **2.30**.

The oxidative cleavage of terminal alkene **2.30** revealed unexpected problems, as subjection to a varaiety of dihydroxylation conditions resulted in complex mixtures and degradation (**Scheme 2.8**). We presumed that the high acidity of the β-ketopyrone protons was hampering the desired reaction outcome. After considerable experimentation, we devised an unusual protecting group strategy by diazotization of compound **2.30** to **2.32**. This made it possible to mildly oxidize the terminal alkene with OsO_4/BAIB to aldehyde **2.33** and smoothly couple α-ketoester fragment **2.28** to complete carbon precursor **2.34**.



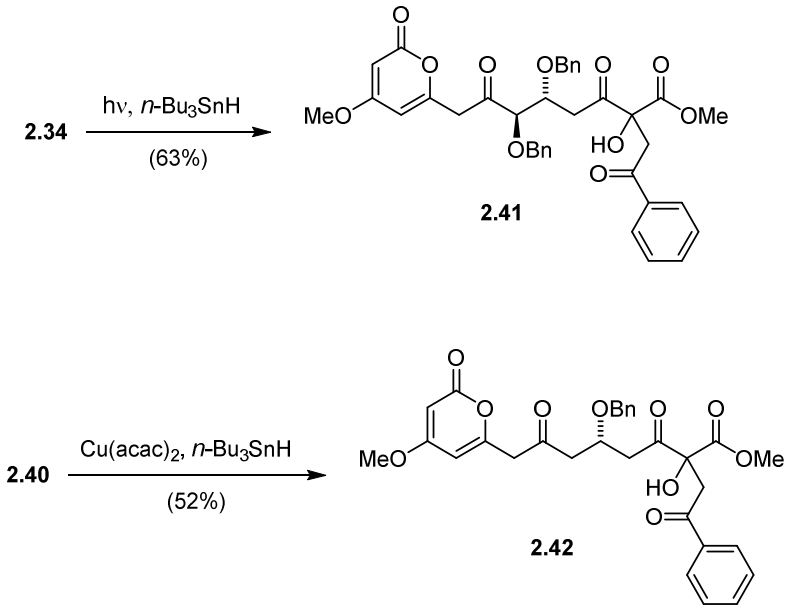
Scheme 2.8 Diazotization of **2.30** to mask acidic alpha protons and coupling of the final fragment to **2.34**.

Thereafter, we proceeded to prepare the precursor to (−)-deoxyenterocin (**1.2**) in similar fashion. Elaboration of known dithiane **2.35** (≥ 97% *ee*)[16] to aldehyde **2.36** delivered multi-gram quantities of the enantioenriched partner to be coupled to pyrone **2.16** (**Scheme 2.9**)**.** Metallation of **2.16** with LDA in Et_2O reliably delivered ketone **2.37**, after oxidation, in moderate yield and was smoothly α-diazotized to **2.38** in quantitative yield. Following protection, it was again possible to mildly oxidize this terminal alkene with OsO_4/BAIB to the corresponding aldehyde (**2.39**), and it was chemoselectively coupled with α-ketoester fragment **2.8**, affording fully elaborated linear precursor **2.40** with 1.2:1 d.r.



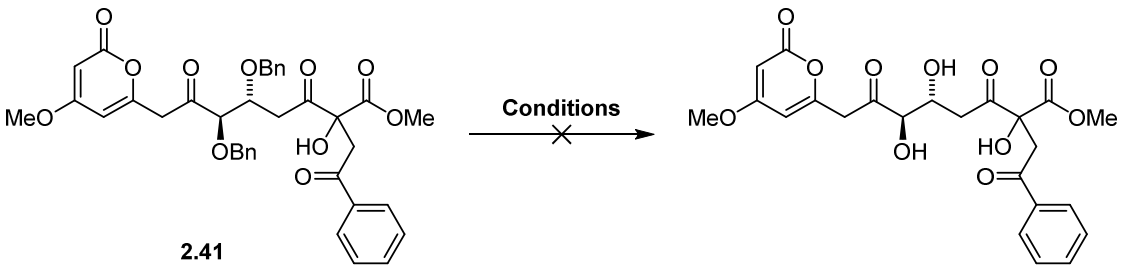
Scheme 2.9 Second generation approach to the construction of a biomimetic precursor.

With both precursors in hand, we progressed to the removal of the diazo protecting group. Treatment of the diazo compounds **2.34** and **2.40** with Pd, Rh[17] or Pt catalysts under hydrogen atmosphere yielded mainly complex mixtures of byproducts, which might arise from metal carbenoid insertion pathways. Additionally, a sequential Staudinger/Wolff-Kishner reduction, a method developed by Bestmann,[18] resulted in decomposition. The use of tin hydrides finally yielded significant amounts of deprotection. Irradiation (Rayonet 420 nm) of dibenzylated diol **2.34** in the presence of an excess of hydride donor delivered **2.41** without noticeable insertion byproducts (**Scheme 2.10**).[19] These byproducts were observed upon heating **2.34** with $Cu(acac)_2$ and *n*-Bu_3SnH thereby emphasizing the difference in C−H insertion rates between free carbenes (hν) and metal carbenoids. In absence of the alpha benzyl ether, it was possible to apply the $Cu(acac)_2$ system, delivering substrate **2.42** in moderate yield.



Scheme 2.10 Mild and orthogonal removal of the masking diazo group.

The final debenzylations were more challenging than expected. We started with hydrogenolysis of dibenzyl substrate **2.41** under various conditions, but mainly recovered starting material or resulted in degradation products (**Scheme 2.11**). Oxidative conditions were ineffective while Lewis acidic conditions (e.g. $FeCl_3$/TMSCl or MsOH) delivered, at best, traces of a single diasteromer of product, indicating that the degradation of the two diasteromers of **2.41** proceeds at different rates.

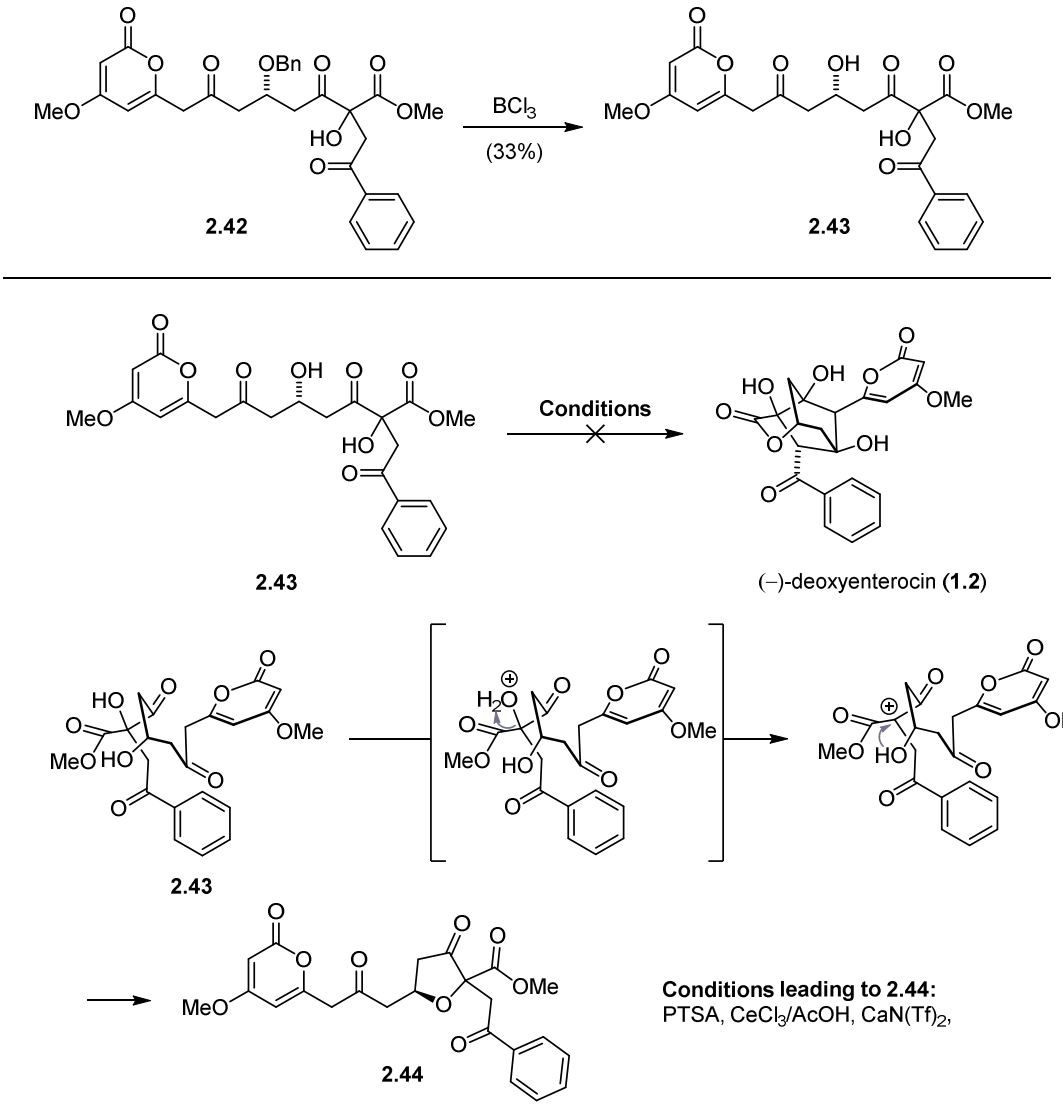


Conditions: $CrCl_2$/LiI, BCl_3/$PhMe_5$, Et_3SiH/I_2, 25% MsOH, HBr•PPh_3, DMDO, $TiCl_4$, TMSCl/$FeCl_3$, Crabtree/H_2, DDQ, $NaBrO_3$, Pd/C H_2, $Pd(OH)_2$/C H_2, $Pd(OH)_2$/C Et_3SiH, Pd/C Et_3SiH, $Pd(OH)_2$/C H_2 (5 atm)

Scheme 2.11 Screening for the double debenzylation of **2.41**.

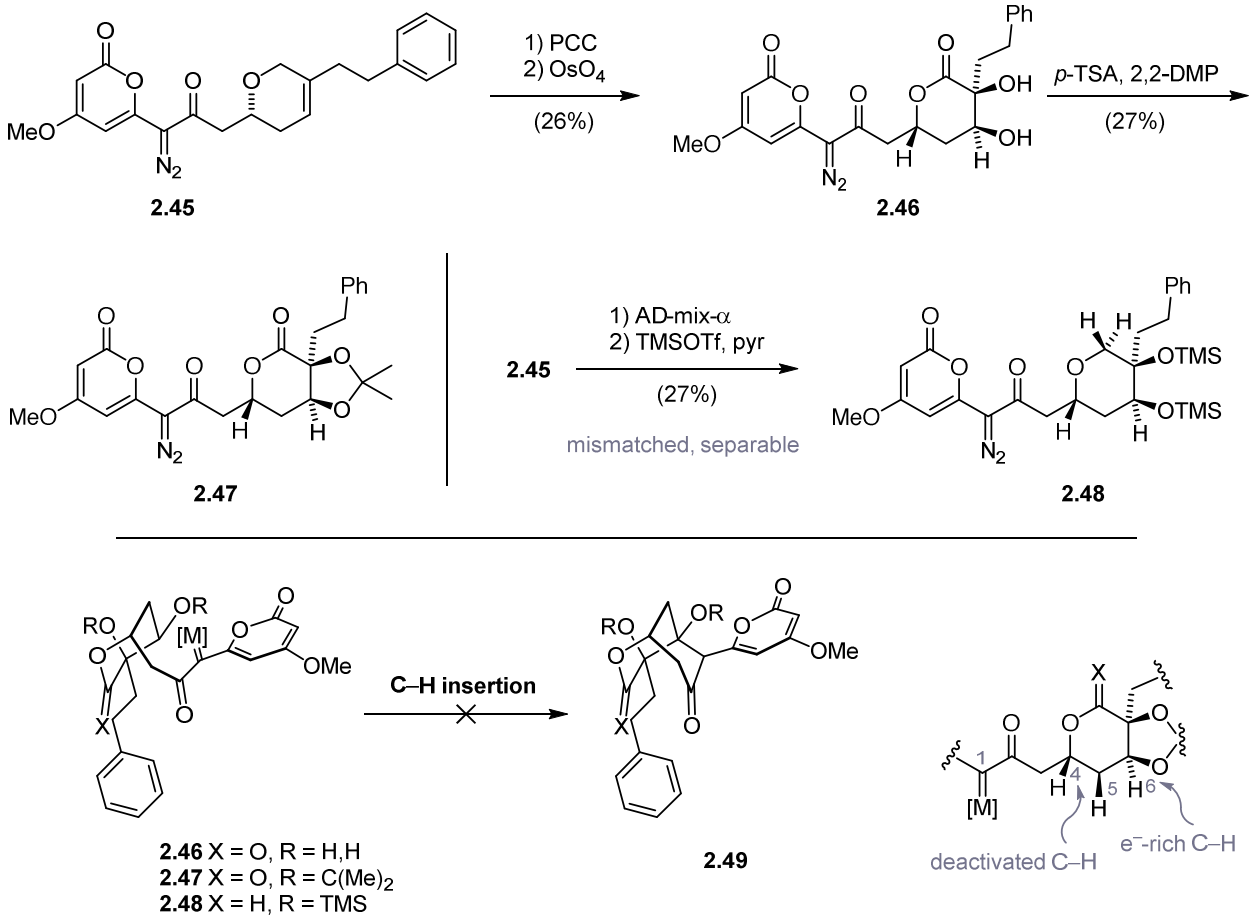
Application of the same conditions to monobenzylated **2.42** provided comparable results. Eventually, treatment of **2.42** with BCl_3/pentamethylbenzene delivered compound **2.43** in low yield (**Scheme 2.12**). Nevertheless, the conciseness of the route permitted us to obtain enough

material to screen the final biomimetic sequence. Proline- and thiourea-based organocatalysts were found to be ineffective, and starting material was reisolated. Stronger bases such as *t*-BuOK, DBU and LDA delivered complete degradation without exceptions, even under cryogenic conditions. Interestingly, although the use of Lewis acidic mixtures was fruitless, the use of $CeCl_3$, $CaN(Tf)_2$ or PTSA, led to the formation of dihydro-3(2*H*)-furanone adduct **2.44**. This probably arises from loss of the tertiary alcohol, whose mass was also observed by HRMS, and subsequent intramolecular trapping by the secondary alcohol.



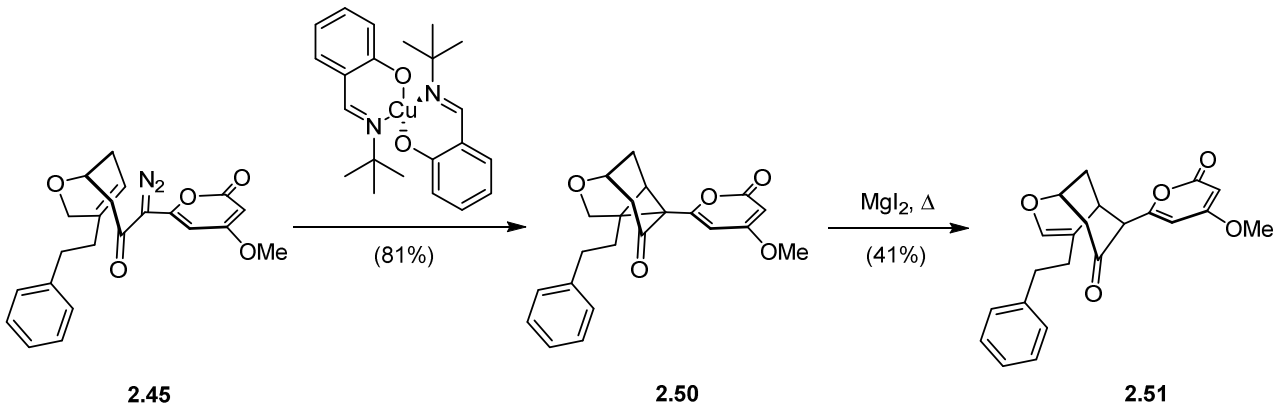
Scheme 2.12 Final deprotection of compound **2.42** and efforts to enact the biomimetic ring-closure.

Due to the inability to effect the biomimetic cascade, we became interested to use the diazo group in a C−H insertion at C_6 (**Scheme 2.13**). As the deprotection with tin hydride is a controlled insertion into a Sn−H bond, we surmised that the diazo group might also undergo a productive C−H insertion with an appropriate catalyst. Therefore, we selectively executed an allylic oxidation of **2.45**, a compound previously synthesized in our laboratories, in the presence of the diazo group using PCC.[20] Notably, oxidation attempts on an unprotected substrate were ineffective. A subsequent stereoselective dihydroxylation[21] delivered diol **2.46** and, after treatment with 2,2-DMP, acetonide **2.47**. This sequence advanced us to two possible substrates to enact the carbenoid insertion α to the C_6 secondary hydroxyl. Moreover, we speculated that the acetonide moiety in **2.47** could block unwanted retro-aldol reactivity.



Scheme 2.13 Construction of diazo compounds for intramolecular C−H insertion and reaction screening.

An analysis of the scaffold's electronics suggests that the formation of a four-membered ring is unlikely due to the lactone deactivation, while the absence of sufficiently electron-rich sites should prevent the formation of a kinetically-favored cyclopentane. Several commercially available Rh- and Cu- based catalysts were subjected to substrates **2.46** and **2.47** by reverse addition, but in all cases decomposition ensued. In this regard, the observation that the pyrone ^{1}H NMR signal were generally absent led us to consider that the rigidity imparted to the system by the lactone might have prevented the substrate from adopting a reactive conformation, therefore leading to skeletal rearrangements. To increase the flexibility of the system we prepared tetrahydropyran **2.48** by asymmetric dihydroxylation and subsequent TMS protection of compound **2.45**. After separation of the diastereomers and structural determination by NOESY analysis, they were subjected to the same catalyst screening. Although we were able to observe a host of products, rather than decomposition, we were unable to isolate any compound with a determinable structure. The difficulty in forming the 2-oxabicyclo[3.3.1]nonane led us to explore a more reactive insertion partner for the carbenoid precursor (**Scheme 2.14**). As olefins show high rates for carbene insertion[22] we decided to use compound **2.45** as a platform to explore this possibility and, after cyclization, implement a late-stage functionalization strategy.



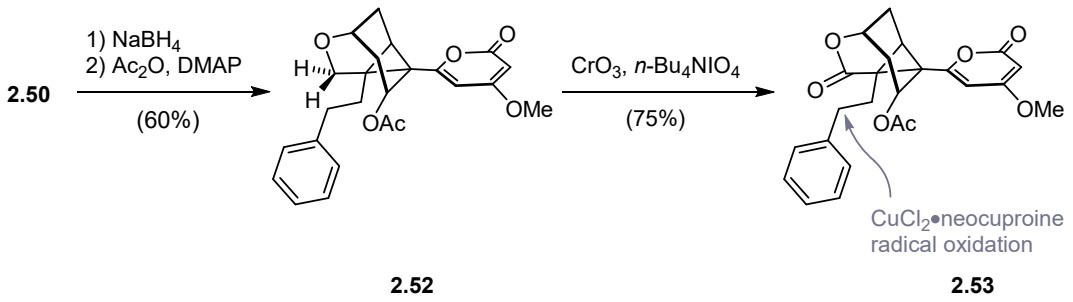
2.45 **2.50** **2.51**

Fragmentation failed conditions: LiBr, $Zn/ZnCl_2$, TMSCl/NaI, TMSOTf/H_2O, PTSA, Rayonet lamp (300 nm), $Cr_2(SO_4)_3/Zn$, $Pd(OH)_2/H_2$, PTSA/NaBr, TMSCl/TBAI, $Yb(OTf)_3$, $BF_3{\bullet}Et_2O$, $In(OTf)_3$

Scheme 2.14 Construction of 2-oxabicyclo[3.3.1]nonane by carbenoid-olefin insertion.

Thus, compound **2.45** was subjected to Rh- and Cu-based catalysts to mediate an intramolecular cyclopropanation to compound **2.50**. Eventually, slow addition to the $Cu(TBS)_2$ catalyst[23] popularized by Corey delivered the tricyclic adduct in good yield and purity.[24] Thanks to this

unintuitive disconnection we forged the 2-oxabicyclo[3.3.1]nonane scaffold with a functionalization pattern suitable for manipulating the tetrahydropyran ring. Successful cyclopropane fragmentation within **2.50** required extensive experimentation. Eventually, it was achieved by treatment with freshly prepared MgI_2 to afford enol ether **2.51** in moderate yield.[25] Although this compound proved to be partially stable, it decomposed under a variety of conditions, probably due to the high acidity of the α-pyrone proton and the endocyclic enol ether.

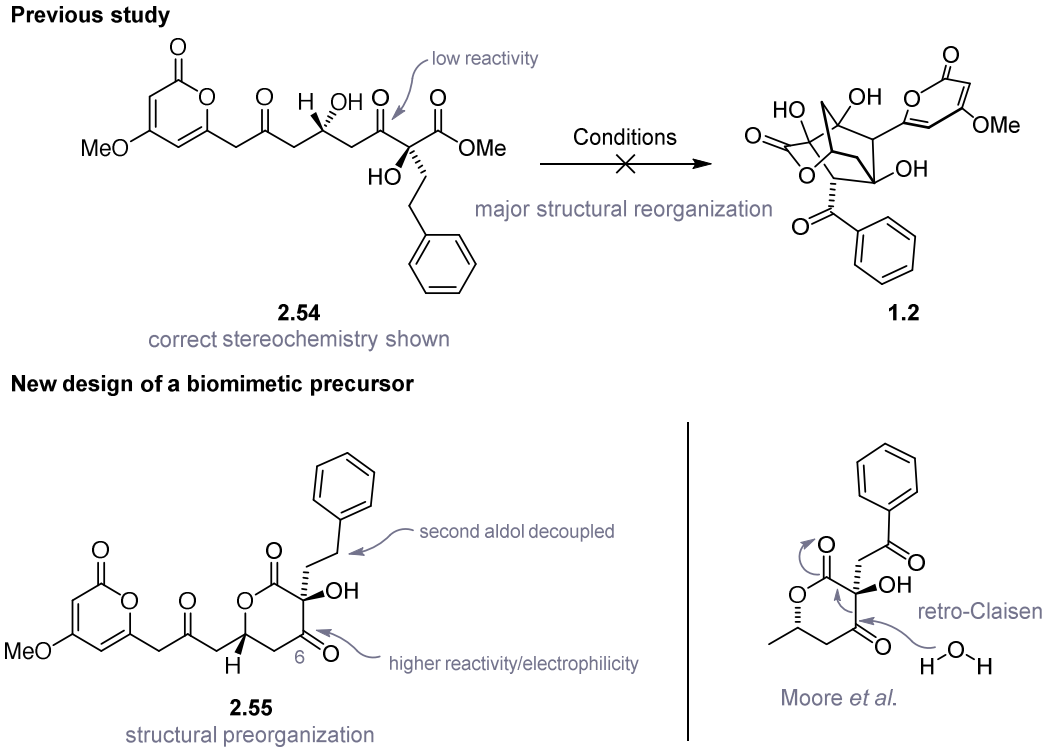


Scheme 2.15 C−H oxidation towards lactone **2.53**.

Cognizant of this, we decided to fragment the tricycle at a later stage and first investigate the functionalization of the caged skeleton. As direct treatment of ketone **2.50** with oxidants was unproductive, we transformed it to the more stable acetate **2.52** and then to the corresponding lactone (**2.53**) by Fuchs' C−H oxidation protocol.[26] Depending on the reaction stoichiometry, we could isolate doubly oxidized benzylic ketone byproducts and therefore conducted experiments to achieve the sequential oxidation in an effective way. We were partially successful by employing a Cu/THBP system,[27] but the reaction rates and output were unacceptable for preparative purposes. Moreover, the presence of the pyrone hampered further oxidation attempts, prompting us to consider the necessity of a different functionalization substrate.

2.2. Further Synthetic Studies on a Partially Cyclized Precursor

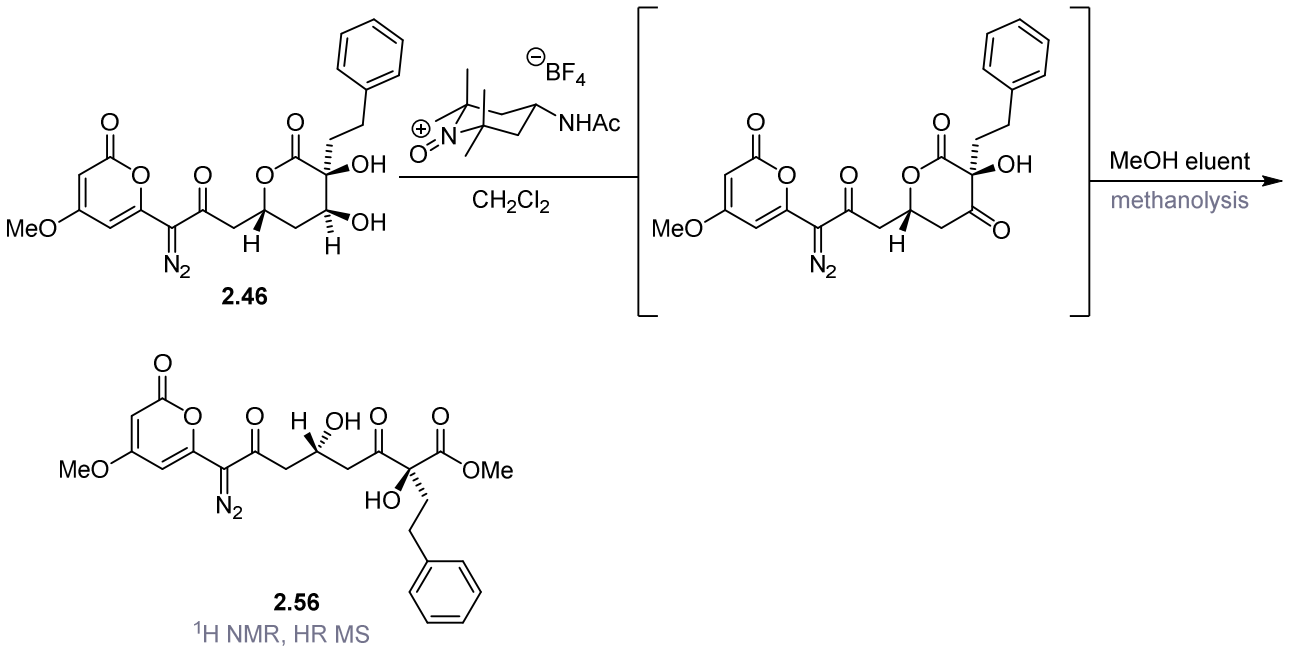
We performed an additional set of synthetic studies on the biomimetic ring closure to the six-membered carbocycle present in (−)-deoxyenterocin (**1.2**) (**Scheme 2.16**).



Scheme 2.16 Failure of a linear to tricyclic biomimetic ring closure and new design of a possible precursor.

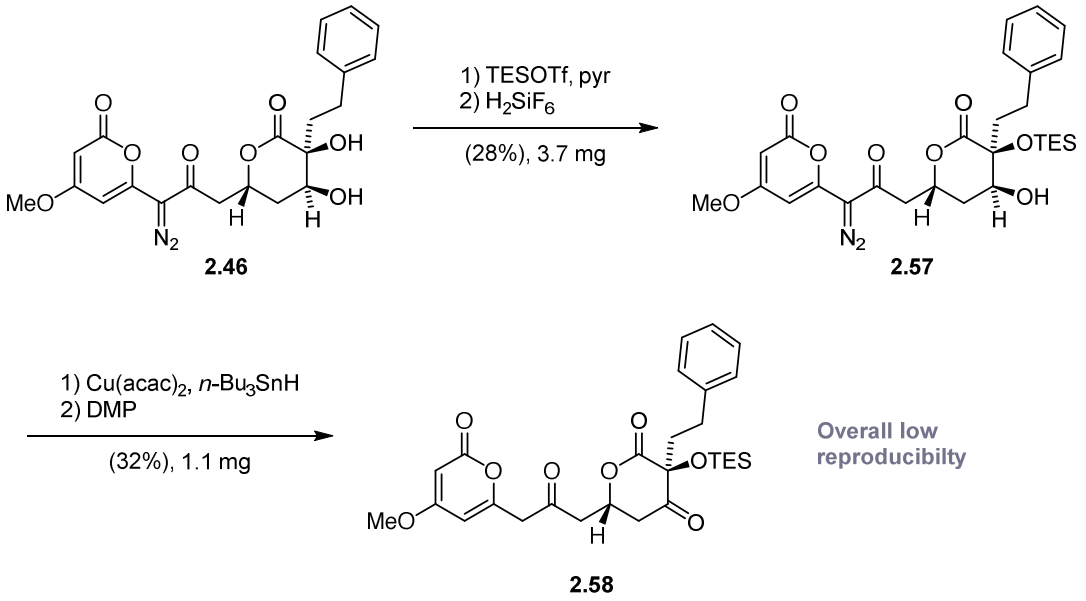
As reported in the previous section, linear compound **2.54** failed to undergo the bioinspired transformation to **1.2**. In view of these results we surmised that a major problem with this proposed cyclization was a low level of preorganization of the linear chain and the poor electrophilicity of the C_6 ketone. Therefore, preparation of a more reactive intermediate with a higher level of structural preorganization was investigated. In this vein, we chose lactone **2.55** for cyclization studies. At the time, we were aware of the report by Moore and coworkers regarding the partial stability of such structures with respect to ring-opening by retro-Claisen reaction.[28] Indeed, we found just two precedents for the synthesis of such motifs,[29] one of which being Bach's approach to enterocin wherein the scaffold's stability is not defined. Additionally, we excised the benzylic ketone to decouple the second aldol closure.

Conveniently, the first approach to the synthesis of compound **2.55** started with **2.46** via mono-oxidation of the diol (**Scheme 2.17**).[30] Although oxidants such as IBX, *N*-oxyls and activated dimethylsulfoxide-based methods (e.g. Swern) failed, use of stoichiometric Bobbit's salt gave a clean reaction, as observed by analytical TLC. Unfortunately, purification techniques tended to decompose the product. Eventually, switching the FCC eluent to a mixture of MeOH/CH_2Cl_2 provided **2.56** in minor quantities. This methanolysis product provides strong evidence that the correct intermediate compound formed in solution.



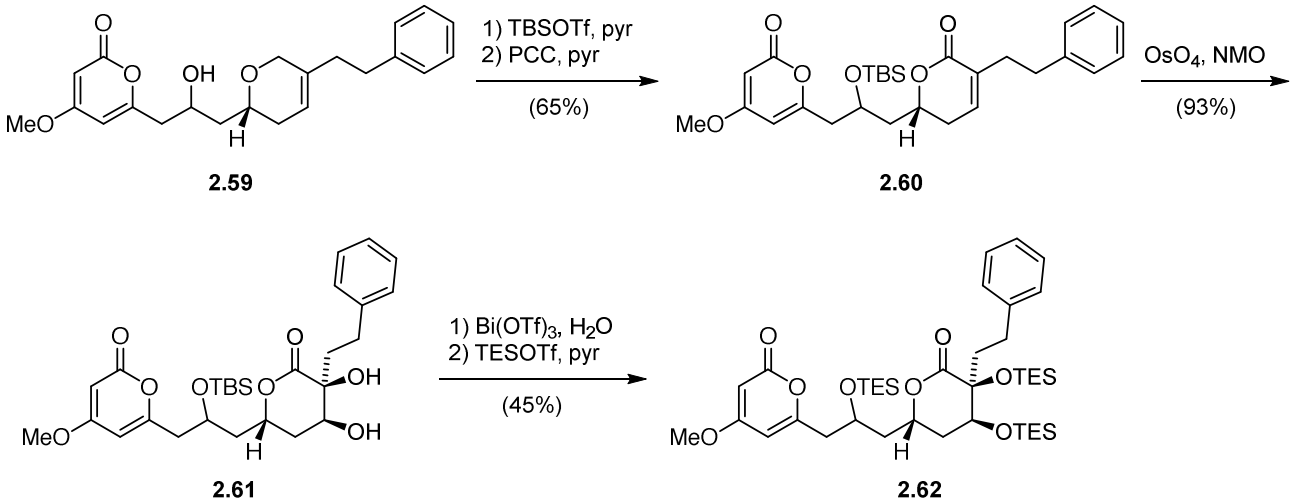
Scheme 2.17 Formation of β-ketolactone and methanolysis to compound **2.56**.

As it appeared that an α-siloxy derivative may enjoy greater stability,[29a] we proceeded to monoprotect diol **2.57** by a two-step sequence (**Scheme 2.18**). Although plagued by silyl migration, and low reproducibility, this sequence permitted diazo protecting group removal and final oxidation with DMP to afford cyclic compound **2.58**. Although we were confident that **2.58** could be isolated, it was clear that progress could not be made unless the scalability and reproducibility issues of the previous route were addressed.



Scheme 2.18 First generation synthesis of compound **2.58**.

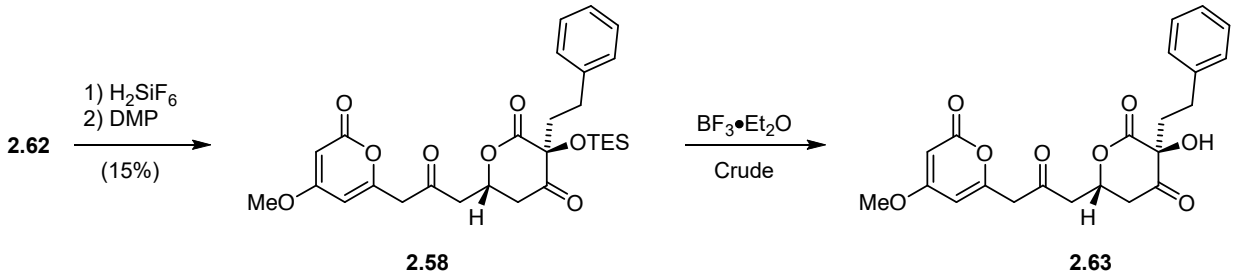
Crude alcohol **2.59**, the product of a pyrone addition to the corresponding aldehyde (**Scheme 2.19**), could be silylated and oxidized to give lactone **2.60** whose homoallylic stereocenter imparts stereocontrol over the following Upjohn dihydroxylation (**2.61**).[31]



Scheme 2.19 Second generation synthesis of compound **2.58**.

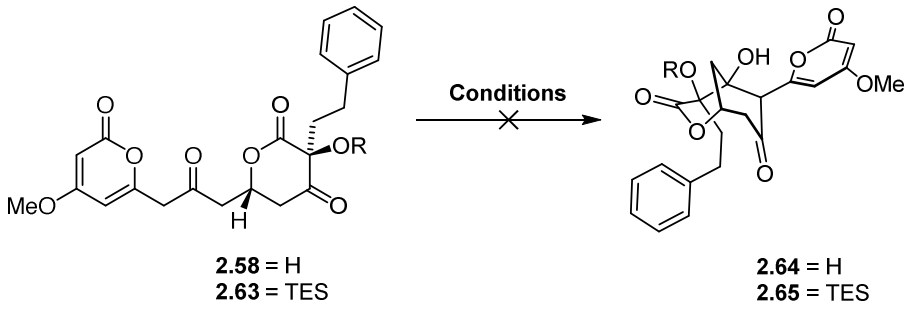
We were then able to intercept compound **2.58** (**Scheme 2.20**) following a somewhat laborious sequence, through the intermediacy of compound **2.62**. Although **2.58** visibly decomposed upon FCC purification, this compound showed higher stability than its unsilylated counterpart (**2.63**)

which was nevertheless isolated as crude with an acceptable level of purity after treatment with $BF_3 \bullet Et_2O$.



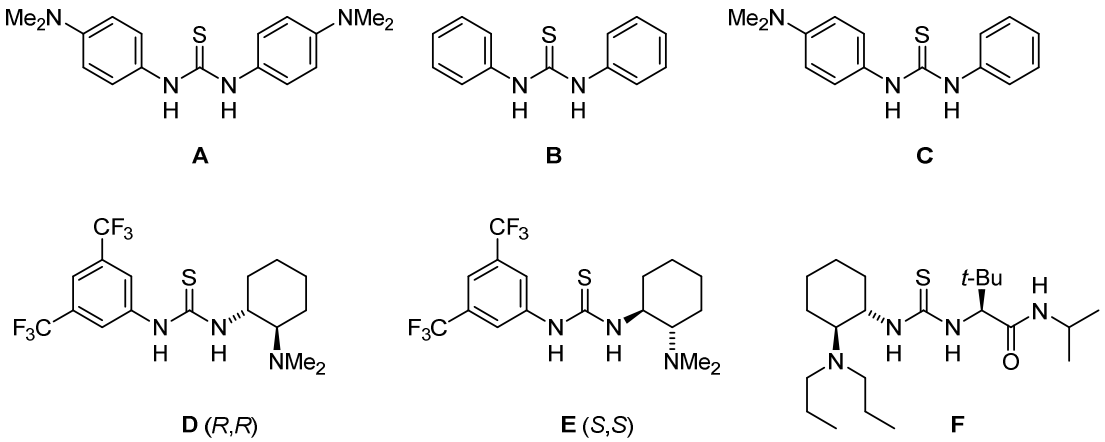
Scheme 2.20 Second generation synthesis of compound **2.58** and synthesis of **2.63**.

With substrate **2.58** and **2.63** in hand we proceeded to screen for suitable aldol conditions (**Scheme 2.21**).



Conditions:
$SiCl_4$/*i*-Pr_2EtN/$POPh_3$, HCl,proline, cat. DIPA, LiCl/DBU, KO*t*-Bu, Amberlyst 15, LDA, $TiCl_4$/*n*-Bu_3N, $Hg(ClO_4)_2 \bullet 3H_2O$, NaOAc, pyrrolidine, NaOAc/18-Crown-6, Al_2O_3, TRIS pH 9.5, Ti(O*i*-Pr)Cl_3/DIPEA, $Zn(OTf)_2$, PTSA, $CeCl_3$/AcOH, $CaN(Tf)_2$, H-bond cat./toluene RT.

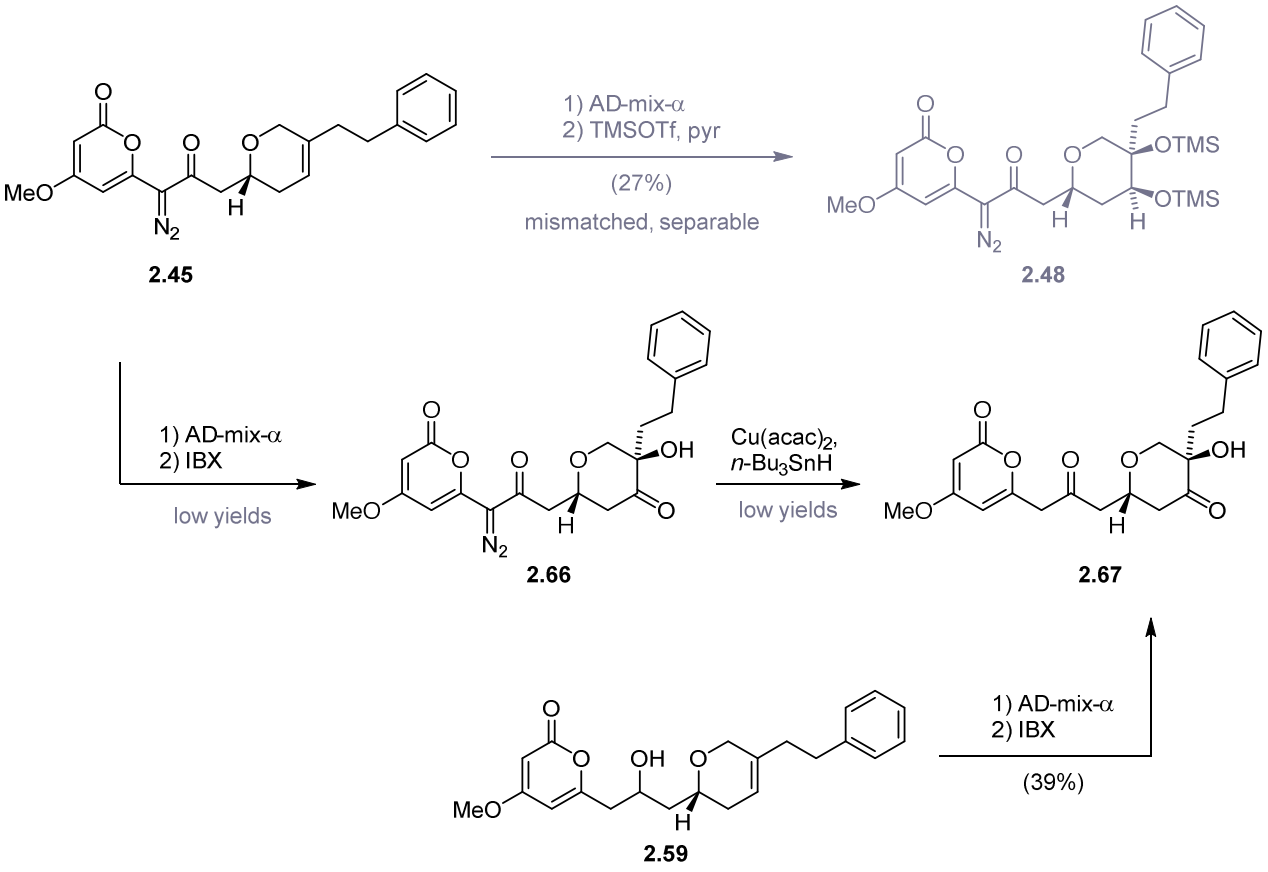
Hydrogen bonding catalysts:



Scheme 2.21 Biomimetic ring-closure trials by H-bonding catalysis.

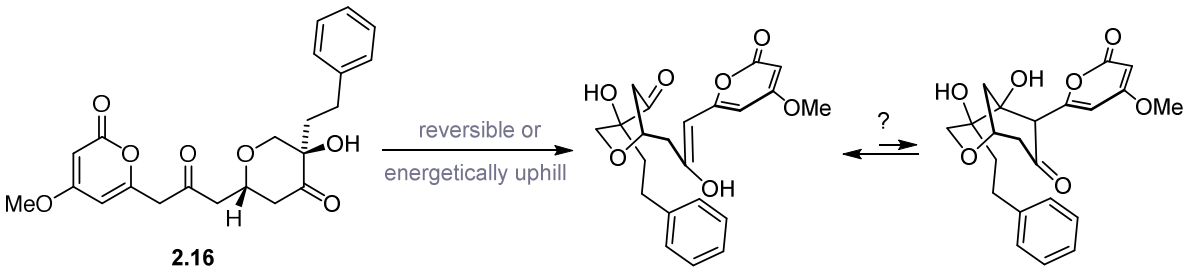
Since most acidic and basic reagents tended to degrade both molecules into intractable mixtures, we opted to use hydrogen bonding catalysts (**A** to **F**).[32] Much to our disappointment, catalysts **B** and **C** were completely ineffective, resulting in starting material recovery even after several days, whereas the bifunctional catalysts (**D** to **F**) produced complex mixtures probably due to their basic amines.

We became concerned that the instability inherent to the β-ketolactone structure was hampering the ring-closure and therefore proposed **2.67** as a more stable model substrate to test the bioinspired aldol (**Scheme 2.22**). To construct this scaffold, **2.45** was subjected to AD-mix-α followed by treatment with IBX to give **2.66**, and deprotection of the diazo group gave access to **2.67** as a single stereoisomer. The same compound could also be obtained by a two-step procedure from **2.59**.



Scheme 2.22 Construction of **2.67** from either diazo **2.45** or alcohol **2.59**.

Compound **2.67** displayed good stability and was subjected to the same host of conditions attempted on its lactone analog **2.58** to no avail (**Scheme 2.23**). Following analysis of these results, taken together with the previous studies from the acyclic substrates, we concluded that the aldol disconnection to construct the 2-oxabicyclo[3.3.1]nonane was simply not viable due to either a lack of necessary reactivity to close the ring or the inherent instability of the resulting bicycle. Therefore, we changed to a strategy which would rely on an irreversible bond-forming event and circumvent the unforgiving thermodynamics of a bioinspired approach.



Scheme 2.23 Failure of the biomimetic approach and unanswered questions regarding the aforementioned aldol.

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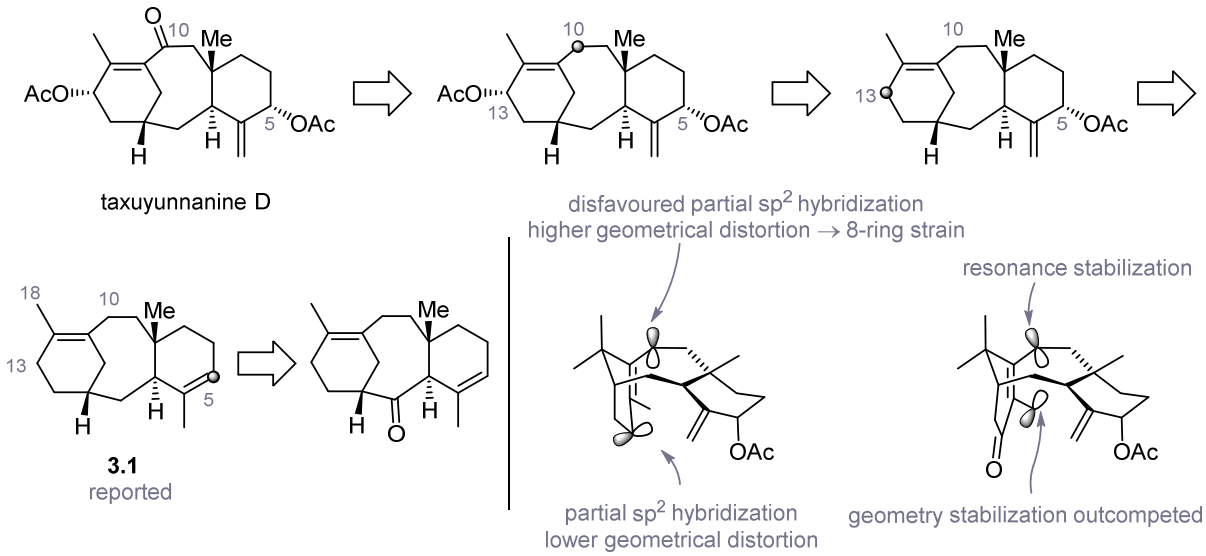
3. Late-Stage Oxidation Approaches Toward Enterocin

3.1. Late-Stage Functionalization of Complex Scaffolds

3.1.1. Total Synthesis of Taxuyunnanine D

Taxol and the other less oxidized members of the taxane family have been the subject of intense investigation by the synthetic community.[1] In this regard, the group of Baran has distinguished itself in recent years for their unique approach based on the preparation of **3.1**[3] (**Scheme 3.1**) which was then optimized to decagram-scale by Albany Molecular Research Inc..[2] To execute the necessary oxidations required to reach taxuyunannine D, they approached the problem with DFT calculations to determine the probable order of events dictated by the scaffold's innate reactivity.[4]

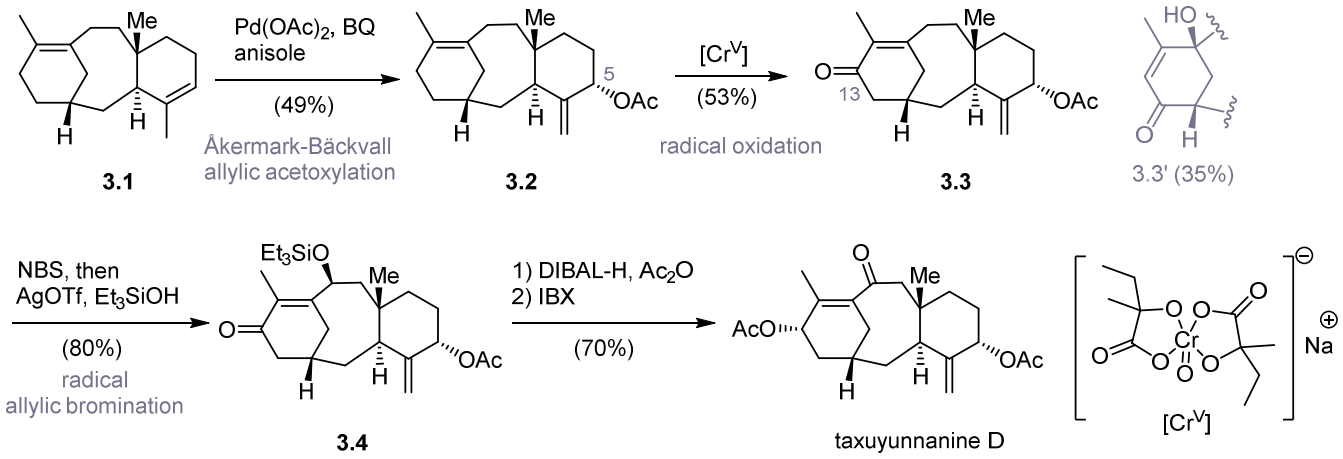


Scheme 3.1 Baran's retrosynthesis of taxuyunnanine D based on sequential "*cyclase phase*" and "*oxidase phase*" strategy.

From previous studies it was clear that the more accessible and reactive site for allylic oxidation of **3.1** was at C_5. Therefore, calculations were carried out on a C_5 acetoxy-taxadiene (**3.2**). Benchmarking the C_{13} allylic radical as $\Delta\Delta G$ = 0 kcal/mol, the calculated relative stability for the C_{10} and C_{18} radicals were $\Delta\Delta G$ = 10.6 kcal/mol and $\Delta\Delta G$ = 6.4 kcal/mol, respectively, therefore suggesting that an H• abstraction would be energetically favored at C_{13}. The higher energy of abstraction at C_{10} can be rationalized if we account for the partial sp^2 character of a hypothetical allyl radical at C_{10}. The rigid 8-membered ring would have to adopt a disadvantageous geometrical

distortion in order for the C_{10} radical to be stabilized by the π-system of the alkene. Instead, stabilizationof the C_{13} radical would require only a minor conformational change to be stabilized. Subsequent calculations on the 5-acetoxy-taxadien-13-one (**3.2**) revealed favorable energetics for a C_{13} H-atom abstraction over C_{18} due to the increased resonance sablization of the α,β-unsaturated enone π-system. This selectivity model was further supported by additional calculations that revealed a reversal in radical stabilities at C_{13} and C_{18} on a 5,13-bisacetoxy-taxadiene.

To carry out this well-laid plan, an "*extensive empirical investigation*" was nevertheless necessary. The synthesis began with allylic acetoxylation of compound **3.1** employing electrophilic Pd^{II} to generate a π-allylpalladium species to introduce oxidation at C_5 (**Scheme 3.2**).[5] The oxidation of **3.2** to **3.3** proved to be the most challenging step in the synthesis. It appeared that oxidations that occur through pericyclic mechanisms, such as in Riley and Schenck ene oxidations, preferred functionalization at the more sterically accessible C_{18}. Chromium^{VI} reagents such as CrO_3•DMP or PCC, which are generally known to have more promiscuous reactivities,[6] provided compound **3.3** with equimolar amounts of overoxidation of the olefin. A major breakthrough was achieved using a commercially available Cr^V reagent[6] which delivered **3.3** in moderate yield along with an overoxidized γ-hydroxyenone **3.3'**. This latter product probably arises from the recombination of the bridgehead C centered radical with the Cr^V reagent, whose resulting Cr^{IV} adduct is not competent in a Babler-Dauben oxidative rearrangement, and therefore oxidizing the allylic alcohol to enone **3.3'**.[4] The final C_{10} allylic oxidation to **3.4** was eventually performed by radical bromination and subsequent AgOTf-induced displacement. Following a trivial two-step redox manipulation, taxuyunnanine D was synthesized.

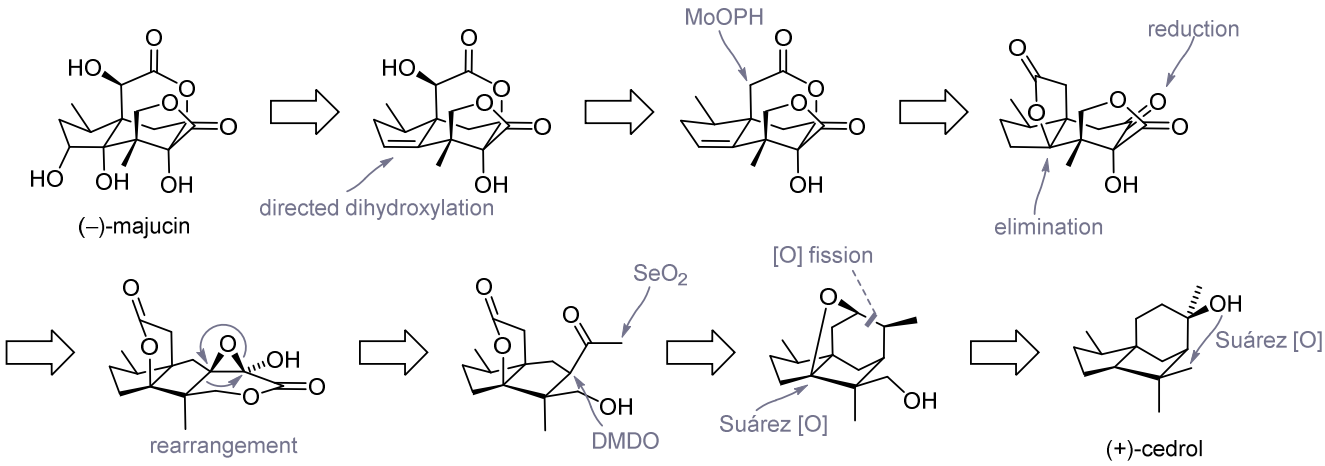


Scheme 3.2 Baran's synthesis of taxuyunnanine D.

To conclude, this research elegantly substantiates the strategic concept of "*cyclase/oxidase phases*" in the context of total synthesis. It does, however, reveal some of its major drawbacks. *A priori* reactivity predictions do not yet preclude extensive screening. Also, the prerequisite of a well-designed scaffold devoid of oxidatively sensitive moieties, such as electron-rich aromatics, limits the concept's applicability. Therefore, reagent and reaction development with more predictable chemoselectivity is necessary to make this concept of late-stage functionalization a more practical strategy for natural product synthesis.

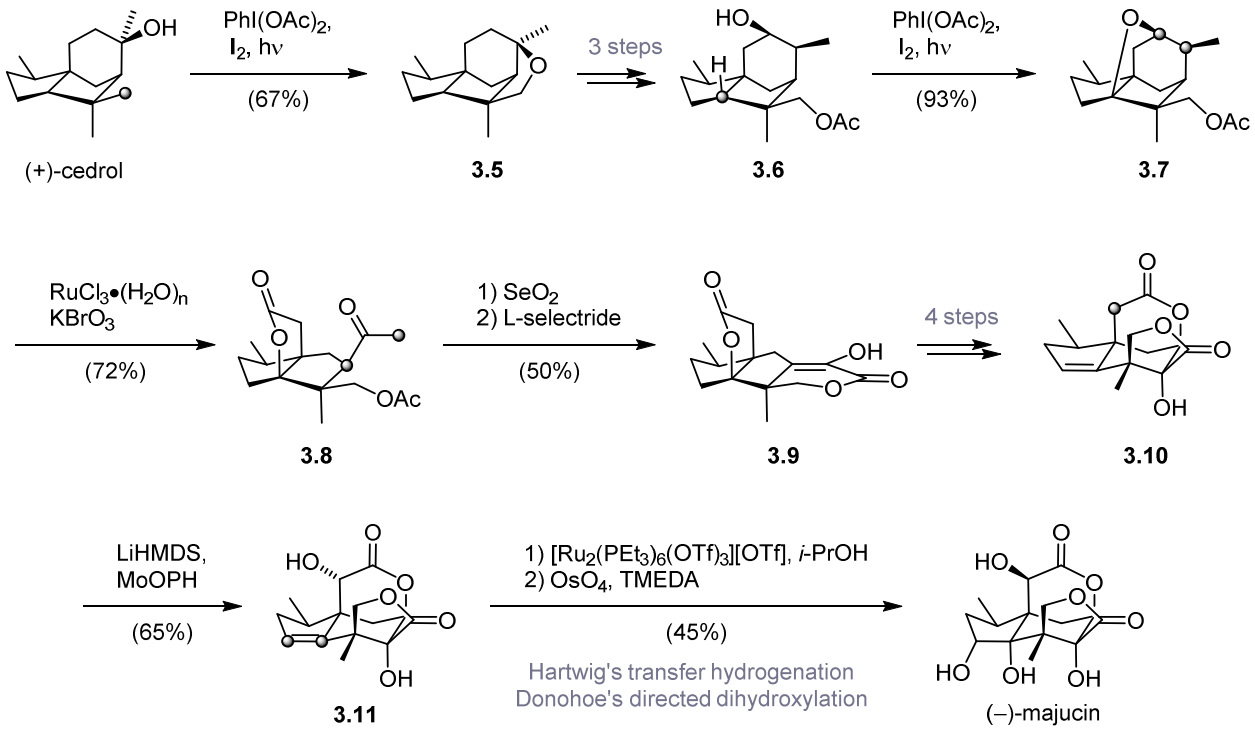
3.1.2. Total Synthesis of Majucin

Illicitum sesquiterpenes, and the majucinoids in particular, are a family of highly oxidized terpenes consisting of over 20 members. In 2017, the Maimone group reported a total synthesis of (−)-majucin (**Scheme 3.3**) based on the oxidative modification of the readily available terpene (+)-cedrol.[7] This strategy, which served them well in their previous synthesis of (+)-pseudoanisatin,[8] was implemented to (−)-majucin by first removing, in the retrosynthetic sense, the vicinal diol and the secondary α-hydroxy. This identified a lower oxidation state dilactone with a hydrindane core whose structure required derivation from cedrol. This was planned to be executed by a sequence of oxidative rearrangements and C−C bond fragmentations that mainly rely on the ability of strategically placed hydroxyl groups to direct H-atom abstraction.



Scheme 3.3 Maimone's[7] retrosynthesis of (−)-majucin.

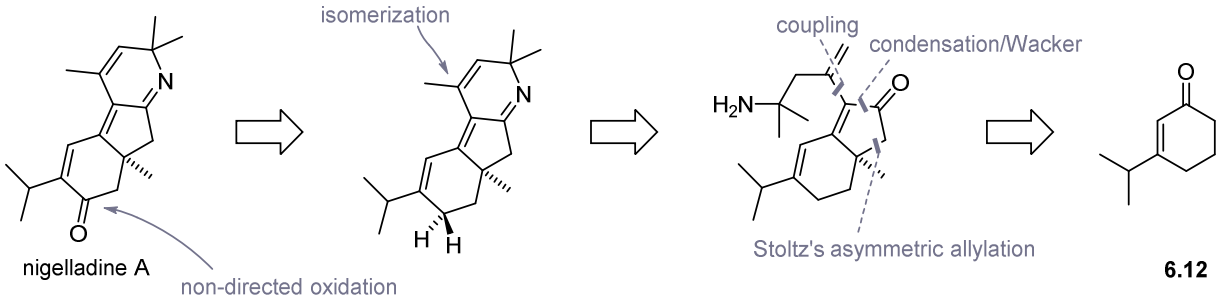
In the forward sense, the tertiary hydroxyl of cedrol was used to monofunctionalize the geminal dimethyl group to tetrahydrofuran **3.5** by the Suárez reaction[9] (**Scheme 3.6**). It was then formally transposed to the vicinal position (**3.6**) and used in a second directed functionalization to tetracycle **3.7**, whose cyclohexane was cleaved by RuO_4 to give oxa-propellane **3.8**. The following exhaustive oxidation of both the ketone's α-carbons produced **3.9** whose carbon core was rearranged in 4 steps to **3.10**. With the anticipated dilactone in hand, installation of the secondary hydroxyl (**3.11**) was achieved utilizing the Vedejs reagent[10] followed by epimerization with Hartwig's transfer hydrogenation catalyst.[11] Finally the directed dihydroxylation protocol from Donohoe[12] delivered the natural product. The synthesis demonstrates that the judicious choice of scaffold, guided by pattern recognition, is fundamental to the successful execution of late-stage aliphatic C–H functionalizations in NP synthesis.



Scheme 3.6 Maimone's synthesis of (−)-majucin.

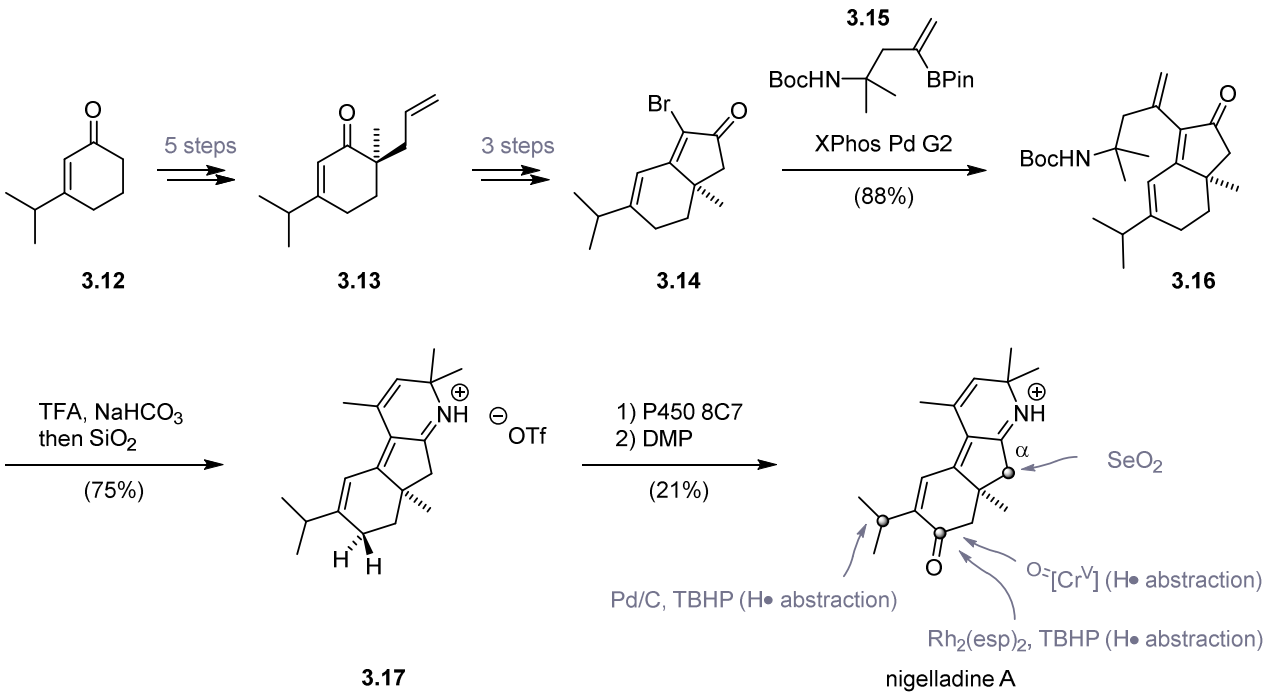
3.1.3. Total Synthesis of Nigelladine A

In 2017, the groups of Stoltz and Arnold reported the total synthesis of nigelladine A (**Scheme 3.7**) with the aim of showcasing the advantage of a non-directed, late-stage oxidation approach to regioselectively install the oxygenation of the extended enone system.[13, 14] With this key step in mind, the subsequent retrosynthetic analysis was greatly simplified.



Scheme 3.7 Stoltz and Arnold's retrosynthesis of nigelladine A.

The tricyclic structure of nigelladine A was traced back to a tetrahydro-indenone, derived from cyclohexenone **3.13** (**Scheme 3.8**), whose quaternary stereocenter was installed enantioselectively by Stoltz's allylation from cyclohexanone **3.12**.[15] Enone **3.13** was elaborated to bromo-tetrahydro-indenone **3.14** in three steps and coupled with vinyl boronic ester **3.15** to give Boc-protected amine **3.16** in good yield. A simple condensation-isomerization afforded the full scaffold necessary for the oxidation campaign. The chemical oxidation of compound **3.17** and its analogues revealed very low site selectivity and over-oxidation. Riley oxidation gave mainly functionalization α to the iminium ion, probably due to the ease of enolization, while hydrogen abstraction methods with various metals resulted in low conversion and poor selectivity for the desired endocyclic H-atom abstraction.



Scheme 3.8 Stoltz and Arnold's synthesis of nigelladine A.

Due to the failure of common reagents to achieve the final oxidation, the report describes the successful implementation of a biocatalytic oxidation as the determinating factor for success of the project. In particular, the use of cytrochrome $P450_{BM3}$ from *Bacillus megaterium* was employed because of its good solubility, fast reaction rates and stability over time ($t_{1/2}$ = 68 min at 50 °C).[13] This enzyme, which normally oxidizes long fatty acid chains in a selective manner, had already been engineered to accept larger substrates and therefore offered a library of "reagents" to be screened. As the original $P450_{BM3}$ showed preference for the hydroxylation at the isopropyl site (1.2:1) twelve mutations were evaluated to find one with overall 1:2.8 selectivity for the desired site. After optimization of the reaction, they could perform the biocatalytic step and the following oxidation to the enone in 21% yield on a 160 mg scale. The merging of microbial catalysis methods and organic chemistry is not in its infancy, as publications from Hudlický and Myers have shown,[16] but the synthetic community still remains resistant to accepting these methodologies as one of the cornerstones of total synthesis. Collaborations as the one discussed here certainly shed a light on the path to follow.

3.2. Toward (–)-Enterocin: An Improved Cuprate Barbier Protocol to Overcome Strain and Sterical Hinderance

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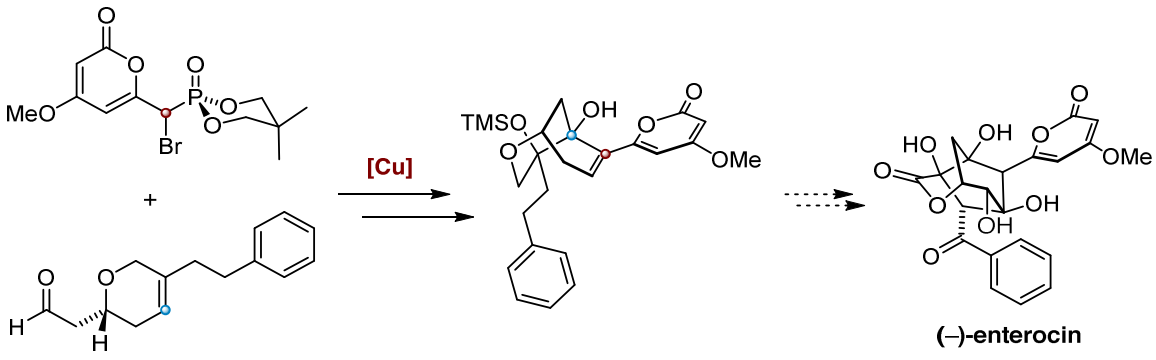

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Toward (−)-Enterocin: An Improved Cuprate Barbier Protocol To Overcome Strain and Sterical Hindrance

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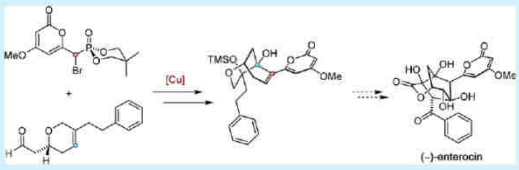
Supporting Information

ABSTRACT: An approach toward (−)-enterocin, an antibiotic isolated from *Streptomyces hygroscopicus*, is described. Its compact, heavily oxidized protoadamantane core represents a daunting challenge for an efficient synthesis. Convergent assembly of its 2-oxabicyclo[3.3.1]nonane core with a cuprate-mediated Barbier reaction is disclosed. Its functionalization to a suitable substrate for a biomimetic aldol to close the final ring of the natural product is evaluated.



(−)-Enterocin (**1**) (also known as vulgamycin, Figure 1) and its biosynthetic precursor (−)-deoxyenterocin (**2**) are metabolites

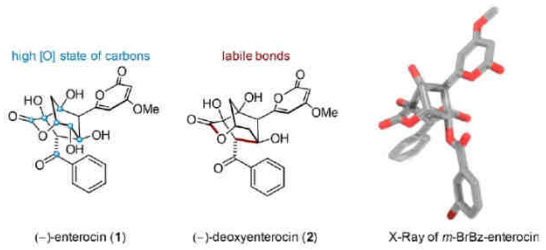
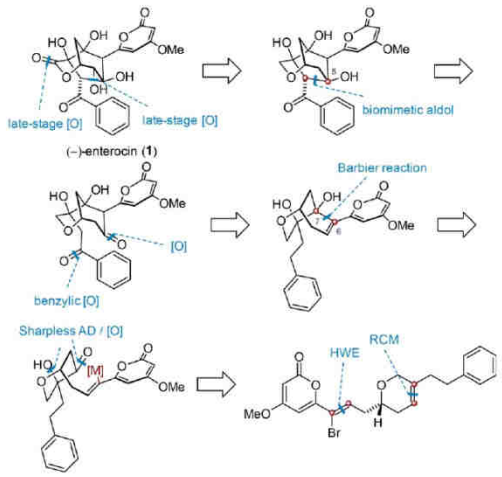


Figure 1. Structure of (−)-enterocin (**1**), its biosynthetic precursor (**2**), and the crystal structure of *m*-BrBz-enterocin.[6]

isolated from *Streptomyces hygroscopicus*.[1] **1** behaves as a bacteriostat against Gram-positive and Gram-negative bacteria, including *Escherichia coli* and species of *Staphylococcus*.[2] Moreover, it exhibits a high degree of herbicidal activity. We became intrigued by the challenge posed by the peculiar caged structure of **1**. Enterocin presents a rare oxa-protoadamantane core,[3] found only in a handful of natural products[4] which have not yet been reached by total synthesis, and is decorated with four hydroxyl groups accounting for four of its seven contiguous stereocenters. These features and the lack of a prior total synthesis[5] of this unusual polyketide prompted our synthetic endeavors.

The high confluence of oxygenation found in **1** confers limitations on tactical considerations toward its synthesis (e.g., issues of chemoselectivity and stability). Strategic deoxygenation was our first retrosynthetic simplification (Scheme 1). Sequential deletion of the secondary alcohol, which is not present in **2**, and the C=O oxygen of the lactone led to the identification of an aldol retron between the C_5 tertiary alcohol and the benzylic

Scheme 1. Retrosynthetic Analysis of 1 and 2



ketone. This first C−C bond disconnection is present in the biosynthesis of **1**[5d] and was therefore chosen as the cornerstone of our retrosynthesis. Despite the reversibility of aldol reactions, we envisioned that the proximity derived from the locked conformation of the 2-oxabicyclo[3.3.1]nonane scaffold would enable successful ring closure to the tricyclic core of **1** and **2**.

Installation of the two ketones was planned by a benzylic oxidation and a formal *anti*-Markovnikov hydration of an endocyclic olefin. A Barbier reaction between a vinyl nucleophile and a ketone was deemed uniquely suitable to overcome the

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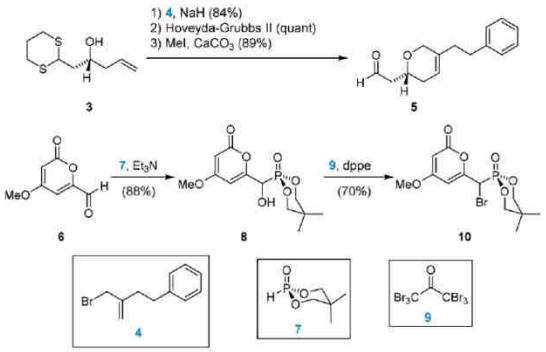
sterical hindrance and strain in forming the C_6-C_7 bond. The required α-hydroxylated ketone was then planned to arise via Sharpless asymmetric dihydroxylation and subsequent oxidation of the resulting secondary alcohol. Intermediate dihydropyran was ultimately traced back to building blocks of similar complexity.

The synthesis commenced with the alkylation of known[7] dithiane **3** (97% ee) with allylic bromide **4**,[8] both prepared in two steps from commercially available starting materials (Scheme 2).

Scheme 2. Preparation of the HWE Partners

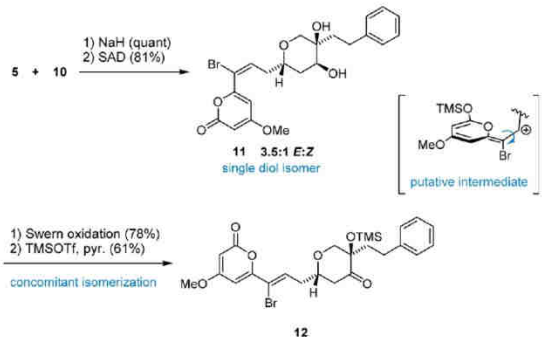


The obtained ether was subjected to standard metathesis conditions using Hoveyda–Grubbs II, followed by alkylative removal of the dithiane. This short sequence delivered multigram quantities of aldehyde **5**, which possesses a handle to introduce the pyrone fragment. Regarding the HWE (Horner–Wadsworth–Emmons) partner, an ad hoc preparation was developed as the difficulty of controlling regioselectivities in radical benzylic brominations of pyrones is well-documented.[9] Our approach encompassed the use of aldehyde **6**[10] in an Abramov–Pudovik reaction with cyclic phosphite **7**.[11] The choice of the latter permitted the facile isolation of solid **8** by simple filtration of the reaction mixture and, more importantly, use of this type of oxaphosphorinane delivers higher *Z*-selectivities in subsequent olefinations.[12] The planned bromination of **8** proved nontrivial[13] but could be achieved by subjection to hexabromoacetone and dppe.[14] Use of dppe in place of triphenylphosphine greatly simplified purification of **10**.

NaH-mediated HWE reaction quantitatively delivered the expected vinyl bromide as a 3.5:1 *E*/*Z* mixture of isomers (Scheme 3).[15] Despite the low isomeric ratio, the inseparable mixture was carried forward to the next reaction. Sharpless asymmetric dihydroxylation installed the first of the tertiary alcohols present in the natural product, delivering diol **11** in good yield. It was observed during the subsequent oxidation–protection sequence (which advanced us to cyclization precursor **12**) that the configuration of the vinyl bromide was subject to thermodynamic control. Under Lewis acidic conditions, as with silylium ions, and under Swern conditions, we noticed that the isomeric ratio was shifted in favor of the desired *Z*-isomer. It appeared that the pyrone could be activated as an extended Michael system. Indeed, use of excess TMSOTf buffered by pyridine and prolonged reaction times delivered desired cyclization precursor **12** as a single isomer.

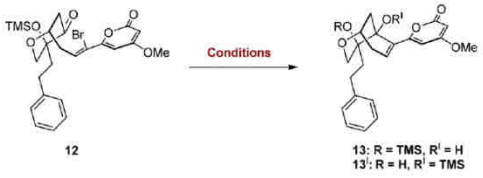
After gaining access to compound **12**, the stage was set for the key cyclization to construct the 2-oxabicyclo[3.3.1]nonane core. In the context of C–C bond formation by organometallic

Scheme 3. Cyclization Precursor Assembly



additions, the challenge of metalating vinyl bromides in the presence of ketones with subsequent 1,2-addition is well-documented. Execution of these two concomitant processes was hampered due to two reasons: the low chemoselectivity of the harsh conditions required to metalate these bromides, and the lack of reactivity of both softer, more chemoselective organometallics and ketones. Intramolecular applications to prepare congested cyclohexenes are scarce.[16] We started our cyclization studies by generating zincated species in an intramolecular Reformatsky reaction (entry 1, Table 1).[17] Application of

Table 1. Exploration and Optimization Studies for Cyclization



entry	reagents	solvent, t °C	result
1	$Rh(PPh_3)_3Cl$, Et_2Zn	THF, 23	reduction
2	*t*-BuLi, TMEDA	Et_2O, −78	decomp.
3	*t*-BuLi	Trapp,[a] −90	decomp.
4	SmI_2	THF, −78	reduction
5	$CrCl_2$, $NiCl_2$	DMSO or DMF, 23	reduction + dimer
6	$CrCl_2$, $NiCl_2$ 4-*t*-Bu-pyr	DMF, 70/90/125	reduction
7	$TMSSnBu_3$	DMF, 60	reduction
8[b]	*n*-Bu_2CuLi·LiI	Et_2O/*n*-hex, −78	traces
9[b]	*n*-Bu_2CuLi·LiI	Et_2O/*n*-hex, −50	15%
10[b]	Np_2CuLi·LiI	Et_2O/*n*-hex, −50	reduction
11[b]	*n*-Bu_2CuLi·LiI	THF, −50	reduction
12[b]	*n*-Bu_2CuLi·LiI	Et_2O, −50	44%
13[c]	*n*-Bu_2CuLi·LiCN	Et_2O, −50	89%
14	***n*-Bu_2CuCN·LiCN**	**Et_2O, −50**	**70%, 1.4 g**

[a]Trapp[16a] 4/4/1 THF/Et_2O/pentane. [b]Conditions: R_2CuX·LiX (12 equiv), 0.01 M, 30 mg scale. [c]Scale: 100 mg. **13**/**13'** = **1**/**1**.

Wilkinson's catalyst provided partial metalation, but the resulting organozinc species lacked the reactivity to close the ring. Therefore, generation of more nucleophilic organolithium species was examined.[18] These processes delivered complex mixtures or decomposition (entries 2 and 3). Employment of SmI_2 provided mainly reduced compounds[19] (entry 4), and under Nozaki–Hiyama–Kishi conditions, dimer formation was observed (entry 5). Although addition of 4-*t*-Bu-pyridine suppressed dimer formation,[20] cyclization to produce the cyclo-

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Org. Lett. XXXX, XXX, XXX−XXX

hexene failed, even at elevated temperatures (entry 6). Use of Shibasaki's conditions ($TMSSnBu_3$, $BnEt_3NCl$) also proved futile (entry 7).[21] The commonly available toolbox of reactions for this type of transformation did not provide the required chemoselectivity and reactivity to forge strained bicycle **13**.

After extensive screening, metalation using dialkylcuprates, as studied by Corey in the 1970s for the synthesis of cyclopentanols, provided trace amounts of **13** for the first time (entry 8).[22] Despite the few successful applications of this method,[23] this procedure proved to be capricious with respect to almost all reaction parameters. Temperature control was necessary to avoid decomposition or transfer of the alkyl ligand onto the alkene (entry 9), and use of nontransferable ligands was deleterious (entry 10).[24] In contrast to the literature precedence,[23a] THF completely abolished reactivity (entry 11). Although Et_2O was able to provide **13** in moderate yield (entry 12), its reproduction was highly variable and, at times, failed.[13]

A major improvement resulted from the realization that CuI as a copper source forms metastable dibutylcuprate salts subject to nonproductive pathways. This realization came upon the empirical observation of particles in solution. Employment of CuCN delivered colorless, homogeneous solutions of dibutylcuprate capable of providing cyclized bicycle **13** with reproducibly high yields on gram scale (entries 13 and 14).[25] Crystals obtained by vapor diffusion permitted determination of absolute and relative stereochemistry (Figure 2).

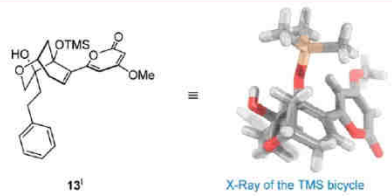
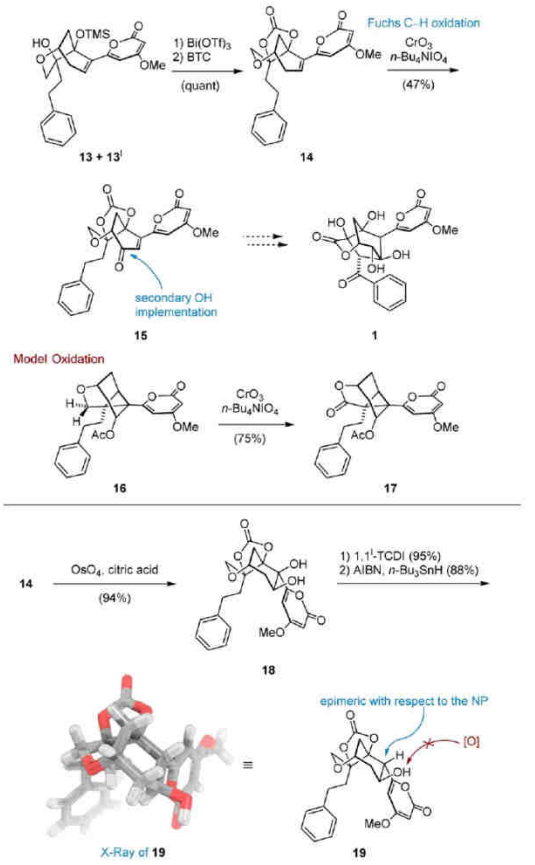


Figure 2. Determination of the absolute configuration of **13'** by X-ray analysis.

A protection/deprotection sequence on substrate **13** + **13'** afforded cyclic carbonate **14**, providing material to probe the reactivity of the endocyclic alkene (Scheme 4, BTC = bis(trichloromethyl)carbonate). Functionalization attempts by epoxidations and various *anti*-Markovnikov hydrofunctionalizations to install the tertiary hydroxyl at C_5 failed.[13] Use of unprotected diol bore the same results, as well as oxidative cleavage by $VO(acac)_2$. Allylic oxidation of **14** could be achieved using Fuchs' conditions to provide corresponding enone **15**.[26] Despite our inability to functionalize this olefin, it permitted us to regioseletively oxidize the carbon bearing **1**'s secondary hydroxyl group. Notably, this same protocol could be efficiently applied to model substrate **16** to oxidize the ether bridge directly to lactone **17**, thereby encouraging our late-stage functionalization strategy.[27]

After considerable experimentation, dihydroxylation with OsO_4 and citric acid[28] was found to be the only method to generate **18**. Diol **18** was then treated with TCDI (1,1′-thiocarbonyldiimidazole), and subsequent radical reduction provided monodeoxygenated alcohol **19** in high yield, albeit with epimeric stereochemistry with respect to enterocin (Scheme 4). The stereochemistry was unequivocally confirmed by X-ray analysis. Efforts to control the diastereoselectivity of hydrogen delivery with different donors or initiators were fruitless.

Scheme 4. Selective Functionalization Studies



Significantly, attempts to epimerize this center following oxidation of the adjacent hydroxyl were thwarted by the inherent instability of the resulting ketone.

In conclusion, a convergent enantioselective synthesis of the heterocyclic core of (−)-enterocin was developed that comprises the complete carbon skeleton of the natural product, with the complete pyrone and two of the three tertiary alcohols in place. Notably, we have systematically investigated and developed a potentially broadly useful intramolecular Barbier reaction. This improved method permitted us to reliably gain access to bicycle **13**, which allowed us to probe the assembly of a suitable substrate for the planned biomimetic aldol. The results indicate that our proposed cyclization precursor is inherently unstable or difficult to muster in a non-enzymatic environment. Efforts toward this last ring closure using minor structural variants of **13** are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00353.

Detailed experimental procedures, spectral data, and X-ray crystallography (PDF)

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Accession Codes

CCDC 1817799−1817800 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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A.R. and D.T. conceived the project. A.R. carried out the experimental work.

Notes

The authors declare no competing financial interest.

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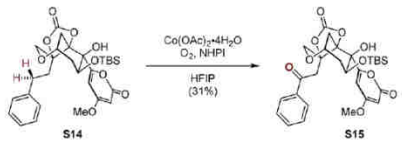
(27) Model substrate **16** was part of a ring-closing cyclopropanation strategy which will be reported in due course. Studies toward late-stage benzylic oxidation are detailed in the Supporting Information. Notably, Co(II) and Cu(II) systems proved capable of achieving this transformation.



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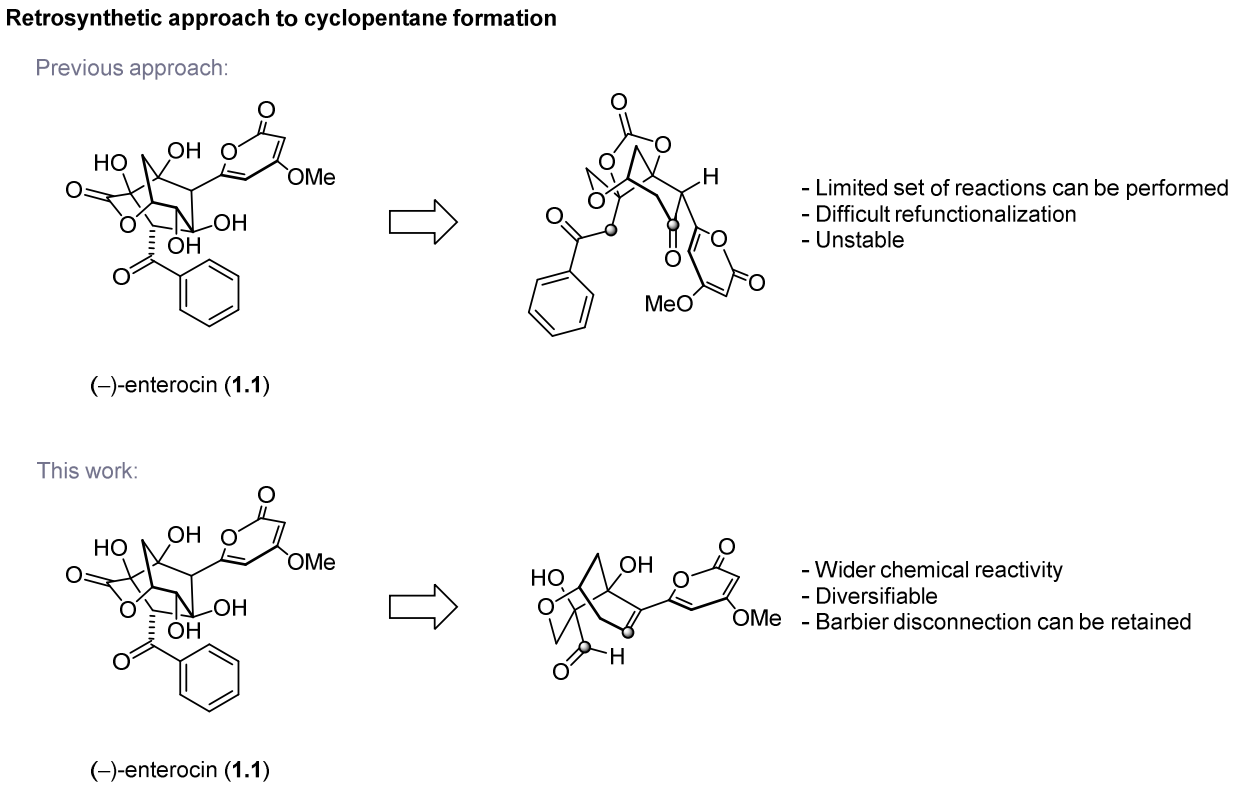
Org. Lett. XXXX, XXX, XXX−XXX

3.3. Second Generation Late-Stage Oxidation Approach Towards Enterocin

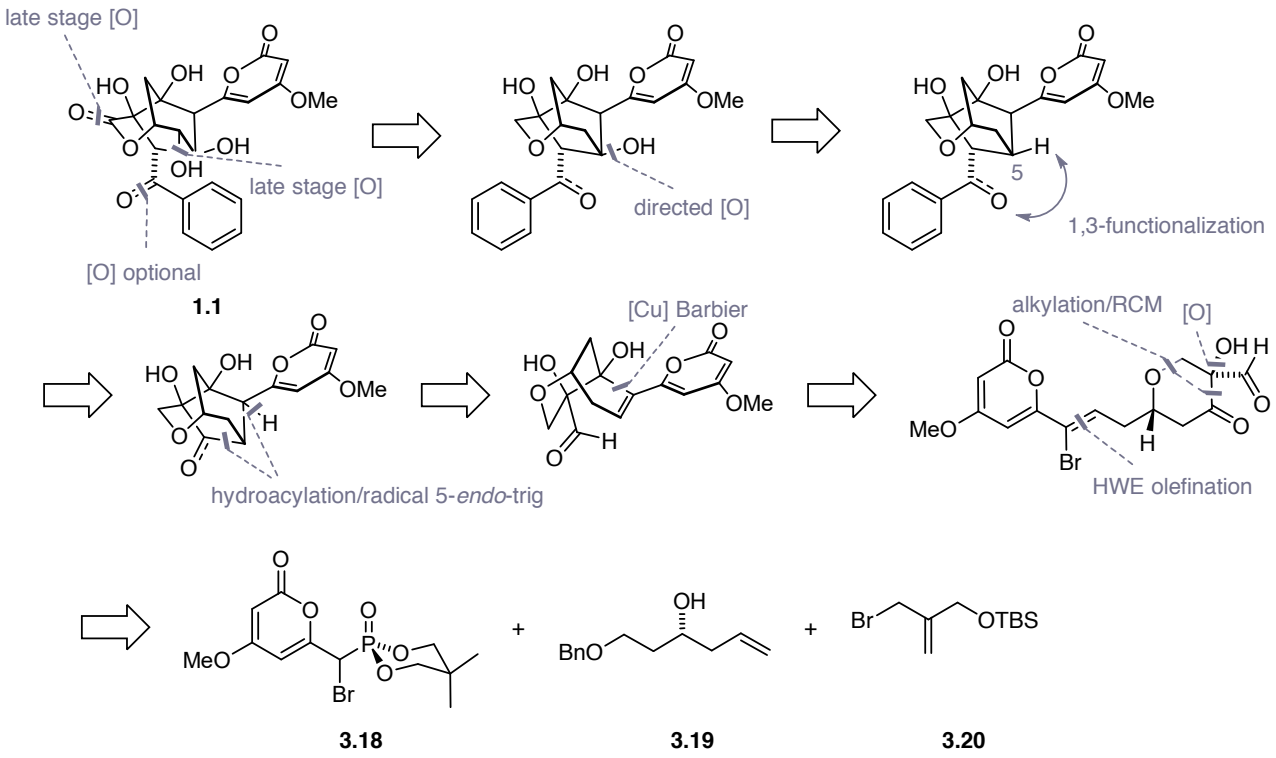
Our synthetic efforts to this point reinforced the idea that the early-stage avoidance of potentially unstable oxidation patterns is paramount[17] in composing the heavily oxidized scaffold of (−)-enterocin (**1.1**). In our first reported late-stage approach, we posited that the biomimetic aldol ring-closure of the cyclopentane ring of **1.1** was not viable due to the instability of the involved substrates (**Scheme 3.9**). Therefore, we opted for a second generation strategy that would implement the chemistry developed thus far to build the 2-oxabicyclo[3.3.1]nonane scaffold, but include a different handle for ring-closure.



Scheme 3.9 Conceptual change in the strategy to ring-close the cyclopentane ring of **1.1**.

In our second retrosynthesis, we sought to introduce the lactone and the secondary hydroxyl during a late-stage of the synthesis (**Scheme 3.10**), requiring C−H oxidation at the C_5 bridgehead position, a daunting transformation in the context of a complex natural product synthesis. We surmised that this specific task could be addressed by a benzylic ketone or alcohol positioned in a 1,3-relationship[18] to C_5. To address the challenging cyclopentane formation, we envisaged two main approaches: (1) an intramolecular hydroacylation, which would close the ring and set stereospecifically the alpha pyrone stereocenter;[19] or (2) a SmI_2 radical cyclization.[20] The

shortcoming of the latter approach is that quenching of the resulting C_6 carbinyl radical is substrate controlled, making it less attractive. The synthesis of the bicyclic intermediate for these key steps could be prepared by taking advantage of the chemistry that we developed previously. Strategic use of a cuprate Barbier to form the strained bicycle, HWE olefination to add the pyrone vinyl bromide, and a dihydroxylation/RCM would trace the 2-oxabicyclo[3.3.1]nonane to three known compounds, providing a concise and convergent route.

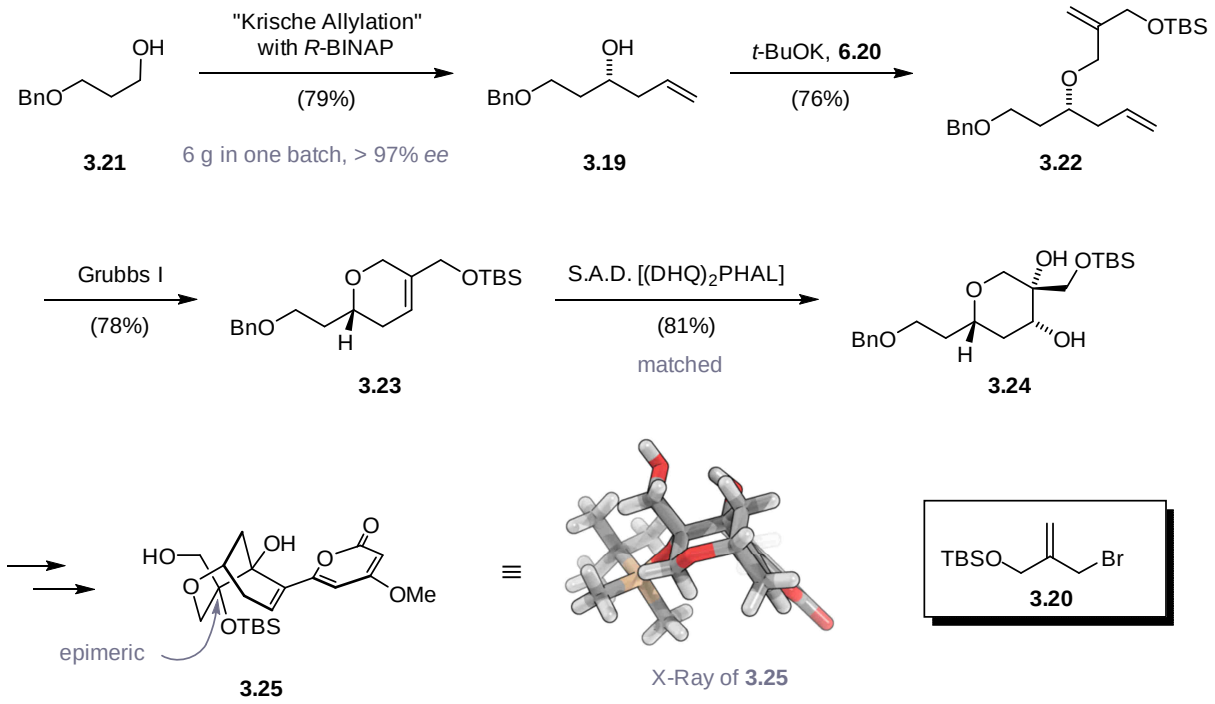


Scheme 3.10 Second generation retrosynthetic approach to **1.1**.

The synthesis start with the preparation of known alcohol **3.19** as described by Krische *et al.*[21] (**Scheme 3.10**). This facile reaction enabled access to several grams of our first chiral building block in high *ee* (>97% *ee*) from commercially available starting materials. Following this, we alkylated **3.19** with known allyl bromide **3.20**[22] forming ether **3.22**. Its treatment with Grubbs I catalyst delivered cyclohexene **3.23** in good yield. The asymmetric dihydroxylation of **3.23** proceeded uneventfully, and displayed clear matched and mismatched behavior.

By analogy to our previous synthesis, we employed the DHQ ligand, which was the matched ligand (**Scheme 3.11**). Major product **3.24** was elaborated to bicycle **3.25** in order to unambiguously confirm its structure.[23] In contrast to the previous route, both NOESY analysis and X-Ray

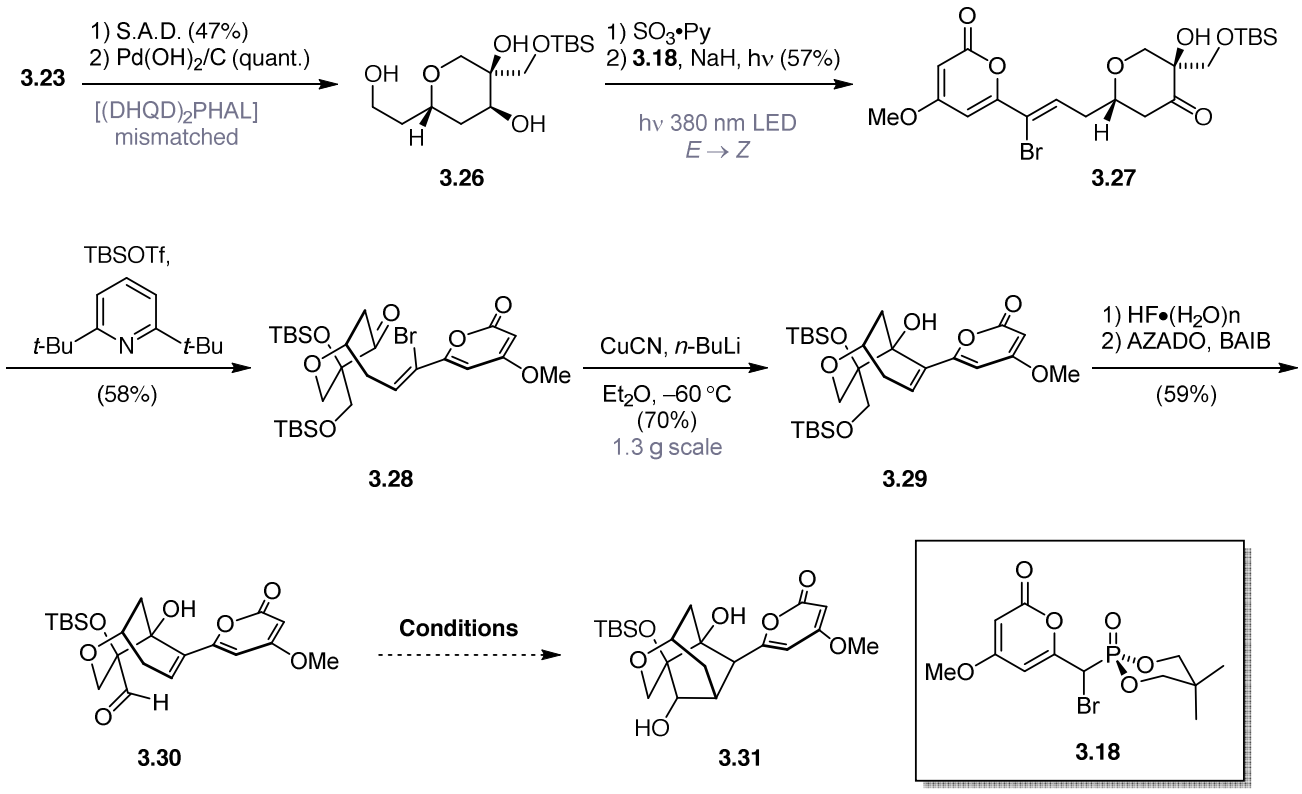
crystallography established the absolute and relative configuration to be epimeric at C_8 the silylated hydroxyl group. Although unfortunate, it provided important information about the impressive reactivity of the cuprate Barbier reaction which can forge highly strained bicyclic structures in the sterically demanding environment imposed by the TBS group.



Scheme 3.11 Preparation of substrate **3.25** and determination of the incorrect configuration of the dihydroxylation provided by $(DHQ)_2PHAL$.

Extending from these results, we took the moderate yield of the mismatched dihydroxylation and, following hydrogenation, isolated crude triol **3.26** (**Scheme 3.12**). Double oxidation afforded a crude keto-aldehyde that was directly subjected to olefination which afforded an inconsequential mixture of (*E*):(*Z*)-isomers (**3.27**). Previously, we had realized and exploited the ability of TMSOTf to isomerize the vinylbromide quantitatively to the (*Z*)-isomer. Alas, protection of this substrate with yielded an unstable compound, thereby forcing us to find an alternative isomerization method. We found that irradiation[24] overnight with (380-400 nm) LEDs gave the thermodynamically more stable (*Z*)-isomer quantitatively. Having gained access to isomerically pure **3.27**, we needed to address the protection of the α-hydroxyl which proved to be more troublesome than expected. Of the several reagents tried, only TBSOTf was able to deliver silylated **3.28**. This was accompanied by several byproducts, primarily the corresponding silyl enol

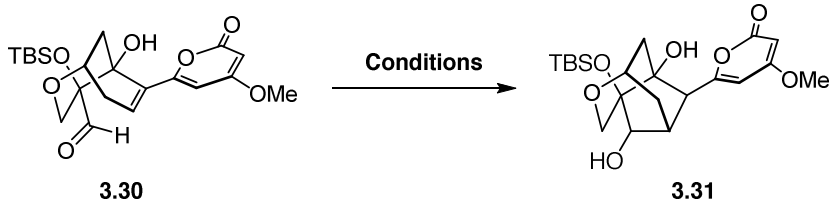
ether. After extensive experimentation, we found that the use of hindered 2,6-di-*t*-Bu-pyridine minimized byproducts, and the slightly more polar dichloroethane, instead of dichloromethane, enhanced the yield.



Scheme 3.12 Elaboration of **3.23** to substrate **3.30**.

Copper-mediated cyclization proceeded smoothly to product **3.29** in good yield (**Scheme 3.12**), and careful NOESY analysis confirmed the expected configuration. Subsequent deprotection and oxidation delivered aldehyde **3.30**. In this regard, it was interesting to note that the C_8 epimers required different deprotection conditions and different *N*-oxyl reagents to reach the aldehyde. In fact, only the sterically unencumbered AZADO delivered **3.30** with acceptable rates and yields.

Table 3.1 Studies towards tricycle **3.31** by 5-*endo*-trig cyclization.



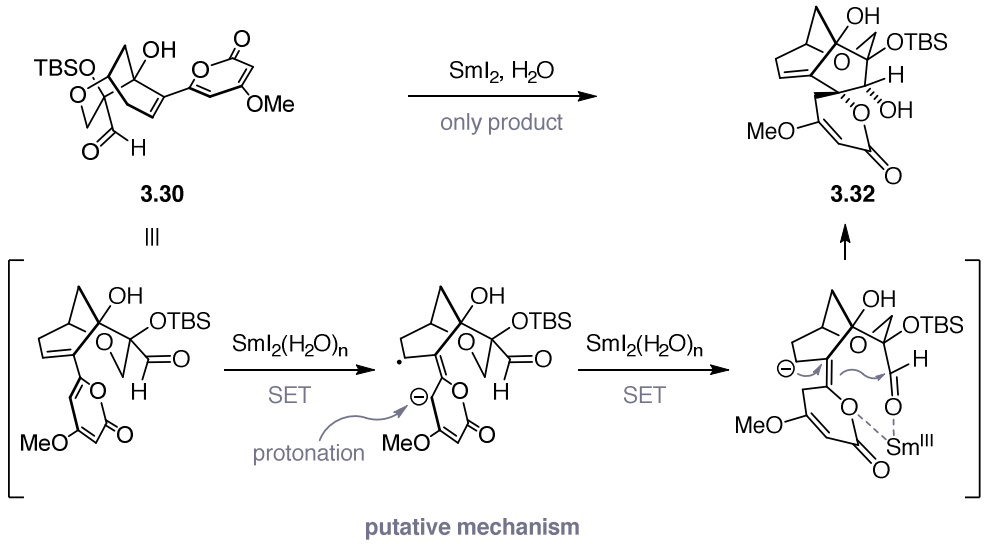
3.30 **3.31**

N.	Reagents	Solvent, T °C	Result
1	Iodine^{III}, blue LED	MeCN, RT	SM
2	$[Rh(nbd)_2]BF_4$, R-DTMBOSEGPhos	Acetone, 60	SM
3	$CoBr_2$, dppe, Mn	DMF, 80	Decomposition
4	AIBN, *n*-Bu_3SnH	Benzene, 80	Decomposition
5	AIBN, diMe-Imid-BH_3	Benzene, 80	Complex mixture
6	4 eq SmI_2, HMPA	THF, 23	Decomposition
7	6 eq SmI_2	Toluene, 0	Complex mixture
8	6 eq SmI_2, *t*-BuOH	THF, 0	Olefin reduction
10	3 eq SmI_2, HMPA, MeOH	THF, −78	Complex mixture
11	6 eq SmI_2, HFIP, H_2O	THF, 0	**3.32**
12	7 eq SmI_2, 100 eq. H_2O	THF, 0	**3.32**

We started our screening campaign by treating aldehyde **3.30** with the 4-(*t*-butyl)benzoate analog of BAIB under photochemical conditions[25] (entry 1, **Table 3.1**), but no reaction ensued. Thereby, we proceeded to explore hydroacylation conditions. Few of the currently available methods were deemed suitable to perform this reaction due to the sterically encumbered nature of the aldehyde and the presence of a tetrasubstituted vicinal carbon. Indeed, both Co-[26] and Rh-mediated[27] methods (entry 2-3) failed to provide cyclized compound **3.31**, although a more extensive screening to rule out this powerful methodology would be necessary.

Therefore, we proceeded to explore a radical mediated 5-*endo*-trig cyclization approach.[28] We surmised that the cyclization would start by a single electron transfer to the carbonyl, but it was soon realized that under most SmI_2 conditions (Entry 6-12) the olefin was the moiety which underwent faster reduction. Indeed, under the conditions developed by Procter *et al*. (entry 12)[29] we could observe the clean transformation of **3.30** to tricyclic structure **3.32** (**Scheme 3.13**), as

determined by extensive 2D-NMR analysis. In analogy to the literature,[30] this probably arises from the reduction/protonation of the pyrone-styrene moiety, whose subsequent anion closes onto the aldehyde by a favorable 5-*exo*-trig to **3.32**.



Scheme 3.13 Mechanistic proposal for the formation of compound **3.32** by reductive 5-*exo*-trig cyclization.

Conceivably, it may be possible to tune the reactivity of the formed anion to close in the ring in a productive manner.

3.4. References

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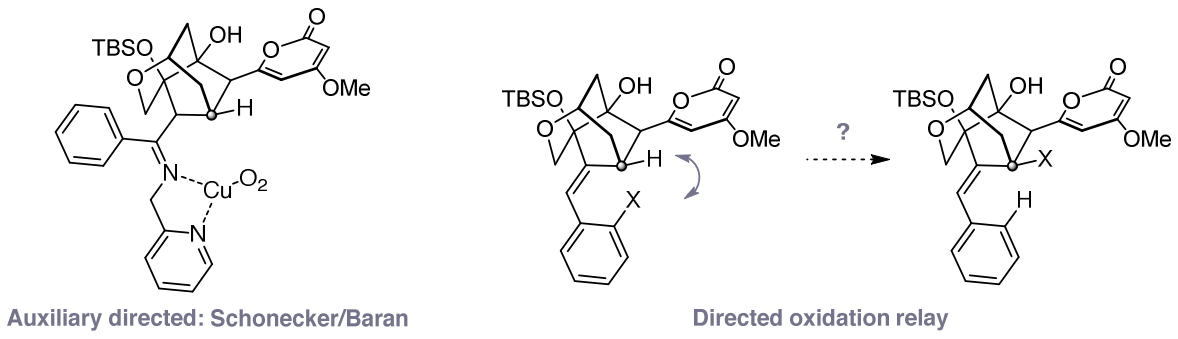
4. Outlook

Over the course of our studies towards the total synthesis of (−)-enterocin (**1.1**), we came to the conclusion that a biomimetic synthesis was an inviable strategy. In contrast, the unique scaffold of the enterocin NP offers the opportunity to develop new strategies that could be successfully be employed in other syntheses. In particular, the direction we started to develop in the latter phase of our research, *e.g.* the late-stage functionalization studies, has proven to be the most appealing and interesting from this standpoint. The oxidation of densely functionalized scaffolds is still an underexplored avenue, and therefore any advancement in that regard is significant. Having achieved significant progress in the early game, closure of the last ring while setting the correct pyrone configuration and oxidation of the methine carbon and the methylene ether bridge would be the next steps to develop. Regarding the latter, it was demonstrated that in principle such transformations could be carried out by direct C–H oxidation. In contrast, for the methine functionalization, there is no clear solution (**Scheme 4.1**). Upon addition of the requisite phenyl ring, this could potentially be used as a synthetic handle to execute this oxidation. For example one might employ auxiliaries such as that developed by Schonecker and optimized by Baran. Nevertheless, a more tempting option would be to install a phenyl ring bearing a handle that could relay oxidation to the C_5 methine. This type of reaction has yet to be reported and would be an audacious synthetic maneuver.

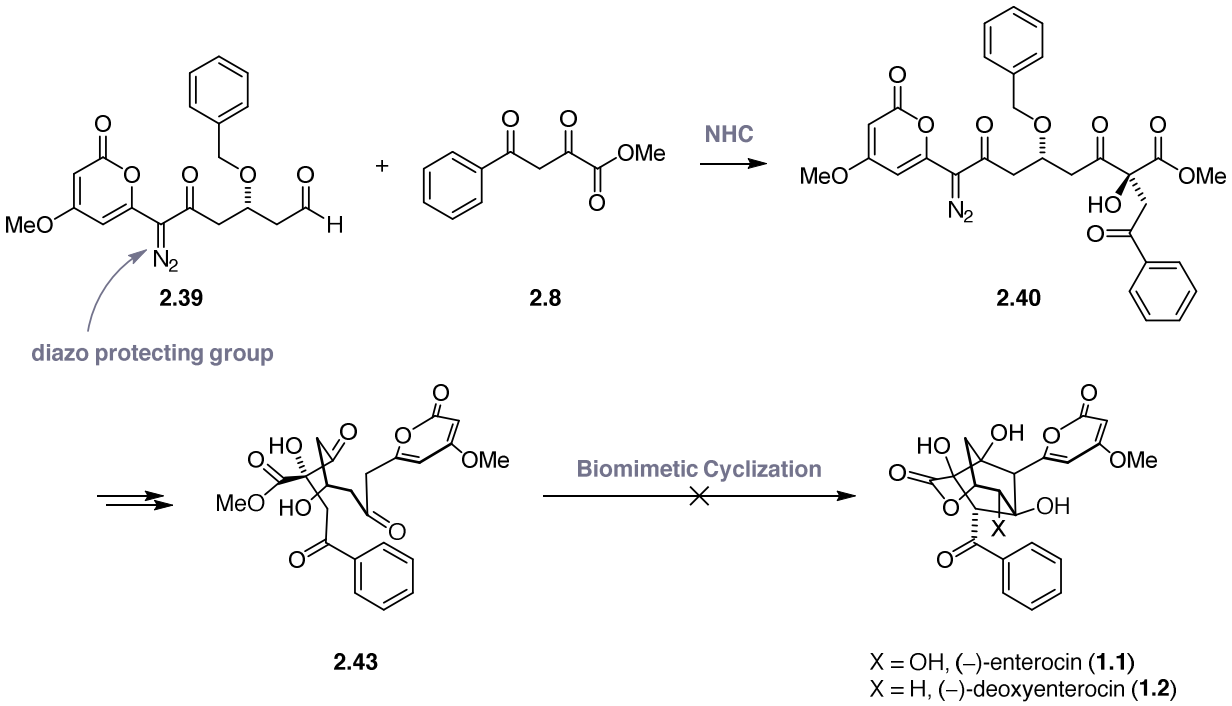


Scheme 4.1 Possible ways to complete the synthesis of the enterocins.

5. Summary

We reported two synthetic approaches to (−)-enterocin (**1.1**) and (−)-deoxyenterocin (**1.2**).

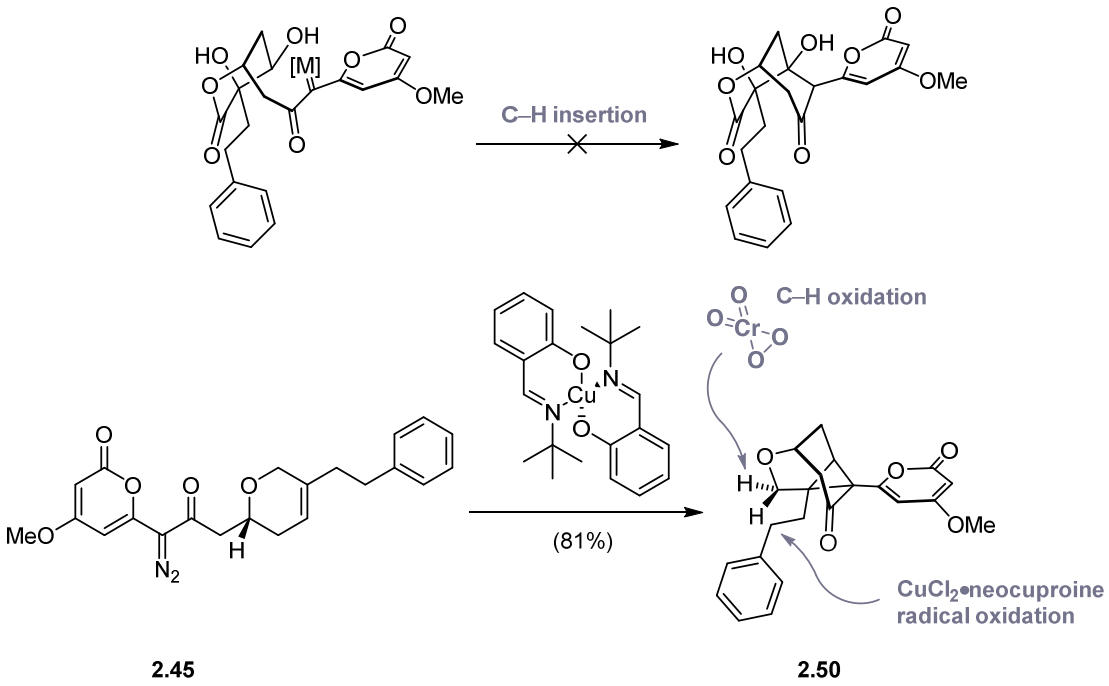
The first comprised of a double aldol biomimetic sequence, which was a proposed step in its biosynthesis. Therefore, we studied the concise assembly of a suitable linear precursor, which was achieved by the preparation of a central chiral fragment and elaborated using a bidirectional functionalization strategy. The key disconnection was formed through an intermolecular acyloin reaction which, to the best of our knowledge, is the most challenging example of this reaction and its first application in natural product synthesis (**Scheme 5.1**). With this advanced intermediate, we proceeded to the final cyclization screening. Most conditions were ineffective or degraded the substrate. These results raised suspicions that the first aldol reaction is likely reversible and energetically disfavored outside of enzymatic control.



Scheme 5.1 Conjunction of aldehyde **2.39** and α-ketoester **2.8** by NHC catalysis (**2.40**) to final compound **2.43** and inviability of the bio-inspired cascade.

To avoid the use of biomimetic aldol chemistry, several C−H insertion substrates were prepared and screened against a set of catalysts that are commonly used in such reactions. None of the conditions bore fruits, but in the case of compound **2.45**, we were able to achieve an

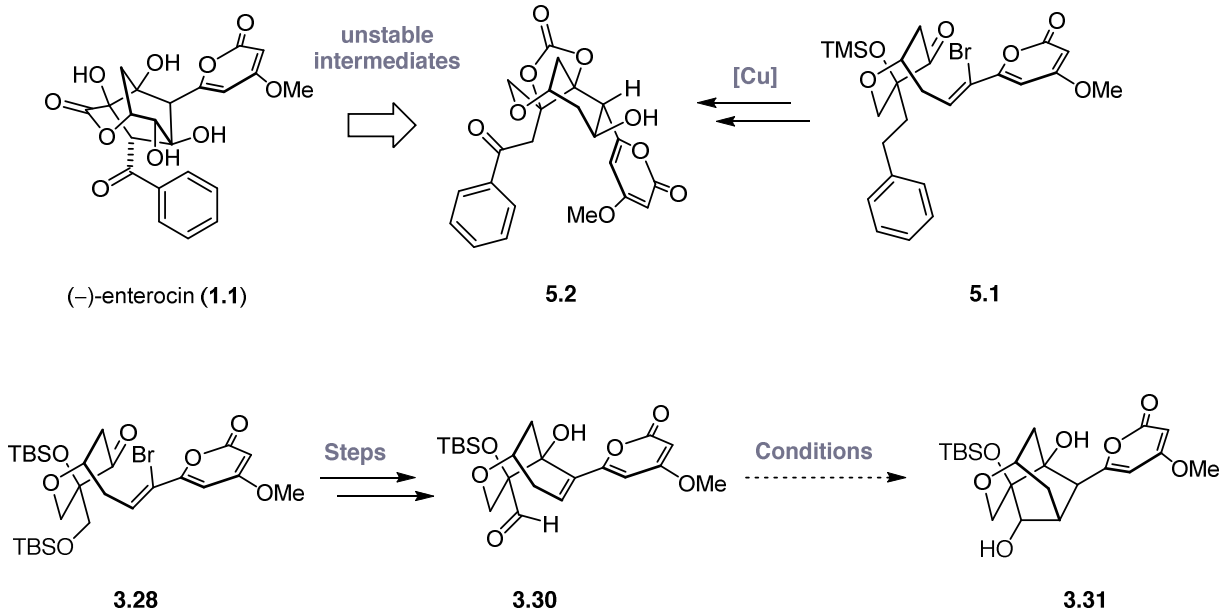
intramolecular cyclopropanation that closed the 2-oxabicyclo[3.3.1]nonane core of enterocin (**Scheme 5.2**). Thereafter, we explored further functionalization of this unusual scaffold to reach the final product.



Scheme 5.2 Evaluation of different insertion strategies to the enterocin scaffold.

Eventually, a convergent enantioselective synthesis of the heterocyclic core of (−)-enterocin (**1.1**) was developed. It possesses of all the carbons in natural enterocin with the complete pyrone and two of the three tertiary alcohols in place. We systematically investigated and developed a challenging intramolecular Barbier reaction from compound **5.1**. This permitted us to reliably gain access to the 2-oxabicyclo[3.3.1]nonane, whose scaffold construction was unreported (**5.2**). Furthermore, we explored the possibility to close the pentacyclic core of the natural product in a biomimetic aldol fashion. The results indicate that the second supposedly biomimetic aldol disconnection, is difficult to muster in a non-enzymatic environment due to competing nonproductive pathways.

Therefore we developed a synthesis to compound **3.30** and commenced studies toward alternative strategies to access the pentacyclic core of enterocin.



Scheme 5.3 Development of Cu-mediated Barbier reaction to close **5.1** to the scaffold of **5.2**; route to **3.30** and evaluation of an alternative ring-closing strategy.

Experimental Section

6. Experimental Section

6.1. General Experimental Details

Magnetic stirring was applied to all the reactions. If air or moisture sensitive, the reactions were carried out under nitrogen atmosphere using standard Schlenk techniques in oven-dried glassware (150 °C oven temperature) and then further dried under vacuum with a heat-gun at 500 °C. All reaction temperatures were recorded using an external thermometer placed into the baths. Reactions under cryogenic conditions were carried out in a Dewar vessel filled with acetone/dry ice (–78 °C to –10 °C) or distilled water/ice (0 °C). High temperature reactions were conducted using a heated silicon oil bath in reaction vessels equipped with a reflux condenser or in a pressure tube. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium and benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylethylamine (DIPEA) were distilled over calcium hydride under a nitrogen atmosphere. All other solvents were purchased from Acros Organics as 'extra dry' reagents. All other reagents with a purity > 95% were obtained from commercial sources (Sigma Aldrich, Acros, TCI, Chempur, Alfa Aesar) and used without further purification.

Flash column chromatography was performed with Merck silica gel 60 (0.040-0.063 mm). To perform thin layer chromatography (TLC) Merck silica gel 60 F254 glassbacked plates were used. Visualization was done under UV light at 254 nm. Ceric ammonium molybdate (CAM), *p*-anisaldehyde (PAA) and potassium permanganate ($KMnO_4$) solutions were used as stains and subsequent heating was used to visualize the result.

High resolution mass spectra (HRMS) were recorded using a Varian MAT CH7A or a Varian MAT 711 MS instrument by electron impact (EI) or electrospray ionization (ESI) techniques.

Infrared spectra (IR) were recorded from 4000 cm^{-1} to 600 cm^{-1} on a PERKIN ELMER Spectrum BX II, FT-IR instrument. Detection: SMITHS DETECTION DuraSamplIR II Diamond ATR sensor. The frequencies of absorption (cm^{-1}) data are reported.

NMR spectra (^{1}H NMR, ^{13}C NMR and ^{31}P NMR) were recorded in deuterated chloroform ($CDCl_3$), benzene (C_6D_6) or methanol (CD_3OD) on a Bruker Avance III HD 400 MHz spectrometer, a Varian VXR400 S spectrometer, a Bruker AMX600 spectrometer or a Bruker Avance III HD 800 MHz spectrometer. ^{1}H NMR spectra are reported as follows: δ (chemical shift) in ppm (multiplicity, coupling constant *J* in Hz, number of protons). ^{13}C NMR spectra are reported as follows: δ (chemical shift) in ppm. Multiplicities abbreviations are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, m = multiplet, or combinations thereof. For internal reference the residual solvent peaks of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), C_6D_6 (δ_H = 7.16 ppm, δ_C = 128.06 ppm) and CD_3OD (δ_H = 4.87 ppm, δ_C = 49.00 ppm) were used. Two dimensional NMR data (COSY, HMBC, HSQC and NOESY experiments) were used to assign spectra.

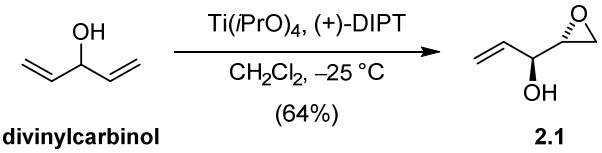
Optical rotation values were recorded on an Anton Paar MCP 200 polarimeter. Specific rotation: $[\alpha]_D^{20\,^{\circ}C}$ = (α × 100) / (c × d). Wavelength (λ) is reported in nm. Temperature (T) is reported in °C. Recorded optical rotation is α. Concentration c is in 1 g/100 mL and length of the cuvette (d) is in dm. Specific rotation: 10^{-1}·deg·cm^2·g^{-1}. Sodium D line (λ = 589 nm) is indicated by D.

X-ray diffraction analysis was carried out by Dr. Peter Mayer (Ludwig-Maximilians-Universität München). The data collections were done on a Bruker D8Venture using MoKα-radiation (λ = 0.71073 Å, graphite monochromator).

6.2. Supporting Information for Chapter 2.1.

6.2.1 Experimental Procedures for Chapter 2.1.

Epoxide (**2.1**)



divinylcarbinol **2.1**

A flame dried flask under argon was charged with oven dried 4 Å MS (4.5 g) and dry CH_2Cl_2 (124 mL). Then, the reaction vessel was cooled to −20 °C and (+)-DIPT (1.83 mL, 10.7 mmol, 0.18 eq.), freshly distilled Ti(*i*PrO)$_4$ (2.80 mL, 9.50 mmol, 0.16 eq.) were added to the mixture. Subsequently, TBHP (21.6 mL, 118.8 mmol, 2.0 eq., 5.5 M in decane with 4 Å MS) was added dropwise and the reaction was stirred for 15 minutes. Then, neat divinylcarbinol (5.0 g, 59.4 mmol, 1.0 eq.) was added and a sudden color change to orange was observed. The reaction was placed in a −25 °C freezer for 7 days. Subsequently, the reaction was diluted with a mixture of acetone (100 mL), H_2O (10 mL) and citric acid monohydrate (1.26 g). The reaction was stirred for 1 h at RT. Afterwards, the solution was filtered over celite, the filtrate was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (Et_2O/pent 1:2) to afford epoxide **2.1** (4.36 g, 43.6 mmol, 73%) as a colorless oil.

R_f: 0.3, EtOAc/*i*hex 4:6, CAM, no UV.

HRMS-EI (m/z): calc. for $C_5H_7O_2$ $[M-H]^{\bullet+}$: 99.0441; found: 99.0440.

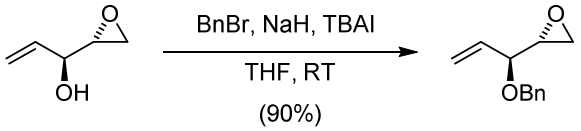
$[\alpha]_D^{20\,°C}$: +63.0 (c = 1.5, $CHCl_3$). Literature: $[\alpha]_D^{20\,°C}$: +48.8 (c = 0.7, $CHCl_3$);[1a] $[\alpha]_D^{20\,°C}$: +57.3 (c = 0.96, $CHCl_3$).[1c]

IR (ATR, neat): ν_{max} = 3398 (b), 3082 (w), 2992 (w), 2875 (w), 1645 (w), 1427 (m), 1251 (s) 1026 (m), 993 (m), 930 (s), 885 (s), 833 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.41 (dt, J = 17.2, 1.3 Hz, 1H), 5.28 (dt, J = 10.4, 1.2 Hz, 1H), 4.44 – 4.30 (m, 1H), 3.15 – 3.04 (m, 1H), 2.82 (dd, J = 5.0, 2.8 Hz, 1H), 2.77 (dd, J = 5.0, 4.0 Hz, 1H).

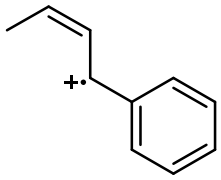
^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.52, 117.94, 77.16, 70.21, 53.96, 43.55.

Benzylether (**2.2**)



2.1 **2.2**

A flame dried flask under argon was sequentially charged with **2.1** (3.43 g, 34.1 mmol, 1.0 eq.), dry THF (80 mL), BnBr (4.89 mL, 41.1 mmol, 1.2 eq.) and TBAI (1.26 g, 3.43 mmol, 0.1 eq.). The reaction vessel was cooled to −20 °C. Then, NaH (1.5 g, 37.7 mmol, 1.1 eq., 60% dispersion in mineral oil) was added to the suspension and the reaction was stirred for 10 minutes. Afterwards, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 5 h). Then, the reaction was quenched by addition of sat. $NH_4Cl_{(aq.)}$. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (Et_2O/pent 5:95) to afford benzylether **2.2** (5.87 g, 30.9 mmol, 90%) as a colorless oil.



R_f: 0.8, Et_2O/pent 1:2, CAM, no UV.

HRMS-EI (m/z): calc. for $C_{10}H_{11}$ $[M-C_2H_3O_2]^{\bullet+}$: 131.0855; found: 131.0855.

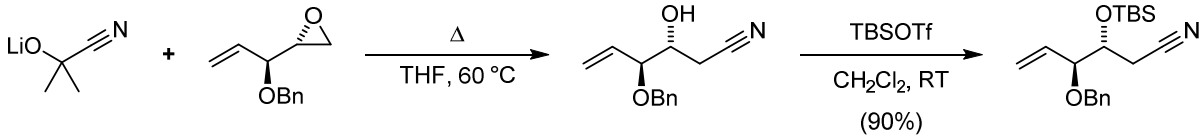
$[\alpha]_D^{20\,°C}$: +35.9 (c = 0.9, $CHCl_3$). Literature: $[\alpha]_D^{20\,°C}$+35.3 (c = 0.93, $CHCl_3$).[1c]

IR (ATR, neat): ν_{max} = 3064 (w), 2990 (w), 2863 (w), 1644 (w), 1606 (w), 1496 (w), 1454 (m), 1251 (w), 1065 (s), 932 (m), 882 (m), 735 (s), 697 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 5H), 5.94 – 5.74 (m, 1H), 5.44 – 5.27 (m, 2H), 4.64 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 3.81 (ddt, J = 7.4, 4.2, 1.0 Hz, 1H), 3.09 (td, J = 4.1, 2.6 Hz, 1H), 2.78 (dd, J = 5.2, 4.0 Hz, 1H), 2.69 (dd, J = 5.2, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.23, 134.57, 128.53, 127.84, 127.79, 119.79, 79.49, 70.76, 53.37, 45.00.

Nitrile (**2.3**)



2.10 **2.2** **2.3**

A flame dried flask under argon, equipped with a reflux condenser, was charged sequentially with benzylehter **2.2** (1.00 g, 5.26 mmol, 1.0 eq.), dry THF (60 mL), Li-cyanohydrin **2.10** (1.05 g, 11.6 mmol, 2.2 eq.) and the reaction vessel was heated to 60 °C. The reaction was monitored by TLC until completion (ca. 1.5 h). Then, the reaction was cooled to RT, the solvent was removed by under reduced pressure and the residue partitioned between H_2O and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude alcohol was used in the next step without further purification.

Data for alcohol:

R_f: 0.2, *i*hex:EtOAc 8:2, CAM, UV

A flame dried flask under argon was charged sequentially with crude alcohol, dry CH_2Cl_2 (60 mL), 2,6-lutidine (1.60 mL, 13.6 mmol, 2.6 eq.) and the reaction vessel was cooled to 0 °C. Neat TBSOTf (1.44 mL, 6.31 mmol, 1.2 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9) to afford **2.3** (1.57 g, 4.75 mmol, 90%) as a yellow oil.

R_f: 0.7, *i*hex:EtOAc 8:2, CAM, PAA (yellow),, UV

HRMS-ESI (m/z): calc. for $C_{19}H_{33}N_2O_2Si$ $[M+NH_4]^+$: 349.23058; found: 349.23062.

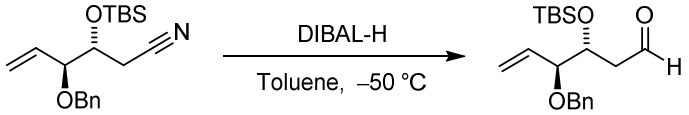
$[\alpha]_D^{20\,°C}$: +15.7 (c = 0.7, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3067 (w), 3032 (w), 2929 (w), 2857 (w), 1471 (w), 1414 (w), 1252 (s), 1108 (s), 994 (m), 924 (m), 836 (s), 777 (s), 697 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 5H), 5.75 (ddd, J = 17.6, 10.5, 7.5 Hz, 1H), 5.49 – 5.27 (m, 2H), 4.61 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.90 (q, J = 5.4 Hz, 1H), 3.80 (t, J = 6.7 Hz, 1H), 2.72 (dd, J = 16.7, 5.5 Hz, 1H), 2.51 (dd, J = 16.7, 4.4 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.96, 135.07, 128.58, 128.08, 127.92, 120.75, 117.98, 82.67, 71.09, 70.84, 25.85, 23.24, 18.13, −4.22, −4.56.

Aldehyde (**2.4**)



2.3 **2.4**

A flame dried flask under argon charged with aldehyde **2.3** (2.07 g, 6.26 mmol, 1.0 eq.) dry toluene (65 mL) was cooled to −50 °C. A solution of DIBAL-H (9.39 mL, 9.39 mmol, 1.5 eq., 1 M in toluene) was added in a single aliquot and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of EtOH, allowed to warm to RT and a sat. solution of Rochelle's salt was added under vigorous stirring (stir for 30 minutes). Then, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 5:95) to afford aldehyde **2.4** (1.67 g, 5.00 mmol, 80%) as a yellow oil.

R_f: 0.5, *i*hex:EtOAc 8:2, CAM, PAA (blue), UV.

HRMS-ESI (m/z): calc. for $C_{19}H_{34}NO_3Si$ $[M+NH_4]^+$: 352.23025; found: 352.23034.

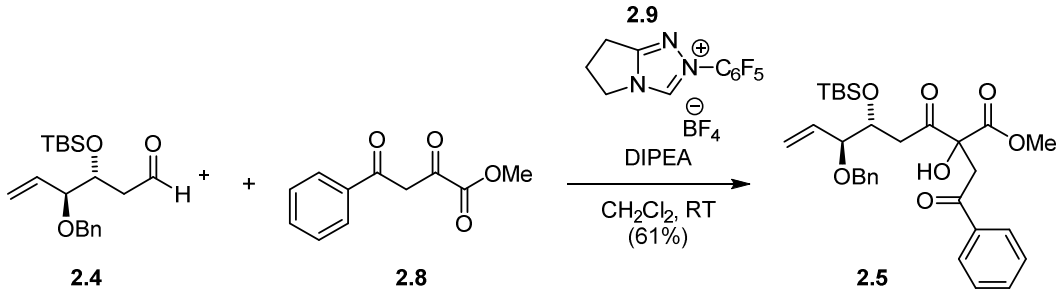
$[\alpha]_D^{20\,°C}$: +20.0 (c = 0.1, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2928 (m), 2856 (m), 1724 (s), 1472 (w), 1252 (s), 1103 (s), 836 (s), 777 (s), 698 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (t, J = 2.5 Hz, 1H), 7.40 – 7.26 (m, 5H), 5.76 (ddd, J = 17.6, 10.4, 7.5 Hz, 1H), 5.42 – 5.23 (m, 2H), 4.59 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.21 (q, J = 5.5 Hz, 1H), 3.73 (dd, J = 7.5, 5.1 Hz, 1H), 2.65 (ddd, J = 15.9, 5.7, 2.5 Hz, 1H), 2.53 (ddd, J = 15.9, 5.6, 2.4 Hz, 1H), 0.85 (s, 9H), 0.05 (d, J = 2.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.59, 138.20, 135.57, 128.49, 128.03, 127.73, 119.96, 83.79, 70.97, 70.75, 48.16, 25.93, 18.20, −4.14, −4.61.

Acyloin (**2.5**)



A flame dried flask under argon was charged with oven dried 4 Å MS (0.2 g), α-ketoester **2.8** (0.74 g, 3.60 mmol, 6.0 eq.) and pre-catalyst **2.9** (0.02 g, 0.06 mmol, 0.2 eq.).Then, a solution of aldehyde **2.4** (0.2 g, 0.59 mmol, 1.0 eq.) in dry CH_2Cl_2 (5 mL + 1 mL to rinse) was added and the mixture was stirred for 5 minutes. Subsequently, dry DIPEA (0.11 mL, 0.59 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 4 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 8:2, long column) to afford acyloin **2.5** (0.2 g, 0.36 mmol, 61%, 1:1.9 d.r.) as an amorphous yellow solid.

R_f: 0.6, *i*hex:EtOAc 8:2, CAM, PAA (blue), UV.

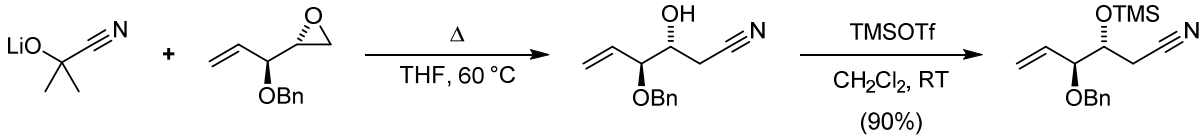
HRMS-ESI (m/z): calc. for $C_{30}H_{44}NO_7Si$ $[M+NH_4]^+$: 558.28816; Found: 558.28849.

IR (ATR, neat): ν_{max} = 3490 (bw), 3066 (w), 2928 (w), 2855 (w), 1746 (m), 1724 (s), 1686 (m), 1358 (m), 1249 (m), 1216 (s), 1091 (s), 832 (s), 777 (s), 688 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 – 7.79 (m, 2H), 7.64 – 7.53 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 4.2 Hz, 5H), 5.80 (dddd, J = 17.8, 10.3, 7.6, 2.3 Hz, 1H), 5.40 – 5.16 (m, 2H), 4.58 (dd, J = 11.8, 5.2 Hz, 1H), 4.46 – 4.31 (m, 2H), 3.88 (dd, J = 18.0, 7.8 Hz, 1H), 3.75 (d, J = 4.4 Hz, 3H), 3.70 (dd, J = 7.8, 4.0 Hz, 1H), 3.56 (dd, J = 18.0, 3.3 Hz, 1H), 3.09 (ddd, J = 30.7, 18.3, 5.5 Hz, 1H), 2.90 – 2.70 (m, 1H), 0.83 (d, J = 9.3 Hz, 9H), 0.11 – -0.03 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.29, 197.65, 197.54, 170.81, 138.64, 136.18, 136.15, 135.37, 133.98, 128.84, 128.39, 128.37, 127.90, 127.86, 127.53, 127.50, 119.86, 119.72, 84.15, 83.93, 82.56, 82.49, 70.50, 70.18, 70.03, 53.80, 53.72, 44.26, 43.97, 42.14, 42.03, 26.06, 26.04, 18.27, 18.25, −4.17, −4.20, −4.70, −4.82.

Nitrile (**2.6**)



2.10 **2.2** **2.6**

A flame dried flask under argon, equipped with a reflux condenser, was charged sequentially with benzylehter **2.2** (1.00 g, 5.26 mmol, 1.0 eq.), dry THF (60 mL), Li-cyanohydrin **2.10** (1.05 g, 11.6 mmol, 2.2 eq.) and the reaction vessel was heated to 60 °C. The reaction was monitored by TLC until completion (ca. 1.5 h). Then, the reaction was cooled to RT, the solvent was removed by under reduced pressure and the residue partitioned between H_2O and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude alcohol was used in the next step without further purification.

Data for alcohol:

R_f: 0.2, *i*hex:EtOAc 8:2, CAM, UV

A flame dried flask under argon was charged sequentially with crude alcohol, dry CH_2Cl_2 (60 mL), 2,6-lutidine (1.60 mL, 13.6 mmol, 2.6 eq.) and the reaction vessel was cooled to 0 °C. Neat TMSOTf (1.14 mL, 6.31 mmol, 1.2 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 5:95) to afford **2.6** (1.37 g, 4.75 mmol, 90%) as a yellow oil.

R_f: 0.7, *i*hex:EtOAc 8:2, CAM, PAA (yellow),, UV

HRMS-EI (m/z): calc. for $C_{16}H_{23}NO_2Si$ $[M]^{+\bullet}$: 289.1493; found: 289.1495.

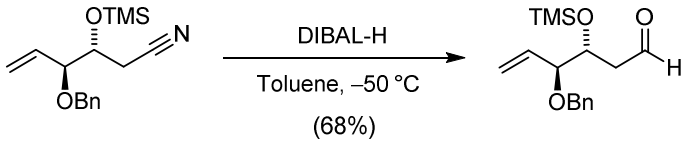
$[\alpha]_D^{20\,°C}$: +30.8 (c = 0.5, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3066 (w), 3032 (w), 2957 (w), 2897 (w), 1454 (w), 1415 (w), 1250 (s), 1107 (s), 994 (w), 925 (m), 839 (s), 749 (m), 697 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.26 (m, 5H), 5.73 (ddd, J = 17.5, 10.4, 7.4 Hz, 1H), 5.47 – 5.27 (m, 2H), 4.62 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.91 (td, J = 6.2, 4.7 Hz, 1H), 3.72 (t, J = 6.9 Hz, 1H), 2.68 – 2.51 (m, 2H), 0.14 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.88, 135.07, 128.58, 128.10, 120.75, 118.26, 82.57, 70.94, 23.43, 0.46.

Aldehyde (**2.S1**)



2.6 **2.S1**

A flame dried flask under argon charged with aldehyde **2.6** (1.37 g, 4.75 mmol,1.0 eq.) dry toluene (40 mL) was cooled to −50 °C. A solution of DIBAL-H (6.65 mL, 6.65 mmol, 1.4 eq., 1 M in toluene) was added in a single aliquot and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of EtOH, allowed to warm to RT and a sat. solution of Rochelle's salt was added under vigorous stirring (stir for 30 minutes). Then, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 5:95) to afford aldehyde **2.S1** (0.94 g, 3.20 mmol, 68%) as a yellow oil.

R_f: 0.7, *i*hex:EtOAc 8:2, CAM, PAA (blue), UV.

HRMS-EI (m/z): calc. for $C_{15}H_{21}O_3Si$ $[M-CH_3]^{+\bullet}$: 277.1254; found: 277.1264.

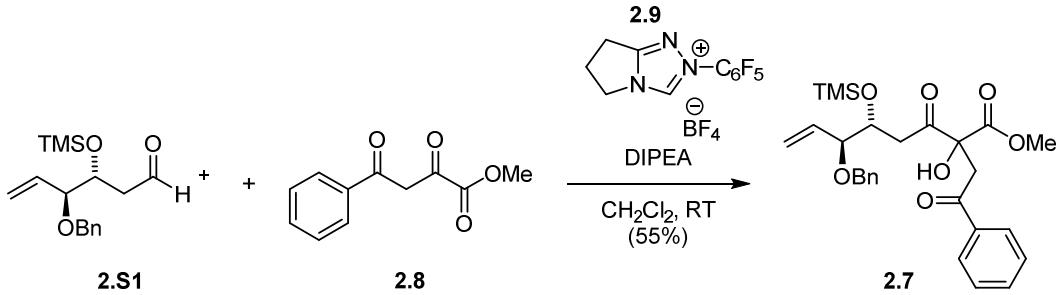
$[\alpha]_D^{20\,°C}$: +39.8 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3066 (w), 2956 (w), 2724 (w), 1724 (s), 1454 (w), 1249 (s), 1091 (bs), 995 (m), 838 (s), 748 (s), 697 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (t, J = 2.3 Hz, 1H), 7.40 – 7.25 (m, 5H), 5.76 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H), 5.45 – 5.24 (m, 2H), 4.61 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.22 (q, J = 5.9 Hz, 1H), 3.68 (dd, J = 7.5, 5.5 Hz, 1H), 2.71 – 2.50 (m, 2H), 0.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.47, 138.14, 135.57, 128.50, 128.07, 127.76, 120.06, 83.48, 70.58, 48.24, 0.51.

Acyloin (**2.7**)



A flame dried flask under argon was charged with oven dried 4 Å MS (0.3 g), α-ketoester **2.8** (0.63 g, 3.08 mmol, 3.0 eq.) and pre-catalyst **2.9** (0.04 g, 0.1 mmol, 0.1 eq.). Then, a solution of aldehyde **2.S1** (0.3 g, 1.02 mmol, 1 eq.) in dry CH_2Cl_2 (18 mL + 2 ml to rinse) was added and the mixture stirred for 5 minutes. Subsequently, dry DIPEA (0.18 mL, 1.02 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 6 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 8:2, long column) to afford acyloin **2.7** (0.27 g, 0.55 mmol, 55%, 1:4 d.r.) as colorless oil.

R_f: 0.7, *i*hex:EtOAc 7:3, CAM, UV.

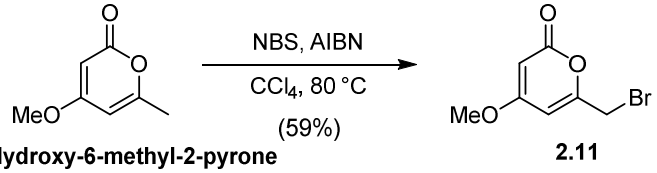
HRMS-ESI (m/z): calc. for $C_{27}H_{38}NO_7Si$ $[M+NH_4]^+$: 516.24121; found: 516.24090.

IR (ATR, neat): ν_{max} = 3485 (bw), 3066 (w), 2955 (w), 2903 (w), 1745 (m), 1723 (s), 1685 (m), 1597 (w), 1449 (m), 1354 (m), 1247 (s), 1216 (s), 1089 (s), 1070 (s), 1001 (m), 929 (m), 839 (s), 753 (s), 688 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 – 7.83 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.38 – 7.26 (m, 5H), 5.78 (ddd, J = 17.7, 10.4, 7.7 Hz, 1H), 5.40 – 5.22 (m, 2H), 4.66 – 4.54 (m, 2H), 4.44 – 4.26 (m, 2H), 3.89 (dd, J = 17.9, 13.4 Hz, 1H), 3.77 (d, J = 2.5 Hz, 2H), 3.71 – 3.54 (m, 2H), 3.16 (dd, J = 17.7, 8.1 Hz, 1H), 3.04 (dd, J = 18.3, 3.4 Hz, 0H), 2.90 (dd, J = 18.2, 8.3 Hz, 0H), 2.77 (dd, J = 17.8, 3.6 Hz, 1H), 0.08 (d, J = 9.1 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.58, 204.52, 197.54, 197.31, 171.32, 170.73, 170.67, 138.46, 136.20, 135.62, 135.53, 133.98, 133.95, 128.85, 128.43, 128.37, 127.93, 127.61, 120.01, 119.92, 83.60, 83.50, 82.62, 82.52, 77.36, 70.52, 60.56, 53.78, 53.69, 44.16, 43.84, 42.06, 41.76, 21.23, 14.35, 0.58, 0.53.

Bromo-pyrone (**2.11**)



A flask was charged with 4-Hydroxy-6-methyl-2-pyrone (1.00 g, 7.14 mmol, 1.0 eq.), CCl_4 (165 mL), NBS (1.39 g, 7.80 mmol, 1.1 eq.), AIBN (0.12 g, 0.71 mmol, 0.1 eq.). The mixture was stirred at 80 °C and illuminated with a 160 W floodlamp. The mixture was monitored by TLC until completion (ca. 1 h). Afterwards, the solvent was distilled under reduced pressure (can be reused in the same reaction) and the crude product was purified by FCC (EtOAc/*i*hex 4:6) to afford bromo-pyrone **2.11** (0.92 g, 4.25 mmol, 59%) as a yellow solid.[2]

R_f: 0.4, EtOAc/*i*hex 1:1, CAM, UV.

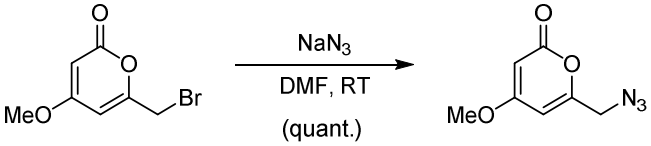
HRMS-EI (m/z): calc. for $C_7H_8BrO_3$ $[M+H]^+$: 218.96513; found: 218.96511.

IR (ATR, neat): ν_{max} = 3032 (w), 1703 (s), 1649 (s), 1565 (s), 1459 (m), 1411 (m), 1333 (w), 1254 (s), 1149 (m), 942 (m), 815 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.09 (d, J = 2.1 Hz, 1H), 5.49 (d, J = 2.1 Hz, 1H), 4.11 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.48, 163.61, 158.73, 102.44, 89.70, 77.16, 56.30, 26.65.

Azido-pyrone (**2.12**)



2.11 **2.12**

A flask was charged with bromo-pyrone **2.11** (0.20 g, 0.92 mmol, 1.0 eq.), dry DMF (165 mL) and NaN_3 (0.11 g, 1.84 mmol, 2.0 eq.). The heterogeneous orange mixture was stirred at RT and monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was partitioned between H_2O and EtOAc, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:1) to afford azido-pyrone **2.12** (0.17 g, 0.92 mmol, quant.) as a white solid.

R_f: 0.4, EtOAc/*i*hex 1:1, CAM, UV.

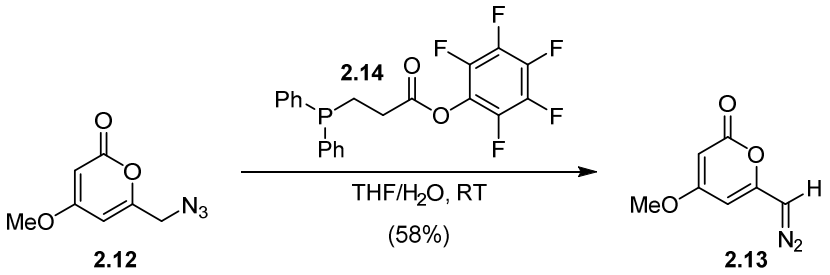
HRMS-EI (m/z): calc. for $C_7H_8N_3O_3$ $[M+H]^+$: 182.05602; Found: 182.05606.

IR (ATR, neat): ν_{max} = 3082 (w), 2107 (s), 1731 (s), 1707 (s), 1652 (s), 1569 (s), 1453 (m), 1415 (m), 1249 (w), 1137 (s), 914 (m), 829 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.09 – 5.97 (m, 1H), 5.48 (t, J = 1.6 Hz, 1H), 4.13 (s, 2H), 3.83 (d, J = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.71, 163.64, 158.69, 101.01, 89.10, 56.26, 51.01.

Diazo-pyrone (**2.13**)



A flask was charged with bromo-pyrone **2.12** (0.10 g, 0.55 mmol, 1.0 eq.), THF (1.0 mL), H_2O (0.15 mL) and phosphine **2.14** (0.25 g, 0.60 mmol, 1.1 eq.). The heterogeneous yellow mixture was stirred at RT and was monitored by TLC until completion (ca. 1 h). Afterwards, a solution of sat. $NaHCO_{3(aq.)}$ (1 mL) was added (gas evolution!). The heterogeneous orange mixture was monitored by TLC until completion (ca. 2 h). Then, the reaction was partitioned between H_2O and CH_2Cl_2, the aqueous phase was extracted three times with CH_2Cl_2, the combined organic fractions were washed with brine, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 2:8) to afford diazo-pyrone **2.13** (0.05 g, 0.32 mmol, 58%) as an orange solid.

R_f: 0.4, EtOAc/*i*hex 1:1, CAM, UV.

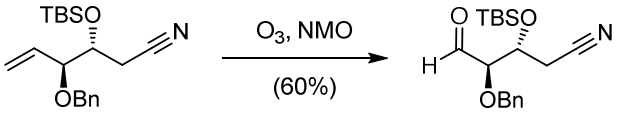
HRMS-EI (m/z): calc. for $C_7H_7N_2O_3$ $[M+H]^+$: 167.04512; found: 167.04514.

IR (ATR, neat): ν_{max} = 3288 (b), 3064 (m), 2148 (w), 2077 (s), 1714 (s), 1616 (m), 1545 (m), 1407 (m), 1243 (m), 1171 (m), 1042 (m), 946 (w), 807 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.56 (t, J = 1.5 Hz, 1H), 5.24 (t, J = 1.5 Hz, 1H), 4.94 (d, J = 1.0 Hz, 1H), 3.79 (d, J = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.82, 163.62, 155.48, 91.75, 84.28, 55.91, 48.48.

Aldehyde (**2.18**)



2.3 **2.18**

A flame dried flask under argon was charged with nitrile **2.3** (0.10 g, 0.30 mmol, 1.0 eq.), *N*-methylmorpholine-*N*-oxide (0.10 g, 0.90 mmol, 3.0 eq.) and dry CH_2Cl_2 (3.0 mL). Then it was cooled to −78 °C. A stream of ozone was passed through the reaction for 1.4 minutes and then the solution was purged with a N_2 stream. The reaction was monitored by TLC for completion. The solution was directly purified by FCC (EtOAc/*i*hex 1:9 to 3:7) to afford aldehyde **2.18** (60.0 mg, 0.18 mmol, 60%) as a yellow oil.

R_f: 0.4, *i*hex:EtOAc 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{18}H_{28}NO_3Si$ $[M+H]^+$: 334.18330; found: 334.18398.

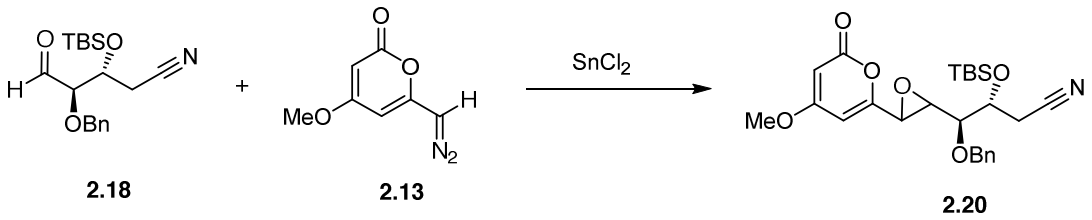
$[\alpha]_D^{20\,°C}$: +19.0 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2930 (w), 2886 (w), 2858 (w), 1734 (s), 1497 (w), 1471 (w), 1463 (w), 1254 (m), 1103 (s), 1005 (m), 912 (m), 837 (s), 778 (s), 736 (m), 697 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.68 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.29 (m, 5H), 4.76 – 4.61 (m, 2H), 4.25 (q, *J* = 5.3 Hz, 1H), 3.86 (dd, *J* = 5.3, 1.5 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.55 (dd, *J* = 16.8, 4.9 Hz, 1H), 0.90 (d, *J* = 1.1 Hz, 9H), 0.12 (d, *J* = 24.7 Hz, 6H).).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.68, 136.63, 128.84, 128.62, 128.43, 117.04, 84.67, 73.79, 69.30, 25.72, 23.22, 18.05, -4.60.

Epoxide (**2.20**)



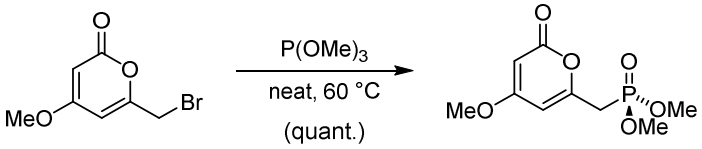
2.18 **2.13** **2.20**

HRMS-ESI (m/z): calc. for $C_{25}H_{34}NO_6Si$ $[M+H]^+$: 472.21499; found: 472.21534.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 7.4 Hz, 3H), 5.93 – 5.86 (m, 1H), 5.41 (d, *J* = 1.8 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.24 (td, *J* = 6.5, 2.4 Hz, 1H), 3.86 – 3.79 (m, 2H), 3.78 (s, 3H), 3.38 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.30 (dd, *J* = 8.3, 2.6 Hz, 1H), 2.70 (qd, *J* = 16.8, 6.4 Hz, 2H), 0.92 (d, *J* = 1.0 Hz, 9H), 0.12 (d, *J* = 28.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.31, 163.33, 158.03, 137.00, 128.58, 128.09, 127.78, 117.76, 100.89, 89.31, 75.48, 72.40, 70.67, 57.32, 56.22, 52.65, 25.85, 22.54, 18.16, -4.43, -4.78.

Phosphonate (**2.21**)



2.11 **2.21**

A flask equipped with a reflux condenser was charged with bromo-pyrone **2.11** (0.20 g, 0.92 mmol, 1.0 eq.) and $P(OMe)_3$ (0.2 mL, 1.61 mmol, 1.7 eq.) at RT. Then, the reaction was heated to 60 °C and was monitored by TLC until completion (ca. 5 h). Afterwards, the reaction was directly purified by FCC (EtOAc/*i*hex 2:1 then MeOH/EtOAc 4:96) to afford phosphonate **2.21** (0.26 g, 0.92 mmol, quant.) as a white solid.

R_f: 0.3, MeOH:EtOAc 4:96, $KMnO_4$, UV.

HRMS-EI (m/z): calc. for $C_9H_{13}O_6P$ $[M]^{+\bullet}$: 248.0444; found: 248.0445.

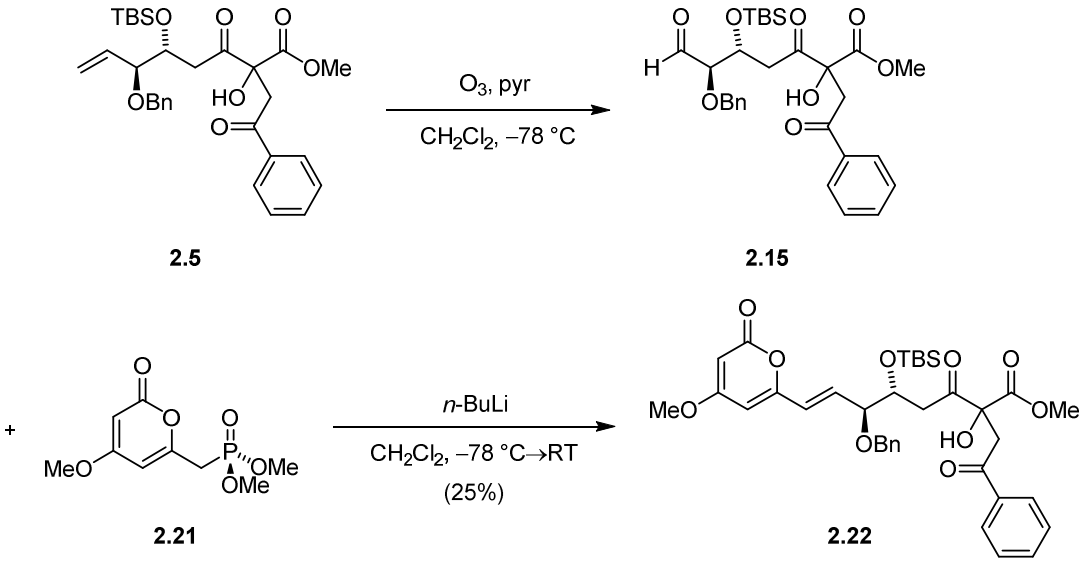
IR (ATR, neat): ν_{max} = 3085 (w), 2957 (w), 2916 (w), 1721 (s), 1650 (s), 1565 (s), 1414 (m), 1242 (s), 1183 (m), 1022 (s), 938 (m), 843 (s), 792 (s), 693 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.01 (t, J = 2.9 Hz, 1H), 5.45 (d, J = 2.1 Hz, 1H), 3.82 (s, 3H), 3.80 (d, J = 3.2 Hz, 6H), 3.04 (d, J = 22.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.00, 164.14, 155.82, 102.85, 88.53, 56.13, 53.40, 32.18, 30.79.

^{31}P NMR (162 MHz, $CDCl_3$) δ = 23.42.

Alkene (**2.22**)



A flame dried flask under argon was charged with acyloin **2.5** (0.02 g, 0.037 mmol, 1.0 eq.), pyridine (12 µL, 0.10 mmol, 3.0 eq.) and dry CH_2Cl_2 (0.55 mL). Then it was cooled to −78 °C. A stream of ozone was passed through the reaction for 1.4 minutes and then the solution was purged with a N_2 stream. The reaction was monitored by TLC for completion. The solution was cannulated directly in the following reaction.

R_f: 0.7, *i*hex:EtOAc 7:3, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{29}H_{42}NO_8Si$ $[M+NH_4]^+$: 560.26742; found: 560.26800.

The crude ^{1}H-NMR spectrum is available in the NMR data section.

A flame dried flask under argon was charged with phosphonate **2.21** (0.01 g, 0.040 mmol, 1.1 eq.), dry THF (0.40 mL) and cooled to −78 °C. A solution of *n*-BuLi (0.04 mL, 0.042 mmol, 1.15 eq, 1 M in hexanes) was added and the reaction was stirred for 30 minutes. Then, the solution of ozonolyzed acyloin was cannulated into the mixture, stirred at the same temperature for 1 h and then the cooling bath was removed. The reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of sat. $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 4:6) to afford alkene **2.22** (6.30 mg, 0.009 mmol, 25%) as a yellow oil.

R_f: 0.6, *i*hex:EtOAc 1:1, CAM, UV.

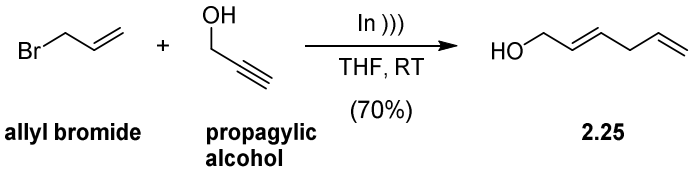
HRMS-ESI (m/z): calc. for $C_{36}H_{48}NO_{10}Si$ $[M+NH_4]^+$: 682.30420; found: 682.30489.

IR (ATR, neat): ν_{max} = 3460 (bw), 3064 (w), 2953 (w), 2928 (w), 2856 (w), 1721 (s), 1690 (m), 1559 (s), 1451 (m), 1248 (s), 1218 (s), 1095 (m), 1036 (m), 832 (s), 777 (s), 732 (m), 689 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.87 (dddd, J = 17.4, 8.5, 2.3, 1.2 Hz, 2H), 7.61 – 7.56 (m, 1H), 7.49 – 7.42 (m, 2H), 7.37 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 6.70 (ddd, J = 15.5, 9.1, 5.8 Hz, 0H), 6.61 (ddd, J = 15.7, 6.9, 5.9 Hz, 1H), 6.31 – 6.08 (m, 1H), 5.85 (dd, J = 13.2, 2.2 Hz, 1H), 5.48 (ddd, J = 4.6, 2.3, 0.9 Hz, 1H), 4.62 – 4.47 (m, 3H), 4.06 (t, J = 4.4 Hz, 0H), 4.02 – 3.96 (m, 1H), 3.92 – 3.84 (m, 1H), 3.81 (d, J = 0.9 Hz, 2H), 3.78 – 3.73 (m, 3H), 3.60 – 3.53 (m, 1H), 3.19 (ddd, J = 18.0, 6.5, 0.8 Hz, 1H), 3.11 – 3.05 (m, 0H), 2.93 – 2.85 (m, 0H), 2.81 – 2.72 (m, 0H), 0.87 – 0.79 (m, 9H), 0.09 – 0.00 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 203.94, 197.53, 197.40, 170.89, 170.85, 170.54, 170.52, 163.83, 163.78, 157.56, 157.53, 137.97, 137.94, 135.99, 135.98, 135.50, 135.48, 133.83, 133.82, 128.72, 128.69, 128.67, 128.40, 128.37, 128.34, 128.22, 127.79, 127.74, 127.72, 127.66, 127.63, 124.23, 124.15, 101.35, 101.30, 89.13, 82.42, 82.33, 82.24, 82.13, 71.63, 71.51, 70.19, 70.02, 55.93, 53.66, 53.60, 44.16, 43.85, 41.79, 41.55, 25.84, 18.03, −4.45, −4.84, −4.97.

Diene (**2.25**)



A flame dried flask under argon was charged with propargylic alcohol (5.70 mL, 100 mmol, 1.0 eq.), dry THF (100 mL), vinyl bromide (5.70 mL, 100 mmol, 1.5 eq.) and In droplets (12.6 g, 110 mmol, 1.1 eq.). The flask was sealed with a rubber septum and fitted with an argon balloon. Then, the mixture was sonicated in a water bath at RT and was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was removed from the bath, quenched by addition of 3 M $HCl_{(aq.)}$ (200 mL) and stirred for 10 minutes. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:5) to afford diene **2.25** (4.94 g, 50.0 mmol, 50%) as a yellow oil.[3a]

R_f: 0.4, EtOAc/*i*hex 2:8, CAM, no UV.

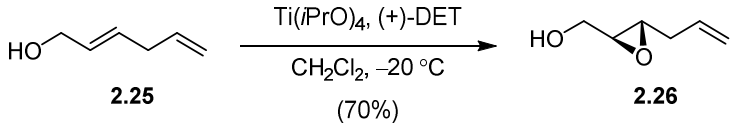
HRMS-EI (m/z): calc. for C_6H_9O $M^{+\bullet}$: 97.0648; found: 97.0648.

IR (ATR, neat): ν_{max} = 3309 (b), 2870 (w), 1711 (m), 1638 (s), 1430 (m), 1413 (m), 1087 (sw), 994 (s), 970 (s), 911 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.70 (dt, J = 7.7, 5.4 Hz, 2H), 5.11 – 4.97 (m, 2H), 4.18 – 4.05 (m, 2H), 2.81 (t, J = 5.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.43, 130.73, 130.16, 115.73, 63.81, 36.46.

Epoxide (**2.26**)



2.25 **2.26**

A flame dried flask under argon was charged with oven dried 4 Å MS (1.0 g) and dry CH_2Cl_2 (97 mL). Then, the reaction vessel was cooled to −20 °C. To the stirring mixture (+)-DET (0.65 mL, 3.80 mmol, 0.12 eq.), freshly distilled Ti(*i*-PrO)$_4$ (0.94 mL, 3.18 mmol, 0.10 eq.) were added. Subsequently, TBHP (11.5 mL, 63.6 mmol, 2.0 eq., 5.5 M in decane with 4 Å MS) was added dropwise and the reaction was stirred for 1 h. Then, a solution of diene **2.25** (3.12 g, 31.8 mmol, 1.0 eq.) in dry CH_2Cl_2 (9 mL) was added and the reaction was monitored by TLC until completion (ca. 24 h). The reaction was diluted with Et_2O (90 mL), placed in an ice bath and a solution of pre-cooled NaOH (2.5 g) in brine (60 mL) was added under vigorous stirring (stir 1 h at the same temperature). Afterwards, the phases were separated, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 4:6 to 1:1) to afford epoxide **2.26** (2.52 g, 22.1 mmol, 70%) as a colorless oil.[3b]

R_f: 0.3, EtOAc/*i*hex 4:6, CAM, no UV.

HRMS-EI (m/z): calc. for $C_6H_{13}O_3$ $[M+H_3O]^{\bullet 2+\bullet}$: 133.09; found: 133.19.

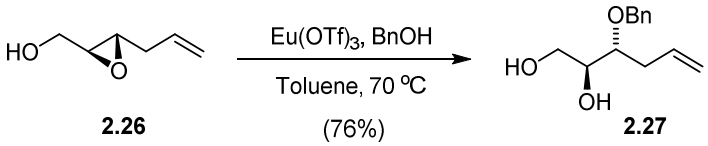
$[\alpha]_D^{20\,°C}$: −34.2 (c = 1.1, $CHCl_3$). Literature: $[\alpha]_D^{20\,°C}$**:** −36.6 (c = 1.1, $CHCl_3$).[3b]

IR (ATR, neat): ν_{max} = 3401 (b), 2982 (w), 2918 (w), 1642 (m), 1429 (w), 1076 (m), 999 (s), 913 (s), 858 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 5.19 – 5.04 (m, 2H), 3.93 (ddd, J = 12.8, 5.4, 2.5 Hz, 1H), 3.64 (ddd, J = 12.2, 7.1, 4.3 Hz, 1H), 3.06 (td, J = 5.5, 2.2 Hz, 1H), 2.97 (dt, J = 4.6, 2.6 Hz, 1H), 2.46 – 2.25 (m, 2H), 1.79 (t, J = 6.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 132.89, 117.89, 61.62, 57.98, 54.82, 35.73.

Diol (**2.27**)



2.26 (76%) **2.27**

A flame dried flask under argon was charged with epoxide **2.26** (2.85 g, 25.0 mmol, 1.0 eq.), dry toluene (125 mL), BnOH (13.5 g, 125.0 mmol, 10.0 eq.), 2,6-Di-tert-butyl-4-methylpyridine (1.07 g, 5.25 mmol, 0.2 eq.), $Eu(OTf)_3$ (2.99 g, 5.0 mmol, 0.2 eq.). Then, the reaction vessel was heated to 70 °C and the reaction was monitored by TLC until completion (ca. 24 h). The solvent was removed and the crude product was purified by FCC (EtOAc/*i*hex 3:7 to 7:3) to afford diol **2.27** (4.22 g, 19.1 mmol, 76%, 20:1 d.r.) as a colorless oil.

R_f: 0.3, EtOAc/*i*hex 1:1, CAM, UV.

HRMS-EI (m/z): calc. for $C_{13}H_{18}O_3$ $[M]^{\bullet+}$: 222.1250; found: 222.1234.

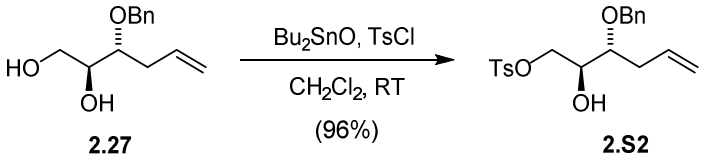
$[\alpha]_D^{20\,°C}$: +1.4 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3386 (b), 2876 (w), 1743 (w), 1640 (w), 1454 (w), 1070 (s), 1027 (s), 912 (s), 867 (m), 734 (s), 696 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.25 (m, 5H), 5.87 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H), 5.26 – 5.03 (m, 2H), 4.68 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 3.90 – 3.68 (m, 3H), 3.64 (q, J = 5.7 Hz, 1H), 2.47 (q, J = 7.5, 6.1 Hz, 2H), 2.37 (dt, J = 15.3, 6.6 Hz, 1H), 2.14 (dd, J = 7.6, 4.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.06, 134.23, 128.69, 128.02, 117.98, 80.70, 72.67, 72.34, 63.34, 35.18.

Tosylate (**2.S2**)



2.27 **2.S2**

A flame dried flask under argon was charged with diol **2.27** (4.22 g, 19.0 mmol, 1.0 eq.), dry CH_2Cl_2 (38 mL), Bn_2SnO (0.09 g, 0.38 mmol, 0.02 eq.), TsCl (3.62 g, 19.0 mmol, 1.0 eq.), Et_3N (2.60 mL, 19.0 mmol, 1.0 eq.). The reaction was stirred at RT and it was monitored by TLC until completion (ca. 24 h). Afterwards, the reaction was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was passed through a short pad of silica (EtOAc/*i*hex 2:8) to afford tosylate **2.S2** (6.85 g, 18.2 mmol, 96%) as a colorless oil.

R_f: 0.7, EtOAc/*i*hex 1:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{20}H_{28}NO_5S$ $[M+NH_4]^+$: 394.16827; found: 394.16835.

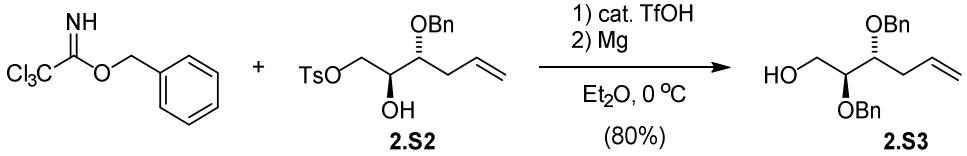
$[\alpha]_D^{20\,°C}$: −26.0 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3526 (b), 2925 (w), 1736 (w), 1356 (s) 1174 (s), 1095 (s), 968 (m), 813 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.63 (m, 2H), 7.33 – 7.16 (m, 7H), 5.76 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.13 – 4.95 (m, 2H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.14 (dd, *J* = 10.3, 3.1 Hz, 1H), 4.05 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.79 (qd, *J* = 6.3, 3.1 Hz, 1H), 3.47 (dt, *J* = 6.5, 5.4 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 1H), 2.17 (d, *J* = 5.9 Hz, 1H), 1.51 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.22, 137.92, 133.74, 132.66, 130.08, 128.58, 128.15, 127.99, 127.96, 118.26, 78.33, 77.36, 72.29, 71.47, 70.74, 34.52, 21.83.

Alcohol (**2.S3**)



A flame dried flask under argon was charged with tosylate **2.S2** (6.85 g, 18.2 mmol, 1.0 eq.), dry Et_2O (76 mL) and Bundle's reagent (8.80 g, 47.0 mmol, 2.6 eq.). The reaction was cooled to 0 °C and a solution of TfOH (0.50 mL, 5.70 mmol, 0.3 eq.) in dry Et_2O (7 mL) was added dropwise to the mixture. The reaction was stirred at the same temperature for 30 minutes, then the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by addition of $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent were removed under reduced pressure. The residue was passed through a short silica pad (Et_2O) and the resulting crude was re-dissolved in dry MeOH (16 mL).

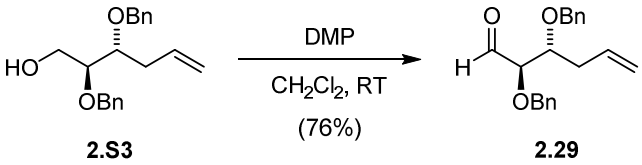
R_f: 0.8, *i*hex:EtOAc 7:3, CAM, UV.

A flame dried flask under argon was charged with Mg (2.28 g, 24.0 mmol, 5.0 eq.), dry MeOH (150 mL) and it was cooled to 0 °C. To this mixture the solution of crude tosylate was added and gas evolution was observed. Then, the bath was removed and the reaction was monitored by TLC until completion (ca. 5 h). Afterwards, the reaction was cooled to 0 °C, quenched by addition of 1 M $HCl_{(aq)}$, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9) to afford alcohol **2.S3** (4.56 g, 14.6 mmol, 80%) as a colorless oil.

R_f: 0.4, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-EI (m/z): calc. for $C_{20}H_{24}O_3$ $[M]^{+\bullet}$: 312.1720; found: 312.1715.
$[\alpha]_D^{20\,°C}$: −13.5 (c = 1.7, $CHCl_3$).
IR (ATR, neat): ν_{max} = 3434 (b), 3064 (w), 3030 (w), 2873 (m), 1640 (w), 1496 (w), 1453 (w), 1207 (w), 1072 (s), 912 (s), 733 (s), 695 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 10H), 5.86 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.19 – 5.04 (m, 2H), 4.71 – 4.54 (m, 4H), 3.81 (ddd, J = 6.2, 4.3, 1.0 Hz, 2H), 3.71 (td, J = 6.0, 5.1 Hz, 1H), 3.52 (dt, J = 6.1, 4.3 Hz, 1H), 2.46 (tdt, J = 7.1, 5.7, 1.3 Hz, 2H), 2.21 (t, J = 6.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.22, 138.16, 134.56, 128.65, 128.59, 128.09, 128.04, 128.03, 127.94, 117.73, 80.20, 78.85, 77.36, 72.64, 72.27, 61.38, 35.46.

Aldehyde (**2.29**)

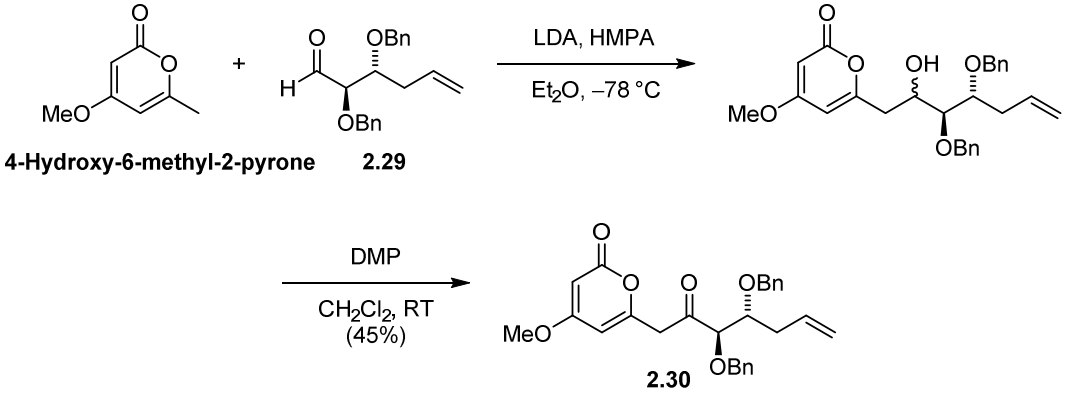


2.S3 **2.29**

A flame dried flask under argon was charged with crude alcohol **2.S3** (3.0 g, 9.60 mmol, 1.0 eq.), dry CH_2Cl_2 (190 mL) and cooled to 0 °C. To this solution was added DMP (4.88 g, 11.6 mmol, 1.2 eq.) and it was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_{3(aq.)}$ and sat. $NaHCO_{3(aq.)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9) to afford ketone **2.29** (2.27 g, 7.31 mmol, 76%) as a colorless solid.

R_f: 0.8, *i*hex:EtOAc 7:3, CAM, UV.
HRMS-EI (m/z): calc. for $C_{20}H_{21}O_3$ $[M]^{+\bullet}$: 309.1485; found: 309.1486.
$[\alpha]_D^{20\,°C}$: +10.2 (c = 0.94, $CHCl_3$).
IR (ATR, neat): ν_{max} = 3064 (w), 3030 (w), 2867 (m), 1731 (s), 1641 (w), 1495 (w), 1453 (w), 1207 (w), 1072 (s), 912 (s), 733 (s), 695 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (d, J = 1.9 Hz, 1H), 7.39 – 7.27 (m, 10H), 5.76 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.65 – 4.57 (m, 3H), 3.96 – 3.89 (m, 1H), 3.84 (td, J = 6.1, 4.3 Hz, 1H), 2.55 – 2.38 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.79, 137.94, 137.33, 133.81, 128.67, 128.55, 128.23, 128.19, 127.95, 118.55, 84.09, 79.60, 77.48, 73.06, 72.26, 35.21.

Ketone (**2.30**)



A flame dried flask under argon was charged with 4-Hydroxy-6-methyl-2-pyrone (0.22 g, 1.59 mmol, 1.2 eq.), HMPA (0.34 mL, 1.99 mmol, 1.5 eq.), dry Et_2O (16 mL) and it was cooled to −78 °C. To this mixture was added slowly a freshly prepared solution of LDA (3.63 mL, 1.59 mmol, 1.2 eq., 0.44 M in THF) and it was stirred at the same temperature for 40 minutes. Then, a solution of aldehyde **2.29** (0.41 g, 1.33 mmol, 1.0 eq.) in dry Et_2O (10 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. Afterwards, the reaction was quenched by adding $Na_2SO_4 \bullet 10H_2O$ (2 eq.) and allowed to warm to RT. The precipitate was filtered, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was passed through a pad of silica (EtOAc/*i*hex 4:6 to 6:4) to afford crude alcohol **2.30** as a yellow oil that was carried through to the next step without further purification.

R_f: 0.3, *i*hex:EtOAc 1:9, CAM, UV.

A flame dried flask under argon was charged with crude alcohol, dry CH_2Cl_2 (26 mL) and cooled to 0 °C. To this solution was added DMP (0.56 g, 1.32 mmol, 1.0 eq.) and it was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_{3(aq)}$ and sat. $NaHCO_{3(aq)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 2:8 to 3:7) to afford ketone **2.30** (0.34 g, 0.59 mmol, 45% over two steps) as a yellowish solid.

R_f: 0.6, *i*hex:EtOAc 1:1, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{27}H_{27}O_6$ $[M-H]^-$: 447.18131; found: 447.18142.

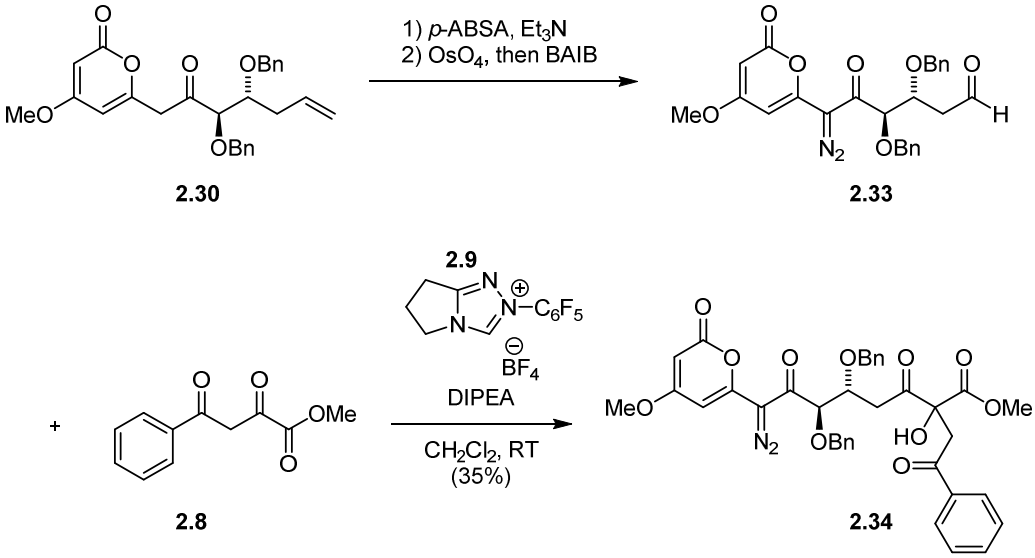
$[\alpha]_D^{20\,°C}$: +23.9 (c = 1.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3064 (w), 2924 (b), 1719 (s), 1650 (s), 156 (s), 1454 (m), 1411 (m), 1247 (s), 1029 (m), 814 (m), 723 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 10H), 5.85 – 5.65 (m, 2H), 5.40 (t, J = 2.6 Hz, 1H), 5.20 – 5.02 (m, 2H), 4.73 – 4.46 (m, 4H), 3.99 (dq, J = 10.0, 4.9, 4.1 Hz, 1H), 3.86 (td, J = 6.0, 4.6 Hz, 1H), 3.82 – 3.68 (m, 4H), 3.54 (d, J = 17.7 Hz, 1H), 2.43 (tdd, J = 7.0, 2.5, 1.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.99, 170.89, 164.52, 158.10, 137.82, 137.04, 133.62, 128.73, 128.60, 128.34, 128.27, 128.04, 128.00, 118.60, 103.13, 88.44, 85.00, 79.74, 73.21, 72.37, 55.99, 44.33, 34.92.

Acyloin (**2.34**)



A flame dried flask under argon was sequentially charged with ketone **2.30** (1.65 g, 3.67 mmol, 1.0 eq.), dry MeCN (25 mL) and *p*-ABSA (0.92 g, 3.85 mmol, 1.05 equiv). To this solution Et_3N (0.77 mL, 5.50 mmol, 1.5 eq.) was added dropwise. The resulting orange suspension was monitored by TLC until completion (ca. 1 h). Afterwards, it was concentrated and passed through a pad of silica (EtOAc/*i*hex 3:7) to afford crude diazo **2.32** that was carried through to the next step without further purification.

Data for diazo **2.32**:

R_f: 0.6, *i*hex:EtOAc 1:1, CAM, UV.

A flask was charged sequentially with crude diazo **2.32**, Acetone/H_2O (10/1, 20 mL), NMO (0.51 g, 4.40 mmol, 1.2 eq.) and 2,6-lutidine (0.85 mL, 7.30 mmol, 2.0 eq.). Then, OsO_4 (0.46 mL, 0.07 mmol, 0.02 eq., 4% in H_2O) was added and the reaction was monitored by TLC until completion (ca. 8 h). Upon complete conversion, BAIB (1.41 g, 4.40 mmol, 1.2 eq.) was added and the reaction monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by adding a sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with sat. $CuSO_{4(aq.)}$, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was passed through a pad of silica (EtOAc/*i*hex 4:6) to afford crude aldehyde **2.33** that was carried through to the next step without further purification.

Data for aldehyde **2.33**:
R_f: 0.7, *i*hex:EtOAc 4:6, CAM, UV.

A flame dried flask under argon was charged with oven dried 4 Å MS (1.0 g), α-ketoester **2.8** (4.10 g, 20.0 mmol, 5.5 eq.) and pre-catalyst **2.9** (0.15 g, 0.40 mmol, 0.1 eq.).Then, a solution of crude aldehyde **2.33** in dry CH_2Cl_2 (30 mL + 10 ml to rinse) was added and the mixture stirred for 5 minutes. Subsequently, dry DIPEA (0.35 mL, 1.80 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 4 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 7:3, long column) to afford acyloin **2.34** (0.72 g, 1.05 mmol, 35%, 1:1.6 d.r.) as an amorphous yellow solid.

R_f: 0.3, *i*hex:EtOAc 4:6, CAM, UV.
HRMS-ESI (m/z): calc. for: $C_{37}H_{38}N_3O_{11}$ $[M+NH_4]^+$: 700.25009; found: 700.25071.

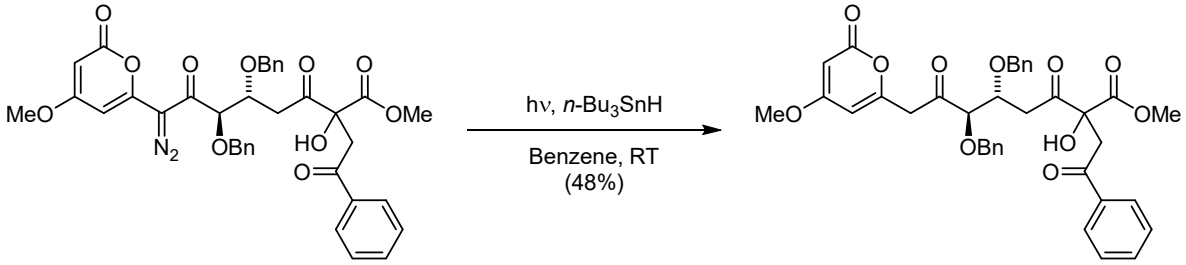
IR (ATR, neat): ν_{max} = 3034 (w), 2123 (s), 1723 (s), 1641 (m), 1546 (s), 1453 (m), 1409 (m), 1227 (s), 1095 (m), 822 (m), 753 (m), 678 (s) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.98 – 7.84 (m, 2H), 7.64 – 7.55 (m, 1H), 7.53 – 7.42 (m, 2H), 7.40 – 7.22 (m, 10H), 6.98 – 6.87 (m, 1H), 5.34 (td, J = 2.2, 0.7 Hz, 1H), 4.73 – 4.52 (m, 5H), 4.45 – 4.37 (m, 1H), 4.17 (ddd, J = 29.2, 4.4, 1.0 Hz, 1H), 3.99 – 3.59 (m, 8H), 3.22 (dddd, J = 50.3, 18.5, 6.0, 0.8 Hz, 1H), 3.04 – 2.88 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 204.59, 204.45, 197.56, 197.38, 189.76, 189.68, 171.94, 170.37, 162.51, 149.52, 149.42, 137.36, 137.36, 136.32, 136.28, 136.09, 136.08, 134.10, 134.08, 128.88,

128.80, 128.79, 128.56, 128.52, 128.52, 128.43, 128.40, 128.39, 128.33, 128.21, 128.20, 128.15, 128.13, 98.45, 98.35, 86.93, 86.63, 86.59, 82.62, 82.56, 75.69, 75.57, 74.46, 74.01, 73.82, 73.62, 73.56, 56.10, 54.01, 53.87, 44.19, 44.04, 39.06, 38.98.

Ketone (**2.41**)



2.34 **2.41**

A flame dried flask under argon was charged with acyloin **2.34** (0.10 g, 0.15 mmol, 1.0 eq.), *n*-Bu_3SnH (0.6 mL, 2.10 mmol, 15.0 eq.) and dry benzene (5.6 mL, degassed by sparging with argon for 20 minutes). Then, the solution was irradiated for 1 h using a Rayonet lamp (420 nm, 250 W). Afterwards, the reaction mixture was directly charged on a silica column (EtOAc/*i*hex 4:6 to 6:4) to afford ketone **2.41** (0.05 g, 0.07 mmol, 48%) as an amorphous yellow solid.

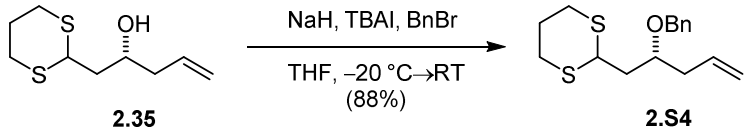
R_f: 0.7, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{37}H_{37}O_{11}$ $[M+H]^+$: 657.23304; found: 657.23254.

IR (ATR, neat): ν_{max} = 3466 (b), 3030 (w), 2952 (w), 1720 (s), 1567 (s), 1453 (m), 1411 (m), 1248 (s), 1217 (s), 1092 (m), 1028 (m), 815 (m), 734 (m), 697 (s) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.96 – 7.85 (m, 2H), 7.63 – 7.56 (m, 1H), 7.51 – 7.42 (m, 2H), 7.39 – 7.24 (m, 10H), 5.78 (dt, J = 2.3, 1.1 Hz, 1H), 5.41 (d, J = 2.2 Hz, 1H), 4.72 – 4.58 (m, 4H), 4.44 (tt, J = 6.4, 3.3 Hz, 1H), 4.04 (ddd, J = 23.5, 3.3, 0.9 Hz, 1H), 3.92 – 3.57 (m, 9H), 3.33 (dd, J = 18.3, 6.3 Hz, 1H), 3.17 – 3.08 (m, 1H), 2.98 (ddd, J = 18.2, 6.6, 0.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 204.70, 204.67, 204.57, 204.53, 197.50, 197.33, 170.94, 170.92, 170.38, 170.34, 164.56, 164.53, 158.10, 158.01, 137.73, 136.94, 136.09, 136.08, 134.06, 134.04, 128.86, 128.75, 128.58, 128.55, 128.42, 128.40, 128.35, 128.26, 128.06, 128.05, 128.01, 103.18, 103.12, 88.44, 88.42, 85.52, 85.47, 82.57, 76.25, 76.13, 73.33, 73.24, 73.22, 73.07, 55.97, 53.91, 53.81, 44.26, 44.21, 44.09, 44.06, 38.84, 38.70.

Ether (**2.S4**)



2.35 **2.S4**

A flame dried flask under argon was charged with alcohol **2.35** (3.00 g, 14.7 mmol, 1.0 eq.) and dry THF (36 mL). The solution was cooled to −20 °C. To this were added sequentially BnBr (2.30 mL, 19.1 mmol, 1.3 eq.), TBAI (0.54 g, 1.47 mmol, 0.1 eq.) and NaH (60% dispersion in mineral oil, 0.77 g, 19.1 mmol, 1.3 eq.). The reaction mixture was allowed to warm to RT and it was monitored by TLC until completion (ca. 10 h). Afterwards, the reaction was quenched by addition of $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 5:95) to afford ether **2.S4** (3.80 g, 12.9 mmol, 88%) as a yellow oil.

R_f: 0.6, *i*hex:EtOAc 9:1, CAM, UV.

HRMS-EI (m/z): calc. for $C_{16}H_{22}OS_2$ $M^{+\bullet}$: 294.1112; found: 294.1104.

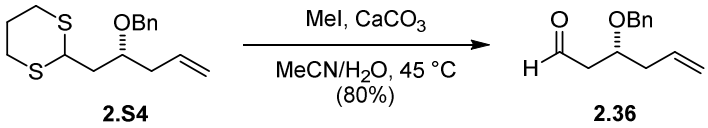
$[\alpha]_D^{20\,°C}$: −38.3 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2898 (w), 1640 (w), 1496 (w), 1453 (w), 1422 (w), 1347 (w),n1275 (w), 1243 (w), 1206 (w), 1179 (w), 1088 (m), 1068 (s), 1027 (m), 992 (m), 908 (m), 734 (s), 695 (s), 663 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.28 (m, 5H), 5.88 – 5.77 (m, 1H), 5.14 – 5.08 (m, 2H), 4.65 – 4.62 (d, 1H), 4.52 – 4.49 (d, 1H), 4.20 – 4.16 (m, 1H), 3.83 – 3.77 (m, 1H), 2.91 – 2.74 (m, 4H), 2.42 – 2.29 (m, 2H), 2.13 – 1.81 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.79, 134.19, 128.49, 128.04, 127.73, 117.89, 75.20, 71.73, 44.11, 40.23, 38.60, 30.52, 30.10, 26.19.

Aldehyde (**2.36**)

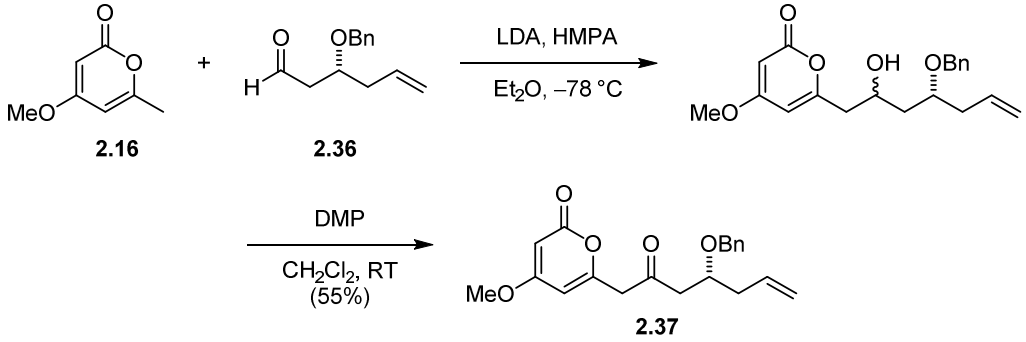


2.S4 **2.36**

A flask was charged sequentially with ether **2.S4** (3.80 g, 12.9 mmol, 1.0 eq.), MeCN/H_2O (9/1, 165 mL), MeI (8.05 mL, 129 mmol, 10.0 eq.) and $CaCO_3$ (6.45 g, 64.5 mmol, 5.0 eq.). The reaction mixture was heated to 45 °C and it was monitored by TLC until completion (ca. 8 h). Afterwards, the solvent was removed and the residue was partitioned between EtOAc and H_2O, the aqueous phase was extracted three times with EtOAc, the combined organic fractions was washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9) to afford aldehyde **2.36** (2.07 g, 10.2 mmol, 80%) as a colorless oil.

R_f: 0.4, *i*hex:EtOAc 9:1, CAM, UV.
HRMS-EI (m/z): calc. for $C_{13}H_{16}O_2$ $M^{+\bullet}$: 204.1145; found: 204.1143.
$[\alpha]_D^{20\,°C}$: −43.3 (c = 1.0, $CHCl_3$).
IR (ATR, neat): ν_{max} = 3066 (w), 2863 (w), 2729 (w), 1722 (s), 1641 (w), 1496 (w), 1454 (w), 1346 (m), 1206 (w), 1090 (m), 1069 (mw), 1027 (m), 995 (m), 916 (m), 735 (s), 696 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 7.30 – 7.18 (m, 5H), 5.80 – 5.70 (m, 1H), 5.09 – 5.05 (m, 2H), 4.57 – 4.54 (d, 1H), 4.47 – 4.44 (d, 1H), 4.00 – 3.94 (m, 1H), 2.65 – 2.58 (m, 1H), 2.53 – 2.47 (m, 1H), 2.42 – 2.28 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.44, 138.10, 133.58, 128.49, 127.83, 118.37, 73.70, 71.31, 48.02, 38.33.

Ketone (**2.37**)



A flame dried flask under argon was charged with pyrone **2.16** (1.85 g, 13.2 mmol, 1.3 eq.), HMPA (2.65 mL, 15.2 mmol, 1.5 eq.) and dry Et_2O (70 mL). This solution was cooled to −78 °C and a freshly prepared solution of LDA (12.7 mL, 12.9 mmol, 1.3 eq., 1.02 M in THF) was added slowly. The reaction was stirred at the same temperature for 40 minutes. Then, a solution of aldehyde **2.36** (2.07 g, 10.1 mmol, 1.0 eq.) in dry Et_2O (30.0 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. Afterwards, the reaction was quenched by adding $Na_2SO_4 \bullet 10H_2O$ (2 eq.) and it was allowed to warm to RT. The precipitate was filtered, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was passed through a silica pad (EtOAc/*i*hex 4:6 to 6:4) to afford crude alcohol as a yellow oil that was carried through to the next step without further purification.

R_f: 0.7, *i*hex:EtOAc 2:3, CAM, UV.
HRMS-EI (m/z): calc. for $C_{20}H_{24}O_5$ $M^{+\bullet}$: 344.1618. Found: 344.1634.

A flame dried flask under argon was charged with crude alcohol, dry CH_2Cl_2 (75 mL) and was cooled to 0 °C. To this solution was added DMP (3.80 g, 8.96 mmol, 0.9 eq.) and it was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_{3(aq.)}$ and sat. $NaHCO_{3(aq.)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 3:7 to 4:6) to afford ketone **2.37** (1.90 g, 5.55 mmol, 55% over two steps) as a colorless solid.

R_f: 0.6, *i*hex:EtOAc 2:8, CAM, UV.

HRMS-EI (m/z): calc. for $C_{20}H_{23}O_5$ $[M+H]^+$: 343.1540; found: 343.1541.

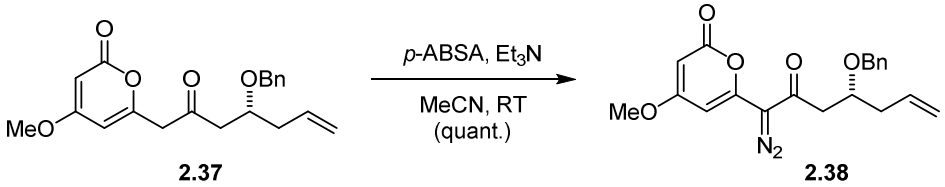
$[\alpha]_D^{20\,°C}$: −36.4 (c = 0.3, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3080 (w), 2918 (m), 1712 (s), 1645 (m), 1565 (s), 1454 (m), 1420 (m), 1394 (m), 1318 (m), 1256 (m), 1129 (m), 1063 (m), 1031 (m), 997 (m), 940 (m), 909 (m), 852 (m), 742 (m), 698 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.28 (m, 5H), 5.84 – 5.74 (m, 2H), 5.44 – 5.43 (d, 1H), 5.14 – 5.10 (m, 2H), 4.62 – 4.59 (d, 1H), 4.48 – 4.45 (d, 1H), 4.06 – 4.00 (m, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 2.82 – 2.76 (m, 1H), 2.63 – 2.58 (m, 1H), 2.44 – 2.30(m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.46, 170.88, 164.38, 157.66, 138.20, 133.67, 128.58, 128.04, 127.91, 118.48, 103.14, 88.58, 75.02, 71.86, 56.08, 48.20, 47.50, 38.28.

Diazo (**2.38**)



2.37 **2.38**

A flame dried flask under argon was charged with ketone **2.37** (0.92 g, 2.70 mmol, 1.0 eq.), dry MeCN (19 mL) and *p*-ABSA (0.77 g, 3.24 mmol, 1.2 equiv). To this solution Et_3N (0.58 mL, 4.05 mmol, 1.5 eq.) was added dropwise The resulting orange suspension was monitored by TLC until completion (ca. 10 h). Afterwards, it was concentrated to the volume of ca. 3 mL and purified by FCC (EtOAc/*i*hex 3:7) to afford diazo **2.38** (0.99 g, 2.70 mmol, quant.) as an orange oil.

R_f: 0.5, *i*hex:EtOAc 1:1, CAM, UV.

HRMS-EI (m/z): calc. for $C_{19}H_{21}O_4$ $[M-N_2-CO+H]^-$: 313.14453; found: 313.14490.

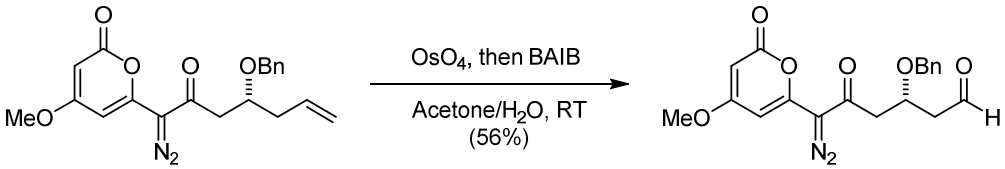
$[\alpha]_D^{20\,°C}$: −37.3 (c = 0.5, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3107 (vw), 3077 (vw), 3029 (vw), 2978 (vw), 2942 (vw), 2908 (vw), 2361 (vw), 2340 (vw), 2099 (s), 1725 (vs), 1651 (s), 1618 (s), 1545 (vs), 1496 (w), 1454 (m), 1408 (s), 1377 (s), 1282 (w), 1228 (vs), 1185 (m), 1086 (m), 1065 (s), 1025 (m), 987 (s), 960 (s), 917 (m), 874 (m), 829 (s), 800 (s), 737 (m), 697 (s) cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.31 – 7.28 (m, 2H), 7.27 – 7.24 (m, 3H), 6.89 (s, 1H), 5.85 – 5.79 (m, 1H), 5.36 (d, J = 2.3 Hz, 1H), 5.16 – 5.12 (m, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.82 (s, 3H), 2.84 – 2.79 (m, 1H), 2.62 – 2.58 (m, 1H), 2.44 – 2.37 (m, 2H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 188.79, 171.84, 162.44, 148.86, 137.99, 133.41, 128.57, 127.98, 127.89, 118.72, 98.72, 86.82, 76.06, 72.14, 56.14, 44.30, 38.45.

Aldehyde (**2.39**)



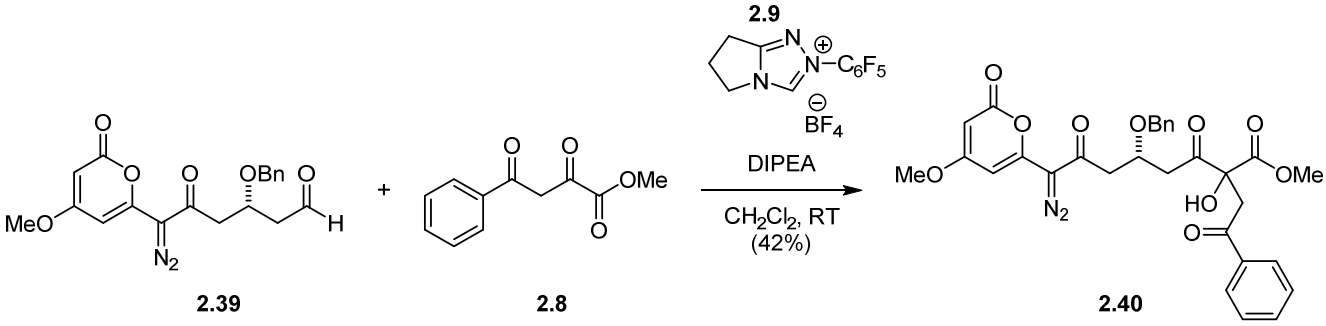
2.38 **2.39**

A flask was charged sequentially with diazo **2.38** (1.00 g, 2.70 mmol, 1.0 eq.), acetone/H_2O (10/1, 20 mL), NMO (0.38 g, 3.20 mmol, 1.2 eq.) and 2,6-lutidine (0.62 mL, 5.40 mmol, 2.0 eq.). Then, OsO_4 (0.30 mL, 0.05 mmol, 0.02 eq., 4% in H_2O) was added and the reaction was monitored by TLC until completion (ca. 8 h). Upon complete conversion, BAIB (1.04 g, 3.24 mmol, 1.2 eq.) was added and the reaction was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by adding a sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed sat. $CuSO_{4(aq.)}$, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:1) to afford aldehyde **2.39** (0.56 g, 1.50 mmol, 56%) as a yellow oil.

Data for diol:
R_f: 0.14, *i*hex:EtOAc 2:8, CAM, UV.

Data for aldehyde **2.39**:
R_f: 0.5, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{19}H_{17}N_2O_6$ $[M-H]^-$: 369.1092; found: 369.1099.
$[\alpha]_D^{20\,°C}$: +17.5 (c = 0.05, $CHCl_3$).
IR (ATR, neat): ν_{max} = 2952 (vs), 2917 (vs), 2838 (m), 2395 (w), 1725 (s, b), 1647 (w), 1567 (m), 1455 (vs), 1408 (w), 1377 (vs), 1253 (m), 1166 (m), 998 (w), 974 (w), 810 (w), 760 (s) cm^{-1}.
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.79 (t, 1H), 7.37 – 7.26 (m, 5H), 5.36 (d, J = 2.3 Hz, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.83 (s, 3H), 2.91 (dd, J = 15.1, 7.1 Hz, 1H), 2.83 – 2.73 (m, 3H).
^{13}C NMR (201 MHz, $CDCl_3$) δ = 200.01, 187.65, 171.75, 162.32, 148.44, 137.45, 128.71, 128.27, 128.07, 98.94, 86.97, 75.09, 72.73, 71.32, 56.18, 48.26, 44.33.

Acyloin (**2.40**)



A flame dried flask under argon was charged with oven dried 4 Å MS (0.60 g), α-ketoester **2.8** (3.00 g, 15.0 mmol, 10.0 eq.) and pre-catalyst **2.9** (0.05 g, 0.15 mmol, 0.1 eq.).Then, a solution of aldehyde **2.39** (0.56 g, 1.50 mmol, 1.0 eq.) in dry CH_2Cl_2 (20 mL + 10 mL to rinse) was added and the mixture stirred for 5 minutes. Subsequently, dry DIPEA (0.26 mL, 1.50 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 4 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent was removed by rotary evaporation. The crude product was purified by FCC (EtOAc/*i*hex 1:1 to 8:2, long column) to afford acyloin **2.40** (0.37 g, 0.64 mmol, 42%, 1:1.3 d.r.) as an amorphous yellow solid.

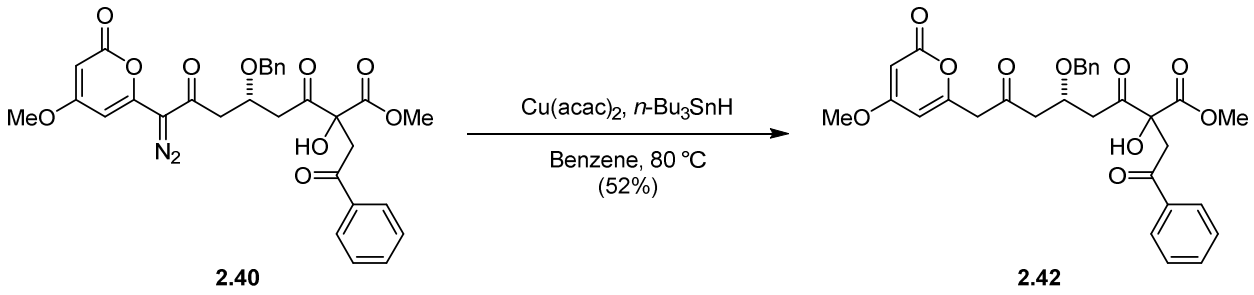
R_f: 0.4, *i*hex:EtOAc 4:6, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{30}H_{28}N_2O_{10}$ $[M+NH_4]^+$: 594.20877; found: 594.20884.

IR (ATR, neat): ν_{max} = 3458 (b), 3108 (vw), 3088 (vw), 3064 (vw), 3030 (vw), 2950 (vw), 2920 (vw), 2361 (vw), 2341 (vw), 2250 (vw), 2102 (m), 1720 (vs), 1687 (m), 1651 (s), 1618 (m), 1597 (m), 1580 (w), 1546 (s), 1496 (vw), 1453 (m), 1410 (m), 1382 (m), 1357 (m), 1282 (m), 1230 (vs), 1185 (m), 1087 (m), 1069 (m), 1025 (m), 1001 (m), 988 (m), 960 (m), 911 (m), 878 (m), 822 (m), 803 (m), 753 (m), 729 (s), 689 (s) cm^{-1}.

^{1}H NMR (800 MHz, $CHCl_3$) δ = 7.92 (tt, 2H), 7.60 (tt, J = 7.3, 1.3 Hz, 1H), 7.47 (tt, 2H), 7.32 – 7.26 (m, 3H), 7.26 – 7.23 (m, 2H), 6.87 (s, 1H), 5.35 (d, J = 2.3 Hz, 1H), 4.65 – 4.55 (m, 2H), 4.51 – 4.43 (m, 2H), 3.87 (d, J = 17.8 Hz, 1H), 3.82 (d, J = 1.7 Hz, 3H), 3.78 (s, 2H), 3.74 (s, 1H), 3.73 – 3.70 (m, 1H), 3.28 (dd, J = 17.7, 5.5 Hz, 0.6H), 3.15 (dd, J = 17.7, 6.2 Hz, 0.4H), 3.07 (dd, J = 17.7, 6.0 Hz, 0.4H), 2.97 (dd, J = 17.7, 6.6 Hz, 0.6H), 2.91 (dd, J = 15.0, 7.4 Hz, 0.4H), 2.86 (dd, J = 14.9, 7.1 Hz, 0.6H), 2.81 (ddd, J = 15.0, 9.1, 4.7 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 204.62, 204.56, 197.55, 197.44, 187.97, 187.95, 171.79, 170.48, 170.45, 162.40, 148.69, 137.73, 137.70, 136.05, 134.15, 128.91, 128.59, 128.56, 128.42, 128.07, 128.04, 98.82, 98.79, 86.86, 82.62, 82.58, 75.05, 72.84, 72.68, 72.41, 72.37, 56.14, 53.96, 53.93, 44.33, 44.25, 44.24, 44.12, 41.63, 41.32.

Ketone (**2.42**)



2.40 **2.42**

A flame dried flask under argon was charged with acyloin **2.40** (0.25 g, 0.42 mmol, 1.0 eq.), *n*-Bu_3SnH (1.14 mL, 4.20 mmol, 10.0 eq.), $Cu(acac)_2$ (1 mg, 0.004 mmol, 0.01 eq.) and dry benzene (17 mL, degassed by sparging with argon for 20 minutes).Then, the solution was immersed in a preheated 80 °C oil bath. The reaction was monitored by TLC until completion (ca. 1 h). Afterwards, the reaction mixture was cooled to RT and directly charged on a silica column (EtOAc/*i*hex 4:6 to 7:3) to afford ketone **2.42** (0.12 g, 0.22 mmol, 52%) as an amorphous yellow solid.

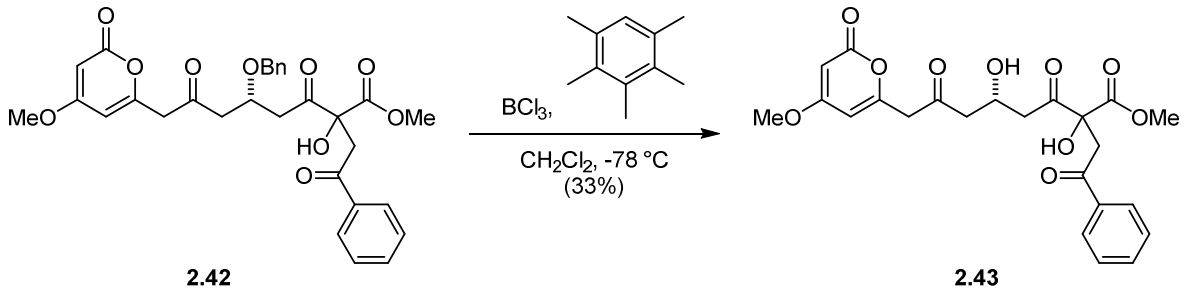
R_f: 0.7, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{30}H_{34}NO_{10}$ $[M+NH_4]^+$: 568.21827; found: 568.21860.

IR (ATR, neat): ν_{max} = 3443 (b), 3089 (vw), 3063 (vw), 3031 (vw), 2951 (vw), 2924 (vw), 2851 (vw), 2106 (vw), 1720 (vs), 1650 (m), 1597 (w), 1567 (s), 1496 (w), 1453 (m), 1413 (m), 1356 (m), 1250 (s), 1219 (m), 1182 (m), 1143 (m), 1089 (m), 1070 (m), 1030 (m), 1001 (w), 943 (w), 819 (w), 755 (w), 738 (w), 691 (w) cm^{-1}.

^{1}H NMR (800 MHz, $CHCl_3$) δ = 7.92 (ddd, J = 8.5, 6.4, 1.3 Hz, 2H), 7.60 (tt, J = 7.4, 1.3 Hz, 1H), 7.47 (tt, J = 7.5, 1.1 Hz, 2H), 7.35 – 7.26 (m, 5H), 5.87 (t, J = 2.2 Hz, 1H), 5.44 (dd, J = 2.3, 0.8 Hz, 1H), 4.64 – 4.54 (m, 2H), 4.51 (dd, J = 11.2, 5.1 Hz, 1H), 4.47 – 4.42 (m, 1H), 3.87 (dd, J = 17.8, 12.4 Hz, 1H), 3.79 (d, J = 2.5 Hz, 3H), 3.74 (d, J = 29.3 Hz, 3H), 3.70 (dd, J = 17.8, 3.3 Hz, 1H), 3.52 (d, J = 3.7 Hz, 2H), 3.27 (dd, J = 17.4, 5.8 Hz, 0.6H), 3.10 – 3.02 (m, 1H), 2.91 – 2.86 (m, 1H), 2.83 (dd, J = 16.4, 6.8 Hz, 0.6H), 2.78 (ddd, J = 16.4, 5.2, 2.1 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 204.59, 204.49, 201.74, 201.72, 197.53, 197.45, 170.87, 170.53, 170.46, 157.52, 157.49, 138.01, 137.98, 136.10, 134.10, 134.10, 128.90, 128.58, 128.55, 128.44, 128.11, 128.09, 127.97, 127.95, 103.21, 103.20, 88.63, 88.62, 82.62, 82.56, 72.45, 71.66, 71.64, 56.08, 53.92, 53.90, 48.01, 47.64, 47.46, 44.15, 44.12, 41.69, 41.50.

Alcohol (**2.43**)



2.42 **2.43**

A flame dried flask under argon was charged with ketone **2.42** (18.6 mg, 0.034 mmol, 1.0 eq.), pentamethylbenzene (30.0 mg, 0.20 mmol, 6.0 eq.) and dry CH_2Cl_2 (0.2 mL). Then, the solution was cooled to –78 °C. Then, BCl_3 (0.1 mL, 0.10 mmol, 3.0 eq., 1 M in CH_2Cl_2) was added dropwise and the color changed to yellow. The reaction was monitored by TLC until completion (ca. 1 h) and then it was quenched by addition of MeOH. The cooling bath was removed, the mixture was allowed to reach RT and then the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 9:1 to 1:0) to afford alcohol **2.43** (5.2 mg, 11 µmol, 33%) as a yellow oil.

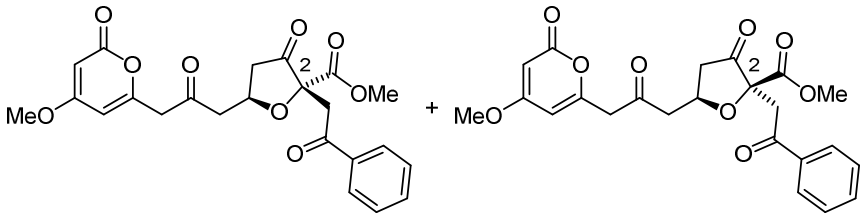
R_f: 0.2, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-ESI (m/z): calc. for $C_{23}H_{28}NO_{10}$ $[M+NH_4]^+$: 478.17132; found: 478.17140.

IR (ATR, neat): ν_{max} = 3440 (b), 2948 (vw), 2849 (vw), 1717 (vs), 1647 (m), 1566 (vs), 1450 (s), 1411 (s), 1247 (s), 1220 (m), 1143 (m), 1037 (m), 942 (m), 815 (w), 755 (w), 738 (w), 689 (s) cm^{-1}.

^{1}H NMR (800 MHz, $CHCl_3$) δ = 7.94 (ddd, J = 8.3, 2.1, 1.2 Hz, 2H), 7.61 (ddt, J = 7.4, 6.4, 1.1 Hz, 1H), 7.50 – 7.46 (m, 2H), 5.93 (d, J = 2.1 Hz, 1H), 5.46 (d, J = 2.2 Hz, 1H), 4.63 (s, 1H), 4.61 – 4.55 (m, 1H), 3.89 (dd, J = 17.8, 10.7 Hz, 1H), 3.83 (d, J = 1.3 Hz, 3H), 3.80 (s, 3H), 3.76 (dd, J = 17.8, 5.4 Hz, 1H), 3.60 (d, J = 3.2 Hz, 2H), 3.19 – 3.09 (m, 1.6H), 3.06 (dd, J = 17.7, 4.1 Hz, 0.4H), 2.89 (dd, J = 17.7, 8.1 Hz, 0.4H), 2.85 (dd, J = 17.6, 4.1 Hz, 0.6H), 2.80 (ddd, J = 17.1, 8.0, 2.1 Hz, 1H), 2.75 (ddd, J = 17.1, 4.2, 1.6 Hz, 1H).

^{13}C NMR (201 MHz, CDCl3) δ = 206.98, 205.99, 202.91, 170.71, 170.25, 164.10, 157.14, 135.87, 134.08, 128.80, 128.32, 103.18, 88.54, 82.29, 64.14, 55.98, 53.90, 48.41, 47.74, 44.17, 43.06, 30.95, 29.70.

Crude data for furane (**A** and **B**) adducts



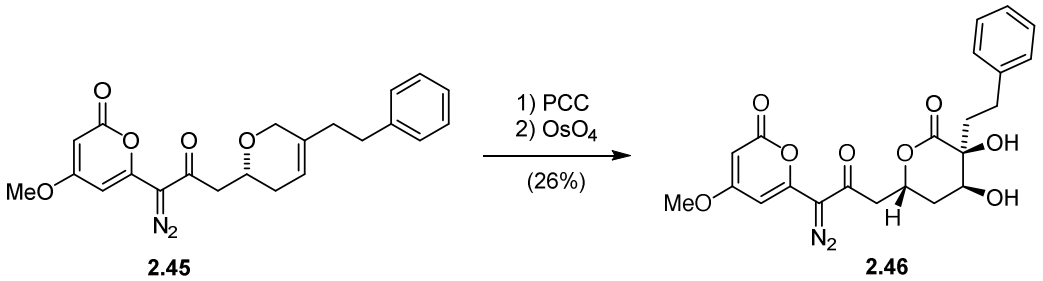
A **B**

HRMS-ESI (m/z): calc. for C23H23O9 $[M+H]^+$: 443.13366; found: 443.13407.

A) The stereochemistry at C_2 is arbitrarily assigned. HSQC is available in the NMR data section.
^{1}H NMR (800 MHz, $CHCl_3$) δ = 7.92 (ddd, *J* = 8.4, 4.4, 1.4 Hz, 2H), 7.59 (ddt, *J* = 8.6, 7.3, 1.2 Hz, 1H), 7.52 – 7.44 (m, 2H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.10 – 5.03 (m, 1H), 3.92 (d, *J* = 18.3 Hz, 1H), 3.80 (d, *J* = 9.1 Hz, 4H), 3.77 – 3.74 (m, 3H), 3.56 (s, 2H), 3.15 (dd, *J* = 17.3, 6.4 Hz, 1H), 2.95 (dd, *J* = 17.3, 6.4 Hz, 1H), 2.92 (dd, *J* = 18.5, 7.5 Hz, 1H), 2.84 (dd, *J* = 18.5, 9.0 Hz, 1H).

B) The stereochemistry at C_2 is arbitrarily assigned. HSQC is available in the NMR data section.
^{1}H NMR (800 MHz, $CHCl_3$) δ = 7.91 (d, *J* = 9.5 Hz, 2H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.46 (t, 2H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 5.05 (qd, *J* = 7.4, 5.6 Hz, 1H), 3.95 – 3.88 (m, 2H), 3.80 (d, *J* = 7.7 Hz, 6H), 3.66 – 3.62 (m, 2H), 3.28 (dd, *J* = 18.3, 7.3 Hz, 1H), 3.19 (dd, *J* = 16.4, 7.2 Hz, 1H), 2.92 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.52 (dd, *J* = 18.3, 8.2 Hz, 1H).

Diol (**2.46**)



2.45 **2.46**

A flame dried flask under argon was charged with 4 Å MS (1.0 g), diazo **2.45** (0.49 g, 1.25 mmol, 1.0 eq.),[4] pyridine (0.6 mL, 7.50 mmol, 6.0 eq.), PCC (1.07 g, 5.00 mmol, 4.0 eq.) and dry CH_2Cl_2 (12.5 mL). The mixture was heated at 40 °C and was monitored by TLC until completion (ca. 20 h, after 12 h 2.8 eq. of PCC were added). Afterwards, the reaction was cooled to RT and celite was added. This mixture was poured into a cake of celite impregnated with EtOAc, filtered and the cake washed with more EtOAc. The solvent was removed under reduced and the residue passed through a silica pad (EtOAc/*i*hex 6:3) to afford the crude lactone (0.24 g) which was used in the next step without further purification.

R_f: 0.4, *i*hex:EtOAc 1:1, CAM, UV.

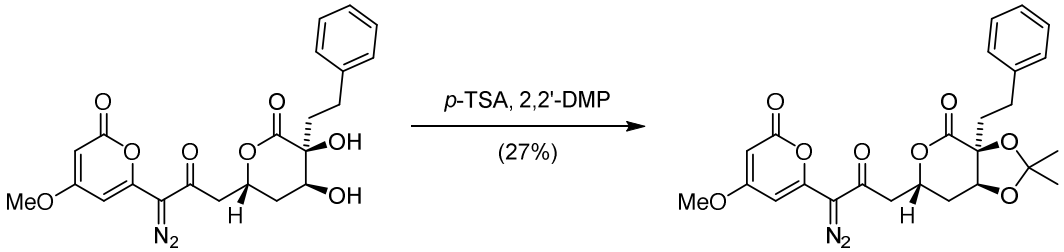
A flask was charged sequentially with the crude lactone, THF/H_2O (5/1, 5.0 mL) and NMO (0.14 g, 1.25 mmol, 1.0 eq.). Then, OsO_4 (0.08 mL, 12.5 µmol, 0.01 eq., 4% in H_2O) was added and the reaction was monitored by TLC until completion (ca. 2 h). Upon complete conversion, the reaction was quenched by adding a solution of sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (MeOH/Acetone/CH_2Cl_2 2:8:90) to afford diol **2.46** (0.14 g, 0.32 mmol, 26%) as a yellow solid.

R_f: 0.2, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-EI (m/z): calc. for $C_{22}H_{26}O_8N_3$ $[M+NH_4]^+$: 460.17199; found: 460.17172.
$[\alpha]_D^{20\,°C}$: −11.7 (c = 3.2, $CHCl_3$).
IR (ATR, neat): ν_{max} = 2919 (w), 2850 (w), 2106 (m), 1641 (s), 1453 (m), 1407 (m), 1232 (m), 1124 (w), 1016 (m), 810 (m), 699 (m) cm^{-1}.
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.31 – 7.27 (m, 2H), 7.22 – 7.19 (m, 1H), 7.18 – 7.15 (m, 2H), 6.92 – 6.81 (m, 1H), 5.37 (d, *J* = 2.3 Hz, 1H), 5.33 – 5.27 (m, 1H), 4.13 (dd, *J* = 3.5, 2.4 Hz, 1H), 3.82 (s, 3H),

2.98 – 2.90 (m, 2H), 2.77 – 2.72 (m, 1H), 2.64 (ddd, *J* = 13.6, 11.5, 5.3 Hz, 1H), 2.29 – 2.24 (m, 2H), 2.02 – 1.94 (m, 2H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 185.65, 175.87, 171.66, 162.24, 140.70, 128.77, 128.46, 126.45, 99.21, 87.15, 76.13, 74.97, 69.84, 56.21, 43.63, 42.91, 39.38, 32.02, 29.86, 29.27.

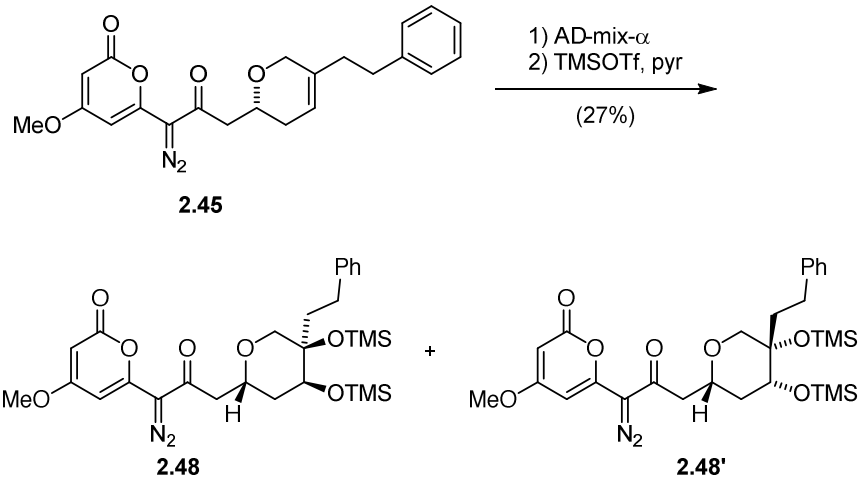
Acetonide (**2.47**)



A flask was charged sequentially with **2.46** (57.0 mg, 0.13 mmol, 1.0 eq.), dry CH_2Cl_2 (1.3 mL), 2,2'-DMP (25 µL, 0.19 mmol, 1.5 eq.) and *p*-TSA (3.0 mg, 13 µmol, 0.1 eq.). The reaction was monitored by TLC until completion (ca. 2 h). Upon complete conversion, the reaction was quenched by adding a solution of sat. $NaHCO_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 6:4) to afford acetonide **2.47** (17 mg, 35 µmol, 27%) as a yellow solid.

R_f: 0.7, *i*hex:EtOAc 2:8, CAM, UV.
HRMS-EI (m/z): calc. for $C_{25}H_{30}O_8N_3$ $[M+NH_4]^+$: 500.20329; found: 500.20308.
$[\alpha]_D^{20\,°C}$: +2.1 (c = 0.5, $CHCl_3$).
IR (ATR, neat): ν_{max} = 2925 (w), 2853 (w), 2104 (vw), 1723 (s), 1568 (s), 1256 (m), 1176 (m), 1089 (m), 1024 (m), 813 (m), 699 (m) cm^{-1}.
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.16 (m, 3H), 6.85 (s, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 5.24 (dddd, *J* = 11.9, 7.2, 5.2, 2.5 Hz, 1H), 4.38 (dd, *J* = 3.6, 2.1 Hz, 1H), 3.81 (s, 3H), 3.01 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.85 (dd, *J* = 15.7, 5.1 Hz, 1H), 2.77 (td, *J* = 12.9, 5.2 Hz, 1H), 2.64 (td, *J* = 12.9, 4.9 Hz, 1H), 2.38 (ddd, *J* = 15.0, 3.6, 2.6 Hz, 1H), 2.24 (ddd, *J* = 14.0, 12.3, 4.9 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.06 – 1.95 (m, 1H), 1.46 (d, *J* = 17.3 Hz, 6H).
^{13}C NMR (201 MHz, $CDCl_3$) δ = 185.72, 171.66, 162.21, 147.96, 140.61, 128.74, 128.38, 126.48, 110.40, 99.20, 87.13, 80.65, 75.48, 75.17, 71.83, 56.20, 43.89, 37.60, 31.08, 30.05, 27.29, 26.77.

TMS diol (**2.48**)



A flask under air was charged with AD-mix-α (0.60 g) and *t*-BuOH/H_2O (1.8 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 min. To the yellow solution diazo **2.45** (0.14 g, 0.37 mmol, 1.0 eq.) and $MeSO_2NH_2$ (0.07 g, 0.74 mmol, 2.0 eq.) were added. The reaction was monitored by TLC analysis until completion (ca. 20 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (0.8 g), stirred for 15 minutes and partitioned between H_2O/EtOAc. The aqueous phase was extracted three times with EtOAc, the combined organic phases were dried with Na_2SO_4, filtered and the was solvent removed under reduced pressure. The crude oil (crude ^1H NMR d.r. 1.6:1) was purified by FCC (MeOH/Acetone/CH_2Cl_2 2.5:2.5:95) to afford the separated diols. Both were contaminated with inseparable $MeSO_2NH_2$ and were therefore used in the next step without further purification.

R_f diol: 0.4, *i*hex:EtOAc 2:8, CAM, UV.

R_f diol': 0.2, *i*hex:EtOAc 2:8, CAM, UV.

A flame dried flask under argon was charged sequentially with crude alcohol, dry CH_2Cl_2 (2 mL), 2,6-lutidine (0.14 mL, 1.2 mmol) and the reaction vessel was cooled to 0 °C. Neat TMSOTf (0.1 mL, 0.60 mmol) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 3:7) to afford **2.48** (56.0 mg, 0.1 mmol, 27%) as a yellow oil. Structural determination was performed by analysis of the 2D NMR data (NOESY) of both diasteromers.

R_f : 0.6, *i*hex:EtOAc 6:4, CAM, UV.
HRMS-EI (m/z): calc. for $C_{28}H_{44}O_7N_3Si_2$ $[M+NH_4]^+$: 590.27178; found: 590.27235.

$[\alpha]_D^{20\,°C}$: +12.8 (c = 0.9, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3026 (vw), 2955 (w), 2103 (s), 1731 (s), 1656 (m), 1549 (s), 1409 (m), 1230 (s), 1124 (m), 1077 (m), 834 (s), 698 (m) cm^{-1}.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.24 – 7.18 (m, 4H), 7.14 – 7.08 (m, 1H), 5.08 (t, *J* = 2.3 Hz, 1H), 4.23 (td, *J* = 7.4, 3.8 Hz, 1H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.79 – 3.73 (m, 1H), 3.43 (dd, *J* = 10.4, 1.4 Hz, 1H), 2.87 (dd, *J* = 5.9, 4.4 Hz, 3H), 2.74 (td, *J* = 12.8, 4.5 Hz, 1H), 2.62 (td, *J* = 12.8, 5.5 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.10 – 2.02 (m, 2H), 1.90 – 1.82 (m, 1H), 1.49 (dddd, *J* = 23.3, 14.2, 11.5, 2.8 Hz, 2H), 0.16 (s, 9H), 0.12 (s, 9H).

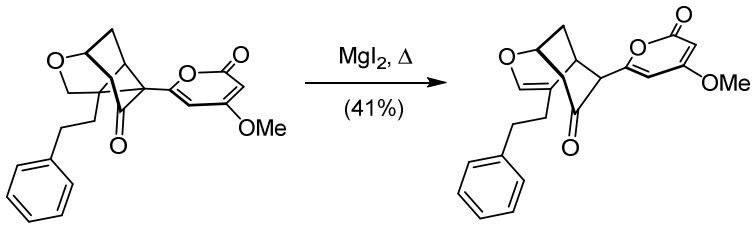
^{13}C NMR (201 MHz, C_6D_6) δ = 187.75, 171.32, 161.09, 149.32, 142.85, 128.89, 128.75, 128.35, 128.29, 126.27, 98.26, 86.77, 75.05, 70.74, 69.67, 69.47, 55.09, 44.88, 39.27, 37.70, 29.67, 3.06, 0.56.

NMR data for **2.48'**.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.19 – 7.11 (m, 4H), 7.06 (tt, *J* = 7.1, 1.4 Hz, 1H), 5.09 (d, *J* = 2.3 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 3.66 (dddd, *J* = 11.7, 7.7, 4.1, 2.1 Hz, 1H), 3.32 (dd, *J* = 11.3, 4.7 Hz, 1H), 2.88 (s, 3H), 2.86 (d, *J* = 11.9 Hz, 1H), 2.65 (ddd, *J* = 13.8, 12.5, 4.5 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.14 (ddd, *J* = 13.9, 12.9, 4.5 Hz, 1H), 2.05 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.84 (q, *J* = 11.7 Hz, 1H), 1.46 (ddd, *J* = 12.3, 4.7, 2.1 Hz, 1H), 1.38 (ddd, *J* = 14.0, 12.5, 5.3 Hz, 1H), 0.32 (s, 9H), 0.05 (s, 9H).

^{13}C NMR (201 MHz, C_6D_6) δ = 187.56, 171.28, 161.03, 149.36, 142.61, 128.89, 128.45, 128.35, 128.29, 126.32, 125.47, 98.22, 75.74, 74.15, 73.88, 73.25, 55.08, 45.16, 37.53, 36.84, 29.75, 3.25, 0.53.

Enol (**2.51**)



2.50 **2.51**

A flame dried flask under argon was sequentially charged with Mg turnings (0.81 g, 33.9 mmol, 1.25 eq.) and dry Et_2O (100 mL). Under vigorous stirring, I_2 (7.00 g, 27.6 mmol, 1.0 eq.), was added and the reaction vessel was placed in a 40 °C preheated oil bath. The reaction mixture turned from dark brown to milky white. Then the solids were filtered under argon, washed three times with dry Et_2O and dried under high vacuum. This material was used without further purification in the following reaction.

A flame dried flask under argon was charged with freshly prepared MgI_2 (0.07 g, 0.25 mmol, 2.0 eq.) and a solution of **2.50** (46.0 mg, 0.12 mmol, 1.0 eq.) in dry toluene (1.2 mL). The reaction vessel was placed in an 80 °C preheated oil bath. The resulting mixture was analyzed by TLC for completion (1 h). The reaction was allowed to cool to RT and then it was quenched by addition of sat. $NaHCO_{3(aq.)}$, the aqueous phase was extracted three times with EtOAc, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 35:65) to afford **2.51** (18.0 mg, 0.05 mmol, 41%) as a slightly yellow oil.

R_f: 0.5, EtOAc/*i*hex 7:3, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{23}O_5$ $[M+H]^+$: 367.1540; found: 367.1543.

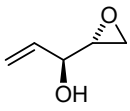
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.17 (m, 1H), 7.16 – 7.13 (m, 2H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.70 (dd, *J* = 2.2, 1.1 Hz, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 4.69 (dd, *J* = 4.0, 2.1 Hz, 1H), 3.80 (s, 3H), 3.59 – 3.54 (m, 1H), 2.84 (dt, *J* = 3.9, 2.2 Hz, 1H), 2.82 – 2.70 (m, 3H), 2.64 (dt, *J* = 13.7, 8.1 Hz, 1H), 2.33 (dt, *J* = 13.9, 2.2 Hz, 1H), 2.21 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 2.09 – 1.99 (m, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 204.11, 170.85, 163.78, 160.76, 141.45, 139.35, 128.57, 128.49, 126.20, 112.26, 101.53, 88.51, 70.22, 56.89, 56.21, 47.47, 34.56, 33.06, 32.46, 24.70.

6.2.2 References

1. (a) M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583; (b) J. Mulzer, K.-D. Graske, B. Kirste, *Liebigs Annalen der Chemie* **1988**, *1988*, 891; (c) Atsumi, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Chem. Pharm. Bull.* **1990**, *38*, 3460
2. J. L. Bloomer, S. M. H. Zaidi, J. T. Strupczewski, C. S. Brosz, L. A. Gudzyk *J. Org. Chem.* **1974** *39 (24)*, 3615.
3. (a) A. Robinson, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 6673; (b) T. Yoshinari, K. Ohmori, M. G. Schrems, A. Pfaltz, K. Suzuki, *Angew. Chem. Int. Ed.* **2010**, *49*, 881.
4. A. Rizzo, D. Trauner, *Org. Lett.* **2018**, ASAP

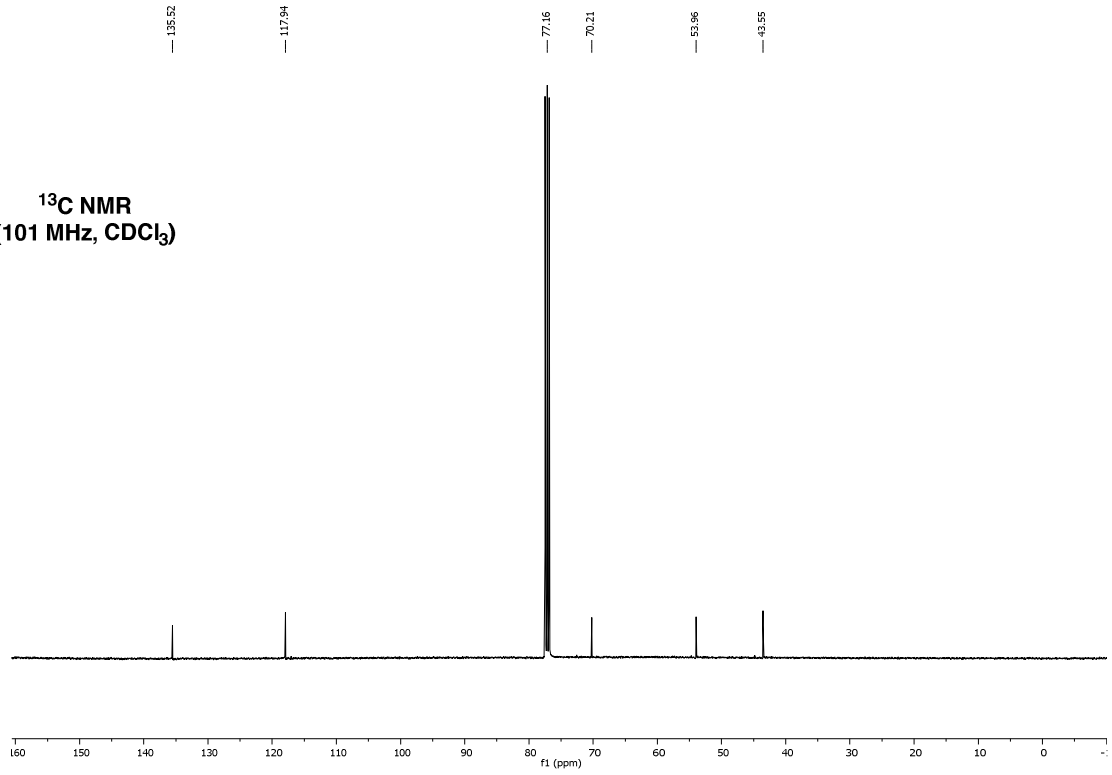
6.2.3 NMR Data for Chapter 2.1

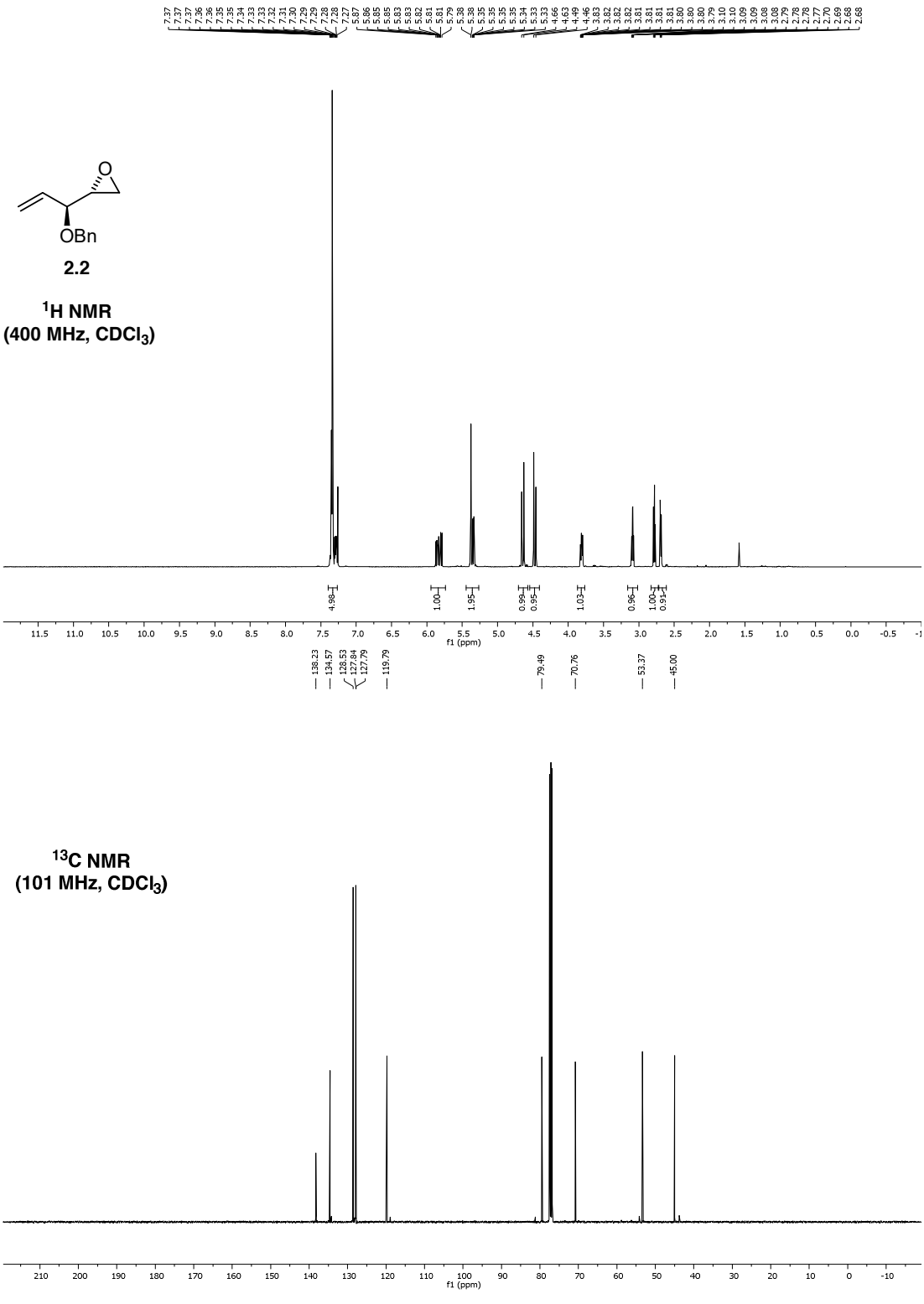


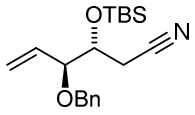
2.1

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)



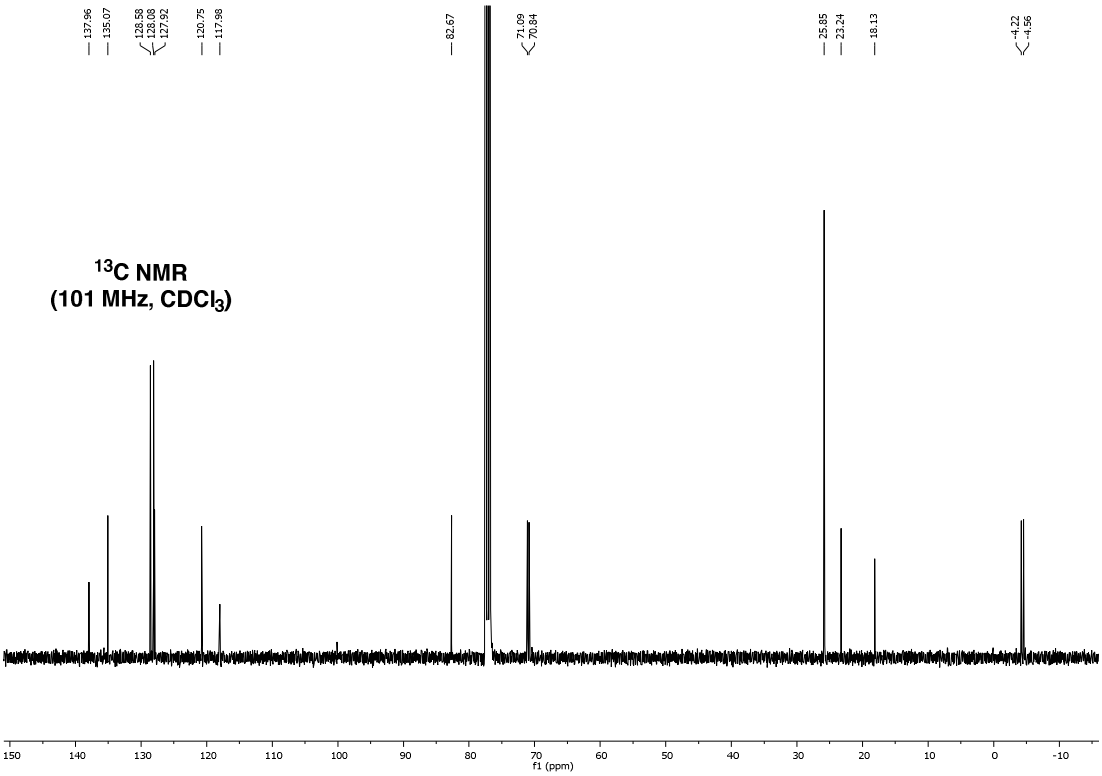

OBn
2.2
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)

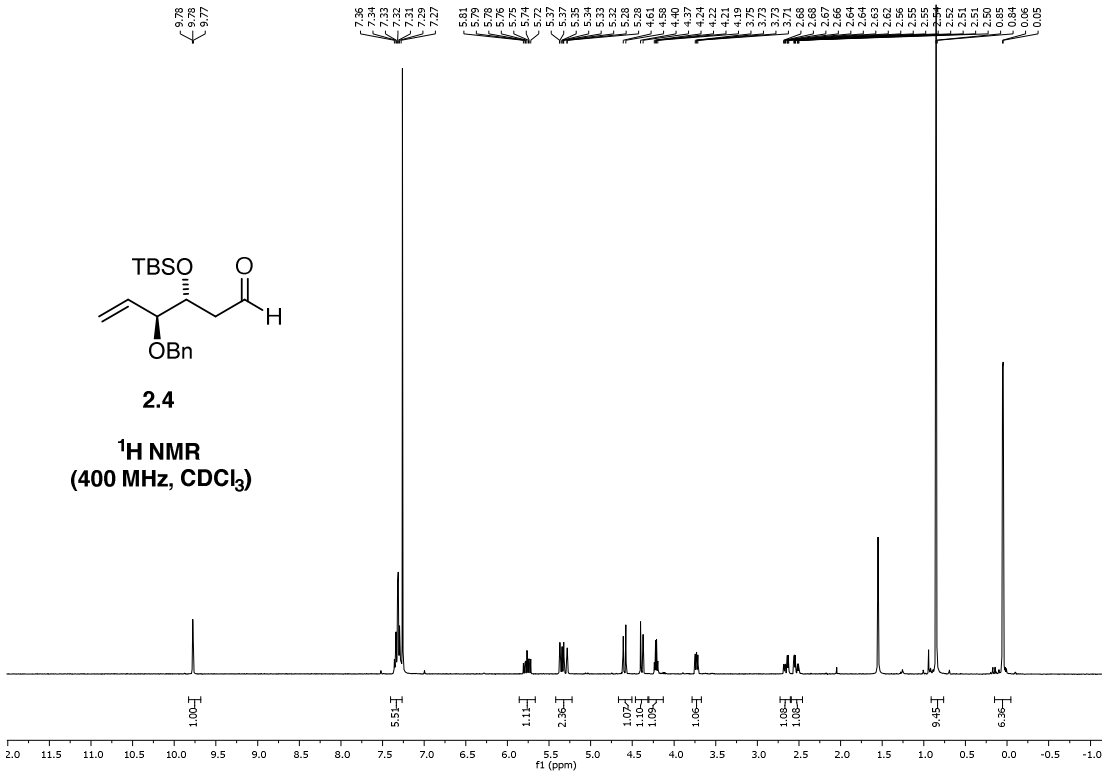


2.3

^{1}H NMR
(400 MHz, $CDCl_3$)

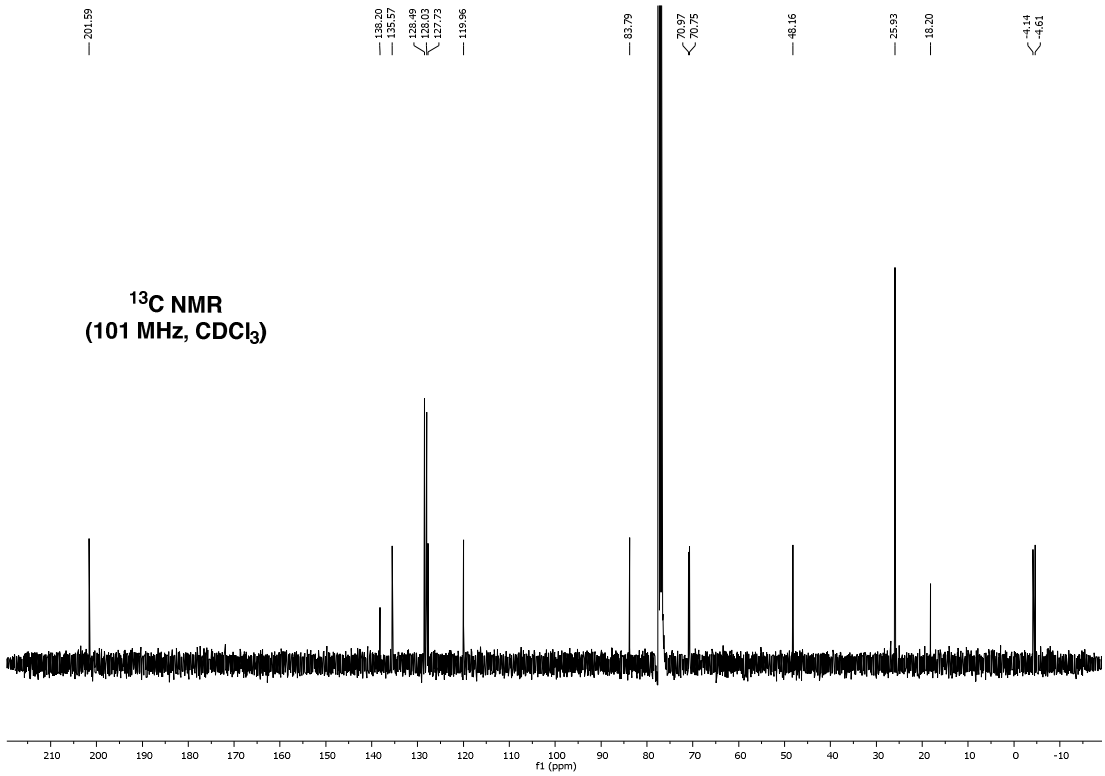
^{13}C NMR
(101 MHz, $CDCl_3$)



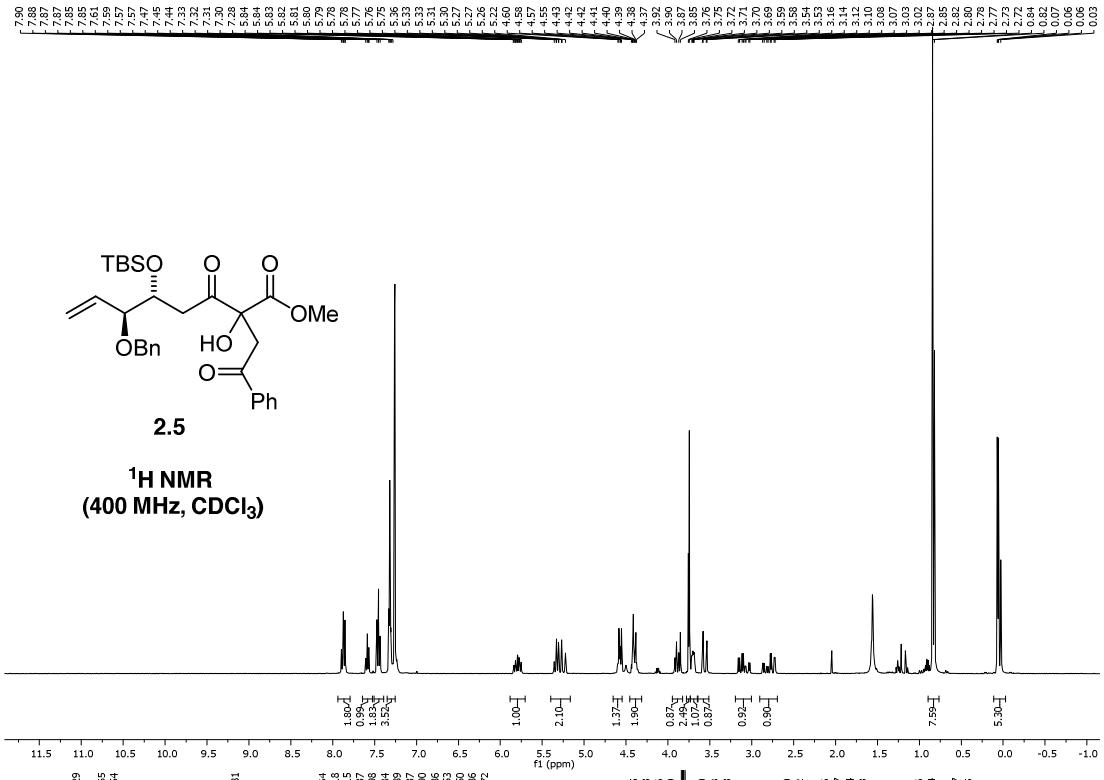


2.4

^{1}H NMR
(400 MHz, $CDCl_3$)

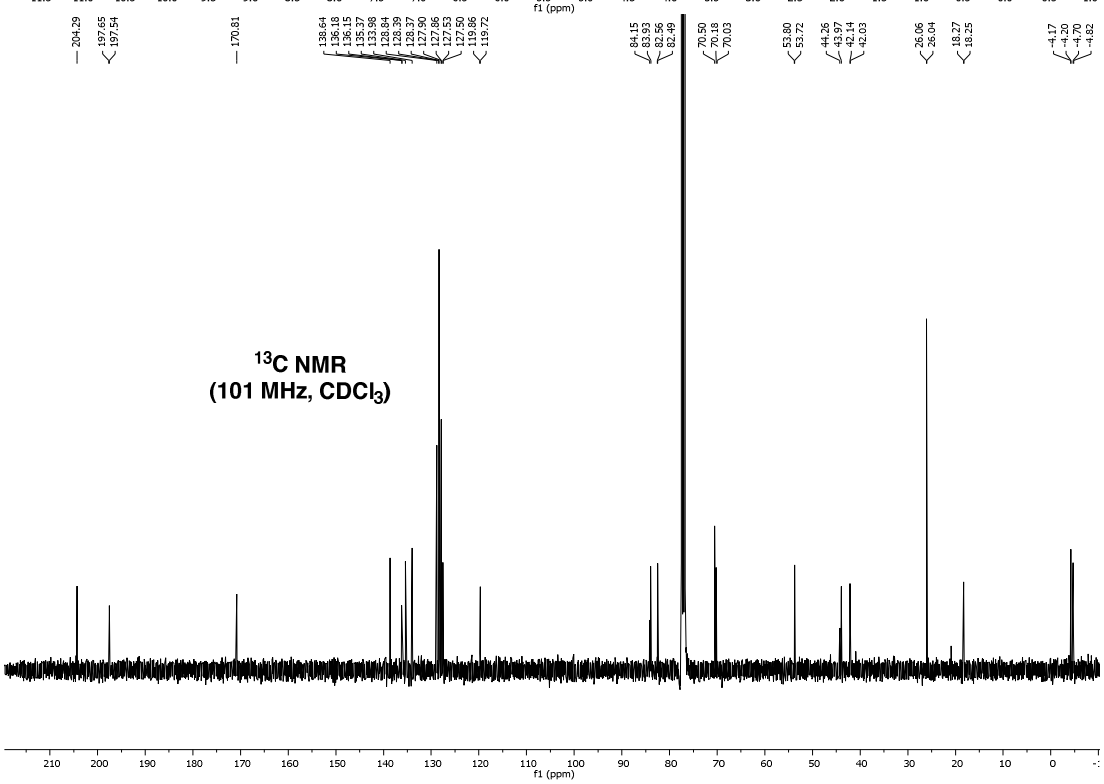


^{13}C NMR
(101 MHz, $CDCl_3$)

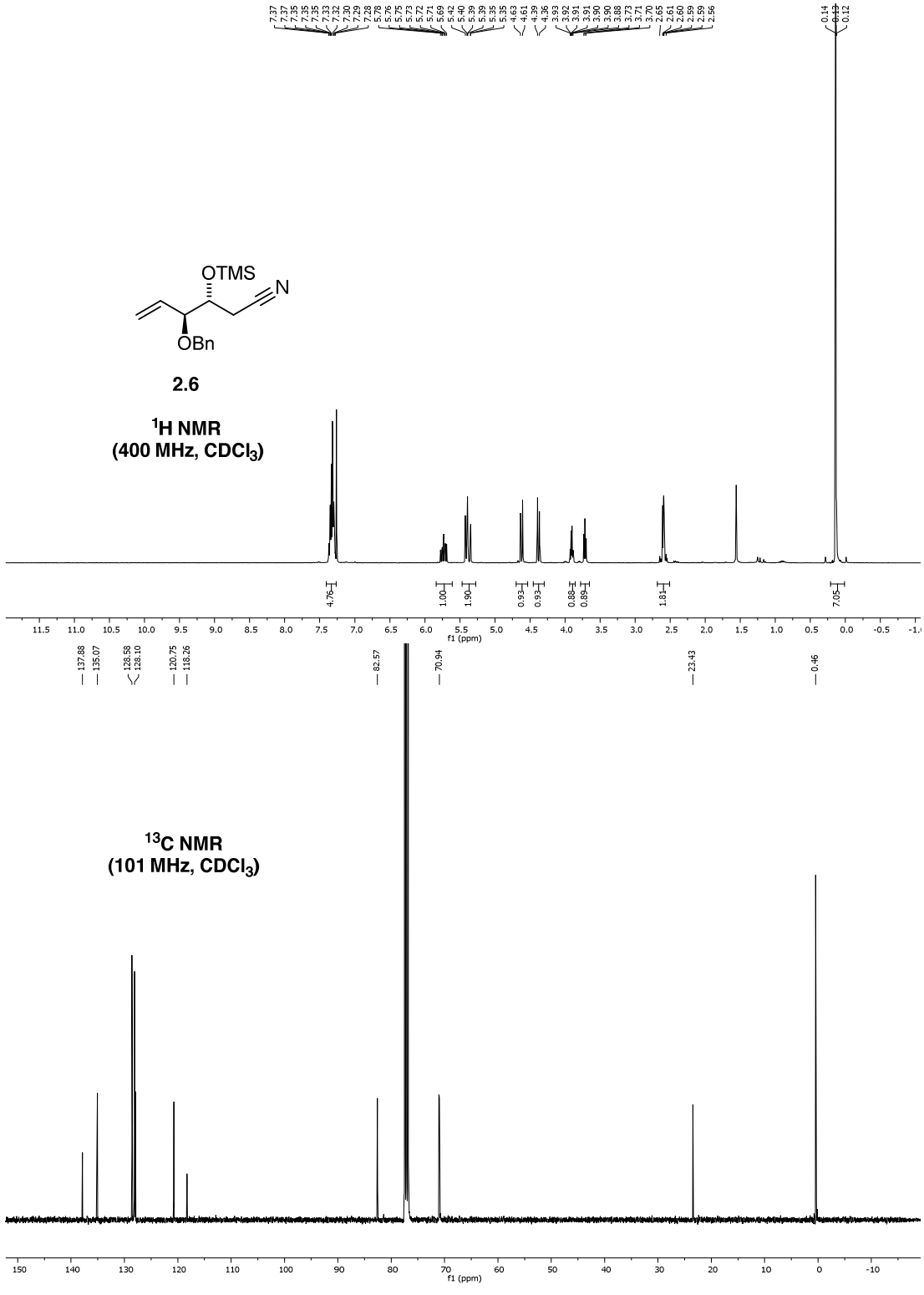


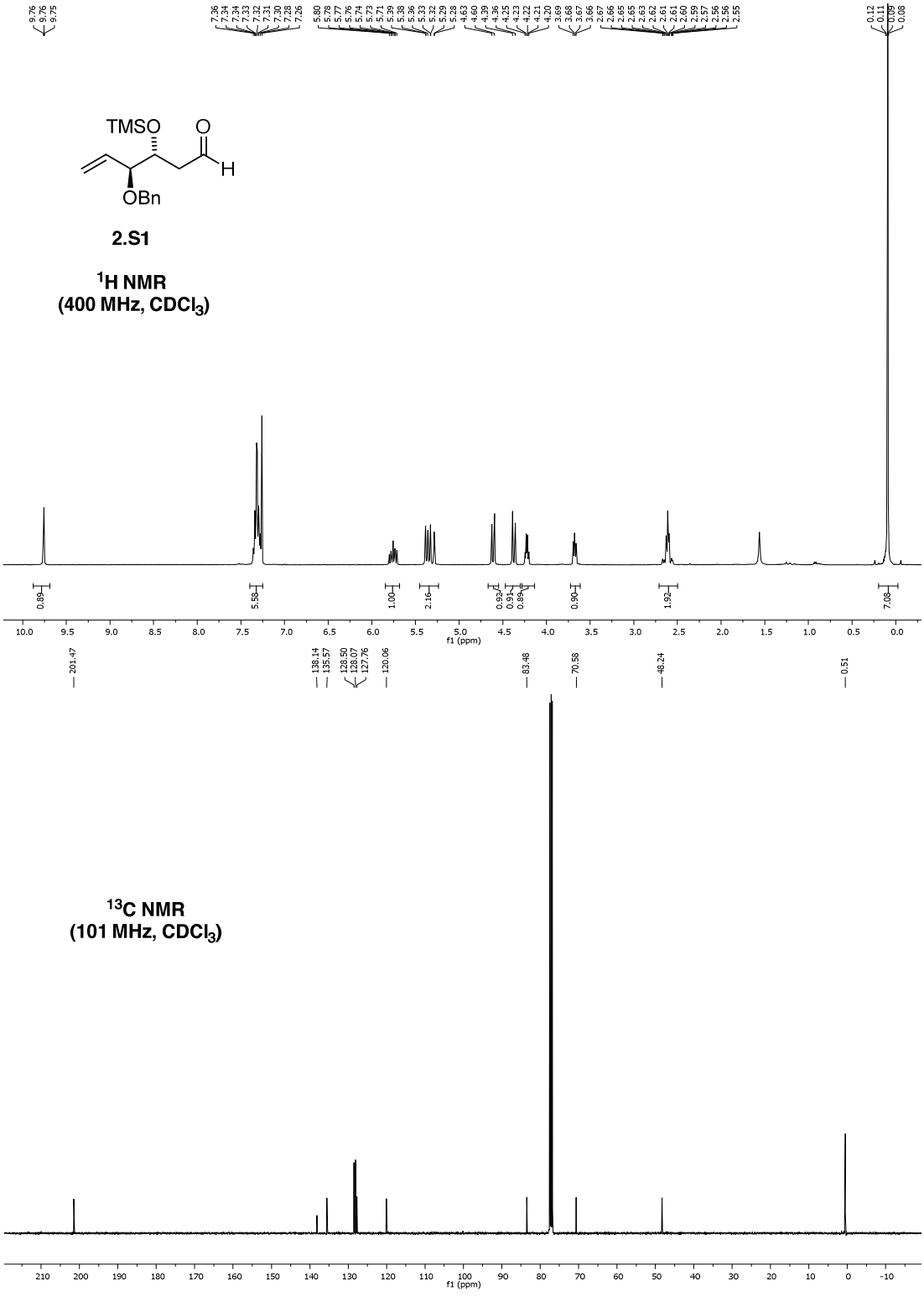
2.5

^{1}H NMR
(400 MHz, $CDCl_3$)



^{13}C NMR
(101 MHz, $CDCl_3$)

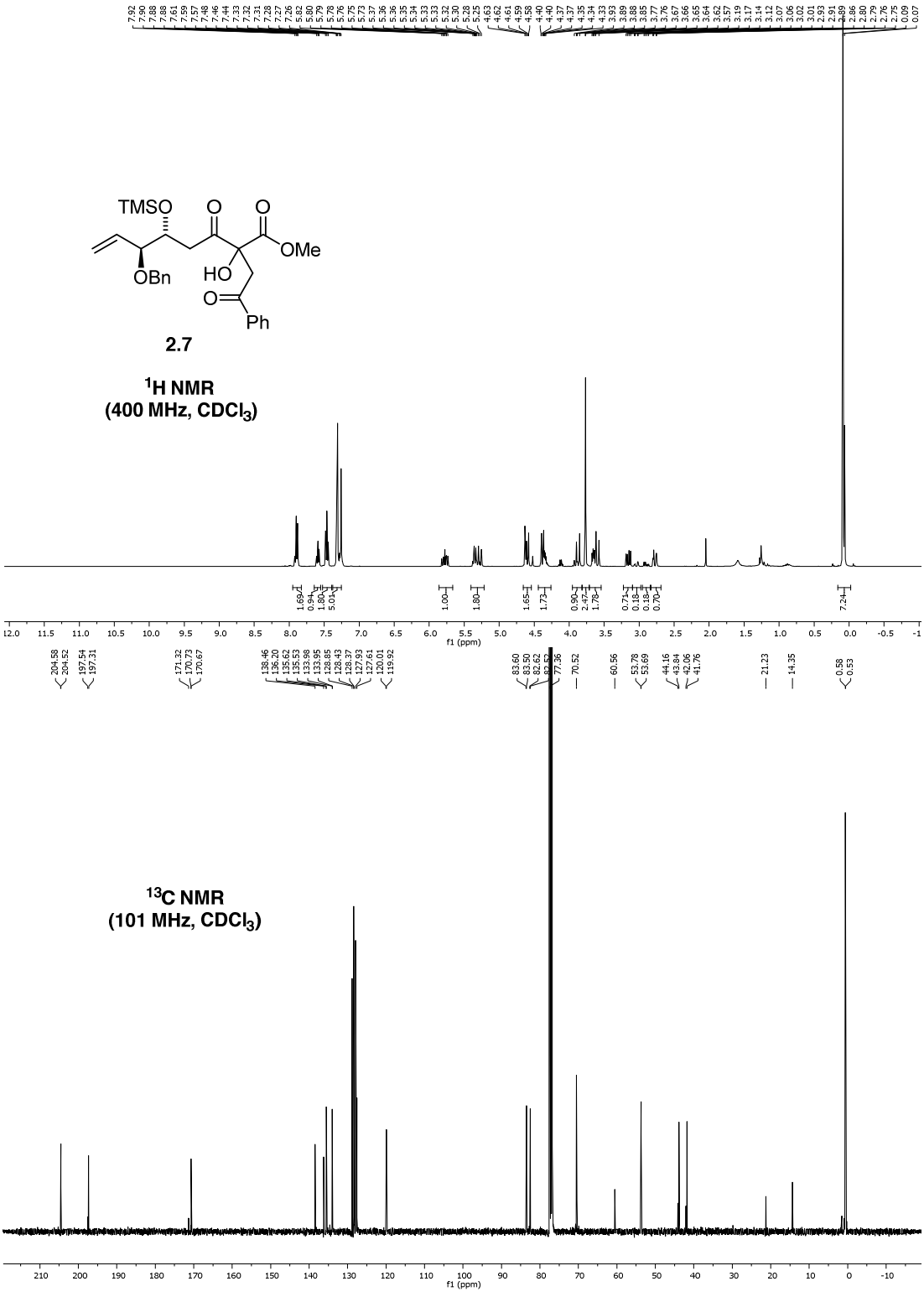

OTMS
N
OBn
2.6
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)

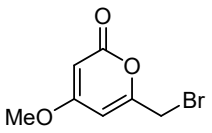


2.S1

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

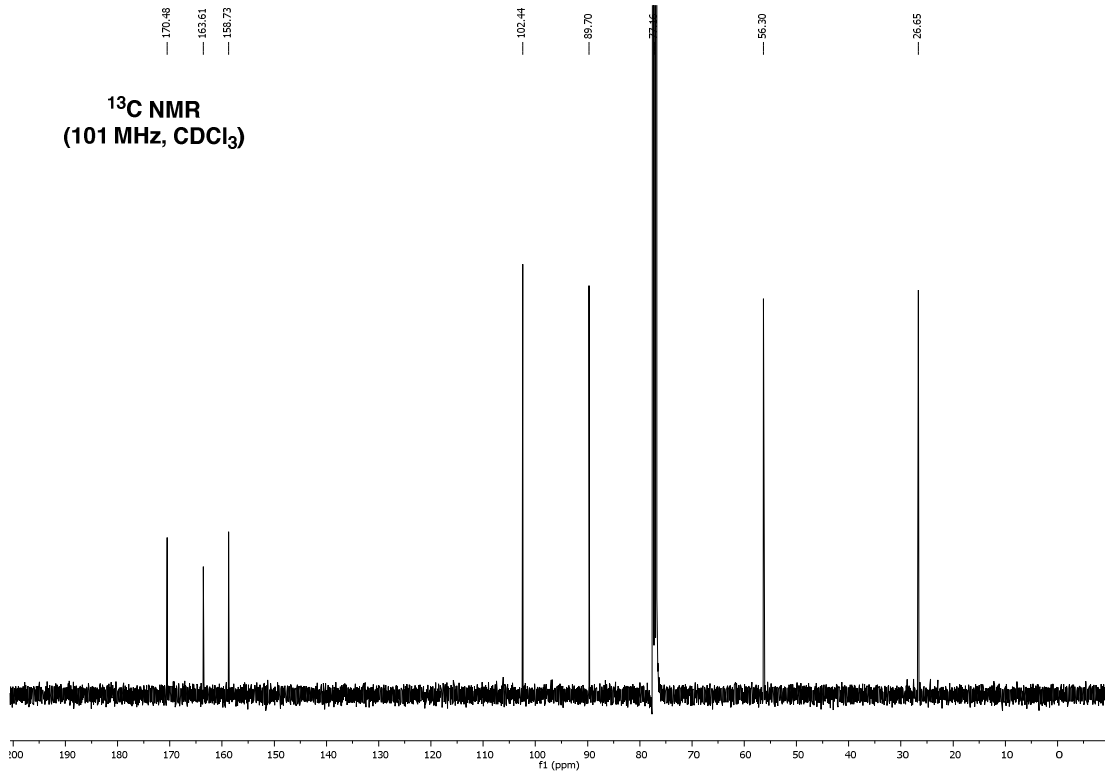

TMSO
O
O
OMe
OBn
HO
O
Ph
2.7
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)

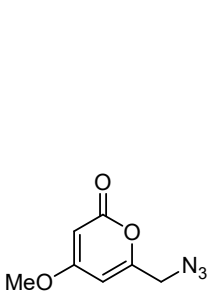


2.11

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)





2.12

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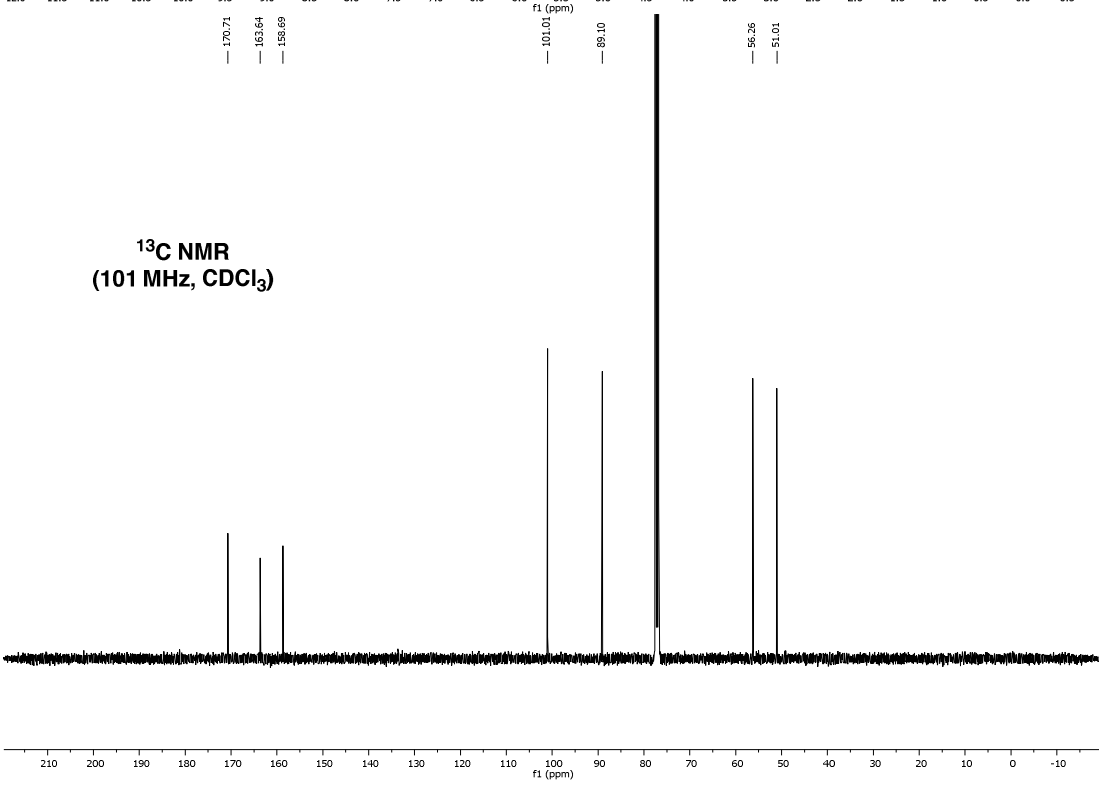
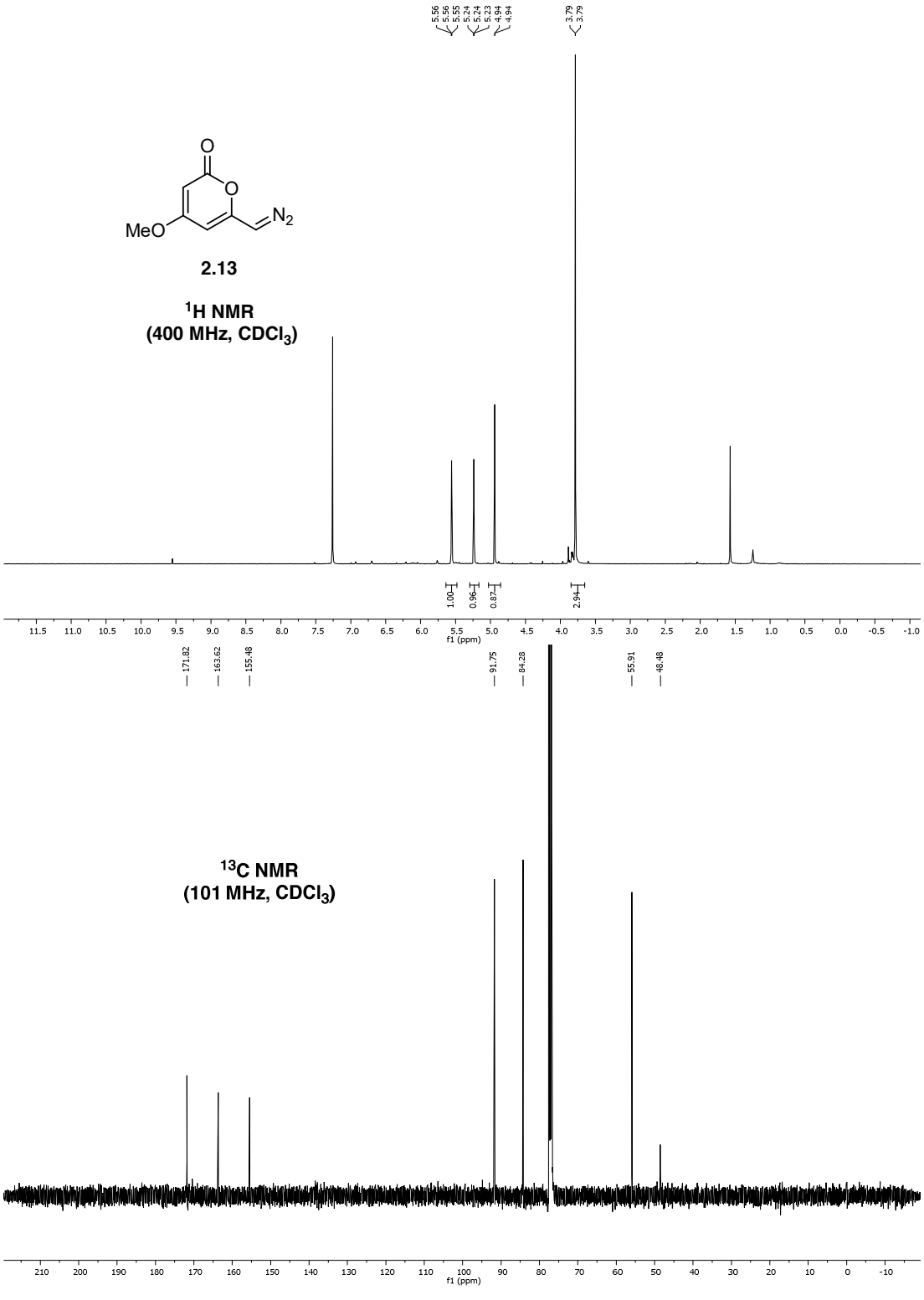
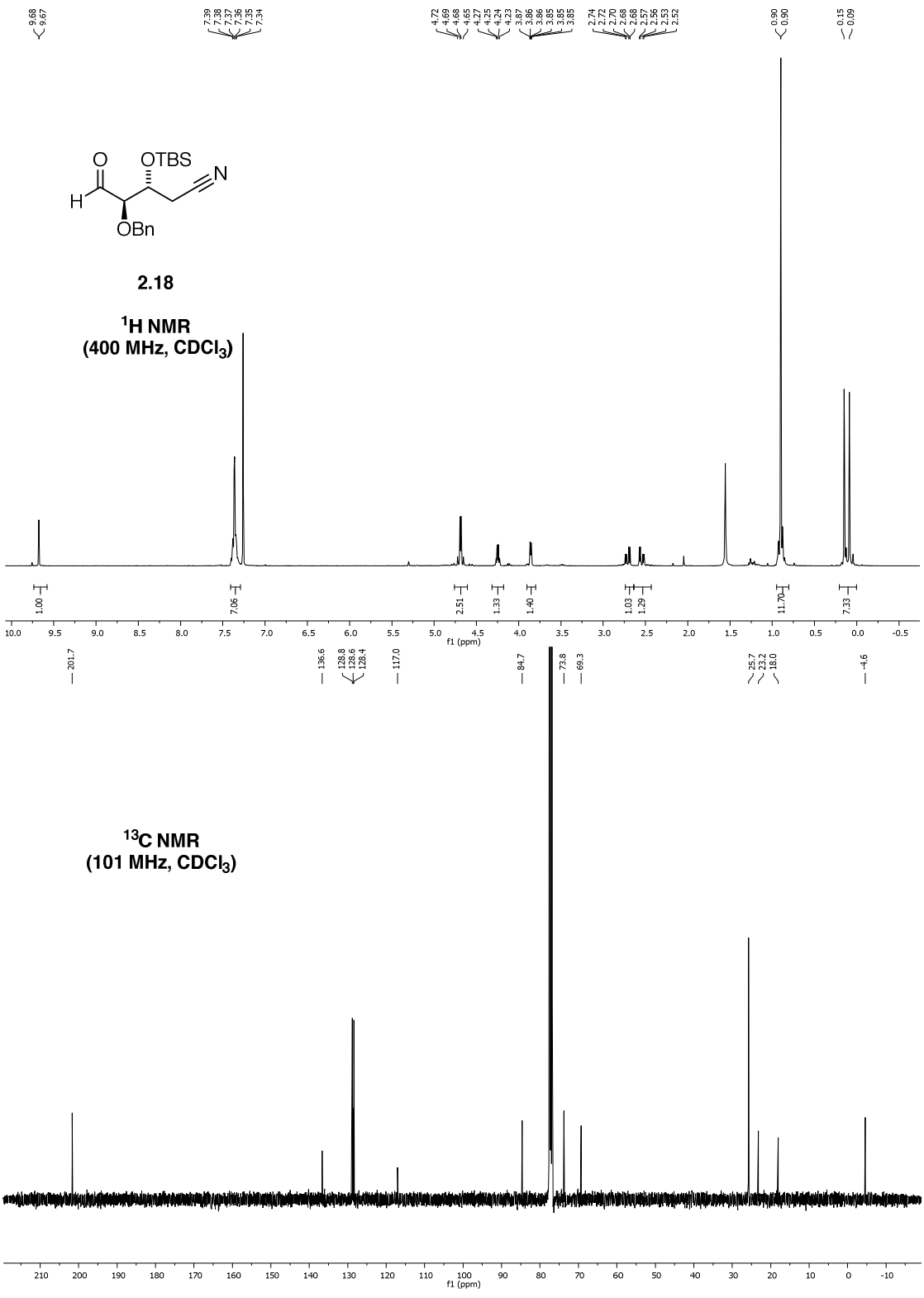
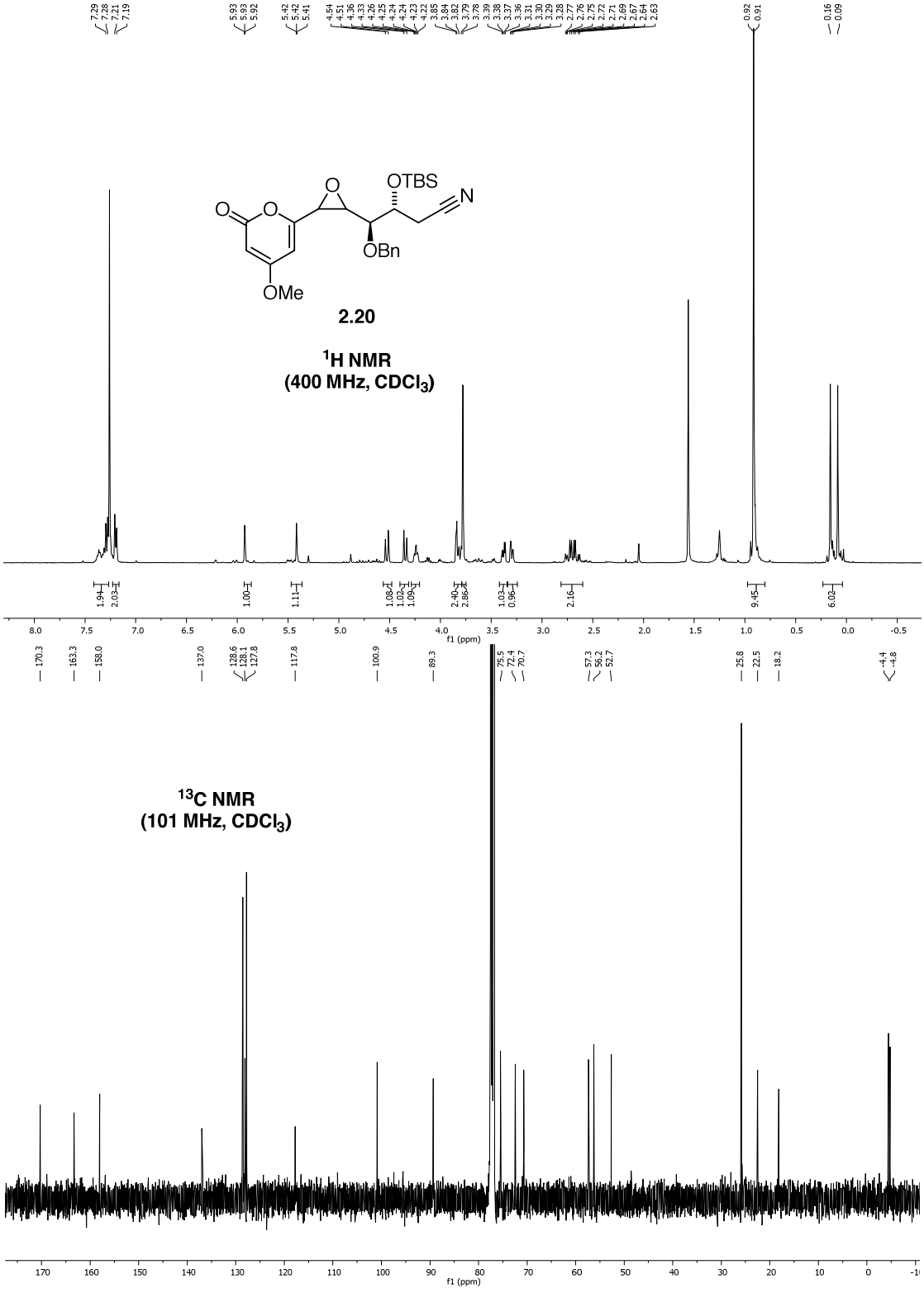
(400 MHz, $CDCl_3$)

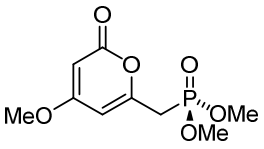
^{13}C NMR
(101 MHz, $CDCl_3$)




MeO
N2
2.13
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)


O
OTBS
N
H
OBn
2.18
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)


OTBS
N
O
O
O
OBn
OMe
2.20
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)



2.21

^{1}H NMR
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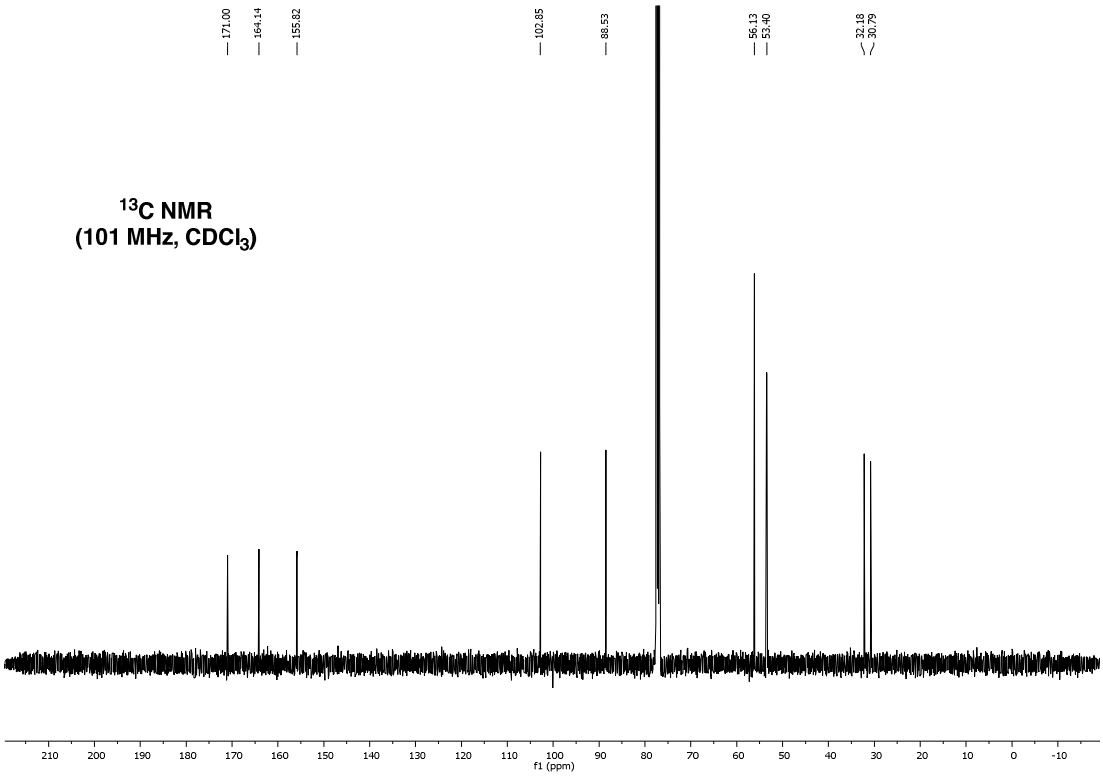
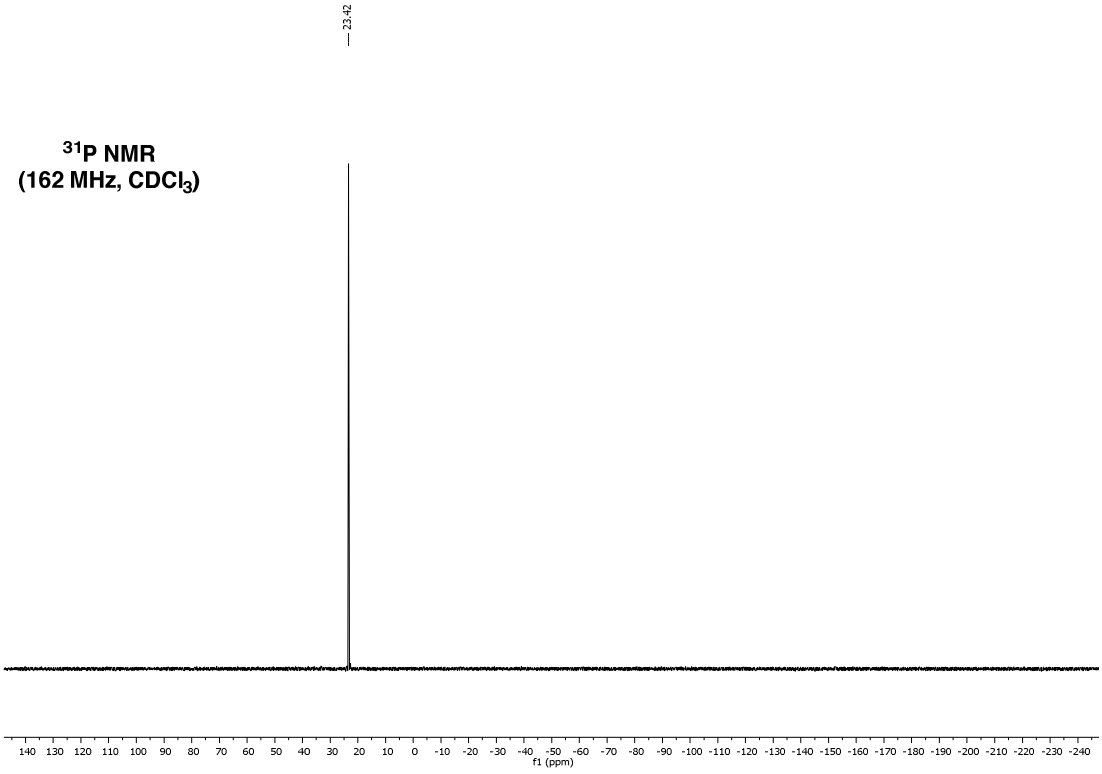
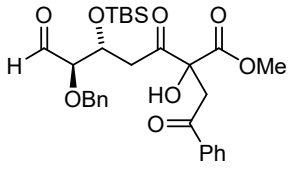
^{13}C NMR
(101 MHz, $CDCl_3$)



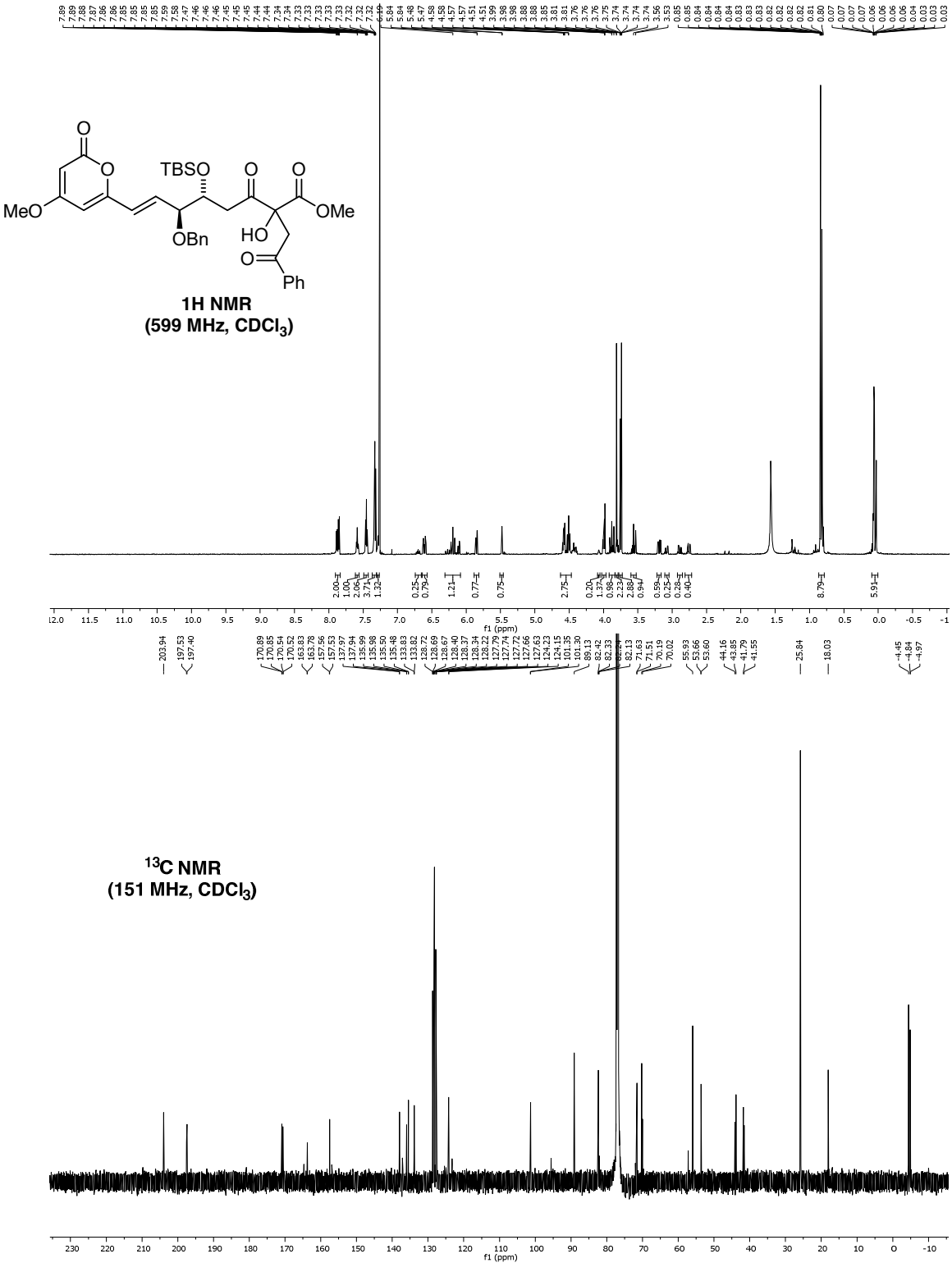
^{31}P NMR
(162 MHz, $CDCl_3$)

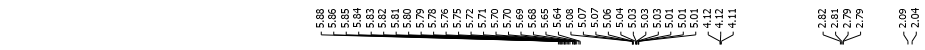


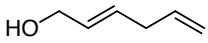


2.15

^{1}H NMR
(400 MHz, $CDCl_3$)

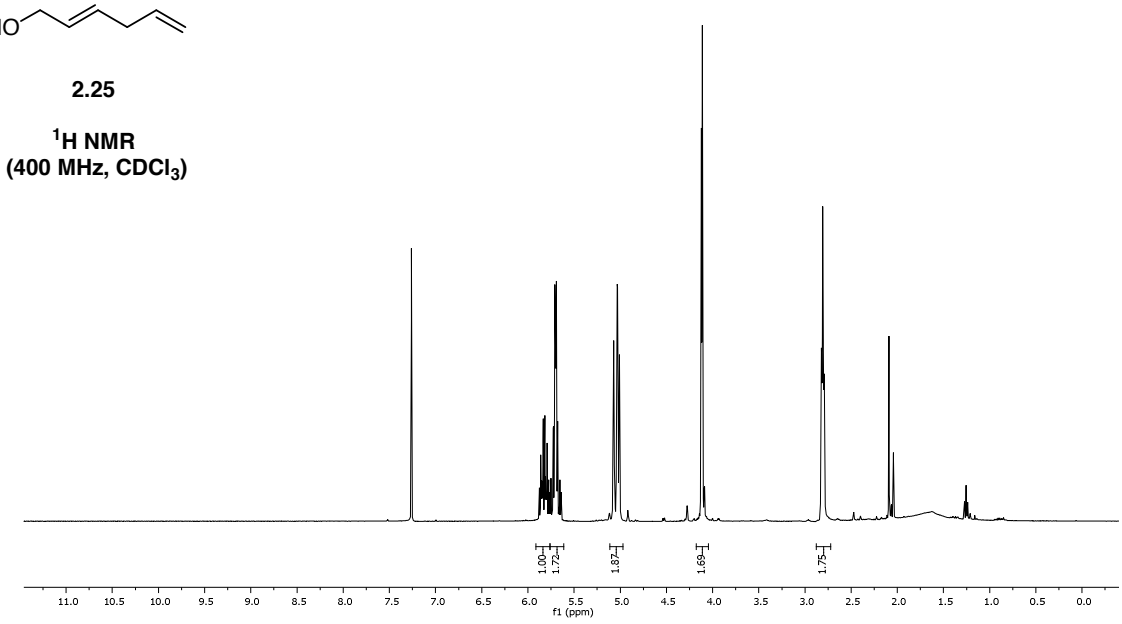

MeO
TBSO
OBn
HO
OMe
Ph
1H NMR
(599 MHz, CDCl3)
13C NMR
(151 MHz, CDCl3)
f1 (ppm)



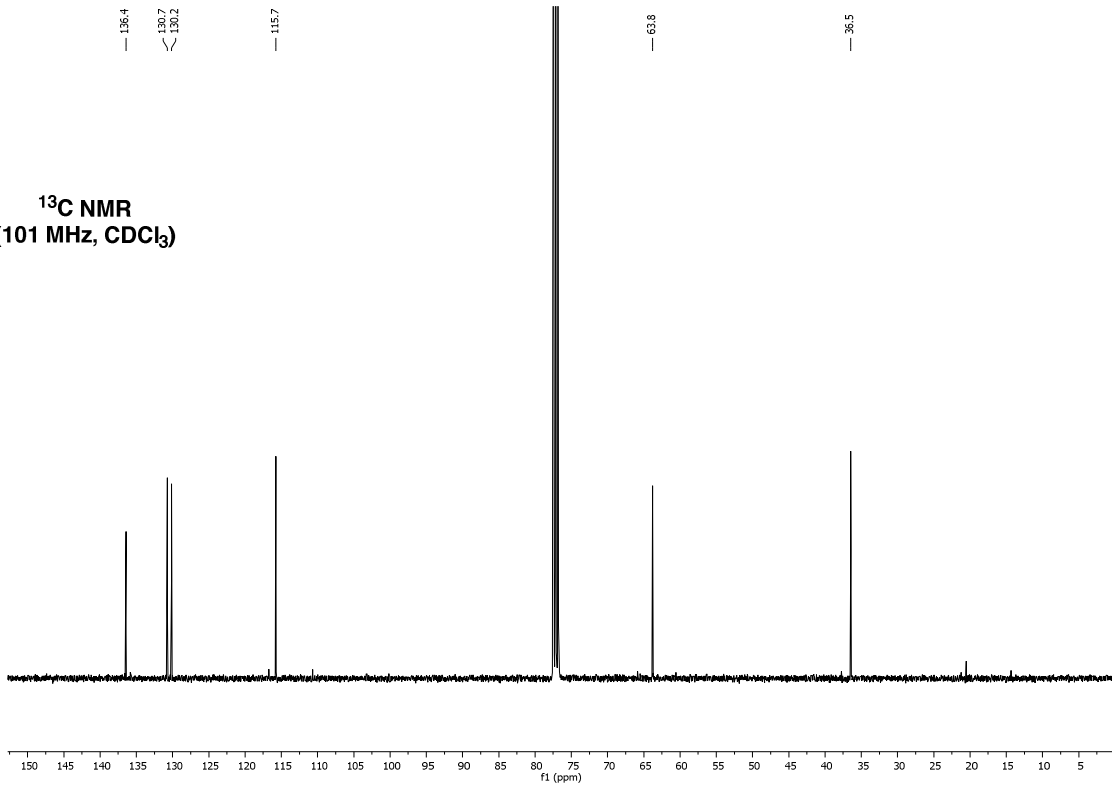


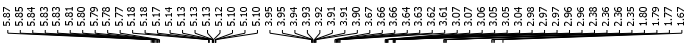
2.25

^{1}H NMR
(400 MHz, $CDCl_3$)



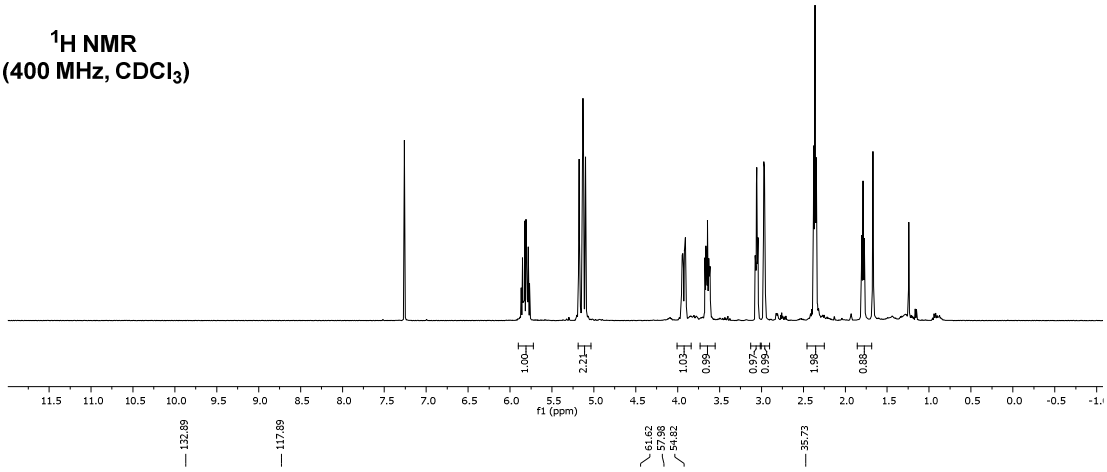
^{13}C NMR
(101 MHz, $CDCl_3$)



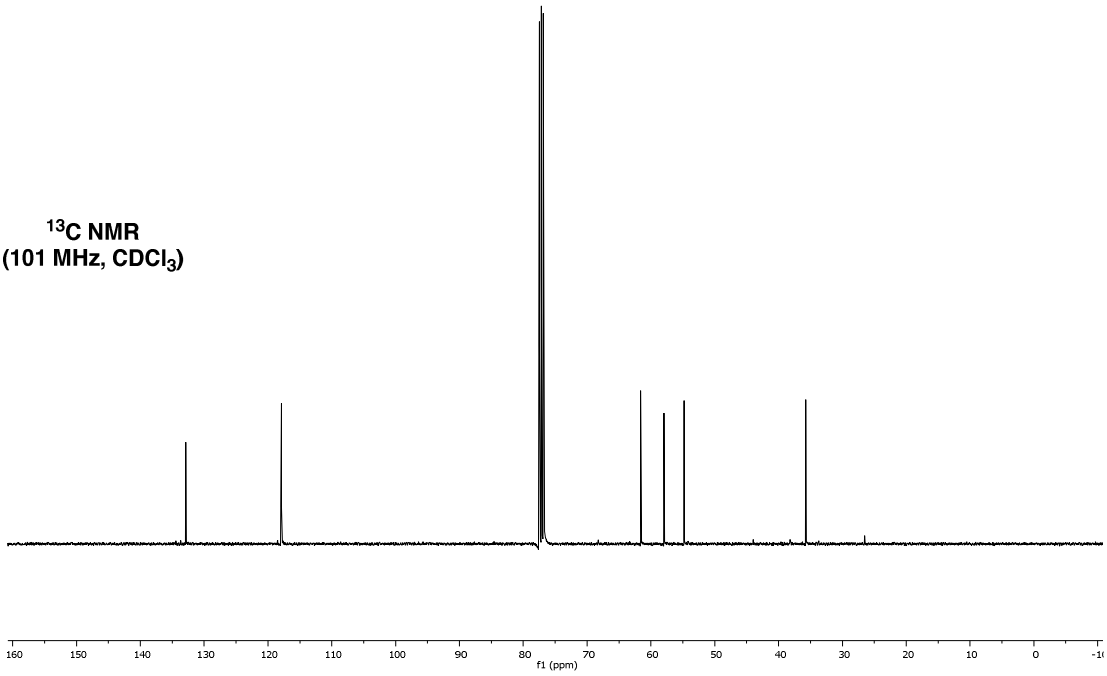


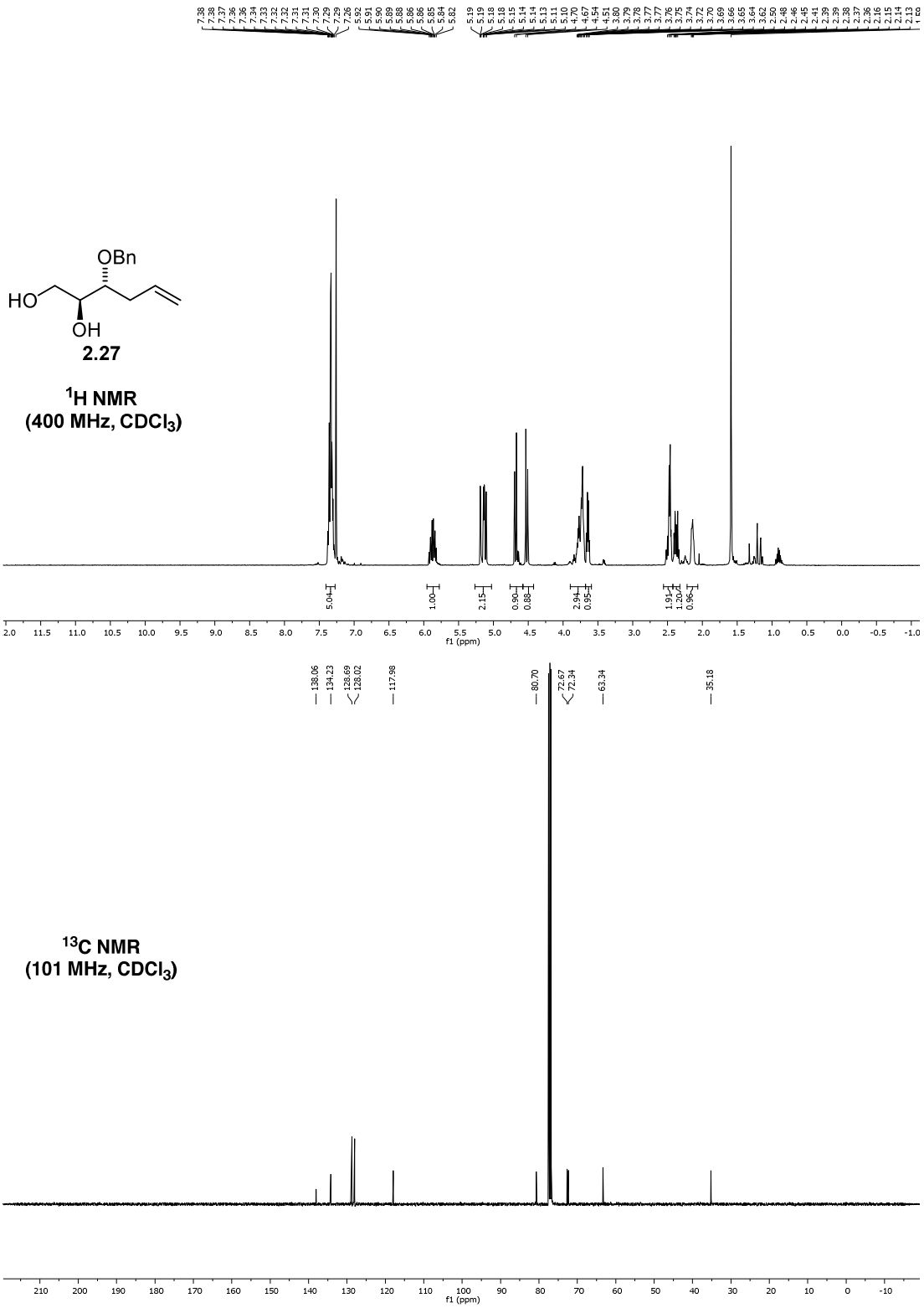
2.26

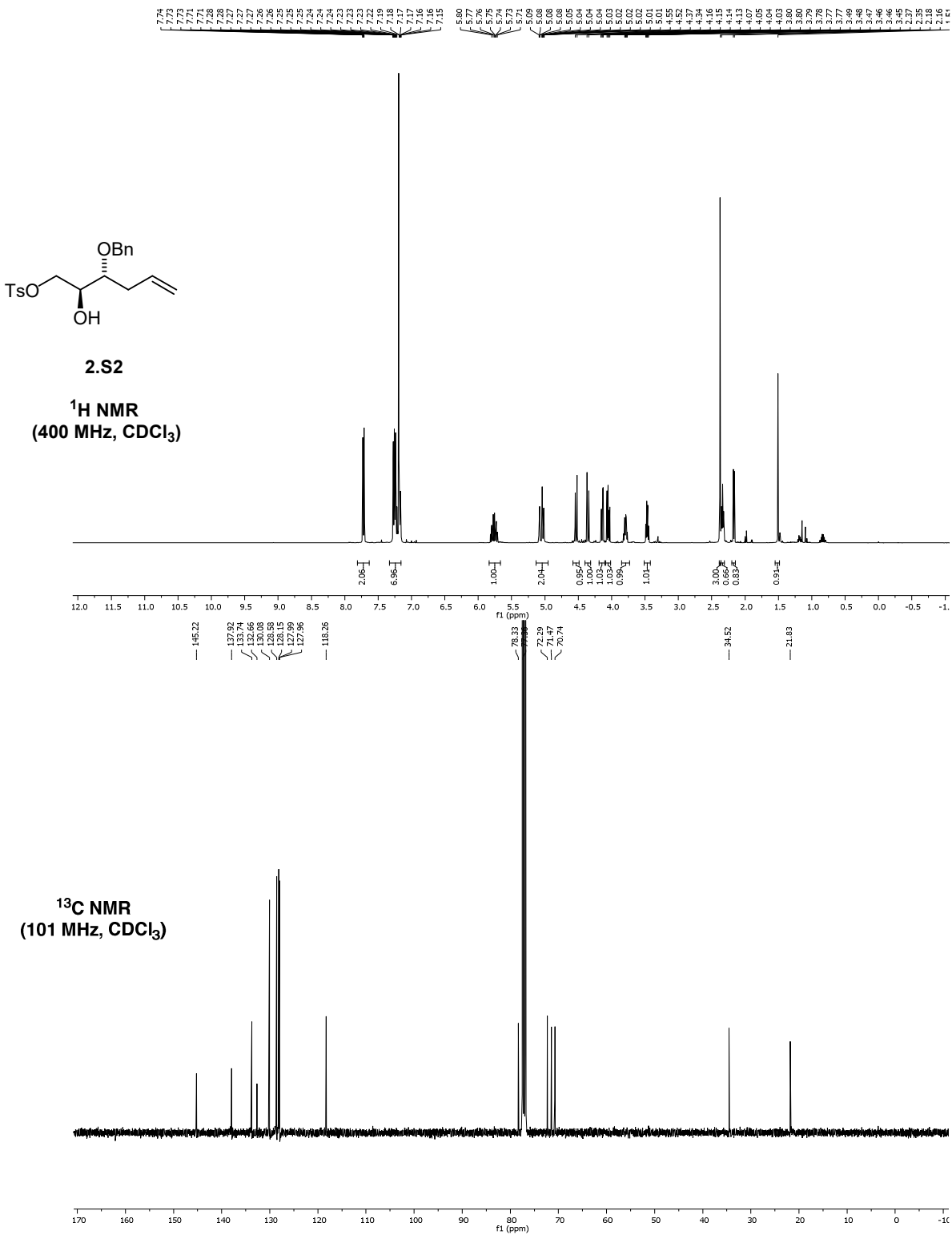
^{1}H NMR
(400 MHz, $CDCl_3$)

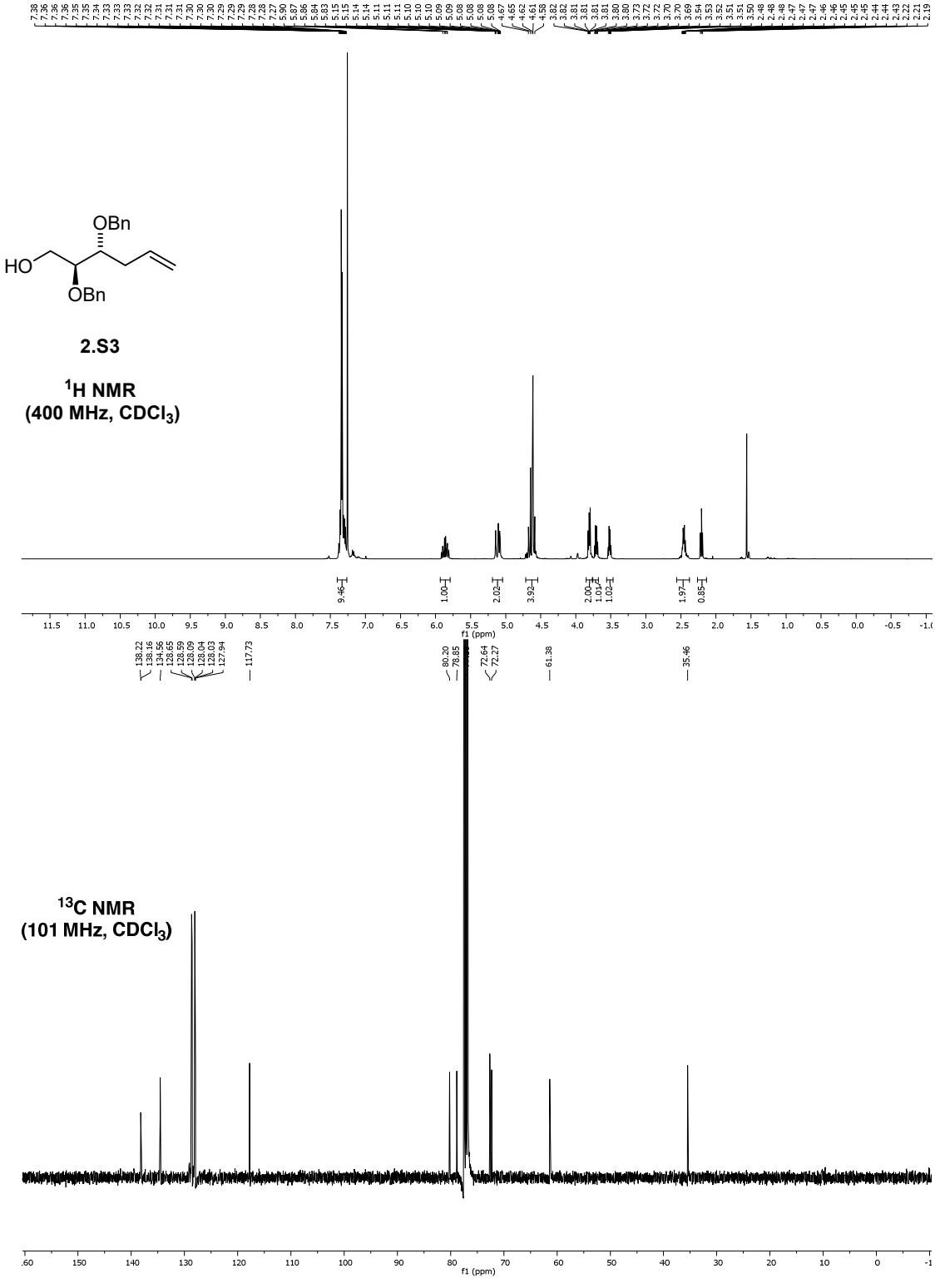


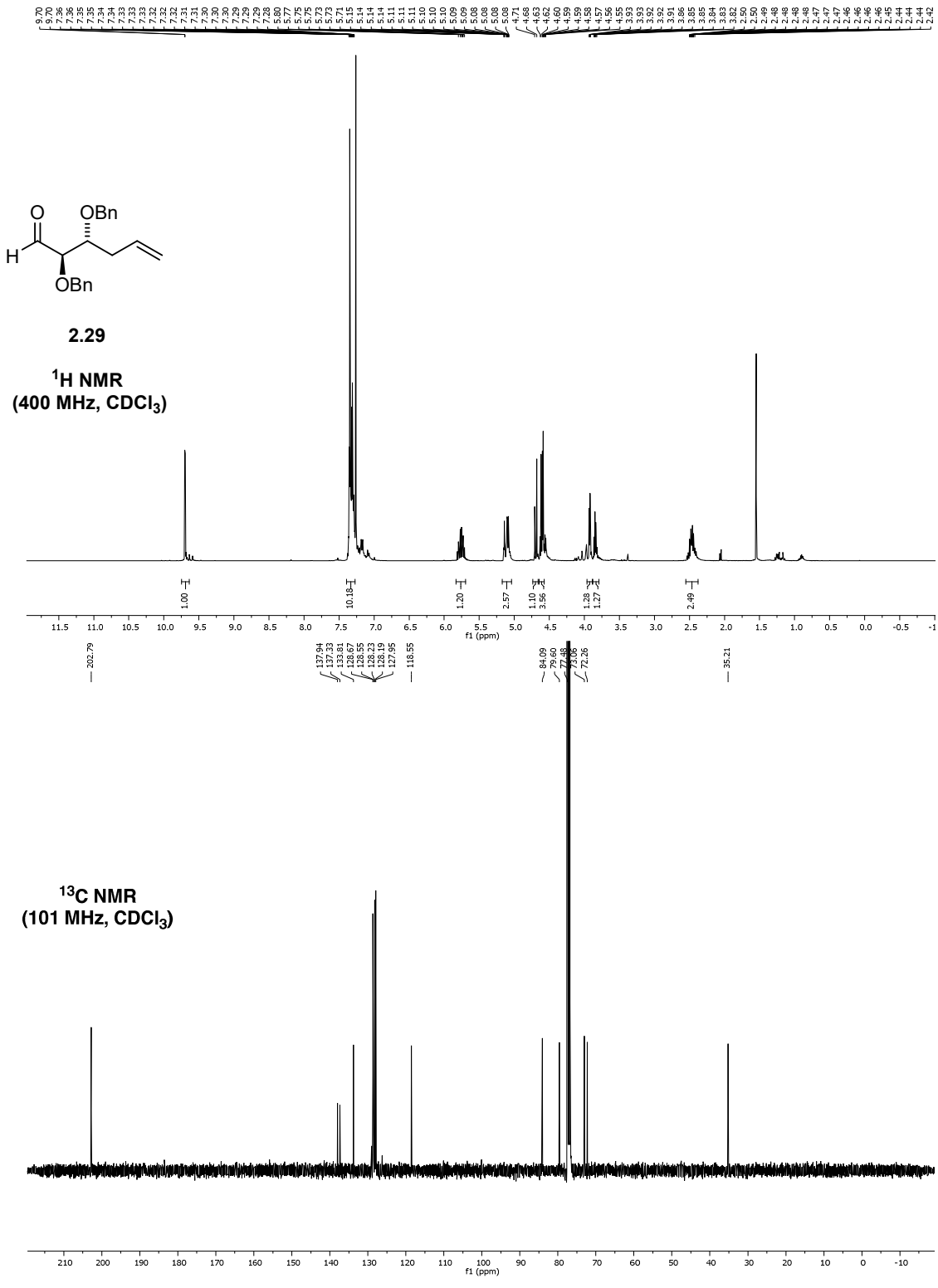
^{13}C NMR
(101 MHz, $CDCl_3$)

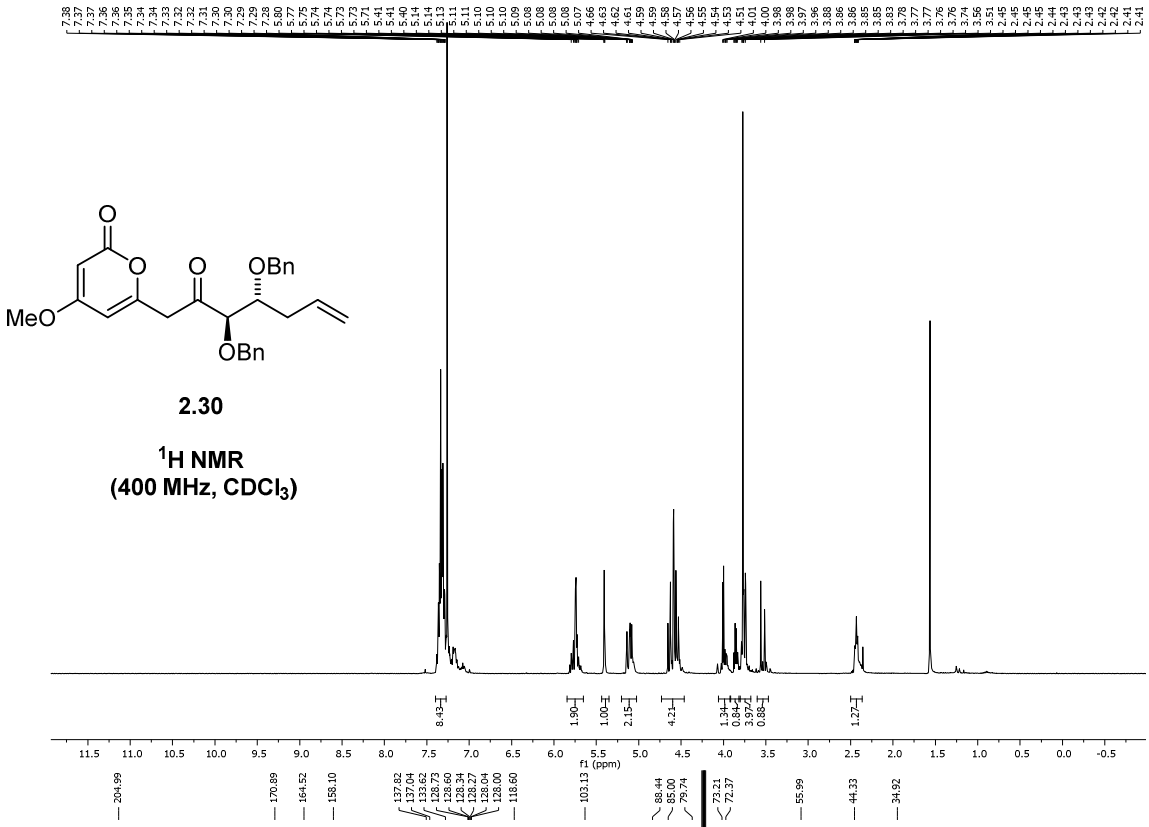



OBn
HO
OH
2.27
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)


OBn
TsO
OH
2.S2
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)


OBn
HO
OBn
2.S3
^{1}H NMR
(400 MHz, CDCl$_3$)
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)

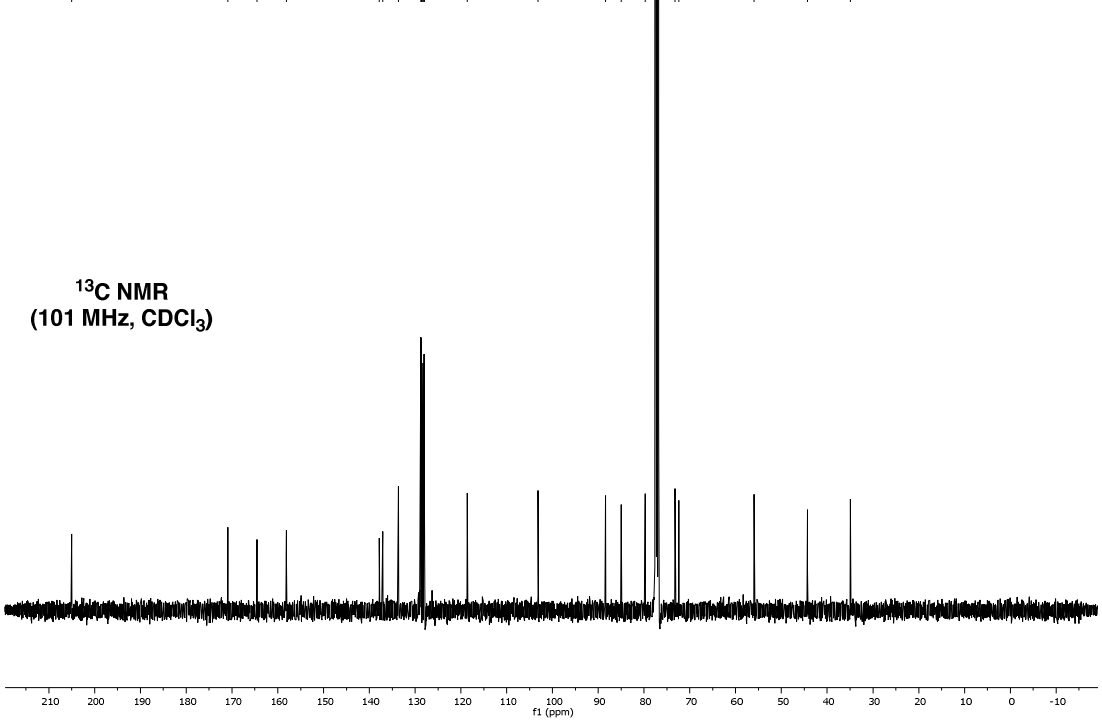

O
OBn
H
OBn
2.29
1H NMR
(400 MHz, CDCl3)
f1 (ppm)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)

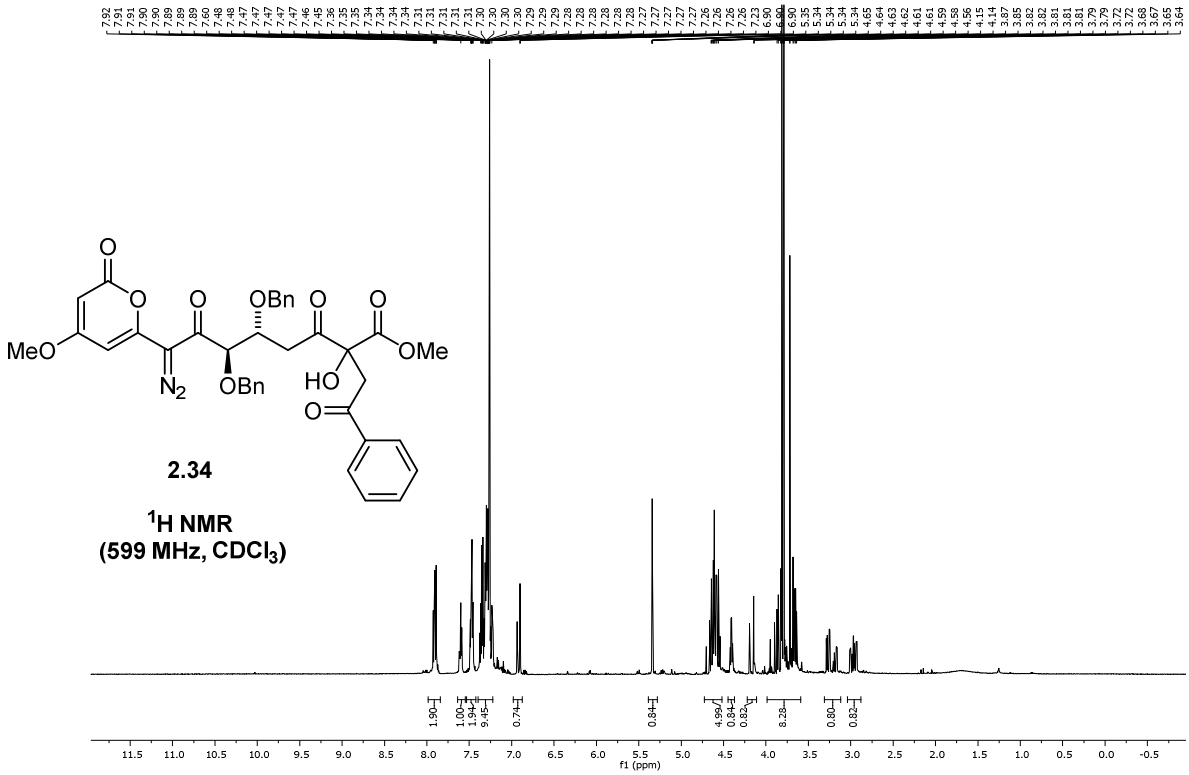


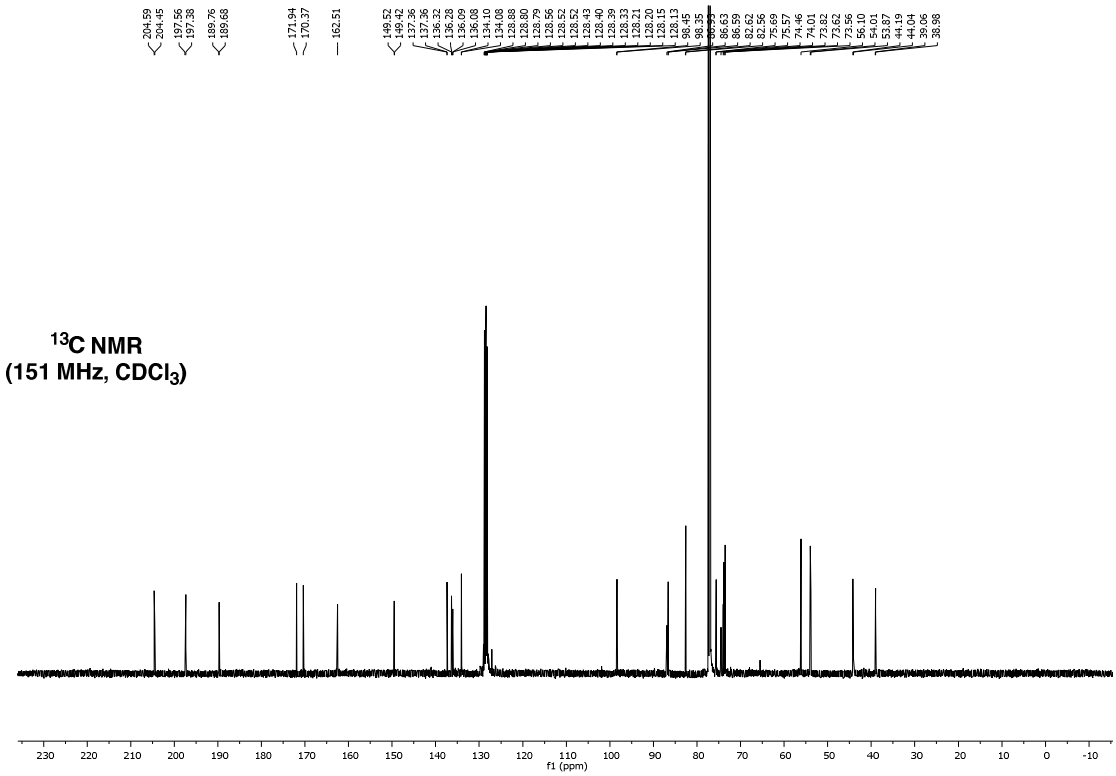
2.30

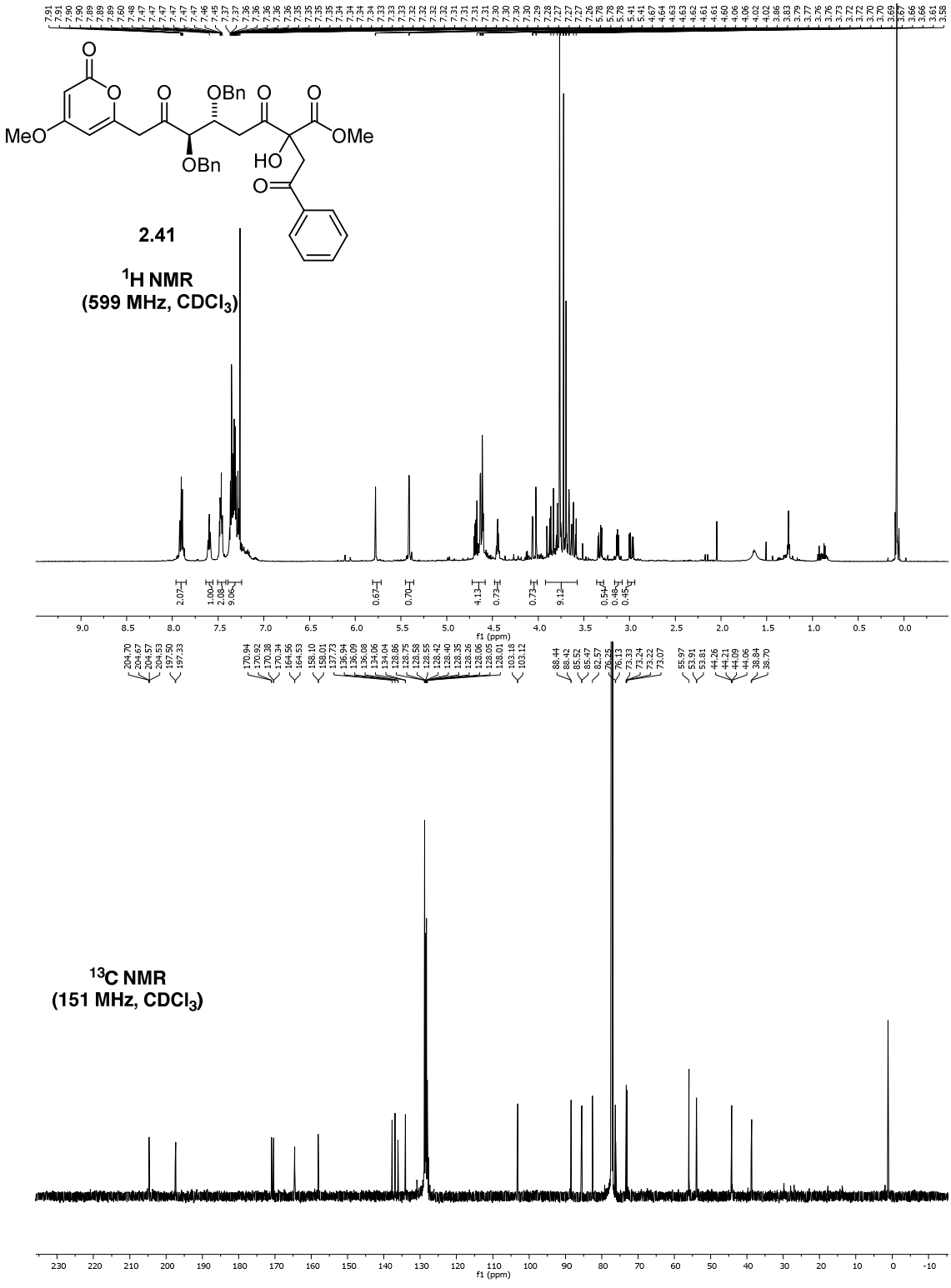
^{1}H NMR
(400 MHz, $CDCl_3$)

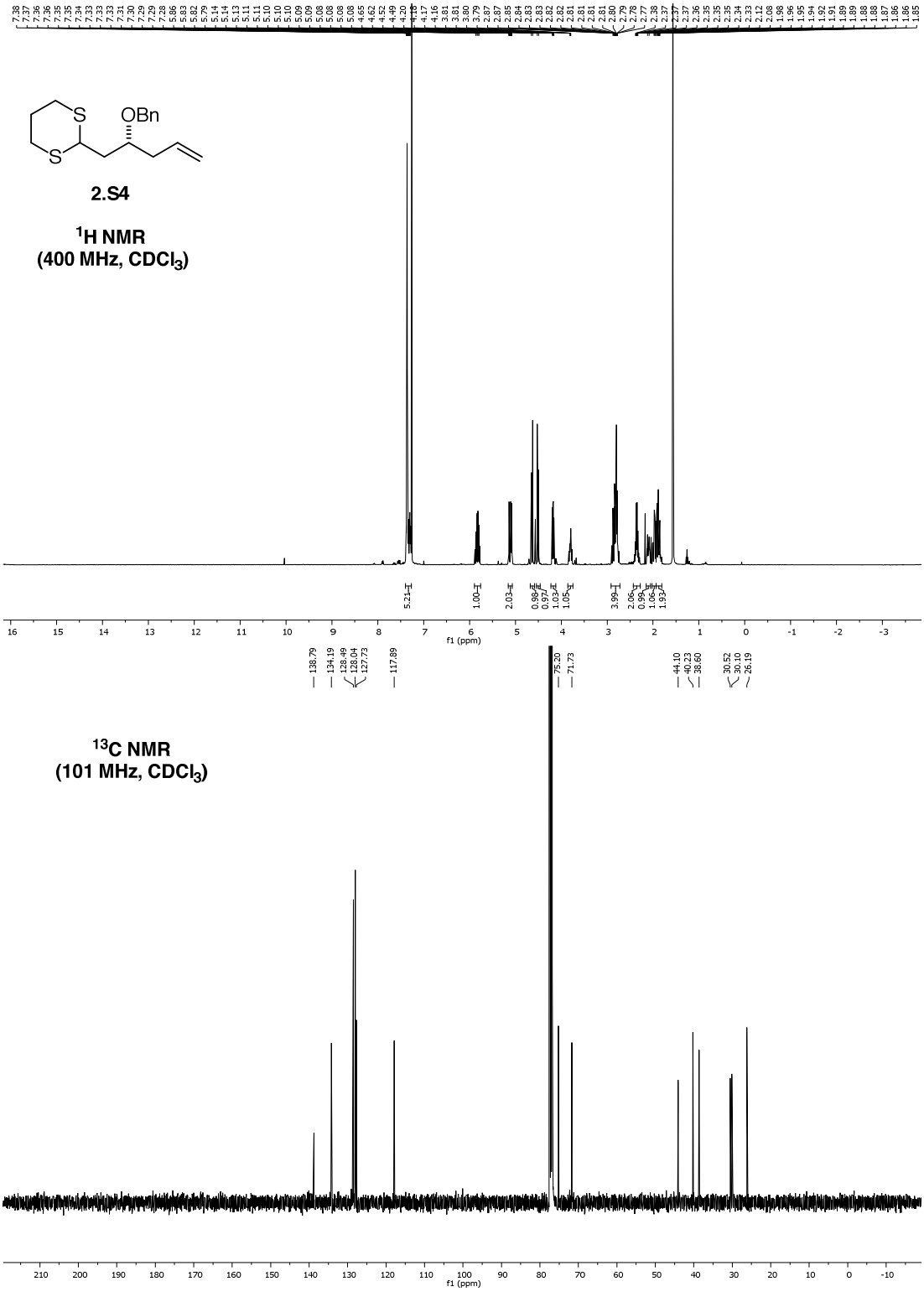
^{13}C NMR
(101 MHz, $CDCl_3$)

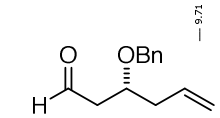



MeO
OBn
OBn
OMe
HO
N2
2.34
1H NMR
(599 MHz, CDCl3)


13C NMR
(151 MHz, CDCl3)


2.41
^{1}H NMR
(599 MHz, CDCl$_3$)
^{13}C NMR
(151 MHz, CDCl$_3$)
f1 (ppm)

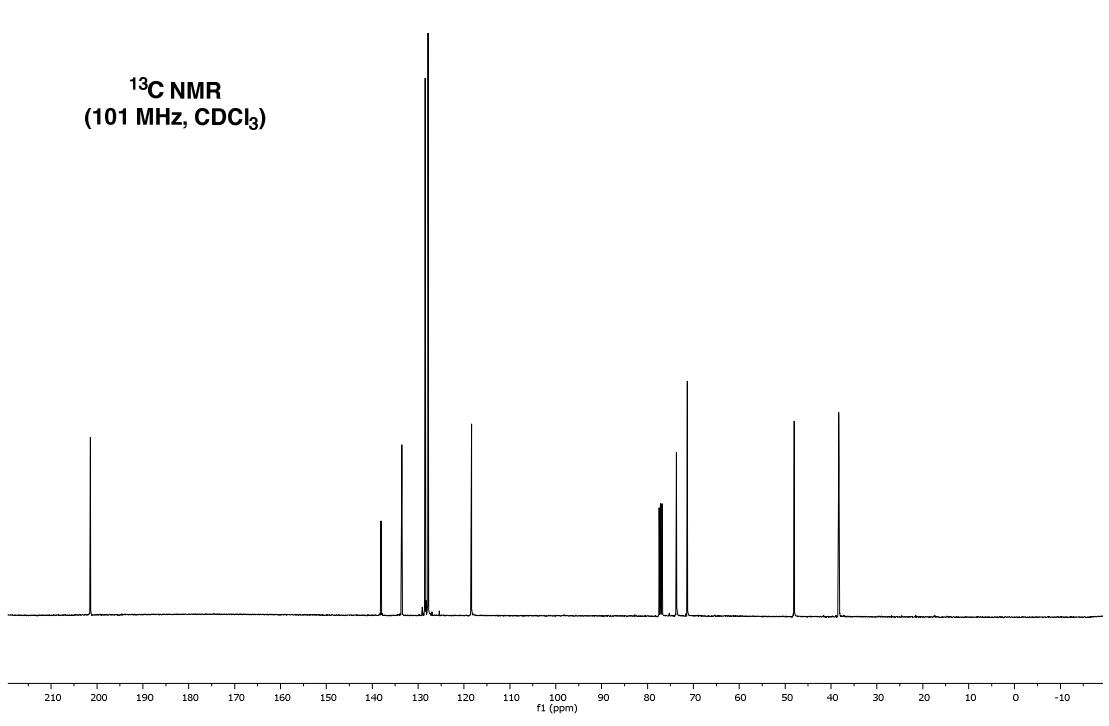

OBn
S
S
2.S4
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)

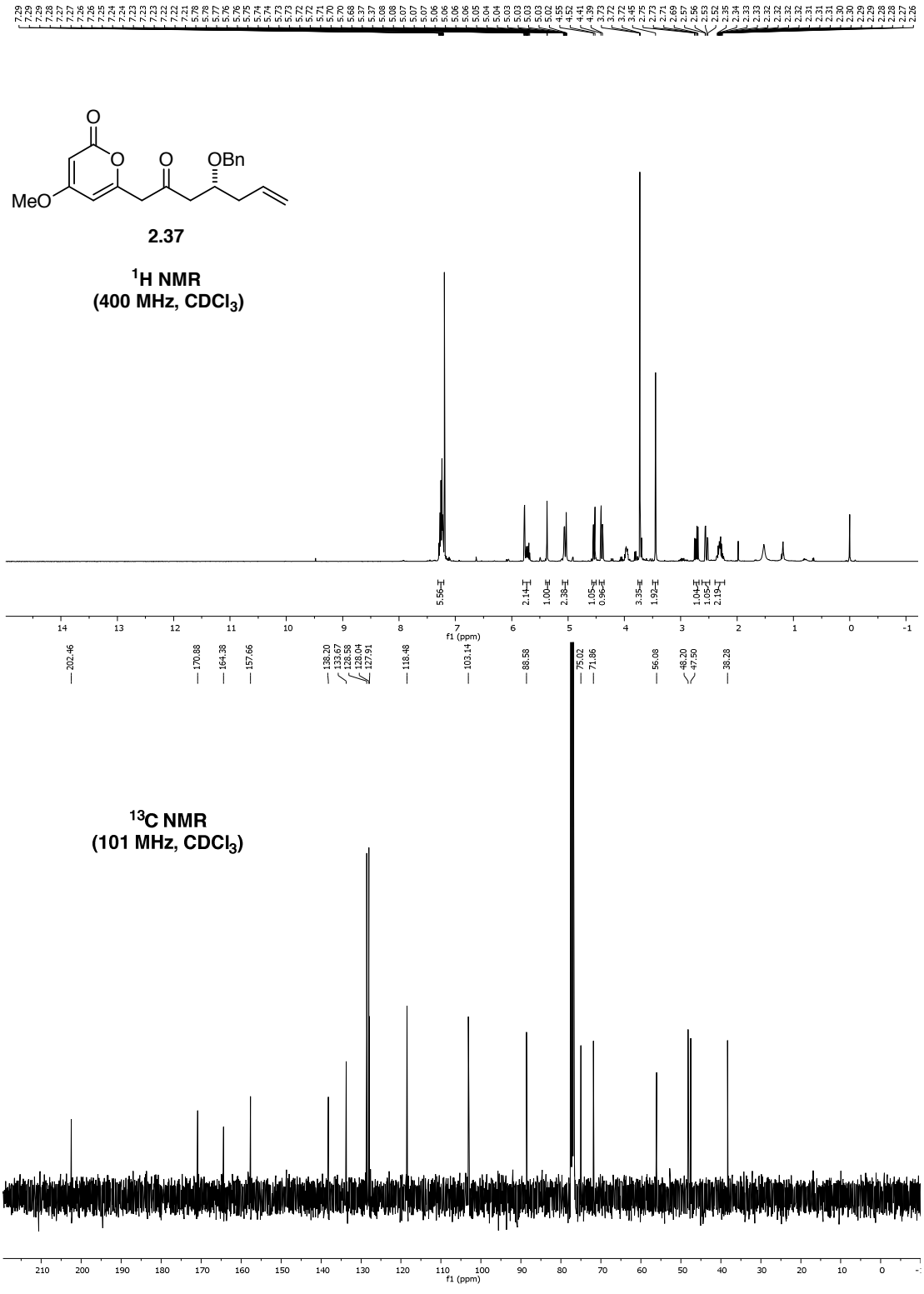


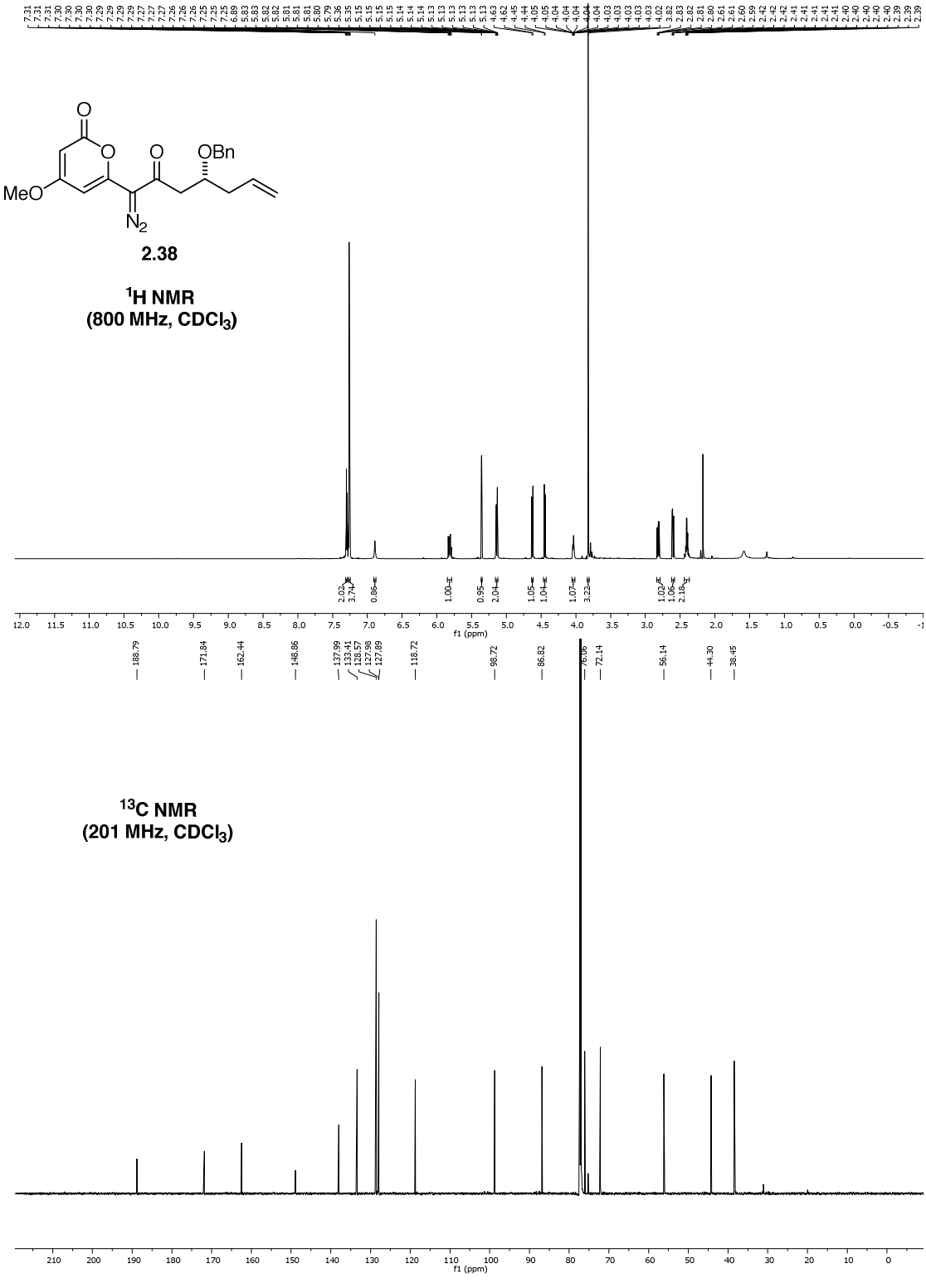
2.36

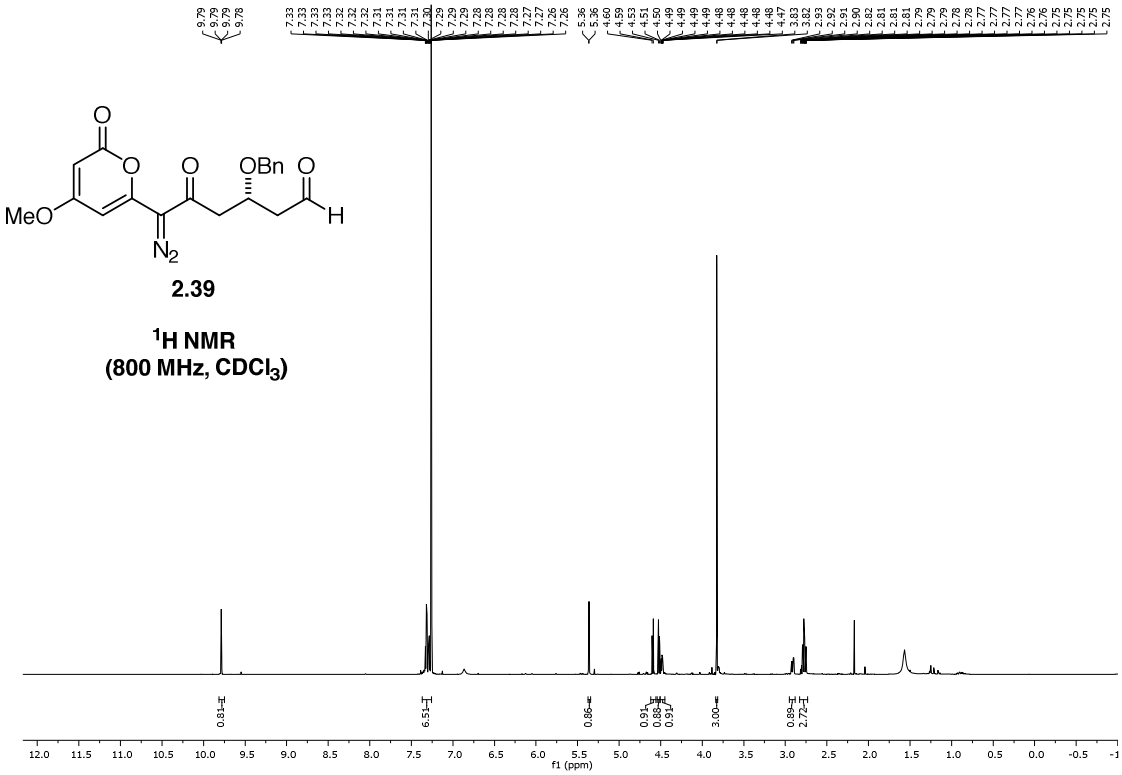
^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)



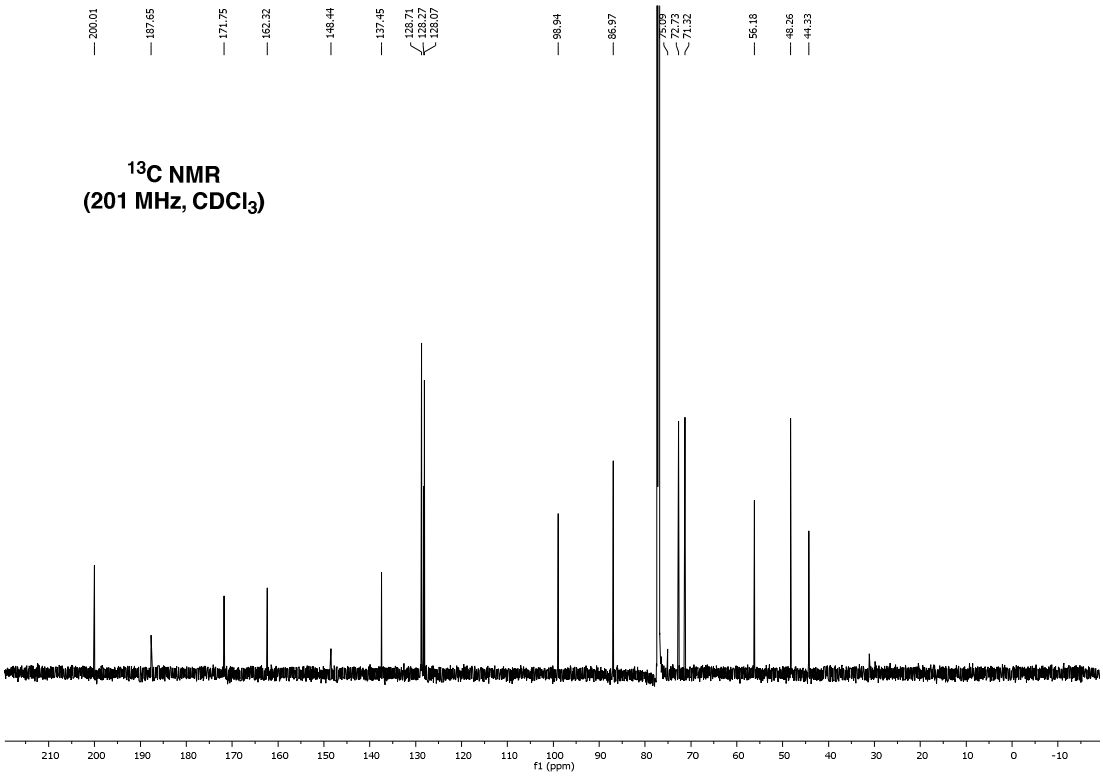

MeO
OBn
2.37
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)


MeO
OBn
N2
2.38
1H NMR
(800 MHz, CDCl3)
13C NMR
(201 MHz, CDCl3)
f1 (ppm)

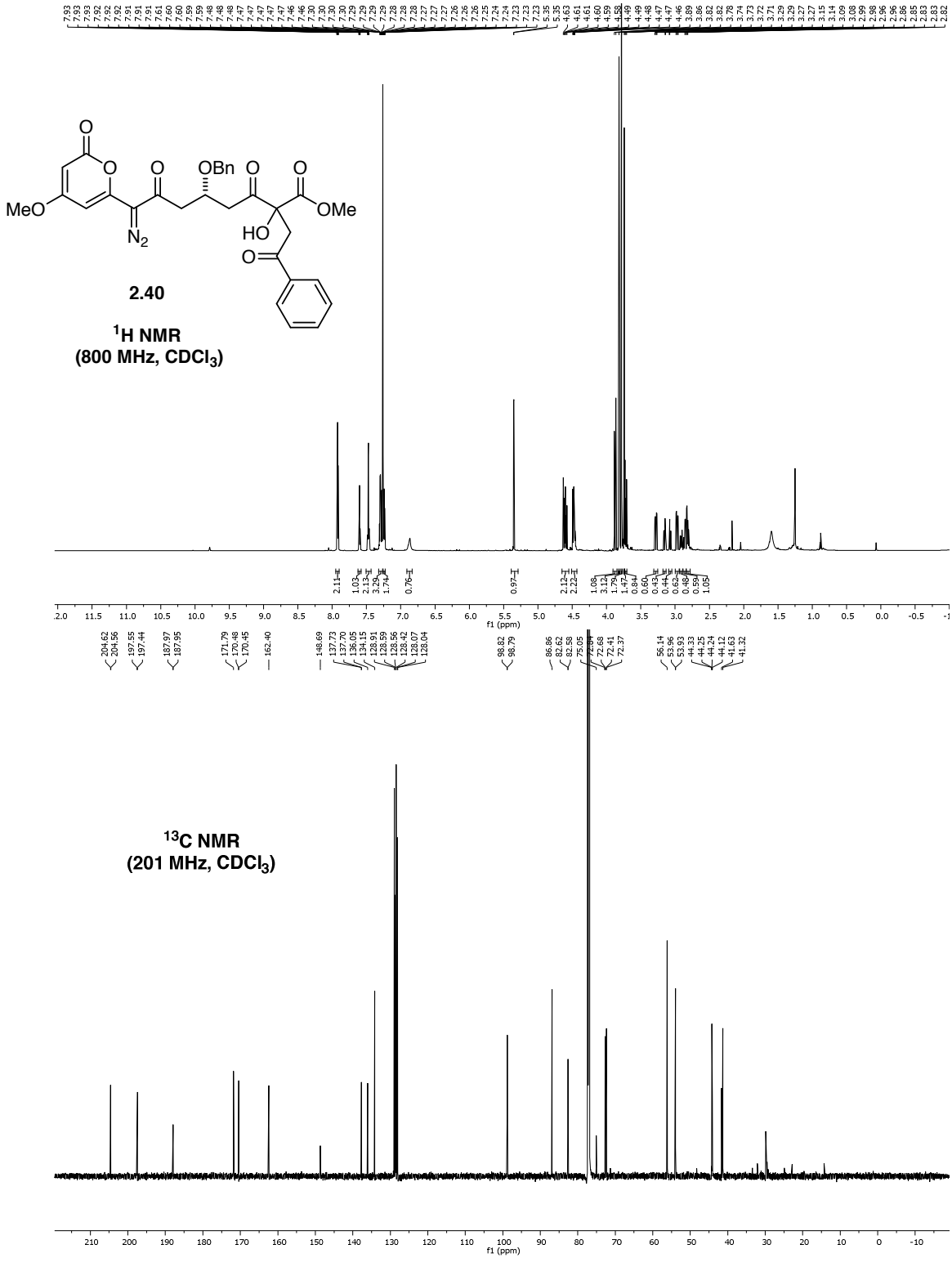


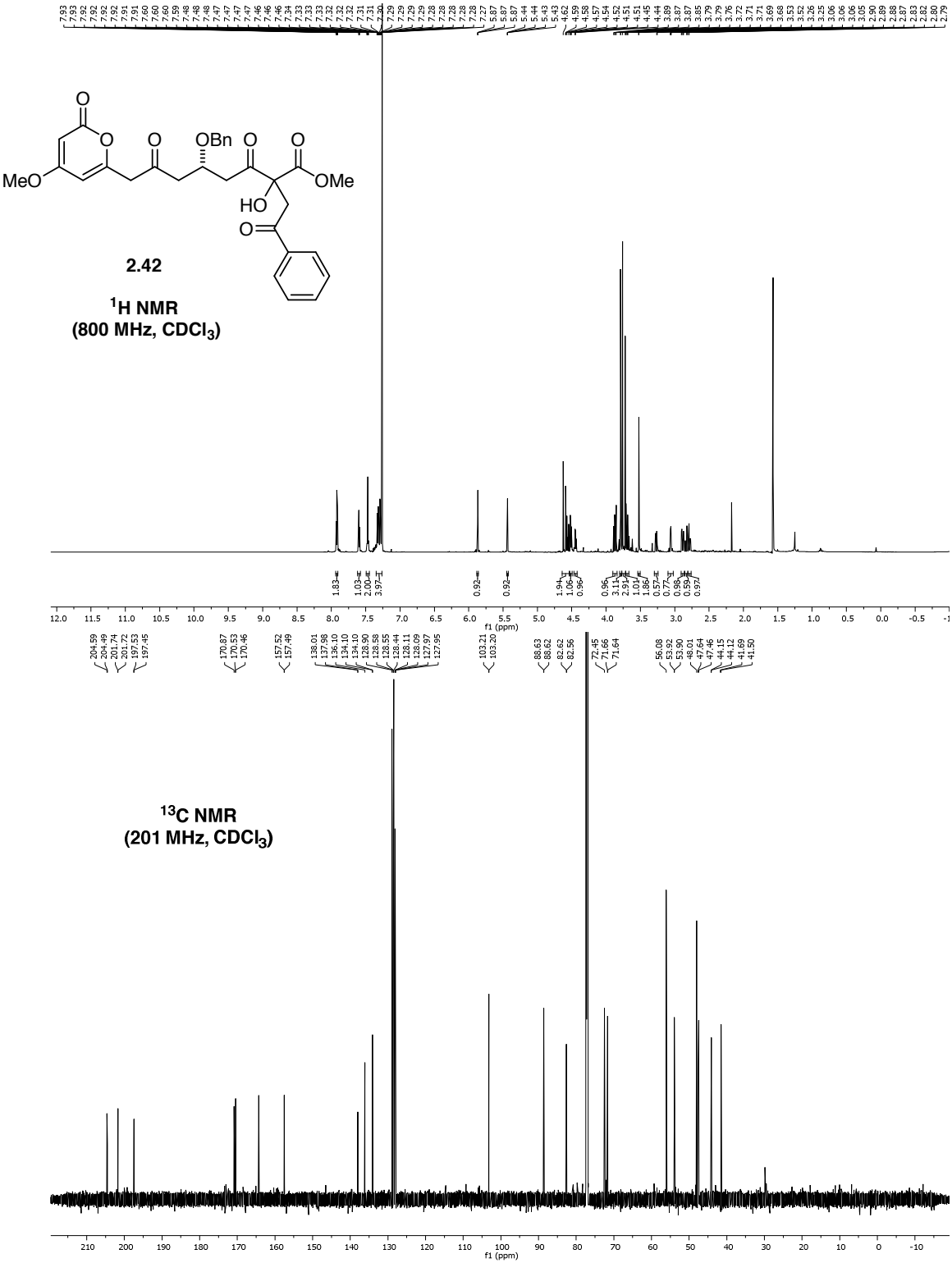
2.39

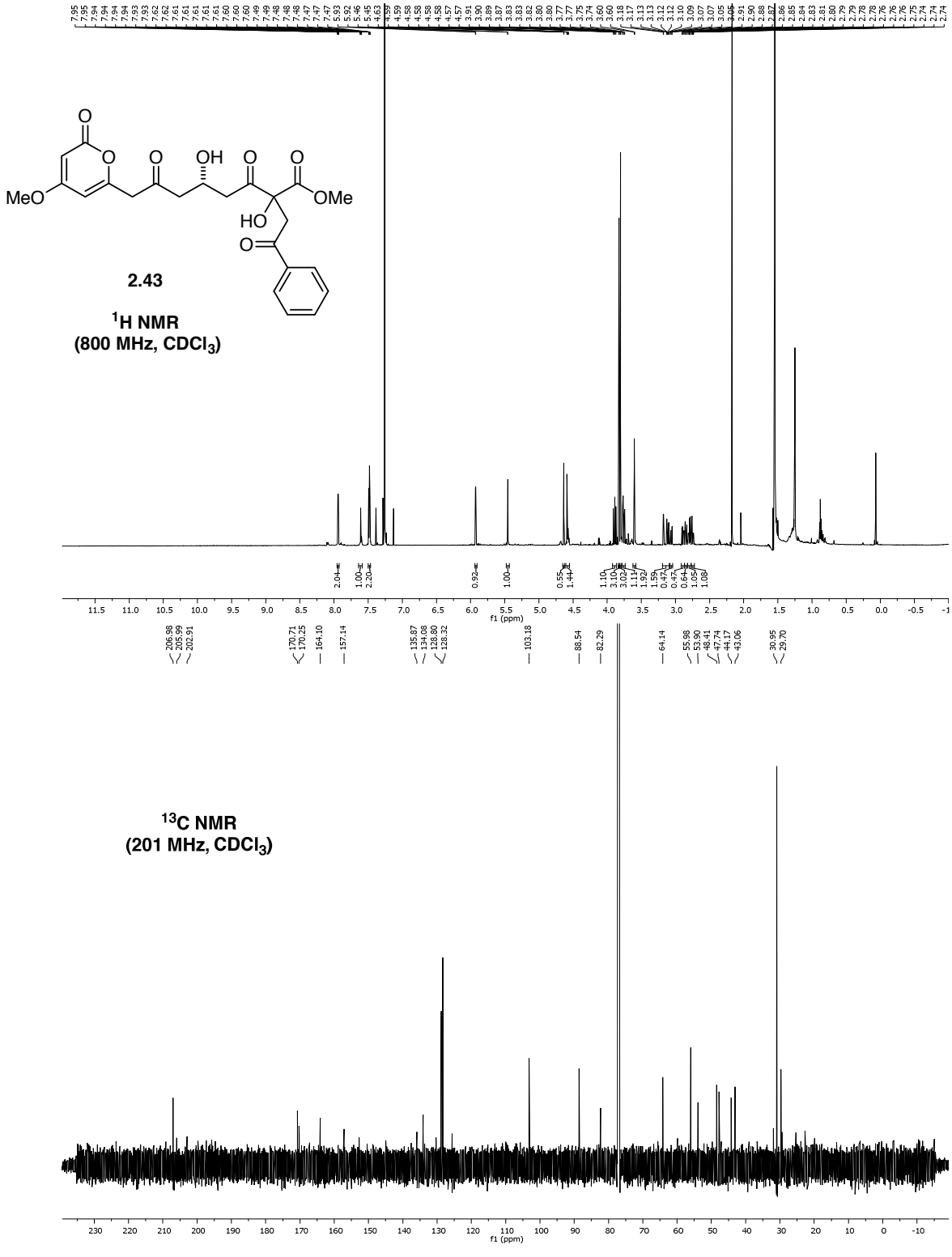
^{1}H NMR
(800 MHz, $CDCl_3$)

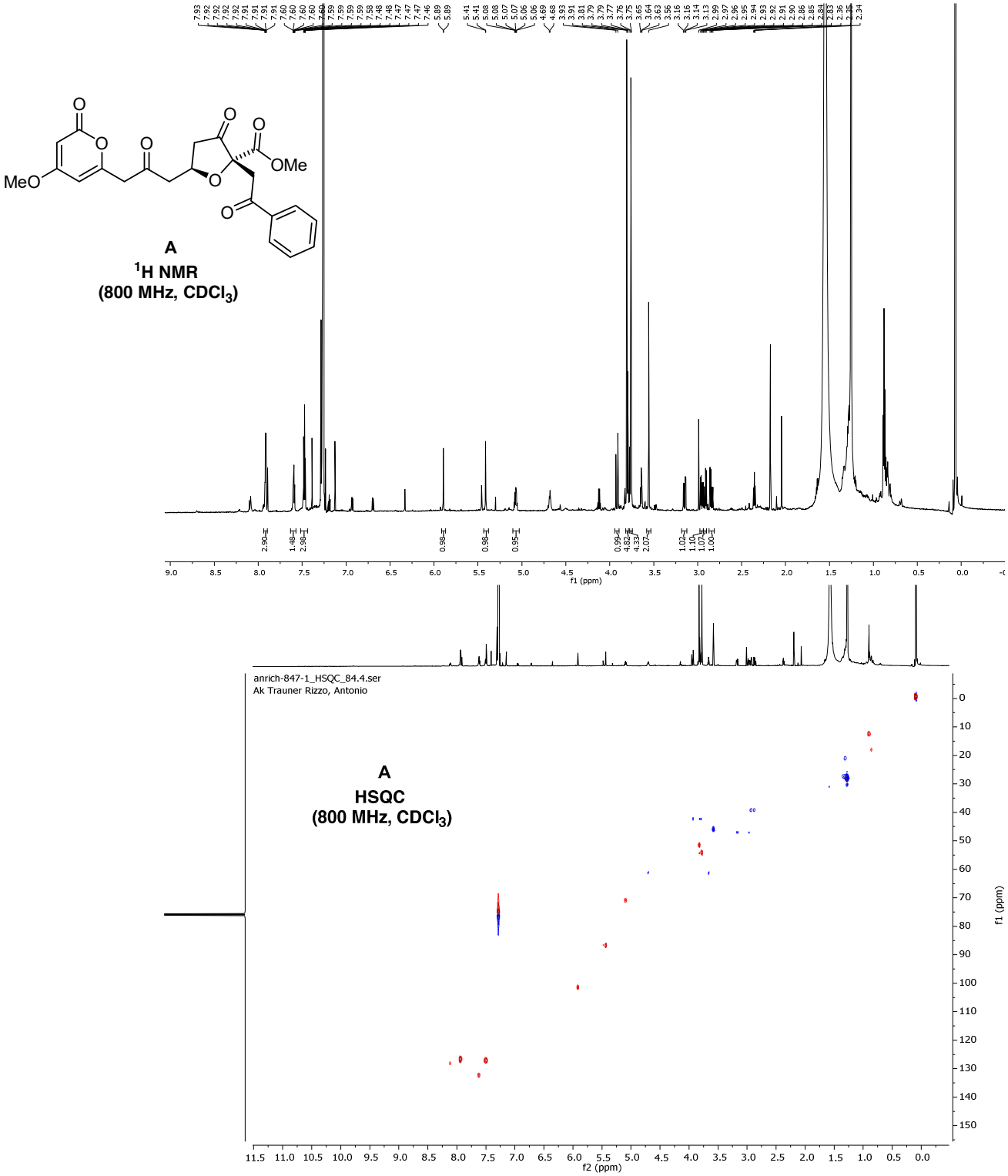


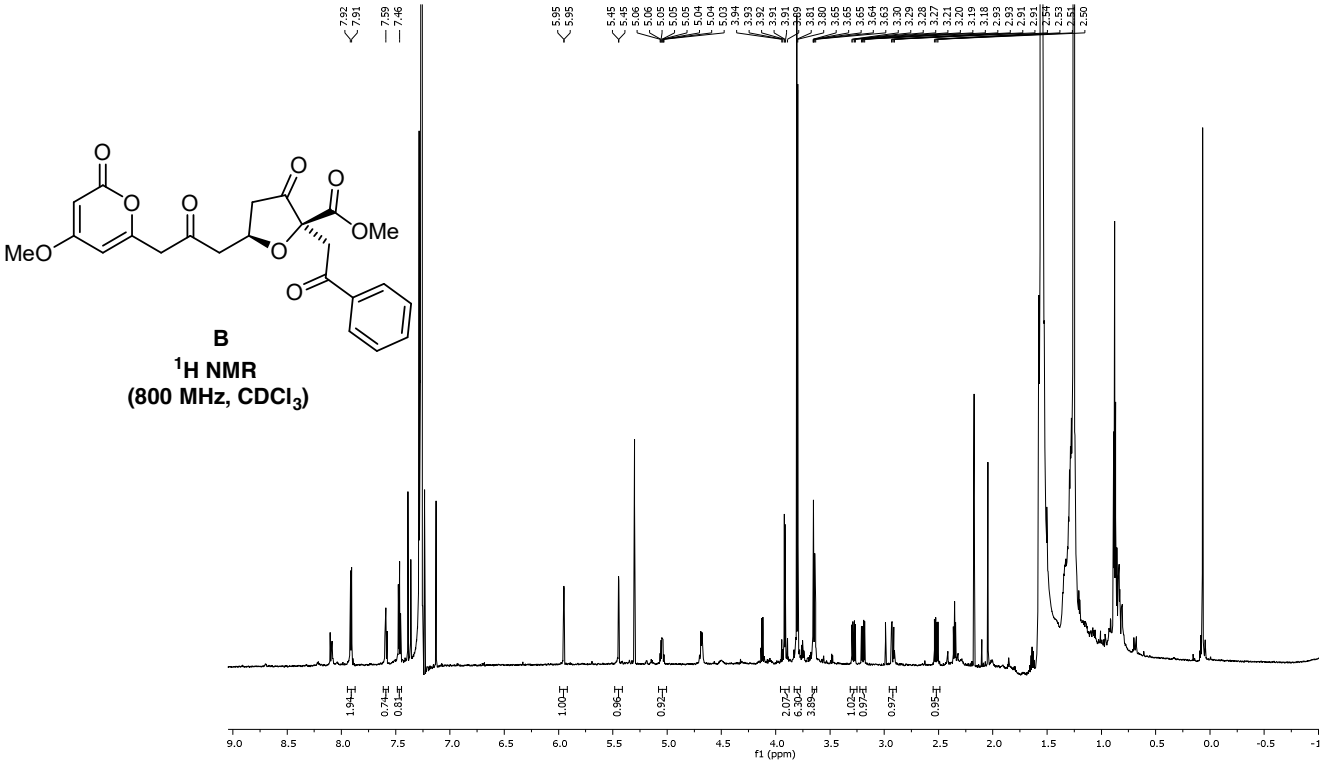
^{13}C NMR
(201 MHz, $CDCl_3$)

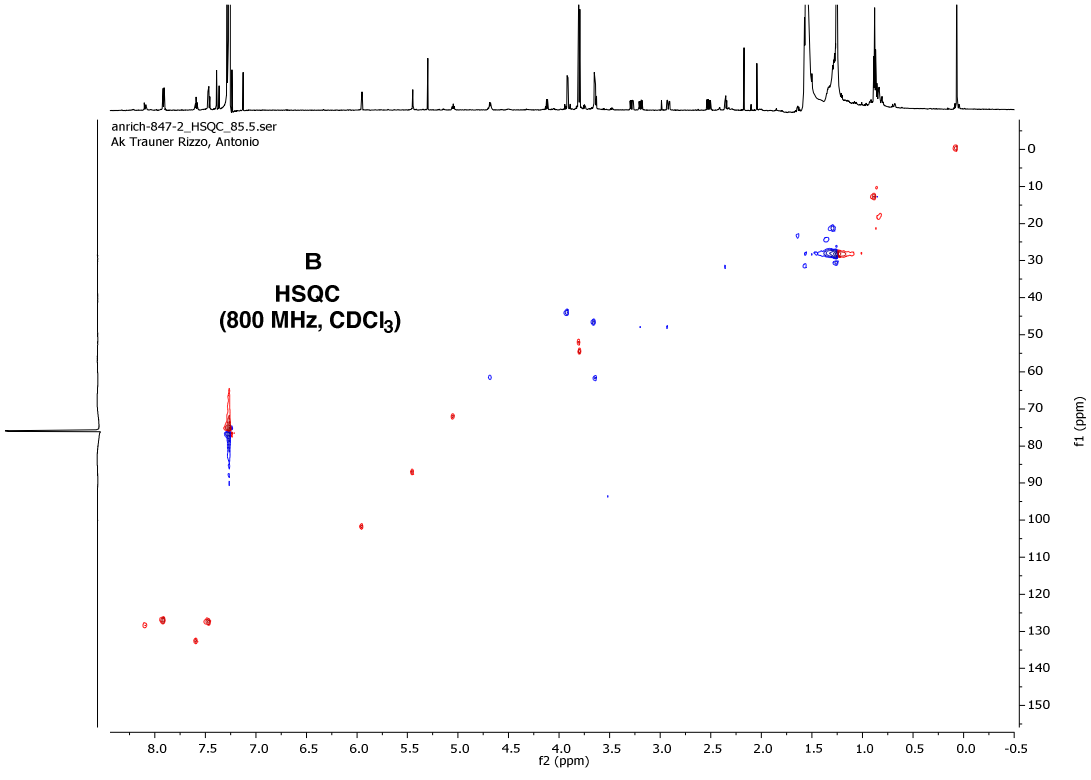

MeO
OBn
OMe
HO
N2
2.40
1H NMR
(800 MHz, CDCl3)
f1 (ppm)
13C NMR
(201 MHz, CDCl3)
f1 (ppm)

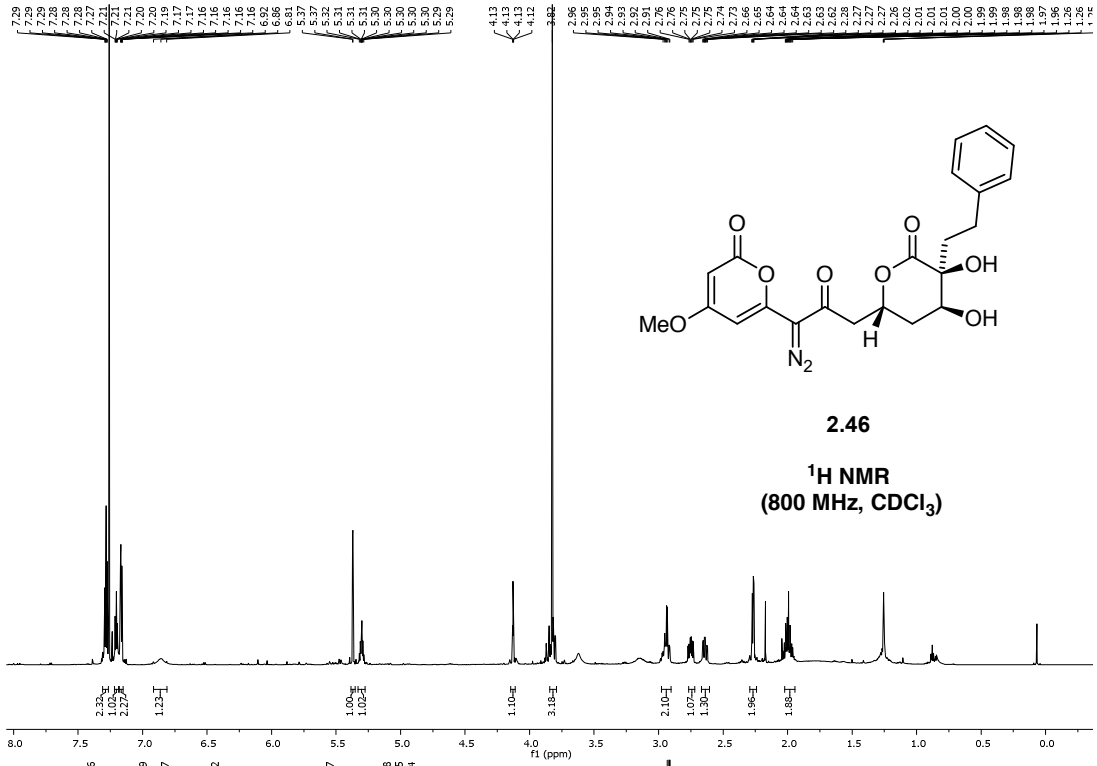

MeO
OBn
OMe
HO
2.42
^{1}H NMR
(800 MHz, CDCl$_3$)
^{13}C NMR
(201 MHz, CDCl$_3$)
f1 (ppm)


MeO
OMe
HO
OH
2.43
^{1}H NMR
(800 MHz, CDCl$_3$)
^{13}C NMR
(201 MHz, CDCl$_3$)
f1 (ppm)


A
^{1}H NMR
(800 MHz, $CDCl_3$)
f1 (ppm)
anrich-847-1_HSQC_84.4.ser
Ak Trauner Rizzo, Antonio
A
HSQC
(800 MHz, $CDCl_3$)
f2 (ppm)
f1 (ppm)

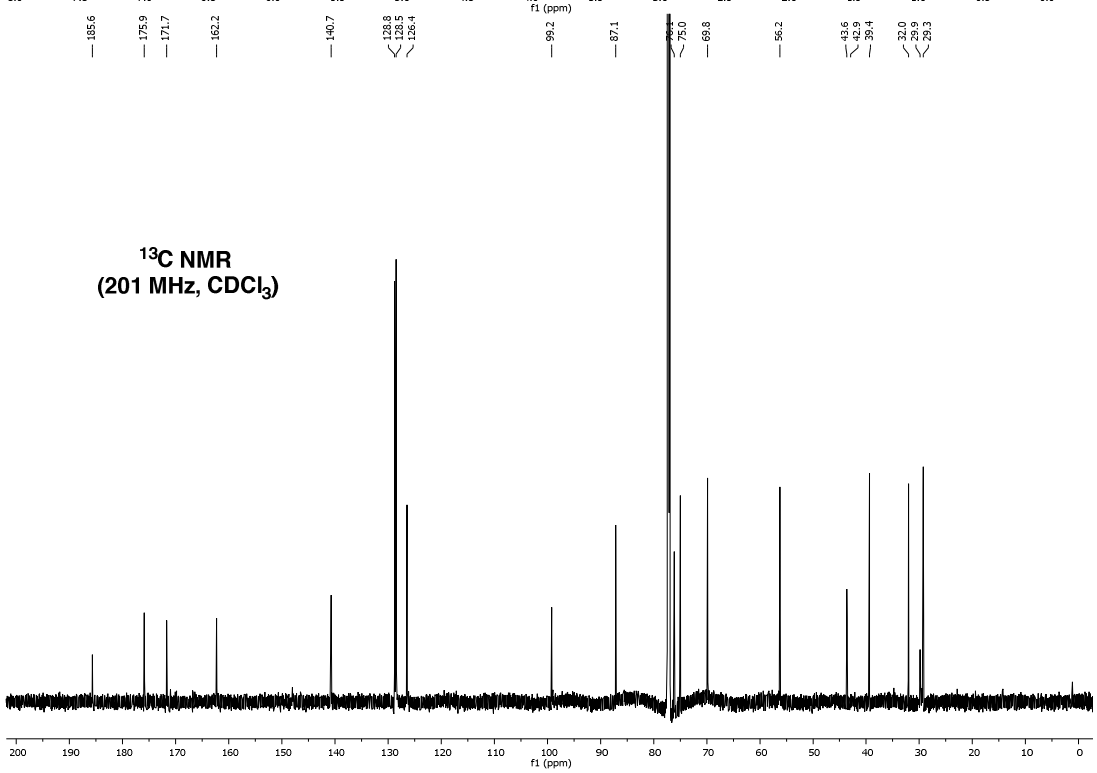

MeO
OMe
B
^{1}H NMR
(800 MHz, CDCl$_3$)
f1 (ppm)


anrich-847-2_HSQC_85.5.ser
Ak Trauner Rizzo, Antonio
B
HSQC
(800 MHz, CDCl$_3$)
f2 (ppm)
f1 (ppm)

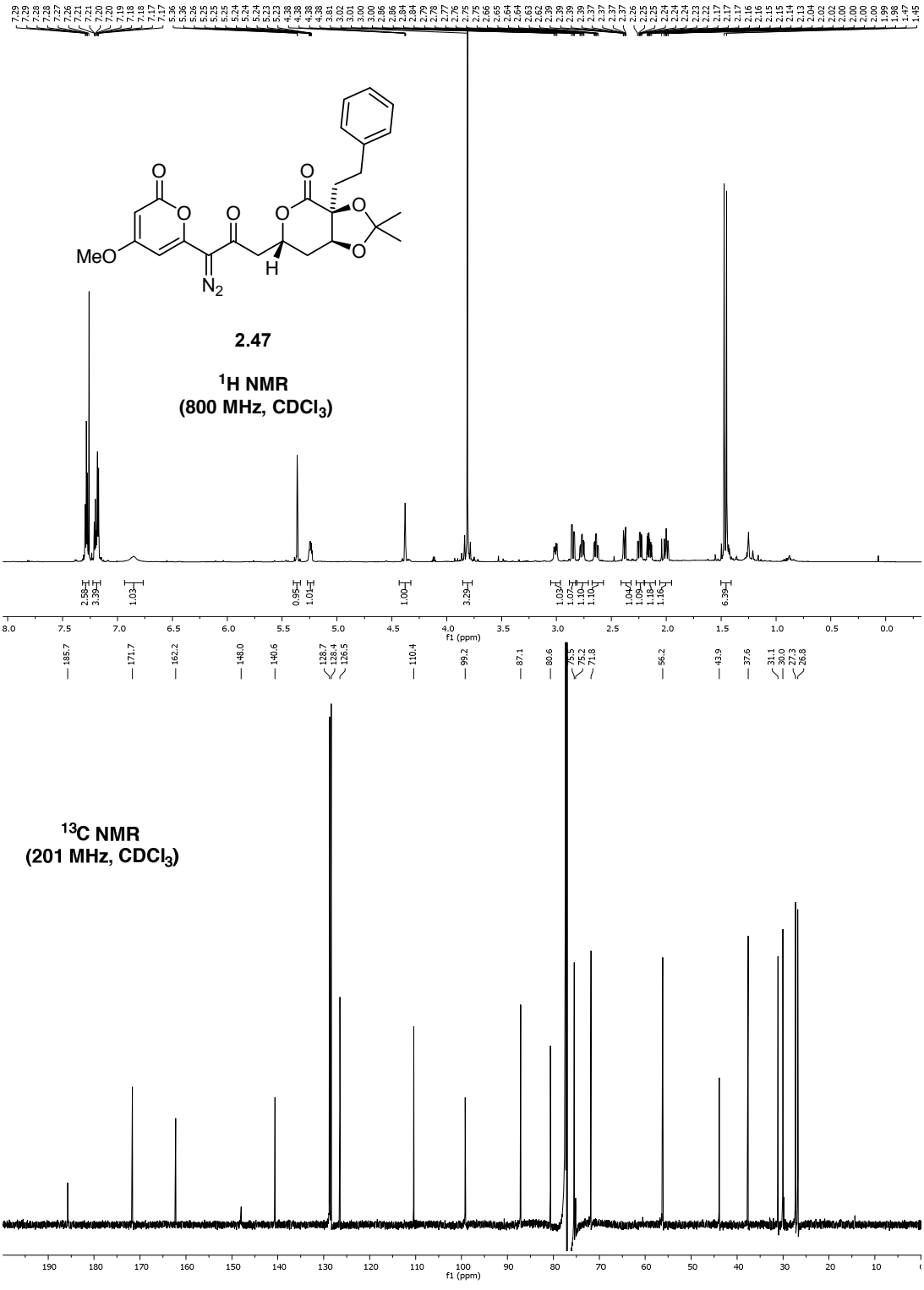


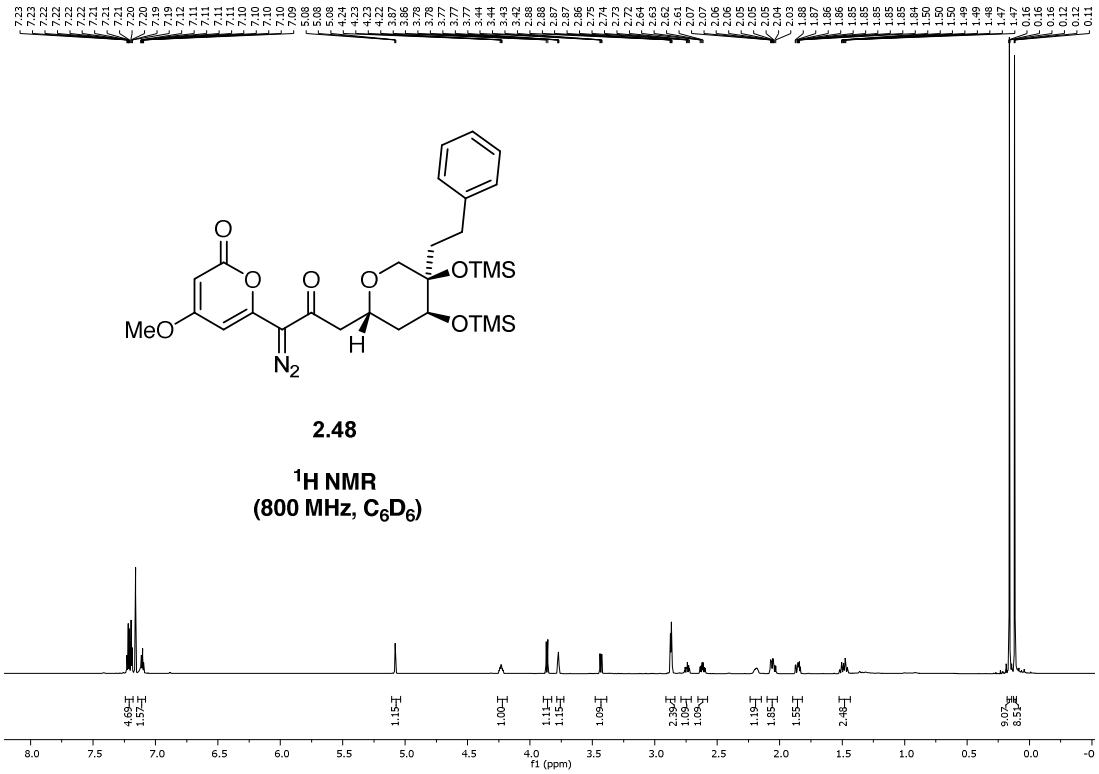
2.46

^{1}H NMR
(800 MHz, $CDCl_3$)



^{13}C NMR
(201 MHz, $CDCl_3$)

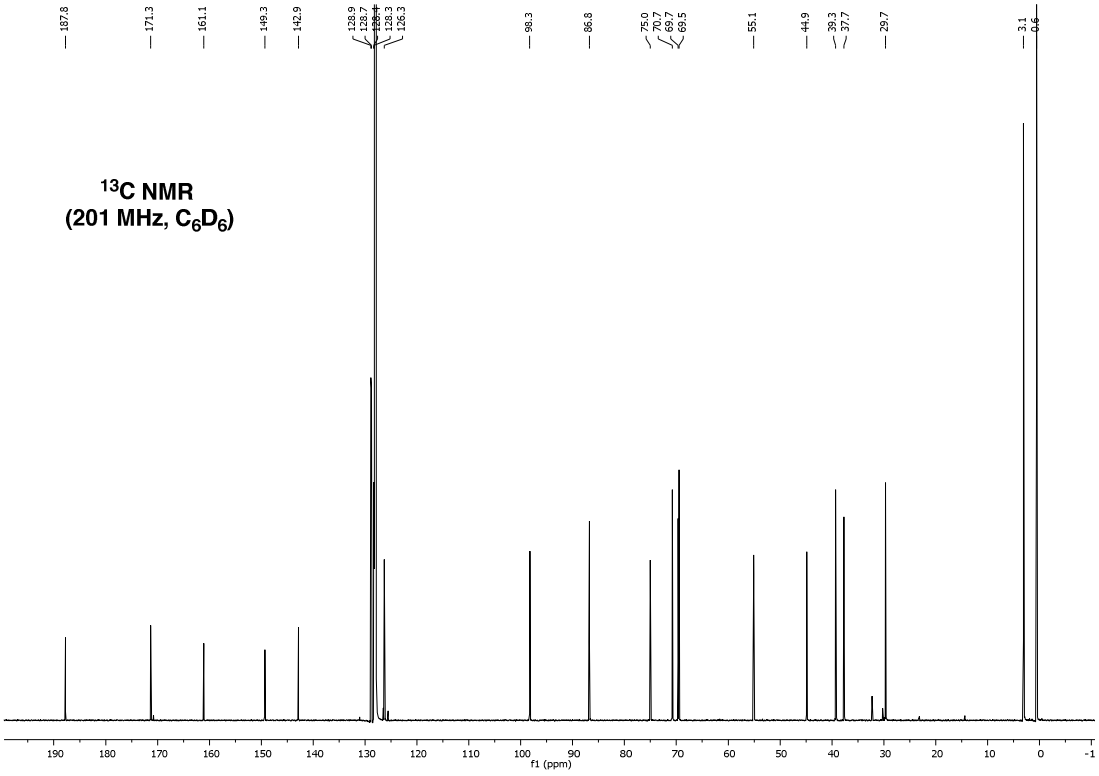

MeO
N2
H
2.47
1H NMR
(800 MHz, CDCl3)
13C NMR
(201 MHz, CDCl3)
f1 (ppm)

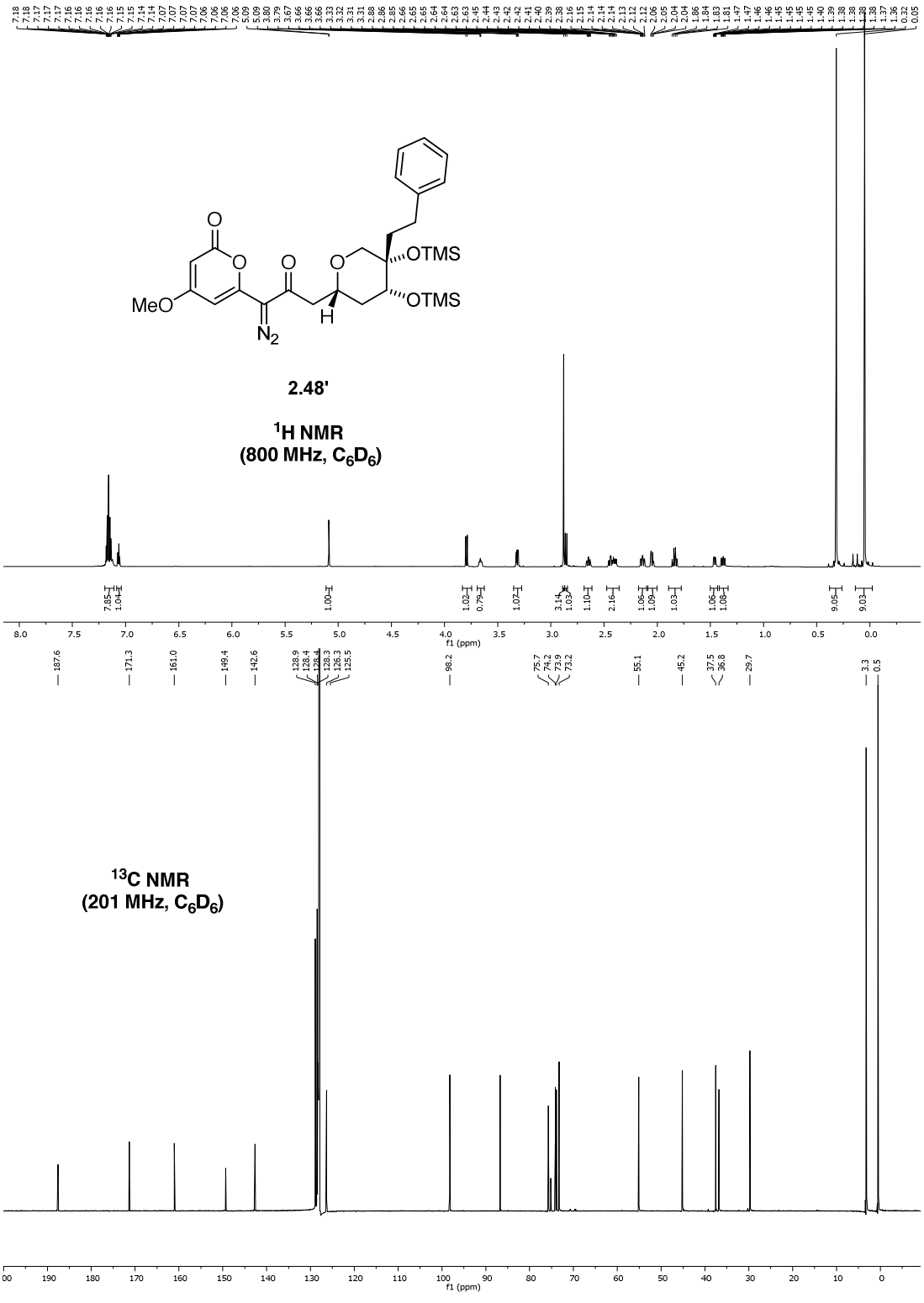


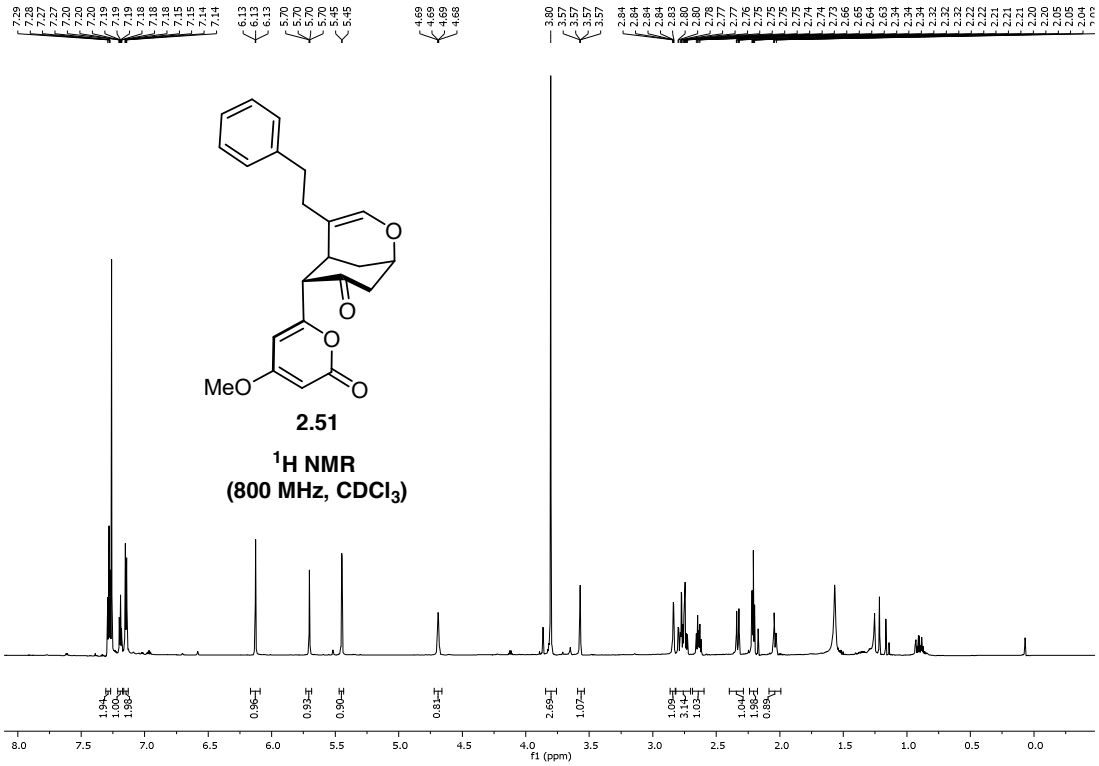
2.48

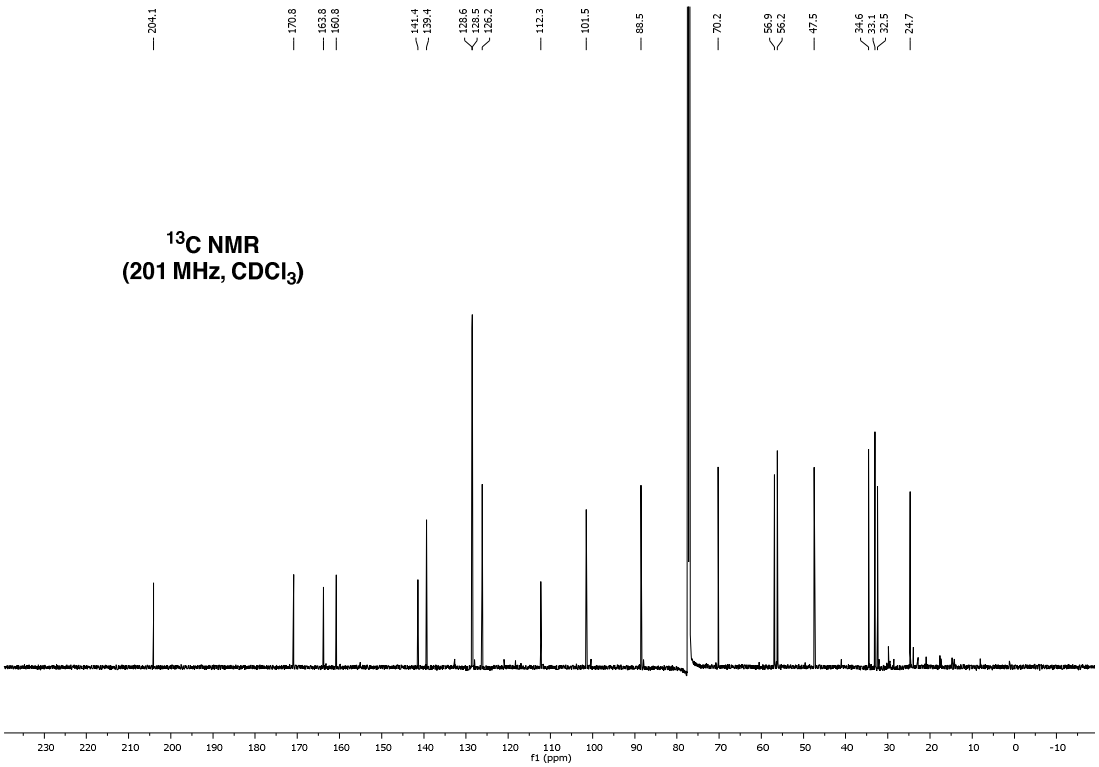
^{1}H NMR
(800 MHz, C_6D_6)

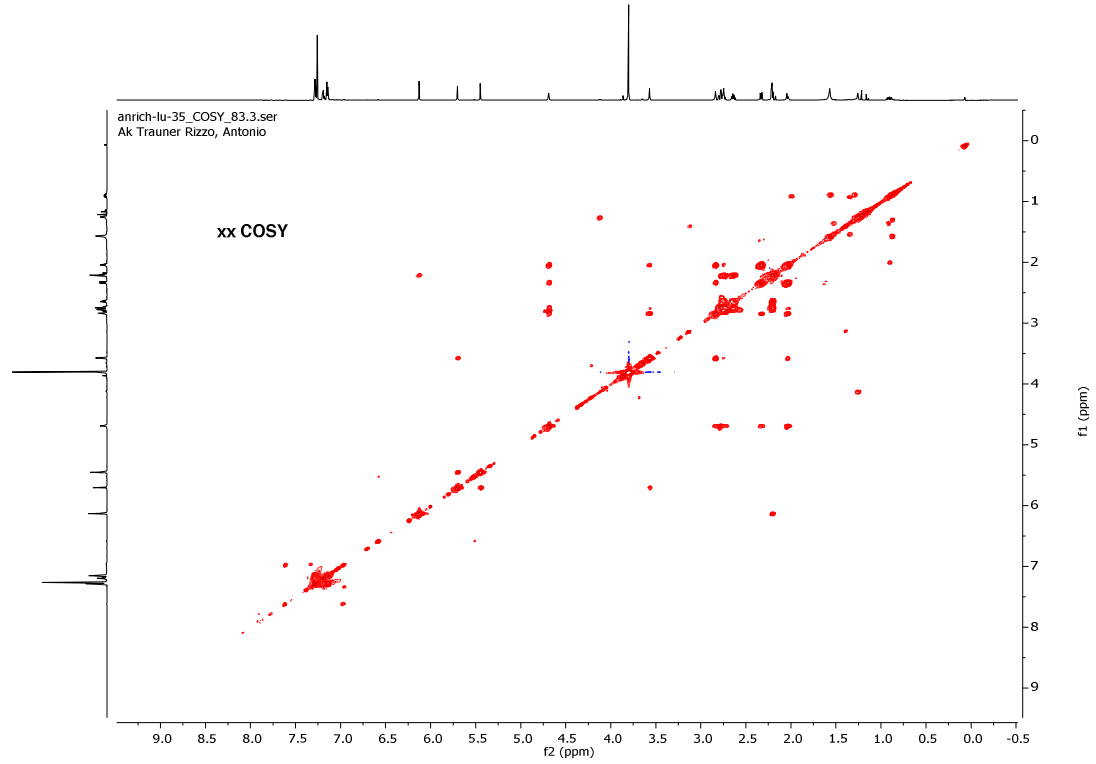
^{13}C NMR
(201 MHz, C_6D_6)

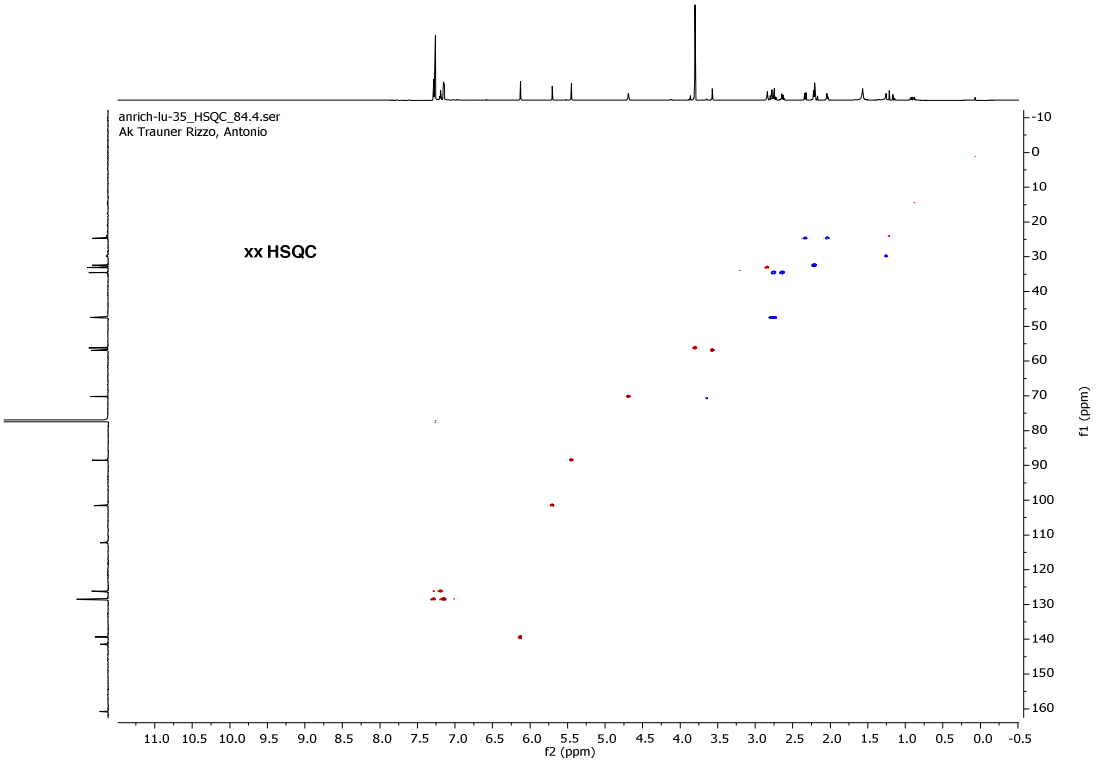


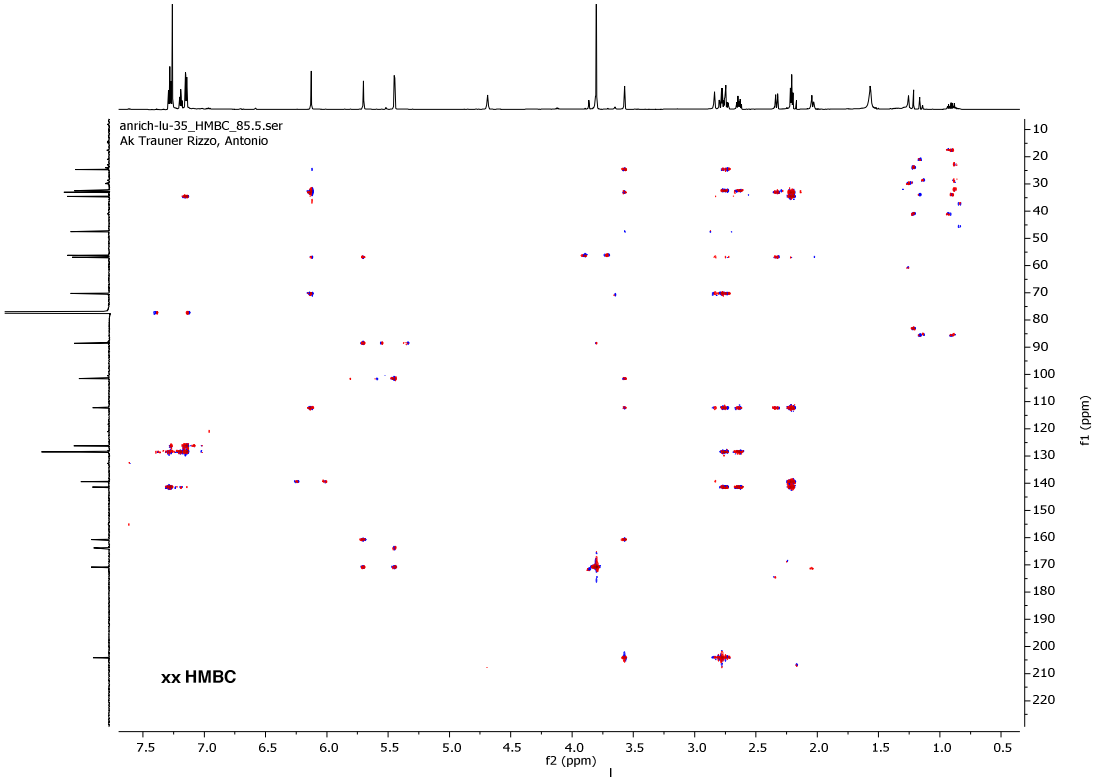

OTMS
OTMS
MeO
H
N_2
2.48'
^{1}H NMR
(800 MHz, C_6D_6)
f1 (ppm)
^{13}C NMR
(201 MHz, C_6D_6)
f1 (ppm)

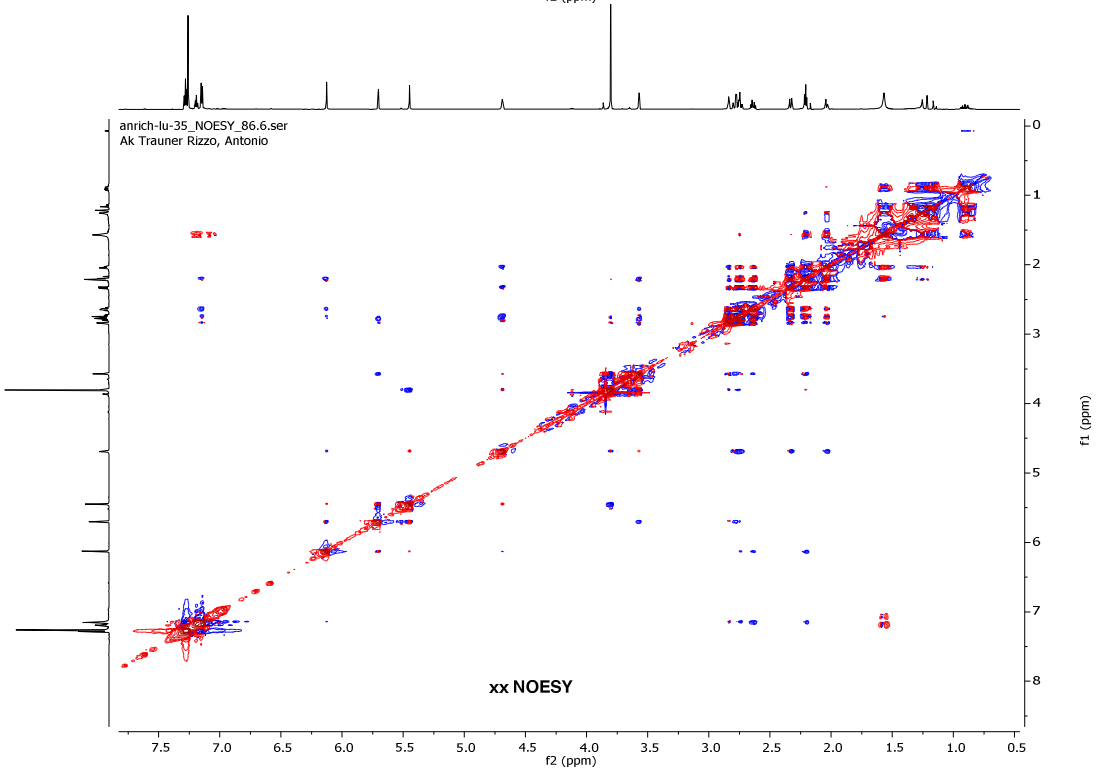

MeO
O
O
O
O
2.51
^{1}H NMR
(800 MHz, CDCl$_3$)
f1 (ppm)


^{13}C NMR
(201 MHz, CDCl$_3$)
f1 (ppm)


anrich-lu-35_COSY_83.3.ser
Ak Trauner Rizzo, Antonio
xx COSY
f2 (ppm)
f1 (ppm)

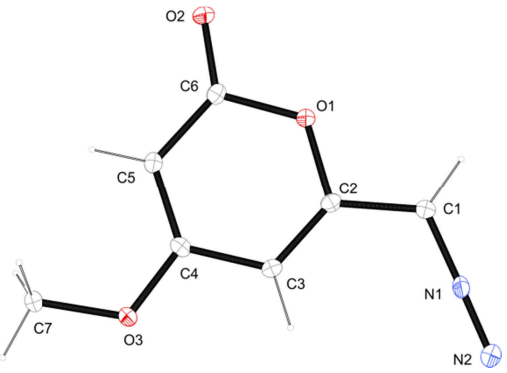

anrich-lu-35_HSQC_84.4.ser
Ak Trauner Rizzo, Antonio
xx HSQC
f2 (ppm)
f1 (ppm)


anrich-lu-35_HMBC_85.5.ser
Ak Trauner Rizzo, Antonio
xx HMBC
f2 (ppm)
f1 (ppm)


anrich-lu-35_NOESY_86.6.ser
Ak Trauner Rizzo, Antonio
xx NOESY
f2 (ppm)
f1 (ppm)

6.2.4 X-ray Data for Chapter 2.1

Diazo-**2.13**



ORTEP of the molecular structure of diazo-pyrone **2.13**.

CCDC 1817801 contains the supplementary crystallographic data for diazo-pyrone **2.13**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table.

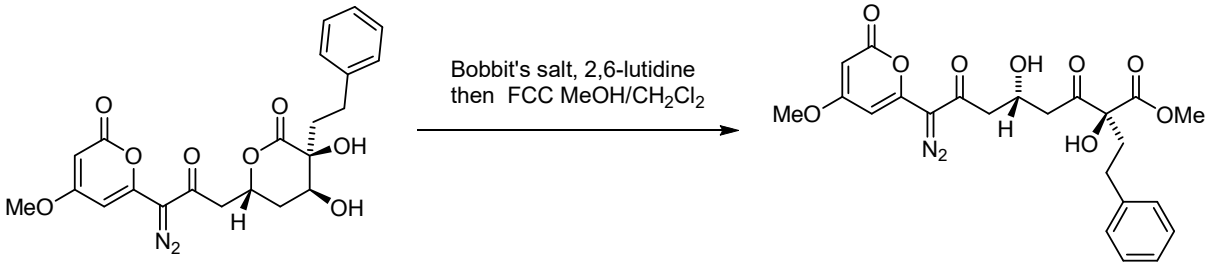
net formula	$C_7H_6N_2O_3$
M_r/g mol^{-1}	166.14
crystal size/mm	0.100 × 0.030 × 0.030
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	'P -1'
a/Å	3.7834(3)
b/Å	9.5523(6)
c/Å	10.0933(7)
α/°	80.562(2)
β/°	80.636(2)
γ/°	80.130(2)
V/Å^3	351.09(4)
Z	2

calc. density/g cm^{-3}	1.572
μ/mm^{-1}	0.126
absorption correction	multi-scan
transmission factor range	0.8994–0.9585
refls. measured	5996
R_{int}	0.0256
mean $\sigma(I)/I$	0.0228
θ range	3.211–26.40
observed refls.	1191
x, y (weighting scheme)	0.0466, 0.0901
hydrogen refinement	constr
refls in refinement	1426
parameters	110
restraints	0
$R(F_{obs})$	0.0320
$R_w(F^2)$	0.0902
S	1.083
$shift/error_{max}$	0.001
max electron density/e $Å^{-3}$	0.218
min electron density/e $Å^{-3}$	−0.182

6.3. Supporting Information for Chapter 2.2.

6.3.1 Experimental Procedures for Chapter 2.2

Data for methanolysed lactone **(2.56)**



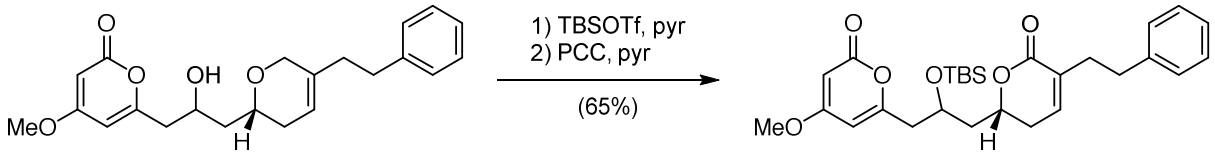
2.46 **2.56**

HRMS-ESI (m/z): calc. for $C_{23}H_{28}N_3O_9$ $[M+NH_4]^+$: 490.18201; found: 490.18235.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (dt, *J* = 6.7, 1.2 Hz, 2H), 7.24 – 7.14 (m, 3H), 6.85 (s, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 4.53 (dt, *J* = 7.6, 3.9 Hz, 1H), 4.21 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.20 (s, 1H), 2.99 (dd, *J* = 17.8, 8.2 Hz, 1H), 2.82 – 2.53 (m, 5H), 2.39 (ddd, *J* = 13.9, 10.6, 5.7 Hz, 1H), 2.28 – 2.16 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.64, 171.71, 171.20, 162.29, 140.64, 128.73, 128.63, 126.43, 98.98, 87.01, 84.05, 64.89, 56.19, 53.90, 44.95, 43.38, 37.14, 29.59.

Lactone (**2.60**)



2.59 **2.60**

A flame dried flask under argon was charged sequentially with crude alcohol **2.59** (3.85 g, 10.4 mmol, 1.0 eq.), dry CH_2Cl_2 (100 mL), pyridine (2.17 mL, 27.0 mmol, 2.6 eq.) and the reaction vessel was cooled to 0 °C. Neat TBSOTf (3.10 mL, 13.5 mmol, 1.3 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:3) to afford TBS ether (4.5 g, 9.2 mmol, 89%) as a yellow oil.

R_f: 0.3, *i*-hex:EtOAc 2:8, CAM, UV

A flame dried flask under argon was charged with 4 Å MS (4.0 g), TBS ether (2.0 g, 4.25 mmol, 1.0 eq.), pyridine (2.0 mL, 25.5 mmol, 6.0 eq.), PCC (3.66 g, 17.0 mmol, 4.0 eq.) and dry CH_2Cl_2 (42.5 mL). The mixture was heated at 40 °C and was monitored by TLC until completion (ca. 20 h, after 12 h 3.7 g of PCC were added). Afterwards, the reaction was cooled to RT and celite was added. This mixture was poured into a cake of celite impregnated with EtOAc, filtered and the cake washed with more EtOAc. The solvent was removed under reduced and the residue passed through a silica pad (EtOAc/*i*hex 3:6) to afford the lactone **2.60** (1.38 g, 2.77 mmol, 65%) which was used in the next step without further purification.

R_f: 0.5, *i*hex:EtOAc 4:6, CAM, UV.

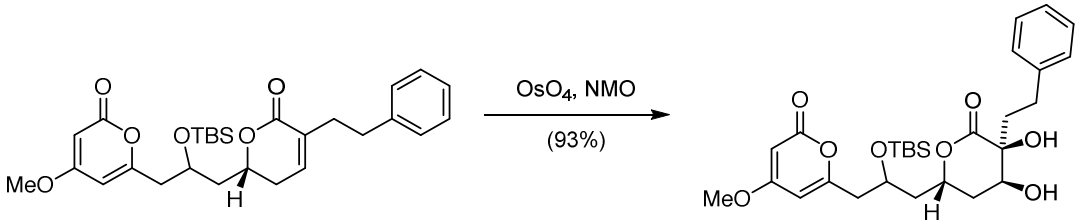
HRMS-ESI (m/z): calc. for $C_{28}H_{39}O_6Si$ $[M+H]^+$: 499.25104; found: 499.25138.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.26 (m, 3H), 7.23 – 7.11 (m, 2H), 6.47 – 6.39 (m, 1H), 5.91 (d, *J* = 2.2 Hz, 0.5H), 5.84 (d, *J* = 2.3 Hz, 0.5H), 5.42 (t, *J* = 2.1 Hz, 1H), 4.60 (ddd, *J* = 14.8, 8.7, 4.6 Hz, 0.5H), 4.50 – 4.38 (m, 0.5H), 4.33 (tdd, *J* = 9.0, 6.3, 3.9 Hz, 1H), 3.79 (d, *J* = 0.7 Hz, 3H), 2.92 – 2.40

(m, 6H), 2.37 – 2.16 (m, 2H), 2.08 – 1.86 (m, 1H), 1.80 – 1.64 (m, 1H), 1.57 (s, 1H), 0.93 – 0.80 (m, 9H), 0.11 – -0.09 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.30, 171.09, 165.17, 165.05, 164.94, 164.80, 162.25, 161.94, 141.26, 139.58, 139.26, 131.90, 131.88, 128.72, 128.49, 128.47, 126.16, 126.13, 102.70, 102.43, 88.16, 88.02, 77.36, 74.12, 66.55, 66.18, 56.02, 42.53, 42.49, 41.75, 41.52, 34.65, 34.59, 33.02, 32.93, 30.40, 30.33, 25.92, 25.86, 18.09, 18.05, -4.48, -4.57, -4.59, -4.79.

Diol (**2.61**)



2.60 **2.61**

A flask was charged sequentially with the crude lactone **2.60** (0.46 g, 0.93 mmol, 1.0 eq.), THF/H_2O (5/1, 9.3 mL) and NMO (0.16 g, 1.4 mmol, 1.5 eq.). Then, OsO_4 (0.46 mL, 46.5 µmol, 0.005 eq., 2.5% in *t*-BuOH) was added and the reaction was monitored by TLC until completion (ca. 4 h). Upon complete conversion, the reaction was quenched by adding a solution of sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (MeOH/Acetone/CH_2Cl_2 2:8:90) to afford diol **2.61** (0.48 g, 0.92 mmol, 93%) as a colorless oil.

R_f: 0.3 and 0.5 (2 diasteromers), *i*hex:EtOAc 2:8, CAM, UV.

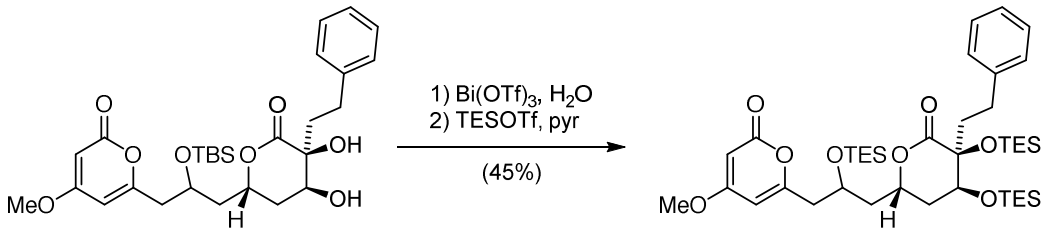
HRMS-ESI (m/z): calc. for $C_{28}H_{41}O_8Si$ $[M+H]^+$: 533.25652; found: 533.25645.

IR (ATR, neat): ν_{max} = 3446 (b), 2929 (w), 2856 (w), 1700 (s), 1648 (m), 1566 (s), 1410 (m), 1248 (s), 1082 (m), 834 (m), 727 (s), 699 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.30 – 7.19 (m, 2H), 7.20 – 7.04 (m, 3H), 5.83 (dd, *J* = 20.5, 2.3 Hz, 1H), 5.41 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.02 (ddt, *J* = 12.1, 8.1, 4.0 Hz, 1H), 4.92 (dddd, *J* = 12.0, 10.2, 3.7, 2.5 Hz, 1H), 4.36 – 4.22 (m, 1H), 4.06 (ddd, *J* = 6.1, 3.9, 1.9 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.74 (d, *J* = 8.9 Hz, 3H), 3.52 – 3.30 (m, 2H), 2.79 – 2.50 (m, 4H), 2.18 – 2.11 (m, 1H), 2.07 (dt, *J* = 14.7, 3.8 Hz, 1H), 2.01 – 1.89 (m, 3H), 1.82 (ddd, *J* = 14.4, 10.2, 3.2 Hz, 0H), 1.74 (ddd, *J* = 14.5, 6.3, 4.1 Hz, 1H), 1.64 (ddd, *J* = 14.4, 9.4, 2.5 Hz, 0H), 0.91 – 0.73 (m, 9H), -0.01 (dd, *J* = 54.3, 40.8 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.31, 176.18, 171.19, 171.04, 164.90, 164.81, 162.20, 161.85, 140.86, 128.59, 128.36, 128.34, 126.23, 102.53, 102.34, 88.07, 87.92, 75.95, 75.85, 75.00, 74.68, 69.83, 66.43, 66.08, 55.92, 53.88, 43.27, 42.93, 42.54, 39.49, 33.62, 33.42, 31.78, 30.94, 29.29, 29.16, 25.83, 25.73, 17.96, 17.90, -4.69, -4.94.

TES ether (**2.62**)



2.61 **2.62**

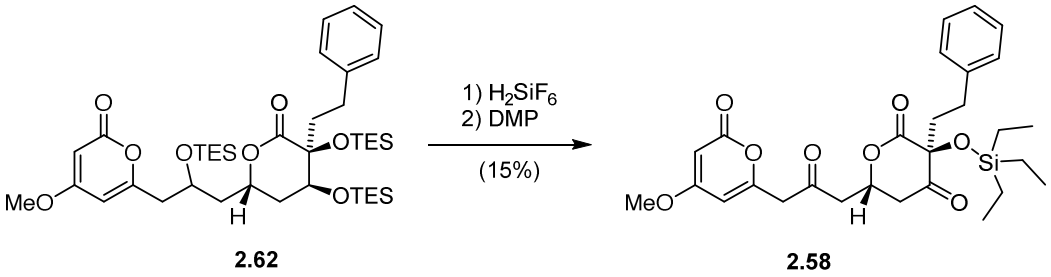
A flask was sequentially charged with diol **2.61** (0.48 g, 0.92 mmol, 1.0 eq.), dry MeCN (5.27 mL), H_2O (0.08 mL, 4.50 mmol, 5.0 eq.) and $Bi(OTf)_3$[5] (60.0 mg, 0.09 mmol, 0.1 eq.). The mixture was stirred at RT and monitored by TLC analysis until completion (ca. 4 h). Then, hexanes were added and the heterogeneous mixture was filtered over a celite plug, the plug was washed with EtOAc and the solvent concentrated under reduced pressure to afford the crude triol which was used directly in the next step without further purification.

R_f: 0.2, *i*hex:EtOAc 2:8, CAM, UV.

A flame dried flask under argon was charged sequentially with triol (0.92 mmol, 1.0 eq.), dry CH_2Cl_2 (9.2 mL), 2,6-lutidine (1.28 mL, 11.0 mmol, 12.0 eq.) and the reaction vessel was cooled to 0 °C. Neat TESOTf (1.25 mL, 5.5 mmol, 6.0 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with $CuSO_{4(aq.)}$, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:4) to afford TBS ether **2.62** (0.35 g, 4.5 mmol, 45%) as a yellow oil.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.33 – 7.30 (m, 2H), 7.27 – 7.14 (m, 4H), 5.92 (dd, *J* = 31.5, 2.1 Hz, 1H), 5.44 (dt, *J* = 19.2, 1.8 Hz, 1H), 5.04 – 4.92 (m, 1H), 4.43 – 4.27 (m, 1H), 4.19 – 4.14 (m, 1H), 3.86 – 3.77 (m, 3H), 2.90 – 2.80 (m, 1H), 2.72 – 2.57 (m, 3H), 2.09 – 1.91 (m, 3H), 1.89 – 1.77 (m, 1H), 1.76 – 1.68 (m, 1H), 1.06 – 0.57 (m, 30H).

B-Ketolactone (**2.58**)



2.62 **2.58**

A flame dried flask under argon was charged sequentially with **2.62** (100 mg, 0.13 mmol, 1.0 eq.) and dry MeCN (6.5 mL). The reaction vessel was cooled to 0 °C. A solution of H_2SiF_6 (0.17 mL, 0.31 mmol, 2.4 eq., 25% in H_2O) was added dropwise and the reaction was stirred at the same temperature. The reaction was monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was quenched by addition of a pH 7 buffer. The aqueous phase was extracted three times with EtOAc, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (CH_2Cl_2/Acetone/MeOH 90:8/2) to afford the triol (34.8 g, 0.065 mmol, 50%) as a colorless oil.

R_f: 0.3, *i*hex:EtOAc 2:8, CAM, UV.

A flame dried flask under argon was charged with triol (34.8 g, 0.065 mmol, 1 eq.), dry CH_2Cl_2 (0.65 mL) and was cooled to 0 °C. To this solution was added DMP (60.0 mg, 0.14 mmol, 2.2 eq.) and it was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_{3(aq.)}$ and sat. $NaHCO_{3(aq.)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:1) to afford ketone **2.58** (17.0 g, 0.03 mmol, 50%) as a colorless oil.

R_f: 0.5, *i*hex:EtOAc 2:8, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{28}H_{37}O_8Si$ $[M+H]^+$: 529.22522; found: 529.22566.

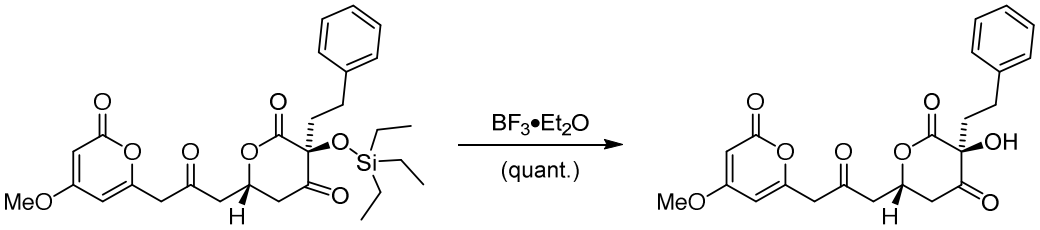
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 8.2, 7.1 Hz, 2H), 7.19 (dtd, *J* = 7.3, 3.4, 1.6 Hz, 3H), 5.96 (d, *J* = 2.2 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 5.18 (dddd, *J* = 12.0, 6.4, 5.5, 3.0 Hz, 1H), 3.82 (s, 3H), 3.64 – 3.56 (m, 2H), 3.11 (dd, *J* = 17.6, 6.4 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.71 (dd, *J* = 16.6, 12.1 Hz,

1H), 2.55 (tq, *J* = 13.5, 6.7, 5.7 Hz, 2H), 2.36 – 2.26 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.64 (qd, *J* = 7.9, 1.4 Hz, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 199.62, 199.17, 170.81, 170.01, 164.02, 156.63, 140.96, 128.65, 128.61, 126.32, 103.58, 88.84, 81.49, 69.92, 56.21, 48.00, 47.23, 42.74, 38.28, 30.03, 6.93, 6.16.

Two dimensional data are available at the NMR data section.

B-Ketolactone (**2.63**)



2.58 **2.63**

A flame dried flask under argon was charged sequentially with **2.58** (2.0 mg, 3.7 µmol, 1.0 eq.) and dry CH_2Cl_2 (0.15 mL). The reaction vessel was cooled to −78 °C. Neat BF_3•Et_2O (10 µL, 74.0 µmol, 20.0 eq.) was added dropwise and the reaction was stirred at the same temperature. The reaction was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by addition of a pH 7 phosphate buffer. The aqueous phase was extracted three times with EtOAc, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product **2.63** was unstable to any further purification technique (1.4 mg, 3.7 µmol, quant.).

R_f: 0.4, *i*hex:EtOAc 2:8, CAM, UV.

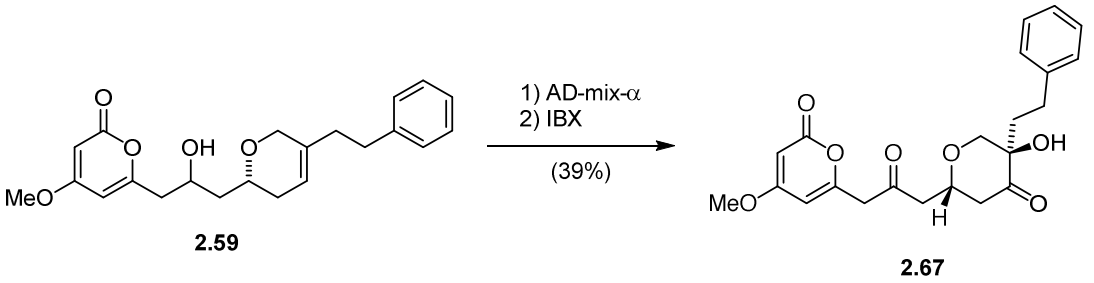
HRMS-ESI (m/z): calc. for $C_{22}H_{23}O_8$ $[M+H]^+$: 415.13874; found: 415.13768.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.31 – 7.28 (m, 2H), 7.23 – 7.20 (m, 1H), 7.20 – 7.17 (m, 2H), 5.99 – 5.84 (m, 1H), 5.47 (d, *J* = 2.2 Hz, 1H), 5.11 (dq, *J* = 8.1, 6.2 Hz, 1H), 4.21 (s, 1H), 3.82 (s, 3H), 3.60 – 3.54 (m, 2H), 3.11 (dd, *J* = 17.8, 6.1 Hz, 1H), 3.03 – 2.91 (m, 5H), 2.38 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.30 (dd, *J* = 13.9, 8.2 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 205.69, 199.59, 172.72, 170.81, 164.06, 156.65, 140.14, 128.80, 128.51, 126.66, 103.57, 88.81, 81.74, 74.52, 56.21, 47.76, 46.75, 39.14, 39.00, 29.66.

Two dimensional data are available at the NMR data section.

Keto alcohol (**2.67**)



2.59 **2.67**

A flask under air was charged with $K_2OsO_4 \bullet 2H_2O$ (5.0 mg, 0.01 mmol, 0.01 eq.), $(DHQ)_2Phal$ (45.0 mg, 0.06 mmol, 0.05 eq.), $K_3[Fe(CN)_6]$ (1.193 g, 3.48 mmol, 3.0 eq.), K_2CO_3 (0.48 g, 3.48 mmol, 3.0 eq.), and *t*BuOH/H_2O (5.9 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 min. The yellow solution was cooled in an ice-bath and **2.59** (0.43 g, 1.16 mmol, 1.0 eq.), $MeSO_2NH_2$ (0.33 g, 3.48 mmol, 3.0 eq.) were added. The reaction was allowed to warm to RT and monitored by TLC analysis until completion (ca. 4 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (2.0 g), stirred for 15 minutes and partitioned between H_2O/EtOAc. The aqueous phase was extracted three times with EtOAc, the combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude oil was purified by FCC (CH_2Cl_2/MeOH/Acetone 90:5:5) to afford the triol (0.45 g, 1.11 mmol, 96% both diol diasteromers) as a white solid.

R_f: 0.3 and 0.6 (undesired), CH_2Cl_2/MeOH/Acetone 90:5:5, CAM, no UV.
The ^{1}H-NMR is available at the NMR data section.

A flame dried flask under argon was charged with triol (0.45 g, 1.11 mmol, 1.0 eq.) and dry EtOAc (11.1 mL). To this solution was added IBX (12.4 g, 4.44 mmol, 4.0 eq.) and the mixture was warmed at 70 °C. The reaction was monitored by TLC until completion (ca. 24 h). Afterwards, the reaction was allowed to cool to RT and the mixture was filtered on a celite pad, the pad was washed with EtOAc and the solvent was removed under reduced pressure. The crude product was purified by FCC (CH_2Cl_2/MeOH/Acetone 97:1.5:1.5) to afford ketone **2.67** (0.18 g, 0.45 mmol, 40%) as a yellow oil.

R_f: 0.7, CH_2Cl_2/MeOH/Acetone 90:5:5, CAM, no UV.
HRMS-ESI (m/z): calc. for $C_{22}H_{28}NO_7$ $[M+NH_4]^+$: 418.18603; found: 418.18623.

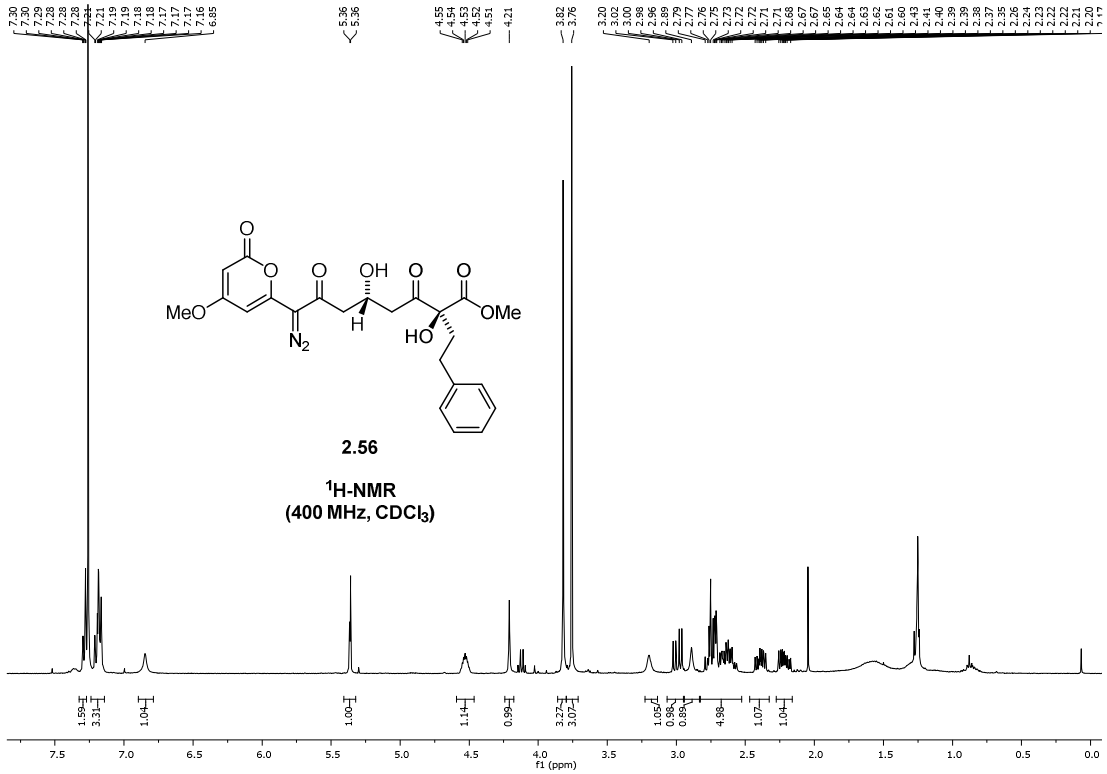
$[\alpha]_D^{20\,°C}$: +65.8 (c = 1.1, $CHCl_3$).

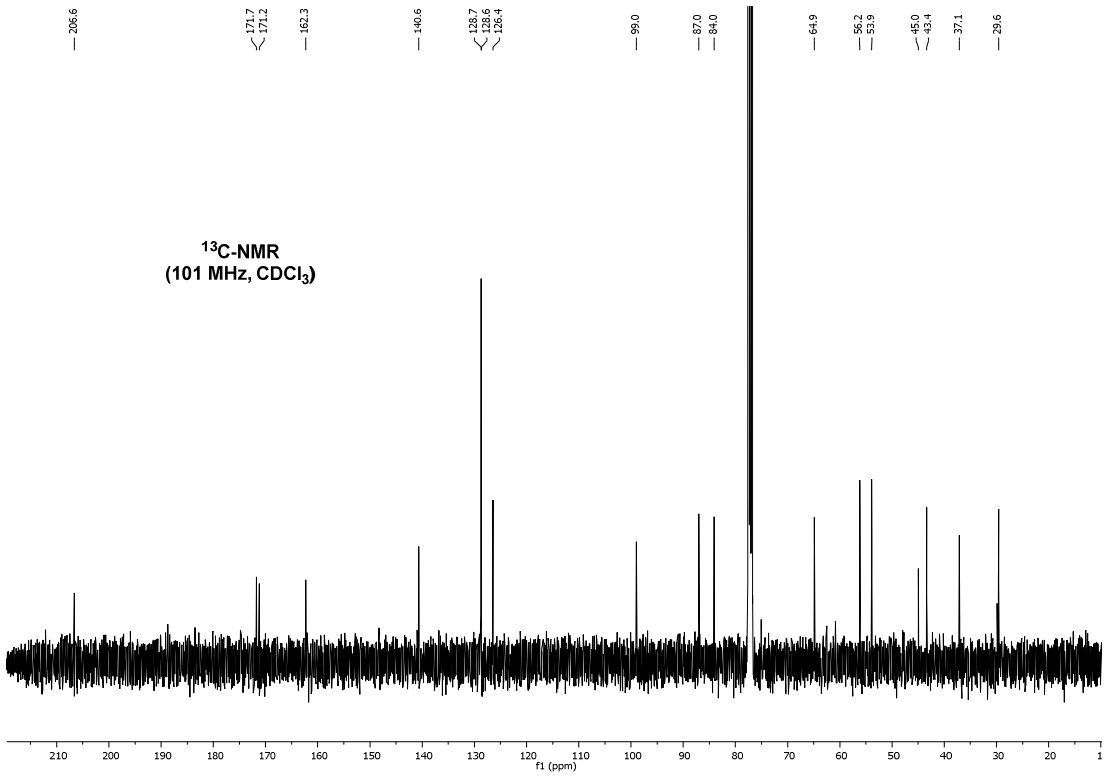
IR (ATR, neat): ν_{max} = 3446 (b), 2924 (w), 2855 (w), 1716 (s), 1651 (m), 1567 (m), 1455 (m), 1251 (m), 1115 (m), 820 (w), 753 (w), 701 (w) cm^{-1}.

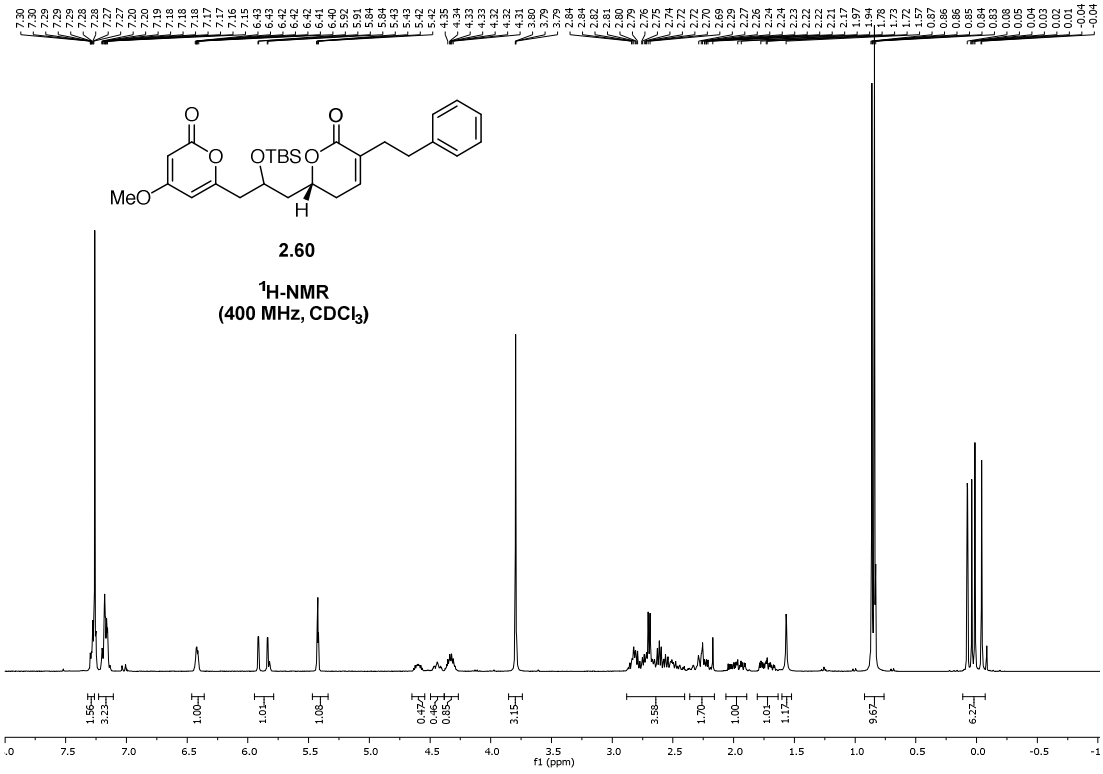
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 5.96 – 5.85 (m, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 4.10 – 4.03 (m, 1H), 4.02 (s, 1H), 3.89 (s, 1H), 3.79 (s, 3H), 3.58 (s, 2H), 3.32 (d, *J* = 11.4 Hz, 1H), 2.92 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.82 – 2.65 (m, 2H), 2.57 – 2.53 (m, 2H), 2.41 – 2.23 (m, 2H), 2.08 (ddd, *J* = 13.8, 11.0, 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.14, 200.36, 170.83, 164.20, 157.07, 141.11, 128.60, 128.54, 126.26, 103.33, 88.66, 78.00, 75.90, 75.43, 56.13, 48.13, 48.10, 44.48, 38.45, 29.04.

6.3.2 NMR Data for Chapter 2.2

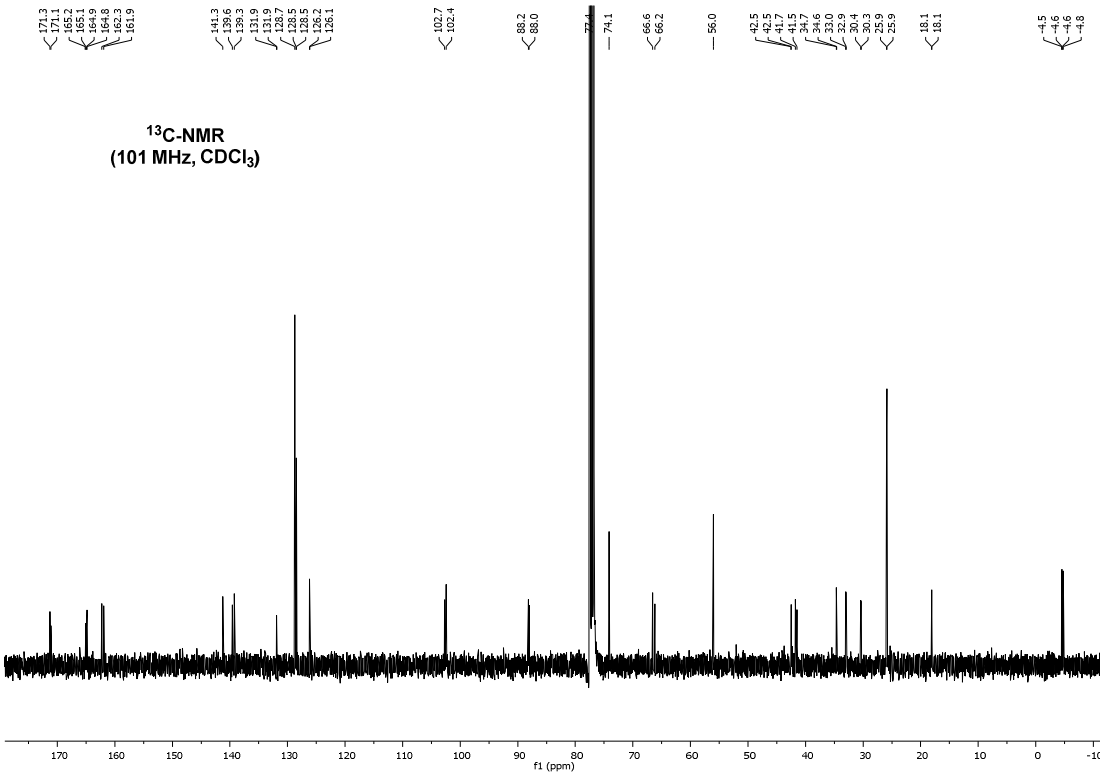




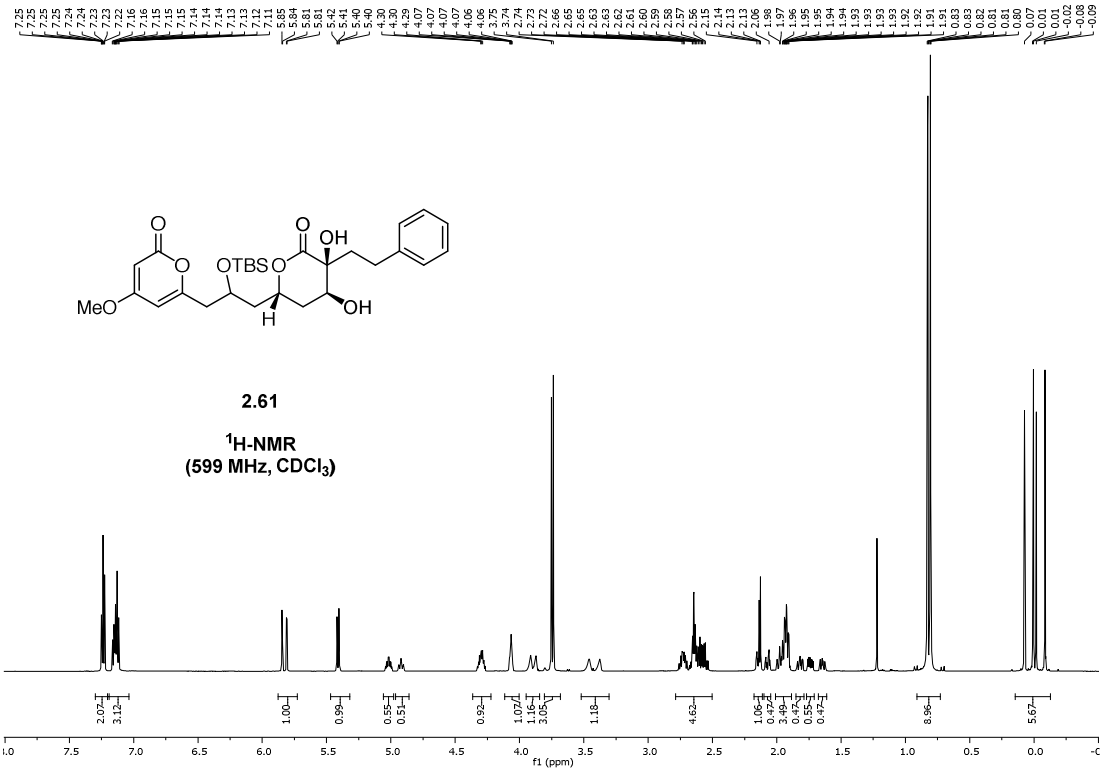


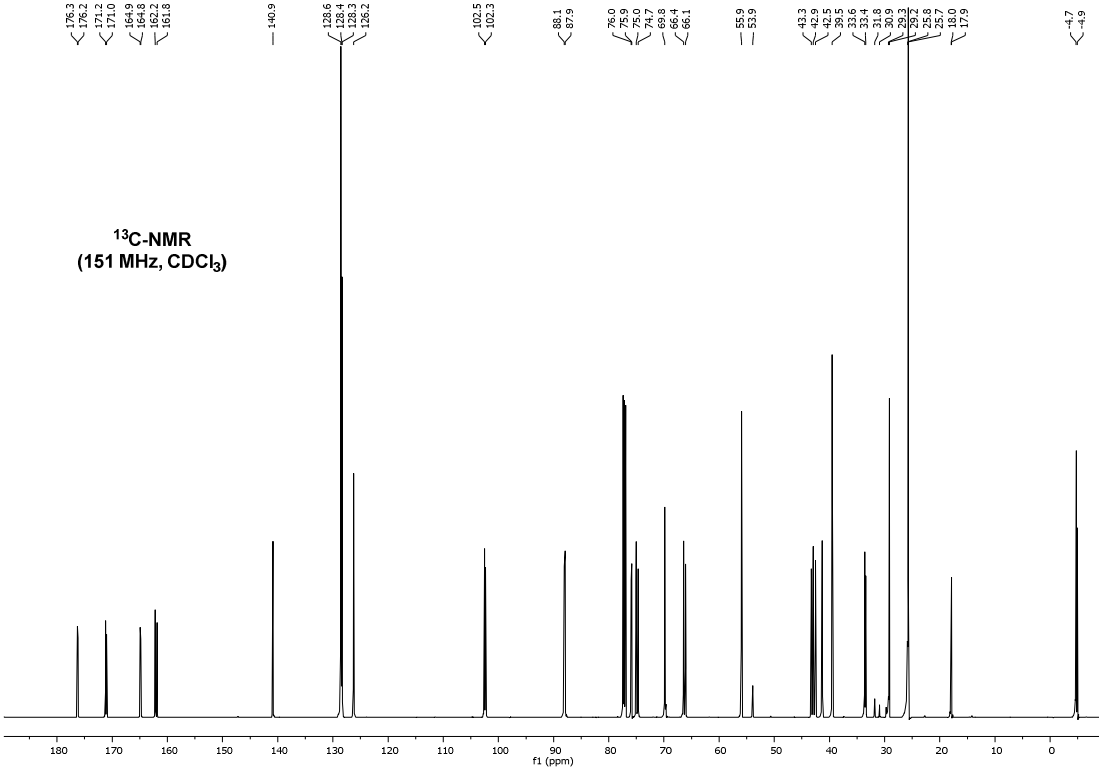
2.60

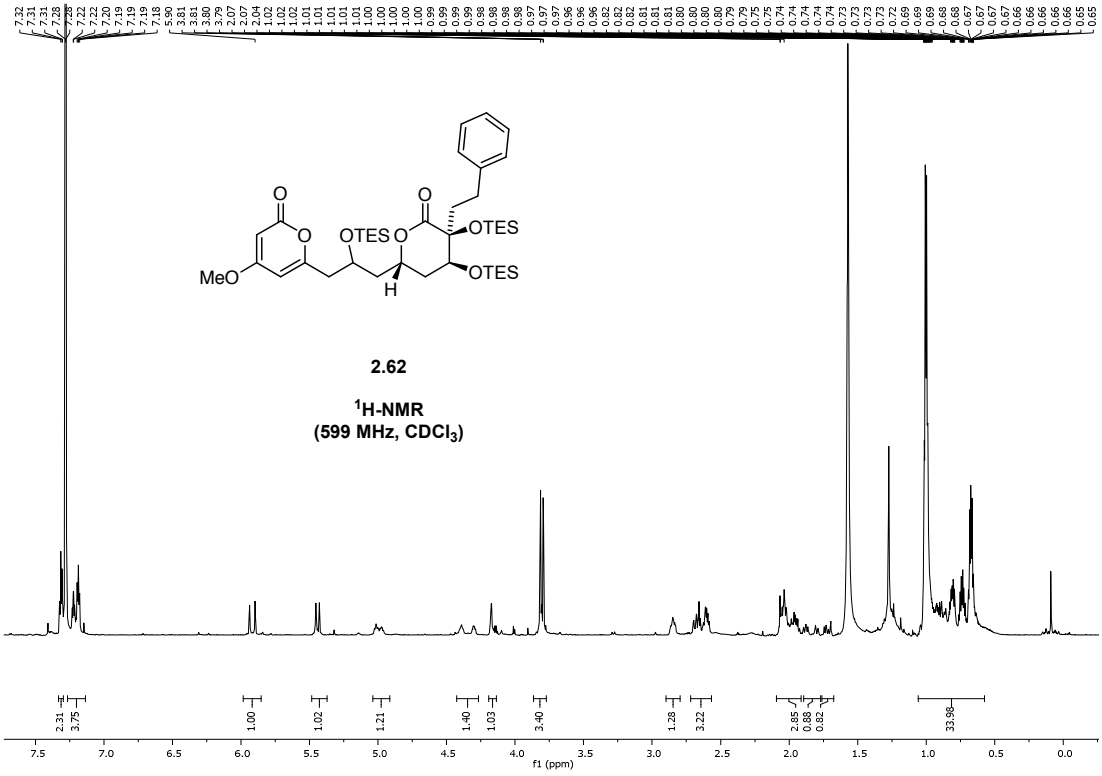
^{1}H-NMR
(400 MHz, $CDCl_3$)

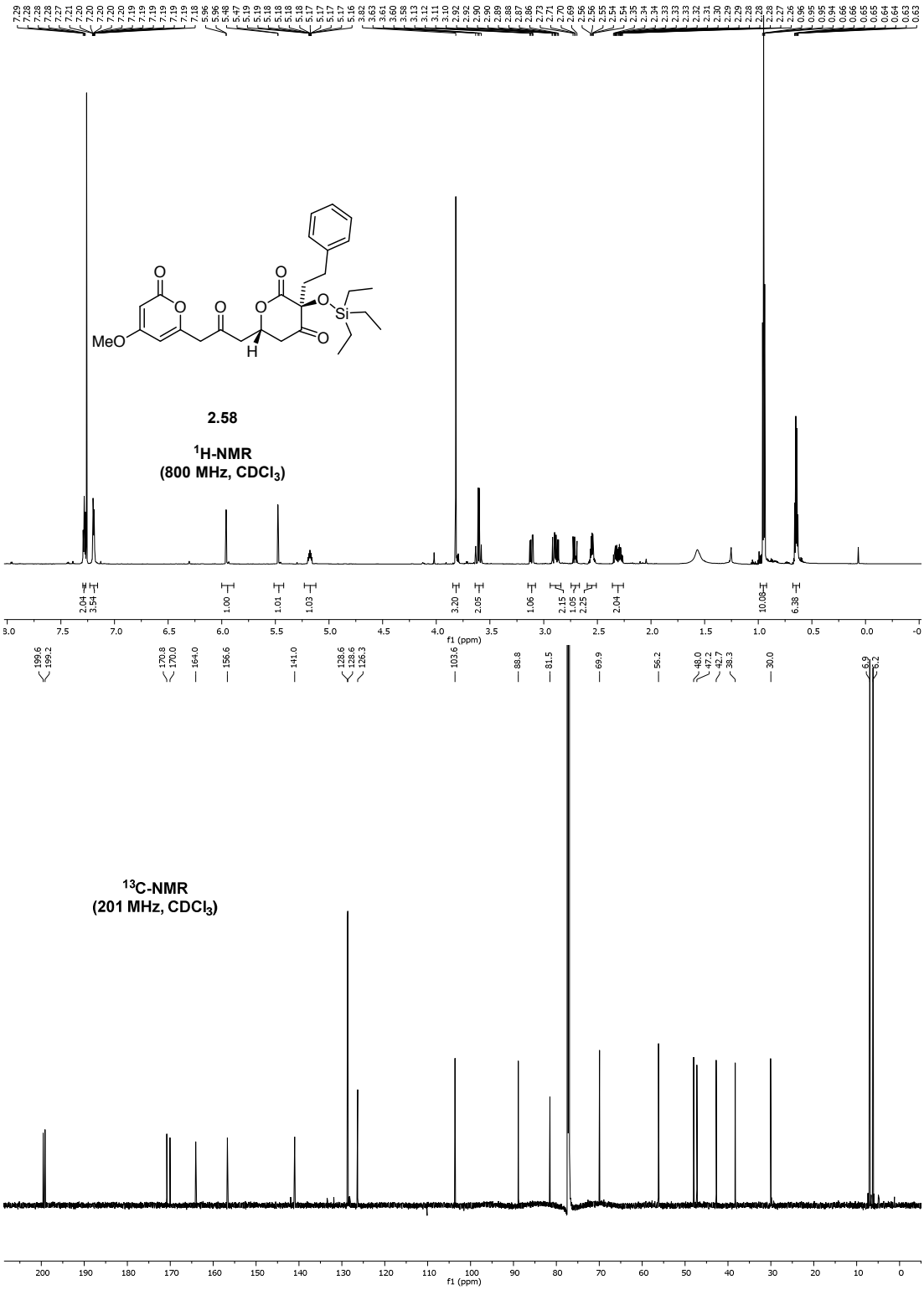


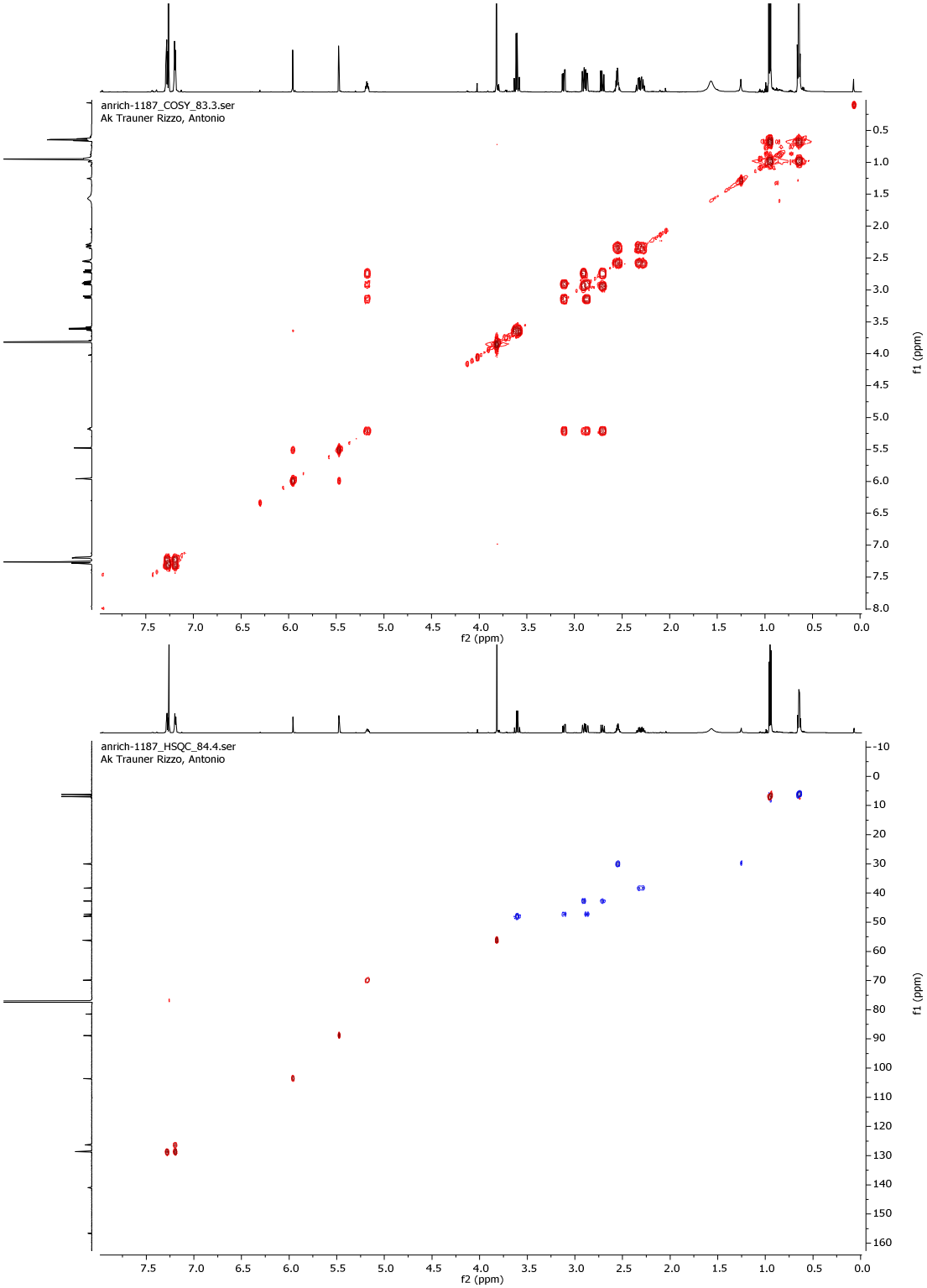
^{13}C-NMR
(101 MHz, $CDCl_3$)


MeO
OTBS
OH
OH
H
2.61
^{1}H-NMR
(599 MHz, CDCl$_3$)
f1 (ppm)


^{13}C-NMR
(151 MHz, CDCl$_3$)
f1 (ppm)


MeO
OTES
OTES
OTES
H
2.62
1H-NMR
(599 MHz, CDCl3)
f1 (ppm)


MeO
O
O
O
O
O
O
Si
H
2.58
^{1}H-NMR
(800 MHz, CDCl$_3$)
^{13}C-NMR
(201 MHz, CDCl$_3$)
f1 (ppm)


anrich-1187_COSY_83.3.ser
Ak Trauner Rizzo, Antonio
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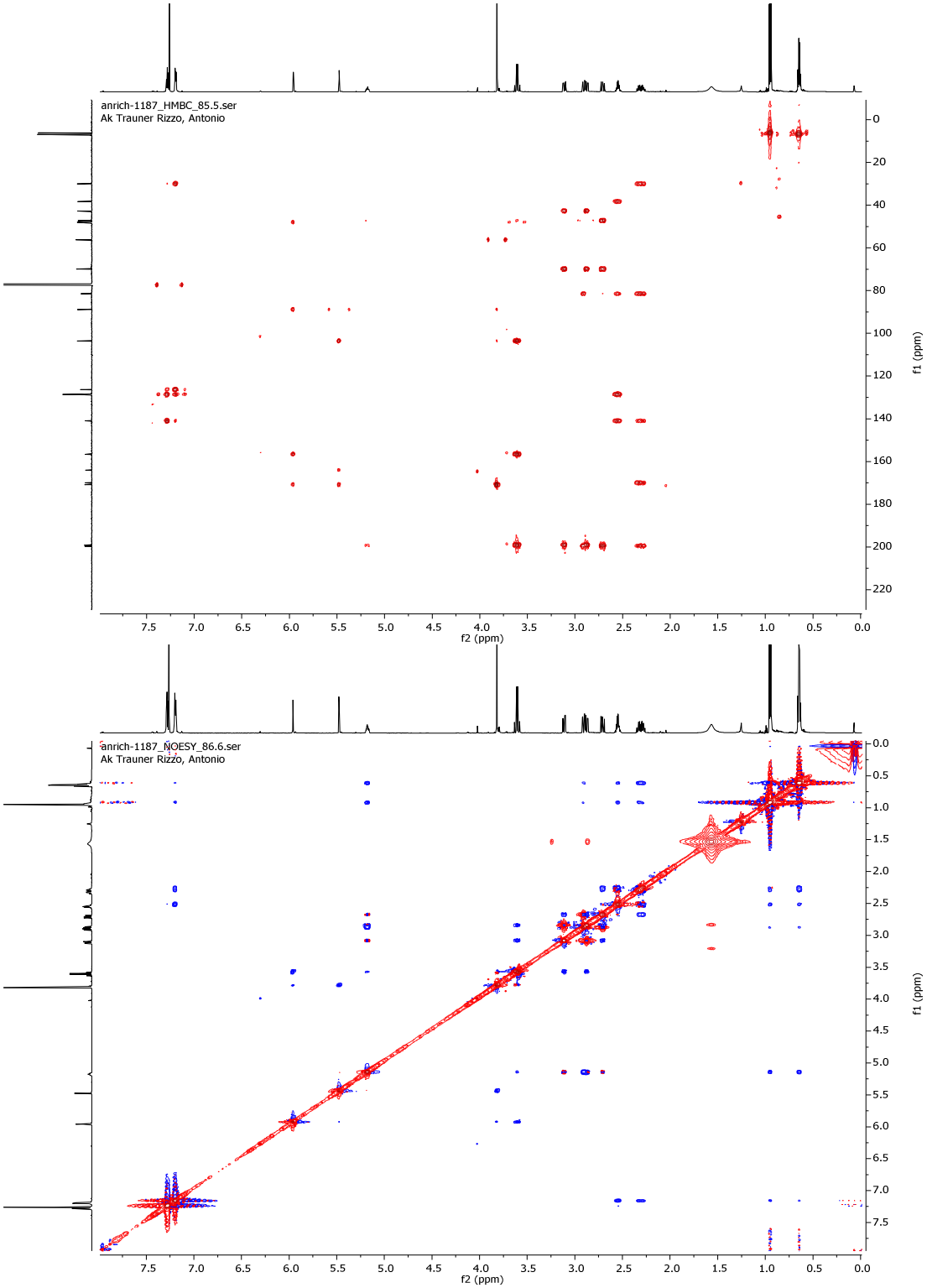
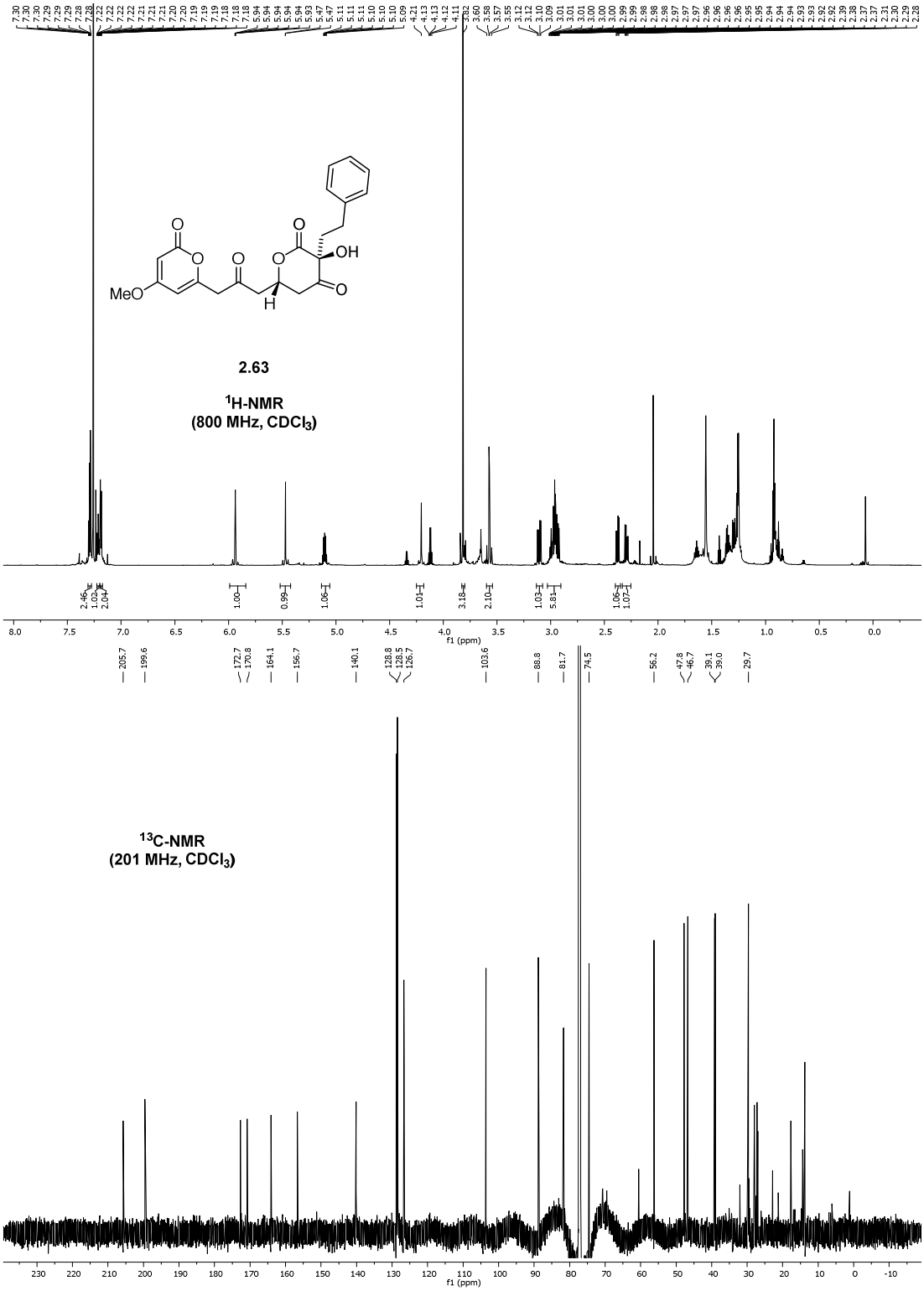
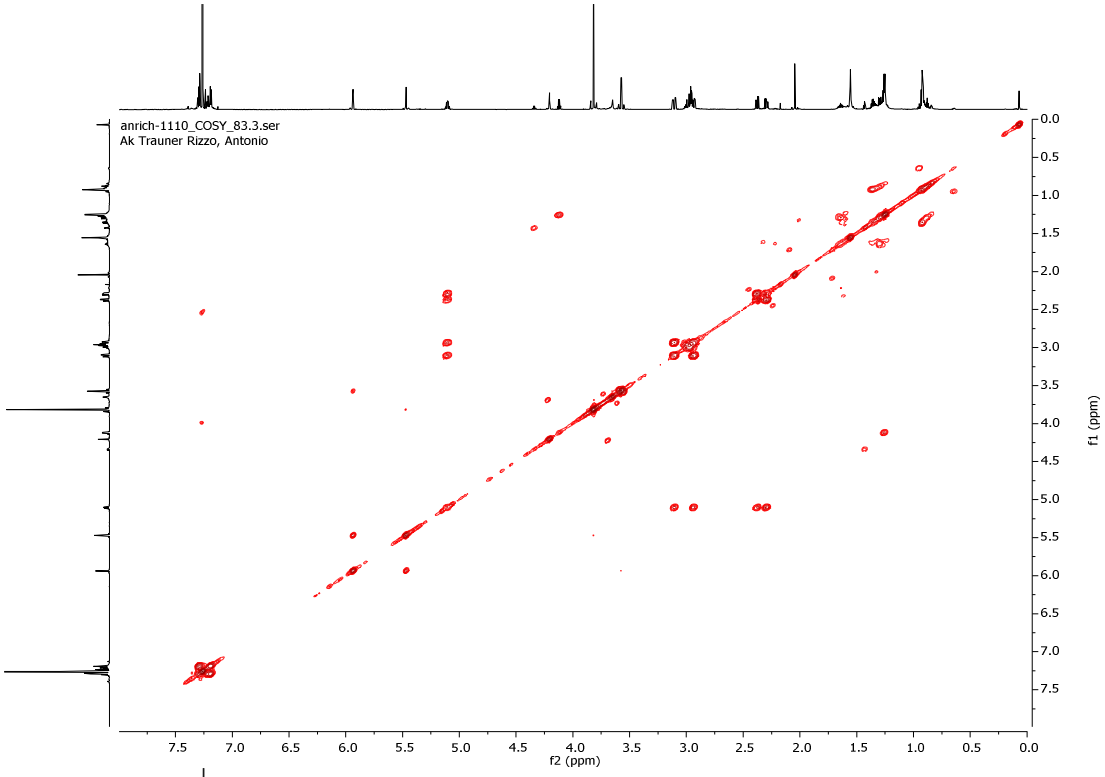
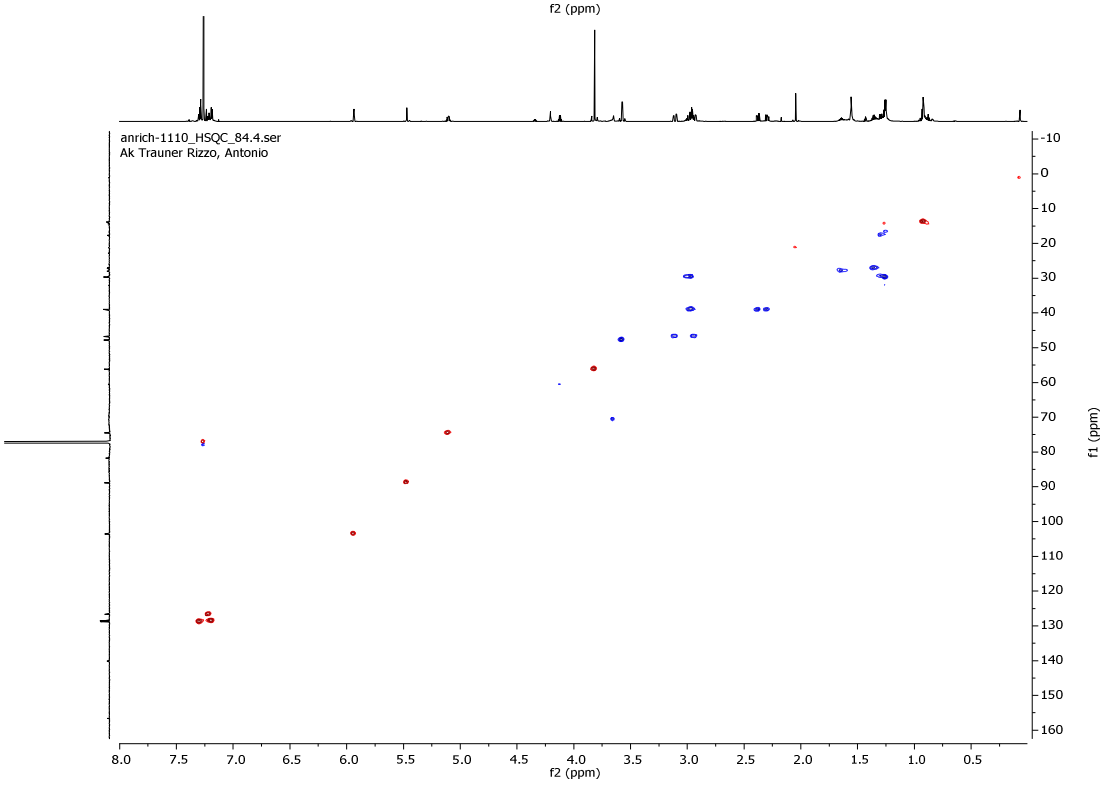
f1 (ppm)
anrich-1187_HSQC_84.4.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


anrich-1187_HMBC_85.5.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)
anrich-1187_NOESY_86.6.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


2.63
^{1}H-NMR
(800 MHz, CDCl$_3$)
^{13}C-NMR
(201 MHz, CDCl$_3$)
f1 (ppm)


anrich-1110_COSY_83.3.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)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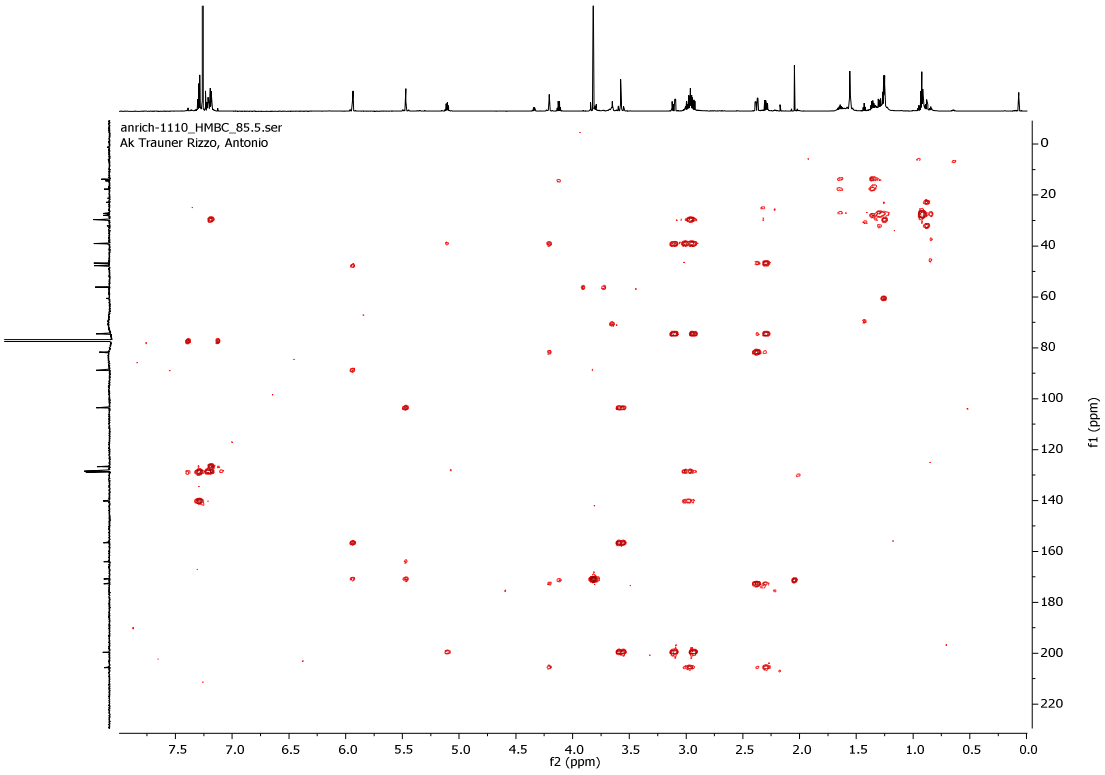
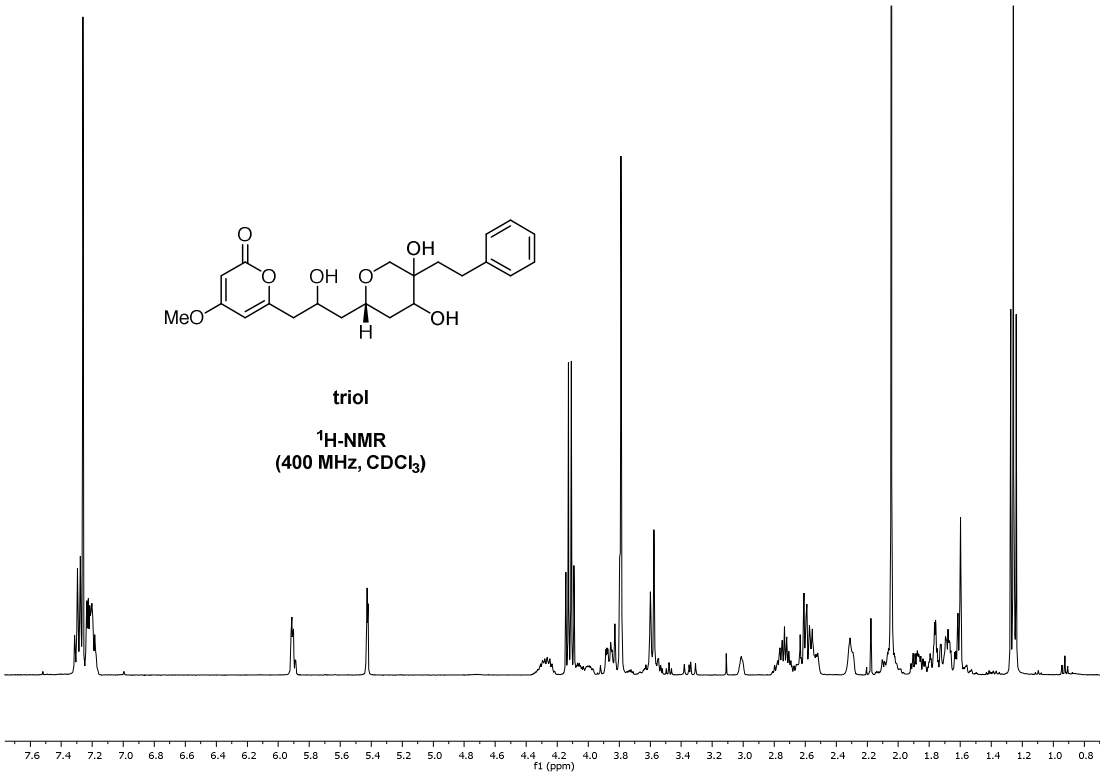
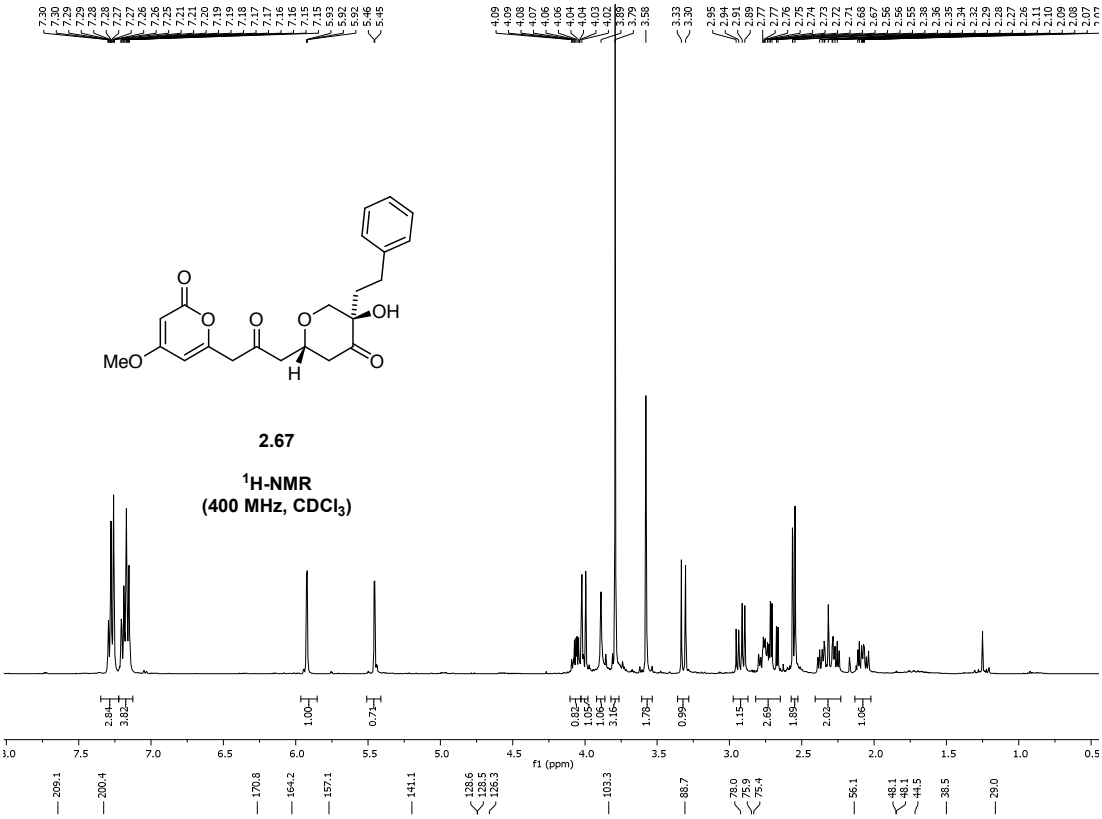
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


anrich-1110_HMBC_85.5.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


MeO
OH
OH
OH
H
triol
1H-NMR
(400 MHz, CDCl3)
f1 (ppm)


MeO
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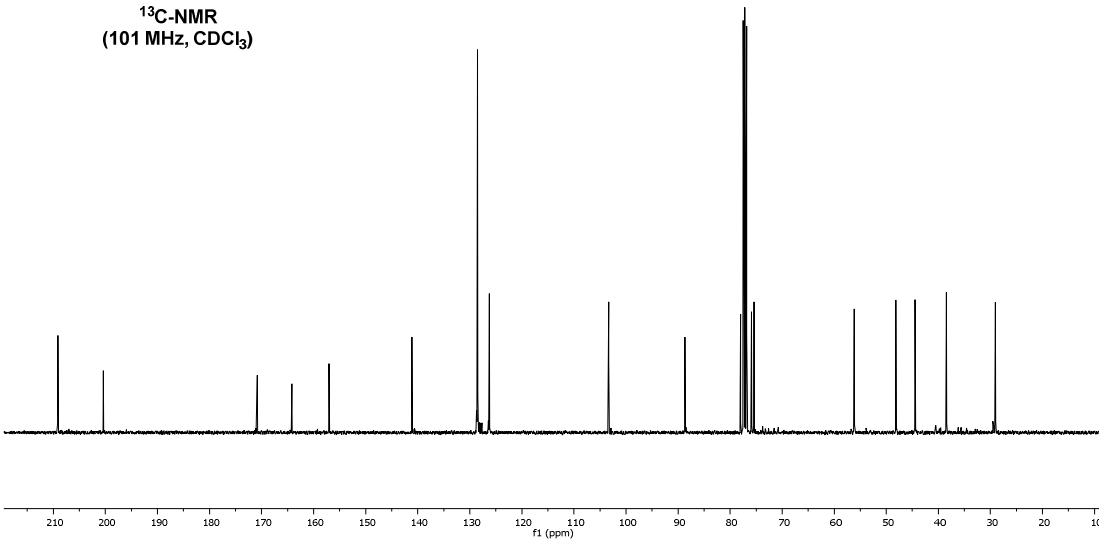
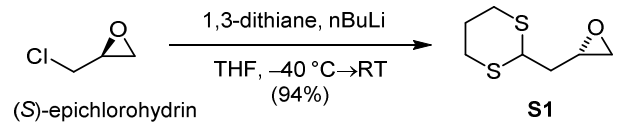
O
O
O
O
OH
H
2.67
^{1}H-NMR
(400 MHz, CDCl$_3$)
f1 (ppm)


^{13}C-NMR
(101 MHz, CDCl$_3$)
f1 (ppm)

6.4. Supporting Information for Chapter 3.2.

6.4.1 Experimental Procedures for Chapter 3.2

Epoxide (**S1**)



A flame dried flask under argon was charged with 1,3-dithiane (10.1 g, 84.2 mmol, 1.1 eq.), dry THF (175 mL) and was cooled to −40 °C with an acetone/dry ice bath. A solution of nBuLi (35.5 mL, 84.2 mmol, 1.1 eq., 2.37 M in hexanes) was added dropwise and the mixture was stirred for 1 h. Then (*S*)-epichlorohydrin (7.1 g, 76.5 mmol, 6.0 mL, 1.0 eq.) was added and the reaction was stirred for 1 h before removing the bath and allowing it to warm to RT. The reaction was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by addition of H_2O. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9 to 2:8) to afford epoxide **S1** (12.6 g, 71.5 mmol, 94%) as a yellow oil. The analytical data was in accordance to the reported one.[1a]

R_f: 0.5, EtOAc/*i*hex 3:7, CAM, no UV.

HRMS-EI (m/z): calc. for $C_7H_{12}OS_2$ $M^{+\bullet}$: 176.0324; found: 176.0323.

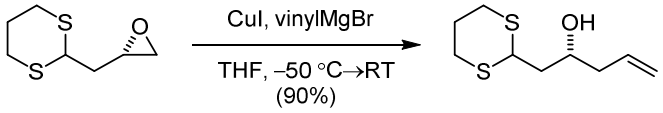
$[\alpha]_D^{20\,°C}$: −5.8 (c = 5.0, $CHCl_3$). Literature:[1a] $[\alpha]_D^{20\,°C}$: −5.8 (c = 5.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3046 (w), 2991 (w), 2898 (m), 2826 (w), 1613 (w), 1479 (w), 1421 (s), 1276 (s), 1183 (m), 977 (w), 951 (w), 909 (s), 833 (s), 746 (m), 663 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 (t, *J* = 7.0 Hz, 1H), 3.16 (tdd, *J* = 5.8, 3.9, 2.6 Hz, 1H), 2.99 – 2.79 (m, 5H), 2.55 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.97 (dd, *J* = 7.0, 5.8 Hz, 2H), 1.94 – 1.83 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 49.80, 47.62, 44.91, 38.78, 30.61, 30.42, 25.78.

Alcohol (**3**)



A flame dried flask under argon was charged with CuI (2.03 g, 10.7 mmol, 0.15 eq.), dry THF (325 mL) and cooled to −50 °C with an acetone bath. A solution of vinylMgBr (107.0 mL, 107.0 mmol, 1 M in THF, 1.1 eq.) was added and the mixture stirred for 10 min. Then a solution of **S1** (12.6 g, 71.5 mmol, 1.0 eq.) in dry THF (51 mL) was added and the reaction stirred for 1 h. Subsequently, the bath was removed and the mixture stirred at RT. The reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9 to 2:8) to afford alcohol **3** (13.0 g, 63.7 mmol, 90%) as a yellow oil. The analytical data was in accordance to the reported one.[1b]

R_f: 0.3, EtOAc/*i*hex 3:7, CAM, no UV.

HRMS-EI (m/z): calc. for $C_9H_{16}OS_2$ $M^{+\bullet}$: 204.0637; found: 204.0635.

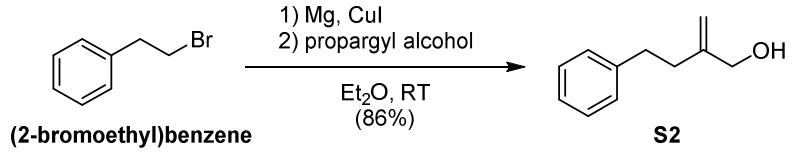
$[\alpha]_D^{20\,°C}$: −26.6 (c = 1.0, $CHCl_3$). Literature:[1b] $[\alpha]_D^{20\,°C}$: +24.2 (c = 1.0, $CHCl_3$, enantiomer).

IR (ATR, neat): ν_{max} = 3412 (w), 3074 (w), 2932 (m), 2900 (m), 1734 (w), 1640 (m), 1422 (s), 1275 (m), 1242 (m), 1172 (m), 1124 (w), 1061 (m), 1045 (m), 1028 (m), 992 (s), 908 (s), 866 (m), 844 (m), 770 (m), 662 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.90 – 5.75 (m, 1H), 5.20 – 5.10 (m, 2H), 4.27 (dd, *J* = 7.9, 6.5 Hz, 1H), 4.04 – 3.94 (m, 1H), 2.99 – 2.77 (m, 4H), 2.30 (dddt, *J* = 14.0, 6.3, 4.7, 1.3 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.18 – 2.08 (m, 1H), 1.97 (d, *J* = 4.2 Hz, 1H), 1.95 – 1.82 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 134.21, 118.75, 67.62, 44.34, 42.22, 42.10, 30.50, 30.19, 26.07.

Alcohol (**S2**)



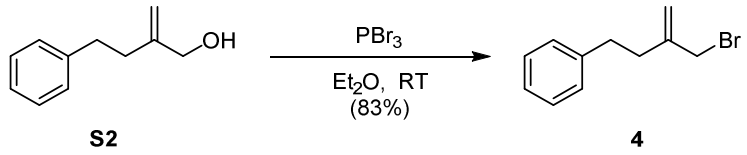
(2-bromoethyl)benzene **S2**

A three necked round bottom flask under argon, equipped with a reflux condenser, was loaded with magnesium turnings (7.92 g, 330 mmol, 3.3 eq.) and dry Et_2O (18 mL) at RT. Neat CH_2Br_2 (0.1 mL) was added and the reaction mixture was stirred for 15 min. Then, a solution of (2-bromoethyl)-benzene (41.1 mL, 300 mmol, 3.0 eq.) in dry Et_2O (106 mL) was added slowly over 20 min (gentle reflux observed). The mixture was further stirred for 15 min. In a second flask a suspension of CuI (3.20 g, 16.8 mmol, 0.17 eq.) in dry Et_2O (152 mL) at 0 °C under Argon was prepared. The freshly prepared solution was cannulated into the CuI suspension and further stirred at 0 °C for 15 min. Then propargyl alcohol (5.80 mL, 100 mmol, 1.0 eq.) was added dropwise over 15 min and the mixture was further stirred for 15 min. The reaction was allowed to warm to RT and stirred for 3 h. Then, the reaction mixture was cooled to 0 °C and quenched carefully with sat. $NH_4Cl_{(aq.)}$, was extracted three times with Et_2O, the combined organic fractions washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 1:9 to 2:8) to afford alcohol **S2** (13.9 g, 85.7 mmol, 86%) as colorless oil. The analytical data was in accordance to the reported one.[2]

R_f: 0.4, EtOAc/*i*hex 2:8, CAM, UV.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.17 (m, 5H), 5.12 – 5.02 (m, 1H), 4.93 (h, *J* = 1.2 Hz, 1H), 4.10 (s, 2H), 2.86 – 2.71 (m, 2H), 2.39 (td, *J* = 7.9, 1.2 Hz, 2H), 1.41 (s, 1H).

Bromide (**4**)

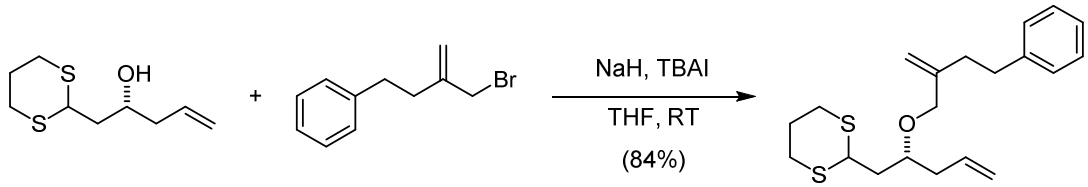


A flame dried flask under Argon was charged sequentially with alcohol **S2** (13.9 g, 85.7 mmol, 1.0 eq.), dry Et_2O (80 mL) and was cooled to 0 °C. Neat PBr_3 (8.4 mL, 89.9 mmol, 1.05 eq.) was added and the reaction was stirred for 10 minutes. Afterwards, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 1 h). Then, the reaction was cooled to 0 °C and quenched carefully by addition of sat. $NaHCO_{3(aq.)}$. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 5:95) to afford benzyl ether **4** (15.97 g, 70.9 mmol, 83%) as a colorless oil. The analytical data was in accordance to the reported one.[2]

R_f: 0.5, EtOAc/*i*hex 5:95, CAM, UV.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.15 (m, 5H), 5.22 (q, *J* = 0.9 Hz, 1H), 5.02 (q, *J* = 1.3 Hz, 1H), 4.00 (d, *J* = 0.8 Hz, 2H), 2.94 – 2.72 (m, 2H), 2.62 – 2.48 (m, 2H).

Ether (**S3**)



3 **4** **S3**

A flame dried flask under argon was charged sequentially with alcohol **3** (10.0 g, 48.9 mmol, 1.0 eq.), dry THF (98 mL), bromide **4** (14.3 g, 63.3 mmol, 1.3 eq.), TBAI (1.8 mL, 40.9 mmol, 0.1 eq.), and the reaction vessel was cooled to −20 °C with an acetone bath. Then, NaH (2.53 g, 63.3 mmol, 1.3 eq., 60% dispersion in mineral oil) was added to the suspension and the reaction was stirred for 10 minutes. Afterwards, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 5 h). Then, the reaction was quenched by addition of sat. $NH_4Cl_{(aq.)}$. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 2:98 to 4:96) to afford ether **S3** (14.3 g, 41.1 mmol, 84%) as a slightly yellow oil.

R_f: 0.4, EtOAc/*i*hex 5:95, CAM, UV.

HRMS-EI (m/z): calc. for $C_{20}H_{28}OS_2$ $[M]^{+\bullet}$: 348.1576; found: 348.1573.

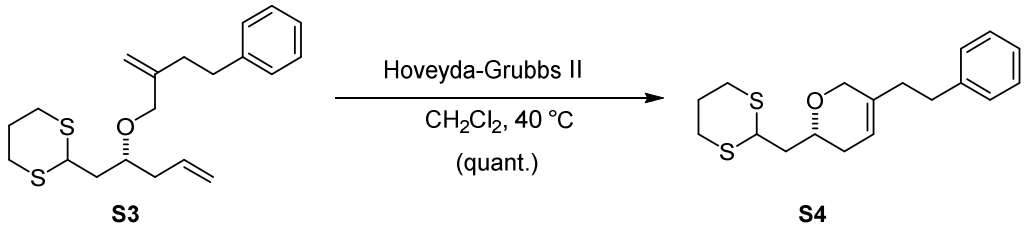
$[\alpha]_D^{20\,°C}$: −27.6 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3075 (w), 2932 (m), 2899 (m), 1737 (m), 1422 (m), 1241 (m), 1076 (s), 907 (s), 746 (s), 697 (vs) cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.28 (tt, *J* = 7.9, 1.8 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.20 – 7.16 (m, 1H), 5.80 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.12 – 5.03 (m, 3H), 4.94 (q, *J* = 1.5 Hz, 1H), 4.21 (dd, *J* = 9.8, 4.8 Hz, 1H), 4.06 (dd, *J* = 11.9, 1.1 Hz, 1H), 3.93 (d, *J* = 11.8 Hz, 1H), 3.70 (dddd, *J* = 8.8, 6.5, 4.8, 3.8 Hz, 1H), 2.84 (ddd, *J* = 14.1, 11.5, 2.6 Hz, 1H), 2.82 – 2.77 (m, 3H), 2.77 – 2.73 (m, 1H), 2.70 (ddd, *J* = 14.1, 11.5, 2.6 Hz, 1H), 2.46 – 2.38 (m, 2H), 2.36 – 2.31 (m, 1H), 2.31 – 2.27 (m, 1H), 2.06 (dtt, *J* = 14.0, 5.1, 2.6 Hz, 1H), 1.95 (ddd, *J* = 14.0, 9.0, 4.8 Hz, 1H), 1.88 – 1.83 (m, 2H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 144.85, 140.95, 132.87, 127.22, 127.19, 124.69, 116.59, 110.94, 73.66, 71.32, 42.88, 38.92, 37.05, 33.88, 33.01, 29.33, 28.82, 24.90.

Alkene (**S4**)



S3 **S4**

A flame dried flask under argon was charged sequentially with ether **S3** (2.70 g, 8.00 mmol, 1.0 eq.), dry CH_2Cl_2 (80 mL), Hoveyda-Grubbs II (25.0 mg, 0.08 mmol, 0.005 eq.) and the reaction vessel was heated to 40 °C. The reaction was monitored by TLC until completion (ca. 5 h, after 4 h further 10.0 mg of catalyst were added). Afterwards, the solvent was removed and the crude product was purified by FCC (EtOAc/*i*hex 5:95 to 1:9) to afford **S4** (2.60 g, 8.00 mmol, quant.) as a white solid.

R_f: 0.9, EtOAc/*i*hex 4:6, CAM, UV.

HRMS-EI (m/z): calc. for $C_{18}H_{24}OS_2$ $[M]^{+\bullet}$: 320.1263; found: 320.1269.

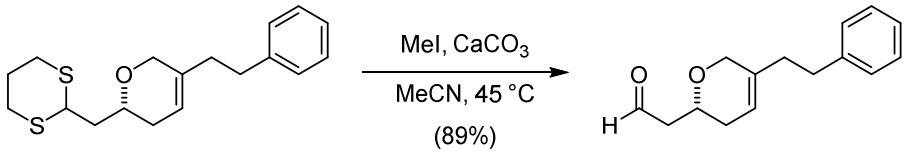
$[\alpha]_D^{20\,°C}$: +62.9 (c = 1.1, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3061 (w), 2900 (m), 2856 (m), 1421 (m), 1273 (m), 1116 (s), 904 (s), 813 (s), 693 (vs) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.27 (m, 2H), 7.18 (td, *J* = 7.2, 6.7, 1.5 Hz, 3H), 5.52 (s, 1H), 4.29 (dd, *J* = 9.7, 4.8 Hz, 1H), 4.10 (q, 2H), 3.76 (dddd, *J* = 9.1, 6.5, 5.6, 3.6 Hz, 1H), 2.99 – 2.78 (m, 4H), 2.77 – 2.63 (m, 2H), 2.20 (t, *J* = 9.8, 7.1, 1.6 Hz, 2H), 2.13 (ddt, *J* = 14.1, 4.9, 2.3 Hz, 1H), 2.05 – 1.92 (m, 3H), 1.92 – 1.79 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.96, 136.61, 128.48, 126.04, 118.22, 70.03, 68.39, 43.73, 41.49, 34.95, 34.34, 30.99, 30.60, 30.19, 26.17.

Aldehyde (**5**)



S4 **5**

A flask was charged sequentially with alkene **S4** (0.96 g, 3.00 mmol, 1.0 eq.), MeCN/H_2O (40 mL, 9:1), $CaCO_3$ (3.0 g, 30.0 mmol, 10.0 eq.), MeI (0.92 mL, 15 mmol, 5.0 eq.) and the reaction vessel was heated to 45 °C. Then, the reaction was monitored by TLC until completion (ca. 5 h). Afterwards, the solvent was removed and the crude mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 2:8) to afford aldehyde **5** (0.61 g, 2.66 mmol, 89%) as a slightly yellow oil.

R_f: 0.5, EtOAc/*i*hex 3:7, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{15}H_{22}NO_2$ $[M+NH_4]^+$: 248.16451; found: 248.16469.

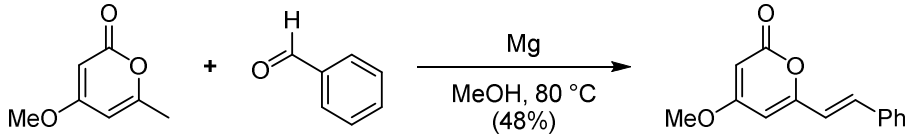
$[\alpha]_D^{20\,°C}$: +28.8 (c = 0.8, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3026 (w), 2921 (w), 2834 (m), 1725 (s), 1453 (m), 1385 (m), 1103 (m), 699 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (s, 1H), 7.31 – 7.21 (m, 2H), 7.16 (t, *J* = 8.6 Hz, 3H), 5.51 (s, 1H), 4.18 – 3.92 (m, 3H), 2.75 – 2.58 (m, 3H), 2.51 (ddd, *J* = 16.5, 4.6, 1.7 Hz, 1H), 2.20 (t, *J* = 8.2 Hz, 2H), 2.10 – 1.99 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.33, 141.79, 136.51, 128.51, 128.43, 126.10, 117.91, 69.07, 68.31, 49.36, 34.88, 34.30, 30.70.

Pyrone (**S5**)



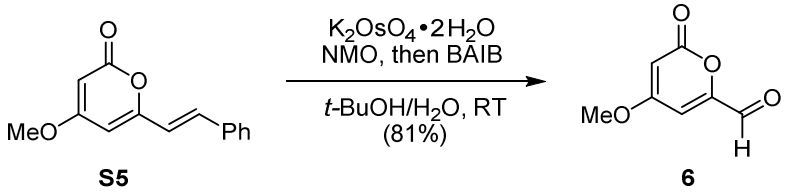
4-methoxy-6-methyl-2*H*-pyran-2-one **S5**

Under nitrogen, magnesium turnings (7.70 g, 320 mmol, 3.0 eq.) were added to a flame dried two-neck flask, fitted with a reflux condenser. Dry MeOH (190 ml) was added and the suspension was stirred at RT until complete disappearance of the metal (ca. 1 h). During that time a gentle reflux was observed. Solid pyrone (15.0 g, 107 mmol, 1.0 eq.) and freshly distilled benzaldehyde (13.6 ml, 128 mmol, 1.2 eq.) were added to the cloudy solution. The color of the mixture changed to yellow. Subsequently, the flask was placed in a preheated oil bath at 80 C and stirred under reflux. Formation of a heterogeneous mixture was observed. The reaction was monitored by TLC analysis until completion (ca. 1.5 h). The reaction flask was removed from the bath and allowed to cool to RT. Afterwards, the solvent was removed under reduced pressure and the residue re-dissolved in DCM. The organic phase was washed with 600 ml of AcOH/H_2O (1/4). The water phase was extracted twice with DCM, the combined organic fractions were washed with H_2O and the solvent removed to afford a yellow solid. This was recrystallized from 75 ml of MeOH. The crystals were washed with cold MeOH to afford pyrone **S5** (9.8 g, 42 mmol, 40 %) as a yellow solid. The analytical data was in accordance to the reported one.[3]

R_f: 0.6, EtOAc:*i*hex 7:3, $KMnO_4$, UV.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 5H), 6.59 (d, *J* = 16.0 Hz, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.51 (d, *J* = 2.2 Hz, 1H), 4.71 (s, 1H), 3.83 (s, 3H).

Aldehyde (**6**)



S5 **6**

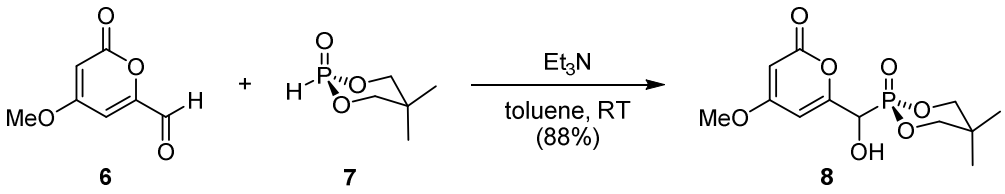
Into a flask under air were added pyrone **S5** (3.18 g, 14.0 mmol, 1.0 eq.), NMO (1.96 g, 17.0 mmol, 1.2 eq.), citric acid monohydrate (5.37 g, 28.0 mmol, 2.0 eq.) and *t*-BuOH/H_2O (140 mL, 1/1). To this stirring dispersion was added K_2OsO_4•$2H_2O$ (0.10 g, 0.27 mmol, 0.02 eq.). The flask was stopped with a septum and the reaction was monitored by TLC analysis until completion (ca. 2 h). The yellow solid disappeared leaving a clear yellow solution. The mixture was diluted with brine/H_2O, extracted three times with EtOAc, the combined organic phases were washed with sat. $Na_2S_2O_{3(aq.)}$, brine, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure to afford a solid residue. The residue was suspended CH_2Cl_2 (50 mL) and BAIB (5.30 g, 16.5 mmol, 1.1 eq.) added under vigorous stirring. The reaction was monitored by TLC analysis until completion (ca. 1 h, the solid disappears). The solvent was partially removed under reduced pressure and directly charged on a FCC (EtOAc/*i*hex 1:1 to 7:3) to deliver aldehyde **6** (1.75 g, 11.4 mmol, 81%) as a white solid. The analytical data was in accordance to the reported one.[4]

R_f diol: 0.2, EtOAc:*i*hex 7:3, $KMnO_4$, UV.

R_f aldeyde: 0.3, EtOAc:*i*hex 7:3, $KMnO_4$, UV.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.49 (s, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H).

Hydroxy-Phosphonate (**8**)



6 **7** **8**

To a flask under inert atmosphere charged with **6** (5.1 g, 33.1 mmol, 1.0 eq.) was added dry toluene (66 mL) and oxa-phosphorinanone **7** (5.2 g, 34.7 mmol, 1.05 eq.). Under vigorous stirring, Et_3N (11.5 mL, 72.0 mmol, 2.2 eq.) was added dropwise to the heterogeneous solution. A mild exothermic reaction was observed and the color changed to orange. The reaction was monitored by TLC analysis until completion (ca. 2.5 h). Then the heterogeneous solution was filtered and the solid was washed several times with EtOAc until a yellow solid was obtained. This was dried under reduced pressure to give hydroxy-phosphonate **8** (8.8 g, 29.0 mmol, 88%) as a yellow solid.

R_f: 0.3, MeOH:EtOAc 5:95, $KMnO_4$, UV.

HRMS-ESI (m/z): calc. for $C_{12}H_{21}NO_7P$ $[M+NH_4]^+$: 322.10501; found: 322.10532.

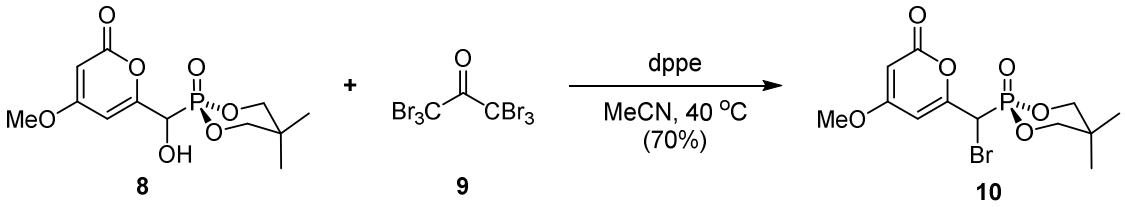
IR (ATR, neat): ν_{max} = 3253 (b), 3081 (w), 2966 (w), 2889 (w), 1723 (s), 1652 (m), 1567 (s), 1412 (m), 1226 (s), 1183 (m), 1089 (s), 987 (m), 814 (s), 714 (m) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ = 6.34 (ddd, *J* = 3.4, 2.3, 0.8 Hz, 1H), 5.60 (t, *J* = 2.0 Hz, 1H), 5.01 (dd, *J* = 16.0, 0.8 Hz, 1H), 4.57 (ddd, *J* = 10.5, 5.5, 2.7 Hz, 2H), 4.13 – 4.01 (m, 2H), 3.87 (s, 3H), 1.27 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ = 173.21, 173.18, 166.20, 162.29, 162.27, 102.48, 102.40, 89.51, 89.49, 80.61, 80.54, 80.31, 80.24, 70.75, 69.15, 57.10, 33.56, 33.48, 21.97, 20.34.

^{31}P NMR (162 MHz, CD_3OD) δ = 10.34.

Bromo-Phosphonate (**10**)



A flask under an inert atmosphere was charged with hydroxyl-phosphonate **8** (3.40 g, 11.1 mmol, 1.0 eq.), dppe (3.70 g, 9.40 mmol, 0.85 eq.) and dry MeCN (37 mL). The mixture was stirred at RT and **9** (3.50 g, 6.60 mmol, 0.6 eq.) was added. The heterogeneous mixture became homogenous and a mild exothermic reaction was observed. The flask was placed into a preheated oil bath at 40 °C and monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was removed from the bath, diluted with EtOAc, filtered on a pad of celite and the cake was washed with EtOAc. The solvent was removed and the crude was purified by FCC (EtOAc/*i*hex 7:3 to acetone/EtOAc 5:95 - the column was charged with ca. 1 cm of sand and 1 cm of eluent) to obtain bromo-phosphonate **10** (2.80 g, 7.80 mmol, 70%) as a white solid.

R_f: 0.6, MeOH:EtOAc 5:95, $KMnO_4$, UV.

HRMS-ESI (m/z): calc. for $C_{12}H_{17}BrO_6P$ $[M+H]^+$: 366.99406; found: 366.99470.

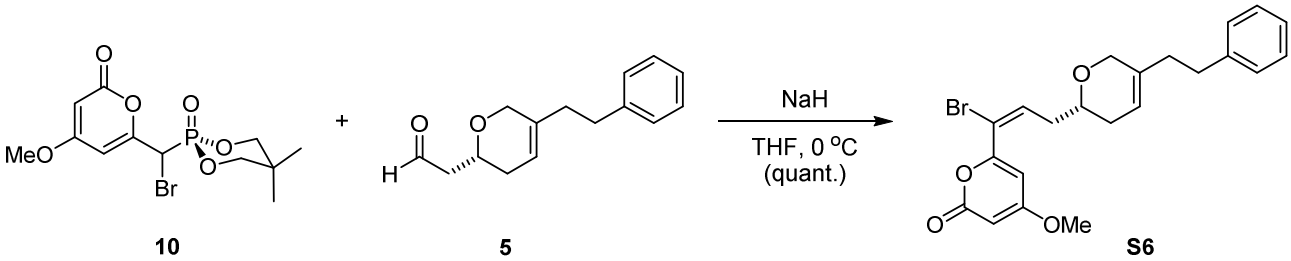
IR (ATR, neat): ν_{max} = 2971 (w), 2935 (w), 1723 (s), 1650 (m), 1563 (s), 1405 (m), 1281 (m), 1255 (s), 1143 (m), 1051 (s), 955 (m), 817 (s), 714 (m) cm^{-1}.

^{1}H NMR (800 MHz, CD_3OD) δ = 6.52 (t, *J* = 2.2 Hz, 1H), 5.69 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.44 (ddd, *J* = 54.6, 10.9, 3.8 Hz, 2H), 4.21 – 4.11 (m, 2H), 3.89 (s, 3H), 1.29 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (201 MHz, CD_3OD) δ = 172.56, 165.29, 157.44, 157.42, 105.46, 105.42, 90.66, 80.25, 80.21, 80.19, 80.15, 57.34, 33.72, 33.68, 21.83, 20.28.

^{31}P NMR (162 MHz, CD_3OD) δ = 5.86.

Vinylbromide (**S6**)



10 **5** **S6**

To a flame dried flask under inert gas were added bromo-phosphonate **10** (1.03 g, 2.82 mmol, 1.1 eq.) and dry THF (20 mL). The flask was placed into an ice-bath and stirred while NaH (123 mg, 3.08 mmol, 1.2 eq., 60% in mineral oil) was added in one portion. The heterogeneous mixture turned clear and dark (ca. 1 h). Then, a solution of aldehyde **5** (0.59 g, 2.57 mmol, 1.0 eq.) in dry THF (10 mL) was added and the reaction was monitored by TLC until completion (ca. 1 h). Afterwards, the mixture was quenched with sat. $NH_4Cl_{(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 3:7) to afford vinylbromide **S6** (1.12 g, 2.57 mmol, quant., 1:3.4 - *Z*:*E* isomers) as a white solid.

R_f: 0.7, EtOAc:*i*hex 1:1, CAM, UV.

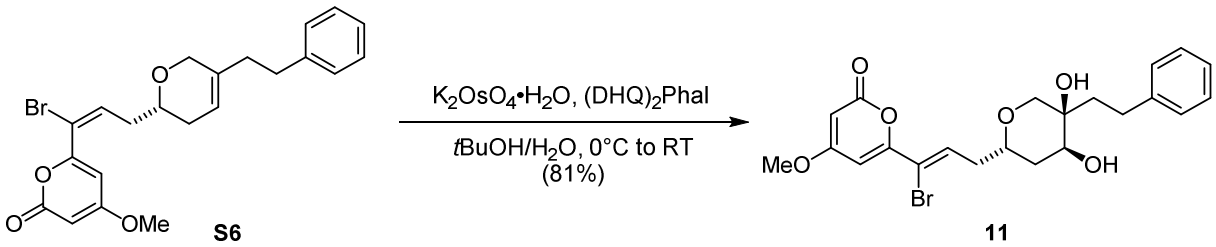
HRMS-EI (m/z): calc. for $C_{22}H_{23}BrO_4$ $[M]^{\bullet+}$: 430.0774; found: 430.0762.

IR (ATR, neat): ν_{max} = 3086 (w), 2920 (w), 2834 (w), 1723 (s), 1634 (m), 1559 (s), 1400 (s), 1242 (s), 1143 (m), 1099 (m), 994 (m), 818 (m), 698 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.29 – 7.23 (m, 3H), 7.21 – 7.13 (m, 5H), 6.58 (t, *J* = 7.6 Hz, 1H **major**), 6.43 (d, *J* = 2.1 Hz, 0H, **minor**), 6.33 (d, *J* = 2.1 Hz, 1H), 5.54 – 5.48 (m, 1H), 5.47 (d, *J* = 2.2 Hz, 2H), 4.14 – 4.00 (m, 3H), 3.81 (d, *J* = 3.8 Hz, 4H), 3.62 (dd, *J* = 6.7, 3.1 Hz, 0H, **minor**), 3.55 (tt, *J* = 8.6, 4.1 Hz, 1H), 2.69 (ddt, *J* = 10.4, 7.2, 4.2 Hz, 4H), 2.66 – 2.55 (m, 2H), 2.20 (q, *J* = 7.7 Hz, 3H), 2.08 – 1.95 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.16, 170.63, 163.42, 163.15, 156.82, 156.21, 141.85, 139.44, 136.55, 136.42, 135.27, 128.46, 128.40, 126.04, 118.18, 118.01, 116.21, 111.65, 104.34, 102.14, 89.45, 89.05, 72.75, 72.17, 68.50, 68.44, 56.23, 38.74, 37.39, 34.85, 34.31, 30.77, 30.54.

Diol (**11**)



A flask under air was charged with $K_2OsO_4 \bullet 2H_2O$ (0.01 g, 0.03 mmol, 0.01 eq.), $(DHQ)_2Phal$ (0.10 g, 0.12 mmol, 0.05 eq.), $K_3[Fe(CN)_6]$ (2.53 g, 7.70 mmol, 3.0 eq.), K_2CO_3 (1.06 g, 7.70 mmol, 3.0 eq.), and *t*BuOH/H_2O (26 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 min. The yellow solution was cooled in an ice-bath and neat vinylbromide **S6** (1.12 g, 2.57 mmol, 1.0 eq.), $MeSO_2NH_2$ (0.73 g, 7.70 mmol, 3.0 eq.) were added. The reaction was allowed to warm to RT and monitored by TLC analysis until completion (ca. 10 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (2.8 g), stirred for 15 minutes and partitioned between H_2O/EtOAc. The aqueous phase was extracted three times with EtOAc, the combined organic phases were dried with Na_2SO_4, filtered and the was solvent removed under reduced pressure. The crude oil was purified by FCC (MeOH/CH_2Cl_2 3:97) to afford diol **11** (0.97 g, 2.08 mmol, 81%, *E* isomer).

R_f: 0.4, EtOAc:*i*hex 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{29}BrNO_6$ $[M+NH_4]^+$: 482.11728; found: 482.11803.

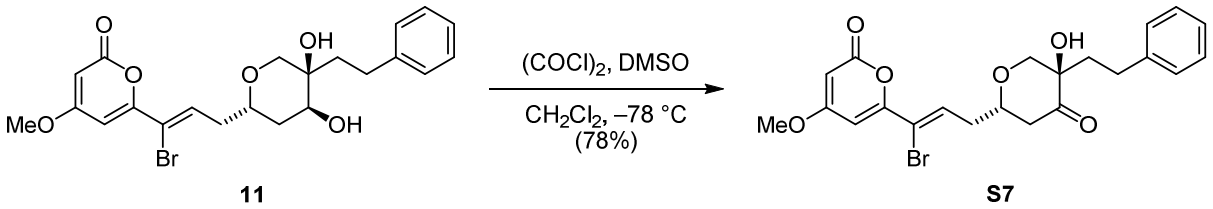
$[\alpha]_D^{20\,°C}$: +9.2 (c = 0.4, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3382 (b), 3086 (w), 2920 (w), 2868 (w), 1687 (s), 1631 (m), 1556 (s), 1401 (s), 1243 (s), 1165 (w), 1044 (m), 819 (m), 701 (m) cm^{-1}.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.19 – 7.16 (m, 3H), 7.10 – 7.06 (m, 1H), 6.51 (t, J = 7.8 Hz, 1H), 6.21 (d, J = 2.2 Hz, 1H), 5.01 (d, J = 2.2 Hz, 1H), 3.70 (dtd, J = 11.9, 6.1, 2.5 Hz, 1H), 3.53 – 3.47 (m, 2H), 3.42 (d, J = 2.8 Hz, 1H), 2.74 (s, 4H), 2.71 – 2.65 (m, 1H), 2.43 (dd, J = 7.8, 6.1 Hz, 2H), 2.00 – 1.94 (m, 2H), 1.89 (d, J = 2.6 Hz, 1H), 1.72 (ddd, J = 14.0, 12.1, 5.2 Hz, 1H), 1.45 – 1.40 (m, 1H), 1.33 (ddd, J = 14.3, 11.4, 2.7 Hz, 1H).

^{13}C NMR (201 MHz, C_6D_6) δ = 170.06, 162.09, 157.13, 142.92, 140.14, 128.84, 128.77, 128.35, 126.13, 112.20, 104.25, 89.42, 71.14, 70.53, 70.06, 55.10, 37.43, 37.37, 36.22, 29.35.

Ketone (**S7**)



A flame-dried flask under argon was charged with oxalyl chloride (4.26 mL, 8.50 mmol, 1.5 eq., 2 M in CH_2Cl_2) and dry CH_2Cl_2 (60 mL). The flask was cooled to −78 °C with an acetone/dry ice bath. Then, dry DMSO (1.20 mL, 16.8 mmol, 3.0 eq.) was added dropwise and the mixture was stirred for 15 minutes. Afterwards, a solution of vinylbromide **11** (2.64 g, 5.69 mmol, 1.0 eq.) in dry CH_2Cl_2 (20 mL) was added dropwise. The reaction was stirred at the same temperature for 2 h and Et_3N (4.71 mL, 33.0 mmol, 6.0 eq.) was added subsequently. The cooling bath was removed and the reaction was allowed to warm to RT. Then, the reaction mixture was diluted with sat. $NH_4Cl_{(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 1:1) to afford ketone **S7** (2.04 g, 4.40 mmol, 78%, 1:3.5 - *E*:*Z* isomers) as a white foam.

R_f: 0.4, EtOAc:*i*hex 1:1, CAM, UV.

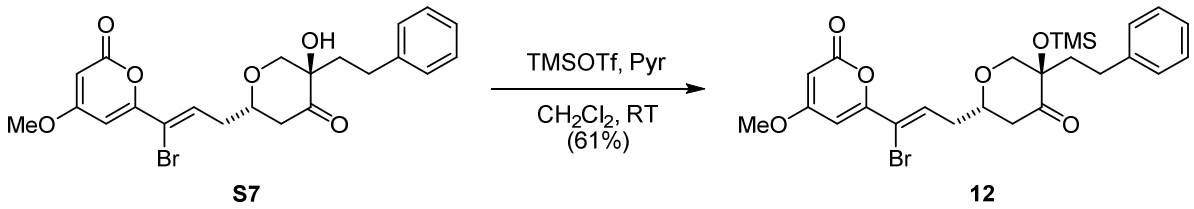
HRMS-ESI (m/z): calc. for $C_{22}H_{27}BrNO_6$ $[M+NH_4]^+$: 480.10163; found: 480.10206.

IR (ATR, neat): ν_{max} = 3476 (b), 3087 (w), 2919 (w), 2856 (w), 1714 (s), 1637 (m), 1610 (m), 1560 (s), 1402 (s), 1251 (s), 1111 (m), 1039 (m), 879 (m), 699 (m) cm^{-1}.

^{1}H NMR (599 MHz, C_6D_6) δ = 7.17 – 7.09 (m, 7H), 7.05 – 6.99 (m, 4H), 6.94 (t, *J* = 6.9 Hz, 1H, **major**), 6.27 – 6.23 (m, 1H), 6.17 (d, *J* = 2.3 Hz, 0H, **minor**), 5.10 – 5.06 (m, 1H), 5.02 (dd, *J* = 2.2, 0.7 Hz, 0H, **minor**), 3.87 (d, *J* = 7.1 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.00 – 2.91 (m, 3H), 2.77 (s, 3H), 2.75 (s, 1H), 2.69 (ddd, *J* = 13.8, 11.3, 5.3 Hz, 1H), 2.43 – 2.30 (m, 2H), 2.21 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.12 – 2.03 (m, 3H), 1.98 – 1.95 (m, 2H), 1.95 – 1.88 (m, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ = 208.97, 170.18, 169.94, 161.75, 161.67, 156.83, 155.90, 141.69, 138.05, 133.19, 126.36, 117.39, 113.08, 104.48, 102.26, 89.50, 78.19, 77.98, 77.55, 75.80, 55.24, 44.54, 44.44, 38.70, 38.61, 37.62, 29.35.

TMS ether (**12**)



S7 **12**

A flame-dried flask under argon was charged with ketone **S7** (2.04 g, 4.40 mmol, 1.0 eq.), pyridine (2.70 mL, 13.0 mmol, 3.0 eq.) and dry CH_2Cl_2 (44 mL). The flask was cooled to 0 °C with an ice bath. Then, TBSOTf (2.36 mL, 13.0 mmol, 3.0 eq.) was added dropwise and the mixture was stirred for 15 minutes at the same temperature. Afterwards, the cooling bath was removed and the reaction was monitored by TLC analysis until completion (ca. 10 h with isomerization). Then, the reaction mixture was diluted with sat. $NaHCO_{3(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 15:85) to afford TMS ether **12** (1.44 g, 4.40 mmol, 61%) as a foam.

R_f: 0.6, EtOAc:*i*hex 1:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{25}H_{31}BrO_6Si$ $[M+NH_4]^+$: 552.14115; found: 552.14088.

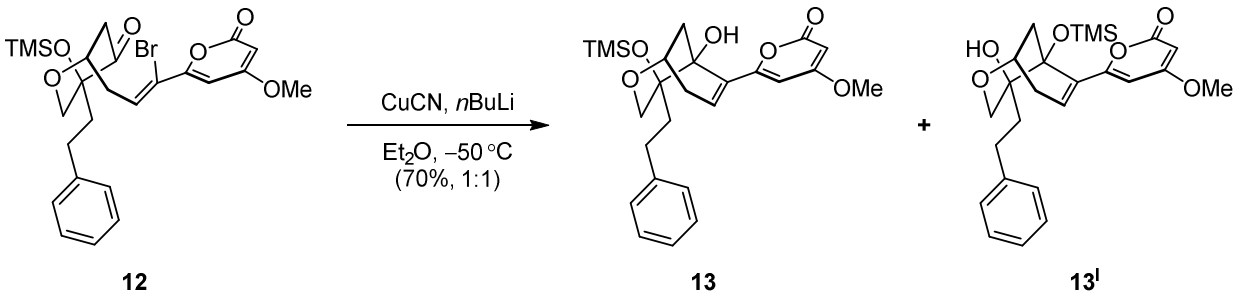
$[\alpha]_D^{20\,°C}$: +61.0 (c = 0.4, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3026 (w), 2955 (w), 2857 (w), 1723 (s), 1638 (m), 1610 (m), 1562 (s), 1401 (s), 1247 (s), 1119 (m), 866 (m), 752 (m) cm^{-1}.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.22 – 7.18 (m, 2H), 7.14 – 7.11 (m, 2H), 7.10 – 7.07 (m, 1H), 7.03 (t, J = 6.9 Hz, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 5.10 (d, *J* = 2.2 Hz, 1H), 3.80 (d, *J* = 11.4 Hz, 1H), 3.09 (d, *J* = 11.5 Hz, 2H), 2.79 (s, 4H), 2.51 (ddd, *J* = 13.7, 11.8, 5.1 Hz, 1H), 2.25 (dt, *J* = 15.8, 7.2 Hz, 1H), 2.12 (ddd, *J* = 15.7, 6.8, 4.5 Hz, 1H), 2.04 (ddd, *J* = 14.0, 11.8, 5.1 Hz, 1H), 2.02 – 1.92 (m, 3H), 0.38 (s, 9H).

^{13}C NMR (201 MHz, C_6D_6) δ = 206.64, 170.19, 161.78, 155.94, 141.88, 133.47, 128.87, 128.35, 126.33, 117.26, 102.23, 89.47, 81.62, 76.90, 74.85, 55.20, 45.69, 39.28, 38.58, 29.51, 3.01.

Bicycle (**13** + **13**^{I})



12 **13** **13**^{I}

To a flame dried flask under inert gas were added CuCN (6.00 g, 67.0 mmol, 25.0 eq.) and dry Et_2O (250 mL). The flask was cooled to −25 °C with an acetone/dry ice bath and *n*-BuLi (33.5 mL, 81.0 mmol, 30.0 eq., 2.42 M in hexanes) was added. The mixture was stirred for 30 minutes at the same temperature. Subsequently, the reaction was cooled to −50 °C. To this stirring solution was added dropwise a solution of **12** (1.44 g, 2.70 mmol, 1.0 eq.) in dry Et_2O (20 mL). A strong color change to cardinal red was observed. The mixture was stirred at the same temperature and monitored by TLC analysis until completion (ca. 1.5 h). The reaction was subsequently cannulated into a pH = 9 $NH_3/NH_4Cl_{(aq.)}$ buffer, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 1:1) to afford bicycle **13** (0.85 g, 1.87 mmol, 70%, 1:1 mixture of TMS isomers) as a yellow foam.

Note: to obtain reproducible and high yields it is necessary to use colorless *n*-BuLi.

R_f: 0.3, EtOAc:*i*hex 1:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{25}H_{33}O_6Si$ $[M+H]^+$: 457.20409; found: 457.20451.

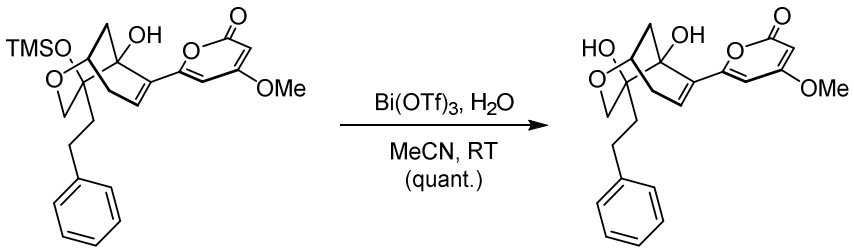
^{1}H NMR (400 MHz, C_6D_6) δ = 7.14 – 6.98 (m, 9H), 6.67 (t, *J* = 4.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.59 (t, *J* = 3.9 Hz, 1H), 5.27 (d, *J* = 2.2 Hz, 1H), 5.16 (d, *J* = 2.1 Hz, 1H), 3.92 (t, *J* = 3.5 Hz, 1H), 3.84 (s, 1H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.14 (dd, *J* = 22.5, 13.1 Hz, 2H), 2.91 (tt, *J* = 11.8, 4.0 Hz, 2H), 2.83 (s, 2H), 2.77 (d, *J* = 9.0 Hz, 4H), 2.50 (qd, *J* = 13.5, 12.9, 4.9 Hz, 3H), 2.13 (ddd, *J* = 15.7, 6.9, 4.2 Hz, 3H), 1.90 (q, *J* = 4.3 Hz, 4H), 1.78 (td, *J* = 13.6, 4.6 Hz, 1H), 1.58 – 1.43 (m, 1H), 1.41 – 1.18 (m, 3H), 0.20 (s, 8H), 0.10 (s, 9H).

Dimer

HRMS-ESI (m/z): calc. for $C_{50}H_{66}NO_{12}Si_2$ $[M+NH_4]^+$: 928.41181; found: 928.41290.

^{1}H NMR spectrum is available on the NMR Spectra section.

Diol (**S8**)



13 + **13**^{I} **S8**

A flask was sequentially charged with bicycle **13** (**+13**^{I}) (0.17 g, 0.36 mmol, 1.0 eq.), dry MeCN (2.20 mL), H_2O (0.03 mL, 1.80 mmol, 5.0 eq.) and $Bi(OTf)_3$[5] (12.0 mg, 0.02 mmol, 0.05 eq.). The mixture was stirred at RT and monitored by TLC analysis until completion (ca. 4 h). Then, the reaction was concentrated under reduced pressure and the residue purified by FCC (MeOH:CH_2Cl_2 2.5:97.5) to afford diol **S8** (0.14 g, 0.36 mmol, quant.) as a yellow solid.

R_f: 0.2, EtOAc:*i*hex 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{28}NO_6$ $[M+NH_4]^+$: 402.19111; found: 402.19184.

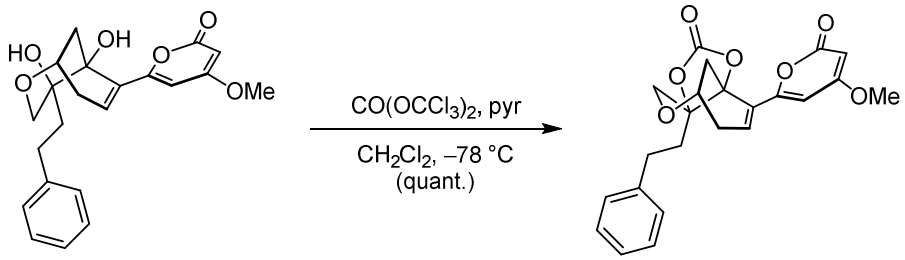
$[\alpha]_D^{20\,°C}$: −122.0 (c = 0.4, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3398 (b), 2940 (w), 2857 (w), 1684 (s), 1610 (m), 1628 (m), 1556 (s), 1401 (s), 1248 (s), 1007 (m), 828 (m), 700 (m) cm^{-1}.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.10 (t, *J* = 7.6 Hz, 2H), 7.05 – 7.03 (m, 3H), 7.01 – 6.96 (m, 1H), 6.56 (t, *J* = 3.9 Hz, 1H), 5.16 (d, *J* = 2.2 Hz, 1H), 3.76 (dq, *J* = 4.5, 2.0 Hz, 1H), 3.35 (d, *J* = 12.8 Hz, 1H), 3.11 (d, *J* = 12.8 Hz, 1H), 2.81 – 2.71 (m, 5H), 2.42 – 2.36 (m, 2H), 2.08 (ddd, *J* = 14.2, 11.8, 4.7 Hz, 1H), 1.95 (s, 1H), 1.87 – 1.82 (m, 2H), 1.76 (dd, *J* = 12.4, 4.0 Hz, 1H), 1.35 (ddd, *J* = 14.2, 11.5, 5.8 Hz, 1H), 1.24 (dd, *J* = 12.3, 1.9 Hz, 1H).

^{13}C NMR (201 MHz, C_6D_6) δ = 170.87, 162.87, 157.46, 142.66, 135.28, 133.60, 128.77, 128.50, 127.72, 126.15, 102.87, 89.08, 75.01, 73.37, 68.48, 66.87, 54.95, 37.76, 34.56, 31.95, 29.45.

Carbonate (**14**)



S8 **14**

A flame dried flask under argon was sequentially charged with diol **S8** (0.13 g, 0.33 mmol, 1.0 eq.), dry CH_2Cl_2 (3.5 mL), pyridine (0.13 mL, 1.65 mmol, 5.0 eq.) and cooled to −78 °C with an acetone/dry ice bath. A solution of triphosgene (78.0 mg, 0.26 mmol, 0.8 eq.) in dry CH_2Cl_2 (2 mL) was added to the solution and the resulting mixture was stirred at the same temperature for 1 h. Then, the cooling bath was removed and the reaction was monitored by TLC analysis until completion (ca. 3 h). Afterwards, the reaction was directly purified by FCC (EtOAc/*i*hex 7:3) to afford carbonate **14** (0.14 g, 0.33 mmol, quant.) as a yellow foam.

R_f: 0.4, EtOAc:*i*hex 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{23}H_{26}NO_7$ $[M+NH_4]^+$: 428.17038; found: 428.17026.

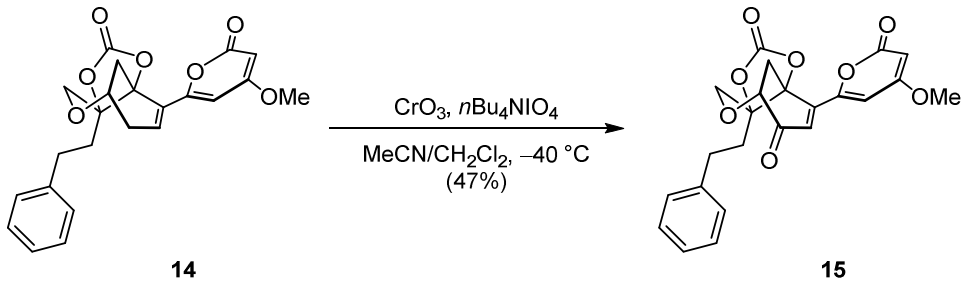
$[\alpha]_D^{20\,°C}$: −90.0 (c = 0.3, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3027 (w), 2932 (w), 1802 (s), 1717 (s), 1633 (m), 1560 (s), 1402 (m), 1230 (s), 1007 (m), 822 (m), 699 (m) cm^{-1}.

^{1}H NMR (599 MHz, C_6D_6) δ = 7.04 (t, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 2H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.20 (t, *J* = 3.9 Hz, 1H), 5.07 (d, *J* = 2.1 Hz, 1H), 3.65 (s, 1H), 3.49 (d, *J* = 13.1 Hz, 1H), 3.34 (d, *J* = 12.7 Hz, 1H), 2.73 (s, 3H), 2.56 (ddd, *J* = 14.1, 11.6, 4.6 Hz, 1H), 2.36 (ddd, *J* = 14.0, 11.5, 5.6 Hz, 1H), 2.07 (ddd, *J* = 15.7, 11.6, 4.7 Hz, 1H), 1.89 – 1.74 (m, 3H), 1.53 (dt, *J* = 21.0, 4.2 Hz, 1H), 1.22 (d, *J* = 12.7 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ = 170.18, 162.07, 155.92, 152.54, 140.67, 135.86, 129.21, 128.89, 128.35, 126.52, 102.00, 89.47, 85.27, 81.93, 67.38, 62.92, 55.09, 35.04, 33.29, 32.76, 28.89.

Enone (**15**)



14 **15**

A flame dried flask under argon was charged with CrO_3 (7.2 mg, 0.07 mmol, 6.0 eq.), dry MeCN/CH_2Cl_2 (0.16 mL, 10/1) and stirred at RT for 15 minutes. Then, the dark solution was cooled to −40 °C with an acetone/dry ice bath and nBu$_4$IO$_4$ (31.0 mg, 0.07 mmol, 6.0 eq.) was added. After 10 minutes the solution became bright orange and **14** (5.0 mg, 0.012 mmol, 1.0 eq.) in dry MeCN/CH_2Cl_2 (0.15 mL, 10/1) was added. The mixture was stirred at the same temperature and monitored by TLC analysis until completion (ca. 30 minutes). Afterwards, the reaction was quenched with sat. $Na_2S_2O_{3(aq.)}$, extracted trice with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by FCC (EtOAc/*i*hex 1:1) to afford **15** (2.4 mg, 5.6 µmol, 47%) as an amorphous yellow solid.

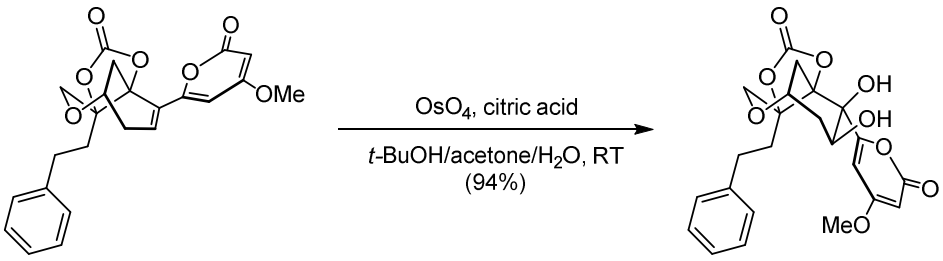
R_f: 0.5, EtOAc:*i*hex 7:3, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{23}H_{24}NO_8$ $[M+NH_4]^+$: 442.14964; found: 442.14950.

^{1}H NMR (800 MHz, C_6D_6) δ = 7.01 (dd, *J* = 8.5, 6.9 Hz, 2H), 6.96 – 6.91 (m, 1H), 6.82 – 6.73 (m, 2H), 6.48 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 4.97 (d, *J* = 2.1 Hz, 1H), 3.77 (dd, *J* = 3.8, 1.9 Hz, 1H), 3.61 (d, *J* = 13.7 Hz, 1H), 3.37 (d, *J* = 13.7 Hz, 1H), 2.63 (s, 3H), 2.47 (ddd, *J* = 13.8, 11.7, 4.3 Hz, 1H), 2.14 (ddd, *J* = 13.8, 11.7, 5.7 Hz, 1H), 1.95 (ddd, *J* = 14.2, 11.7, 4.3 Hz, 1H), 1.81 (dd, *J* = 13.4, 3.9 Hz, 1H), 1.60 – 1.53 (m, 1H), 1.50 (dd, *J* = 13.3, 2.0 Hz, 1H).

^{13}C NMR (201 MHz, C_6D_6) δ = 191.94, 168.68, 160.48, 153.05, 151.47, 144.98, 139.99, 128.98, 128.95, 127.72, 126.71, 106.92, 91.93, 83.49, 80.93, 72.80, 64.41, 55.22, 36.60, 35.30, 28.64.

Diol (**18**)



14 **18**

A flask was sequentially charged with carbonate **14** (0.14 g, 0.33 mmol, 1.0 eq.), *t*BuOH/acetone/H_2O (3.3 mL, 1/1/1), Trimethylamine *N*-oxide (51.0 mg, 0.68 mmol, 2.0 eq.) citric acid monohydrate (0.130 g, 0.68 mmol, 2.0 eq.) and OsO_4 (0.2 mL, 0.03 mmol, 0.1 eq., 4% in H_2O). Then, the mixture was heated at 50 °C with a preheated oil bath. The reaction was monitored by TLC analysis until completion (ca. 4 h). Afterwards, the reaction was cooled to RT, diluted with brine, extracted five times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by FCC (MeOH:CH_2Cl_2 3:97) to afford diol **18** (0.138 g, 0.31 mmol, 94%) as a white solid.

R_f: 0.2, MeOH:CH_2Cl_2 3:97, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{23}H_{28}NO_9$ $[M+NH_4]^+$: 462.17586; found: 462.17569.

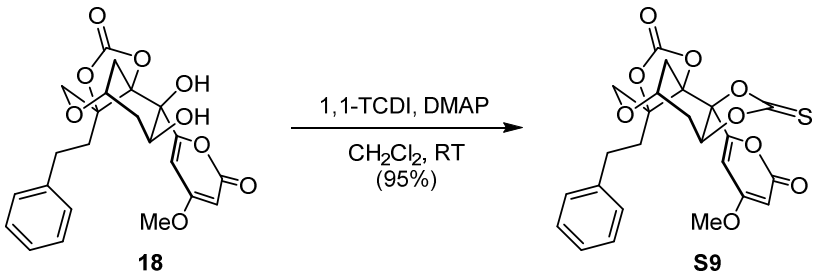
$[\alpha]_D^{20\,°C}$: −64.5 (c = 0.4, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3378 (b), 2935 (w), 1803 (s), 1708 (s), 1563 (s), 1454 (m), 1248 (s), 1055 (s), 798 (m), 700 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.22 (m, 3H), 7.21 – 7.14 (m, 1H), 7.09 – 7.03 (m, 2H), 6.61 (d, *J* = 2.3 Hz, 1H), 5.28 (d, *J* = 2.3 Hz, 1H), 4.86 (dd, *J* = 10.5, 6.0 Hz, 1H), 4.43 – 4.31 (m, 1H), 4.02 (d, *J* = 12.7 Hz, 1H), 3.89 (dd, *J* = 12.6, 2.2 Hz, 1H), 3.75 (s, 3H), 2.70 – 2.56 (m, 3H), 2.36 (ddd, *J* = 13.5, 5.3, 1.8 Hz, 1H), 2.33 – 2.21 (m, 2H), 1.65 (ddd, *J* = 13.6, 10.5, 1.7 Hz, 1H), 1.40 (dtd, *J* = 13.5, 7.8, 6.9, 2.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.42, 163.24, 162.40, 152.57, 139.95, 128.71, 128.00, 126.49, 106.80, 88.93, 87.21, 87.10, 76.93, 68.34, 65.81, 65.27, 56.29, 34.58, 33.99, 29.12, 28.18.

Thiocarbonate (**S9**)



A flame dried flask under argon was sequentially charged with diol **18** (0.13 g, 0.29 mmol, 1.0 eq.), dry CH_2Cl_2 (2.9 mL), DMAP (35.0 mg, 0.29 mmol, 1.0 eq.) and 1,1-TCDI (77.0 mg, 0.43 mmol, 1.5 eq.). Then, the mixture stirred at RT and monitored by TLC analysis until completion (ca. 12 h). Afterwards, the reaction was directly purified by FCC (EtOAc:*i*hex 3:7 to 1:1) to afford thiocarbonate **S9** (0.134 g, 0.27 mmol, 95%) as a white foam.

R_f: 0.8, EtOAc:*i*hex 9:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{24}H_{26}NO_9S$ $[M+NH_4]^+$: 504.13228; found: 504.13218.

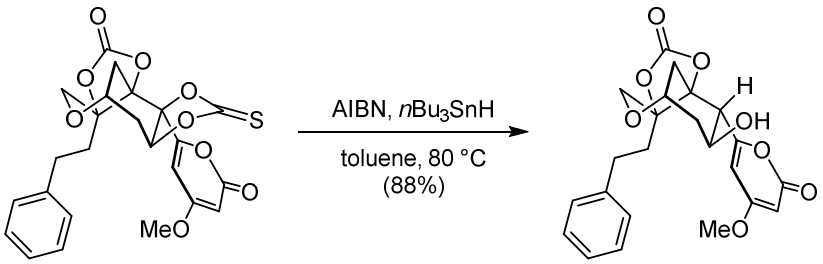
$[\alpha]_D^{20\,°C}$: +100 (c = 0.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2941 (w), 1814 (s), 1729 (s), 1567 (m), 1453 (m), 1300 (s), 1253 (m), 1061 (m), 993 (m), 700 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.21 (tt, J = 7.4, 1.2 Hz, 2H), 7.07 (td, J = 7.3, 1.2 Hz, 1H), 7.01 – 6.91 (m, 2H), 6.50 (dd, J = 2.1, 1.3 Hz, 1H), 5.44 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 4.80 (dd, J = 2.2, 1.0 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.37 (d, J = 3.0 Hz, 1H), 3.11 (dd, J = 12.6, 2.3 Hz, 1H), 2.53 (d, J = 1.0 Hz, 3H), 2.48 (ddd, J = 15.2, 11.7, 4.1 Hz, 1H), 2.31 (ddd, J = 14.2, 11.1, 5.3 Hz, 1H), 2.10 (dddd, J = 13.4, 11.6, 5.3, 1.3 Hz, 1H), 1.97 (dddd, J = 14.4, 8.4, 3.6, 1.9 Hz, 1H), 1.64 (ddd, J = 14.2, 5.7, 2.0 Hz, 1H), 1.55 (dddd, J = 13.4, 11.1, 4.2, 2.3 Hz, 1H), 1.49 (d, J = 14.1 Hz, 1H), 0.82 (ddd, J = 14.5, 7.2, 2.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 187.67, 169.49, 160.25, 154.99, 151.22, 139.93, 128.97, 126.74, 106.79, 90.14, 87.60, 87.07, 83.94, 79.88, 67.73, 64.44, 55.28, 33.90, 33.55, 28.31.

Alcohol (**19**)



S9 **19**

A flame dried flask under argon was charged with thiocarbonate **S9** (92.0 mg, 0.19 mmol, 1.0 eq.) and dry toluene (12.0 mL). The reaction was placed into a preheated oil bath at 80 °C. Subsequently, a solution of AIBN (15.0 mg, 0.09 mmol, 0.5 eq.) and nBu$_3$SnH[6] (0.82 mL, 2.8 mmol, 15.0 eq.) in dry toluene (5.0 mL) was slowly added to the mixture. The reaction was stirred at the same temperature and monitored by TLC analysis until completion (ca. 1 h). Afterwards, the reaction was cooled, the solvent was partially removed under reduced pressure and the mixture was directly purified by FCC (MeOH:CH_2Cl_2 3:97) to afford alcohol **19** (78.0 mg, 0.18 mmol, 95%) as a transparent foam.

R_f: 0.3, EtOAc:*i*hex 9:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{23}H_{28}NO_8$ $[M+NH_4]^+$: 446.18094; found: 446.18088.

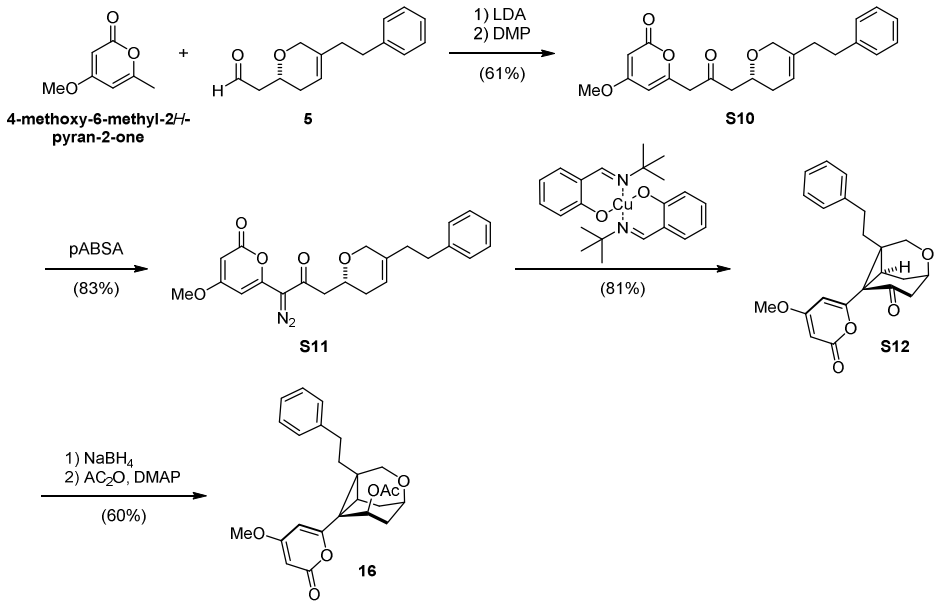
$[\alpha]_D^{20\,°C}$: −135 (c = 0.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3375 (s), 2964 (w), 1808 (s), 1696 (s), 1567 (m), 1457 (m), 1250 (s), 1045 (s), 1014 (m), 966 (m), 806(m) cm^{-1}.

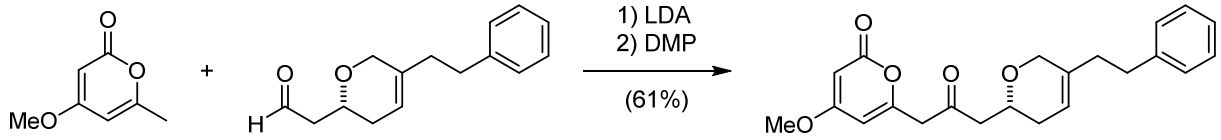
^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.19 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 2.3 Hz, 1H), 4.85 (td, *J* = 10.4, 6.0 Hz, 1H), 4.47 (s, 1H), 4.03 – 3.95 (m, 2H), 3.83 (dd, *J* = 12.6, 2.2 Hz, 1H), 3.76 (d, *J* = 1.5 Hz, 3H), 3.22 (d, *J* = 10.5 Hz, 1H), 2.70 (ddd, *J* = 9.9, 5.5, 3.5 Hz, 2H), 2.62 (ddd, *J* = 13.5, 5.5, 2.0 Hz, 1H), 2.47 (dd, *J* = 11.9, 5.8 Hz, 1H), 2.36 (ddd, *J* = 13.7, 10.2, 6.8 Hz, 1H), 1.79 (d, *J* = 13.3 Hz, 1H), 1.61 (dddd, *J* = 13.9, 9.2, 5.8, 2.2 Hz, 1H), 1.55 – 1.45 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.92, 163.24, 160.73, 157.71, 152.44, 139.89, 128.79, 127.97, 126.54, 107.11, 88.86, 87.29, 84.27, 77.37, 69.02, 64.96, 64.55, 56.16, 53.73, 38.87, 35.82, 33.66, 28.01.

Model substrate **16** synthetic route



Pyrone (**S10**)



4-methoxy-6-methyl-2*H*-pyran-2-one **5** **S10**

A flame dried flask under argon was charged with pyrone (1.83 g, 13.0 mmol, 1.3 eq.), HMPA (2.65 mL, 15.2 mmol, 1.5 eq.), dry Et_2O (70 mL) and was cooled to −78 °C. A freshly prepared solution of LDA (12.7 mL, 12.9 mmol, 1.3 eq., 1.02 M in THF) was slowly added and the mixture was stirred at the same temperature for 40 minutes. Then, a solution of aldehyde **5** (2.32 g, 10.1 mmol, 1.0 eq.) in dry Et_2O (30.0 mL) was added dropwise and the reaction mixture was stirred for another 1.5 h. Afterwards, the reaction was quenched by adding $Na_2SO_4 \bullet 10H_2O$ (2 eq.) and was allowed to warm to RT. The precipitate was filtered, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was passed through a silica plug (EtOAc/*i*hex 4:6 to 6:4) to afford the crude alcohol as a yellow oil that was used in the next step without further purification.

Data for alcohol:

R_f: 0.2, *i*hex:EtOAc 1:1, CAM, UV.

A flame dried flask under argon was charged with crude alcohol, dry CH_2Cl_2 (75 mL) and was cooled to 0 °C. To this solution DMP (3.77 g, 8.96 mmol, 0.9 eq.) was added and the mixture was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_{3(aq.)}$ and sat. $NaHCO_{3(aq.)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 3:7 to 4:6) to afford ketone **S10** (1.90 g, 616 mmol, 61%) as a white solid.

R_f: 0.5, EtOAc/*i*hex 6:4, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{28}NO_5$ $[M+NH_4]^+$: 386.19620; found: 386.19645.

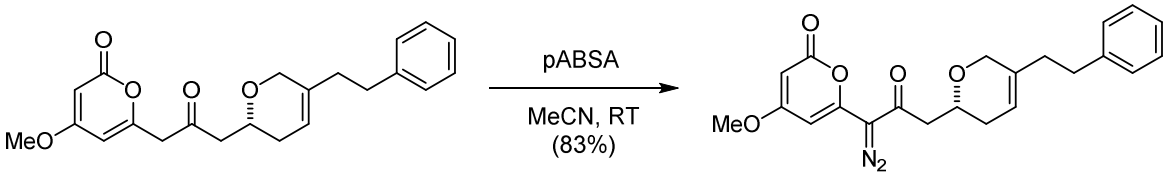
$[\alpha]_D^{20\,°C}$: +33.1 (c = 0.8, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3078 (w), 2899 (w), 1716 (s), 1653 (m), 1564 (s), 1259 (s), 1053 (m), 825 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.15 (m, 3H), 5.93 (s, 1H), 5.51 (s, 1H), 5.45 (s, 1H), 4.11 (dt, *J* = 15.5, 3.0 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.96 – 3.89 (m, 1H), 3.80 (s, 3H), 3.66 – 3.56 (m, 2H), 2.78 (dd, *J* = 15.8, 8.3 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.59 (dd, *J* = 15.7, 4.2 Hz, 1H), 2.21 (t, *J* = 8.2 Hz, 2H), 2.02 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 201.84, 170.73, 164.18, 157.57, 141.61, 136.21, 128.30, 128.22, 125.88, 117.77, 102.97, 88.39, 69.92, 68.21, 55.88, 48.59, 47.82, 34.65, 34.10, 30.42.

Diazo (**S11**)



S10 **S11**

A flame dried flask under argon was sequentially charged with ketone **S10** (1.50 g, 4.07 mmol, 1.0 eq.), dry MeCN (28 mL), *p*-ABSA (1.25 g, 5.24 mmol, 1.3 equiv) at RT. To this solution Et_3N (0.84 mL, 6.00 mmol, 1.5 eq.) was added dropwise. The resulting orange suspension was monitored by TLC until completion (ca. 2 h). The reaction was concentrated to the volume of ca. 4 mL under reduced pressure and purified by FCC (EtOAc/*i*hex 1:1) to afford diazo **S11** (1.35 g, 3.70 mmol, 83%) as a yellow solid.

R_f: 0.7, EtOAc/*i*hex 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{23}N_2O_5$ $[M+H]^+$: 395.16015; found: 395.11006.

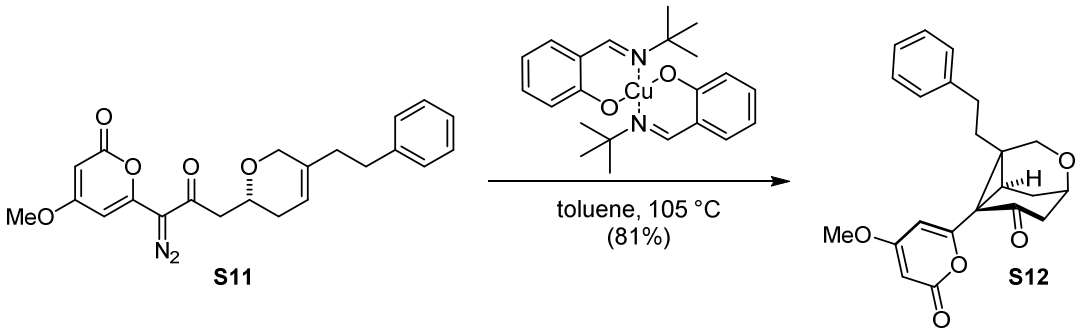
$[\alpha]_D^{20\,°C}$: +98.0 (c = 0.7, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2836 (w), 2091 (s), 1726 (s), 1635 (s), 1555 (s), 1411 (m), 1226 (s), 1015 (m), 957 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.25 (m, 2H), 7.24 – 7.10 (m, 3H), 6.94 (d, J = 2.2 Hz, 1H), 5.52 (s, 1H), 5.36 (d, J = 2.2 Hz, 1H), 4.07 (q, 2H), 3.99 – 3.89 (m, 1H), 3.82 (s, 3H), 2.82 (dd, J = 14.4, 8.4 Hz, 1H), 2.76 – 2.59 (m, 3H), 2.21 (t, J = 8.1 Hz, 2H), 2.14 – 1.99 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.51, 171.88, 162.49, 148.94, 141.77, 136.51, 128.51, 128.42, 126.11, 117.80, 98.76, 86.82, 75.38, 71.27, 68.56, 56.14, 45.55, 34.83, 34.27, 30.66.

Cyclopropane (**S12**)



A flame dried flask under argon was sequentially charged with $Cu(TBS)_2$[7] (200 mg, 0.05 mmol, 0.1 eq.), dry toluene (16 mL) and the reaction vessel was placed in a 105 °C preheated oil bath. To this solution was added diazo **S11** (0.20 g, 0.50 mmol, 1.0 eq.) in dry toluene (16 mL) using a syringe pump (2 mL/h). At the end of the addition the resulting mixture was analyzed by TLC for completion. Afterwards, the reaction was cooled to RT, concentrated to the volume of ca. 1 mL and purified by FCC (EtOAc/*i*hex 1:1 to 6:4) to afford cyclopropane **S12** (0.15 g, 4.08 mmol, 81%) as a yellow oil.

R_f: 0.3, EtOAc/*i*hex 6:4, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{22}H_{23}O_5$ $[M+H]^+$: 367.15400; found: 367.15445.

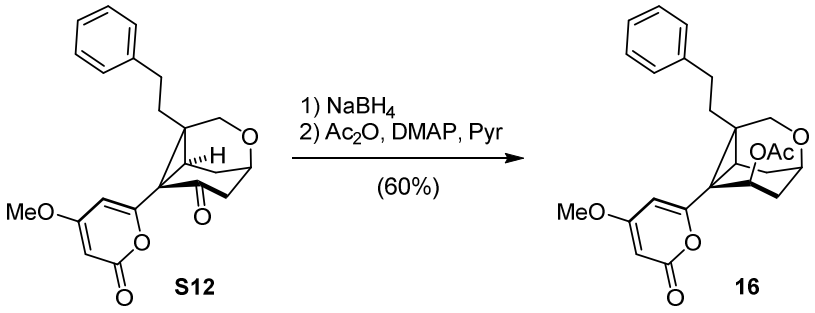
$[\alpha]_D^{20\,°C}$: +62.6 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3025 (w), 2940 (w), 1713 (s), 1686 (s), 1645 (m), 1452 (m), 1402 (m), 1241 (s), 1088 (m), 1006 (s), 822 (m), 727 (m) cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 6.1 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.11 – 7.06 (m, 2H), 6.11 (d, *J* = 2.2 Hz, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 4.29 (d, *J* = 13.1 Hz, 1H), 4.22 (dq, *J* = 4.4, 2.1 Hz, 1H), 4.18 (d, *J* = 13.1 Hz, 1H), 3.80 (s, 3H), 2.83 (ddd, *J* = 14.2, 10.2, 4.4 Hz, 1H), 2.73 (dt, *J* = 19.7, 1.9 Hz, 1H), 2.66 (ddd, *J* = 13.8, 10.0, 7.2 Hz, 1H), 2.44 (dd, *J* = 19.6, 4.4 Hz, 1H), 2.28 (dt, *J* = 3.4, 2.0 Hz, 1H), 2.23 (dddd, *J* = 13.4, 4.6, 3.1, 1.7 Hz, 1H), 1.87 (dt, *J* = 13.5, 2.0 Hz, 1H), 1.73 (ddd, *J* = 14.4, 10.0, 4.4 Hz, 1H), 1.41 (ddd, *J* = 14.4, 10.2, 7.2 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 201.68, 170.85, 164.35, 157.91, 140.62, 128.74, 128.56, 126.49, 105.89, 89.02, 66.11, 62.92, 56.10, 48.26, 42.22, 37.89, 36.56, 32.06, 29.18, 24.10.

Acetate (**16**)



A flask was sequentially charged with cyclopropane **S12** (73.0 mg, 0.2 mmol, 1.0 eq.), EtOH (1.4 mL) and the reaction vessel was cooled to 0 °C. $NaBH_4$ (22.0 mg, 0.6 mmol, 3.0 eq.) was added to the solution and the reaction was stirred at the same temperature. The reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by adding sat. $NH_4Cl_{(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The material was passed through a pad of silica (EtOAc/*i*hex 7:3) to afford a crude product that was dissolved in neat dry pyridine (0.5 mL). To this solution were added DMAP (26.0 mg, 0.21 mmol, 1.05 eq.) and Ac_2O (0.05 mL, 0.50 mmol, 2.5 eq.). The reaction was stirred and monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was quenched by adding pH 7 phosphate buffer. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 6:4) to afford acetate **16** (48.4 g, 0.12 mmol, 60%) as a slightly yellow oil.

R_f: 0.6, EtOAc/*i*hex 8:2, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{24}H_{27}O_6$ $[M+H]^+$: 411.18022; found: 411.18167.

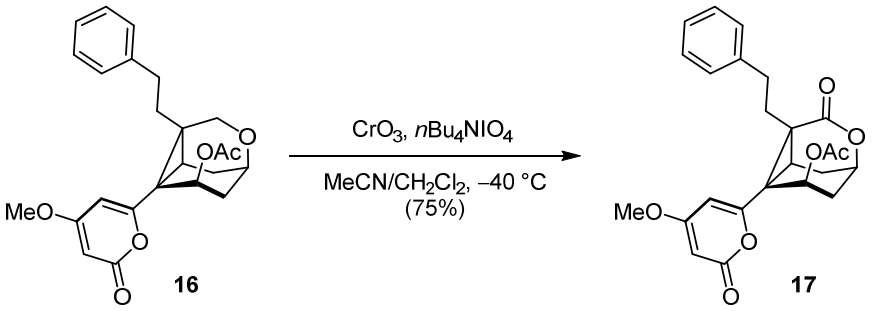
$[\alpha]_D^{20\,°C}$: +2.3 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2939 (w), 1716 (vs), 1641 (s), 1564 (s), 1452 (m), 1402 (m), 1231 (vs), 1013 (s), 814 (m), 728 (s) cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.24 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.18 – 7.15 (m, 1H), 7.10 – 7.07 (m, 2H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.59 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.17 (d, *J* = 12.1 Hz, 1H), 4.02 (s, 1H), 3.77 (s, 3H), 2.79 (ddd, *J* = 13.8, 10.8, 4.5 Hz, 1H), 2.64 (ddd, *J* = 13.7, 10.7, 6.5 Hz, 1H), 2.23 (ddd, *J* = 16.2, 10.3, 4.1 Hz, 1H), 2.17 (s, 3H), 2.10 – 2.04 (m, 1H), 1.87 (dd, *J* = 16.2, 2.2 Hz, 1H), 1.74 (d, *J* = 2.8 Hz, 1H), 1.66 (ddd, *J* = 14.9, 10.7, 4.5 Hz, 1H), 1.63 – 1.58 (m, 1H), 1.45 (ddd, *J* = 14.4, 10.8, 6.6 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 170.94, 164.41, 164.18, 141.47, 128.59, 128.54, 126.18, 102.41, 88.67, 69.63, 65.93, 62.84, 56.03, 36.77, 34.72, 34.60, 32.53, 29.88, 23.43, 23.11, 21.51.

Lactone (**17**)



A flame dried flask under Argon was charged with CrO_3 (23.0 mg, 0.23 mmol, 2.5 eq.) and dry MeCN/CH_2Cl_2 (1.26 mL, 10:1) and was stirred for 20 minutes at RT. Then, the brown solution (there can still be some undissolved CrO_3) was cooled to −40 °C with an acetone bath. To this mixture was added *n*BuNIO$_4$ (0.1 g, 0.23 mmol, 2.5 eq.) and it was stirred at the same temperature for 15 minutes (the solution becomes bright orange). Then, a solution of acetate **16** (39.0 mg, 0.1 mmol, 1.0 eq.) in dry MeCN/CH_2Cl_2 (1.26 mL, 10:1) was added dropwise and the reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*hex 6:4) to afford lactone **17** (30.5 mg, 0.07 mmol, 75%) as a colorless oil.

R_f: 0.5, EtOAc/*i*hex 8:2, $KMnO_4$, UV.

HRMS-ESI (m/z): calc. for $C_{24}H_{28}NO_7$ $[M+NH_4]^+$: 442.18603; found: 442.18714.

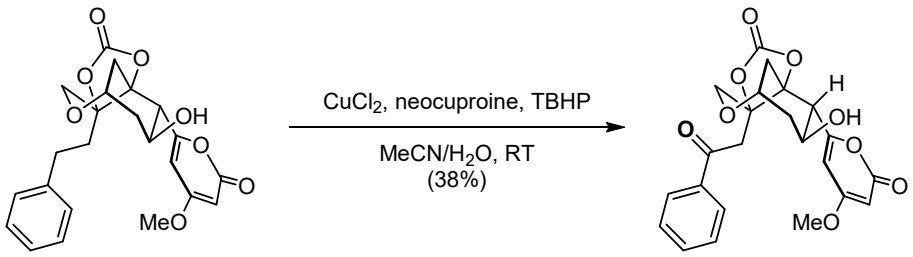
$[\alpha]_D^{20\,°C}$: +28.6 (c = 0.8, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3021 (w), 2933 (w), 1717 (vs), 1646 (m), 1566 (s), 1453 (m), 1403 (m), 1244 (m), 1005 (m), 812 (m), 747 (vs) cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.29 – 7.25 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.60 (d, *J* = 7.8 Hz, 1H), 5.44 (d, *J* = 2.2 Hz, 1H), 4.62 (dd, *J* = 4.5, 2.5 Hz, 1H), 3.79 (s, 3H), 2.89 (td, *J* = 9.4, 4.7 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.62 (ddd, *J* = 13.4, 8.9, 4.0 Hz, 1H), 2.20 (ddd, *J* = 16.0, 4.8, 1.8 Hz, 1H), 2.13 (s, 3H), 2.09 (q, *J* = 2.3 Hz, 1H), 2.00 (ddd, *J* = 14.1, 4.7, 2.2 Hz, 1H), 1.90 (ddd, *J* = 16.0, 7.9, 1.7 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.04 (dt, *J* = 14.2, 8.6 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 170.65, 170.32, 168.73, 163.34, 161.35, 141.19, 128.84, 128.66, 126.33, 102.65, 89.23, 71.47, 69.61, 56.22, 36.83, 35.41, 34.65, 34.25, 32.88, 25.85, 22.97, 21.15.

Ketone (**S13**)



19 **S13**

A flask was charged with **19** (14.0 mg, 0.032 mmol, 1.0 eq.), MeCN (0.06 mL) and a solution of $CuCl_2$ (0.06 mL, 0.2 eq., 11 mg $CuCl_2$•$2H_2O$in 0.5 mL of H_2O).[8] Subsequently, neocuproine (1.3 mg, 6.5 µmol, 0.2 eq.) was added. The solution was stirred while TBHP (33.0 µL, 0.25 mmol , 8.0 eq., 70% in H_2O) was added. An aliquot of TBHP was added once a day. The reaction was monitored by TLC until completion (ca. 4 days). Afterwards, the reaction was diluted with water, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (MeOH/CH_2Cl_2 2:98) to afford lactone **S13** (5.4 mg, 0.01 mmol, 38%) as a white foam.

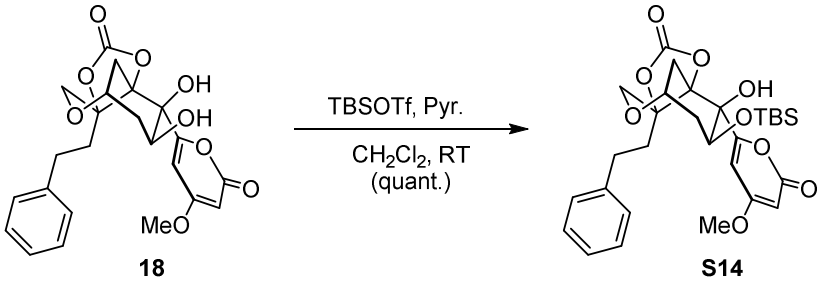
R_f: 0.2, MeOH/CH_2Cl_2 4:96, PAA (grey), UV.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.88 – 7.85 (m, 2H), 7.57 (ddt, *J* = 8.6, 7.1, 1.2 Hz, 1H), 7.48 – 7.44 (m, 2H), 6.27 (dd, *J* = 2.2, 0.8 Hz, 1H), 5.47 (d, *J* = 2.2 Hz, 1H), 4.86 (td, *J* = 10.5, 5.9 Hz, 1H), 4.48 (t, *J* = 4.9 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.81 (s, 3H), 3.77 – 3.73 (m, 1H), 3.28 (d, *J* = 10.9 Hz, 1H), 3.23 (dd, *J* = 17.4, 2.3 Hz, 1H), 2.71 (ddd, *J* = 13.6, 5.8, 2.0 Hz, 1H), 2.50 (dd, *J* = 13.6, 1.9 Hz, 1H), 1.80 (d, *J* = 13.5 Hz, 1H), 1.52 (ddd, *J* = 13.7, 10.3, 1.6 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 193.53, 171.30, 164.06, 157.86, 152.31, 136.44, 133.98, 128.95, 128.20, 108.06, 88.90, 85.24, 84.18, 68.85, 66.98, 64.55, 56.32, 54.35, 40.94, 39.19, 35.72.

Two dimensional data are available on the NMR Spectra section.

TBS alcohol (**S14**)



A flame-dried flask under argon was charged with **18** (50.0 mg, 0.1 mmol, 1.0 eq.), pyridine (0.02 mL, 0.26 mmol, 2.4 eq.) and dry CH_2Cl_2 (1.1 mL). The flask was cooled to 0 °. Then, TBSOTf (0.03 mL, 0.13 mmol, 1.2 eq.) was added dropwise and the mixture was stirred for 15 minutes at the same temperature. Afterwards, the cooling bath was removed and the reaction was monitored by TLC analysis until completion (ca. 10 h). Then, the reaction mixture was diluted with sat. $NaHCO_{3(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 3:7) to afford **S14** (65.5 mg, 0.09 mmol, quant.) as a white foam.

R_f: 0.6, EtOAc/*i*hex 4:6, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{29}H_{42}NO_9Si$ $[M+NH_4]^+$: 576.26288; found: 576.26251.

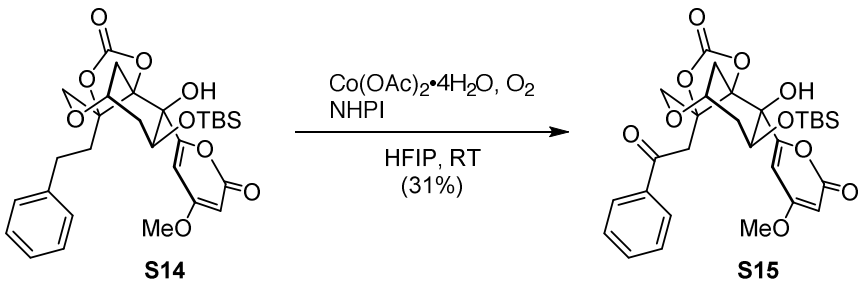
$[\alpha]_D^{20\,°C}$: −11.0 (c = 0.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3516 (bw), 3027 (w), 2930 (w), 1808 (s), 1727 (s), 1642 (m), 1565 (m), 1406 (m), 1248 (s), 1058 (s), 837 (m), 781 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.56 (dd, *J* = 2.3, 0.8 Hz, 1H), 5.30 – 5.24 (m, 1H), 4.84 (dd, *J* = 9.8, 6.2 Hz, 1H), 4.37 (s, 1H), 4.03 – 3.96 (m, 2H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.75 (d, *J* = 0.8 Hz, 3H), 2.73 – 2.65 (m, 2H), 2.59 (d, *J* = 13.3 Hz, 1H), 2.41 – 2.33 (m, 2H), 2.28 (d, *J* = 14.1 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.43 (s, 1H), 0.81 – 0.74 (m, 9H), 0.16 (d, *J* = 22.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.91, 162.32, 152.70, 139.96, 128.72, 128.11, 126.45, 106.09, 88.97, 87.76, 87.38, 68.61, 67.31, 65.57, 56.09, 36.44, 33.80, 29.30, 28.24, 25.72, 17.95, -3.82, -5.11.

Ketone (**S15**)



A flask was charged with **S14** (10.0 mg, 0.018 mmol, 1.0 eq.), NHPI (0.3 mg, 1.8 µmol, 0.1 eq.), HFIP (0.05 mL) and $Co(OAc)_2•4H_2O$ (0.1 mg, 0.3 µmol, 0.02 eq.).[9] The flask was sealed and placed under an atmosphere of O_2 (balloon). The reaction was stirred vigorously and monitored by TLC analysis until completion (ca. 4 h). Then, the reaction mixture was directly purified by FCC (EtOAc/*i*hex 3:7) to afford **S15** (3.1 mg, 5.6 µmol, 31%) as a white foam.

R_f: 0.7, EtOAc/*i*hex 1:1, CAM, UV.

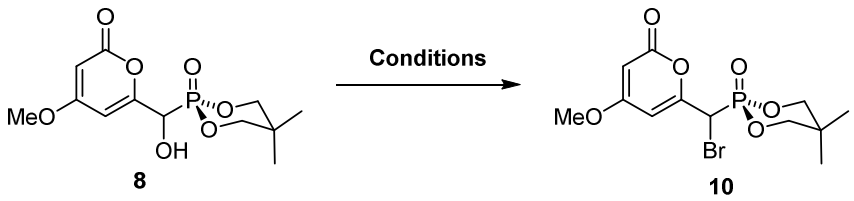
^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.85 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.41 (m, 2H), 6.70 (d, *J* = 2.3 Hz, 1H), 5.47 (d, *J* = 2.3 Hz, 1H), 4.86 (dd, *J* = 9.8, 6.2 Hz, 1H), 4.37 (d, *J* = 13.2 Hz, 1H), 4.12 (dd, *J* = 13.0, 2.4 Hz, 1H), 3.82 (s, 3H), 3.69 (d, *J* = 17.1 Hz, 1H), 3.61 (s, 1H), 3.09 (dd, *J* = 17.1, 2.4 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.45 (ddd, *J* = 13.4, 5.5, 1.8 Hz, 1H), 2.30 (dt, *J* = 11.5, 3.8 Hz, 1H), 0.80 (d, *J* = 2.7 Hz, 9H), 0.19 (d, *J* = 3.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 193.72, 171.40, 162.99, 162.67, 152.52, 136.70, 133.87, 128.89, 128.25, 106.85, 89.03, 87.30, 85.80, 68.38, 67.53, 67.46, 56.28, 41.03, 36.42, 29.13, 25.72, 17.94, -3.71, -5.13.

Two dimensional data are available on the NMR Spectra section.

6.4.2 Screening Tables

Table 1. Bromination trials of compound **8**.

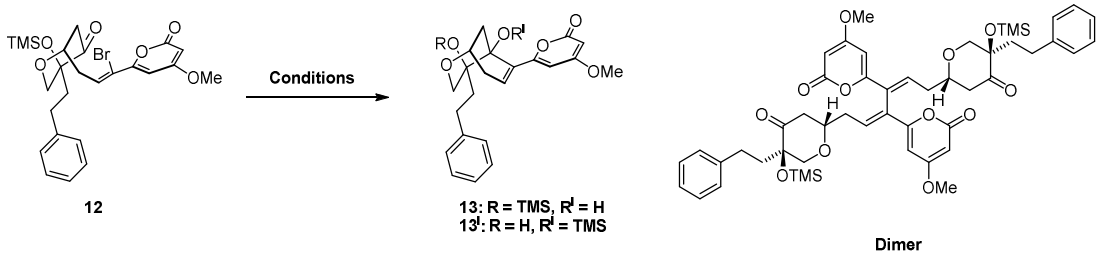


8 **10**

N.	Reagents (eq.)	Solvent, T °C	Result
1	PBr_3 (1.1 eq.)	CH_2Cl_2, RT	Complex mixture
2	TBAB, DDQ, PPh_3 (all 2 eq.)	CH_2Cl_2, RT	SM copolar with $POPh_3$
3	$SOBr_2$ (1.3 eq.)	THF, RT	Degradation
4	PBr_3 (0.3 eq.)	CH_2Cl_2, 0 °C	SM
5	CDI (1.5 eq.), Allyl Bromide (10 eq.)	MeCN, 150 °C	38% (90 mg)
6	Tf_2O then Br source	CH_2Cl_2, 0 °C	Mixture
7	TBAB, DDQ, polymer-supported PPh_3 (all 2 eq.)	CH_2Cl_2, RT	Difficult to purify
8	Br_2PPh_3, Pyr. (all 1.1 eq.)	MeCN, -20 °C	Degradation
9	TBAB, DDQ, PPh_3 (all 1 eq.)	THF or CH_2Cl_2, RT	42%-60%, difficult to purify
10	DCC, $Cu(OTf)_2$ then AcBr	THF, RT	SM
11	TCT, DMF, NaBr	CH_2Cl_2, RT	Decomposition
12	*h*BrAcetone, dppe(all 1 eq.)	MeCN, 40 °C	71%, 3 g
13	Formylmorpholine, $(COBr)_2$	CH_2Cl_2, 0 °C	Complex mixture

Abbreviations: TBAB (tetrabutyl-ammonium bromide); DDQ (2,3-Dichlor-5,6-dicyano-1,4-benzochinon); CDI (1,1'-Carbonyldiimidazole); DCC (*N*,*N*'-Dicyclohexylcarbodiimide); TCT (2,4,6-Trichloro-1,3,5-triazine); dppe (1,2-Bis(diphenylphosphino)ethane).

Table 2. Exploration and optimization studies to compound **13**.



12

13: R = TMS, R^I = H
13^I: R = H, R^I = TMS

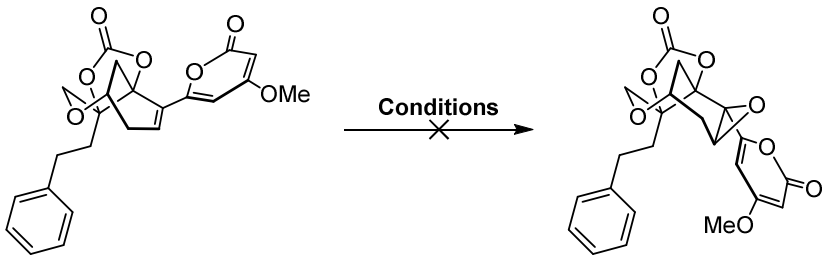
Dimer

Entry	Reagents (eq.)	Solvent, T °C	Result
1	$Rh(PPh_3)_3Cl$ (0.05 eq.), Et_2Zn (2.2 eq.)	THF, RT	SM + Reduction
2	*t*BuLi (2 eq.), TMEDA (1 eq.)	Et_2O, −78 °C	Decomposition
3	*t*BuLi (2 eq.)	THF/Et_2O/Pentane, −90 °C	Complex mixture
4	SmI_2 (3 eq.)	THF, −78 °C	Reduction
5	SmI_2 (29 eq.), HMPA (19 eq.)	THF, −78 °C	Decomposition
6	$CrCl_2$ (5 eq.), $NiCl_2$ (1 eq.)	DMSO or DMF, RT	Reduction + Dimer
7	$CrCl_2$ (6 eq.), $NiCl_2$ (0.1 eq.)	DMF, 50 °C	Reduction
9	$CrCl_2$ (6 eq.), $NiCl_2$•neocuproine (0.1 eq.)	DMF, RT	Reduction + trace Dimer
10	$CrCl_2$ (5 eq.), $NiCl_2$ (1 eq.), *t*Bu-pyr (25 eq.)	DMF, RT	Reduction
11	$CrCl_2$ (10 eq.), $NiCl_2$ (1 eq.), *t*Bu-pyr (30 eq.)	DMF or THF or THF/DMF 2/1, 50 °C	Reduction
12	$CrCl_2$ (10 eq.), $NiCl_2$ (1 eq.), *t*Bu-pyr (30 eq.)	DMF, 70 or 90 or 125 °C	Reduction
13	$TMSSnBu_3$ (2 eq.), $BnEt_3NCl$ (3 eq.)	DMF, 60 °C	Reduction
14	***n*Bu_2CuLi•LiI (5 eq.)**	**Et_2O /*n*-hex 1/1, −78 °C**	**Traces**

N.	Scale	Reagents (eq.)	Solvent, T °C	Result
15	3 mg	*n*Bu_2CuLi•LiI (16 eq.)	Et_2O/*n*-hex 1/1, −78 °C	Traces
16	3 mg	*s*Bu_2CuLi•LiI (5 eq.)	Et_2O	Decomposition
17	3 mg	*n*Bu_2CuLi•LiI (6 eq.)	Et_2O/*n*-hex 1/1, −50 °C	Ox. Coupling + Product
18	3 mg	*n*Bu_2CuLi•LiI (6 eq.)	Et_2O/*n*-hex 1/1, −25 °C	Ox. Coupling + Product, more impurities than −50°C
19	3 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/*n*-hex 1/1, −78 °C	More Ox. Coupling
20	10 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/ *n*-hex 1/1, −50 °C	Ox. Coupling + Product + Reduction
21	10 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/*n*-hex 1.6/1, −30 °C	57%
22	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/*n*-hex 1.6/1, −30 °C	29%
23	65 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/*n*-hex 1.6/1, −20 °C	Decomposition
24	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 1/5.7, −30 to °C	Decomposition
25	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 1.6/1, −30 °C	43%
26	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 1/1, −30 to −10 °C	21%
27	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 1/1.25, −30 °C	40%
28	30 mg	*n*Bu_2CuLi•LiI (7 eq.)	Et_2O/Pentane 1/1.1, −30 °C	28%
29	65 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/*n*-hex 1.7/1, −30 to −10 °C	8%
30	25 mg	Np_2CuLi•LiI (4.5 eq.)	Et_2O, −50 °C	Reduction
31	30 mg	*s*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 2/1, −50 °C	Reduction + Impurities

32	30 mg	*n*Bu_2CuLi•LiI (4.5 eq.)	Et_2O/Pentane 1/1.1, −40 °C	15%
33	30 mg	*n*Bu_2CuLi•LiI (6 eq.)	Et_2O, −50 °C	44%
34	30 mg	*n*Bu_2CuLi•LiI (7 eq.)	THF/Hexane 3/1, −50 °C	Reduction
35	30 mg	*n*Bu_2CuLi•LiI (7 eq.)	THF, −50 °C	Reduction
36	60 mg	*n*Bu_2CuLi•LiI (6 eq.)	Et_2O, −50 °C	46%
37	60 mg	*n*Bu_2CuLi•LiI (9 eq.)	Et_2O, −50 °C	49%
38	120 mg	*n*Bu_2CuLi•LiI (10 eq.)	Et_2O, −50 °C	47%
39	**100 mg**	***n*Bu_2CuLi•LiCN (12 eq.)**	**Et_2O, −50 °C**	**89%**
40	**1.4 g**	***n*Bu_2CuLi•LiCN (12 eq.)**	**Et_2O, −50 °C**	**70%**

Table 3. Epoxidation trials of compound **14**.

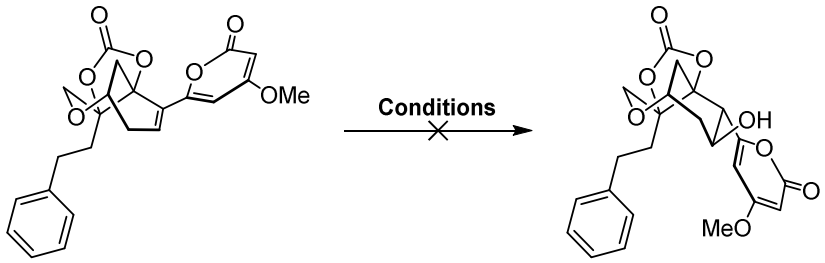


14

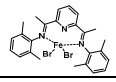
Entry	Reagents	Solvent, T °C	Result
1	mCPBA	CH_2Cl_2, RT	SM
2	DMDO	Acetone, 0 °C	Decomposition
3	$[((phen)_2(H_2O)Fe^{III})_2(\mu\text{-}O)](ClO_4)_4$, PAA	MeCN, 0 °C	SM
4	$Mn(OTf)_2$, Picolinic acid, PAA	MeCN, 0 °C	Decomposition
5	$MeReO_3$, H_2O_2, Pyr.	DCM, RT	SM
On Diol **S8**			
1	$K_2[\{W(O)(O_2)_2(H_2O)\}_2(O)]$ •$2H_2O$, H_2O_2	Toluene, RT	SM
2	$VO(acac)_2$, $TBHP_{decane}$	CH_2Cl_2, 0°C	[O] cleavage
3	$[((phen)_2(H_2O)Fe^{III})_2(\mu\text{-}O)](ClO_4)_4$, PAA	MeCN, 0 °C	SM
4	mCPBA	CH_2Cl_2, 0 °C	SM
5	$MeReO_3$, UHP	$CHCl_3$, RT	SM
6	$VO(acac)_2$, Lutidine, $TBHP_{decane}$	CH_2Cl_2, 0 °C	[O] cleavage
7	$VO(acac)_2$, 2,6-*t*Bu-pyr, $TBHP_{decane}$	CH_2Cl_2, 0 °C	[O] cleavage
8	MMPP•$6H_2O$	MeCN, reflux	SM + [O] cleavage
9	N(*n*-hex)$_4$PW, H_2O_2	DCE/H_2O, reflux	Decomposition
10	Ti(*i*PrO)$_4$, TBHP	CH_2Cl_2, 0 °C	[O] cleavage

Abbreviations: mCPBA (3-Chloroperbenzoic acid); DMDO (Dimethyldioxirane); PAA (Peracetic acid); TBHP (tertButyl-hydroperoxide); MMPP (Magnesium monoperoxyphthalate).

Table 4. *Anti*-Markovnikov functionalization of compound **14**.

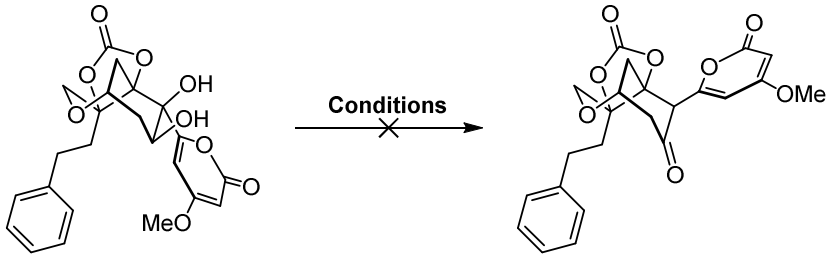


14 **19**

Entry	Reagents	Solvent, T °C	Result
1	$TiCl_4$, $NaBH_4$	DME, RT	SM
2	Acridinium cat. **A**, sulfinic acid	MeCN, RT	Decomposition
3	BH_3•DMS (large excess)	Toluene, 40 °C	Decomposition
4	$TiCl_4$, Et_3BnNBH_4	CH_2Cl_2, RT	Decomposition
5	9-BBN	THF, 40 °C	SM
6	BH_3•THF, pyr, I_2	THF, 0 °C	Decomposition
7	$B(C_6F_5)_3$-$PhMe_2SiH$	THF, 0 °C	SM
8	 , Silane	CH_2Cl_2, RT	SM

Abbreviations: 9-BBN (9-Borabicyclo(3.3.1)nonane); acridinium cat. **A** (9-Mesityl-10-methylacridinium tetrafluoroborate).

Table 5. Semipinacol trials on compound **18**.

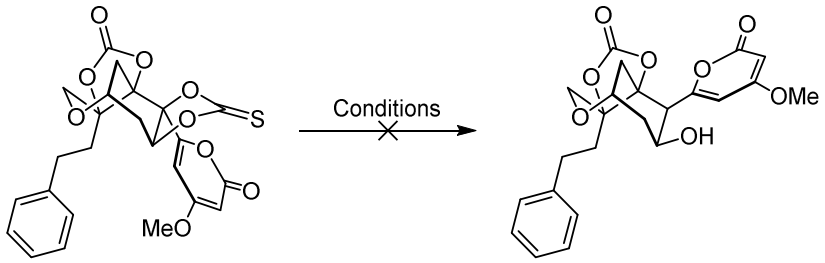


18

Entry	Reagents	Solvent, T °C	Result
1	PPh_3, C_2Cl_6	MeCN, 0 °C to RT	Decomposition
2	$SnCl_4$, $CH(OMe)_3$	CH_2Cl_2, RT	SM
3	PPh_3, DEAD	Benzene, RT	SM
4	PPh_3, C_2Cl_6, then $NaBH_4$	MeCN, 0 °C to RT	Decomposition

Abbreviations: DEAD (Diethyl azodicarboxylate).

Table 6. Screening to direct hydrogen delivery on **S9**.



S9

Entry	Reagents	Solvent, T °C	Result
1	Bu_3SnH	Benzene, 80 °C	Epimer
2	Ph_3SnH	Benzene, 80 °C	Epimer
3	SmI_2	THF, RT	Corey-Winter, **14**
4	Et_3B, O_2, $(TMS)_2SiH$	Benzene, RT	SM
5	NHC•BH_3, AIBN	Benzene, 80 °C	Corey-Winter, **14**
6	NHC•BH_3, Et_3B, O_2	Benzene, RT	Adduct
7	NHC•BH_3, Et_3B, O_2	Benzene, 0 °C	SM

NHC adduct was isolated, purified by FCC on silica and the HRMS found:

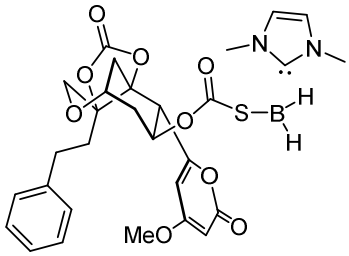
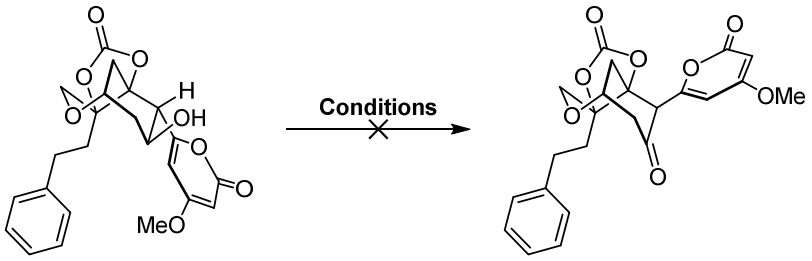


Table 7. Oxidation screening of compound **19**.

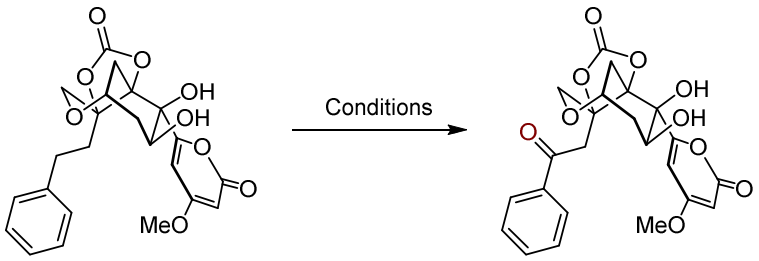


19

Entry	Reagents	Solvent, T °C	Result
1	DMP	CH_2Cl_2, RT	Decomposition
2	Bobbit's salt	CH_2Cl_2, RT	SM
3	Bobbit *N*-oxyl, *p*TsOH	CH_2Cl_2, RT	SM
4	IBX	EtOAc, 55 °C	SM
5	DMP, $NaHCO_3$	CH_2Cl_2, RT	Decomposition
6	$(COCl)_2$, DMSO	CH_2Cl_2, -78 °C	Decomposition
7	TPAP, NMO	CH_2Cl_2, RT	Decomposition
8	2,2-Bipyridine, NMI, ABNO	MeCN, RT	SM
10	BAIB, AZADO	CH_2Cl_2, RT	Decomposition
11	PCC	CH_2Cl_2, RT	SM
12	BAIB, ABNO	CH_2Cl_2, RT	Decomposition
13	BAIB, AZADO	CD_2Cl_2, RT	Decomposition monitored by ^{1}HNMR

Abbreviations: DMP (Dess–Martin periodinane); IBX (2-iodoxybenzoic acid); Bobbit's salt (CAS Number 219543-09-6); Bobbit *N*-oxyl (CAS Number 14691-89-5); TPAP (Tetrapropylammonium perruthenate); NMO (*N*-Methylmorpholine *N*-oxide); NMI (1-Methylimidazole); PCC (Pyridinium Chlorochromate); ABNO (9-Azabicyclo[3.3.1]nonane *N*-oxyl); AZADO (2-Azaadamantane-*N*-oxyl); BAIB (Diacetoxyiodobenzene).

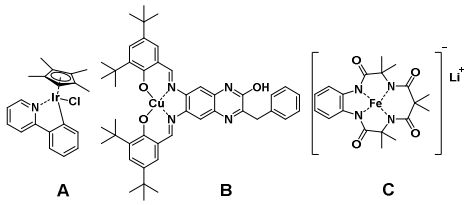
Table 8. Benzylic oxidation screening of compound **14**.



14 **Unstable**

Entry	Reagents	Result
1	Ir cat. **A**, $NaIO_4$	SM
2	$Mn(OTf)_3$, PAA	Decomposition
3	$RuCl_3$, TBHP	SM
4	$Ru(TACN)Cl_3$, TBHP	Decomposition
5	$ReO(PPh_3)Cl_3$, TBHP	SM
6	Cu cat. **B**, TBHP	Decomposition
7	$CrO_2(OAc)_2$, $n$$Bu_4NIO_4$	SM
8	$FeCl_3$, THA, H_2O_2	SM
9	Fe cat. **C**, TBHP	**Product, low conversion**
10	$FeCl_3$, TBHP	SM
11	$Rh_2(cap)_4$, TBHP	**Product, low conversion**
12	$Rh_2(esp)_2$, TBHP	Decomposition
13	DMDO	Decomposition
14	KO_2, NsCl	Decomposition
15	CrO_3, TBHP	Decomposition
16	CrO_3, AcOH	Decomposition
17	CrO_3, $n$$Bu_4NIO_4$	SM
18	$Co(OAc)_4$•$4H_2O$, O_2, NHPI, HFIP	**Full conversion**

The product was observable by ^{1}HNMR but revealed to be unstable.



6.4.3 References

[1] (a) B. Wu, Q. S. Liu, B. H. Jin, T. Qu, G. A. Sulikowski, *Eur. J. Org. Chem.* **2005**, 277-284. (b) F. Yokokawa, T. Asano, T. Shioiri, *Tetrahedron* **2001**, *57*, 6311-6327.

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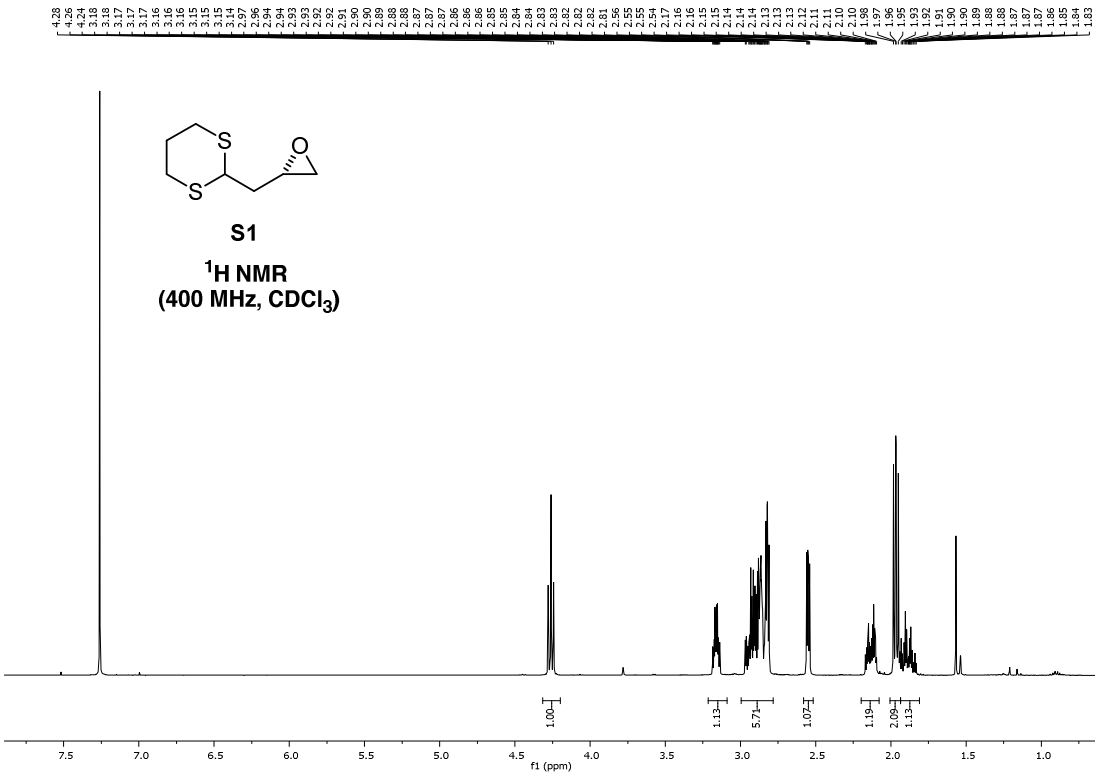
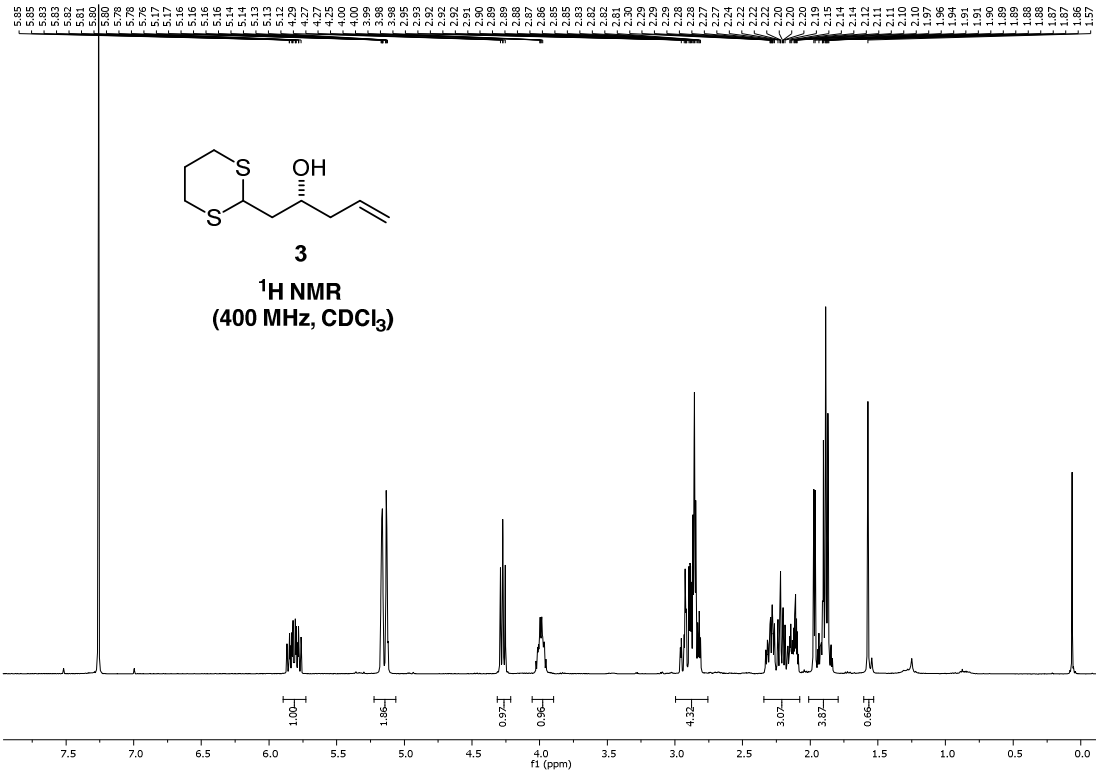
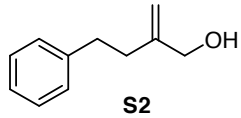
6.4.4 NMR Data for Chapter 3.2

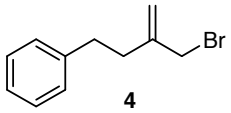






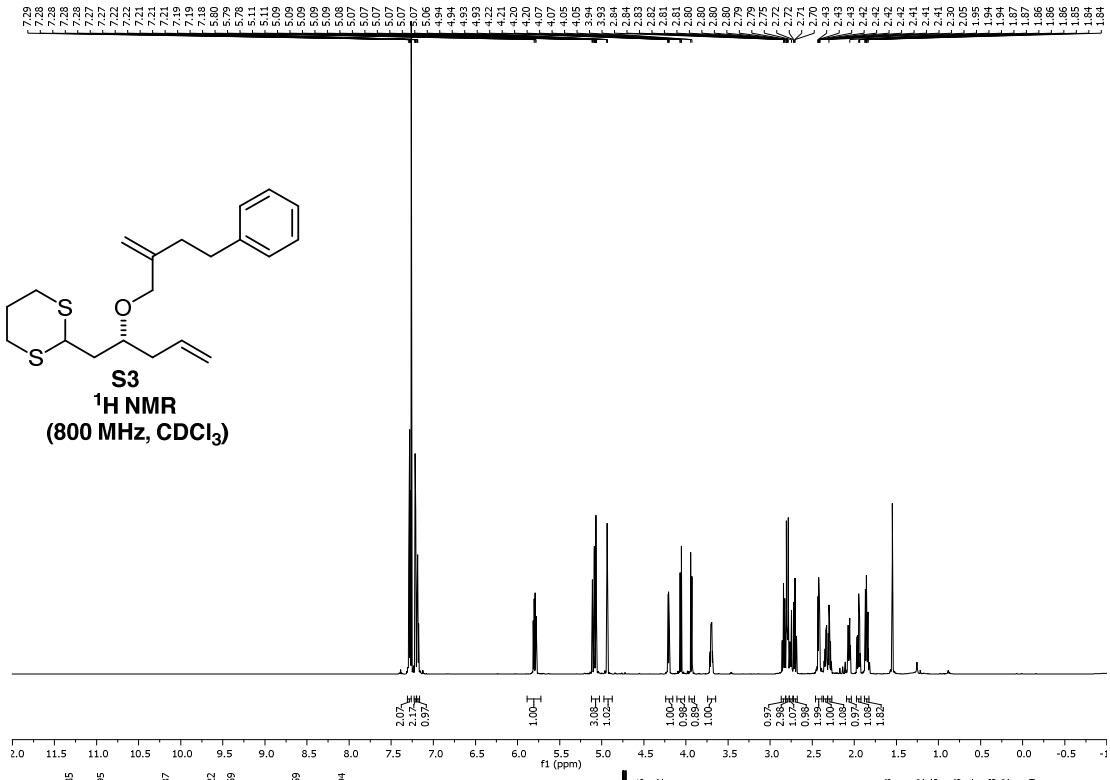
S2

^{1}H NMR
(400 MHz, $CDCl_3$)

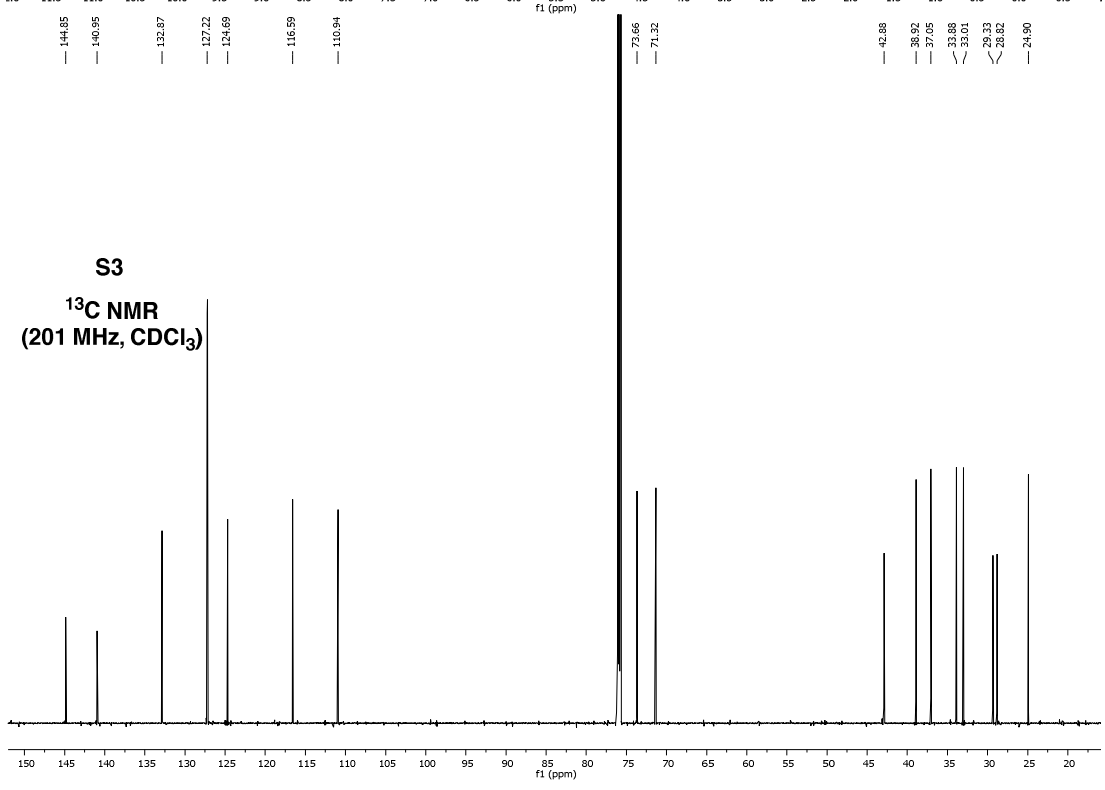


4

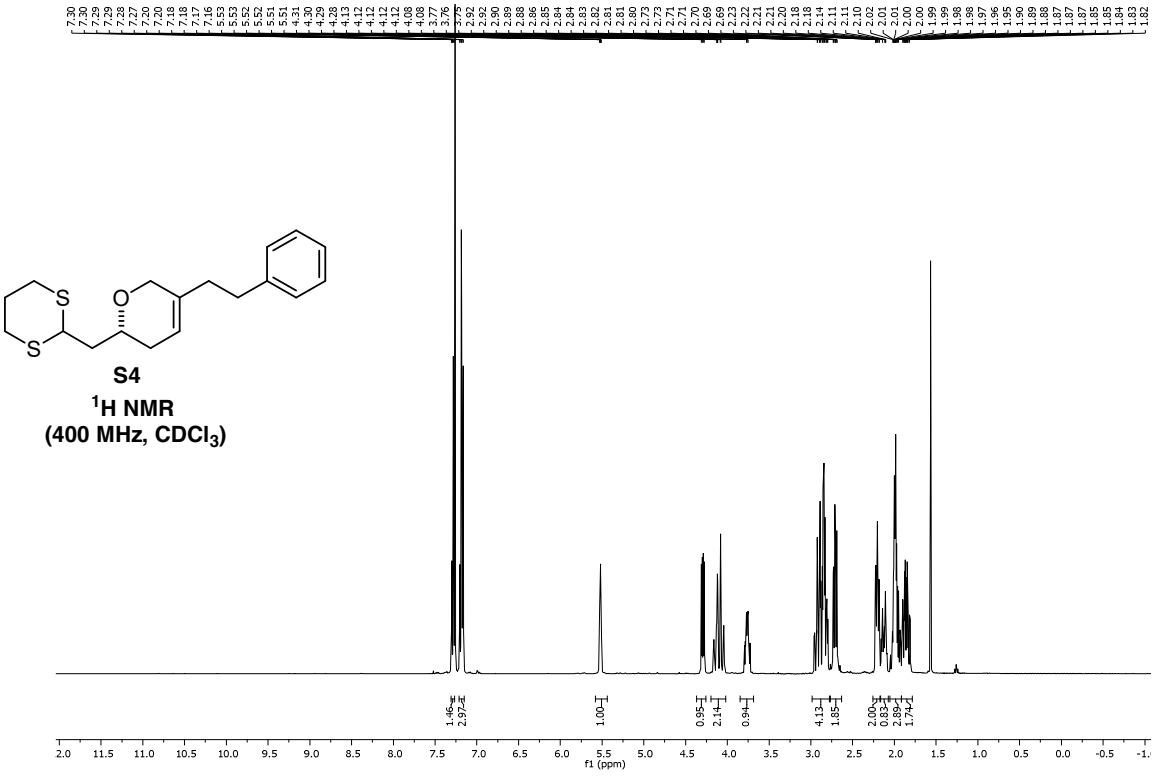
^{1}H NMR
(400 MHz, $CDCl_3$)



S3
^{1}H NMR
(800 MHz, $CDCl_3$)



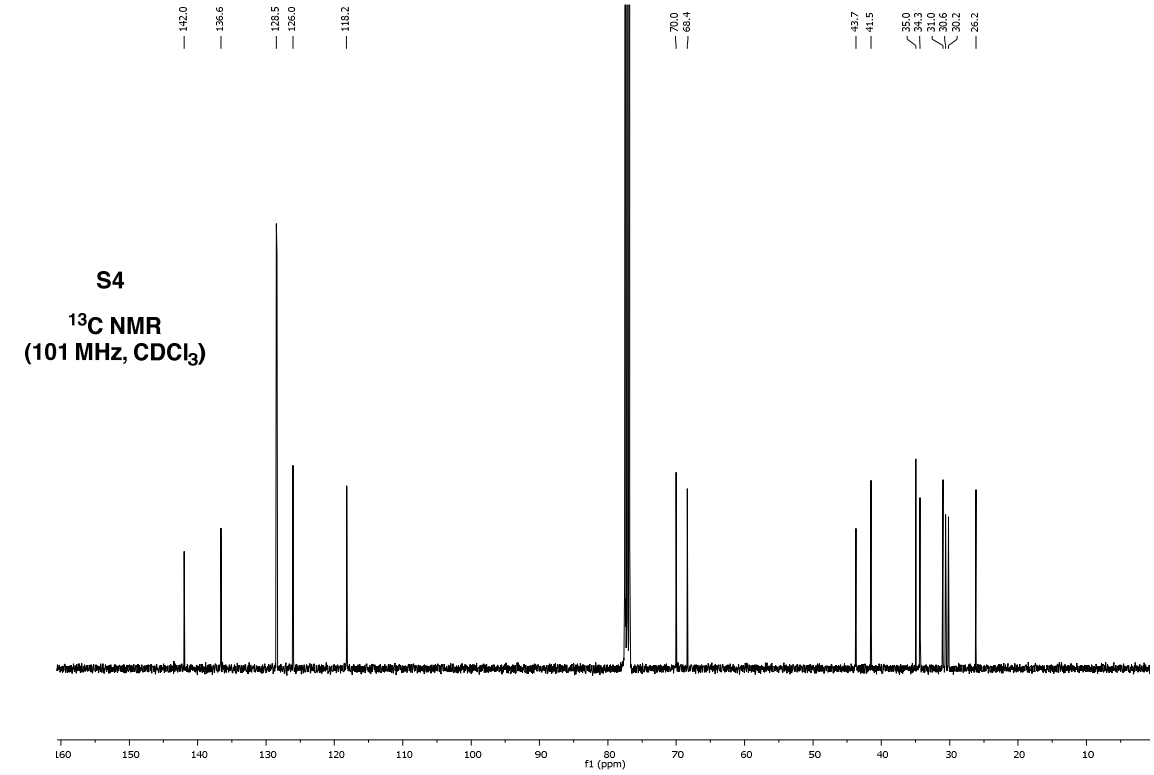
S3
^{13}C NMR
(201 MHz, $CDCl_3$)



S4

^{1}H NMR

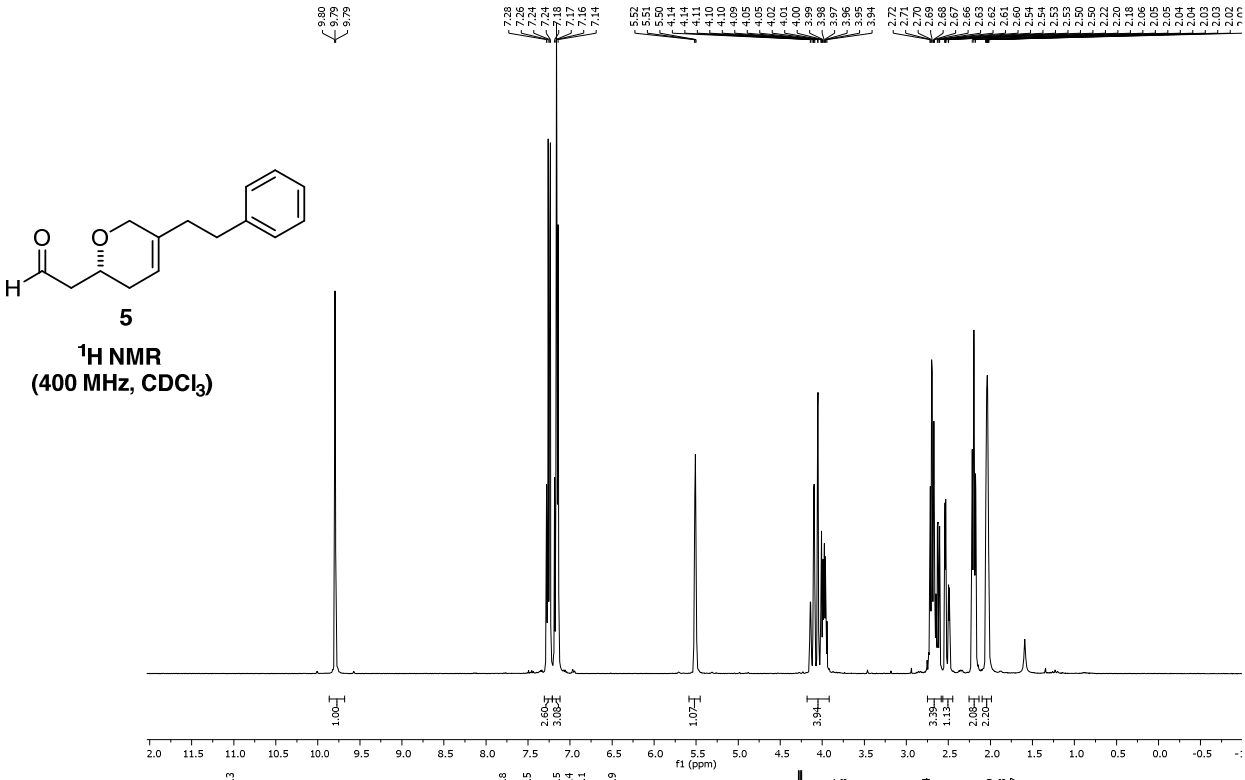
(400 MHz, $CDCl_3$)



S4

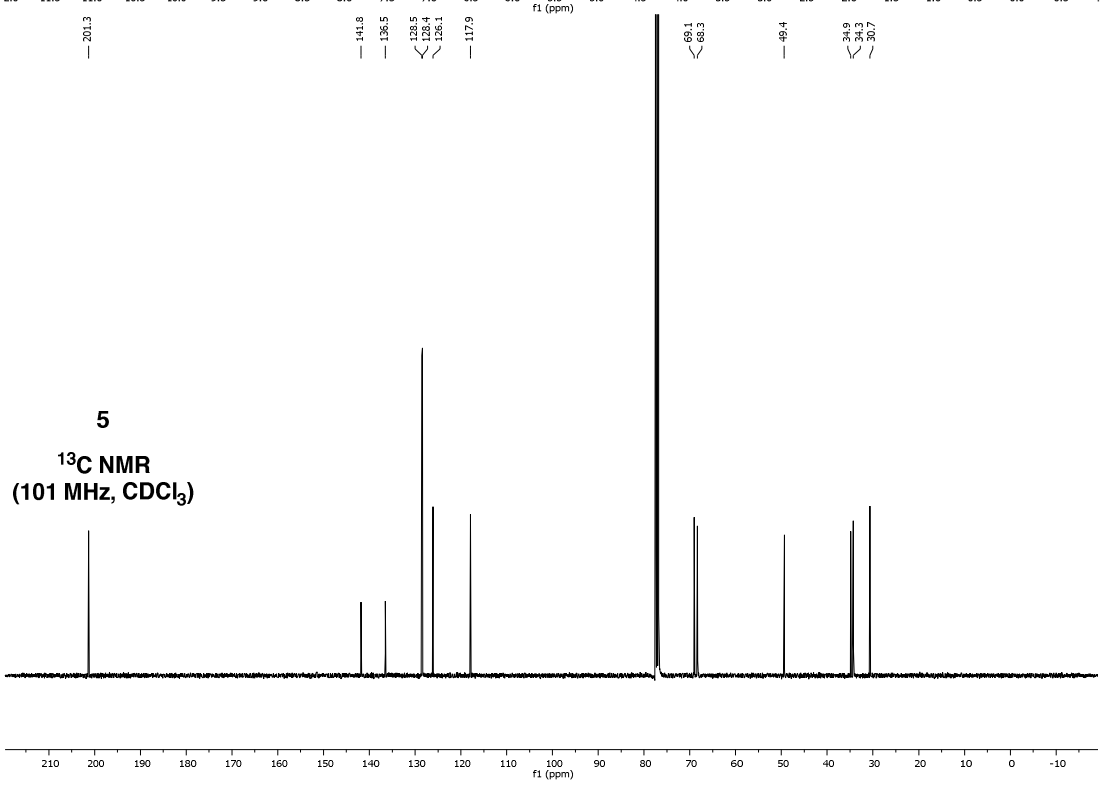
^{13}C NMR

(101 MHz, $CDCl_3$)



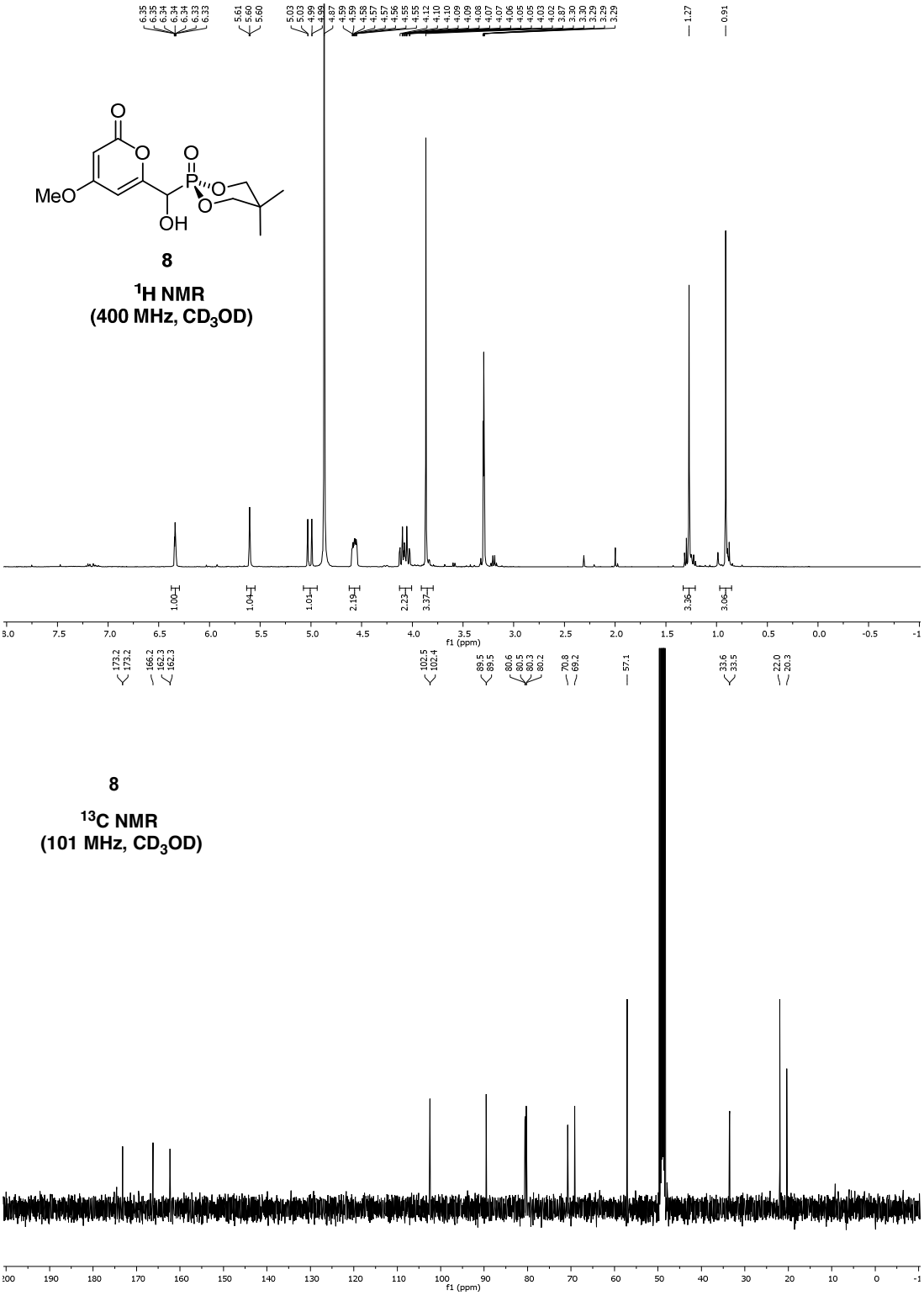
5

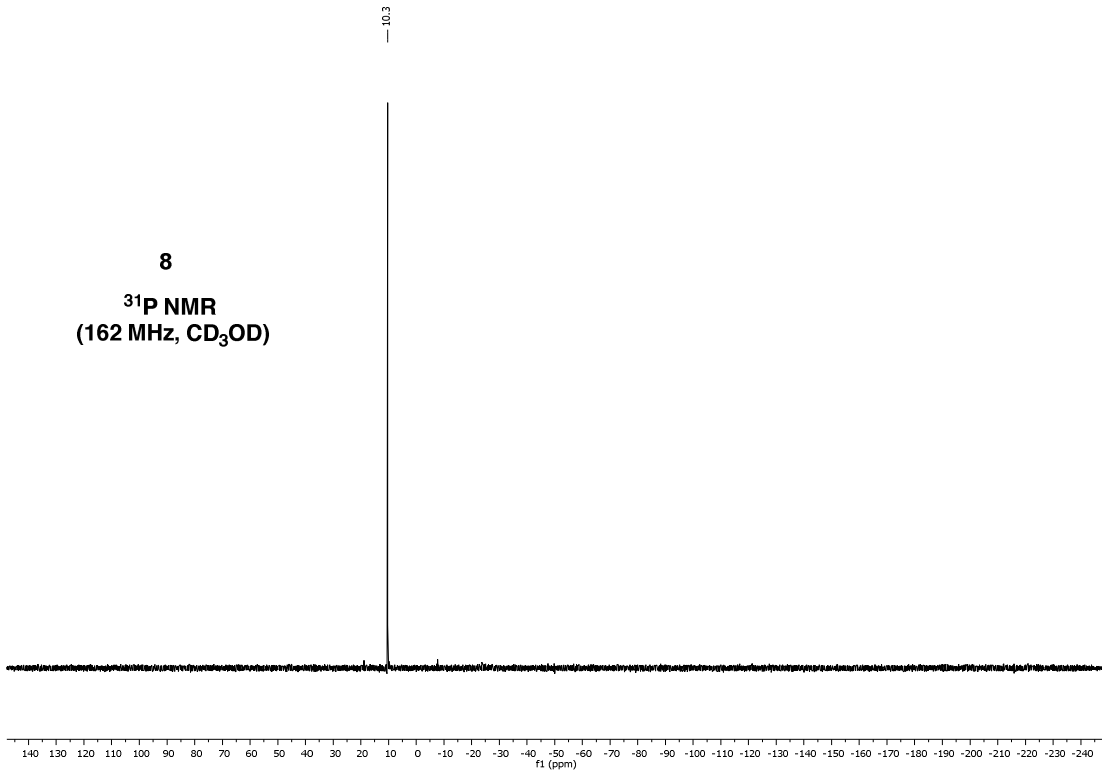
^{1}H NMR
(400 MHz, $CDCl_3$)

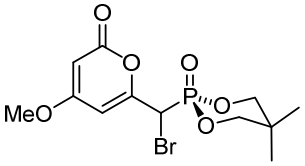


5

^{13}C NMR
(101 MHz, $CDCl_3$)


MeO
OH
8
1H NMR
(400 MHz, CD3OD)
f1 (ppm)
8
13C NMR
(101 MHz, CD3OD)
f1 (ppm)


10.3
8
31P NMR
(162 MHz, CD3OD)
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

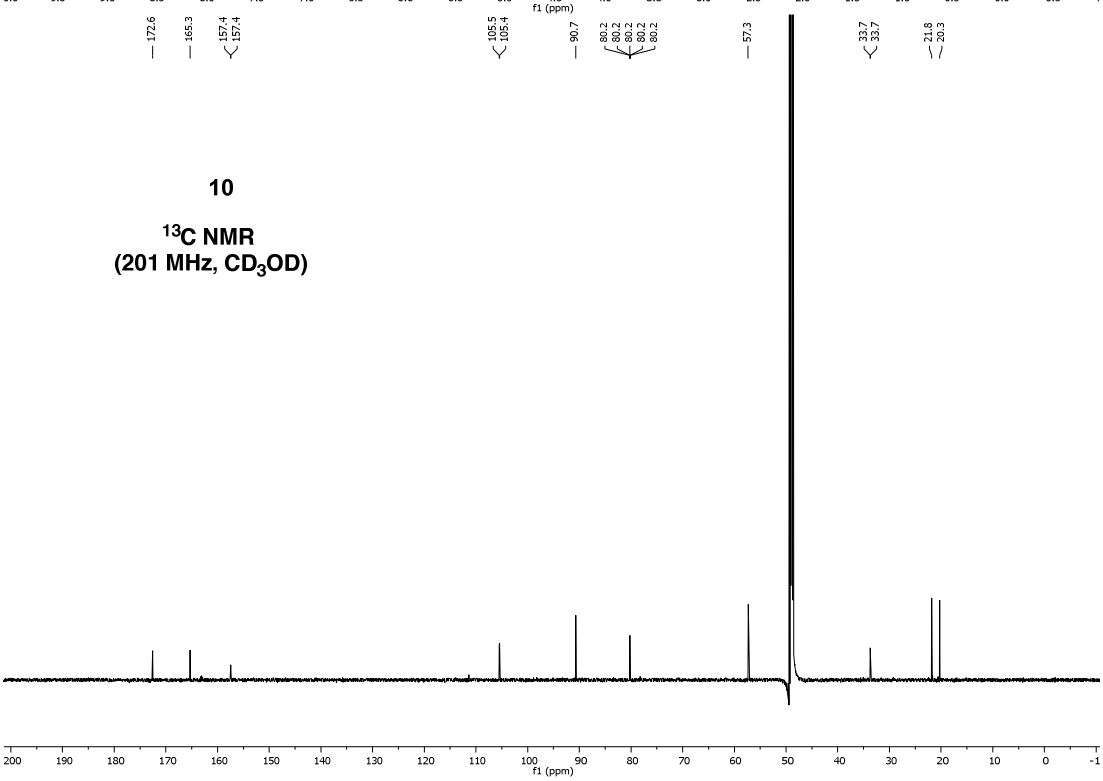


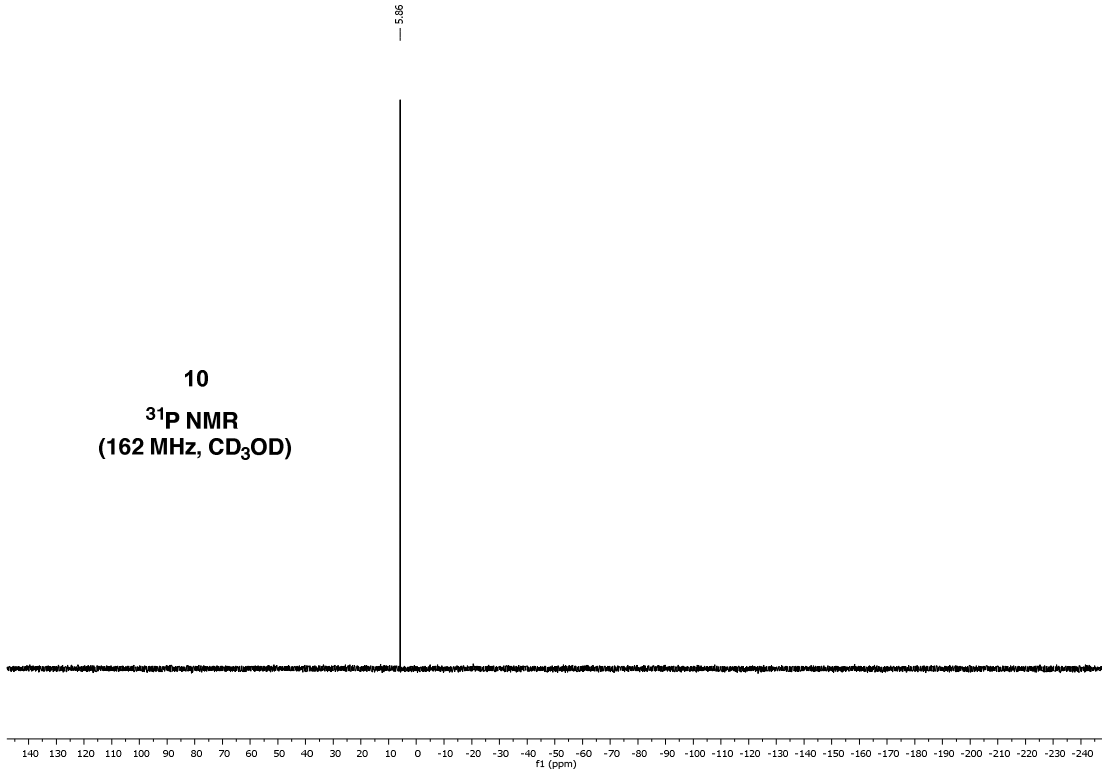
10

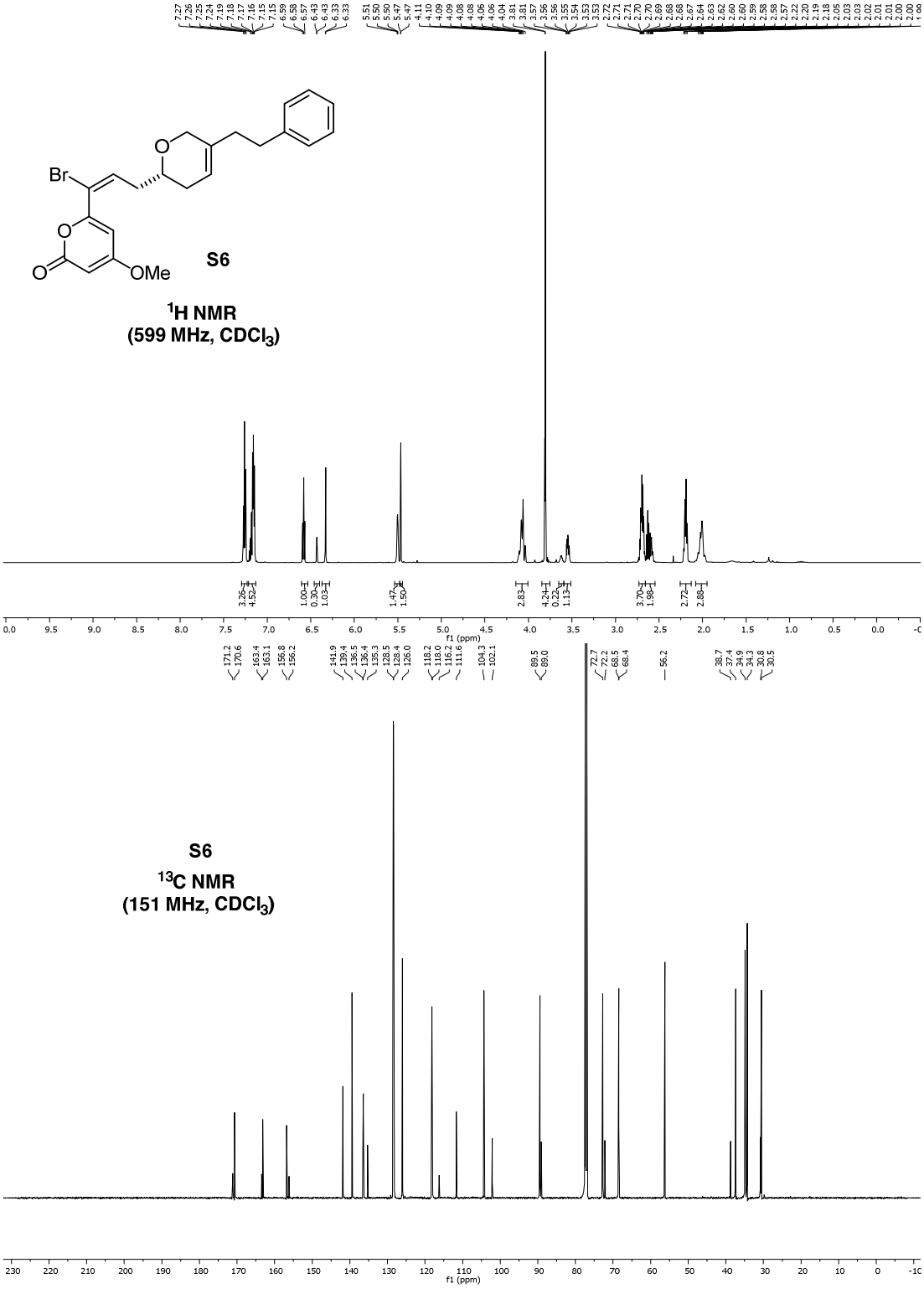
^{1}H NMR
(800 MHz, CD_3OD)

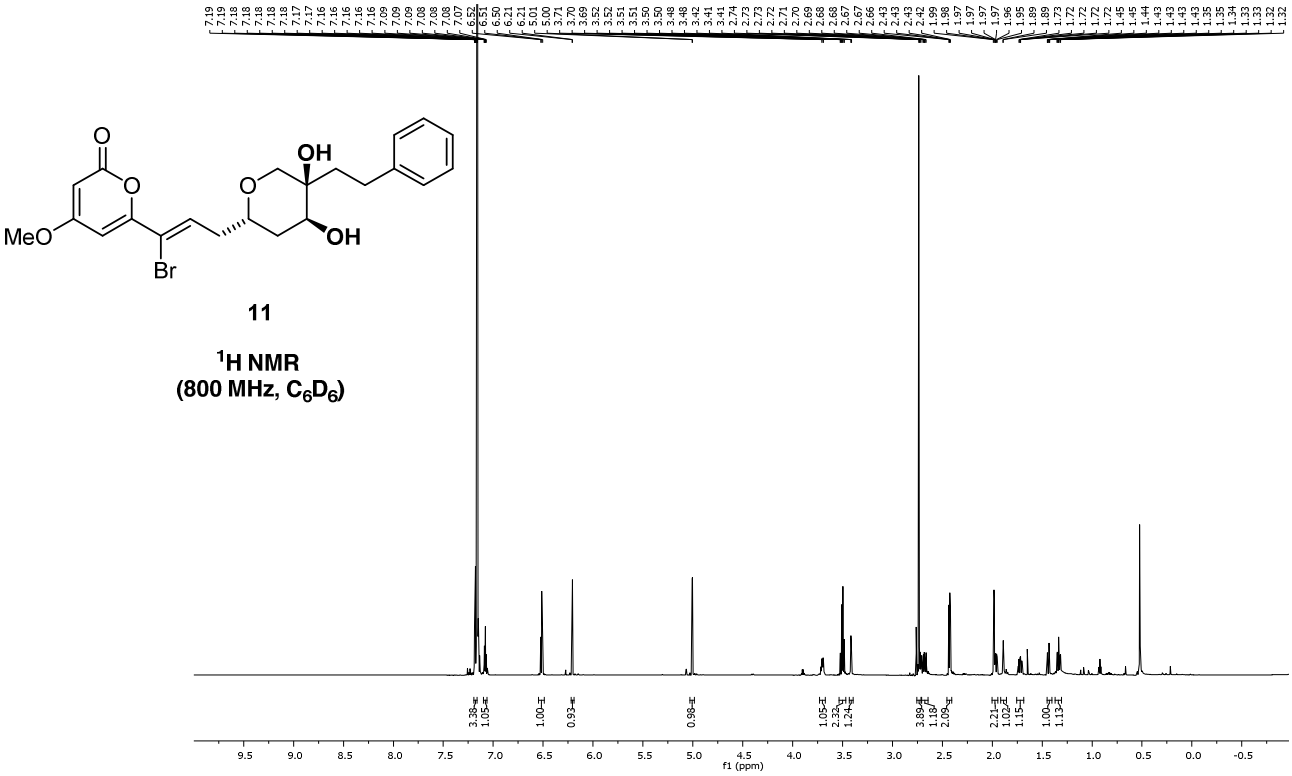
10

^{13}C NMR
(201 MHz, CD_3OD)




5.86
10
31P NMR
(162 MHz, CD3OD)
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)


Br
O
O
O
OMe
S6
1H NMR
(599 MHz, CDCl3)
S6
13C NMR
(151 MHz, CDCl3)

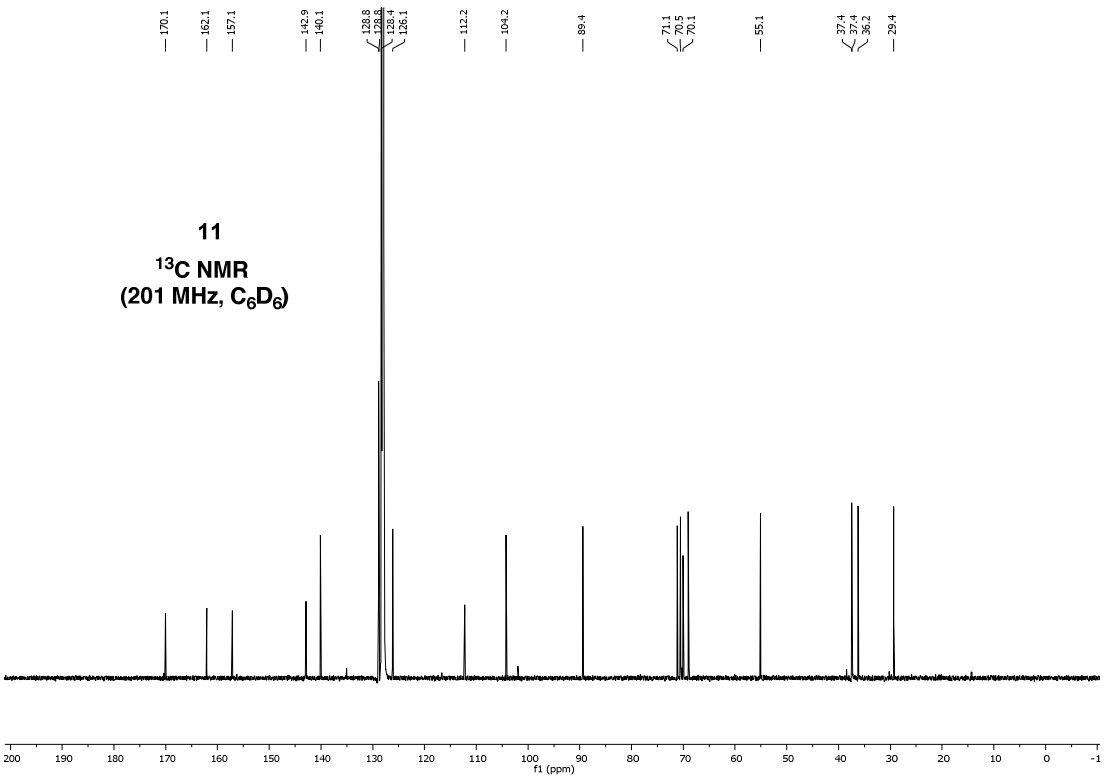


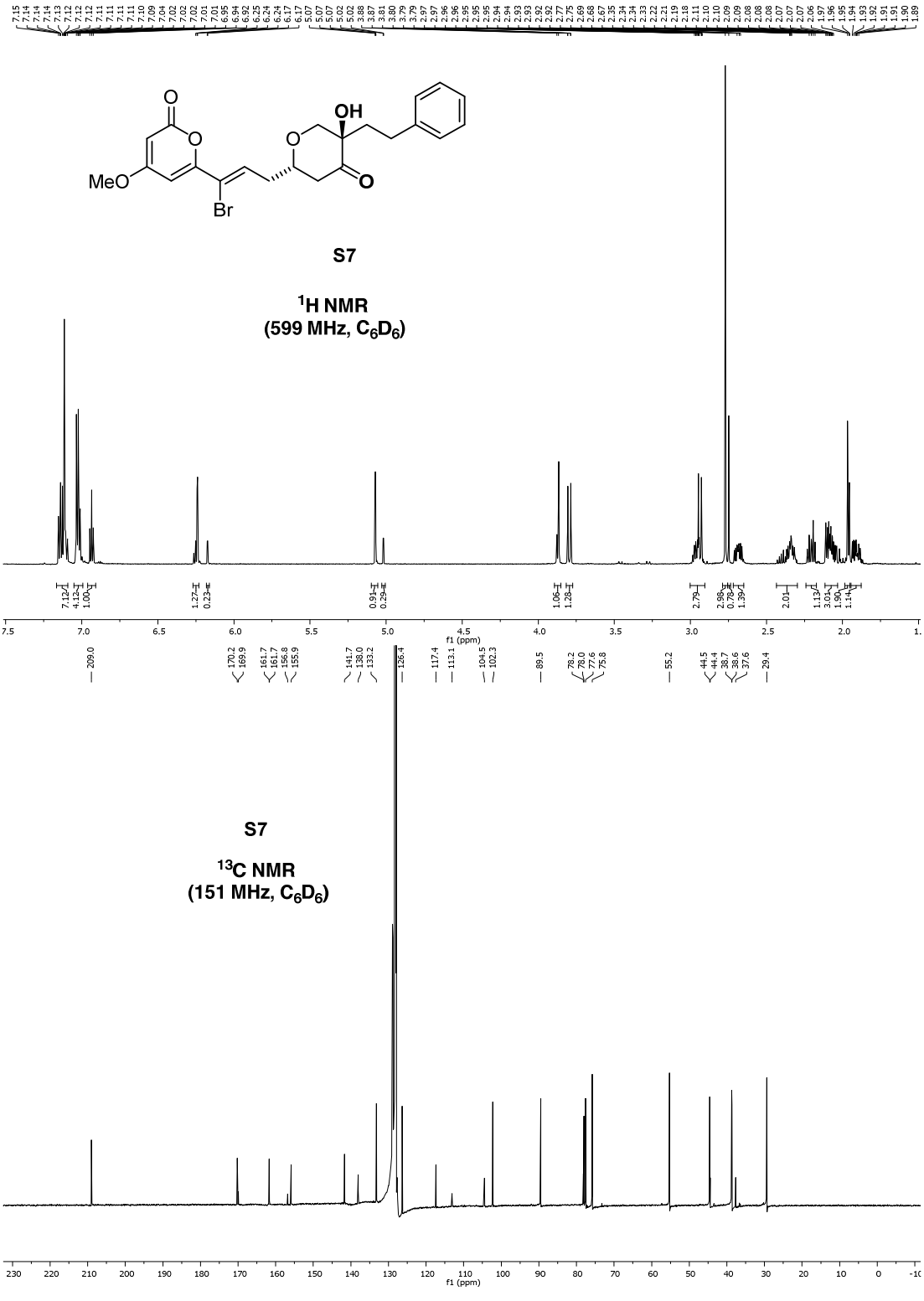
11

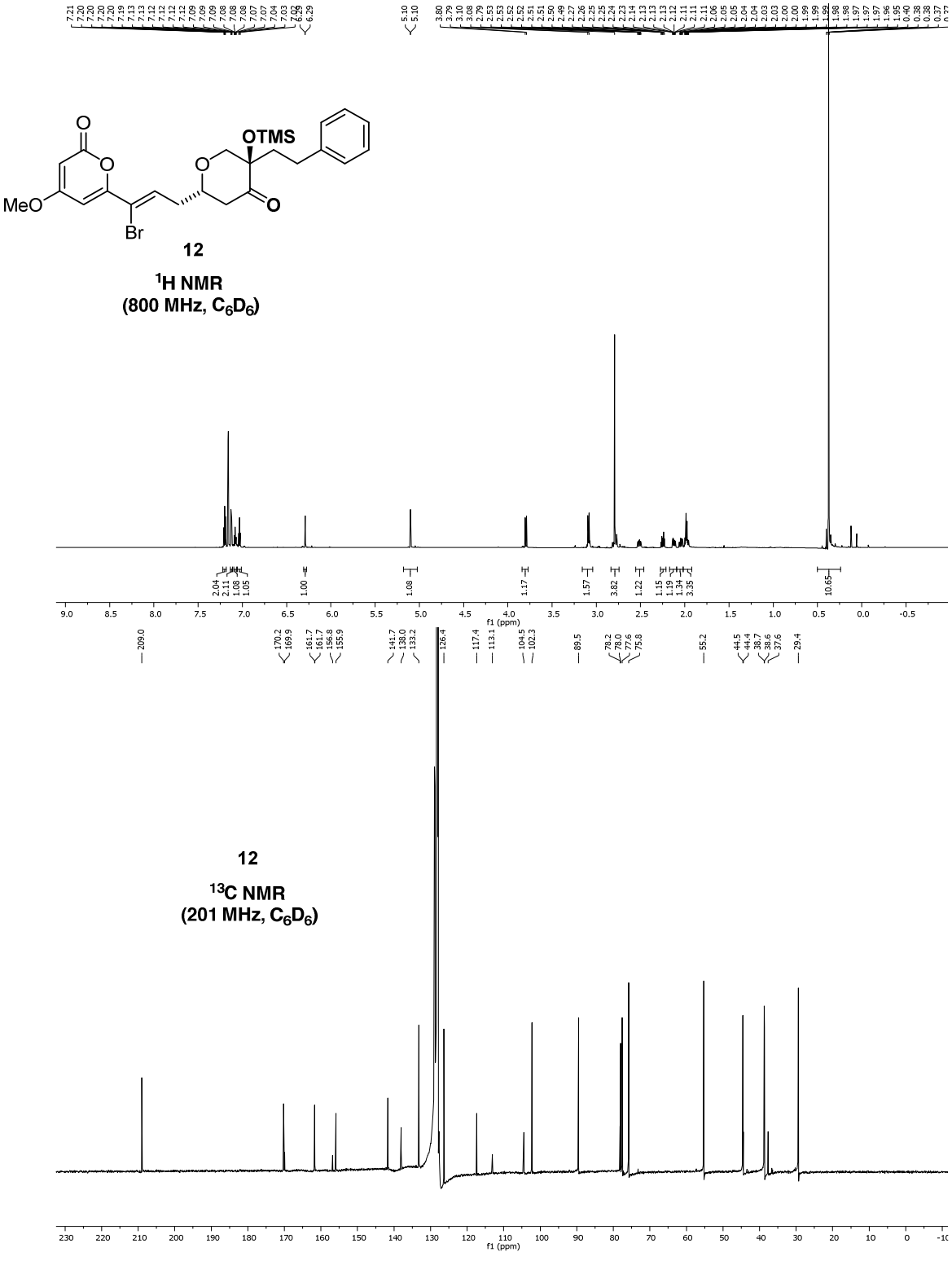
^{1}H NMR
(800 MHz, C_6D_6)

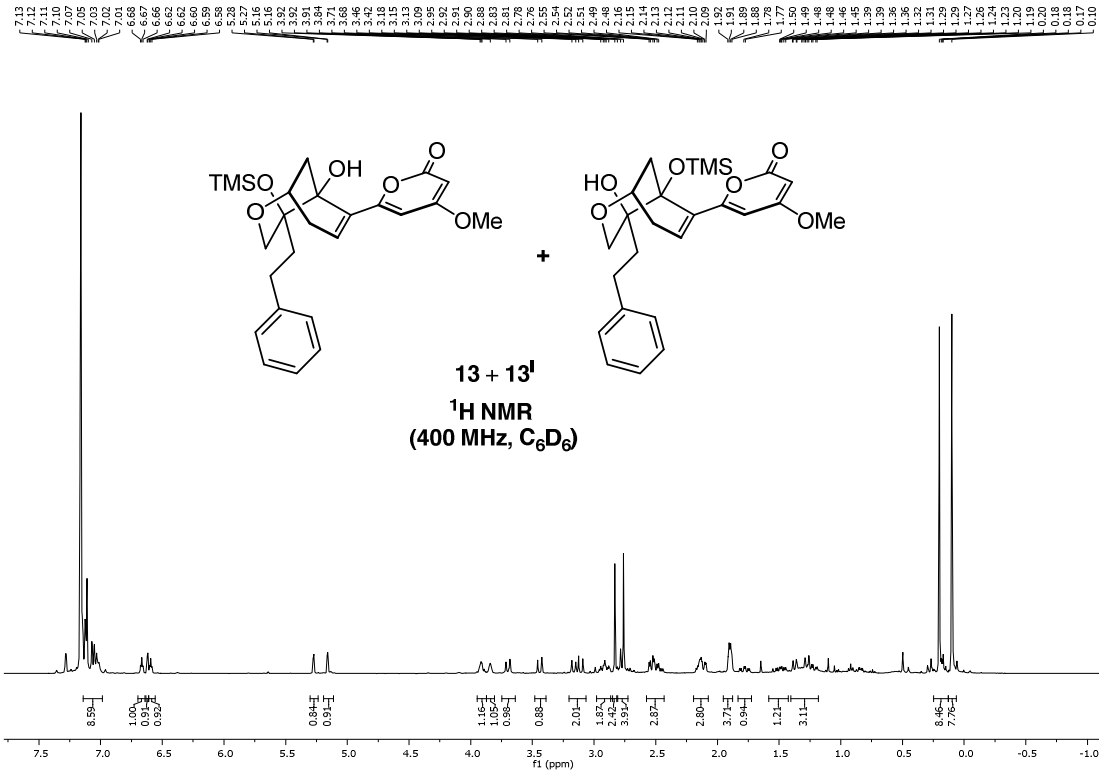
11

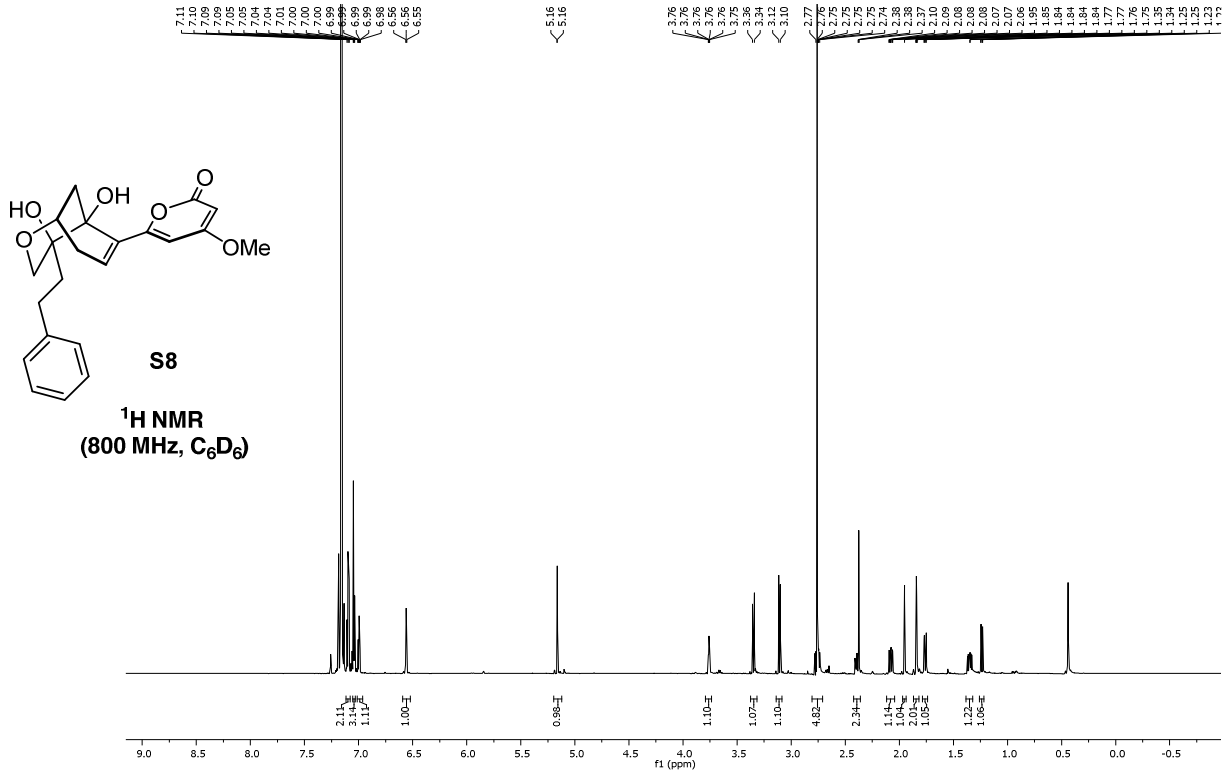
^{13}C NMR
(201 MHz, C_6D_6)

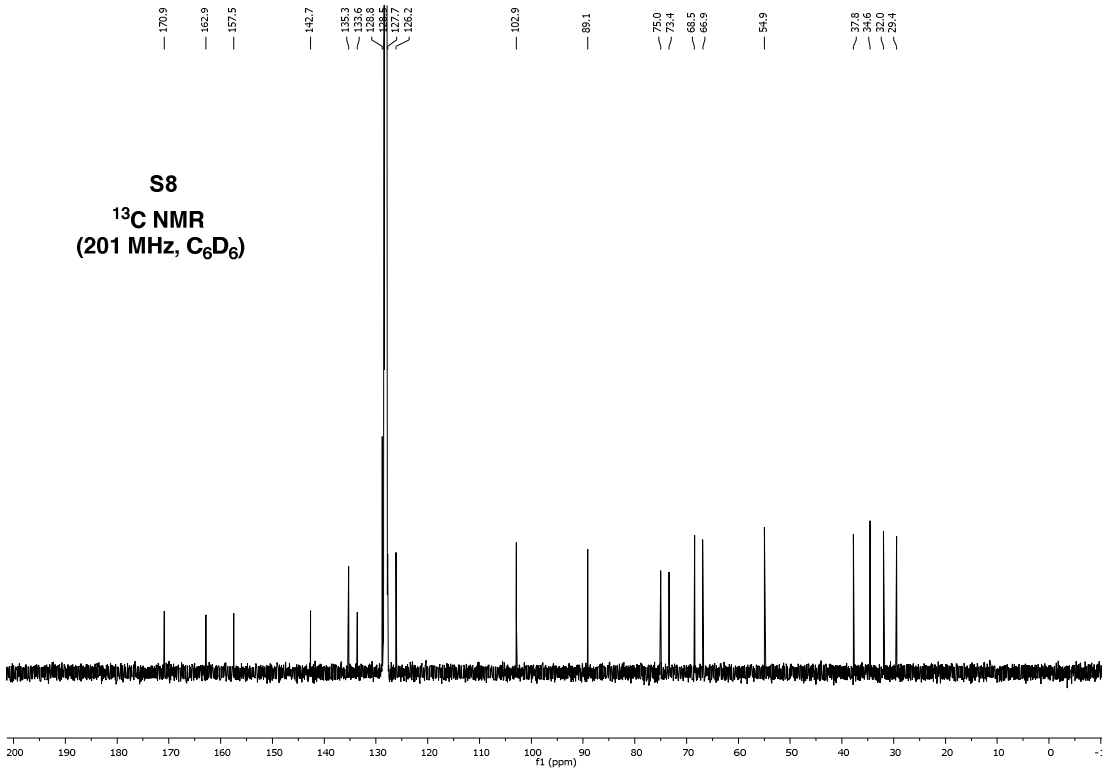


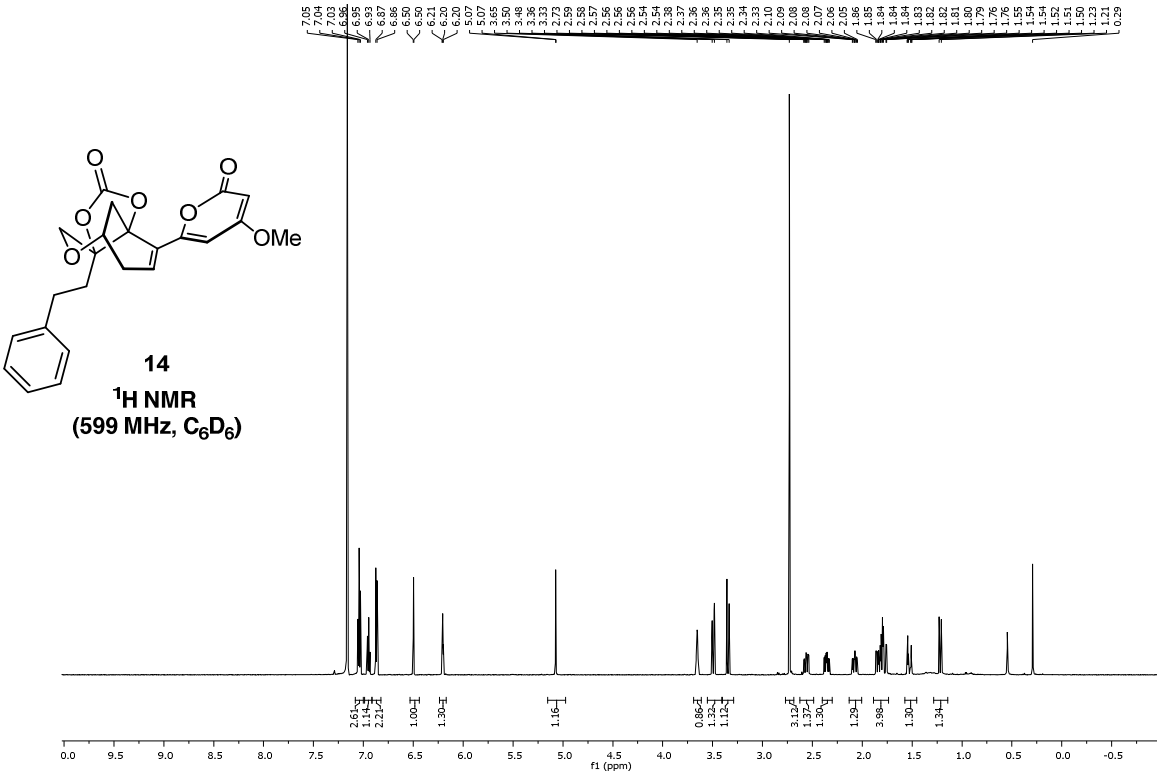

OH
O
O
O
MeO
Br
O
S7
1H NMR
(599 MHz, C6D6)
f1 (ppm)
S7
13C NMR
(151 MHz, C6D6)
f1 (ppm)

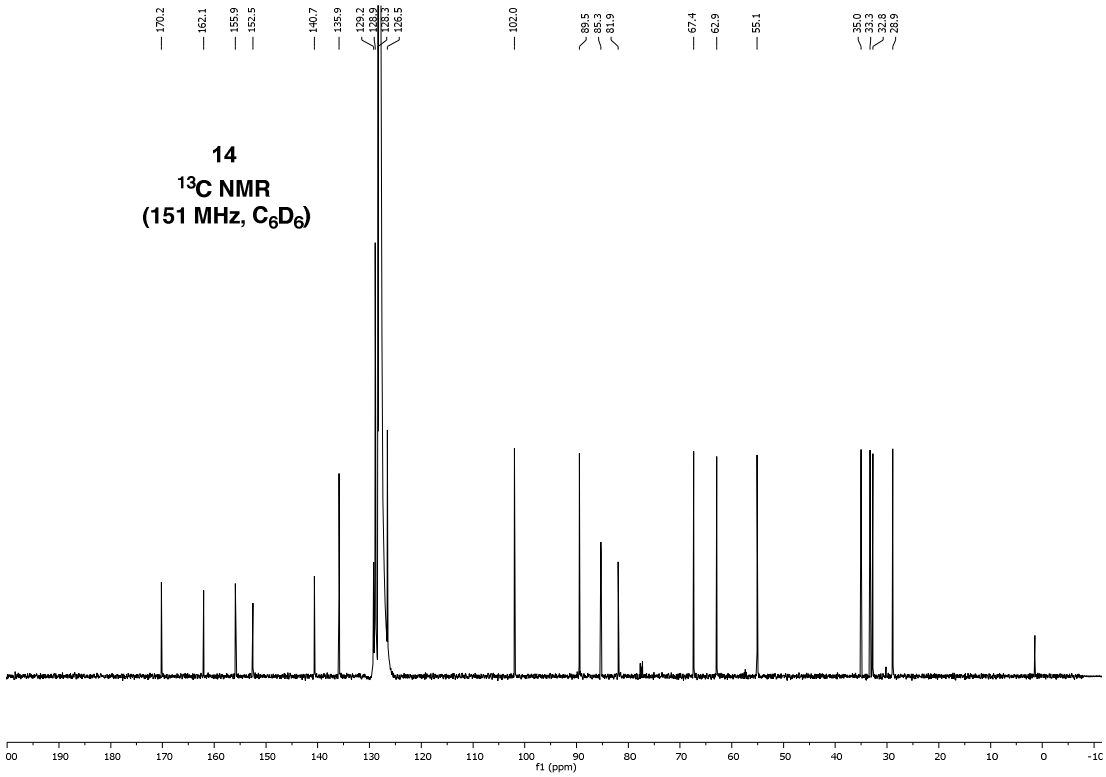

OTMS
MeO
Br
12
1H NMR
(800 MHz, C6D6)
12
13C NMR
(201 MHz, C6D6)
f1 (ppm)

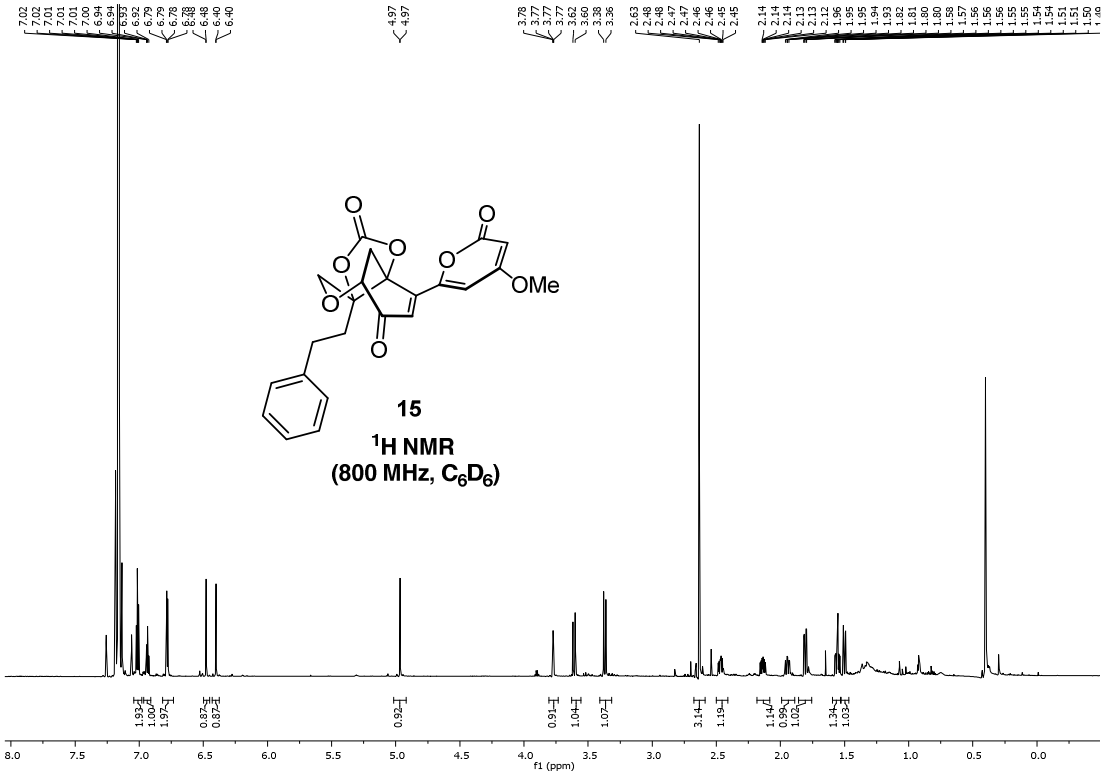

TMSO
OH
O
O
OMe
+
HO
OTMS
O
O
OMe
13 + 13I
1H NMR
(400 MHz, C6D6)
f1 (ppm)

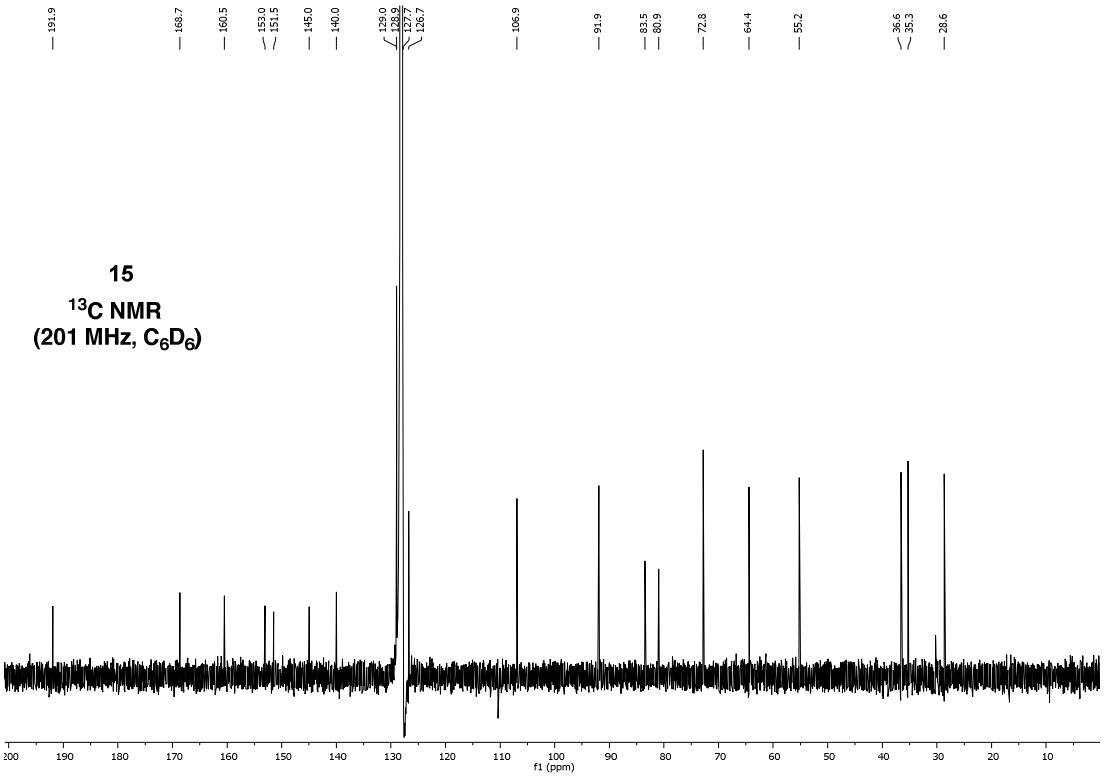

HO
O
OH
O
O
OMe
S8
1H NMR
(800 MHz, C6D6)
f1 (ppm)

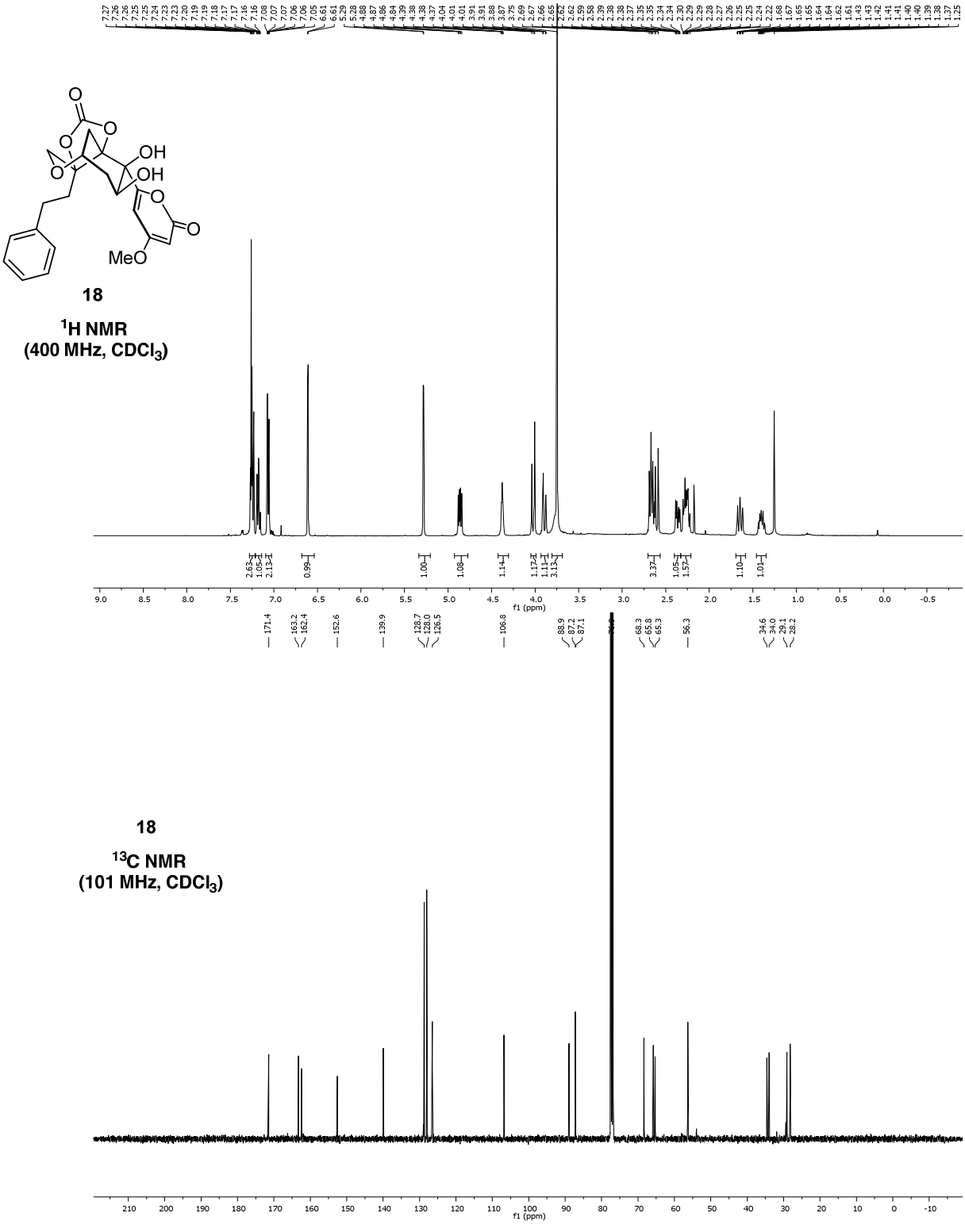

S8
13C NMR
(201 MHz, C6D6)
f1 (ppm)

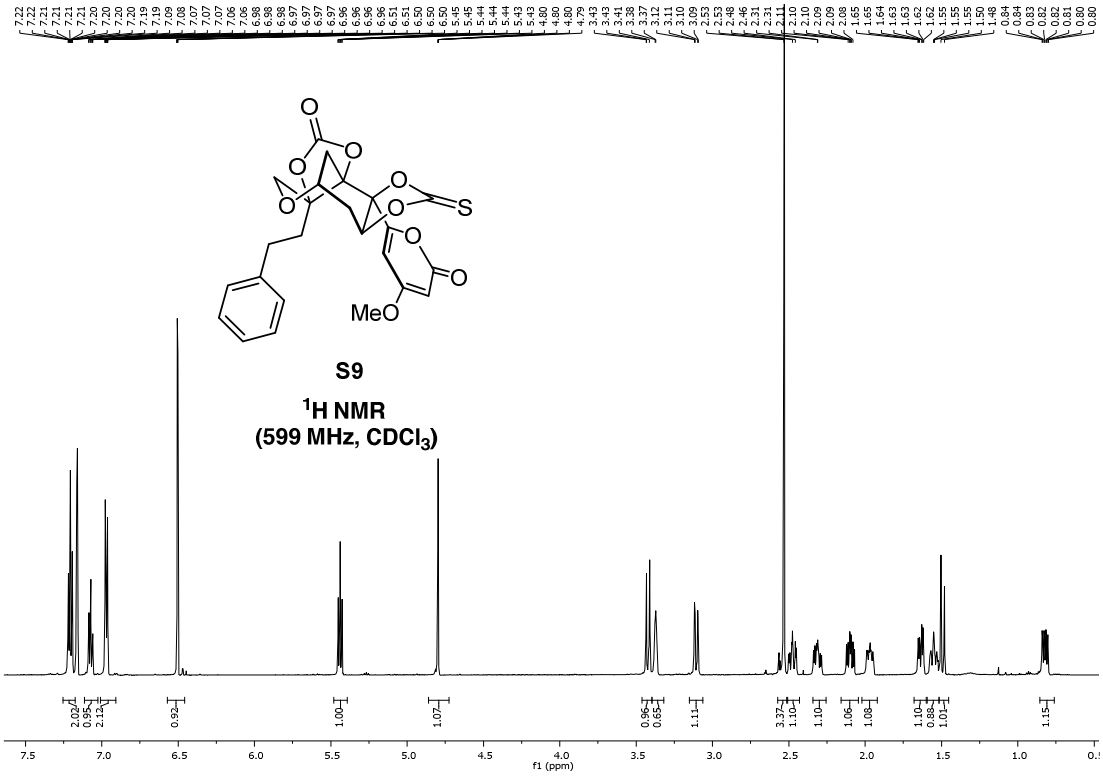

OMe
14
^{1}H NMR
(599 MHz, C_6D_6)

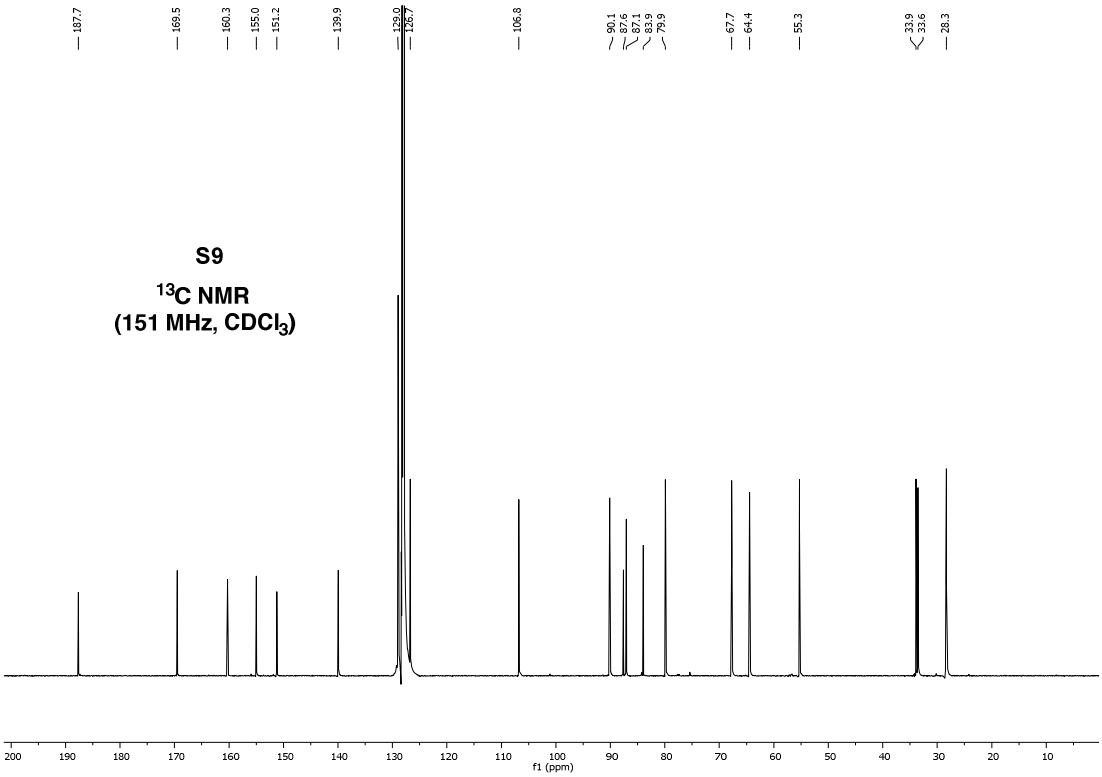

14
^{13}C NMR
(151 MHz, C_6D_6)

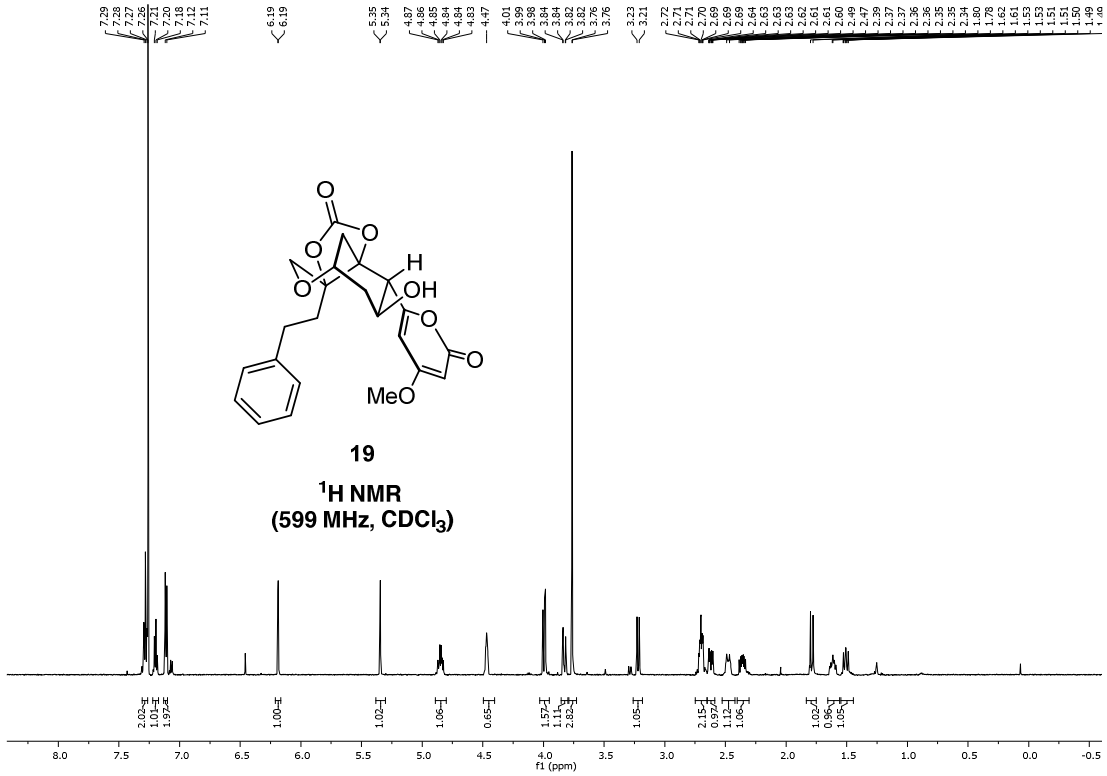

OMe
15
^{1}H NMR
(800 MHz, C_6D_6)
f1 (ppm)

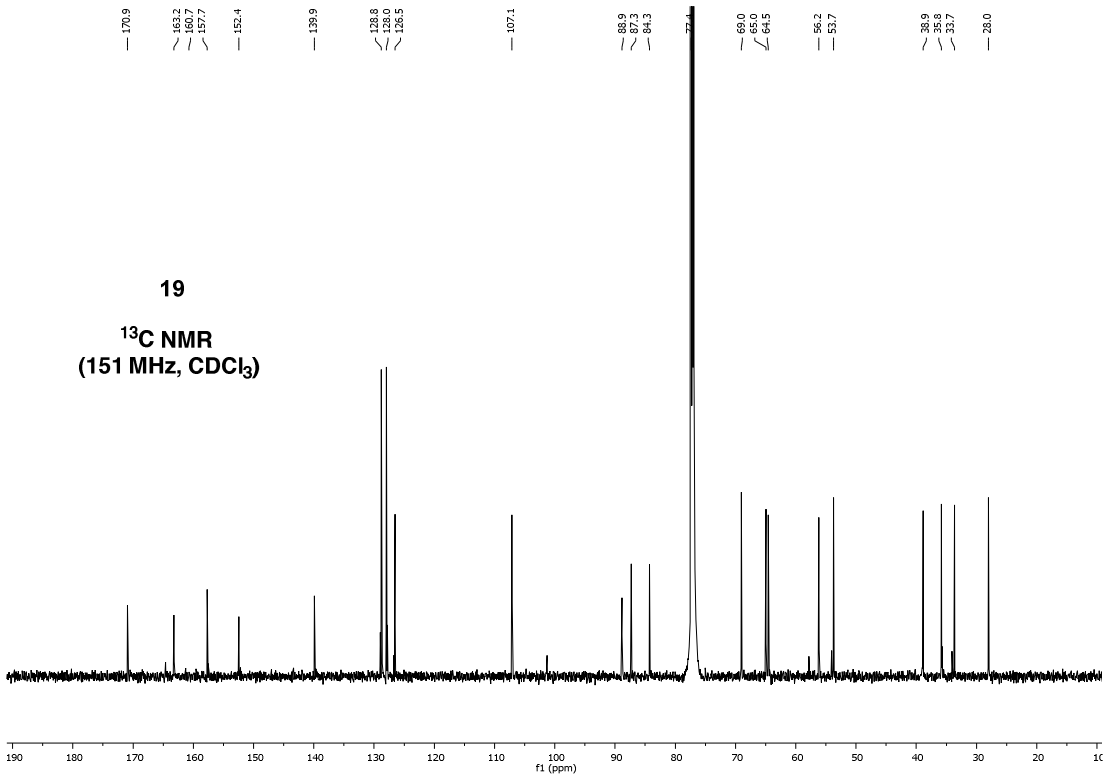

15
^{13}C NMR
(201 MHz, C_6D_6)
f1 (ppm)

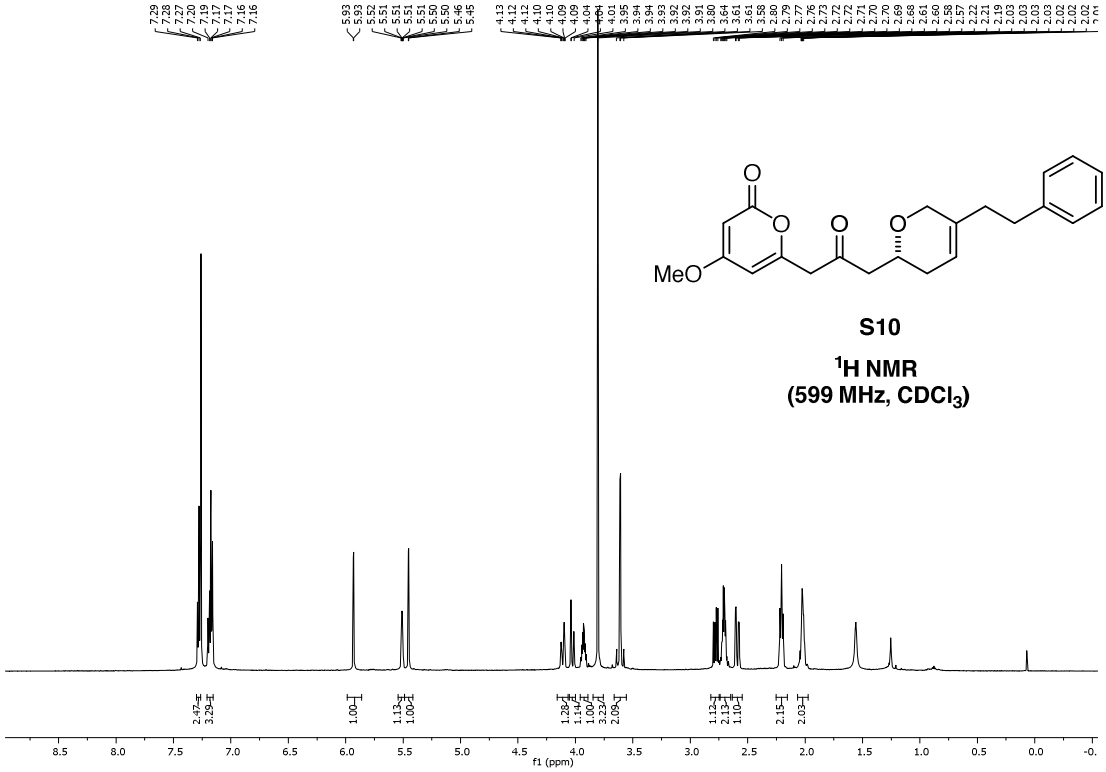

OH
OH
O
O
MeO
18
^{1}H NMR
(400 MHz, CDCl$_3$)
18
^{13}C NMR
(101 MHz, CDCl$_3$)
f1 (ppm)


S9
^{1}H NMR
(599 MHz, $CDCl_3$)
f1 (ppm)


S9
^{13}C NMR
(151 MHz, $CDCl_3$)
f1 (ppm)

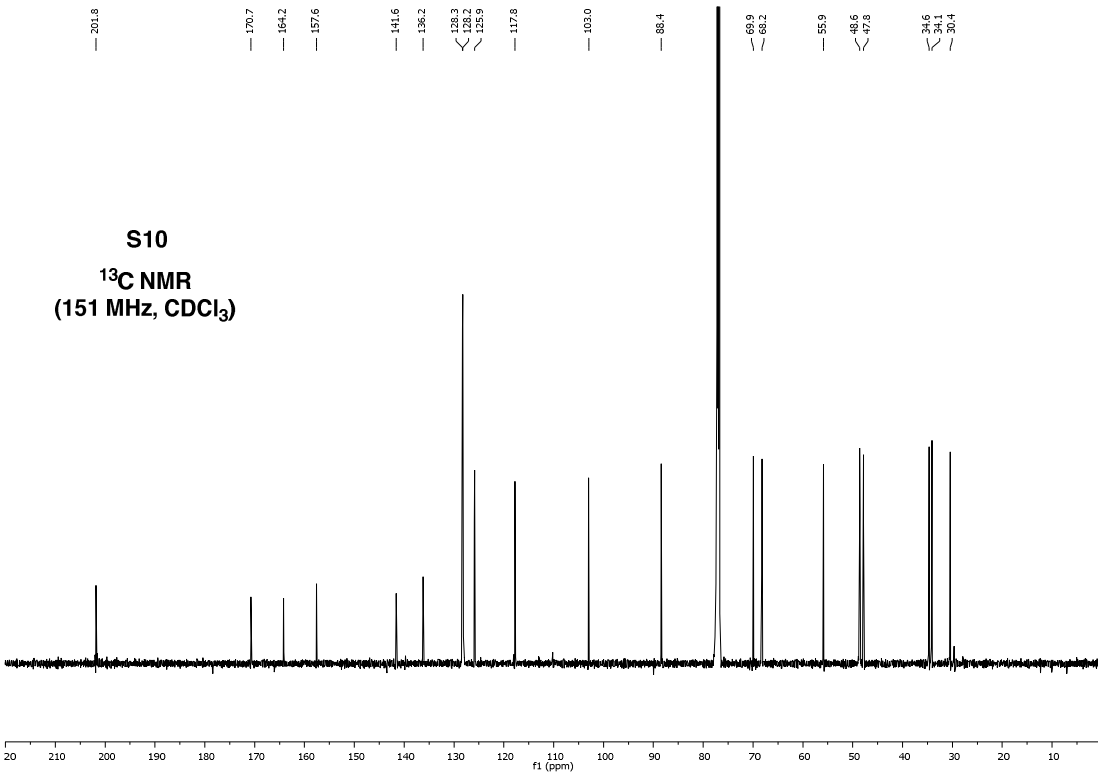

19
^{1}H NMR
(599 MHz, $CDCl_3$)


19
^{13}C NMR
(151 MHz, $CDCl_3$)



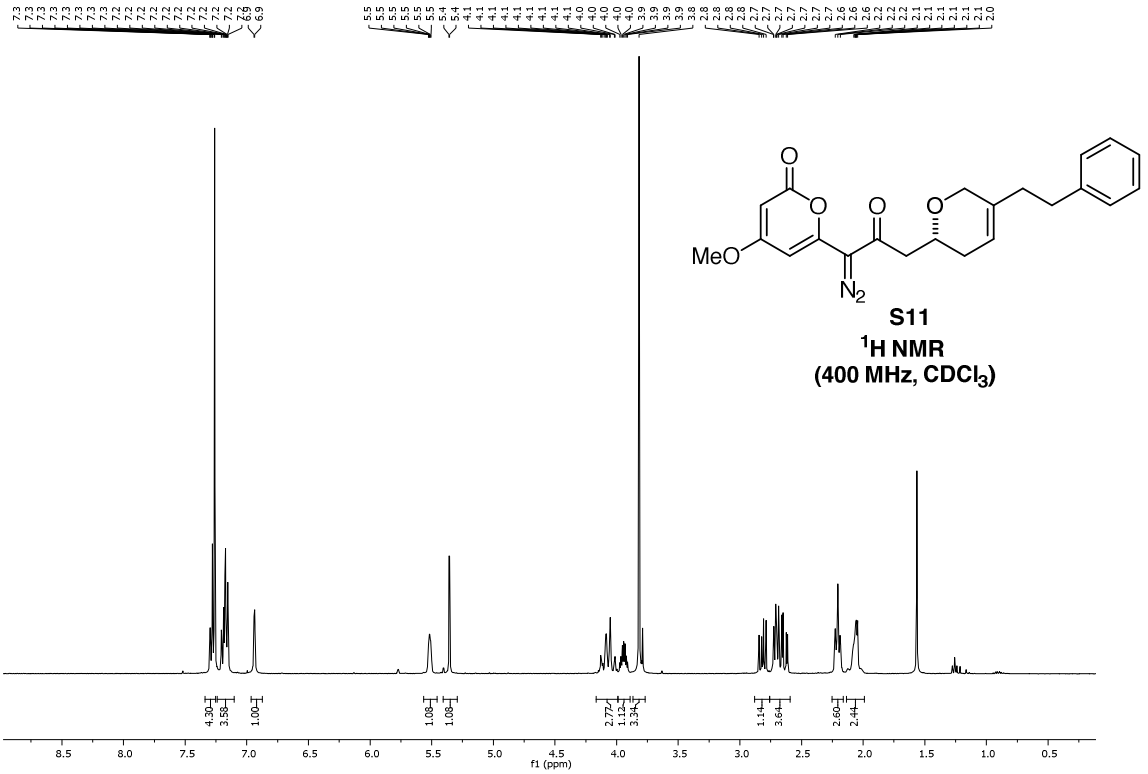
S10

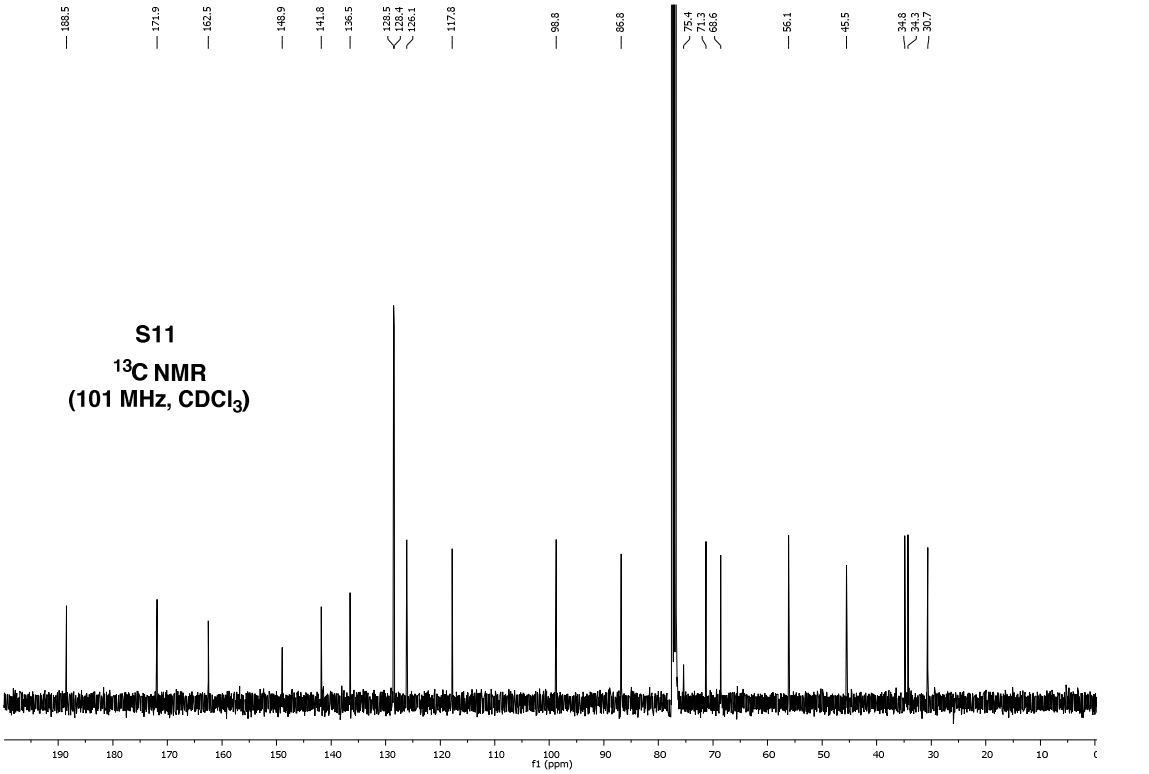
^{1}H NMR
(599 MHz, $CDCl_3$)

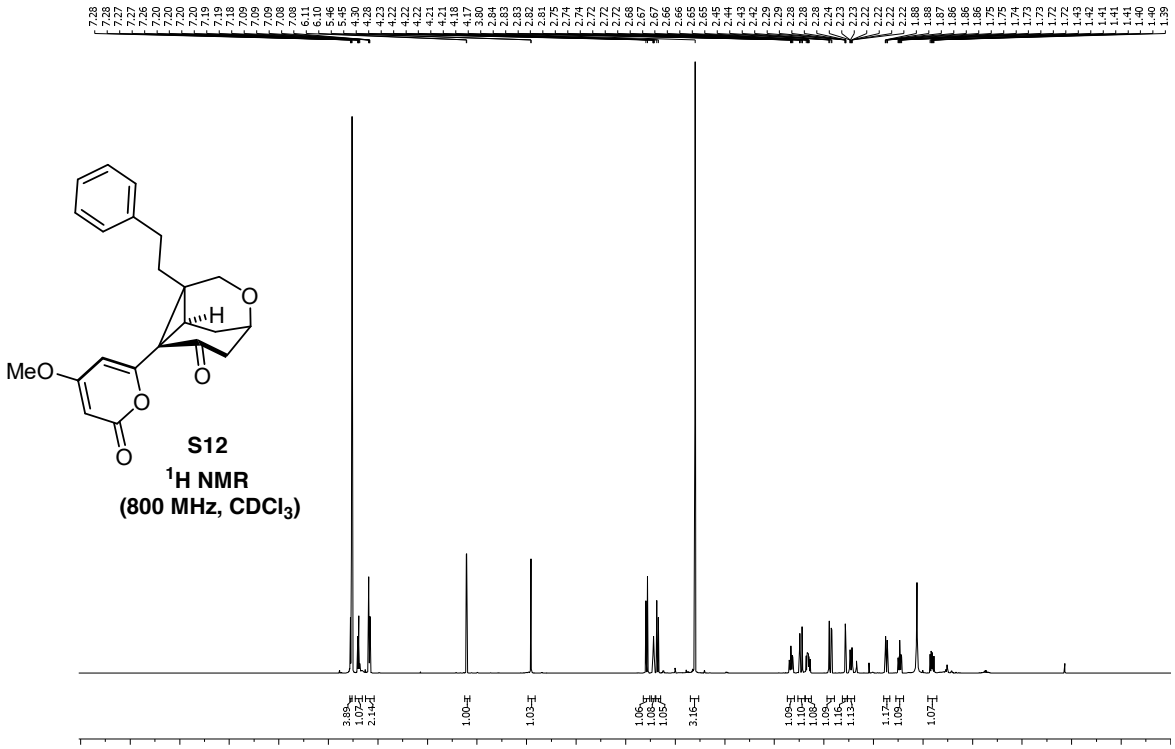


S10

^{13}C NMR
(151 MHz, $CDCl_3$)


MeO
N2
S11
1H NMR
(400 MHz, CDCl3)


S11
13C NMR
(101 MHz, CDCl3)

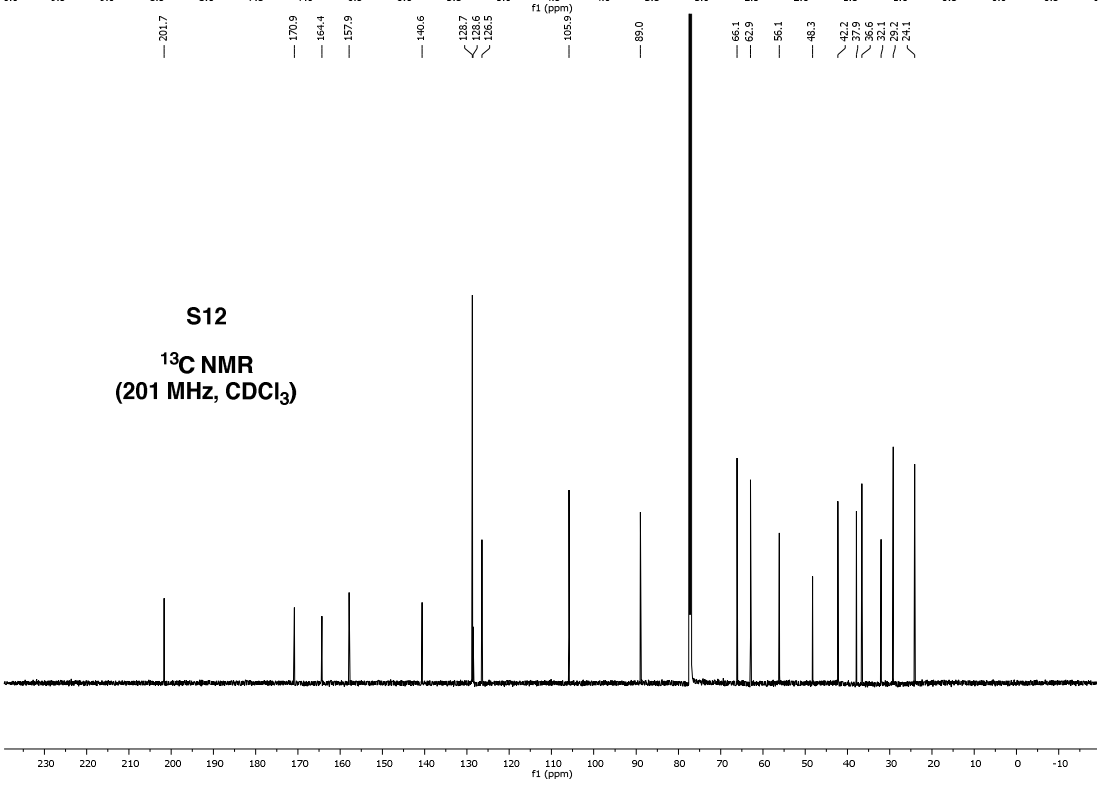


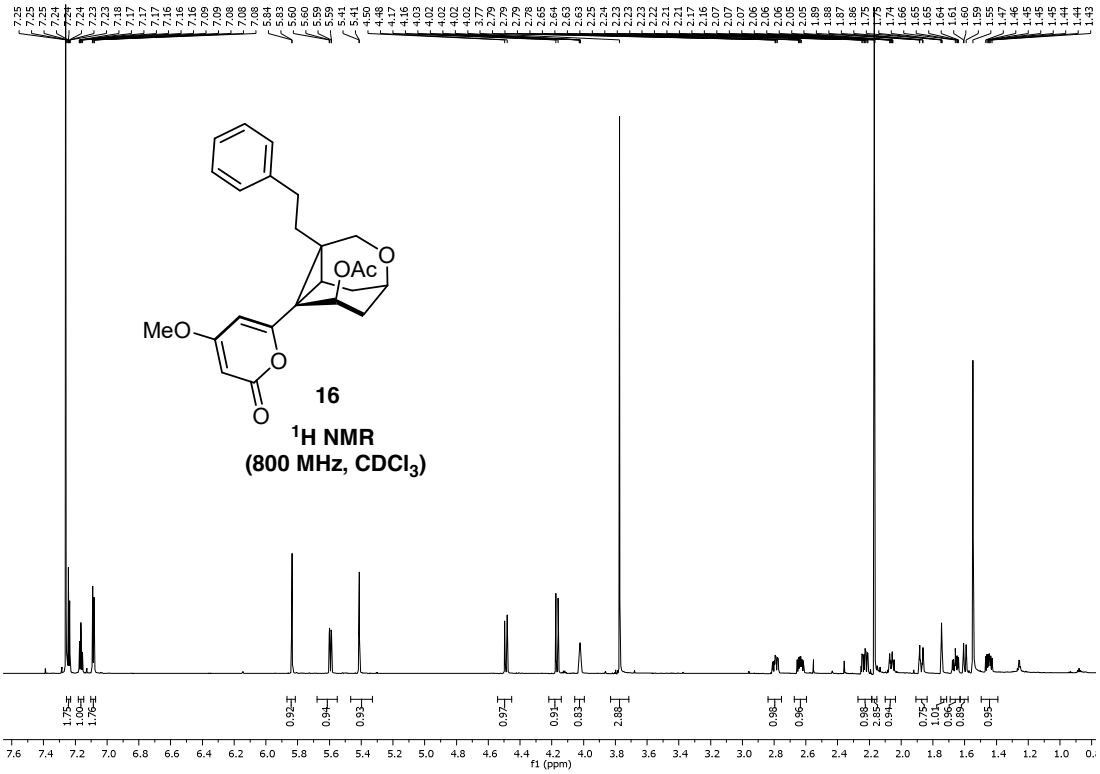
S12

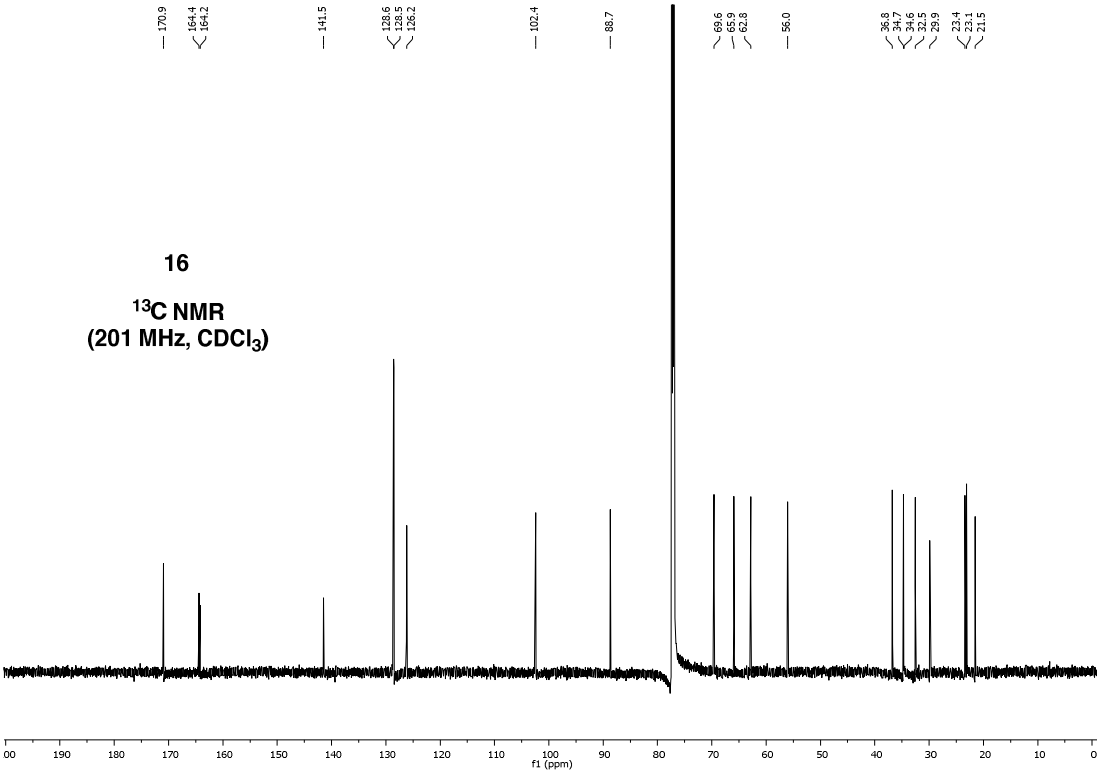
^{1}H NMR
(800 MHz, $CDCl_3$)

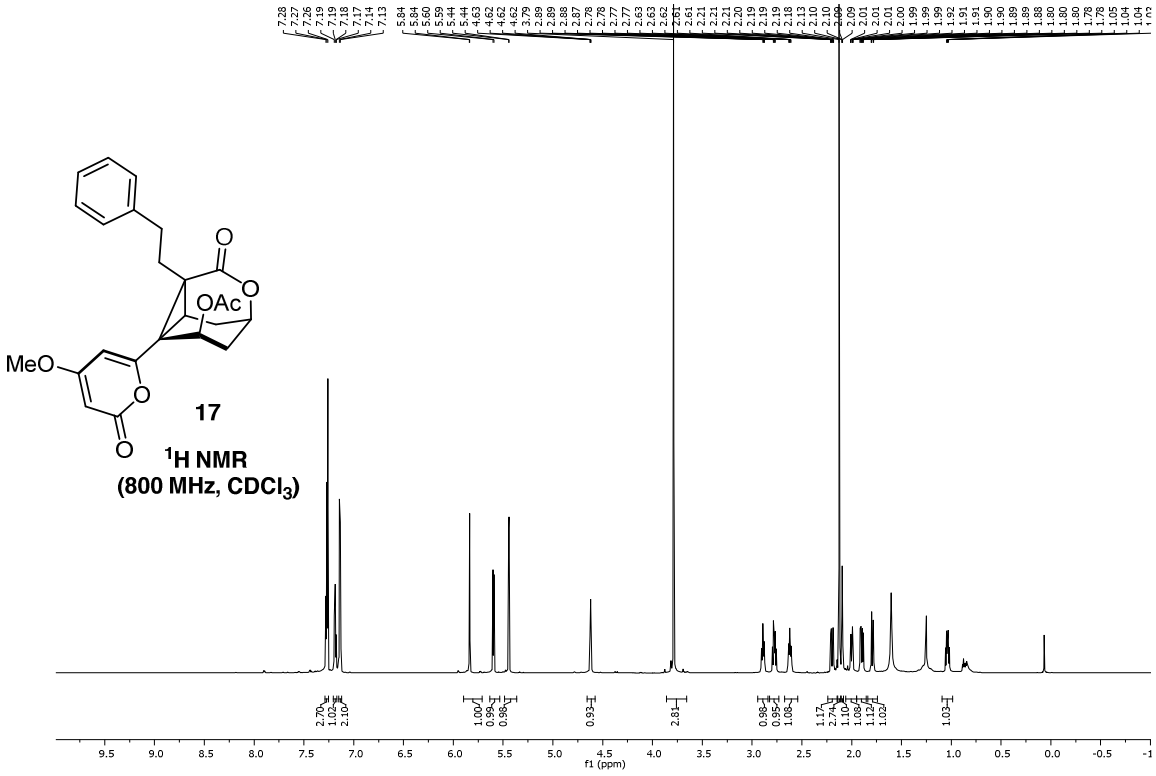
S12

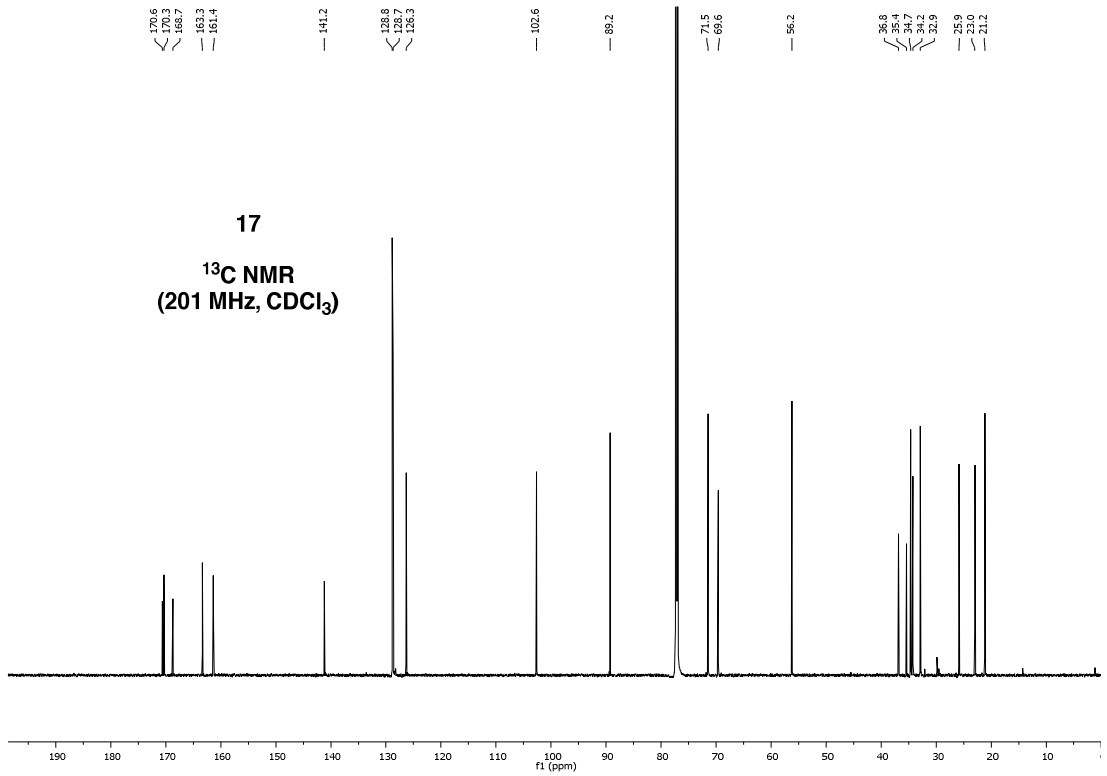
^{13}C NMR
(201 MHz, $CDCl_3$)

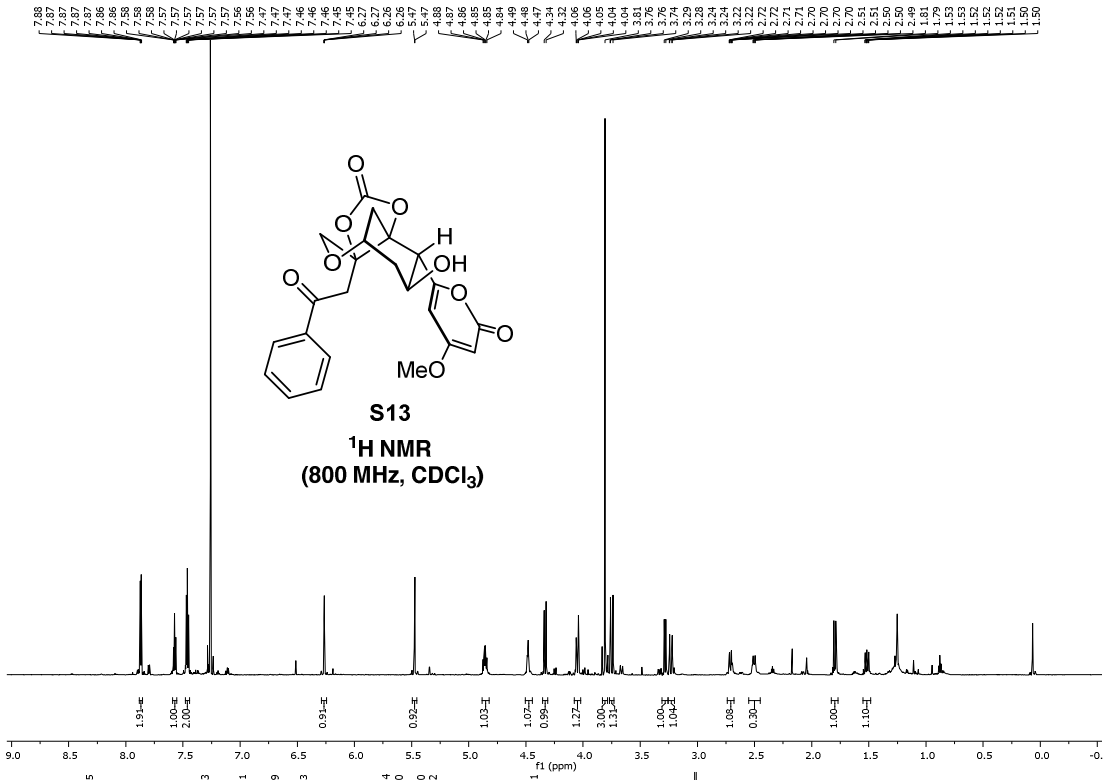


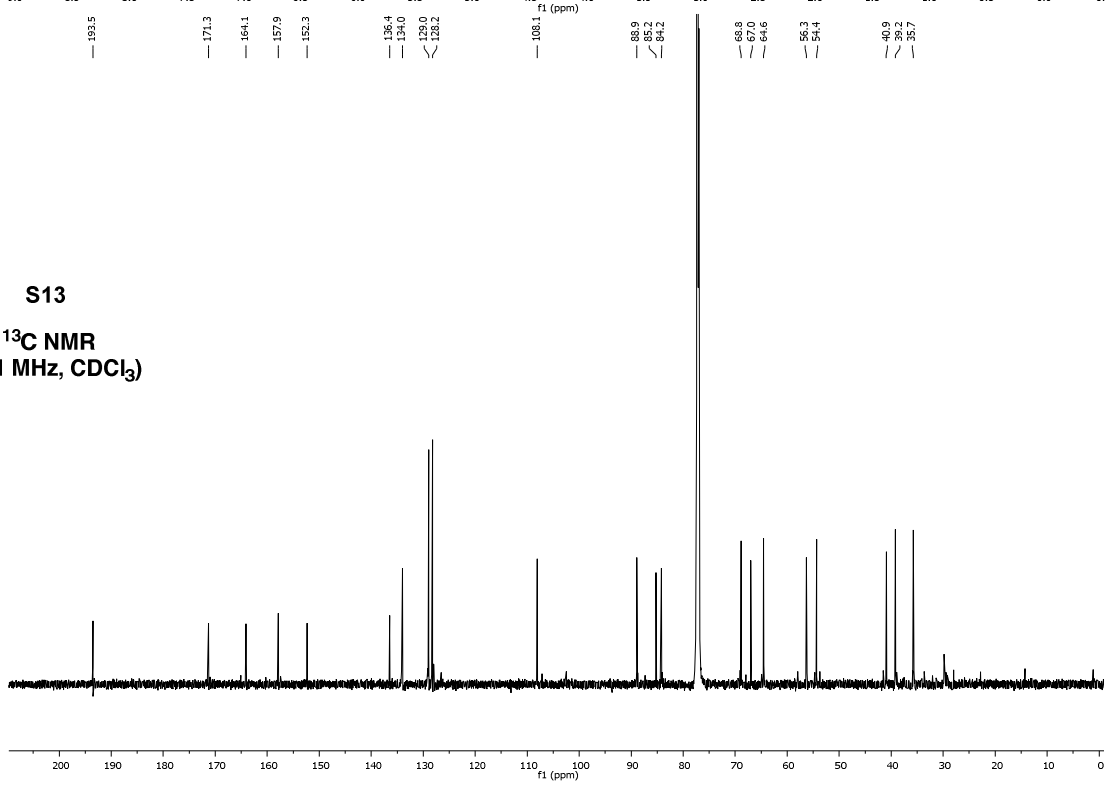

OAc
O
MeO
O
O
16
^{1}H NMR
(800 MHz, CDCl$_3$)

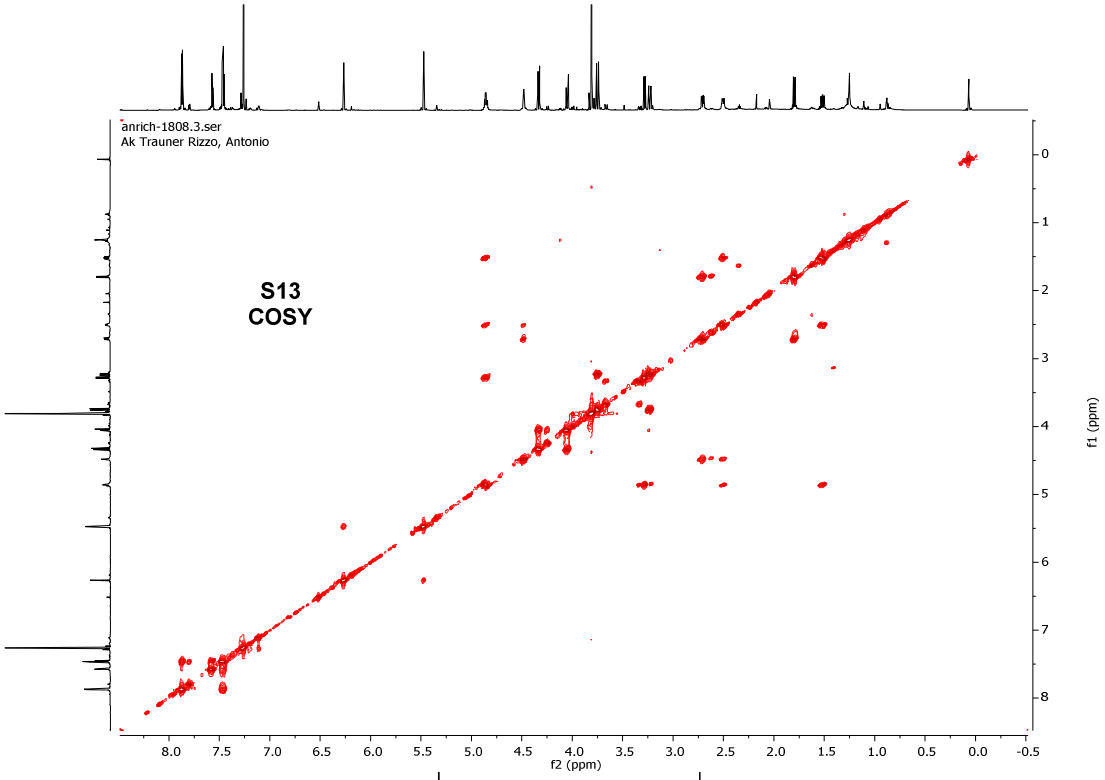

16
^{13}C NMR
(201 MHz, CDCl$_3$)
f1 (ppm)

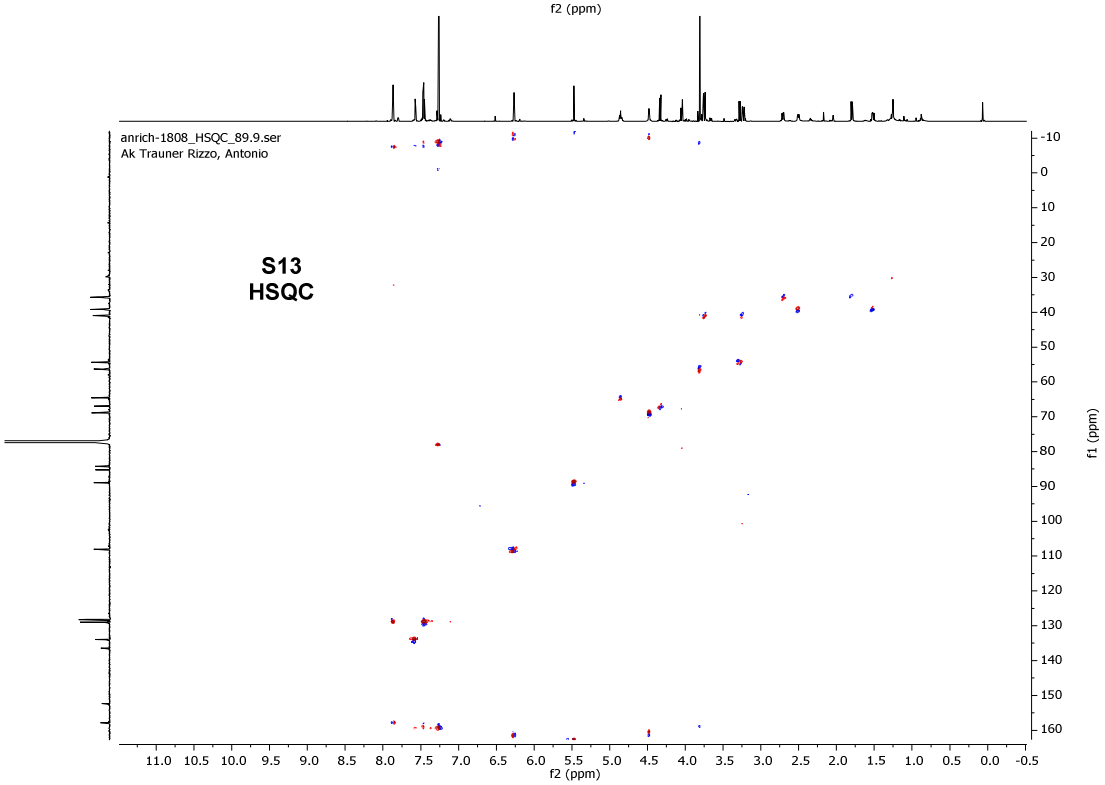

OAc
MeO
17
^{1}H NMR
(800 MHz, CDCl$_3$)

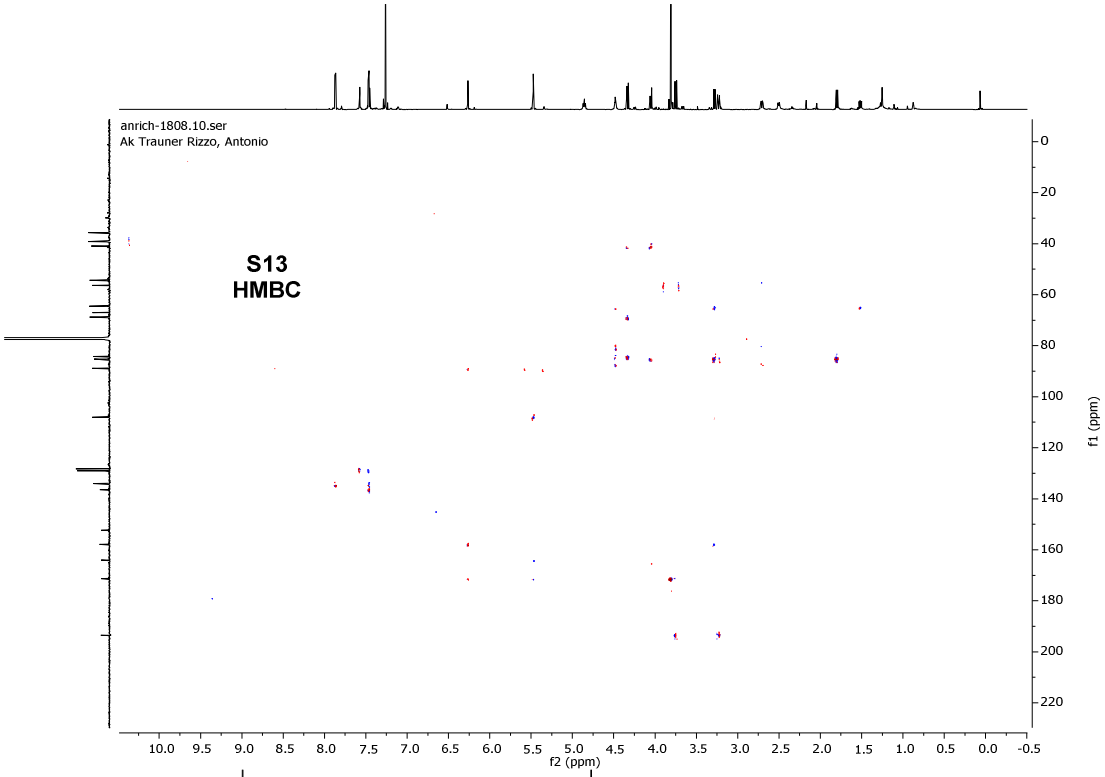

17
^{13}C NMR
(201 MHz, CDCl$_3$)

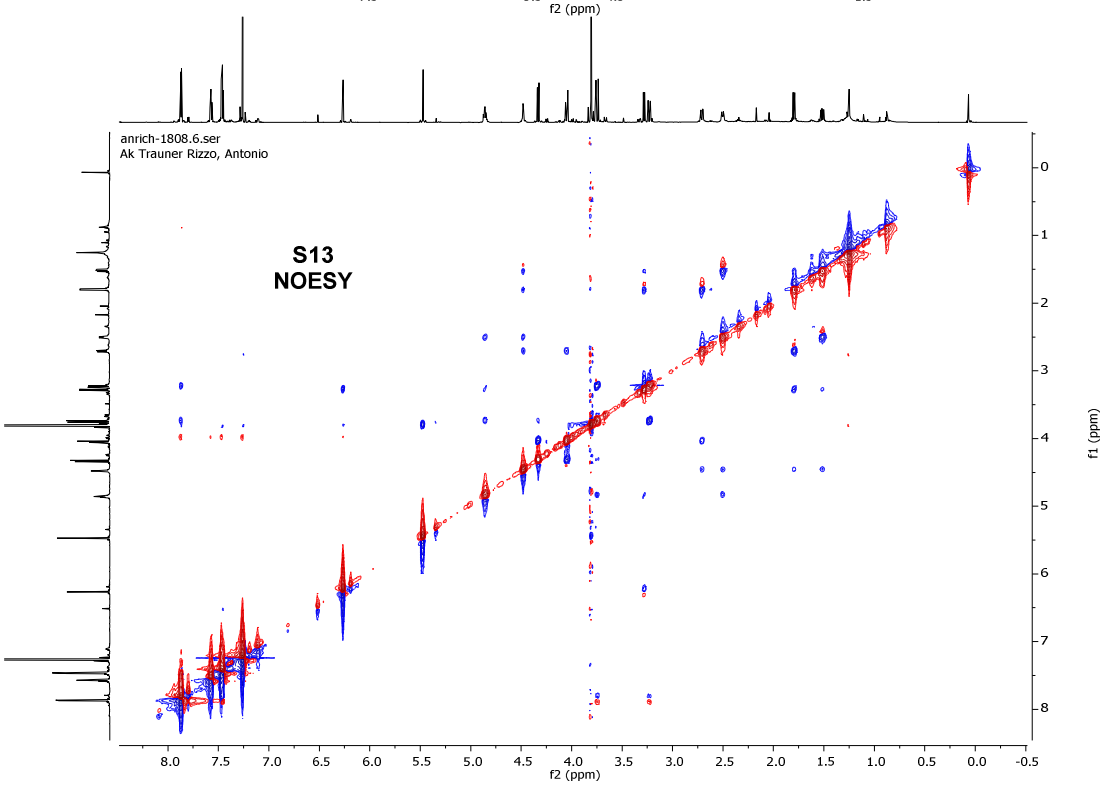

S13
^{1}H NMR
(800 MHz, $CDCl_3$)

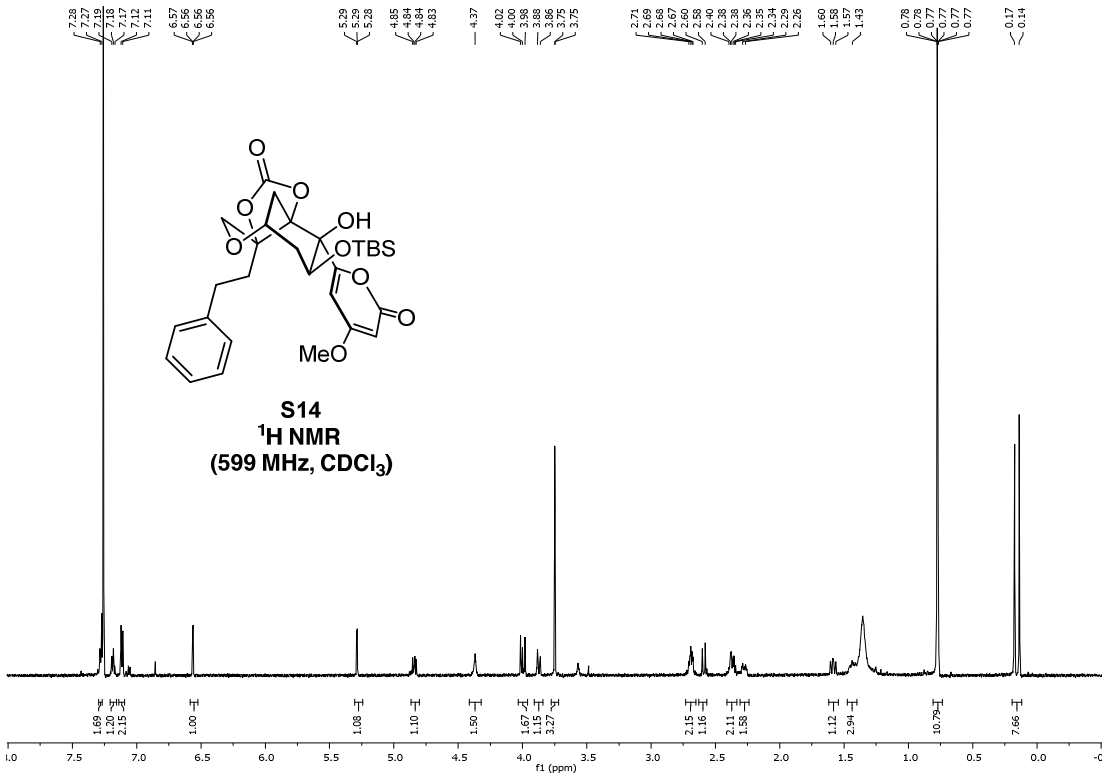

S13
^{13}C NMR
(201 MHz, $CDCl_3$)


anrich-1808.3.ser
Ak Trauner Rizzo, Antonio
S13
COSY
f2 (ppm)
f1 (ppm)

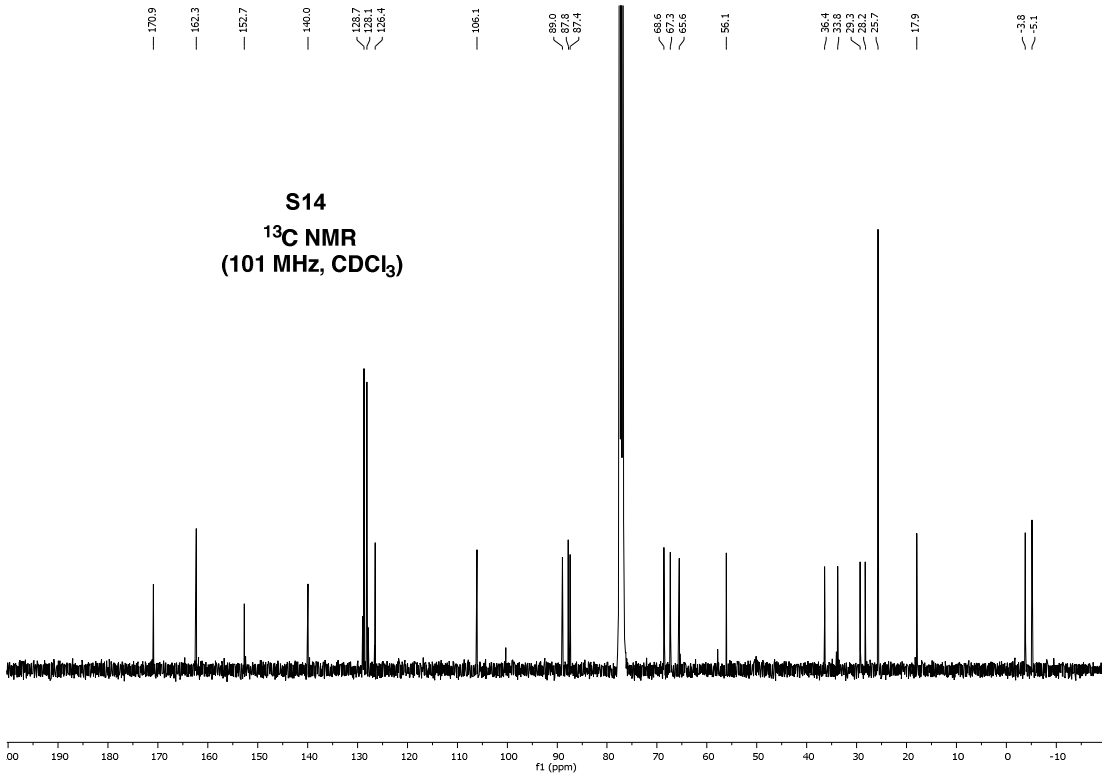

anrich-1808_HSQC_89.9.ser
Ak Trauner Rizzo, Antonio
S13
HSQC
f2 (ppm)
f1 (ppm)


anrich-1808.10.ser
Ak Trauner Rizzo, Antonio
S13
HMBC
f2 (ppm)
f1 (ppm)

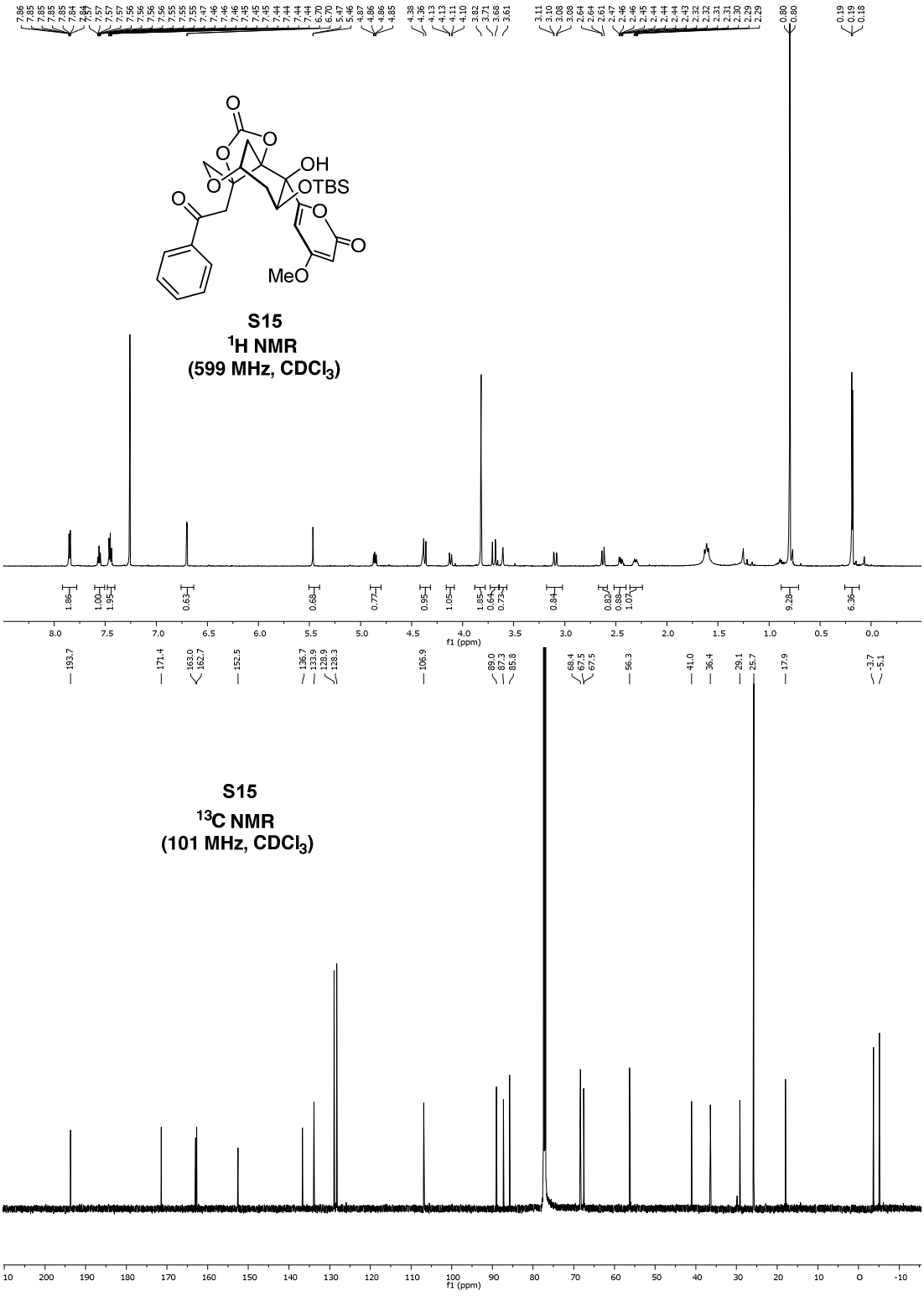

anrich-1808.6.ser
Ak Trauner Rizzo, Antonio
S13
NOESY
f2 (ppm)
f1 (ppm)

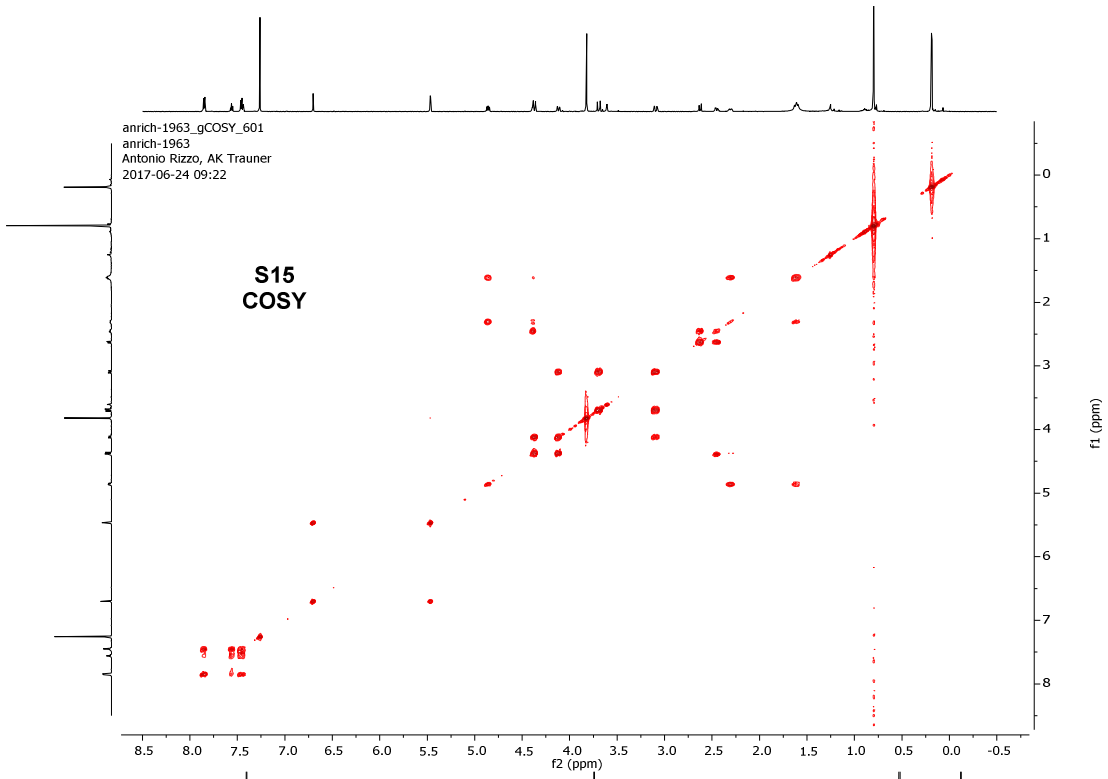


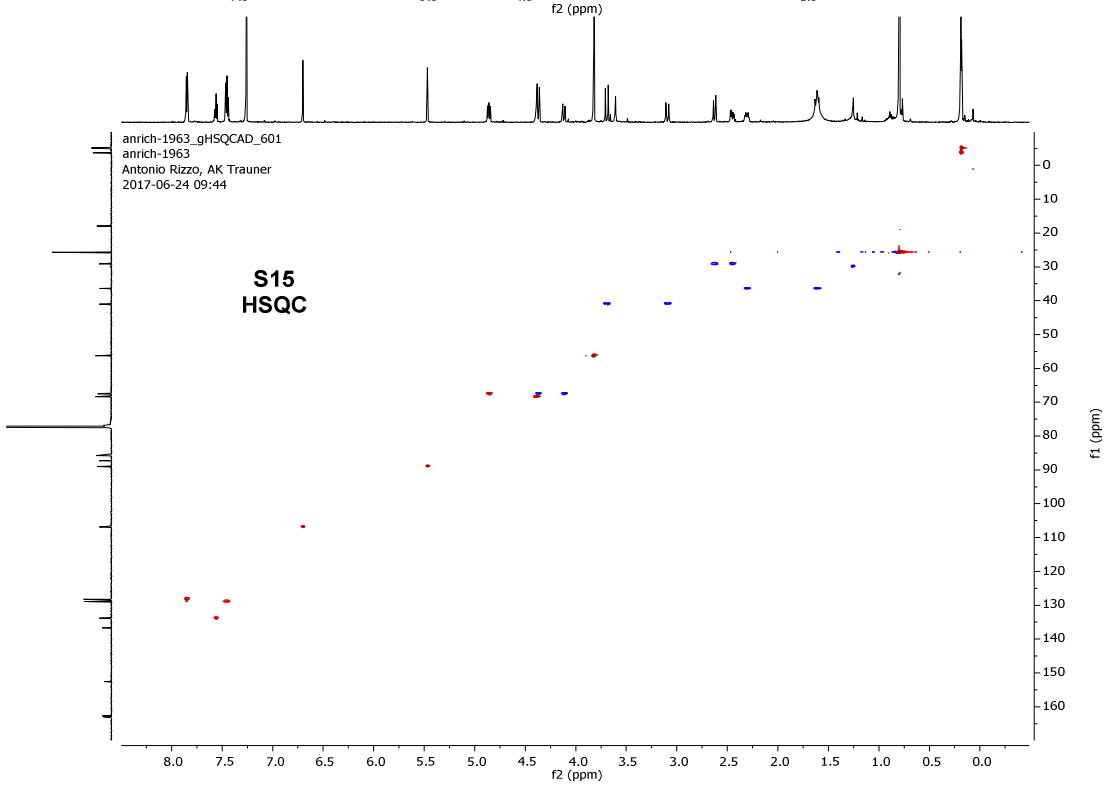
S14
^{1}H NMR
(599 MHz, $CDCl_3$)

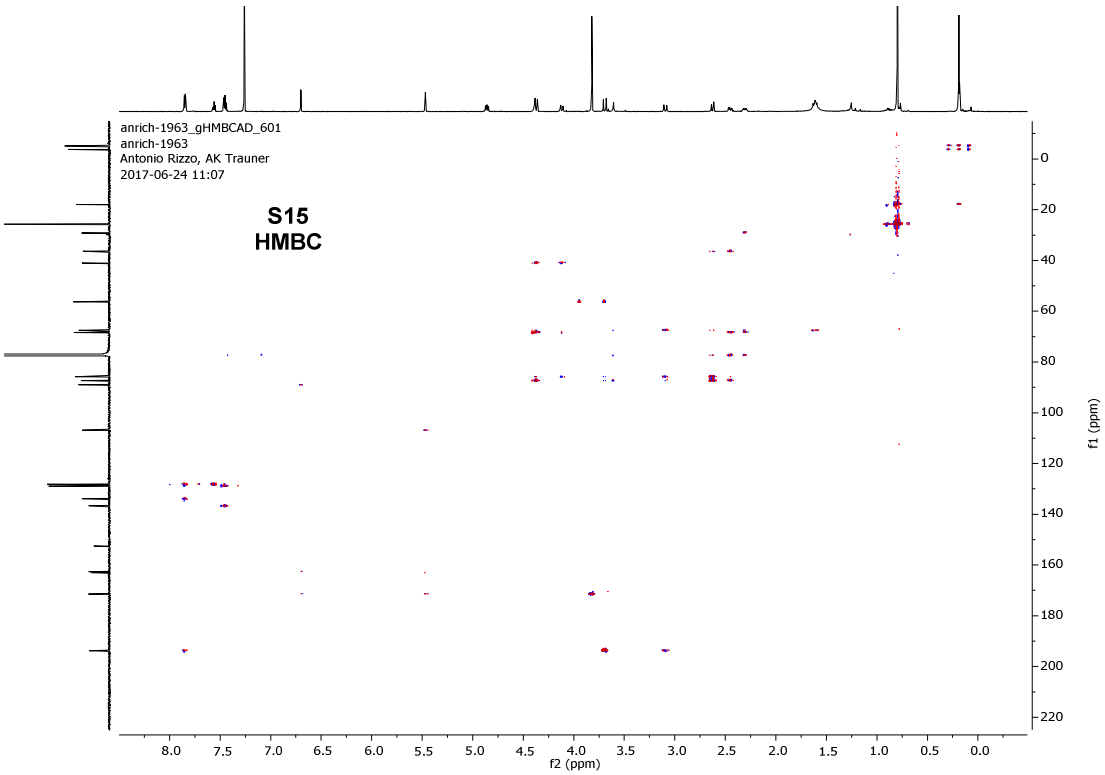


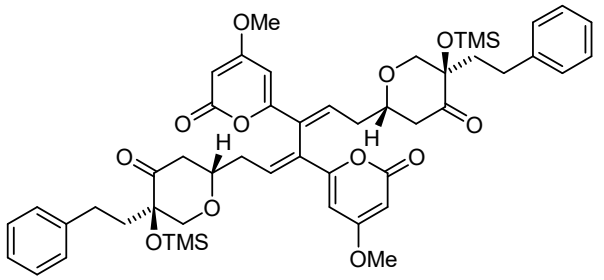
S14
^{13}C NMR
(101 MHz, $CDCl_3$)


OH
OTBS
MeO
S15
1H NMR
(599 MHz, CDCl3)
f1 (ppm)
S15
13C NMR
(101 MHz, CDCl3)
f1 (ppm)


anrich-1963_gCOSY_601
anrich-1963
Antonio Rizzo, AK Trauner
2017-06-24 09:22
S15
COSY
f2 (ppm)
f1 (ppm)


anrich-1963_gHSQCAD_601
anrich-1963
Antonio Rizzo, AK Trauner
2017-06-24 09:44
S15
HSQC
f2 (ppm)
f1 (ppm)





^{1}H NMR
(400 MHz, C_6D_6)

6.4.5 X-ray Data for Chapter 3.2

1. TMS bicycle **13**^{I}

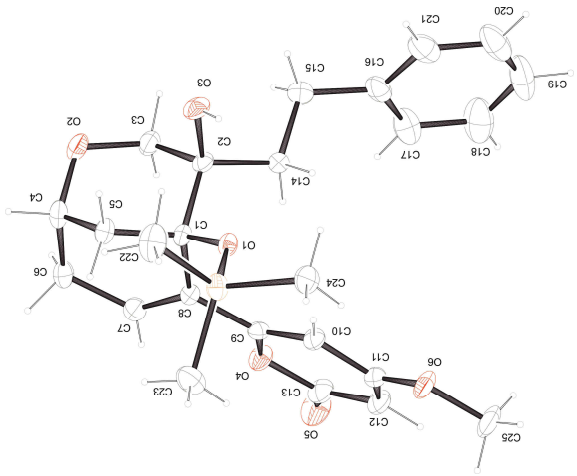


Figure 1. ORTEP of the molecular structure of TMS bicycle **13**^{I}.

CCDC 1817799 contains the supplementary crystallographic data for compound **13**^{I}. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

$C_{25}H_{32}O_6Si$_vv027_trauner

Table 9.

net formula	$C_{25}H_{32}O_6Si$
M_r/g mol^{-1}	456.59
crystal size/mm	0.100 × 0.070 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	10.9381(3)
b/Å	13.4302(4)
c/Å	16.6422(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	2444.75(12)
Z	4
calc. density/g cm^{-3}	1.241
μ/mm^{-1}	0.133
absorption correction	Multi-Scan

transmission factor range	0.9281–0.9705
refls. measured	37155
R_{int}	0.0402
mean σ(*I*)/*I*	0.0260
θ range	3.271–27.480
observed refls.	5245
x, y (weighting scheme)	0.0460, 0.6155
hydrogen refinement	H(C) constr, H(O) refall
Flack parameter	0.01(3)
refls in refinement	5599
parameters	297
restraints	0
$R(F_{obs})$	0.0343
$R_w(F^2)$	0.0878
S	1.065
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.251
min electron density/e Å^{-3}	−0.213

2. Cyclic carbonate **19**

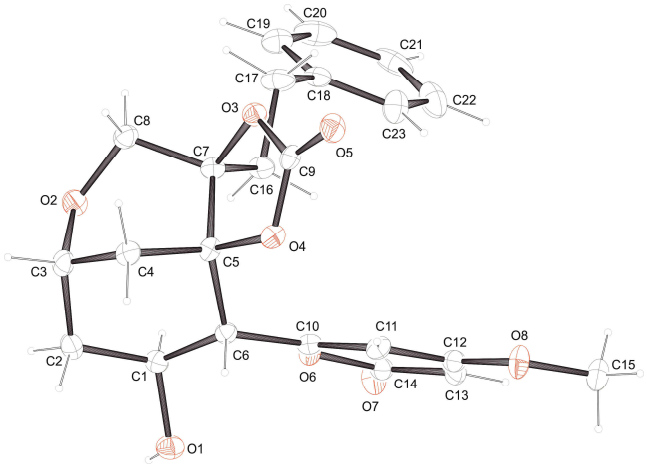


Figure 2. ORTEP of the molecular structure of cyclic carbonate **19**.

CCDC 1817800 contains the supplementary crystallographic data for compound **19**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

$C_{23}H_{24}O_8$_vv380_trauner

Table 10.

	1
net formula	$C_{23}H_{24}O_8$

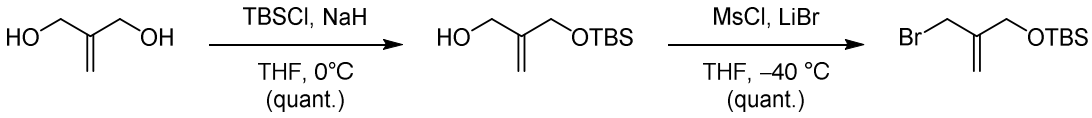
M_r/g mol^{-1}	428.42
crystal size/mm	0.090 × 0.070 × 0.040
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	8.8534(2)
b/Å	10.9476(3)
c/Å	21.0165(6)
α/°	90
β/°	90
γ/°	90
V/Å^3	2036.99(9)
Z	4
calc. density/g cm^{-3}	1.397
μ/mm^{-1}	0.106
absorption correction	Multi-Scan
transmission factor range	0.9165–0.9705
refls. measured	25405
R_{int}	0.0403
mean σ(I)/I	0.0274
θ range	3.453–26.361
observed refls.	3905
x, y (weighting scheme)	0.0312, 0.5936
hydrogen refinement	H(C) constr, H(O) refall
Flack parameter	0.4(3)
refls in refinement	4155
parameters	285
restraints	0
$R(F_{obs})$	0.0301
$R_w(F^2)$	0.0700
S	1.042
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.272
min electron density/e Å^{-3}	−0.174

Configuration of C3 known from synthesis!

6.5. Supporting Information for Chapter 3.3

6.5.1 Experimental Procedures for Chapter 3.3

Bromide (**3.20**)



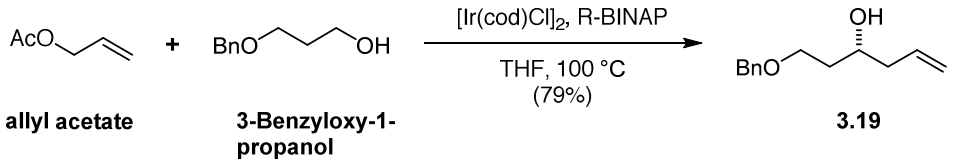
2-Methylene-1,3-propanediol **3.20**

In to a flame dried flask under inert gas were mixed 2-Methylene-1,3-propanediol (5.0 g, 56 mmol, 1.0 eq.) and dry THF (170 ml). The flask was cooled to 0 °C and NaH (2.24 g, 56 mmol, 1.0 eq., 60% in mineral oil) was added. After ca. 40 minutes the same temperature, solid TBSCl (8.4 g, 56 mmol, 1.0 eq.) was added in one portion. Gas evolution was observed. The reaction was monitored by TLC analysis until completion (ca. 1 h). The reaction mixture was diluted with H_2O, extracted three times with Et_2O, the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude TBS mono protected alcohol was isolated as a cloudy, colorless oil (12.2 g, 56 mmol, quant.) and carried directly to the next step. The proton NMR fits the literature.[1]

R_f: 0.5, 30% EtOAc/*i*hex, CAM

The crude (12.2 g, 56 mmol, 1.0 eq.), was dissolved in dry THF (125 mL), cooled at −40 °C and dry Et_3N (16.4 mL, 117 mmol, 2.1 eq.) and MsCl (6.8 mL, 89 mmol, 1.6 eq.) were added. The mixture was stirred at the same temperature for 1.5 h, warmed at 0 °C and anhydrous LiBr (5.3 g, 61 mmol, 1.1 eq.) was added. The mixture was let to warm to RT and stirred for ca. 10 h. Afterwards, it was quenched with a sat. $NaHCO_{3(aq.)}$ and extracted three times with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was dissolved in Et_2O and passed through a silica plug, eluted with more Et_2O and then was removed to deliver crude **3.20** as an orange oil (14.8 g, 56 mmol, quant). The proton NMR fits the literature.[1] The material was used for the next reaction without further purification.

Alcohol (**3.19**)



To a sealed pressure tube under an argon atmosphere charged with 3-Benzyloxy-1-propanol (6.0 mL, 36 mmol, 1.0 eq.), $[Ir(cod)Cl]_2$ (0.6 g, 0.9 mmol, 0.025 eq.), (R)-BINAP (1.11 g, 1.8 mmol, 0.05 eq.), Cs_2CO_3 (2.34 g, 7.2 mmol, 0.2 eq.) and 4-Cl-3-NO_2-BzOH (0.72 g, 3.6 mmol, 0.1 eq.) was added dry THF (180 mL) and allyl acetate (38.0 mL, 360 mmol, 10.0 eq.). The septum was quickly replaced with a teflon screw cap and the reaction mixture was allowed to stir at 100 °C for 3 days. The reaction mixture was allowed to cool to RT, and the solution was evaporated onto celite. Purification by FCC (EtOAc:*i*hex 5:95 to 1:9) provided alcohol **3.19** (5.8 g, 28.6 mmol, 79%). The proton NMR fits the literature.[2]

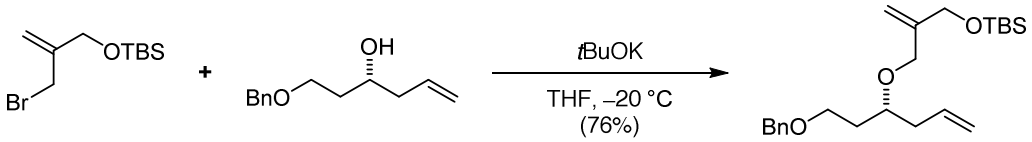
R_f: 0.5, EtOAc:*i*hex 3:7, CAM, no UV.

$[\alpha]_D^{20\,°C}$: +2.5 (c = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.26 (m, 5H), 5.84 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.17 – 5.05 (m, 2H), 4.53 (s, 2H), 3.93 – 3.82 (m, 1H), 3.72 (dt, *J* = 9.3, 5.3 Hz, 1H), 3.65 (ddd, *J* = 9.3, 7.0, 5.5 Hz, 1H), 2.25 (ddt, *J* = 7.4, 6.2, 1.3 Hz, 2H), 1.84 – 1.66 (m, 2H).

Mosher's ester data comparison is available at the NMR data section.

Ether (**3.22**)



3.20 **3.19** **3.22**

In to a flame dried flask under inert gas were mixed alcohol **3.19** (5.8 g, 28.6 mmol, 1.0 eq.), bromide **3.20** (9.6 g, 36.0 mmol, 1.3 eq.) and dry THF (112 mL). The flask was cooled to −20 °C and anhydrous *t*-BuOK (6.3 g, 56.0 mmol, 2.0 eq.) was added. The mixture was stirred at the same temperature and monitored by TLC until completion (ca. 5 h). The heterogeneous reaction mixture was quenched with sat. $NH_4Cl_{(aq.)}$, extracted three times with Et_2O, the organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc:*i*hex 5:95) to afford ether **3.22** (7.4 g, 18.8 mmol, 67%) as a colorless oil.

R_f: 0.8, EtOAc:*i*hex 1:9, CAM, no UV.

HRMS-EI (m/z): calc. for $C_{23}H_{37}O_3Si$ $[M-H]^{\bullet+}$: 389.2506; found: 389.2500.

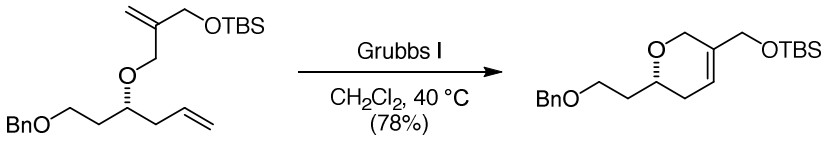
$[\alpha]_D^{20\,°C}$: −15.2 (c = 1.1, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2954 (w), 2928 (w), 2856 (w), 1471 (w), 1252 (m), 1076 (s), 910 (m), 834 (s), 774 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.20 (m, 5H), 5.75 (ddt, J = 17.3, 10.2, 7.1 Hz, 1H), 5.13 – 4.95 (m, 4H), 4.42 (s, 2H), 4.13 – 4.05 (m, 3H), 4.00 – 3.94 (m, 1H), 3.92 – 3.83 (m, 1H), 3.49 (tdd, J = 6.8, 6.0, 3.0 Hz, 3H), 2.22 (ddt, J = 7.1, 5.7, 1.3 Hz, 2H), 1.79 – 1.67 (m, 2H), 0.84 (d, J = 2.6 Hz, 9H), 0.00 (d, J = 4.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.84, 138.63, 134.79, 128.50, 127.80, 127.68, 117.29, 111.54, 75.81, 73.14, 69.97, 67.09, 64.12, 38.59, 34.31, 26.05, 18.51.

Ether (**3.23**)



3.22 **3.23**

In to a flame dried flask under argon were mixed ether **3.22** (7.4 g, 18.8 mmol, 1.0 eq.), Grubbs I (0.6 g, 0.73 mmol, 0.04 eq.) and dry CH_2Cl_2 (190 mL). The reaction vessel was placed in a preheated 40 °C oil bath and monitored by TLC until completion (ca. 8 h). If necessary, another portion of catalyst was added (0.1 g, 0.12 mmol, 0.013 eq.). The dark mixture was cooled to RT, DMSO (1.6 mL) added and the reaction stirred for at least 5 h. The reaction mixture was concentrated under reduced pressure and directly purified by FCC (EtOAc:*i*hex 5:95) to afford ether **3.23** (5.3 g, 14.7 mmol, 78%) as a colorless oil.

R_f: 0.7, EtOAc:*i*hex 1:9, CAM, no UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{35}O_3Si$ $[M+H]^+$: 363.23500; found: 363.23503.

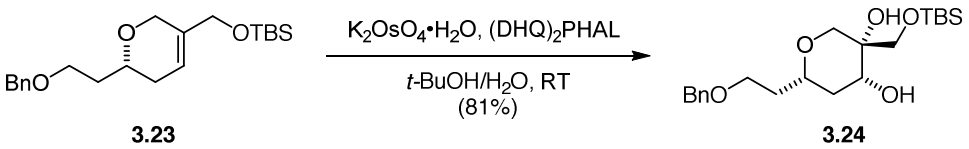
$[\alpha]_D^{20\,°C}$: +38.4 (c = 2.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2951 (w), 2928 (w), 2885 (w), 1471 (w) 1360 (m), 1250 (m), 1074 (s), 834 (s), 774 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.16 (m, 5H), 5.69 – 5.58 (m, 1H), 4.45 (s, 2H), 4.15 – 4.01 (m, 2H), 3.98 (dq, *J* = 1.7, 0.9 Hz, 2H), 3.66 – 3.47 (m, 3H), 1.95 (ddt, *J* = 5.0, 3.2, 1.6 Hz, 2H), 1.85 – 1.68 (m, 2H), 0.84 (s, 9H), -0.00 (d, *J* = 1.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.66, 136.90, 128.47, 127.75, 127.64, 119.21, 73.11, 71.08, 66.91, 66.46, 64.45, 36.09, 30.88, 26.02, 18.47, -5.18.

Diol (**3.24**)



3.23 **3.24**

Into a flask were mixed $K_2OsO_4 \bullet H_2O$ (54.0 mg, 0.14 mmol, 0.01 eq.), $(DHQ)_2PHAL$ (0.54 g, 0.70 mmol, 0.05 eq.), $K_3[Fe(CN)_6]$ (14.5 g, 44 mmol, 3.0 eq.), K_2CO_3 (6.0 g, 44 mmol, 3.0 eq.), and *t*-BuOH/H_2O (150 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 min. The yellow solution was cooled to 0°C and neat **3.23** (5.3 g, 14.7 mmol, 1.0 eq.) and $MeSO_2NH_2$ (4.1 g, 44 mmol, 3.0 eq.) were added. The reaction was allowed to reach RT over time and monitored by TLC analysis until completion (ca. 6 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (14 g), stirred for 15 minutes, partitioned between H_2O/EtOAc, the water phase was extracted trice with EtOAc, the organic phases dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude oil was purified by FCC (EtOAc:*i*hex 2:8 to 1:1) to afford diol **3.24** (4.7 g, 11.9 mmol, 81%, major) as a colorless oil.

R_f: 0.4 major, EtOAc:*i*hex 4:6, CAM, no UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{37}O_5Si$ $[M+H]^+$: 397.24048; found: 397.24016.

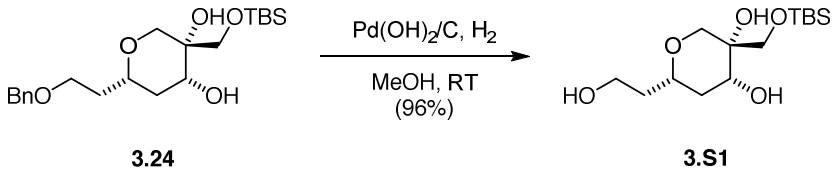
$[\alpha]_D^{20\,°C}$: +6.9 (c = 0.7, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3425 (b), 2951 (w), 2928 (w), 2856 (w), 1723 (w) 1361 (w), 1250 (m), 1085 (s), 835 (s), 776 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ =7.40 – 7.27 (m, 5H), 4.50 (s, 2H), 3.88 – 3.69 (m, 2H), 3.69 – 3.53 (m, 4H), 3.48 (dddd, *J* = 11.4, 8.2, 4.4, 2.0 Hz, 1H), 3.29 (d, *J* = 12.4 Hz, 1H), 2.51 (s, 2H), 1.93 – 1.70 (m, 3H), 1.53 (dt, *J* = 12.9, 11.5 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.58, 128.50, 127.78, 127.71, 73.53, 73.13, 71.78, 71.40, 69.51, 66.53, 66.13, 36.33, 36.02, 25.93, 18.30, -5.42.

Triol (**3.S1**)



3.24 **3.S1**

A flask under air was charged with $Pd(OH)_2/C$ (470 mg), diol **3.24** (4.7 g, 11.9 mmol, 1.0 eq.) and dry MeOH (40 mL). The flask was closed with a septum, H_2 was bubbled through the solution for ten seconds.Then, the reaction was stirred under an H_2 atmosphere (balloon) and monitored by TLC analysis until completion (ca. 14 h). Upon completion, the solution was passed through a pad of celite and the pad was rinsed with MeOH. The solvent was removed under reduced pressure to afford crude triol **3.S1** (3.5 g, 11.4 mmol, 96%) as a deliquescent solid.

R_f: 0.2 EtOAc:*i*hex 7:3, CAM, no UV.

HRMS-ESI (m/z): calc. for $C_{14}H_{31}O_5Si$ $[M+H]^+$: 307.19353; found: 307.19363.

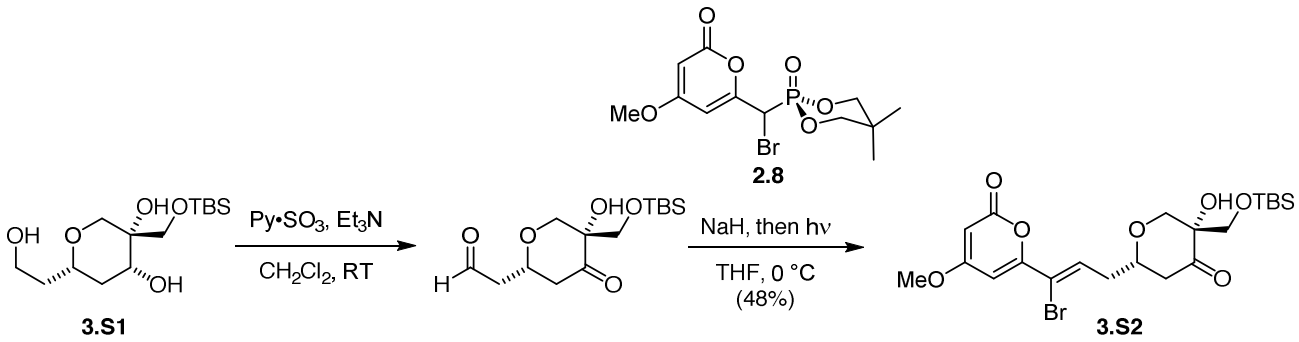
$[\alpha]_D^{20\,°C}$: +12.6 (c = 1.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3383 (b), 2951 (w), 2928 (w), 2857 (w), 1742 (w) 1250 (m), 1083 (s), 1054 (s), 834 (s), 775 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.83 (d, *J* = 12.4 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.64 (d, *J* = 10.1 Hz, 1H), 3.61 – 3.50 (m, 2H), 3.34 (d, *J* = 12.4 Hz, 1H), 1.91 – 1.79 (m, 2H), 1.73 (dddd, *J* = 14.5, 6.0, 4.5, 3.5 Hz, 1H), 1.63 (dt, *J* = 12.8, 11.5 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 76.39, 71.83, 71.28, 69.30, 66.13, 61.03, 37.80, 36.27, 25.94, 18.31, -5.45.

Vinyl bromide (**3.S2**)



In to a flame dried flask under inert gas were mixed triol **3.S1** (0.50 g, 1.60 mmol, 1.0 eq.), Et_3N (2.00 mL, 16.0 mmol, 10.0 eq.), DMSO dry (1.10 mL, 16.0 mmol, 10.0 eq.), and dry CH_2Cl_2 (16 mL). The reaction was placed in a water bath and Py•SO_3 (1.2 g, 8.10 mmol, 5.0 eq.) was added. The reaction was monitored by TLC until completion (ca. 2 h). The reaction mixture was diluted with H_2O, extracted four times with EtOAc, washed with sat. $CuSO_{4(aq.)}$, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was passed through a short pad of silica (EtOAc:*i*hex 3:7) to afford the keto aldehyde which was carried directly to the next step.

R_f: 0.8 EtOAc:*i*hex 7:3, CAM, no UV.

To a flame dried flask under inert gas was added phosphonate **2.8** (0.47 g, 1.3 mmol, 0.8 eq.) and dry THF (9 mL). The reaction was cooled to 0°C and stirred while NaH (56.0 mg, 1.4 mmol, 0.9 eq., 60% in mineral oil) was added in one portion. The heterogeneous mixture turned clear and dark within ca. 1 h (if this does not occur allow to RT for 30 minutes and then cool to 0°C), and at this point a solution of keto aldehyde in dry THF (9 mL) was added. The reaction was monitored by TLC until completion (ca. 1 h). The reaction mixture was quenched with sat. $NH_4Cl_{(aq.)}$, extracted trice with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude oil was purified by FCC (EtOAc:*i*hex 35:65) to afford vinyl bromide **3.S2** (0.39 g, 0.78 mmol, 48%) as a slightly yellow solid. This was dissolved in ca. 3 mL of benzene and irradiated with UV light (12 V, 380 – 400 nm LED) until complete isomerization (ca. 10 h).

R_f: 0.5 EtOAc:*i*hex 4:6, CAM, UV; 0.3 for the isomer.

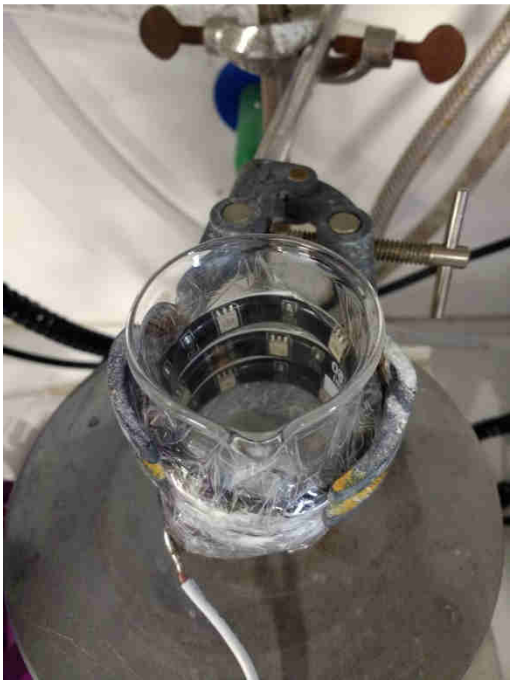
HRMS-ESI (m/z): calc. for $C_{21}H_{32}BrO_7Si$ $[M+H]^+$: 503.10952; found: 503.10928.

$[\alpha]_D^{20\,°C}$: −5.4 (c = 0.26, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3389 (b), 2955 (w), 2930 (w), 2857 (w), 1715 (s), 1558 (s), 1403 (s), 1253 (s), 1039 (m), 832 (s), 773 (m) cm^{-1}.

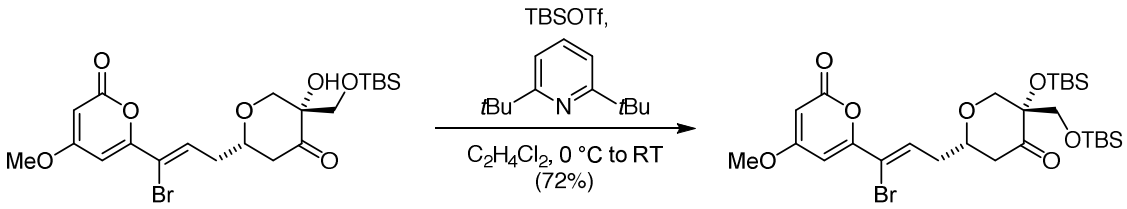
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (t, *J* = 6.9 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.49 (d, *J* = 2.1 Hz, 1H), 4.21 (dq, *J* = 9.0, 5.4 Hz, 1H), 4.12 – 4.00 (m, 1H), 3.82 (d, *J* = 13.6 Hz, 5H), 3.75 – 3.60 (m, 2H), 2.72 (dtd, *J* = 15.5, 13.9, 5.6 Hz, 3H), 2.56 (ddd, *J* = 16.1, 7.0, 5.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.46, 171.07, 163.29, 155.76, 133.06, 117.11, 102.69, 89.33, 77.90, 75.96, 71.14, 65.46, 56.33, 44.12, 36.67, 25.89, 18.34, -5.33, -5.38.



Coiled LEDs for UV irradiation.

TBS ether (**3.S3**)



3.S2 **3.S3**

A flame-dried flask under argon was charged with vinyl bromide **2.S2** (0.27 g, 0.54 mmol, 1.0 eq.), 2,6-di-tert-butylpyridine(0.7 mL, 3.2 mmol, 6.0 eq.) and dry $C_2H_4Cl_2$ (5.4 mL). The flask was cooled to 0 °C. Then, TBSOTf (0.37 mL, 1.6 mmol, 3.0 eq.) was added dropwise and the mixture stirred for 15 minutes at the same temperature. Afterwards, the cooling bath was removed and the reaction monitored by TLC analysis until completion (ca. 2 h). Then, the reaction mixture was diluted with sat. $NaHCO_{3(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 15:85) to afford TBS ether **3.S3** (0.24 g, 0.39 mmol, 72%) as a yellow solid.

R_f: 0.5 EtOAc:*i*hex 3:7, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{27}H_{46}BrO_7Si_2$ $[M+H]^+$: 617.19600; found: 617.19616.

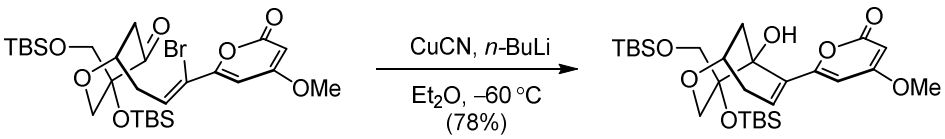
$[\alpha]_D^{20\,°C}$: +15.6 (c = 0.5, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2954 (w), 2929 (w), 2857 (w), 2361 (w), 1731 (s), 1563 (m), 1403 (m), 1253 (s), 1104 (m), 836 (s), 778 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (t, *J* = 6.9 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H), 4.18 – 4.00 (m, 1H), 3.91 – 3.76 (m, 5H), 3.71 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 12.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 10.5 Hz, 1H), 2.79 – 2.53 (m, 2H), 2.36 (dd, *J* = 13.8, 3.0 Hz, 1H), 0.88 (d, *J* = 3.0 Hz, 18H), 0.19 (s, 3H), 0.13 – -0.01 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.25, 171.08, 163.30, 155.94, 133.83, 116.84, 102.51, 89.24, 78.81, 76.68, 73.75, 64.54, 56.31, 44.64, 38.58, 26.02, 25.90, 18.54, 18.46, -2.48, -2.89, -5.36, -5.49.

Bicycle (**3.S4**)



3.S3 **3.S4**

To a flame dried flask under inert gas were added CuCN (0.86 g, 9.7 mmol, 25.0 eq.) and dry Et_2O (30 mL). The flask was cooled to −25 °C and *n*-BuLi (4.9 ml, 11.7 mmol, 30.0 eq., 2.38 M in hexanes) was added. The mixture was stirred for 30 minutes at the same temperature. Subsequently, the reaction was cooled to −60 °C. To this stirring solution was added dropwise TBS ether **3.S3** (0.22 g, 0.36 mmol, 1.0 eq.) in dry Et_2O (10 mL). A stark color change to cardinal red was observed. The mixture was stirred at the same temperature and monitored by TLC analysis until completion (ca. 1.5 h). Then, the reaction was cannulated in a pH = 9 $NH_3/NH_4Cl_{(aq.)}$ buffer, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 1:1) to afford bicycle **3.S4** (0.15 g, 0.28 mmol, 78%) as a white foam.

Note: to obtain reproducible and high yields it is necessary to use colorless *n*-BuLi.

R_f: 0.2 EtOAc:*i*hex 4:6, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{27}H_{47}O_7Si_2$ $[M+H]^+$: 539.28548; found: 539.28517.

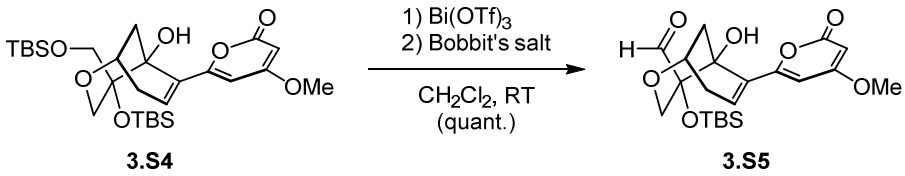
$[\alpha]_D^{20\,°C}$: −72.0 (c = 0.2, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3438 (b), 2928 (w), 2882 (w), 2856 (w), 1708 (m), 1656 (s), 1560 (s), 1406 (s) 1360 (w), 1249 (s), 1091 (s), 831 (s), 771 (m) cm^{-1}.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 2.2 Hz, 1H), 6.99 (t, *J* = 4.0 Hz, 1H), 5.57 (s, 1H), 5.48 – 5.38 (m, 1H), 4.53 (dd, *J* = 11.5, 0.9 Hz, 1H), 4.26 (s, 1H), 3.90 (dd, *J* = 11.5, 1.1 Hz, 1H), 3.78 (d, *J* = 1.0 Hz, 3H), 3.43 (d, *J* = 11.7 Hz, 1H), 3.34 – 3.22 (m, 1H), 2.60 (dt, *J* = 21.3, 4.7 Hz, 1H), 2.36 (dd, *J* = 21.2, 4.0 Hz, 1H), 2.14 (dd, *J* = 12.9, 4.2 Hz, 1H), 2.01 – 1.91 (m, 1H), 0.97 (t, *J* = 1.1 Hz, 9H), 0.73 (d, *J* = 1.1 Hz, 9H), 0.18 (dd, *J* = 22.6, 1.0 Hz, 6H), 0.09 (d, *J* = 1.1 Hz, 3H), -0.02 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.10, 164.87, 157.52, 134.48, 133.86, 104.00, 88.55, 76.72, 69.48, 69.24, 67.65, 55.92, 40.11, 32.79, 25.99, 18.54, 18.20, -1.74, -1.93, -5.28, -5.64.

Aldehyde (**3.S5**)



3.S4 **3.S5**

A flask was charged with bicycle **3.S4** (0.15 g, 0.28 mmol, 1.0 eq.), dry THF (2.8 mL), H_2O (25 µL) and $Bi(OTf)_3$ (0.14 g, 0.22 mmol,0.8 eq.). The mixture was stirred at RT and monitored by TLC analysis until completion (ca. 3 h). Then, the reaction was directly passed through a silica pad (EtOAc) to afford the crude alcohol **3.25** as a colorless foam.

R_f: 0.2 EtOAc:*i*hex 8:2, CAM, UV.

In to a flame dried flask under inert gas were mixed the crude alcohol **3.25**, Bobbit's salt (0.21 g, 0.72 mmol, 2.5 eq.), 2,6-lutidine (0.08 ml, 0.65 mmol, 2.25 eq.), and dry CH_2Cl_2 (0.7 mL). The reaction was stirred at RT and monitored by TLC until completion (ca. 2 h), while a color change from yellow to pink-orange was observed. The reaction mixture was concentrated under reduced pressure and Et_2O was added. The mixture was stirred until solids separated from the solution, then it was filtered and concentrated under reduced pressure. The crude residue was purified by FCC (EtOAc:*i*hex 1:1 to 6:4) to afford aldehyde **3.S5** (0.12 mg, 0.28 mmol, quant.) as a white foam.

R_f: 0.4 EtOAc:*i*hex 7:3, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{31}O_7Si$ $[M+H]^+$: 423.18336; found: 423.18301.

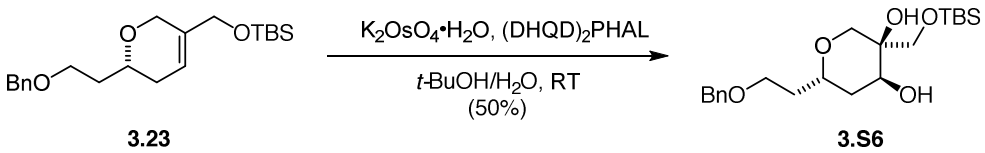
$[\alpha]_D^{20\,°C}$: −92.3 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3476 (b), 3355 (b), 2929 (w), 2856 (w), 1731 (m), 1671 (s), 1552 (s), 1404 (s) 1359 (w), 1250 (s), 1092 (s), 833 (s), 775 (m) cm^{-1}.

^{1}H NMR (599 MHz, C_6D_6) δ = 10.12 (s, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.42 (t, *J* = 3.9 Hz, 1H), 5.16 (t, *J* = 1.2 Hz, 1H), 3.93 (d, *J* = 4.6 Hz, 1H), 3.85 (d, *J* = 11.8 Hz, 1H), 3.44 (d, *J* = 2.7 Hz, 1H), 3.34 (d, *J* = 11.9 Hz, 1H), 2.89 (t, *J* = 1.3 Hz, 3H), 2.09 (dd, *J* = 12.9, 4.1 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.67 (dd, *J* = 13.0, 1.7 Hz, 1H), 0.76 (s, 9H), 0.27 (s, 3H), -0.07 (s, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ = 201.35, 171.47, 163.94, 157.83, 134.47, 133.47, 103.48, 88.85, 81.97, 74.43, 68.54, 65.41, 55.14, 38.55, 31.94, 26.17, 18.71, -2.15, -2.28.

Diol (**3.S6**)



3.23 **3.S6**

Into a flask were mixed $K_2OsO_4 \bullet H_2O$ (40.0 mg, 0.11 mmol, 0.01 eq.), $(DHQD)_2PHAL$ (0.42 g, 0.55 mmol, 0.05 eq.), $K_3[Fe(CN)_6]$ (10.8 g, 33.0 mmol, 3.0 eq.), K_2CO_3 (4.50 g, 33.0 mmol, 3.0 eq.), and *t*-BuOH/H_2O (110 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 minutes. The yellow solution was cooled to 0°C and neat **3.23** (4.0 g, 11.0 mmol, 1.0 eq.) and $MeSO_2NH_2$ (3.1 g, 33.0 mmol, 3.0 eq.) were added. The reaction was allowed to reach RT and it was monitored by TLC analysis until completion (ca. 8 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (11 g), stirred for 15 minutes, partitioned between H_2O/EtOAc, the water phase was extracted trice with EtOAc, the organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude oil was purified by FCC (EtOAc:*i*hex 3:7) to afford diol **3.S6** (2.19 g, 5.5 mmol, 50%, major) as a colorless oil.

R_f: 0.6 major, EtOAc:*i*hex 4:6, CAM, no UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{37}O_5Si$ $[M+H]^+$: 397.24048; found: 397.24025.

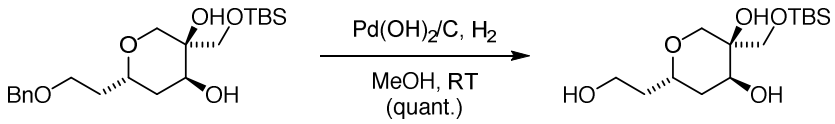
$[\alpha]_D^{20\,°C}$: +15.7 (c = 0.8, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3451 (b), 2951 (w), 2927 (w), 2857 (w), 1361 (w), 1253 (m), 1089 (s), 835 (s), 776 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.26 (m, 5H), 4.50 (s, 2H), 3.87 (td, *J* = 4.2, 2.3 Hz, 2H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.68 – 3.51 (m, 4H), 3.48 (dd, *J* = 11.2, 1.2 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.75 (dtd, *J* = 6.9, 5.7, 5.1, 3.6 Hz, 2H), 1.49 (ddd, *J* = 14.3, 11.2, 2.9 Hz, 1H), 0.90 (s, 9H), 0.09 (d, *J* = 1.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.62, 128.48, 127.76, 127.63, 73.11, 70.55, 69.34, 67.81, 67.12, 67.10, 65.28, 35.91, 35.59, 25.98, 18.41, -5.36.

Triol (**3.26**)



3.S6 **3.26**

A flask under air was charged with $Pd(OH)_2/C$ (1.0 g), diol **3.S6** (2.19 g, 5.50 mmol, 1.0 eq.) and dry MeOH (18 mL). The flask was closed with a septum, H_2 was bubbled through the solution for ten seconds. Then, the reaction was stirred under an H_2 atmosphere (balloon) and monitored by TLC analysis until completion (ca. 5 h). Upon completion, the solution was passed through a pad of celite and the pad was rinsed with MeOH. The solvent was removed under reduced pressure to afford crude triol **3.26** (1.66 g, 5.5 mmol, quant.) as a deliquescent solid.

R_f: 0.2 EtOAc:*i*hex 4:6, CAM, no UV.

HRMS-ESI (m/z): calc. for $C_{14}H_{31}O_5Si$ $[M+H]^+$: 307.19353; found: 307.19361.

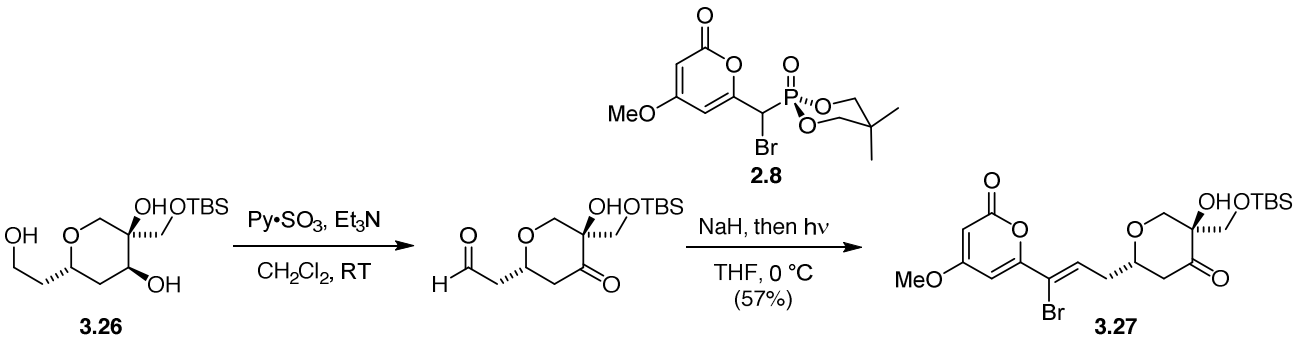
$[\alpha]_D^{20\,°C}$: +16.9 (c = 2.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3397 (b), 2951 (w), 2928 (w), 2857 (w), 1463 (w) 1253 (m), 1083 (s), 1050 (s), 833 (s), 775 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.02 – 3.92 (m, 1H), 3.85 (d, *J* = 3.3 Hz, 1H), 3.83 – 3.71 (m, 3H), 3.68 – 3.56 (m, 2H), 3.52 (d, *J* = 11.1 Hz, 1H), 1.85 (dt, *J* = 14.5, 2.9 Hz, 1H), 1.69 (tt, *J* = 8.0, 4.6 Hz, 2H), 1.54 (ddd, *J* = 14.3, 11.3, 2.9 Hz, 1H), 0.91 (s, 9H), 0.09 (d, *J* = 1.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 72.67, 70.42, 67.76, 66.94, 65.01, 61.72, 37.23, 35.87, 25.98, 18.42, -5.29, -5.34.

Vinyl bromide (**3.27**)



In to a flame dried flask under inert gas were mixed triol **3.26** (1.6 g, 5.4 mmol, 1.0 eq.), Et_3N (7.79 mL, 54.0 mmol, 10.0 eq.), DMSO dry (3.8 mL, 54.0 mmol, 10.0 eq.), and dry CH_2Cl_2 (54 mL). The reaction was placed in a water bath and Py•SO_3 (4.86 g, 32.0 mmol, 6.0 eq.) was added. The reaction was monitored by TLC until completion (after ca. 12 h were added 3/5/5 eq. of Py•SO_3/ Et_3N/DMSO). The reaction mixture was diluted with H_2O, extracted four times with EtOAc, washed with sat. $CuSO_{4(aq.)}$, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was passed through a short pad of silica (EtOAc:*i*hex 3:7) to afford keto aldehyde which was carried directly to the next step.

R_f: 0.6 EtOAc:*i*hex 4:6, CAM, no UV.

To a flame dried flask under inert gas was added phosphonate **2.8** (1.75 g, 4.8 mmol, 0.9 eq.) and dry THF (40 mL). The reaction was cooled to 0°C and stirred while NaH (0.2 g, 5.2 mmol, 0.96 eq., 60% in mineral oil) was added in one portion. The heterogeneous mixture was allowed to reach RT and stirred until it turned clear and dark (ca. 1 h). The mixture was cooled to 0°C and a solution of crude keto aldehyde in dry THF (15 mL) was added. The reaction was monitored by TLC until completion (ca. 1 h). The reaction mixture was quenched with sat. $NH_4Cl_{(aq.)}$, extracted trice with EtOAc, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude oil was purified by FCC (EtOAc:*i*hex 35:65) to afford vinyl bromide **3.27** (1.57 g, 3.12 mmol, 57%) as a slightly yellow solid. This was dissolved in ca. 8 mL of C_6D_6 and irradiated with UV light (12 V, 380 – 400 nm LEDs) until complete isomerization.

R_f: 0.4 EtOAc:*i*hex 4:6, CAM, UV.

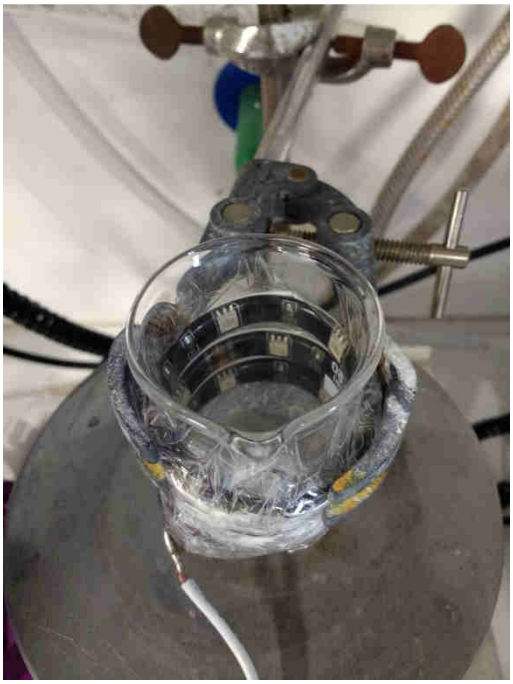
HRMS-ESI (m/z): calc. for $C_{21}H_{32}BrO_7Si$ $[M+H]^+$: 503.10952; found: 503.10938.

$[\alpha]_D^{20\,°C}$: +37.7 (c = 1.4, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3384 (b), 2952 (w), 2927 (w), 2855 (w), 1722 (s), 1561 (s), 1401 (s), 1247 (s), 1105 (m), 833 (s), 775 (m) cm^{-1}.

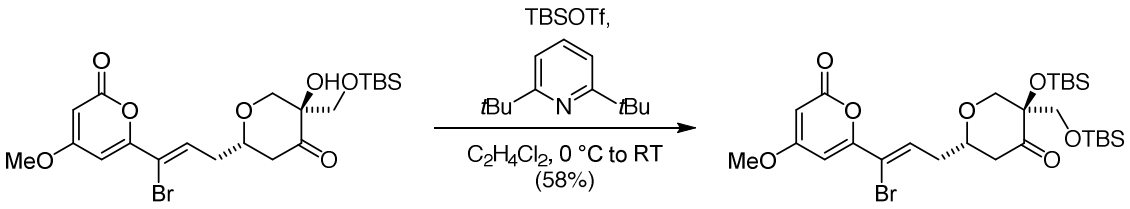
^{1}H NMR (400 MHz, C_6D_6) δ = 6.98 (t, *J* = 7.0 Hz, 1H), 6.28 (d, *J* = 2.1 Hz, 1H), 5.11 (d, *J* = 2.2 Hz, 1H), 4.14 (d, *J* = 10.9 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 3.12 – 2.95 (m, 2H), 2.80 (s, 3H), 2.40 – 2.20 (m, 2H), 2.20 – 2.07 (m, 2H), 0.92 (s, 9H), 0.05 (d, *J* = 8.6 Hz, 6H).

^{13}C NMR (101 MHz, C_6D_6) δ = 206.35, 170.19, 161.81, 155.88, 133.25, 117.39, 102.28, 89.48, 79.63, 77.36, 72.96, 68.17, 55.23, 44.97, 38.62, 25.98, 18.45, -5.16, -5.40.



Coiled LEDs for UV irradiation.

TBS ether (**3.28**)



3.27 **3.28**

A flame-dried flask under argon was charged with vinyl bromide **3.27** (1.56 g, 3.12 mmol, 1.0 eq.), 2,6-di-tert-butylpyridine (2.2 mL, 13.0 mmol, 4.3 eq.) and dry $C_2H_4Cl_2$ (30.0 mL). The flask was cooled to 0 °C. Then, TBSOTf (1.54 mL, 6.7 mmol, 2.15 eq.) was added dropwise and the mixture stirred for 15 minutes at the same temperature. Afterwards, the cooling bath was removed and the reaction monitored by TLC analysis until completion (ca. 4 h). Then, the reaction mixture was diluted with sat. $NaHCO_{3(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 15:85) to afford TBS ether **3.28** (1.12 g, 1.82 mmol, 58%) as a yellow foam.

R_f: 0.6 EtOAc:*i*hex 3:7, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{27}H_{46}BrO_7Si_2$ $[M+H]^+$: 617.19600; found: 617.19636.

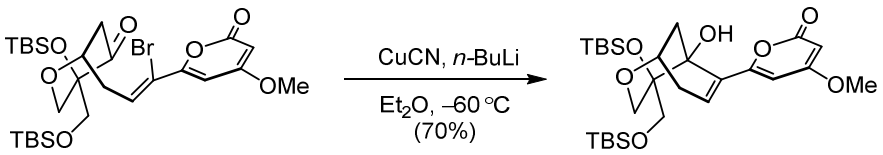
$[\alpha]_D^{20\,°C}$: +36. (c = 3.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2952 (w), 2928 (w), 2856 (w), 2389 (w), 1731 (s), 1562 (m), 1401 (m), 1246 (s), 1108 (m), 831 (s), 776 (m) cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6) δ = 7.06 (t, *J* = 7.0 Hz, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 5.11 (d, *J* = 2.2 Hz, 1H), 4.07 (d, *J* = 10.6 Hz, 1H), 3.73 (d, *J* = 11.4 Hz, 1H), 3.60 (d, *J* = 10.6 Hz, 1H), 3.11 (dddd, *J* = 11.5, 7.0, 4.6, 2.8 Hz, 1H), 3.02 (d, *J* = 11.3 Hz, 1H), 2.79 (s, 3H), 2.32 – 2.09 (m, 4H), 1.04 (s, 9H), 0.94 (s, 9H), 0.48 (s, 3H), 0.31 (s, 3H), 0.07 (d, *J* = 5.5 Hz, 6H).

^{13}C NMR (101 MHz, C_6D_6) δ = 204.17, 170.23, 161.85, 155.93, 133.38, 117.40, 102.28, 89.46, 83.25, 76.91, 73.07, 68.42, 55.21, 46.43, 38.48, 26.39, 26.07, 18.98, 18.53, -2.06, -2.10, -5.25, -5.47.

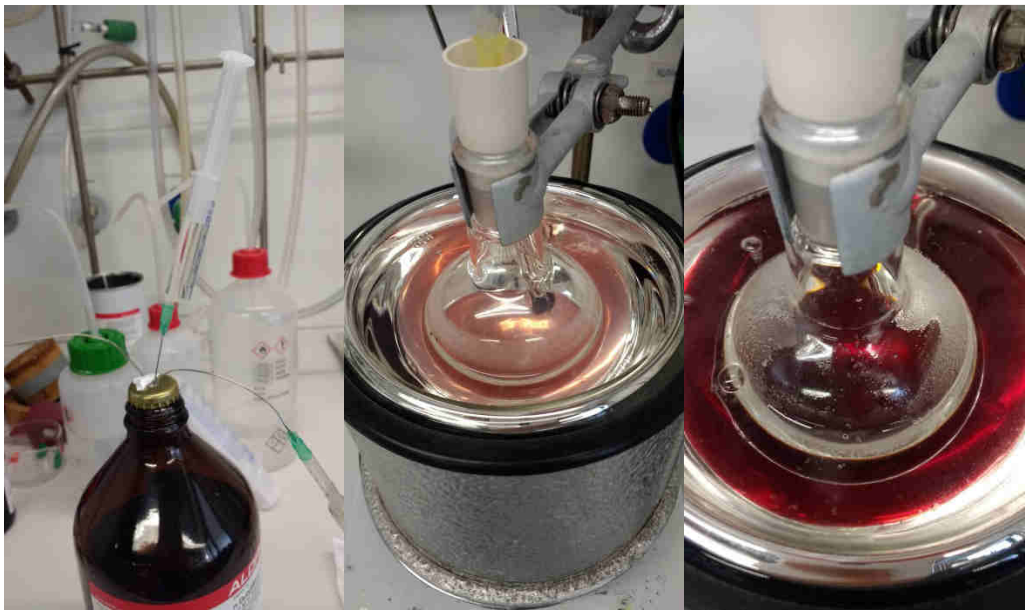
Bicycle (**3.29**)



3.28 **3.29**

To a flame dried flask under inert gas were added CuCN (4.0 g, 45.0 mmol, 25.0 eq.) and dry Et_2O (160 mL). The flask was cooled to −25 °C and *n*-BuLi (22.4 ml, 54.0 mmol, 30.0 eq., 2.4 2.38 M in hexanes) was added. The mixture was stirred for 30 minutes at the same temperature. Subsequently, the reaction was cooled to −60 °C. To this stirring solution was added dropwise TBS ether **3.28** (1.12 g, 1.82 mmol, 1.0 eq.) in dry Et_2O (20.0 mL). A stark color change to cardinal red was observed. The mixture was stirred at the same temperature and monitored by TLC analysis until completion (ca. 1.5 h). Then, the reaction was cannulated in a pH = 9 $NH_3/NH_4Cl_{(aq.)}$ buffer, extracted three times with EtOAc, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by FCC (EtOAc/*i*hex 2:8 to 3:7) to afford bicycle **3.29** (0.694 g, 1.29 mmol, 70%) as a white solid.

Note: to obtain reproducible and high yields it is necessary to use colorless *n*-BuLi.



Colorless *n*-BuLi – Before SM addition – After SM addition

R_f: 0.5 EtOAc:*i*hex 4:6, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{27}H_{47}O_7Si_2$ $[M+H]^+$: 539.28548; found: 539.28526.

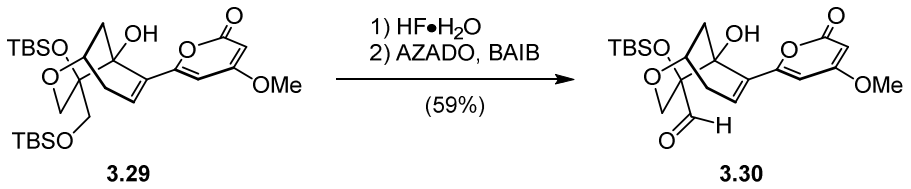
$[\alpha]_D^{20\,°C}$: −101.0 (c = 1.0, $CHCl_3$).

IR (ATR, neat): ν_{max} = 3538 (wb), 2928 (w), 2882 (w), 2856 (w), 1719 (m), 1656 (s), 1630 (m), 1559 (s), 1405 (s), 1249 (s), 1001 (s), 829 (s), 775 (m) cm^{-1}.

^{1}H NMR (599 MHz, C_6D_6) δ = 7.11 (d, *J* = 2.2 Hz, 1H), 6.60 (t, *J* = 3.9 Hz, 1H), 5.27 (d, *J* = 2.2 Hz, 1H), 4.03 (d, *J* = 13.3 Hz, 1H), 3.97 – 3.85 (m, 2H), 3.73 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 13.4 Hz, 1H), 2.98 (s, 1H), 2.88 (s, 3H), 2.36 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.02 – 1.83 (m, 2H), 1.39 (dd, *J* = 12.0, 1.9 Hz, 1H), 0.98 (s, 9H), 0.87 (s, 9H), 0.35 (s, 3H), 0.21 (s, 3H), 0.00 (d, *J* = 9.4 Hz, 6H).

^{13}C NMR (151 MHz, C_6D_6) δ = 170.96, 162.81, 157.91, 136.19, 133.32, 102.66, 88.98, 80.10, 73.02, 68.59, 66.73, 64.44, 55.04, 37.55, 32.47, 26.38, 26.23, 19.05, 18.81, -2.43, -2.80, -5.43, -5.48.

Aldehyde (**3.30**)



3.29 **3.30**

A flask was charged with bicycle **3.29** (0.10 g, 0.18 mmol, 1.0 eq.), dry MeCN (1.8 mL) and it was cooled to 0 °C. The mixture was stirred at the same temperature and HF (0.2 mL, from a stock solution made with 0.05 mL of HF 50% in H_2O and 0.95 mL of MeCN) was added. Another aliquot of HF was added after 1 h and the reaction was monitored by TLC analysis until completion (ca. 3 h). Then, the reaction mixture was diluted with sat. $NaHCO_{3(aq.)}$, extracted three times with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was purified used directly in the next reaction.

R_f: 0.2 EtOAc:*i*hex 1:1, CAM, UV.

Into a flask were mixed the crude alcohol, AZADO (0.5 mg, 3.7 µmol, 0.02 eq.), BAIB (15.0 g 0.55 mmol, 3.0 eq.), and dry CH_2Cl_2 (3.0 mL). The reaction was stirred at RT and monitored by TLC until completion (ca. 5 h). The solution was directly purified by FCC (EtOAc:*i*hex 6:4) to afford aldehyde **3.30** (0.44 mg, 0.10 mmol, 59%) as a white foam.

R_f: 0.3 EtOAc:*i*hex 1:1, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{31}O_7Si$ $[M+H]^+$: 423.18336; found: 423.18310.

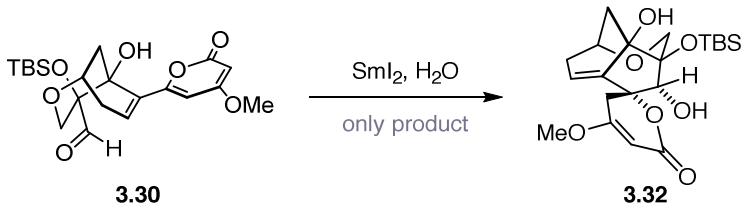
$[\alpha]_D^{20\,°C}$: −73.7 (c = 0.5, $CHCl_3$).

IR (ATR, neat): ν_{max} = 2930 (w), 2856 (w), 1722 (s), 1632 (s), 1560 (s), 1451 (m) 1401 (m), 1249 (s), 1092 (w), 826 (s), 779 (m) cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6) δ = 9.50 (s, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.74 (t, *J* = 4.0 Hz, 1H), 5.20 (d, *J* = 2.2 Hz, 1H), 3.86 – 3.66 (m, 2H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.05 (s, 1H), 2.80 (s, 3H), 2.16 (dd, *J* = 12.1, 4.0 Hz, 1H), 1.85 (t, *J* = 3.6 Hz, 2H), 1.30 (dd, *J* = 12.0, 2.0 Hz, 1H), 0.91 (s, 9H), 0.08 (d, *J* = 22.1 Hz, 6H).

^{13}C NMR (101 MHz, C_6D_6) δ = 200.47, 170.93, 162.89, 156.70, 137.38, 131.20, 103.23, 89.61, 83.43, 73.20, 68.76, 63.36, 55.26, 37.04, 32.38, 26.28, 19.04, -2.59, -2.99.

Tetracycle (**3.32**)



3.30 **3.32**

R_f: 0.7 EtOAc:*i*hex 6:4, CAM, UV.

HRMS-ESI (m/z): calc. for $C_{21}H_{33}O_7Si$ $[M+H]^+$: 425.19901; found: 425.19910.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 6.11 (ddd, *J* = 7.1, 2.1, 1.0 Hz, 1H), 5.20 (s, 1H), 4.25 – 4.22 (m, 1H), 4.18 (s, 1H), 4.00 (d, *J* = 13.3 Hz, 1H), 3.76 (s, 3H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.24 – 3.19 (m, 1H), 3.14 – 3.08 (m, 1H), 2.60 (s, 1H), 2.48 (ddd, *J* = 18.7, 3.3, 2.0 Hz, 1H), 2.33 (ddt, *J* = 18.8, 7.0, 2.5 Hz, 1H), 2.11 – 2.06 (m, 1H), 1.81 (dd, *J* = 12.4, 1.4 Hz, 1H), 0.94 (s, 9H), 0.21 (d, *J* = 9.3 Hz, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 172.03, 166.04, 140.79, 128.42, 90.27, 84.95, 83.16, 79.70, 74.43, 70.98, 67.81, 56.30, 37.93, 32.70, 32.46, 29.86, 25.99, 18.40, 1.17, -2.98, -3.12.

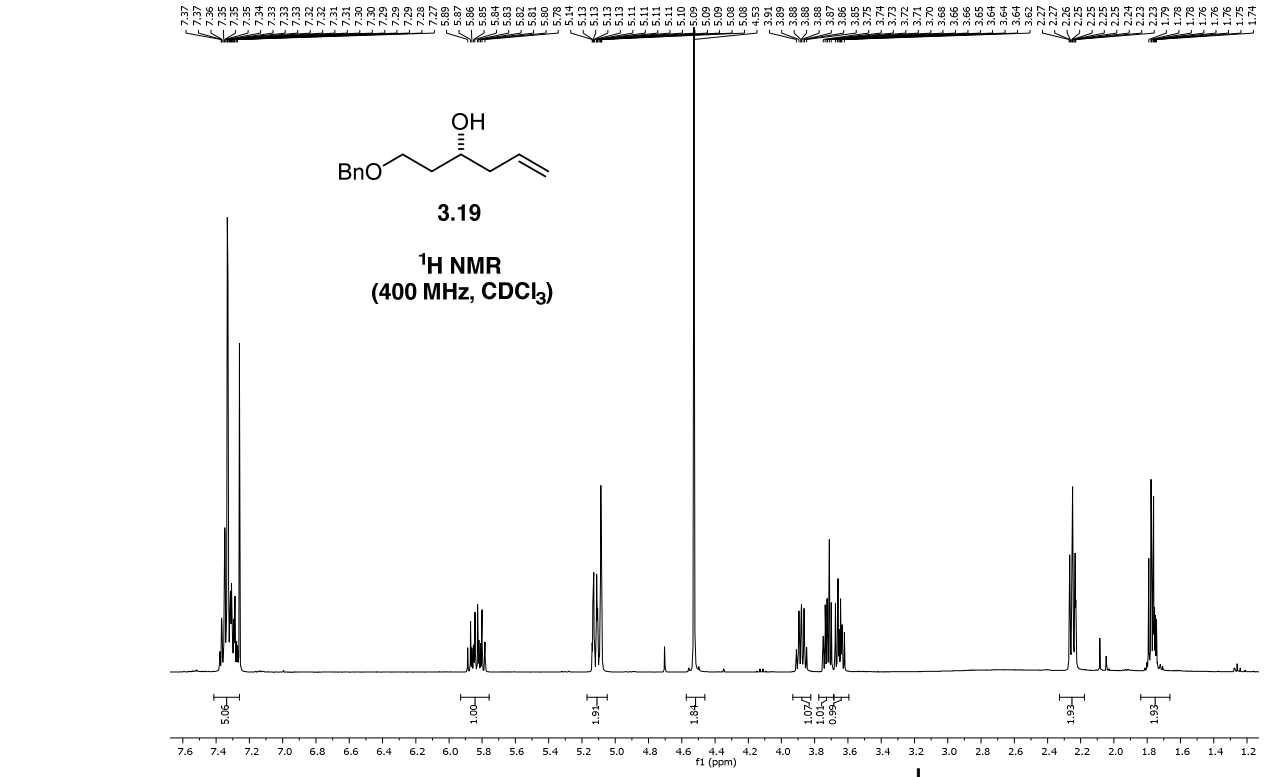
The 2D NMR data are available at the corresponding NMR data Chapter.

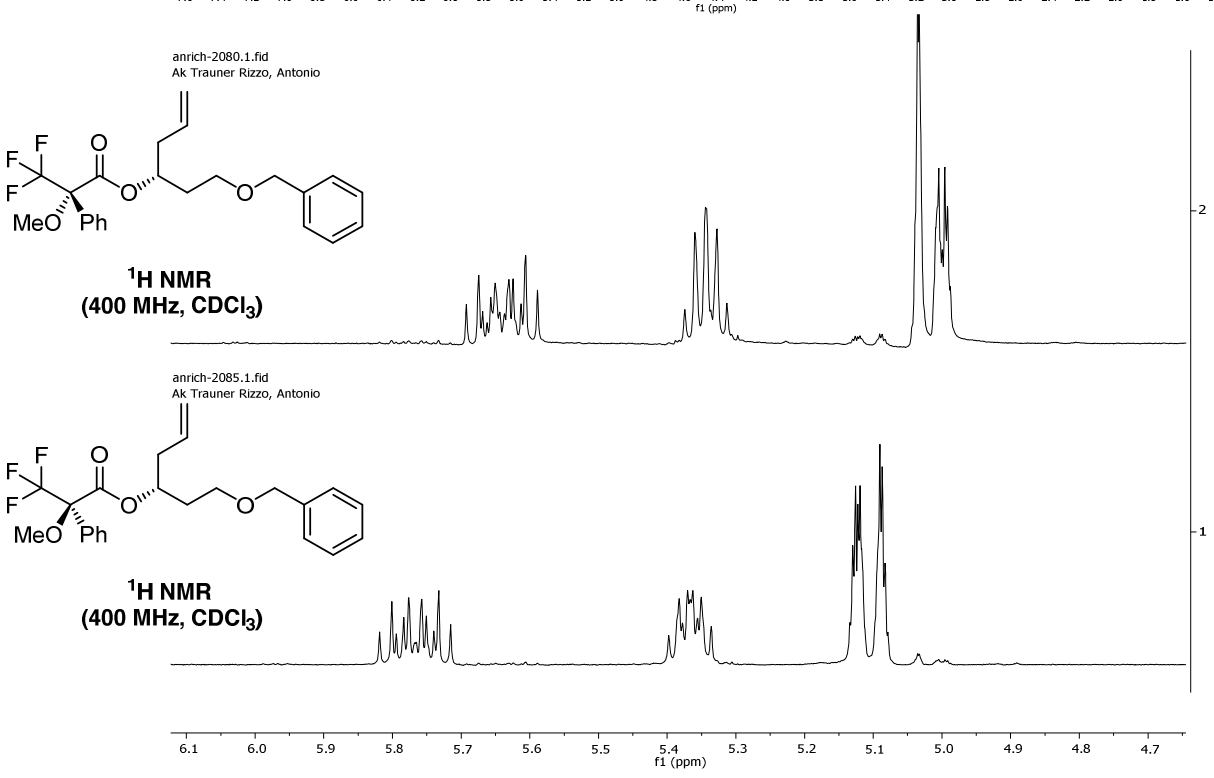
6.5.2 References

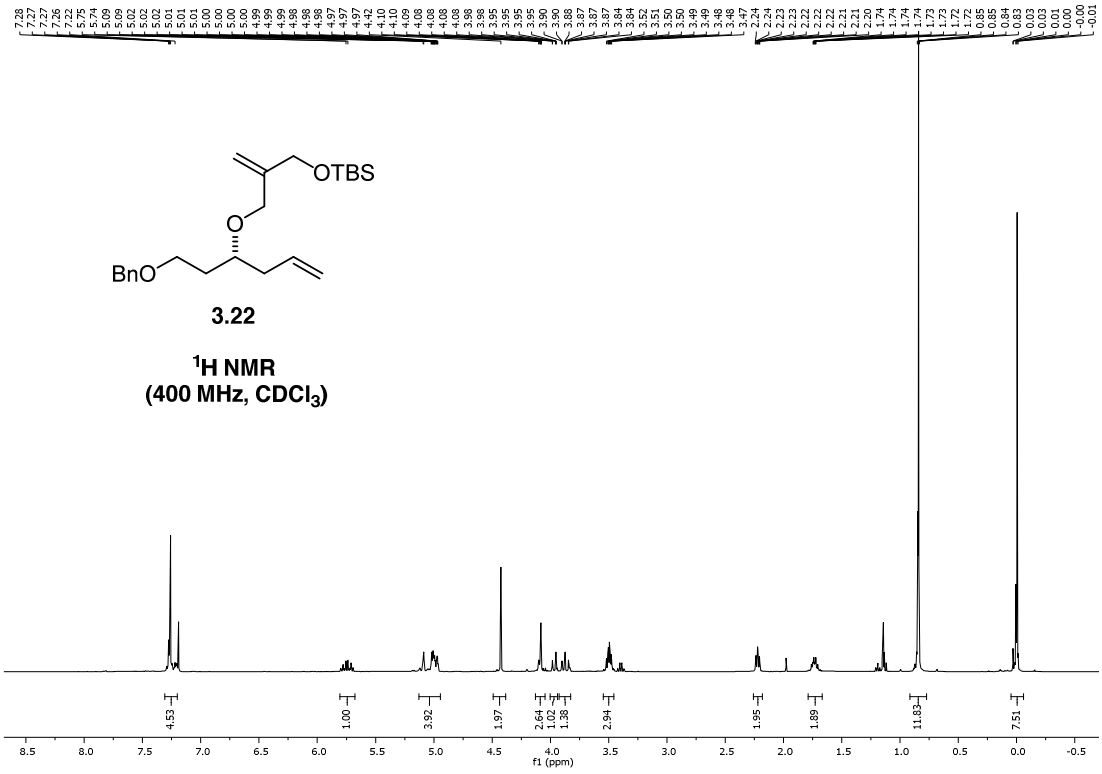
1. E. A. Couladouros, M. Dakanali, K. D. Demadis, V. P. Vidali, *Org. Lett.* **2009**, *11*, 4430.

2. E. Brun, V. Bellosta, J. Cossy, *J. Org. Chem.* **2016**, *81*, 8206.

6.5.3 NMR Data for Chapter 3.2



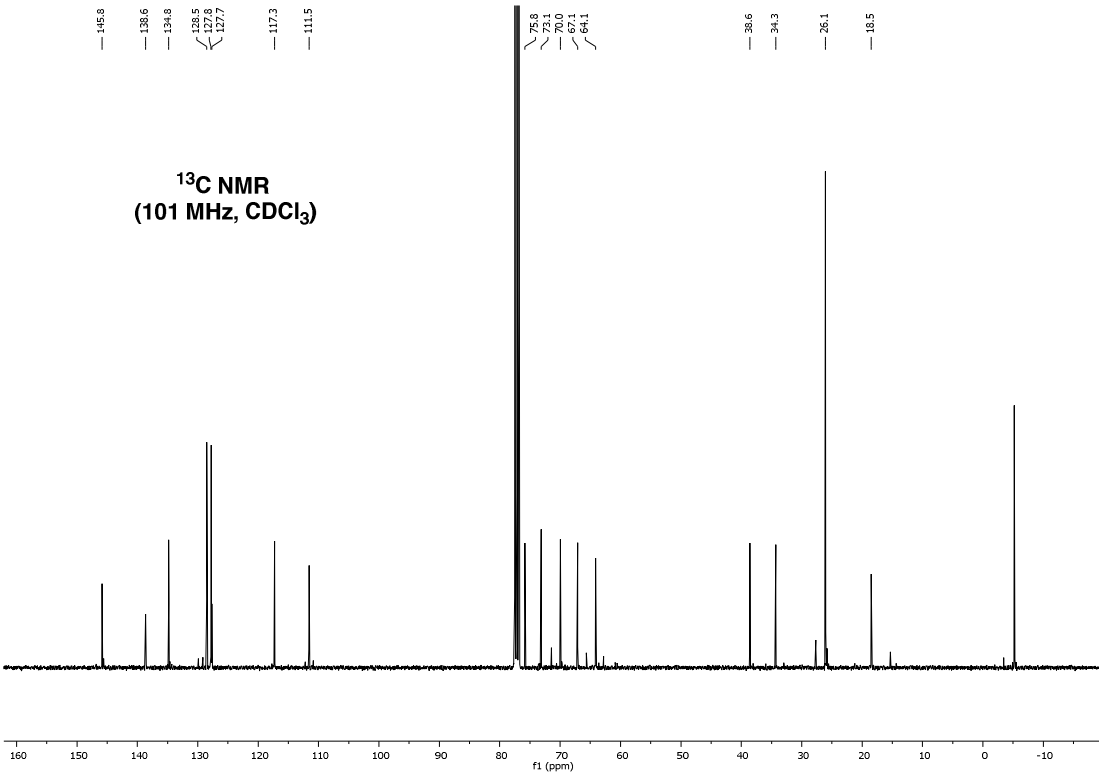


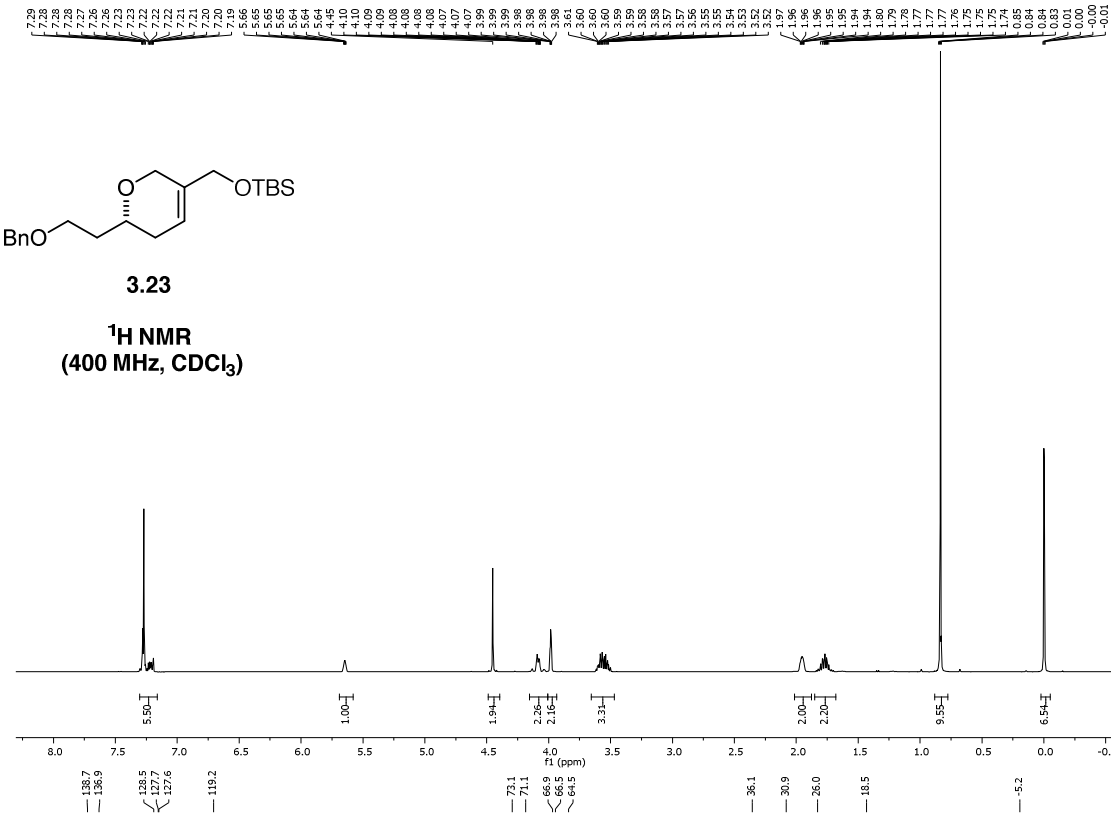


3.22

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

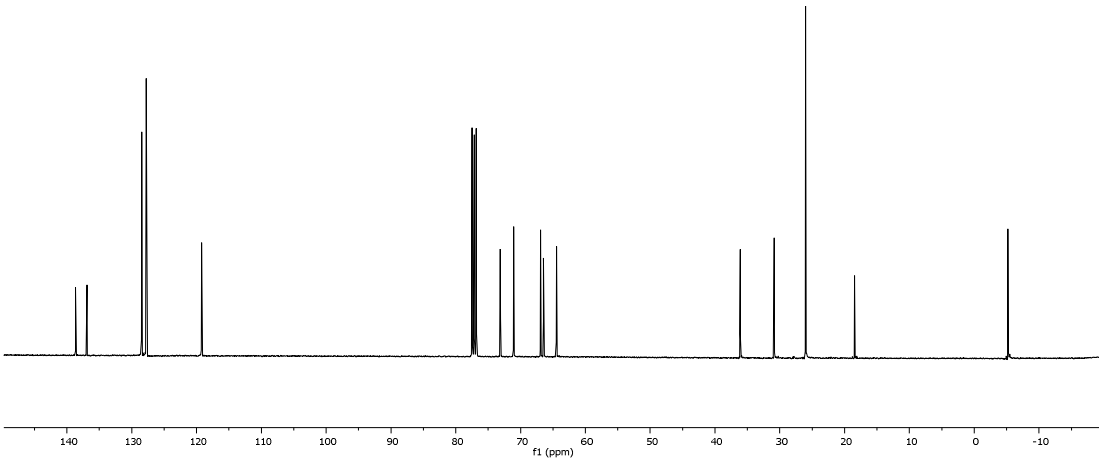


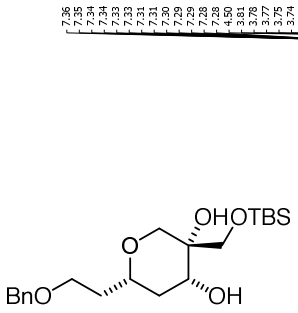


3.23

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

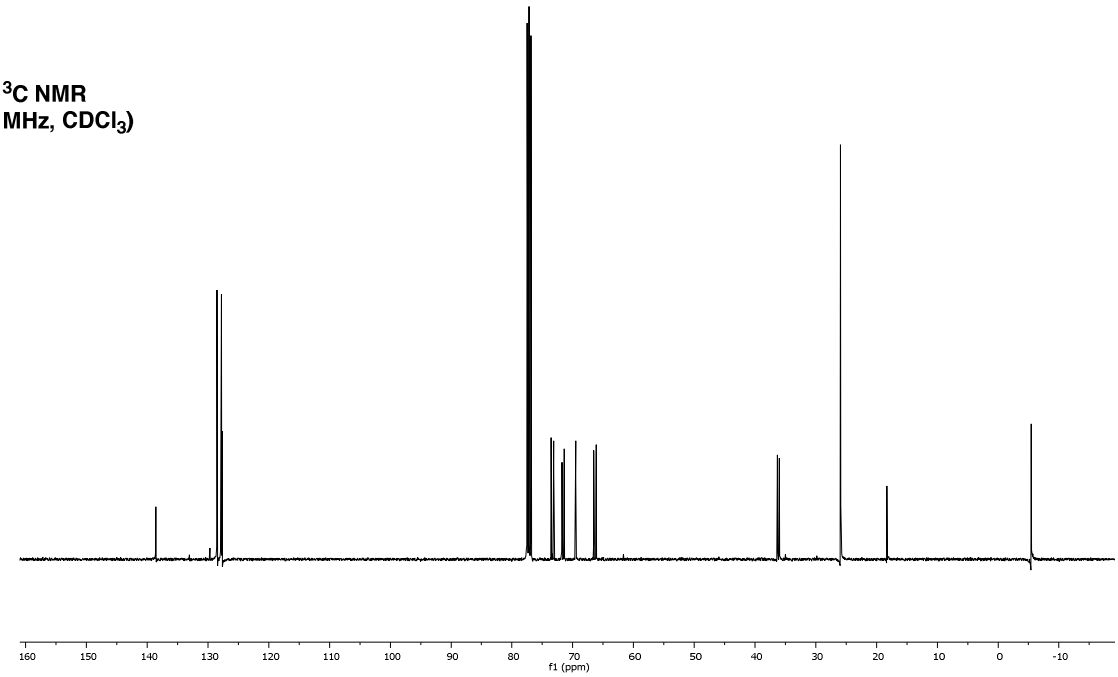


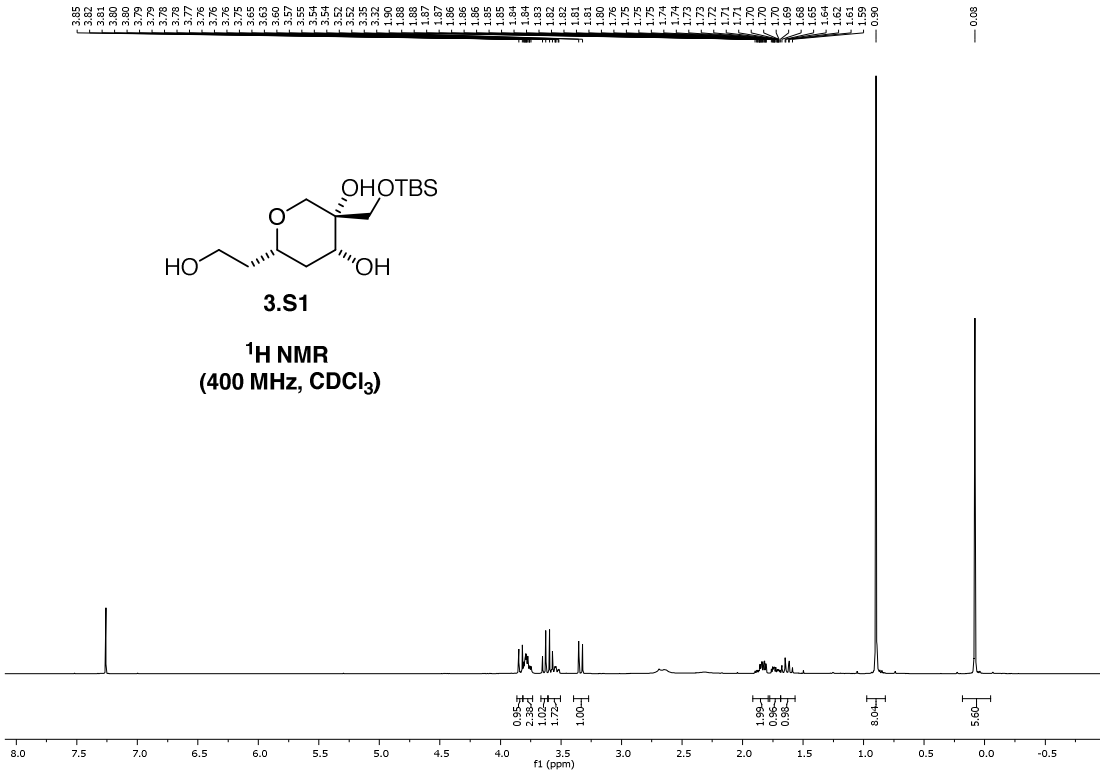


3.24

^{1}H NMR
(400 MHz, $CDCl_3$)

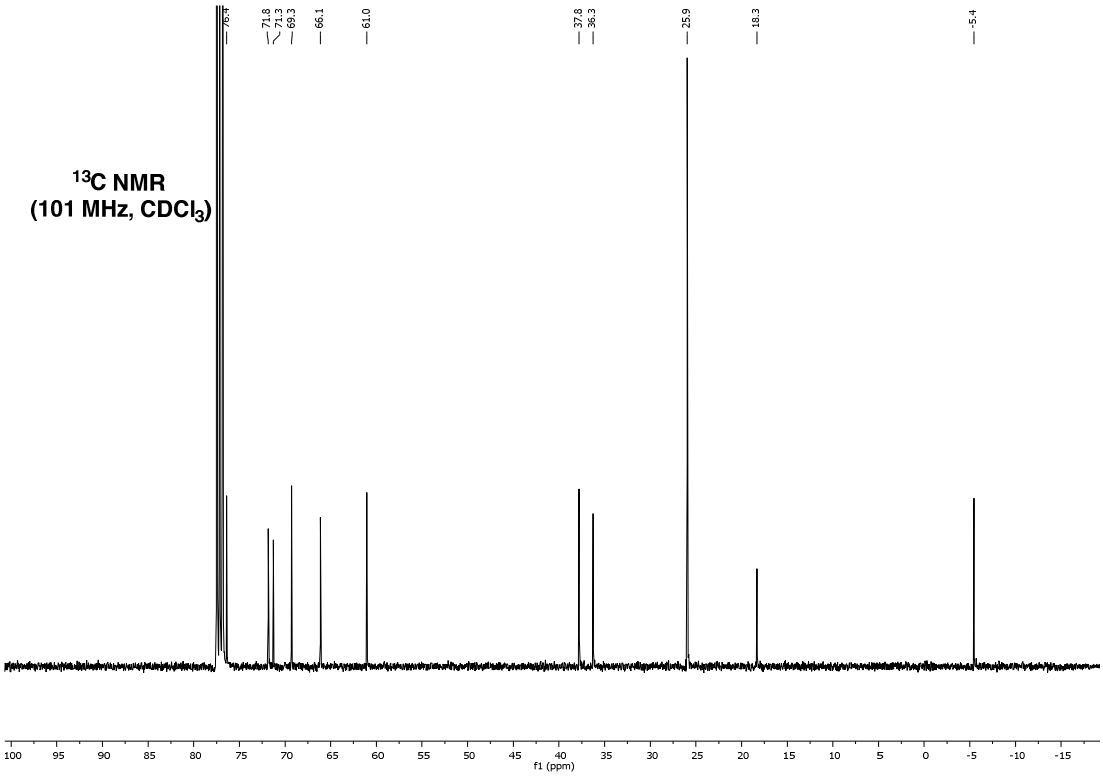
^{13}C NMR
(101 MHz, $CDCl_3$)



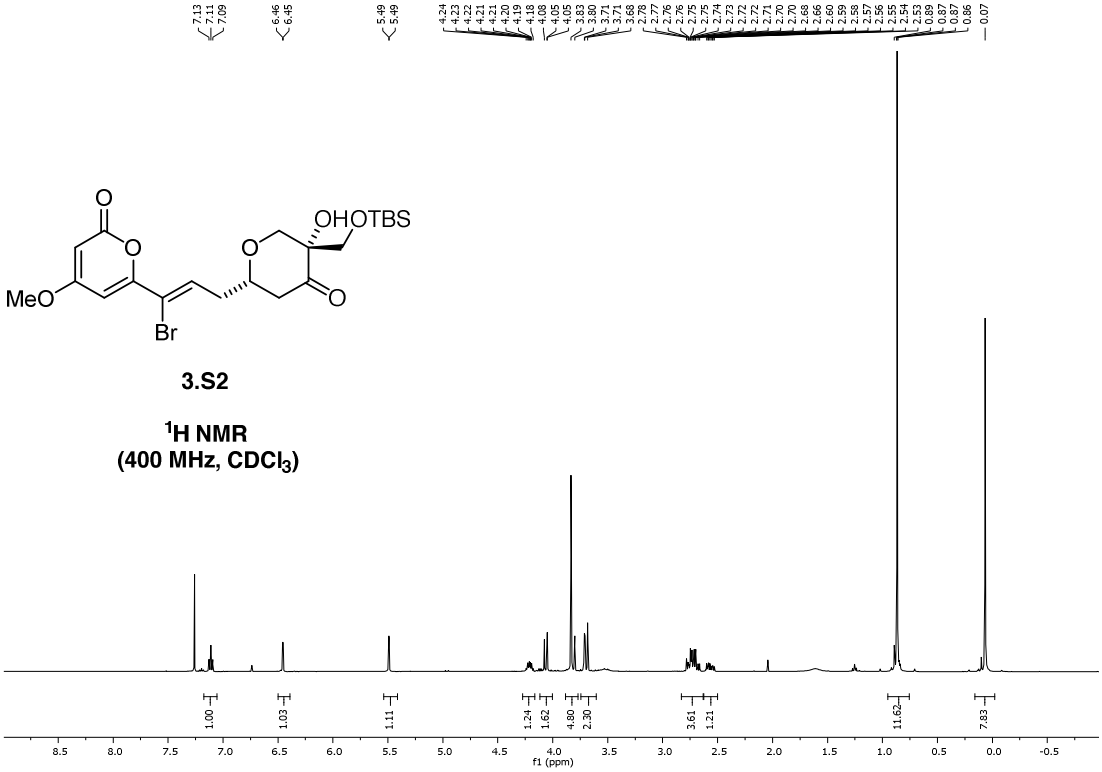


3.S1

^{1}H NMR
(400 MHz, $CDCl_3$)



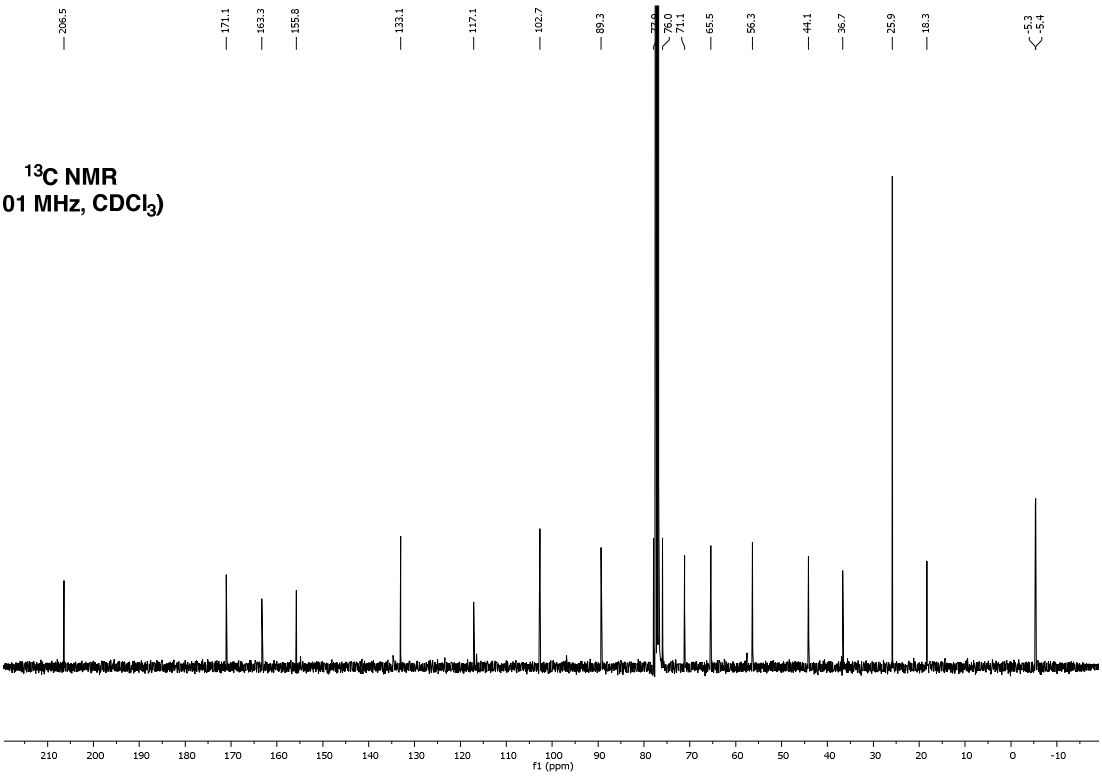
^{13}C NMR
(101 MHz, $CDCl_3$)

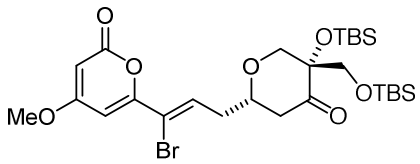


3.S2

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

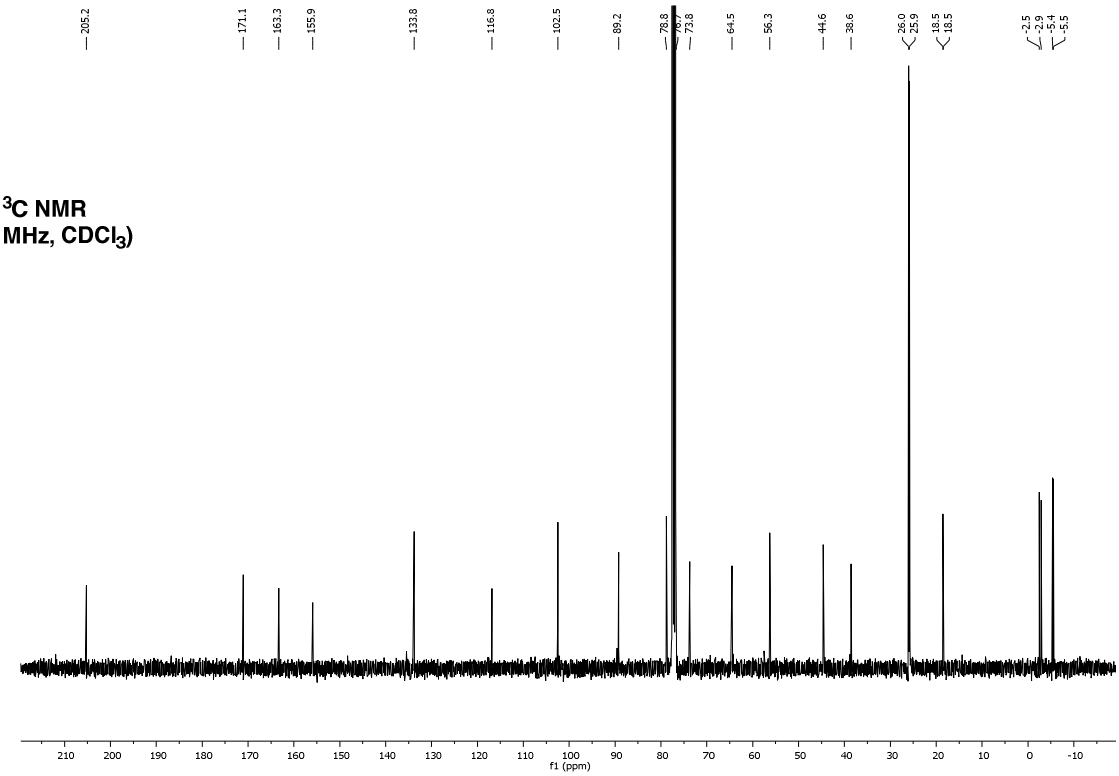


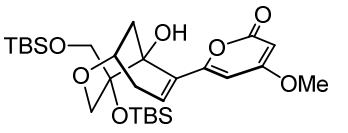


3.S3

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

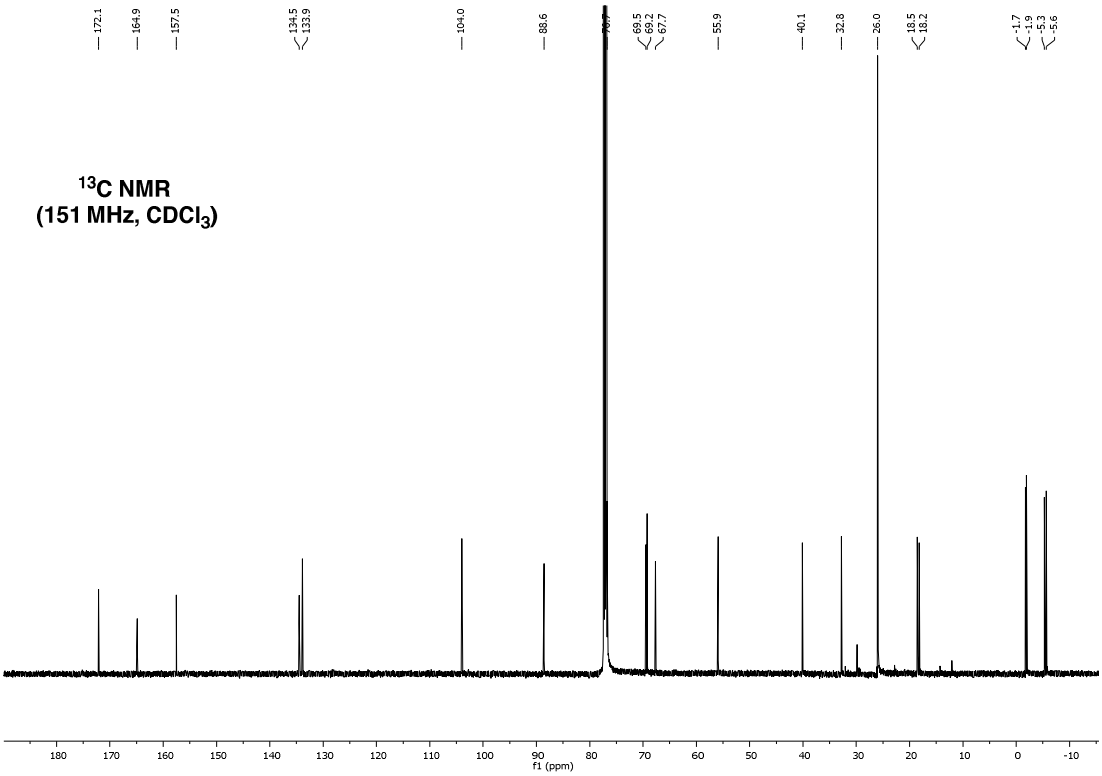


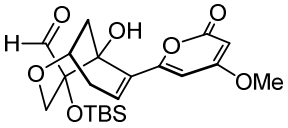


3.S4

^{1}H NMR
(599 MHz, $CDCl_3$)

^{13}C NMR
(151 MHz, $CDCl_3$)

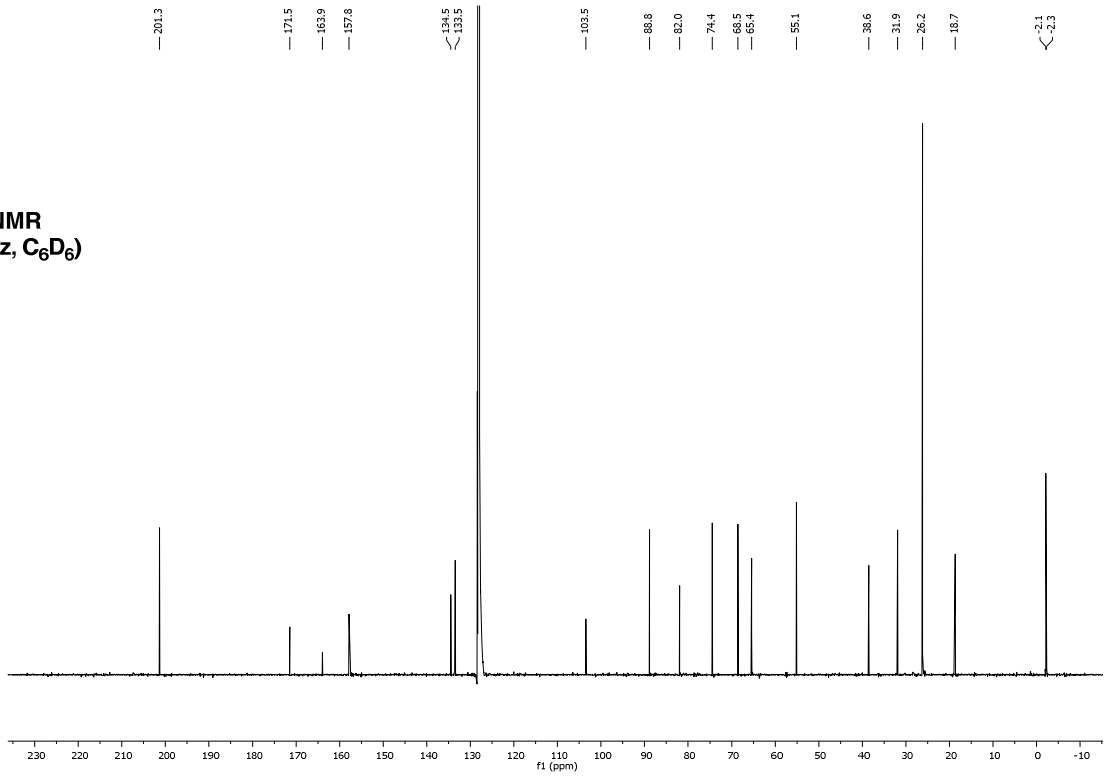


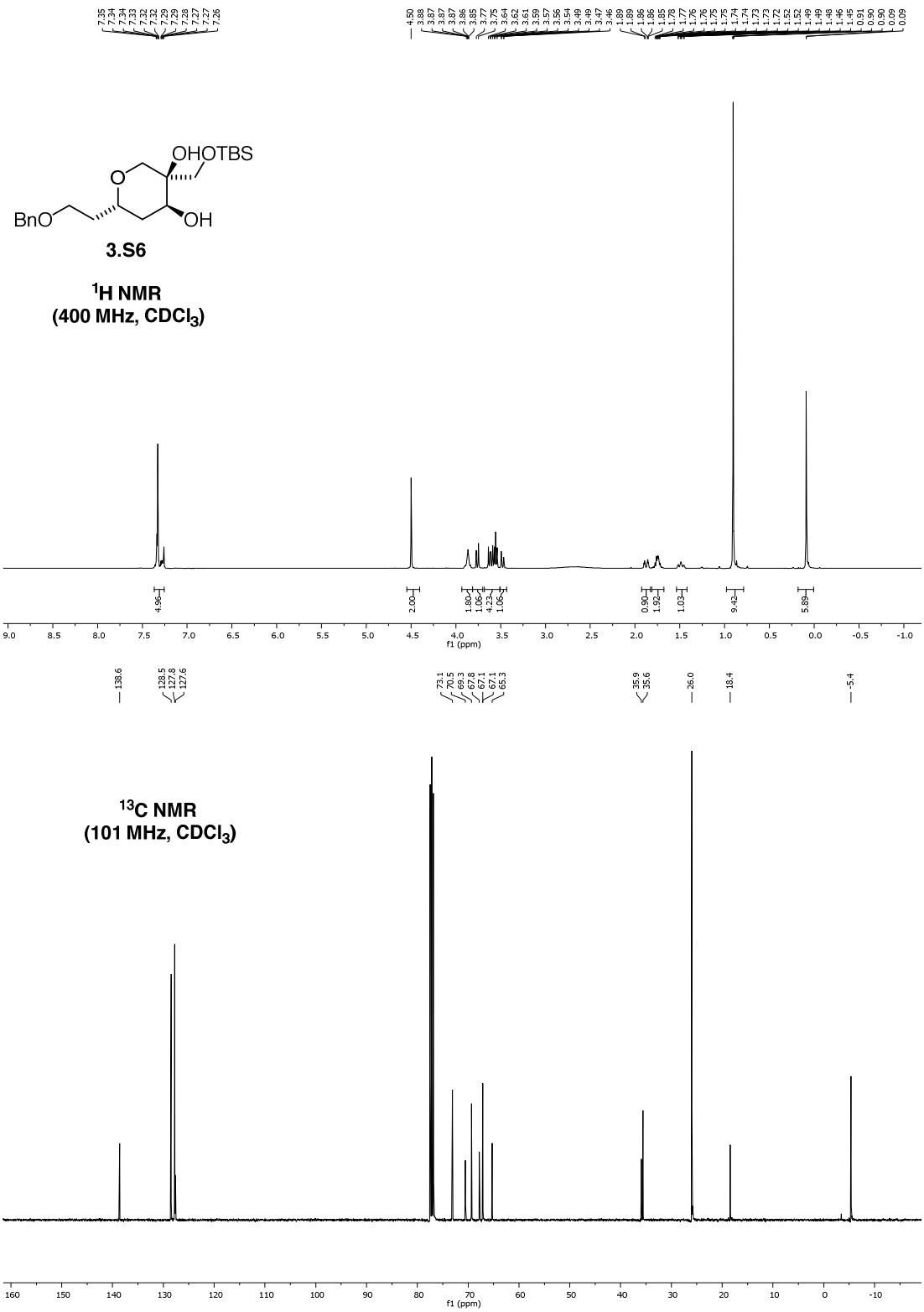


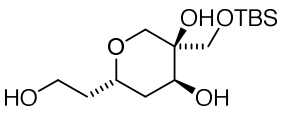
3.S5

^{1}H NMR
(599 MHz, C_6D_6)

^{13}C NMR
(151 MHz, C_6D_6)



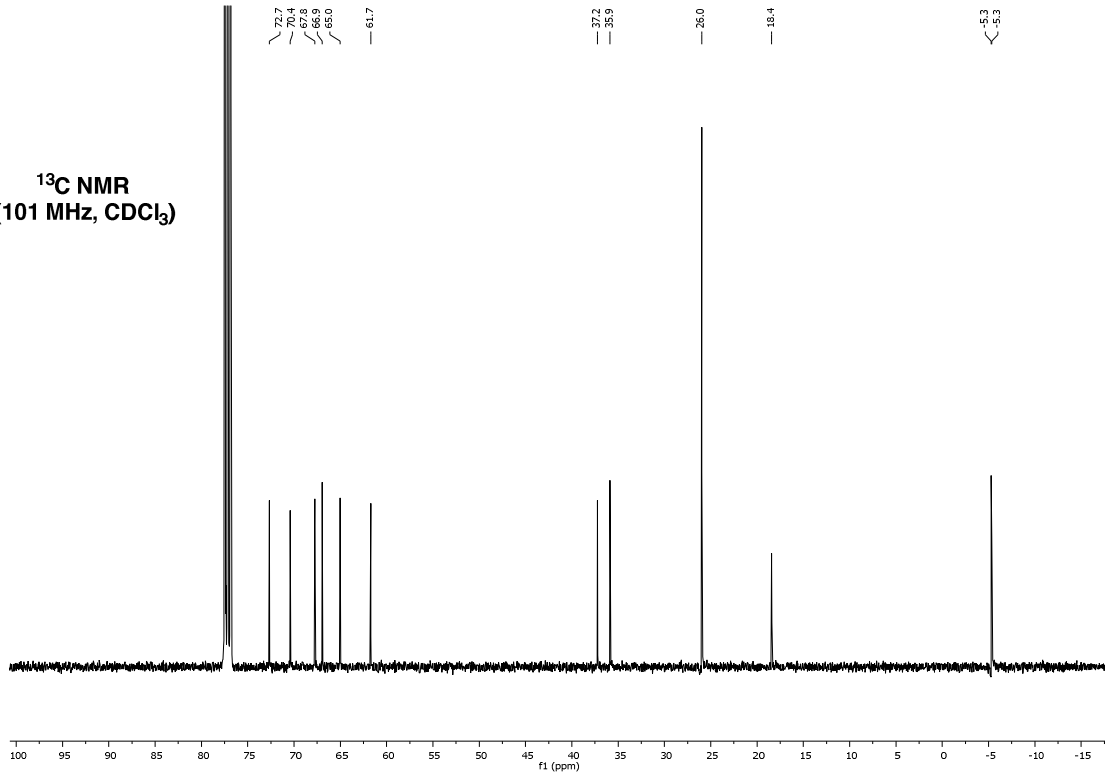

OHOTBS
O
BnO
OH
3.S6
1H NMR
(400 MHz, CDCl3)
13C NMR
(101 MHz, CDCl3)
f1 (ppm)
f1 (ppm)

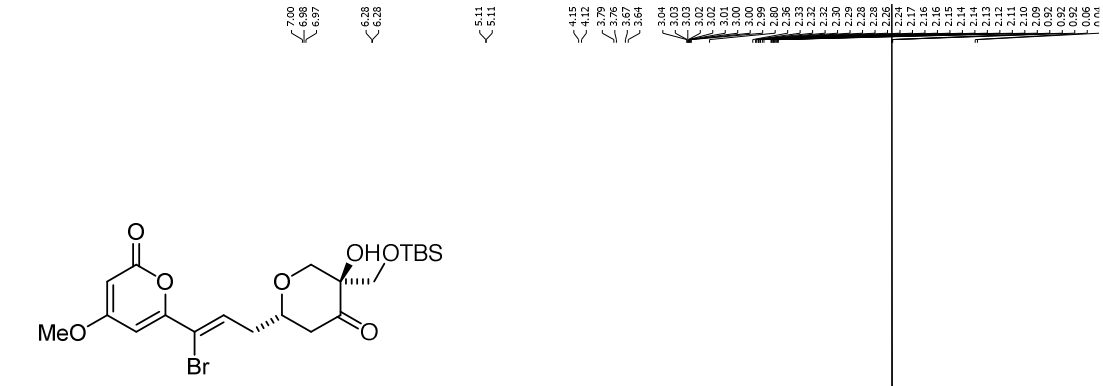


3.26

^{1}H NMR
(400 MHz, $CDCl_3$)

^{13}C NMR
(101 MHz, $CDCl_3$)

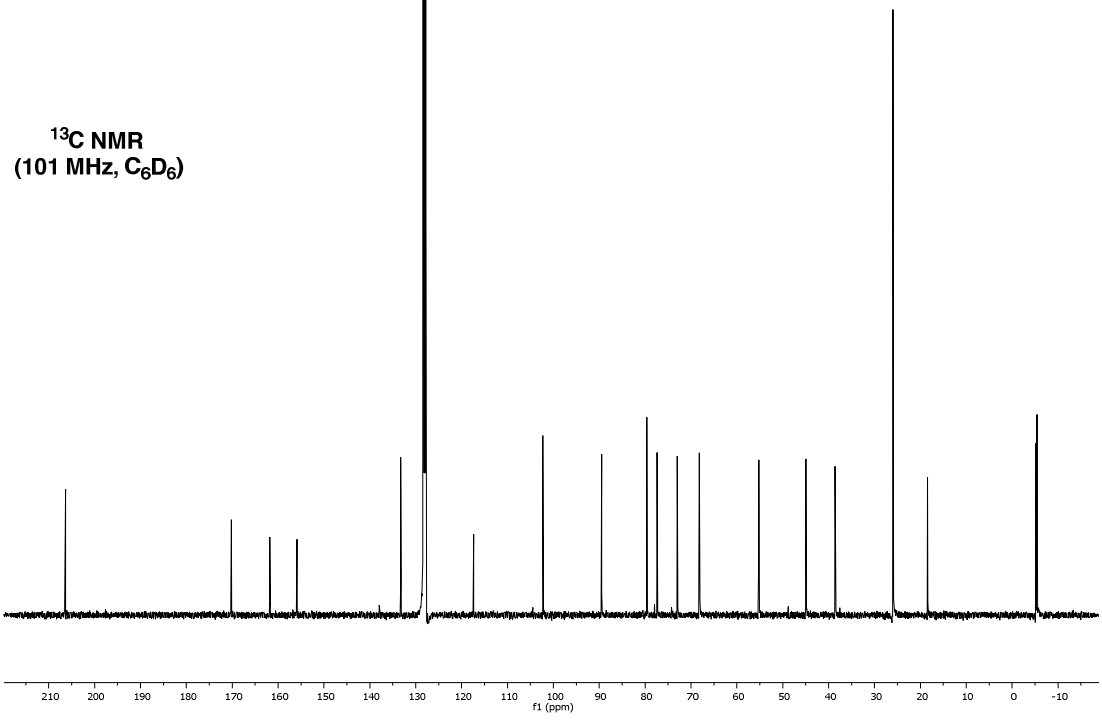


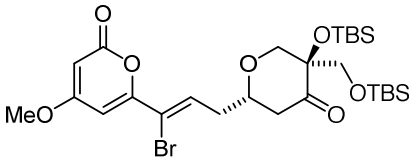


3.27

^{1}H NMR
(400 MHz, C_6D_6)

^{13}C NMR
(101 MHz, C_6D_6)

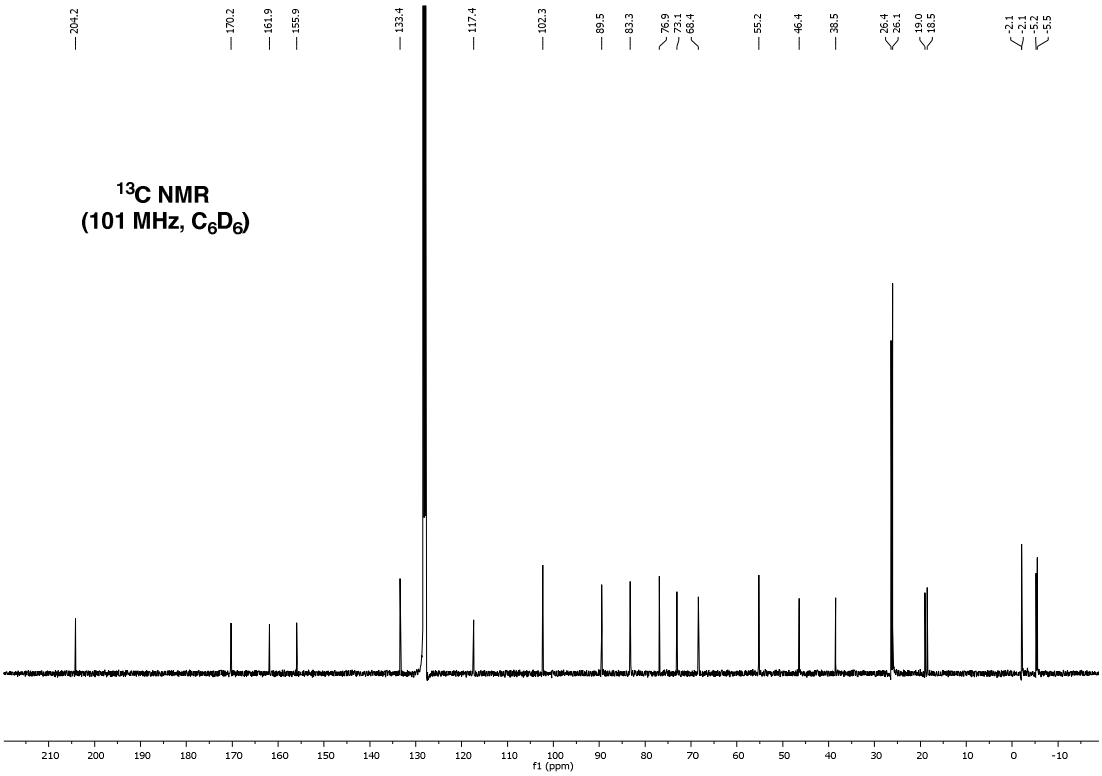


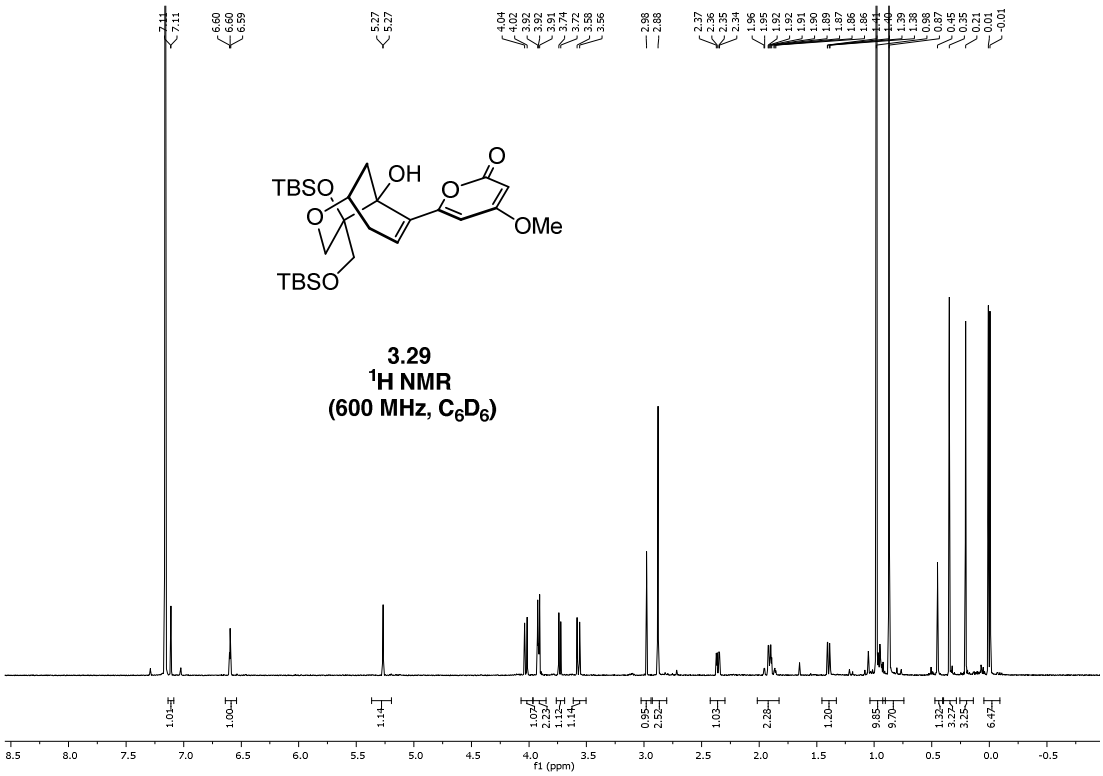


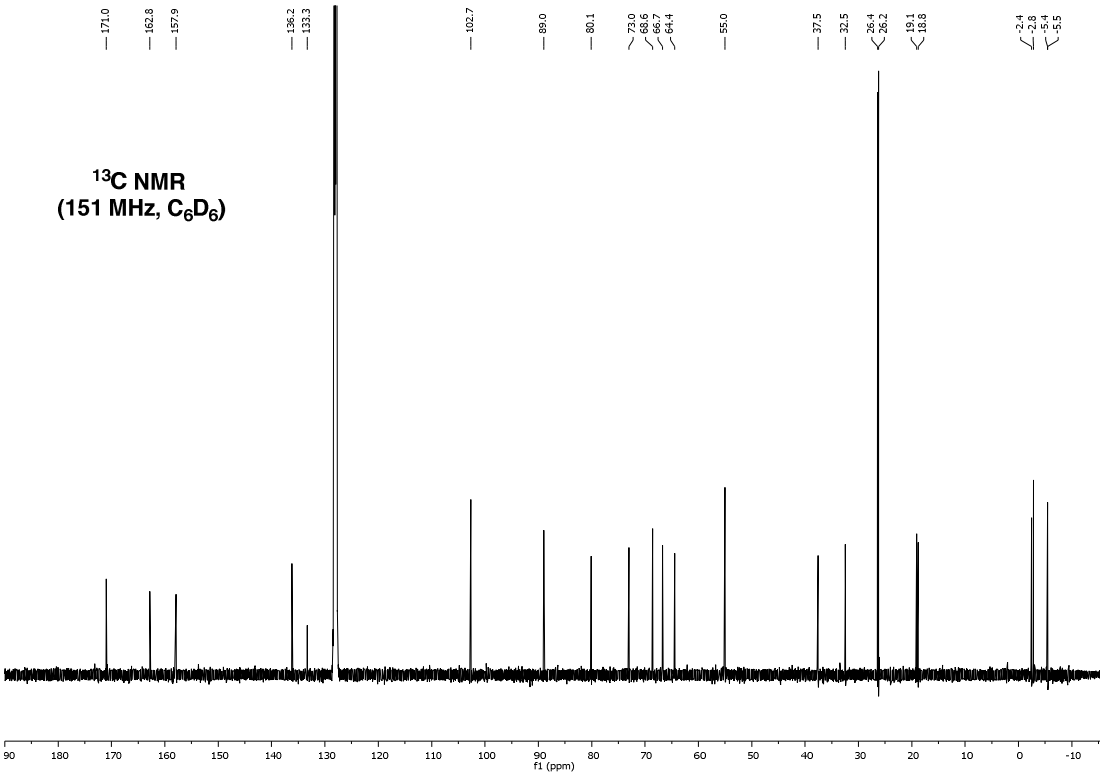
3.28

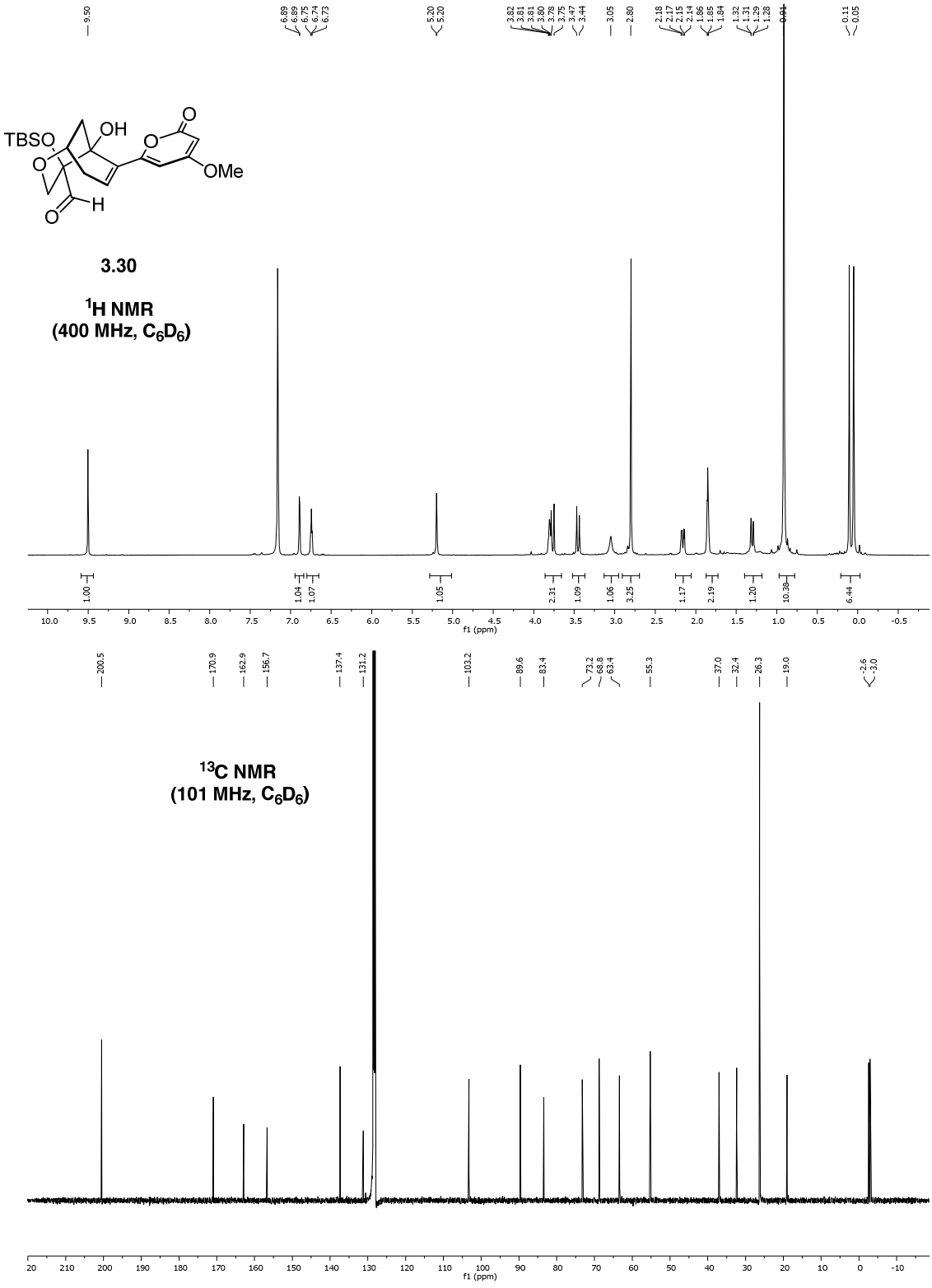
^{1}H NMR
(400 MHz, C_6D_6)

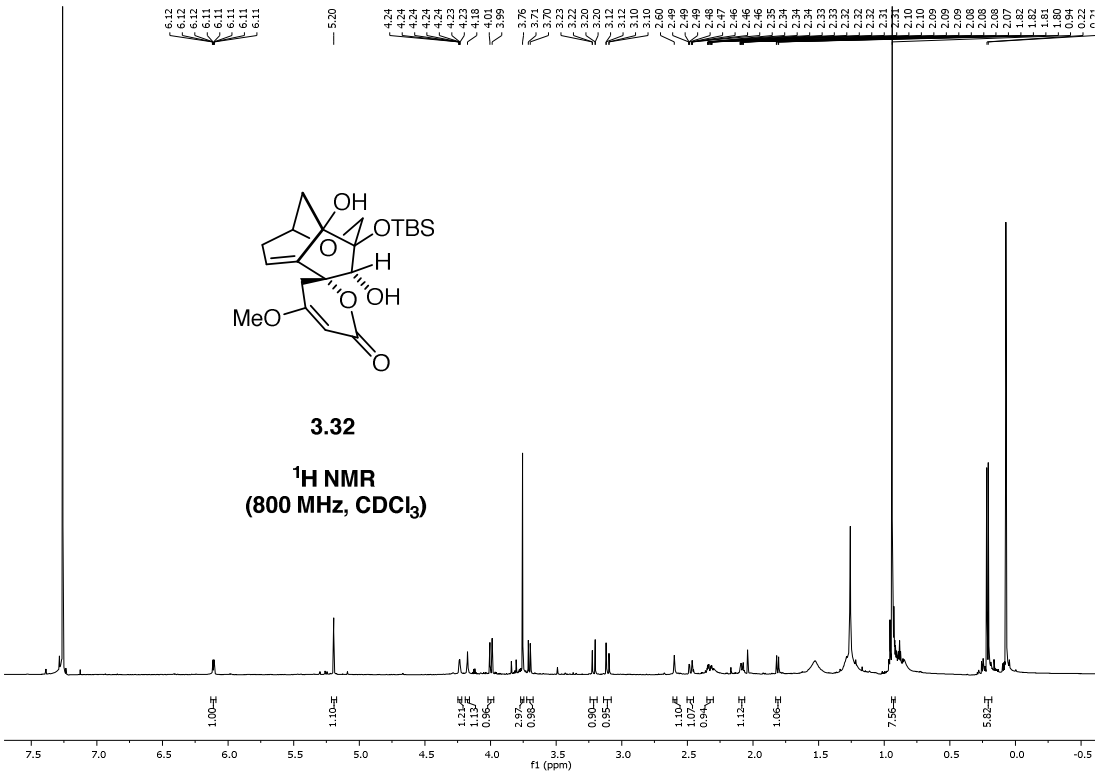
^{13}C NMR
(101 MHz, C_6D_6)




TBSO
OH
O
O
O
OMe
TBSO
3.29
^{1}H NMR
(600 MHz, C_6D_6)


^{13}C NMR
(151 MHz, C_6D_6)

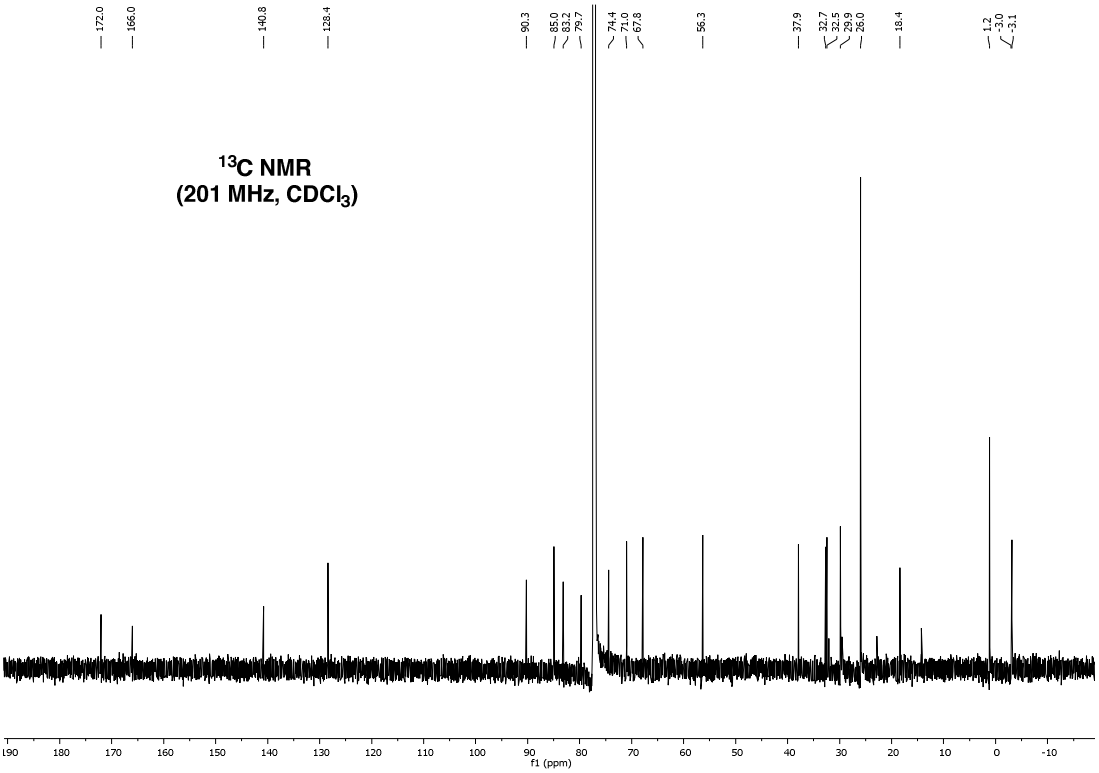

TBSO
OH
O
O
O
OMe
O
H
3.30
1H NMR
(400 MHz, C6D6)
13C NMR
(101 MHz, C6D6)
f1 (ppm)

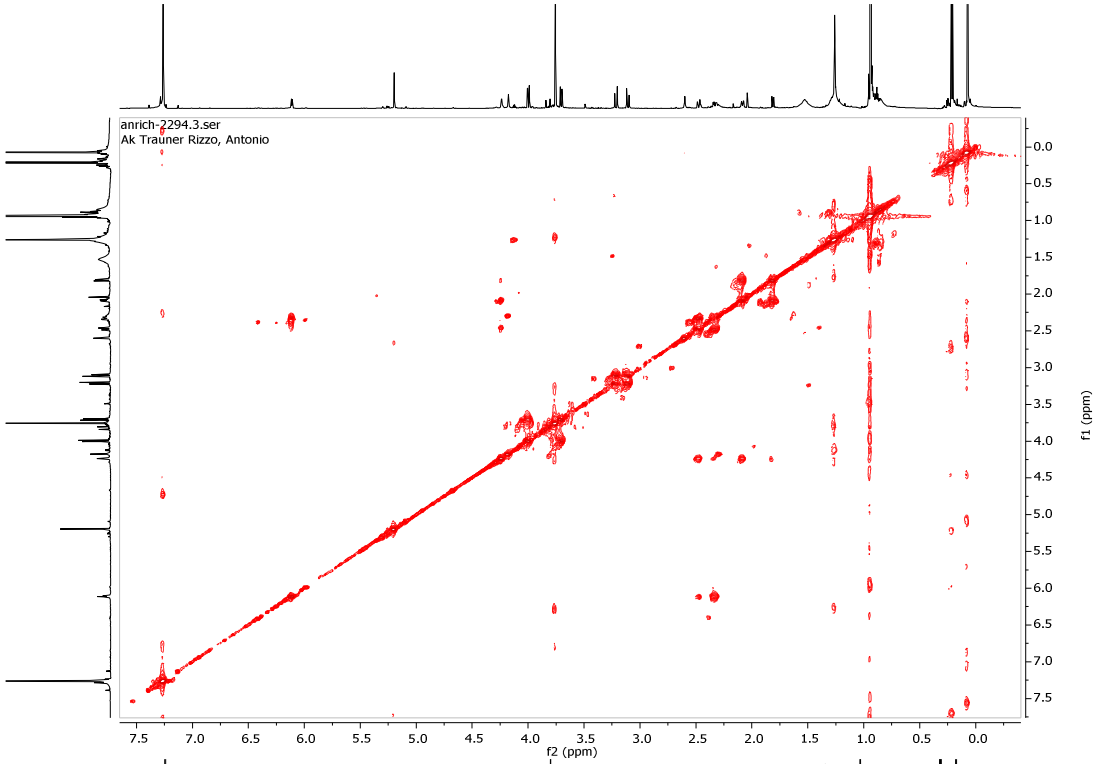


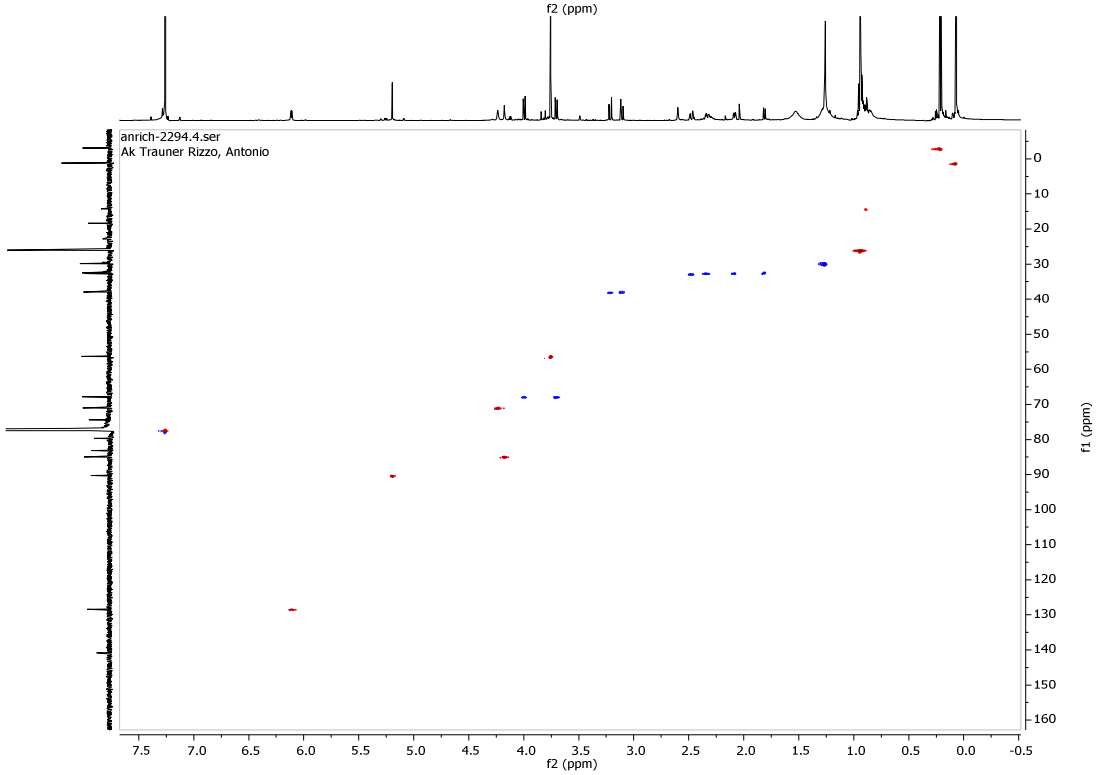
3.32

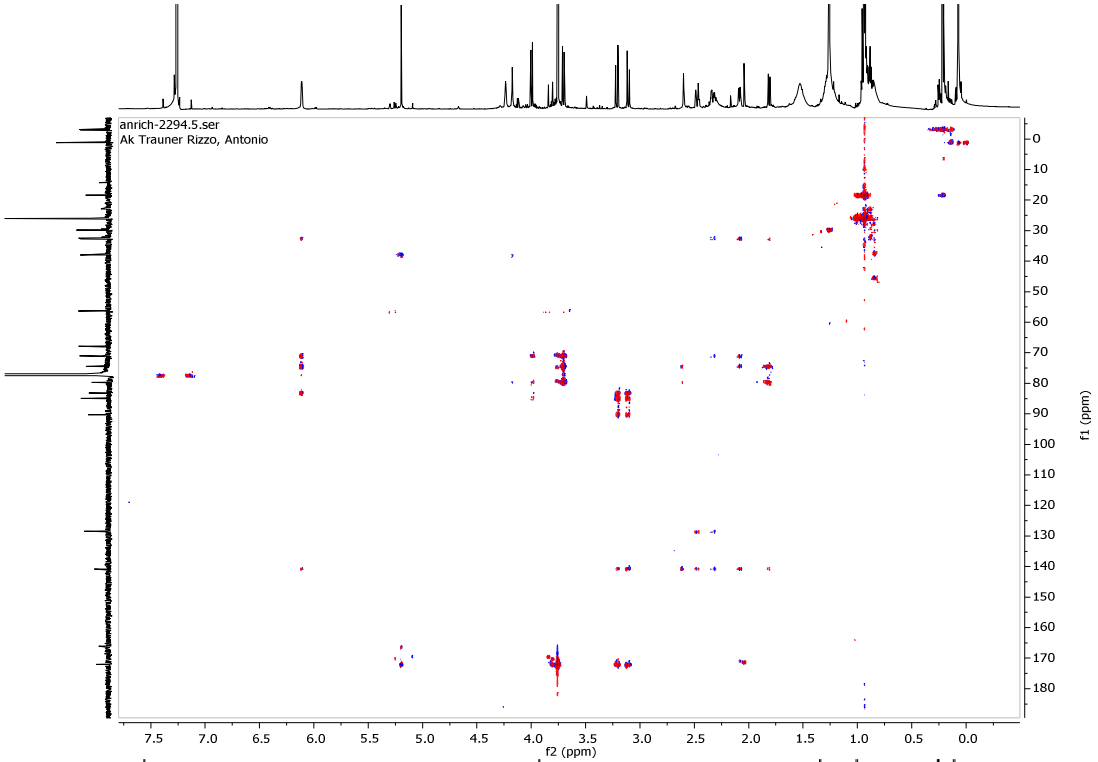
^{1}H NMR
(800 MHz, $CDCl_3$)

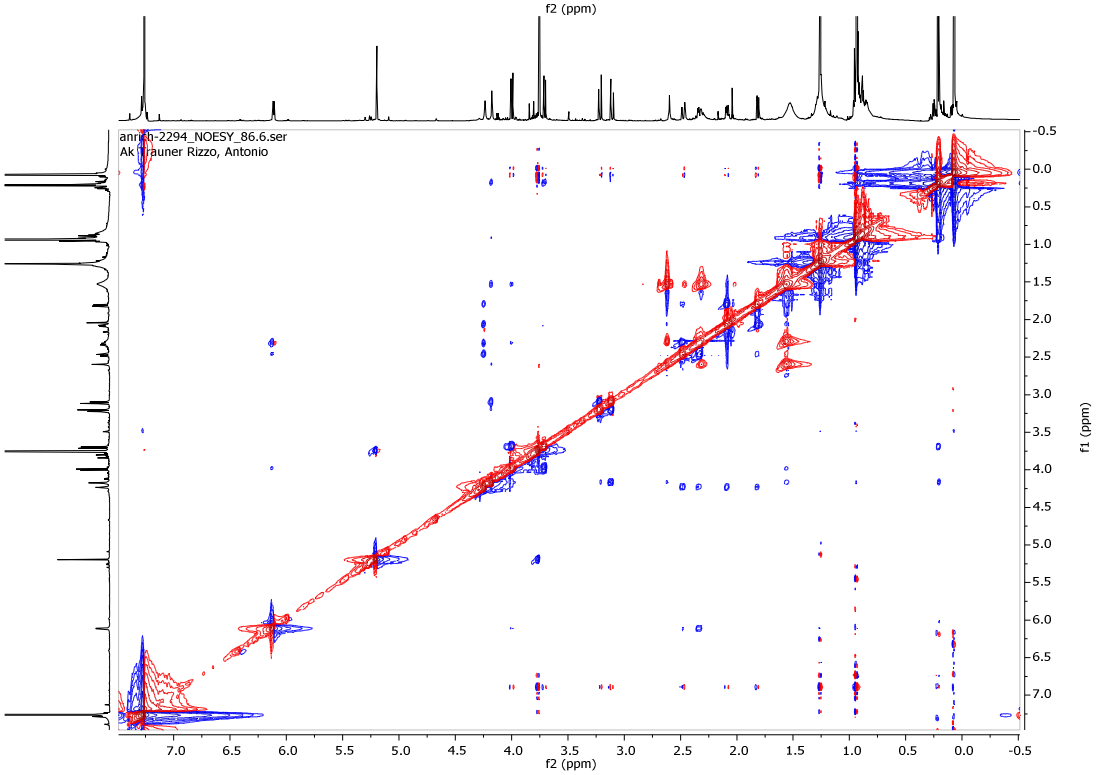
^{13}C NMR
(201 MHz, $CDCl_3$)




anrich-2294.3.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)

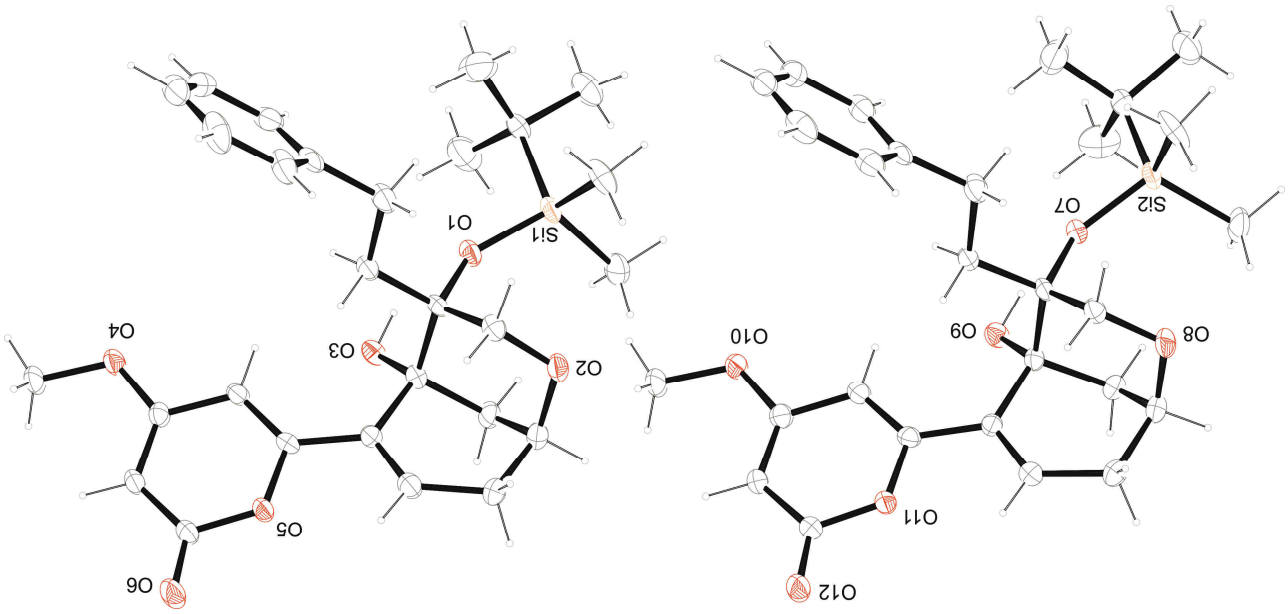

anrich-2294.4.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


anrich-2294.5.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)


anrich-2294_NOESY_86.6.ser
Ak Trauner Rizzo, Antonio
f2 (ppm)
f1 (ppm)

6.5.4 X-ray Data for Chapter 3.2

Compound **3.S7**



ORTEP of the molecular structure of **3.S7**

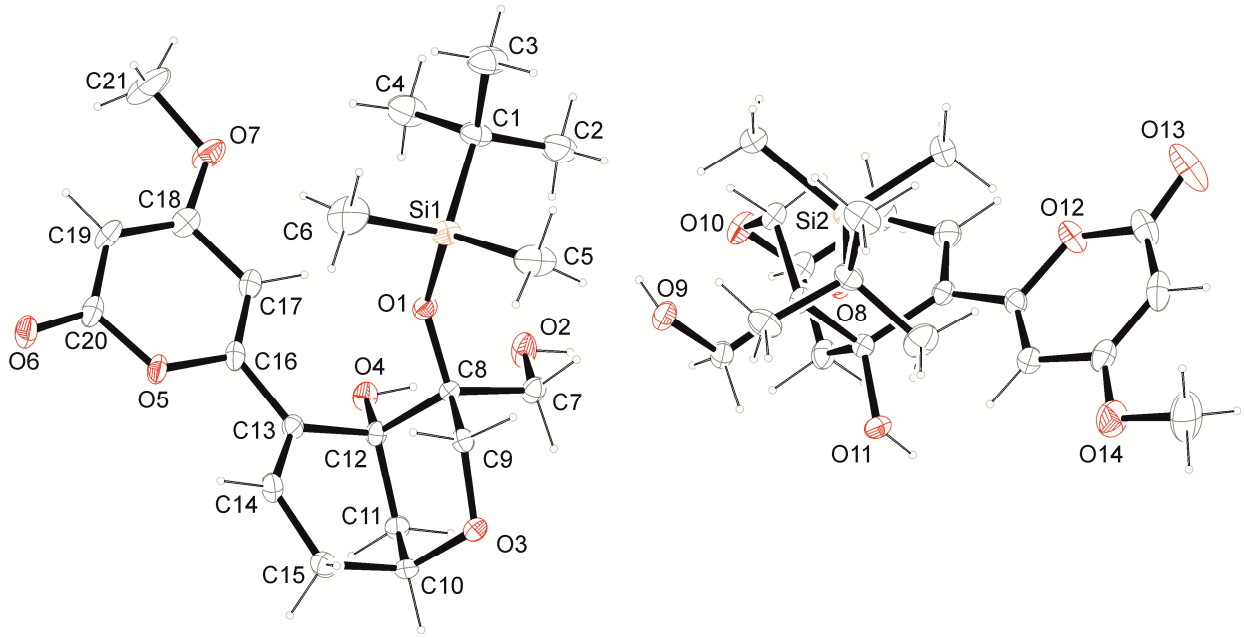
CCDC 1830003 contains the supplementary crystallographic data for **3.S7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table.

net formula	$C_{28}H_{38}O_6Si$
M_r/g mol^{-1}	498.67
crystal size/mm	0.100 × 0.040 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'C 1 2 1'
a/Å	34.0229(13)
b/Å	8.0898(3)
c/Å	24.2075(10)

α/°	90
β/°	124.6910(10)
γ/°	90
V/Å^3	5478.4(4)
Z	8
calc. density/g cm^{-3}	1.209
μ/mm^{-1}	0.124
absorption correction	Multi-Scan
transmission factor range	0.9162–0.9705
refls. measured	41392
R_{int}	0.0409
mean σ(I)/I	0.0448
θ range	3.196–27.477
observed refls.	11054
x, y (weighting scheme)	0.0417, 2.8286
hydrogen refinement	H(C) constr, H(O) refall
Flack parameter	0.01(4)
refls in refinement	12386
parameters	651
restraints	1
$R(F_{obs})$	0.0409
$R_w(F^2)$	0.0942
S	1.042
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.286
min electron density/e Å^{-3}	−0.288

Compound **3.25**



ORTEP of the molecular structure of **3.25**

CCDC 1830004 contains the supplementary crystallographic **3.25**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table.

net formula	$C_{21}H_{32}O_7Si$
M_r/g mol^{-1}	424.55
crystal size/mm	0.060 × 0.050 × 0.040
T/K	103.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P 1'
a/Å	7.8025(3)
b/Å	8.8347(3)
c/Å	16.3097(6)
α/°	77.4328(12)

β/°	83.0073(12)
γ/°	89.5062(12)
V/Å^3	1088.99(7)
Z	2
calc. density/g cm^{-3}	1.295
μ/mm^{-1}	0.147
absorption correction	Multi-Scan
transmission factor range	0.97–0.99
refls. measured	22921
R_{int}	0.0308
mean σ(I)/I	0.0399
θ range	3.451–26.371
observed refls.	8182
x, y (weighting scheme)	0.0401, 0.2027
hydrogen refinement	H(C) constr, H(O) refall
Flack parameter	0.06(4)
refls in refinement	8780
parameters	551
restraints	3
$R(F_{obs})$	0.0344
$R_w(F^2)$	0.0792
S	1.021
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.280
min electron density/e Å^{-3}	−0.206