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SYNTHESIS OF HALOGENATED NAPHTHOLS

AND

STUDIES TOWARDS THE TOTAL SYNTHESIS OF JERANTININE E

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Univ.-Prof. Dr. Thomas Magauer betreut.

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Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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TO MY FAMILY

Parts of this work have been published in peer-reviewed journals:

"Development of a β-C–H Bromination Approach Towards the Synthesis of Jerantinine E" T. Huber,† T. A. Preuhs,† C. K. G. Gerlinger, T. Magauer, *J. Org. Chem.* **2017**, *82,* 7410–7419. († These authors contributed equally to this work.)

"Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin" T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem., Int. Ed.* **2016**, *55*, 9763–9767. (HOT PAPER)

Submitted publications, which are not discussed in this thesis:

"Carbon-Fluorine Bond Activation for the Synthesis of Functionalized Molecules" T. A. Unzner, T. Magauer, *Tetrahedron Lett.* **2015**, *56*, 877–883 (Review).

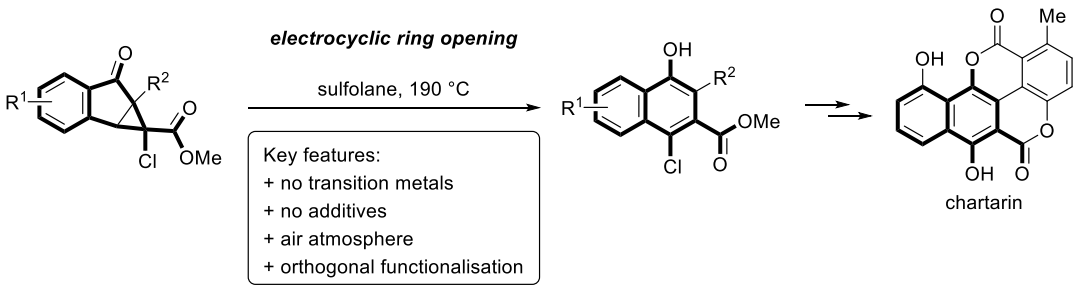
"A transition metal-free synthesis of fluorinated naphthols" J. M. Hammann, T. A. Unzner, T. Magauer, *Chem. Eur. J.* **2014**, *20*, 6733–6738.
This work was highlighted in SYNFACTS*:* P. Knochel, D. Haas, *Synfacts* **2014**, *10*, 853.

ABSTRACT

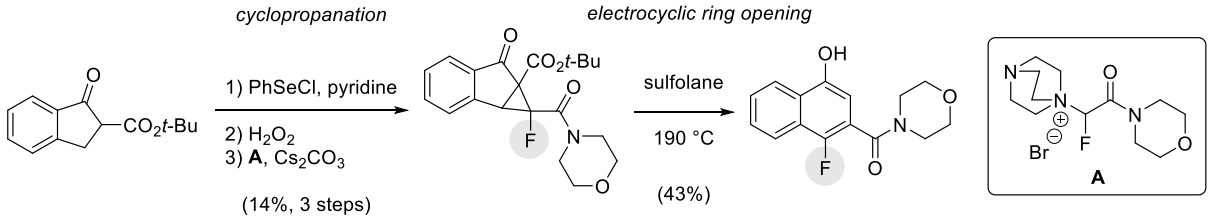
CHAPTER I:

SYNTHESIS OF HALOGENATED NAPHTHOLS

Substituted naphthalenes are common structural motifs present in many biologically active compounds and pharmaceuticals. The first chapter of this Ph.D. thesis describes the development of a novel ring-opening reaction for the synthesis of halogenated naphthols. The efficient and practical procedure enabled the preparation of a library of polysubstituted 1-naphthols in three steps from commercially available indanones via oxidation, cyclopropanation and an electrocyclic ring opening. This operationally simple method does not require any additives or transition metal catalysts and can be performed under an air atmosphere. The reaction mechanism is assumed to proceed through a thermally induced disrotatory 2π-electrocyclic ring opening of the cyclopropanated indanone followed by a chloride migration to preferentially afford the *para*-chloro substituted 1-naphthols. The developed method was successfully applied to the total synthesis of chartarin, a potent anticancer natural product. The synthesis revealed the remarkable potential of this method for the construction of highly substituted, sterically hindered biaryl compounds.



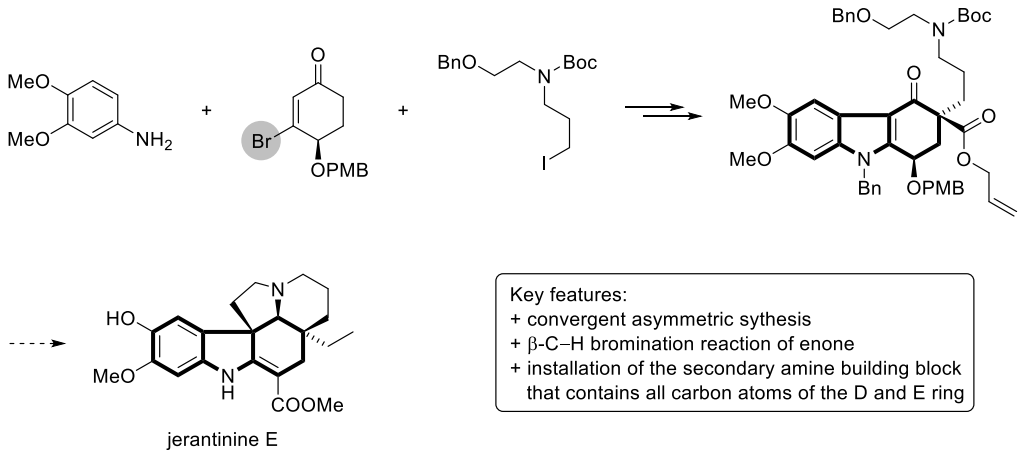
In addition, our synthetic efforts towards applying this method for the synthesis of fluorinated naphthols are illustrated. Various methods for the preparation of fluorinated cyclopropane-indanones were examined; however, a general method could not be developed. The development of one successful approach is described, which afforded an exemplary fluorinated 1-naphthol. However, all attempts to generalize this methodology were met with failure.



CHAPTER II:

STUDIES TOWARDS THE TOTAL SYNTHESIS OF JERANTININE E

The second chapter of this thesis describes our efforts towards the total synthesis of jerantinine E, an *Aspidosperma* alkaloid which was isolated in 2008 from the Malayan plant *Tabernaemontana corymbosa*. The pentacyclic 6,5,6,6,5-ring system of jerantinine E exhibits three contiguous stereogenic centers and a highly oxygenated tetrahydrocarbazolone core. The synthetic route towards an advanced intermediate in the synthesis of jerantinine E features a β-C–H bromination reaction, a palladium-catalyzed amination and an oxidative indole formation. The installation of the secondary amine building block, which contains all carbon atoms of the D and E rings of jerantinine E, was enabled by the incorporation of an ally ester. A palladium-catalyzed decarboxylative allylation reaction of the ester was envisioned to set the first quaternary stereocenter.



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LIST OF ABBREVIATIONS

5'-FDA	5'-fluoro-5'-deoxyadenosine
5'-FDAS	5'-fluoro-5'-deoxyadenosine synthase
9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångstrom
Ac	acetate
ADME	absorption, distribution, metabolism and excretion
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR spectroscopy)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad (IR spectroscopy)
brs	broad singlet (NMR spectroscopy)
Bu	butyl
cal	calorie
calcd	calculated
CAM	ceric ammonium molybdate(IV)
CAN	ceric ammonium nitrate
CMIT-F	*N*-fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-dioxide
conc.	concentrated
COSY	homonuclear correlation spectroscopy
CSA	camphorsulfonic acid
d	douplet (NMR spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	tris(dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	dichloroacetic acid
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DFI	2,2-difluoro-1,3-dimethylimidazolidine
CHD	1,4-cyclohexadiene
DIBAL-H	diisobutylaluminium hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	diisopropylethylamine Hünig's base)
DMAP	4-(dimethylamino)-pyridine
DMF	*N*,*N*-dimethylformamide
DMG	directing metalation group
CMIT-F	(*N*-Fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-dioxide
DMSO	dimethylsulfoxide
DoM	directed *ortho*-metalation
DPP	dipeptidyl peptidase
dppf	1,1´-bis(diphenylphosphino) ferocene
dppp	1,3-bis(diphenylphosphino) propane
DreM	directed remote metalation
dtbbpy	4,4'-di-tert-butyl-2,2'-bipyridine
e.g.	*exempli gratia* (for example)

ED_{50}	median effective dose
ee	enantiomeric excess
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
G10H	geraniol-10-hydroxylase
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HQ	hydroquinidine
HRMS	high resolution mass spectra
HSQC	heteronuclear single quantum coherence
Hz	Hertz (frequenzy)
i	*iso* (isomer)
IC_{50}	half maximal inhibitory concentration
im	imidazole
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium *N*,*N*-diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	medium ((IR spectroscopy)
m	multiplet (NMR spectroscopy)
M.p.	melting point
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MDCA	methyl dichloroacetate
Min	minutes
mL	milliliter
MEM	2-methoxyethoxymethyl
MS	molecular sieves
MTC	monoterpene cyclase
NBS	*N*-bromosuccinimide
NFOBS	*N*-fluoro-*o*-benzenedi-sulfonimide
NFSI	*N*-fluorobenzenesulfonamide
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
Np	naphthyl
o	*ortho*
p	*para*
p-ABSA	4-acetamidobenzenesulfonyl azide
PBSF	perfluoro-1-butanesulfonyl fluoride
Pd/C	palladium on charcoal
PET	positron emission tomography
Ph	phenyl
PHOX	phosphinooxazoline
pin	pinacol
Piv	pivaloyl
PMB	*para*-methoxybenzyl

PMDETA	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
ppy	2-(2-pyridinyl)phenyl
Pr	propyl
PTC	phase transfer catalyst
py	pyridine
q	quartet (NMR spectroscopy)
quant.	quantitative
R	undefined substituent
RCM	ring-closing metathesis
R_f	retardation factor (TLC)
s	singlet (NMR spectroscopy)
s	strong (IR spectroscopy)
SAM	*S*-adenosyl-L-methionine
SLS	secologanin synthase
S_N	nucleophilic substitution
t	triplet (NMR spectroscopy)
t	*tert* (tertiary)
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMAF	tetramethylammonium fluoride
TMG	1,1,3,3-tetramethylguanidine
TMP	bis(2,2,6,6-tetramethylpiperamide)
TMS	trimethylsilyl
tol	tolyl
Ts	tosyl (*para*-toluenesulfonyl)
TSE	2-(trimethylsilyl)-ethyl
vs	very strong (IR spectroscopy)
w	weak (IR spectroscopy)

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CHAPTER III: EXPERIMENTAL PART

CHAPTER I

SYNTHESIS OF HALOGENATED NAPHTHOLS

1 Introduction

1.1 Synthesis of Polyfunctionalized Naphthalenes

Substituted naphthalenes are important structural motifs that can be found in many biologically active compounds or pharmaceuticals. They are common building blocks in natural product synthesis and various naphthalene-containing natural products have been reported to date, including elsamicin A (**I.1**),[1] the atropisomers michellamines A–C (**I.2**)[2] and lactonamycin (**I.3**) (Figure 1).[3]

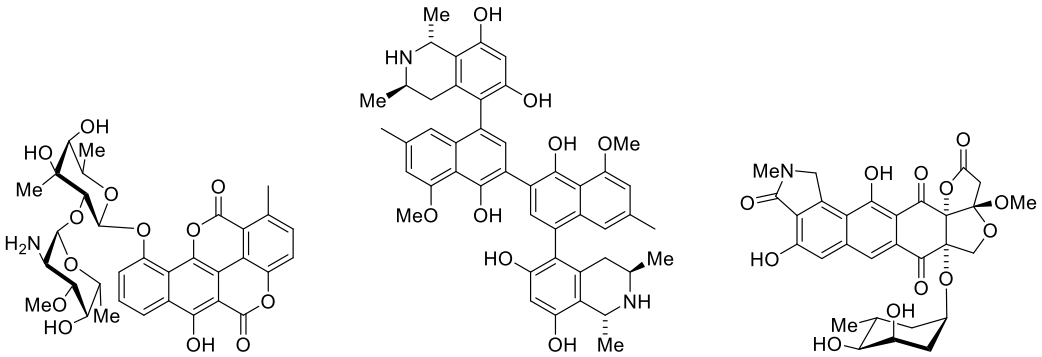


Figure 1. Natural products containing variously substituted naphthalene motifs.

Traditionally, polysubstituted naphthalenes were prepared by conventional methods, such as electrophilic or nucleophilic aromatic substitution reactions. However, these methods often rely on a stepwise functionalization from readily available naphthalene precursors and can be rather inefficient due to low stereochemical control. In recent years, several methods based on annulation, cyclization or ring expansion reactions were developed.

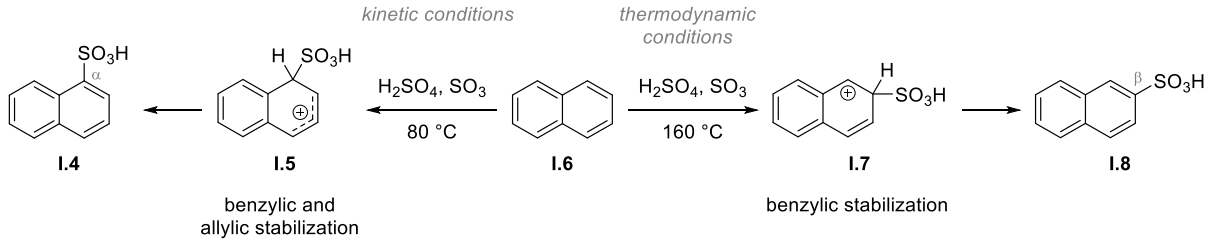
1.1.1 Preparation of Polysubstituted Naphthalenes from Naphthalene Precursors

1.1.1.1 Electrophilic Aromatic Substitution

For several decades, the electrophilic aromatic substitution was widely used to functionalize aromatic compounds. In general, polycyclic aromatic hydrocarbons like naphthalene, anthracene, and phenanthrene are more reactive than benzene and can undergo a variety of electrophilic aromatic substitution reactions. This can be explained by the preservation of more of the initial resonance stabilization in fused ring systems like naphthalenes, resulting in a lower localization energy for the formation of the cationic intermediate. The calculated localization energies for benzene, naphthalene, and anthracene are 36.3, 15.4, and 8.3 kcal/mol, respectively.[4]

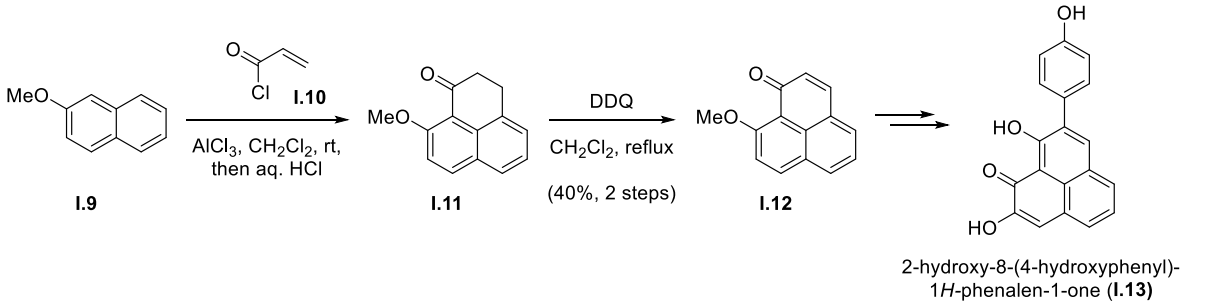
Under kinetically controlled reaction conditions, the electrophilic attack occurs in the α-position of the naphthalene (**I.6**) due to a better stabilization of the cationic intermediate **I.5**. The cationic intermediate

benefits from an allylic and benzylic stabilization whereas the attack at the β-position provides only a benzylic carbocation. However, the β-substituted naphthalene can be obtained under thermodynamic conditions. For example, the sulfonation of naphthalene under kinetic conditions (80 °C) provided predominantly naphthalene-1-sulfonic acid (**I.4**), whereas the reaction at elevated temperature gave the more stable thermodynamic product naphthalene-2-sulfonic acid (**I.8**) (Scheme 1).[5]



Scheme 1. Sulfonation of naphthalene (**I.6**) under kinetic and thermodynamic conditions.

Since its discovery, the Friedel–Crafts acylation[6] was frequently applied in the synthesis of functionalized aromatic compounds. Recently, Ospina et al. reported the synthesis of 2-hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**I.13**) using a Friedel–Crafts acylation/Michael addition cascade. The reaction of 2-methoxynaphthalene (**I.9**) with acryloyl chloride (**I.10**) in the presence of aluminum chloride followed by an acidic workup afforded 9-methoxy-2,3-dihydro-1*H*-phenalen-1-one (**I.11**). Subsequent dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) provided **I.12** in 40% yield over two steps (Scheme 2).[7]



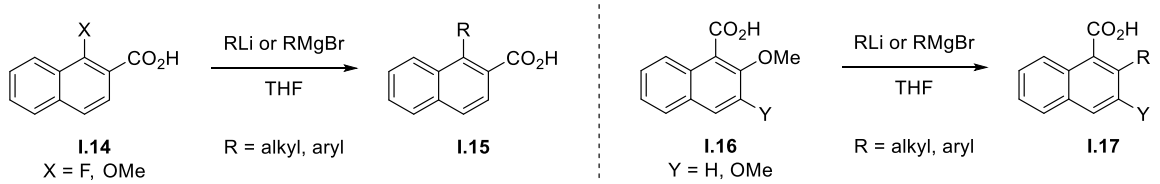
Scheme 2. Synthesis of 2-hydroxy-8(4-hydroxyphenyl)-1H-phenalen-1-one (**I.13**) using a Friedel–Crafts acylation/Michael addition reaction.

1.1.1.2 Nucleophilic Aromatic Substitution

The increased reactivity of naphthalenes as compared to benzenes in electrophilic aromatic substitution reactions also holds true for nucleophilic aromatic substitutions. This can be explained with a greater stabilization of the generated negative charge. This effect was further demonstrated by the 10–100 times faster reaction of 1-chloro-2,4-dinitronaphthalene with common nucleophiles as compared to the reactions of 1-chloro-2,4-dinitrobenzene.[8]

In 2012, the group of Montier described the nucleophilic aromatic substitution of 1- and 2-naphthoic

acids **I.14** and **I.16**. The substitution reaction of an *ortho*-fluoro or *ortho*-methoxy substituent with a variety of organolithium species or Grignard reagents proceeded in good yield (Scheme 3).[9] A similar reaction with other electron-withdrawing groups was also reported by Miyano.[10]



Scheme 3. Nucleophilic aromatic substitution of unprotected 1- and 2-naphthoic acids.

1.1.1.3 Directed Metalation

The directed metalation of arenes in the presence of an appropriate directing metalation group (DMG) by organolithium reagents is an important method for the regioselective functionalization of arenes. One can distinguish between directed *ortho*-metalation (DoM) of arenes, directed remote metalation (DreM) of polyarenes, peri-metalation of naphthalenes, metalation of metal-complexed arenes (mainly chromium complexes) and heteroatom-promoted lateral metalation (Figure 2).[11] *Ortho*-metalation is favored if the DMG is F, Cl, CF_3, OCF_3 or $CONR_2$. Peri-lithiation is predominant in naphthalenes having a DMG which can coordinate to the base and does not acidify, and thereby activate, the *ortho*-position, including OLi, NLi_2, NLiMe, NMe_2, and CH_2NMe_2.[12]

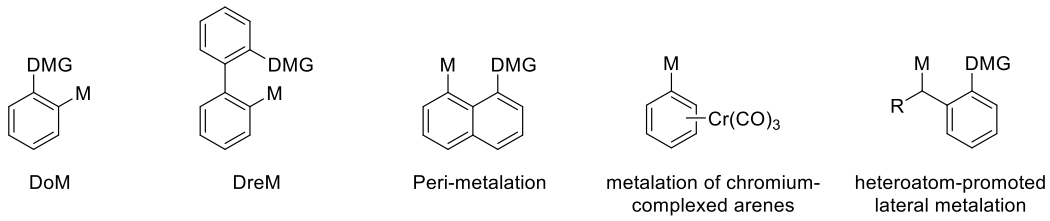
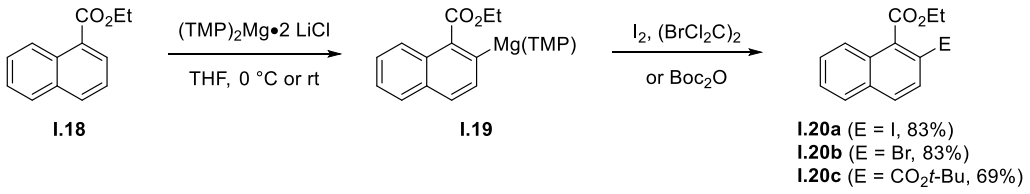


Figure 2. Different types of directed metalation of arenes.

Besides *ortho*-lithiation, directed magnesiation of naphthalenes with magnesium bases was reported by the group of Knochel. The metalation of ethyl 1-naphthoate (**I.18**) was achieved with magnesium bis(2,2,6,6-tetramethylpiperamide) ($Mg(TMP)_2$) complexed with two equivalents of lithium chloride ($(TMP)_2Mg{\cdot}2$ LiCl). The resulting magnesiated intermediate **I.19** reacted with electrophiles to furnish **I.20** (Scheme 4) or was used in cross-coupling reactions.[13]

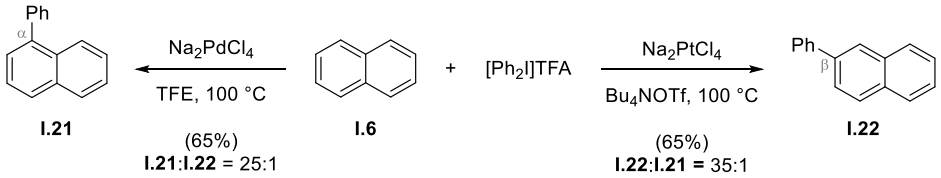


Scheme 4. Directed *ortho*-magnesiation of naphthalenes with $(TMP)_2Mg{\cdot}2$ LiCl and their reaction with electrophiles.

1.1.1.4 C–H Activation

In recent years, there has been vast progress in the development of site-selective metal-catalyzed C–H functionalization of arenes. Generally, the selectivity arises from directing groups,[14] the use of tethered coupling partners[15] or the inherent reactivity of heteroarene substrates.[16] However, the site-selective functionalization of unactivated arenes, such as naphthalene, remains challenging.

A catalyst-controlled site-selective arylation of naphthalene was reported by Sanford. While the arylation of naphthalene (**I.6**) with diaryl iodonium salts in the presence of sodium tetrachloropalladate(II) (Na_2PdCl_4) furnished the α-arylated naphthalenes **I.21**, the change to sodium tetrachloroplatinate(II) (Na_2PtCl_4) resulted in the formation of the corresponding β-isomer **I.22** (Scheme 5).[17] In a similar procedure for the preparation of α-arylated naphthalenes, palladium on charcoal (Pd/C) was successfully utilized as the catalyst.[18]



Scheme 5. Site-selective arylation of naphthalenes by Sanford.

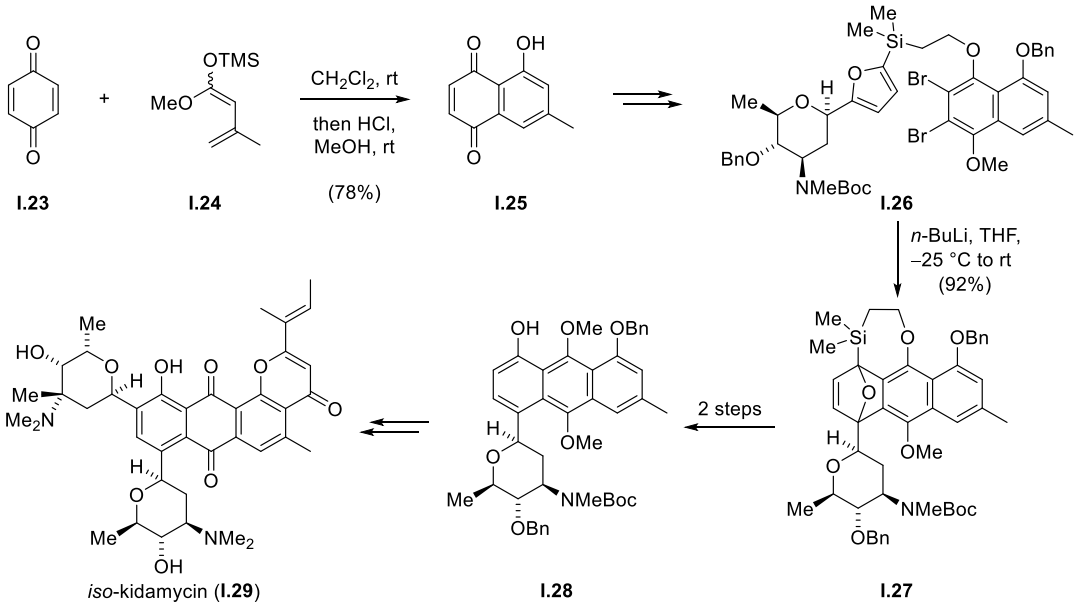
1.1.2 De novo Approaches Towards Naphthalenes

In contrast to the aromatic substitution reactions for the synthesis of functionalized naphthalenes, the synthesis from functionalized non-aromatic precursors can circumvent problems concerning the regiochemistry. In the following chapters, several methods for the preparation of naphthalenes are described. However, only selected examples are presented due to the number of reported methods.

1.1.2.1 Pericyclic Reactions

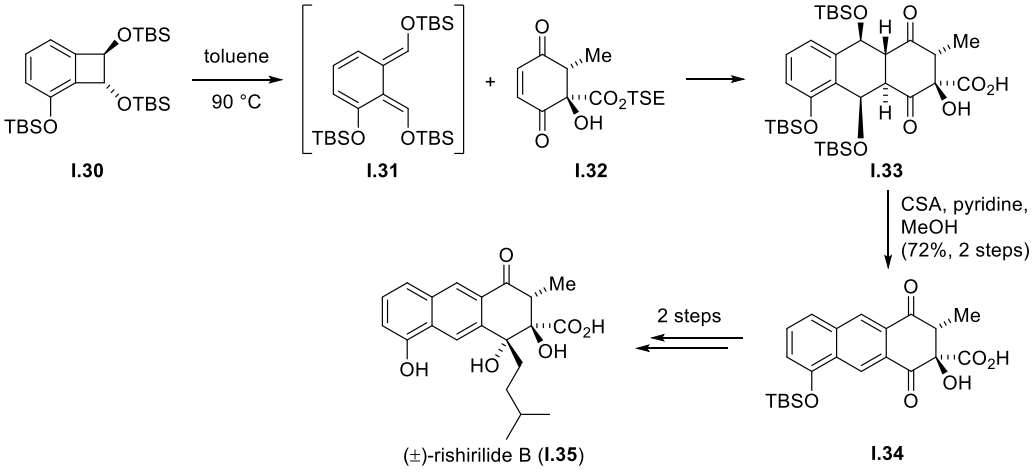
1.1.2.1.1 [4+2] Cycloaddition Reactions

For several decades, vinyl ketene acetals, like the Danishefsky diene[19] or Brassad's diene (**I.24**),[20] have served as dienes in Diels–Alder cycloaddition reactions. The reaction of these dienes with quinones can generate functionalized naphthalenes after aromatization. This method was utilized in the synthesis of *iso*-kidamycin by Martin (**I.29**). In addition, the authors employed an intramolecular benzyne Diels–Alder reaction to generate an anthracene motif after removal of the silicon tether (Scheme 6).[21]



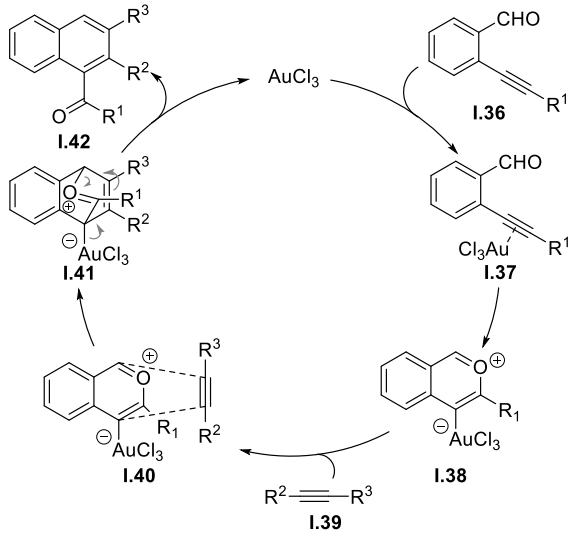
Scheme 6. The Diels–Alder reaction of **I.24** with **I.23** and an intramolecular benzyne Diels–Alder reaction in the total synthesis of *iso*-kidamycin (**I.29**).

Several reviews cover the generation and the application of *ortho*-quinodimethanes in organic synthesis.[22] The group of Danishefsky employed the *ortho*-quinodimethane Diels–Alder reaction in the synthesis of (±)-rishilide B (**I.35**). Ring opening of a substituted benzocyclobutane **I.30** generated the *ortho*-quinodimethane **I.31** which reacted in a Diels–Alder reaction with quinone **I.32** to furnish **I.34** after aromatization (Scheme 7).[23]



Scheme 7. *ortho*-Quinodimethane Diels–Alder reaction in the synthesis of (±)-rishilide B (**I.35**). TSE = 2-(trimethylsilyl)-ethyl.

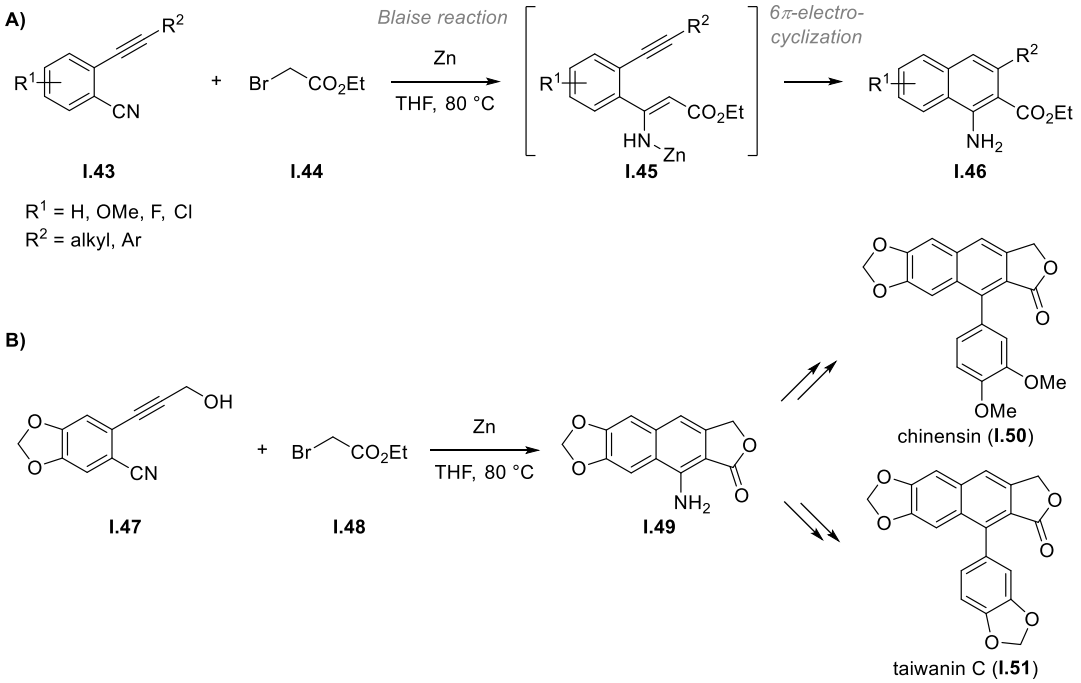
In 2002, the group of Yamamoto reported a $AuCl_3$-catalyzed formal [4+2] benzannulation of *o*-alkynyl-benzaldehydes **I.36** with alkynes **I.39**. The mechanistic proposal involved a nucleophilic attack of the carbonyl oxygen to the gold-activated alkyne to form an intermediate auric ate complex **I.38** followed by an intramolecular [4+2] cycloaddition with alkyne **I.39**. Regeneration of the catalyst resulted in formation of naphthalene **I.42** (Scheme 8).[24] A copper-catalyzed variant of this reaction was reported as well.[25]



Scheme 8. Mechanism of the $AuCl_3$-catalyzed formal [4+2] benzannulation of *o*-alkynylbenzaldehydes **I.36** with alkynes **I.39**.

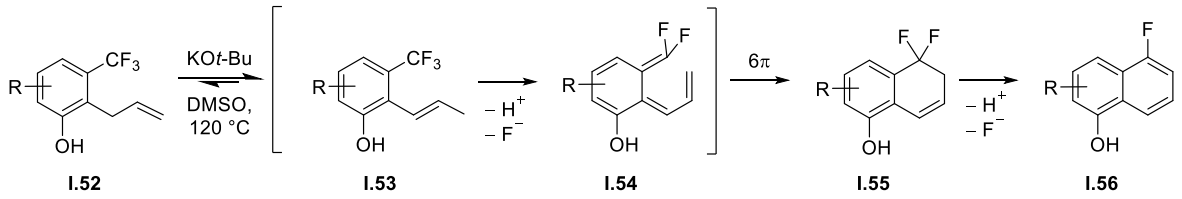
1.1.2.1.2 6π-Electrocyclization Reactions

The construction of naphthalenes via 6π-electrocyclizations was illustrated by a method reported by He et al.[26] In an initial Blaise reaction, 2-alkynylbenzonitriles **I.43** reacted with the organozinc compound derived from α-bromoester **I.44** to give intermediate **I.45**. The following 6π-electrocyclization furnished ethyl 1-amino-2-naphthoates **I.46** in good yields (Scheme 9A). If the R_2 substituent is a hydroxymethylene group (CH_2OH), lactonization was observed. This reaction was employed for the synthesis of the naturally occurring arylnaphthalene lactones chinensin (**I.50**) and taiwanin C (**I.51**) (Scheme 9B).



Scheme 9. A) Naphthalene synthesis via Blaise reaction followed by 6π-electrocyclization. B) Application in the total syntheses of chinensin (**I.50**) and taiwanin C (**I.51**).

The synthesis of fluorinated naphthols can be achieved through a base induced 6π-electrocyclization of C2-allylated (trifluoromethyl)phenols **I.52**, which are derived from (trifluoromethyl)phenols via allylation and subsequent Claisen rearrangement. Treatment of **I.52** with potassium *tert*-butoxide (KO*t*-Bu) in dimethylsulfoxide (DMSO) at 120 °C formed the thermodynamically favored isomer **I.53**. Subsequent deprotonation and elimination of a fluoride anion generated the intermediate **I.54**. A 6π-electrocyclization furnishes **I.55**, which rearomatized under concomitant loss of a second fluoride anion to provide naphthol **I.56** (Scheme 10).[27]

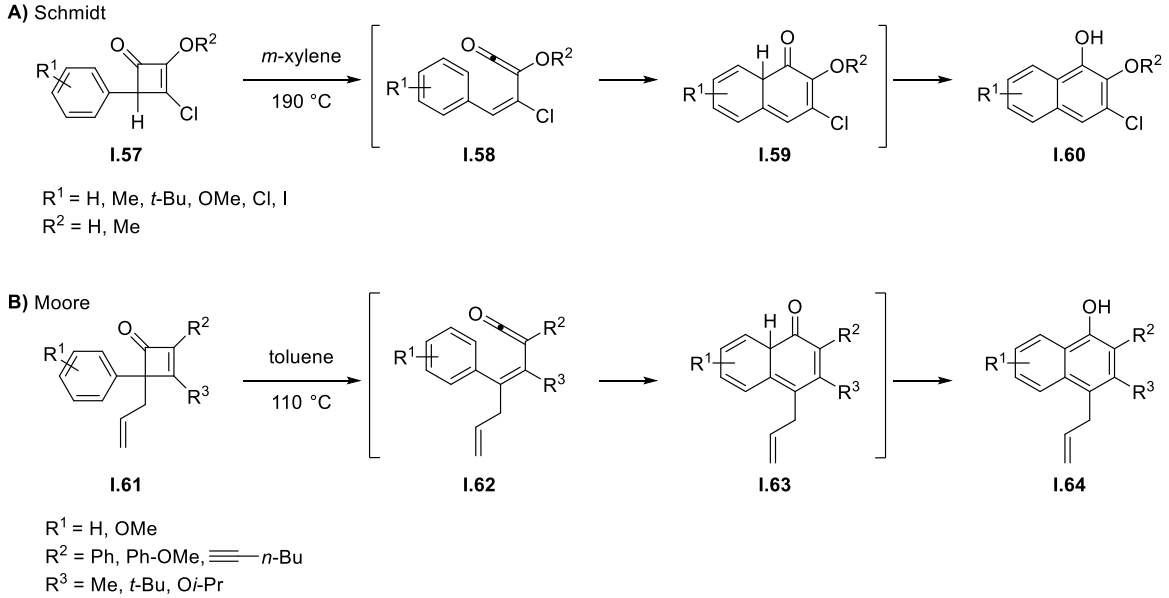


Scheme 10. 6π-Electrocyclization of C2-allylated (trifluoromethyl)phenols **I.52** to provide fluorinated naphthols **I.56**.

1.1.2.1.3 Ring-Expansion Reactions

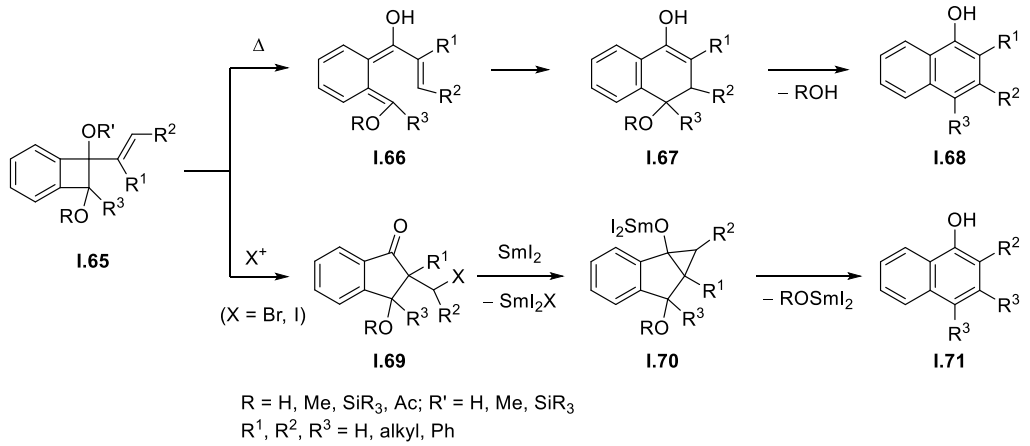
Rearrangement of Cyclobutenones

Several methods are known to prepare naphthalenes from cyclobutenones.[28] A 4π-electrocyclic ring opening results in the formation of a vinyl ketene intermediate, which cyclizes in a 6π-electrocyclization to give the corresponding naphthols.[29] Two examples, developed by the group of Schmidt[30] and Moore,[31] are depicted in Scheme 11.



Scheme 11. Synthesis of naphthalenes from cyclobutenones via 4π-electrocyclic ring opening followed by 6π-electrocyclization.

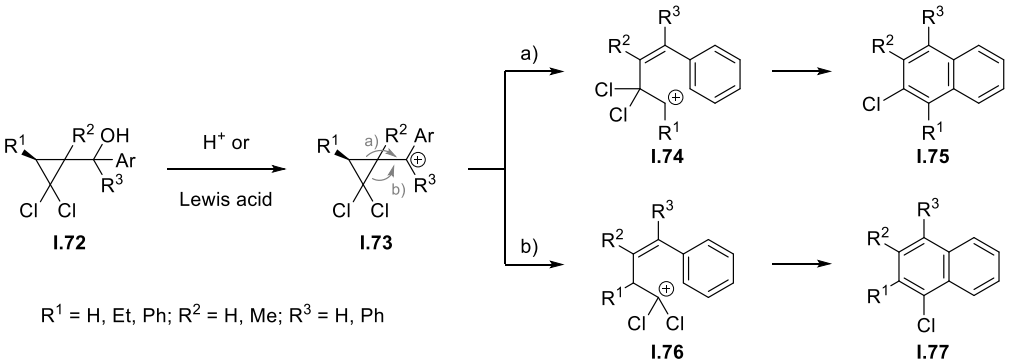
The group of Suzuki reported a method for the preparation of naphthalenes via a similar thermal 4π-electrocyclic ring opening of benzocyclobutenones followed by a 6π-electrocyclization (Scheme 12).[32] The corresponding benzocyclobutenones were prepared by the [2+2] cycloaddition of benzynes and ketene silyl acetals.[33] However, the same starting material **I.65** could be converted into isomeric naphthols **I.71** in a two-step process, involving two consecutive ring enlargements. Ring expansion of the alkenyl benzocyclobutene **I.65** by a halonium ion furnished indanone **I.69**. The second ring expansion proceeds via a SmI_2-promoted intramolecular Barbier-type reaction followed by a Grob fragmentation of the cyclopropanol intermediate **I.70** with concomitant loss of $ROSmI_2$.[34]



Scheme 12. Synthesis of isomeric naphthalenes **I.68** and **I.71** from alkenyl benzocyclobutene **I.65**.

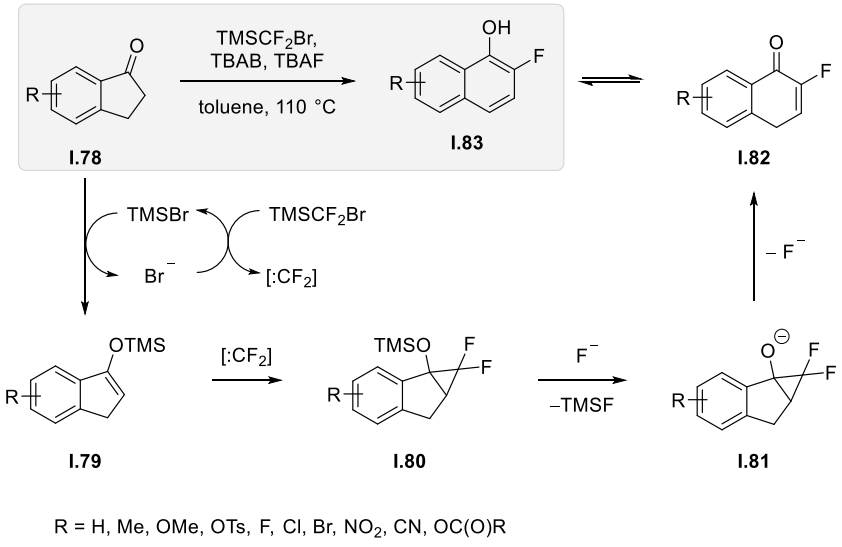
Rearrangement of Cyclopropanes

In addition to the rearrangement of cyclobutanes, various methods for the rearrangement of cyclopropanes have been reported. Tanabe et al. described the synthesis of halogenated naphthalenes from substituted *gem*-dichloro cyclopropanes **I.72**. In the first step, two different acid-catalyzed bond cleavages could occur, depending on the stability of the resulting carbocation. A subsequent intramolecular Friedel–Crafts reaction and aromatization with concomitant elimination of hydrogen chloride afforded the corresponding naphthalenes **I.75** or **I.77** (Scheme 13).[35]



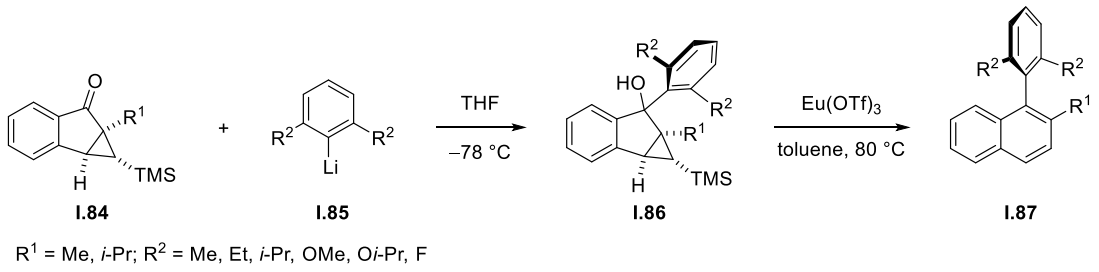
Scheme 13. Rearrangement of cyclopropanes **I.72** to give halogenated naphthalenes **I.75** and **I.77**.

Another reaction in this category is the synthesis of fluorinated 1-naphthols **I.83** from commercially available indanones **I.78** and (bromomethyl)trimethylsilane ($TMSCH_2Br$), catalyzed by tetrabutylammonium bromide (TBAB). At the outset, the silyl enol ether **I.79** was formed in the presence of bromotrimetylsilane (TMSBr), which was generated from $TMSCF_2Br$ and TBAB, and subsequently cyclopropanated with difluorocarbene. A fluoride-induced desilylation induced a ring opening/aromatization sequence to provide *ortho*-fluorinated naphthols **I.83** (Scheme 14).[36]



Scheme 14. Synthesis of fluorinated 1-naphthols **I.83** from indanones **I.78**.

In 2008, Glass et al. reported a ring-opening reaction of cyclopropylcarbinol **I.84** to provide functionalized naphthalenes.[37] **I.84** could be prepared from indenones by treatment with commercially available trimethylsilyldiazomethane in the presence of $Pd(OAc)_2$ followed by nucleophilic addition of Grignard reagents or organolithium species. A beneficial feature of this methodology was the possibility to synthesize tetra-*ortho*-substituted biaryl compounds **I.87** (Scheme 15).[38] The advantage of this method is that the formation of the key C–C bond was achieved through a simple nucleophilic addition.

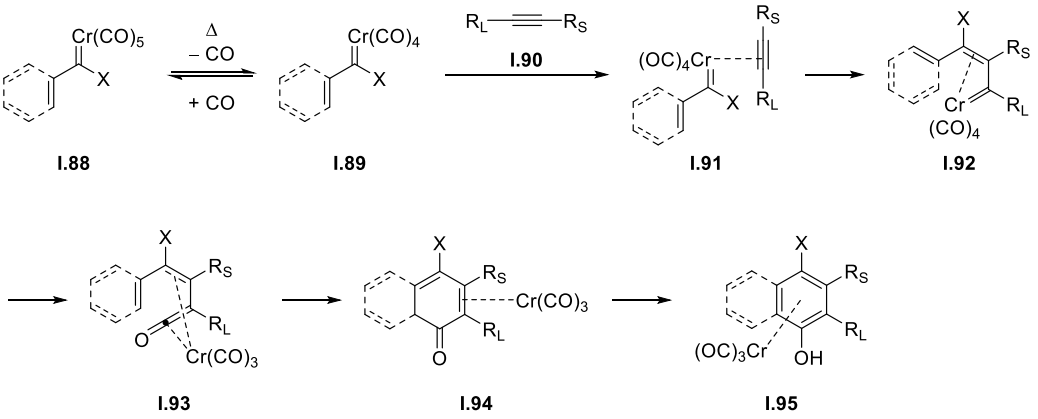


Scheme 15. Synthesis of tetra-*ortho*-substituted biaryl compounds **I.87** via ring opening of cyclopropyl carbinols **I.84**.

1.1.2.2 Transition Metal-Catalyzed Reaction

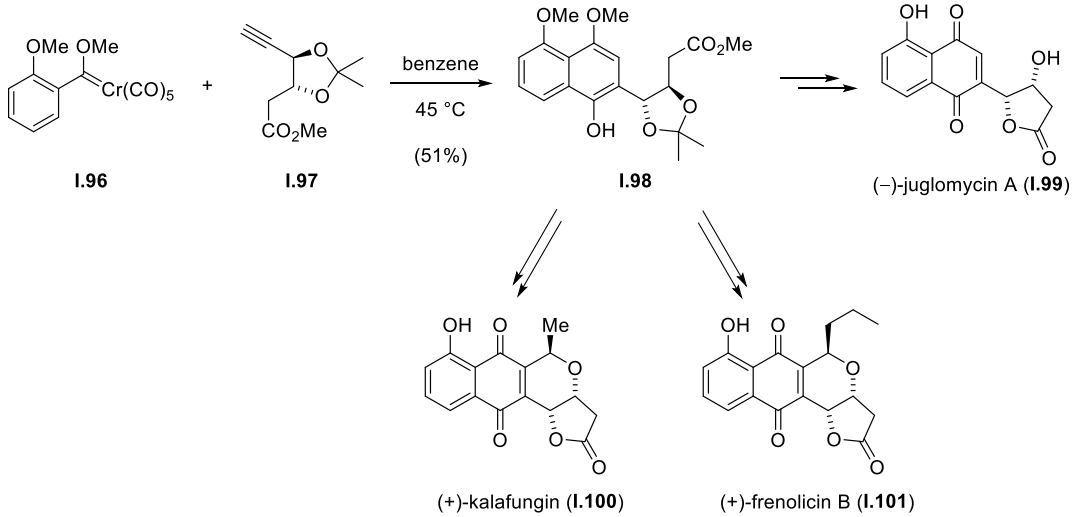
1.1.2.2.1 Dötz Reaction

The Dötz reaction, a thermal [3+2+1]-benzannulation reaction of alkynes with α,β-unsaturated Fisher carbine complexes, was discovered in 1975[39] and is widely used in organic chemistry and natural product synthesis.[40] The mechanism commences with the rate-determining reverse dissociation of carbon monoxide from the initial pentacarbonyl carbine complex **I.88** to form the coordinatively unsaturated tetracarbonyl carbene complex **I.89** (Scheme 16). Coordination of the alkyne **I.90** to the 16-electron complex and insertion into the metal-carbon bond furnishes the (η^1:η^3)-vinylcarbene complex **I.92**. Carbon monoxide insertion to form a η^4-vinylketene **I.93** and subsequent electrocyclic ring closure gives η^4-cyclohexadienone **I.94**. The final tautomerization led to the formation of phenol **I.95**.



Scheme 16. Mechanism of the Dötz reaction.

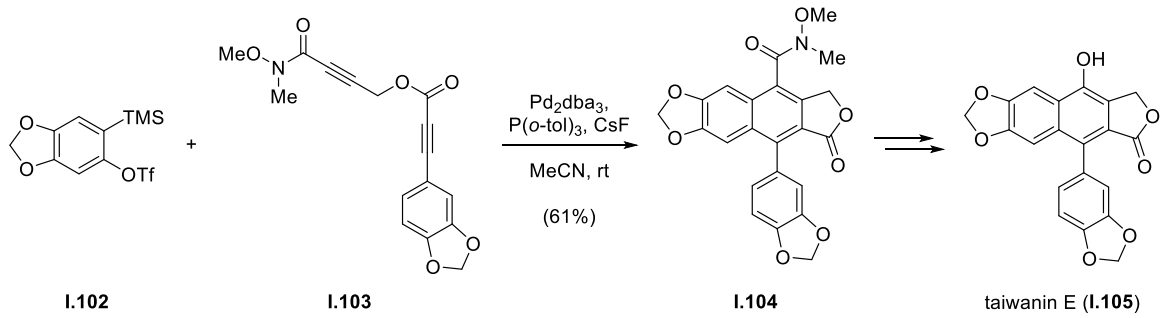
The naphthol intermediate **I.98** in the synthesis of (−)-juglomycin A (**I.99**) was derived via a Dötz benzannulation reaction of Fischer carbene **I.96** with alkyne **I.97** in 51% yield. The same intermediate was utilized in the synthesis of (+)-kalafungin (**I.100**) and (+)-frenolicin B (**I.101**) (Scheme 17).[41]



Scheme 17. Total synthesis of (−)-juglomycin A (**I.99**), (+)-kalafungin (**I.100**) and (+)-frenolicin B (**I.101**) via Dötz reaction.

1.1.2.2.2 [2+2+2] Cyclization Reactions

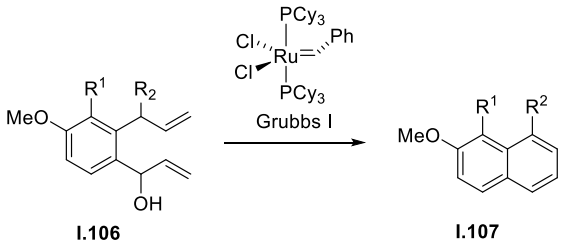
The application of a palladium(0)-catalyzed [2+2+2] cyclization for the preparation of functionalized naphthalenes was reported in the synthesis of the natural arylnaphthalene lignans taiwanin C (**I.51**) and taiwanin E (**I.105**).[42] Generation of a benzyne intermediate from **I.102** with cesium fluoride followed by a cyclotrimerization reaction with **I.103** furnished arylnaphthalene **I.104** (Scheme 18).



Scheme 18. A [2+2+2] cyclization reaction in the synthesis of taiwanin E (**I.105**).

1.1.2.2.3 Ring-closing Metathesis Reactions

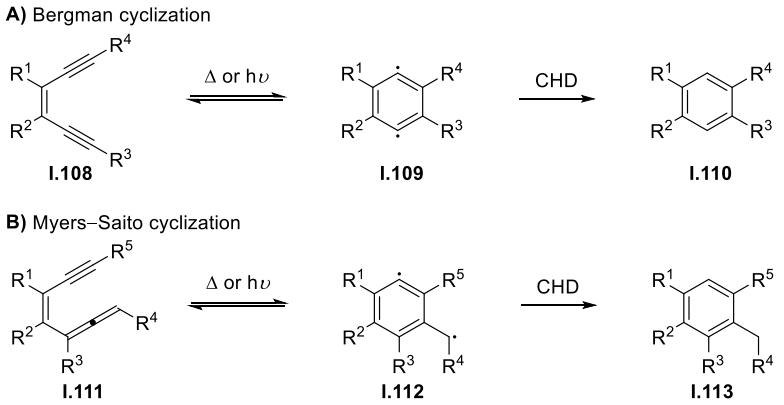
The ring-closing metathesis (RCM) is a versatile method to construct small- and medium-sized cyclic compounds and was also reported for the synthesis of naphthols. With suitable RCM precursors **I.105**, the RCM reaction with Grubbs I catalyst and concomitant elimination of water smoothly provided the corresponding functionalized naphthalenes **I.107** in good yields (Scheme 19).[43]



Scheme 19. RCM approach for the synthesis of functionalized naphthalenes.

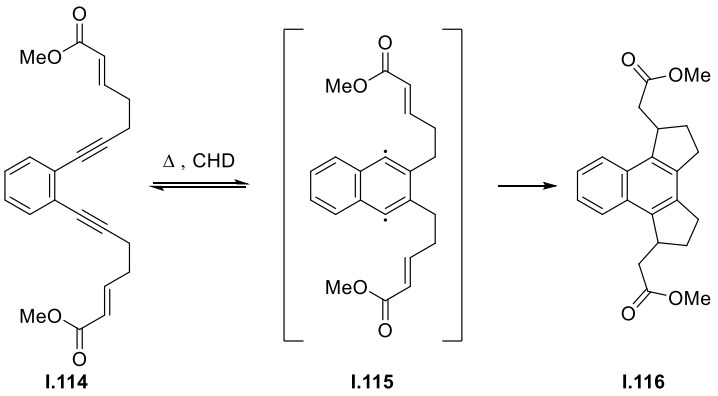
1.1.2.3 Radical Reactions

The Bergman cyclization[44] is a thermal or photochemical cycloaromatization of enediynes in the presence of a hydrogen radical donor and allows the construction of substituted arenes. In the Bergman cyclization, an enediyne **I.108** cyclizes to form a 1,4-benzenediyl diradical **I.109**, which reacts with a hydrogen radical donor like 1,4-cyclohexadiene (CHD) to give the corresponding arenes **I.110** (Scheme 20A).[45] In a related radical cyclization, the Myers–Saito cyclization, allenyl enynes **I.111** were cyclized to the corresponding arenes **I.113** (Scheme 20B). The advantage of this reaction is a much lower reaction temperature.[46]



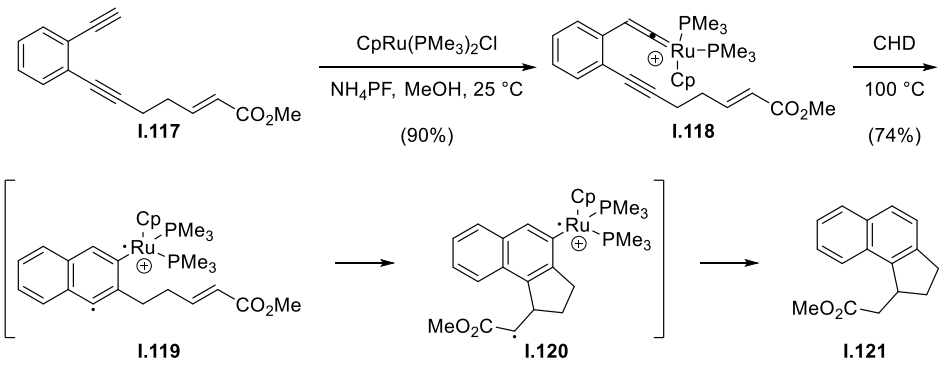
Scheme 20. Mechanism of A) the Bergman cyclization and B) the Myers–Saito cyclization; (CHD = 1,4-cyclohexadiene).

The use of the Bergman cyclization for the synthesis of fused ring systems was reported in 1996. Alkenes tethered to the enediyene unit were synthesized. The cycloaromatized diradical **I.115** then underwent further 5-*exo-trig* cyclizations to form additional saturated rings (Scheme 21).[47]



Scheme 21. Bergman cyclization for the synthesis of fused ring systems (CHD = 1,4-cyclohexadiene).

In an example reported by Finn,[48] a ruthenium catalyst was used to generate ruthenium-allene precursor **I.118**, which could be cyclized under relatively low temperatures. The proceeding cyclization can be regarded as a Myers–Saito cyclization that gives rise to a metal-centered radical in naphthalene **I.119**. A subsequent 5-*exo-trig* cyclization gave the fused naphthalene **I.121** (Scheme 22).

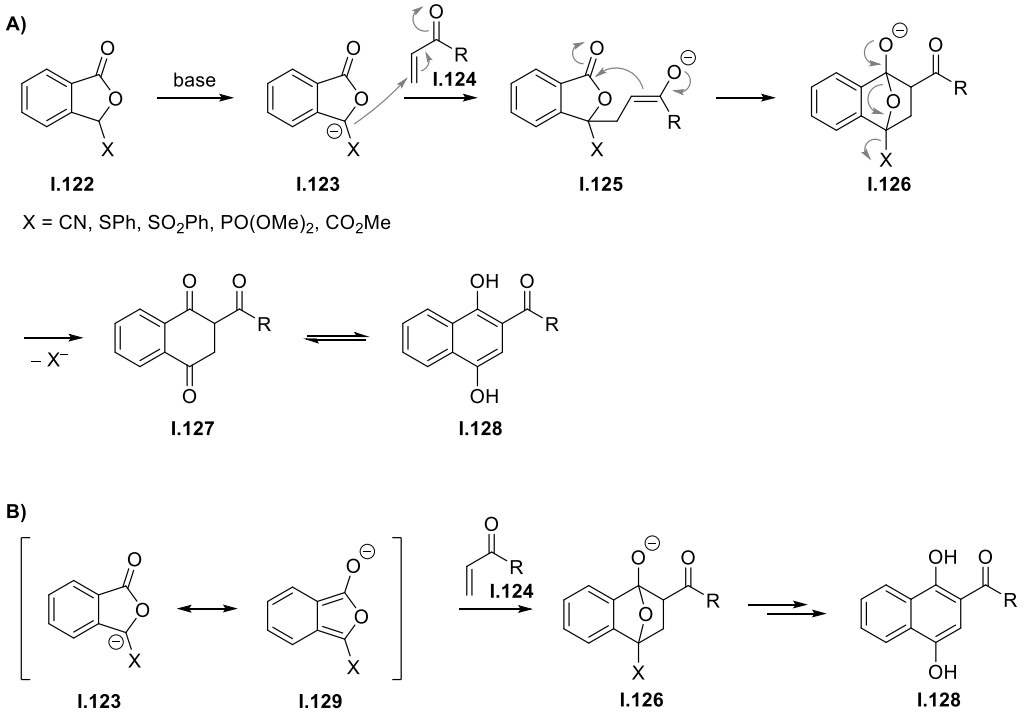


Scheme 22. Myers–Saito cyclization of ruthenium allene **I.118** to give fused naphthalene **I.121**.

1.1.2.4 Annulation Reactions

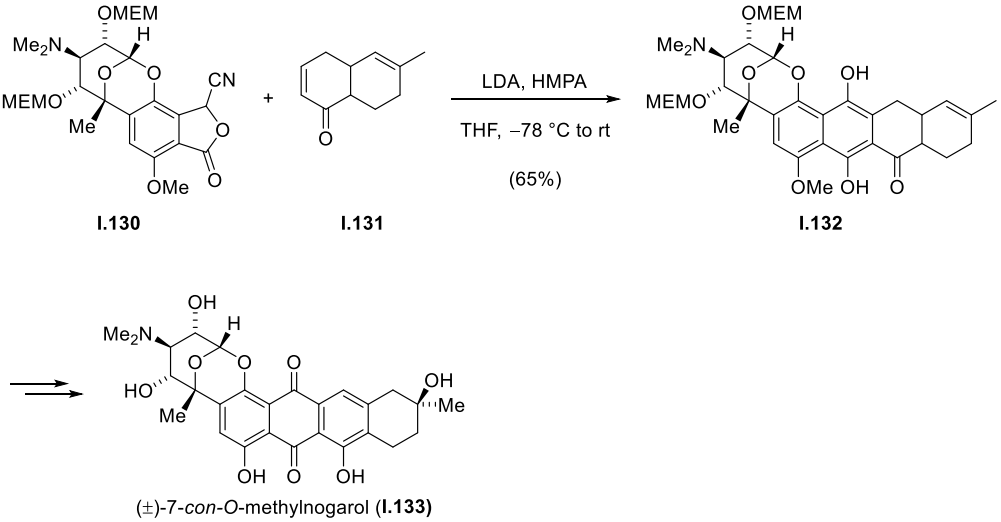
1.1.2.4.1 Hauser–Kraus Annulation

The annulation reaction of 3-substituted phthalides with Michael acceptors was developed by Hauser[49] and Kraus.[50] There are two mechanisms reported in the literature.[51] In the originally proposed mechanism, the generated anion **I.123** of phthalide **I.122** underwent a Michael reaction with enone **I.124** followed by an intramolecular Dieckmann cyclization. Elimination of the C3-substituent and final tautomerization resulted in the formation of the naphthoquinol **I.128** (Scheme 23A). Alternatively, the reaction could proceed via a concerted [4+2] cycloaddition of the *ortho*-quinodimethane intermediate **I.128** (Scheme 23B).



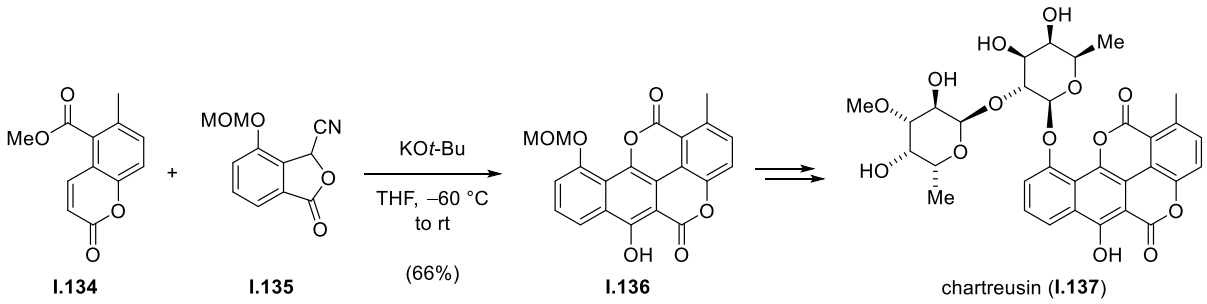
Scheme 23. Mechanism of the Hauser–Kraus annulation via A) Michael addition and Dieckmann cyclization or B) Diels–Alder reaction.

The Hauser–Kraus reaction was applied in several total syntheses. For example, the reaction was successfully applied to the total synthesis of (±)-7-*con*-*O*-methylnogarol (**I.133**) by Hauser.[52] Cyano-phthalide **I.130**, prepared in 15 steps from commercially available 2,5-dimethoxyacetophenone, was treated with lithium *N*,*N*-diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) and the generated anion reacted with tetrahydronaphthalenone **I.131** to give hydroquinone **I.132** in 65% yield (Scheme 24). A further 14 step sequence completed the total synthesis of **I.133**.



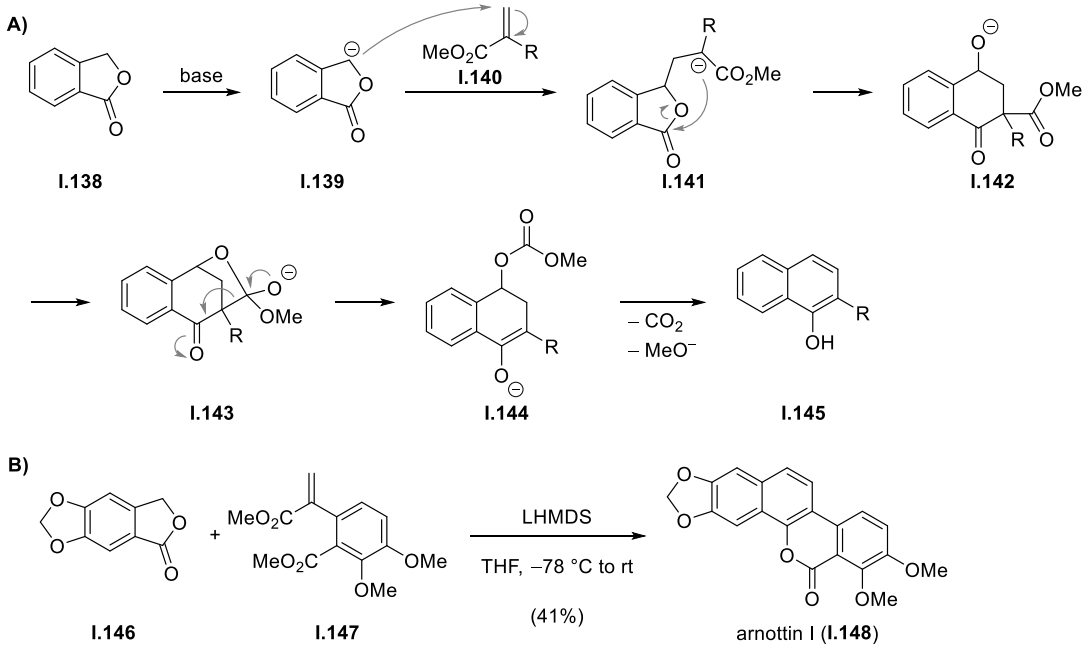
Scheme 24. Total synthesis of (±)-7-*con*-*O*-methylnogarol (**I.133**) via Hauser–Kraus reaction.

In the synthesis of chartreusin (**I.137**) and its analogues by Hertweck, the protected polycyclic aromatic aglycon (**I.136**) could be rapidly assembled by a Hauser–Kraus annulation of coumarin **I.134** and phthalide **I.135** (Scheme 25). The aglycon was successfully glycosylated using cultures of a ΔchaABC mutant.[53]



Scheme 25. Synthesis of chartreusin (**I.137**) via Hauser–Kraus reaction.

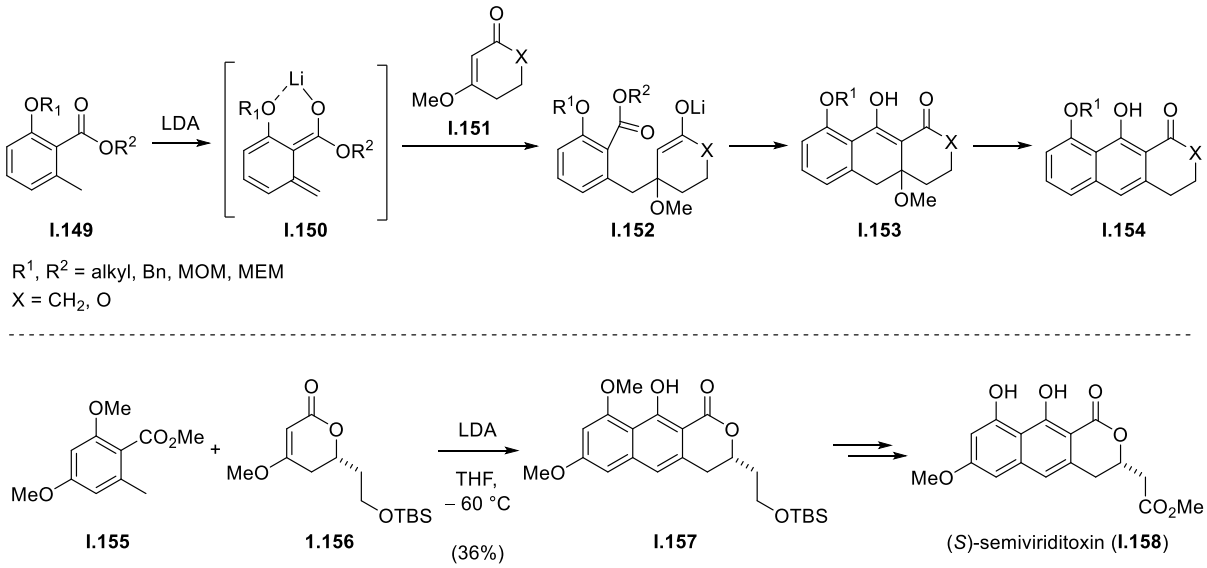
In 2011, Mal et al. reported a benzannulation reaction that is related to the Hauser–Kraus reaction, leading to C2-substituted 1-naphthols. Similar to the Hauser–Kraus reaction, the mechanism commences with a Michael addition of the deprotonated phthalide **I.139** to the Michael acceptor **I.140** followed by a Dieckmann condensation. As a consequence of the missing C3-leaving group, an intramolecular nucleophilic attack of the alkoxy anion occurred to form in carbonate **I.144** after fragmentation. The elimination of the carbonate as CO_2 and MeO^- resulted in the formation the C2-substituted 1-naphthol **I.145** (Scheme 26A). This reaction was employed in the total synthesis of arnottin I (**I.148**) (Scheme 26B).[54]



Scheme 26. A) Benzannulation reaction for the synthesis of C2-substituted 1-naphthols. B) Synthesis of arnottin I (**I.148**).

1.1.2.4.2 Staunton–Weinreb Annulation

The Staunton–Weinreb annulation was discovered independently by Staunton[55] and Weinreb[56] and is a stepwise naphthol synthesis involving a Michael addition followed by a Dieckmann condensation and subsequent aromatization (Scheme 27). A variety of *o*-toluates and α,β-unsaturated esters or ketones could be employed. However, the reaction generally required an ether group *ortho* to the ester functionality in order to stabilize the generated anion. The annulation reaction was used in the total synthesis of (*S*)-semiviriditoxin (**I.158**) to prepare the tricyclic core **I.157** in 36% yield.[57]



Scheme 27. Mechanism of the Staunton–Weinreb annulation and its application in the synthesis of (*S*)-semiviriditoxin (**I.158**).

1.2 Synthesis and Applications of Fluorinated Compounds

1.2.1 Properties of Fluorine

The application of organofluorine compounds include materials, pharmaceuticals, medical applications, agrochemicals and fine chemicals. The incorporation of fluorine can have a tremedous influence on chemical and physical properties of compounds, such as acidity, lipophilicity, boiling points and conformation.

Fluorine has the highest electronegativity in the periodic table. Commonly, fluorine replaces hydrogen in organic molecules although the van der Waals radius of fluorine and the C–F bond length are more comparable to the van der Waals radius of oxygen and the C–O bond (Table 1). The C–F bond is the strongest bond in organic chemistry. It is highly polarized and has more ionic than covalent character, leading to strong dipoles.[58] The fluorine substitution strengthens adjacent C–C single bonds, but weakens allylic C=C double bonds. Organofluorine substituents are poorly polarizable, thereby influencing intermolecular interactions.[59]

Table 1. Electronegativity, van der Waals radius, bond dissociation energy and bond length of selected atoms and bonds in organic chemistry.

Atom	Pauling's electronegativity χ_P[60]	van der Waals radius [Å][61]	Bond dissociation energy CH_3–X [kcal mol^{-1}][62]	Bond length C–X [Å][63]
H	2.20	1.20	105	1.09
F	**3.98**	**1.47**	**115**	**1.35**
Cl	3.16	1.74	84	1.79
Br	2.96	1.85	72	1.97
I	2.66	1.98	57	2.16
C	2.55	1.70	90	1.51
N	3.04	1.55	85	1.47
O	3.44	1.52	92	1.43

In most cases, fluorination increases the lipophilicity of a molecule. A quantitative measurement for the lipophilicity is the Hansch–Leo hydrophobic parameter (π). It is derived from octanol–water partition coefficients ($\pi_X = \log(P_X/P_H)$ (octanol–water)) and higher π-values indicate a higher lipophilicity.[64] As depicted in Table 2, fluorination can increase the lipophilicity up to two orders of magnitude on partition coefficients. Aromatic fluorination, per-/polyfluorination and fluorination adjacent to atoms with π-bonds can increase the lipophilicity, whereas monofluorination or trifluorination of saturated alkyl groups decreases the lipophilicity (Table 3). A reason for the decline is the relatively polar character of monofluoro- and trifluoromethylalkanes. In the presence of heteroatoms in the molecule, the lipophilicity is only decreased when the fluorination is more than three C–C bonds remote from the heteroatom (in the case of terminal trifluoromethyl groups).[64]

Table 2. Hydrophobic parameters π_X of functional groups.

	π_X[a)] **X = H**	π_X **X = F**
CX_3	0.56	0.88
OCX_3	−0.02	1.04
SCX_3	0.61	1.44
$CX_3C(O)$	0.02	0.55
$CX_3C(O)NH$	−1.27	0.08
CX_3SO_2	−1.63	0.55

a) $\pi_X = \log(P_X/P_H)$ (octanol–H_2O)

Table 3. Hydrophobic parameters π_X of alkanes and alcohols.

	π_X[a)] **X = H**	π_X **X = F**
CH_3CHX_2	1.81	0.75
$CH_3(CH_2)_3CH_2X$	3.11	2.33
CX_3CH_2OH	−0.32	0.36
$CX_3(CH_2)_2OH$	0.34	0.39
$CX_3(CH_2)_3OH$	0.88	0.90
$CX_3(CH_2)_4OH$	1.19	1.15

a) $\pi_X = \log(P_X/P_H)$ (octanol–H_2O)

Due to its high electronegativity, fluorine incorporation has a remarkable effect on the acidity of functional groups and can induce pK_a shifts of several orders of magnitude. For instance, a strong effect on the dissociation constants of simple carboxylic acids is perceivable.[65] In general, fluorination increases hydrogen bond and Brønsted acidity and decreases hydrogen bond and Brønsted basicities (Table 4).[64]

Table 4. Comparison of pK_a values of selected (fluorinated) acids and bases.[64]

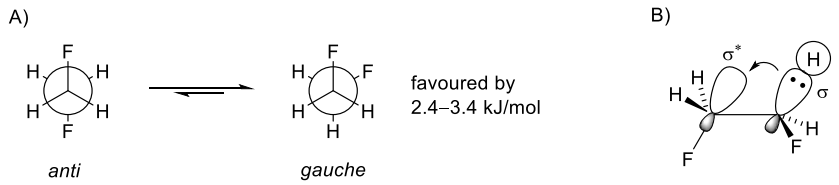
acid	**pK_a X= H**	**pK_a X= F**	**base**	**pK_{BH}+ X= H**	**pK_{BH}+ X= F**
$C\mathbf{X}_3CO_2H$	4.76	0.52	$C\mathbf{X}_3CH_2NH_2$	10.7	5.9
$C_6\mathbf{X}_5CO_2H$	4.21	1.75	$C_6\mathbf{X}_5NH_2$	4.6	−0.36
$C\mathbf{X}_3CH_2OH$	15.9	12.4			
$(C\mathbf{X}_3)_2CHOH$	16.1	9.3			
$(C\mathbf{X}_3)_3COH$	19.0	5.4			
$C_6\mathbf{X}_5OH$	10.0	5.5			

The C–H acidity is, in most cases, enhanced by α-fluorination. An exception is the decrease of the C–H acidity when the geometry of the generated conjugated carbanion is almost planar due to the greater lone-pair repulsion. However, the effect of fluorination is less intense than the effect of other halogenations. β-Fluorination always increases the C–H acidity through inductive and hyperconjugative resonance stabilization.[64] Some examples are shown in Table 5.

Table 5. C–H acidities of selected (fluorinated) molecules.[64]

compound	pK_a
CH_4	68-70
CF_3H	30.5
CCl_3H	24.4
CBr_3H	22.7
$CH_3CO_2CH_3$	28.2
$CH_2FCO_2CH_3$	21
$C_6H_5C(O)CH_2C(O)C_6H_5$	10.7
$C_6H_5C(O)CHFC(O)C_6H_5$	8.5

Furthermore, fluorination has a major influence on the conformation of organic molecules. For instance, *n*-butane preferentially adapts the *anti* conformation whereas 1,2-difluoroethane prefers the *gauche* conformation (Scheme 28A).[66] The *gauche* rotamer has a lower energy than the *anti* rotamer by 2.4–3.4 kJ/mol[67] and is stabilized by hyperconjugation of the C–H σ-orbital donating into the C–F σ*-orbital (Scheme 28B).[68]



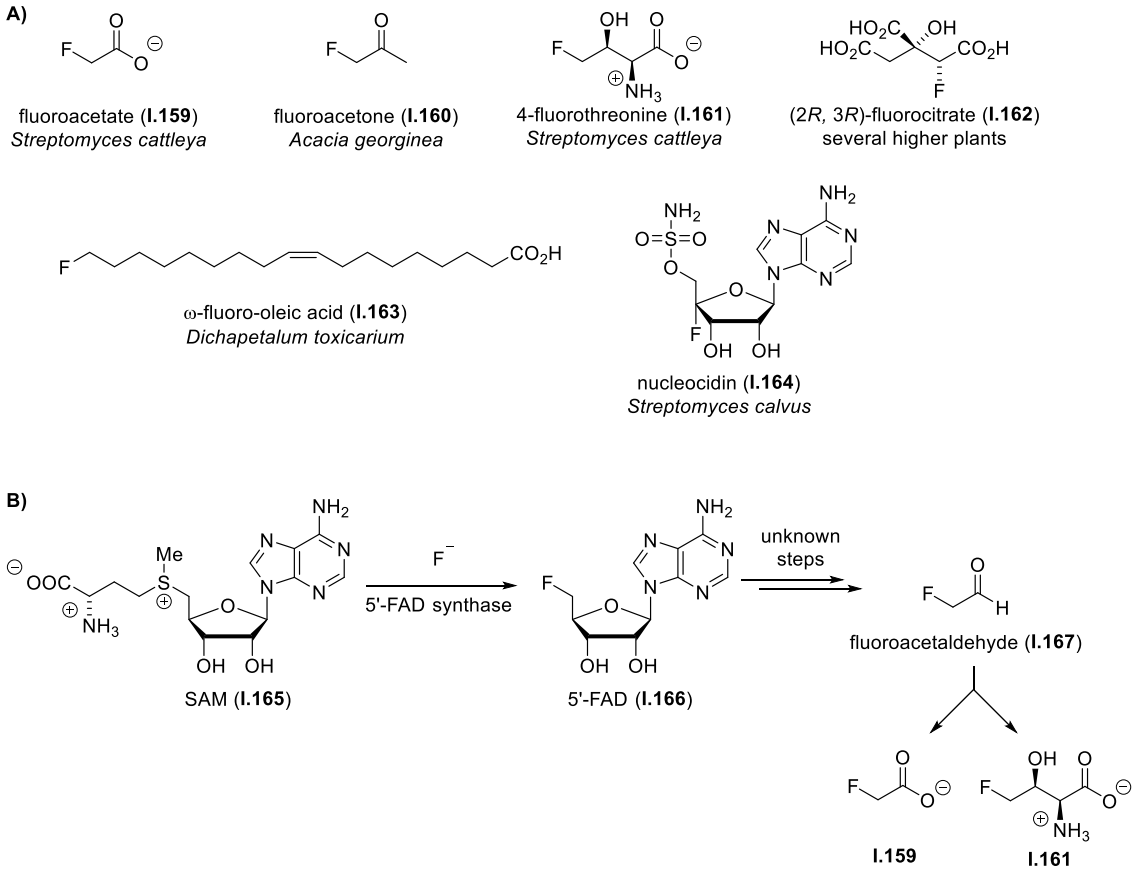
Scheme 28. A) Conformation of 1,2-difluoroethane. B) Stabilization of the *gauche* conformer by hyperconjugation.

Another example of this influence is the different conformations of methoxyphenol and trifluoromethoxyphenol. In the preferred conformation, the methoxy group lies in the plane of the phenyl ring, which is explained by the possible conjugation of the sp^2-hybridized p-orbital with the aromatic π-system. Due to steric and stereoelectronic effects, the trifluoromethoxy group is orientated orthogonal to the plane of the aromatic ring. The orientation of the C–F bonds antiperiplanar to the lone pairs of the sp^3-hybridized oxygen account for an anomeric conjugation of the n_O and the σ^*_{C-F} bonds. This results in longer C–F bonds, thereby reducing the conjugation of oxygen and the aromatic π-system.[59]

1.2.2 Natural Occurance of Organofluorine Compounds

Fluorine in the form of fluoride minerals is the thirteenth most abundant element and most abundant halogen in the Earth's crust.[69] Nevertheless, only few a fluorine containing natural products are known. Toxic fluoroacetate (**I.159**) is the most common organofluorine compound (Scheme 29A).[70] The first known natural fluorinating enzyme 5'-fluoro-5'-deoxyadenosine synthase (5'-FDAS), isolated from *Streptomyces cattleya* in 2003, is supposed to dehydrate solvated fluoride in the active site and thereby

increasing the nucleophilicity of fluoride.[69] 5'–FDAS is involved in the biosynthesis of fluoroacetate (**I.159**) and 4-fluorothreonine (**I.161**), catalyzing the reaction between *S*-adenosyl-L-methionine (SAM, **I.165**) and a fluoride ion to generate 5'-fluoro-5'-deoxyadenosine (5'-FDA, **I.166**) (Scheme 29B).[71]



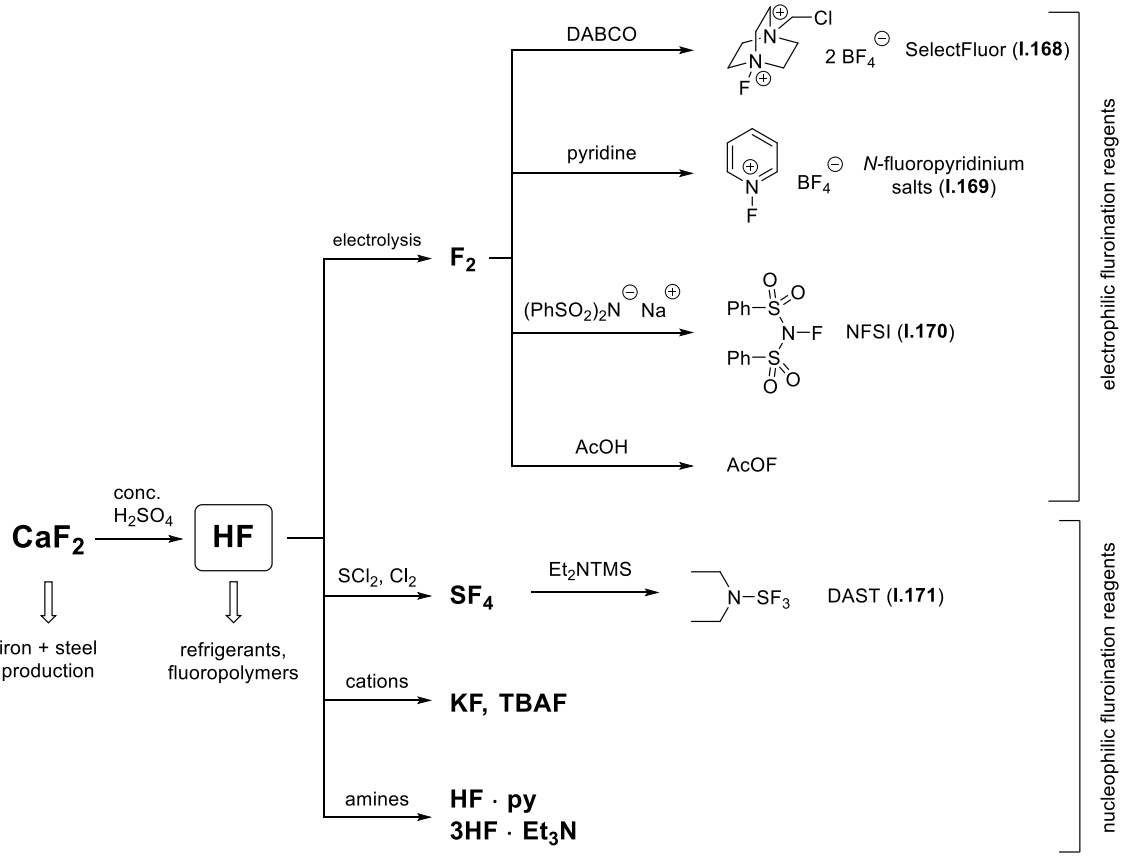
Scheme 29. A) Selected naturally-occurring organofluorine compounds. B) Proposed biosynthesis of fluoroacetate (**I.159**) and 4-fluorothreonine (**I.161**).

1.2.3 Synthesis of Fluorinated Compounds

1.2.3.1 Nucleophilic and Electrophilic Fluorination Reagents

Organofluorine compounds have a variety of applications and many methods for fluorination have been developed in recent years. Traditional methods often require harsh conditions and are often unselective and functional group intolerant. This problem derives from the high reactivity of most fluorine sources. On industrial scale, fluorination of simple molecules is well elaborated and a variety of nucleophilic and electrophilic fluorination reagents are commercially available.

Today, all fluorination reagents are derived from fluorite (CaF_2, fluorspar). Approximately half of all CaF_2 is employed to reduce melting points and increase the viscosity of metals in iron and steel manufacturing. The remaining CaF_2 is used to produce anhydrous hydrogen fluoride (HF), which is the starting point for the preparation of all other fluorination reagents (Scheme 30).[72]



Scheme 30. Preparation of fluorination reagents from fluroite (CaF_2).

In general, one distinguishes between nucleophilic and electrophilic fluorination reagents. Common nucleophilic fluorination reagents besides fluoride salts (KF, CsF, AgF, $[R_4N]F$), triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and hydrogen fluoride pyridine (HF·py) are depicted in Figure 3.

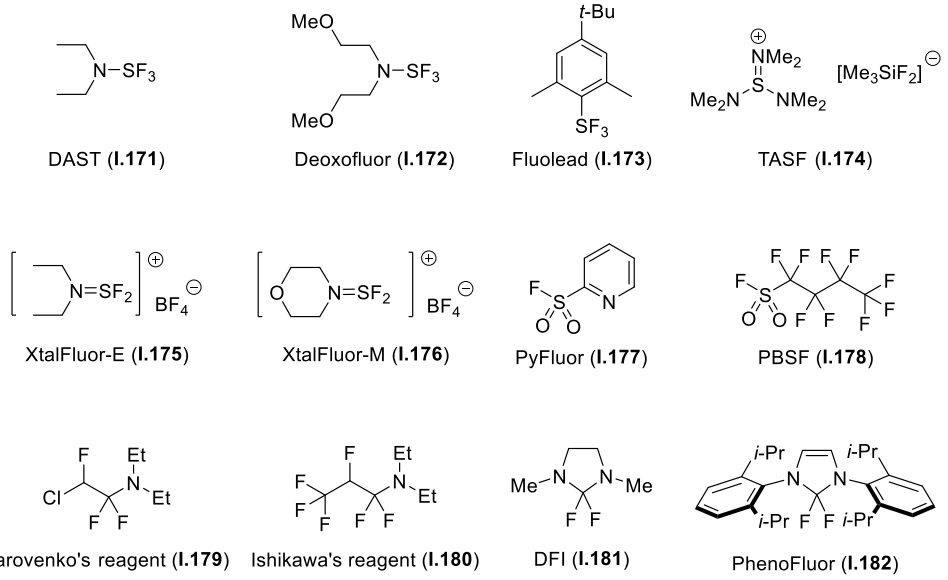


Figure 3. Common nucleophilic fluorination reagents.[73]

Besides the nucleophilic reagents, there are various electrophilic fluorination reagents known.[74] Some examples include SelectFluor (**I.168**),[75] *N*-fluoropyridinium-2-sulfonates (**I.183**),[76] *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**I.184**)[77] and *N*-fluorosulfonimides such as *N*-fluoro-*o*-benzenedisulfonimide (NFOBS, **I.185**) and *N*-fluorobenzenesulfonimide (NFSI, **I.170**) (Figure 4A).[78] Additionally, a number of chiral *N*-fluorosulfonimides are known, including (+)-*N*-fluoro-2,10-camphorsultam (**I.186**), *N*-fluoro-2,10-(3,3-dichlorocamphorsultam (**I.187**), (*R*)-CMIT-F (*N*-Fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-dioxide, **I.188**) and 2-fluoro-14-methyl-11-(methylethyl)-spiro[4*H*-benzo[*e*]-1,2-thiazine-3,2'-cyclohexane]-1,1-dione (**I.189**) (Figure 4B).[79]

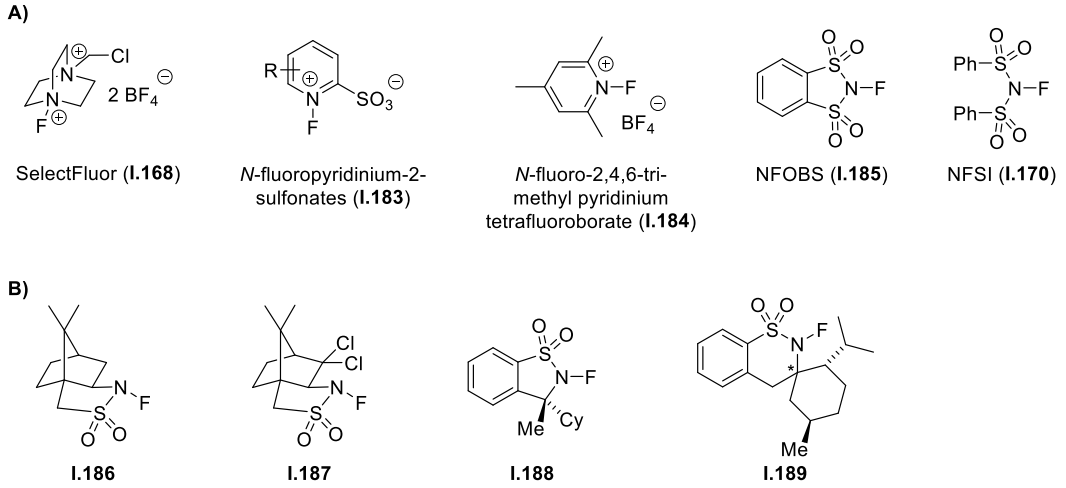
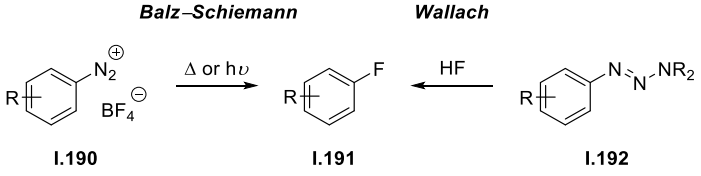


Figure 4. A) Common electrophilic fluorination reagents. B) Chiral *N*-fluorosulfonimides for enantioselective fluorination.

1.2.3.2 Fluorination of Arenes

Aromatic fluorination is a fundamental challenge. The electrophilic fluorination of arenes, in particular, is ambitious because the rate-determining step – the formation of the halocyclohexadienyl cation – is hindered by the electronegativity of fluorine.[80]

Early examples of the fluorination of arenes were reported by Wallach in 1888 and by Balz and Schiemann in 1927.[81] They developed a method for the nucleophilic fluorination of arenes via thermal decomposition of aryl diazonium tetrafluoroborate salts or aryl triazines in the presence of hydrogen fluoride (Scheme 31).

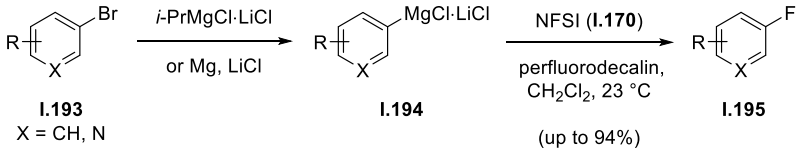


Scheme 31. Balz–Schiemann and Wallach reactions for the preparation of fluorinated arenes.

The displacement of chlorine substituents with fluorine in electron-poor arenes was achieved at high

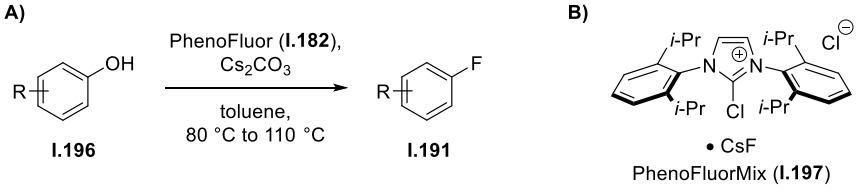
temperatures with anhydrous potassium fluoride (the Halex process).[82] A more practical method was established by employing anhydrous tetrabutylammonium fluoride (TBAF) in DMSO or tetramethylammonium fluoride (TMAF) in *N*,*N*-dimethylformaide (DMF) at room temperature. Various (hetero)aromatic fluorides were prepared with this methods.[83]

The group of Knochel describes a synthesis of fluorinated arenes starting from the corresponding aryl bromides **I.193**.[84] Insertion of magnesium into the C–Br bond by using either *i*-propylmagnesium chloride lithium chloride (*i*-PrMgCl·LiCl) or magnesium together with lithium chloride (LiCl), followed by fluorination with NFSI (**I.170**) in CH_2Cl_2/perfluorodecaline at 23 °C furnished fluorinated benzenes and pyridines (Scheme 32). Using this method, fluorinated derivatives of important classes of heterocycles were prepared, including an isoquinoline, a pyrrole, a benzo[*b*]thiophene, thiophenes, and a furan.



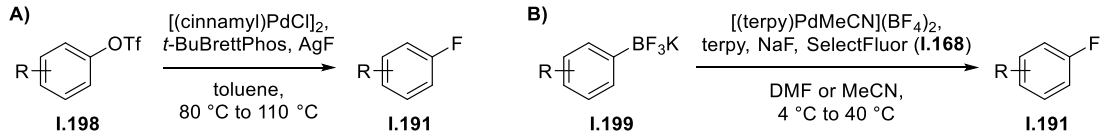
Scheme 32. Preparation and fluorination of Grignard reagents.

The synthesis of fluorinated arenes via deoxyfluorination of phenols was reported by Ritter. The reaction of phenol with PhenoFluor (**I.182**) in the presence of cesium carbonate (Cs_2CO_3) in toluene at 80–110 °C smoothly furnished the corresponding fluorides in high yields (Scheme 33A). The reaction tolerates functional groups such as nitro groups, esters, α,β-unsaturated esters, ketones, amides, amines, protected alcohols and halogens. Furthermore, flurorinated indoles, carbazoles, pyridines and quinolones could be prepared. By using this method, the fluorination of complex molecules like estrone, zearalenone and quinine was achieved.[73k] A more stable variant of PhenoFluor (**I.182**) is PhenoFluorMix (**I.197**), consisting of cesium fluoride (CsF) and *N*,*N*'-1,3-bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride, which is not air- and moisture-sensitive and can be stored under an air atmosphere (Scheme 33B).[85]



Scheme 33. A) Deoxyfluorination of phenols with PhenoFluor (**I.182**). B) Moisture stable PhenoFluorMix (**I.197**).

In addition, a couple of palladium-catalyzed methods for the fluorination of arenes exist. In 2009, Buchwald disclosed a methodology for the synthesis of fluorinated arenes and heteroarenes from the corresponding aryl triflates **I.198**. With CsF in the presence of a palladium(0) catalyst and *t*-BuBrettPhos, various fluorinated arenes were prepared in good yield (Scheme 34A). An additional method was developed by the group of Ritter. Trifluoroborate salts **I.199** were successfully employed in cross-coupling reactions with SelectFluor (**I.168**) as fluoride source (Scheme 34B).[86]

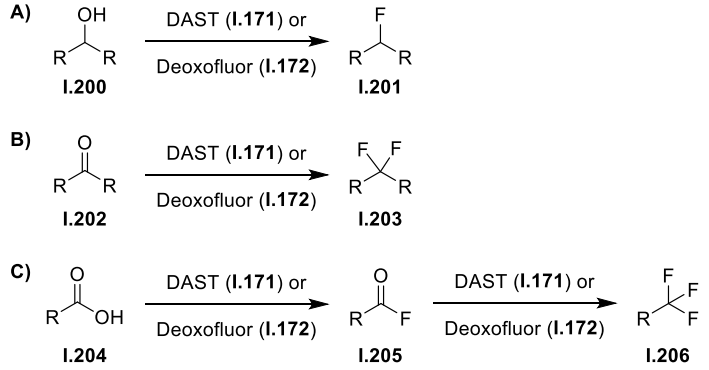


Scheme 34. Palladium catalyzed fluorination of A) triflates by Buchwald and B) trifluoroborates by Ritter. (terpy = 2,6-bis(2-pyridyl)pyridine.

More examples of arene fluorination are described in rewiews by Gouverneur and Ritter.[87]

1.2.3.3 C_{sp^3}–F Bond Formation

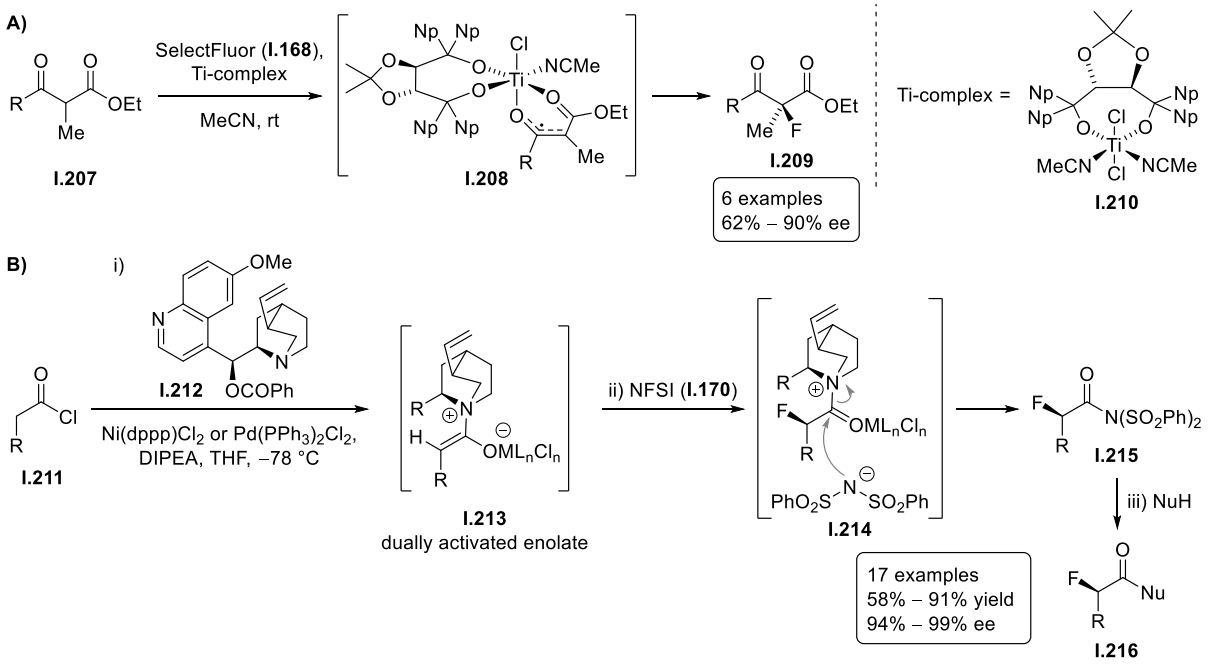
A common way to introduce aliphatic fluorides is the deoxyfluorination of an alcohol **I.200** or a ketone **I.202**, which are replaced by one or two fluorides respectively. Additionally, carboxylic acids (**I.208**) can be converted to acid fluorides I**.204** or trifluoromethyl groups (Scheme 35). Two of the most commonly employed reagents for deoxyfluorination reactions are DAST (**I.171**) and Deoxofluor (**I.172**). Deoxofluor is more stable than DAST, which can decomposes explosively at temperatures above 90 °C.[88] The same reactivity is observed with XtalFluor-E (**I.175**) and XtalFluor-M (**I.176**) in combination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$), except for the formation of trifluoromethyl groups from acid fluorides. XtalFluor-E (**I.175**) and XtalFluor-M (**I.176**) are more stable than DAST (**I.171**) and Deoxofluor (**I.172**) and do not generate free hydrofluoric acid.[73e]



Scheme 35. Conversion of A) alcohols, B) ketons and C) carboxylic acids into A) mono-fluorinated, B) geminal difluorinated products and C) carboxylic acid fluorides or trifluoromethyl groups by DAST (**I.171**) or Deoxofluor (**I.172**).

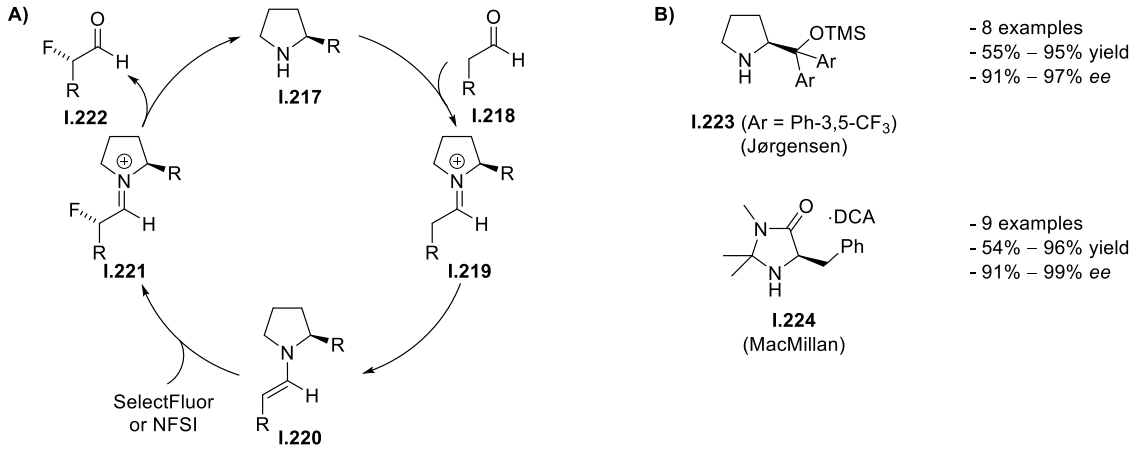
Several procedures for the enantioselective α-fluorination of ketones and aldehydes have been described. The catalytic enantioselective fluorination of β-ketoesters was achieved with SelectFluor (**I.168**) in the presence of a chiral titanium complex ([$TiCl_2$(1-naphthyl-TADDOLato)($MeCN)_2$], **I.210**) (Scheme 36A).[89] Furthermore, α-fluorination can be catalyzed by cinchona alkaloids. For example, acid chlorides **I.215** can be activated by benzoylquinidine (**I.212**) and nickel or palladium catalysts to give a dually activated intermediate **I.213**, which can be fluorinated by NFSI (**I.170**). The resulting amide **I.215** can be converted to the corresponding carboxylic acid, ester, amide or peptide depending on the nucleophile used to quench the reaction (Scheme 36B).[90] Comparable methods for the enantioselective α-fluorination of

ketones or aldehydes with SelectFluor (**I.169**) or NFSI (**I.171**) catalyzed by cinchona alcaloids were reported by the groups of Shibata and MacMillan.[91] In addition, the group of Toste applied phase transfer catalysts (PTCs) for enantioselective α-fluorination and could also realize a dearomatising *ortho*-fluorination of phenols.[92]



Scheme 36. A) Titanium-catalyzed enantioselective α-fluorination of β-ketoesters. B) Benzoylquinidine and metal-catalyzed enantioselective α-fluorination of acid chlorides followed by nucleophilic quenching.

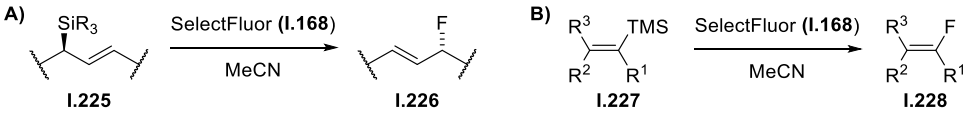
In addition, the enantioselective α-fluorination with Selectfluor (**I.168**) or NFSI (**I.170**) can be catalyzed by the proline-derived Jørgensen catalysts like **I.223** or the imidazolidin-4-one-derived MacMillan catalysts **I.224** as disclosed by Jørgensen and MacMillan (Scheme 37).[93]



Scheme 37. A) Catalytic cycle for the proline-catalyzed α-fluorination. B) Catalysts for the enantioselective α-fluorination.

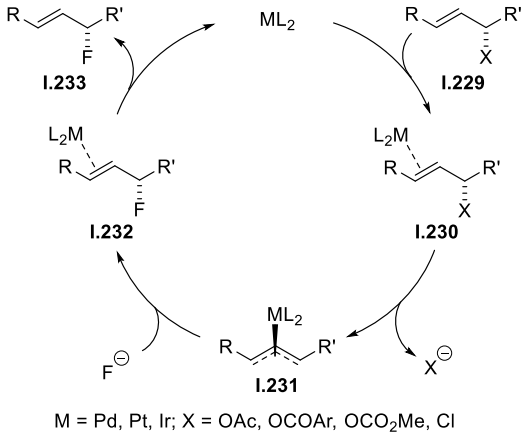
Another method to introduce fluorine substituents is the fluorodesilylation of linear or cyclic

allylsilanes **I.225**. The reaction occurs via an S_N2' mechanism where the addition of the fluorinating reagent SelectFluor (**I.168**) occurs *anti* with respect to the silane, furnishing the allylic fluoride. Using achiral substrates, cinchona alkaloids can be employed to induce enantioselectivity (Scheme 38.A).[94] In addition, the fluorodesilylation can be applied to prepare vinyl fluorides **I.228** from the corresponding vinyl silanes **I.227** (Scheme 38.B).[95]



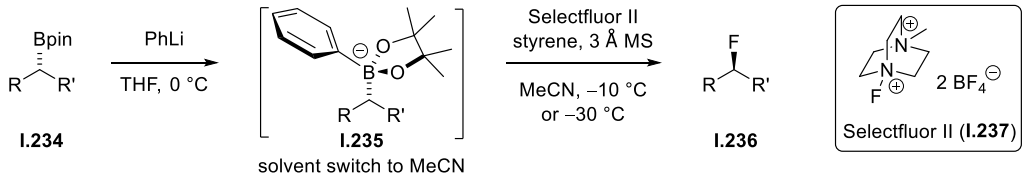
Scheme 38. A) Fluorodesilylation of linear or cyclic allyl silanes with SelectFluor. B) Fluorodesilylation of vinyl silanes.

Allylic fluorides can also be obtained by metal-catalyzed nucleophilic fluorination. S_N2-type attack of fluoride on an electrophilic palladium(II)-allyl intermediate **I.231** furnishes allylic fluorides **I.233** with an overall retention of configuration (Scheme 39).[96]



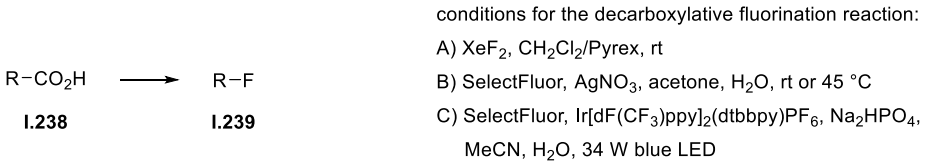
Scheme 39. Mechanism of the metal-catalyzed nucleophilic allylic fluorination.

In 2015, Aggarwal reported the enantioselective electrophilic fluorination of alkyl boronic esters.[97] The intermediate boronate complex (**I.235**) was generated by treatment of a secondary boronic acid **I.234** with phenyl lithium. A solvent switch to acetonitrile (MeCN) followed by the addition of SelectFluor II (**I.237**)[75] enabled the preparation of the corresponding secondary fluorides **I.236** (Scheme 40). Stryrene was crucial as an additive for the reaction as it is believed to act as a radical trap that prevents radical propagation, thereby suppressing racemization.



Scheme 40. Enantioselective electrophilic fluorination of alkyl boronic esters.

A last example for the synthesis of alkyl fluorides is a decarboxylative fluorination process via alkyl radicals, generated from the corresponding primary, secondary or tertiary carboxylic acids. This reaction can be achieved by employing xenon difluoride (XeF_2), SelectFluor/$AgNO_3$ or SelectFluor/Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (Scheme 41).[98]



Scheme 41. Conditions for the decarboxylative fluorination reaction.

1.2.4 Applications of Organofluorine Compounds

Organofluorine compounds are widely used in pharmaceuticals and agrochemicals, and many of the leading blockbuster pharmaceuticals contain fluorine.[99] 5-Fluorouracil is one of the first fluorinated anticancer drugs synthesized in 1957. 5-Fluoro-deoxyuridine monophosphate, its pharmacologically active metabolite, inhibits the thymidylate synthase in the synthesis of thymidine.[100]

The absorption and distribution of drugs are predominantly controlled by the balance of lipophilicity and hydrophilicity and the ionization state of the molecule. An increased lipophilicity from fluorine substitution can result in a more advantageous partitioning between the less polar receptor site and the aqueous solution.[59] The incorporation of fluorine can lead to higher selectivity, potency and better absorption, distribution, metabolism and excretion (ADME) properties.[101]

The metabolic stability, a determining factor for the bioavailability (% of the dose reaching the circulatory system) of a drug, can be enhanced by blocking the labile metabolic site with fluorine. Oxidation by cytochrome P450 monooxygenases in the liver, decreasing the lipophilicity of compounds, is thereby prohibited.[102] This strategy is illustrated by the development of the cholesterol absorption inhibitor SCH 58235 (Ezetimibe, **I.241**) from SCH 48461 (**I.240**) (Figure 5). Aromatic fluorination to hamper undesired metabolism led to a 50 fold increased potency (ED_{50} = 0.4 mg/kg/day) compared to SCH 48461 (ED_{50} = 2.2 mg/kg/day).[103]

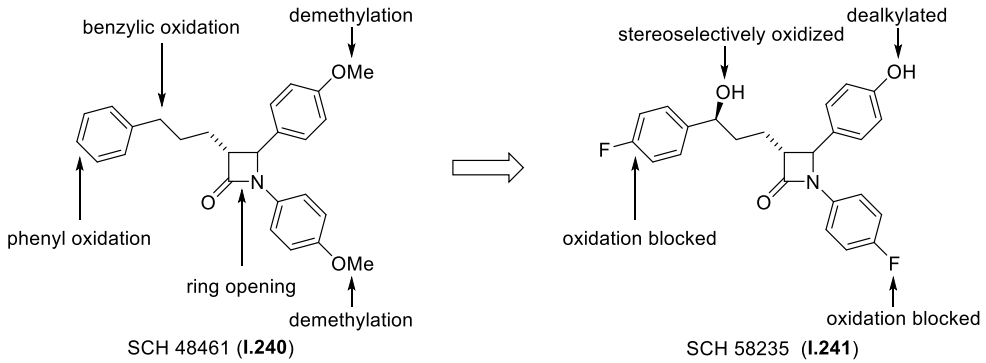
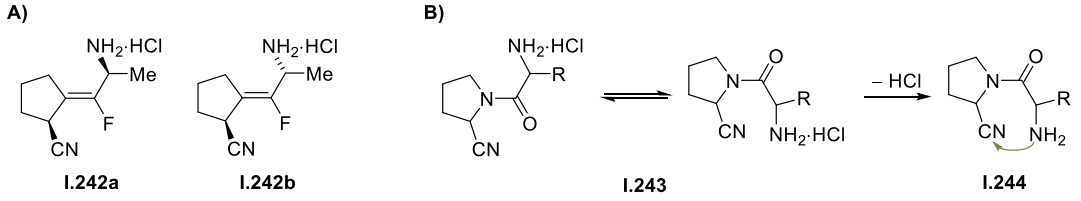


Figure 5. Design of the cholesterol absorption inhibitor SCH 58235 (Ezetimibe, **I.241**) from SCH 48461 (**I.240**).

The use of bioisosteric replacements in lead optimization is prevalent.[104] Bioisosterism is the capacity to interchange atoms or functional groups with similar sizes or shapes without a significant change in the biological behavior, such as binding affinity.[59] A fluorovinyl group (C=CHF) is an isoster of the peptide bond, mimicking the planarity and the size of the functional group. This strategy is highlighted in the development of the DPP IV inhibitor 2-(2-amino-1-fluoro-propylidene)-cyclopentanecarbonitriles (**I.242,** Scheme 42A). The replacement of the amide bond in the original inhibitor **I.243** resulted in the suppression of the undesired cyclization of the free *N*-terminal amino group with the reactive site of the inhibitor (Scheme 42B).[105]



Scheme 42. A) DPP IV inhibitor 2-(2-amino-1-fluoro-propylidene)-cyclopentanecarbonitriles **I.242a** and **I.242b**. B) Undesired cyclization of **I.244**.

A second example for a bioisosteric replacement is the optimization of the cathepsin K inhibitor odanacatib (**I.246**). The original inhibitors **I.245** suffers from low potency, amide hydrolysis and leucine hydroxylation followed by lactonization. The poor potency could be circumvented by the replacement of the C=O group with an isosteric C-CF_3 fragment.[106] The basicity of the NH-fragment is thereby minimized to maintain the hydrogen bond capability of an amide, which is required for the activity.[107] Additionally, the reduced amine basicity affects the membrane permeability.[59] This substitution resulted in a 10–20-fold higher potency. Fluorination of the *iso*-butyl group and introduction of a cyclopropyl fragment suppressed the hydroxylation and subsequent lactonization (Figure 6).[108]

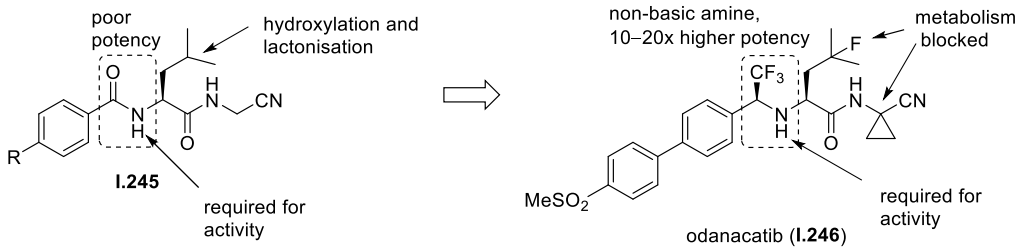
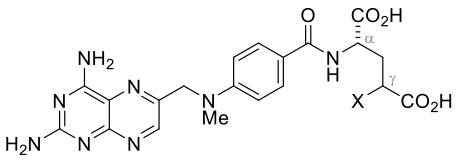


Figure 6. Optimization of cathepsin K inhibitors leading to odanacatib (**I.250**).

The adjustment in pK_a value by fluorination was successfully applied in the optimization of methotrexate (**I.247**, Figure 7), used against various types of cancers and rheumatoid arthritis. Continued treatment with methotrexate revealed disadvantageous effects including gastrointestinal toxicity, stomatitis, hematologic toxicity, hepatotoxicity, and pulmonary toxicity. The decrease of the toxicity of methotrexate could be achieved by a monofluorination at the γ-carboxylic acid group. The resulting increased acidity prevents the

formation of polyglutamates. These metabolites are responsible for a prolonged retention within the cells, which is related to the adverse effects in the treatment with methotrexate.[109]



methotrexate (**I.247**): X = H
γ-fluoromethotrexate (**I.248**): X = F

Figure 7. Structure of methotrexate (**I.247**) and γ-flurormethotrexate (**I.248**).

Fluorinated compounds can also be used as anesthetic drugs, agrochemicals and as radiopharmaceutical for positron emission tomography (PET).[102,110] Fluorine substitution can be applied in biochemical and binding assays to evaluate the strength of intermolecular interactions by ^{19}F Nuclear Magnetic Resonance (^{19}F NMR) spectroscopy.[111] In material chemistry, the development of fluoropolymers like polytetrafluoroethylene (Teflon) at DuPont by Roy Plunkett in 1938 opened up the presumably largest commercial application of organofluorine compounds. With properties like high thermal and oxidative stability, low dielectric constant, low moisture absorption, low flammability, low surface energy, excellent biocompatibility, marked gas permeability and excellent resistance to most chemicals, they are widely used as thermoplastics, elastomers, coatings, fluids and membranes.[70]

2 Results and Discussion

2.1 Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin

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Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin

*Teresa A. Unzner, Adriana S. Grossmann, and Thomas Magauer**

Abstract: *We report the synthesis of orthogonally functionalized naphthalenes from simple, commercially available indanones in four steps. The developed method proceeds through a two-step process that features a thermally induced fragmentation of a cyclopropane indanone with simultaneous 1,2-chloride shift. Migration of the chloride substituent occurs in a regioselective manner to preferentially afford the para-chloronaphthol substitution pattern. The obtained naphthols are versatile building blocks that can be selectively modified and used for the efficient construction of biologically active molecules. This has enabled the total synthesis of the potent anticancer natural product chartarin through a highly convergent retrosynthetic bond disconnection.*

Substituted naphthalenes are common substructural units in many biologically active molecules.[1,2] These include the antiproliferative natural products chartarin (**1**), the aglycon of chartreusin (**2**) and elsamicin,[3] justicidin A (**3**),[4] furomollugin (**4**)[5] and drugs such as the dopamine antagonist nafadotride (**5**)[6] and the nonsteroidal *anti*-inflammatory drug naproxene (Figure 1 a).[7] Traditional strategies for the functionalization of this structural motif hinge on a stepwise approach, that is the electrophilic aromatic substitution of partially substituted naphthalene building blocks.[8] Owing to the inherent low substrate selectivity and the complex substitution pattern found in many natural products, stepwise functionalization from readily available naphthalene precursors is rather inefficient and thus inapplicable for polyfunctionalized molecules. In recent years, methods based on annelation,[2,9] cycloaddition[10] or ring expansion[11] reactions have emerged as possible alternatives to access the bicyclic aromatic system. However, these concepts often require the use of expensive catalysts, involve relatively harsh reaction conditions with inherent lack of functional group compatibility or are dependent on multistep sequences to access the substrates. As a consequence, their application in the synthesis of more complex molecules has remained rather restricted.

As part of our ongoing program to develop practical and scalable methods for the synthesis of polysubstituted, highly functionalized arenes and heteroarenes,[12] we designed a strategy that would allow us to address the current limitations in a highly efficient manner (Figure 1 b). After considering various options, we identified indanone-cyclopropane **A**, readily accessible from a plethora of commercially available, inexpensive indanones via oxidation and cyclopropanation,[13] as the ideal substrate. The envisaged thermally induced disrotatory 2π-electrocyclic ring opening[14] of **A** was expected to be operationally simple on large-scale without requiring additional promoters and requires temporary carbon-halogen bond cleavage. This step produces the benzylallyl cation **B.** Regioselective attack by the chloride anion at the benzylic position affords enone **C** that should spontaneously isomerize to the orthogonally functionalized naphthol **D**. By virtue of the orthogonal functionalization present in **D**, rapid access to selectively modified products would be possible.

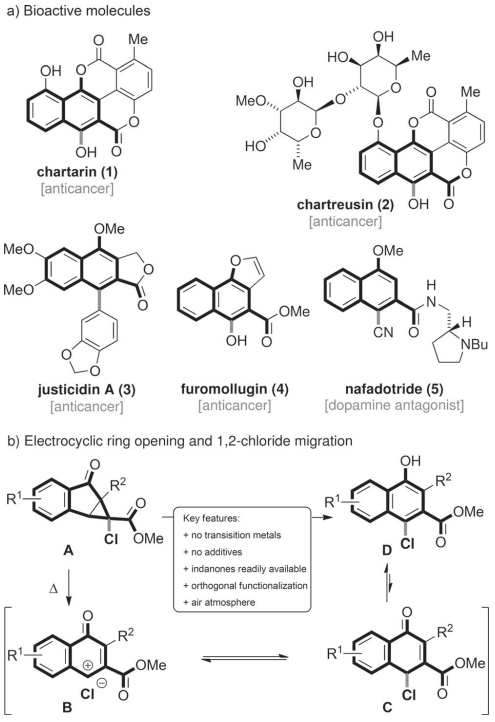

Figure 1. a) Occurrence of naphthalene pharmacophores and b) synthetic design.

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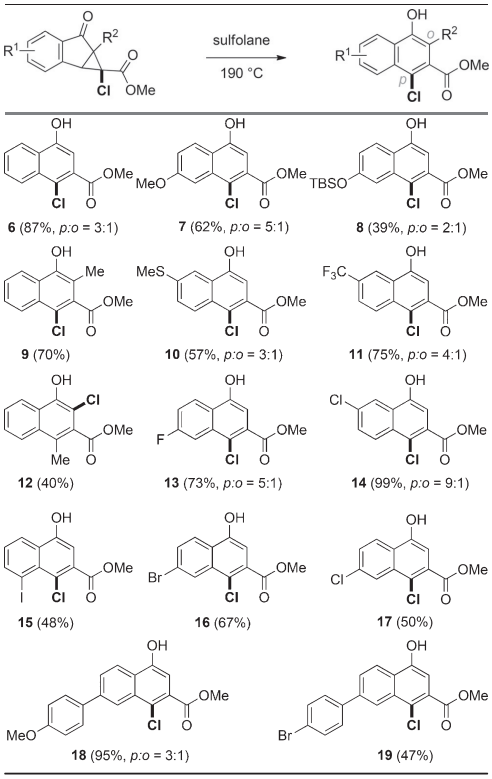
At the outset, we were curious if conditions that were previously developed in our group for the preparation of methyl 3-hydroxybenzoates[12a] could be adapted to this novel substrate class. After a short evaluation of possible reaction conditions, we were pleased to see that the envisaged ring-opening/1,2-migration could be successfully promoted for a panel of compounds upon heating a 0.5 M solution of our substrates in sulfolane at 190 °C (Table 1).

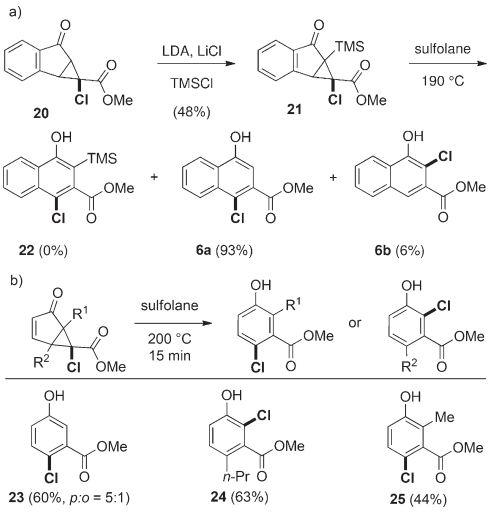
Table 1: Evaluation of substituents in the electrocyclic ring opening to give orthogonally functionalized naphthalenes.[a]



[a] Yield of the isolated product.

At this temperature, the reaction went cleanly to full conversion within less than 30 minutes in most cases. Removal of sulfolane could be best accomplished by repeatedly washing an ethereal (diethyl ether; *tert*-butyl methyl ether) product solution with water. We then investigated the scope of this transformation by varying the substitution pattern of our substrates and evaluated the observed regioselectivity.[15] For the majority of substrates, moderate to high yields were obtained with a strong preference for the formation of the *para*-chloronaphthol substitution pattern. The choice of substituents along the ring junction enabled us to fully direct the migration of the chloride to either the *para*-(compound **9**) or the *ortho*-position (compound **12**). Within this context it is interesting to note that the observed lower yield for **12** might be a result of the inherent substrate preference for the *para*-position. While steric hindrance was expected to affect the regioselectivity to a minor extent, a low degree of delocalization that results in the predominance of the highly stabilized mesomeric resonance structure **B** might account for this observation.

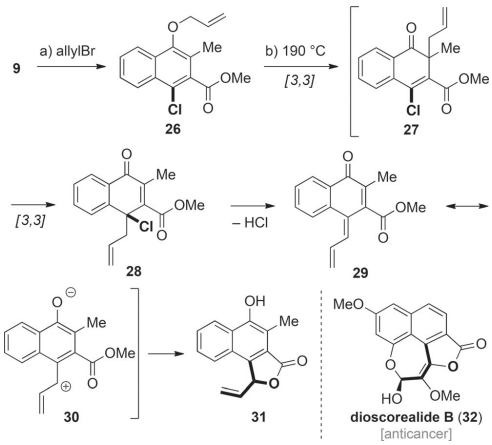
Having established a robust platform for the synthesis of several polyfunctionalized naphthalenes, we evaluated different strategies to further increase the chloride attack at the *para*-position. As illustrated in Scheme 1a, site-selective



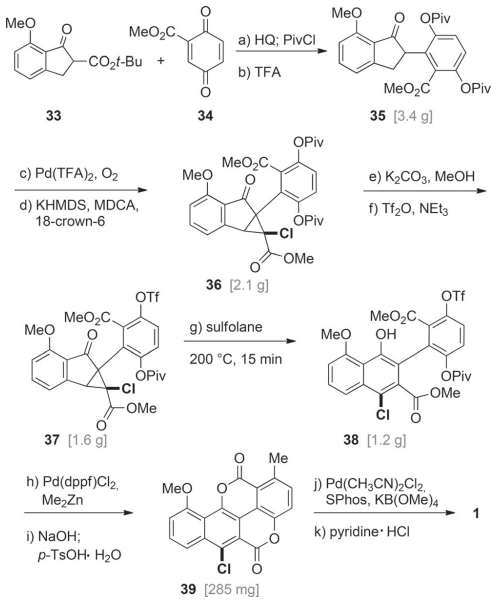
Scheme 1. a) Directed chlorine migration with concomitant carbon-silicon cleavage and b) ring opening of bicyclo[3.1.0]hex-3-en-2-ones to give chlorinated benzoates.

lithiation of the ring opening precursor **20** followed by quenching with trimethylsilyl chloride[16] afforded **21**, which, upon exposure to the standard reaction conditions, was smoothly opened to afford **6a** in excellent yields (93%). This transformation is viewed to proceed via **22**, which undergoes a spontaneous Brook rearrangement at elevated temperatures.[17] The developed transformation was not only limited to bicyclic ring systems, but could also be realized for bicyclo[3.1.0]hex-3-en-2-one substrates as shown in Scheme 1b.

Having synthesized a library of polysubstituted naphthalenes, we wanted to evaluate the selective modification of our products by taking advantage of the orthogonal reactivity of the hydroxy, chloro and ester substituents. We found out that allyl ether **26** could be converted to tricycle **31** via an unprecedented cascade cyclization (Scheme 2). This sequence is initiated by thermal Claisen rearrangement of **26** to **27**, which then reacts in a subsequent Cope rearrangement to the thermally unstable chloride **28**. Elimination of hydrogen



Scheme 2. One-pot functionalization of naphthyl allyl ether **26** through sequential Claisen–Cope lactonization. Reagents and conditions: a) allylBr, K_2CO_3, acetone, 89%, b) sulfolane, *p*-TsOH·H_2O, 190°C, 15 min, 40%. *p*-Ts = *para*-toluenesulfonyl.



Scheme 3. Application of the ring opening protocol to the total synthesis of chartarin (**1**). Reagents and conditions: a) **33** (1 equiv), **34** (1 equiv), HQ (20 mol%), CH_2Cl_2, −20°C; NEt_3, PivCl, 23°C, 70%; b) TFA, CH_2Cl_2, 23°C, 89%; c) $Pd(TFA)_2$ (20 mol%), 4,5-diazafluoren-9-one (20 mol%), O_2 (1 atm), DMSO, 80°C, 67%, 24% **35**; d) KHMDS, MDCA, 18-crown-6 (10 mol%), THF, −78 to 23°C, 75%; e) K_2CO_3, MeOH, 23°C, 74%; f) Tf_2O, NEt_3, CH_2Cl_2, −78°C to 23°C, 98%; g) sulfolane, 200°C, 15 min, 75%; h) $Pd(dppf)Cl_2$, Me_2Zn, 1,4-dioxane, 95°C, 83%; i) NaOH, CH_2Cl_2, MeOH, 23°C; *p*-TsOH·H_2O, toluene, 80°C, 98%; j) $Pd(CH_3CN)_2Cl_2$ (5 mol%), SPhos (8 mol%), $KB(OMe)_4$, 1,4-dioxane, 90°C, 87%; k) pyridine·HCl, 195°C, 69%. dppf = 1,1′-bis(diphenylphosphino)ferrocene, HQ = hydroquinidine, KHMDS = potassium hexamethyldisilazane, MDCA = methyl dichloroacetate, Piv = pivaloyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

chloride generates a *para*-quinone methide structure **29** and its tautomeric form **30**, respectively. Termination of the sequence could be facilitated by capture of residual water to give a benzylic alcohol that undergoes an acid catalyzed (*p*-TsOH·H_2O) lactonization to afford **31**. Since formation of **31** was also observed under anhydrous conditions, a competing pathway that involves direct attack of the ester might be also operative. The realization of this one-pot cyclization method gives rapid access to annulated naphthalene lactones, an important structural motif that is also part of dioscorealide B (**32**).[18]

An additional remarkable feature of the developed ring-expansion reaction is the possibility to design powerful retrosynthetic bond disconnections for the construction of highly substituted, sterically hindered biaryl compounds. The first application of this strategy could be realized in the convergent total synthesis of the potent anticancer natural product chartarin (**1**).[3b] We began our synthesis with the coupling of indanone **33**, derived from commercially available 7-methoxy-1-indanone in one synthetic operation, to the known *para*-quinone **34** (Scheme 3).[19] For the conjugate addition of **33** to **34,** we relied on a previously reported protocol by Jørgensen.[20] Thus, in the presence of catalytic amounts of hydroquinidine (20 mol%), immediate consumption of the equimolar mixture of reactants occurred. Trapping of the formed hydroquinone as its bis-pivalate ester prevented oxidation to the quinone, and subsequent addition of trifluoroacetic acid promoted decarboxylation of the *tert*-butyl ester to afford the 2-arylated indanone **35** in good overall yield on gram scale. Next, oxidation of **36** to the indenone could be accomplished using Stahl's palladium-catalyzed aerobic dehydrogenation conditions.[21] In order to overcome the low reactivity of the 2-substituted indenone in the following cyclopropanation reaction, we had to modify the standard reaction conditions. Replacement of lithium hexamethyldisilazane (LHMDS) by its potassium derivative KHMDS in the presence of 18-crown-6 allowed us to improve the initial low yield of **36** to 75%. Sequential treatment of **36** with methanolic potassium carbonate and then triflic anhydride provided **37**. Having prepared sufficient amounts of the crucial intermediate (1.6 g), we turned our attention to the key-step of the synthesis. Heating a solution of triflate **37** in sulfolane at 200°C for 15 min induced the desired ring opening reaction and led to clean conversion to the biaryl intermediate **38** (75%, 1.2 g). For the installation of the methyl group, a site-selective coupling of the triflate had to be developed. Careful experimentation revealed that, upon exposure of **38** to an excess of dimethyl zinc in the presence of $Pd(dppf)Cl_2$ at 95°C for 1 h, the chloride was left unreacted and exclusive insertion at the triflate occurred.[22]

Lactone formation with loss of the biaryl axis was promoted upon hydrolysis of the remaining pivalate

(NaOH, MeOH) and acid catalyzed (*p*-TsOH·H_2O) ring closure at elevated temperature (toluene, 80 °C) gave **39**. Substitution of the chloride with a hydroxyl group was initially investigated with a model substrate that was lacking the methoxy substituent (see Supporting Information for further details). To our surprise, this seemingly trivial coupling reaction was not successful under a variety of reaction conditions[23] and, in most cases, only dehalogenation of the starting material was observed. Fortunately, when a solution of the more electron rich naphthalene **39** in 1,4-dioxane (0.05 M) was exposed to potassium tetramethoxyborate in the presence of bis(acetonitrile)dichloropalladium(II) (5 mol%) and SPhos (8 mol%) at 90 °C for 3 h, efficient incorporation of the desired methoxy group occurred (87%).[24] For the completion of the synthesis, simultaneous removal of both methyl substituents was accomplished by treatment of **39** with pyridine hydrochloride at elevated temperature (195 °C) for 16 h. Chartarin (**1**) crystallized from methanol as a yellow-brownish powder whose spectroscopic data (^{1}H and ^{13}C NMR, mp, HRMS) were in full agreement with those reported for the naturally occurring substance.[3b,25]

In conclusion, we have developed an efficient and practical ring opening/1,2-migration transformation for the synthesis of orthogonally functionalized naphthalenes. The reaction is operationally simple, does not require any additives, occurs in a regioselective manner with a strong preference for the *para*-chloronaphthol substitution pattern and enables novel, powerful retrosynthetic bond disconnections. A translation of this method to natural product synthesis was realized for the preparation of the potent anticancer agent chartarin (**1**). The developed route can be conducted on gram scale, provides efficient access to the highly substituted, polycyclic carbon framework and enables rapid diversification by standard transformations. Further applications of this concept in the synthesis of complex naphthalene containing molecules are currently underway in our laboratories.

Acknowledgements

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Keywords: arenes · naphthalenes · natural products · ring expansion · total synthesis

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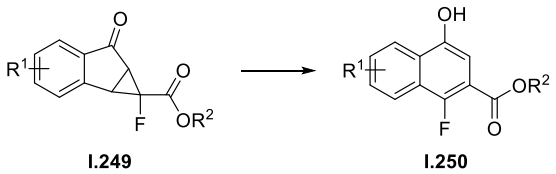
2.2 Synthesis of Fluorinated Naphthols

The selective synthesis of fluorinated naphthols from non-halogenated precursors is a demanding challenge. In recent years, many new processes for the introduction of fluorine atoms into aromatic molecules have been developed. However, established strategies often require the use of expensive transition metals or harsh conditions. The reactions often lack regiocontrol or rely on multistep sequences. As part of our ring-expansion strategy for the synthesis of halogenated phenols and naphthols, we envisioned to the application of the method for the preparation of fluorinated naphthols (Scheme 43).



I.249 **I.250**

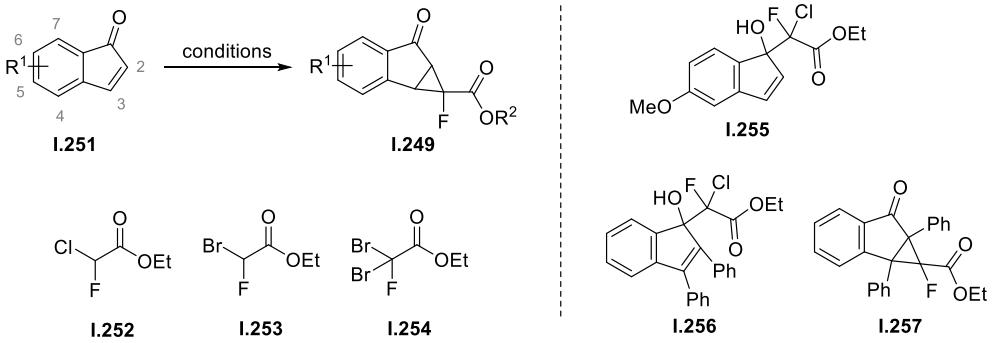
Scheme 43. Synthesis of fluorinated naphthols from cyclopropanated indanones.

2.2.1 Cyclopropanation of Indenones

The first goal for the development of a protocol for the synthesis of fluorinated naphthols was the preparation of the fluorinated cyclopropane. Few methods are known to produce such cyclopropanes, [112] and they have not been applied to indenones. At the beginning of this project, we envisioned to apply the conditions used previously for the synthesis of chlorinated cyclopropanes, replacing the common methyl dichloroacetate (MDCA) with commercially available fluorinated derivatives: ethyl chlorofluoroacetate (**I.252**), ethyl bromofluoroacetate (**I.253**) and ethyl dibromofluoroacetate (**I.254**). The examined conditions for the cyclopropanation of indenones are summarized in Table 6.

Initially, following the standard procedure for the synthesis of the cyclopropane derivatives, 5-methoxy-indenone, prepared via bromination and elimination from 5-methoxy-indanone, was reacted with lithium bis(trimethylsilyl)amide (LHMDS) and ethyl chlorofluoroacetate (**I.252**), but the desired product could not be obtained (Table 6, entry 1). Surprisingly, a 1,2-addition occurred to give **I.255** in only 6% yield. This transformation was not observed when methyl dichloroacetate was used. Additionally, the indenone polymerized under the reaction conditions which accounted for the low yield. For further studies, we employed 2,3-diphenyl-indenone due to higher stability and commercially availability. When 2,3-diphenyl-indenone was used, the 1,2-addition product **I.256** was obtained in excellent yield (89%) (Table 6, entry 2). With HMPA as additive,[113] the desired cyclopropane **I.257** could be obtained for the first time in 11% yield (Table 6, entry 3). Employing an excess of reagent and base, the yield could be improved to 29% (Table 6, entry 4). The influence of other additives which could promote the 1,4-addition was briefly investigated next. While no product formation was observed with copper iodide (CuI, Table 6, entry 5),[114] the use of to zinc bromide ($ZnBr_2$, Table 6, entry 6) or lithium chloride (LiCl, Table 6, entry 7) afforded only traces of the 1,2-adduct.

Table 6. Examined conditions for the cyclopropanation of indenones with **I.256**, **I.257** and **I.258**.



entry	R^1	nucleophile	reagents	additive	solvent, temperature	result
1	5-OMe	**I.252**	LHMDS	-	THF, −78 °C to 23 °C	**I.255** (6%)
2	2,3-Ph	**I.252**	LHMDS	-	THF, −78 °C to 23 °C	**I.256** (89%)
3	2,3-Ph	**I.252**	LHMDS	HMPA	THF, −78 °C to 23 °C	**I.257** (11%)
4[b]	2,3-Ph	**I.252**	LHMDS	HMPA	THF, −78 °C to 23 °C	**I.257** (29%)
5	2,3-Ph	**I.252**	LHMDS	CuI	THF, −78 °C to 23 °C	starting material
6	2,3-Ph	**I.252**	LHMDS	$ZnBr_2$	THF, −78 °C to 23 °C	traces of **I.256**
7	2,3-Ph	**I.252**	LDA	LiCl	THF, −78 °C to 23 °C	traces of **I.256**
8	2,3-Ph	**I.252**	LDA	LiCl, HMPA	THF, −78 °C to 23 °C	**I.257** (24%)
9	2,3-Ph	**I.252**	KHMDS	18-crown-6	THF, −78 °C to 23 °C	decomposition
10	2,3-Ph	**I.252**	NaH	-	THF, 23 °C	complex mixture
11	2,3-Ph	**I.252**	NaH	-	DMF, 23 °C to 50 °C	starting material
12	2,3-Ph	**I.252**	Cs_2CO_3	-	DMF, 23 °C to 50 °C	starting material
13	2,3-Ph	**I.252**	TMPZnCl·LiCl	-	THF, 0 °C to 23 °C	starting material
14[b]	5-OMe	**I.252**	LHMDS	HMPA	THF, −78 °C to 23 °C	polymerization of the indenone
15	5-F	**I.253**	LHMDS	-	THF, −78 °C to 23 °C	-[c]
16[d]	5-OMe	**I.254**	1) Zn	TESCl	MeCN, 23 °C	complex mixture
			2) DBU	-	DMF, 23 °C	
17[e]	H	**I.254**	1) Zn	TESCl	MeCN, 23 °C	complex mixture
18[f]	2,3-Ph	**I.254**	Zn	LiCl	THF, DMSO, 0 °C	Traces of 1,4-adduct
19[f]	H	**I.254**	Zn	LiCl	THF, DMSO, 0 °C	polymerization of the indenone

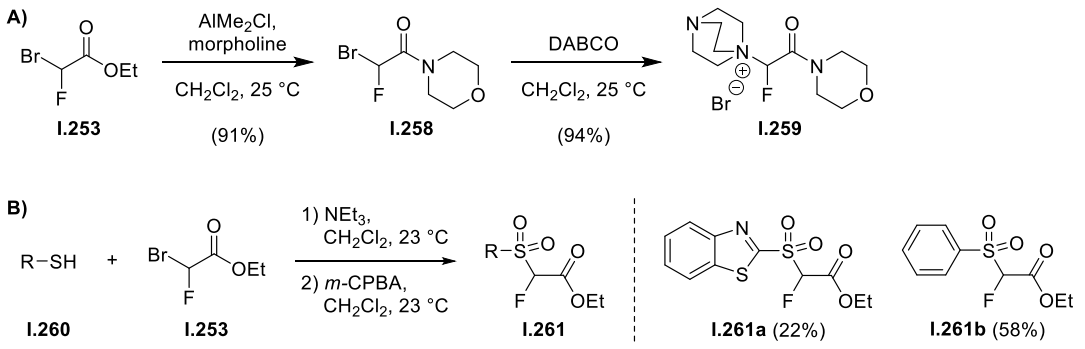
[a] The reactions were performed using 1.1 equivalents of reagent. [b] 3 Equivalents of reagent A were used. [c] No conversion was observed and the starting material decomposed over time. [d] The reactions were performed using Zn (2.0 equiv), TESCl (2.2 equiv) and reagent **I.254** (2.5 equiv). [e] The reactions were performed using Zn (6.0 equiv), TESCl (6.6 equiv) and reagent **I.254** (7.5 equiv). [f] The reactions were performed using Zn (3.0 equiv), LiCl (3.0 equiv) and reagent **I.254** (2.0 equiv).

Additionally, employing LDA as base together with HMPA and LiCl also did not improve the reaction outcome and the general problem of low conversion remained (Table 6, entry 8). Furthermore, extensive screening using other bases failed to provide the desired cyclopropane in good yield. We either observed

decomposition of the substrate (KHMDS/18-crown-6, Table 6, entry 9), the formation of a complex product mixture (NaH in THF, Table 6, entry 10) or no consumption of the starting material (NaH in DMF, Cs_2CO_3, TMPZnCl·LiCl, Table 6, entries 11–13). When the optimized conditions (LHMDS (3 equiv.), HMPA (3 equiv.), THF, −78 °C to 23 °C) were applied to 5-methoxy-indanone, only polymerization of the indenone was observed under the reaction conditions (Table 6, entry 14). Furthermore, the use of ethyl bromofluoroacetate (**I.253**) as nucleophile was also met with failure (Table 6, entry 15).

As a conclusion, the attempt to adapt the developed conditions for the chloro-cyclopropanation or modification thereof for the synthesis of fluoro-cyclopropanes was not effective. Although no protocol for the synthesis of fluorocyclopropanated indanones is reported in the literature, a couple of different methods have been described for the preparation of fluoro-cyclopropanes. In 2002, Nakazato et al. reported a method for the cyclopropanation of cyclopentenone.[115] This procedure involved the reaction of zinc, activated by triethylsilyl chloride (TESCl), with ethyl dibromofluoroacetate (**I.254**) to form the corresponding zinc enolate, which attacks cyclopentenone to form the 1,4-adduct. Closure of the 3-membered ring was achieved by using DBU. With 5-methoxyindenone or unsubstituted indenone, the reaction of the zinc enolate resulted in a complex and inseparable mixture of the 1,4-adduct and cyclized product in low yields (Table 6, entries 16–17). The attempt to close the cyclopropane ring resulted in the *exo*-elimination product. When the reaction was conducted with the more stable 2,3-diphenyl-indenone in a mixture of tetrahydrofuran (THF) and DMSO with LiCl to activate the zinc, only traces of the corresponding 1,4-adduct were obtained (Table 6, entry 18). Furthermore, the unsubstituted indenone polymerized under these conditions (Table 6, entry 19) and the use of degassed THF or the addition of hydroquinone did not prevent this side reaction.

So far, no general method for the synthesis of fluorinated cyclopropanes using the commercially available halogenated acetates could be established. Therefore, we focused on the synthesis of different nucleophiles. A search in the literature revealed a method for the cyclopropanation by the group of Pannecoucke.[112e] They describe the cyclopropanation of linear enones using 1,4-diazabicyclo[2.2.2]octane (DABCO) salt **I.259** and cesium carbonate (Cs_2CO_3). **I.259** was prepared from ethyl bromofluoroacetate (**I.253**) by converting it to the morpholine amide **I.258** followed by reaction with DABCO (Scheme 44A).

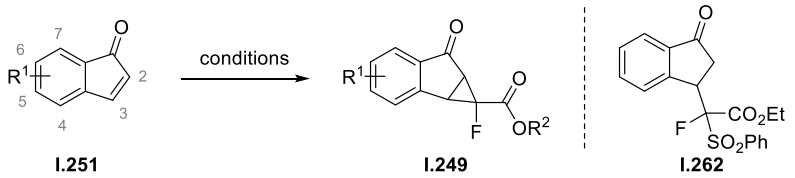


Scheme 44. Synthesis of cyclopropanation reagents DABCO salt **I.259**, sulfone **I.261a** and sulfone **I.261b**.

In addition, two new cyclopropanation reagents containing a fluorine substituent were synthesized (Scheme 44B). Addition of a sulfide **I.260** to ethyl bromofluoroacetate (**I.253**) gave the corresponding thioether which was oxidized using *meta*-chloroperbenzoic acid (*m*-CPBA) to give sulfone **I.261a** in 22% yield and sulfone **I.261b** in 58% yield.[116]

With these three new cyclopropanation reagents in hand, we set out to examine conditions for the cyclopropanation of indenones. The applied conditions are depicted in Table 7.

Table 7. Examined conditions for the cyclopropanation of indenones with **I.259**, **I.261a** or **I.261b**.



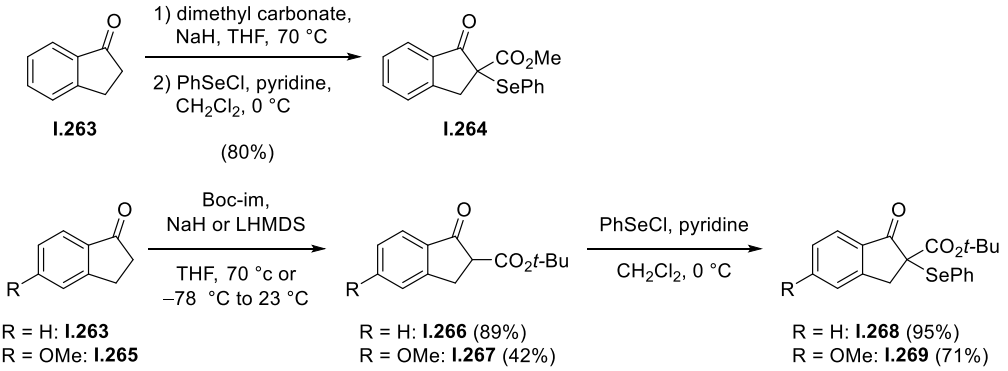
entry	R	nucleophile	base	additive	solvent, temperature	result
1	H	**I.259**	Cs_2CO_3	-	1,4-dioxane, 50 °C	starting material
2	2,3-Ph	**I.259**	Cs_2CO_3	-	1,4-dioxane, 50 °C	starting material
3	2,3-Ph	**I.259**	Cs_2CO_3	-	MeCN, 80 °C	starting material
4	2,3-Ph	**I.259**	Cs_2CO_3	$BF_3{\cdot}OEt_2$	MeCN, 80 °C	starting material
5	H	**I.261a**	hydroquinidine	-	1,4-dioxane, 23 °C	-[a)]
6	2,3-Ph	**I.261a**	hydroquinidine	-	1,4-dioxane, 23 °C	starting material
7	2,3-Ph	**I.261a**	NaH	-	toluene, 0 °C to 23 °C	decomposition
8	H	**I.261b**	NaH		THF, 0 °C to 23 °C	decomposition
9	H	**I.261b**	LHMDS	HMPA	THF, 0 °C to 23 °C	**I.262** (7%)

[a)] No conversion was observed and the starting material decomposed over time.

First, the reaction with the DABCO salt **I.259** was screened. Unfortunately, a combination of **I.259** with Cs_2CO_3 did not react with unsubstituted indenone or 2,3-diphenyl-indenone in 1,4-dioxane at 50 °C or MeCN at 80 °C. The addition of boron trifluoride etherate to activate the enone did not improve the reaction (Table 7, entries 1–4). When sulfone **I.261a** was used as cyclopropanation reagent together with hydroquinidine as base, no reaction was detected with the unsubstituted indenone and 2,3-diphenyl-indenone (Table 7, entries 5–6). Switching to sodium hydride (NaH) as base resulted in the decomposition of the starting material (Table 7, entry 7). The same result was observed with sulfone **I.261b** (Table 7, entry 8). Finally, the 1,4-adduct **I.262** was observed in 7% yield when unsubstituted indenone was treated with sulfone **I.261b**, LHMDS as base and HMPA as additive. Unfortunately, the yield of this reaction could not be improved and the attempt to prepare the cyclopropane with DBU resulted in the formation of the *exo*-double bond.

Given the difficulties associated with the 1,4-addition of nucleophiles to indenones, we decided to increase the reactivity of the enone system by the introduction of an electron-withdrawing group at the C2-position of the indenone. The corresponding α-ester was prepared with NaH and dimethyl carbonate in THF at

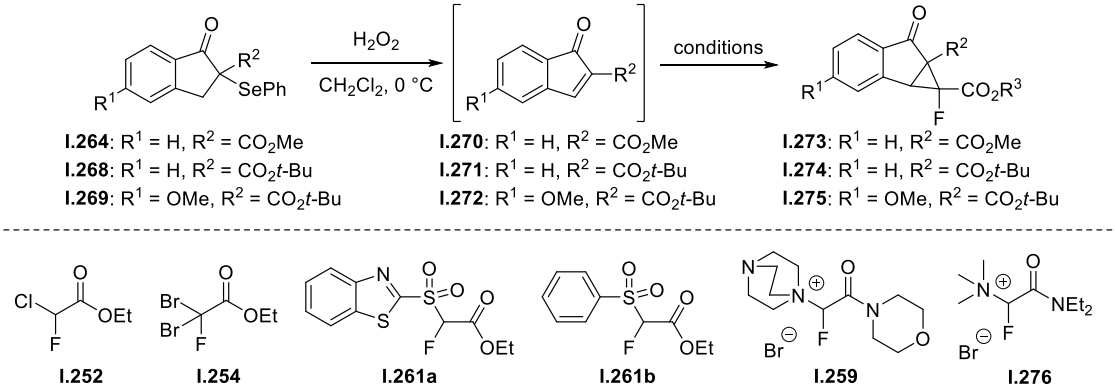
50 °C or NaH and Boc-imidazol in THF at 70 °C and the introduction of a phenylselenide moiety was achieved using phenylselenyl chloride and pyridine in dichloromethane (CH_2Cl_2) at 0 °C (Scheme 45).

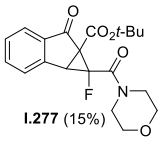
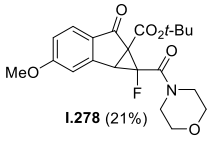


Scheme 45. Synthesis of α-selenides **I.264**, **I.268** and **I.269**.

The C2-substituted indenones were prepared from the corresponding α-selenides **I.264**, **I.268** and **I.269** via oxidative elimination. The applied conditions for the cyclopropanation are shown in Table 8.

Table 8. Conditions for the cyclopropanation of C2-substituted indenones.

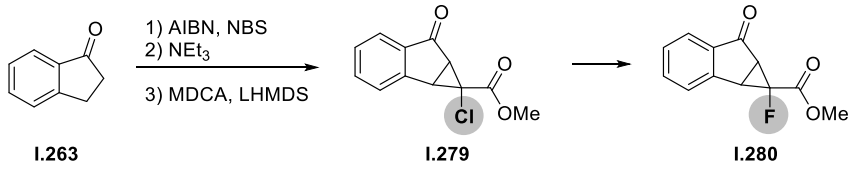


entry	substrate	nucleophile	reagent	additive	solvent, temperature	result
1	**I.270**	**I.252**	LHMDS	-	THF, −78 °C to 23°C	decomposition
2	**I.270**	**I.254**	Zn	TESCl	MeCN, −20 °C to 23 °C	decomposition
3	**I.270**	**I.261a**	LHMDS	HMPA	THF, −78 °C to 23°C	decomposition
4	**I.270**	**I.261b**	LHMDS	HMPA	THF, −78 °C to 23°C	decomposition
5	**I.271**	**I.259**	Cs_2CO_3	-	1,4-dioxane, 50 °C	 **I.277** (15%)
6	**I.272**	**I.259**	Cs_2CO_3	-	1,4-dioxane, 50 °C	 **I.278** (21%)
7	**I.272**	**I.276**	Cs_2CO_3	-	1,4-dioxane, 50 °C	decomposition

At the outset, the cyclopropanation of **I.270** was investigated with various previously described nucleophiles. Unfortunately, the employment of ethyl chlorofluoroacetate (**I.252**), ethyl dibromofluoroacetate (**I.254**), sulfone **I.261a** and sulfone **I.261b** resulted only in decomposition of the starting material (Table 8, entries 1–4). When the reaction was investigated with the DABCO salt **I.259** and Cs_2CO_3 the corresponding cyclopropanes **I.277** and **I.278** were obtained in 15% and 21 % yield respectively (Table 8, entries 5–6). Interestingly, the use of a similar triethylamine salt **I.276** again led to decomposition of the starting material (Table 8, entry 7).

2.2.2 Halogen Exchange Reactions

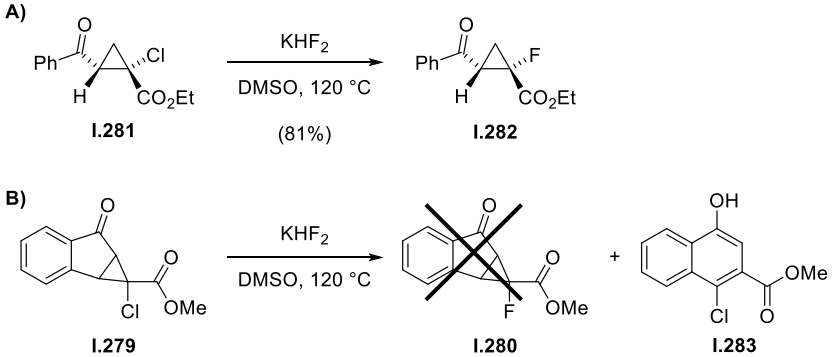
The aim to establish a general strategy for the synthesis of fluorinated cyclopropanes was not achieved by the cyclopropanation of indenones with an appropriate fluoride-containing nucleophile. Therefore, we revised our strategy and attempted a halogen exchange reaction for the introduction of the fluoride substituent (Scheme 46). This would allow us to utilize the previously described chlorinated cyclopropanes which could be synthesized efficiently from the corresponding indanones.



I.263 I.279 I.280

Scheme 46. Envisioned synthesis of fluorinated cyclopropanes via a halogen exchange reaction.

Zhang et al.[112f] reported a chlorine–fluorine exchange reaction on cyclopropyl derivatives. Upon exposure to potassium bifluoride (KHF_2) in DMSO at 120 °C, the fluorinated cyclopropane **I.282** could be generated efficiently (Scheme 47A). Adopting this process, cyclopropane **I.279** was treated with KHF_2, but in our hand, aromatization occurred and the chlorinated naphthol **I.283** was obtained (Scheme 47B). The reason for this reaction pathway might be the fused ring system of **I.279**. This structural feature prevents the formation of a cyclopropene intermediate, which was postulated in the reported mechanism.

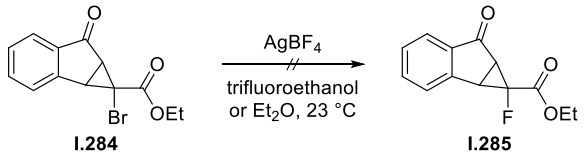


I.281 I.282

I.279 I.280 I.283

Scheme 47. A) Chlorine–fluorine exchange on cyclopropanes. B) Attempted chlorine–fluorine exchange on cyclopropanated indanones.

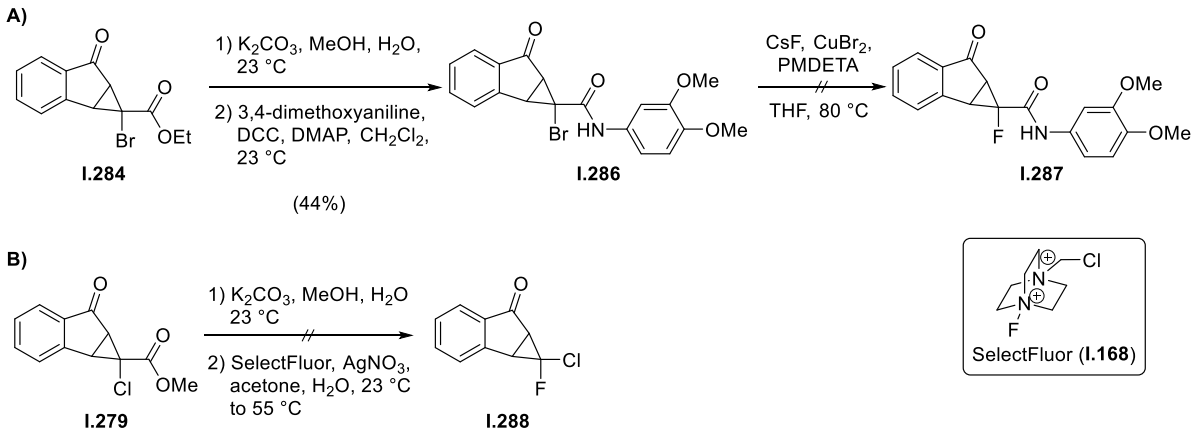
In addition to the fluorination of the chloro-cyclopropane, the corresponding brominated substrate was also investigated. We supposed that the bromide is a better leaving group than the chloride and therefore, milder conditions could be employed. Thus, bromo-cyclopropane **I.284** was exposed to silver tetrafluoroborate ($AgBF_4$) in trifluoroethanol or diethyl ether (Et_2O), but no conversion was observed and only the starting material could be recovered (Scheme 48).



Scheme 48. Attempted bromine–fluorine exchange.

In 2016, Nishikata et al. reported a method for the selective formation of tertiary fluorides from α-bromoamides.[117] They could efficiently convert various α-bromoamides into the corresponding fluorides with CsF catalyzed by copper bromide (CuBr) and *N*,*N*,*N*',*N*",*N*"-pentamethyldiethylene-triamine (PMDETA) in THF at 80 °C. To employ this methodology, amide **I.286** was prepared from **I.284** in 44% yield in two steps via saponification with potassium carbonate (K_2CO_3) followed by an amide coupling with 3,4-dimethoxyaniline in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)-pyridine (DMAP) (Scheme 49A). In our hand, the fluorination reaction of **I.286** resulted in decomposition of the starting material, presumably due to the fused cyclopropane structure. Additionally, we treated ethyl ester **I.284** with the same conditions, but only the starting material and traces of the dehalogenated naphthol were observed.

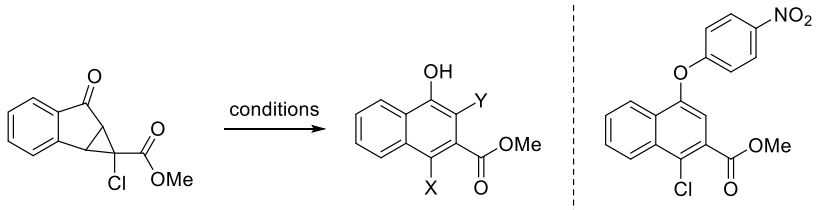
Finally, we tried to employ a decarboxylative fluorination, which was reported to smoothly furnish aliphatic fluorides by the treatment of carboxylic acids with SelectFluor (**I.168**) and a catalytic amount of silver nitrate ($AgNO_3$).[98b] Applying these conditions to our system, no conversion was observed at 23 °C and decomposition occurred at 55 °C (Scheme 49B).



Scheme 49. Attempts for the introduction of a fluoride substituent. PMDETA = *N*,*N*,*N*',*N*",*N*"-pentamethyldiethylenetriamine.

The observation of the aromatization during the attempted halogen exchange led to the idea of performing the halogen exchange during the aromatization reaction. Therefore, various fluoride sources, reported for halogen exchange reactions, were investigated. The results for the one-pot halogen exchange/aromatization reaction are summarized in Table 9.

Table 9. Examined conditions for the one pot halogen exchange/aromatization reaction.



I.279 | **I.283** (X = Cl, Y = H), **I.289** (X = H, Y = Cl), **I.290** (X = F, Y = H), **I.291** (X, Y = H) | **I.292**

entry	fluoride source	Additive	conditions	result
1	AgF	-	sulfolane, 190 °C	**I.283**[a)]
2	AgF	-	sulfolane, 140 °C	decomposition
3	TBAF	-	sulfolane, 140 °C	decomposition
4	KF	Ph_4PBr	DMSO, 170 °C	decomposition
5	KF	Ph_4PBr	sulfolane, 170 °C	**I.291**[a)]
6	KF	Ph_4PBr, 1-fluoro-4-nitrobenzene	sulfolane, 170 °C	**I.292** (62%)
7	-	Ph_4PBr, 1-fluoro-4-nitrobenzene	sulfolane, 170 °C	decomposition
8	KF	Ph_4PBr, nitrobenzene	sulfolane, 170 °C	**I.283**, **I.289**, **I.291**[a)]

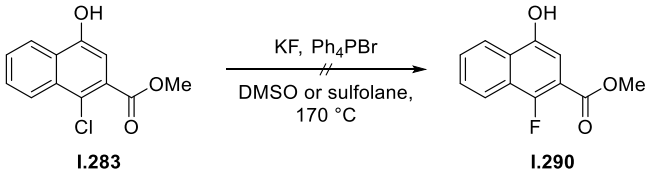
[a)] The reaction was monitored by thin layer chromatography (TLC).

Thus, silver fluoride (AgF) was added and the reaction mixture was heated to 190 °C in sulfolane for 30 min. The analysis of the product showed that the chloro-naphthol **I.283** was obtained and no traces of the fluoro-naphthol **I.290** were observed (Table 9, entry 1). A slow reaction rate for the introduction of fluoride and a fast reaction rate for the aromatization might be the reason. To investigate this assumption, the reaction was performed at 140 °C with a prolonged reaction time to decelerate the aromatization reaction (Table 9, entry 2). But only decomposition was observed. The same result was obtained with TBAF as fluoride source (Table 9, entry 3).

In the literature, potassium fluoride (KF) in combination with the phase-transfer catalyst tetraphenylphosphonium bromide (Ph_4PBr) is reported to convert aromatic halides into aromatic fluorides (the so-called halex reaction).[118] Following this reported procedure, a mixture of cyclopropane **I.279**, KF and Ph_4PBr in DMSO was heated to 170 °C for 2 h, but only decomposition was observed (Table 9, entry 4). Switching the solvent to sulfolane resulted in the formation of the dehalogenated product **I.291** (Table 9, entry 5). The addition of a radical scavenger (*e.g.* 1-fluoro-4-nitrobenzene to inhibit the dehalogenation did not provide the desired fluorinated naphthol. Instead a nucleophilic aromatic

substitution occurred to give **I.292** in 62% yield (Table 9, entry 6). A control experiment with Ph_4PBr/1-fluoro-4-nitrobenzene (Table 9, entry 7) showed that KF induces the nucleophilic aromatic substitution. Using nitrobenzene as radical scavenger to prevent the substitution reaction was not successful and only the chlorinated naphthol **I.283**, as well as the *ortho*-chloro-naphthol **I.289** and the dehalogenated naphthol **I.291** were obtained (Table 9, entry 8).

To check whether the halex reaction would work for our substrates, the reported conditions were used for the conversion of chloro-naphthol **I.283** to fluoro-naphthol **I.290**. Using KF and Ph_4PBr in DMSO led to decomposition, and performing the reaction in sulfolane afforded only the dehalogenated product (Scheme 50).

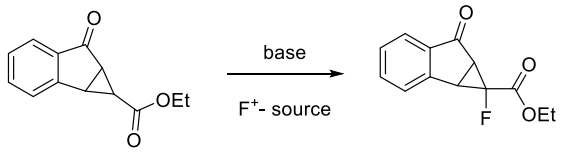


I.283 **I.290**

Scheme 50. Halex reaction of chloro-naphthol **I.283**.

2.2.3 Direct Fluorination of Cyclopropanes

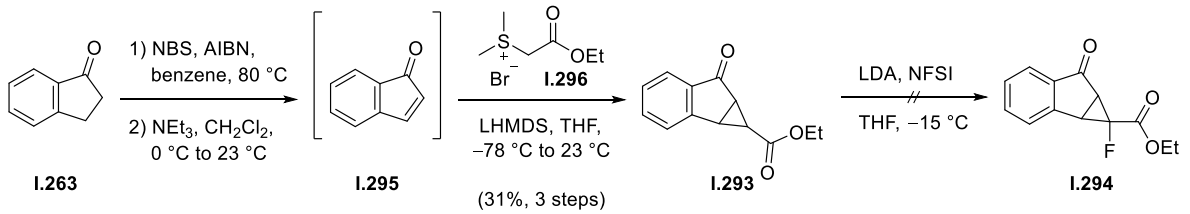
As a result of the difficulties in developing a synthesis of fluorinated cyclopropanes through direct cyclopropanation or a chloride–fluoride exchange reaction, we aimed for the electrophilic fluorination of cyclopropyl anions (Scheme 51).



I.293 **I.294**

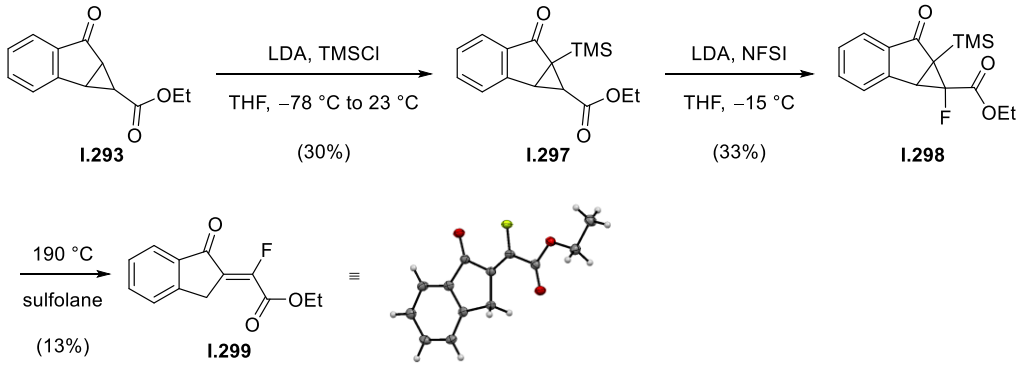
Scheme 51. Envisioned fluorination of mono-substituted cyclopropanated indanones.

The non-halogenated cyclopropane **I.293** was prepared from 1-indanone (**I.263**) in three steps. First, benzylic bromination was achieved using *N*-bromosuccinimide (NBS) and 2,2'-azobis(2-methylpropionitrile) (AIBN) in benzene at 80 °C. Elimination with NEt_3 in CH_2Cl_2 afforded the enone **I.295**, which was treated with LHMDS and sulfonium salt **I.296** (prepared in 1 step from ethyl bromoacetate in 72% yield) as cyclopropanation agent[119] to afford **I.293** in 31% yield over three steps. Unfortunately, the fluorination could not be accomplished using LDA and NFSI as fluorinating reagent (Scheme 52). Presumably, the concomitant generation of a carbanion at the α-position of the ketone led to decomposition of the starting material.



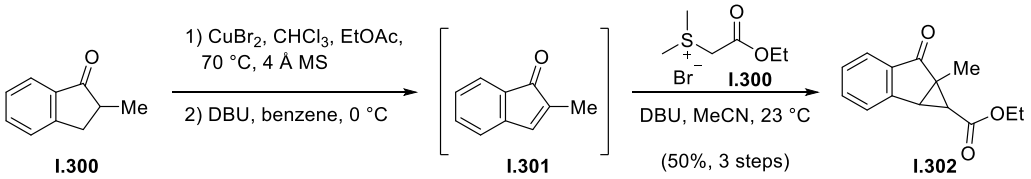
Scheme 52. Cyclopropanation of 1-indanone (**I.263**) with sulfonium salt **I.296** and attempted fluorination of **I.293**.

To block this position, we introduced a trimethylsilyl (TMS) group at the α-position of the ketone. This remarkable reaction was achieved by a slow addition of LDA to a premixed solution of **I.293** and an excess of TMSCl in THF at −78 °C and **I.297** was obtained in 30% yield (Scheme 53). The generated anion is supposed to be very unstable because ring strain prevents the resonance stabilization. Therefore, it is essential to directly trap the anion with an excess of the electrophile. Finally, fluorination was successful employing LDA and NFSI at −15 °C in THF. However, the product **I.298** was obtained in moderate yield and could not be purified using flash column chromatography. Nevertheless, **I.298** was subjected to fragmentation conditions (190 °C, sulfolane). The cyclopropane did not open to form a six-membered ring, however, the formation of an *exo*-double bond was observed. The structure of **I.299** was unambiguously confirmed by single-crystal X-ray diffraction.



Scheme 53. Synthesis and fragmentation of fluoro derivative **I.298**.

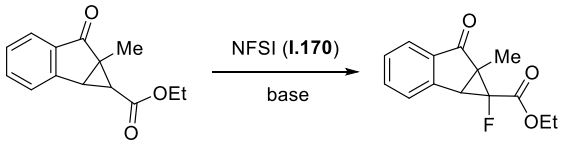
We speculated that the TMS group directed the undesired bond cleavage which led to the formation of **I.299**. Therefore, substrate **I.302** was synthesized, bearing a methyl substituent at the α-position. Starting from 2-methyl-1-indanone (**I.300**), α-bromination was conducted with copper(II) bromide[120] and subsequent elimination with DBU[121] gave indenone **I.301**. The cyclopropanation was accomplished using sulfonium salt **I.296**. Thereby, cyclopropane **I.302** was obtained 50% yield in 3 steps (Scheme 54).



Scheme 54. Synthesis of methyl substituted cyclopropane **I.302**.

Substrate **I.302** was used to investigate the fluorination at the α-position next to the ester. The conditions are summarized in Table 10.

Table 10. Examined fluorination of **I.302**.



I.302 **I.303**

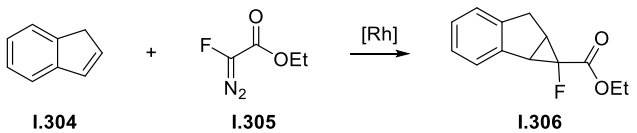
entry	base	conditions	result
1	LDA	THF, −78 °C to 23 °C	decomposition
2	LDA[a)]	THF, −100 °C to 23 °C	decomposition
3	TMPZnCl·LiCl	THF, 0 °C to 23 °C	starting material

[a)] LDA was added dropwise to a mixture of NFSI (**I.170**) and substrate (**I.302**).

Neither the deprotonation of **I.302** with LDA and subsequent treatment with NFSI (**I.170**) nor the reverse addition of LDA to a mixture of NFSI (**I.170**) and **I.302** (Table 10, entries 1–2) led to product formation. Instead, decomposition of the starting material occurred. Using TMPZnCl·LiCl as base, no conversion was observed and the starting material could be recovered (Table 10, entry 3). Additionally, the electrophilic fluorination was investigated under flow conditions,[122] but no improvement was achieved.

2.2.4 Rhodium-Catalyzed Cyclopropanations

A common way to synthesis cyclopropanes is the rhodium-catalyzed cyclopropanation of simple double bonds. However, indenone substrates are rare.[37,38,123] Therefore, we planned to cyclopropanate indene (**I.304**) and its derivatives, which should be oxidized at the benzylic position thereafter (Scheme 55).

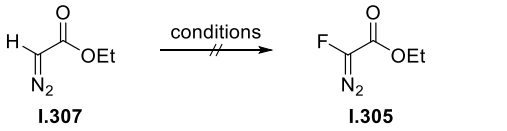


I.304 **I.305** **I.306**

Scheme 55. Envisioned Rh-catalyzed cyclopropanation of indene (**I.304**) with ethyl diazofluoroacetate (**I.305**).

The first key target for the aimed synthesis of fluorinated cyclopropanes was the preparation of ethyl diazofluoroacetate (**I.305**). Ethyl diazofluoroacetate (**I.305**) has never been synthesized, although the chlorinated and brominated variants are known. The group of Hansen described the synthesis of ethyl diazochloroacetate and ethyl diazobromoacetate from commercially available ethyl fluoroacetate (**I.307**), though the fluorination has not been reported.[124] In accordance to their preparation, we envisioned the preparation of ethyl diazofluoroacetate by deprotonation of ethyl diazoacetate with an appropriate base

and subsequent trapping of the generated anion by an electrophilic fluorinating reagent. But in our hand, analysis of the crude reaction mixture revealed that no product was formed in the reaction of **I.307** with DBU and NFSI (**I.170**) in dichloromethane or with DABCO and SelectFluor (**I.168**) (Scheme 56).



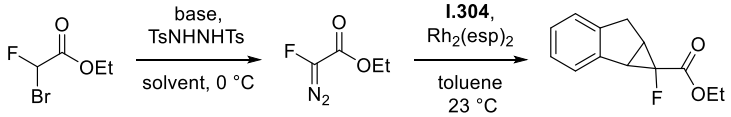
I.307 **I.305**

conditions: a) DBU, NFSI (**I.171**), CH_2Cl_2, 0 °C
b) DABCO, SelectFluor (**I.169**), MeCN, 0 °C

Scheme 56. Attempted synthesis of ethyl diazofluoroacetate (**I.305**).

Further efforts focused on the preparation of **I.305** from different fluoroacetates through introduction of the diazo moiety. Thus, the reaction of ethyl bromofluoroacetate (**I.253**) and *N,N*-ditosylhydrazine (TsNHNHTs) was briefly investigated. Due to the supposed instability of **I.305**, the rhodium-catalyzed cyclopropanation was pursued directly afterwards. The tested conditions are summarized in Table 11.

Table 11. Conditions for the synthesis of diazo compound **I.305** and their use in the rhodium catalyzed cyclopropanation.



I.253 **I.305** **I.306**

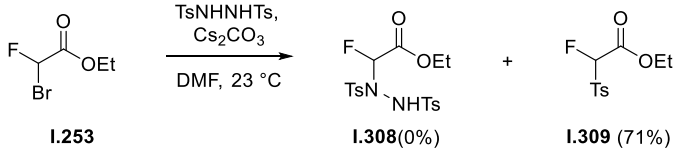
entry	base	solvent	work-up	result
1	DBU	THF	aqueous	traces of **I.306**
2	DBU	THF	filtration	no product
3[a)]	DBU	THF-d_8	-	traces of **I.305** visible in the ^{1}H NMR spectrum
4	DBU	toluene	-	no product
5	DBU	CH_2Cl_2	-	no product
6	DBU	CH_2Cl_2	aqueous	no product
7	DBU	MeCN	filtration	no product
8	TMG	THF	filtration	no product
9	NaH	THF	-	decomposition of **I.253**

[a)] NMR experiment; TMG = 1,1,3,3-tetramethylguanidine

The reaction of ethyl bromofluoroacetate (**I.253**) with *N,N*-ditosylhydrazine and DBU followed by an aqueous workup and subsequent cyclopropanation of 1-*H*-indene with bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$) gave only traces of **I.306** (Table 11, entry 1). We assumed that **I.305** might not tolerate an aqueous workup. Therefore, the crude reaction mixture was filtered through a celite plug before its use in the cyclopropanation reaction, but the desired product was not obtained (Table 11, entry 2). To further investigate this reaction, the experiment was conducted in deuterated THF and was monitored by ^{1}H NMR spectroscopy (Table 11, entry 3). The NMR analysis showed the

formation of the desired diazo compound as minor product together with two other unidentified products. To improve the reaction outcome, different solvents like toluene, CH_2Cl_2 and MeCN, were tested, but no cyclopropane formation was observed (Table 11, entries 4–7). Changing the base to 1,1,3,3-tetramethylguanidine (TMG) or NaH did not improve the reaction (Table 11, entries 8–9).

Due to these disappointing results, we choose to use a two-step procedure for the diazo formation, addition of *N*,*N*-ditosylhydrazine followed by base-induced diazo formation. But the addition reaction with Cs_2CO_3 in DMF at 23 °C did not furnish the addition product **I.308**. Instead, after nitrogen elimination,[125] the tosyl anion could attack acetate **I.253** to give adduct **I.309**. Similar results were obtained with K_2CO_3 or DBU as bases (Scheme 57).

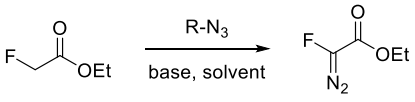


I.253 **I.308**(0%) **I.309** (71%)

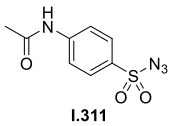
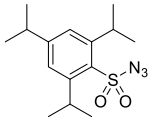
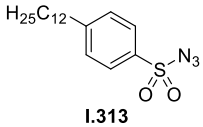
Scheme 57. Addition reaction *N*,*N*-ditosylhydrazine to **I.253**.

We then set out to examine various diazo-transfer reagents to achieve the synthesis of **I.305** from ethyl fluoroacetate (**I.310**). The examined conditions are shown in Table 12.

Table 12. Reaction of ethyl fluoroacetate (**I.310**) with diazo transfer reagents.



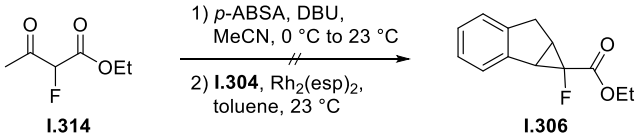
I.310 **I.305**

entry	R-N_3	base	solvents	result
1	Tf-N_3	pyridine	MeCN, CH_2Cl_2, 0 °C	no product
2	 **I.311**	DBU	MeCN, 23 °C	no product
3	 **I.312**	DBU	MeCN, 23 °C	no product
4	 **I.313**	DBU	MeCN, 23 °C	6% conversion

Different azides were tested in the diazo transfer reactions. First, triflic azide (Tf-N_3) was reacted with ethyl fluoroacetate (**I.310**) in the presence of pyridine in MeCN at 23 °C, but no product was observed by ^{1}H NMR spectroscopy (Table 12, entry 1). The same result was obtained when

4-acetamidobenzenesulfonyl azide (*p*-ABSA, **I.311**) or 2,4,6-triisopropylbenzenesulfonyl azide (**I.312**) together with DBU were used (Table 12, entries 2–3). When **I.310** was treated with 4-dodecylbenzenesulfonyl azide (**I.312**) as diazo transfer reagent in the presence of DBU in MeCN at 23 °C, 6% conversion was observed (Table 12, entry 4). All attempts to further optimize this reaction were successful.

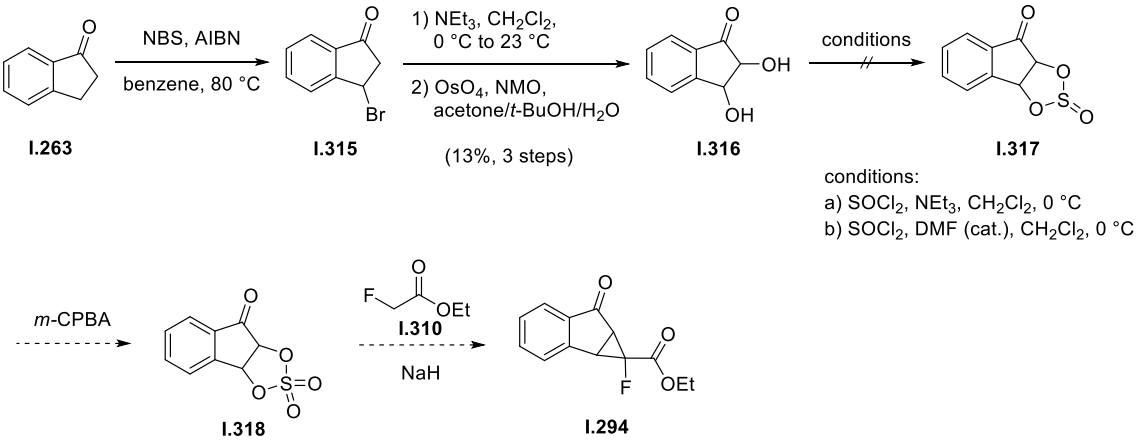
In a final attempt, ethyl 2-fluoroacetoacetate (**I.314**) was treated with *p*-ABSA and DBU in MeCN to give **I.305**. Subsequent reaction with indene and catalytic amounts of $Rh_2(esp)_2$ did not furnish the desired product (Scheme 58). Presumably, the formation of ethyl diazofluoroacetate (**I.305**) was not successful.



Scheme 58. Diazo-transfer reaction with *p*-ABSA and attempted cyclopropanation of indene (**I.308**).

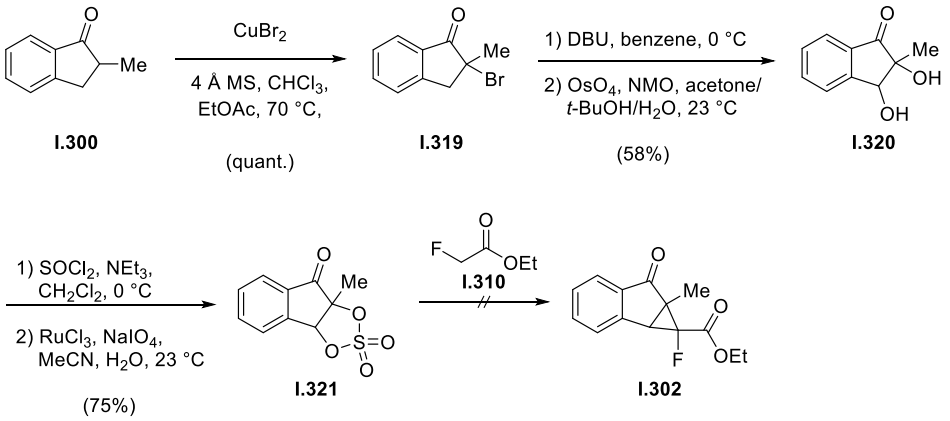
2.2.5 Cyclic sulfate Approach

In 1988, Sharpless reported a cyclopropanation reaction of a cyclic sulfate with dimethyl malonate and NaH.[126] With the cyclic sulfate acting as a double leaving group, the cyclopropanation with ethylfluoroacetate (**I.310**) should give rise to the fluorinated cyclopropane **I.294** (Scheme 59). Dihydroxylation of indenone **I.295**, derived from bromo-indanone **I.315** through elimination, with catalytic amounts of osmium tetroxide (OsO_4) and 4-methylmorpholine *N*-oxide (NMO) as oxidant provided diol **I.316** in 13% yield, which could not be purified using flash column chromatography or recrystallization methods. The reaction to form the cyclic sulfite **I.317** with either thionyl chloride ($SOCl_2$) and triethylamine or $SOCl_2$ and a catalytic amount of DMF did not take place. Under basic conditions, deprotonation at the α-position can occur which could induce the cleavage of the sulfate to give an α-substituted enone.



Scheme 59. Attempted synthesis of the cyclic sulfate **I.318** and planned cyclopropanation with **I.310**.

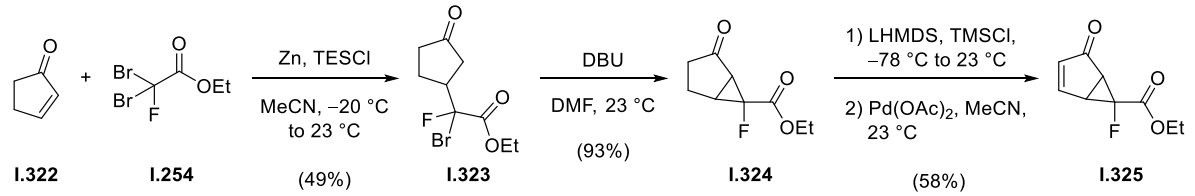
To prevent the observed side reaction, the α-position of the indenone should be substituted for further studies. 2-Methyl-1-indanone (**I.300**) was quantitatively α-brominated using $CuBr_2$ in a mixture of chloroform ($CHCl_3$) and ethyl acetate (EtOAc) at 70 °C (Scheme 60).[120] Subsequent elimination with DBU and dihydroxylation with OsO_4 and NMO furnished diol **I.320** in 58% yield. Treatment of **I.320** with $SOCl_2$ and NEt_3 in CH_2Cl_2 at 0 °C followed by oxidation of the intermediate sulfite by ruthenium(III) chloride ($RuCl_3$) and sodium periodate ($NaIO_4$) in MeCN/H_2O at 23 °C resulted in the formation of cyclic sulfate **I.1** However, the cyclic sulfate could not be transformed into cyclopropane **I.302** by using LHMDS or NaH and ethyl fluoroacetate (**I.310**) under various conditions.



Scheme 60. Synthesis of cyclic sulfate **I.321** and tested cyclopropanation.

2.2.6 Diels–Alder Approach

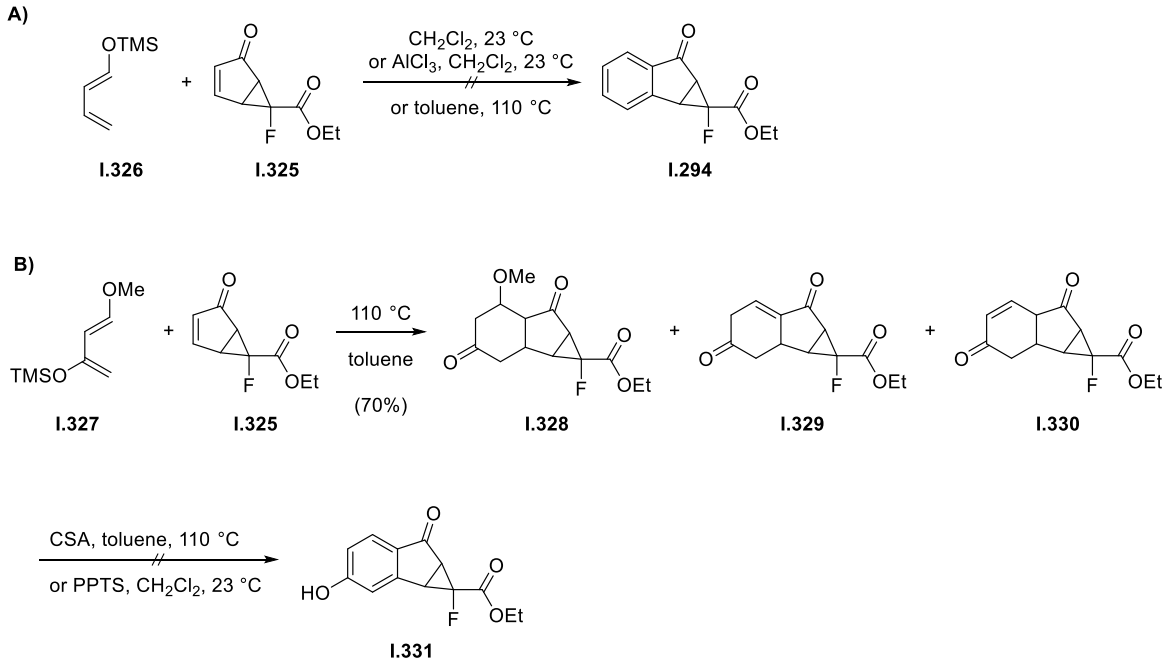
The synthesis of fluorinated cyclopropanes of cyclopentanone is literature known.[115] To benefit from this fact, we aimed to introduce the benzene ring of the desired fluorocyclopropanated indanones through a Diels–Alder/aromatization sequence. Following the literature known procedure, the Michael addition of the generated zinc enolate of ethyl dibromofluoroacetate (**I.254**) to 2-cyclopentene-1-one (**I.322**) furnished **I.323** in 49% yield (Scheme 61.). Ring closure to provide the cyclopropane ring was performed in excellent yield with DBU. A Saegusa–Ito reaction gave the fused cyclopentenone **I.325**, which set the stage for the key cycloaddition reaction.



Scheme 61. Preparation of cyclopentenone **I.325** as precursor for the Diels–Alder/aromatization sequence.

With **I.325** in hand, we tested the cycloaddition reaction with two different dienes. The reaction of **I.326** and **I.325** in CH_2Cl_2 at 23 °C, in the presence of aluminum chloride ($AlCl_3$) as Lewis acid or in toluene at

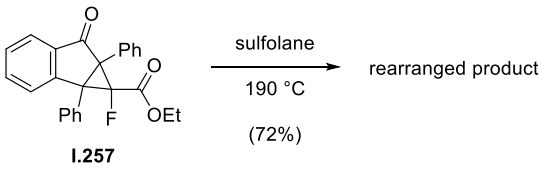
110 °C did not led to product formation (Scheme 62.A). Next, the Danishefsky diene (**I.327**) together with **I.325** was heated to 110 °C in toluene. The reaction furnished the addition product **I.328** as well as two isomeric enones **I.329** and **I.330** after elimination of methanol as inseparable mixture in 70% yield (Scheme 62.B). Yet, the aromatization with camphorsulfonic acid (CSA) in toluene at 110 °C or with pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 at 23 °C did not proceed.



Scheme 62. Diels–Alder reactions for the synthesis of fluorocyclopropanated indanones.

2.2.7 Ring Opening–Aromatization Reaction

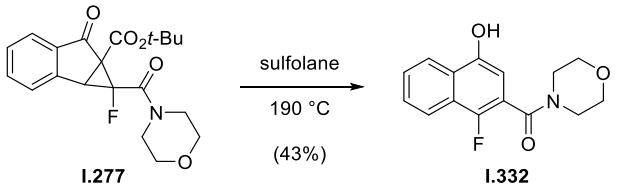
With some fluorocyclopropanated indanones in hand, the stage was set to investigate the ring-expansion/aromatization reaction for the synthesis of fluorinated 1-naphthols. The diphenyl substituted cyclopropane **I.257** was subjected to the conditions for the ring-expansion reaction (sulfolane, 190 °C) and a rearranged product was obtained in 72% yield (Scheme 63). The structure of the formed product could not be unambiguously determined by 2D NMR spectroscopy. However, the ^{13}C peaks of the cyclopropyl moiety disappeared and the mass spectroscopy revealed the same mass for the product as for the starting material.[127]



Scheme 63. Ring opening–aromatization reaction of the fluoride substituted cyclopropane **I.27**.

Encouraged by this promising result, the ring-expansion reaction was examined with cyclopropane **I.277**

having the morpholine ester. Indeed, heating **I.277** to 190 °C in sulfolane provided naphthol **I.336** although the *tert*-butyl ester was cleaved under these conditions (Scheme 64). On a 0.016 mmol scale, naphthol **I.332** was obtained in 43% yield. To examine whether the yield of the reaction is superior without the *tert*-butyl ester, we treated **I.277** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 23 °C to cleave the ester, but only decomposition occurred under the reaction conditions.

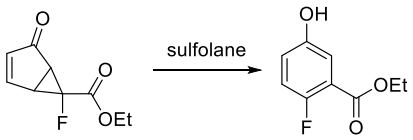


I.277 **I.332**

Scheme 64. Ring-expansion reaction of **I.277**.

Finally, the ring-expansion reaction of the cyclopentene derivative **I.325** to give fluorinated phenols was investigated. The tested conditions are summarized in Table 13.

Table 13. Examined conditions for the ring-expansion reaction of **I.325**.



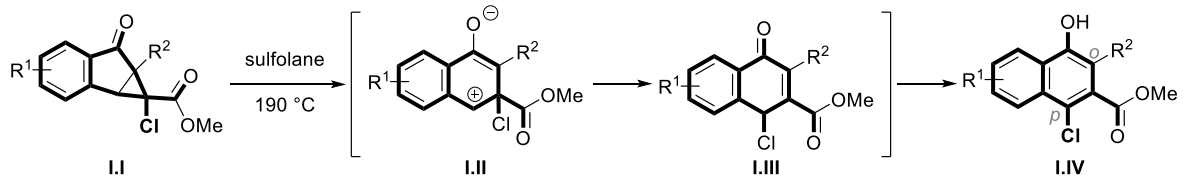
I.325 **I.333**

entry	temperature	time	result
1	190 °C	30 min	decomposition
2	120 °C	3 h	starting material
3	140 °C	3 h	starting material
4	160 °C	2 h	starting material
5	170 °C	2 h	starting material
6	170 °C	8 h	decomposition

Under the standard ring-expansion conditions only decomposition was observed (Table 13, entry 1). This result was surprising because the corresponding chlorinated substrate smoothly fragmented to furnish the two isomeric phenols in 60% yield.[128] Conducting the reaction at lower temperatures (120 °C to 170 °C), no conversion could be detected and the starting material was recovered (Table 13, entries 2–5) and at longer reaction times, decomposition occurred again (Table 13, entry 6).

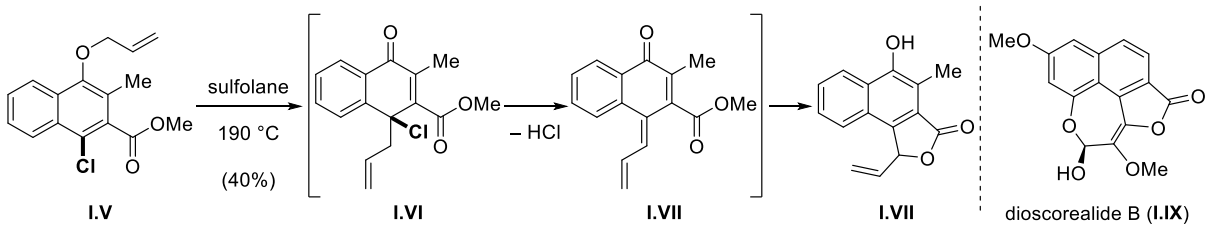
3 Conclusion and Further Directions

Chapter one of this thesis details the development of an efficient and practical ring opening reaction for the synthesis of halogenated 1-naphthols. The procedure enabled the preparation of a variety of polysubstituted 1-naphthols from cyclopropanated indanones. The reaction is supposed to proceed through a thermally-induced disrotatory 2π-electrocyclic ring opening of the cyclopropanated indanone followed by a chloride migration, preferentially in the *para*-position (Scheme 65). The cyclopropanated indanones could be readily obtained from commercially available, inexpensive indanones via Wohl–Ziegler bromination, base-induced elimination followed by cyclopropanation with LHMDS and methyl dichloroacetate (MDCA). It should be noted that the generated indanones are unstable and tend to polymerize. The operationally simple method did not require any additives or transition metal catalysts and could be performed in a flask open to air atmosphere. Various functional groups, including alkyl, ether, halogen substituents as well as protected alcohols and thioethers, were tolerated. The use of bromocyclopropanated indanones was also possible and the corresponding bromonaphthols were obtained by using modified reaction conditions (DMSO, 120 °C). Furthermore, the ring opening/1,2-migration reaction was successfully adapted for the synthesis of chlorinated phenols from bicyclo[3.1.0]hex-3-en-2-ones.



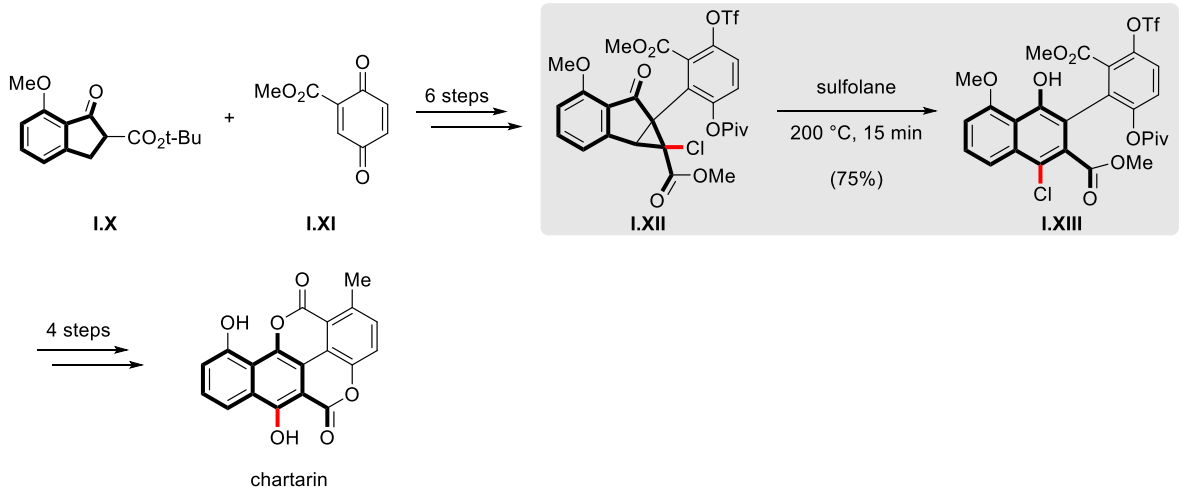
Scheme 65. Mechanism of the ring opening reaction.

The applicability of the prepared orthogonally functionalized 1-naphthols was highlighted by the development of an unprecedented cascade reaction, involving a Claisen–Cope rearrangement followed by elimination of hydrogen chloride and lactone formation, to give access to annulated naphthalene lactones, the structural motif of dioscorealide B (Scheme 66).



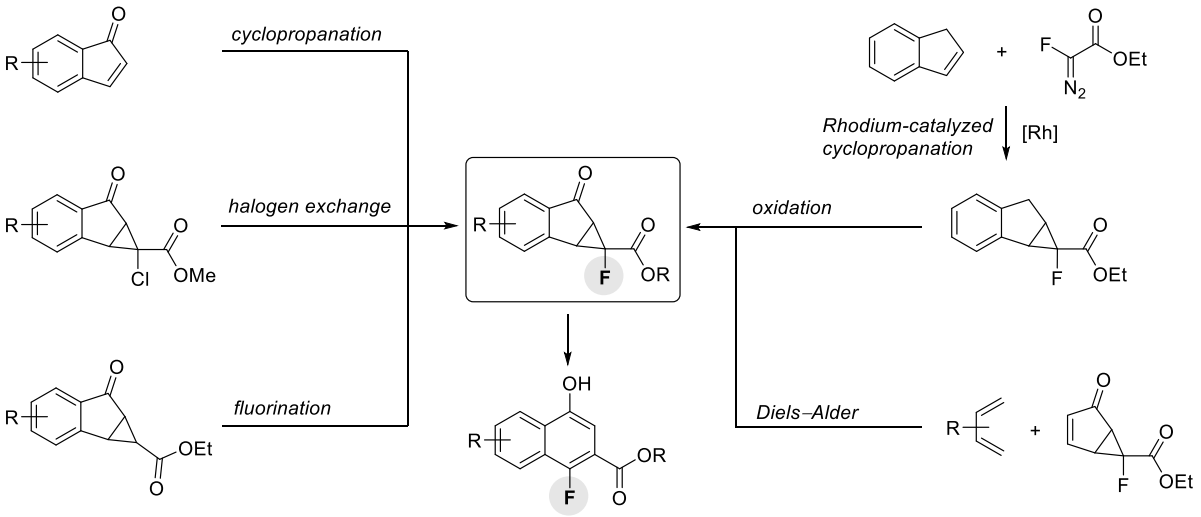
Scheme 66. Cascade reaction to give annulated naphthalene lactones.

Additionally, the ring opening reaction was successfully implemented in the total synthesis of chartarin, the aglycon of elsamicin A and B and chartreusin. The construction of a highly substituted, sterically hindered biaryl bond was thereby achieved. Upon heating to 200°C in sulfolane, the ring opening reaction smoothly furnished the desired sterically hindered biaryl intermediate. A sequence of standard transformations accomplished the synthesis of chartarin in 11 steps overall (Scheme 67).



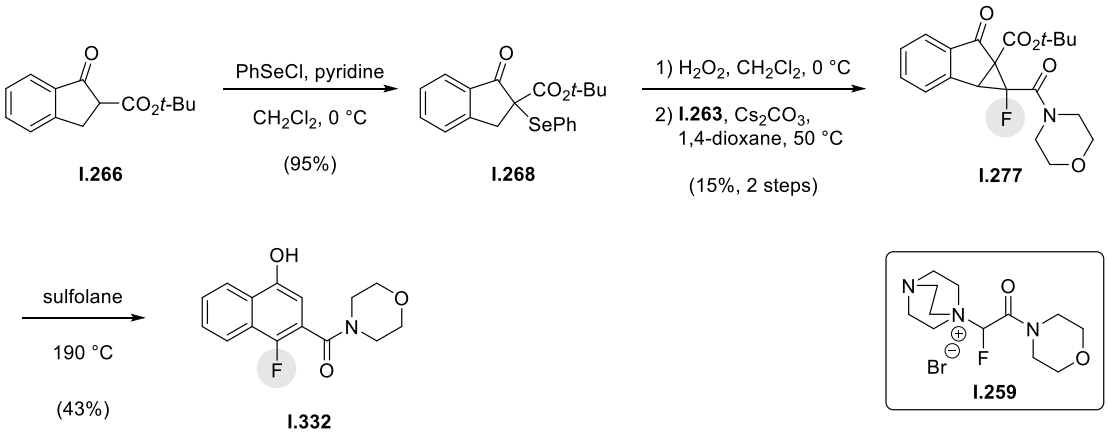
Scheme 67. Synthesis of chartarin.

In addition to the synthesis of chlorinated 1-naphthols, we planned to extend this method to the synthesis of fluorinated naphthols. The first challenge for the development of a synthesis of fluorinated naphthols was the preparation of a fluorocyclopropanated indanone. Different methods for the preparation of this key intermediate were examined, including the cyclopropanation of indenones, a halogen exchange reaction, the fluorination of non-halogenated cyclopropanes, a rhodium-catalyzed cyclopropanation followed by benzylic oxidation and the construction of the aromatic ring by a Diels–Alder reaction (Scheme 68). However, a general method could not be developed.



Scheme 68. Overview of examined methods for the preparation of the key fluorocyclopropanated indanone.

A representative fluorinated cyclopropane could be prepared from indanone **I.266** by introduction of an α-phenylselenyl substituent, followed by oxidative elimination and cyclopropanation with the DABCO salt **I.259**. The prepared substrate was successfully subjected to the standard reaction conditions, giving rise to the fluorinated 1-naphthol **I.332** (Scheme 69).



Scheme 69. Synthesis of fluorinated naphthol **I.332**.

Future studies will be directed at the development of a general procedure for the preparation of fluorocyclopropanated indanones with DABCO salt **I.259**. Moreover, the Diels–Alder reaction could be examined employing different dienes. Ultimately, a general method for the synthesis fluorinated 1-naphthols would allow its implementation in the development of fluorinated compounds as pharmaceuticals.

CHAPTER II

STUDIES TOWARDS THE TOTAL SYNTHESIS OF JERANTININE E

4 Introduction

4.1 Monoterpenoid Indole Alkaloids

Alkaloids are a diverse class of natural products which exhibit a variety of biological activities. Due to their structural diversity, a general definition of alkaloids is difficult. In general, they are described as cyclic, nitrogen-containing compounds of plant or animal origin, prominent examples being morphine (**II.1**), quinine (**II.2**), nicotine (**II.3**) or caffeine (**II.4**) (Figure 8). Commonly, members of the alkaloid family are classified according to their nitrogen-containing core structure or according to their biological origin.

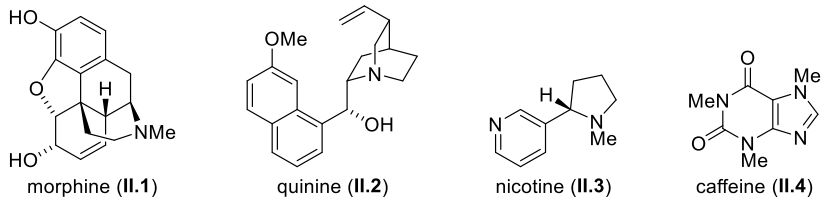
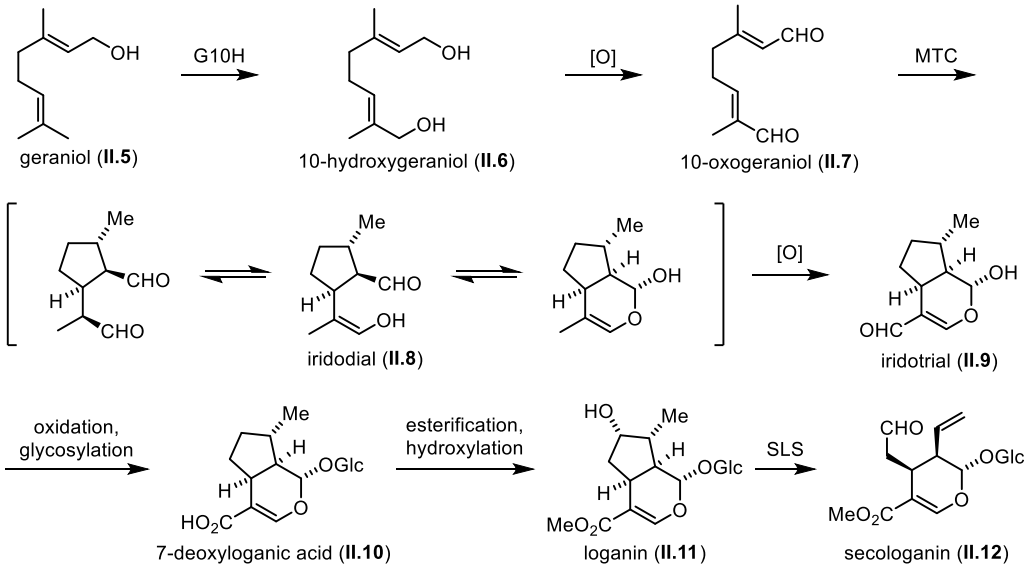


Figure 8. Structures of the alkaloids morphine (**II.1**), quinine (**II.2**), nicotine (**II.3**) and caffeine (**II.4**).

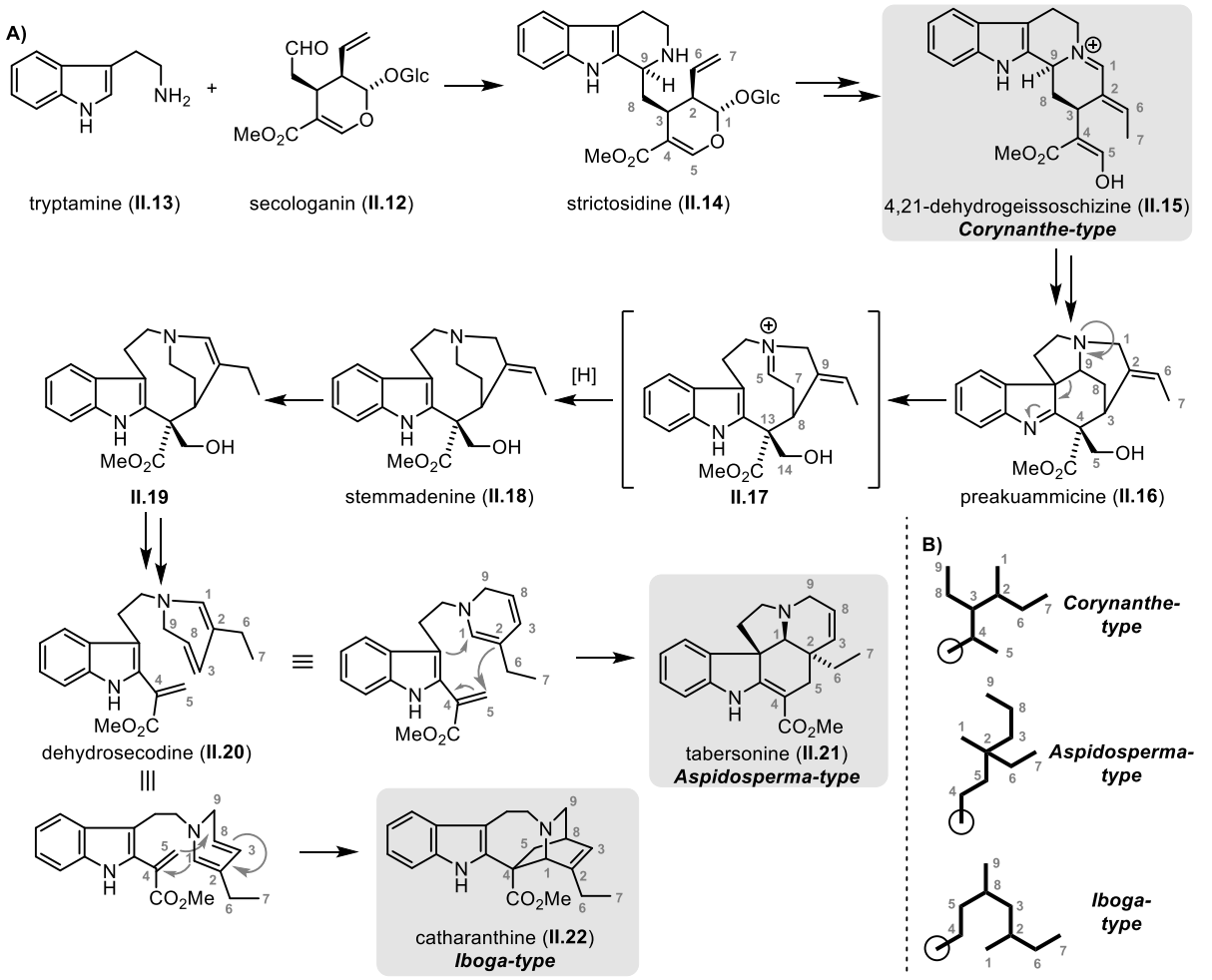
With their fascinating structural complexity and their interesting bioactivity, monoterpenoid indole alkaloids are of high interest for natural product synthesis and medical applications. Monoterpenoid indole alkaloids biosynthetically originate from a secologanin-derived C_9 or C_{10} terpene unit which is condensed to a tryptamine.[129] The secoiridiol secologanin (**II.12**) itself is a natural product synthesized from geraniol (**II.5**) (Scheme 70). However, the biosynthetic pathway has not been fully elucidated. Starting from geraniol (**II.5**), iridotrial (**II.8**) is synthesized through a four-step sequence. A geraniol-10-hydroxylase (G10H) catalyzed allylic hydroxylation followed by an oxidation provides 10-oxogeraniol (**II.7**). Subsequent monoterpene cyclase (MTC) catalyzed cyclization and oxidation gives iridotrial (**II.8**).



Scheme 70. Biosynthesis of secologanin (**II.12**) from geraniol (**II.5**).

II.8 is further oxidized and glycosylated to generate 7-deoxyloganic acid (**II.10**), which is esterified and hydroxylated. Finally, oxidative cleavage of loganin (**II.11**) by the secologanin synthase (SLS), presumably through a radical process, results in the formation of secologanin (**II.12**).[130]

In the first step of the monoterpenoid indole alkaloid biosynthesis, the enzyme strictosidine synthase catalyzes a stereoselective Pictet–Spengler condensation between tryptamine (**II.13**) and secologanin (**II.12**) to generate the tetrahydro-β-carboline structure, producing strictosidine (**II.14**). The hydrolysis of the glycoside function leads to an opening of the hemiacetal to generate an aldehyde, which reacts with the secondary amine to form a Schiff base. Subsequent isomerization of the *exo* double bond gives 4,21-dehydrogeissoschizine (**II.15**).[131] 4,21-Dehydrogeissoschizine (**II.15**), having the *Corynanthe*-type skeleton, is the biosynthetic precursor of *Aspidosperma* and *Iboga* alkaloids. Rearrangement of the secologanin unit furnished strychnine-related alkaloids like preakuammicine (**II.16**). However, the operational mechanism remains unknown. Ring opening and reduction furnishes stemmadenine (**II.18**), which rearranges to give, hypothetically, the acrylic ester dehydrosecodine (**II.20**). **II.20** is believed to react in a Diels–Alder reaction to give either the *Aspidosperma*-type skeletons as in tabersonine (**II.21**) or the *Iboga*-type skeletons (catharanthine, **II.22**) (Scheme 71A).



Scheme 71. A) Proposed biosynthetic pathway of *Corynanthe*, *Aspidosperma* and *Iboga* alkaloids. B) Secologanin skeleton; the circle indicates the missing carbon atoms in the alkaloids which contain the C_9 fragment instead of C_{10}.

In general, the subfamilies of the monoterpenoid indole alkaloid family are classified by the different carbon skeleton of the terpenoid units derived from secologanin **II.12** (Scheme 71B).[130a,132]

4.2 The Aspidosperma Subclass

The *Aspidosperma* alkaloid class of natural products consists of more than 250 members which exhibit potent biological activities. Many of them have been synthesized so far,[133] including the archetypical members (−)-aspidospermine (**II.23**),[134] (+)-aspidospermidine (**II.24**)[135] and (+)-tabersonine (**II.21**)[136] (Figure 9A) as well as more complex compounds like (−)-aspidophytine (**II.25**),[137] (+)-aspidofractinine (**II.26**),[138] (−)-subincanadine A (**II.27**)[139] and (−)-conophylline (**II.28**) (Figure 9B).[140]

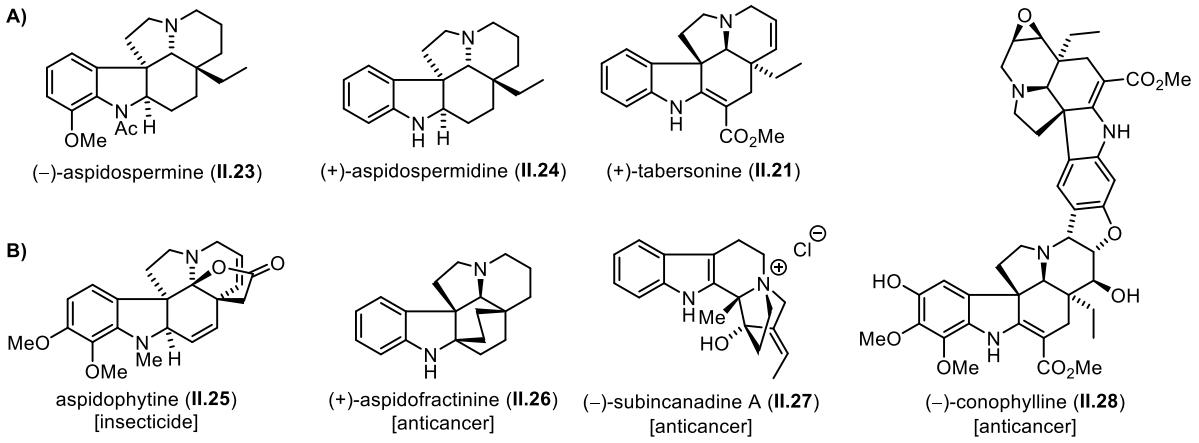


Figure 9. Selected examples of *Aspidosperma* alkaloids.

4.3 Jerantinine E

In 2008, seven new *Aspidosperma* alkaloids, jerantinine A–G (Figure 10), were isolated from leaf extracts of the Malayan plant *Tabernaemontana corymbosa*.[141] They possess a pentacyclic 6,5,6,6,5-ring system including a highly oxygenated tetrahydrocarbazolone core. Its complex structure and oxygenated indole core make jerantinine E (**II.33**) a challenging target molecule for total synthesis.

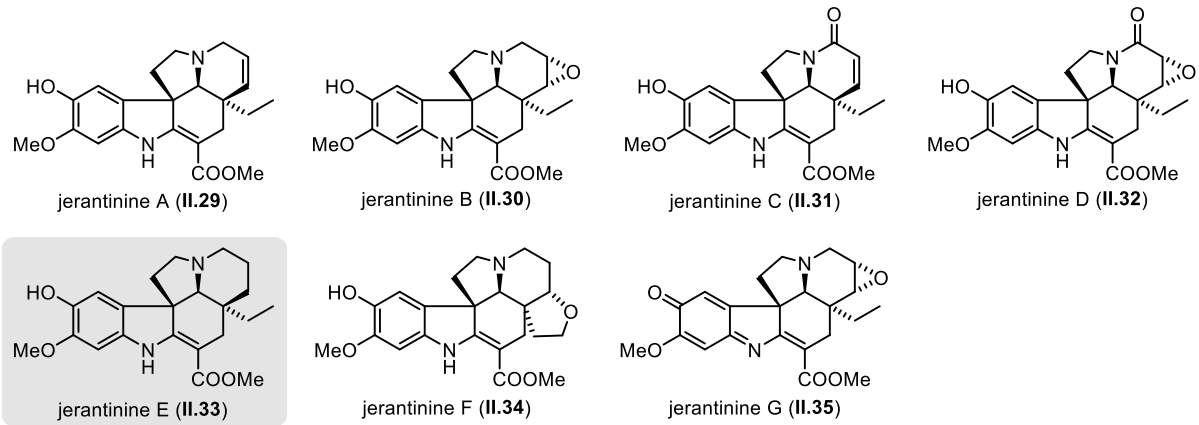
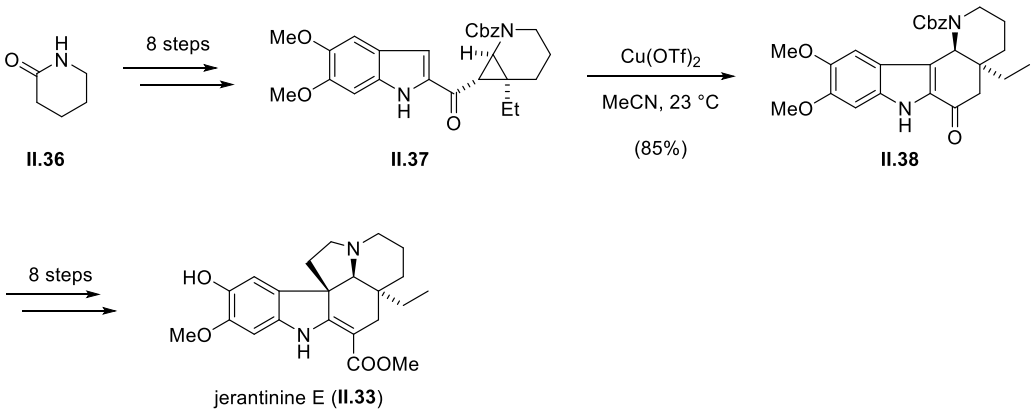


Figure 10. Structures of the *Aspidosperma* alkaloids jerantinine A–G.

Jerantinine E (**II.33**), structurally related to vincadifformine, displays cytotoxicity against vincristine-sensitive (IC_{50} = 2.55 μM) and vincristine-resistant (IC_{50} = 2.03 μM) epidermoid carcinoma cell lines.[141] Additionally, jerantinine E (**II.33**) exhibits cytotoxic effects against breast and lung cancer cell lines. The cell growth of moderately invasive and highly invasive breast cancer cell lines (MCF-7 and MDA-MB-231) from breast ductal carcinoma were inhibited with the same efficiency (IC_{50} = 4.4–6.0 μM). In lung cancer cell lines, the highest cytotoxicity was reported for the human adenocarcinoma cell line (A549) from alveolar ephithelial cells (IC_{50} = 4.2 and 1.0 μM after 24 and 72 h).[142] Furthermore, a cell migratory assay and an impedance study revealed that the activity of jerantinine E (**II.33**) relies on inhibition of the tubulin polymerization, thereby disrupting the microtubule network. An IC_{50} value of 0.45 μM showed that (−)-jerantinine E (**II.33**) is even more active than the known microtubule skeleton disruptor colchicine.

In 2013, the first total synthesis of jerantinine E (**II.33**) was reported by Waser and was realized in 17 steps with an overall yield of 16% starting from commercially available δ-valerolactam (**II.36**).[142] The synthesis included a highly stereoselective formal homo-Nazarov cyclization of (**II.37**), which was developed by the Waser group,[143] furnishing the *cis*-diastereomer (**II.38**) in 85% yield with high C3 regioselectivity (Scheme 72). The final selective demethylation was achieved by a ceric ammonium nitrate (CAN) oxidation followed by in situ reduction with sodium dithionite to give jerantinine E (**II.33**).



Scheme 72. Synthesis of jerantinine E (**II.33**) by Waser.

5 Results and Discussion

5.1 Development of a β-C–H Bromination Approach Towards the Synthesis of Jerantinine E

† These authors contributed equally to this work.

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Development of a β-C−H Bromination Approach toward the Synthesis of Jerantinine E

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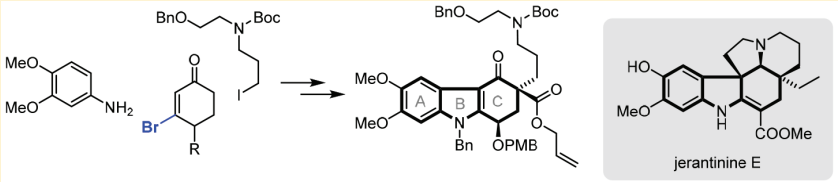
Supporting Information



ABSTRACT: The development of an asymmetric and highly convergent three-component synthesis of the functionalized ABC ring system of the *Aspidosperma* alkaloid jerantinine E is reported. The presented synthetic strategy relies on our recently developed method for the one-pot β-C−H bromination of enones, which allows for rapid construction of the tricyclic tetrahydrocarbazolone core via a palladium-catalyzed amination and oxidative indole formation. Moreover, a secondary amine building block that contains all carbon atoms of the D and E ring of the natural product could be installed in three additional steps.

INTRODUCTION

Monoterpenoid indole alkaloids have been attractive targets for synthetic chemists for several decades, and many of their unique skeletons have been synthesized in the past.[1] In addition to their daunting structural complexity, a variety of biological activities and medicinal applications have been reported, including anticancer (e.g., jerantinine E, vinblastine, brucine)[2] and insecticidal (e.g., aspidophytine)[3] activities (Figure 1A). The *Aspidosperma* alkaloid subfamily consists of more than 250 different members and biosynthetically originates from the condensation of tryptamine with a rearranged secologanin-derived C_9 or C_{10} terpene unit.[4] The secondary metabolites jerantinine A−G (Figure 1B) were isolated in 2008 from leaf extracts of the Malayan plant *Tabernaemontana corymbosa* and exhibit cytotoxic effects against vincristine-sensitive and vincristine-resistant epidermoid carcinoma cell lines (IC_{50} = 0.68−2.55 μM).[2a] In 2013, Waser reported the first synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**) in 17 steps[5] and disclosed its antiproliferative activity against several human-derived breast and lung cancer cell lines (IC_{50} = 1.0−6.0 μM) mediated by inhibition of tubulin polymerization.

In the course of our studies toward novel methods for the site-selective functionalization of α,β-unsaturated compounds,[6] we identified several monoterpenoid indole alkaloids that could be retrosynthetically traced back to a β-halogenated enone. Despite significant advances made in the functionalization of α,β-unsaturated compounds in recent years,[7] only two examples for the direct β-halogenation of enones are known.[8] The syntheses of *Aspidosperma* alkaloids by Desmaële[9] and Qiu[10] both require multistep sequences relying on prefunctionalized vinylogous thioesters for the preparation of the crucial β-enaminone subunit common to several *Aspidosperma* alkaloids (Scheme 1A). We could circumvent these rather inefficient transformations by our two-step sequence starting from simple enones (Scheme 1B). Herein, we describe a convergent synthesis of the ABC ring system of the oxygenated indole alkaloid jerantinine E (**1**) employing our recently developed protocol for the one-pot β-C−H bromination of enones.[6]

RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** was guided by the proposed use of β-bromo enone **11** (Figure 1B) as a general entry to polycyclic indole alkaloids. Identification of this subunit in jerantinine E (**1**) inspired the strategy illustrated in Scheme 2A. In our analysis, tetracycle **12** would arise from the sequential diastereoselective alkylation of the tetrahydrocarbazolone **13** with iodide **14** and ethyl iodide. For the construction of the D-ring of **1**, we envisioned a sequence that would be initiated by the reduction of the ketone and subsequent acid-mediated elimination of the alcohol followed by in situ addition of the free amine to the resultant vinylogous iminium ion **19** (Scheme 2B).[11] The tetrahydrocarbazolone **13** was traced back to 3,4-dimethoxyaniline (**15**) and β-bromo enone **16** which in turn could be accessed via β-C−H bromination of the parent enone.

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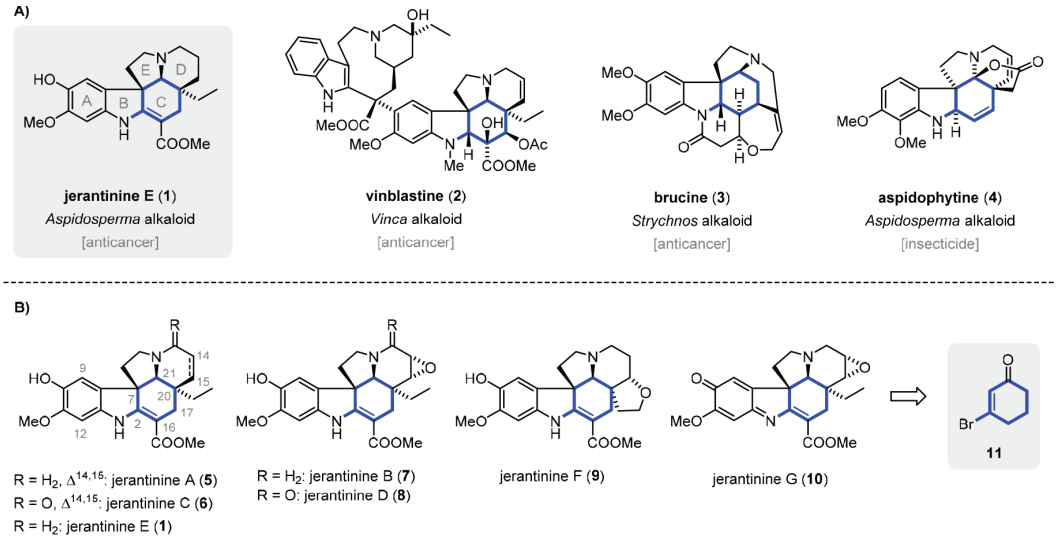
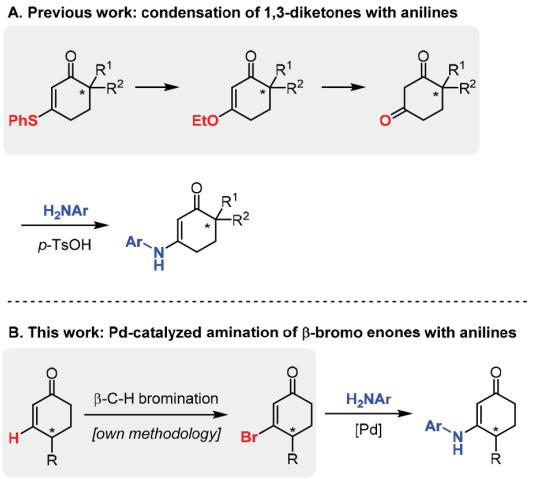


Figure 1. (A) Naturally occurring indole alkaloids and (B) structures of jerantinines A–G.

Scheme 1. Methods for the Preparation of Functionalized *β*-Enaminones for the Synthesis of *Aspidosperma* Alkaloids



In an initial attempt to synthesize jerantinine E (**1**), we targeted racemic intermediate **12**. The synthesis started with our previously reported preparation of tetrahydrocarbazolone *rac*-**13**, prepared in three steps from enone **21** utilizing a *β*-C–H bromination, a palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**), and oxidative indole formation (Scheme 3).[6] Finally, tetrahydrocarbazolone *rac*-**13** was Boc-protected to give **22** in a good yield (88%). To examine the introduction of secondary amine **14**, we performed first alkylation with 1-chloro-3-iodopropane as a model electrophile. Treatment of **22** with lithium bis(trimethylsilyl)amide (LHMDS) and an excess of 1-chloro-3-iodopropane followed by nucleophilic displacement of the chloride provided azide **23**. Unfortunately, alkylation of **23** by treatment with LHMDS and ethyl iodide did not give the desired product. Instead, the elimination of the benzyl ether to give alkene **24** was observed,[12] which was prone to aromatization upon exposure to traces of acid.

Since **23** underwent undesired elimination under basic alkylation conditions, we contemplated exchange of the CH_2OBn moiety for a protected hydroxy group in the *γ*-position of the enone. Our revised retrosynthetic analysis featured the synthesis of a modified, asymmetric tetrahydrocarbazolone core structure which could be constructed from 3,4-dimethoxyaniline (**15**), secondary amine building block **14**, and enantiopure *β*-bromo enone **27** (Scheme 4). The stereocenter of the latter component was planned to direct the sequential introduction of the side chains and enable the asymmetric total synthesis of jerantinine E (**1**).

We began our endeavor with the synthesis of known chiral alcohol **29**, itself derived from 1,4-cyclohexanedione monoethylene acetal (**28**) in four steps.[13] Protection of **29** as its *para*-methoxybenzyl ether (PMB) using Dudley's reagent II (2-(4-methoxybenzyloxy)-4-methylquinoline)[14] furnished **30**. Enone **30** was then subjected to our conditions for one-pot *β*-C–H bromination, which includes (1) umpolung of the enone by hydrazone formation with *tert*-butyl carbazate (*tert*-butoxycarbonyl hydrazide), (2) selective *β*-C–H bromination with *N*-bromosuccinimide (NBS) followed by addition of triethylamine to isomerize the allyl bromide, and (3) hydrolysis of the hydrazone moiety, to afford **27** in 57% yield on a 340 mg scale (Scheme 5). Palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**) employing Buchwald's SPhos second generation precatalyst[15] followed by an oxidative indole formation[16] using palladium acetate and copper acetate furnished **32**. It is noteworthy that careful monitoring of the C–H activation reaction proved to be crucial to avoid overoxidation and subsequent hydrolysis of the PMB ether with extended reaction times. Benzyl protection of the tetrahydrocarbazolone **32** provided **33**,[17] whose structure could be validated by single-crystal X-ray diffraction.[18]

Having developed a short and efficient synthesis of key intermediate **33**, the stage was set for the installation of the quaternary stereocenter as the crucial handle to construct the DE ring system of jerantinine E (**1**). However, in sharp contrast to the results obtained for the alkylation of **22**, direct alkylation of **33** with ethyl iodide was not feasible under a variety of conditions. The use of LHMDS, LDA, or LDA/HMPA only led

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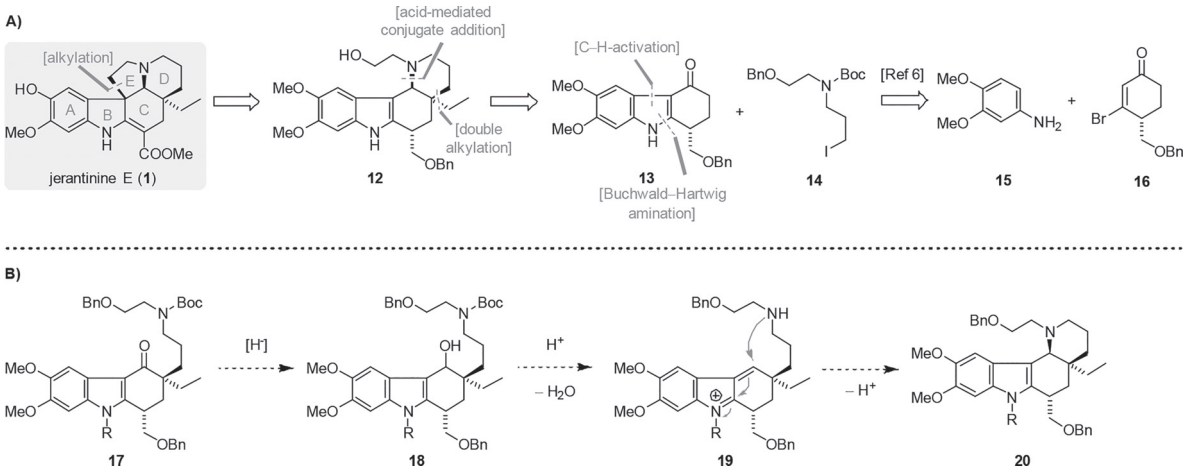
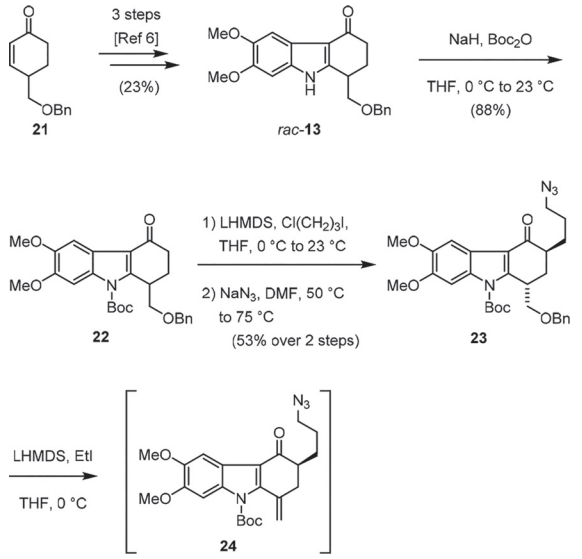
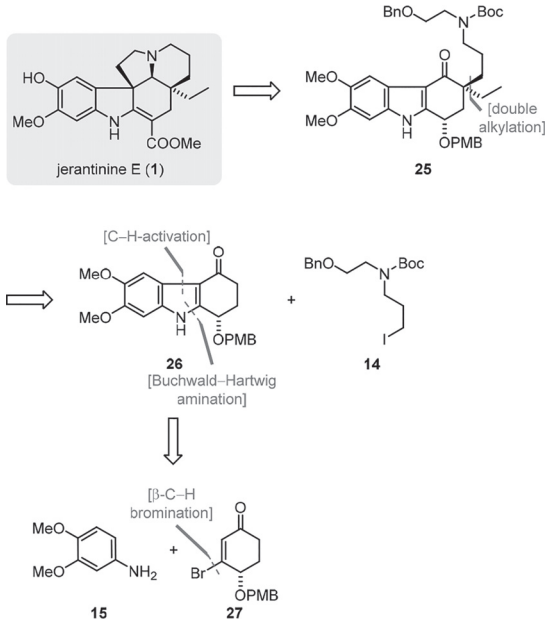
Scheme 2. (A) Initial Retrosynthetic Analysis of Jerantinine E (1) and (B) Envisioned Cascade Reaction for the Construction of the D-Ring



Scheme 3. Synthesis of Tetrahydrocarbazolone 22 and Alkylation with a Model Electrophile



Scheme 4. Revised Retrosynthetic Analysis of Jerantinine E (1)



to recovered starting material. The exact influence of the substituent at the γ-position of the ketone and the protecting groups (Bn and PMB) on the alkylation is unclear.

To overcome this poor reactivity, we investigated the acylation of **33**. Surprisingly, exposure of **33** to LHMDS and Mander's reagent[19] (methyl cyanoformate) at −78 °C followed by alkylation with sodium hydride and ethyl iodide proceeded cleanly and furnished **34** in good yields (Scheme 6). Next, we attempted to convert **34** to **35** by means of a decarboxylation using lithium chloride in aqueous dimethylformamide and subsequent reaction using acrylonitrile as a reactive model electrophile. Although traces of the decarboxylated product were observed, we were unable to detect any of the conjugate addition product.

Based on the successful alkylation of the β-keto ester with ethyl iodide, we decided to investigate the alkylation of **33** using iodide **14**. Thus, the Boc-protected amine building block **14** was synthesized as illustrated in Scheme 7A. Alkylation of commercially available *tert*-butyl *N*-allylcarbamate (**36**) with literature known iodide **37** under standard conditions (NaH, DMF) afforded **38** in good yield (80%).[20] Hydroboration of **38** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup using aqueous hydrogen peroxide furnished alcohol **39**. The latter was then transformed into iodide **14**, employing Appel's conditions (I_2, PPh_3, imH). With iodide **14** and tricyclic key intermediate **33** in hand, we were poised to examine the challenging fragment coupling. Acylation of **33** followed by reaction of the β-keto ester with sodium hydride and iodide **14** furnished the quaternary stereocenter in **40** in good yield (Scheme 7B). Thus, the introduction of the secondary amine building block could be accomplished in an efficient manner. The methyl ester of **40** could then be

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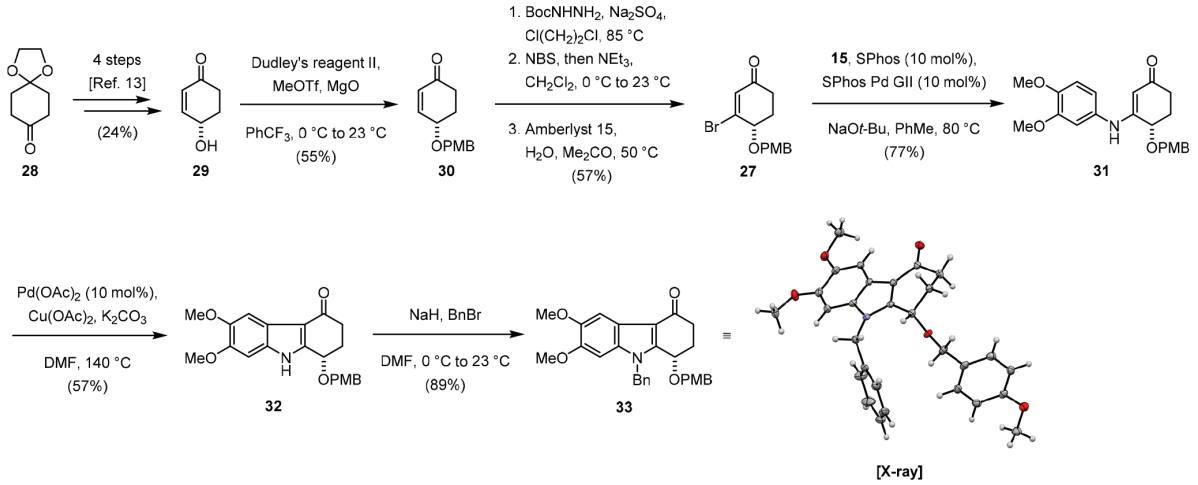
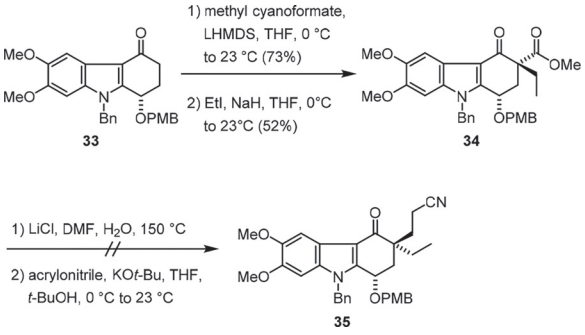
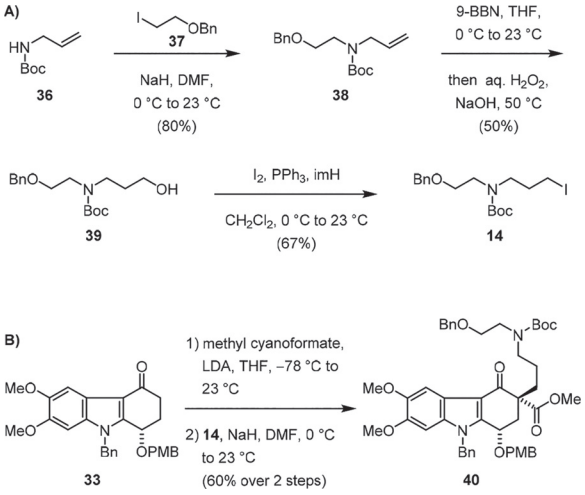
Scheme 5. Synthesis of Tetrahydrocarbazolone 33



Scheme 6. Attempted Formation of the Quaternary Stereocenter



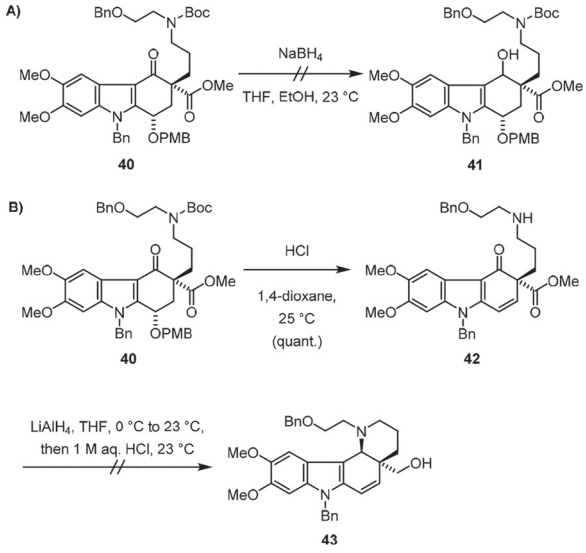
Scheme 7. (A) Preparation of the Boc-Protected Amine Building Block 14 and (B) Introduction of the Quaternary Stereocenter



transformed to the ethyl group of the natural product at a later stage of the synthesis.

For the construction of the D-ring of **1** (see Scheme 1B), we first tried to selectively reduce **40** using sodium borohydride (Scheme 8A). Since these conditions turned out to be

Scheme 8. Attempted Closure of the D-Ring of Jerantinine E



ineffective and no conversion was observed, we opted for more forcing conditions. As direct reduction of **40** with lithium aluminum hydride could not be considered due to concomitant reduction of the Boc protecting group, **40** was treated with 4 M hydrochloric acid in 1,4-dioxane to remove the Boc protecting group (Scheme 8B). Unfortunately under these conditions, deprotection of the Boc group and elimination of the PMB ether occurred, giving compound **42** as the major product. Exposure of the crude reaction mixture to lithium aluminum hydride followed by treatment with either 1 M aqueous hydrochloric acid or Rochelle's salt did not afford any detectable amounts of tetracycle **43**. Attempts to remove the Boc group under basic conditions (K_2CO_3, DMSO/H_2O, 65 °C; DIBAL-H, CH_2Cl_2, 23 °C) without affecting the PMB

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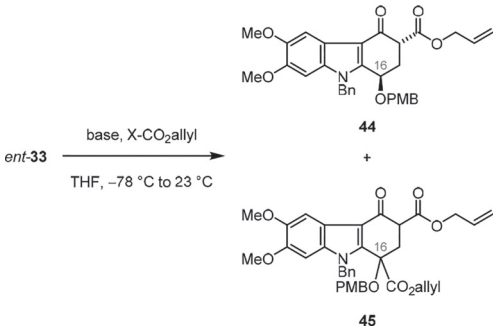
group were unsuccessful, and only complex product mixtures were obtained.

In order to avoid these undesired pathways in the functionalization of **40**, we decided to replace the methyl with an allyl ester and set the quaternary stereocenter in a subsequent diastereoselective palladium-catalyzed decarboxylative allylation reaction.[21] The obtained allyl group could then be converted to the ethyl group in three additional steps.[22] We anticipated that the stereochemical outcome of the allylation step could be controlled by the stereocenter at C16. To obtain the desired stereochemistry in the decarboxylative allylation reaction, we prepared *ent*-**33** according to the route described above.[23]

For the incorporation of the allyl ester, we examined the conditions shown in Table 1. Initially, the acylation reaction of

Table 1. Screen of Conditions for the Acylation of *ent*-33[a]



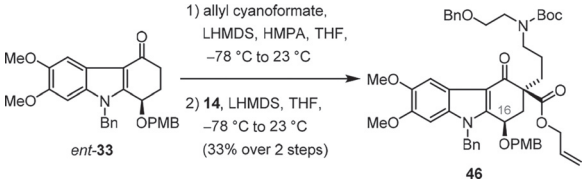
entry	base	X	product: yield[b]
1[c]	NaH	Cl	–
2	LDA	Cl	**45**: 24%
3	LHMDS	Cl	**45**[d]
4	LiTMP	Cl	**45**[d]
5	LTBTA	Cl	**45**[d]
6	LDA	im	**45**[d]
7	LHMDS	im	**45**[d]
8	LDA	CN	**44**: 42%
9	LHMDS	CN	**44**: 62%
10[e]	**LHMDS, HMPA**	**CN**	**44: 70%**

[a]All reactions were performed on a 0.02 mmol scale in THF (c = 0.02 M) with 1.1−1.2 equiv of base and 1.2 equiv of electrophile. [b]Yields of isolated products. [c]The reaction was performed at 0 °C. [d]The reactions were monitored by ^{1}H NMR spectroscopy. The yields were not determined. [e]2 equiv of HMPA were used as additive. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, LTBTA = lithium *tert*-butyltrityl-amide, im = 1-imidazoyl.

ent-**33** with sodium hydride (1.1 equiv) and commercially available allyl chloroformate (1.2 equiv) at −78 °C resulted in no product formation. Surprisingly, treatment of *ent*-**33** with lithium diisopropylamide (LDA, 1.2 equiv) and allyl chloroformate (1.2 equiv) resulted in the formation of the diacylated product **45** (entry 2). Extensive screening using a variety of lithium amide bases and allyl chloroformate or allyl 1*H*-imidazole-1-carboxylate failed to provide β-keto ester **44**, and only formation of the diacylated product was observed (entries 3−7). Based on our previous findings that acylation of **44** works best with methyl cyanoformate, we investigated the use of allyl cyanoformate. This modification resulted in the formation of β-keto ester **44** for the first time (entry 8, 42%). Further optimization of the reaction conditions by variation of lithium amide bases and solvents revealed that the use of LHMDS (1.5 equiv) in the presence of hexamethylphosphoramide (HMPA, 2 equiv) is crucial to reproducibly obtain **44** in good yield (70%).

Finally, treatment of **44** with LHMDS, HMPA, and iodide **14** resulted in the smooth formation of β-keto ester **46** (Scheme 9). Other alkylation conditions explored (Cs_2CO_3, MeCN; NaH, DMF; KHMDS, THF) were inferior. Unfortunately, initial attempts to induce the palladium-catalyzed decarboxylative allylation reaction ($Pd(PPh_3)_4$ or $Pd_2(dba)_3$, (*S*)-*t*-Bu-PHOX)[24] only resulted in decarboxylation without incorporation of the allyl group. A more exhaustive screen of ligands is currently underway in our laboratories and should ultimately allow us to complete the total synthesis of jerantinine E.

Scheme 9. Successful Alkylation with Building Block 14



CONCLUSION

We have reported a synthetic route toward the total synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**). The presented strategies rely on an efficient one-pot β-C−H bromination protocol to provide the C-ring subunit of the target structure. A palladium-catalyzed amination reaction was used to further functionalize the β-bromo enones and oxidative indole formation enabled formation of the tricyclic ABC tetrahydrocarbazolone fragment of jerantinine E (**1**). Our initial strategy to construct the functionalized tricyclic key intermediate of the natural product was hampered by the base-mediated elimination of the benzyl ether at C16 of the C-ring. Starting from a γ-hydroxylated enone instead, we were able to prepare highly functionalized precursor **46**. The overall sequence to the functionalized tetrahydrocarbazolone core of **1** proceeds in 11 linear steps from commercially available ketone **28** and the secondary amine component **14**. The latter contains all carbon atoms of the D and E rings of the natural product. The presented strategy is amenable to rapid modification to give a variety of tetrahydrocarbazolone structural motifs.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried or flame-dried glassware fitted with rubber septa under a positive pressure of argon unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone and sodium prior to use. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and *N*,*N*-diisopropylamine (DIPA) were distilled from CaH_2 prior to use. Commercially available *N*-bromosuccinimide (NBS) was purified by recrystallization from water.[25] All other reagents and solvents were purchased from commercial suppliers and were used without further purification. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC). The TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and exposure to either an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or CD_2Cl_2. Proton chemical shifts are expressed in parts per million (δ scale) and

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are calibrated using residual undeuterated solvent as an internal reference. Additionally to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. Infrared (IR) spectra were recorded on an FT-IR spectrometer. IR data are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) or electron ionization (EI) using a sector field mass spectrometer. Melting points (Mp's) were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG. Optical rotations were recorded on a PerkinElmer 241 or Anton Paar MCP 200 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T[^oC]}$ (c [g/100 mL], solvent). X-ray structural analyses were performed on a diffractometer using Mo Kα radiation (λ = 0.71073 Å, graphite monochromator).

Preparation of Azide 19. *N-Boc-tetrahydrocarbazolone* ***22***. To a solution of tetrahydrocarbazolone *rac*-**13**[6] (80 mg, 0.22 mmol, 1 equiv) in tetrahydrofuran (2.74 mL) was added sodium hydride (13 mg, 0.3 mmol, 1.5 equiv, 60% dispersion in mineral oil) at 0 °C. After 30 min, di-*tert*-butyl dicarbonate (72 mg, 0.3 mmol, 1.5 equiv) was added and the solution was allowed to warm to 23 °C. After 1.5 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **22** as a white solid (90 mg, 88%). TLC (25% ethyl acetate in hexane): R_f = 0.38 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.71 (s, 1H), 7.34−7.24 (m, 5H), 4.60 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.09−4.02 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.78 (dd, J = 9.2, 3.8 Hz, 1H), 3.62 (app t, J = 9.1 Hz, 1H), 2.72 (ddd, J = 17.4, 14.4, 5.2 Hz, 1H), 2.52−2.42 (m, 2H), 2.33−2.22 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 149.7, 149.4, 147.9, 147.6, 138.1, 130.3, 128.5, 127.9, 127.9, 118.6, 117.9, 102.9, 99.3, 85.5, 73.2, 69.4, 56.3, 56.2, 34.8, 33.9, 28.2, 25.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2937, 1736, 1660, 1550, 1493, 1475, 1453, 1369, 1307, 1251, 1209, 1134 cm^{-1}. HR-MS (EI): calcd for $(C_{27}H_{31}O_6N)^+$: 465.2146; found, 465.2150.

Azide ***23***. *N*-Boc-tetrahydrocarbazolone **22** (12 mg, 0.026 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.3 mL) and 1-chloro-3-iodopropane (21.1 mg, 0.10 mmol, 4.00 equiv) was added. The solution was cooled to 0 °C, and a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 36 μL, 0.036 mmol, 1.40 equiv) was added dropwise over 6 min. After 2 h, the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with diethyl ether (5 mL), one drop of acetic acid was added, and the resulting suspension was filtered through a fritted glass funnel (Por. 4). The filter cake was rinsed with diethyl ether (10 mL). The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the chloride as a colorless oil (8.8 mg, dr = 5:1). No separation of the two diastereomers could be achieved, and the diastereomeric mixture was used for the next step.

The chloride was dissolved in *N*,*N*-dimethylformamide (0.16 mL), and sodium azide (5.3 mg, 0.08 mmol, 5.00 equiv) was added. The reaction mixture was stirred at 50 °C for 2 h, and then the temperature was increased to 75 °C. After 5 h, heating was ceased and the reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **23** as a yellow oil (7.5 mg, 53% over 2 steps, dr = 5:1). The major diastereomer could be separated by flash column chromatography. TLC (25% ethyl acetate in hexanes): R_f = 0.48 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (s, 1H), 7.37−7.25 (m, 5H), 4.63 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.09−4.04 (m, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.80 (dd, J = 9.1, 3.9 Hz, 1H), 3.63 (t, J = 9.1 Hz, 1H), 3.33 (t, J = 7.0 Hz, 2H), 2.67 (ddd, J = 17.9, 8.3, 4.7 Hz, 1H), 2.52 (ddd, J = 13.4, 4.7, 2.1 Hz, 1H), 2.11−1.99 (m, 2H), 1.76−1.70 (m, 2H), 1.67 (s, 9H), 1.48−1.43 (1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 149.7, 148.8, 147.9, 147.6, 138.0, 130.5, 128.6, 128.0, 128.0, 118.7, 117.8, 102.8, 99.4, 85.6, 73.3, 69.5, 56.3, 56.2, 51.9, 41.5, 35.2, 31.1, 28.2, 26.9, 26.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 2096, 1737, 1654, 1476, 1371, 1309, 1206, 1141, 1105 cm^{-1}. HR-MS (ESI): calcd for $(C_{30}H_{37}O_6N_4)^+$ $(M + H)^+$: 549.2713; found, 549.2706.

Preparation of Tetrahydrocarbazolone 33. *(S)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (****30****).* To a suspension of (*S*)-4-hydroxycyclohex-2-en-1-one (**29**)[26] (2.30 mg, 20.5 mmol, 1 equiv), magnesium oxide (1.66 g, 41.0 mmol, 2.00 equiv, vacuum-dried), and Dudley reagent II[14] (11.5 g, 41.0 mmol, 2.00 equiv) in α,α,α-trifluorotoluene (200 mL) was added dropwise methyl triflate (4.64 mL, 41.0 mmol, 2.00 equiv) at 0 °C. Upon completion of the addition, the reaction mixture was allowed to warm to 23 °C. After 75 min, ethyl acetate (40 mL) was added and the suspension was filtered through a fritted glass funnel. The filter cake was rinsed with ethyl acetate (2 × 20 mL). The filtrate was washed with water (50 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (9% to 14% ethyl acetate in hexanes) to afford **30** as a colorless oil (2.60 mg, 55%). The obtained characterization data were in full agreement with those values reported in the literature.[27]

*(S)-3-Bromo-4-[(4-methoxyphenyl)oxy]cyclohex-2-en-1-one (****27****).* (*S*)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (**30**) (340 mg, 1.46 mmol, 1 equiv) was added to a mixture of sodium sulfate (643 mg, 4.53 mmol, 3.10 equiv) and *tert*-butyl carbazate (203 mg, 1.54 mmol, 1.05 equiv) in degassed 1,2-dichloroethane (1.2 mL) in a pressure flask. The resulting suspension was heated to 85 °C. After 4.5 h, the orange mixture was allowed to cool to 23 °C. Dichloromethane (4.4 mL) was added, the solution was cooled to 0 °C, and recrystallized *N*-bromosuccinimide (274 mg, 1.54 mmol, 1.05 equiv) was added. After 1 h at 0 °C, triethylamine (427 μL, 3.07 mmol, 2.10 equiv) was added in one portion. The resulting orange solution was stirred for 24 h at 23 °C. Acetone−water (v/v = 9:2, 6.1 mL) and Amberlyst 15 (1.76 g) were added, and the yellow suspension was heated to 50 °C. After 12 h, the reaction mixture was allowed to cool to 23 °C and then was diluted with dichloromethane (3 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **27** as a yellow oil (261 mg, 57%). TLC (20% ethyl acetate in hexane): R_f = 0.32 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 2H), 6.94−6.87 (m, 2H), 6.48 (s, 1H), 4.68 (s, 2H), 4.26 (t, J = 4.7 Hz, 1H), 3.81 (s, 3H), 2.72−2.61 (m, 1H), 2.36 (dt, J = 16.9, 5.6 Hz, 1H), 2.23−2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 159.7, 149.4, 133.8, 129.8, 129.4, 114.0, 76.0, 72.6, 55.4, 33.2, 28.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934, 2836, 1682, 1611, 1513, 1464, 1331, 1302, 1278, 1247, 1174, 1084 cm^{-1}. HR-MS (EI): calcd for $(C_{14}H_{15}{}^{79}BrO_3)^+$, 310.0199; found, 310.0200. $[\alpha]_{589}^{20}$ = −46.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Enaminone ***31***. To an oven-dried pressure tube were added chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (126 mg, 0.18 mmol, 0.10 equiv), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (72 mg, 0.18 mmol, 0.10 equiv), sodium *tert*-butoxide (252 mg, 2.63 mmol, 1.50 equiv), 3,4-dimethoxyaniline (**15**) (402 mg, 2.63 mmol, 1.50 equiv), and toluene (12 mL). (*S*)-3-Bromo-4-[(4-methoxyphenyl)-oxy]cyclohex-2-en-1-one (**27**) (545 mg, 1.75 mmol, 1 equiv) was added, and the dark red suspension was heated to 80 °C for 18 h. The reaction mixture was allowed to cool to 23 °C and was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (30 mL). The filtrate was concentrated and the residual red oil was

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purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford **31** as a brown foam (474 mg, 77%). TLC (2% methanol in dichloromethane): R_f = 0.22 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 2H), 6.98 (s, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.5, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.39 (s, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.41 (dd, J = 11.4, 4.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.60−2.40 (m, 2H), 2.34 (ddd, J = 17.2, 13.4, 4.6 Hz, 1H), 1.99 (qd, J = 11.9, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 162.0, 159.9, 149.5, 147.3, 130.7, 129.9, 129.1, 116.8, 114.3, 111.5, 108.5, 97.9, 74.1, 71.4, 56.2, 56.1, 55.5, 35.1, 27.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3250, 2393, 1611, 1581, 1500, 1463, 1235, 1196, 1172, 1026 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{25}NO_5)^+$, 383.1727; found, 383.1727. $[\alpha]_{589}^{20}$ = +12.8 (c = 0.31 × 10 g·mL^{-1}, CH_2Cl_2).

*Tetrahydrocarbazolone **32**.* A solution of enaminone **31** (485 mg, 1.26 mmol, 1 equiv) in *N*,*N*-dimethylformamide (16 mL) was added to an oven-dried pressure tube containing palladium(II) acetate (28.4 mg, 0.13 mmol, 0.10 equiv), copper(II) acetate (689 mg, 3.79 mmol, 3.00 equiv), and potassium carbonate (524 mg, 3.79 mmol, 3.00 equiv). The resulting green-brown mixture was placed in a preheated oil bath at 140 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C, and the dark solution was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (40 mL). The filtrate was concentrated. The residual black oil was purified by flash column chromatography on silica gel (50% to 66% ethyl acetate in hexanes) to afford **32** as a gray solid (275 mg, 57%). TLC (1% methanol in dichloromethane): R_f = 0.12 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.66 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 4.88 (dt, J = 8.8, 3.2 Hz, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.75 (dt, J = 15.5, 4.0 Hz, 1H), 2.60−2.46 (m, 2H), 2.29−2.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 159.6, 148.7, 147.8, 146.9, 130.1, 129.8, 129.7, 117.5, 114.2, 112.8, 103.1, 94.8, 71.0, 70.8, 56.3, 56.2, 55.4, 36.3, 30.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3294, 2949, 1626, 1585, 1540, 1513, 1466, 1340, 1295, 1247, 1135 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{23}NO_5)^+$, 381.1571; found, 381.1570. Mp 196−199 °C. $[\alpha]_{589}^{20}$ = −1.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

*N-Benzyltetrahydrocarbazolone **33**.* Tetrahydrocarbazolone **32** (203 mg, 0.532 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (2.7 mL), and the solution was cooled to 0 °C. Sodium hydride (25.5 mg, 0.639 mmol, 1.20 equiv, 60% dispersion in mineral oil) was added, and the suspension was stirred for 1 h at 0 °C. Benzyl bromide (76 μL, 0.639 mmol, 1.20 equiv) was added, and the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (60% ethyl acetate in hexanes) to afford **33** as a slightly beige solid (224 mg, 89%). Crystals that were suitable for X-ray diffraction analysis were obtained by crystallization from dichloromethane. TLC (50% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67 (s, 1H), 7.27−7.22 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 6.7, 2.8 Hz, 2H), 6.84−6.76 (m, 2H), 6.64 (s, 1H), 5.22 (q, J = 16.7 Hz, 2H), 4.76 (t, J = 3.6 Hz, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.43 (d, J = 11.1 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 2.88 (ddd, J = 16.4, 11.8, 4.4 Hz, 1H), 2.57−2.49 (m, 1H), 2.41 (dt, J = 16.6, 4.2 Hz, 1H), 2.26 (ddt, J = 15.0, 11.7, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2, 160.0, 148.7, 147.8, 146.7, 137.1, 132.1, 130.3, 130.2, 129.3, 128.1, 126.7, 117.6, 114.3, 113.7, 103.8, 94.4, 71.1, 67.5, 56.6, 56.5, 55.8, 47.9, 34.3, 27.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 1700, 1647, 1558, 1540, 1513, 1483, 1444, 1303, 1270, 1248, 1173, 1106 cm^{-1}. HR-MS (ESI): calcd for $(C_{29}H_{29}NO_5)^+$, 471.2046; found, 471.2054. Mp 139−144 °C. $[\alpha]_{589}^{20}$ = −6.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Tetrahydrocarbazolone 34. *Tetrahydrocarbazolone **34**.* *N*-Benzyltetrahydrocarbazolone **33** (49 mg, 0.10 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.12 mL, 0.12 mmol, 1.2 equiv) and hexamethylphosphoramide (36 μL, 0.20 mmol, 2.0 equiv) in tetrahydrofuran (0.5 mL) at −78 °C. After 1 h, methyl cyanoformate (12 μL, 0.15 mmol, 1.5 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 20 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford the β-keto ester as a red oil (40 mg, 73%) containing minor impurities. The β-keto ester was used without additional purification for the next step.

Sodium hydride (2.5 mg, 62 μmol, 1.5 equiv, 60% suspension in mineral oil) was added a solution of the β-keto ester (22 mg, 41 μmol, 1 equiv) in *N*,*N*-dimethylformamide (0.4 mL) at 0 °C. After 1 h, ethyl iodide (13 μL, 0.16 mmol, 4.0 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **34** as a brown oil (12 mg, 52%, dr = 4:1). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.40 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.26−7.24 (m, 3H), 7.16−7.11 (m, 2H), 6.98−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.59 (s, 1H), 5.42−5.29 (m, 2H), 5.21 (dd, J = 7.7, 5.4 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.05 (dd, J = 13.3, 5.3 Hz, 1H), 2.29 (dd, J = 13.9, 7.5 Hz, 1H), 2.24 (dd, J = 13.2, 7.8 Hz, 1H), 2.09 (dd, J = 14.1, 7.3 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 172.5, 159.6, 148.1, 147.3, 146.2, 136.5, 132.4, 129.8, 128.9, 127.7, 126.3, 117.8, 114.0, 112.7, 103.4, 93.8, 70.5, 68.9, 58.9, 56.3, 55.4, 52.7, 48.3, 36.0, 28.2, 9.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 2252, 1726, 1648, 1483, 1441, 1246, 1162, 1029 cm^{-1}, HR-MS (EI): calcd for $(C_{33}H_{35}NO_7)^+$, 557.2408; found, 557.2403.

Synthesis of the Tertiary Amine Building Block 14. *((2-Iodoethoxy)methyl)benzene (**37**).* 2-Benzyloxyethanol (5.00 g, 32.9 mmol, 1 equiv) was dissolved in dichloromethane (95 mL), and triphenylphosphine (12.9 g, 49.3 mmol, 1.50 equiv) and imidazole (3.36 g, 49.3 mmol, 1.50 equiv) were added. Iodine (12.5 g, 49.3 mmol, 1.5 equiv) was carefully added in three portions, and the yellow suspension was stirred at 23 °C. After 18 h, aqueous sodium thiosulfate solution (1 M, 100 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **37** (8.00 g, 93%) as a colorless oil. The obtained characterization data were in full agreement with those values reported in the literature.[20]

*tert-Butyl N-Allyl-N-(2-benzyloxyethyl) Carbamate (**38**).* *tert*-Butyl allylcarbamate (**36**) (3.14 g, 20.0 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (66 mL) and was added dropwise to a suspension of sodium hydride (1.20 g, 30.0 mmol, 1.50 equiv, 60% dispersion in mineral oil) in *N*,*N*-dimethylformamide (100 mL) at 0 °C. After 45 min, ((2-iodoethoxy)methyl)benzene (**37**) (6.81 g, 26.0 mmol, 1.30

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equiv) was added dropwise. The reaction mixture then was allowed to warm to 23 °C. After 16 h, the reaction mixture was carefully diluted with ammonium chloride solution (200 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **38** as a colorless oil (4.65 g, 80%). TLC (33% ethyl acetate in hexanes): R_f = 0.83 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38−7.25 (m, 5H), 5.79 (dddd, J = 17.7, 9.8, 6.0, 5.2 Hz, 1H), 5.15−5.06 (m, 2H), 4.51 (s, 2H), 3.88 (br s, 2H), 3.58 (t, J = 5.9 Hz, 2H), 3.39 (br s, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 155.8, 139.3, 135.2, 128.8, 128.0, 128.0, 116.3, 116.0, 79.8, 73.4, 69.4, 51.3, 50.7, 46.9, 28.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976, 2930, 2861, 1690, 1477, 1454, 1405, 1365, 1244, 1173, 1150, 1103, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{26}NO_3)^+$ (M + H)$^+$, 292.1913; found, 292.1909.

*tert-Butyl N-(3-Hydroxypropyl)-N-(2-benzyloxyethyl) Carbamate (**39**).* *tert*-Butyl *N*-allyl-*N*-(2-benzyloxyethyl) carbamate (**38**) (3.1 g, 10.6 mmol, 1 equiv) was dissolved in tetrahydrofuran (5.6 mL), and a solution of 9-borabicyclo[3.3.1]nonane (0.5 M solution in tetrahydrofuran, 29.8 mL, 14.9 mmol, 1.40 equiv) was added at 0 °C. After 3 h at 0 °C, the reaction mixture was allowed to warm to 23 °C. After 16 h, aqueous sodium hydroxide solution (10 wt %, 4.9 mL) and aqueous hydrogen peroxide solution (30 wt %, 4.9 mL) were added dropwise and the reaction was heated to 50 °C. After 2 h, heating was ceased and the solution was allowed to cool to 23 °C. The reaction mixture was saturated with sodium carbonate, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **39** as a colorless oil (1.64 g, 50%). TLC (9% ethyl acetate in hexanes): R_f = 0.10 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.51 (s, 2H), 3.80 (t, J = 7.1 Hz, 1H), 3.67−3.31 (m, 8H), 1.87−1.59 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.1, 128.6, 127.9, 127.7, 80.4, 73.3, 68.8, 58.4, 47.3, 43.9, 30.7, 28.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444, 2974, 2866, 1688, 1667, 1479, 1454, 1413, 1366, 1246, 1166, 1139, 1103 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{28}NO_4)^+$ (M + H)$^+$, 310.2018; found, 310.2015.

*tert-Butyl N-(3-Iodopropyl)-N-(2-benzyloxyethyl) Carbamate (**14**).* Iodine (541 mg, 2.13 mmol, 1.20 equiv) was added to a solution of triphenylphosphine (559 mg, 2.13 mmol, 1.20 equiv) and imidazole (145 mg, 2.13 mmol, 1.20 equiv) in dichloromethane (17.5 mL) at 0 °C. After 15 min, a solution of *tert*-butyl *N*-(3-hydroxypropyl)-*N*-(2-phenoxyethyl) carbamate (**39**) (550 mg, 1.78 mmol, 1 equiv) in dichloromethane (3.5 mL) was added dropwise. Upon completion of the addition, the yellow suspension was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with water (15 mL) and ethyl acetate (15 mL). The layers were separated, and the organic layer was washed with aqueous sodium thiosulfate solution (1 M, 40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **14** as a yellow oil (592 mg, 79%). TLC (20% ethyl acetate in hexanes): R_f = 0.68 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 4.52 (s, 2H), 3.68−3.51 (m, 2H), 3.49−3.37 (m, 2H), 3.34 (t, J = 7.0 Hz, 2H), 3.18−3.08 (m, 2H), 2.18−1.98 (m, 2H), 1.47 (s, 5H), 1.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ∼1:1 rotamer ratio, asterisk denotes signals of the second rotamer) δ 155.6, 138.3, *138.3, 132.5, *132.4, *128.6, 128.6, *127.8, 127.7, 80.0, *79.8, 73.2, 69.1, *69.0, 49.2, *47.9, 47.6, 40.6, 32.7, *32.5, 28.6, *28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974, 1671, 1477, 1465, 1454, 1409, 1366, 1241, 1156, 1114 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{27}NO_3I)^+$ (M + H)$^+$, 420.1036; found, 420.1034.

Preparation of Tetrahydrocarbazolone 40. *Tetrahydrocarbazolone **40**.* *N*-Benzyltetrahydrocarbazolone **33** (50 mg, 0.11 mmol, 1 equiv) was dissolved in tetrahydrofuran (1.1 mL) and was added dropwise to a solution of lithium diisopropylamide (0.5 M in tetrahydrofuran, 320 μL, 0.16 mmol, 1.50 equiv; freshly prepared) at −78 °C. After 1 h, methyl cyanoformate (17 μL, 0.21 mmol, 2.00 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 14 h, the red solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester as an orange oil (43 mg, dr = 2.5:1) which contained minor impurities. The β-keto ester was used without additional purification for the next step. To a suspension of sodium hydride (4.9 mg, 0.12 mmol, 1.5 equiv, 60% suspension in mineral oil) in *N*,*N*-dimethylformamide (0.4 mL) was added a solution of β-keto ester (43 mg, 0.08 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.8 mL) at 0 °C. After 30 min, *tert*-butyl *N*-(3-iodopropyl)-*N*-(2-phenoxyethyl) carbamate (**14**) (136 mg, 0.33 mmol, 4.00 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **40** as a yellow solid (54 mg, 60% over 2 steps). Partial separation of the diastereomeric mixture could be achieved by flash column chromatography on silica gel (25% ethyl acetate in hexanes). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.79 (s, 1H), 7.34−7.27 (m, 5H), 7.27−7.21 (m, 3H), 7.15−7.11 (m, 2H), 6.96−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.60 (s, 1H), 5.34 (q, J = 16.5 Hz, 2H), 5.19 (dd, J = 7.9, 5.4 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.51 (s, 2H), 4.44 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 3.64−3.55 (m, 2H), 3.42 (t, J = 5.9 Hz, 2H), 3.36−3.25 (m, 3H), 3.02 (dd, J = 13.2, 5.5 Hz, 1H), 2.28−2.11 (m, 2H), 2.02 (td, J = 13.3, 12.6, 4.7 Hz, 1H), 1.63 (ddt, J = 31.4, 13.1, 6.2 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 189.3, 172.5, 159.8, 155.7, 148.4, 147.7, 146.3, 138.7, 136.6, 132.6, 129.9, 128.9, 128.5, 127.7, 126.4, 118.2, 114.2, 112.8, 103.9, 94.4, 79.5, 73.3, 70.5, 69.1, 69.0, 58.4, 56.5, 56.4, 55.5, 52.6, 48.5, 47.4, 36.8, 32.5, 28.7, 28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1727, 1689, 1658, 1650, 1513, 1494, 1483, 1452, 1365 cm^{-1}. HR-MS (ESI): calcd for $(C_{48}H_{57}N_2O_{10})^+$, 821.4013; found, 821.4008. $[\alpha]_{589}^{20}$ = −3.6 (c = 0.5 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Amine 42. *Amine **42**.* Tetrahydrocarbazolone **40** (13.5 mg, 16.4 μmol, 1 equiv) was added to a solution of hydrogen chloride in 1,4-dioxane (4 M, 0.1 mL) at 23 °C. After 2 h, the reaction mixture was diluted with saturated aqueous potassium carbonate solution (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (4% to 8% methanol in dichloromethane) to afford **41** (9.6 mg, quant.) which contained minor impurities. The product was used without additional purification for the next step. HR-MS (ESI): calcd for $(C_{35}H_{39}N_2O_6)^+$ (M + H)$^+$: 583.2808; found, 583.2805.

Preparation of Allyl Cyanoformate. *Allyl Cyanoformate.* Trimethylsilyl cyanide (1.98 g, 20.0 mmol, 1 equiv) was added to a suspension of allyl chloroformate (2.41 g, 20.0 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (12.30 mg, 0.110 mmol, 0.005 equiv) at 0

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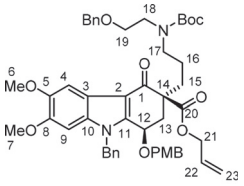
°C. The solution was allowed to warm to 23 °C. After 12 h, 1,4-diazabicyclo[2.2.2]octane was removed by filtration to afford allyl cyanoformate as a yellow oil (1.80 g, 81%). The product was used without further purification for the next step. The obtained characterization data were in full agreement with those values reported in the literature.[28]

Preparation of Diacylated Tetrahydrocarbazolone 45. *Diacylated Tetrahydrocarbazolone* ***45****.* *N*-Benzyltetrahydrocarbazolone **33** (92 mg, 0.19 mmol, 1 equiv) was dissolved in tetrahydrofuran (2 mL) and was added dropwise to a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.036 mL, 0.25 mmol, 1.3 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.10 mL, 0.23 mmol, 1.2 equiv)) in tetrahydrofuran (3 mL) at −78 °C. After 1 h, allyl chloroformate (0.041 mL, 0.39 mmol, 2.0 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 18 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **45** as a yellow oil (30 mg, 24%). TLC (50% ethyl acetate in hexanes): R_f = 0.60 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27−7.20 (m, 3H), 7.19−7.10 (m, 2H), 6.87−6.78 (m, 4H), 6.59 (s, 1H), 5.94 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.80 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dq, J = 17.2, 1.6 Hz, 1H), 5.27−5.02 (m, 5H), 4.79−4.71 (m, 3H), 4.66 (d, J = 11.2 Hz, 1H), 4.64−4.50 (m, 2H), 4.37 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.28 (dd, J = 14.5, 3.7 Hz, 1H), 2.99 (dd, J = 14.4, 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 168.4, 168.1, 159.7, 148.4, 147.5, 144.9, 136.0, 132.0, 131.5, 130.5, 128.9, 127.9, 126.1, 118.7, 118.4, 117.6, 113.9, 112.1, 103.4, 93.6, 70.5, 66.8, 66.8, 65.1, 64.8, 56.3, 56.2, 55.4, 47.5, 34.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 1731, 1658, 1611, 1542, 1514, 1485, 1443, 1272, 1247, 1164, 1075, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{37}H_{38}NO_9)^+$ $(M + H)^+$, 640,2547; found, 640.2542.

Preparation of Tetrahydrocarbazolone 46.



46

Tetrahydrocarbazolone ***46****.* *N*-Benzyltetrahydrocarbazolone *ent*-**33** (10 mg, 0.020 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.5 mL), and hexamethylphosphoramide (0.040 mL, 0.040 mmol, 2.00 equiv) was added. A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.30 mL, 0.30 mmol, 1.5 equiv) was added dropwise at −78 °C. After 1 h, allyl cyanoformate (4.71 mg, 0.04 mmol, 2.00 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 13 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (2 mL) and ethyl acetate (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester **44** as a beige foam, which contained minor impurities. **44** was used without additional purification for the next step. To a solution of β-keto ester **44** (12 mg, 0.020 mmol, 1 equiv) and carbamate **7** (36.2 mg, 0.080 mmol, 4.0 equiv) in tetrahydrofuran (0.5 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.04 mL, 0.040 mmol, 2.0 equiv) dropwise over 15 min at −78 °C. The solution was allowed to warm to 23 °C. After 12 h, the reaction mixture was diluted with ethyl acetate (2 mL) and saturated aqueous sodium bicarbonate solution (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **46** as a yellow oil (4.0 mg, 33% over 2 steps). TLC (50% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM). *Protons of diastereotopic methylene groups are reported as HA and HB, where HA is the more downfield shifted proton. In cases where resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g., the* ^{13}*C assignment "130.0 (PMB, Bn)" indicates that the resonance at 130.0 is either PMB or Bn).* ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.80 (s, 1H, H-4), 7.35−7.27 (m, 4H, Bn), 7.26−7.22 (m, 4H, Bn), 7.16−7.10 (m, 2H, PMB), 6.91−6.89 (m, 2H, Bn), 6.81−6.76 (m, 2H, PMB), 6.59 (s, 1H, H-9), 5.78 (ddt, $^3J_{22/23}$ = 17.2, $^3J_{22/23}$ = 10.4, $^3J_{22/21}$ = 5.5 Hz, 1H, H-22), 5.40 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.28 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.20−5.06 (m, 3H, H-12, H-23), 4.68 (app t, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 4.54 (d, $^3J_{21/22}$ = 5.5 Hz, 2H, H-21), 4.51 (s, 2H, Bn), 4.42 (d, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 3.94 (s, 3H, H-6), 3.78 (s, 3H, PMB), 3.76 (s, 3H, H-7), 3.63−3.52 (m, 2H, H-19), 3.41 (br s, 2H, H-18), 3.31 (br s, 2H, H-17), 3.03 (t, $^3J_{13/12}$ = 12.7 Hz, 1H, H_A-13), 2.31−2.09 (m, 3H, H_B-13, H-15), 1.66−1.56 (m, 2H, H-16), 1.43 (app d, J = 10.0 Hz, 9H, Boc). ^{13}C NMR (100 MHz, $CDCl_3$, asterisks denotes rotamer peaks) δ 189.3 (C-1), 171.5 (C-20), 159.6 (PMB), 155.7 (Boc), 155.5* (Boc), 148.1 (C-8), 147.3 (C-5), 146.1 (C-11), 145.9* (C-11), 138.5 (Bn), 136.4 (Bn), 132.4 (C-10), 131.7 (C-22), 130.0 (PMB, Bn), 129.8 (PMB, Bn), 129.2 (PMB), 128.9 (Bn), 128.5 (Bn), 127.6 (Bn), 126.2 (Bn), 118.5 (C-3, C-23), 117.7 (C-3, C-23), 114.0 (PMB), 112.7 (C-2), 103.3 (C-4), 93.7 (C-9), 79.5 (Boc), 73.1 (Bn), 70.3 (PMB), 69.0 (C-12), 68.7 (C-19), 65.9 (C-21), 58.3 (C-14), 56.3 (C-6), 56.2 (C-7), 55.4 (PMB), 48.2 (Bn), 47.2 (C-17), 47.0 (C-18), 36.5 (C-13), 32.3 (C-15), 32.1* (C-15), 28.6 (Boc), 24.2 (C-16), 23.7* (C-16). IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932, 1728, 1689, 1513, 1453, 1411, 1365, 1248, 1163, 1103, 1067, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{50}H_{59}N_2O_{10})^+$ $(M + H)^+$, 847.4170; found, 847.4155.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01095.

Experimental procedures, X-ray crystallographic data for **33**, NMR spectra of products (PDF)

Crystallographic data for **33** (CIF)

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1547827 contains the supplementary crystallographic data for compound **33**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.
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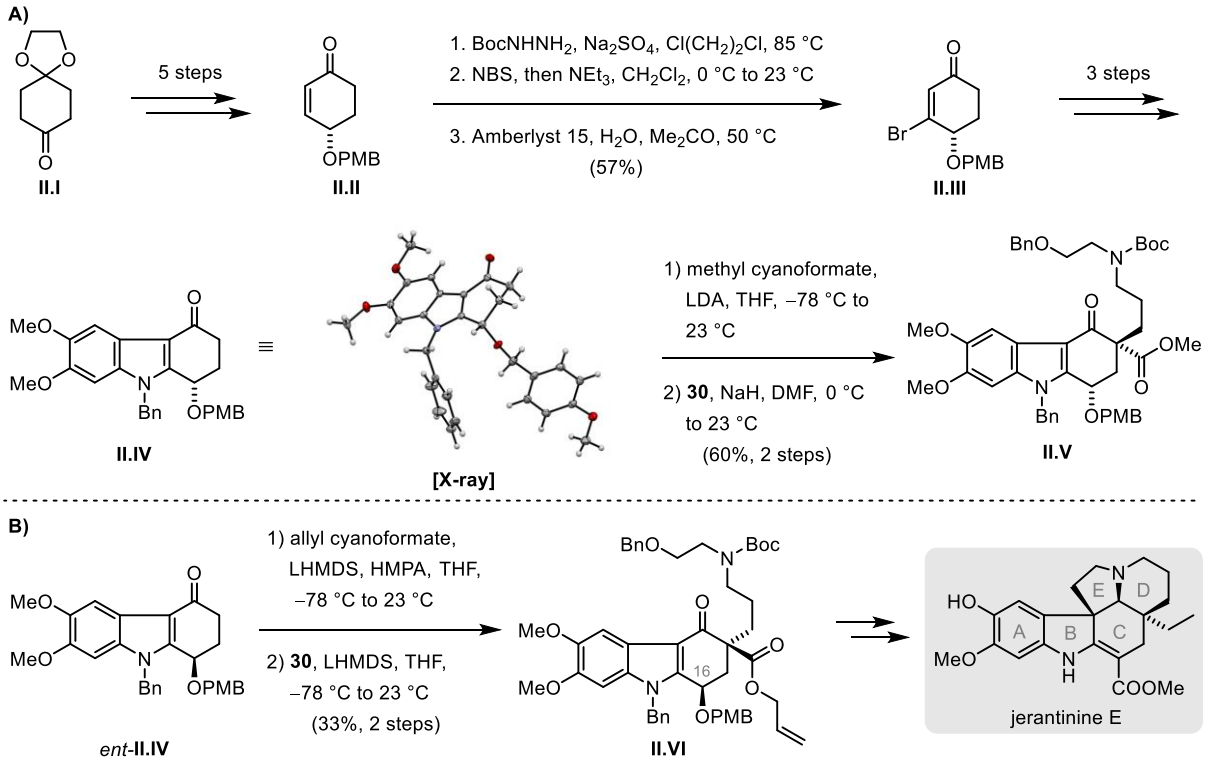
6 Conclusion and Further Directions

In chapter two, the synthesis of an advanced intermediate in the synthesis of the alkaloid jerantinine E was presented. The initial route employing a CH_2OBn-substituted enone suffered from a base-induced elimination of the benzyl ether at C16 of the C-ring. However, utilizing an enantiopure γ-hydroxylated enone, we succeeded in the preparation of the functionalized tetrahydrocarbazolone core of jerantinine E. The synthesis features an one-pot β-C–H bromination reaction developed in our laboratory, a palladium-catalyzed amination with 3,4-dimethoxyaniline, and an oxidative indole formation. Benzyl protection furnished the tetrahydrocarbazolone core, whose structure could be validated by single-crystal X-ray diffraction.

The installation of the secondary amine building block, which contains all carbon atoms of the D and E rings of jerantinine E, was initially accomplished by the incorporation of a methyl ester (Scheme 73A). However, the closure of the D-ring failed and, additionally, the methyl ester could not be converted to the ethyl side chain. Thus, we replaced the methyl ester with an allyl ester which would allow us to set the quaternary stereocenter in a diastereoselective palladium-catalyzed decarboxylative allylation reaction. The stereocenter at C16 was predicted to control the stereochemical outcome of the allylation step, prompting us to prepare the enantiomeric tetrahydrocarbazolone according to the established route. Acylation with allyl cyanoformate followed by alkylation with the secondary amine building block resulted in the formation of β-ketoester **II.VI**, the substrate for the decarboxylative allylation reaction (Scheme 73B).



Scheme 73. Synthesis of advanced intermediates in the synthesis of jerantinine E bearing a methyl ester (A) or an allyl ester (B).

In further experiments, the use of different ligand/catalyst/solvent combinations ($Pd_2(dba)_3$, $Pd(PPh_3)_4$; DACH- or PHOX-ligands; THF, 1,4-dioxane)[144] for the diastereoselective palladium-catalyzed decarboxylative allylation reaction will be investigated. This should ultimately allow us to complete the total synthesis of jerantinine E.

CHAPTER III

EXPERIMENTAL PART

7 Experimental Procedures

7.1 General Experimental Details

All reactions were performed in oven-dried or flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (–78 °C), H_2O/ice (0 °C). Reaction temperatures above 23 °C were conducted in a heated oil bath. The ring opening reactions were conducted in a dram vial and were heated in an aluminum heating block. The reactions were carried out with magnetic stirring and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates pre-coated with silica gel (0.25 mm, 60 Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or stained by submersion in aqueous ceric ammonium molybdate solution (CAM) or potassium permanganate solution ($KMnO_4$), and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.[145] using silica gel (60 Å, 40-63 μm, Merck KGaA) and with a pressure of 1.3–1.5 bar.

Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone and sodium prior to use. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), *N*,*N*-diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base) were distilled from CaH_2 prior to use. Dimethyl sulfoxide (DMSO), benzene, toluene (PhMe), acetonitrile (MeCN), dimethyl formamide (DMF), 1,4-dioxane, 1,2-dichloroethane and methanol (MeOH) were purchased from *Acros Organics* as ‚extra dry' reagents and used as received. Commercially available *N*-bromosuccinimide (NBS) was purified by recrystallization from water.[146] All other reagents were purchased from chemical suppliers (*Sigma-Aldrich*, *Acros Organics*, *Alfa Aesar*, *Strem Chemicals*, *ABCR*) and were used without further purification. Solvents for extraction and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three titraions).[147]

NMR Spectroscopy

^1H and ^{13}C NMR spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400, VNMRS 600, Bruker Avance III HD 400 or Bruker Avance HD 800 spectrometers. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent

($CHCl_3$: δ 7.26, $CDHCl_2$: δ 5.32, acetone: δ 2.05). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_2Cl_2: δ 53.84, acetone: δ 29.84). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Following abbreviations were used for signal multiplicities: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported at the center of the resonance range. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 9.0 from Mestrelab Research S. L.*

Mass Spectroscopy

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument from. Mass spectra were recorded in high-resolution.

IR Spectroscopy

Infrared (IR) spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit. Data are presented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (*br* = broad, *vs* = very strong, *s* = strong, *m* = medium, *w* = weak).

Melting Point

Melting points (M.p.) were determined on a B-450 melting point apparatus from *BÜCHI Labortechnik AG*. The values are uncorrected.

Optical Rotation

Optical rotations were recorded on an *Anton Paar MCP 200* polarimeter with a sodium lamp and. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

The optical rotation is measured using the sodium D line (λ = 589 nm) at the given temperature φ in °C and concentration (*c* in 10 mg/ mL) in a cell with a path length (d) of 0.5 dm. α represents the recorded optical rotation at the apparatus. The optical rotation is reported as $[\alpha]_D^{T[°C]}$(*c* g/100 mL, solvent).

7.2 Supporting Information for Chapter 2.1

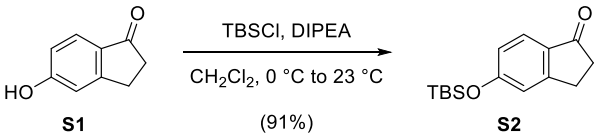
Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin

T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem., Int. Ed.* **2016**, *55*, 9763–9767.

7.2.1 Experimental Procedures

Synthesis of Precursors

5-((*Tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1*H*-inden-1-one (S2):



S1 **S2**

A solution of 5-hydroxy-1-indanone (**S1**) (0.29 mg, 2.0 mmol, 1 equiv) and *tert*-butyldimethylsilyl chloride (0.45 mg, 3.0 mmol, 1.5 equiv) in dichloromethane (5 mL) was treated with *N*,*N*-diisopropylethylamine (0.52 mL, 3.0 mmol, 1.5 equiv) at 0 °C. After 1 h, the solution was allowed to warm to 23 °C. After 14 h, water (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **S2** (0.47 mg, 91%) as a beige solid. Characterization data for **S2** were in full agreement with those reported in the literature.[148]

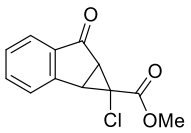
Synthesis of Cyclopropanes

General Procedure for the Cyclopropanation of Indanones: In a pressure vessel, a solution of indanone (1 equiv), *N*-bromosuccinimide (1.1 equiv) and 2,2'-azobis(2-methylpropionitrile) (0.010 equiv) in benzene (0.1–0.2 M) was stirred at 80 °C for 12–14 h. The solution was allowed to cool to 23 °C, and then was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were washed with saturated aqueous sodium chloride solution (1×) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the crude bromo-indanone in dichloromethane (0.1 M) was added triethylamine (5.0 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 30 min, the solution was concentrated. Diethyl ether was added, the mixture was filtered through a short plug of Celite and the filtrate was concentrated. The crude product was used in the next step without further purification.

Methyl dichloroacetate (1.5 equiv) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1.5 equiv) in tetrahydrofuran (0.5 M) at −78 °C. After 30 min, a solution of the crude indenone in tetrahydrofuran (0.5 M) was added dropwise at −78 °C. The solution was allowed to warm to 23 °C. After 16 h, saturated aqueous ammonium chloride solution was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×) and the combined organic layers were washed with

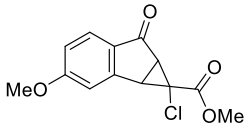
saturated aqueous sodium chloride solution (1×). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel.



20

Following the general procedure, 1-indanone (**S42**) (1.00 g, 7.57 mmol) provided cyclopropane **20** (1.12 g, 62%) as a brown solid after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

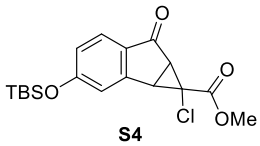
TLC (20% ethyl acetate in hexanes), R_f = 0.28 (UV, CAM). **M.p.**: 78 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 3.82 (s, 3H), 3.66 (d, *J* = 5.9 Hz, 1H), 3.13 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 196.1, 167.0, 147.4, 136.3, 134.7, 129.1, 126.9, 124.3, 62.4, 54.1, 38.6, 35.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3074 (*w*), 2956 (*w*), 2256 (*w*), 1717 (*vs*), 1605 (*m*), 1470 (*w*), 1436 (*m*), 1286 (*m*), 1273 (*s*), 1252 (*vs*), 1204 (*m*), 1181 (*m*), 1102 (*m*), 1055 (*m*), 953 (*w*), 907 (*s*), 863 (*m*), 773 (*s*), 725 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_9{}^{35}ClO_3$ $[M]^+$: 236.0235; found: 236.0235.



S3

Following the general procedure, 5-methoxy-1-indanone (453 mg, 2.79 mmol) provided cyclopropane **S3** (400 mg, 54%) as an orange solid after flash column chromatography on silica gel (20% ethyl acetate in hexanes).

TLC (20% ethyl acetate in hexanes), R_f = 0.20 (UV, CAM). **M.p.**: 105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.61 (dt, *J* = 8.5, 0.5 Hz, 1H), 6.98 (dt, *J* = 2.2, 0.4 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.58 (dt, *J* = 5.9, 0.5 Hz, 1H), 3.12 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.4, 167.1, 165.2, 150.2, 129.2, 126.0, 115.2, 112.0, 62.1, 56.0, 54.1, 39.0, 34.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3066 (*w*), 2955 (*w*), 2839 (*w*), 1712 (*vs*), 1600 (*vs*), 1486 (*m*), 1436 (*m*), 1340 (*m*), 1256 (*vs*), 1117 (*m*), 1073 (*w*), 1025 (*w*), 829 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{12}{}^{35}ClO_4$ $[M+H]^+$: 267.0419; found: 267.0420.

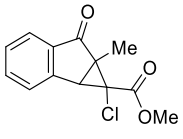


S4

Following the general procedure, indanone **S2** (105 mg, 0.400 mmol) provided cyclopropane **S4** (31.0 mg, 21%) as an orange oil after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

TLC (5% ethyl acetate in hexanes): R_f = 0.24 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.84 (s, 3H), 3.55 (d, *J* = 5.9 Hz, 1H), 3.10 (d, *J* = 5.8 Hz, 1H), 0.99 (s, 9H), 0.25 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.5, 167.1, 162.0, 150.1, 129.7, 126.0, 121.0, 118.4, 62.1, 54.1, 38.9, 34.8, 25.7, 18.4, −4.2, −4.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930 (*w*), 1715 (*vs*), 1599 (*s*), 1482 (*m*), 1298 (*s*), 1252 (*vs*), 1105 (*m*), 949 (*m*),

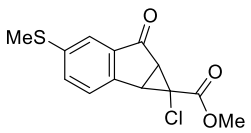
840 (*vs*), 784 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{23}{}^{35}ClO_4Si$ [M]$^+$: 366.1049; found: 366.1053.



S5

Following the general procedure, 2-methyl-1-indanone (500 mg, 3.42 mmol) provided cyclopropane **S5** (283 mg, 33%) as a yellow solid after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

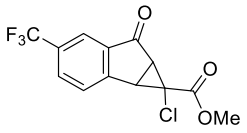
TLC (20% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM). **M.p.**: 59 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 7.7 Hz, 1H), 7.57 (td, *J* = 7.5, 1.0 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.41 (td, *J* = 7.5, 1.0 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 1H), 1.53 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 198.6, 166.2, 147.8, 135.8, 134.6, 128.7, 126.5, 124.2, 65.6, 53.8, 42.5, 37.9, 9.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1717 (*vs*), 1605 (*m*), 1436 (*w*), 1280 (*s*), 1243 (*m*), 1209 (*m*), 1096 (*w*), 953 (*m*), 758 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{35}ClO_3$ [M]$^+$: 250.0391; found: 250.0384.



S6

Following the general procedure, 6-(methylthio)-1-indanone (100 mg, 0.561 mmol) provided cyclopropane **S6** (21.0 mg, 13%) as an orange oil after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

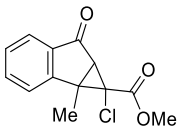
TLC (20% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 1.6 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.62 (d, *J* = 5.9 Hz, 1H), 3.15 (d, *J* = 5.9 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.7, 166.8, 143.9, 140.9, 136.9, 132.4, 126.8, 120.6, 62.5, 54.1, 38.7, 35.0, 15.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1715 (*vs*), 1603 (*m*), 1435 (*s*), 1250 (*vs*), 1197 (*vs*), 1051 (*m*), 828 (*m*), 737 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{35}ClO_3S$ [M]$^+$: 282.0112; found: 282.0110.



S7

Following the general procedure, 6-(trifluoromethyl)-1-indanone (200 mg, 1.00 mmol) provided cyclopropane **S7** (85.5 mg, 28%) as a yellow solid after flash column chromatography on silica gel (20% ethyl acetate in hexanes).

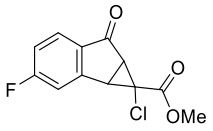
TLC (20% ethyl acetate in hexanes): R_f = 0.20 (UV, CAM). **M.p.**: 153 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.93 (dq, *J* = 1.5, 0.8 Hz, 1H), 7.84 (ddd, *J* = 7.9, 1.6, 0.7 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.76 (d, *J* = 5.8 Hz, 1H), 3.25 (d, *J* = 5.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.5, 166.6, 150.5 (q, *J* = 1.3 Hz), 136.8, 131.7 (q, *J* = 33.4 Hz), 131.3 (q, *J* = 3.6 Hz), 127.4, 123.6 (q, *J* = 272.7 Hz), 121.4 (q, *J* = 3.9 Hz), 61.5, 54.3, 39.1, 35.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3073 (*w*), 2958 (*w*), 1728 (*vs*), 1625 (*m*), 1438 (*w*), 1328 (*vs*), 1257 (*vs*), 1190 (*s*), 1169 (*s*), 1124 (*vs*), 1053 (*m*), 848 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_8{}^{35}ClF_3O_3$ [M]$^+$: 304.0109; found: 304.0094.



S8

Following the general procedure, 3-methyl-1-indanone (200 mg, 1.37 mmol) provided cyclopropane **S8** (62.0 mg, 18%) as a dark orange oil after flash column chromatography on silica gel (12.5% ethyl acetate in hexanes).

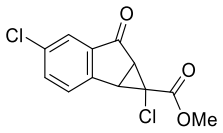
TLC (20% ethyl acetate in hexanes), R_f = 0.45 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.71–7.57 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 3.86 (s, 3H), 3.24 (s, 1H), 1.76 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 196.8, 166.3, 151.8, 135.9, 134.6, 128.9, 124.9, 123.8, 65.0, 53.8, 41.7, 40.2, 11.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1714 (*vs*), 1604 (*m*), 1435 (*m*), 1275 (*vs*), 1202 (*vs*), 1055 (*s*), 862 (*s*), 767 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{35}ClO_3$ $[M]^+$: 250.0391; found: 250.0386.



S9

Following the general procedure, 5-fluoro-1-indanone (200 mg, 1.33 mmol) provided cyclopropane **S9** (181 mg, 53%) as a yellow solid after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

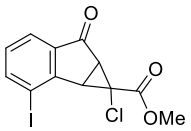
TLC (dichloromethane), R_f = 0.56 (UV, CAM). **M.p.**: 125 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.19 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.10 (td, *J* = 8.6, 2.3 Hz, 1H), 3.84 (s, 3H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.16 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.1, 166.8 (d, *J* = 257.3 Hz), 166.7, 150.2 (d, *J* = 10.6 Hz), 132.5 (d, *J* = 2.4 Hz), 126.4 (d, *J* = 10.6 Hz), 116.7 (d, *J* = 23.5 Hz), 114.4 (d, *J* = 23.8 Hz), 61.8, 54.1, 38.9, 34.6 (d, *J* = 2.5 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3071 (*w*), 2956 (*w*), 1715 (*vs*), 1613 (*s*), 1596 (*s*), 1479 (*m*), 1436 (*m*), 1336 (*m*), 1251 (*vs*), 1229 (*vs*), 1197 (*s*), 1100 (*s*), 946 (*m*), 837 (*m*), 803 (*m*), 731 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}ClFO_3$ $[M]^+$: 254.0141; found: 254.0136.



S10

Following the general procedure, 6-chloro-1-indanone (300 mg, 1.80 mmol) provided cyclopropane **S10** (197 mg, 40%) as a pale yellow solid after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

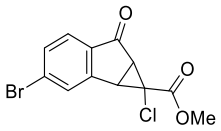
TLC (ethyl acetate in hexane), R_f = 0.26 (UV, CAM). **M.p**.: 170 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.64 (dq, *J* = 2.0, 0.5 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.0, 0.3 Hz, 1H), 7.46 (ddt, *J* = 8.1, 0.6, 0.3 Hz, 1H), 3.86 (d, *J* = 0.4 Hz, 3H), 3.68–3.64 (m, 1H), 3.19 (dd, *J* = 5.9, 0.3 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.7, 166.7, 145.5, 137.8, 135.5, 134.5, 127.9, 124.4, 62.0, 54.2, 39.0, 34.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3067 (*w*), 2956 (*w*), 1726 (*vs*), 1467 (*w*), 1437 (*w*), 1301 (*m*), 1254 (*vs*), 1198 (*m*), 1121 (*w*), 1056 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}Cl_2O_3$ $[M]^+$: 269.9845; found: 269.9843.



S11

Following the general procedure, 4-iodo-1-indanone (200 mg, 0.775 mmol) provided cyclopropane **S11** (214 mg, 76%) as a white solid after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

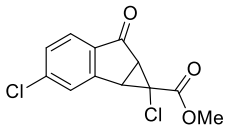
TLC (20% ethyl acetate in hexanes): R_f = 0.35 (UV, CAM). **M.p.**: 112 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.95 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.18 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.5, 166.5, 151.9, 143.6, 137.7, 130.6, 123.8, 95.2, 61.6, 54.3, 39.0, 39.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3416 (*w*), 2950 (*w*), 1718 (*vs*), 1582 (*m*), 1436 (*s*), 1398 (*m*), 1245 (*s*), 1206 (*s*), 1017 (*m*), 922 (*m*), 771 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}Cl^{127}IO_3$ $[M]^+$: 361.9201; found: 361.9207.



S12

Following the general procedure, 5-bromo-1-indanone (1.06 g, 5.00 mmol) provided cyclopropane **S12** (642 mg, 41%) as an orange solid after flash column chromatography on silica gel (12.5% ethyl acetate in hexanes).

TLC (20% ethyl acetate in hexanes), R_f = 0.73 (UV, CAM). **M.p.**: 114 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 1.6 Hz, 1H), 7.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.16 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.7, 166.7, 149.0, 135.1, 132.6, 130.2, 129.9, 125.3, 61.7, 54.2, 38.7, 34.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1718 (*vs*), 1596 (*s*), 1435 (*m*), 1320 (*m*), 1257 (*vs*), 1058 (*m*), 835 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{79}Br^{35}ClO_3[M]^+$: 313.9340; found: 313.9341.



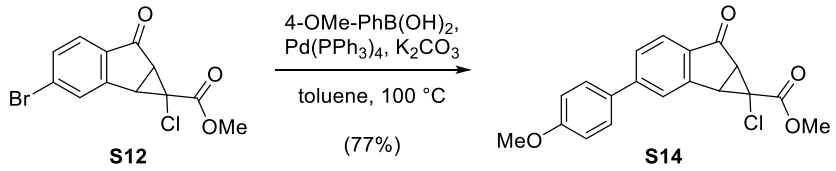
S13

Following the general procedure, 5-chloro-1-indanone (200 mg, 1.20 mmol) provided cyclopropane **S13** (126 mg, 31%) as an orange solid after flash column chromatography on silica gel (10% ethyl acetate in hexanes).

TLC (20% ethyl acetate in hexanes): R_f = 0.25 (UV). **M.p.**: 91 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.41 (dd, *J* = 8.1, 1.8 Hz, 1H), 3.86 (s, 3H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.17 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.4, 166.7, 148.9, 141.2, 134.8, 129.6, 127.3, 125.3, 61.7, 54.2, 38.8, 34.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1748 (*m*), 1719 (*vs*), 1599 (*s*), 1434 (*m*), 1252 (*vs*), 1167 (*m*), 1110 (*s*), 844 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}Cl_2O_3$ $[M]^+$: 269.9845; found: 269.9837.

Functionalization of Cyclopropanes

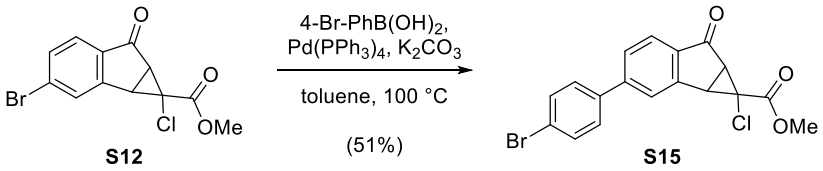
Cyclopropane S14:



In a pressure vessel, a solution of cyclopropane **S12** (0.10 g, 0.32 mmol, 1 equiv), 4-methoxy-phenylboronic acid (72 mg, 0.48 mmol, 1.5 equiv), tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.032 mmol, 0.10 equiv) and potassium carbonate (66 mg, 0.48 mmol, 1.5 equiv) in toluene (2 mL) was stirred at 100 °C. After 16 h, the solution was allowed to cool to 23 °C, and then was concentrated. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **S14** (84 mg, 77%) as a yellow oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.17 (UV, CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.71 (s, 1H), 7.70–7.57 (m, 4H), 7.05–6.96 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.71 (d, J = 5.8 Hz, 1H), 3.16 (d, J = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 195.6, 167.0, 160.7, 148.7, 147.5, 134.7, 132.1, 128.9, 127.6, 125.0, 124.5, 114.8, 62.6, 55.7, 54.2, 39.2, 35.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (*w*), 2838 (*w*), 1716 (*vs*), 1601 (*vs*), 1519 (*s*), 1436 (*m*), 1248 (*vs*), 1179 (*s*), 1119 (*s*), 1019 (*m*), 954 (*m*), 827 (*s*), 704 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{15}{}^{35}ClO_4$ $[M]^+$: 342.0653; found: 342.0648.

Cyclopropane S15:



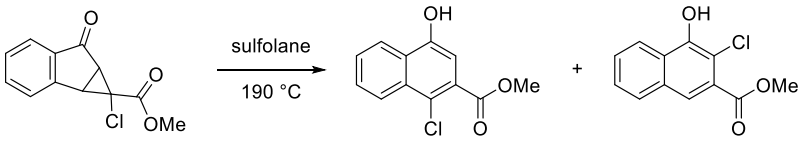
In a pressure vessel, a solution of cyclopropane **S12** (32 mg, 0.10 mmol, 1 equiv), 4-bromo-phenylboronic acid (31 mg, 0.15 mmol, 1.5 equiv), tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.010 mmol, 0.10 equiv) and potassium carbonate (21 mg, 0.15 mmol, 1.5 equiv) in toluene (0.4 mL) was stirred at 100 °C, After 18 h, the solution was allowed to cool to 23 °C, and then was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S15** (20 mg, 51%) as an orange oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.33 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.73 (dt, J = 7.9, 0.7 Hz, 1H), 7.70–7.66 (m, 1H), 7.64–7.57 (m, 3H), 7.53–7.46 (m, 2H), 3.87 (s, 3H), 3.71 (d, J = 5.9 Hz, 1H), 3.20 (d, J = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.5, 166.9, 148.3, 146.5, 138.6, 135.3, 132.3, 129.1, 127.9, 125.3, 124.7, 123.3, 62.1, 54.1, 39.0, 35.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3064 (*w*), 2954 (*w*), 1717 (*vs*), 1607 (*s*), 1435 (*m*), 1325 (*m*), 1269 (*s*), 1250 (*s*), 1074 (*m*), 1007 (*m*), 822 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{12}{}^{79}Br^{35}ClO_3$ $[M]^+$: 389.9653; found: 389.9667.

Ring opening Reaction of Cyclopropanes

Methyl 1-chloro-4-hydroxy-2-naphthoate (6a) and methyl 3-chloro-4-hydroxy-2-naphthoate (6b):



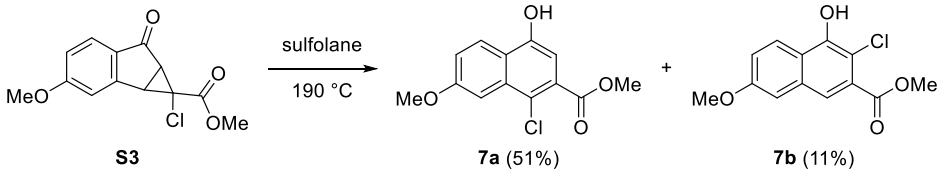
20 **6a** (66%) **6b** (21%)

A solution of cyclopropane **20** (47 mg, 0.20 mmol, 1 equiv) in sulfolane (0.4 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **6a** (31 mg, 66%) and **6b** (10 mg, 21%) as yellow solids.

6a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.24 (UV, CAM). **M.p.**: 177 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.64 (s, 1H), 8.35 (t, J = 9.2 Hz, 2H), 7.62 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.69 (ddd, J = 7.9, 6.9, 1.2 Hz, 1H), 3.93 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.2, 153.1, 132.5, 129.7, 129.3, 128.1, 127.8, 125.9, 123.5, 121.4, 108.6, 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3285 (*m*), 3078 (*w*), 2951 (*w*), 1695 (v*s*), 1596 (*s*), 1454 (*m*), 1435 (*s*), 1391 (*m*), 1350 (*s*), 1294 (*s*), 1244 (*vs*), 1150 (*s*), 1078 (*s*), 1014 (*m*), 965 (*m*), 874 (*m*), 783 (*m*), 758 (*vs*), 658 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_9{}^{35}ClO_3$ $[M]^+$: 236.0235; found: 236.0244.

6b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.45 (UV, CAM). **M.p.**: 88 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.3 Hz, 1H), 8.06 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.68–7.47 (m, 2H), 6.46 (d, J = 1.1 Hz, 1H), 3.99 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.1, 148.4, 131.5, 128.8, 128.4, 127.7, 126.4, 125.7, 124.7, 122.5, 111.6, 52.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3426 (*w*), 2952 (*w*), 1725 (*vs*), 1584 (*m*), 1453 (*m*), 1402 (*s*), 1300 (*s*), 1230 (*vs*), 1013 (*m*), 779 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_9{}^{35}ClO_3$ $[M]^+$: 236.0235; found: 236.0228.

Methyl 1-chloro-4-hydroxy-7methoxy-2-naphthoate (7a) and methyl 3-chloro-4-hydroxy-7-methoxy-2-naphthoate (7b):



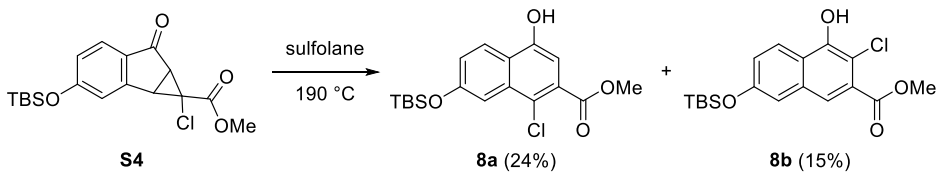
S3 **7a** (51%) **7b** (11%)

A solution of cyclopropane **S3** (100 mg, 0.375 mmol, 1 equiv) in sulfolane (0.6 mL) was stirred at 190 °C for 90 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (40 mL). The organic layer was washed sequentially with water (2 × 30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% dichloromethane in hexanes) to afford **7a** (51 mg, 51%) as a yellow solid and **7b** (11 mg, 11%) as a yellow oil.

7a: **TLC** (50% dichloromethane in hexanes), R_f = 0.12 (UV, CAM). **M.p.**: 168 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.51 (s, 1H), 8.23 (dd, J = 9.2, 0.5 Hz, 1H), 7.63 (dt, J = 2.5, 0.4 Hz, 1H), 7.29 (dd, J = 9.2, 2.5 Hz, 1H), 7.08 (s, 1H), 4.01–3.95 (m, 3H), 3.92 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.4, 160.7, 153.2, 134.2, 130.5, 125.4, 122.7, 120.3, 119.9, 106.9, 104.3, 55.8, 52.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3298 (*m*), 2950 (*w*), 1690 (*vs*), 1597 (*s*), 1442 (*s*), 1380 (*s*), 1221 (*vs*), 1135 (*vs*), 1083 (*s*), 1018 (*s*), 933 (*m*), 829 (*s*), 782 (*vs*), 714 (*m*), 667 (*s*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{10}{}^{35}ClO_4$ [M-H]$^-$: 265.0273; found: 265.0273.

7b: **TLC** (50% dichloromethane in hexanes), R_f = 0.38 (UV, CAM). **^{1}H NMR** (800 MHz, CD_2Cl_2) δ: 8.13 (d, J = 9.1 Hz, 1H), 7.93 (s, 1H), 7.26 (dd, J = 9.1, 2.5 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 6.46 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H). **^{13}C NMR** (200 MHz, CD_2Cl_2) δ: 166.2, 159.4, 148.8, 133.5, 127.6, 124.2, 123.4, 121.1, 121.1, 109.8, 106.9, 55.8, 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (w), 2950 (*w*), 1727 (*vs*), 1593 (*s*), 1438 (*s*), 1396 (*vs*), 1230 (*vs*), 1170 (*s*), 1093 (*m*), 1026 (*s*), 921 (*m*), 828 (*m*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{10}{}^{35}ClO_4$ [M–H]$^-$: 265.0273; found: 265.0273.

Methyl 7-((*tert*-butyldimethylsilyl)oxy)-1-chloro-4-hydroxy-2-naphthoate (8a) and methyl 7-((*tert*-butyldimethylsilyl)oxy)-3-chloro-4-hydroxy-2-naphthoate (8b):



S4 **8a** (24%) **8b** (15%)

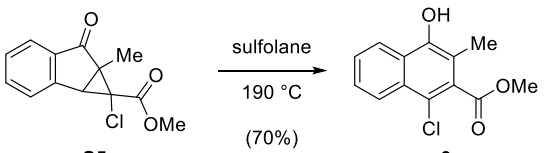
A solution of cyclopropane **S4** (33 mg, 0.090 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool 23 °C and then was diluted with diethyl ether

20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **8a** (8 mg, 24%) as an orange solid and **8b** (5 mg, 15%) as a yellow oil.

8a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.27 (UV, CAM). **M.p.**: 138 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.58 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 9.0, 2.4 Hz, 1H), 7.08 (s, 1H), 3.92 (s, 3H), 1.05 (s, 9H), 0.32 (s, 6H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.3, 156.8, 153.3, 134.2, 130.4, 125.7, 123.7, 123.2, 119.6, 113.2, 107.0, 52.8, 26.0, 18.9, −4.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3405 (*w*), 2954 (*m*), 2858 (*w*), 1711 (*m*), 1598 (*s*), 1463 (*s*), 1384 (*s*), 1236 (*vs*), 994 (*s*), 827 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{23}{}^{35}ClO_4Si$ [M]$^+$: 366.1049; found: 366.1056.

8b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.44 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.11 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 9.1, 2.5 Hz, 1H), 7.00 (s, 1H), 5.39 (s, 1H), 3.98 (s, 3H), 1.08 (s, 9H), 0.29 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 167.3, 155.6, 150.9, 133.9, 128.6, 125.5, 125.4, 122.1, 119.2, 110.7, 108.2, 52.8, 26.0, 18.6, −4.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3405 (*w*), 2929 (*m*), 2858 (*m*), 1713 (*m*), 1595 (*m*), 1421 (*s*), 1364 (*s*), 1219 (*s*), 1100 (*s*), 846 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{23}{}^{35}ClO_4Si$ [M]$^+$: 366.1049; found: 366.1045.

Methyl 1-chloro-4-hydroxy-3-methyl-2-naphthoate (9):

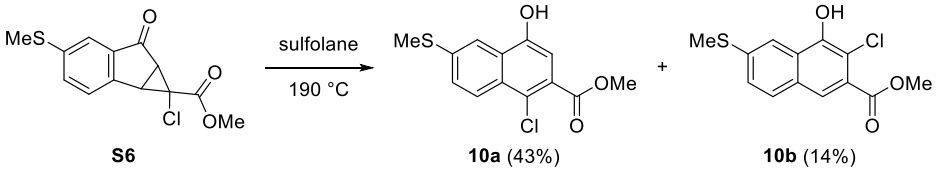


S5 **9**

A solution of cyclopropane **S5** (125 mg, 0.500 mmol, 1 equiv) in sulfolane (1 mL) was stirred at 190 °C for 45 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (40 mL). The organic layer was washed sequentially with water (2 × 30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **9** (88 mg, 70%) as a colorless oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.20 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08–7.99 (m, 2H), 7.53–7.45 (m, 2H), 5.87 (brs, 1H), 4.02 (s, 3H), 2.26 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.0, 148.2, 132.3, 129.4, 127.2, 127.0, 125.8, 124.6, 121.6, 119.9, 114.7, 53.0, 13.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3458 (*w*, *br*), 2952 (*w*), 1712 (*vs*), 1594 (*m*), 1438 (*s*), 1389 (*s*), 1293 (*vs*), 1225 (*vs*), 1052 (*s*), 920 (*s*), 757 (*vs*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{10}{}^{35}ClO_3$ [M−H]$^-$: 249.0324; found: 249.0323.

Methyl 1-chloro-4-hydroxy-6-(methylthio)-2-naphthoate (10a) and methyl 3-chloro-4-hydroxy-6-(methylthio)-2-naphthoate (10b):



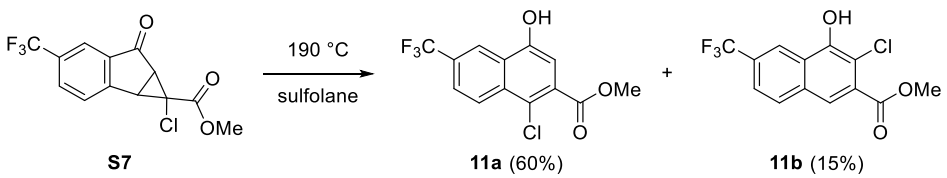
S6 **10a** (43%) **10b** (14%)

A solution of cyclopropane **S6** (21 mg, 0.074 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **10a** (9 mg, 43%) as a yellow solid and **10b** (3 mg, 14%) as a brown solid.

10a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.19 (UV, CAM). **M.p.**: 177 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.59 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 9.1, 1.9 Hz, 1H), 7.25 (s, 1H), 3.92 (s, 3H), 2.65 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.0, 151.9, 140.4, 130.1, 128.3, 128.3, 128.1, 126.3, 121.9, 117.6, 109.7, 52.7, 14.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3356 (*m*), 2943 (*w*), 1710 (*s*), 1689 (*s*), 1614 (*m*), 1588 (*m*), 1357 (*m*), 1296 (*m*), 1236 (*vs*), 1099 (*m*), 966 (*m*), 778 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{35}ClO_3S$ [M]$^+$: 282.0112; found: 282.0113.

10b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.28 (UV, CAM). **M.p.**: 134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.90 (d, J = 1.3 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.42 (dd, J = 8.8, 1.8 Hz, 1H), 6.41 (s, 1H), 3.97 (s, 3H), 2.62 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.0, 147.3, 140.5, 129.0, 128.8, 126.9, 126.2, 125.1, 124.7, 116.4, 112.6, 52.7, 15.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3426 (*w*), 2951 (*w*), 1722 (*vs*), 1568 (*m*), 1450 (*s*), 1410 (*s*), 1294 (*s*), 1227 (*vs*), 1104 (*s*), 1017 (*m*), 929 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{35}ClO_3S$ [M]$^+$: 282.0112; found: 282.0115.

Methyl 1-chloro-4-hydroxy-6-(trifluoromethyl)-2-naphthoate (11a) and methyl 3-chloro-4-hydroxy-6-(trifluoromethyl)-2-naphthoate (11b):



S7 **11a** (60%) **11b** (15%)

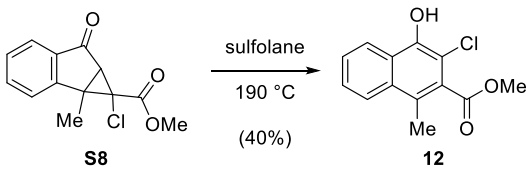
A solution of cyclopropane **S7** (40 mg, 0.13 mmol, 1 equiv) in sulfolane (0.26 mL) was stirred at 190 °C for 90 min. The reaction mixture was allowed to cool 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium

chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **11a** (24 mg, 60%) and **11b** (6 mg, 15%) as yellow solids.

11a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.24 (UV, CAM). **M.p.**: 224 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 10.09 (s, 1H), 8.64 (dp, J = 1.8, 0.9 Hz, 1H), 8.54 (dp, J = 9.1, 0.8 Hz, 1H), 7.97 (ddd, J = 9.0, 2.0, 0.6 Hz, 1H), 7.34 (s, 1H), 3.96 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 166.9, 153.9, 134.0 (q, J = 1.0 Hz), 132.5, 129.1 (q, J = 32.5 Hz), 127.7, 126.7, 125.2 (q, J = 271.5 Hz), 124.6 (q (J = 3.1 Hz), 121.5 (q, J = 4.6 Hz), 110.1, 110.0, 53.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3323 (*m*, *br*), 1698 (*vs*), 1600 (*m*), 1441 (*m*), 1359 (*m*), 1324 (*s*), 1250 (*vs*), 1173 (*s*), 1114 (*vs*), 822 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_8{}^{35}ClF_3O_3$ $[M]^+$: 304.0109; found: 304.0101.

11b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.46 (UV, CAM). **M.p.**: 108 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.56 (d, J = 0.9 Hz, 1H), 8.07 (s, 1H), 7.97 (dd, J = 8.5, 0.7 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 6.57 (s, 1H), 4.05–3.98 (m, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 165.7, 149.2, 132.7, 130.0 (J = 33.1 Hz), 129.8, 128.9, 124.6, 124.1 (J = 272.2 Hz), 123.9, 123.4, 120.7, 113.1, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3421 (*w*), 2957 (*w*), 1727 (*s*), 1594 (*w*), 1417 (*m*), 1320 (*s*), 1291 (*vs*), 1229 (*s*), 1166 (*s*), 1124 (*vs*), 1096 (*vs*), 1016 (*m*), 908 (*m*), 818 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_8{}^{35}ClF_3O_3$ $[M]^+$:304.0109; found: 304.0111.

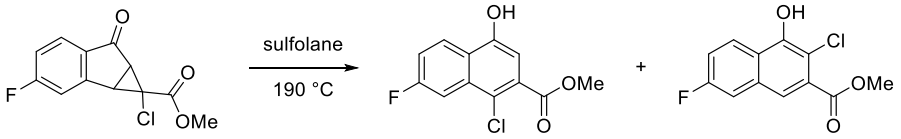
Methyl 3-chloro-4-hydroxy-1-methyl-2-naphthoate (12):



A solution of cyclopropane **S8** (50 mg, 0.20 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 60 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (40 mL). The organic layer was washed sequentially with water (2 × 30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **12** (20 mg, 40%) as a yellow solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.56 (UV, CAM). **M.p.**: 112 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.30–8.21 (m, 1H), 8.02–7.93 (m, 1H), 7.64–7.53 (m, 2H), 6.02 (s, 1H), 4.01 (s, 3H), 2.57 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.3, 146.1, 131.9, 130.2, 127.5, 127.0, 124.8, 124.7, 124.7, 122.8, 109.4, 52.9, 16.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3433 (*w*, *br*), 2950 (*w*), 1725 (*vs*), 1588 (*s*), 1434 (*s*), 1399 (*vs*), 1288 (*s*), 1225 (*vs*), 1088 (*s*), 1047 (*vs*), 891 (*s*), 758 (*s*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{10}{}^{35}ClO_3$ $[M-H]^-$: 249.03240; found: 249.03208.

Methyl 1-chloro-7-fluoro-4-hydroxy-2-naphthoate (13a) and methyl 3-chloro-7-fluoro-4-hydroxy-2-naphthoate (13b):



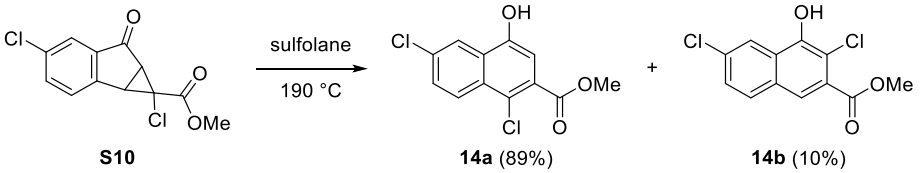
S9 **13a** (61%) **13b** (12%)

A solution of cyclopropane **S9** (51 mg, 0.20 mmol, 1 equiv) in sulfolane (0.4 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **13a** (31 mg, 61%) and **13b** (6 mg, 12%) as yellow solids.

13a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.26 (UV, CAM). **M.p.**: 231 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.80 (s, 1H), 8.39 (dd, J = 9.2, 5.8 Hz, 1H), 7.96 (dd, J = 11.0, 2.6 Hz, 1H), 7.52 (ddd, J = 9.1, 8.2, 2.6 Hz, 1H), 7.19 (s, 1H), 3.94 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.0, 163.3 (d, J = 246.8 Hz), 153.4 (d, J = 1.1 Hz), 134.0 (d, J = 9.7 Hz), 131.3, 127.1 (d, J = 9.5 Hz), 124.74 (d, J = 0.7 Hz), 120.3 (d, J = 5.3 Hz), 118.0 (d, J = 25.4 Hz), 109.6 (d, J = 24.2 Hz), 108.3 (d, J = 2.2 Hz), 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3312 (*s*), 1704 (*vs*), 1598 (*s*), 1438 (*m*), 1357 (*s*), 1310 (*s*), 1242 (*vs*), 1198 (*s*), 1139 (*s*), 1083 (*s*), 990 (*m*), 937 (*m*), 859 (*vs*), 820 (*s*), 786 (*s*), 751 (*m*), 717 (*m*), 673 (*s*) cm^{-1}. **HRMS** (ESI) calcd for $C_{12}H_7{}^{35}ClFO_3$ $[M-H]^-$: 253.00732; found: 253.00704.

13b: **TLC** (10% ethyl acetate in hexanes), R_f = 0.33 (UV, CAM). **M.p.**: 101 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.25 (dd, J = 9.2, 5.5 Hz, 1H), 7.96 (s, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.37 (td, J = 9.1, 2.4 Hz, 1H), 6.48 (s, 1H), 3.99 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.9, 161.7 (d, J = 249.0 Hz), 148.6 (d, J = 1.4 Hz), 132.6 (d, J = 9.6 Hz), 127.8, 125.4 (d, J = 9.2 Hz), 123.5 (d, J = 5.3 Hz), 122.7, 118.6 (d, J = 25.3 Hz), 111.9 (d, J = 21.2 Hz), 111.1 (d, J = 2.6 Hz), 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3387 (w), 2954 (*w*), 1729 (*s*), 1705 (*vs*), 1582 (*vs*), 1446 (*s*), 1399 (*vs*), 1281 (*s*), 1223 (*vs*), 1018 (*s*), 821 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}ClFO_3$ $[M]^+$: 254.0141; found: 254.0143.

Methyl 1,6-dichloro-4-hydroxy-2-naphthoate (14a) and methyl 3,6-dichloro-4-hydroxy-2-naphthoate (14b):



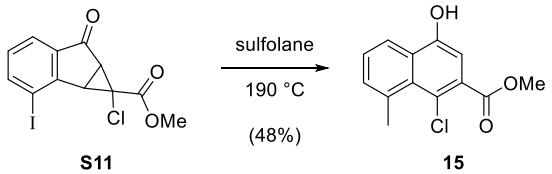
S10 **14a** (89%) **14b** (10%)

A solution of cyclopropane **S10** (100 mg, 0.37 mmol, 1 equiv) in sulfolane (0.7 mL) was stirred at 190 °C for 90 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **14a** (89 mg, 89%) as a white solid and **14b** (10 mg, 10%) as a yellow solid.

14a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.32 (UV, CAM, $KMnO_4$). **M.p.**: 216 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.80 (s, 1H), 8.39–8.33 (m, 1H), 8.28 (dt, J = 2.3, 0.4 Hz, 1H), 7.73 (dd, J = 9.1, 2.2 Hz, 1H), 7.28 (s, 1H), 3.94 (d, J = 0.3 Hz, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 166.9, 152.3, 134.1, 131.1, 130.2, 129.9, 128.5, 128.3, 122.5, 121.5, 110.0, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3308 (*m*, *br*), 1699 (*vs*), 1591 (*s*), 1466 (*w*), 1436 (*m*), 1389 (*m*), 1293 (*m*), 1244 (*s*), 1101 (*m*), 965 (*w*), 809 (*w*), 782 (*m*) cm^{-1}. **HRMS** (ESI) calcd for $C_{12}H_7{}^{35}Cl_2O_3$ [M−H]$^-$: 268.9778; found: 268.9777.

14b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.54 (UV, CAM, $KMnO_4$). **M.p.**: 132 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.22 (dt, J = 2.1, 0.7 Hz, 1H), 8.02 (t, J = 0.6 Hz, 1H), 7.78 (dt, J = 8.8, 0.5 Hz, 1H), 7.49 (dd, J = 8.7, 2.1 Hz, 1H), 6.45 (s, 1H), 3.98 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 165.8, 147.7, 134.6, 130.3, 129.7, 128.8, 126.7, 126.3, 124.3, 121.8, 112.9, 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3359 (*m*), 1703 (*vs*), 1574 (*m*), 1452 (*m*), 1412 (*s*), 1304 (*s*), 1235 (*s*), 1192 (*m*), 1106 (*m*), 1015 (m), 805 (*m*) cm^{-1}. **HRMS** (ESI) calcd for $C_{12}H_7{}^{35}Cl_2O_3$ [M−H]$^-$: 268.9778; found: 268.9776.

Methyl 1-chloro-4-hydroxy-8-iodo-2-naphthoate (15):



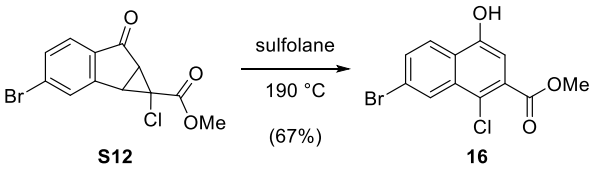
S11 **15**

A solution of cyclopropane **S11** (25 mg, 0.069 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 90 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was

filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **15** (12 mg, 48%) as an orange solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.35 (UV, CAM). **M.p.**: 135 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ: 8.30–8.21 (m, 1H), 8.15 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.28 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.48 (s, 1H), 4.02 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.7, 148.3, 139.2, 132.5, 128.9, 128.4, 127.8, 126.0, 123.2, 112.6, 99.7, 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3416 (w), 2950 (*w*), 1718 (*vs*), 1582 (*m*), 1436 (*s*), 1206 (*s*), 1017 (*m*), 922 (*m*), 771 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}Cl^{127}IO_3$ $[M]^+$: 361.9201; found: 361.9207.

Methyl 7-bromo-1-chloro-4-hydroxy-2-naphthoate (16):

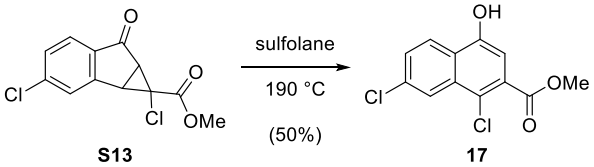


S12 **16**

A solution of cyclopropane **S12** (30 mg, 0.095 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **16** (20 mg, 67%) as brown solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.20 (UV, CAM). **M.p.**: 208 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.86 (s, 1H), 8.49 (d, *J* = 1.9 Hz, 1H), 8.25 (d, *J* = 8.9 Hz, 1H), 7.79 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.25 (s, 1H), 3.94 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 166.9, 153.4, 133.7, 131.3, 131.1, 127.9, 126.3, 125.9, 123.6, 120.0, 109.3, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3332 (*m*), 1694 (*vs*), 1586 (*m*), 1434 (*w*), 1358 (*m*), 1245 (*vs*), 1153 (*m*), 1084 (*m*), 1031 (*m*), 970 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{79}Br^{35}ClO_3$ $[M]^+$: 313.9340; found: 313.9339.

Methyl 1,7-dichloro-4-hydroxy-2-naphthoate (17):

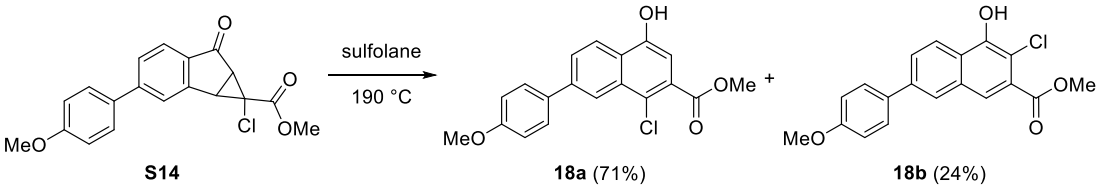


S13 **17**

A solution of cyclopropane **S13** (50 mg, 0.18 mmol, 1 equiv) in sulfolane (0.4 mL) was stirred at 190 °C for 120 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium

chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **17** (25 mg, 50%) as an orange solid. **TLC** (20% ethyl acetate in hexanes), R_f = 0.28 (UV, CAM). **M.p.**: 209 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.90 (brs, 1H), 8.33 (d, J = 6.9 Hz, 1H), 8.31 (s, 1H), 7.66 (dd, J = 8.9, 2.1 Hz, 1H), 7.24 (s, 1H), 3.94 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 166.9, 153.3, 135.2, 133.4, 131.2, 128.7, 126.1, 126.0, 124.6, 120.1, 109.2, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3321 (m), 2956 (*w*), 1705 (*vs*), 1591 (*s*), 1433 (*s*), 1353 (*s*), 1261 (*vs*), 1240 (*vs*), 1147 (*s*), 1090 (*vs*), 977 (*s*), 865 (*s*), 815 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_8{}^{35}Cl_2O_3$ [M]$^+$: 269.9845; found: 269.9851.

Methyl 1-chloro-4-hydroxy-7-(4-methoxyphenyl)-2-naphthoate (18a) and methyl 3-chloro-4-hydroxy-7-(4-methoxyphenyl)-2-naphthoate (18b):



S14 **18a** (71%) **18b** (24%)

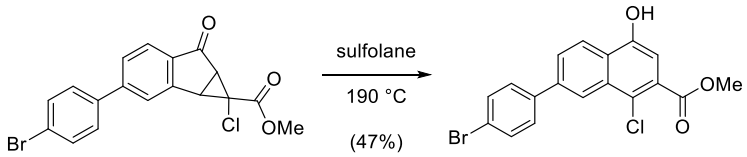
A solution of cyclopropane **S14** (21 mg, 0.061 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **18a** (15 mg, 71%) and **18b** (5 mg, 24%) as a yellow solids.

18a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.25 (UV, CAM). **M.p.**: 160 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.64 (s, 1H), 8.51 (t, J = 1.3 Hz, 1H), 8.37 (d, J = 8.7 Hz, 1H), 7.96 (dt, J = 8.7, 1.4 Hz, 1H), 7.82–7.76 (m, 2H), 7.20 (s, 1H), 7.16–7.07 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.3, 160.9, 153.1, 141.5, 133.3, 133.0, 130.2, 129.3, 127.3, 126.5, 124.3, 122.6, 121.4, 115.4, 108.5, 55.7, 52.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3326 (*m*), 2955 (*w*), 1705 (*s*), 1604 (*s*), 1522 (*m*), 1438 (*m*), 1386 (*m*), 1244 (*vs*), 1180 (*s*), 1088 (*m*), 1028 (*m*), 821 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{15}{}^{35}ClO_4$ [M]$^+$: 342.0653; found: 342.0652.

18b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.45 (UV, CAM). **M.p.**: 153 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.28 (d, J = 8.6 Hz, 1H), 8.09 (s, 1H), 7.98 (s, 1H), 7.85 (dt, J = 8.7, 1.4 Hz, 1H), 7.69–7.61 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.45 (s, 1H), 3.99 (s, 3H), 3.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.1, 159.8, 148.4, 140.1, 132.7, 132.0, 128.6, 127.9, 126.8, 125.7, 124.8, 124.4, 123.0, 114.6, 111.3, 55.6, 52.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3447 (*w*), 2953 (*w*), 1728 (*s*), 1608 (*m*), 1519 (*s*), 1441 (*m*), 1398 (*m*), 1249 (*vs*), 1180 (*s*), 1026 (*m*), 924 (*m*), 822 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{15}{}^{35}ClO_4$ [M]$^+$: 342.0653;

found: 342.0660.

Methyl 7-(4-bromophenyl)-1-chloro-4-hydroxy-2-naphthoate (19):



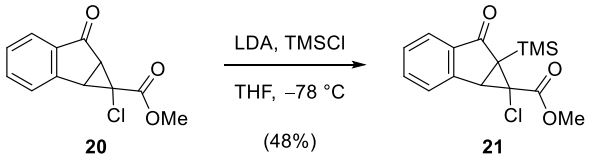
S15 **19**

A solution of cyclopropane **S15** (15 mg, 0.038 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 30 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **19** (7 mg, 47%) as a brown solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.09 (UV, CAM). **M.p.**: 219 °C. **^{1}H NMR** (400 MHz, acetone-d_6) δ: 9.73 (s, 1H), 8.57 (s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.00 (dd, J = 8.7, 1.7 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 3.95 (s, 3H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 167.2, 153.2, 140.5, 140.3, 133.0, 132.8, 130.5, 130.2, 127.2, 127.0, 124.7, 123.5, 122.8, 121.5, 109.0, 55.0, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3311 (*m*), 2953 (*w*), 1708 (*vs*), 1604 (*s*), 1433 (*m*), 1356 (*s*), 1262 (*s*), 1149 (*m*), 1089 (*m*), 1010 (*m*), 806 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{12}{}^{79}Br^{35}ClO_3$ $[M]^+$: 389.9653; found: 389.9647.

Synthesis of TMS-protected cyclopropane 21

TMS protected cyclopropane 21:



20 **21**

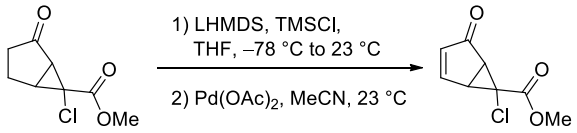
To a solution of diisopropylamine (60 µL, 0.42 mmol, 2.0 equiv) in tetrahydrofuran (0.8 mL) was added dropwise with *n*-buthyllithium (2.31 M in hexanes, 0.18 mL, 0.42 mmol, 2.0 equiv) at –78 °C. The mixture was warmed to 0 °C for 10 min and then was cooled to –78 °C. This lithium diisopropylamide solution was added dropwise to a solution of cyclopropane **20** (50 mg, 0.21 mmol, 1 equiv) and freshly distilled trimethylsilyl chloride (0.14 mL, 1.1 mmol, 5.0 equiv) in tetrahydrofuran (1.5 mL) at –78 °C. The solution was allowed to warm to 23 °C over 5 h. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The

washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **21** (31 mg, 48%) as a pale yellow solid.

TLC (10% ethyl acetate in hexanes), R_f = 0.68 (UV, CAM). **M.p.**: 86 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 4.1 Hz, 2H), 7.40 (dq, *J* = 8.0, 4.1 Hz, 1H), 3.84 (s, 3H), 3.65 (s, 1H), 0.18 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 199.6, 166.8, 148.6, 137.2, 134.0, 128.6, 126.5, 124.0, 66.0, 53.6, 38.5, 35.7, –1.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1734 (*m*), 1700 (*s*), 1602 (*m*), 1440 (*m*), 1285 (*s*), 1249 (*s*), 1208 (*m*), 1183 (*m*), 1005 (*m*), 930 (*m*), 882 (*m*), 844 (*vs*), 770 (*s*), 732 (*m*), 686 (*m*) cm^{-1}. **HRMS** (ESI) calcd for $C_{15}H_{17}{}^{35}ClO_3Si$ $[M]^+$: 308.0635; found: 308.0625.

Synthesis of bicyclo[3.1.0]hex-3-en-2-ones

Methyl 6-chloro-4-oxobicyclo[3.1.0]hex-2-ene-6-carboxylate (S17):



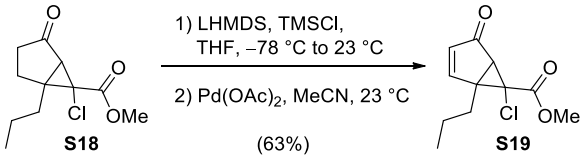
S16 **S17**

A solution of cyclopropane **S16**[149] (500 mg, 2.65 mmol, 1 equiv) in tetrahydrofuran (7 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 3.18 mL, 3.18 mmol, 1.20 equiv) in tetrahydrofuran (0.5 mL) at –78 °C. After 1 h, trimethylsilyl chloride (510 µL, 3.98 mmol, 1.50 equiv) was added dropwise. After 45 min, the solution was allowed to warm to 23°C over 6 h and then was concentrated. The crude product was dissolved in hexanes (10 mL) and filtered through a short plug of Celite. The filtrate was concentrated to provide the crude silyl enol ether.

A solution of crude silyl enol ether in acetonitrile (7 mL) was treated with palladium(II) acetate (655 mg, 2.92 mmol, 1.10 equiv) at 23 °C. After 15 h, the mixture was filtered through a short plug of Celite and the filter cake was washed with diethyl ether (100 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S17** (384 mg, 78%) as a yellow oil.

TLC (20% ethylacetate in hexanes): R_f = 0.32 (UV; $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.45 (dd, *J* = 5.5, 2.9 Hz, 1H), 6.07 (d, *J* = 5.6 Hz, 1H), 3.81 (s, 3H), 3.27 (dd, *J* = 5.5, 2.9 Hz, 1H), 2.82 (d, *J* = 5.5 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 199.4, 167.0, 155.2, 134.0, 63.9, 54.1, 35.9, 35.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3074 (*w*), 2958 (*w*), 1706 (*vs*), 1577 (*w*), 1436 (*m*), 1337 (*m*), 1279 (*s*), 1246 (*vs*), 1179 (*s*), 1066 (*s*), 940 (*w*), 887 (*m*), 811 (*m*), 729 (*m*), 707 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_8H_7{}^{35}ClO_3$ $[M]^+$: 186.0078; found: 186.0077.

Methyl 6-chloro-4-oxo-1-propylbicyclo[3.1.0]hex-2-ene-6-carboxylate (S19):

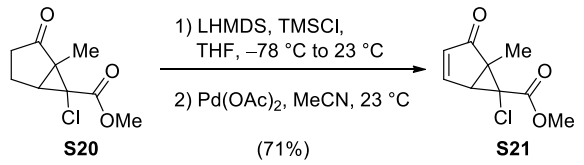


A solution of cyclopropane **S18** (53 mg, 0.23 mmol, 1 equiv) in tetrahydrofuran (0.75 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.28 mL, 0.28 mmol, 1.2 equiv) in tetrahydrofuran (0.5 mL) at –78 °C. After 1 h, trimethylsilyl chloride (44 µL, 0.35 mmol, 1.5 equiv) was added dropwise. After 45 min, the solution was allowed to warm to 23°C over 6 h and then was concentrated. The crude product was dissolved in hexanes (10 mL) and filtered through a short plug of Celite. The filtrate was concentrated to provide the crude silyl enol ether.

A solution of crude silyl enol ether in acetonitrile (2.5 mL) was treated with palladium(II) acetate (57 mg, 0.25 mmol, 1.1 equiv) at 23 °C. After 15 h, the mixture was filtered through a short plug of Celite and the filter cake was washed with diethyl ether (50 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S19** (33 mg, 63%) as a colorless oil.

TLC (10% ethyl acetate in hexanes), R_f = 0.20 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39 (dd, *J* = 5.5, 1.3 Hz, 1H), 6.04 (dd, *J* = 5.6, 0.9 Hz, 1H), 3.83 (s, 3H), 2.90 (t, *J* = 1.1 Hz, 1H), 1.91 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 1.69–1.58 (m, 1H), 1.54–1.35 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 200.4, 166.4, 159.0, 133.3, 66.3, 53.8, 46.1, 37.8, 28.6, 20.4, 14.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (*w*), 1712 (*vs*), 1436 (*m*), 1259 (*vs*), 1177 (*m*), 1088 (*m*), 820 (*m*), 712 (*m*) cm^{-1}.

Methyl 6-chloro-5-methyl-4-oxobicyclo[3.1.0]hex-2-ene-6-carboxylate (S21):



A solution of cyclopropane **S20** (50 mg, 0.25 mmol, 1 equiv) in tetrahydrofuran (0.75 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.29 mL, 0.29 mmol, 1.2 equiv) in tetrahydrofuran (0.5 mL) at –78 °C. After 1 h, trimethylsilyl chloride (47 µL, 0.37 mmol, 1.5 equiv) was added dropwise. After 45 min. The solution was allowed to warm to 23°C over 6 h and then was concentrated. The crude product was dissolved in hexanes (10 mL) and filtered through a short plug of Celite. The filtrate was concentrated to provide the crude silyl enol ether.

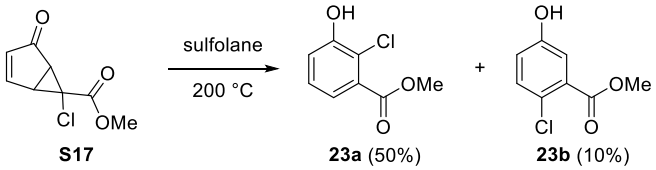
A solution of crude silyl enol ether in acetonitrile (2.5 mL) was treated with palladium(II) acetate (61 mg, 0.27 mmol, 1.1 equiv) at 23 °C. After 15 h, the mixture was filtered through a short plug of Celite and the filter cake was washed with diethyl ether (50 mL). The filtrate was concentrated and the crude product was

purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S21** (35 mg, 71%) as a colorless oil.

TLC (10% ethyl acetate in hexanes), R_f = 0.20 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 5.6, 3.2 Hz, 1H), 6.09 (d, *J* = 5.6 Hz, 1H), 3.83 (s, 3H), 3.33 (d, *J* = 3.2 Hz, 1H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 201.8, 166.1, 155.9, 132.7, 67.1, 53.8, 39.3, 38.2, 9.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (*w*), 1711 (*vs*), 1436 (*m*), 1282 (*s*), 1216 (*vs*), 1300 (*s*), 1032 (*m*), 823 (*m*), 712 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_9H_{10}{}^{35}ClO_3$ $[M+H]^+$: 201.0313; found: 201.0314.

Ring opening of bicyclo[3.1.0]hex-3-en-2-ones

Methyl 2-chloro-3-hydroxybenzoate (23a) and methyl 2-chloro-5-hydroxybenzoate (23b):



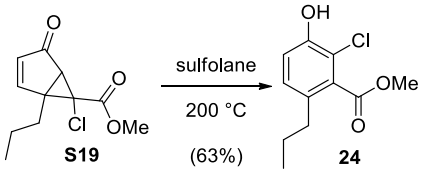
S17 **23a** (50%) **23b** (10%)

A solution of cyclopropane **S17** (30 mg, 0.16 mmol, 1 equiv) in sulfolane (0.3 mL) was stirred at 200 °C for 15 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **23a** (15 mg, 50%) as a yellow oil and **23b** (3 mg, 10%) as a white solid.

23a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.70 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 11.35 (s, 1H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.84 (t, *J* = 7.9 Hz, 1H), 3.97 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.4, 157.4, 135.9, 128.5, 122.3, 119.4, 113.8, 52.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3095 (*w*, *br*), 2956 (*m*), 1677 (*vs*), 1608 (*m*), 1439 (*vs*), 1324 (*vs*), 1255 (*vs*), 1199 (*s*), 1153 (*vs*), 1074 (*m*), 975 (*m*), 754 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_8H_7{}^{35}ClO_3$ $[M]^+$: 186.0078; found: 186.0084.

23b: Characterization data for **23b** were in full agreement with those reported in the literature.[150]

Methyl 2-chloro-3-hydroxy-6-propylbenzoate (24):



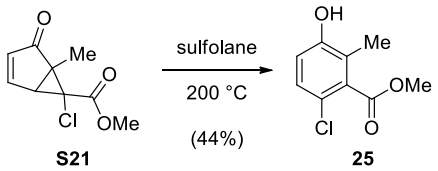
S19 **24**

A solution of cyclopropane **S19** (30 mg, 0.13 mmol, 1 equiv) in sulfolane (0.3 mL) was stirred at 200 °C

for 15 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **24** (19 mg, 63%) as a colorless oil.

TLC (10% ethyl acetate in hexanes), R_f = 0.42 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 11.14 (s, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 3.96 (s, 3H), 2.55–2.46 (m, 2H), 1.59 (dt, *J* = 15.0, 7.5 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.5, 155.4, 136.1, 133.9, 128.0, 121.8, 113.3, 52.8, 36.9, 24.6, 13.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3111 (*w*), 2958 (*m*), 2360 (*w*), 1678 (*vs*), 1442 (*vs*), 1331 (*s*), 1256 (*vs*), 1197 (*s*), 1103 (*w*), 988 (*w*), 792 (*s*), 745 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{11}H_{13}{}^{35}ClO_3$ [M]$^+$: 228.0548; found: 228.0543.

Methyl 6-chloro-3-hydroxy-2-methylbenzoate (25):



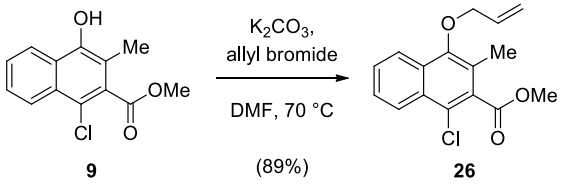
S21 **25**

A solution of cyclopropane **S21** (30 mg, 0.090 mmol, 1 equiv) in sulfolane (0.3 mL) was stirred at 200 °C for 15 min. The reaction mixture was allowed to cool to 23 °C. Diethyl ether (20 mL) was added and the organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **25** (13.2 mg, 44%) as a white solid.

TLC (10% ethyl acetate in hexanes), R_f = 0.36 (UV, $KMnO_4$). **M.p.**: 54 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 5.74 (s, 1H), 3.89 (s, 3H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 167.7, 150.1, 130.5, 128.1, 125.7, 123.4, 122.7, 52.3, 13.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3412 (*m*), 2970 (*m*), 1713 (*vs*), 1592 (*m*), 1440 (*s*), 1312 (*s*), 1228 (*vs*), 1190 (*s*), 1051 (*vs*), 857 (*m*), 763 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_9H_9{}^{35}ClO_3$ [M]$^+$: 200.0235; found: 200.0242.

Synthesis and One-pot Claisen-Cope-cyclization Cascade of Naphthyl Allyl Ether (26):

Methyl 4-(allyloxy)-1-chloro-3-methyl-2-naphthoate (26):

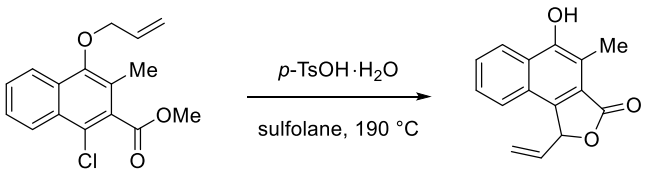


9 **26**

A suspension of naphthol **9** (180 mg, 0.718 mmol, 1 equiv), potassium carbonate (149 mg, 1.08 mmol, 1.50 equiv) and allyl bromide (68.3 µL, 0.790 mmol, 1.10 equiv) in dimethylformamide (2.5 mL) was stirred at 70 °C. After 1.5 h, the reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with aqueous 2 M hydrochloric acid solution (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. Product **26** was obtained as yellow oil (185 mg, 89%) which was used in the next step without further purification.

TLC (9% ethyl acetate in hexanes), R_f = 0.32 (UV; $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.25 (dd, *J* = 6.1, 3.5 Hz, 1H), 8.10 (dd, *J* = 6.2, 3.4 Hz, 1H), 7.59 (dd, *J* = 6.4, 3.2 Hz, 2H), 6.18 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.51 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.46 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.02 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.0, 152.0, 133.4, 133.3, 130.2, 129.4, 127.8, 127.3, 125.2, 124.0, 123.9, 122.5, 118.1, 75.1, 52.9, 13.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1735 (*vs*), 1331 (*m*), 1280 (*vs*), 1213 (*vs*), 1051 (*s*), 924 (*w*), 764 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{16}H_{15}{}^{35}ClO_3$ $[M]^+$: 290.0704; found: 290.0707.

5-Hydroxy-4-methyl-1-vinylnaphtho[1,2-c]furan-3(1*H*)-one (31):



26 **31**

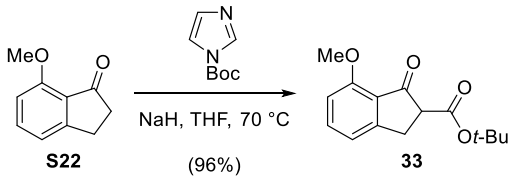
A solution of **26** (20.0 mg, 0.0688 mmol, 1 equiv) and *p*-toluenesolfonic acid monohydrate (13.1 mg, 0.0688 mmol, 1 equiv) in sulfolane (0.2 mL) was stirred at 190 °C for 15 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (3 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to afford **31** (6.6 mg, 40%) as a yellow solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.19 (UV; $KMnO_4$). **M.p.**: 118 °C. **^{1}H NMR** (400 MHz,

$CDCl_3$) δ: 8.32 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.88 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 6.05 (d, *J* = 6.1 Hz, 1H), 5.91 (ddd, *J* = 17.0, 10.0, 7.9 Hz, 1H), 5.76 (dt, *J* = 17.0, 1.0 Hz, 1H), 5.52 (ddd, *J* = 10.0, 1.2, 0.7 Hz, 1H), 5.49 (brs, 1H), 2.73 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.2, 150.8, 140.5, 134.5, 128.6, 127.4, 127.2, 126.4, 124.0, 123.2, 122.1, 121.5, 113.2, 80.7, 9.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3417 (*w*), 1732 (*vs*), 1579 (*w*), 1404 (*w*), 1032 (*w*), 978 (*w*), 764 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{15}H_{12}O_3$ $[M]^+$: 240.0781; found: 240.0787.

Synthesis of Chartarin (1)

β-Ketoester 33:

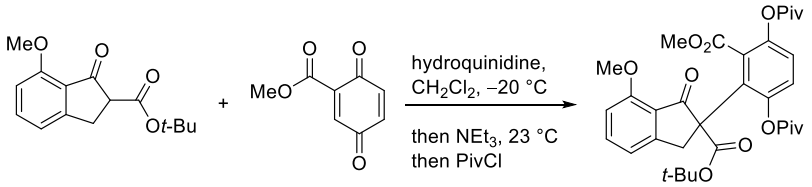


S22 **33**

A solution of 7-methoxy-1-indanone (**S22**) (1.85 g, 11.4 mmol, 1 equiv) and *tert*-butyl 1*H*-imidazole-1-carboxylate (2.87 g, 17.1 mmol, 1.50 equiv) in tetrahydrofuran (60 mL) was treated with sodium hydride (910 mg, 22.8 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred at 70 °C for 5 h. The reaction mixture was allowed to cool to 23 °C and then was diluted with saturated aqueous ammonium chloride solution (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL), the washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **33** (2.87 g, 96%) as a colorless oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.33 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 3.58 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.43 (dd, *J* = 17.4, 4.0 Hz, 1H), 3.24 (dd, *J* = 17.3, 8.3 Hz, 1H), 1.48 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 197.6, 168.7, 158.8, 156.4, 137.1, 123.7, 118.3, 109.3, 82.1, 55.9, 54.9, 30.0, 28.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (*w*), 1705 (*vs*), 1595 (*s*), 1481 (*s*), 1367 (*m*), 1276 (*s*), (*vs*), 1067 (*m*), 984 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{15}H_{18}O_4$ $[M]^+$: 262.1200; found: 262.1205.

α-Aryl S23:

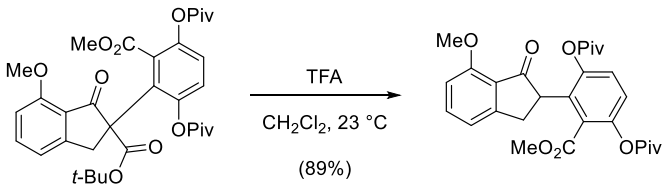


33 **34** **S23**

A solution of β-ketoester **33** (2.86 g, 10.9 mmol, 1 equiv) and quinone **34**[151] (1.81 g, 10.9 mmol, 1 equiv) in dichloromethane (40 mL) was cooled −20 °C. After 15 min, hydroquinidine (712 mg, 2.18 mmol, 0.200 equiv) was added. After 3 h, triethylamine (7.58 mL, 54.5 mmol, 5.00 equiv) was added and the mixture was allowed to warm to 23 °C. After 1 h, pivalic acid chloride (5.57 mL, 54.5 mmol, 5.00 equiv) was added. After 2 h, saturated aqueous sodium bicarbonate solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S23** (4.58 g, 70%) as a foam.

TLC (30% ethyl acetate in hexanes), R_f = 0.28 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.00–6.94 (m, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.99 (d, *J* = 17.2 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 3H), 3.17 (d, *J* = 17.2 Hz, 1H), 1.29 (s, 9H), 1.28 (s, 9H), 1.22 (brs, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.3, 177.1, 176.2, 167.9, 165.6, 158.8, 154.9, 147.9, 145.9, 137.0, 133.1, 127.1, 124.8, 123.2, 122.4, 117.7, 109.1, 82.9, 65.6, 55.7, 52.0, 39.4, 39.1, 39.0, 27.6, 27.1, 27.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (*w*), 1751 (*s*), 1711 (*s*), 1596 (*m*), 1481 (*m*), 1369 (*m*), 1278 (*s*), 1151 (*s*), 1086 (*vs*), 1001 (*m*), 912 (*m*), 729 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{33}H_{40}O_{10}$ $[M]^+$: 596.2616; found: 596.2623.

Aryl Indanone 35:



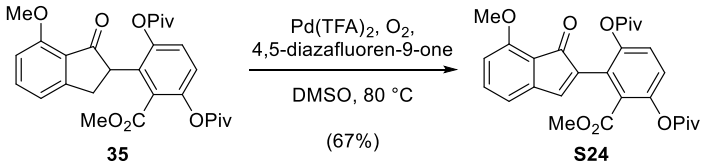
S23 **35**

A solution of **S23** (4.58 g, 7.68 mmol, 1 equiv) in dichloromethane (60 mL) was treated with trifluoroacetic acid (5.71 mL, 76.8 mmol, 10.0 equiv) at 23 °C. After 12 h, the mixture was diluted with dichloromethane (600 mL) and washed sequentially with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed organic solution was dried over sodium sulfate and the dried

solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **35** (3.40 g, 89%) as a white foam.

TLC (33% ethyl acetate in hexanes), R_f = 0.22 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (t, J = 7.9 Hz, 1H), 7.07 (brs, 2H), 6.98 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 4.04–2.96 (brm, 9H), 1.30 (s, 9H), 1.05 (brs, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 200.9, 176.7, 176.2, 166.3, 158.4, 154.7, 136.6, 131.4, 131.3, 125.1, 124.6, 122.5, 118.2, 115.4, 109.3, 55.8, 52.5, 39.2, 39.2, 34.6, 27.1, 26.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (*w*), 1753 (*s*), 1717 (*s*), 1595 (*m*), 1480 (*m*), 1272 (*s*), 1094 (*vs*), 732 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{28}H_{31}O_8$ $[M]^+$: 496.2092; found: 496.2088.

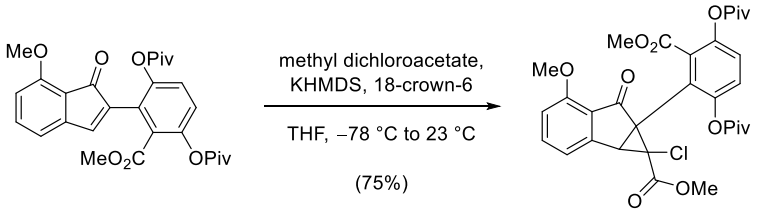
Aryl Indenone S24:



A Schlenk tube was charged with indanone **35** (3.40 g, 6.84 mmol, 1 equiv), palladium(II) trifluoroacetate (455 mg, 1.37 mmol, 0.200 equiv) and 4,5-diazofluoren-9-one (249 mg, 1.37 mmol, 0.200 equiv). The Schlenk tube was equipped with an O_2-balloon and the tube was flushed with O_2. Dimethyl sulfoxide (60 mL) was added. The solution was sparged with O_2 for 1 min and then was stirred at 80 °C under an O_2-atmosphere. After for 5 d, the solution was allowed to cool to 23 °C and then was diluted with diethyl ether (100 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (200 mL) and saturated aqueous sodium chloride solution (200 mL), the washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S24** (2.28 mg, 67%) as yellow foam and **35** (800 mg, 24%).

TLC (33% ethyl acetate in hexanes), R_f = 0.38 (UV, $KMnO_4$, CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.37 (dd, J = 8.7, 7.0 Hz, 1H), 7.30 (s, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 7.1, 0.6 Hz, 1H), 3.94 (s, 3H), 3.68 (s, 3H), 1.33 (s, 9H), 1.20 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 192.8, 176.8, 176.8, 165.6, 157.4, 147.2, 146.5, 146.3, 144.5, 136.8, 133.4, 128.0, 126.4, 125.7, 124.1, 116.2, 115.3, 114.9, 56.3, 52.8, 39.4, 39.3, 27.2, 27.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (*w*), 1752 (*s*), 1709 (*s*), 1595 (*m*), 1463 (*m*), 1271 (*s*), 1095 (*vs*), 955 (*m*), 708 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{28}H_{30}O_8$ $[M]^+$: 494.1935; found: 494.1943.

Cyclopropane 36:



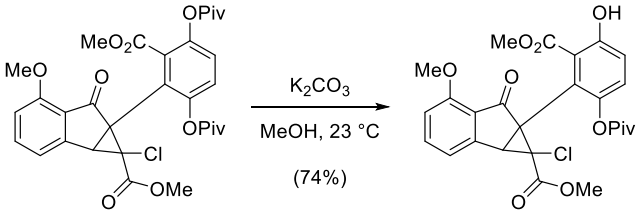
S24 **36**

Methyl dichloroacetate (0.715 mL, 6.91 mmol, 1.50 equiv) was added dropwise to a solution of potassium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 7.37 mL, 7.37 mmol, 1.60 equiv) and 18-crown-6 (122 mg, 0.461 mmol, 0.100 equiv) in tetrahydrofuran (10 mL) at –78 °C. After 30 min, indenone **S24** (2.28 mg, 4.61 mmol, 1 equiv) in tetrahydrofuran (13 mL) was added dropwise. The solution was then allowed to warm to 23 °C. After 18 h, saturated aqueous ammonium chloride solution (30 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **36** (2.08 g, 75%, mixture of two diastereoisomers) as a white foam.

36a: **TLC** (30% ethyl acetate in hexanes), R_f = 0.17 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 7.10–7.05 (m, 2H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 1H), 3.48 (s, 3H), 3.22 (s, 3H), 1.39 (s, 9H), 1.28 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 190.3, 177.0, 176.3, 165.2, 164.6, 158.6, 149.1, 148.9, 145.1, 136.2, 128.4, 125.2, 123.5, 123.5, 122.1, 118.5, 112.1, 65.5, 56.1, 53.7, 52.0, 47.5, 39.6, 39.2, 38.2, 27.4, 27.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*w*), 1754 (*s*), 1727 (*s*), 1598 (*m*), 1473 (*m*), 1268 (*s*), 1205 (*m*), 1091 (*vs*), 1029 (*w*), 728 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{31}H_{33}{}^{35}ClO_{10}$ $[M]^+$: 600.1762; found: 600.1748.

36b: **TLC** (30% ethyl acetate in hexanes), R_f = 0.14 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.11–7.05 (m, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 3.98 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H), 1.32 (s, 9H), 1.03 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 190.7, 176.5, 176.2, 165.5, 165.1, 158.6, 148.9, 148.4, 146.7, 136.3, 129.1, 125.3, 124.7, 123.9, 122.8, 118.9, 112.1, 66.6, 56.2, 53.9, 53.4, 46.5, 40.3, 39.2, 38.2, 27.2, 27.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (*w*), 1753 (*s*), 1728 (*s*), 1597 (*m*), 1466 (*m*), 1266 (*s*), 1219 (*m*), 1093 (*vs*), 1030 (*w*), 734 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{31}H_{33}{}^{35}ClO_{10}$ $[M]^+$: 600.1757; found: 600.1763.

Phenol S25:



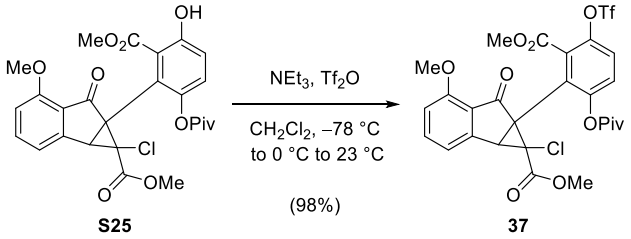
36 **S25**

A solution of cyclopropane **36** (2.08 g, 3.45 mmol, 1 equiv) in methanol (8.5 mL) was treated with potassium carbonate (477 mg, 3.45 mmol, 1 equiv) at 23 °C. After 2 h, saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (40 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S25** (1.32 mg, 74%, mixture of two diastereoisomers) as a yellow foam.

S25a: **TLC** (30% ethyl acetate in hexanes), R_f = 0.28 (UV, CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 11.28 (s, 1H), 7.55 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.55 (s, 3H), 0.98 (s, 9H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 191.1, 177.2, 170.8, 165.5, 160.3, 158.6, 149.1, 144.3, 136.4, 129.2, 125.7, 122.7, 119.5, 118.9, 113.9, 111.9, 67.6, 56.2, 54.4, 53.8, 47.3, 40.5, 39.2, 26.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (*w*), 1747 (*s*), 1721 (*s*), 1668 (*s*), 1596 (*s*), 1458 (*s*), 1268 (*s*), 1213 (*vs*), 1092 (*vs*), 981 (*m*), 912 (*s*), 730 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{26}H_{25}{}^{35}ClO_9$ $[M]^+$: 516.1182; found: 516.1190.

S25b: **TLC** (30% ethyl acetate in hexanes), R_f = 0.10 (UV, CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 10.18 (s, 1H), 7.56 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.17 (d, *J* = 9.2 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 3H), 3.76 (s, 1H), 3.51 (s, 3H), 3.13 (s, 3H), 1.38 (s, 9H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 191.3, 177.5, 169.7, 165.2, 158.5, 158.3, 149.6, 145.3, 136.0, 129.2, 124.8, 122.3, 118.6, 118.5, 113.7, 112.0, 66.3, 56.1, 53.7, 52.3, 48.1, 40.5, 39.5, 27.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3424 (w), 2957 (*w*), 1749 (*s*), 1723 (*vs*), 1673 (*m*), 1597 (*s*), 1461 (*s*), 1270 (*vs*), 1210 (*vs*), 1092 (*vs*), 981 (*m*), 911 (*m*), 735 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{26}H_{25}{}^{35}ClO_9$ $[M]^+$: 516.1187; found: 516.1182.

Triflate 37:

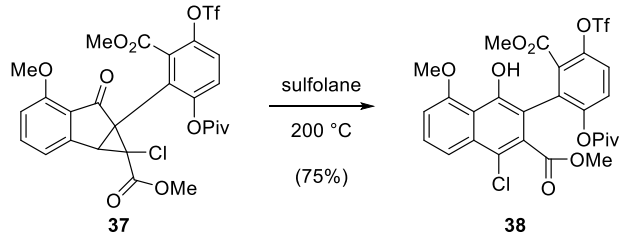


S25 **37**

A solution of phenol **S25** (1.32 g, 2.55 mmol, 1 equiv) in dichloromethane (25 mL) was treated sequentially with triethylamine (0.532 mL, 3.82 mmol, 1.50 equiv) and trifluoromethanesulfonic anhydride (0.635 mL, 3.82 mmol, 1.50 equiv) at –78 °C. The mixture was stirred at –78 °C for 15 min, then at 0 °C for further 15 min and was then allowed to warm to 23 °C. After 30 min, saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (100 mL) were added and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **37** (1.62 mg, 98%, inseparable mixture of two diastereoisomers) as a yellow oil.

TLC (30% ethyl acetate in hexanes), R_f = 0.20 (UV, CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.59–7.52 (m, 1.5H), 7.33 (d, *J* = 9.0 Hz, 0.5H), 7.31 (s, 2H), 7.12–7.08 (m, 1.5H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 0.5H), 4.02 (s, 0.4H), 3.97 (s, 1H), 3.95 (s, 3H), 3.93 (s, 1H), 3.84 (s, 1H), 3.64 (s, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 1.39 (s, 9H), 1.06 (s, 3H). *Note: Asterisks denotes signal of the major isomer.* **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 190.3, 190.0*, 176.8*, 176.2, 165.7, 164.6*, 163.9, 163.8*, 158.7*, 151.3*, 150.6, 148.7, 148.6*, 144.5, 142.7*, 136.6, 136.5*, 129.9, 129.4*, 127.1, 125.9*, 125.6, 125.4*, 122.8, 122.7, 122.3*, 121.8*, 118.9, 118.6 (q, *J* = 320.4 Hz)*, 118.5*, 112.3*, 112.1, 66.7, 65.3*, 56.2*, 53.9, 53.8*, 52.7*, 47.4, 46.22 40.3, 39.7*, 39.3, 38.5*, 27.4*, 26.9. *Note: One CF_3 group is not visible in the ^{13}C NMR spectra. The presence of the CF_3 group was verified by the ^{19}F NMR spectra.* **^{19}F NMR** (375 MHz, $CDCl_3$) δ: –73.5, –73.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (*w*), 1726 (*s*), 1598 (*s*), 1483 (*m*), 1426 (*s*), 1267 (*s*), 1209 (*vs*), 1139 (*m*), 1089 (*vs*), 1026 (*w*), 912 (*w*), 857 (*m*), 735 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{27}H_{24}{}^{35}ClF_3O_{11}{}^{32}S$ $[M]^+$: 648.0674; found: 648.0679.

Naphthol 38:



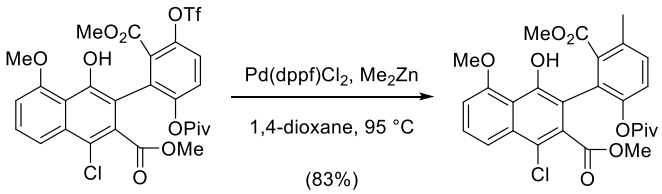
37 **38**

A solution of triflate **37** (1.62 g, 2.49 mmol, 1 equiv) in sulfolane (5 mL) was stirred at 200 °C for 15 min.

The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **38** (1.21 mg, 75%) as a yellow oil.

TLC (30% ethyl acetate in hexanes), R_f = 0.36 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.54 (t, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 9.1 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.06 (s, 3H), 3.71 (s, 3H), 3.59 (s, 3H), 0.92 (s, 9H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 175.4, 166.0, 163.4, 156.4, 151.4, 148.9, 144.1, 133.1, 132.5, 130.9, 128.6, 128.3, 126.4, 122.5, 119.3, 118.7, 115.5, 113.9, 106.4, 56.7, 52.7, 52.4, 39.2, 26.6. *Note: The CF_3 group is not visible in the ^{13}C NMR spectra. The presence of the CF_3 group was verified by the ^{19}F NMR spectra.* **^{19}F NMR** (375 MHz, $CDCl_3$) δ: –73:6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3352 (*w*), 2956 (*w*), 1740 (*s*), 1606 (*w*), 1425 (*s*), 1366 (*s*), 1282 (*s*), 1213 (*vs*), 1100 (*vs*), 983 (*m*), 904 (*m*) cm^{-1}. **HRMS** (ESI) calcd for $C_{27}H_{23}{}^{35}ClF_3O_{11}S$ $[M-H]^-$: 647.06072; found: 647.06065.

Naphthol S26:

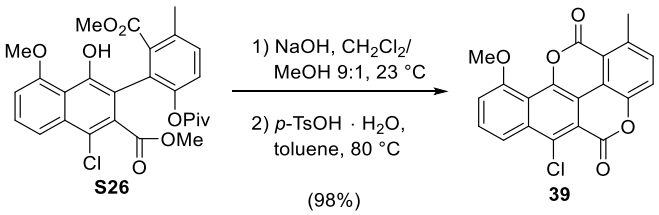


Based on a literature procedure,[152] a solution of triflate **38** (1.20 g, 1.85 mmol, 1 equiv) and 1,1-bis(diphenylphosphino)-ferrocenedichloropalladium(II) (135 mg, 0.185 mmol, 0.100 equiv) in 1,4-dioxane (18.5 mL) was treated with dimethylzinc (1.2 M in toluene, 7.70 mL, 9.25 mmol, 5.00 equiv) and the solution was stirred at 95 °C. After 1 h, the reaction was allowed to cool to 23 °C, and then was diluted with methanol (0.5 mL) and diethyl ether (200 mL). The organic layer was washed with 1 M hydrochloric acid solution (20 mL) and with saturated aqueous sodium chloride (20 mL), the washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S26** (792 mg, 83%) as a pale yellow foam.

TLC (40% ethyl acetate in hexanes), R_f = 0.30 (UV, CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 9.76 (s, 1H), 7.93 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.55 (dd, *J* = 8.7, 7.8 Hz, 1H), 7.30 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.99 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.06 (s, 3H), 3.57 (s, 3H), 3.53 (s, 3H), 2.42 (s, 3H), 0.89 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2): δ: 175.9, 168.1, 166.4, 156.7, 151.8, 147.5, 135.2, 133.8, 133.6, 132.9, 131.4,

128.4, 127.2, 124.4, 118.9, 118.1, 115.8, 115.7, 106.6, 57.0, 52.2, 51.9, 39.1, 26.7, 20.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3358 (*w*, *br*), 2952 (*w*), 1730 (*s*), 1606 (*w*), 1435 (*m*), 1364 (*s*), 1263 (*s*), 1237 (*s*), 1207 (*s*), 1098 (*vs*), 982 (*s*), 908 (*s*), 806 (*m*), 726 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{27}H_{27}{}^{35}ClO_8$ [M]$^+$: 514.1389; found: 514.1402.

Lactone 39:

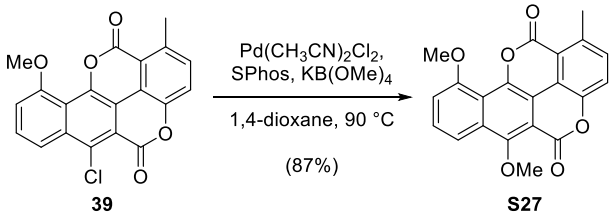


A solution of naphthol **S26** (410 mg, 0.796 mmol, 1 equiv) in dichloromethane/methanol (9:1, 8 mL) was treated with sodium hydroxide (318 mg, 7.96 mmol, 10.0 equiv) at 23 °C. After 30 min, the mixture was acidified with 1 M hydrochloric acid (20 mL) and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride (50 mL) and the washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated.

A solution of the crude diol in toluene (20 mL) was treated with *p*-toluenesulfonic acid monohydrate (30.3 mg, 0.159 mmol, 0.200 equiv) and the resulting mixture was stirred at 80 °C. After 1 h, the solution was allowed to cool to 23 °C and the yellow precipitate was separated by filtration and washed with toluene (30 mL) and hexanes (30 mL) to afford **39** (285 mg, 98%) as an amorphous yellow solid.

TLC (30% ethyl acetate in hexanes), R_f = 0.23 (UV, CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 8.35 (d, *J* = 8.5 Hz, 1H), 7.74 (t, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 4.14 (s, 3H), 2.91 (s, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 158.6, 157.5, 156.8, 146.9, 146.0, 139.7, 134.6, 133.5, 133.2, 130.2, 121.1, 119.1, 118.9, 117.8, 117.0, 114.4, 111.6, 110.6, 56.8, 22.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2933 (*w*), 2360 (*w*), 1748 (*vs*), 1738 (*vs*), 1608 (*w*), 1490 (*m*), 1347 (*s*), 1250 (*s*), 1129 (*m*), 1069 (*s*), 914 (*m*), 770 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{11}{}^{35}ClO_5$ [M]$^+$: 366.0290; found: 366.0274.

Chartarin dimethylether(S27):

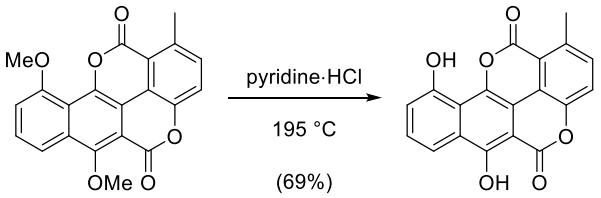


39 **S27**

A solution of lactone **39** (77 mg, 0.21 mmol, 1 equiv), bis(acetonitrile)palladium(II) dichloride (3.0 mg, 0.011 mmol, 0.050 equiv), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (6.9 mg, 0.017 mmol, 0.080 equiv) and potassium tetramethoxyborate (55 mg, 0.32 mmol, 1.5 equiv) in 1,4-dioxane (3 mL) was stirred at 95 °C. After 3 h, the solution was allowed to cool to 23 °C, and then was filtered through a short plug of Celite. The filter cake was washed with ethyl acetate (200 mL). The filtrate was concentrated to provide a brown solid. The crude product was suspended in hexanes and the resulting yellow precipitate was separated by filtration and washed with hexanes (30 mL) to afford chartarin dimethylether (**S27**) (66 mg, 87%) as a yellow solid.

TLC (30% ethyl acetate in hexanes), R_f = 0.14 (UV, CAM). **M.p.**: 240 °C (dec.). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 8.09 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.70–7.65 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.51–7.49 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 4.16 (s, 3H), 4.14 (s, 3H), 2.92 (s, 4H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 159.2, 157.5, 156.7, 147.2, 143.2, 139.4, 133.1, 132.2, 129.1, 120.9, 119.5, 118.8, 117.3, 116.5, 110.8, 110.7, 109.9, 107.9, 63.6, 56.7, 22.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935 (*w*), 2847 (*w*), 1748 (*vs*), 1610 (*w*), 1491 (*m*), 1453 (*m*), 1363 (*m*), 1250 (*s*), 1104 (*m*), 1073 (*s*), 917 (*w*), 775 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{14}O_6$ $[M]^+$: 362.0785; found: 362.0785.

Chartarin (1):



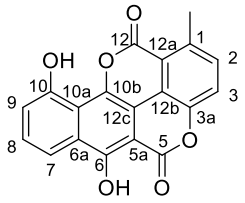
S27 **1**

A mixture of chartarin dimethylether (30.0 mg, 82.8 μmol, 1 equiv) and pyridine hydrochloride (478 mg, 4.14 mmol, 50.0 equiv) was stirred at 195 °C. After 16 h, methanol (3 mL) was added to the warm solution. The yellow precipitate was separated by filtration and washed with cold methanol (5 mL) to afford chartarin (**1**) (19 mg, 69%) as a yellow-brownish solid.

TLC (5% methanol in chloroform), R_f = 0.85 (UV, CAM). **M.p.**: 295 °C (Lit. 280 °C (sublimed),[153] 306.5 °C).[53a] **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 11.63 (s, 1H), 8.66 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 2.92 (s, 3H). **^{13}C**

NMR (200 MHz, $CDCl_3$) δ: 164.7, 158.6, 157.3, 153.8, 146.9, 140.9, 139.2, 133.2, 129.5, 126.7, 122.4, 121.9, 117.8, 117.2, 116.6, 116.1, 107.6, 96.0, 22.5. **^{1}H NMR** (400 MHz, pyridine-d_5) δ: 8.16 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 2.84 (s, 3H). **^{13}C NMR** (100 MHz, pyridine) δ: 165.1, 159.4, 157.7, 156.6, 147.2, 140.2, 139.8, 133.1, 129.4, 127.8, 121.3, 120.6, 118.4, 118.2, 117.3, 115.6, 108.3, 97.3, 22.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3227 (*w*), 2925 (*w*), 1754 (*m*), 1692 (*vs*), 1608 (*m*), 1582 (*w*), 1506 (*w*), 1372 (*s*), 1291 (*m*), 1255 (*m*), 1221 (*m*), 1151 (*m*), 1117 (*m*), 1074 (*w*), 986 (*w*), 778 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{10}O_6$ $[M]^+$: 334.0472; found: 334.0473.

^{1}H and ^{13}C NMR Comparison of Synthetic Chartarin with Literature Values[53a]



^{1}H Position	**Literature (600 MHz, pyridine-d_5)**	**synthetic chartarin (1) (400 MHz, pyridine-d_5)**	**Δδ (ppm)**
1-CH_3	2.88 (s, 3 H)	2.84 (s, 3H)	0.04
2	7.39 (d, J = 8.4 Hz, 1 H)	7.35 (d, J = 8.0 Hz, 1H)	0.04
7	8.26 (dd, J = 8.2, 1.1 Hz, 1 H)	8.16 (d, J = 7.9 Hz, 1H)	0.1
8	7.63 (t, J = 7.9 Hz, 1 H)	7.55 (d, J = 7.6 Hz, 1H)	0.08

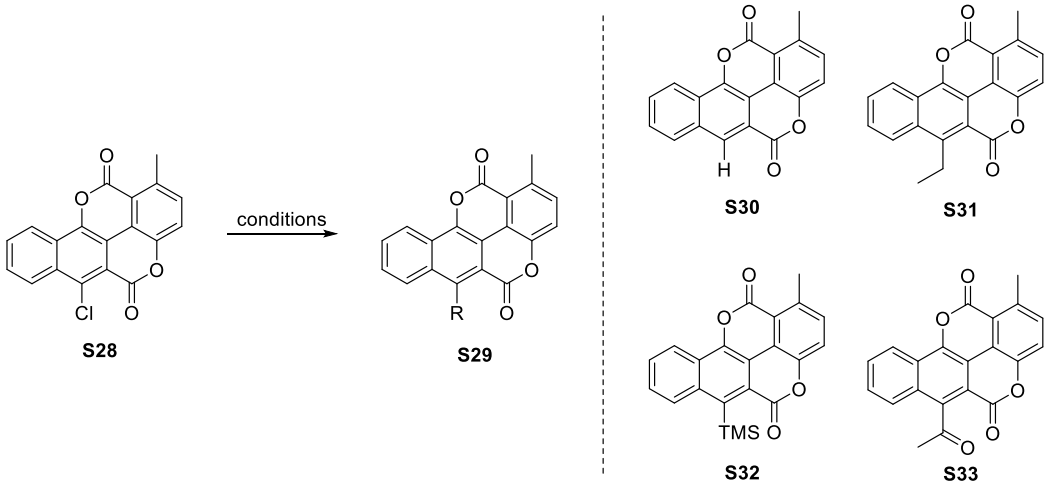
Resonances of all other protons occur as overlapping multiplets and are not listed in this table.

^{13}C Position	Literature (150 MHz, pyridine)	synthetic chartarin (1) (100 MHz, pyridine)	Δδ (ppm)
1-CH_3	22.6	22.6	0
1	139.9	139.8	0.1
2	133.2	133.1	0.1
3	121.3	121.3	0
3a	147.3	147.2	0.1
5	165.2	165.1	0.1
5a	97.4	97.3	0.1
6	157.4	157.7	0
6a	128.0	127.8	0.2
7	115.7	115.6	0.1
8	129.5	129.4	0.1
9	117.4	117.3	0.1
10	156.6	156.6	0
10a	120.7	120.6	0.1
10b	140.3	140.2	0.1
12	159.5	159.4	0.1
12a	118.3	118.2	0.1
12b	118.6	118.4	0.2
12c	108.5	108.3	0.2

Screening of Conditions for the Substitution of the Chloride with a Hydroxyl Group

The substitution reaction was investigated on model substrate **S28**.

Table 14. Tested conditions for the coupling of aryl chloride **S28**.



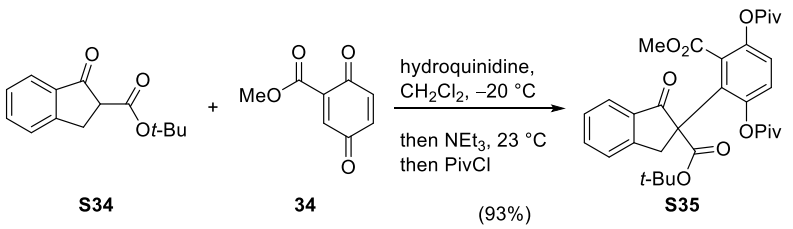
	R	Reagent	Catalyst	Additive	Condition	Result
1	OH	KOH	Pd_2dba_3, 4Me-*t*-BuXPhos[a]	-	1,4-dioxane/H_2O 1:1, 100 °C	no conversion
2	OH	KOH	Pd_2dba_3, *t*-BuXPhos[b]	-	1,4-dioxane/H_2O 1:1, 100 °C	decomposition
3	BPin	B_2Pin_2	Pd_2dba_3, XPhos[c]	KOAc	1,4-dioxane, 80 °C	traces of **S30**[d]
4	BPin	B_2Pin_2	XPhos Pd G3, XPhos	KOAc	1,4-dioxane, 80 °C	traces of **S30**[d]
5	BPin	B_2Pin_2	$Pd(OAc)_2$[e]	KOAc	DMF, 80 °C	traces of **S30**[d]
6	BPin	B_2Pin_2	$Pd(dppf)Cl_2$	KOAc	DMF, 80 °C	decomposition
7	BPin	HBPin	$Pd(CH_3CN)_2Cl_2$, SPhos[f]	NEt_3	1,4-dioxane, 110 °C	traces of **S30**[d]
8	BPin	B_2Pin_2	$Pd(CH_3CN)_2Cl_2$, SPhos	CsF	1,4-dioxane, 90 °C	traces of **S30**[d]
9	Ph	$PhB(OH)_2$	$Pd(OAc)_2$, SPhos[g]	K_3PO_4	THF, 23 °C	decomposition
10	C(O)Me	butyl vinyl ether,	$Pd(OAc)_2$, dppp[h]	KOH	ethylene glycol, 145 °C	no reaction
11	OMe	-	$Pd(OAc)_2$, *t*-BuXPhos[i]	Cs_2CO_3	toluene, MeOH, 70 °C	decomposition
12	TMS	Si_2Me_6	Pd_2dba_3, *t*-BuDavePhos[j]	H_2O, KF	DMF, 100 °C	traces of **S30**[d]
13	$O(CH_2)_2OH$	-	$CuCl_2$[k]	K_2CO_3	ethylene glycol, 130 °C	no reaction
14	I	Zn, then I_2	$CoCl_2$, XantPhos,	LiCl	THF, 70 °C	traces of **S30**[d]

			1,2-dibromoethan, TMSCl[l]			
15	$B(OMe)_2$	Zn, then $B(OMe)_3$	$CoCl_2$, XantPhos, 1,2-dibromoethan, TMSCl[l]	LiCl	THF, 70 °C	decomposition
16	Et	Et_2Zn	$Pd(CH_3CN)_2Cl_2$, SPhos	-	1,4-dioxane, 95 °C	**S31** (56%)[m]
17	OMe	MeOH	$Pd(CH_3CN)_2Cl_2$, SPhos	NEt_3	1,4-dioxane, 95 °C	decomposition
18	CH_2OPiv	$ClZnCH_2OPiv$	$Pd(CH_3CN)_2Cl_2$, SPhos	-	1,4-dioxane, 95 °C	decomposition
19	TMS	TMSZnCl[n]	$Pd(CH_3CN)_2Cl_2$, SPhos	-	1,4-dioxane, 90 °C	traces of **S32**[d]
20	C(O)Me		$Pd(CH_3CN)_2Cl_2$, SPhos	-	1,4-dioxane, 90 °C	**S33** (65%)[p]
21	OMe	$KB(OMe)_4$	$Pd(CH_3CN)_2Cl_2$, SPhos	-	1,4-dioxane, 95 °C	decomposition

[a] K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695. [b] B. J. Morgan, S. Dey, S. W. Johnson, M. C. Kozlowski, *J. Am. Chem. Soc.* **2009**, *131*, 9413–9425. [c] K. L. Billingsley, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363. [d] Detected with HRMS (EI). [e] T. Kano, M. Takeda, R. Sakamoto, K. Maruoka, *J. Org. Chem* **2014**, *79*, 4240–4244. [f] S. Birkett, D. Ganame, B. C. Hawkins, S. Meiries, T. Quach, M. A. Rizzacasa, *Org. Lett.* **2011**, 13, 1964–1967. [g] T. Iwasawa, T. Komano, A. Tajima, M. Tokunaga, Y. Obora, T. Fujihara, Y. Tsuji, *Organometallics* **2006**, *25*, 4665–4669. [h] J. Ruan, J. A. Iggo, N. G. Berry, J. Xiao, *J. Am. Chem. Soc.* **2010**, *132*, 16689–16699. [i] P. Dash, M. Janni, S. Peruncheralathan, *Eur. J. Org. Chem.* **2012**, 4914–4917. [j] E. McNeill, T. E. Barder, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 3785–3788. [k] Y. Liu, S. K. Park, Y. Xiao, J. Chae, *Org. Biomol. Chem.* **2014**, *12*, 4747–4753. [l] M.-Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972–1978. [m] The ethyl side chain could not be converted into a hydroxyl group. [n] TMSZnCl was prepared from hexamethyldisilane, MeLi and $ZnCl_2$: H. Azuma, K. Okano, H. Tokuyama, *Chem. Lett.* **2011**, *40*, 959–961. [o] Prepared from ethyl vinyl ether, *t*-BuLi and $ZnCl_2$: A. B. Smith, III, G. K. Friestad, J. Barbosa, E. Bertounesque, J. J.-W. Duan, K. G. Hull, M. Iwashima, Y. Qiu, P. G. Spoors, B. A. Salvatore, *J. Am. Chem. Soc.***1999**, *121*, 10478–10486. [p] Product after hydrolysis with 1 M HCl. The ketone substituent could not be converted into a hydroxyl group via a Baeyer-Villiger oxidation.

Synthesis of Model System S28

α-Aryl S35:



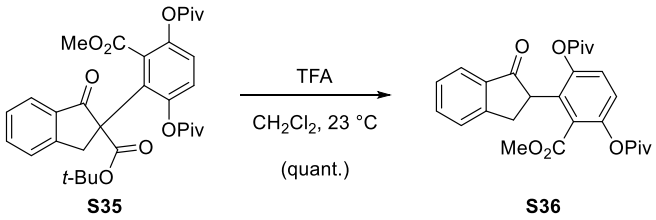
S34 **34** **S35**

A solution of β-ketoester **S34** (814 mg g, 3.50 mmol, 1 equiv) and quinone **34**[151] (657 mg, 3.96 mmol,

1 equiv) in dichloromethane (40 mL) was cooled to −20 °C. After 15 min, hydroquinidine (229 mg, 0.700 mmol, 0.200 equiv) was added. After 3 h, triethyamine (2.44 mL, 17.5 mmol, 5.00 equiv) was added and the mixture was allowed to warm to 23 °C. After 1 h, pivalic acid chloride (1.79 mL, 17.5 mmol, 5.00 equiv) was added. After 20 h, saturated aqueous sodium bicarbonate solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **S35** (1.85 g, 93%) as a white foam.

TLC (20% ethyl acetate in hexanes), R_f = 0.36 (UV, CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.05 (s, 2H), 4.03 (d, *J* = 17.0 Hz, 1H), 3.44 (s, 3H), 3.23 (d, *J* = 17.0 Hz, 1H), 1.31(s, 9H), 1.26 (s, 9H), 1.22 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 198.7, 177.6, 176.9, 167.6, 165.6, 153.1, 148.5, 146.6, 135.8, 135.3, 133.2, 127.7, 126.5, 125.7, 125.0, 123.2, 83.3, 66.2, 52.1, 39.7, 39.3, 27.6, 27.2, 27.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (*w*), 2875 (*w*), 1751 (*s*), 1714 (*s*), 1607 (*w*), 1460 (*m*), 1368 (*m*), 1264 (*s*), 1248 (*s*), 1216 (*m*), 1150 (*s*), 1087 (*vs*), 1028 (*s*), 956 (*m*), 896 (*m*), 841 (*m*), 742 (*m*), 710 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{32}H_{38}O_9$ $[M]^+$: 566.2510; found: 566.2514.

Aryl Indanone S36:



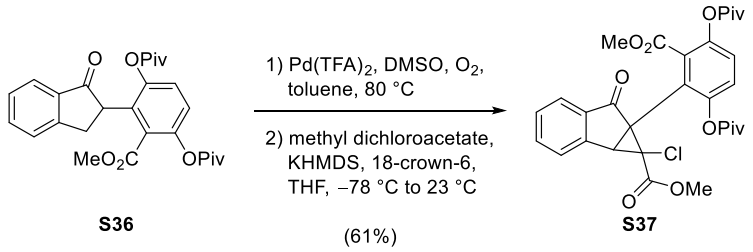
S35 **S36**

A solution of **S35** (1.64 g, 2.89 mmol, 1 equiv) in dichloromethane (30 mL) was treated with trifluoroacetic acid (2.14 mL, 28.9 mmol, 10.0 equiv at 23 °C. After 4.5 h, the mixture was diluted with dichloromethane (30 mL) and washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S36** (1.35 g, quant.) as a white foam.

TLC (20% ethyl acetate in hexanes), R*f* = 0.33 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 7.6 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.46 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 2H), 4.13–3.06 (brm, 6H), 1.31 (s, 9H), 1.01 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 203.5, 176.8, 176.2, 166.2, 152.3, 147.2, 146.1, 136.6, 134.9, 131.1, 127.8, 126.6, 125.3, 124.3, 122.7, 52.4, 48.5, 39.3, 39.2, 35.1, 27.2, 26.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (*w*), 2875 (*w*), 2362 (*w*), 1753 (*s*), 1724 (*s*), 1609 (*w*), 1466 (*m*), 1267 (*s*), 1204 (*m*), 1091 (*vs*), 1028 (*m*), 999 (*m*), 954 (*m*), 890 (*w*), 755 (*m*), 709 (*s*) cm^{-1}. **HRMS** (EI)

calcd for $C_{27}H_{30}O_7$ [M]$^+$: 466.1986; found: 466.1990.

Cyclopropane S37:



A Schlenk tube was charged with indanone **S36** (550 mg, 1.18 mmol, 1 equiv) and palladium(II) trifluoroacetate (78.4 mg, 0.236 mmol, 0.200 equiv). The Schlenk tube was equipped with an O_2-balloon and the tube was flushed with O_2. Dimethyl sulfoxide (33.5 µL, 0.472 mmol, 0.400 equiv) and toluene (10 mL) were added. The solution was sparged with O_2 for 1 min and then was stirred at 80 °C under an O_2-atmosphere. After 2.5 days, the solution was allowed to cool to 23 °C and then was concentrated. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the corresponding indenone.

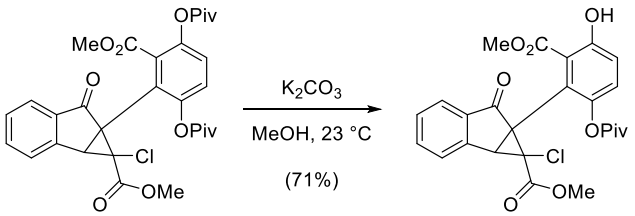
Methyl dichloroacetate (183 µL, 1.77 mmol, 1.50 equiv) was added dropwise to a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.78 mL, 1.89 mmol, 1.60 equiv) and 18-crown-6 (31.2 mg, 0.118 mmol, 0.100 equiv) in tetrahydrofuran (4 mL) at –78 °C. After 30 min, indenone in tetrahydrofuran (10 mL) was added dropwise. The solution was then allowed to warm to 23 °C. After 18 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S37** (413 mg, 61%, mixture of two diastereoisomers) as a colorless oil.

S37a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.18 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.4 Hz, 1H), 7.61 (td, *J* = 7.4, 1.1 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.0 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 3.93 (s, 1H), 3.49 (s, 3H), 3.14 (s, 3H), 1.39 (s, 9H), 1.29 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.1, 177.1, 176.5, 165.1, 164.4, 149.0, 146.6, 145.3, 135.2, 134.4, 129.3, 128.4, 126.3, 125.4, 124.9, 123.7, 123.4, 66.5, 53.8, 52.0, 47.3, 39.6, 39.2, 38.6, 27.4, 27.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*w*), 1753 (*s*), 1730 (*vs*), 1473 (*m*), 1267 (*s*), 1221 (*m*), 1093 (*vs*), 1029 (*m*), 730 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{30}H_{31}{}^{35}ClO_9$ [M]$^+$: 570.1651; found: 570.1652.

S37b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.15 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 7.5 Hz, 1H), 7.60 (td, *J* = 7.4, 1.2 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.45 (td, *J* = 7.4, 1.1 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 4.09 (s, 1H), 3.87 (s, 3H), 3.62 (s, 3H), 1.33 (s, 9H), 0.98 (s,

9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 193.1, 176.5, 176.3, 165.3, 165.1, 148.4, 146.7, 146.6, 135.7, 134.4, 129.3, 129.1, 126.7, 125.3, 125.1, 124.9, 124.1, 67.3, 54.0, 53.4, 46.3, 40.8, 39.2, 39.2, 27.2, 26.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*w*), 1754 (*vs*), 1732 (*s*), 1471 (*m*), 1269 (*s*), 1098 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{30}H_{31}{}^{35}ClO_9$ $[M]^+$: 570.1651; found: 570.1648.

Phenol S38:



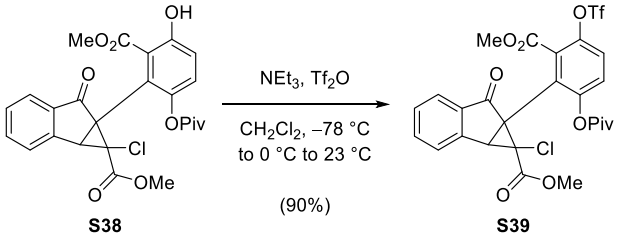
S37 **S38**

A solution of cyclopropane **S37** (440 mg, 0.771 mmol, 1 equiv) in methanol (5 mL) was treated with potassium carbonate (106 mg, 0.771 mmol, 1 equiv) at 23 °C. After 4 h, saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (20 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **S38** (268 mg, 71%, mixture of two diastereoisomers) as a yellow foam.

S38a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.46 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 11.28 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.62 (td, *J* = 7.5, 1.1 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.46 (td, *J* = 7.3, 1.0 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 1H), 4.13 (s, 1H), 3.99 (s, 3H), 3.56 (s, 3H), 0.92 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.6, 177.1, 170.6, 165.3, 160.4, 146.8, 144.3, 135.7, 134.6, 129.3, 129.2, 127.1, 126.7, 125.7, 125.0, 119.7, 113.7, 68.4, 54.4, 53.9, 47.1, 41.0, 39.1, 26.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 2359 (*w*), 2257 (*w*), 1747 (*s*), 1727 (*vs*), 1669 (*s*), 1605 (*m*), 1458 (*s*), 1437 (*s*), 1341 (*m*), 1272 (*s*), 1215 (*vs*), 1105 (*vs*), 914 (*m*), 731 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{25}H_{23}{}^{35}ClO_8$ $[M]^+$: 486.1076; found: 486.1076.

S38b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.26 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 10.15 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.63 (td, *J* = 7.4, 1.2 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.50 (td, *J* = 7.4, 1.1 Hz, 1H), 7.19 (d, *J* = 9.2 Hz, 1H), 7.00 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 1H), 3.53 (s, 3H), 3.04 (s, 3H), 1.38 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.0, 177.6, 169.6, 165.0, 158.4, 147.3, 145.2, 135.5, 134.2, 129.4, 129.1, 126.3, 124.8, 124.6, 118.8, 113.8, 67.2, 53.8, 52.3, 47.9, 40.9, 39.5, 27.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (*w*), 2360 (*w*), 2257 (*w*), 1748 (*s*), 1726 (*vs*), 1673 (*s*), 1607 (*m*), 1460 (*s*), 1436 (*s*), 1328 (*m*), 1270 (*s*), 1209 (*vs*), 1099 (*vs*), 912 (*s*), 728 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{25}H_{23}{}^{35}ClO_8$ $[M]^+$: 486.1076; found: 486.1072.

Triflate S39:



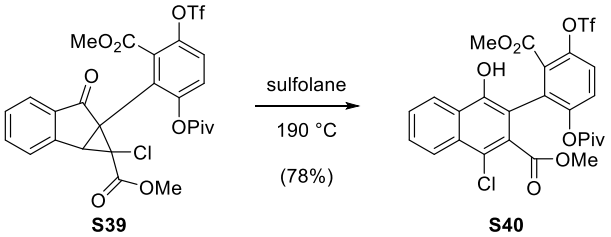
S38 **S39**

A solution of phenol **S38** (259 mg, 0.532 mmol, 1 equiv) in dichloromethane (1 mL) was treated sequentially with triethylamine (0.111 mL, 0.798 mmol, 1.50 equiv) and trifluoromethanesulfonic anhydride (0.132 mL, 0.798 mmol, 1.50 equiv) at –78 °C. The mixture was stirred at –78 °C for 15 min, then at 0 °C for further 15 min and was then allowed to warm to 23 °C. After 30 min, saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) were added and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **S39** (297 mg, 90%, mixture of two diastereoisomers) as a yellow oil.

S39a: **TLC** (20% ethyl acetate in hexanes), R_f = 0.21 (UV, CAM). *Note: the second isomer is visible in the 1H and 13C NMR!* **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.0 Hz, 1H), 7.65–7.57 (m, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 4.11 (s, 1H), 3.97 (s, 3H), 3.66 (s, 3H), 1.00 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 192.8, 176.1, 165.5, 163.9, 150.6, 146.4, 144.5, 135.5, 134.7, 129.8, 129.4, 127.2, 126.7, 125.8, 125.2, 123.0, 118.6 (q, *J* = 325.4 Hz), 67.4, 54.1, 53.8, 46.1, 40.9, 39.2, 26.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (*w*), 2361 (*w*), 1731 (*vs*), 1607 (*w*), 1466 (*m*), 1426 (*s*), 1278 (*s*), 1216 (*vs*), 1139 (*s*), 1090 (*vs*), 1023 (*m*), 869 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{26}H_{22}{}^{35}ClF_3O_{10}{}^{32}S$ $[M]^+$: 618.0569; found: 618.0575.

S39b: **TLC** (20% ethyl acetate in hexanes), R_f = 0.18 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.5 Hz, 1H), 7.64 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.50 (td, *J* = 7.6, 1.0 Hz, 1H), 7.39–7.29 (m, 2H), 3.93 (s, 1H), 3.50 (s, 3H), 3.31 (s, 3H), 1.40 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 192.8, 176.8, 164.4, 163.7, 151.2, 146.4, 142.9, 134.9, 134.7, 129.5, 129.3, 126.4, 126.2, 125.3, 125.1, 122.5, 118.6 (q, *J* = 320.5 Hz), 66.3, 53.9, 52.7, 47.2, 39.7, 39.0, 27.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (*w*), 2361 (*w*), 1731 (*vs*), 1607 (*w*), 1470 (*m*), 1427 (*s*), 1278 (*s*), 1216 (*vs*), 1139 (*s*), 1089 (*vs*), 1023 (*m*), 9456 (*m*), 868 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{26}H_{22}{}^{35}ClF_3O_{10}{}^{32}S$ $[M]^+$: 618.0569; found: 618.0573.

Naphthol S40:

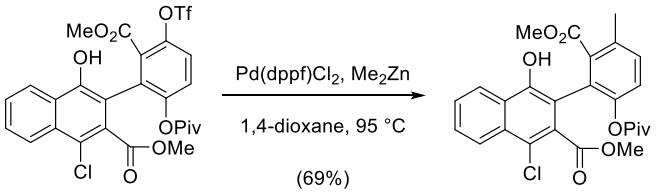


S39 **S40**

A solution of triflate **S39** (100 mg, 0.162 mmol, 1 equiv) in sulfolane (2 mL) was stirred at 190 °C for 40 min. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **S40** (78.0 mg, 78%) as a yellow foam.

TLC (20% ethyl acetate in hexanes), R_f = 0.26 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.40–8.34 (m, 1H), 8.33–8.27 (m, 1H), 7.71 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 5.84 (s, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 0.85 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.1, 166.2, 163.8, 149.9, 149.3, 144.0, 131.4, 130.9, 130.4, 129.2, 129.1, 127.8, 126.7, 126.5, 125.0, 124.1, 123.5, 121.3, 118.7 (q, *J* = 320.2 Hz), 112.8, 53.3, 52.5, 39.1, 26.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (*w*, *br*), 2958 (*w*), 2361 (*w*), 1738 (*vs*), 1591 (*w*), 1465 (*m*), 1427 (*s*), 1297 (*s*), 1267 (*s*), 1215 (*vs*), 1139 (*s*), 1103 (*s*), 1025 (*m*), 949 (*m*), 885 (*w*), 832 (*m*) 761 (*m*) cm^{-1}. HRMS (EI) calcd for $C_{26}H_{22}{}^{35}ClF_3O_{10}{}^{32}S$ $[M]^+$: 618.0569; found: 618.0565.

Naphthol S41:



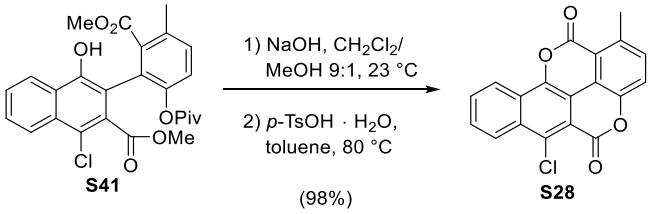
S40 **S41**

A solution of triflate **S40** (76 mg, 0.12 mmol, 1 equiv) and 1,1-bis(diphenylphosphino)-ferrocenedichloropalladium(II) (4.5 mg, 0.0061 mmol, 0.050 equiv) in 1,4-dioxane (3 mL) was treated with dimethylzinc (1.2 M in toluene, 0.21 mL, 0.25 mmol, 2.0 equiv) and the solution was stirred at 95 °C. After 3 h, the reaction was allowed to cool to 23 °C, and then was diluted with methanol (3 drops) and diethyl ether (30 mL). The organic layer was washed with 1 M hydrochloric acid solution (20 mL) and with saturated aqueous sodium chloride (20 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by

flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **S41** (41 mg, 69%) as an amorphous pale yellow foam.

TLC (20% ethyl acetate in hexanes), R_f = 0.12 (UV, CAM) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.67 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 5.82 (s, 1H), 3.61 (s, 3H), 3.54 (s, 3H), 2.43 (s, 3H), 0.84 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.8, 168.2, 166.5, 149.3, 148.1, 136.5, 134.0, 132.8, 131.7, 131.1, 128.6, 127.4, 126.2, 124.9, 124.8, 124.3, 123.5, 120.4, 113.9, 52.3, 52.3, 39.0, 26.6, 19.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3449 (*w*, *br*), 2953 (*w*), 2258 (*w*), 1731 (*s*), 1448 (*m*), 1386 (*m*), 1269 (*s*), 1237 (*s*), 1109 (*vs*), 1030 (*s*), 907 (*s*), 727 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{26}H_{25}{}^{35}ClO_7$ $[M]^+$: 484.1283; found: 484.1283.

Lactone S28:

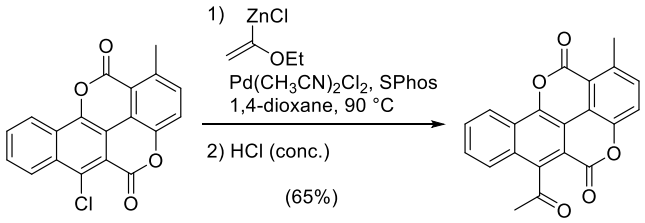


A solution of naphthol **S41** (78 mg, 0.16 mmol, 1 equiv) in dichloromethane/methanol (9:1, 2 mL) was treated with sodium hydroxide (64 mg, 1.6 mmol, 10 equiv) at 23 °C. After 2 h, the mixture was acidified with 1 M hydrochloric acid (5 mL) and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were with washed with saturated aqueous sodium chloride solution (30 mL) and the washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated.

A solution of the crude diol in toluene (2 mL) was treated with *p*-toluenesulfonic acid monohydrate (6.1 mg, 32 μmol, 0.20 equiv) and the resulting mixture was stirred at 80 °C. After 2 h, the solution was allowed to cool to 23 °C and the yellow precipitate was separated by filtration and washed with hexanes (30 mL) to afford **S28** (53 mg, 98%) as an amorphous yellow solid.

TLC (20% ethyl acetate in hexanes), R_f = 0.24 (UV, CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 8.77–8.73 (m, 1H), 8.67–8.64 (m, 1H), 7.90 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.87 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.57–7.53 (m, 1H), 2.93 (d, *J* = 0.8 Hz, 3H), 1.52 (s, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 158.5, 156.8, 147.2, 144.6, 140.1, 133.9, 133.7, 132.4, 130.9, 129.9, 127.2, 125.7, 122.3, 121.4, 118.8, 117.7, 113.6, 111.6, 22.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3368 (*w*, *br*), 2918 (*w*), 2850 (*w*), 2361 (*w*), 1763 (*vs*), 1752 (*vs*), 1487 (*w*), 1438 (*w*), 1371 (*w*), 1339 (*w*), 1241 (*m*), 1185 (*m*), 1124 (*s*), 1082 (*m*), 1026 (*m*), 952 (*m*), 832 (*m*), 760 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_9ClO_4$ $[M]^+$: 336.0184; found: 36.0180.

Ketone S33:



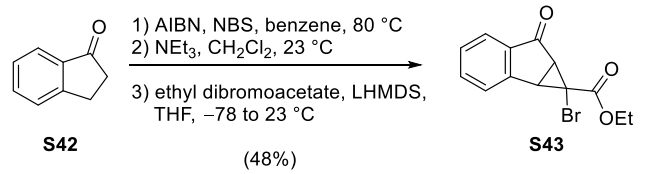
S28 **S33**

A solution of **S28** (15 mg, 0.045 mmol, 1 equiv), bis(acetonitrile)palladium(II) dichloride (0.30 mg, 0.89 μmol, 0.020 equiv) and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (1.5 mg, 3.6 μmol, 0.080 equiv) in 1,4-dioxane (2 mL) was treated with vinyl zinc (0.14 M in THF, 0.96 mL, 0.13 mmol, 3.0 equiv) and the mixture was stirred at 90 °C. After 3 h, the mixture was allowed to cool to 23 °C, and then was diluted with 6 M aqueous hydrochloric acid solution (3 mL), After 1.5 h, the layers were separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **S38** (10 mg, 65) as an amorphous yellow solid.

TLC (% ethyl acetate in hexanes), R_f = 0.12 (UV, CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 8.68 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.93 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.88 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.78 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 8.2, 1.0 Hz, 1H), 2.93 (s, 3H), 2.79 (s, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 204.1, 158.9, 158.7, 147.1, 146.0, 141.2, 140.6, 133.8, 130.5, 129.9, 129.7, 126.6, 125.2, 122.6, 121.7, 118.9, 117.9, 112.2, 110.0, 32.7, 22.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2931 (*w*), 2367 (*w*), 2260 (*w*), 1733 (*vs*), 1702 (*s*), 1614 (*w*), 1491 (*m*), 1407 (*m*), 1255 (*s*), 1205 (*vs*), 1150 (*s*), 1078 (*vs*), 1044 (*s*), 916 (*m*), 758 (*m*), 725 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{12}O_5$ $[M]^+$: 344.0679; found: 344.0680.

Synthesis and Ring opening reaction of Bromo-cyclopropane S43

Cyclopropane S43:



S42 **S43**

In a pressure vessel, a solution of 1-indanone (**S42**) (200 mg, 1.51 mmol, 1 equiv), *N*-bromosuccinimide (296 mg, 1.66 mmol, 1.10 equiv) and 2,2'-azobis(2-methylpropionitrile) (2.49 mg, 15.1 μmol, 0.0100 equiv) in benzene (5 mL) was stirred at 80 °C. After 16 h, the solution was allowed to cool to 23 °C, and then was diluted with water (10 mL) and diethyl ether (10 mL). The layers were separated and the aqueous layer

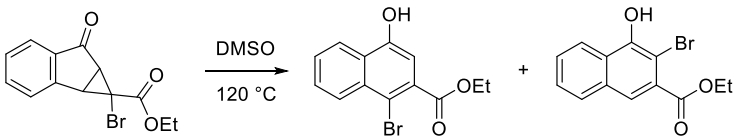
was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (1 × 40 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the crude bromo-indanone in dichloromethane (15 mL) was added triethylamine (1.05 mL, 7.55 mmol, 5.00 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 30 min, the solution was concentrated. Diethyl ether (50 mL) was added, the mixture was filtered through a short plug of Celite and the filtrate was concentrated. The crude product was used in the next step without further purification.

Ethyl dibromoacetate (293 μL, 2.27 mmol, 1.50 equiv) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 2.27 mL, 2.27 mmol, 1.50 equiv) in tetrahydrofuran (2 mL) at −78 °C. After 30 min, a solution of the crude indenone in tetrahydrofuran (8 mL) was added dropwise at −78 °C. The solution was allowed to warm to 23 °C. After 15 h, saturated aqueous ammonium chloride solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S43** (215 mg, 48%) as an orange oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.68 (ddt, *J* = 7.6, 1.3, 0.7 Hz, 1H), 7.58 (td, *J* = 7.4, 1.2 Hz, 1H), 7.50 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.43 (td, *J* = 7.4, 1.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.54 (d, *J* = 5.9 Hz, 1H), 3.10 (d, *J* = 5.9 Hz, H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 196.7, 166.1, 149.1, 136.1, 134.5, 129.1, 126.6, 124.4, 63.6, 54.4, 38.4, 34.7, 14.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2983 (*w*), 1713 (*vs*), 1606 (*m*), 1470 (*m*), 1368 (*w*), 1241 (*vs*), 1203 (*s*), 1101 (*m*), 1050 (*m*), 996 (*m*), 771 (*s*) cm^{-1}. **HRMS** (ESI) calcd for $C_{13}H_{12}{}^{79}BrO_3$ $[M+H]^+$: 294.9964; found: 294.9968.

Ethyl 3-bromo-4-hydroxy-2-naphthoate (S44a) and ethyl 1-bromo-4-hydroxy-2-naphtoate (S44b):



S43 **S44a** (29%) **S44b** (35%)

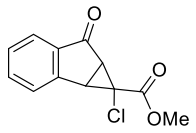
A solution of cyclopropane **S43** (20 mg, 0.68 mmol, 1 equiv) in dimethyl sulfoxide (1 mL) was stirred at 120 °C for 2 h. The reaction mixture was allowed to cool to 23 °C and then was diluted with diethyl ether (20 mL). The organic layer was washed sequentially with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column

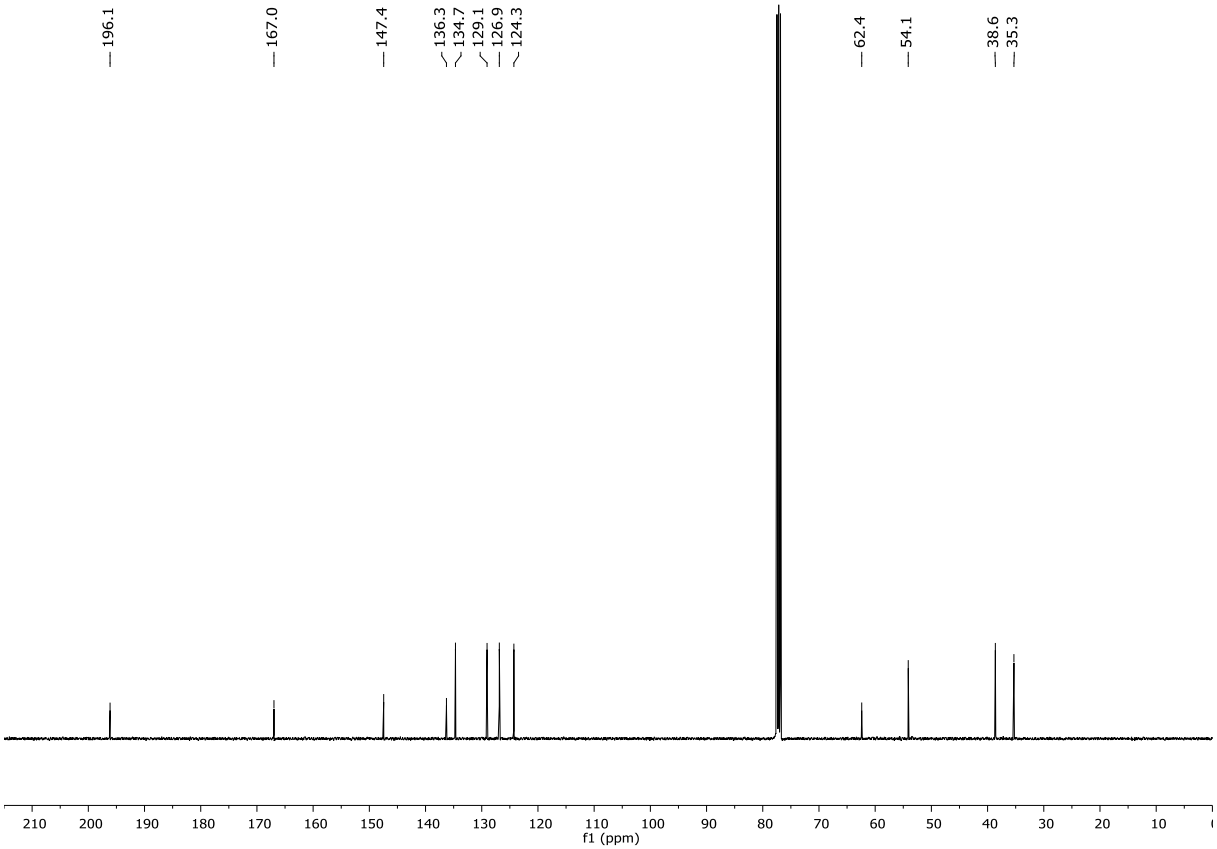
chromatography on silica gel (10% ethyl acetate in hexanes) to afford **S44a** (89 mg, 89%) and **S44b** (10 mg, 10%) as orange oils.

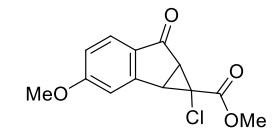
S44a: **TLC** (20% ethyl acetate in hexanes): R_f = 0.29 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.40 (ddd, *J* = 8.5, 1.3, 0.7 Hz, 1H), 8.23 (ddd, *J* = 8.3, 1.5, 0.7 Hz, 1H), 7.66 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.12 (s, 1H), 5.99 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 167.8, 151.4, 133.3, 131.2, 128.7, 128.6, 127.6, 126.7, 122.4, 113.1, 108.9, 62.3, 14.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3392 (*m*), 2359 (*m*), 1706 (*vs*), 1597 (*s*), 1465 (*m*), 1396 (*s*), 1352 (*s*), 1299 (*s*), 1243 (*vs*), 1172 (*m*), 1079 (*s*), 1019 (*m*), 760 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{79}BrO_3$ $[M]^+$: 293.9886; found: 293.9883.

S44b: **TLC** (20% ethyl acetate in hexanes): R_f = 0.56 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.30–8.23 (m, 1H), 8.01 (s, 1H), 7.90–7.82 (m, 1H), 7.66–7.55 (m, 2H), 6.52 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.1, 149.4, 132.1, 128.6, 128.4, 128.3, 127.9, 125.6, 124.5, 122.8, 102.0, 61.9, 14.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3447 (*w*), 2983 (*w*), 2363 (*m*), 1726 (*vs*), 1577 (*m*), 1399 (*s*), 1298 (*s*), 1229 (*vs*), 1080 (*m*), 1023 (*m*), 778 (*m*), cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}{}^{79}BrO_3$ $[M]^+$: 293.9886; found 293.9887.

7.2.2 ^{1}H and ^{13}C NMR Spectra






O
MeO
O
Cl
OMe

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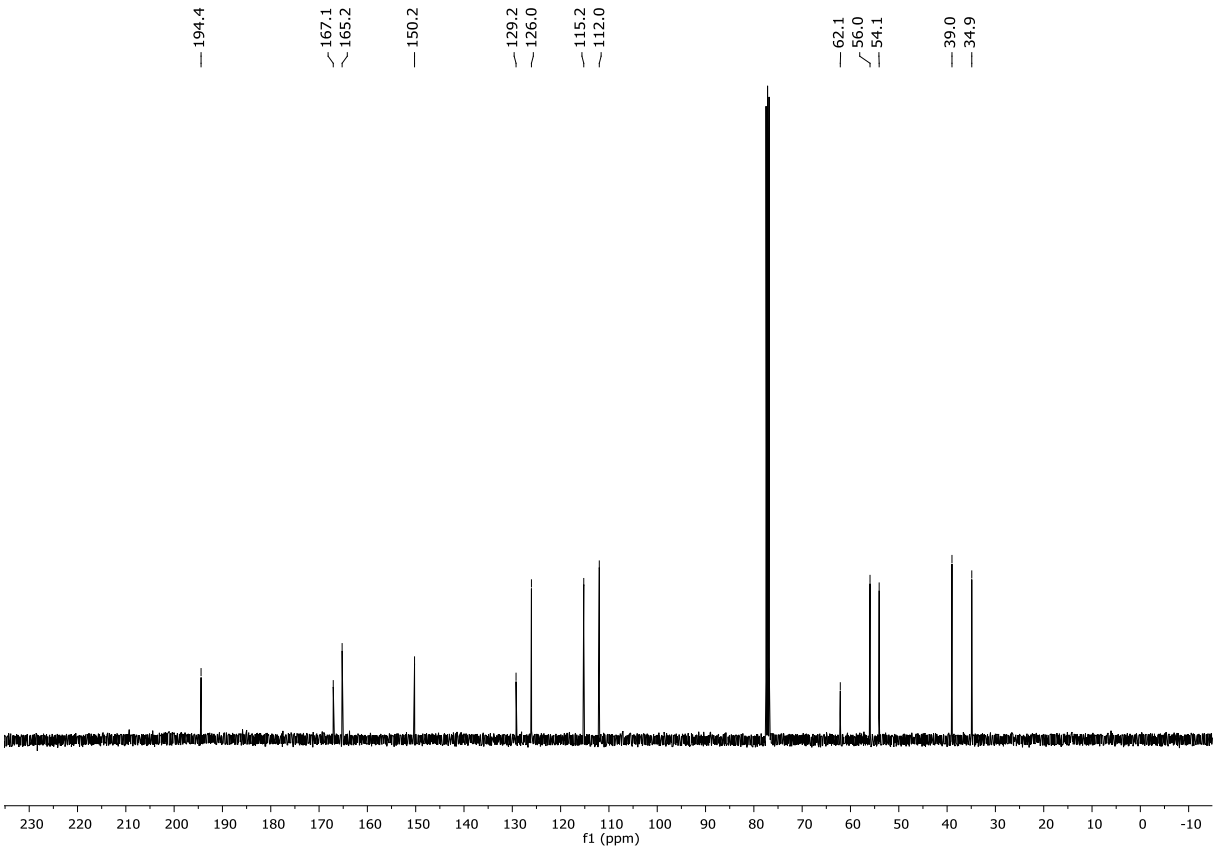
1.03
1.06
3.16
3.01
1.01
0.96
f1 (ppm)


194.4
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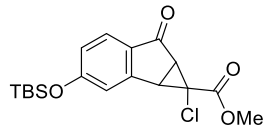
165.2
150.2
129.2
126.0
115.2
112.0
62.1
56.0
54.1
39.0
34.9
f1 (ppm)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TBSO
O
Cl
OMe

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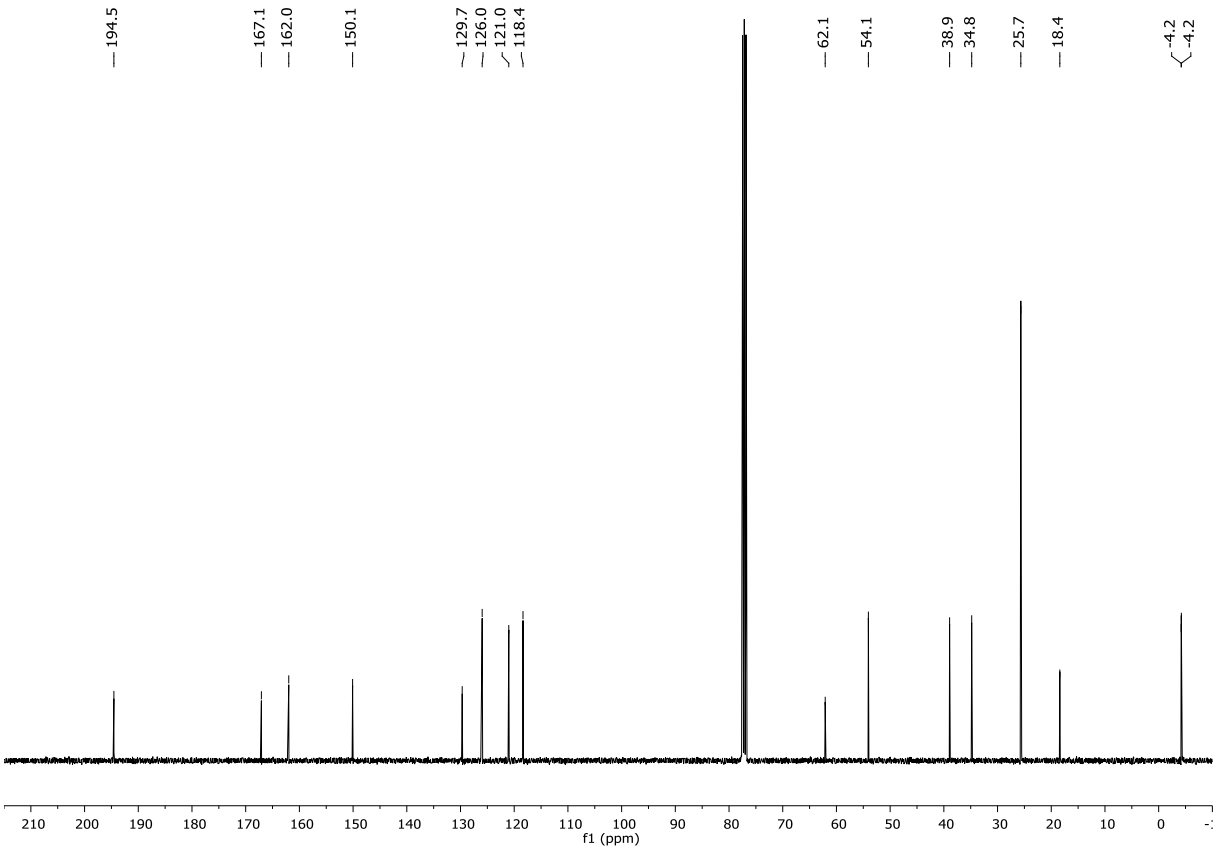
1.00
1.02
3.05
1.02
0.97
9.47
6.21
f1 (ppm)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167.1
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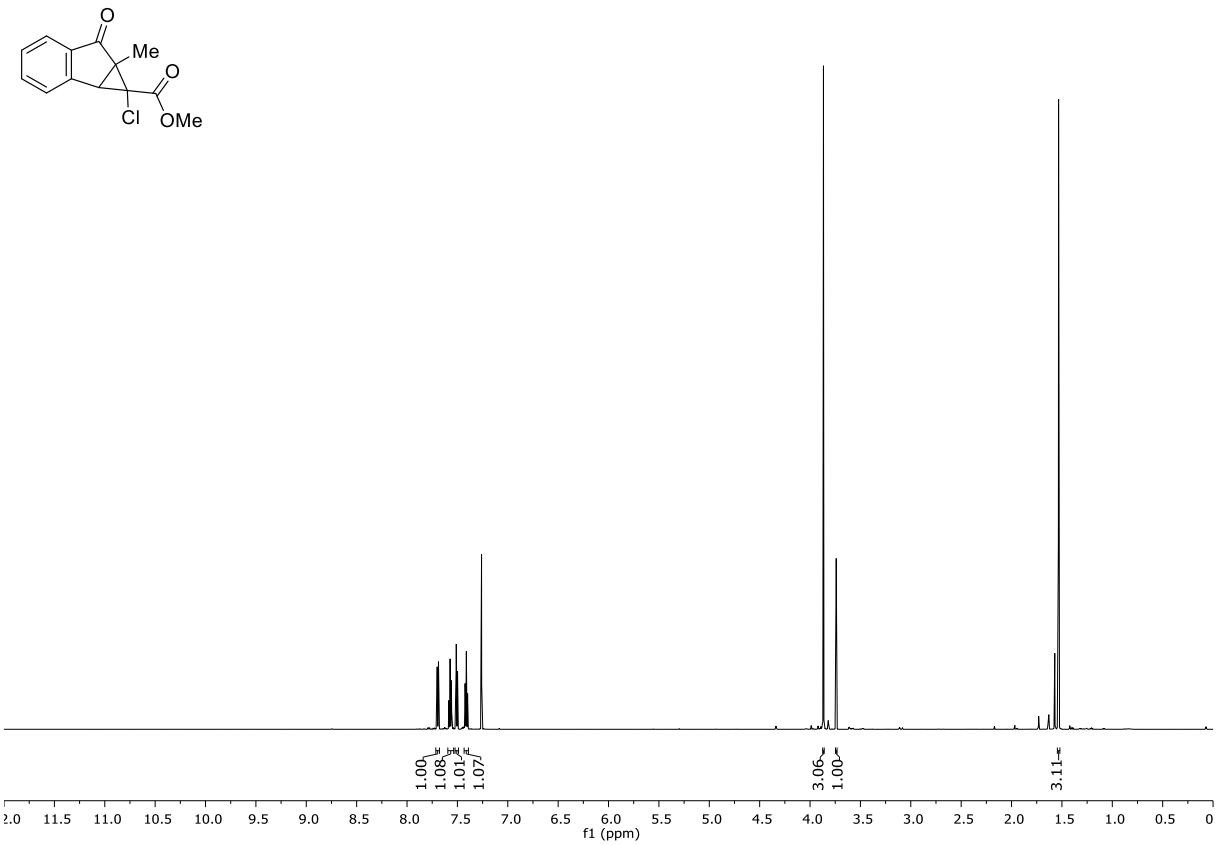
150.1
129.7
126.0
121.0
118.4
62.1
54.1
38.9
34.8
25.7
18.4
-4.2
-4.2
f1 (ppm)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Me
O
Cl
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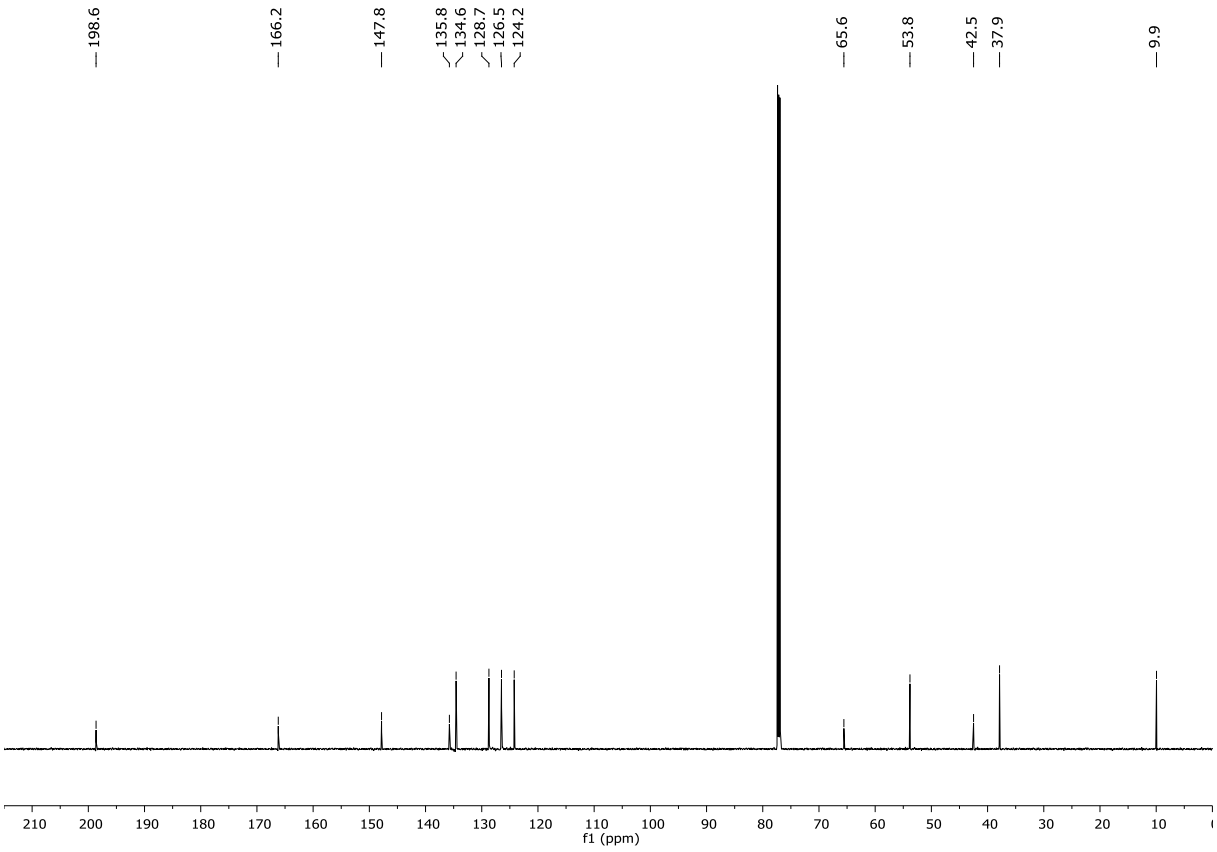
1.01
1.07
3.06
1.00
3.11
f1 (ppm)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135.8
134.6
128.7
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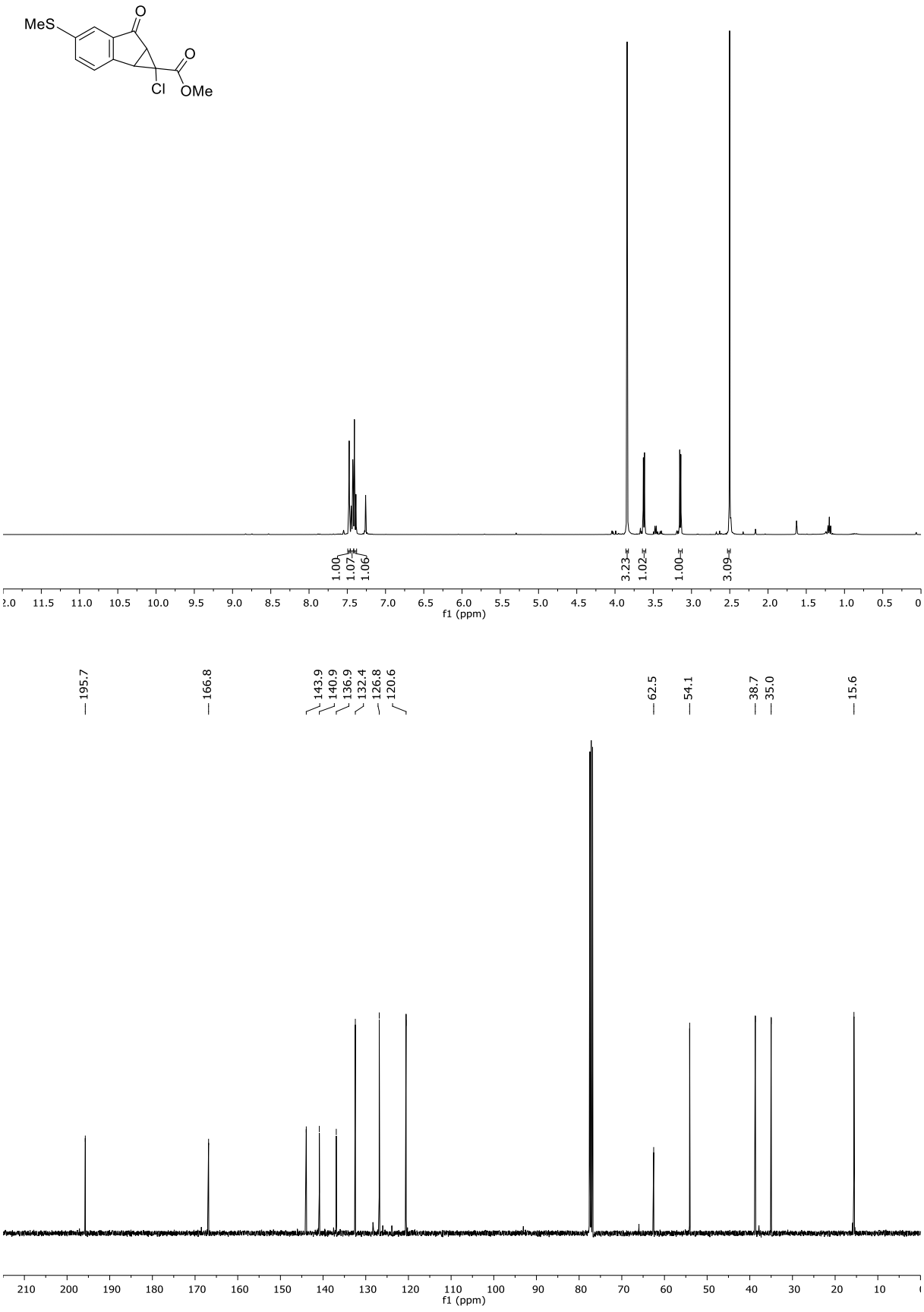
124.2
65.6
53.8
42.5
37.9
9.9
f1 (ppm)


MeS
O
O
Cl
OMe
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1.07
1.06
3.23
1.02
1.00
3.09
f1 (ppm)
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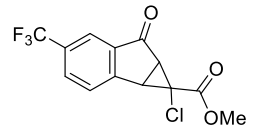
143.9
140.9
136.9
132.4
126.8
120.6
62.5
54.1
38.7
35.0
15.6
f1 (ppm)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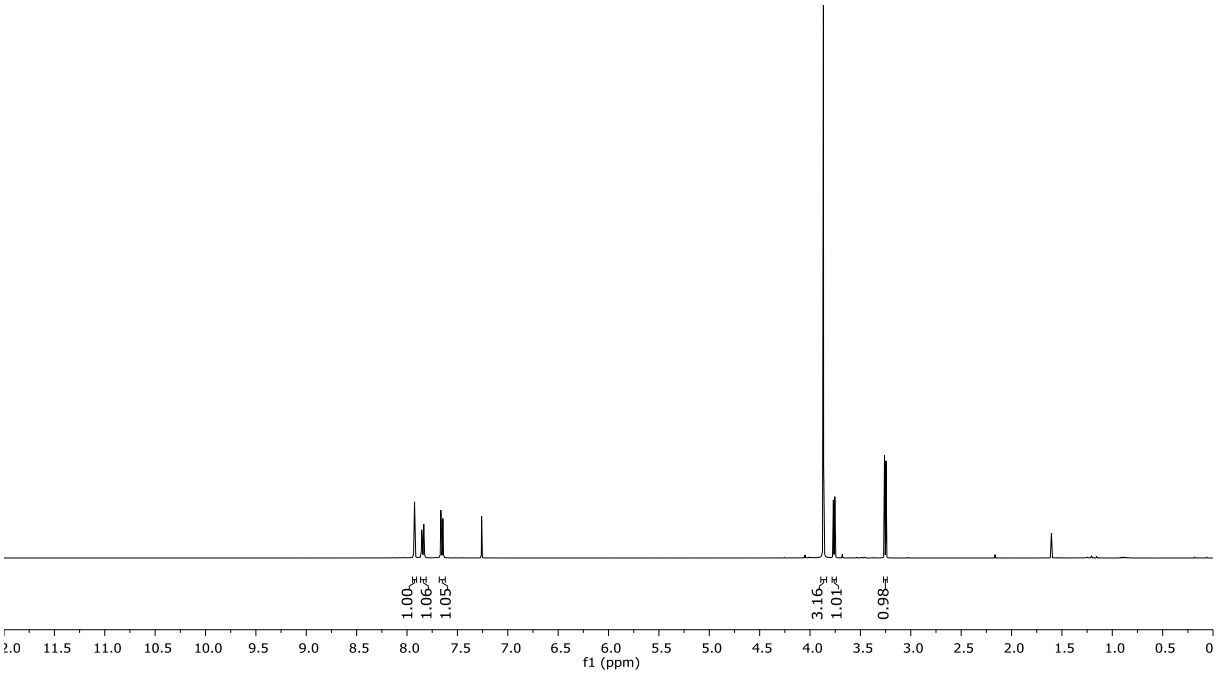
F3C
O
Cl
OMe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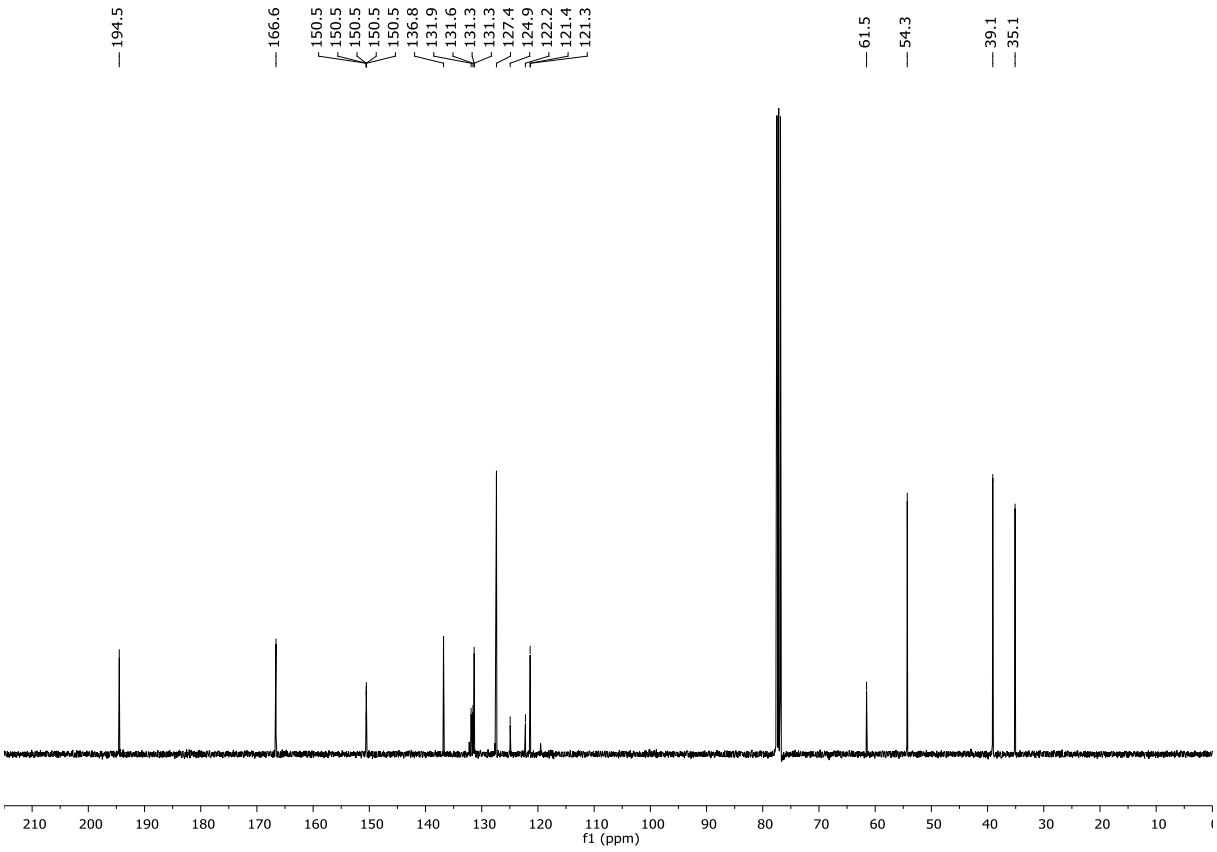
1.06
1.05
3.16
1.01
0.98
f1 (ppm)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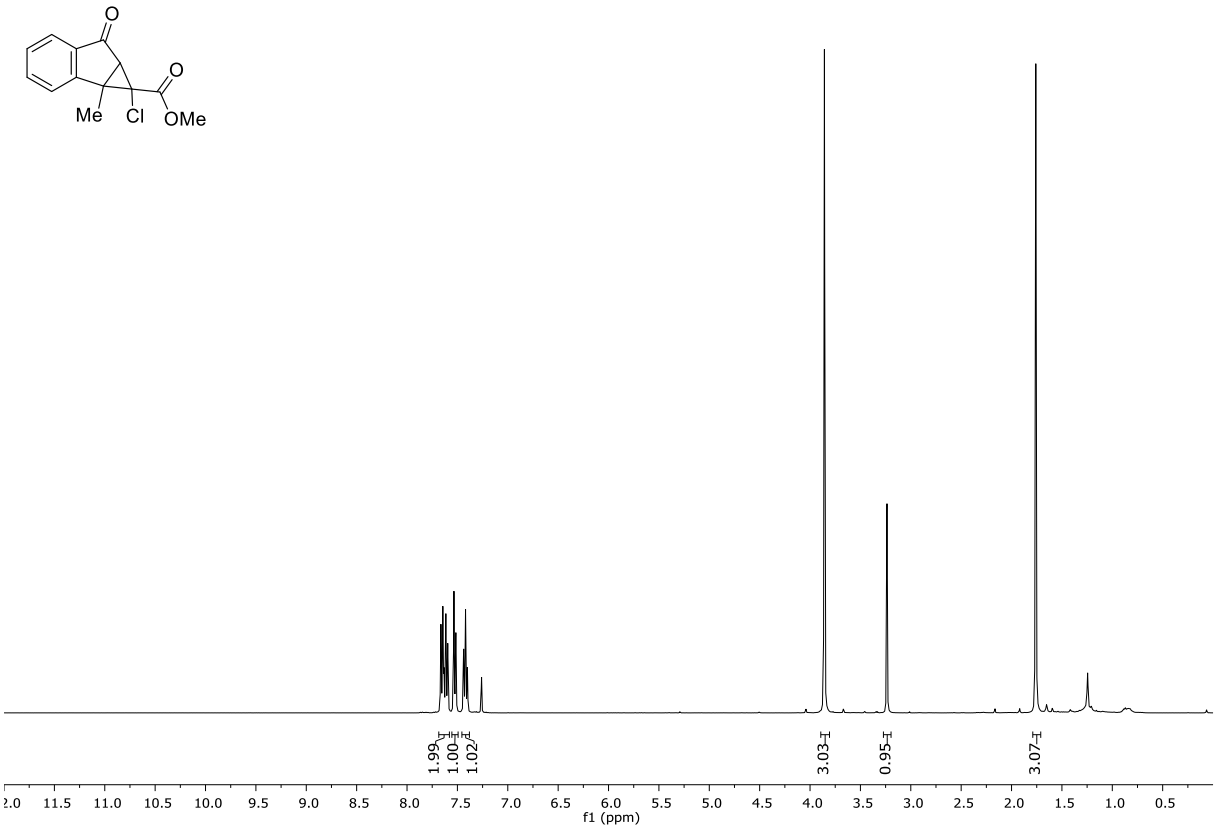
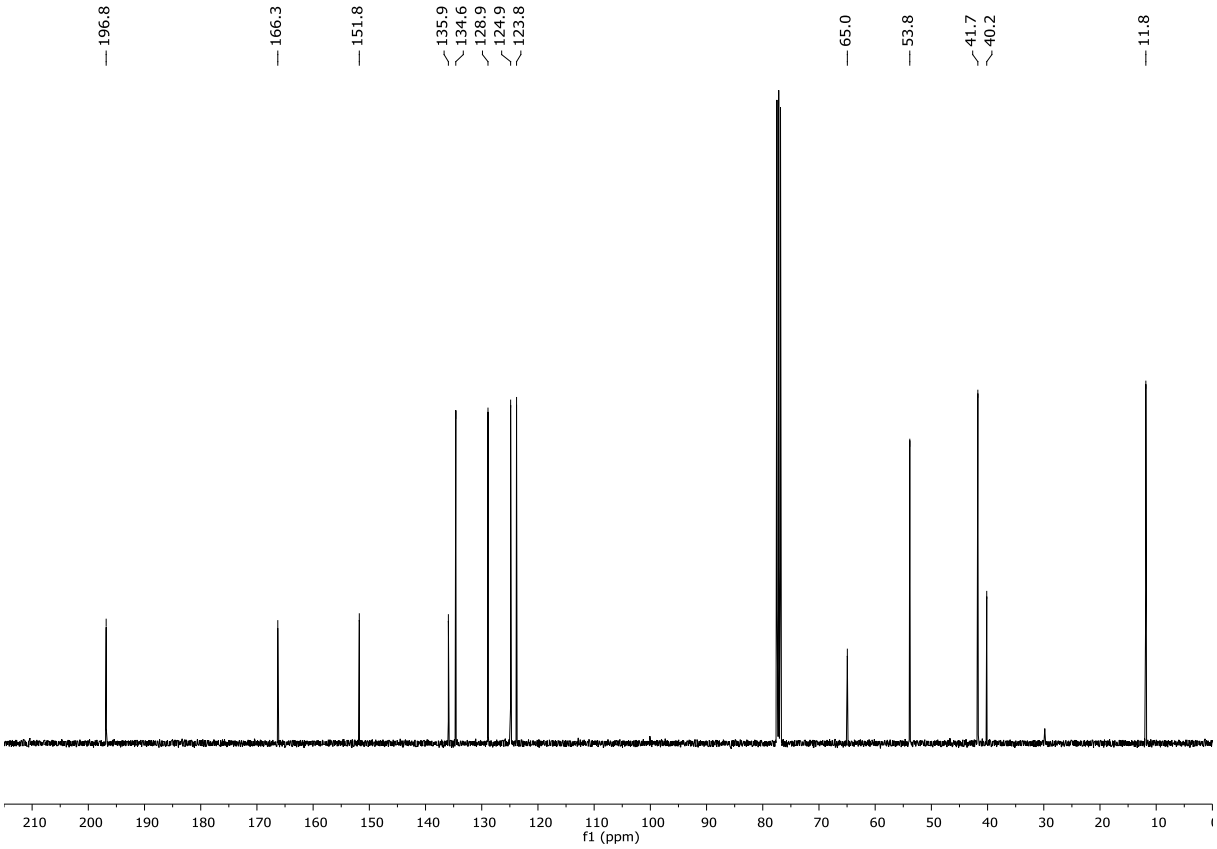
166.6
150.5
150.5
150.5
150.5
150.5
136.8
131.9
131.6
131.3
131.3
127.4
124.9
122.2
121.4
121.3
61.5
54.3
39.1
35.1
f1 (ppm)


O
O
Me
Cl
OMe
1.99
1.00
1.02
3.03
0.95
3.07
f1 (ppm)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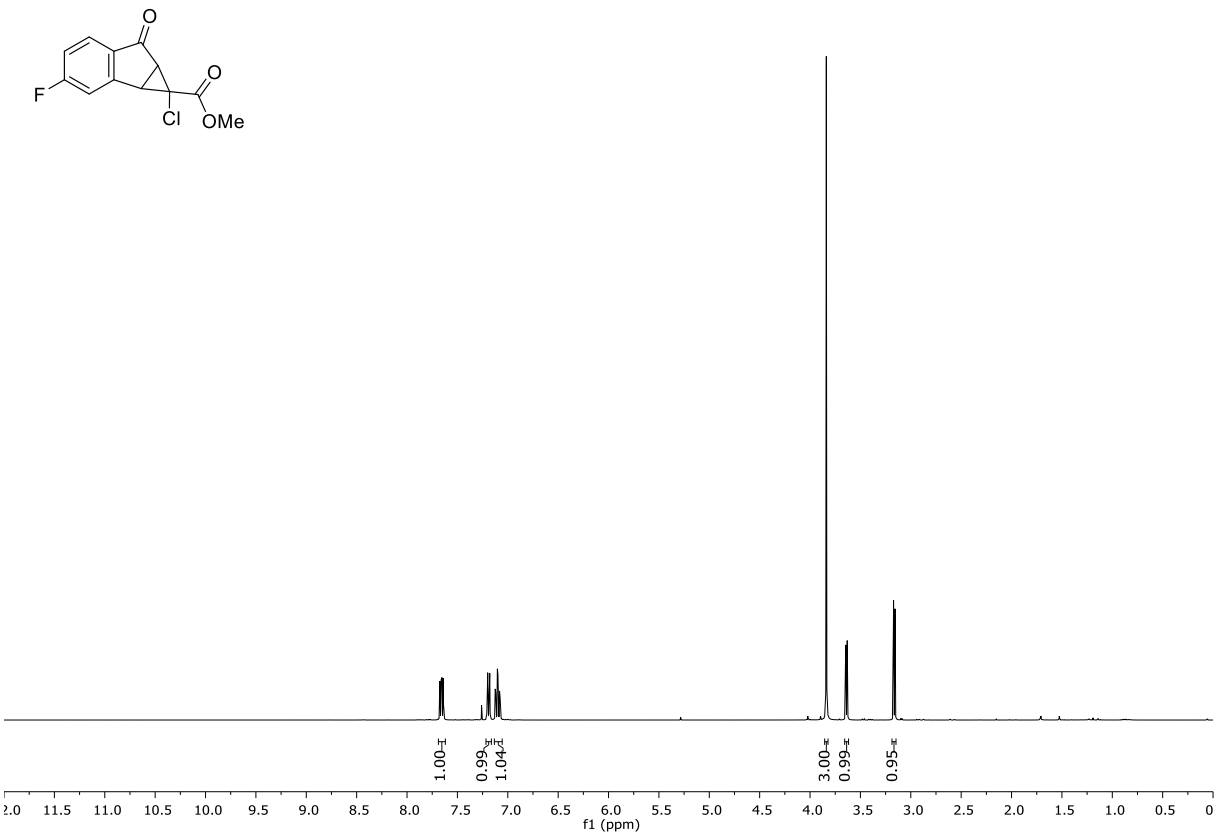
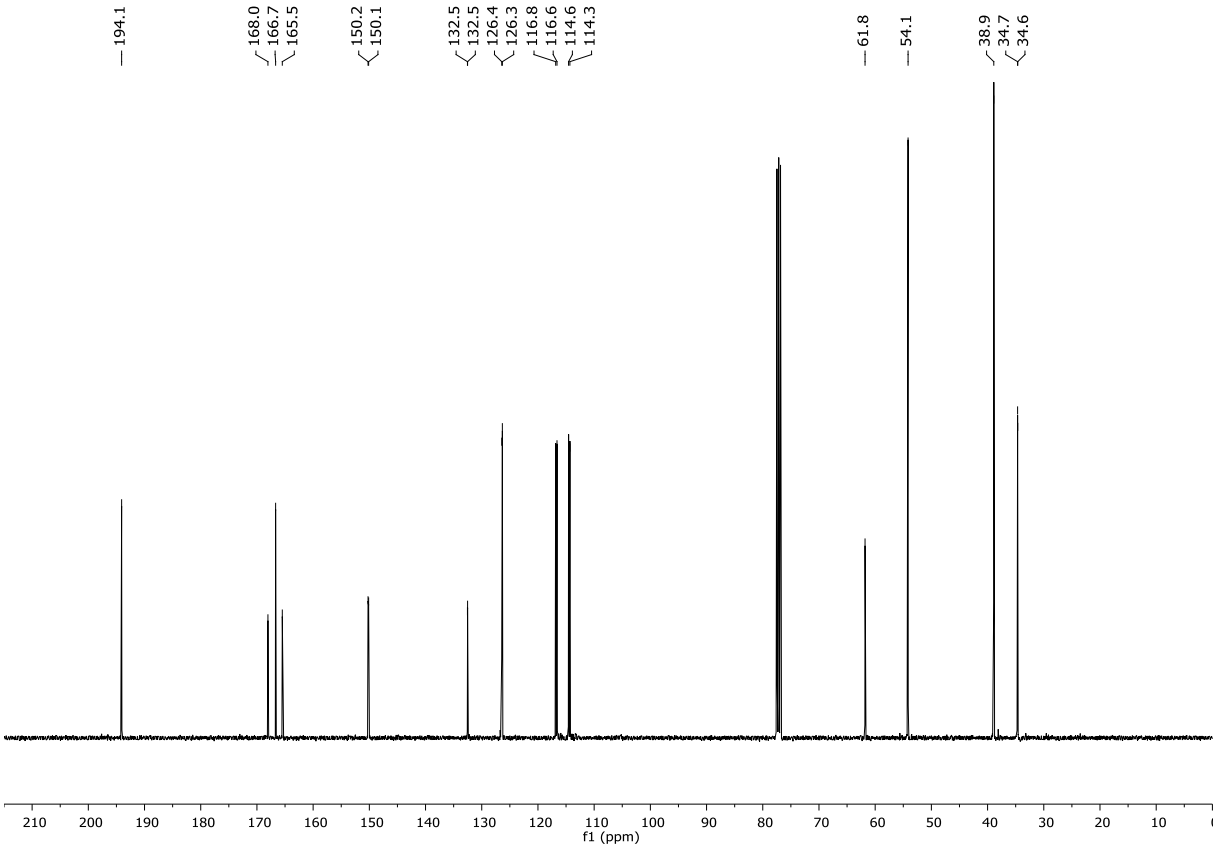
166.3
151.8
135.9
134.6
128.9
124.9
123.8
65.0
53.8
41.7
40.2
11.8
f1 (ppm)


O
O
F
Cl
OMe
1.00
0.99
1.04
3.00
0.99
0.95
f1 (ppm)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166.7
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150.2
150.1
132.5
132.5
126.4
126.3
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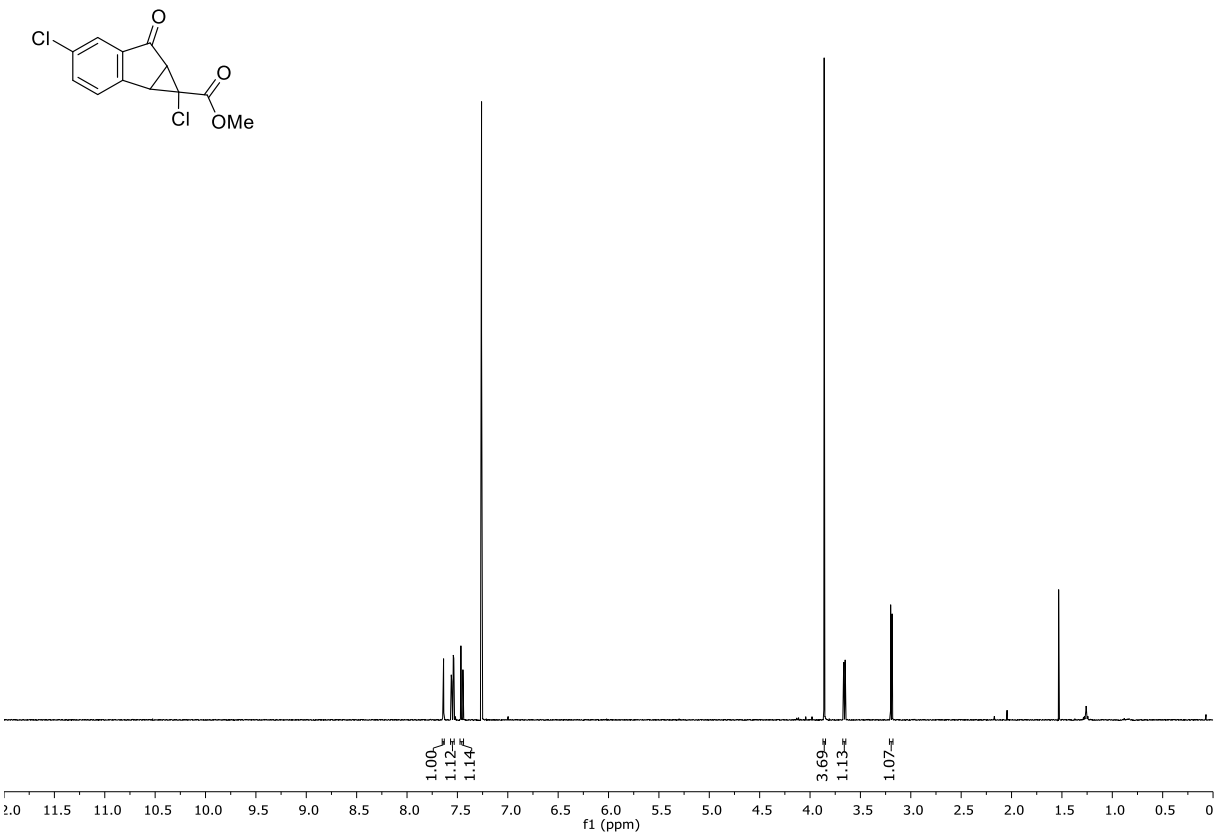
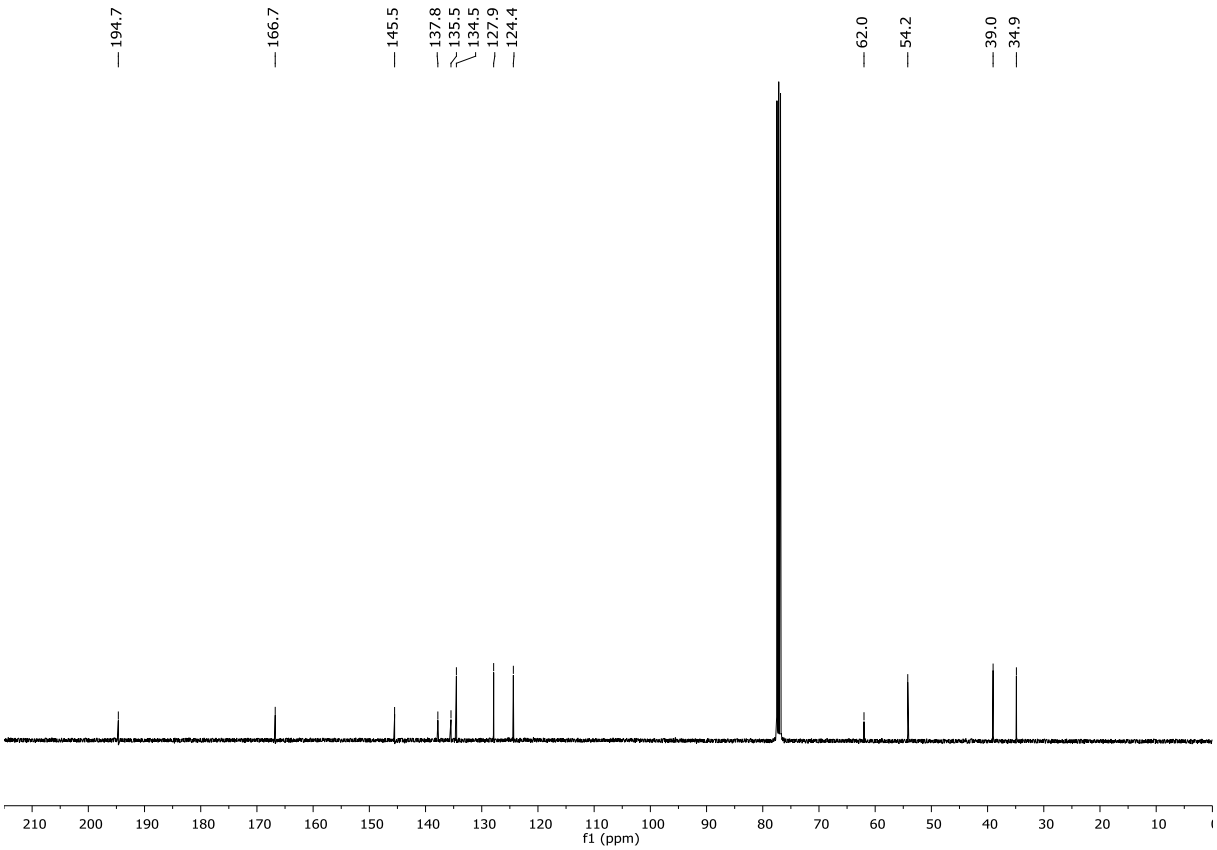
116.6
114.6
114.3
61.8
54.1
38.9
34.7
34.6
f1 (ppm)


Cl
O
O
Cl
OMe
1.00
1.12
1.14
3.69
1.13
1.07
f1 (ppm)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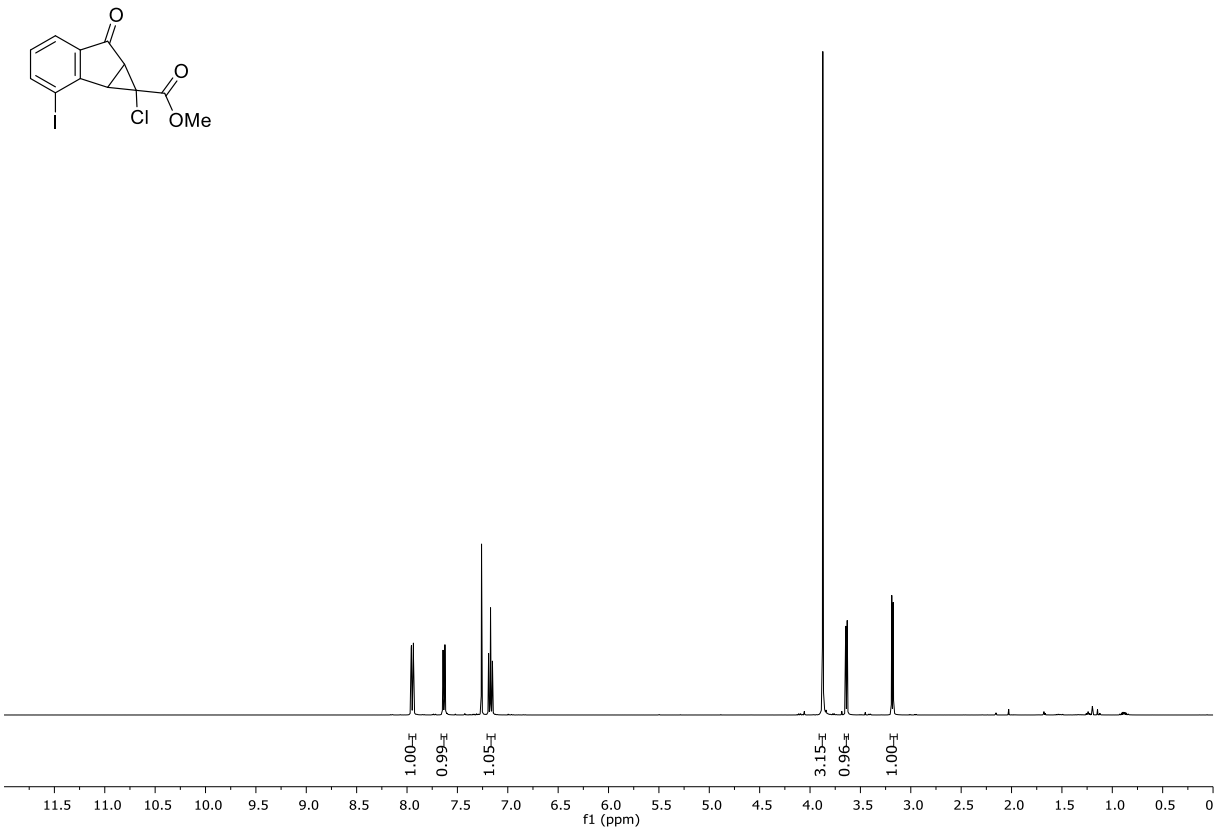
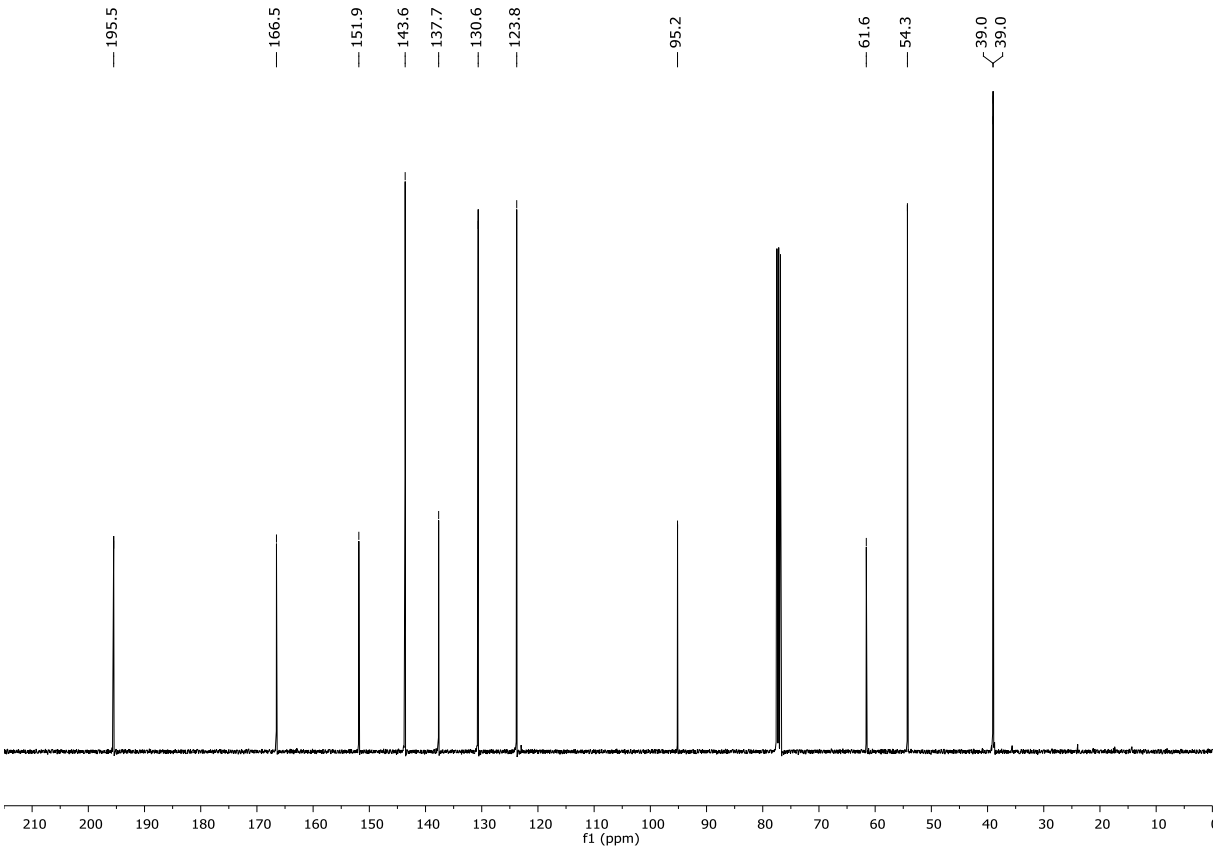
166.7
145.5
137.8
135.5
134.5
127.9
124.4
62.0
54.2
39.0
34.9
f1 (ppm)


O
O
Cl
OMe
I
1.00
0.99
1.05
3.15
0.96
1.00
f1 (ppm)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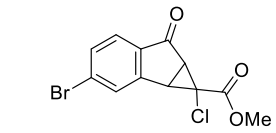
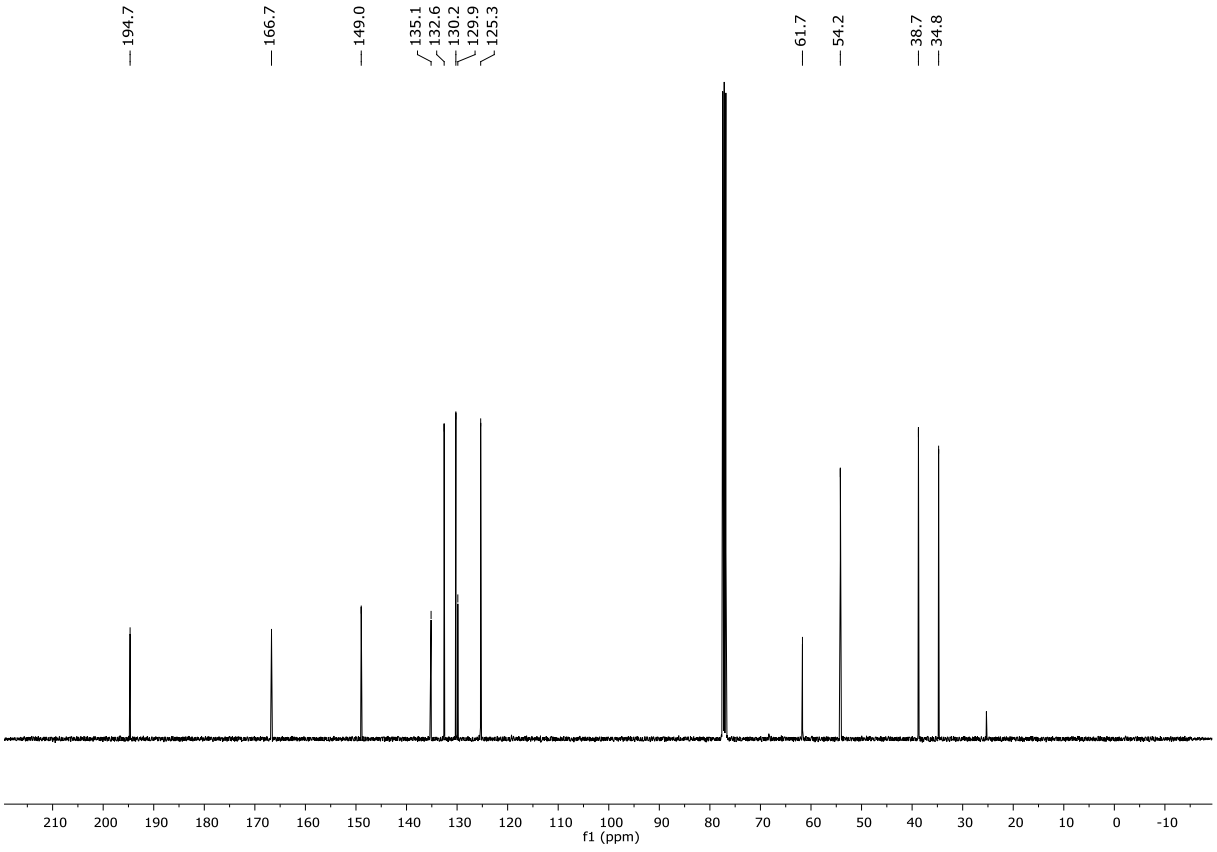
166.5
151.9
143.6
137.7
130.6
123.8
95.2
61.6
54.3
39.0
39.0
f1 (ppm)


O
O
Br
Cl
OMe

1.00
1.05
1.02
3.12
1.01
0.96
f1 (ppm)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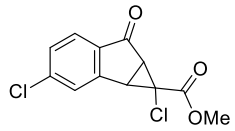
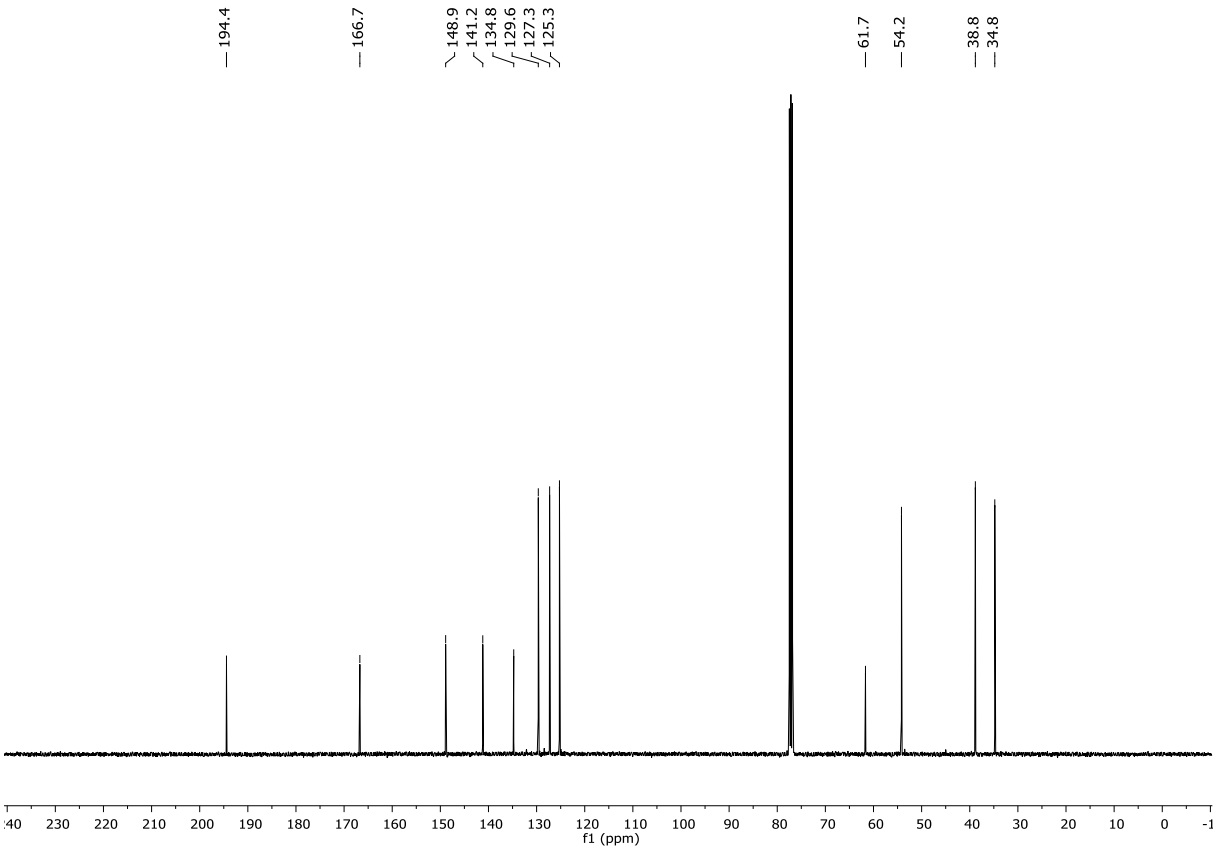
166.7
149.0
135.1
132.6
130.2
129.9
125.3
61.7
54.2
38.7
34.8
f1 (ppm)


O
O
Cl
Cl
OMe

1.00
0.97
1.00
3.01
1.00
0.98
f1 (ppm)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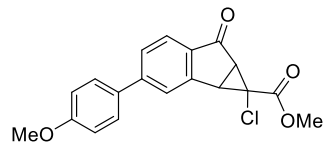
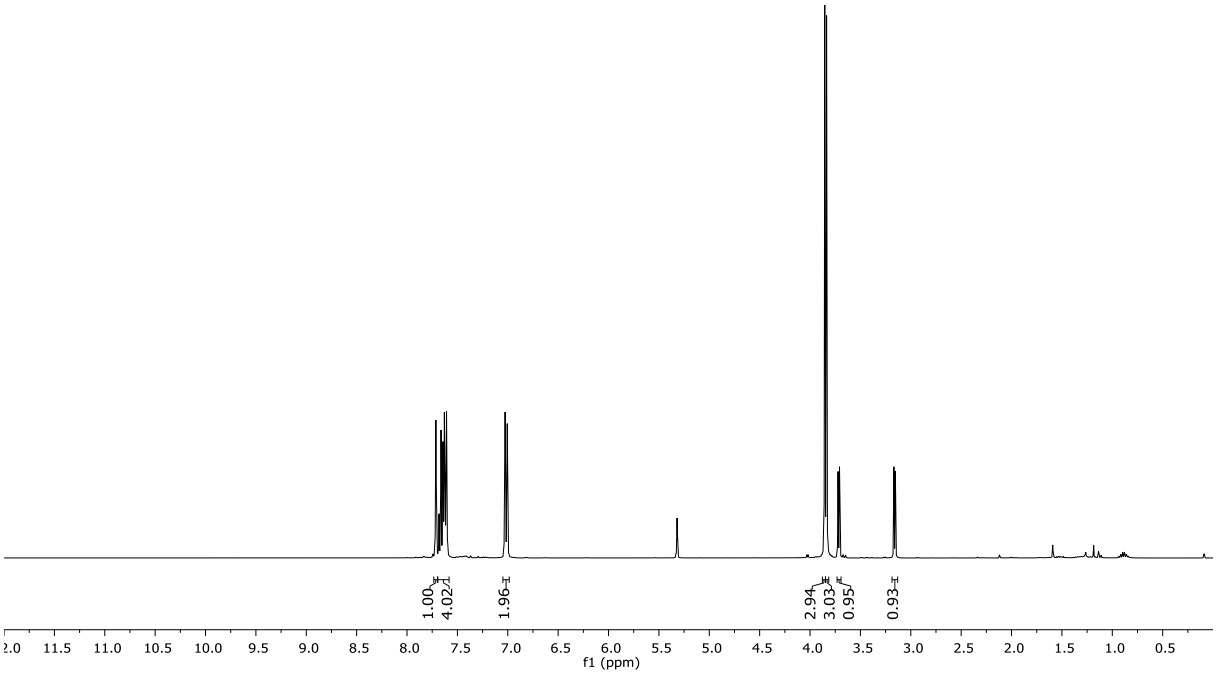
166.7
148.9
141.2
134.8
129.6
127.3
125.3
61.7
54.2
38.8
34.8
f1 (ppm)


O
O
Cl
OMe
MeO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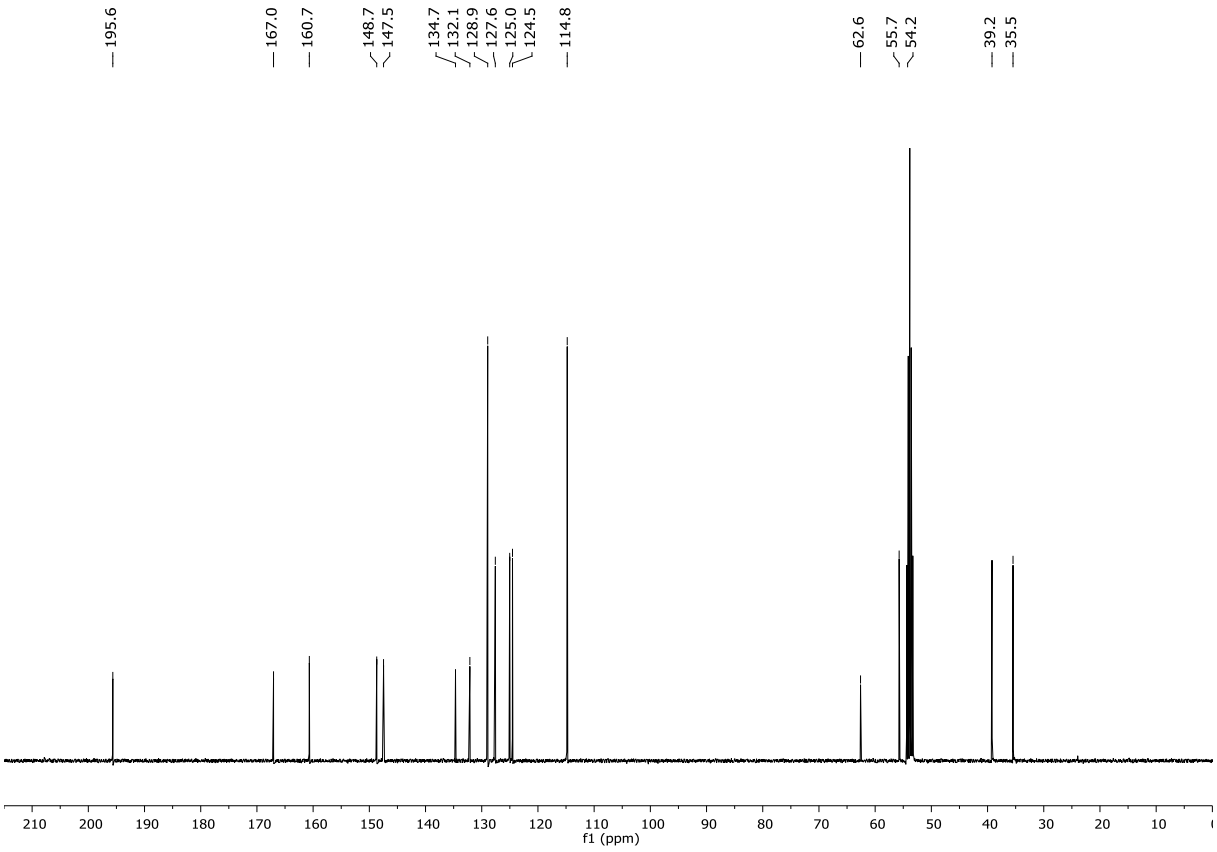
1.96
2.94
3.03
0.95
0.93
f1 (ppm)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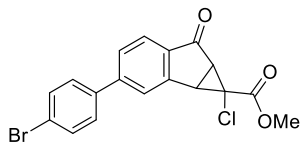
167.0
160.7
148.7
147.5
134.7
132.1
128.9
127.6
125.0
124.5
114.8
62.6
55.7
54.2
39.2
35.5
f1 (ppm)


O
O
Cl
OMe
Br

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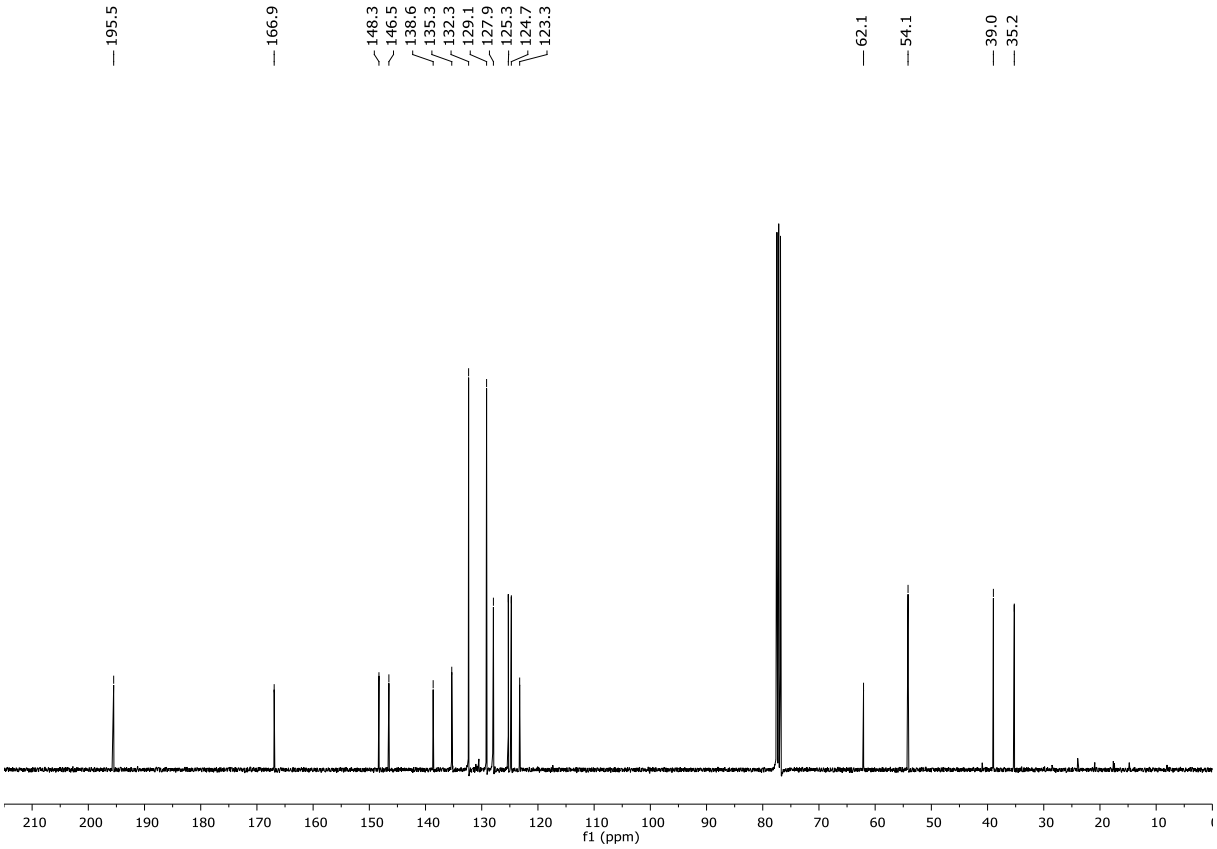
1.80
2.58
0.83
0.84
f1 (ppm)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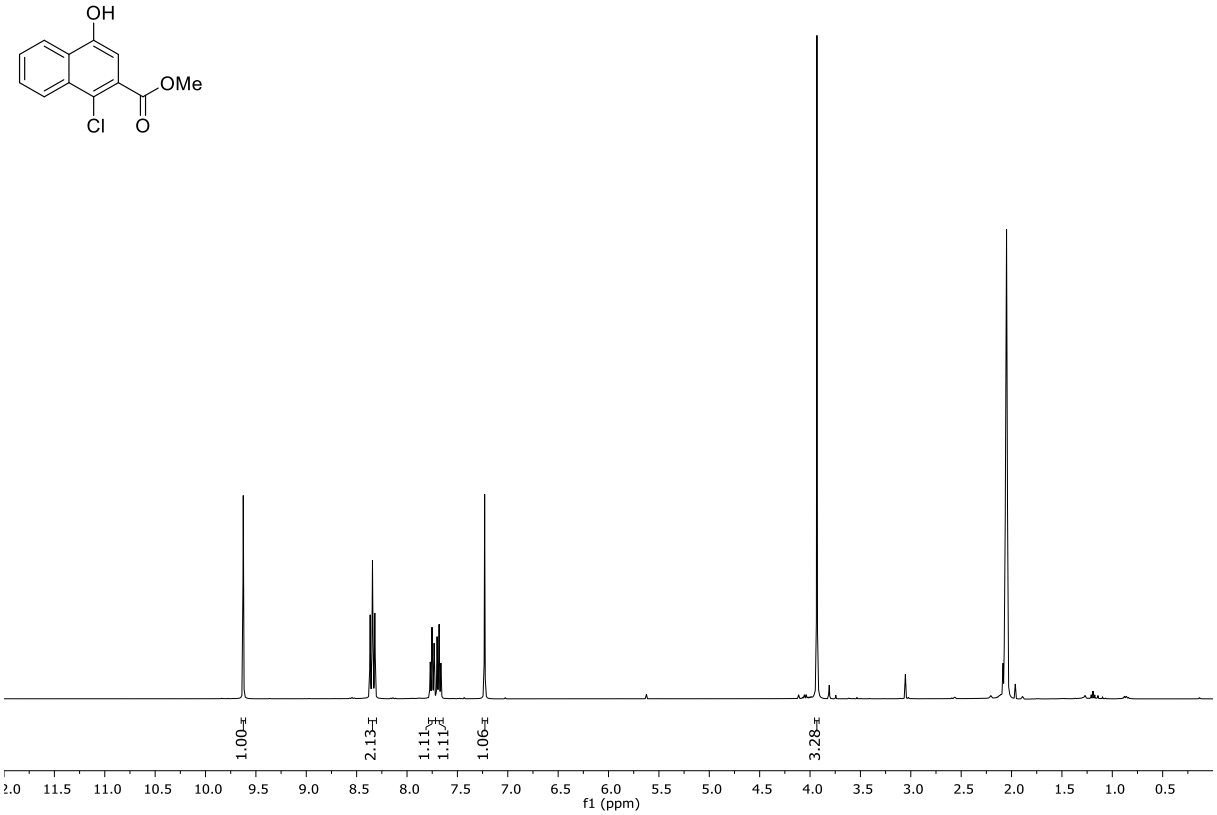
166.9
148.3
146.5
138.6
135.3
132.3
129.1
127.9
125.3
124.7
123.3
62.1
54.1
39.0
35.2
f1 (ppm)


OH
OMe
Cl
O
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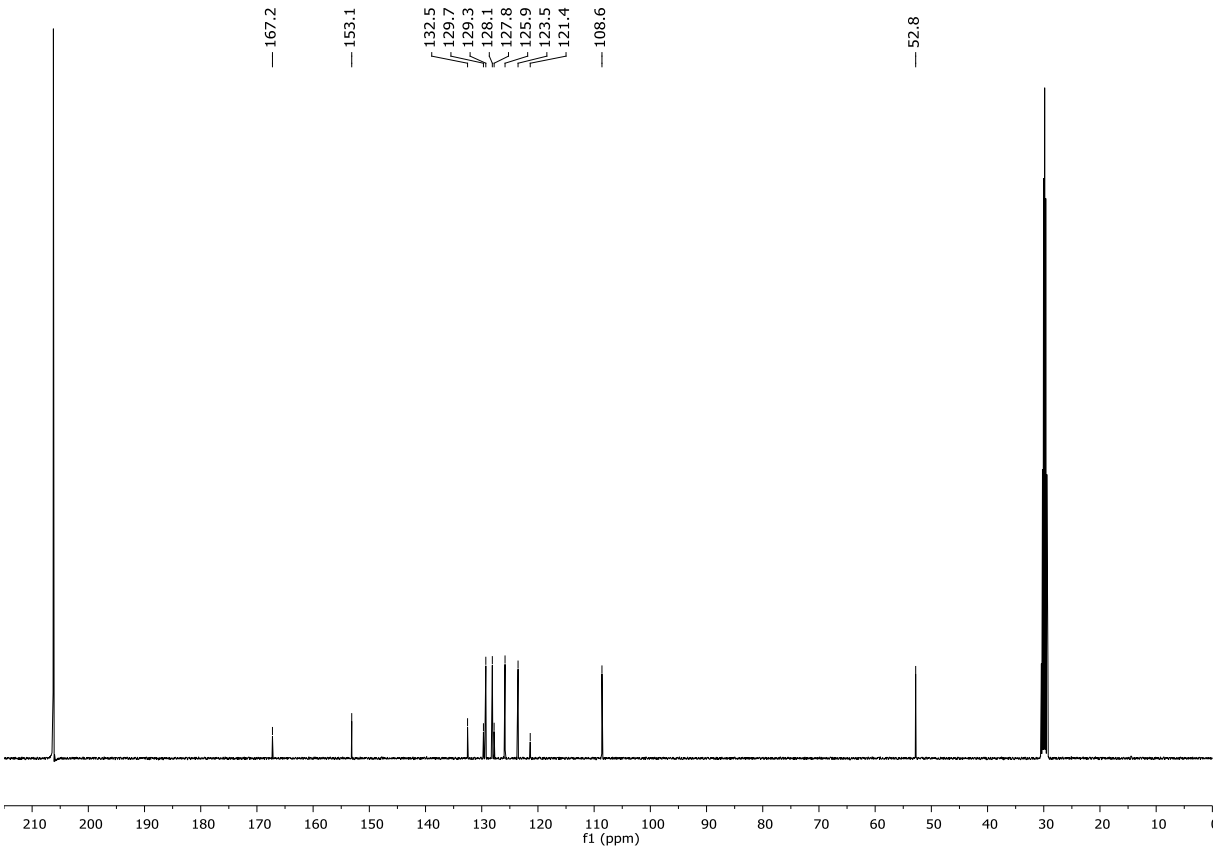
2.13
1.11
1.11
1.06
3.28
f1 (ppm)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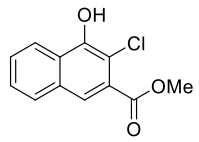
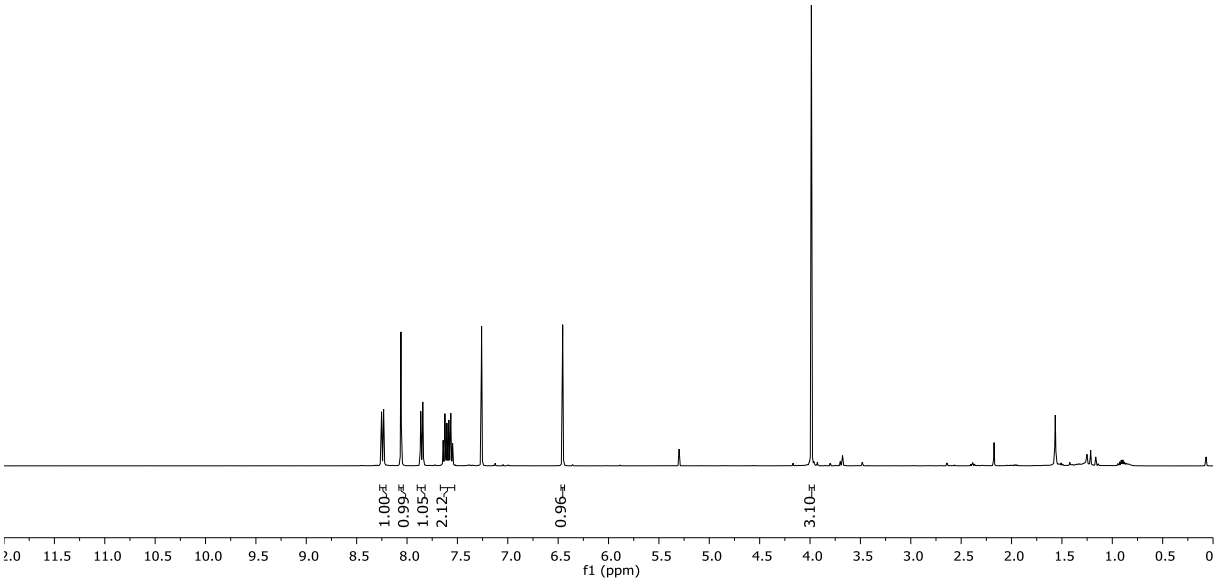
153.1
132.5
129.7
129.3
128.1
127.8
125.9
123.5
121.4
108.6
52.8
f1 (ppm)


OH
Cl
OMe
O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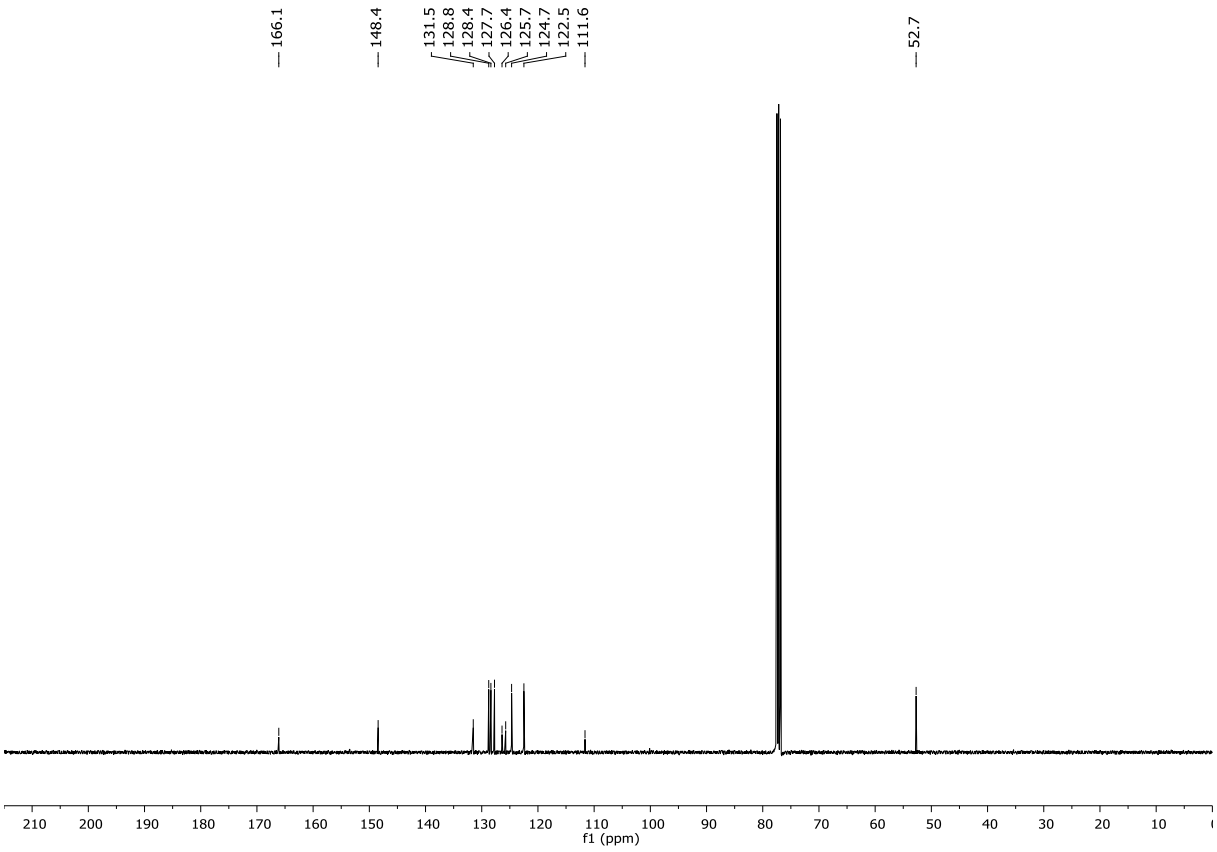
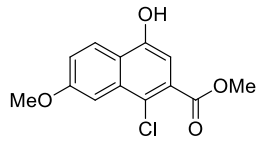
1.05
2.12
0.96
3.10
f1 (ppm)


166.1
148.4
131.5
128.8
128.4
127.7
126.4
125.7
124.7
122.5
111.6
52.7
f1 (ppm)


OH
MeO
OMe
Cl
O

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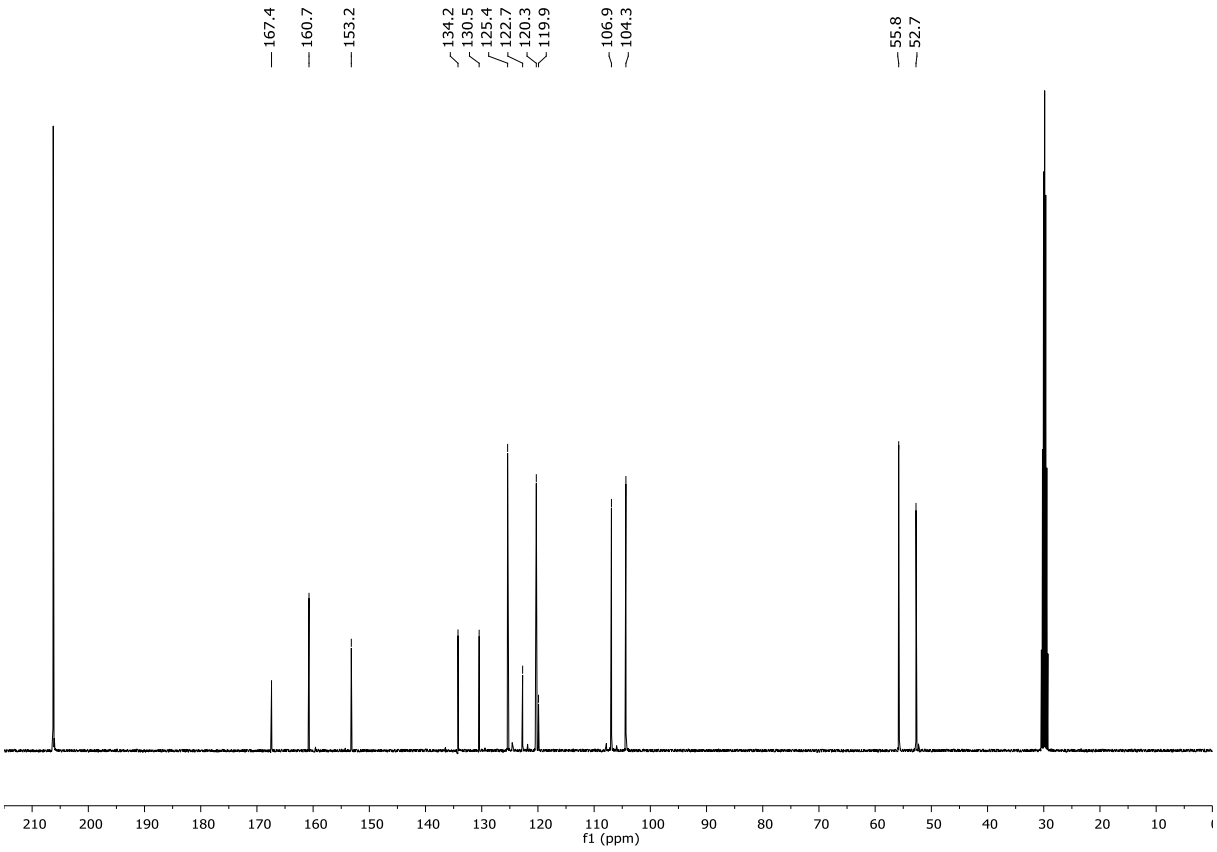
1.07
1.05
1.07
1.04
3.17
3.13
f1 (ppm)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160.7
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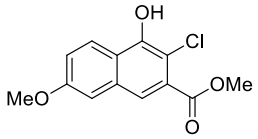
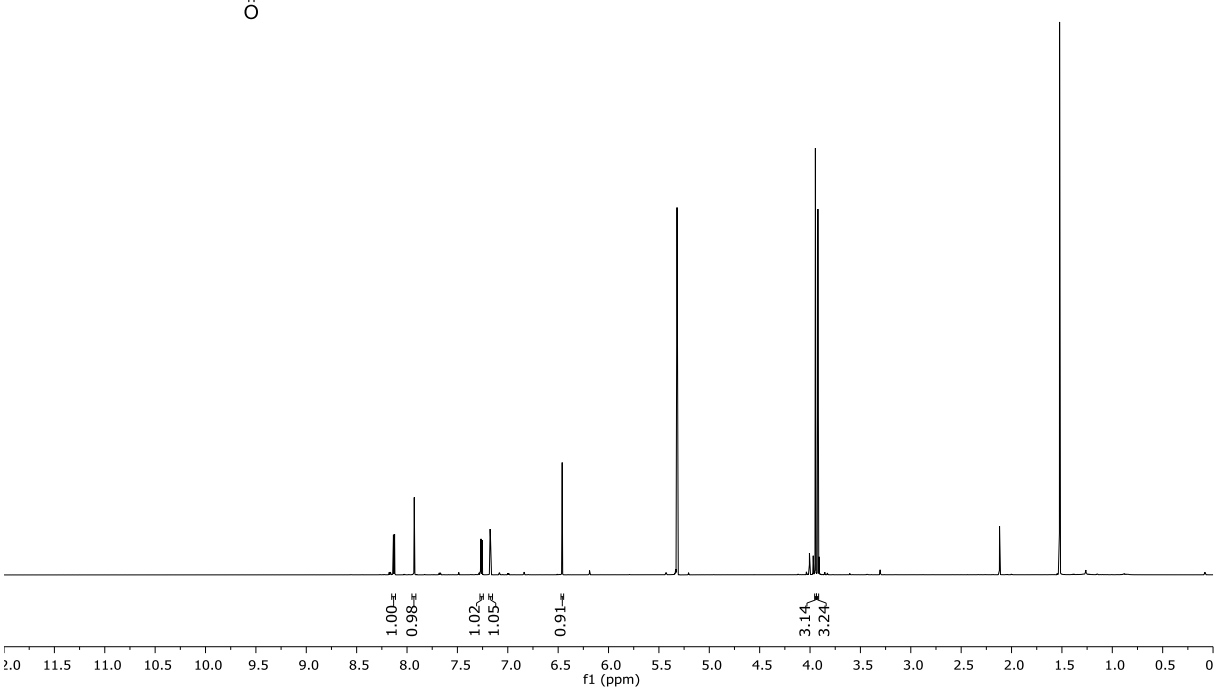
134.2
130.5
125.4
122.7
120.3
119.9
106.9
104.3
55.8
52.7
f1 (ppm)


OH
Cl
MeO
OMe
O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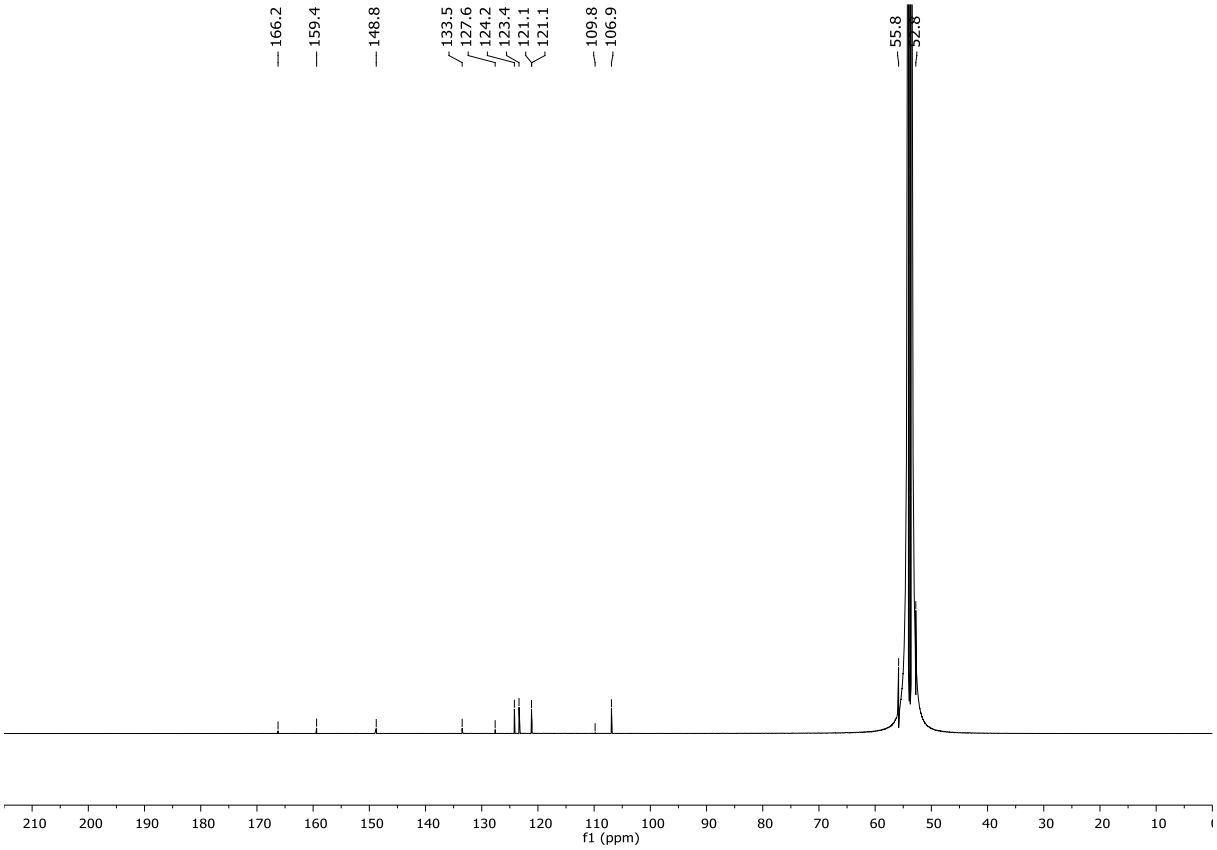
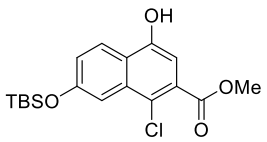
3.24
f1 (ppm)


166.2
159.4
148.8
133.5
127.6
124.2
123.4
121.1
121.1
109.8
106.9
55.8
52.8
f1 (ppm)


OH
TBSO
OMe
Cl
O

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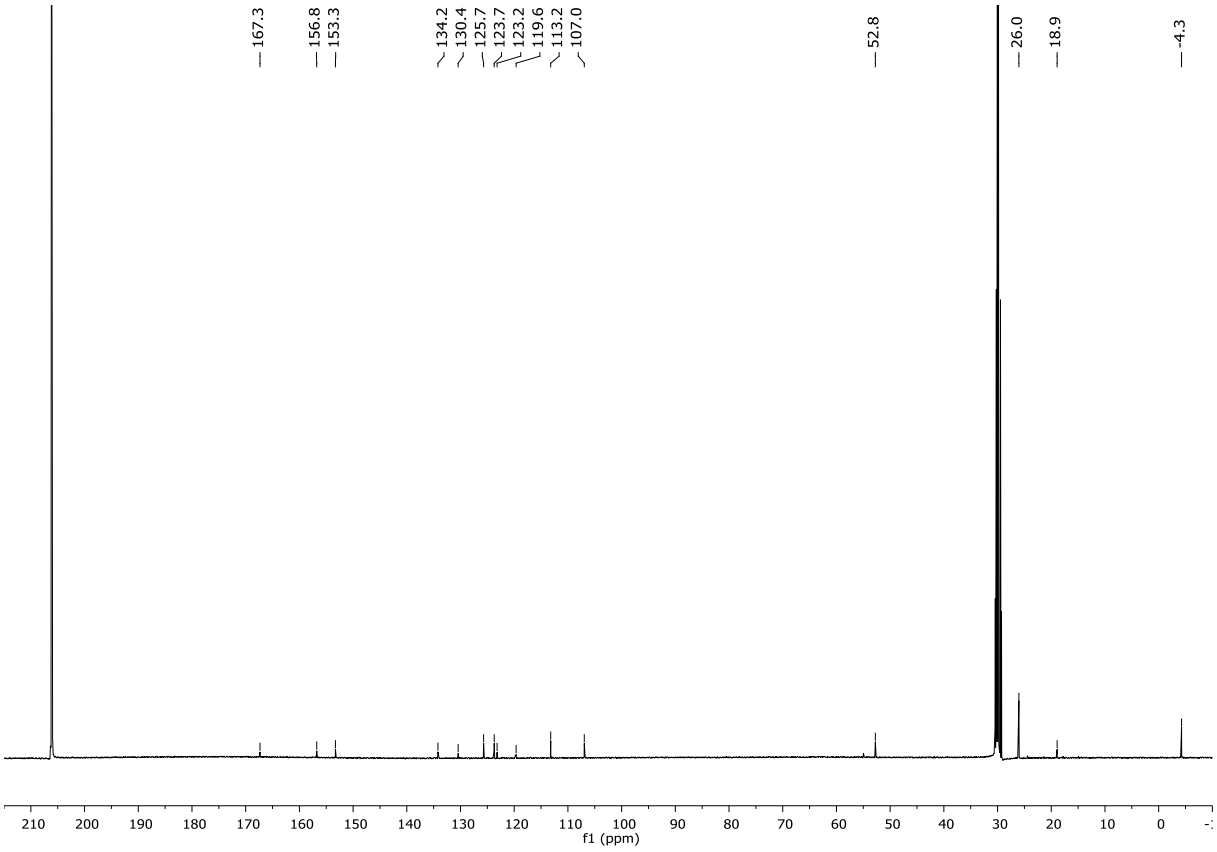
0.95
1.09
0.98
3.16
9.46
6.04
f1 (ppm)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156.8
153.3
134.2
130.4
125.7
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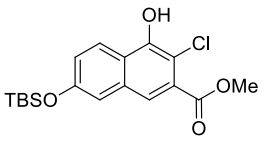
123.2
119.6
113.2
107.0
52.8
26.0
18.9
-4.3
f1 (ppm)


OH
Cl
TBSO
OMe
O

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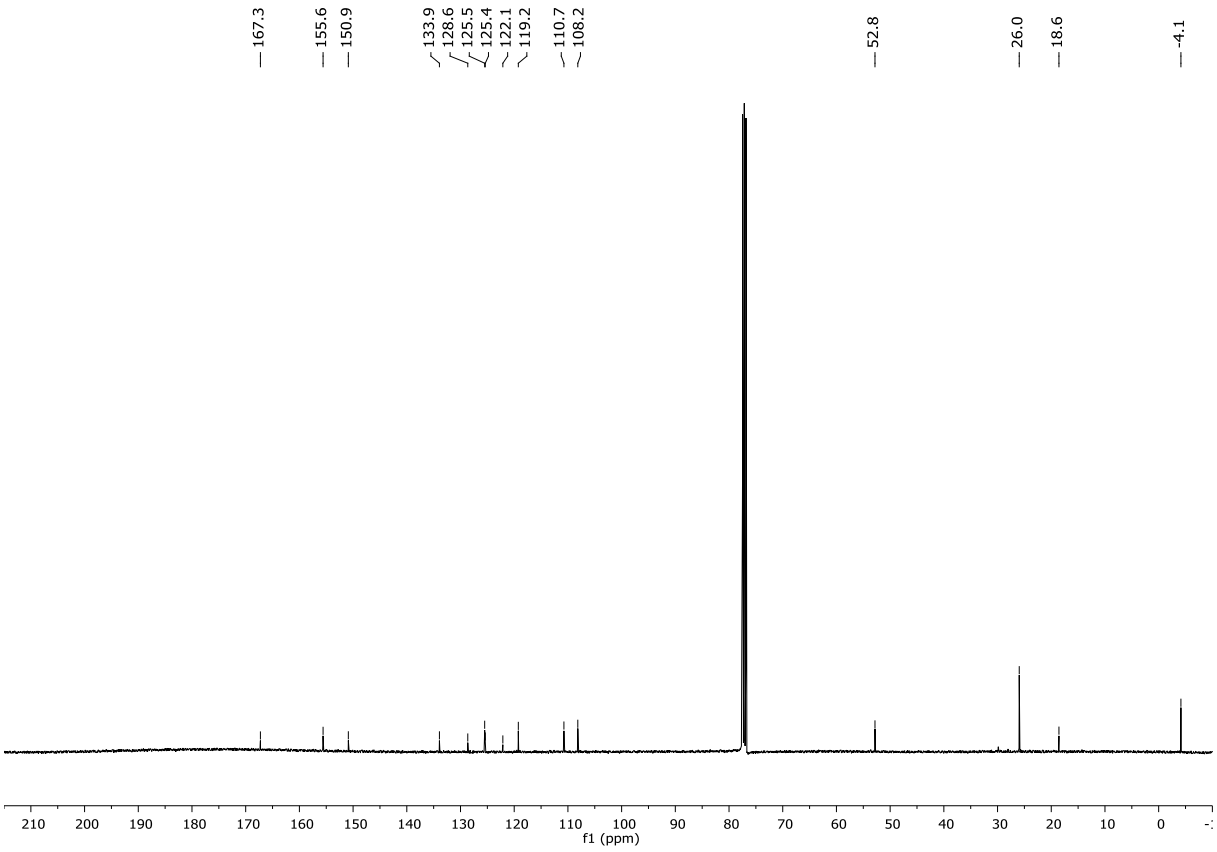
1.01
1.10
0.99
1.05
3.23
9.12
6.03
f1 (ppm)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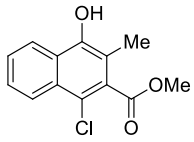
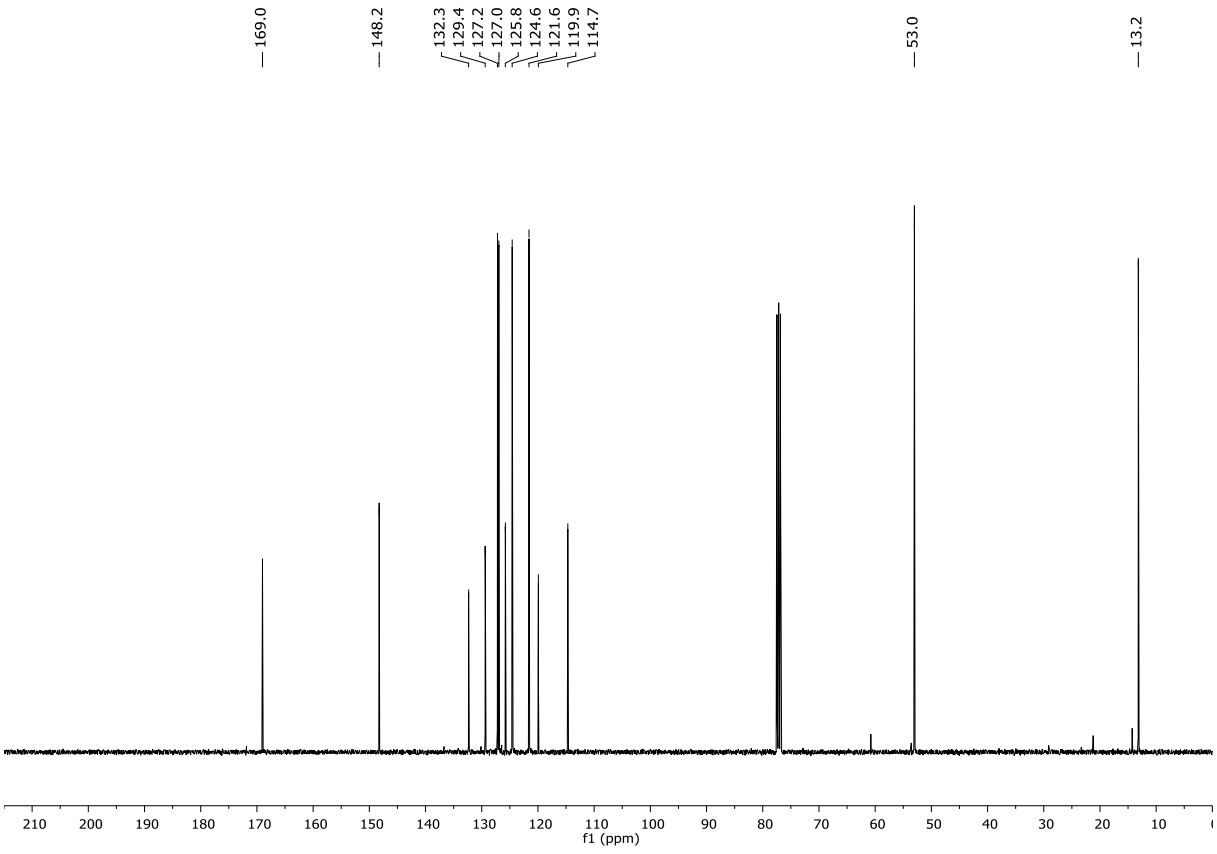
155.6
150.9
133.9
128.6
125.5
125.4
122.1
119.2
110.7
108.2
52.8
26.0
18.6
-4.1
f1 (ppm)


OH
Me
OMe
Cl
O

2.00
2.03
0.81
3.04
3.04
f1 (ppm)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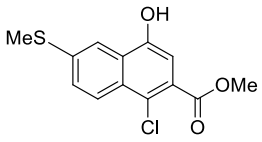
148.2
132.3
129.4
127.2
127.0
125.8
124.6
121.6
119.9
114.7
53.0
13.2
f1 (ppm)


OH
MeS
OMe
Cl
O

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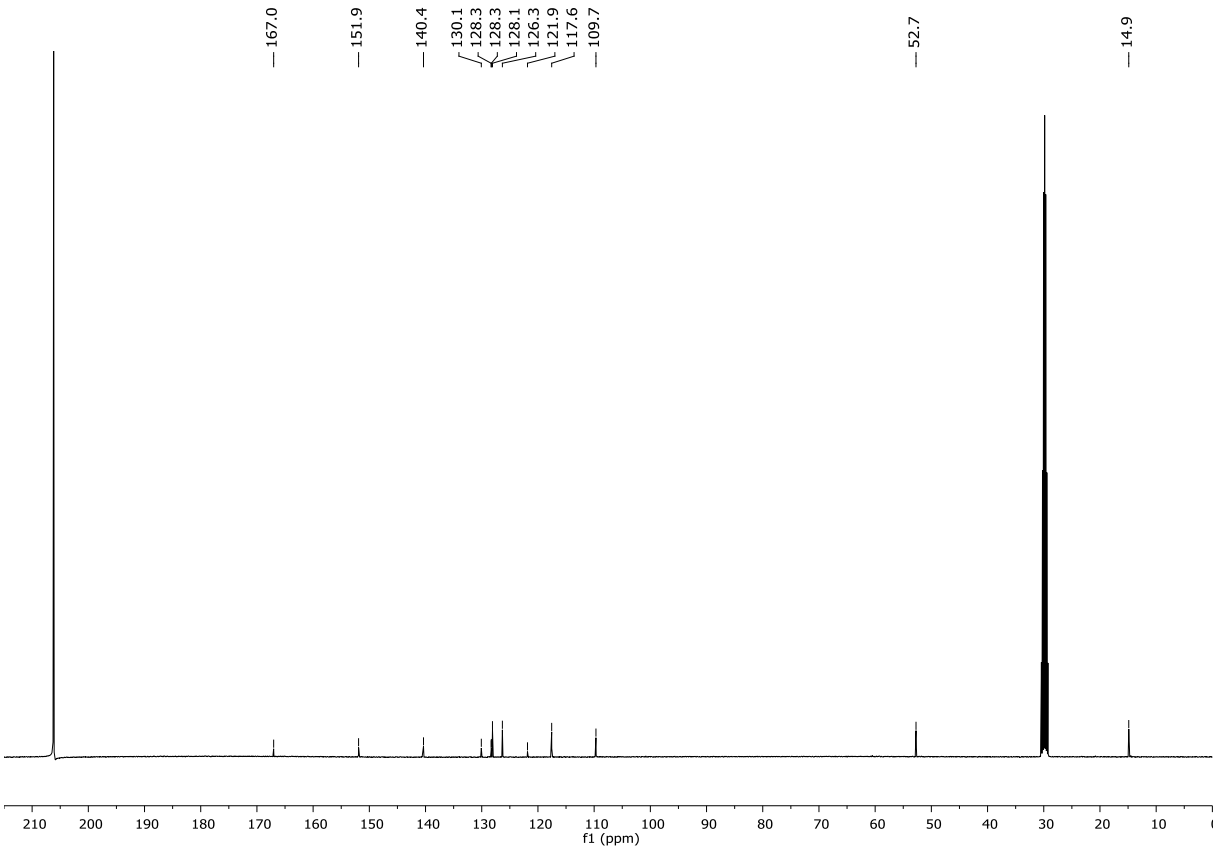
1.00
1.07
1.03
1.02
3.14
3.16
f1 (ppm)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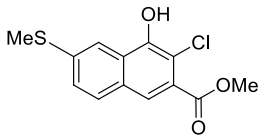
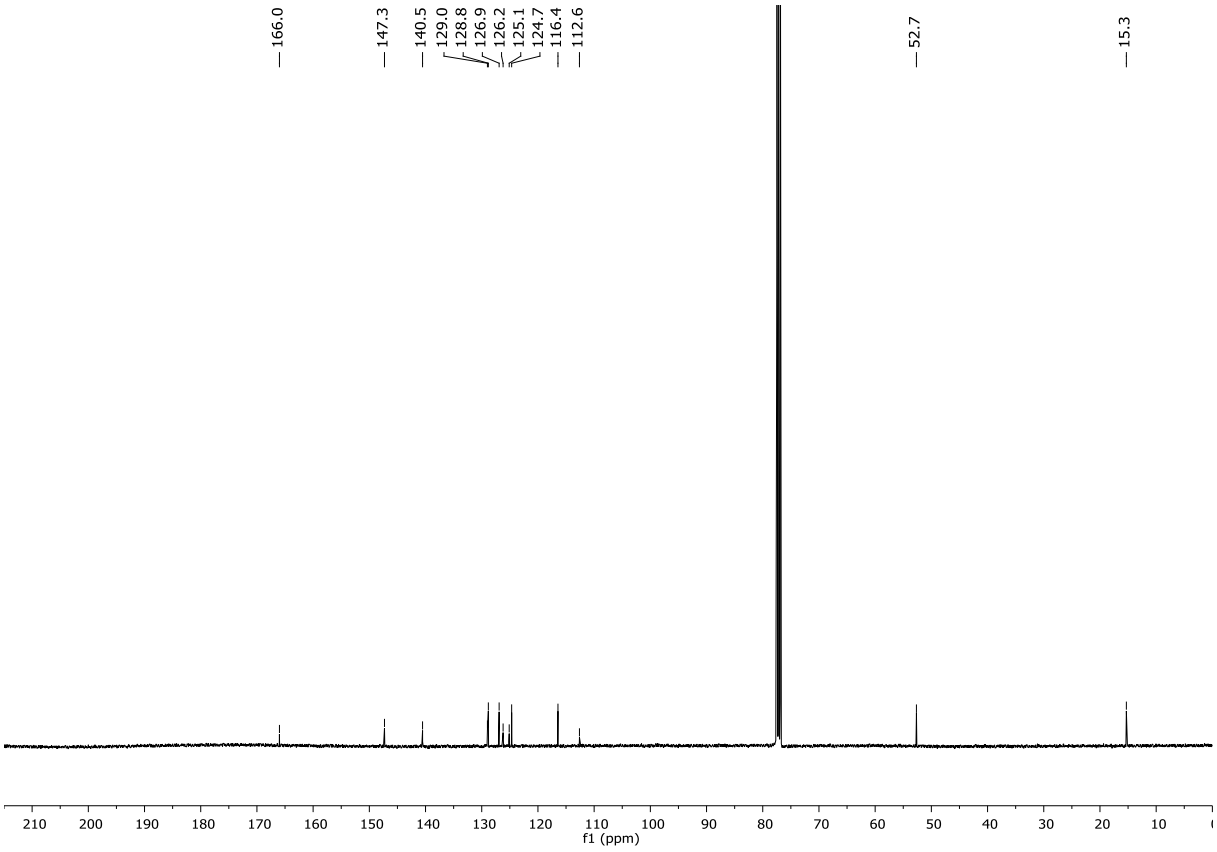
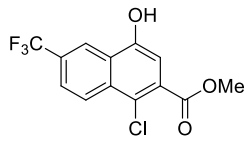
151.9
140.4
130.1
128.3
128.3
128.1
126.3
121.9
117.6
109.7
52.7
14.9
f1 (ppm)

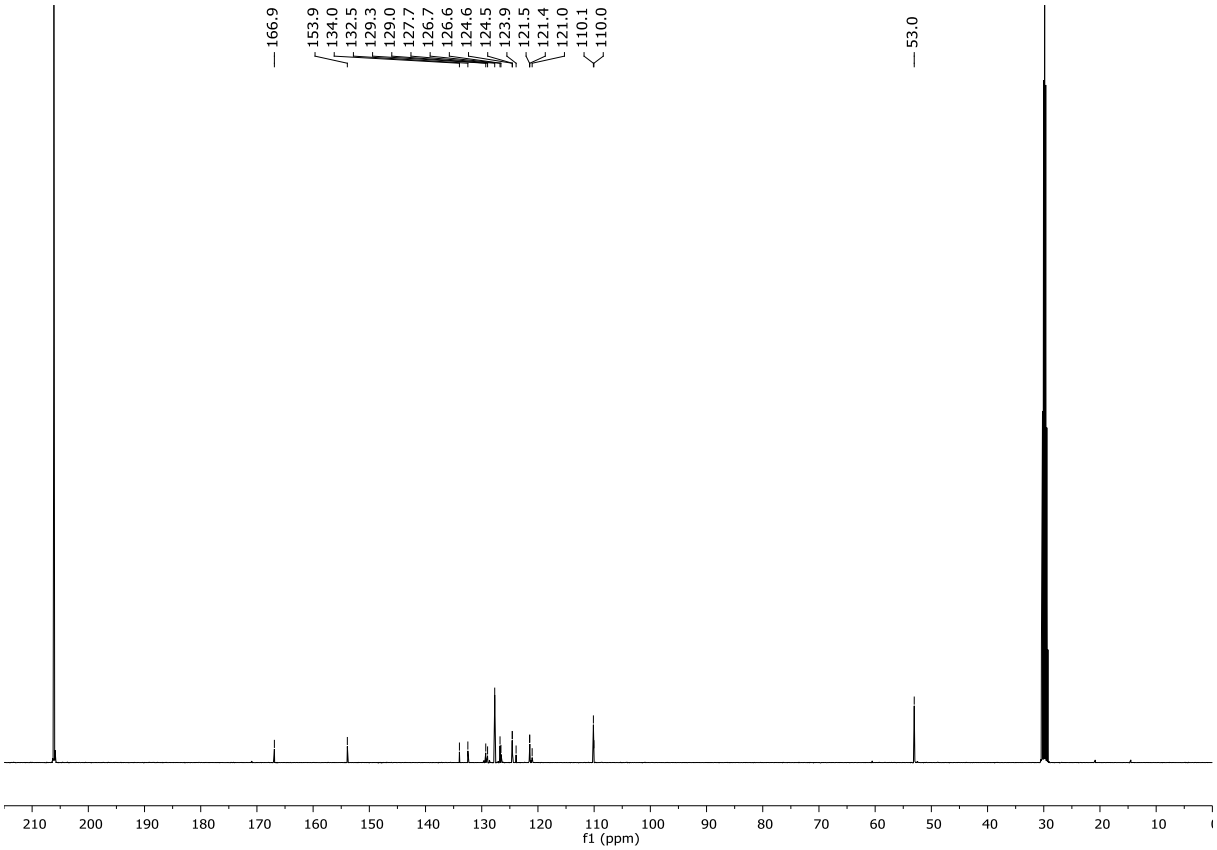

OH
MeS
Cl
OMe
O

1.00
1.01
1.05
1.01
0.99
3.11
3.22
f1 (ppm)


166.0
147.3
140.5
129.0
128.8
126.9
126.2
125.1
124.7
116.4
112.6
52.7
15.3
f1 (ppm)


OH
F3C
OMe
Cl
O

0.89
1.00
1.06
1.07
1.00
3.17
f1 (ppm)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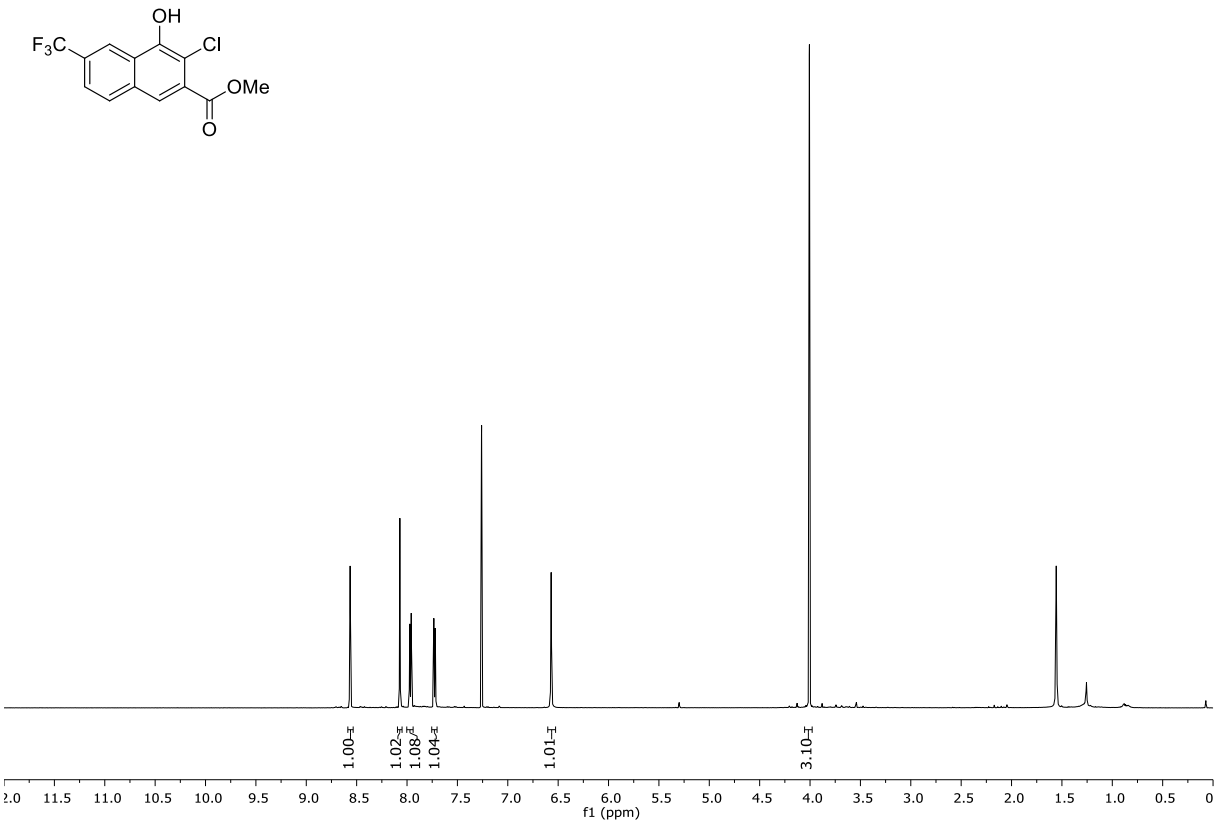
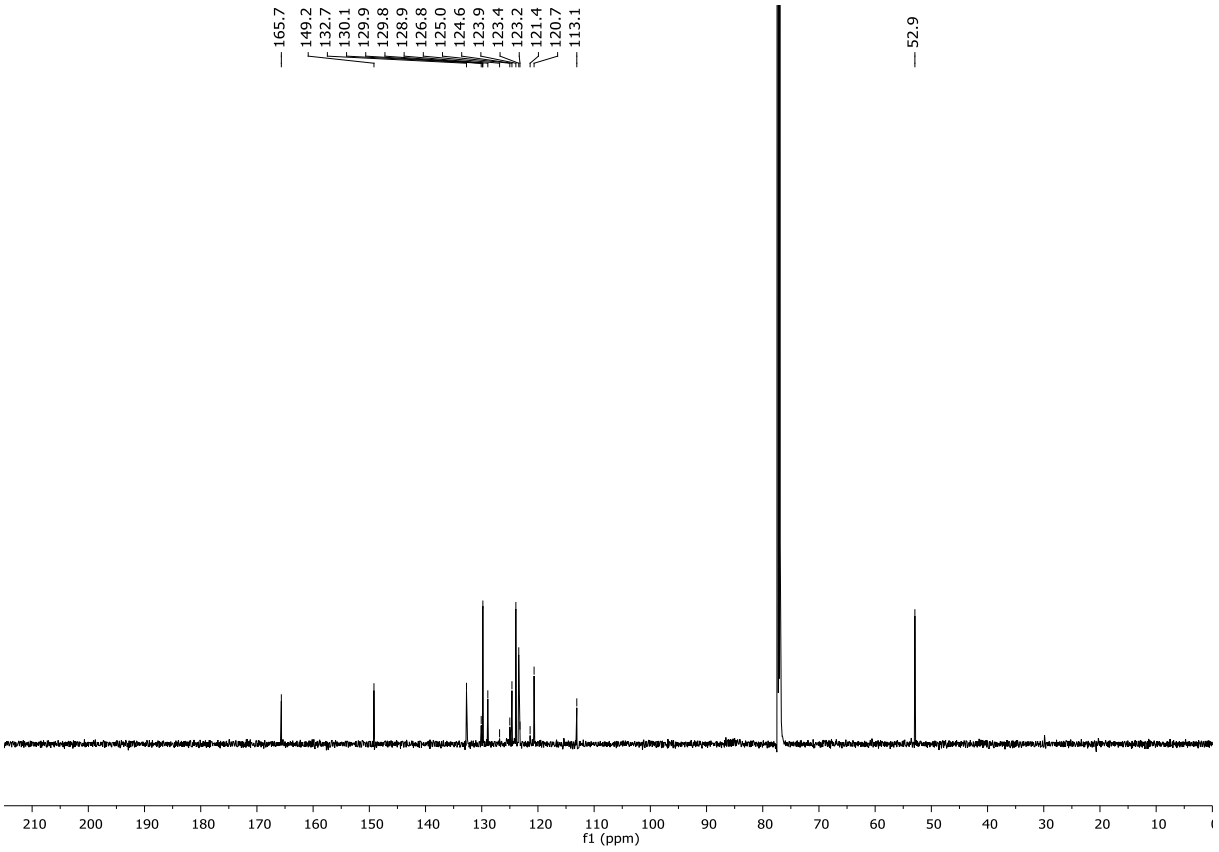
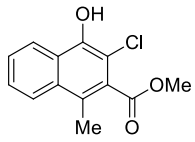
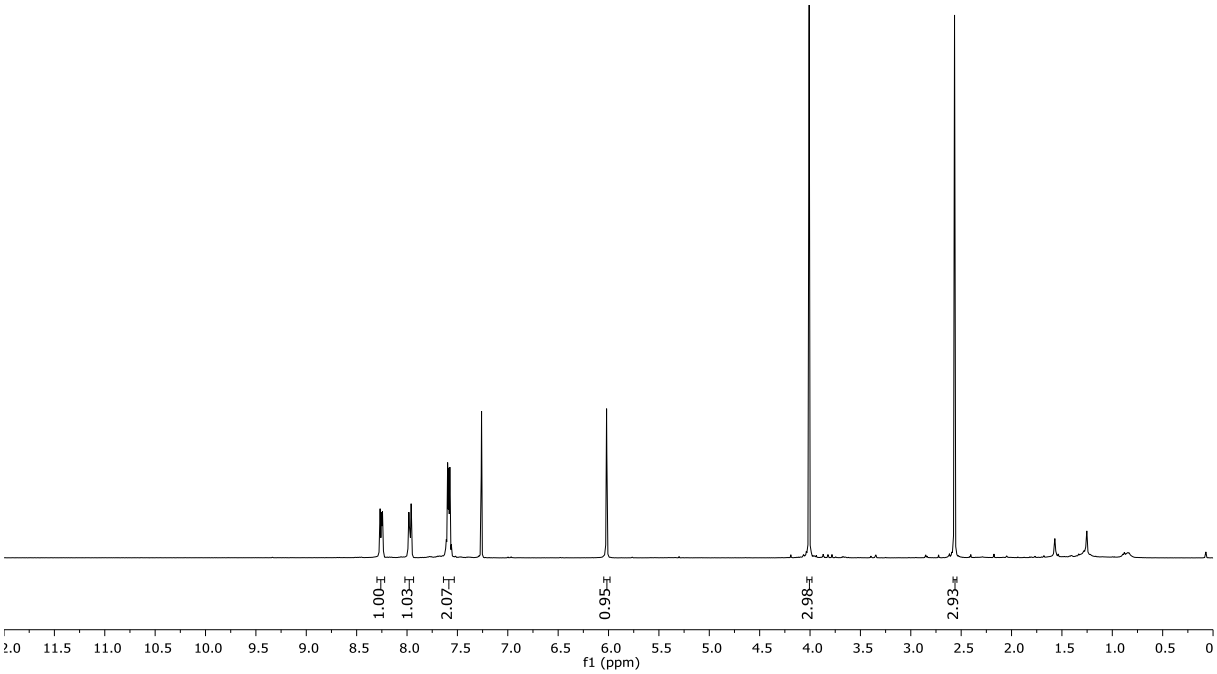
153.9
134.0
132.5
129.3
129.0
127.7
126.7
126.6
124.6
124.5
123.9
121.5
121.4
121.0
110.1
110.0
53.0
f1 (ppm)


OH
F3C
Cl
OMe
O
1.00
1.02
1.08
1.04
1.01
3.10
f1 (ppm)


165.7
149.2
132.7
130.1
129.9
129.8
128.9
126.8
125.0
124.6
123.9
123.4
123.2
121.4
120.7
113.1
52.9
f1 (ppm)


OH
Cl
OMe
Me
O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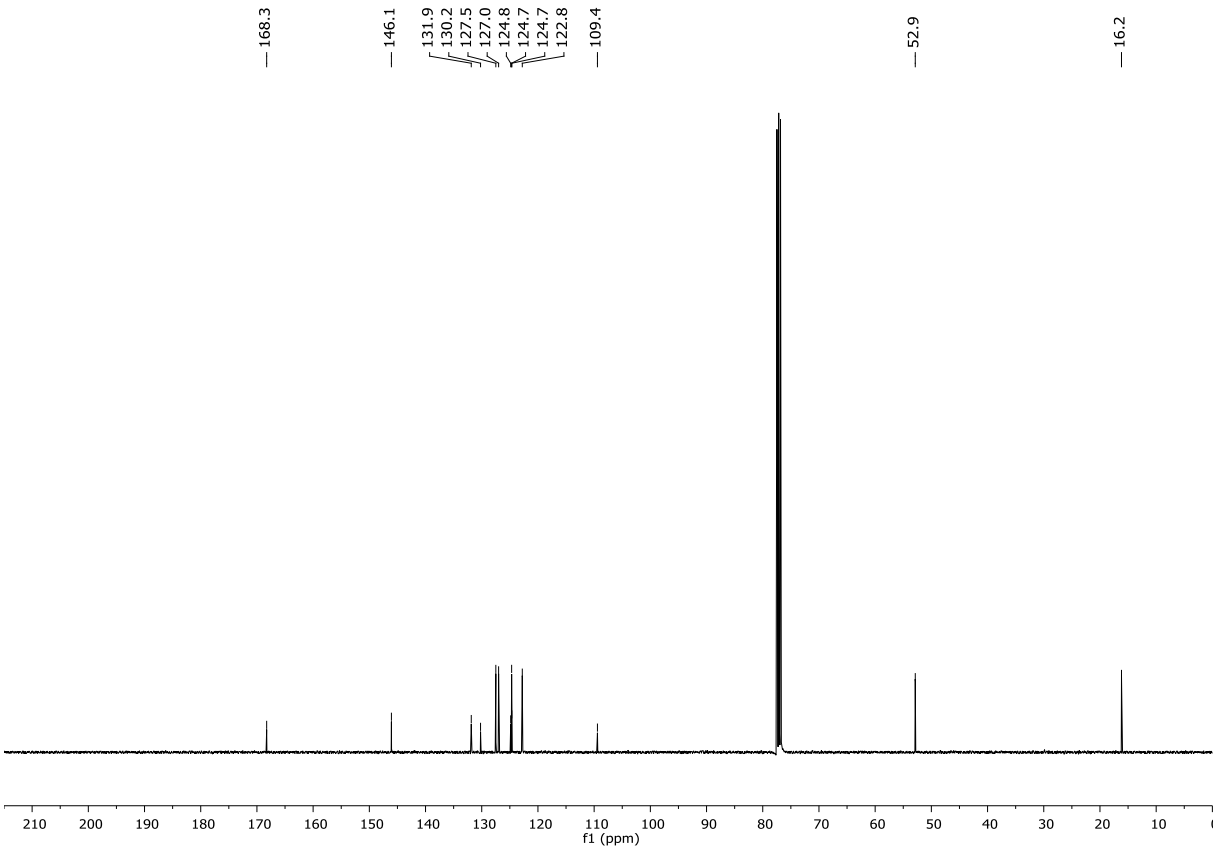
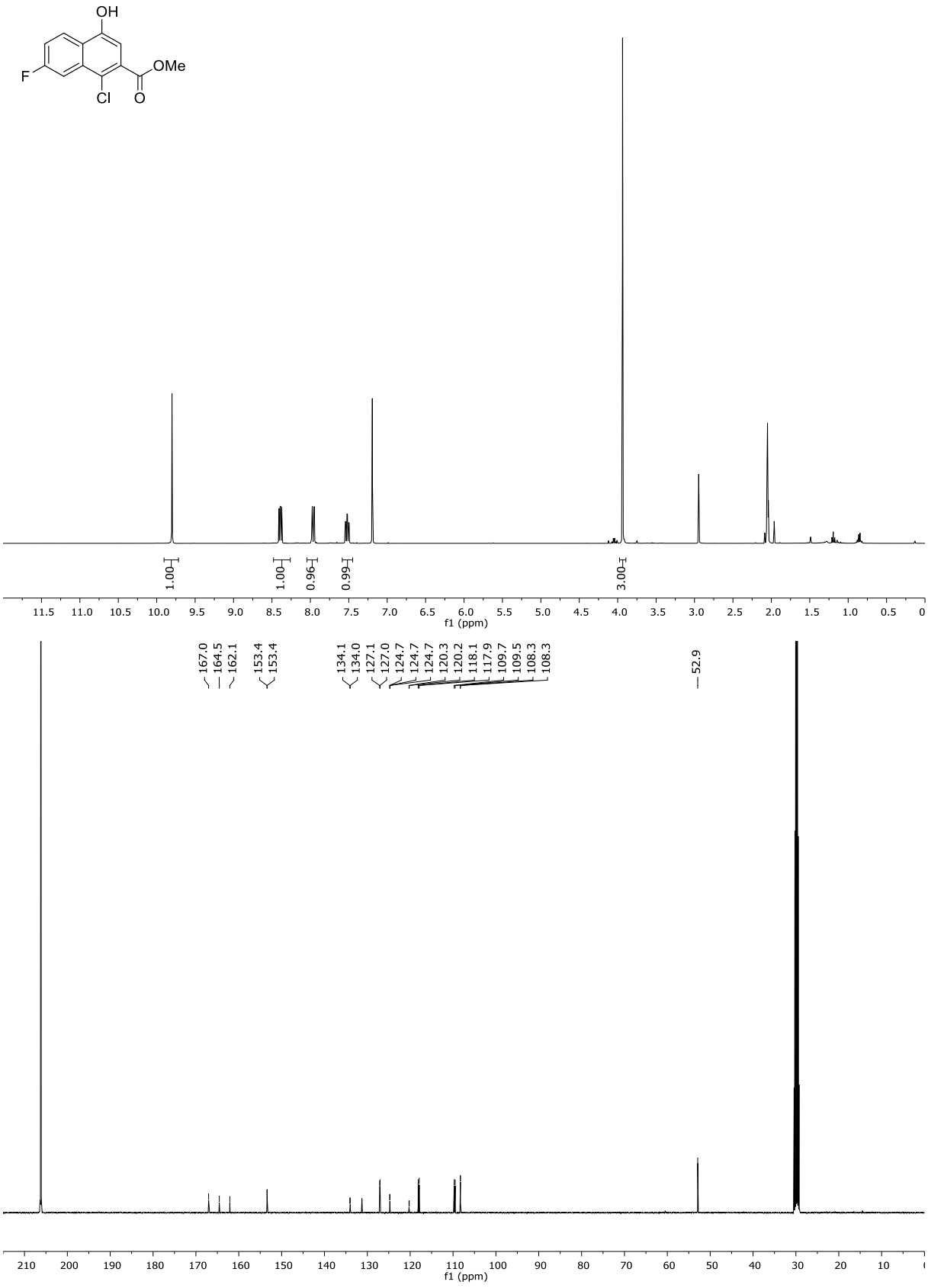
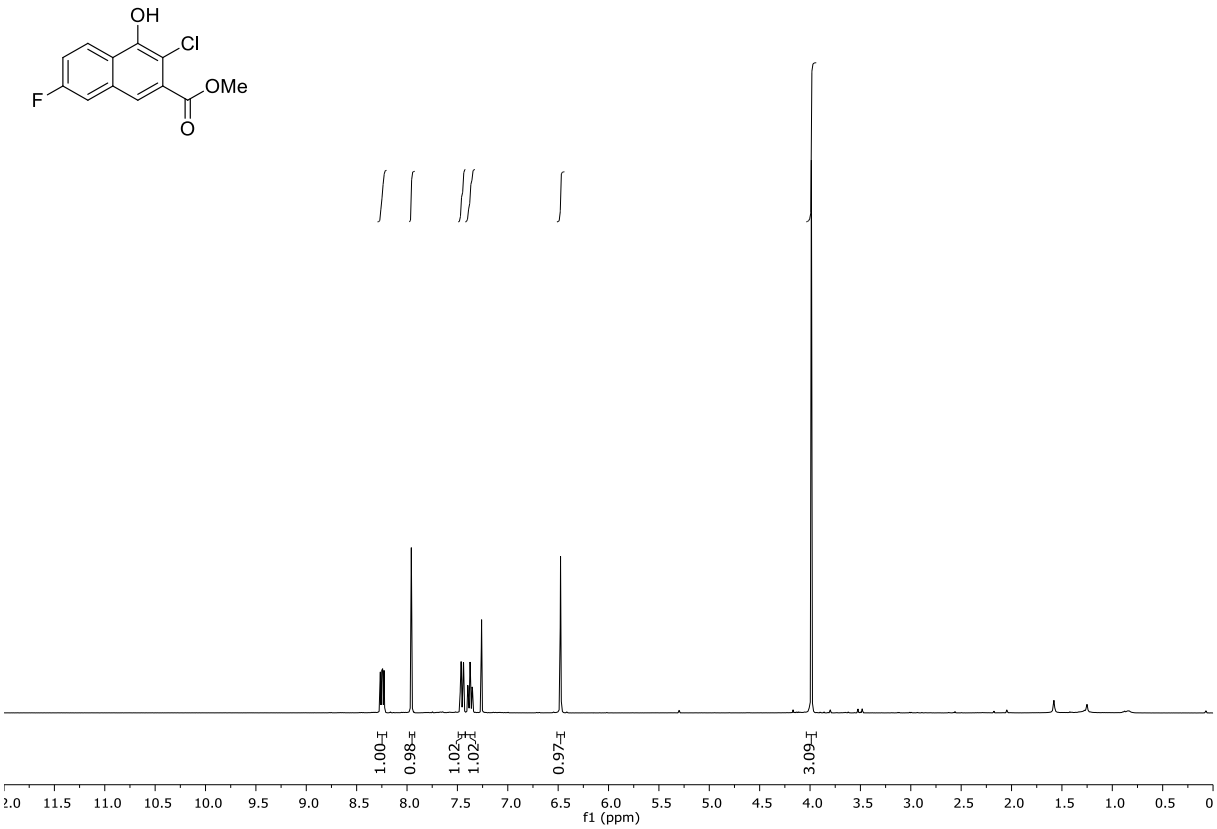
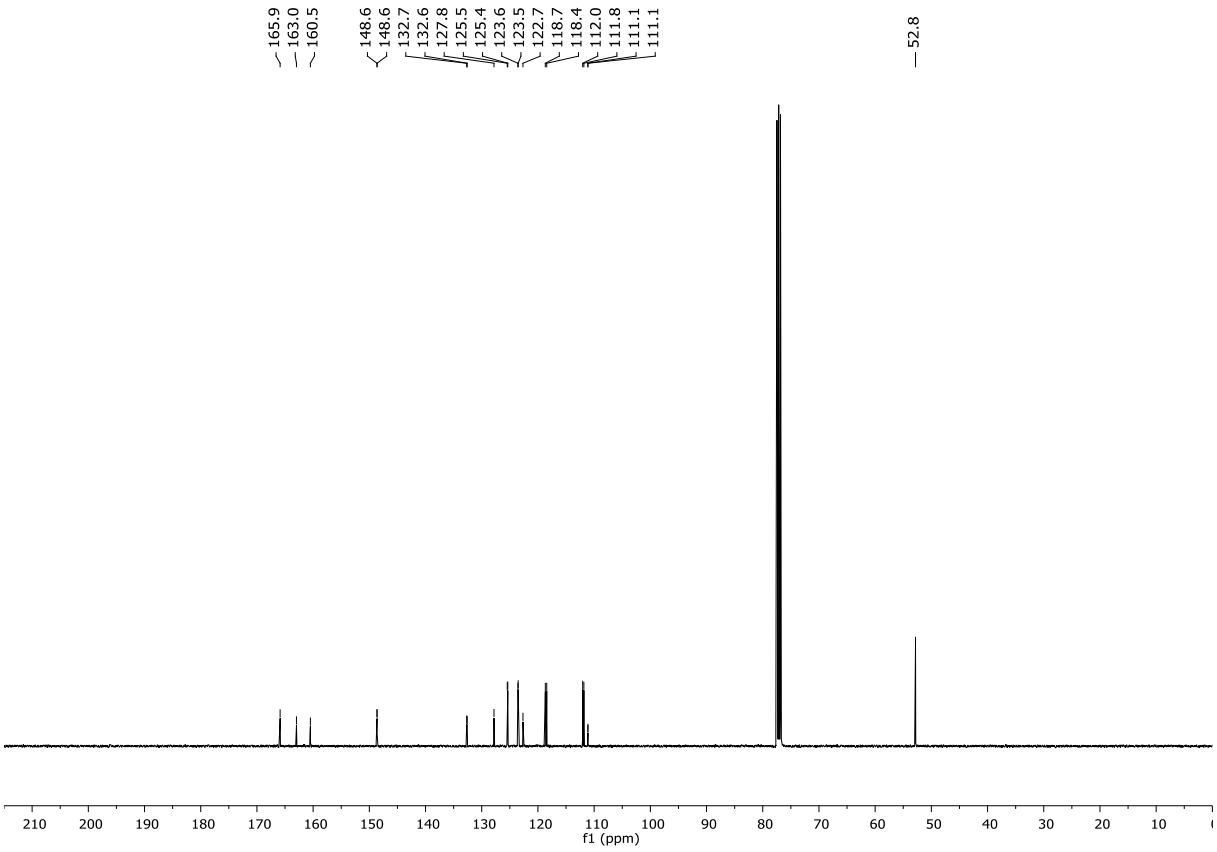
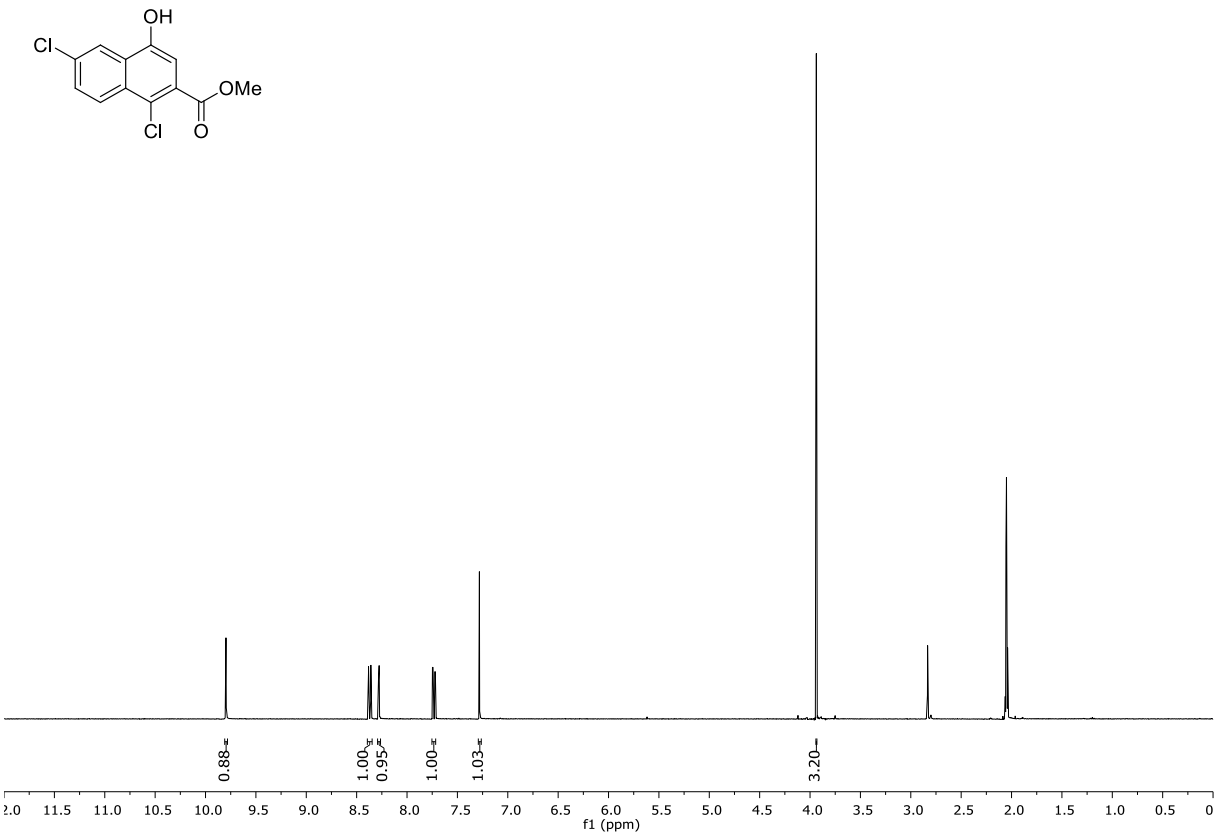
1.03
2.07
0.95
2.98
2.93
f1 (ppm)


168.3
146.1
131.9
130.2
127.5
127.0
124.8
124.7
124.7
122.8
109.4
52.9
16.2
f1 (ppm)


OH
F
OMe
Cl
O
1.00
1.00
0.96
0.99
3.00
f1 (ppm)
167.0
164.5
162.1
153.4
153.4
134.1
134.0
127.1
127.0
124.7
124.7
124.7
120.3
120.2
118.1
117.9
109.7
109.5
108.3
108.3
52.9
f1 (ppm)


OH
Cl
F
OMe
O
1.00
0.98
1.02
1.02
0.97
3.09
f1 (ppm)


165.9
163.0
160.5
148.6
148.6
132.7
132.6
127.8
125.5
125.4
123.6
123.5
122.7
118.7
118.4
112.0
111.8
111.1
111.1
52.8
f1 (ppm)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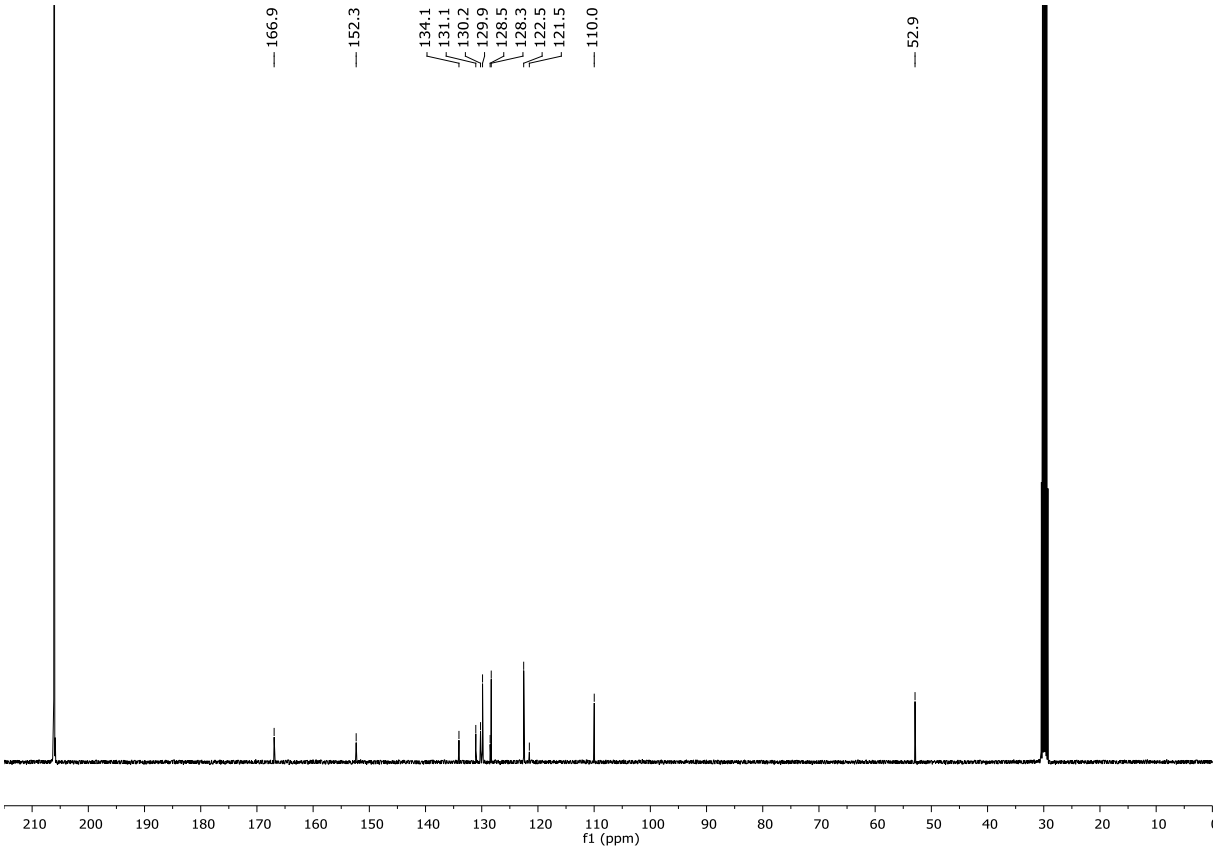
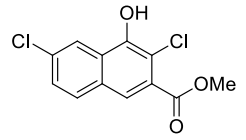
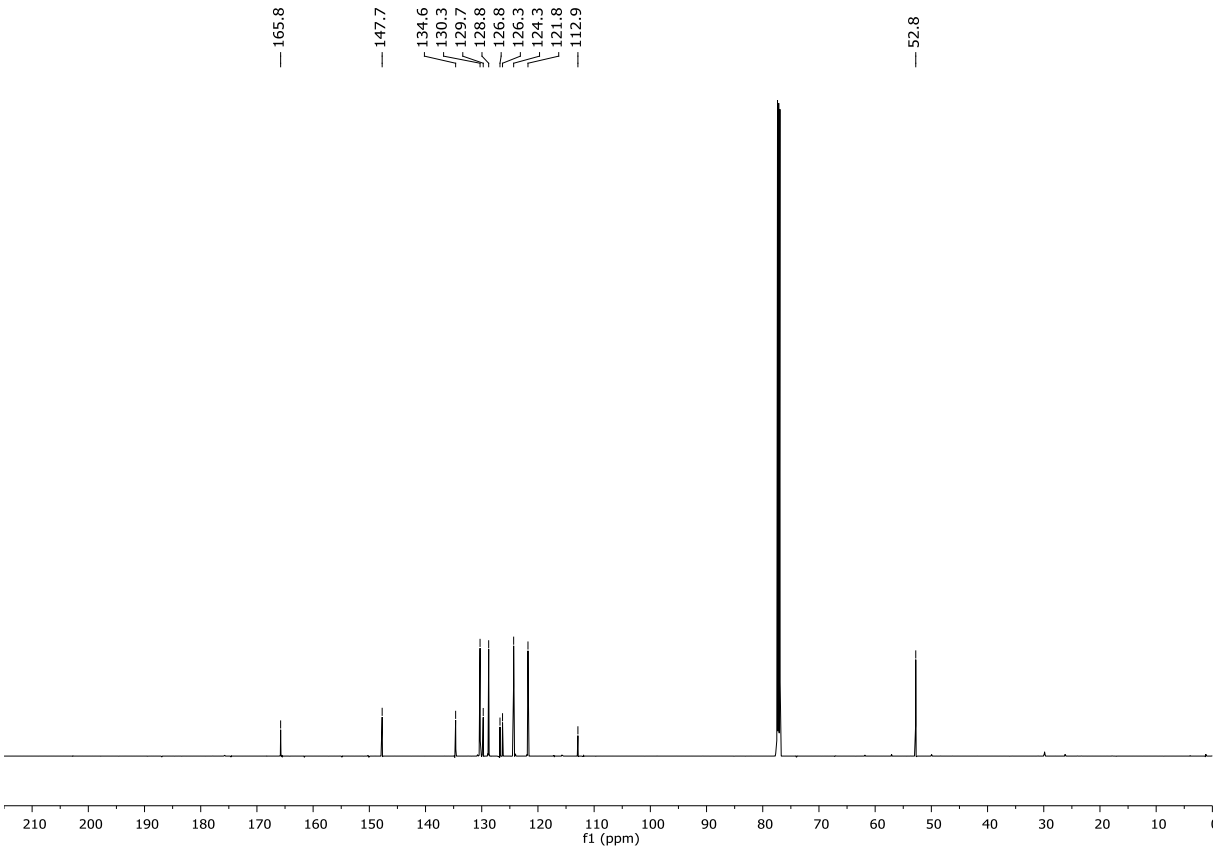
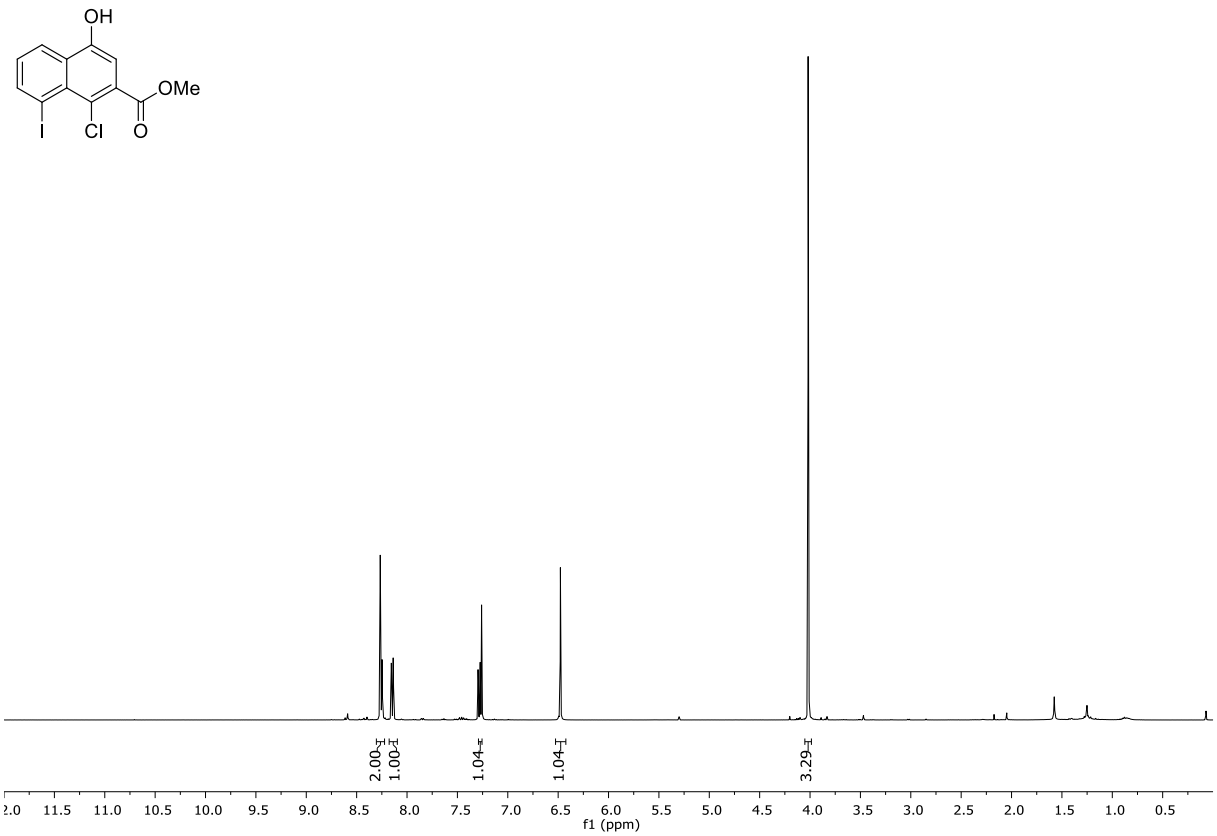
Cl
OMe
Cl
O
0.88
1.00
0.95
1.00
1.03
3.20
f1 (ppm)

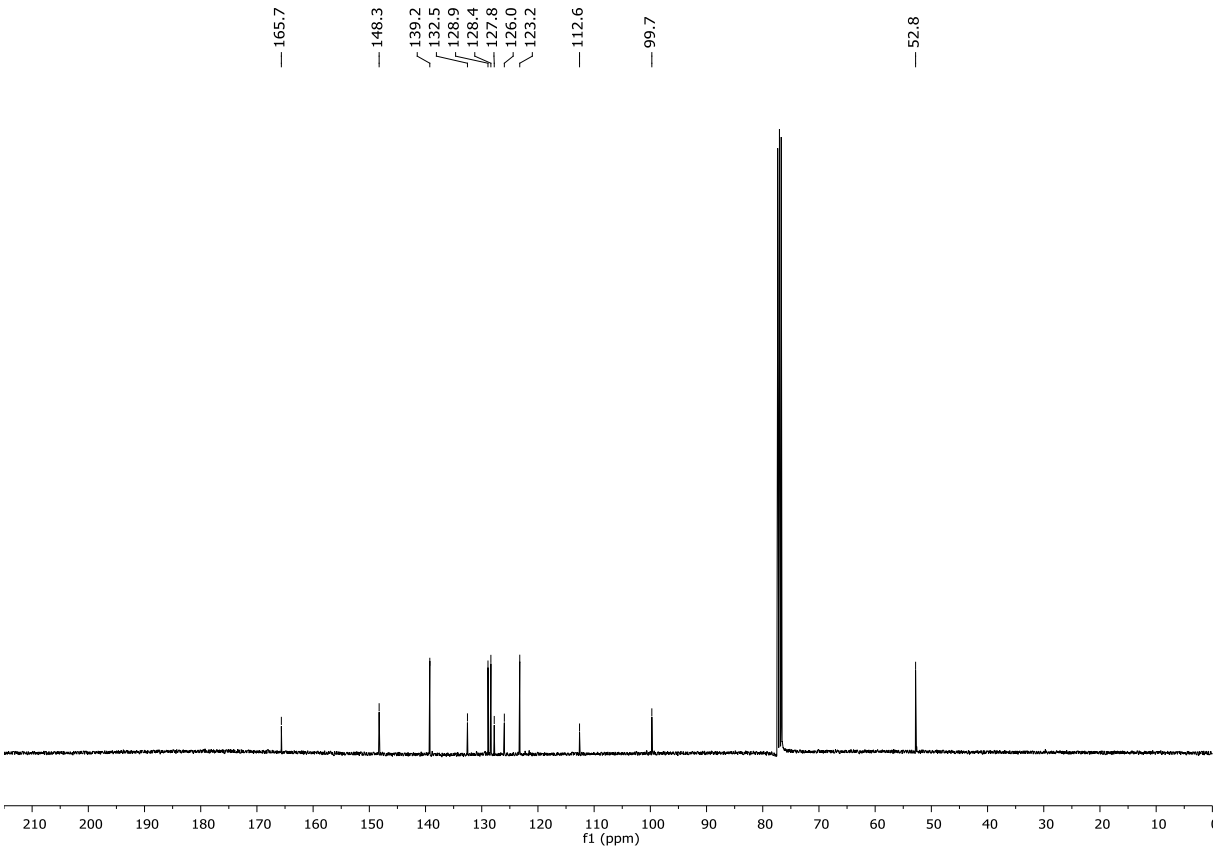

166.9
152.3
134.1
131.1
130.2
129.9
128.5
128.3
122.5
121.5
110.0
52.9
f1 (ppm)

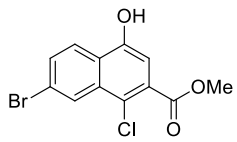

OH
Cl
Cl
OMe
O

1.00
1.02
1.08
1.04
1.02
3.32
f1 (ppm)

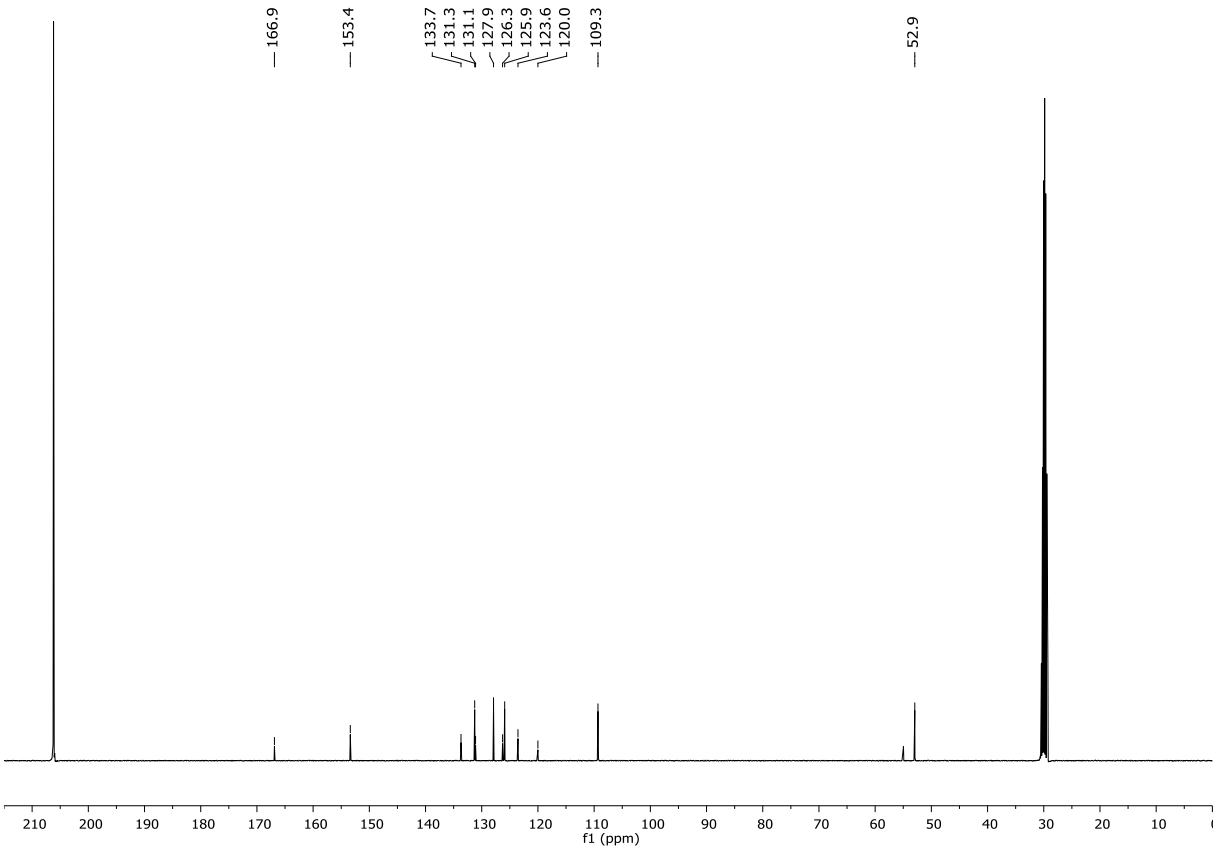

165.8
147.7
134.6
130.3
129.7
128.8
126.8
126.3
124.3
121.8
112.9
52.8
f1 (ppm)

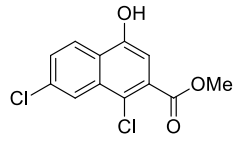

OH
OMe
I
Cl
O
2.00
1.00
1.04
1.04
3.29
f1 (ppm)


165.7
148.3
139.2
132.5
128.9
128.4
127.8
126.0
123.2
112.6
99.7
52.8
f1 (ppm)

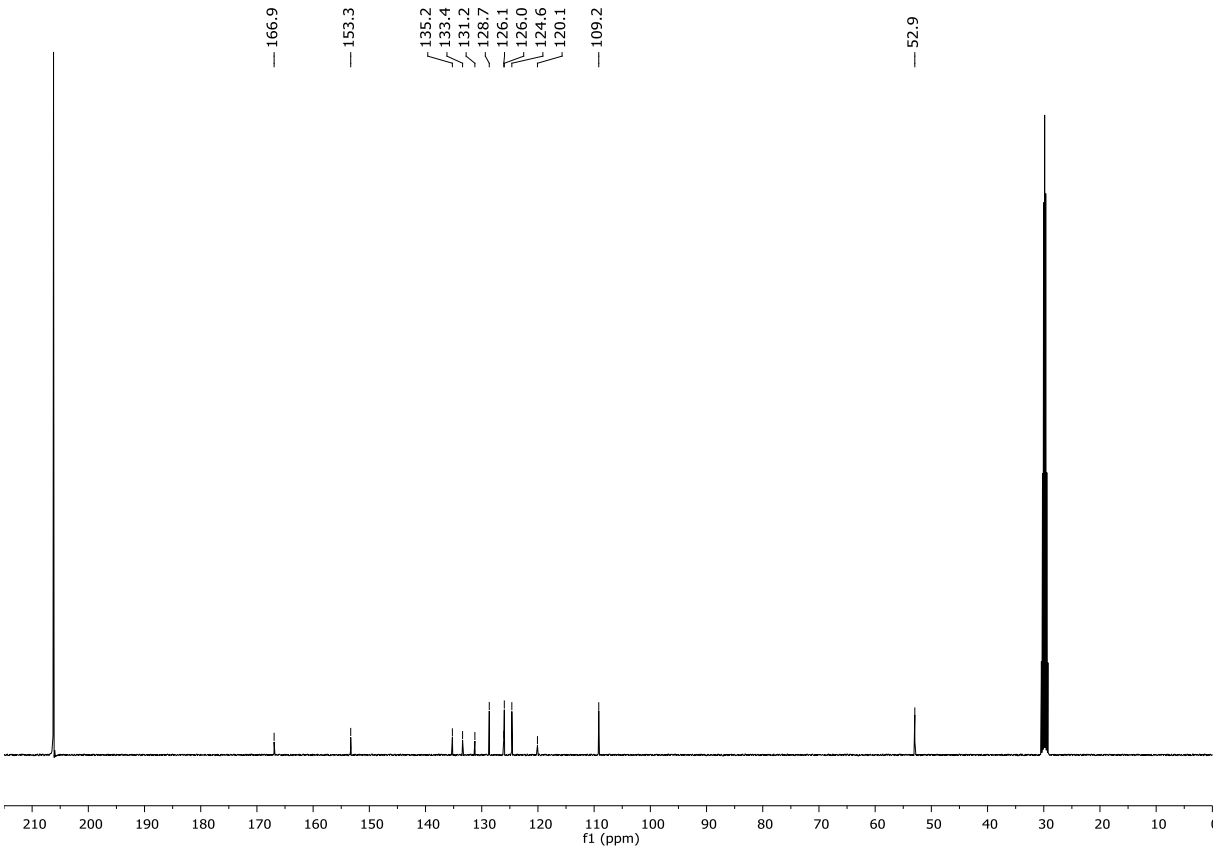

OH
Br
OMe
Cl
O

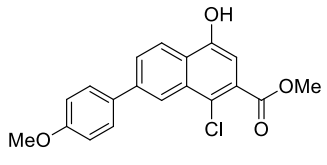
1.00
0.97
1.05
1.04
1.04
3.26
f1 (ppm)


166.9
153.4
133.7
131.3
131.1
127.9
126.3
125.9
123.6
120.0
109.3
52.9
f1 (ppm)

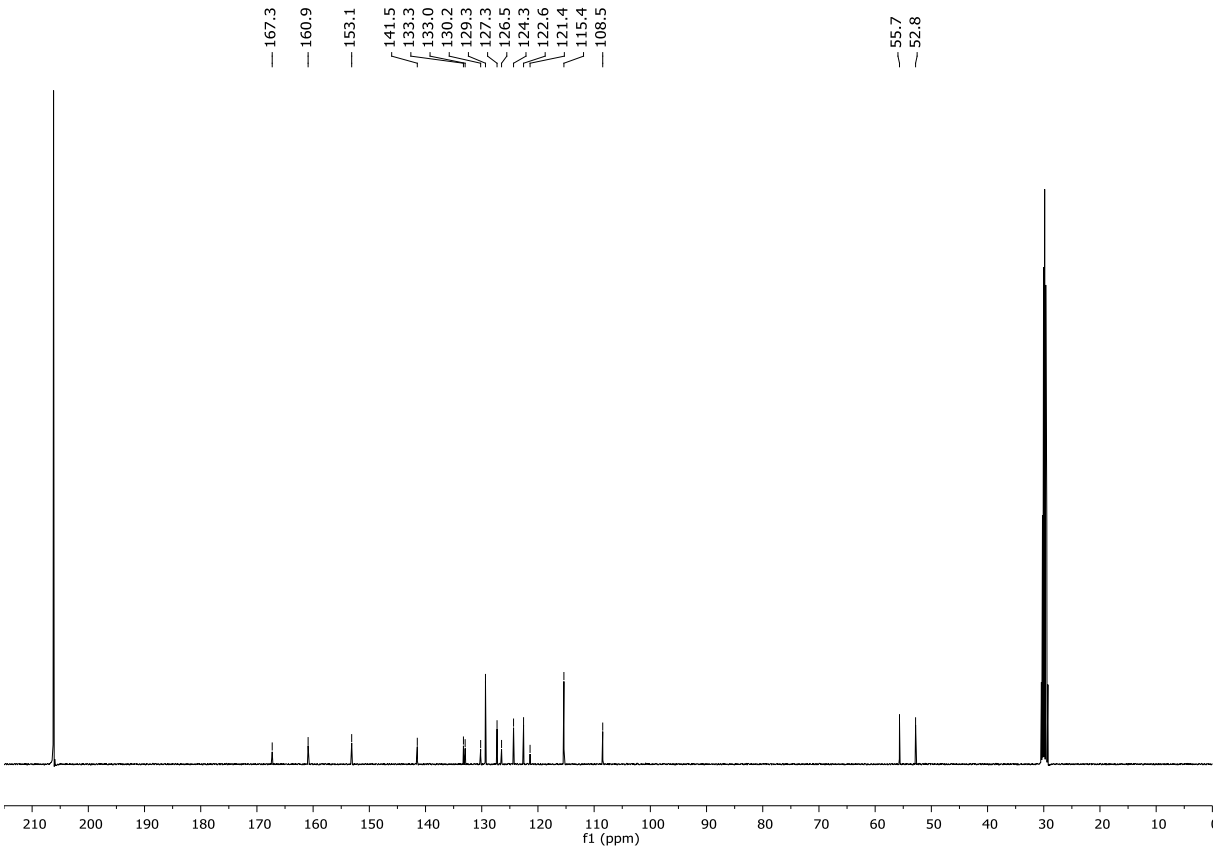

OH
Cl
OMe
Cl
O

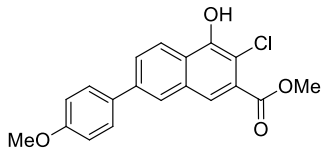
0.47
0.98
0.94
1.00
1.00
3.09
f1 (ppm)

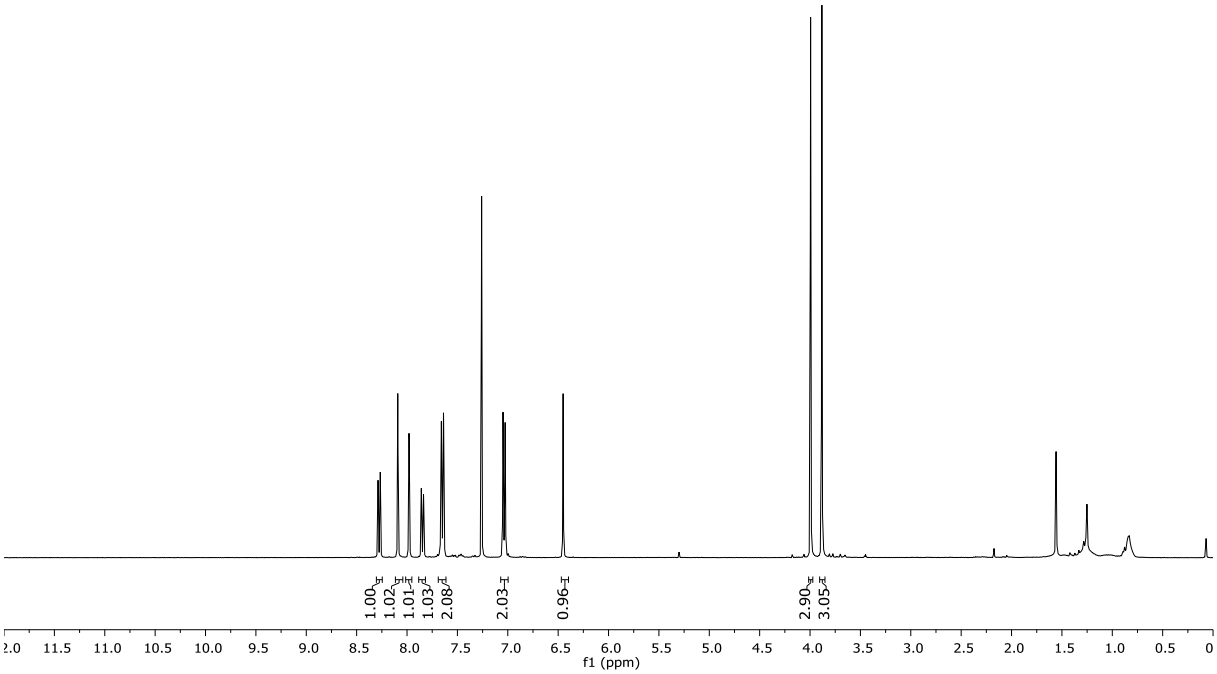

166.9
153.3
135.2
133.4
131.2
128.7
126.1
126.0
124.6
120.1
109.2
52.9
f1 (ppm)


OH
OMe
MeO
Cl
O

1.00
1.07
1.09
1.14
2.26
1.08
2.30
3.24
3.29
f1 (ppm)


167.3
160.9
153.1
141.5
133.3
133.0
130.2
129.3
127.3
126.5
124.3
122.6
121.4
115.4
108.5
55.7
52.8
f1 (ppm)


OH
Cl
OMe
O
MeO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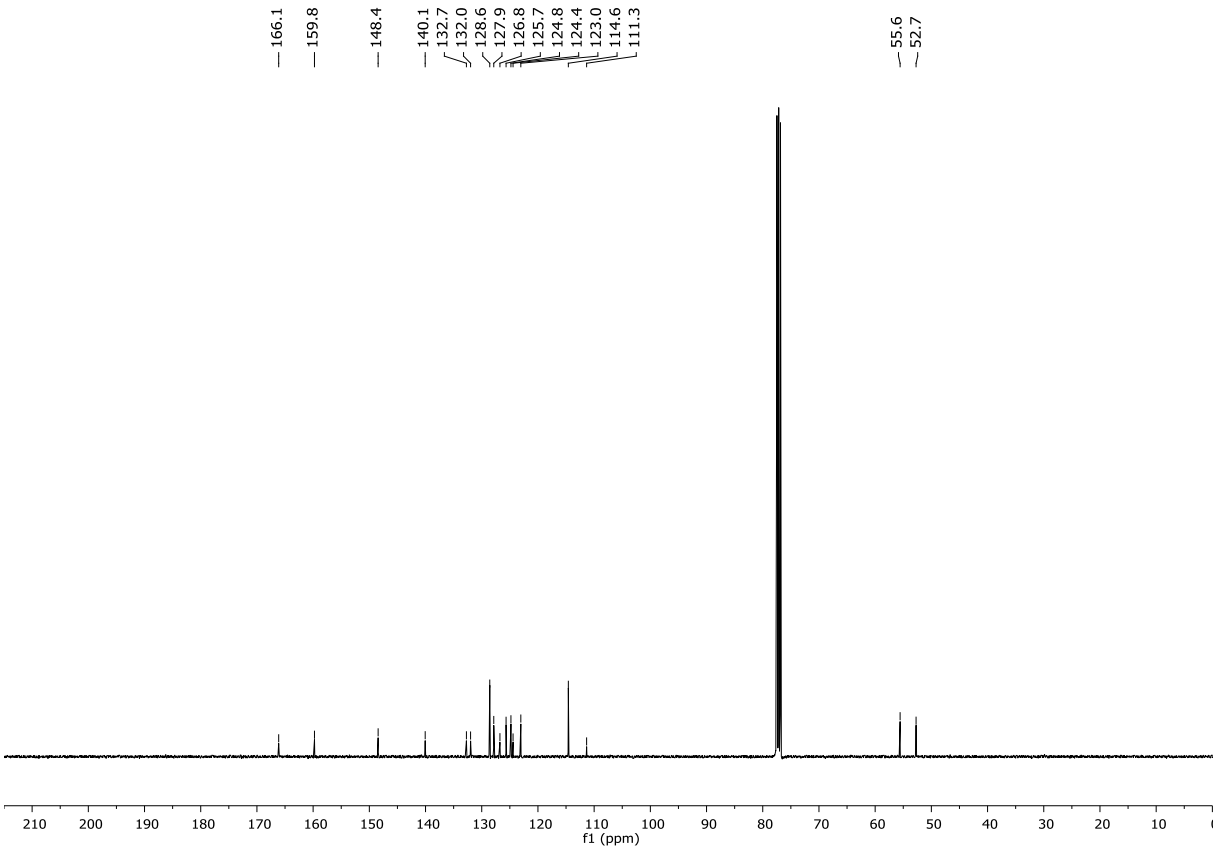
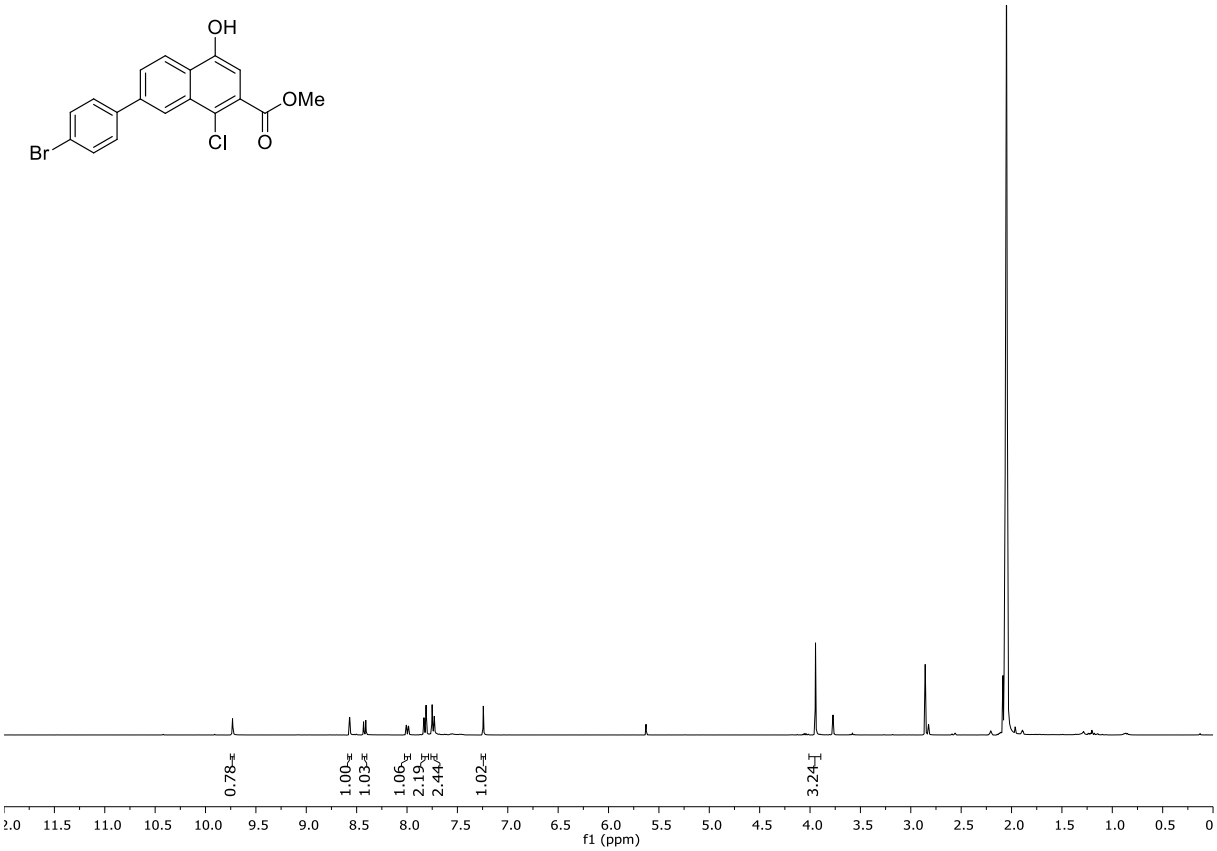
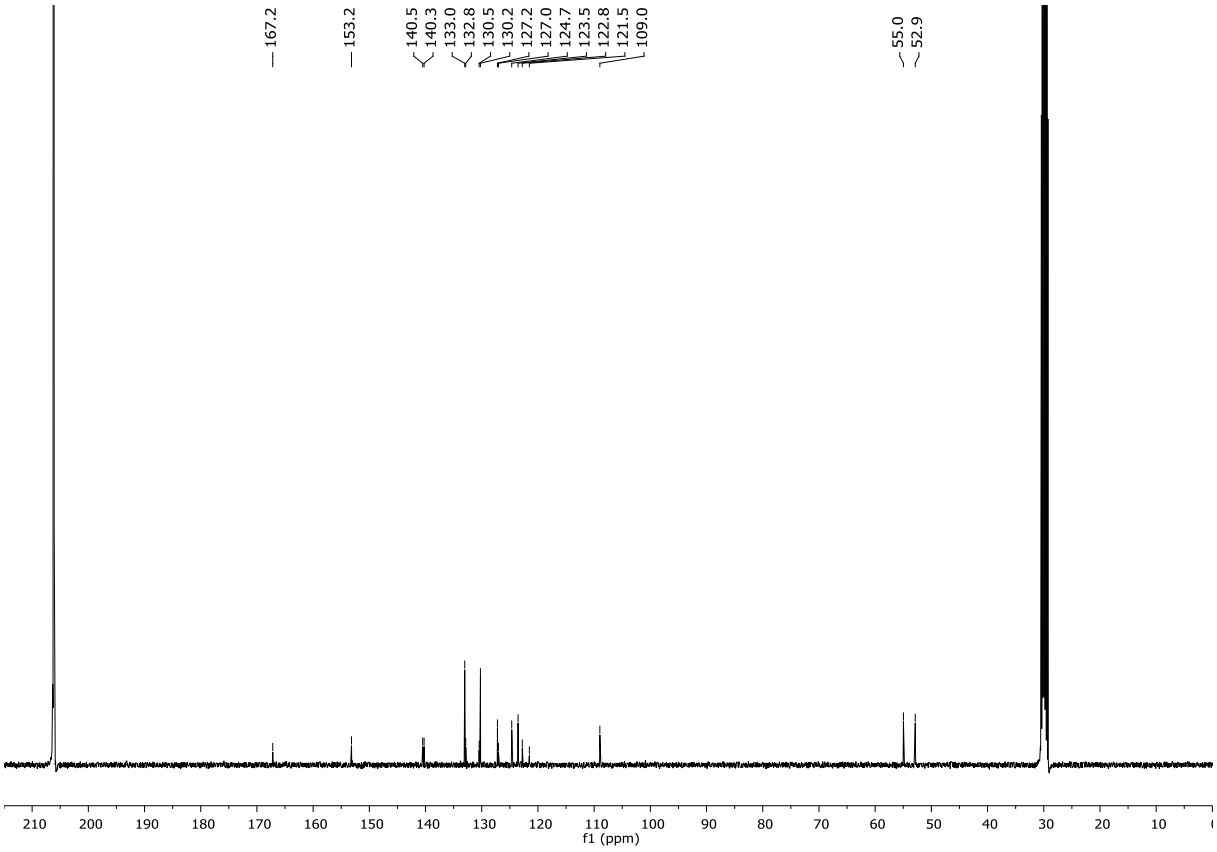
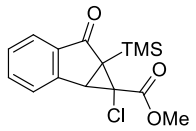
1.02
1.01
1.03
2.08
2.03
0.96
2.90
3.05
f1 (ppm)

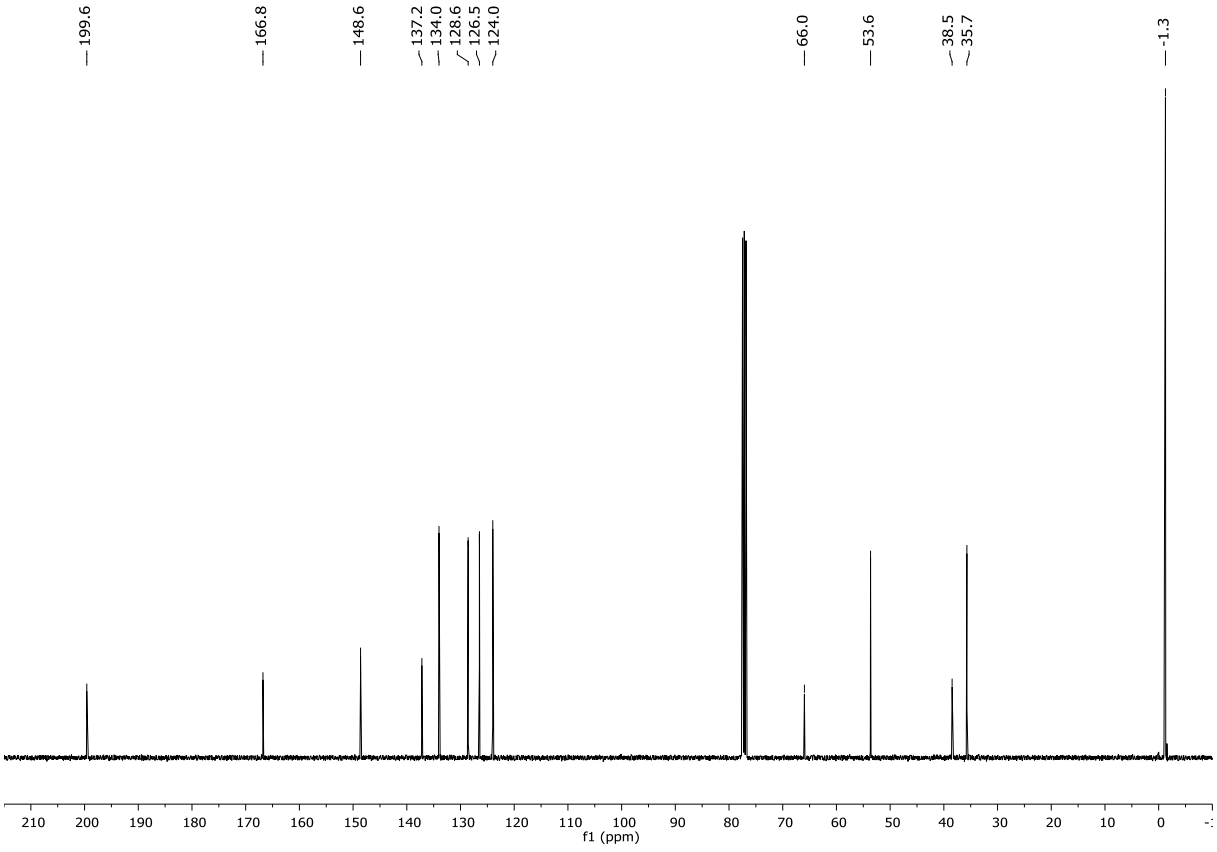

166.1
159.8
148.4
140.1
132.7
132.0
128.6
127.9
126.8
125.7
124.8
124.4
123.0
114.6
111.3
55.6
52.7
f1 (ppm)

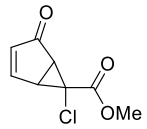

OH
OMe
Cl
O
Br
0.78
1.00
1.03
1.06
2.19
2.44
1.02
3.24
f1 (ppm)

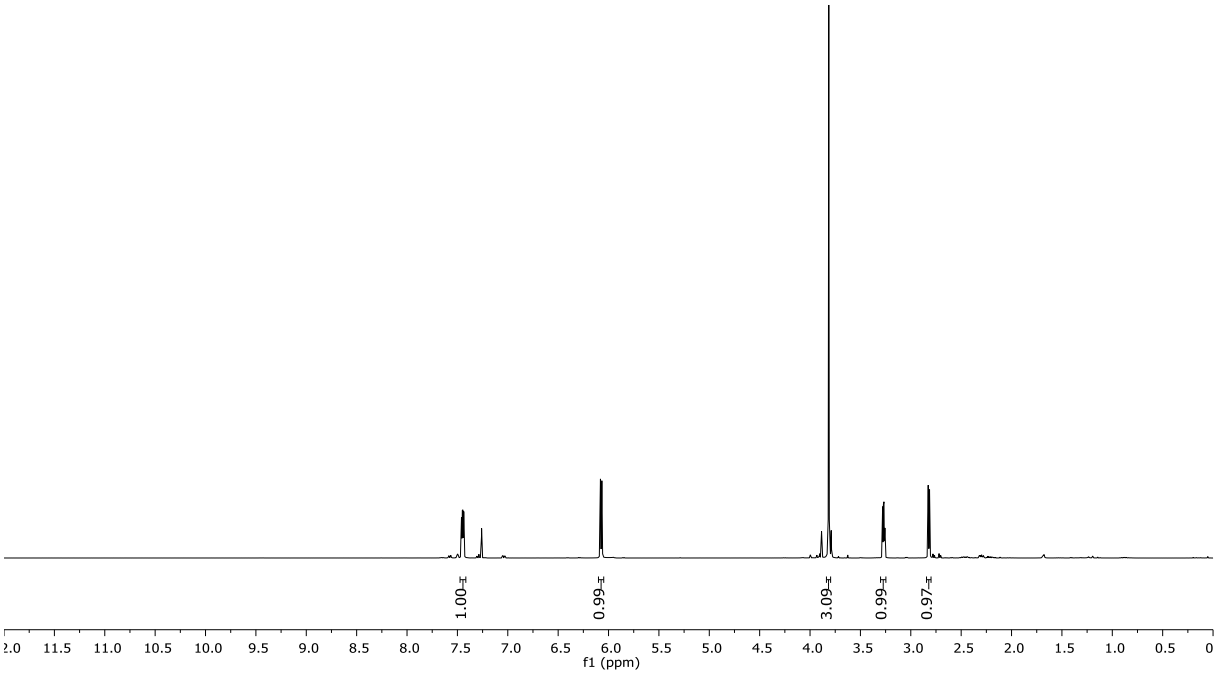

167.2
153.2
140.5
140.3
133.0
132.8
130.5
130.2
127.2
127.0
124.7
123.5
122.8
121.5
109.0
55.0
52.9
f1 (ppm)

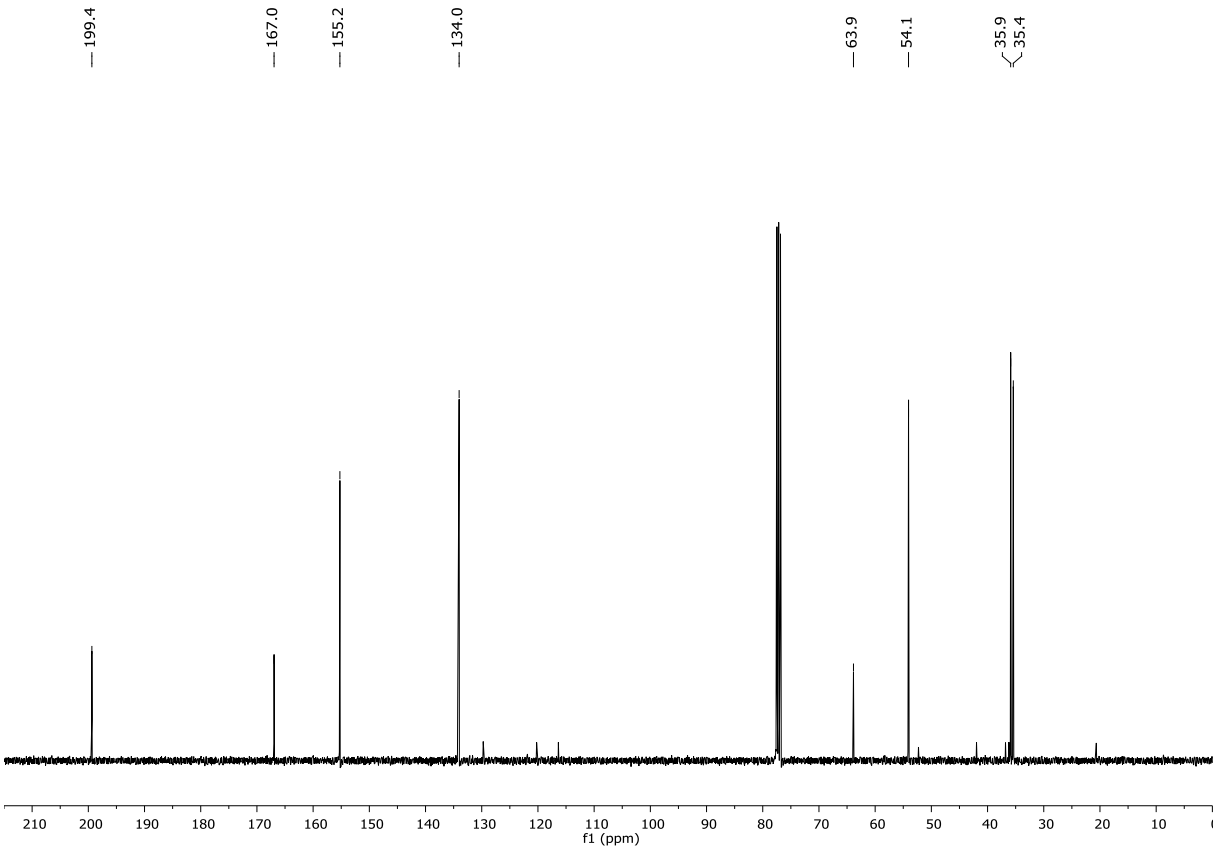

O
TMS
O
Cl
OMe

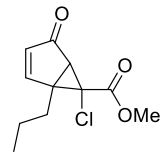
1.00
2.03
1.05
3.09
1.00
9.10
f1 (ppm)


199.6
166.8
148.6
137.2
134.0
128.6
126.5
124.0
66.0
53.6
38.5
35.7
-1.3
f1 (ppm)

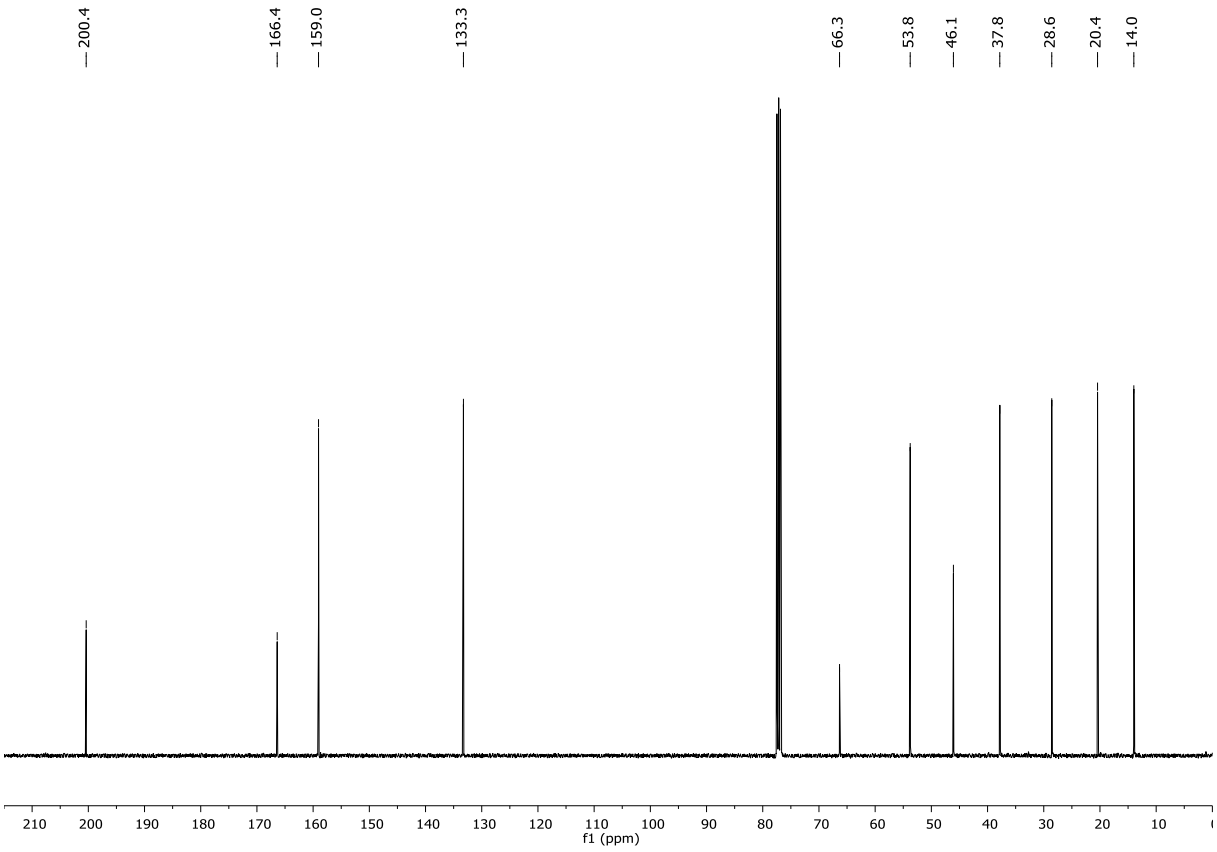

O
O
Cl
OMe

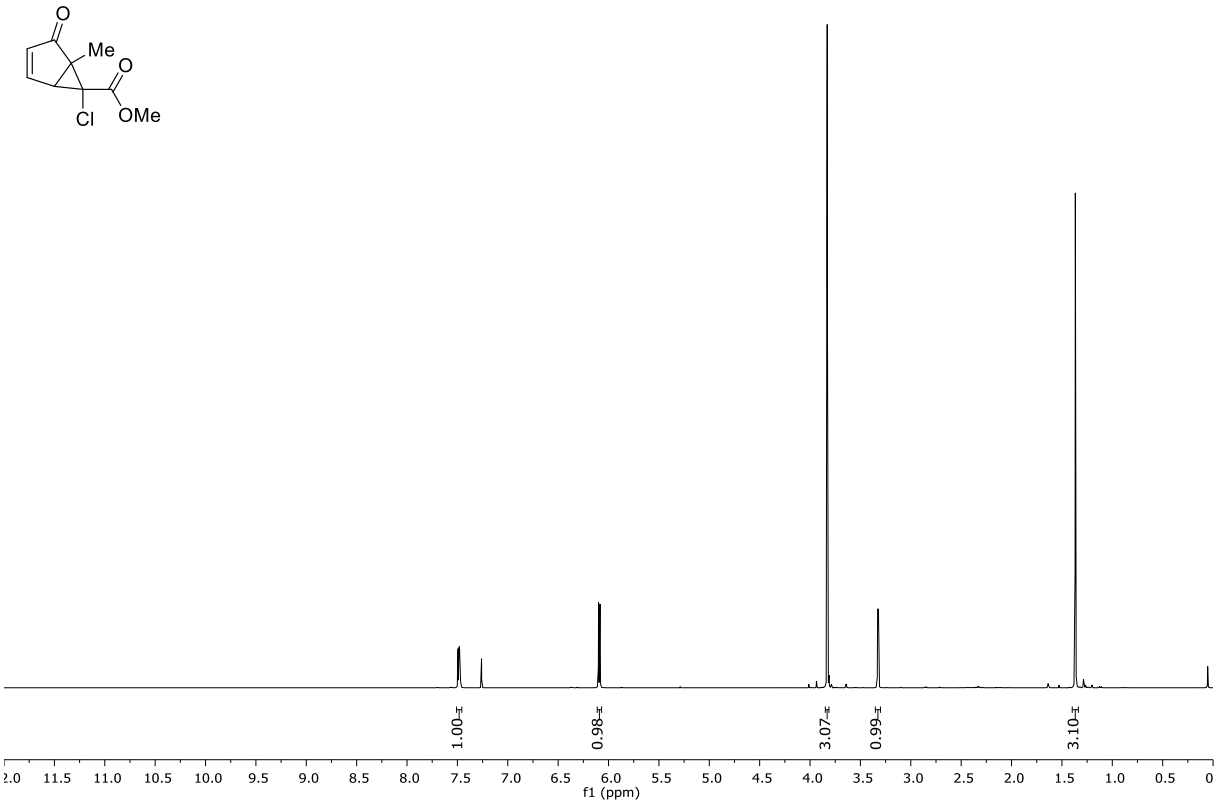

1.00
0.99
3.09
0.99
0.97
f1 (ppm)

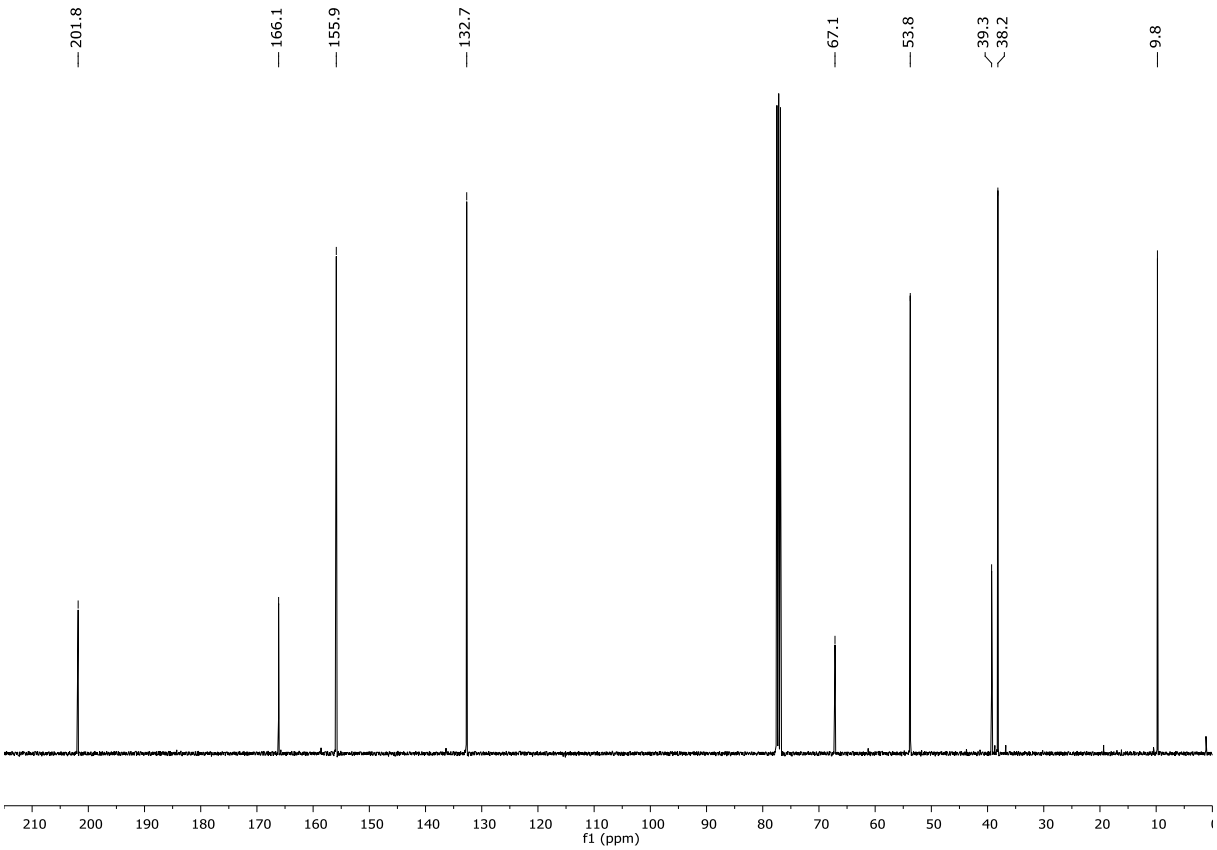

199.4
167.0
155.2
134.0
63.9
54.1
35.9
35.4
f1 (ppm)

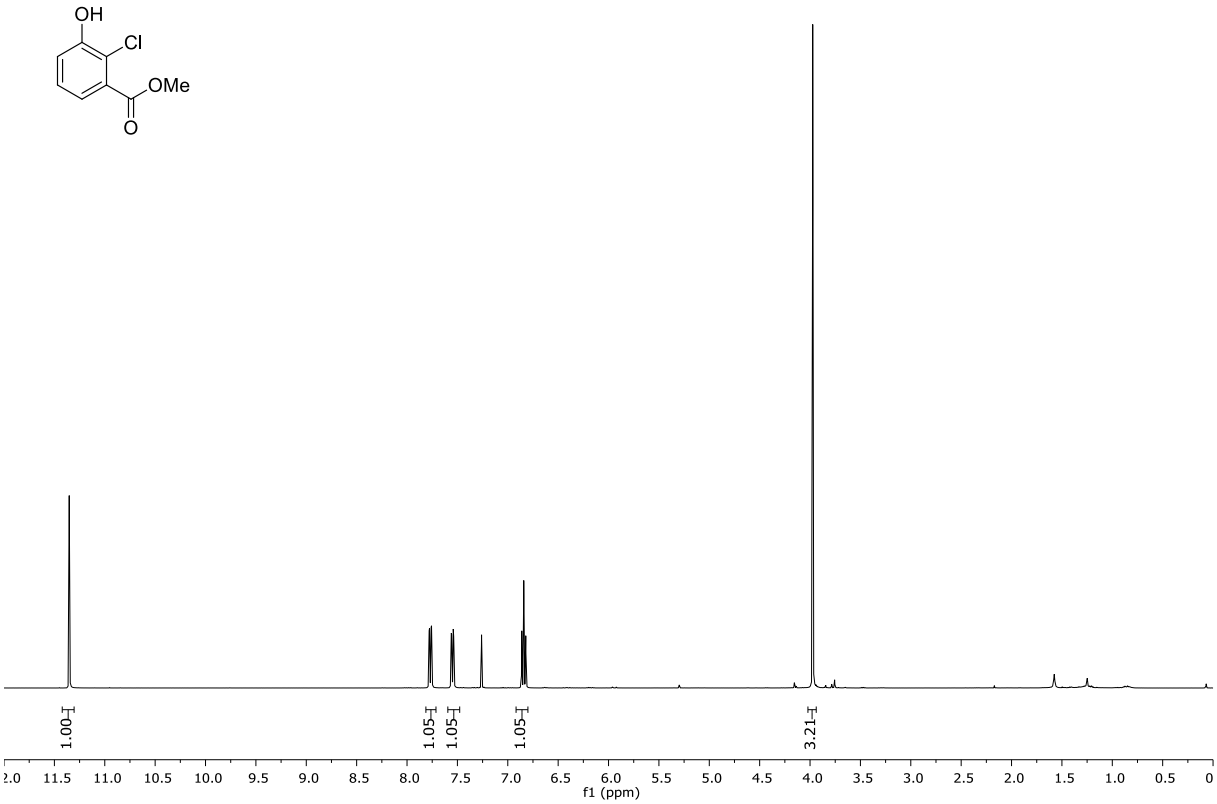

O
O
Cl
OMe

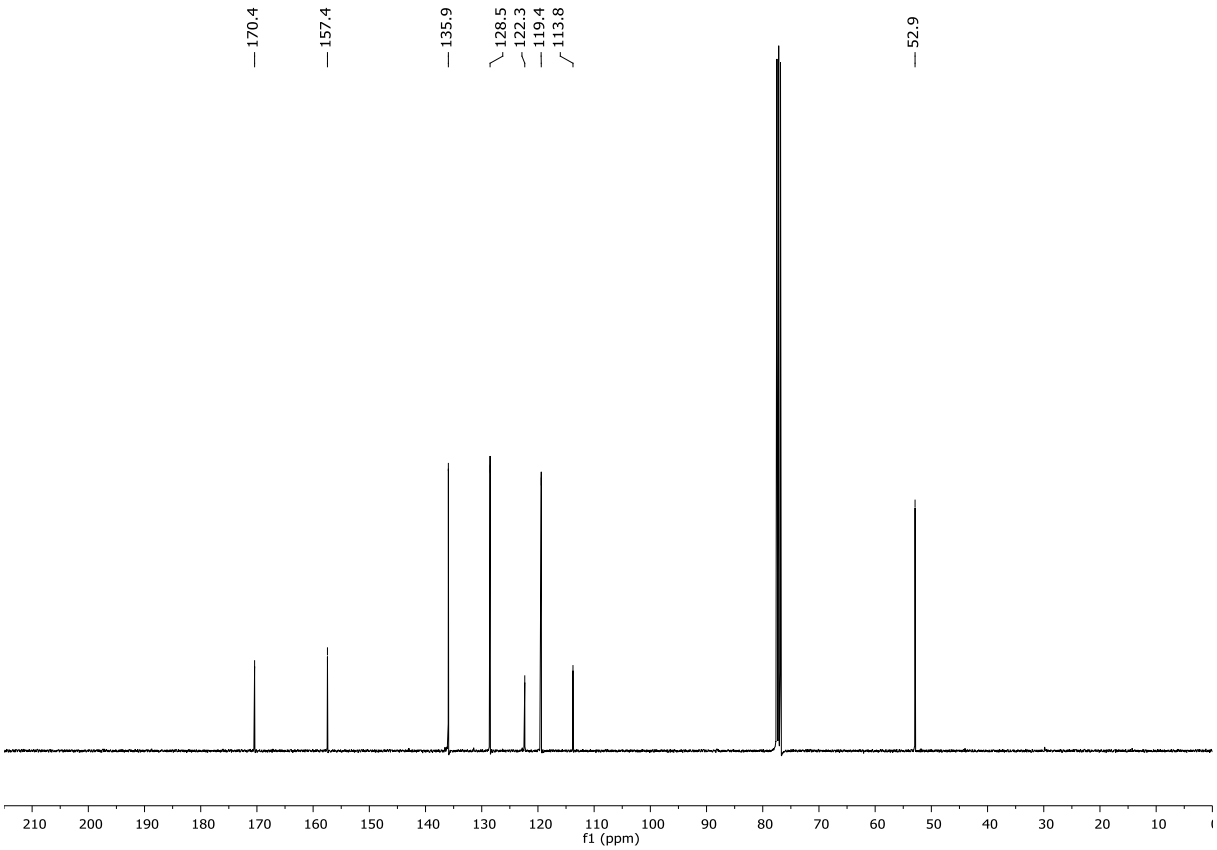
1.00
0.97
3.10
0.98
1.04
1.21
2.17
3.17
f1 (ppm)

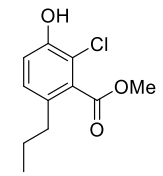

200.4
166.4
159.0
133.3
66.3
53.8
46.1
37.8
28.6
20.4
14.0
f1 (ppm)


O
Me
O
Cl
OMe
1.00
0.98
3.07
0.99
3.10
f1 (ppm)

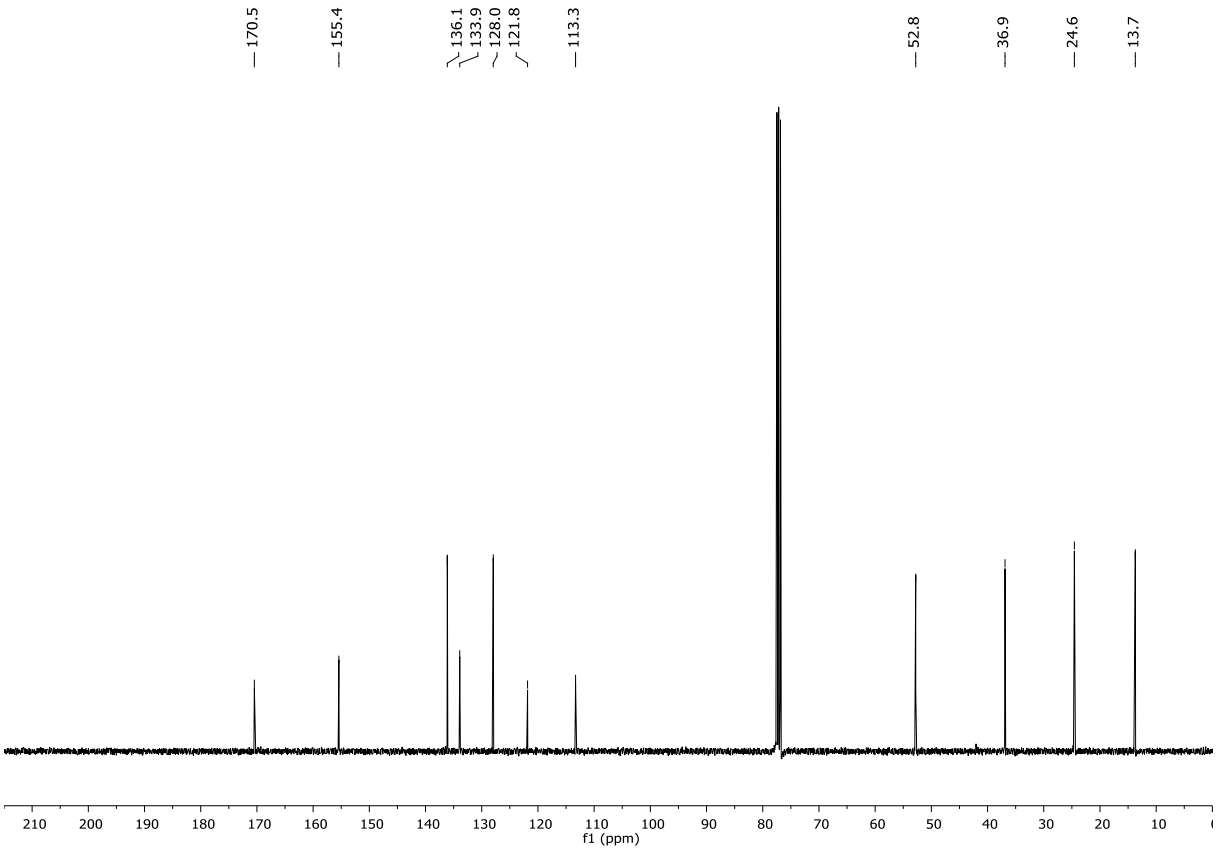

201.8
166.1
155.9
132.7
67.1
53.8
39.3
38.2
9.8
f1 (ppm)

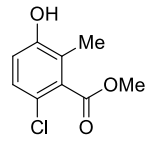

OH
Cl
OMe
O
1.00
1.05
1.05
1.05
3.21
f1 (ppm)


170.4
157.4
135.9
128.5
122.3
119.4
113.8
52.9
f1 (ppm)

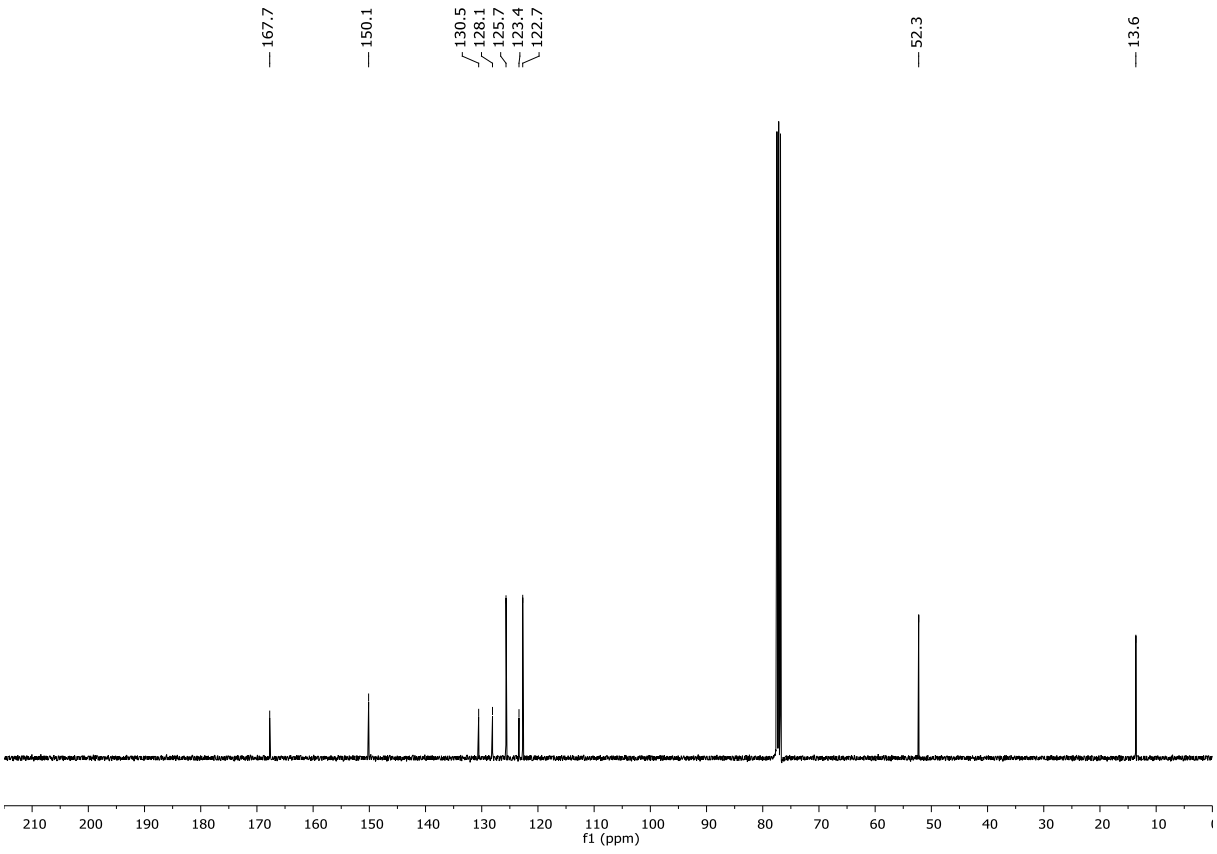

OH
Cl
OMe
O

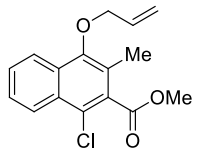
1.00
1.04
1.04
3.17
2.15
2.31
3.26
f1 (ppm)


170.5
155.4
136.1
133.9
128.0
121.8
113.3
52.8
36.9
24.6
13.7
f1 (ppm)

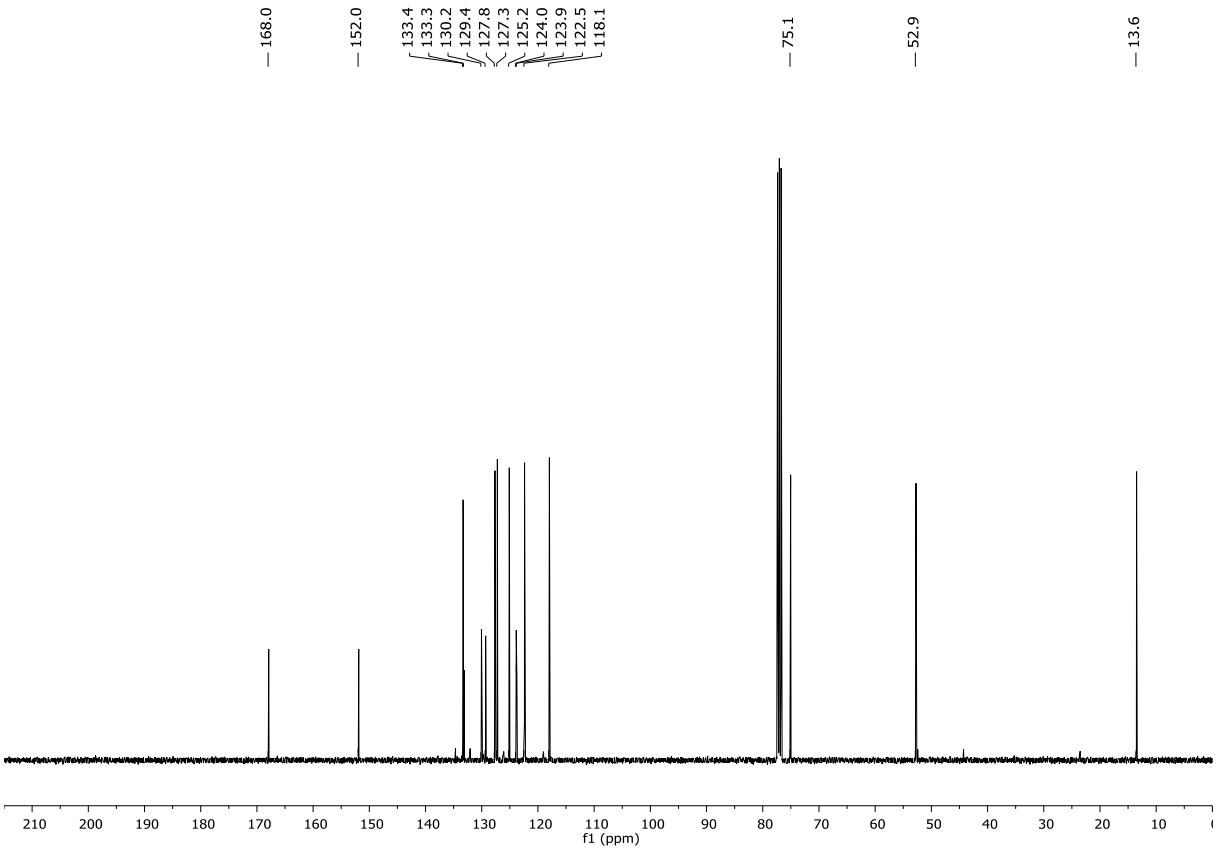

OH
Me
OMe
Cl
O

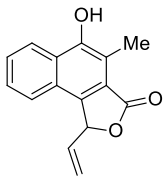
1.00
1.00
0.97
3.06
3.11
f1 (ppm)

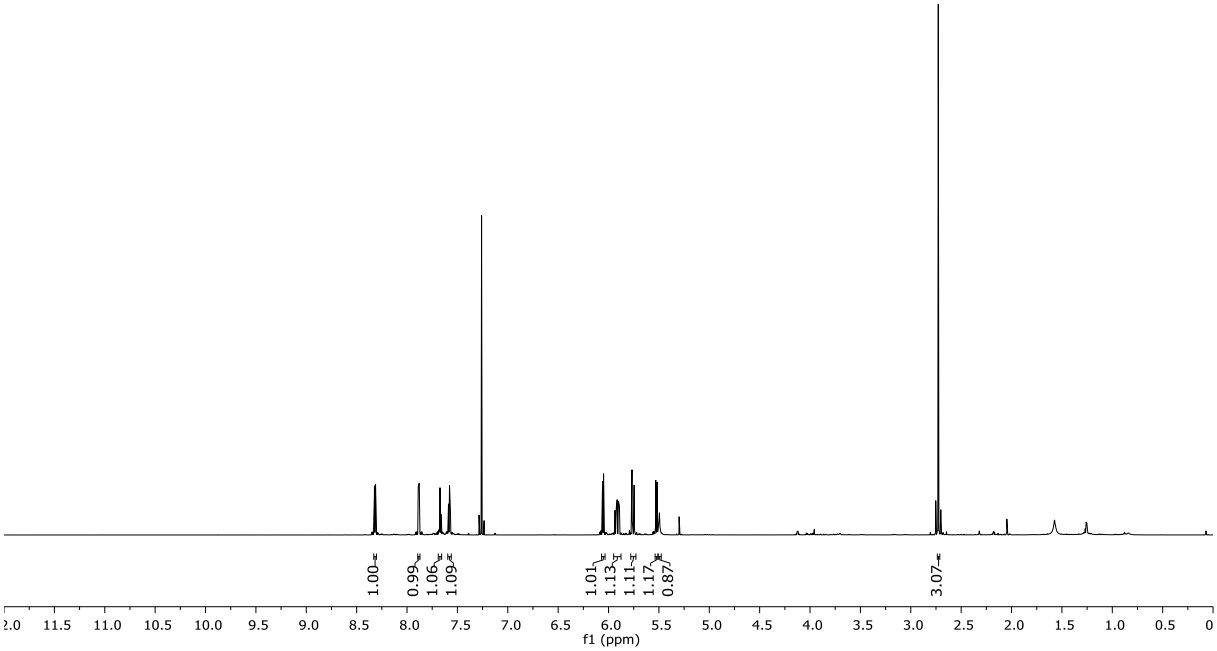

167.7
150.1
130.5
128.1
125.7
123.4
122.7
52.3
13.6
f1 (ppm)

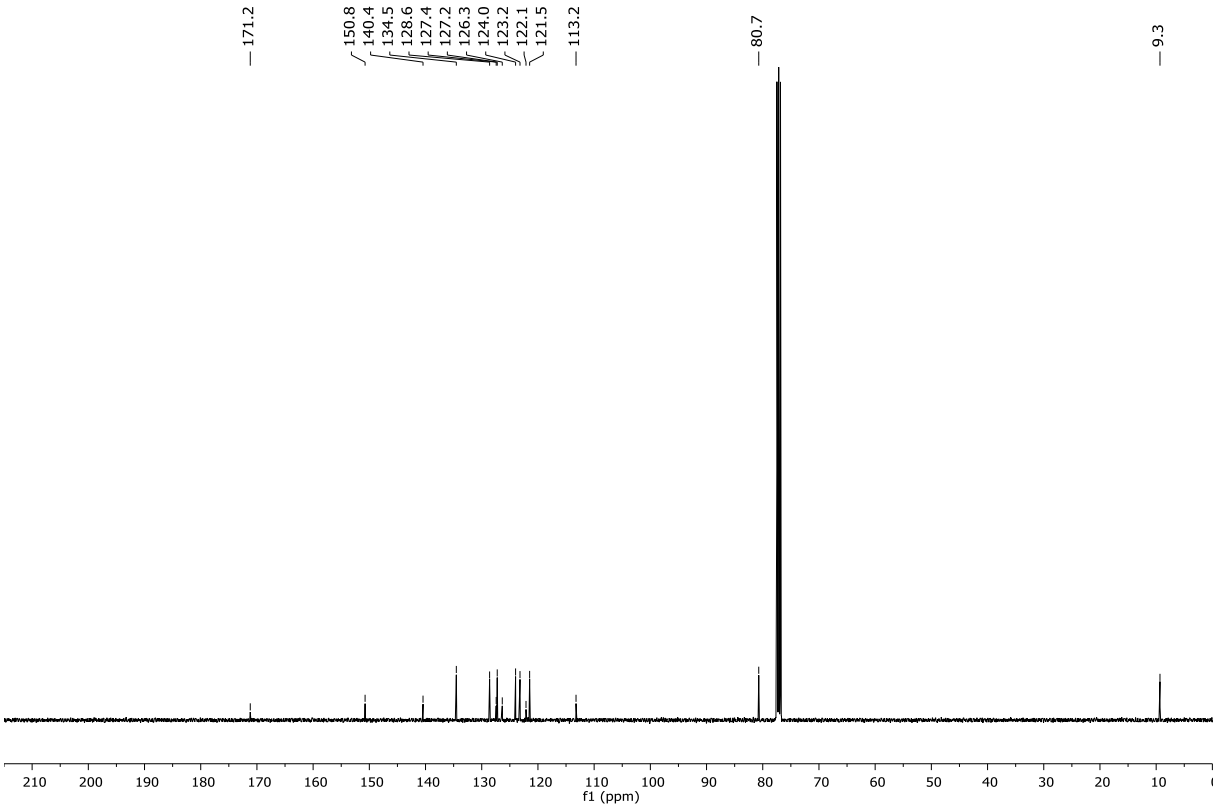

O
Me
OMe
Cl
O

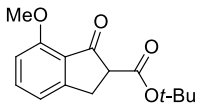
1.00
1.03
2.05
0.98
1.04
1.01
2.06
3.06
3.08
f1 (ppm)


168.0
152.0
133.4
133.3
130.2
129.4
127.8
127.3
125.2
124.0
123.9
122.5
118.1
75.1
52.9
13.6
f1 (ppm)

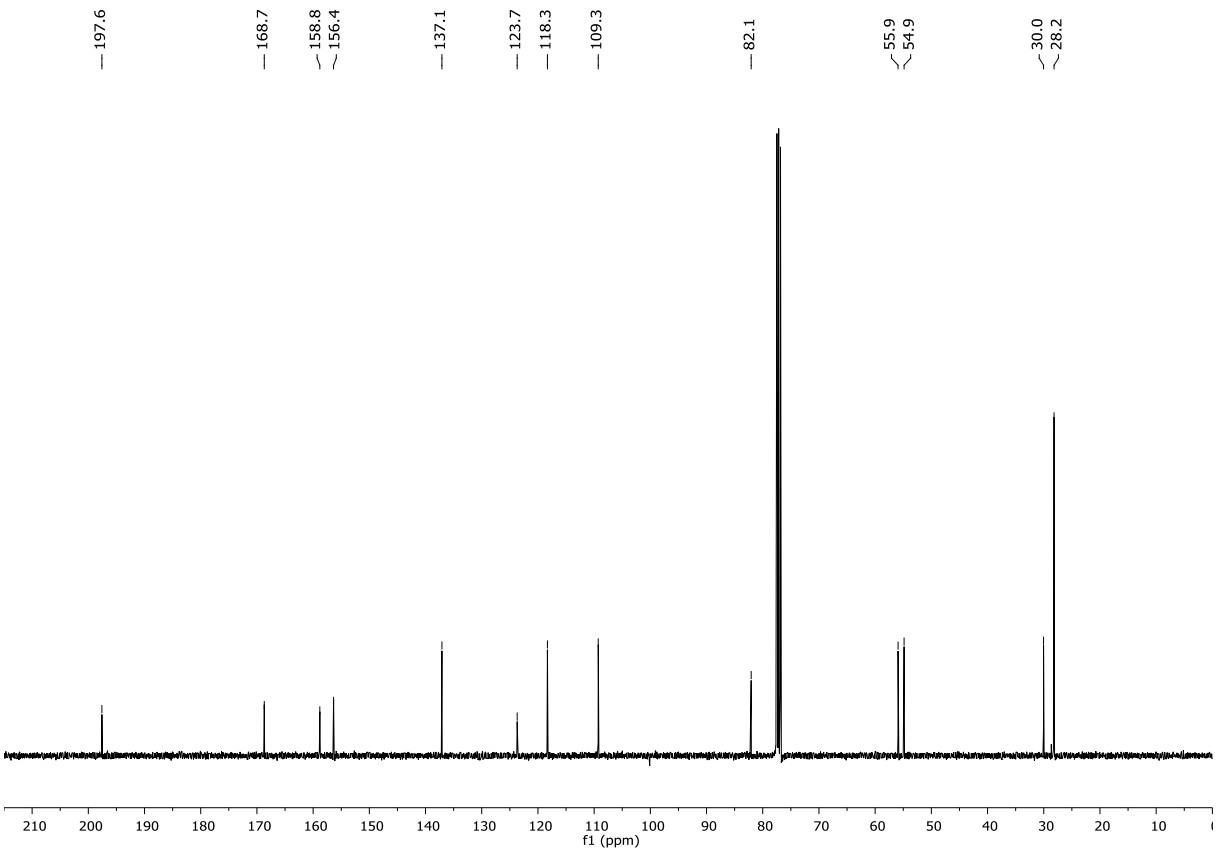

OH
Me
O
O

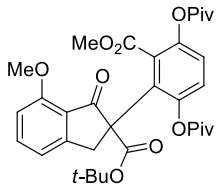

1.00
0.99
1.06
1.09
1.01
1.13
1.11
1.17
0.87
3.07
f1 (ppm)


171.2
150.8
140.4
134.5
128.6
127.4
127.2
126.3
124.0
123.2
122.1
121.5
113.2
80.7
9.3
f1 (ppm)

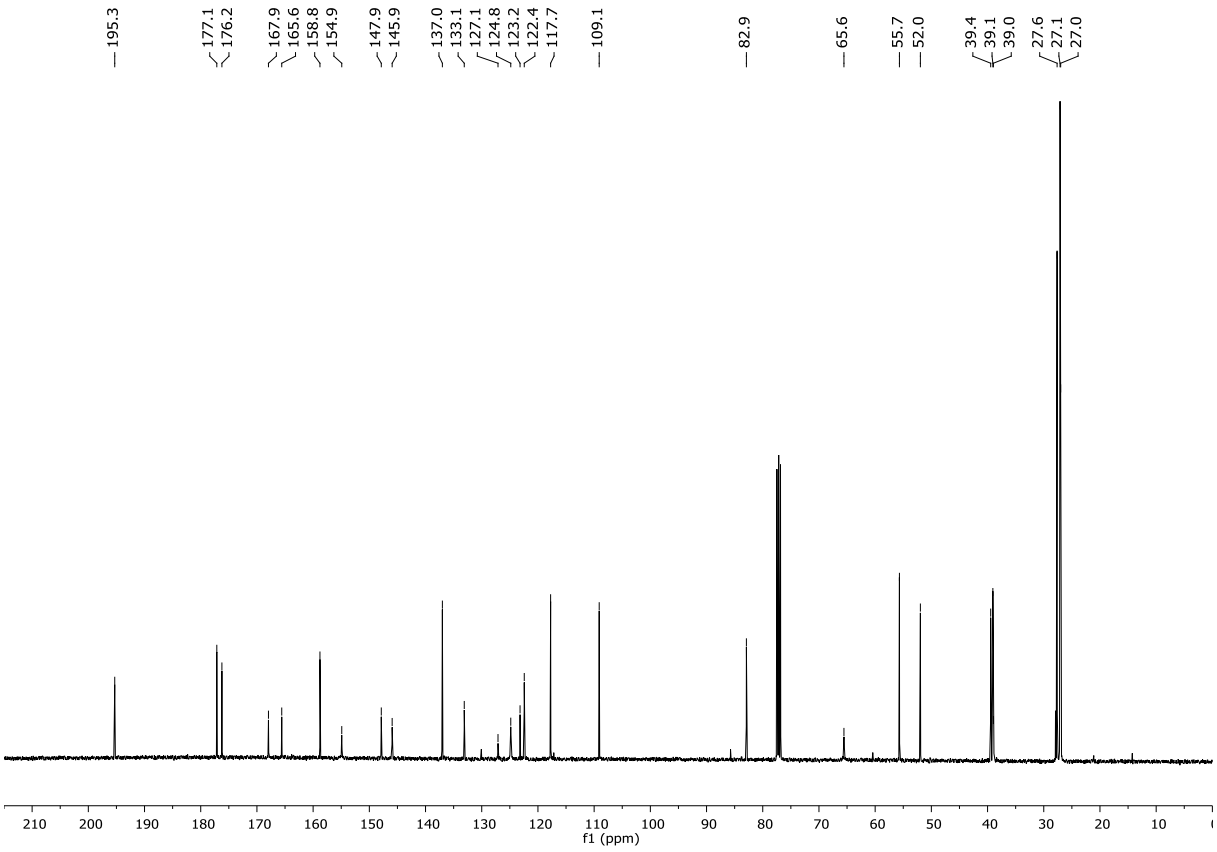

MeO
O
O
Ot-Bu

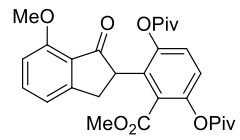
1.00
1.02
1.00
3.00
0.97
1.10
1.02
9.12
f1 (ppm)

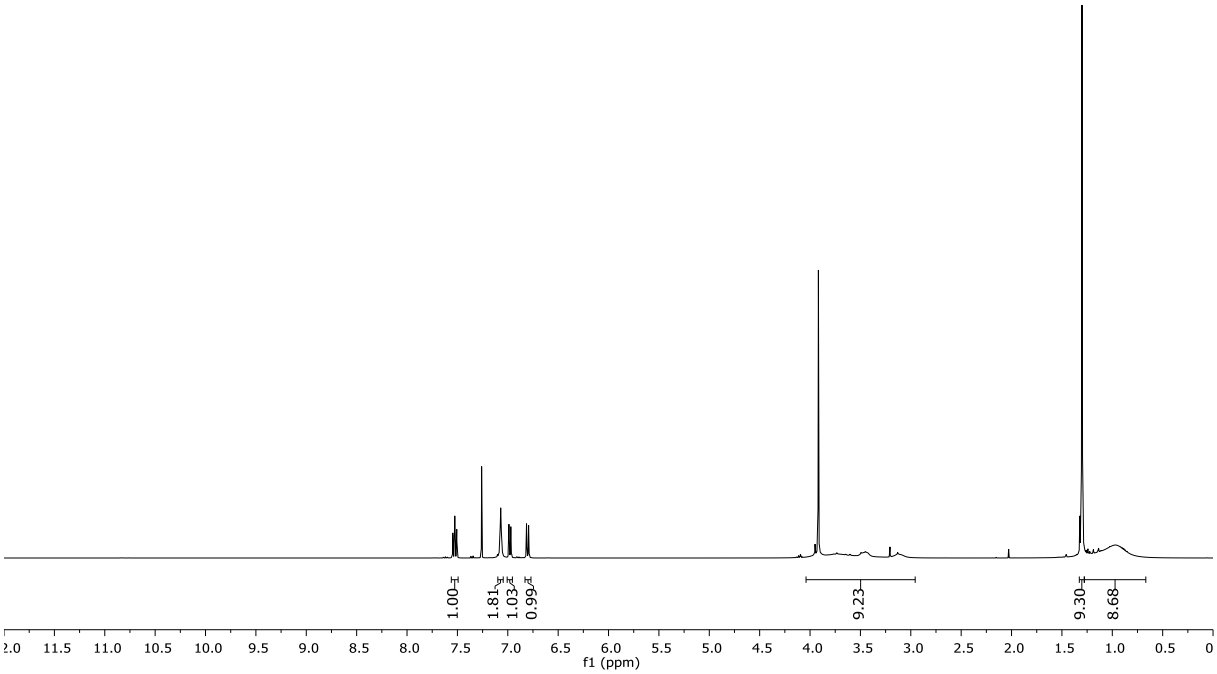

197.6
168.7
158.8
156.4
137.1
123.7
118.3
109.3
82.1
55.9
54.9
30.0
28.2
f1 (ppm)

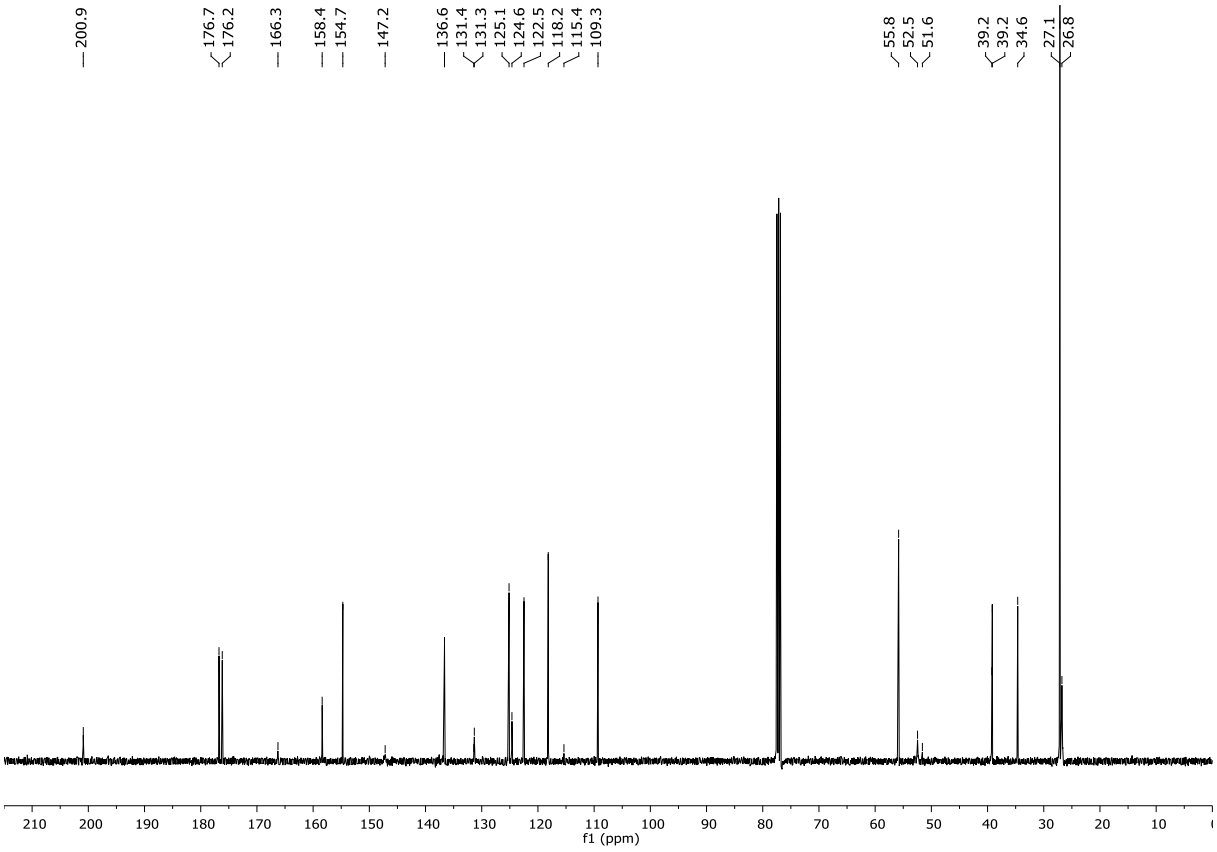

OPiv
MeO2C
MeO
O
OPiv
O
t-BuO

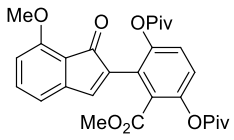
1.00
1.01
2.01
1.03
0.97
2.95
2.77
1.00
8.88
9.14
8.82
f1 (ppm)


195.3
177.1
176.2
167.9
165.6
158.8
154.9
147.9
145.9
137.0
133.1
127.1
124.8
123.2
122.4
117.7
109.1
82.9
65.6
55.7
52.0
39.4
39.1
39.0
27.6
27.1
27.0
f1 (ppm)

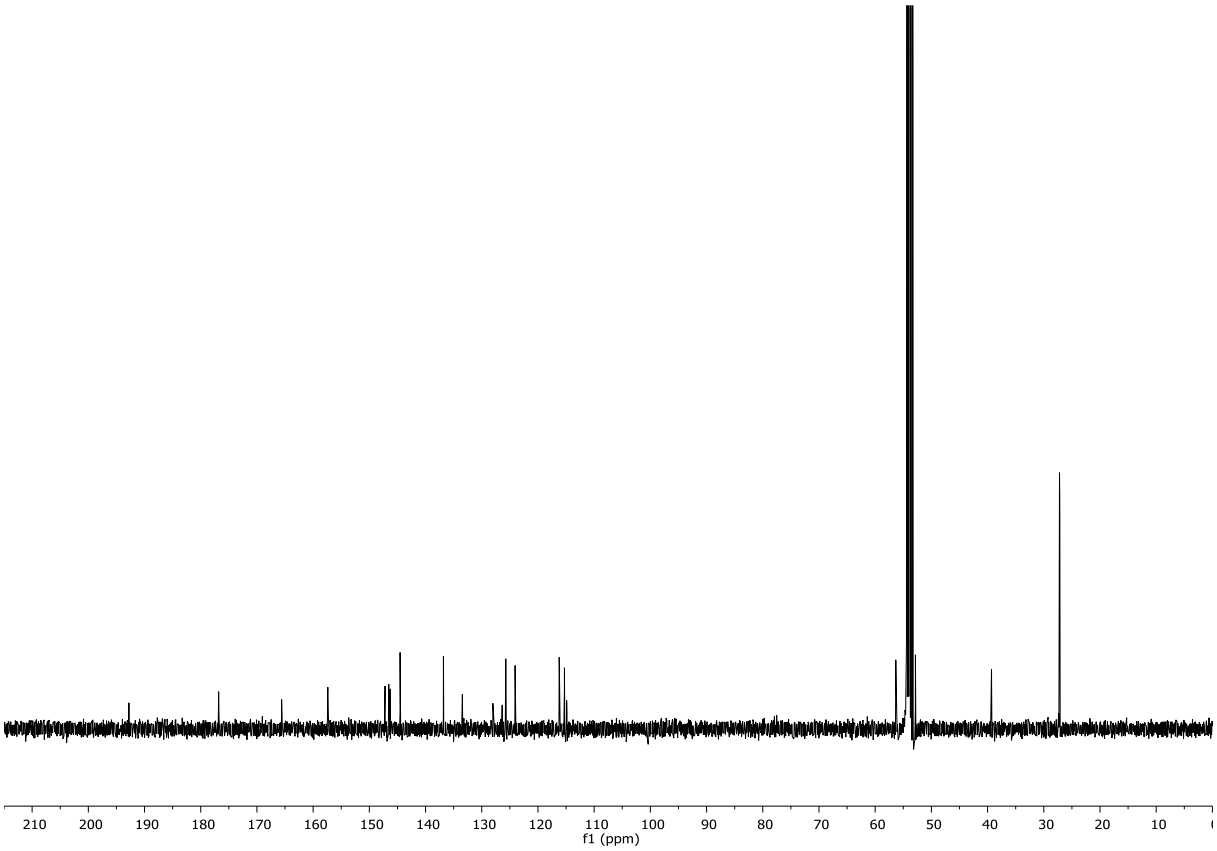

MeO
O
OPiv
MeO2C
OPiv

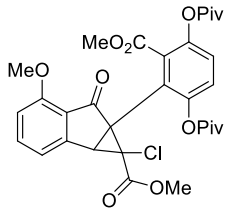

1.00
1.81
1.03
0.99
9.23
9.30
8.68
f1 (ppm)


200.9
176.7
176.2
166.3
158.4
154.7
147.2
136.6
131.4
131.3
125.1
124.6
122.5
118.2
115.4
109.3
55.8
52.5
51.6
39.2
39.2
34.6
27.1
26.8
f1 (ppm)


MeO
O
OPiv
MeO2C
OPiv

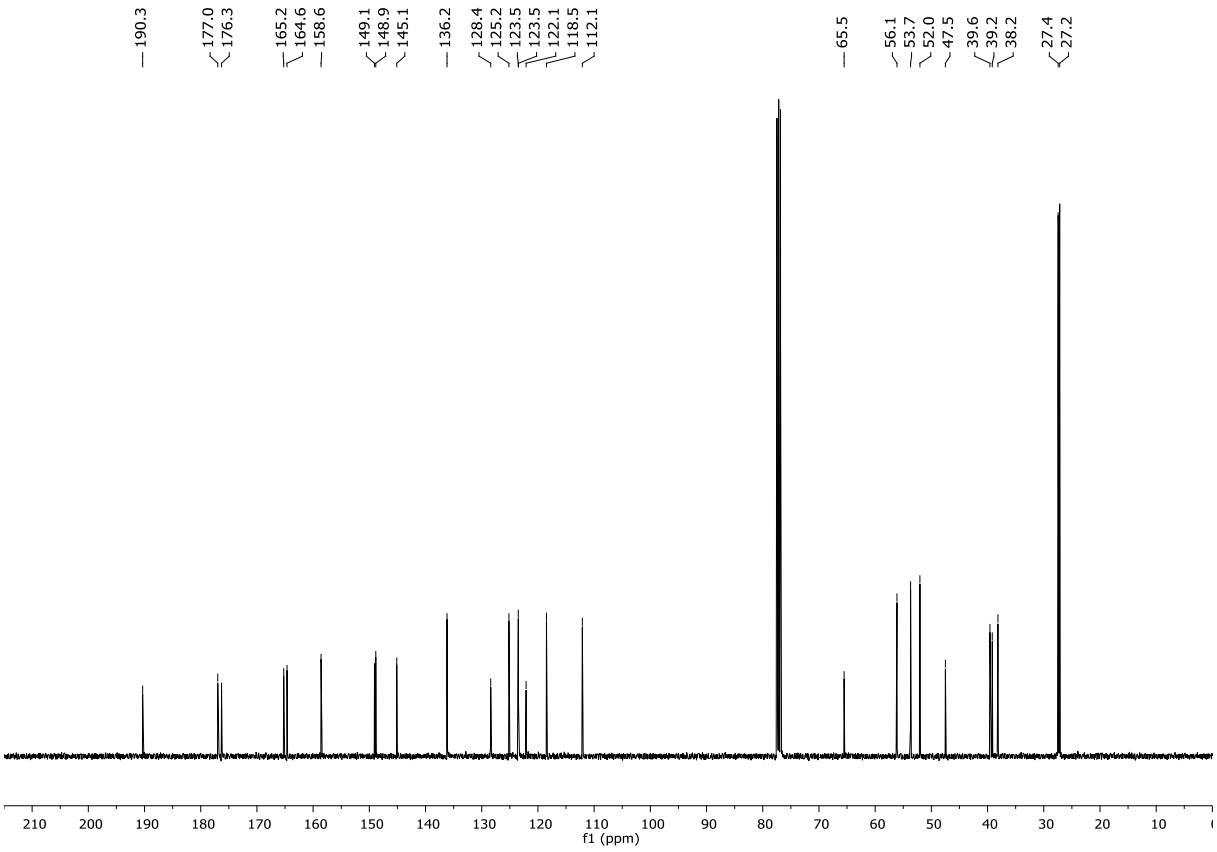
1.08
0.93
1.03
1.02
1.02
0.99
3.00
2.88
9.07
9.25
f1 (ppm)

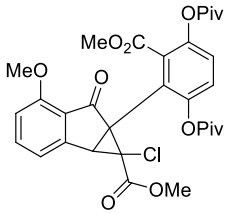

f1 (ppm)


OPiv
MeO2C
MeO
O
OPiv
Cl
OMe
O

36a

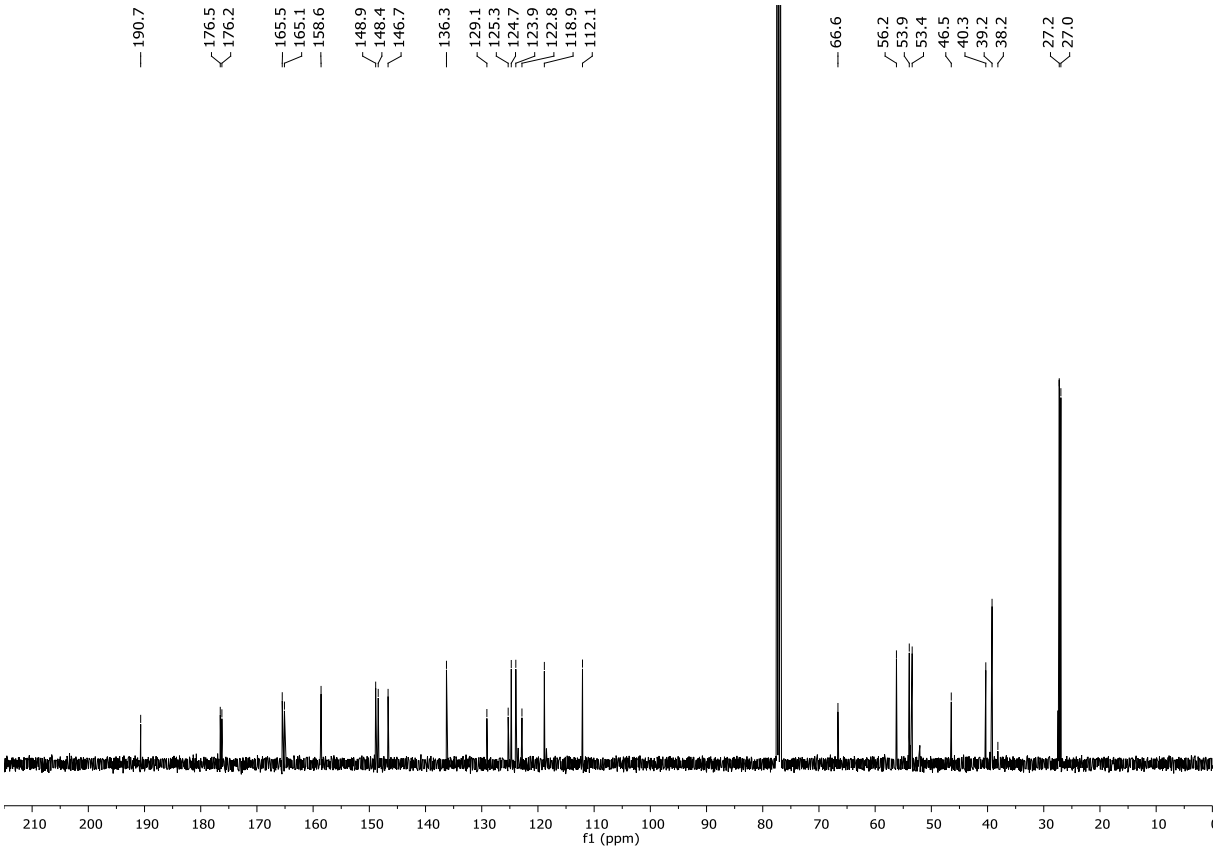
1.02
1.03
2.02
1.00
2.99
0.99
2.98
2.96
9.02
9.09
f1 (ppm)

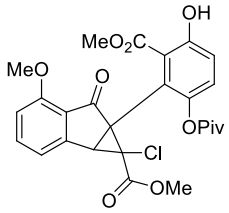

190.3
177.0
176.3
165.2
164.6
158.6
149.1
148.9
145.1
136.2
128.4
125.2
123.5
123.5
122.1
118.5
112.1
65.5
56.1
53.7
52.0
47.5
39.6
39.2
38.2
27.4
27.2
f1 (ppm)


OPiv
MeO2C
MeO
O
OPiv
Cl
OMe
O

36b

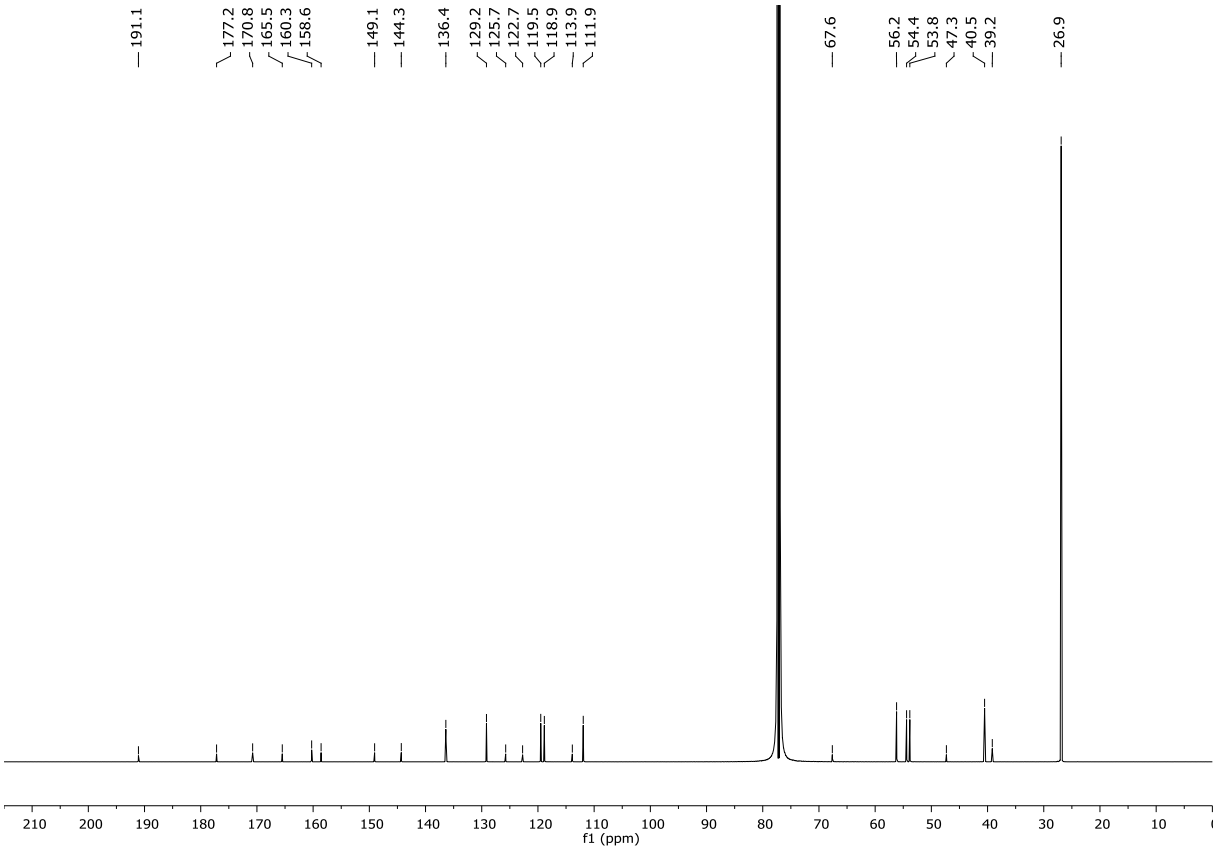
1.12
2.27
0.98
1.00
0.96
2.88
2.88
2.89
8.94
8.76
f1 (ppm)

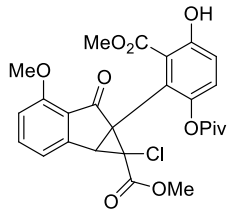

190.7
176.5
176.2
165.5
165.1
158.6
148.9
148.4
146.7
136.3
129.1
125.3
124.7
123.9
122.8
118.9
112.1
66.6
56.2
53.9
53.4
46.5
40.3
39.2
38.2
27.2
27.0
f1 (ppm)


OH
MeO2C
MeO
O
OPiv
Cl
OMe
O

S25a

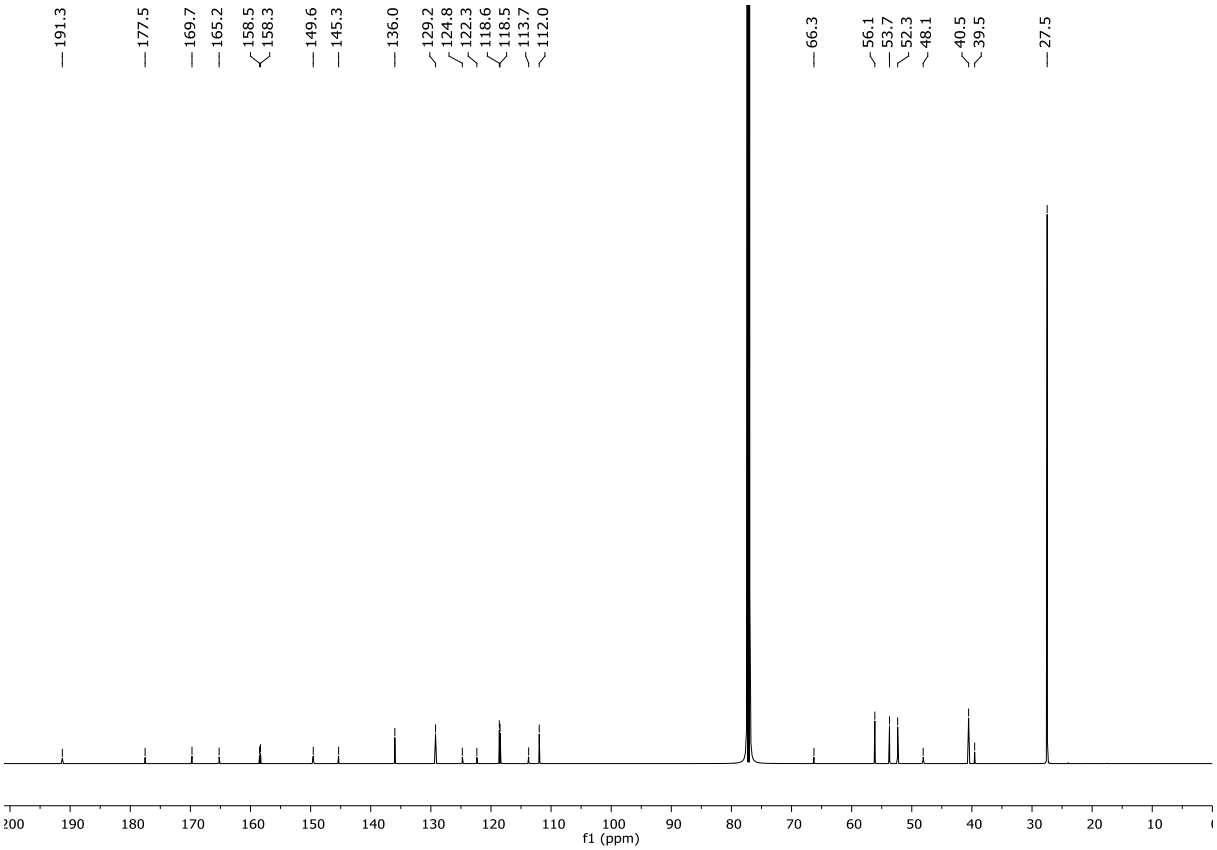
1.00
1.07
1.00
0.98
1.02
1.07
0.96
3.07
3.06
3.00
9.24
f1 (ppm)

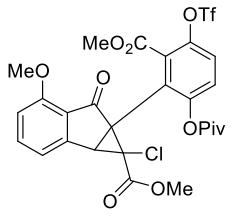

191.1
177.2
170.8
165.5
160.3
158.6
149.1
144.3
136.4
129.2
125.7
122.7
119.5
118.9
113.9
111.9
67.6
56.2
54.4
53.8
47.3
40.5
39.2
26.9
f1 (ppm)


OH
MeO2C
MeO
O
OPiv
Cl
O
OMe

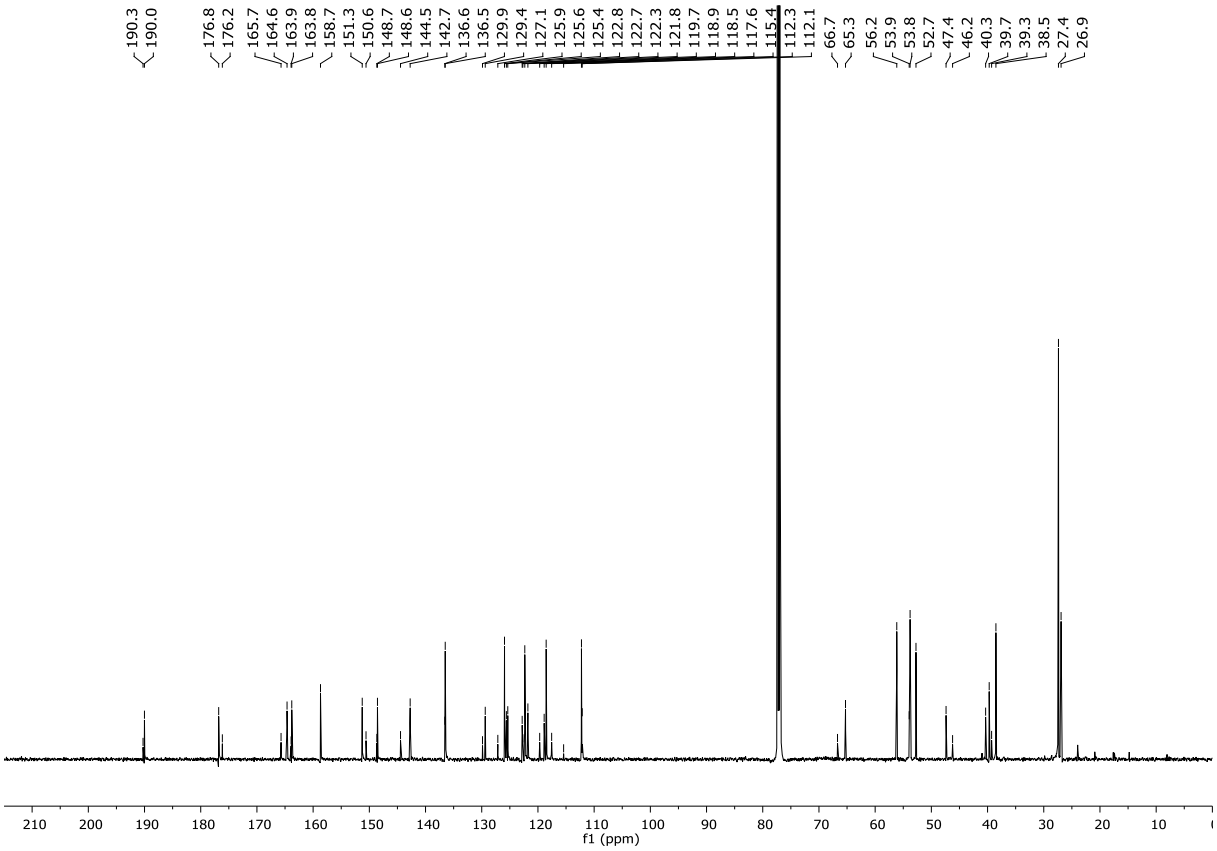
S25b

1.00
1.08
1.00
1.03
1.06
1.05
3.00
0.98
3.03
2.96
9.15
f1 (ppm)


191.3
177.5
169.7
165.2
158.5
158.3
149.6
145.3
136.0
129.2
124.8
122.3
118.6
118.5
113.7
112.0
66.3
56.1
53.7
52.3
48.1
40.5
39.5
27.5
f1 (ppm)


OTf
MeO2C
MeO
O
OPiv
Cl
OMe
O

1.53
0.50
1.95
1.81
1.10
0.45
0.40
1.15
3.04
1.09
1.06
1.06
2.97
3.00
9.27
3.13
f1 (ppm)


190.3
190.0
176.8
176.2
165.7
164.6
163.9
163.8
158.7
151.3
150.6
148.7
148.6
144.5
142.7
136.6
136.5
129.9
129.4
127.1
125.9
125.6
125.4
122.8
122.7
122.3
121.8
119.7
118.9
118.5
117.6
115.4
112.3
112.1
66.7
65.3
56.2
53.9
53.8
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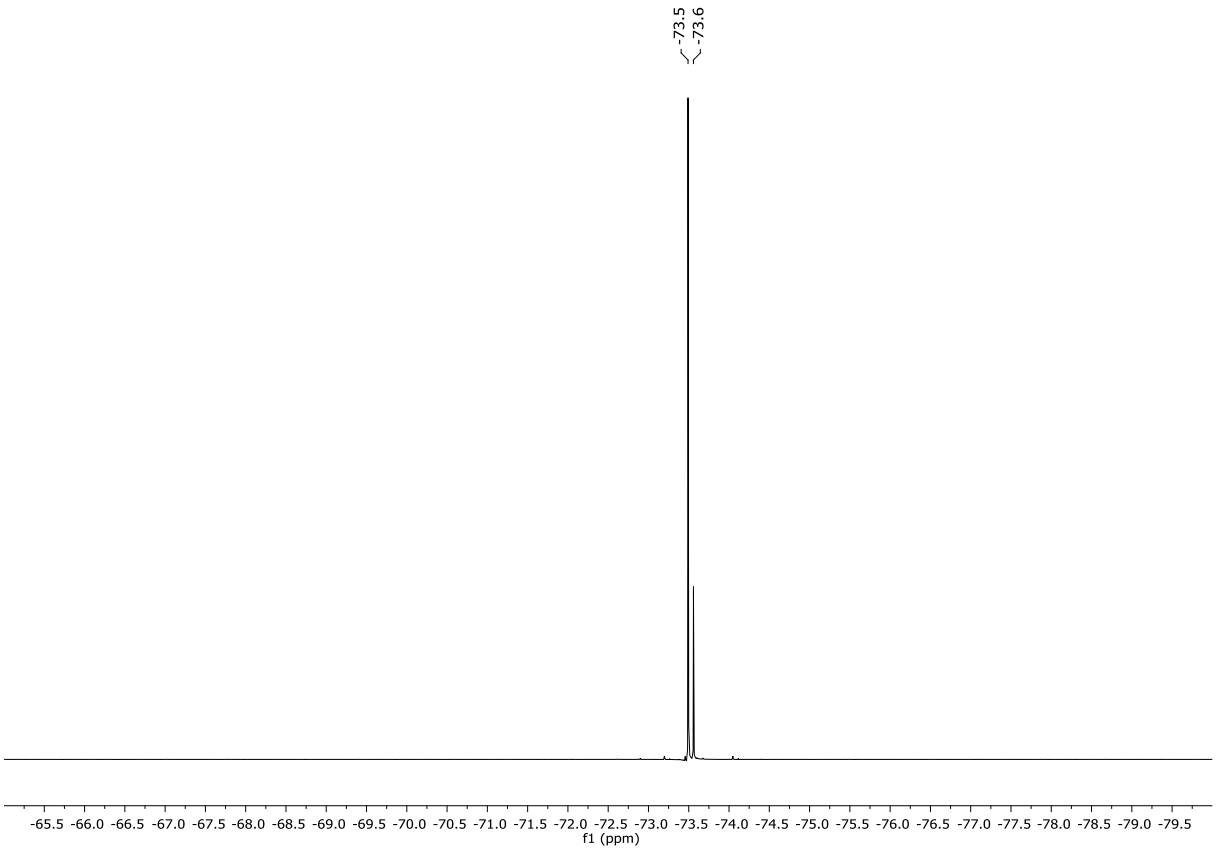
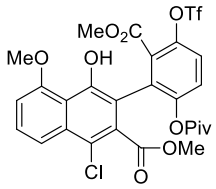
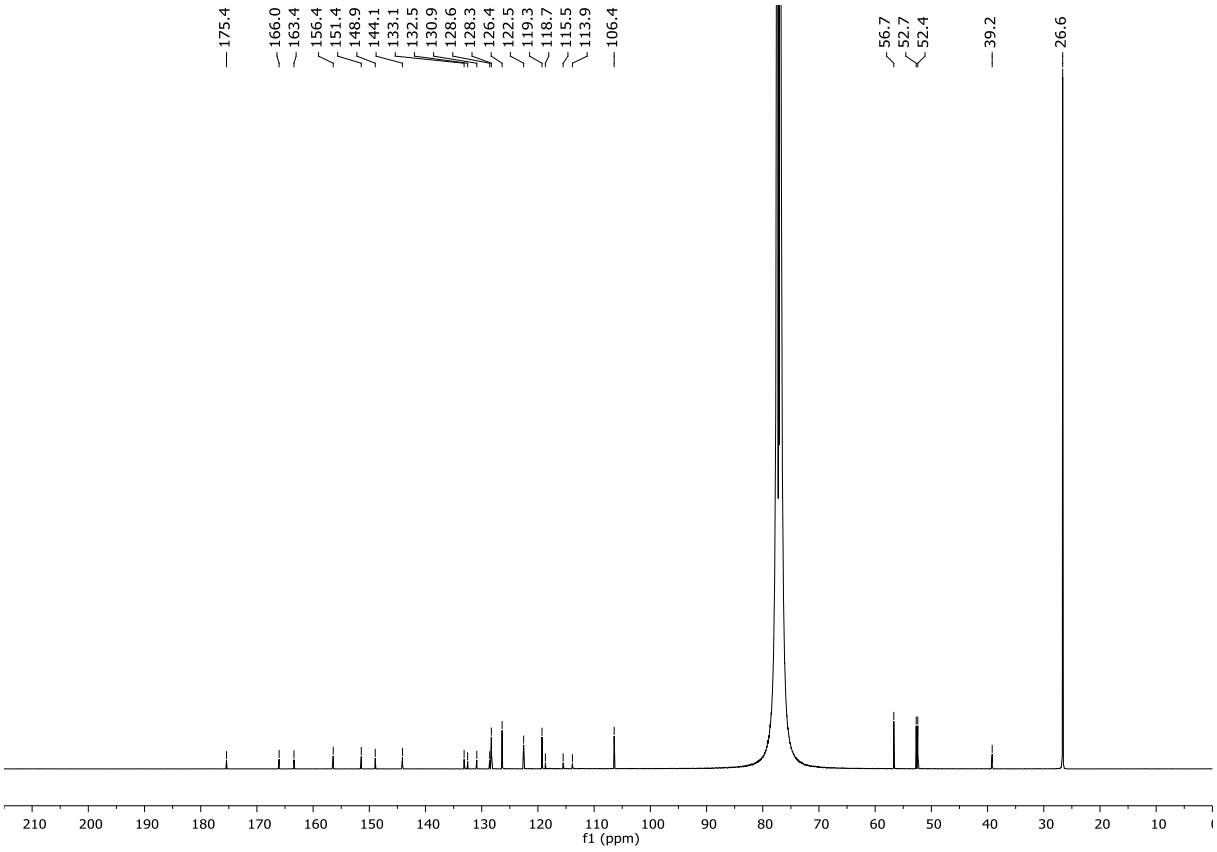
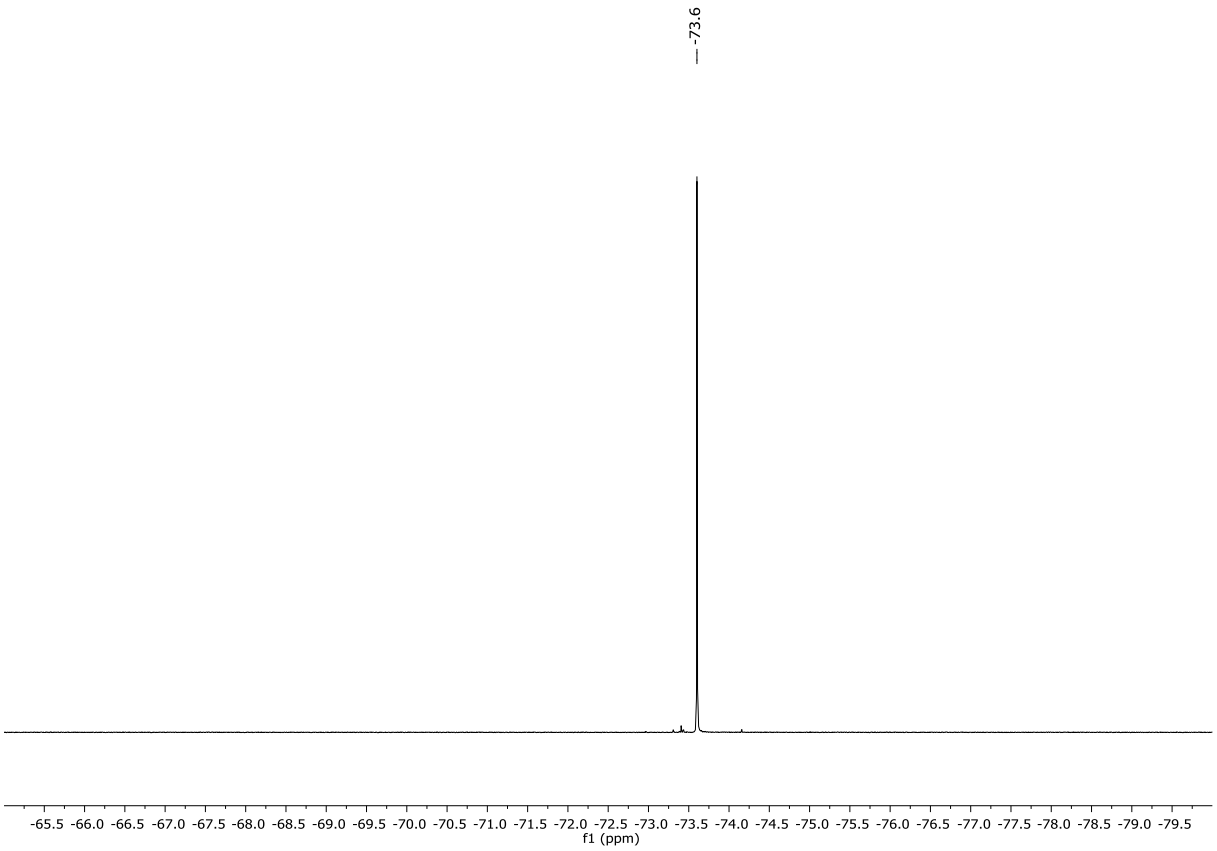
47.4
46.2
40.3
39.7
39.3
38.5
27.4
26.9
f1 (ppm)

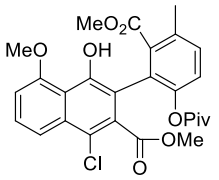

-73.5
-73.6
-65.5 -66.0 -66.5 -67.0 -67.5 -68.0 -68.5 -69.0 -69.5 -70.0 -70.5 -71.0 -71.5 -72.0 -72.5 -73.0 -73.5 -74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5
f1 (ppm)


OTf
MeO2C
MeO
OH
OPiv
OMe
Cl
O

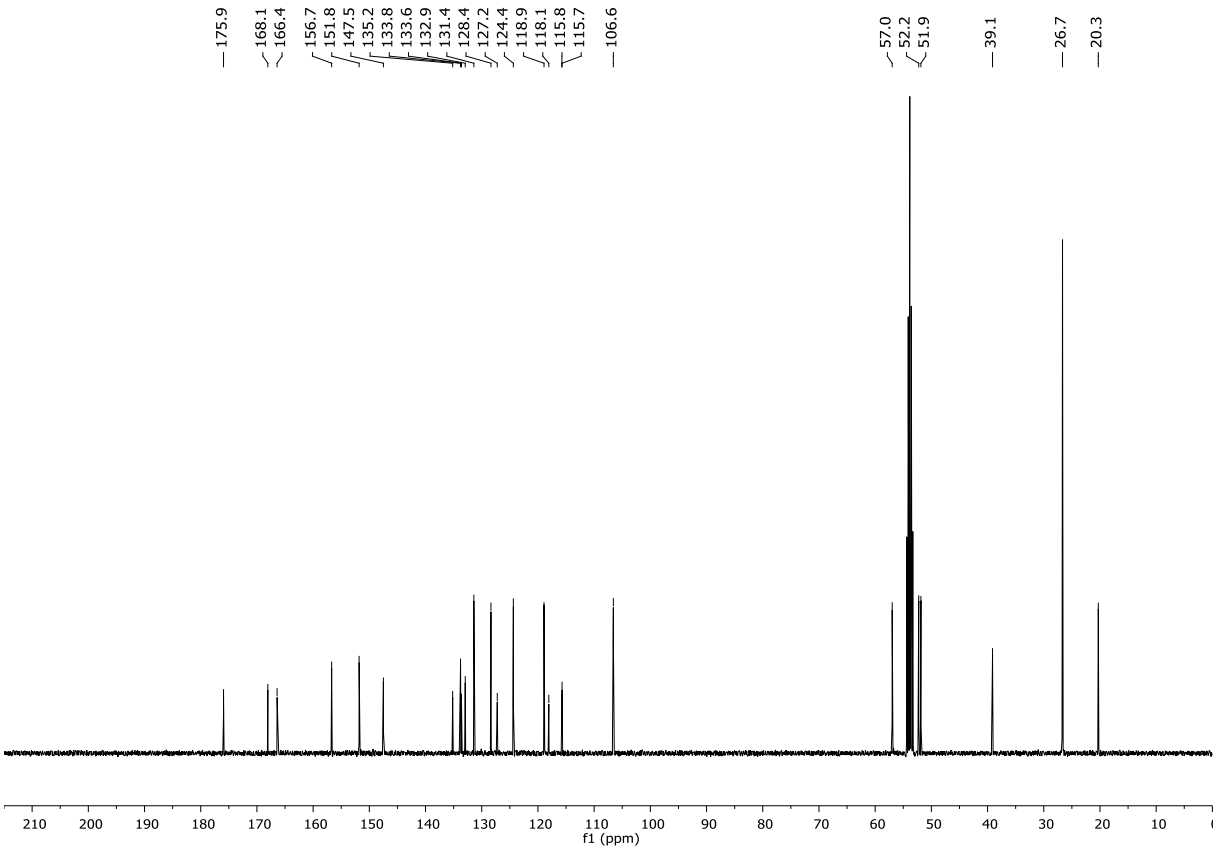
1.00
1.01
1.08
1.23
1.07
1.02
3.15
2.99
3.25
9.41
f1 (ppm)

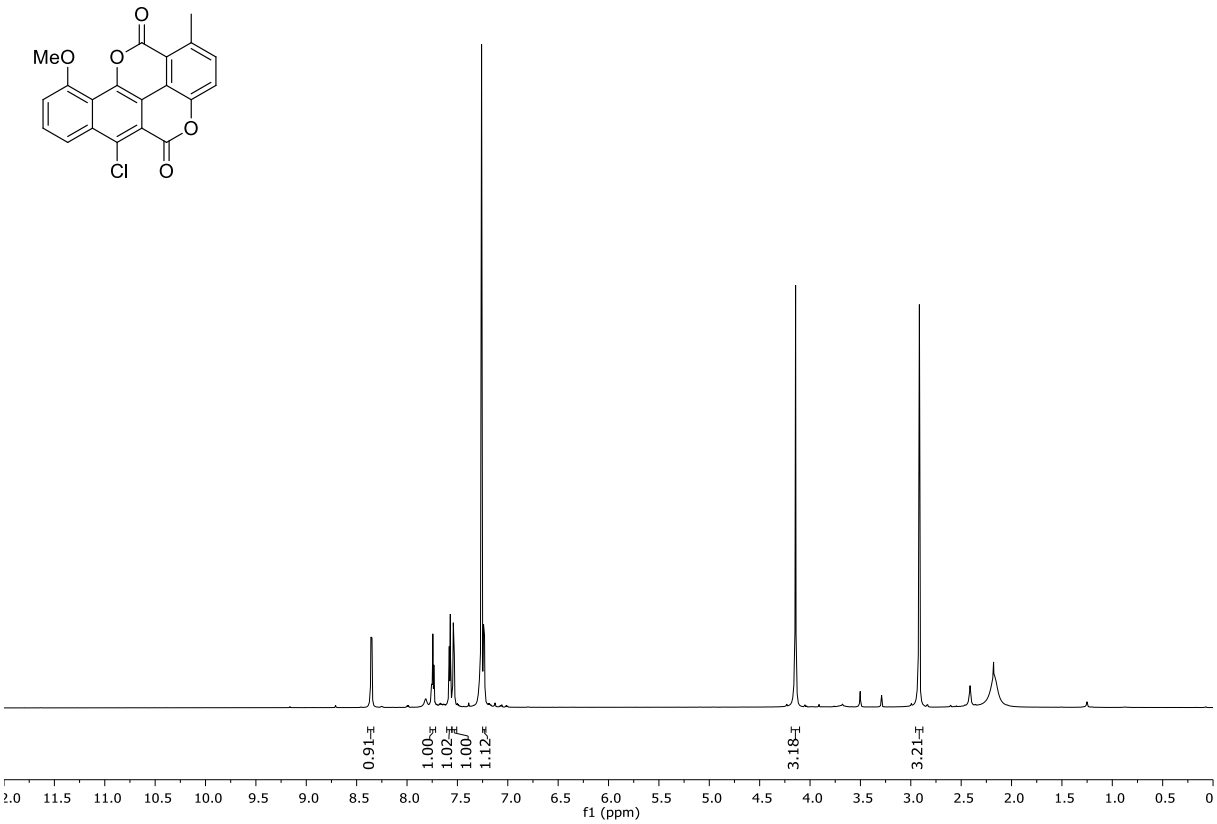

175.4
166.0
163.4
156.4
151.4
148.9
144.1
133.1
132.5
130.9
128.6
128.3
126.4
122.5
119.3
118.7
115.5
113.9
106.4
56.7
52.7
52.4
39.2
26.6
f1 (ppm)

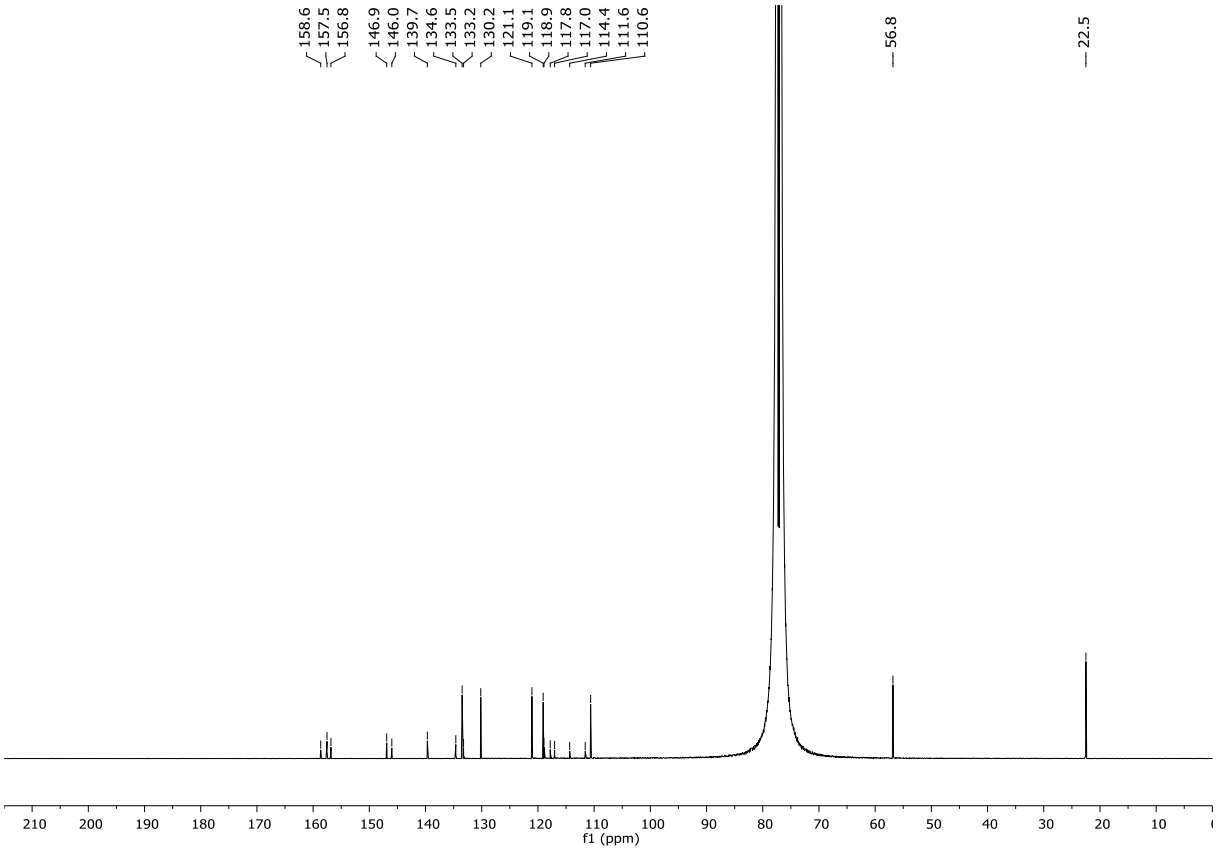

-73.6
-65.5 -66.0 -66.5 -67.0 -67.5 -68.0 -68.5 -69.0 -69.5 -70.0 -70.5 -71.0 -71.5 -72.0 -72.5 -73.0 -73.5 -74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5
f1 (ppm)

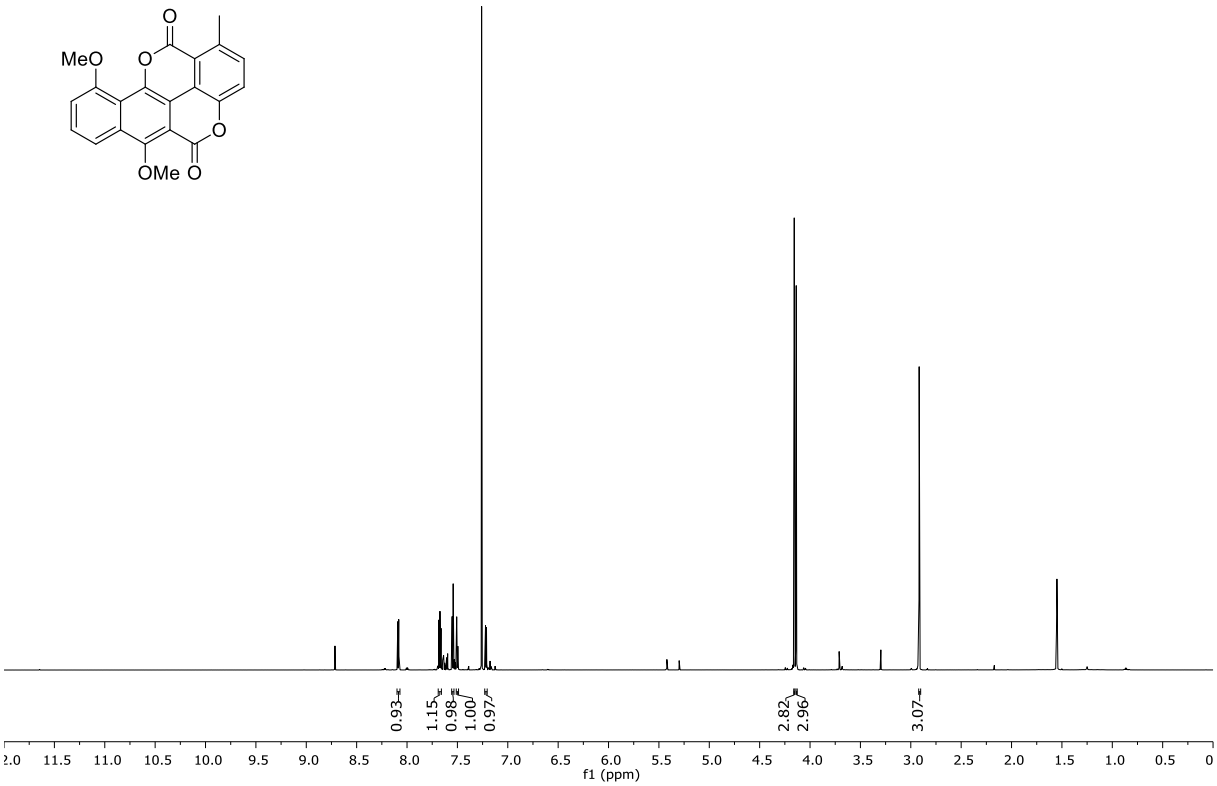

MeO2C
MeO
OH
OPiv
OMe
Cl
O

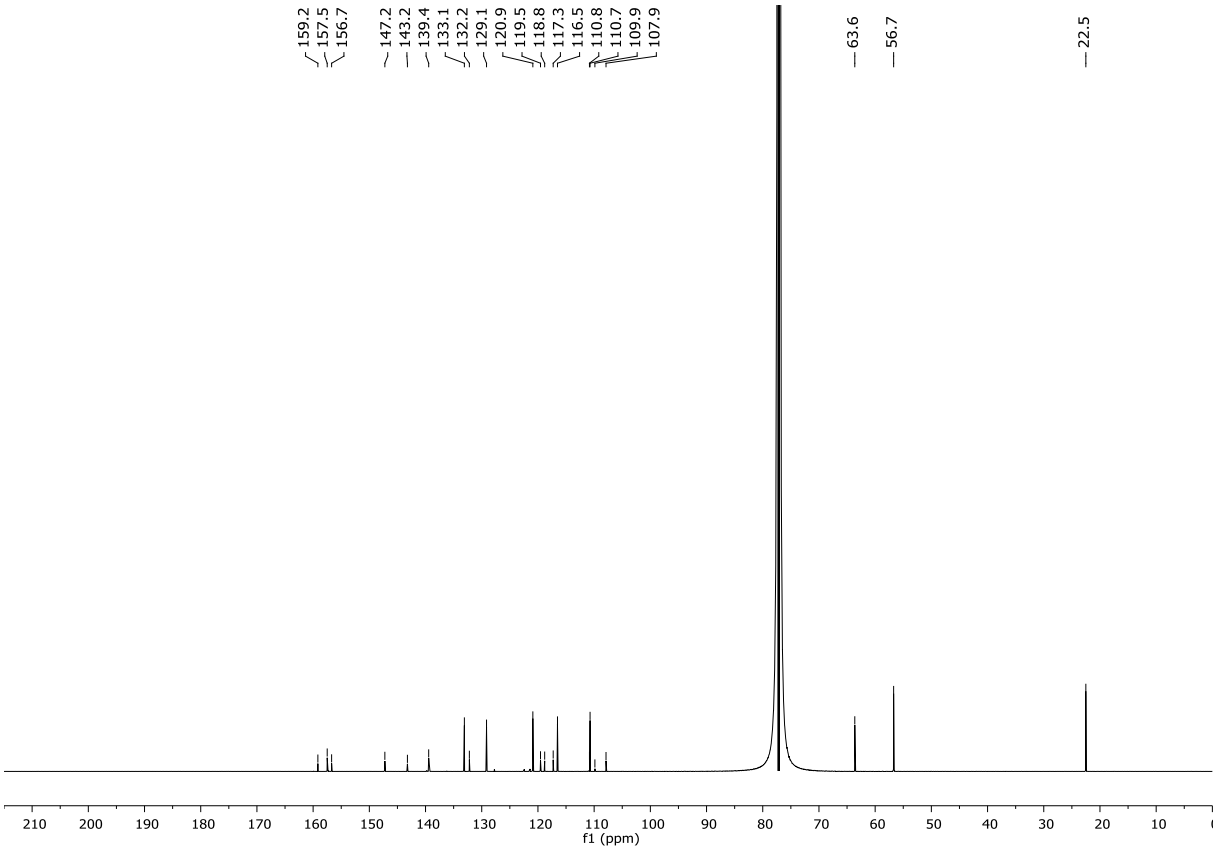
0.95
1.00
1.09
1.02
1.04
1.03
3.03
3.07
3.00
2.95
9.16
f1 (ppm)

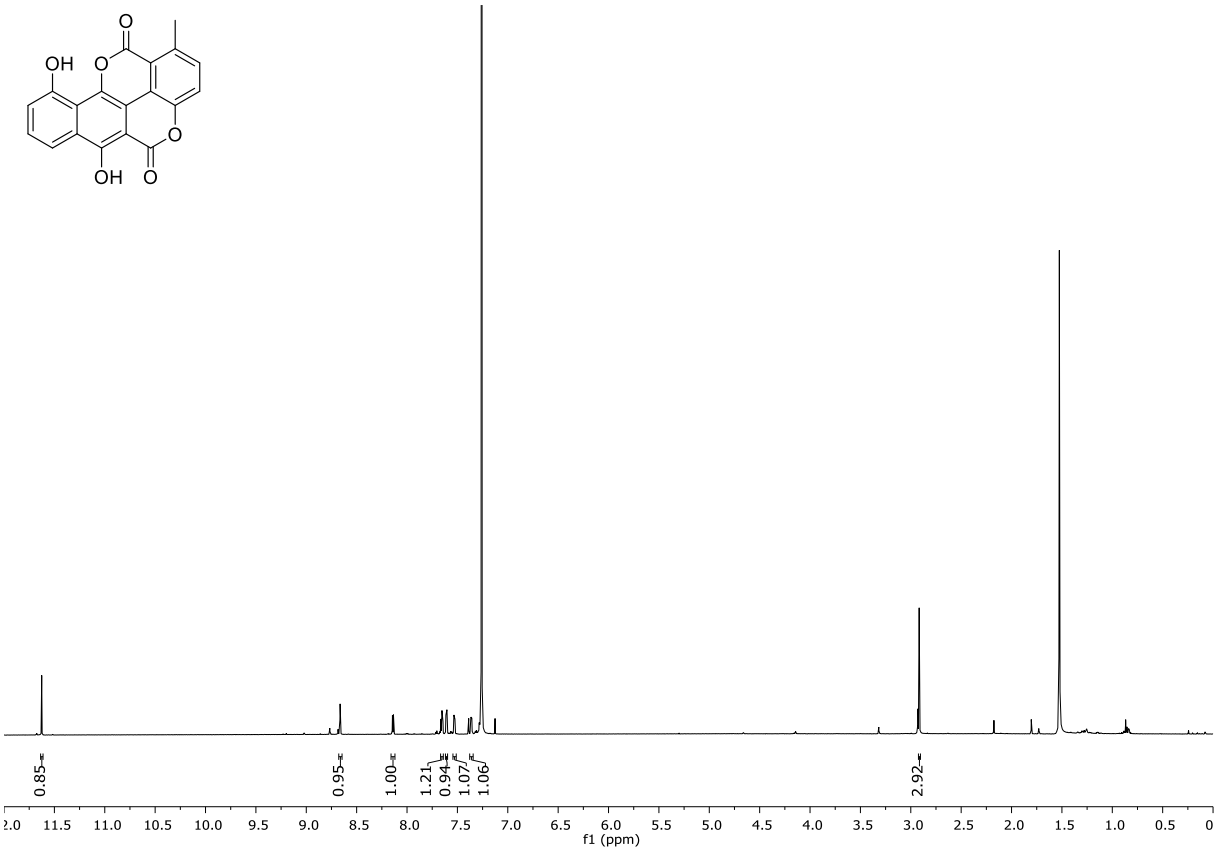

175.9
168.1
166.4
156.7
151.8
147.5
135.2
133.8
133.6
132.9
131.4
128.4
127.2
124.4
118.9
118.1
115.8
115.7
106.6
57.0
52.2
51.9
39.1
26.7
20.3
f1 (ppm)

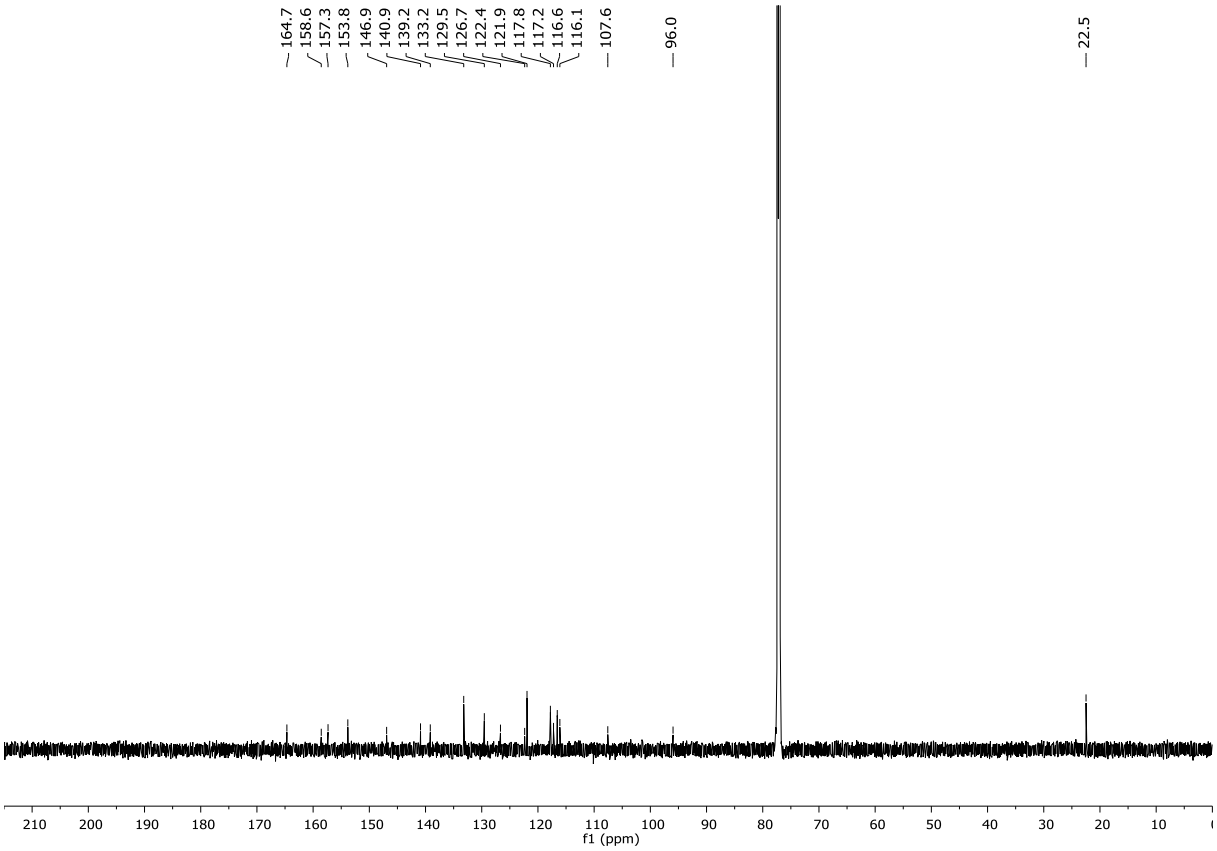

MeO
O
O
O
Cl
O
0.91
1.00
1.02
1.00
1.12
3.18
3.21
f1 (ppm)

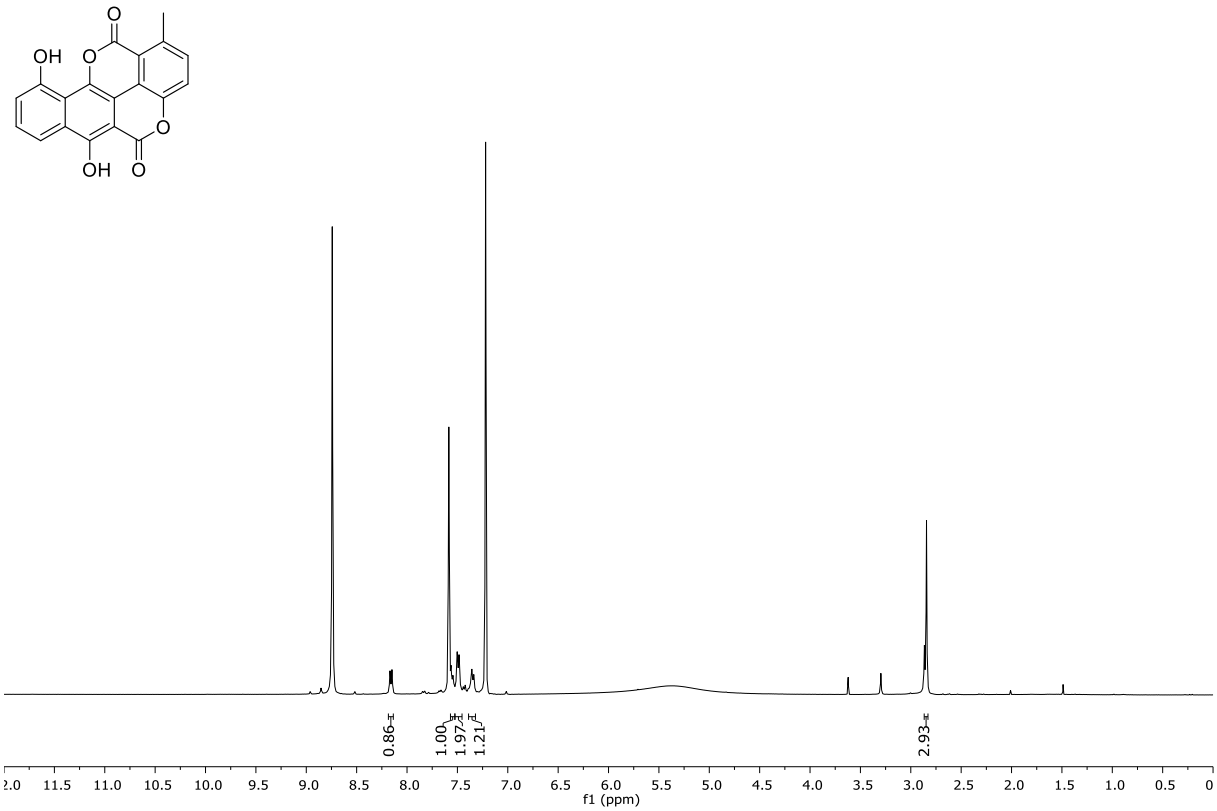

158.6
157.5
156.8
146.9
146.0
139.7
134.6
133.5
133.2
130.2
121.1
119.1
118.9
117.8
117.0
114.4
111.6
110.6
56.8
22.5
f1 (ppm)

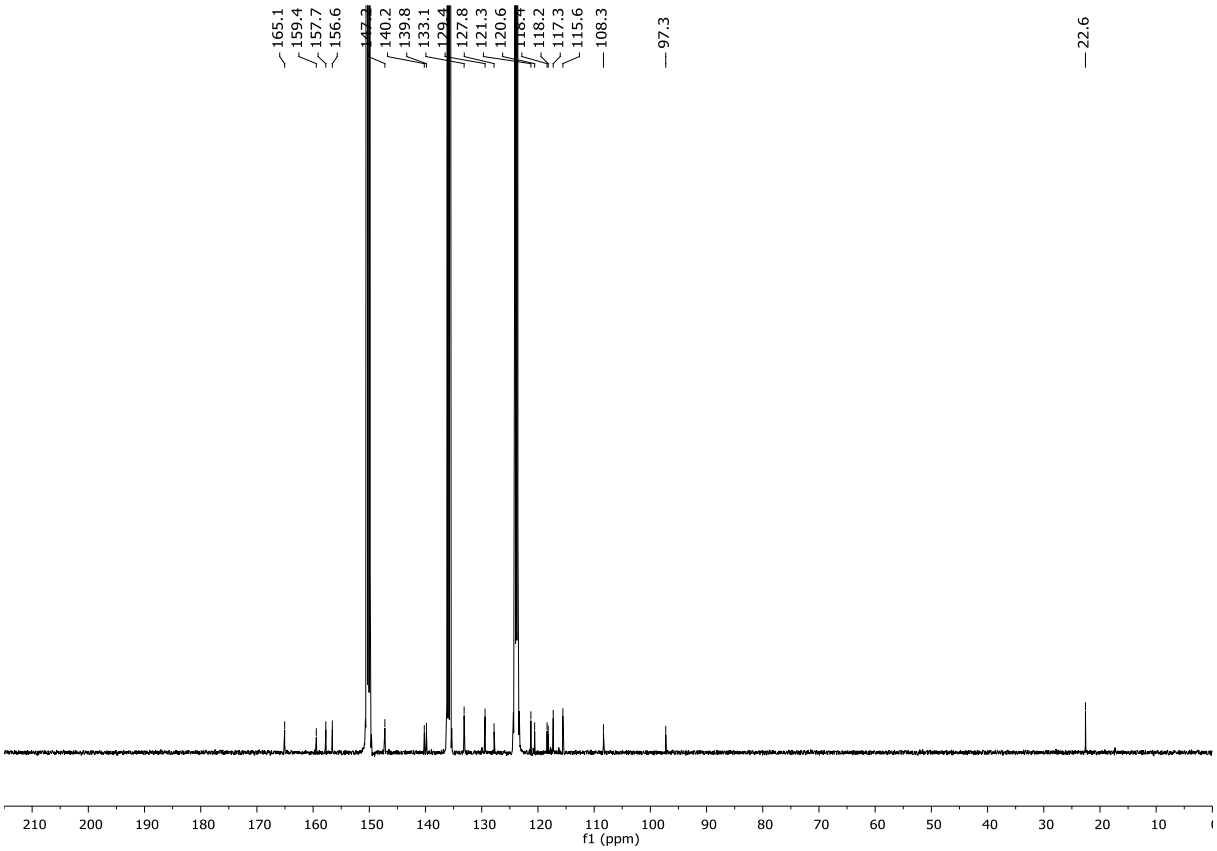

MeO
O
O
O
OMe
O
O
0.93
1.15
0.98
1.00
0.97
2.82
2.96
3.07
f1 (ppm)

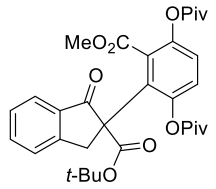

159.2
157.5
156.7
147.2
143.2
139.4
133.1
132.2
129.1
120.9
119.5
118.8
117.3
116.5
110.8
110.7
109.9
107.9
63.6
56.7
22.5
f1 (ppm)


OH
O
O
O
OH
O
0.85
0.95
1.00
1.21
0.94
1.07
1.06
2.92
f1 (ppm)

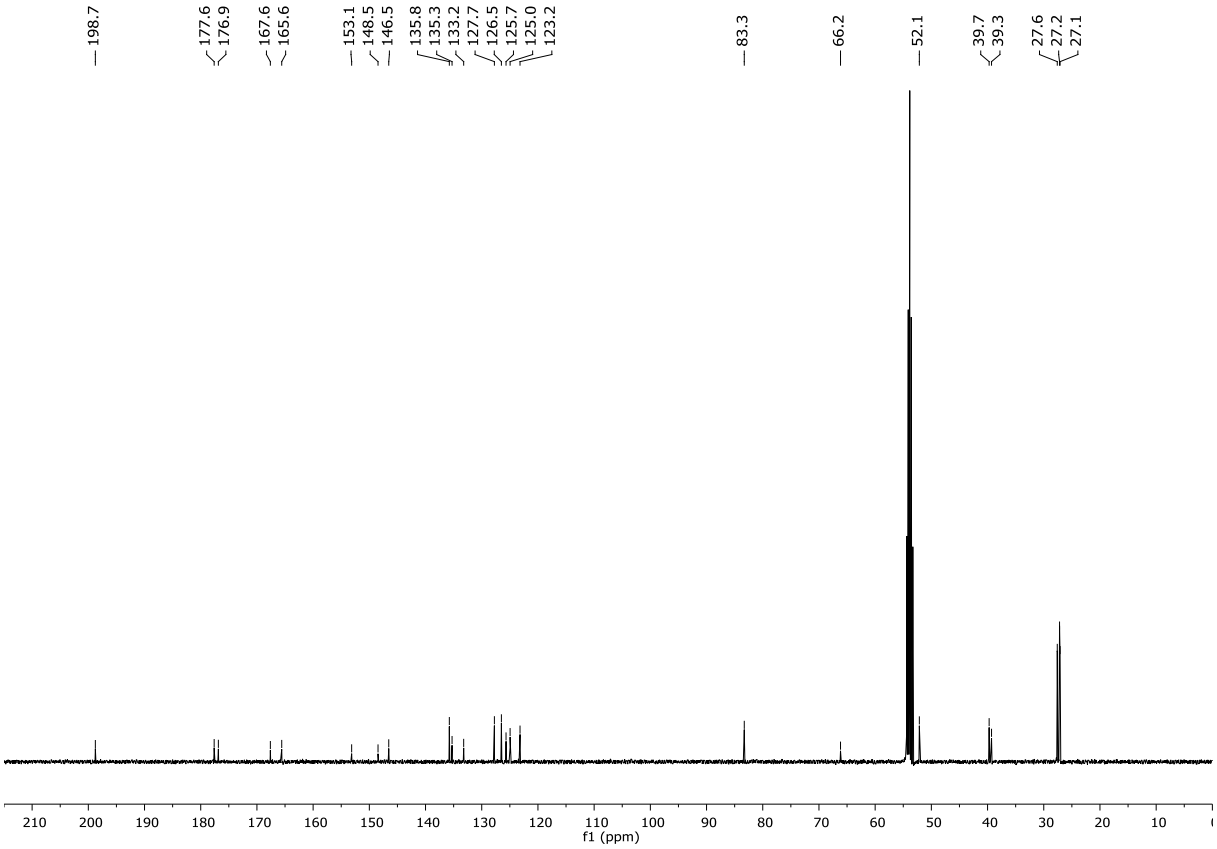

164.7
158.6
157.3
153.8
146.9
140.9
139.2
133.2
129.5
126.7
122.4
121.9
117.8
117.2
116.6
116.1
107.6
96.0
22.5
f1 (ppm)

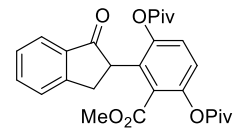

OH
O
O
O
OH
O
0.86
1.00
1.97
1.21
2.93
f1 (ppm)

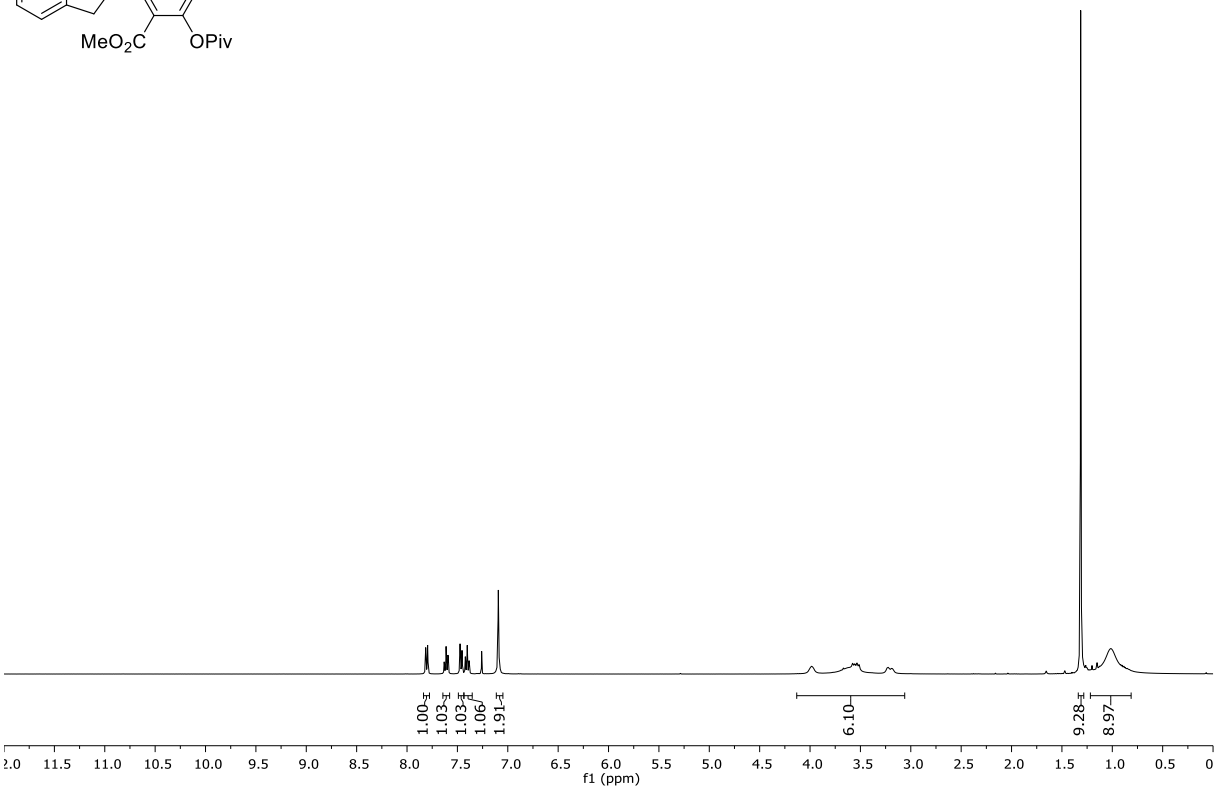

165.1
159.4
157.7
156.6
147.2
140.2
139.8
133.1
129.4
127.8
121.3
120.6
118.4
118.2
117.3
115.6
108.3
97.3
22.6
f1 (ppm)

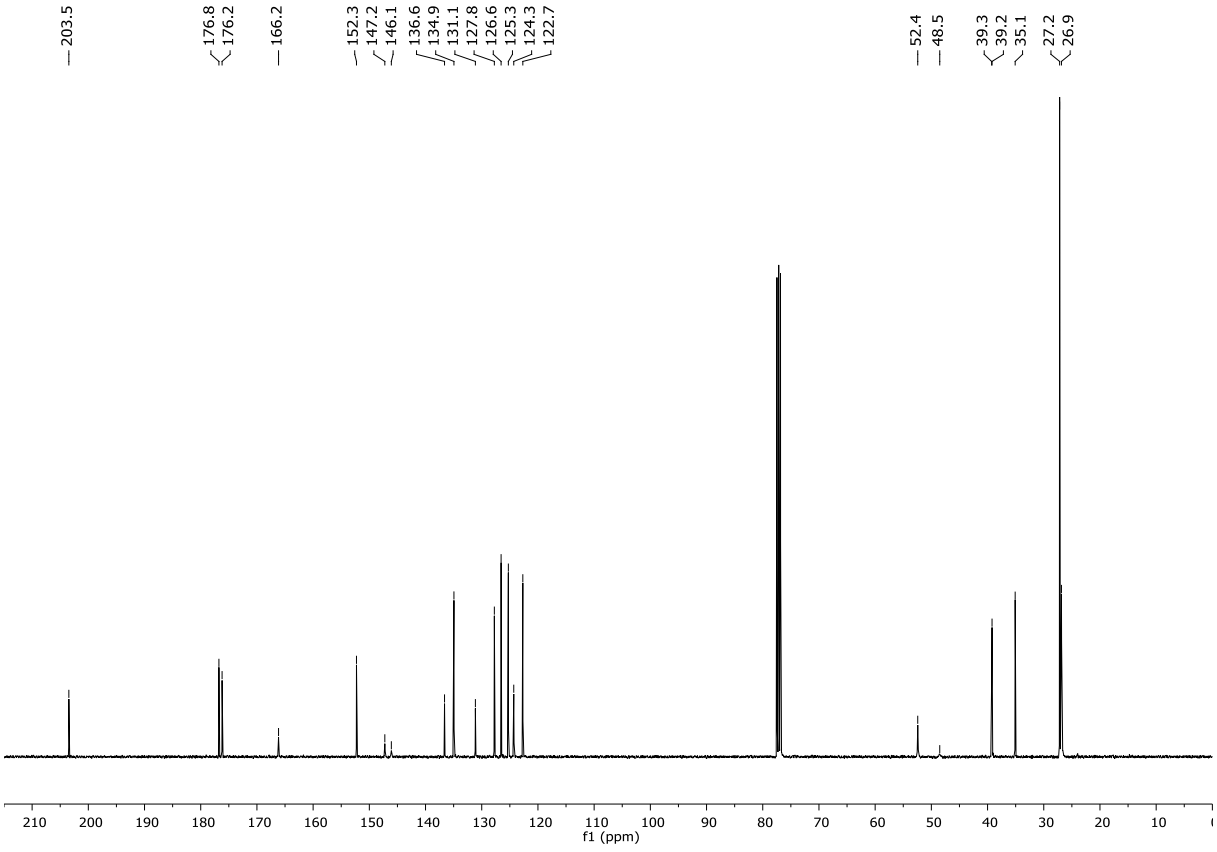

OPiv
MeO2C
O
OPiv
O
t-BuO

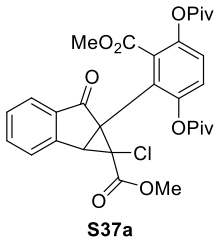
1.00
1.04
1.03
1.06
1.98
1.01
2.90
1.05
9.36
9.44
8.66
f1 (ppm)


198.7
177.6
176.9
167.6
165.6
153.1
148.5
146.5
135.8
135.3
133.2
127.7
126.5
125.7
125.0
123.2
83.3
66.2
52.1
39.7
39.3
27.6
27.2
27.1
f1 (ppm)


O
OPiv
MeO2C
OPiv

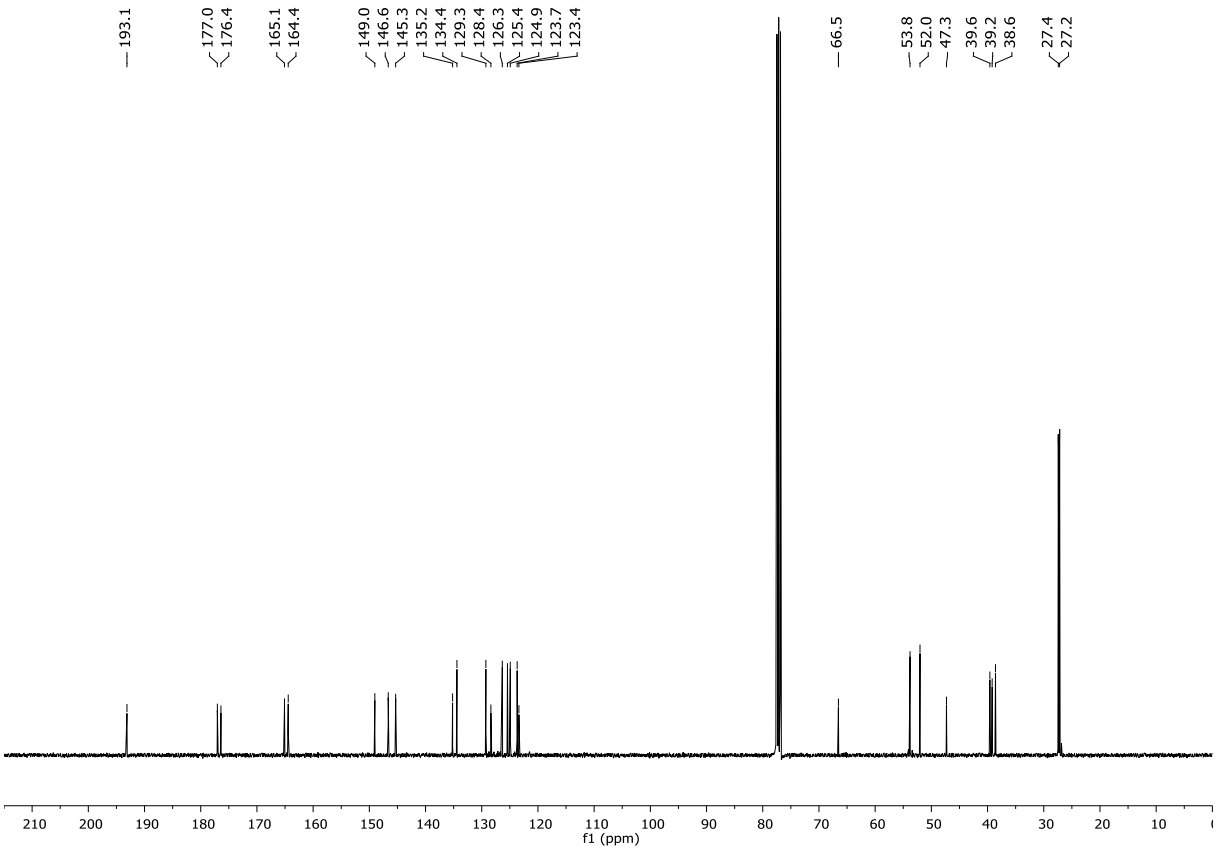

1.00
1.03
1.03
1.06
1.91
6.10
9.28
8.97
f1 (ppm)

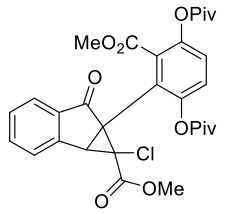

203.5
176.8
176.2
166.2
152.3
147.2
146.1
136.6
134.9
131.1
127.8
126.6
125.3
124.3
122.7
52.4
48.5
39.3
39.2
35.1
27.2
26.9
f1 (ppm)


OPiv
MeO2C
O
OPiv
Cl
O
OMe

S37a

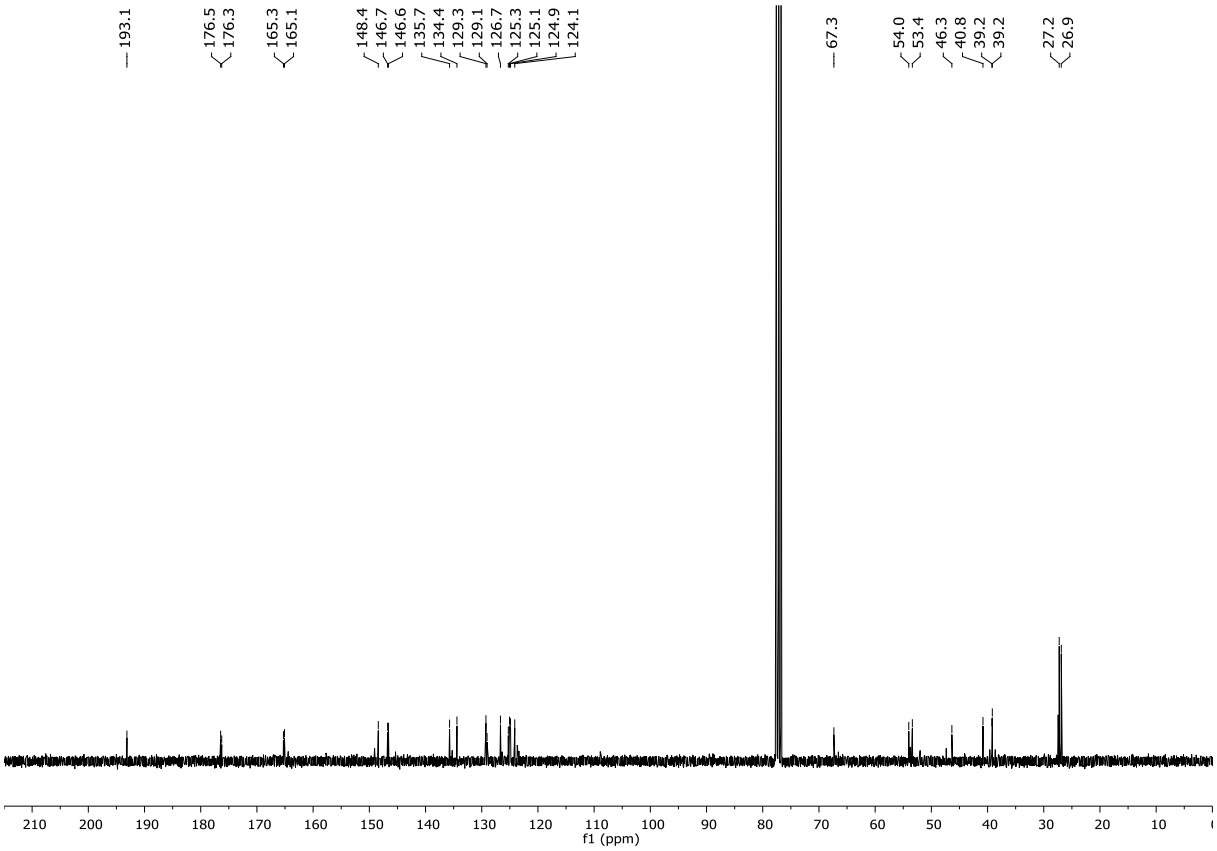
1.00
1.03
1.02
1.08
1.51
1.01
1.00
3.05
3.11
9.42
9.49
f1 (ppm)

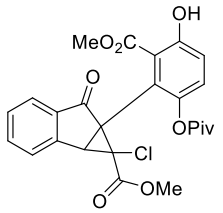

193.1
177.0
176.4
165.1
164.4
149.0
146.6
145.3
135.2
134.4
129.3
128.4
126.3
125.4
124.9
123.7
123.4
66.5
53.8
52.0
47.3
39.6
39.2
38.6
27.4
27.2
f1 (ppm)


OPiv
MeO2C
O
OPiv
Cl
O
OMe

S37b

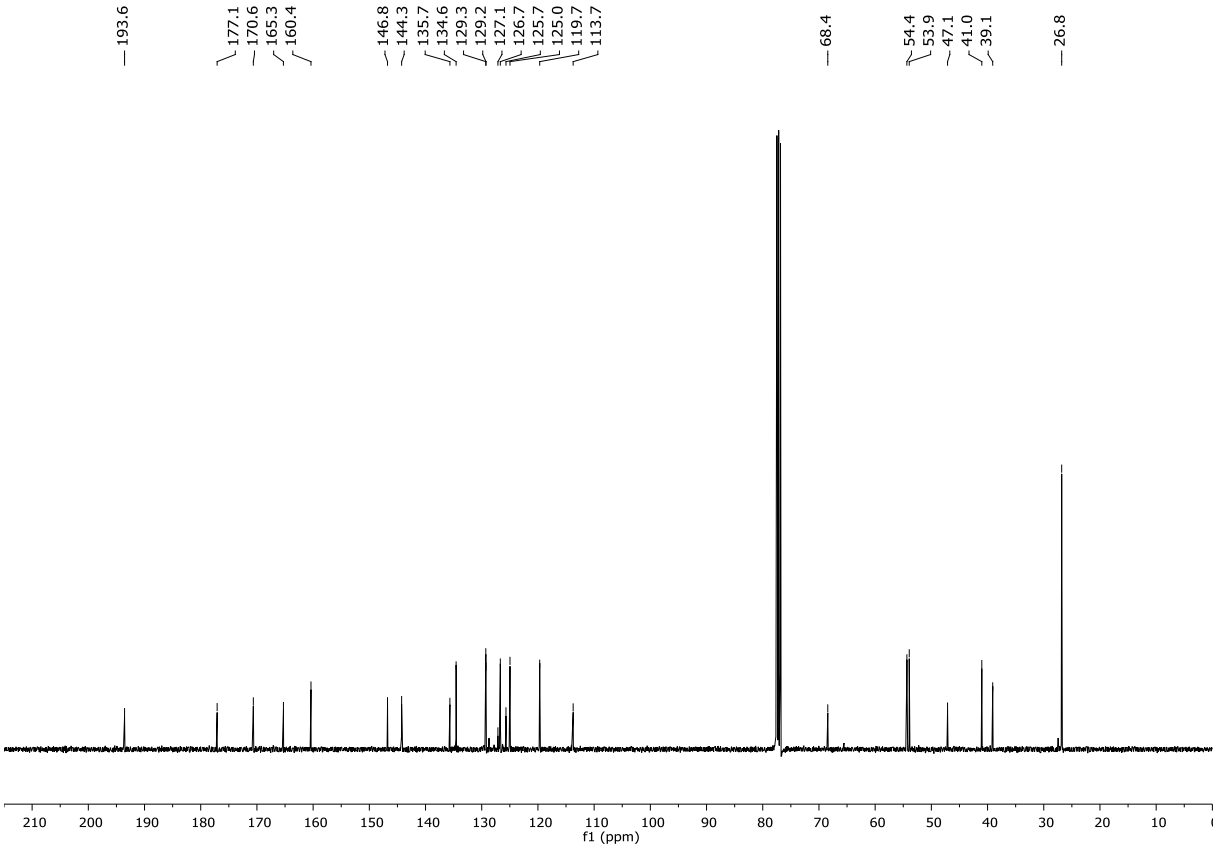
1.00
0.99
1.07
1.07
0.95
0.96
0.86
2.75
2.76
8.98
8.53
f1 (ppm)

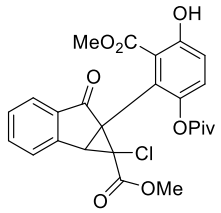

193.1
176.5
176.3
165.3
165.1
148.4
146.7
146.6
135.7
134.4
129.3
129.1
126.7
125.3
125.1
124.9
124.1
67.3
54.0
53.4
46.3
40.8
39.2
39.2
27.2
26.9
f1 (ppm)


OH
MeO2C
O
OPiv
Cl
O
OMe

S38a

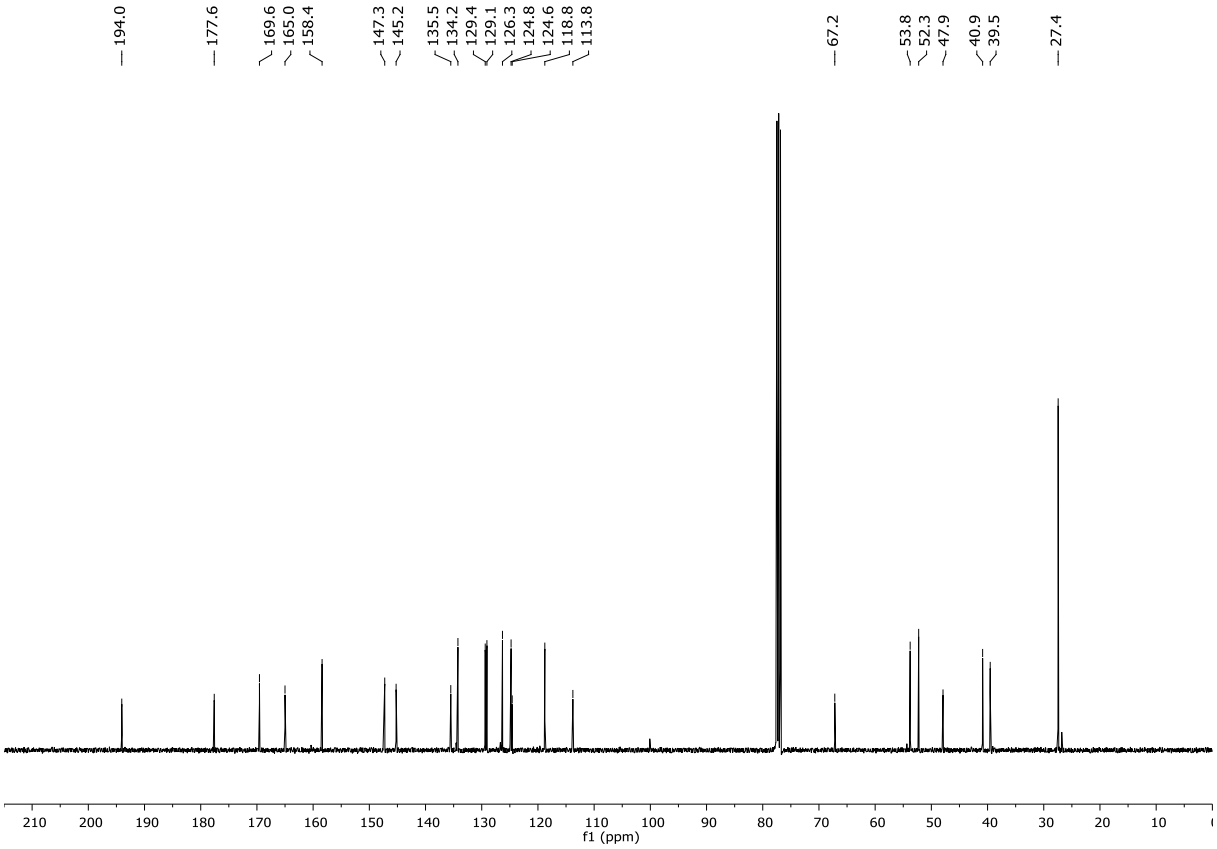
1.00
1.05
1.11
1.15
1.14
1.03
1.13
1.00
3.02
3.09
9.19
f1 (ppm)

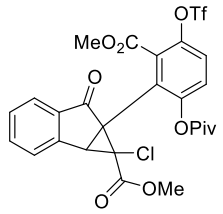

193.6
177.1
170.6
165.3
160.4
146.8
144.3
135.7
134.6
129.3
129.2
127.1
126.7
125.7
125.0
119.7
113.7
68.4
54.4
53.9
47.1
41.0
39.1
26.8
f1 (ppm)


OH
MeO2C
O
OPiv
Cl
O
OMe

S38b

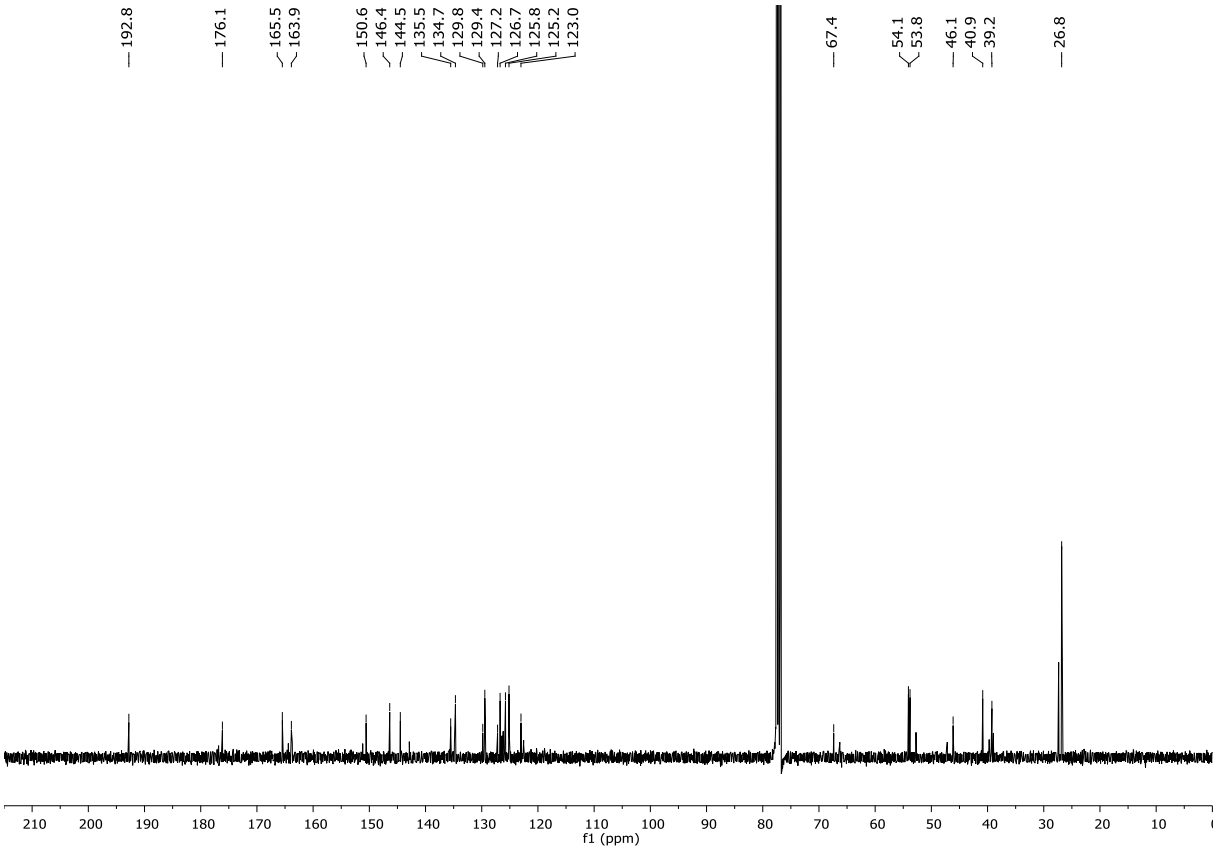
1.00
1.05
1.11
1.09
1.18
1.03
1.14
0.99
3.06
3.00
9.27
f1 (ppm)

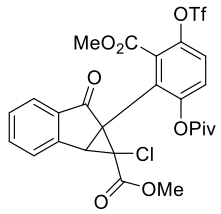

194.0
177.6
169.6
165.0
158.4
147.3
145.2
135.5
134.2
129.4
129.1
126.3
124.8
124.6
118.8
113.8
67.2
53.8
52.3
47.9
40.9
39.5
27.4
f1 (ppm)


OTf
MeO2C
O
OPiv
Cl
O
OMe

S39a

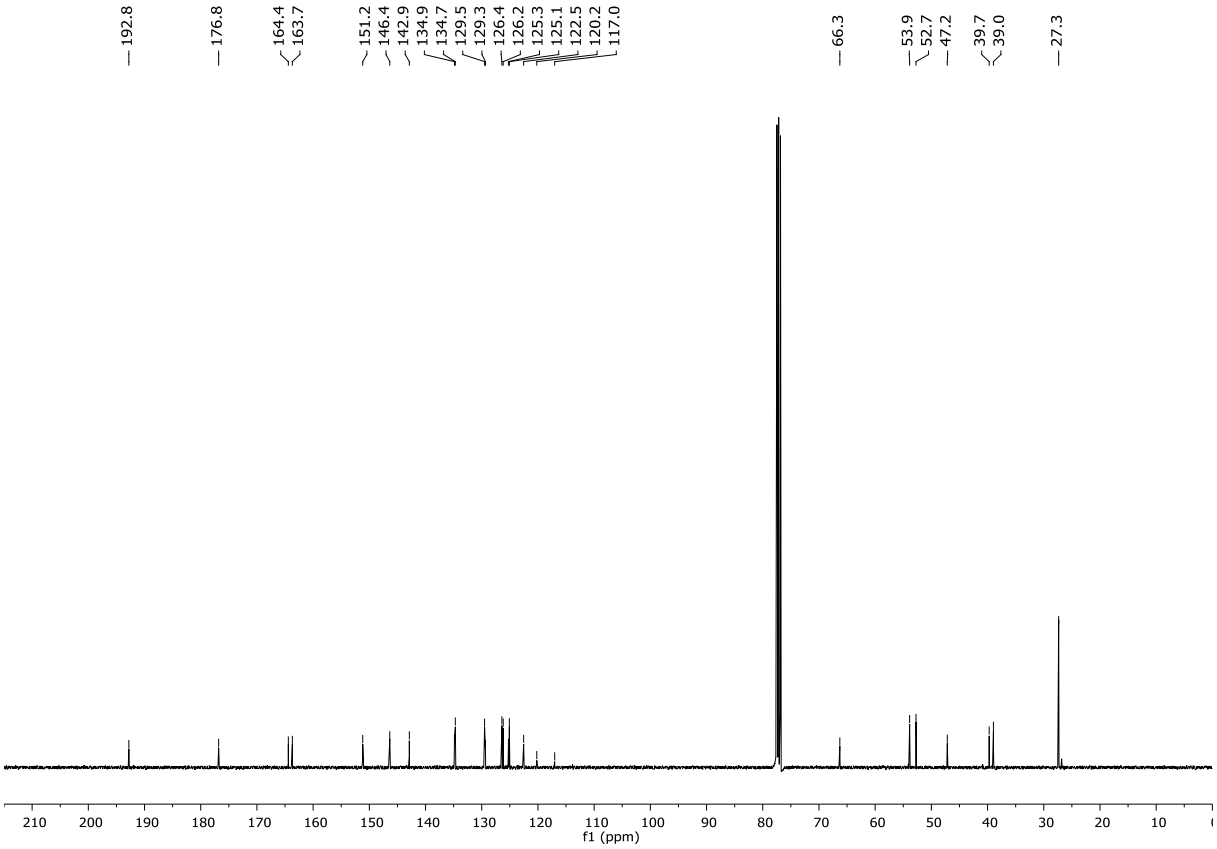
1.00
1.01
1.43
1.09
1.07
0.96
0.98
2.90
3.00
8.91
f1 (ppm)

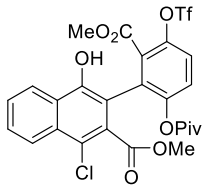

192.8
176.1
165.5
163.9
150.6
146.4
144.5
135.5
134.7
129.8
129.4
127.2
126.7
125.8
125.2
123.0
67.4
54.1
53.8
46.1
40.9
39.2
26.8
f1 (ppm)


OTf
MeO2C
O
OPiv
Cl
O
OMe

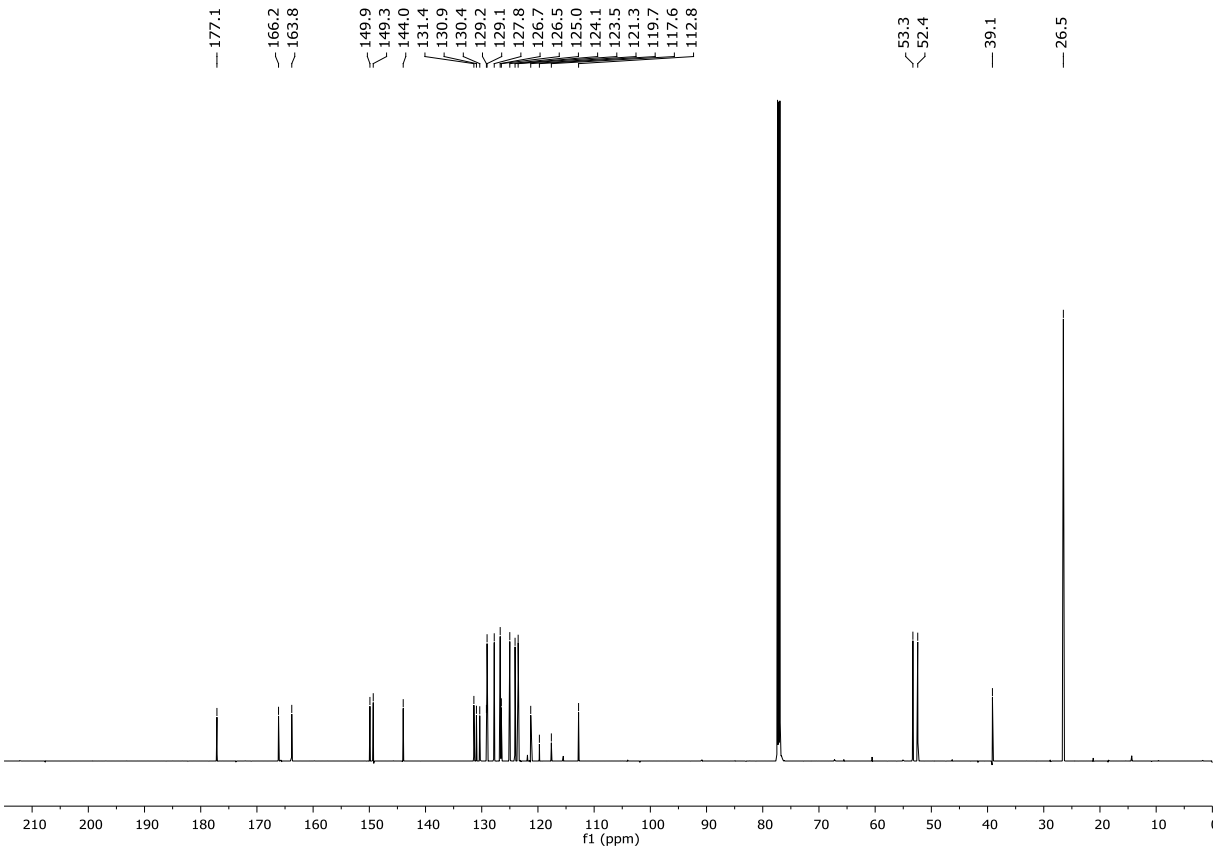
S39b

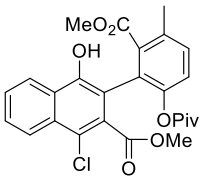
1.00
1.05
1.08
1.12
2.12
0.99
3.07
3.04
9.30
f1 (ppm)


192.8
176.8
164.4
163.7
151.2
146.4
142.9
134.9
134.7
129.5
129.3
126.4
126.2
125.3
125.1
122.5
120.2
117.0
66.3
53.9
52.7
47.2
39.7
39.0
27.3
f1 (ppm)

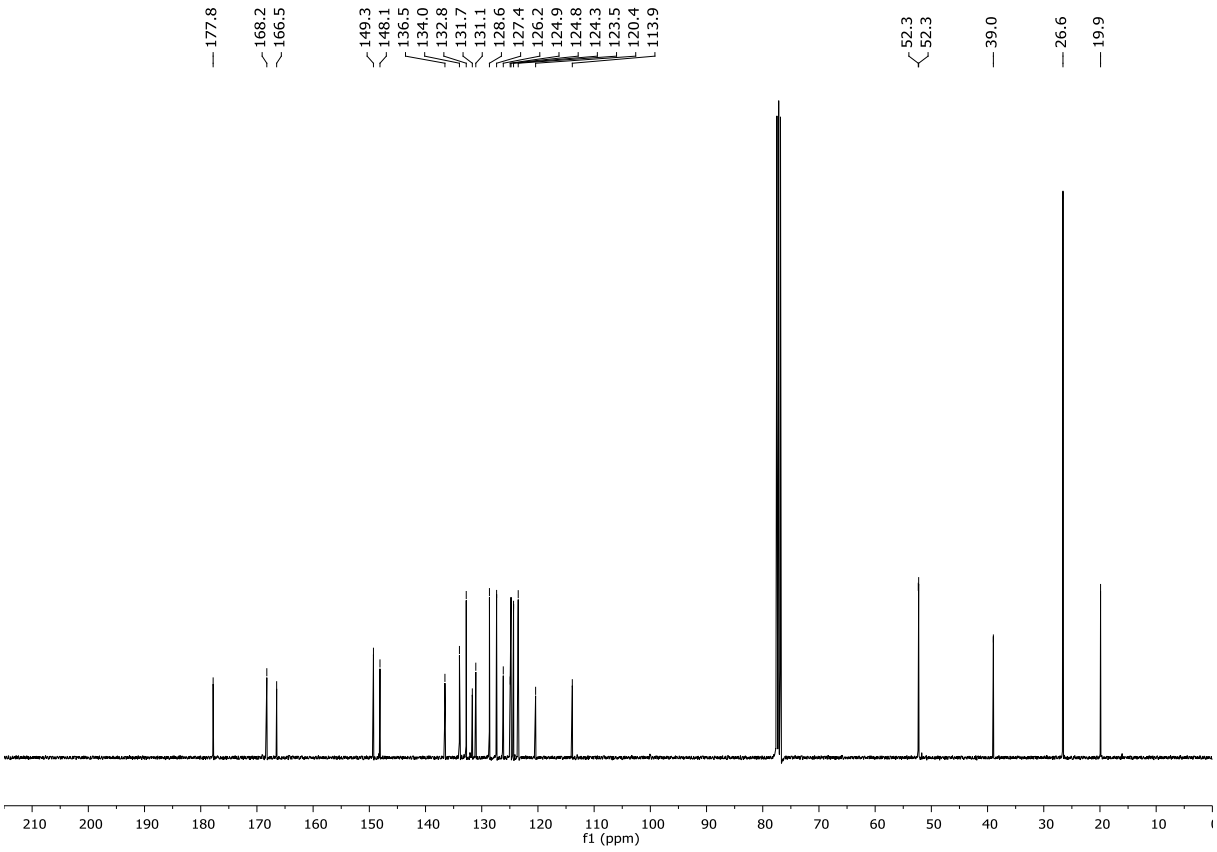

OTf
MeO2C
OH
OPiv
OMe
Cl
O

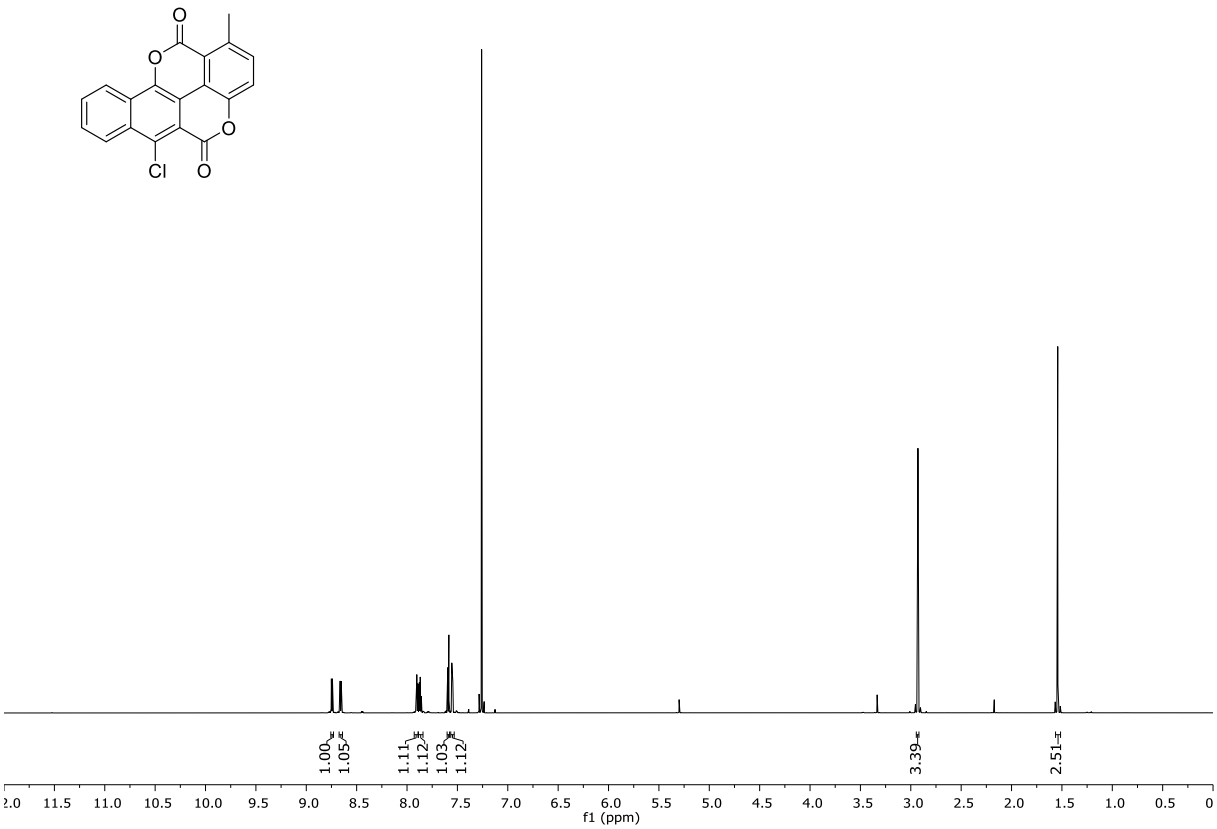
1.00
1.02
1.01
1.05
1.04
1.03
0.97
3.11
2.88
9.29
f1 (ppm)


177.1
166.2
163.8
149.9
149.3
144.0
131.4
130.9
130.4
129.2
129.1
127.8
126.7
126.5
125.0
124.1
123.5
121.3
119.7
117.6
112.8
53.3
52.4
39.1
26.5
f1 (ppm)


MeO2C
OH
OPiv
OMe
Cl
O

1.00
0.96
0.99
1.06
1.00
0.98
0.93
2.92
3.04
3.04
8.82
f1 (ppm)


177.8
168.2
166.5
149.3
148.1
136.5
134.0
132.8
131.7
131.1
128.6
127.4
126.2
124.9
124.8
124.3
123.5
120.4
113.9
52.3
52.3
39.0
26.6
19.9
f1 (ppm)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O
O
Cl
O
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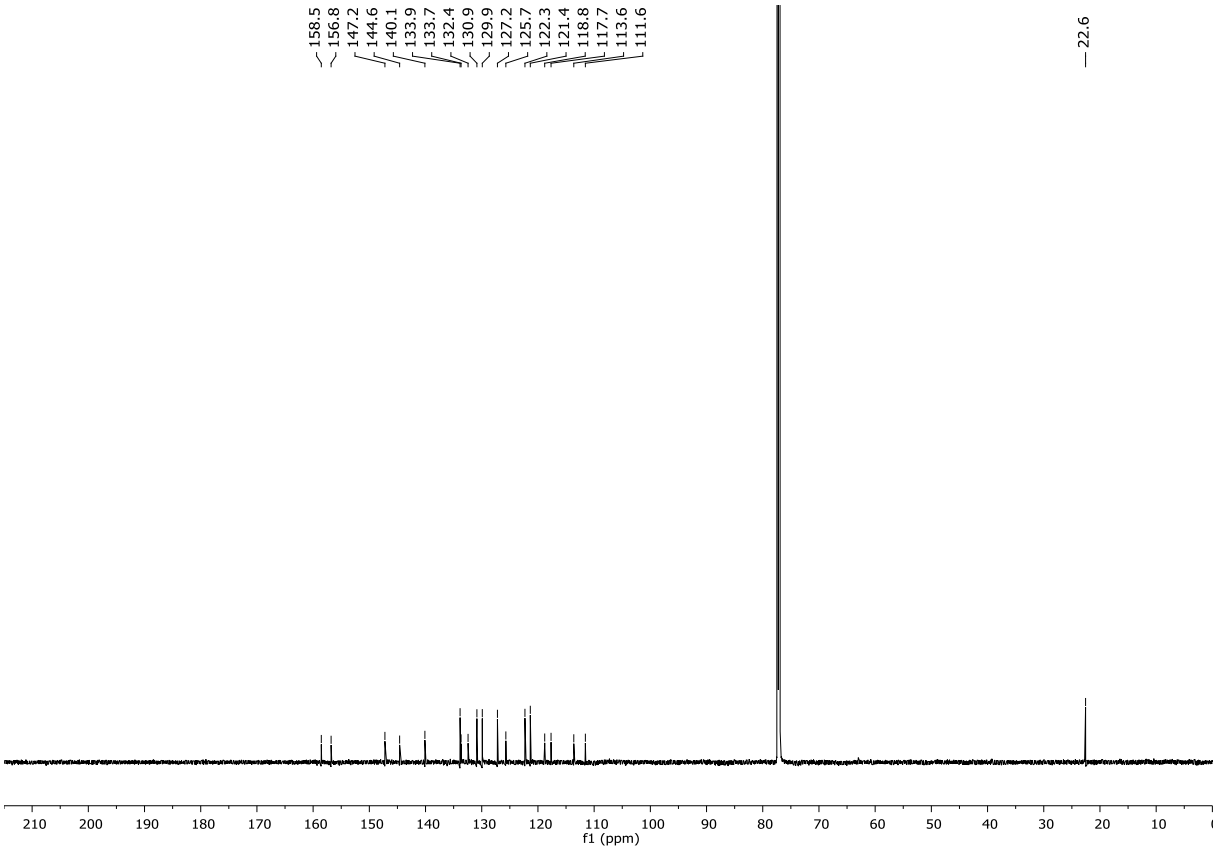
1.05
1.11
1.12
1.03
1.12
3.39
2.51
f1 (ppm)


158.5
156.8
147.2
144.6
140.1
133.9
133.7
132.4
130.9
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127.2
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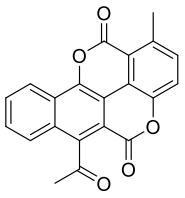
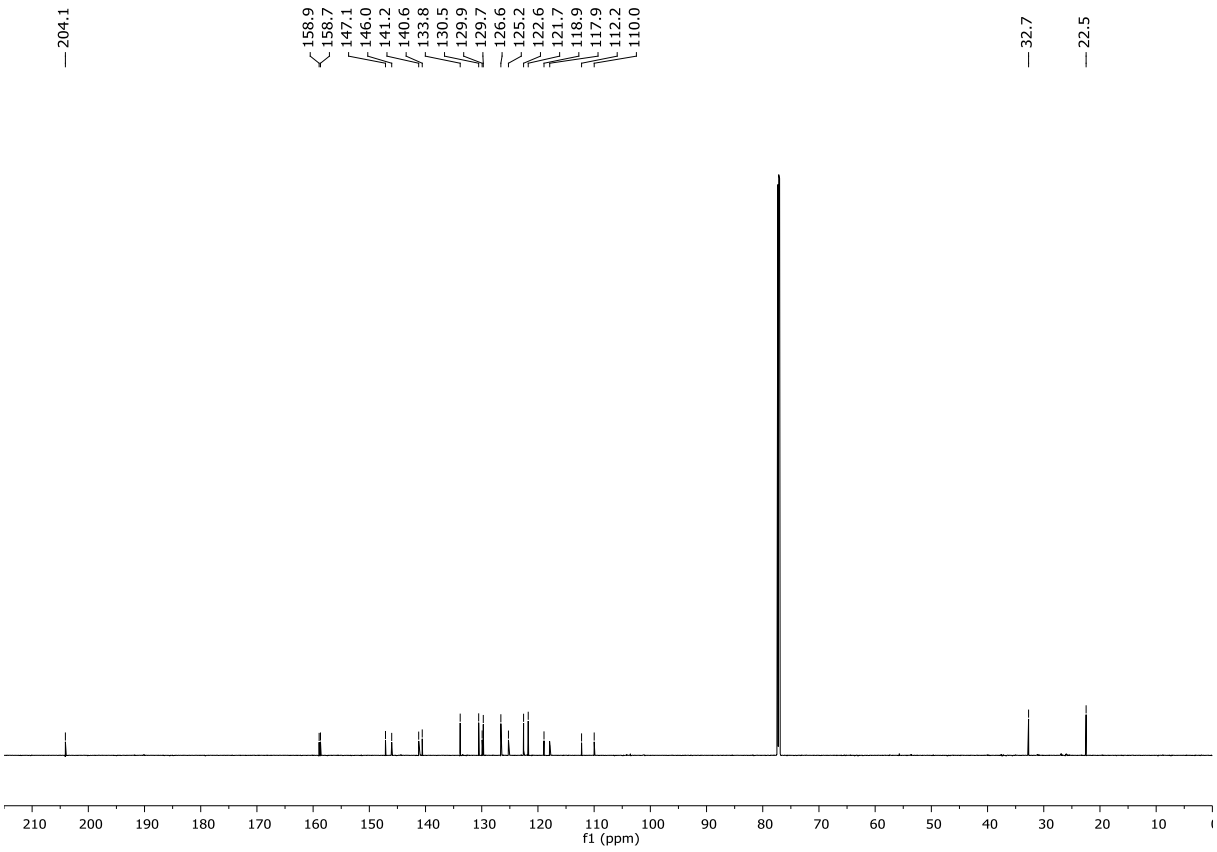
122.3
121.4
118.8
117.7
113.6
111.6
22.6
f1 (ppm)



1.00
0.99
1.07
1.02
0.98
1.06
3.20
3.05
f1 (ppm)


204.1
158.9
158.7
147.1
146.0
141.2
140.6
133.8
130.5
129.9
129.7
126.6
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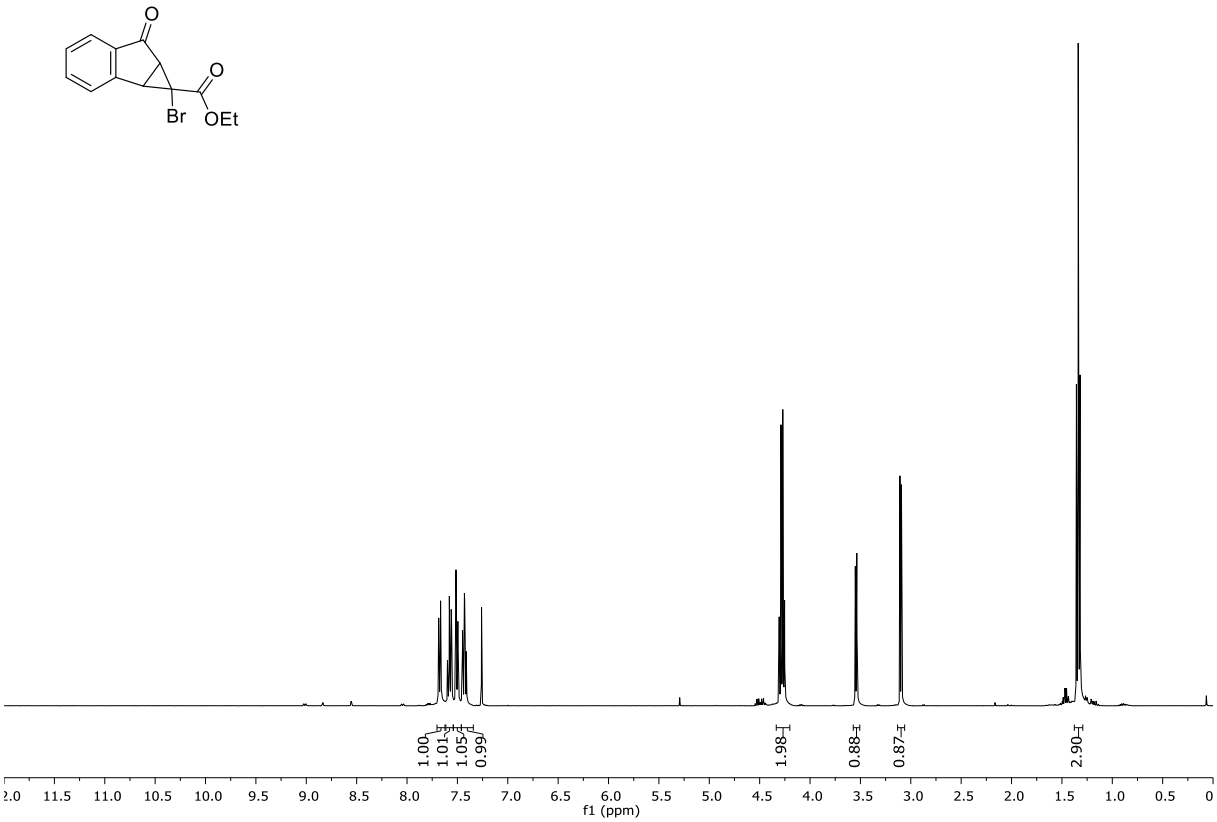
117.9
112.2
110.0
32.7
22.5
f1 (ppm)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O
Br
OEt
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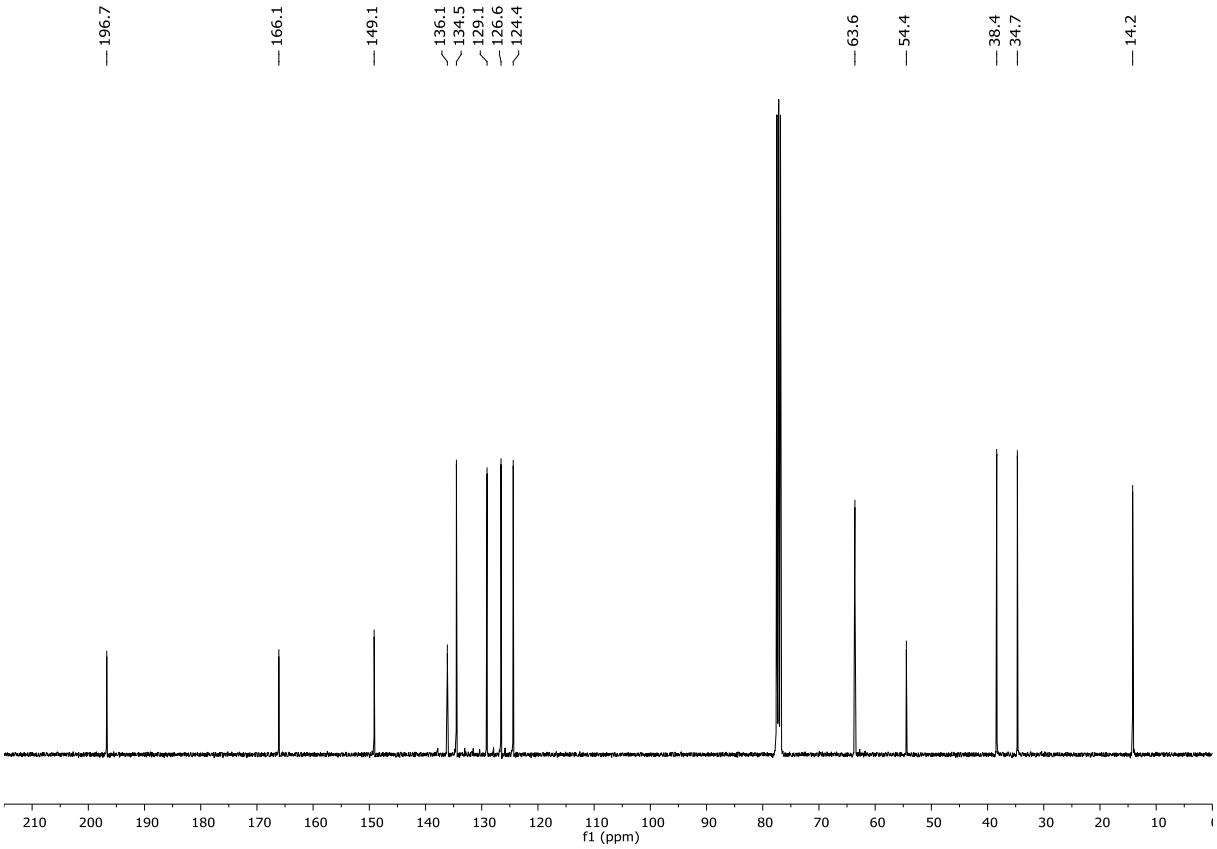
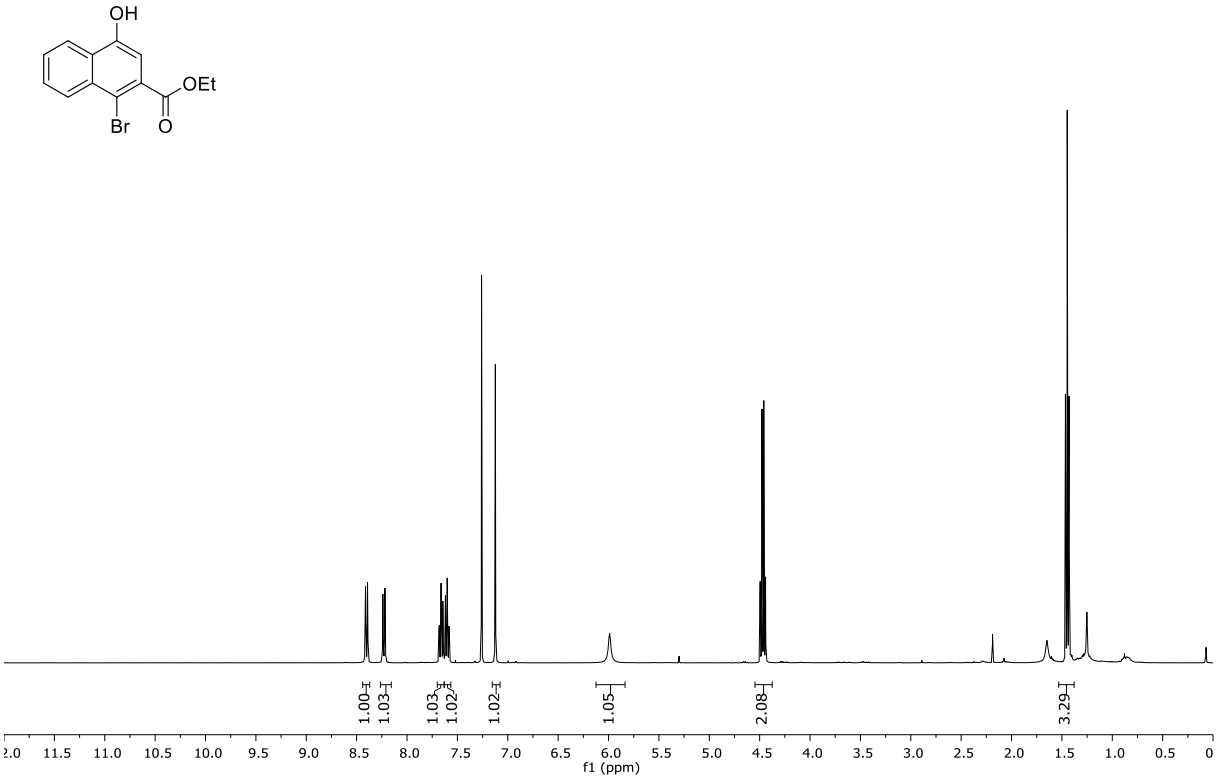
1.01
1.05
0.99
1.98
0.88
0.87
2.90
f1 (ppm)


196.7
166.1
149.1
136.1
134.5
129.1
126.6
124.4
63.6
54.4
38.4
34.7
14.2
f1 (ppm)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OEt
Br
O
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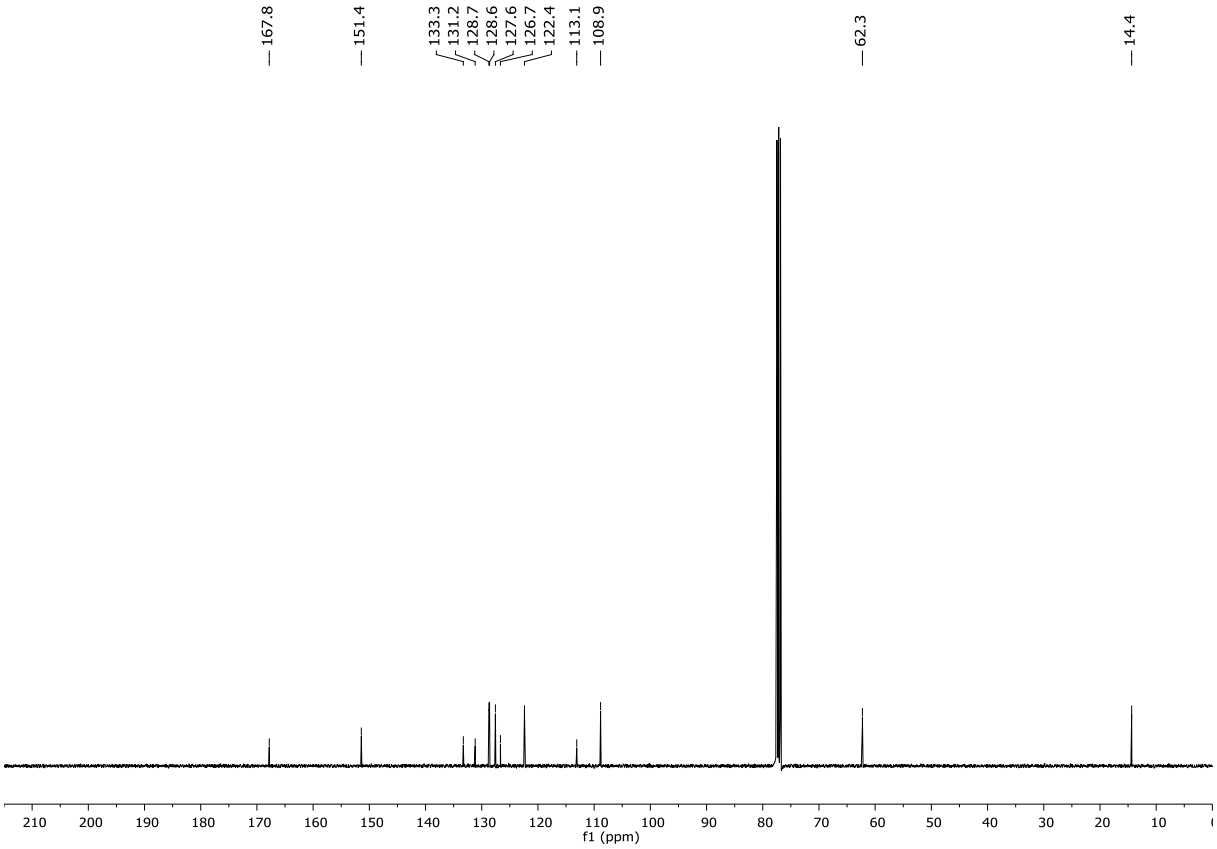
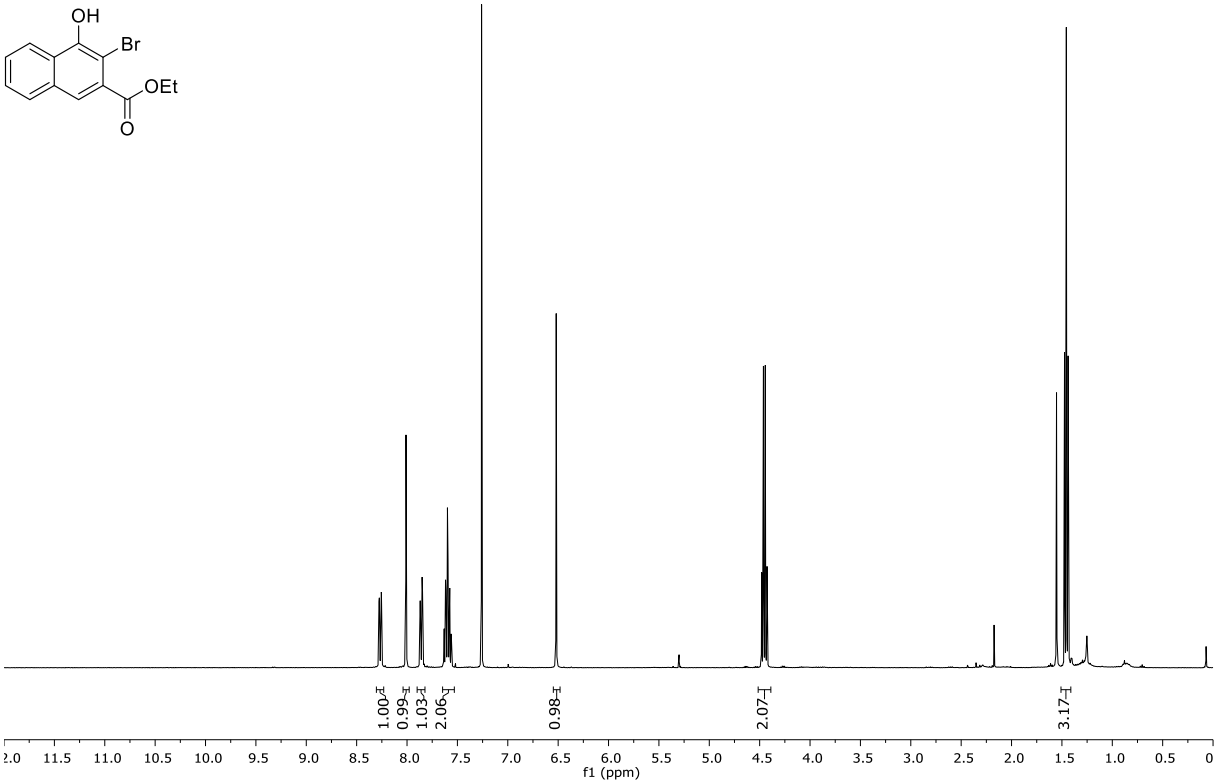
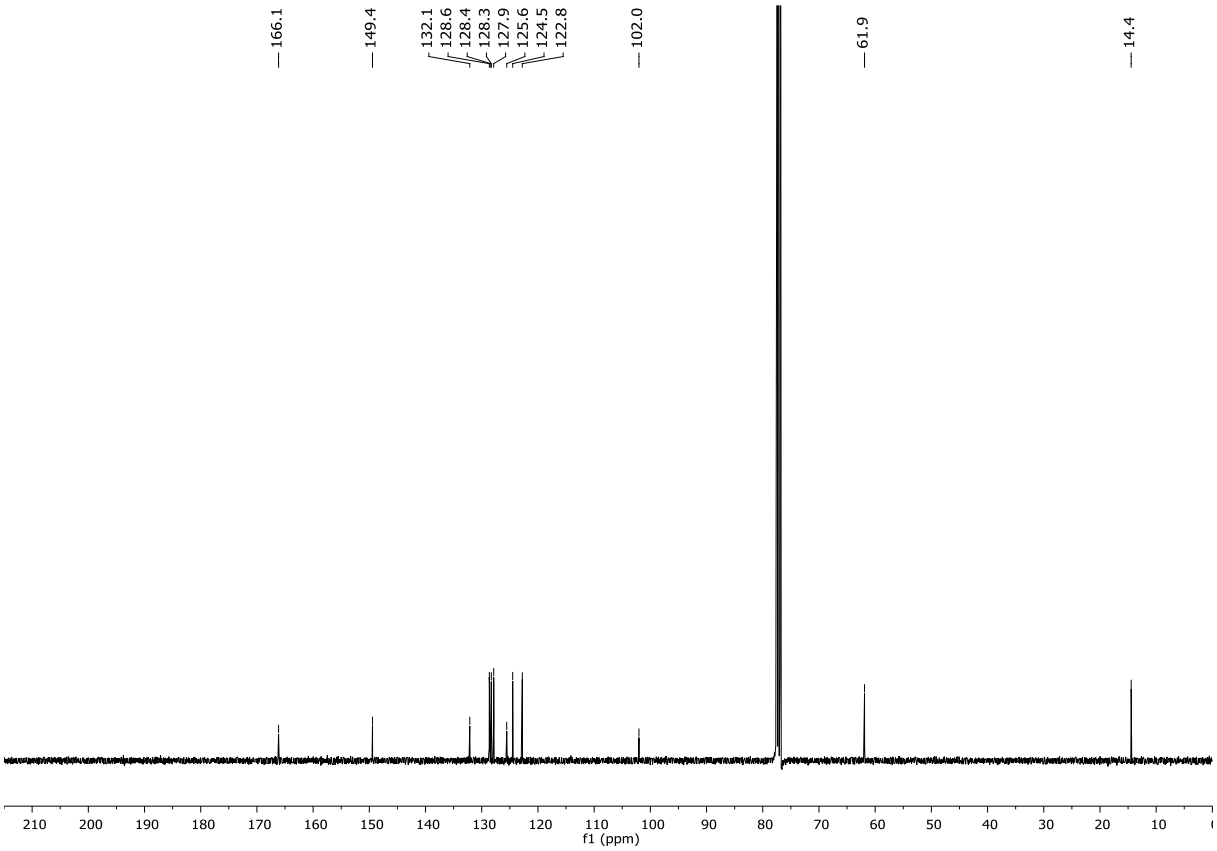
1.03
1.03
1.02
1.02
1.05
2.08
3.29
f1 (ppm)


167.8
151.4
133.3
131.2
128.7
128.6
127.6
126.7
122.4
113.1
108.9
62.3
14.4
f1 (ppm)

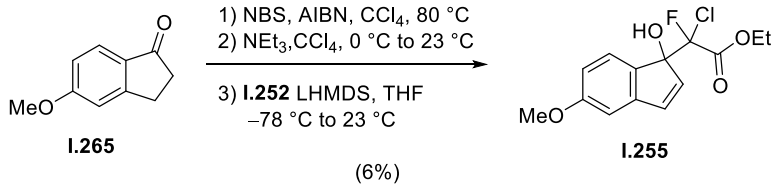

OH
Br
OEt
O
1.00
0.99
1.03
2.06
0.98
2.07
3.17
f1 (ppm)


166.1
149.4
132.1
128.6
128.4
128.3
127.9
125.6
124.5
122.8
102.0
61.9
14.4
f1 (ppm)

7.3 Supporting Information for Chapter 2.2

7.3.1 Experimental Procedures

Tertiary alcohol I.255:



In a pressure vessel, a solution of 5-methoxy-1-indanone (**I.265**) (300 mg, 1.85 mmol, 1 equiv), *N*-bromosuccinimide (362 mg, 2.03 mmol, 1.10 equiv) and 2,2'-azobis(2-methylpropionitrile) (3.00 mg, 0.0185 mmol, 0.0100 equiv) in carbon tetrachloride (8 mL) was stirred at 80 °C for 2 h. The solution was allowed to cool to 23 °C, and then was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

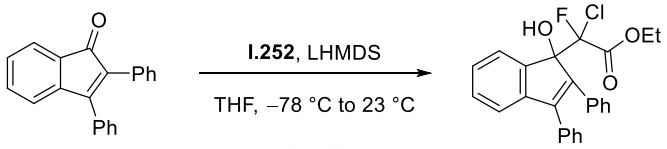
To a solution of the crude bromo-indanone in carbon tetrachloride (10 mL) was added triethylamine (0.900 mL, 6.47 mmol, 3.50 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 1 h, dichloromethane (9 mL) and hexanes (21 mL) were added. The mixture was filtered through a short plug of Celite and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 2.03 mL, 2.03 mmol, 1.10 equiv) in tetrahydrofuran (2 mL) was added ethyl chlorofluoroacetate (**I.252**) (0.225 mL, 1.94 mmol, 1.05 equiv) dropwise at −78 °C. After 30 min, a solution of the crude indenone in tetrahydrofuran (4 mL) was added dropwise at −78 °C. The solution was allowed to warm to 23 °C. After 2 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.255** (36 mg, 6%, dr = 1:0.8) as an orange oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.20 (UV, $KMnO_4$). *Note: Asterix denote the major isomer.* **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.51 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 2.2Hz, 1H)*, 6.78 (d, *J* = 2.4 Hz, 1H)*, 6.77–6.66 (m, 5H, *2 protons of the major isomer and 3 protons of the minor isomer*), 6.55 (d, *J* = 5.8 Hz, 1H)*, 6.30 (d, *J* = 5.8 Hz), 1H), 4.35 (qd, *J* = 7.1, 1.9 Hz, 2H)*, 4.16 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H)*, 3.79 (s, 3H), 3.29 (s, 1H), 3.13 (s, 1H)*, 1.33 (t, *J* = 7.1 Hz, 3H)*, 1.12 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ: 165.2 (d, *J* = 28.6 Hz)*, 164.5 (d, *J* = 27.2 Hz), 161.6, 161.5*, 145.2*, 145.0, 137.3 (d, *J* = 2.4 Hz), 137.2 (d, *J* = 2.8 Hz)*, 135.4 (d, *J* = 0.8 Hz), 135.4 (d, *J* = 0.8 Hz)*, 134.3 (d, *J* = 0.4 Hz), 133.6*, 125.5 (d, *J* = 2.8 Hz), 125.1 (d, *J* = 4.5 Hz)*, 111.0, 110.9*, 109.0, 109.0*, 107.0 (d, *J* = 263,5 Hz), 105.0 (d, *J* = 263.2 Hz)*, 87.3 (d, *J* = 21.9 Hz)*, 86.5 (d, *J* = 22.0 Hz), 63.6 (d, *J* = 0.6 Hz)*, 63.4 (d, *J* = 0.5 Hz), 55.6 (*1 carbon of the major isomer and 1 carbon of the minor isomer*), 14.0*, 13.8. **^{19}F NMR** (282 MHz, $CDCl_3$) δ: −121.3*, −124.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3455 (*br*, *w*), 2981 (*w*), 1752 (*s*), 1613 (*m*), 1568 (*m*), 1474 (*m*), 1273 (*vs*), 1070 (*vs*), 1013 (*vs*), 956 (*s*), 855 (*vs*), 729 (*s*), 691 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{14}O_4ClF$ $[M]^+$: 300.0559; found: 300.0565.

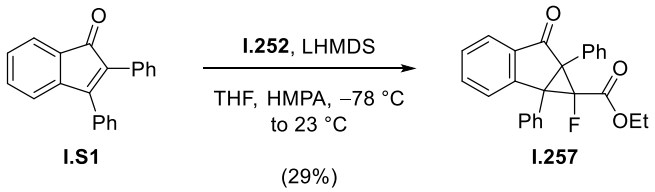
Tertiary alcohol I.256:



To a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 1.86 mL, 1.86 mmol, 1.05 equiv) in tetrahydrofuran (15 mL) was added ethyl chlorofluoroacetate (**I.252**) (0.226 mL, 1.95 mmol, 1.10 equiv) dropwise at −78 °C. After 30 min, 2,3-diphenyl-indenone (**I.S1**) (500 mg, 1.77 mmol, 1 equiv) was added at −78 °C. The solution was allowed to warm to 23 °C. After 4 h, saturated aqueous ammonium chloride solution was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to provide **I.256** (667 mg, 89%, dr = 1:0.6) as a colorless oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.37 (UV, $KMnO_4$). *Note: Asterix denote the major isomer.* **^{1}H NMR** (400 MHz, $CDCl_3$) 7.87 (ddd, *J* = 7.0, 1.6, 0.7 Hz, 1H)*, 7.72 (7.71 (ddd, *J* = 7.3, 2.1, 1.0 Hz, 1H), 7.38–7.14 (m, 22.4H, *14 protons of the major isomer and 14 protons of the minor isomer*), 4.48 (s, 1H)*, 4.08–3.79 (m, 2H), 3.97 (s, 1H), 3.76–3.59 (m, 2H)*, 1.10 (t, *J* = 7.2 Hz, 3H)*, 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.3 (d, *J* = 26.7 Hz)*, 164.4 (d, *J* = 280 Hz), 145.2 (d, *J* = 1.5 Hz)*, 145.1, 144.1, 144.0*, 142.8 (d = 1.5 Hz), 141,9*, 141,4, 141.3*, 134.4, 133.8*, 133.5, 133.5*, 130.4*, 130.1, 130.1*, 129.9, 129.2*, 129.2, 128.5, 128.4*, 128.1*, 128.0, 128,0*, 128.0*, 127.9, 127.8, 127.1, 126.8*, 125.8 (d, *J* = 1.6 Hz)*, 124.4 (d, *J* = 2.2 Hz), 121.3*, 121.2, 107.9 (d, *J* = 261.8 Hz), 105.4 (d, *J* = 266.4 Hz)*, 88.5 (d, *J* = 21.7 Hz), 87.9 (d, *J* = 24.4 Hz)*, 63.6, 63.6*, 13.7, 13.6*. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (*br*, *w*), 3055 (*w*), 2984 (*w*), 1754 (*m*), 1443 (*m*), 1266 (*m*), 1116 (*m*), 1040 (*m*), 953 (*s*), 881 (*m*), 697 (*vs*) cm^{-1}. **HRMS** (ESI) calcd for $C_{25}H_{20}O_3ClFNa$ $[M+Na]^+$: 445.09789; found: 445.09827.

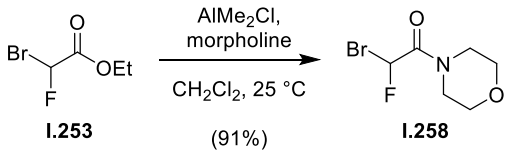
Cyclopropane I.257:



To a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 1.06 mL, 1.06 mmol, 3.00 equiv) in tetrahydrofuran (1 mL) and hexamethylphosphoramide (1 mL) was added ethyl chlorofluoroacetate (**I.252**) (0.123 mL, 1.49 mmol, 3.00 equiv dropwise at −78 °C. After 30 min, 2,3-diphenyl-indenone (**I.S1**) (100 mg, 0.354 mmol, 1 equiv) was added in one portion at −78 °C. The solution was allowed to warm to 23 °C. After 4 h, saturated aqueous ammonium chloride solution was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to provide **I.257** (40 mg, 29%) as a yellow solid. Crystals that were suitable for X-Ray diffraction analysis were obtained by crystalliza-tion from dichloromethane/hexanes.

TLC (20% ethyl acetate in hexanes) R_f = 0.27 (UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (ddd, *J* = 7.5, 1.3, 0.7 Hz, 1H), 7.52 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48–7.26 (m, 11H), 7.02 (dt, *J* = 7.7, 0.8 Hz, 1H), 3.83 (qd, *J* = 7.1, 1.5 Hz, 2H), 0.64 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.7 (d, *J* = 4.9 Hz), 164.0 (d, *J* = 29.4 Hz), 150.7 (d, *J* = 5.1 Hz), 135.1, 133.5 (d, *J* = 0.9 Hz), 132.1 (d, *J* = 1.9 Hz), 130.8 (d, *J* = 1.4 Hz), 130.7 (d, *J* = 1.6 Hz), 130.4 (d, *J* = 1.5 Hz), 128.7, 128.7, 128.3, 128.2, 128.0, 126.4, 124.2, 92.0 (d, *J* = 248.9 Hz), 61.8 (d, *J* = 0.8 Hz), 56.1 (d, *J* = 13.8 Hz), 53.4 (d, *J* = 12.5 Hz), 13.2. **^{19}F NMR** (282 MHz, $CDCl_3$) δ: −194.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2983 (*w*), 1741 (*vs*), 1726 (*vs*), 1602 (*w*) 1463 (*m*), 1277 (*s*), 1113 (*m*), 1014 (*m*), 743 (*m*), 699 (*vs*) cm^{-1}. **HRMS** (ESI) calcd for $C_{25}H_{19}O_3FNa$ $[M+Na]^+$: 409.12159; found: 409.12122.

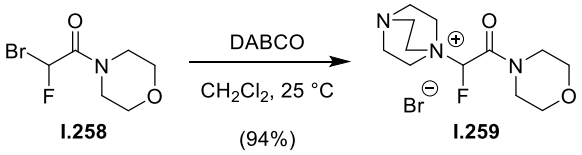
2-Bromo-2-fluoro-1-morpholine-1-yl-ethanone (I.258):



To a solution of dimethylaluminum chloride (1 M in hexanes, 50 mL, 50 mmol, 2.0 equiv) in dichloromethane (100 mL) was added morpholine (4.4 mL, 50 mmol, 2.0 equiv) dropwise at 0 °C. After 30 min, ethyl bromofluoroacetate (**I.253**) (3.0 mL, 25 mmol, 1 equiv) was added dropwise and the solution was allowed to warm to 23 °C, After 3 h, 0.5 M aqueous hydrochloric acid (100 mL) was carefully added

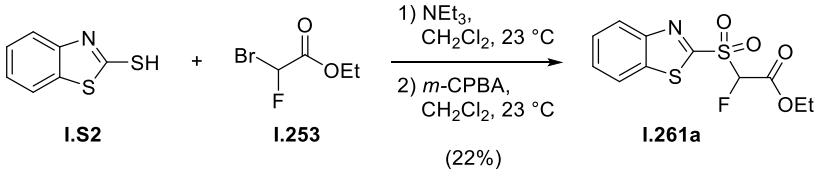
and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to provide **I.258** (5.14 g, 91%) as a white solid. The obtained characterization data were in full agreement with those values reported in the literature.[112e]

DABCO salt (I.259):



To a solution of 2-bromo-2-fluoro-1-morpholine-1-yl-ethanone (**I.258**) (5.14 g, 22.7 mmol, 1 equiv) in dichloromethane (55 mL) was added 1,4-diazabicyclo[2.2.2]octane (2.63 g, 23.4 mmol, 1.03 equiv) at 23 °C. After 5 h, the precipitate was filtered and the filter cake was washed with dichloromethane (100 mL). The crude product was dried under high vacuum to give **I.259** (7.40 g, 94%) as a white solid. The product was used without further purification. The obtained characterization data were in full agreement with those values reported in the literature.[112e]

Sulfone I.261a:

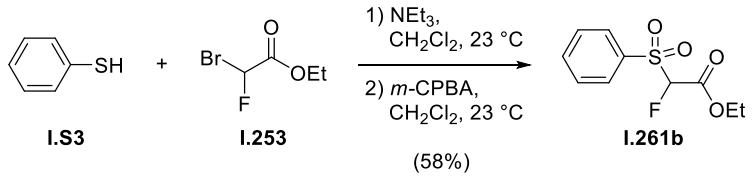


Based on a slightly modified literature procedure,[116] a solution of 2-mercaptobenzothiazole (**I.S2**) (1.53 g, 9.16 mmol, 1.10 equiv) and ethyl bromofluoroacetate (**I.253**) (1.00 mL, 8.33 mmol, 1 equiv) in dichloromethane (10 mL) was treated with triethylamine (1.27 mL, 9.16 mmol, 1.10 equiv) at 23 °C. After 3 h, dichloromethane (10 mL) was added and the organic layer was washed with 1 M aqueous hydrochloric acid (10 mL), saturated aqueous sodium bicarbonate solution (10 mL) and water (10 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used in the next step without further purification.

To a solution of crude thioether in dichloromethane (50 mL) was added *meta*-chloroperbenzoic acid (6.32 g, 27.5 mmol, 3.00 equiv) in three portions at 0 °C. After 30 min, the solution was allowed to warm to 23 °C. After 4.5 h, saturated aqueous sodium thiosulfate solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL), the combined

organic layers were washed with saturated aqueous sodium bicarbonate solution (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (50% dichloromethane in hexanes) to provide **I.261a** (616 mg, 22%) as a yellow solid. The obtained characterization data were in full agreement with those values reported in the literature.[154]

Sulfone I.261b:



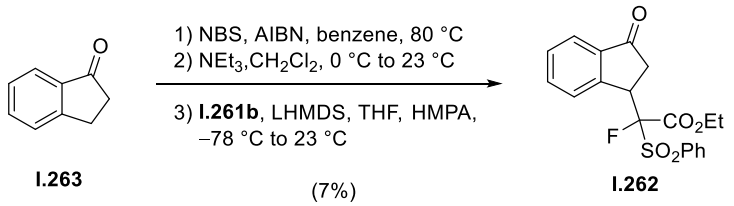
I.S3 I.253 I.261b

Based on a slightly modified literature procedure,[116] a solution of thiophenol (**I.S3**) (0.469 mL, 4.58 mmol, 1.1 equiv) and ethyl bromofluoroacetate (**I.253**) (0.500 mL, 4.16 mmol, 1 equiv) in dichloromethane (5 mL) was treated with triethylamine (0.637 mL, 4.58 mmol, 1.10 equiv) at 23 °C. After 3 h, dichloromethane (10 mL) was added and the organic layer was washed with 1 M aqueous hydrochloric acid (10 mL), saturated aqueous sodium bicarbonate solution (10 mL) and water (10 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was used in the next step without further purification.

To a solution of crude thioether in dichloromethane (25 mL) was added *meta*-chloroperbenzoic acid (2.87 g, 12.5 mmol, 3.00 equiv) in three portions at 0 °C. After 30 min, the solution was allowed to warm to 23 °C. After 16 h, saturated aqueous sodium thiosulfate solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.261b** (590 mg, 58%) as a colorless oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.23 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.98–7.91 (m, 2H), 7.79–7.72 (m, 1H), 7.66–7.58 (m, 2H), 5.56 (d, *J* = 48.0 Hz, 1H), 4.30 (qd, *J* = 7.2, 1.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.1 (d, *J* = 23.8 Hz), 135.5, 134.8, 130.0, 129.5, 97.5 (d, *J* = 232.3 Hz), 63.7, 14.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: –180.33 (d, *J* = 48.0 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2985 (*w*), 1756 (*vs*), 1448 (*m*), 1338 (*vs*), 1243 (*s*), 1148 (*s*), 1080 (*s*), 1019 (*m*), 837 (*m*), 762 (*m*), 686 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{10}H_{11}FO_4{}^{32}S$ [M]$^+$: 246.0357; found: 246.0361.

1,4-Addukt I.262:



I.263 (7%) **I.262**

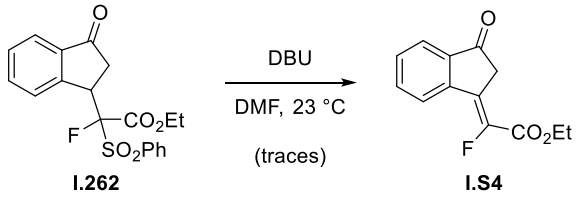
In a pressure vessel, a solution of 1-indanone (**I.263**) (54 mg, 0.407 mmol, 1 equiv), *N*-bromosuccinimide (80 mg, 0.45 mmol, 1.1 equiv) and 2,2'-azobis(2-methylpropionitrile) (0.7 mg, 4.1 μmol, 0.010 equiv) in benzene (2.5 mL) was stirred at 80 °C for 18 h. The solution was allowed to cool to 23 °C, and then was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the bromo-indanone in dichloromethane (10 mL) was added triethylamine (0.198 mL, 1.43 mmol, 3.50 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 30 min., the solution was concentrated. Diethyl ether (20 mL) was added and the mixture was filtered through a short plug of Celite. The filtrate was concentrated and the crude product was used in the next step without further purification.

To a solution of the crude indenone, sulfone **I.261b** (120 mg, 0.488 mmol, 1.20 equiv) and hexamethylphosphoramide (0.106 mL, 0.610 mmol, 1.5 equiv) in tetrahydrofuran (2 mL) was added lithium bis(trimethylsilyl)amide (1 M in THF, 0.610 mL, 0.610 mmol, 1.50 equiv) dropwise at −78 °C. After 2 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.262** (610 mg, 7%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95–7.89 (m, 2H), 7.84–7.78 (m, 1H), 7.76–7.70 (m, 1H), 7.61–7.51 (m, 3H), 7.46 (tt, *J* = 7.4, 0.9 Hz, 1H), 7.32 (dq, *J* = 7.9, 0.9 Hz, 1H), 4.74 (ddd, *J* = 28.2, 8.2, 3.2 Hz, 1H), 4.14–4.00 (m, 2H), 3.43 (ddd, *J* = 19.3, 3.1, 0.9 Hz, 1H), 3.00 (ddd, *J* = 19.3, 8.2, 1.1 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.9, 164.2 (d, *J* = 23.5 Hz), 148.9, 138.3, 135.4, 135.2, 134.9, 130.4, 129.5, 129.4, 126.3, 124.5, 107.5 (d, *J* = 244.6 Hz), 63.6, 41.0 (d, *J* = 20.7 Hz), 37.5 (d, *J* = 3.8 Hz), 13.7. **^{19}F NMR** (282 MHz, $CDCl_3$) δ: −164.3 (d, *J* = 28.1 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2984 (*w*), 1717 (*vs*), 1602 (*w*), 1448 (*m*), 1336 (*s*), 1283 (*s*), 1159 (*s*), 1084 (*m*), 1012 (*w*), 718 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{18}FO_5{}^{32}S$ $[M+H]^+$: 377.0853; found: 377.0872.

***Exo*-elimination product I.S4:**

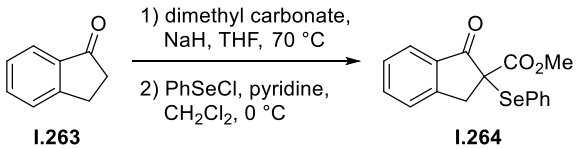


I.262 **I.S4**

To a solution of 1,4-adduct **I.262** (10 mg, 0.027 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.3 mL) was added 1,4-diazabicyclo[2.2.2]octane (40 μL, 0.27 mmol, 10 equiv) at 23 °C. After 1 h, 1 M aqueous hydrochloric acid (5 mL) was carefully added. The aqueous layer was extracted with ethylacetate (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide traces **I.S4** as yellow oil. The configuration of the double bond was not assigned.

TLC (25% ethyl acetate in hexanes) R_f = 0.51 (UV, CAM). *Note: The geometry of the double bond was not assigned.* **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.16 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.88 (ddd, *J* = 7.7, 1.3, 0.8 Hz, 1H), 7.74 (dddd, *J* = 7.9, 7.3, 1.2, 0.6 Hz, 1H), 7.57 (td, *J* = 7.5, 0.9 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.69 (d, *J* = 1.9 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 201.0, 161.1 (d, *J* = 33.5 Hz), 145.9, 143.0 (d, *J* = 265.4 Hz), 138.0, 135.6, 131.1, 123.8, 128.2 (d, *J* = 15.6 Hz), 125.2 (d, *J* = 11.4 Hz), 62.2, 40.8, 14.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ: –123.1 (t, *J* = 2.0 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2988 (*w*), 1718 (*vs*), 1663 (*m*), 1595 (*w*), 1469 (*w*), 1371 (*m*), 1285 (*vs*), 1136 (*m*), 1043 (*m*), 768 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}FO_3$ $[M]^+$: 234.0687; found: 234.0686.

α-Selenide I.264:



I.263 **I.264**

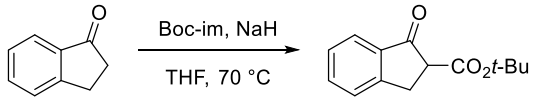
(80%)

To a solution of sodium hydride (182 mg, 4.54 mmol, 2.00 equiv) and dimethyl carbonate (0.383 mL, 4.54 mmol, 2.00 equiv) in tetrahydrofuran (10 mL) was added a solution of 1-indanone (**I.263**) (300 mg, 2.27 mmol, 1 equiv) in tetrahydrofuran (10 mL) at 23 °C and the mixture was heated to 70 °C. After 14 h, saturated aqueous ammonium chloride solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of phenylselenyl chloride (478 mg, 2.50 mmol, 1.10 equiv) in dichloromethane (4 mL) were added pyridine (0.275 mL, 3.41 mmol, 1.5 equiv) and a solution of the crude indanone in dichloromethane (5 mL) at 0 °C. After 4 h, 1 M aqueous hydrochloric acid (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.264** (693 mg, 80%) as an orange oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.26 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.69 (d, *J* = 7.7 Hz, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50–7.45 (m, 2H), 7.37–7.28 (m, 2H), 7.23 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.21–7.16 (m, 2H), 3.91 (d, *J* = 18.3 Hz, 1H), 3.74 (s, 3H), 3.28 (d, *J* = 18.3 Hz, 1H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 197.6, 170.1, 150.9, 138.1, 135.6, 134.9, 130.1, 129.1, 128.3, 126.7, 126.3, 125.0, 57.3, 39.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3056 (w), 2951 (w), 1736 (s), 1708 (vs), 1606 (m), 1437 (m), 1242 (s), 1172 (m), 1074 (m), 1000 (m), 743 (s), 692 (s) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{14}O_3Se$ [M]$^+$: 346.0103; found: 346.0101.

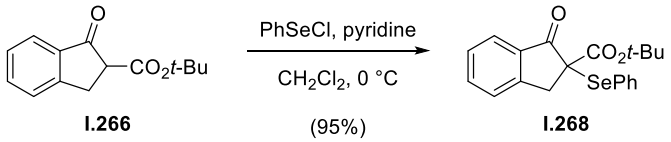
β-Keto ester I.266:



I.263 (89%) **I.266**

A solution of 1-indanone (**I.263**) (1.66 g, 12.5 mmol, 1 equiv) and *tert*-butyl 1*H*-imidazole-1-carboxylate (4.22 g, 25.1 mmol, 2.00 equiv) in tetrahydrofuran (20 mL) was added to a suspension of sodium hydride (1.00 g, 25.1 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred at 70 °C for 7.5 h. The reaction mixture was allowed to cool to 23 °C and then was diluted with saturated aqueous ammonium chloride solution (40 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), the washed organic solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **I.266** (2.59 g, 89%) as a brown oil. The obtained characterization data were in full agreement with those values reported in the literature.[155]

α-Selenide I.268:

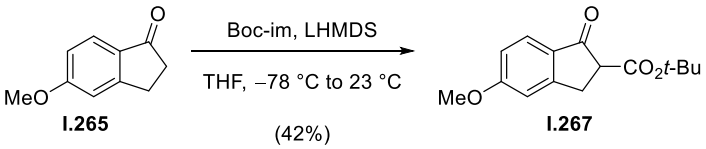


I.266 I.268

To a solution of phenylselenyl chloride (91 mg, 0.47 mmol, 1.1 equiv) in dichloromethane (2 mL) were added pyridine (0.052 mL, 0.65 mmol, 1.5 equiv) and a solution of the β-keto ester **I.266** (0.10 g, 0.43 mmol, 1 equiv) in dichloromethane (2 mL) at 0 °C. After 3.5 h, 1 M aqueous hydrochloric acid (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to provide **I.268** (152 mg, 95%) as an orange oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.53 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.66 (d, *J* = 7.7 Hz, 1H), 7.50–7.40 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 3.86 (d, *J* = 18.2 Hz, 1H), 3.25 (d, *J* = 18.2 Hz, 1H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ: 198.5, 168.5, 151.2, 137.9, 135.3, 135.2, 129.7, 128.9, 128.1, 126.9, 126.2, 124.8, 83.5, 58.6, 39.6, 27.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2979 (*w*), 1705 (*vs*), 1605 (*m*) 1464 (*m*), 1368 (*m*), 1249 (*s*), 1146 (*vs*), 1079 (*m*), 989 (*m*), 906 (*m*), 954 (*s*), 839 (*m*), 740 (*vs*), 692 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{20}O_3{}^{80}Se$ $[M]^+$: 388.0572; found: 388.0575.

β-Keto ester I.267:

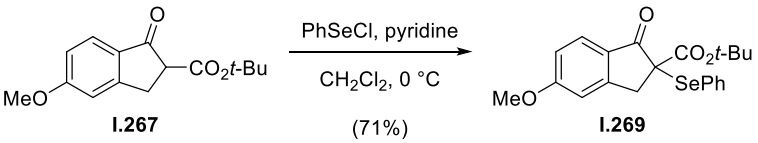


I.265 I.267

To a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.32 mL, 2.3 mmol, 1.5 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.97 mL, 2.3 mmol, 1.5 equiv)) in tetrahydrofuran (1 mL) was added a solution of 5-methoxy-1.indanone (**I.265**) (0.24 g, 1.5 mmol, 1 equiv) in tetrahydrofuran (2 mL) at −78 °C. After 15 min, *tert*-butyl 1*H*-imidazole-1-carboxylate (0.38 g, 2.3 mmol, 1.5 equiv) in one portion and the reaction mixture was allowed to warm slowly to 23 °C. After 23 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash

column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **I.267** (0.17 g, 42%) as a white solid.[156]

α-Selenide I.269:

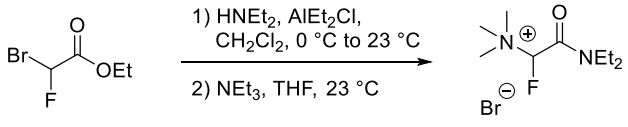


I.267 **I.269**

To a solution of phenylselenyl chloride (133 mg, 0.692 mmol, 1.10 equiv) in dichloromethane (3 mL) were added pyridine (76.0 μL, 0.944 mmol, 1.50 equiv) and a solution of the β-keto ester **I.267** (165 mg, 0.629 mmol, 1 equiv) in dichloromethane (2 mL) at 0 °C. After 6 h, 1 M aqueous hydrochloric acid (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (dichloromethane) to provide **I.269** (205 mg, 71%) as a yellow oil.

TLC (dichloromethane): R*f* = 0.56 (UV, CAM, $KMnO_4$). **^{1}H NMR** (400 MHz, CH_2Cl_2) δ: 7.57 (d, *J* = 8.6 Hz, 1H), 7.50–7.44 (m, 2H), 7.28–7.22 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 6.83 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.62–6.52 (m, 1H), 3.81 (d, *J* = 18.1 Hz, 1H), 3.78 (s, 3H), 3.20 (d, *J* = 18.2 Hz, 1H), 1.43 (s, 9H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 196.5, 168.3, 165.7, 154.1, 137.5, 129.2, 128.5, 127.9, 126.6, 126.1, 115.7, 108.8, 83.0, 59.0, 55.7, 39.3, 27.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2980 (*w*), 1703 (*s*), 1598 (*s*), 1490 (*w*), 1369 (*m*), 1253 (*vs*), 1148 (*vs*), 1082 (*m*), 1023 (*m*), 953 (*vs*), 845 (*m*), 709 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{22}O_4{}^{80}Se$ $[M]^+$: 418.0678; found: 418.0665.

Triethylamine salt I.276:



I.253 **I.276**

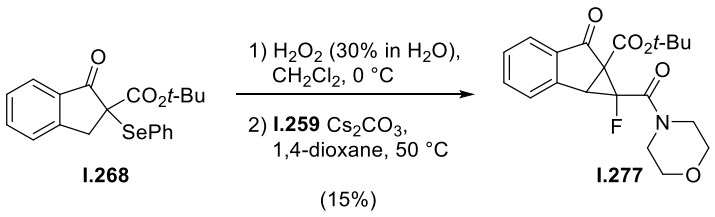
To a solution of diethylaluminum chloride (1 M in hexanes, 3.33 mL, 3.33 mmlol, 2.00 equiv) in dichloromethane (15 mL) was added diethylamine (0.343 mL, 3.33 mmol, 2.00 equiv) dropwise at 0 °C. After 30 min, ethyl bromofluoroacetate (**I.253**) (0.200 mL, 1.67 mmol, 1 equiv) was added dropwise and the solution was allowed to warm to 23 °C, After 4 h, 0.5 M aqueous hydrochloric acid (15 mL) was carefully added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution

(30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of crude 2-bromo-2-fluoro-*N*,*N*-dimethylacetamide (354 mg 1.67 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added triehylamine (0.136 mL, 1.72 mmol, 1.03 equiv) at 23 °C. After 2 h, the precipitate was filtered and the filter cake was washed with ethyl acetate (20 mL). The crude product was dried under high vacuum to give **I.276** (393 mg, 84%) as a white solid. The product was used without further purification.

M.p.: 142 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 42.8 Hz, 1H), 4.07 (dqd, *J* = 14.5, 7.1, 2.8 Hz, 1H), 3.67 (d, *J* = 1.7 Hz, 11H), 3.58–3.45 (m, 1H), 3.47–3.35 (m, 1H), 3.38–3.26 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 159.2 (d, *J* = 21.1 Hz), 96.0 (d, *J* = 228.0 Hz), 51.1 (d, *J* = 2.5 Hz), 43.4, 41.9, 14.8, 12.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: –165.2 (d, *J* = 43.4 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (*w*), 1666 (*vs*), 1473 (*m*), 1360 (*m*), 1276 (*m*), 1212 (*m*), 1130 (*m*), 1105 (*s*), 961 (*s*), 877 (*s*), 694 (*s*) cm^{-1}. **HRMS** (ESI) calcd for $C_9H_{20}FN_2O$ [M–Br]$^+$: 191.15542; found:191.15553.

Fluoro-cyclopropane I.277:



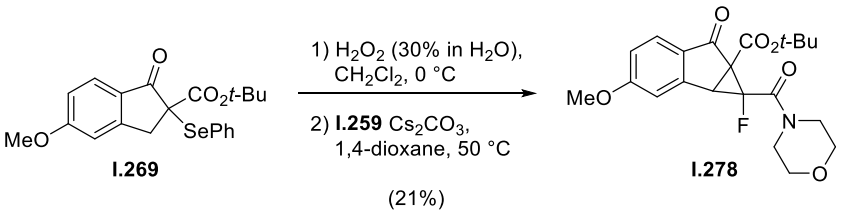
T a solution of α-selenide **I.268** (103 mg, 0.266 mmol, 1 equiv) in dichloromethane (20 mL) was added hydrogen peroxide (30% in H_2O, 81.5 μL, 0.798 mmol, 3.00 equiv) dropwise at 0 °C. After 2 h, dichlormethane (20 mL) and the solution was washed with saturated aqueous sodium bicarbonate solution (40 mL). The washed solution was dried over sodium sulfate and the dried soltion was concentrated. The crude product was used in the next step without further purification.

To DABCO salt **I.259** (98.9 mg, 0.293 mmol, 1.10 equiv) and cesium carbonate (433 mg, 1.33 mmol, 5.00 equiv) was added a solution of crude indenone in 1,4-dioxane (5 mL) and the mixture was heated to 50 °C. After 14 h, the suspension was filtered through a short plug of Celite. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to provide **I.277** (15 mg, 15%) as a yellow oil.

TLC (25% ethyl acetate in hexanes) R_f = 0.21 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 7.6 Hz, 1H), 7.66–7.57 (m, 2H), 7.47–7.41 (m, 1H), 4.22 (s, 1H), 3.86–3.45 (m, 8H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 191.3 (d, *J* = 4.3 Hz), 163.3, 161.1 (d, *J* = 22.4 Hz), 144.2 (d, *J* = 3.6 Hz), 135.8, 135.4, 128.8, 126.9, 124.6, 94.0 (d, *J* = 259.9 Hz), 83.7, 66.6, 66.5, 49.5 (d, *J* = 14.9 Hz), 46.5 (d, *J* = 6.6 Hz), 43.3, 36.3 (d, *J* = 12.3 Hz), 28.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: –193.3. **IR** (Diamond-ATR,

neat) $\tilde{\nu}_{max}$: 2979 (*w*), 1622 (*vs*), 1665 (*vs*) 1441 (*s*), 1370 (*s*), 1303 (*s*), 1238 (*s*), 1152 (*vs*), 1116 (*vs*), 914 (*s*), 849 (*m*), 731 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{22}FNO_5$ [M]$^+$: 375.1482; found: 375.1473.

Fluoro-cyclopropane I.278:

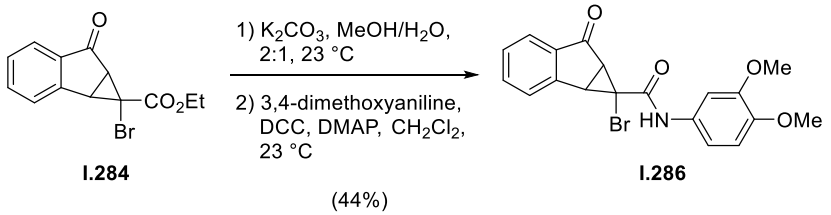


T a solution of α-selenide **I.269** (185 mg, 0.443 mmol, 1 equiv) in dichloromethane (20 mL) was added hydrogen peroxide (30% in H_2O, 0.136 mL, 1.33 mmol, 3.00 equiv) dropwise at 0 °C. After 2 h, dichlormethane (20 mL) and the solution was washed with saturated aqueous sodium bicarbonate solution (40 mL). The washed solution was dried over sodium sulfate and the dried soltion was concentrated. The crude product was used in the next step without further purification.

To DABCO salt **I.259** (165 mg, 0.488 mmol, 1.10 equiv) and cesium carbonate (722 mg, 2.22 mmol, 5.00 equiv) was added a solution of crude indenone in 1,4-dioxane (9 mL) and the mixture was heated to 50 °C. After 12 h, the suspension was filtered through a short plug of Celite. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to provide **I.278** (37 mg, 21%) as a yellow oil.

TLC (25% ethyl acetate in hexanes): R*f* = 0.14 (UV, CAM). **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.10 (d, *J* = 1.3 Hz, 1H), 3.89 (s, 3H), 3.81–3.47 (m, 8H), 1.45 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 189.4 (d, *J* = 4.0 Hz), 165.8, 163.4, 161.2 (d, *J* = 22.5 Hz), 147.2 (d, *J* = 3.9 Hz), 128.6, 126.4, 115.5, 111.5, 93.5 (d, *J* = 259.8 Hz), 83.5, 66.6, 66.5, 56.0, 49.7 (d, *J* = 15.1 Hz), 46.5 (d, *J* = 6.7 Hz), 43.3, 35.7 (d, *J* = 12.3 Hz), 28.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ: –193.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (*w*), 1716 (*s*), 1661 (*s*), 1600 (*s*), 1441 (*m*), 1369 (*m*), 1248 (*vs*), 1152 (*vs*), 1084 (*vs*), 907 (*s*), 834 (*s*), 728 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{24}FNO_6$ [M]$^+$: 405.1582; found: 405.1572.

Bromo-cyclopropane I.286:



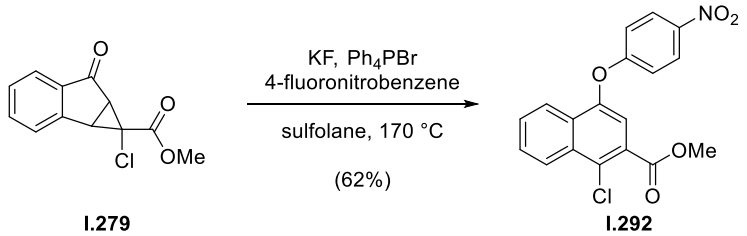
To a solution of bromo-cyclopropane **I.284** (20 mg, 0.068 mmol, 1 equiv) in methanol (1.2 mL) and water

(0.6 mL) was added potassium carbonate (47 mg, 0.34 mmol, 5.0 equiv) at 23 °C. After 2 h, 2 M aqueous hydrochloric acid (5 mL) was carefully added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the crude acid in dichloromethane (3 mL) were added 3,4-dimethoxyaniline (13 mg, 0.081 mmol, 1.2 equiv), *N*,*N*'-dicyclohexylcarbidiimide (DCC) (17 mg, 0.081 mmol, 1.2 equiv) and 4-dimethylaminopyridine (1.7 mg, 0.014 mmol, 0.20 equiv) at 23 °C, After 20 h, the solution was concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide **I.286** (12 mg, 44%) as colorless oil, which contains minor impurities of *N*,*N*'-dicyclohexylcarbidiimide.

TLC (50% ethyl acetate in hexanes) R_f = 0.47 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.70 (ddt, *J* = 7.6, 1.3, 0.6 Hz, 1H), 7.60 (td, *J* = 7.4, 1.2 Hz, 1H), 7.53 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.45 (td, *J* = 7.4, 1.1 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.73 (d, *J* = 5.9 Hz, 1H), 3.21 (d, *J* = 5.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 197.4, 162.8, 149.8, 149.2, 146.8, 136.1, 134.6, 130.3, 129.0, 126.6, 124.5, 112.7, 111.3, 105.1, 60.0, 56.2, 56.1, 38.7, 34.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3336 (*w*), 2935 (*w*), 2254 (*w*), 1715 (*s*) 1669 (*s*), 1605 (*s*), 1512 (*vs*), 1464 (*s*), 1406 (*m*), 1226 (*s*), 1136 (*s*), 1025 (*s*), 910 (*s*), 727 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{16}BrNO_4$ $[M]^+$: 401.0257; found: 401.0250.

Chloronaphthol I.292:



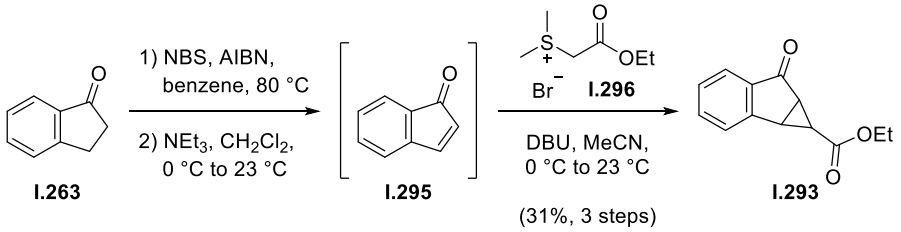
I.279 **I.292**

A solution of cyclopropane **I.279** (50 mg, 0.21 mmol, 1 equiv) potassium fluoride (14 mg, 0.23 mmol, 1.1 equiv), tetraphenylphosphonium bromide (4.4 mg, 0.011 mmol, 0.050 equiv) and 4-fluoronitrobenzene (25 μL, 0.23 mmol, 1.1 equiv) in sulfolane (2 mL) was heated to 170 °C. After 0.5 h, water (10 mL) and diethyl ether (10 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (15% ethyl acetate in hexanes) to provide **I.292** (47 mg, 62%) as an orange solid.

TLC (20% ethyl acetate in hexanes) R_f = 0.61 (UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.54 (dt, J = 8.5, 1.0

Hz, 1H), 8.25–8.19 (m, 2H), 8.03 (ddd, *J* = 8.3, 1.3, 0.7 Hz, 1H), 7.74 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.65 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.48 (s, 1H), 7.10–7.03 (m, 2H), 3.97 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.0, 163.1, 149.5, 143.3, 132.7, 129.4, 129.2, 129.0, 129.0, 127.8, 126.6, 126.4, 122.1, 117.4, 116.4, 53.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1732 (*m*), 1589 (*s*), 1517 (*s*), 1454 (*m*), 1339 (*vs*), 1240 (*vs*), 1163 (*m*), 1110 (*m*), 1062 (*m*), 861 (*m*), 764 (*m*) (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{12}{}^{35}ClNO_5$ $[M]^+$: 357.0399; found: 357.0401.

Cyclopropane I.293:

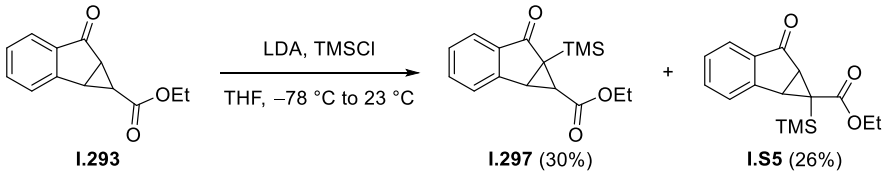


In a pressure vessel, a solution of 1-indanone (**I.263**) (106 mg, 0.800 mmol, 1 equiv), *N*-bromosuccinimide (157 mg, 0.88 mmol, 1.10 equiv) and 2,2'-azobis(2-methylpropionitrile) (1.3 mg, 8.00 μmol, 0.0100 equiv) in benzene (4 mL) was stirred at 80 °C for 8 h. The solution was allowed to cool to 23 °C, and then was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the bromo-indanone in dichloromethane (8 mL) was added triethylamine (0.556 mL, 4.00 mmol, 5.00 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 30 min., the solution was concentrated. Diethyl ether (20 mL) was added and the mixture was filtered through a short plug of Celite. The filtrate was concentrated and the crude product was used in the next step without further purification.

To a solution of (ethoxycarbonylmethyl)dimethylsulfonium bromide (**I.296**) (183 mg, 0.800 mmol, 1 equiv) in acetonitrile (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.143 mL, 0.960 mmol, 1.20 equiv) dropwise at 0 °C. After 45 min the crude indenone (**I.295**) in acetonitrile (3 mL) was dropwise and the solution was allowed to warm to 23 °C. After 15 h, 1 M aqueous hydrochloric acid (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to provide **I.293** (54 mg, 31%) as a yellow oil. The obtained characterization data were in full agreement with those values reported in the literature.[157]

TMS-cyclopropanes I.297 and I.S5:

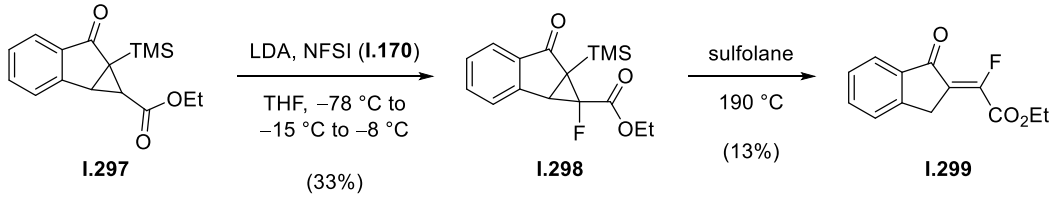


To a solution of cyclopropane **I.293** (156 mg, 0.721 mmol, 1 equiv) and trimethylsilyl chloride (0.461 mL, 3.60 mmol, 5.00 equiv) was added a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.204 mL, 1.44 mmol, 2.00 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.624 mL, 1.44 mmol, 2.00 equiv)) in tetrahydrofuran (0.4 mL) dropwise at −78 °C and the solution was allowed to warm slowly to 23 °C. After 23.5 h, saturated aqueous bicarbonate solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude mixture was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to provide **I.297** (62 mg, 30%) as a yellow oil and **I.S5** (54 mg, 26%) as a yellow oil.

I.297: TLC (20% ethyl acetate in hexanes), R_f = 0.72 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 7.5 Hz, 1H), 7.53–7.43 (m, 2H), 7.34–7.25 (m, 1H), 4.23–4.07 (m, 2H), 3.28 (d, *J* = 3.0 Hz, 1H), 2.14 (d, *J* = 3.0 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.23 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 203.3, 168.3, 153.2, 133.9, 133.8, 127.5, 125.0, 124.8, 61.4, 48.5, 33.6, 31.0, 14.3, −0.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1729 (*s*), 1703 (*vs*), 1603 (*m*), 1468 (*m*), 1406 (*m*), 1247 (*s*), 1182 (*vs*), 1110 (*s*), 1048 (*m*), 992 (*m*), 803 (*vs*), 759 (*vs*) cm^{-1}. **HRMS** (EI) calcd for $C_{16}H_{20}O_3Si$ [M]$^+$: 288.1176; found: 288.1164.

I.S5: TLC (15% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.62–7.56 (m, 1H), 7.54–7.42 (m, 2H), 7.31 (ddd, *J* = 7.5, 6.2, 2.2 Hz, 1H), 3.83 (dddd, *J* = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 3.15 (d, *J* = 7.9 Hz, 1H), 2.54 (d, *J* = 7.8 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 2H), 0.18 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 202.3, 168.5, 147.2, 138.2, 133.3, 127.9, 125.7, 123.0, 61.2, 44.9, 32.4, 31.1, 13.8, –2.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (w), 1701 (vs), 1606 (m), 1464 (m), 1382 (w), 1249 (s), 1173 (vs), 1113 (s), 1029 (m), 924 (m), 840 (vs), 756 (s) cm^{-1}. **HRMS** (EI) calcd for $C_{16}H_{20}O_3Si$ [M]$^+$: 288.1176; found: 288.1164.

***Exo*-enone I.299:**



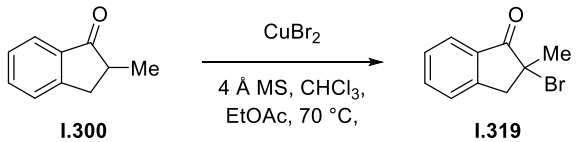
To a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.071 mL, 0.16 mmol,

1.1 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.023 mL, 0.16 mmol, 1.1 equiv)) in tetrahydrofuran (0.5 mL) was added a solution of cyclopropane **I.297** (43 mg, 0.15 mmol, 1 equiv) in tetrahydrofuran (1 mL) dropwise at −78 °C and the solution was allowed to warm slowly to −15 °C. After 1 h, the solution was allowed to warm to −8 °C and NFSI (**I.170**) (71 mg, 0.22 mmol, 1.5 equiv) was added. After 45 min, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide **I.298** (15 mg, 33%) as colorless oil, which contains minor impurities.

A solution of cyclopropane **I.298** (10 mg, 0.33 mmol, 1 equiv) in sulfolane (0.2 mL) was heated to 190 °C. After 1 h, water (10 mL) and diethyl ether (10 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide **I.299** (1 mg, 13%) as a yellow oil. Crystals that were suitable for X-Ray diffraction analysis were obtained by crystalliza-tion from dichloromethane/hexanes.

^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 7.6 Hz, 1H), 7.64 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 (ddt, *J* = 7.6, 1.9, 0.8 Hz, 1H), 7.44–7.41 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.12 (d, J = 0.9 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 191.2, 161.2 (d, *J* = 33.9 Hz), 149.4, 147.0 (d, *J* = 290.2 Hz), 137.9, 135.5, 128.1, 126.3, 125.1 (d, *J* = 5.0 Hz), 124.7, 62.7, 31.6, 14.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: –115.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2924 (*w*), 1706 (*vs*), 1603 (*m*), 1469 (*w*), 1365 (*m*), 1308 (*vs*), 1274 (*s*), 1182 (*s*), 1122 (*m*), 1008 (*m*), 895 (*m*), 744 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{11}FO_3$ $[M]^+$: 234.0687; found: 234.0687.

2-Bromo-2-methyl-1-indanone (I.319):



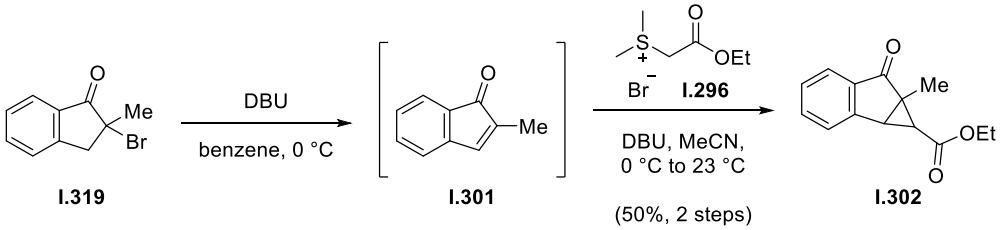
I.300 **I.319**

(quant.)

To a solution of 2-methyl-1-indanone (**I.300**) (0.940 mL, 6.84 mmol, 1 equiv) in ethyl acetate (30 mL) and chloroform (30 mL) was added 4 Å molecular sieves (6.84 g) and copper(II) bromide (3.06 g, 13.7 mmol, 2.00 equiv) and the suspension was heated to 70 °C. After 16 h, the solution was filtered through a short plug of silica and the filter cake was washed with ethyl acetate. The filtrate was concentrated and **I.319** was obtained a pale yellow solid. The crude product was used in the next step without further purification. The

obtained characterization data were in full agreement with those values reported in the literature.[158]

Cyclopropane I.302:

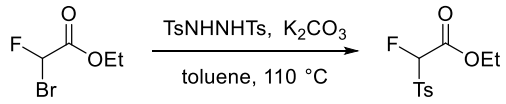


To a solution of the bromo-indanone **I.319** (1.54 g, 6.84 mmol, 1 equiv) in benzene (14 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (3.07 mL, 20.5 mmol, 3.00 equiv) at 0 °C. After 1 h, diethyl ether (40 mL) was added and the organic layer was washed with saturated aqueous ammonium chloride solution (2 × 30 mL) saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of (ethoxycarbonylmethyl)dimethylsulfonium bromide (**I.296**) (1.57 g, 6.84 mmol, 1 equiv) in acetonitrile (8.5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.23 mL, 8.21 mmol, 1.20 equiv) dropwise at 0 °C. After 45 min the crude indenone **I.301** in acetonitrile (20 mL) was dropwise and the solution was allowed to warm to 23 °C. After 15 h, 1 M aqueous hydrochloric acid (30 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **I.302** (784 mg, 50%) as a yellow oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.40 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 4.16 (q, *J* = 7.4 Hz, 2H), 3.25 (d, *J* = 2.8 Hz, 1H), 2.22 (d, *J* = 2.2 Hz, 2H), 1.58 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.4, 167.4, 152.0, 134.5, 133.0, 127.7, 125.2, 124.8, 61.4, 48.0, 38.2, 32.4, 14.5, 8.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (*w*), 1711 (*vs*), 1609 (*m*), 1469 (*m*), 1406 (*m*), 1296 (*m*), 1177 (*s*), 1096 (*w*), 1045 (*w*), 964 (*w*), 757 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0937; found: 230.0945.

Tosyl acetate I.309:

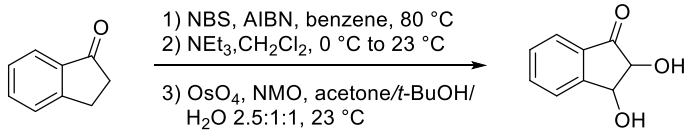


I.253 (71%) **I.309**

A solution of ethyl bromofluoroacetate (**I.253**) (60 μL, 0.50 mmol, 1 equiv), *N*,*N*-ditosylhydrazine (0.17 g, 0.50 mmol, 1 equiv) and potassium carbonate (69 mg, 0.50 mol, 1 equiv) in toluene (2 mL) was heated to 110 °C. After 5 h, the solution was allowed to cool to 23 °C. The solution was filtered and the filter cake was washed with ethyl acetate. The filtrate was concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide **I.309** (92 mg, 71%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.54 (d, *J* = 48.1 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.3 (d, *J* = 23.2 Hz), 146.9, 131.6, 130.2, 130.0, 97.5 (d, *J* = 231.6, Hz) 63.6, 22.0, 14.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2984 (*w*), 1758 (*vs*), 1596 (*m*), 1340 (*vs*), 1242 (*s*), 1198 (*m*), 1146 (*s*), 1109 (*s*), 1018 (*m*), 816 (*m*), 669 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{11}H_{13}FO_4{}^{32}S$ $[M]^+$: 260.0513; found: 260.0513.

Diol I.316:



I.263 (13%) **I.316**

In a pressure vessel, a solution of 1-indanone (**I.263**) (96.0 mg, 0.725 mmol, 1 equiv), *N*-bromosuccinimide (142 mg, 0.798 mmol, 1.1 equiv) and 2,2'-azobis(2-methylpropionitrile) (1.2 mg, 4.1 μmol, 0.010 equiv) in benzene (3.5 mL) was stirred at 80 °C for 18 h. The solution was allowed to cool to 23 °C, and then was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was used in the next step without further purification.

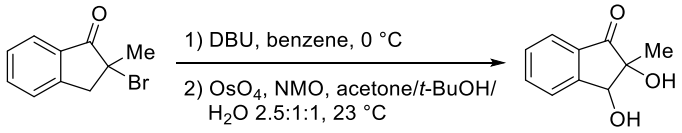
To a solution of the bromo-indanone in dichloromethane (5 mL) was added triethylamine (0.353 mL, 2.54 mmol, 3.50 equiv) at 0 °C. The solution was allowed to warm to 23 °C and after 30 min., the solution was concentrated. Diethyl ether (20 mL) was added and the mixture was filtered through a short plug of Celite. The filtrate was concentrated and the crude product was used in the next step without further purification.

To a solution of the crude indenone in acetone (2.8 mL), *tert*-butanol (1.1 mL) and water (1.1 mL) was added osmium tetroxide (4% in water, 71.0 μL, 7.25 μmol, 0.0100 equiv) and *N*-methylmorpholine *N*-

oxide (127 mg, 1.09 mmol, 1.5 equiv) at 23 °C. After 1 h, sodium thiosulfite (1 spatula) and water (5 mL) were added and the mixture was stirred for 5 min. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.316** (16 mg, 13%) as a colorless oil.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.80–7.73 (m, 2H), 7.65 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.56–7.51 (m, 1H), 5.35 (d, *J* = 6.3 Hz, 1H), 5.02 (dd, *J* = 6.2, 4.5 Hz, 1H), 4.96 (d, *J* = 5.4 Hz, 1H), 4.31 (dd, *J* = 5.4, 4.4 Hz, 1H), 2.89 (s, 2H). **^{13}C NMR** (100 MHz, acetone-d_6) δ: 201.8, 152.7, 136.3, 134.6, 129.8, 126.4, 123.3, 84.2, 75.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3403 (*s, br*), 2879 (*w*), 1720 (*vs*), 1608 (*m*), 1468 (*w*), 1320 (*w*), 1206 (*m*), 1102 (*m*), 1063 (*m*), 982 (*m*), 753 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_9H_8O_3$ [M]$^+$: 164.0468; found: 164.0466.

Diol I.320:



I.319 (58%) **I.320**

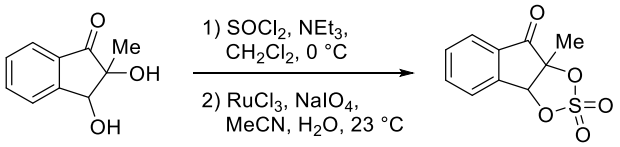
To a solution of bromo-indanone **I.319** (702.0 mg, 3.12 mmol, 1 equiv) in benzene (12.5 mL) was added 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (1.40 mL, 9.36 mmol, 3.00 equiv) at 0 °C. After 1°h, diethyl ether (30 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride solution (2 × 20 mL) and with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The product was used in the next step without further purification.

To a solution of the crude indenone in a mixture of acetone (10 mL), *tert*-butanol (4 mL) and water (4 mL) at 23 °C were added osmium tetroxide (4% in water 305 µL, 31.2 µmol, 0.01 equiv) and *N*-methylmorpholine *N*-oxide (NMO) (481 µL, 4.68 mmol, 1.5 equiv). After 2 h, sodium thiosulfite (2 spatula) and water (30 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica gel (5% acetone in dichloromethane) to provide **I.320** (324 mg, 58%) as an amorphous white solid.

TLC (5% acetone in dichloromethane): R_f = 0.33 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 7.7 Hz, 1H), 7.74–7.71 (m, 2H), 7.53 (ddd, *J* = 7.8, 4.5, 3.5 Hz, 1H), 4.91 (d, *J* = 4.6 Hz, 1H), 3.53–3.24 (m, 2H), 1.43 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 205.4, 151.8, 136.3, 133.5, 130.3, 127.3, 124.8, 75.0, 53.6, 23.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3390 (*br*, *m*), 2973 (w), 1714 (*vs*), 1606 (*s*), 1468 (*m*), 1372 (*m*),

1293 (*m*), 1203 (*s*), 1046 (*s*), 972 (*m*), 900 (*m*), 732 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{10}H_{10}O_3$ [M]$^+$: 178.0624; found: 178.0619.

Cyclic sulfate I.321:



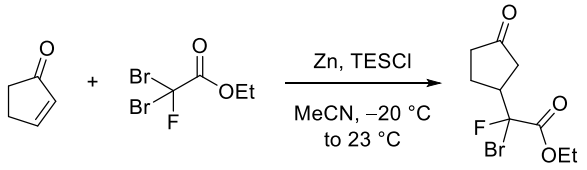
I.320 (75%) **I.321**

To a solution of diol **I.320** (284 mg, 1.59 mmol, 1 equiv) in dichloromethane (8.5 mL) was added triethylamine (554 µL, 3.98 mmol, 2.50 equiv) and thionyl chloride (173 µL, 2.39 mmol, 1.50 equiv) at 0 °C. After 2 h, dichloromethane (20 mL) was added and the organic layer was washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The product was used in the next step without further purification.

To a solution of the crude sulfite in acetonitrile (7 mL) was added sodium periodate (680 mg, 3.18 mmol, 2.00 equiv), ruthenium(III) chloride (16.5 mg, 79.5 µmol, 0.0500 equiv) and water (7 mL) at 23 °C. After 30 min, diethyl ether (20 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 × 20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica gel (40% ethyl acetate in hexanes) to provide **I.321** (286 mg, 75%) as an amorphous white solid.

TLC (40% ethyl acetate in hexanes): R_f = 0.38 (UV, CAM). **^{1}H NMR** (400 MHz, CDCl3) δ: 7.97 (ddt, *J* = 7.8, 1.3, 0.6 Hz, 1H), 7.90 (td, *J* = 7.5, 1.2 Hz, 1H), 7.85–7.78 (m, 1H), 7.75 (td, *J* = 7.5, 1.1 Hz, 1H), 5.92 (s, 1H), 1.90 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.8, 143.9, 137.8, 134.8, 133.1, 128.2, 126.0, 87.3, 84.0, 19.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2360 (*w*), 1737 (*vs*), 1396 (*s*), 1213 (*vs*), 963 (*s*), 885 (*m*), 835 (*m*), 738 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{10}H_8O_3{}^{32}S$ [M]$^+$: 240.0087; found: 240.0089.

1,4-Adduct I.323:



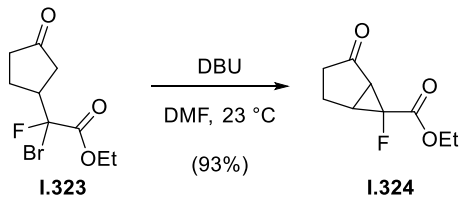
I.322 **I.254** (49%) **I.323**

To a suspension of zinc dust (488 mg, 7.46 mmol, 2.00 equiv) in acetonitrile (15 mL) was added triethylsilyl chloride (1.39 mL, 8.21 mmol, 2.20 equiv) at –20 °C. Ethyl dibromofluoroacetate (**I.254**)

(1.3 mL, 9.33 mmol, 2.50 equiv) was added dropwise. After 2 h, 2-cyclopenten-1-one (**I.322**) (306 mg, 3.73 mmol, 1 equiv) was added at –20 °C. The solution was allowed to warm to 23 °C. After 18 h, 1 M aqueous hydrochloric acid solution (10 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified with flash column chromatography on silica gel (10% ethyl acetate in hexanes) to provide **I.323** (486 mg, 49%) as a colorless oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.45 (CAM, $KMnO_4$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.36 (qd, *J* = 7.2, 1.0 Hz, 2H), 3.33–3.07 (m, 1H), 2.55–2.03 (m, 6H), 1.36 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 215.1, 165.6 (d, *J* = 27.1 Hz), 99.6 (d, *J* = 268.0 Hz), 63.6, 46.2 (d, *J* = 20.8 Hz), 39.9 (d, *J* = 2.2 Hz), 38.3, 24.5 (d, *J* = 2.4 Hz), 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –127.69 (d, *J* = 24.1 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (*w*), 1741 (*m*), 1463 (*w*), 1405 (*w*), 1262 (*s*), 1180 (*s*), 1131 (*s*), 1041 (*s*), 899 (*m*), 869 (*m*) cm^{-1}.

Fluoro-cyclopropane I.324:

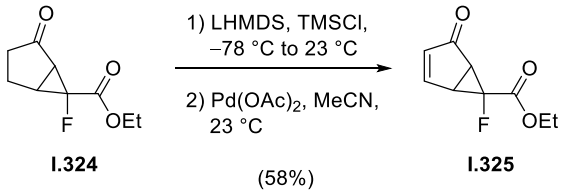


I.323 **I.324**

To a solution of cyclopentanone **I.323** (486 mg, 1.82 mmol, 1 equiv) in *N*,*N*-dimethylformamide (20 mL) was added diazabicyclo[5,4,0]-7-undecene (DBU) (2.72 mL, 18.2 mmol, 10.0 equiv) at 23 °C. After 1 h, 1 M aqueous hydrochloric acid (50 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.324** (314 mg, 93%) as a colorless oil.

TLC (20% ethyl acetate in hexanes) R_f = 0.38 (CAM, $KMnO_4$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 4.29 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.72 (td, *J* = 6.3, 1.9 Hz, 1H), 2.58 (d, *J* = 6.5 Hz, 1H), 2.51–2.40 (m, 1H), 2.36–2.27 (m, 2H), 2.28–2.16 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 209.1, 167.3 (d, *J* = 25.3 Hz), 80.0 (d, *J* = 247.2 Hz), 62.7, 40.4 (d, *J* = 13.1 Hz), 35.7, 34.4 (d, *J* = 12.2 Hz), 19.7 (d, *J* = 4.6 Hz), 14.3. **^{19}F NMR** (282 MHz, Chloroform-*d*) δ −210.9 (d, *J* = 3.2 Hz). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2982 (*w*), 1729 (*vs*), 1372 (*m*), 1325 (*s*), 1272 (*s*), 1213 (*vs*), 1149 (*m*), 1096 (*vs*), 1013 (*m*), 954 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_9H_{11}FO_3$ [M]$^+$: 186.0687; found: 186.0682.

Fluoro-cyclopropane I.325:



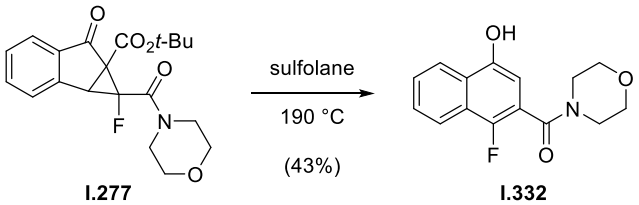
I.324 **I.325**

To a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 2.02 mL, 2.02 mmol, 1.20 equiv) in tetrahydrofuran (4 mL) was added dropwise a solution of cyclopropane **I.324** (314 mg, 1.69 mmol, 1 equiv) in tetrahydrofuran (16 mL) at –78 °C. After 1 h, trimethylsilyl chloride (323 µL, 2.53 mmol, 1.50 equiv) was added dropwise at –78 °C. After 50 min, the solution was allowed to warm to 23 °C. After 3.5 h, the solution was concentrated and hexanes (20 mL) was added. The mixture was filtered through a plug of Celite and the filtrate was concentrated. The crude product was used in the next step without further purification.

To a solution of the crude enol ether in acetonitrile (16 mL) was added palladium(II) acetate (417 mg, 1.86 mmol, 1.10 equiv) at 23°C. After 13 h, diethyl ether (20 mL) was added. The mixture was filtered through a plug of Celite and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **I.325** (179 mg, 58%) as colorless oil.

TLC (20% ethyl acetate in hexanes): R*f* = 0.23 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 7.28 (dd, *J* = 5.6, 2.9 Hz, 1H), 6.01 (t, *J* = 5.3 Hz, 1H), 4.20 (qd, *J* = 7.1, 4.6 Hz, 2H), 3.18 (ddd, *J* = 14.5, 6.2, 2.9 Hz, 1H), 2.71 (ddd, *J* = 17.4, 6.3, 0.9 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 199.3, 164.3 (d, *J* = 25.6 Hz), 151.1, 136.1 (d, *J* = 7.0 Hz), 88.9 (d, *J* = 246.7 Hz), 63.0, 34.5 (d, *J* = 11.7 Hz), 33.9 (d, *J* = 8.2 Hz).14.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2986 (*w*), 1740 (*vs*), 1711 (*vs*), 1376 (*m*), 1304 (*vs*), 1263 (*s*), 1179 (*vs*), 1151 (*vs*), 1126 (*s*), 1091 (*m*), 1015 (*m*), 809 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_9H_9FO_3$ $[M]^+$: 184.0530; found: 184.0528.

Fluoronaphthol I.332:



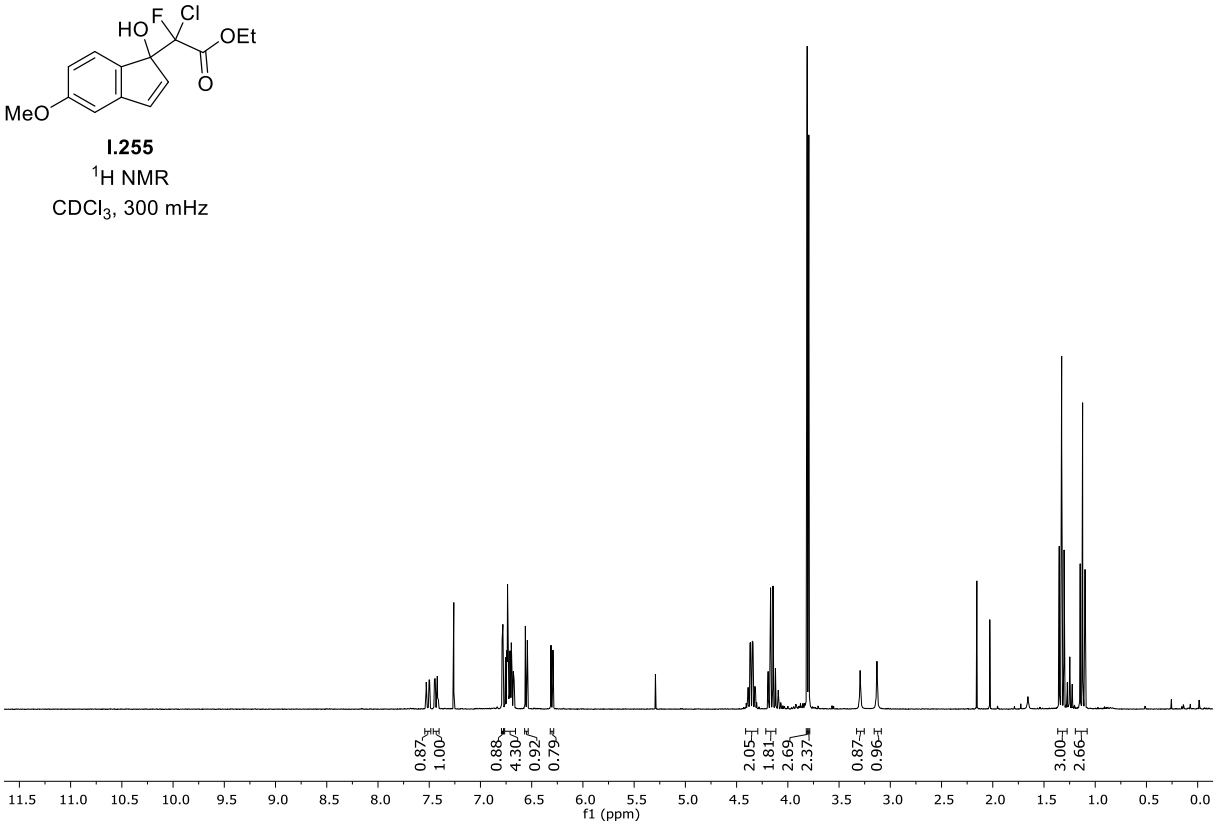
I.277 **I.332**

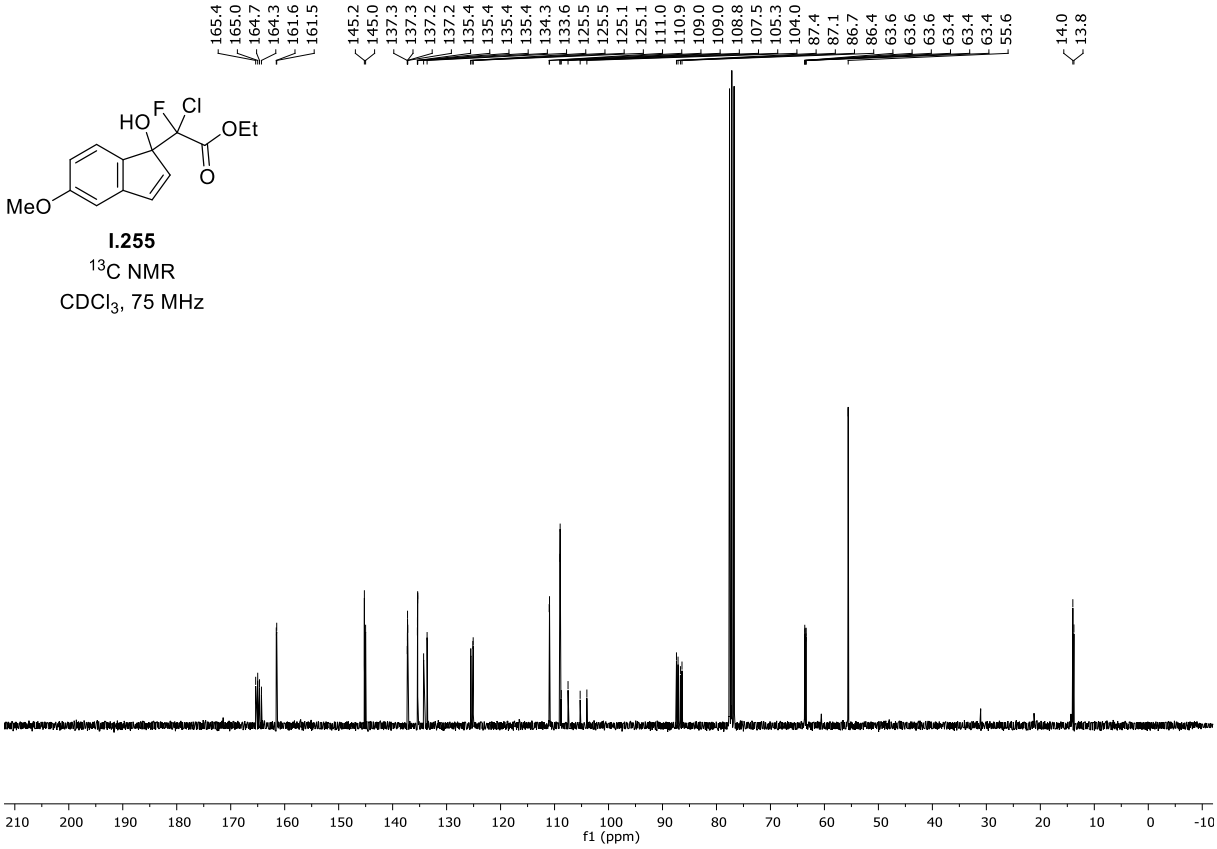
A solution of cyclopropane **I.277** (6.0 mg, 0.016 mmol, 1 equiv) in sulfolane (0.2 mL) was heated to 190 °C. After 0.5 h, water (5 mL) and diethyl ether (5 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium

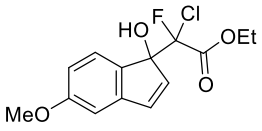
sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide **I.332** (2.6 mg, 43%) as a colorless oil.

TLC (40% ethyl acetate in hexanes) R_f = 0.21 (UV, CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ: 8.16–8.12 (m, 1H), 8.04–7.99 (m, 1H), 7.62–7.52 (m, 2H), 7.53–7.47 (m, 1H), 6.88 (d, *J* = 5.1 Hz, 1H), 3.86 (t, *J* = 4.9 Hz, 2H), 3.79 (t, *J* = 4.9 Hz, 2H), 3.69–3.59 (m, 3H), 3.53–3.39 (m, 2H). **^{19}F NMR** (376 MHz, CD_2Cl_2) δ: −34.3 (d, *J* = 4.9 Hz). **HRMS** (EI) calcd for $C_{15}H_{13}FNO_3$ $[M-H]^-$: 274.08850; found: 274.08854.

7.3.2 ^{1}H, ^{13}C and ^{19}F NMR Spectra



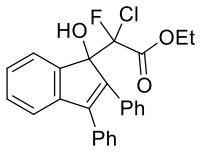




I.255

^{19}F NMR

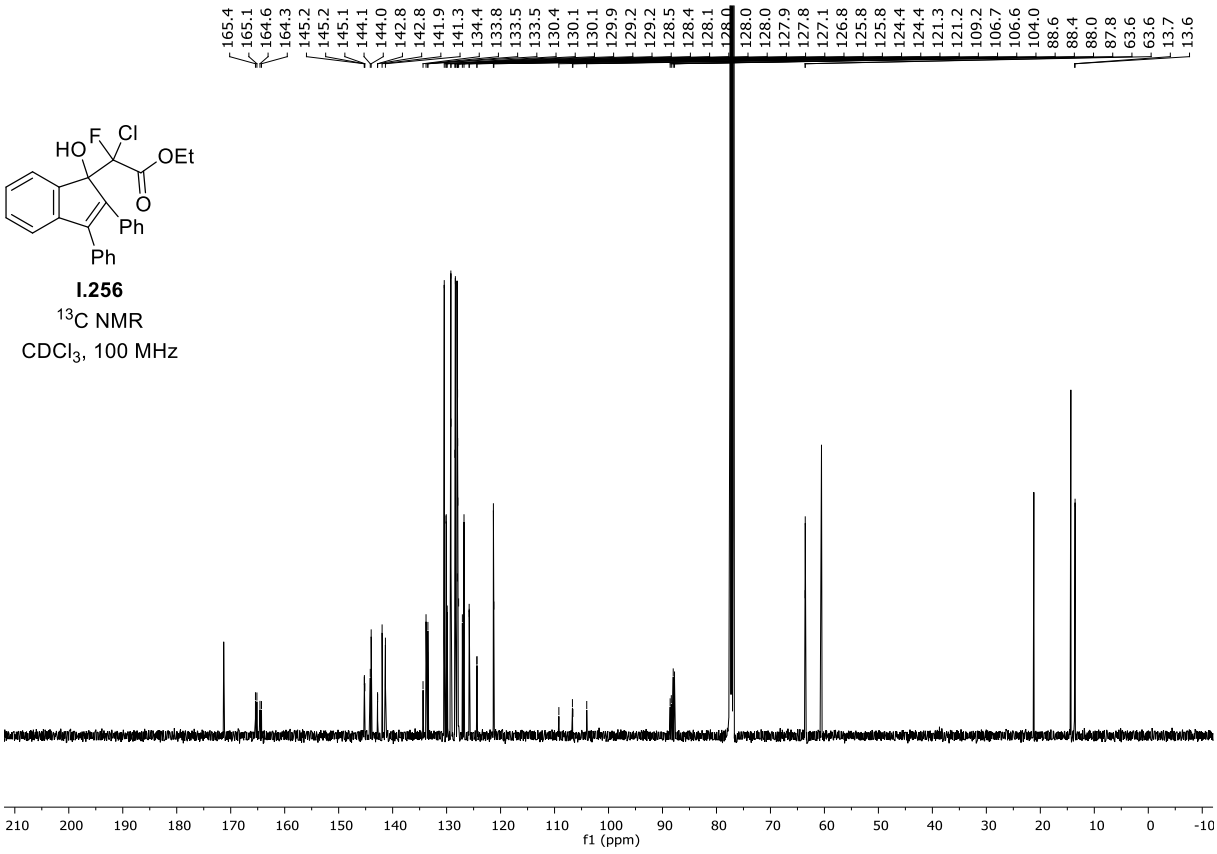
$CDCl_3$, 282 MHz



I.256

^{1}H NMR

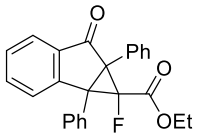
$CDCl_3$, 400 MHz



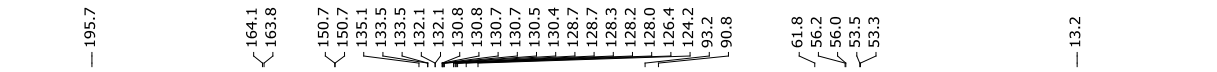
I.256

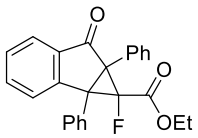
^{13}C NMR

$CDCl_3$, 100 MHz

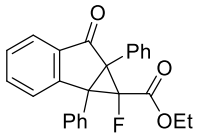


I.257
^{1}H NMR
$CDCl_3$, 400 MHz

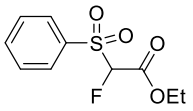




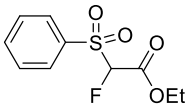
I.257
^{13}C NMR
$CDCl_3$, 100 MHz



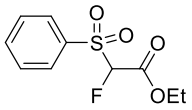
I.257
^{19}F NMR
$CDCl_3$, 282 MHz



I.261b
^{1}H NMR
$CDCl_3$, 400 MHz



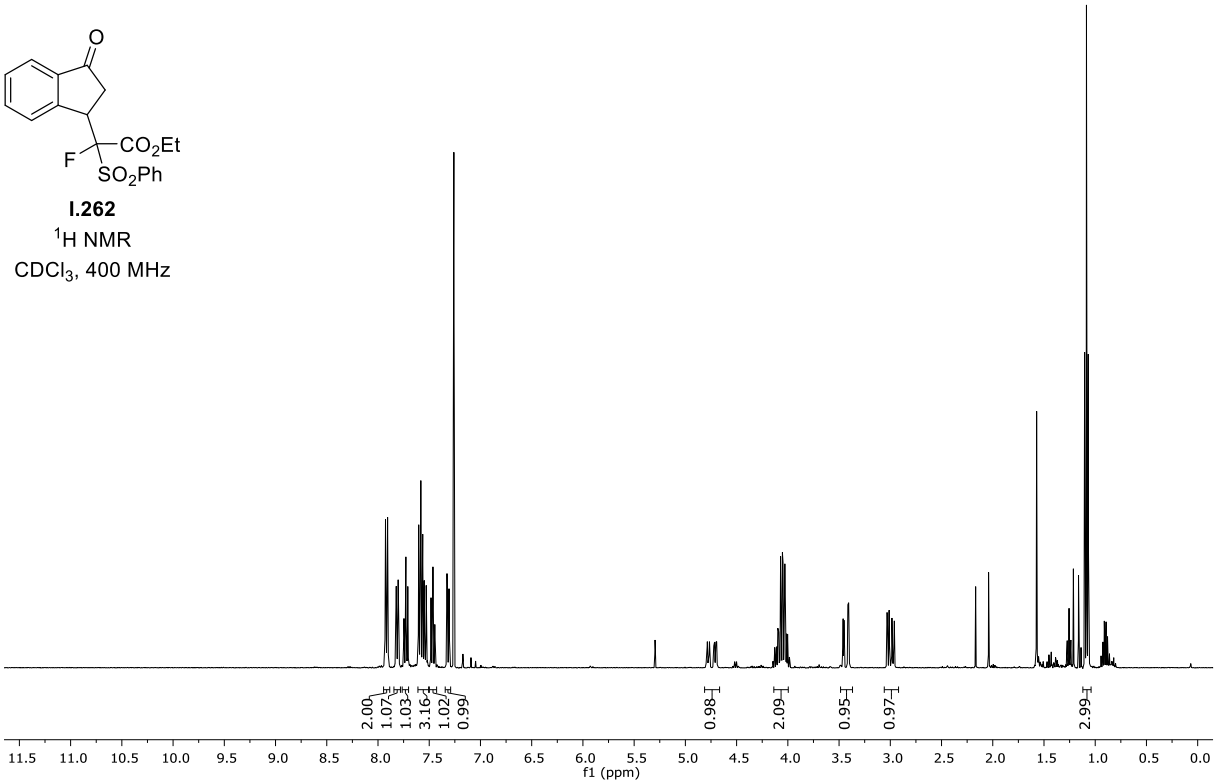
I.261b
^{13}C NMR
$CDCl_3$, 100 MHz

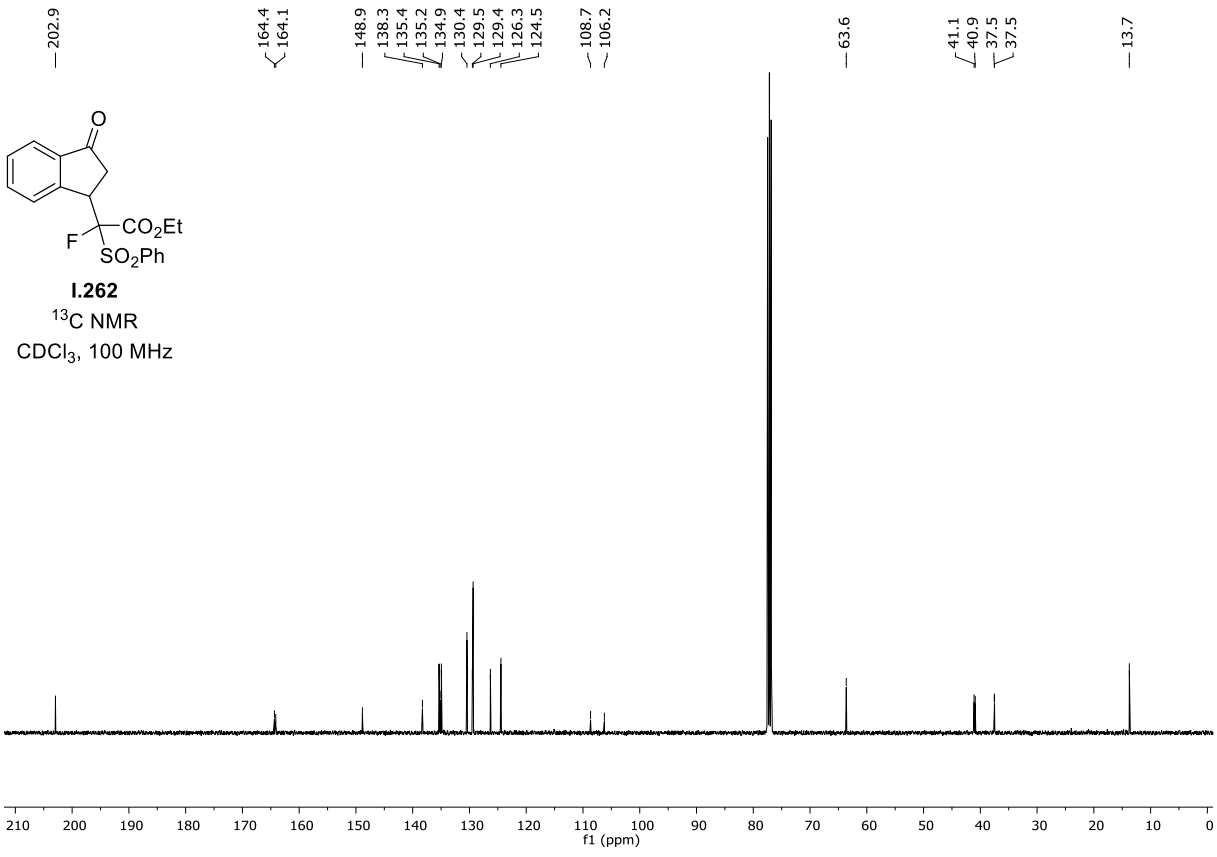


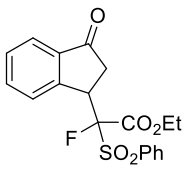
I.261b

^{19}F NMR

$CDCl_3$, 376 MHz


O
F
CO2Et
SO2Ph
I.262
1H NMR
CDCl3, 400 MHz
2.00
1.07
1.03
3.16
1.02
0.99
0.98
2.09
0.95
0.97
2.99
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

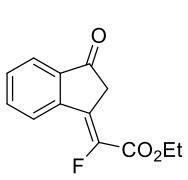

202.9
164.4
164.1
148.9
138.3
135.4
135.2
134.9
130.4
129.5
129.4
126.3
124.5
108.7
106.2
63.6
41.1
40.9
37.5
37.5
13.7
O
F
CO2Et
SO2Ph
I.262
13C NMR
CDCl3, 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



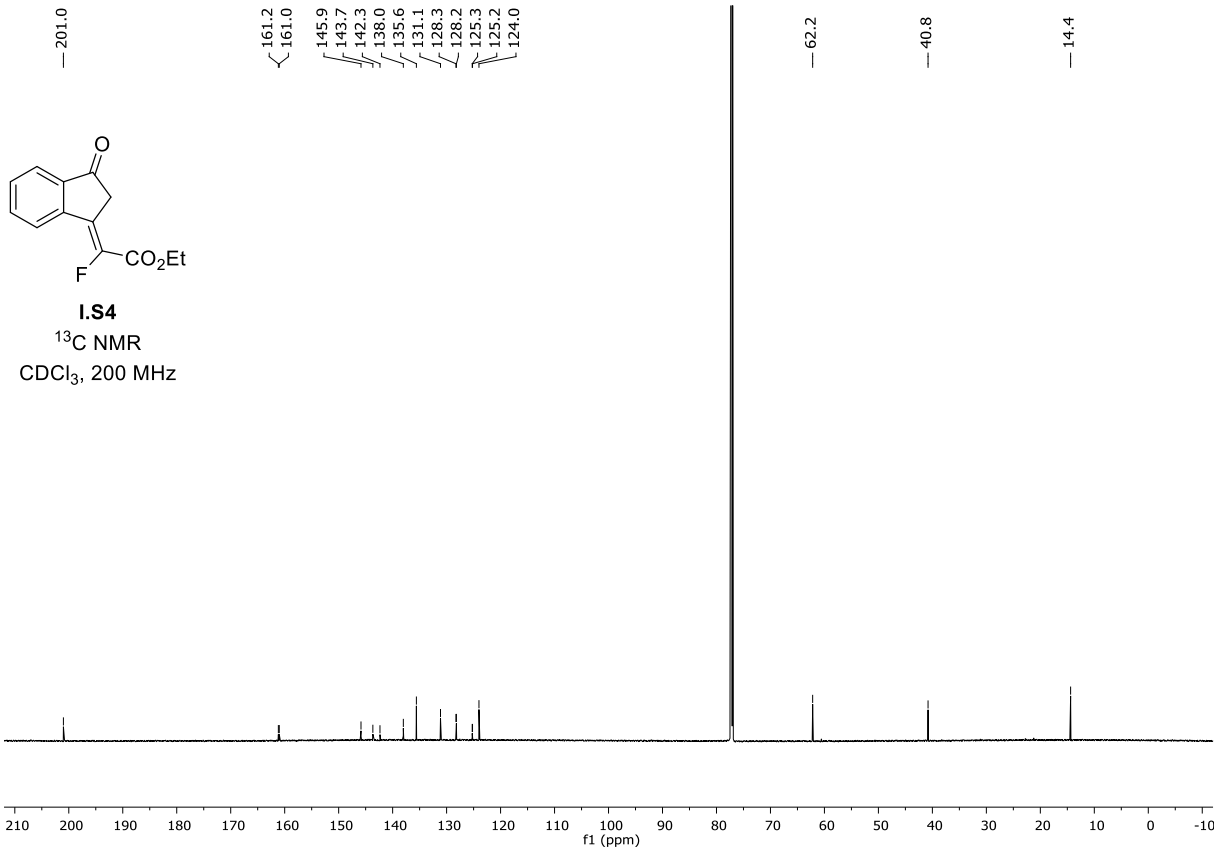
I.262

^{19}F NMR

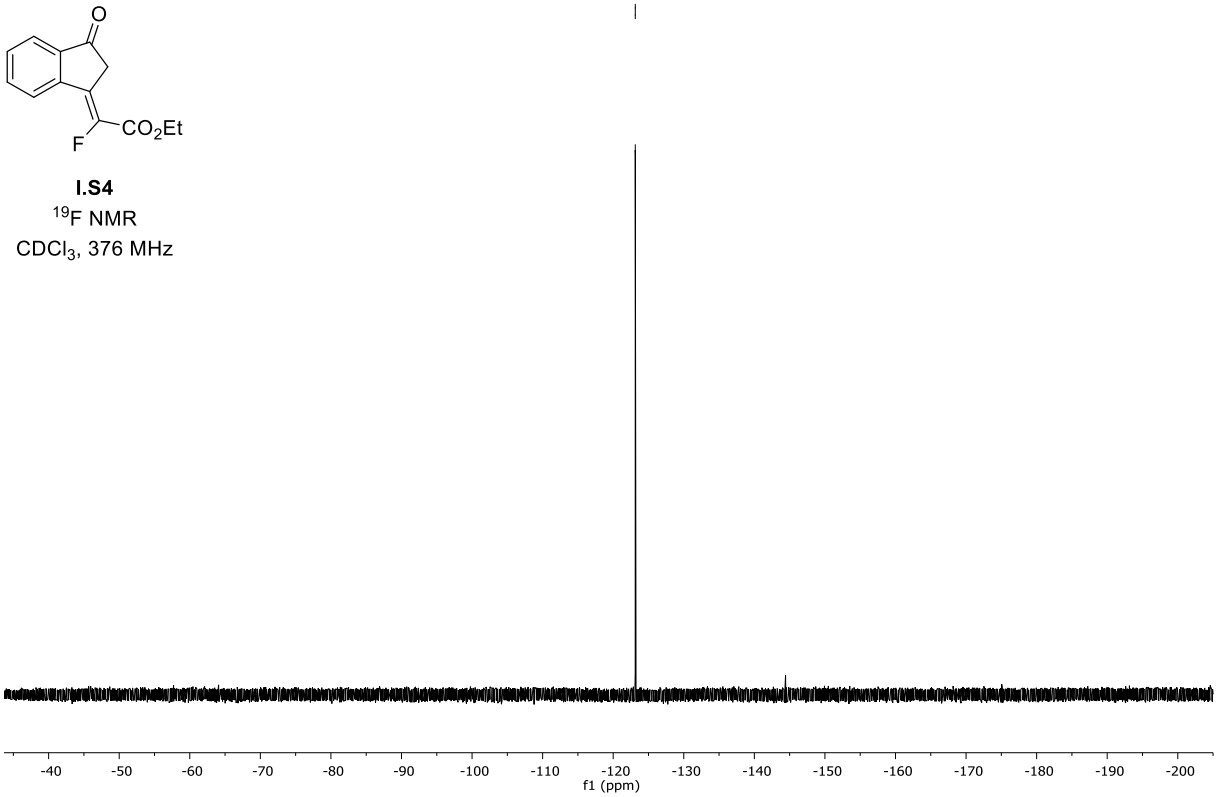
$CDCl_3$, 282 MHz



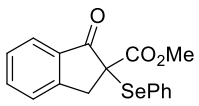
I.S4
^{1}H NMR
$CDCl_3$, 600 MHz



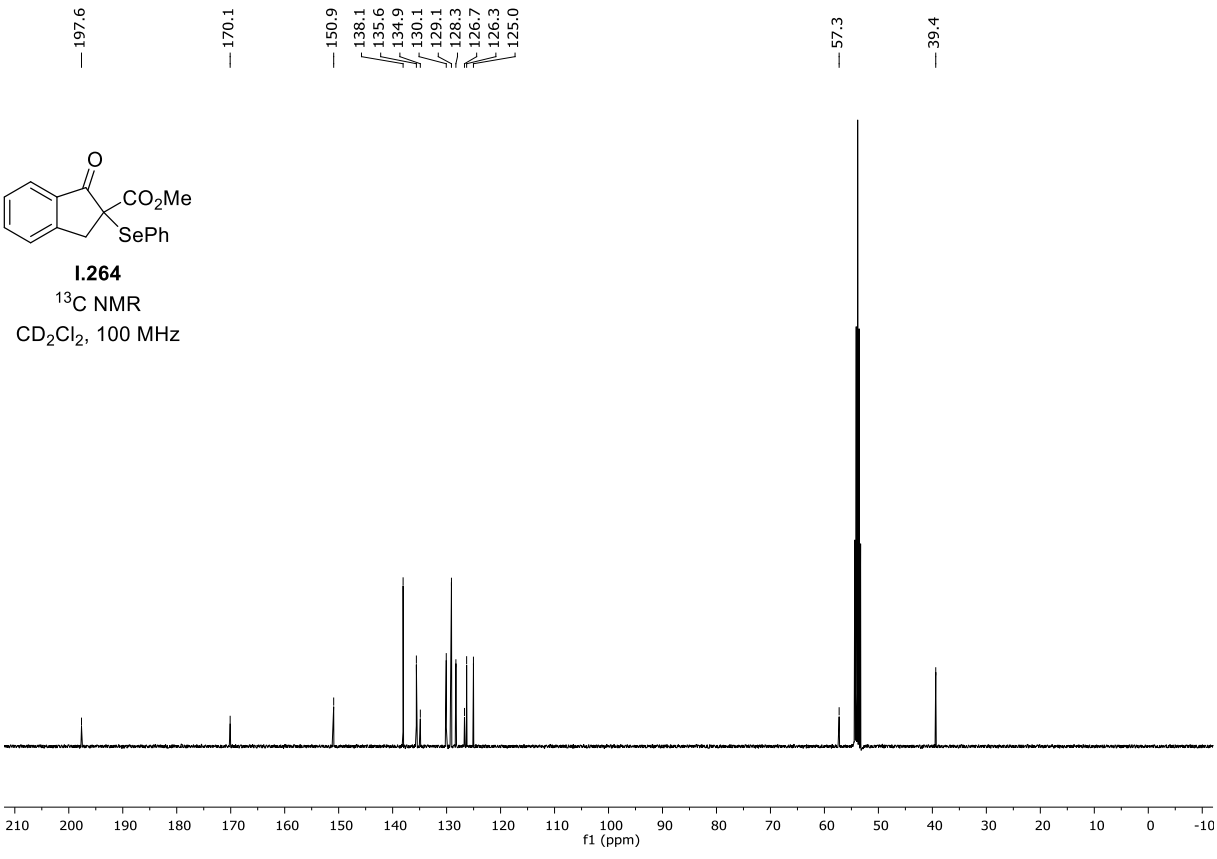
I.S4
^{13}C NMR
$CDCl_3$, 200 MHz



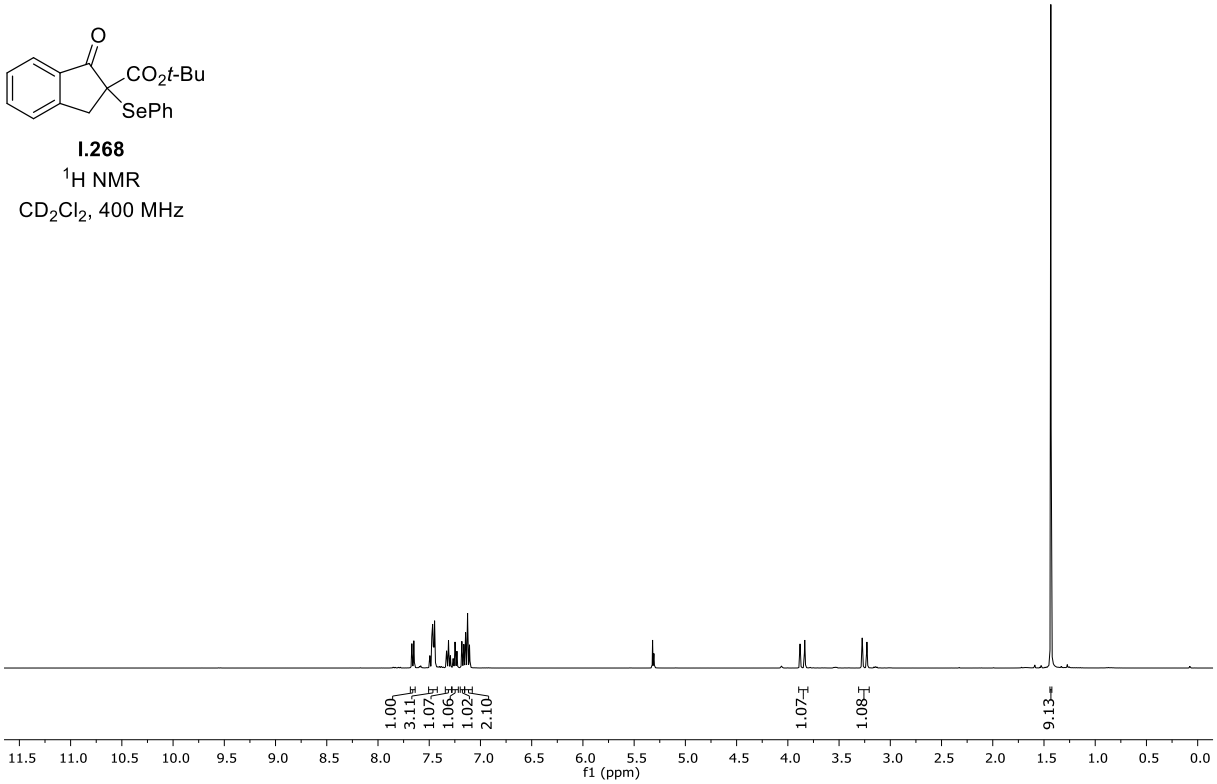
I.S4
^{19}F NMR
$CDCl_3$, 376 MHz

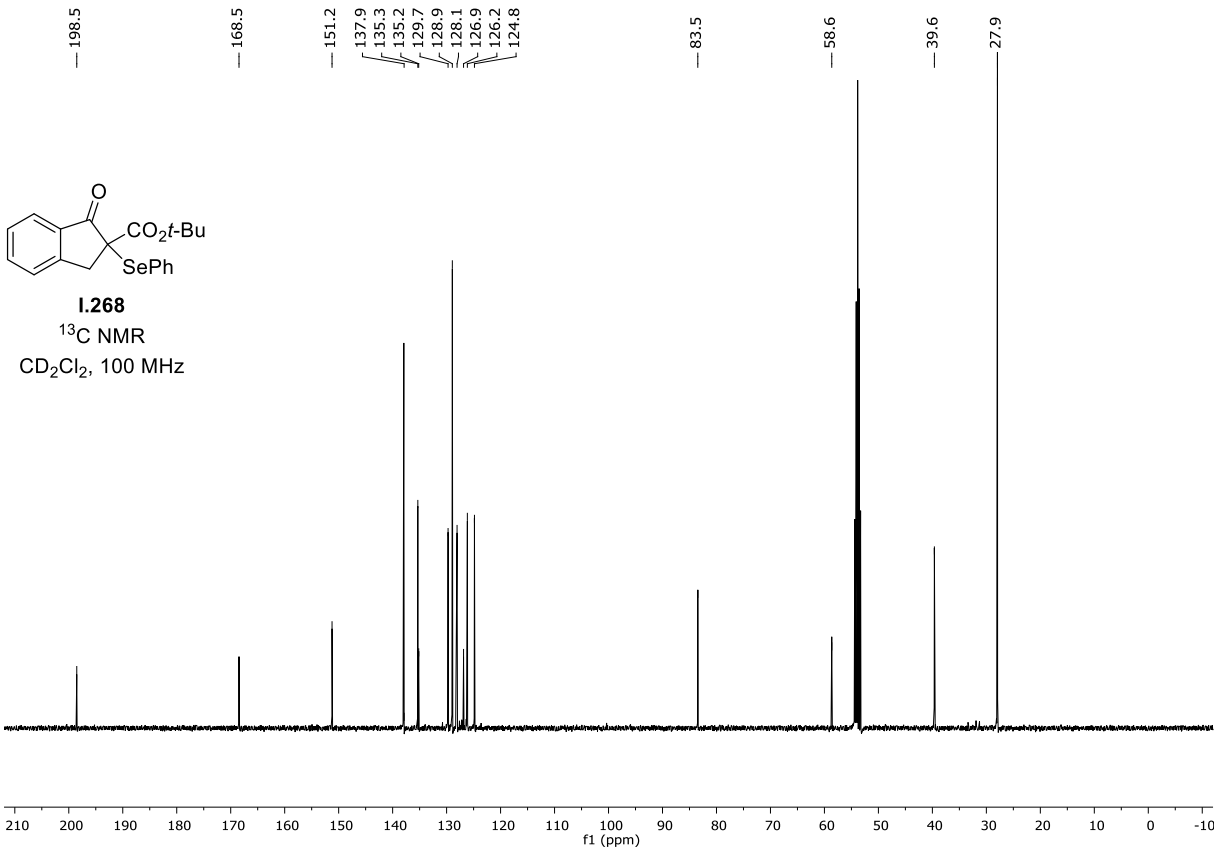


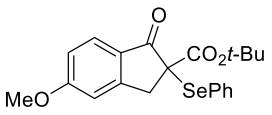
I.264
^{1}H NMR
CD_2Cl_2, 400 MHz



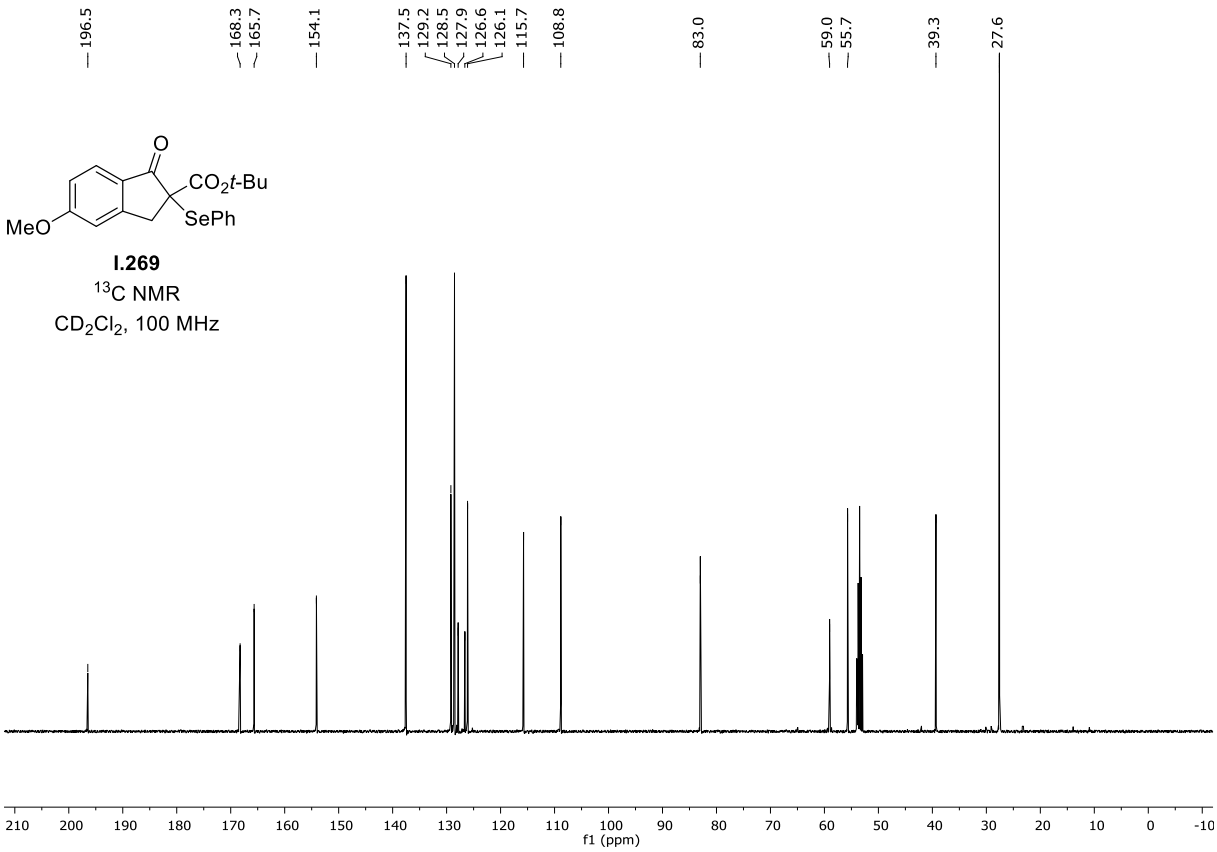
I.264
^{13}C NMR
CD_2Cl_2, 100 MHz


O
CO2t-Bu
SePh
I.268
1H NMR
CD2Cl2, 400 MHz
1.00
3.11
1.07
1.06
1.02
2.10
1.07
1.08
9.13
f1 (ppm)

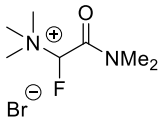

198.5
168.5
151.2
137.9
135.3
135.2
129.7
128.9
128.1
126.9
126.2
124.8
83.5
58.6
39.6
27.9
O
CO2t-Bu
SePh
I.268
13C NMR
CD2Cl2, 100 MHz
f1 (ppm)



I.269
^{1}H NMR
CD_2Cl_2, 400 MHz



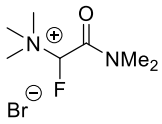
I.269
^{13}C NMR
CD_2Cl_2, 100 MHz



I.276

^{1}H NMR

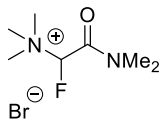
$CDCl_3$, 400 MHz



I.276

^{13}C NMR

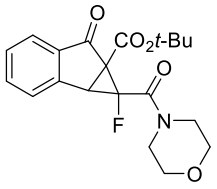
$CDCl_3$, 100 MHz



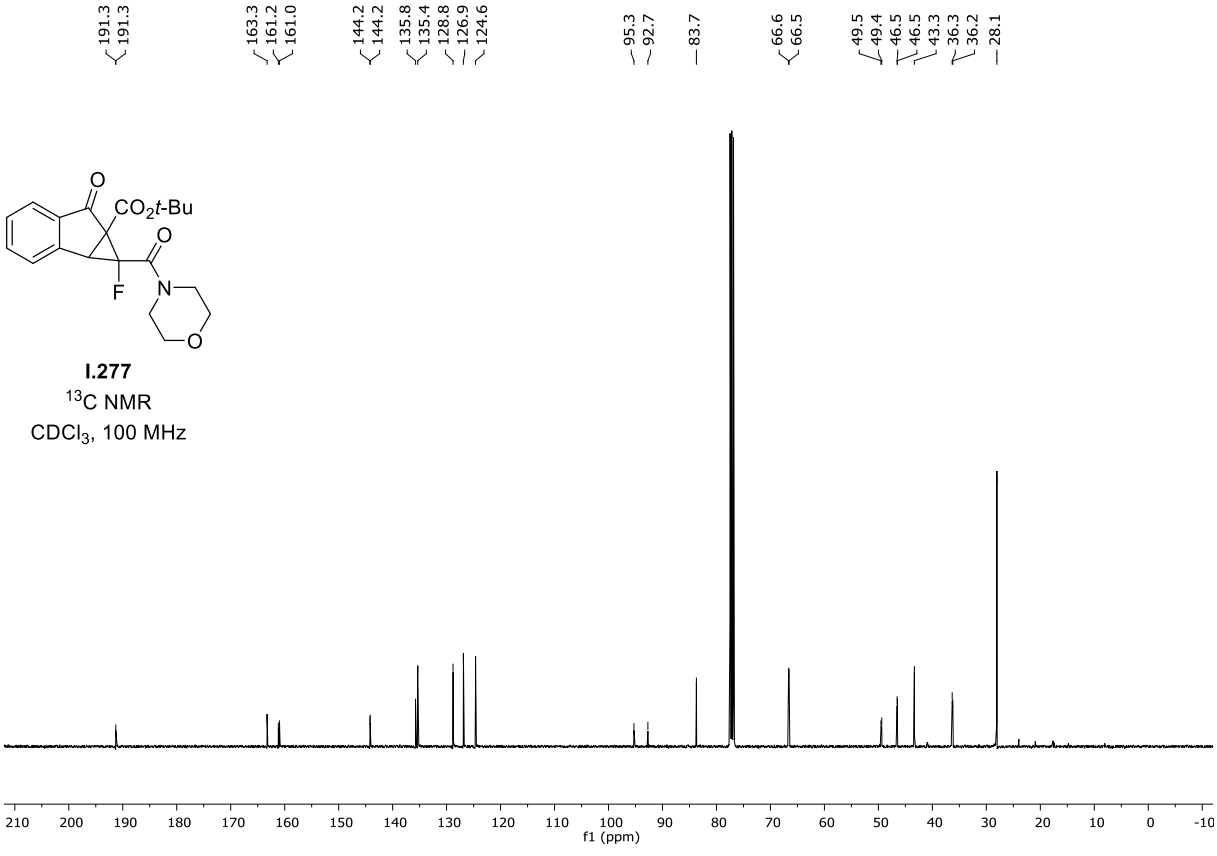
I.276

^{19}F NMR

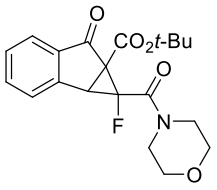
$CDCl_3$, 376 MHz



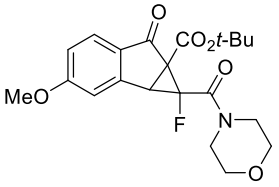
I.277
^{1}H NMR
$CDCl_3$, 400 MHz



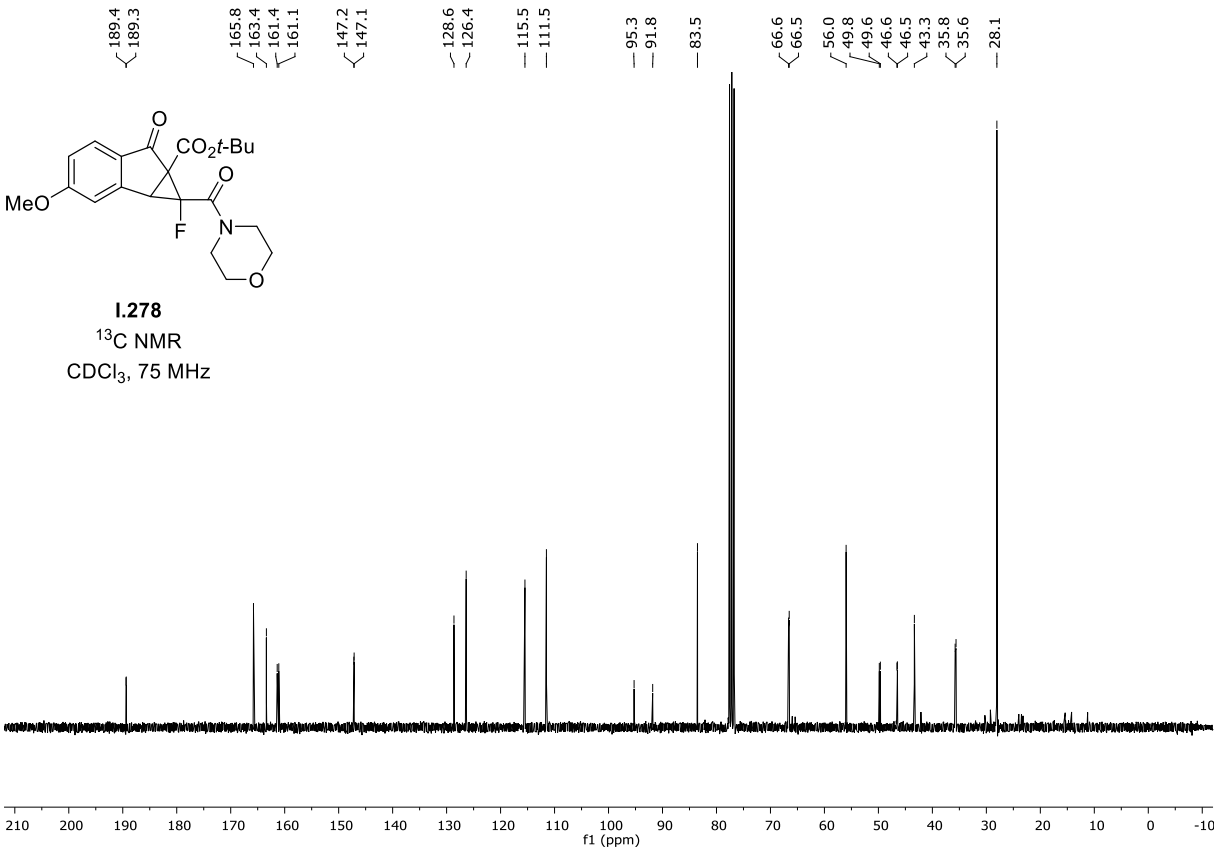
I.277
^{13}C NMR
$CDCl_3$, 100 MHz



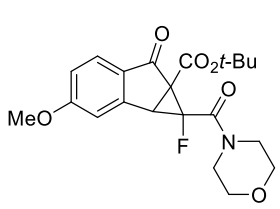
I.277
^{19}F NMR
$CDCl_3$, 376 MHz



I.278
^{1}H NMR
$CDCl_3$, 300 MHz



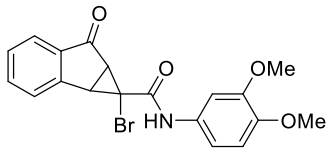
I.278
^{13}C NMR
$CDCl_3$, 75 MHz



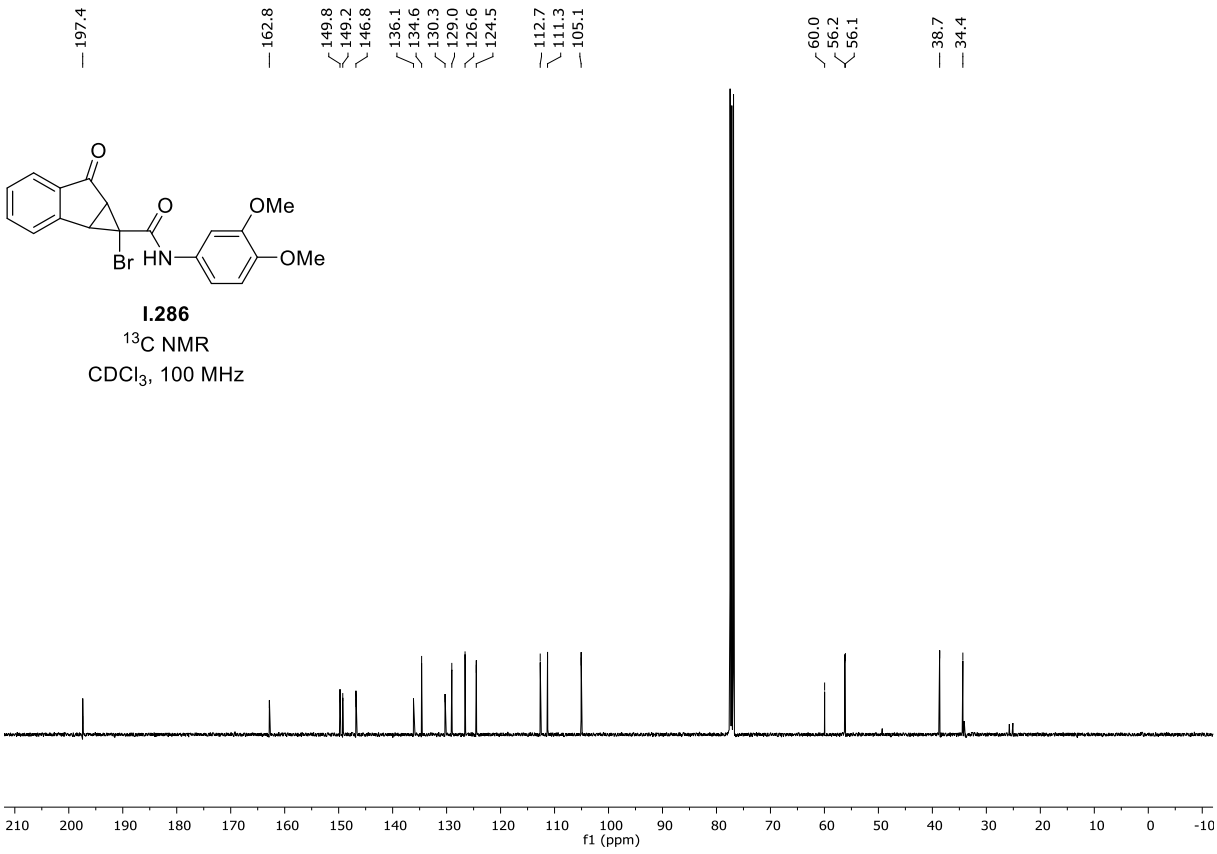
I.278

^{19}F NMR

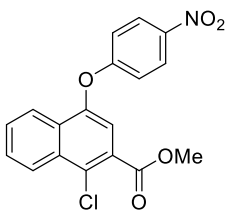
$CDCl_3$, 282 MHz



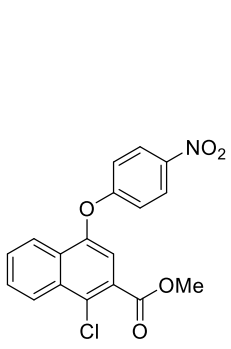
I.286
^{1}H NMR
$CDCl_3$, 400 MHz



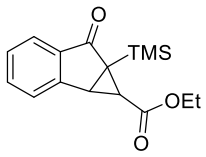
I.286
^{13}C NMR
$CDCl_3$, 100 MHz



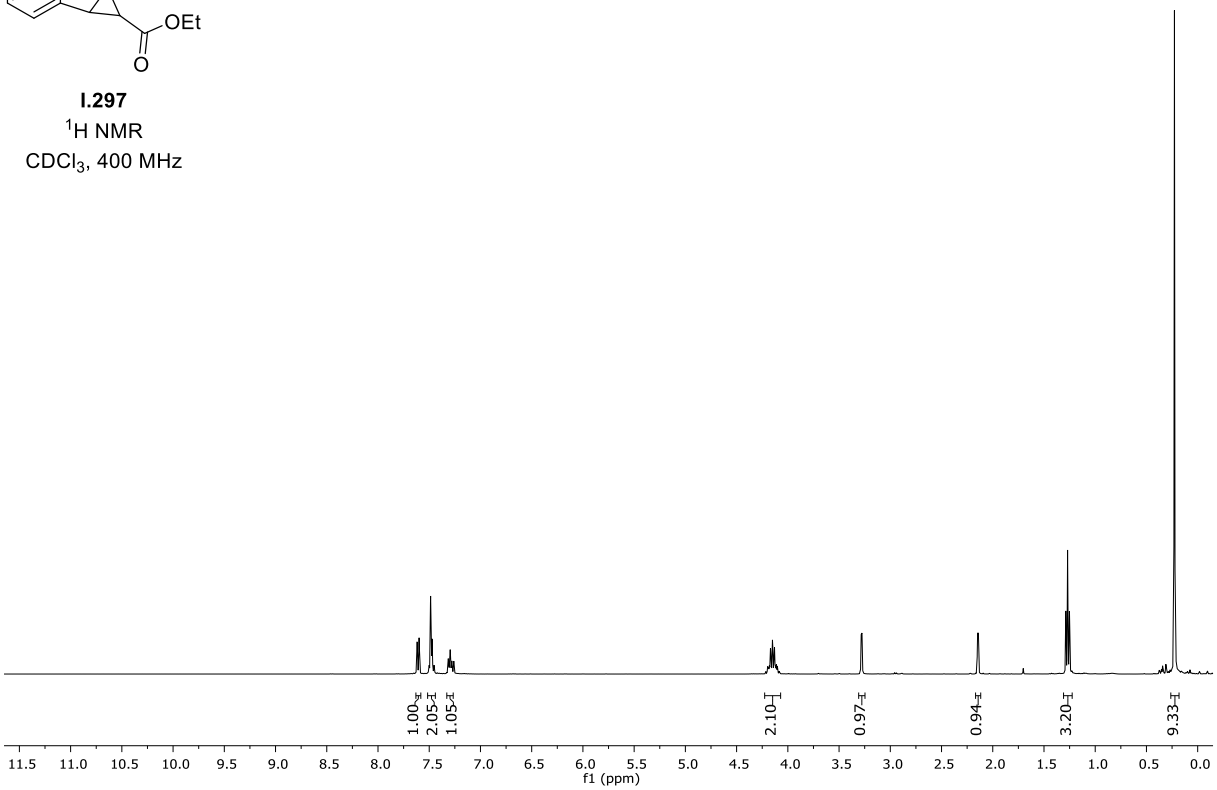
I.292
^{1}H NMR
$CDCl_3$, 400 MHz

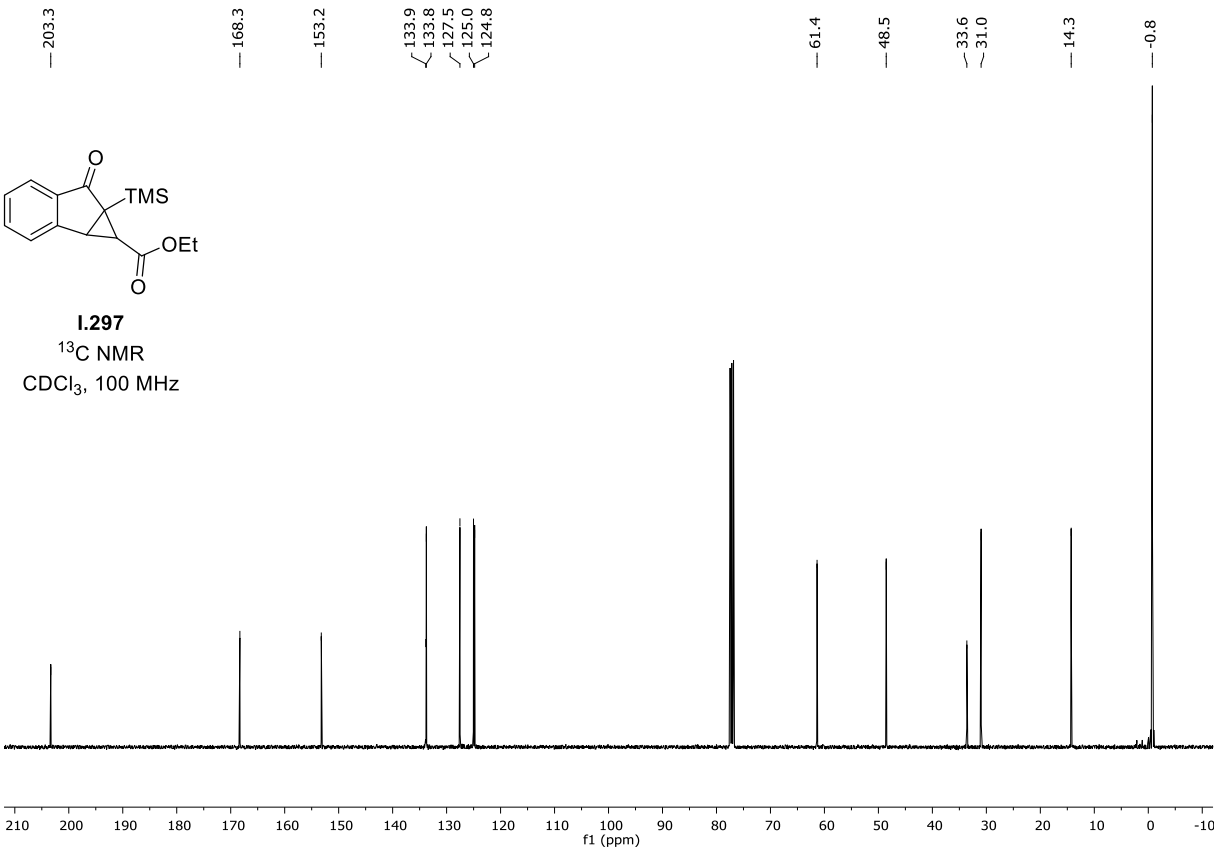


I.292
^{13}C NMR
$CDCl_3$, 100 MHz

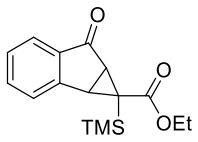


I.297
^{1}H NMR
$CDCl_3$, 400 MHz

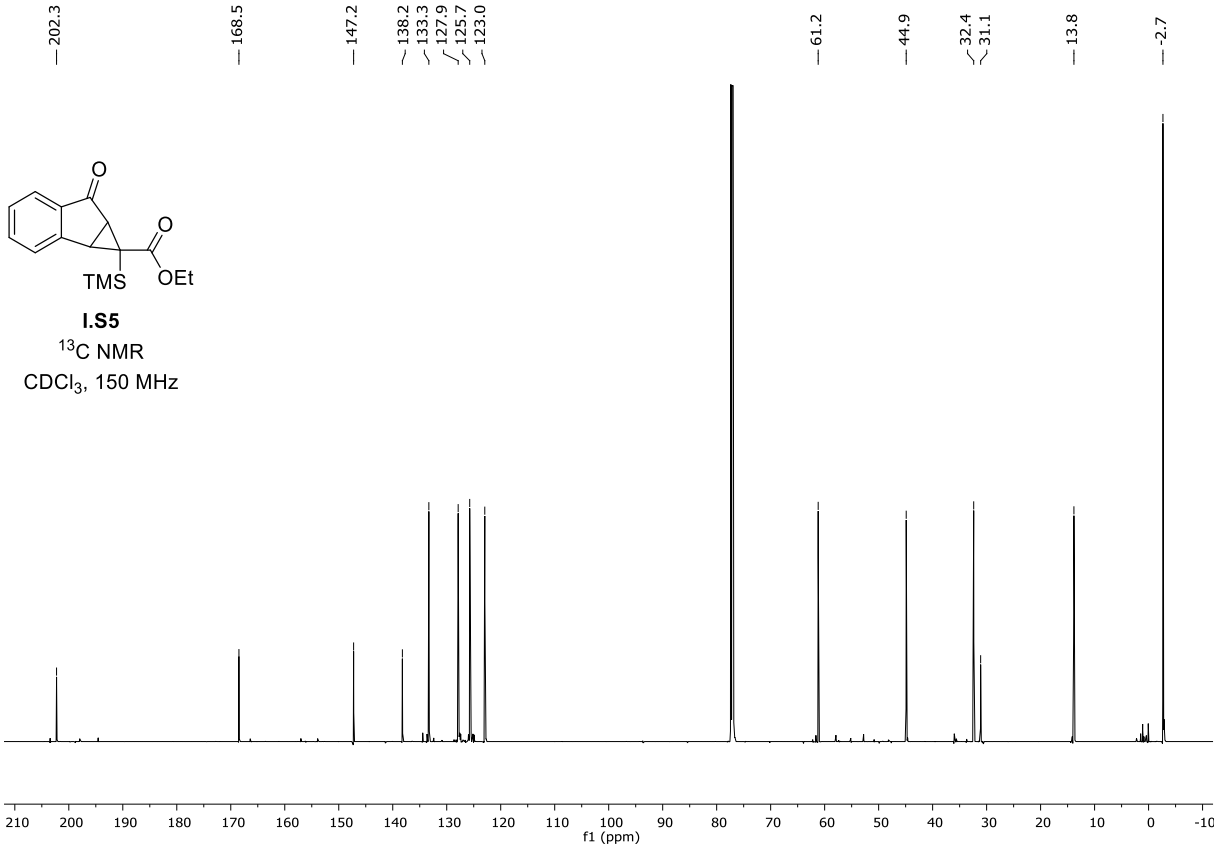




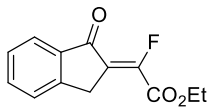
I.297
^{13}C NMR
$CDCl_3$, 100 MHz



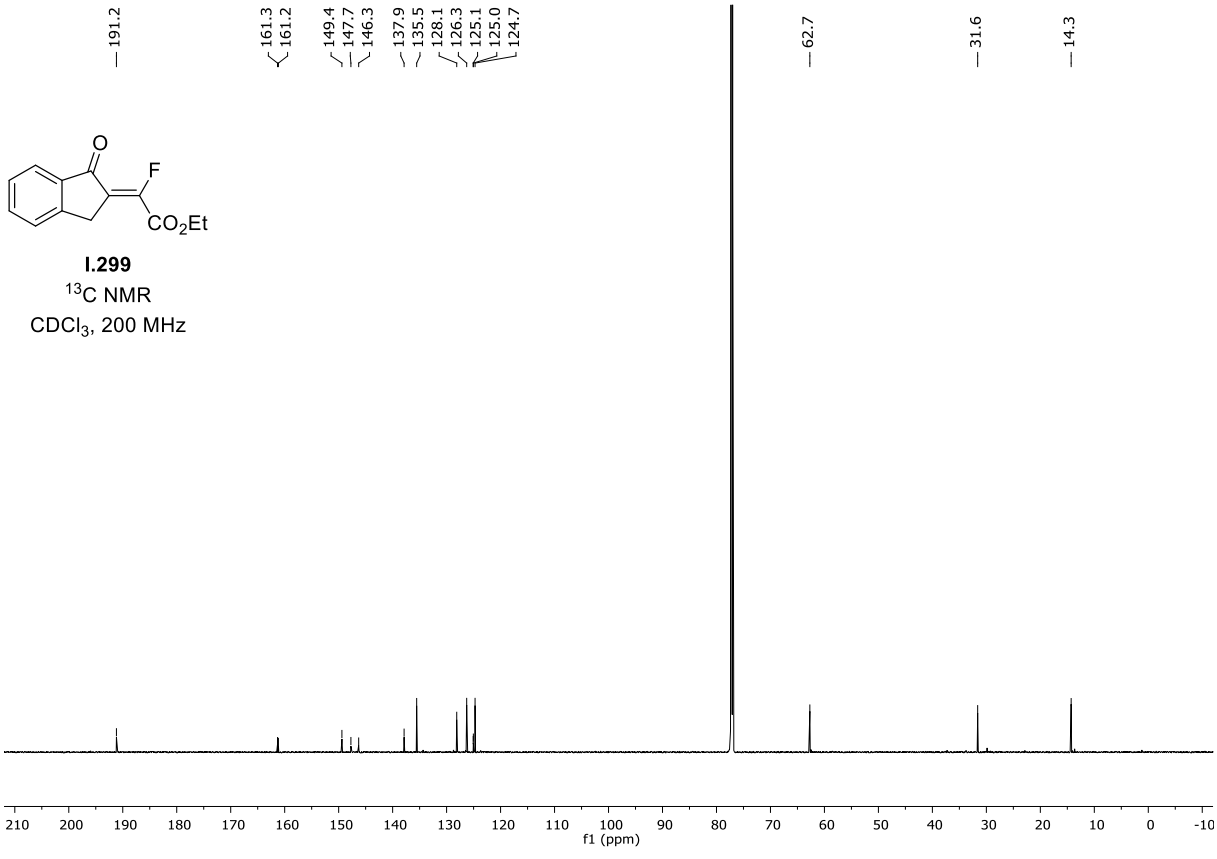
I.S5
^{1}H NMR
$CDCl_3$, 600 MHz



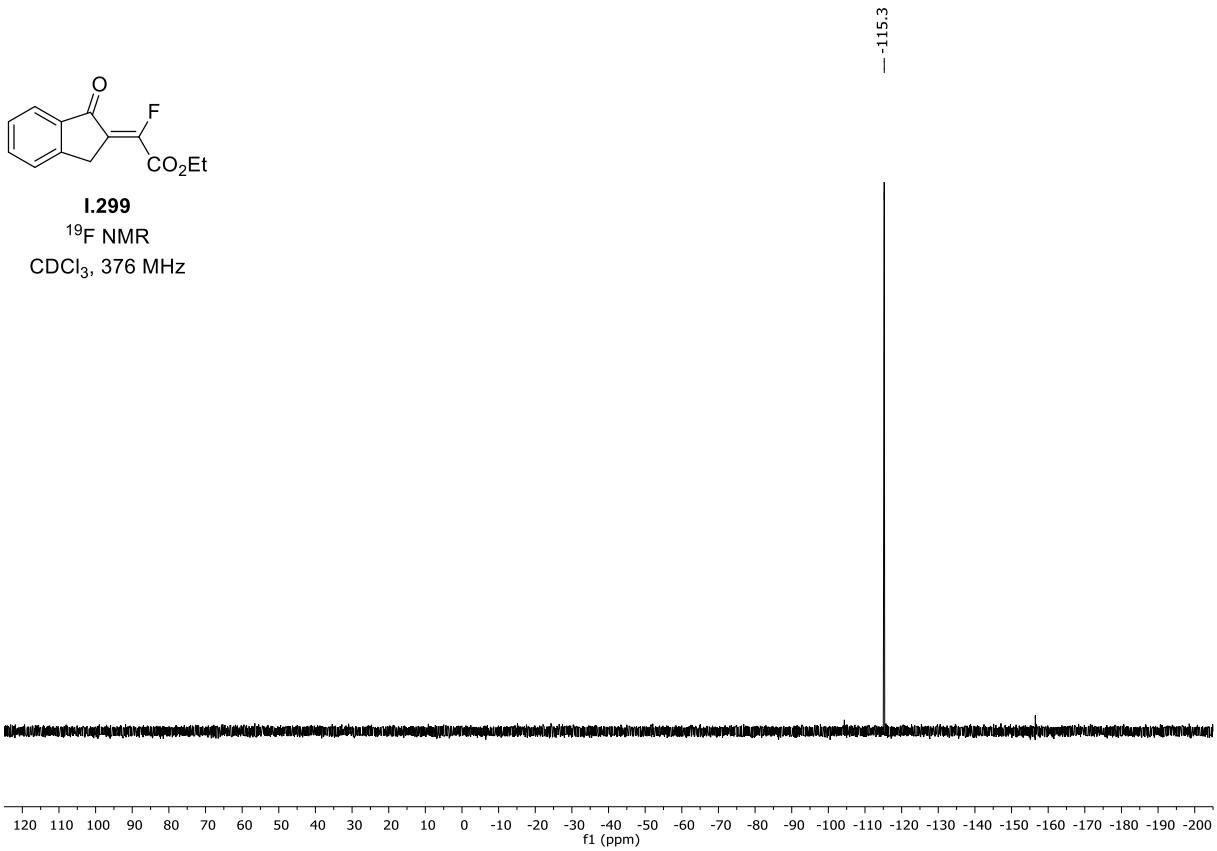
I.S5
^{13}C NMR
$CDCl_3$, 150 MHz



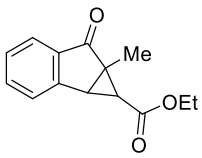
I.299
^{1}H NMR
$CDCl_3$, 800 MHz



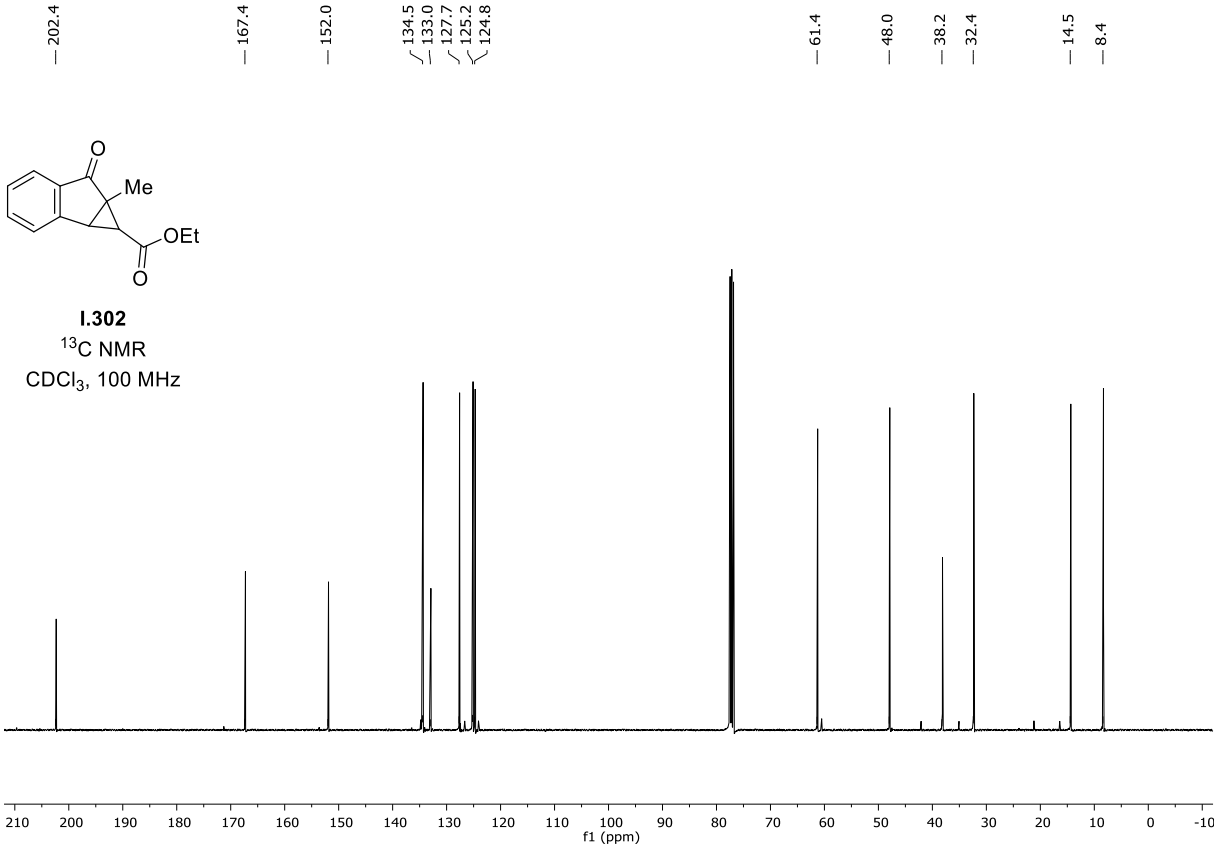
I.299
^{13}C NMR
$CDCl_3$, 200 MHz



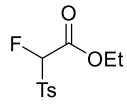
I.299
^{19}F NMR
$CDCl_3$, 376 MHz



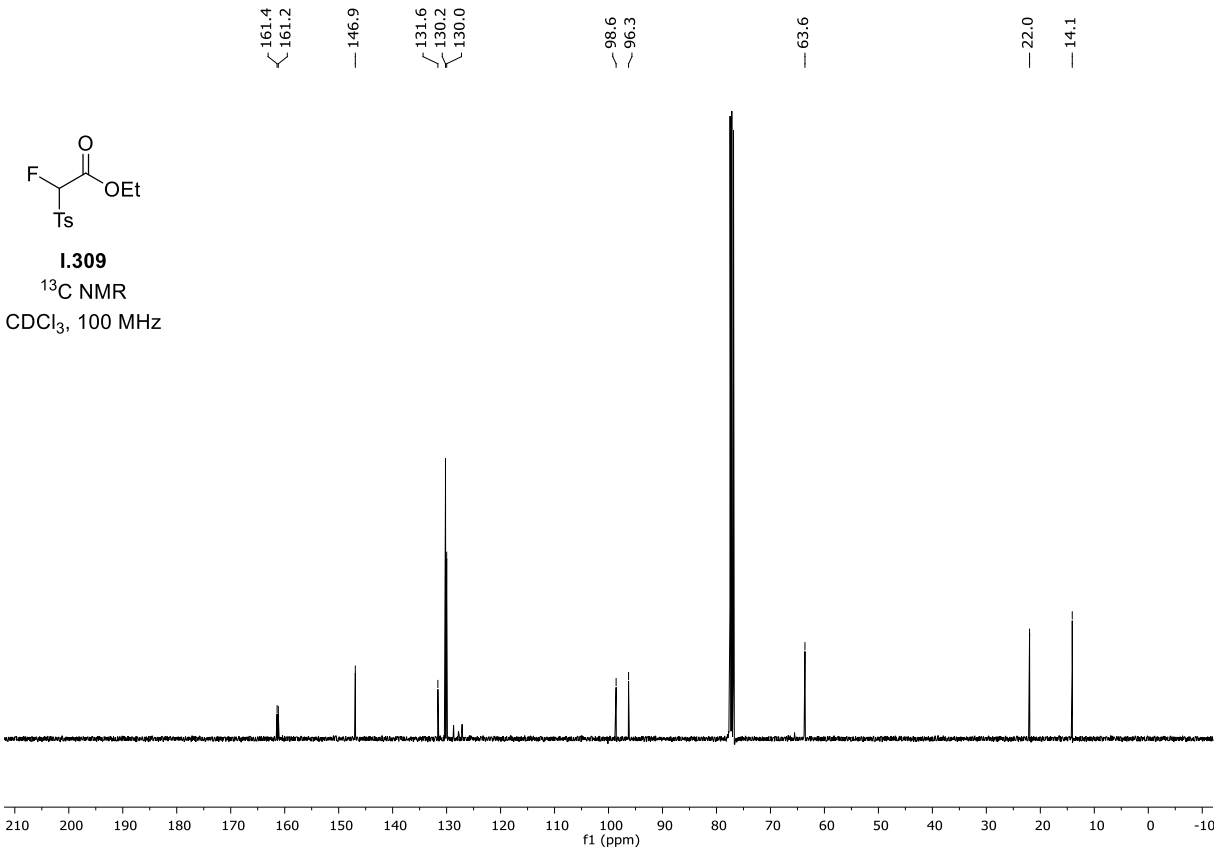
I.302
^{1}H NMR
$CDCl_3$, 400 MHz



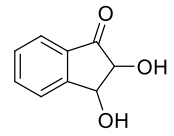
I.302
^{13}C NMR
$CDCl_3$, 100 MHz



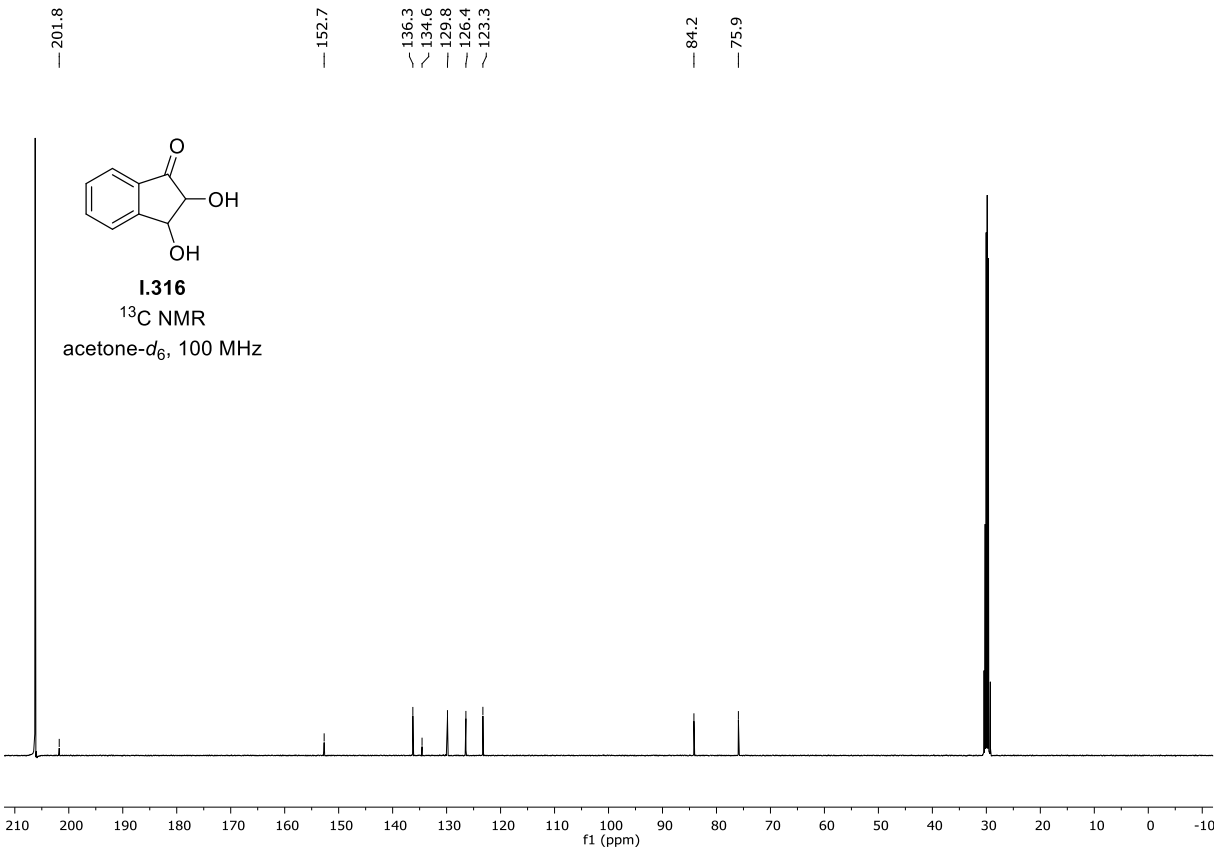
I.309
^{1}H NMR
$CDCl_3$, 400 MHz



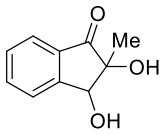
I.309
^{13}C NMR
$CDCl_3$, 100 MHz



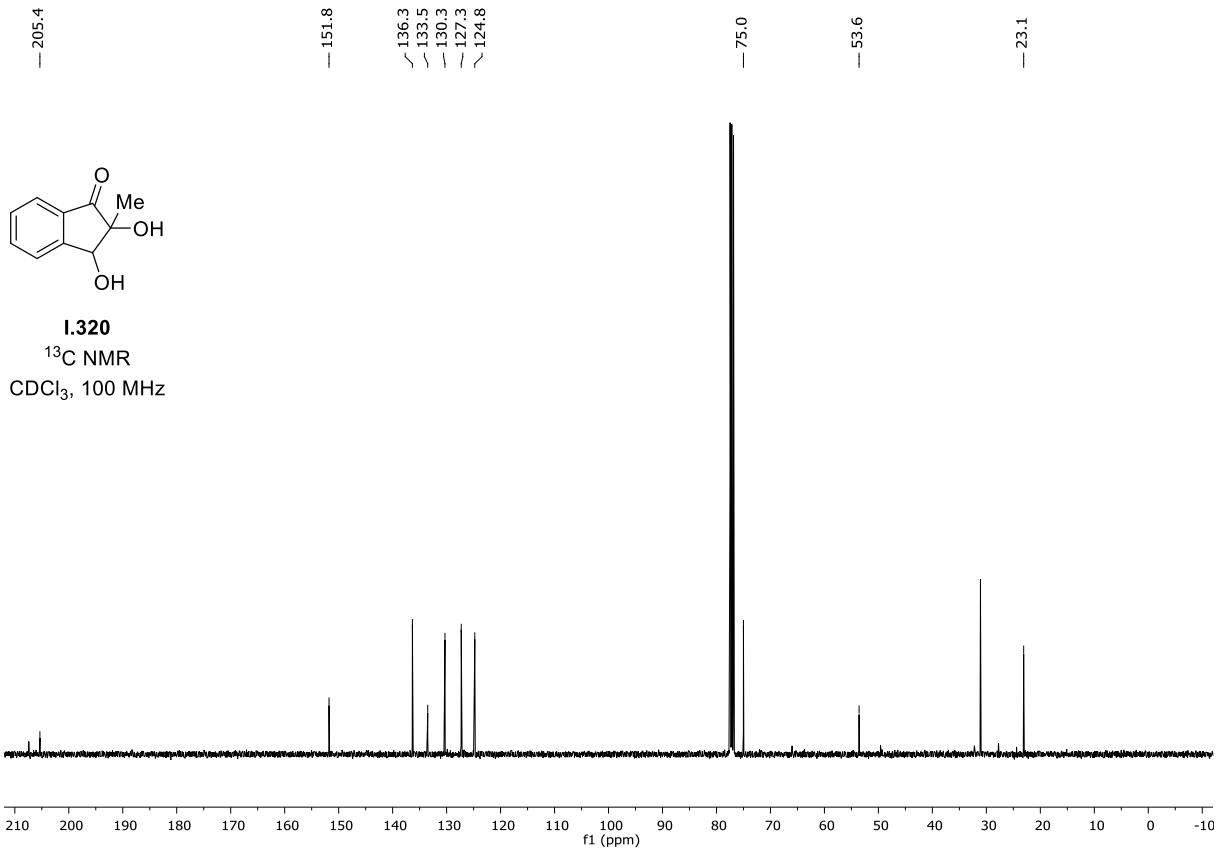
I.316
^{1}H NMR
acetone-d_6, 400 MHz



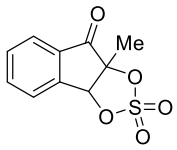
I.316
^{13}C NMR
acetone-d_6, 100 MHz



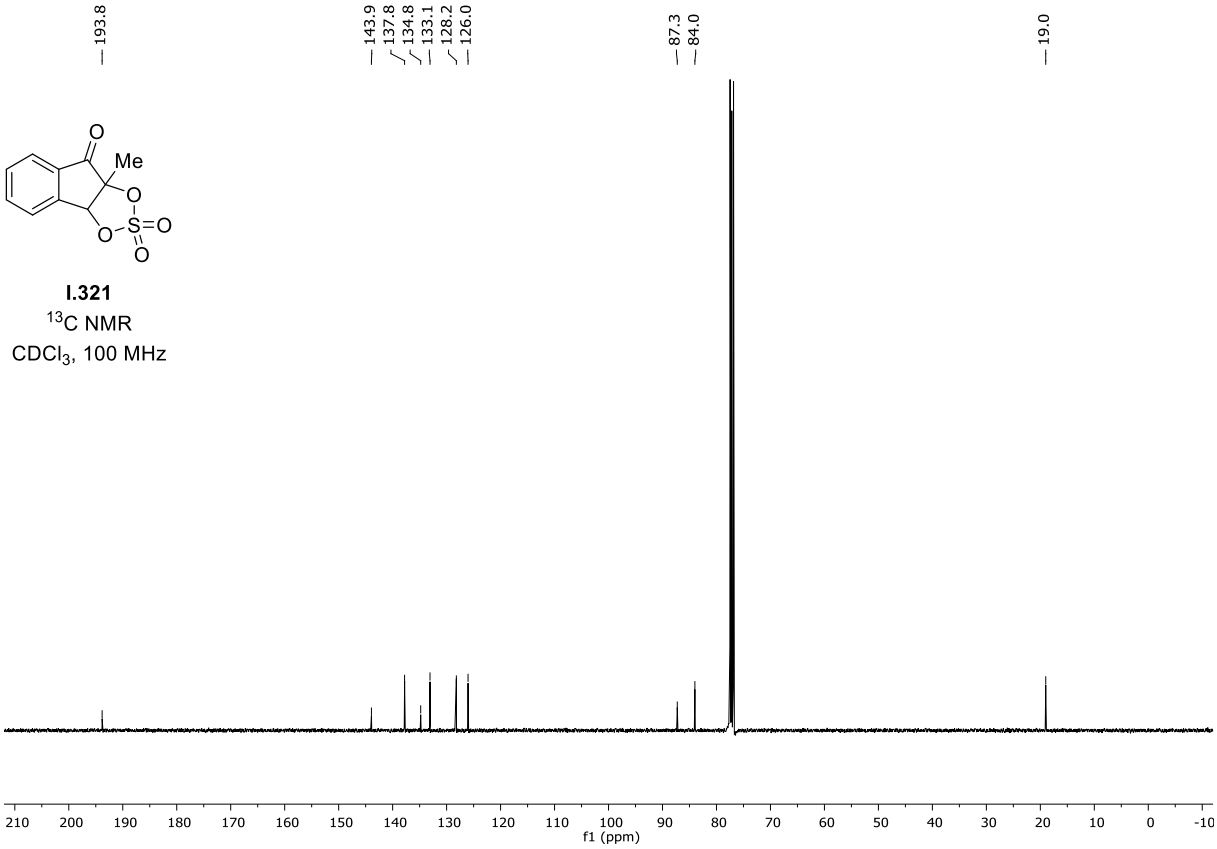
I.320
^{1}H NMR
$CDCl_3$, 400 MHz



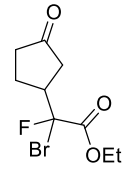
I.320
^{13}C NMR
$CDCl_3$, 100 MHz



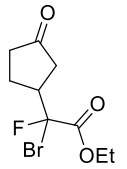
I.321
^{1}H NMR
$CDCl_3$, 400 MHz



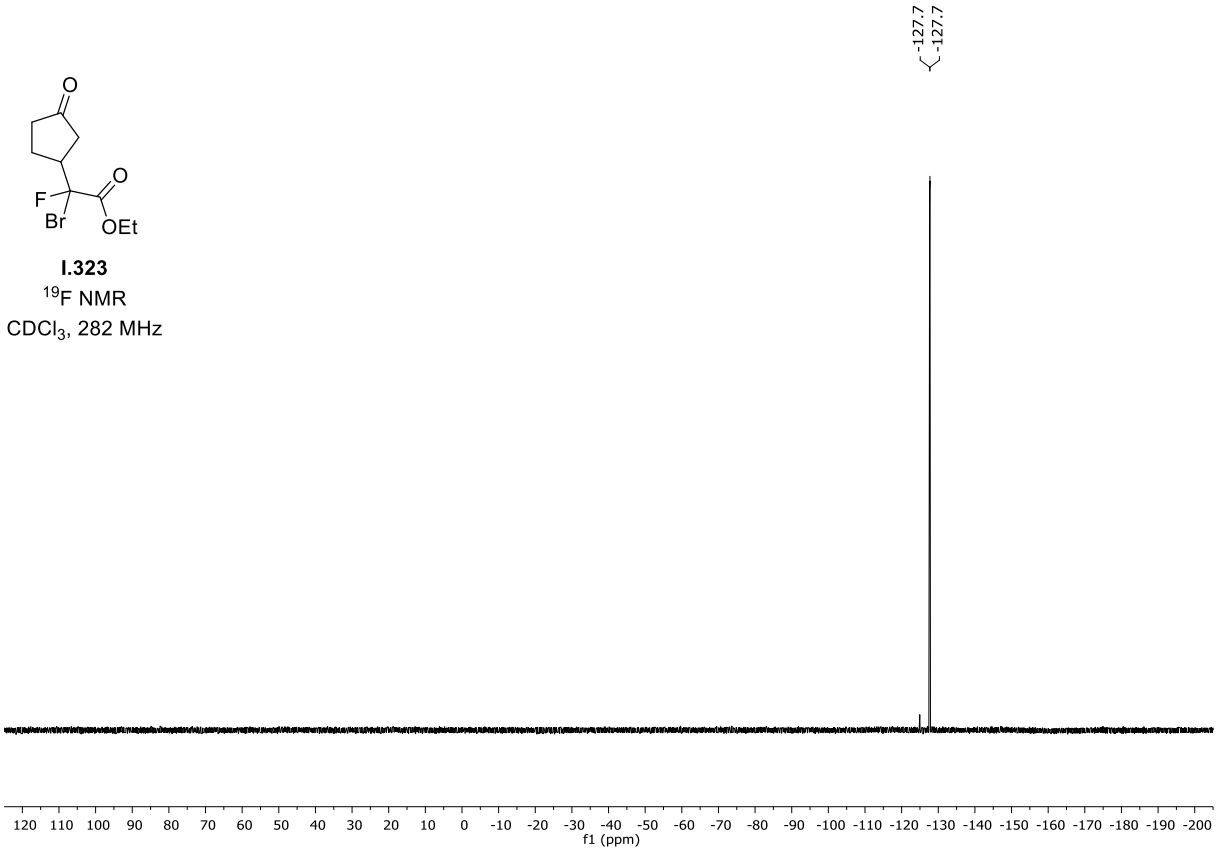
I.321
^{13}C NMR
$CDCl_3$, 100 MHz



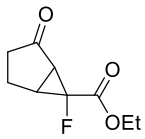
I.323
^{1}H NMR
$CDCl_3$, 300 MHz



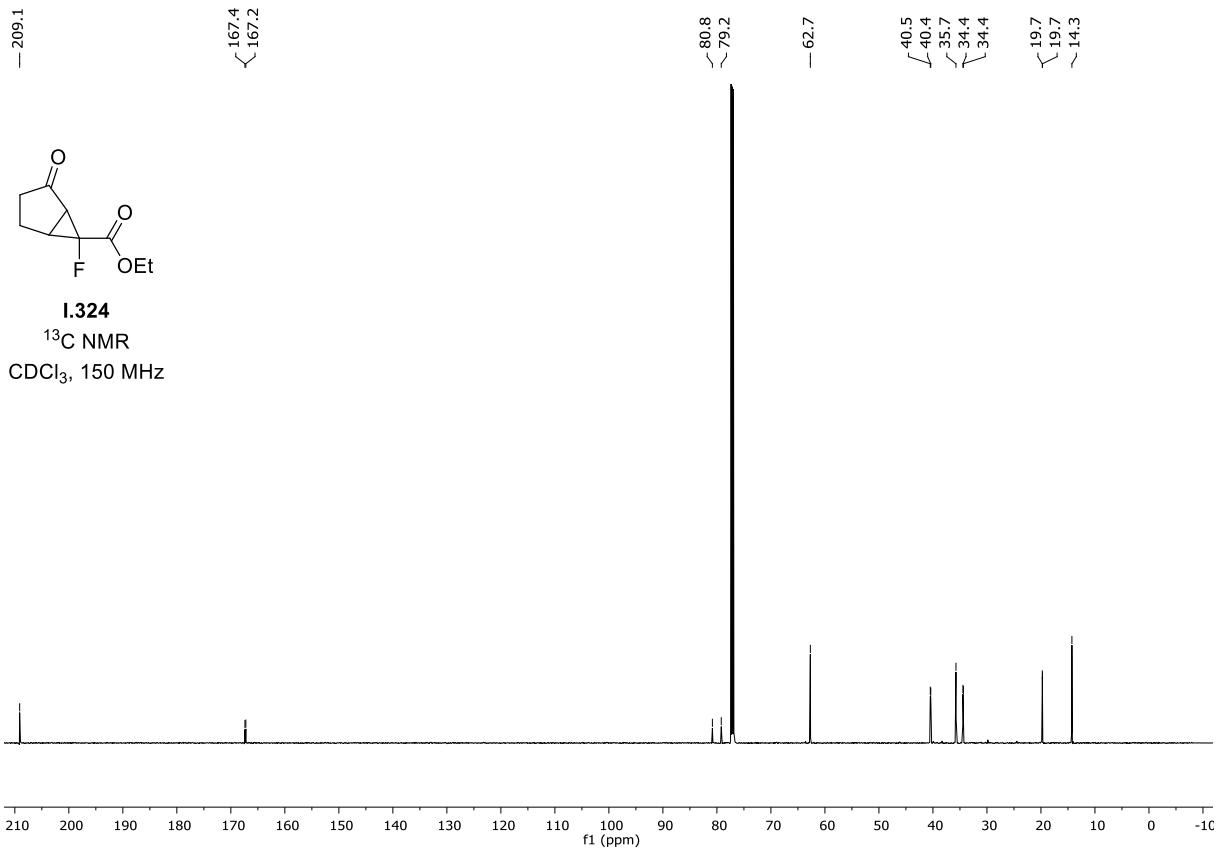
I.323
^{13}C NMR
$CDCl_3$, 75 MHz



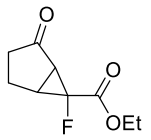
I.323
^{19}F NMR
$CDCl_3$, 282 MHz



I.324
^{1}H NMR
$CDCl_3$, 600 MHz



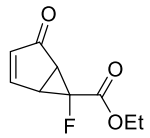
I.324
^{13}C NMR
$CDCl_3$, 150 MHz



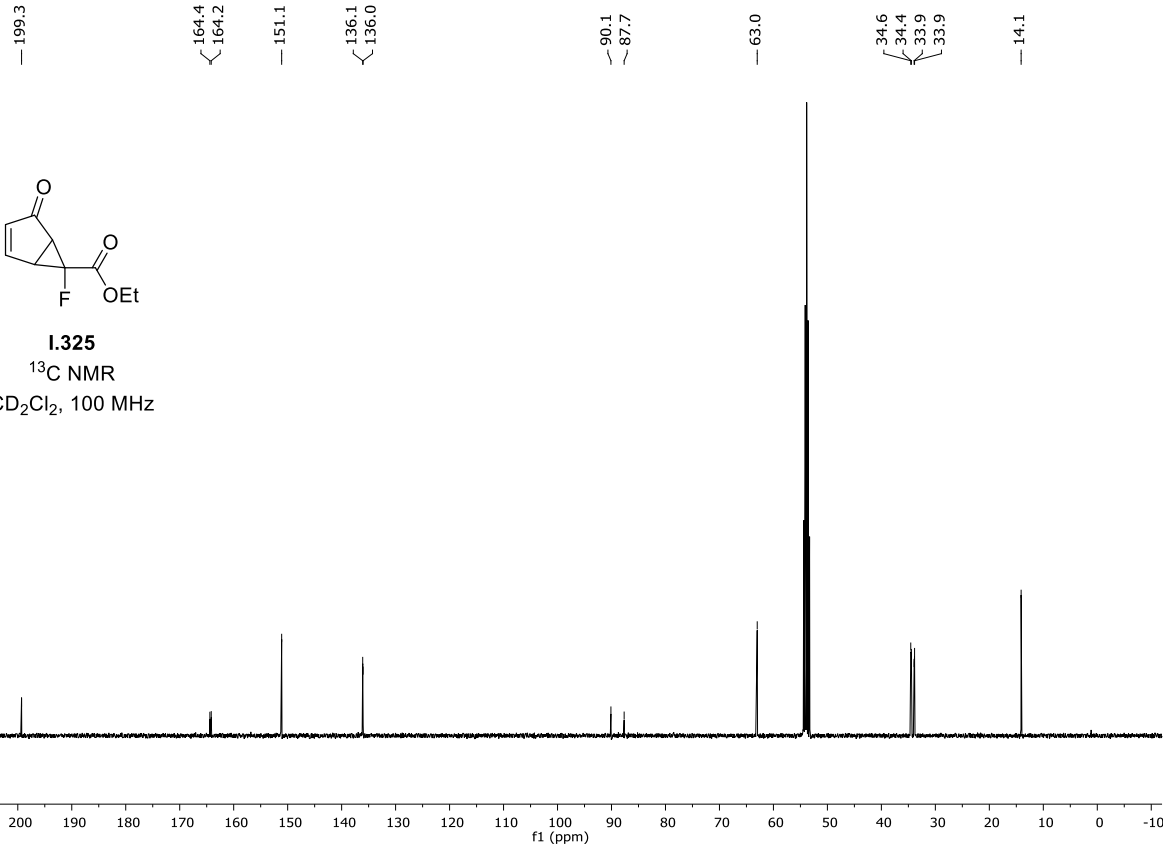
I.324

^{19}F NMR

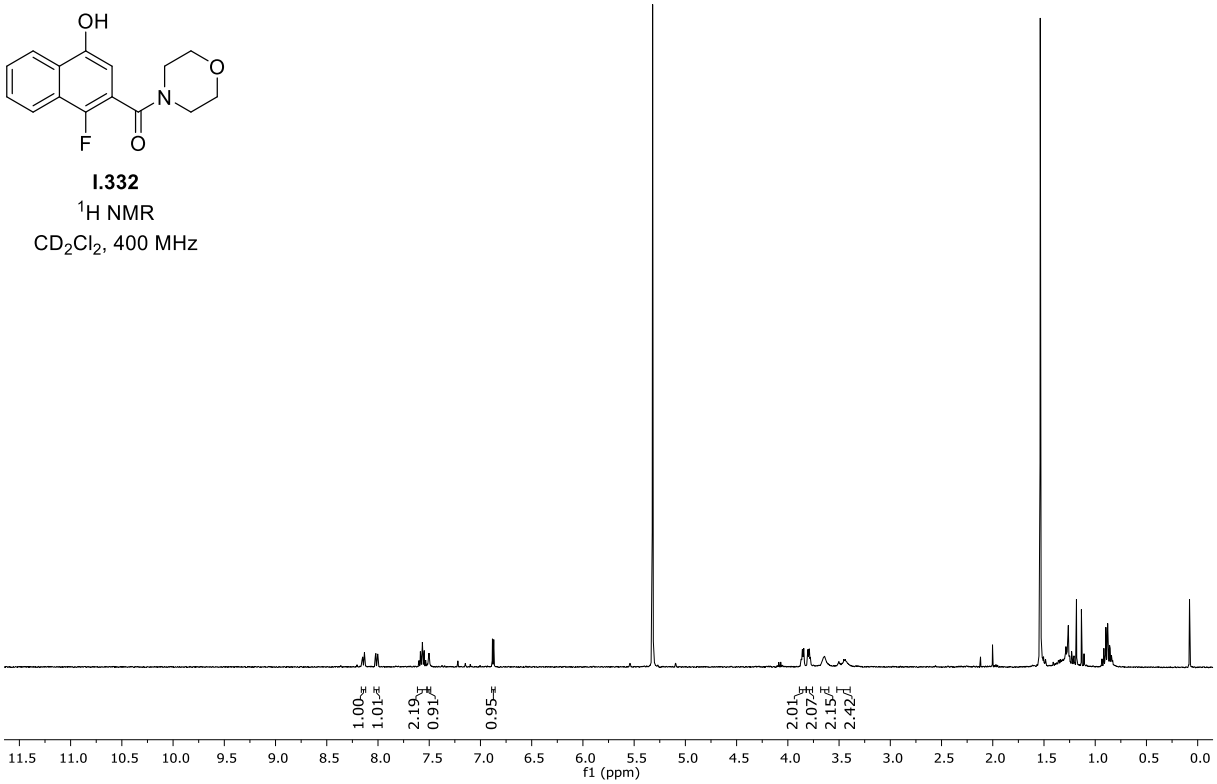
$CDCl_3$, 282 MHz



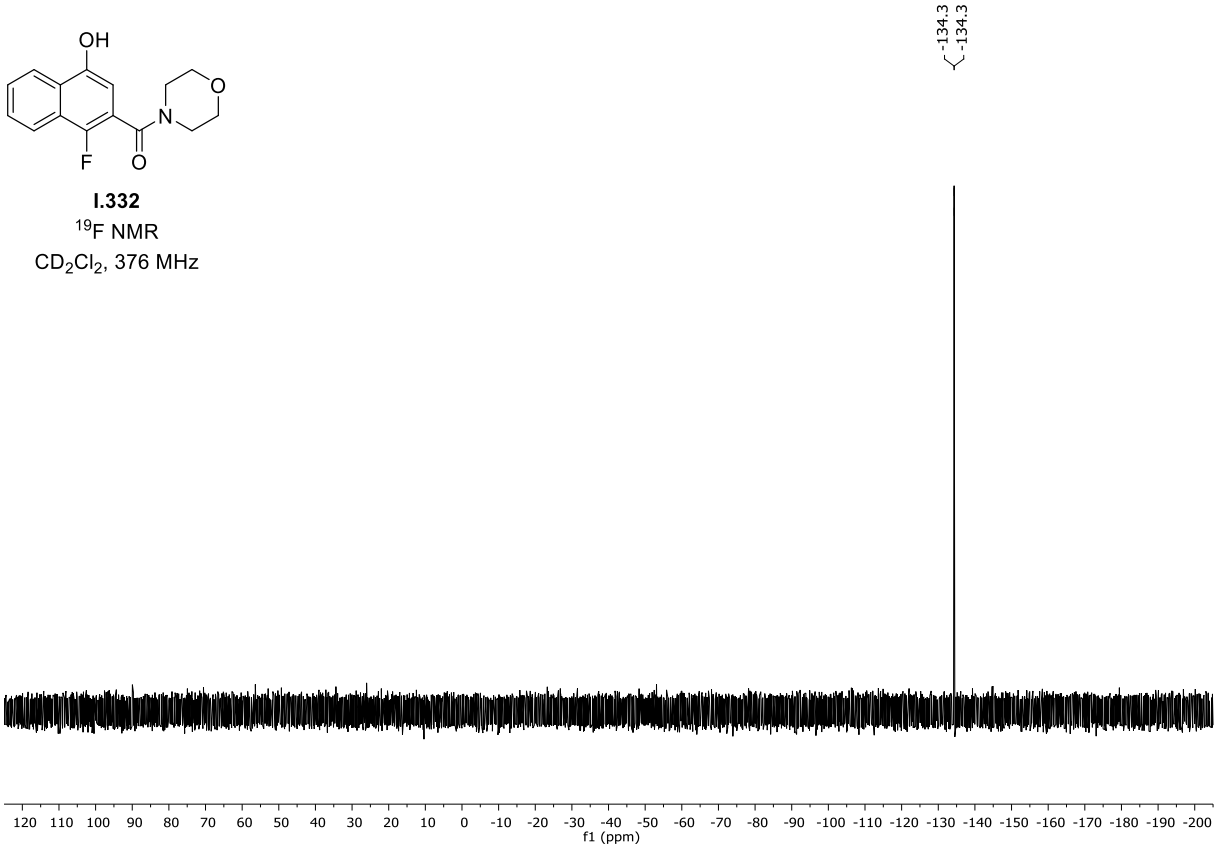
I.325
^{1}H NMR
CD_2Cl_2, 400 MHz



I.325
^{13}C NMR
CD_2Cl_2, 100 MHz



I.332
^{1}H NMR
CD_2Cl_2, 400 MHz



I.332
^{19}F NMR
CD_2Cl_2, 376 MHz

7.3.3 X-Ray Crystallographic Data

The single-crystal X-ray analyses were carried out by Dr. Peter Mayer in the analytic department. The X-Ray structural analyses were performed on an Oxford Diffraction Xcalibur, Bruker D8Quest or Bruker D8Venture diffractometer using Mo-K*a* radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 and refined by least-squares methods against F^2 with SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms.

Table 15. Crystallographic data for cyclopropane **I.257**.

net formula	$C_{25}H_{19}FO_3$
M_r/g mol^{-1}	386.415
crystal size/mm	0.191 × 0.113 × 0.068
T/K	173(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Quest'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	14.6512(13)
b/Å	9.1204(9)
c/Å	15.5982(14)
α/°	90
β/°	111.692(2)
γ/°	90
V/Å^3	1936.7(3)
Z	4
calc. density/g cm^{-3}	1.3253(2)
μ/mm^{-1}	0.093
absorption correction	multi-scan
transmission factor range	0.9194–0.9580
refls. measured	28523
R_{int}	0.0868
mean σ(I)/I	0.0505
θ range	2.64–25.39
observed refls.	2289
x, y (weighting scheme)	0.0456, 1.0359

hydrogen refinement	constr
refls in refinement	3546
parameters	263
restraints	0
$R(F_{obs})$	0.0485
$R_w(F^2)$	0.1195
S	1.025
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.254
min electron density/e Å^{-3}	−0.236

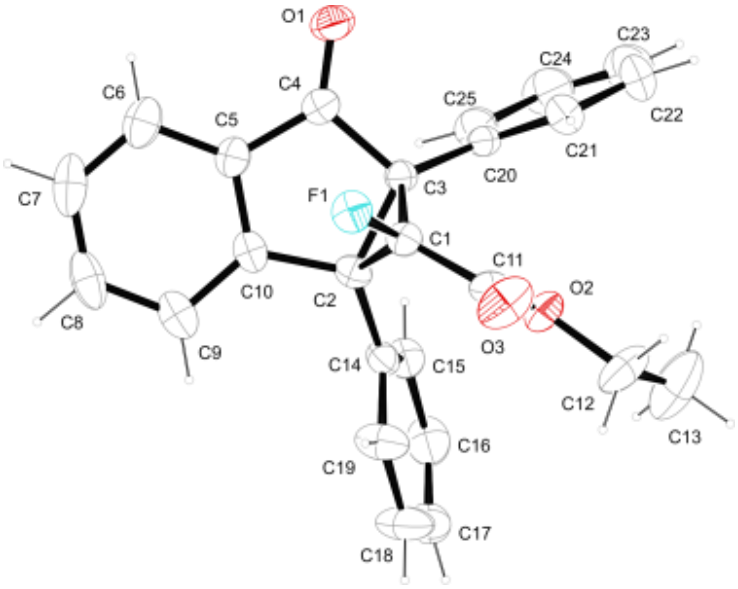
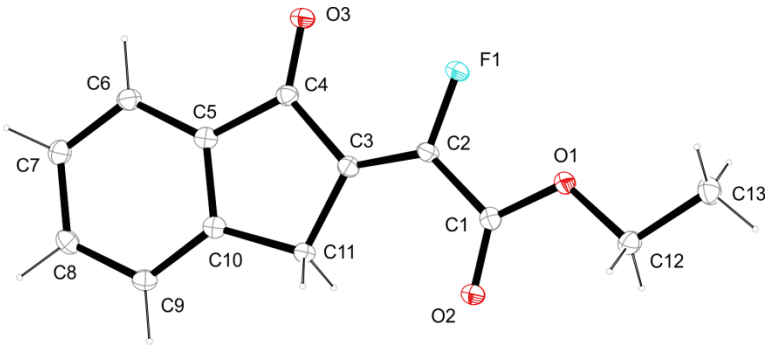


Table 16. Crystallographic data for **I.299**.

net formula	$C_{13}H_{11}FO_3$
M_r/g mol^{-1}	234.22
crystal size/mm	0.100 × 0.080 × 0.060
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	'P -1'
a/Å	7.7116(5)
b/Å	8.3039(5)

c/Å	9.4619(5)
α/°	92.0946(18)
β/°	103.2287(18)
γ/°	110.7448(18)
V/Å^3	546.97(6)
Z	2
calc. density/g cm^{-3}	1.422
μ/mm^{-1}	0.112
absorption correction	multi-scan
transmission factor range	0.8876–0.9585
refls. measured	9365
R_{int}	0.0285
mean σ(I)/I	0.0276
θ range	2.924–26.38
observed refls.	1804
x, y (weighting scheme)	0.0637, 0.2950
hydrogen refinement	constr
refls in refinement	2244
parameters	155
restraints	0
$R(F_{obs})$	0.0440
$R_w(F^2)$	0.1251
S	1.044
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.442
min electron density/e Å^{-3}	−0.185

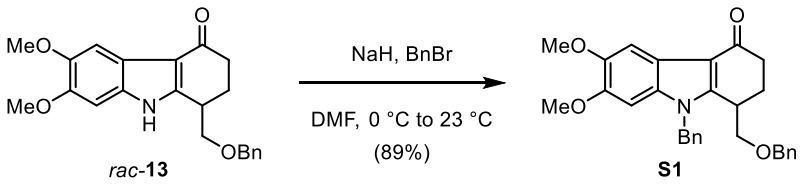


7.4 Supporting Information for Chapter 5.1

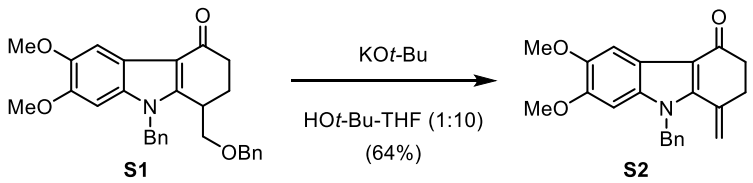
Development of a β-C–H Bromination Approach Towards the Synthesis of Jerantinine E

T. Huber, T. A. Preuhs, C. K. G. Gerlinger**,** T. Magauer**,** *J. Org. Chem.* **2017**, *82,* 7410–7419.

7.4.1 Experimental Procedures



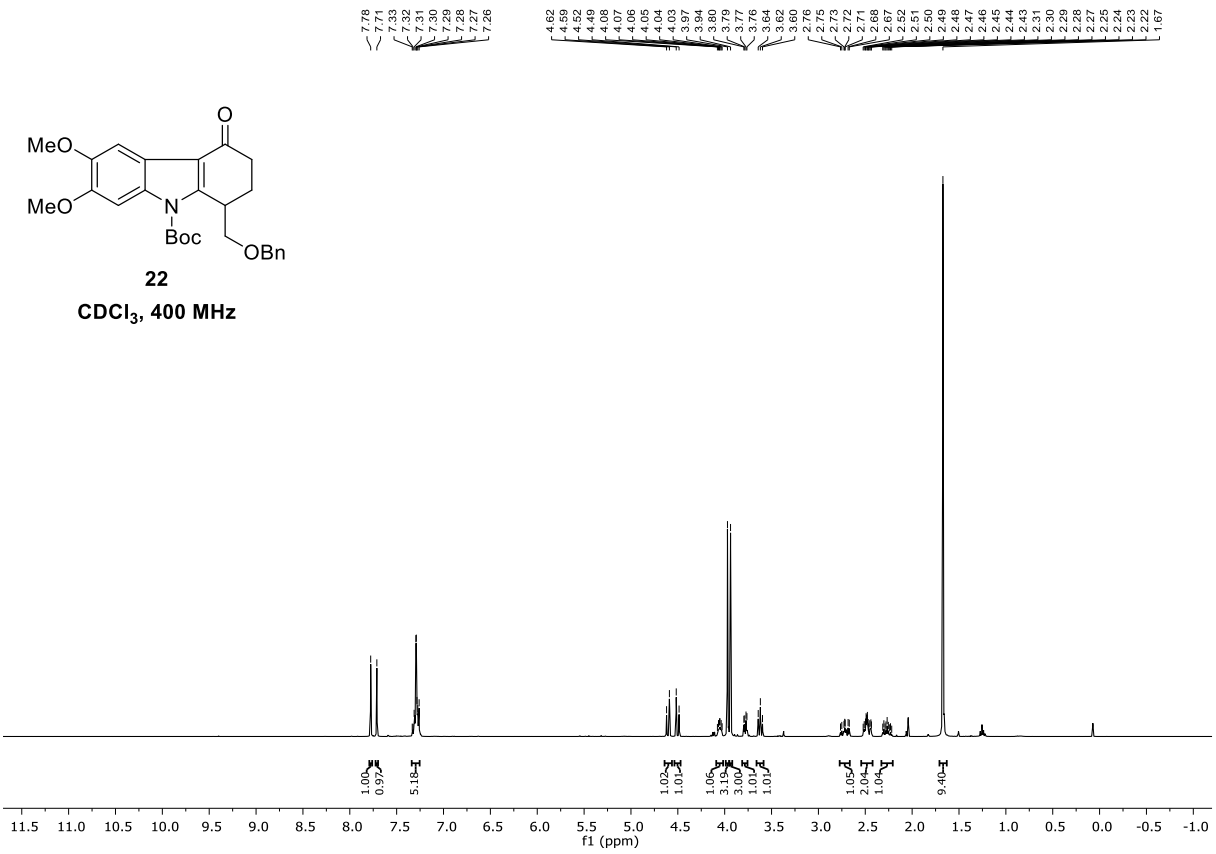
***N*-Benzyltetrahydrocarbazolone S1**. To a solution of tetrahydrocarbazolone *rac*-**13** (90 mg, 0.25 mmol, 1 equiv) in *N,N*-dimethylformamide (1.2 mL) was added sodium hydride (15 mg, 0.37 mmol, 1.5 equiv, 60% dispersion in mineral oil) at 0 °C. After 30 min, benzyl bromide (51 mg, 0.30 mmol, 1.5 equiv) was added and the solution was allowed to warm to 23 °C. After 2 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **S1** as a white foam (100 mg, 89%). TLC (50% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (s, 1H), 7.36–7.20 (m, 8H), 7.02–6.93 (m, 2H), 6.65 (s, 1H), 5.49 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 4.48–4.38 (m, 2H), 3.89 (s, 3H), 3.73 (s, 4H), 3.72–3.68 (m, 1H), 3.61 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.41–3.30 (m, 1H), 2.66 (ddd, *J* = 18.3, 13.6, 5.4 Hz, 1H), 2.45–2.20 (m, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 193.9, 150.8, 148.1, 147.7, 138.6, 137.2, 131.9, 129.4, 128.9, 128.2, 128.1, 126.5, 118.2, 113.2, 103.7, 94.7, 73.7, 71.5, 56.7, 56.6, 47.9, 34.5, 33.5, 27.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1728, 1640, 1584, 1526, 1494, 1481, 1450, 1359, 1333, 1308, 1269, 1207, 1194, 1157, 1104, 1071 cm^{-1}. HR-MS (ESI): calcd for $(C_{29}H_{30}O_4N)^+$ $(M+H)^+$: 456.2175, found: 456.2164.

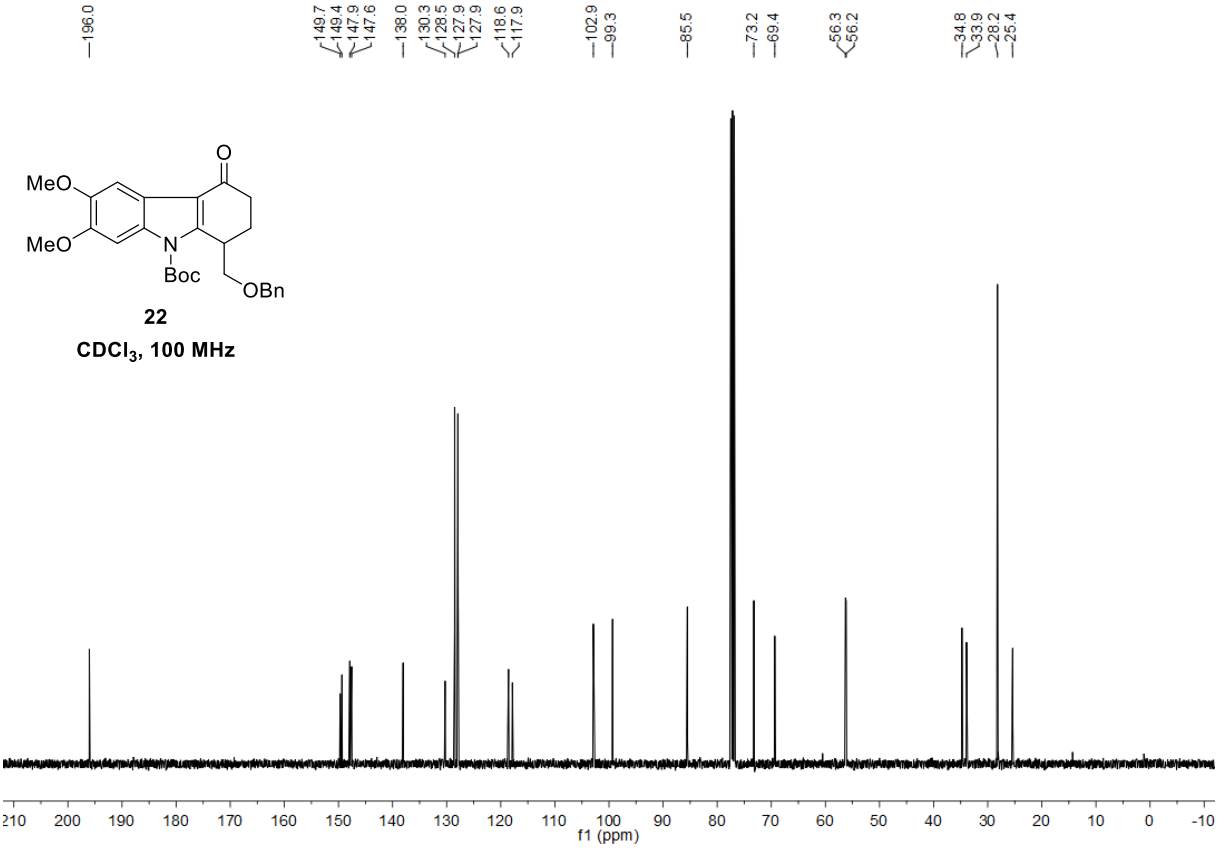


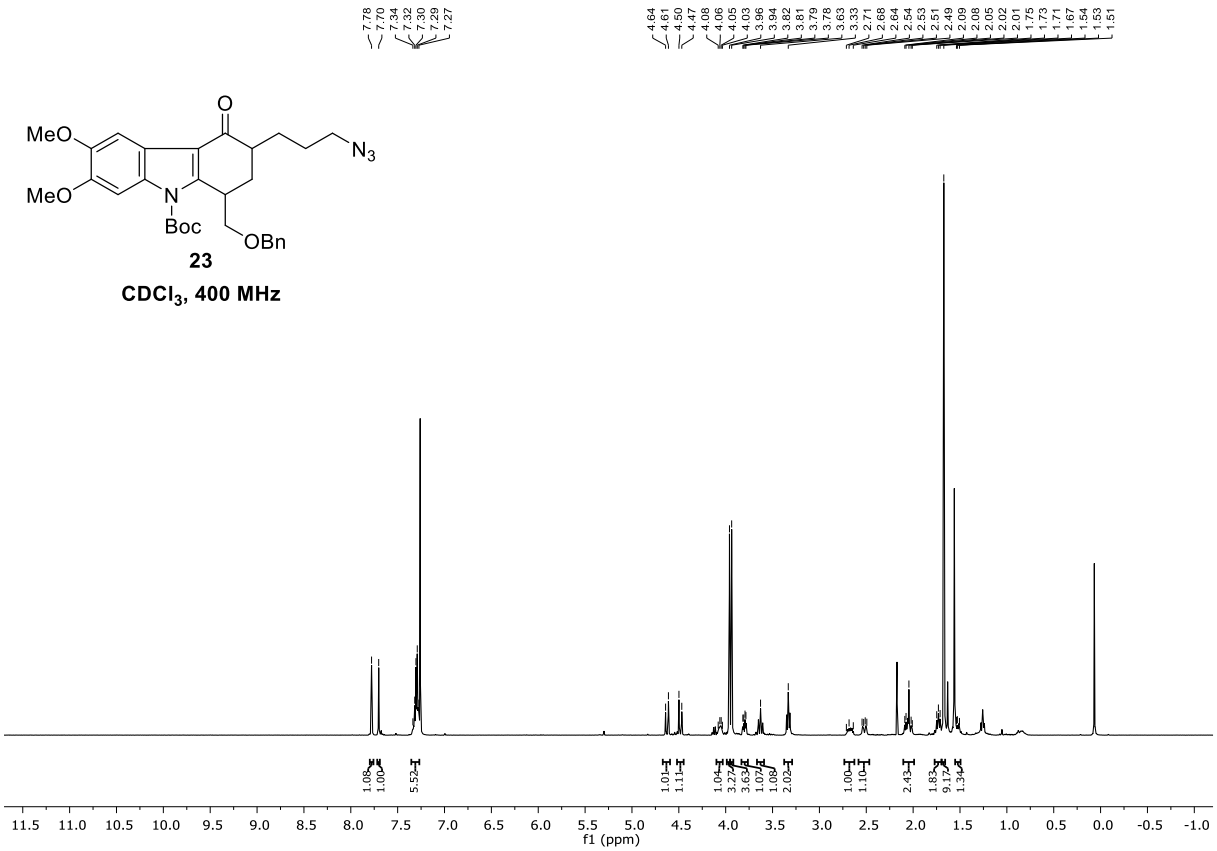
Elimination Product S2. To a solution *N*-benzyltetrahydrocarbazolone **S1** (17.5 mg, 38.4 μmol, 1 equiv) in tetrahydrofuran (0.3 mL) and *tert*-butanol (30 μL) was added potassium *tert*-butoxide (15.1 mg, 0.134 mmol, 3.50 equiv) at 0 °C and the solution was allowed to warm to 23 °C. After 1 h, the solution was diluted with saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to

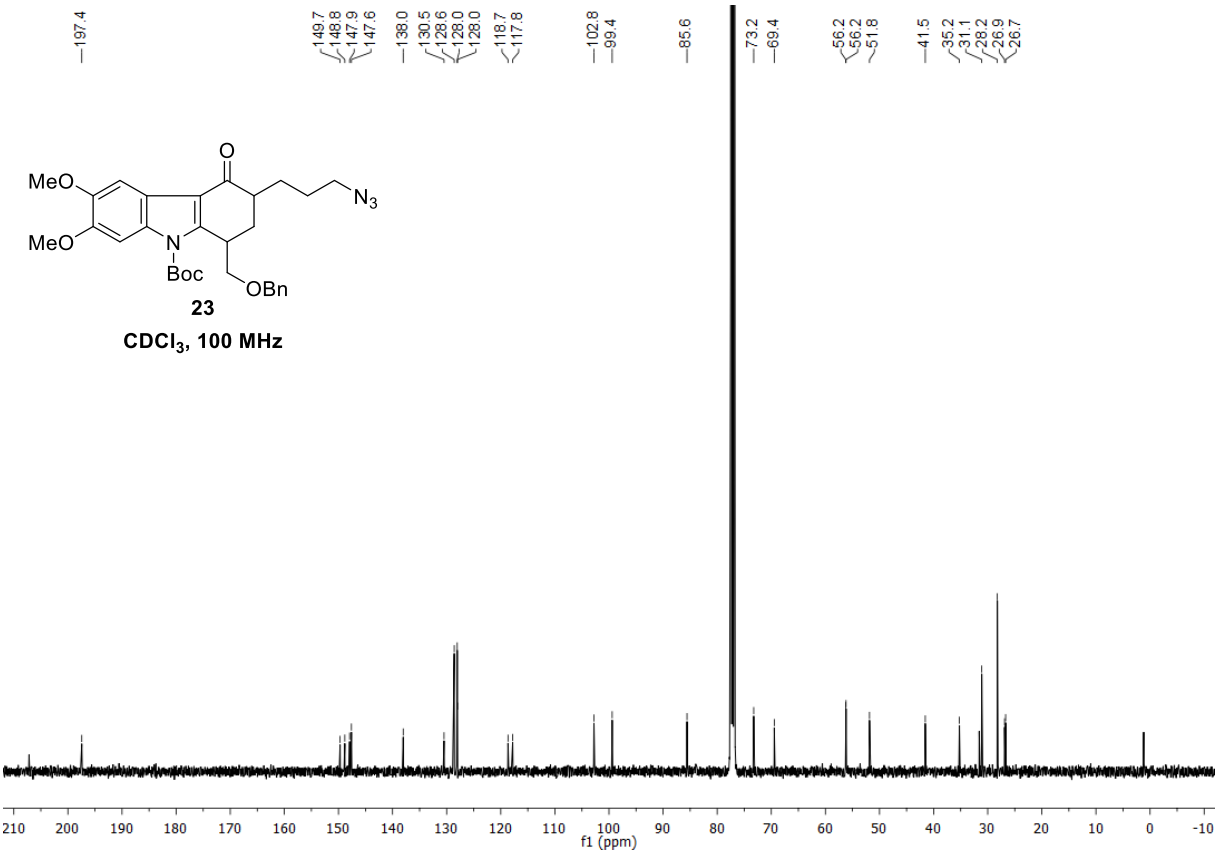
afford **S2** as a brown solid (8.5 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.39–7.29 (m, 3H), 7.13–7.07 (m, 2H), 6.64 (s, 1H), 5.51 (s, 2H), 5.34 (s, 1H), 5.13 (s, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 2.86 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 148.8, 147.6, 145.1, 136.5, 135.1, 133.6, 129.3, 127.9, 125.8, 117.5, 114.3, 113.1, 103.4, 93.3, 56.5, 56.3, 48.7, 39.4, 35.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2945, 1646, 1559, 1497, 1480, 1448, 1360, 1270, 1194, 1141, 1095, 1027 cm^{-1}. HR-MS (ESI): calcd for $(C_{22}H_{22}O_3N)^+$: 348.1600, found: 348.1591.

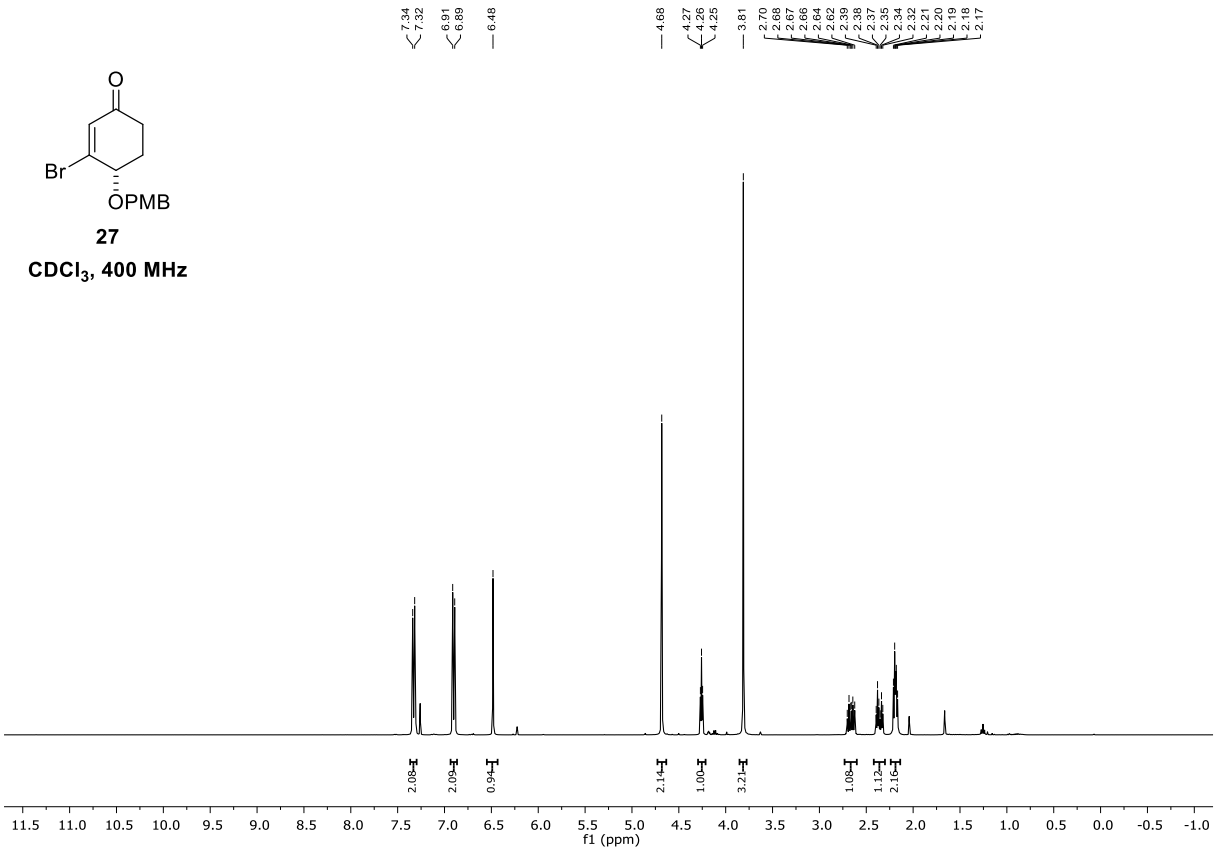
7.4.2 ^{1}H and ^{13}C NMR Spectra





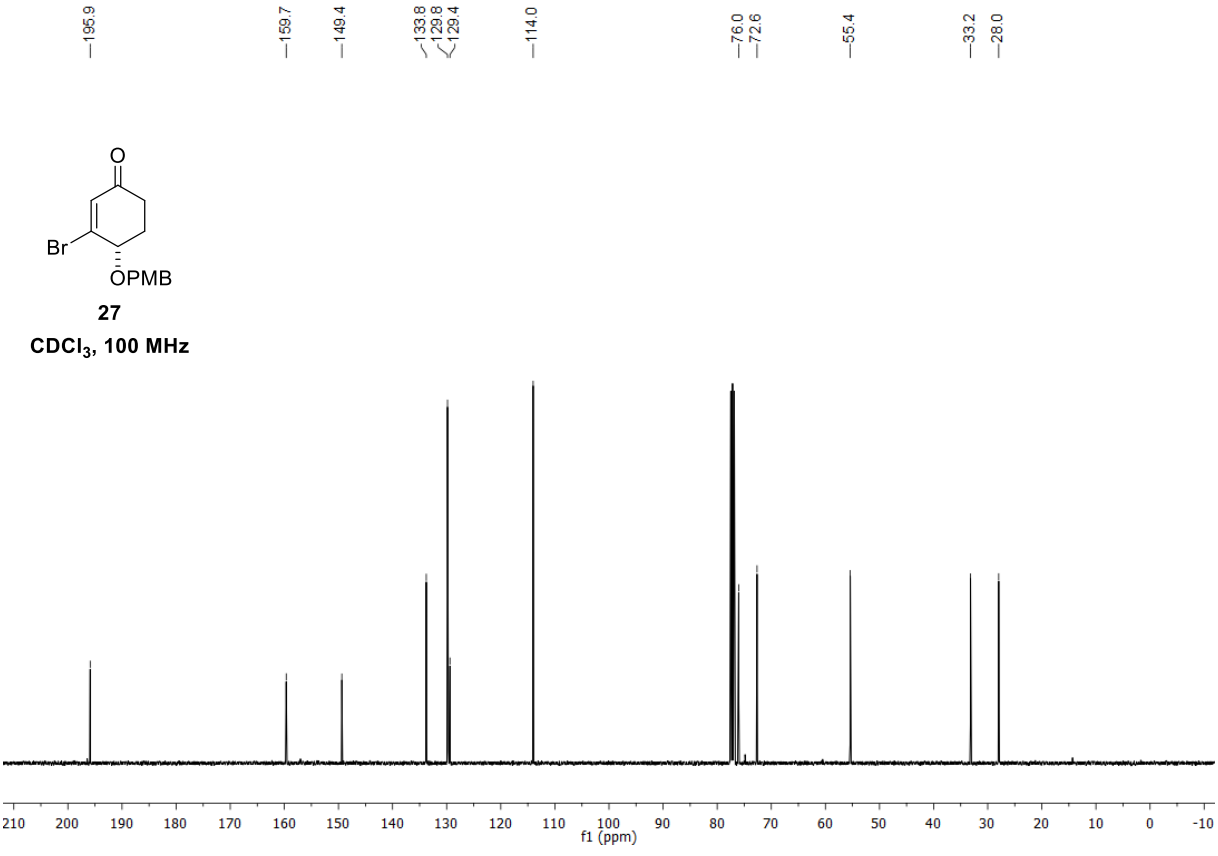

MeO
MeO
O
N
Boc
OBn
N3
23
CDCl3, 400 MHz
f1 (ppm)


MeO
MeO
O
N
Boc
OBn
N3
23
CDCl3, 100 MHz
f1 (ppm)



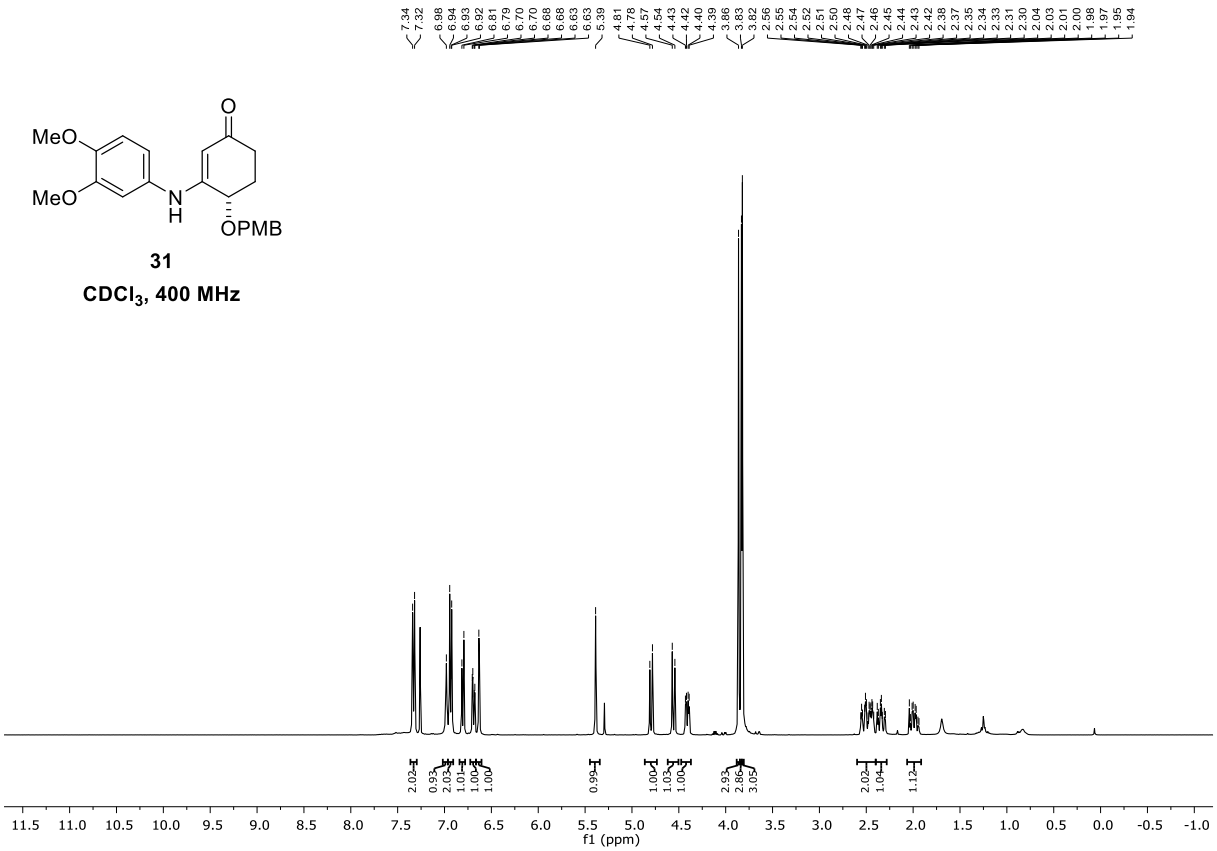
27

$CDCl_3$, 400 MHz



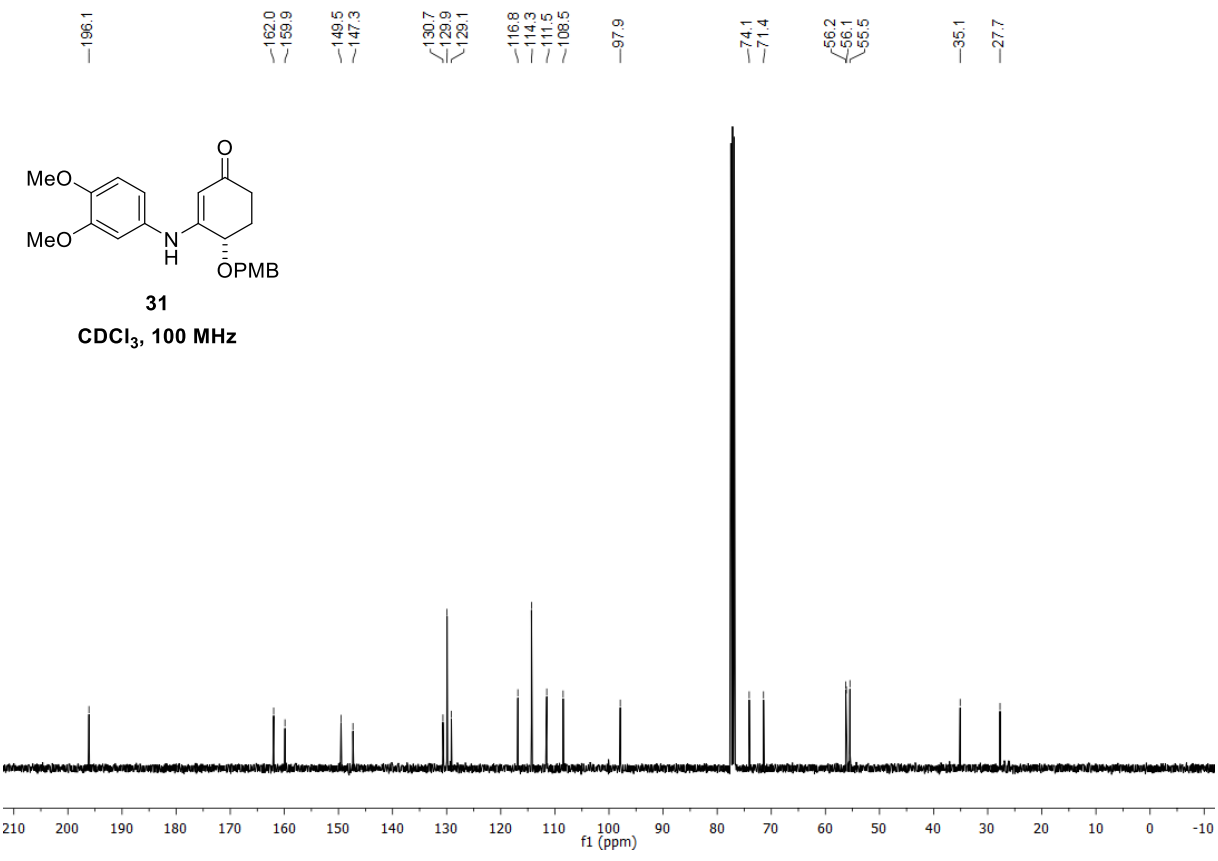
27

$CDCl_3$, 100 MHz



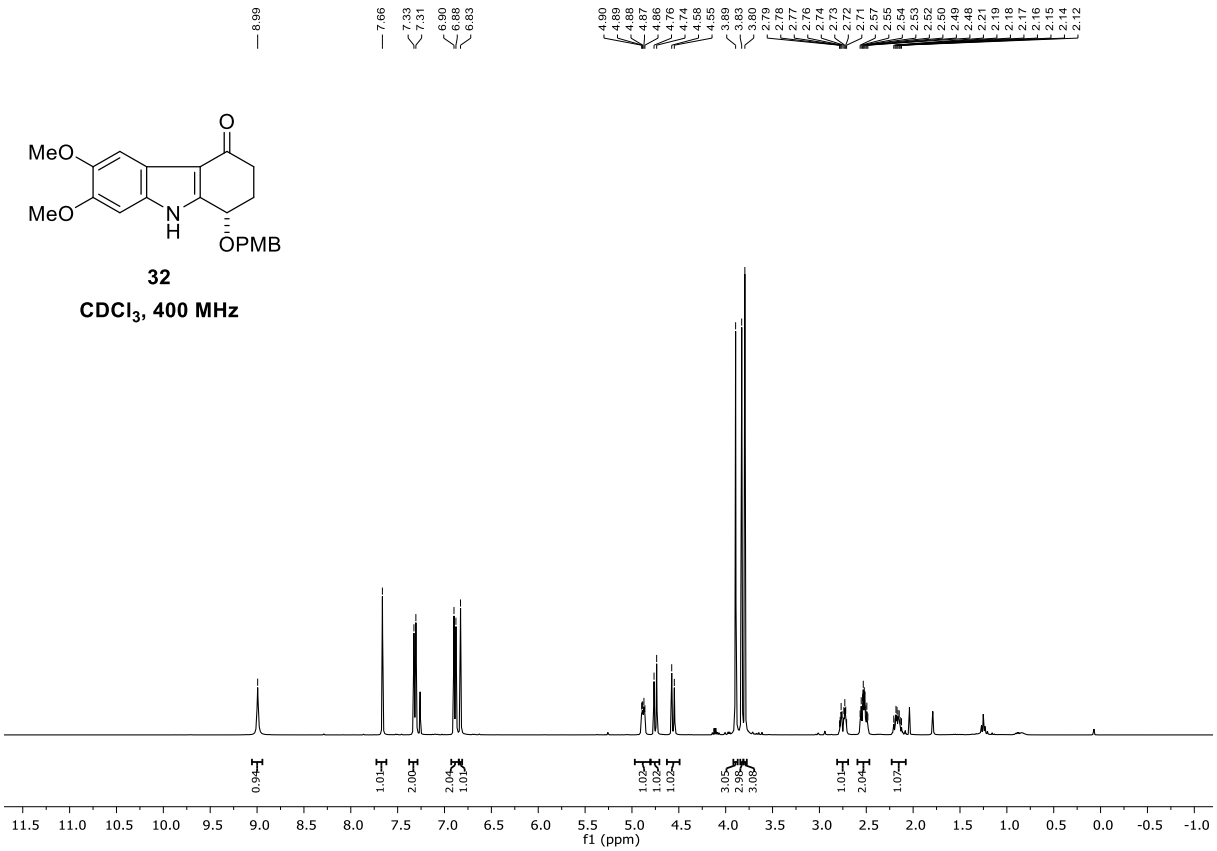
31

$CDCl_3$, 400 MHz



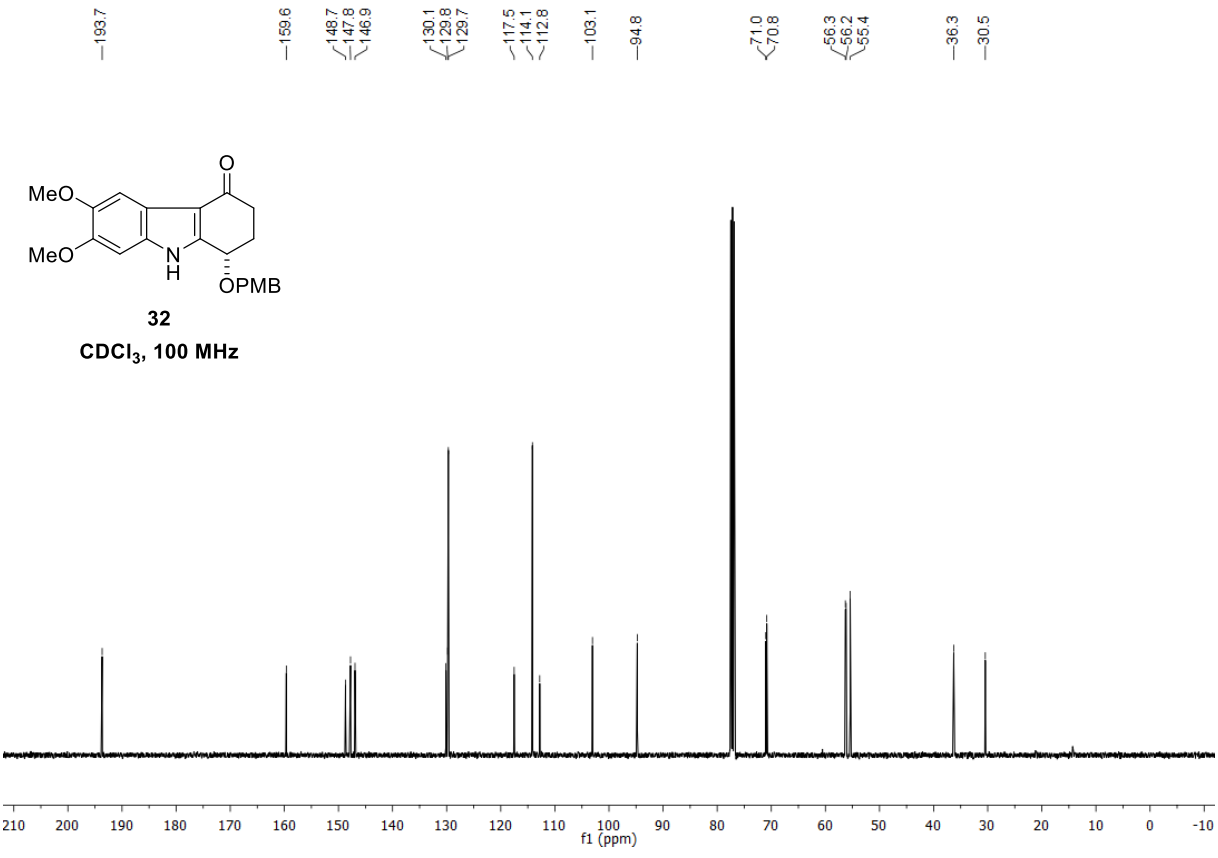
31

$CDCl_3$, 100 MHz



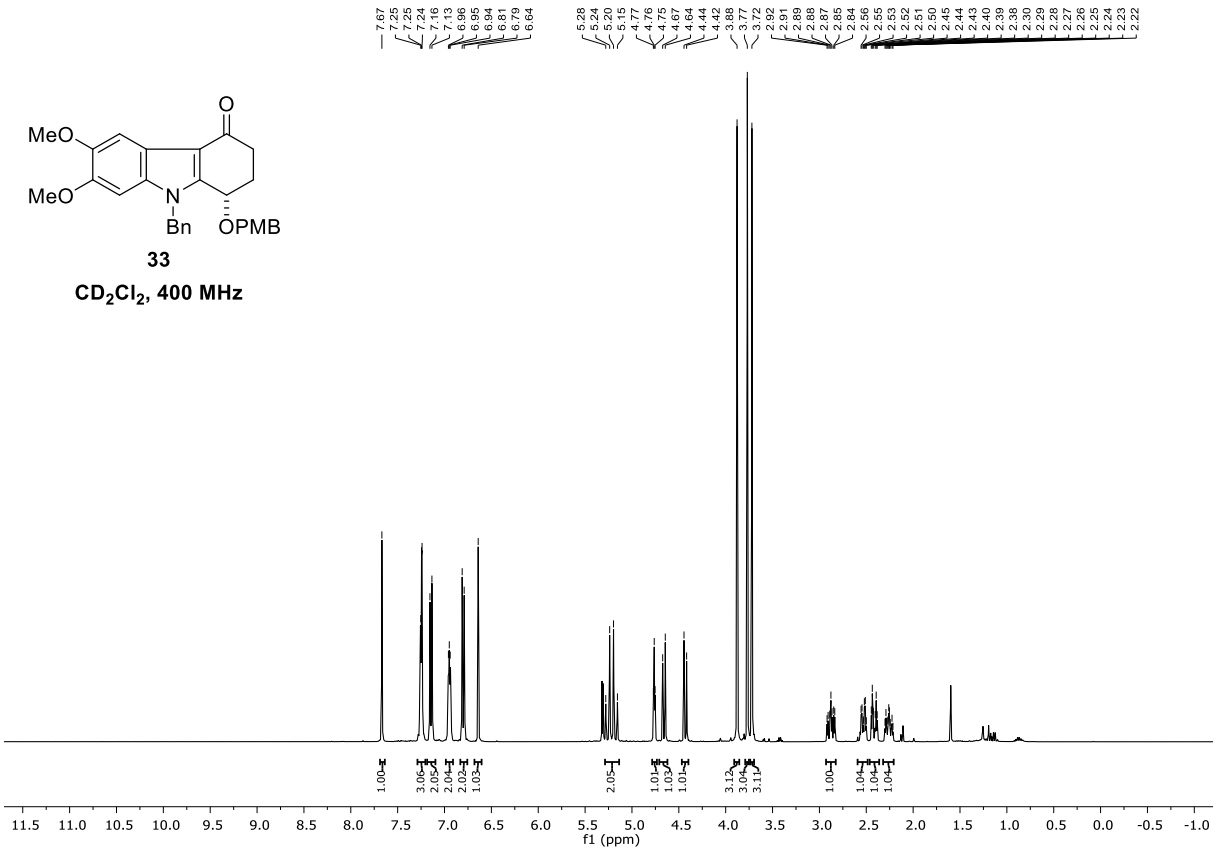
32

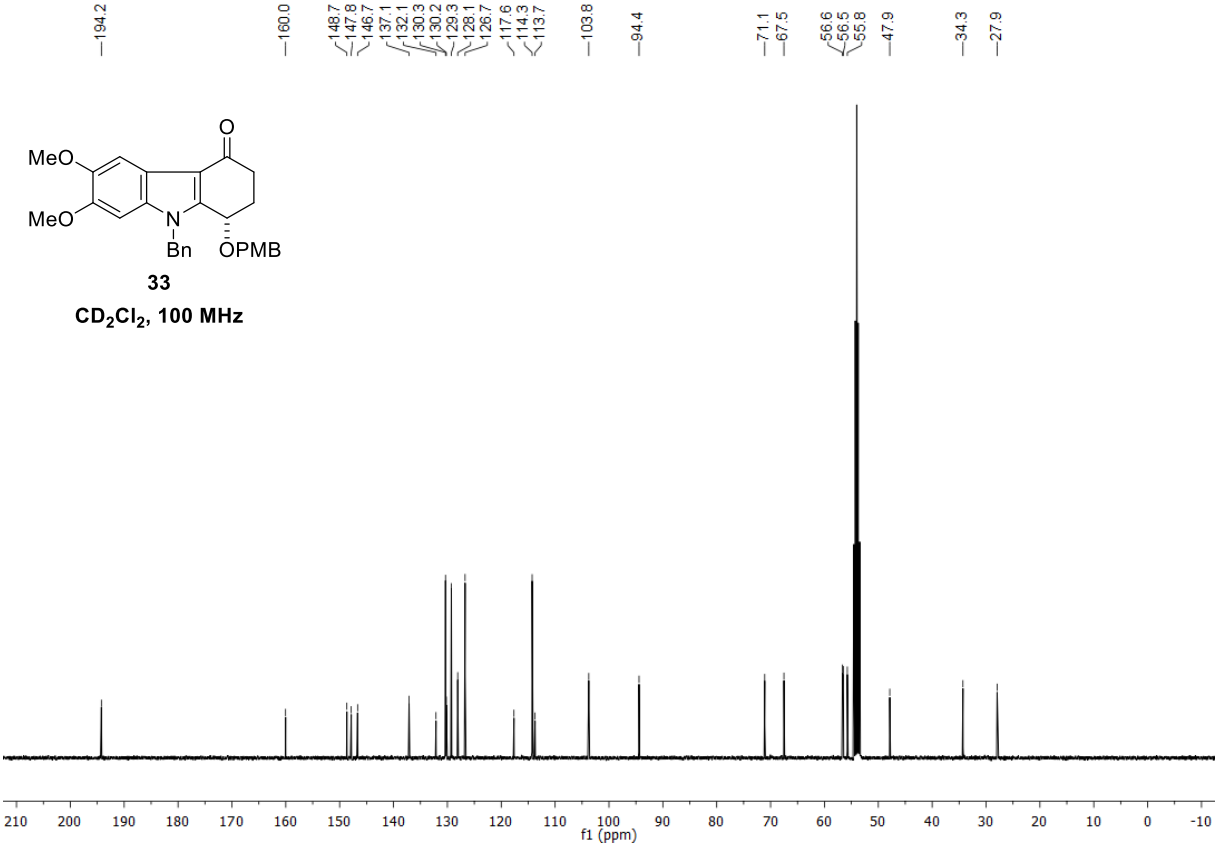
$CDCl_3$, 400 MHz

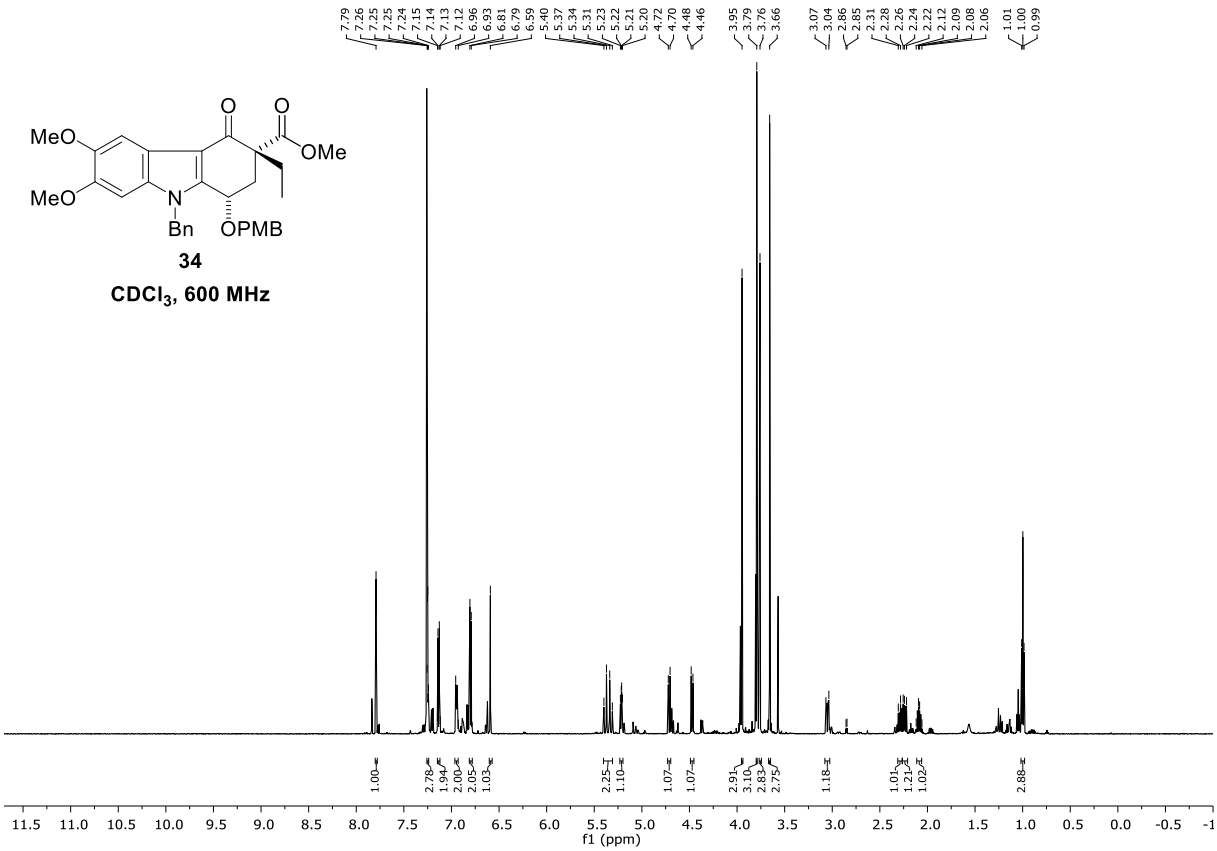


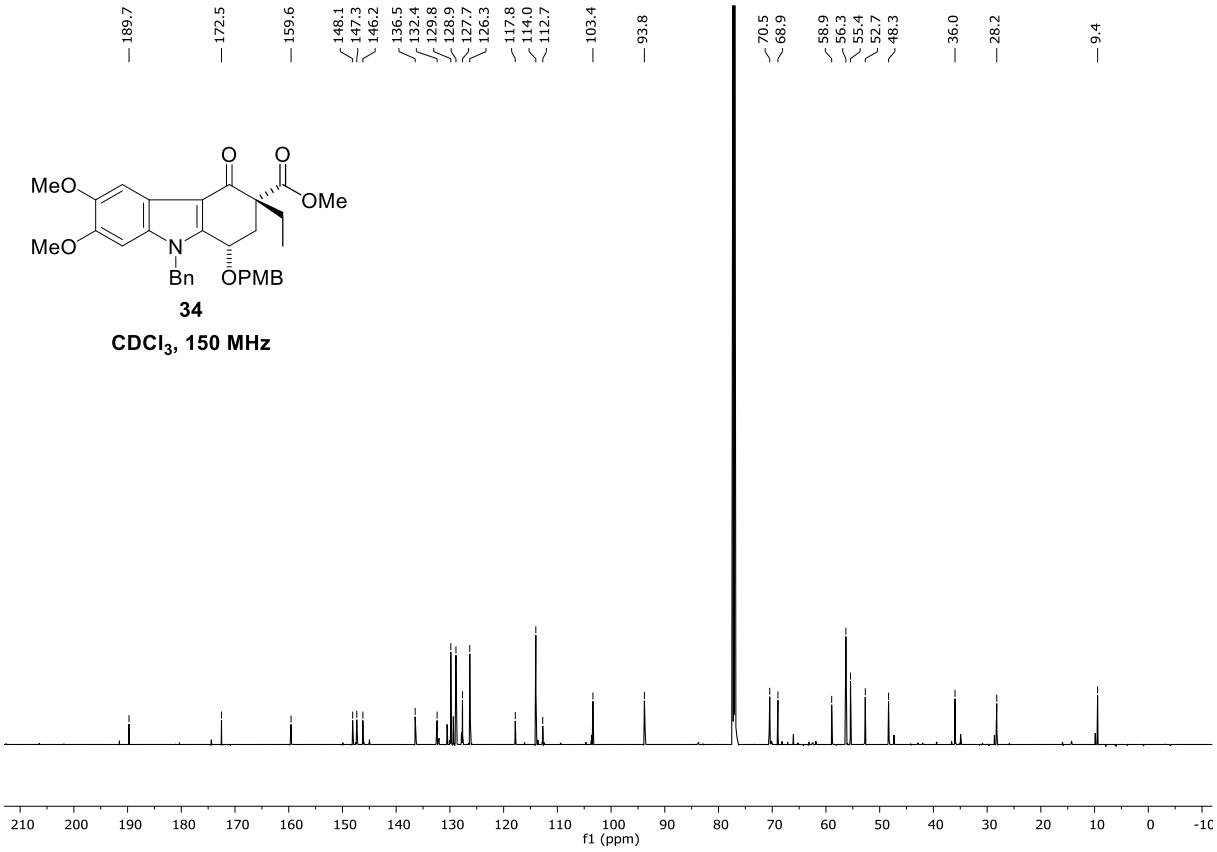
32

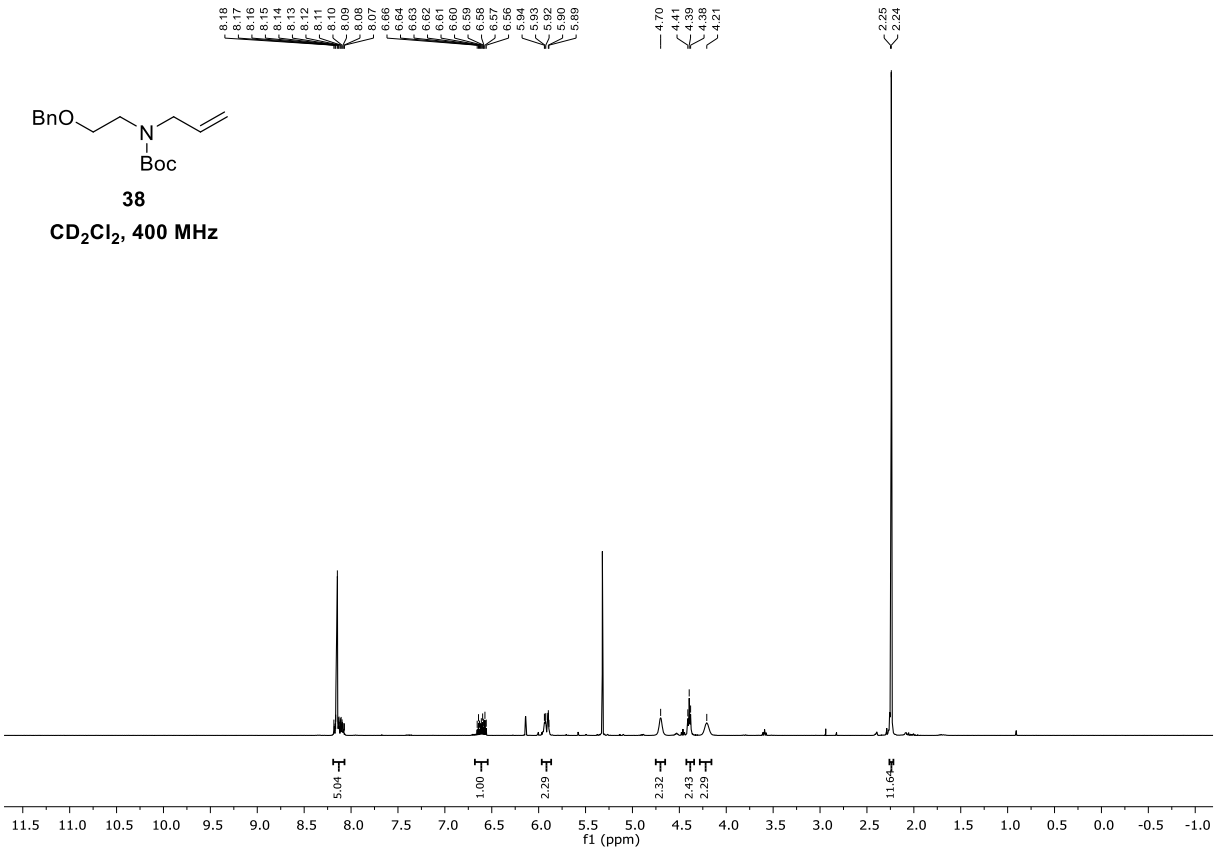
$CDCl_3$, 100 MHz


MeO
MeO
N
Bn
OPMB
O
33
CD2Cl2, 400 MHz
f1 (ppm)


MeO
MeO
N
Bn
OPMB
O
33
CD2Cl2, 100 MHz
f1 (ppm)

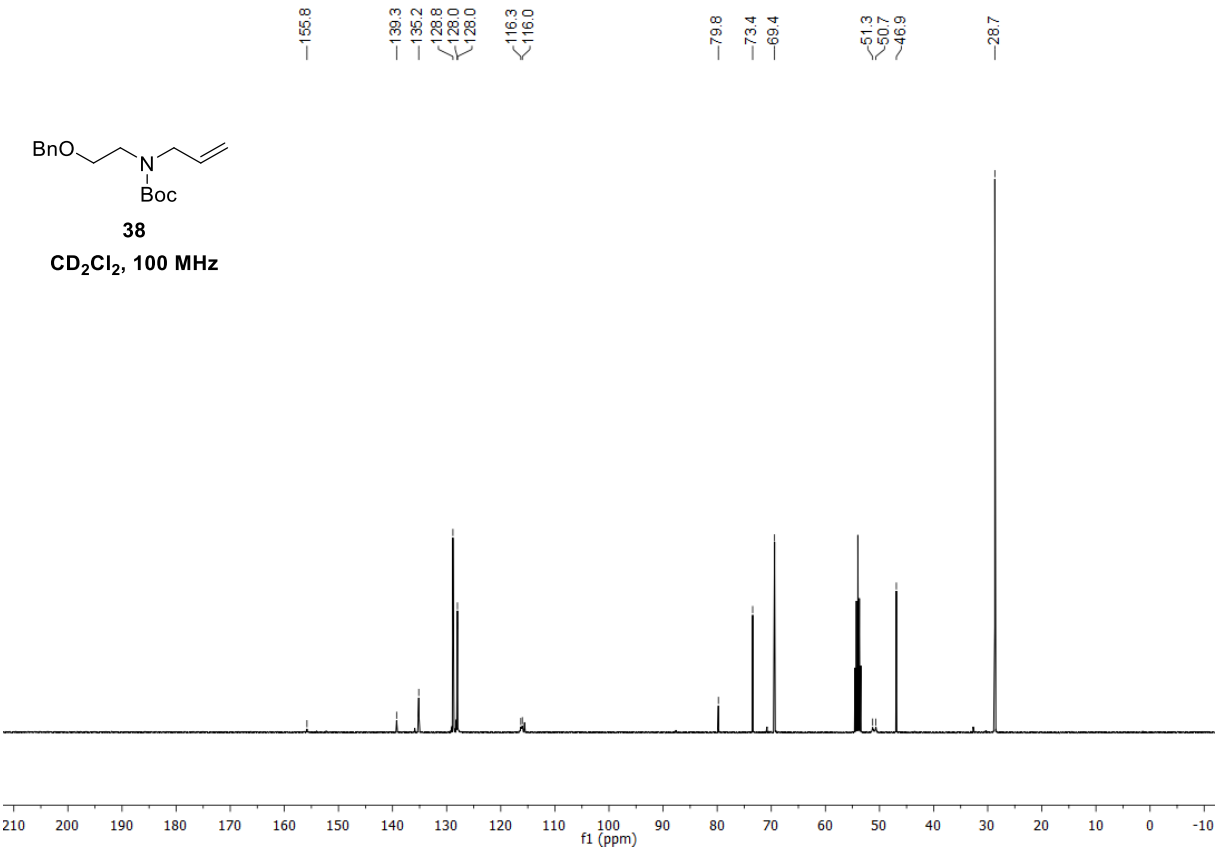

MeO
MeO
O
O
OMe
N
Bn
OPMB
34
CDCl3, 600 MHz
f1 (ppm)


MeO
MeO
O
O
OMe
N
Bn
OPMB
34
CDCl3, 150 MHz
f1 (ppm)



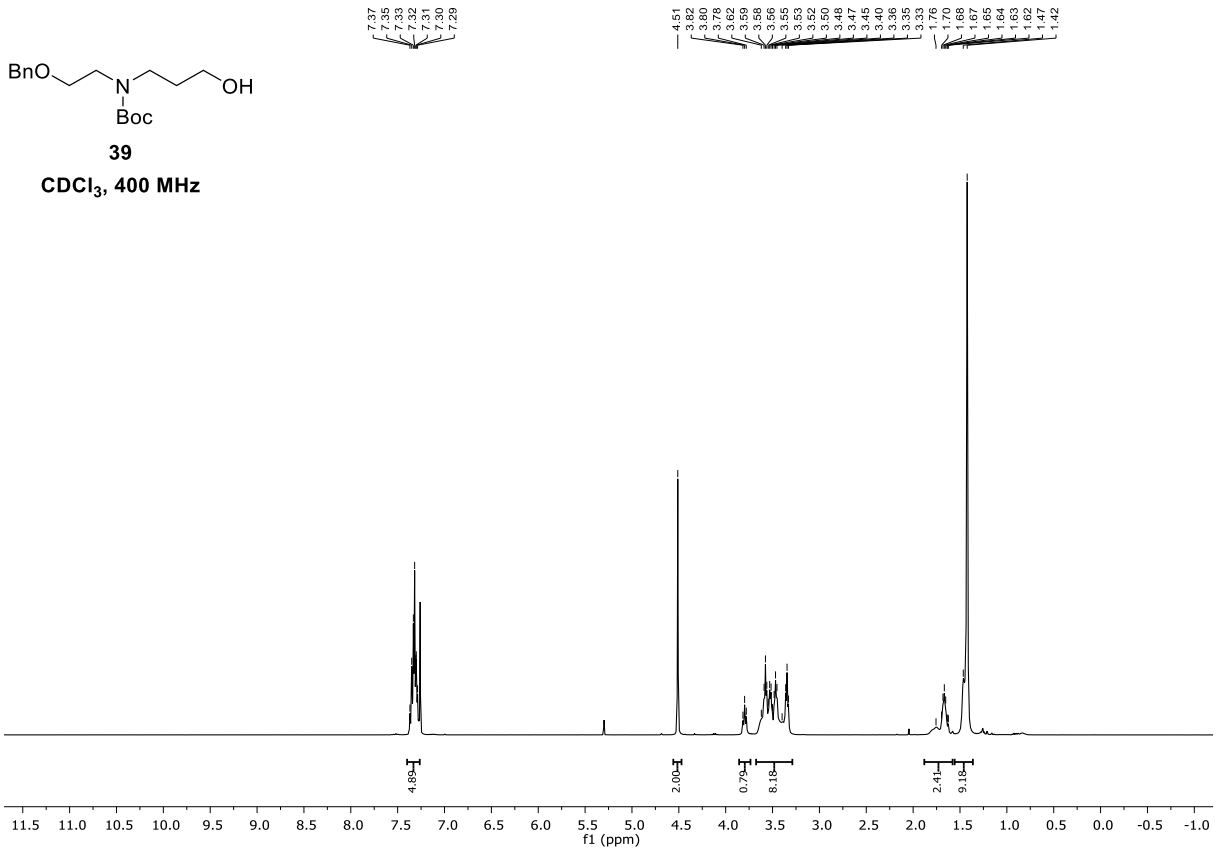
38

CD_2Cl_2, 400 MHz



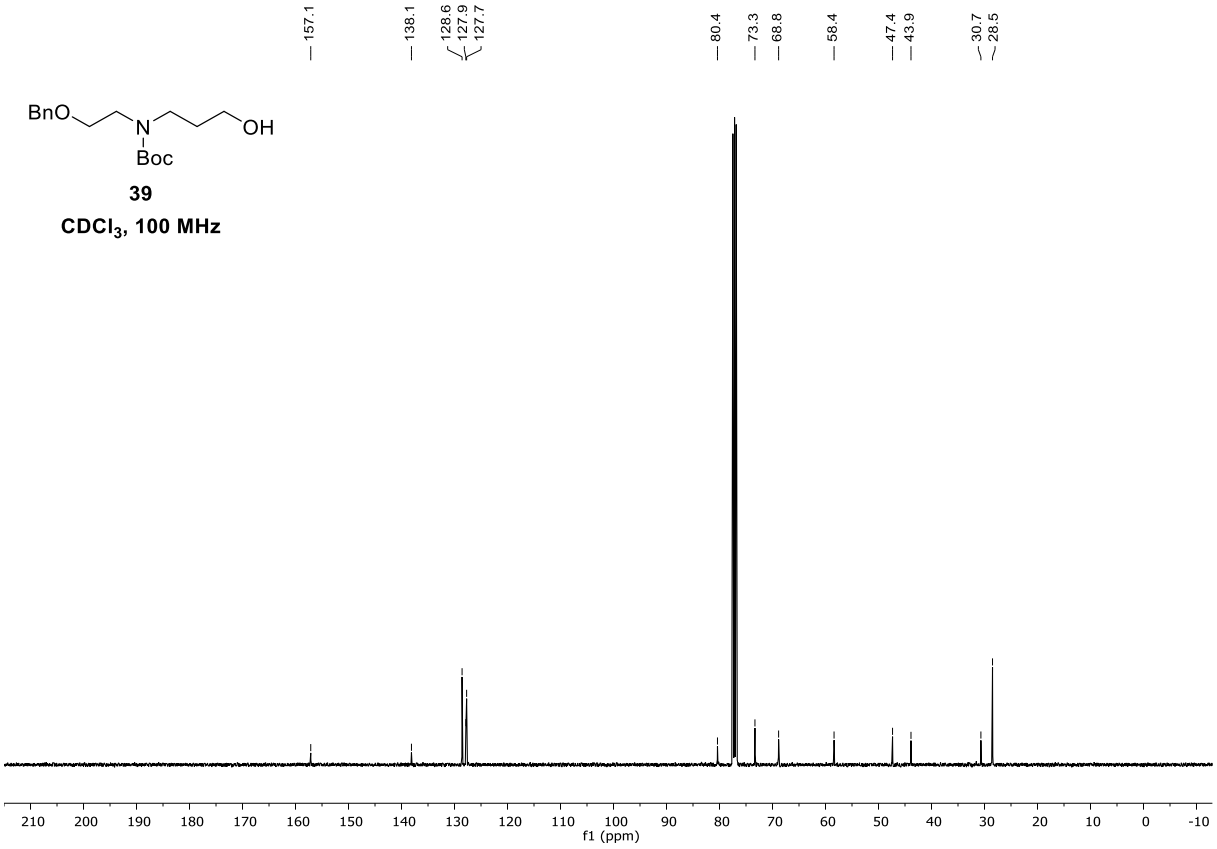
38

CD_2Cl_2, 100 MHz



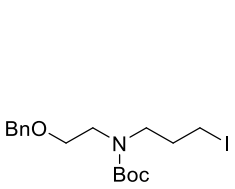
39

$CDCl_3$, 400 MHz



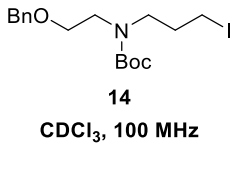
39

$CDCl_3$, 100 MHz



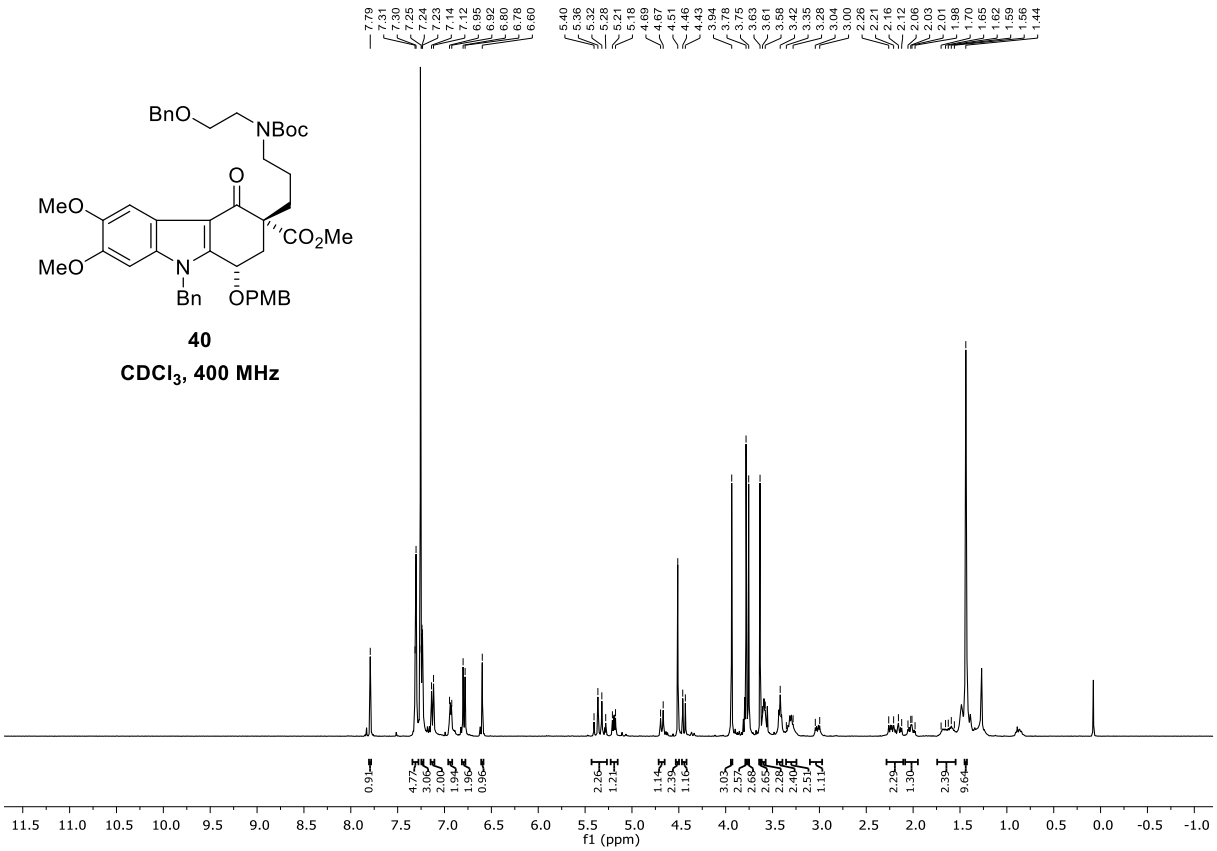
14

$CDCl_3$, 400 MHz



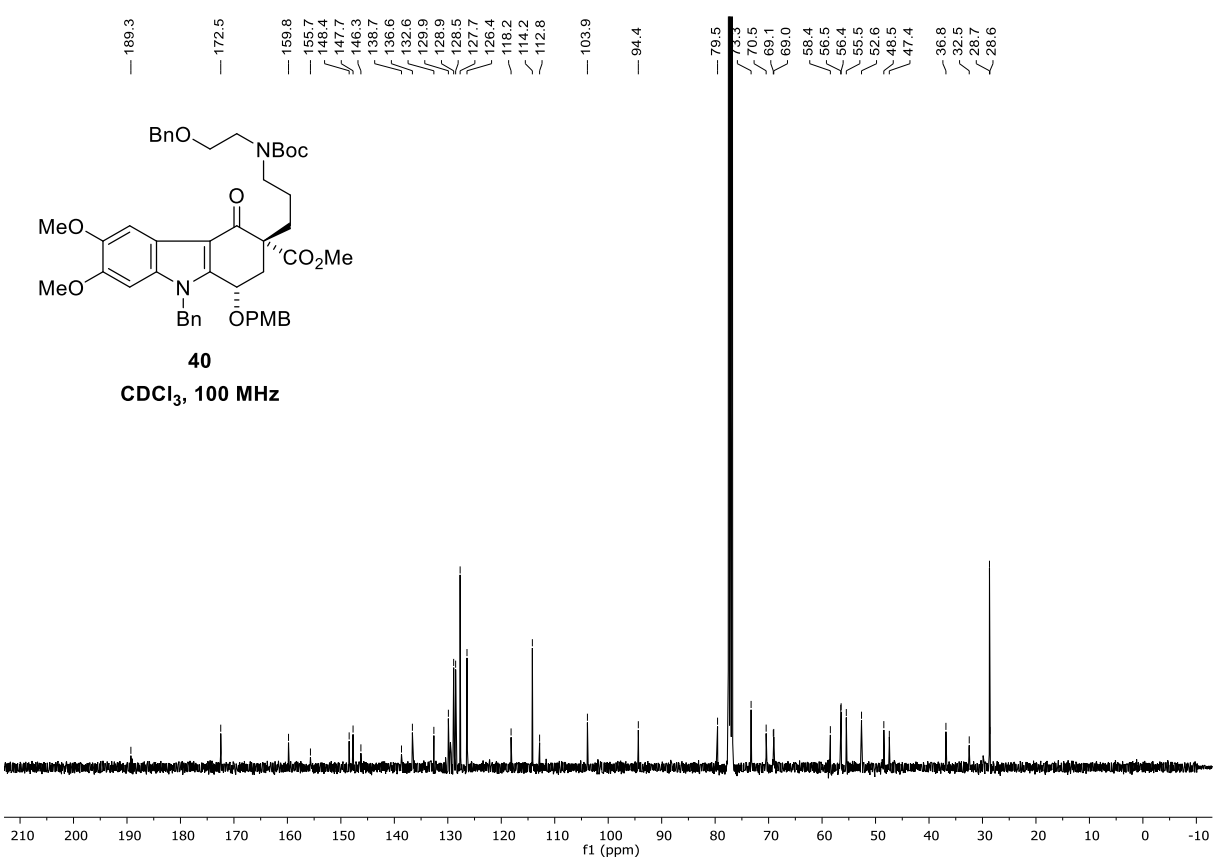
14

$CDCl_3$, 100 MHz



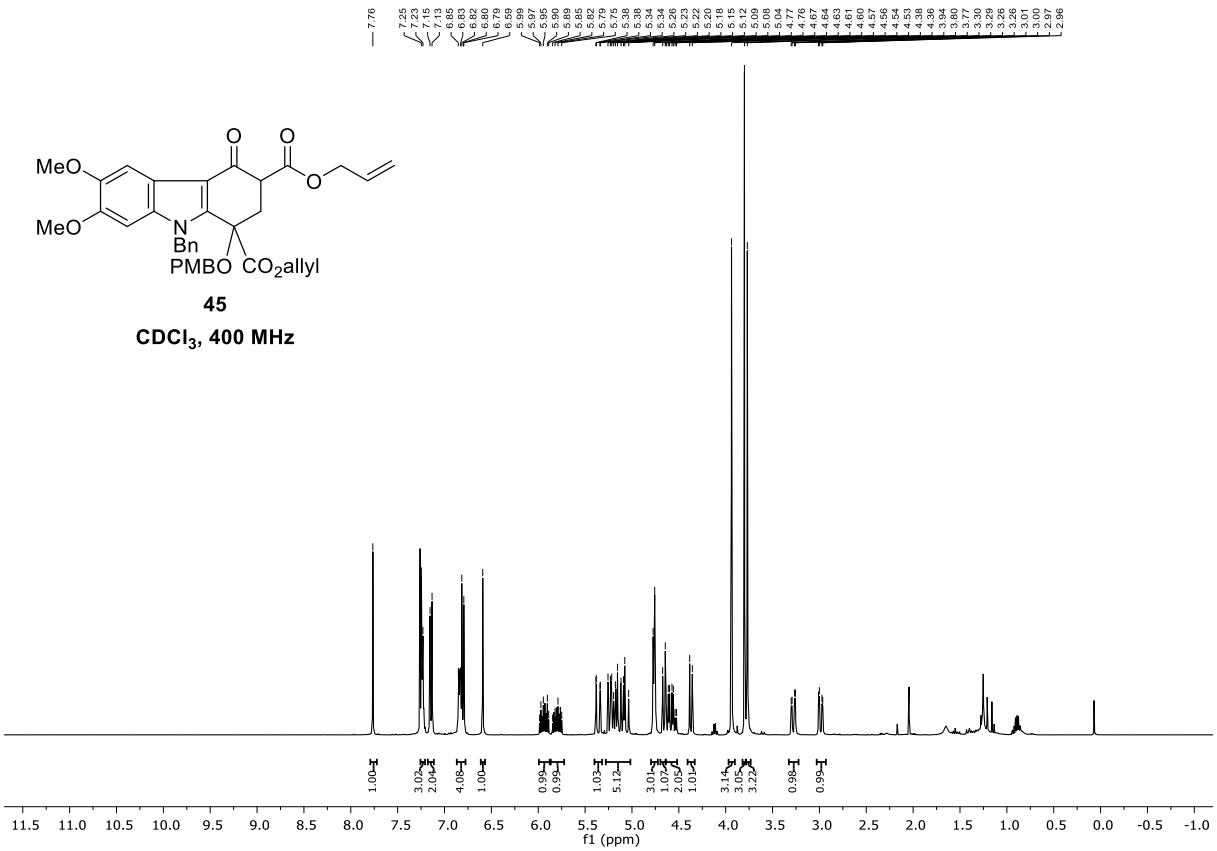
40

$CDCl_3$, 400 MHz



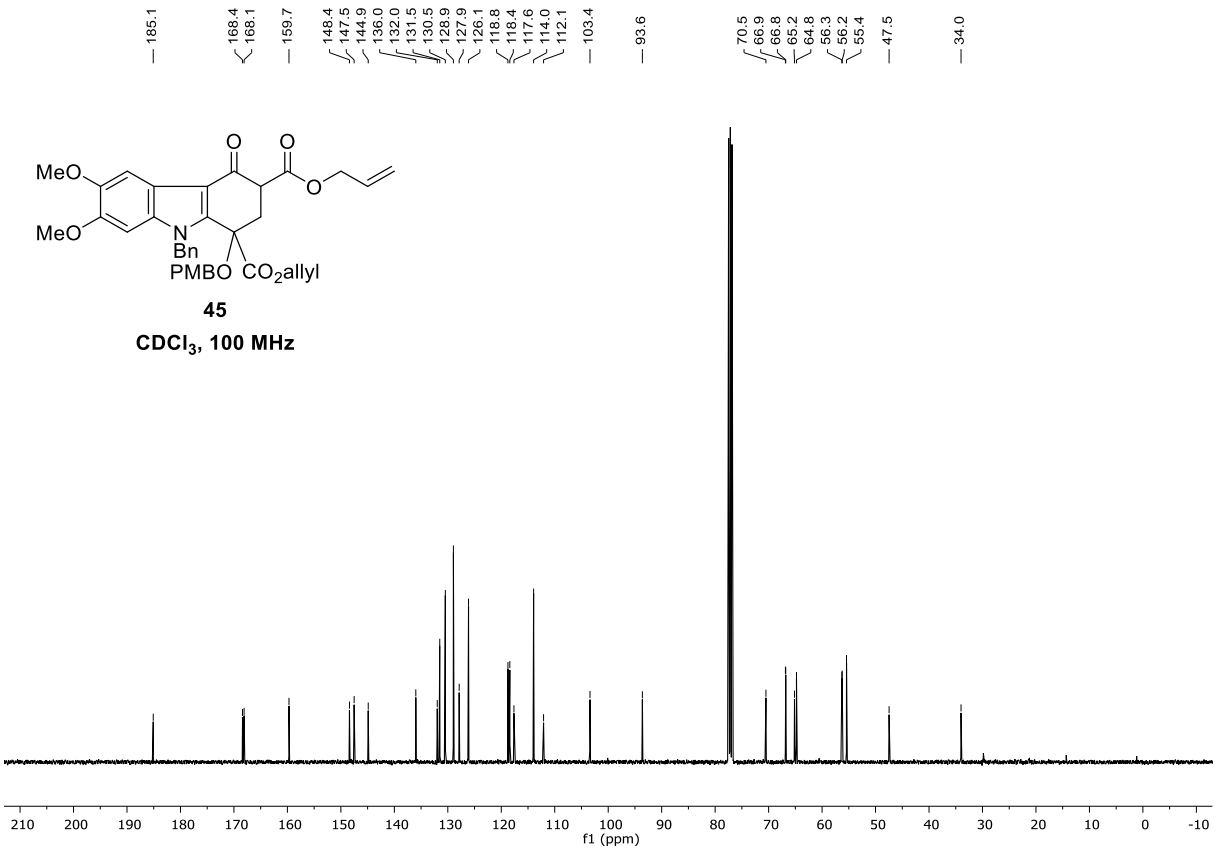
40

$CDCl_3$, 100 MHz



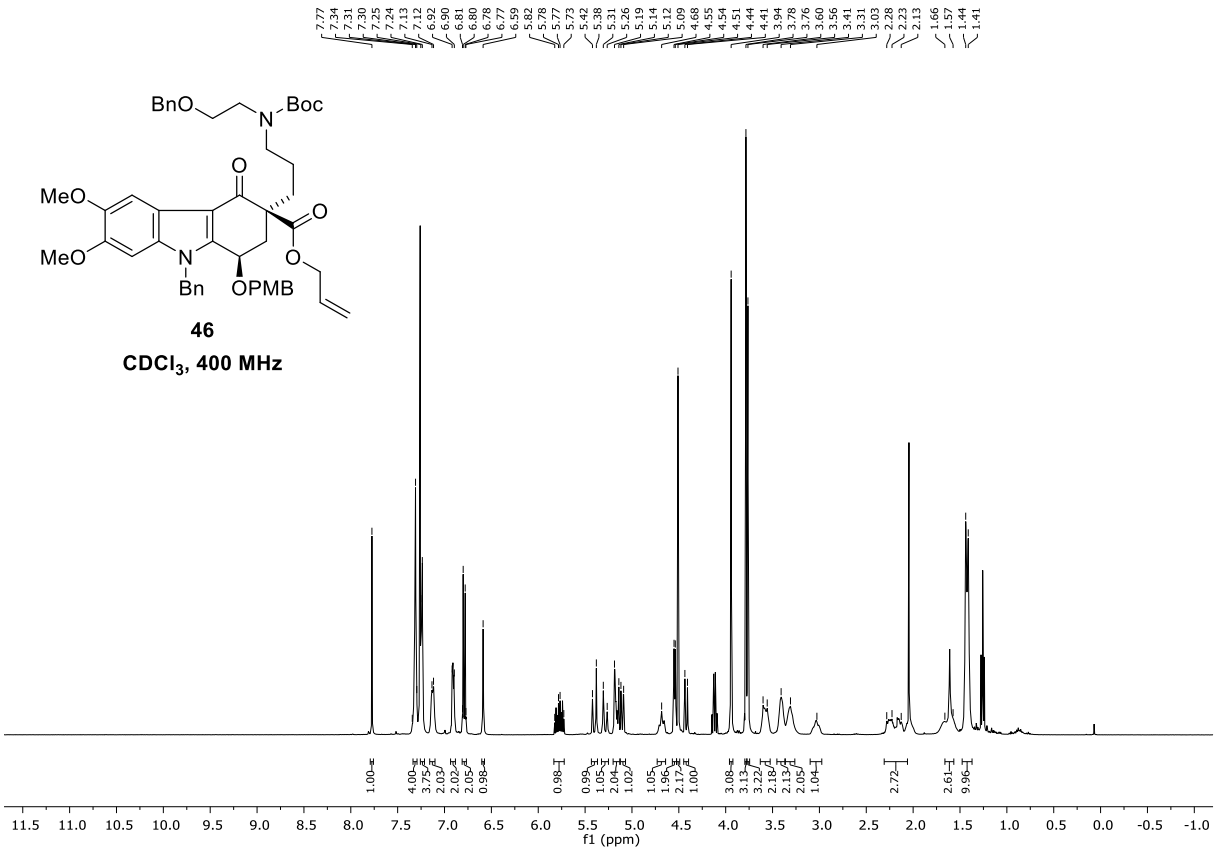
45

$CDCl_3$, 400 MHz



45

$CDCl_3$, 100 MHz



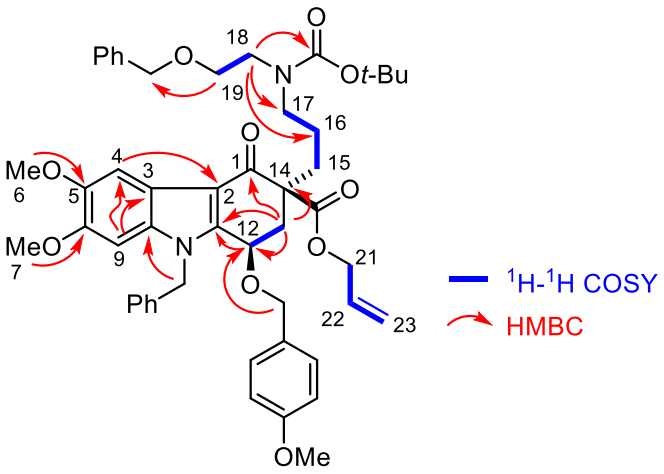
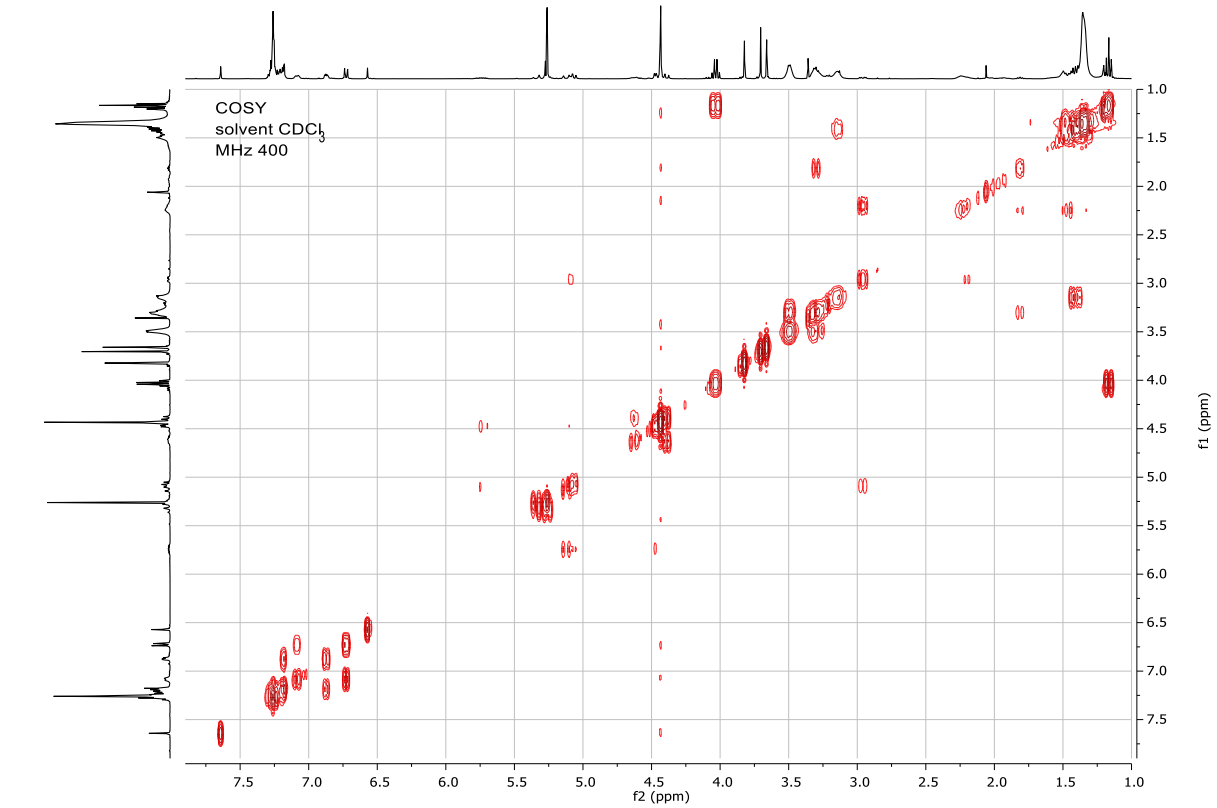
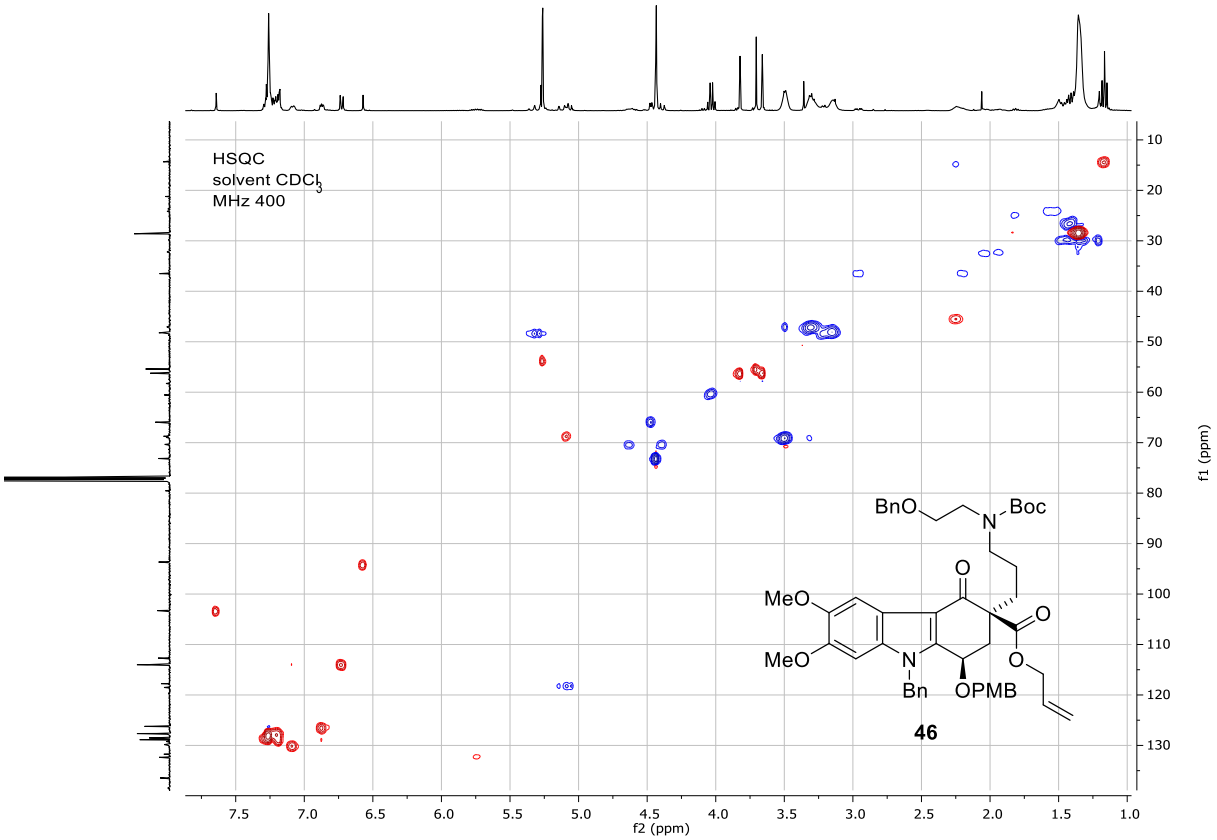
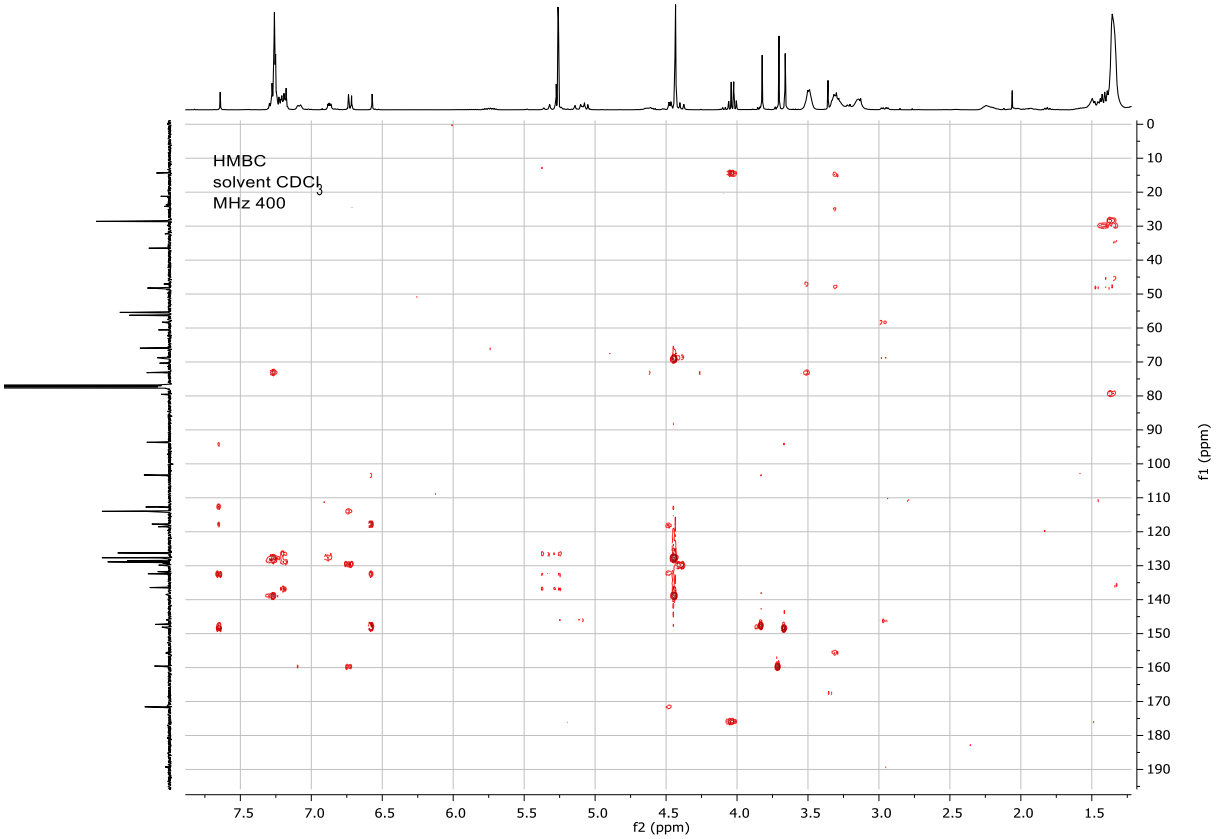


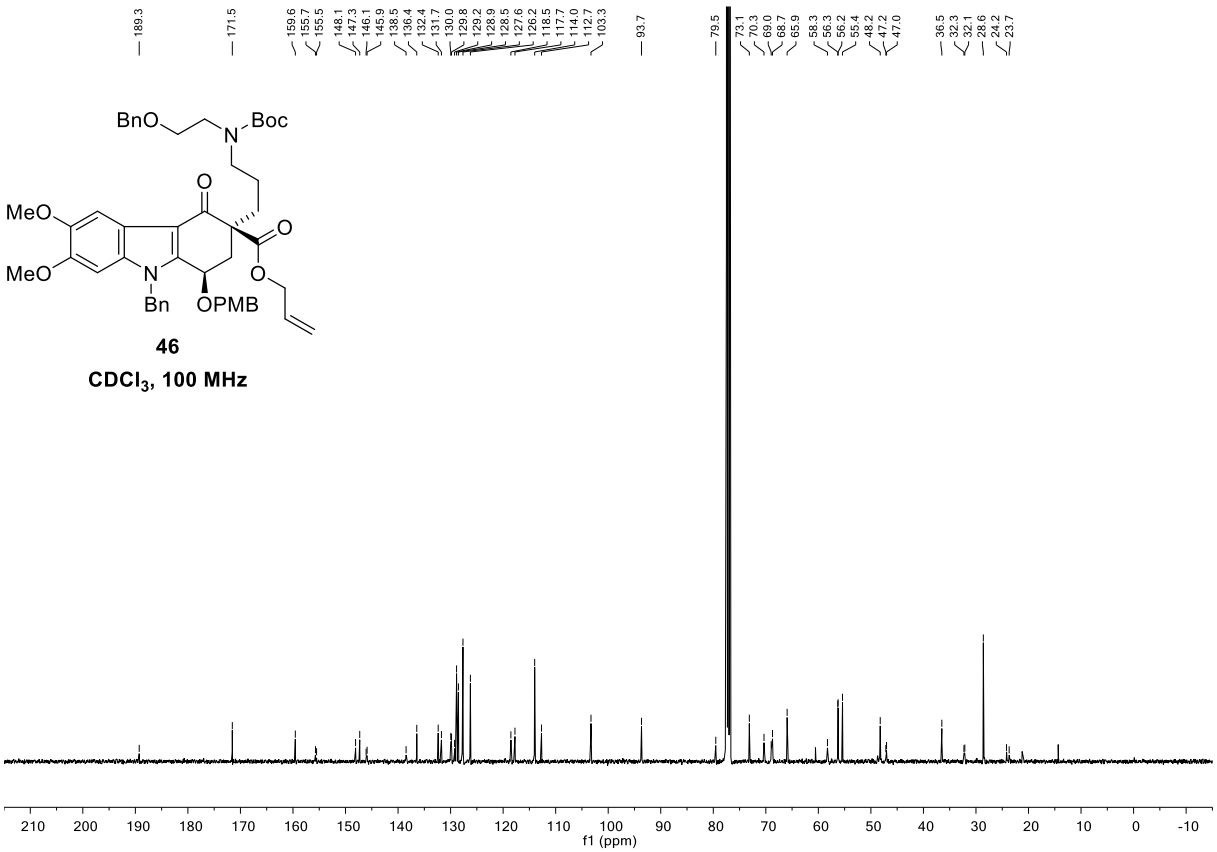
Figure S2. Key ^{1}H-^{1}H COSY and HMBC correlations of **46**.


COSY
solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)


HSQC
solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)
BnO
N
Boc
MeO
MeO
O
O
O
N
Bn
OPMB

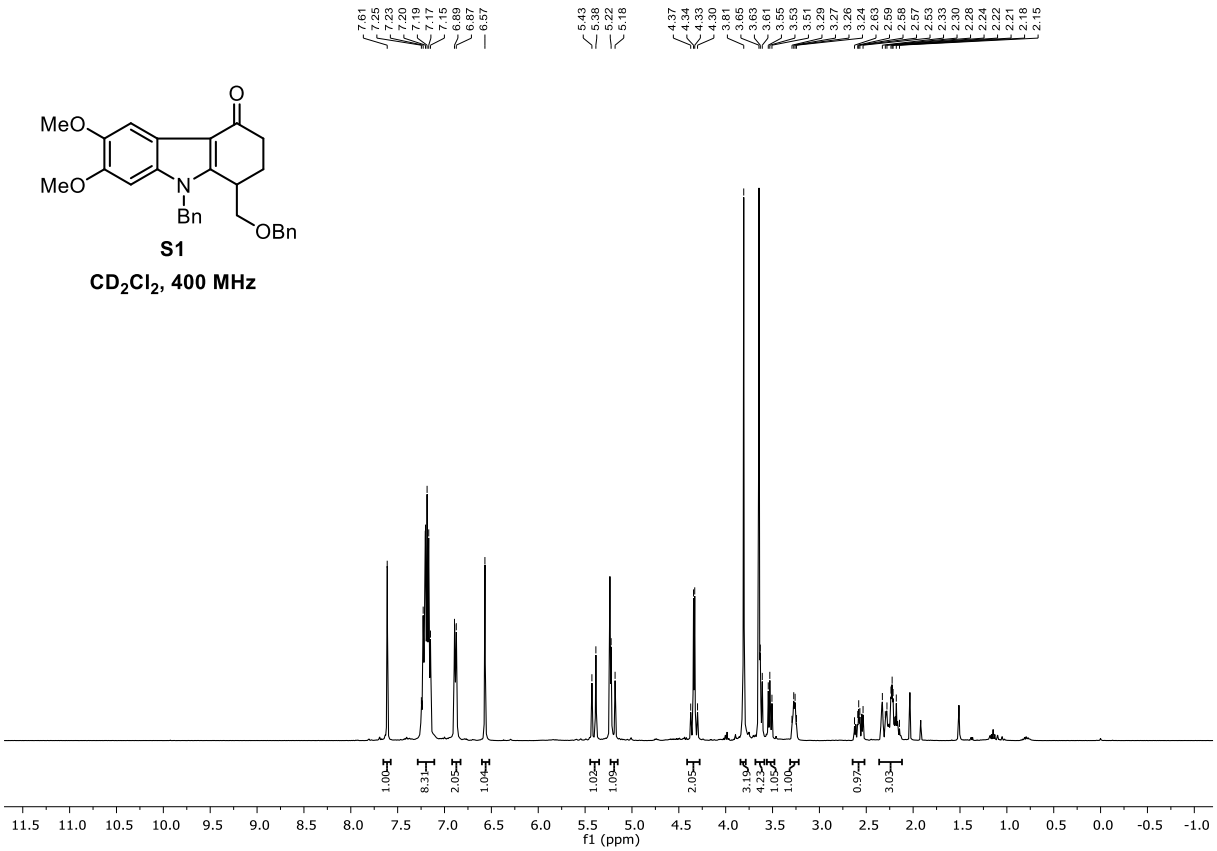
46

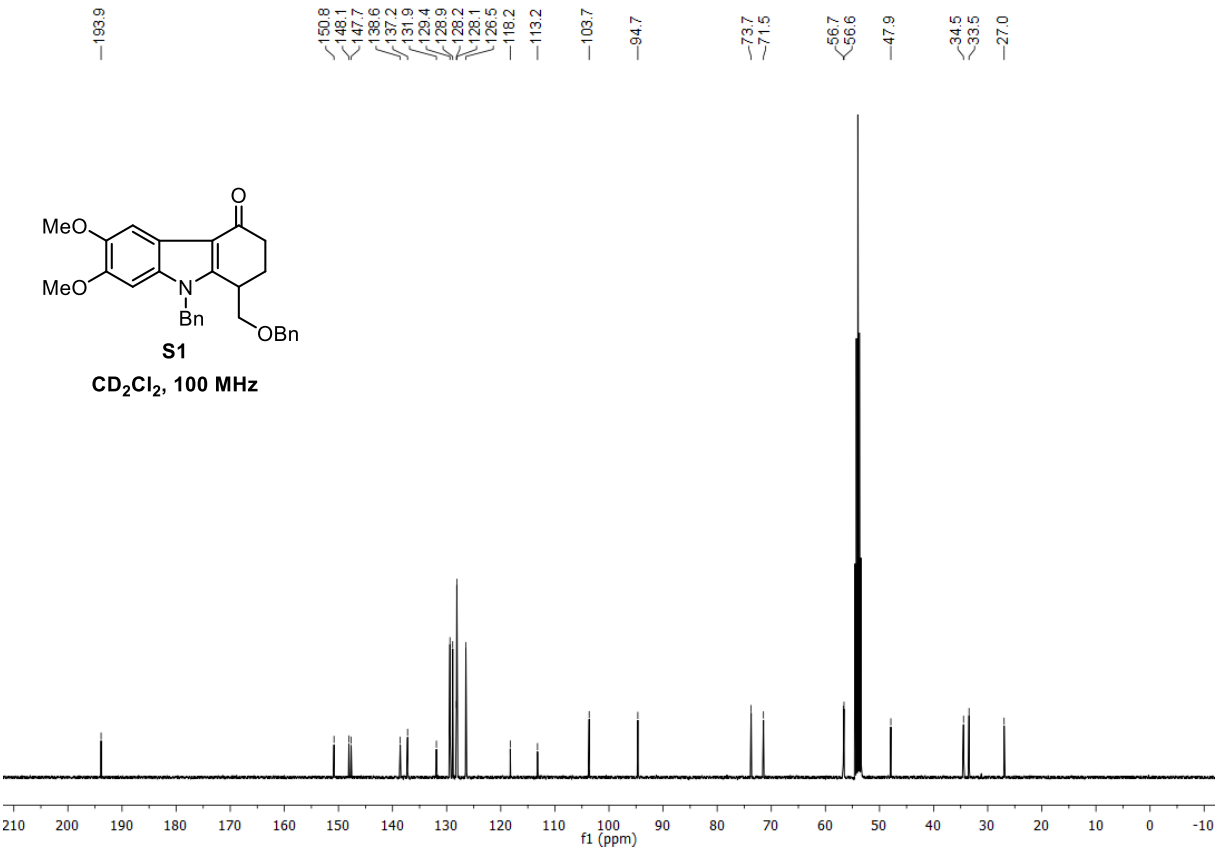


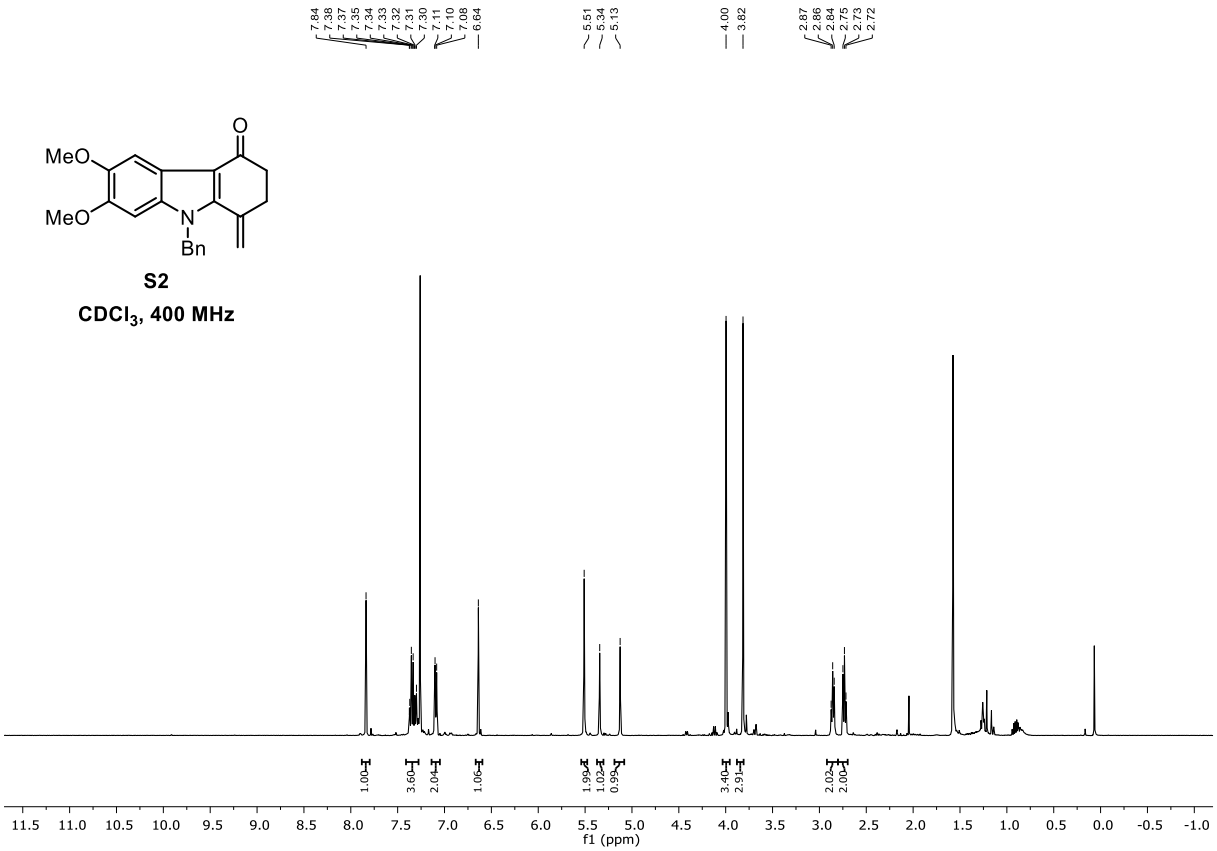


46

$CDCl_3$, 100 MHz

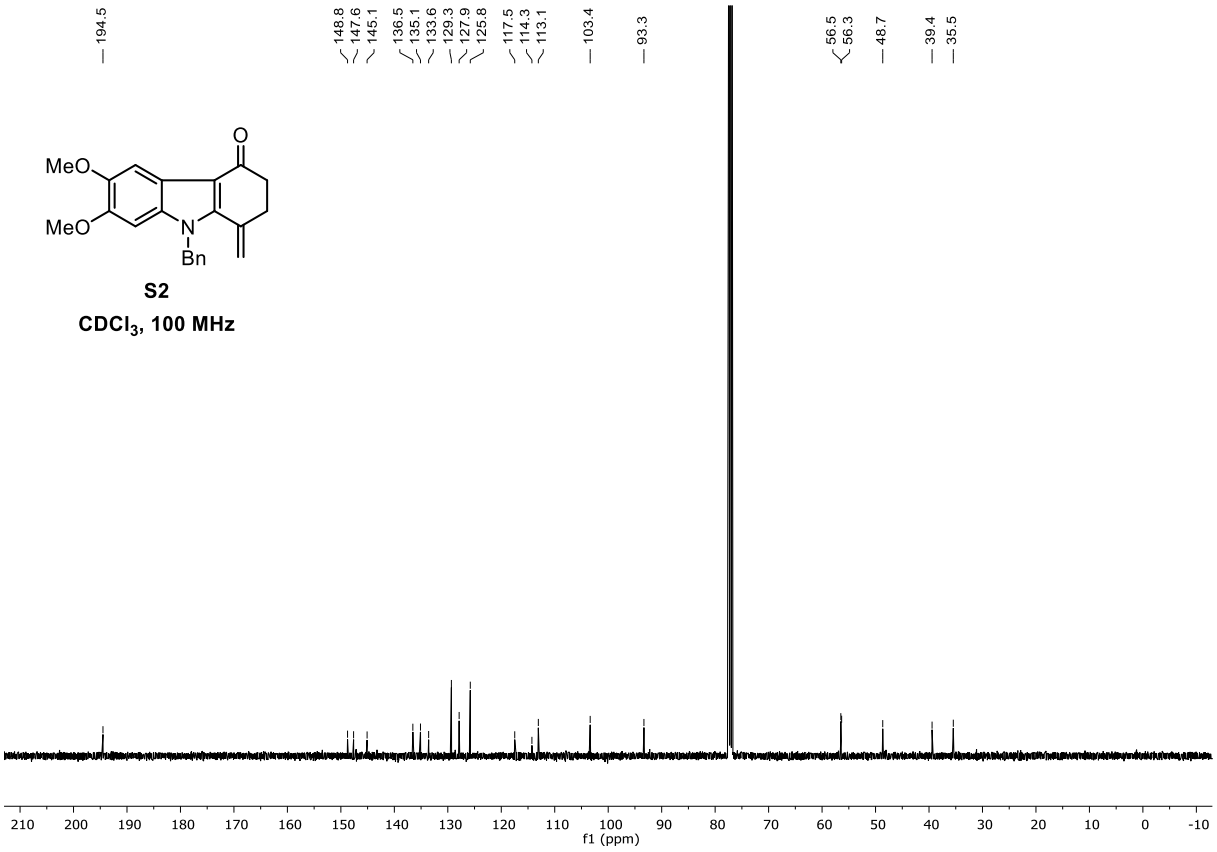

MeO
MeO
N
Bn
O
OBn
S1
CD2Cl2, 400 MHz
f1 (ppm)


MeO
MeO
N
Bn
O
OBn
S1
CD2Cl2, 100 MHz
f1 (ppm)



S2

$CDCl_3$, 400 MHz



S2

$CDCl_3$, 100 MHz

7.4.3 X-Ray Crystallographic Data

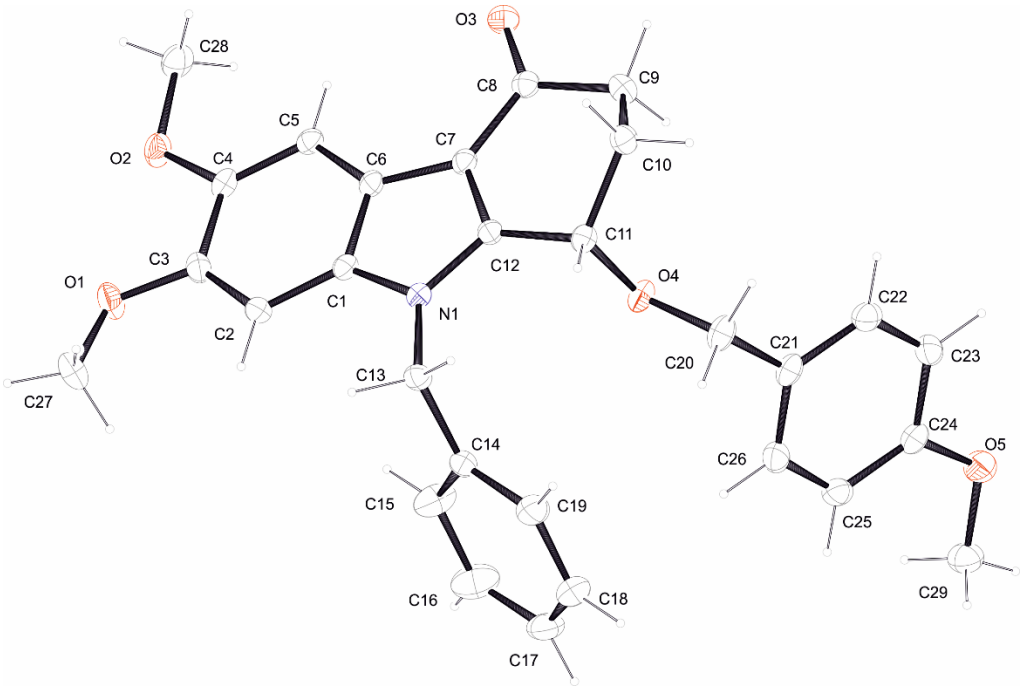
CCDC 1547827 contains the supplementary crystallographic data for tetrahydrocarbazolone **33**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 17. Crystallographic data for tetrahydrocarbazolone **33**.

net formula	$C_{29}H_{29}NO_5$
M_r/g mol^{-1}	471.53
crystal size/mm	0.100×0.050×0.030
T/K	100(2)
radiation	Mo Kα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	10.5106(2)
b/Å	4.96800(10)
c/Å	44.4015(9)
α/°	90
β/°	91.3250(10)
γ/°	90
V/Å^3	2317.88(8)
Z	4
calc. density/g cm^{-3}	1.351
μ/mm^{-1}	0.092
absorption correction	Multi-Scan
transmission factor range	0.9211–0.9705
refls. measured	22871
R_{int}	0.0297
mean σ(I)/I	0.0256
θ range	3.331–26.372
observed refls.	4074
x, y (weighting scheme)	0.0343, 1.5990
hydrogen refinement	constr
refls in refinement	4723
parameters	319
restraints	0

$R(F_{obs})$	0.0395
$R_w(F^2)$	0.0946
S	1.038
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.263
min electron density/e Å^{-3}	−0.209

Figure S1. Molecular structure of tetrahydrocarbazolone **33**. Displacement ellipsoids are drawn at the 50% probability level.



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