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DER FAKULTÄT FÜR CHEMIE UND PHARMAZIE
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STUDIES TOWARD THE SYNTHESIS OF GILVOCARCIN NATURAL PRODUCTS AND AXIALLY CHIRAL BIARYLS

von

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

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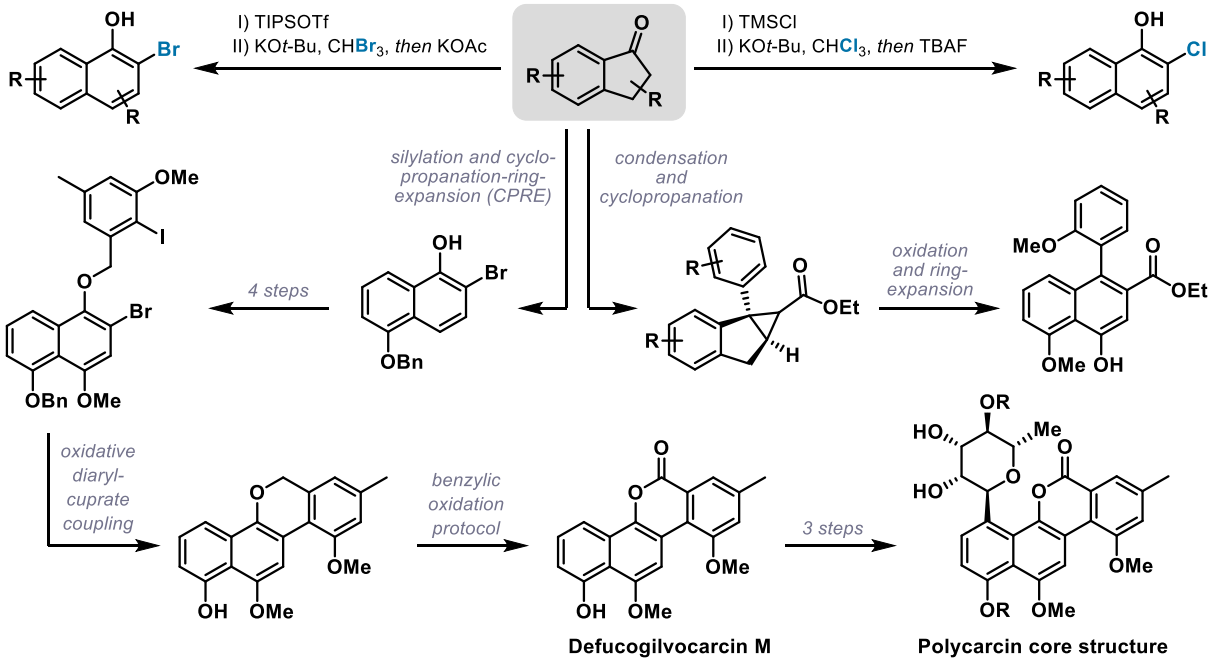
Für meine Eltern

Abstract

The 1-naphthol structural motif is found not only in several natural products but also in pharmacologically active compounds. Moreover, 1-naphthols represent valuable intermediates in total synthesis and have been used as substrates for various synthetic methodologies. In the course of investigating the ring-expansion of five-membered carbocycles to afford phenols and naphthols, we developed a methodology that allows for the synthesis of 2-bromo- and 2-chloro-1-naphthols from readily available indanones. This two-step procedure includes the conversion of indanones to their corresponding silyl enol ether and a subsequent cyclopropanation, followed by a spontaneous ring-expansion and aromatization. The generality of our methodology was demonstrated by successfully applying it to 30 substrates, while its potential was shown by the total synthesis of defucogilvocarcin M. Formation of the crucial biaryl bond of this natural product was achieved via an oxidative coupling of an *in situ* generated diaryl cuprate emphasizing the utility of the halogen-handle. These findings culminated in efforts to realize a late-stage glycosylation and the synthesis of an advanced intermediate *en route* to the polycarcin natural products.

The second part of this thesis addresses the investigation of indanones to serve as suitable substrates for the formation of highly functionalized axially chiral biaryls. One-step synthesis of 3-phenyl-1*H*-indenes enables a rhodium-catalyzed cyclopropanation with subsequent benzylic oxidation to a cyclopropyl ketone. A Lewis acid-catalyzed ring-opening furnishes hydroxy naphthoate-based biaryls. Studies and considerations on an enantioselective approach are also shown and discussed in this thesis.



Scheme A: Indanones as versatile intermediates for the preparation of 2-halo-1-naphthols and axially chiral biaryls and as suitable starting materials for the preparation of gilvocarcin natural products.

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List of Abbreviations

°C	degree Celsius
Ac	acetyl
AIBN	azoisobutyronitrile
Ar	undefined aryl substituent
Bn	benzyl
Br	broad (NMR spectroscopy, IR spectroscopy)
Bu	butyl
calc.	calculated
CDI	1,1'-carbonyldiimidazole
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet (NMR spectroscopy)
D	dexter ("right")
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	tris(dibenzylideneacetone)
dr	diastereomeric ratio
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-4,5-dicyano-1,3-benzoquinone
DHP	3,4-dihydropyran
DIBAL-H	diisobutylaluminum hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
(*R*)-DOSP	[(*R*)-(+)-*N*-(*p*-dodecyl-sulfonyl)prolinato]
e.g.	exempli gratia
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimid-hydrochlorid
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
Et	ethyl phenylsulfonylionization
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
gem	geminal
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
Hz	Hertz (frequency)
i	*iso* (isomer)
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
imid	imidazole
IR	infrared
HMDS	hexamethyldisilazide
KHMDS	potassium bis(trimethylsilyl)amide

LDA	lithium *N*,*N*-diisopropylamide
L_n	ligand(s)
m.p.	melting point
M.S.	molecular sieves
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
Me	methyl
min	minute(s)
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MS	mass spectrometry
Ms	methanesulfonyl
n	normal (unbranched isomer)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
Nu	nucleophile
o	*ortho* (isomer)
p	*para* (isomer)
PCC	pyridinium chlorochromate
Pd/C	palladium on charcoal
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
pin	pinacol
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
py	pyridine
q	quartet (NMR spectroscopy)
R	undefined substituent
R_f	retardation factor
Rh_2esp_2	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
s	strong (IR spectroscopy)
s	singlet (NMR spectroscopy)
SM	starting material
T	temperature
t	triplet (NMR spectroscopy)
t	(*tert*-) tertiary (isomer)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
Ts	*para*-toluenesulfonyl
vs	very strong (IR spectroscopy)
w	weak (IR spectroscopy

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PART I

Studies Toward the Synthesis of Gilvocarcin Natural Products

1. Introduction

1.1 *C*-Glycosides: Therapeutic Targets and Synthetic Approaches

Among all organic substances found in nature, carbohydrates probably constitute the most abundant type of biomolecule with diverse functions in living organisms. Not only do they represent essential structural components in cells, but also serve as a major energy source throughout metabolism. Carbohydrates can occur as monomers as well as covalently linked oligo- and polymers. This feature expands the potential of this class as an essential part of living cells. The electrophilic character of the anomeric center is susceptible to a variety of nucleophiles, with alcohols (oxygen-based) and amines (nitrogen-based) as the most prominent examples seen in nature. As a result, carbohydrates can be part of different metabolites influencing their biological activity. In addition to heteroatoms, nature provides several examples in which a rather nucleophilic carbon is connected to the anomeric center representing a subgroup of glycosides, namely the *C*-glycosides. In any case, the sugar moiety influences physical and chemical properties of the attached metabolite by changing its solubility, polarity, rigidity and the mechanism of recognition by enzymes or cell membranes. Among others, the aryl *C*-glycosides represent a major sub-class, of which vitexin (**1**)[1], formycin A (**2**)[2] and showdomycin (**3**)[3] are three of the earliest known members (Figure 1). With the isolation of these and several other *C*-glycosylated

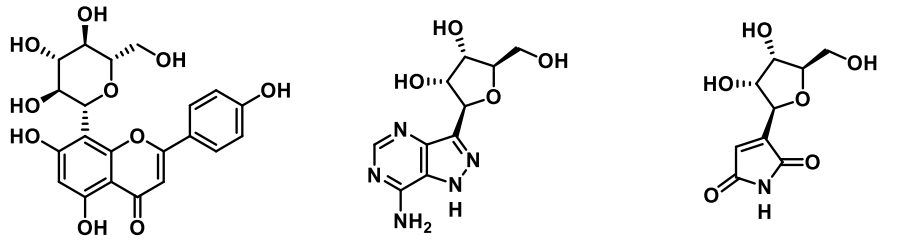


Figure 1: Selected examples of naturally occurring aryl-*C*-glycosides with important biological activities.

natural products the interest of synthetic and medicinal chemists has been sparked likewise. While the influence of the carbohydrate ligand on the pharmacokinetics, including absorption, distribution, metabolism and excretion (ADME) of a drug was known at that time, the difference between a C–O and a C–C bond has broadened the possibilities of drug research. This is mainly due to the presence of a

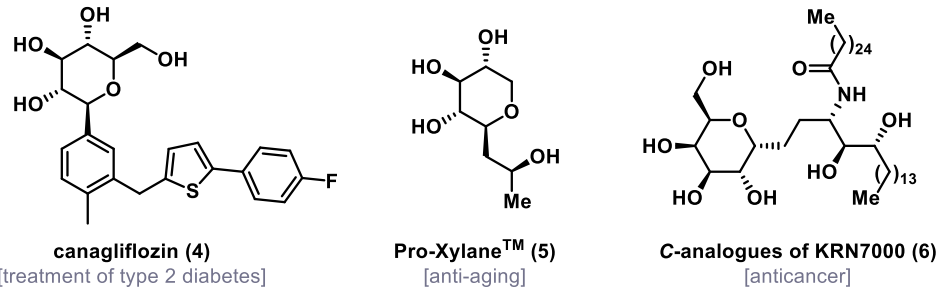
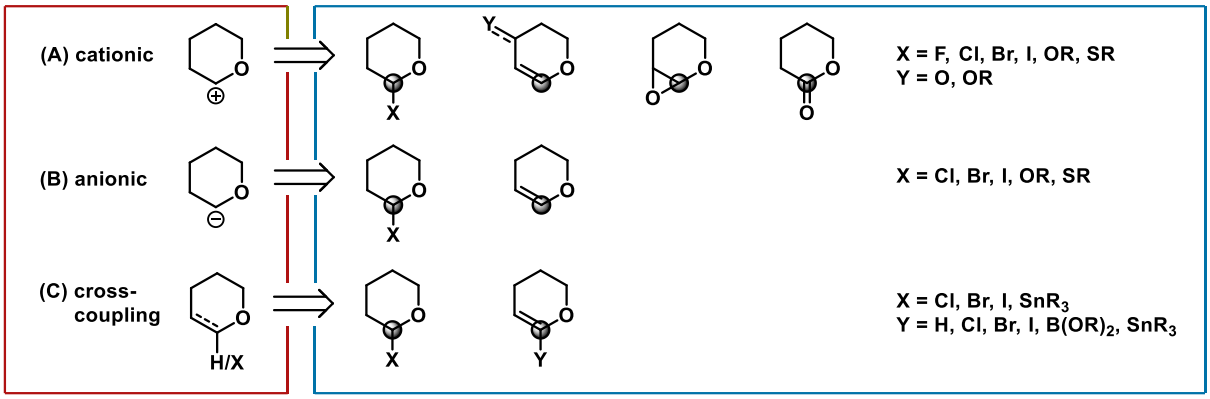


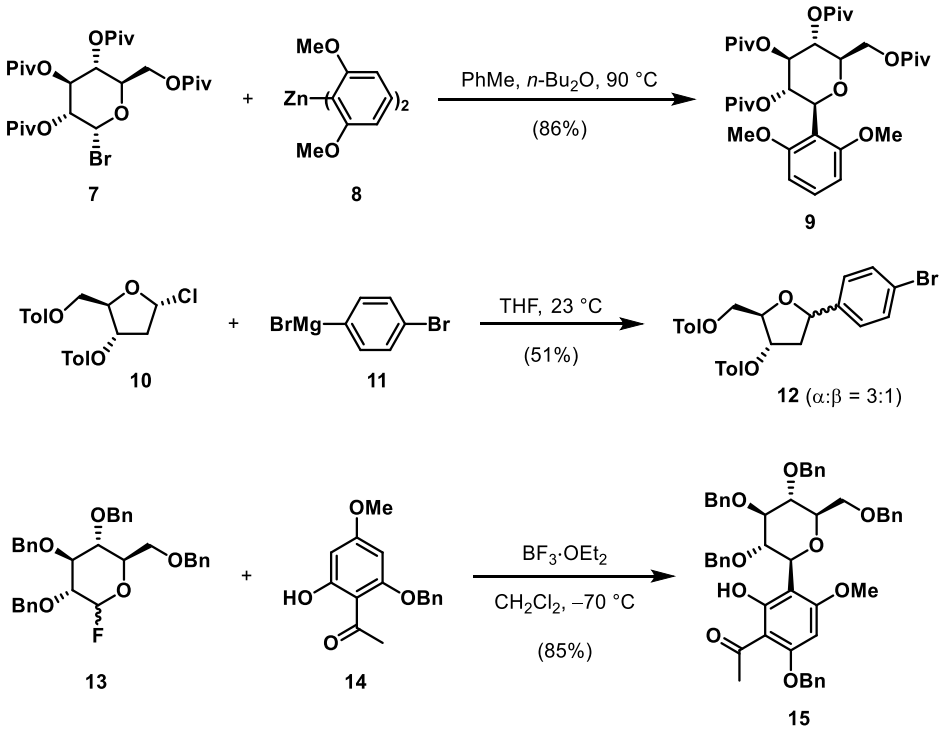
Figure 2: Selected examples of unnatural aryl-*C*-glycosides with important biological activities.

carbon, which, unlike an acetal, resists acidic or glycosidase-induced hydrolysis. This knowledge resulted in the development of several synthetic aryl-*C*-glycoside-based drugs such as canagliflozin (**4**)[4], Pro-Xylane (**5**)[TM][5], or *C*-analogues of KRN7000 (**6**)[6] (Figure 2). In the course of approaching diverse aryl *C*-glycosides, several strategies have evolved. They can be generally classified into three main types based on the nature and activation of the sugar as depicted in Scheme 1: glycosylation



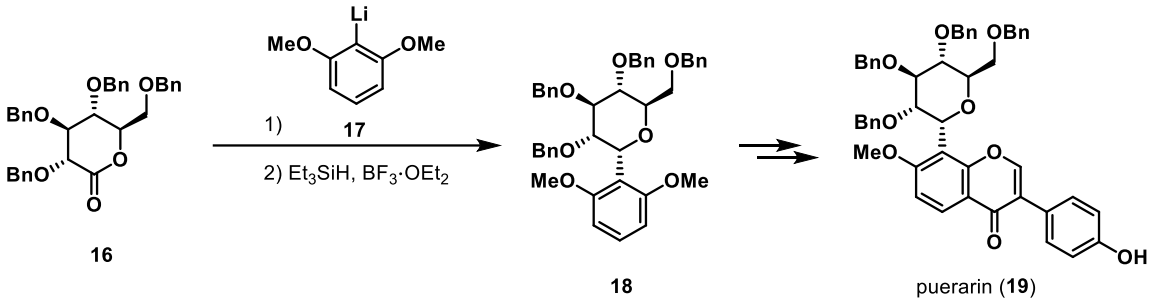
Scheme 1: General strategies for *C*-arylation.

through an (A) electrophilic species, through a (B) nucleophilic glycosyl species, or via (C) transition-metal catalyzed cross-coupling. Most frequently used precursors for the cationic pathway possess a leaving group at the anomeric center like halides and acetates or a meta-stable epoxide. This position can be substituted by different species including aryl-zinc-[7] and Grignard-reagents[8] or with unfunctionalized electron-rich arenes in a Friedel–Crafts-type reaction (Scheme 2). It is noteworthy that the mechanism of this common glycosylation via π-nucleophiles can be described either by a direct



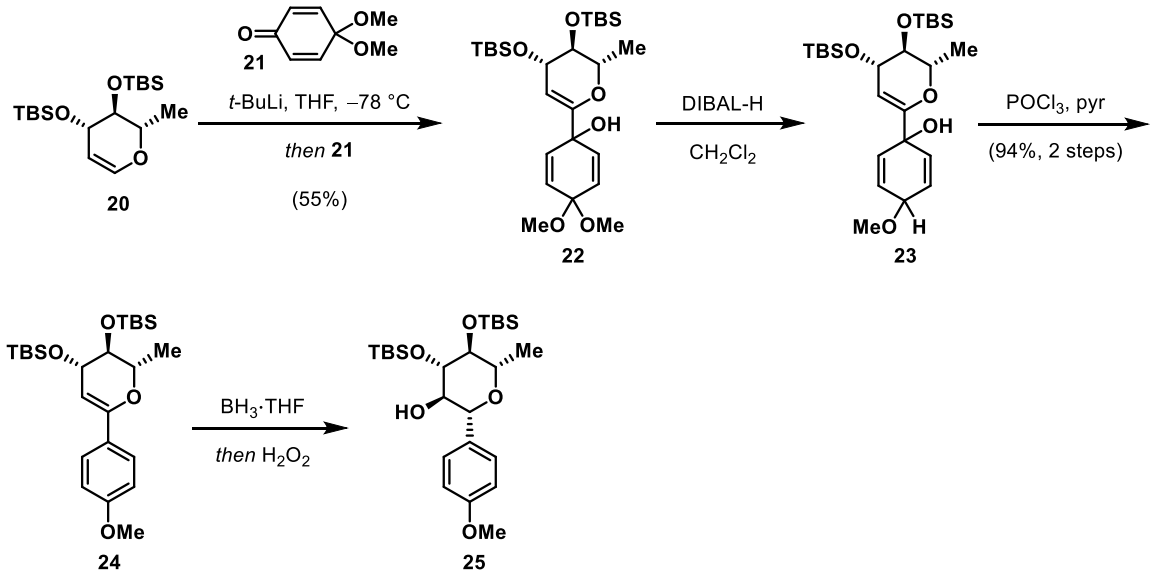
Scheme 2: Selected examples for the cationic *C*-glycosylation of arenes.

attack of the aryl carbon or by a stepwise process according to the Fries rearrangement.[9] The latter usually occurs with unprotected phenols and naphthols by attack of the free hydroxy group to first give an *O*-glycoside. The presence of Lewis acid would induce the dissociation of the sugar, generating an oxonium species and a Lewis acid coordinated phenolate. These intermediates are prone to recombine to give the more stable *C*-glycoside regiospecifically, *ortho* to the hydroxy group. This *O*→*C*-glycoside rearrangement was discovered in 1988 independently by the groups of Kometani[10] and Suzuki.[11] Besides these approaches, another strategy commonly seen is the nucleophilic attack into a gluconolactone which would provide the corresponding aryl ketal as shown in the synthesis of puerarin (**19**) by the group of Lee (Scheme 3).[12] The hydroxy group can be subsequently reduced by employment



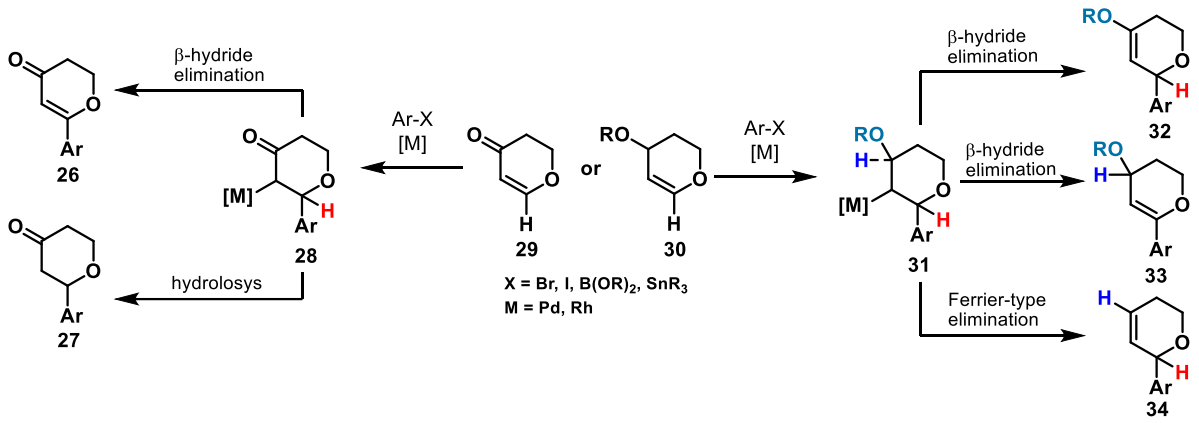
Scheme 3: Two-step cationic *C*-glycosylation through nucleophilic addition into a gluconolactone.

of a silane in combination with a Lewis acid.[13] In contrast to these cationic strategies, the anionic approach relies on an umpolung of the glycoside. This can be achieved on both sp^2- and sp^3-hybridized anomeric centers, however, the latter usually requires an adjacent electron-withdrawing group for deprotonation[14] or results from a lithium–metal exchange using butyl lithium.[15] Glycosylation using sp^3-hybridized species are rare and usually are employed on aliphatic or olefinic systems, while direct arylation is underexplored.[16] However, glycals can be transformed into their corresponding sp^2-anion by simple deprotonation using butyl lithium without further pre-functionalization (Scheme 4). Parker



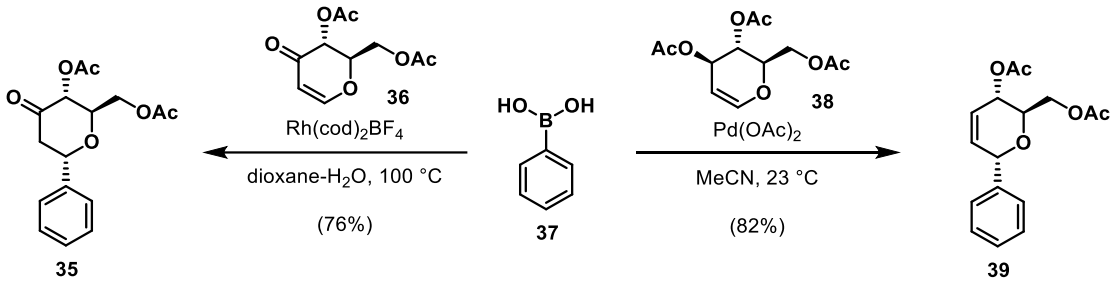
Scheme 4: Selected example for a formal anionic *C*-glycosylation of an arene.

and co-workers have exploited this strategy for the glycosylation of several substrates to approach the natural product class of pluramycins and gilvocarcins, mainly based on quinones as suitable electrophiles.[17] The obtained anomeric double bond could be subjected to hydroboration which affords a *trans-trans*-configuration between C1, C2 and C3 of the sugar, representing an alternative to the glycosyl-epoxide approach. Among these strategies, the most recent one is based on transition-metal catalysis and comprises unfunctionalized glycals as well as halogenated glycosides or boron- and tin-glycosides that can be directly coupled (Scheme 5). The initial attack of the arene results in the formation



Scheme 5: General overview of aryl *C*-glycosylation strategies based on cross-coupling reactions.

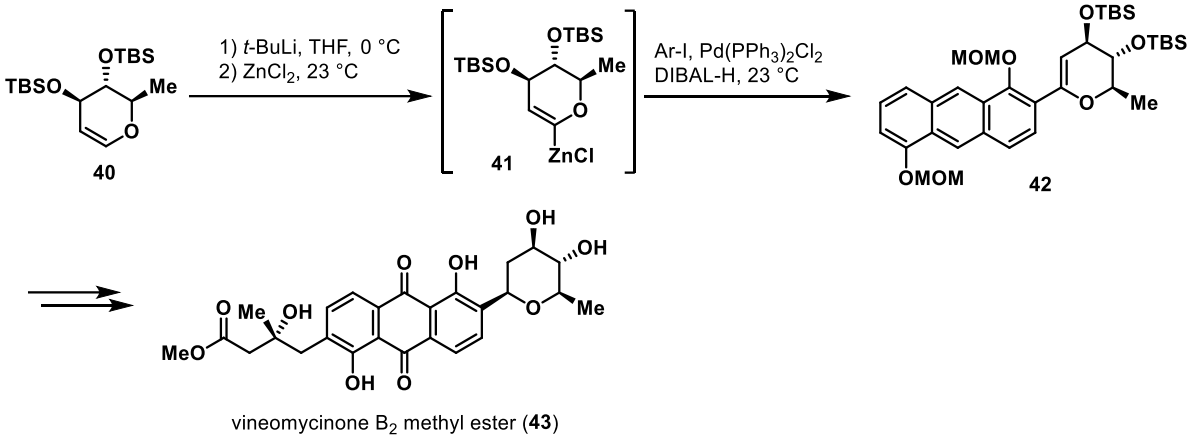
of intermediates **28** and **31**, respectively, which can undergo different elimination pathways strongly depending on the residue attached to the glycosyl-C3-position and the employed catalyst. In general, two consecutive reactions are possible for enones and three different outcomes have been observed for glycals. As reported by Maddaford, enones of type **28** formally undergo 1,4-addition if hydrolytic conditions or a rhodium catalyst are present (Scheme 6).[18] The same group describes the formation of



Scheme 6: Aryl *C*-glycosylation via formal Michael addition or Ferrier-type reaction.

a carbon-Ferrier-type product upon Pd(II)-catalysis,[19] which was previously limited to Lewis acids.[20] More likely, a subsequent β-hydride elimination is observed, however, a significant dependency on the protecting group adjacent to the glycal double bond has been described in literature. According to studies by Ye[21] and Daves,[22] the corresponding enol-ether **32** is only formed if a silyl protecting group is present. An acetyl or benzyl group prevented Heck coupling. Negishi coupling conditions have been shown to be suitable if β-hydride elimination towards the anomeric center is desired. This strategy

allowed Tius for the total synthesis of vineomycinone B_2 methyl ester **43** (Scheme 7).[23] A few years before Suzuki's first total synthesis of gilvocarcin M, Daves and co-workers developed a promising



Scheme 7: Tius' total synthesis of vineomycinine B_2 methy ester (**43**) based on a Negishi coupling.

glycosylation towards gilvocarcin E.[22,24] Their advanced glycosylated intermediates featured nearly the full-carbon skeleton, however, with several oxygens missing. Despite these results, no example of a gilvocarcin synthesis via Daves' Heck-type coupling is known to date.

1.2 Gilvocarcin Family of Natural Products

After the structural elucidation of the first known aryl *C*-glycoside aquamycin (Figure 3),[25] this class of natural products has constantly increased, so that several subgroups for this family could be

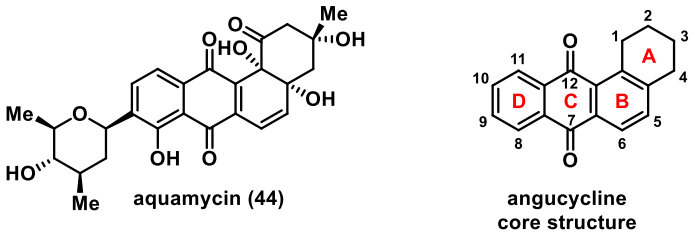


Figure 3: The first known aryl *C*-glycoside aquamycin (**44**) and the aquamycins' general core structure.

identified.[16] Among others, the angucyclines represent one of the biggest subgroups, which are classified based on their angular arranged tetracyclic benz[*a*]anthracene core.[26] More than one hundred secondary metabolites of microbial origin belong to this class. Apart from a few exceptions, *Streptomyces* are the main-producing origin of angucyclines.[27] In the course of isolating and investigating these decaketides, another subgroup closely related to the angucyclines has emerged and is known as the gilvocarcin natural products to date.[28] Their structural characteristics can be highlighted by: 1) a rearranged angucyclinone core structure and, more remarkable, 2) a *para*-*C*-glycosylation motif.

Figure 4 comprises all known natural and semi-natural products belonging to the gilvocarcin family. While all representatives have a benzonaphthopyranone core in common, variations are found in the attached sugar as well as the C8-substituent.

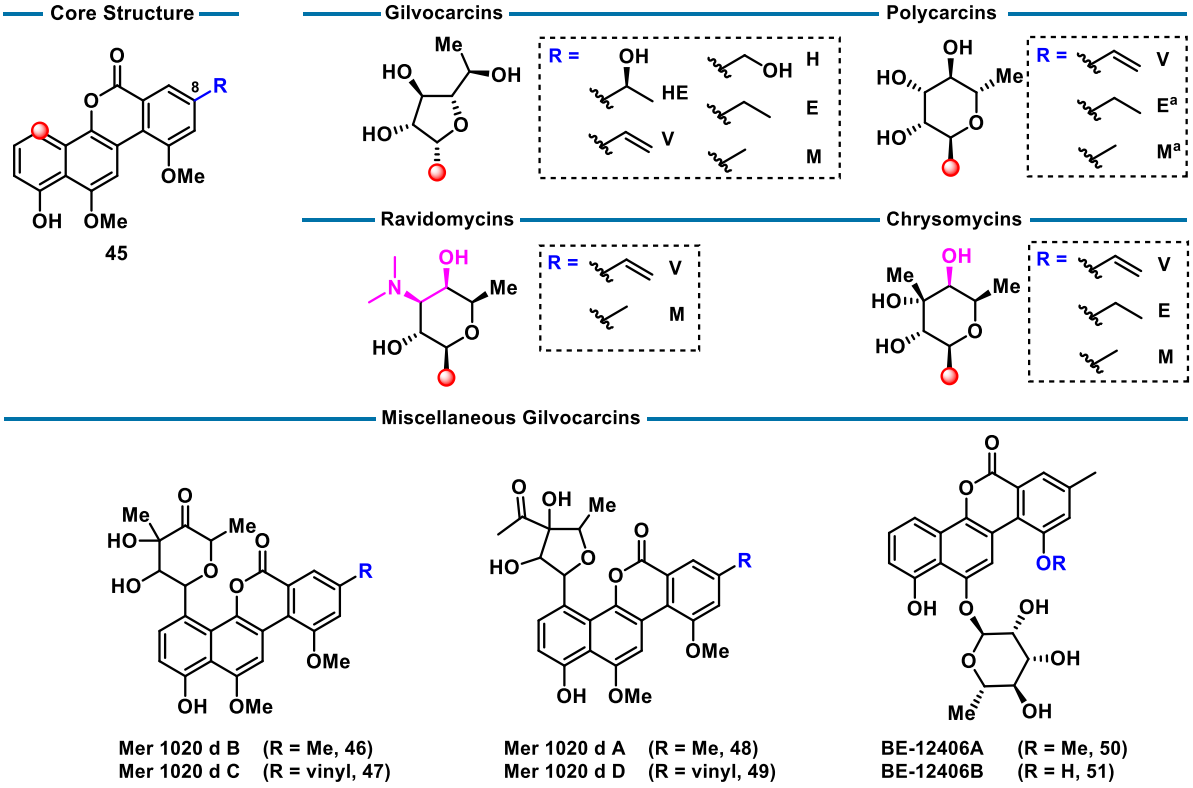


Figure 4: Overview of all known gilvocarcins classified by their attached sugar moiety. Further variations of the sugar moiety (see ravidomycins and chrysomycins) are indicated by pink coloration. [a]Isolated from genetically modified *Streptomyces*.

Nomenclature

During the 1970's and 1980's, several independent reports about the isolation of a new type of aryl-*C*-glycosides were published. The simultaneousness of these studies and the unawareness about the work of other groups on the same substrates during that time led to different designations for identical members of the gilvocarcins. According to today's knowledge, two main characteristics can serve as distinctive features: the attached sugar and the substitution at C8 of the aglycone. All representatives together should be termed as "the gilvocarcin natural products". Four main sugars could be identified so far, which are eponymous for each subclass of the gilvocarcins. In addition, five different naturally occurring substituents at C8 are known, whose one-letter-abbreviation provides additional specification. The four subclasses defined by the *C*-linked sugar are: gilvocarcins (D-fucofuranose), chrysomycins (D-virenose), ravidomycins (D-ravidosamine) and polycarcins (L-rhamnose). These subclasses are specified by the letters: M (for methyl), E (for ethyl), V (for vinyl), HE (for 1-hydroxy ethyl) and H (for hydroxy methyl).[27] The only *O*-glycosylated representative known to date is gilvocarcin BE.[29,30] Furthermore, all of the depicted glycosylated members were also isolated as aglycones, except for gilvocarcin HE and

H. Aglycones are denoted by the suffix "defuco". Throughout the last decades, the names used in Figure 4 have been established and hence, are used within this thesis. Members with different denotations found in literature are: gilvocarcin V (toromycin, anandimycin A), gilvocarcin M (anandimycin B), gilvocarcin E (anandimycin C), chrysomycin V (chrysomycin A, virenomycin V, albacarcin V), chrysomycin M (chrysomycin B, virenomycin M, albacarcin M), ravidomycin V (ravidomycin). Exceptions of this nomenclature are the chrysomycins Mer-120dA–D (presumably emerged via rearrangement of chrysomycins V and M) and the *O*-glycosylated congeners gilvocarcins 12406A–B.

1.2.1 Isolation and Structural Elucidation

In 1955, Strelitz described the isolation of a yellow, crystalline substance from an unidentified *Streptomyces*, which they named chrysomycin.[31] With the limited analytical tools and insufficient purification techniques available at that time, structural elucidation remained unsolved. However, the molecule's elemental nature was revealed to be based exclusively on carbon, oxygen and hydrogen. In addition, similarities within the UV-spectra compared to aureolic acid[32] indicated aromatic, as well as, glycosidic elements. Finally, a slight optical rotation revealed a non-racemic chirality.[31] The research on chrysomycins was not brought forth until Weiss performed additional experiments in the early 80's on the very same chrysomycin sample isolated by Strelitz decades before. In parallel, several other groups reported the isolation of the very same or additional representatives of this natural product family. A brief chronological overview summarizing the isolation and structural elucidation of all known naturally occurring members is shown:

1955[31] Isolation of chrysomycin V and M (as a mixture) from an unidentified *Streptomyces* (later referred as *Streptomyces* A-19). (no structural elucidation)

1971[33] Isolation of gilvocarcin V from *Streptomyces collinus*. (no structural elucidation)

1977[34][35] Isolation of chrysomycin V from *Streptomyces virens*. (no structural elucidation)

1978[36] Structural elucidation of the chrysomycins' sugar moiety (virenose) including relative and absolute stereochemistry.

1980[37] Synthesis of virenose and validation of the previously proposed structure.

1980[38] Isolation of gilvocarcin V from *Streptomyces collinus* including structural elucidation of the aglycone core and partial structural elucidation of the sugar.[39]

1981[40][41][42] Isolation of gilvocarcin V and M from *Streptomyces gilvotanareus*[43] and structural elucidation by chemical degradation, NMR- and mass-spectroscopy. (no absolute configuration)

1981[44] Isolation of gilvocarcin V and M from *Streptomyces griseologilbus* and *Streptomyces gilvotanareus*. X-Ray analysis of gilvocarcin M. (no absolute configuration)

1981[45] Isolation of gilvocarcin V, M and E from *Streptomyces anandii*.

1981[46][47] Isolation of ravidomycin V from *Streptomyces ravidus*. Structural elucidation without absolute configuration and wrong relative configuration of the C4′ -methyl group.

1982[48] Structural elucidation of chrysomycin V and M.[49] (no absolute configuration)

1982[50][51] Structural elucidation of chrysomycin V with opposite optical rotation. The suggestion that "virenomycin" might be the natural enantiomer could never be clarified.

1982[52] Isolation of gilvocarcin V and M from *Streptomyces aranae*.

1983[53] Demonstration of a *p*-TsOH-induced rearrangement of gilvocarcin V into its corresponding C-α-fucofuranoside and *C*-β-fucopyranoside. Defining of the gilvocarcins. as a new class of antibiotics with gilvocarcin V as the first known *C*-glycoside antibiotic.

1985[54] Isolation of defucogilvocarcin V[41], gilvocarcin V and M from *Streptomyces aranae*.

1989[55] Isolation of ravidomycin V, deacetylravidomycin V and deacetylravidomycin V *N*-oxide from *Streptomyces ravidus*. Structural elucidation with relative, but without absolute configuration and wrong relative configuration of the C4'-methyl group.

1989[56] Isolation of chrysomycin V and M from *Streptomyces albaduncus*.

1991[29,30] Isolation of gilvocarcins BE–12406 A and B with correct relative and absolute structure.

1992[57] Revision of absolute stereochemistry of gilvocarcin M by total synthesis.

1996[58] Validation of gilvocarcin BE's structure by total synthesis.

1998[59] Isolation of ravidomycin (V) FE35A and B from *Streptomyces rochei* and structural elucidation with relative (but without absolute) configuration and wrong relative configuration of the C4′-methyl group.

2000[60] Isolation of chrysomycins (M) Mer-1020 dA, (M) Mer-1020 dB, (V) Mer-1020 dC, (V) Mer-1020 dD and defucogilvocarcin M from *Streptomyces* sp. Mer-1020 and structural elucidation without relative or absolute configuration.

2000[61] Revision of ravidomycins' relative and absolute configuration by total synthesis.

2001[62,63] Isolation of deacetylravidomycin M and V from *Streptomyces* sp. WK-6326 and structural elucidation.

2008[64] Isolation of polycarcin V and gilvocarcin V from *Streptomyces polyformus*. Structural elucidation reveals the first L-sugar among this family. First example of a bacterium producing two distinct furanosyl and pyranosyl *C*-glycosides sharing the same aglycone.

2012[65] Isolation of gilvocarcin H, HE, V and M from *Streptomyces* sp. QD01-2 and structural elucidation.

2013[66] Isolation of chrysomycin E, V and M from *Streptomyces sporoverrucosus* and structural elucidation.

2013[67] Isolation of 4'-acetylchrysomycin V and M from *Streptomyces* sp. strain MG271-CF2 and structural elucidation.

2014[68] Validation of the structure of polycarcin V by total synthesis.

2020[69,70] Validation of chrysomycin V's structure and negative optical rotation by total synthesis.

1.2.2 Biological Activity

Besides the synthetic challenges associated with the gilvocarcin natural products, this group of aryl-*C*-glycosides attracted the interest of scientists by showing promising antibacterial and antitumor activities combined with relatively high LD_{50} values. Similarities and differences of these features are reported in the following section.

Chrysomycins

Although not aware of the chemical properties of the yellow, crystalline substance, which they isolated from an unidentified *Streptomyces*, Strelitz *et al*. revealed promising biological activities for the isolated mixture of chrysomycin V and M. Minimum inhibitory concentrations (MICs) were determined for Staphylophage 14, Coliphage T1, *B. subtilis* phage C.S.C., Cholera phage C and *B. cereus* phage, of which the latter showed by far the lowest MIC (0.01 µg/mL). In terms of antibacterial activity, low MICs were detected against gram-positive bacteria *Micrococcus pyogenes, B. cereus,* B. *subtilis* and *Mycobacterium smegmatis*, (0.1–0.6 µg/mL), while activity with MICs between 25 and 50 µg/mL were detected against gram-negative bacteria *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Eschericha coli*. In concentrations of 50–100 µg/mL, chrysomycin V and M inhibited the growth of the fungi *Aspergillus niger, Chaetomium con vuluta, Memnoniella chinata, Myrothecium verrucana, Penicillium notatum, Phycomyces blakesleeanus, Saccharomyces cerevisiae, Stemphylium consortiale* and *Trichophyton mentagraphytes*.[31] In parallel to these promising activities, mice of 20 g body mass survived intraperitoneal exposure of up to 250 mg/kg without negative long-term effects.[31] With their isolation of virenomycin V and M from *Streptomyces virens* (which later turned out to be identical to chrysomycin V and M), Brazhnikova provided further insights for these substrates. Antibiotic activity has been observed, although crystalline virenomycin had a comparatively low antitumor activity and narrow spectrum.[34] Separation of both congeners revealed significant differences regarding antibacterial action *in vitro*: virenomycin V was two to four times more active than virenomycin M against a number of microbes.[50] It was Weiss[48] and Wei[71] who continued the research on the chrysomycins using the very same samples extracted by Strelitz in the mid 1950's. Similar to the gilvocarcins, chrysomycins proved active in the biochemical induction assay (BIA). The sample tested by Weiss contained 86% chrysomycin V and 14% chrysomycin M. Supply limitations confined the testing to a single dose, administered intraperitoneally 24 hours after inoculation with the leukemia cells. At 400 mg/kg chrysomycin produced an increase of the life span (ILS) of the treated mice of 54%, while exhibiting no lethal toxicity. These data are very similar to those (ILS 57 %, LD50 > 1,000 mg/kg) reported for gilvocarcin V.[40] With chrysomycin V in hand (also isolated from the original stock provided by Strelitz) Wei studied the mechanism of action of chrysomycin V.[71] Bactericidal activity was studied resulting in a MIC for chrysomycin V against *Bacillus subtilis* of 0.5 µg/mL. Twice the MIC resulted in at least a 1000-fold decrease in viability of *B. subtilis* within five minutes. Effect upon macromolecular synthesis were likewise studied in *B. subtilis*: Chrysomycin V inhibited DNA synthesis

earlier and to a greater extent than RNA synthesis. Protein synthesis was the least inhibited under these conditions (gilvocarcin V showed the same results, but already at half the concentration). *In vivo* tests with *B. subtilis* showed no DNA degradation upon exposure to chrysomycin V, even at higher concentrations. This led the authors to the assumption, that the event of DNA degradation is not part of chrysomycins' bactericidal nature.[71] In a publication from 1984, Elespuru and Gonda showed that chrysomycin A does possess prophage-induction activity in *E. coli*, but only under light irradiation.[72] Very low concentrations of chrysomycin V (0.01 µg/mL) are detected as DNA damaging agents following illumination under normal laboratory conditions.[72] Doyle could show that both, chrysomycin V and M were active against P388 and L1210 lymphatic leukemia and against B16 melanoma in mice, however, with chrysomycin V being twice as potent as chrysomycin M.[56] Isolated chrysomycin derivatives Mer-120d A(Me), B(Me), C(vinyl) and D(vinyl) were tested against various human cancer cell lines in comparison to chrysomacin V and M and defucogilvocarcin M. In accordance with previous reports, the lowest activity with IC_{50}-values between 8 and 19 µg/mL was shown for defugogilvocarcin M, however, in contrast to that, glycosylated congener Mer-120dA (methyl) showed best results against colic cancer, reticulogranuloma cells, mammary cancer cells, pulmonary cancer cells and gastric cancer cells (even higher than chrysomycin V). Only for leukemic cells, dA showed slightly lower activities compared to dB, dC, dD and chrysomycin V.[60] A comparison of chrysomycins V, M and E revealed that, V and M displayed potent cytotoxicity in HL-60 cells with IC_{50}-values lower than 1 µM, while C showed no significant DNA damage at 1 µM. Interestingly, chrysomycin M showed higher activities compared to chrysomycin V against tested lung cancer cells, colon cancer cells, prostate cancer cells and pancreatic cancer cells (except for HL-60 cells).[66] The two 4'-acetylated congeners of chrysomycin V and M, isolated in 2017, showed activity against gram-positive bacteria. MICs of 0.5 to 2 µg/mL were observed for V, while values of 2 or more than 64 µg/mL were evaluated for chrysomycin M. Good results were also shown in cytotoxicity assays against most of the tested cancer cells, with IC_{50}-values below 10 ng/mL.[67] In a recent study, Muralikrishnan showed that chrysomycin V was also active against Mycobacterium Tuberculosis at a MIC of 3.1 µg/mL.[73]

Gilvocarcins

During the 70's and early 80's the group of Mizuno was first to describe a new anti-tumor antibiotic, which they named toromycin (later referred to as gilvocarcin V). It was active against gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis, B. cereus, B. brevis, Sarcina lutea, Micrococcus flavus*) with MICs comparable to chrysomycins (0.2–0.5 µg/mL), mycobacteria (*Mycobacterium* sp. *TAKEO, M.* sp. 607, *M. phlei*, *M. smegmatis*), mycoplasma (*Mycoplasma gallisepticum*) and trichomonad (*Trichomonas vaginalis*), but not active against gram-negative bacteria (*E. coli, Proteus vulgaris*) or tested fungi (*Aspergillus niger, Candida albicans*), with the exceptions for *Xanthomonas oryzae* and *Pyricularia oryzae*. The antibiotic was also active against DNA viruses such as Vaccinia virus, Herpes Simplex virus at 0.03 µg/mL and inhibited the plaque formation of λ, Φ 170, T1, T3 and

T5 phages at 50 to 100 µg/mL, but was not active against New Castle disease virus, and Q_β, Φ×174, T2 and T4 phages. It is noteworthy, that gilvocarcin V showed higher antibacterial activity than the structurally related chartreusin. In the acute toxicity tests, mice tolerated 1,000 mg/kg of the antibiotic by intraperitoneal administration.[38] In a follow-up paper addressing the structural elucidation of gilvocarcin V, the group modified the substance obtaining an unidentified isomer under acidic conditions, which showed comparable or slightly higher MICs against several microbes.[38] Later, Jain proved this isomer to be the pyranose form of gilvocarcin V.[53] In a collaboration between two groups, Nakano[40], Takahashi[41] and Morimoto[42] isolated gilvocarcin V and its methylated derivative gilvocarcin M, which they submitted to bioactivity tests. As already shown by Mizuno,[38] they recognized that gilvocarcin V is highly active against gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, while gram-negative bacteria (*Klebsiella pneumoniae, E. coli, Shigella sonnei*) showed high resistance. Thereby, the antibacterial activity of V was about one order greater than that of M.[40] In particular, these groups were interested in the antitumor activity of gilvocarcins. They could demonstrate that gilvocarcin V showed activity against experimental tumor sarcoma 180 (without showing a decrease in white blood cell counts) upon injection, while no effect was detected upon oral administration.[40][42] Furthermore, gilvocarcin V was active against Methylcholanthrene Induced Fibrosarcoma in mice with a higher effectiveness than mitomycin C (Mitomycin C is a mitomycin that is used as a chemotherapeutic agent by virtue of its antitumor activity[74]). In their experiments, gilvocarcin V displayed stronger activity than mitomycin C or adriamycin against Ehrlich carcinoma. In particular, 40% of treated mice bearing Ehrlich ascites carcinoma survived for 60 days, after intraperitoneal administration of gilvocarcin V.[42] Gilvocarcin V was also active against MH134 hepatoma and lymphocytic leukemia P388, although it was less effective against P388 than mitomycin C, while gilvocarcin M and A did not show antitumor activity against P388.[40][42] Gilvocarcin V was marginally active against B16 melanoma and did not produce prolongation of lifespan of mice bearing Lewis lung carcinoma. Gilvocarcins M and A were 50 times less effective than gilvocarcin V on the growth of KB cells. Gilvocarcin A, V and M have different solubilities which might also contribute to their biological activity.[42] Gilvocarcin V was not toxic to mice at a single dose of 1,000 mg/kg by oral or intraperitoneal administration, while the LD_{50}-range for intravenous administration was between 300 and 375 mg/kg or higher. For gilvocarcin M, the LD_{50} was 450 mg/kg by a single intravenous administration.[40][42] In a following publication, Tomita showed that gilvocarcin A had no antibacterial activity except for *Staphylococcus aureus*. Gilvocarcin V was not only shown to be able to inhibit cell growth of *Bacillus subtilis* but also to induce cell lysis at 0.5 µg/mL. They also showed that protein synthesis was inhibited by gilvocarcin V only marginally, while RNA synthesis was inhibited to some greater extent. However, DNA synthesis was severely inhibited within five minutes already at 0.1 µg/mL, where even growth inhibition was marginal.[75] In parallel to these publications, Balitz. isolated gilvocarcin V and M, as well as a new member, gilvocarcin E, from *Streptomyces anandii*. In agreement with the other publications, their sample of gilvocarcin V was active against gram-positive

bacteria, such as *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus* and *Streptococcus faecalis*, while no or only little effect was observed on gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Serratia marcescens, Enterococcus cloacae, Pseudomonas aeruginosa*). However, contrary to other observations, their probe of Gilvocarcin M showed only slightly higher MICs compared to gilvocarcin V, indicating a similar activity, with only one significant difference in the case of gram-negative bacteria *Proteus vulgaris*, which was inhibited by gilvocarcin V in a 30-fold lower MIC compared to gilvocarcin M.[45] Little or no effect was also observed in tests against fungi (*Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis, Candida albicans, Candida tropicalis, Candida krusei*), for both, gilvocarcin V and M. In addition to both showing antimicrobial activity, only gilvocarcin V demonstrated potential as an antitumor agent against P388 leukemia in mice upon injection.[45] Gilvocarcin V was also tested for its ability to induce bacteriophage production in the lysogenic strain of *Escherichia coli* W1709 using the methods of Price.[76] In their prophage induction tests, there was no evidence of induction at levels up to 1.6 µg/mL, which was toxic to the host cells.[45] With their biochemical version of the prophage induction assay (here: BIA) based on the work of Elespuru *et al*.[77], Wei *et al*. revealed the gilvocarcins ability to interact with DNA. In particular, compared to gilvocarcin M, gilvocarcin V showed high activity in the BIA spot test, however, the same sample showed no significant prolongation of life of mice in tests against murine P388 lymphocytic leukemia in vivo.[52] In a following publication, Wei studied the mechanism of action of gilvocarcin V (and chrysomycin V) in more detail.[71] Bactericidal activity was studied for both with similar results: MIC of gilvocarcin V (and of chrysomycin V) against *Bacillus subtilis* was 0.5 µg/mL. Twice the MIC resulted in at least a 1,000-fold decrease in viability of *B. subtilis* within five minutes (same for chrysomycin V). Effect upon macromolecular synthesis were likewise studied in *B. subtilis*: Gilvocarcin V inhibited DNA synthesis earlier and to a greater extent than RNA synthesis. Protein synthesis was the least inhibited under these conditions (same for chrysomycin V, but at twice the concentration). However, DNA degradation *in vivo* was detected only at very high concentrations (7 to 50 µg/mL), while chrysomycin showed no DNA degradation at all. This led the authors to the assumption, that the event of DNA degradation must be unrelated to their bactericidal nature.[71] In a publication from 1984, Elespuru and Gonda showed that gilvocarcin V does possess prophage-induction activity in *E. coli*, but only under light irradiation, while Gilvocarcin M was inactive in both, with and without light exposure.[72] Interestingly, Gilvocarcin V showed 10^3 to 10^5 times higher activities than the well-known phototoxic psoralens.[78] Very low concentrations of gilvocarcin V (0.01 µg/mL) are detected as DNA damaging agents following illumination under normal laboratory conditions.[72] Experiments on other microorganisms have indicated no instance in which gilvocarcin V exhibited toxicity in the absence of light.[72] With the isolation of defucogilvocarcin V in 1985, Misra[54] described its light dependent prophage-inducing activity, that is identical to that observed with gilvocarcin V.[72] Defucogilvocarcin V shows antimicrobial activity (upon room light irradiation for one hour) against gram-positive bacteria (*Staphylococcus aureus, Micrococcus luteus, Bacillus subtilis*), but is inactive

against wild type *E. coli* and *Candida albicans*. While gilvocarcin V showed slightly lower MICs under the same testing conditions against gram-positive bacteria, gram-negative bacteria *E. coli* and yeast *Candida albicans* were only affected by gilvocarcin V (although in higher concentrations), but not by its aglycone, which represents an interesting discrimination.[54] Activity tests for gilvocarcin V against B16 mouse melanoma cells and HT-29, human colon carcinoma cells have been done by Mirabelli showing IC_{50}-values between 0.06 and 0.1 µg/mL.[79] In 1986, Greenstein showed, that gilvocarcin V was active against several (gram-positive) strains of *Staphylococcus aureus, Enterococcus* and *Bacillus subtilis* with MICs between 1 and 4 µg/mL under light exclusion, while no activity against gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae AD, Serratia* sp. strain TUV-78-15, *Serratia marcescens, Citrobacter freundii, Providencia stuartii, Proteus morganii, Proteus vulgaris, Proteus rettgeri, Acinetobacter calcoaceticus* and *Pseudomonas aeruginosa*) was detected under the same conditions. Interestingly, gilvocarcin V's MIC against these gram-positive bacteria was lowered to less than 0.06 µg/mL when tests were conducted upon light exposure, while even some gram-negative bacteria were moderately repressed in growth.[80] *O*-glycosylated gilvocarcins BE-12406 A and B, having a methyl group at C8 inhibited the growth of doxorubicin-resistant or vincristine-resistant P388 murine leukemia cell lines. Compared to the methyl congener, vinylated BE-12406 A was also active against transplanted mouse S-180 tumor cells. Investigations of the LD_{50}-values on mice showed that BE-12406 A was not toxic at 100 mg/kg after five days after single intraperitoneal injection.[29,30] With the studies on gilvocarcins HE and H, two further gilvocarcins lacking a vinyl group were shown to possess significant biological activities. Both showed potent antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*, with MIC-values of 0.5–5.0 µM for gilvocarcin HE, which is comparable to activities revealed for gilvocarcin V. Gilvocarcin H`s MIC-values were higher and comparable to gilvocarcin M. In anti-tumor essays, HE and H showed slightly lower activities compared to gilvocarcin M and significantly lower activities than gilvocarcin V.[65]

Ravidomycins

During the early 1980's, the groups of Findlay[47] and Sehgal[46], independently isolated the antitumor antibiotic ravidomycin from *Streptomyces ravidus*. With the structural elucidation by the former group, Sehgal identified *S. ravidus* as a new strain (named "ravidus", which means: gray) and also revealed that ravidomycin was biologically active against gram-positive bacteria (*Staphylococcus pyogenes, Streptococcus faecalis, Mycobacterium tuberculosis, Mycobacterium fortuitum*) but weakly active against gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Enterobacter aerogenes, Salmonella pullorum, Proteus mirabilis, Proteus vulgaris, Klebsiella pneumoniae, Serratia marcescens*) and no activity against fungi (*Candida albicans*).[46] Ravidomycin was shown to exhibit potent antitumor activity in mice against P388 lymphocytic leukemia, Colon 38 tumor and against CD8F1 mammary tumor in rats (upon single intraperitoneal injections on several days). Toxicity tests revealed that the

acute intraperitoneal LD_{50} in mice was 400 mg/kg of body weight.[46] Rakhit, Singh showed that deacetylation of ravidomycin V to deacetylravidomycin V increased its antitumor activities in tests against the P388 leukemia in mice, while being more toxic at lower concentrations (100 mg/kg) than the parent. More surprisingly, reduction of the vinyl into an ethyl group increased toxicity and potency against P388 leukemia. In the course of antimicrobial tests, deacetylation showed slightly higher activities. (Deacetyl-)ravidomycin V shows higher antitumor activities than the gilvocarcins and the chrysomycins.[81] In parallel, the same group also studied its effect on macromolecular biosynthesis in *Bacillus subtilis*.[82] Ravidomycin V mainly inhibited DNA synthesis, followed by RNA synthesis, while protein synthesis was inhibited marginally, similar to chrysomycins[71] and gilvocarcins[75]. Another resemblance to chrysomycin V is that ravidomycin V had no detectable effect upon cellular DNA.[82] In 1986, Greenstein showed that ravidomycin V and deacetylravidomycin V were active in the BIA at concentrations of 0.01 and 100 µg/mL depending on wavelength and intensity of the light source used, while no activity was observed under light exclusion.[80] The group also showed the antibacterial activity of both drugs against several (gram-positive) strains of *Staphylococcus aureus, Enterococcus* and *Bacillus subtilis* with MICs between 0.12 and 4 µg/mL under light exclusion, while little or no activity against gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae AD, Serratia* sp. strain TUV-78-15, *Serratia marcescens, Citrobacter freundii, Providencia stuartii, Proteus morganii, Proteus vulgaris, Proteus rettgeri, Acinetobacter calcoaceticus* and *Pseudomonas aeruginosa*) was detected with MICs of 64 to more than 128 µg/mL under the same conditions. Although these activities were present without the need for light, irradiation dramatically increased the activity for both drugs against gram-positive as well as gram-negative bacteria, showing that the ravidomycins are in principle likewise active against gram-negative bacteria. The greatest increase of activity was shown for deacetylravidomycin V against gram-negative *Proteus morganii* and *Proteus vulgaris* (>256-fold). Similar to the BIA, ravidomycins showed activity in a human colon carcinoma clonogenicity assay only upon light irradiation, with deacetylravidomycin V showing in average a 20-times higher activity than ravidomycin V. Even at concentrations of 0.0002 µg/mL deacetylravidomycin V showed significant cytotoxicity against the tested carcinoma. Discrimination in activity between gram-positive and gram-negative bacteria was also observed for deacetylravidomycin V *N*-oxide. The *N*-oxide, as well as all other known congeners revealed activity against P388 leukemia and Meth A Fibrosarcoma. Interestingly, *N*-oxidation was shown to decrease toxicity.[55] The LD_{50} of deacetylravidomycin V *N*-oxide was over 1,000 mg/kg with no death in mice after 14 days, while the value for deacetylravidomycin V was 50 mg/kg by a single intraperitoneal administration. Deacetylation might also be beneficial considering the low LD_{50}-value (150 mg/kg) of ravidomycin and ravidomycin *N*-oxide. In addition, light exposure was shown to increase deacetylravidomycin V *N*-oxide's antibacterial activity dramatically (16 to 1,020-fold more active).[55] *N*-acetylated ravidomycins FE35A and B were isolated by Yamashita. In their bioactivity studies, they could show that both possess cytotoxicity against U937 leukemia cells by acting as apoptosis inducers.[59] Deacetylravidomycin M was the first repre-

sentative of the ravidomycins exposing a methyl group instead of the vinyl group. Comparison studies with deacetylravidomycin V showed a 10-times lower cytotoxicity for the methyl congener, however, this was accompanied by a likewise lower biological activity against tested gram-positive bacteria.[62,63] With a MIC of 25 µg/mL, deacetylravidomycin M showed moderate activity against *B. subtilis* and *M. luteus*. On the other hand, M showed significant inhibitory activity during interleukin (IL)-4 signal transduction, while no interferences were observed upon treatment with V.[63]

Polycarcins

Studies on the biological activity of polycarcins are scarce due to its novelty, however, in their isolation paper Hertweck successfully demonstrated potent cytotoxicity with a pronounced selectivity for non-small-cell lung cancer, breast cancer and melanoma cells in tests against 37 tumor cell lines.[64]

1.2.3 Mode of Action

With the structural elucidation and differentiation of the several members of the antineoplastic and bactericidal gilvocarcin family during the early 80's (see chapter 1.2.1), the door was open for considerations about the structural mode of action of these molecules and the fundament of their biological activity. In their paper elucidating the structure of gilvocarcin M by single crystal-ray analysis, which they isolated in parallel to gilvocarcin V, Hirayama *et al.* postulated that the biological activity might arise from intercalating to DNA, with vinyl being less sterically bulky than methyl in terms of this intercalating interaction between the base pairs.[44] In this context they emphasize the similarity of this compound to benz[*a*]antharacenes of which many examples are known for their ability to interact with DNA.[83] Several publications compared gilvocarcins V,M, E and A with respect to their biological activities, with the same overall result, as gilvocarcin V being by far the most active member, especially in terms of antitumor activity.[40][42][75] Since the only difference was the substituent at C8, the vinyl group as most active functional group raised the scientists' attention. Already in 1955, Strelitz reported that the yellow crystals of chrysomycin turned brown upon light exposure, indicating their sensitivity to light.[31] Wei described that a solution of gilvocarcin V (10 µg/ml) in tetrahydrofuran – MeOH (1: 9) had a half-life of 50 hours under normal fluorescent room light.[52] Based on these observations and examples of light-induced biological activities Wei measured the mobility of DNA in the presence of chrysomycin A and gilvocarcin V, respectively, upon agarose gel electrophoresis. These tests indicated intercalative binding of the drugs to DNA without causing DNA damage. However, when the same experimental setup was conducted under directed light exposure (visible or near-ultraviolet light), accumulation of damaged DNA (strand breaks) has been observed with both gilvocarcin V and chrysomycin V.[71] Gilvocarcin A, however, had no effect on the mobility.[75] These indications led Elespuru and Gonda to the assumption that reported inconsistencies regarding gilvocarcins' prophage-induction activity (e.g. see Balitz[45] vs. Wei[52]) might be due (among other factors) to inconsistencies in terms of light exposure during the process of the tests. Hence, they conducted prophage-induction

tests similar to the ones described before (based on their own work from 1979[77]), but with specifically being focused on light exposure versus light exclusion during the processes. Thereby, they were able to show, that visible light does activate gilvocarcin V and chrysomycin V to induce bacteriophage lambda in *Escherichia coli* by a DNA-dependent mechanism.[72] Whereas both compounds showed strong prophage-inducing activity after a 15- or 20-minute exposure of solutions to fluorescent light, no activity was seen when the experiment was performed in the dark (or under yellow lights). It is noteworthy, that prophage induction only occurred when the bacteria and chemical were present together during light exposure, a result reminiscent of the behavior of psoralens. Highest activity was revealed to be induced upon exposure to light between 320 and 430 nm. Longer wavelengths did not induce prophage activity. The lack of antitumor-activity for gilvocarcin M was reported before.[45][42] As a proof, gilvocarcin M was also negative in the prophage induction experiments under several conditions of illumination, even though its absorption spectrum was similar to that of gilvocarcin V.[41] The structurally related antitumor agent chartreusin showed only slight prophage-inducing activity that was independent of irradiation. As a result of these findings, the vinyl group was found to be a critical structural element for activity of the gilvocarcins. Detected antitumor activity in mice tissue without intentional irradiation suggests, that activity *in vivo* might be induced enzymatically. In addition, the absence of systemic toxicity of gilvocarcins *in vivo* may indicate that gilvocarcins undergo selective distribution into or activation at specific target tissues. Gilvocarcins might thus provide opportunities for several modes of cancer therapy, involving *in vivo* activation at the sites of tumors, or activation via external irradiation.[72] Misra[54] could show that the aglycone (defucogilvocarcin V) shows an identical light dependent prophage-inducing activity, like gilvocarcin V[72], suggesting that this activity is independent of the sugar moiety. While biological activities against gram-positive bacteria were comparable between both, gilvocarcin V and its aglycone, gram-positive bacteria *E. coli* and yeast *Candida albicans* were only affected by gilvocarcin V (4 µg/mL). Hence, the sugar moiety might stimulate the uptake of the drug by the organism.[54] Studies based on modifications of the ravidomycins by Rakhit, Singh confirmed the impact of the sugar moiety while de-emphasizing the role of the vinyl group.[81] In addition, their results suggest that the antitumor potency follows that of antimicrobial activities. In parallel, the same group has studied ravidomycin's mechanism of action by analyzing its effect on macromolecular biosynthesis in *Bacillus subtilis*, showing that it mainly inhibits DNA synthesis, followed by RNA synthesis, without affecting protein synthesis.[82] In a study by Steinberg, in which they established the photobacterium induction assay (PIA) as prescreen for antitumor agents, ravidomycin was shown to bind to DNA or affect DNA synthesis.[84] With their established assay, Mirabelli demonstrated the DNA-binding abilities of gilvocarcin V and chrysomycins.[79] In 1986, Greenstein showed that the bioactivity of ravidomycin and deacetylravidomycin strongly depends on light induction. They observed that both showed no activity in the BIA under light exclusion, while concentrations of 0.025 (ravidomycin) and 0.045 µg/mL (deacetylravidomycin) were sufficient when conducted upon irradiation of 400 nm.[80] Activity was 20- to 30-fold lower at 362 nm and even 200-fold lower at 497 nm, while at 597 nm no activity was observed

at all. Their findings also showed that light does not transform the drug into an active form, but induces a chemical reaction with the DNA or any other bacterial component. Although, light is in general not needed to induce antibacterial activity of ravidomycins (which might be due to intercalative drug binding to DNA, presumably possible for all gilvocarcins), Greenstein showed that their activities can be increased dramatically upon light irradiation. Based on an electrophoretic mobility shift assay McGee and co-workers observed gilvocarcins' preference to covalently bind to thymidine nucleotides upon light exposure, thereby introducing single strand breaks. [85] They assume that the sugar residue may stabilize non-covalent binding of gilvocarcin V to DNA, allowing further covalent attachments. Interesting insights were likewise given by the group of Elespuru demonstrating light-induced DNA-to-protein cross links in human P3 cells.[86] In addition, they confirmed the substrate's preference for AT-rich DNA sequences and even higher affinity for AT-alternating homopolymers.[87] Similar results were found by Knobler[88], while further studies revealing the ability to induce DNA-protein cross links followed.[89] In parallel to these results, gilvocarcin V was found to be a potent topoisomerase II inhibitor hampering transcription.[90] Shortly after, with Histone H3 and Heat Shock Protein GRP78, two specific proteins could be identified to be selectively cross-linked.[91] A possible *in vivo* mechanism of gilvocarcin V during DNA-protein cross linking is provided by Rohr (Figure 5).[92] In this context, masking of the

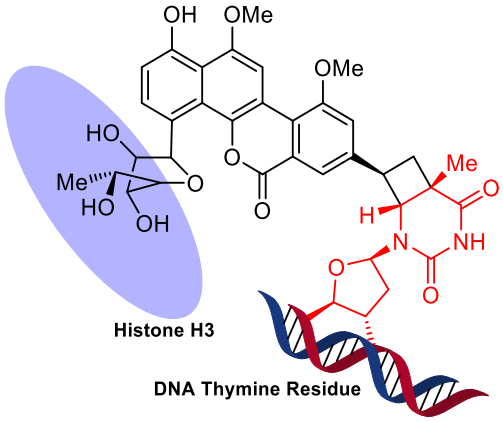
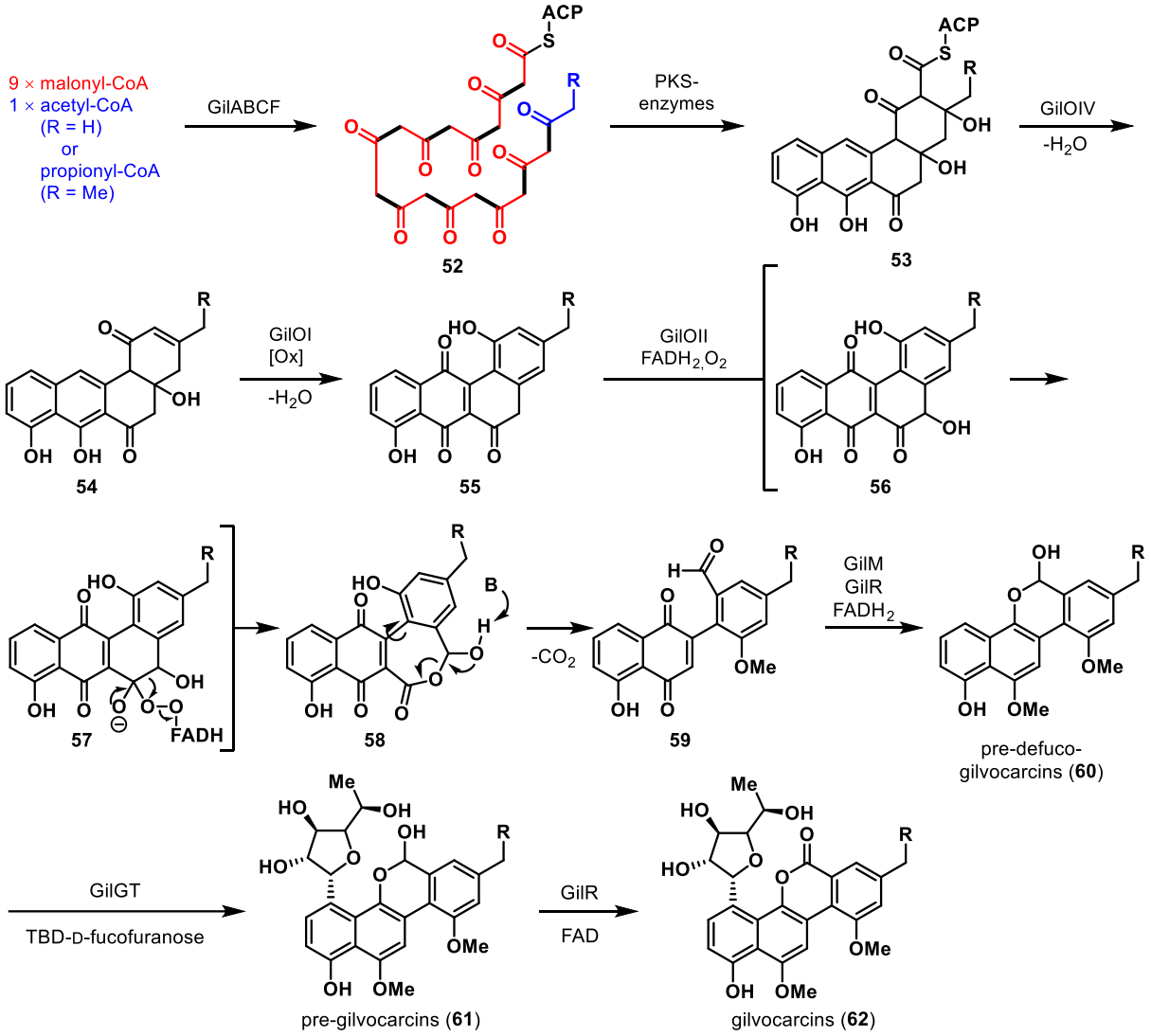


Figure 5: Gilvocarcin V induces protein-DNA-cross linking by covalently binding to DNA-thymidine-residues.

sugar's free hydroxy groups via methylation resulted in decreased affinity for the protein, confirming the role of the sugar in this process. These results raised the question about the specific activation by light.[93] Quantum yield studies based on gilvocarcin V and M showed that both, type I (involves production of $O_2^{\bullet-}$ which disproportionates to H_2O_2 giving $^{\bullet}OH$, in the presence of trace metals) and type II (generation of $^1O_2$) photochemistries are not important pathways in the cytotoxicity of gilvocarcin V, since M and V showed similar photoactivities, whereas only V is photocytotoxic.[94][95] The final proof of a photoinduced covalent bonding of gilvocarcin V to thymidine was provided by Misra and McGee by the isolation of the gilvocarcin V–thymine photoadduct.[96] However, activity studies with vinyl-lacking congeners like gilvocarcins BE[29] or modifications of the vinyl group of gilvocarcin V maintained the search for other factors ensuring biological activity.[97]

1.2.4 Biosynthesis



Scheme 7: Proposed biosynthesis of the gilvocarcins.

With the structural elucidation of the gilvocarcin natural products during the early 1980's, the question about its biosynthetic pathway was raised. Earliest investigations based on carbon- and hydrogen-labeled acetate- and propionate-incorporation[43] led to the assumption of an underlying acetate/polyketide-pathway, as known for similar polyketides like chartarin.[98][99][100] While the question for the general pathway was answered rather early, aspects regarding the transformation of the so-formed angucycline core (*vide supra*) into the dibenzochromenone-core or the origin of the different C8-substitutents (methyl vs. ethyl vs. vinyl) were open for debate. The C8-diversity was first explained by a secondary addition of a propionate-based alkyl group.[43][48] The C_2-unit (vinyl, ethyl) might subsequently undergo decarbonylation to afford the methyl group. In contrast to that, Carter came to the conclusion of a propionate-initiated decaketide chain for the vinyl and the ethyl group, of which the latter might be transformed into the former via dehydrogenation.[49][101] The methylated variants of the gilvocarcin family were suggested to be either made from an acetate-initiated decaketide chain or by late-stage demethylation. However, the degradative hypothesis was refuted by the same group as a result

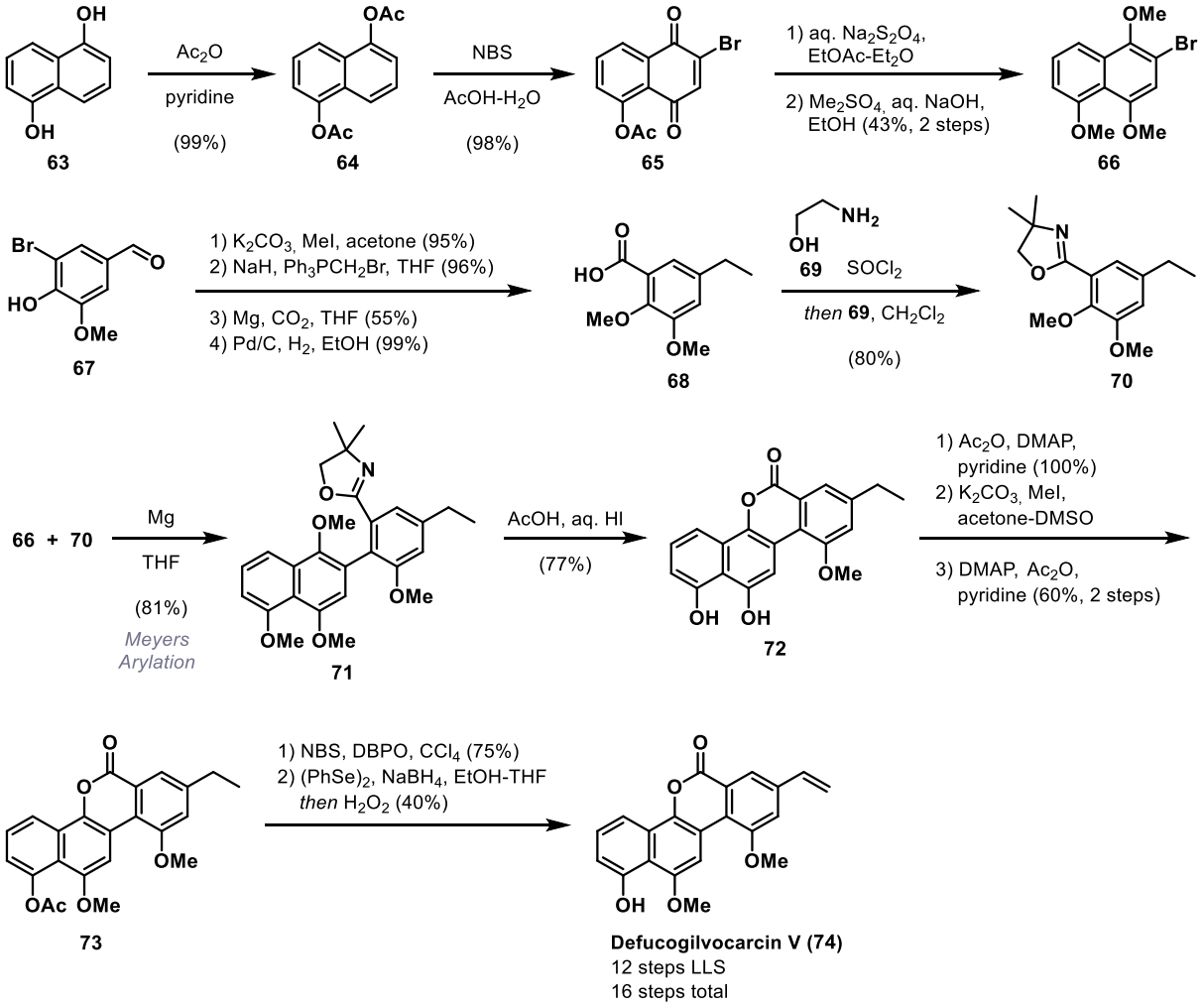
of further labeling-studies on chrysomycins V and M.[49] The origin of the acetate-units for the gilvocarcins was suggested to be amino acids glycine and aspartate.[102] It was the group of Jürgen Rohr who brought forth the studies on the gilvocarcins' biosynthesis. Different from the previous groups, Rohr and co-workers approached this issue by analyzing and identifying specific gene-clusters responsible for the synthesis.[103,104] Their continuous investigations and efforts, which are still ongoing, led to the following proposed biosynthetic pathway (Scheme 7): Starting from nine malonate-units and one acetyl- (for C8-Me) or propionyl-unit (for C8-vinyl/ethyl), polyketide-chain **52** is formed which is further modulated (in a J-shaped manner[105]) by a type II polyketide synthase (PKS) undergoing several condensation and dehydration steps.[103,106] The so-formed angular tetracycle **53** undergoes dehydration, which is catalyzed by the oxygenases GilOIV and GilOI.[107] One of the major questions that remained unsolved for decades addressed the C–C-bond cleavage of intermediate **55**.[108] In 2012, Rohr and co-workers were able to isolate a key-intermediate, which turned out to be hydroxyoxepinone **58**. In accordance with further experiments, a Baeyer–Villiger-type oxidation could be confirmed. GilMT, a typical SAM-dependent *O*-methyltransferase, was found to be responsible for subsequent decarboxylation and methylation to give biaryl **59**. GilM-assisted quinone reduction, hemiacetal formation, and *O*-methylation leads to pre-defucogilvocarcins **60**,[109] which then gets glycosylated, a process still not completely understood.[110] However, several enzymes involved in the synthesis of the sugar moieties have been identified.[111]

1.2.5 Previous Syntheses of Gilvocarcin Aglycones

Ever since the structural elucidation of the gilvocarcins during the early 1980's, the idea of a synthetic approach has attracted the attention of organic chemists. Interestingly, the characteristic and unique 6*H*-dibenzo[*c*,*h*]chromen-6-one core was not known as core structure of the gilvocarcins or any other natural product before 1981. However, the first synthesis of this scaffold was described by the group of Onda in 1979 in the course of investigating benzo[*c*]phenanthridines.[112] The crucial biaryl coupling was thereby achieved via Meerwein arylation. In the following, all known total and formal syntheses of gilvocarcins and their aglycones are described and shown in chronological order. Besides these examples, publications describing the synthesis of closely related or highly advanced intermediates towards the gilvocarcins will not be discussed in this thesis. Moreover, the enzymatic total synthesis of gilvocarcin M by the group of Rohr from 2012 will be also excluded.[113]

Findlay, 1987 (Danishefsky, 1988) – via Meyers Coupling

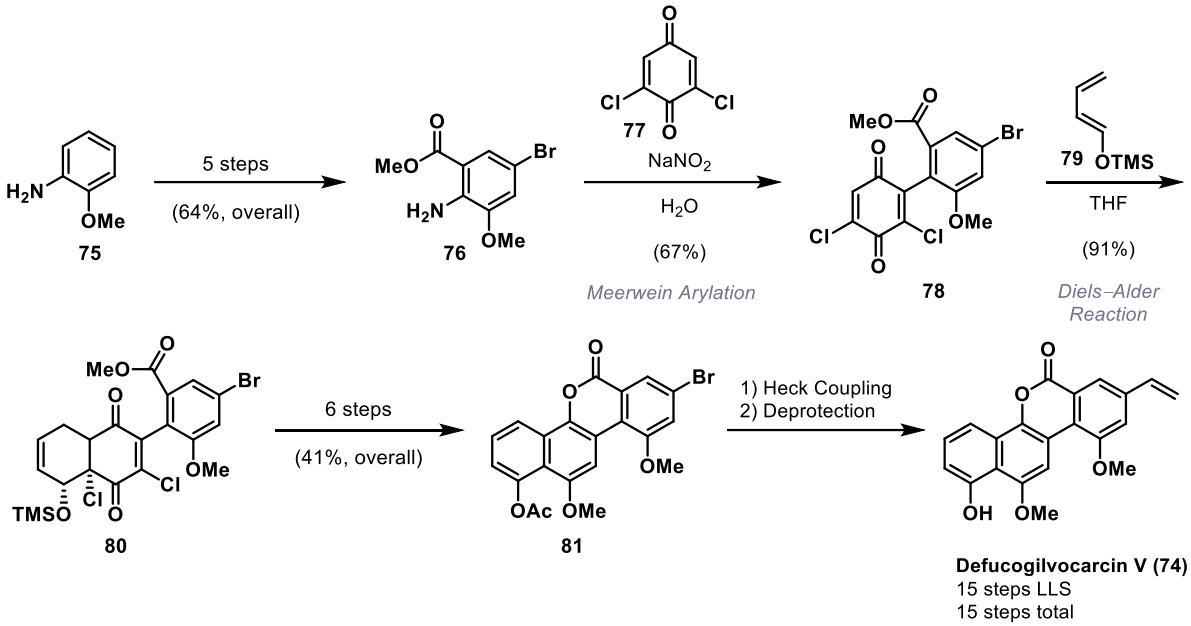
It was not until 1987, that the first synthesis of the aglycone defucogilvocarcin V was reported by Findlay.[114] Preparation of naphthalene **63** was based on the methodology of Grunwell and Heinzman to rapidly access bromojuglone **65**.[115] Bromo-vanillin **67** served as starting point for fragment B nearly similar to substrates prepared by the group of Meyers.[116] Consequently, the crucial biaryl coupling followed Meyers' procedure. Subsequent unmasking of the carboxyl group and lactonization afforded demethylated defucogilvocarcin E. Noteworthy, the existence of the ethylated derivative (defuco-/gilvocarcin E) was not known at that time. Five further consecutive steps were needed to achieve the first total synthesis of defucogilvocarcin V. This very similar strategy starting from the same substrates **63** and **67**, however, with a slightly shorter longest linear sequence, was reported by the group of Danishefsky the year after.[117]



Scheme 8: First total synthesis of a gilvocarcin natural product.

McKenzie, 1987 – via Meerwein Arylation and Diels–Alder Reaction

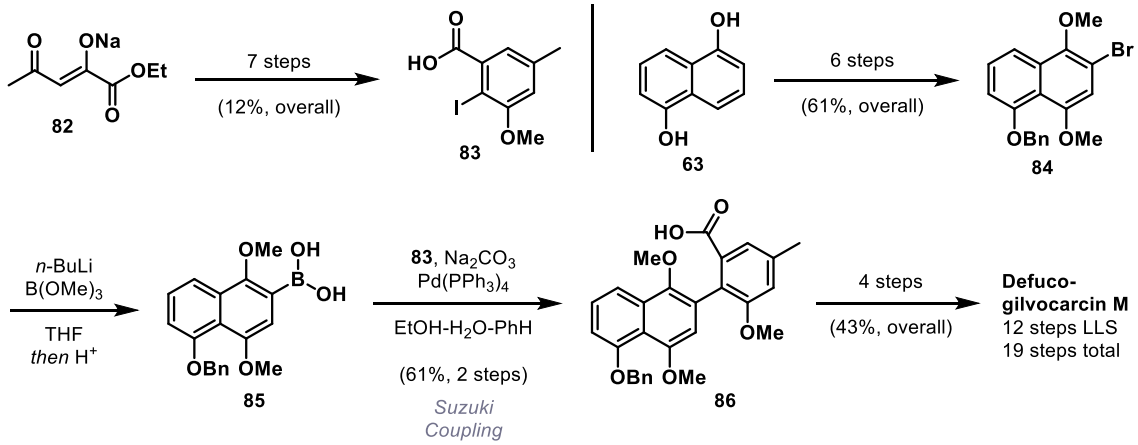
Shortly after the report of Findlay, McKenzie published their results on the synthesis of defucogilvocarcin V based on a Meerwein arylation, similar to the findings of Onda several years before.[118] A subsequent Diels–Alder reaction furnished the naphthalene core of **80**. Their route resulted in formation of the corresponding acetylated aglycone with a substituted bromide at the crucial C8-position, which served as handle for a divergent late-stage alkylation towards all three then known defucogilvocarcins (M, E and V) via Heck coupling.[119]



Scheme 9: McKenzie's total synthesis of defucogilvocarcins V, M and E.

Jung, 1988 – via Intermolecular Suzuki Coupling

A Suzuki cross-coupling served as key step in the total synthesis of defucogilvocarcin M by Jung.[120] Benzoate **83** was achieved via formation of 3-hydroxy-5-methyl-benzoic acid following Claisen's



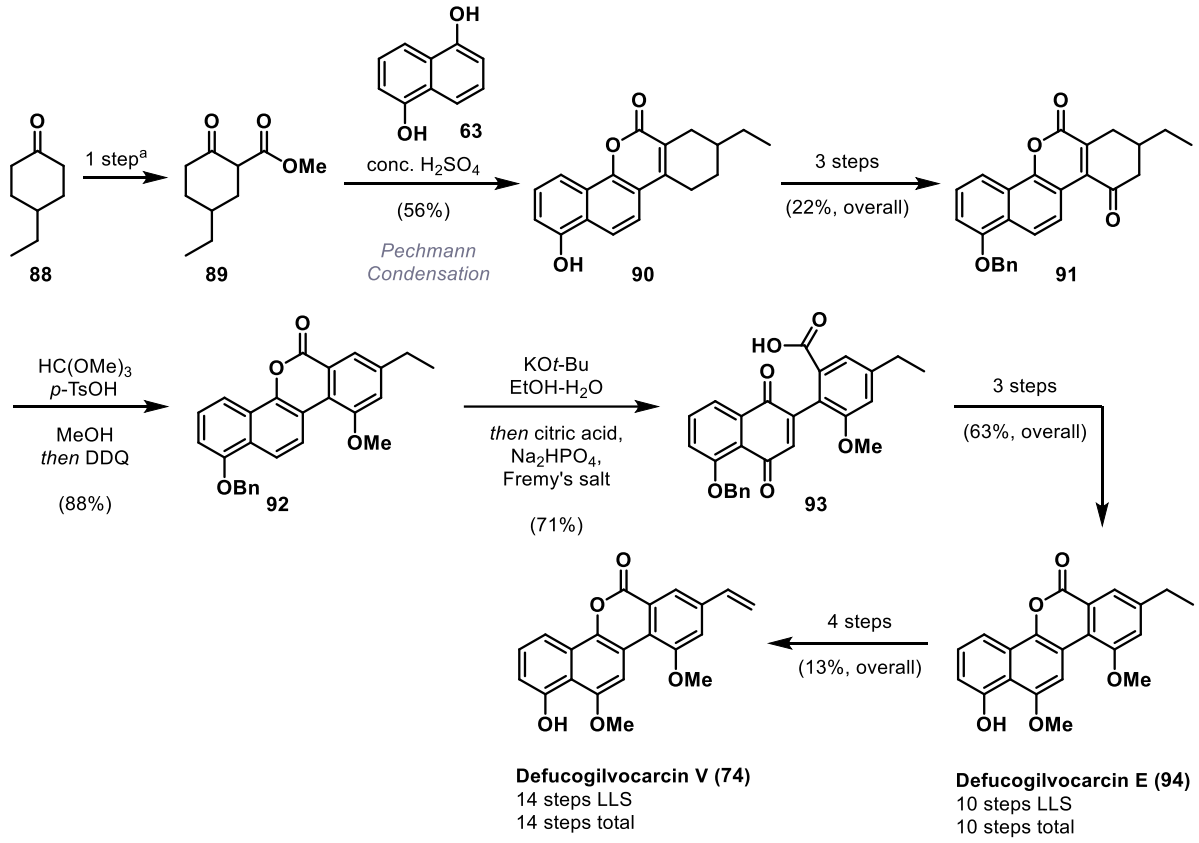
Scheme 10: Jung's synthesis of defucogilvocarcin M based on a Suzuki Coupling.

procedure from 1889[121] and five further steps resulting in iodo benzoate **83**. Main fragment **84** was made according to the procedure of Findlay and Danishefsky (see above) with additional replacement

of the acetyl protecting group by a benzyl group. Borylation with subsequent intramolecular Suzuki coupling afforded all-carbon intermediate **86**, which was converted into defucogilvocarcin M (**87**) by four further transformations.

McGee, 1988 – via Pechmann Condensation

As in the synthesis by McKenzie, McGee developed a linear route rather than the favorable late-stage connection of two functionalized main fragments, which is usually seen for the construction of gilvocarcins.[122] The envisioned Pechmann condensation with subsequent aromatization represents a unique approach towards the tetracycle, which was achieved in two simple steps. In contrast, the following aromatization and oxidation towards the dihydroquinone motif turned out to be tedious. Nevertheless, their strategy remains to this date the shortest synthesis of defucogilvocarcin E. Post-functionalization within four steps was achieved by a modified protocol of Findlay. Further studies on the Pechmann condensation towards the gilvocarcin core structure were reported a few years later by Hua.[123]

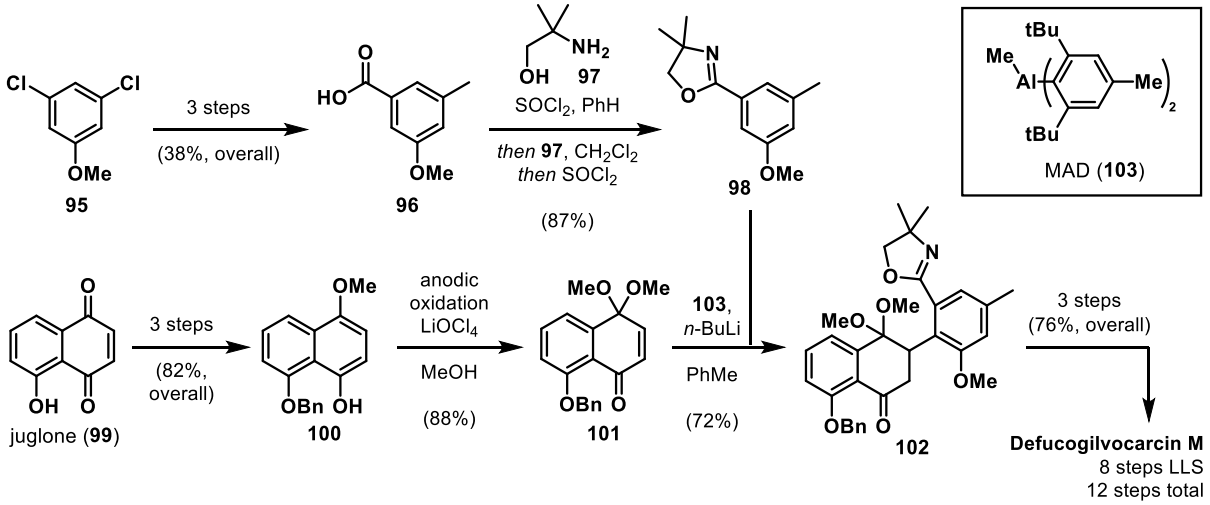


Scheme 11: A Pechmann Condensation enables the fast construction of the gilvocarcins tetracyclic core. [a]The authors did not provide a specific procedure for this step.

Hart, 1989 – via Michael Addition

Hart and Merriman's approach towards defucogilvocarcin M relies on a conjugate addition of lithiated **98** to enone **101**.[124] The reaction is mediated by the exceptionally bulky and oxygenophilic organoaluminum reagent MAD **103** (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), which was developed by Yamamoto.[125] The construction of benzoate **96**, one of the most applied and crucial

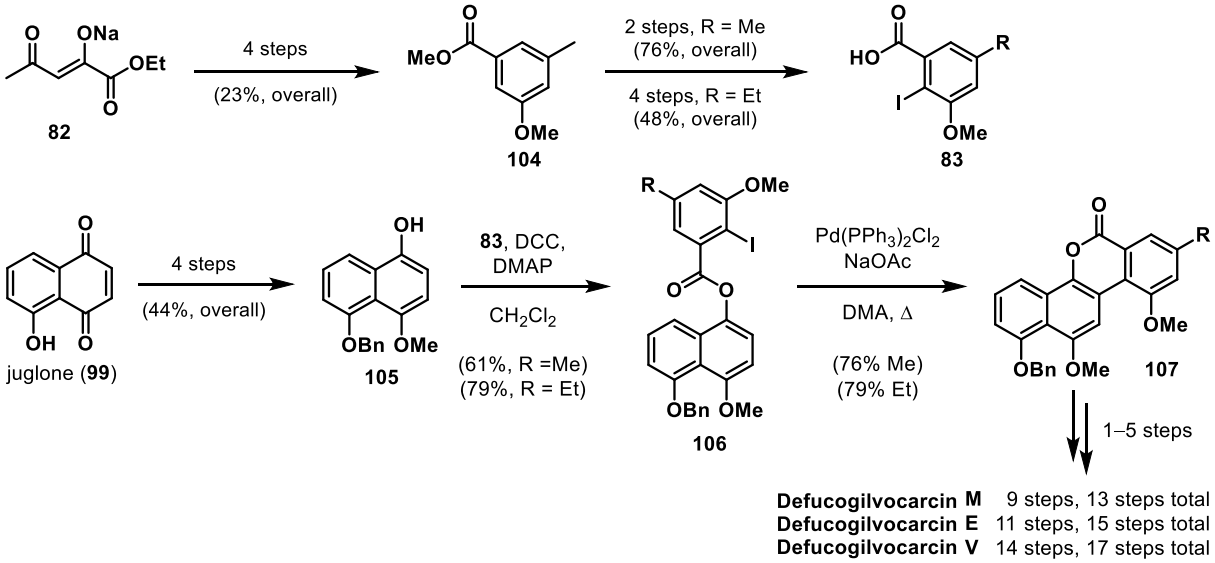
intermediates among all known gilvocarcin syntheses, was improved by developing a three-step sequence based on Rieke-Mg-activation. Their efforts culminated in a concise synthesis of defucogilvocarcin M with eight steps as longest linear sequence (LLS).



Scheme 12: Hart's synthesis of defucogilvocarcin M.

Martin, 1990 – via Intramolecular Heck Coupling

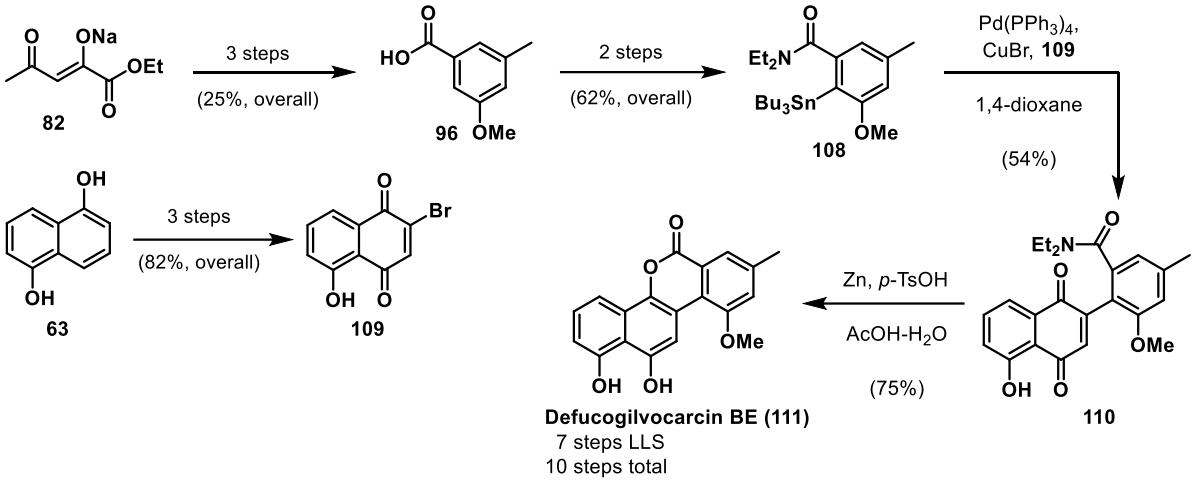
Martin and Deshpande developed a route towards ketone **102**, which would serve as key intermediate in the (formal) synthesis of gilvocarcins M, E and V.[126] While the preparation of the key-intermediates **83** (see Jung) and **100** (see Hart) are based on previously described routes with a few differences in procedure and conditions, key feature of their strategy is an efficient intramolecular Heck-type coupling. Compared to Jung's strategy employing a Suzuki coupling, this intramolecular biaryl formation proceeds without additional functionalization of the naphthalene core. Again, this synthesis highlights the challenges associated with the preparation of seemingly simple benzoates derivatives like **104** and **83**, which were achieved in not less than four to eight steps, respectively.



Scheme 13: Martin's intramolecular Heck coupling represents the most frequently adapted key-step for the construction of gilvocarcins by other groups.

Echavarren, 1996 – via Intermolecular Stille Coupling

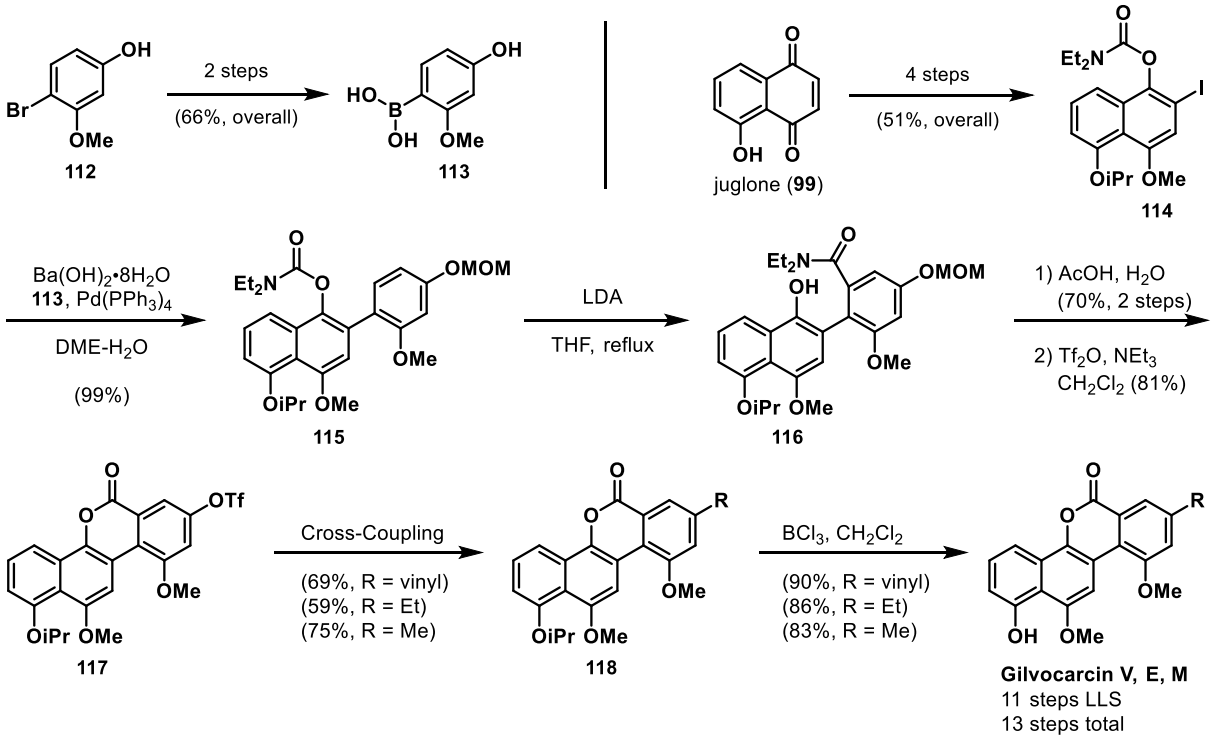
Another synthesis, which relies on the known key-intermediates **82** and **109** was published by de Frutos and Echavarren in 1996.[127] With previously reported strategies for the crucial biaryl-bond formation via Heck and Suzuki coupling (see above), the repertoire of suitable cross couplings towards the synthesis of gilvocarcins was extended by the Stille coupling employing stannane **108**. A subsequent one-pot reduction–cyclization sequence afforded defucogilvocarcin BE.



Scheme 14: An intramolecular Stille coupling was used by Echavarren to prepare defucogilvocarcin BE.

Snieckus, 1997 – via Directed Remote-Metalation–Carbamoyl Migration

Addressing the challenges of cross-couplings to form biaryl-bonds using *ortho*-*ortho*-disubstituted arenes, James and Snieckus envisioned a late-stage intramolecular *ortho*-substitution of the

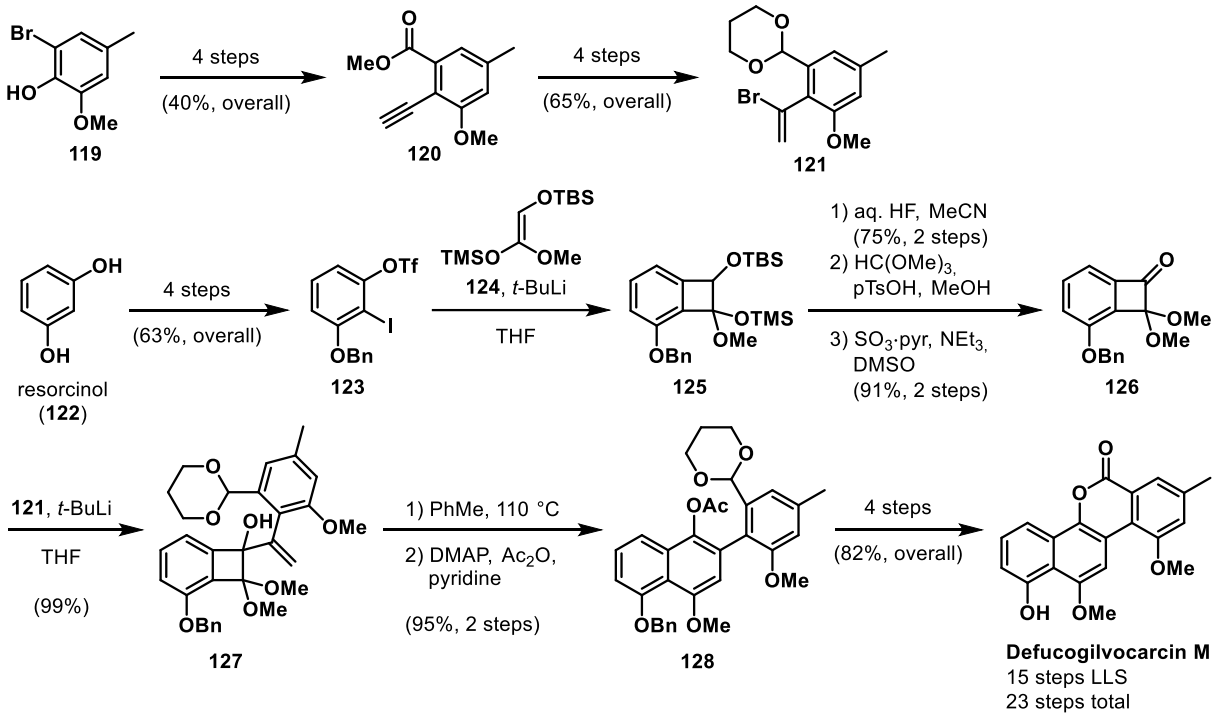


Scheme 14: A late-stage directed *ortho*-metalation enables the synthesis of defucogilvocarcins V, E and M.

gilvocarcins' phenyl unit.[128] Careful screening and the absence of a second *ortho*-substituent on intermediate **113** resulted in quantitative Suzuki cross coupling to give naphthalene **115**. The subsequent key-step was tested with different protecting groups of which the MOM-protecting group resulted in highest yields. Mechanistically, the amide moiety enables a directed remote-metalation using lithium diisopropylamide to give the *ortho*-anion of biaryl **115**. The metalated position subsequently attacks the amide via electrophilic aromatic substitution, by which the amide group is transferred to the phenyl residue (rather than resulting in direct cyclization) to give the corresponding lactone. Although envisioned to proceed in the same step, lactonization was achieved by subsequent treatment with acetic acid to additionally remove the MOM-group. Triflation of the hydroxy group gave tetracycle **117** which allowed for the divergent preparation of defucogilvocarcins V, E and M via different cross-couplings.

Suzuki, 2004 – via [2+2+2] cyclization

In their publication from 2002, Suzuki and co-workers describe a strategy to access benzocyclobutenediones via [2+2]-addition between silyl ketene acetals and *in situ* generated arynes.[129] These butenediones can undergo a retro-[2+2] reaction to give reactive *ortho*-quinonedimethanes, which



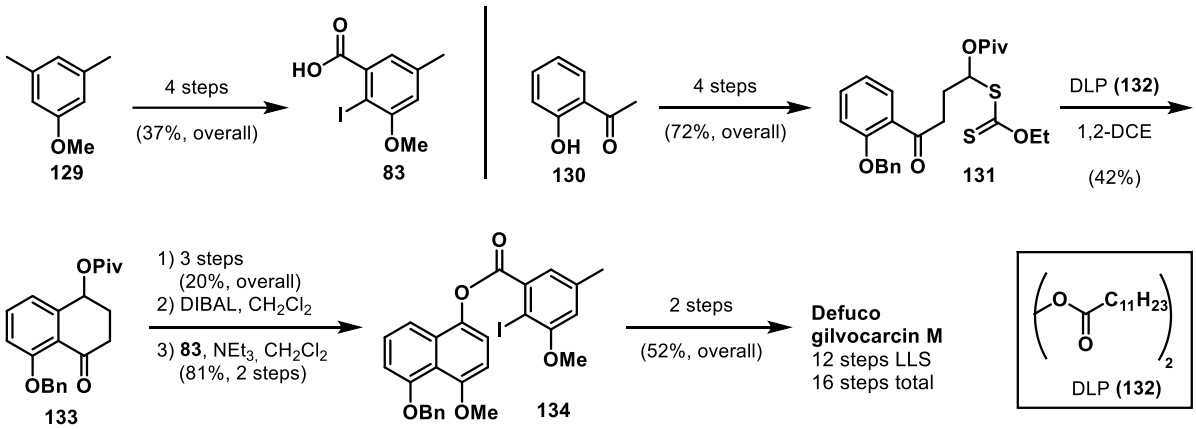
Scheme 15: Suzuki's [2+2+2]-approach towards defucogilvocarcin M.

they describe as a formal umpolung. Based on these finding, the same group extended their methodology to perform a [2+2+2]-reaction by adding a suitable alkene as third component.[130] As a consequence, efforts were made to embed this strategy into the total synthesis of defucogilvocarcin M. Starting with resorcinol, aryne-precursor **123** was made in four steps. Treatment with *tert*-butyl lithium, followed by the addition of silyl ketene acetal **124** afforded benzocyclobutene **125**. The corresponding ketone **126** was obtained via three consecutive steps, which was then used for the following 1,2-addition with alkene

121. Thermal conditions induced retro-[2+2]-reaction to generate the anticipated benzocyclobutenedione, which directly undergoes the crucial intramolecular [2+2+2]-reaction resulting in biaryl **128**. Finally, lactonization and deprotection completed the synthesis of defucogilvocarcin M.

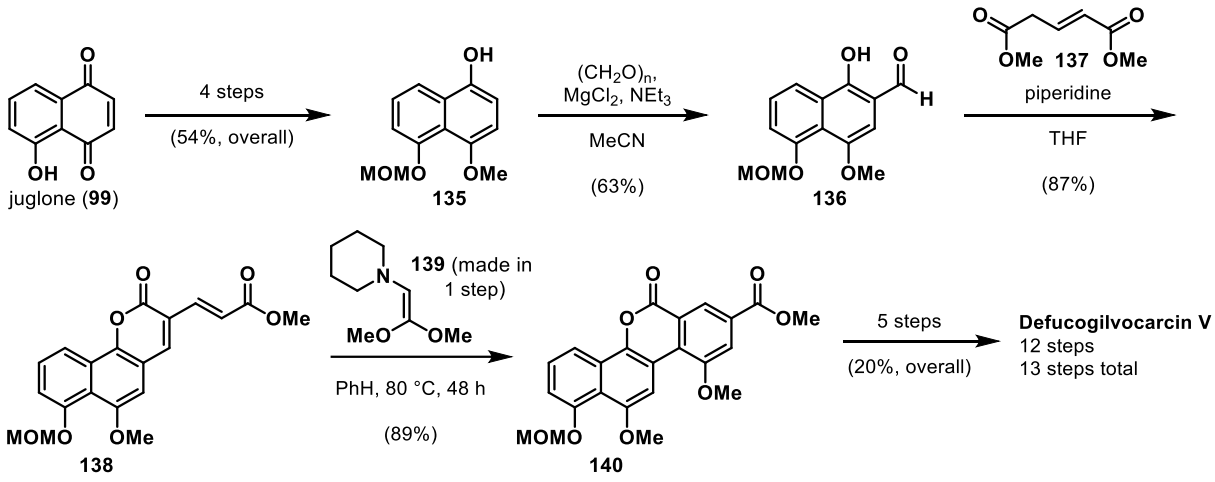
Cordero-Vargas, 2010 – via Xanthane-Based Free Radical Cyclization

A formal synthesis of defucogilvocarcin M was reported by Cordero-Vargas in 2010.[131] While adopting the very same end-game strategy of Martin employing an intramolecular Heck coupling (see above), formation of the naphthalene core was achieved via a novel radical-addition cyclization. Therefore, xanthate **131** was treated with 1.40 equivalents of peroxide **132** to initiate radical cyclization resulting in the formation of tetralone **133**. Subsequent aromatization gave the corresponding naphthoquinone **105** already described by Martin. While iodo-benzoate **83** was previously made in six steps (see above), Cordero-Vargas combined recently developed and known reactions from the literature to synthesize this crucial intermediate in four steps.[132,133]



Scheme 16: Radical formation of tetralones as starting point for the synthesis of defucogilvocarcin M.

Bodwell, 2012 – via Inverse Electron Demand Diels–Alder Reaction (IEDDAR)



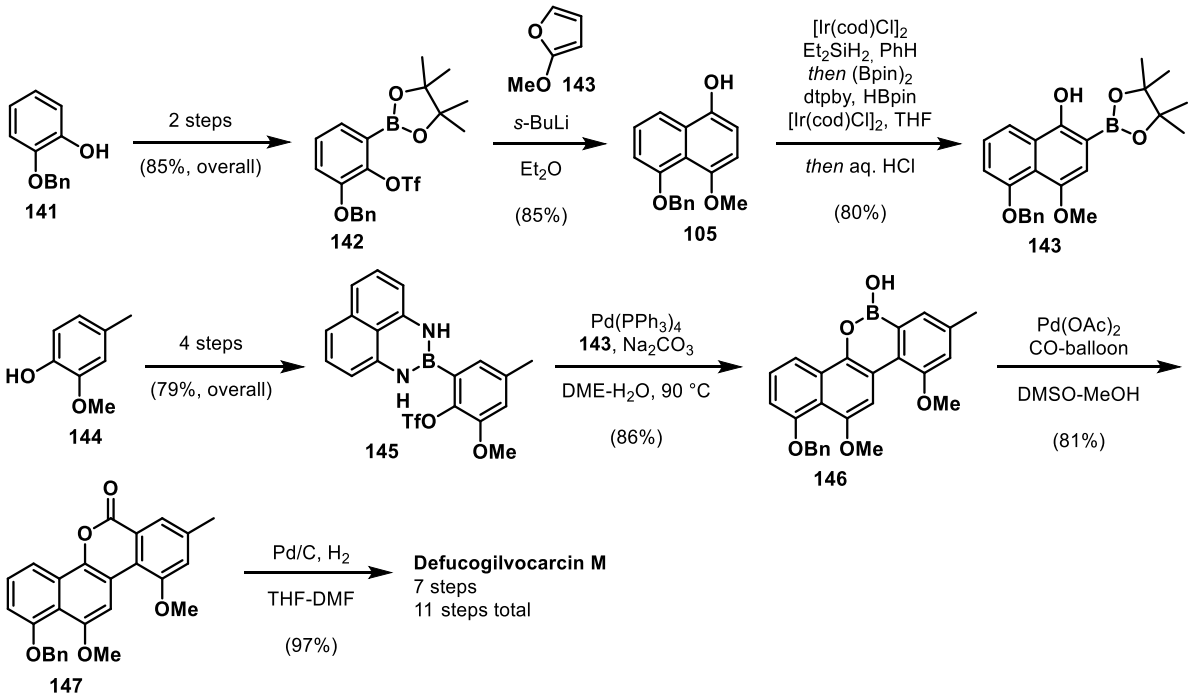
Scheme 17: Bodwell employs an IEDDAR to construct the gilvocarcin tetracycle.

In contrast to the prevailing synthetic strategies towards gilvocarcins based on the connection of two aromatic fragments, usually a phenyl and a naphthyl core, Bodwell envisioned a linear route entailing a

late-stage construction of the eastern fragment via an inverse electron demand Diels–Alder reaction (IEDDAR).[134] As seen in several previous syntheses, their route starts from juglone, which was transformed into aldehyde **136** in five steps. Formation of key-precursor **138** was realized by a vinylogous Knoevenagel condensation with subsequent esterification in high yields. The following IEDDAR proceeded without the need for an additional catalyst upon heating for 48 hours in benzene. The synthesis was completed by five further steps affording defucogilvocarcin V.

Hosoya, 2012 – via Boron-selective Suzuki Coupling towards Dibenzoxaborins

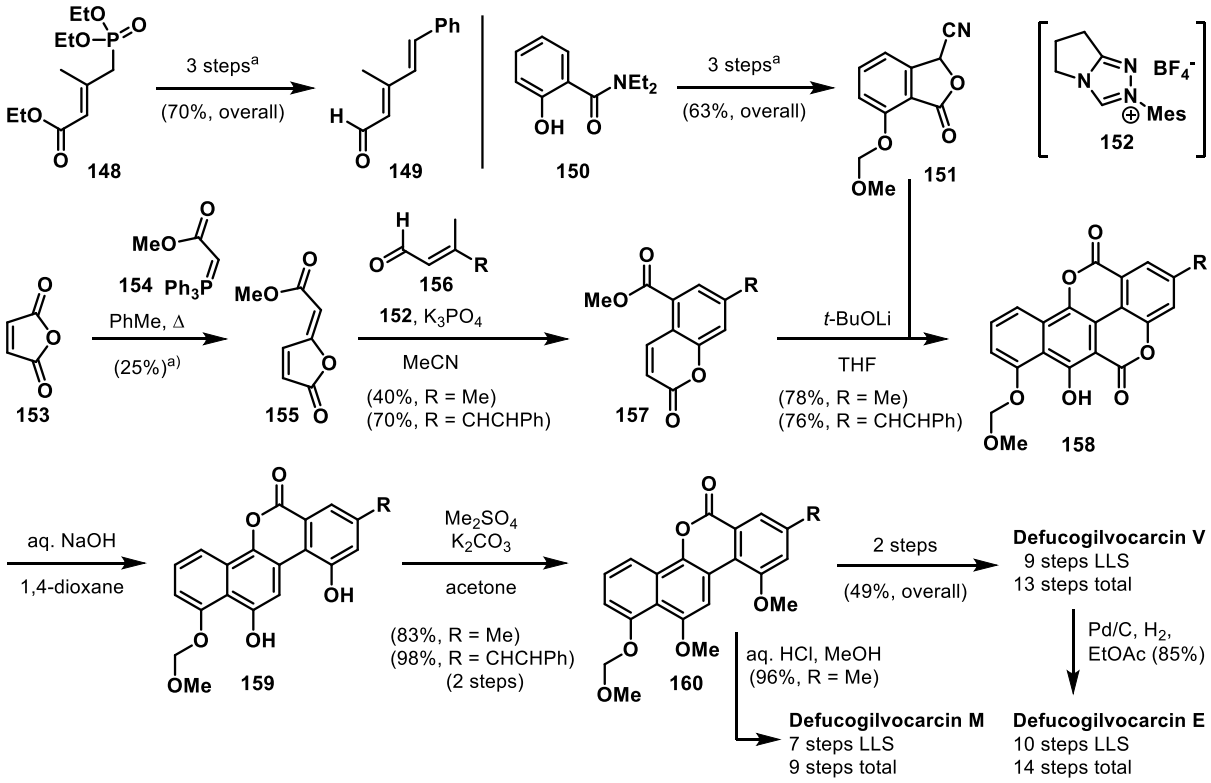
Hosoya developed a strategy by which two aryl-boronates were coupled with selectivity regarding the boron functional group to afford dibenzoxaborins.[135] Differentiation was possible by previous 1,8-diaminonaphthalene-protection of one of the two aryl-boronates, a strategy previously developed by the group of Suginome.[136] These findings were applied to the synthesis of defucogilvocarcin M. Boronate **143** was accomplished in four steps exploiting Hartwig's iridium-catalyzed *ortho*-borylation as entry and completing step,[137] while a Diels–Alder reaction (similar to Suzuki, 1992) constructed the naphthalene core of **105**. Functionalization of phenol **144** started likewise using Hartwig's protocol with three further steps resulting in protected boronate **145**. Key-coupling of both fragments **143** and **145** involving spontaneous deprotection and cyclization afforded dibenzoxaborin **146** in high yield. Palladium-catalyzed CO-insertion and debenzylation completed their synthesis of defucogilvocarcin M.



Scheme 18: Hosoya's total synthesis of defucogilvocarcin M.

Chi, 2017 – via Formal [5+5] Addition and Hauser–Kraus Reaction

Another aglycone synthesis which resulted from a developed in-house-methodology was reported by Chi.[138] Defucogilvocarcins M, V and E originated from protected chartarin **158** via selective decarboxylative lactone opening followed by minor late-stage modifications. While the application of the used Hauser–Kraus reaction was already reported for the synthesis of chartarin,[139] Chi and co-workers improved the synthesis by developing an NHC-catalyzed formal [5+5]-reaction towards chromenones **157**. Unfortunately, the paper does not provide any information or reference for the synthesis of intermediates **148**[140], **151**[141] and **155**.[142] However, the shortest literature-known procedures are representatively shown in Scheme 19. With seven linear and nine total steps, this synthesis represents the shortest route towards defucogilvocarcin M to date.



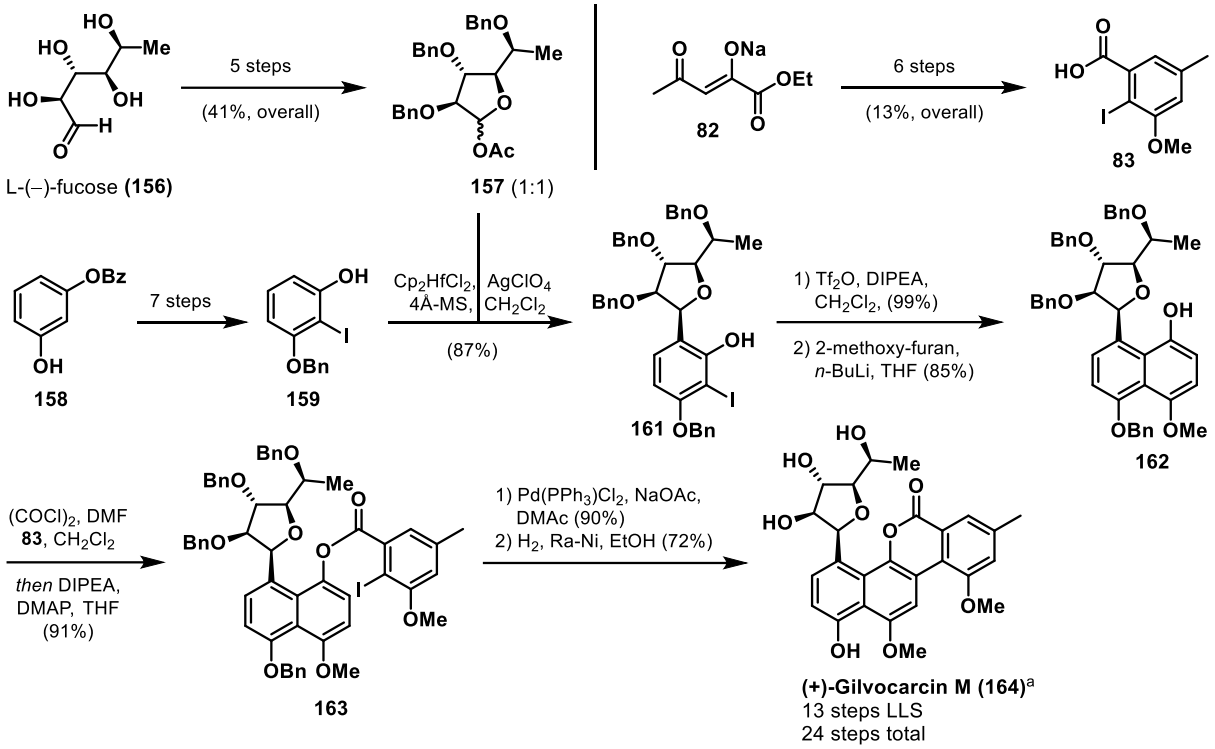
Scheme 19: A Hauser–Kraus annulation enables the shortest synthesis of defucogilvocarcin M. [a]Procedures not provided by the authors, but found in literature.

1.2.6 Previous Syntheses of Glycosylated Gilvocarcins

Since the first total synthesis by Findlay in 1987, numerous efforts towards the aglycones have been reported by applying various strategies (*vide supra*). In contrast, only a few successful syntheses of the glycosylated gilvocarcins have been reported, and even less different strategies for attaching the sugar moiety were developed in this context. This contradiction emphasizes the challenges associated with the aryl-*C*-glycosylation of these natural products. Pioneering work was done by the group of Suzuki having achieved the total synthesis of gilvocarcins M, V, BE 12406 A and ravidomycin V between the years 1992 and 2011. Only two further groups, Minehan (polycarcin V, 2014) and Lei (polycarcin V, chrysomycin V, gilvocarcin V, 2018), followed this endeavor. Suzuki's and Minehan's strategies rely on an early-stage glycosylation of rather simple building block, followed by up to 17 post-functionalization steps to furnish the natural product, depending on the attached sugar. Due to the promising biological activities with recognizable dependence on the sugar moiety, a more general synthesis that provides access to a library of different glycosylation patterns would be desirable. It was not until recently that Lei and co-workers were able to demonstrate a late-stage glycosylation allowing for a divergent approach towards diversely glycosylated gilvocarcins. Their findings represent a major step forward in this field, however, low yields accompanied by possible sugar-dependent stereo- and regioselectivities render this a limited protocol leaving space for improvement. All mentioned efforts are summarized chronologically in the following.

Suzuki, 1992 – Gilvocarcin M, via a Cp_2HfCl_2-catalyzed Contrasteric *O–C*-Rearrangement–Glycosylation and Regioselective [4+2]-Addition and

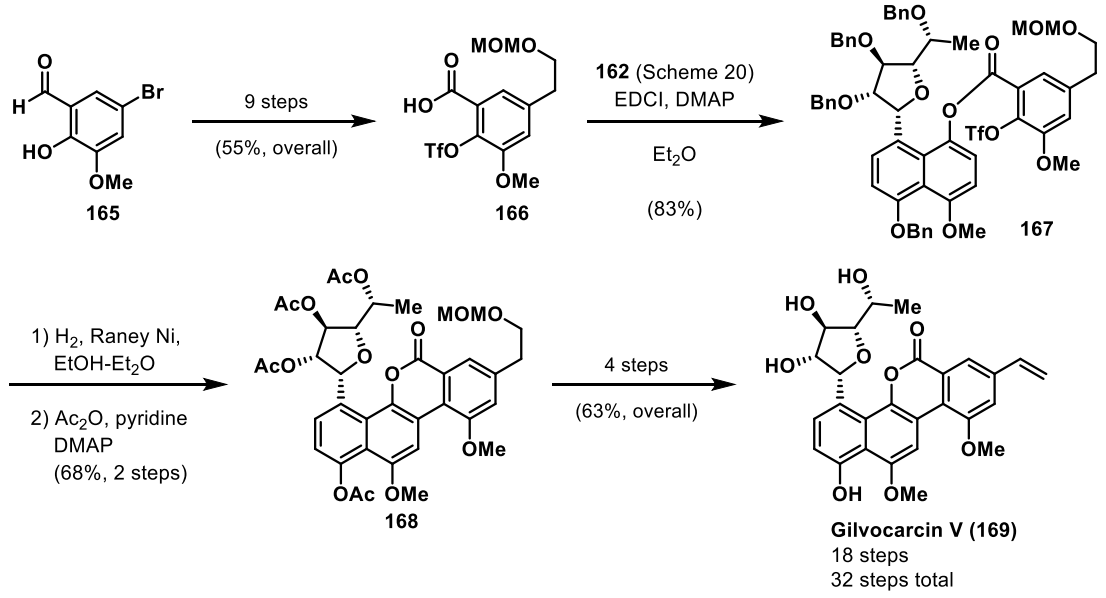
One of the outstanding characteristics found among the gilvocarcins is the *para*-phenol-positioned sugar moiety prevailing in this natural product family. This is special insofar, that natural aryl *C*-glycosylation is assumed to occur usually via an *O*-glycosylation followed by an *O–C*-rearrangement to the *ortho*-position of the hydroxy group. Suzuki used this behavior in order to end up with a formal phenol-*para*-glycosylation.[57] The unprotected and directing hydroxy group of intermediate **159** initiated the anticipated *ortho*-glycosylation, however, is subsequently transformed into an aryne, which serves as starting point for the following regioselective cycloaddition to construct the naphthalene core of **162**. The diastereoselectivity of the glycosylation is rationalized by steric effects, while the required regioselectivity of the *head-to-head* cycloaddition is assumed to originate from inductive rather than resonance effects.[143] The following esterification and intramolecular Heck-coupling were accomplished according to the protocol of Martin (*vide supra*). It is noteworthy, that this synthesis has put light on the absolute configuration of the sugar, which turned out to be D-fucose, while the L-form was previously assumed in literature without evidence.



Scheme 20: The first total synthesis of a glycosylated gilvocarcin natural product. [a]The synthesized natural product turned out to be the enantiomer of the naturally occurring gilvocarcin.

Suzuki, 1994 – Gilvocarcin V, via a Cp_2HfCl_2-catalyzed Contrasteric *O*–*C*-Rearrangement–Glycosylation and Regioselective [4+2]-Addition and

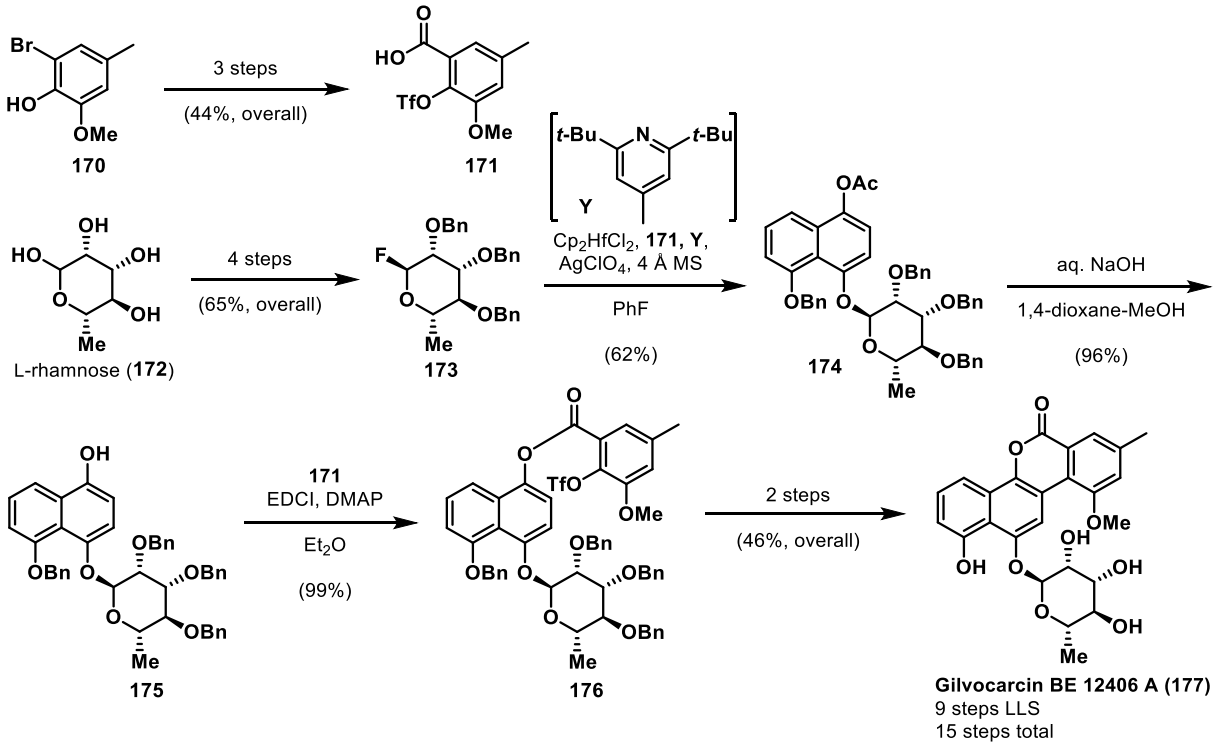
The very same strategy was applied shortly after in the total synthesis of gilvocarcin V.[144] Despite some variations, the only differences were based on the formation and post-transformation of the eastern fragment. This synthesis proved to be rather lengthy in overall steps.



Scheme 21: Suzuki's total synthesis of gilvocarcin V according to the strategy used for gilvocarcin M.

Suzuki, 1994 – Gilvocarcin BE-12406 A, via a Cp_2HfCl_2-Catalyzed *O*-glycosylation

Having established a reliable route towards *C*-glycosylated gilvocarcins M and V, Suzuki strived for the total synthesis of the *O*-glycosylated analogue BE–12406 A.[58] Despite the similarity in conditions used for the *C*-glycosylation, naphthalenic system **171** (prepared from juglone **99** according to previous reports) allowed for a selective *O*-glycosylation. Major challenge was prevention of *C*-glycosylation, which was overcome by careful chose of solvent. Aromatic solvents turned out to suppress this behavior, while fluorinated aromatic solvents led to improved yields. The following steps were comparable to their earlier approaches resulting in a concise synthesis of the desired product within nine linear steps. In a following publication by the same group, this procedure was used for the synthesis of the vinyl analogue of gilvocarcin BE–12406 A, whose isolation hasn't been reported so far.[145]

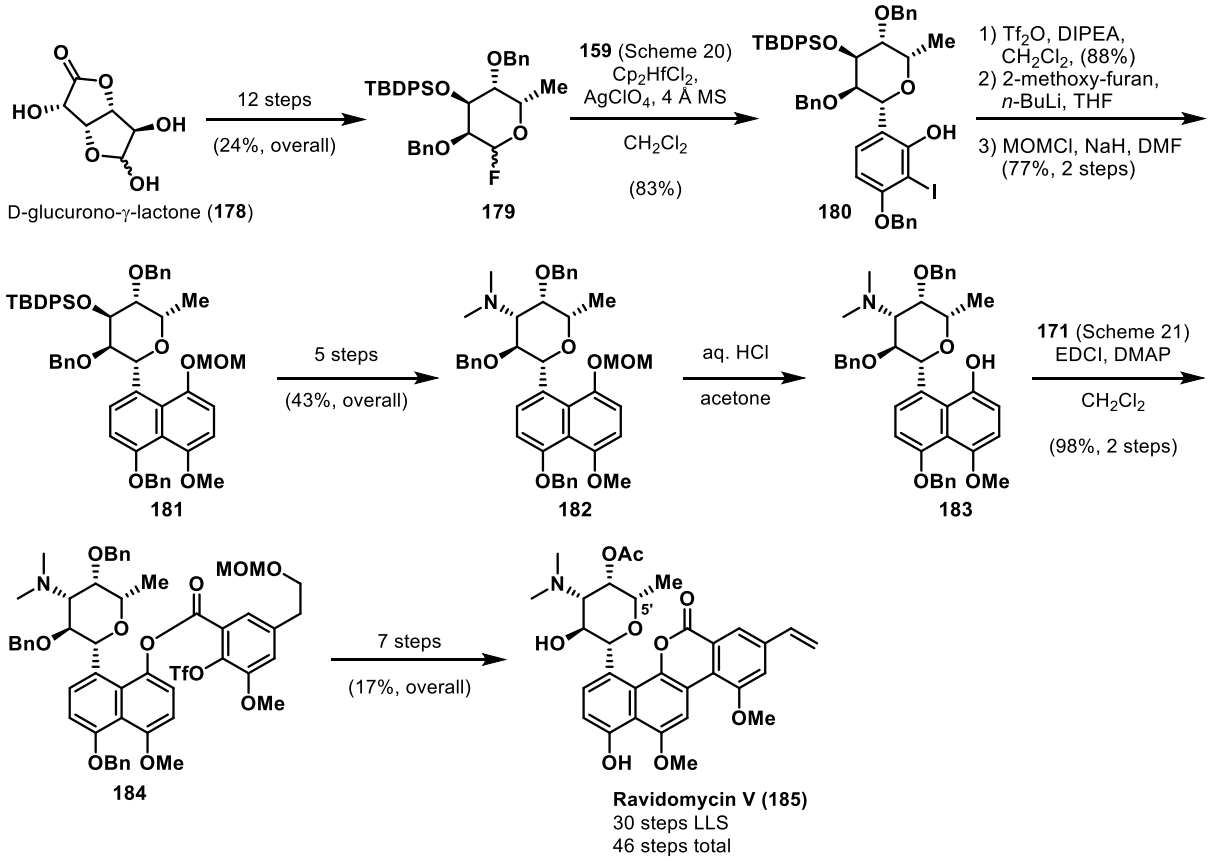


Scheme 22: Suzuki's total synthesis of gilvocarcin BE 12406 A.

Suzuki, 2000 – Ravidomycin V, via a Cp_2HfCl_2-Catalyzed *O*–*C*-Rearrangement–Glycosylation

The generality of their developed Cp_2HfCl_2-$AgClO_4$-catalyzed contrasteric *O*–*C*-rearrangement–glycosylation was additionally confirmed by its application in the synthesis of ravidomycin V.[61] While the majority of the presented steps followed their previously reported procedures, this synthesis revealed the challenges of pre-constructing and post-modifying the present sugar. Starting from γ-lactone **178**, 12 steps were required to afford intermediate **179** not bearing the characteristic dimethylamino-group. Several post-modifications to achieve amination followed the naphthalene construction resulted in the longest synthesis of a gilvocarcin to date, with 46 total and 30 linear steps. However, major contribution of this synthesis turned out to be not only the revision of the absolute but also of the relative

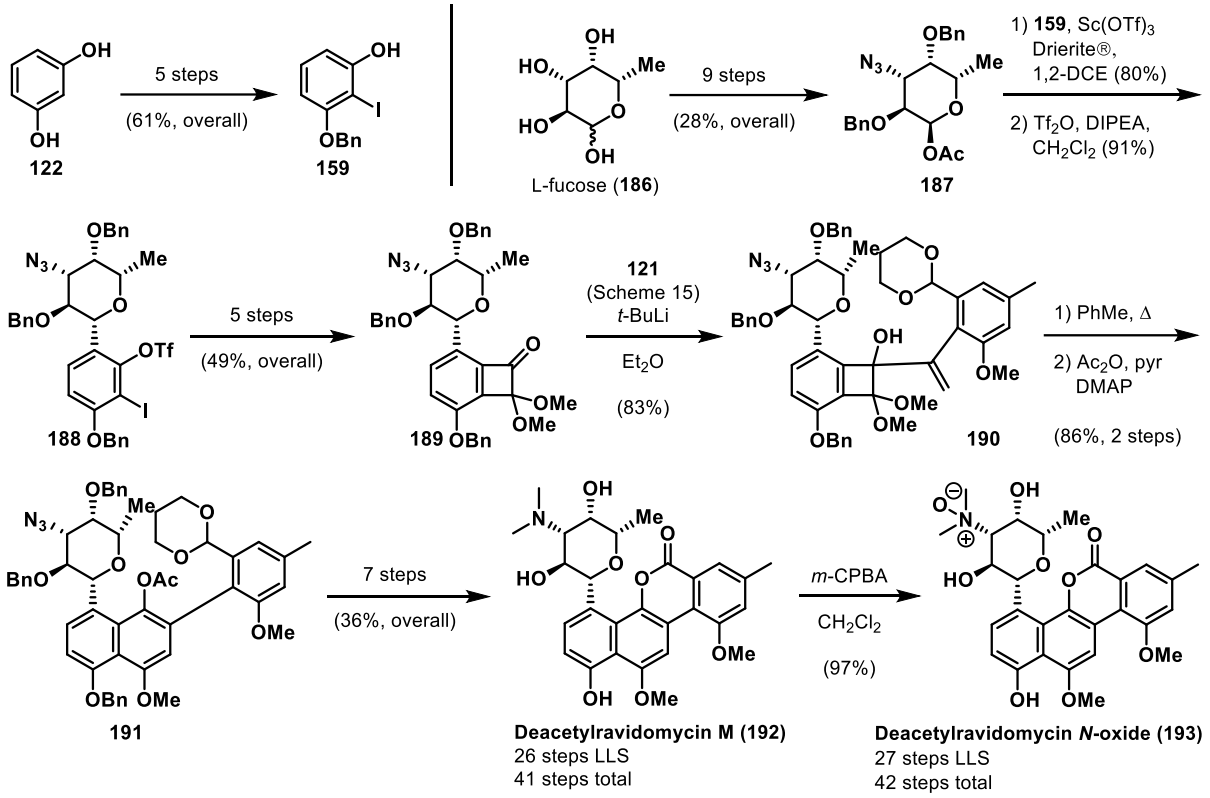
stereochemistry of the sugar moiety. Since the first isolation of a ravidomycin in 1981 Findlay,[47] every following publication addressing the ravidomycins depicted the structure with the wrong relative orientation of the C5'-methyl group.



Scheme 23: Suzuki's total synthesis of ravidomycin V reveals the correct relative stereochemistry of the sugar.

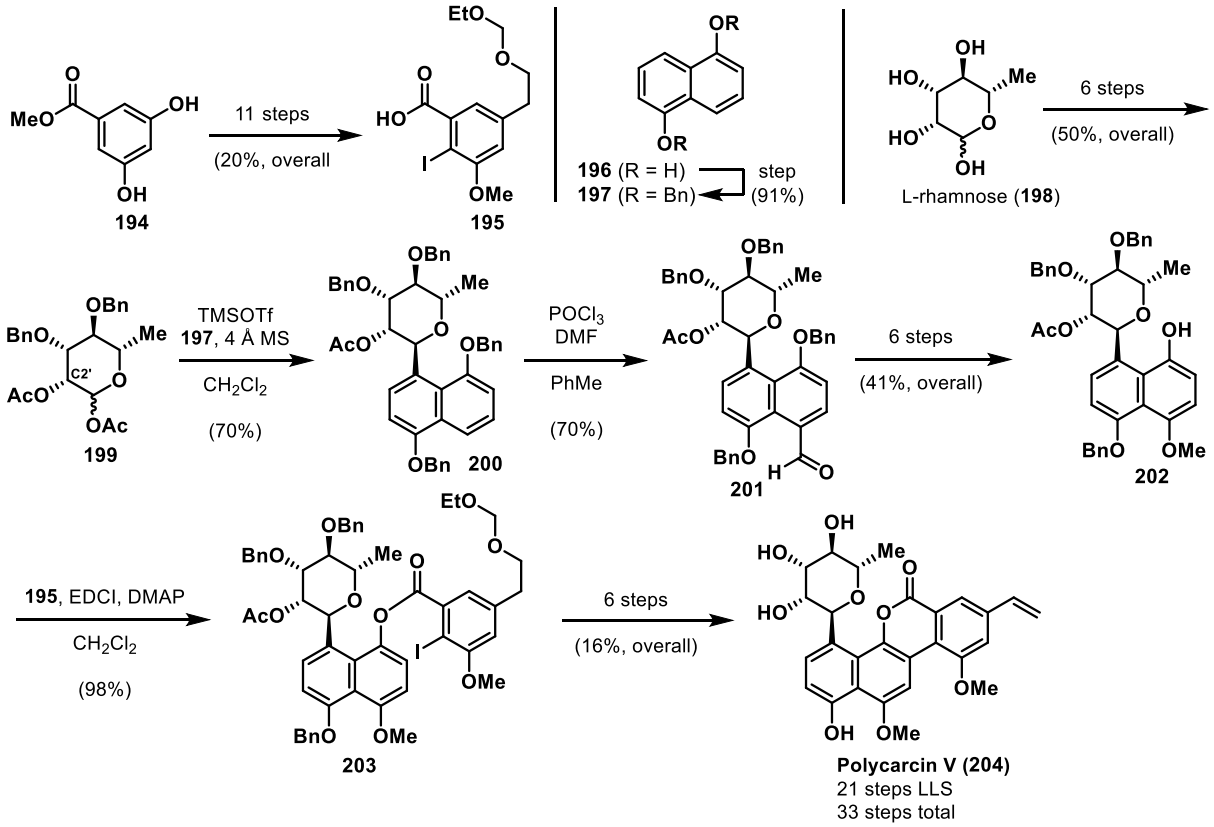
Suzuki, 2011 – Deacetylravidomycin M (*N*-oxide), via a Cp_2HfCl_2-Catalyzed Contrasteric *O*–*C*-Rearrangement–Glycosylation and [2+2+2]-Addition

Based on their elaborated methodology of conducting a [2+2+2]-reaction[129], Suzuki extended its utility by employing it to the synthesis of deacetylravidomycin M (Scheme 24).[146] In accordance to their structural revision of ravidomycin V (*vide supra*), the same stereochemical misassignment was revealed for its analogue deacetylravidomycin M. In course of elaborating a suitable route, improvements regarding the synthesis of the sugar could be achieved. In this context, the group demonstrated the straightforwardness of converting the sugar's dimethylamine into its *N*-oxide form using *m*-CPBA, which resulted in the first synthesis of deacetylravidomycin-*N*-oxide.



Scheme 24: Suzuki's total synthesis of deacetylravidomycins via [2+2+2]-cyclization.

Minehan, 2014 – Polycarcin V, via Regio- and stereo-controlled Friedel–Crafts-type Glycosylation

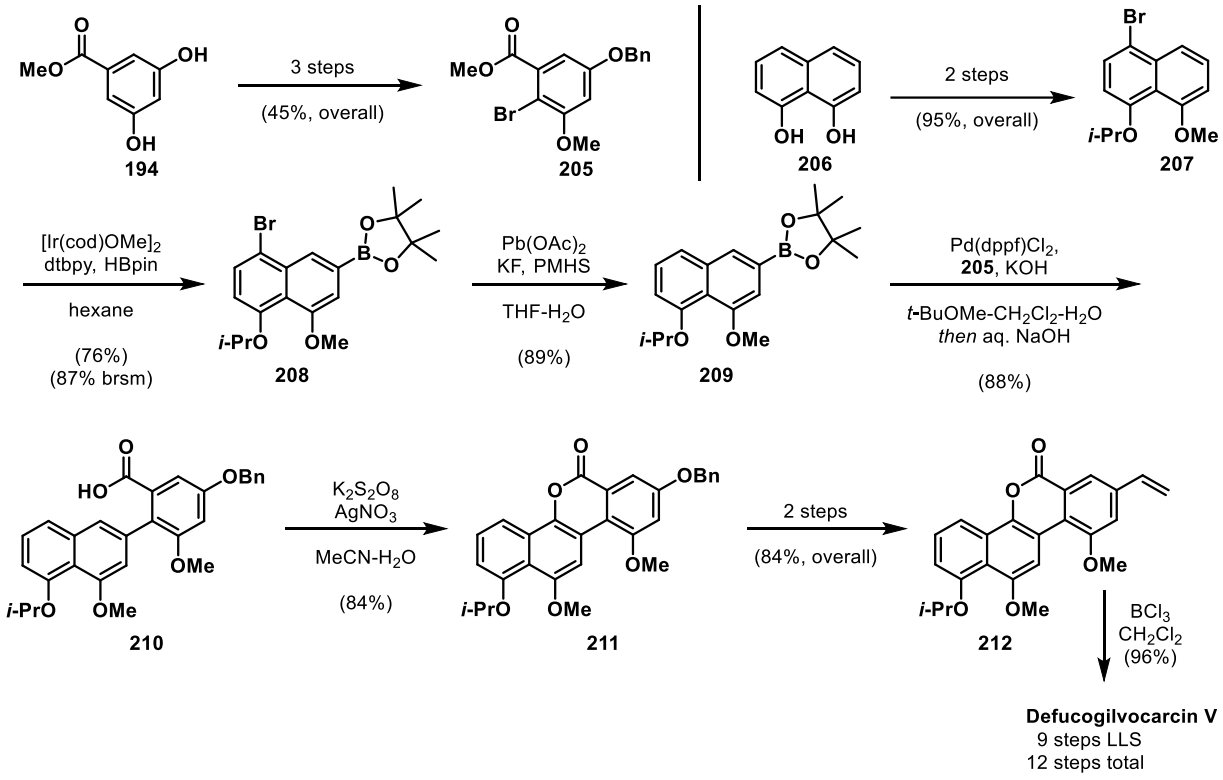


Scheme 25: First total synthesis of polycarcin V by the group of Minehan.

While gilvocarcins and ravidomycins were successfully synthesized by Suzuki, the total synthesis of chrysomycins and polycarcins remained unsolved. The latter was addressed by the group of Minehan in 2014 resulting in the first synthesis of polycarcin V.[68] The synthesis commenced with preparation of fragment **195**, which was decorated with a protected primary alcohol representing a masked vinyl group as previously seen in the synthesis of gilvocarcin V (1994) by Suzuki. L-rhamnose **198** was used as starting point towards glycoside **199**. Friedel–Crafts type aryl-*C*-glycosylation proceeded under TMSOTf-catalysis in good yields and high diastereoselectivity. The letter can be explained by the anchimeric participation of the C2'-ester preventing a nucleophilic attack from the same side. Regioselective formylation using Vilsmeier–Haack conditions[147] followed by a Baeyer–Villiger oxidation enabled the installation of a *para*-hydroxy group within two steps. The following steps, including esterification and intramolecular Heck coupling proceeded according to previous protocols furnishing polycarcin V in 21 linear and 33 total steps starting from commercially available substrates.

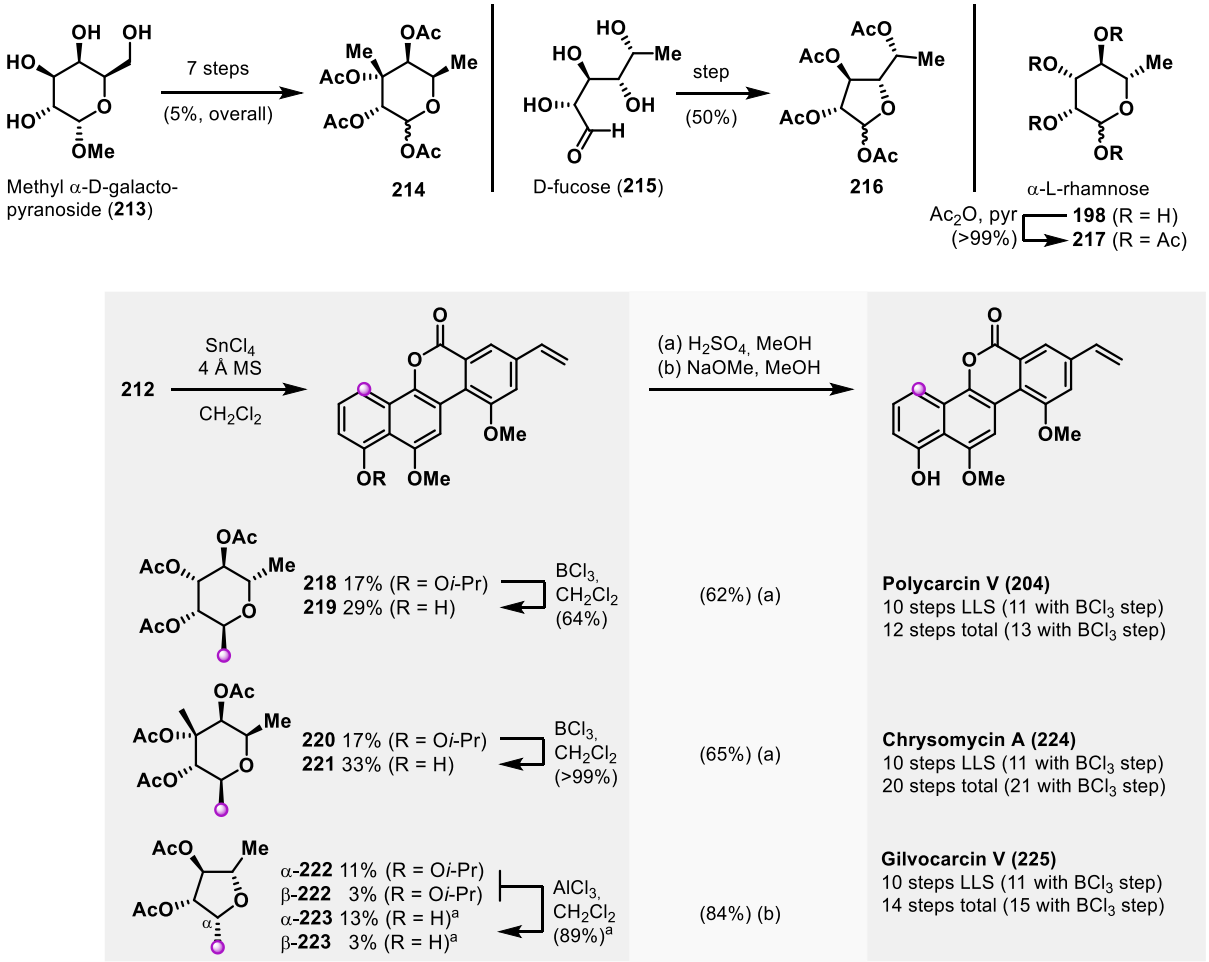
Lei, 2018/2020 – Gilvocarcin V, Chrysomycin V, Polycarcin V, via late-stage glycosylation

Inspired by the reported syntheses of the gilvocarcins and their aglycones, Lei and co-workers envisioned a concise synthesis of defucogilvocarcin V followed by a general late-stage glycosylation protocol to approach a variety of gilvocarcin natural products and their analogues.[69,70] The strength of their strategy relies on sequential regioselective C–H-functionalizations starting from symmetric



Scheme 26: Lei provided the shortest synthesis of defucogilvocarcin V with nine linear steps.

naphthalenediol **206**. Selective borylation to access the crucial biaryl bond was possible by previous installation of a removable bromine acting as a blocking group. Suzuki cross-coupling between naphthoboronate **209** and readily available benzoate **205** with subsequent hydrolysis of the ester afforded biaryl **210** on a 20 g scale. Regioselectivity of the following remote C–H-oxygenation was achieved after application of different conditions, of which potassium persulfate in combination with silver(I)-nitrate gave the highest yield and selectivity. Debenzylation and triflation of tetracycle **211** furnished a useful intermediate for late-stage diversification towards various analogues with respect to that particular position. Considering a subsequent de-isopropylation, this route represents the shortest synthesis of defucogilvocarcin V to date with 9 linear and 13 total steps. For the anticipated late-stage glycosylation (Scheme 27), protected aglycone **212** was subjected to tin(IV)-chloride in the presence of



Scheme 27: First example of a late-stage glycosylation towards gilvocarcin natural products. [a]$AlCl_3$ treatment causes partial *para*- to *ortho*-shift of the sugar moiety.

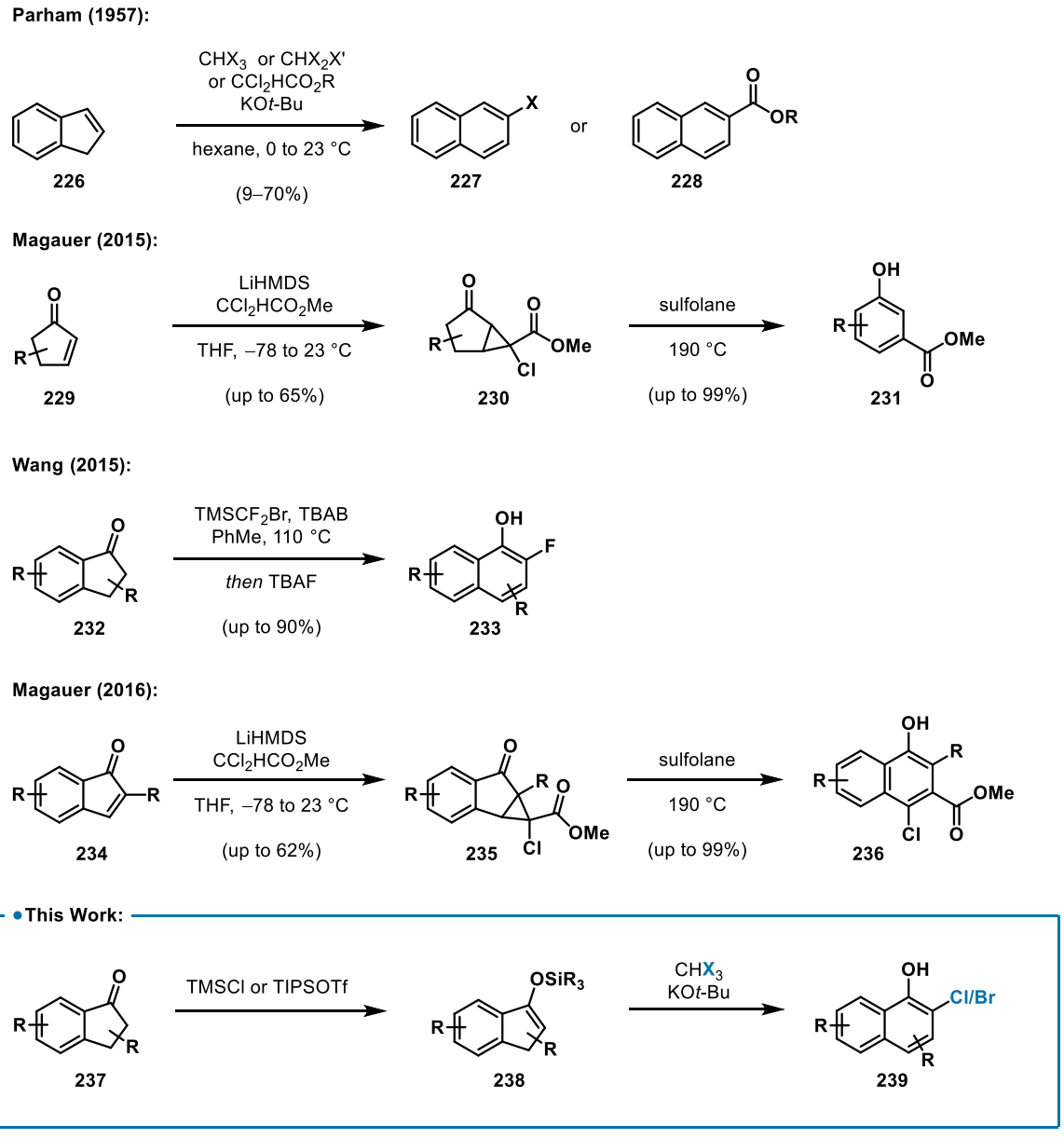
sugars **214**, **216** or **217**. The directing nature of the steric isopropyl group in combination with a distinct nucleophilicity of the naphthalene core made a pre-functionalization obsolete. Glycosylation proceeded in 46–50% yield for polycarcin V and chrysomycin A with partial removal of the protecting group. Full conversion to **219** and **212** was assured by the additional treatment with BCl_3 in 64–99% yield. Final deacetylation under acidic conditions completed the synthesis of polycarcin V and the first total

synthesis of chrysomycin A in ten linear steps. While this late-stage glycosylation protocol gave rather satisfying results for pyranones, a significant decrease in yield, stereo- and regio-selectivity was observed for the applied furanone of gilvocarcin V. Glycosylation afforded 24% of the desired product as an almost 1:1 mixture of protected and unprotected **222** accompanied by 6% of the undesired diastereomer. The following deprotection showed high yields, however resulted in a partial rearrangement to give a 2:1 mixture of *para*- and *ortho*-glycosylated **223**. Finally, gilvocarcin V was obtained after basic hydrolysis representing an alternative to Suzuki's synthesis from 1992. The strength of Lei's glycosylation is obvious, however, the need for a significant excess of the aglycone (3 equivalents) during this step must be noted.

2. Results and Discussion: Ring-expansion of Indanones to Construct 1-Naphthols

2.1 Previous Work on the Ring-expansion of Cyclopentenes to Arenes

Based on his observations on chloroform's behavior upon treatment with ethanolic potassium hydroxide in 1862, Anton Geuther published one of the first manuscripts that describes a dihalocarbene.[148] Since then, dihalocarbenes have found widespread application in organic synthesis,[149] out of which famous



Scheme 28: Selected examples for the cyclopropanation of cyclopentenes with subsequent ring-expansion.

name reactions like the Reimer–Tiemann reaction (1876)[150] or the Doering–LaFlamme allene synthesis (1958)[151] have emerged. The former enables formylation of arenes, while the latter describes the formation of dihalocyclopropanes starting from an alkene with chloro- or bromoform, which

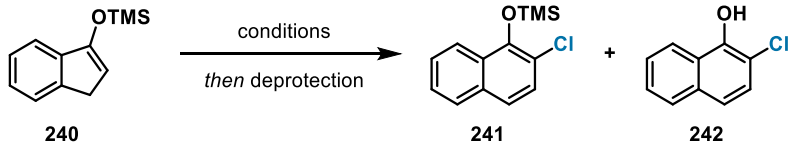
subsequently rearranges to an allene if treated with a reducing metal or an organolithium reagent. While the tendency of dihalocarbenes to undergo cyclopropanation in the presence of alkenes was known in 1957, Parham and co-workers brought forth this reaction's applicability by recognizing its potential as intermediate for ring-expansion (Scheme 28). His group described the cyclopropanation of indenes in the presence of chloroform and KO*t*-Bu, which underwent spontaneous fragmentation to form naphathalenes, while isolation of the cyclopropane intermediate possible when changing the conditions.[152,153] Apart from the successful employment of chloroform, bromoform and mixed haloforms to make various 2-halonaphthalenes, they were able to obtain 2-naphthoates when *tert*-butyl dichloroacetate was used.[153] Despite the early discovery of this transformation, no further investigations or broader applications were reported in the following decades. As a consequence, our group has started to exploit the cyclopropnatation-ring-expansion of cyclopentenones to form diverse phenols and naphthols. While cyclopentenones have been successfully transformed into various *meta*-hydroxy benzoates[154], 1-chloro-4-hydroxy-2-naphthoates were accessible when indenones have been treated under similar conditions.[155] Contemporaneously, Wang and co-workers have developed a methodology to transform indanones into their corresponding 2-fluoro-1-naphthols.[156] As a result of these achievements, we were prompted to develop a protocol which would allow for a rapid access to 2-chloro- and 2-bromo-1-naphthols starting from indanones. While Wang's protocol is restricted to 2-fluoro-1-naphthols and is based on an expensive halogen source of limited stability ($TMSCF_2Br$), we envisioned a procedure that would use inexpensive and easy-to-handle chloroform and bromoform. Furthermore, other than fluorine, the so installed chloride and bromide in *ortho*-position would represent a useful handle for post-modifications, especially when considering the large number of known bioactive 1-naphthols with *ortho*-substituents.[157] Parts of chapter 2.2 show results provided by Dr. Ben Marsh.

2.2 Methodology Development and Scope

We began our investigations by studying the cyclopropanation–ring-expansion (CPRE) of 1-indanone employing the trimethylsilyl enol ether **240**[158] (Table 1). While standard conditions using aqueous bases[159][160] were met with failure, we were delighted to find out, that upon treatment with potassium *tert*-butoxide and chloroform in pentane at cryogenic temperatures[160][161] ring-expansion was observed with subsequent *in situ* deprotection to 1-naphthol **242**. To ensure complete trimethylsilyl-deprotection, hydrochloric acid or *tert*-butyl ammonium fluoride (TBAF) was added, of which the latter was chosen for substrate compatibility of a broader scope. It is noteworthy, that the use of sublimed grade potassium *tert*-butoxide showed significantly higher yields compared to reagent grade batches. With the optimized conditions in hand, we investigated the conversion of several substrates to the corresponding 2-chloronaphthols (Table 2). We found that halogens (**242**–**248**) were generally best tolerated resulting in good yields, which underpins the strength of this methodology, since a straightforward access to diversely halogenated naphthalenes is limited in literature and therefore highly desirable.[162] Other

functional groups like ethers (**249**–**252**), silylethers (**252**) and esters (**254**, **255**) turned out to be likewise stable under these conditions giving the desired products in decent yields. The presence of a methoxy group (**251**, **252**), however, as well as an attached CF_3-group (**247**) led to noticeable reduction in yield.

Table 1. Screening for CPRE-conditions to obtain 2-chloro-1-naphthol (**242**).



240 241 242

Entry	Reagents[a]	Temperature	Time	Deprotection[b]	Solvent	241	242
1	CCl_3CO_2Et, NaOMe	0 °C	4 h	-	pentane-H_2O (0.5 M)	0%	0%
2	$CHCl_3$, NaOH, $BnEt_3NCl$	45 °C	3 d	-	CH_2Cl_2-H_2O (0.5 M)	0%	0%
3	$CHCl_3$, KO*t*-Bu	0 to 23 °C	2 h	-	pentane (0.5 M)	18%	12%
4	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	3 h	-	pentane (0.5 M)	10%	55%
5	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	3 h	aq. HCl	pentane (0.5 M)	0%	86%
6	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	2 h	aq. HCl	CH_2Cl_2 (0.5 M)	0%	40%
7	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	2 h	aq. HCl	PhMe (0.5 M)	0%	40%
8	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	2 h	aq. HCl	MeCN (0.5 M)	0%	5%
9	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	2 h	aq. HCl	$CHCl_3$ (0.5 M)	0%	35%
10	$CHCl_3$, KO*t*-Bu	–78 to 23 °C	2 h	TBAF	pentane (0.2 M)	0%	59%
11	**$CHCl_3$, KO*t*-Bu**	**–78 to 23 °C**	**2 h**	**TBAF**	**pentane (0.2 M)**	**0%**	**80%**

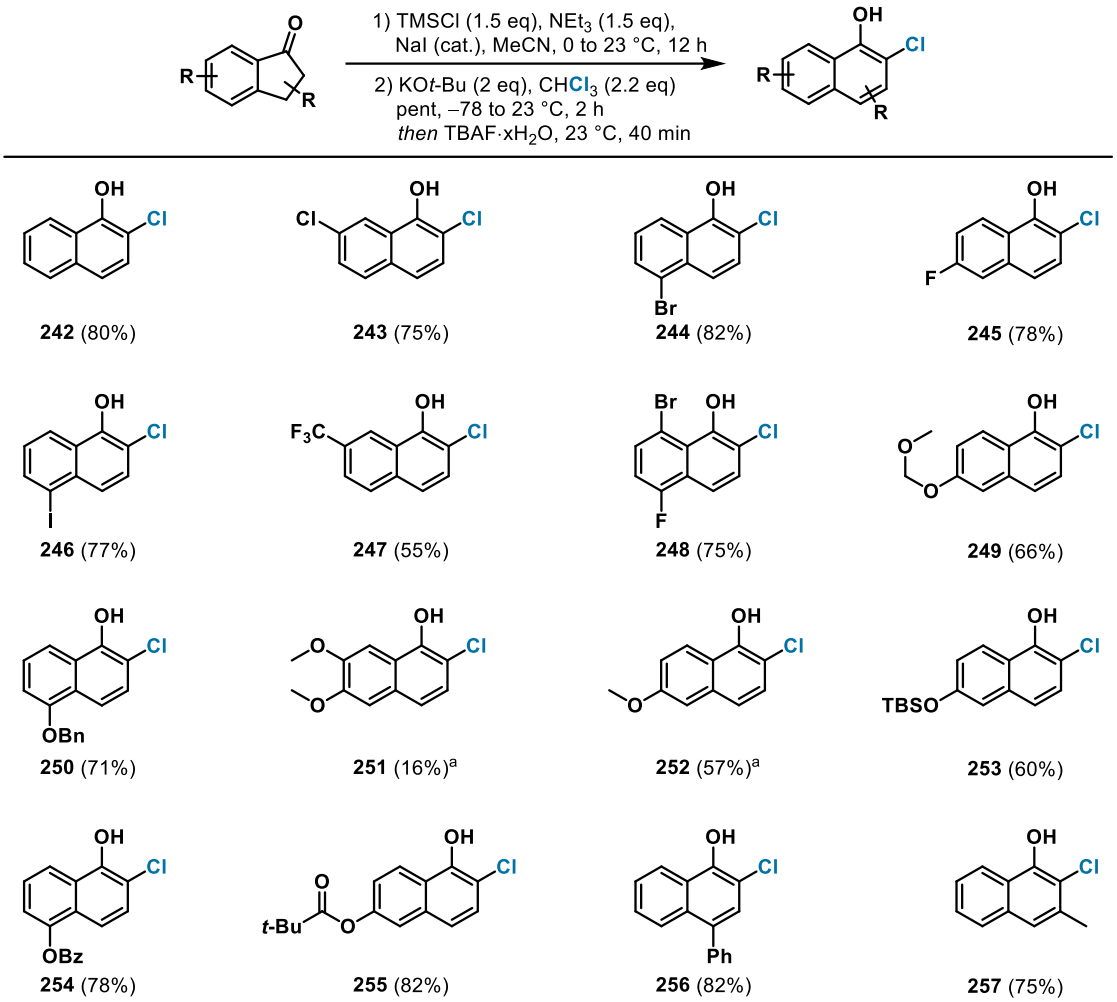
[a] 2.2 equivalents of Cl-source and 2.0 equivalents of base were used.
[b] Protocol A: 4 M HCl, 40 min, 23 °C. Protocol B: 1.1 eq TBAF (1 M in THF), 30 min, 23 °C.

Despite concerns about potential steric effects, we were delighted to see, this transformation is also adaptable on 1-indanones with substituents at the C2- and C3-position leading to the formation of aryl-naphthol **256** and alkyl-naphthol **257** in 82% and 75% yield, respectively.

In hand with a panel of chlorinated naphthols, we were seeking for options to access brominated 1-naphthols as a presumably more reactive species compared to the chlorinated equivalent in the context of further functionalization. First attempts by simply exchanging chloroform for bromoform gave unsatisfactory 33% of the desired naphthol **275** (Table 4, Entry 1, *vide infra*) when KO*t*-Bu was added at 23 °C and bromoform was added at –78 °C. Lowering the temperature of base-addition to 0 °C or even –10 °C did not improve the yield. As a result, we investigated the influence of the protecting group. In order to reduce steric repulsion to a minimum while ensuring a certain stability, we switched to the corresponding methyl enol ether **262** (Scheme 29). All attempts using iodoform failed or gave yields lower that 7%. In contrast, we were able to isolate bromo-methoxynaphthalene **266** in 87% when

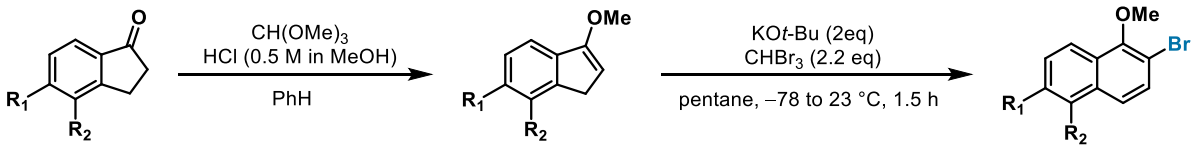
bromoform was used. The same conditions have been applied on three further substrates which were successfully transformed into naphthalenes **267**, **268** and **269** in moderate to good yields. With these

Table 2. Scope for the CPRE of various 1-indanones to obtain the corresponding 2-chloro-1-naphthols.



[a]For improved yields using modified conditions, see page 45.

encouraging results in hand we reconsidered the ring-expansion of 1-indanones by using a *tert*-butyldimethylsilyl protecting group as a more stable variant. To increase the overall yield over two steps starting from unprotected indanones, TBS-protection had to be screened in the first place (Table 3). Surprisingly, the amount of the solvent turned out to be a crucial factor with low concentrations leading



258 R_1 = H R_2 = H
259 R_1 = F R_2 = H
260 R_1 = H R_2 = Br
261 R_1 = H R_2 = I

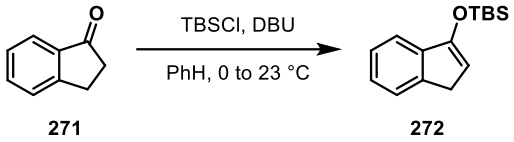
262 (55%)
263 (59%)
264 (60%)
265 (42%)

266 (87%)
267 (65%)
268 (72%)
269 (61%)

Scheme 29: First successful attempts of a bromoform-based CPRE using methoxy-indenes.

to lower conversion, even after prolonger reaction-time or additional equivalents of reagents. It is worth of note that excess of both, TBSCl and DBU, was needed for full conversion. As a result, subsequent removal of remaining reagents and unintentionally formed silanes (here: TBSX) was necessary to

Table 3. Screening of TBS-protection of 1-indanone regarding concentration, equivalents and work-up.



271 272

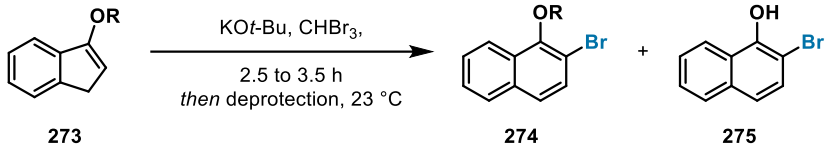
Entry	TBSCl	DBU	Conc.	Time	Work-Up	TBSX	271	272
1	1.10 eq	1.30 eq	0.95 M	17 h	distillation	--[a]	--[a]	83%
2	1.10 eq	1.30 eq	0.95 M	20 h	celite filtration	--[a]	20%	80%
3	1.10 eq	1.30 eq	0.95 M	19 h	silica filtration	<0.1 eq	11%	87%
4	1.20 eq	1.40 eq	0.95 M	20 h	aq. work-up	<0.1 eq	9%	86%
5	1.20 eq	1.40 eq	0.95 M	20 h	aq. work-up + silica filtration	<0.1 eq	4%	90%
6	**1.30 eq**	**1.50 eq**	**0.95 M**	**21 h**	**celite filtration**	**0.18 eq**	**0%**	**98%**
7	1.25 eq	1.40 eq	0.50 M	15 h	silica filtration	<0.1 eq	47%	53%
8	1.25 eq	1.40 eq	0.50 M	20 h	celite filtration	0.20 eq	58%	41%
9	1.30 eq	1.40 eq	0.90 M	17 h	silica filtration	<0.1 eq	10%	90%
10	**1.30 eq**	**1.50 eq**	**0.95 M**	**19 h**	**silica filtration**	**<0.1 eq**	**2%**	**94%**

[a]Yield/equivalents not determined.

prevent detrimental interactions during the cyclopropanation step. Filtration over a short plug of silica turned out to be the best compromise between removal of impurities and unwanted deprotection of the silyl enol ether to give intermediate **272** in 94% yield.

With the purified starting material **273** in hand we next screened for the cyclopropanation (Table 4). After a brief survey of conditions, we were delighted to see that treatment with KO*t*-Bu in pentane or hexane allowed for the preparation of protected 2-bromo-1-naphthol in 80% yield (Entry 8).[163] For this substrate, process of achieving full conversion was accelerated when performed at 23 °C and excess of base and bromoform were used. Combination of these conditions with various deprotection protocols led to unprotected bromo-naphthol **275**. Best yields were achieved when DBU in acetonitrile and catalytic amounts of water was used (79%, Entry 11).[164] However, repetition of reaction conditions revealed a limited reliability. Yields for Entry 7 and Entry 12 could drop to 61% and 56%, respectively. Further discouraging results were obtained when the optimized conditions were applied to a broader substrate scope (Table 5). While even halogens showed only moderate to low yields, methoxylated indanones **279** and **280** gave little to no yield over two steps of the desired bromonaphthols. It was found

Table 4. Screening for CPRE-conditions on TBS-protected 1-indanone to obtain 2-bromo-1-naphthol.

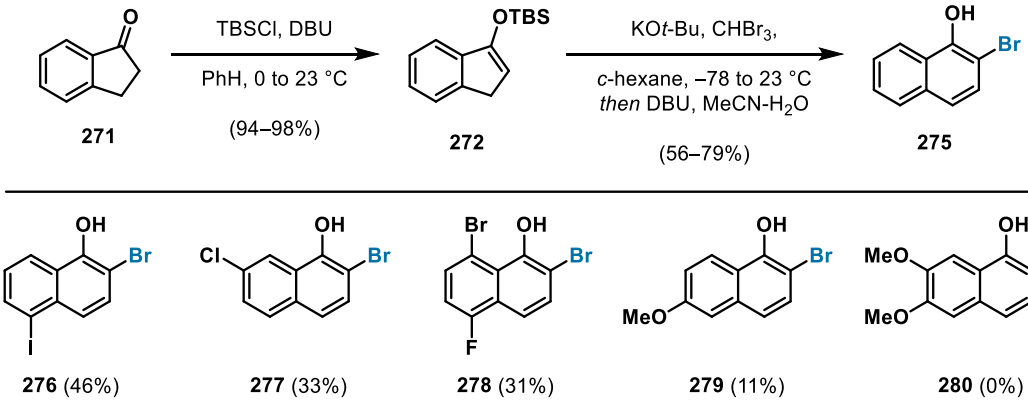


273 274 275

Entry	R	KOtBu	$CHBr_3$	Solvent	Temperature[a]	Deprotection	273[b]	274[b]	275[b]
1	TMS	2.0 eq	2.2 eq	pentane	–78 to 23 °C	TBAF·xH_2O, THF, 0.5 h	0%	0%	33%
2	TBS	2.0 eq	2.2 eq	pentane	–78 to 23 °C	–	43%	36%	0%
3	TBS	6.0 eq	5.0 eq	pentane	–78 to 23 °C	–	3%	61%	0%
4	TBS	6.0 eq	5.0 eq	pentane	–78 to 23 °C	–	5%	76%	0%
5	TBS	6.0 eq	5.0 eq	*n*-hexane	23 °C	–	0%	79%	0%
6	**TBS**	**6.0 eq**	**5.0 eq**	***n*-hexane**	**23 °C**	**–**	**0%**	**80%**	**0%**
7	TBS	6.0 eq	5.0 eq	*c*-hexane	23 °C	aq. HCl (2 M), 1 h	0%	74%	0%
8	TBS	6.0 eq	5.0 eq	*c*-hexane	23 °C	TBAF (1 M in THF), 0.5 h	0%	0%	64%
9	TBS	6.0 eq	5.0 eq	*c*-hexane	23 °C	KF, MeCN-H_2O, 22 h	0%	12%	36%
10	TBS	6.0 eq	5.0 eq	*c*-hexane	23 °C	KF-Al_2O_3, MeCN-THF, 4.5 h	0%	1%	25%
11	**TBS**	**6.0 eq**	**5.0 eq**	***c*-hexane**	**23 °C**	**DBU, MeCN-H_2O, 1.5 h**	**0%**	**0%**	**79%**

[a] Base was added at 23 °C. $CHBr_3$ was added at temperature provided in the table with subsequent warming to 23 °C.
[b] For reactions that were performed more than once, the best yield is given in the table. Repeating reaction conditions revealed a limited reproducibility of the yield. For detailed information, see text.

Table 5. CPRE of TBS-protected indanones showed limited reliability and low yields of a broader scope.

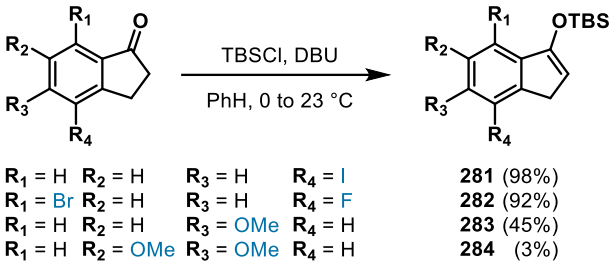


276 (46%) **277** (33%) **278** (31%) **279** (11%) **280** (0%)

that, at least for electron-rich substrates like **283** and **284**, the protection conditions to form the enol ether were not robust enough, rendering the TBS-based CPRE in most circumstances synthetically unattractive (Scheme 30).

As a result, we decided to change the protecting group by implementing a triisopropylsilyl variant (Table 6). A first noticeable advantage towards the TBS-enol ethers was the reliability of the protection-

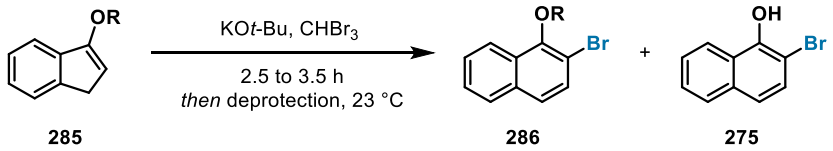
step, a protocol which was not sensitive to little differences in concentration, equivalents or work-up.[165] While stability on silica was slightly higher as well, electron-rich enol ethers showed also low yields. This problem was solved when activated basic aluminum oxide (Brockmann I, Honeywell Fluka™) was used for filtration. A short plug was sufficient to remove any impurities and residuals from the crude



Scheme 30: TBS-protection as a limiting step during the CPRE of 1-indanones.

mixture while undesired deprotection was only observed for methoxylated substrates to an acceptable extend. The following CPRE sequence was met with success affording the desired TIPS-protected bromo-naphthol **285** in high yields (Table 6, Entry 1). Unfortunately, we were again confronted with limited reproducibility of the obtained yield. A journey of screening addressing the CPRE as well as the subsequent deprotection resulted in lowering the equivalents of both, KO*t*-Bu and bromoform, and with

Table 6. Elaboration of conditions for the ring-expansion of silylenol ether **285**.



Entry	R	KOtBu	$CHBr_3$	Solvent	Base Addition	Deprotection	286[c]	275[c]
1	TIPS	6.0 eq	5.0 eq	pentane	at 23 °C[a]	–	83%	0%
2	TIPS	6.0 eq	5.0 eq	pentane	at 23 °C[a]	TBAF (1 M in THF)	0%	60%
3	TIPS	4.5 eq	2.0 eq	pentane	at 23 °C[a]	–	72%	0%
4	TIPS	4.5 eq	2.0 eq	*n*-hexane	at 23 °C[a]	KOAc, DMF-H_2O	0%	77%
5	TIPS	4.5 eq	2.0 eq	*n*-hexane	at –78 °C[b]	–	88%	0%
6	**TIPS**	**4.5 eq**	**2.0 eq**	***c*-hexane**	**at –78 °C[b]**	**KOAc, DMF-H_2O**	**0%**	**85%**
7	TMS	2.0 eq	2.2 eq	pentane	at –78 °C[b]	TBAF (1 M in THF)	0%	57%

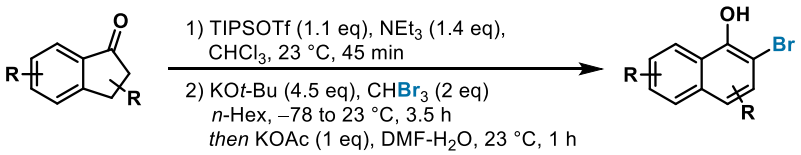
[a]Base and bromoform were added at 23 °C and the mixture was stirred at the same temperature.
[b]Bromoform was added at –78 °C and the reaction was slowly warmed to 23 °C while stirring.
[c]In case a reaction was performed more than once, the best yield is given in the Table. Repeating reaction conditions revealed a limited reproducibility of the yield. For detailed information, see text.

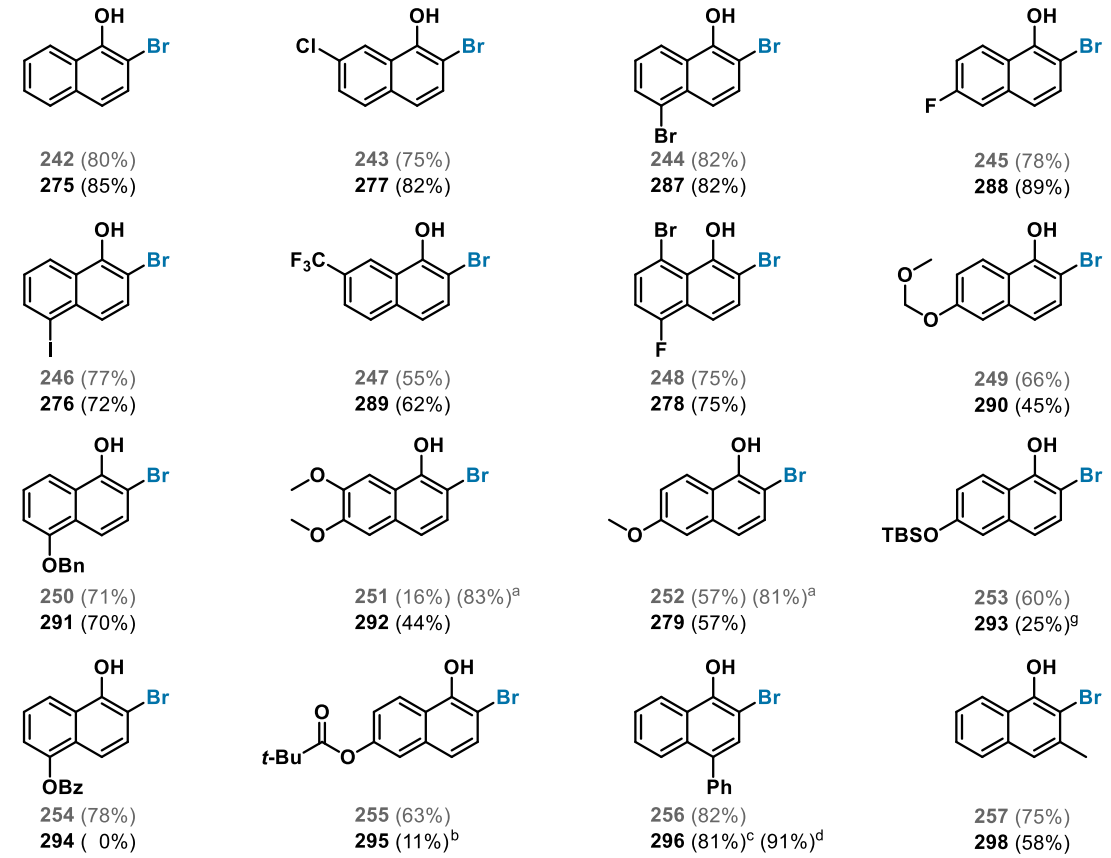
potassium acetate in DMF-water as the mildest and most promising deprotection conditions (Entry 4).[166] However, it was not until careful optimization of the KO*t*-Bu addition that reliable and

high yields were achieved. We found that it was crucial to prepare a suspension of the base in *n*-hexane and cool it to –78 °C prior to slow addition of the substrate solution (Entry 7). Furthermore, treatment with base should not extend a duration of five to ten minutes before bromoform is added, otherwise diminished yields were observed. Occurrence of a deep purple color indicates unwanted side-reactions and decomposition, which was observed when KO*t*-Bu was added at temperatures between –10 and 23 °C. In contrast, the color of the mixture remained pale-yellow when base treatment was performed at –78 °C. Efforts to identify and characterize possible side products as a result of competing aryne formation were unsuccessful. It is worth of note, that application of this modified protocol to the former TMS-based conditions (Table 4, Entry 1) improved the yield from 33% to 57% (Table 6, Entry 7).

Having optimized conditions to the best of our ability, we turned our attention to the substrate scope. Yields for halogenated and benzylated substrates were comparable to those of the 2-chloronaphthols

Table 7. Substrate scope for the two-step CPRE of various indanones to afford 2-bromo-1-naphthols.



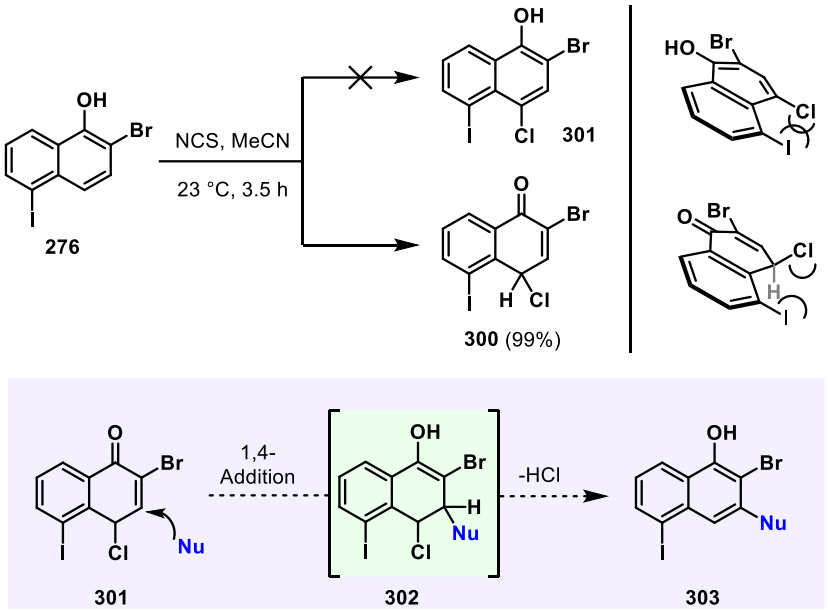


Yields in grey refer to 2-chloronaphthols (see Table 2). [a]Obtained yields when TIPS-protocol was used with chloroform and subsequent TBAF deprotection. [b]TBAF deprotection. [e]NMR-yield; TBAF deprotection. [f]Without deprotection. [g]Accompanied by 32% of globally deprotected 2-bromo-1,6-dihydroxynaphthalene.

with a slightly higher yield on average. It is noteworthy that the TIPS-protection of 5-fluoro-8-bromo-naphthol **278** was in the need for a prolonged reaction time and significant excess of TIPSOTf and NEt_3 were required to reach full conversion. Steric repulsion between the TIPS-group and the bromine might play a role in this context. Indanones with a C2-substitution or an acetal showed less tolerance under bromoform- conditions affording naphthols **298** and **290** in significant lower yields. Again, no side-products were isolated indicating decomposition events. To our surprise, methoxyindanones **279** and **292** showed considerably higher yields. We observed that KOAc-promoted deprotection was slower compared to the other substrates, whereby TIPS removal was brought to full conversion only at elevated temperatures (40–45 °C). In addition, we found that the yields for methoxylated 2-chloronaphthols **251** and **252** could be improved to 83% and 81%, respectively, when TIPS-conditions in combination with chloroform and subsequent TBAF deprotection were employed. TBS-protected indanone was in general likewise stable under bromoform conditions to undergo CPRE, however, subsequent KOAc-deprotection not only removed the TIPS-protecting group but also partially the TBS group resulting in 25% of the desired product **293** and 32% of the globally deprotected naphthol **299**. When preparing 2-bromo-4-phenyl-naphthol **296**, we were confronted with stability problems of the desired product. We noticed coloration to deep blue within seconds when the crude naphthol was extracted from water with ethyl acetate or when spotted on silica gel or aluminum oxide plates. The same observation was made when left exposed to air for several minutes. Omitting the subsequent deprotection allowed for the isolation of silica- and air-stable TIPS-naphthol **297** in 91% yield. In combination with KOAc-deprotection we found the desired naphthol **296** to be formed in 81% NMR-yield. Rapid filtration over a short plug of silica provided analytically pure product, however, with significant decrease in yield. Unforeseen incompatibilities were also observed for esters **294** and **295**. While TIPS-protection resulted in quantitative yields of the enol ether intermediates, treatment with bromoform and KO*t*-Bu induced saponification for both substrates. Pivaloyl ester **295** was isolated in 11% yield, while benzoyl ester **294** led to little, if any product. Extensive screenings and exclusion of moisture to the best of our abilities were of no avail.

2.3 Unprecedented Naphthoketonization of 2-Bromo-5-iodo-1-naphthol

In the course of investigating further postmodifications of the obtained 2-halo-1-naphthols, we observed an unusual dearomatization event. When 2-bromo-5-iodonaphthol **276** was treated with *N*-chloro-succinimide (NCS) in acetonitrile at 23 °C, quantitative conversion to enone **300** was observed without subsequent re-aromatization to naphthol **301** (Scheme 31). Simple removal of the solvent afforded a clean spectrum only showing enone **300** and succinimide. To our surprise, the crude mixture turned out to be bench-stable and not sensitive to air. In addition, filtration over a short plug of silica to remove the succinimide afforded clean enone **300** with only little decomposition to an unknown side-product in less than 10%. Aqueous basic work-up ($NaHCO_3$), however, resulted in partial decomposition accompanied by significant enolization. Decomposition upon thin-layer-chromatography on aluminum oxide-plates underpins its sensitivity to basic conditions. Isolable 1-naphthols in their keto-tautomeric form are very scarce in literature[167] and the exploitation of their potential reactivity hasn't been described so far.

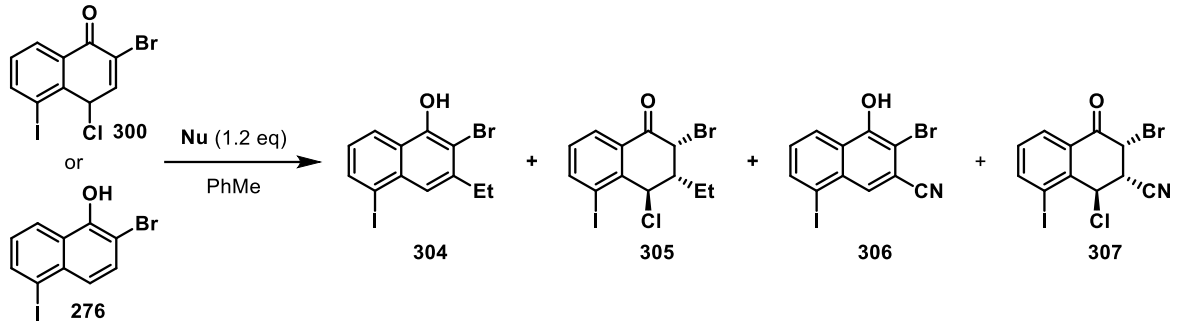


Scheme 31. NCS-treatment of naphthol **276** affords dearomatized and bench-stable enone **300**.

We observed conjugate addition to enone **300** and re-aromatization upon treatment with different nucleophiles (Table 8). Similar transformations have been reported for *para*-substituted naphthols and phenols but never for *para*-unsubstituted congeners as seen in this case.[168] Interestingly, in a first try, the use of Nagata's reagent (–78 to 23 °C within 2.5 hours) led to nucleophilic attack of both, the ethyl and the cyanide (Table 8, Entry 1), to give a mixture of ethyl-naphthol **304** and cyano-tetralone **307** (1.0 : 0.6). Ethyl-naphthol **304** was isolated in 41% yield, while any attempt to purify cyano-tetralone **307** resulted in decomposition or re-aromatization to cyano-naphthol **306**. Notably, the reaction was accompanied by retro-dearomatization to the initial naphthol **276** in 12% yield. The crude ^{1}H-NMR did not indicate the presence of the corresponding ethyl-tetralon **305** or cyano-naphthol **306**. This is contradictive to the expectation that HCl elimination would be preferred in the presence of an α-

substituted electron-withdrawing cyanide compared to an ethyl residue. Investigations to clarify if the conjugate addition is directed by chlorine-coordination to the aluminum species might explain the diastereoselectivity of the reaction and thereby the preference for HCl-elimination for each intermediate. Repeating this reaction on a larger scale with slight variation of the stirring time (1 hour at –78 °C, then warm to 23 °C within 1 hour) resulted in the same products but changed ratios (Entry 2). NMR-analysis

Table 8. Formal *meta*-C–H-functionalization of 2-bromo-5-iodo-1-naphthol.



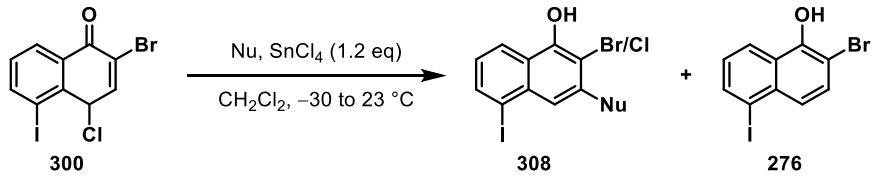
Entry	Substrate	Nu	Procedure	304	305	306	307	276
1	**300**	Et_2AlCN	A	41%	0%	0%	25%[a]	12%
2	**300**	Et_2AlCN	B	8%	0%	58% (0%)[a]	0% (63%)[a]	10%
3	**300**	$AlEt_3$	C	60%	25%	-	-	15%
4	**276**	$AlEt_3$	D	41%	58%	-	-	<2%

[a] NMR-Yield before silica-CC. A) Add Nu at –78 °C and stir for 2.5 h while warming to 23 °C. B) Add Nu at –78 °C and stir for 1 h, then slowly warm to 23 °C within 50 minutes and stir for 10 minutes at 23 °C. C) Add Nu at –78 °C and stir for 15 min. D) Conditions from Scheme 31, then remove MeCN and dissolve in PhH. Add Nu at –78 °C and stir for 10 min.

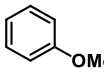
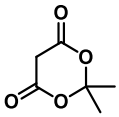
of the crude mixture revealed a combination of ethyl-naphthol **304**, cyano-tetralon **307** and unsubstituted naphthol **276** in 0.12 : 1.00 : 0.16. NMR-analysis of the crude sample confirmed the existence of tetralone **307**. After purification over silica, ethyl-naphthol **304** was isolated in 8% and cyano-naphthol **306** was isolated in 58%, while unstable tetralone **307** could not be isolated. It is noteworthy that a visual change in color of this reaction from green to red occurs at 0 °C upon warming from –78 to 23 °C indicating the temperature at which the crucial transformation might take place. By employing $AlEt_3$ the yield of isolated ethyl-naphthol **304** was improved to 60% (Entry 3). Other than for Nagata's reagent, full conversion was achieved within five minutes at –78 °C. Interestingly, we were able to isolate 25% of ethyl-tetralone **305** as a single diastereomer, which turned out to be relatively stable upon silica purification. NOE-experiments indicate a *trans*-configuration between the ethyl group and the chloride. The need for an antiperiplanar configuration between the chloride and the proton to induce HCl-elimination might explain its stability and the non-existence of the other diastereomer. A one-pot transformation, starting from naphthol **276** showed almost quantitative overall yield (Entry 4). Again, a change in the ratio was observed with a distribution of 0.7 : 1.0 in favor of the ethyl-tetralone **305**, hence,

influence by the remaining succinimide on the addition step should be considered. In light of these results, we approached the conjugate-addition-elimination sequence with different nucleophiles (Table 9). We found that the use of additional $SnCl_4$ allowed for the application of Mukaiyama-Aldol conditions (Entry 1). We were able to isolate 37% of the expected naphthyl-acetone **308**, however, as a

Table 9. Testing for different types of nucleophiles for the conjugate addition of naphthoketones **308**.



300 308 276

Entry	Nu	Equivalents	Time	308	Ratio Br/Cl	276
1	 309	8	5 h	37%	2 : 1	11%[a]
2	 310	20	2 h	38%	4 : 1	14%
3	 311	10	8 h	0%	-	-

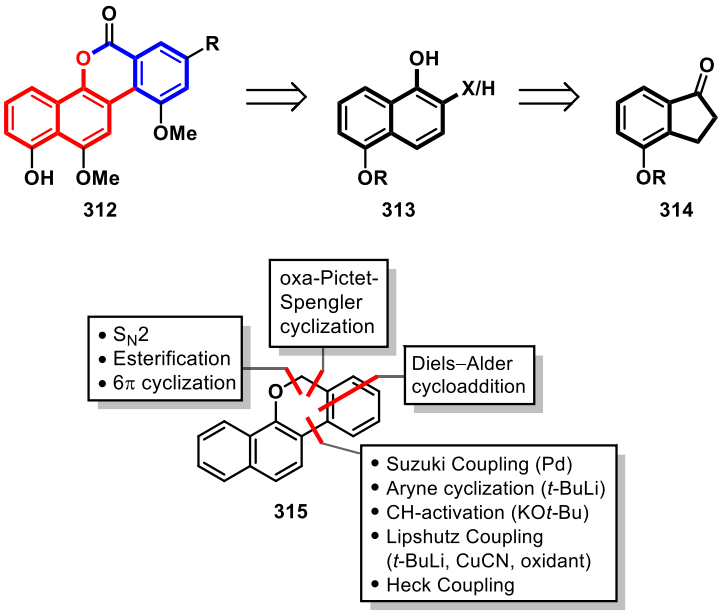
[a]NMR-Yield.

2:1 mixture between 2-bromo- and 2-chloronaphthol. It is assumed that the attached chloride originates from $SnCl_4$ rather than from the enone, however, no further investigations have been made so far. The use of $SnBr_4$ instead of $SnCl_4$ might suppress halogen shuffling at this position. These conditions were also efficient to introduce unfunctionalized anisole **310** (Entry 2) in 38% yield (NMR-yield). Again, a mixture of bromo- and chloro-naphthol was formed (1:1). Halogen-shuffling was reduced to a ratio of 4:1 in favor of the bromide when stirring at cryogenic temperatures was prolonged (80 minutes instead of 10 minutes) before warming to 23 °C. Unfortunately, the obtained phenyl-naphthol turned out to be highly sensitive to purification over silica or aluminum oxide (see Table 7, substrate **296**). Monitoring of the reaction was only possible on silica-TLC using cyclohexane-ethyl acetate in a nitrogen-flushed TLC-chamber. Other solvents like dichloromethane immediately caused decomposition (indicated by occurrence of a blue color). Hence, only semi-purification via flash-column-chromatography (N_2-stream) was possible to confirm the products structure via NMR-analysis. An attempt with Meldrum's acid **311** under the same conditions failed.

3. Results and Discussion: Towards the Synthesis of Gilvocarcins

3.1 Retrosynthetic Analysis

Our studies towards the synthesis of gilvocarcin natural products have led to various strategies starting from 2-halo-1-naphthol **313** (Scheme 32). With 6*H*-dibenzo[*c,h*]chromen-6-one **315** as the core structure of the gilvocarcin natural product family, all efforts aimed for the construction and connection of the eastern fragment (blue) to the main core (red) including post-modifications. A general overview of all retrosynthetic considerations approached during this thesis are depicted in Scheme 32, however, detailed retrosynthetic analysis will be found in each particular chapter. Parts of chapter 3.2.1 show results provided by Dr. Ben Marsh.



Scheme 32: Overview of all attempted strategies towards the gilvocarcin core structure discussed in this thesis.

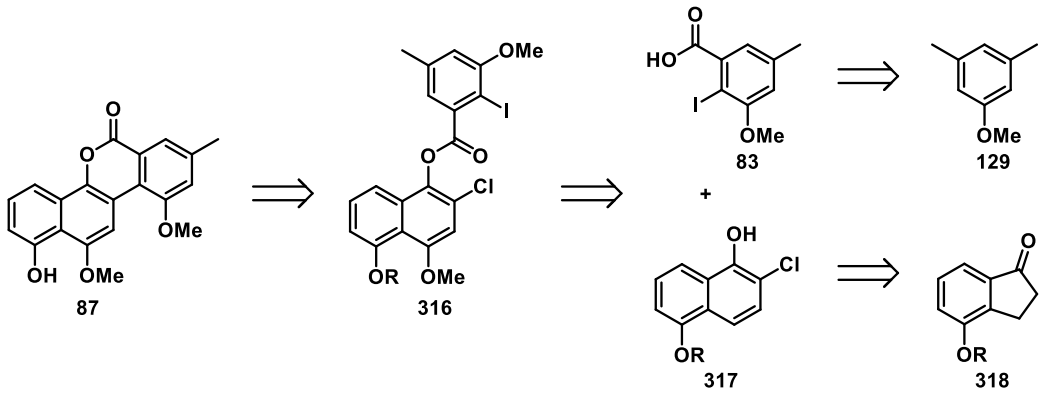
3.2 Strategies for the Synthesis of Defucogilvocarcin M and Derivatives

3.2.1 Intramolecular Aryl-Cl–Aryl-I Coupling

In our initial retrosynthetical considerations we considered a late-stage intramolecular biaryl-coupling between chloro-naphthol **317**, which was obtained by our methodology (see chapter 2) and aryl-iodide **83** to furnish the all-carbon tetracycle towards defucogilvocarcin M (Scheme 33). Both fragments would start from inexpensive compounds with full functionalization of each prior to the anticipated intramolecular esterification.

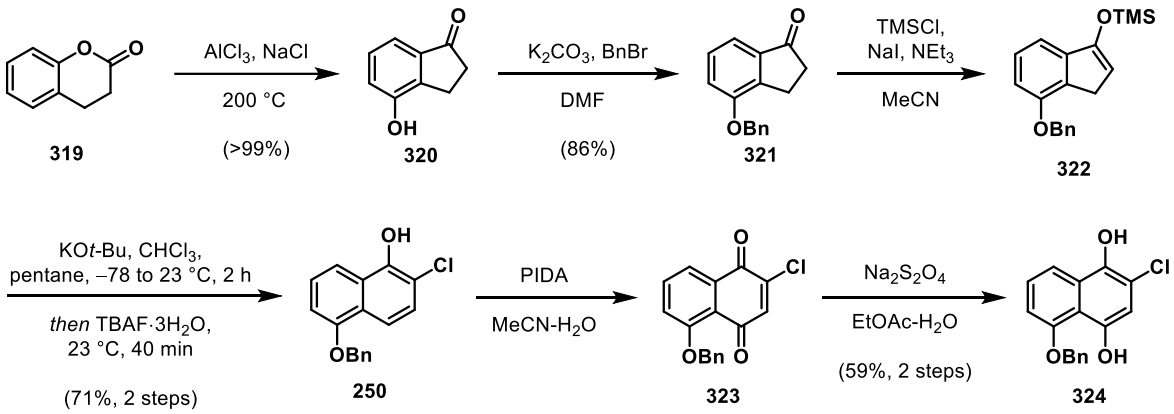
Our synthesis started from commercially available dihydrocumarin **319** (Scheme 34). Friedel–Crafts acylation[169] with subsequent benzylation set the stage for our developed cyclopropanation–ring-expansion strategy. Gram-scale preparation of 2-chloronaphthol **250** was followed by an oxidation–reduction sequence to obtain dihydroquinone **324**. Preparation of fragment B was initiated by radical

benzylic oxidation of anisol **129** to give benzyl alcohol **326** in two steps (Scheme 35).[170] Unanticipated difficulties were encountered us upon scale-up of this reaction with aromatic bromination as the major



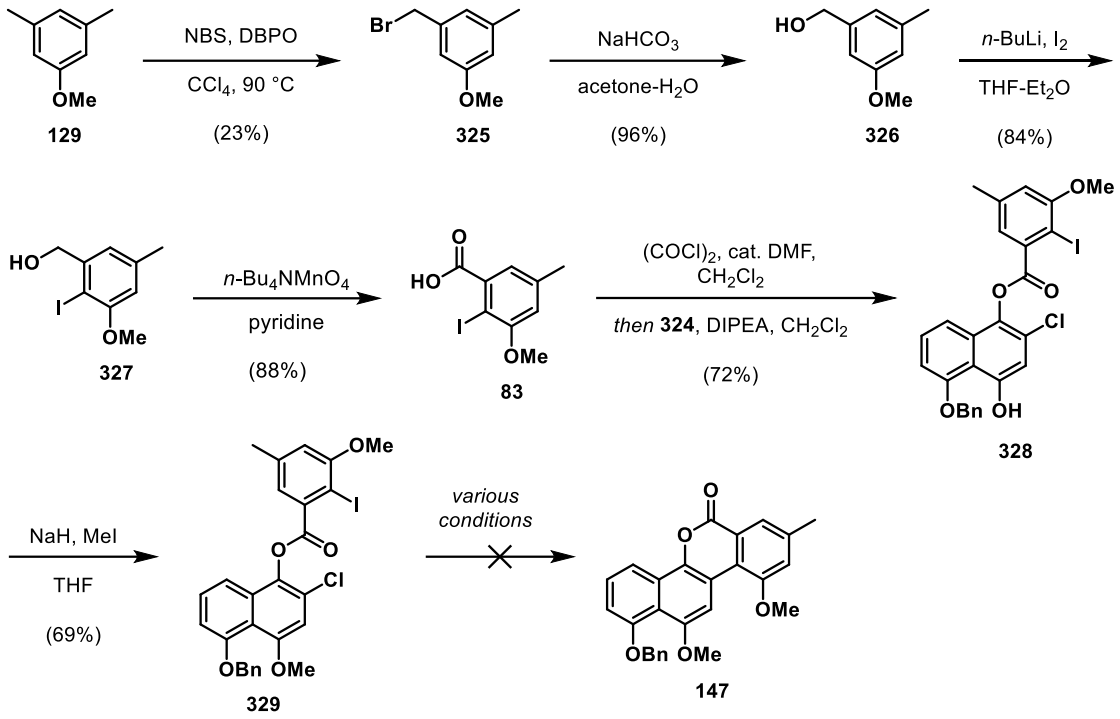
Scheme 33: Retrosynthetical considerations of the 1st generation approach.

side-product, however, enough material could be obtained for continuing this route. Selective iodination[133] with subsequent permanganate oxidation following Suzuki's protocol[144] provided benzoic acid **83** in large quantities. Regioselective esterification and methylation set the stage for our anticipated biaryl-coupling. Unfortunately, neither Ullman conditions nor nickel- or palladium catalyzed



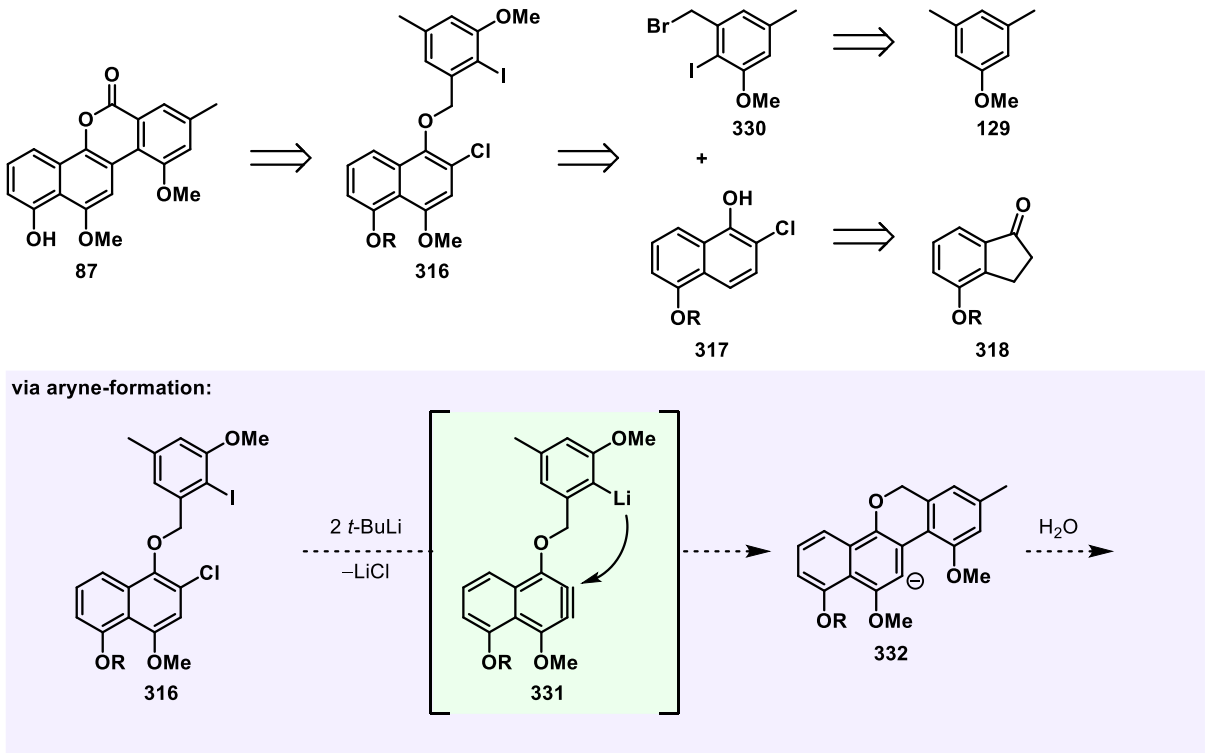
Scheme 34: Synthesis of dihydroquinone **324** employing the CPRE methodology.

couplings resulted in tetracycle **147**. Either no reaction, decomposition or reduction of the iodine were observed, which raised the assumption of the chlorine to be unreactive towards all tested conditions. This is supported by the literature, which does not provide examples for these types of chromenone constructions with a chlorine at this position, while examples for bromine[171] and iodine[172] are known.



Scheme 35: Attempted synthesis of the all-carbon framework of defucogilvocarcin M based on a late-stage biaryl coupling.

3.2.2 Anionic Benzyne Cyclization

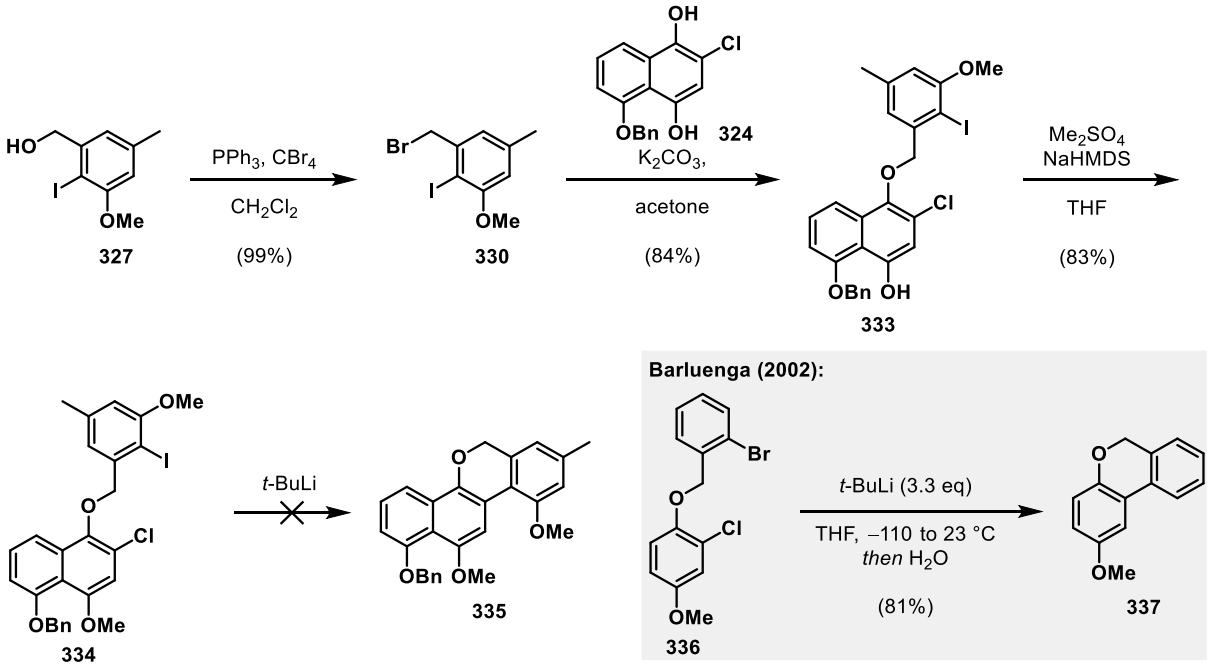


Scheme 36: Retrosynthesis of defucogilvocarcin M based on an anionic aryne cyclization.

Having established a concise route to the all-carbon intermediate **329** (Scheme 35), we reasoned that it would be expeditious to initiate our next synthetic efforts based on a similarly accessible intermediate.

Anionic benzyne cyclization established by Barluenga and co-workers[173] inspired us for its application to envisioned ether **316** (Scheme 36) which would allow for a transition-metal-free route towards defucogilvocarcin M. Mechanistically, *tert*-butyllithium initiated lithium–iodine exchange with simultaneous LiCl elimination on the naphthalene would give reactive intermediate **331** followed by intramolecular nucleophilic addition and proton abstraction upon aqueous work-up.

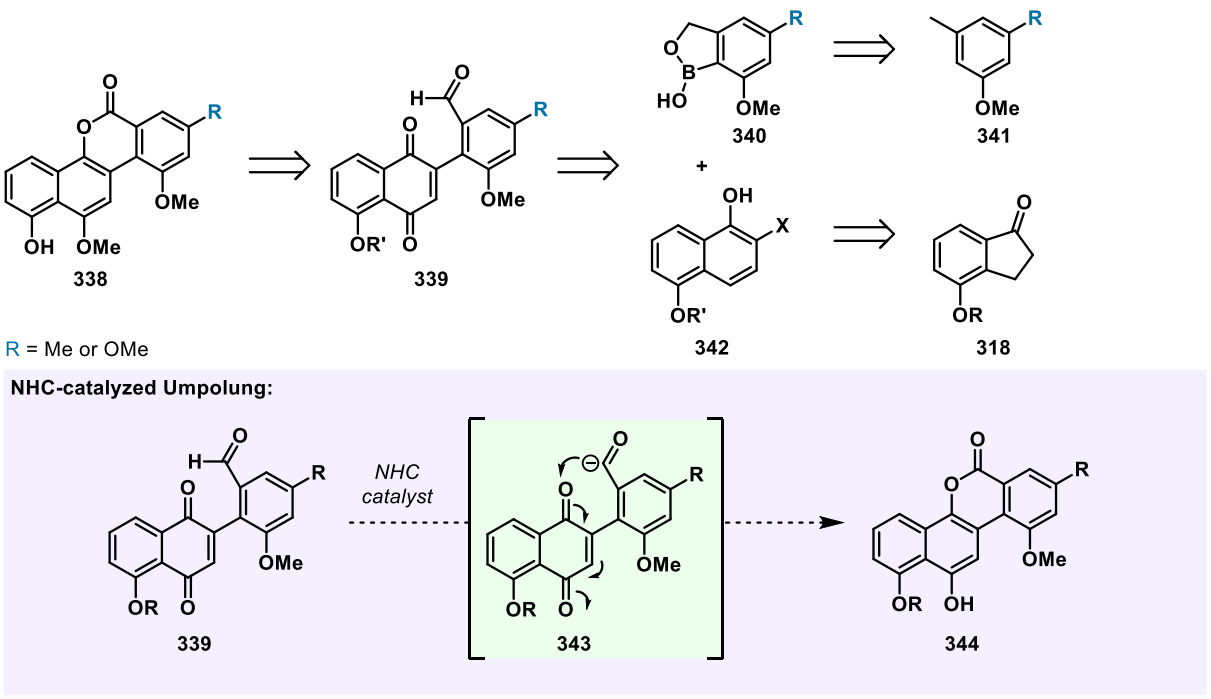
Key-step intermediate **334** was accessed by starting with an Appel reaction of available benzyl alcohol **327** followed by regioselective nucleophilic substitution and methylation of ether **333** in high yields (Scheme 37). Unfortunately, all attempts to obtain tetracycle **335** failed in our hands. Problematic issues evolved by maintaining the reported temperature of –110 °C. While higher temperatures would increase the risk of undesired side reactions, slightly lower temperatures already led to freezing of the reaction mixture since the melting point of THF is referenced as –108 °C. Mainly decomposition accompanied by iodine reduction was observed. These negative results might be due to the more complex substitution pattern of substrate **334** compared to the literature's examples **336** (Scheme 37, grey box). Ether **334** was also submitted to transition metal conditions (as described in chapter 3.2.1) but turned out to be unsuccessful as well.



Scheme 37: Failed attempts of the anticipated anionic aryne-cyclization.

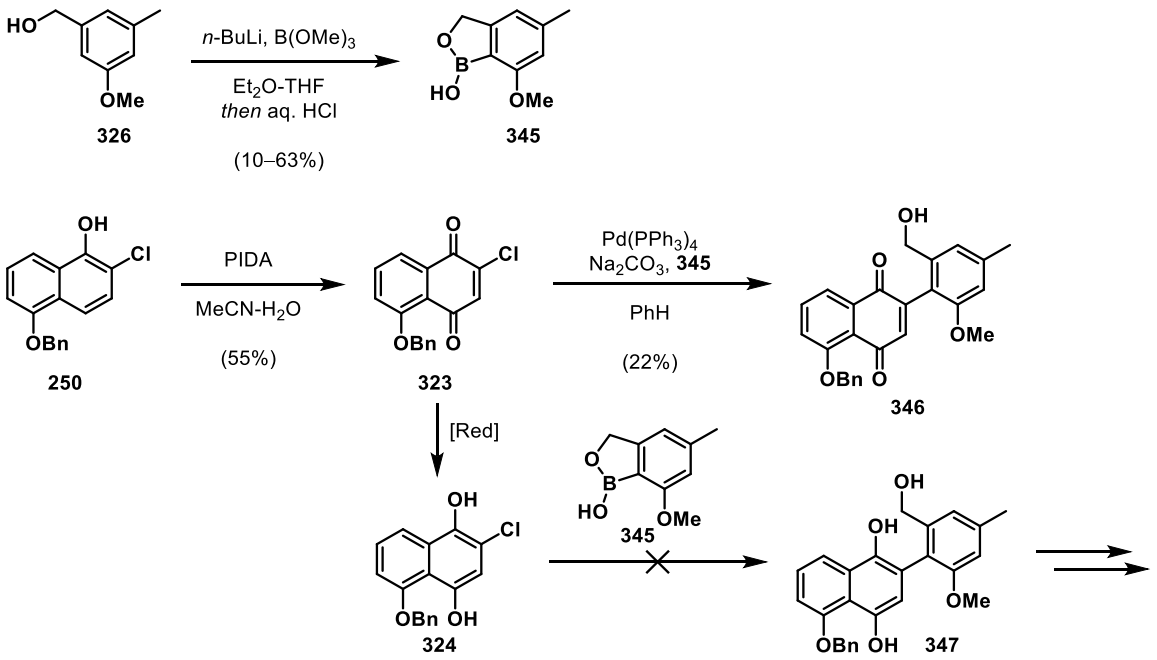
3.2.3 Inter- and Intramolecular Suzuki Coupling

In light of these disappointing results, a change of the strategy was required. As a result, we anticipated an intermolecular Suzuki coupling prior to cyclization of the lactone ring (Scheme 38). Although coupling of dihydroquinone **324** (Scheme 37) and the corresponding 2-boryl benzoate would be desirable due to the desired oxidation state of both parts in the final natural product, previous investigations revealed the need for an electron-poor aryl bromide (benzoquinone vs. dihydroquinone)



Scheme 38: Envisioned intermolecular Suzuki coupling followed by an NHC-catalyzed cyclization.

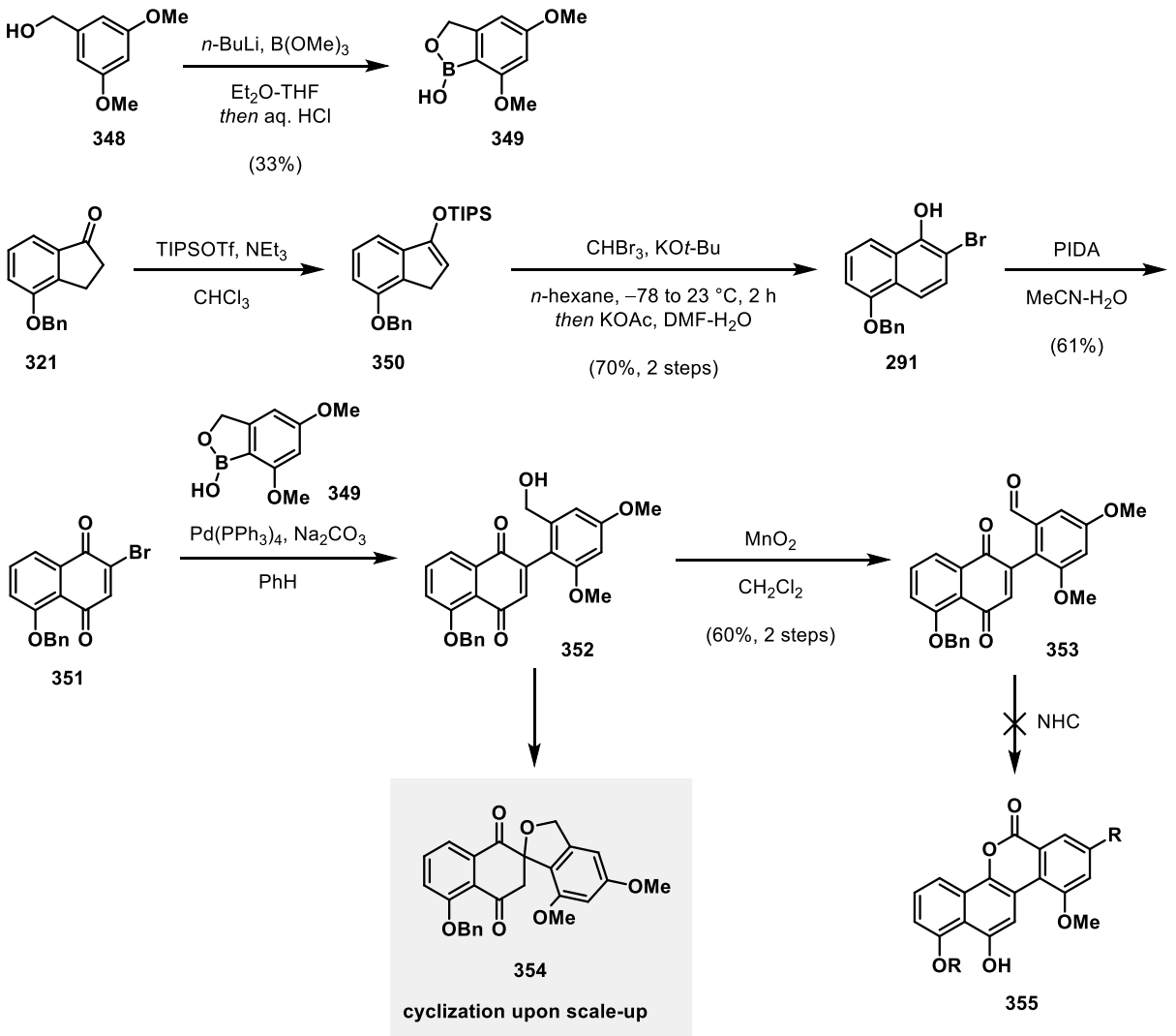
and an electron-rich boronate (benzyl alcohol vs. benzoate) to allow for a successful cross-coupling. Therefore, we aimed for the coupling of chloro-benzoquinone **323** and oxaborole **345** with subsequent intramolecular adjustment of the oxidation-states (Scheme 39). While a stepwise sequence including



Scheme 39: Biaryl formation via an intermolecular Suzuki coupling using oxaborole **345**.

reduction of the benzoquinone, oxidation of the benzyl alcohol and final esterification might result in a rather lengthy route, an NHC-catalyzed cyclization via a formal hydride shift was envisioned to allow for these transformations in one step. With benzylic alcohol **326** in hand (see chapter 3.2.1), we started

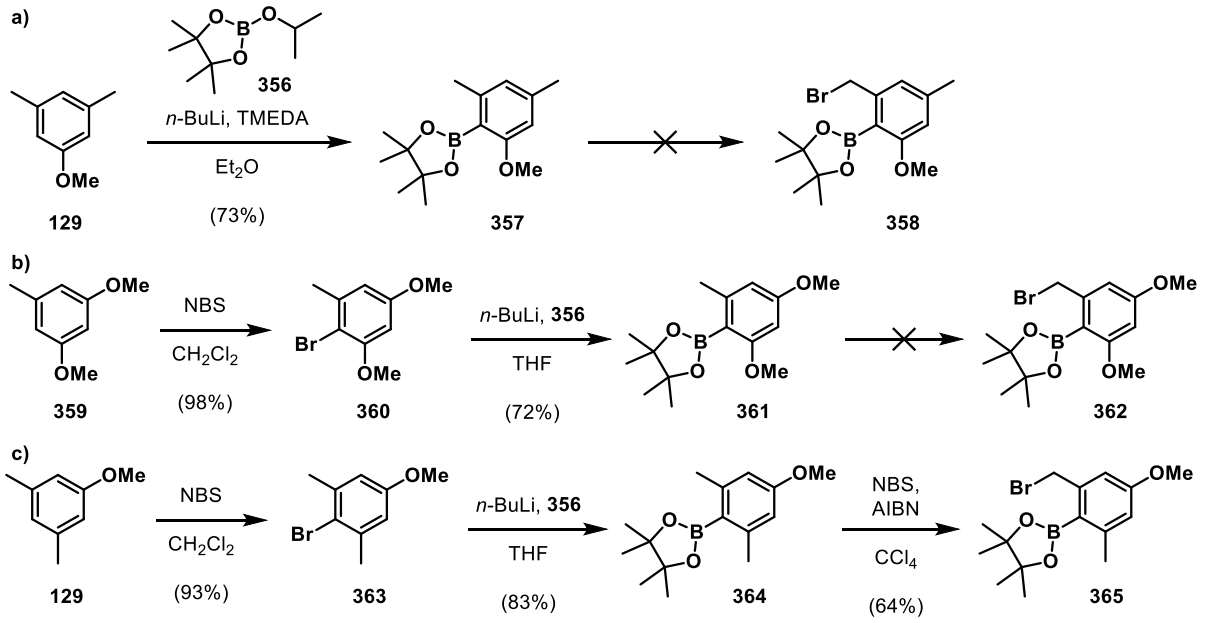
the preparation of oxaborole **345** via selective aromatic lithiation to give the corresponding anion, which was quenched with trimethyl borate and then subjected to a hydrochloric work-up. To our surprise, we were confronted with complications when trying to isolate the desired material in high amounts and in satisfactory purities. Limited selectivity during *ortho*-lithiation and an incomplete hydrolysis might explain the formation of complex mixtures. Procedures from the literature on comparable substrates[174] rarely provide yields above 50% rendering this reaction as one of limited reliability. However, we provided enough material to test for our envisioned intermolecular Suzuki–coupling which resulted in 22% of the desired alcohol **346** (Scheme 39). In order to progress our synthesis beyond the Suzuki coupling, a more reliable alternative was required. Thus, we replaced bromo-benzoquinone **351** for chloro-benzoquinone **323** as a more reactive species for the cross-coupling (see chapter 2.2). In addition, we decided to aim for a divergent route towards the gilvocarcin natural products with regards to the C8-position. Starting from symmetrical dimethoxybenzyl alcohol **348** (Scheme 40) instead of the methyl congener **345** (Scheme 39) would give gilvocarcin precursor **355** showing a methoxy group at the crucial C8-position. Selective deprotection followed by triflation would lead to a valuable precursor for the



Scheme 40: Dimethoxy oxaborole **349** as starting point for a divergent route towards the gilvocarcins.

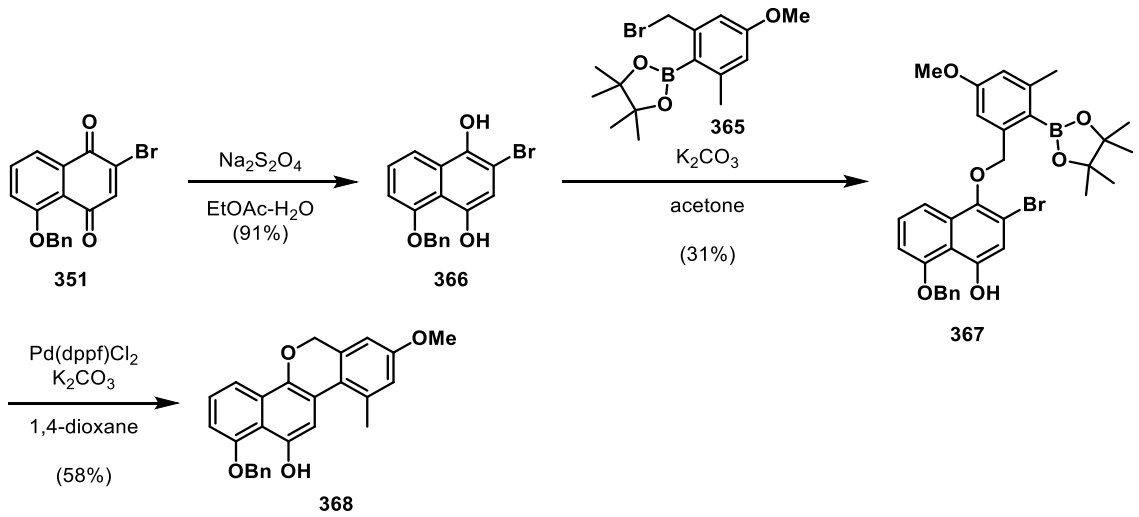
installation of different substituents at a later stage. Similar to oxaborole **345**, high yields remained unreached for oxaborole **349** in our hands, however, with a higher reliability.[169] Yields for the preparation of bromo-naphthol **291** on a gram-scale using our methodology were comparable to chloronaphthol **250**. PIDA-mediated oxidation to naphthoquinone **351** set the stage for Suzuki cross-coupling. Adduct **352** was obtained in higher yields than observed for chloride **346**, which was subjected to manganese(IV) oxidation without the benefit of full purification. It is noteworthy that a scale-up of the coupling reaction exclusively resulted in cyclized product **354** in comparable yields. With key-aldehyde **353** in hand, we strived for the application of the NHC-catalyzed cyclization,[175] however attempts using different 4-methylthiazolium catalysts were unfruitful.

Encouraged by the Suzuki cross-coupling as a suitable strategy to form the biaryl bond, we envisioned an intramolecular approach installing the biaryl-bond subsequent to the connection of both fragments. Dimethylanisol-derived benzyl bromide **358** would pave the way for construction of gilvocarcin M (Scheme 41a). Unfortunately, we failed in functionalizing the benzylic position of aryl boron **357**. Therefore, we changed to dimethyl orcinol **359** (b) as starting point for our above described divergent



Scheme 41: Preparation of the eastern fragment towards an intramolecular Suzuki coupling.

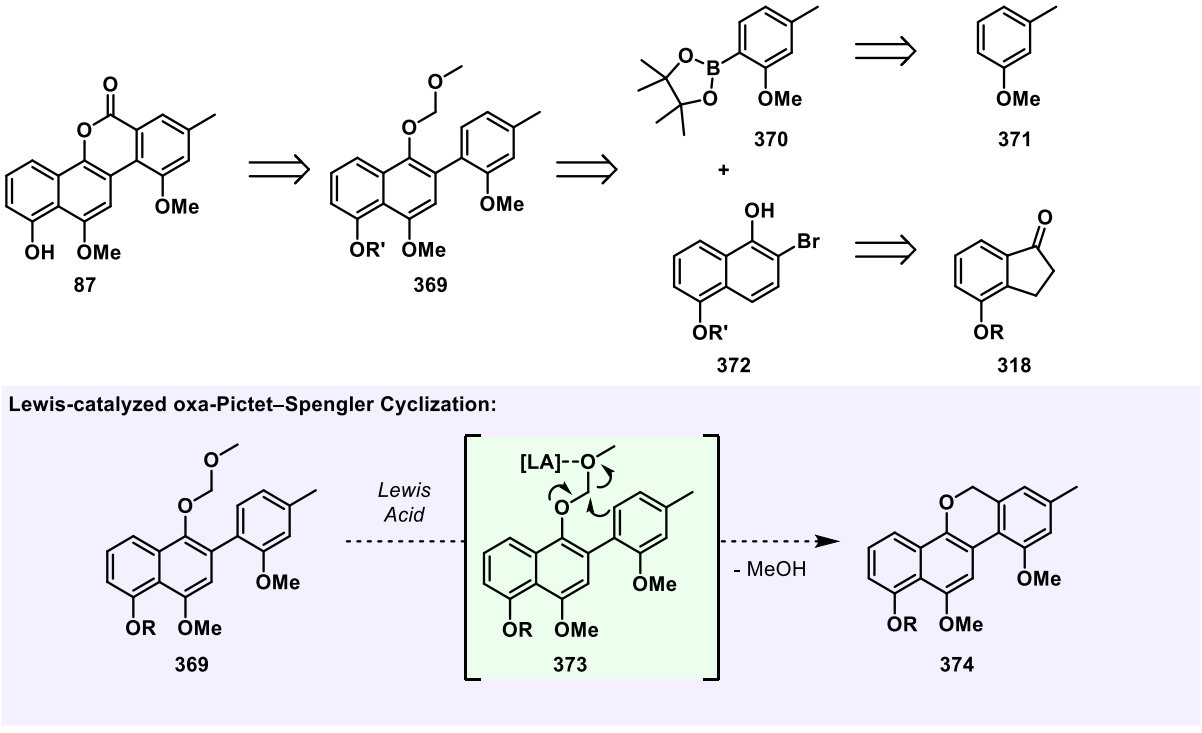
route. Again, intentions were fulfilled up to the stage of the arylboronate (**361**), which resisted any conditions tested to oxidize the benzylic position. In contrast, high yields were obtained over three consecutive steps when the strategy was changed to prepare boronate **365** (c). With this intermediate in hand, we were poised to address the following benzylation and biaryl formation, while efforts to prepare either **358** or **362** were ongoing. Nucleophilic substitution turned out to be scalable, however, afforded ether **367** in only moderate yields (Scheme 42). We were pleased to see that unoptimized conditions for the Suzuki coupling resulted in 58% yield of tetracycle **368**. Despite these results, any further efforts to obtain boronate derivatives **358** or **362** were met with failure, which prompted us to seek for other strategies.



Scheme 42: Successful construction of the all-carbon framework of *iso*-defucogilvocarcin M.

3.2.4 Oxa-Pictet–Spengler Cyclization

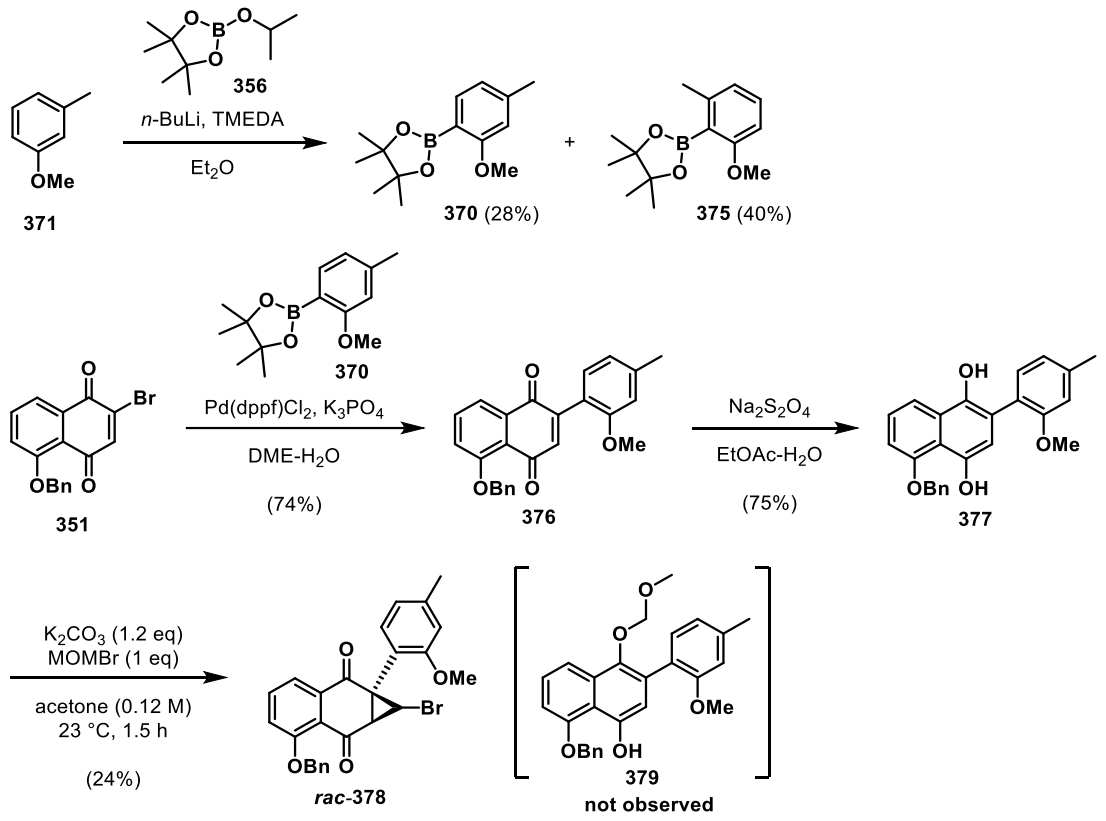
Preserving the idea of biaryl-bond formation via Suzuki cross-coupling we envisioned a concise approach towards the desired tetracycle by late-stage installation of a C_1-unit. The Literature provides several examples of an oxa-Pictet-Spengler cyclization to construct chromane core structures.[176]



Scheme 43: Retrosynthetic considerations based on an Oxa-Pictet–Spengler cyclization.

Applying this strategy to our system would lead to the construction of intermediate **373**, which is planned to undergo cyclization upon Lewis acid catalysis affording cyclic ether **374** (Scheme 43). Fragment **375** was thereby prepared in a single step from commercially available 3-methylanisole **371** (Scheme 44). We obtained a mixture of two regioisomers **370** and **375** in 68% overall yield. Surprisingly

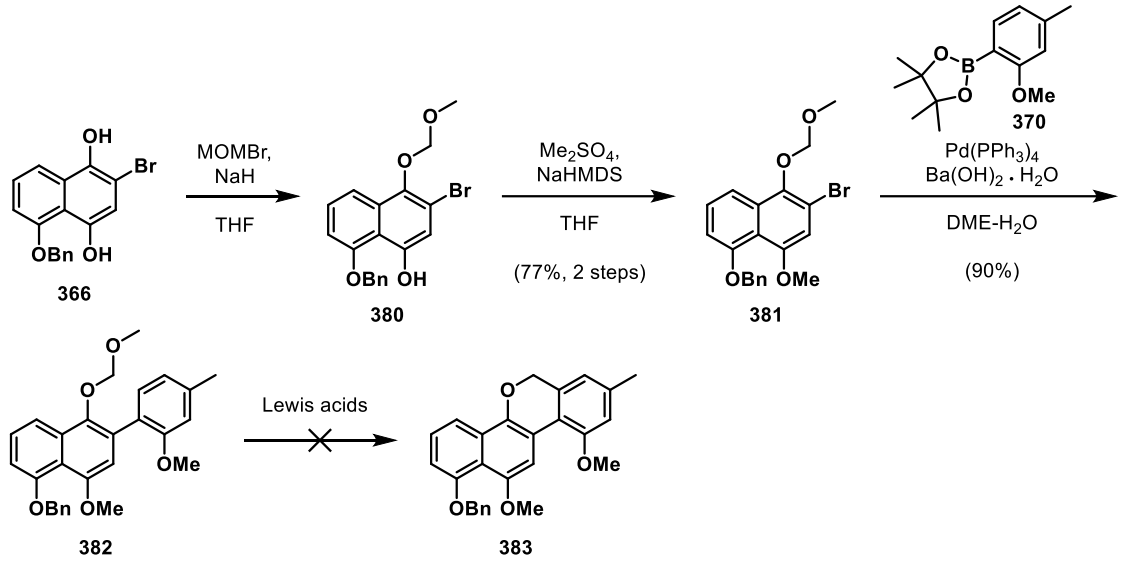
the opposite selectivity was observed of what was expected based on steric considerations and directing effects. Subsequent cross-coupling afforded benzoquinone **376** in good yields, which was transformed into dihydroquinone **377** in one further step. Unfortunately, standard MOM-protection conditions gave a complex mixture of products, which we reason to be a result of steric and electronic effects around the



Scheme 44: First attempts towards the anticipated oxa-Pictet–Spengler cyclization.

hydroxy-group of interest. HPLC-purification, allowed for the isolation and characterization of bromocyclopropane **378** in 24% yield. Further investigations to understand the mechanism underlying this product formation are currently ongoing in our laboratories. We cannot exclude that undesired oxidation to the benzoquinone occurred prior to the cyclopropanation event, since compound **377** turned out to be sensitive to oxygen. In a second attempt to synthesize the crucial precursor **369**, we commenced with MOM-protection of **366**, which proceeded smoothly, followed by methylation to give intermediate **381** (Scheme 45). Subsequent cross-coupling was high-yielding and provided precursor **382** in amounts enough for testing the key-cyclization. Unfortunately, none of the tested Lewis acids (TMSOTf, BF_3, $TiCl_3$, $AlCl_3$) gave the desired product. Decomposition was observed within seconds to minutes, even at cryogenic temperatures. We assume that the selectivity between the naphtholate and methanolate acting as a leaving group during this process is limited and therefore leads to uncontrollable reactions. However, simple MOM-deprotection was not observed. Another aspect might be the surprisingly low stability of the benzyl protecting group towards Lewis acids as we found out during other investigations. Furthermore, despite the vast number of examples provided by the literature on these types of oxa-

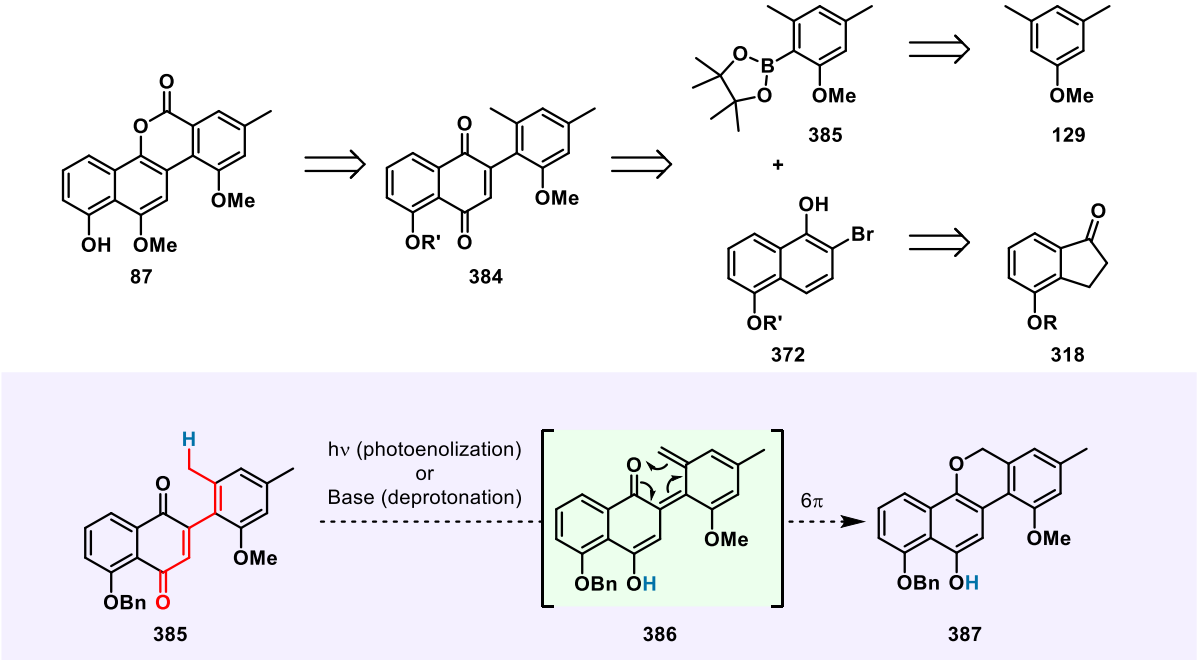
Pictet–Spengler cyclizations, no example is known to date on a MOM-protected phenolic alcohol to undergo this reaction. Our results left this ongoing challenge unsolved.



Scheme 45: Failed attempts to induce the anticipated oxa-Pictet–Spengler cyclization.

3.2.5 Base-/Photo-induced 6π-Electrocyclization

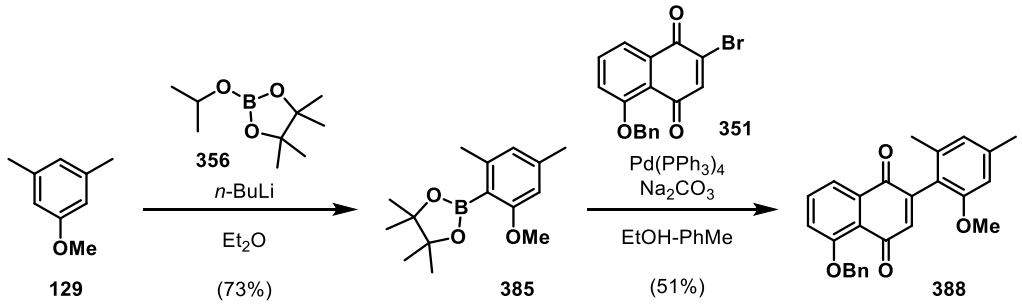
Since its discovery by Yang and Rivas in 1961, the photoenolization of *ortho*-metyhlbenzophenones has been the subject of several mechanistic studies,[177] methodological applications[178] and key-transformation in total syntheses.[179] Usually, these short-lived *ortho*-quinodimethanes are used to



Scheme 46: Envisioned photo- or base-induced electrocyclization to furnish all-carbon tetracycle **387**.

undergo additions, either intramolecularly[180] or intermolecularly[181]. In the course of ongoing studies, the application of this reaction in the presence of quinones has attracted our interest. Excitation of *para*-

quinones are mechanistically well studied,[182] while less examples are known for the photoenolization of *para*-naphthoquinones as reported by Wirz[183] and Klimenko[184]. We anticipated, that the conjugated system of substrate **385** might allow for a formal keto-enolization to intermediate **386**, which would undergo spontaneous 6π-electrocylization to give tetracycle **387** (Scheme 46). We were aware of the fact that examples for these types of enolization have only been reported for 1,4-conjugated systems, but not for 1,6-conjugated system, so far.[185] In light of this challenging task, we started with the preparation of



Scheme 47: Preparation of precursor **388** for the envisioned 6π-electrocyclization.

precursor **388** in a cross-coupling reaction between benzoquinone **351** and boronate **385** (Scheme 47). The UV/VIS-spectrum of naphthoquinone **388** is shown in Figure 6. Unfortunately, all attempts to induce cyclization under photo-irradiation resulted in complex mixtures. Although, starting material was consumed almost completely within one hour or less, isolation of specific products was not possible. Parker[186] described a cyclization very similar to the one anticipated by us (Scheme 48). Spontaneous enolization at the acidic α-ester-position in conjugation with the quinone induced the ring closing

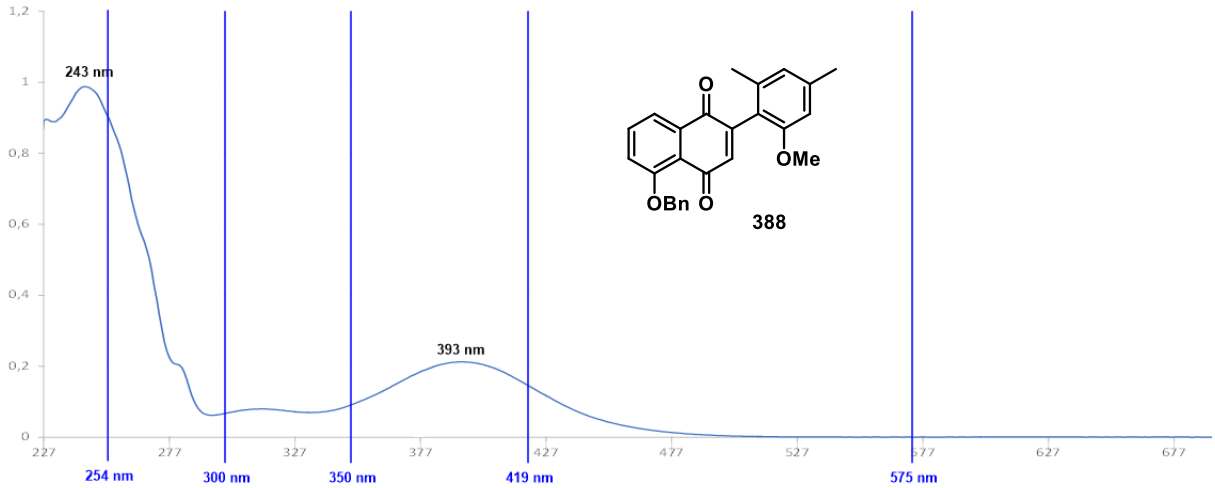
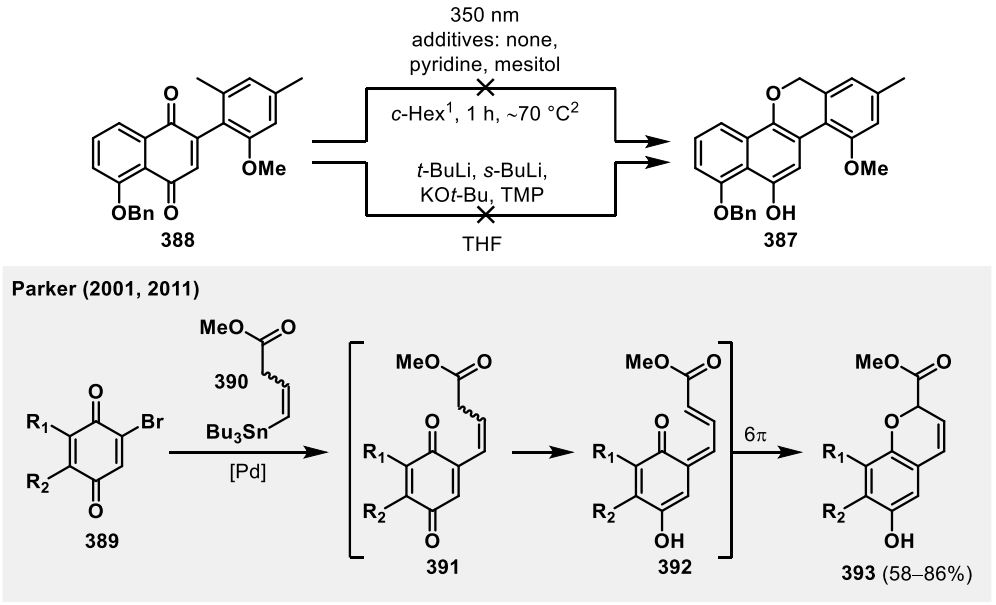


Figure 6: UV/VIS-spectrum of intermediate **388**. Blue lines indicate accessible wave-lengths using a Rayonet©.

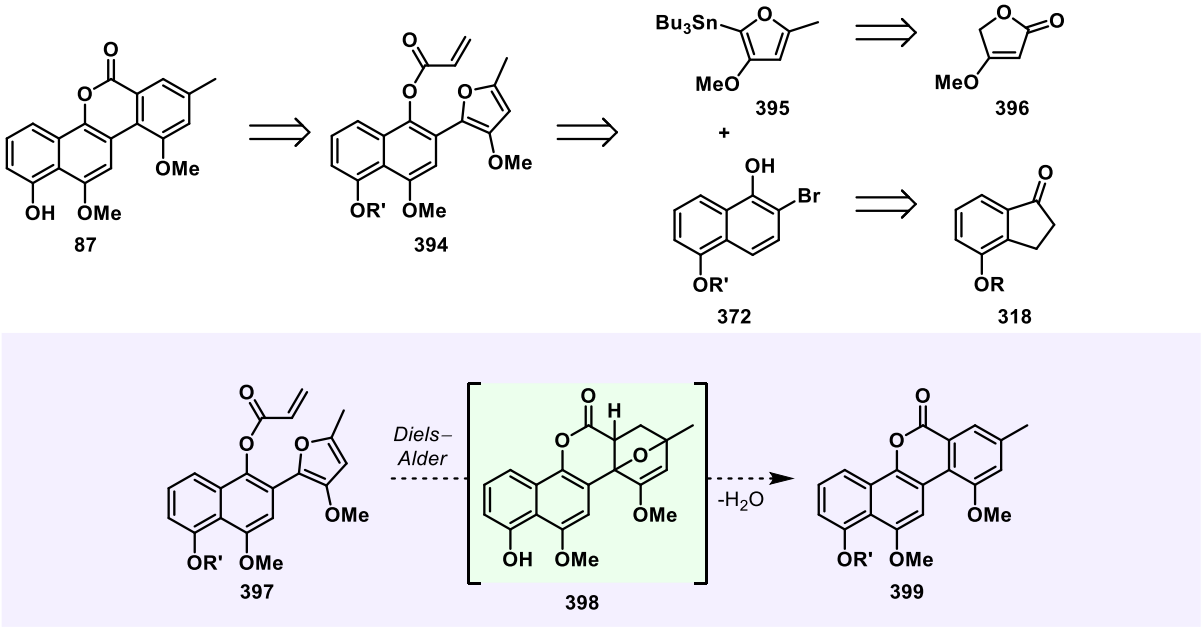
cyclization, hence, we searched for conditions to deprotonate aromatic methyl groups. Different bases have been tested based on examples from the literature. However, neither TMP[187], LDA[188], KO*t*-Bu[189], *t*-BuLi[190] or combinations thereof resulted in the desired reaction sequence. Deuterium experiments revealed no selectivity during the deprotonation process resulting in complex mixtures of deuteration. As a result, no further investigations towards this route were made.



Scheme 48: Attempts to realize a base-induced 6π-electrocyclization. [1]degassed. [2]caused by light tubes.

3.2.6 Intramolecular Diels–Alder Cycloaddition

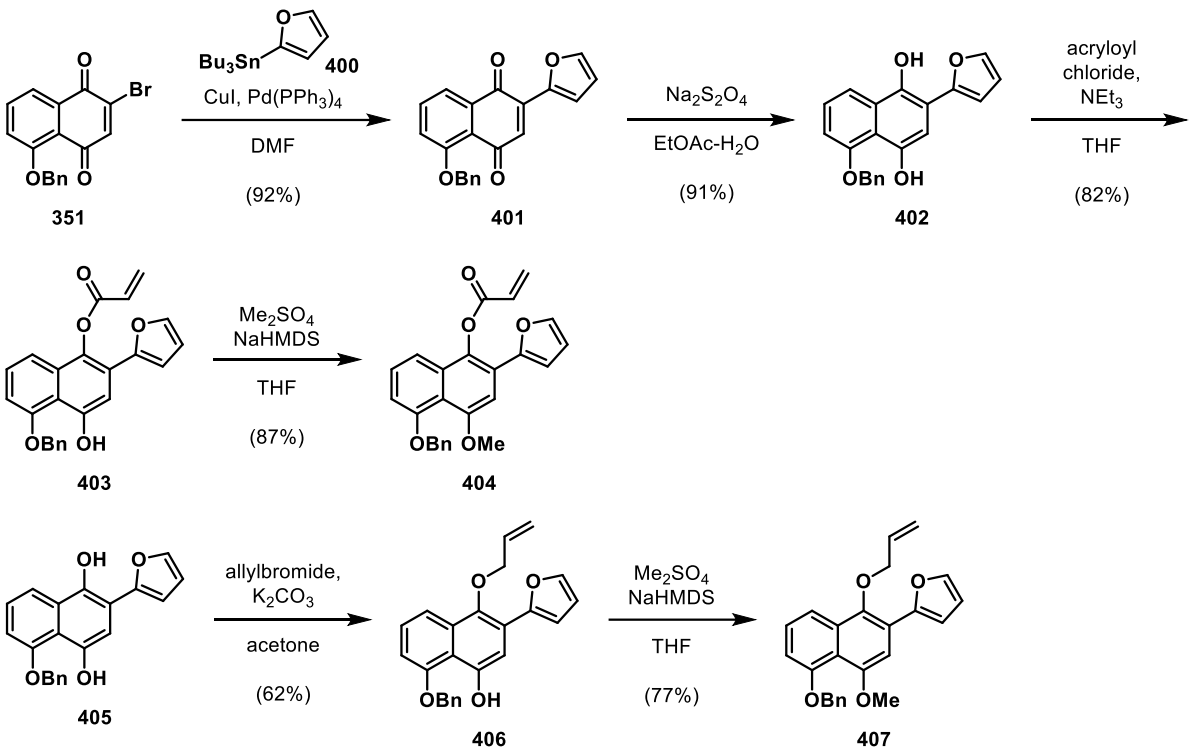
While previously focusing on sequential formation of the biaryl- and the ester/ether bond between the naphthalene and the benzene core, we envisioned a late-stage construction of the eastern fragment via an intramolecular Diels–Alder reaction. Although, intramolecular cycloadditions between furans and allyl-[191] or acryloyl-[192] groups are known in literature, the formation of a six-membered cycle via this



Scheme 49: An envisioned intramolecular Diels–Alder reaction to furnish defucogilvocarcin M **399**.

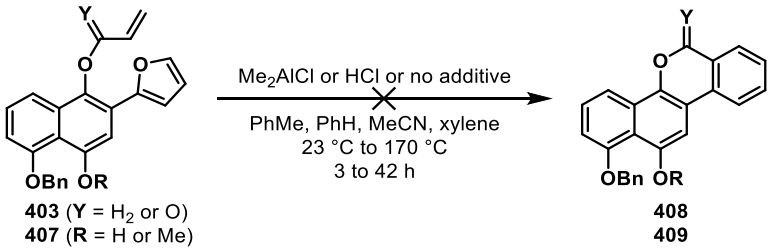
strategy still remains underexplored. Deeper investigations into this transformation have been conducted by the group of Gundersen[193] for the cycloadditions of allyl groups and furans, however, their focus

mainly relies on allyl amines, while *O*-allylated substrates for the construction of chromanes are underrepresented in their studies.



Scheme 50: Synthesis of precursors **404** and **407** for the anticipated intramolecular Diels–Alder reaction.

We reasoned that it would be expeditious to initiate our synthetic efforts with the unsubstituted furan **400** while efforts towards the construction of methyl-methoxy-furan **395** were ongoing (Scheme 50). This might allow for validation of this late-stage transformation before attempting to introduce a more complex substitution pattern. Straightforward assembly of precursor **404** was achieved in four steps using

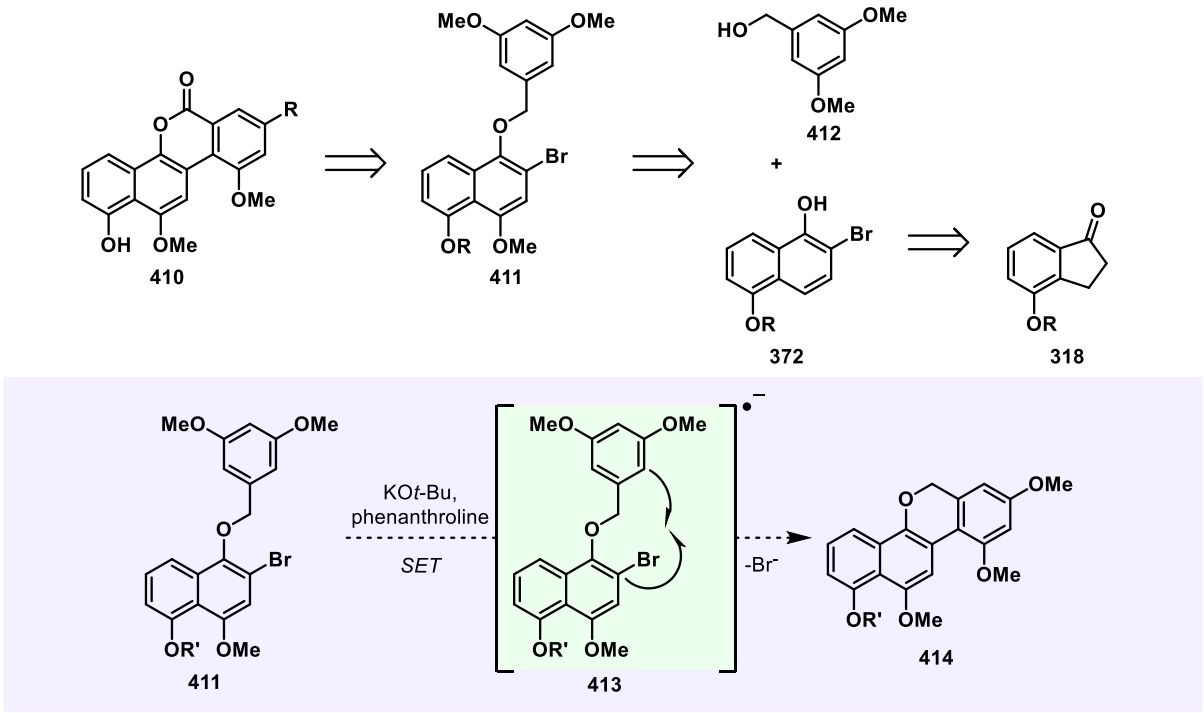


Scheme 51: Failed attempts to induce a furan-based intramolecular Diels–Alder reaction.

commercially available furyl-stannane **400**. The same strategy was used to prepare its allylic analogue. With both intermediates **403** and **407** in hand we tested several thermal conditions to induce the cycloaddition (Scheme 51). Unfortunately, all tested precursors resisted thermal or Lewis acidic conditions or began to decompose at temperatures higher than 150 °C. In parallel, efforts towards the synthesis of substituted furan **395** have met with failure, which necessitated exploration of an alternative route to produce the desired tetracycle.

3.2.7 Biaryl Coupling by KO*t*-Bu-induced C–H-activation

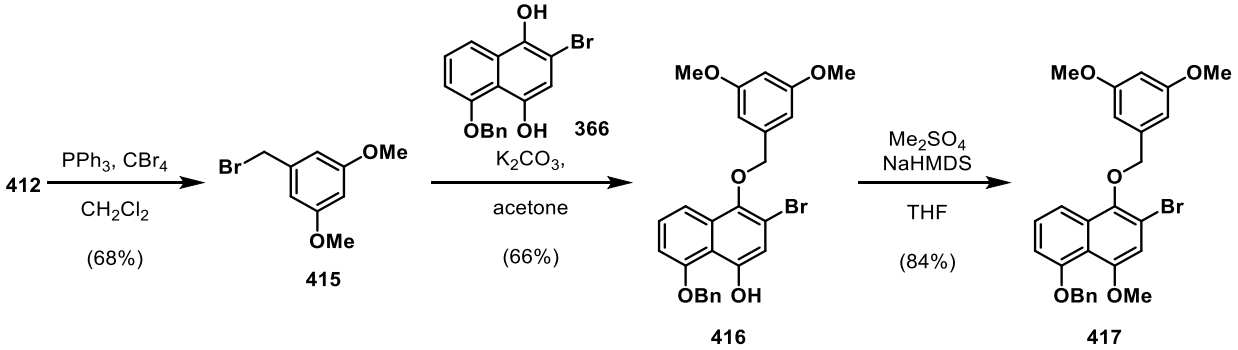
Reviving the idea of a metal-free synthesis towards the gilvocarcin core led to considerations implementing a KO*t*-Bu/phenanthroline induced radical C–H-activation (Scheme 51).[194] Although previous reports proposed a transient aryne formation[195], later studies strengthened the assumption of a radical process via single-electron-transfer.[196] Examples of regioselectivities have been described for



Scheme 52: A transition metal-free cyclization towards the gilvocarcin core-structure.

unsymmetrical arenes, however, only to moderate extend. Therefore, we decided to implement the previously described divergent route starting from symmetrical benzyl alcohol **412** (Scheme 52).

The desired precursor **417** was prepared in three steps starting from previously prepared compounds **366** and **412** in good yields (Scheme 53). With ether **417** in hand, we applied standard conditions found in

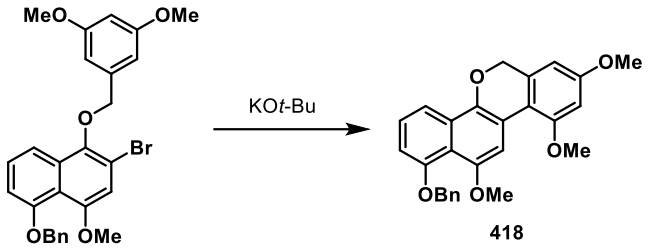


Scheme 53: Synthesis of key-precursor **417**.

the literature for this type of transformation (Table 10). Due to the complexity of the obtained crude NMR-spectra and thin-layer-chromatographical analysis, the outcome of the single experiments was evaluated by relative abundance of significant signals in the ^{1}H-spectra. Only the most promising

reaction was subjected to chromatographical purification (Entry 5). According to literature procedures, the performed reactions were not followed by TLC-monitoring, instead they were left stirring for a defined time span and then stopped by direct filtration over Celite. In a first attempt, 1.25 equivalents of KO*t*-Bu at 140 °C were used showing almost no consumption of the starting material. Doubling of the equivalents in combination with a prolonged reaction time led to full consumption of the starting material with the most prominent signals in NMR-analysis belonging to the desired product. The reaction was accompanied by proto-dehalogenation (–Br) and the formation of two

Table 10. Screening for the KO*t*-Bu-catalyzed intramolecular cyclization.



417 418

Entry	KO*t*-Bu	Solvent	1,10-phe	Temp	Time	SM	–Br	418	Y	Z	418[a]
1	1.25 eq	1,4-dioxane	-	140 °C	3 h	1.0	-	-	-	-	n.d.
2	2.50 eq	1,4-dioxane	-	140 °C	19	-	0.2	1.0	0.2	0.1	n.d.
3	2.50 eq	1,4-dioxane	0.40 eq	80 °C	9 h	1	-	-	-	-	n.d.
4	2.50 eq	1,4-dioxane	0.40 eq	100 °C	4 h	1	-	-	-	-	n.d.
5	2.50 eq	1,4-dioxane	0.40 eq	100 °C	7 h	-	0.1	1.0	0.2	0.2	19%
6	2.50 eq	mesitylene	0.40 eq	100 °C	7 h	1.0	0.6	1.0	0.8	0.7	n.d.
7	3.00 eq	mesitylene	0.40 eq	100 °C	18 h	-	0.8	1.0	1.4	1.0	n.d.
8	2.50 eq	benzene	0.40 eq	100 °C	7 h	4.5	0.1	1.0	0.1	-	n.d.
9	2.50 eq	pyridine	0.40 eq	100 °C	24 h	1	-	-	-	-	n.d.

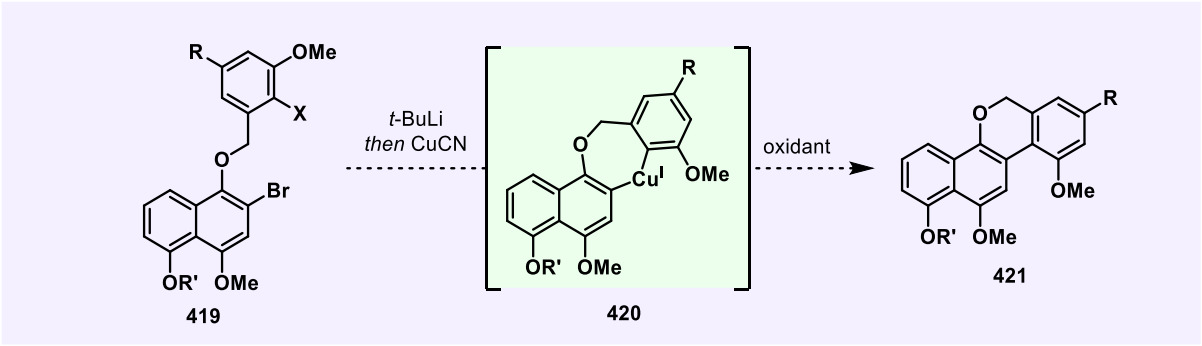
[a] isolated yield. 1,10-phe = 1,10-phenanthrolin; –Br = protodehalogenated **417**; n.d. = not determined. Y, Z = unknown.

further products, Y and Z, which we were not able to characterize or isolate with sufficient purity. With these promising results in hand, we screened for further conditions implementing 1,10-phenanthroline in catalytic amounts. Both, reaction time and temperature could be reduced while ensuring full conversion of **417**. Best results were obtained at 100 °C after seven hours affording 19% of tetracycle **418** after purification. Further experiments using different solvents did only lead to lower conversion or increased formation of side-products. Despite having observed the formation of the desired product, we were not confident about further optimization of this reaction due to the limited range of possible variables. In addition, all reactions were accompanied by major decomposition events or formation of

complex mixtures, which resulted in challenging purifications. Therefore, we considered these results as a proof of concept for a metal-free and concise approach towards the gilvocarcin core structure.

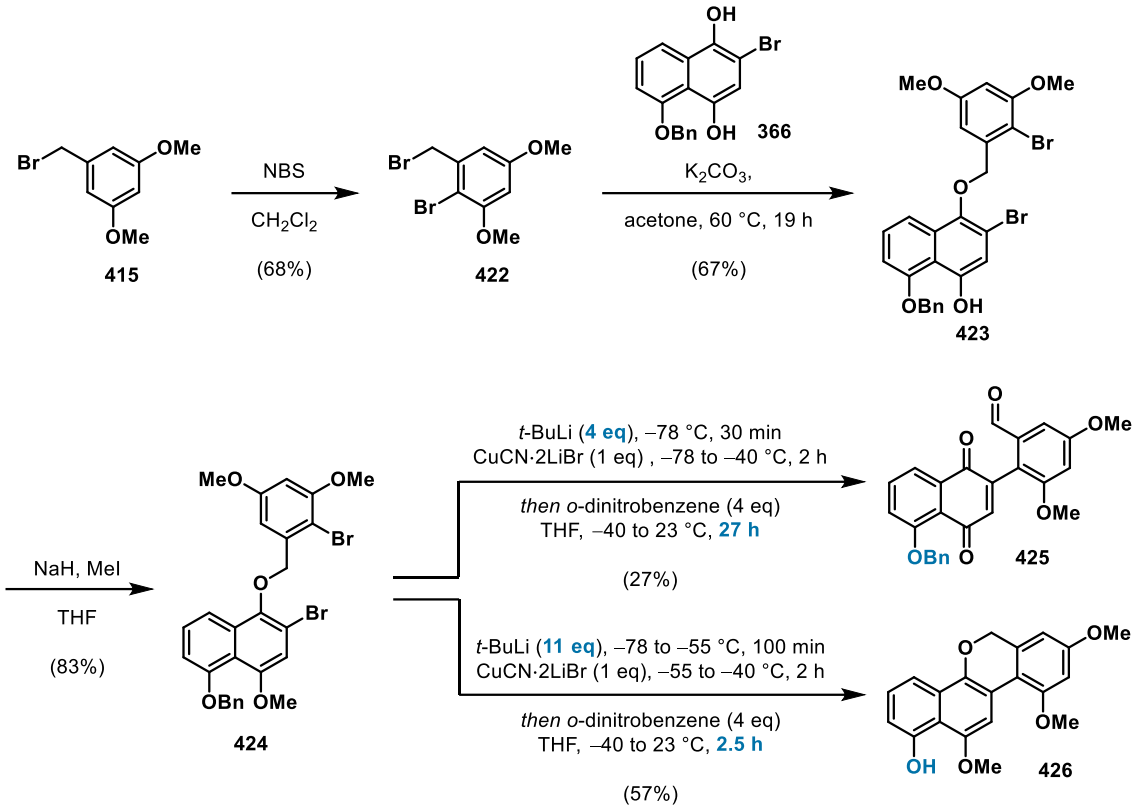
3.2.8 Intramolecular Oxidative Coupling of CuCN-derived Diaryl-Cuprates

Several strategies to form the crucial biaryl bond via ArX–ArX coupling (see chapter 3.2.1) using common procedures failed in our hands. In light of these experiences, we considered a mechanistically different approach, namely an oxidative coupling via transient formation of a diaryl-cuprate (Scheme 54).[197] Besides plentiful examples on organocuprate-based C–C-couplings,[198] major contributions have been made by Lipshutz and co-workers towards oxidative intramolecular biaryl couplings.[199,200] We considered substrate **419** to be susceptible to these conditions, however, examples for the construction of six-membered rings via this strategy in comparison to larger ring-sizes are underrepresented.[201]



Scheme 54: Oxidative Coupling of an *in situ*-formed diaryl cuprate.

Precursor **424** was prepared according to the previously described strategy including selective nucleophilic substitution with subsequent methylation (Scheme 55). For the envisioned key-step we followed modified Lipshutz-conditions by Schreiber *et al*. implementing LiBr and *ortho*-dinitrobenzene (*o*-DNB) as oxidant.[202] First attempts resulted in formation of the desired biaryl-bond, however, we observed overoxidation affording benzoquinone-aldehyde **425**. Reducing the time of *o*-DNB treatment was sufficient to avoid overoxidation. Best results were obtained for reaction times between 1.5 and 2.5 hours. Debenzylation was observed when a huge excess of *t*-BuLi (11 eq) was used affording the desired tetracycle **426** in 57% yield. Although aware of the harsh conditions rendering such a protocol undesirable for most purposes, we were surprised not being able to find any example in literature for debenzylating an alcohol under these or similar conditions.[203] Only a few examples are known for amines or amides.[204]

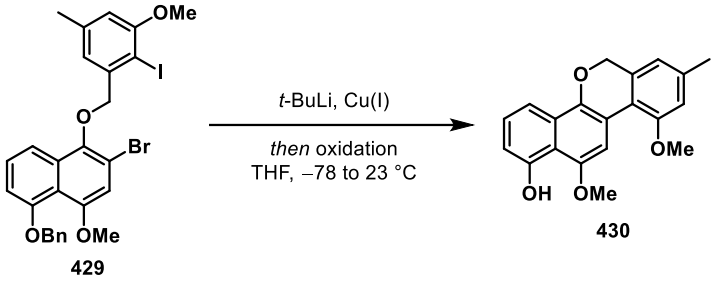


Scheme 55: Successful construction of tetracycle **426** via Lipshutz' oxidative biaryl coupling.

With these promising results in hand we strived for its application to the synthesis of defucogilvocarcin M. Key-intermediate **429** was prepared according to the procedure from chapter 3.2.1 using the above described intermediates **366** and **330.** Ether **429** was then subjected to the same reaction conditions as elaborated for substrate **424** (Table 11). Despite several attempts with slightly varied temperatures and reactions times, we were not able to achieve comparable yields as obtained for substrate **424**. Moreover, we were confronted with observations implying that this reaction is very sensitive to little changes in the protocol, predominantly resulting in diminished yields. These assumptions are supported by the concept of "kinetic higher order cuprates" developed by Lipshutz and co-workers.[199] They describe major changes in behavior of cuprate-based oxidative coupling by simply varying temperature and reaction times. As a result, significantly higher yields could be obtained as a result of only changing the mode of preparing the transient cuprate. Unfortunately, these procedures are only applicable for intermolecular coupling since the two organyl-residues of the resulting cuprate are attached upon different temperatures to the copper reagent, which is not possible in an intramolecular fashion. As a consequence, we were not able to recognize direct coherences between yield and reaction conditions, while yields remained constantly in the range of 30 to 40%. Major challenges occurred during the purification step. The obtained crude product always turned out to be a very complex mixture of innumerable side-products exhibiting the full range of retardation factors on TLC. In addition, *o*-DNB, which was necessarily used in excess, was difficult to remove from the product via silica gel chromatography. Efforts to remove excess of *o*-DNB by sublimation under reduced pressure at elevated temperatures (40 to 50 °C) were successful, however, were accompanied by partial decomposition of

the product. The problem of purification was only overcome by applying two consecutive cycles of silica-chromatography using two different eluent-mixtures (cyclohexane/dichloromethane and cyclohexane/ethyl acetate). Efforts to improve this coupling are ongoing.

Table 11. Screening for the oxidative biaryl coupling developed by Lipshutz.

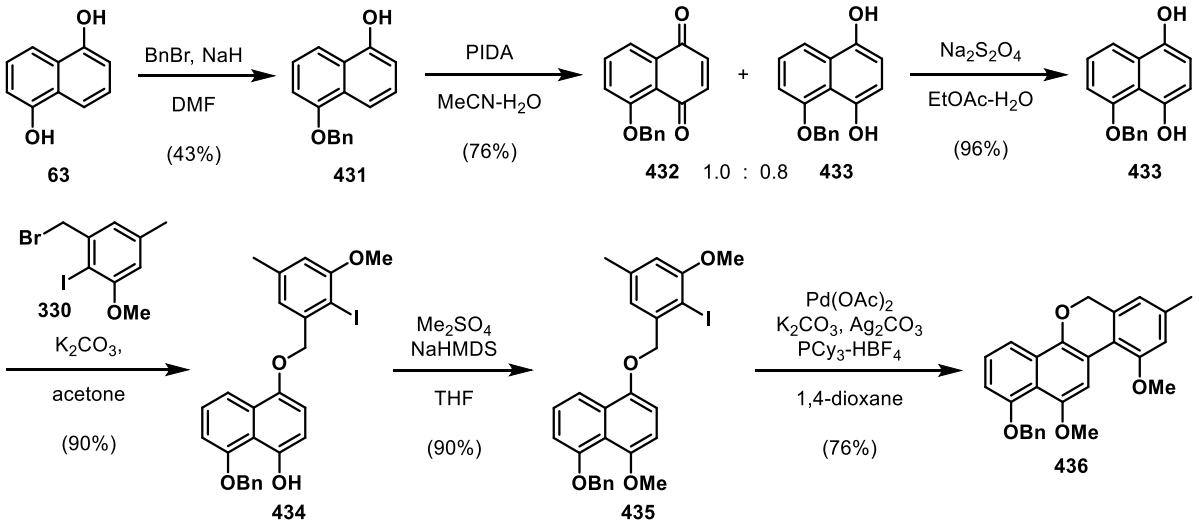


Entry	Preparation of Ar-Li/Li-Ar	Preparation of Ar-Cu(I)-Ar	Oxidation	430
1	*t*-BuLi (11 eq) –78 °C, 1 h	–78 to –25 °C, 1.5 h –40 to –20 °C, 30 min	*o*-DNB (4 eq) –40 to 23 °C, 2.5 h	32%
2	*t*-BuLi (11 eq) –78 °C, 1 h	–78 to –50 °C, 2 h	*o*-DNB (4 eq) –50 to 23 °C, 2 h	38%
3	*t*-BuLi (11 eq) –78 to –60 °C, 40 min	–60 to –25 °C, 1.5 h –40 to 10 °C, 1 h	*o*-DNB (4 eq) –40 to 23 °C, 3.5 h	30%
4	*t*-BuLi (11 eq) –78 °C, 20 min	–78 to –35 °C, 2 h	*o*-DNB (4 eq) –35 to 23 °C, 2 h	18%
5	*t*-BuLi (4.2 eq) –78 °C, 30 min	–78 °C, 2 min –40 °C, 30 min	O_2, –78 °C, 30 min O_2, 0 °C, 1.5 h	0%
6	*t*-BuLi (4.2 eq) –78 °C, 30 min	–78 to –40 °C, 2 h	*o*-DNB (4 eq) –40 to 23 °C, 2 h	25%

3.2.9 Intramolecular Heck Coupling

In parallel to the above described efforts towards the all-carbon tetracycle of the gilvocarcin natural products starting from bromonaphthol **291**, we were interested in the development of a more concise route. Rather than starting from indanones, we envisioned to employ an intramolecular biaryl-coupling to an intermediate prepared from inexpensive 1,5-dihydroxy-naphthalene **63**. As depicted in Scheme 56, we commenced with benzylation of **63**. This reaction revealed limited selectivity with significant amounts of unreacted and dibenzylated naphthalene. For the next step, PIDA-oxidation was employed. Interestingly, an almost equivalent mixture of naphthoquinone **432** and dihydroquinone **433** was observed. Full conversion toward the naphthohydroquinone was ensured by the additional dithionite reduction. A following nucleophilic substitution and methylation gave ether **434** in high yields. After a short screening of conditions, we were able to obtain benzylated tetracycle **436** in 76% upon Heck conditions. Minor amounts of unreacted starting material and proto-dehalogenation were unavoidable,

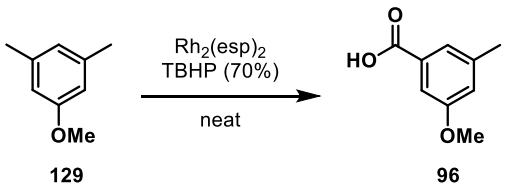
which represented a bothersome issue in terms of purification due to a distinct co-polarity of all three compounds. However, this route was reliable and scalable up to grams and was basis for further functionalization reactions towards the gilvocarcin natural products.



Scheme 56: A scalable alternative route for the construction of the gilvocarcin core-structure.

Based on these finding, we envisioned to develop an even shorter route addressing both, linear sequence and total steps. Bottle-neck of most of the previous aglycone syntheses was a rather lengthy preparation of a 3,5-dimethylanisole-derived benzoate (see chapter 1.2.5). The most commonly used intermediate is 2-iodo-3-methoxy-5-methyl benzoate **83**, which is prepared in four[205] to six[57] steps in a longest linear sequence. Usual procedures would require at least three steps to transform 3,5-dimethylanisole into 3-

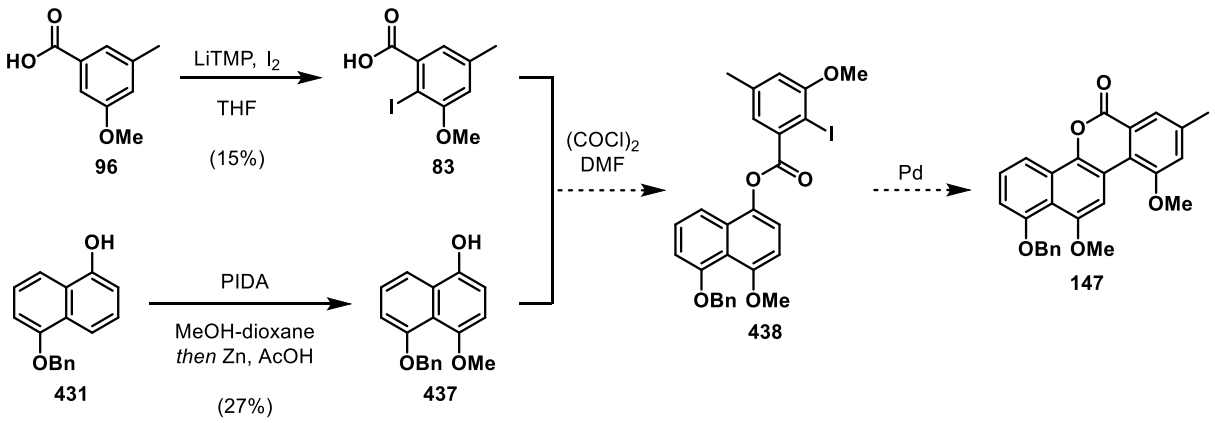
Table 12. Selective benzylic oxidation of 3,5-dimethylanisole using $Rh_2(esp)_2$.



Entry	$Rh_2(esp)_2$	TBHP	Atmosphere	Temperature	Time	SM:P	Yield
1	0.1 mol%	5 eq	argon	0 to 23 °C	24 h	2:1	16%
2	0.1 mol%	5 eq	argon	0 to 23 °C	72 h	1:4	n.d.[a]
3	0.1 mol%	5 eq	air	0 to 23 °C	72 h	1:7	n.d.[a]
4	0.1 mol%	15 eq	air	0 to 23 °C	72 h	1:6	46%
5	0.1 mol%	15 eq	argon	0 to 23 °C	72 h	1:6	47%
6	0.1 mol%	30 eq	argon	0 to 23 °C	72 h	1:100	43%
7	1.0 mol%	7 eq	argon	23 to 60 °C	1.5 h	3:1	16%

[a]n.d. = yield not determined.

methoxy-5-methyl-benzoate (radical benzylic bromination, basic aqueous substitution, oxidation). In the course of our efforts to prepare a suitable intermediate serving as the desired eastern fragment, we found conditions which would allow for the selective mono-oxidation of 3,5-dimethylanisole to common benzoate **96** by applying Wang's $Rh_2(esp)_2$/TBHP-based protocol.[206] The advantage of this transformation is a very low catalyst loading (down to 0.1 mol%) employing solvent-free conditions. Furthermore, the set-up does not require the exclusion of moisture or air and is performed at ambient temperature. A short screening resulted in a reliable yield of 47% on gram-scale. We were not able to isolate any other major side-product, indicating mostly random decomposition events as side-reaction. To the best of our knowledge, we are not aware of any other example of selective mono-oxidation of symmetrical polymethyl-arenes upon rhodium catalysis. Known examples are mainly based on cobalt catalysis but usually need harsh conditions (high temperatures,[207] high pressure,[208] irradiation[209]) or give random mixtures of the corresponding alcohol, aldehyde and carboxylic acid.[210] This achievement set the stage for a concise synthesis of defucogilvocarcin M **147** within four steps (Scheme 57). In a first attempt, direct iodination of the obtained benzoic acid to give fragment **83** was possible, by which the preparation of this commonly used compound was reduced to two steps. Further optimization of the iodination to increase the yield is ongoing. In parallel, main fragment **437** was likewise prepared in two overall steps, again in low yields for the second step. Further investigations will focus on improving both steps. Envisioned esterification with subsequent intramolecular Heck-type coupling are known for a similar substrate rendering the final steps promising.[57]

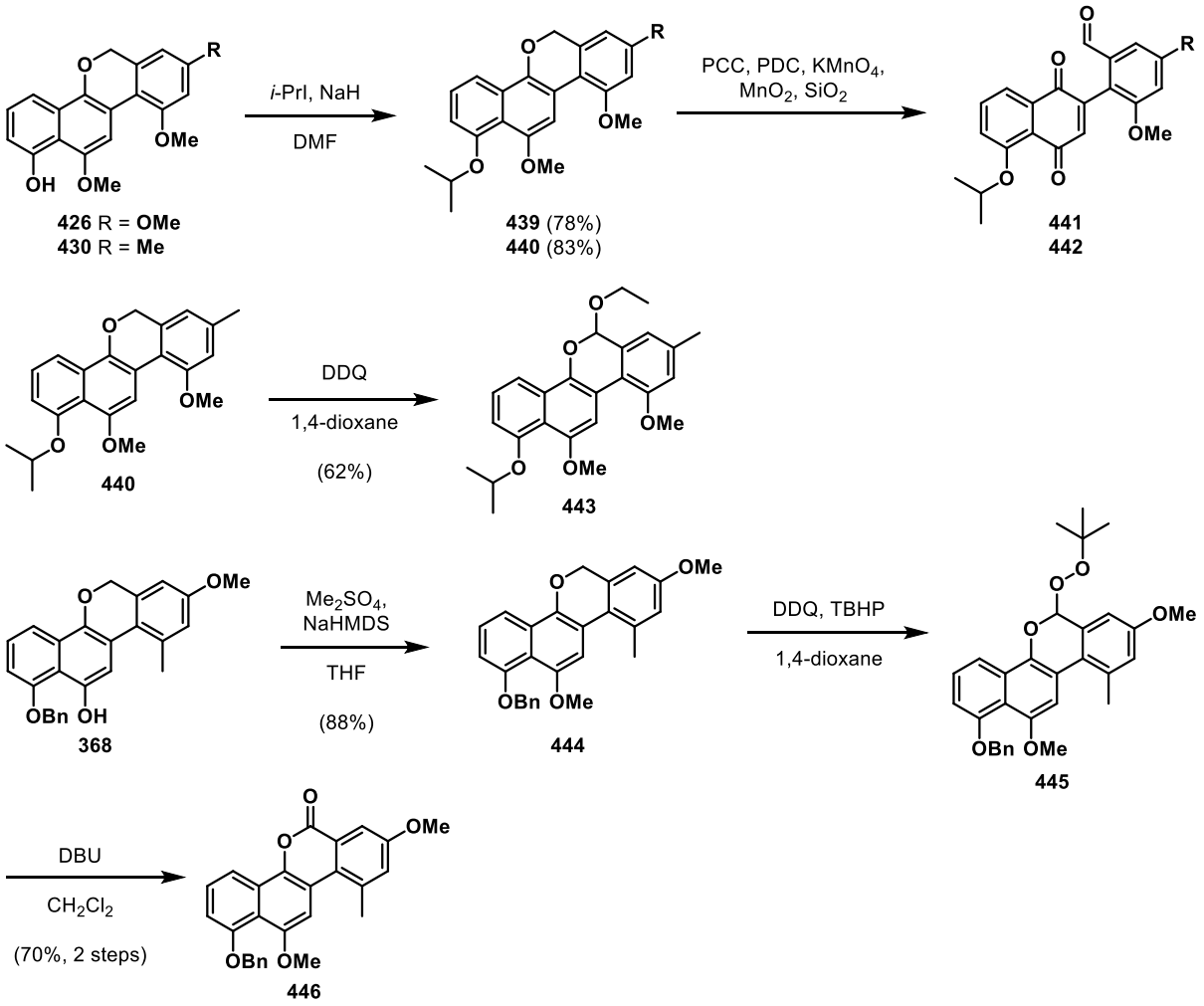


Scheme 57: Envisioned four-step synthesis of benzylated defucogilvocarcin M.

3.2.10 Oxidation of Quinone-based Benzochromenes

Having successfully constructed the all-carbon framework, our next goal was addressing a late-stage oxidation of the chromene core to furnish defucogilvocarcin M. Benzylic oxidation of 2*H*-(benzo)chromenes to their corresponding chromenones are known in literature and usually employ Cr(VI)[211] or Mn(IV)[212] reagents. Reasonable and metal-free alternatives are provided by the groups of Du[213] and Kouznetsov[214] using a combination of *tert*-butyl hydroperoxide and iodine or potassium iodide, while Fan and co-workers[191] could show that this reaction can be performed solely upon

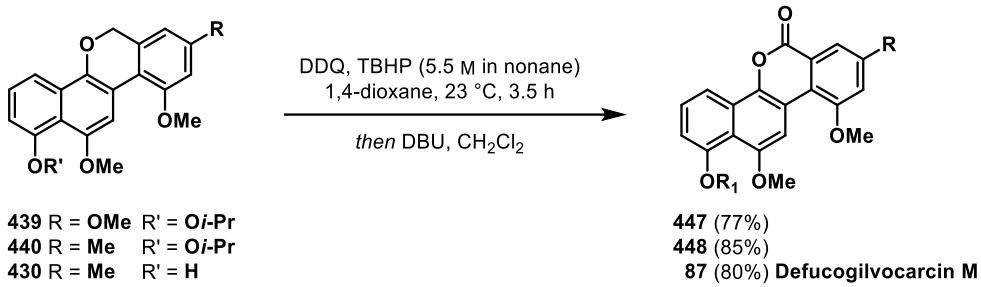
treatment with aqueous H_2O_2 in ethanol at elevated temperatures, however, restricted to a relatively specific type of substrates. A third alternative seen in the literature is the simple employment of DDQ in various solvents.[215] With this selection of possible strategies we approached the final oxidation with previously protecting the free hydroxy-group of tetracycles **439** and **440** (Scheme 58). Unfortunately, attempts using PDC, PCC, MnO_2, $KMnO_4$ and SeO_2 led to overoxidation of the substrates within minutes which afforded the corresponding aldehydes **441** and **442**. We conclude, that this sensitivity might be one reason why examples for the oxidation on quinone-based chromenes are rarely found in literature.



Scheme 58: A combination of DDQ and TBHP enables the selective benzylic oxidation of the chromene core.

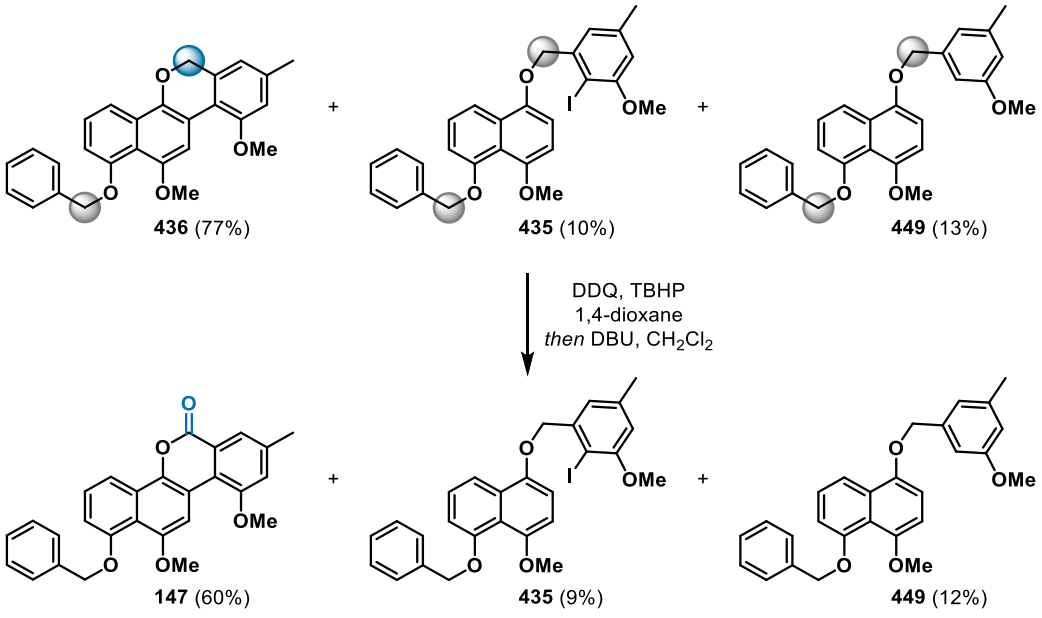
Peroxide-based alternatives only led to no conversion or complex mixtures in our hands. Interestingly, when defucogilvocarcin M precursor **440** was treated with DDQ in 1,4-dioxane we were able to isolate 62% of acetal **443**. According to these results DDQ was sufficient to activate the benzylic position of tetracycle **440** without causing overoxidation. As a result, we considered addition of stoichiometric amounts of TBHP to the mixture as oxygen source. When tetracycle **444** as model substrate was subjected to these conditions, we were able to observe the formation of peroxoacetal **445**, which was of

limited stability upon silica filtration. When this intermediate was treated with DBU in dichloromethane, initiated Kornblum–DeLaMare fragmentation afforded the desired benzochromenone **446** in 70% yield.



Scheme 59: One-pot oxidation–elimination of different defucogilvocarcin M derivatives.

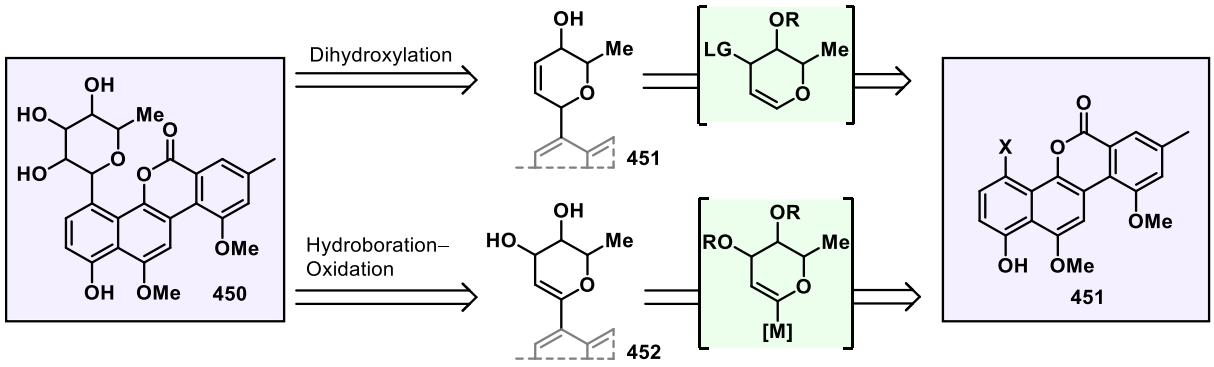
To our delight, these two steps could be combined to enable a one-pot reaction as seen for substrates **439** and **440** (Scheme 59). In addition, we found, that the free hydroxy group of tetracycle **430** was tolerated by these conditions affording defucogilvocarcin M in 80% yield. Another advantage of this procedure was found when the above-mentioned product mixture (see chapter 3.2.9, Scheme 56) consisting of **436**, starting material **435** and its dehalogenated side-product **449** was subjected to these conditions (Scheme 60). Among six different oxidizable benzylic positions, only the desired one was susceptible to oxidation, resulting in almost quantitative recovery of the former starting material **435** and side-product **449**. Moreover, this facilitated the above-mentioned challenging purification of the desired product **436**. In summary, we found a mild, selective and metal-free oxidation protocol for quinone-based and non-quinone-based chromenes to their corresponding chromenones.



Scheme 60: Selective oxidation of benzochromenes in the presence of several benzylic positions.

3.3 Glycal-based Late-Stage Glycosylation

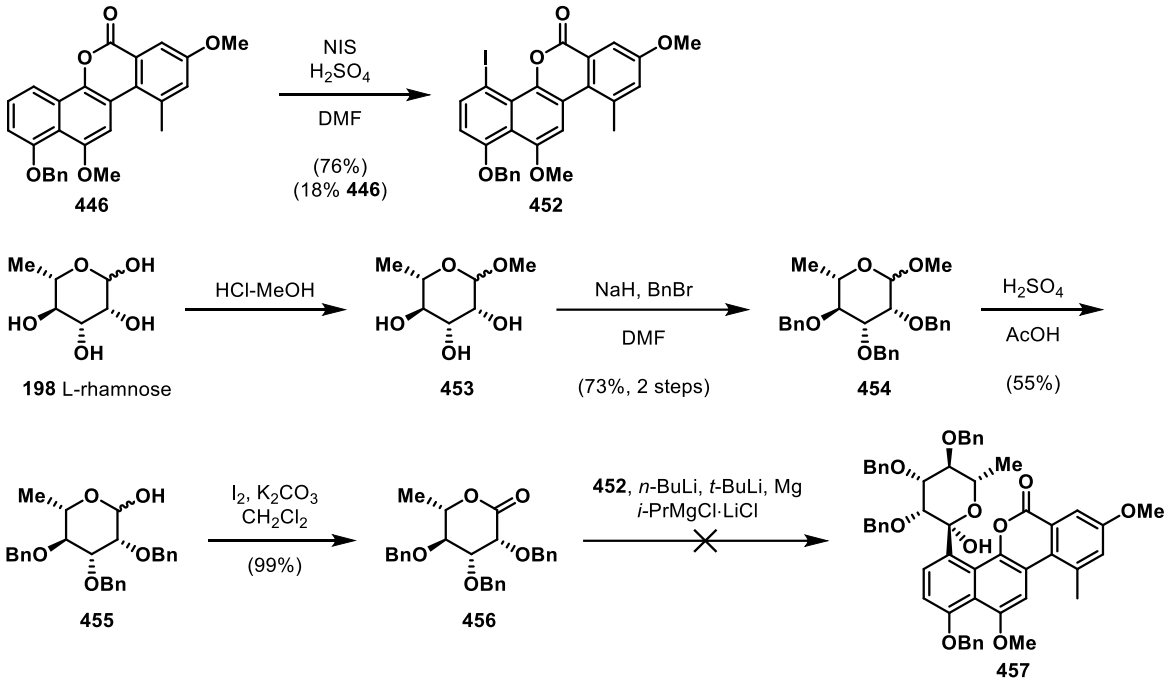
Having successfully synthesized defucogilvocarcin M and derivatives **447** and **448**, we were prompted to approach a late-stage glycosylation. In comparison to the numerous syntheses of the aglycones, synthetic efforts towards the glycosylated gilvocarcins remain rare (see chapter 1.2.6). Strategies are usually based on an early-stage glycosylation with subsequent construction of the aromatic core structure. In the course of our efforts towards the synthesis of the gilvocarincs, Lei reported the first example for a late-stage glycosylation to furnish members of this natural product family.[69,70] The advantage of this strategy is a reduced longest-linear sequence due to pre-construction of the sugar moiety. In addition, no special pre-functionalization of the sugar or the aglycone were needed. However, their results show limitations with reagrds to regio- and diastereoselectivities, as well as moderate yields requiring an excess of the valuable aglycones (sugar 1:3 aglycone). Based on these results, we envisioned a strategy which would not only face the challenges of regio- and diastereoselectivities but also enable a divergent approach towards the different gilvocarcin natural products. We considered glycals (dihydropyranes) to be a valuable and readily available source of glycoside-precursors with useful reactivities (Scheme 61). Retrosynthetically, two possible adducts, **451** and **452** could serve as



Scheme 61: Strategies for a glycal-based late-stage glycosylation of gilvocarcin natural products.

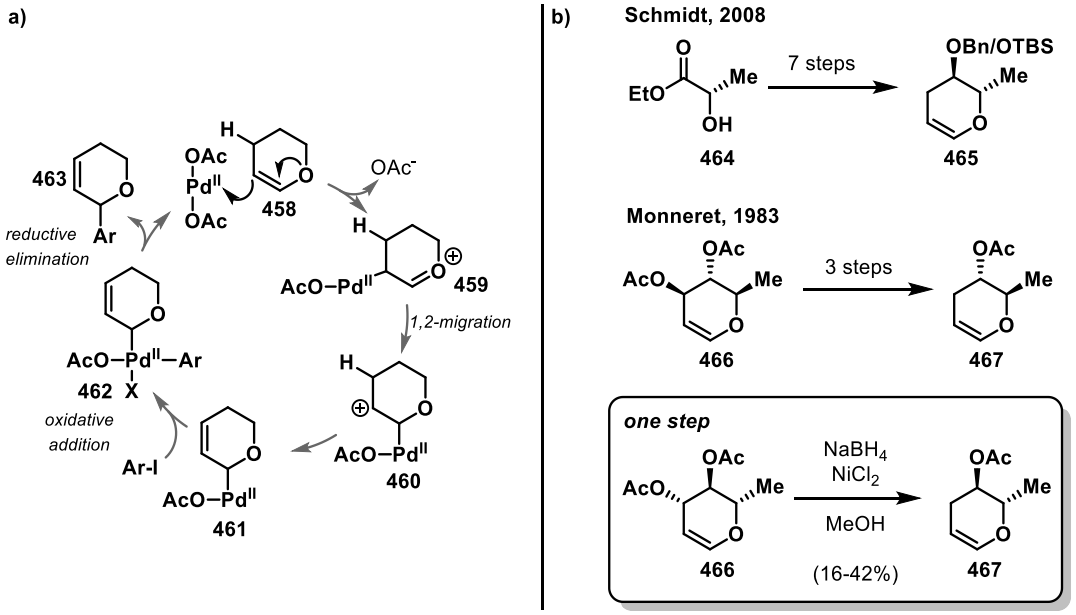
highly functionalizable intermediates, based on pre-functionalization of the aglycone. While **451** was planned to be prepared by Tsuji–Trost- or Ferrier-type conditions, **452** could result from cross-coupling or nucleophilic attack into a gluconolactone with subsequent water elimination.

Beginning with the selective pre-functionalization of aglycone **452** as model substrate, we recognized the need for a (sterically demanding) protecting group to induce selective halogenation in *para*-position, otherwise *ortho*-halogenation was preferred (Scheme 62). We commenced with approaching a stepwise glycosylation implicating the addition into a suitable gluconolactone with subsequent acetal reduction using Et_3SiH and $BF_3 \cdot OEt_2$. Preparation of **456** was achieved in four steps starting from L-rhamnose, however attempts towards a nucleophilic addition via lithiation or Grignard-formation were unsuccessful, presumably due to a failed activation of the iodide in proximity to the lactone.[216]



Scheme 62: Failed attempt for a late-stage glycosylation based on the nucleophilic addition to lactone **456**.

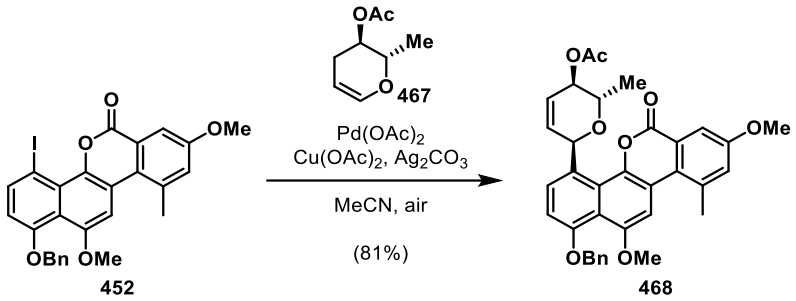
We changed our strategy and aimed for Pd-catalyzed couplings with unfunctionalized dihydropyranes. When Tsuji–Trost-[217] and Ferrier-type[218] conditions on substrate **466** (with Lewis acid- or Pd(II)-employment) turned out to be unpromising, we considered employing conditions developed by Ye *et al*.[21] The group reported a Pd(II)-catalyzed Heck-type coupling with isomerization of the dihydropyrane double-bond, a mechanism proposed by the group of Kapur (Scheme 63, a).[219] For that



Scheme 63: One-step preparation of desired glycal **467**.

purpose, furnishing of deoxy-dihydropyran **467** was required. Known strategies towards this compound are either lengthy in steps (Schmidt)[220], or were of limited reproducibility in our hands (Monneret).[221] However, when employing Yin's protocol on commercially available glycal **466**, we obtained the

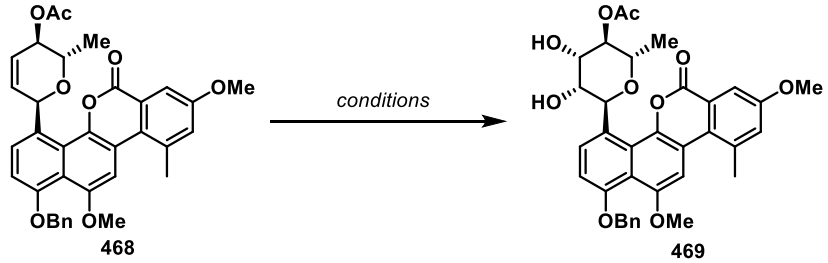
desired deoxygenated precursor in a single step (Scheme 63, b).[222] Due to the volatility of the product, careful handling during work-up and purification was required, however, isolated product yields could only be obtained in a range between 16% and 42%. The stage was set for the anticipated coupling. We were delighted to see that product **468** was formed in 81% yield as single diastereomer (Scheme 64).



Scheme 64: Diastereoselective glycal coupling on *iso*-defucogilvocarcin M.

The *anti*-conformation between the pyrane's methyl group and the aglycone (confirmed by NOE-spectra) guided our efforts towards the synthesis of the polycarcins. Even with the critical coupling accomplished, serious issues remained to be overcome. Seemingly straightforward dihydroxylation turned out to be very challenging (Table 13). Several variations of OsO_4-catalyzed oxidations, as well as employment of $RuCl_3$-based conditions remained unfruitful. In parallel, we were able to prepare

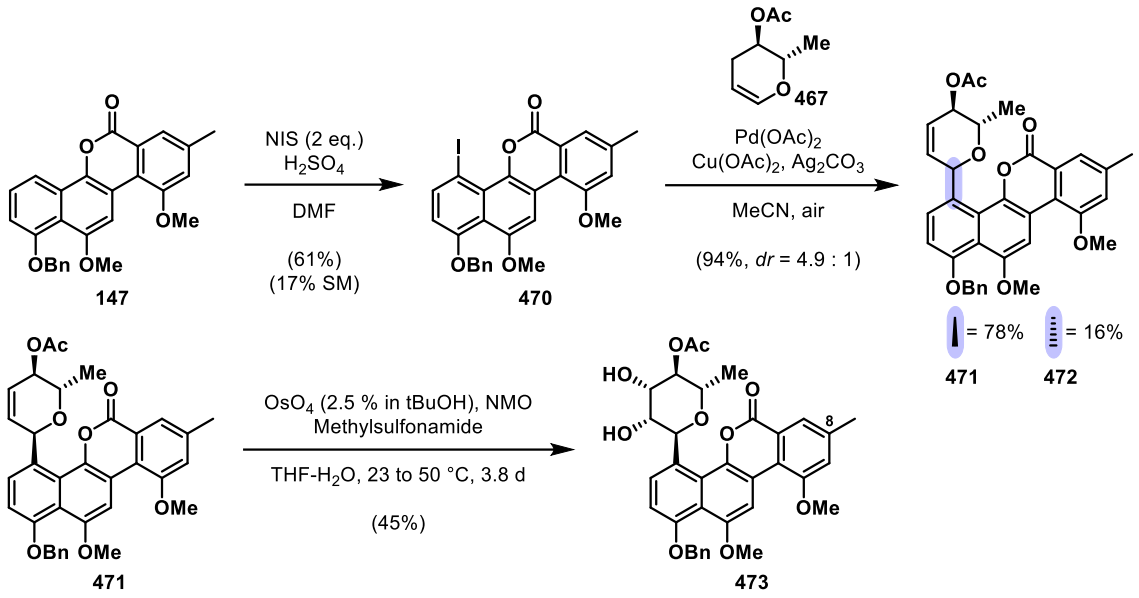
Table 13. Failed dihydroxylation towards *iso*-polycarcin M.



Entry	Oxidant	Co-oxidant	Additive	Solvent	Temp	Time	Result
1	OsO_4 (in H_2O)	NMO (solid)	DABCO	acetone-H_2O	23 °C	3 d	mostly SM
2	OsO_4 (in H_2O)	NMO (in H_2O)	DABCO	acetone-H_2O	90 °C	5 d	decomposition
3	OsO_4 (in *t*-BuOH)	-	-	acetone	23 °C	2 d	decomposition
4	OsO_4 (solid)	-	-	CH_2Cl_2	23 °C	5 h	mostly SM
5	$RuCl_3$	$NaIO_4$	argon	EtOAc-MeCN-H_2O	23 °C	13 h	mostly SM

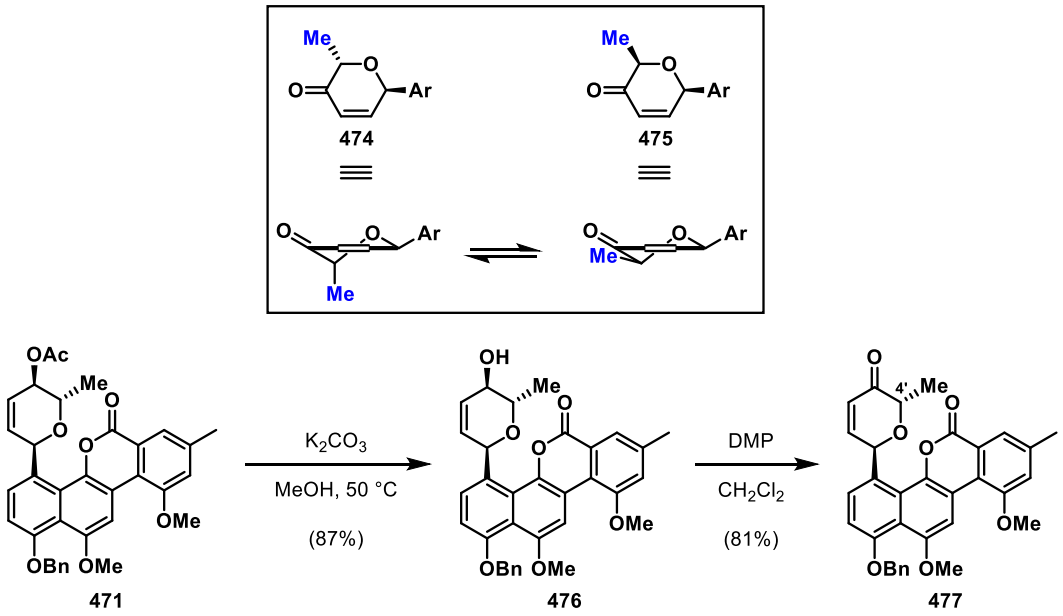
sufficient amounts of benzylated defucogilvocarcin M moving away from model substrate **446**. Despite the seemingly miniscule variation between *iso*-defucogilvocarcin M **446** and defucogilvocarcin M **147**, the following steps revealed certain differences in yield and selectivity. Iodination showed a significant drop in yield affording 61% of the desired product with 17% isolation of starting material (Scheme 65).

The latter was unavoidable, since longer reaction times or increased amounts of sulfuric acid and *N*-iodosuccinimide led to decomposition via oxidation of the substrate. In addition, we were surprised to obtain a mixture of two diastereomers (4.9 : 1), which was not observed for the coupling of **452**.



Scheme 65: Successful preparation of protected polycarcin M.

Separation of both diastereomers **471** and **472** was possible by conventional silica column chromatography. We were delighted to see, that the envisioned dihydroxylation was realizable when methylsulfonamide was used as additive. The desired diol was isolated in 45% yield while NMR-analysis indicated additional formation of two further products in presumably 18% and 10% (NMR-

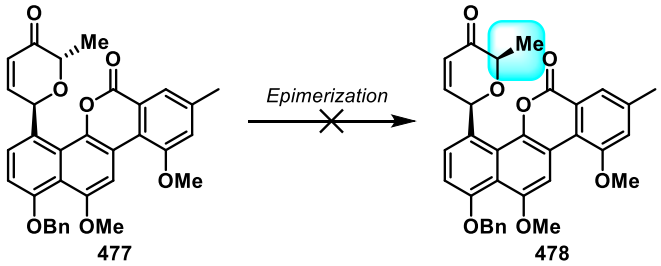


Scheme 66: Preparation of precursor **477** for an anticipated late-stage epimerization.

yield) of which both could not be isolated or characterized. Although, product **473** confirms the successful development of a general strategy towards the polycarcin core structure, further studies on

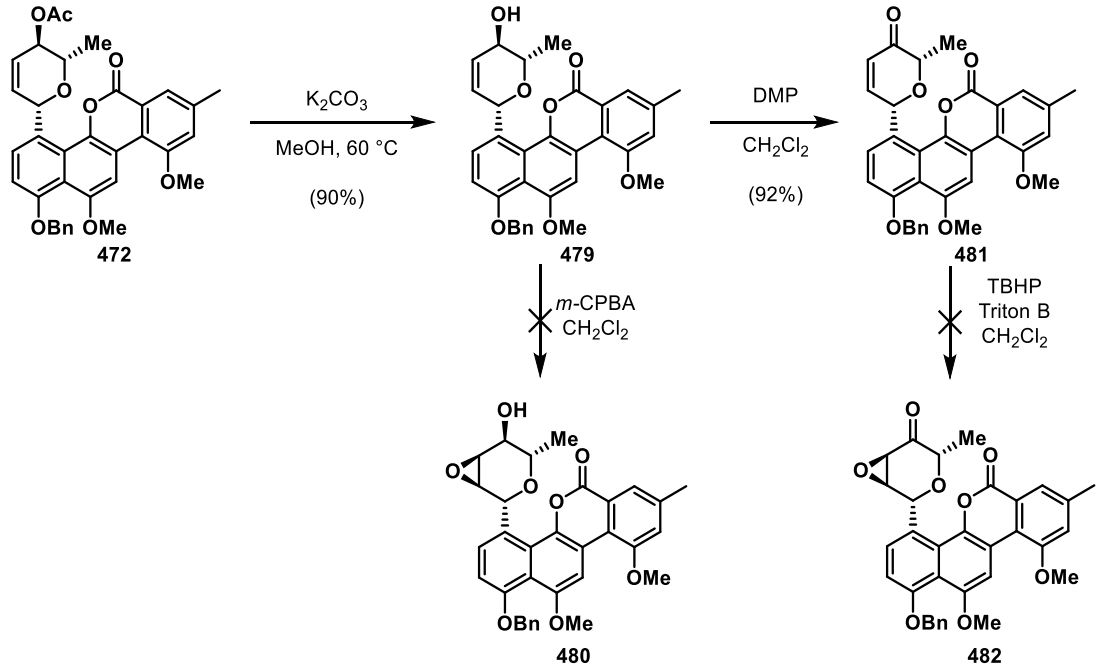
the C8-methyl derivative (**473**) to synthesize polycarcin M were discontinued. Despite the natural occurrence of a C8-methyl analogue among any of the known gilvocarcin sub-groups (e.g. gilvocarcin M, ravidomycin M, chrysomycin M) polycarcin M is the only representative do date, which has not been isolated naturally, but only as a metabolite of genetically modified strains of *Streptomyces lividans*, for which the corresponding authors do not provide analytical data.[223] As a consequence, we took the path towards our envisioned divergent route. Inversion of the pyrane-C4'-methyl-group represents the centerpiece of this concept and would open the door for approaching chrysomycins and ravidomycins in parallel to the polycarcins. Based on considerations regarding the spatial orientation of the attached dihydropyrane, we planned to transform the allylic alcohol into its enone-form generating α-acidity at C4' (Scheme 66), which then might be inverted to obtain diastereomer **478** upon treatment with basic or slightly acidic conditions. Two steps including deprotection and oxidation afforded enone **477** in good yields and paved the way for the envisioned epimerization. Extensive screening of bases met with failure showing either remained starting material or decomposition (Table 14). Nevertheless, we were prompted

Table 14. Failed attempts to accomplish epimerization.



Entry	Base	Solvent	Temp	Time	Quench	Result
1	NEt_3	CH_2Cl_2	23 to 40 °C	2 h	H_2O	mostly SM
2	DBU	CH_2Cl_2	23 to 40 °C	2 h	H_2O	SM + decomposition
3	LiHMDS	THF	23 °C	15 min	H_2O	decomposition
4	LiHMDS	THF	–78 °C	10 min	MeOH-d_4	decomposition
5	NaOH	MeOH	50 °C	45 min	-	decomposition
6	NaOMe	MeOH	50 °C	1 h	-	decomposition
7	NaOMe	MeOH-CH_2Cl_2	23 °C	10 min	-	decomposition
8	silica gel	$CDCl_3$	23 °C	3 d	-	mostly SM

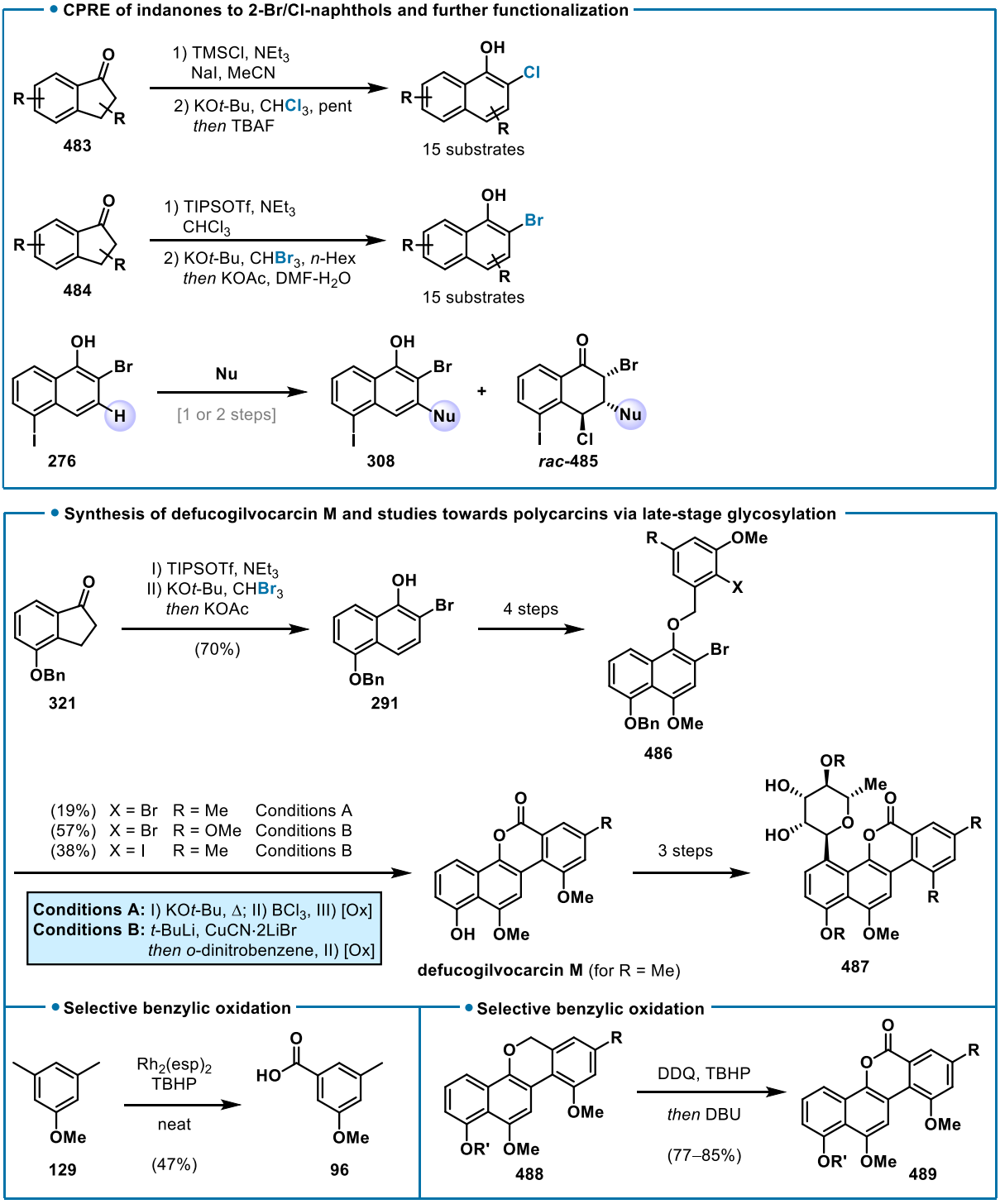
to investigate the further functionalization of epimer **478** towards the chrysomycins and ravidomycins. For that purpose, undesired coupling product **472** (see Scheme 65) was subjected to the same conditions as **471** affording **481** (Scheme 67), which represents the enantiomer of previously anticipated **478**. First attempts to epoxidize enone **481** or alcohol **479** using *m*-CPBA or TBHP failed, however, are still part of our ongoing work.



Scheme 67: Attempts for a late-stage oxidation towards chrysomycins and ravidomycins.

4. Summary and Outlook

In summary, we developed a two-step-methodology to synthesize 2-chloro- and 2-bromonaphthol starting from readily available indanones (Scheme 68). A broad scope of 30 substrates was established showing that the reaction conditions are compatible with halogens, esters, ethers, acetals, aryls and alkyls. In this context, we found a dearomative chlorination of 2-bromo-5-iodonaphthol upon NCS treatment, which was exploited for selective *meta*-functionalization of this substrate. Furthermore, the initial preparation of 2-halonaphthols was used as entry point for investigations towards the total

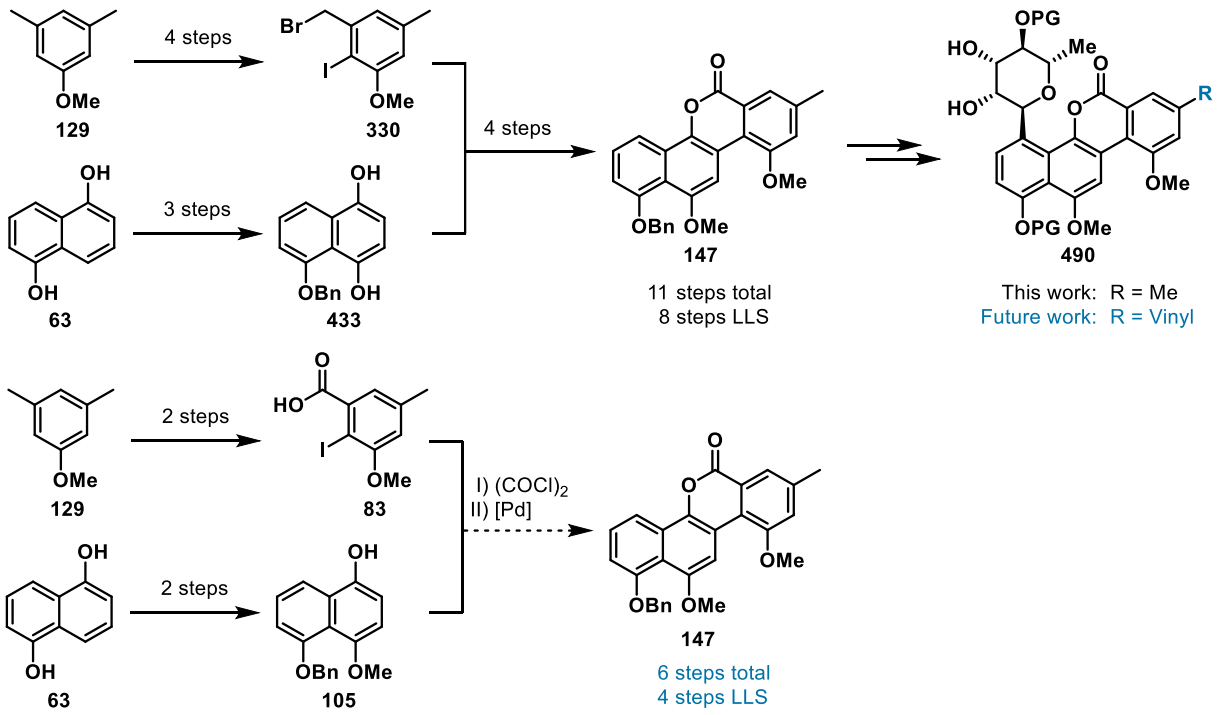


Scheme 68: Summary of the results discussed in this thesis.

synthesis of gilvocarcin natural products. We could demonstrate its applicability by synthesizing defucogilvocarcin M. Key-step of this synthesis is a Cu(II)-mediated oxidative biaryl-coupling according to the conditions of Lipshutz and Schreiber. Furthermore, studies towards the realization of gilvocarcin M generated a one-step synthesis of benzoic acid **96**, a crucial intermediate used in more than six total syntheses and further studies, which was previously prepared in three to six steps. In addition, a mild and chemoselective protocol to oxidize 2*H*-chromenes to afford the corresponding chromenones was developed, which appeared very useful for the oxidation of sensitive dihydroquinone-based chromenes. Finally, highly advanced intermediates towards the synthesis of glycosylated chrysomycins, ravidomycins and polycarcins were obtained by late-stage Heck-type-coupling using readily available desoxyglucal **467**. The coupling afforded high yields with good diastereoselectivities and is insensitive towards moisture or air.

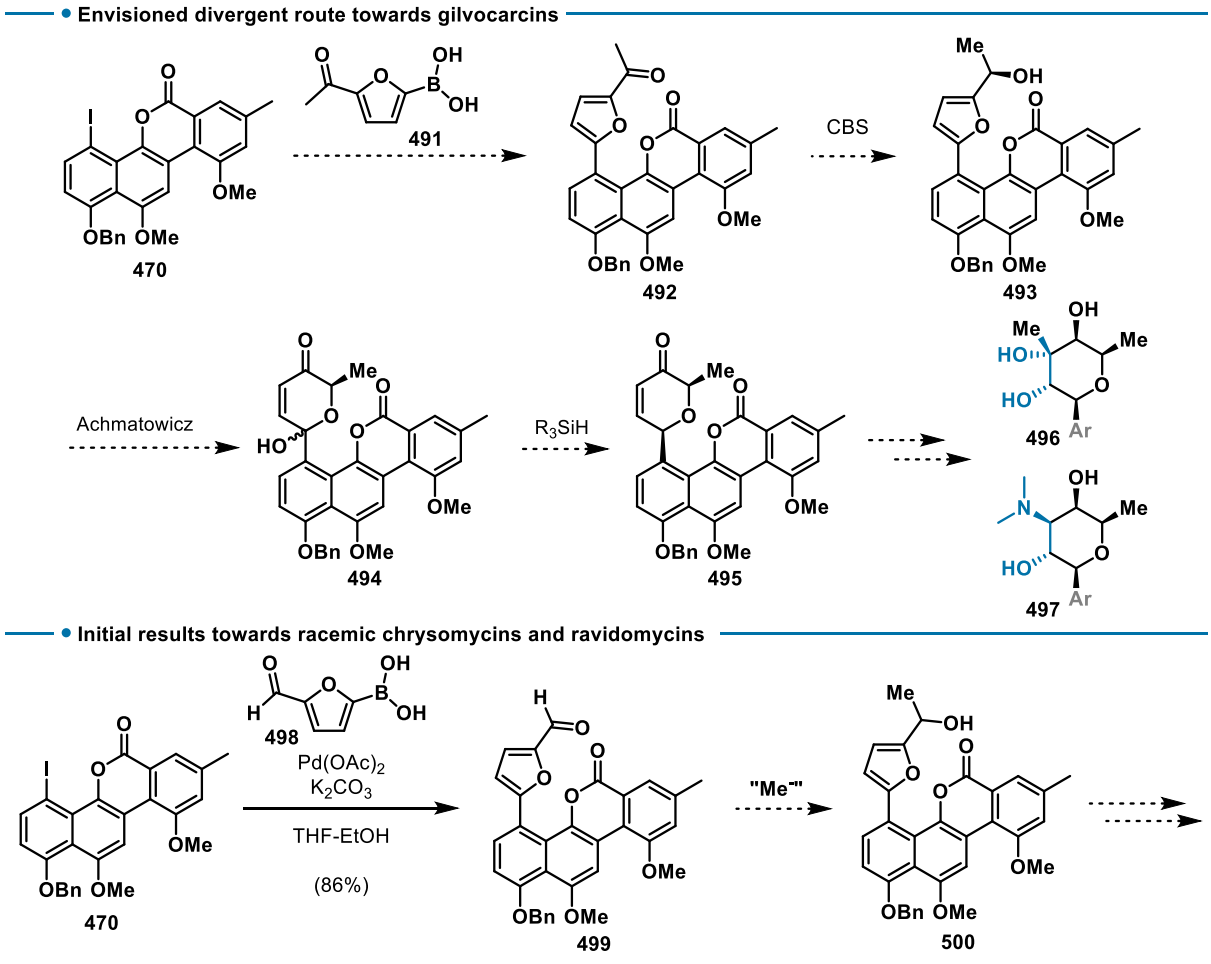
Outlook

Future studies will be directed towards the generality of the *meta*-functionalization of **276** and its derivatives. Apart from further variations of the nucleophiles, we plan to investigate the role of the *ortho*-bromide and moreover the necessity of the iodide in the *ipso*-position. Assuming that the iodide promotes the ketonization by steric effects, it would be worthwhile to replace it by different sterically demanding groups with limited activating properties like *tert*-butyl or phenyl-groups. Another question would tackle the observed halogen-shuffle upon $SnCl_4$-catalysis, which might be suppressed by using $SnBr_4$ and thereby clarify if the chloride emerged from the Lewis acid or *N*-chlorosuccinimide. Based on the successful formation of biaryl **308** by this strategy, an enantioselective alternative towards axially chiral biaryls would be desirable.



Scheme 69: Envisioned synthesis of polycarcin V and 4-steps synthesis of aglycone **147**.

Regarding the total synthesis of gilvocarcins, promising results have been obtained for the development of a four-step-synthesis of protected defucogilvocarcin M **147** (Scheme 69). The subsequent glycosylation was shown to be applicable for the synthesis of intermediate **490** towards polycarcin M. Following this, modification of the route to obtain the biologically more active polycarcin V will be considered. Ongoing efforts cope with an Achmatowicz-reaction-based preparation of intermediate **493**, which would allow for the preparation of the chrysomycins, as well as the ravidomycins upon further functionalization (Scheme 70). While the initial plan includes an enantioselective CBS-reduction of ketone **492**, we commenced with a racemic route. Several studies addressed the biological activity based on modifications of the aglycone, however, investigations based on variations of the sugar moiety are scarce. We hope that development of a divergent route will allow for the preparation of a broad substrate libraries regarding the sugar moiety, and thereby leading to a deeper insight into the role of the attached sugar.



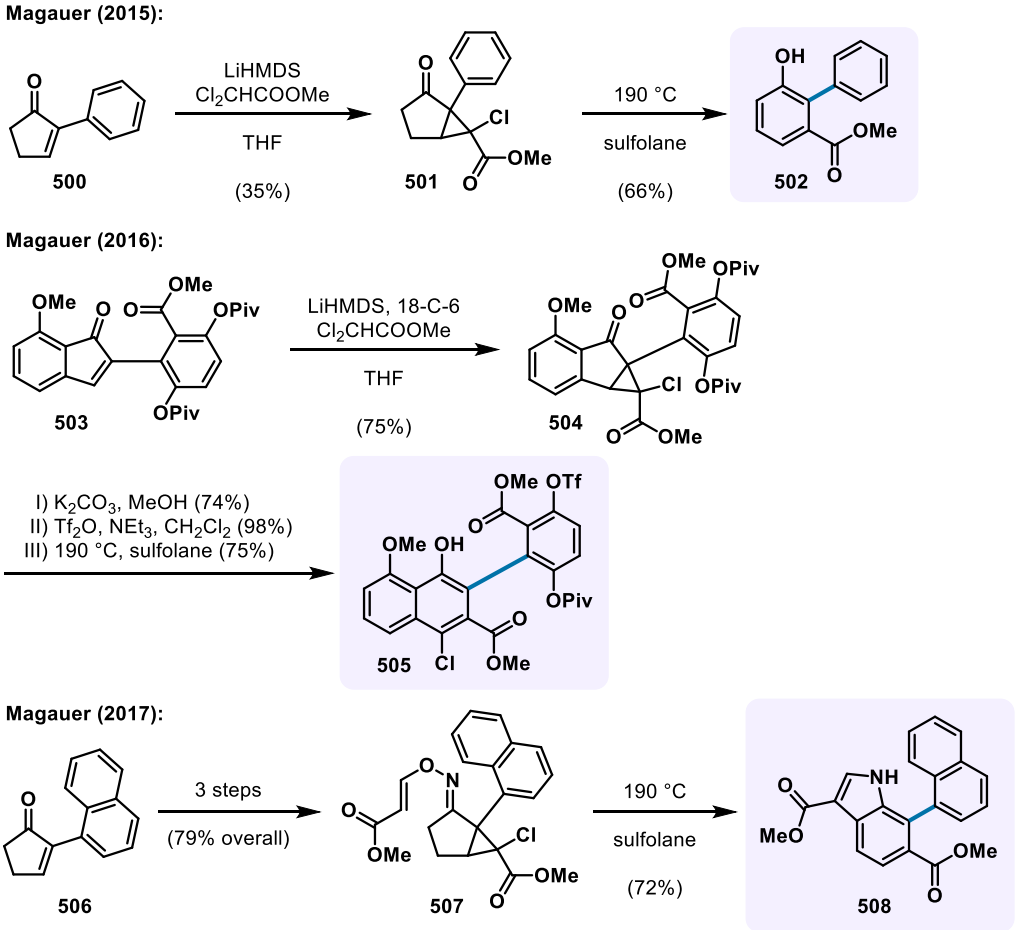
Scheme 70: An Achmatowicz-reaction-based approach towards chrysomycins and gilvocarcins.

PART II

Studies Toward the Synthesis of Axially Chiral Biaryls

5. Introduction and Previous Efforts

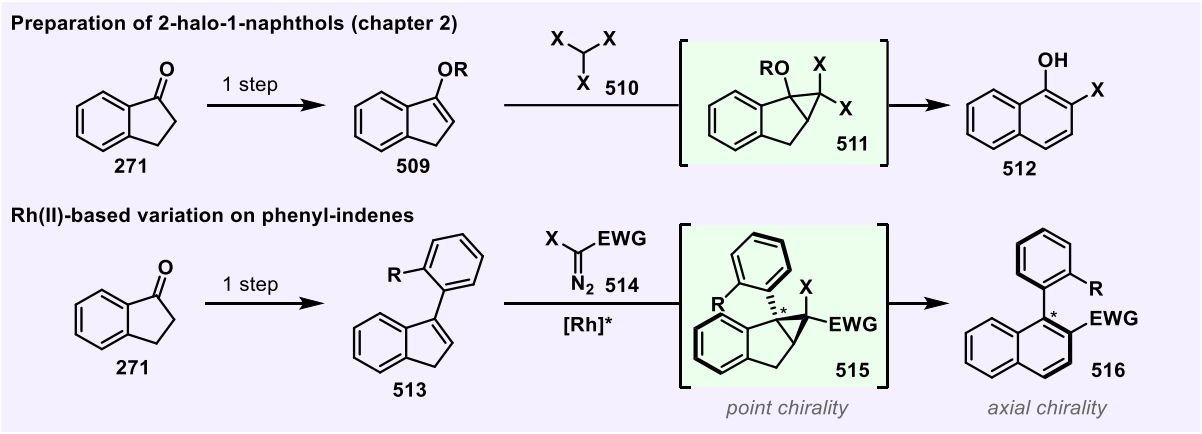
The development of a cyclopropanation–ring-expansion (CPRE) strategy for indanones to obtain naphthalenes prompted us to seek for a modified protocol to approach the enantioselective synthesis of axially chiral biarlys. Previous works on CPRE-reactions in our group have constructed racemic biaryls starting from cyclopentenones (Scheme 71).[154] Biphenyls (**502**) were obtained in good yields, while tetra-substituted naphthyl-phenyls (**504**) were likewise accessible.[155] Further developments led to the construction of hetero-biaryls based on indoles with comparable good yields.[224] These results paved the way for an enantioselective protocol in our group, based on the same strategy. So far, studies have resulted in the successful formation of an enantio-enriched tetra-substituted biaryl, however, the initial stereoinformation still emerges from a previous enzymatic resolution step.[225] Furthermore, this enrichment is reduced from >99% *ee* to 56% *ee* during the ring-expansion, which proceeds at 180 °C. These high temperatures are detrimental for the *ee* and have to be overcome in order to obtain higher



Scheme 71: Strategies developed in this group to furnish racemic biaryls via CPRE.

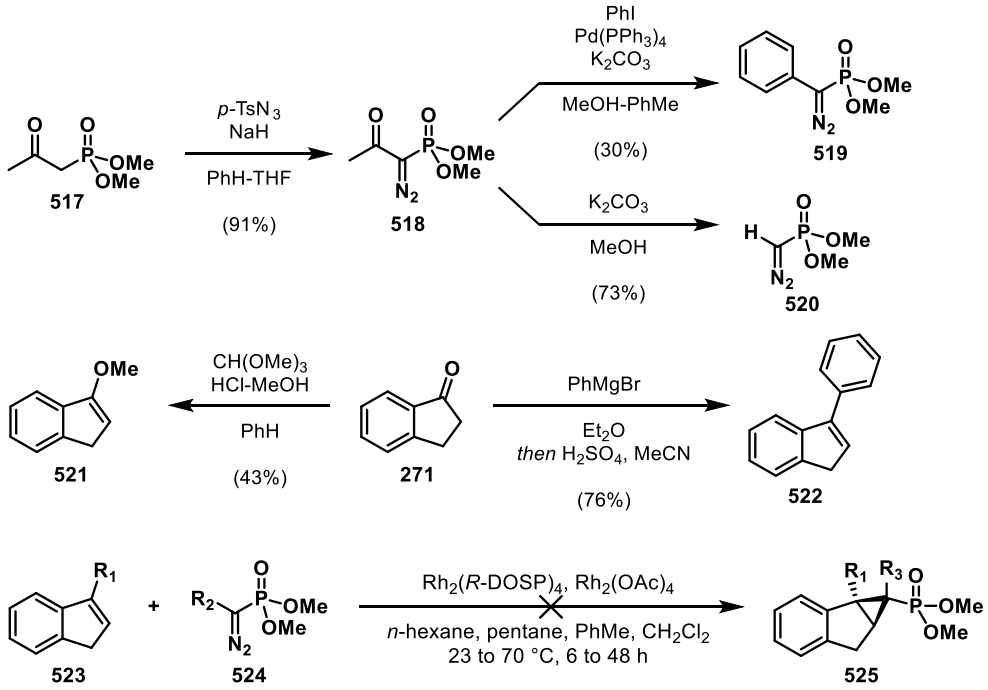
selectivity. In parallel to these ongoing efforts in our laboratories, we envisioned another approach to axially chiral biaryls via a rhodium-catalyzed cyclopropanation of indenes upon milder conditions (Scheme 72). This strategy would also address the reduction of overall steps for the preparation of the starting materials, since our current efforts rely on substrates, which are made in more than seven steps.

6. Results and Discussion



Scheme 72: General idea of a Rh(II)-catalyzed enantioselective cyclopropanation of aryl-indenes to approach an enantioselective preparation of axially chiral biaryls (EWG = phosphonate, carboxylate, sulfonate).

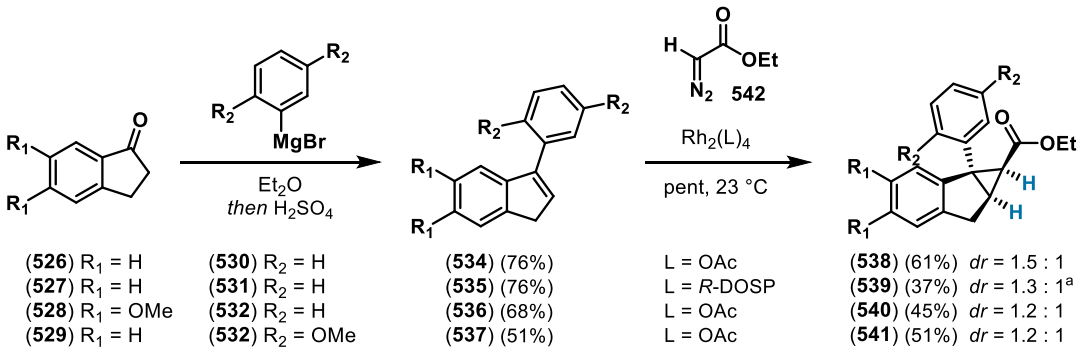
Scheme 72 demonstrates the analogy of our elaborated methodology towards 2-bromonaphthols and an envisioned modification to obtain axially chiral biaryls. Rhodium-catalyzed enantioselective cyclopropanation of alkenes are well studied and have found diverse applications in organic chemistry.[226–228] Despite the challenges of applying these protocols to sterically demanding alkenes,[229] examples to construct poly-arylated cyclopropanes have been reported with good selectivities and yields.[227,230] For reasons of stability and preparation, the employed diazo-substrates are usually found in combination with adjacent electron-withdrawing groups, which are diverse in nature and can be based on esters[231], sulfonates[228] or phosphonates[227]. Apart from prevailing examples for intermolecular reactions, intramolecular variations are also known.[232] Our plan would needs to address the challenges of an enantioselective cyclopopanating of sterically demanding alkenes and the transfer of point to axial



Scheme 73: Failed attempts for cyclopropanation using diazophosphonates.

chirality.[233] Indenes **513** are readily available from simple indanones in one step via condensation of aryl-Grignard substrates. Generation of halo-cyclopropane **515** could be realized in either one step by an *in-situ* formation of diazo-halide **514** with subsequent cylopropanation or in a two-step manner by post-halogenation of the afforded cyclopropane. In both cases, spontaneous ring-expansion upon halide elimination is anticipated similar to our developed methodology (see chapter 2).

Among the variety of different diazo-compounds, our first choice was the construction of phosphonates **519** and **520**, while indenes **521** and **522** would serve as model substrates (Scheme 73). Unfortunately, both strategies have met with failure leading to either isolation of starting material or slow decomposition with decreased temperatures and reaction times. However, when moving from phosphonate-based diazo-substrates to ethyl diazoacetate (**542**), we observed yields between 45% and 61% on several substrates with rhodium(II) acetate as the catalyst (Scheme 74). Unsubstituted phenylindene **534** underwent cyclopropanation with 1.5 : 1 diastereoselectivity in favor of the *cis*-product (relation intecated with the protons in blue), while slightly lower selectivity was observed for methoxylated derivatives **528** and **529**. Comparable diastereoselectivity was achieved with the achiral catalyst Rh_2(*R*-DOSP)$_4$, but in lower yields. In order to confirm this strategy's general viability prior to its selectivity, diastereomeric as well as enantiomeric outcome has been left to chance during the following studies without optimization of the cyclopropanation step. Since attempts to install the

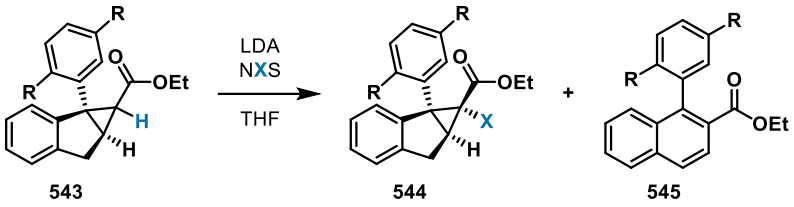


Scheme 74: Successful cyclopropanation of phenyl-indenes using ethyl diazo acetate and $Rh_2(OAc)_4$. [a]no enantioselectivity was observed.

halogen onto the afforded cylopropane in a one-pot fashion failed, a post-halogenation was needed. The halogenation was tested on substrates with and without *ortho*-substitution and with different diastereomeric purities (Table 15). In addition, the compatibility with various halogens was investigated. Isolation of unreacted starting material indicates a sterically demanding environment around the carbon-atom of interest, however, synthetically relevant amounts of the desired halogenated products could be obtained (Entries 1–3). These steric considerations are underpinned by the correlation between the diastereomeric ratio and the size of the halogen used with a *dr* up to 11.3 : 1 in favor of the *cis*-product (relation intecated with the protons in blue). While no spontaneous ring-expansion was observed for chloro- and bromo-**544**, iodination of **543** resulted in formation of biaryl **545** in 32% yield accompanied by remained iodo-cyclopropane **544** in 26% yield at ambient temperature. With these encouraging results in hand, we applied the same conditions to *ortho*-substituted cyclopropanes **543** (Entries 4–6).

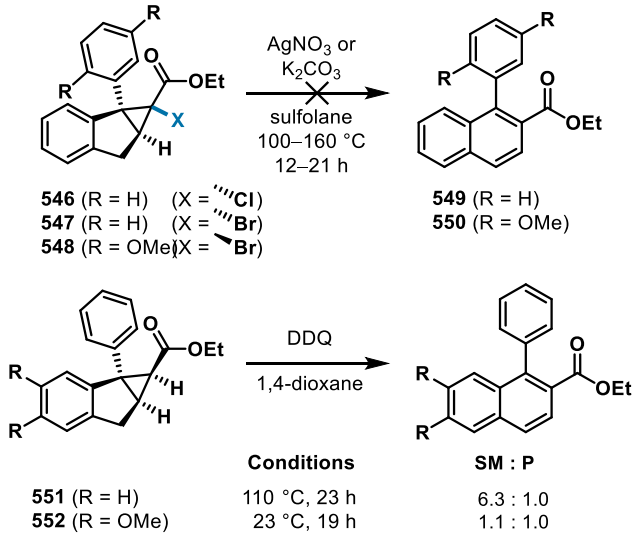
While chlorination and bromination resulted in comparable yields, major differences have been observed with regards to diastereoselectivity. Only traces of both *cis*-products were detected by NMR

Table 15. Halogenation of cyclopropanes **543**.



Entry	R =	*cis:trans* (543)	X =	recovered 543	544	*cis:trans* (544)	545
1	H	1.3 : 1	Cl	49%	**33%**	2.7 : 1	**0%**
2	H	1.3 : 1	Br	57%	**29%**	8.7 : 1	**0%**
3	H	7.3 : 1	I	26%	**37%**	11.3 : 1	**32%**
4	OMe	99 : 1	Cl	59%	**21%**	1 : 99	**0%**
5	OMe	99 : 1	Br	43%	**39%**	1 : 99	**0%**
6	OMe	1 : 99	I	>90%	**0%**	-	**0%**

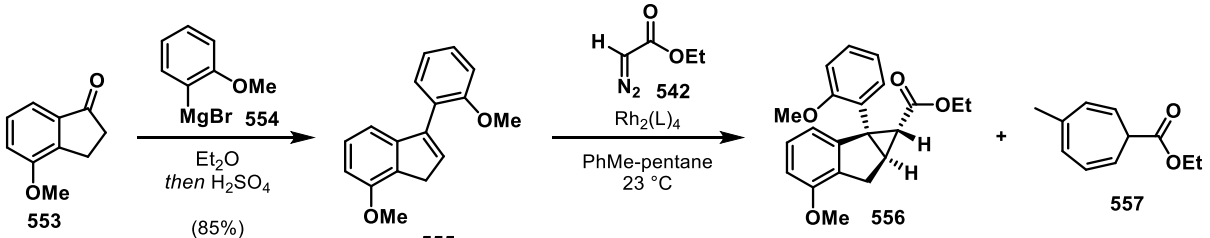
and only pure *trans*-products of **544** could be isolated. Again, no spontaneous ring-expansion took place. Moreover, iodination resulted solely in isolation of the starting material without altered diastereomeric ratio. It still has to be clarified if deprotonation of the *trans*-cyclopropane is slower than the *cis*-cyclopropane. With sufficient amounts of chloro-and bromo-**544** in hand we tested the feasibility of the anticipated ring-expansion towards *ortho*-substituted biaryls **549** and **550** (Scheme 75). We were



Scheme 75: Studies on the ring-expansion of halogenated cyclopropanes **546–548**.

surprised to see that temperatures of up to 160 °C and employment of additives like silver-salts or mild bases did not induce the ring-expansion. Only either unreacted starting material or decomposition were

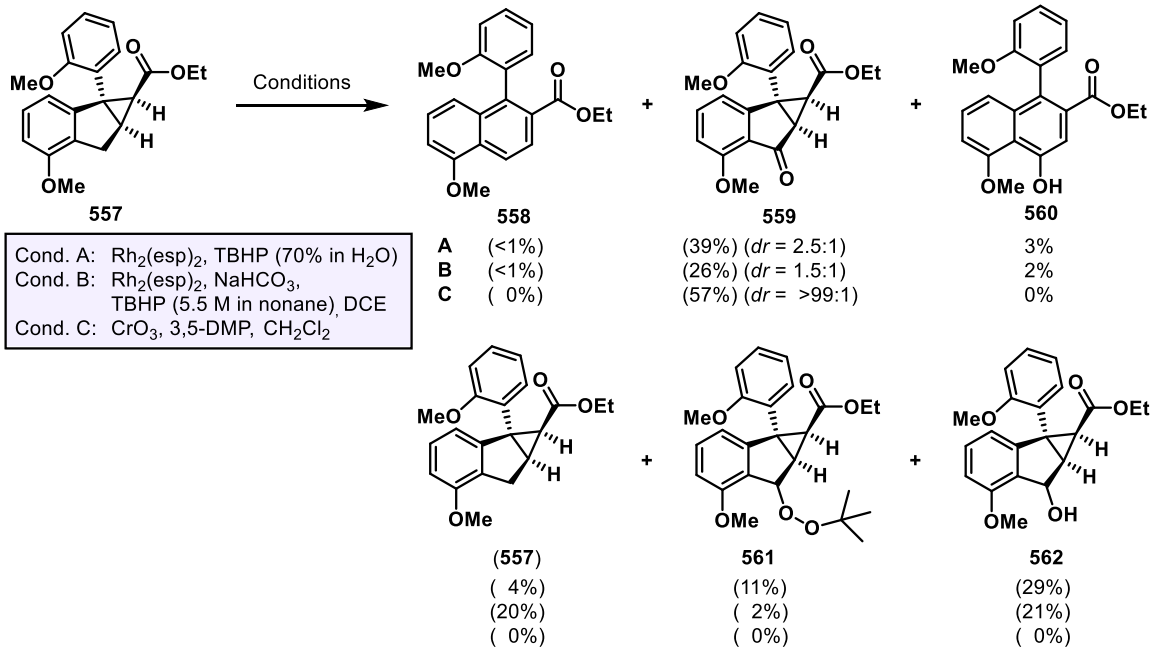
observed. To remain in accordance with the intention of a ring-expansion under mild conditions, we tested for a halogen-free approach upon oxidative cyclopropane opening. Instead of generating a cationic cyclopropane after loss of X^-, we exploited the nature of the adjacent benzylic position to undergo oxidation. Indeed, simple employment of DDQ induced ring-expansion, however, with a high



	(555)	556	cis:trans	ee	557
L = OAc	17%	**50%**	1 : 1.3	-	15%
L = *R*-DOSP	42%	**14%**	1.4 : 1	<10%	17%

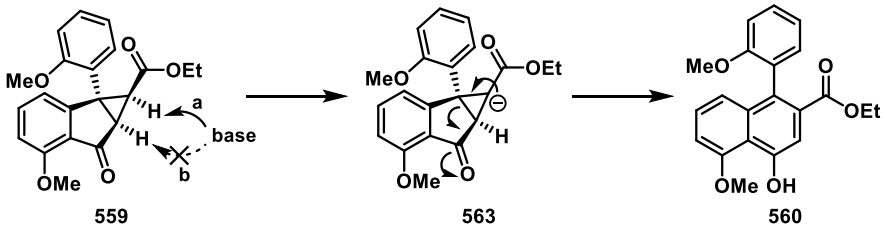
Scheme 76: Cyclopropanation of model substrate **555**.

dependency on the electron-richness of the substrate. While unsubstituted biaryl **551** was only formed at 110 °C in minor abundance compared to the starting material, additional methoxy-groups could decrease the temperature to 23 °C with significantly higher conversion. As a consequence, we designed a suitable model substrate which would combine the need for an *ortho*-substituent with an increased electron-density at the indene moiety (Scheme 76). Yields for the cyclopropanation using rhodium(II) acetate were in the same range as for substrates **535**, **536** and **537**, however, favoring the *trans*-conformation. Due to solubility issues, additional toluene was used which partially consumed ethyl diazoacetate **542** via a Buchner reaction to give cycloheptatriene **557**. The influence of the solvent on the diasterochemical outcome remains to be clarified. Unfortunately, the employment of chiral catalyst Rh_2(*R*-DOSP)$_4$ not only led to diminished yields but also did not exhibit enantioselectivity. However,



Scheme 77: Oxidative ring-opening of the cyclopropane afforded several oxygenated products.

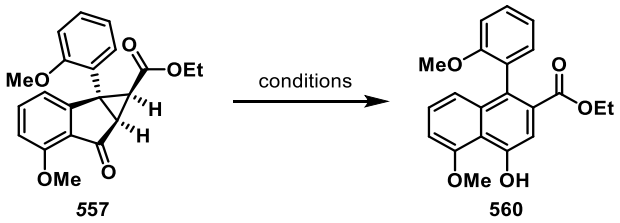
we were prompted to see if further oxidative conditions would allow for a reliable ring-expansion of the cyclopropanes. In due consideration of our experiences on benzylic oxidation using $Rh_2(esp)_2$ (see chapter 3.2.10) we employed the same conditions (A and B) to substrate **557** (Scheme 77). Several oxidation events took place leading to various products. While the initially anticipated biaryl **558** was only formed in traces, the main product turned out to be ketone **559**. In both runs, two diastereomers of



Scheme 78: Rationale for the ring-expansion of cyclopropane-ketone **560**.

the ketone were formed indicating epimerization of the carboxy group upon employed conditions, since starting material was diastereomerically pure. We assume that ketone **559** emerged from peroxide **561** via Kornblum–DeLaMare elimination. Formation of alcohol **562** is presumably formed by the presence of water (Conditions A), however, significant amounts are also observed under non-aqueous conditions (B). Of most interest was a minor product, which turned out to be hydroxy biarly **560**. Due to its

Table 16. Optimization of the ring-expansion of **557**.

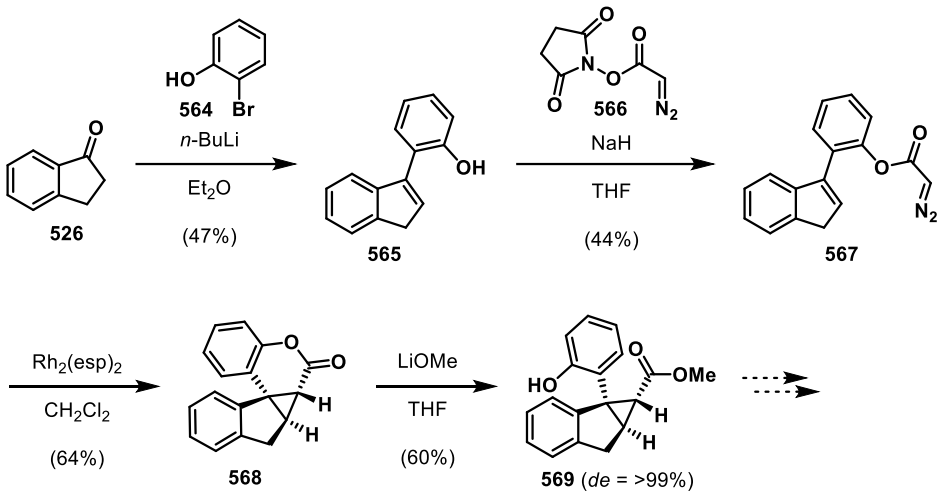


Entry	Reagent		Temp.	Time	SM:P (Yield)[b]
1	NEt_3	5 equiv	23 °C	15 h	only SM
2	SmI_2	3 equiv	23 °C	20 h	only SM
3	KHMDS	5 equiv	–78 °C	3 h	decomposition
4	$TiCl_4$	5 equiv	–78 °C	2 h	1 : 0.86 (n.d.)
5	$BF_3 \cdot OEt_2$	5 equiv	–78 °C	2 h	0.40 : 1 (n.d.)
6[a]	$BF_3 \cdot OEt_2$	5 equiv	–78 °C	2 h	1 : 0.42 (n.d.)
7	$BF_3 \cdot OEt_2$	**10 equiv**	**–78 to 23 °C**	**22 h**	**0.01 : 1 (73%)**

[a]*trans*-**557** was used. [b]n.d. = not determined.

formation, we rationalized a Grob-type fragmentation outgoing from ketone **557** as depicted in scheme 78. This observation prompted us to purposely approach oxidation to ketone **557**. This was achieved via chromium(VI) treatment without formation of major side products. With the ketone in hand, we screened

for conditions to induce ring-opening (Table 16). Simple treatment with amine bases had no effect on the substrate. Cyclopropane opening similar to radical clock experiments[234] by ketone reduction with samarium(II)-iodide also showed no change while KHMDS led to decomposition. Different from these results, the employment of Lewis acids appeared to be best suitable with our system inducing clean ring-opening to biaryl **560**. With BF_3 in combination with prolonged reaction times and excess of the reagent full conversion could be assured resulting in 73% of the desired biaryl **560**. Again, differences in activity could be observed between the *cis*- and the *trans*-isomer (Entry 6). Furthermore, the remarkable difference regarding the activation barrier between the non-halogenated cyclopropane **557** and the chlorinated cyclopropanes from scheme 75 (23 °C versus 190 °C) to undergo ring-expansion indicates a different reaction pathway for the ring-opening. Assuming that not only the enantioselectivity, but also

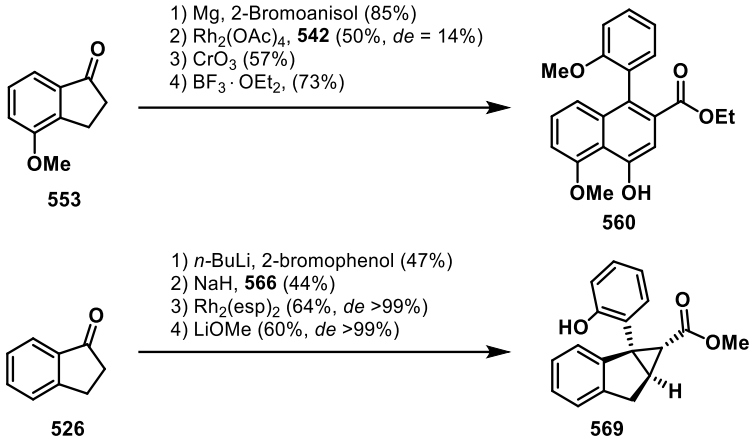


Scheme 79: Control of the diastereoselectivity via intramolecular cyclopropanation.

the diastereoselectivity might play a significant role during the ring-expansion, we developed an intramolecular strategy which would allow for the exclusive preparation of *trans*-cyclopropanes **569** (Scheme 77). Starting with commercially available indanone **526** deprotonation–lithiation of phenol **564** using *n*-BuLi afforded condensation product **565**. Esterification with active-ester **566** gave diazo-precursor **567** in 44% yield. After a short survey of conditions, we were able to obtain racemic cyclopropane **568** in 64% yield. Subsequent hydrolysis using lithium methanolate finally afforded *trans*-cyclopropane **569** in 60% yield with retention of the diastereomeric excess. This approach might serve as platform for further investigations into the anticipated enantioselective synthesis of biaryls.

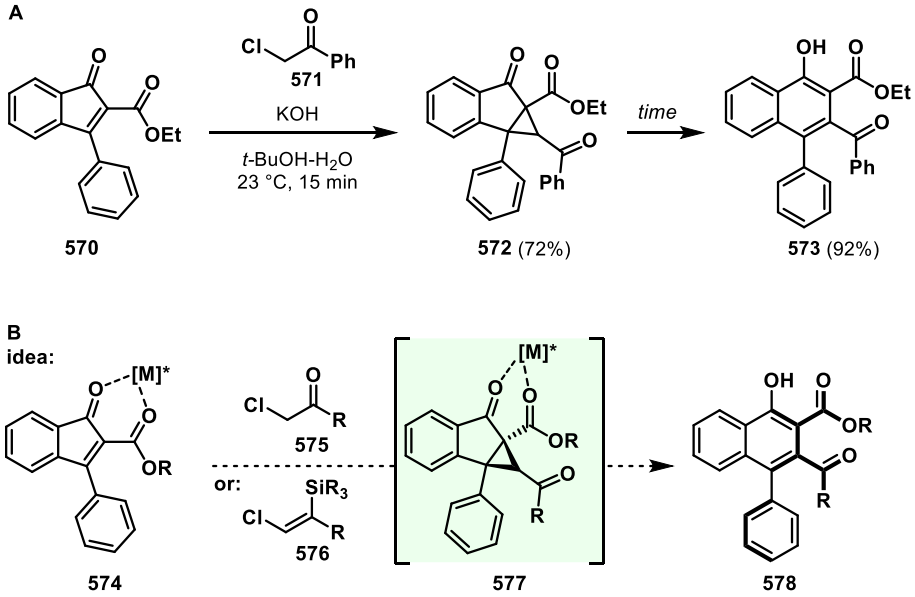
7. Conclusion and Outlook

In summary, we developed a straight forward synthesis of biaryls **560** in four steps starting from readily available indanones (Scheme 80). Both steps, cyclopropanation and ring-expansion, proceeded at ambient temperatures assuring conditions which might be essential considering enantioselectivity. The



Scheme 80: Racemic 4-step synthesis of a highly functionalized biaryl and studies towards diastereoselectivity.

advancement of this procedure towards existing protocols are a fast access to obtain the substrates and the Grob-type fragmentation, which allows for drastic reduction of the needed temperature. In addition, we addressed the problem of limited diastereoselectivity with preference for the *cis*-cyclopropane in an intermolecular cyclopropanation by developing an intramolecular strategy. By that, we were able to control the selectivity in favor of the *trans*-cyclopropane to the extent of over 99%. While these results



Scheme 81: Envisioned enantioselective cyclopropanation based on the findings by Koelsch.

confirmed the basic feasibility of the CPRE-strategy to obtain polyfunctionalized biarlys, the implementation of enantioselectivity remains unsolved. Keeping the idea of a Lewis acid promoted ring-expansion of the α-keto-cyclopropanes, we envisioned a modified access to the precursors. In a

publication from 1961, Koelsch describes the synthesis of biaryl **573** in good yields via cyclopropanation of indenone **570** under mild conditions (Scheme 81. A). It is reasonable that employment of a (chiral) Lewis acid might affect this reaction in different ways. On the one hand, the Lewis acid could activate the electrophile while on the other hand, the presence of a chiral ligand might control the conjugate addition along with a selective subsequent ring-opening. A protocol based on Mukaiyama-Michael conditions using the corresponding silyl enol ether should be considered as another option.

8. Experimental

8.1 Methods and Equipment

All reactions were carried out with magnetic stirring and, if moisture or air sensitive, under nitrogen or argon atmosphere using standard Schlenk techniques in oven-dried glassware (100 °C oven temperature). If required glassware was further dried under vacuum with a heat-gun at 650 °C. External bath thermometers were used to record all reaction temperatures. Low temperature reactions were carried out in a Dewar vessel filled with acetone and dry ice (–78 °C) or equipped with an electronically regulated cryostat in acetone (between –78 °C and 0 °C) or with distilled water and ice (0 °C). High temperature reactions were conducted in reaction vessels equipped with a reflux condenser or in a pressure tube using a heated silicon oil bath or a metal block. Tetrahydrofuran (THF) was dried over molecular sieve (4Å) prior to use. All other solvents were purchased from Acros Organics as 'extra dry' reagents. If required, solvents were degassed by bubbling argon through the solvent with a balloon under sonication. All other reagents with a purity > 95% were obtained from commercial sources (Sigma Aldrich, Acros, Alfa Aesar and others) and used without further purification unless otherwise stated.

Flash column chromatography (FCC) was carried out with Merck silica gel 60 (0.040–0.063 mm). Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60 F254 aluminum foils and visualized under UV light at 254 nm. Staining was performed with ceric ammonium molybdate (CAM) or by staining with an aqueous potassium permanganate solution and subsequent heating.

High pressure liquid chromatography (HPLC) was carried out on normal-phase Varian Dynamax columns. For semipreparative separations a 250 x 21.4 mm Microsorb 60–8 Si column and for preparative separations a 250 x 41.4 mm Microsorb 60-8 Si column was used.

NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform (chloroform-*d*), deuterated benzene (benzene-d_6), deuterated dichloromethane (dichloromethane-d_2) or deuterated pyridine (pyridine-d_5) on a Bruker Avance Neo 400 MHz spectrometer, or a Bruker Avance II 600 MHz spectrometer and are reported as follows: chemical shift δ in ppm (multiplicity, coupling constant *J* in Hz, number of protons) for ^{1}H NMR spectra and chemical shift δ in ppm for ^{13}C NMR spectra. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, br = broad, m = multiplet, or combinations thereof. For ^{1}H NMR the residual protic solvent peak served as internal reference (chloroform-*d*: 7.26 ppm, benzene-d_6: 7.16 ppm, dichloromethane-d_2: 5.32 ppm, pyridine-d_5: 8.74 ppm for the signal with the highest shift). For ^{13}C NMR the central carbon resonance of chloroform-*d* (77.16 ppm or 77.00 ppm for comparison of synthetic and isolated natural products), benzene-d_6 (128.06 ppm), dichloromethane-d_2 (54.00 ppm) or pyridine-d_5 (150.35 ppm for the signal with the highest shift) served as internal reference. NMR spectra were assigned using information ascertained from COSY, HMBC, HSQC and NOESY experiments.

High resolution mass spectra (HRMS) were recorded on a Thermo Scientific™ LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Mass Spectrometer at the Institute of Organic Chemistry and Center for Molecular Biosciences, University of Innsbruck.

Infrared spectra (IR) were recorded from 4000 cm^{-1} to 450 cm^{-1} on a Bruker™ ALPHA FT-IR Spectrometer from Bruker. Samples were prepared as a neat film or a film by evaporation of a solution in Chloroform-*d*, Benzene-d_6 or ethyl acetate. IR data in frequency of absorption (cm^{-1}) is reported as follows: *w* = weak, *m* = medium, *s* = strong, *br* = broad or combinations thereof.

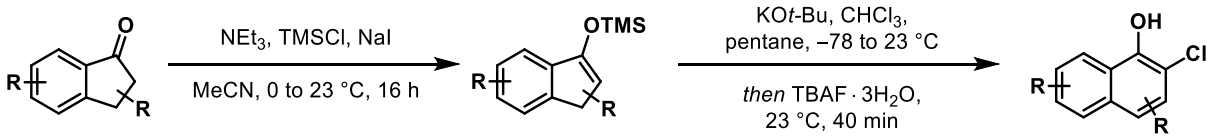
Melting points were measured with an SRS MPA120 EZ-Melt Melting Point Apparatus in open glass capillaries and are uncorrected.

Optical rotation values were recorded on a Schmidt+Haensch UniPol L1000 Peltier polarimeter. The specific rotation is calculated as follows: $[\alpha]_{\lambda}^{T} = \frac{\propto \times 100}{c \times d}$. Thereby, the wavelength λ is reported in nm and the measuring temperature in °C. α represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2 g^{-1}. Use of the sodium *D* line (λ = 589 nm) is indicated by *D* instead of the wavelength in nm. The sample concentration as well as the solvent is reported in the relevant section of the experimental part.

X-Ray diffraction analysis was carried out by Dr. Klaus Wurst at the Institute of Inorganic and Theoretical Chemistry and Center for Molecular Biosciences, University of Innsbruck. The data collections were performed on a Bruker D8 Quest diffractometer (Photon 100 detector) equipped with a microfocus source generator (Incoatec GmbH, Geesthacht, Germany) combined with multi-layer optics (monochromatized Mo *Kα* radiation, λ = 71.073 pm). The Bruker Apex III software was applied for the integration, scaling and multi-scan absorption correction of the data. The structure was solved with SHELXS[1] (version 2013/1). Structure refinement (full-matrix least-squares against F^2) with SHELXL[2] (version 2014/7). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Relevant details of the data collection and evaluation are listed in chapter 9.1.

All yields are isolated, unless otherwise specified.

8.2 Experimental Data for Part I

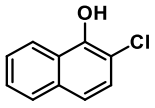


General Procedure Towards 2-Chloronaphthols (Procedure A)

Triethylamine (158 µL, 1.13 mmol, 1.50 equiv) and trimethylsilyl chloride (145 µL, 1.13 mmol, 1.50 equiv) were added in sequence to a suspension of sodium iodide (11.3 mg, 75.7 µmol, 10 mol%) and indanone (757 µmol, 1 equiv) in acetonitrile (910 µL, 0.83 M) at 0 ˚C. The resulting suspension was allowed to warm to 23 ˚C and stirred for 16 hours. After removal of the solvent under reduced pressure, the residue was dissolved in *n*-hexane (5 mL). and the suspension was filtered through a short plug of Celite. The filtrate was then concentrated under reduced pressure to afford the crude silyl enol ether. This material was used immediately without further purification.

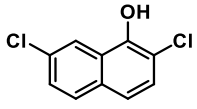
The crude silyl enol ether was dissolved in pentane (900 µL, 0.84 M), cooled to –78 °C and slowly added to a suspension of potassium *tert*-butoxide (sublimed grade, 170 mg, 1.51 mmol, 2.00 equiv) in pentane (1.51 mL, 1 M) at –78 ˚C. The flask of the crude silyl enol ether was rinsed for three times with pentane (3 × 800 µL) and added to the reaction in the same fashion. A solution of chloroform (133 µL, 1.67 mmol, 2.20 equiv) in pentane (1.67 mL, 1 M) was added dropwise to the mixture and the suspension was stirred at –78 ˚C for 30 minutes before allowing to warm to 23 ˚C. After stirring for 1.5 hours, water (2 mL) was added to the reaction mixture and the resulting solution was concentrated to 4 mL under reduced pressure. Tetrabutylammonium fluoride trihydrate (358 mg, 1.13 mmol, 1.50 equiv) was added in one portion and the solution was stirred vigorously for 40 minutes. Aqueous hydrochloric acid (1 M, 5 mL) was added and the resulting solution was extracted with ethyl acetate (3 × 10 mL). The organic layer was then washed with water (2 × 10 mL) and a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. Filtration of the dried solution followed by concentration under reduced pressure gave the crude product, which was purified by silica gel chromatography to give the desired 2-chloronaphthols.

2-Chloronaphthalen-1-ol 242



Data consistent with literature: *Angew. Chem. Int. Ed.*, **2013**, *52*, 5271–5274.

2,7-Dichloronaphthalen-1-ol 243



Yellow oil

TLC (20% diethyl ether in pentane): R_f = 0.70 (UV, $KMnO_4$).

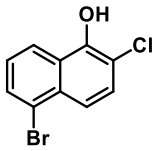
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.20 (d, *J* = 2.1, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.38 – 7.32 (m, 2H), 6.00 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 146.5, 132.3, 131.5, 129.3, 127.7, 126.3, 125.1, 121.4, 120.8, 114.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3513 (m, br), 3466 (m), 1586 (w), 1576 (w), 1439 (m), 1265 (s), 1090 (vs), 899 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_5OCl_2$ [M-H]$^-$: 210.9723 found: 210.9724.

5-Bromo-2-chloronaphthalen-1-ol 244



Orange solid

TLC (20% diethyl ether in pentane): R_f = 0.75 (UV, $KMnO_4$).

mp: 86–90 °C.

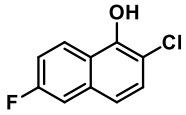
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 11.6, 8.3 Hz, 2H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.04 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 147.1, 131.8, 130.9, 127.2, 126.5, 125.6, 122.6, 122.1, 120.3, 114.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3509 (w), 1619 (m), 1587 (w), 1496 (m), 1455 (m), 1395 (w), 1365 (m), 1338 (m), 1237 (s), 1192 (vs), 1146 (s), 1075 (s), 870 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_5BrClO$ [M-H]$^-$: 254.9218 found: 254.9220.

2-Chloro-6-fluoronaphthalen-1-ol 245



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.80 (UV, $KMnO_4$).

mp: 82–85 °C.

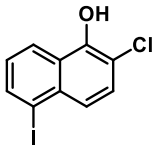
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.10 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.20 – 7.13 (m, 2H), 5.92 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 161.3 (d, *J* = 247 Hz), 147.3 (d, *J* = 1.3 Hz), 134.3 (d, *J* = 9.4 Hz), 127.2, 124.9 (d, *J* = 9.2 Hz), 121.4, 120.2 (d, *J* = 5.1 Hz), 116.3 (d, *J* = 25.3 Hz), 112.9 (d, *J* = 2.8 Hz), 110.9 (d, *J* = 20.9 Hz).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3521 (w), 1632 (m), 1601 (s), 1580 (s), 1511 (vs), 1466 (m), 1431 (s), 1379 (m), 1257 (s), 1197 (s), 1152 (s), 1138, (m) 1064 (m), 955 (m), 867 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_5ClFO$ $[M-H]^-$: 195.0018 found: 195.0018.

5-Iodo-2-chloronaphthalen-1-ol 246



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.80 (UV, $KMnO_4$).

mp: 79–80 °C.

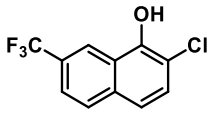
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.24 (dt, *J* = 8.4, 1.0 Hz, 1H), 8.08 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.62 (dd, *J* = 9.1, 0.9 Hz, 1H), 7.43 (d, *J* = 9.1 Hz, 1H), 7.18 (dd, *J* = 8.4, 7.3 Hz, 1H), 6.02 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 146.9, 138.4, 134.1, 127.3, 127.0, 125.3, 124.8, 123.1, 114.6, 98.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3430 (w), 1583 (m), 1493 (m), 1455 (s), 1391 (s), 1359 (m), 1245 (vs), 1189 (m), 1147 (s), 1070 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_5OICl$ $[M-H]^-$: 302.9079 found: 302.9080.

2-Chloro-7-(trifluoromethyl)naphthalen-1-ol 247



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.69 (UV, $KMnO_4$).

mp: 98–99 °C.

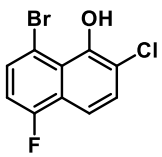
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.54 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.68 – 7.66 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 6.11 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 174.9, 134.3, 128.8, 128.3, 128.0 (q, *J* = 32.5 Hz), 124.3 (q, *J* = 272 Hz), 123.4, 122.4 (q, *J* = 3.1 Hz), 120.8, 120.4 (q, *J* = 4.6 Hz), 114.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3399 (w), 1599 (s), 1458 (m), 1377 (s), 1301 (m), 1266 (m), 1243 (m), 1199 (vs), 1159 (s), 1113 (m), 1078 (w), 909 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_5ClF_3O$ $[M-H]^-$: 244.9987 found: 244.9987.

8-Bromo-2-chloro-5-fluoronaphthalen-1-ol 248



Yellow solid

TLC (20% diethyl ether in pentane): R_f = 0.80 (UV, $KMnO_4$).

mp: 92–94 °C.

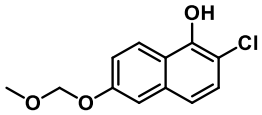
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.69 – 7.64 (m, 2H), 7.55 – 7.51 (m, 2H), 6.99 (t, *J* = 8.9, Hz, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 158.4 (d, *J* = 253 Hz), 147.7 (d, *J* = 3.5 Hz), 132.6 (d, *J* = 8.5 Hz), 128.5 (d, *J* = 1.9 Hz), 125.8 (d, *J* = 17.6 Hz), 122.8 (d, *J* = 4.1 Hz), 118.9, 114.0 (d, *J* = 8.2 Hz), 110.8 (d, *J* = 21.7 Hz), 110.1 (d, *J* = 4.4 Hz).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3491 (w), 3460 (m), 3089 (w), 1598 (m), 1564 (s), 1502 (s), 1445 (s), 1416 (m), 1353 (w), 1315 (s), 1209 (m), 1140 (m), 920 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_4BrClFO$ $[M\text{-}H]^-$: 272.9124 found: 272.9124.

2-Chloro-6-(methoxymethoxy)naphthalen-1-ol 249



Brown solid

TLC (20% diethyl ether in pentane): R_f = 0.79 (UV, $KMnO_4$).

mp: 261 °C (decomposition).

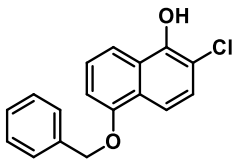
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, *J* = 9.1 Hz, 1H), 7.33 (d, *J* = 3.3 Hz, 1H), 7.31 (d, *J* = 10.1 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.01 (s, 1H), 5.30 (s, 2H), 3.53 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.8, 147.2, 134.7, 126.7, 123.9, 120.4, 120.1, 119.0, 112.0, 109.9, 94.5, 56.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3550 (w), 3060, (m) 1598 (s), 1590 (s), 1472 (m), 1365 (vs), 1390 (m), 1320 (vs), 1068 (m), 855 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{12}H_{10}ClO_3$ $[M\text{-}H]^-$: 237.0324 found: 237.0323.

5-(Benzyloxy)-2-chloronaphthalen-1-ol 250



Yellowish gum

TLC (20% diethyl ether in pentane): R_f = 0.50 (UV, $KMnO_4$).

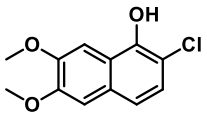
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.87 (dd, *J* = 9.0, 0.89 Hz, 1H), 7.80 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.52 – 7.51 (m, 2H), 7.44 – 7.40 (m, 3H), 7.37 – 7.34 (m, 2H), 6.93 (dd, *J* = 7.7, 0.9 Hz, 1H), 5.97 (s, 1H), 5.24 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.5, 146.9, 137.0, 128.8, 128.2, 127.5, 126.4, 125.7, 125.2, 115.6, 114.7, 114.6, 106.3, 70.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3550 (w), 3425 (w), 1621 (m), 1512 (vs), 1457 (s), 1289 (m), 1110 (m), 1008 (w) cm^{-1}.

HRMS (EI) calc. for $C_{17}H_{13}ClO_2$ $[M]^+$: 284.0599 found: 284.0599.

2-Chloro-6,7-dimethoxynaphthalen-1-ol 251



Grey solid

TLC (50% dichloromethane in cyclohexane): R_f = 0.23 (UV, CAM).

mp: 99–103 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.45 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.01 (s, 1H), 6.05 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H).

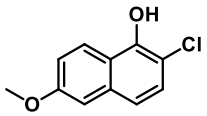
^{13}C NMR (101 MHz, chloroform-*d*) δ 150.0, 149.6, 146.0, 129.2, 124.2, 119.8, 119.4, 112.4, 106.3, 101.0, 56.0, 55.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3525 (w), 3071 (w), 2925 (w), 1693 (m), 1590 (m), 1501, (s) 1427 (vs), 1370 (s), 1288 (s), 1219 (m), 1163 (s), 1020 (m), 871 (w), 869 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{12}H_{10}ClO_3$ $[M\text{-}H]^-$: 237.0324 found: 237.0322.

Note: Higher yields were obtained following the general procedure B using chloroform instead of bromoform.

2-Chloro-6-methoxynaphthalen-1-ol 252



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.58 (UV, $KMnO_4$).

mp: 72–74 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.97 (d, *J* = 9.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 7.02 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 5.86 (s, 1H), 3.75 (s, 3H).

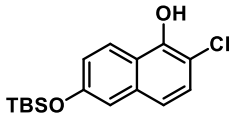
^{13}C NMR (101 MHz, chloroform-*d*) δ 158.3, 147.3, 134.8, 126.6, 123.8, 119.8, 119.7, 118.7, 111.6, 105.8, 55.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3512 (w), 3069 (m), 2935 (w), 1628 (s), 1592 (vs), 1508 (s), 1431 (m), 1375 (w), 1257 (m), 1230, (s) 1164 (m), 1025 (m), 871 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_8ClO_2$ $[M\text{-}H]^-$: 207.0218 found: 207.0219.

Note: Higher yields were obtained following the general procedure B using chloroform instead of bromoform.

6-((*Tert*-butyldimethylsilyl)oxy)-2-chloronaphthalen-1-ol 253



Colorless oil

TLC (20% diethyl ether in pentane): R_f = 0.92 (UV, $KMnO_4$).

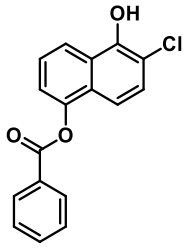
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.13 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.16 – 7.10 (m, 2H), 5.97 (s, 1H), 1.05 (s, 9H), 0.27 (s, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.4, 147.3, 134.9, 126.5, 123.9, 122.2, 120.2, 119.8, 115.0, 111.7, 25.8, 18.4, –4.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3538 (w), 2955 (m), 2929 (m), 2857 (w), 1629 (vs), 1592 (m), 1504 (m), 1431 (s), 1256 (m), 1200 (w), 1159 (s), 1070 (m), 972 (s), 858 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{16}H_{20}ClO_2Si$ $[M-H]^-$: 307.0926 found: 277.0639.

6-Chloro-5-hydroxynaphthalen-1-yl benzoate 254



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.78 (UV, $KMnO_4$).

mp: 138–140 °C (decomposition).

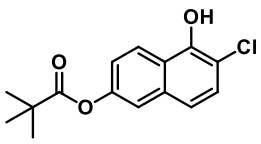
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.33 (d, *J* = 7.6 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.57 (q, *J* = 8.0 Hz, 3H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 6.09 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 165.2, 147.4, 146.8, 134.1, 130.5, 129.3, 128.9, 127.0, 126.7, 126.1, 125.9, 120.5, 119.4, 114.6, 114.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3560 (m), 3082 (w), 1730 (vs), 1593 (s), 1420 (m), 1322 (vs), 1320 (w), 1068 (m), 859 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{10}ClO_3$ $[M-H]^-$: 297.0324 found: 297.0324.

6-Chloro-5-hydroxynaphthalen-2-yl pivalate 255



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.82 (UV, $KMnO_4$).

mp: 141–143 °C (decomposition).

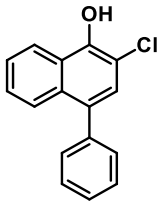
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.20 (d, *J* = 9.1 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.22 (dd, *J* = 9.1, 2.1 Hz, 1H), 6.05 (s, 1H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 177.4, 149.6, 147.3, 133.9, 126.9, 124.0, 122.5, 121.4, 120.6, 118.4, 113.5, 39.3, 27.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3426 (w), 2956 (m), 1730 (vs), 1578 (s), 1479 (m), 1389 (s), 1289 (m), 1179 (w), 1152 (m), 1067 (s), 869 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{14}ClO_3$ $[M\text{-}H]^-$: 277.0637 found: 277.0639.

2-Chloro-4-phenylnaphthalen-1-ol 256



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.67 (UV, $KMnO_4$).

mp: 123–125 °C.

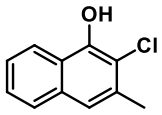
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.32 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.55 (t, *J* = 7.5Hz, 1H), 7.52 – 7.41 (m, 6H), 7.36 (s, 1H), 6.04 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 146.6, 139.6, 133.9, 131.5, 130.3, 128.5, 127.5, 126.9, 126.7, 126.2, 124.7, 122.5, 113.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3513 (w), 3057 (w), 1587 (m), 1509 (vs), 1456 (s), 1372 (m), 1340 (m), 1220 (s), 1068 (m), 850 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{16}H_{10}ClO$ $[M\text{-}H]^-$: 253.0426 found: 253.0427.

2-Chloro-3-methylnaphthalen-1-ol 257



Colorless solid

TLC (20% diethyl ether in pentane): R_f = 0.90 (UV, $KMnO_4$).

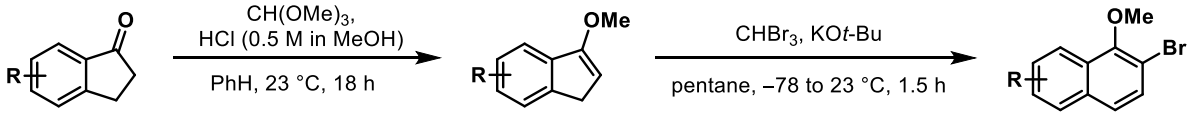
mp: 68–70 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.32 – 8.07 (m, 1H), 7.77 – 7.64 (m, 1H), 7.53 – 7.37 (m, 2H), 7.29 (s, 1H), 6.08 (s, 1H), 2.52 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 147.1, 133.4, 132.6, 126.9, 126.8, 125.2, 122.9, 122.1, 120.6, 115.6, 20.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3517 (w), 2451 (m), 3056 (m), 2920 (w), 1590 (vs), 1505 (m), 1401 (s), 1230 (m), 1224 (s), 1084 (m), 1033 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_8ClO$ $[M-H]^-$: 191.0269 found: 191.0269.

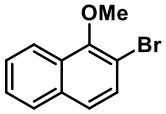


General Procedure Towards 2-Bromo-1-methoxynaphthalenes

A solution of hydrogen chloride (1.25 M in methanol, 15 mol%) was added dropwise to a solution of indanone (1.10 mmol, 1 equiv) and trimethyl orthoformate (168 µL, 1.54 mmol, 1.40 equiv) in benzene (2.20 mL, 0.5 M) at 23 °C. After 18 hours, the solvent was removed under reduced pressure and the crude residue was subjected to distillation using a Hickman apparatus.

The obtained enol ether was dissolved in pentane (5.50 mL, 0.2 M) before potassium *tert*-butoxide (247 mg, 2.20 mmol, 2.00 equiv) was added at 23 °C in one portion to the solution. The resulted suspension was cooled to –78 °C and a solution of bromoform (212 µL, 2.42 mmol, 2.20 equiv) in pentane (484 µL, 5 M) was added dropwise. After 30 minutes, the reaction was allowed to warm to 23 °C and stirred for further 1.5 hours. Water (3 mL) was added to the reaction and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure to give the crude mixture. Purification via flash column chromatography over silica (pentane/ether) afforded the desired 2-bromonaphthols.

2-Bromo-1-methoxynaphthalene 266



Colorless oil

TLC (pentane): R_f = 0.18 (UV, $KMnO_4$).

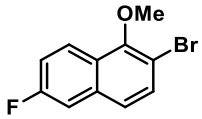
^{1}H (400 MHz, chloroform-*d*) δ 8.18 – 8.11 (m, 1H), 7.86 – 7.80 (m, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.57 – 7.49 (m, 3H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.3, 134.1, 130.2, 129.2, 128.2, 126.9, 126.7, 125.4, 122.2, 112.8, 61.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3515 (w), 3060 (m), 2934 (w), 1688 (w), 1595 (vs), 1548 (s), 1434 (m), 1381 (w), 1165 (m), 1020 (m), 891 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_{10}BrO$ $[M+H]^+$: 236.9910 found: 236.9901.

2-Bromo-6-fluoro-1-methoxynaphthalene 267



Yellow oil

TLC (pentane): R_f = 0.23 (UV, $KMnO_4$).

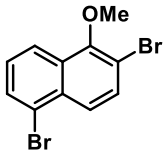
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.13 (dd, *J* = 9.3, 5.6 Hz, 1H), 7.59 (dd, *J* = 8.9, 0.9 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.30 (ddd, *J* = 9.2, 8.4, 2.5 Hz, 1H), 4.01 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 161.3 (d, *J* = 248 Hz), 153.6 (d, *J* = 1.3 Hz), 135.0 (d, *J* = 9.4 Hz), 131.6, 126.28, 125.05 (d, *J* = 9.1 Hz), 124.63 (d, *J* = 5.3 Hz), 117.2 (d, *J* = 25.3 Hz), 111.9 (d, *J* = 2.8 Hz), 111.4 (d, *J* = 20.9 Hz), 61.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3517 (w), 3050 (m), 2943 (w), 1689 (m), 1594 (vs), 1548 (s), 1434 (m), 1280 (w), 1160 (s), 1004 (m), 791 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_9BrFO$ $[M+H]^+$: 254.9815 found: 254.9832.

2,5-Dibromo-1-methoxynaphthalene 268



Off-white solid

TLC (pentane): R_f = 0.19 (UV, $KMnO_4$).

mp: 58 °C.

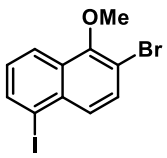
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.78 (d, *J* = 6.5 Hz, 1H), 7.70 – 7.60 (m, 1H), 7.42 – 7.30 (m, 1H), 4.00 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.2, 132.5, 131.4, 130.7, 130.4, 127.2, 124.6, 123.0, 122.1, 113.9, 61.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3510 (w), 3060 (m), 2944 (w), 1868 (w), 1593 (vs), 1498 (s), 1432 (m), 1380 (w), 1166 (m), 1020 (m), 923 (s), 881 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_9Br_2O$ $[M+H]^+$: 314.9015 found: 314.9044.

2-Bromo-5-iodo-1-methoxynaphthalene 269



Beige solid

TLC (pentane): R_f = 0.19 (UV, $KMnO_4$).

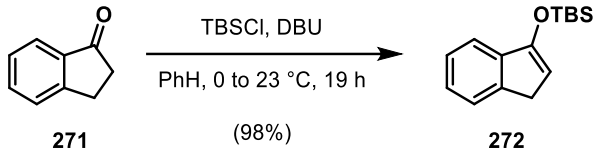
mp: 61–63 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (dq, *J* = 8.5, 1.0 Hz, 1H), 8.09 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.77 (dq, *J* = 9.1, 0.9 Hz, 1H), 7.66 (dd, *J* = 9.1, 1.3 Hz, 1H), 7.21 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 4.00 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.0, 138.2, 134.8, 131.5, 129.6, 129.6, 127.7, 123.0, 113.6, 99.2, 61.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3515 (w), 3060 (m), 2924 (w), 1688 (w), 1575 (s), 1548 (s), 1534 (w), 1381 (m), 1220 (m), 871 (w), 777 (m) cm^{-1}.

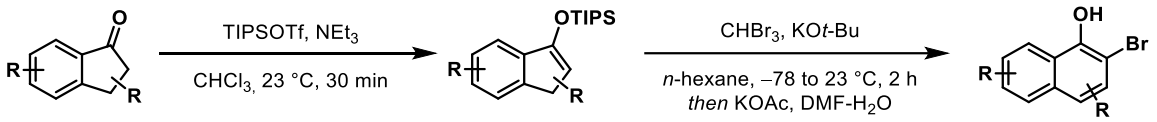
HRMS (ESI) calc. for $C_{11}H_9BrIO$ $[M+H]^+$: 362.8876 found: 362.8820.



((1*H*-Inden-3-yl)oxy)(*tert*-butyl)dimethylsilane 272

1,8-Diazabicyclo[5.4.0]undec-7-en (254 µL, 1.70 mmol, 1.50 equiv) was added dropwise to a solution of indanone **271** (150 mg, 1.14 mmol, 1 equiv) in benzene (1.19 mL, 0.95 M) at 0 °C. The mixture was stirred for 19 hours while slowly warming to 23 °C. The solvent was removed under reduced pressure to give a viscous oil, which was re-dissolved in diethyl ether and then filtered over a short plug of silica. The solvent was removed under reduced pressure to give clean silyl enol ether **272** (274 mg, 1.11 mmol, 98%) as a yellowish oil.

Data consistent with literature: *J. Organomet. Chem.*, **1998,** *558,* 181–188.



General Procedure Towards 2-Bromonaphthols (Procedure B)

Triethylamine (82.0 µL, 588 µmol, 1.40 equiv) and triisopropylsilyl trifluoromethanesulfonate (124 µL, 462 µmol, 1.10 equiv) were sequentially added to a solution of indanone (420 µmol, 1 equiv) in chloroform (5.25 mL, 0.08 M) at 23 ˚C. The reaction was stirred until full conversion (0.5 to 1.5 h). Progress was visualized by basic Al_2O_3-TLC-monitoring. If remaining starting material was indicated after two hours of stirring, additional triethylamine (199 µL, 1.43 mmol, 3.40 equiv) and triisopropylsilyl trifluoromethanesulfonate (158 µL, 588 µmol, 1.40 equiv) were added and stirred until full conversion (only needed for substrate **278** in our hands). The mixture was diluted with cyclohexane (5 mL), filtered through a short plug of silica and the filtrate was concentrated under reduced pressure at 23 °C. The crude silyl enol ether was used immediately without further purification.

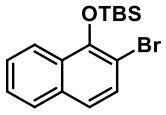
The crude silyl enol ether was dissolved in *n*-hexane (600 µL, 0.7 M), cooled to –78 °C and added to a suspension of potassium *tert*-butoxide (sublimed grade, 212 mg, 1.89 mmol, 4.50 equiv) in *n*-hexane

(859 µL, 2.2 M) at –78 ˚C. The flask of the crude silyl enol ether was rinsed with *n*-hexane (3 × 500 µL) and added to the reaction in the same fashion. After 20 minutes, a solution of freshly distilled bromoform (73.0 µL, 840 µmol, 2.00 equiv) in *n*-hexane (859 µL, 2.2 M) was added dropwise at –78 ˚C and stirred at that temperature for one hour. The reaction was then warmed to 23 °C within one hour and stirred for an additional hour. The solvent was removed under reduced pressure to give the crude silylated 2-bromonaphthol, which was dissolved in *N*,*N*-dimethylformamide-water (20:1, 1.68 mL, 0.25 M). Potassium acetate (41.0 mg, 420 µmol, 1.00 equiv) was added and the reaction was stirred for one hour at 23 ˚C. If silica-TLC-monitoring indicated remaining starting material after 1.5 hours, additional potassium acetate (41.0 mg, 420 µmol, 1.00 equiv) was added and the reaction mixture was stirred at 45 °C until full conversion (only needed for substrates **279** and **292** in our hands). Water (4 mL) was added to the reaction mixture and the resulting solution was extracted with diethyl ether (6 × 4 mL). The combined organic layers were washed with water (8 mL) and a saturated aqueous solution of sodium chloride (8 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography gave the desired 2-bromonaphthols.

General Procedure Towards 2-Bromonaphthols for substrates 295 and 296 (Procedure C)

Procedure C follows the protocol of Procedure B with difference in deprotection. Instead of dissolving the crude silylated 2-bromonaphthol in *N*,*N*-dimethylformamide-water, it was dissolved in tetrahydrofuran (10.5 mL, 0.04 M) and cooled to 0 °C, before tetrabutylammonium fluoride (1 M in tetrahydrofuran, 675 µL, 675 µmol, 1.50 equiv) was added dropwise to the mixture and stirred for one hour at that temperature. Aqueous hydrochloric acid (1 M, 4 mL) was added and the mixture was poured onto a mixture of water and ethyl acetate (1:1, 10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (8 mL) and a saturated aqueous solution of sodium chloride (8 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography gave the desired 2-bromonaphthols.

((2-Bromonaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane 274



Colorless oil

TLC (pentane): R_f = 0.64 (UV, CAM).

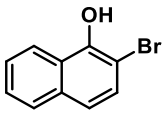
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.08 (dt, *J* = 6.8, 3.3 Hz, 1H), 7.78 (dq, *J* = 6.0, 3.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.47 (dt, *J* = 6.4, 3.4 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 1.14 (s, 9H), 0.30 (s, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 148.9, 134.1, 130.6, 129.0, 127.9, 126.4, 125.7, 123.2, 122.7, 110.1, 26.4, 19.1, –2.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3548 (w), 2939 (w), 2856 (w), 1639 (vs), 1602 (m), 1514 (m), 1431 (s), 1070 (m), 972 (s), 858 (m) cm^{-1}.

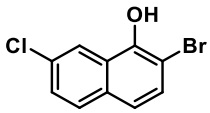
HRMS (ESI) calc. for $C_{16}H_{22}BrOSi$ $[M+H]^+$: 337.0618 found: 337.0599.

2-Bromonaphthalen-1-ol 275



Data consistent with literature: *J. Org. Chem.*, **2018**, *83*, 8036–8053.

2-Bromo-7-chloronaphthalen-1-ol 277



Off-white solid

TLC (25% dichloromethane in cyclohexane): R_f = 0.50 (UV, CAM).

mp: 78–81 °C

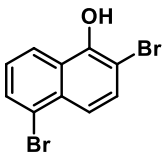
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.22 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 5.97 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 147.6, 132.3, 132.1, 129.3, 128.8, 127.9, 125.1, 121.7, 121.2, 105.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3503 (m), 3466 (m), 1589 (w), 1566 (m), 1539 (m), 1265 (vs), 1091 (vs), 808 (w) cm^{-1}.

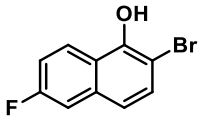
HRMS (ESI) calc. for $C_{10}H_5BrClO$ $[M-H]^-$: 254.9218 found: 254.9214.

2,5-Dibromophthalen -1-ol 287



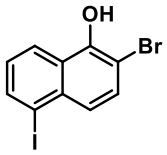
Data consistent with literature: *Tetrahedron Lett.*, **2005**, *46*, 4187–4191.

2-Bromo-6-fluoronaphthalen-1-ol 288



Data consistent with literature: *Org. Biomol. Chem.*, **2004**, *2*, 3018–3025.

2-Bromo-5-iodonaphthalen-1-ol 276



Beige solid

TLC (25% ethyl acetate in cyclohexane): R_f = 0.55 (UV, CAM).

mp: 61–63 °C.

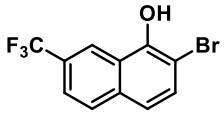
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.25 (dt, *J* = 8.3, 0.9 Hz, 1H), 8.09 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.57 (dd, *J* = 9.1, 0.7 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.17 (dd, *J* = 8.4, 7.3 Hz, 1H), 5.99 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 148.1, 138.6, 134.7, 129.9, 127.1, 125.8, 124.8, 123.4, 105.1, 98.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3332 (w), 1573 (m), 1483 (m), 1447 (s), 1409 (m), 1301 (s), 1241 (vs), 1179 (m), 1107 (m), 1074 (s), 999 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_5BrIO$ [M-H]$^-$: 346.8574 found: 346.8570.

2-Bromo-7-(trifluoromethyl)naphthalen-1-ol 289



White solid

TLC (cyclohexane): R_f = 0.27 (UV, CAM).

mp: 83 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.58 – 8.54 (m, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.08 (s, 1H).

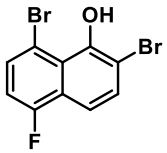
^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.1, 135.0 (d, *J* = 0.8 Hz), 130.9, 128.8, 128.1 (q, *J* = 32.5 Hz), 124.4 (q, *J* = 272 Hz), 123.4, 122.6 (q, *J* = 3.1 Hz), 121.2, 120.7 (q, *J* = 4.6 Hz), 105.4.

^{19}F NMR (376 MHz, chloroform-*d*) –62.3 (s).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3359 (w), 3298 (m), 1508 (m), 1397 (s), 1300 (m), 1276 (s), 1203 (m), 1129 (vs), 1103 (m), 1010 (m), 978 (w), 909 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_6BrF_3O$ [M-H]$^-$: 288.9481 found: 288.9480.

2,8-Bibromo-5-fluoronaphthalen-1-ol 278



Colorless crystals

TLC (13% ethyl acetate in cyclohexane): R_f = 0.56 (UV, CAM).

mp: 72 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.68 – 7.61 (m, 3H), 7.57 (dd, *J* = 9.0, 0.8 Hz, 1H), 6.98 (dd, *J* = 9.4, 8.3 Hz, 1H).

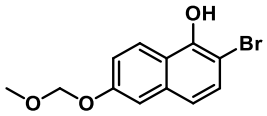
^{13}C NMR (101 MHz, chloroform-*d*) δ 158.5 (d, *J* = 253 Hz), 148.6 (d, *J* = 3.5 Hz), 132.4 (d, *J* = 8.5 Hz), 131.2 (d, *J* = 1.8 Hz), 126.2 (d, *J* = 17.5 Hz), 122.7 (d, *J* = 4.2 Hz), 114.2 (d, *J* = 8.1 Hz), 110.9 (d, *J* = 21.7 Hz), 110.0 (d, *J* = 4.4 Hz), 109.2 (d, *J* = 0.7 Hz).

^{19}F NMR (376 MHz, chloroform-*d*) δ –119.9 (dd, *J* = 9.4, 5.3 Hz).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3391 (w), 3257 (m), 3069 (w), 1554 (vs), 1514 (s), 1503 (vs), 1425 (s), 1420 (m), 1333 (m), 1310 (s), 1120 (m), 880 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_4Br_2FO$ $[M\text{-}H]^-$: 316.8618 found: 316.8622.

2-Bromo-6-(methoxymethoxy)naphthalen-1-ol 290



Brownish oil

TLC (14% ethyl acetate in cyclohexane): R_f = 0.44 (UV, CAM).

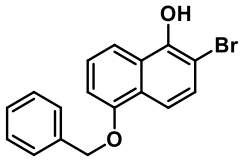
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.16 (dt, *J* = 9.2, 0.7 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.25 – 7.19 (m, 2H), 5.95 (s, 1H), 5.29 (s, 2H), 3.53 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 156.0, 148.4, 135.2, 129.1, 124.2, 120.7, 120.4, 119.0, 109.9, 102.2, 94.6, 56.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3552 (w), 3160, (w) 1618 (s), 1577 (s), 1493 (s), 1335 (m), 1309 (m), 1230 (s), 1071 (m), 775 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{12}H_{10}BrO_3$ $[M\text{-}H]^-$: 280.9819 found: 280.9822.

5-(Benzyloxy)-2-bromonaphthalen-1-ol 291



White solid

TLC (20% diethyl ether in pentane): R_f = 0.50 (UV, $KMnO_4$).

mp: 89 °C.

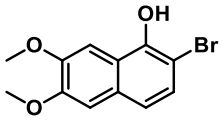
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.87 (dd, *J* = 9.0, 0.89 Hz, 1H), 7.80 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.52 – 7.51 (m, 2H), 7.44 – 7.40 (m, 3H), 7.37 – 7.34 (m, 2H), 6.93 (dd, *J* = 7.7, 0.9 Hz, 1H), 5.97 (s, 1H), 5.24 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.5, 148.0, 137.0, 128.8, 128.2, 127.7, 127.5, 126.5, 126.2, 125.7, 116.0, 114.9, 106.4, 105.3, 70.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3546 (w), 3399 (w), 1701 (s), 1525 (s), 1461 (vs), 1343 (m), 1210 (m), 948 (m) cm^{-1}.

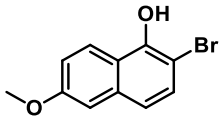
HRMS (ESI) calc. for $C_{17}H_{12}BrO_2$ $[M\text{-}H]^-$: 327.0026 found: 327.0028.

2-Bromo-6,7-dimethoxynaphthalen-1-ol 292



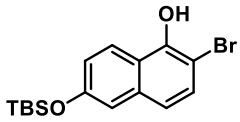
Data consistent with literature: *Tetrahedron*, **1998**, *54*, 9875–9894.

2-Bromo-6-methoxynaphthalen-1-ol 279



Data consistent with literature: *Tetrahedron Lett.*, **2005**, *46*, 4187–4191.

2-Bromo-6-((tert-butyldimethylsilyl)oxy)naphthalen-1-ol 293



White solid

TLC (13% dichloromethane in cyclohexane): R_f = 0.38 (UV, $KMnO_4$).

mp: 58 °C.

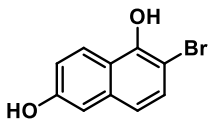
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.09 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.90 (s, 1H), 1.02 (s, 9H), 0.25 (s, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.6, 148.4, 135.5, 128.9, 124.1, 122.2, 120.3, 120.2, 115.0, 101.9, 25.8, 18.4, –4.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3499 (w), 3025 (m), 2945 (m), 2740 (w), 1702 (s), 1588 (vs), 1420 (s), 1250 (m), 1121 (w), 1094, (m) 1072 (s), 970 (s), 845 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{16}H_{20}BrO_2Si$ $[M\text{-}H]^-$: 351.0421 found: 351.0424.

2-Bromonaphthalene-1,6-diol 293b



White solid

TLC (57% dichloromethane in cyclohexane): R_f = 0.12 (UV, $KMnO_4$).

mp: 90 °C.

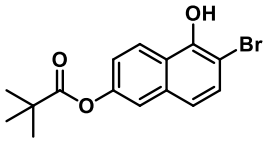
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.12 – 7.06 (m, 2H), 5.93 (s, 1H), 5.19 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.4, 148.5, 135.4, 129.3, 124.7, 120.0, 119.9, 117.8, 109.6, 101.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3451 (w), 1624 (s), 1601 (m), 1587 (vs), 1385 (m), 1230 (s), 1171 (w), 972 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_6BrO_2$ $[M\text{-}H]^-$: 236.9557 found: 236.9561.

6-Bromo-5-hydroxynaphthalen-2-yl pivalate 295



Colorless solid

TLC (50% dichloromethane in cyclohexane): R_f = 0.51 (UV, CAM).

mp: 122–124 °C

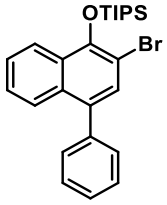
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, *J* = 9.1 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.05 – 6.96 (m, 3H), 5.77 (s, 1H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 177.3, 149.8, 148.5, 134.5, 129.4, 124.2, 122.4, 121.4, 121.1, 118.4, 103.8, 39.3, 27.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3420 (w), 3054 (w), 1831 (s), 1670 (vs), 1481 (m), 1393 (s), 1212 (m), 1150 (w), 1067 (s), 889 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{14}BrO_3$ $[M\text{-}H]^-$: 321.0132 found: 321.0133.

((2-Bromo-4-phenylnaphthalen-1-yl)oxy)triisopropylsilane 297



Colorless oil

TLC (12% dichloromethane in cyclohexane): R_f = 0.79 (UV, CAM).

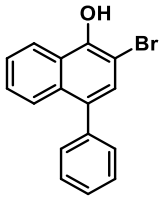
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.39 (m, 8H), 1.60 (h, *J* = 7.5 Hz, 3H), 1.20 (d, *J* = 7.6 Hz, 18H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 149.5, 139.6, 134.9, 132.1, 131.2, 130.3, 129.2, 128.4, 127.5, 126.5, 126.4, 125.9, 123.1, 109.0, 18.3, 14.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3518 (w), 2957 (m), 1587 (vs), 1509 (m), 1456 (s), 1372 (w), 1340 (vs), 850 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{32}BrOSi$ $[M+H]^+$: 455.1400 found: 455.1407.

2-Bromo-4-phenylnaphthalen-1-ol 296



Crude mixture: yellow-brown solid in oily film

TLC (12% dichloromethane in cyclohexane): R_f = 0.45 (UV, CAM).

mp: 118 °C.

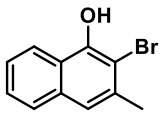
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.33 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.38 (m, 8H), 6.01 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 147.8, 139.5, 134.3, 132.1, 130.3, 129.1, 128.5, 127.5, 127.0, 126.2, 126.2, 124.7, 122.7, 103.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3522 (w), 3157 (w), 1621 (m), 1534 (s), 1457 (vs), 1402 (m), 1341 (m), 1320 (s), 1113 (m), 828 (w), 797 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{16}H_{10}BrO$ $[M-H]^-$: 296.9921 found: 296.9924.

2-Bromo-3-methylnaphthalen-1-ol 298



Orange crystals

TLC (25% dichloromethane in cyclohexane): R_f = 0.50 (UV, CAM).

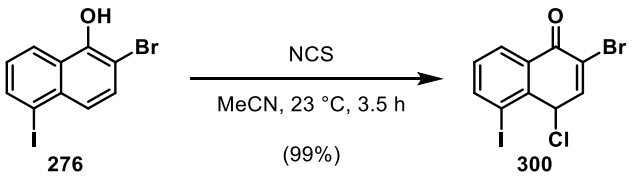
mp: 60–63 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.31 (t, *J* = 1.1 Hz, 1H), 6.09 (s, 1H), 2.54 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 148.3, 134.7, 133.2, 127.1, 126.9, 125.3, 122.7, 122.4, 120.6, 108.4, 23.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3243 (w), 2500 (w), 3021 (m), 2721 (m), 1691 (s), 1599 (s), 1321 (vs), 1212 (w), 1124 (m), 1084 (m), 903 (s) cm^{-1}.

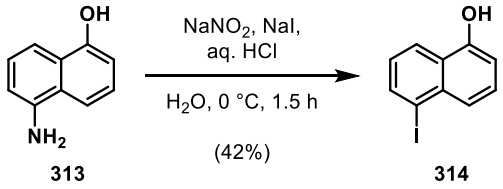
HRMS (ESI) calc. for $C_{11}H_8BrO$ $[M-H]^-$: 234.9764 found: 234.9759.



2-Bromo-4-chloro-5-iodonaphthalen-1(4*H*)-one 300

N-Chlorosuccinimide (66.0 mg, 495 µmol, 1.10 equiv) was added to a solution of naphthol **276** (157 mg, 450 µmol, 1 equiv) in acetonitrile (3.00 mL, 0.15 M) in three portions over 30 minutes at 23 °C. After three hours, the mixture was diluted with a mixture of cyclohexane and ethyl acetate (1:1) and quickly filtered over a short plug of silica to obtain the desired product **300** in approximately 95% purity (171 mg, 446 µmol, 99%).

TLC (14% ethyl acetate in cyclohexane): R_f = 0.38 (UV, CAM, $KMnO_4$).
mp: 75 °C (decomposition).
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.22 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.62 (d, *J* = 5.3 Hz, 1H), 7.30 – 7.22 (m, 1H), 5.67 (d, *J* = 5.3 Hz, 1H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 177.2, 145.1, 144.0, 141.2, 131.9, 131.2, 128.8, 126.4, 100.5, 56.9.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3253 (w), 2949 (w), 1732 (m), 1593 (m), 1523 (w), 821 (s), 723 (m), 702 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{10}H_4BrClIO$ $[M\text{-}H]^-$: 380.8184 found: 380.8188.

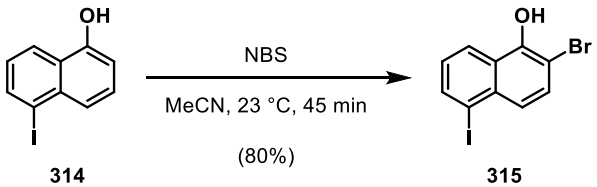


313 314

5-Iodonaphthalen-1-ol 314

A solution of sodium nitrite (463 mg, 6.72 mmol, 1.07 equiv) in water (3.36 mL, 2 M) was cooled to 0 °C added to a solution of naphthol **313** (1.00 g, 6.28 mmol, 1 equiv) in 2 M hydrochloric acid (31.4 mL, 0.2 M) at 0 °C and stirred for 20 minutes. A solution of sodium iodide (1.88 g, 12.6 mmol, 2.00 equiv) in water (6.61 mL, 1.9 M) was cooled to 0 °C added to the reaction. After 1.5 hours, the reaction was stopped by the addition of ethyl ether (150 mL) and water (50 mL) and filtered through cotton before being extracted with diethyl ether (3 × 40 mL). The combined organic layers were concentrated under reduced pressure and the crude mixture was purification by silica gel chromatography (20% ethyl acetate in cyclohexane) to give the title compound **314** (712 mg, 2.64 mmol, 42%) as a white solid.

Data consistent with literature: *J. Med. Chem.*, **2005**, *48*, 5580–5588.



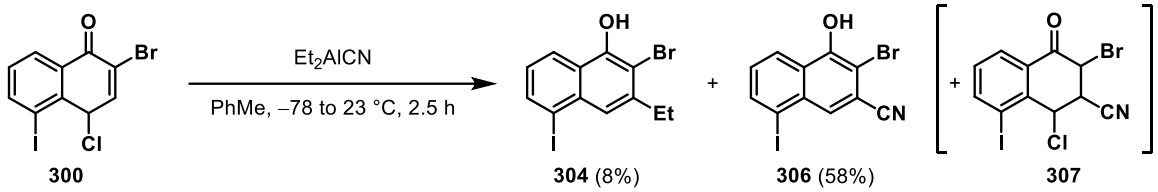
314 315

2-Bromo-5-iodonaphthalen-1-ol 315

A freshly prepared solution of *N*-bromosuccinimide (428 mg, 2.41 mmol, 1.00 equiv) in acetonitrile (5.23 mL, 0.46 M) was added to a solution of naphthol **314** (650 mg, 2.41 mmol, 1 equiv) in acetonitrile

(80.2 mL, 0.03 M) at 23 ˚C and stirred for 45 minutes at that temperature. The reaction was stopped by removal of the solvent under reduced pressure. Purification by silica gel chromatography (13% ethyl acetate in cyclohexane) gave the title compound **315** (673 mg, 1.93 mmol, 80%) as a beige solid.

For analytical data: *see above.*



300 **304** (8%) **306** (58%) **307**

2-Bromo-3-ethyl-5-iodonaphthalen-1-ol 304
3-Bromo-4-hydroxy-8-iodo-2-naphthonitrile 306

Diethylaluminium cyanide (Nagata's reagent) (1 M in PhMe, 138 µL, 138 µmol, 1.20 equiv) was added dropwise to a solution of enone **300** (44.0 mg, 115 µmol, 1 equiv) in toluene (1.15 mL, 0.1 M) at –78 ˚C. After two hours of stirring at that temperature, the residual solid dry-ice was removed from the external acetone bath to initiate slow warming to 23 °C within 50 minutes. After stirring for ten minutes at 23 °C, the red solution was diluted with water (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure to give a crude mixture containing 9% of **304** and 63% of **307** as indicated by ^{1}H-NMR. Purification by silica gel chromatography (11% ethyl acetate in cyclohexane + 2% acetic acid) afforded compound **304** (3.50 mg, 9.20 µmol, 8%) as a white solid and compound **306** (24.9 mg, 66.7 µmol, 58%) as a yellow solid.

Compound **304**

TLC (14% diethyl acetate in cyclohexane): R_f = 0.59 (UV, CAM, $KMnO_4$).

mp: 69 °C

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.11 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.57 (s, 1H), 7.15 (dd, *J* = 8.4, 7.3 Hz, 1H), 6.19 (s, 1H), 2.95 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 148.3, 142.0, 138.7, 134.0, 126.3, 123.8, 123.5, 123.4, 108.9, 98.5, 30.3, 14.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3302 (w), 3104 (w), 1521 (s), 1501 (m), 1434 (vs), 1409 (m), 1331 (m), 1291 (s), 1209 (s), 1197 (m), 1144 (s), 798 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{12}H_9BrIO$ $[M-H]^-$: 374.8887 found: 374.8891.

Compound **306**

TLC (14% diethyl acetate in cyclohexane): R_f = 0.17 (UV, CAM, $KMnO_4$).

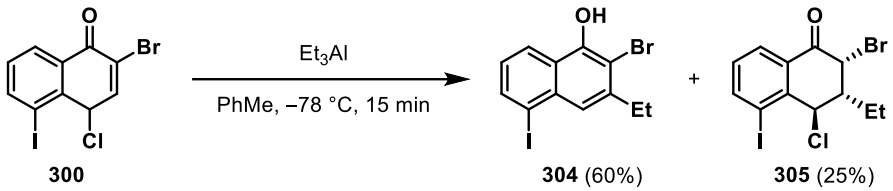
mp: 70–72 °C

^{1}H NMR (400 MHz, dichloromethane-d_2) δ 8.63 (dd, J = 7.4, 1.3 Hz, 1H), 8.50 (dd, J = 8.4, 1.3 Hz, 1H), 7.37 (dd, J = 8.4, 7.4 Hz, 1H), 7.22 (s, 1H).

^{13}C NMR (101 MHz, dichloromethane-d_2) δ 154.3, 147.5, 130.7, 130.7, 130.0, 126.1, 125.2, 117.5, 114.9, 110.8, 89.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3527 (w), 3332 (w), 2248 (s), 1639 (m), 1599 (s), 1394 (m), 1301 (vs), 1203 (s), 1123 (vs), 982 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_4BrINO$ [M-H]$^-$: 371.8526 found: 371.8529.



300 **304** (60%) **305** (25%)

2-Bromo-3-ethyl-5-iodonaphthalen-1-ol 304
2-Bromo-4-chloro-3-ethyl-5-iodo-3,4-dihydronaphthalen-1(2*H*)-one 305

Triethylaluminium (25 wt% in PhMe, 23.0 µL, 51.3 µmol, 1.20 equiv) was added dropwise to a solution of enone **300** (16.4 mg, 42.8 µmol, 1 equiv) in toluene (428 µL, 0.1 M) at –78 ˚C. After 15 minutes of stirring at that temperature, the red solution was diluted with water (2 mL) and extracted with diethyl ether (3 × 3 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (4 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (3% ethyl acetate in cyclohexane) afforded compound **304** (9.70 mg, 25.7 µmol, 60%) as a while solid and compound **305** (4.40 mg, 10.7 µmol, 25%) as a reddish solid.

For analytical data of compound **304**: *see above*.

Compound **305**

TLC (20% dichloromethane in pentane): R_f = 0.24 (UV, CAM, $KMnO_4$).

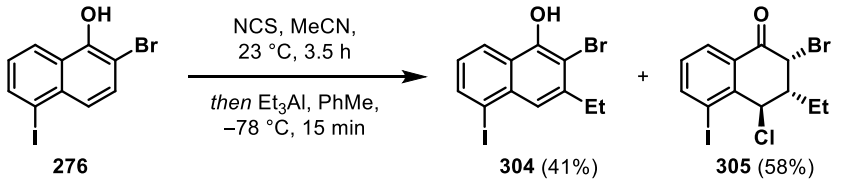
mp: 69 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (dd, J = 7.9, 1.3 Hz, 1H), 8.10 (dd, J = 7.8, 1.4 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 5.88 (d, J = 4.3 Hz, 1H), 5.51 (d, J = 3.0 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.12 – 1.94 (m, 1H), 1.07 – 0.95 (m, 4H).

^{13}C NMR (151 MHz, chloroform-*d*) δ 188.2, 146.2, 141.1, 131.3, 131.2, 128.7, 101.5, 64.8, 55.2, 52.6, 21.5, 12.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3012 (w), 1732 (s), 1637 (m), 1584 (s), 1494 (m), 1429 (s), 1192 (m), 1038 (vs), 721 (w) $^{-1}$.

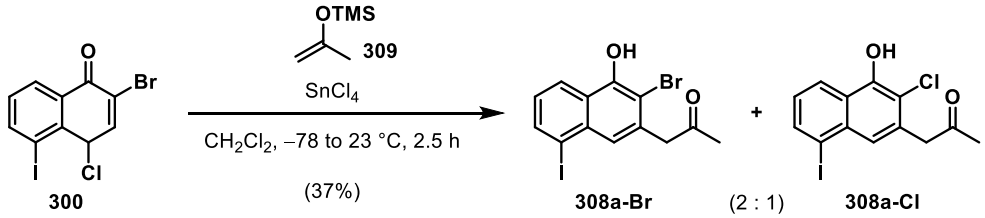
HRMS (ESI) calc. for $C_{12}H_{12}BrClIO$ [M+H]$^+$: 412.8799 found: 412.8797.



2-Bromo-3-ethyl-5-iodonaphthalen-1-ol 304
2-Bromo-4-chloro-3-ethyl-5-iodo-3,4-dihydronaphthalen-1(2*H*)-one 305

N-Chlorosuccinimide (8.40 mg, 63.0 µmol, 1.10 equiv) was added to a solution of naphthol **276** (20.0 mg, 57.3 µmol, 1 equiv) in acetonitrile (600 µL, 0.10 M) in two portions over 15 minutes at 23 °C. After three hours, the solvent was removed under reduced pressure. The obtained crude solid was re-dissolved in toluene (800 µL, 0.07 M) and cooled to –78 °C before triethylaluminium (25 wt% in PhMe, 31.4 µL, 68.8 µmol, 1.20 equiv) was added dropwise. After ten minutes of stirring at that temperature, the solution was diluted with water (2 mL) and extracted with diethyl ether (3 × 3 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (4 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (3% ethyl acetate in cyclohexane) to afford compound **304** (8.90 mg, 23.5 µmol, 41%) as a while solid and compound **305** (13.7 mg, 33.2 µmol, 58%) as a reddish solid.

For analytical data: *see above.*



1-(3-Bromo-4-hydroxy-8-iodonaphthalen-2-yl)propan-2-one 308a-Br
1-(3-Chloro-4-hydroxy-8-iodonaphthalen-2-yl)propan-2-one 308a-Cl

Tin(IV)-chloride (1 M in dichloromethane, 42.2 µL, 42.2 µmol, 1.10 equiv) was added dropwise to a solution of ketone **300** (14.7 mg, 38.3 µmol, 1 equiv) and silyl enol ether **309** (85% purity, 8.00 µL, 42.2 µmol, 1.10 equiv) in dichloromethane (500 µL, 0.08 M) at –78 ˚C. The reaction was stirred for two hours while slowly warming to 23 °C. Additional silyl enol ether **309** (85% purity, 50.0 µL, 264 µmol, 6.88 equiv) was added dropwise and the reaction was stirred at 23 °C for 30 minutes. After addition of water (4 mL), the crude mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered. The filtrate was evaporated under reduced pressure and purified by silica gel chromatography (15% dichloromethane in cyclohexane) to give the title compounds **308a-Br** and **308a-Cl** (5.40 mg, 13.3 mmol, 37%) as an inseparable mixture in a ratio of 2:1.

Mixture (2:1) of **308a-Br** and **308a-Cl**

TLC (80% dichloromethane in cyclohexane): R_f = 0.32 (UV, CAM, $KMnO_4$).

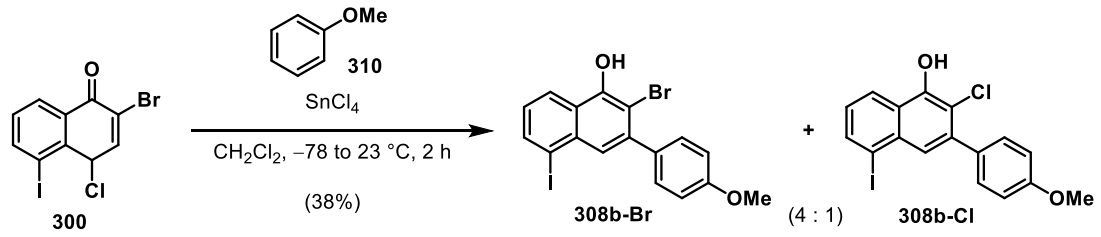
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.25 (dt, *J* = 8.4, 1.0 Hz, 1H), 8.22 (dt, *J* = 8.4, 1.0 Hz, 0.5H), 8.10 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.09 (dd, *J* = 7.4, 1.1 Hz, 0.5H), 7.56 (s, 1H), 7.55 (s, 0.5H), 7.19 – 7.15 (m, 1.5H), 6.13 (s, 1H), 6.12 (s, 0.5H), 4.05 (s, 2H), 4.03 (s, 1H), 2.28 (s, 4.5H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 204.7, 204.7, 148.8, 147.6, 139.1, 138.9, 134.0, 133.5, 133.4, 132.0, 127.0, 127.0, 126.8, 126.7, 124.1, 123.9, 123.5, 123.3, 115.9, 108.6, 98.5, 98.5, 51.8, 49.4, 29.9, 29.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3432 (w), 3394 (w), 1761 (s), 1620 (s), 1501 (s), 1330 (m), 1229 (s), 1201 (m), 1093 (s), 983 (m), 938 (m), 798 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{13}H_8BrIO_2$ $[M–H]^-$: 402.8836 found: 402.8831.

HRMS (ESI) calc. for $C_{13}H_8ClIO_2$ $[M–H]^-$: 358.9341 found: 358.9337.



2-Bromo-5-iodo-3-(4-methoxyphenyl)naphthalen-1-ol 308b-Br
2-Chloro-5-iodo-3-(4-methoxyphenyl)naphthalen-1-ol 308b-Cl

Tin(IV)-chloride (1 M in dichloromethane, 242 µL, 242 µmol, 1.20 equiv) was added dropwise to a solution of ketone **300** (42.0 mg, 110 µmol, 1 equiv) and anisole **310** (239 µL, 2.19 mmol, 20.0 equiv) in dichloromethane (1.38 mL, 0.08 M) at –30 °C. The reaction was slowly warmed to 23 °C within 1.5 hours and then stirred for further 30 minutes at that temperature. The solvent was removed under reduced pressure to give an orange-brown solid. The sensitive crude product was dissolved in a mixture of cyclohexane and ethyl acetate (19:1) and immediately subjected to flash-column-chromatography on silica gel under a nitrogen-stream to give an inseparable mixture of fairly purified compounds **308b-Br** and **308b-Cl** (19.0 mg, 41.8 µmol, 38%) in a ratio of 4:1.

Mixture (4:1) of **308b-Br** and **308b-Cl**

TLC (14% ethyl acetate in cyclohexane): R_f = 0.45 (UV, CAM, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.40 (dd, *J* = 8.4, 1.3 Hz, 1.25H), δ 8.31 – 8.21 (m, 0.5H), 8.25 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.11 (td, *J* = 7.3, 1.2 Hz, 0.5H), 7.50 (s, 1.25H), 7.21 – 7.16 (m, 2.5H), 7.12 (dd, *J* = 8.4, 7.3 Hz, 1.25H), 7.00 – 6.94 (m, 2.5H), 5.98 (s, 1.25H), 3.89 (s, 0.75H), 3.89 (s, 3H).

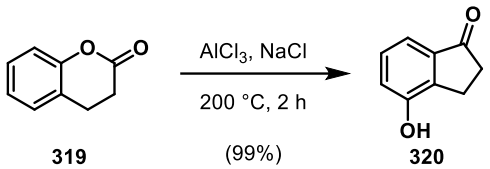
^{13}C NMR (101 MHz, chloroform-*d*)[1] δ 159.7, 147.8, 143.2, 135.2, 133.0, 132.7, 132.7, 131.7, 126.8, 126.4, 123.6, 113.5, 103.7, 92.4, 55.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3131 (w), 1689 (m), 1643 (w), 1601 (m), 1573 (s), 1513 (vs), 1407 (s), 1411 (m), 1289 (s), 1241 (vs), 1179 (m), 1074 (s), 999 (m), 783 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{11}BrIO_2$ $[M-H]^-$: 452.8993 found: 452.8995.

HRMS (ESI) calc. for $C_{17}H_{11}ClIO_2$ $[M-H]^-$: 408.9498 found: 408.9492.

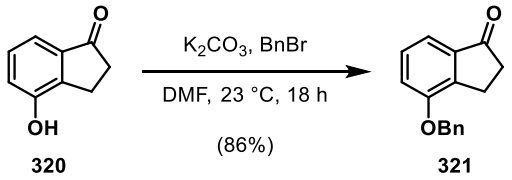
[1]*Only the set of signals for the 2-bromo-naphthol **308b-Br** is given due to the low intensity of the 2-chloro-naphtho-signals.*



4-Hydroxy-1-indanone 320

Aluminium(III) chloride (63.8 g, 479 mmol, 5.50 equiv) and sodium chloride (16.3 g, 278 mmol, 3.20 equiv) were placed in an oven-dried one-necked round-bottom flask equipped with a magnetic stirring bar and connected to a Dreschel bottle containing sodium hydroxide (2 M). The mixture was heated to 160 °C until liquefaction was reached. The glass joint was slightly elevated by which the dihydrocoumarin (11.0 mL, 87.0 mmol, 1 equiv) could be added to the mixture via syringe. The glass joint was closed again and the mixture was stirred at 200 °C. After two hours, the oil bath was removed and the reaction was allowed to cool down to 23 °C. (CAUTION: remove Dreschel bottle before removing the oil bath! Cooling down generates underpressure within seconds, which forces the aqueous basic solution into the reaction flask!) The flask was put into a cooling bath at 0 °C before 20 g crushed ice and concentrated hydrochloric acid (30 mL) were slowly added until a viscous suspension was obtained. After stirring for 30 minutes at 0 °C, the suspension was filtered through a Büchner funnel equipped with filter paper and washed with water (100 mL). The supernatant was put into an oven and dried for 16 hours at 80 °C to obtain 13.1 g (quant.) of the desired product as a grey solid without the need for further purification.

Data consistent with literature: *Angew. Chem. Int. Ed.*, **2020**, *59*, 270–274.



4-(Benzyloxy)-1-indanone 321

Benzyl bromide (12.5 mL, 87.0 mmol, 1.20 equiv) was added dropwise to a solution of potassium carbonate (24.1 g, 174 mmol, 2.00 equiv) and 4-hydroxyindanone **320** (13.1 g, 87.0 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (145 mL, 0.6 M) at 23 °C. After 18 hours, water (400 mL) was added to the resulting suspension and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with water (3 × 150 mL) and a saturated aqueous solution of sodium chloride (200 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and

the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (20% ethyl acetate in cyclohexane) gave the title compound **321** (17.8 g, 74.8 mmol, 86%) as a colorless solid.

TLC (20% diethyl ether in pentane): R_f = 0.56 (UV, $KMnO_4$).

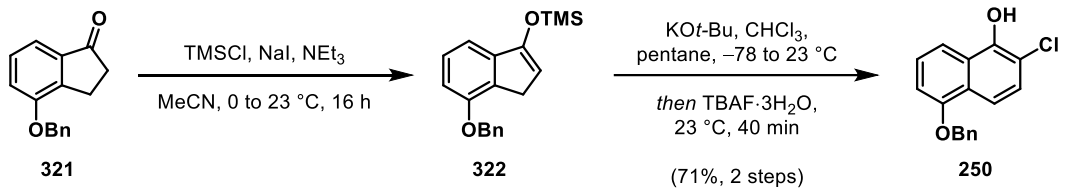
mp: 78–79 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51 – 7.28 (m, 70H), 7.09 (dd, *J* = 7.7, 1.0 Hz, 1H), 5.17 (s, 2H), 3.19 – 3.06 (m, 2H), 2.74 – 2.62 (m, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 207.2, 156.4, 144.6, 138.9, 136.7, 128.9, 128.8, 128.3, 127.4, 116.4, 115.8, 70.2, 36.3, 22.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2918 (m), 2885 (w), 1693 (m), 1593 (vs), 1478 (m), 1263 (s), 1227 (m), 1020 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{16}H_{15}O_2$ $[M+H]^+$: 239.1067 found: 239.1067.



5-(Benzyloxy)-2-chloronaphthalen-1-ol 250

Triethylamine (1.32 mL, 9.51 mmol, 1.50 equiv) and trimethylsilyl chloride (1.21 mL, 9.51 mmol, 1.50 equiv) were added in sequence to a suspension of sodium iodide (9.50 mg, 63.8 µmol, 1 mol%) and indanone **321** (1.51 g, 6.34 mmol, 1 equiv) in acetonitrile (7.64 mL, 0.83 M) at 0 ˚C. The resulting suspension was allowed to warm to 23 ˚C. After 16 hours, the solvent was removed under reduced pressure and the residue was dissolved in *n*-hexane (5 mL). The suspension was filtered through a short plug of Celite and the filtrate was evaporated under reduced pressure to afford the crude silyl enol ether. This material was used immediately without further purification.

The crude intermediate was dissolved in pentane (7.55 mL, 0.84 M), cooled to –78 °C and slowly added to a suspension of potassium *tert*-butoxide (sublimed grade, 1.42 g, 12.7 mmol, 2.00 equiv) in pentane (12.7 mL, 1.0 M) at –78 ˚C. The flask of the crude intermediate was rinsed with pentane (3 × 6.70 mL) and added to the reaction in the same fashion. A solution of chloroform (1.12 mL, 13.9 mmol, 2.20 equiv) in pentane (13.9 mL, 1.0 M) was added dropwise to the mixture and the suspension was stirred at –78 ˚C for 30 minutes before being allowed to warm to 23 ˚C. After 1.5 hours, water (5 mL) was added and the resulting solution was concentrated to 20 mL under reduced pressure. Tetrabutylammonium fluoride trihydrate (3.00 g, 9.51 mmol, 1.50 equiv) was added in one portion and the solution was stirred vigorously for 40 minutes. Aqueous hydrochloric acid (1 M, 15 mL) was added and the resulting solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (40 mL) and a saturated aqueous solution of sodium chloride (50 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and filtrate was evaporated

under reduced pressure. Purification by silica gel chromatography (5% ethyl acetate in cyclohexane) gave the title compound **250** (1.29 g, 4.53 mmol, 71%) as a slightly yellow gum.

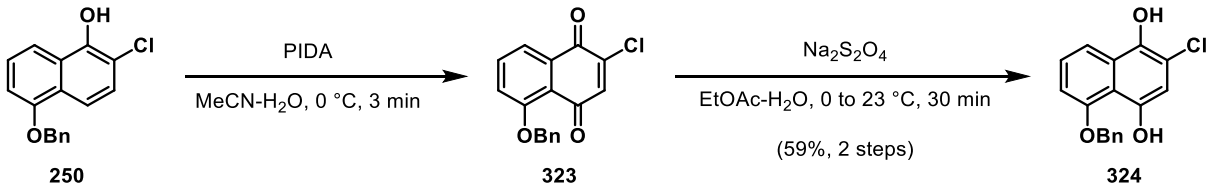
TLC (20% diethyl ether in pentane): R_f = 0.50 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.87 (dd, *J* = 9.0, 0.89 Hz, 1H), 7.80 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.52 – 7.51 (m, 2H), 7.44 – 7.40 (m, 3H), 7.37 – 7.34 (m, 2H), 6.93 (dd, 7.7, 0.9 Hz, 1H), 5.97 (s, 1H), 5.24 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.5, 146.9, 137.0, 128.8, 128.2, 127.5, 126.4, 125.7, 125.2, 115.6, 114.7, 114.6, 106.3, 70.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3550 (w), 3425 (m), 1621 (vs), 1512 (m), 1457 (m), 1289 (vs), 1110 (m) cm^{-1}.

HRMS (EI) calc. for $C_{17}H_{13}ClO_2$ $[M]^+$: 284.0599 found: 284.0599.



250 **323** **324**

5-(Benzyloxy)-2-chloronaphthalene-1,4-diol 324

(Diacetoxyiodo)benzene (7.39 g, 22.9 mmol, 2.20 equiv) was added portionwise to a solution of naphthol **250** (2.97 g, 10.4 mmol, 1 equiv) in acetonitrile/water (2:1, 260 mL, 0.04 M) at 0 ˚C. After three minutes, the solution was concentrated to 150 mL under reduced pressure and the residue was diluted with ethyl acetate (50 mL). This solution was washed with water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered. The filtrate was evaporated under reduced pressure to give crude quinone **323** as a yellow oil. A solution of the quinone in ethyl acetate (104 mL, 0.1 M) was added portionwise to a solution of sodium dithionite (9.05 g, 52.0 mmol, 5.00 equiv) in water (130 mL, 0.4 M) at 0 ˚C. The mixture was stirred vigorously at 23 ˚C for 30 minutes before it was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered. The filtrate was evaporated under reduced pressure to give a brown oil. Purification was performed by silica gel chromatography (15% ethyl acetate in cyclohexane). In order to remove some residual quinone, the product was additionally triturated with hexane (3 × 5 mL) to give pure hydroquinone **324** (1.86 g, 6.19 mmol, 59%) as a slightly yellow solid.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.43 (UV, $KMnO_4$).

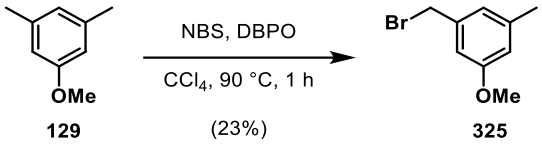
mp: 147 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.05 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.33 (m, 6H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.78 (s, 1H), 5.54 (s, 1H), 5.27 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.2, 148.2, 139.8, 135.1, 129.2, 129.06, 128.1, 126.5, 126.3, 116.3, 115.0, 114.8, 109.7, 106.4, 71.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3313 (w), 3057 (m), 1630 (s), 1610 (m), 1453 (s), 1416 (m), 1307 (w), 1277 (vs), 1013 (m), 823 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{12}ClO_3$ $[M\text{-}H]^-$: 299.0480 found: 299.0482.

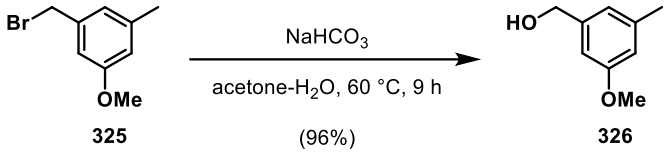


1-(Bromomethyl)-3-methoxy-5-methylbenzene 325

Freshly recrystallized *N*-bromosuccinimide (1.96 g, 11.0 mmol, 1.00 equiv) and dibenzoyl peroxide (27.0 mg, 110 µmol, 1 mol%) were added to a stirring solution of 3,5-dimethylanisole (1.56 mL, 11.0 mmol, 1 equiv) in tetrachloromethane (122 mL, 0.09 M) at 23 °C. The flask was directly transferred to an oil bath of 90 °C and the reaction mixture was refluxed at this temperature for one hour. The reaction was allowed to cool to 23 °C and the cooled solution was filtered through Celite. Evaporation of the solvent gave the crude product, which was purified by silica gel chromatography (20% dichloromethane in cyclohexane) to give the title compound **325** (545 mg, 2.53 mmol, 23%) as a colorless oil.

Data consistent with literature: *Synthesis*, **2007**, *1*, 65–74.

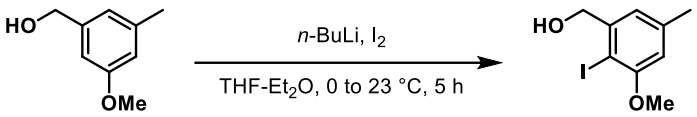
Note: Yields varied between 1% and 63%. Given is the yield obtained on the largest scale tested.



(3-Methoxy-5-methylphenyl)methanol 326

A solution of sodium hydrogen carbonate (328 mg, 3.91 mmol, 1.25 equiv) in water (26.0 mL, 0.12 M) was added to a solution of benzyl bromide **325** (672 mg, 3.12 mmol, 1 equiv) in acetone (15.6 mL, 0.2 M) and stirred at 80 °C for nine hours. The reaction was allowed to cool to 23 °C and the solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (30% diethyl ether in pentane) gave the title compound **326** (456 mg, 3.00 mmol, 96%) as a white solid.

Data consistent with literature: *Synthesis*, **2007**, *1*, 65–74.

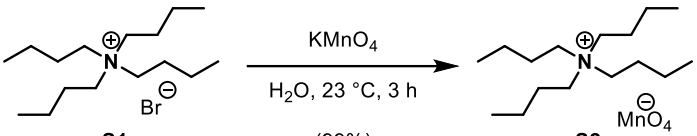


326 327

(2-Iodo-3-methoxy-5-methylphenyl)methanol 327

To a solution of benzyl alcohol **326** (6.41 g, 42.1 mmol, 1 equiv) in diethyl ether (281 mL, 0.15 M) *n*-butyllithium (2.44 M in *n*-hexane, 38.0 mL, 92.7 mmol, 2.20 equiv) was added dropwise at 0 °C. After stirring for 3.5 hours at 23 °C, the reaction was cooled to 0 °C before tetrahydrofuran (140 mL, 0.3 M) was added. To this mixture a solution of iodine (31.2 g, 51.8 mmol, 1.23 equiv) in tetrahydrofuran (1 mL, 52 M) was added dropwise and stirred for 30 minutes at 0 °C. The mixture allowed to warm to 23 °C before a saturated solution of sodium thiosulfate (120 mL) was added. The aqueous layer was discarded and a saturated solution of ammonium chloride (120 mL) was added. The mixture was extracted with diethyl ether (3 × 200 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (17% diethyl ether in pentane) gave the title compound **327** (9.84 g, 35.4 mmol, 84%) as a white solid.

Data consistent with literature: *Org. Lett.*, **2007**, *9*, 2915–2918.

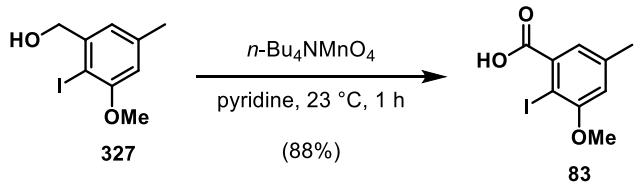


S1 S2

Tetra-*n*-butylammonium permanganate S2

A solution of tetra-*n*-butylammonium bromide (5.01 g, 15.5 mmol, 1.12 equiv) in water (19.9 mL, 0.78 M) was added to a solution of potassium permanganate (2.19 g, 13.9 mmol, 1 equiv) in water (49.5 mL, 0.28 M) and stirred for three hours at 23 °C. The mixture was filtered and the precipitate was washed with water (20 mL) and diethyl ether (20 mL). The precipitate was dried for 24 hours under high-vacuum to give the title compound **S2** (4.20 g, 11.6 mmol, 84%) as a purple solid.

Data consistent with literature: *J. Phys. Chem. B*, **1999,** *103*, 7416–7428.



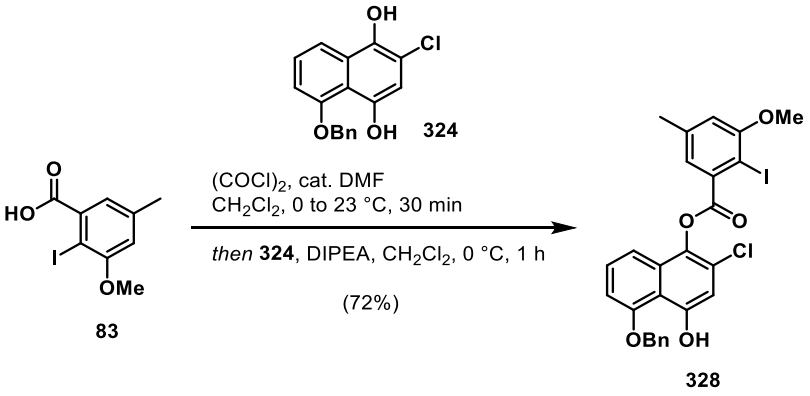
327 83

2-Iodo-3-methoxy-5-methylbenzoic acid 83

To a solution of benzyl alcohol **327** (1.09 g, 3.92 mmol, 1 equiv) in pyridine (19.6 mL, 0.2 M), tetra-*n*-butylammonium permanganate (1.84 g, 5.10 mmol, 1.30 equiv) was added portionwise over a period of

five minutes and then stirred at 23 °C. After one hour, the mixture was poured onto a solution of sodium sulfite (900 mg, 7.14 mmol, 1.82 equiv) in 1 M hydrochloric acid (40 mL). The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (50% diethyl ether in pentane + 1% triethylamine, then 1% acetic acid) gave benzoic acid **83** (1.01 g, 3.45 mmol, 88%) as a white solid.

Data consistent with literature: *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015.



5-(Benzyloxy)-2-chloro-4-hydroxynaphthalen-1-yl 2-iodo-3-methoxy-5-methylbenzoate 328

Oxalyl chloride (63.0 µL, 736 µmol, 1.10 equiv) was added dropwise to a solution of benzoic acid **83** (215 mg, 736 µmol, 1.10 equiv) in dichloromethane (3.68 mL, 0.2 M) at 0 ˚C. Two drops of *N*,*N*-dimethylformamide were added and the reaction was allowed to warm to 23 ˚C and stirred for 30 minutes. This solution was then added dropwise to a solution of hydroquinone **324** (201 mg, 669 µmol, 1 equiv) and *N*,*N*-diisopropylethylamine (350 µL, 2.01 mmol, 3.00 equiv) in dichloromethane (3.35 mL, 0.2 M) at 0 ˚C and stirred for one hour at that temperature. After addition of ethyl acetate (4 mL) and water (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 water (10 mL) and a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (10% ethyl acetate in cyclohexane) gave the title compound **328** (278 mg, 483 µmol, 72%) as a yellow oil.

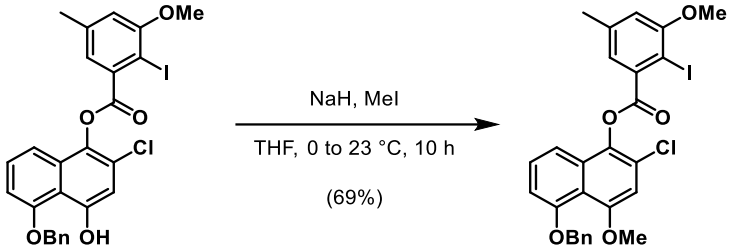
TLC (20% diethyl ether in pentane): R_f = 0.76 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.46 (s, 1H), 7.61 (s, 1H), 7.57 (d, *J* = 8.5, 1H), 7.51 – 7.37 (m, 6H), 6.95 – 6.92 (m, 2H), 6.87 (s, 1H), 5.30 (s, 2H), 3.95 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 164.8, 158.9, 155.5, 153.2, 140.0, 136.3, 134.8, 134.7, 130.3, 129.2, 129.1, 128.1, 127.7, 125.4, 124.3, 115.5, 115.2, 114.5, 110.9, 106.3, 83.8, 72.0, 56.9, 21.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3377 (w), 2940 (w), 1754 (m), 1708 (m), 1606 (s), 1435 (m), 1395 (vs), 1313 (m), 1140 (w), 1012 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{19}ClIO_5$ $[M-H]^-$: 572.9971 found: 572.9961.



328 329

5-(Benzyloxy)-2-chloro-4-methoxynaphthalen-1-yl 2-iodo-3-methoxy-5-methylbenzoate 329

Sodium hydride (60% dispersion in mineral oil, 24.5 mg, 613 µmol, 1.30 equiv) was added to a stirring solution of phenol **328** (271 mg, 471 µmol, 1 equiv) in tetrahydrofuran (471 µL, 1 M) at 0 ˚C. After five minutes, methyl iodide (440 µL, 7.07 mmol, 15.0 equiv) was added dropwise. The reaction was stirred at 0 ˚C for 20 minutes before being allowed to warm to 23 ˚C. After ten hours, water (1 mL) was added and the solution was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with water (2 mL) and a saturated aqueous solution of sodium chloride (2 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (10% ethyl acetate in cyclohexane) gave the title compound **329** (192 mg, 326 µmol, 69%) as a yellow solid.

TLC (20% diethyl ether in pentane): R_f = 0.79 (UV, $KMnO_4$).

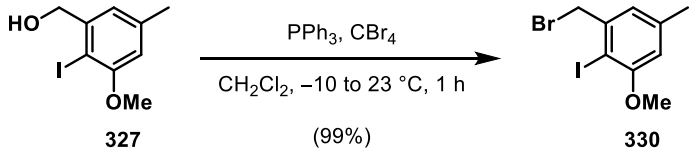
mp: 155–157 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.64 (s, 1H), 7.60 – 7.54 (m, 3H), 7.47 – 7.40 (m, 3H), 7.34 (t, 1H), 6.98 (d, *J* = 7.7, 1H), 6.88 (m, 2H), 5.22 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 164.8, 159.0, 156.6, 156.1, 140.1, 137.3, 136.3, 136.1, 131.1, 128.6, 128.5, 127.8, 127.1, 124.4, 124.2, 117.5, 115.4, 114.4, 109.4, 106.6, 84.0, 71.5, 57.0, 56.7, 21.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2935 (w), 1759 (s), 1575 (m), 1393 (s), 1322 (m), 1267, (vs) 1180 (m), 1050 (vs), 1013 (m), 840 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{23}ClIO_5$ $[M+H]^+$: 589.0273 found: 589.0275.



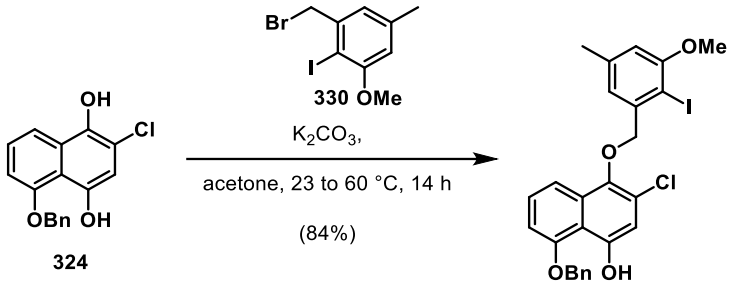
327 330

1-(Bromomethyl)-2-iodo-3-methoxy-5-methylbenzene 330

Triphenylphosphine (18.4 g, 70.1 mmol, 2.00 equiv) was added to a stirring solution of benzyl bromide **327** (9.75 g, 35.1 mmol, 1 equiv) in dichloromethane (351 mL, 0.1 M) at 23 °C and stirred for ten minutes

before the mixture was cooled to –10 ˚C. A solution of tetrabromomethane (23.3 g, 70.1 mmol, 2.00 equiv) in dichloromethane (1 mL) was added dropwise to the reaction and stirred for one hour at 23 °C. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (10% dichloromethane in cyclohexane) to give benzyl bromide **330** (12.0 g, 35.1 mmol, 99%) as a white solid.

Data consistent with literature: *Chem. Commun.***, 2018**, **54**, 1885–1888.



8-(Benzyloxy)-3-chloro-4-((2-iodo-3-methoxy-5-methylbenzyl)oxy)naphthalen-1-ol 333

Potassium carbonate (410 mg, 2.97 mmol, 1.10 equiv) was added to a stirring solution of dihydroquinone **324** (1.06 g, 3.51 mmol, 1.30 equiv) in acetone (8.77 mL, 0.4 M) at 23 ˚C. After five minutes, benzyl bromide **330** (920 mg, 2.70 mmol, 1 equiv) was added in one portion to the mixture and then stirred for 14 hours at 60 °C. The reaction was allowed to cool to 23 ˚C before addition of water (4 mL) and extraction with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (5% ethyl acetate in cyclohexane) gave the title compound **333** (1.27 g, 2.27 mmol, 84%) as yellowish foam.

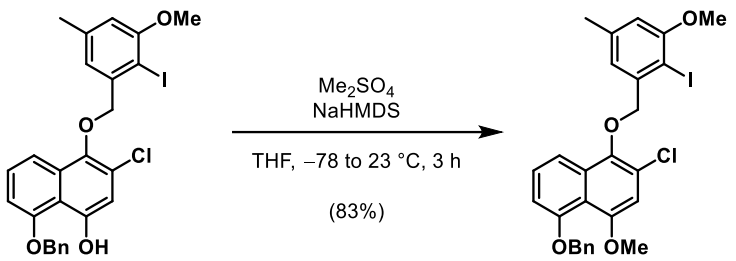
TLC (10% ethyl acetate in cyclohexane): R_f = 0.30 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.30 (s, 1H), 7.75 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.52 – 7.40 (m, 5H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.35 (m, 1H), 6.92 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.87 (s, 1H), 6.67 (d, *J* = 1.3 Hz, 1H), 5.28 (s, 2H), 5.04 (s, 2H), 3.91 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.8, 155.7, 151.6, 142.8, 141.2, 139.9, 135.0, 131.5, 129.2, 129.1, 128.1, 127.1, 125.3, 122.1, 116.4, 114.8, 111.4, 111.3, 106.2, 85.1, 79.3, 72.0, 56.6, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3471 (m), 2947 (w), 1616 (m), 1602 (m), 1435 (w), 1411 (s), 1396 (s), 1326 (m), 1126 (vs), 1022 (m), 928 (s), 838 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{23}ClIO_4$ $[M+H]^+$: 561.0324 found: 561.0318.



333 334

5-(Benzyloxy)-2-chloro-1-((2-iodo-3-methoxy-5-methylbenzyl)oxy)-4-methoxynaphthalene 334

Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.28 mL, 2.28 mmol, 1.01 equiv) was added to a stirring solution of dihydroquinone **333** (1.27 g, 2.26 mmol, 1 equiv) in tetrahydrofuran (2.82 mL, 0.8 M) at –78 ˚C. After addition of dimethyl sulfate (238 µL, 2.51 mmol, 1.11 equiv), the reaction was allowed to warm to 23 °C and stirred for three hours (*Note: On smaller scales we observed the mixture turning into a viscous gel. In that case, more tetrahydrofuran was added until a solution was obtained.*). A saturated solution of sodium hydrogen carbonate (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (5% ethyl acetate in cyclohexane) gave the title compound **334** (1.08 g, 1.88 mmol, 83%) as a white foam.

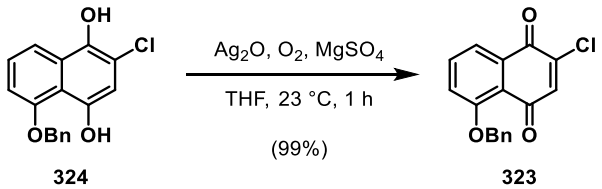
TLC (10% ethyl acetate in cyclohexane): R_f = 0.40 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.47 – 7.39 (m, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.85 (s, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.8, 156.6, 154.4, 143.9, 141.3, 139.8, 137.4, 132.3, 128.5, 127.8, 127.7, 127.0, 123.8, 122.0, 117.7, 115.2, 111.4, 109.2, 107.3, 85.0, 79.2, 71.5, 56.6, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3569 (m), 3144 (w), 1876 (m), 1692 (m), 1477 (m), 1424 (vs), 1398 (s), 1333 (m), 1026 (vs), 1002 (s), 999 (w), 767 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{25}ClIO_4$ $[M+H]^+$: 575.0481 found: 575.0477.



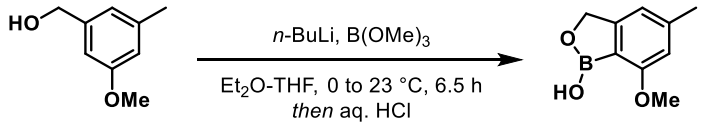
324 323

5-(Benzyloxy)-2-chloronaphthalene-1,4-dione 323

Dihydroquinone **324** (130 mg, 432 µmol, 1 equiv) was dissolved in tetrahydrofuran (8.64 mL, 0.05 M) and then purged with oxygen for two minutes. To this solution was added silver(I) oxide (801 mg, 3.46 mmol, 8.00 equiv) and magnesium sulfate (520 mg, 4.32 mmol, 10.0 equiv) and the reaction

mixture was purged again for two minutes and then stirred at 23 °C. After 30 minutes, the mixture was filtered through a short plug of silica using dichloromethane as eluent. Removal of the solvent under reduced pressure gave the title compound **323** (129 mg, 0.431 mmol, 99%) as a yellow solid.

TLC (25% diethyl ether in pentane): R_f = 0.34 (UV, CAM, $KMnO_4$).
mp: 131 °C (decomposition).
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.30 (m, 4H), 7.13 (s, 1H), 5.31 (s, 2H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 181.7, 178.5, 158.9, 143.7, 138.0, 135.9, 135.1, 133.7, 128.9, 128.2, 126.8, 120.7, 120.4, 71.1.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3192 (w), 3001 (w), 1793 (s), 1767 (m), 1702 (s), 1485 (w), 1283 (vs), 1194 (m), 1100 (s), 839 (w) cm^{-1}.
HRMS (ESI) calc. for $C_{17}H_{12}ClO_3$ $[M+H]^+$: 299.0469 found: 299.0468.



326 (63%) 345

7-Methoxy-5-methylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol 345
To a solution of benzyl alcohol **326** (100 mg, 657 µmol, 1 equiv) in diethyl ether (4.38 mL, 0.15 M) *n*-butyllithium (2.44 M in *n*-hexane, 593 µL, 1.45 mmol, 2.20 equiv) was added dropwise at 0 °C. After stirring for five hours at 23 °C, tetrahydrofuran (2.19 mL, 0.3 M) was added and the mixture was stirred for one hour. To this solution trimethyl borate (732 µL, 6.57 mmol, 10.0 equiv) was added in one portion and stirred for 30 minutes at 23 °C. A saturated solution of ammonium chloride (5 mL) was added and stirred for 15 minutes before it was acidified with aqueous hydrochloric acid (2 M, 10 mL). The mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (dichloromethane grading to 1.3% methanol in dichloromethane) gave oxaborole **345** (73.7 mg, 414 µmol, 63%) as a beige solid.

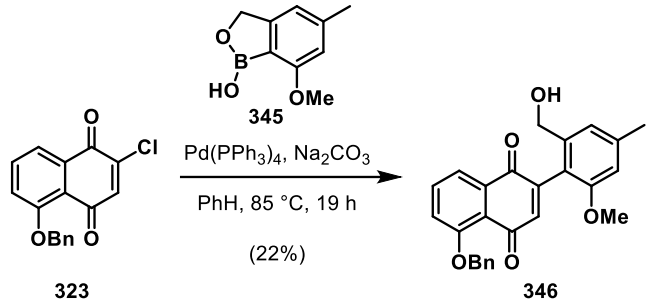
TLC (5% diethyl ether in pentane): R_f = 0.59 (CAM).
mp: 87–89 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 6.75 (s, 1H), 6.57 (s, 1H), 5.14 (s, 1H), 5.01 (s, 2H), 3.87 (s, 3H), 2.41 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 162.2, 156.6, 144.6, 114.6, 113.9[1], 109.4, 71.1, 55.3, 22.4.
^{11}B NMR (128 MHz, chloroform-*d*) δ 32.3

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3321 (w), 3291 (w), 2401 (m), 1483 (s), 1385 (vs), 1193 (s), 1103 (m), 523 (m) cm^{-1}.

HRMS (ESI) calc. for $C_9H_{10}BO_3$ $[M\text{-}H]^-$: 177.0728 found: 177.0729.

[1]*detected only via HMBC analysis (signal not visible in* [13]*C-spectrum)*

Note: We observed uncontrollable varieties in yield ranging from 10% to 63%. Given is the highest yield obtained.



5-(Benzyloxy)-2-(2-(hydroxymethyl)-6-methoxy-4-methylphenyl)naphthalene-1,4-dione 346

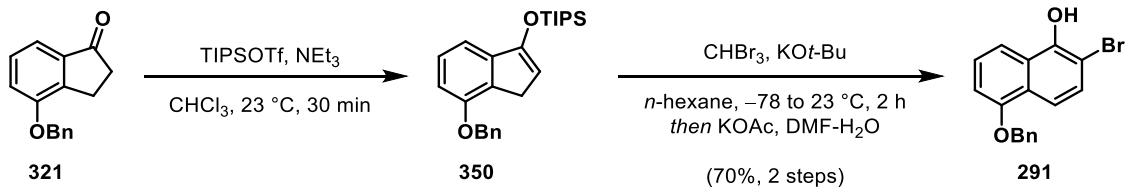
Benzoquinone **323** (23.0 mg, 77.0 µmol, 1 equiv), oxaborole **345** (17.0 mg, 95.5 µmol, 1.20 equiv), sodium carbonate (37.0 mg, 350 µmol, 4.40 equiv) and tetrakis(triphenylphosphine)palladium(0) (9.20 mg, 7.96 µmol, 0.10 equiv) were placed in a flask and purged for three times with argon. Degassed benzene (398 µL, 0.2 M) and degassed water (175 µL, 0.46 M) were added via syringe and the reaction was stirred at 85 °C for 19 hours. Water (1 mL) was added and the solution was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (25% ethyl acetate in cyclohexane) gave a rotameric mixture (ratio ca. 1:2) of compound **346** (7.00 mg, 16.9 µmol, 22%) as a beige solid of limited stability (major decomposition was observed after less than three weeks at –20 °C).

TLC (50% diethyl ether in pentane): R_f = 0.43 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.84 (d, *J* = 7.7 Hz, 0.38H), 7.76 (d, *J* = 6.9 Hz, 0.65H), 7.70 – 7.28 (m, 8H), 6.77 (s, 0.75H), 6.73 (s, 0.70H), 6.66 (s, 1.24H), 6.60 (s, 0.35H), 5.31 – 5.28 (m, 2H), 5.15 (s, 0.69H), 4.64 (s, 1.38H), 3.80 (s, 2.06H), 3.68 (s, 1.05H), 2.38 (s, 1.03H), 2.33 (s, 2.07H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3694 (w), 3509 (w), 3402 (m), 3128 (m), 2894 (w), 1874 (s), 1673 (m), 1601 (m), 1384 (s), 1294 (w), 1201 (vs), 1193 (m), 1020 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{21}O_5$ $[M\text{-}H]^-$: 413.1394 found: 413.1392.



5-(Benzyloxy)-2-bromonaphthalen-1-ol 291

Triethylamine (833 µL, 6.01 mmol, 1.40 equiv) and triisopropylsilyl trifluoromethanesulfonate (1.27 mL, 4.72 mmol, 1.10 equiv) were added in sequence to a solution of indanone **321** (1.02 g, 4.29 mmol, 1 equiv) in chloroform (53.6 mL, 0.08 M) at 23 ˚C. The reaction was stirred for two hours. The mixture was diluted with 30 mL of cyclohexane, filtered through a short plug of silica and the filtrate was evaporated under reduced pressure at 23 °C to afford the crude silyl enol ether. This material was used immediately without further purification.

The crude intermediate **350** was dissolved in *n*-hexane (6.13 mL, 0.7 M), cooled to –78 °C and slowly added to a suspension of potassium *tert*-butoxide (sublimed grade, 2.17 g, 19.3 mmol, 4.50 equiv) in *n*-hexane (8.78 mL, 2.2 M) at –78 ˚C. The flask of the crude intermediate was rinsed for three times (3 × 5.11 mL) and added to the reaction in the same fashion. After 20 minutes, a solution of freshly distilled bromoform (751 µL, 8.58 mmol, 2.00 equiv) in *n*-hexane (3.90 mL, 2.2 M) was added dropwise to the mixture and stirred for one hour at –78 ˚C. The reaction was warmed to 23 °C within one hour and stirred for an additional hour at that temperature. The solvent was removed under reduced pressure to give the crude silylated 2-bromonaphthol, which was dissolved in *N*,*N*-dimethylformamide-water (20:1, 17.2 mL, 0.25 M). Potassium acetate (548 mg, 5.58 mmol, 1.30 equiv) was added and the reaction was stirred for two hours at 23 ˚C. Water (40 mL) was added to the reaction mixture and the resulting solution was extracted with diethyl ether (6 × 40 mL). The combined organic layers were washed with water (80 mL) and a saturated aqueous solution of sodium chloride (80 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (30% grading to 70% dichloromethane in cyclohexane) gave bromonaphthol **291** (987 mg, 3.00 mmol, 70%) as a beige solid.

TLC (25% diethyl ether in pentane): R_f = 0.71 (UV, CAM).

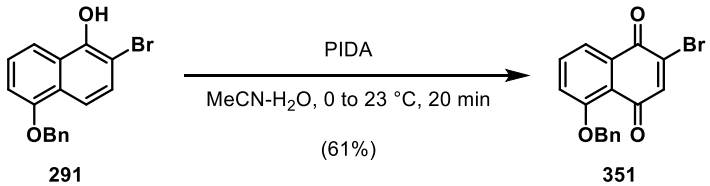
mp: 89 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (td, *J* = 8.5, 0.8 Hz, 1H), 7.81 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.46 – 7.33 (m, 4H), 6.94 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.93 (s, 1H), 5.24 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 154.54, 148.03, 137.01, 128.78, 128.18, 127.74, 127.54, 126.50, 126.23, 125.70, 116.04, 114.87, 106.43, 105.30, 70.38.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3546 (w), 3399 (w), 1701 (s), 1525 (s), 1461 (vs), 1343 (m), 1210 (m), 948 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{13}BrO_2$ $[M]^+$: 284.0599 found: 284.0599.



291 351

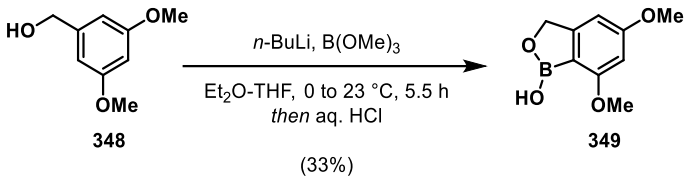
5-(Benzyloxy)-2-bromonaphthalene-1,4-dione 351

5-(benzyloxy)-2-bromonaphthalen-1-ol **291** (4.00 g, 12.2 mmol, 1 equiv) was dissolved in acetonitrile (203 mL, 0.061 M) upon gentle heating. Then the solution was cooled to 0 °C and a suspension of (diacetoxyiodo)benzene (8.61 g, 26.7 mmol, 2.20 equiv) in water (100 mL, 0.27 M) was slowly added to the mixture. The cooling bath was removed and the reaction was stirred for 20 minutes at 23 °C before a saturated aqueous solution of sodium hydrogen carbonate (150 mL) was added. The mixture was extracted with dichloromethane (3 × 300 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride (150 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (30% grading to 80% dichloromethane in cyclohexane) gave the desired benzoquinone **351** (2.54 g, 7.41 mmol, 61%) as yellow needles.

Data consistent with literature: *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1612–1623.

We want to annotate one significant difference:

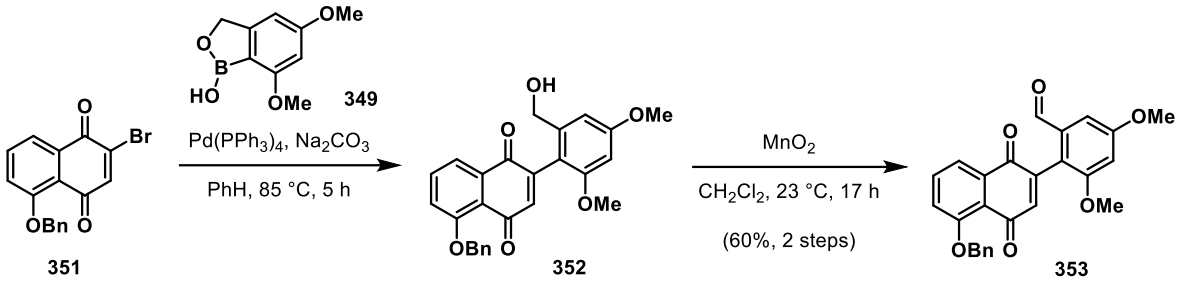
Data from Literature: **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.73 (dd, *J* = 8.5, 1.1 Hz, 1H).
Our obtained data: **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.84 (dd, *J* = 7.7, 1.0 Hz, 1H).



5,7-Dimethoxybenzo[*c*][1,2]oxaborol-1(3*H*)-ol 349

To a solution of benzyl alcohol **348** (111 mg, 657 µmol, 1 equiv) in diethyl ether (4.38 mL, 0.15 M) *n*-butyllithium (2.44 M in *n*-hexane, 593 µL, 1.45 mmol, 2.20 equiv) was added dropwise at 0 °C. After stirring for four hours at 23 °C, tetrahydrofuran (2.19 mL, 0.3 M) was added and the mixture was stirred for one hour. To this solution trimethyl borate (732 µL, 6.57 mmol, 10.0 equiv) was added in one portion and stirred for 30 minutes at 23 °C. A saturated solution of ammonium chloride (5 mL) was added and stirred for 15 minutes before it was acidified with aqueous hydrochloric acid (2 M, 10 mL). The mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was evaporated under reduced pressure. Two consecutive purification steps by silica gel chromatography (dichloromethane grading to 0.8% methanol in dichloromethane) gave oxaborole **349** (42 mg, 216 µmol, 33%) as a beige solid.

Data consistent with literature: *Chem. Eur. J.*, **1999**, *5*, 2584–2601.



2-(5-(Benzyloxy)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3,5-dimethoxybenzaldehyde 352

Benzoquinone **351** (40.0 mg, 117 µmol, 1 equiv), oxaborole **352** (27.0 mg, 140 µmol, 1.20 equiv), sodium carbonate (54 mg, 513 µmol, 4.40 equiv) and tetrakis(triphenylphosphine)palladium(0) (14.0 mg, 7.96 µmol, 0.10 equiv) were placed in a flask and purged for three times with argon. Degassed benzene (398 µL, 0.2 M) and degassed water (257 µL, 0.46 M) were added via syringe and the reaction was stirred at 85 °C for 5.5 hours. Water (1 mL) was added and the solution was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (5% methanol in dichloromethane, R_f = 0.47) was of limited effectivity, hence, the impure mixture was used in the next step without further purification.

2-(5-(Benzyloxy)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3,5-dimethoxybenzaldehyde 353

To a solution of the crude mixture containing benzyl alcohol **352** in dichloromethane (3.90 mL, 0.03 M) was added manganese dioxide (508 mg, 5.85 mmol, 50.0 equiv) and stirred at 23 °C for 17 hours. The solution was diluted with diethyl ether (10 mL) and filtered through Celite. The solvent was removed under reduced pressure. Purification by silica gel chromatography (25% ethyl acetate in cyclohexane) gave aldehyde **353** (30 mg, 70.2 µmol, 60%) as a beige solid.

TLC (66% diethyl ether in pentane): R_f = 0.40 (UV, CAM).

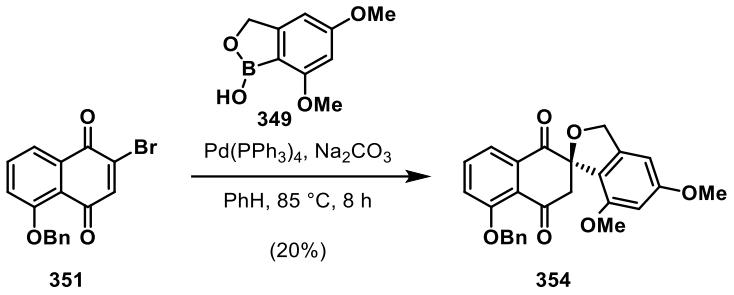
mp: 157 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.88 (s, 1H), 7.78 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 3H), 7.35 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.84 (s, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 5.33 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 190.8, 184.4, 184.0, 161.7, 158.7, 158.6, 142.5, 140.6, 136.5, 136.3, 134.9, 134.8, 128.8, 128.5, 128.1, 126.9, 120.3, 119.7, 117.5, 105.6, 104.6, 71.1, 56.3, 55.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3101 (w), 3028 (m), 2884 (w), 1850 (s), 1799 (s), 1703 (s), 1623 (m), 1599 (m), 1281 (s), 1204 (vs), 1123 (m), 1110 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{21}O_6$ $[M+H]^+$: 429.1333 found: 429.1331.



5'-(Benzyloxy)-5,7-dimethoxy-1'*H*,3*H*-spiro[isobenzofuran-1,2'-naphthalene]-1',4'(3*H*)-dione 354

Benzoquinone **351** (848 mg, 2.47 mmol, 1 equiv), oxaborole **349** (719 mg, 3.71 mmol, 1.50 equiv), sodium carbonate (1.15 g, 10.9 mmol, 4.40 equiv) and tetrakis(triphenylphosphine)palladium(0) (286 mg, 247 µmol, 0.10 equiv) were placed in a flask and purged for three times with argon. Degassed benzene (12.4 mL, 0.2 M) and degassed water (5.44 mL, 0.46 M) were added via syringe and the reaction was stirred at 85 °C for one hour while the solvent evaporated through a leak. Both solvents, benzene and water, were added to the reaction in the same fashion as described above and stirred for five hours. Then, 100 mg (515 µmol, 0.40 equiv) of oxaborole **349** were added and the reaction was stirred for further two hours. Water (5 mL) was added and the solution was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (dichloromethane) gave spiro-ether **354** (212 mg, 493 µmol, 20%) as a beige solid.

TLC (5% methanol in dichloromethane): R_f = 0.83 (CAM, UV).

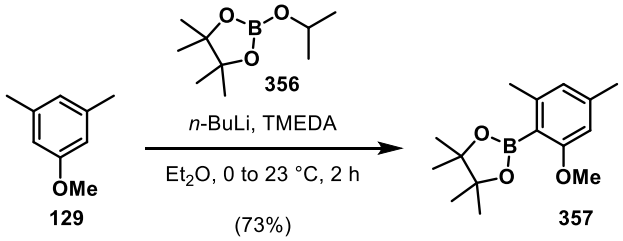
mp: 85 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.76 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.27 (m, 2H), 6.40 – 6.32 (m, 2H). 5.30 (d, *J* = 12.3 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 3.84 (d, *J* = 15.4 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.23 (d, *J* = 15.4 Hz, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 193.0, 192.4, 162.8, 157.9, 155.5, 143.0, 136.4, 136.2, 134.4, 128.7, 128.0, 126.9, 125.3, 120.7, 119.9, 118.6, 98.1, 97.3, 90.4, 74.1, 71.2, 55.8, 55.4, 51.4.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3183 (w), 3019 (m), 1777 (s), 1739 (m), 1639 (m), 1694 (w), 1494 (vs), 1402 (s), 1349 (m), 1139 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{23}O_6$ $[M+H]^+$: 431.1489 found: 431.1491.



2-(2-Methoxy-4,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 357

A solution of *n*-butyl lithium (2.40 M in pentane, 458 µL, 1.10 mmol, 1.50 equiv) was slowly added to a solution of dimethyl anisole (100 mg, 734 µmol, 1 equiv) and tetramethylethylenediamine (166 µL, 1.10 mmol, 1.50 equiv) in diethyl ether (2.45 mL, 0.3 M) at 0 °C. The solution was allowed to warm to 23 °C and stirred for two hours. The solution was cooled to –78 °C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan **356** (300 µL, 1.47 mmol, 2.00 equiv) was slowly added and the reaction was stirred at that temperature for 1.5 hours. After addition of a saturated aqueous solution of ammonium chloride (10 mL), the mixture was allowed to warm to 23 °C. The layers were separated and the organic layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (33% grading to 50% dichloromethane in cyclohexane) gave the title compound **357** (140 mg, 536 µmol, 73%) as a colorless oil which solidifies to a white solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.33 (CAM).

mp: 45 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 6.57 (s, 1H), 6.45 (s, 1H), 3.75 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 1.37 (s, 12H).

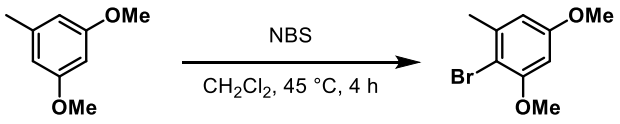
^{13}C NMR (101 MHz, chloroform-*d*) δ 164.5, 143.2, 137.0, 121.2, 114.7[1], 111.6, 83.4, 55.9, 24.9, 22.1.

^{11}B NMR (128 MHz, chloroform-*d*) δ 30.7

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 1600 (m), 1481 (m), 1402 (m), 1390 (m), 1302 (vs), 1209 (m), 1155 (s), 1073 (m), 763 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{24}BO_3$ $[M+H]^+$: 263.1813 found: 263.1810.

[1]*detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)*

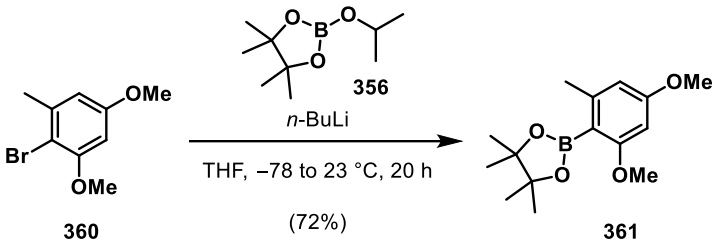


359 **360**

2-Bromo-1,5-dimethoxy-3-methylbenzene 360

N-bromosuccinimide (3.58 g, 20.1 mmol, 1.02 equiv) was added to a solution of 3,5-dimethoxytoluene (3.00 g, 19.7 mmol, 1 equiv) in dichloromethane (152 mL, 0.13 M) and stirred for four hours at 45 °C. The reaction was allowed to cool to 23 °C and the solvent was removed. Purification by silica gel chromatography (25% grading to 50% dichloromethane in cyclohexane) gave the title compound **360** (4.47 g, 19.3 mmol, 98%) as a beige solid.

Data consistent with literature: *J. Org. Chem.*, **2007**, *72*, 2068–2076.



2-(2,4-Dimethoxy-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 361

A solution of *n*-butyl lithium (2.44 M in pentane, 7.78 mL, 19.0 mmol, 1.10 equiv) was slowly added to a solution of bromide **360** (3.99 g, 17.2 mmol, 1 equiv) in tetrahydrofuran (50.7 mL, 0.34 M) at –78 °C and stirred for one hour. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan (3.87 mL, 19.0 mmol, 1.10 equiv) was slowly added and the reaction was stirred for 20 hours while being allowed to warm to 23 °C. The reaction was stopped by the addition of a saturated aqueous solution of ammonium chloride (40 mL) and the organic layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (150 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (60% dichloromethane in cyclohexane) gave the title compound **361** (3.47 g, 12.4 mmol, 72%) as a yellowish oil which solidifies to a beige solid.

TLC (66% dichloromethane in cyclohexane): R_f = 0.23 (CAM, UV).

mp: 37–39 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 6.29 (d, *J* = 2.1 Hz, 1H), 6.22 (d, *J* = 2.1 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.34 (s, 3H), 1.36 (s, 12H).

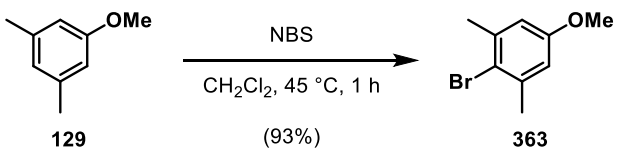
^{13}C NMR (101 MHz, chloroform-*d*) δ 164.6, 162.0, 144.5, 111.4[1], 106.6, 95.2, 83.5, 55.7, 55.2, 24.9, 22.3.

^{11}B NMR (128 MHz, chloroform-*d*) δ 31.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3058 (w), 1703 (m), 1699 (m), 1481 (m), 1413 (m), 1401 (w), 1391 (m), 1242 (s), 1224 (vs), 1146 (s), 1093 (m), 799 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{24}BO_4$ $[M+H]^+$: 279.1762 found: 279.1760.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)

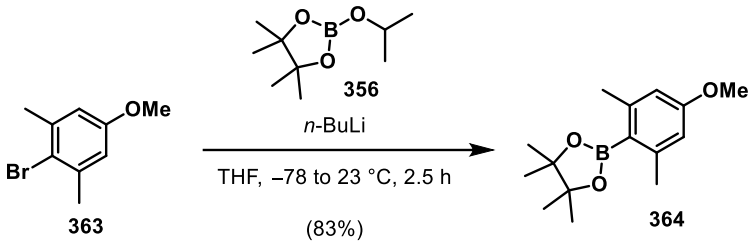


2-Bromo-5-methoxy-1,3-dimethylbenzene 363

N-bromosuccinimide (2.67 g, 15.0 mmol, 1.02 equiv) was added to a solution of 3,5-dimethylanisole (2.00 g, 14.7 mmol, 1 equiv) in dichloromethane (113 mL, 0.13 M) and stirred for one hour at 45 °C. The reaction was allowed to cool to 23 °C and the solvent was removed. Purification by silica gel

chromatography (25% grading to 50% dichloromethane in cyclohexane) gave the title compound **363** (2.94 g, 13.7 mmol, 93%) as a colorless oil which solidifies to a white solid.

Data consistent with literature: *J. Org. Chem.*, **2019**, *84*, 11103–11113.



2-(4-Methoxy-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 364

A solution of *n*-butyl lithium (2.44 M in pentane, 6.75 mL, 16.5 mmol, 1.12 equiv) was slowly added to a solution of bromide **363** (2.95 g, 13.7 mmol, 1 equiv) in tetrahydrofuran (50.7 mL, 0.34 M) at –78 °C and stirred for one hour. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan (3.36 mL, 16.5 mmol, 1.20 equiv) was slowly added via syringe and the reaction was stirred for 30 minutes at –78 °C before it was allowed to warm to 23 °C. After 2.5 hours, the mixture was treated with a saturated aqueous solution of ammonium chloride (40 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (150 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (60% dichloromethane in cyclohexane) gave the title compound **364** (2.99 g, 11.4 mmol, 83%) as a yellowish oil which solidifies to a beige solid.

TLC (40% dichloromethane in cyclohexane): R_f = 0.32 (UV, CAM).

mp: 31 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 6.51 (s, 2H), 3.76 (s, 3H), 2.40 (s, 6H), 1.37 (s, 12H).

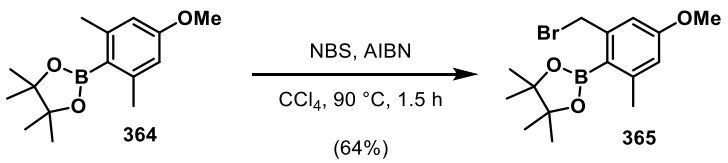
^{13}C NMR (101 MHz, chloroform-*d*) δ 160.4, 144.5, 121.8[1], 112.4, 83.4, 54.9, 24.9, 22.6.

^{11}B NMR (128 MHz, chloroform-*d*) δ 32.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3061 (w), 1743 (m), 1690 (m), 1485 (m), 1443 (s), 1427 (m), 1395 (m), 1240 (s), 1200 (vs), 1148 (s), 1095 (m), 755 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{24}BO_3$ $[M+H]^+$: 263.1813 found: 263.1812.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)



2-(2-(Bromomethyl)-4-methoxy-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 365

Freshly recrystallized *N*-bromosuccinimide (1.22 g, 6.84 mmol, 1.10 equiv) and azobisisobutyronitril (102 mg, 622 µmol, 10 mol%) were added to a stirring solution of boronate **364** (1.63 g, 6.22 mmol, 1 equiv) in tetrachloromethane (36.6 mL, 0.17 M) at 23 °C. This flask was directly placed into an oil bath at 90 °C and the mixture was refluxed at this temperature for 1.5 hours. The reaction was allowed to cool to 23 °C and filtered through Celite. Evaporation of the solvent gave the crude product **365**, which was purified by silica gel chromatography (25% dichloromethane in cyclohexane) to give the title compound **365** (1.36 g, 4.38 mmol, 64%) as a colorless oil.

TLC (50% dichloromethane in cyclohexane): R_f = 0.42 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 6.73 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 4.76 (s, 2H), 3.79 (s, 3H), 2.45 (s, 3H), 1.41 (s, 12H).

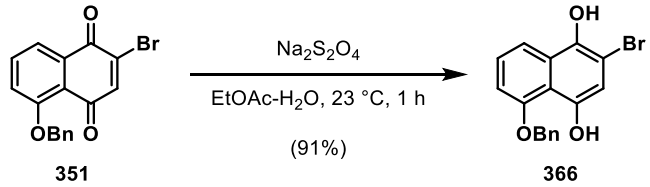
^{13}C NMR (101 MHz, chloroform-*d*) δ 160.7, 146.3, 145.0, 121.6[1], 115.6, 112.9, 83.8, 55.2, 34.7, 25.1, 22.9.

^{11}B NMR (128 MHz, chloroform-*d*) δ 31.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3128 (w), 1733 (m), 1623 (m), 1501 (m), 1493 (m), 1441 (w), 1398 (m), 1303 (s), 1298 (s), 1197 (vs), 1113 (m), 843 (m), 786 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{23}BBrO_3$ $[M+H]^+$: 341.0918 found: 341.0918.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)



351 366

5-(Benzyloxy)-2-bromonaphthalene-1,4-diol 366

A solution of sodium dithionite (11.5 g, 65.9 mmol, 5.22 equiv) in water (165 mL, 0.4 M) was slowly added to a solution of 5-(benzyloxy)-2-bromonaphthalene-1,4-dione **351** (4.33 g, 12.6 mmol, 1 equiv) in ethyl acetate (126 mL, 0.1 M) within ten minutes via a dropping funnel and then vigorously stirred for one hour at 23 °C. The solution was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (20% grading to 50% dichloromethane in cyclohexane) to afford air-sensitive dihydroquinone **366** (3.97 g, 11.5 mmol, 91%) as a brown solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.41 (CAM).

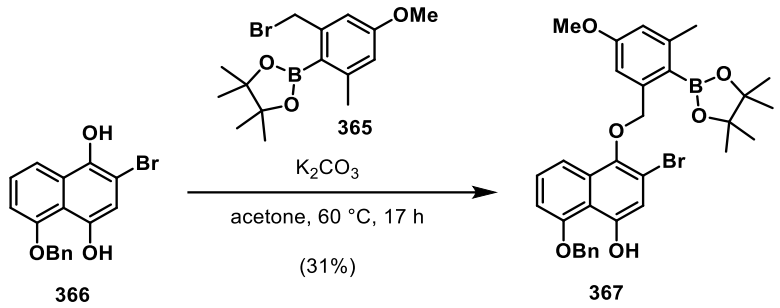
mp: 132–134 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.02 (s, 1H), 7.83 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.51 – 7.39 (m, 5H), 7.36 (dd, *J* = 8.6, 7.7 Hz, 1H), 6.94 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.91 (s, 1H), 5.51 (s, 1H), 5.27 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.3, 148.3, 141.1, 135.1, 129.3, 129.1, 128.2, 126.4, 126.3, 116.7, 115.3, 112.1, 106.7, 105.3, 72.0.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3203 (w), 3117 (m), 1720 (s), 1701 (m), 1523 (s), 1312 (m), 1301 (w), 1222 (vs), 1015 (w), 921 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{12}BrO_3$ [M-H]$^-$: 342.9975 found: 342.9976.



8-(Benzyloxy)-3-bromo-4-((5-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzyl)oxy)naphthalen-1-ol 367

Potassium carbonate (428 mg, 3.09 mmol, 1.10 equiv) was added to a stirring solution of dihydroquinone **366** (971 mg, 2.81 mmol, 1 equiv) in acetone (1.41 mL, 2 M) at 23 ˚C. After five minutes, benzyl bromide **365** (959 mg, 2.81 mmol, 1.00 equiv) was added in one portion to the mixture and then stirred for 17 hours at 60 °C. The reaction was allowed to cool to 23 ˚C before it was poured on water (30 mL) and the solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (20 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (50% dichloromethane in cyclohexane) gave the title compound **367** (527 mg, 872 µmol, 31%) as a red foam.

TLC (50% dichloromethane in cyclohexane): R_f = 0.24 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.18 (s, 1H), 7.67 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.44 – 7.28 (m, 5H), 7.26 – 7.16 (m, 2H), 6.93 (s, 1H), 6.82 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.18 (s, 2H), 5.12 (s, 2H), 3.76 (s, 3H), 2.40 (s, 3H), 1.19 (s, 12H).

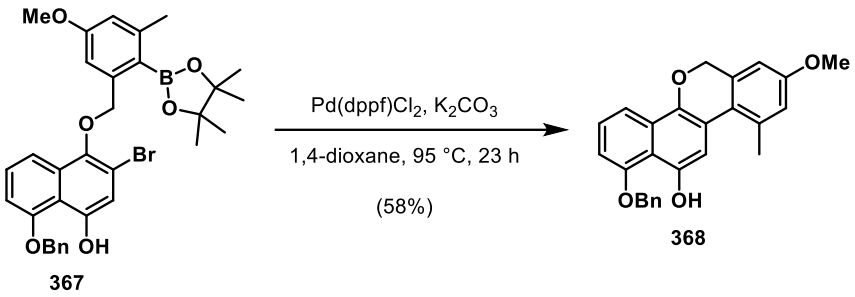
^{13}C NMR (101 MHz, chloroform-*d*) δ 161.0, 155.6, 151.3, 145.1, 144.8, 144.7, 135.1, 131.6, 129.3, 129.2, 128.2, 126.8, 119.7[1], 117.1, 115.2, 115.1, 114.6, 114.0, 109.9, 106.3, 83.7, 75.4, 72.0, 55.2, 25.0, 22.9.

^{11}B NMR (128 MHz, chloroform-*d*) δ 33.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3101 (w), 3002 (m), 2948 (m), 1735 (m), 1523 (m), 1501 (m), 1472 (m), 1414 (w), 1378 (m), 1299 (s), 1153 (vs), 1123 (m), 938 (w), 843 (m), 750 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{32}H_{35}BBrO_6$ [M+H]$^+$: 605.1705 found: 605.1699.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)



367 368

1-(Benzyloxy)-8-methoxy-10-methyl-6*H*-dibenzo[*c*,*h*]chromen-12-ol 368

Ether **367** (512 mg, 846 µmol, 1 equiv), potassium carbonate (351 mg, 2.54 mmol, 3.00 equiv) and [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (31 mg, 42.3 µmol, 5 mol%) were placed in a flask and purged for three times with argon. Degassed 1,4-dioxane (5.64 mL, 0.15 M) was added via syringe and the reaction was stirred at 95 °C for 23 hours. The suspension was allowed to cool to 23 °C and then filtered through a short plug of silica with dichloromethane as eluent. Purification by silica gel chromatography (50% dichloromethane in cyclohexane) gave tetracycle **368** (195 mg, 491 µmol, 58%) as an orange gel.

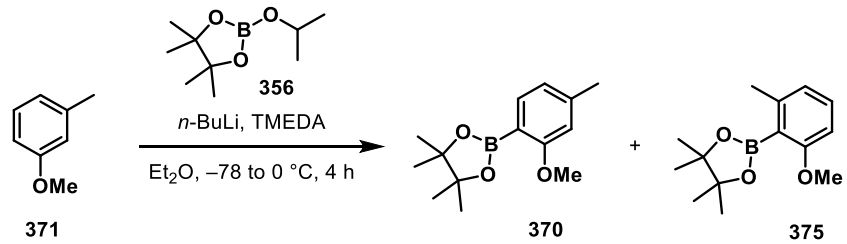
TLC (50% dichloromethane in cyclohexane): R_f = 0.33 (UV, CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.03 (s, 1H), 7.89 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 2H), 7.48 – 7.37 (m, 3H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 5.29 (s, 2H), 5.03 (s, 2H), 3.84 (s, 3H), 2.67 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 158.7, 155.3, 147.9, 144.0, 136.5, 136.2, 135.5, 129.2, 129.0, 128.1, 127.6, 125.6, 122.7, 121.3, 117.3, 116.4, 114.4, 108.9, 108.4, 106.0, 71.8, 70.4, 55.5, 23.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3369 (w), 3204 (m), 1582 (m), 1498 (s), 1343 (s), 1296 (vs), 1123 (m), 1061 (w), 842 (m), 756 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{21}O_4$ [M-H]$^-$: 397.1445 found: 397.1443.



371 370 375

(28%) (40%)

2-(2-Methoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 370

2-(2-Methoxy-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 375

A solution of *n*-butyl lithium (2.40 M in pentane, 1.83 mL, 4.41 mmol, 1.50 equiv) was slowly added to a solution of 3-methyl anisole (359 mg, 2.94 mmol, 1 equiv) and tetramethylethylenediamine (664 µL, 4.41 mmol, 1.50 equiv) in diethyl ether (9.80 mL, 0.3 M) at 0 °C. The solution was allowed to warm to 23 °C and stirred for two hours. The solution was cooled to –78 °C and 2-isopropoxy-4,4,5,5-

tetramethyl-1,3,2-dioxaborolan (1.20 mL, 5.87 mmol, 2.00 equiv) was slowly added and the reaction was stirred for two hours while warming to –20 °C. The reaction was stopped by the addition of a saturated aqueous solution of ammonium chloride (20 mL), warmed to 23 °C and the solution was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (30 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (5% diethyl ether in pentane) gave the title compounds **370** (204 mg, 823 µmol, 28%) and **375** (292 mg, 1.12 mmol, 40%) as colorless oils which solidified after storage.

TLC (10% diethyl ether in pentane): R_f = 0.17 (CAM).

mp: 34 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.58 (d, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 6.68 (s, 1H), 3.82 (s, 3H), 2.35 (s, 3H), 1.35 (s, 12H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 164.5, 143.2, 137.0, 121.2, 114.7[1], 111.6, 83.4, 55.9, 24.9, 22.1.

^{11}B NMR (128 MHz, chloroform-*d*) δ 30.7

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2988 (w), 1634 (m), 1463 (m), 1422 (s), 1391 (vs), 1309 (m), 1149 (m), 1105 (s), 1044 (m), 783 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{14}H_{22}BO_3$ $[M+H]^+$: 249.1657 found: 249.1659.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)

TLC (10% diethyl ether in pentane): R_f = 0.41 (CAM).

mp: 37 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 2.35 (s, 3H), 1.39 (s, 12H).

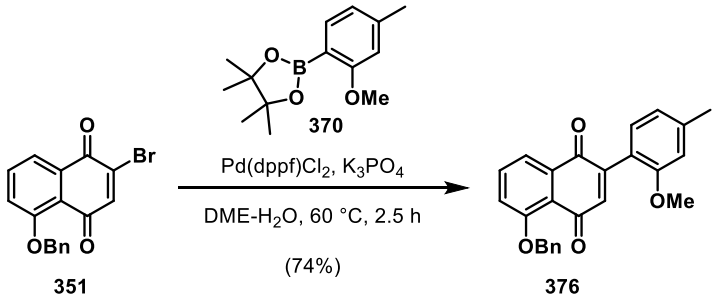
^{13}C NMR (101 MHz, chloroform-*d*) δ 162.9, 142.8, 130.4, 122.1, 119.6[1], 107.2, 83.8, 55.7, 24.9, 21.8.

^{11}B NMR (128 MHz, chloroform-*d*) δ 32.1

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2986 (w), 1630 (m), 1619 (w), 1460 (m), 1434 (s), 1320 (vs), 1324 (m), 1209 (m), 1117 (s), 1048 (m), 799 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{14}H_{22}BO_3$ $[M+H]^+$: 249.1657 found: 249.1661.

[1]detected only via HMBC analysis (signal not visible in ^{13}C-spectrum)



5-(Benzyloxy)-2-(2-methoxy-4-methylphenyl)naphthalene-1,4-dione 376

Benzoquinone **351** (30.0 mg, 87.7 µmol, 1 equiv), boronate **370** (32.0 mg, 129 µmol, 1.47 equiv), potassium phosphate (84.0 mg, 395 µmol, 4.50 equiv) and [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (13.0 mg, 17.6 µmol, 20 mol%) were placed in a flask and purged for three times with argon. A mixture of degassed 1,2-dimethoxyethane (2.92 mL, 0.03 M) and degassed water (395 µL, 0.22 M) was added via syringe and the reaction was stirred at 60 °C for 2.5 hours. The suspension was allowed to cool to 23 °C, poured onto water (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (50% grading to 80% dichloromethane in cyclohexane) afforded quinone **376** (25.1 mg, 65.4 µmol, 74%) as an orange solid.

TLC (67% dichloromethane in cyclohexane): R_f = 0.26 (UV, CAM).

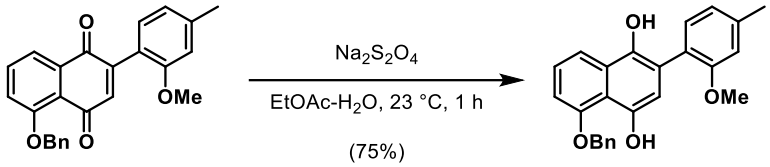
mp: 128 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.80 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.63 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.45 – 7.39 (m, 2H), 7.35 – 7.30 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.94 (s, 1H), 6.85 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 6.8 (bs, 1H), 5.32 (s, 2H), 3.77 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 184.7, 184.1, 158.4, 157.3, 145.7, 141.6, 138.8, 136.4, 135.2, 134.7, 130.5, 128.8, 128.1, 126.8, 121.5, 120.8, 120.3, 120.2, 119.5, 112.3, 71.1, 55.8, 22.0.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3063 (w), 2995 (w), 2902 (m), 2898 (w), 2860, (m) 1650 (s), 1578 (m), 1423 (s), 1368 (vs), 1324 (m), 1259 (s), 1124 (s), 1056 (m), 1031 (w), 969 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{21}O_4$ $[M+H]^+$: 385.1434 found: 385.1428.



376 377

5-(Benzyloxy)-2-(2-methoxy-4-methylphenyl)naphthalene-1,4-diol 377

A solution of sodium dithionite (59.0 mg, 340 µmol, 5.22 equiv) in water (849 µL, 0.4 M) was slowly added to a solution of benzoquinone **376** (25.0 mg, 65.0 µmol, 1 equiv) in ethyl acetate (650 µL, 0.1 M) and then vigorously stirred for one hour at 23 °C. The solution was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (10% diethyl ether in pentane) afforded dihydroquinone **377** (18.9 mg, 49.0 mmol, 75%) as an orange solid.

TLC (25% diethylether in pentane): R_f = 0.41 (CAM).

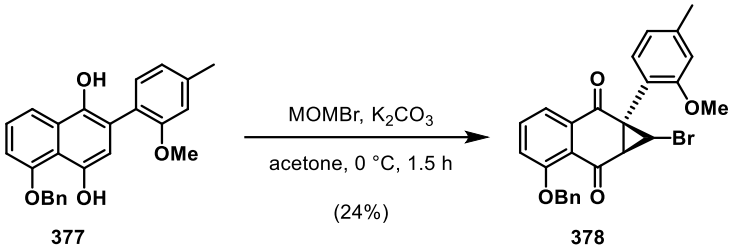
mp: 134–137 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.99 (s, 1H), 8.01 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.46 – 7.39 (m, 3H), 7.35 (dd, *J* = 8.6, 7.7 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 6.60 (s, 1H), 5.30 (s, 2H), 3.92 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.3, 155.2, 147.8, 141.8, 139.5, 135.5, 132.5, 129.2, 128.9, 128.3, 128.1, 125.3, 124.6, 123.3, 121.6, 117.4, 115.4, 112.9, 112.4, 106.2, 71.8, 56.5, 21.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3402 (m), 3392 (m), 3190 (w), 3060 (w), 2994 (w), 2901 (m), 2857, (m) 1623 (m), 1578 (m), 1323 (m), 1229 (s), 1124 (s), 1030 (w), 928 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{21}O_4$ [M-H]$^-$: 385.1455 found: 385.1458.



377 378

6-(Benzyloxy)-1-bromo-1*a*-(2-methoxy-4-methylphenyl)-1a,7a-dihydro-1*H*-cyclopropa [*b*]naphthaalene-2,7-dione 378

Potassium carbonate (8.00 mg, 58.7 µmol, 1.20 equiv) and dihydroquinone **377** (18.9 mg, 48.9 µmol, 1 equiv) were placed in a flask and purged with argon for three times. Degassed acetone (400 µL, 0.12 M) was added. To the obtained suspension was slowly added a solution of bromomethyl methyl ether (4.00 µL, 48.9 µmol, 1.00 equiv) in degassed acetone (98.0 µL, 0.5 M) and stirred for 1.5 hours at 23 °C. The deep purple suspension was diluted with water (3 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (50% grading to 70% dichloromethane in cyclohexane) to afford dihydroquinone **378** (5.60 mg, 11.7 µmol, 24%) as an orange solid.

TLC (67% dichloromethane in cyclohexane): R_f = 0.37 (UV, CAM).

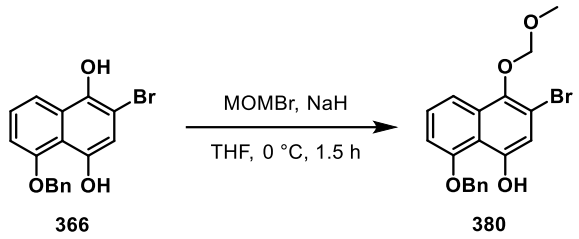
mp: 132 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.77 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.61 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.47 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.81 (s, 1H), 5.35 (s, 2H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.07 (d, *J* = 8.9 Hz, 1H), 3.73 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 184.0, 181.9, 158.8, 156.6, 144.5, 143.9, 141.3, 136.3, 134.8, 129.4, 128.9, 128.1, 121.5, 120.8, 120.0, 119.7, 118.7, 112.2, 71.2, 55.8, 24.8, 24.7, 22.0.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3014 (m), 2938 (w), 1738 (m), 1703 (s), 1638 (s), 1603 (m), 1394 (w), 1029 (m), 948 (m), 749 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{22}BrO_4$ $[M\text{-}H]^-$: 477.0696 found: 477.0689.

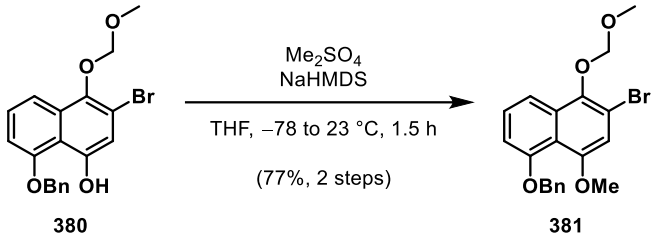


366 380

8-(Benzyloxy)-3-bromo-4-(methoxymethoxy)naphthalen-1-ol 380

A solution of **366** (100 mg, 290 µmol, 1 equiv) in tetrahydrofuran (1.45 mL, 0.2 M) was slowly added to a suspension of sodium hydride (60% dispersion on mineral oil, 14 mg, 348 µmol, 1.20 equiv) in tetrahydrofuran (579 µL, 0.5 M) at 0 °C and stirred for 30 minutes. Bromomethoxymethane (24.0 µL, 290 µmol, 1.00 equiv) was added to the brown suspension at 0 °C and stirred for 30 minutes at that temperature. The orange suspension was diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (20 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered. The filtrate was evaporated under reduced pressure to give the crude product, which was filtered through a short plug of silica (20% diethyl ether in pentane) to afford dihydroquinone **380** as an orange solid, which was used in the next step without further purification.

TLC (25% diethyl ether in pentane): R_f = 0.64 (UV, CAM).



380 381

5-(Benzyloxy)-2-bromo-4-methoxy-1-(methoxymethoxy)naphthalene 381

Sodium bi(trimethylsilyl)amide (1 M in tetrahydrofuran, 279 µL, 279 µmol, 1.05 equiv) was added to a solution of bromide **380** (103 mg, 265 µmol, 1 equiv) in tetrahydrofuran (379 µL, 0.7 M) at –78 °C followed by dimethyl sulfate (28.0 µL, 294 µmol, 1.11 equiv). The reaction was allowed to warm to 23 °C and stirred for one hour at that temperature. A saturated aqueous solution of sodium hydrogen carbonate (4 mL) was added and the solution was extracted with ethyl acetate (2 × 6 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel

chromatography (6% grading to 10% diethyl ether in pentane) to afford naphthalene **381** (82.0 mg, 203 µmol, 77% over two steps) as a pale-yellow solid.

TLC (17% diethyl ether in pentane): R_f = 0.43 (UV, CAM).

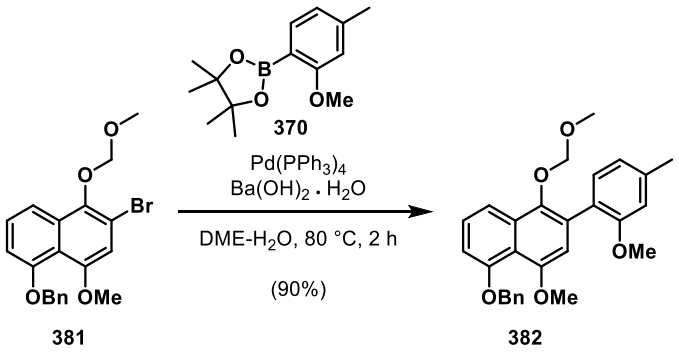
mp: 91 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.78 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.47 – 7.38 (m, 3H), 7.37 – 7.29 (m, 1H), 6.98 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.93 (s, 1H), 5.20 (s, 2H), 5.19 (s, 2H), 3.92 (s, 3H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 156.5, 154.4, 144.1, 137.4, 132.6, 128.5, 127.7, 127.6, 127.0, 118.1, 115.5, 113.1, 109.8, 109.4, 100.2, 71.5, 58.4, 56.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2851 (m), 1664 (m), 1607 (m), 1444 (m), 1370 (m), 1336 (m), 1317 (m), 1244 (m), 1081 (m), 1025 (m), 931 (m), 798 (m), 723 (m), 703 cm^{-1}.

HRMS (ESI) calc. for $C_{20}H_{20}BrO_4$ $[M+H]^+$: 403.0539 found: 403.0540.



5-(Benzyloxy)-4-methoxy-2-(2-methoxy-4-methylphenyl)-1-(methoxymethoxy)naphthalene 382

Dihydroquinone **381** (16.7 mg, 41.4 µmol, 1 equiv), boronate **370** (21.0 mg, 82.8 µmol, 2.00 equiv), barium(II) hydroxide monohaydrate (16.0 mg, 82.8 µmol, 2.00 equiv) and tetrakis(triphenylphosphine)-palladium(0) (1.10 mg, 0.828 µmol, 2 mol%) were placed in a flask and purged for three times with argon. A mixture of degassed 1,2-dimethoxyethane (319 µL, 0.13 M) and degassed water (52.0 µL, 0.8 M) was added via syringe and the reaction was stirred at 80 °C for two hours. The suspension was allowed to cool to 23 °C, poured onto water (1 mL) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (4 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (5% grading to 10% ethyl acetate in cyclohexane) afforded quinone **382** (15.6 mg, 37.3 µmol, 90%) as an orange solid.

TLC (25% ethyl acetate in cyclohexane): R_f = 0.61 (UV, CAM).

mp: 109 °C (decomposition).

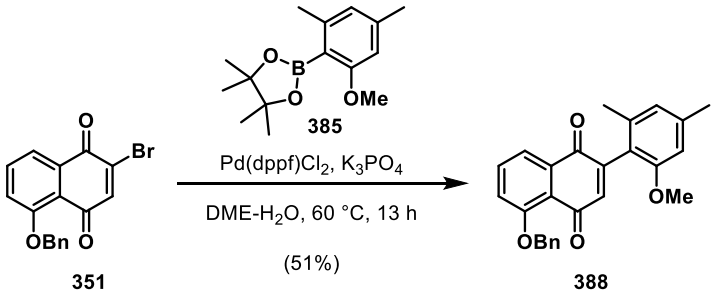
Note: The product was obtained as a mixture of rotamers (ratio: 6 : 1).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.88 (dd, *J* = 8.5, 0.8 Hz, 0.85H), 7.87 (dd, *J* = 8.2, 1.2 Hz, 0.15H), 7.64 – 7.58 (m, 2H), 7.46 – 7.37 (m, 3H), 7.37 – 7.27 (m, 1.85H), 7.23 (d, *J* = 2.0 Hz, 0.15H), 7.16 (dd, *J* = 8.3, 1.8 Hz, 0.15H), 6.97 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 0.15H), 6.88 (d, *J* = 7.6 Hz, 0.85H), 6.85 (s, 0.85H), 6.80 (s, 1H), 5.23 (s, 2H), 4.77 (s, 0.29H), 4.76 (s, 1.71H), 3.92 (s, 0.43H), 3.91 (s, 2.57H), 3.81 (s, 2.57H), 3.79 (s, 0.43H), 3.17 (s, 2.57H), 3.14 (s, 0.43H), 2.44 (s, 2.57H), 2.35 (s, 0.43H).

^{13}C NMR (101 MHz, chloroform-*d*) δ [26 signals of highest intensity:] 157.0, 156.4, 153.0, 144.0, 139.2, 137.9, 132.3, 131.9, 128.5, 128.1, 127.6, 127.2, 126.6, 125.3, 121.3, 118.6, 116.0, 112.3, 109.9, 109.5, 99.6, 71.9, 57.3, 56.8, 55.9, 21.8. [21 additional signals of minor intensity:] 156.4, 155.1, 153.1, 143.8, 137.9, 132.7, 132.3, 129.8, 129.3, 128.5, 128.3, 128.0, 126.7, 118.7, 116.0, 111.5, 109.7, 99.6, 57.3, 56.1, 20.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3383 (m), 2922 (m), 1734 (m), 1663 (m), 1567 (m), 1491 (m), 1370 (m), 1335 (m), 1253 (m), 1242 (m), 1150 (m), 1025 (m), 951 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{28}H_{29}O_5$ [M-H]$^-$: 445.2010 found: 445.2010.



5-(Benzyloxy)-2-(2-methoxy-4,6-dimethylphenyl)naphthalene-1,4-dione 388

Benzoquinone **351** (297 mg, 864 µmol, 1 equiv), boronate **385** (333 mg, 1.27 mmol, 1.47 equiv), potassium phosphate (825 mg, 3.89 mmol, 4.50 equiv) and [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (126 mg, 173 µmol, 20 mol%) were placed in a flask and purged for three times with argon. A mixture of degassed 1,2-dimethoxyethane (28.8 mL, 0.03 M) and degassed water (3.89 mL, 0.22 M) was added via syringe and the reaction was stirred at 60 °C for 13 hours. The suspension was allowed to cool to 23 °C, poured onto water (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (10% grading to 15% diethyl ether in pentane) afforded quinone **388** (176 mg, 442 µmol, 51%) as an orange solid.

TLC (33% diethyl ether in pentane): R_f = 0.41 (UV, CAM).

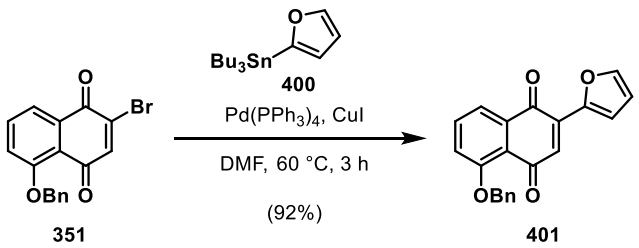
mp: 87 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.80 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.46 – 7.39 (m, 2H), 7.35 – 7.30 (m, 2H), 6.79 (s, 1H), 6.73 (dt, *J* = 1.5, 0.7 Hz, 1H), 6.62 (s, 1H), 5.33 (s, 2H), 3.70 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 184.5, 184.2, 158.4, 157.1, 145.4, 140.4, 139.9, 137.1, 136.3, 135.0, 134.7, 128.8, 128.0, 126.8, 123.4, 120.8, 120.2, 120.0, 119.4, 109.4, 71.0, 55.8, 21.8, 20.0.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3058 (w), 2913 (m), 2888 (w), 1650 (s), 1587 (m), 1425 (s), 1369 (vs), 1324 (m), 1261 (s), 1125 (s), 1106 (m), 1008 (w), 997 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{23}O_4$ $[M+H]^+$: 399.1591 found: 399.1586.



5-(Benzyloxy)-2-(furan-2-yl)naphthalene-1,4-dione 401

Benzoquinone **351** (200 mg, 583 µmol, 1 equiv), stannane **400** (250 mg, 688 µmol, 1.18 equiv), copper(I)-iodide (18.0 mg, 93.7 µmol, 16 mol%) and tetrakis(triphenylphosphine)palladium(0) (27.0 mg, 23.4 µmol, 4 mol%) were placed in a flask and purged for three times with argon. Degassed *N*,*N*-dimethylformamide (6.86 mL, 0.085 M) was added via syringe and the reaction was stirred at 60 °C for four hours. The suspension was allowed to cool to 23 °C, poured onto a saturated aqueous solution of lithium chloride (10 mL) and diluted with water (10 mL). The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (50% dichloromethane in cyclohexane) afforded quinone **401** (179 mg, 542 µmol, 93%) as long orange needles.

TLC (50% dichloromethane in cyclohexane): R_f = 0.17 (UV, CAM).

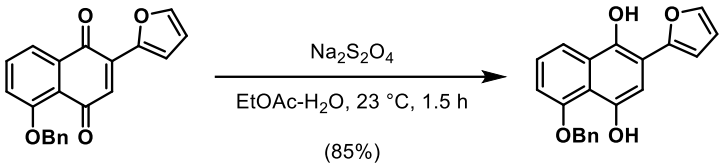
mp: 148 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.61 (dd, *J* = 8.3, 7.9 Hz, 1H), 7.61 – 7.57 (m, 3H), 7.55 (d, *J* = 3.5 Hz, 1H), 7.41 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.21 (s, 1H), 6.58 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.29 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 184.2, 183.2, 158.3, 146.5, 145.1, 136.3, 134.8, 134.6, 133.7, 130.7, 128.8, 128.0, 126.8, 120.5, 120.0, 119.9, 118.1, 113.3, 71.1.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3103 (w), 3063 (m), 2925 (w), 2830 (m), 1659 (m), 1593 (m), 1461 1240 (s), 1202 (w), 1193 (m), 1039 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{15}O_4$ $[M+H]^+$: 331.0965 found: 331.0962.



5-(Benzyloxy)-2-(furan-2-yl)naphthalene-1,4-diol 402

A solution of sodium dithionite (253 mg, 1.45 mmol, 5.22 equiv) in water (3.64 mL, 0.4 M) was added dropwise to a solution of benzoquinone **401** (92.2 g, 279 µmol, 1 equiv) in ethyl acetate (2.79 mL, 0.1 M) at 23 °C. After 1.5 hours of vigorous stirring, the mixture was diluted with water (7 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (33% grading to 50% dichloromethane in cyclohexane) gave dihydroquinone **402** (78.7 mg, 237 µmol, 85%) as a white solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.30 (UV, CAM).

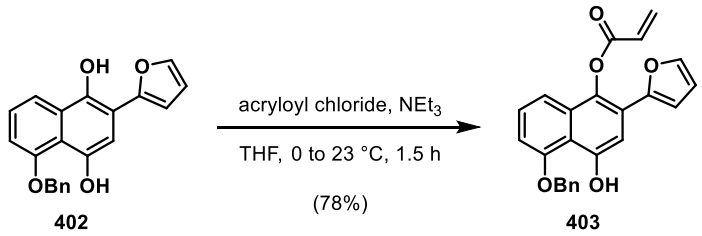
mp: 169 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.96 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.47 – 7.39 (m, 3H), 7.35 (t, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.69 (d, *J* = 3.5 Hz, 1H), 6.57 (dd, *J* = 3.5, 1.9 Hz, 1H), 5.27 (s, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.2, 153.6, 147.5, 141.3, 141.1, 135.4, 129.2, 129.0, 128.1, 126.8, 125.8, 117.0, 115.7, 112.0, 110.7, 107.0, 106.7, 106.2, 71.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3422 (m), 3392 (w), 3110 (w), 3043 (m), 2915 (w), 2837 (m), 1593 (m), 1432 1221 (s), 1193 (m), 1020 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{17}O_4$ $[M+H]^+$: 333.1121 found: 333.1151.

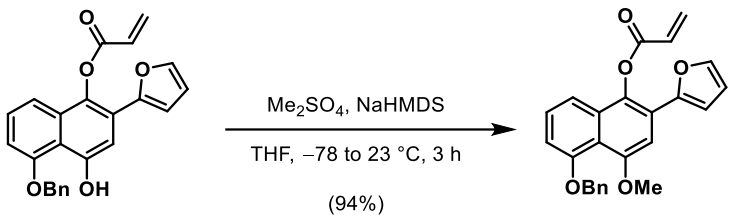


5-(Benzyloxy)-2-(furan-2-yl)-4-hydroxynaphthalen-1-yl acrylate 403

Triethylamine (11.0 µL, 75.8 µmol, 1.20 equiv) was added dropwise to a solution of dihydroquinone **402** (21.2 mg, 63.2 µmol, 1 equiv) in tetrahydrofuran (54.0 µL, 1.17 M) at 0 °C and stirred for ten minutes. A solution of acryloyl chloride in tetrahydrofuran (118 µL, 0.59 M) was added dropwise to the reaction and stirred for 15 minutes at 0 °C. The reaction was allowed to warm to 23 °C and stirred for further 1.5 hours. Water (5 mL) was added to the reaction and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution

of sodium chloride (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography (33% grading to 50% dichloromethane in cyclohexane) afforded ester **403** (19.0 mg, 49.3 µmol, 78%) as an orange solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.30 (UV, CAM).
mp: 147–149 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 9.34 (s, 1H), 7.53 – 7.37 (m, 6H), 7.35 (s, 1H), 7.34 (d, *J* = 2.7 Hz, 1H), 7.32 (s, 1H), 6.89 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.54 (dd, *J* = 17.4, 10.4 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.15 (dd, *J* = 10.5, 1.3 Hz, 1H), 5.28 (s, 2H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 164.8, 155.6, 152.7, 149.7, 142.7, 135.1, 133.9, 133.4, 130.4, 129.2, 129.1, 128.1, 127.9, 127.2, 122.1, 115.7, 115.0, 112.0, 109.9, 107.4, 106.3, 72.0.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3492 (w), 3294 (w), 3104 (m), 1837 (m), 1638 (w), 1604 (m), 1599 (s), 1398 (s), 1194 (vs), 1003 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{24}H_{19}O_5$ $[M+H]^+$: 387.1227 found: 387.1223.



5-(Benzyloxy)-2-(furan-2-yl)-4-methoxynaphthalen-1-yl acrylate 404
Sodium bi(trimethylsilyl)amide (1 M in tetrahydrofuran, 53.8 µL, 53.8 µmol, 1.05 equiv) was added to a solution of naphthol **403** (19.8 mg, 51.2 µmol, 1 equiv) in tetrahydrofuran (400 µL, 0.13 M) at –78 °C followed by dimethyl sulfate (5.40 µL, 56.9 µmol, 1.11 equiv). The reaction was allowed to warm to 23 °C and stirred for three hours at that temperature. A saturated aqueous solution of sodium hydrogen carbonate (3 mL) was added and the solution was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (5% grading to 10% diethyl ether in pentane) to afford ester **404** (19.3 mg, 48.1 µmol, 94%) as an orange solid.

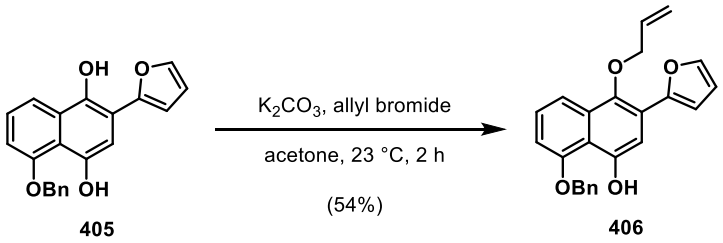
TLC (10% diethyl ether in pentane): R_f = 0.28 (UV, CAM).
mp: 134 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.64 – 7.57 (m, 2H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.47 – 7.31 (m, 5H), 7.31 (s, 1H), 6.96 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.83 – 6.74 (m, 2H), 6.54 (dd, *J* = 17.2, 10.4 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.9 Hz, 1H), 6.16 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.22 (s, 2H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 164.7, 156.5, 155.6, 149.8, 142.4, 137.6, 135.2, 133.4, 131.1, 128.5, 128.0, 127.9, 127.7, 127.1, 120.6, 118.1, 114.7, 112.2, 109.8, 109.6, 103.0, 71.7, 56.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2204 (m), 1832 (m), 1348 (w), 1304 (m), 1289 (s), 1198 (s), 1106 (vs), 995 (m), 984 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{21}O_5$ $[M+H]^+$: 401.1384 found: 401.1386.



4-(Allyloxy)-8-(benzyloxy)-3-(furan-2-yl)naphthalen-1-ol 406

Potassium carbonate (22.1 mg, 158 µmol, 1.20 equiv) and dihydroquinone **405** (35.0 mg, 131 µmol, 1 equiv) were put in a flask and purged with argon for three times. Degassed acetone (700 µL, 0.19 M) was added to obtain a suspension. A solution of allylbromide (11.4 µL, 131 µmol, 1.00 equiv) in degassed acetone (100 µL, 1.31 M) was slowly added and stirred for two hours at 23 °C. The suspension was diluted with water (3 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (20% grading to 50% dichloromethane in cyclohexane), which afforded allyl quinone **406** (26.4 mg, 71.0 µmol, 54%) as an orange solid.

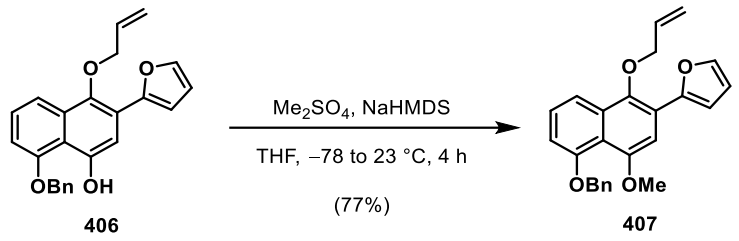
TLC (50% dichloromethane in cyclohexane): R_f = 0.34 (UV, CAM).

mp: 93 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.18 (s, 1H), 7.74 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.50 – 7.48 (m, 2H), 7.45 – 7.41 (m, 3H), 7.36 (dd, *J* = 7.9, 8.6 Hz, 1H), 7.32 (s, 1H), 7.21 (dd, *J* = 3.4, 0.8 Hz, 1H), 7.10 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.89 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.18 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.55 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.5 Hz, 1H), 5.28 (s, 2H), 5.22 (d, *J* = 12.2 Hz, 1H), 4.38 (dt, *J* = 5.2, 1.6 Hz, 2H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3329 (w), 3249 (m), 3100 (w), 2801 (w), 1790 (m), 1439 (s), 1229 (vs), 1193 (m), 1018 (w), 993 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{24}H_{19}O_4$ $[M-H]^-$: 371.1289 found: 371.1293.



406 407

2-(1-(Allyloxy)-5-(benzyloxy)-4-methoxynaphthalen-2-yl)furan 407

Sodium bi(trimethylsilyl)amide (1 M in tetrahydrofuran, 47.3 µL, 47.3 µmol, 1.05 equiv) was added to a solution of naphthol **406** (16.8 mg, 45.1 µmol, 1 equiv) in tetrahydrofuran (400 µL, 0.11 M) at –78 °C followed by dimethyl sulfate (4.70 µL, 50.2 µmol, 1.11 equiv). The reaction was allowed to warm to 23 °C and stirred for three hours at that temperature. A saturated aqueous solution of sodium hydrogen carbonate (3 mL) was added and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (33% dichloromethane in cyclohexane) to afford ester **407** (13.4 mg, 34.7 µmol, 77%) as an orange solid.

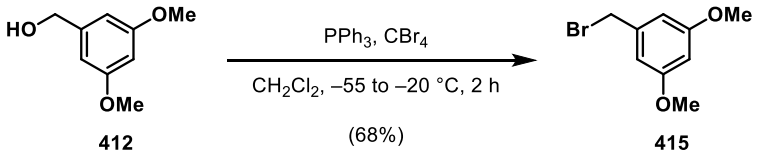
TLC (50% dichloromethane in cyclohexane): R_f = 0.28 (UV, CAM).

mp: 89 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.76 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.54 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.38 – 7.29 (m, 2H), 7.13 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.57 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.19 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.57 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.5 Hz, 1H), 5.22 (s, 2H), 4.40 (dt, *J* = 5.1, 1.6 Hz, 2H), 4.01 (s, 3H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2801 (w), 1791 (m), 1542 (s), 1476 (s), 1220 (vs), 1193 (m), 1018 (w), 993 (w), 987 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{23}O_4$ $[M+H]^+$: 387.1591 found: 387.1591.



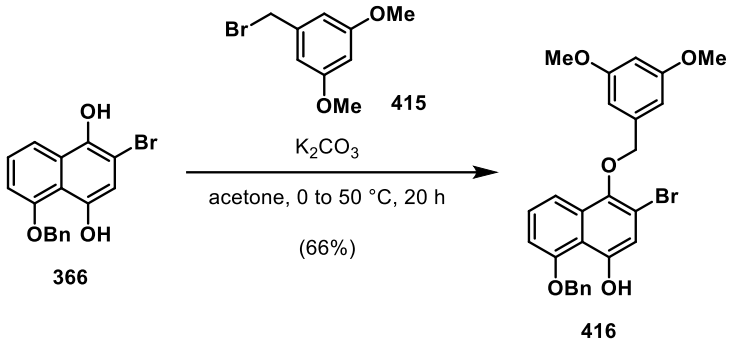
412 415

1-(Bromomethyl)-3,5-dimethoxybenzene 415

Triphenylphosphine (5.96 g, 22.7 mmol, 2.00 equiv) was added to a solution of benzyl alcohol **412** (1.91 g, 11.4 mmol, 1 equiv) in dichloromethane (45.4 mL, 0.25 M) and stirred for ten minutes. The solution was cooled to –55 °C and tetrabromomethane (7.53 g, 22.7 mmol, 2.00 equiv) in dichloromethane (2.27 mL, 10 M) was added to the reaction via syringe. After warming to –20 °C, the reaction was stirred for two hours at that temperature and then allowed to warm to 23 °C. The reaction was diluted with a mixture of ethyl acetate and cyclohexane (1:1, 20 mL), passed through a short plug

of silica and rinsed with ethyl acetate. Purification by silica gel chromatography (5% diethyl ether in pentane) gave the title compound **415** (1.79 g, 7.75 mmol, 68%) as a white solid.

Data consistent with literature: *J. Org. Chem.*, **2017**, *82*, 2630–2640.



8-(Benzyloxy)-3-bromo-4-((3,5-dimethoxybenzyl)oxy)naphthalen-1-ol 416

Potassium carbonate (69.1 mg, 499 µmol, 1.20 equiv) and dihydroquinone **366** (158 mg, 458 µmol, 1.10 equiv) were put in a flask and purged with argon for three times. Degassed acetone (458 µL, 1.00 M) was added. To the obtained suspension was slowly added a solution of benzyl bromide **415** (96.0 mg, 416 µmol, 1 equiv) in degassed acetone (1.50 mL, 0.23 M) at 0 °C and stirred for ten minutes before it was allowed to warm to 23 °C. After two hours, the reaction was warmed to 50 °C and stirred for further 17 hours. Water (10 mL) was added and the crude mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (10% ethyl acetate in cyclohexane), which afforded ether **416** (136 mg, 275 µmol, 66%) as red solid along with recovered benzyl bromide **415** (13.0 mg, 56.3 µmol, 14%).

TLC (25% ethyl acetate in cyclohexane): R_f = 0.37 (UV, CAM, $KMnO_4$).

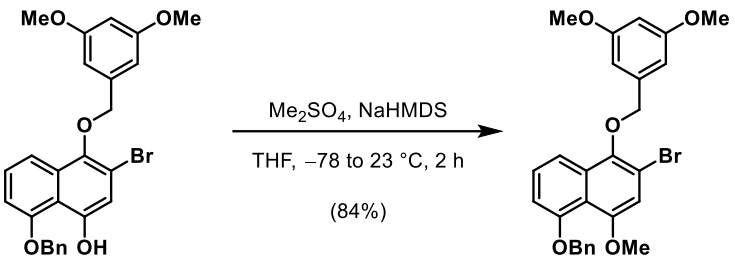
mp: 126 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.30 (s, 1H), 7.74 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.50 – 7.39 (m, 5H), 7.34 (t, *J* = 8.1 Hz, 1H), 7.03 (s, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 2H), 6.51 (t, *J* = 2.3 Hz, 1H), 5.22 (s, 2H), 4.97 (s, 2H), 3.85 (s, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 161.1, 155.7, 151.5, 144.2, 139.5, 135.0, 131.4, 129.2, 129.1, 128.2, 127.0, 116.4, 115.2, 114.7, 113.9, 106.3, 105.9, 100.3, 75.5, 72.0, 55.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3485 (m), 3103 (m), 2790 (w), 1749 (m), 1494 (s), 1293 (vs), 1193 (m), 939 (m), 793 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_2BrO_5$ $[M\text{-}H]^-$: 493.0656 found: 493.0659.



416 417

5-(Benzyloxy)-2-bromo-1-((3,5-dimethoxybenzyl)oxy)-4-methoxynaphthalene 417

Sodium bi(trimethylsilyl)amide (1 M in tetrahydrofuran, 288 µL, 288 µmol, 1.05 equiv) was added to a solution of naphthol **416** (136 mg, 275 µmol, 1 equiv) in tetrahydrofuran (393 µL, 0.70 M) at –78 °C followed by dimethyl sulfate (29.0 µL, 305 µmol, 1.11 equiv). The reaction was allowed to warm to 23 °C and stirred for two hours at that temperature. A saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added and the solution was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (5% grading to 10% ethyl acetate in cyclohexane) to afford ether **417** (118 mg, 231 µmol, 84%) as an orange solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.46 (UV, CAM, $KMnO_4$).

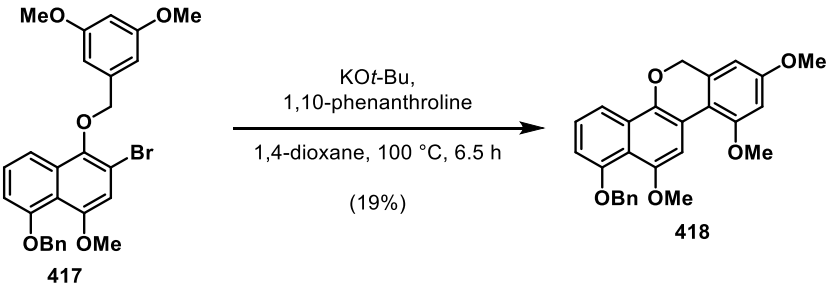
mp: 131–134 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.74 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.45 – 7.40 (m, 3H), 7.37 – 7.31 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.96 (s, 1H), 6.79 (d, *J* = 2.3 Hz, 2H), 6.49 (t, *J* = 2.3 Hz, 1H), 5.21 (s, 2H), 5.00 (s, 2H), 3.94 (s, 3H), 3.85 (s, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 161.1, 156.7, 154.3, 145.5, 139.6, 137.4, 132.2, 128.5, 127.8, 127.7, 127.1, 118.2, 115.3, 113.3, 109.8, 109.3, 105.9, 100.3, 75.4, 71.6, 56.7, 55.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2791 (w), 1752 (m), 1494 (s), 1297 (vs), 1203 (m), 1183 (m), 959 (m), 790 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{26}BrO_5$ $[M+H]^+$: 509.0958 found: 509.0961.

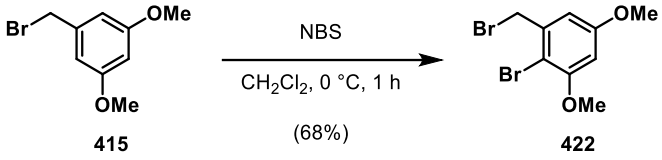


417 418

1-(Benzyloxy)-8,10,12-trimethoxy-6*H*-dibenzo[*c*,*h*]chromene 418

Ether **417** (12.0 mg, 22.8 µmol, 1 equiv) was placed in a flask and then purged for three times with argon. This flask was transferred to a glove-box. Then potassium *tert*-butoxide (6.60 mg, 59.0 µmol, 2.50 equiv) and 1,10-phenanthroline (1.70 mg, 9.42 µmol, 0.40 equiv) were added under a nitrogen atmosphere to the flask. After removal from the glove-box, 1,4-dioxane (472 µL, 0.05 M) was added to the flask via syringe and then stirred at 100 °C for 6.5 hours. The reaction was stopped by the addition of hydrochloric acid (1 M, 2 mL) and subsequently extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (50% dichloromethane in cyclohexane) gave the title compound **418** (1.92 mg, 4.48 µmol, 19%) as a red film.

TLC (66% dichloromethane in cyclohexane): R_f = 0.27 (UV, CAM).
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.96 (s, 1H), 7.91 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.44 – 7.40 (m, 2H), 7.38 – 7.32 (m, 2H), 6.95 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.23 (s, 2H), 5.10 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 160.3, 157.8, 155.8, 150.9, 144.0, 137.9, 135.7, 128.5, 128.3, 127.6, 127.2, 126.0, 117.9, 117.7, 115.4, 112.7, 109.4, 107.6, 102.1, 99.3, 71.8, 69.7, 57.5, 56.0, 55.6.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2204 (m), 1572 (m), 1496 (s), 1322 (s), 1271 (vs), 1183 (m), 1023 (w), 852 (m), 757 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{27}H_{25}O_5$ $[M+H]^+$: 429.1697 found: 429.1691.

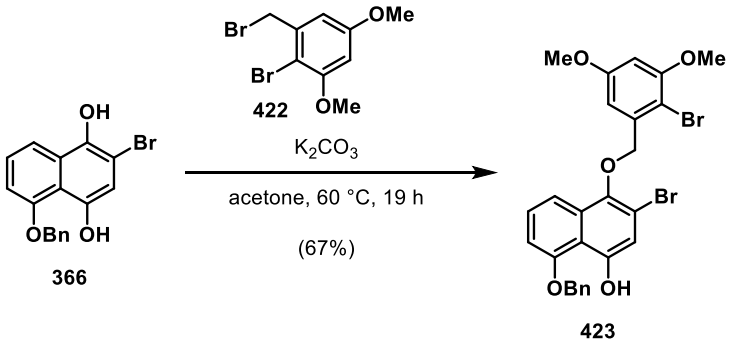


415 **422**

2-Bromo-1-(bromomethyl)-3,5-dimethoxybenzene 422

N-Bromosuccinimide (420 mg, 2.36 mmol, 0.50 equiv) was added to a solution of benzyl bromide **415** (1.09 g, 4.72 mmol, 1 equiv) in dichloromethane (47.2 mL, 0.1 M) at 0 °C and stirred for 30 minutes at that temperature. Then, more *N*-bromosuccinimide (420 mg, 2.36 mmol, 0.50 equiv) was added and the reaction was stirred for 30 minutes at 0 °C. The reaction was diluted with a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and water (10 mL) and then extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (30 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (5% grading to 10 % diethyl ether in pentane) gave the title compound **422** (995 mg, 3.21 mmol, 68%) as a beige solid.

Data consistent with literature: *J. Org. Chem.*, **2012**, *77*, 8762–8767.



8-(Benzyloxy)-3-bromo-4-((2-bromo-3,5-dimethoxybenzyl)oxy)naphthalen-1-ol 423

Potassium carbonate (264 mg, 1.91 mmol, 1.10 equiv) was added to a stirring solution of dihydroquinone **366** (600 mg, 1.74 mmol, 1 equiv) in acetone (3.48 mL, 0.5 M) at 23 ˚C. After five minutes of stirring, benzyl bromide **422** (539 mg, 1.74 mmol, 1.00 equiv) was added in one portion to the mixture and then stirred for 19 hours at 60 °C. The reaction was allowed to cool to 23 ˚C before water (5 mL) was added and the aqueous layer extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (20 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (33% grading to 50% dichloromethane in cyclohexane) gave the title compound **423** (669 mg, 1.17 mmol, 67%) as a beige solid.

TLC (60% dichloromethane in cyclohexane): R_f = 0.57 (UV, CAM, $KMnO_4$).

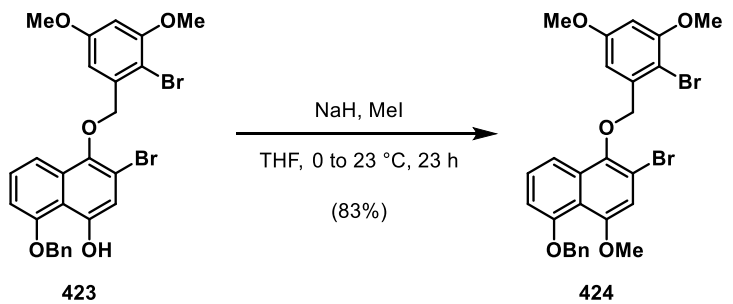
mp: 103 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.29 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.45 (dt, *J* = 15.9, 7.1 Hz, 5H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.17 (s, 1H), 7.02 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 5.28 (s, 2H), 5.09 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 160.2, 156.6, 155.8, 151.7, 144.2, 138.9, 135.0, 131.4, 129.3, 129.2, 128.2, 127.2, 116.4, 115.3, 114.8, 113.9, 106.4, 105.1, 102.1, 99.4, 74.7, 72.1, 56.6, 55.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3477 (m), 3123 (m), 2680 (w), 1848 (s), 1490 (s), 1284 (vs), 1173 (m), 937 (m), 893 (w), 799 (w) cm^{-1}.

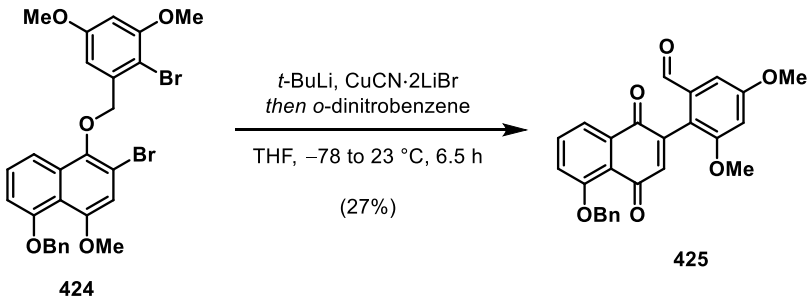
HRMS (ESI) calc. for $C_{26}H_{21}Br_2O_5$ $[M\text{-}H]^-$: 570.9761 found: 570.9758.



5-(Benzyloxy)-2-bromo-1-((2-bromo-3,5-dimethoxybenzyl)oxy)-4-methoxynaphthalene 424

Sodium hydride (60% dispersion in mineral oil, 55.6 mg, 1.39 mmol, 1.30 equiv) was added to a stirring solution of naphthol **423** (574 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (4.00 mL, 0.25 M) at 0 °C and stirred for five minutes. Then, iodomethane (436 µL, 7.00 mmol, 7.00 equiv) was added and the reaction was stirred for 20 minutes at that temperature before it was allowed to warm to 23 °C. After 13 hours, water (5 mL) was carefully added within three minutes and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (33% to 66% dichloromethane in cyclohexane) gave the title compound **424** (489 mg, 832 µmol, 83%) as a white solid.

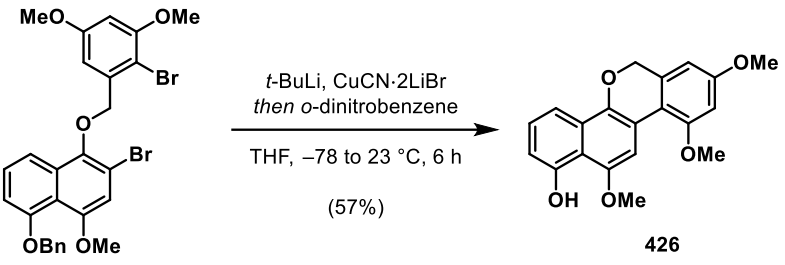
TLC (50% dichloromethane in cyclohexane): R_f = 0.53 (UV, CAM, $KMnO_4$).
mp: 97 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.73 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.37 (m, 3H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.96 (s, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 160.2, 156.7, 156.6, 154.5, 145.3, 138.9, 137.4, 132.1, 128.5, 127.9, 127.8, 127.1, 118.2, 115.2, 113.3, 109.8, 109.4, 105.0, 102.0, 99.3, 74.5, 71.5, 56.7, 56.5, 55.9.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2971 (w), 1893 (m), 1465 (s), 1287 (s), 1282 (vs), 1123 (s), 959 (w), 892 (w), 791 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{27}H_{25}Br_2O_5$ $[M+H]^+$: 587.0063 found: 587.0065.



2-(5-(Benzyloxy)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3,5-dimethoxybenzaldehyde 425
Dibromoether **424** (50 mg, 85.0 µmol, 1 equiv) was azeotropically dried using benzene (3 × 2 mL) before it was dissolved in dry tetrahydrofuran (850 µL, 0.1 M) and cooled to –78 °C. Then, *t*-butyllithium(1.64 M in pentane, 204 µL, 334 µmol, 4.00 equiv) was added dropwise to the reaction and stirred for 1.5 hours. Lithium bromide (dried under 0.1 mbar at 160 °C for three hours) (14.8 mg, 170 µmol, 2.00 equiv) and copper(I) cyanide (dried under 0.1 mbar at 160 °C for three hours) (15.2 mg, 85.0 µmol, 1.00 equiv) were placed in a flame-dried flask and dissolved in tetrahydrofuran (85 µL, 1 M) and vigorously shaken for two minutes while turning from a yellow suspension to a green solution, indicating complex formation. This solution was slowly added to the reaction at –78 °C and stirred for

two hours while warming to –40 °C. A solution of *o*-dinitronbenzene (57 mg, 334 µmol, 4.00 equiv) in tetrahydrofuran (334 µL, 1 M) was added dropwise and stirred for two hours while warming to 23 °C. The reaction was stopped by the addition of 2 mL hydrochloric acid (1 M in methanol, 2 mL), stirred for 30 minutes and the solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (dichloromethane grading to 5% methanol in dichloromethane) gave the title compound **425** (9.8 mg, 22.9 µmol, 27%) as a red film.

For analytical data: *see above*.



424 **426**

8,10,12-Trimethoxy-6*H*-dibenzo[*c*,*h*]chromen-1-ol 426

Dibromoether **424** (100 mg, 170 µmol, 1 equiv) was azeotropically dried using benzene (3 × 3 mL) before it was dissolved in dry tetrahydrofuran (1.7 mL, 0.1 M) and cooled to –78 °C. Then, *t*- butyllithium (1.64 M in pentane, 1.16 mL, 1.90 mmol, 11.2 equiv) was added dropwise to the reaction and stirred for one hour and 45 minutes while warming to –55 °C. Lithium bromide (dried under 0.1 mbar at 160 °C for three hours) (30 mg, 340 µmol, 2.00 equiv) and copper(I) cyanide (dried under 0.1 mbar at 160 °C for three hours) (15 mg, 170 µmol, 1.00 equiv) were placed in a flame-dried flask and dissolved in tetrahydrofuran (170 µL, 1 M) and vigorously shaken for two minutes while turning from a yellow suspension to a green solution, indicating complex formation. This solution was slowly added to the reaction at –55 °C and stirred for two hours while warming to –40 °C. A solution of *o*-dinitronbenzene (114 mg, 680 µmol, 4.00 equiv) in tetrahydrofuran (680 µL, 1 M) was added dropwise and stirred for two hours while warming to 23 °C. The reaction was stopped by the addition of 2 mL hydrochloric acid (1 M in methanol, 2 mL) and the solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (20% dichloromethane in cyclohexane) gave the title compound **426** (33 mg, 97.5 µmol, 57%) as a white solid.

TLC (60% dichloromethane in cyclohexane): R_f = 0.43 (UV, CAM).

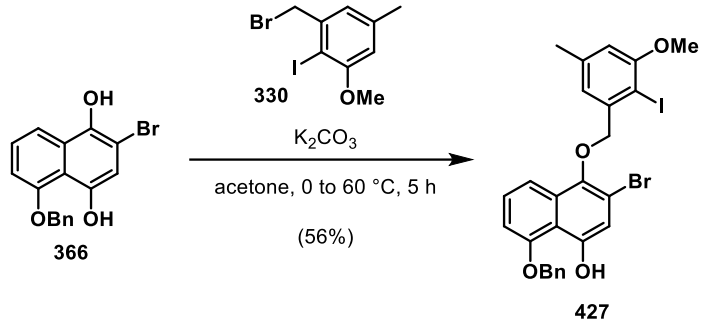
mp: 167 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.44 (s, 1H), 7.86 (s, 1H), 7.72 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.08 (s, 2H), 4.09 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 160.3, 157.6, 154.4, 150.0, 144.7, 135.6, 127.8, 127.4, 116.9, 114.5, 113.2, 112.5, 110.9, 104.1, 102.1, 99.3, 69.6, 56.4, 56.0, 55.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3593 (m), 3294 (m), 3020 (w), 1738 (w), 1602 (w), 1284 (m), 1249 (s), 1193 (vs), 1039 (m), 992 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{20}H_{17}O_5$ $[M\text{-}H]^-$: 337.1081 found: 337.1086.



8-(Benzyloxy)-3-bromo-4-((2-iodo-3-methoxy-5-methylbenzyl)oxy)naphthalen-1-ol 427

5-(benzyloxy)-2-bromonaphthalene-1,4-diol **366** (611 mg, 1.77 mmol, 1 equiv) and potassium carbonate (245 mg, 1.95 mmol, 1.10 equiv) were placed into a flask and purged three times with argon. The flask was put into an ice-bath before degassed acetone (3.54 mL, 0.5 M) was cooled to 0 °C and added via syringe. The mixture was stirred for 20 minutes at 0 °C and then a solution of 1-(bromomethyl)-2-iodo-3-methoxy-5-methylbenzene **330** (604 mg, 1.77 mmol, 1.00 equiv) in acetone (3.22 mL, 0.55 M) was added dropwise to the reaction. The mixture was heated to 60 °C and stirred for five hours. The mixture was allowed to cool to 23 °C and diluted with water (50 mL) and then extracted with ethyl acetate (1 × 200 mL, 2 × 70 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (20% grading to 50% dichloromethane in cyclohexane) to afford quinone **427** (596 mg, 985 µmol, 56%) as an orange foam, accompanied by recovered benzyl bromide **330** (137 mg, 407 µmol, 23%).

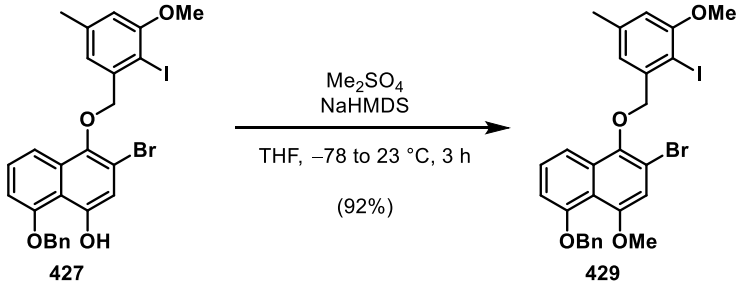
TLC (50% dichloromethane in cyclohexane): R_f = 0.54 (CAM).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.29 (s, 1H), 7.75 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.51 – 7.40 (m, 5H), 7.40 – 7.38 (m, 1H), 7.35 (dd, *J* = 8.6, 7.7 Hz, 1H), 7.03 (s, 1H), 6.93 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.67 (s, 1H), 5.28 (s, 2H), 5.04 (s, 2H), 3.91 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.8, 155.8, 151.6, 144.2, 141.2, 139.9, 135.0, 131.4, 129.3, 129.2, 128.2, 127.1, 122.1, 116.5, 115.3, 114.8, 113.9, 111.4, 106.4, 85.0, 79.3, 72.0, 56.7, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3498 (m), 3390 (w), 3104 (w), 1780 (m), 1593 (w), 1495 (s), 1394 (vs), 1123 (s), 909 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{26}H_{21}BrIO_4$ $[M-H]^-$: 602.9673 found: 602.9668.



5-(Benzyloxy)-2-bromo-1-((2-iodo-3-methoxy-5-methylbenzyl)oxy)-4-methoxynaphthalene 429

Sodium bi(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.55 mL, 1.59 mmol, 1.05 equiv) was added to a solution of naphthol **427** (919 mg, 1.52 mmol, 1 equiv) in tetrahydrofuran (2.17 mL, 0.7 M) at –78 °C followed by dimethyl sulfate (160 µL, 1.69 mmol, 1.11 equiv). The reaction was allowed to warm to 23 °C and stirred for three hours at that temperature. A saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added and the solution was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification was performed by silica gel chromatography (20% grading to 70% dichloromethane in cyclohexane) to afford quinone **429** (864 mg, 1.40 mmol, 92%) as a white solid.

TLC (30% dichloromethane in cyclohexane): R_f = 0.54 (CAM).

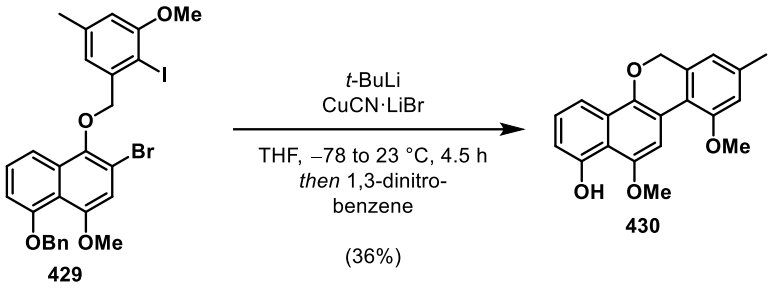
mp: 94–96 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.75 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.37 (m, 4H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.98 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.97 (s, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 5.21 (s, 2H), 5.07 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.8, 156.7, 154.5, 145.3, 141.3, 139.9, 137.5, 132.2, 128.6, 127.8, 127.8, 127.1, 122.0, 118.2, 115.4, 113.3, 111.4, 109.8, 109.4, 84.9, 79.2, 71.6, 56.8, 56.7, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2193 (w), 1790 (m), 1623 (w), 1473 (s), 1374 (vs), 1223 (s), 909 (m), 712 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{25}BrIO_4$ $[M+H]^+$: 618.9975 found: 618.9970.



10,12-Dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-1-ol 430

Tert-butyllithium (1 M in pentane, 9.70 mL, 14.7 mmol, 11.0 equiv) was added dropwise to a solution of ether **429** (825 mg, 1.33 mmol, 1 equiv) in tetrahydrofuran (13.3 mL, 0.1 M) at –78 °C and stirred for 30 minutes. A freshly prepared solution of CuCN·2LiBr (351 mg, 1.33 mmol, 1.00 equiv) in tetrahydrofuran (3.51 mL, 0.38 M) was added dropwise to the reaction and stirred for two hours while warming to –40 °C. A solution of 1,3-dinitrobenzene (896 mg, 5.33 mmol, 4.00 equiv) in tetrahydrofuran (8.96 mL, 0.59 M) was added and the reaction was warmed to 23 °C over a period of 30 minutes and stirred for two hours at that temperature. The reaction was stopped by the addition of methanolic hydrochloric acid (15 mL) and stirred for 30 minutes, before a saturated aqueous solution of ammonium chloride (15 mL) was added. The mixture was extracted with diethyl ether (3 × 60 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Residual dinitrobenzene was largely removed by sublimation at 0.1 mbar and 40 °C for 20 hours. The remaining crude mixture was purified by two consecutive applications of silica gel chromatography (A: 25% dichloromethane in cyclohexane; B: 5% diethyl ether in pentane) to afford dibenzochromene **430** (155 mg, 0.480 mmol, 36%) as a yellow solid.

TLC (50% dichloromethane in cyclohexane): R_f = 0.26 (CAM).

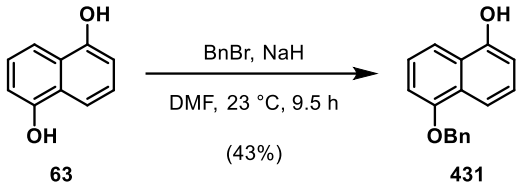
mp: 174 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.44 (s, 1H), 7.91 (s, 1H), 7.73 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.35 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.79 (s, 1H), 6.69 (dt, *J* = 1.7, 0.8 Hz, 1H), 5.08 (s, 2H), 4.09 (s, 3H), 3.95 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 156.2, 154.4, 149.9, 145.4, 139.1, 134.4, 127.8, 127.4, 118.4, 116.8, 116.5, 114.8, 113.4, 112.8, 111.1, 104.3, 69.4, 56.4, 56.0, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3553 (m), 3092 (m), 3019 (w), 2004 (m), 1741 (w), 1652 (w), 1273 (m), 1223 (s), 1103 (vs), 1030 (m), 972 (s) cm^{-1}.

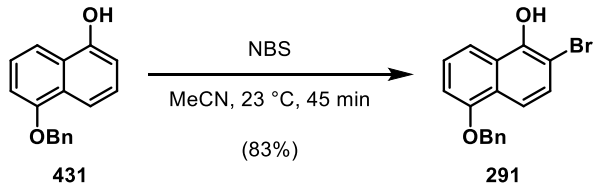
HRMS (ESI) calc. for $C_{20}H_{17}O_4$ [M-H]$^-$: 321.1132 found: 321.1137.



5-(Benzyloxy)naphthalen-1-ol 431

Sodium hydride (60% dispersion in mineral oil, 11.0 g, 274 mmol, 2.19 equiv) was added to a stirring solution of naphthol **63** (20 g, 125 mmol, 1 equiv) in *N*,*N*-dimethylformamide (214 mL, 0.6 M) at 0 ˚C and stirred for 2.5 hours at that temperature. A solution of benzyl bromide (15.3 mL, 129 mmol, 1.03 equiv) in *N*,*N*-dimethylformamide (214 mL, 0.6 M) was added dropwise to the mixture and then stirred for seven hours while slowly warming to 23 °C. The reaction was acidified by the addition of aqueous hydrochloric acid (1 M, 50 mL) and the solution was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (80% grading to 100% dichloromethane in cyclohexane) gave the title compound **431** (13.5 g, 53.7 mmol, 43%) as a greenish solid.

Data consistent with literature: *Tetrahedron*, **2018**, *74*, 4994–4999.



5-(Benzyloxy)-2-bromonaphthalen-1-ol 291

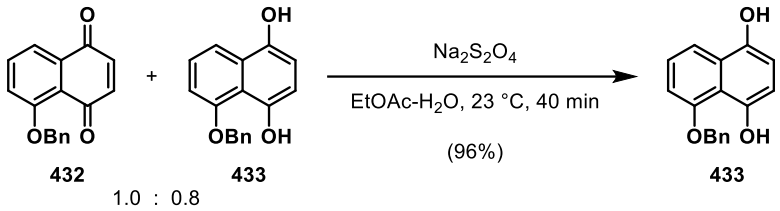
A solution of *N*-bromosuccinimide (3.87 g, 21.7 mmol, 1.00 equiv) in acetonitrile (47.2 mL, 0.46 M) was added dropwise to a stirring solution of naphthol **431** (5.44 g, 21.7 mmol, 1 equiv) in acetonitrile (724 mL, 0.03 M) within 15 minutes at 23 ˚C. After 30 minutes, the solvent was removed under reduced pressure. Purification by silica gel chromatography (15% grading to 20% ethyl acetate in pentane) gave the title compound **291** (5.95 g, 18.1 mmol, %) as a greenish solid.

For analytical data: *see above.*

5-(Benzyloxy)naphthalene-1,4-dione 432 and **5-(benzyloxy)naphthalene-1,4-diol 433**

Water (208 mL, 0.12 M) was added to a solution of naphthol **291** (6.26 g, 25.0 mmol, 1 equiv) in acetonitrile (417 mL, 0.06 M) at 23 ˚C. (Diacetoxyiodo)benzene (16.8 g, 52.0 mmol, 2.08 equiv) was added in one portion to the mixture and stirred for ten minutes at 23 °C. The reaction was stopped by the addition of a saturated aqueous solution of sodium hydrogen carbonate (250 mL) and the organic layer was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (150 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (25% ethyl acetate in cyclohexane, R_f = 0.31–0.33 for both products) afforded a mixture of the two title compounds **432** and **433** (5.07 g, 19.1 mmol, 76% combined) as a yellow solid. The mixture was used in the next step without further separation.

Data for **432** consistent with literature: *Org. Biomol. Chem.*, **2020**, *18*, 750–754.



5-(Benzyloxy)naphthalene-1,4-diol 433

A solution of sodium dithionite (17.4 g, 99.7 mmol, 5.22 equiv) in water (250 mL, 0.4 M) was added dropwise to a solution of the above obtained mixture of **432** and **433** (5.07 g, 19.1 mmol, 1 equiv) in ethyl acetate (191 mL, 0.1 M) at 23 °C. After one hour of vigorous stirring, the mixture was diluted with water (100 mL) and the solution extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (150 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (15% grading to 25% ethyl acetate in cyclohexane) gave dihydroquinone **433** (4.88 g, 18.3 mmol, 96%) as a white solid.

TLC (dichloromethane): R_f = 0.15 (UV, CAM).

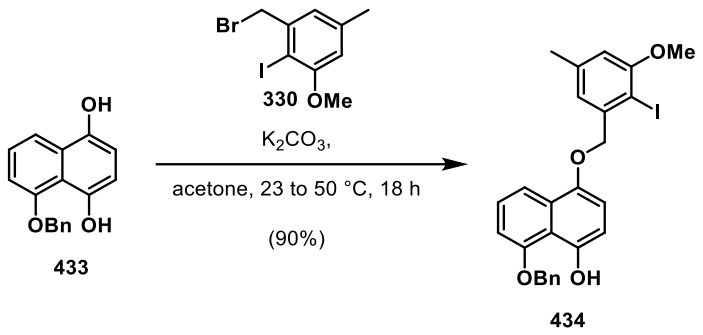
mp: 77 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.00 (s, 1H), 7.77 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.46 – 7.37 (m, 3H), 7.34 (dd, *J* = 8.6, 7.7 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.28 (s, 2H), 4.73 (s, 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 155.4, 148.5, 143.8, 135.4, 129.2, 129.0, 128.1, 127.0, 125.4, 116.0, 115.8, 111.0, 109.6, 106.3, 71.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3322 (w), 3061 (m), 1845 (s), 1719 (m), 1553 (s), 1498 (m), 1317 (w), 1242 (vs), 1011 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{15}O_3$ $[M+H]^+$: 267.1016 found: 267.1012.



8-(Benzyloxy)-4-((2-iodo-3-methoxy-5-methylbenzyl)oxy)naphthalen-1-ol 434

Potassium carbonate (227 mg, 1.64 mmol, 1.20 equiv) was added to a stirring solution of dihydroquinone **433** (400 mg, 1.50 mmol, 1.10 equiv) in degassed acetone (1.50 mL, 1 M) at 23 ˚C. After ten minutes of stirring, a solution of benzyl bromide **330** (466 mg, 1.37 mmol, 1 equiv) in degassed acetone (2.73 mL, 0.5 M) was added to the mixture, warmed to 50 °C and stirred for 18 hours at that temperature. The reaction was allowed to cool to 23 ˚C and water (2 mL) was added, which caused coloration of the solution to dark-red accompanied by solidification. The obtained suspension was dissolved in dichloromethane (20 mL) and filtered through a short plug of silica. Purification by silica gel chromatography (25% grading to 50% dichloromethane in cyclohexane) gave the title compound **434** (650 mg, 1.24 mmol, 90%) as a pale-yellow solid.

TLC (75% dichloromethane in cyclohexane): R_f = 0.58 (UV, CAM).

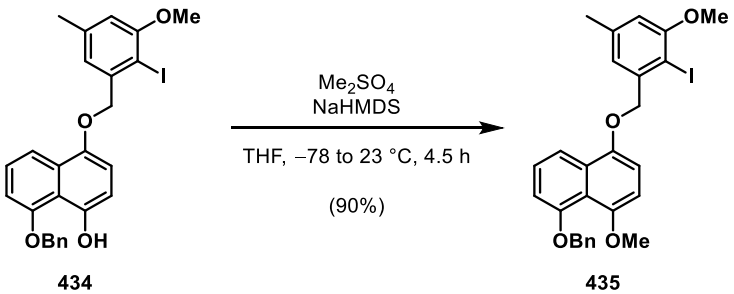
mp: 91 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.04 (s, 1H), 8.00 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.37 (m, 3H), 7.35 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.08 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 3.91 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 158.0, 155.3, 148.5, 147.1, 141.0, 139.7, 135.4, 129.2, 128.96, 128.3, 128.1, 125.4, 122.0, 116.6, 115.9, 111.4, 109.4, 108.6, 106.4, 85.4, 75.4, 71.8, 56.6, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3375 (m), 3273 (m), 2810 (w), 1659 (m), 1514 (s), 1398 (vs), 1213 (m), 965 (m), 721 (m) cm^{-1}.

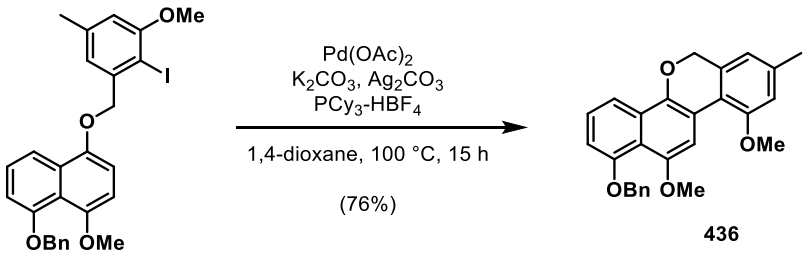
HRMS (ESI) calc. for $C_{26}H_{24}IO_4$ $[M+H]^+$: 527.0714 found: 527.0740.



5-(Benzyloxy)-1-((2-iodo-3-methoxy-5-methylbenzyl)oxy)-4-methoxynaphthalene 435

Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 7.92 mL, 7.92 mmol, 1.05 equiv) was added to a stirring solution of naphthalene **434** (3.97 g, 7.54 mmol, 1 equiv) in tetrahydrofuran (10.8 mL, 0.7 M) at –78 ˚C. After two minutes, dimethyl sulfate (794 µL, 8.37 mmol, 1.11 equiv) was added dropwise to the green solution, which was allowed to warm to 23 °C and then stirred for two hours. A saturated aqueous solution of sodium hydrogen carbonate (4 mL) was added to the dark-red solution and the mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (100 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (15% ethyl acetate in cyclohexane) gave the title compound **435** (3.68 g, 6.81 mmol, 90%) as a yellowish solid.

TLC (25% ethyl acetate in cyclohexane): R_f = 0.46 (UV, CAM).
mp: 84 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.02 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.09 (s, 1H), 7.02 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.64 (s, 1H), 5.22 (s, 3H), 5.19 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.36 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 158.0, 156.0, 151.5, 148.4, 141.0, 139.8, 137.8, 129.3, 128.5, 127.7, 127.2, 126.1, 121.9, 119.2, 115.6, 111.4, 109.8, 106.8, 106.5, 85.3, 75.2, 71.8, 57.3, 56.7, 21.7.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2610 (w), 1859 (m), 1616 (s), 1594 (w), 1499 (m), 1365 (vs), 1203 (m), 971 (m), 743 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{27}H_{26}IO_4$ $[M+H]^+$: 541.0870 found: 541.0875.

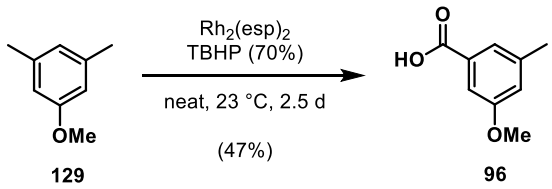


1-(Benzyloxy)-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromene 436

Ether **435** (4.00 g, 7.40 mmol, 1 equiv), palladium(II) acetate (83 mg, 370 µmol, 5 mol%), potassium carbonate (2.05 g, 14.8 mmol, 2.00 equiv), silver carbonate (1.02 g, 3.70 mmol, 0.50 equiv) and tricyclohexylphosphine tetrafluoroborate (273 mg, 740 µmol, 10 mol%) were placed in a flask and purged three times with argon. Degassed 1,4-dioxane (37.0 mL, 0.2 M) was added via syringe and the mixture was stirred for 15 hours at 100 ˚C in a sealed flask. The reaction was allowed to cool to 23 ˚C and filtered through a short plug of silica using dichloromethane as eluent to afford 3.01 g of a clean mixture of starting material **435**, desired product **436** and dehalogenated side product **449** (1.0 : 7.7 :

1.0). This mixture was either used in the next step (see preparation of **147** on page **168**) or purified by silica gel chromatography (17% grading to 33% dichloromethane in cyclohexane) to obtain title compound **436** (2.31 g, 5.61 mmol, 76%) as a white solid.

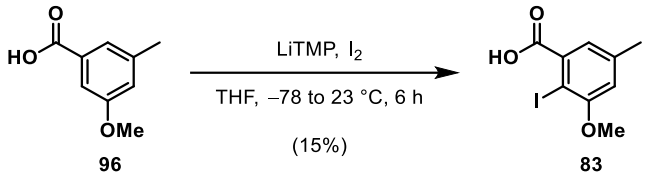
TLC (57% dichloromethane in cyclohexane): R_f = 0.37 (UV, CAM).
mp: 167–169 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00 (s, 1H), 7.91 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.44 – 7.40 (m, 2H), 7.35 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.35 – 7.31 (m, 2H), 6.95 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.79 (s, 1H), 6.69 (s, 1H), 5.22 (s, 2H), 5.09 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.40 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 156.4, 155.8, 150.8, 144.8, 139.0, 137.9, 134.6, 128.5, 128.3, 127.6, 127.2, 126.0, 118.3, 118.2, 117.7, 116.7, 115.6, 112.9, 109.7, 107.8, 71.8, 69.5, 57.5, 56.0, 21.7.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2104 (w), 1590 (m), 1377 (m), 1346 (s), 1286 (s), 1133 (vs), 1051 (s), 843 (m), 756 (w) cm^{-1}.
HRMS (ESI) calc. for $C_{27}H_{25}O_4$ $[M+H]^+$: 413.1747 found: 413.1772.



3-Methoxy-5-methylbenzoic acid 96

Tert-butyl hydroperoxide (70% in H_2O, 372 mL, 2.68 mol, 20.0 equiv) was added dropwise to a suspension of bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (100 mg, 132 µmol, 0.1 mol%) in 3,5-dimethylanisole **129** (18.3 g, 134 mmol, 1 equiv) at 0 °C. The external ice-bath was removed to allow warming to 23 °C and then the mixture was stirred for 60 hours at that temperature in an open flask. A saturated aqueous solution of sodium thiosulfate (100 mL) was added to the green suspension and stirred for 15 minutes until a red-brown suspension was observed. The mixture was basified with an aqueous solution of sodium hydroxide (2 M) to pH 13 and then extracted with ethyl acetate (3 × 150 mL). The combined organic layers were extracted with an aqueous solution of sodium hydroxide (2 M) until TLC-monitoring indicated no residual product in the organic phase. All combined aqueous layers were acidified with a solution of hydrochloric acid (2 M) to pH 1 and extracted with ethyl acetate (5 × 100 mL). The combined organic layers were washed with water (300 mL), a saturated aqueous solution of sodium chloride (300 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give the desired benzoic acid **96** as an off-white solid (10.5 g, 63.0 mmol, 47%).

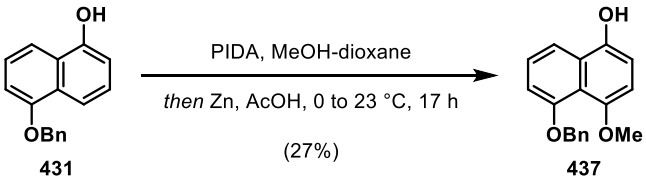
Data consistent with literature: *J. Org. Chem.*, **1985**, *50*, 2273–2277.



2-Iodo-3-methoxy-5-methylbenzoic acid 83

n-Butyl lithium (2.50 M in hexane, 180 µL, 448 µmol, 4.00 equiv) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (76.0 µL, 448 µmol, 4.00 equiv) in tetrahydrofuran (3.73 mL, 0.12 M) at 0 °C and then stirred for 30 minutes at that temperature before it was cooled to –78 °C. A solution of benzoic acid **96** (18.6 mg, 112 µmol, 1 equiv) was dissolved in tetrahydrofuran (160 µL, 0.70 M) and slowly added at –78 °C. The reaction was warmed to 0 °C and stirred for 2.5 hours at that temperature before it was cooled to –78 °C. A solution of iodine (142 mg, 560 µmol, 5.00 equiv) in tetrahydrofuran (373 µL, 1.50 M) was slowly added to the mixture and stirred for three hours while slowly warming to 23 °C. The reaction was stopped by the addition of hydrochloric acid (2 M, 500 µL) and the solution was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (3 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (25% ethyl acetate in cyclohexane + 2% acetic acid) afforded benzoic acid **83** (4.90 mg, 16.8 mmol, 15%) as a white solid.

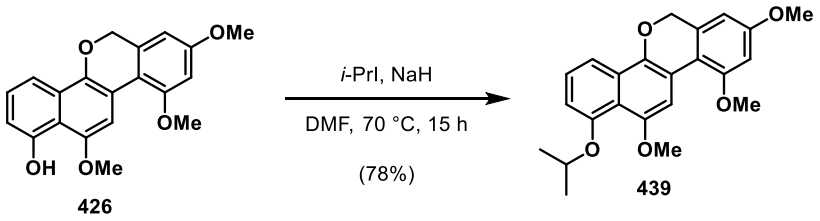
Data consistent with literature: *J. Org. Chem.*, **2000**, *65*, 7187–7194.



5-(Benzyloxy)-4-methoxynaphthalen-1-ol 437

Methanol (484 µL, 0.19 M) was added to a solution of naphthalene **431** (23.0 mg, 91.9 µmol, 1 equiv) in 1,4-dioxane (164 µL, 0.56 M) and then cooled to 0 °C. (Diacetoxy)iodobenzene (62.0 mg, 193 µmol, 2.10 equiv) was dissolved in methanol (1.10 mL, 0.18 M), added dropwise to the reaction and stirred for 17 hours while slowly warming to 23 °C. Then, acetic acid (99 µL, 0.93 M) and zinc-dust (18.0 mg, 276 µmol, 3.00 equiv) were added subsequently to the mixture and stirred for 30 minutes. The reaction was taken up with ethyl acetate and filtered through a short plug of silica to obtain the crude product. Purification by silica gel chromatography (5% ethyl acetate in cyclohexane) afforded dihydroquinone **437** (6.95 mg, 24.8 mmol, 27%) as a yellow solid.

Data consistent with literature: *Org. Lett.*, **2014**, *16*, 6240–6243.



1-Isopropoxy-8,10,12-trimethoxy-6*H*-dibenzo[*c,h*]chromene 439

Sodium hydride (60% dispersion in mineral oil, 6.96 mg, 174 µmol, 1.30 equiv) was added to a solution of naphtol **426** (49 mg, 145 µmol, 1 equiv) in *N,N*-dimethylformamide (1.12 mL, 0.13 M) at 23 ˚C. After 30 minutes, 2-iodopropane (29 µL, 290 µmol, 2.00 equiv) was added in one portion to the mixture and then stirred for 15 hours at 70 °C. The reaction was allowed to cool to 23 ˚C before addition of water (2 mL) and extraction of the solution with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (50% dichloromethane in cyclohexane) gave the title compound **439** (43 mg, 113 µmol, 78%) as a yellow solid.

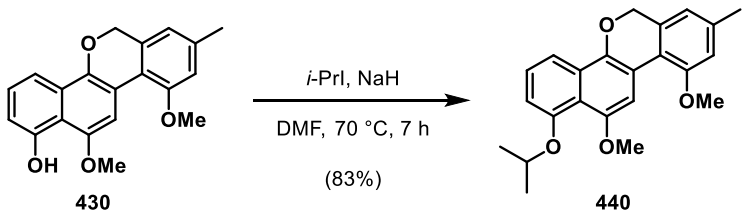
TLC (75% dichloromethane in cyclohexane): R_f = 0.29 (UV, CAM).

mp: 193 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.93 (s, 1H), 7.91 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.35 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 5.09 (s, 2H), 4.57 (hept, *J* = 6.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H), 1.42 (d, *J* = 6.1 Hz, 6H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3019 (m), 2981 (m), 2894 (m), 1588 (m), 1422 (m), 1385 (m), 1284 (m), 1200 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{23}H_{25}O_5$ $[M+H]^+$: 381.1697 found: 381.1690.



1-Isopropoxy-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c,h*]chromene 440

Sodium hydride (60% dispersion in mineral oil, 5.04 mg, 129 µmol, 1.30 equiv) was added to a solution of naphtol **430** (32.0 mg, 99.3 µmol, 1 equiv) in *N,N*-dimethylformamide (764 µL, 0.13 M) at 0 ˚C. After 30 minutes, 2-iodopropane (20 µL, 200 µmol, 2.00 equiv) was added in one portion to the mixture and then stirred for seven hours at 70 °C. The reaction was allowed to cool to 23 ˚C before water (2 mL) was added and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced

pressure. Purification by silica gel chromatography (5% ethyl acetate in cyclohexane) gave the title compound **440** (30.0 mg, 82.4 µmol, 83%) as a white solid.

TLC (10% ethyl acetate in cyclohexane): R_f = 0.34 (UV, CAM, $KMnO_4$).

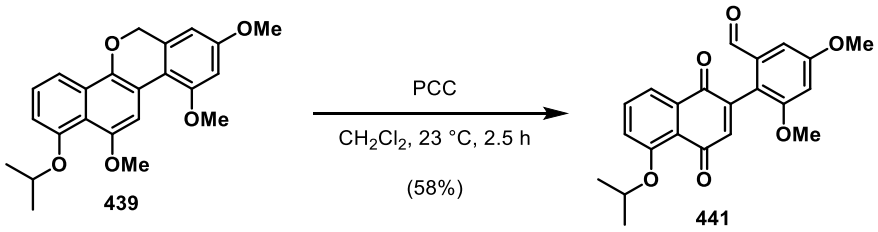
mp: 179 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.96 (s, 1H), 7.91 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.78 (s, 1H), 6.68 (s, 1H), 5.08 (s, 2H), 4.56 (hept, *J* = 5.8 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.39 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 156.4, 154.5, 150.6, 145.1, 138.9, 134.5, 128.5, 125.8, 119.8, 118.3, 117.4, 116.8, 115.9, 114.1, 112.8, 108.6, 73.2, 69.5, 57.9, 56.0, 22.2, 21.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3031 (m), 2970 (m), 2914 (m), 1534 (m), 1421 (m), 1302 (m), 1274 (m), 1249 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{23}H_{25}O_4$ $[M+H]^+$: 365.1747 found: 365.1742.



2-(5-Isopropoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3,5-dimethoxybenzaldehyde 441

Pyridinium chlorochromate (15 mg, 37.1 µmol, 1.09 equiv) was added to a solution of tetracycle **439** (13 mg, 34.2 µmol, 1 equiv) in dichloromethane (683 µL, 0.05 M) at 23 °C. After stirring for one hour at 40 °C, additional pyridinium chlorochromate (7 mg, 32.5 µmol, 0.95 equiv) was added and the reaction was stirred for two hours at 40 °C. The reaction was allowed to cool to 23 ˚C and was filtered through a short plug of silica using diethyl ether as eluent. Purification by silica gel chromatography (60% dichloromethane in cyclohexane) gave the title compound **441** (7.5 mg, 19.8 µmol, 58%) as a yellow solid.

TLC (dichloromethane): R_f = 0.39 (UV, CAM).

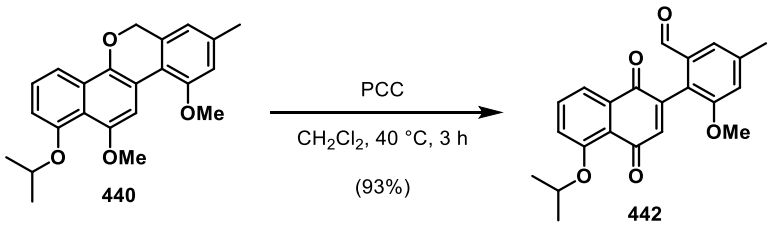
mp: 181 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.87 (s, 1H), 7.75 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.32 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.79 (s, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 4.72 (hept, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 1.48 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 190.7, 184.5, 183.9, 161.64, 158.7, 158.4, 142.1, 140.9, 136.4, 135.0, 134.6, 121.4, 121.3, 120.0, 117.8, 105.2, 104.6, 72.5, 56.3, 55.9, 22.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3102 (w), 2922 (m), 2841 (m), 2603 (w), 1651 (m), 1603 (m), 1472 (m), 1313 (s), 1293 (s), 1194 (w), 1020 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{21}O_6$ $[M+H]^+$: 381.1333 found: 381.1338.



2-(5-Isopropoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methoxy-5-methylbenzaldehyde 442

Pyridinium chlorochromate (4.73 mg, 22.0 µmol, 1.00 equiv) was added to a stirring solution of tetracycle **440** (8.00 mg, 22.0 µmol, 1 equiv) in dichloromethane (439 µL, 0.05 M) at 23 ˚C and stirred for one hour at 40 °C. Then, pyridinium chlorochromate (4.73 mg, 22.0 µmol, 1.00 equiv) was added to the mixture and stirred for further two hours at 40 °C. The reaction was allowed to cool to 23 ˚C, taken up with dichloromethane and filtered through a short plug of silica to obtain the desired product **442** (7.43 mg, 20.4 µmol, 93%) as a yellow solid after evaporation under reduced pressure.

TLC (75% dichloromethane in cyclohexane): R_f = 0.13 (UV, CAM).

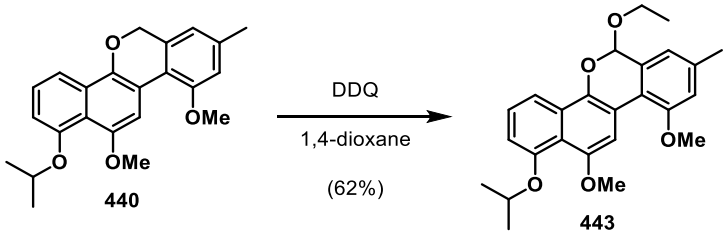
mp: 201 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 9.81 (s, 1H), 7.68 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.57 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.29 (s, 1H), 7.24 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.97 (s, 1H), 6.69 (s, 1H), 4.64 (hept, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 2.41 (s, 3H), 1.41 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 191.5, 184.4, 184.0, 158.4, 157.4, 142.9, 141.1, 140.1, 135.6, 135.1, 134.5, 124.2, 121.4, 121.3, 121.1, 120.0, 117.6, 72.5, 56.3, 22.2, 21.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3112 (w), 2862 (w), 2646 (m), 2615 (w), 1751 (m), 1703 (s), 1472 (m), 1326 (s), 1284 (s), 1192 (w), 1023 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{21}O_5$ $[M+H]^+$: 365.1384 found: 365.1380.



6-Ethoxy-1-isopropoxy-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromene 443

To a solution of cyclic ether **440** (9 mg, 24.7 µL, 1 equiv) in 1,4-dioxane (274 µL, 0.09 M) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (11 mg, 49.4 µL, 2.00 equiv) and stirred for two hours at 23 °C. The solvent was removed under reduced pressure and the residual crude solid was dissolved in dichloromethane (5 mL) and filtered through a short plug of silica. Purification by silica gel chromatography (60% dichloromethane in cyclohexane) gave the title compound **443** (5.8 mg, 15.3 µmol, 63%) as a yellow solid.

TLC (dichloromethane): R_f = 0.39 (UV, CAM).

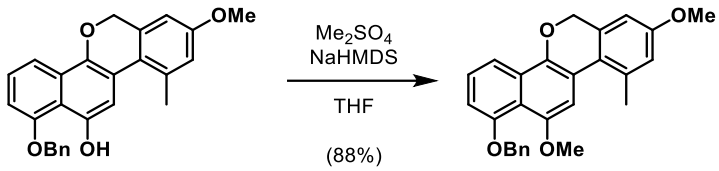
mp: 174 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.12 (s, 1H), 8.03 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.36 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.95 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.85 (s, 2H), 6.10 (s, 1H), 4.57 (hept, *J* = 6.1 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.94 (q, *J* = 7.1 Hz, 1H), 3.79 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.42 (s, 3H), 1.45 – 1.39 (m, 6H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.8, 155.7, 151.6, 142.8, 141.2, 139.9, 135.0, 131.5, 129.2, 129.1, 128.1, 127.1, 125.3, 122.1, 116.4, 114.8, 111.4, 111.3, 106.2, 85.1, 79.3, 72.0, 56.65, 21.67.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3027 (w), 2856 (m), 2645 (m), 1539 (m), 1421 (w), 1402 (m), 1294 (s) 1254 (m), 1211 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{28}O_5$ $[M]^+$: 408.1931 found: 408.1925.



368 **444**

1-(Benzyloxy)-8,12-dimethoxy-10-methyl-6*H*-dibenzo[*c*,*h*]chromene 444

Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran) (403 µL, 403 µmol, 1.05 equiv) was added to a stirring solution of phenolic tetracycle **368** (153 mg, 384 µmol, 1 equiv) in tetrahydrofuran (998 µL, 0.4 M) at –78 °C. After two minutes, dimethyl sulfate (40 µL, 426 µmol, 1.11 equiv) was added dropwise to the mixture, which was allowed to warm to 23 °C and then stirred for three hours. A saturated aqueous solution of sodium hydrogen carbonate (2 mL) was added and the mixture was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (15% grading to 50% diethyl ether in pentane) gave the title compound **444** (140 mg, 340 µmol, 88%) as a beige solid.

TLC (25% diethyl ether in pentane): R_f = 0.38 (UV, CAM).

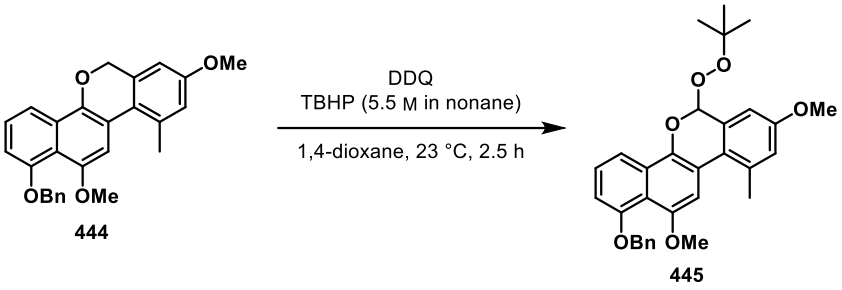
mp: 224 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.95 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.48 – 7.35 (m, 4H), 7.34 (s, 1H), 6.98 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 5.25 (s, 2H), 5.08 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 2.72 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 158.7, 155.9, 150.9, 145.5, 137.7, 136.2, 135.5, 128.6, 128.5, 127.7, 127.2, 126.3, 122.9, 119.7, 117.8, 117.4, 115.3, 109.2, 108.5, 107.4, 71.6, 70.4, 57.7, 55.5, 23.2.

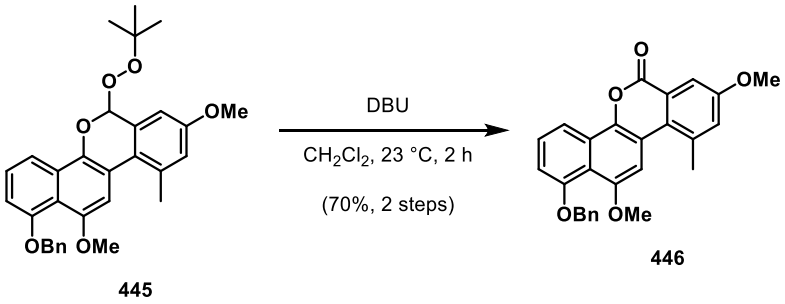
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2894 (w), 1984 (m), 1698 (w), 1443 (s), 1285 (vs), 1147 (m), 1092 (w), 889 (m), 799 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{25}O_4$ $[M+H]^+$: 413.1747 found: 413.1751.



1-(Benzyloxy)-6-(tert-butylperoxy)-8,12-dimethoxy-10-methyl-6*H*-dibenzo[*c*,*h*]chromene 445

To a solution of cyclic ether **444** (123 mg, 298 µL, 1 equiv) in 1,4-dioxane (3.31 mL, 0.09 M) was added *tert*-butyl hydroperoxide (5.5 M in nonane, 108 µL, 596 µmol, 2.00 equiv) and stirred for two minutes at 23 °C. Then, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (68.0 mg, 298 µL, 1.00 equiv) was added turning the reaction to dark-green and stirred for 2.5 hours at 23 °C. The solvent was removed under reduced pressure and the residual crude solid was taken up in cyclohexane-dichloromethane (1:5) and filtered through a short plug of silica. The crude peroxyacetal **445** was immediately used in the next step without further purification due to its instability.



1-(Benzyloxy)-8,12-dimethoxy-10-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 446

To residual crude peroxoacetal **445** was dissolved in dichloromethane (5.96 mL, 0.05 M) and 1,8-diazabicyclo[5.4.0]undec-7-ene (134 µL, 894 µmol, 3.00 equiv) was added dropwise to the solution and stirred for two hours at 23 °C. After removal of the solvent under reduced pressure, the crude mixture was purified by silica gel chromatography (60% dichloromethane in cyclohexane) to give lactone **446** (89.0 mg, 209 µmol, 70%) as a yellow solid. In addition, starting material **445** (25.0 mg, 60.6 µmol, 20%) was recovered.

TLC (25% diethyl ether in pentane): R_f = 0.36 (UV, CAM, $KMnO_4$).

mp: 226 °C.

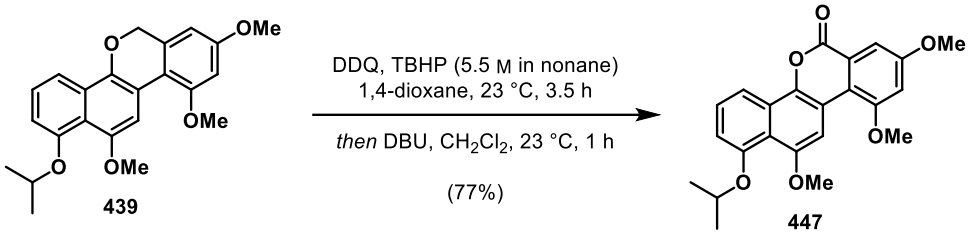
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.27 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.88 (d, *J* = 2.9 Hz, 1H), 7.70 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.27 (1H)[1], 7.09 (d, *J* = 7.7 Hz, 1H), 5.26 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 2.99 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 162.0, 159.0, 155.8, 153.1, 140.6, 137.4, 136.9, 128.6, 128.0, 128.0, 127.8, 127.7, 127.4, 127.2, 124.6, 117.8, 115.4, 115.2, 110.2, 110.2, 103.6, 71.6, 57.1, 55.8, 25.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1722 (m), 1582 (m), 1365 (s), 1342 (w), 1288 (vs), 1167 (s), 1049 (m), 848 (w), 755 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{23}O_5$ $[M+H]^+$: 427.1540 found: 427.1548.

[1]*partially overlaid by solvent-peak ($CHCl_3$).*



1-Isopropoxy-8,10,12-trimethoxy-6*H*-dibenzo[*c*,*h*]chromen-6-one 447

To a solution of cyclic ether **439** (8 mg, 21.0 µL, 1 equiv) in 1,4-dioxane (234 µL, 0.09 M) was added *tert*-butyl hydroperoxide (5.5 M in nonane, 8 µL, 42.1 µmol, 2.00 equiv) and stirred for two minutes at 23 °C. Then, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (4.8 mg, 21.0 µL, 1.00 equiv) was added turning the reaction to dark-green and stirred for two hours at 23 °C. The solvent was removed under reduced pressure and the residual crude solid was dissolved in dichloromethane (234 µL, 0.09 M). 1,8-diazabicyclo[5.4.0]undec-7-ene (9.4 µL, 63.1 µmol, 3.00 equiv) was added dropwise to the solution and stirred for 1.5 hours at 23 °C. After removal of the solvent under reduced pressure, the crude mixture was purified by silica gel chromatography (60% dichloromethane in cyclohexane) to give lactone **447** (6.4 mg, 16.2 µmol, 77%) as a yellow solid.

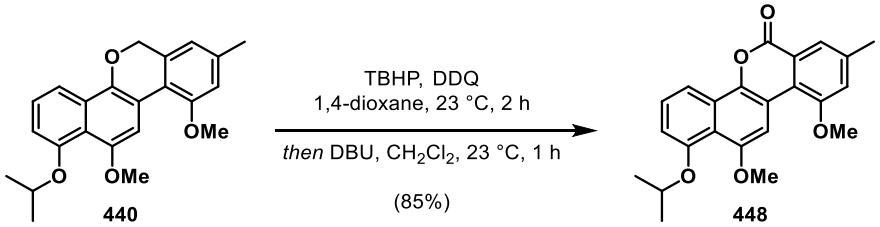
TLC (dichloromethane): R_f = 0.43 (UV, $KMnO_4$).

mp: 245 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.35 (s, 1H), 8.23 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.57 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 4.59 (h, *J* = 6.1 Hz, 1H), 4.05 (s, 3H), 4.00 (s, 3H), 3.95 (s, 3H), 1.44 (d, *J* = 6.1 Hz, 6H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3394 (w), 3218 (w), 2988 (m), 1942 (m), 1849 (s), 1591 (m), 1423 (s), 1395 (vs), 1203 (m) cm^{-1}.

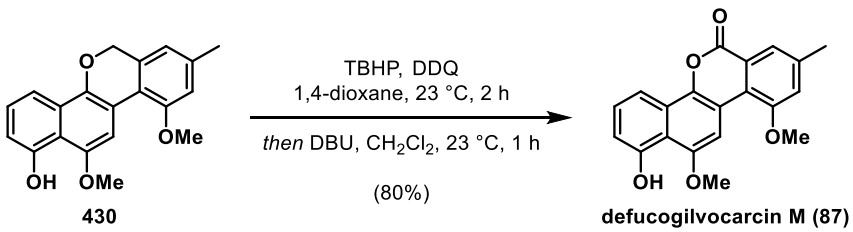
HRMS (ESI) calc. for $C_{23}H_{23}O_6$ $[M+H]^+$: 395.1489 found: 395.1489.



1-Isopropoxy-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 448

Tert-butyl hydroperoxide (5.5 M in nonane, 15.0 µL, 82.4 µmol, 2.00 equiv) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (14.0 mg, 61.8 µmol, 1.50 equiv) were added to a solution of tetracycle **440** (15 mg, 41.2 µmol, 1 equiv) in 1,4-dioxane (458 µL, 0.09 M) at 23 ˚C and stirred for two hours at that temperature. The solvent was removed under reduced pressure and the crude solid was re-dissolved in dichloromethane (458 µL, 0.09 M). 1,8-Diazabicyclo(5.4.0)undec-7-ene (30.7 µL, 206 µmol, 5.00 equiv) was added and the mixture was stirred for one hour at 23 °C. The solvent was removed and the crude mixture was directly subjected to silica gel chromatography (10% cyclohexane in dichloromethane) to afford isopropylated defucogilvocarcin M **448** (13.2 mg, 35.0 µmol, 85%) as a yellowish solid.

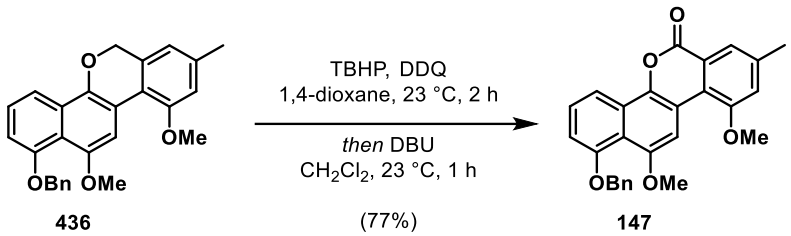
Data consistent with literature: *J. Org. Chem.*, **2009**, *74*, 4080–4093.



Defucogilvocarcin M 87

Tert-butyl hydroperoxide (5.5 M in nonane, 56.4 µL, 310 µmol, 2.00 equiv) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (44.0 mg, 194 µmol, 1.25 equiv) were added to a solution of tetracycle **430** (50.0 mg, 155 µmol, 1 equiv) in 1,4-dioxane (1.72 mL, 0.09 M) at 23 ˚C and stirred for two hours at that temperature. The solvent was removed under reduced pressure and the crude solid was re-dissolved in dichloromethane (3.10 mL, 0.09 M). 1,8-Diazabicyclo(5.4.0)undec-7-ene (69.5 µL, 465 µmol, 3.00 equiv) was added and the mixture was stirred for one hour at 23 °C. The solvent was removed under reduced pressure and the crude mixture was directly subjected to silica gel chromatography (60% diethyl ether in cyclohexane) to afford defucogilvocarcin M **87** (41.7 mg, 124.1 µmol, 80%) as a white solid.

Data consistent with literature: *Org. Lett.*, **2014**, 16, *23*, 6240–6243.



1-(Benzyloxy)-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 147

Cyclic ether **436** (of 77 wt% purity, as a 7.7 : 1 : 1 mixture with ethers **435** and **449**, *vide supra*) (1.02 g, 2.46 mmol, 1 equiv) was dissolved in 1,4-dioxane (27.4 mL, 0.09 M). 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (839 mg, 3.70 mmol, 1.50 equiv) was added to the solution, followed by *tert*-butyl

hydroperoxide (5.5 M in nonane, 896 µL, 2.93 mmol, 2.00 equiv) and stirred for two hours at 23 °C. The solvent was removed under reduced pressure and the residual crude solid was dissolved in dichloromethane (49.3, 0.05 M). 1,8-Diazabicyclo(5.4.0)undec-7-ene (1.47 mL, 9.84 mmol, 4.00 equiv) was added and the mixture was stirred for one hour at 23 °C. The solvent was removed and the crude mixture was directly subjected to silica gel chromatography (10% grading to 1% cyclohexane in dichloromethane) to afford aglycone **147** (807 mg, 1.89 mmol, 77%) as a white solid.

TLC (25% ethyl acetate in cyclohexane): R_f = 0.27 (UV, CAM).

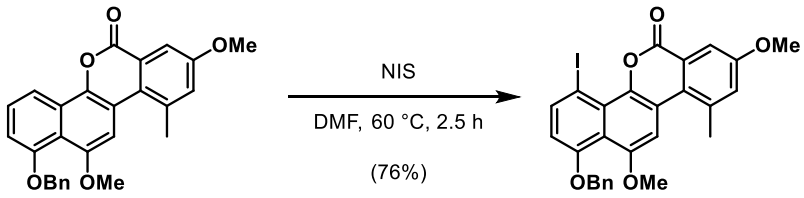
mp: 221 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.36 (s, 1H), 8.22 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.92 (s, 1H), 7.64 – 7.59 (m, 2H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.43 (dd, *J* = 8.5, 7.8 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.11 (s, 1H), 7.04 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.22 (s, 2H), 4.06 (s, 3H), 3.99 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 157.3, 155.8, 153.0, 140.6, 139.9, 137.6, 128.5, 127.7, 127.2, 127.1, 126.9, 123.3, 122.9, 122.1, 118.2, 118.1, 115.4, 113.9, 110.3, 104.4, 71.6, 56.6, 56.3, 21.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1716 (m), 1592 (s), 1398 (m), 1336 (s), 1297 (vs), 1122 (w), 1062 (m), 852 (m), 746 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{23}O_5$ $[M+H]^+$: 427.1540 found: 427.1547.



446 **452**

1-(Benzyloxy)-4-iodo-8,12-dimethoxy-10-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 452

N-iodosuccinimide (49 mg, 216 µmol, 1.26 equiv) was added to a solution of chromenone **446** (73 mg, 171 µmol, 1 equiv) in *N*,*N*-dimethylformamide (3.42 mL, 0.05 M) at 23 ˚C. After addition of two drops of concentrated sulfuric acid, the flask was immediately put into a pre-heated oil bath at 60 °C and stirred for two hours and 20 minutes at that temperature. The reaction was removed from the oil bath, diluted with a saturated aqueous solution of lithium chloride (15 mL) and the solution was extracted with dichloromethane (2 × 70 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (70 % dichloromethane in cyclohexane) gave the title compound **452** (71.7 mg, 130 µmol, 76%) as a yellow solid along with 13.1 mg (22.3 µmol, 18%) recovered starting material.

TLC (dichloromethane): R_f = 0.61 (UV, CAM).

mp: 188 °C.

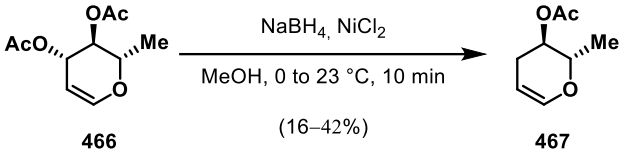
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.27 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.70 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.43 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.26 (1H)[1)], 6.70 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 2.95 (s, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 160.6, 159.3, 156.5, 152.7, 143.6, 139.1, 137.0, 128.7, 128.0, 127.9, 127.8, 127.2, 126.1, 124.8, 119.7, 116.5, 111.2, 109.8, 105.5, 74.8, 71.7, 57.4, 55.9, 29.9, 25.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2130 (w), 1704 (m), 1612 (s), 1370 (s), 1358 (m), 1273 (vs), 1227 (s), 1061 (m), 847 (w), 789 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{22}IO_5$ $[M+H]^+$: 553.0506 found: 553.0505.

[1)]partially overlaid by solvent-peak ($CHCl_3$).



466 **467**

(2*S*,3*R*)-2-Methyl-3,4-dihydro-2*H*-pyran-3-yl acetate 467

Nickel(II) chloride (52.0 mg, 403 µmol, 20 mol%) was added to a stirring solution of glucal **466** (432 mg, 2.02 mmol, 1 equiv) in methanol (6.11 mL, 0.33 M) at 23 ˚C and then cooled to 0 °C. Sodium borohydride (763 mg, 20.2 mmol, 10.0 equiv) was added portionwise to the reaction within ten minutes (caution: very exothermic reaction with extensive generation of hydrogen gas!) and stirred for five minutes at that temperature. After removal of the external ice bath, the reaction was stirred for ten minutes at 23 °C before water (10 mL) was slowly added to stop the reaction. The crude mixture was extracted with diethyl ether (2 × 5 mL), washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under normal pressure at 50 °C external bath temperature. Purification by silica gel chromatography (15% diethyl ether in pentane) gave the title compound **467** (90 mg, 577 µmol, 29%) as a colorless oil. NOTE: We observed varying yields (16–42% for scales of 56 mg to 3.13 g) for this reaction, even on similar reaction scales, which we assume to be due to the product's volatility.

TLC (25% diethyl ether in pentane): R_f = 0.69 (CAM, $KMnO_4$).

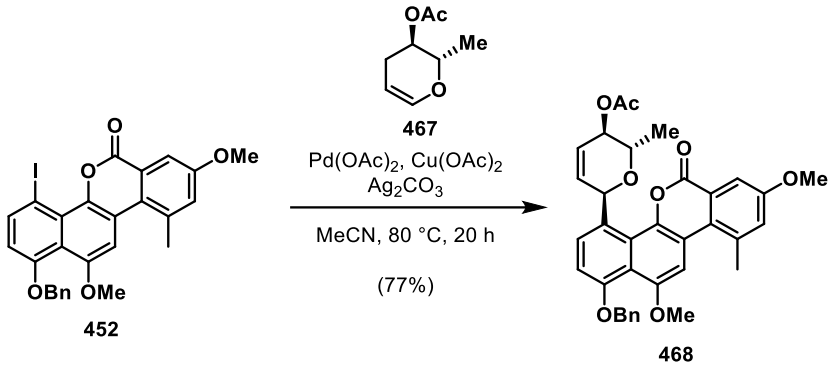
^{1}H NMR (400 MHz, chloroform-*d*) δ 6.31 (dt, *J* = 6.1, 2.0 Hz, 1H), 4.81 (td, *J* = 6.5, 5.6 Hz, 1H), 4.64 (dt, *J* = 6.1, 3.8 Hz, 1H), 3.98 (pd, *J* = 6.4, 0.9 Hz, 1H), 2.40 (dddd, *J* = 17.2, 5.8, 4.1, 1.9 Hz, 1H), 2.09 (s, 3H), 2.04 (ddddd, *J* = 17.2, 6.4, 3.3, 2.1, 0.9 Hz, 1H), 1.26 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 170.5, 142.6, 97.3, 72.2, 70.3, 25.0, 21.3, 17.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3084 (w), 2989 (m), 2942 (w), 2877 (m), 1765 (s), 1637 (vs), 1382 (m), 1262 (s), 1089 (m), 753 (w) cm^{-1}.

HRMS (ESI) calc. for $C_8H_{13}O_3$ $[M+H]^+$: 157.0859 found: 157.0862.

$[\alpha]_D^{20} = -109.8$ (c = 16.2 in $CHCl_3$).



(2*S*,3*R*,6*R*)-6-(1-(Benzyloxy)-8,12-dimethoxy-10-methyl-6-oxo-6*H*-dibenzo[*c*,*h*]chromen-4-yl)-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate 468

Iodide **452** (12.3 mg, 22.3 µmol, 1 equiv), palladium(II) acetate (1 mg, 4.45 µmol, 0.20 equiv), copper(II) acetate (8.1 mg, 44.5 µmol, 2.00 equiv), silver(I) carbonate (3.6 mg, 13.4 µmol, 0.60 equiv) and dihydropyrane **467** (19.8 mg, 127 µmol, 5.70 equiv) were placed in a high-pressure tube under air and mixed with acetonitrile (318 µL, 0.07 M) to give a light-green suspension. The tube was sealed and the reaction was heated to 80 °C for 20 hours under stirring. The deep-green suspension was allowed to cool to 23 °C and filtered through a short plug of silica using a mixture of cyclohexane and ethyl acetate (1:3) as eluent. Purification by silica gel chromatography (15% grading to 66% ethyl acetate in cyclohexane) gave the title compound **468** (10 mg, 17.1 µmol, 77%) as a yellow solid.

TLC (25% ethyl acetate in cyclohexane): R_f = 0.17 (UV, CAM, $KMnO_4$).

mp: 189 °C.

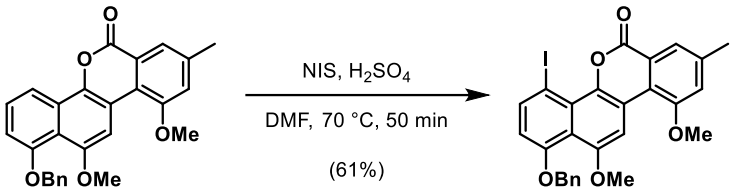
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 2.7 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.45 (d, *J* = 10.4 Hz, 1H), 5.98 (ddd, *J* = 10.3, 4.7, 2.2 Hz, 1H), 5.26 (s, 2H), 5.02 (bs, 1H), 4.18 (dd, *J* = 6.7, 2.9 Hz, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 2.99 (s, 3H), 2.15 (s, 3H), 1.48 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 171.1, 161.2, 159.2, 155.7, 153.4, 141.7, 137.7, 137.0, 136.0, 129.1, 128.9, 128.6, 128.2, 127.9, 127.9, 127.2, 125.3, 124.1, 121.1, 119.2, 116.2, 109.9, 109.6, 104.9, 71.7, 70.7, 69.5, 69.3, 57.4, 55.8, 25.2, 21.5, 16.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2938 (w), 2840 (w), 1756 (s), 1733 (s), 1703 (s), 1592 (w), 1566 (w), 1476 (m), 1250 (m), 1242 (m), 1121 (m), 1077 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{35}H_{33}O_8$ $[M+H]^+$: 581.2170 found: 581.2166.

$[\alpha]_D^{20} = -8.19$ (c = 3.33 in $CHCl_3$).



147 470

1-(Benzyloxy)-4-iodo-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 470

Aglycone **147** (88 mg, 206 µmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (6.87 mL, 0.03 M) and stirred for three minutes at 70 °C. To this mixture a solution of *N*-iodosuccinimide (93 mg, 413 µmol, 2.00 equiv) in *N*,*N*-dimethylformamide (2.07 mL, 0.2 M) was added quickly in one portion, immediately followed by the addition of 1 drop of concentrated sulfuric acid. After 50 minutes of stirring at 70 °C, the reaction was poured on 30 mL of a saturated aqueous solution of lithium chloride. The mixture was diluted by 30 mL of water and extracted with dichloromethane (60 mL). The organic layer was washed with a saturated aqueous solution of lithium chloride (2 × 30 mL) and a saturated aqueous solution of sodium chloride (30 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (90 % dichloromethane in cyclohexane) gave the title compound **470** (69.4 mg, 126 µmol, 61%) as a yellow solid along with 14.9 mg (35.0 µmol, 17%) recovered starting material. Note: In some cases, we observed formation of a side-product (presumably *ortho*-iodination, <6%) which turned out to be co-polar to the desired product in various eluents. Separation was possible by means of trituration. Therefore, the mixture was dissolved in a minimum amount of chloroform upon gentle heating. After two hours, the desired product precipitates to an amorphous solid and the supernatant containing the side-product was carefully removed by pipette. Crystals of the product **470** were obtained by dissolving the obtained amorphous solid in a minimum amount of dichloromethane upon gentle heating and standing at 23 °C for one to three hours.

TLC (dichloromethane): R_f = 0.83 (UV, CAM, $KMnO_4$).

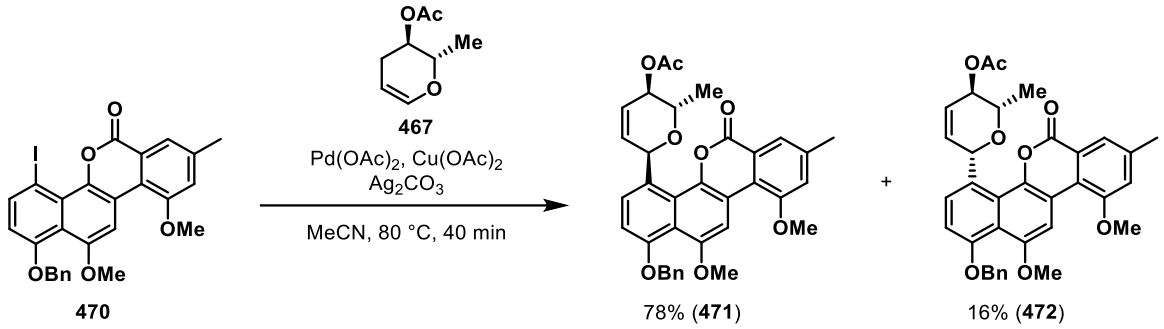
mp: 191 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.59 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.48 – 7.42 (m, 2H), 7.39 – 7.31 (m, 1H), 7.24 (d, *J* = 1.7 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.19 (s, 2H), 4.10 (s, 3H), 3.98 (s, 3H), 2.53 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.9, 157.1, 153.1, 143.7, 141.1, 139.1, 137.8, 131.9, 128.9, 128.2, 127.6, 123.7, 122.5, 121.9, 120.1, 118.6, 115.7, 111.4, 106.1, 82.9, 74.6, 71.9, 57.0, 56.8, 21.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2127 (w), 1788 (m), 1592 (vs), 1411 (s), 1344 (m), 1262 (s), 1231 (vs), 1057 (w), 857 (m), 791 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{27}H_{22}IO_5$ $[M+H]^+$: 553.0506 found: 553.0511.



(2*S*,3*R*,6*R*)-6-(1-(benzyloxy)-10,12-dimethoxy-8-methyl-6-oxo-6*H*-dibenzo[*c*,*h*]chromen-4-yl)-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate 471

(2*S*,3*R*,6*S*)-6-(1-(benzyloxy)-10,12-dimethoxy-8-methyl-6-oxo-6*H*-dibenzo[*c*,*h*]chromen-4-yl)-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate 472

Iodide **470** (185 mg, 335 µmol, 1 equiv), palladium(II) acetate (15 mg, 67.0 µmol, 20 mol%), copper(II) acetate (122 mg, 670 µmol, 2.00 equiv), silver(I) carbonate (55.0 mg, 201 µmol, 60 mol%) and dihydropyrane **467** (340 mg, 2.18 mmol, 6.50 equiv) were placed in a high-pressure tube under air and mixed with acetonitrile (9.57 mL, 0.035 M) to give a light-green suspension. The tube was sealed and the reaction was heated to 80 °C for 40 minutes under stirring. The deep-green suspension was allowed to cool to 23 °C and filtered through a short plug of silica using a mixture of cyclohexane and ethyl acetate (1:3) as eluent. Purification by silica gel chromatography (dichloromethane) gave the title compound **471** (152 mg, 261 µmol, 78%) as a yellow solid along with diastereomer **472** (31.1 mg, 53.6 µmol, 16%) as a yellow solid.

Product **471:**

TLC (33% ethyl acetate in cyclohexane): R_f = 0.34 (UV, CAM, $KMnO_4$).

mp: 168 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.53 (s, 1H), 7.91 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.30 (m, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.88 (q, *J* = 2.2 Hz, 1H), 6.42 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.94 (ddd, *J* = 10.3, 4.6, 2.2 Hz, 1H), 5.22 (s, 2H), 5.00 (dt, *J* = 4.9, 2.4 Hz, 1H), 4.15 (dp, *J* = 6.8, 3.4 Hz, 1H), 4.08 (s, 3H), 3.99 (s, 3H), 2.50 (s, 3H), 2.13 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 171.1, 160.7, 157.4, 155.6, 153.4, 141.8, 140.2, 137.5, 136.1, 129.1, 128.6, 128.6, 127.8, 127.2, 124.8, 122.7, 122.5, 122.2, 120.9, 119.5, 118.4, 115.0, 110.1, 105.5, 71.8, 70.6, 69.5, 69.3, 57.0, 56.5, 21.8, 21.5, 16.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2898 (w), 2851 (w), 1702 (s), 1693 (s), 1705 (s), 1622 (m), 1569 (w), 1499 (m), 1203 (m), 1190 (m), 1115 (m), 1037 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{35}H_{33}O_8$ $[M+H]^+$: 581.2170 found: 581.2165.

$[\alpha]_D^{20} = +13.7$ (c = 2.72 in $CHCl_3$).

Product **472:**

TLC (33% ethyl acetate in cyclohexane): R_f = 0.44 (UV, CAM, $KMnO_4$).

mp: 188–190 °C.

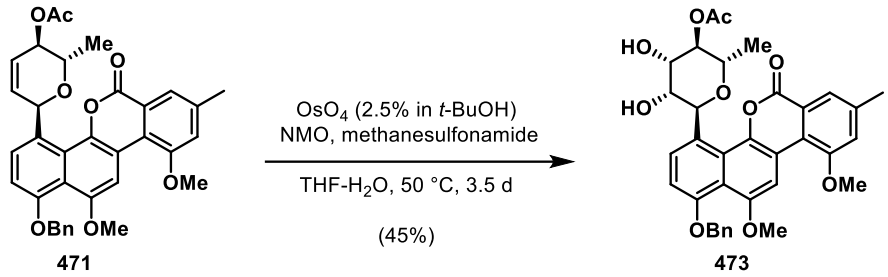
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.56 (s, 1H), 7.94 (d, *J* = 1.6 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.46 – 7.38 (m, 2H), 7.38 – 7.30 (m, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.78 (q, *J* = 3.2, 2.6 Hz, 1H), 6.27 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.80 (dt, *J* = 10.3, 2.2 Hz, 1H), 5.29 – 5.25 (m, 1H), 5.22 (s, 2H), 4.16 – 4.10 (m, 1H), 4.10 (s, 3H), 3.99 (s, 3H), 2.53 (s, 3H), 2.13 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*)) δ 171.1, 160.7, 157.4, 155.6, 153.5, 141.7, 140.1, 137.5, 134.4, 129.8, 128.5, 128.2, 127.8, 127.2, 124.7, 123.0, 122.7, 122.4, 122.2, 119.4, 118.4, 114.9, 110.3, 105.5, 75.6, 73.5, 71.8, 71.5, 57.0, 56.5, 21.8, 21.4, 18.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2878 (w), 2822 (m), 1776 (s), 1701 (s), 1640 (s), 1622 (w), 1543 (w), 1528 (m), 1311 (m), 1220 (m), 1105 (m), 1001 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{35}H_{33}O_8$ $[M+H]^+$: 581.2170 found: 581.2165.

$[\alpha]_D^{20} = -1.50$ (c = 0.73 in $CHCl_3$).

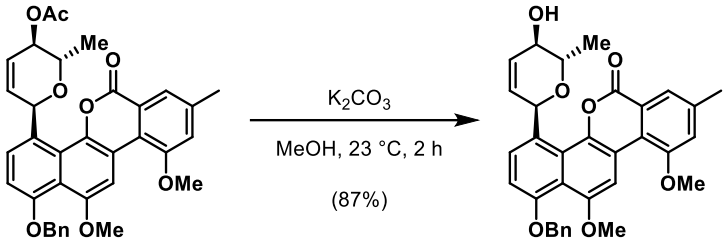


(2*S*,3*R*,4*S*,5*R*,6*S*)-6-(1-(Benzyloxy)-10,12-dimethoxy-8-methyl-6-oxo-6*H*-dibenzo[*c*,*h*]chromen-4-yl)-4,5-dihydroxy-2-methyltetrahydro-2*H*-pyran-3-yl acetate 473

Alkene **471** (29.0 mg, 50.0 µmol, 1 equiv) was dissolved in tetrahydrofuran (2.50 mL, 0.02 M) upon gentle warming with a heat-gun. *N*-methylmorpholin-*N*-oxide (23.4 mg, 200 µmol 4.00 equiv) was added, followed by water (400 µL, 0.12 M) and methanesulfonamide (7.10 mg, 74.9 µmol, 1.50 equiv). Then, osmium(VIII)-oxide (2.5% in *t*-BuOH, 60 µL, 5.29 µmol, 11 mol%) was added and the reaction was stirred at 23 °C. After 13 hours, *N*-methylmorpholin-*N*-oxide (23.4 mg, 200 µmol 4.00 equiv), methanesulfonamide (7.10 mg, 74.9 µmol, 1.50 equiv) and osmium(VIII)-oxide (2.5% in *t*-BuOH, 60 µL, 5.29 µmol, 11 mol%) were added and stirred at 23 °C. After 26 hours, *N*-methylmorpholin-*N*-oxide (11.7 mg, 100 µmol 2.00 equiv), methanesulfonamide (4.73 mg, 49.9 µmol, 1.00 equiv) and osmium(VIII)-oxide (2.5% in *t*-BuOH, 200 µL, 17.6 µmol, 37 mol%) were added and the reaction was stirred at 50 °C. After 14 hours, *N*-methylmorpholin-*N*-oxide (11.7 mg, 100 µmol 2.00 equiv), methanesulfonamide (4.73 mg, 49.9 µmol, 1.00 equiv) and osmium(VIII)-oxide (2.5% in *t*-BuOH, 100 µL, 8.80 µmol, 18 mol%) were added and stirred for further 24 hours at 50 °C. The solution was allowed to cool to 23 ˚C, diluted with a mixture of dichloromethane (5 mL) and an aqueous solution of sodium

sulfite (5 mL) and stirred for five minutes until the yellow solution turned dark-red. The layers were separated and the organic layer was washed with a saturated aqueous solution of sodium chloride (5 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (50% ethyl acetate in cyclohexane) gave the title compound **473** (13.8 mg, 22.5 µmol, 45%) as a yellow solid.

TLC (66% ethyl acetate in cyclohexane): R_f = 0.34 (UV, CAM, $KMnO_4$).
mp: 223–225 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.49 (s, 1H), 7.87 (dd, *J* = 2.2, 1.3 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.47 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 3.3 Hz, 1H), 5.21 (s, 2H), 5.13 (dd, *J* = 7.6, 5.0 Hz, 1H), 4.63 (bs, 1H), 4.38 (s, 1H), 4.22 (dt, *J* = 11.8, 6.5 Hz, 1H), 4.09 (s, 3H), 3.98 (s, 3H), 3.85 (m, 1H), 3.07 (m, 1H), 2.50 (s, 3H), 2.15 (s, 3H), 1.55 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 170.9, 162.5, 157.5, 155.5, 153.9, 140.8, 140.6, 137.4, 128.6, 128.4, 127.9, 127.2, 127.0, 124.9, 122.4, 122.3, 121.6, 119.4, 119.0, 115.1, 110.0, 105.2, 76.6, 75.7, 75.1, 73.3, 71.7, 70.4, 57.0, 56.5, 21.8, 21.4, 18.0.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3584 (s), 3495 (m), 3219 (w), 3099 (w), 2984 (w), 1793 (s), 1642 (m), 1603 (w), 1480 (w), 1429, (m), 1384 (m), 1051 (s), 991 (w) cm^{-1}.
HRMS (ESI) calc. for $C_{35}H_{33}O_{10}$ $[M\text{-}H]^-$: 613.2079 found: 613.2079.
$[\alpha]_D^{20} = -8.23$ (c =2.42 in $CHCl_3$).



471 476

1-(Benzyloxy)-4-((2*R*,5*R*,6*S*)-5-hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-yl)-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 476

Acetate **471** (20.0 mg, 34.5 µmol, 1 equiv) was stirred in methanol (1.00 mL, 0.03 M) at 23 °C until a fine yellow suspension was reached. Then, potassium carbonate (8.30 mg, 60.1 µmol, 1.70 equiv) was added and the reaction was stirred for one hour at 23 °C before more potassium carbonate (4.76 mg, 34.5 µmol, 1.00 equiv) was added. After 50 minutes of stirring, the solvent was removed under reduced pressure. Purification by silica gel chromatography (1.7% methanol in cyclohexane) gave the title compound **476** (256 mg, mmol, 87%) as a yellow solid.

TLC (1.7% methanol in cyclohexane): R_f = 0.16 (UV, CAM, $KMnO_4$).

mp: 189–191 °C.

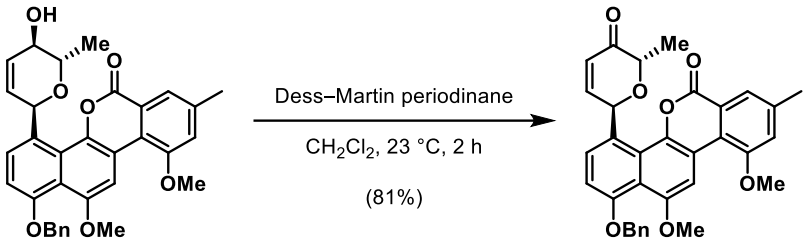
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.57 (s, 1H), 7.94 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.47 – 7.38 (m, 2H), 7.39 – 7.30 (m, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.87 (q, *J* = 2.1 Hz, 1H), 6.26 (ddd, *J* = 10.3, 2.2, 0.9 Hz, 1H), 6.01 (ddd, *J* = 10.2, 4.0, 2.3 Hz, 1H), 5.23 (s, 2H), 4.10 (s, 3H), 4.04 – 4.00 (m, 1H), 4.00 (s, 3H), 3.85 (s, 1H), 2.53 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 160.7, 157.4, 155.6, 153.5, 141.8, 140.1, 137.5, 133.8, 129.1, 128.5, 128.2, 127.8, 127.2, 125.8, 124.9, 122.8, 122.5, 122.2, 119.7, 118.4, 115.0, 109.8, 105.7, 73.2, 71.7, 70.1, 67.6, 57.0, 56.5, 21.8, 16.7.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: : 3592 (s), 3262 (m), 2878 (w), 2849 (w), 1683 (w), 1622 (m), 1571 (w), 1464 (m), 1213 (m), 1201 (m), 1135 (m), 1007 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{33}H_{29}O_7$ $[M\text{-}H]^-$: 537.1919 found: 537.1921.

$[\alpha]_D^{20} = -9.32$ (c = 1.70 in $CHCl_3$).



1-(Benzyloxy)-10,12-dimethoxy-8-methyl-4-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl)-6*H*-dibenzo[*c*,*h*]chromen-6-one 477

Dess–Martin periodinane (15.3 mg, 36.1 µmol, 1.20 equiv) was added in one portion to a solution of allyl alcohol **476** (16.2 mg, 30.1 µmol, 1 equiv) in dichloromethane (1.20 mL, 0.025 M), which was then stirred for two hours at 23 °C. The reaction was stopped by removal of the solvent under removed pressure. Purification by silica gel chromatography (dichloromethane) gave the title compound **477** (13.1 mg, 24.4 µmol, 81%) as a yellow solid.

TLC (1.7% methanol in cyclohexane): R_f = 0.61 (UV, CAM, $KMnO_4$).

mp: 224–226 °C.

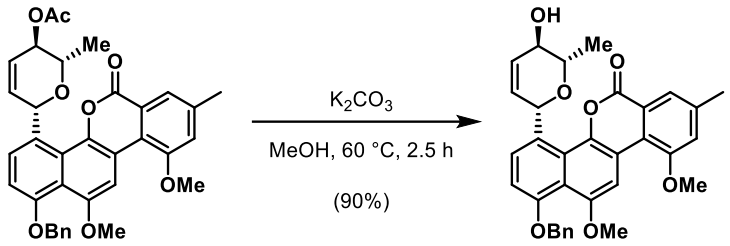
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.59 (s, 1H), 7.94 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.47 – 7.39 (m, 2H), 7.38 – 7.32 (m, 2H), 7.26 – 7.19 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.18 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.24 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 2.53 (s, 3H), 1.57 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) 198.0, 176.5, 160.5, 157.5, 156.1, 153.6, 152.2, 141.4, 140.4, 137.3, 136.2, 133.3, 131.4, 129.4, 128.7, 127.9, 126.9, 124.6, 124.5, 122.6, 122.5, 118.5, 115.3, 109.4, 105.7, 75.4, 71.6, 69.5, 57.0, 56.5, 21.8, 15.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3018 (w), 2999 (w), 2891 (w), 1752 (s), 1740 (s), 1699 (m), 1660 (m), 1604 (w), 1465 (w), 1399 (w), 1239 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{33}H_{29}O_7$ $[M+H]^+$: 537.1908 found: 537.1911.

$[\alpha]_D^{20} = -2.54$ (c = 1.09 in $CHCl_3$).



472 479

1-(Benzyloxy)-4-((2*S*,5*R*,6*S*)-5-hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-yl)-10,12-dimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one 479

Acetate **472** (8.10 mg, 14.0 µmol, 1 equiv) was stirred in methanol (1.40 mL, 0.01 M) at 23 °C until a fine yellow suspension was reached. Then, potassium carbonate (5.80 mg, 42.0 µmol, 3.00 equiv) was added and the reaction was stirred at 60 °C. After an hour, more potassium carbonate (3.85 mg, 27.9 µmol, 2.00 equiv) and methanol (500 µL) were added and the reaction was stirred for 1.5 hours at 60 °C. After cooling to 23 °C, the solvent was removed under reduced pressure. Purification by silica gel chromatography (1.7% methanol in cyclohexane) gave the title compound **479** (4.70 mg, 8.72 µmol, 90%) as a yellow solid.

TLC (1.7% methanol in dichloromethane): R_f = 0.13 (UV, CAM, $KMnO_4$).

mp: 198 °C.

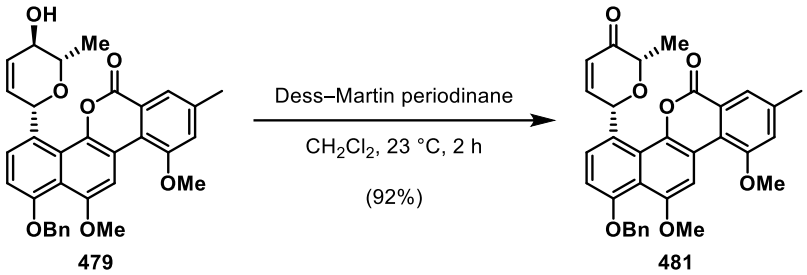
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.55 (s, 1H), 7.93 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.57 (m, 3H), 7.46 – 7.38 (m, 2H), 7.36 – 7.31 (m, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.73 (q, *J* = 2.4 Hz, 1H), 6.22 (dt, *J* = 10.2, 1.8 Hz, 1H), 5.87 (dt, *J* = 10.2, 2.2 Hz, 1H), 5.22 (s, 2H), 4.10 (s, 3H), 4.10 – 4.02 (m, 1H), 3.99 (s, 3H), 3.88 (dq, *J* = 8.4, 6.2 Hz, 1H), 2.53 (s, 3H), 1.47 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 160.8, 157.4, 155.5, 153.5, 141.7, 140.2, 137.5, 133.5, 130.3, 128.5, 128.3, 127.9, 127.8, 127.2, 124.7, 122.6, 122.5, 122.2, 119.4, 118.4, 114.9, 110.5, 105.5, 77.0, 75.5, 71.8, 70.1, 57.0, 56.5, 21.8, 18.8.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: : 3533 (s), 3212 (m), 2718 (w), 2742 (w), 1677 (w), 1603 (m), 1561 (w), 1460 (m), 1193 (m), 1203 (m), 1140 (m), 1027 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{33}H_{29}O_7$ $[M-H]^-$: 537.1919 found: 537.1924.

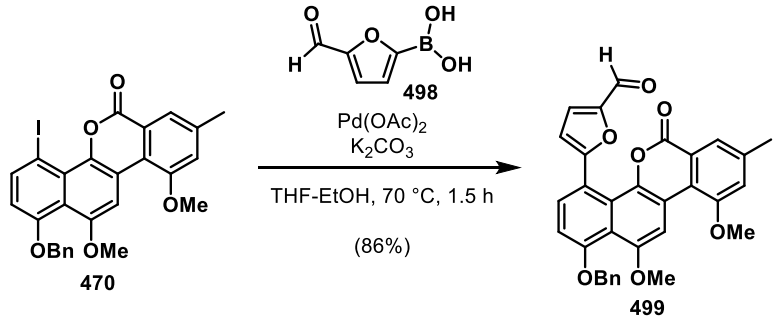
$[\alpha]_D^{20} = -1.67$ (c = 0.81 in $CHCl_3$).



1-(Benzyloxy)-10,12-dimethoxy-8-methyl-4-((2*S*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl)-6*H*-dibenzo[*c*,*h*]chromen-6-one 481

Dess–Martin periodinane (4.40 mg, 10.5 µmol, 1.20 equiv) was added in one portion to a solution of allyl alcohol **479** (4.70 mg, 873 µmol, 1 equiv) in dichloromethane (650 µL, 0.013 M), which was then stirred for two hours at 23 °C. The reaction was stopped by removal of the solvent under reduced pressure. Purification by silica gel chromatography (dichloromethane) gave the title compound **481** (4.31 mg, 8.03 µmol, 92%) as a yellow solid.

TLC (40% ethyl acetate in cyclohexane): R_f = 0.55 (UV, CAM, $KMnO_4$).
mp: 231 °C (decomposition).
^{1}H NMR (400 MHz, chloroform-*d*) δ 8.57 (s, 1H), 7.93 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.47 – 7.39 (m, 2H), 7.38 (dd, *J* = 10.3, 1.6 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 6.20 (dd, *J* = 10.2, 2.6 Hz, 1H), 5.24 (s, 2H), 4.61 (qd, *J* = 6.6, 1.8 Hz, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 2.53 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, chloroform-*d* + methanol-d_4) 197.6, 160.8, 157.5, 155.9, 153.6, 153.1, 143.7, 141.4, 141.3, 140.5, 137.2, 131.4, 130.3, 129.9, 128.7, 128.5, 127.8, 127.2, 125.8, 122.5, 122.0, 118.6, 118.2, 115.3, 110.0, 105.7, 77.4, 71.7, 69.9, 57.0, 56.5, 21.7, 15.5.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$3010 (w), 3109 (w), 2982 (w), 1763 (s), 1751 (s), 1713 (m), 1643 (m), 1624 (w), 1471 (w), 1412 (w), 1209 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{33}H_{29}O_7$ $[M+H]^+$: 537.1908 found: 537.1909.
$[\alpha]_D^{20} = -1.55$ (c = 0.61 in $CHCl_3$).

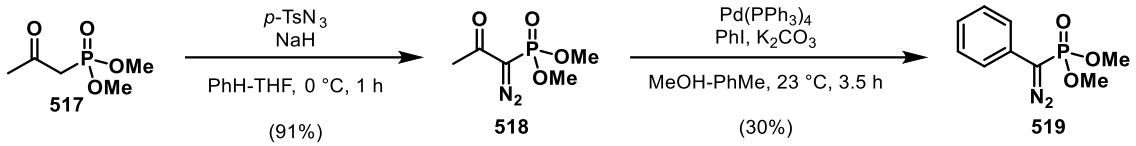


5-(1-(Benzyloxy)-10,12-dimethoxy-8-methyl-6-oxo-6*H*-dibenzo[*c*,*h*]chromen-4-yl)furan-2-carbaldehyde 499

Iodine **470** (64.0 mg, 116 µmol, 1 equiv), boronic acid **498** (22.0 mg, 156 µmol, 1.35 equiv), potassium carbonate (64.0 mg, 463 µmol, 4.00 equiv) and palladium(II) acetate (3.20 mg, 14.3 µmol, 12 mol%) were placed in a flask and purged for three times with argon. A mixture of degassed tetrahydrofuran (580 µL, 0.2 M) and ethanol (580 µL, 0.2 M) was added via syringe and the mixture was stirred for 1.5 hours at 70 °C. The reaction was allowed to cool to 23 °C and diluted with dichloromethane (30 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (20 mL) and dried over magnesium sulfate. Filtration and evaporation under reduced pressure gave the crude product, which was purified via silica gel chromatography (50% ethyl acetate in cyclohexane) to afford the title product **499** (52.0 mg, 99.8 µmol, 86%) as a yellow solid.

TLC (50% ethyl acetate in cyclohexane): R_f = 0.43 (UV, CAM, $KMnO_4$).
mp: 279–283 °C.
^{1}H NMR (400 MHz, chloroform-*d*) δ 9.66 (s, 1H), 8.58 (s, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.48 – 7.42 (m, 3H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.15 (s, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 3.5 Hz, 1H), 5.30 (s, 2H), 4.09 (s, 3H), 4.02 (s, 3H), 2.47 (s, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 168.8, 162.8, 159.8, 157.7, 157.5, 153.3, 152.2, 140.5, 140.4, 137.0, 132.6, 128.7, 128.0, 127.2, 125.1, 123.3, 122.8, 121.6, 119.2, 118.7, 118.3, 118.2, 115.8, 109.9, 108.3, 106.2, 71.5, 57.0, 56.5, 21.8.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3002 (w), 2984 (w), 2902 (m), 2840 (m), 1741 (s), 17 38 (m), 1722 (m), 1574 (w), 1485 (w), 1393 (w), 1078 (m), 1029 (w) cm^{-1}.
HRMS (ESI) calc. for $C_{32}H_{25}O_7$ $[M+H]^+$: 521.1595 found: 521.1590.

8.3 Experimental Data for Part II



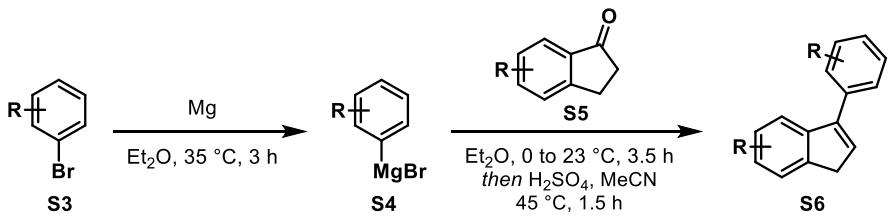
Dimethyl (diazo(phenyl)methyl)phosphonate 518

Keto phosphonate **517** (3.00 g, 18.0 mmol, 1 equiv) was dissolved in benzene (13.9 mL, 1.30 M) and slowly added to a suspension of sodium hydride (455 mg, 19.0 mmol, 1.05 equiv) in benzene (67.7 mL, 0.28 M) and tetrahydrofuran (10.8 mL, 1.75 M) at 0 °C and stirred for one hour at that temperature. A solution of tosyl azide (3.74 g, 19.0 mmol, 1.05 equiv) in benzene (13.9 mL, 1.30 M) was added to the reaction via syringe and stirred for 2.5 hours at 0 °C. The mixture was allowed to warm to 23 °C and filtered over Celite before the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography (50% ethyl acetate in cyclohexane) to give acyl phosphonate **518** (3.17 g, 16.4 mmol, 91%) as a yellow oil.

Data consistent with literature: *Tet. Lett.*, **2013**, *54*, 5865–5868.

Acyl phosphonate **518** (1.18 g, 6.14 mmol, 1.25 equiv) was dissolved in a mixture of benzene (2.30 mL, 2.67 M) and methanol (2.30 mL, 2.67 M) and slowly added to a suspension of iodobenzene (1.00 g, 4.91 mmol, 1 equiv), potassium carbonate (1.36 g, 9.82 mmol, 2.00 equiv) and tetrakis(triphenyl-phosphine)palladium(0) (284 mg, 246 µmol, 5 mol%) in benzene (10.0 mL, 0.49 M) and methanol (10.0 mL, 0.49 M) at 23 °C. The reaction was stirred for 3.5 hours at that temperature before it was filtered through a short plug of silica. The crude product was purified by silica gel chromatography (25% grading to 66% dichloromethane in cyclohexane) to afford phenyl phosphonate **519** (331 mg, 1.47 mmol, 30%) as a red oil.

Data consistent with literature: *Angew. Chem. Int. Ed.*, **2014**, *53*, 11625–11628.

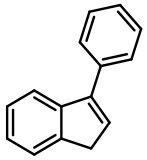


General Procedure Towards 3-phenyl-1*H*-indenes

Magnesium powder (239 mg, 9.84 mmol, 1.30 equiv) was suspended in diethyl ether (2 mL, 4.92 M) followed by the addition of iodine (3.00 mg, 11.8 µmol, 0.15 mol%) and stirred until the purple color disappeared. A small amount of aryl bromide **S3** (0.35 mmol, 0.05 equiv) was added and the mixture was started by gentle heating with a heat gut for ten minutes, before a solution of aryl bromide **S3** (9.46 mmol, 1.25 equiv) in diethyl ether (3.64 mL, 2.70 M) was slowly added within 2.5 hours. After stirring for additional three hours at 23 °C, the solution was diluted with diethyl ether (20 mL) and

slowly added to a solution of indanone **S5** (7.57 mmol, 1 equiv) in diethyl ether (9.96 mL, 0.76 M) at 0 °C within 15 minutes. After stirring for 3.5 hours at 23 °C, the reaction was stopped by slow addition of a saturated aqueous solution of ammonium chloride (10 mL). The layers were separated and the organic layer was filtered through a short plug of celite and finally dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure afforded a mixture of the alcohol and indene **S6**. This mixture was dissolved in acetonitrile (10 mL) before sulfuric acid (5 wt% in water, 1 mL) was added and the mixture was stirred for 1.5 hours at 45 °C. After stirring for further 19 hours at 23 °C, a saturated aqueous solution of sodium chloride (20 mL) was added and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the solvent was removed under reduced pressure to give the crude indene. Purification by silica gel chromatography (ethyl acetate in cyclohexane) afforded the desired phenyl indene **S6**.

3-Phenyl-1*H*-indene 535

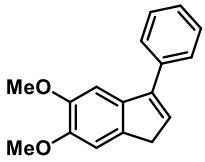


Yellow oil (76%)

TLC (*n*-hexane): R_f = 0.49 (UV, $KMnO_4$).

Data consistent with literature: *Org. Lett.*, **2015**, *17*, 6102–6105.

5,6-Dimethoxy-3-phenyl-1*H*-indene 536

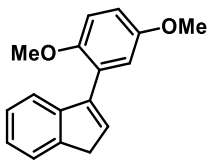


White solid (68%)

TLC (66% dichloromethane in cyclohexane): R_f = 0.31 (UV, $KMnO_4$).

Data consistent with literature: *J. Org. Chem.*, **2017**, *82*, 4226–4234.

3-(2,5-Dimethoxyphenyl)-1*H*-indene 537



Yellow solid (51%)

mp: 54 °C.

TLC (66% dichloromethane in cyclohexane): R_f = 0.62 (UV, $KMnO_4$).

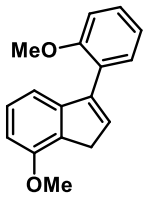
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.61 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.43 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.38 (td, *J* = 7.4, 1.3 Hz, 1H), 7.32 (td, *J* = 7.2, 1.5 Hz, 1H), 7.10 (d, *J* = 2.9 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.70 (t, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.62 (d, *J* = 2.2 Hz, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.6, 151.5, 144.7, 144.0, 142.3, 132.6, 126.2, 126.0, 124.6, 123.8, 121.1, 116.4, 113.5, 112.4, 56.1, 55.8, 38.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1607 (w), 1482 (m), 1245 (m), 1164 (s), 1121 (m), 1095 (vs), 1034 (s), 752 (w), 698 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223 found: 253.1219.

7-Methoxy-3-(2-methoxyphenyl)-1*H*-indene 555



Pale-yellow solid (85%)

mp: 93 °C.

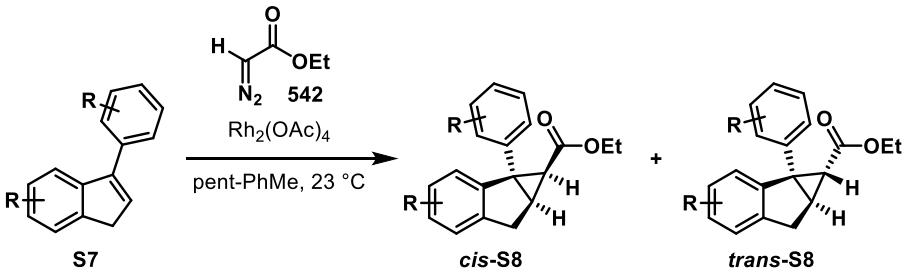
TLC (50% dichloromethane in cyclohexane): R_f = 0.43 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42 – 7.31 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.59 (t, *J* = 2.1 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.50 (d, *J* = 2.1 Hz, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 157.3, 155.5, 146.8, 142.3, 132.7, 131.0, 130.8, 129.0, 127.6, 125.4, 120.7, 114.5, 111.1, 107.1, 55.5, 55.4, 36.0.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1711 (w), 1491 (m), 1204 (m), 1155 (s), 1132 (m), 1125 (vs), 1038 (s), 767 (w), 701 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{17}H_7O_2$ $[M+H]^+$: 253.1223 found: 253.1220.

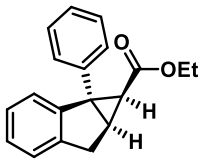


General Procedure for the Cyclopropanation of 3-Phenyl-1*H*-indenes

Indene **S7** (0.50–2.30 equiv) was mixed with pentane (0.1 M) followed by addition of a small amount of toluene (0.01–0.10 M) until a solution was observed. Rhodium(II) acetate (12.3 mg, 27.9 μmol, 3 mol%) was added to the mixture, before ethyl diazoacetate **542** (15 wt% in toluene, 708 μL, 931 μmol, 1 equiv)

was slowly added over a period of one to six hours at 23 °C. The reaction was stirred until TLC-monitoring indicated no further consumption of starting material (6 to 20 hours). The solvent was removed under reduced pressure and the crude residual was subjected to silica gel chromatography to obtain diastereomers ***cis*-S8** and ***trans*-S8**.

Ethyl 1a-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 539



Procedure: indene **535** (542 mg, 2.14 mmol, 2.30 equiv), PhMe (991 µL, 0.94 M), add over 20 minutes, stir for 1.5 hours.

Yield: 61% (*cis* : *trans* = 1.5 : 1.0)

***cis*-539,** colorless solid

mp: 86 °C.

TLC (66% dichloromethane in cyclohexane): R_f = 0.48 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.50 – 7.42 (m, 2H), 7.41 – 7.32 (m, 2H), 7.34 – 7.25 (m, 1H), 7.20 (ddd, *J* = 7.5, 1.6, 0.8 Hz, 1H), 7.15 (td, *J* = 7.3, 1.3 Hz, 1H), 7.09 (td, *J* = 7.4, 1.5 Hz, 1H), 6.99 (dt, *J* = 7.7, 0.7 Hz, 1H), 3.87 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.48 (d, *J* = 17.0 Hz, 1H), 3.41 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.60 (d, *J* = 8.2 Hz, 1H), 2.38 (ddd, *J* = 8.3, 6.0, 1.5 Hz, 1H), 0.95 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 169.3, 143.9, 143.2, 140.6, 129.4, 128.6, 127.3, 126.8, 126.3, 125.3, 124.2, 60.2, 46.8, 32.7, 31.3, 29.9, 14.1.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3022 (w), 1723 (s), 1454 (m), 1437 (m), 1326 (w), 1204 (m), 1134 (s), 1113 (w), 1041 (w), 983 (m), 934 (m), 815 (w), 735 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_9O_2$ $[M+H]^+$: 279.1380 found: 279.1386.

***trans*-539,** colorless crystals

mp: 91 °C.

TLC (66% dichloromethane in cyclohexane): R_f = 0.42 (UV, $KMnO_4$).

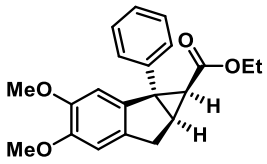
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42 – 7.37 (m, 2H), 7.34 (ddd, *J* = 7.8, 6.8, 1.0 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.22 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.14 (td, *J* = 6.9, 2.3 Hz, 1H), 7.11 – 7.05 (m, 2H), 3.91 (qd, *J* = 7.7, 7.2 Hz, 2H), 3.49 (dd, *J* = 17.4, 6.3 Hz, 1H), 3.15 (d, *J* = 17.4 Hz, 1H), 2.93 (dd, *J* = 6.0, 3.8 Hz, 1H), 1.68 (d, *J* = 3.8 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 170.4, 147.3, 141.0, 136.8, 130.3, 128.5, 127.4, 126.7, 126.4, 125.5, 123.8, 60.4, 49.1, 36.6, 35.4, 30.0, 14.1.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3101 (w), 1765 (m), 1474 (m), 1397 (w), 1235 (m), 1145 (s), 1093 (w), 1051 (w), 977 (m), 931 (m), 822 (w), 745 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_9O_2$ $[M+H]^+$: 279.1380 found: 279.1385.

Ethyl 3,4-dimethoxy-1a-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 540



Procedure: indene **536** (235 mg, 931 µmol, 1 equiv), PhMe (6.65 mL, 0.14 M), add over one hour, stir for 18 hours.

Yield: 45% (*cis* : *trans* = 1.2 : 1.0)

***cis*-540,** colorless oil

TLC (25% diethyl ether in pentane): R_f = 0.23 (UV, $KMnO_4$).

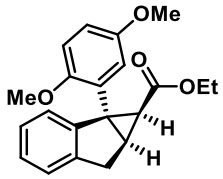
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.48 – 7.40 (m, 2H), 7.41 – 7.32 (m, 2H), 7.34 – 7.25 (m, 1H), 6.73 (s, 1H), 6.50 (s, 1H), 3.89 (ddt, *J* = 10.7, 7.2, 3.6 Hz, 2H), 3.85 (s, 3H), 3.71 (s, 3H), 3.44 – 3.29 (m, 2H), 2.59 (d, *J* = 8.2 Hz, 1H), 2.30 (ddd, *J* = 7.9, 5.5, 1.9 Hz, 1H), 0.98 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 169.4, 148.6, 148.1, 140.7, 135.7, 135.0, 129.2, 128.7, 127.2, 108.4, 107.3, 60.2, 56.2, 56.0, 46.6, 32.5, 31.9, 29.9, 29.8, 14.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3354 (w), 3028 (m), 1756 (s), 1632 (m), 1593 (s), 1437 (m), 1204 (m), 1190 (s), 1123 (w), 1039 (w), 990 (m), 835 (w), 803 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591 found: 339.1593.

Ethyl 1a-(2,5-dimethoxyphenyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 541



Procedure: indene **537** (235 mg, 931 µmol, 1 equiv), PhMe (991 µL, 0.94 M), add over six hours, stir for 20 hours.

Yield: 51% (*cis* : *trans* = 1.2 : 1.0)

***cis*-541,** yellowish oil

TLC (66% dichloromethane in cyclohexane): R_f = 0.22 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21 – 7.14 (m, 1H), 7.12 (td, *J* = 7.3, 1.3 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.96 (ddd, *J* = 7.5, 1.3, 0.7 Hz, 1H), 6.86 – 6.80 (m, 2H), 3.88 (qd, *J* = 7.1, 5.7 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.52 – 3.36 (m, 2H), 2.41 (ddd, *J* = 8.1, 4.8, 2.5 Hz, 1H), 2.35 (d, *J* = 8.1 Hz, 1H), 0.98 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 169.7, 153.5, 153.4, 143.8, 142.9, 130.3, 126.5, 126.0, 124.5, 123.8, 117.8, 112.9, 112.5, 60.0, 56.5, 55.9, 43.7, 32.7, 30.6, 14.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3274 (w), 3025 (m), 1796 (m), 1679 (s), 1529 (vs), 1484 (m), 1226 (m), 1173 (s), 1143 (w), 1037 (m), 993 (m), 874 (w), 813 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591 found: 339.1595.

***trans*-541,** yellowish oil

TLC (66% dichloromethane in cyclohexane): R_f = 0.13 (UV, $KMnO_4$).

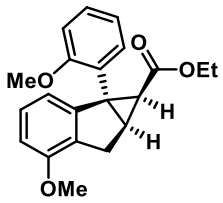
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.13 (ddd, *J* = 7.3, 4.7, 3.7 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.76 (bs, 6H), 3.50 (ddd, *J* = 17.3, 6.2, 1.1 Hz, 1H), 3.15 (d, *J* = 17.3 Hz, 1H), 2.80 (dd, *J* = 6.1, 3.9 Hz, 1H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 171.0, 153.5, 153.2, 147.2, 141.1, 126.5, 126.4, 126.4, 125.3, 124.0, 117.9, 113.3, 111.4, 60.2, 55.9, 55.8, 45.3, 36.4, 35.4, 31.0, 14.3.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3344 (w), 3108 (m), 1723 (s), 1602 (m), 1613 (s), 1442 (m), 1256 (m), 1197 (s), 1100 (w), 1072 (w), 991 (m), 848 (w), 807 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591 found: 339.1590.

Ethyl 5-methoxy1a(2-methoxyphenyl)1,1a,6,6a-tetrahydrocyclopropa[*a*]indene1carboxylate 556



Procedure: indene **555** (118 mg, 466 µmol, 0.50 equiv), PhMe (991 µL, 0.94 M), add over five hours, stir 15 hours.

Yield: 50% (*cis* : *trans* = 1.0 : 1.3)

***cis*-556,** yellow solid

mp: 95–97 °C.

TLC (25% diethyl ether in pentane): R_f = 0.48 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.64 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.55 (dd, *J* = 7.5, 0.8 Hz, 1H), 3.88 (qq, *J* = 7.2, 3.7 Hz, 2H), 3.72 (s, 3H), 3.40 (d, *J* = 17.2 Hz, 1H), 3.29 (dd, *J* = 17.3, 6.4 Hz, 1H), 2.39 (ddd, *J* = 7.4, 6.4, 0.9 Hz, 1H), 2.32 (d, *J* = 8.1 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 169.7, 159.2, 155.3, 144.9, 131.6, 131.0, 129.0, 128.8, 127.5, 120.5, 117.1, 111.1, 108.2, 59.9, 55.8, 55.3, 43.8, 30.7, 30.6, 29.8, 14.1.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3303 (w), 3031 (m), 1765 (s), 1630 (m), 1610 (s), 1442 (m), 1211 (m), 1085 (s), 1001 (w), 990 (m), 840 (w), 823 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591 found: 339.1589.

***trans*-556,** colorless solid

mp: 88 °C.

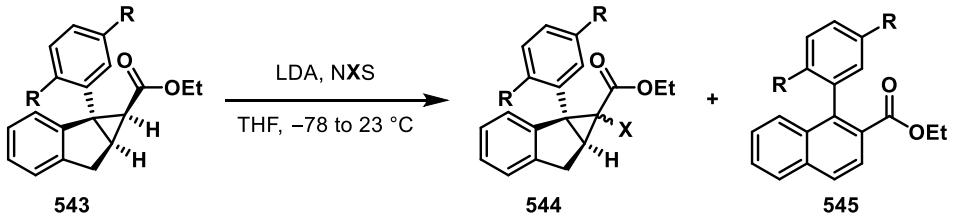
TLC (25% diethyl ether in pentane): R_f = 0.39 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28 – 7.23 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.93 (qd, *J* = 7.1, 3.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.35 (dd, *J* = 17.6, 6.2 Hz, 1H), 3.11 (d, *J* = 17.6 Hz, 1H), 2.79 (dd, *J* = 6.1, 3.9 Hz, 1H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 171.1, 158.8, 156.5, 149.3, 132.0, 128.7, 128.5, 128.0, 125.5, 120.5, 116.6, 110.5, 108.3, 60.1, 55.4, 55.3, 45.4, 36.4, 32.6, 31.3, 14.2.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3293 (w), 3231 (m), 1770 (s), 1627 (m), 1602 (s), 1543 (w), 1452 (s), 1219 (m), 1091 (s), 1031 (w), 990 (m), 847 (w), 823 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591 found: 339.1589.

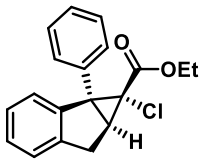


General Procedure for the Halogenation of Cyclopropane S10

Preparation of a 0.28 M LDA-stock solution (in tetrahydrofuran): N,N-diisopropylamine (69.0 µL, 494 µmol, 1.09 equiv) was dissolved in tetrahydrofuran (1.35 mL, 0.37 M) and cooled to –78 °C. Then, *n*-butyl lithium (2.39 M in hexane, 190 µL, 453 µmol, 1.00 equiv) was added dropwise to the solution and stirred for five minutes at that temperature before it was warmed to 0 °C and stirred for further 30 minutes.

Lithiumdiisopropylamide (0.28 in tetrahydrofuran, 1.20–1.80 equiv) was slowly added to a solution of cyclopropane **543** (216 µmol, 1 equiv) in tetrahydrofuran (719 µL, 0.3 M) within five minutes at –78 °C and stirred for 30 minutes. Then, NXS (1.20–1.80 equiv) was dissolved in tetrahydrofuran (1.40 mL, 0.26–0.99 M) and directly transferred to the solution at –78 °C within five minutes. The reaction was stirred for 1.5 hours at –78 °C before it was allowed to warm to 23 °C and stirred until TLC-monitoring indicated no further consumption of starting material (1–10 hours).

Ethyl 1-chloro-1a-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 544-Cl



Procedure: NCS (259 µmol, 1.20 equiv), LDA (259 µmol, 1.20 equiv), stir for one hour.

Yield 544: 33% (*cis* : *trans* = 2.7 : 1.0)

***cis*-544-Cl,** colorless solid

mp: 101 °C.

TLC (66% dichloromethane in cyclohexane): R_f = 0.54 (UV, $KMnO_4$).

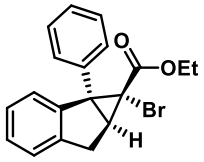
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.57 – 7.48 (m, 2H), 7.49 – 7.39 (m, 2H), 7.41 – 7.32 (m, 1H), 7.20 – 7.04 (m, 4H), 3.90 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.64 (d, *J* = 17.3 Hz, 1H), 3.47 (dd, *J* = 17.3, 6.6 Hz, 1H), 2.66 (dd, *J* = 6.6, 0.8 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 165.6, 142.6, 141.6, 135.9, 130.4, 128.5, 127.8, 127.5, 126.7, 125.2, 124.9, 61.4, 50.2, 49.3, 37.0, 34.0, 13.6.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3253 (w), 1754 (s), 1552 (m), 1442 (m), 1331 (w), 1278 (m), 1162 (s), 1102 (w), 1018 (w), 983 (m), 966 (m), 815 (w), 756 (s) cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_{18}ClO_2$ $[M+H]^+$: 313.0990 found: 313.0992.

Ethyl 1-bromo-1a-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 544-Br



Procedure: NCS (324 µmol, 1.50 equiv), LDA (324 µmol, 1.50 equiv), stir for 2.5 hours.

Yield 544: 29% (*cis* : *trans* = 8.7 : 1.0)

***cis*-544-Br,** colorless solid

mp: 89 °C.

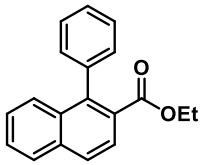
TLC (66% dichloromethane in cyclohexane): R_f = 0.55 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.57 – 7.49 (m, 2H), 7.45 (tt, *J* = 8.1, 1.7 Hz, 2H), 7.42 – 7.33 (m, 1H), 7.20 – 7.04 (m, 8H), 3.87 (ddd, *J* = 10.3, 7.0, 3.4 Hz, 1H), 3.81 (ddd, *J* = 10.7, 7.0, 3.4 Hz, 1H), 3.63 (d, *J* = 17.3 Hz, 1H), 3.40 (dd, *J* = 17.3, 6.7 Hz, 1H), 2.73 (dd, *J* = 6.6, 0.7 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3220 (w), 1722 (s), 1562 (s), 1411 (m), 1298 (w), 1258 (m), 1132 (s), 1091 (w), 1016 (w), 922 (m), 893 (m), 822 (w), 776 cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_{18}BrO_2$ $[M+H]^+$: 357.0485 found: 357.0488.

Ethyl 1-phenyl-2-naphthoate 545



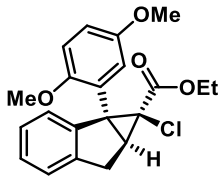
Procedure: NCS (324 µmol, 1.50 equiv), LDA (324 µmol, 1.50 equiv), stir for four hours.

Yield 544-I: 37% (*cis* : *trans* = 11.3 : 1.0), **Yield 545:** 32%

TLC (66% dichloromethane in cyclohexane): R_f = 0.55 (UV, $KMnO_4$).

Data consistent with literature: *Chem. Commun.*, **2019**, *55*, 13610–13613.

Ethyl 1-bromo-1(2,5-dimethoxyphenyl)1,1,6,6-tetrahydrocyclopropa[*a*]indene-1-carboxylate 544



Procedure: NCS (389 µmol, 1.80 equiv), LDA (389 µmol, 1.80 equiv), stir for ten hours.

Yield 544: 21% (*cis* : *trans* = 1.0 : 99.0)

***trans*-544-Cl-OMe,** colorless solid

mp: 112 °C.

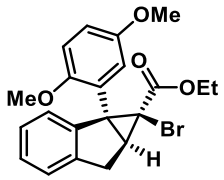
TLC (66% dichloromethane in cyclohexane): R_f = 0.31 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.20 – 7.16 (m, 1H), 7.15 – 7.09 (m, 1H), 7.08 – 7.01 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 1.7 Hz, 2H), 3.94 – 3.81 (m, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.47 – 3.41 (m, 2H), 2.41 (ddd, *J* = 7.4, 4.8, 2.4 Hz, 1H), 2.35 (d, *J* = 8.1 Hz, 1H), 0.98 (t, *J* = 7.1 Hz, 3H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3233 (m), 3146 (w), 2908 (w), 2822 (m), 1701 (m), 1694 (m), 1509 (w), 1411 (m), 1390 (s), 1255 (m), 1124 (s), 744 (m), 715 (w) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{22}ClO_4$ $[M+H]^+$: 373.1201 found: 373.1205.

Ethyl 1-bromo-1(2,5-dimethoxyphenyl)1,1,6,6-tetrahydrocyclopropa[*a*]indene-1-carboxylate 544



Procedure: NBS (389 µmol, 1.80 equiv), LDA (389 µmol, 1.80 equiv), stir for nine hours.

Yield 544: 39% (*cis* : *trans* = 1.0 : 99.0)

***trans*-544-Br-OMe,** colorless solid

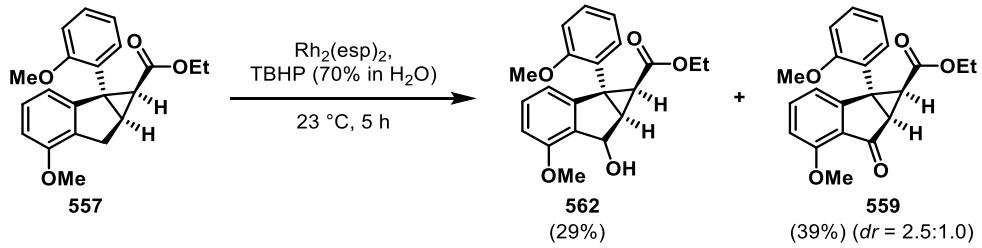
mp: 105 °C.

TLC (66% dichloromethane in cyclohexane): R_f = 0.29 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.19 – 7.09 (m, 3H), 7.06 (td, *J* = 7.1, 2.0 Hz, 1H), 6.93 – 6.82 (m, 2H), 3.89 – 3.64 (m, 8H), 3.59 (d, *J* = 17.1 Hz, 1H), 3.39 (dd, *J* = 17.1, 6.6 Hz, 1H), 2.67 (d, *J* = 6.5 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3102 (m), 3019 (w), 2918 (w), 2837 (m), 1753 (s), 1733 (m), 1613 (m), 1589 (w), 1480 (m), 1455 (w), 1390 (s), 1255 (vs), 1194 (s), 784 (s), 723 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{22}BrO_4$ $[M+H]^+$: 417.0696 found: 417.0692.



Ethyl-6-hydroxy-5-methoxy-1a-(2-methoxyphenyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 552
Ethyl-5-methoxy-1a-(2-methoxyphenyl)-6-oxo-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate *cis*-559

Tert-butyl hydroperoxide (70% in H_2O, 154 µL, 1.11 mmol, 20.0 equiv) was added to a solution of cyclopropane **557** (18.8 mg, 55.6 µmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (aiming for 0.40 mg, 0.56 µmol, 1 mol%) at 23 °C and stirred for five hours at that temperature. The solvent was removed under reduced pressure to give the crude product. The solid was dissolved in dichloromethane and the solution was filtered through a short plug of silica. Purification by silica gel chromatography (20% dichloromethane in cyclohexane) gave alcohol **562** (5.70 mg, 16.1 µmol, 29%) as yellow oil and ketone ***cis*-559** (7.60 mg, 21.7 µmol, 39%) as a yellow solid.

Alcohol **562**

TLC (10% *iso*-propanol in cyclohexane): R_f = 0.31 (UV, $KMnO_4$).

mp: 155 °C (decomposition).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.54 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.36 – 7.26 (m, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.02 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.71 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.56 (d, *J* = 7.4 Hz, 1H), 5.50 (d, *J* = 9.7 Hz, 1H), 3.89 (s, 3H), 3.87 – 3.77 (m, 2H), 3.71 (s, 3H), 2.60 (d, *J* = 8.2 Hz, 1H), 2.36 (d, *J* = 8.2 Hz, 1H), 2.31 (d, *J* = 9.8 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3405 (m), 3339 (s), 2728 (w), 2699 (m), 1813 (s), 1544 (m), 1481 (m), 1392 (w), 1230 (m), 1181 (m), 1022 (w), 1026 (m), 826 (w), 799 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{21}O_5$ $[M\text{-}H]^-$: 353.1394 found: 353.1390.

cis-Ketone **559**

TLC (10% *iso*-propanol in cyclohexane): R_f = 0.24 (UV, $KMnO_4$).

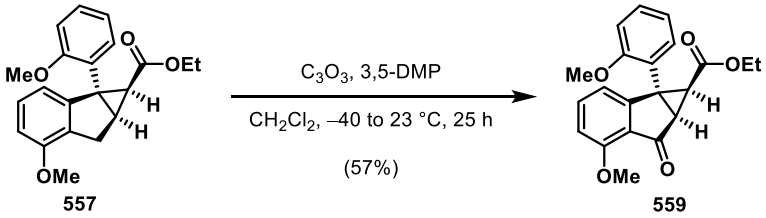
mp: 136 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 (dd, *J* = 1.6, 7.4 Hz, 1H), 7.37−7.30 (m, 2H), 7.02−6.99 (m, 1H), 6.91−6.89 (m, 1H), 6.77−6.75 (m, 1H), 6.67−6.65 (m, 1H), 3.94−3.91 (m, 5H), 3.70 (s, 3H), 2.91−2.89 (m, 1H), 2.71−2.71 (m, 1H), 0.99 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 197.7, 168.1, 159.0, 157.2, 152.9, 135.6, 131.6, 129.8, 125.1, 122.7, 120.7, 117.5, 111.1, 110.4, 61.1, 55.9, 55.6, 46.5, 40.3, 37.66, 13.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2922 (br), 2851 (m), 1713 (s), 1595 (m), 1481 (m), 1463 (m), 1397 (w), 1249 (m), 1220 (m), 1179 (m), 1122 (w), 1074 (m), 1026 (m), 796 (w), 755 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{21}O_5$ $[M+H]^+$: 353.1384 found: 353.1376.



Ethyl 5-methoxy-1a-(2-methoxyphenyl)-6-oxo-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 559

To a solution of chromium(VI) oxide (90.0 mg, 900 µmol, 20.0 equiv) and 3,5-dimethyl-pyrazole (85.0 mg, 890 µmol, 20.0 equiv) in dichloromethane (2 mL, 0.45 M) was added a solution of cyclopropane **557** (15.0 mg, 40.0 µmol, 1 equiv) in dichloromethane (600 µL, 0.07 M) at −40 °C. The reaction was allowed to warm to 23 °C and was stirred for 25 hours at that temperature, before the solvent was removed under reduced pressure. The obtained crude product was subjected to flash column chromatography on silica gel (dichloromethane) to yield ketone **559** (8.90 mg, 57%) as a yellow solid.

For analytical data of *cis*-Ketone **559**: *see above.*

trans-Ketone **559**

TLC (50% ethyl acetate in cyclohexane): R_f = 0.44 (UV, $KMnO_4$).

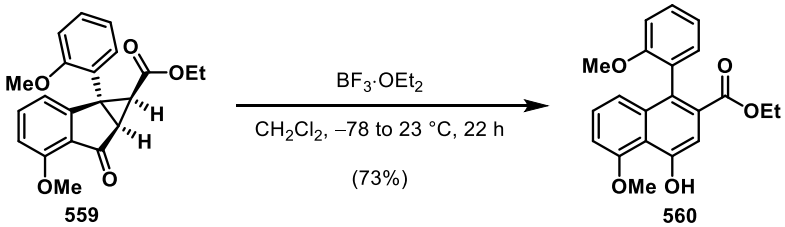
mp: 134 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 − 7.29 (m, 3H), 6.97 − 6.92 (m, 2H), 6.77 − 6.75 (m, 2H), 3.96 − 3.90 (m, 5H), 3.79 (s, 3H), 3.23 (d, *J* = 3.4 Hz, 1H), 2.73 (d, *J* = 3.4 Hz, 1H), 1.01 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 198.6, 166.7, 158.9, 158.6, 157.8, 136.2, 131.7, 129.6, 121.7, 120.8, 119.9, 116.9, 110.8, 110.3, 60.8, 56.0, 55.5, 47.9, 39.1, 38.6, 14.1.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2938 (br), 1712 (s), 1594 (m), 1499 (w), 1481 (m), 1463 (m), 1439 (w), 1327 (w), 1282 (m), 1246 (m), 1205 (m), 1178 (m), 1122 (w), 1075 (m), 1026 (m), 755 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{21}O_5$ $[M+H]^+$: 353.1384 found: 353.1366.

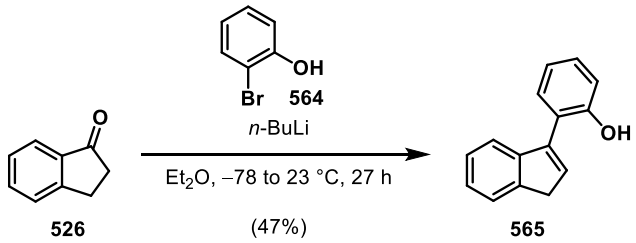


Ethyl 4-hydroxy-5-methoxy-1-(2-methoxyphenyl)-2-naphthoate 560

Boron trifluoride diethyl etherate (48 wt%, 70.0 µL, 270 µmol, 5.00 equiv) was added to a solution of ketone **559** (19.0 mg, 50.0 µmol, 1 equiv) in dichloromethane (1.10 mL, 0.05 M) at −78 °C. After four

hours, boron trifluoride diethyl etherate (48 wt%, 70.0 µL, 270 µmol, 5.00 equiv) was added and the reaction was allowed to warm to 23 °C. After 18 hours, water (1 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 1 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (2 mL) and the washed solution was dried over magnesium sulfate. The dried solution was concentrated and the residue was purified by flash column chromatography on silica gel (1% grading to 10% ethyl acetate in cyclohexane) to yield biaryl **560** (12.8 mg, 36.5 µmol, 73%) as an orange oil.

TLC (50% ethyl acetate in cyclohexane): R_f = 0.52 (UV, $KMnO_4$).
^{1}H NMR (400 MHz, chloroform-*d*) δ 9.39 (s, 1H), 7.30 − 7.28 (m, 1.5H), 7.14 − 7.09 (m, 1.5H), 7.01 − 6.99 (m, 1H), 6.97 − 6.96 (m, 1H), 6.92 − 6.90 (m, 1H), 6.89 − 6.87 (m, 1H), 6.75 − 6.73 (m, 1H), 3.96 (s, 3H), 3.95 − 3.91 (m, 2H), 3.54 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 167.9, 157.7, 156.2, 154.1, 135.9, 131.6, 130.7, 128.9, 128.7, 128.6, 126.2, 121.7, 120.5, 116.8, 110.9, 110.5, 105.6, 60.8, 56.5, 55.8, 13.9.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3386 (br), 2929 (br), 1708 (m), 1613 (m), 1571 (m), 1494 (m), 1463 (m), 1433 (m), 1253 (s), 1177 (m), 1074 (m), 986 (w), 910 (w), 872 (w), 811 (w), 785 (w), 730 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{21}H_{21}O_5$ $[M+H]^+$: 353.1384 found: 353.1373.



2-(1*H*-inden-3-yl)phenol 565

To a solution of 2-bromophenol **564** (2.95 mL, 27.8 mmol, 1 equiv) in diethyl ether (100 mL, 0.28 M) was added *n*-butyllithium (2.5 M in hexane, 24.5 mL, 55.1 mmol, 2.00 equiv) at 0 °C. After stirring for three hours at that temperature, the reaction was cooled to −78 °C and a solution of 1-indanone **526** (4.01 g, 30.3 mmol, 1.10 equiv) in ethyl acetate (147 mL, 0.21 M) was added dropwise *via* syringe. The reaction mixture was allowed to warm to 23 °C and stirred for 27 hours before an aqueous solution of hydrochloric acid (12 M, 12.5 mL) was added. After two hours of stirring, water (30 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 16 mL). The combined organic layers were washed with water (15 mL) and a saturated aqueous solution of sodium chloride (15 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% dichloromethane in cyclohexane, grading to 40% dichloromethane in cyclohexane) to yield aryl indene **565** (2.72 g, 13.1 mmol, 47%) as a pale-yellow oil.

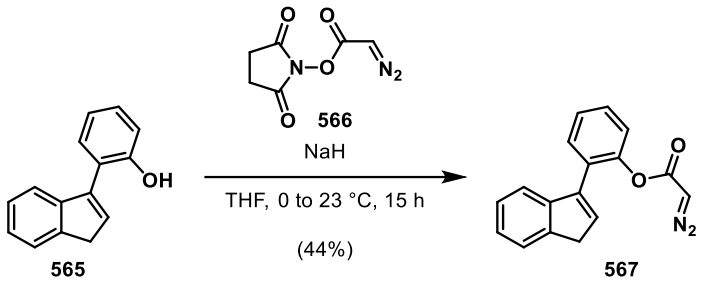
TLC (dichloromethane): R_f = 0.77 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.59 − 7.57 (m, 1H), 7.39 − 7.29 (m, 5H), 7.07 − 7.01 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 1H), 5.39 (s, 1H), 3.62 (d, *J* = 2.0 Hz, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.3, 144.5, 143.9, 140.7, 133.0, 129.7, 129.5, 126.6, 125.7, 124.3, 121.8, 120.8, 120.6, 115.8, 38.9.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3593 (m), 3492 (m), 3193 (w), 2994 (w), 2848 (w), 1480 (m), 1428 (s), 1395 (vs), 1285 (s), 1203 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{15}H_{13}O$ $[M+H]^+$: 209.0961 found: 209.0958.



2-(1*H*-Inden-3-yl)phenyl 2-diazoacetate 567

A solution of indene **565** (923 mg, 4.43 mmol, 1 equiv) in tetrahydrofuran (25 mL, 0.18 M) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 228 mg, 5.57 mmol, 1.25 equiv) in tetrahydrofuran (25 mL, 0.22 M) at 0 °C. After 30 minutes, a solution of diazoacetate **566** (852 mg, 4.65 mmol, 1.05 equiv) in tetrahydrofuran (25 mL, 0.19 M) was added dropwise *via* a dropping funnel within 30 minutes. After two hours, the reaction was allowed to warm to 23 °C and after 13 hours, the solvent was removed under reduced pressure. The obtained residue was dissolved in ethyl acetate (40 mL). The solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (dichloromethane) to yield a rotameric mixture of ester **567** (541 mg, 1.95 mmol, 44%) as an orange oil.

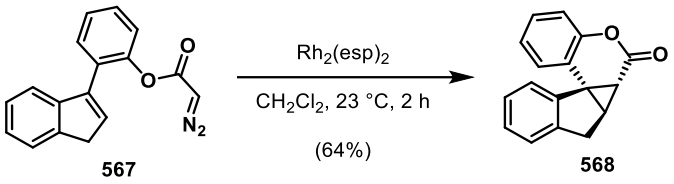
TLC (50% dichloromethane in cyclohexane): R_f = 0.67 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, chloroform-*d*), [ratio of rotamers 1.00 : 0.36]: 7.59 − 7.57 (m, 0.36H), 7.54−7.52 (m, 1H), 7.51 − 7.48 (m, 1H), 7.44 − 7.40 (m, 1H), 7.38 − 7.33 (m, 2H), 7.32 − 7.28 (m, 3.44H), 7.26 − 7.22 (m, 1H), 7.08 − 7.06 (m, 0.36H), 7.04 − 7.03 (m, 0.36H), 7.02 − 6.99 (m, 0.36H), 6.68 (t, *J* = 2.1 Hz, 0.36H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.38 (br s, 0.36H), 4.67 (br s, 1H), 3.62 (d, *J* = 1.9 Hz, 0.72H), 3.54 (d, *J* = 1.9 Hz, 2H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 153.3, 148.1, 144.5, 144.4*, 143.9*, 141.1, 140.7, 133.2*, 133.0, 130.7*, 129.7, 129.5, 129.4, 128.8*, 126.7, 126.3*, 125.7, 124.9*, 124.3, 123.9*, 123.2*, 121.8, 120.8, 120.7*, 120.6, 115.8, 46.7, 38.9, 38.7*, 31.7.

Asterisks mark the signals of the major rotamer.

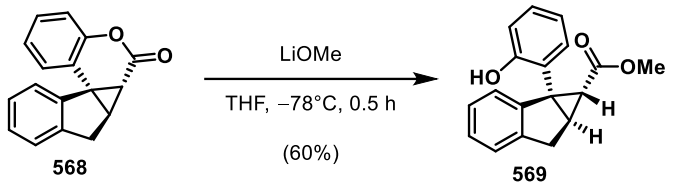
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3428 (br), 3111 (br), 2115 (s), 1708 (s), 1484 (w), 1447 (w), 1366 (s), 1342 (m), 1215 (m), 1195 (s), 1182 (s), 1146 (s), 1104 (w), 1086 (w), 920 (w), 767 (s), 721 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{17}H_{12}N_2NaO_2$ $[M+Na]^+$: 299.0791 found: 299.0784.



6b,7-Dihydroindeno[1',2':2,3]cyclopropa[1,2-*c*]chromen-6(6a*H*)-one 568

To a solution of diazoacetate **567** (313 mg, 1.13 mmol, 1 equiv) in dichloromethane (27 mL, 0.04 M) was added bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (10.0 mg, 10.0 µmol, 1 mol%) at 23 °C. After two hours, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (dichloromethane) to yield lactone **568** (179 mg, 720 µmol, 64%) as an orange oil.

TLC (dichloromethane): R_f = 0.66 (UV, $KMnO_4$).
^{1}H NMR (400 MHz, chloroform-*d*) δ 7.64 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.53 − 7.50 (m, 1H), 7.31 − 7.27 (m, 4H), 7.18 − 7.11 (m, 2H), 3.53 − 3.47 (m, 1H), 3.28 − 3.23 (m, 1H), 2.28 − 2.25 (m, 1H), 1.86 (d, *J* = 3.6 Hz, 1H).
^{13}C NMR (101 MHz, chloroform-*d*) δ 166.3, 150.4, 141.8, 141.4, 128.2, 127.9, 126.9, 126.5, 126.3, 124.4, 124.4, 121.1, 117.6, 41.7, 35.0, 34.2, 31.3.
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3041 (br), 1754 (s), 1586 (w), 1499 (m), 1477 (m), 1451 (m), 1356 (w), 1267 (m), 1212 (s), 1188 (s), 1113 (w), 1039 (w), 954 (m), 921 (m), 815 (w), 761 (s), 730 (m) cm^{-1}.
HRMS (ESI) calc. for $C_{17}H_{13}O_2$ $[M+H]^+$: 249.0910 found: 249.0905.



Ethyl 1a-(2-hydroxyphenyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate 569

To a solution of lactone **568** (156 mg, 630 µmol, 1 equiv) in tetrahydrofuran (2.3 mL, 0.27 M) was added a solution of lithium methoxide (0.084 M in methanol, 1.55 mL) at −78 °C. After 30 minutes, a saturated aqueous solution of ammonium chloride (4 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over magnesium sulfate and the dried solution was filtered. The filtrate was evaporated under reduced pressure and the residue was purified

by flash column chromatography over silica gel (dichloromethane) to yield cyclopropane **569** (106 mg, 0.39 mmol, 60%) as a beige solid.

TLC (dichloromethane): R_f = 0.24 (UV, $KMnO_4$).

mp: 175 °C.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.24 − 7.10 (m, 6H), 6.93 − 6.87 (m, 2H), 5.08 (br s, 1H), 3.55 − 3.49 (m, 4H), 3.22 − 3.18 (m, 1H), 2.90 (dd, *J* = 6.1, 3.9 Hz, 1H), 1.80 (d, *J* = 3.8 Hz 1H).

^{13}C NMR (101 MHz, chloroform-*d*) δ 170.8, 155.2, 145.9, 140.9, 131.6, 129.3, 127.1, 126.8, 125.6, 123.9, 122.4, 120.9, 115.9, 51.9, 44.3, 36.1, 35.2, 30.5.

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3386 (br), 3037 (br), 1705 (s), 1594 (w), 1475 (w), 1349 (m), 1275 (m), 1219 (m), 1174 (m), 1096 (w), 1049 (w), 1015 (m), 911 (w), 860 (w), 825 (w), 756 (m), 729 (m) cm^{-1}.

HRMS (ESI) calc. for $C_{18}H_{17}O_3$ $[M+H]^+$: 281.1172 found: 281.1165.

9. Appendix

9.1 Single-crystal X-ray Analysis

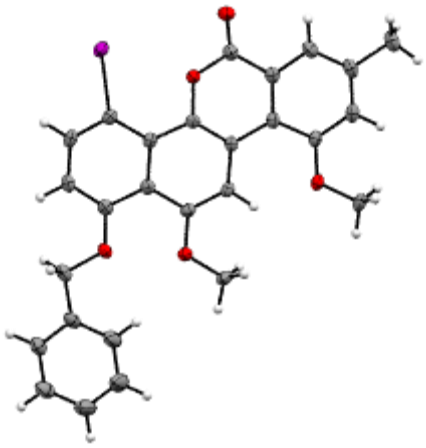


Table 16. Crystal data and structure refinement for compound **470**.

Identification code	mar196	
Empirical formula	C_{21} H_{22} O_4	
Formula weight	338.38	
Temperature	183(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1 (no. 2)	
Unit cell dimensions	a = 7.5089(5) Å	α= 102.090(3)°.
	b = 8.1549(6) Å	β= 92.523(3)°.
	c = 15.0809(10) Å	γ = 104.412(3)°.
Volume	870.05(10) $Å^3$	
Z	2	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	360	
Crystal size	0.130 x 0.090 x 0.050 mm^3	
Theta range for data collection	2.648 to 24.998°.	
Index ranges	-8<=h<=8, -9<=k<=9, -17<=l<=17	
Reflections collected	21263	
Independent reflections	3056 [R(int) = 0.0532]	
Completeness to theta = 24.998°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.006 and 0.991	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3056 / 2 / 235	

Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1032
R indices (all data)	R1 = 0.0565, wR2 = 0.1084
Extinction coefficient	0.038(4)
Largest diff. peak and hole	0.180 and -0.185 e.$Å^{-3}$

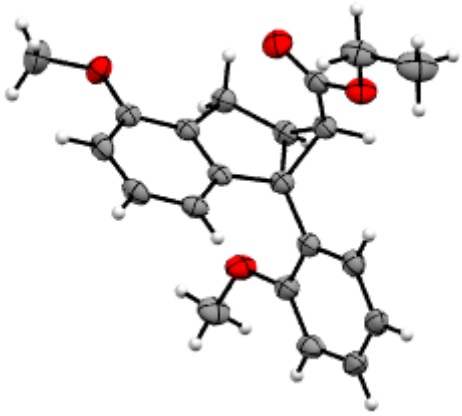
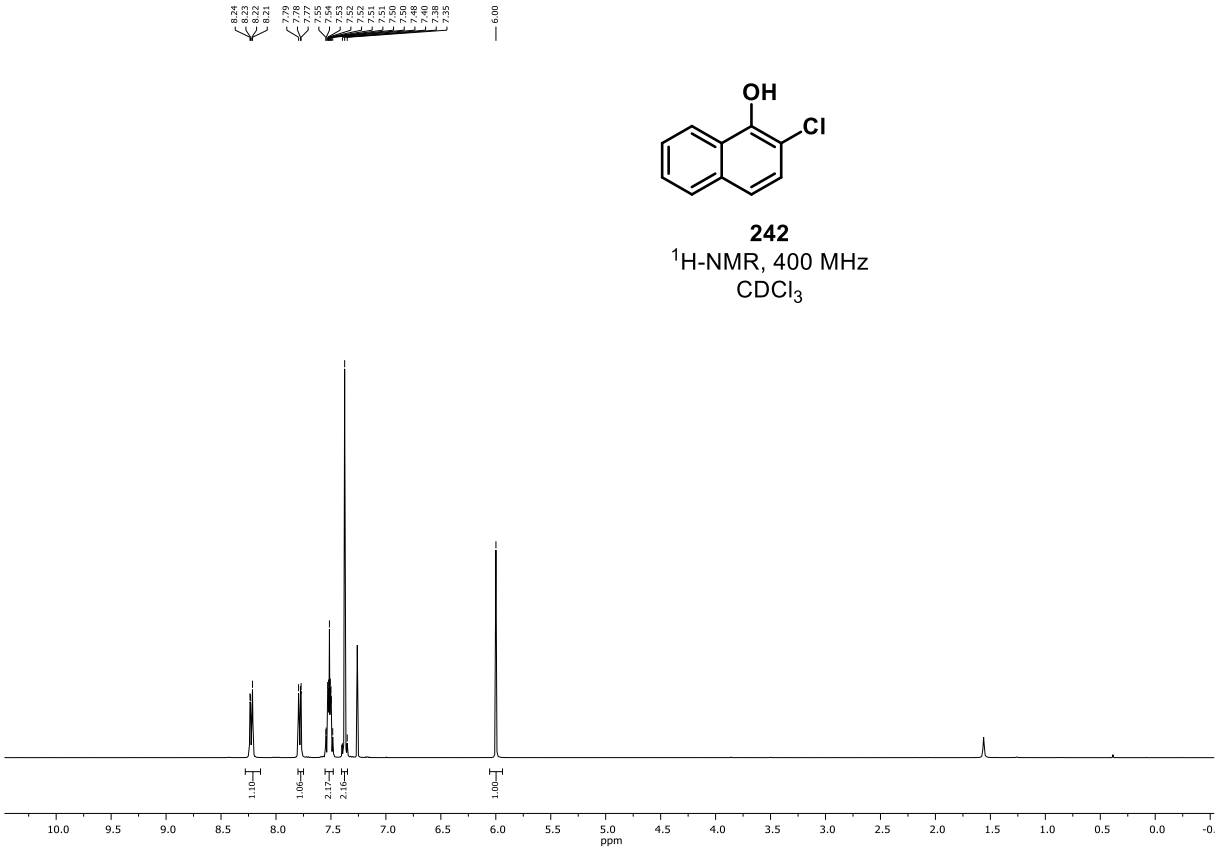


Table 17. Crystal data and structure refinement for compound **557**.

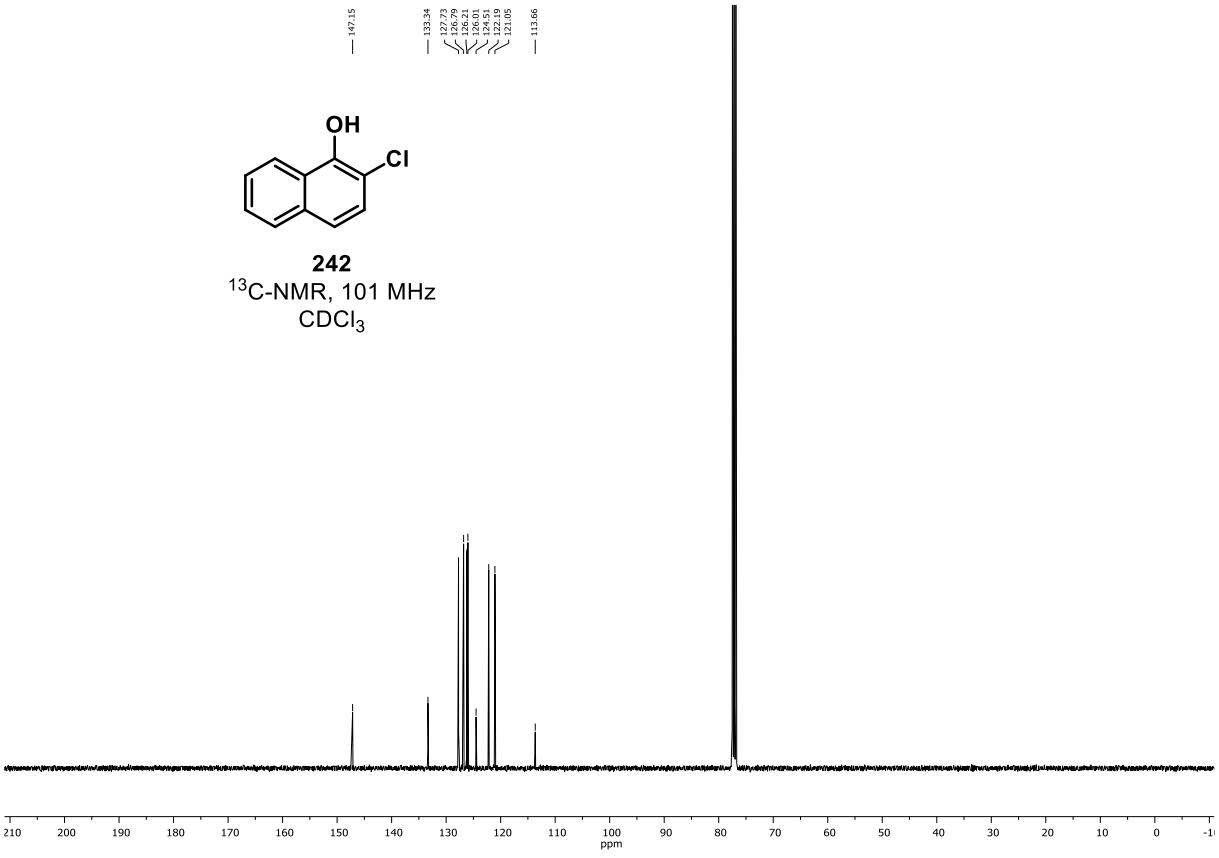
Identification code	mar20-13	
Empirical formula	C_{27} H_{21} I O_5 x CH_2Cl_2	
Formula weight	637.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (no. 14)	
Unit cell dimensions	a = 16.1499(7) Å	α= 90°.
	b = 7.9519(3) Å	β= 100.830(1)°.
	c = 19.8879(8) Å	γ = 90°.
Volume	2508.56(18) $Å^3$	
Z	4	
Density (calculated)	1.687 Mg/m^3	
Absorption coefficient	1.528 mm^{-1}	
F(000)	1272	
Crystal size	0.180 x 0.060 x 0.040 mm^3	
Theta range for data collection	1.799 to 25.500°.	
Index ranges	-19<=h<=19, -9<=k<=9, -24<=l<=24	
Reflections collected	32080	
Independent reflections	4662 [R(int) = 0.0306]	
Completeness to theta = 25.242°	99.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.875 and 0.777
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4662 / 0 / 354
Goodness-of-fit on F^2	1.124
Final R indices [I>2sigma(I)]	R1 = 0.0244, wR2 = 0.0555
R indices (all data)	R1 = 0.0282, wR2 = 0.0566
Extinction coefficient	0.00234(17)
Largest diff. peak and hole	0.376 and -0.536 e.$Å^{-3}$

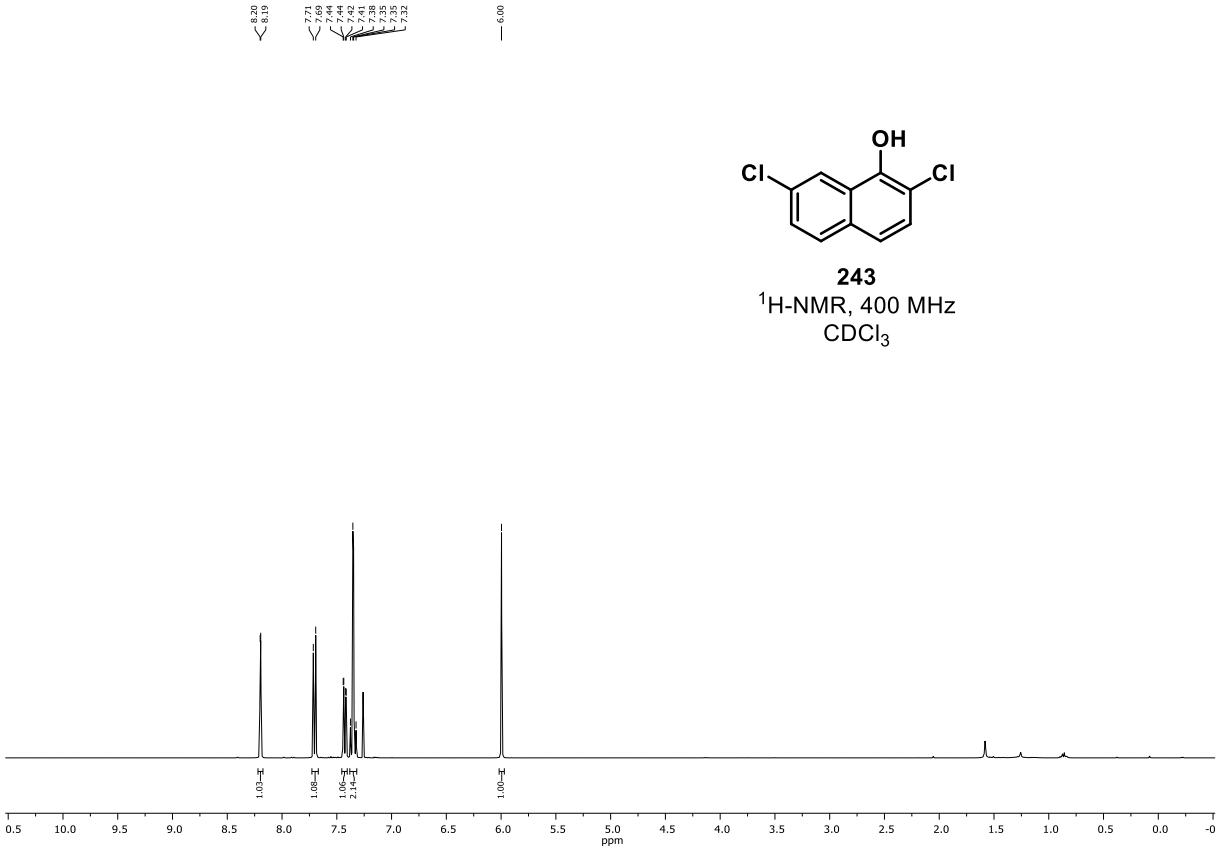
9.2 NMR Spectra for Part I



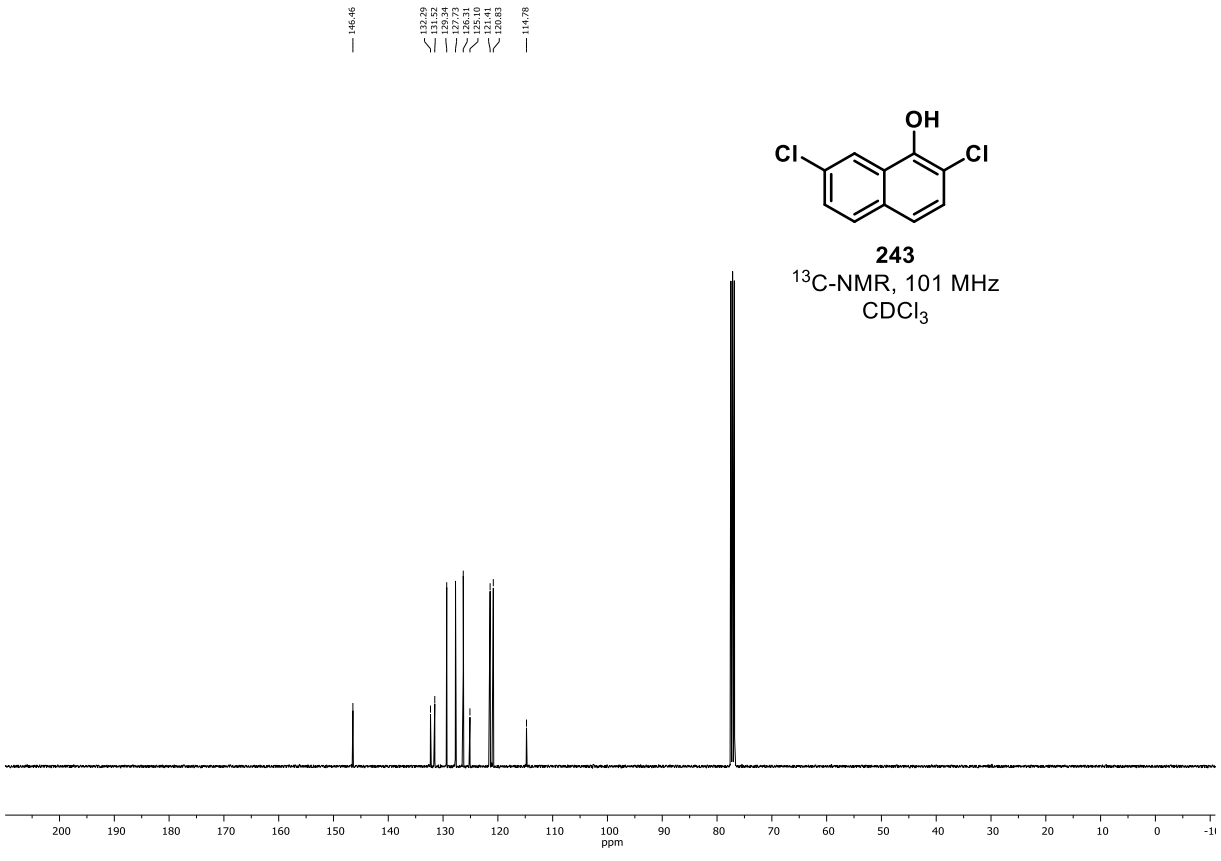
242
^{1}H-NMR, 400 MHz
$CDCl_3$



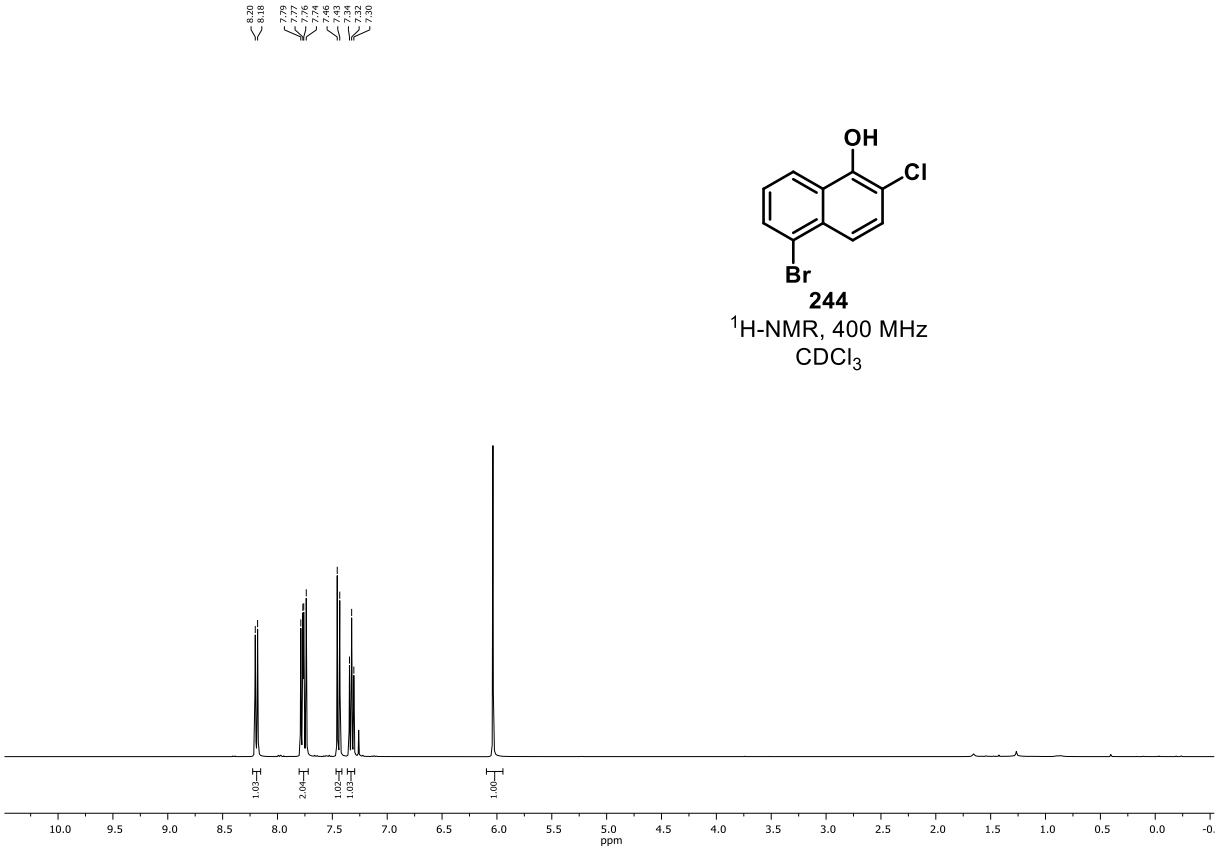
242
^{13}C-NMR, 101 MHz
$CDCl_3$



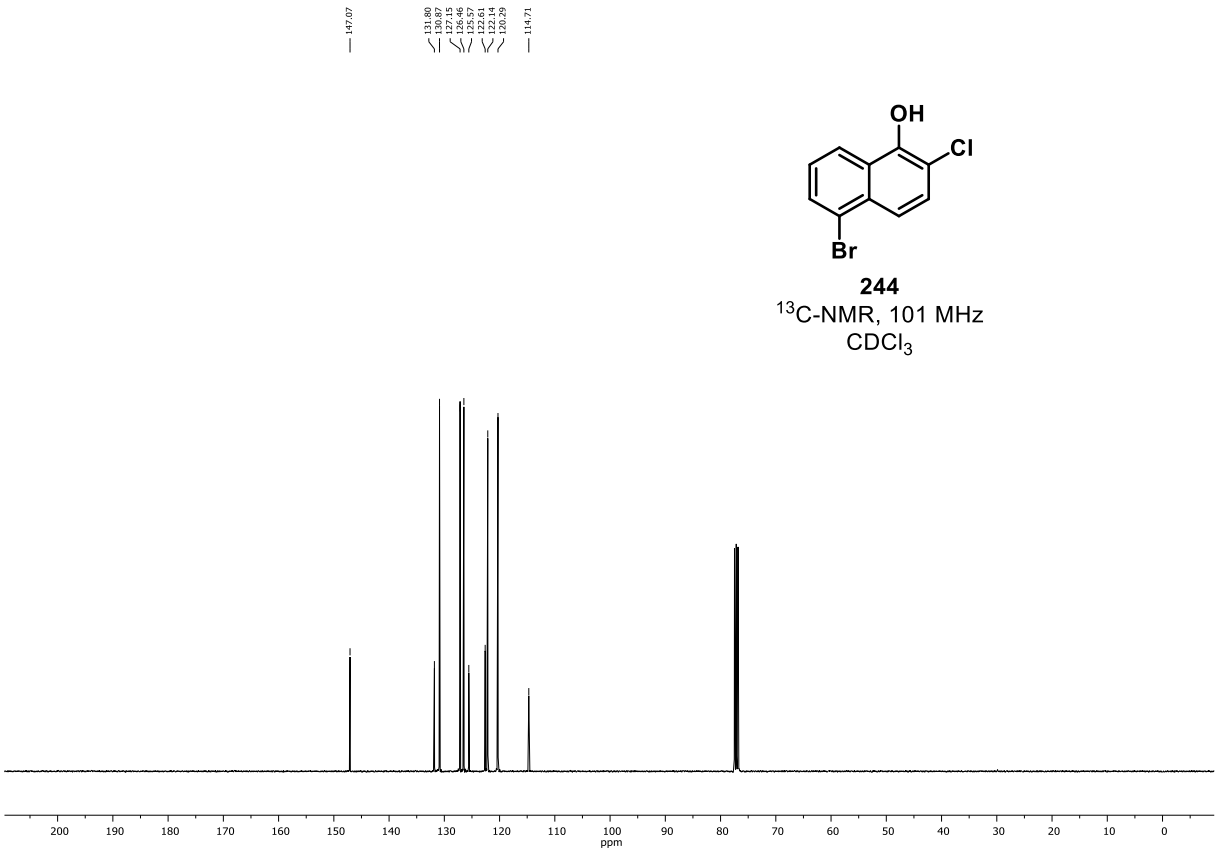
243
^{1}H-NMR, 400 MHz
$CDCl_3$



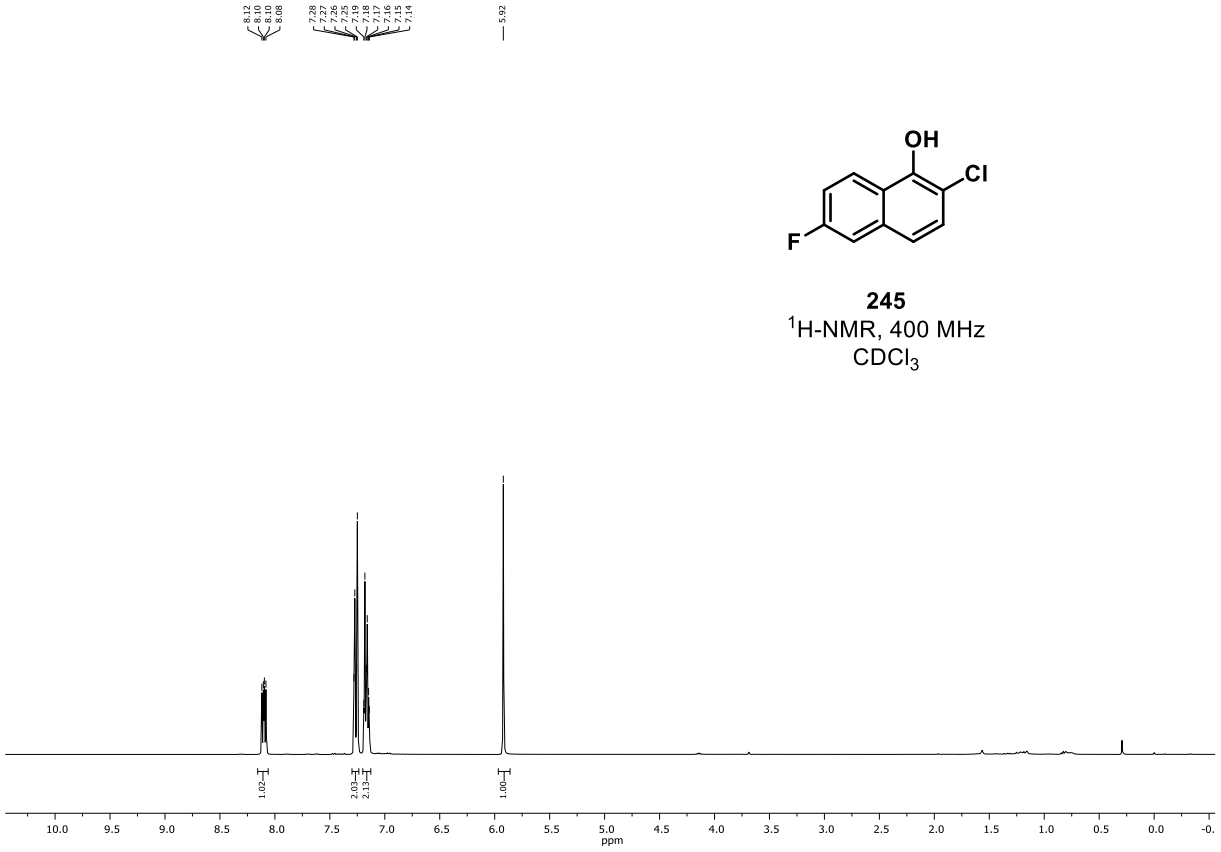
243
^{13}C-NMR, 101 MHz
$CDCl_3$



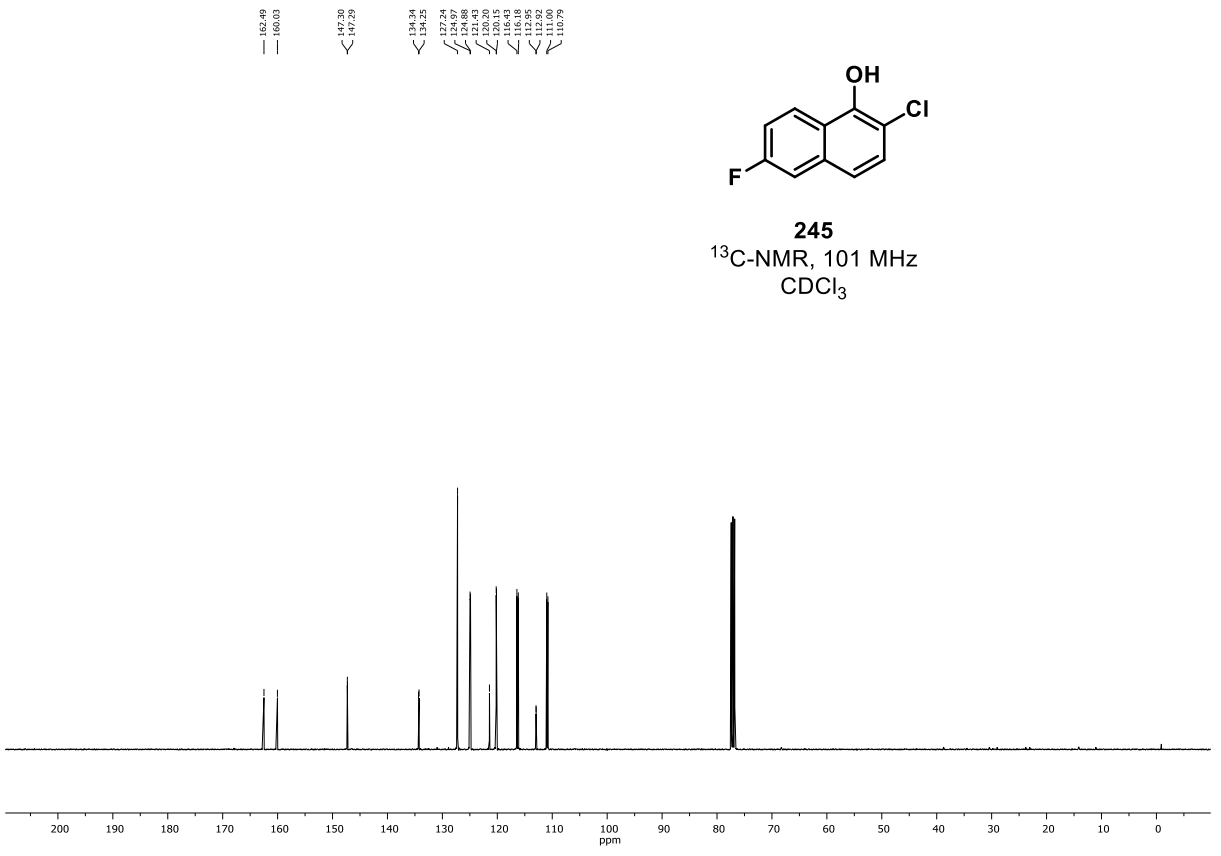
244
^{1}H-NMR, 400 MHz
$CDCl_3$



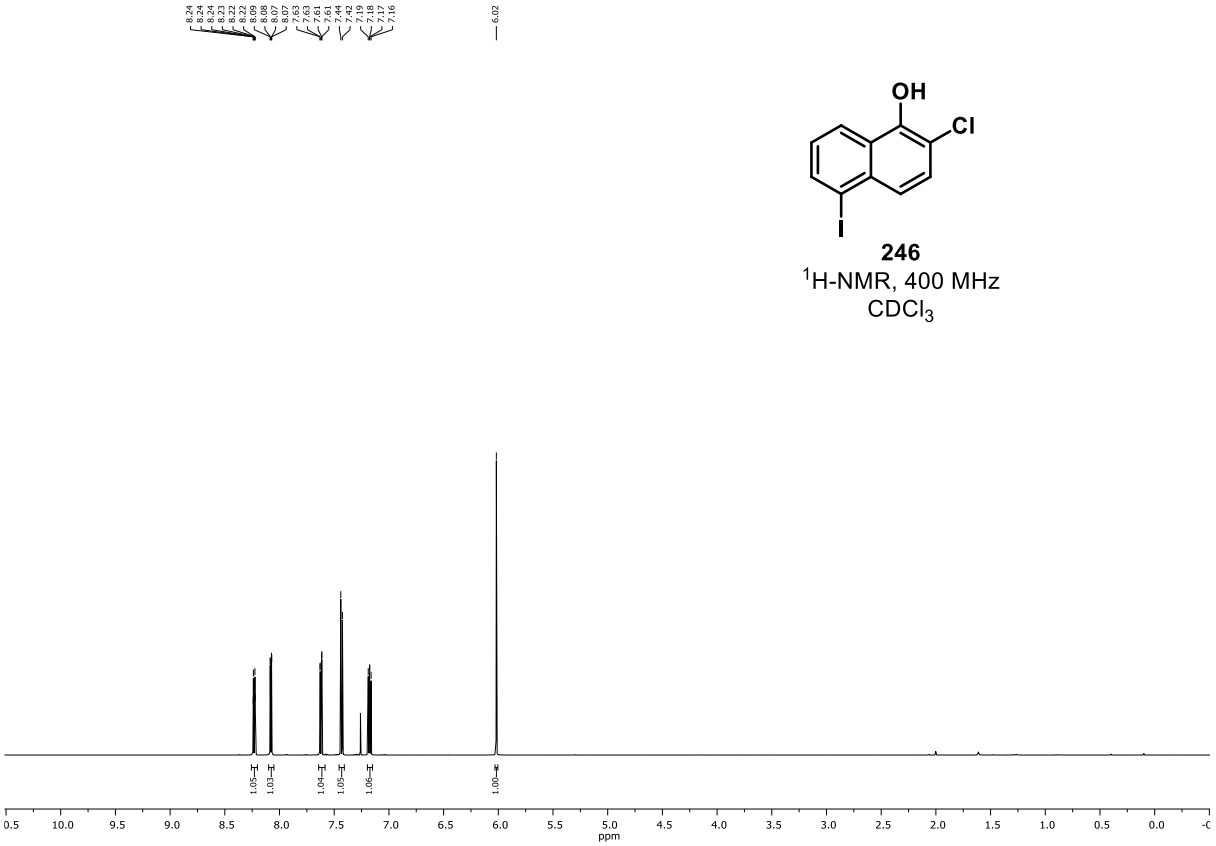
244
^{13}C-NMR, 101 MHz
$CDCl_3$



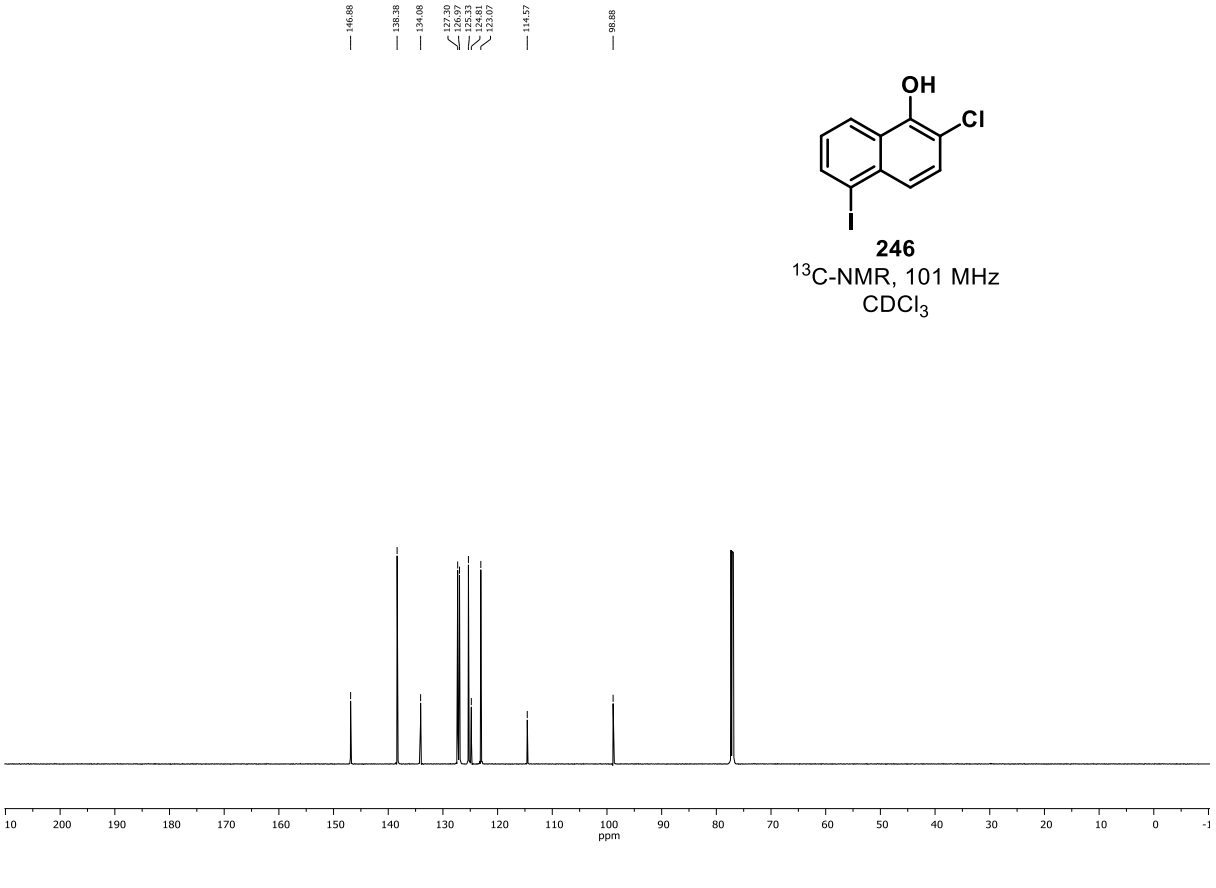
245
^{1}H-NMR, 400 MHz
$CDCl_3$



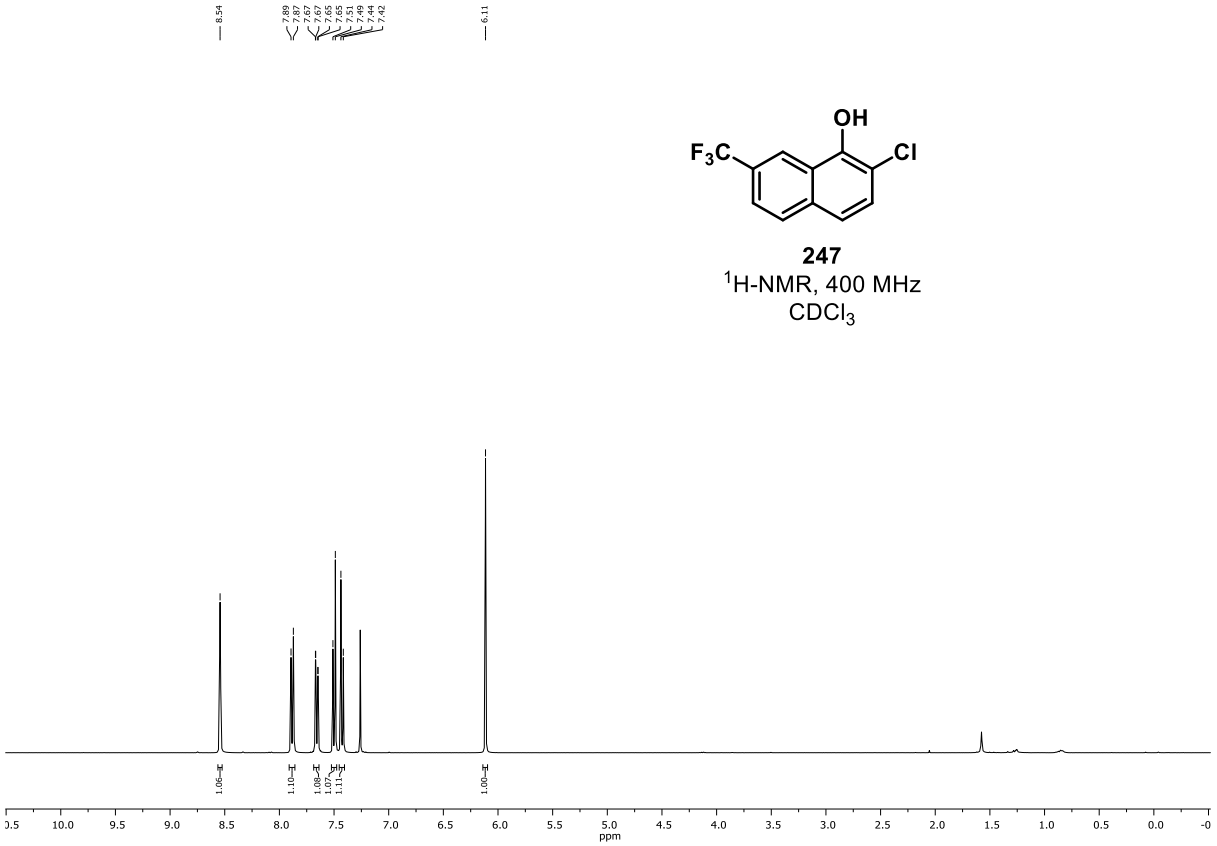
245
^{13}C-NMR, 101 MHz
$CDCl_3$



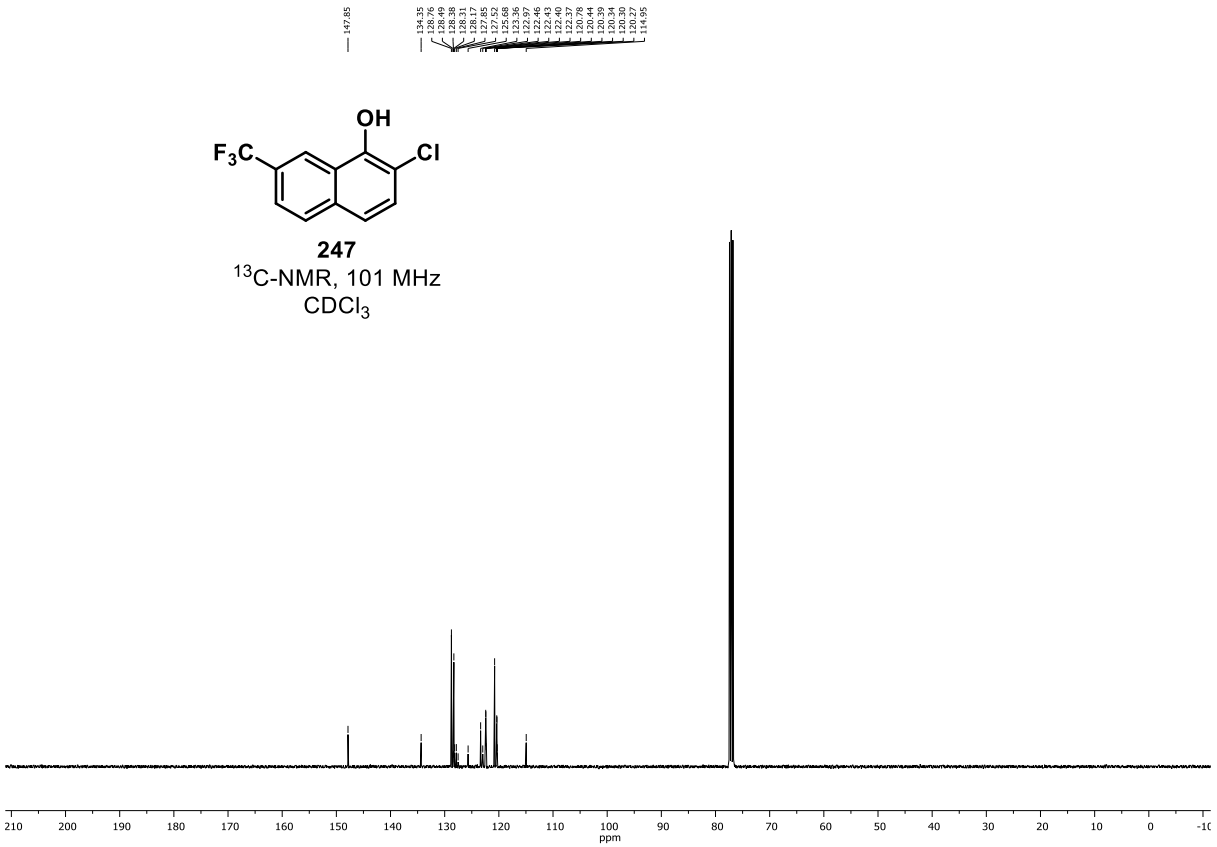
246
^{1}H-NMR, 400 MHz
$CDCl_3$



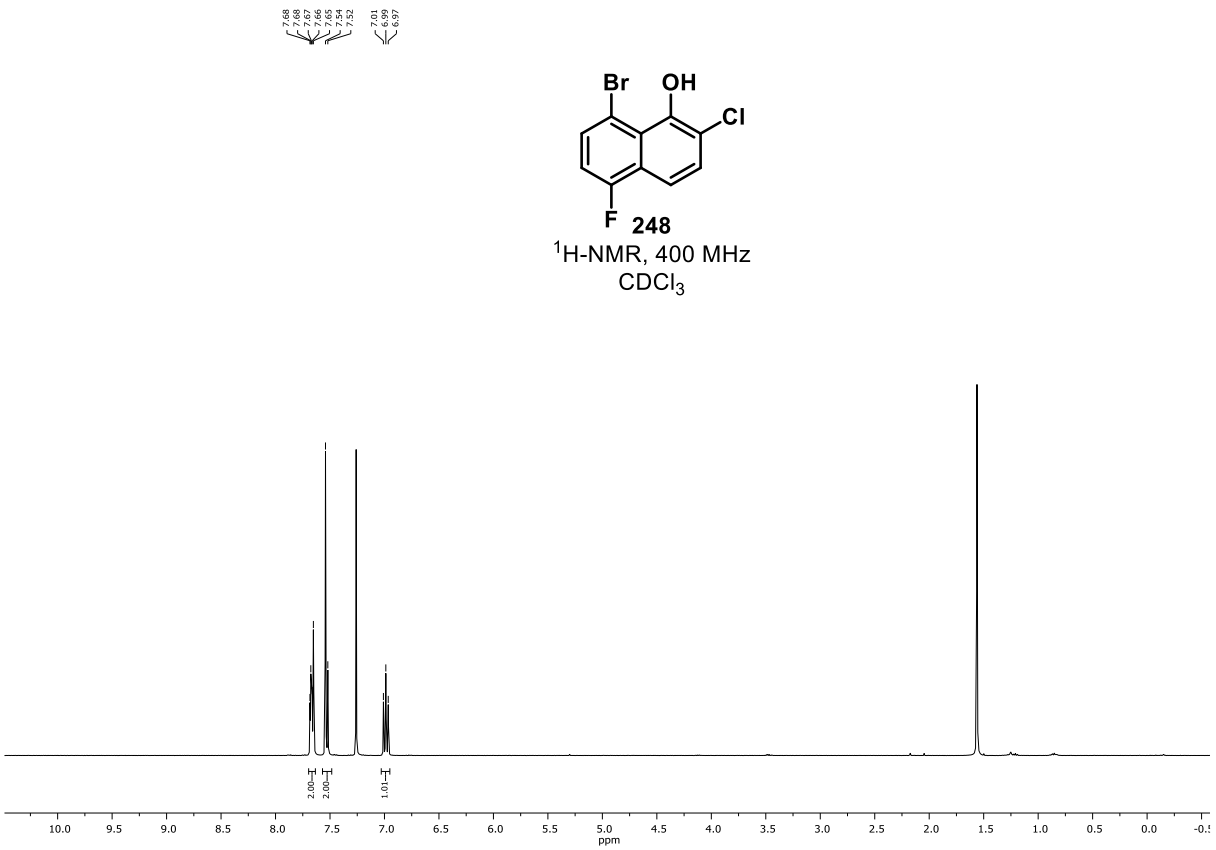
246
^{13}C-NMR, 101 MHz
$CDCl_3$



247
^{1}H-NMR, 400 MHz
$CDCl_3$



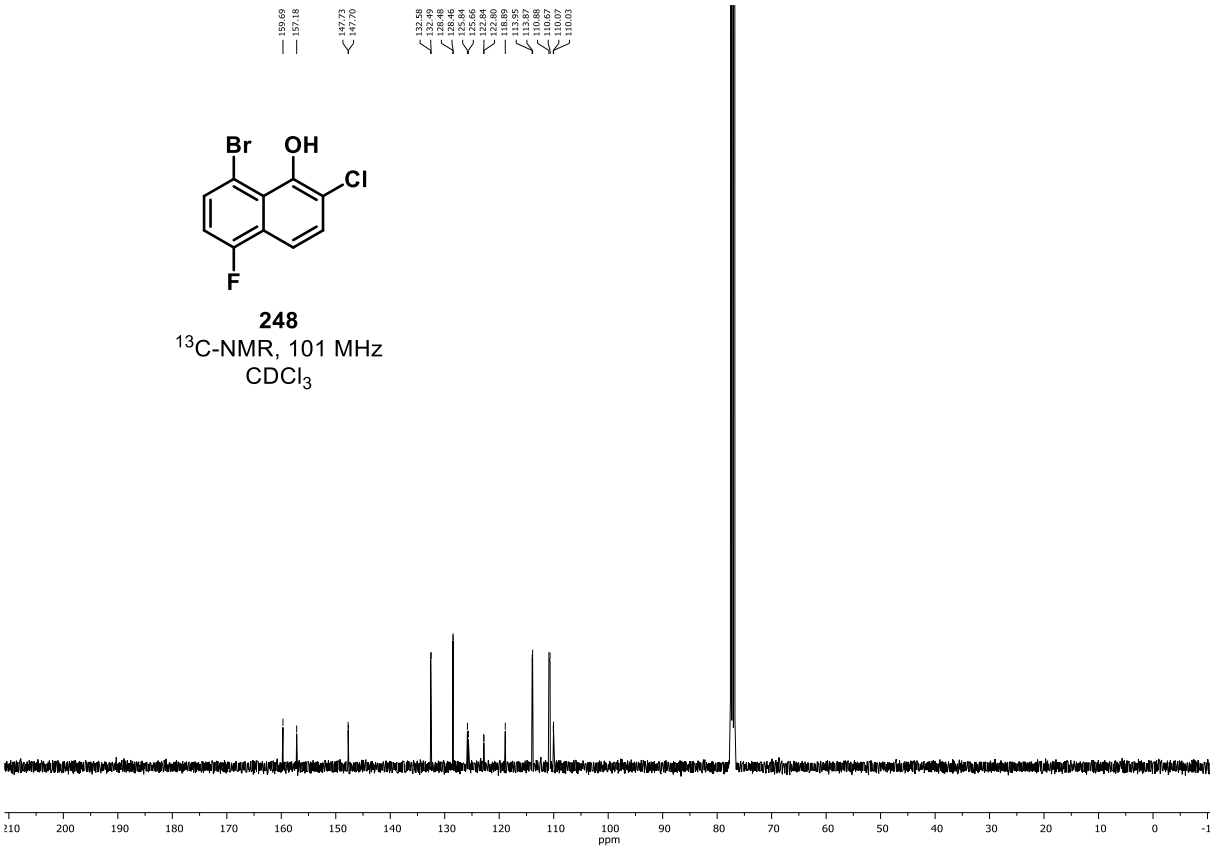
247
^{13}C-NMR, 101 MHz
$CDCl_3$



248

^{1}H-NMR, 400 MHz

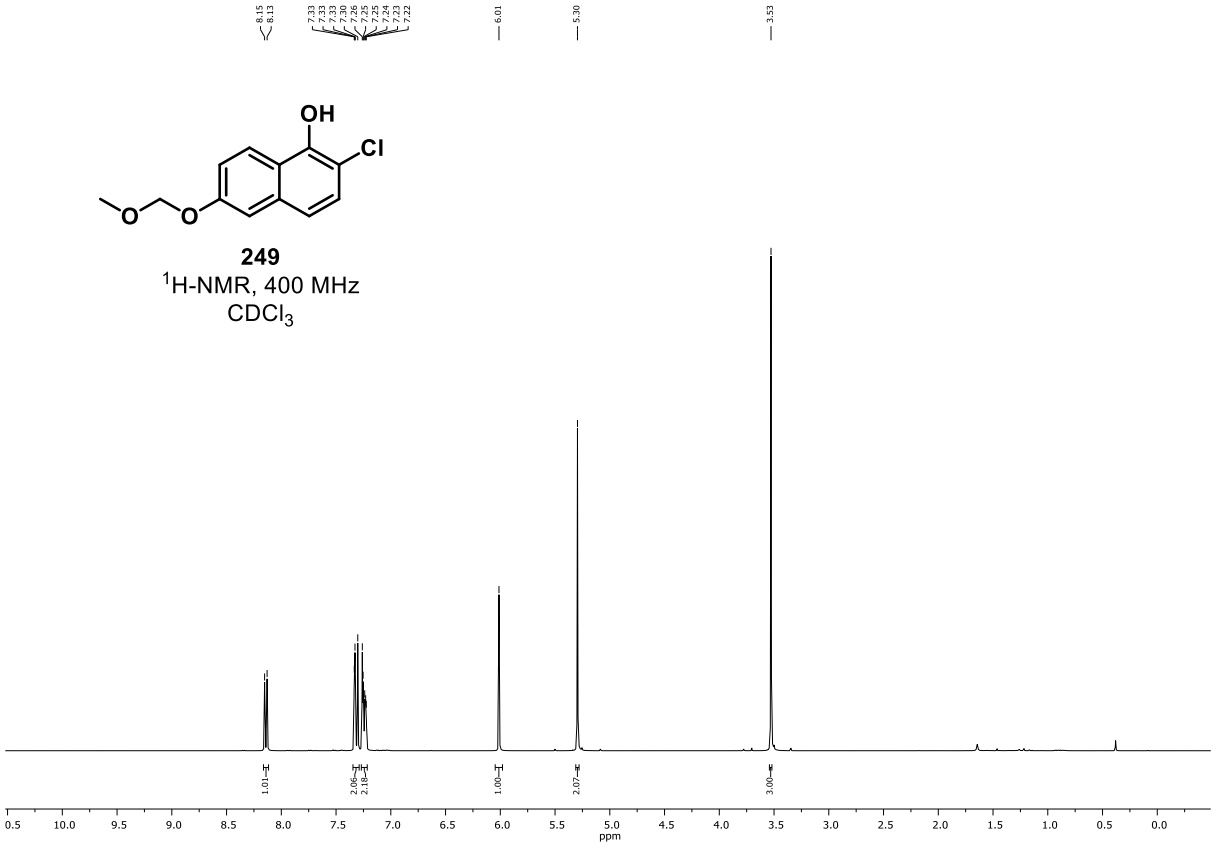
$CDCl_3$



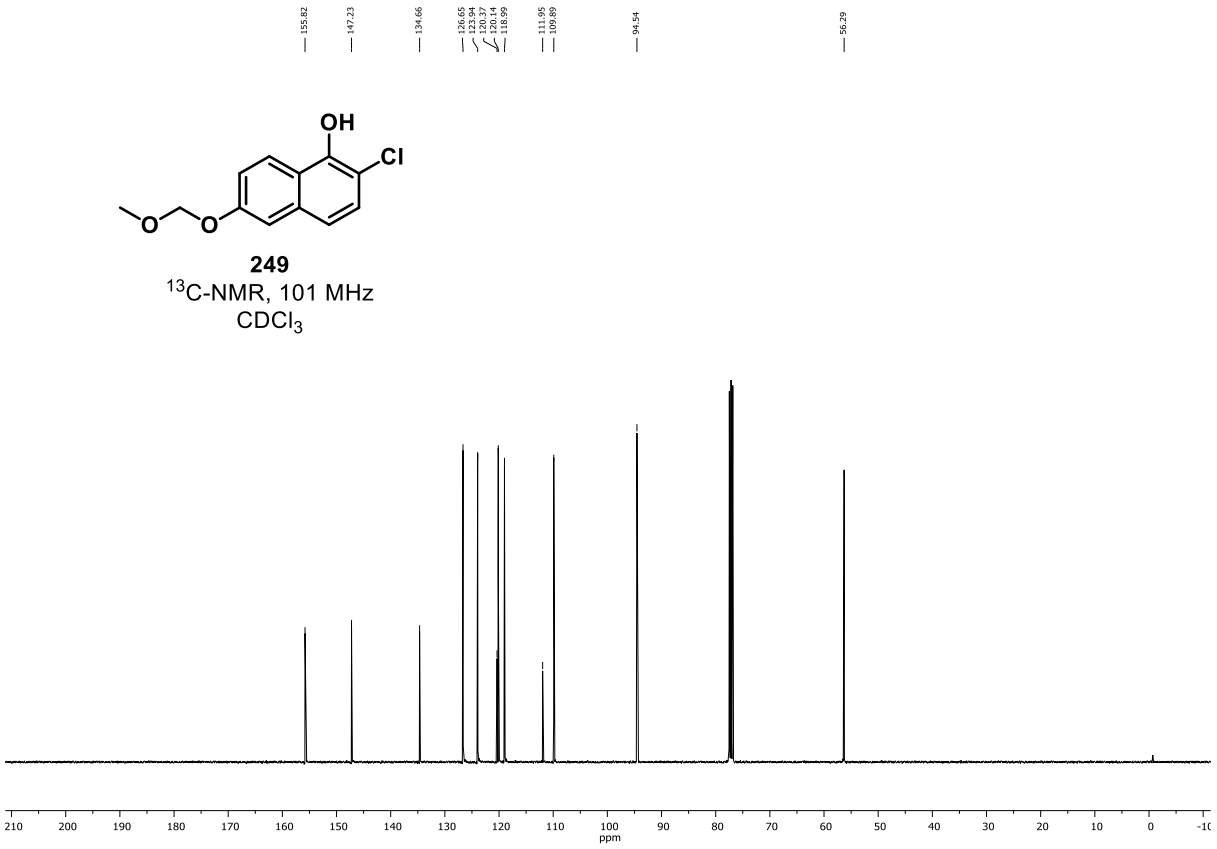
248

^{13}C-NMR, 101 MHz

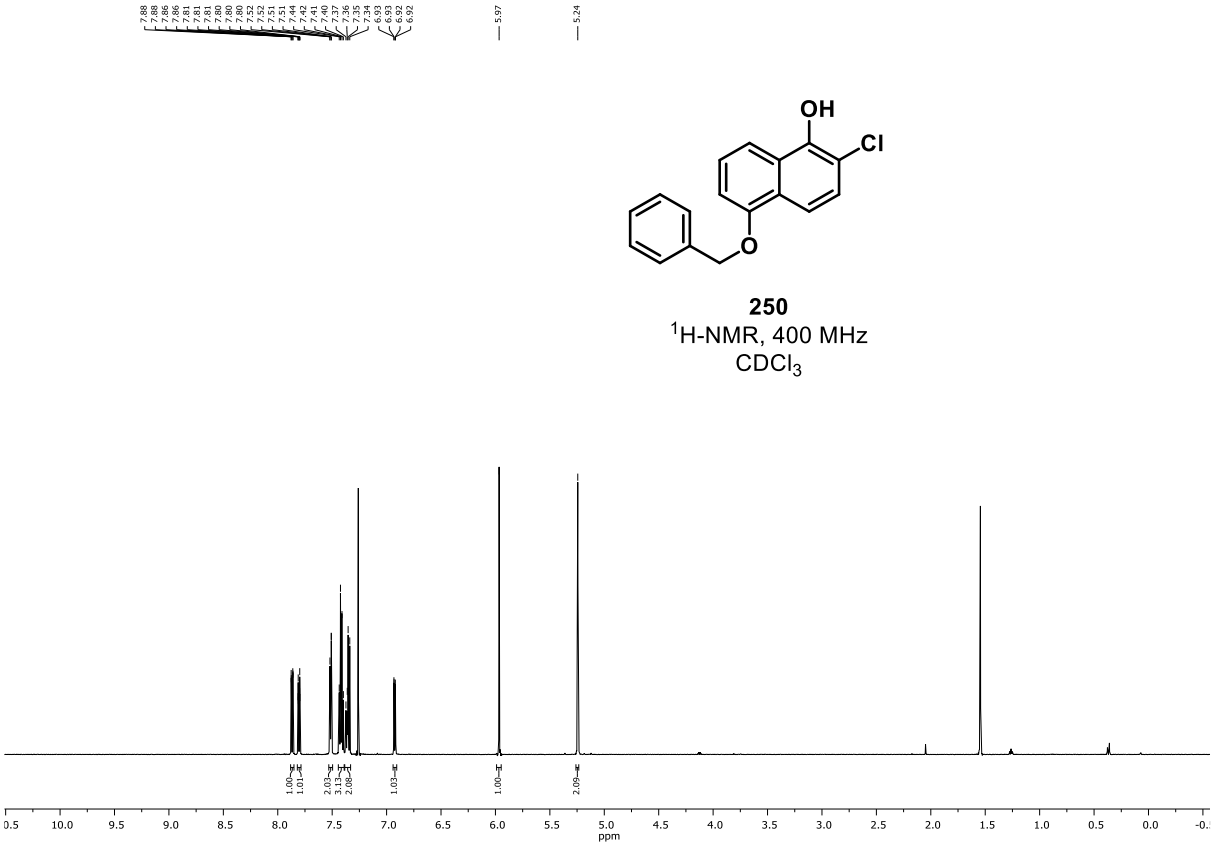
$CDCl_3$



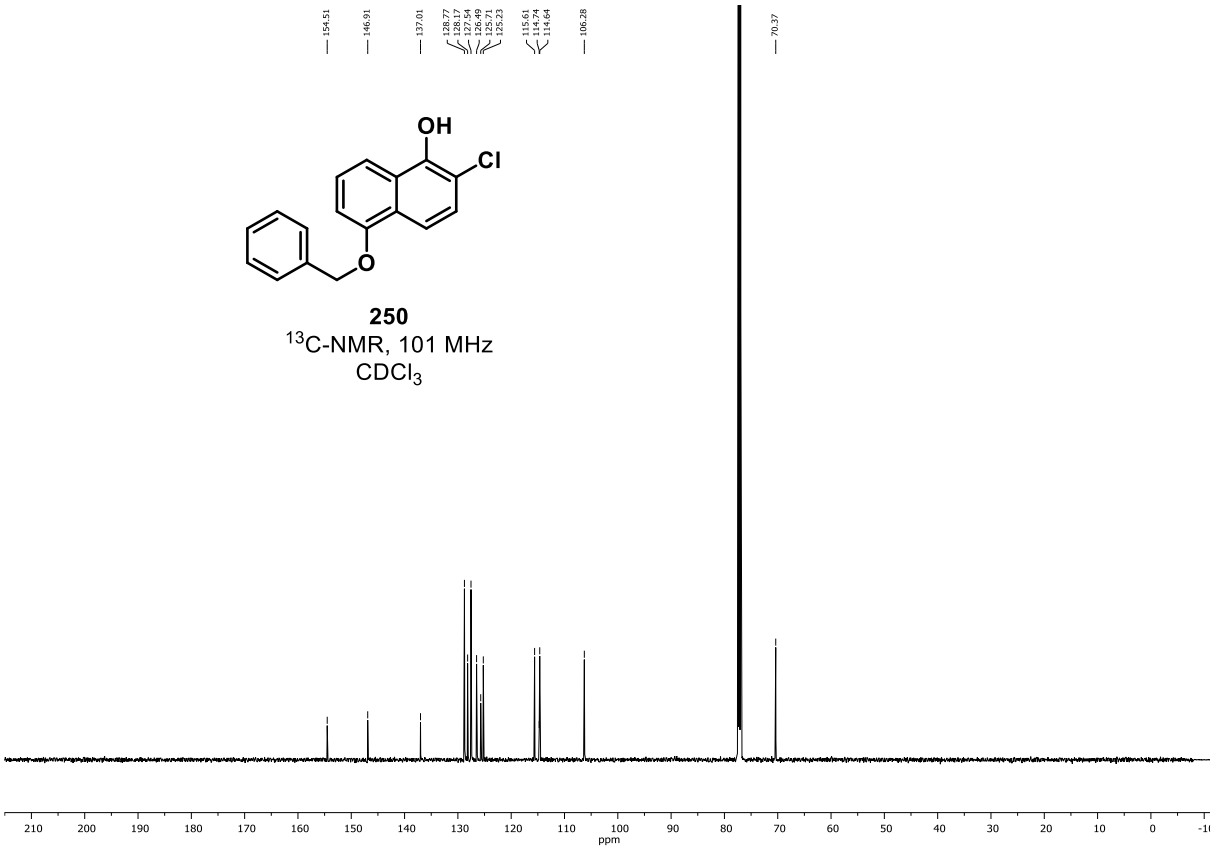
249
^{1}H-NMR, 400 MHz
$CDCl_3$



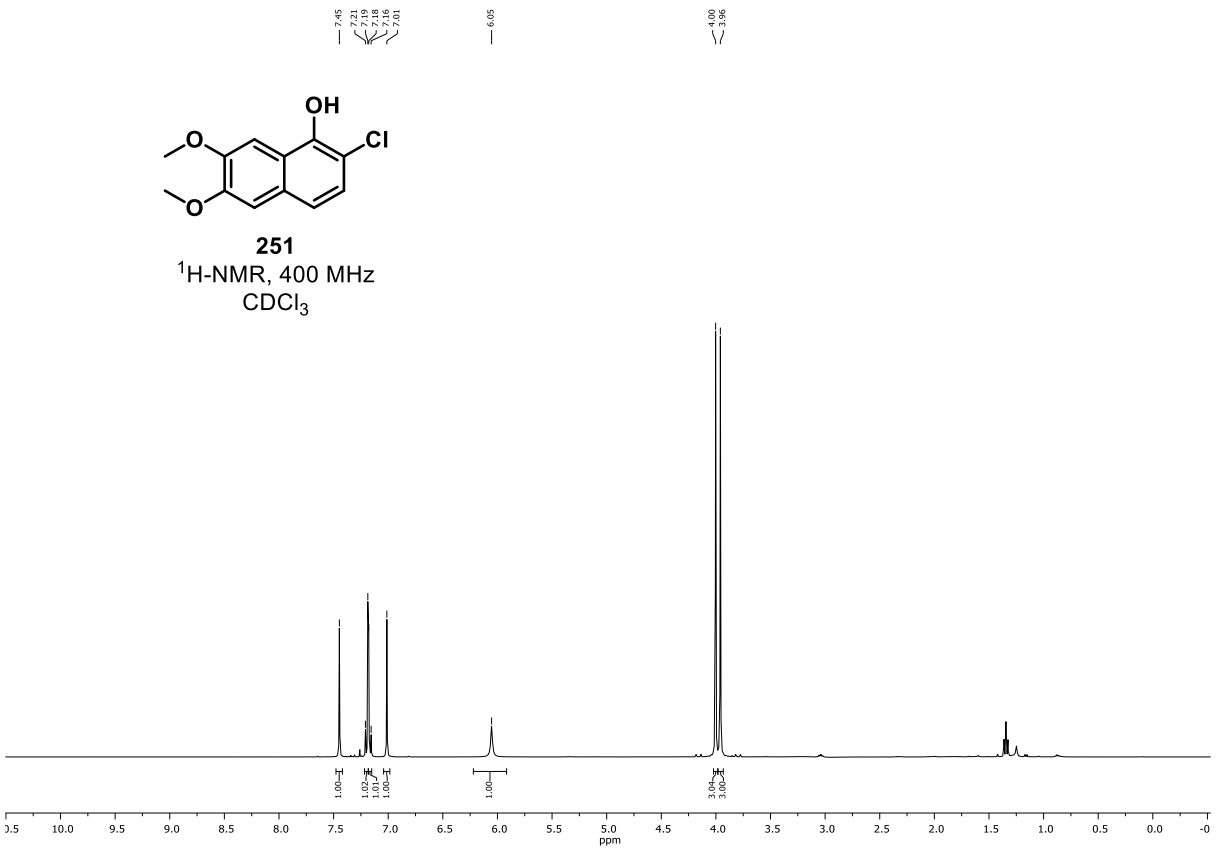
249
^{13}C-NMR, 101 MHz
$CDCl_3$



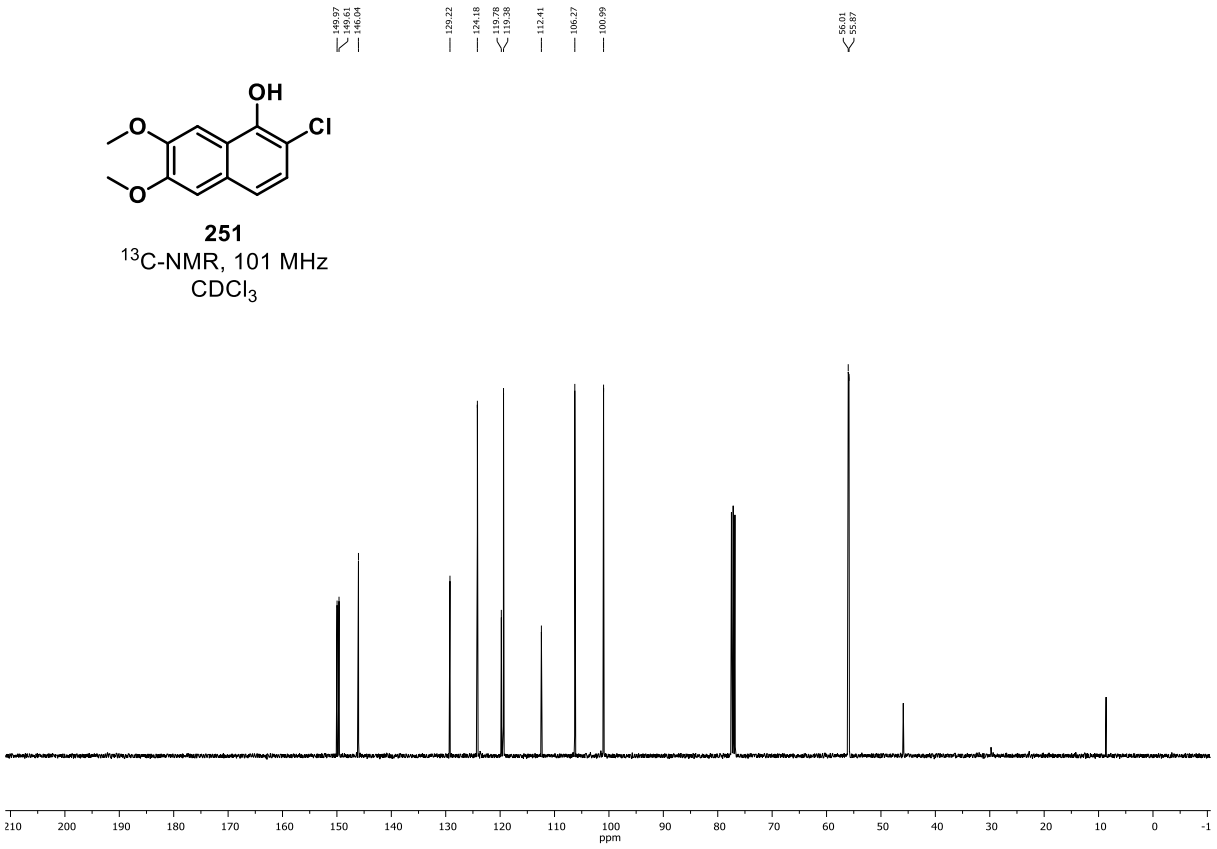
250
^{1}H-NMR, 400 MHz
$CDCl_3$



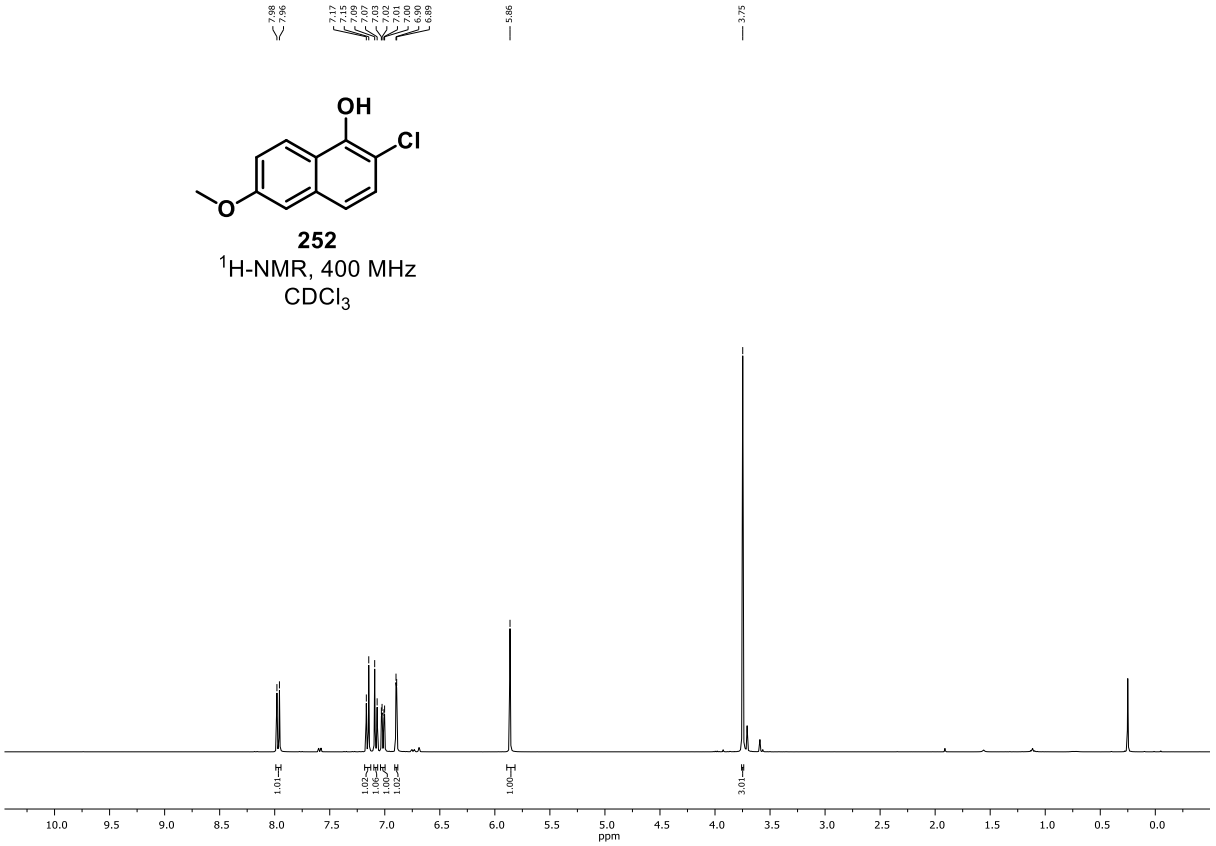
250
^{13}C-NMR, 101 MHz
$CDCl_3$



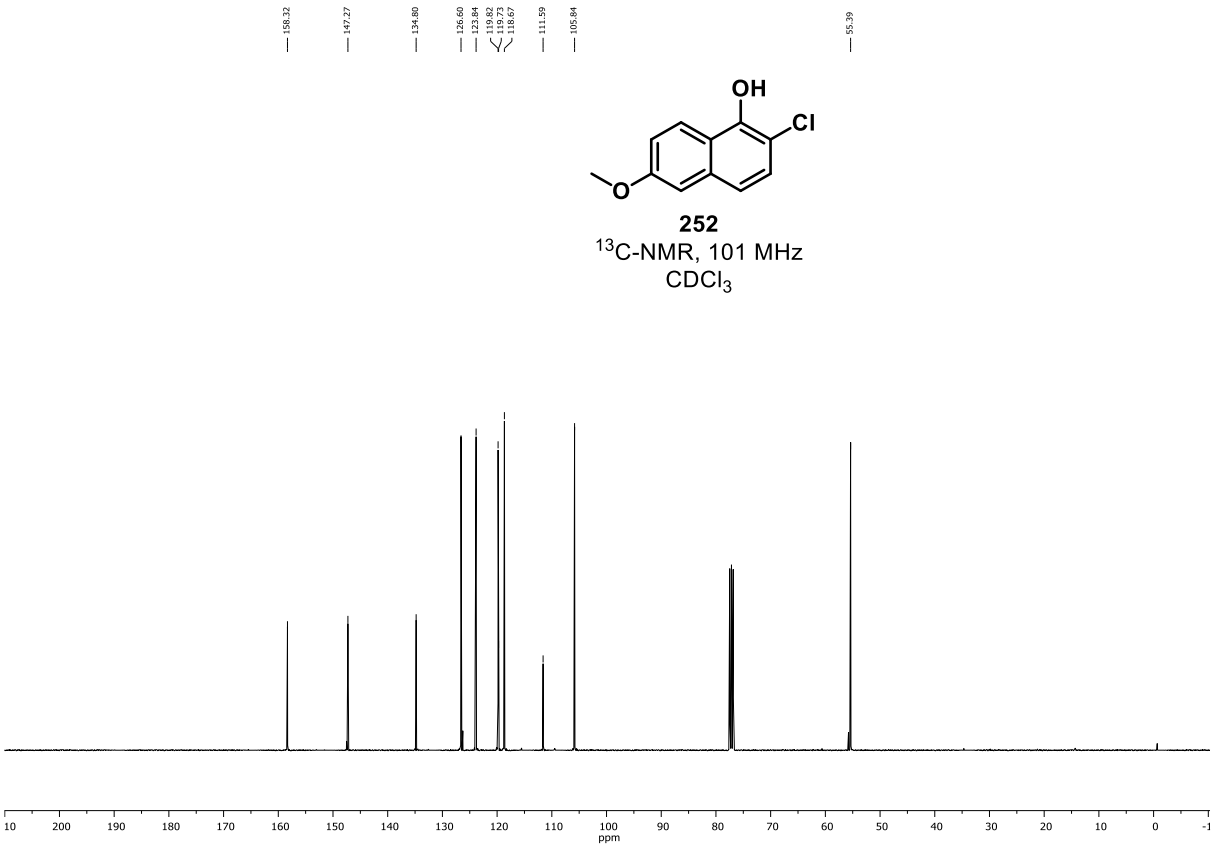
251
^{1}H-NMR, 400 MHz
$CDCl_3$



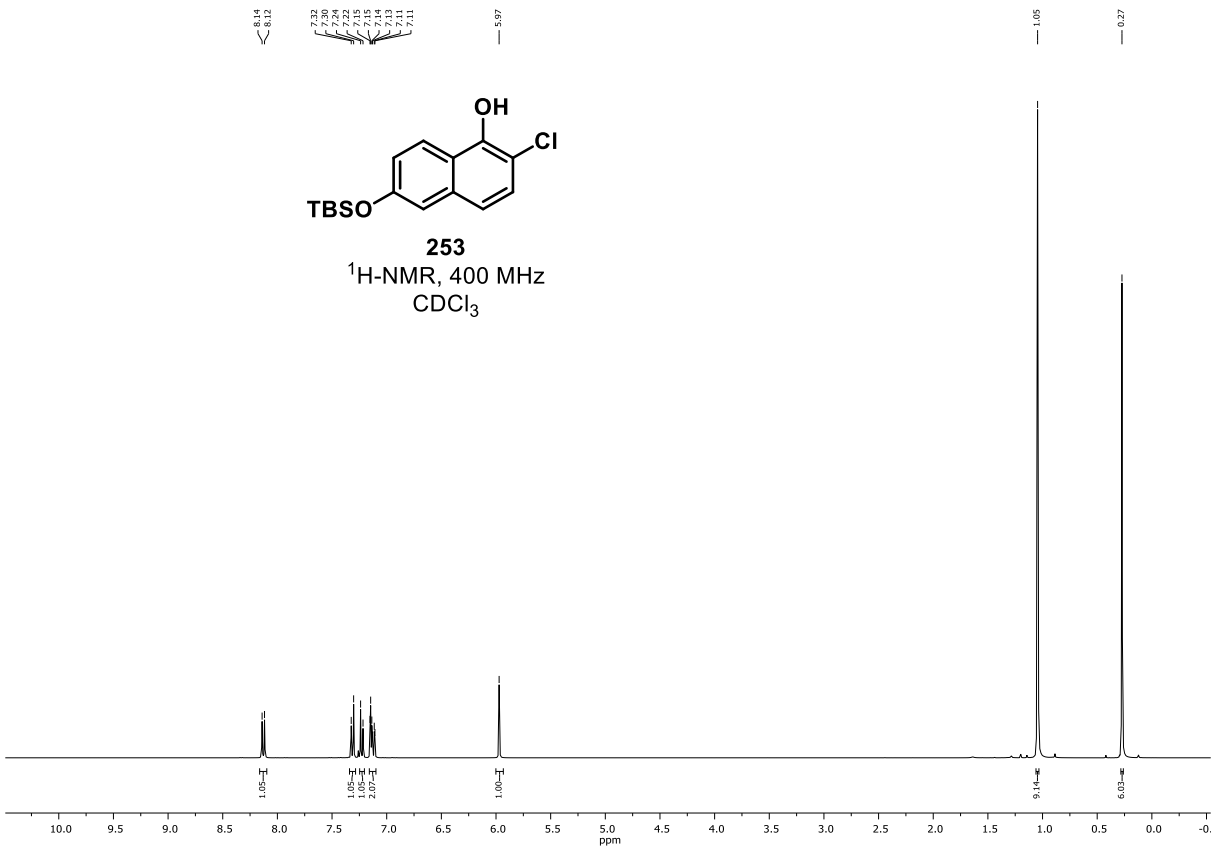
251
^{13}C-NMR, 101 MHz
$CDCl_3$

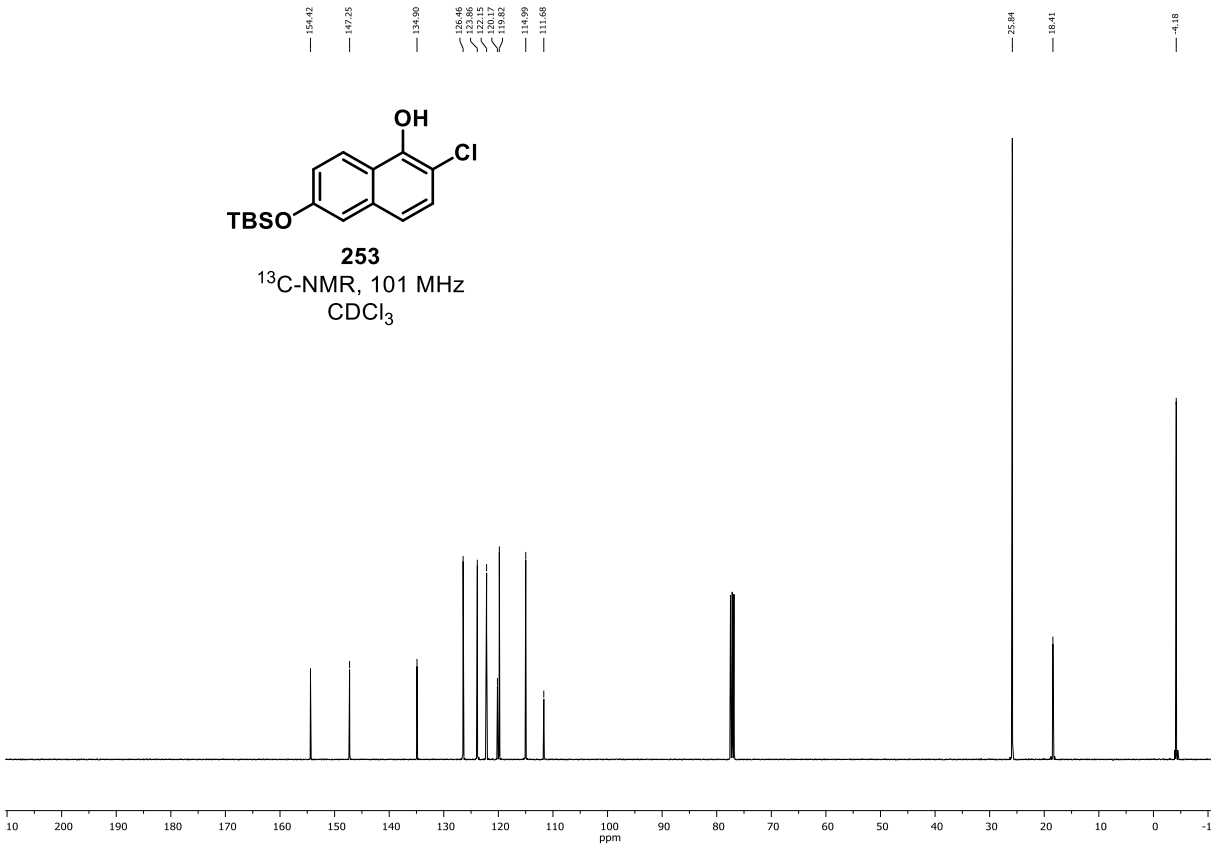


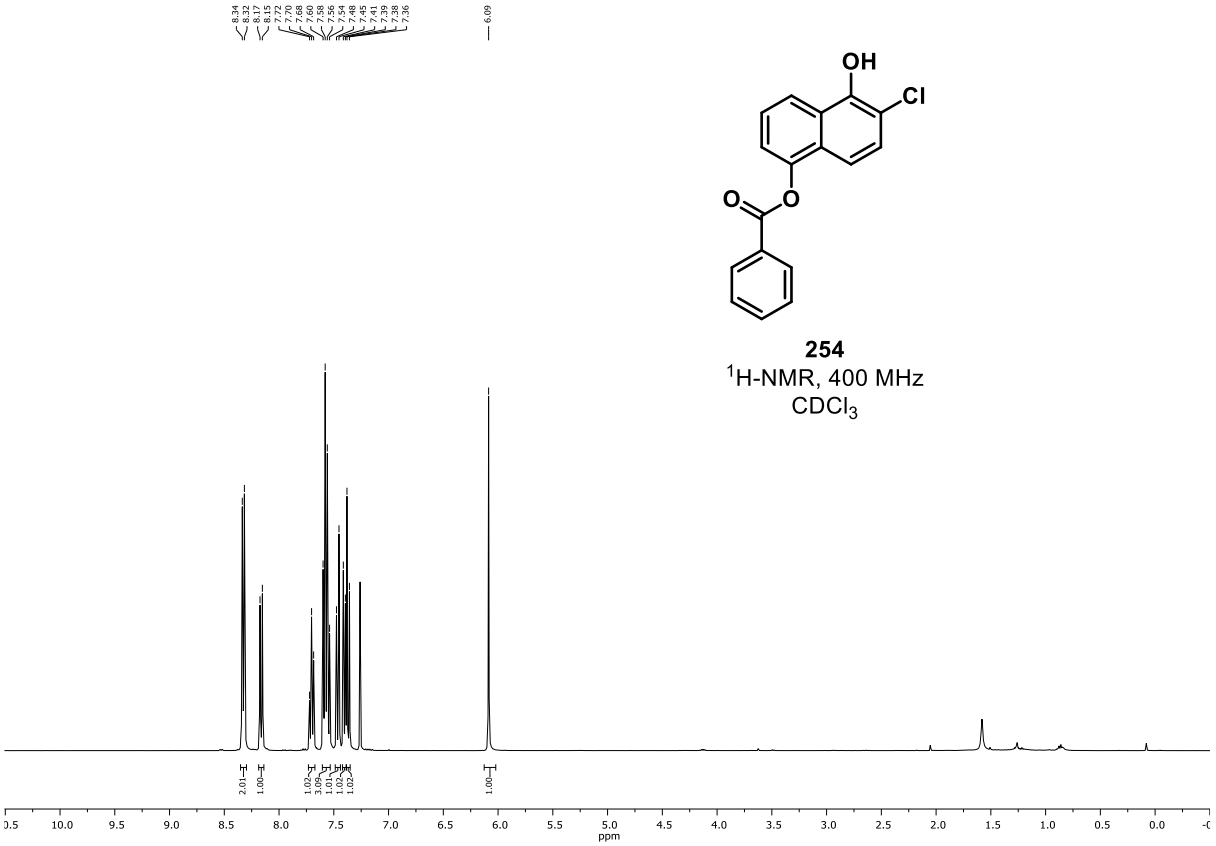
252
^{1}H-NMR, 400 MHz
$CDCl_3$



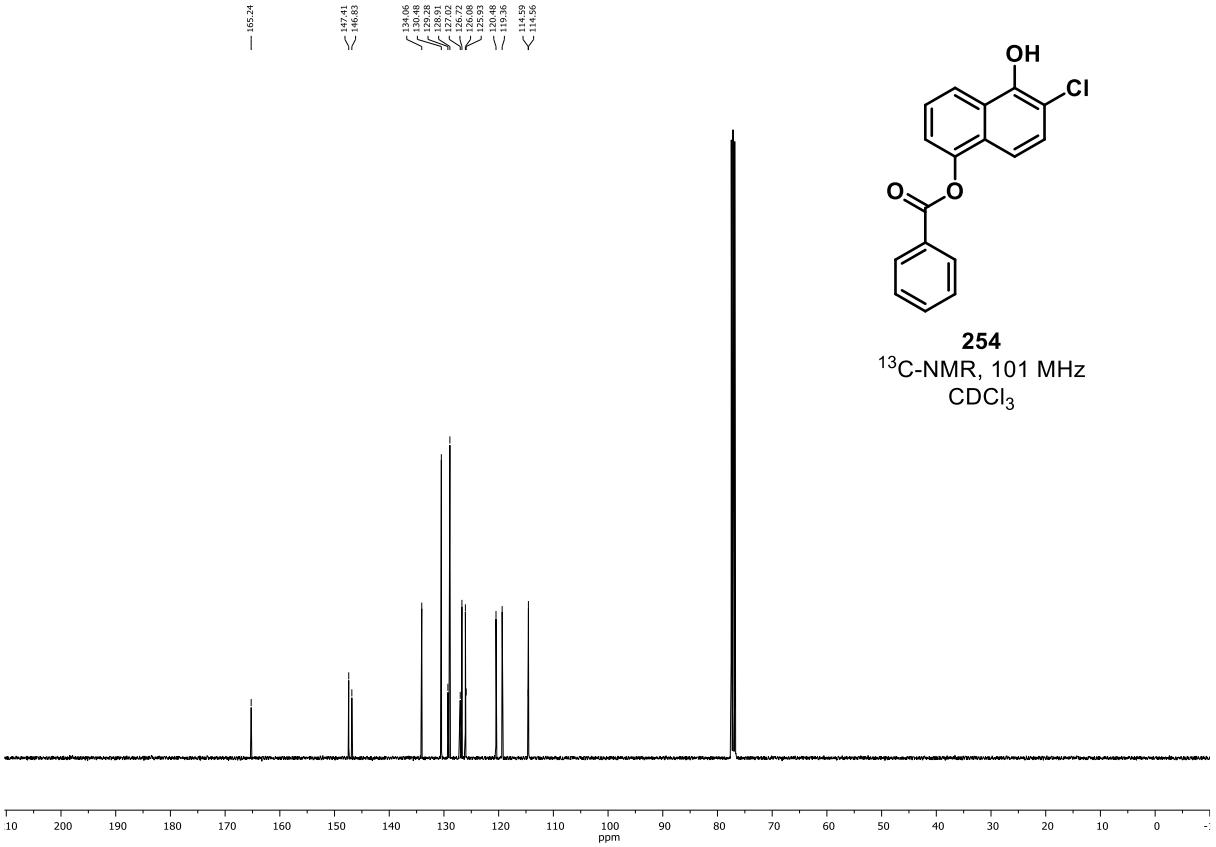
252
^{13}C-NMR, 101 MHz
$CDCl_3$


OH
Cl
TBSO
253
1H-NMR, 400 MHz
CDCl3
ppm

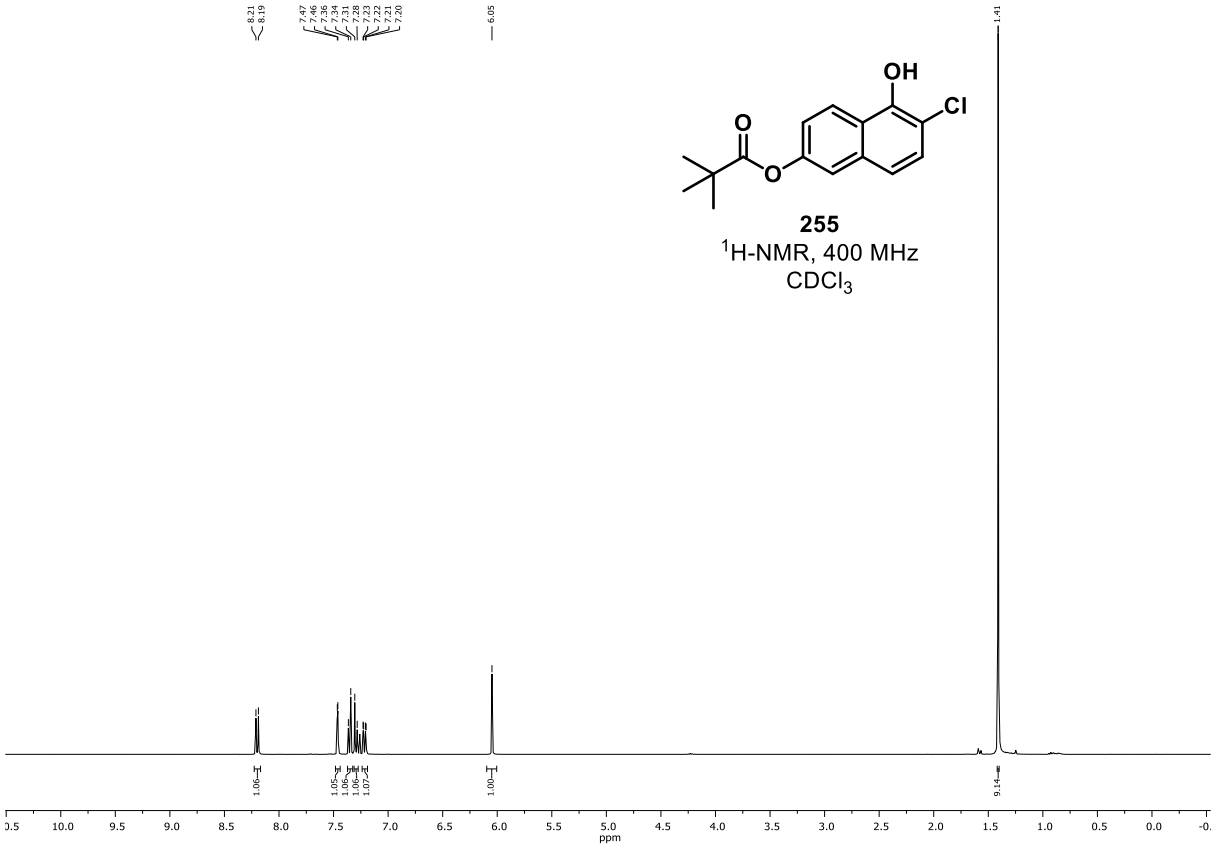

OH
Cl
TBSO
253
13C-NMR, 101 MHz
CDCl3
ppm



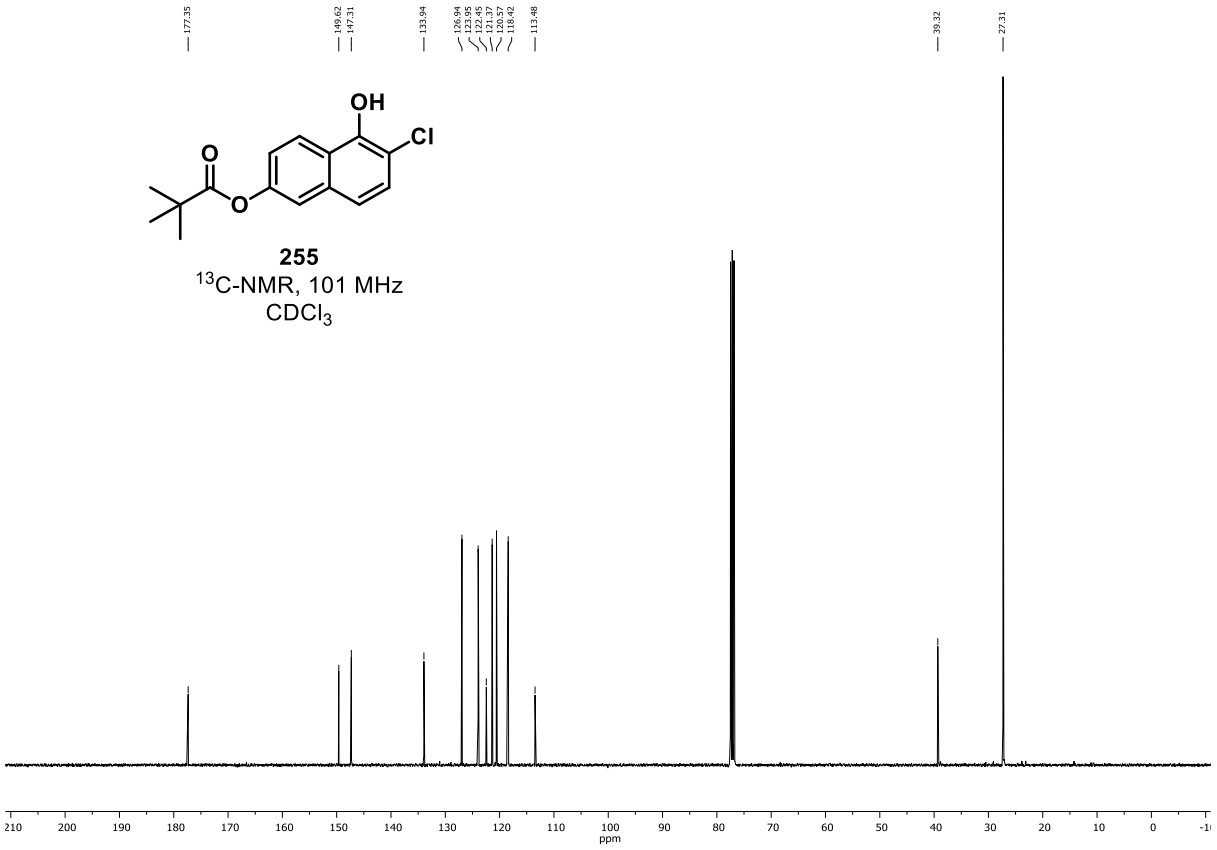
254
^{1}H-NMR, 400 MHz
$CDCl_3$



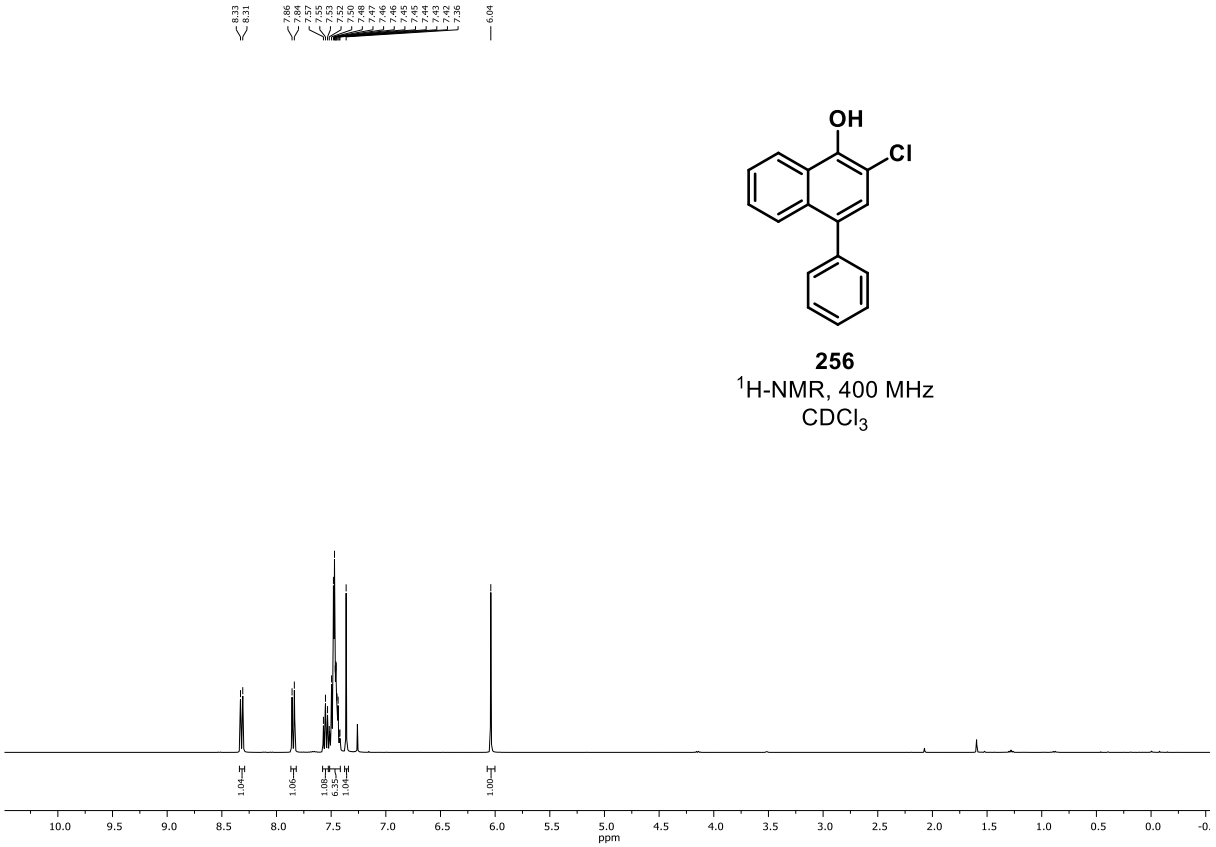
254
^{13}C-NMR, 101 MHz
$CDCl_3$



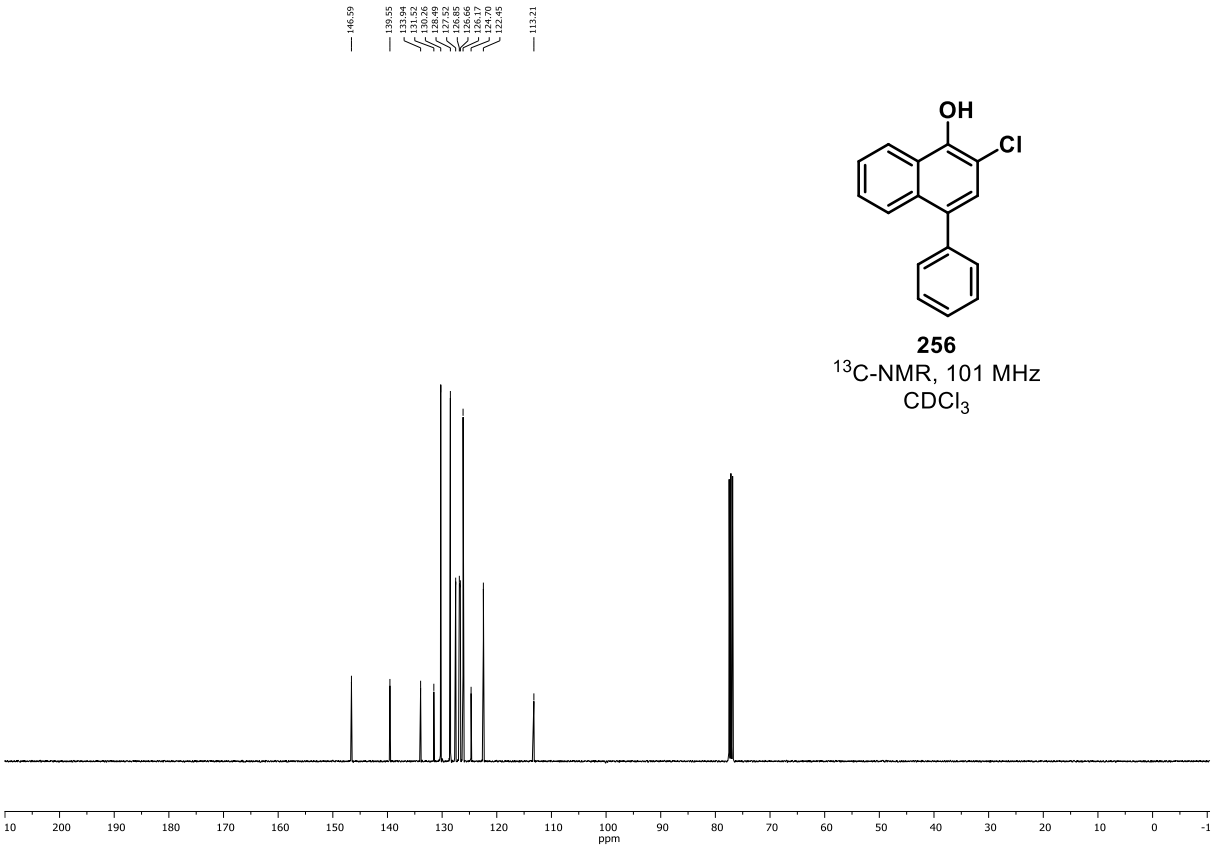
255
^{1}H-NMR, 400 MHz
$CDCl_3$



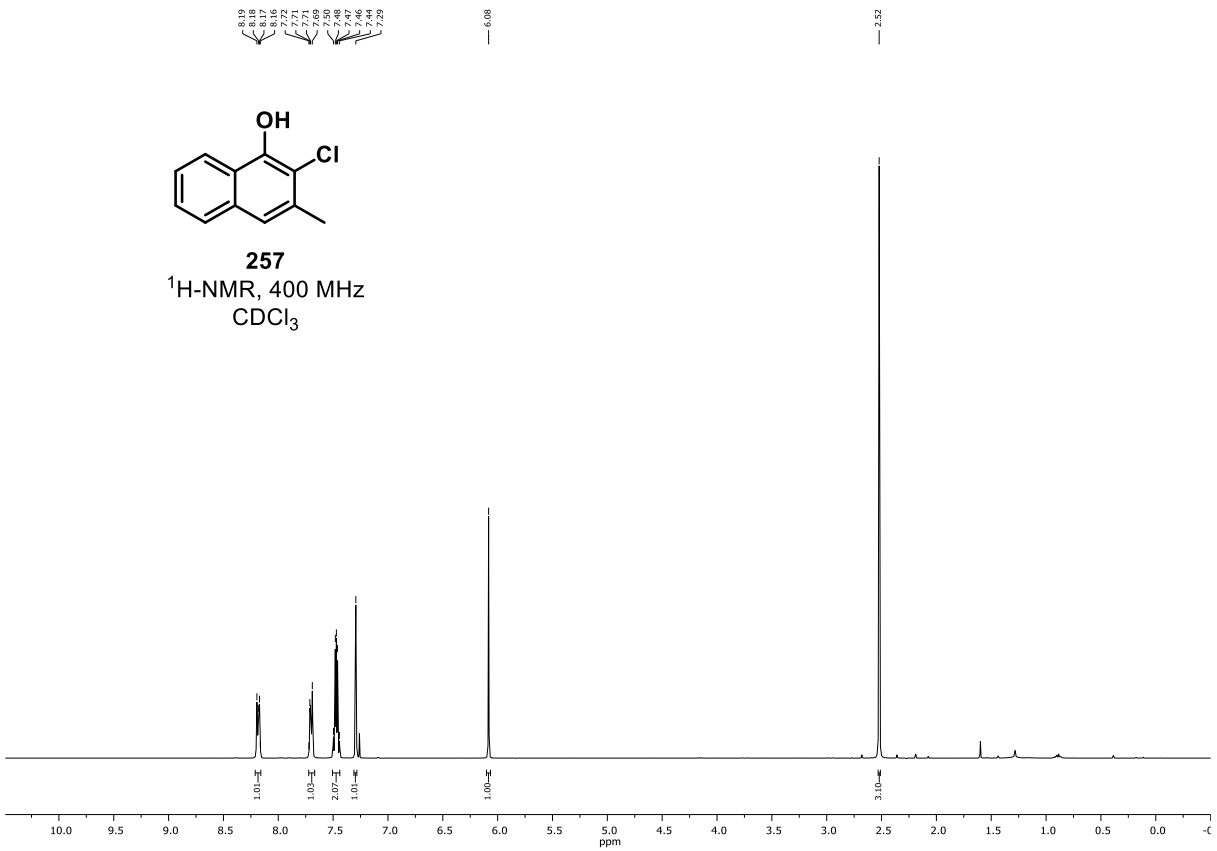
255
^{13}C-NMR, 101 MHz
$CDCl_3$



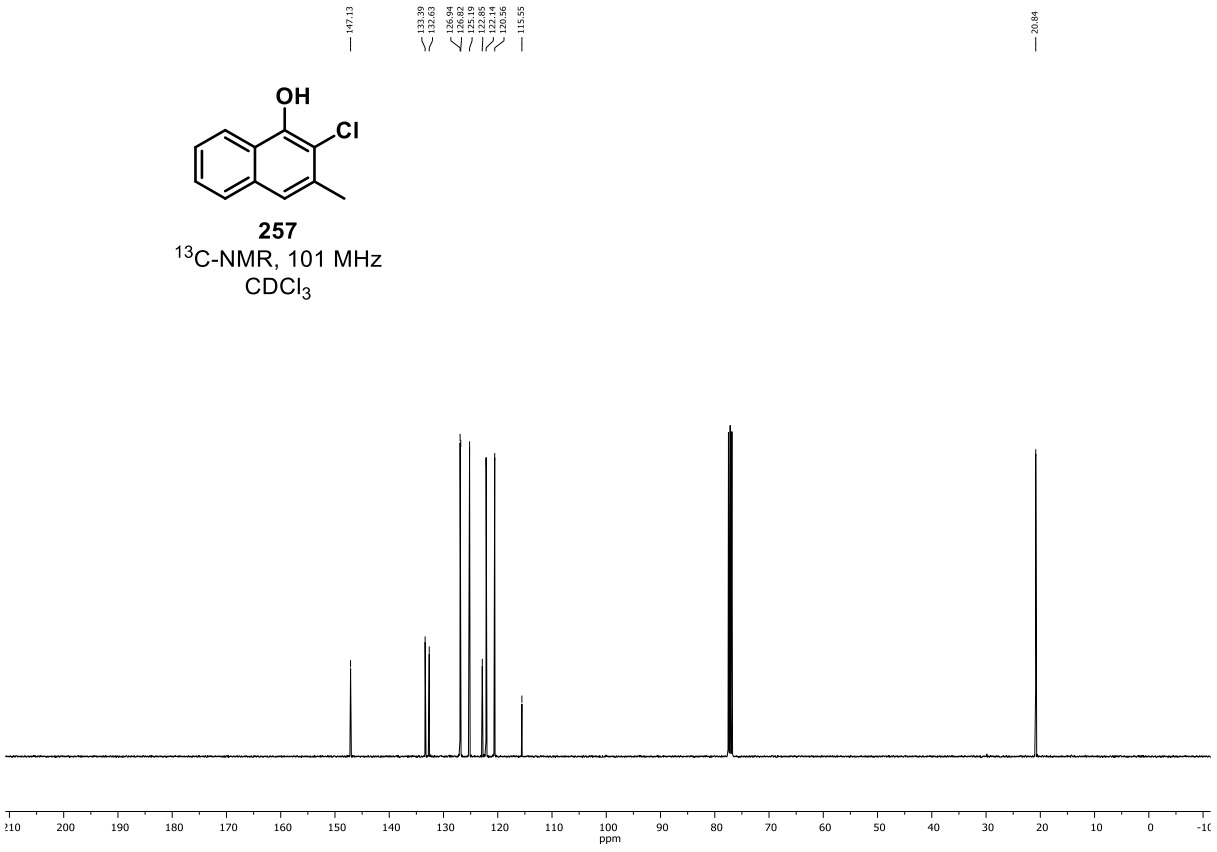
256
^{1}H-NMR, 400 MHz
$CDCl_3$



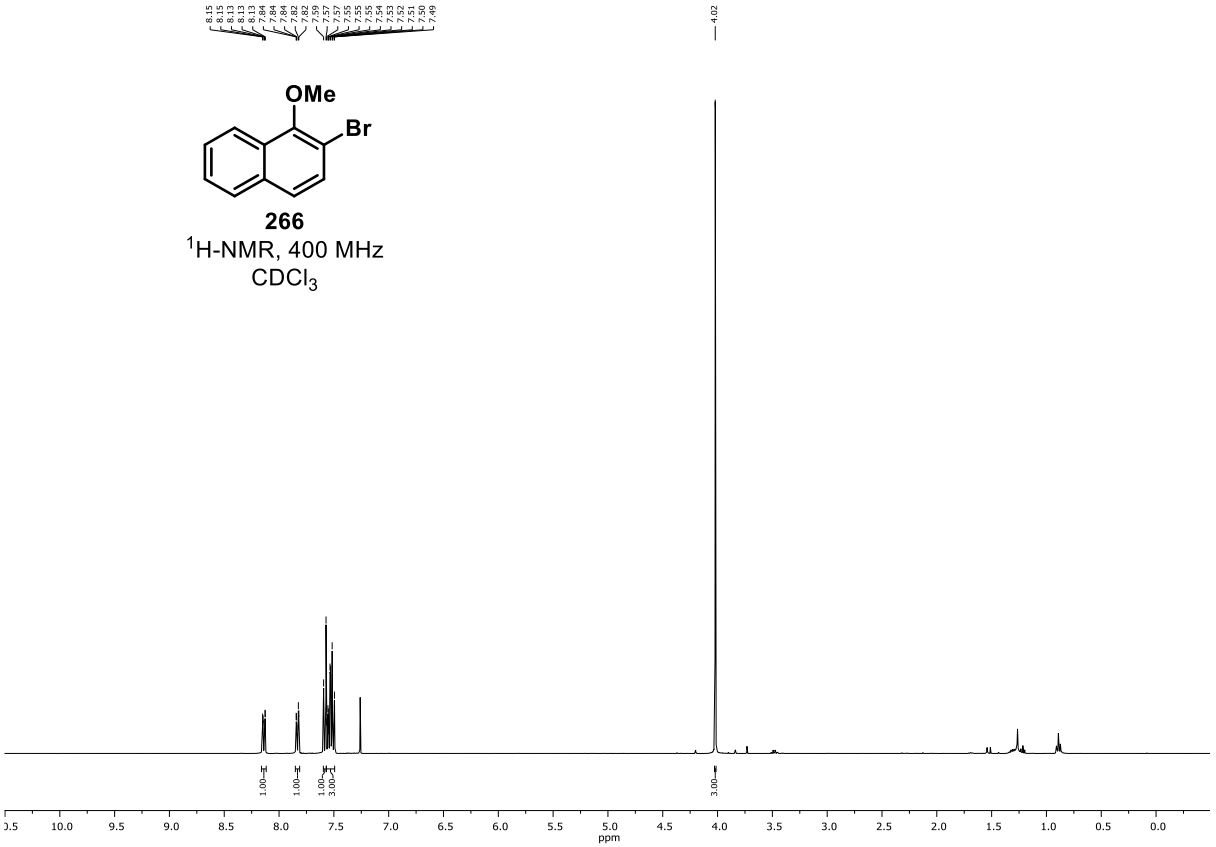
256
^{13}C-NMR, 101 MHz
$CDCl_3$



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



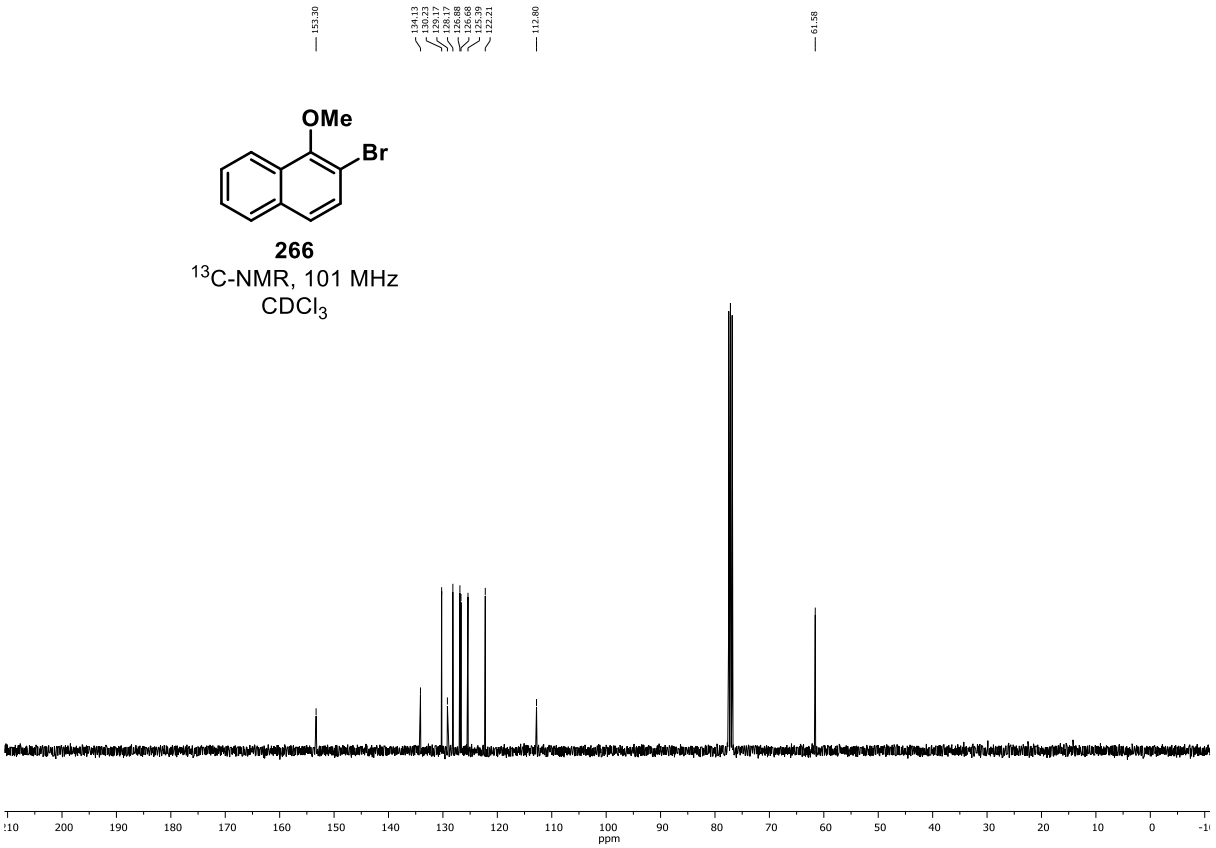
257
^{13}C-NMR, 101 MHz
$CDCl_3$



266

^{1}H-NMR, 400 MHz

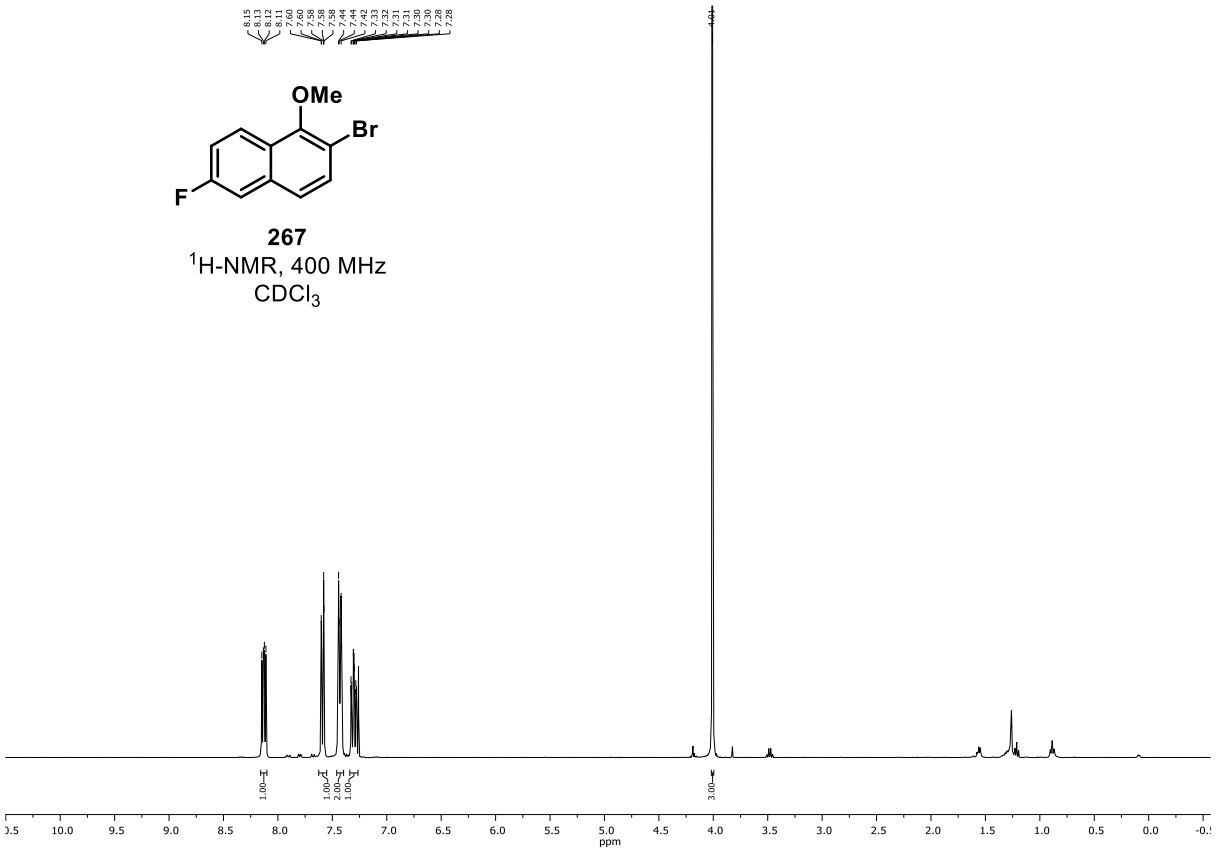
$CDCl_3$



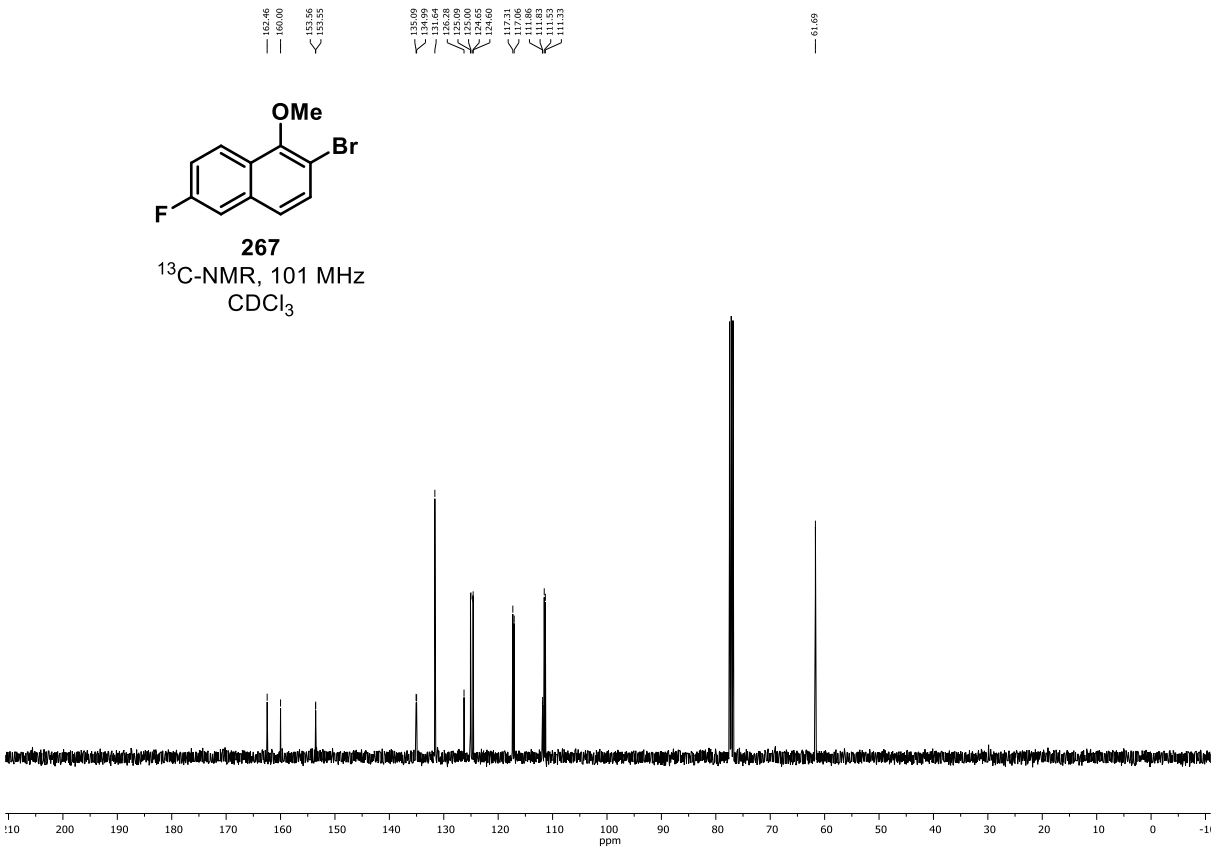
266

^{13}C-NMR, 101 MHz

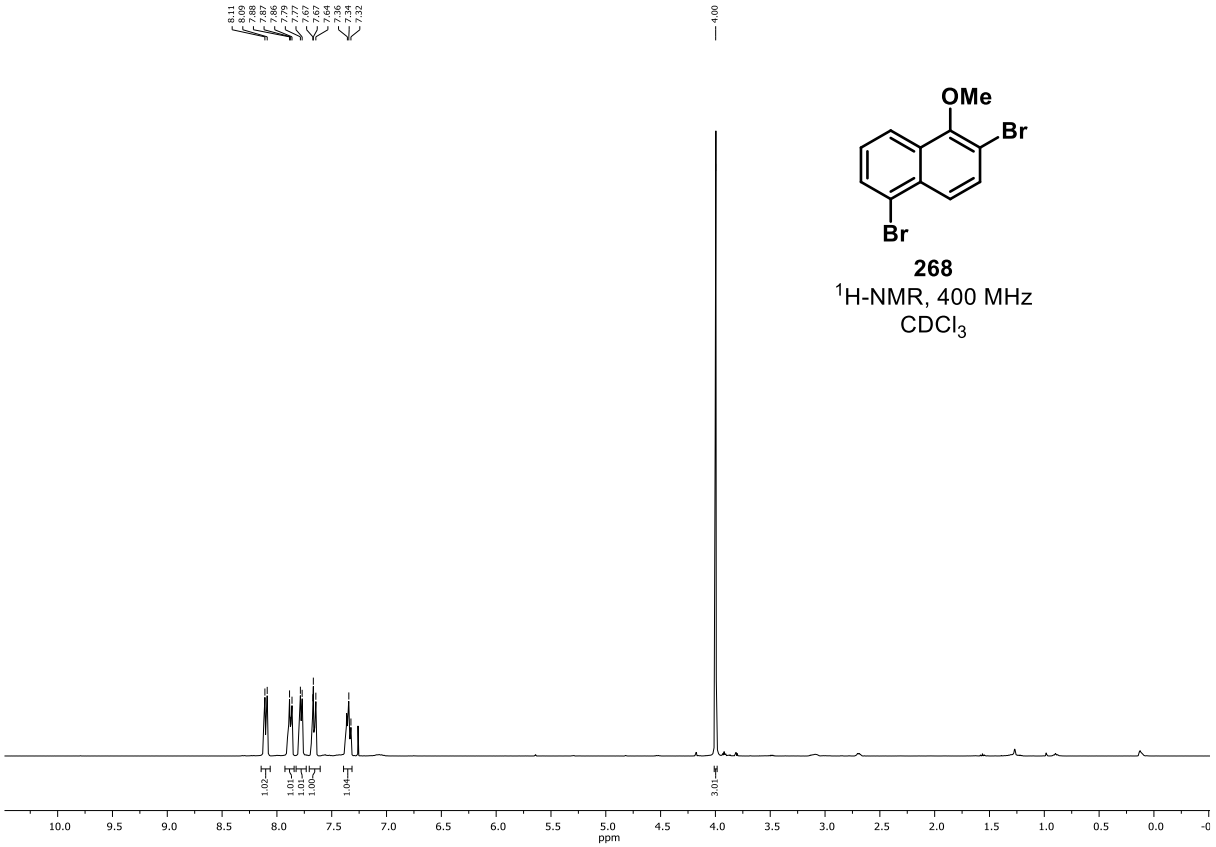
$CDCl_3$



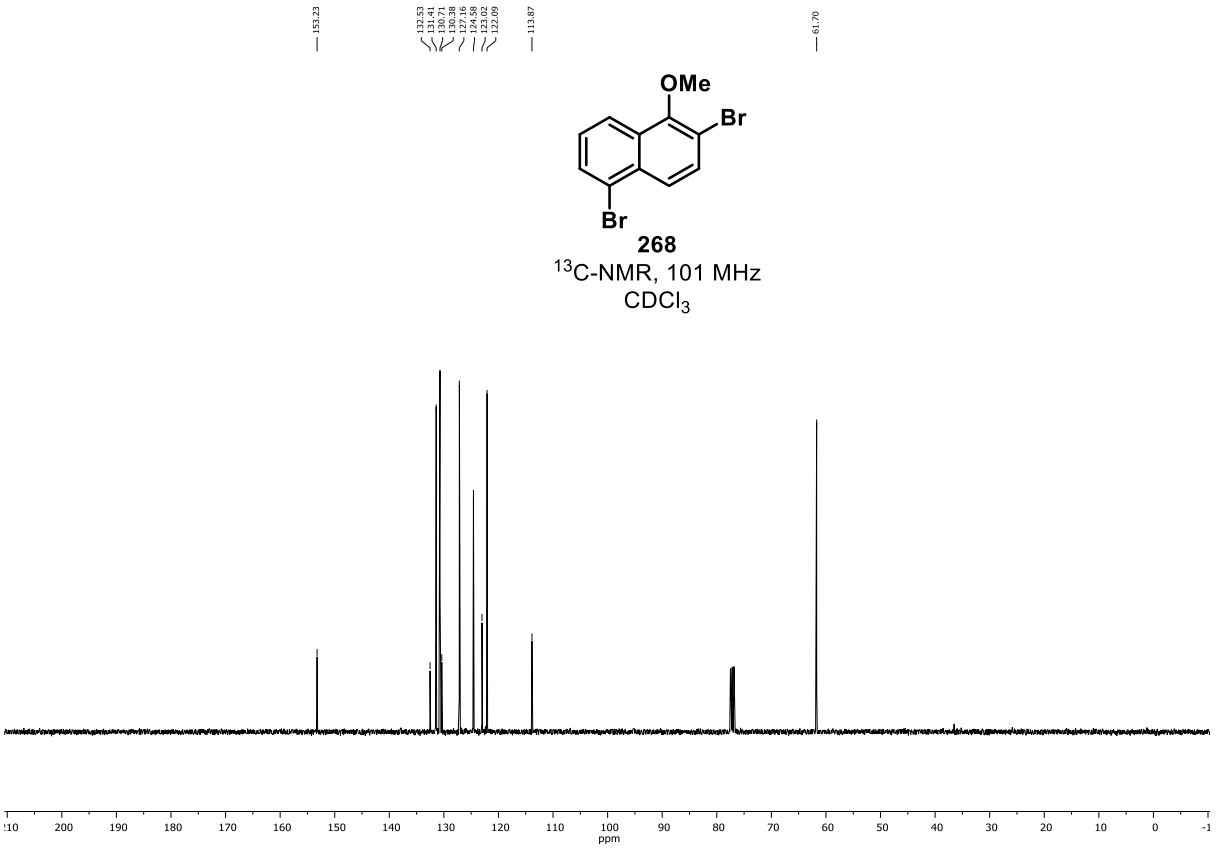
267
^{1}H-NMR, 400 MHz
$CDCl_3$



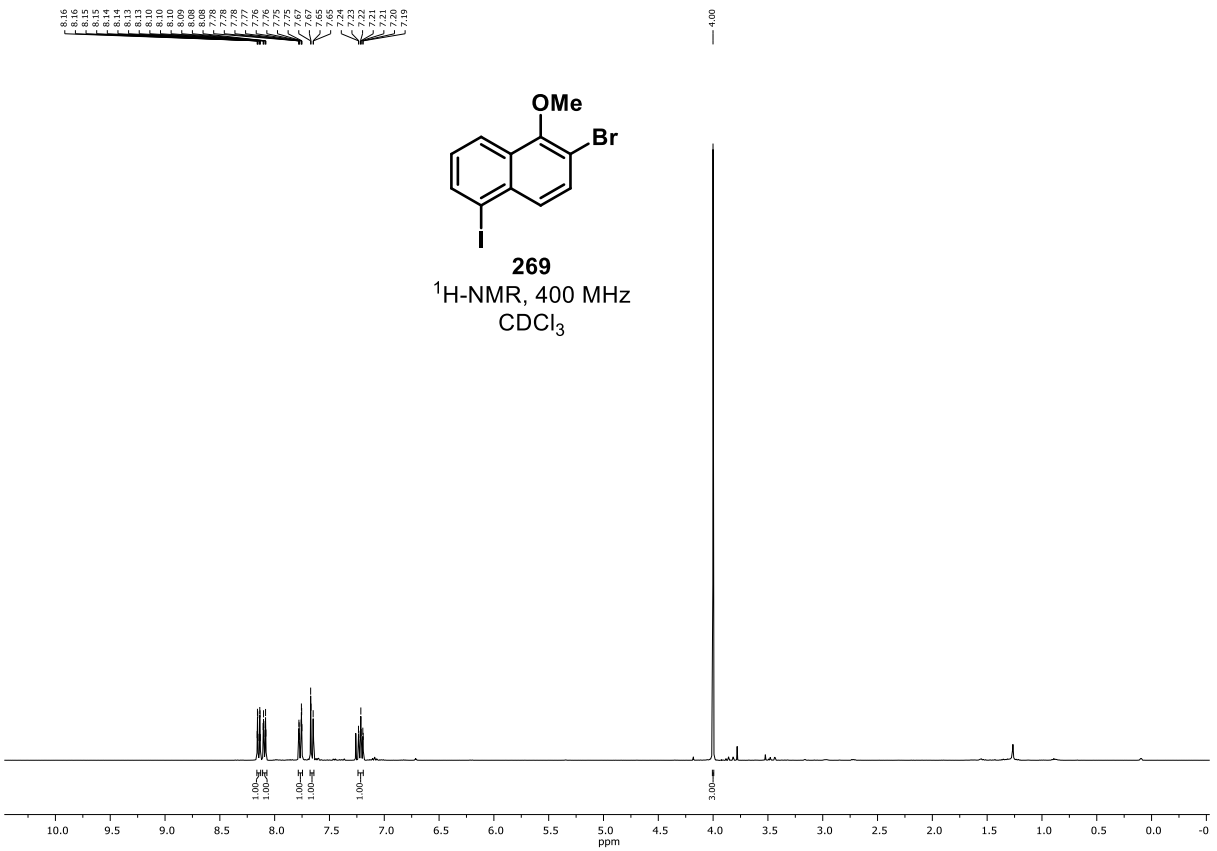
267
^{13}C-NMR, 101 MHz
$CDCl_3$

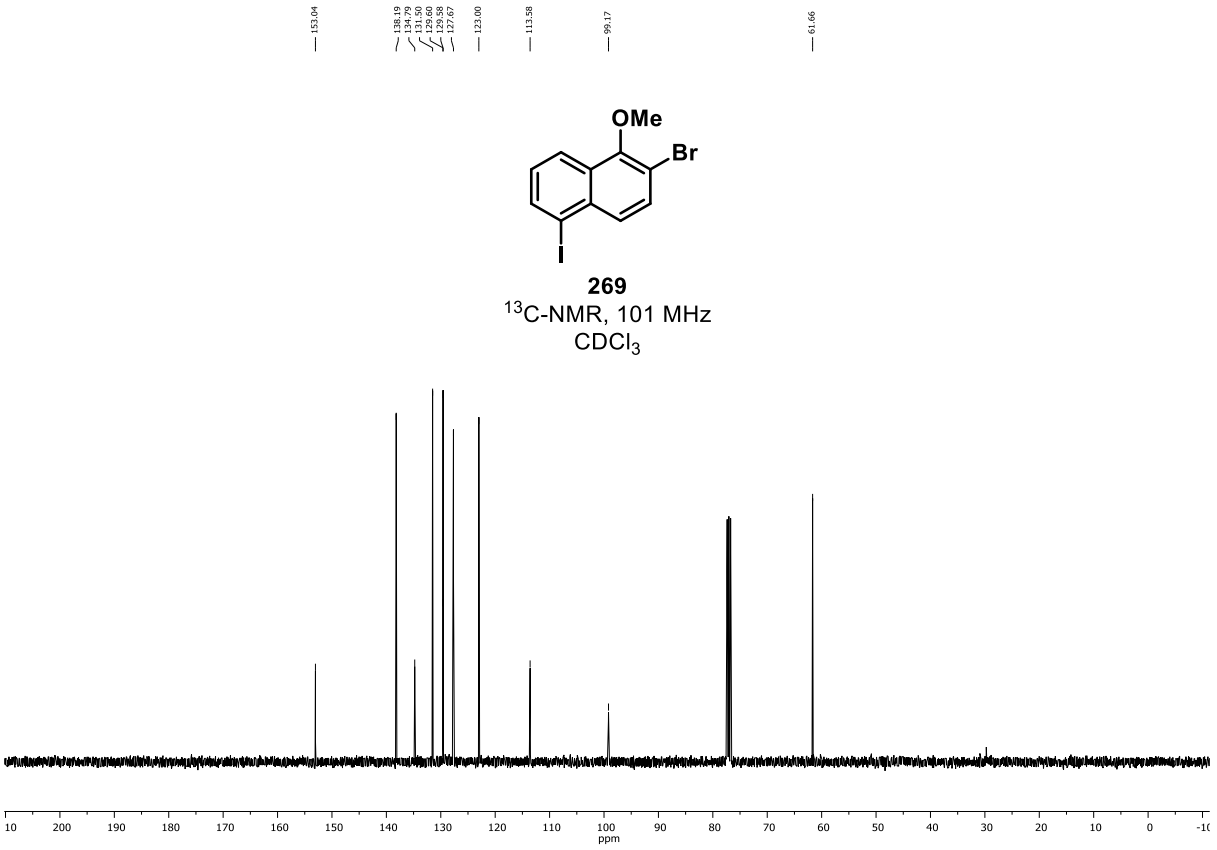


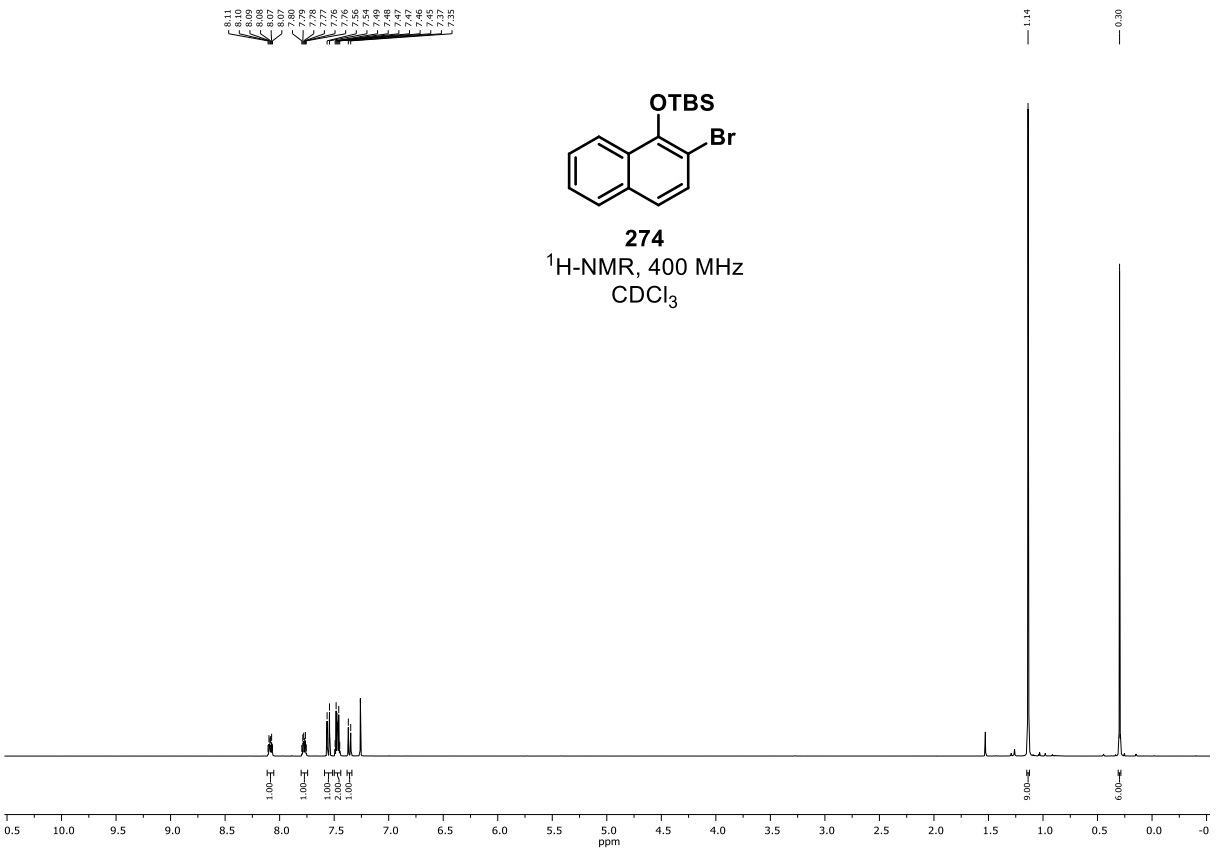
268
^{1}H-NMR, 400 MHz
$CDCl_3$

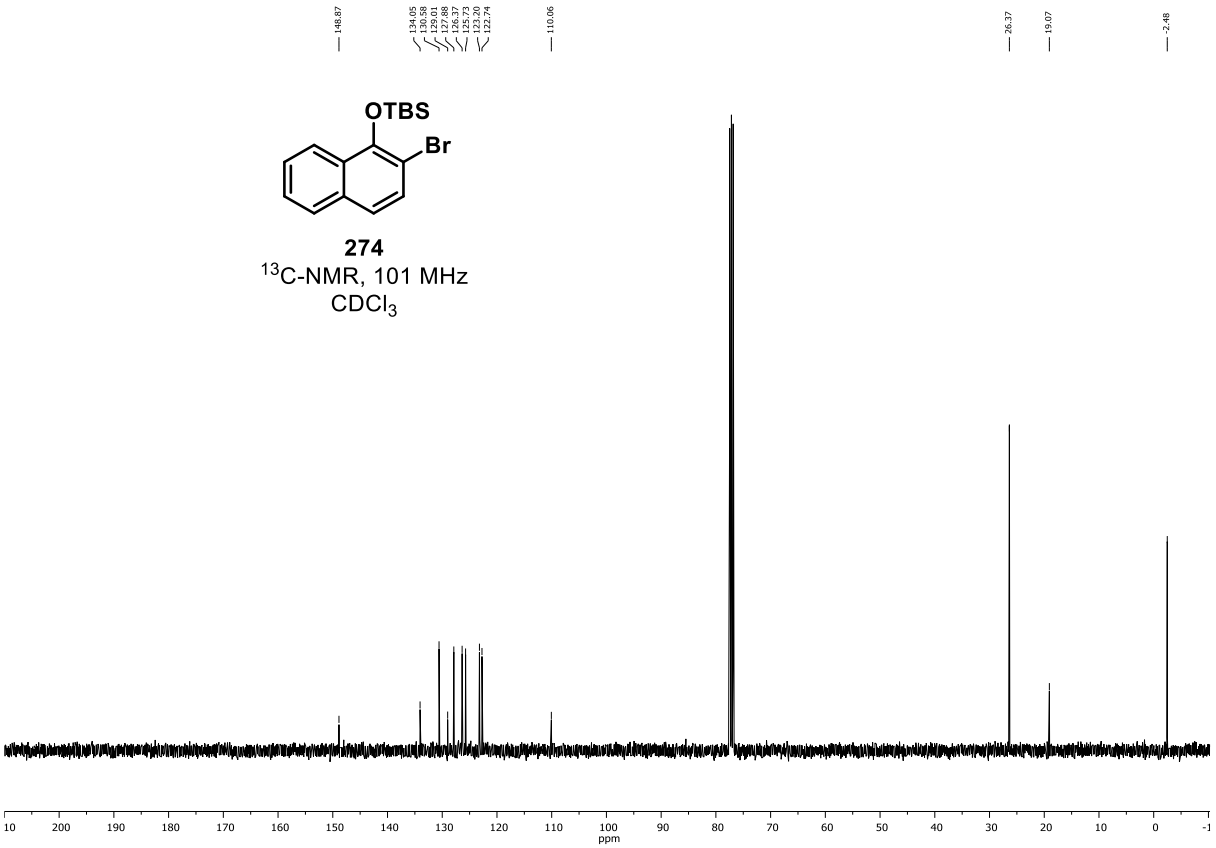


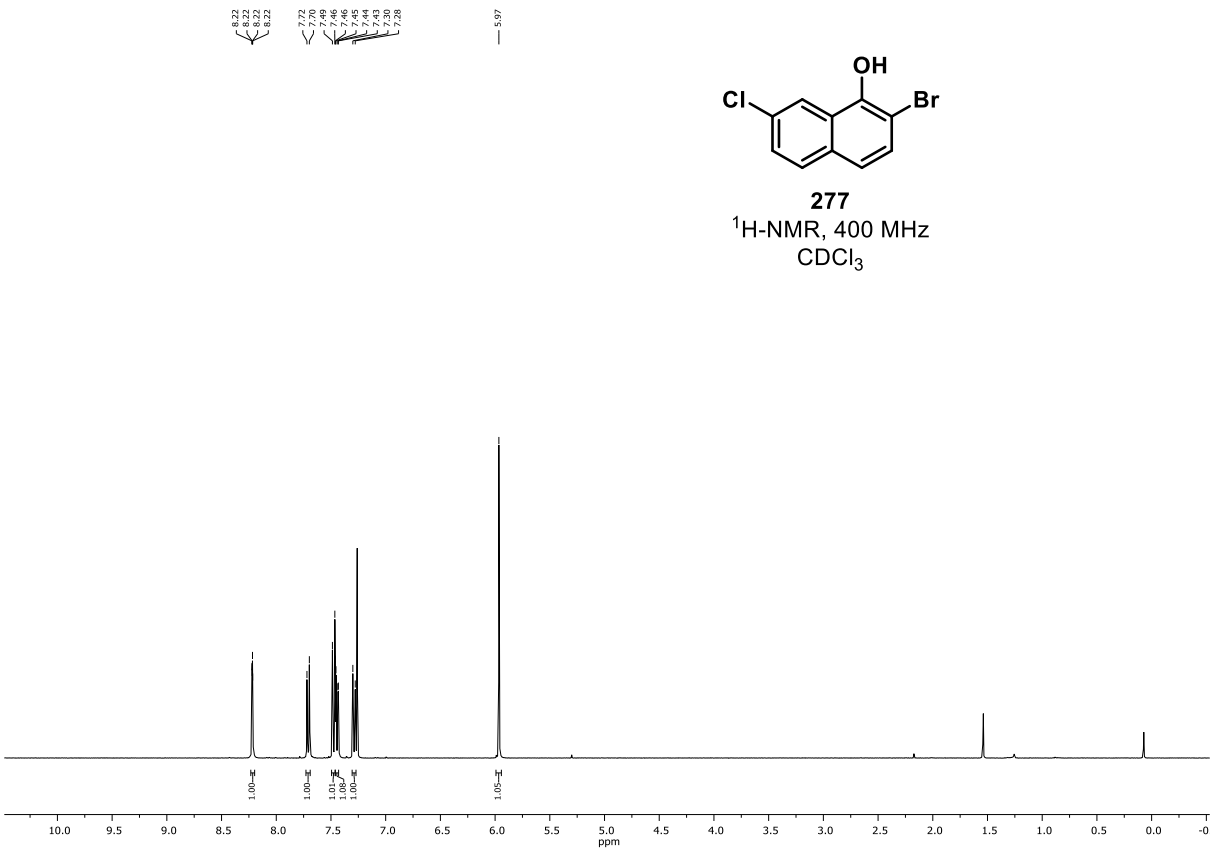
268
^{13}C-NMR, 101 MHz
$CDCl_3$


OMe
Br
269
1H-NMR, 400 MHz
CDCl3
ppm

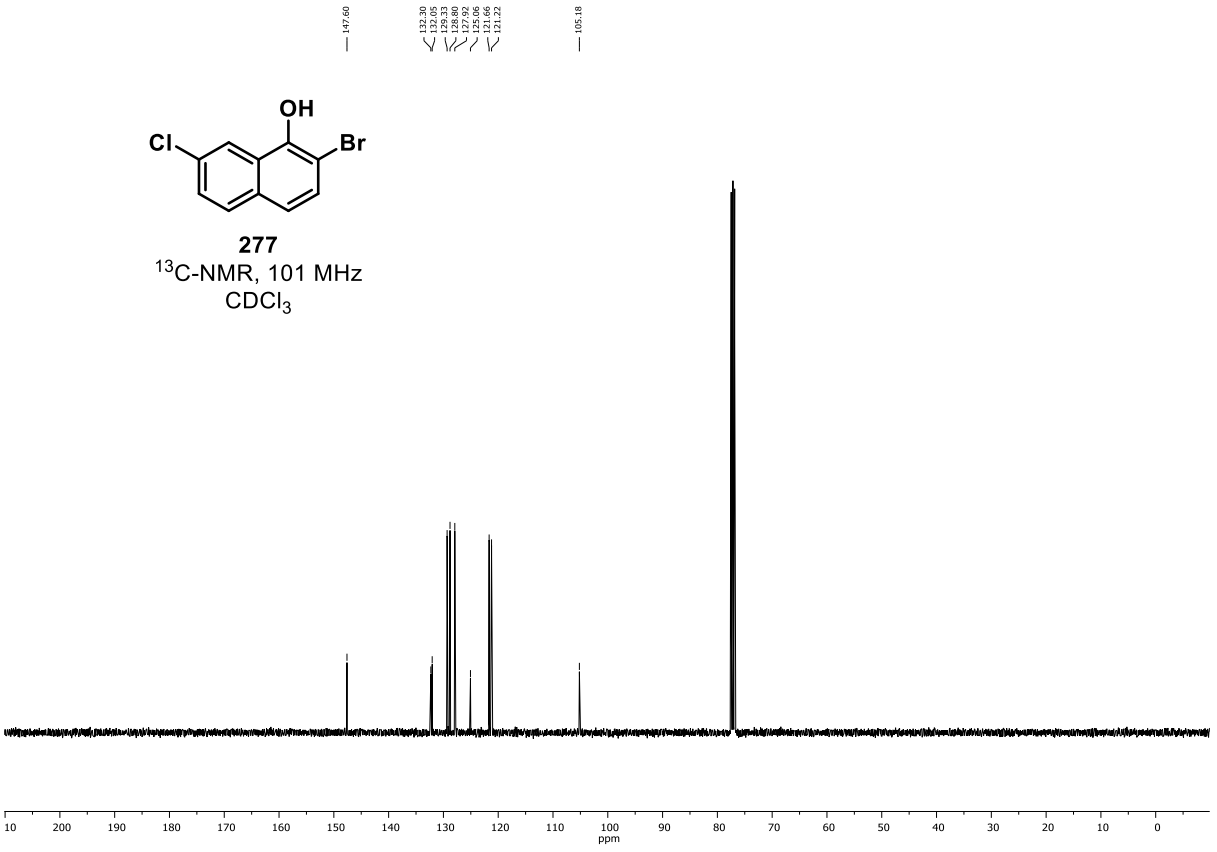

OMe
Br
269
13C-NMR, 101 MHz
CDCl3
ppm


OTBS
Br
274
1H-NMR, 400 MHz
CDCl3
ppm

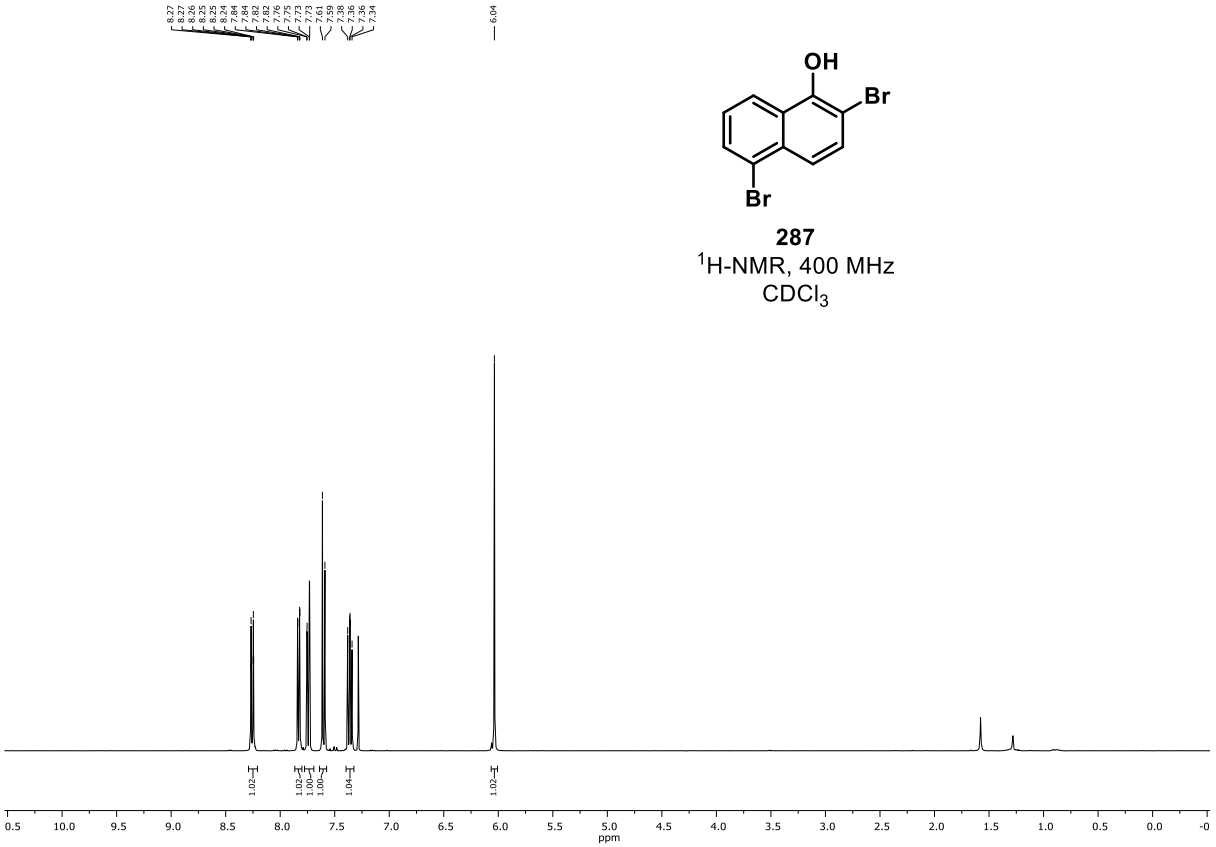

OTBS
Br
274
13C-NMR, 101 MHz
CDCl3
ppm



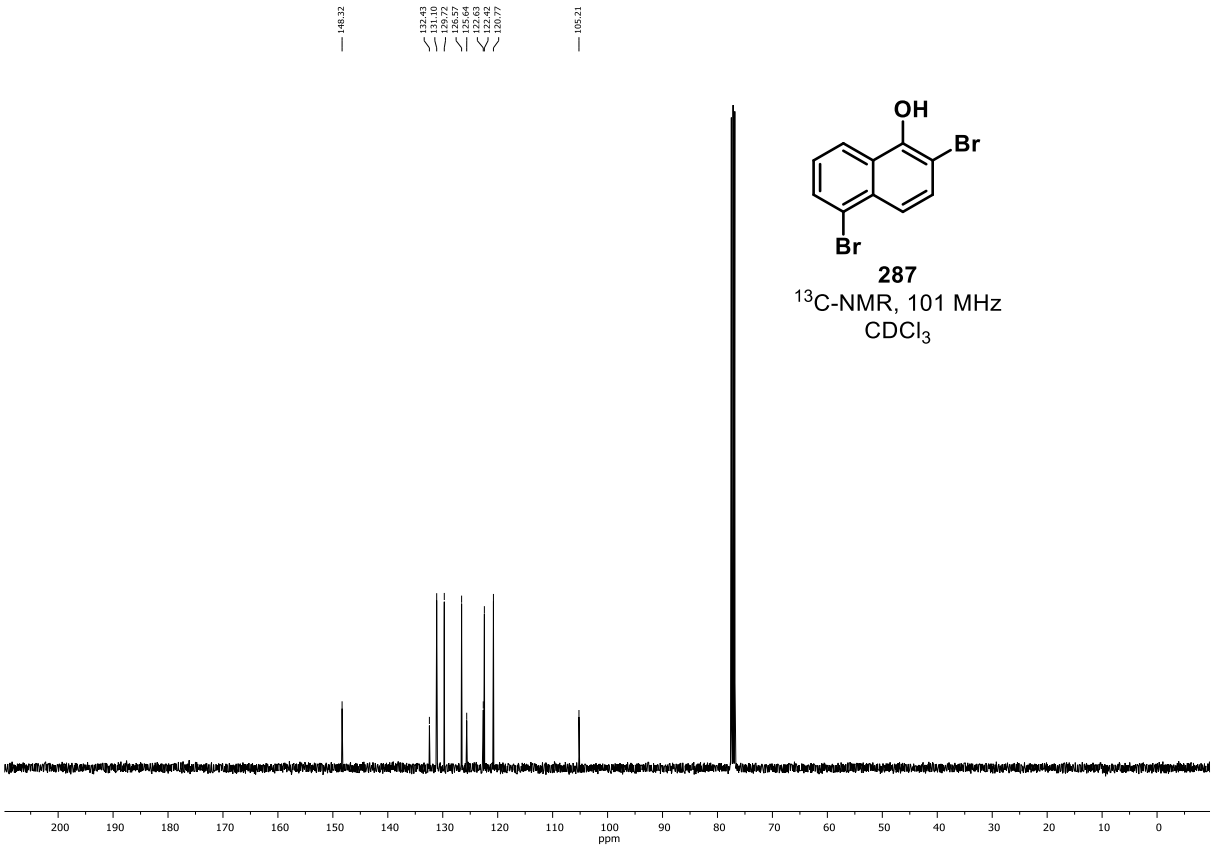
277
^{1}H-NMR, 400 MHz
$CDCl_3$



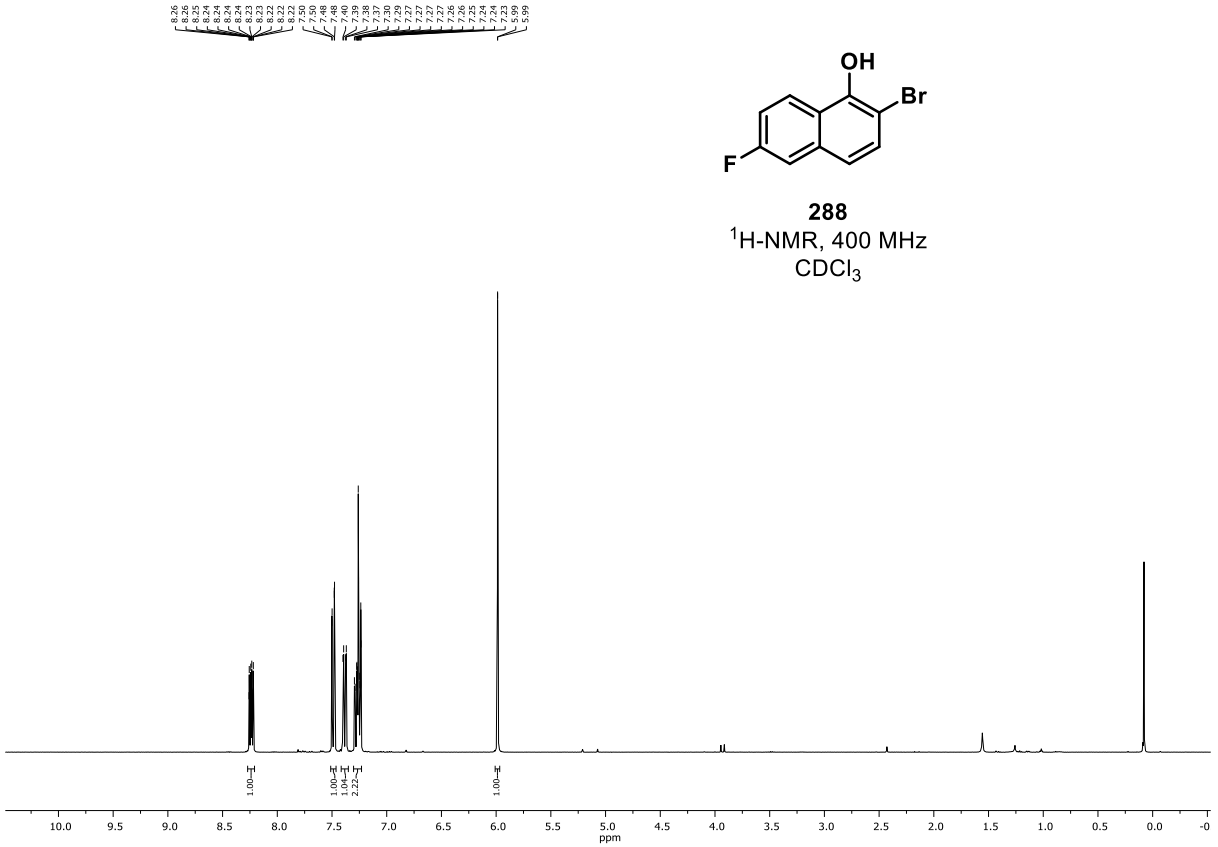
277
^{13}C-NMR, 101 MHz
$CDCl_3$

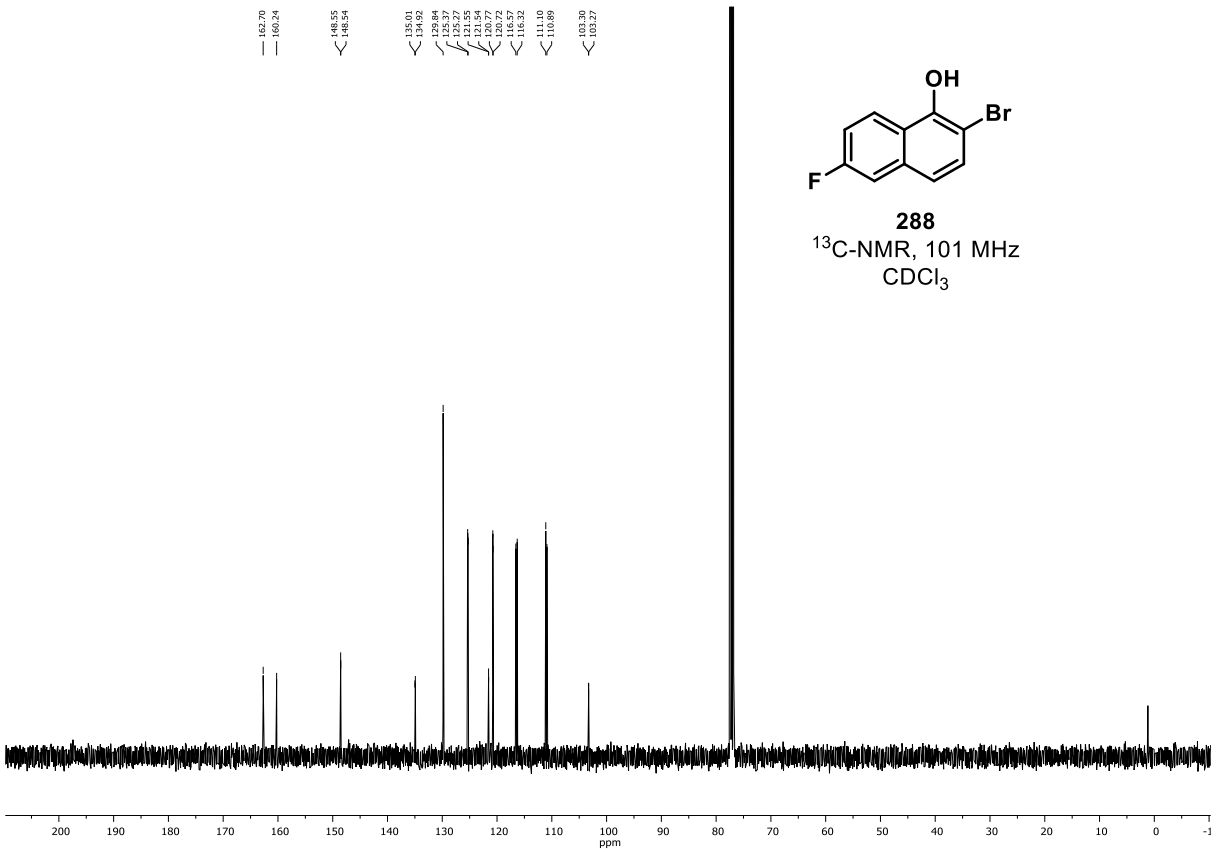


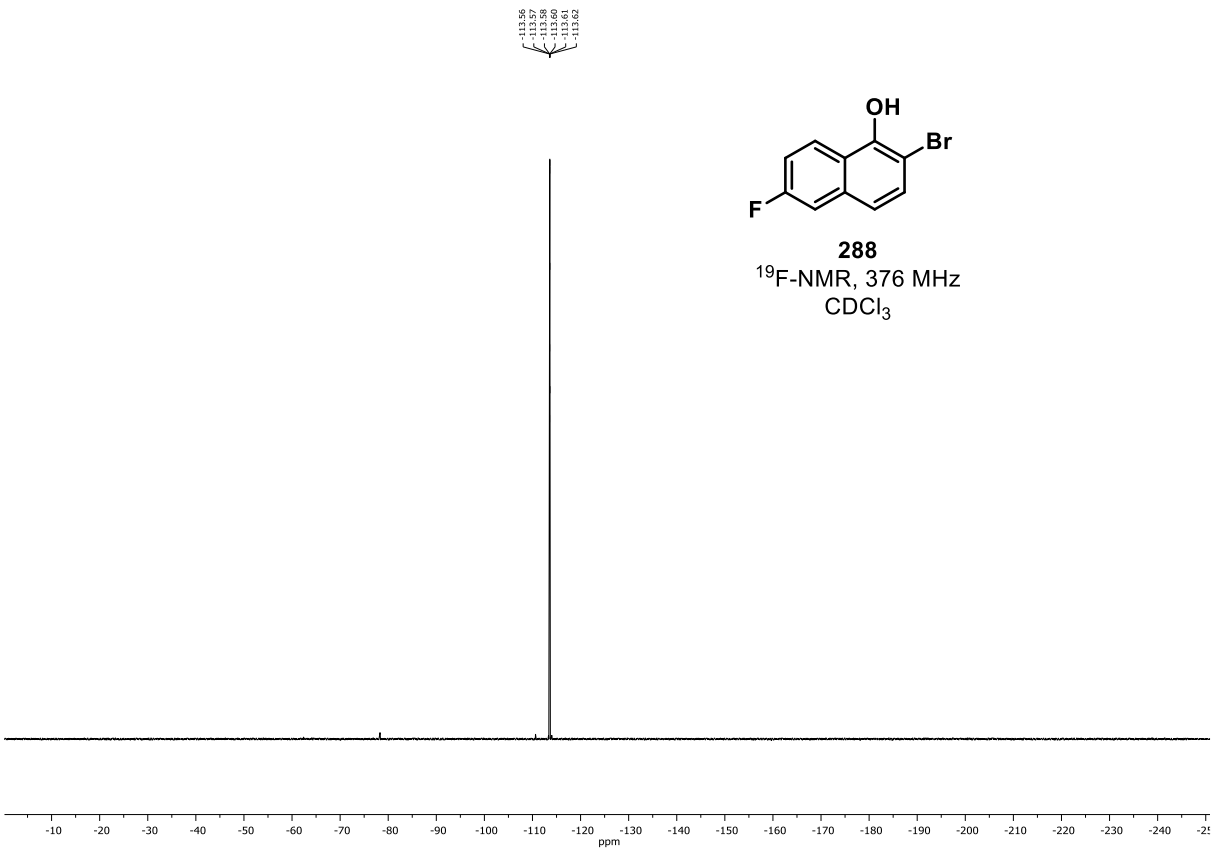
287
^{1}H-NMR, 400 MHz
$CDCl_3$

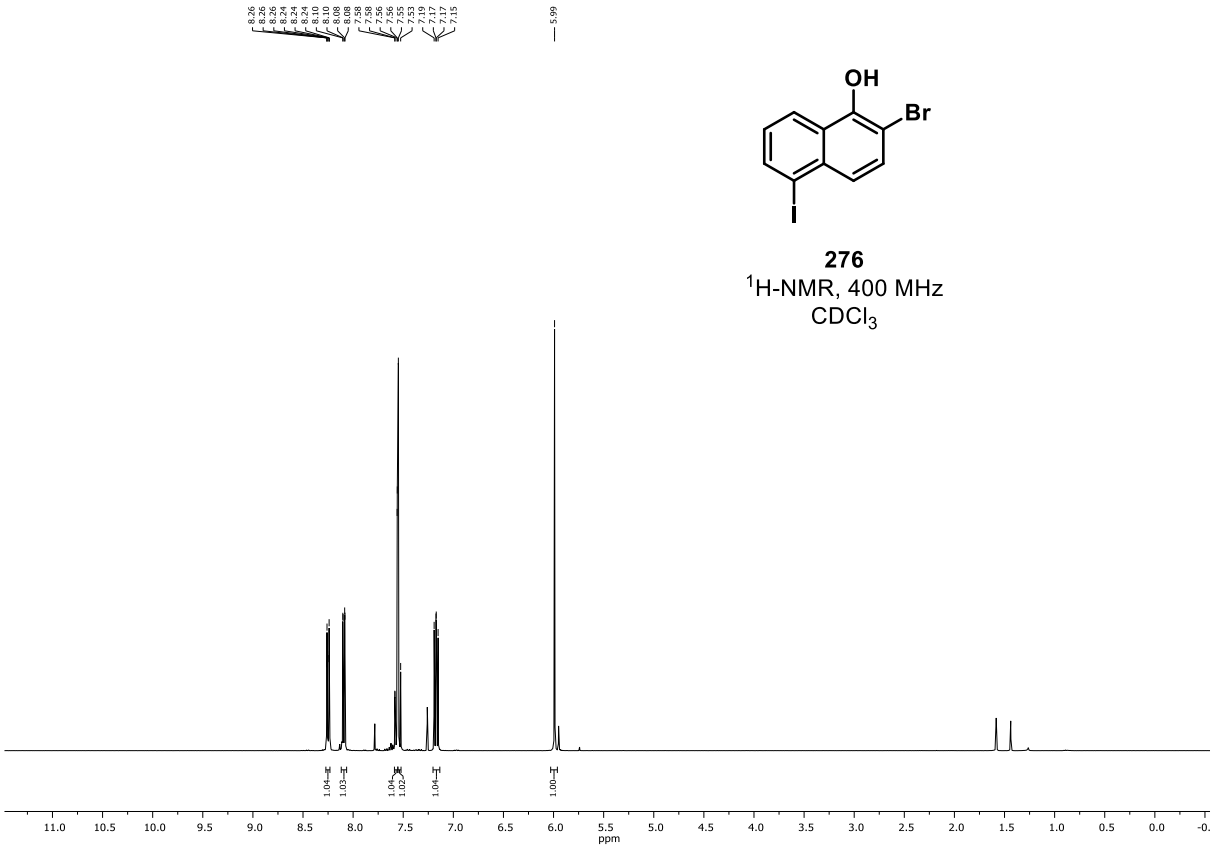


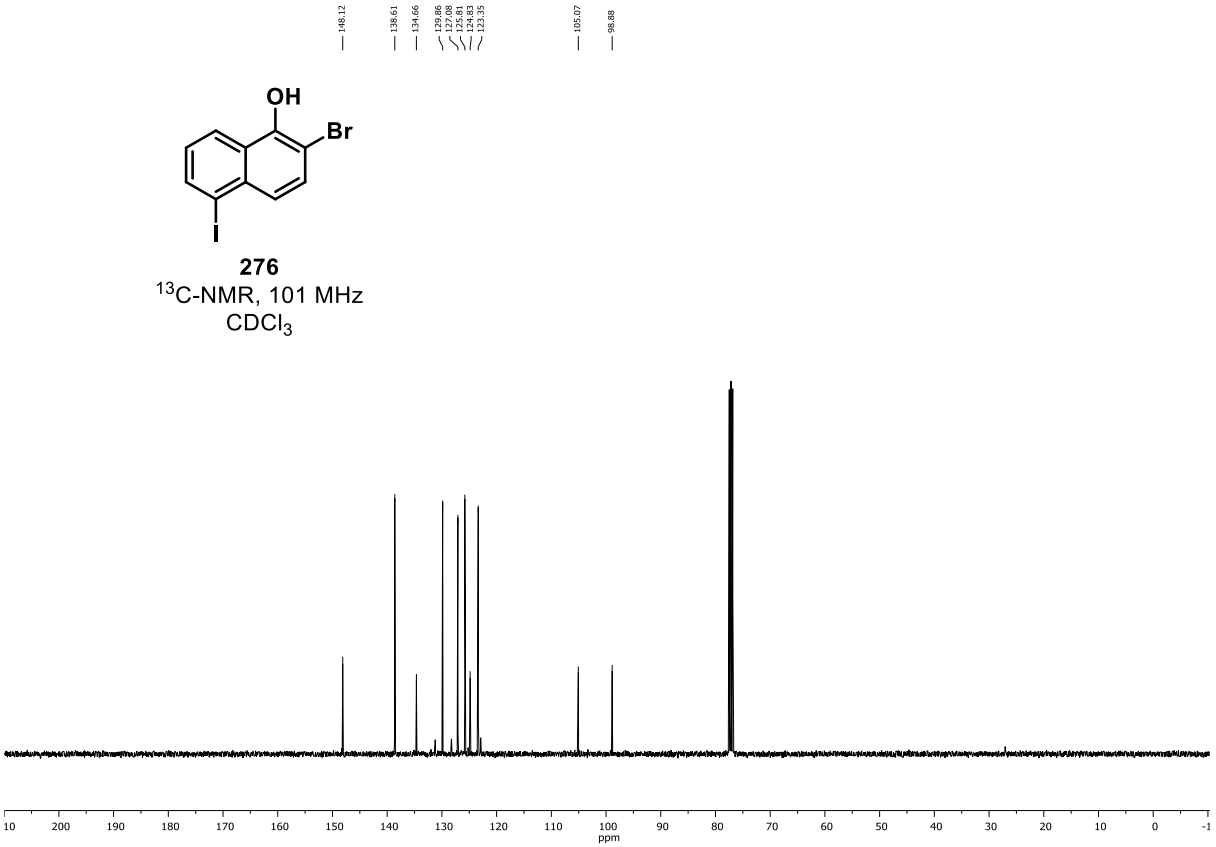
287
^{13}C-NMR, 101 MHz
$CDCl_3$


OH
Br
F
288
1H-NMR, 400 MHz
CDCl3
ppm

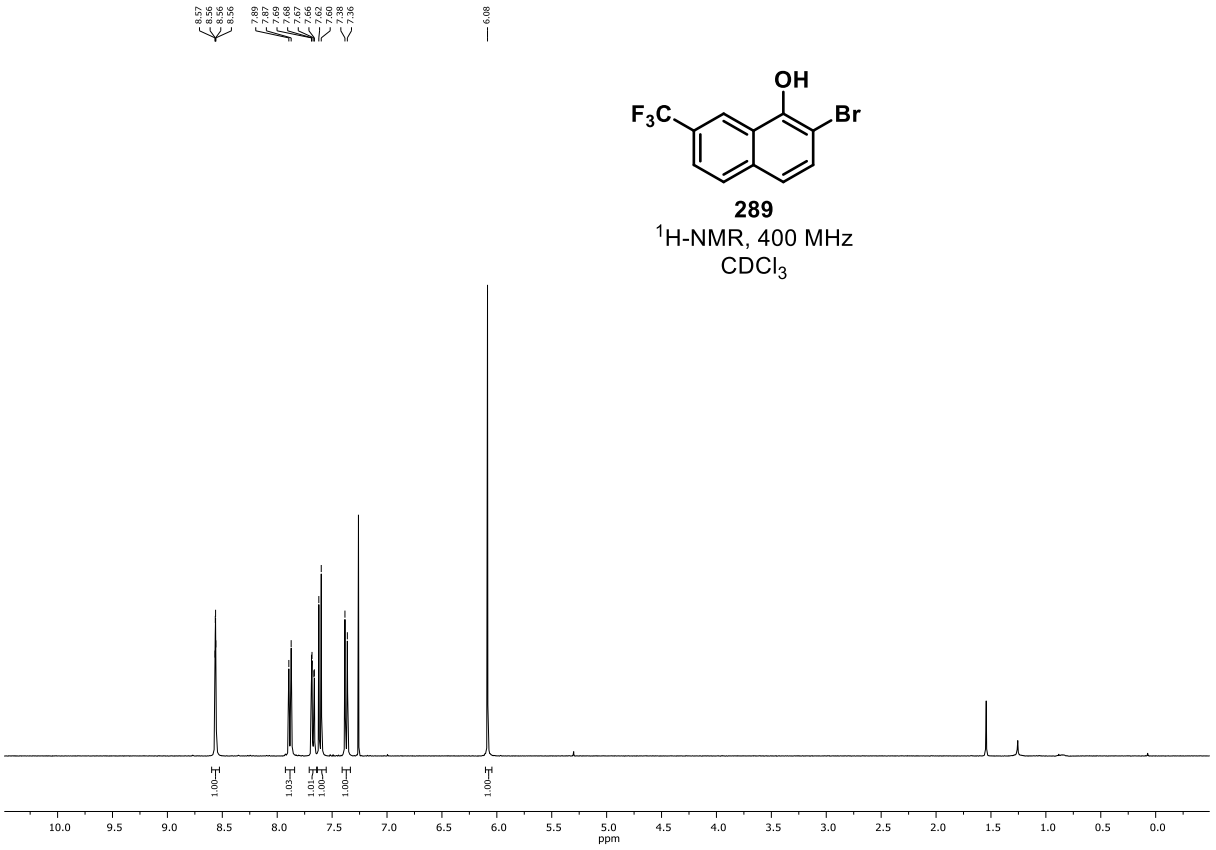

OH
Br
F
288
13C-NMR, 101 MHz
CDCl3
ppm


-113.56
-113.57
-113.58
-113.60
-113.61
-113.62
OH
Br
F
288
19F-NMR, 376 MHz
CDCl3
ppm

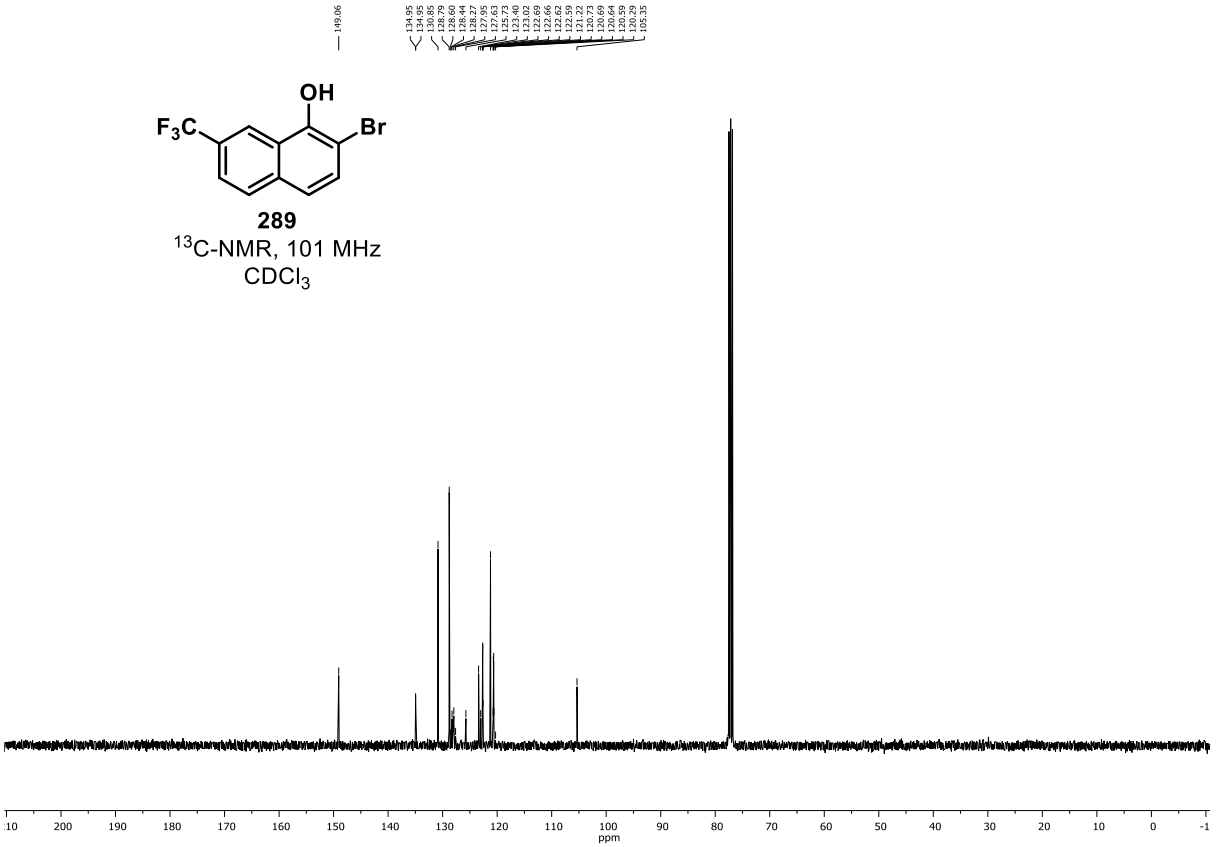

8.26
8.26
8.26
8.24
8.24
8.24
8.10
8.10
8.08
8.08
7.58
7.58
7.56
7.56
7.55
7.53
7.19
7.17
7.17
7.15
5.99
OH
Br
I
276
1H-NMR, 400 MHz
CDCl3
1.04
1.03
1.04
1.02
1.04
1.00
ppm

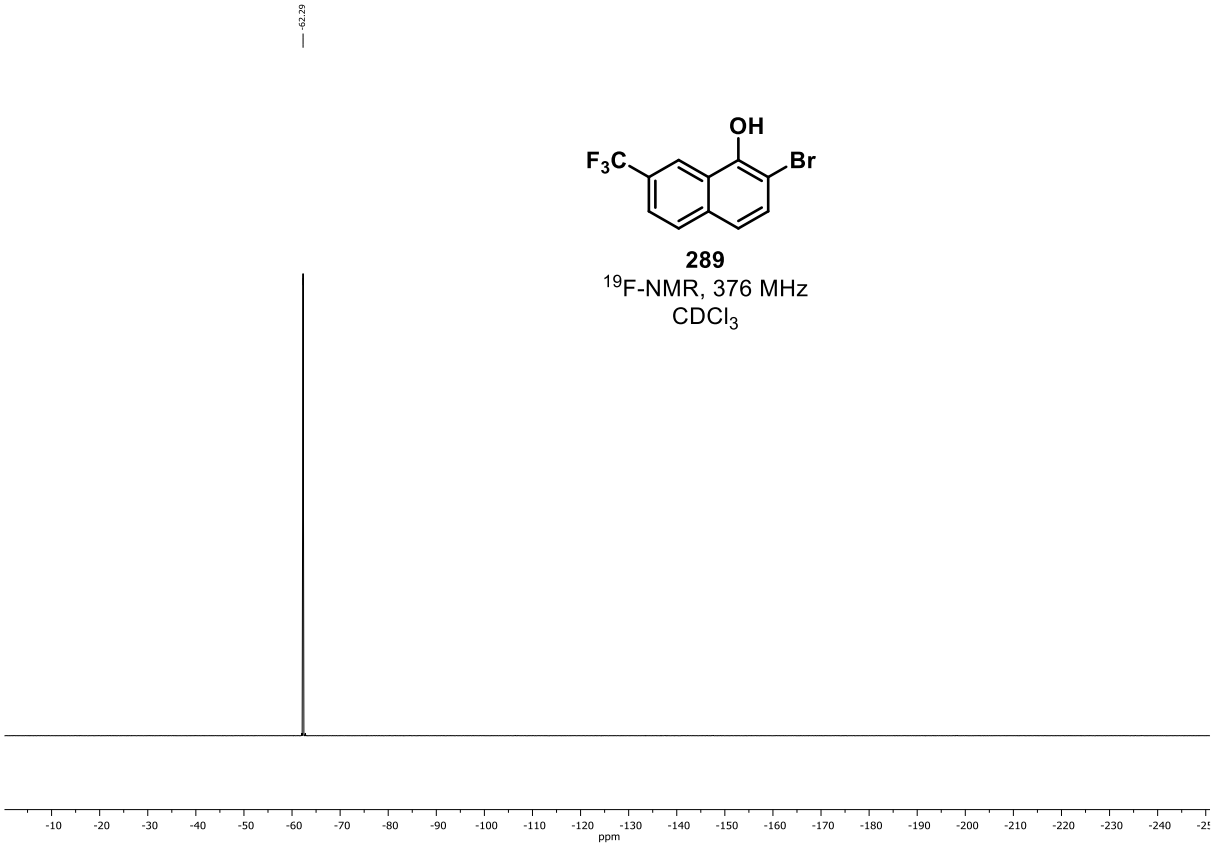


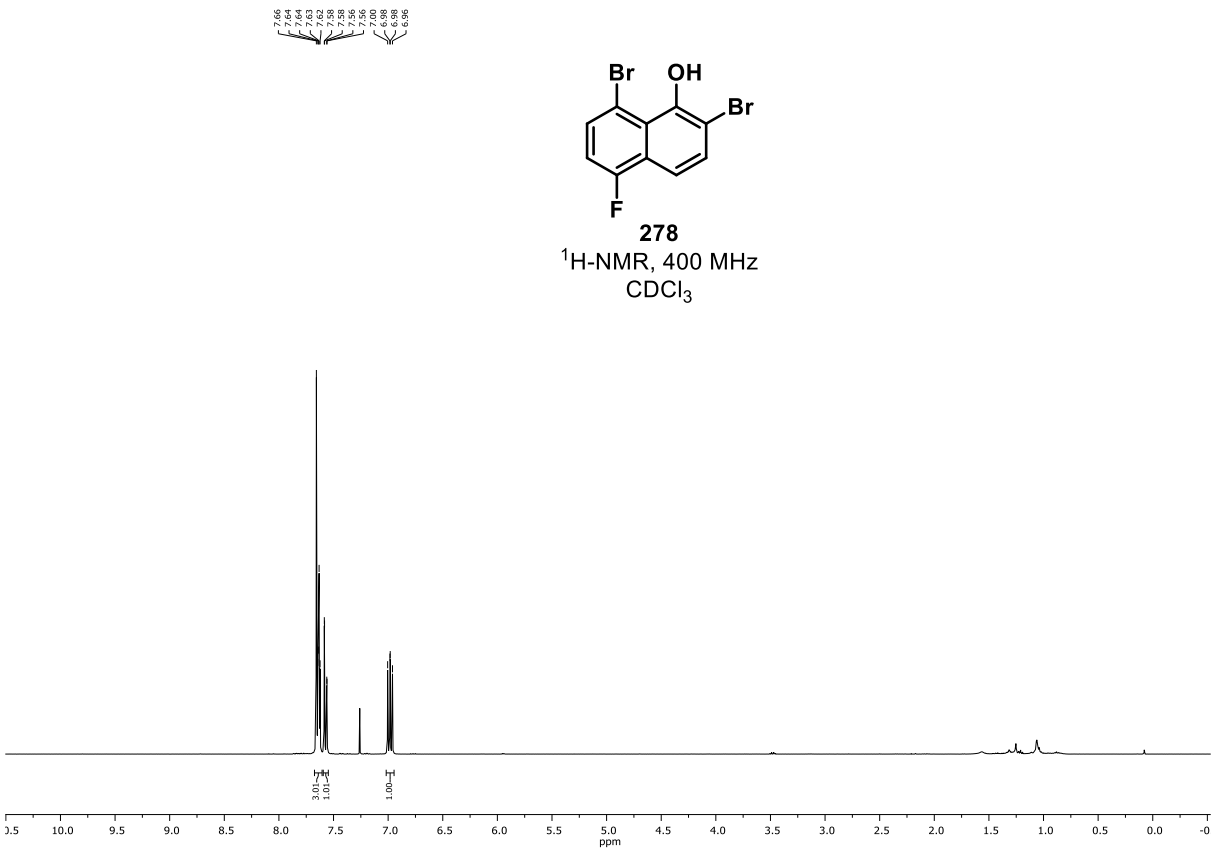
276
^{13}C-NMR, 101 MHz
$CDCl_3$

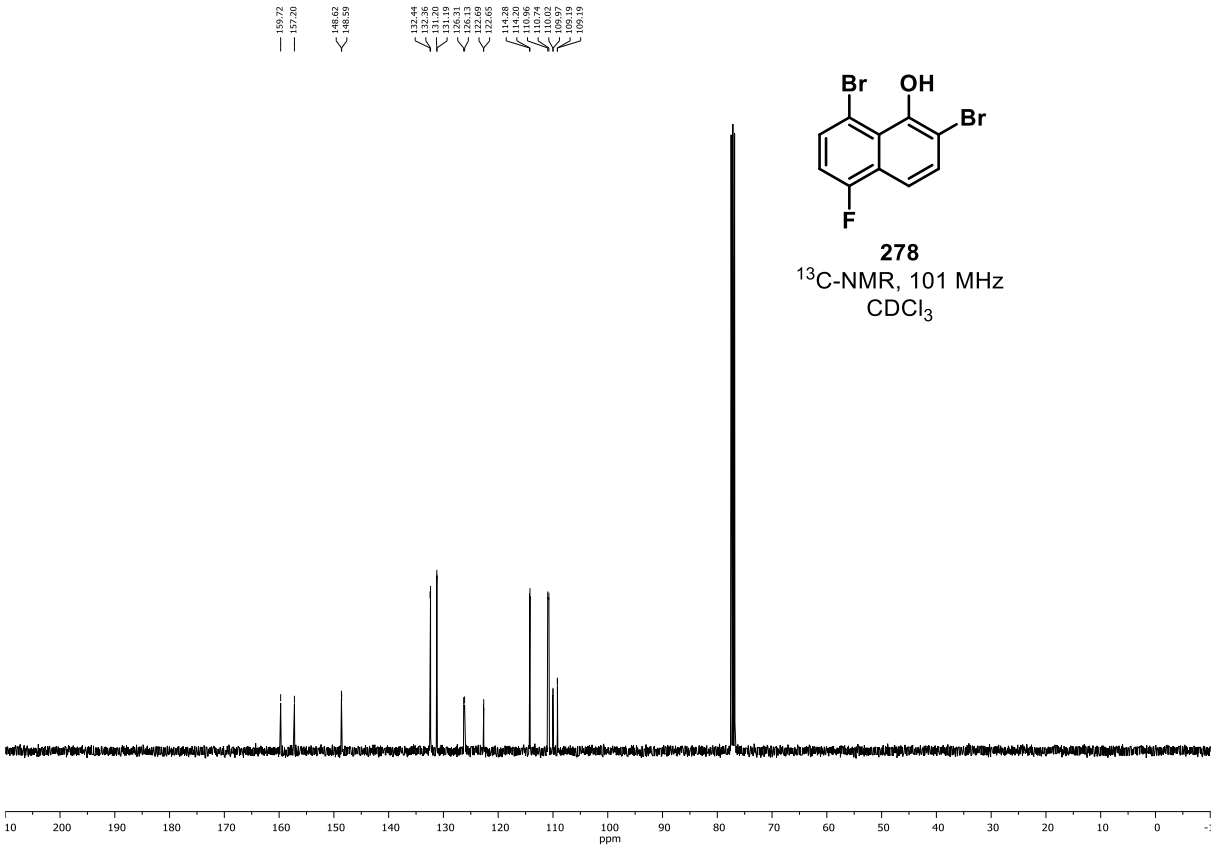


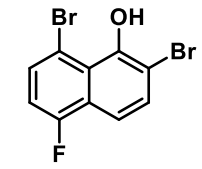
289
^{1}H-NMR, 400 MHz
$CDCl_3$


149.06
134.95
134.95
130.85
128.79
128.65
128.44
128.27
127.95
127.63
125.73
123.40
122.02
121.69
122.66
122.62
122.59
121.22
120.73
120.69
120.64
120.59
120.29
105.35
OH
F3C
Br
289
13C-NMR, 101 MHz
CDCl3
ppm

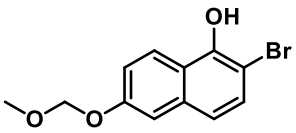

-62.29
OH
F3C
Br
289
19F-NMR, 376 MHz
CDCl3
ppm


7.66
7.64
7.64
7.63
7.62
7.58
7.58
7.56
7.56
7.00
6.98
6.98
6.96
Br
OH
Br
F
278
1H-NMR, 400 MHz
CDCl3
3.01
1.01
1.00
ppm

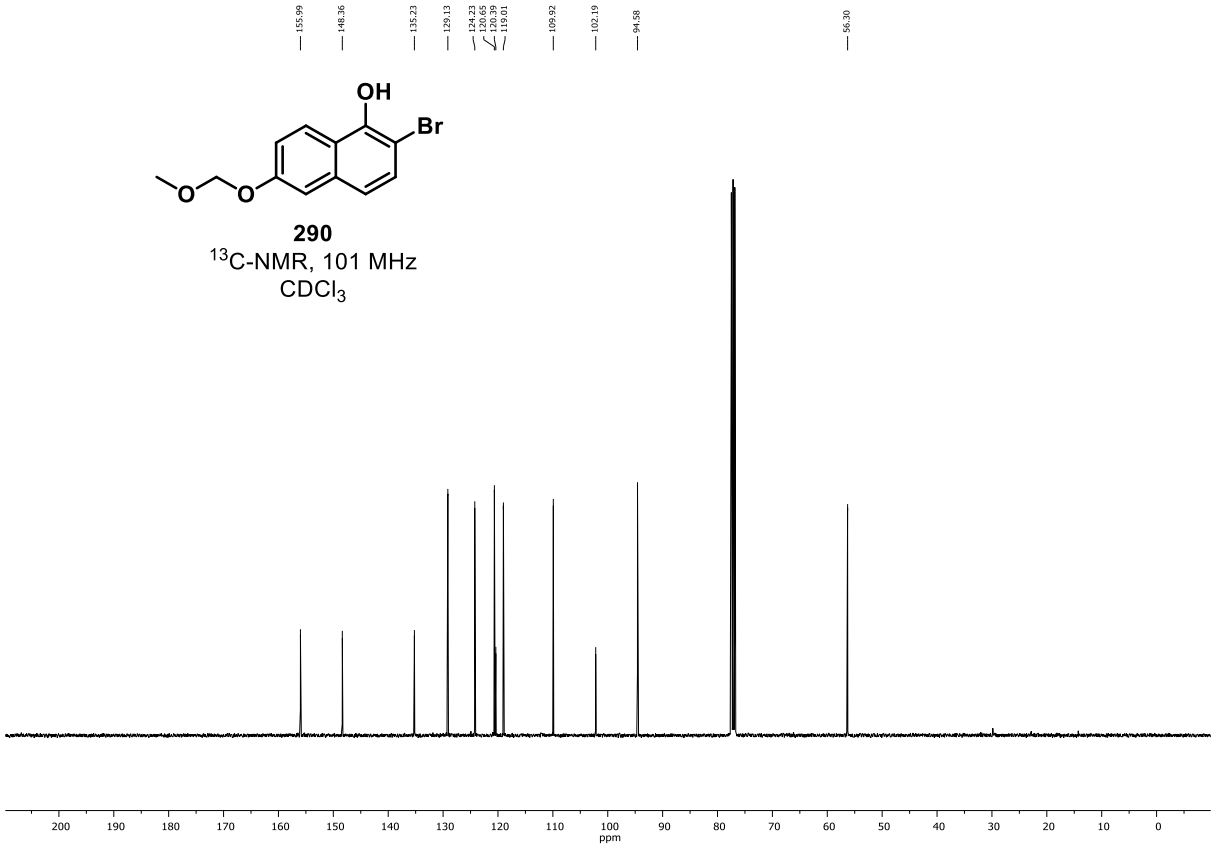

159.72
157.20
148.62
148.59
132.44
132.36
131.20
131.19
126.31
126.13
122.68
122.65
114.28
114.20
110.96
110.74
110.02
109.97
109.19
109.19
Br
OH
Br
F
278
13C-NMR, 101 MHz
CDCl3
ppm



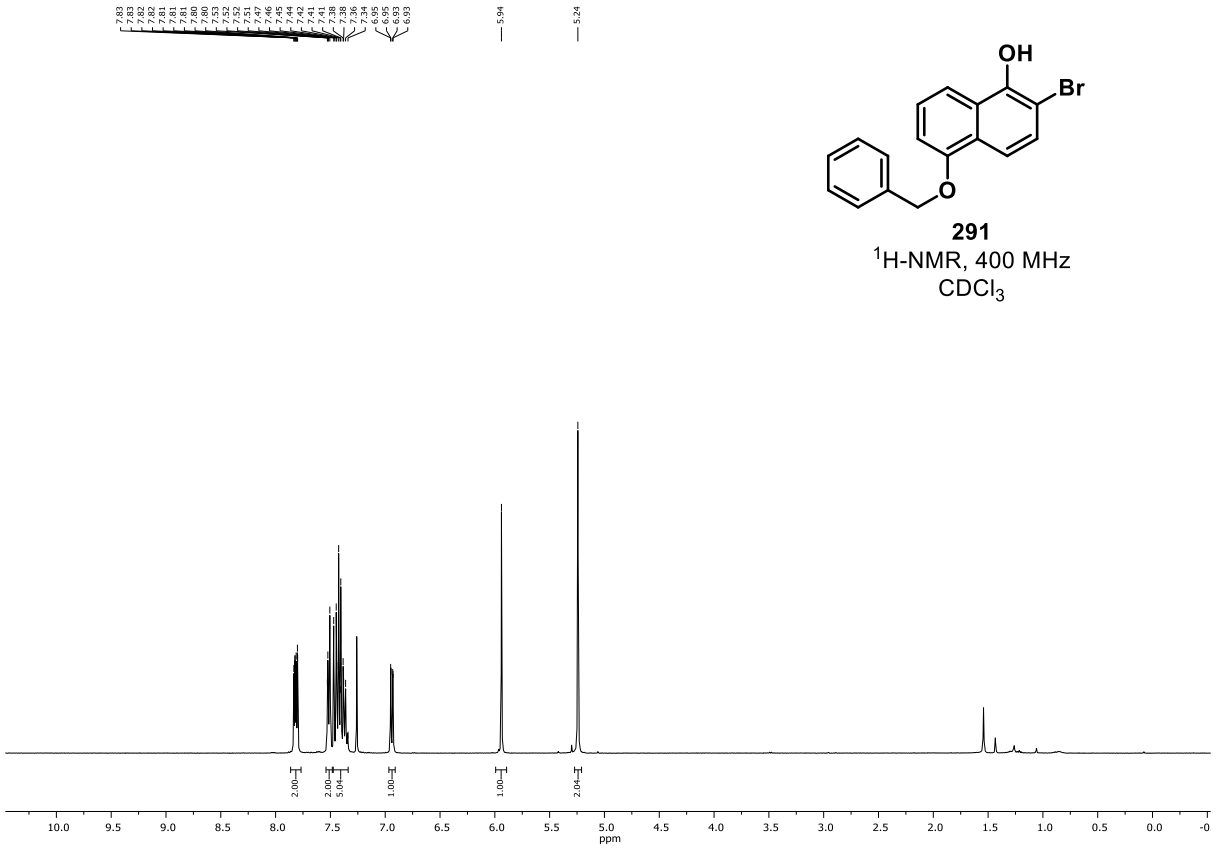
278
^{19}F-NMR, 376 MHz
$CDCl_3$



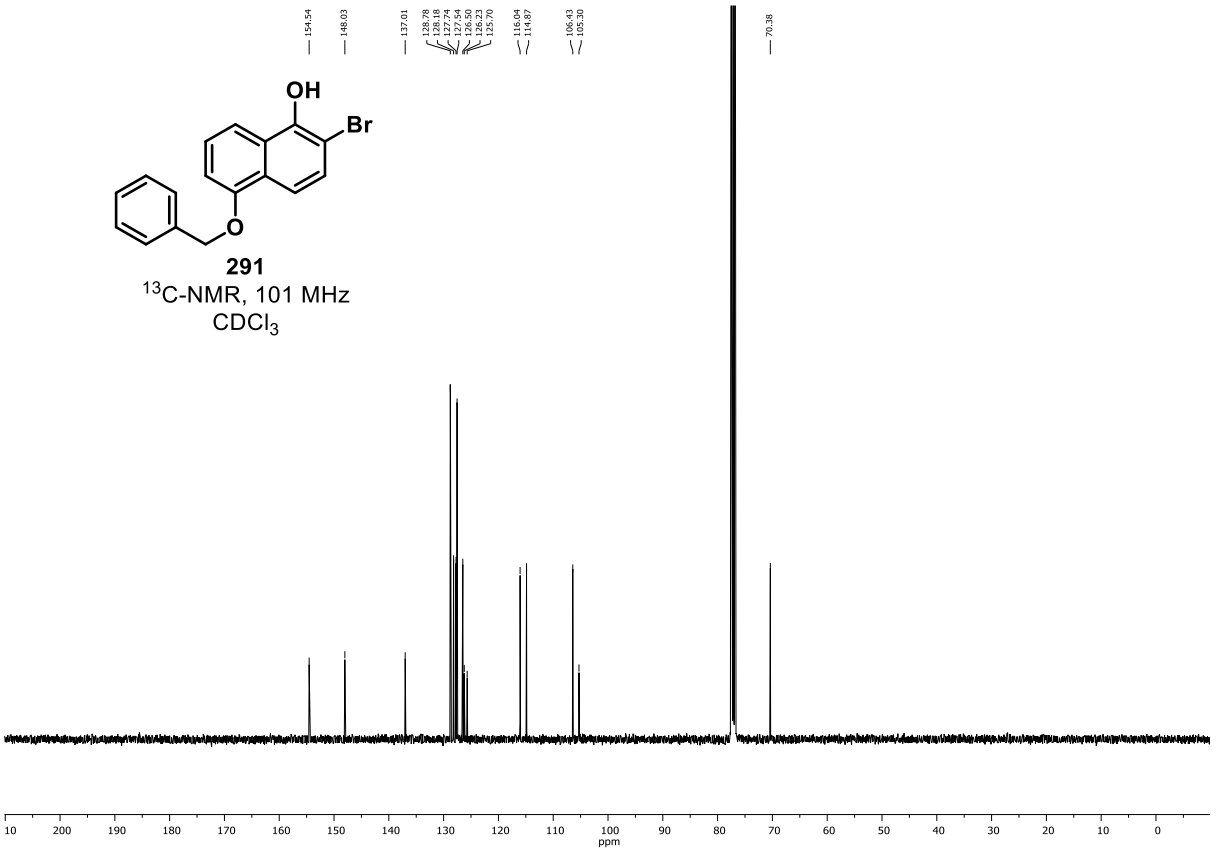
290
^{1}H-NMR, 400 MHz
$CDCl_3$

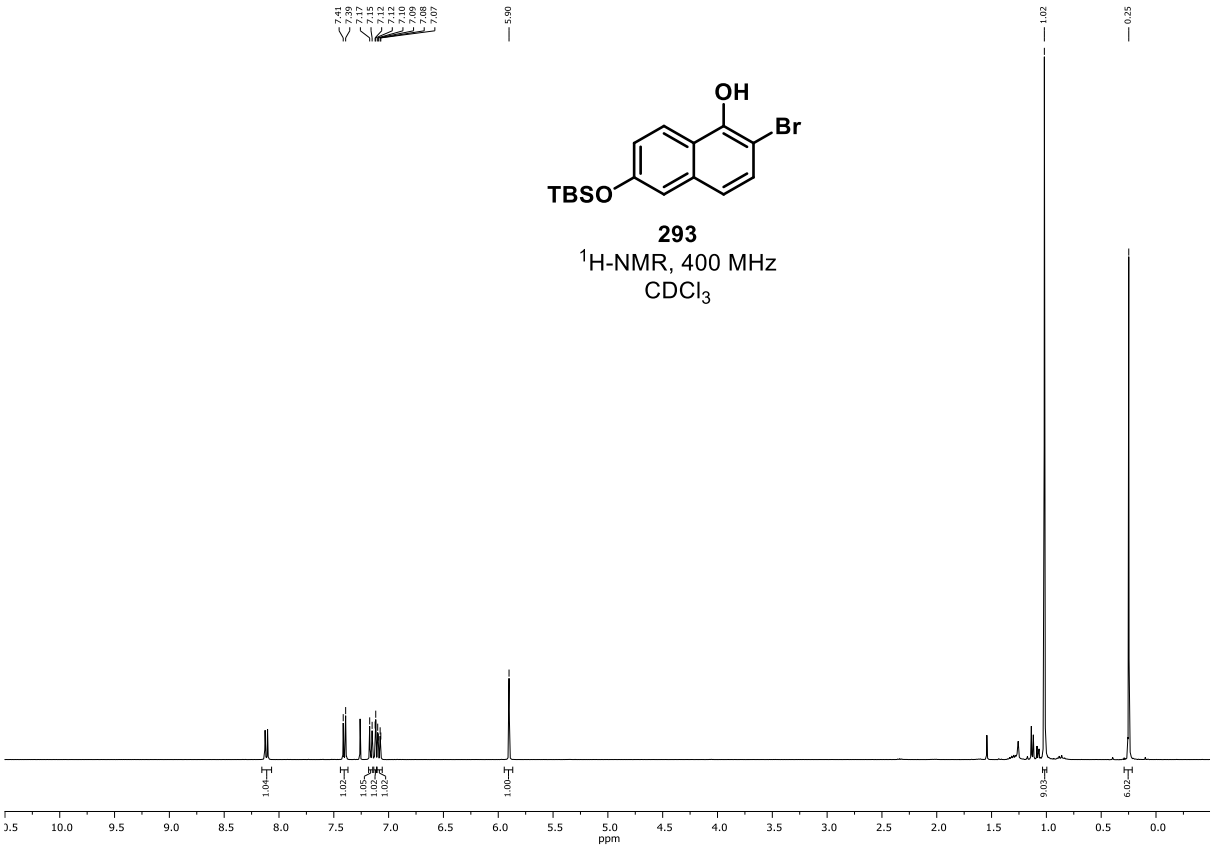


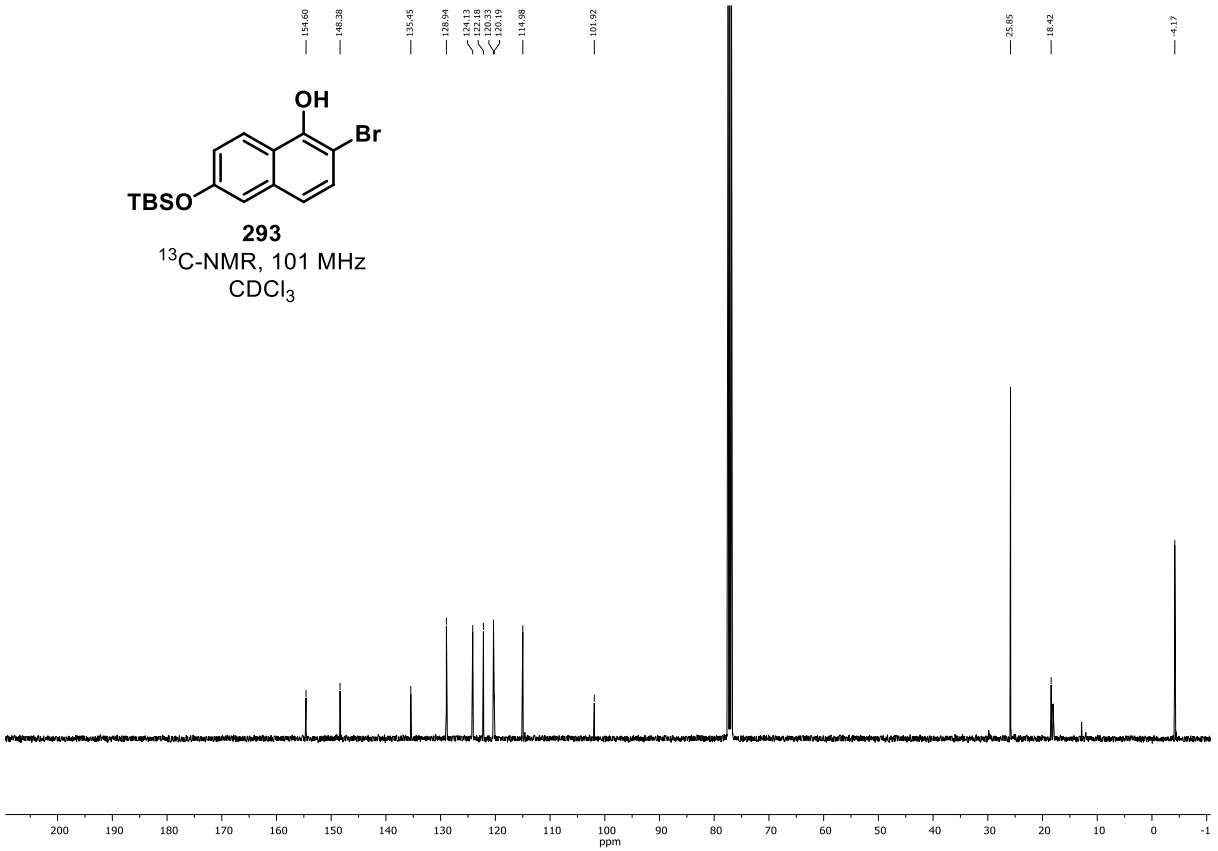
290
^{13}C-NMR, 101 MHz
$CDCl_3$



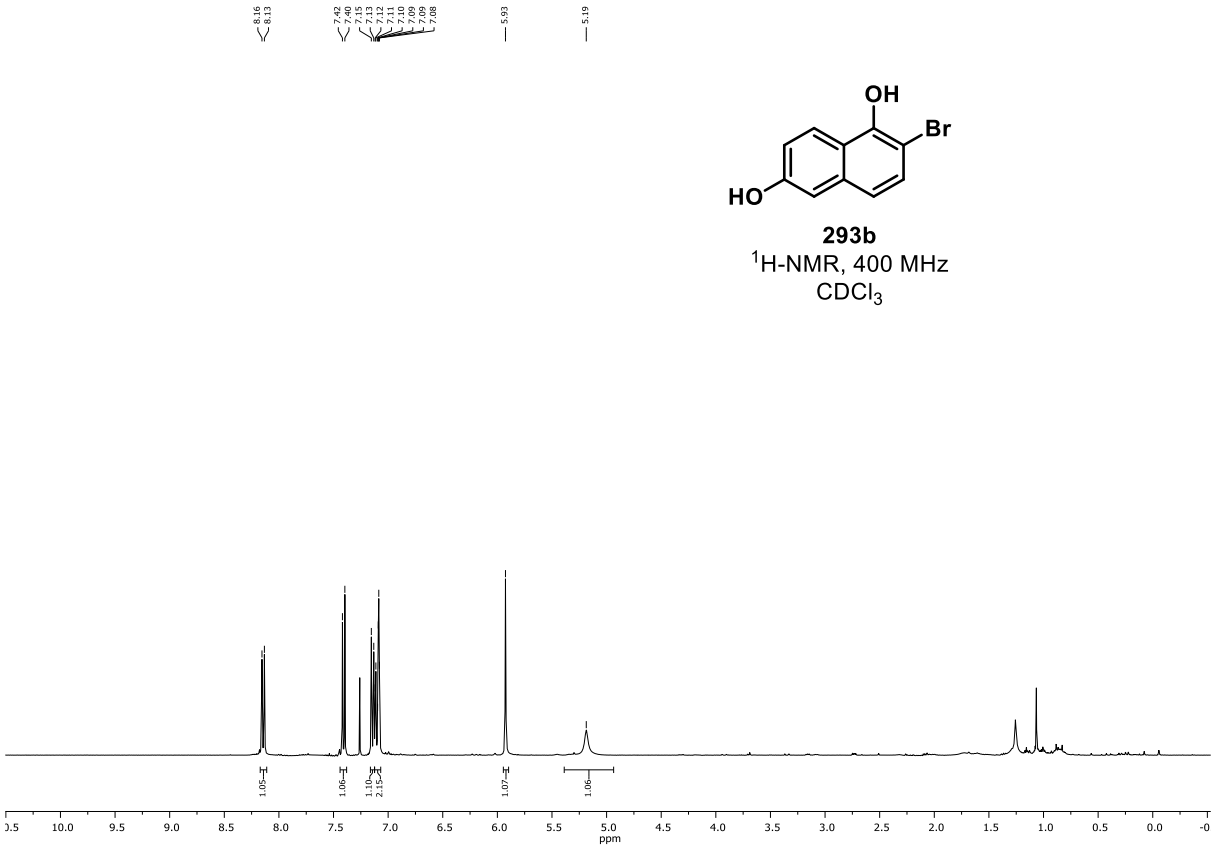
291
^{1}H-NMR, 400 MHz
$CDCl_3$


154.54
148.03
137.01
128.78
128.18
127.74
127.54
126.66
126.23
125.70
116.04
114.87
106.43
105.30
70.38
OH
Br
O
291
13C-NMR, 101 MHz
CDCl3
ppm

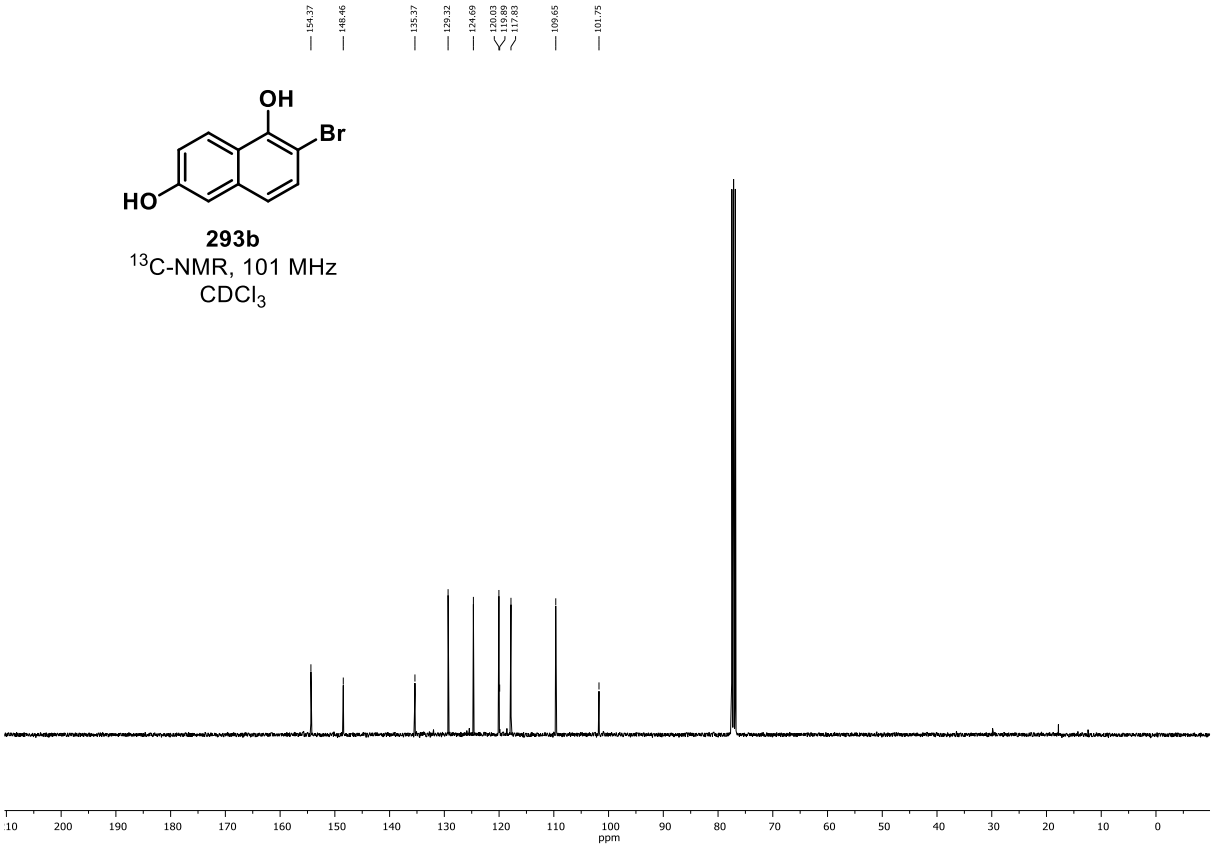

7.41
7.39
7.17
7.15
7.12
7.10
7.09
7.08
7.07
5.90
1.02
0.25
OH
Br
TBSO
293
1H-NMR, 400 MHz
CDCl3
1.04
1.02
1.05
1.02
1.00
9.03
6.02
ppm



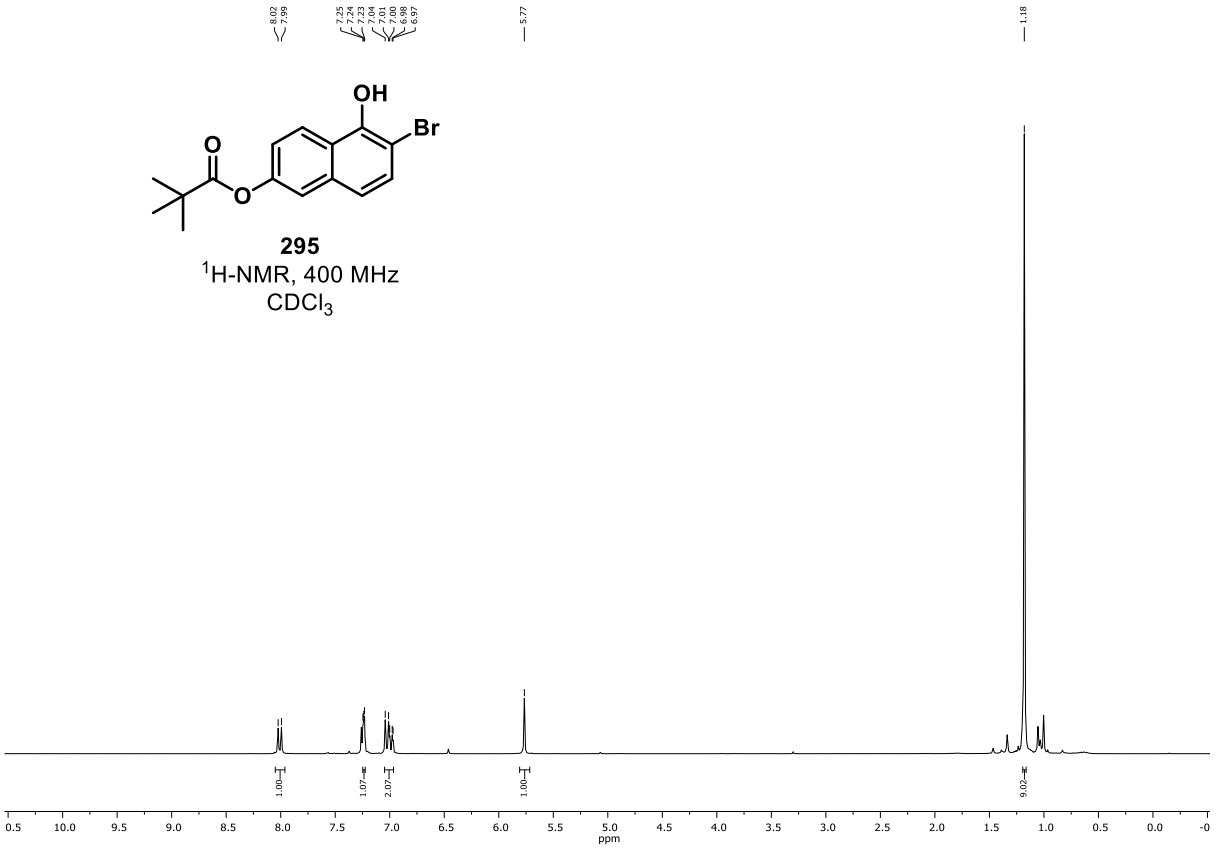
293
^{13}C-NMR, 101 MHz
$CDCl_3$



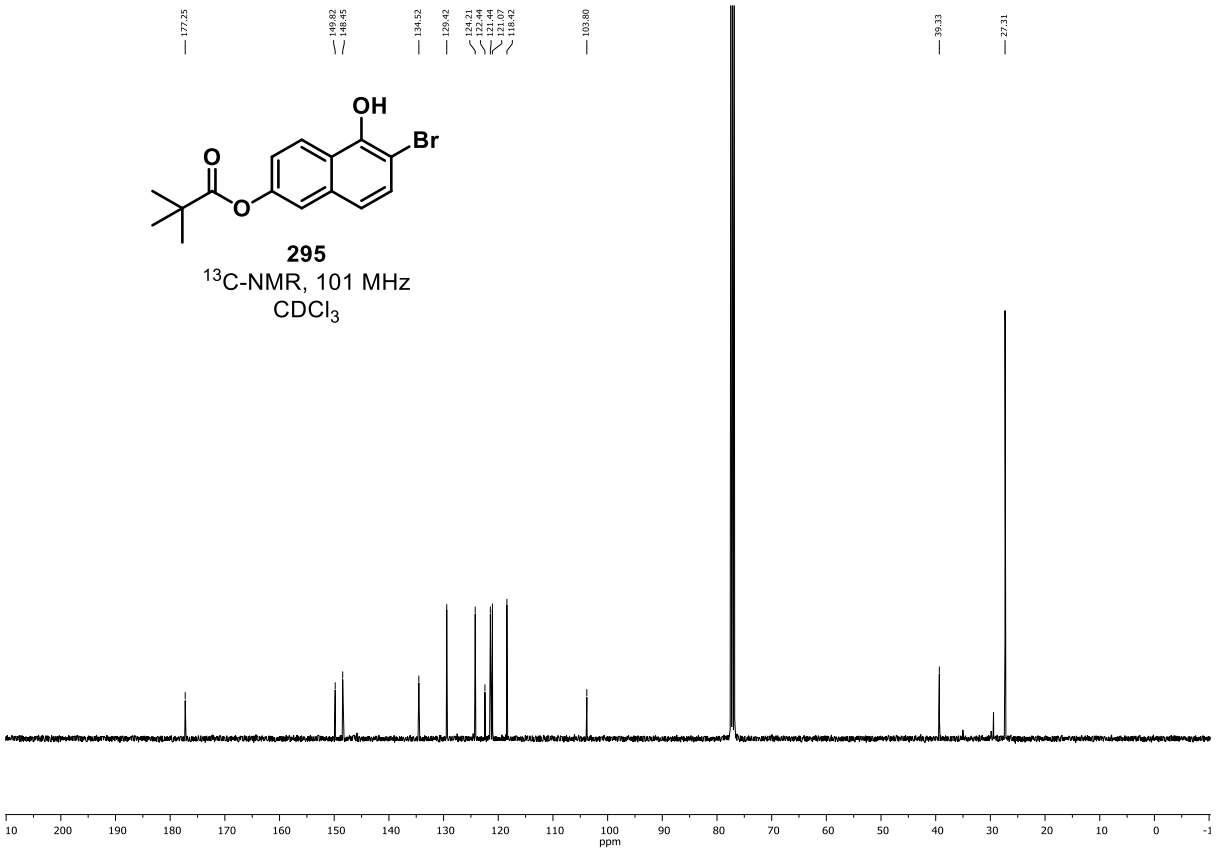
293b
^{1}H-NMR, 400 MHz
$CDCl_3$

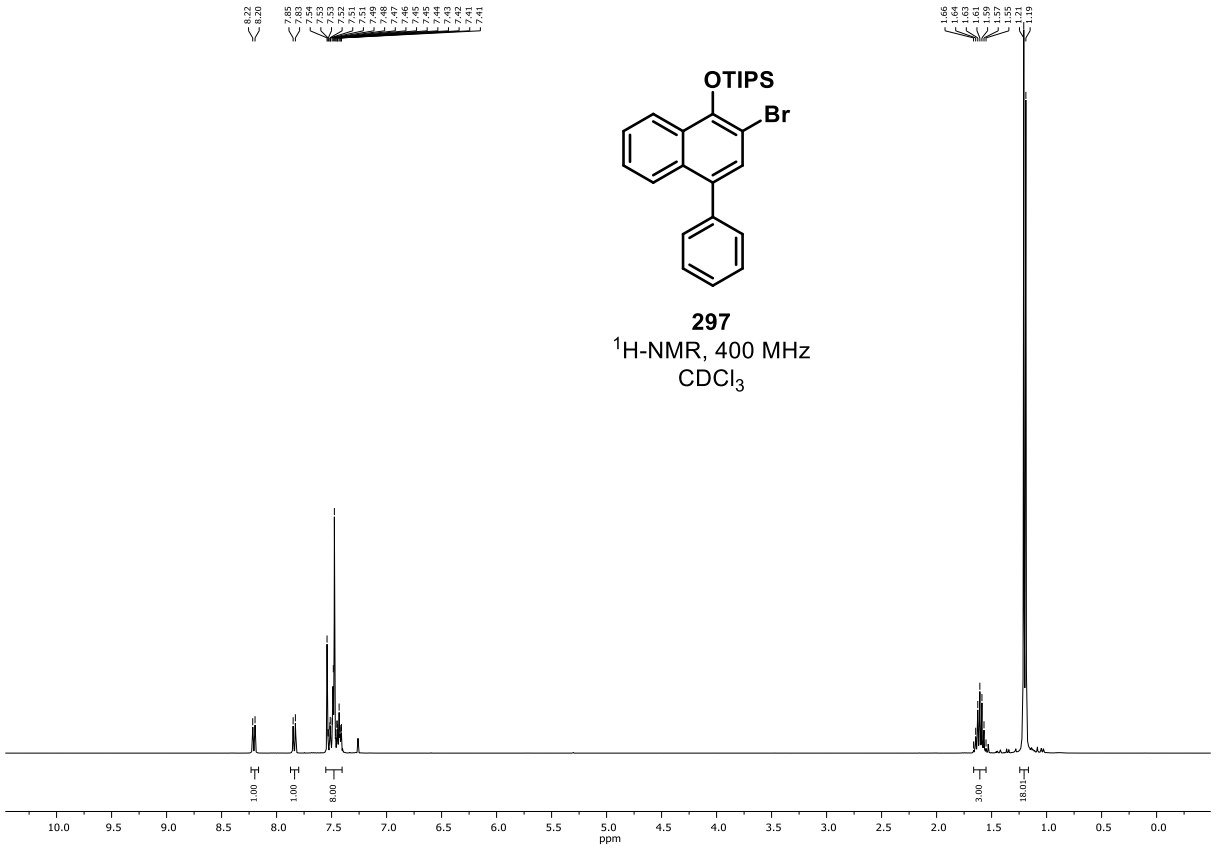


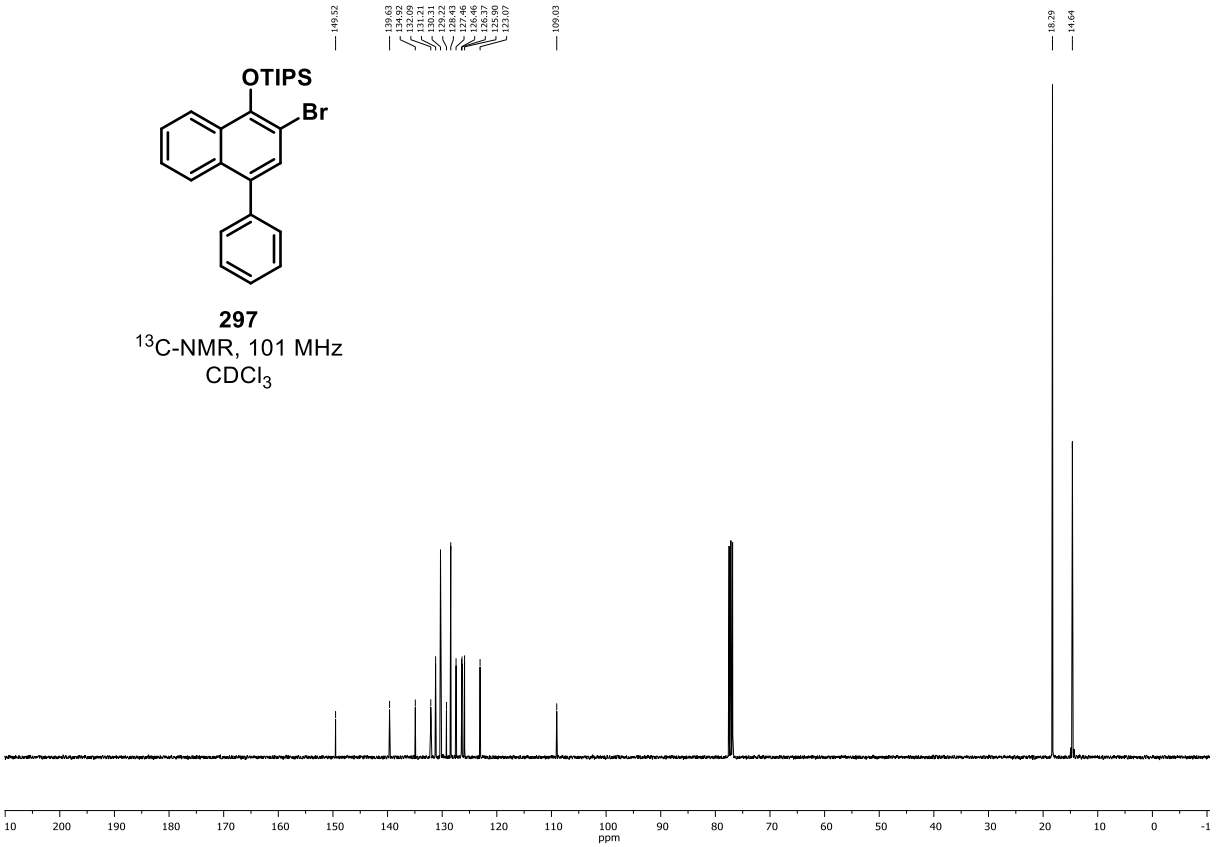
293b
^{13}C-NMR, 101 MHz
$CDCl_3$

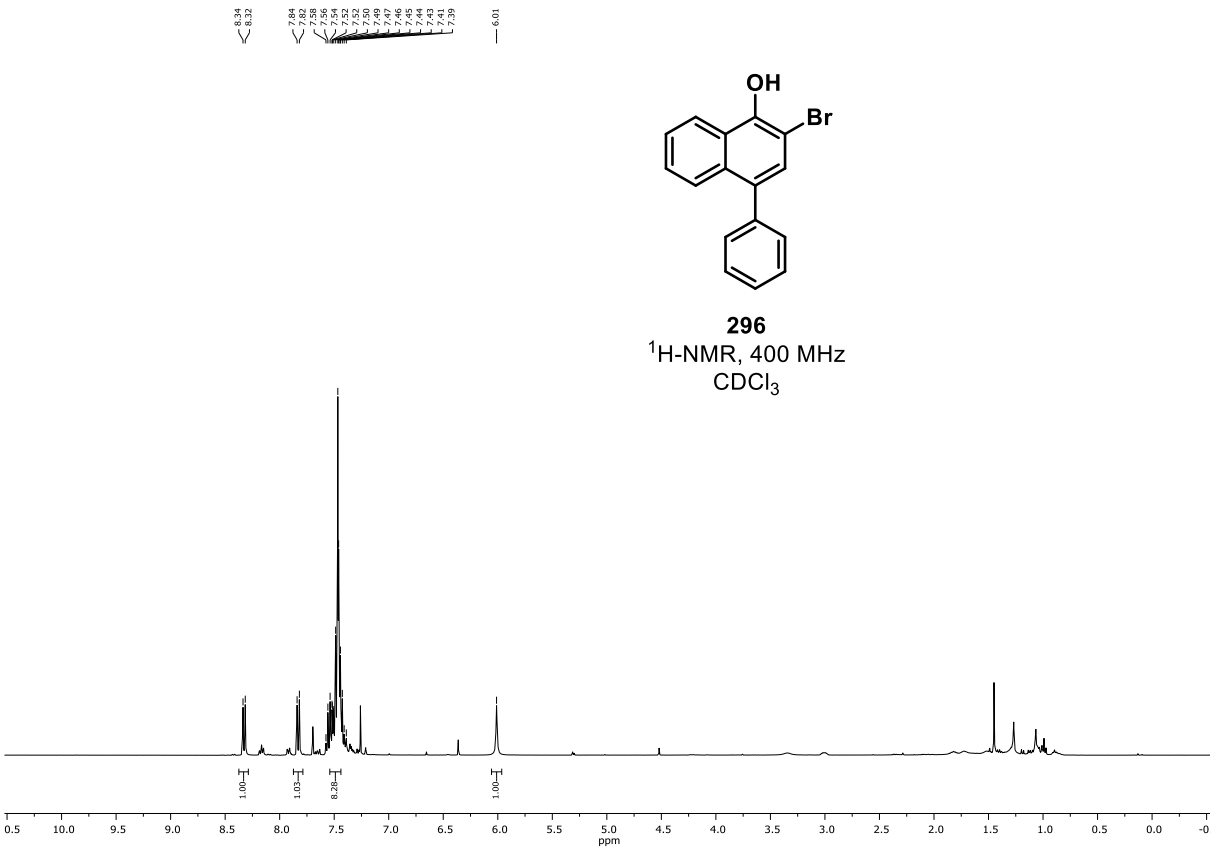


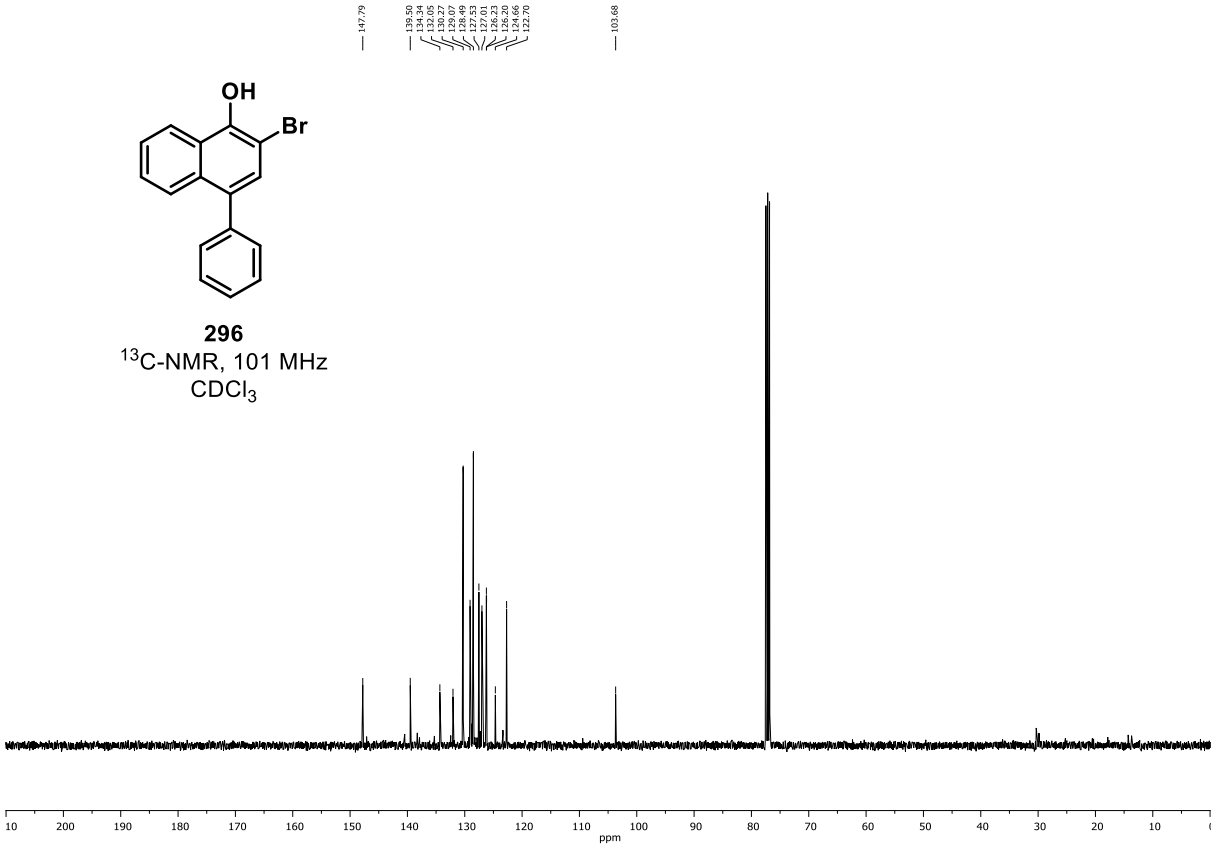
295
^{1}H-NMR, 400 MHz
$CDCl_3$

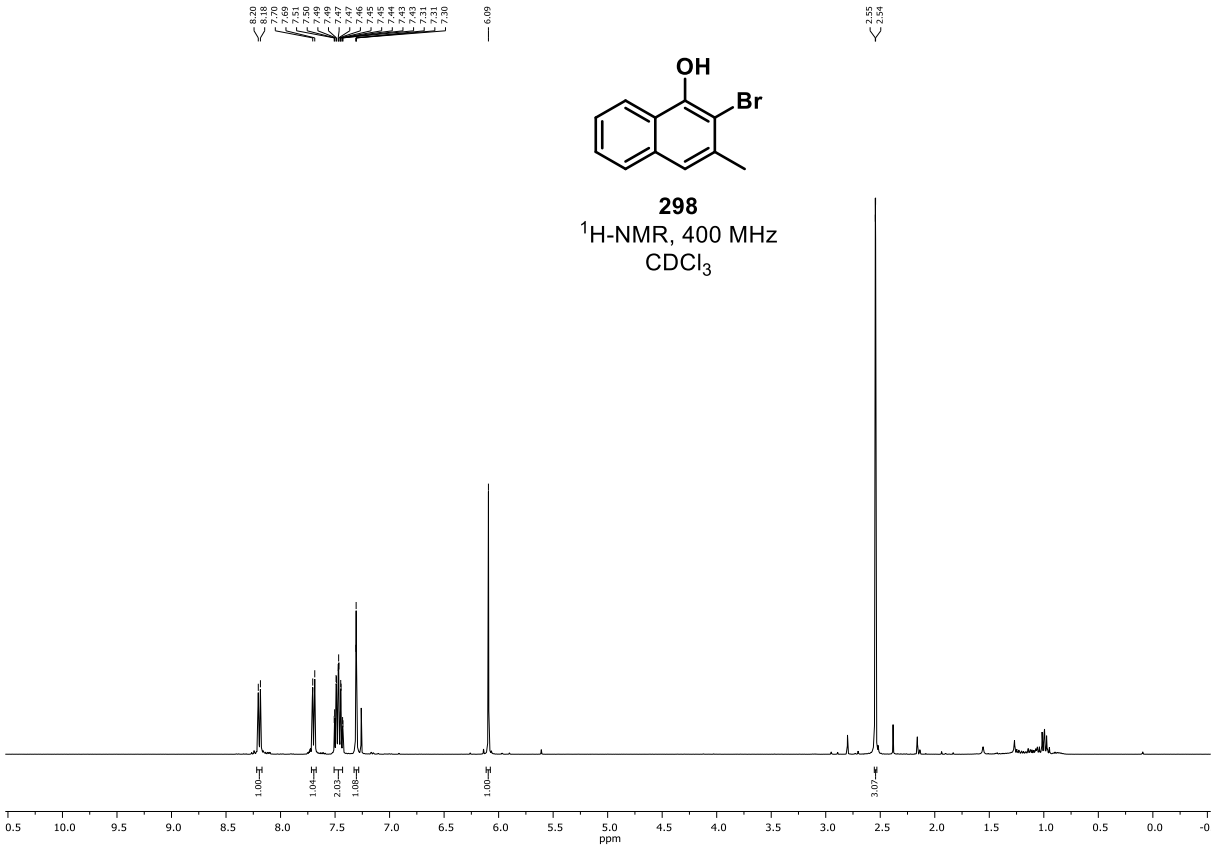

177.25
149.82
148.45
134.52
129.42
124.21
122.44
121.44
121.07
118.42
103.80
39.33
27.31
OH
Br
O
O
295
13C-NMR, 101 MHz
CDCl3
ppm

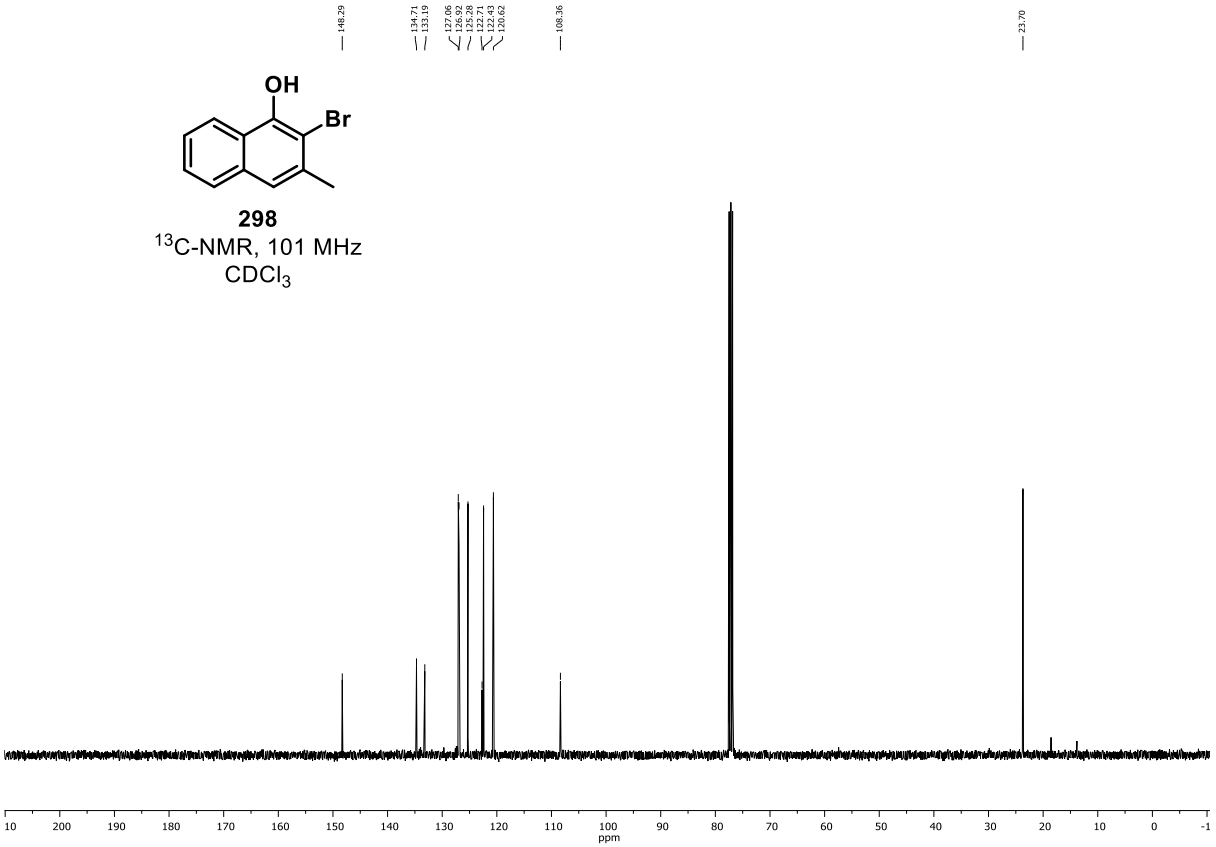

8.22
8.20
7.85
7.83
7.54
7.53
7.52
7.51
7.51
7.49
7.48
7.47
7.46
7.45
7.45
7.44
7.43
7.42
7.41
7.41
1.66
1.64
1.63
1.61
1.59
1.57
1.55
1.21
1.19
OTIPS
Br
297
1H-NMR, 400 MHz
CDCl3
1.00
1.00
8.00
3.00
18.01
ppm

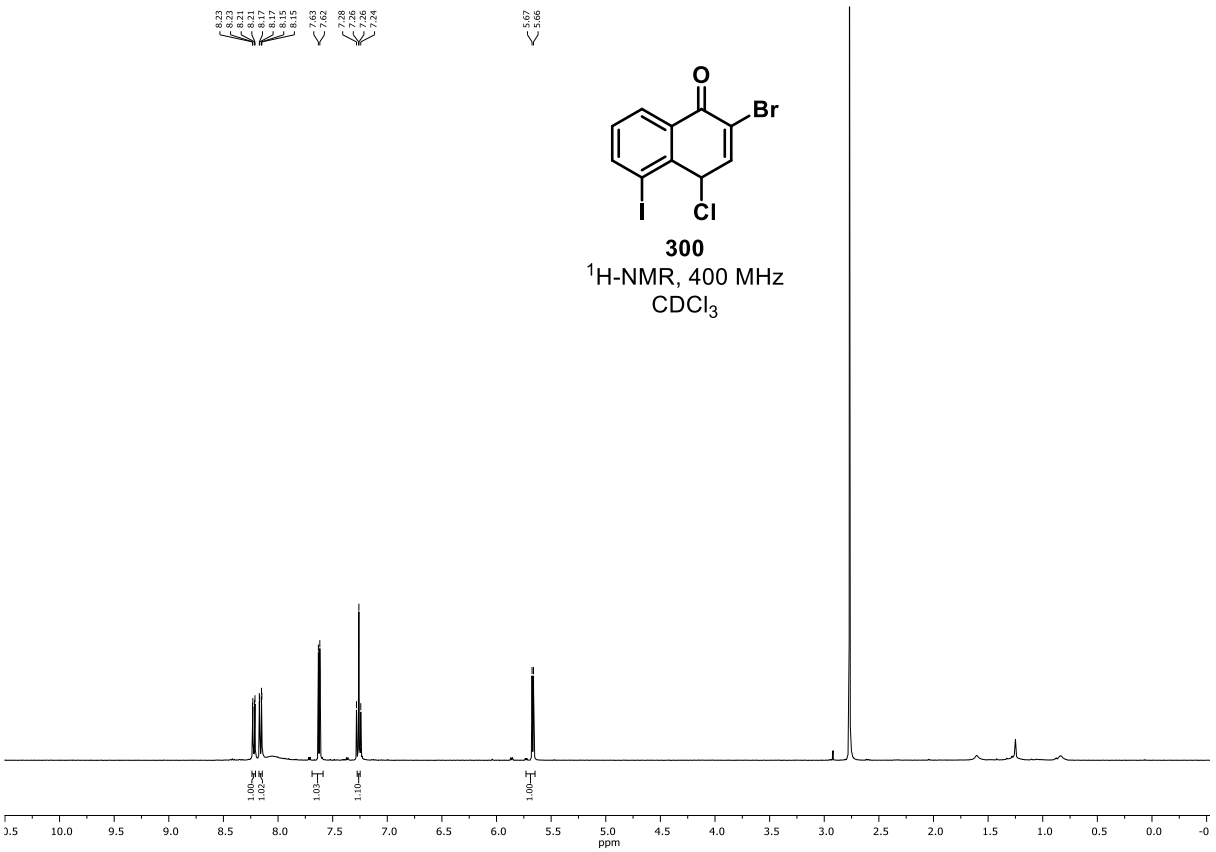

149.52
139.63
130.31
128.43
127.46
126.46
126.37
123.07
109.03
18.29
14.64
OTIPS
Br
297
13C-NMR, 101 MHz
CDCl3
ppm

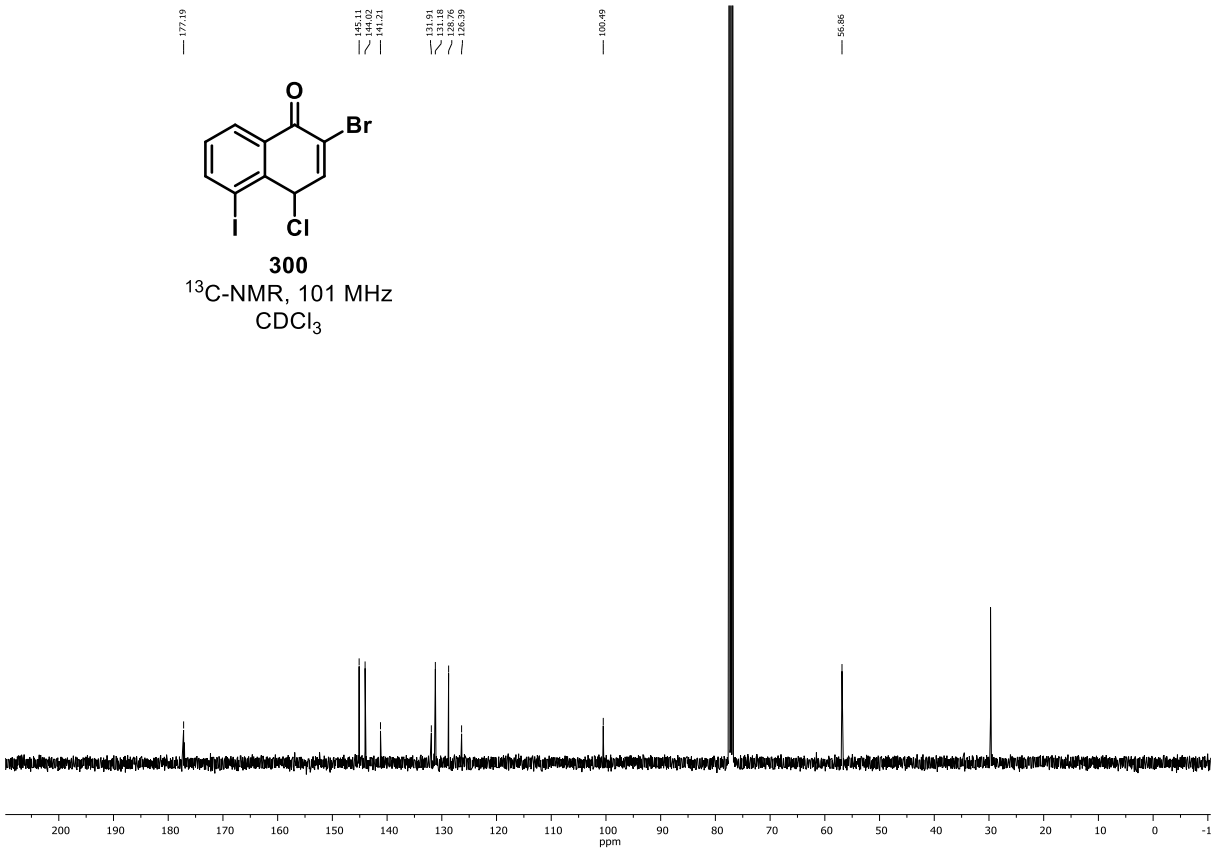

8.34
8.32
7.84
7.82
7.58
7.56
7.54
7.52
7.52
7.50
7.49
7.47
7.46
7.45
7.44
7.43
7.41
7.39
6.01
OH
Br
296
1H-NMR, 400 MHz
CDCl3
1.00
1.03
8.28
1.00
ppm


147.79
139.50
134.34
132.05
130.27
129.07
128.46
127.53
127.01
126.23
126.20
124.66
122.70
103.68
OH
Br
296
13C-NMR, 101 MHz
CDCl3
ppm

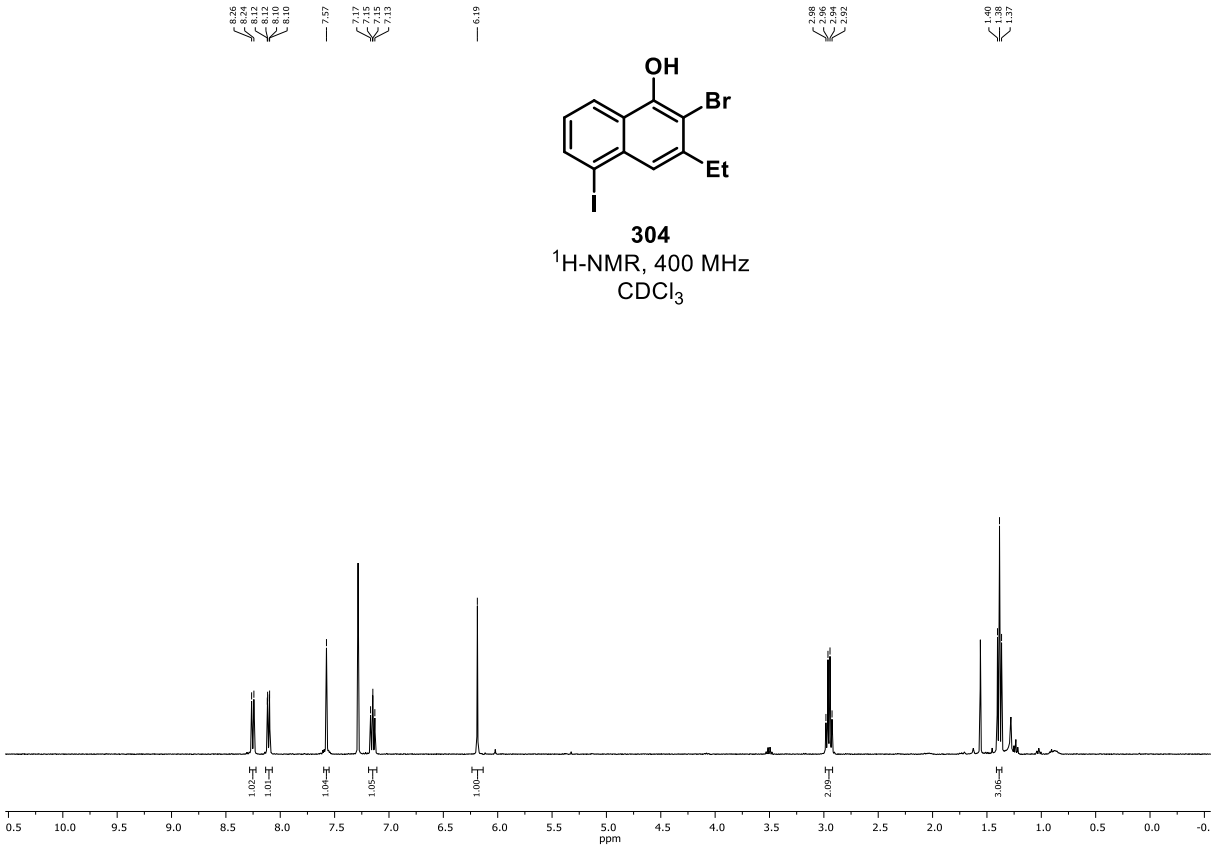

8.20
8.18
7.70
7.69
7.51
7.50
7.49
7.49
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.43
7.43
7.31
7.31
7.30
6.09
2.55
2.54
OH
Br
298
1H-NMR, 400 MHz
CDCl3
1.00
1.04
2.03
1.08
1.00
3.07
ppm


148.29
134.71
131.19
127.06
126.92
125.28
122.71
122.43
120.62
108.36
23.70
OH
Br
298
13C-NMR, 101 MHz
CDCl3
ppm

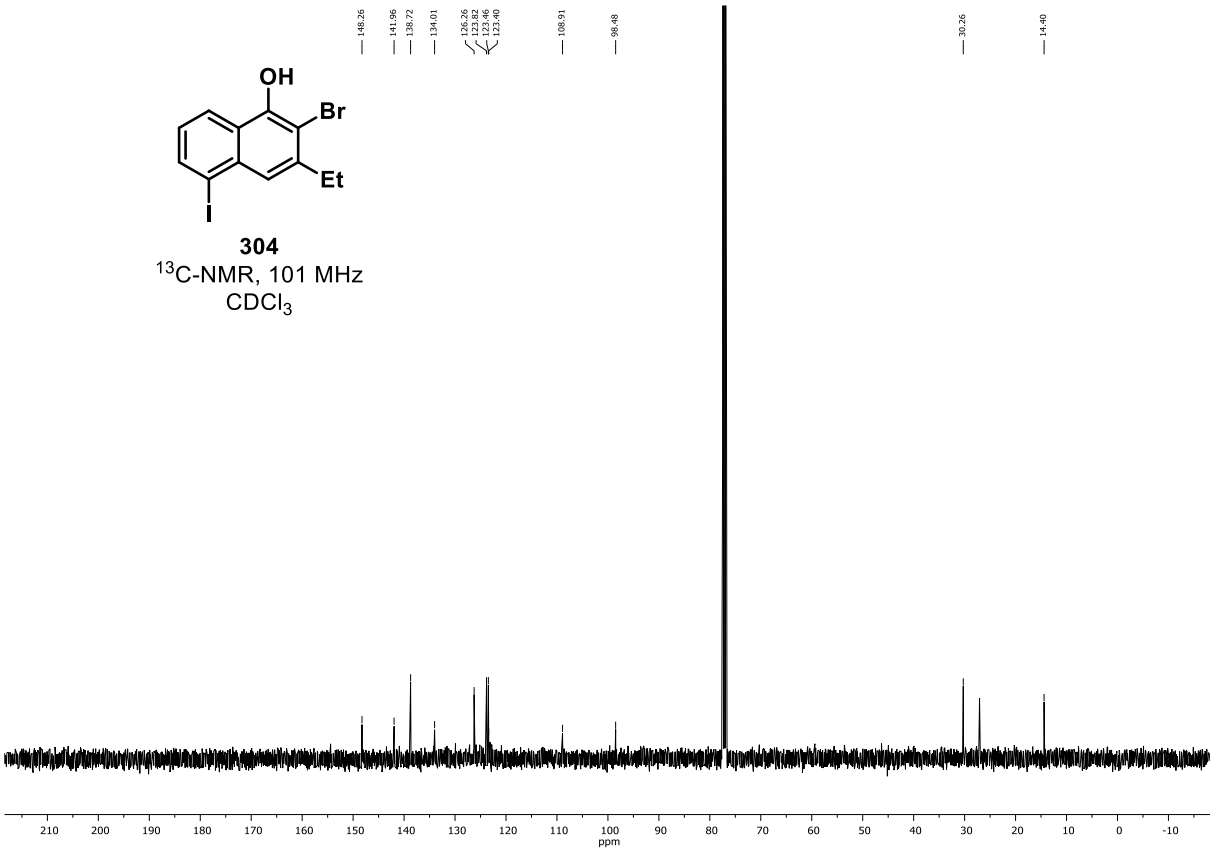

8.23
8.23
8.21
8.21
8.17
8.17
8.15
8.15
7.63
7.62
7.28
7.26
7.26
7.24
5.67
5.66
O
Br
I
Cl
300
1H-NMR, 400 MHz
CDCl3
1.00
1.02
1.03
1.10
1.00
ppm



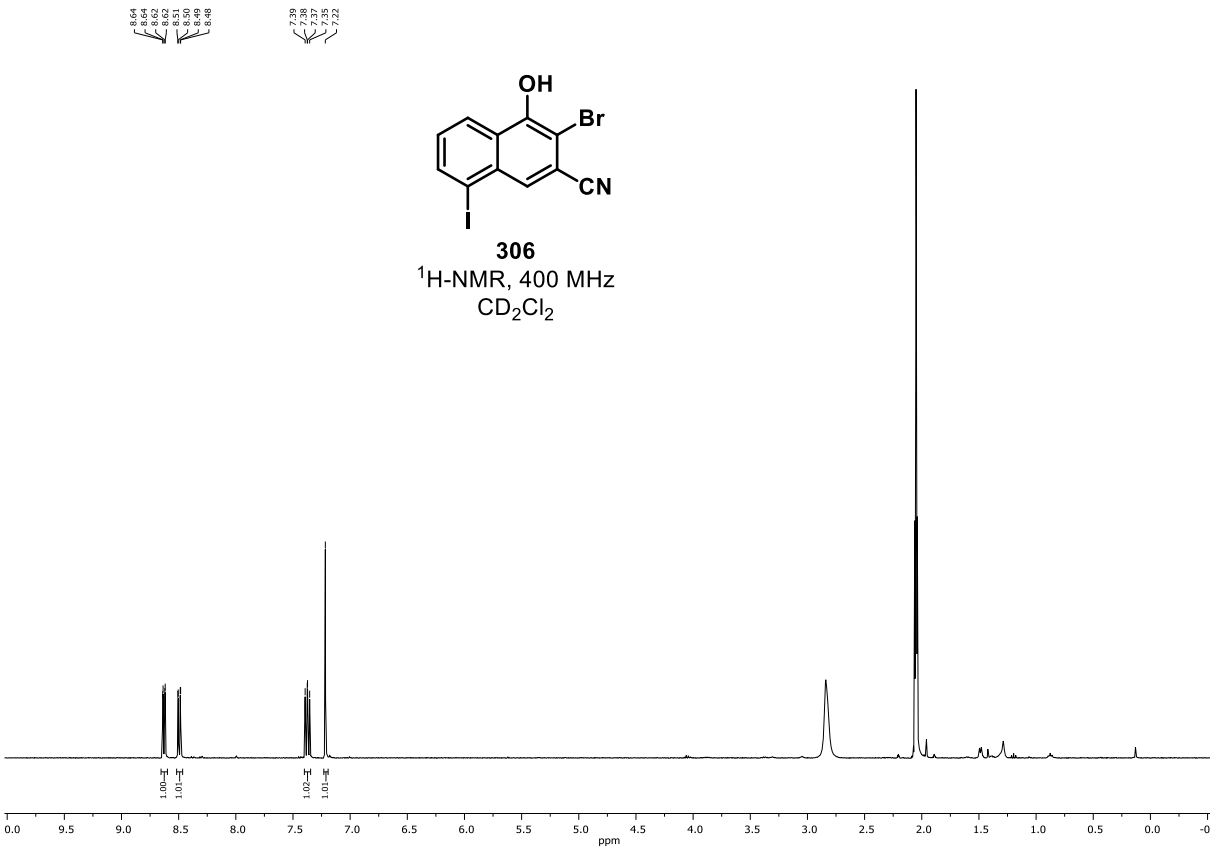
300
^{13}C-NMR, 101 MHz
$CDCl_3$



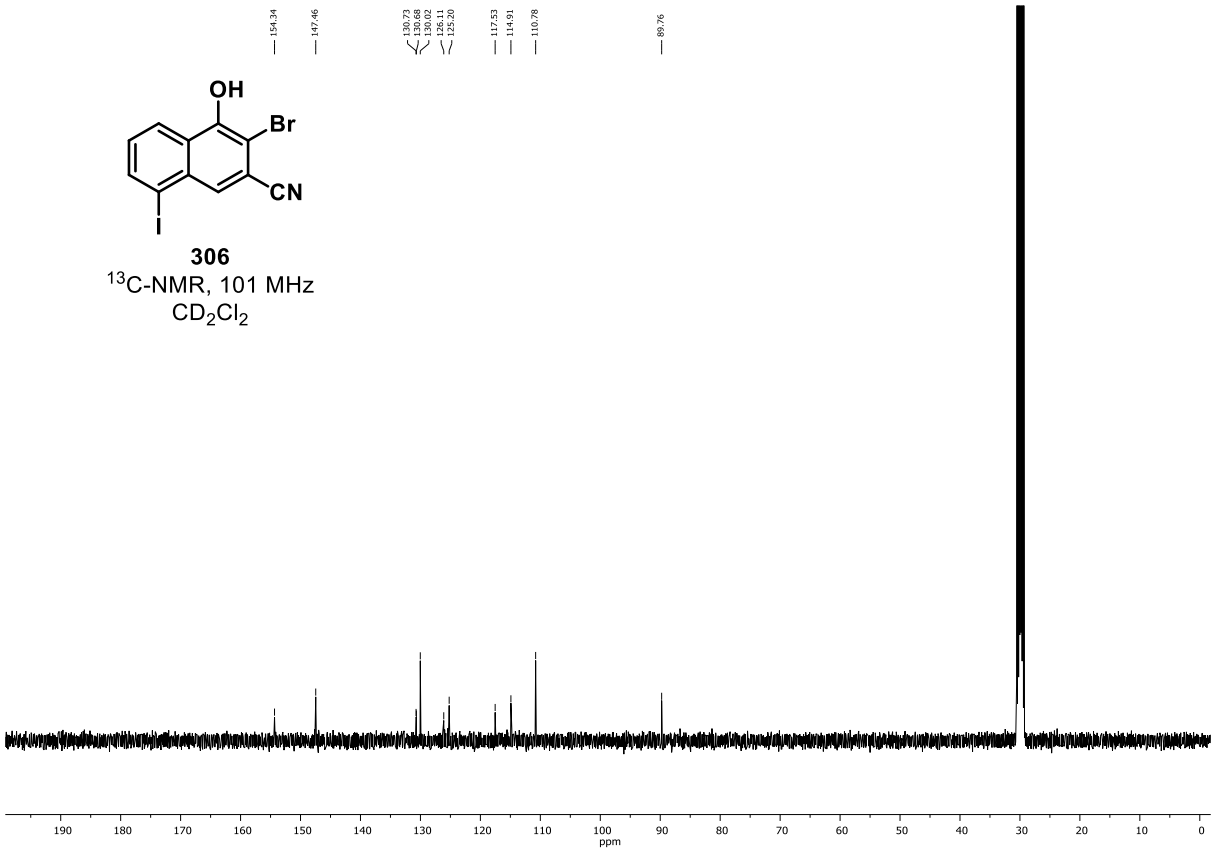
304
^{1}H-NMR, 400 MHz
$CDCl_3$



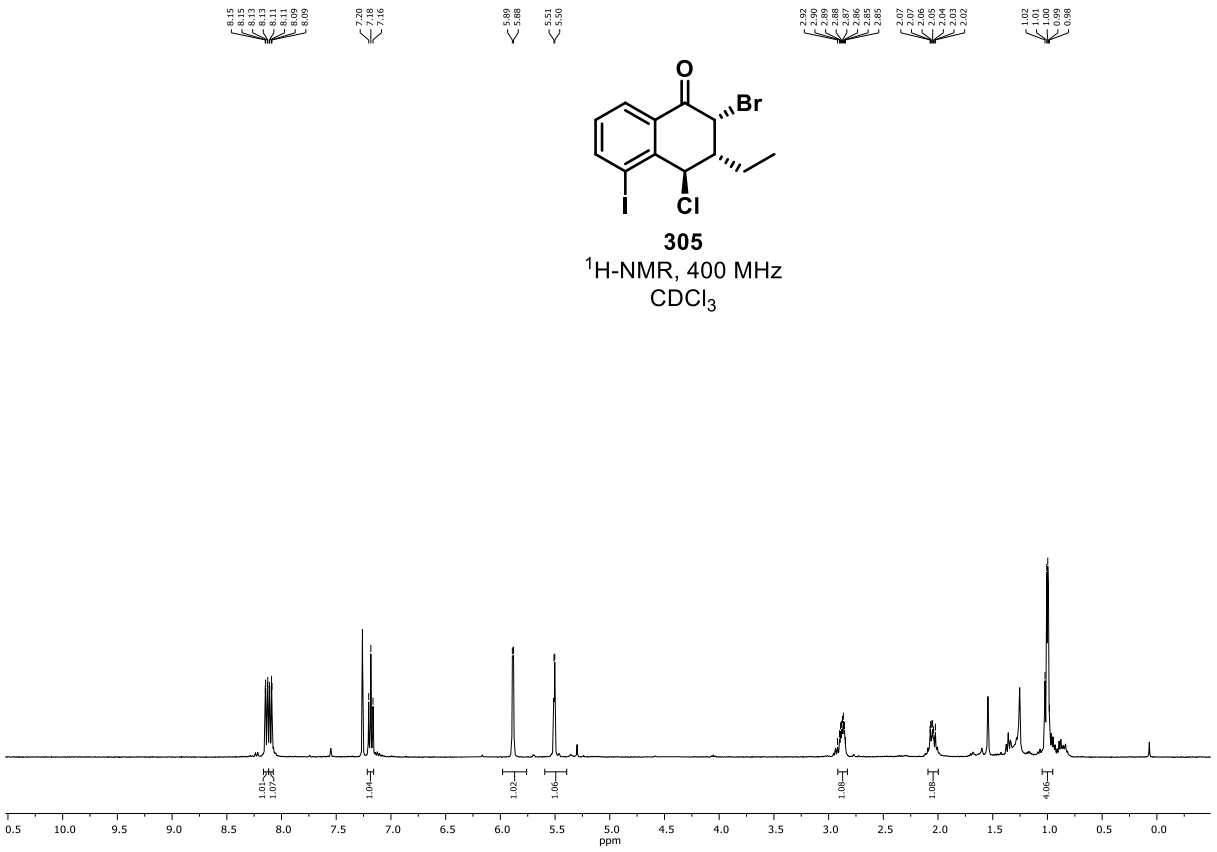
304
^{13}C-NMR, 101 MHz
$CDCl_3$



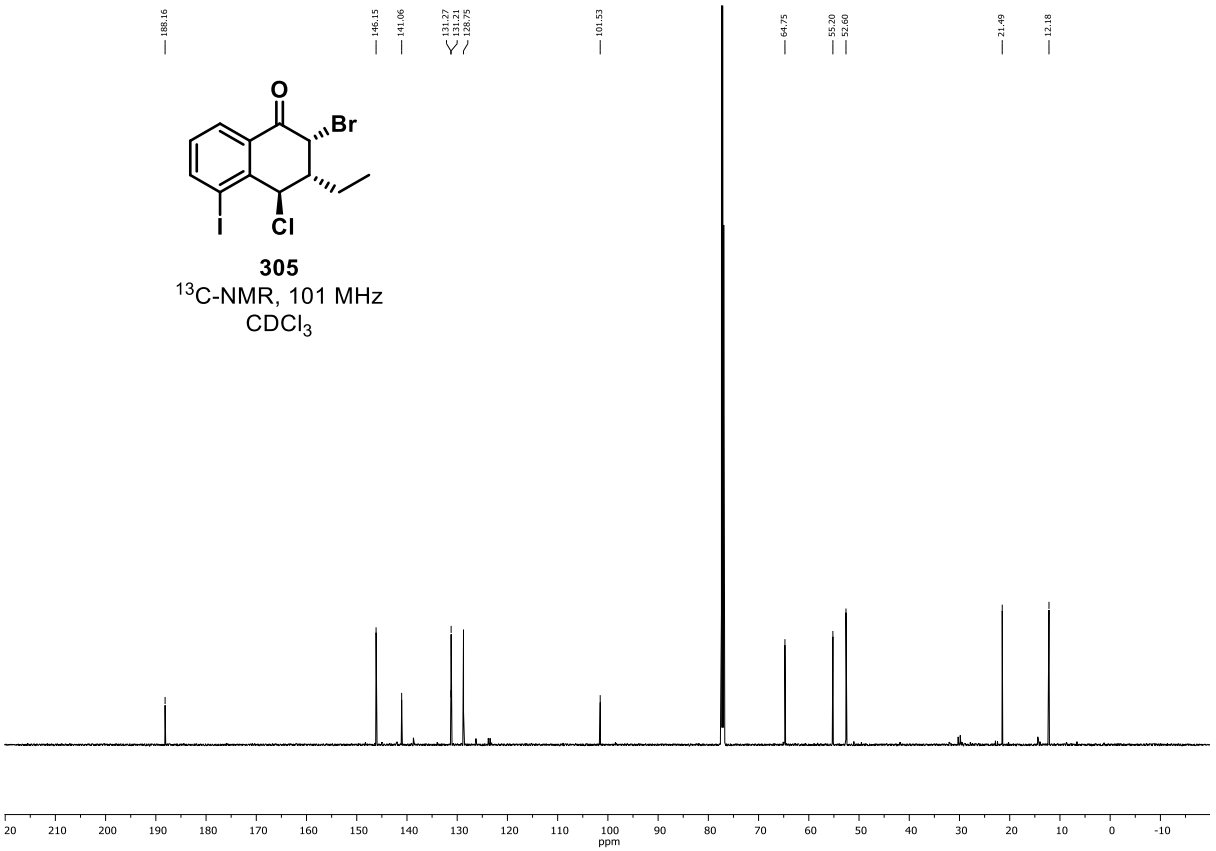
306
^{1}H-NMR, 400 MHz
CD_2Cl_2



306
^{13}C-NMR, 101 MHz
CD_2Cl_2



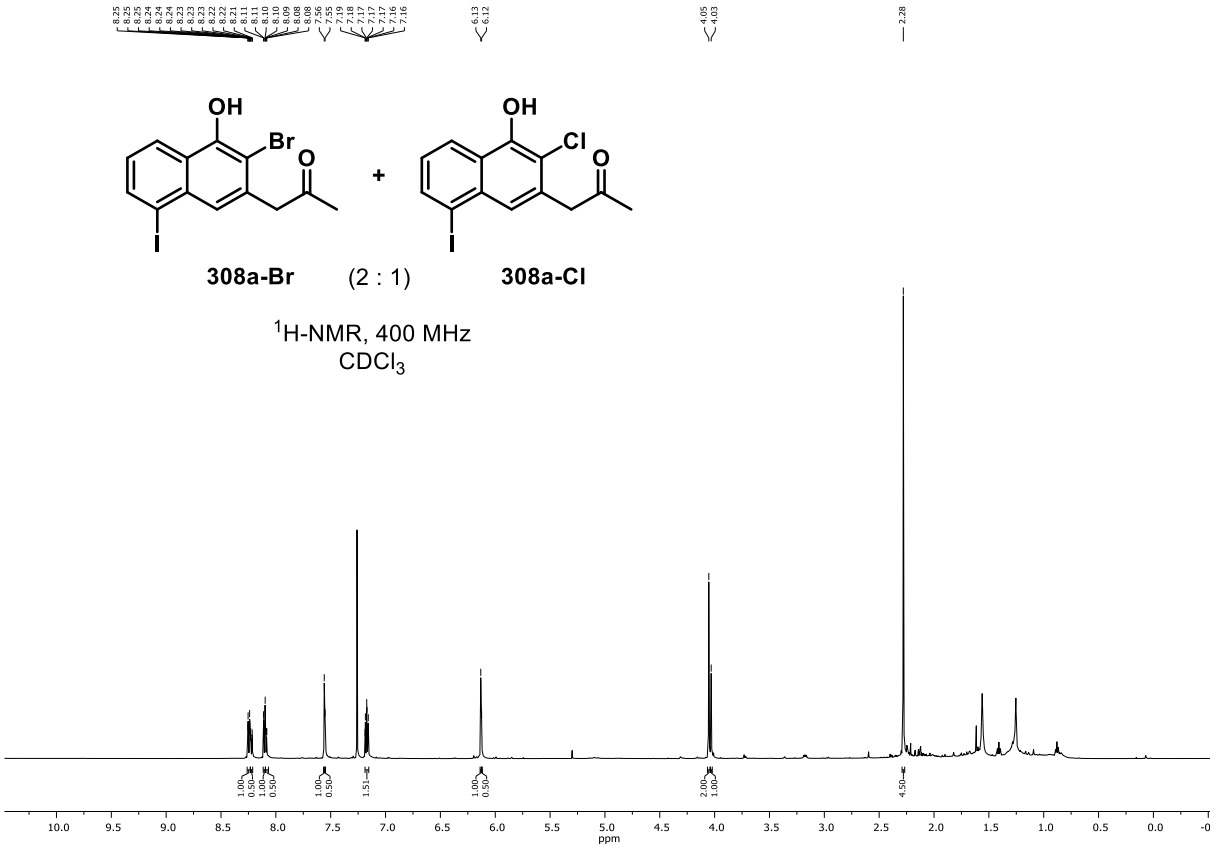
305
^{1}H-NMR, 400 MHz
$CDCl_3$



305

^{13}C-NMR, 101 MHz

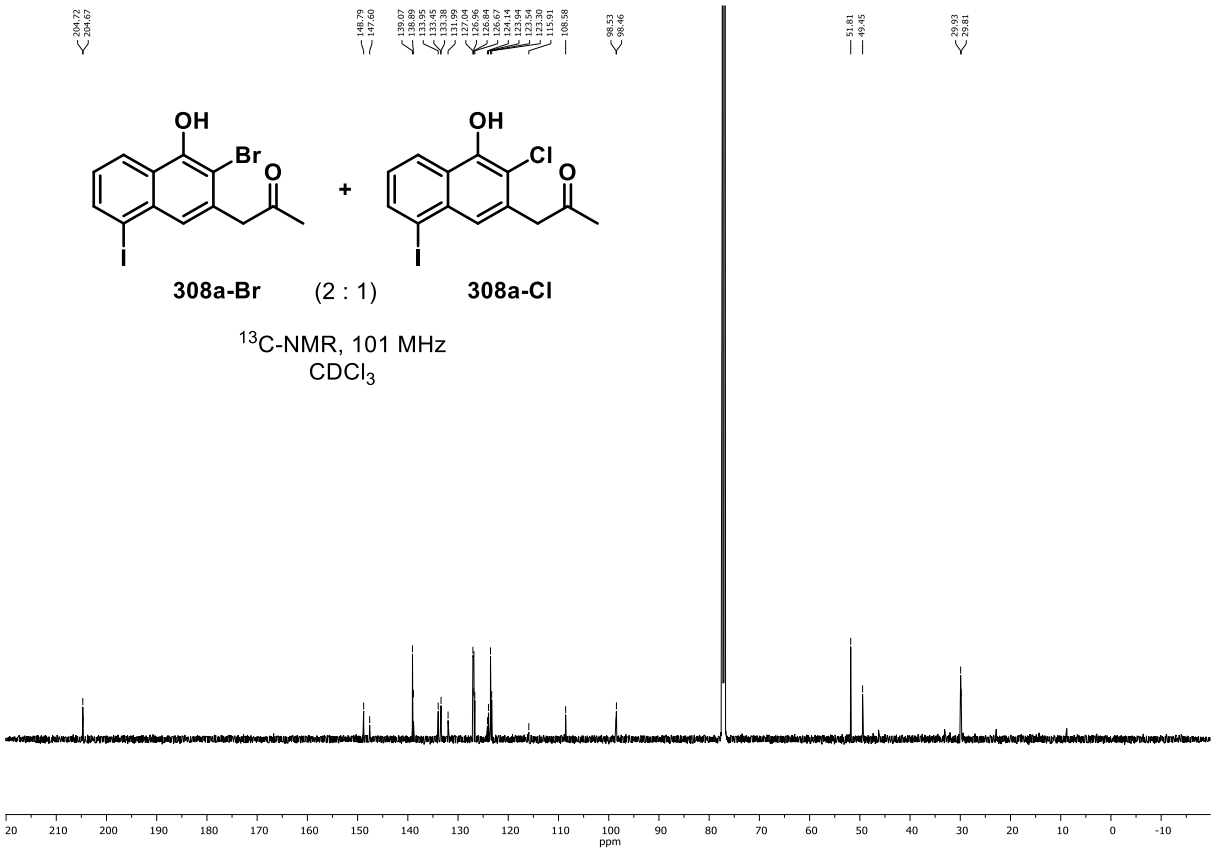
$CDCl_3$

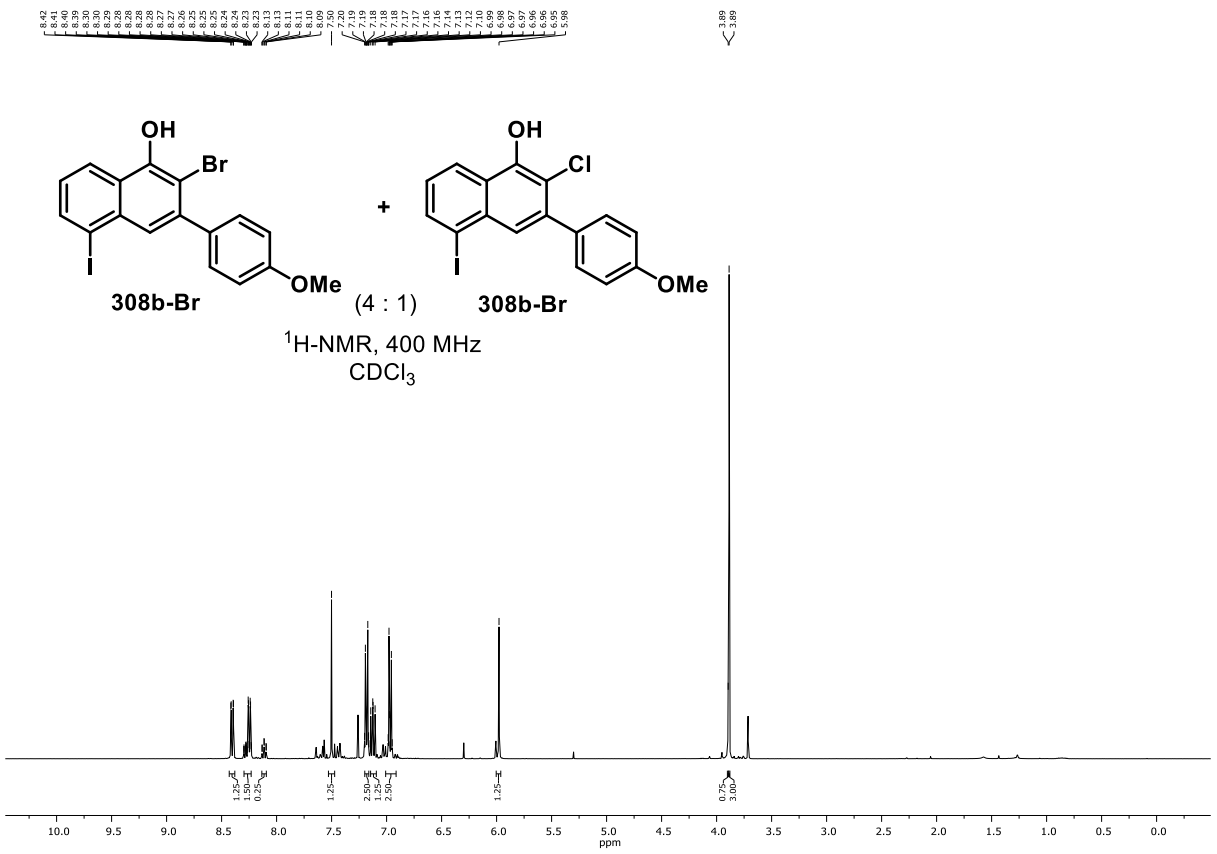


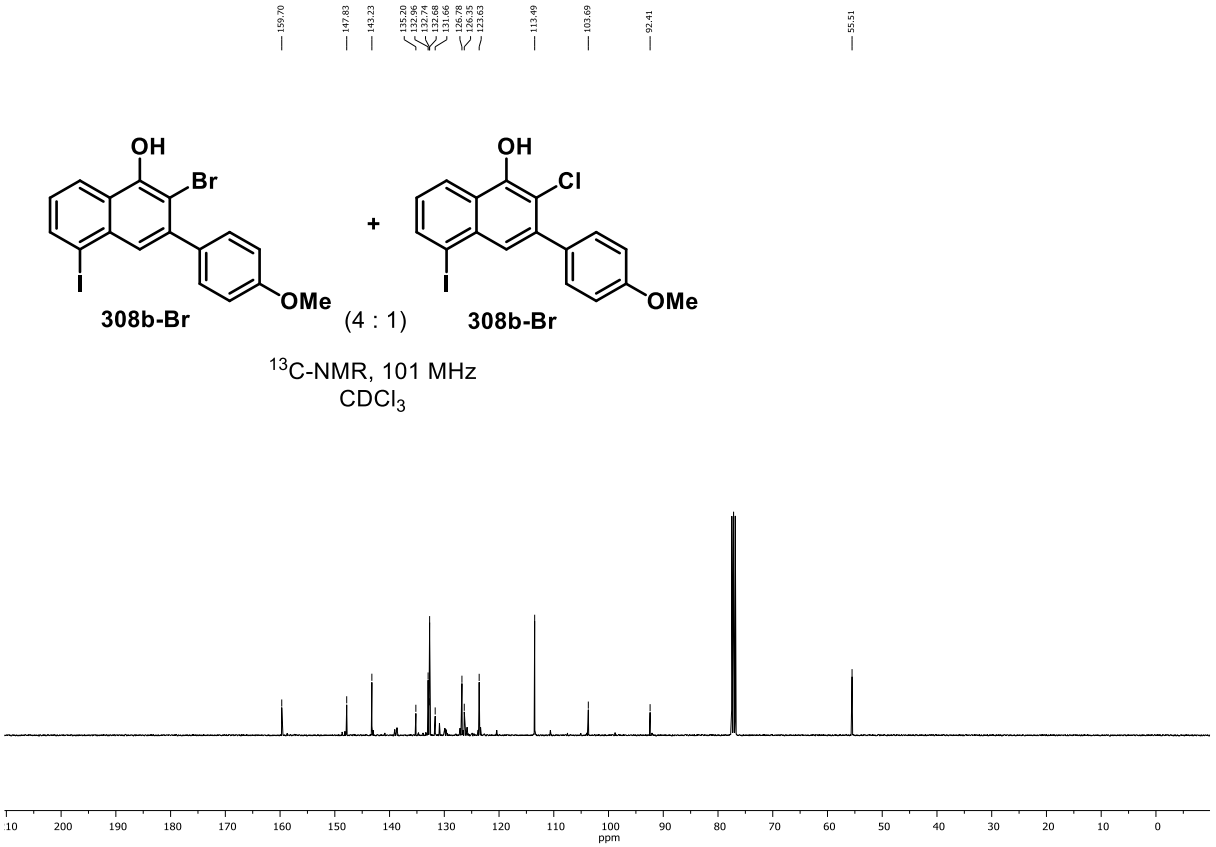
308a-Br (2 : 1) **308a-Cl**

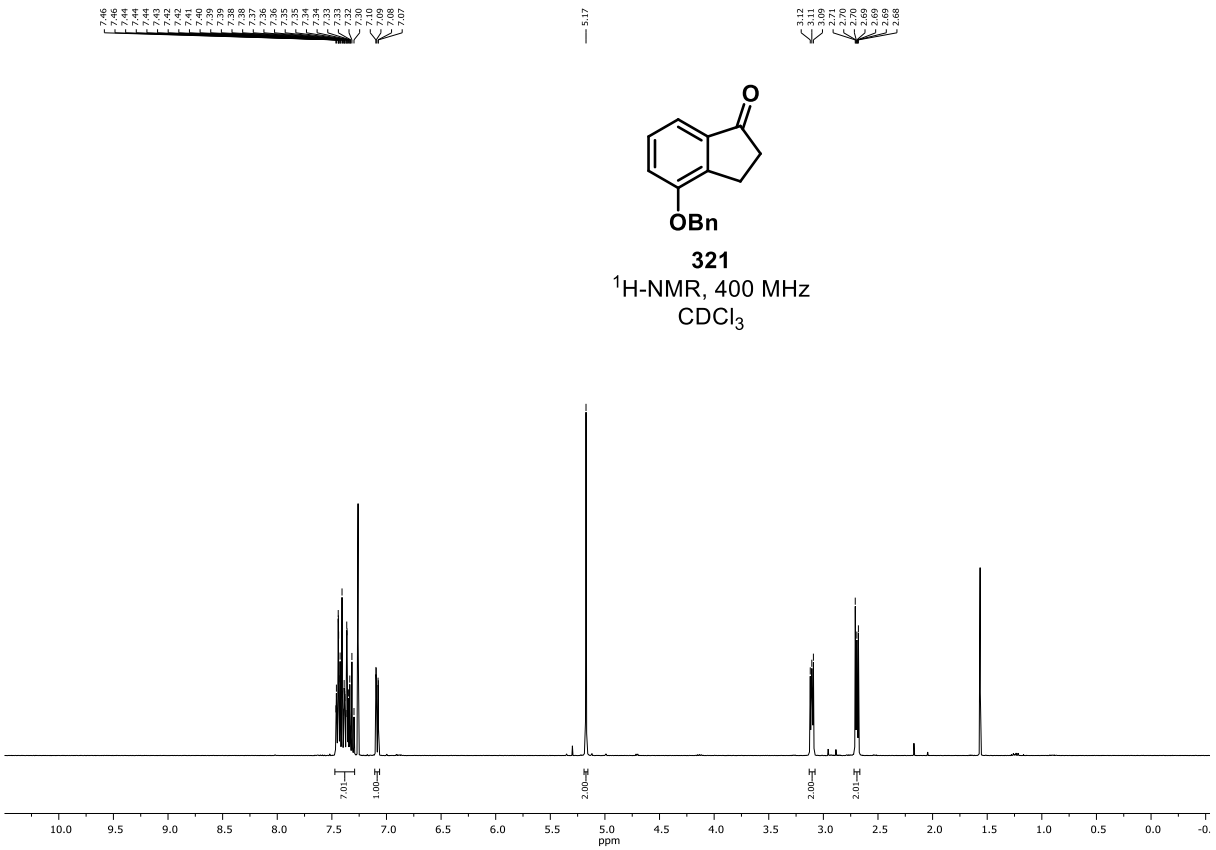
^{1}H-NMR, 400 MHz

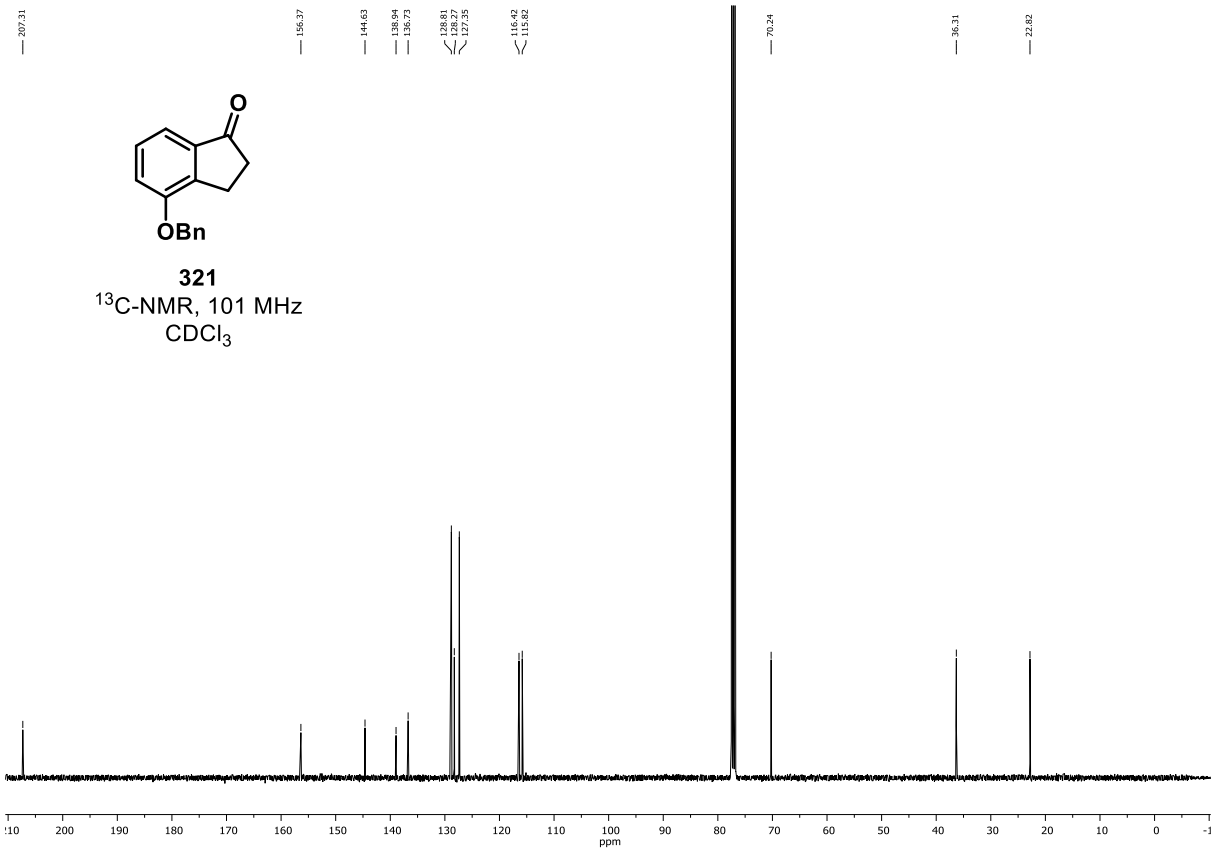
$CDCl_3$


OH
Br
O
+
OH
Cl
O
I
I
308a-Br
(2 : 1)
308a-Cl
13C-NMR, 101 MHz
CDCl3
ppm

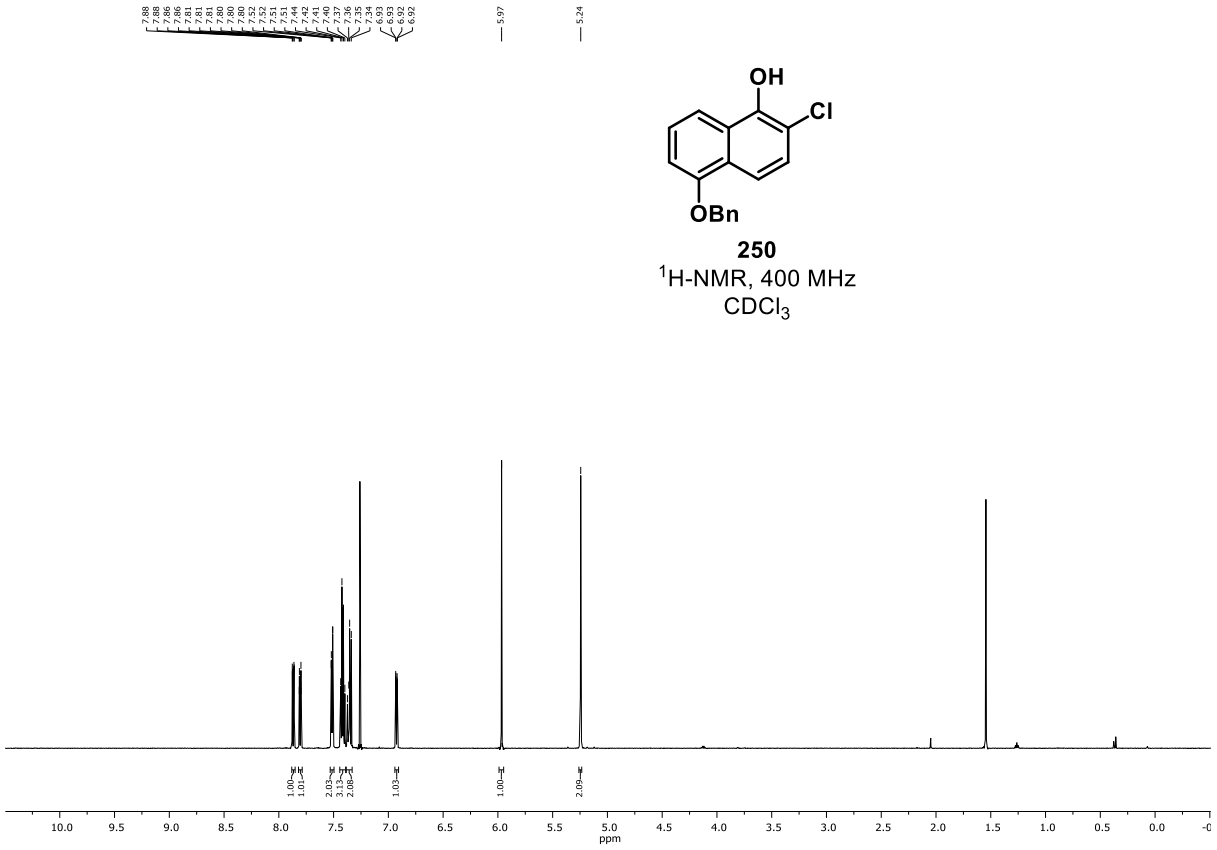

OH
Br
+
OH
Cl
I
I
OMe
OMe
308b-Br
(4 : 1)
308b-Br
1H-NMR, 400 MHz
CDCl3
ppm


159.70
147.83
143.23
135.20
130.96
132.94
132.68
131.66
126.78
126.35
125.63
113.49
103.69
92.41
55.51
OH
Br
I
OMe
308b-Br
+
OH
Cl
I
OMe
308b-Br
(4 : 1)
13C-NMR, 101 MHz
CDCl3
ppm

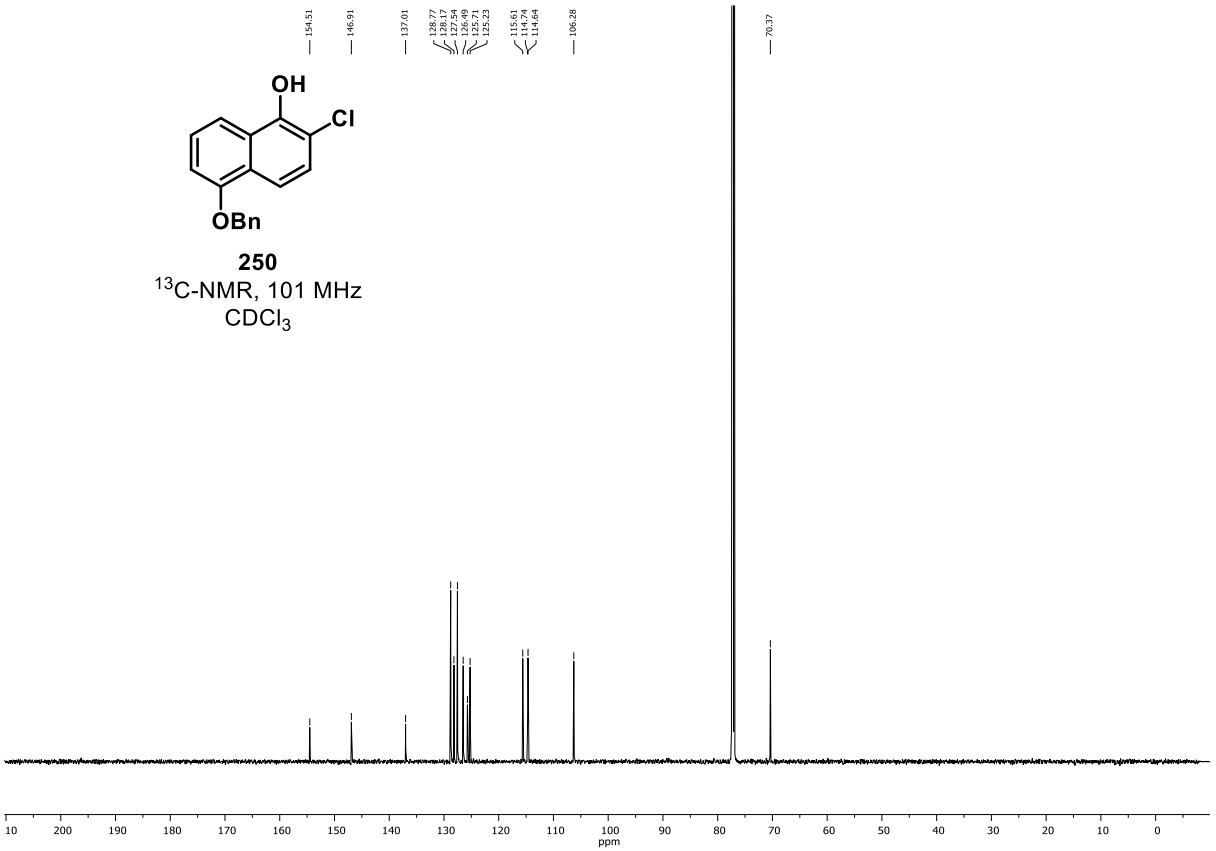

7.46
7.46
7.44
7.44
7.44
7.43
7.42
7.42
7.41
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.30
7.10
7.09
7.08
7.07
5.17
3.12
3.11
3.09
3.71
2.70
2.70
2.69
2.69
2.69
2.68
O
OBn
321
1H-NMR, 400 MHz
CDCl3
7.01
1.00
2.00
2.00
2.01
ppm



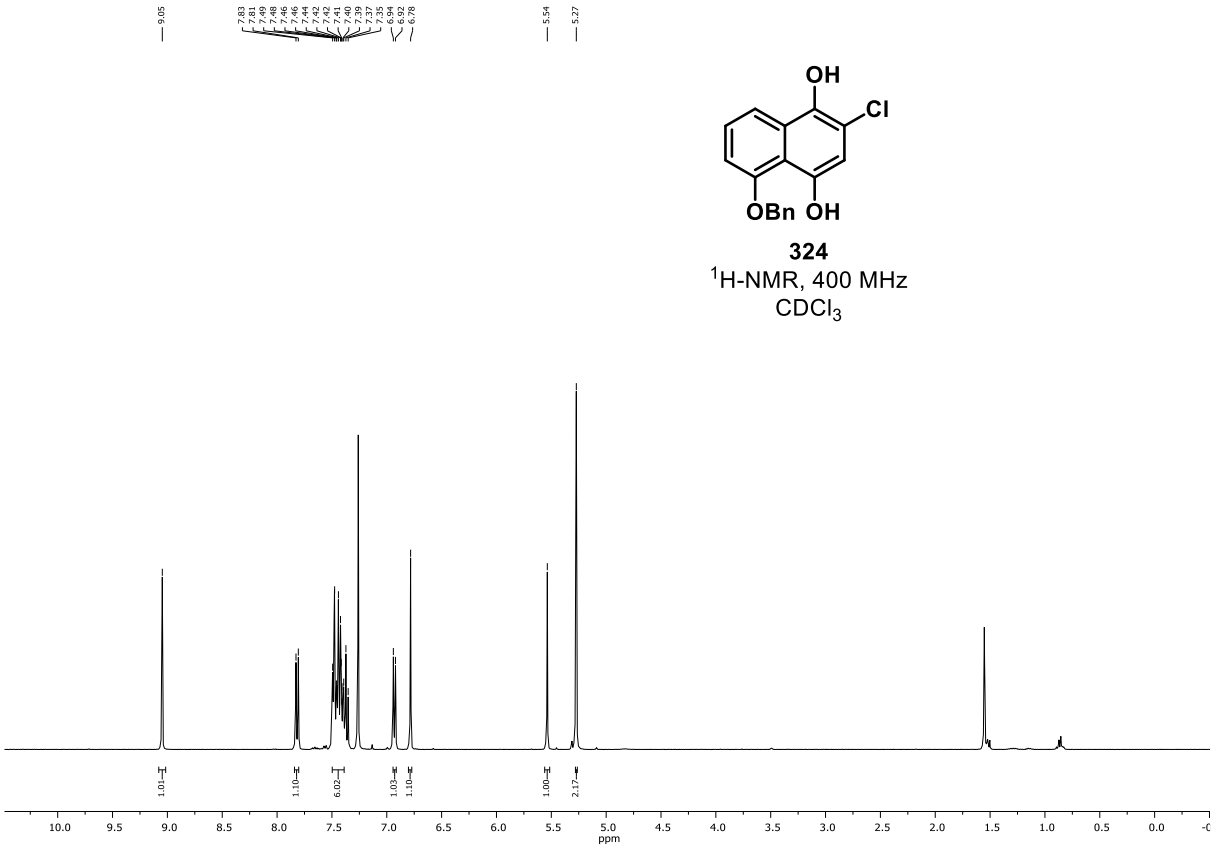
321
^{13}C-NMR, 101 MHz
$CDCl_3$



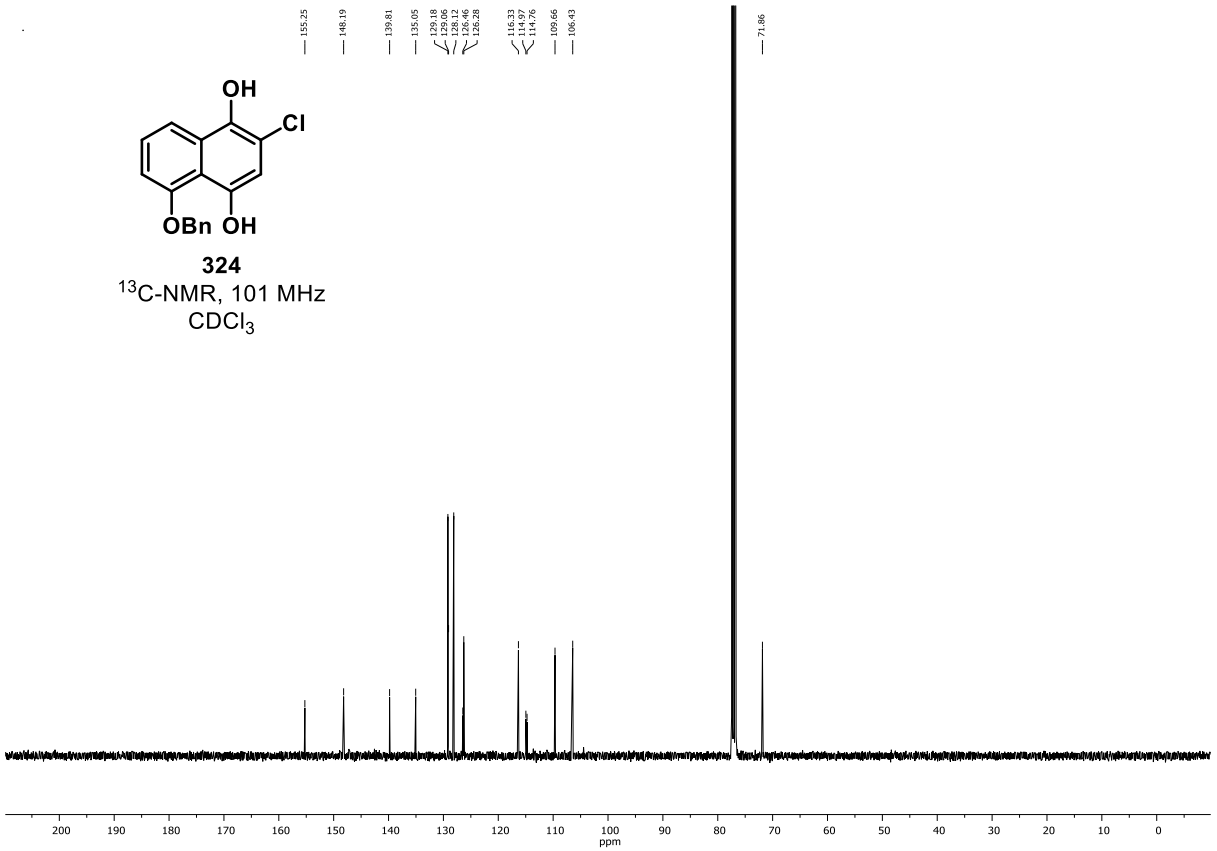
250
^{1}H-NMR, 400 MHz
$CDCl_3$



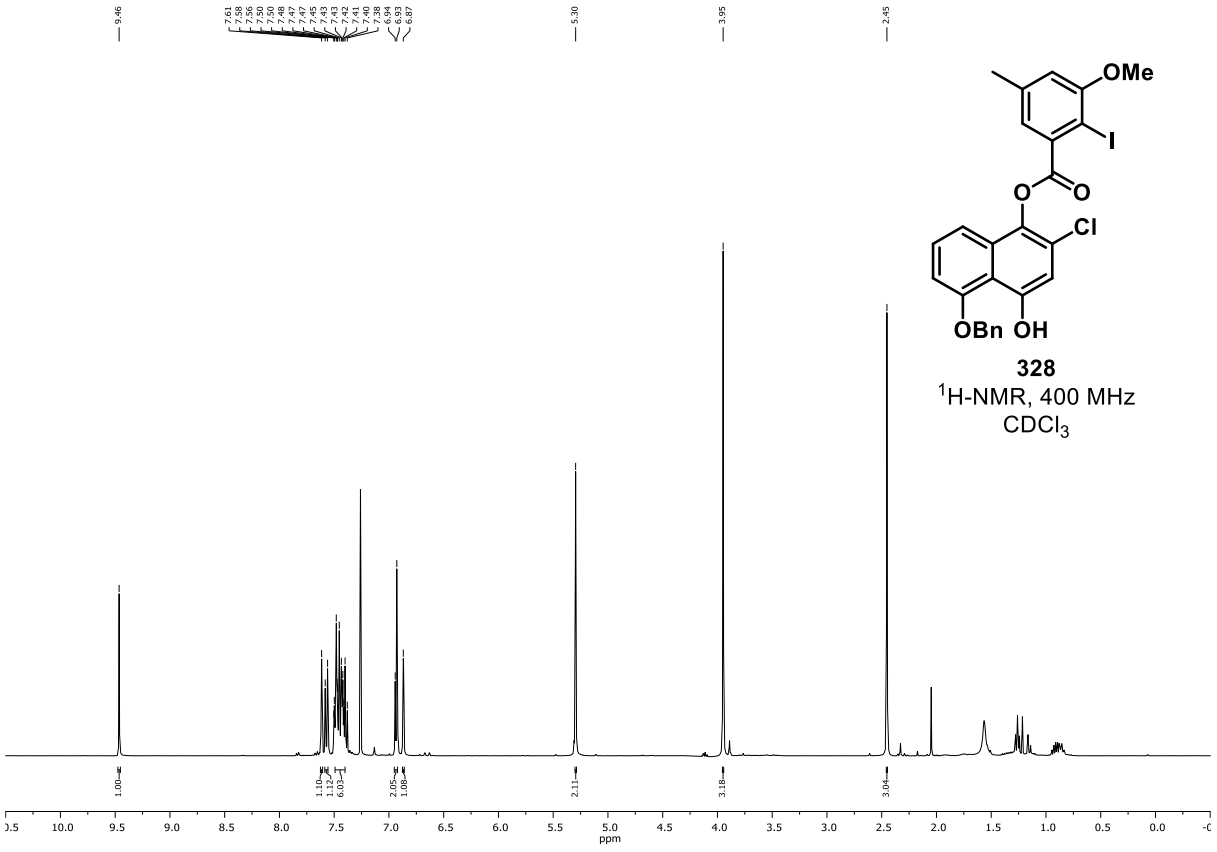
250
^{13}C-NMR, 101 MHz
$CDCl_3$



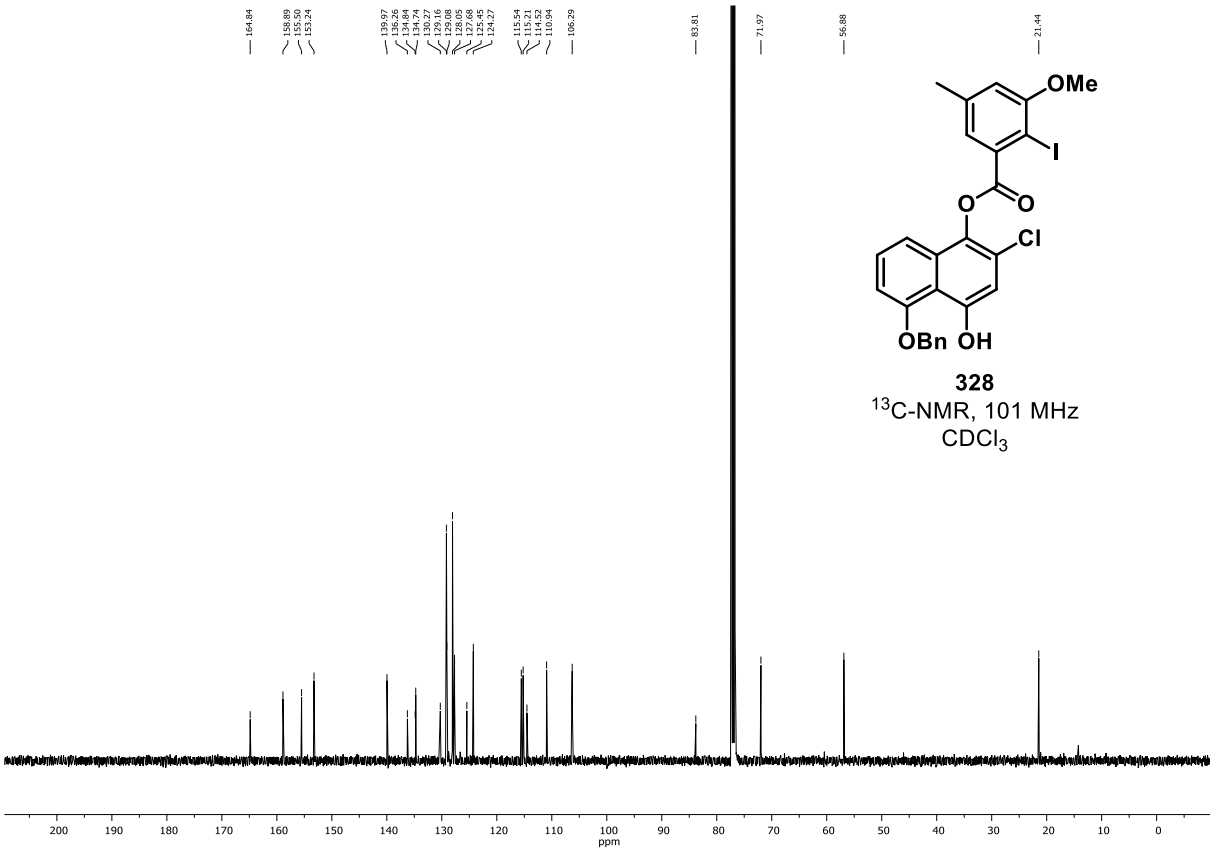
324
^{1}H-NMR, 400 MHz
$CDCl_3$



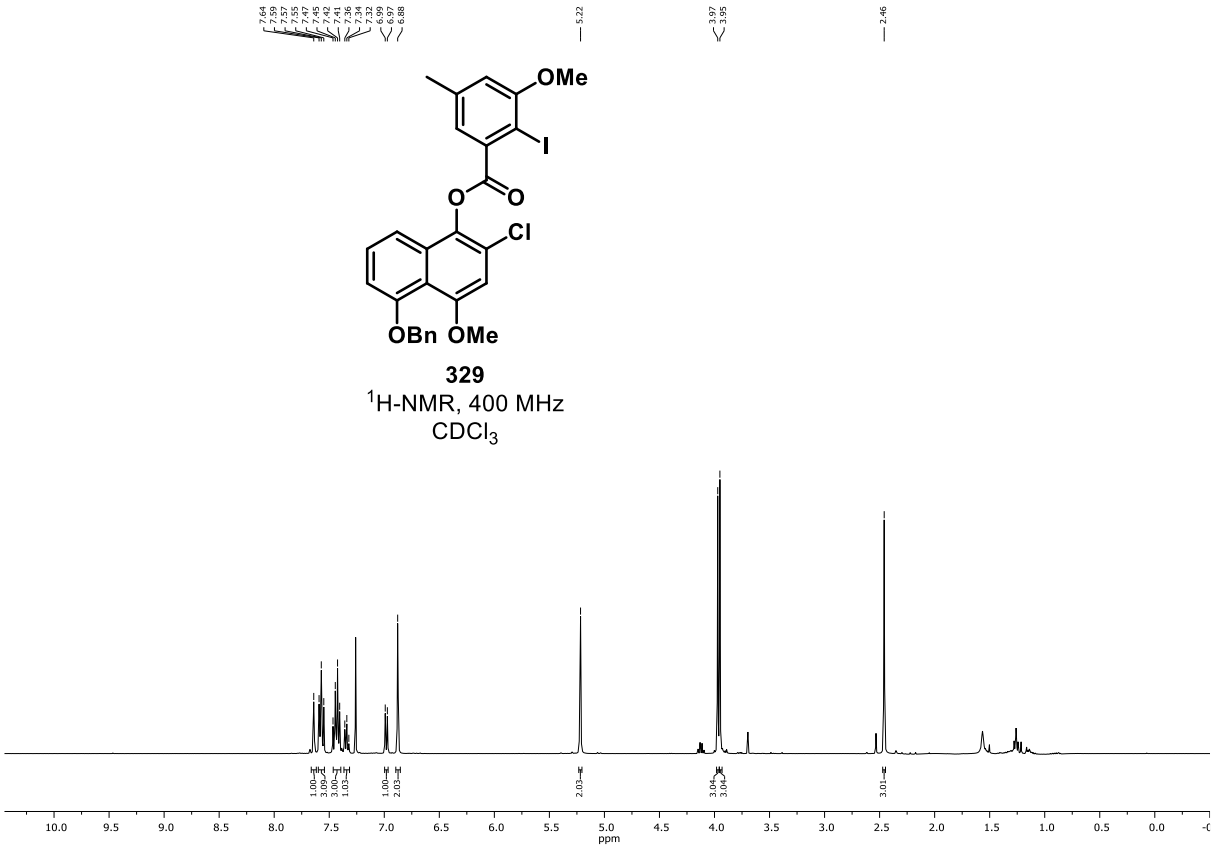
324
^{13}C-NMR, 101 MHz
$CDCl_3$



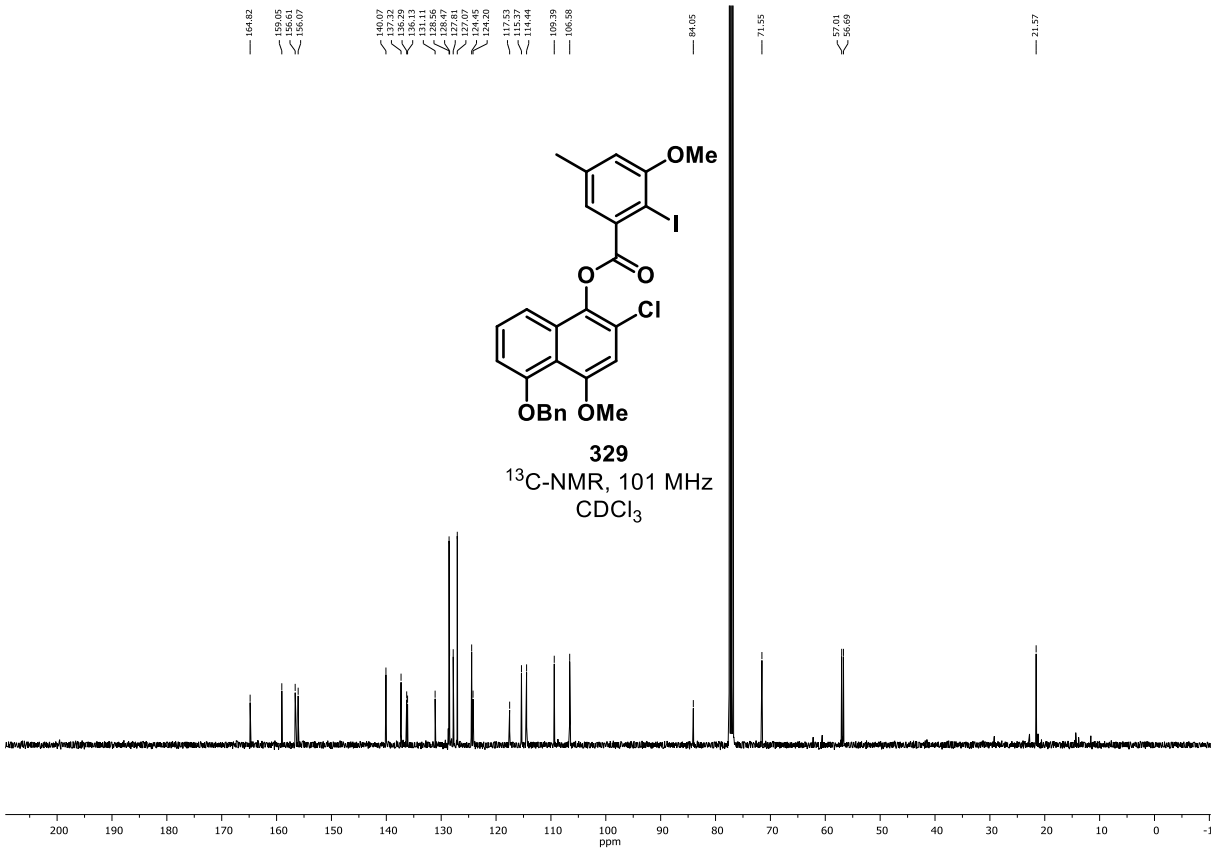
328
^{1}H-NMR, 400 MHz
$CDCl_3$



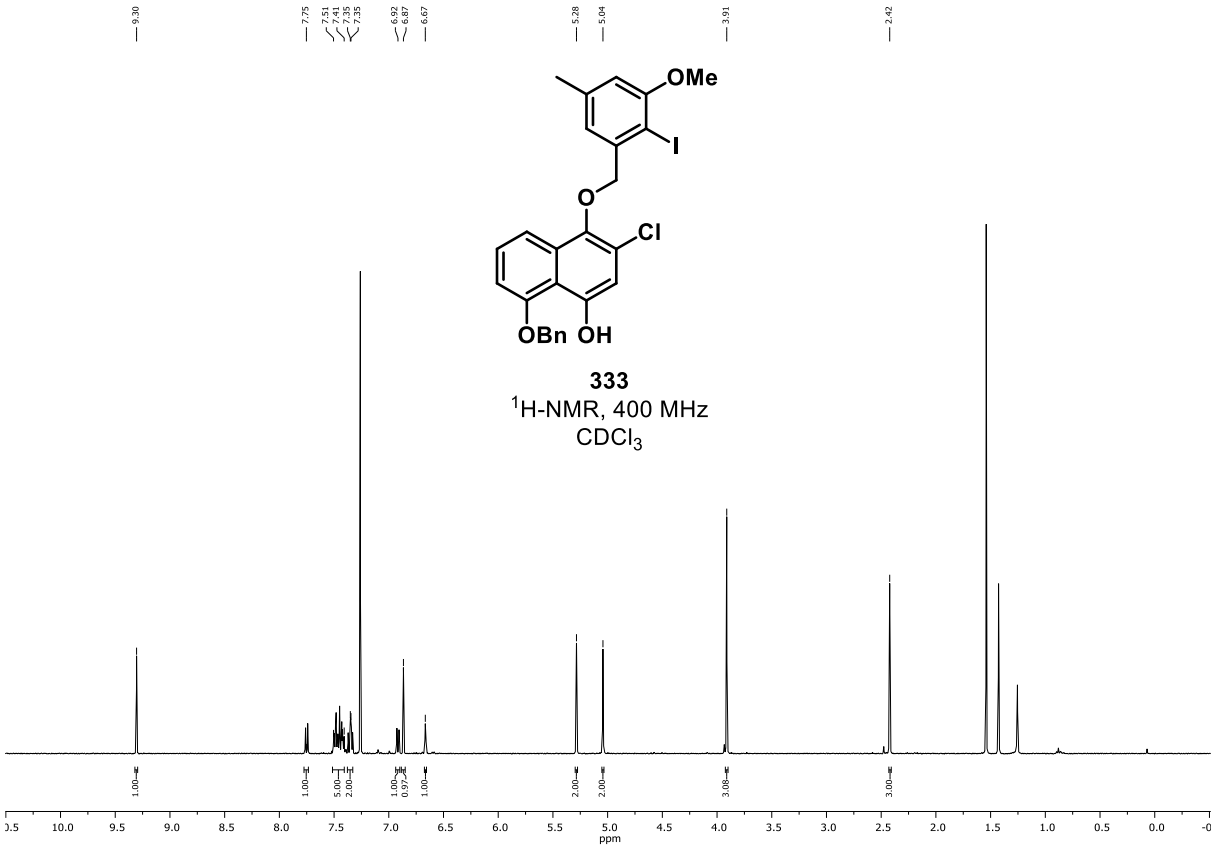
328
^{13}C-NMR, 101 MHz
$CDCl_3$



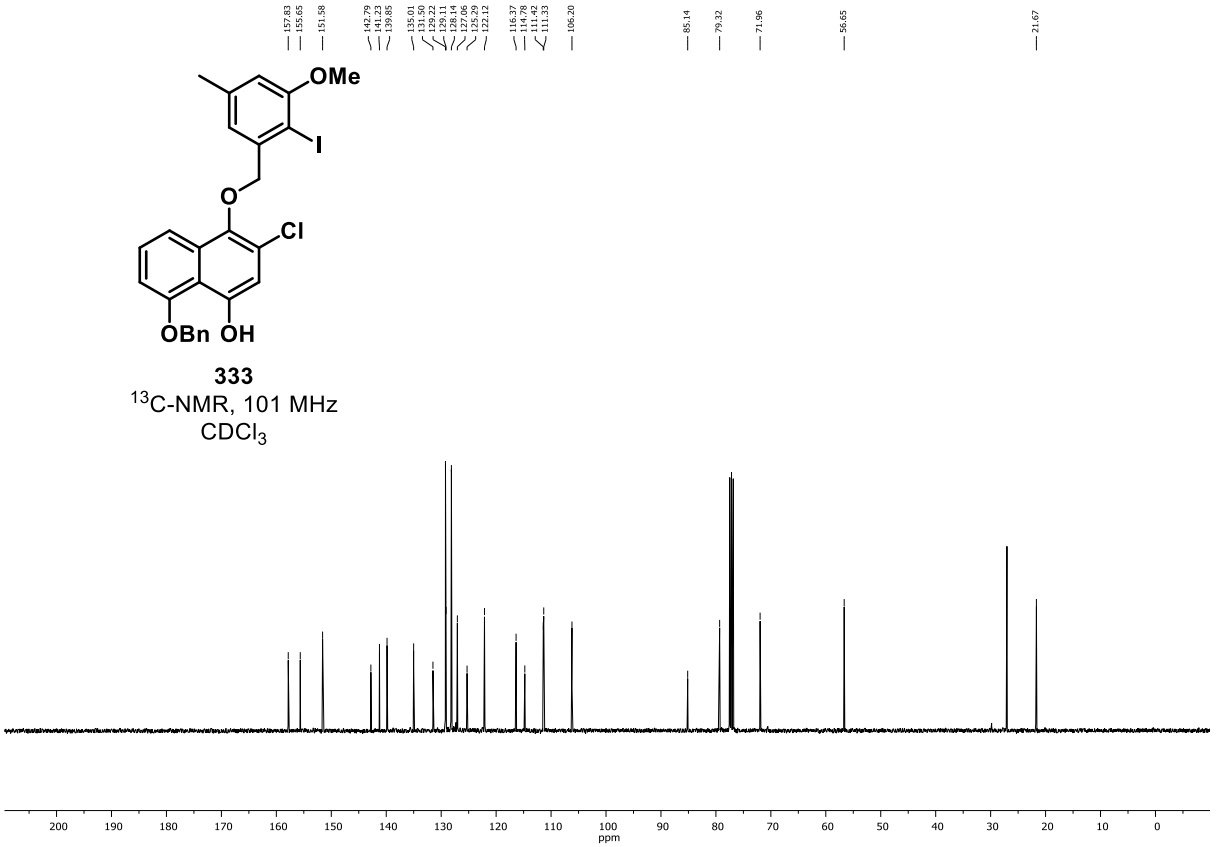
329
^{1}H-NMR, 400 MHz
$CDCl_3$



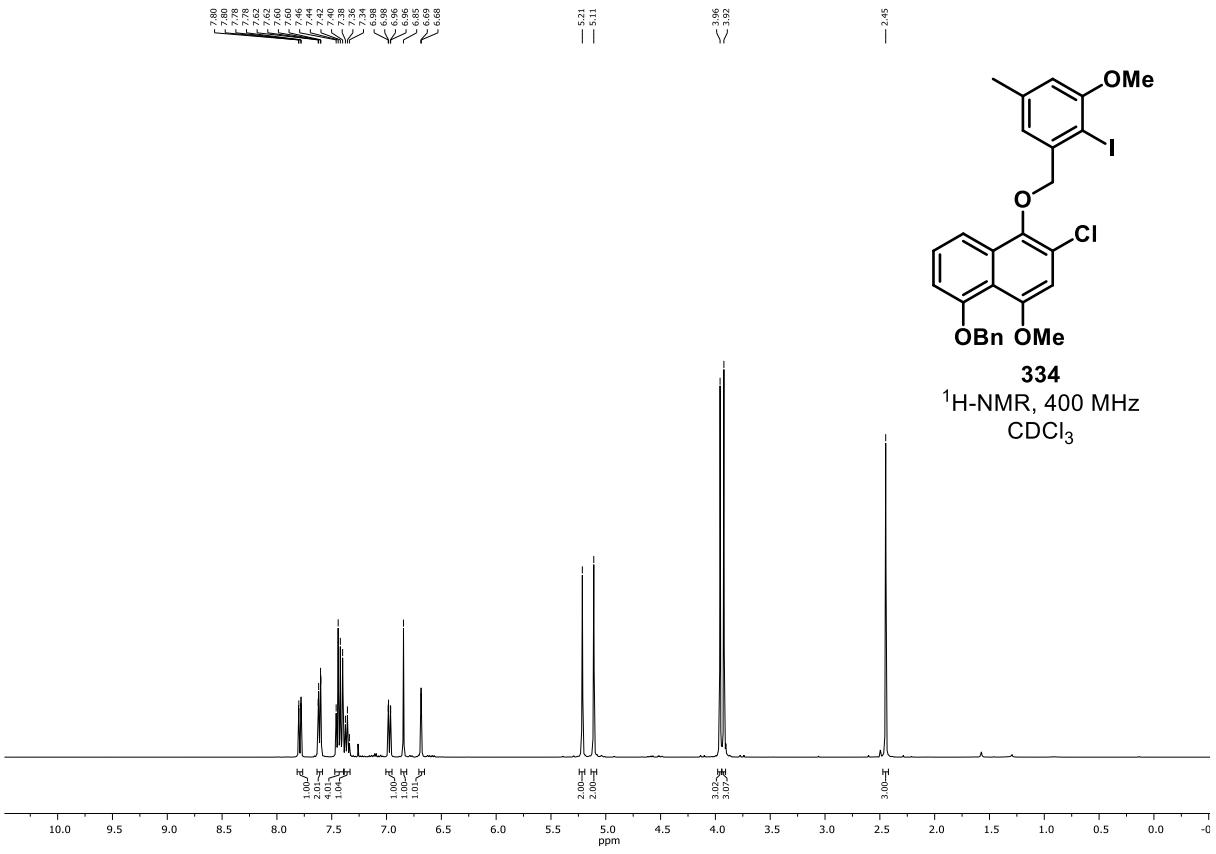
329
^{13}C-NMR, 101 MHz
$CDCl_3$



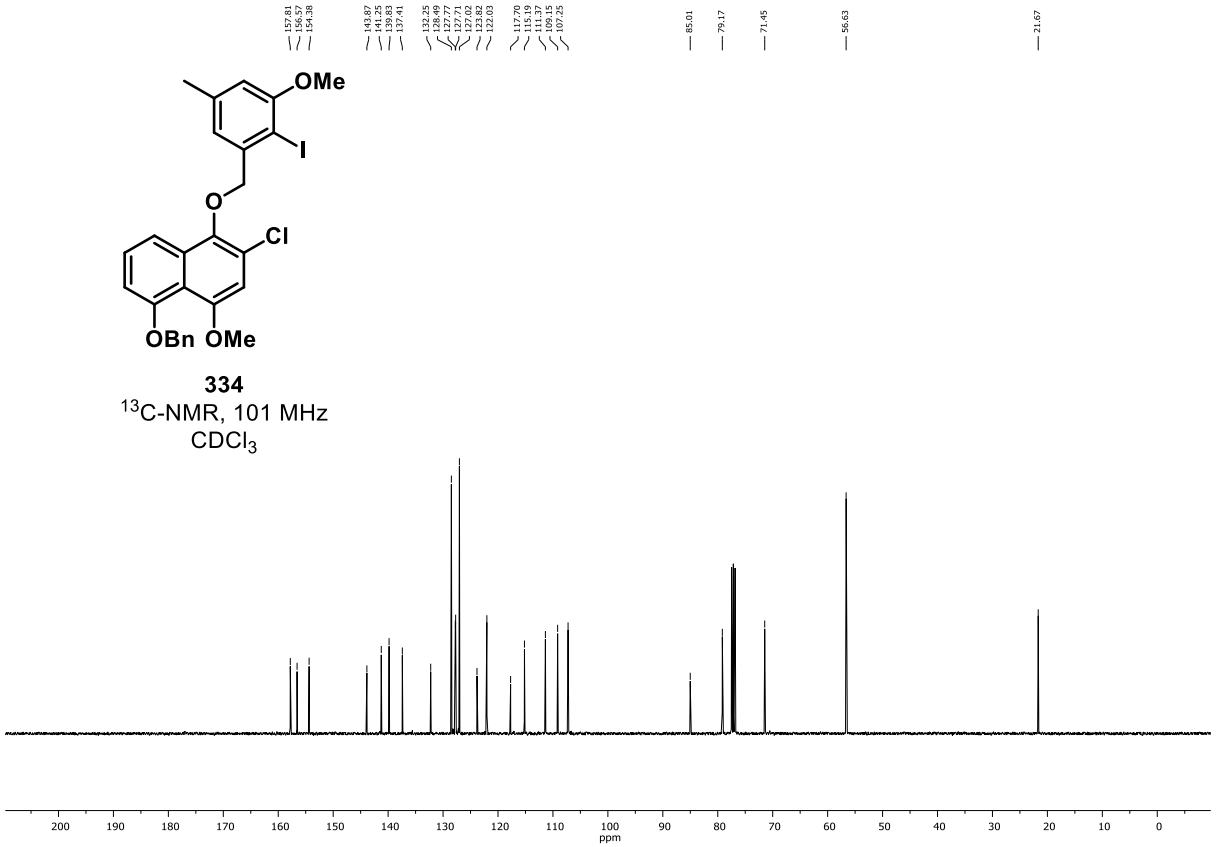
333
^{1}H-NMR, 400 MHz
$CDCl_3$



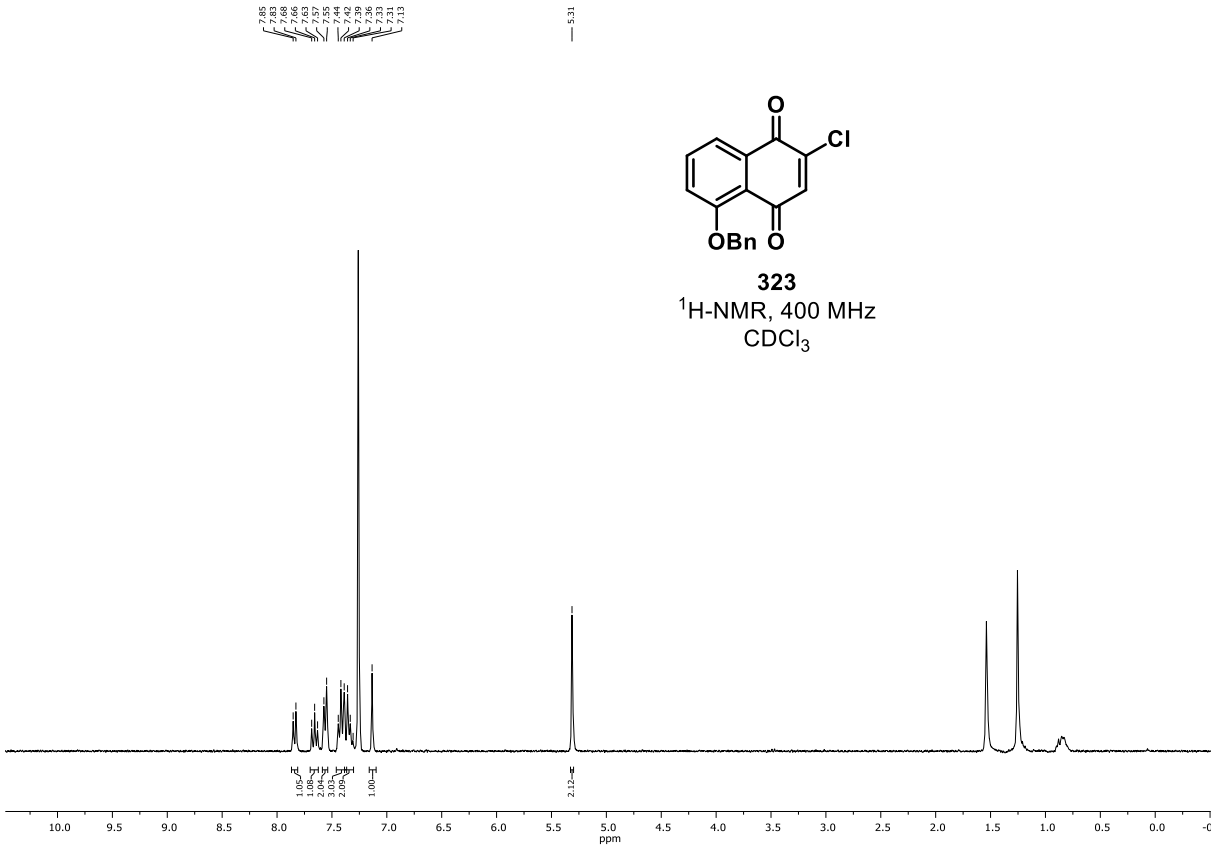
333
^{13}C-NMR, 101 MHz
$CDCl_3$



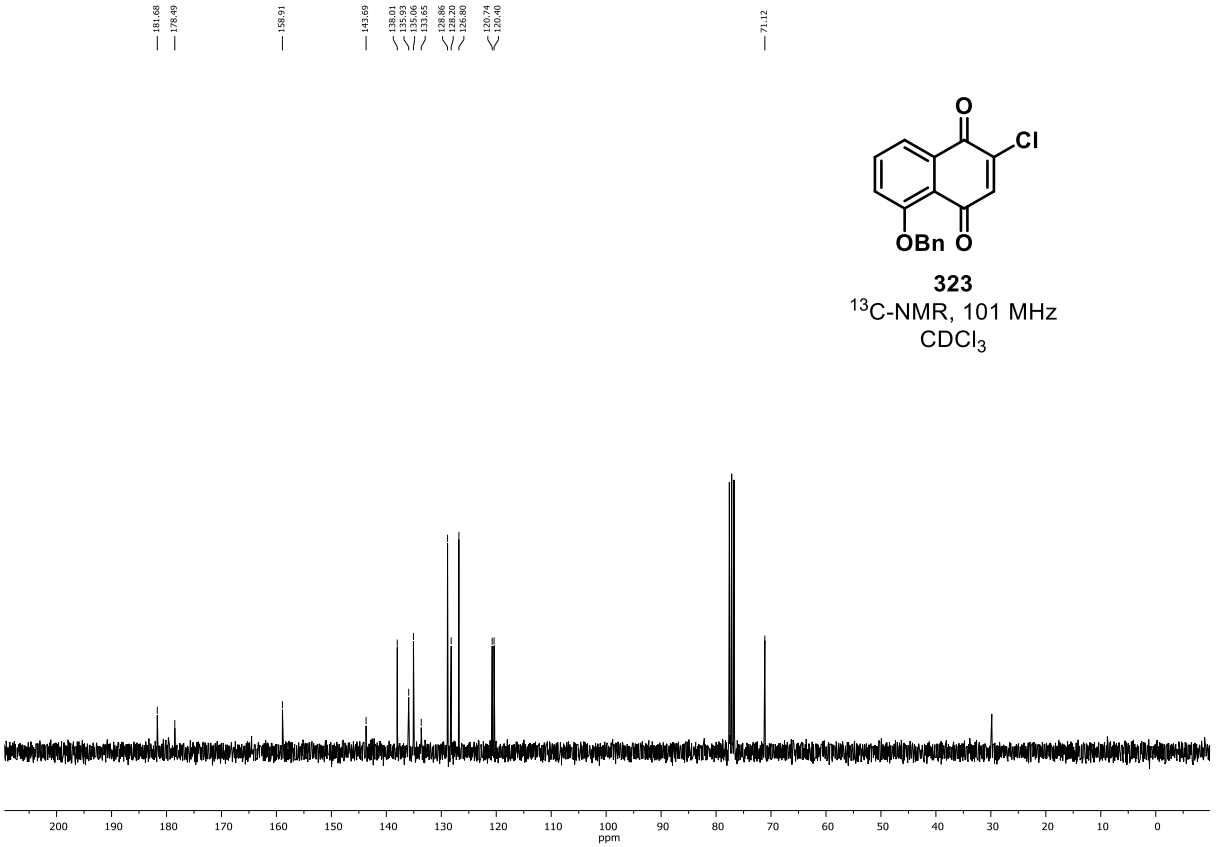
334
^{1}H-NMR, 400 MHz
$CDCl_3$



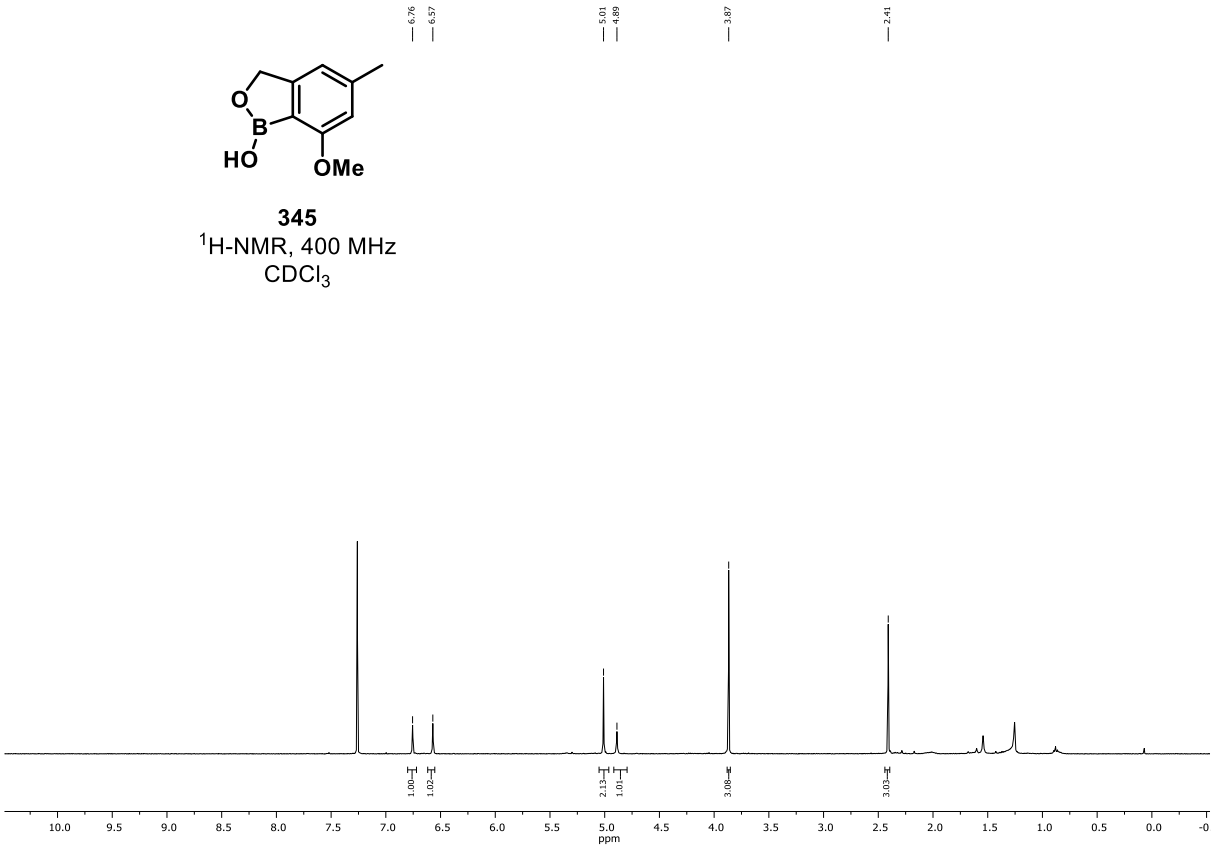
334
^{13}C-NMR, 101 MHz
$CDCl_3$



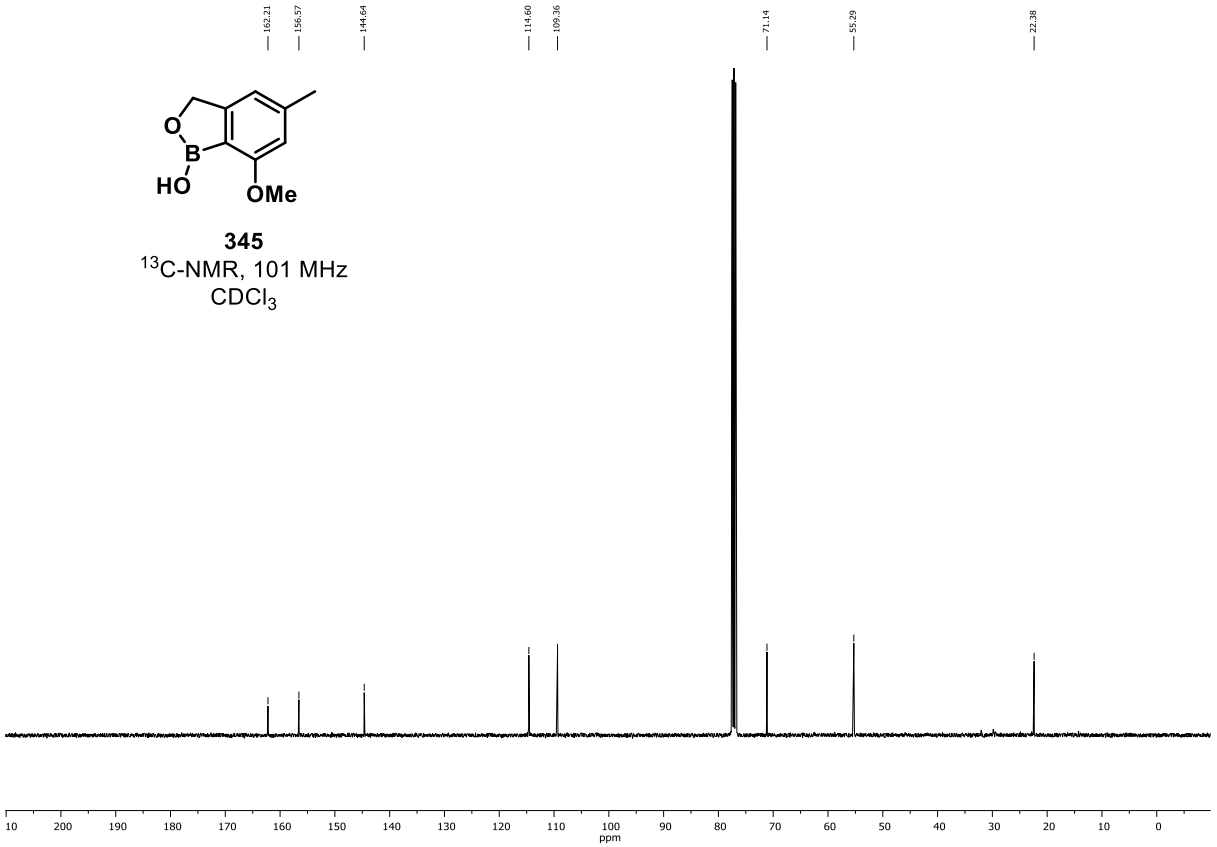
323
^{1}H-NMR, 400 MHz
$CDCl_3$



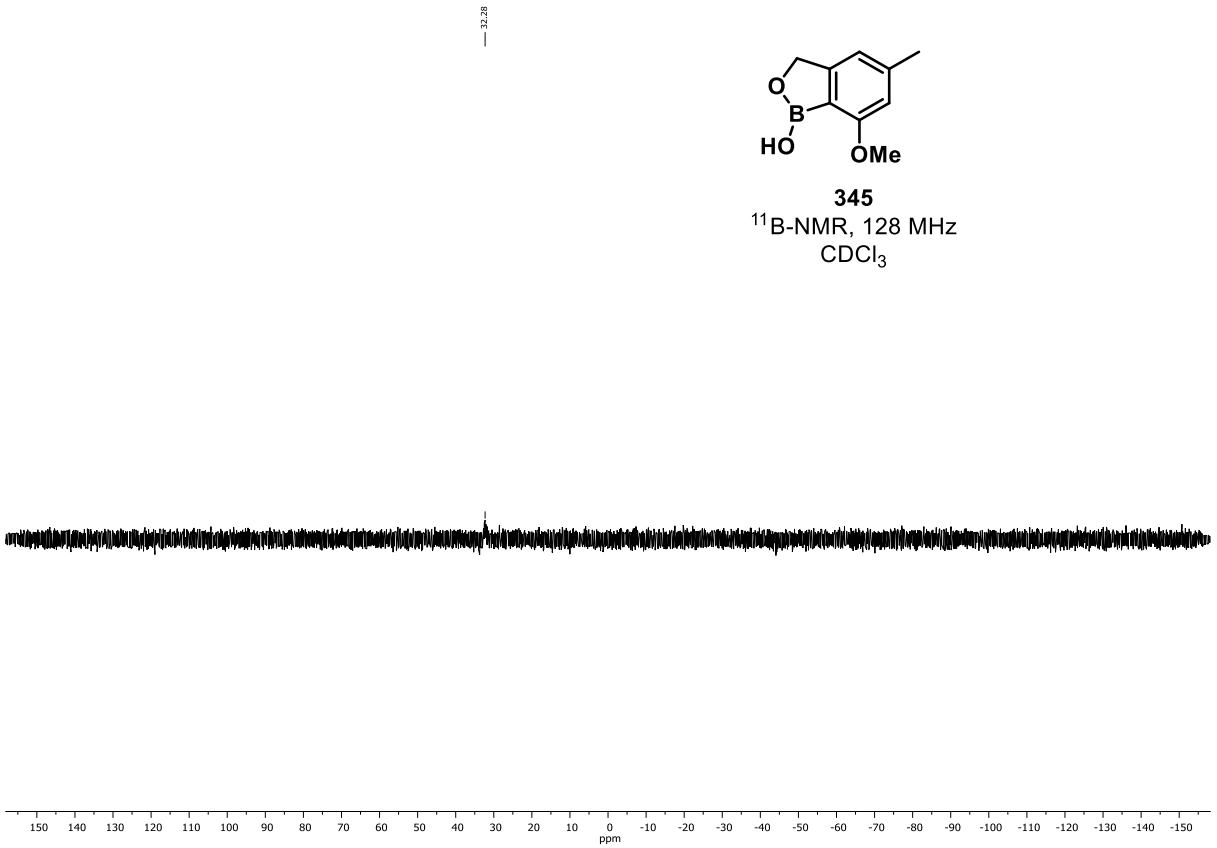
323
^{13}C-NMR, 101 MHz
$CDCl_3$



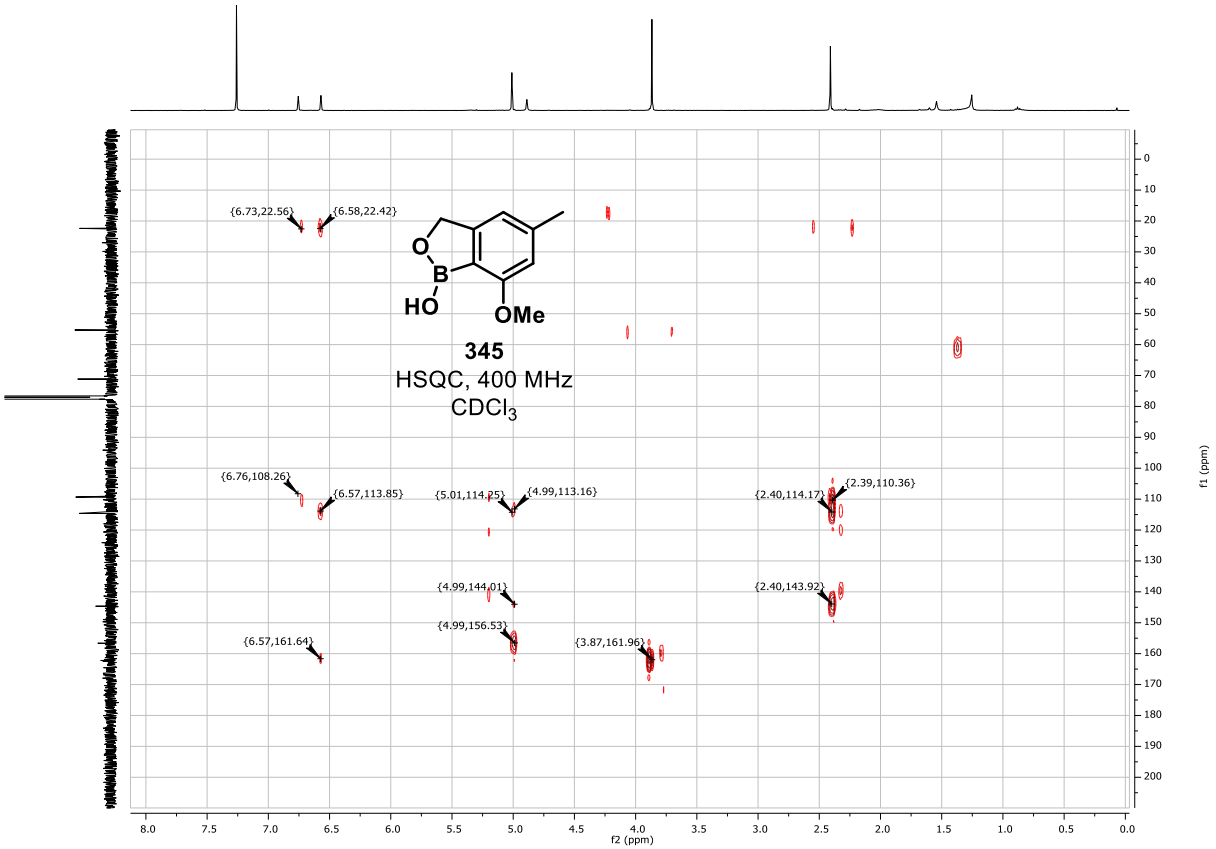
345
^{1}H-NMR, 400 MHz
$CDCl_3$



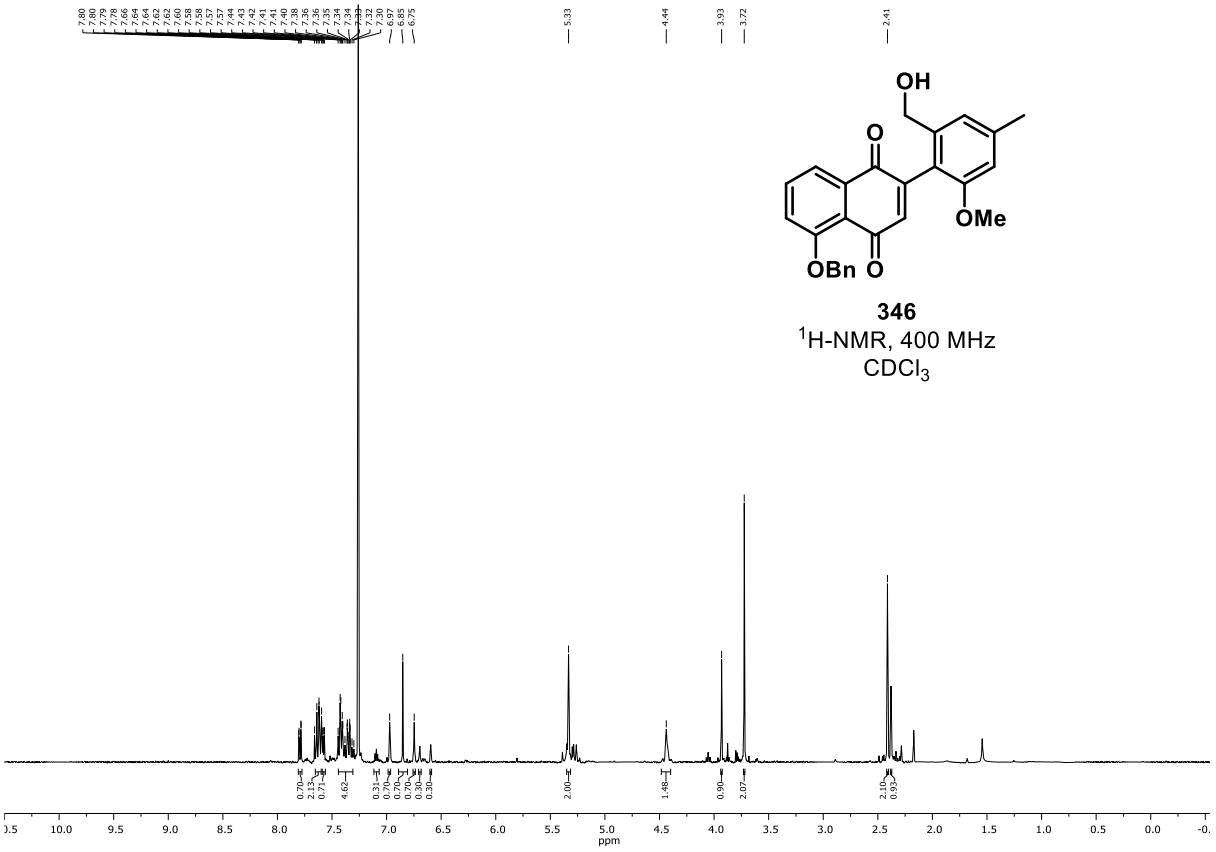
345
^{13}C-NMR, 101 MHz
$CDCl_3$



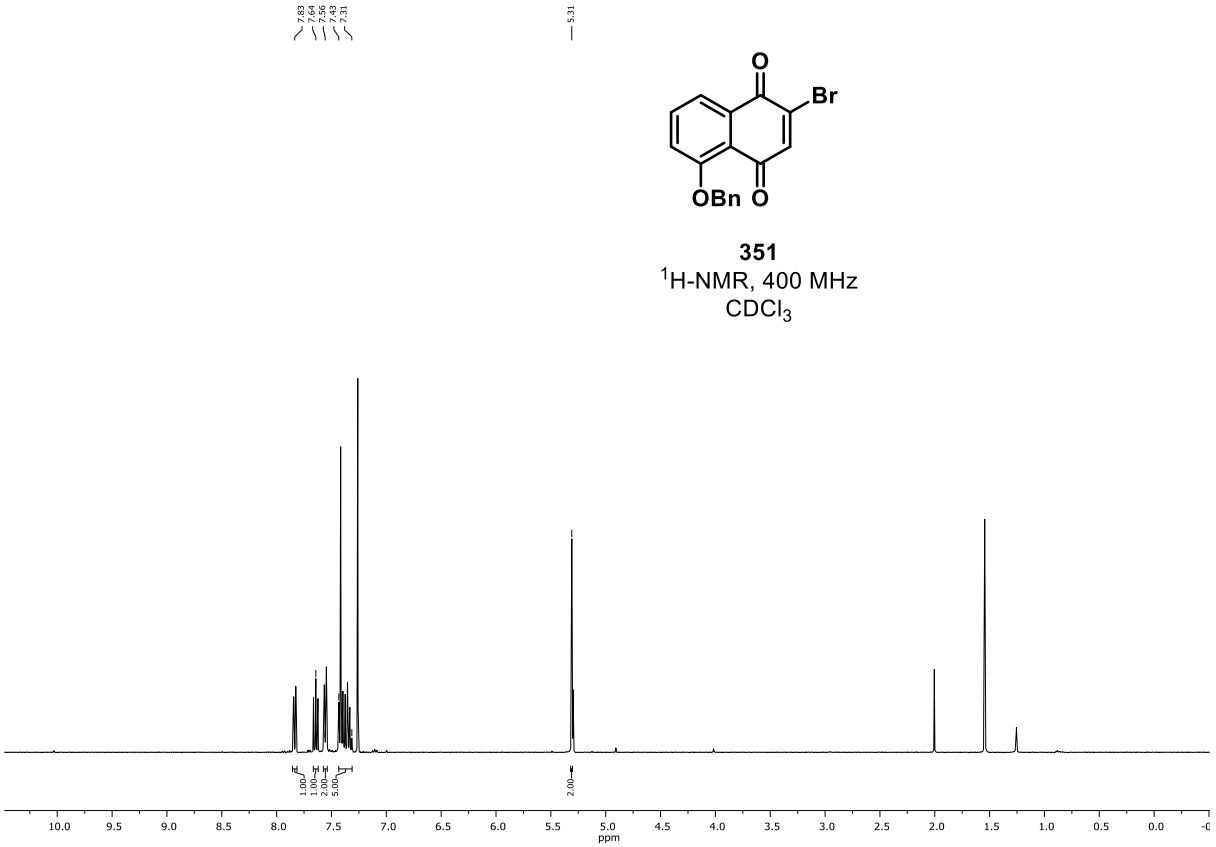
345
^{11}B-NMR, 128 MHz
$CDCl_3$



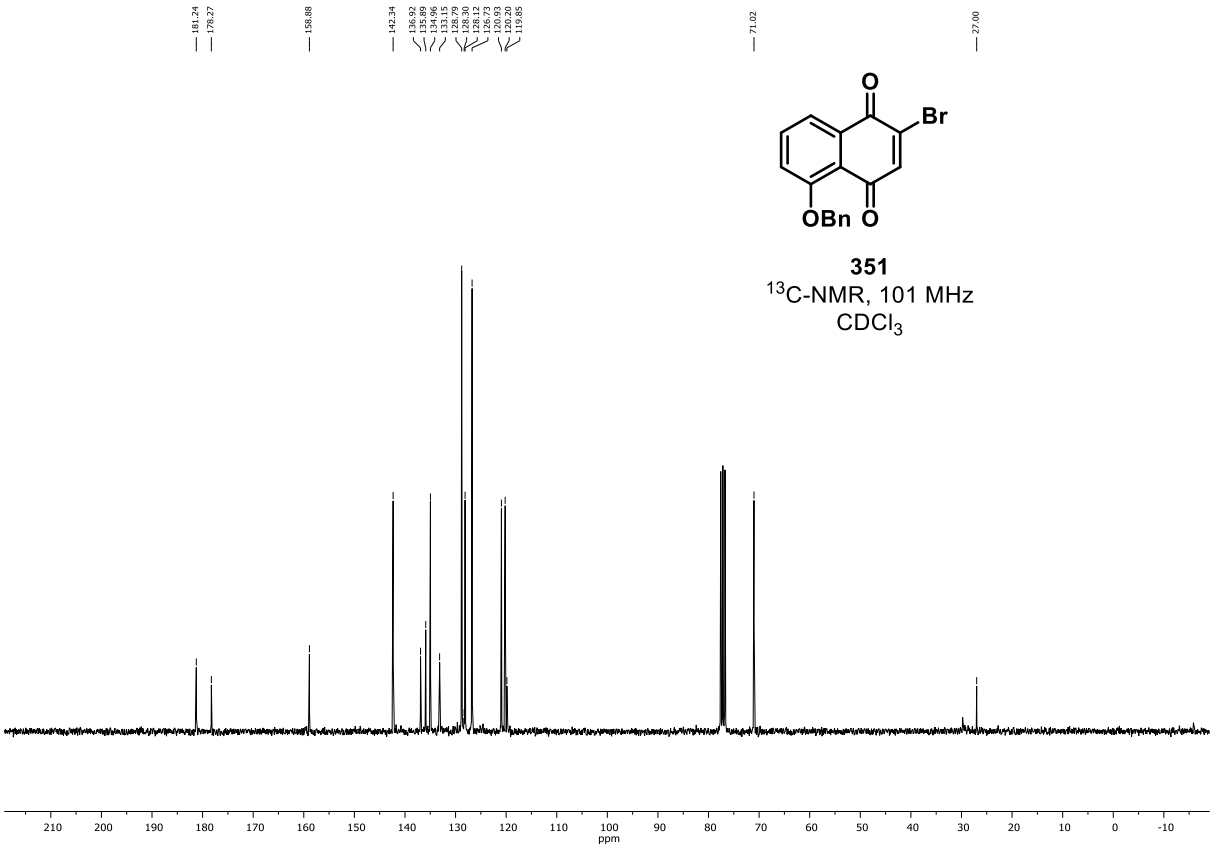
345
HSQC, 400 MHz
$CDCl_3$



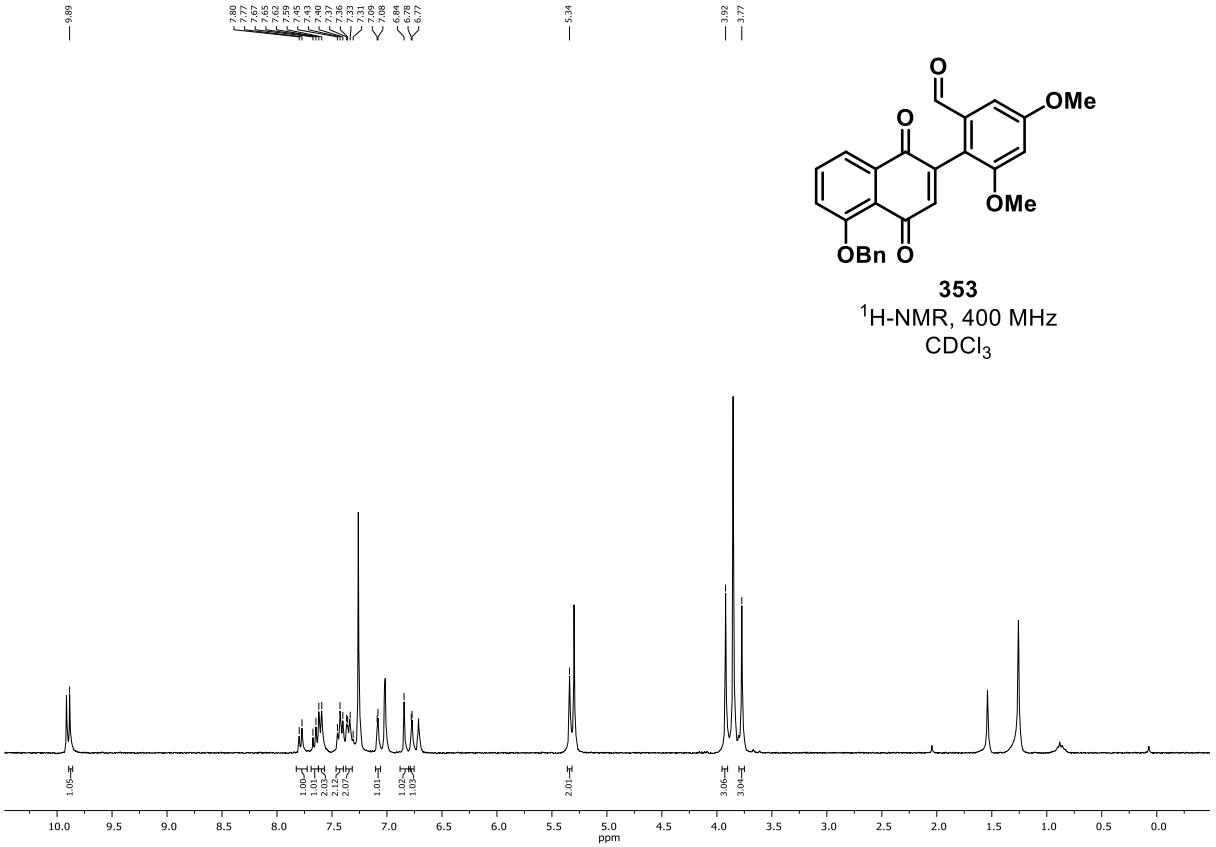
346
^{1}H-NMR, 400 MHz
$CDCl_3$



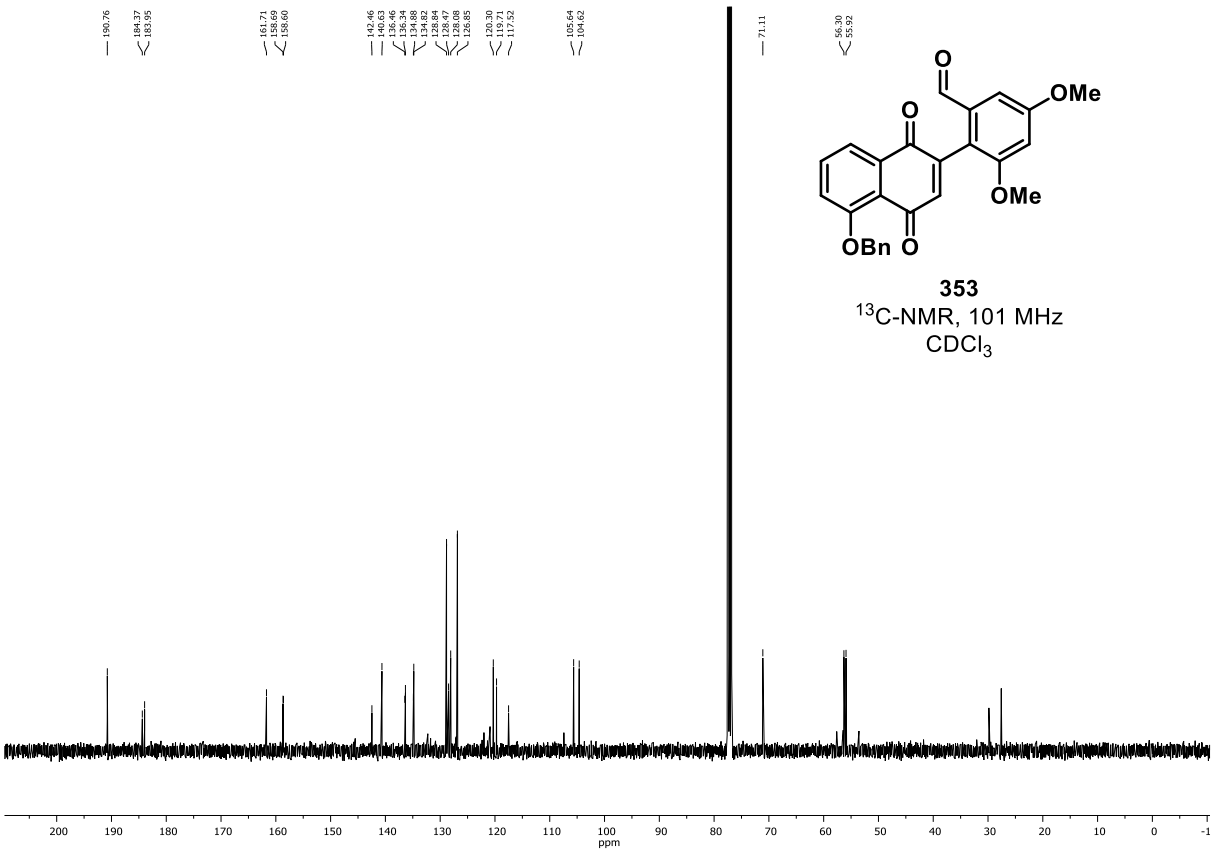
351
^{1}H-NMR, 400 MHz
$CDCl_3$



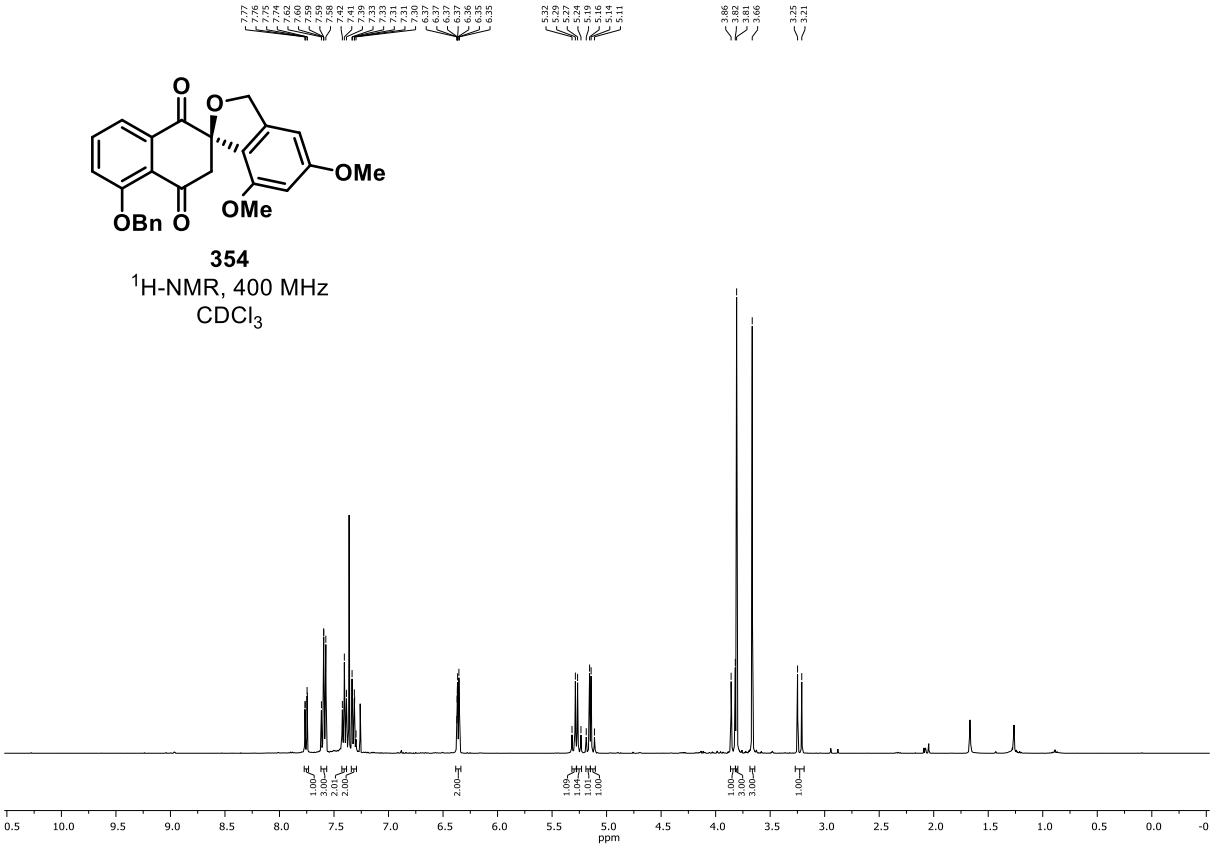
351
^{13}C-NMR, 101 MHz
$CDCl_3$

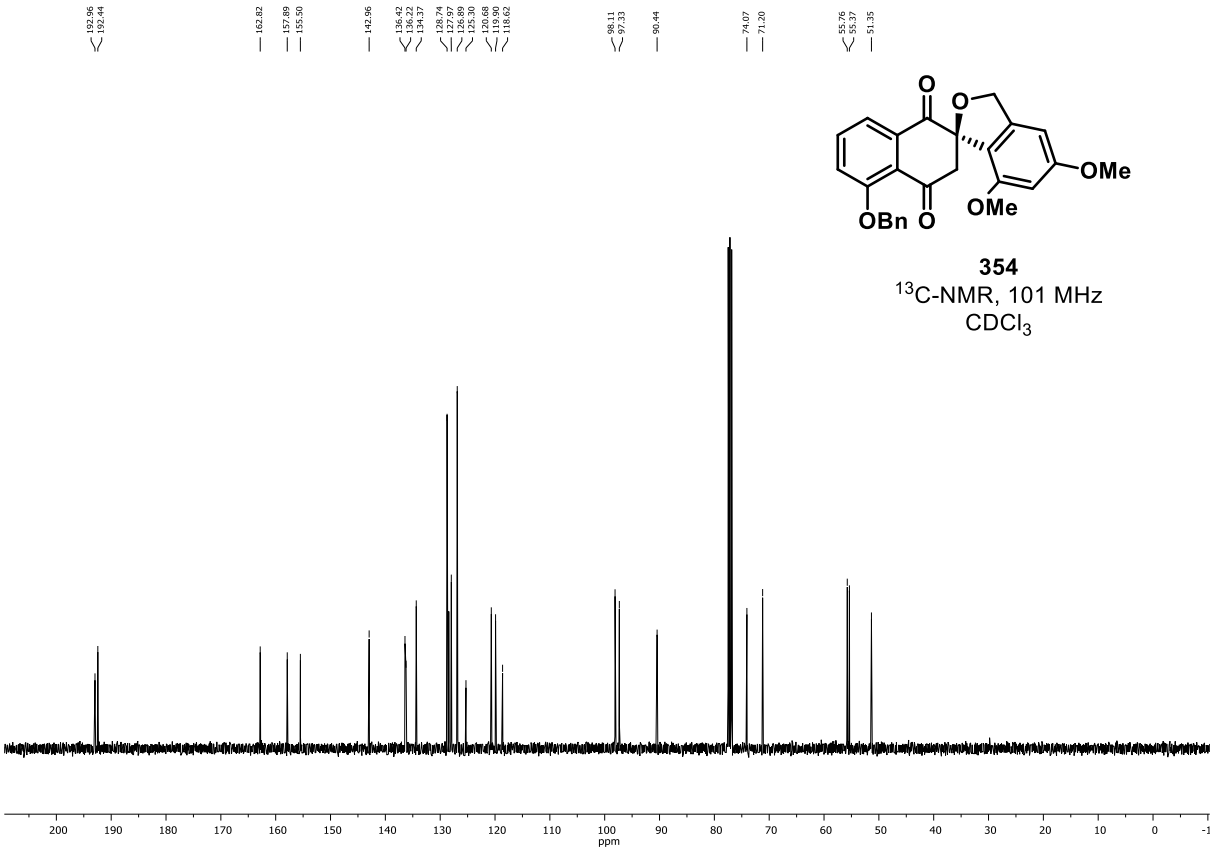


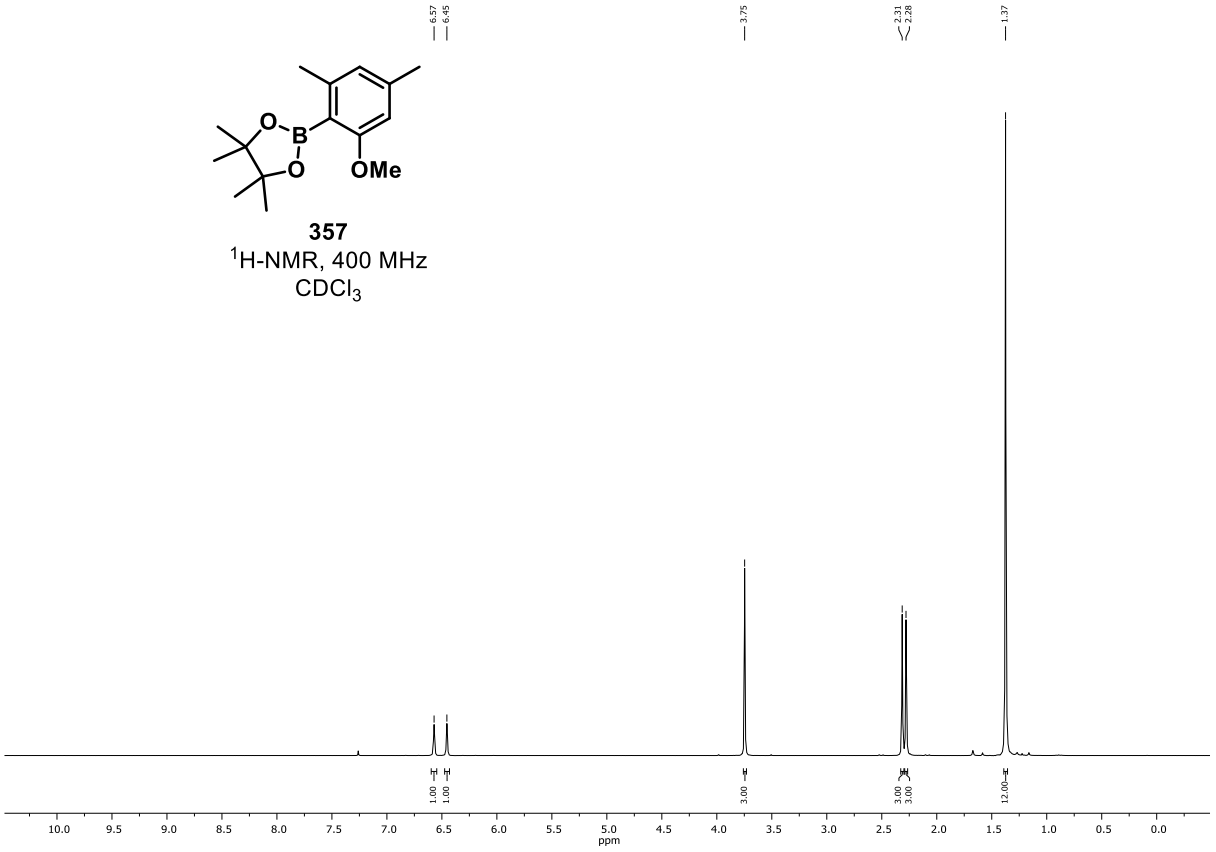
353
^{1}H-NMR, 400 MHz
$CDCl_3$



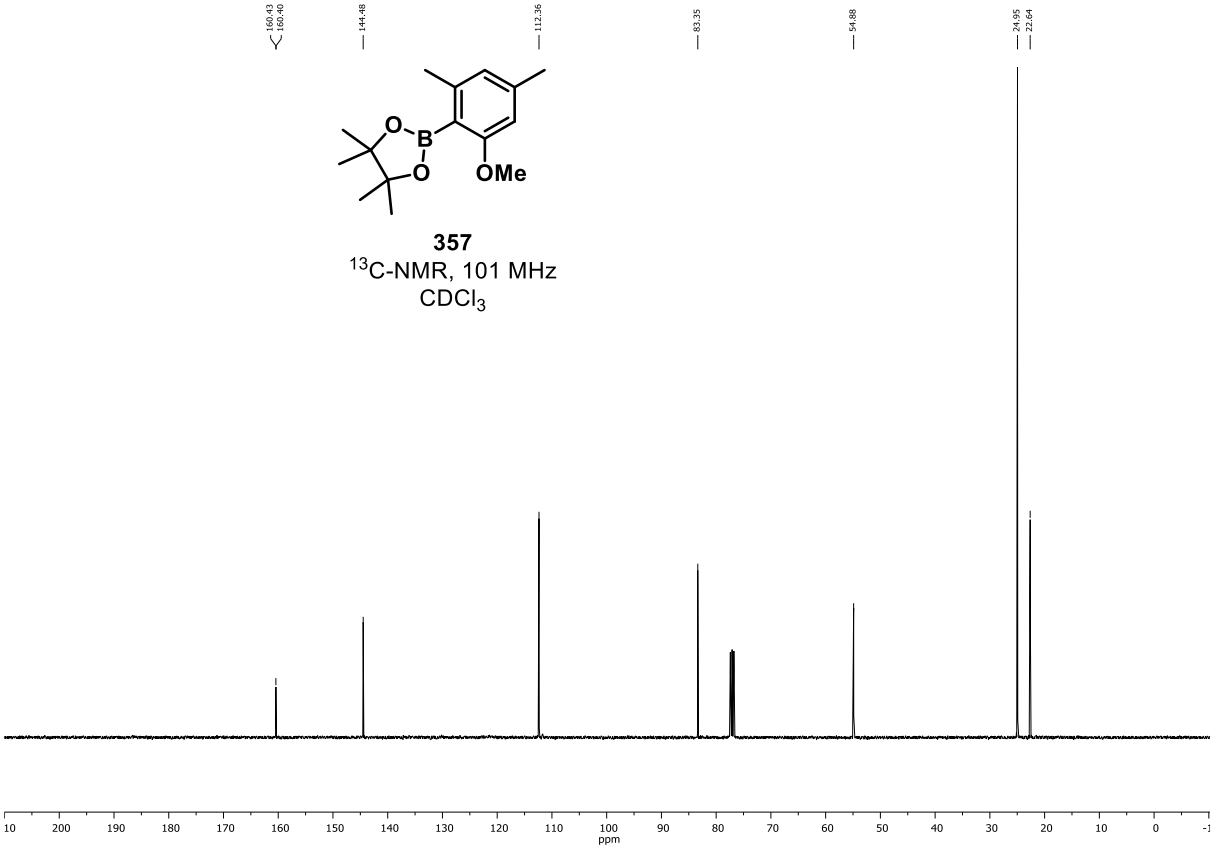
353
^{13}C-NMR, 101 MHz
$CDCl_3$


OBn O
OMe
OMe
354
1H-NMR, 400 MHz
CDCl3
ppm

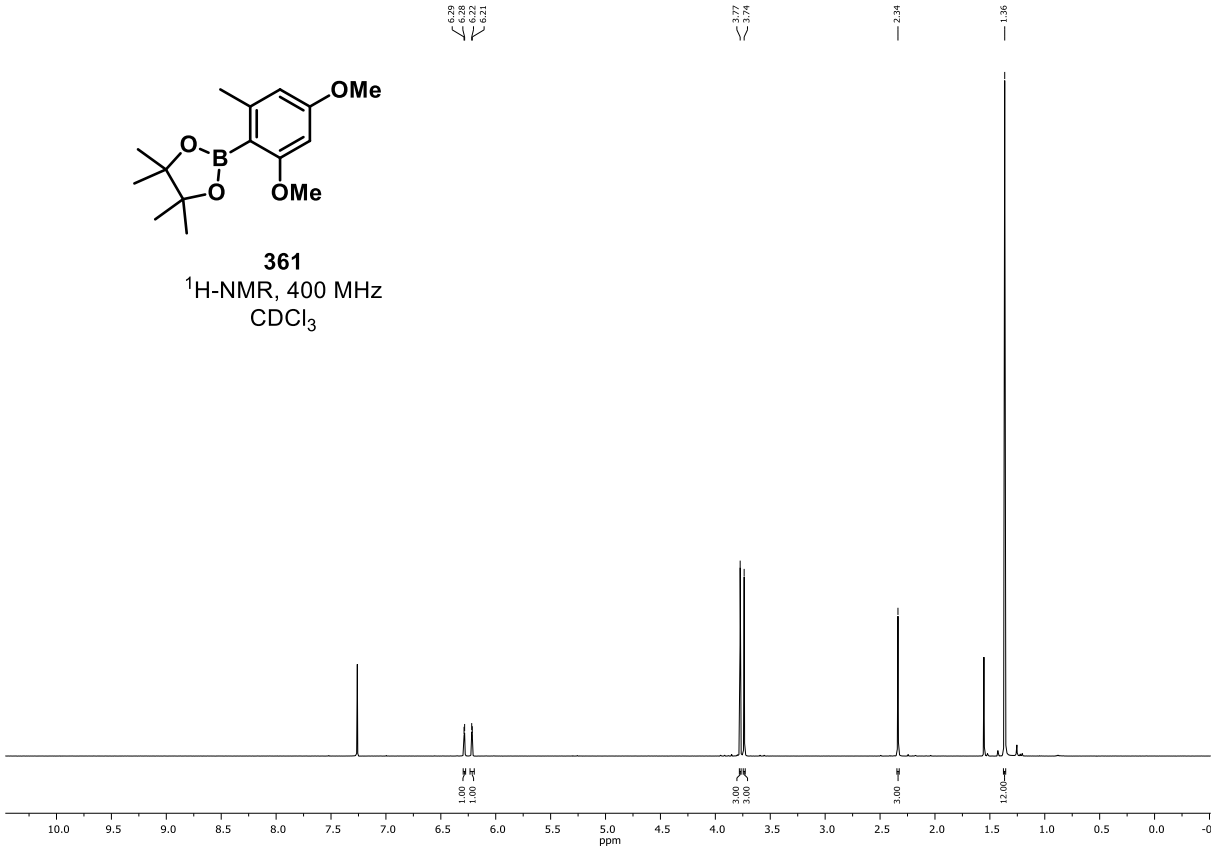

OBn O
OMe
OMe
354
13C-NMR, 101 MHz
CDCl3
ppm



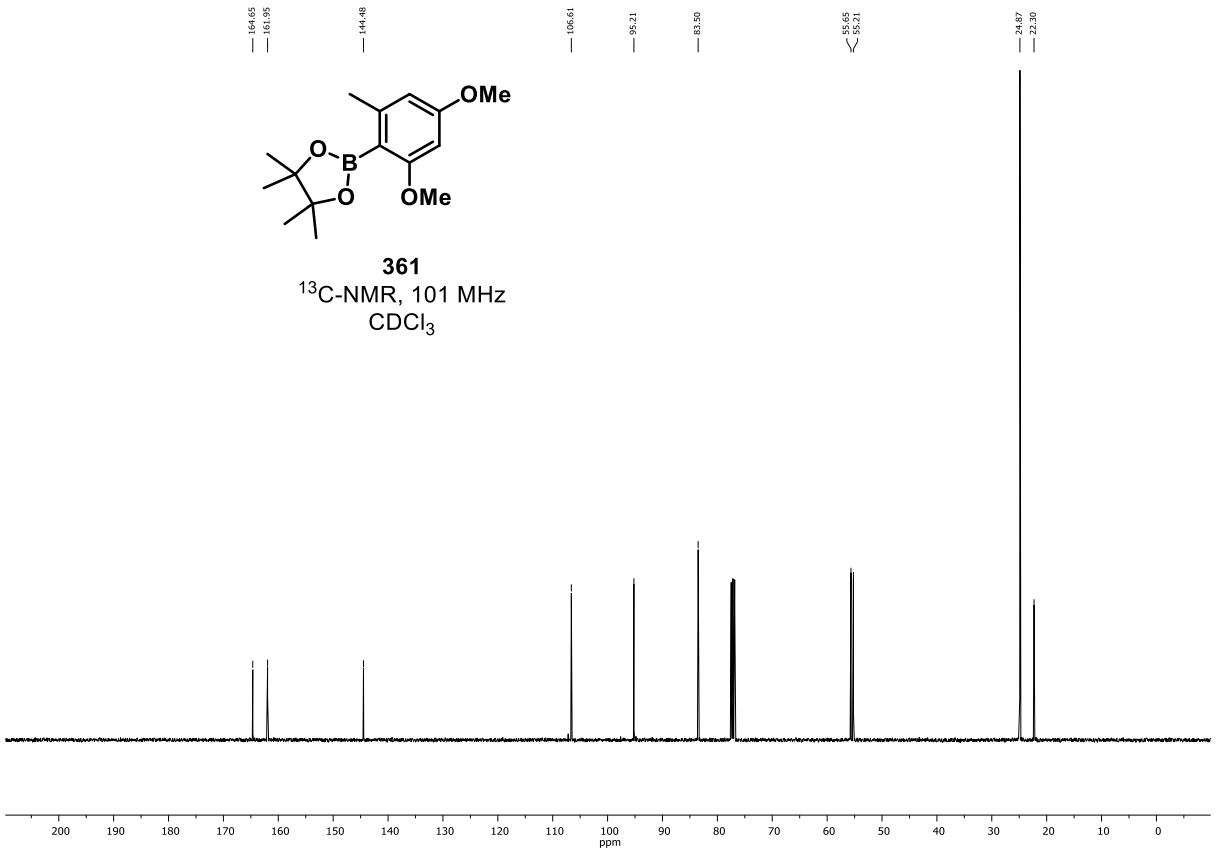
357
^{1}H-NMR, 400 MHz
$CDCl_3$



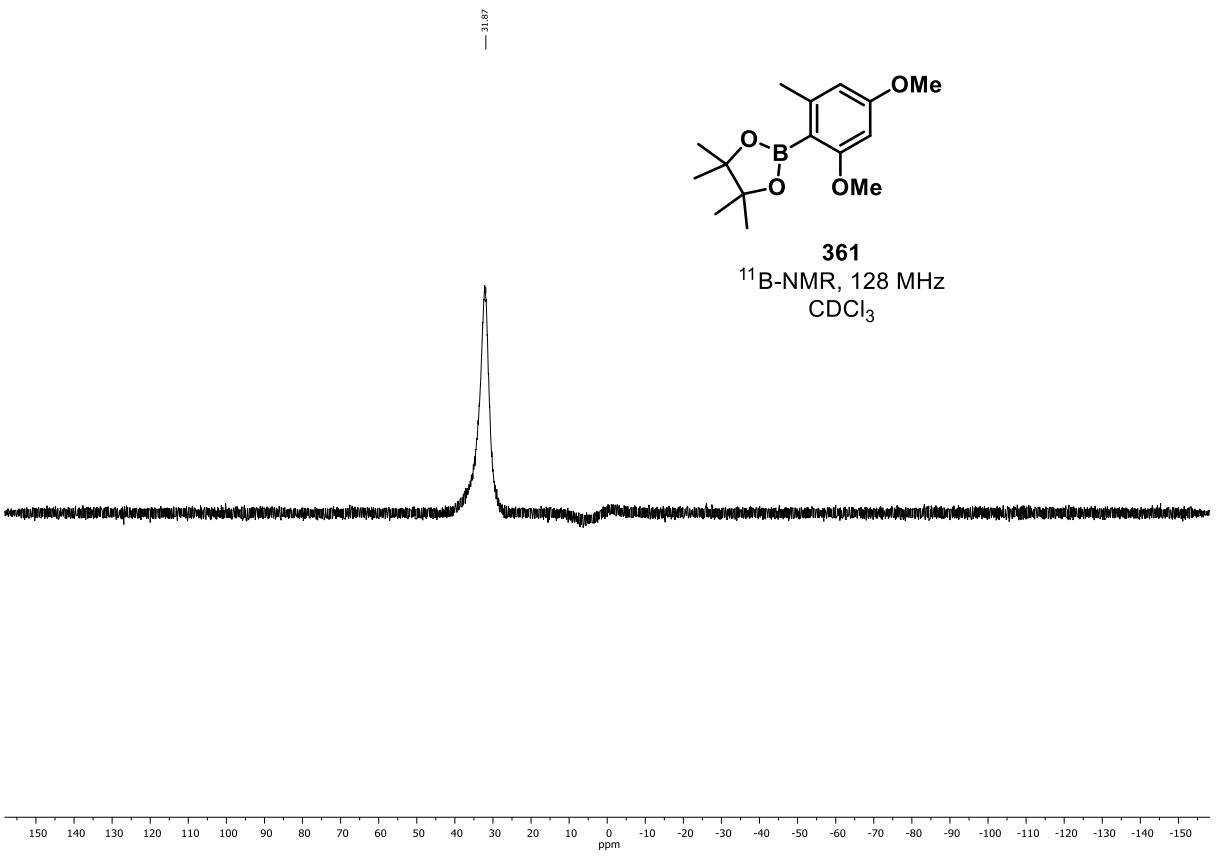
357
^{13}C-NMR, 101 MHz
$CDCl_3$

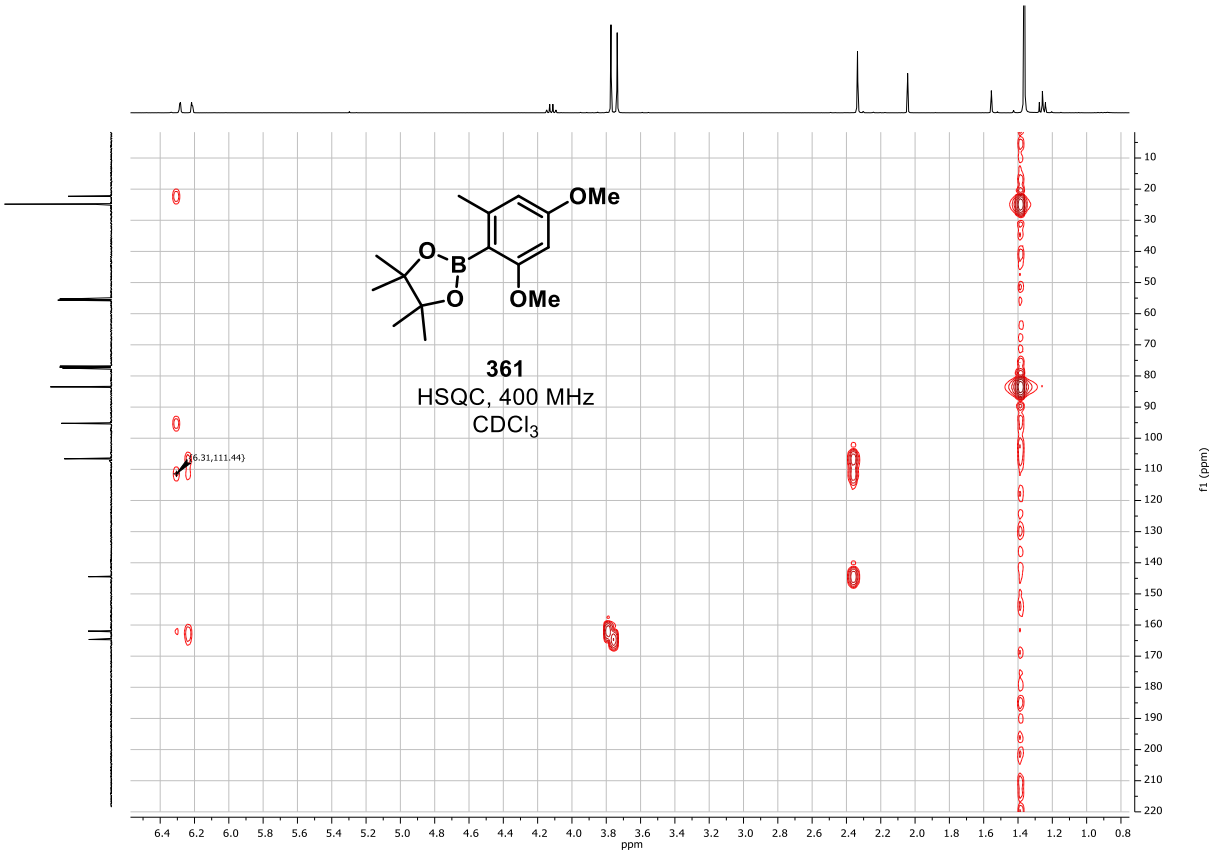


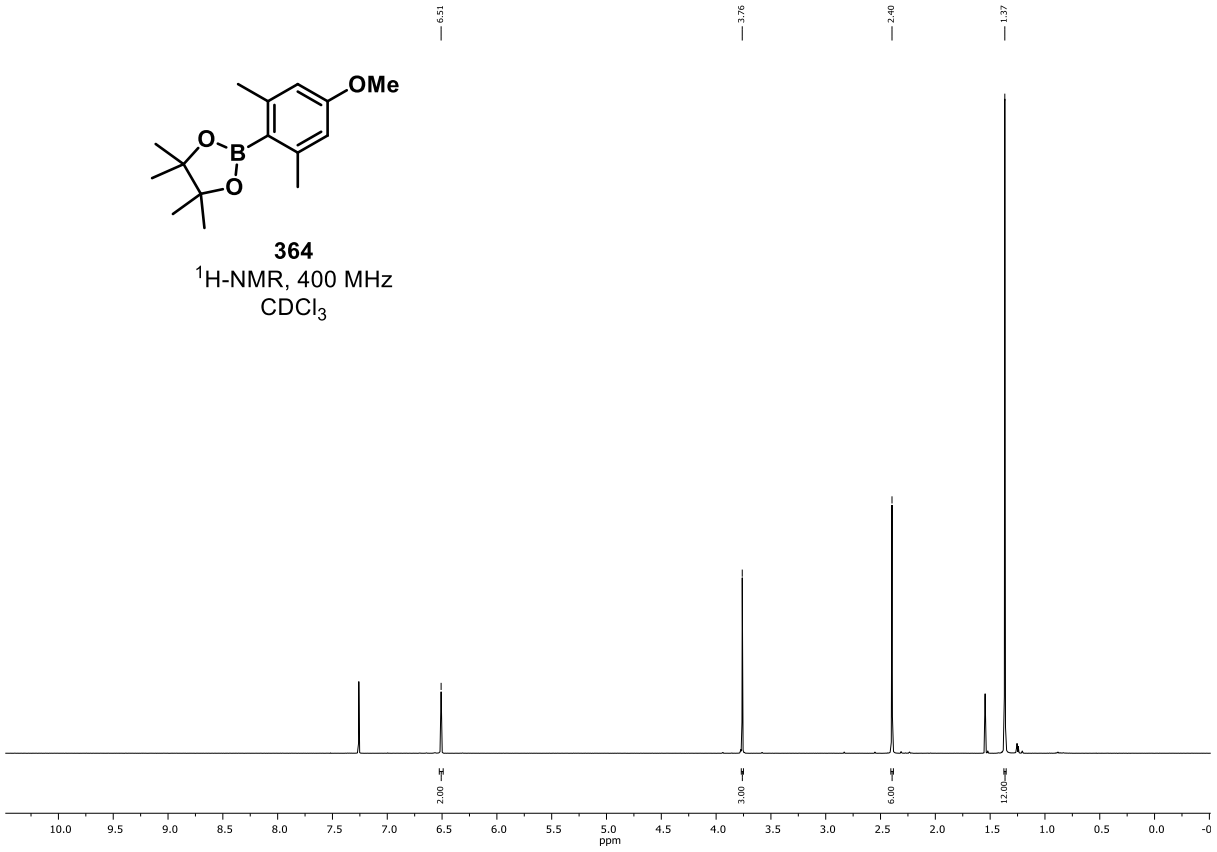
361
^{1}H-NMR, 400 MHz
$CDCl_3$



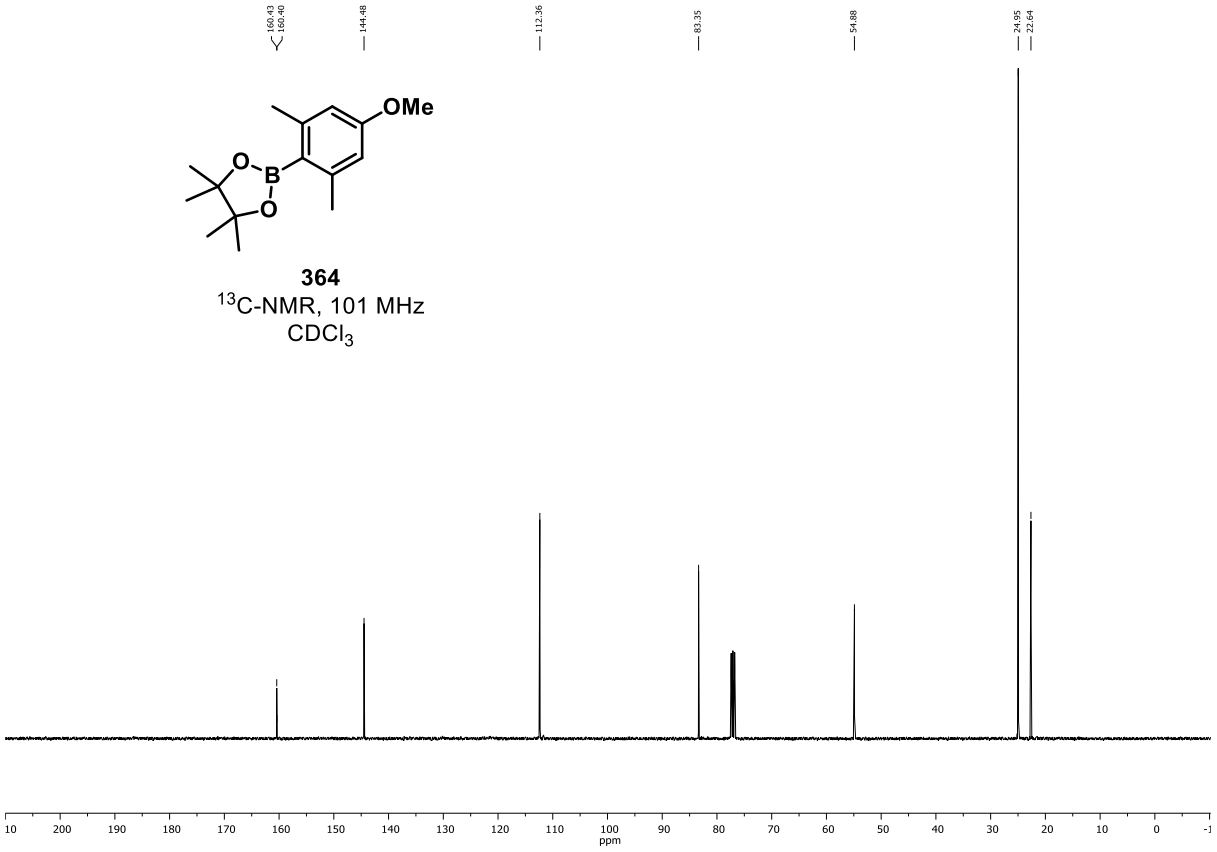
361
^{13}C-NMR, 101 MHz
$CDCl_3$


31.87
OMe
O
B
O
OMe
361
11B-NMR, 128 MHz
CDCl3
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
ppm

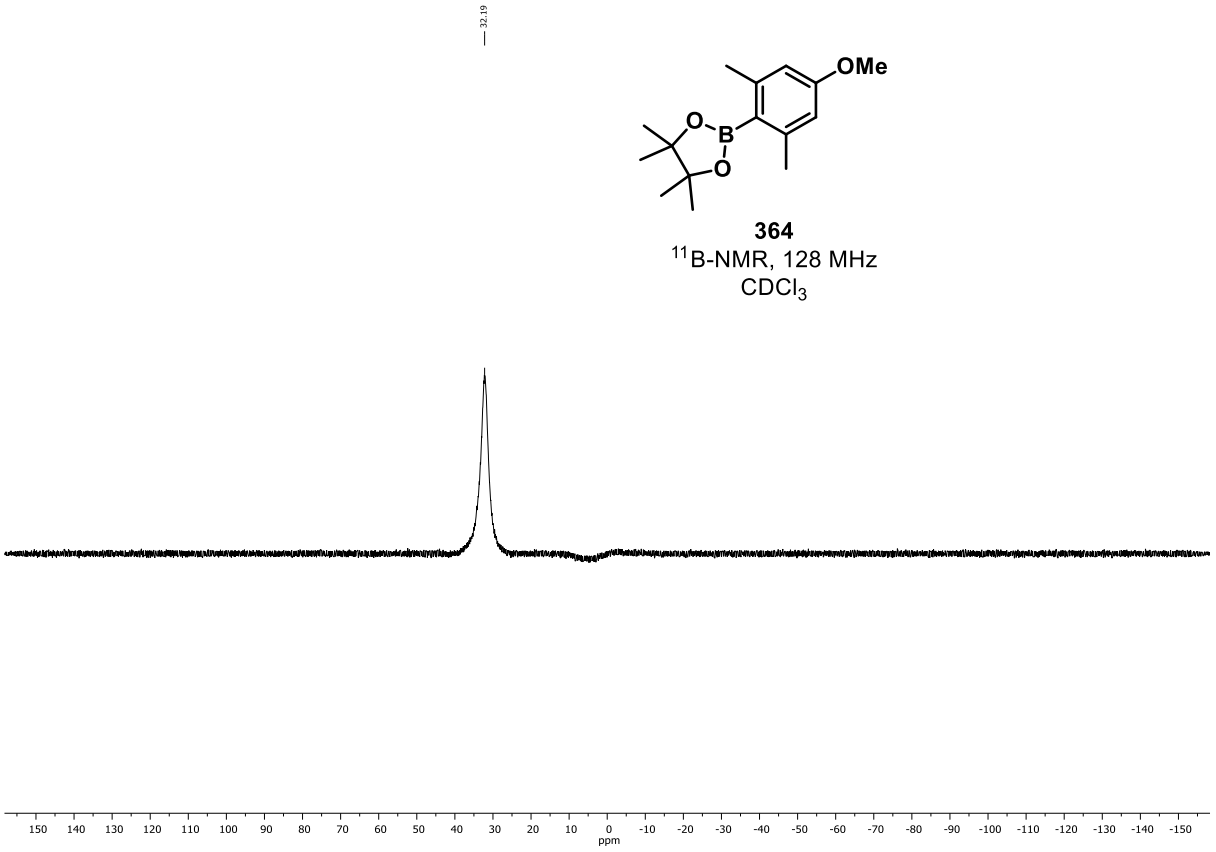

OMe
O
B
O
OMe
361
HSQC, 400 MHz
CDCl3
(6.31,111.44)
6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
f1 (ppm)

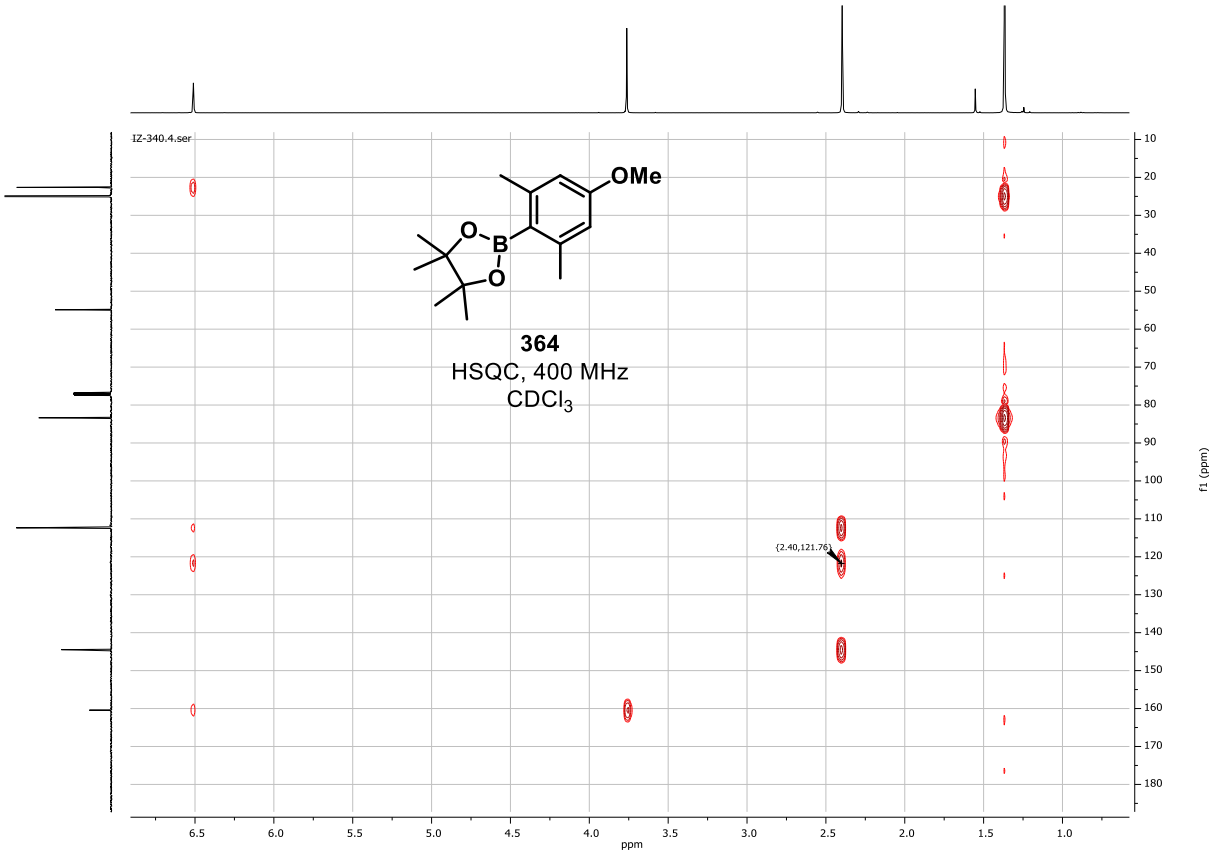


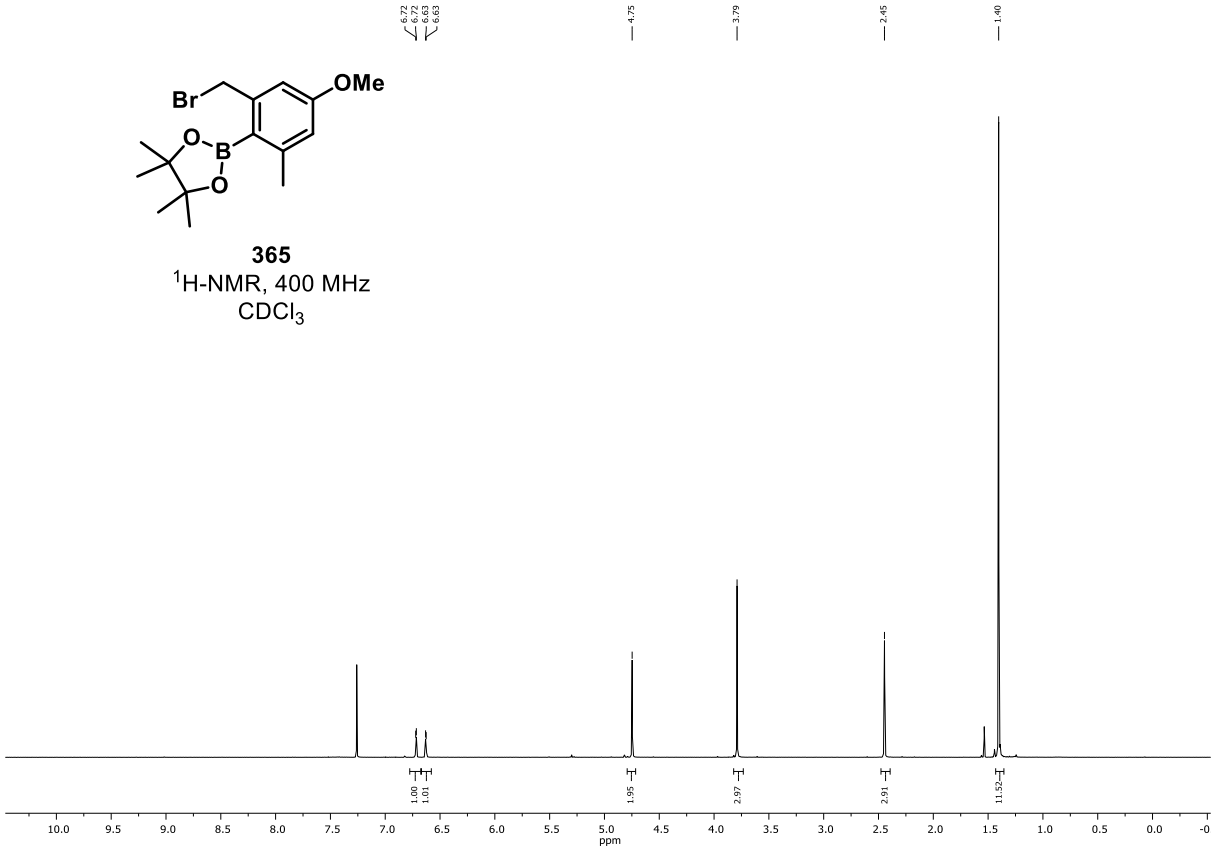
364
^{1}H-NMR, 400 MHz
$CDCl_3$



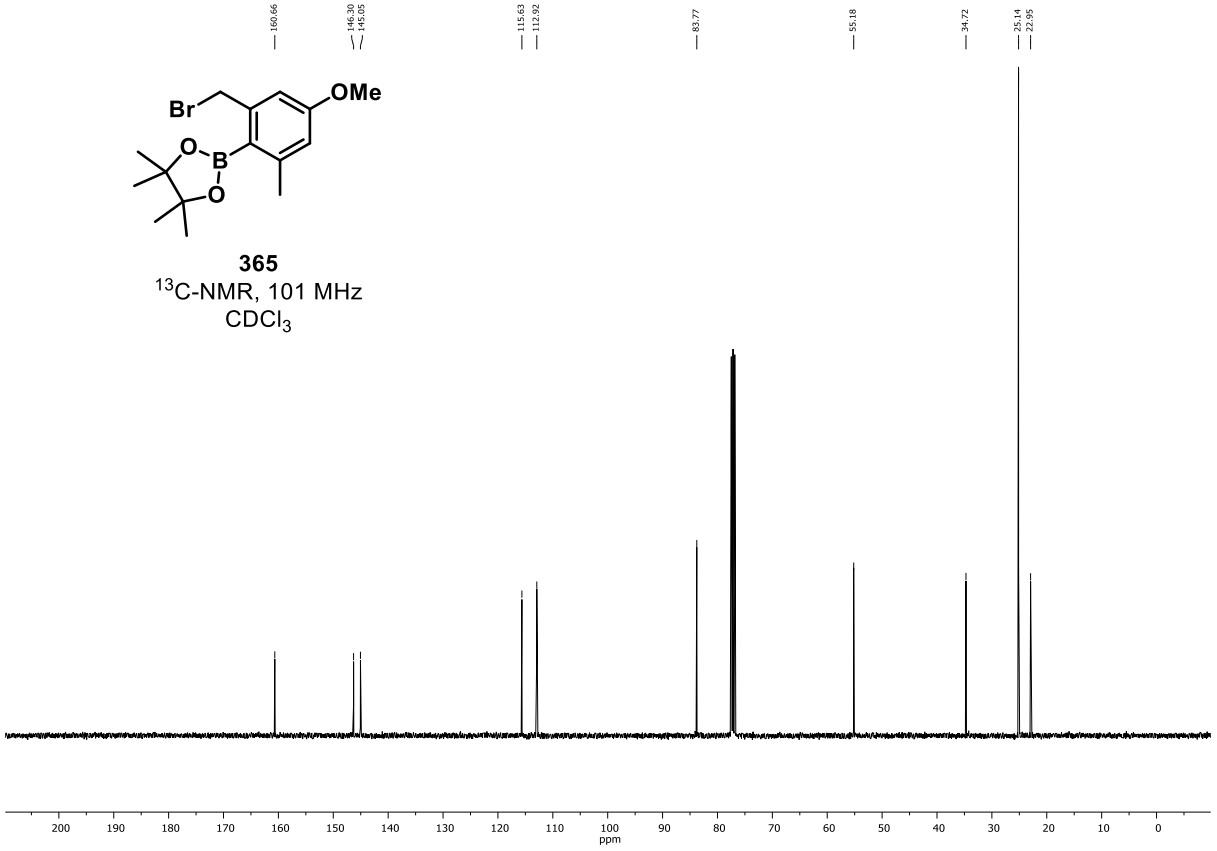
364
^{13}C-NMR, 101 MHz
$CDCl_3$


32.19
OMe
O
B
O
364
11B-NMR, 128 MHz
CDCl3
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
ppm

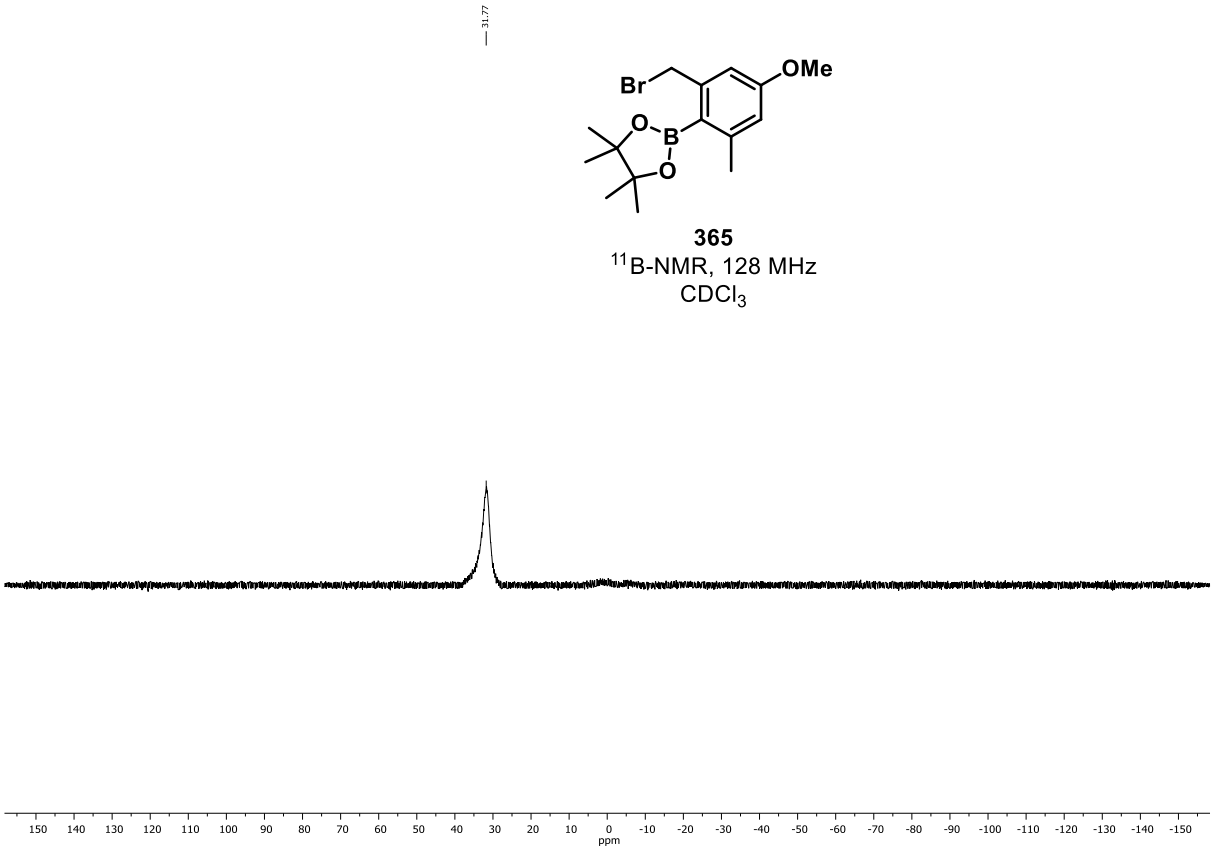

IZ-340.4.ser
OMe
O
B
O
364
HSQC, 400 MHz
CDCl3
{2.40,121.76}
6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)



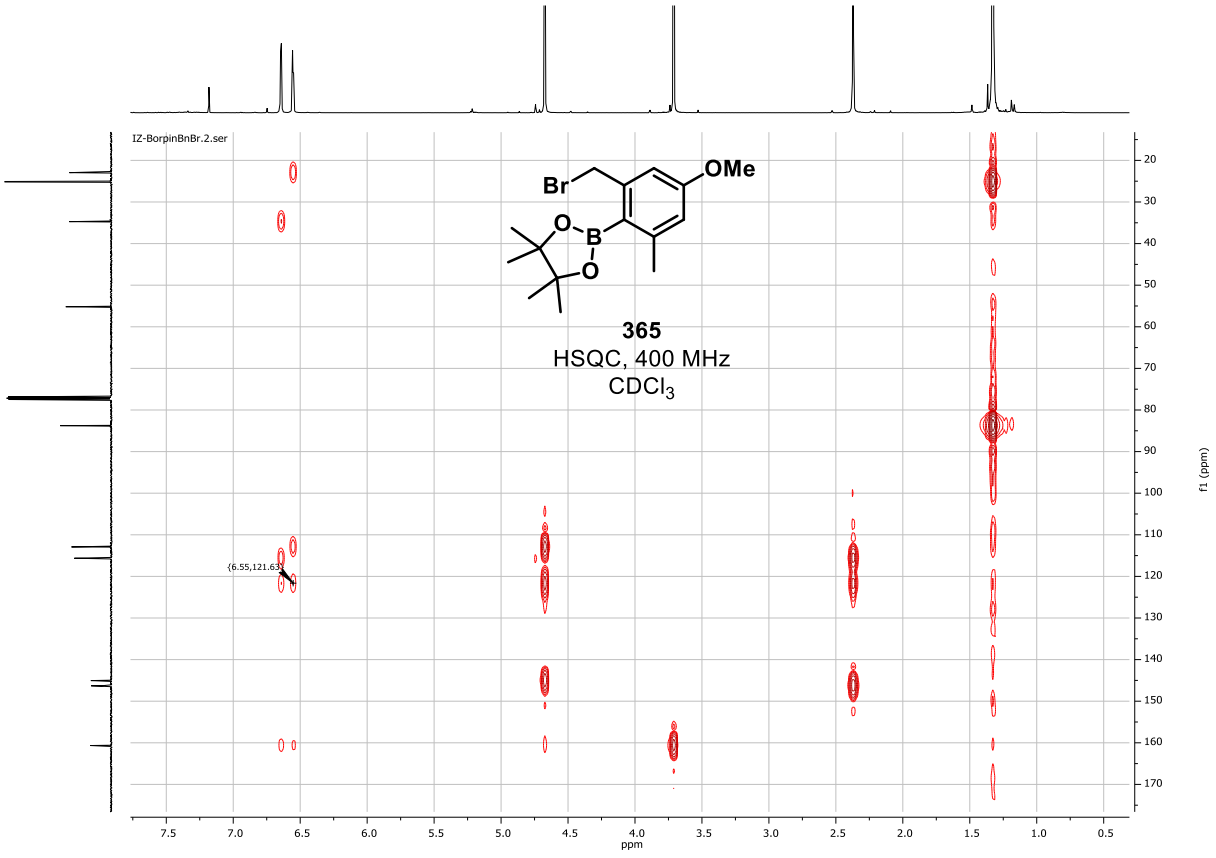
365
^{1}H-NMR, 400 MHz
$CDCl_3$



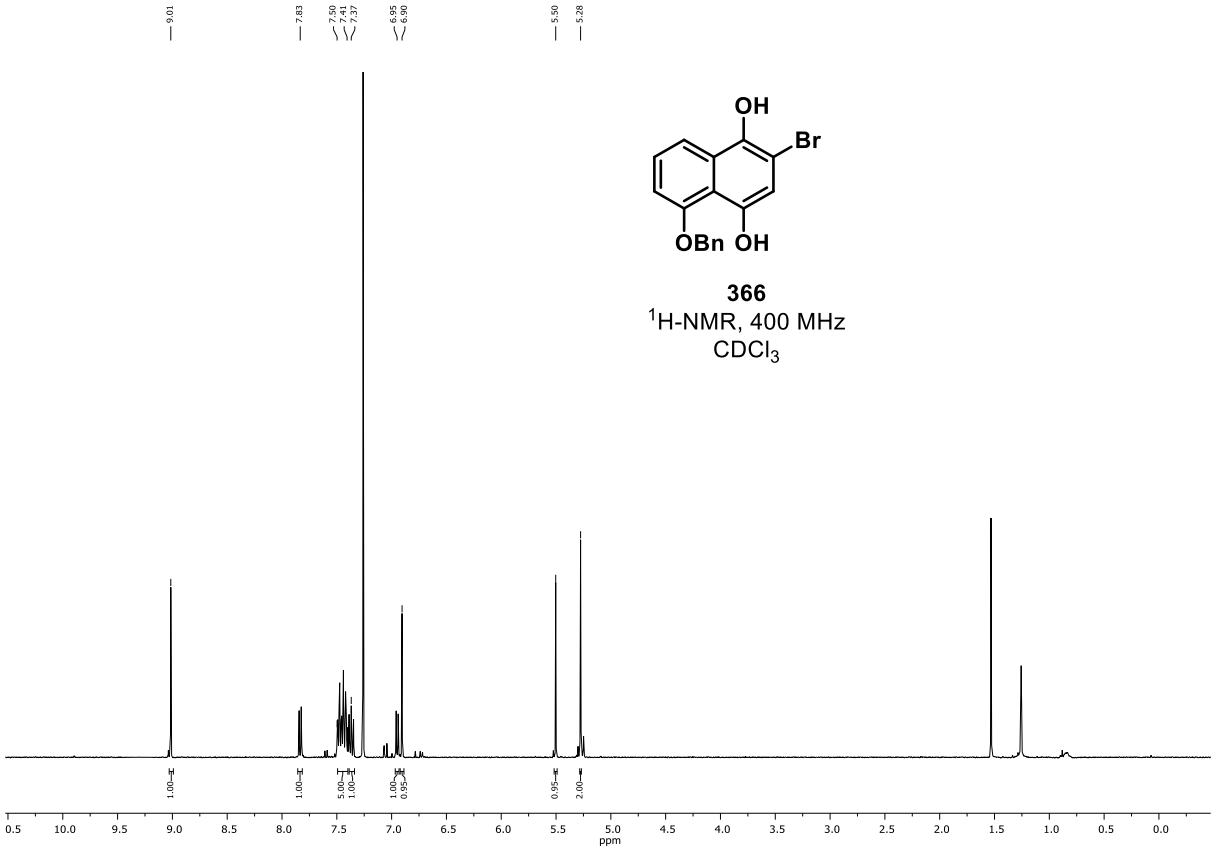
365
^{13}C-NMR, 101 MHz
$CDCl_3$



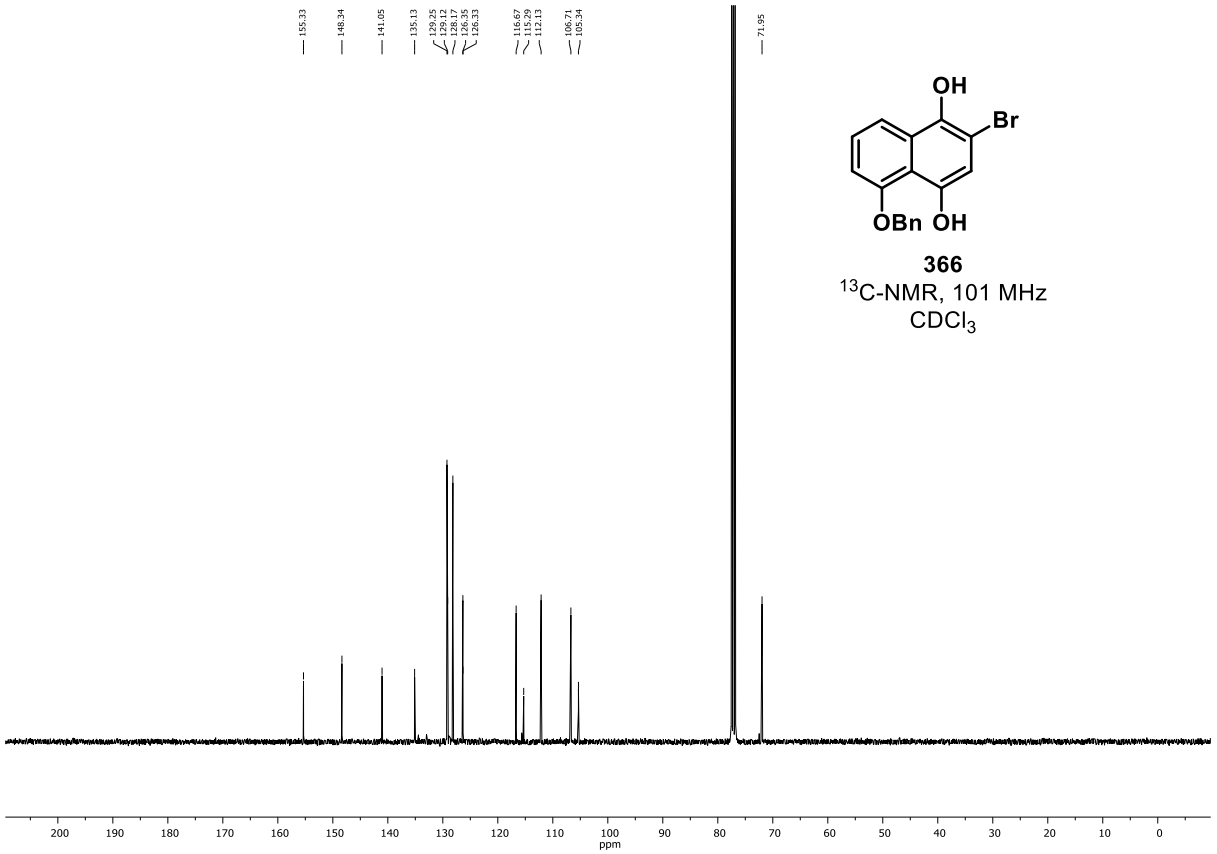
365
^{11}B-NMR, 128 MHz
$CDCl_3$



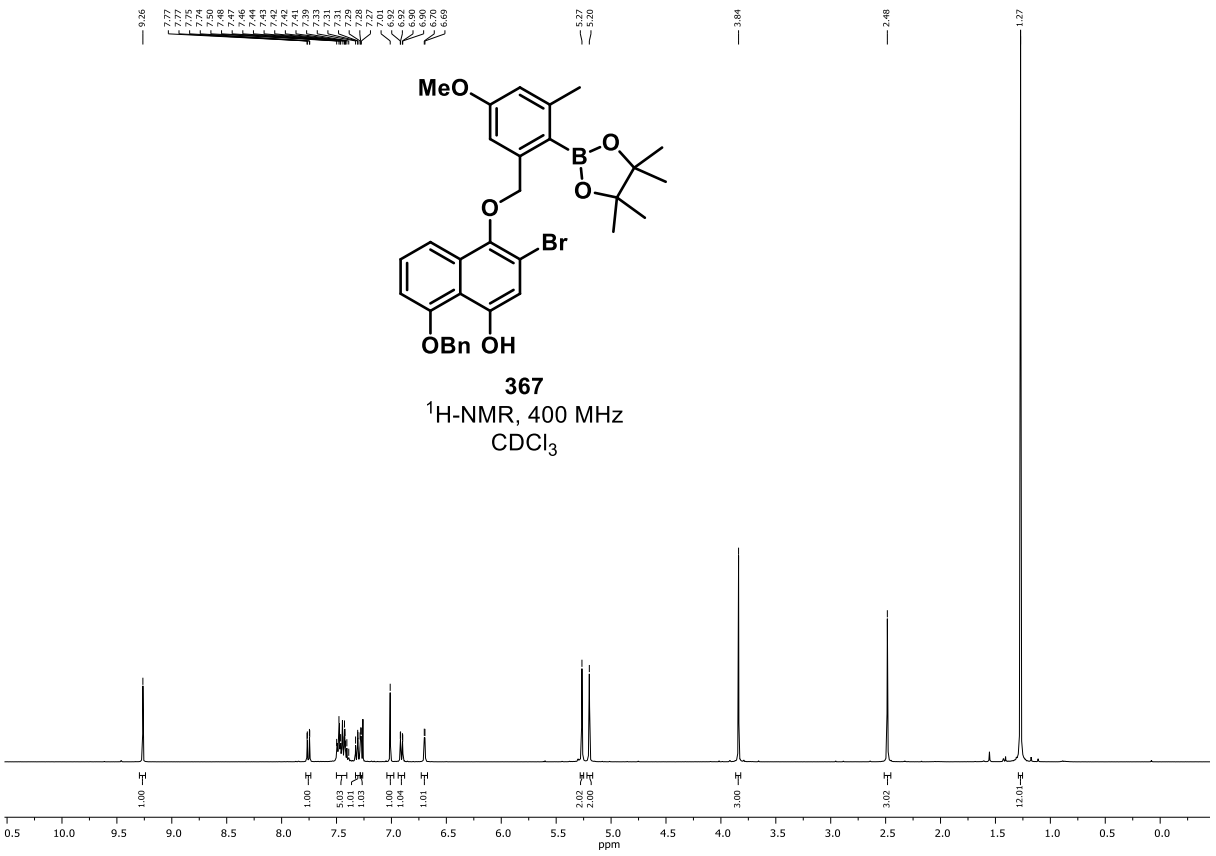
365
HSQC, 400 MHz
$CDCl_3$



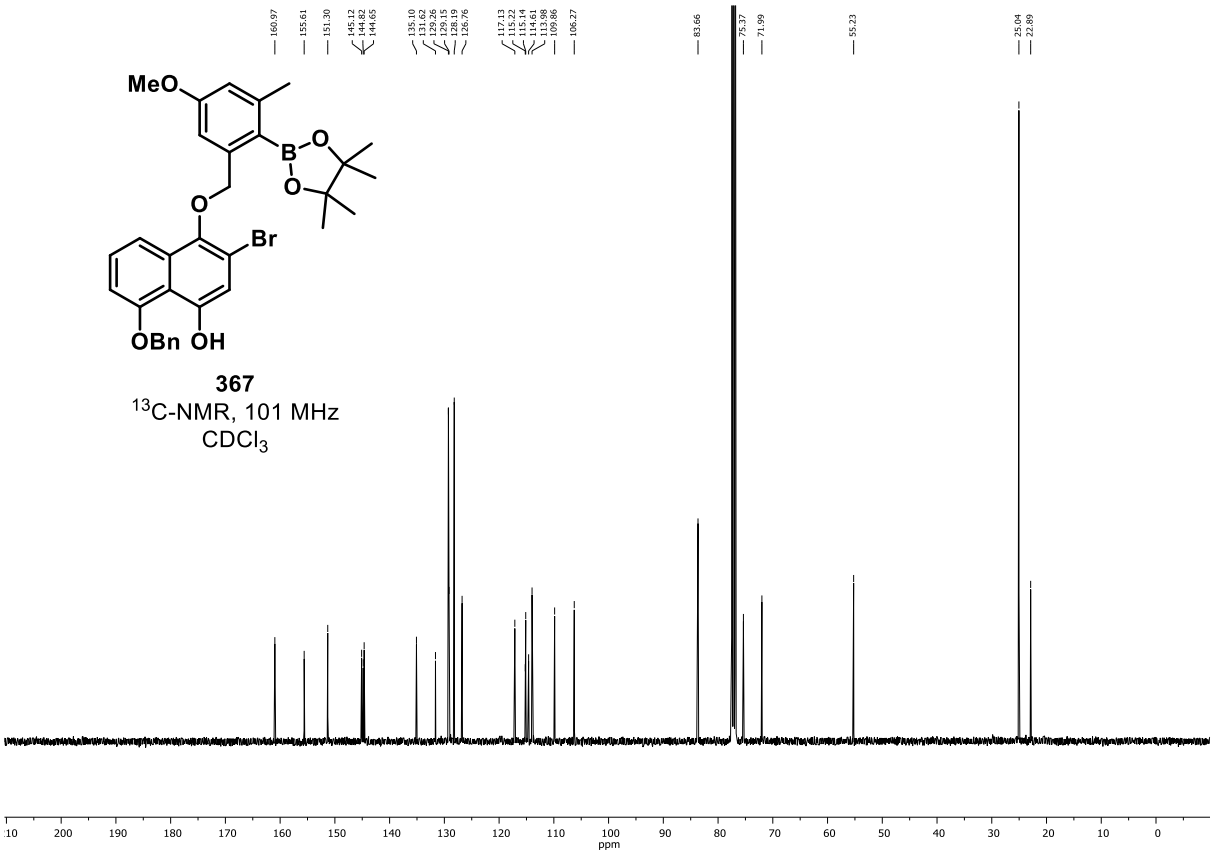
366
^{1}H-NMR, 400 MHz
$CDCl_3$



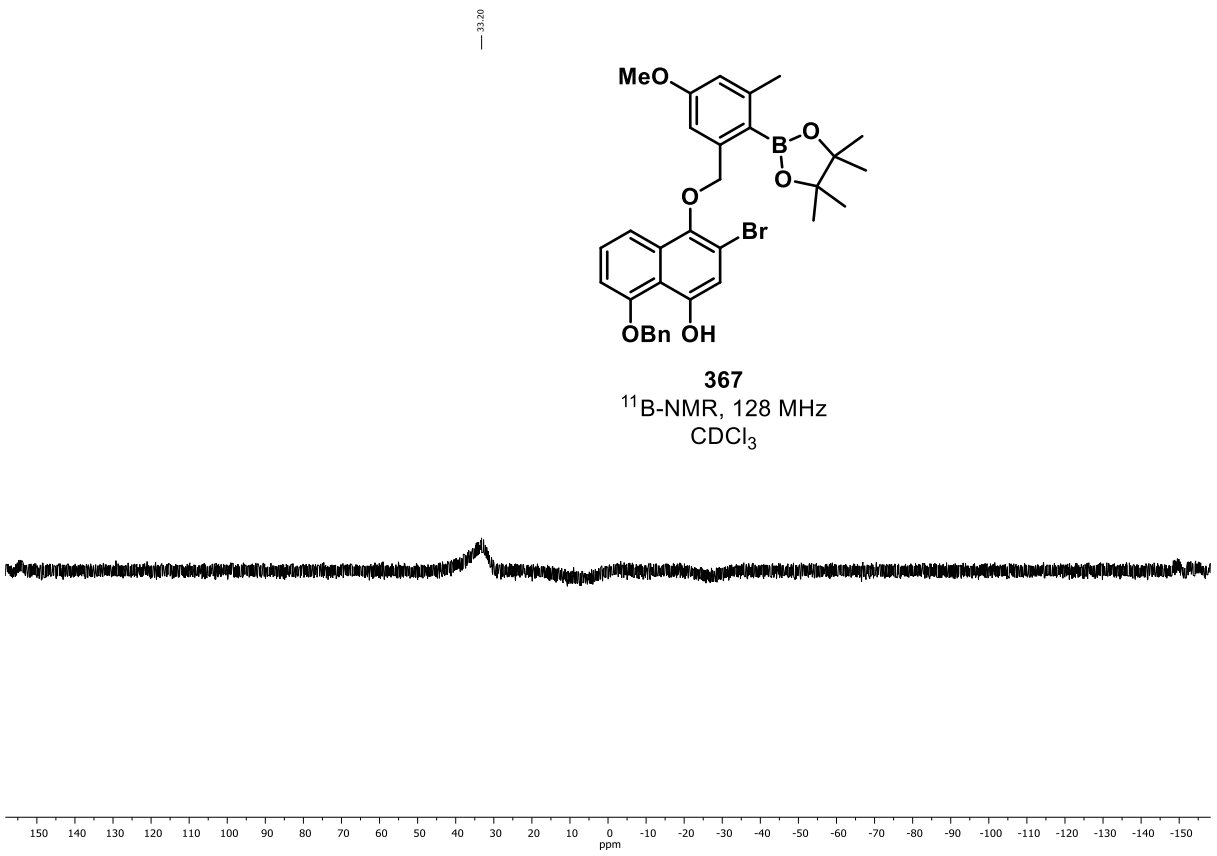
366
^{13}C-NMR, 101 MHz
$CDCl_3$

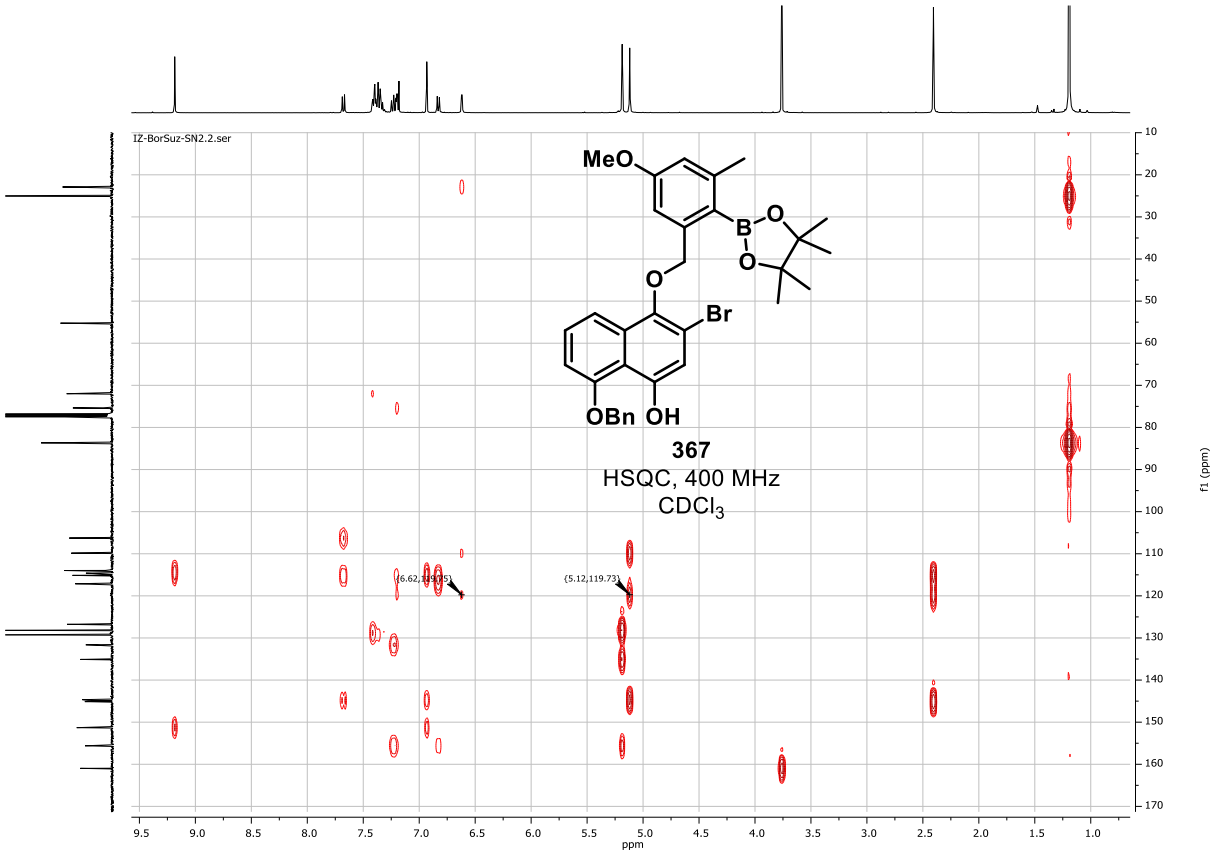


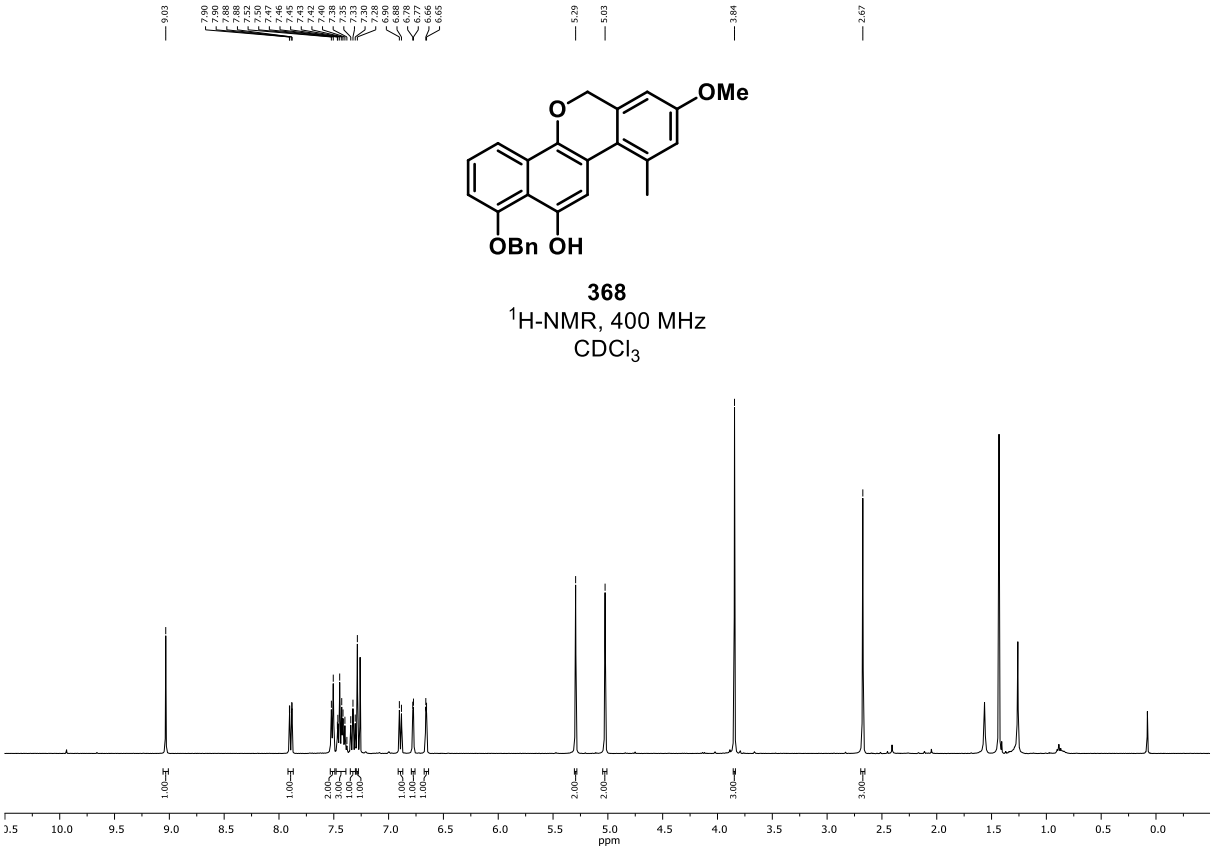
367
^{1}H-NMR, 400 MHz
$CDCl_3$



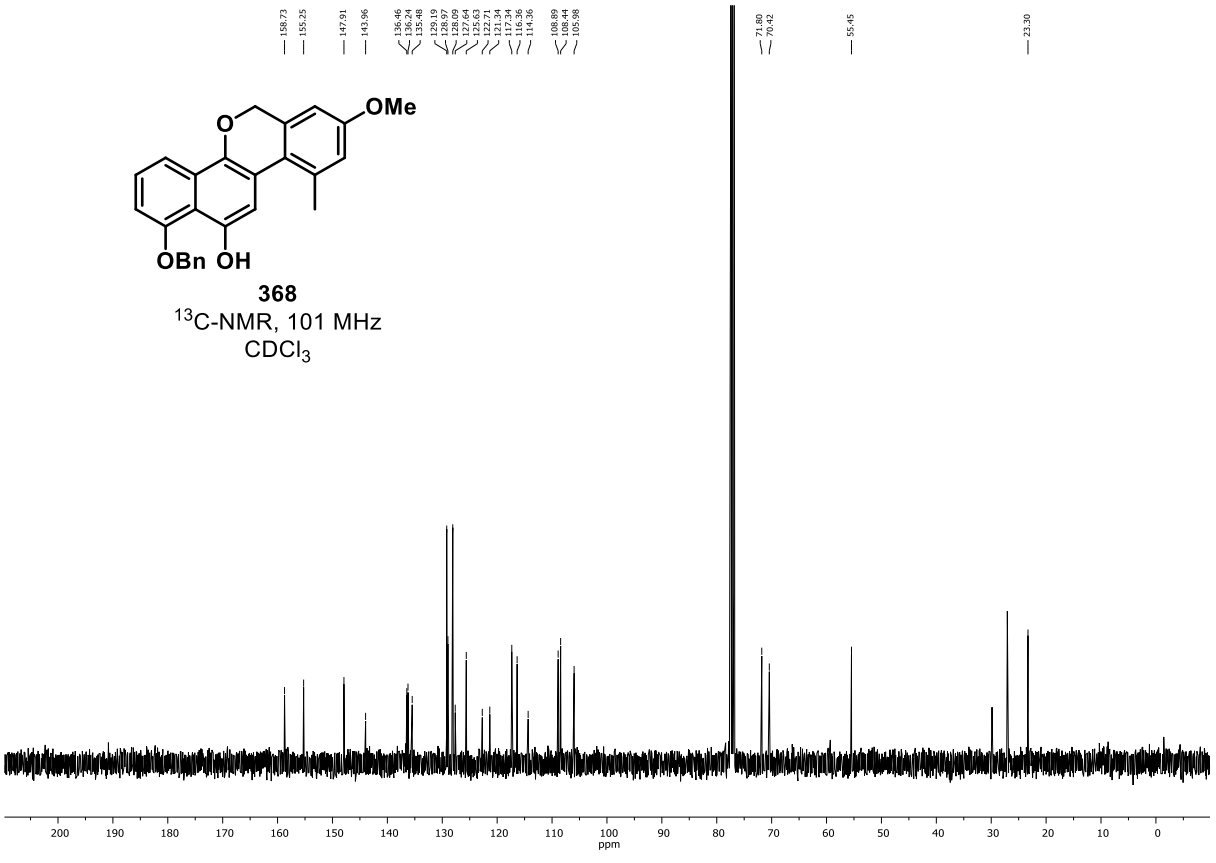
367
^{13}C-NMR, 101 MHz
$CDCl_3$


33.20
MeO
B
O
O
O
Br
OBn OH
367
11B-NMR, 128 MHz
CDCl3
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
ppm

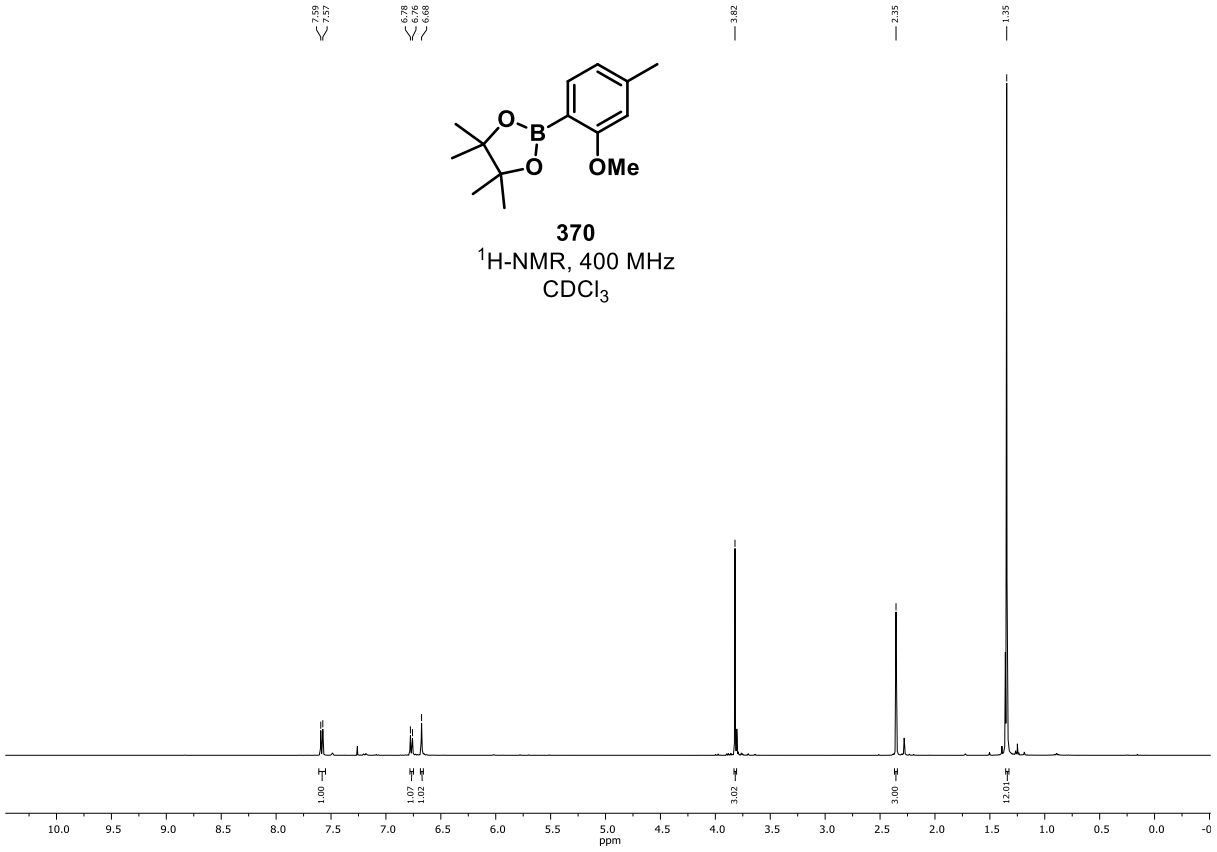

IZ-BorSuz-SN2.2.ser
MeO
B
O
O
O
Br
OBn OH
367
HSQC, 400 MHz
CDCl3
(5.12,119.73)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
f1 (ppm)



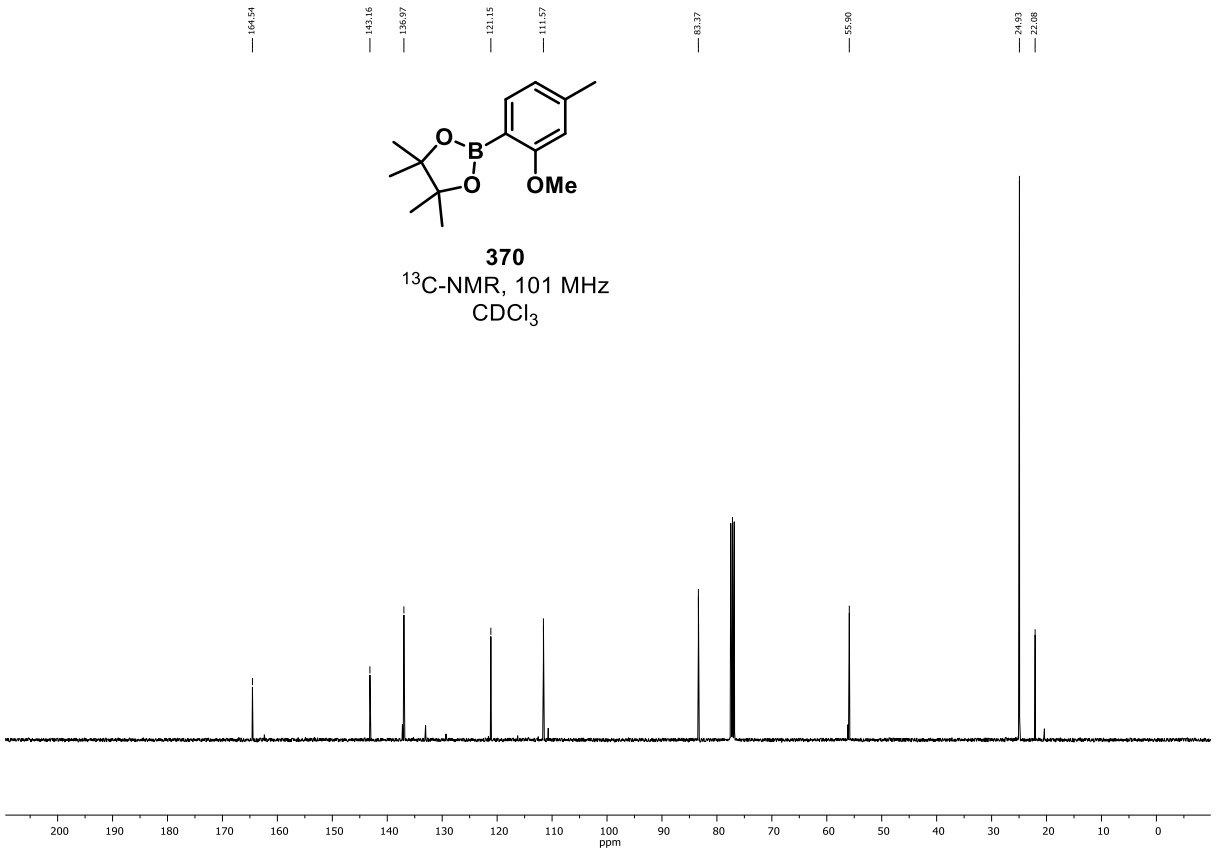
368
^{1}H-NMR, 400 MHz
$CDCl_3$



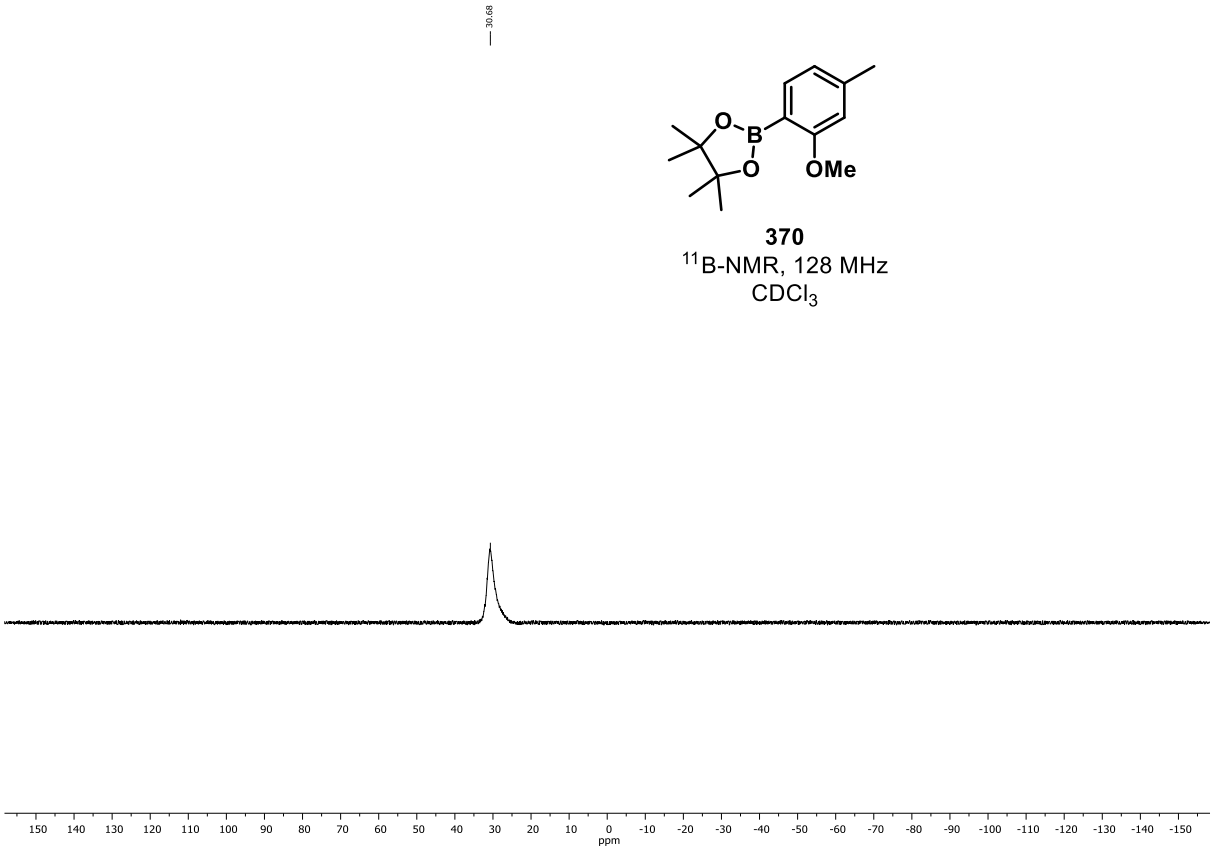
368
^{13}C-NMR, 101 MHz
$CDCl_3$



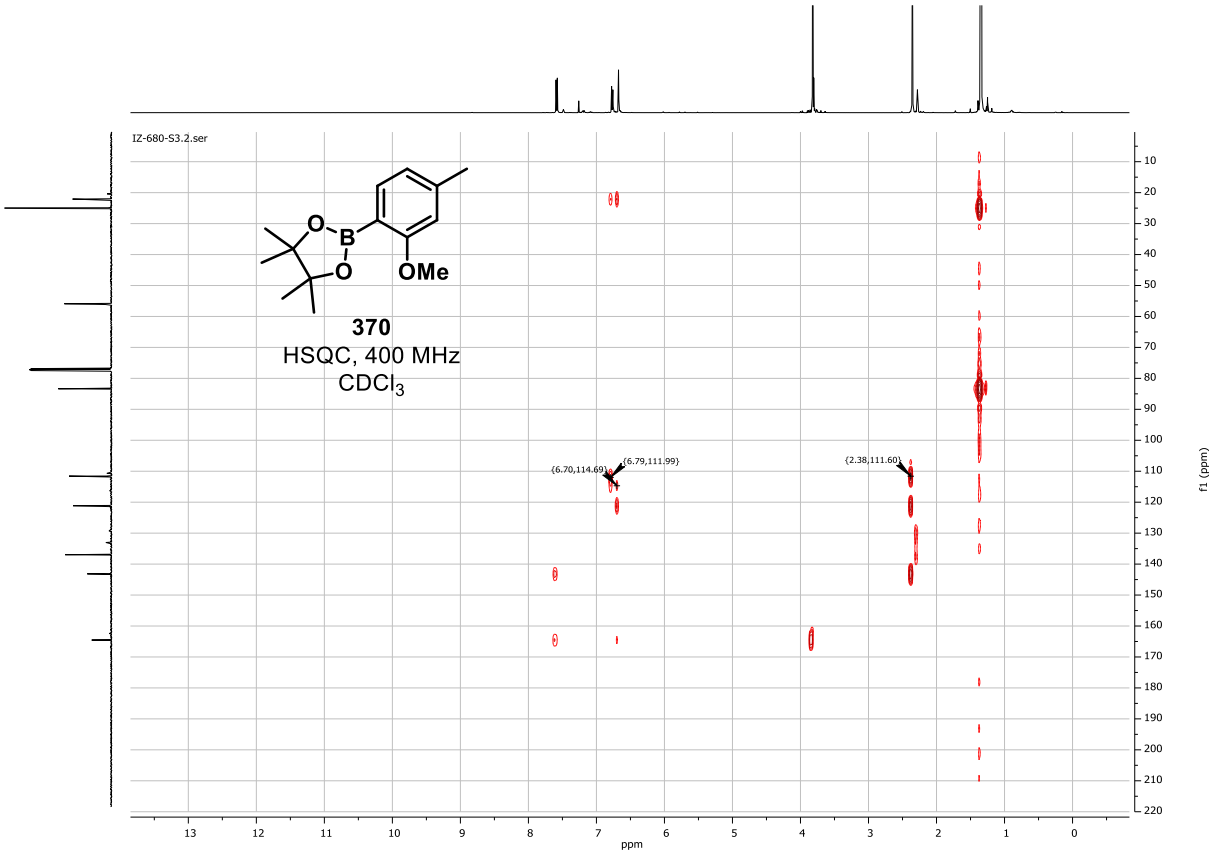
370
^{1}H-NMR, 400 MHz
$CDCl_3$



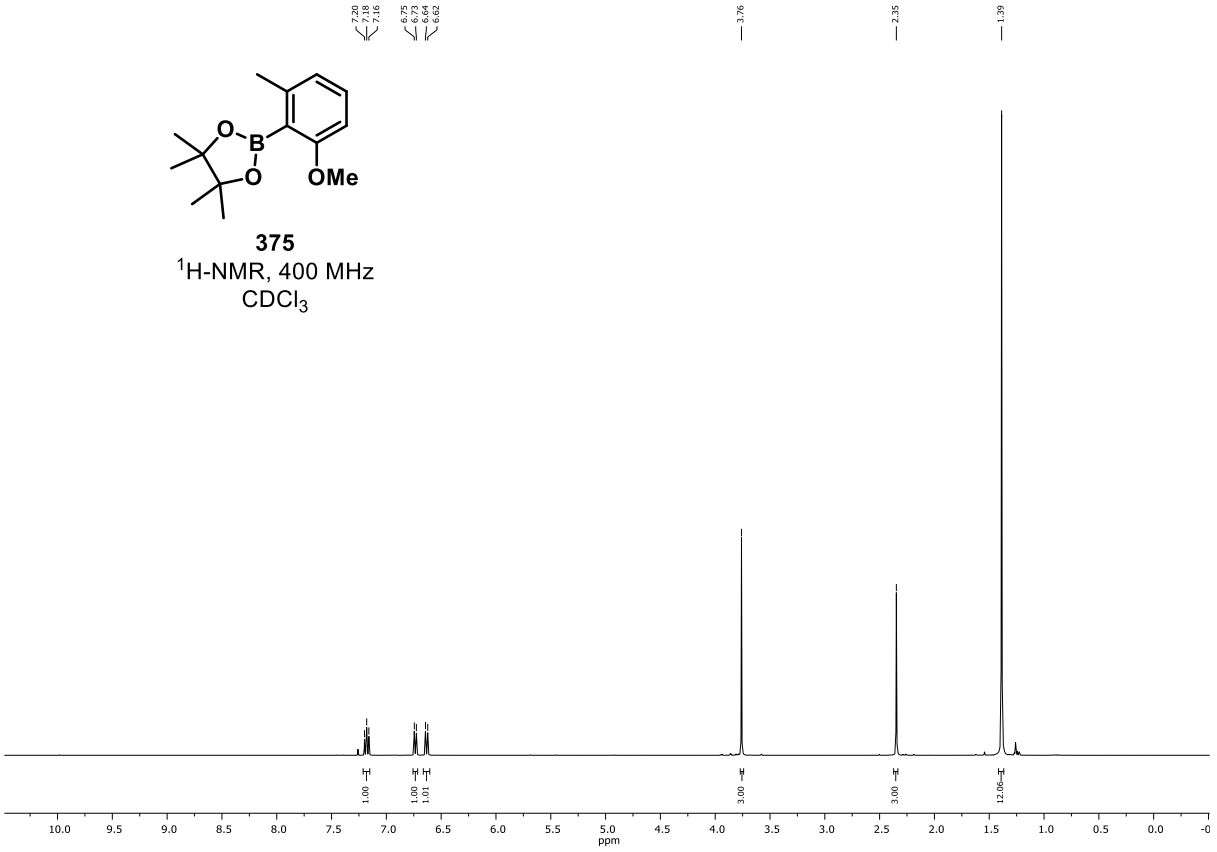
370
^{13}C-NMR, 101 MHz
$CDCl_3$

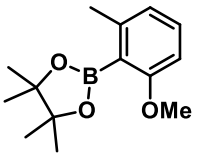


370
^{11}B-NMR, 128 MHz
$CDCl_3$



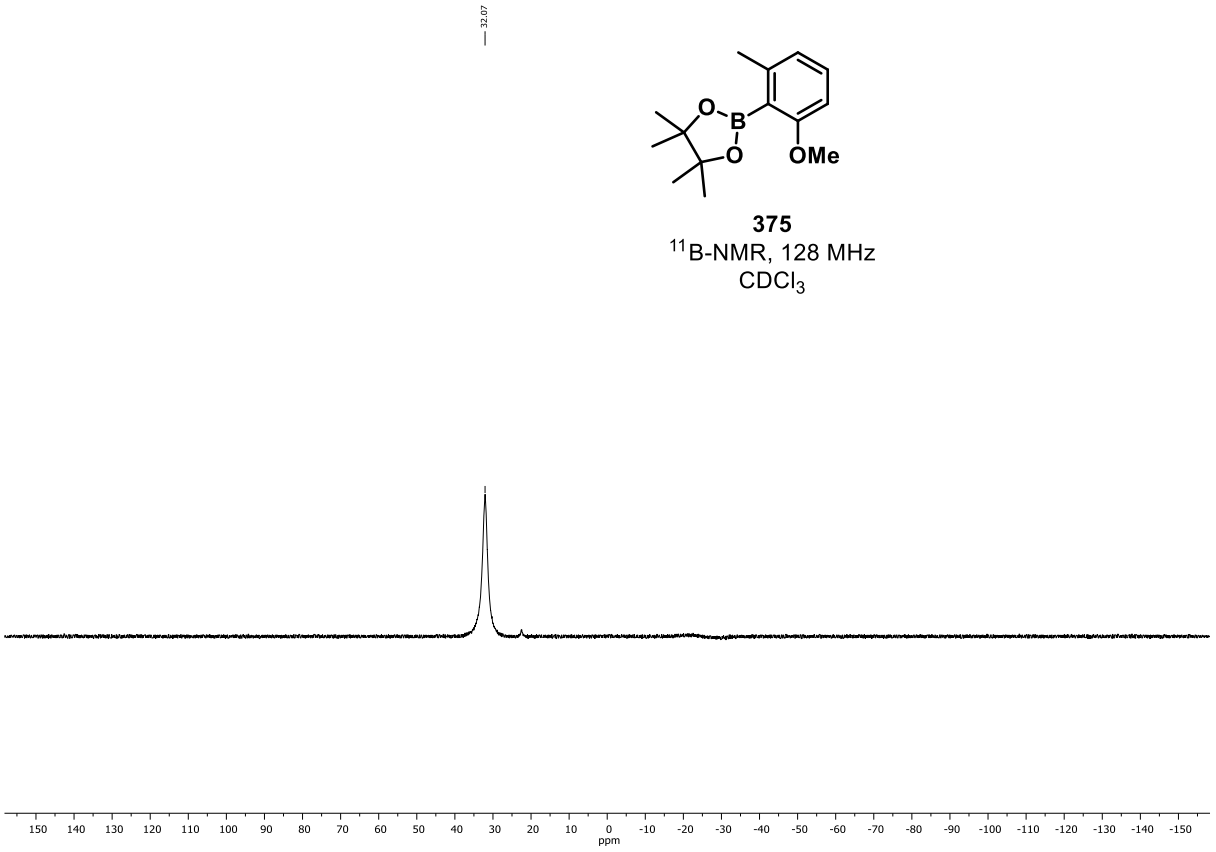
370
HSQC, 400 MHz
$CDCl_3$

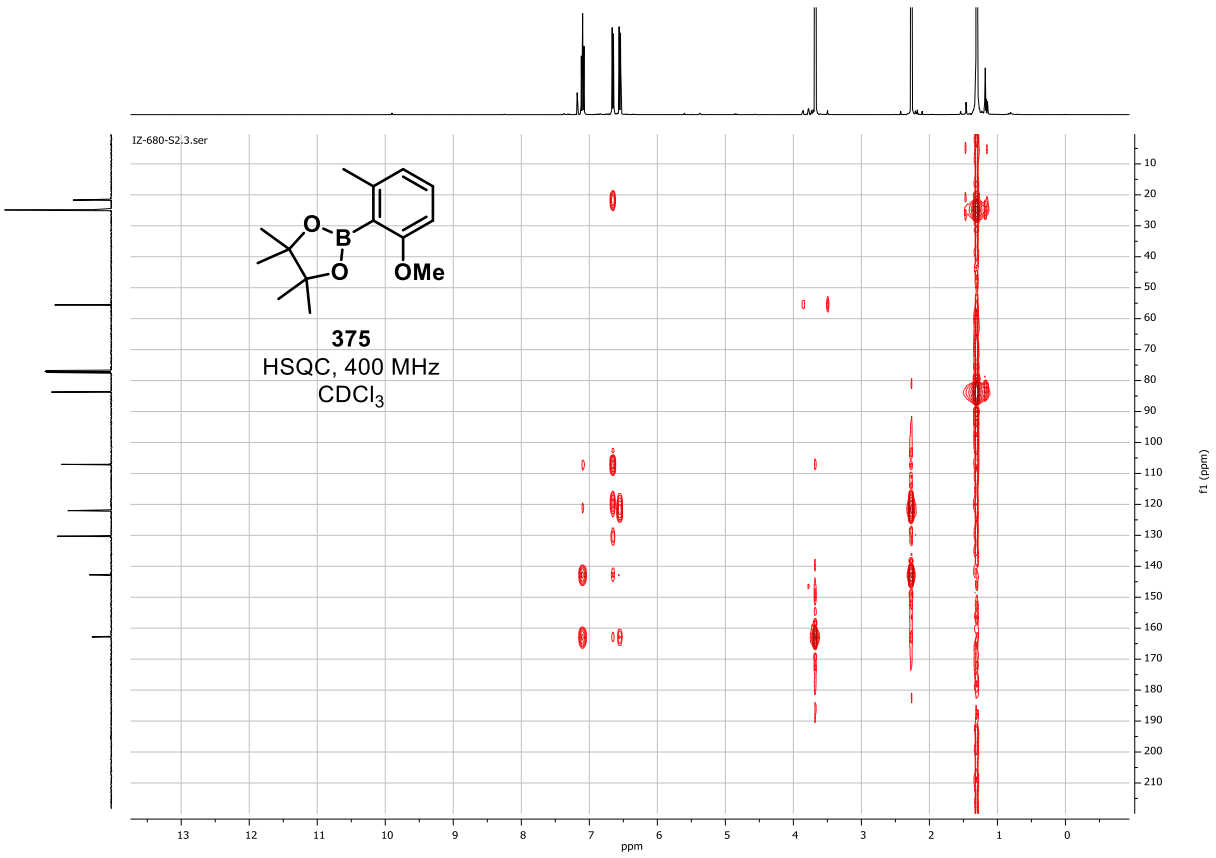


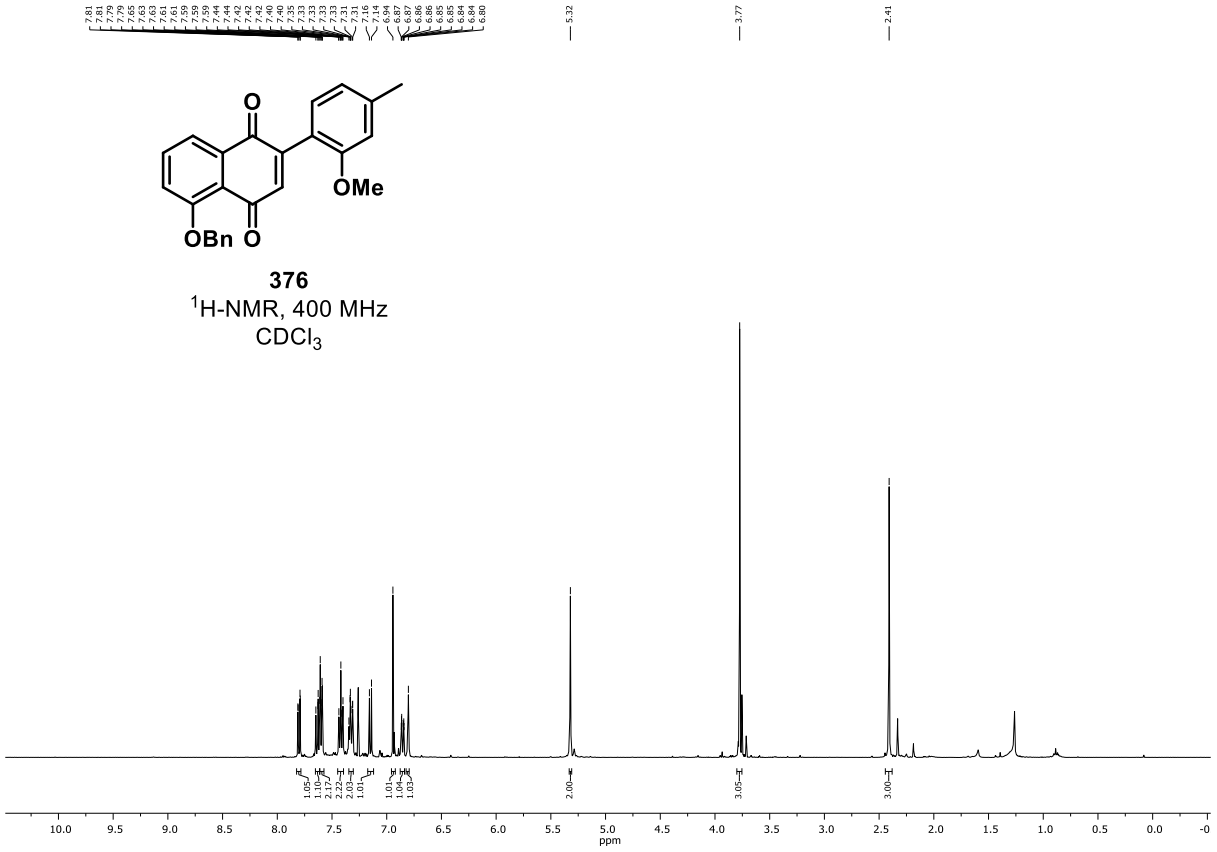


375
^{1}H-NMR, 400 MHz
$CDCl_3$

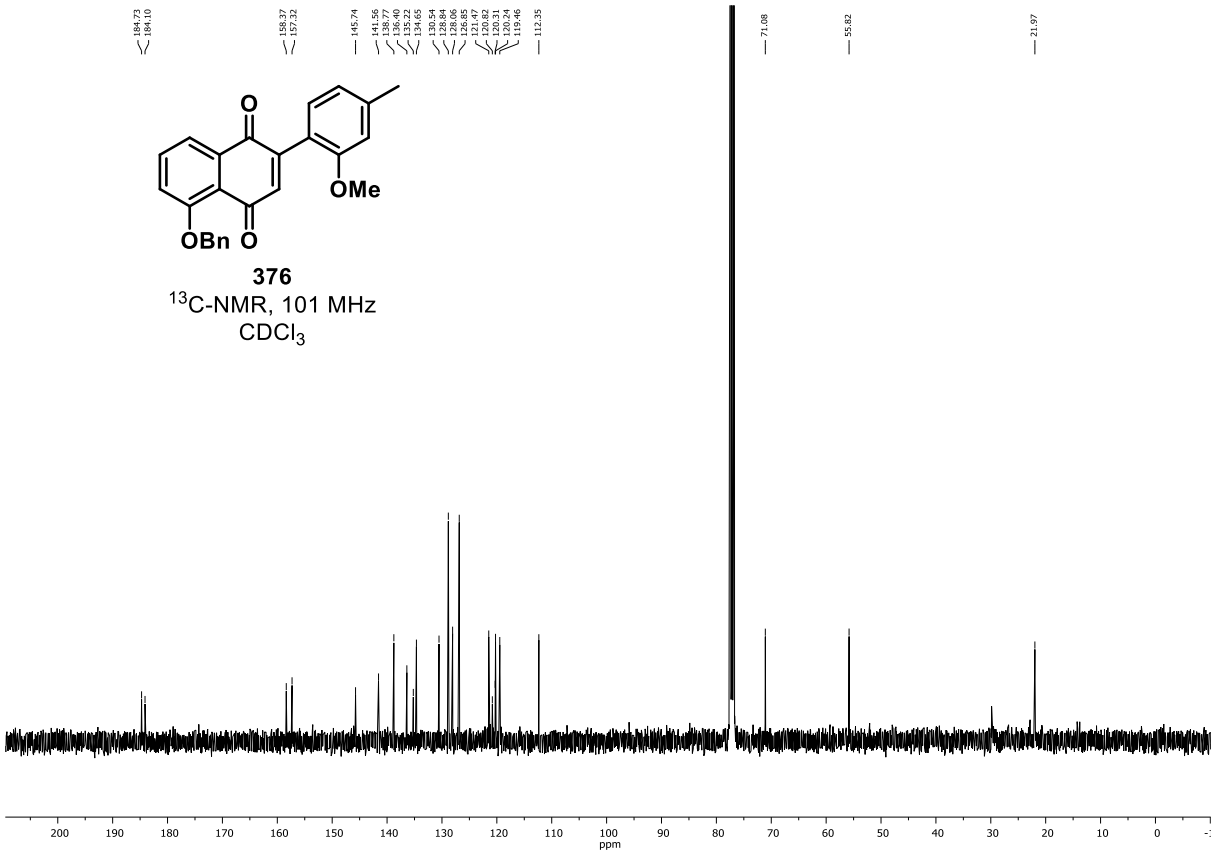
375
^{13}C-NMR, 101 MHz
$CDCl_3$


32.07
O
B
O
OMe
375
11B-NMR, 128 MHz
CDCl3
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
ppm

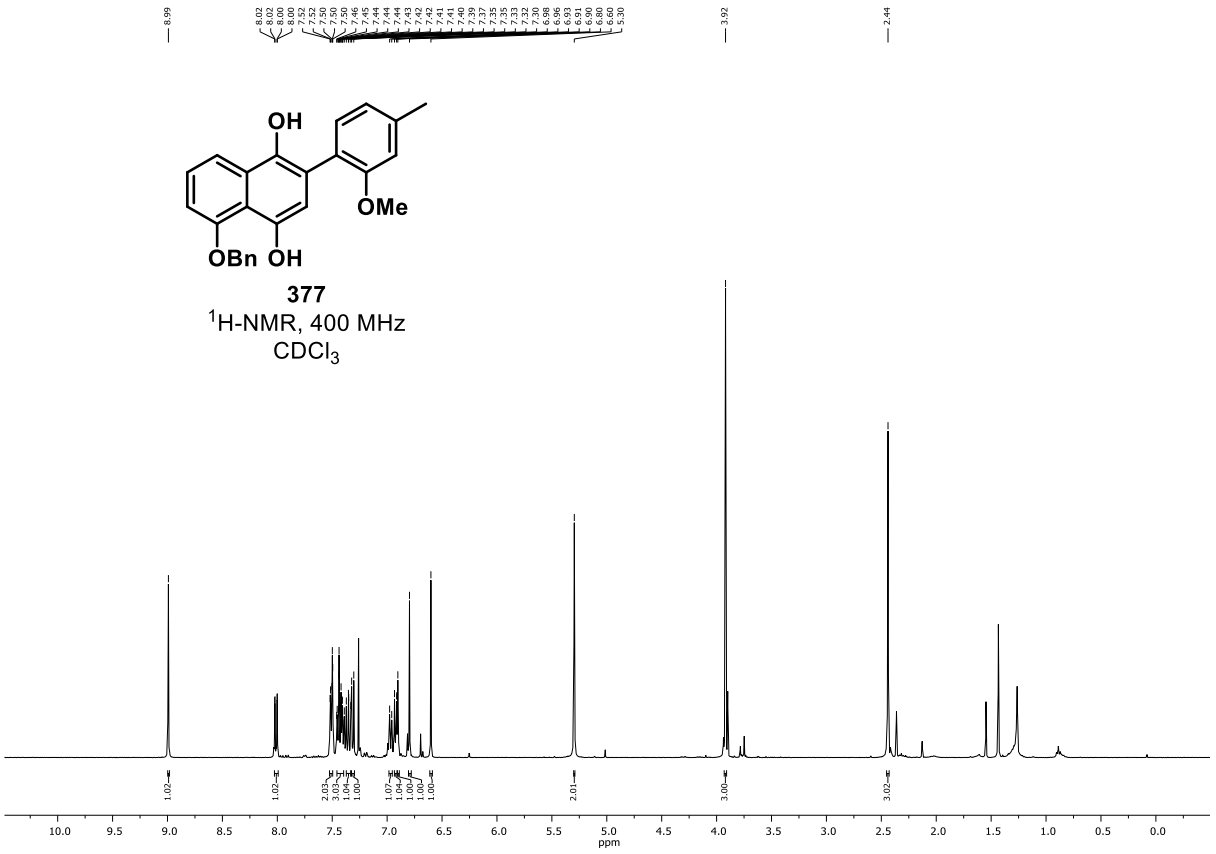

IZ-680-S2.3.ser
O
B
O
OMe
375
HSQC, 400 MHz
CDCl3
13 12 11 10 9 8 7 6 5 4 3 2 1 0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

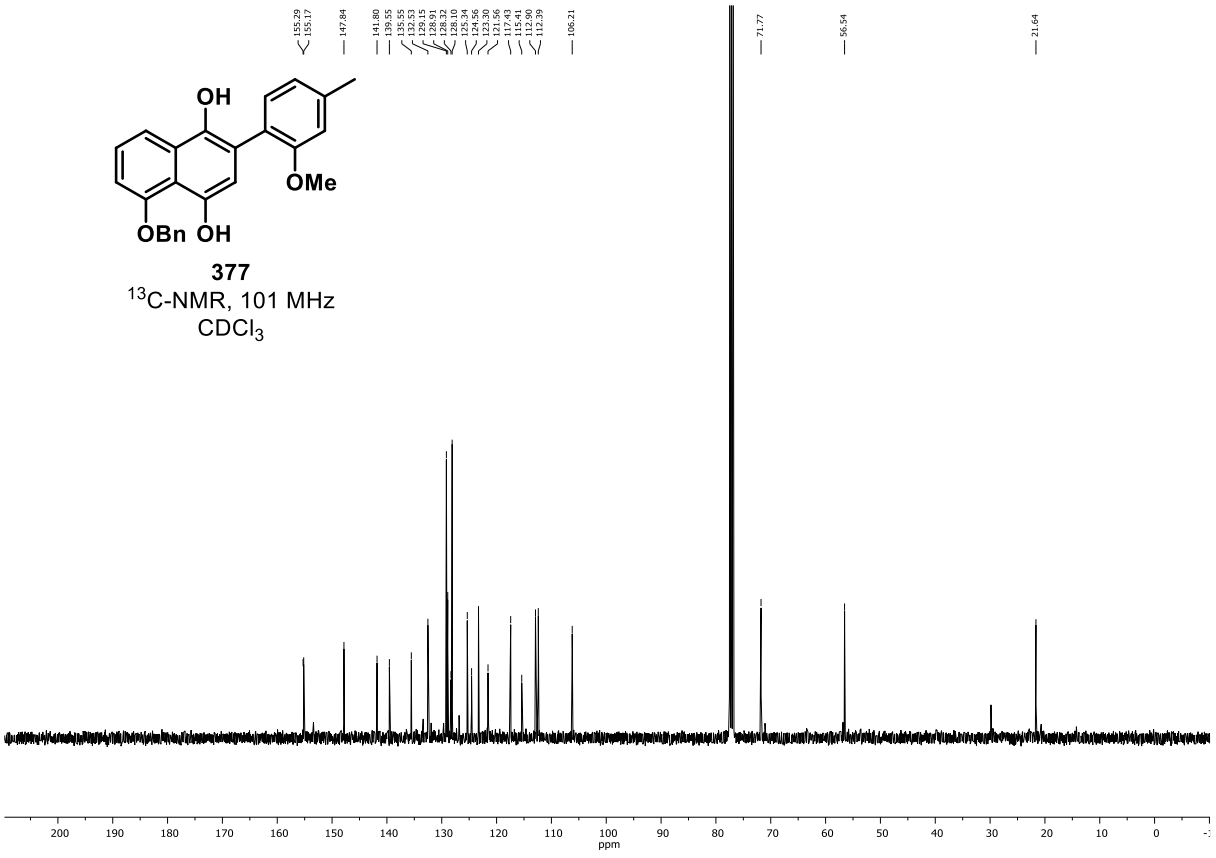


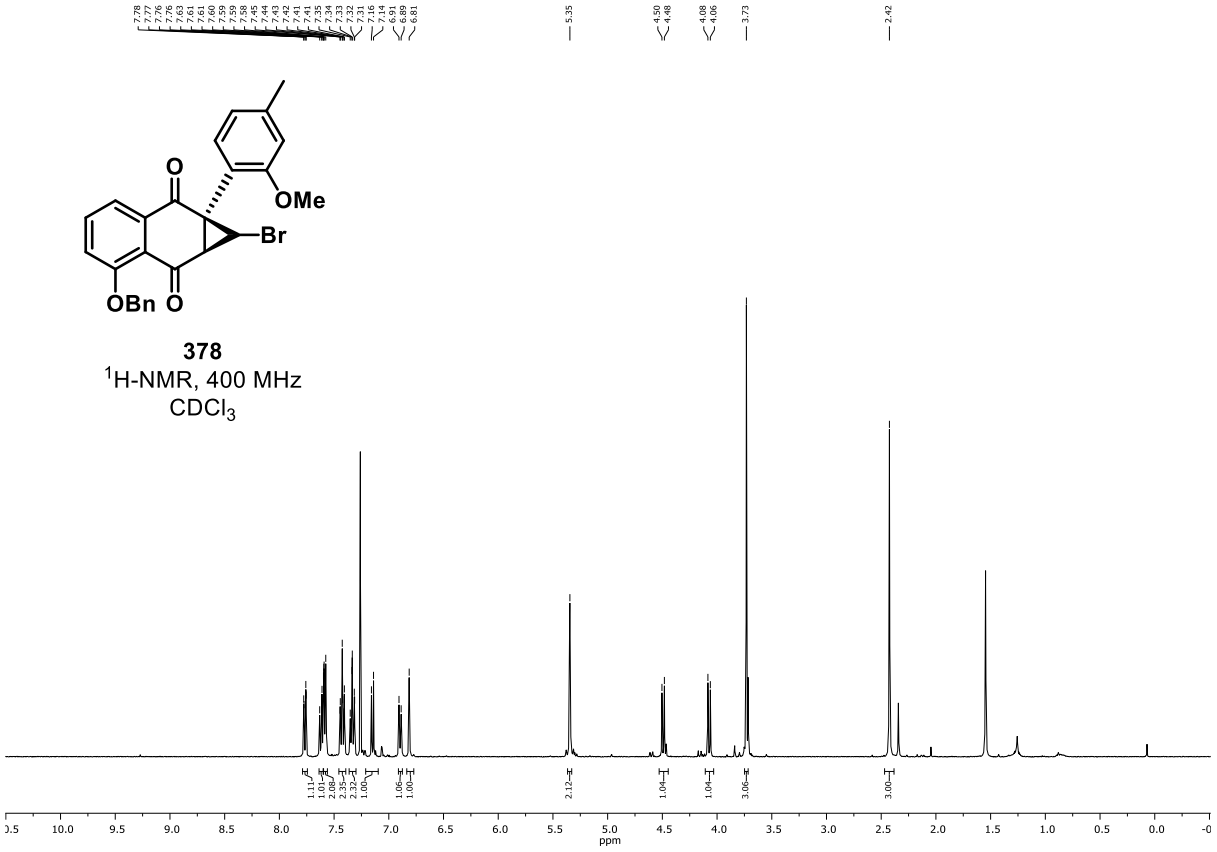
376
^{1}H-NMR, 400 MHz
$CDCl_3$



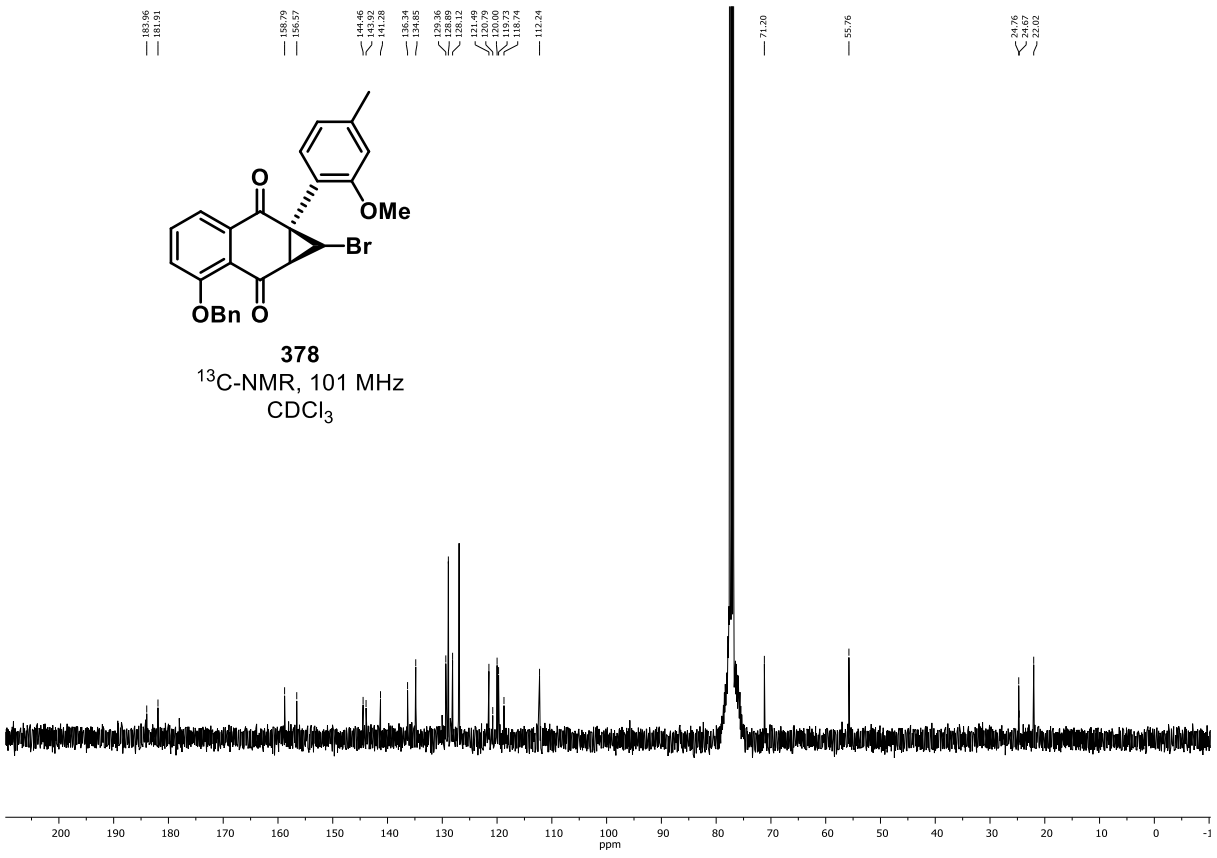
376
^{13}C-NMR, 101 MHz
$CDCl_3$


OH
OMe
OBn OH
377
1H-NMR, 400 MHz
CDCl3
ppm

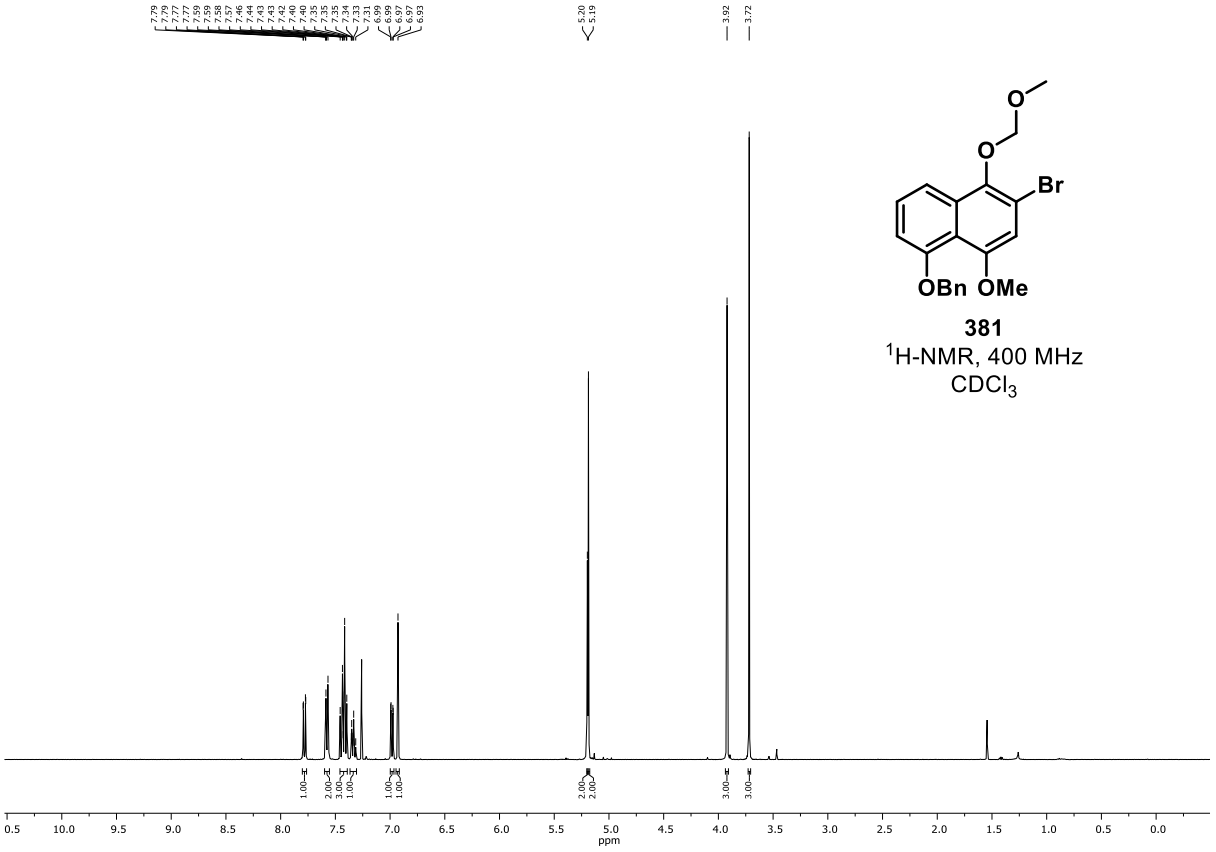

OH
OMe
OBn OH
377
13C-NMR, 101 MHz
CDCl3
ppm



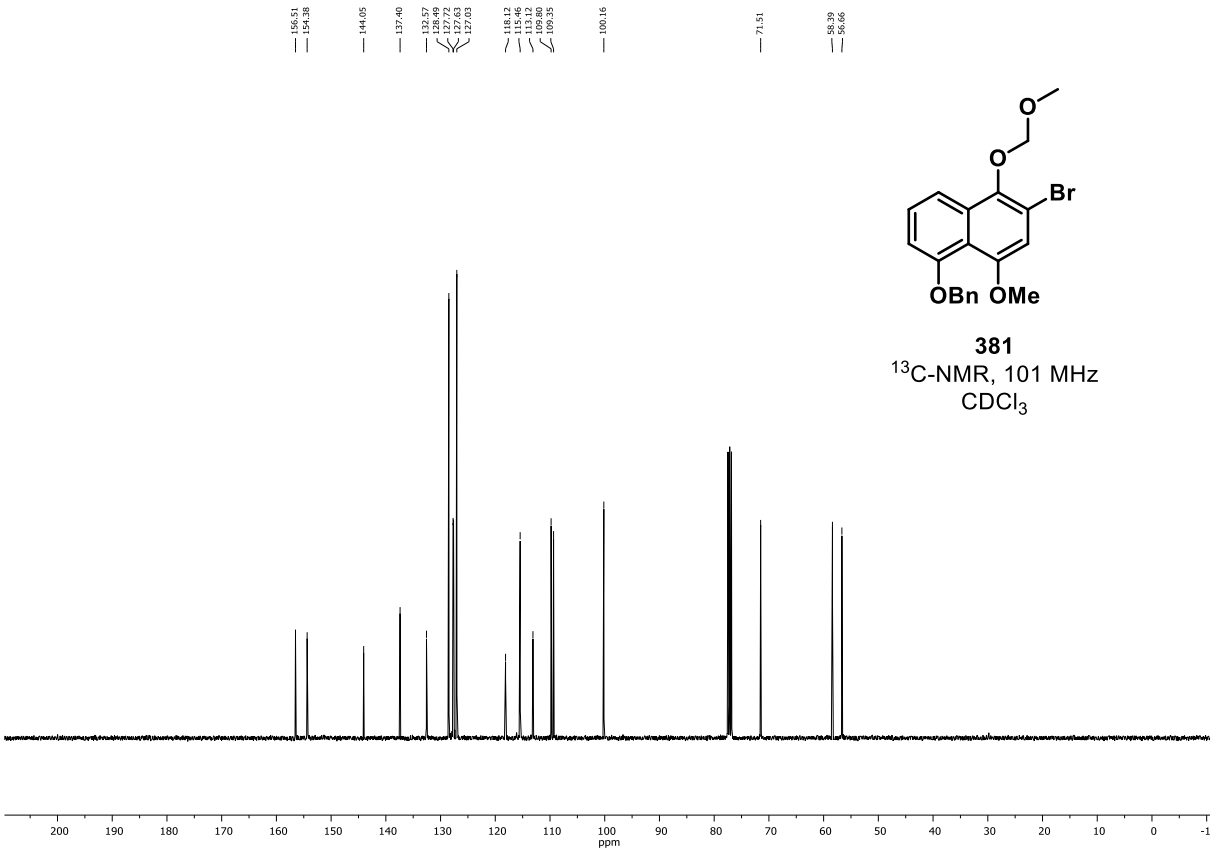
378
^{1}H-NMR, 400 MHz
$CDCl_3$



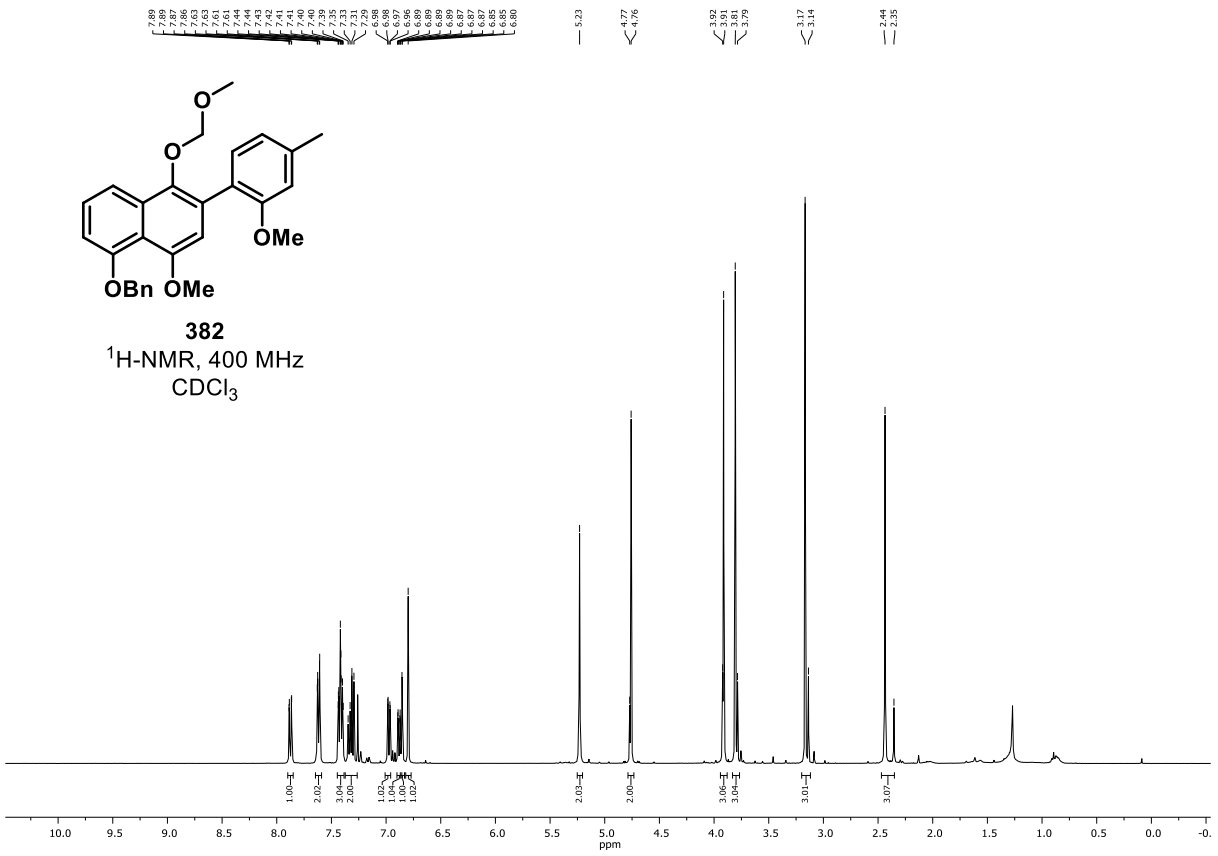
378
^{13}C-NMR, 101 MHz
$CDCl_3$



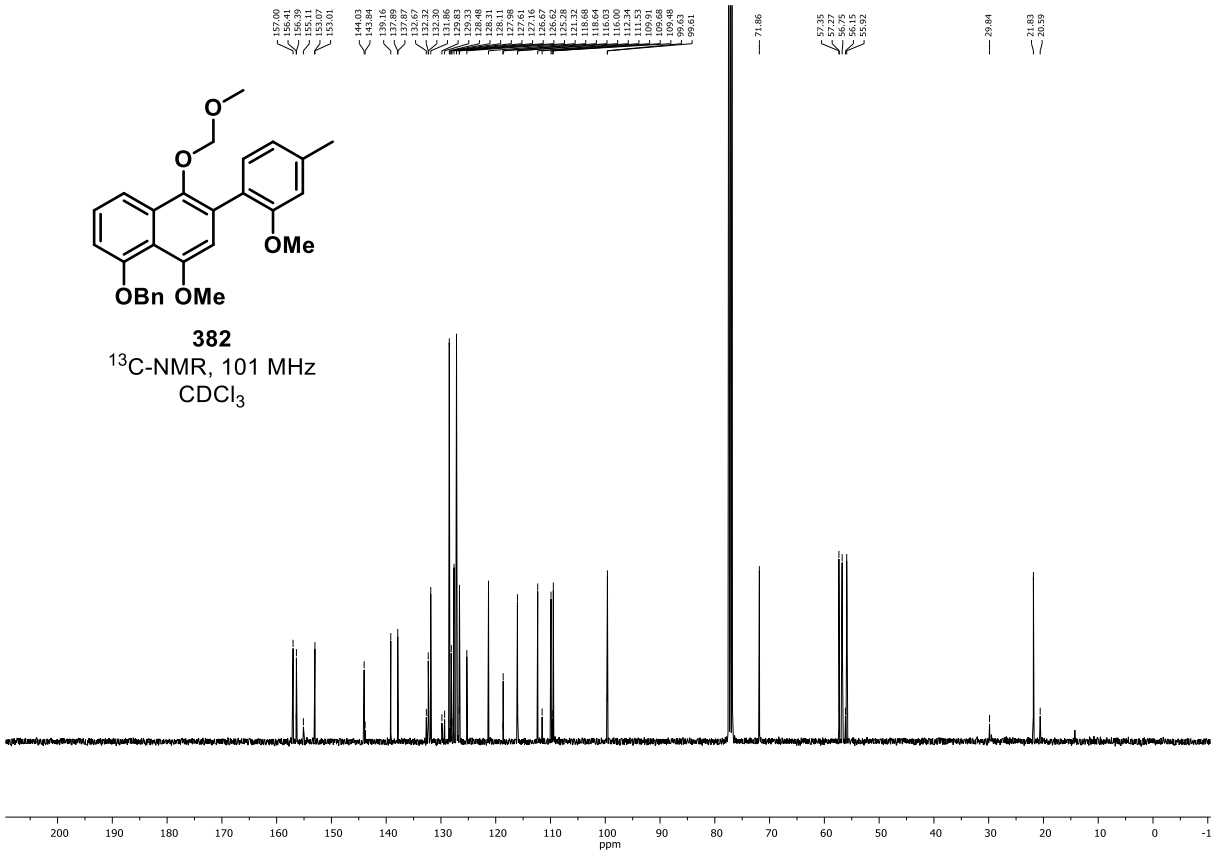
381
^{1}H-NMR, 400 MHz
$CDCl_3$



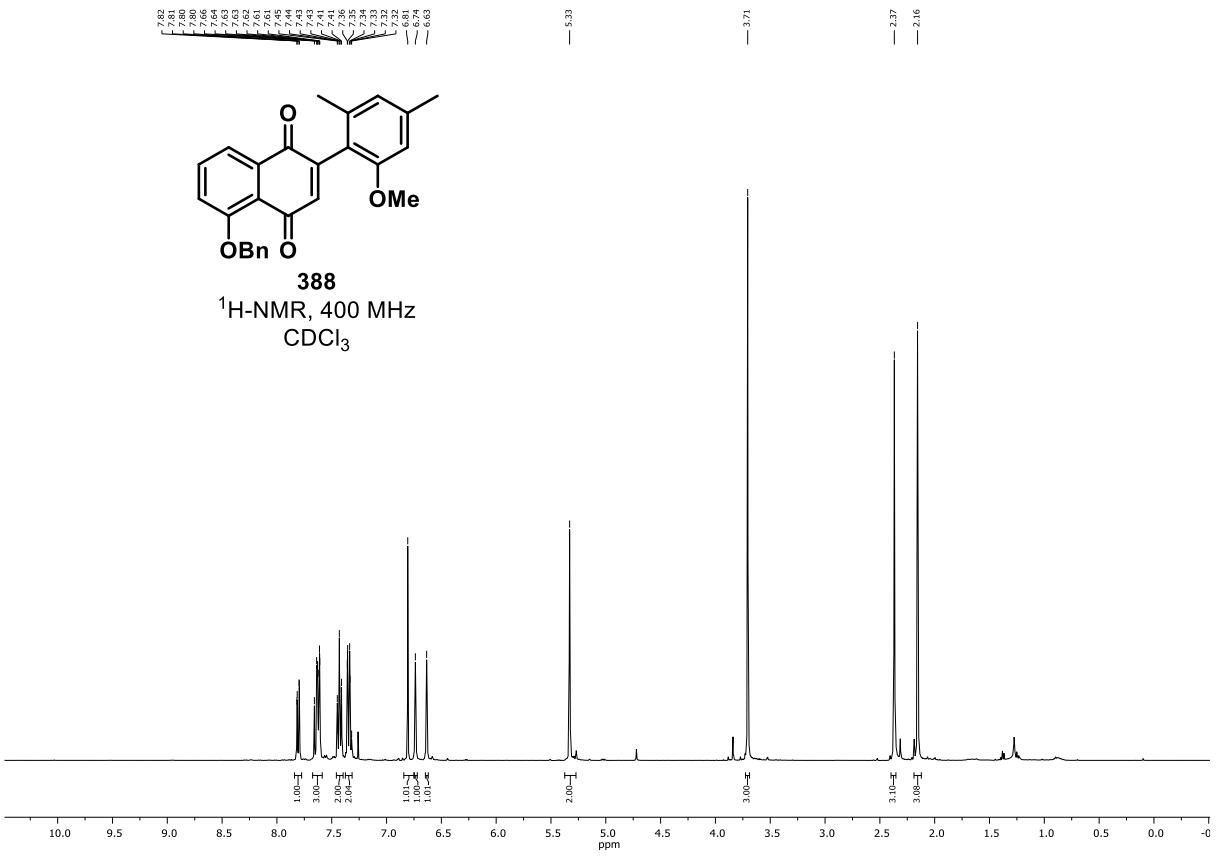
381
^{13}C-NMR, 101 MHz
$CDCl_3$



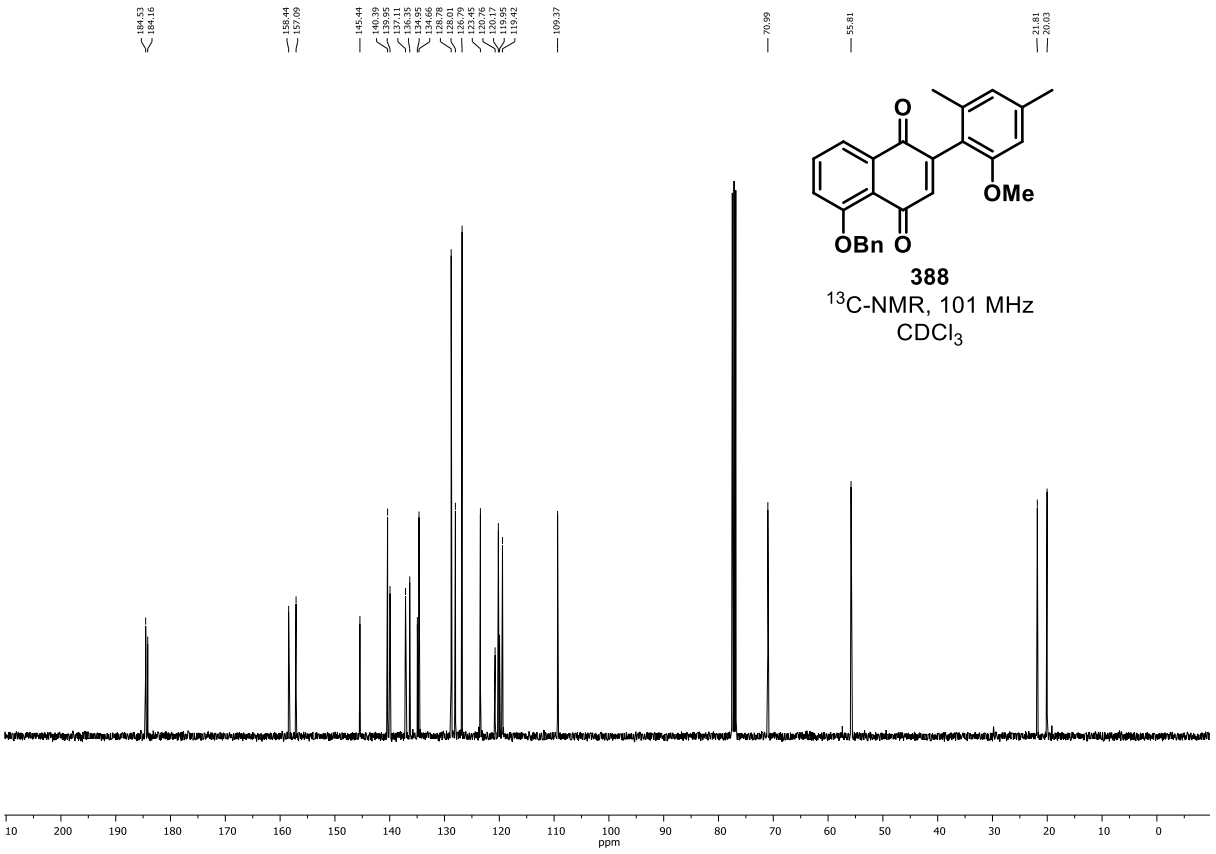
382
^{1}H-NMR, 400 MHz
$CDCl_3$



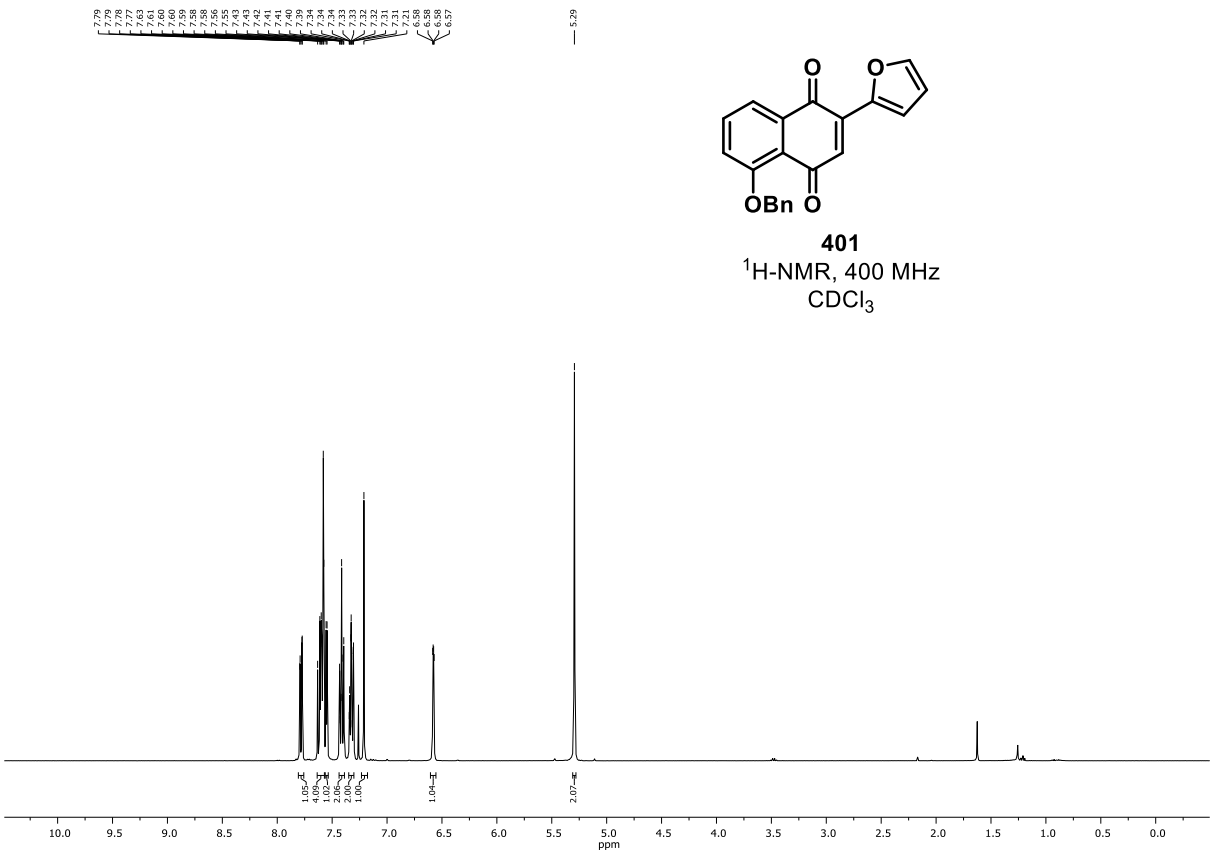
382
^{13}C-NMR, 101 MHz
$CDCl_3$



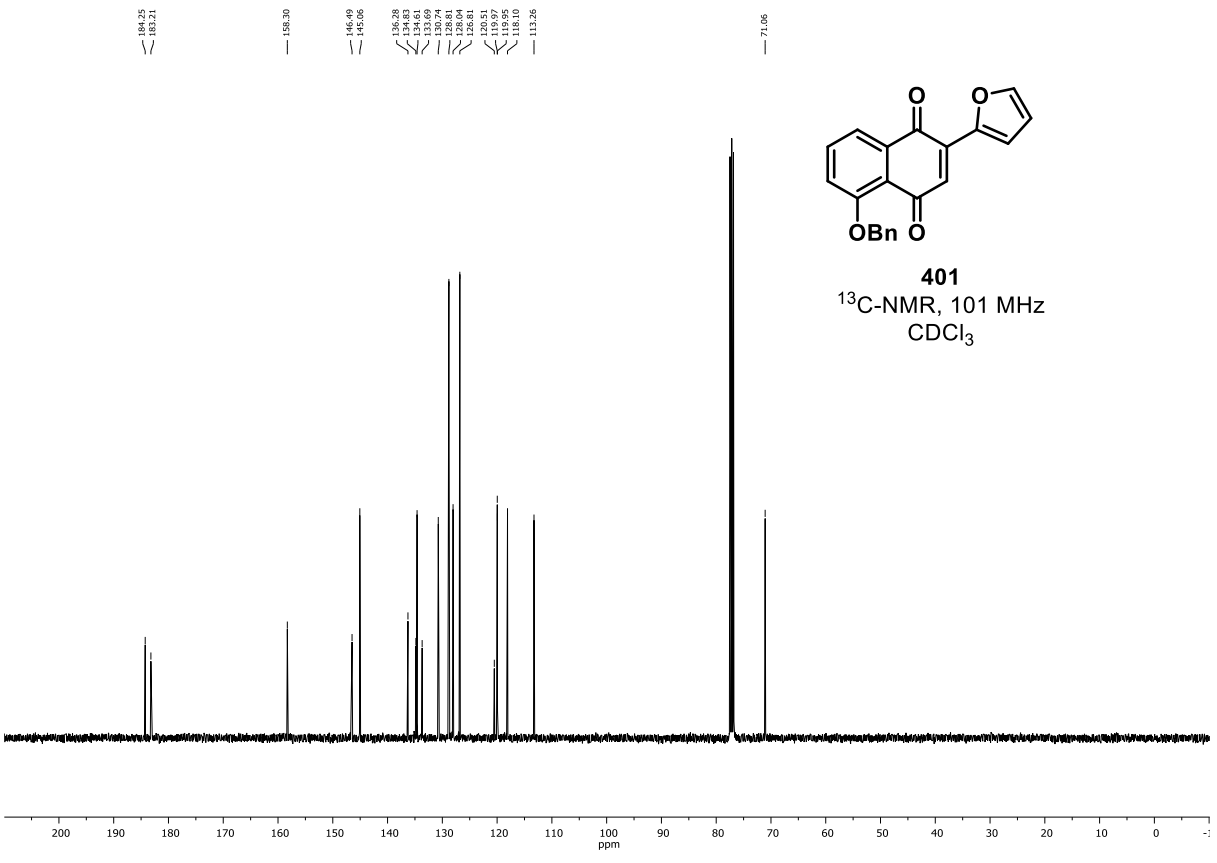
388
^{1}H-NMR, 400 MHz
$CDCl_3$



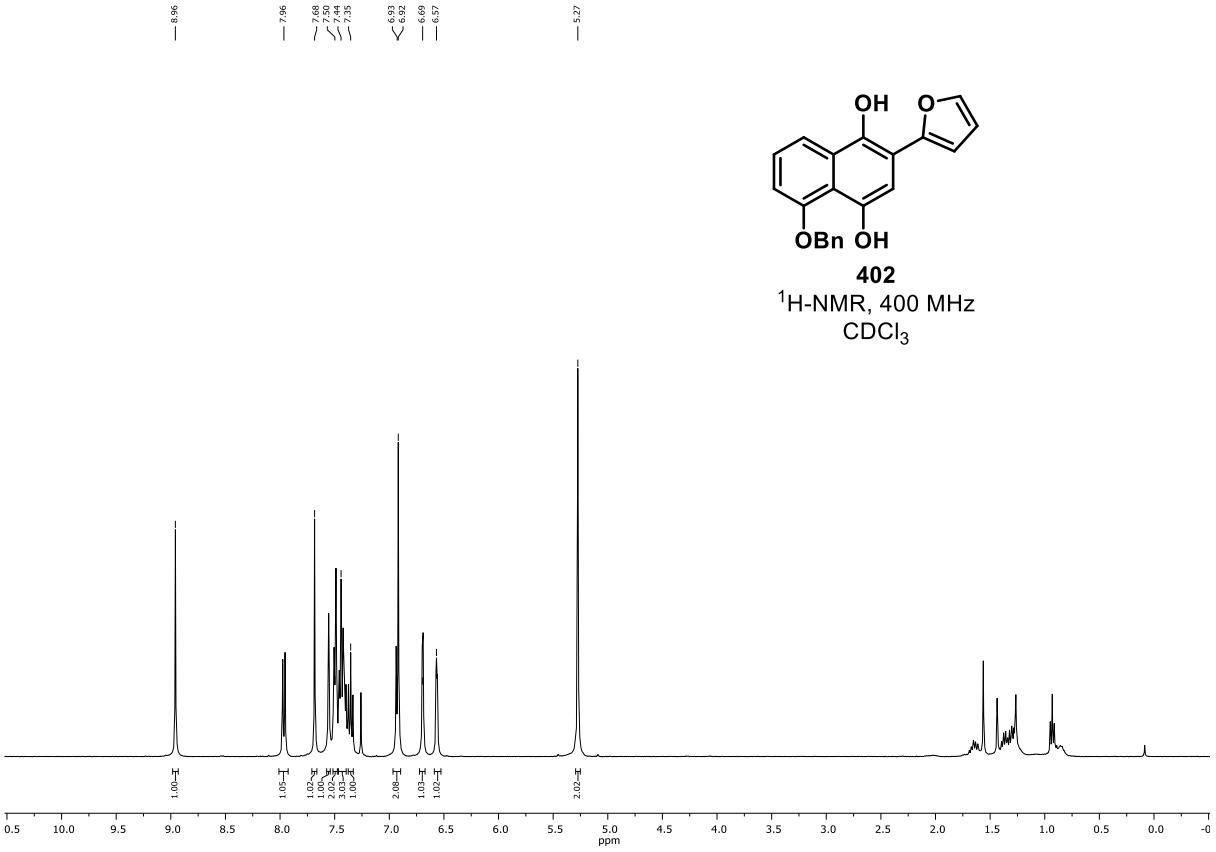
388
^{13}C-NMR, 101 MHz
$CDCl_3$

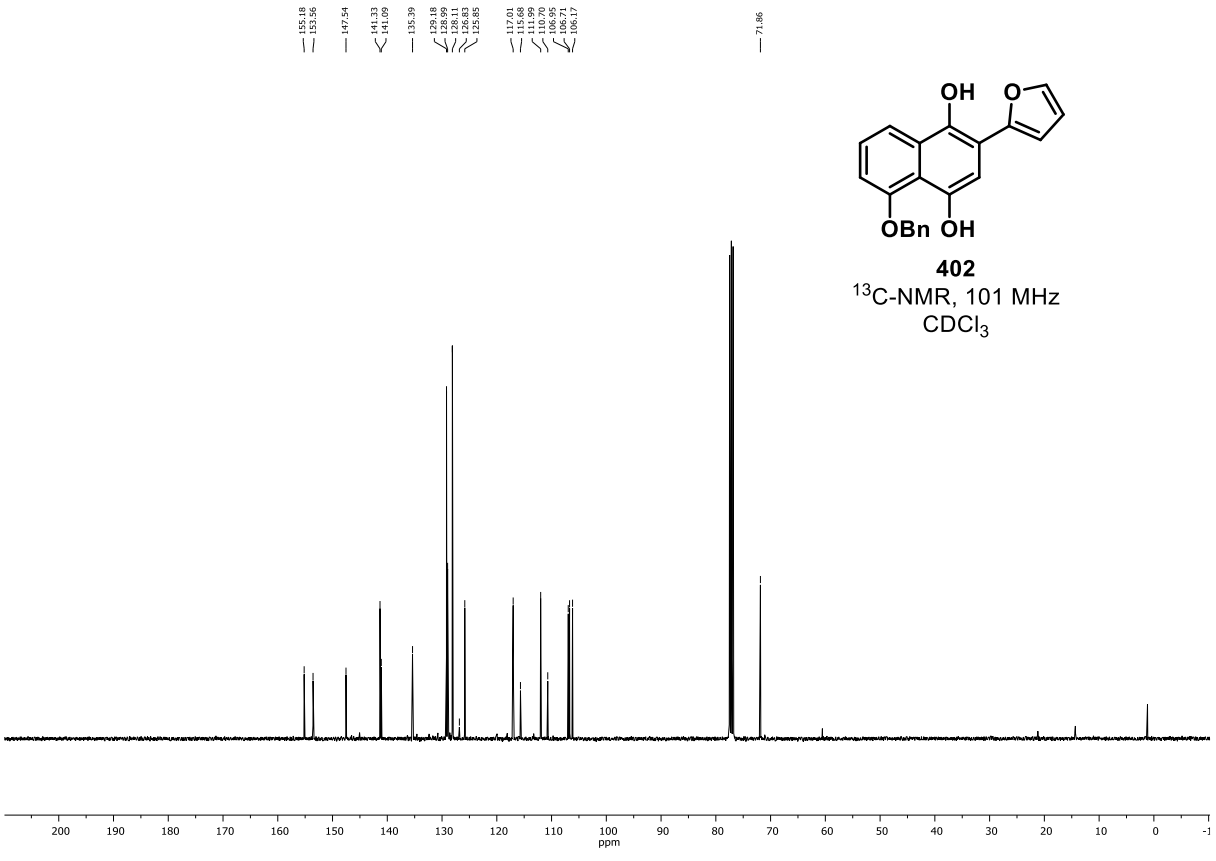


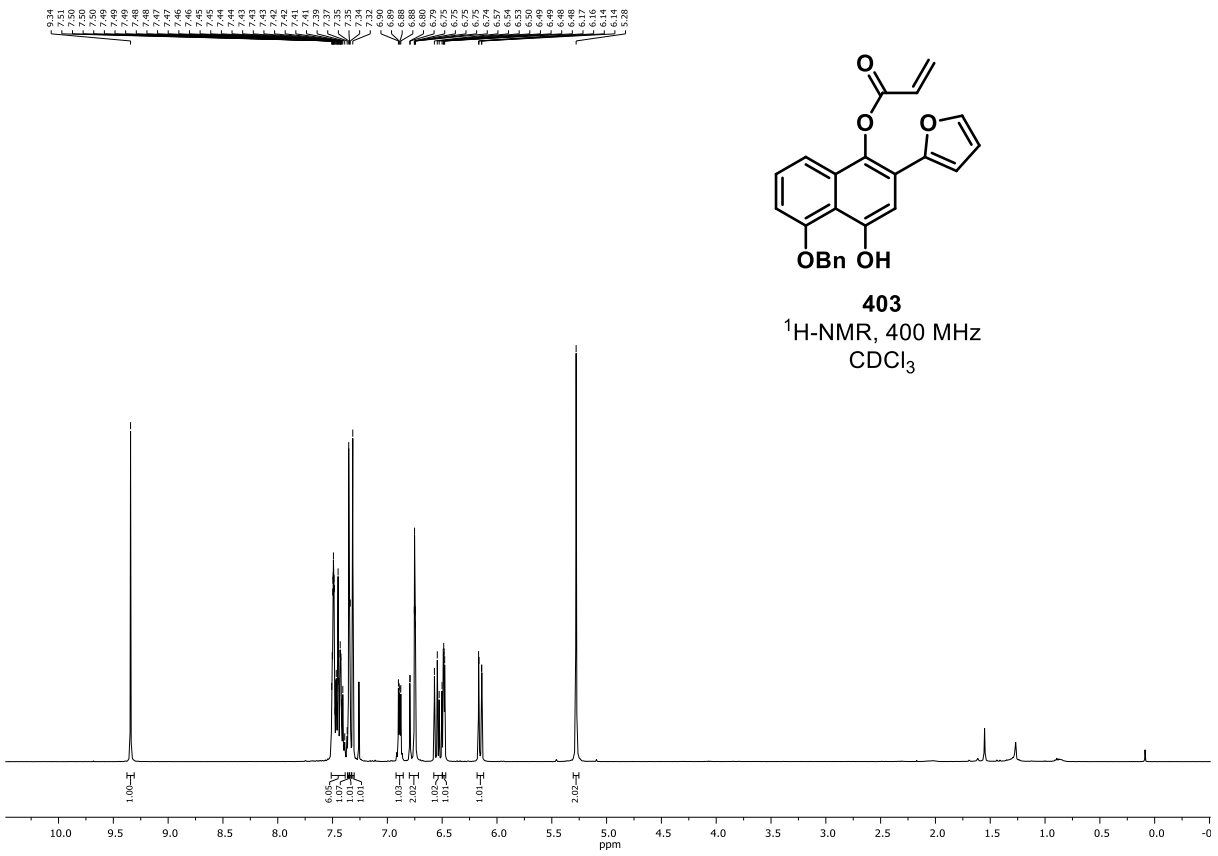
401
^{1}H-NMR, 400 MHz
$CDCl_3$



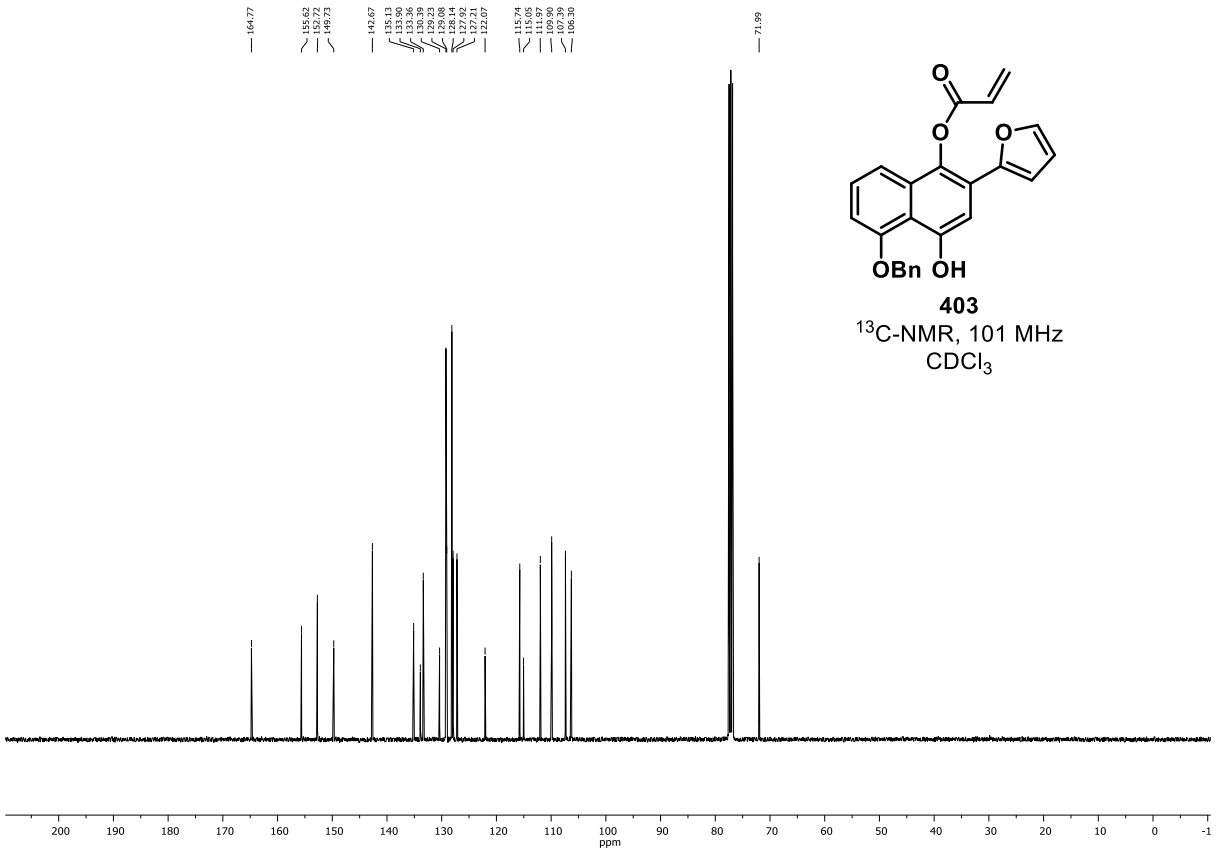
401
^{13}C-NMR, 101 MHz
$CDCl_3$


8.96
7.96
7.68
7.50
7.44
7.35
6.93
6.92
6.69
6.57
5.27
OH
O
OBn OH
402
1H-NMR, 400 MHz
CDCl3
ppm

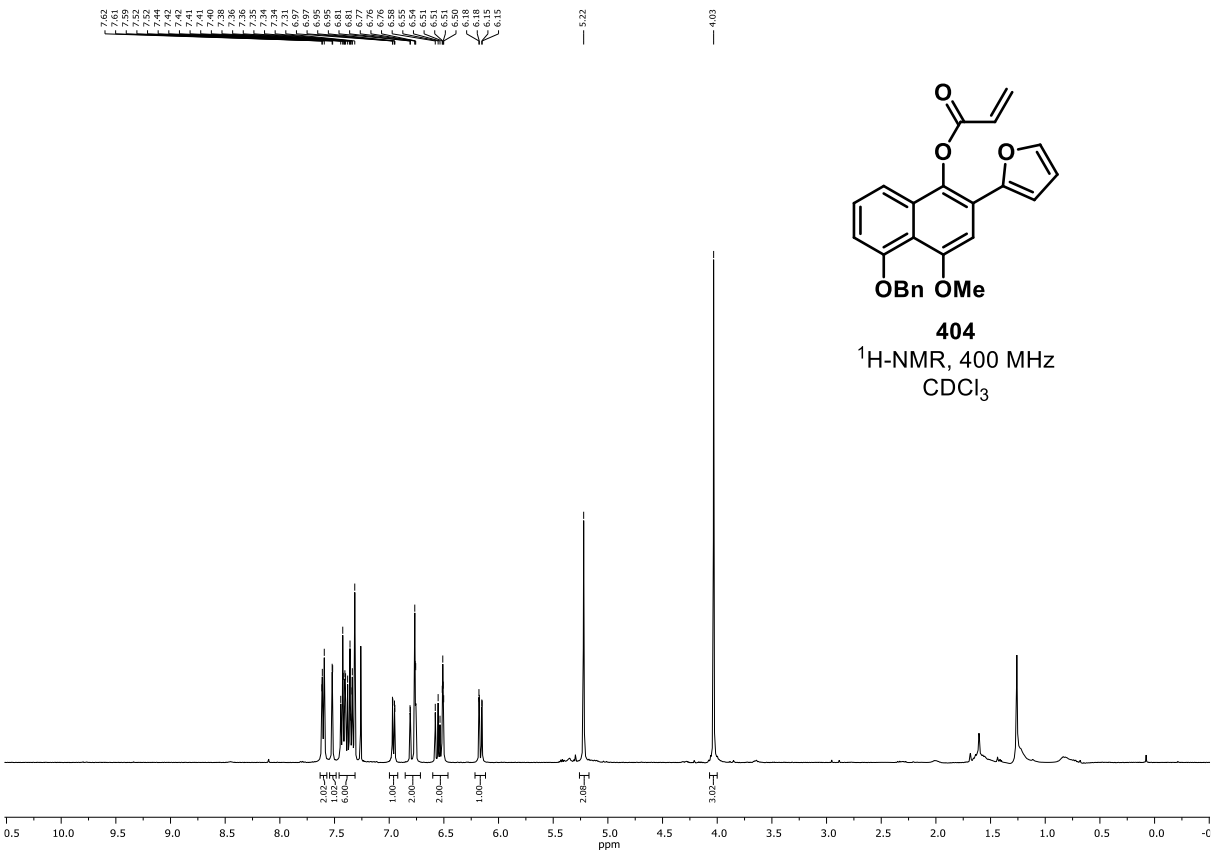

155.18
153.96
147.54
141.33
141.09
135.39
129.18
128.99
128.11
126.83
125.85
117.01
115.68
111.99
110.70
106.55
106.21
106.17
71.86
OH
O
OBn OH
402
13C-NMR, 101 MHz
CDCl3
ppm

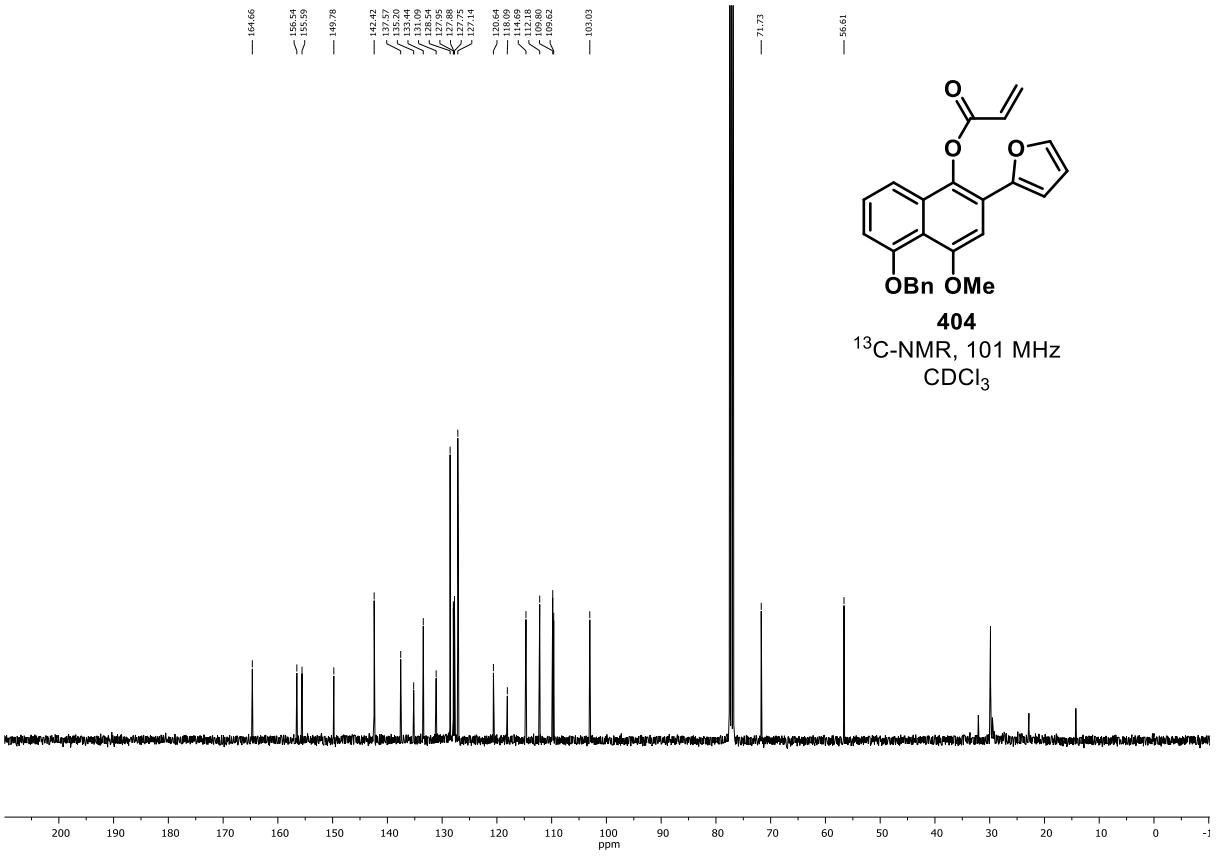


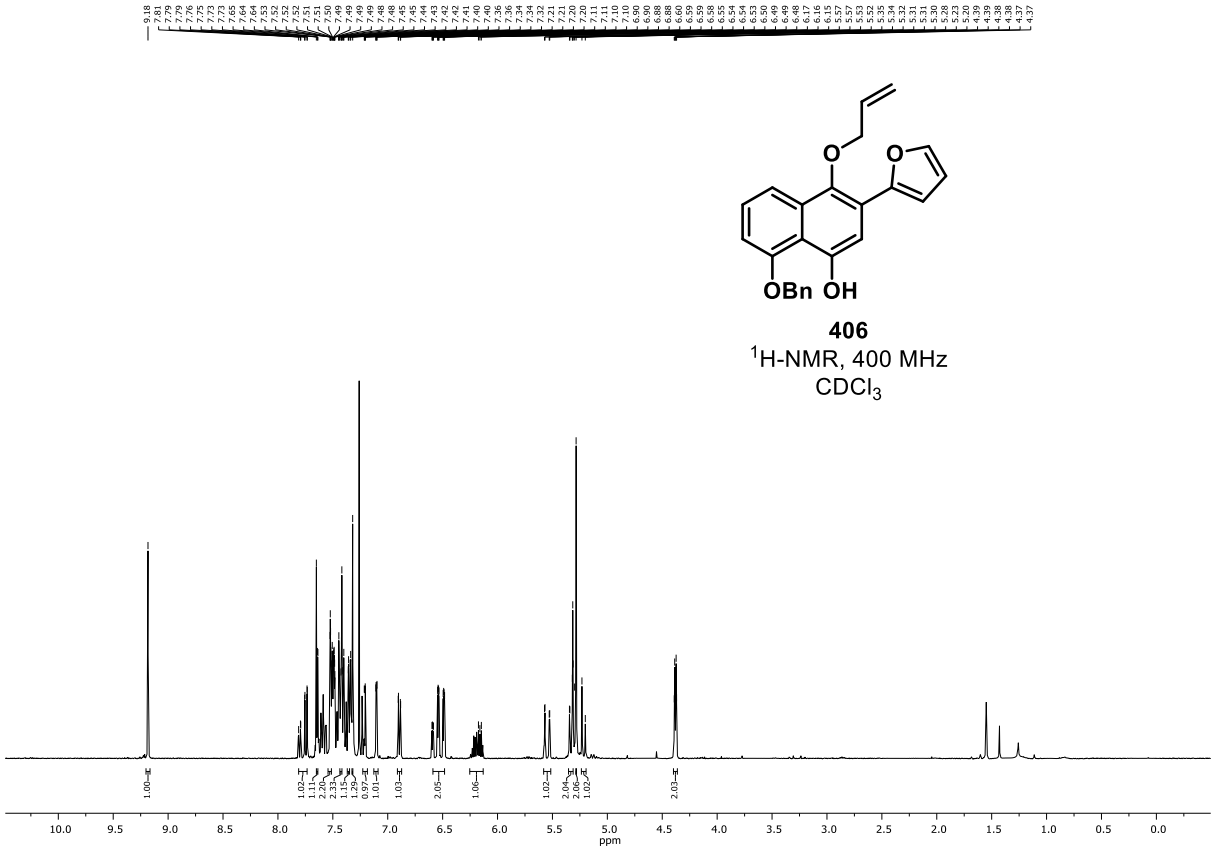
403
^{1}H-NMR, 400 MHz
$CDCl_3$



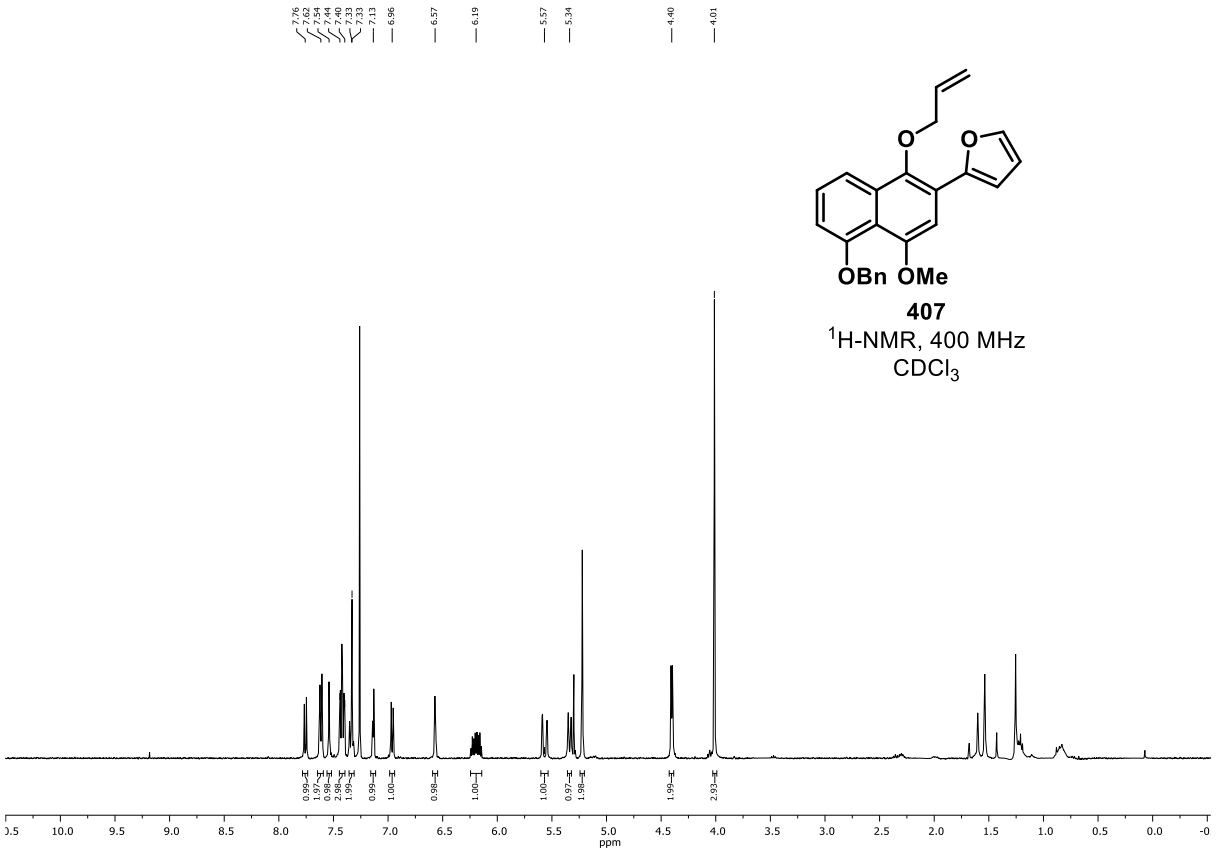
403
^{13}C-NMR, 101 MHz
$CDCl_3$


OBn OMe
404
1H-NMR, 400 MHz
CDCl3
ppm

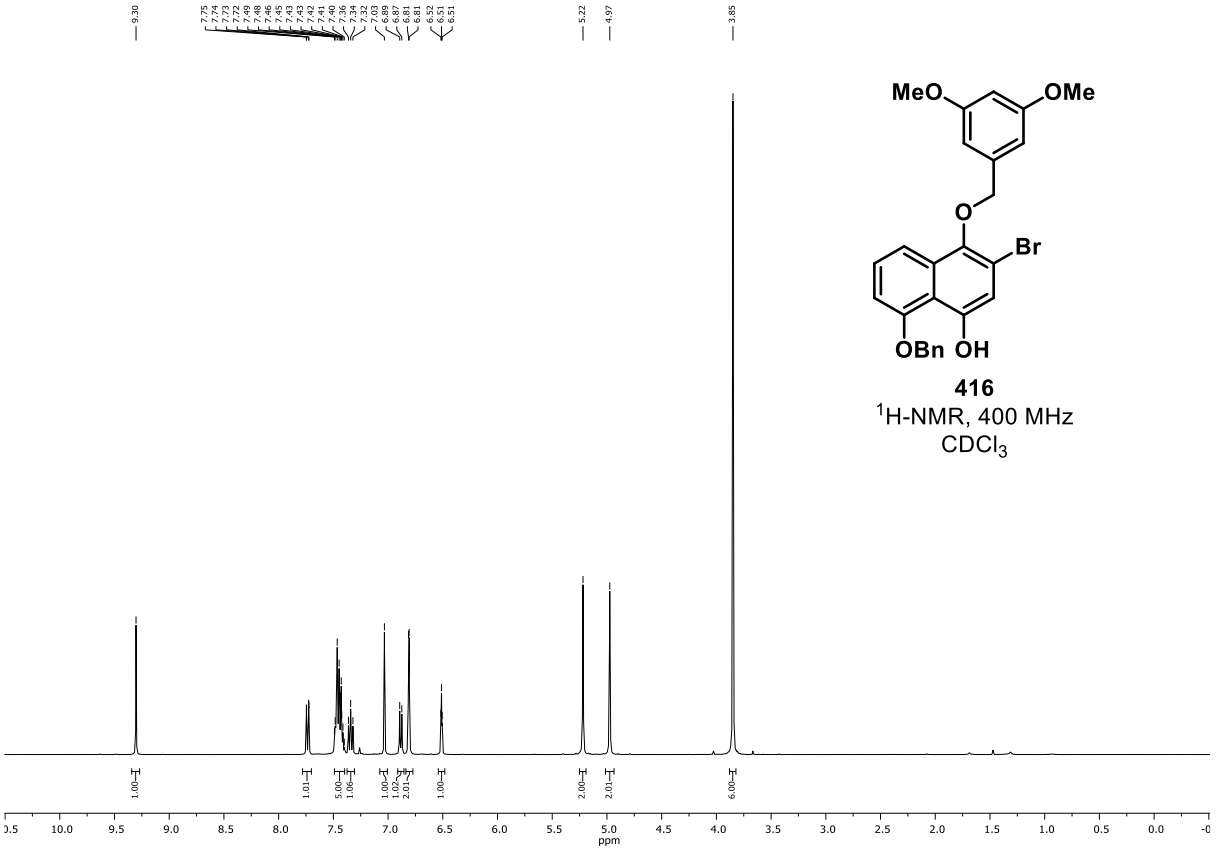

OBn OMe
404
13C-NMR, 101 MHz
CDCl3
ppm



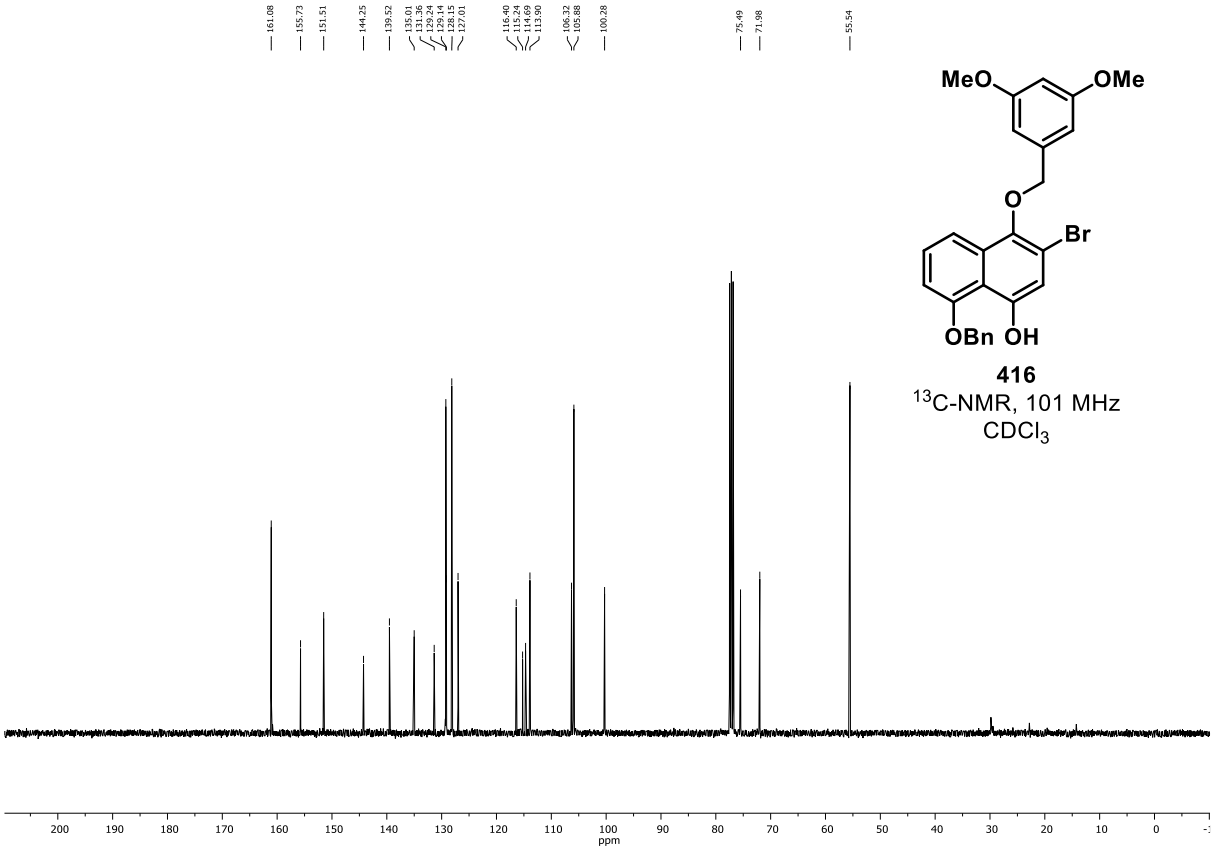
406
^{1}H-NMR, 400 MHz
$CDCl_3$



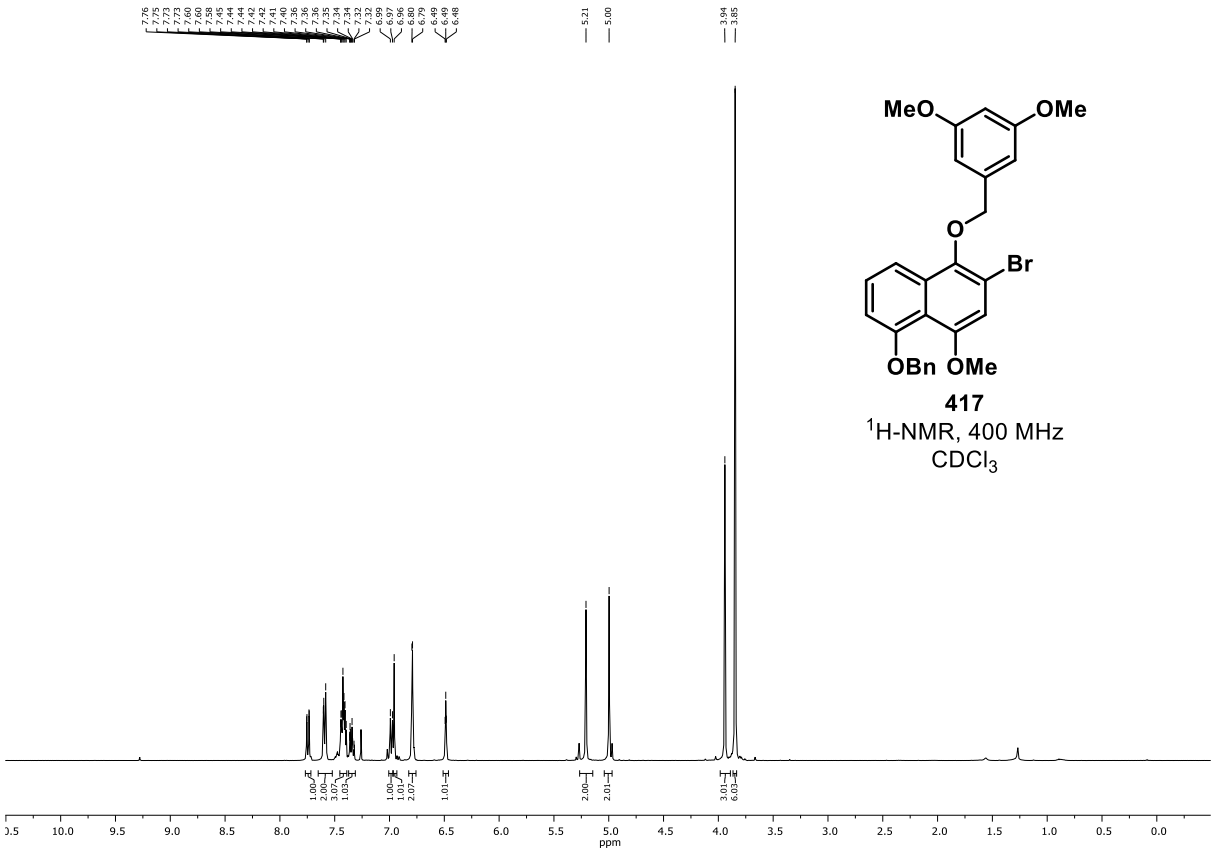
407
^{1}H-NMR, 400 MHz
$CDCl_3$

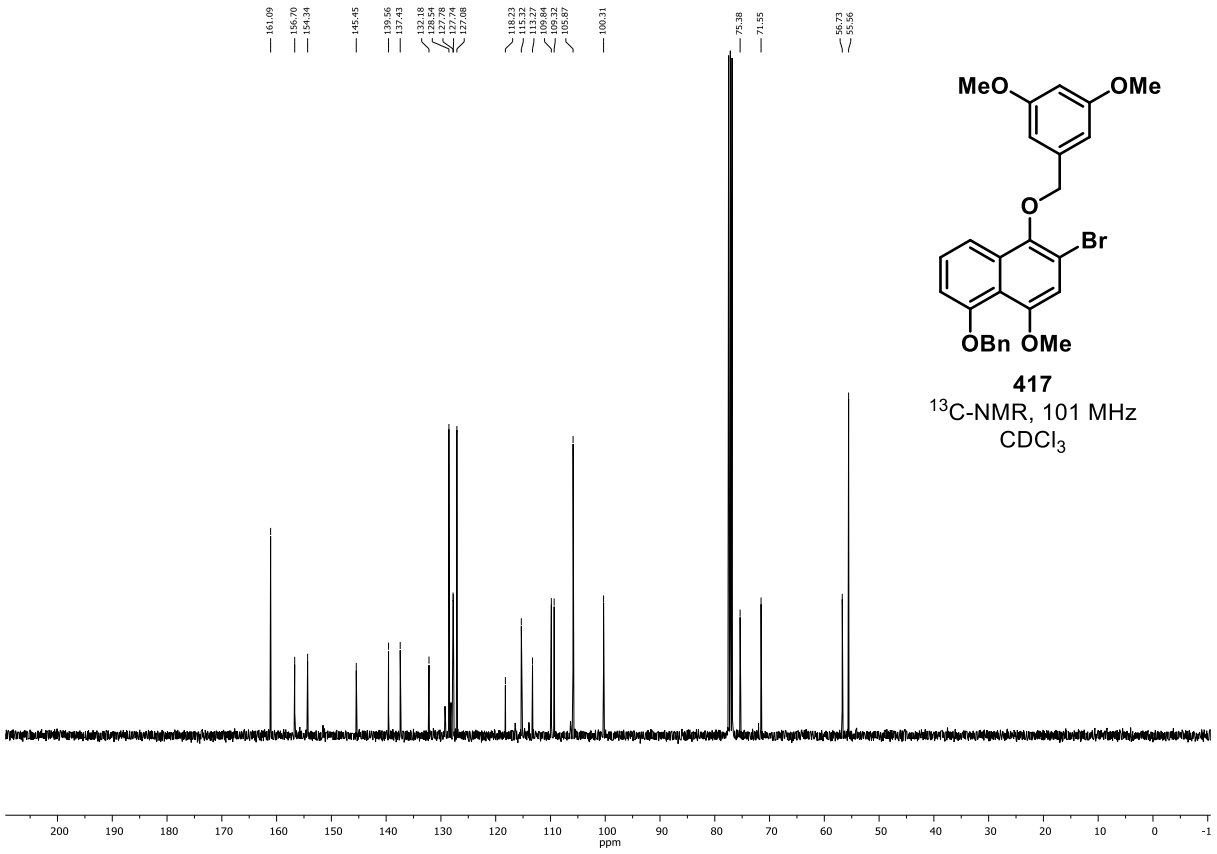


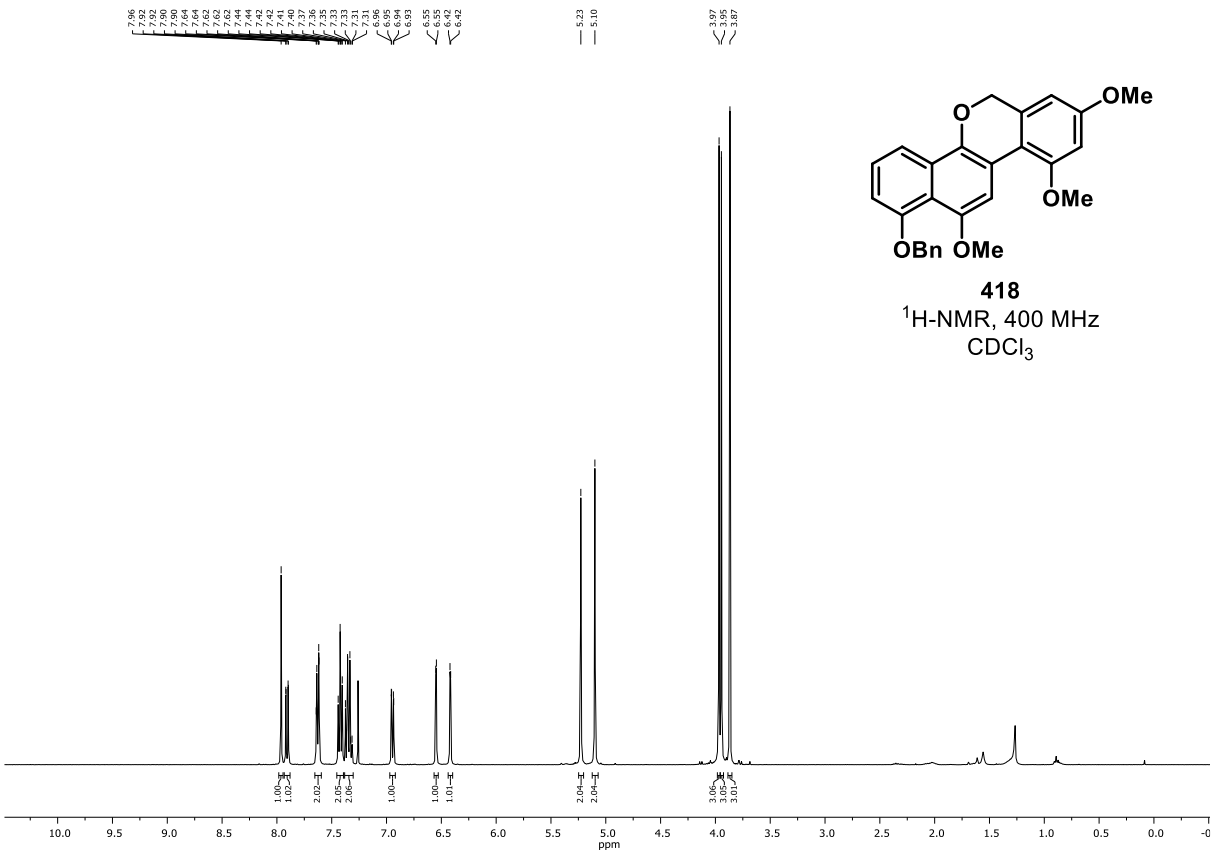
416
^{1}H-NMR, 400 MHz
$CDCl_3$



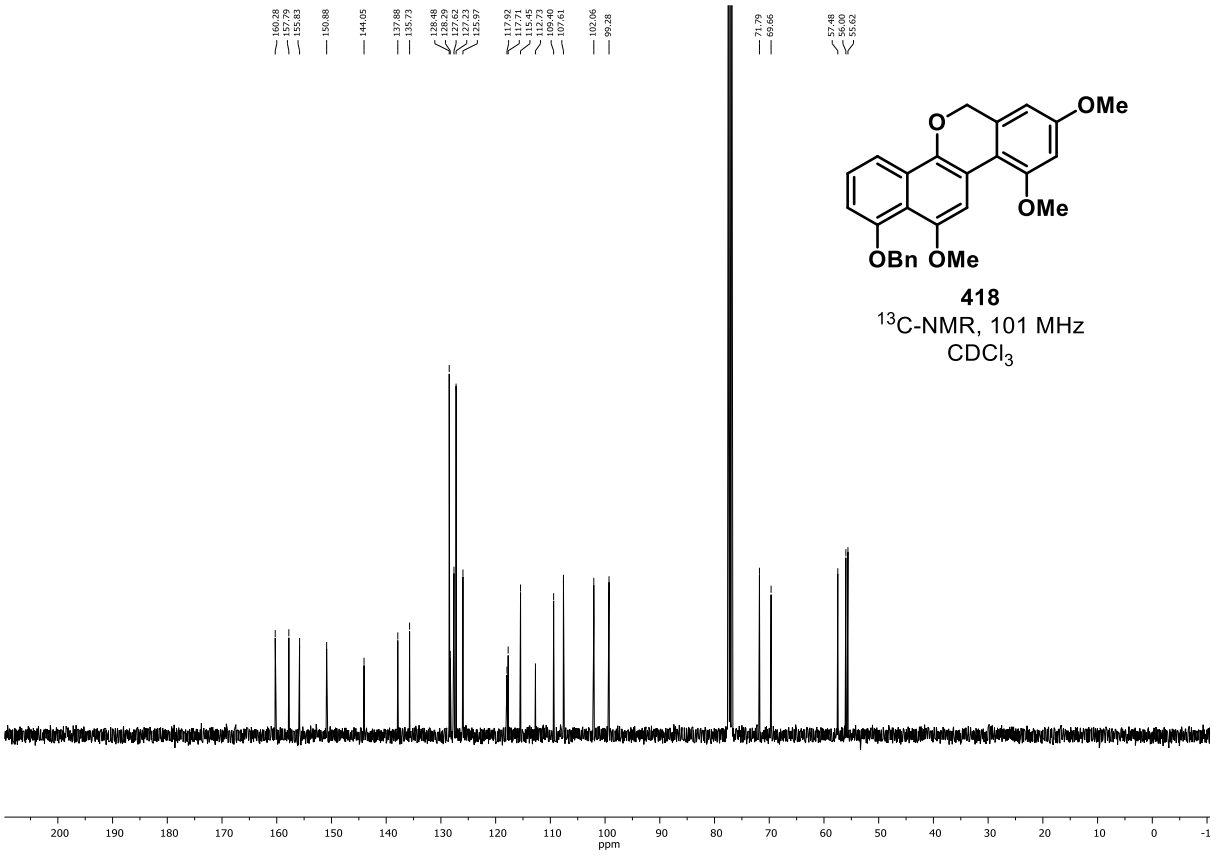
416
^{13}C-NMR, 101 MHz
$CDCl_3$


MeO
OMe
O
Br
OBn OMe
417
1H-NMR, 400 MHz
CDCl3
ppm

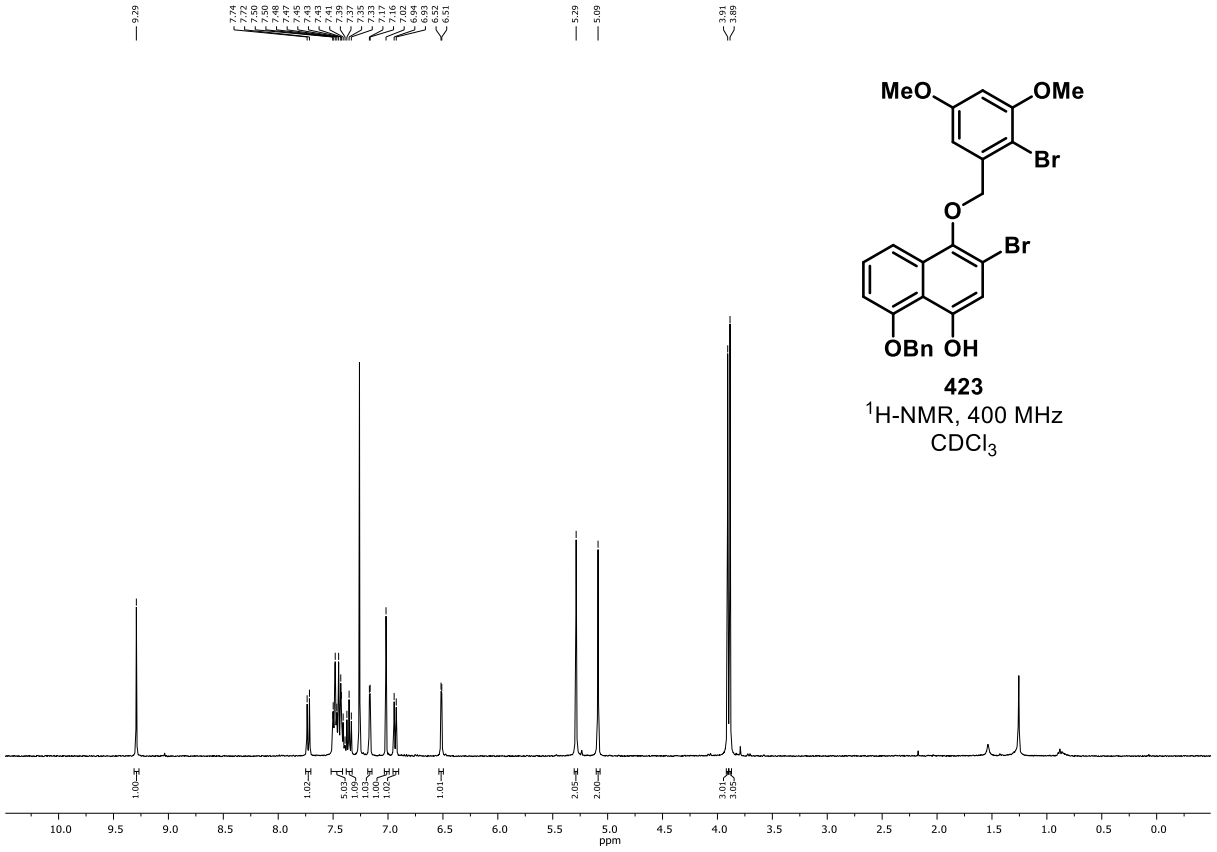

MeO
OMe
O
Br
OBn OMe
417
13C-NMR, 101 MHz
CDCl3
ppm



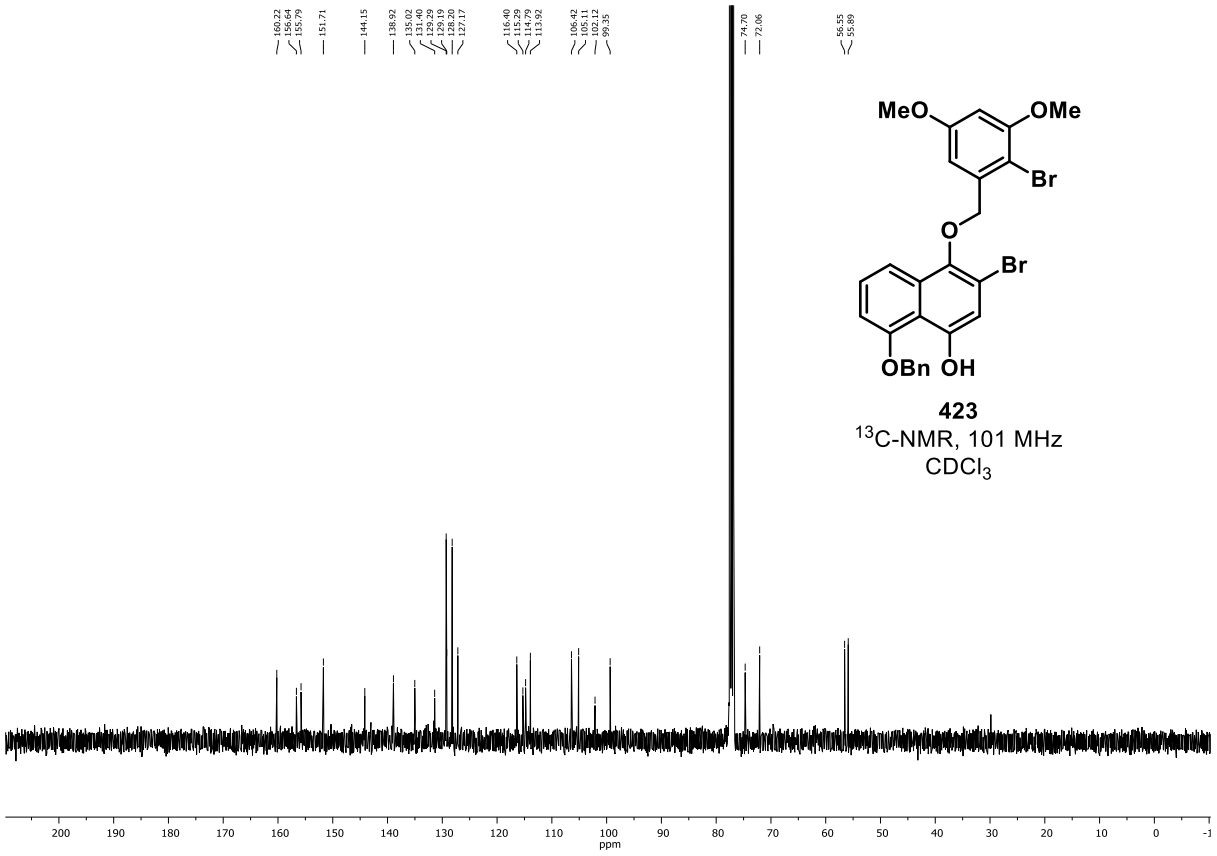
418
^{1}H-NMR, 400 MHz
$CDCl_3$



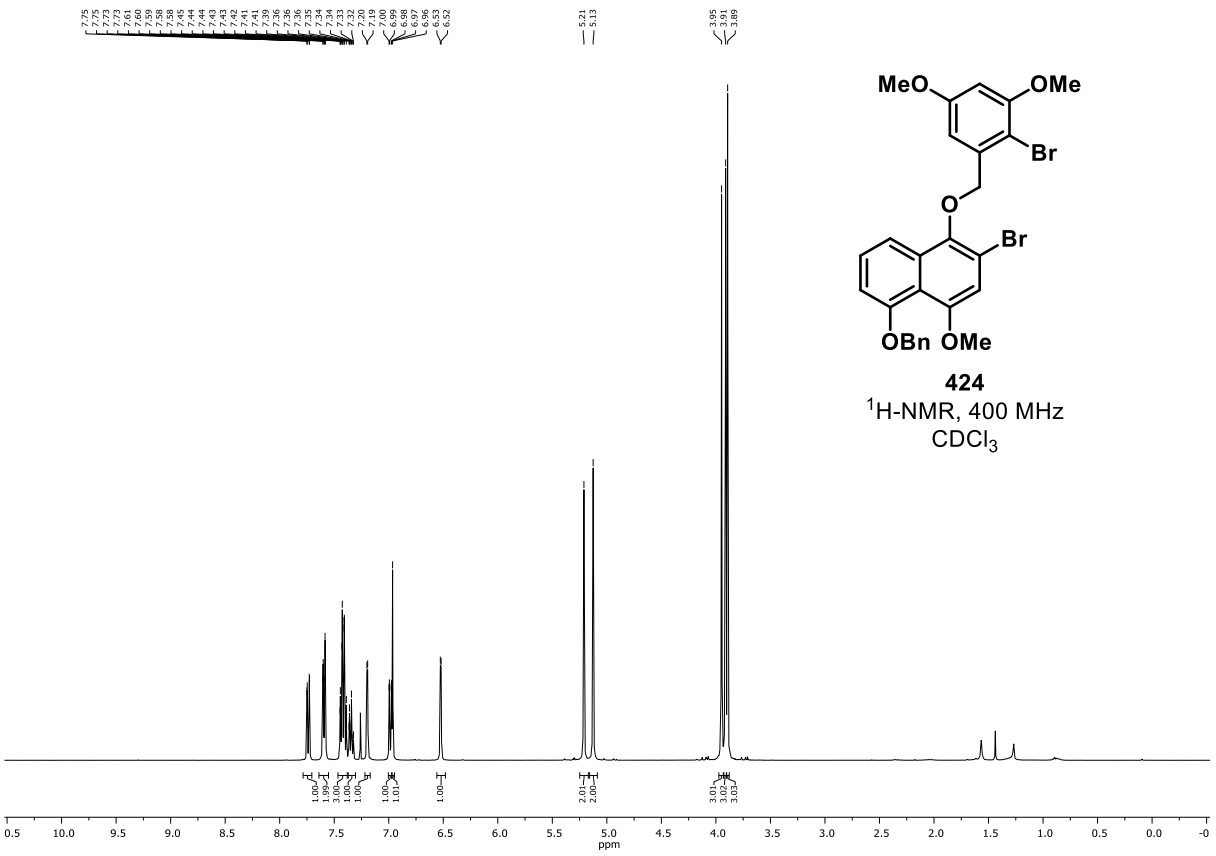
418
^{13}C-NMR, 101 MHz
$CDCl_3$



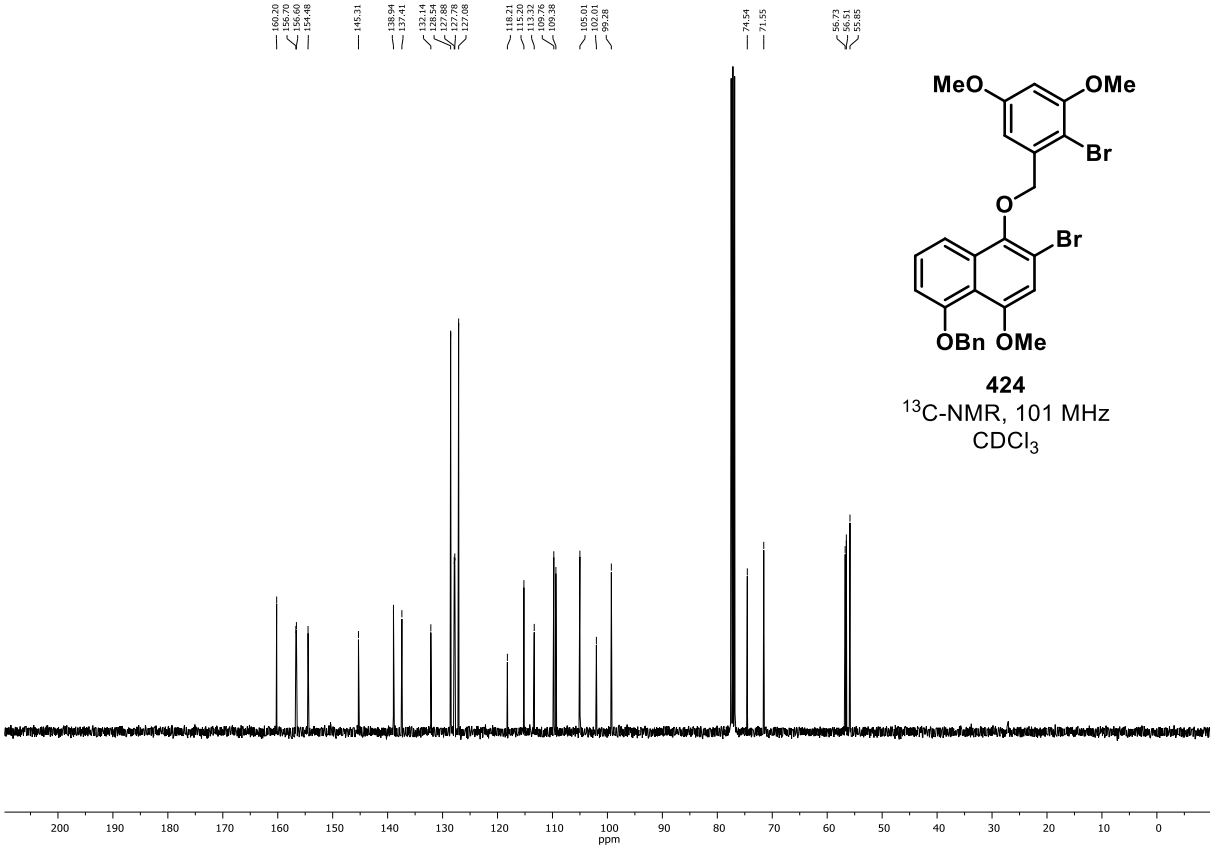
423
^{1}H-NMR, 400 MHz
$CDCl_3$



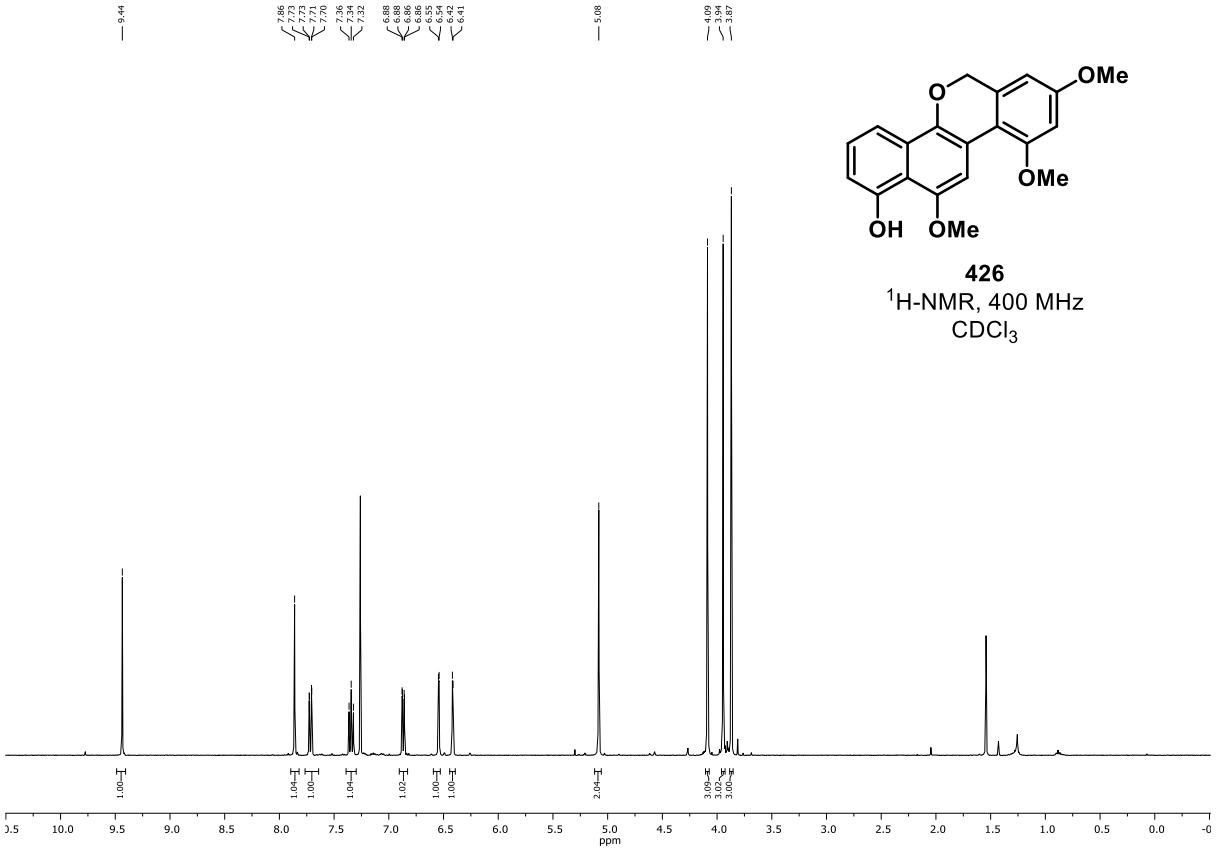
423
^{13}C-NMR, 101 MHz
$CDCl_3$



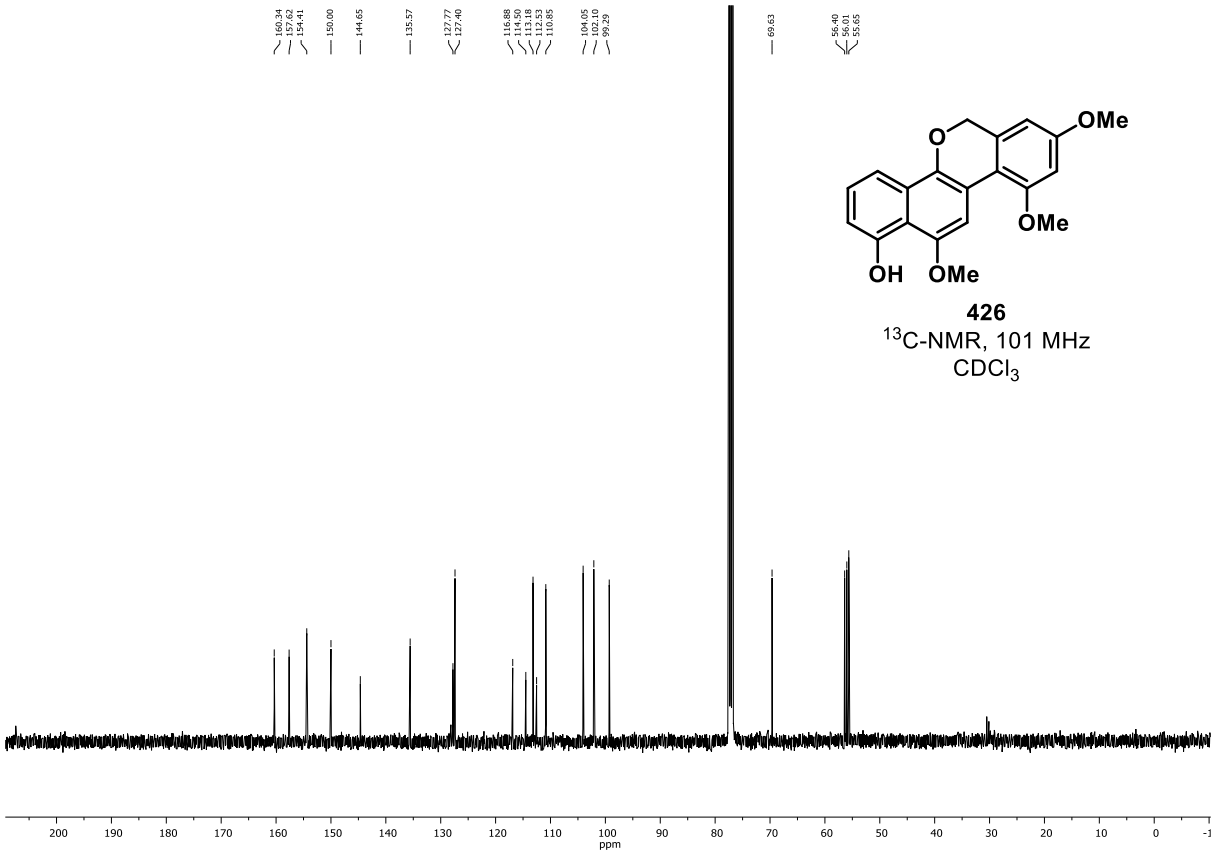
424
^{1}H-NMR, 400 MHz
$CDCl_3$



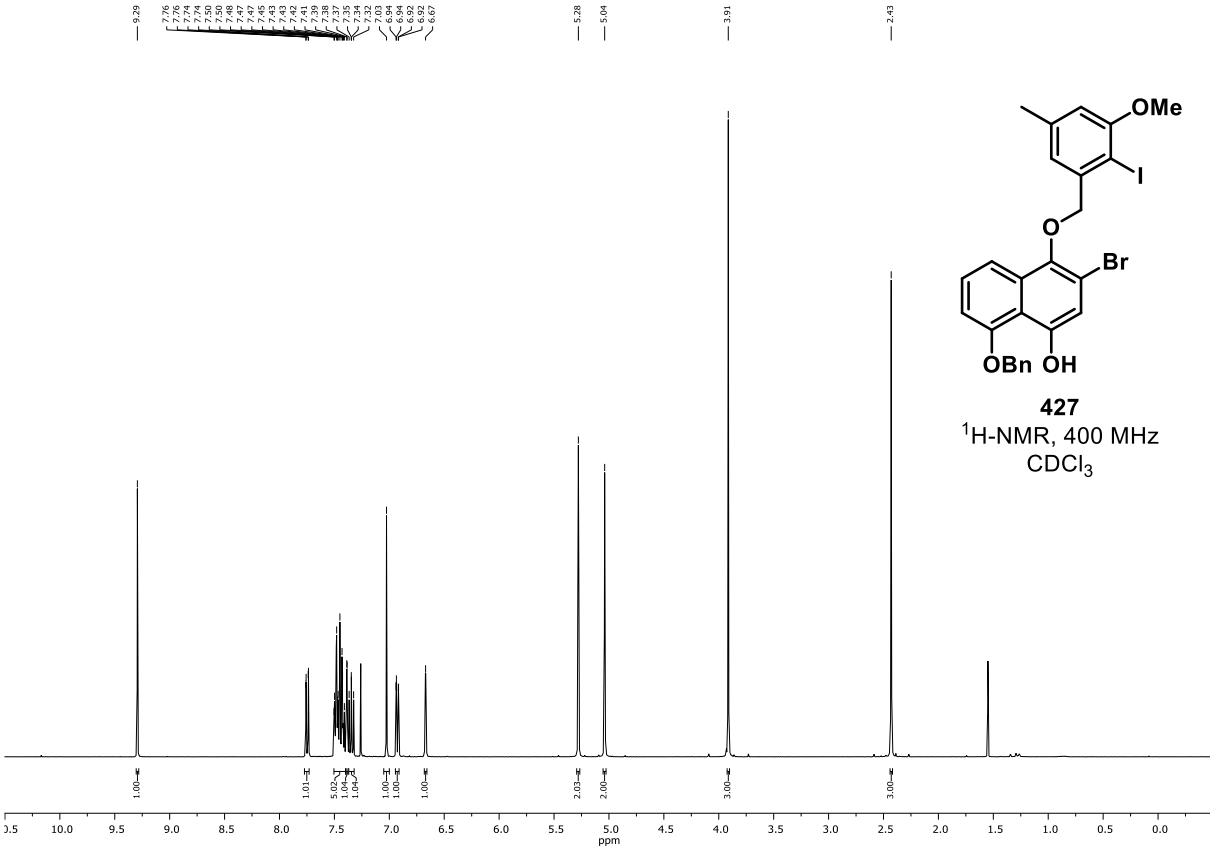
424
^{13}C-NMR, 101 MHz
$CDCl_3$

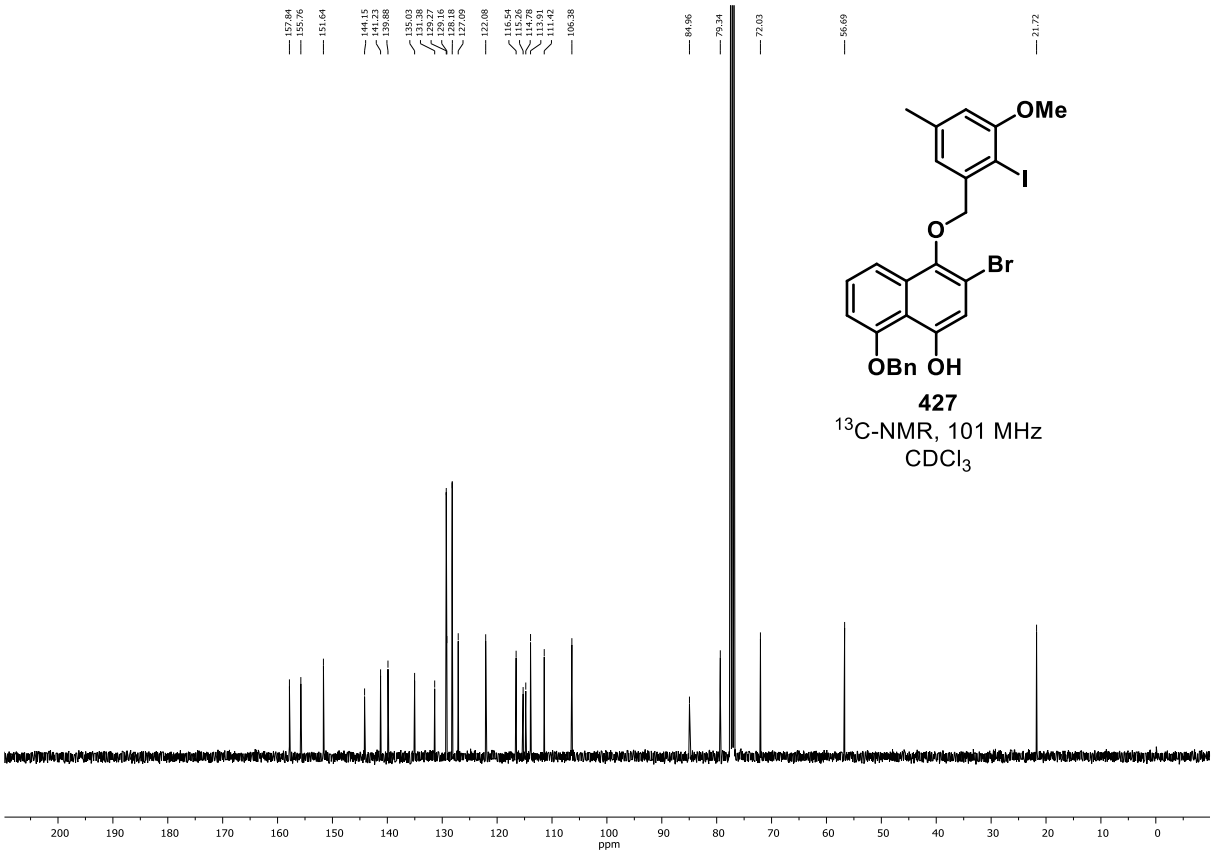


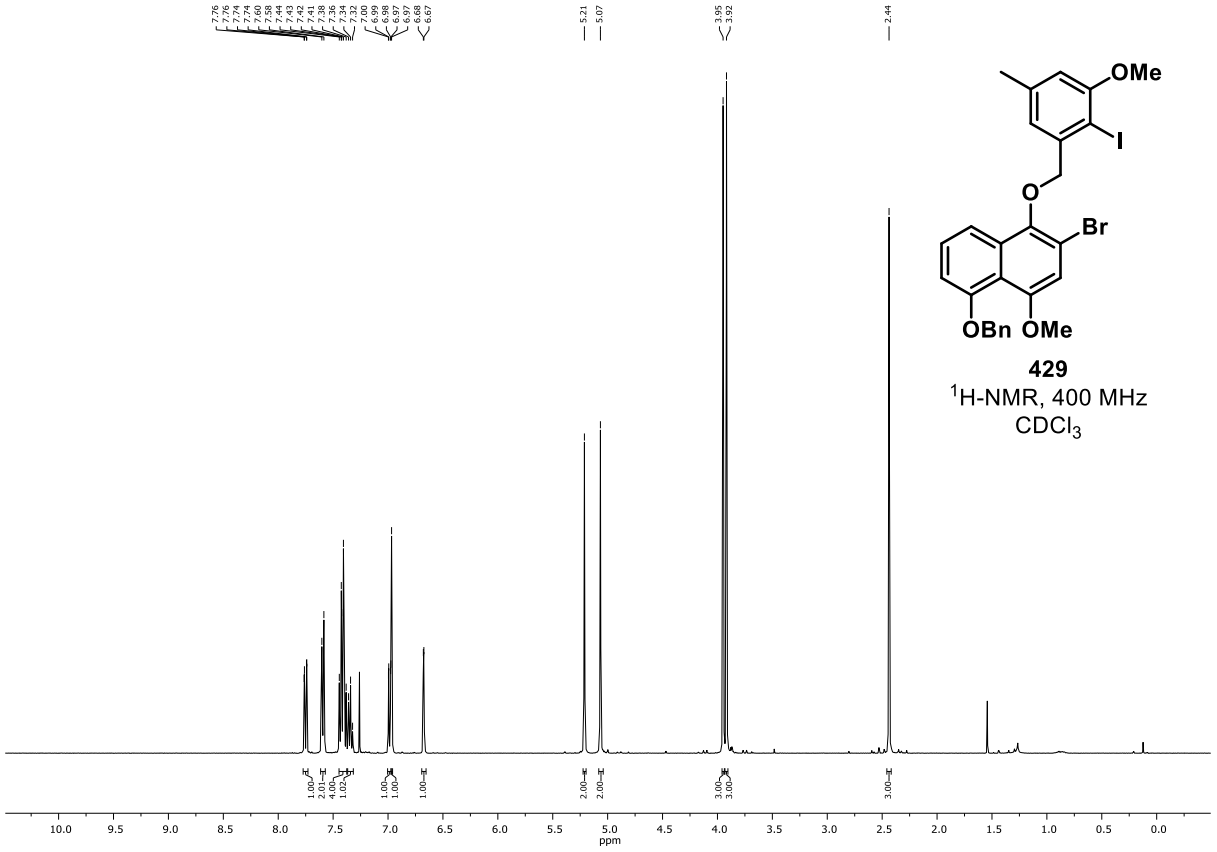
426
^{1}H-NMR, 400 MHz
$CDCl_3$

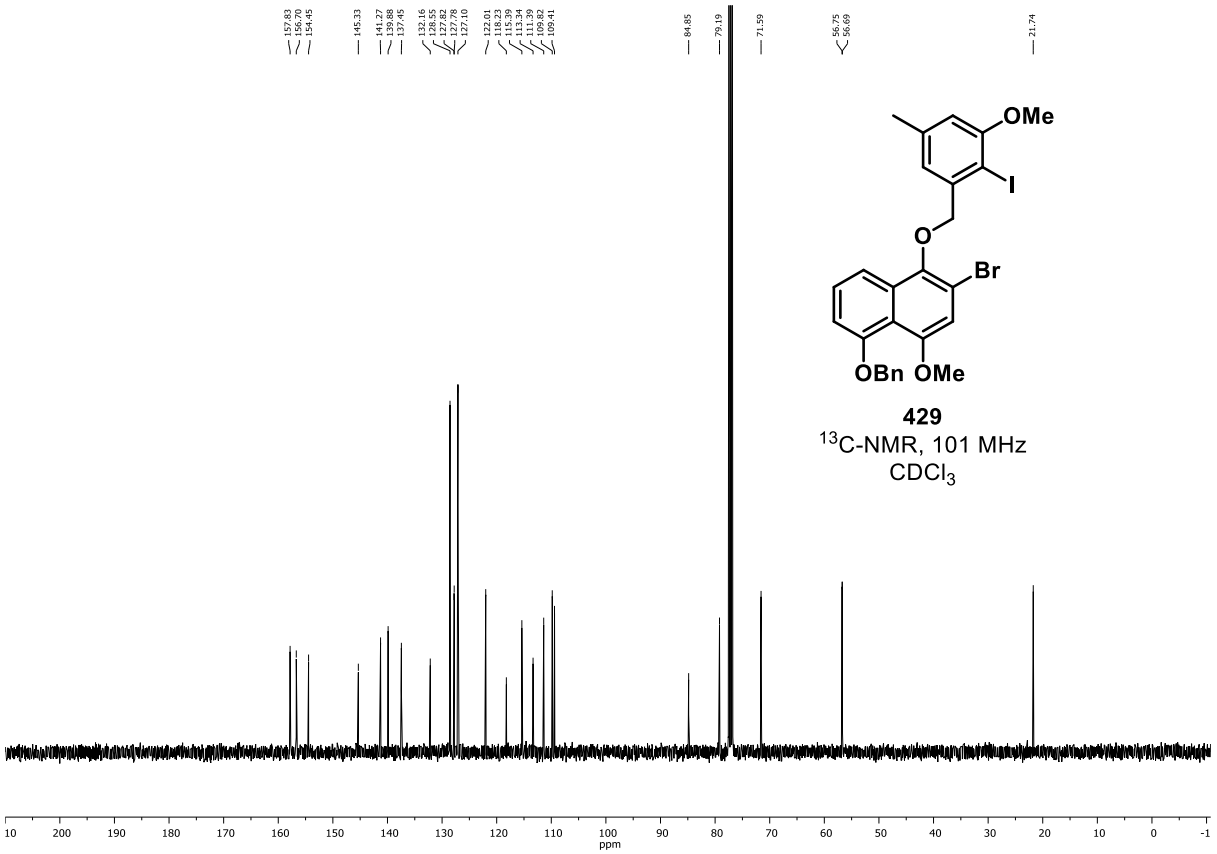


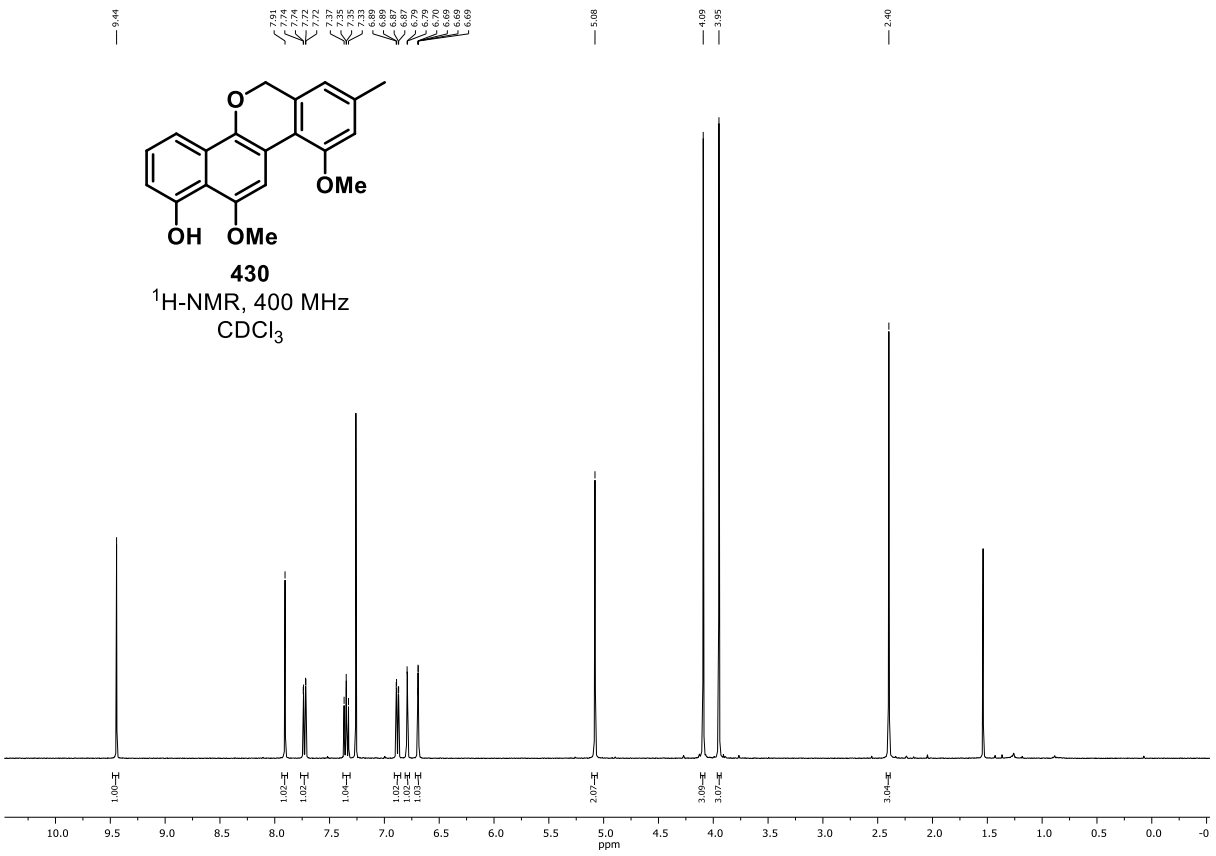
426
^{13}C-NMR, 101 MHz
$CDCl_3$


OMe
I
O
Br
OBn OH
427
1H-NMR, 400 MHz
CDCl3
ppm

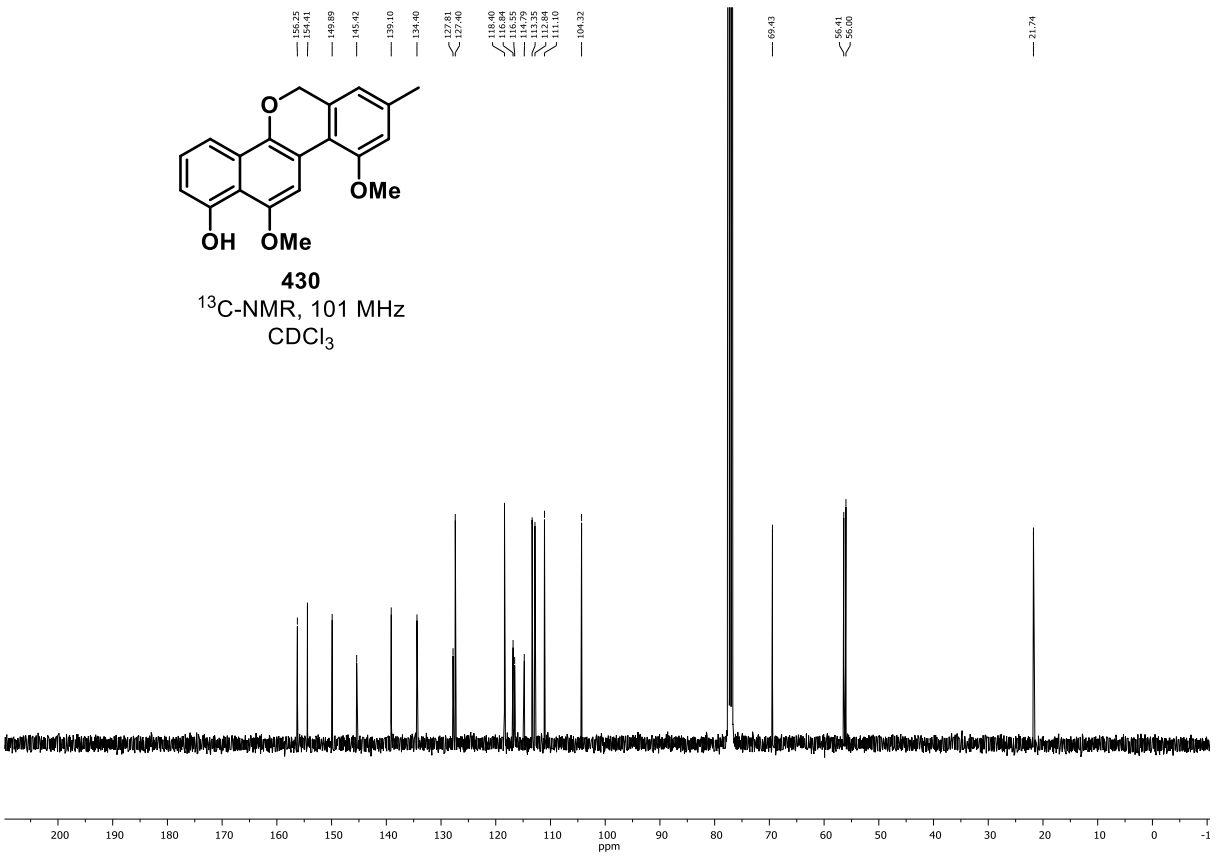

OMe
I
O
Br
OBn OH
427
13C-NMR, 101 MHz
CDCl3
ppm


OMe
I
O
Br
OBn OMe
429
1H-NMR, 400 MHz
CDCl3

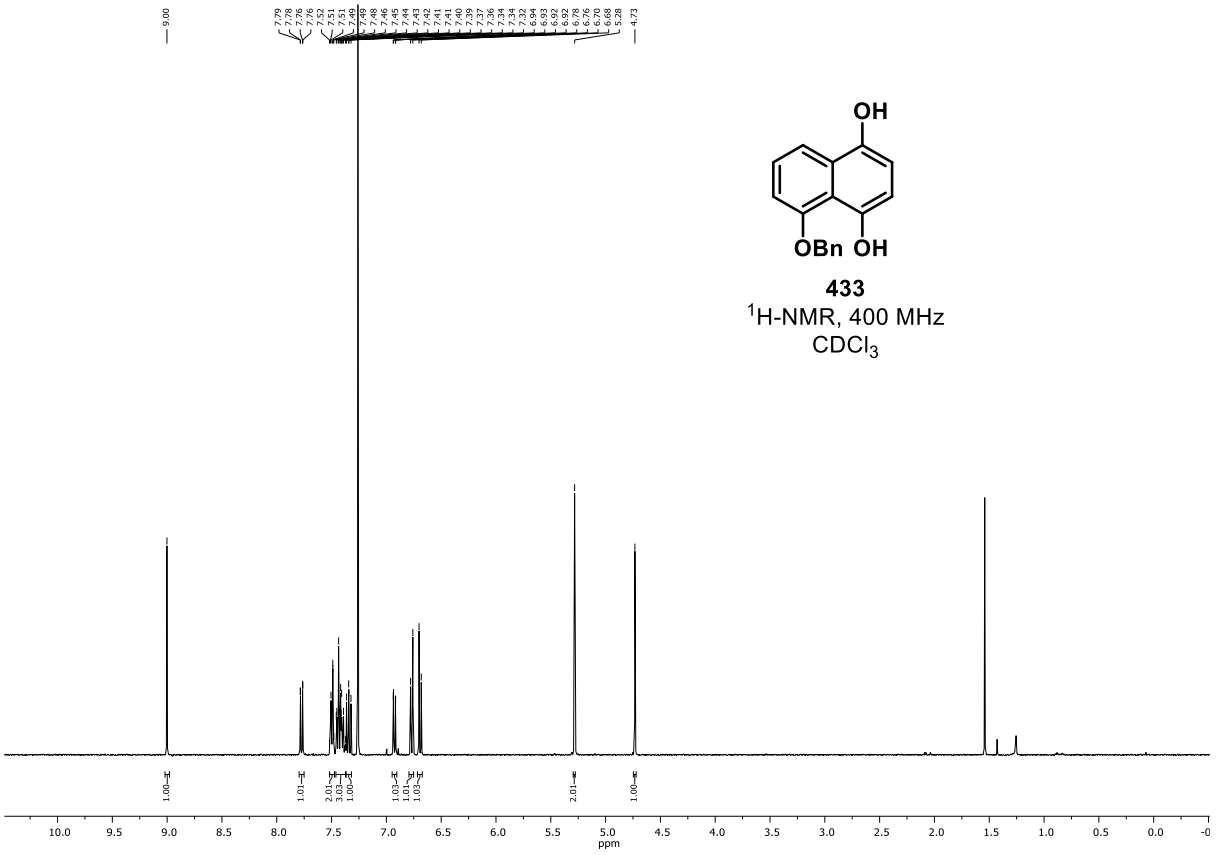

OMe
I
O
Br
OBn OMe
429
13C-NMR, 101 MHz
CDCl3



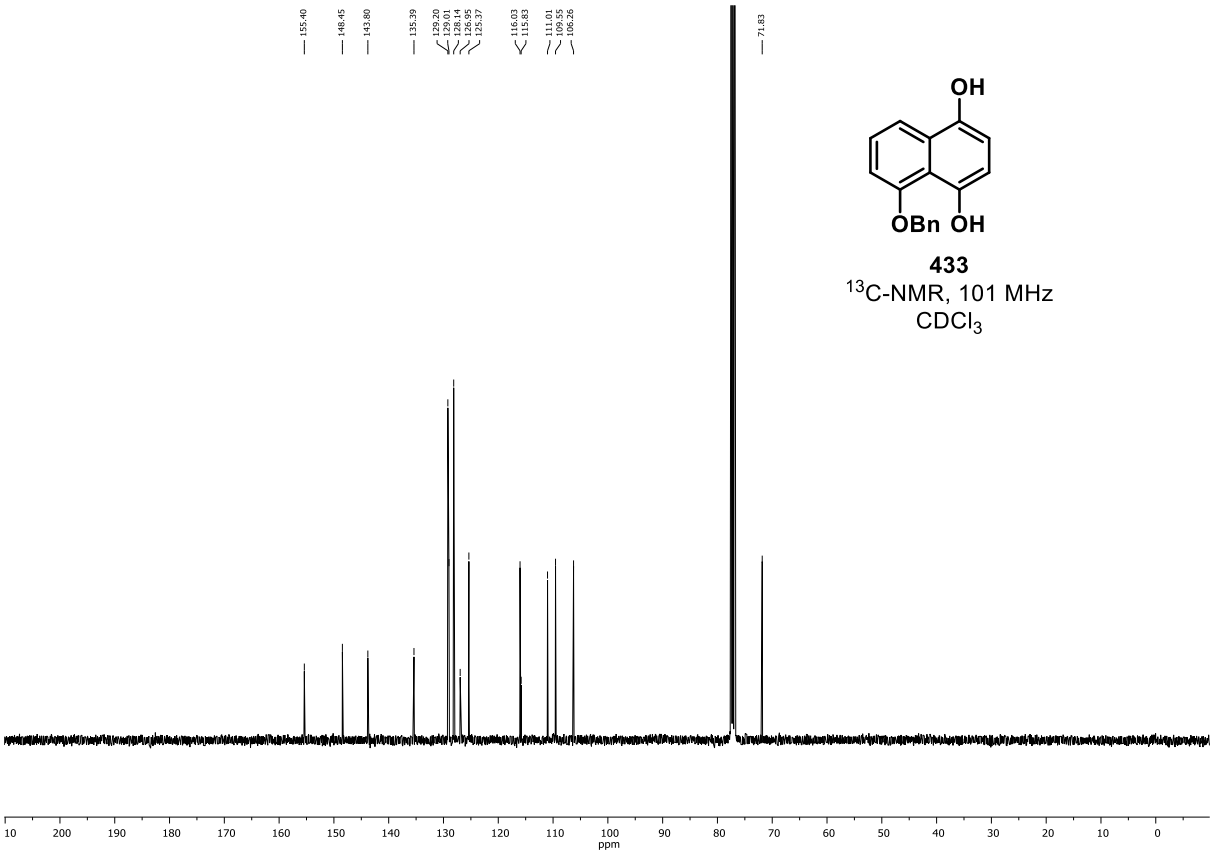
430
^{1}H-NMR, 400 MHz
$CDCl_3$



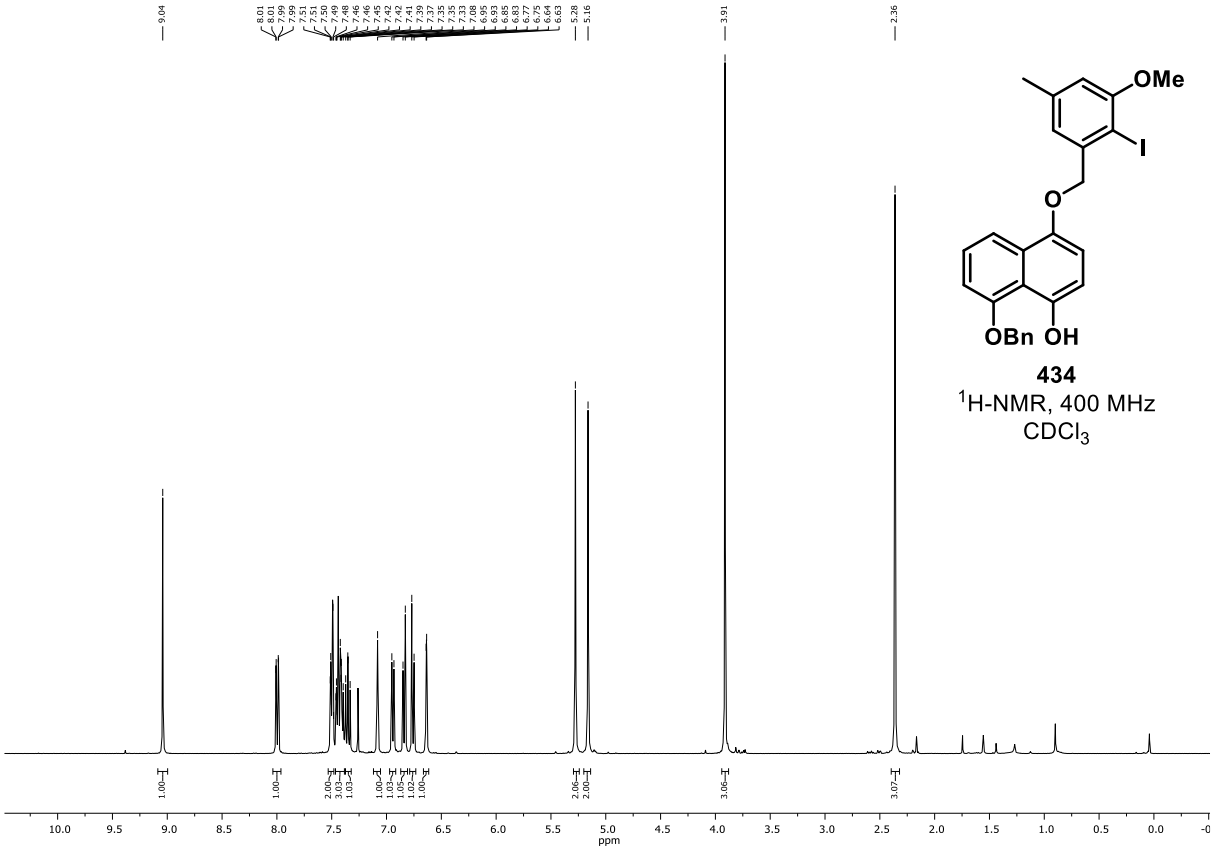
430
^{13}C-NMR, 101 MHz
$CDCl_3$

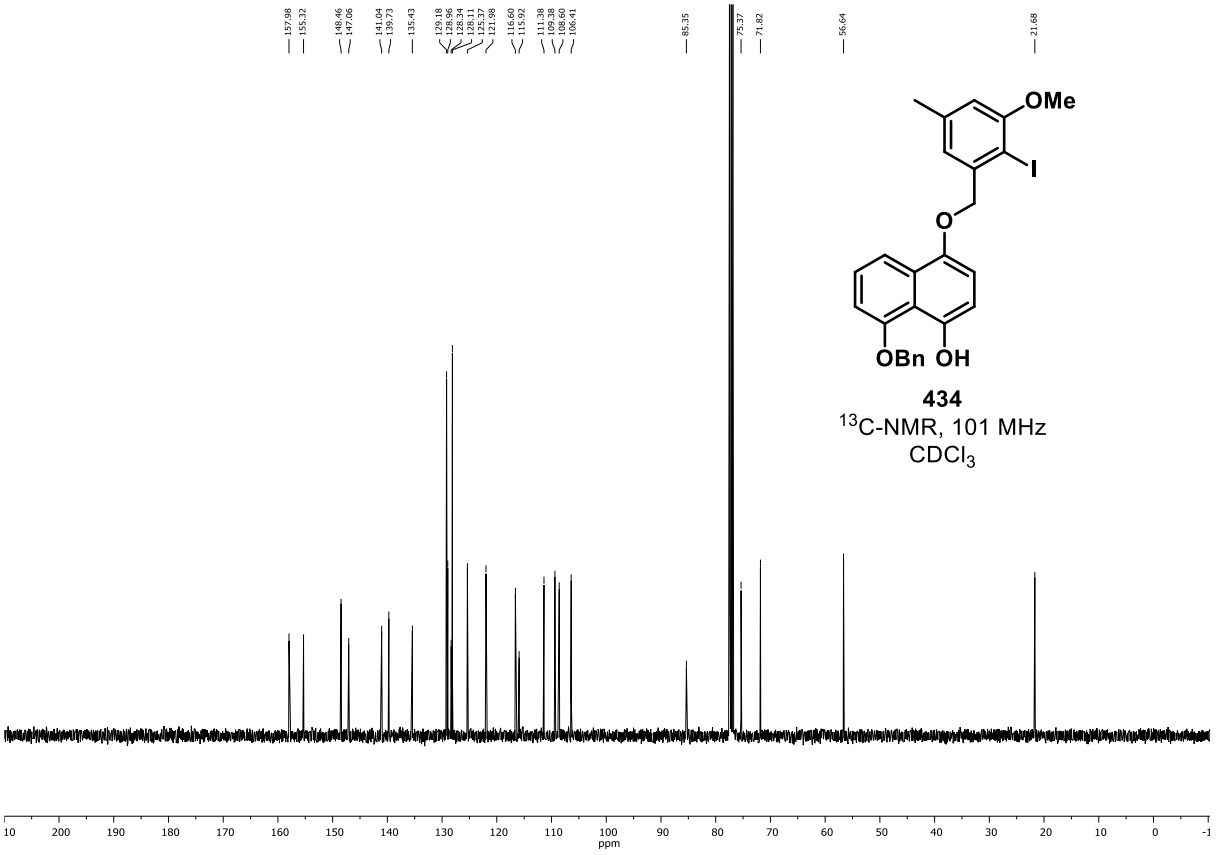


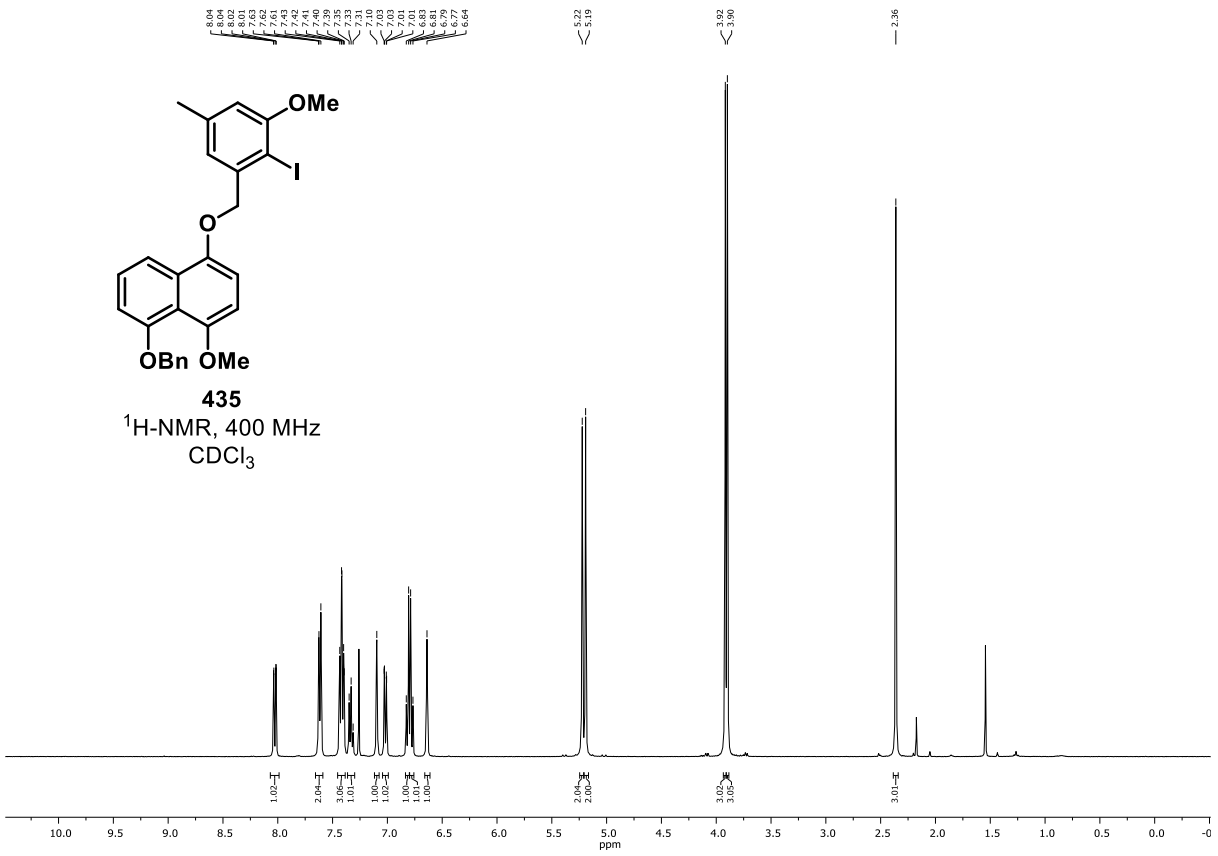
433
^{1}H-NMR, 400 MHz
$CDCl_3$

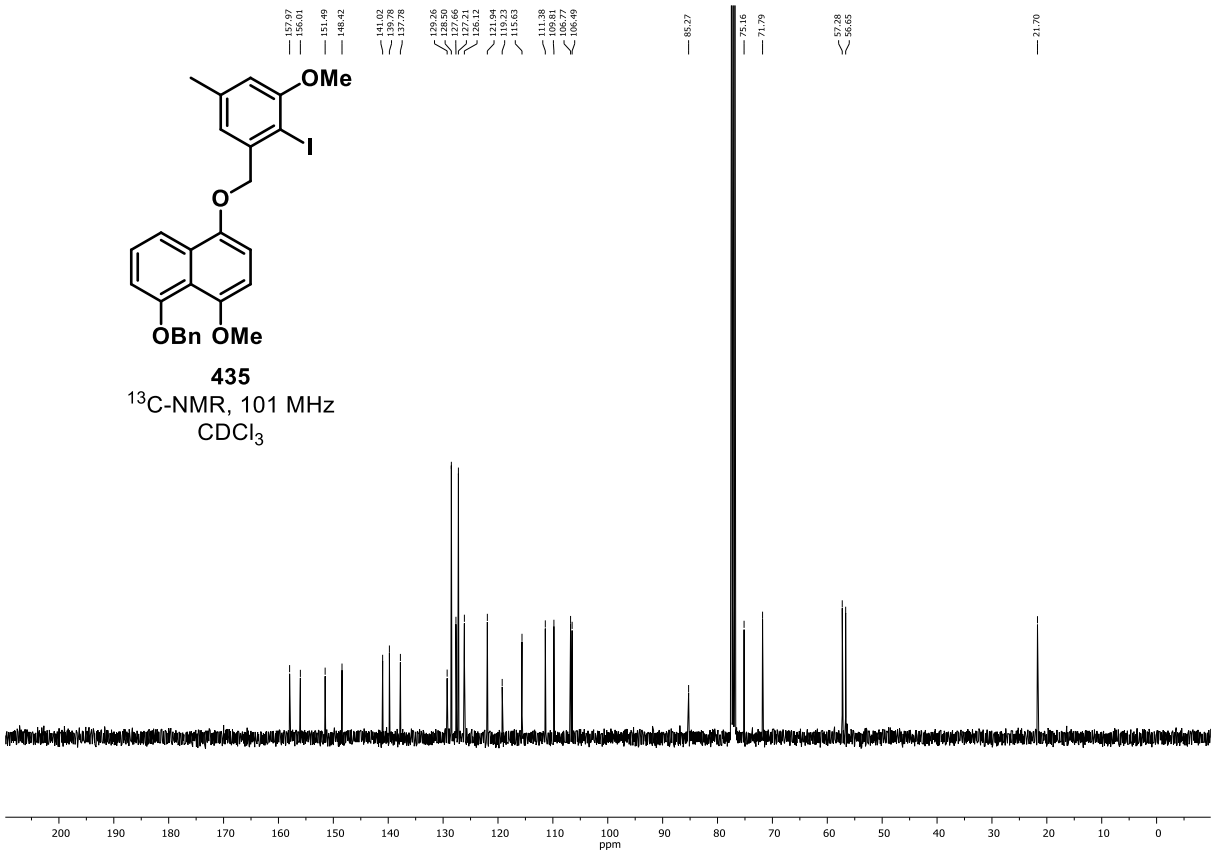


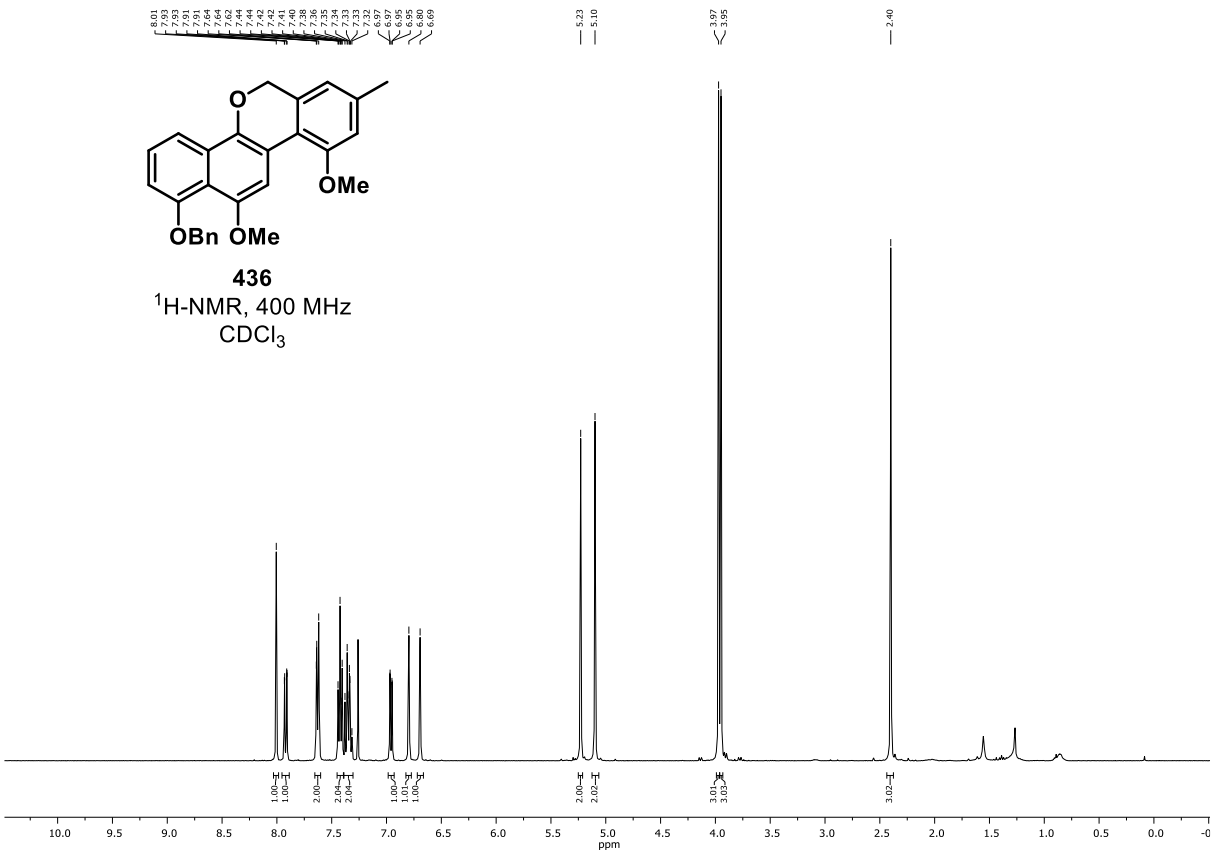
433
^{13}C-NMR, 101 MHz
$CDCl_3$

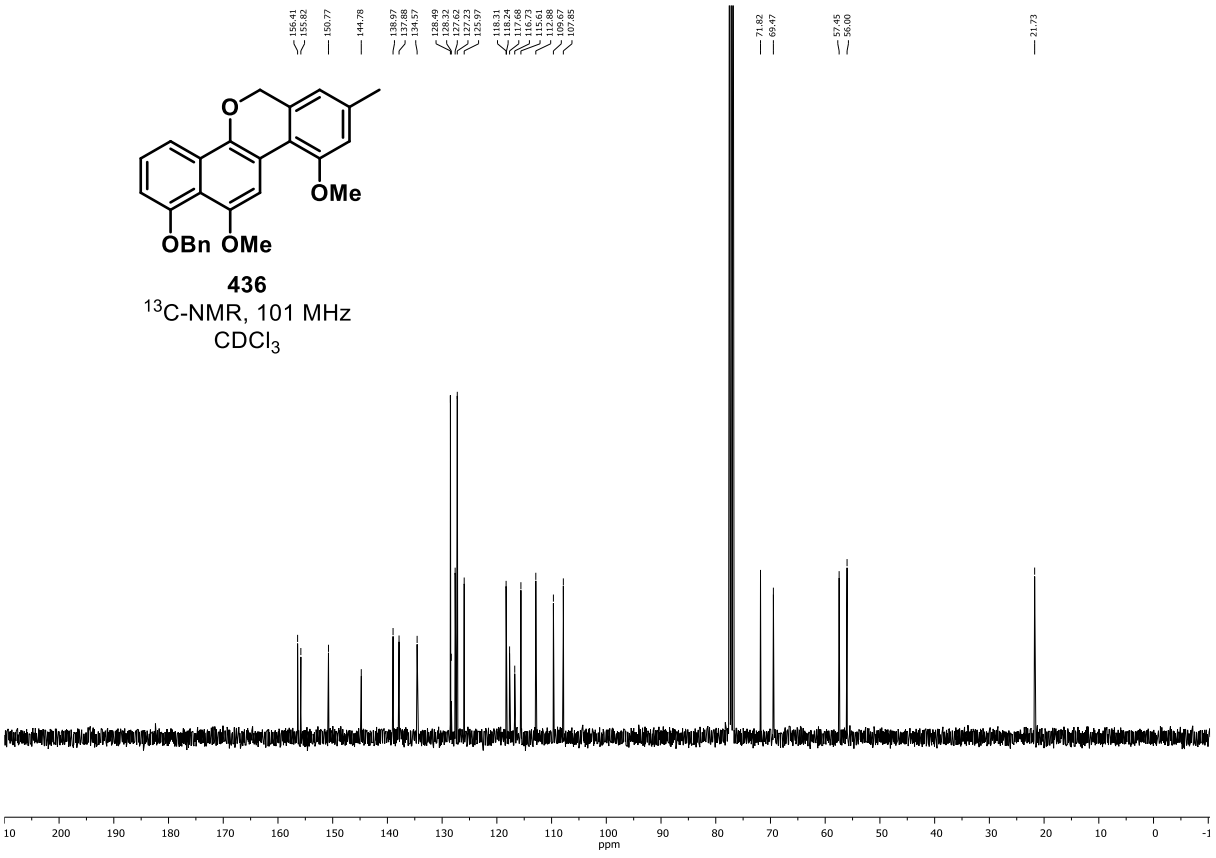

OMe
I
O
OBn OH
434
1H-NMR, 400 MHz
CDCl3
ppm

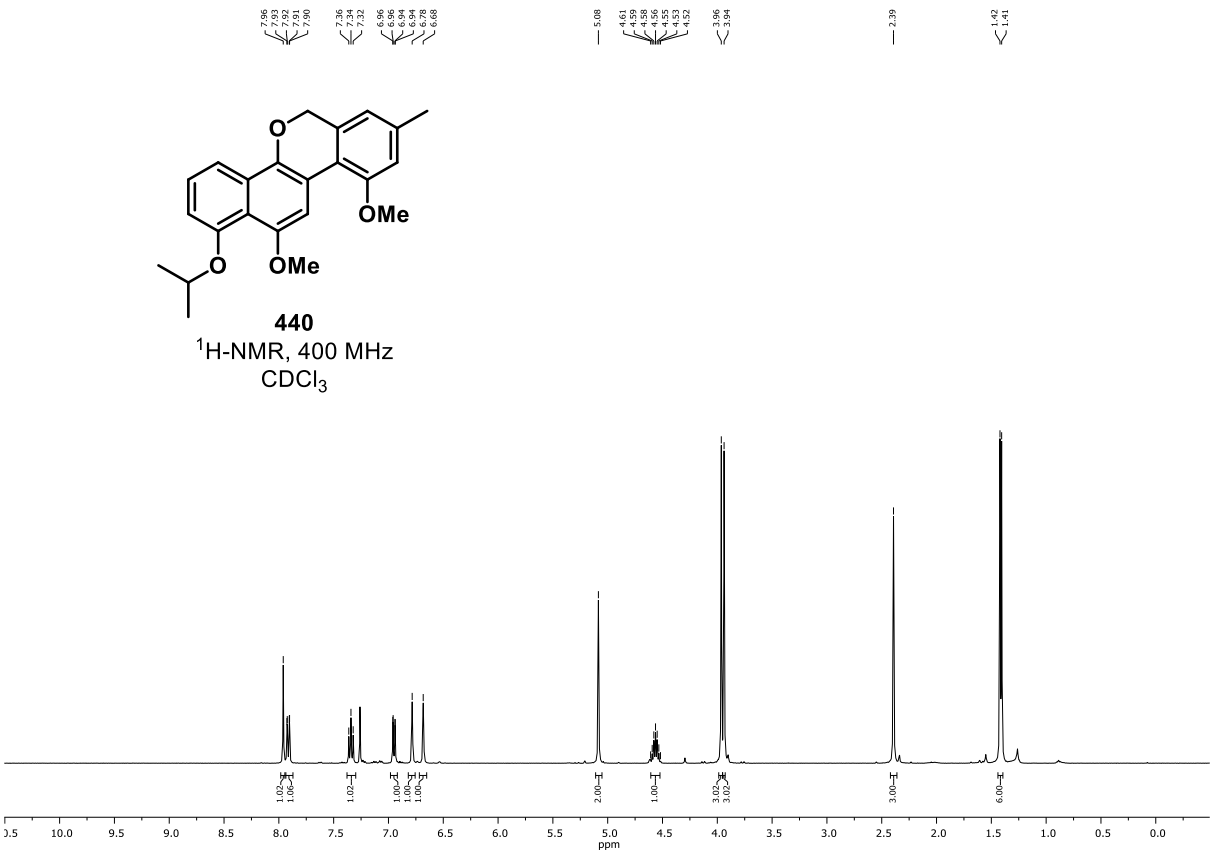

OMe
I
O
OBn OH
434
13C-NMR, 101 MHz
CDCl3
ppm


OMe
I
O
OBn OMe
435
1H-NMR, 400 MHz
CDCl3
ppm

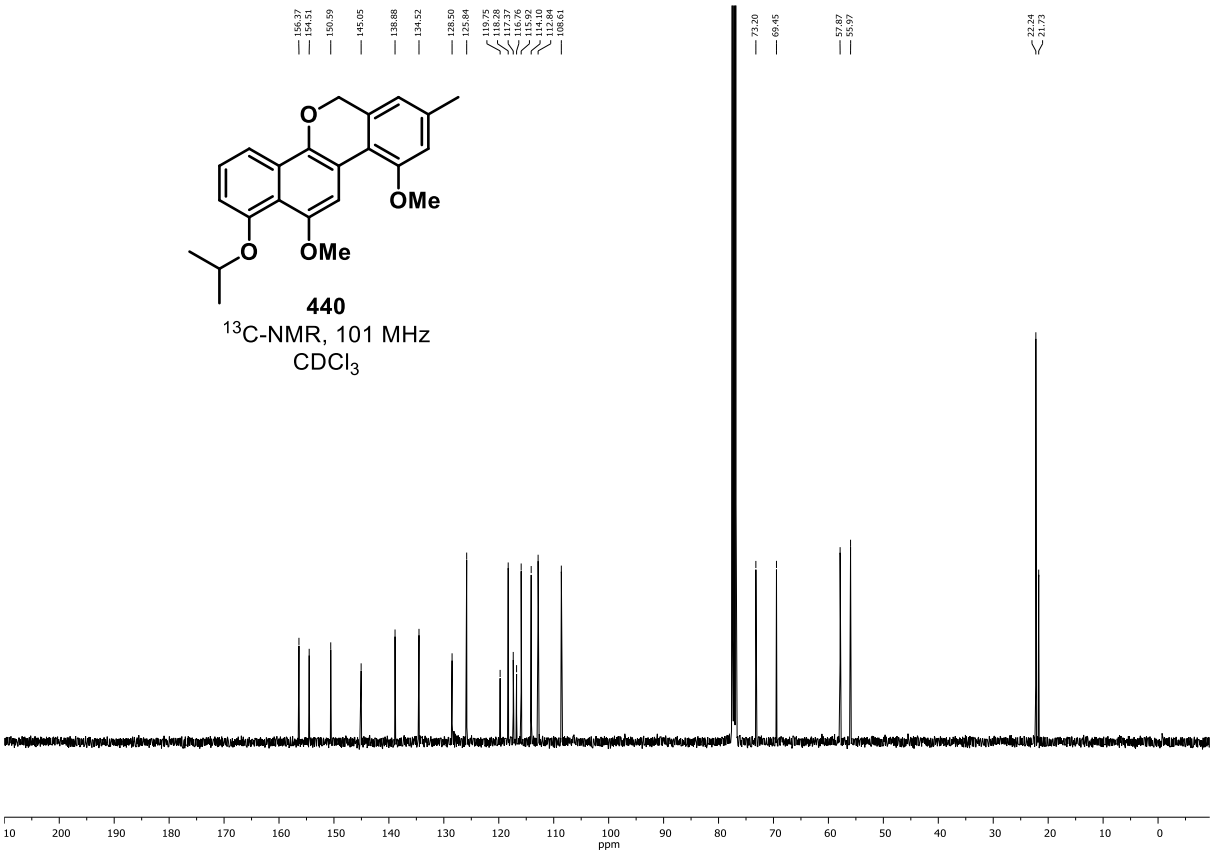

OMe
I
O
OBn OMe
435
13C-NMR, 101 MHz
CDCl3
ppm


OMe
OBn OMe
436
^{1}H-NMR, 400 MHz
$CDCl_3$
ppm

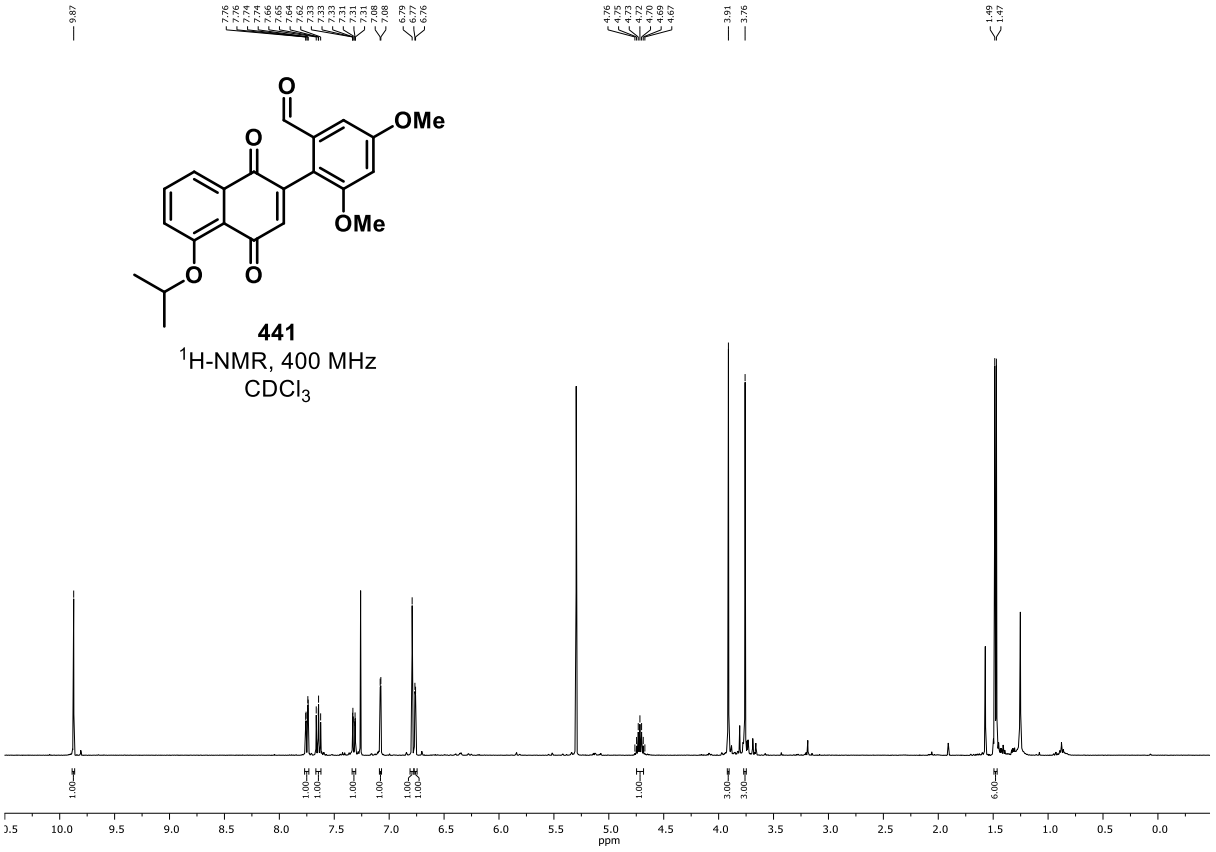

OMe
OBn OMe
436
^{13}C-NMR, 101 MHz
$CDCl_3$
ppm

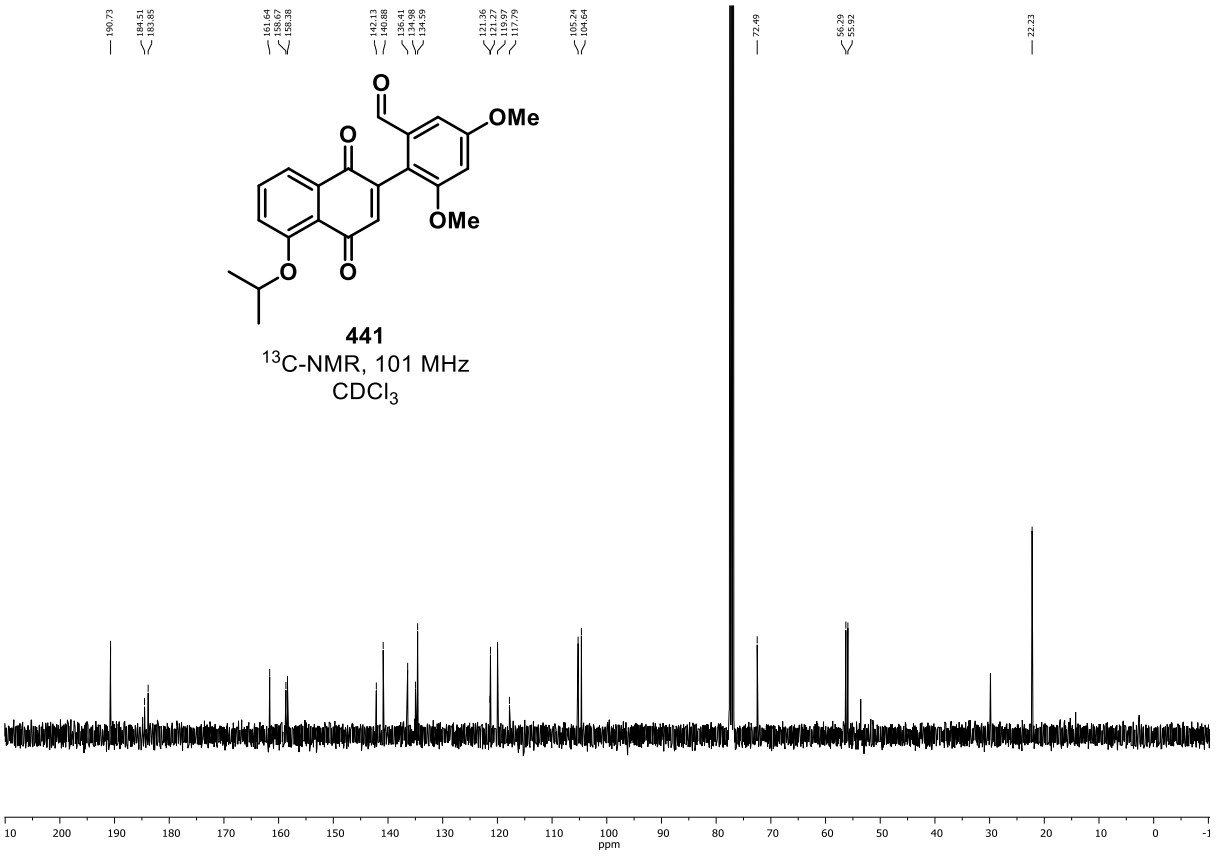


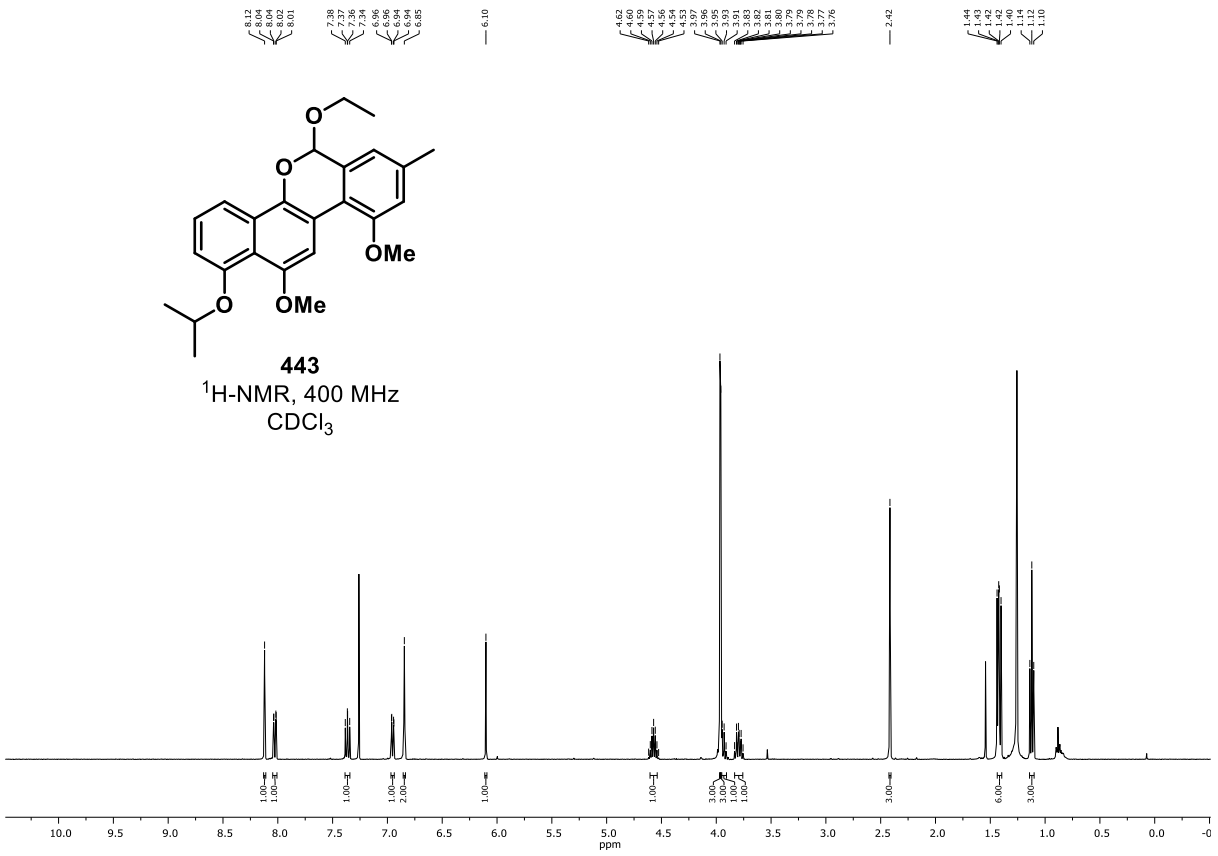
440
^{1}H-NMR, 400 MHz
$CDCl_3$

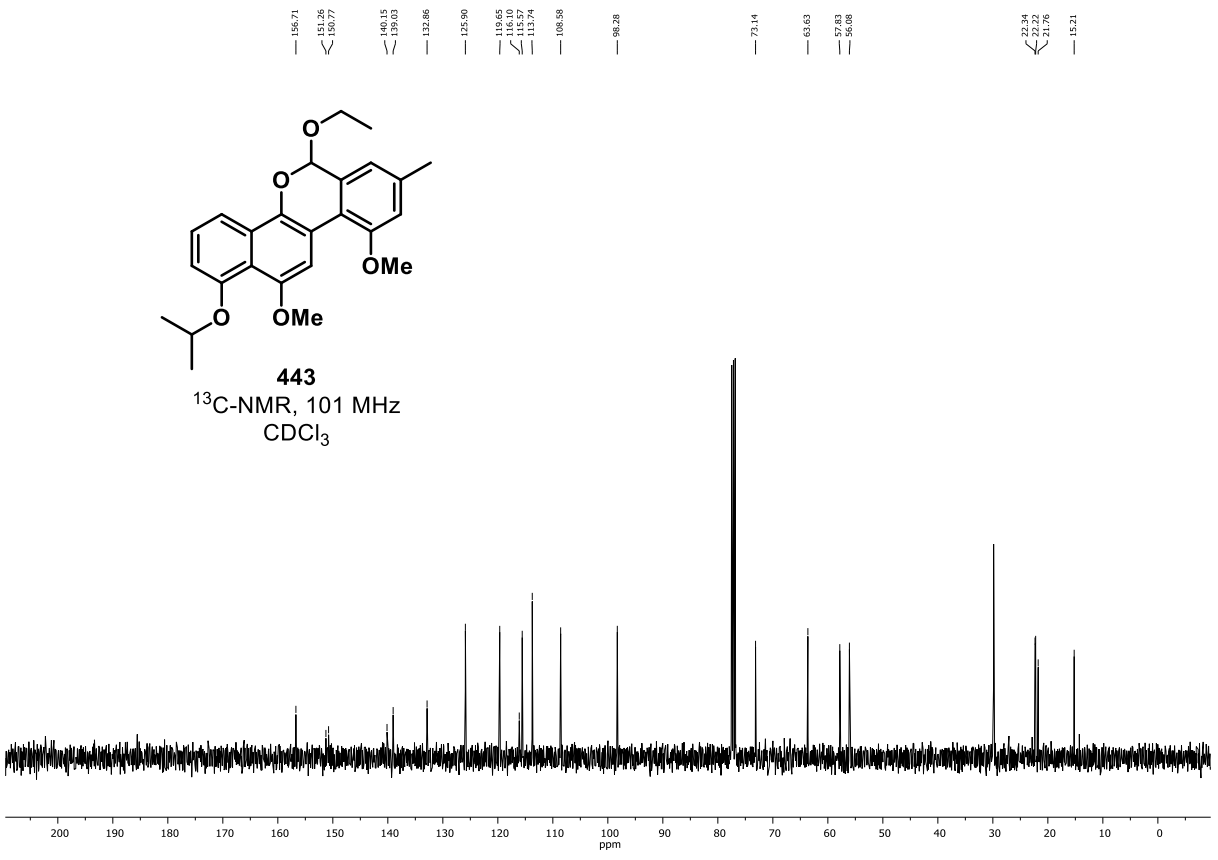


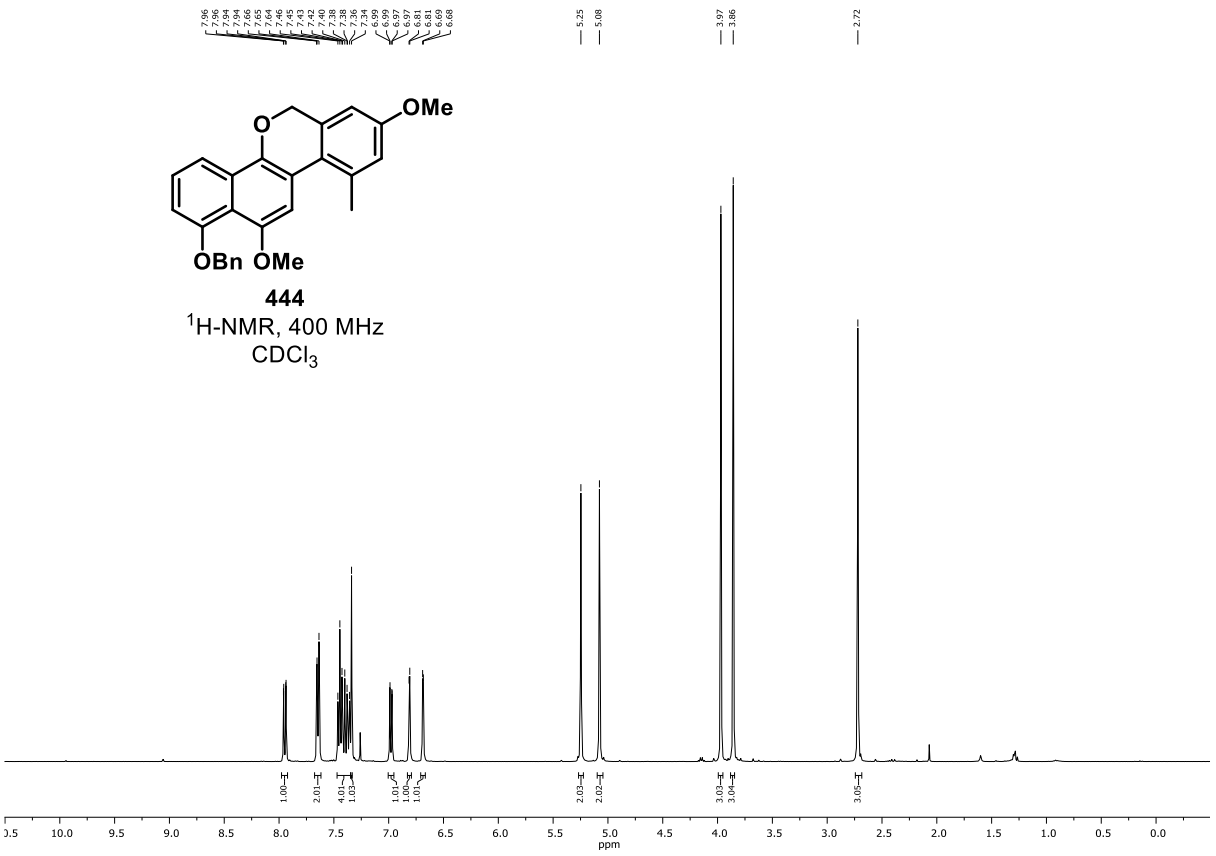
440
^{13}C-NMR, 101 MHz
$CDCl_3$


OMe
OMe
441
1H-NMR, 400 MHz
CDCl3
ppm


OMe
OMe
441
13C-NMR, 101 MHz
CDCl3
ppm


8.12
8.04
8.04
8.02
8.01
7.38
7.37
7.36
7.34
6.96
6.96
6.94
6.94
6.85
6.10
4.62
4.60
4.59
4.57
4.56
4.54
4.53
3.97
3.96
3.95
3.93
3.91
3.83
3.82
3.81
3.80
3.79
3.79
3.78
3.77
3.76
2.42
1.44
1.43
1.42
1.42
1.40
1.14
1.12
1.10
OMe
OMe
O
O
O
443
^{1}H-NMR, 400 MHz
$CDCl_3$
ppm

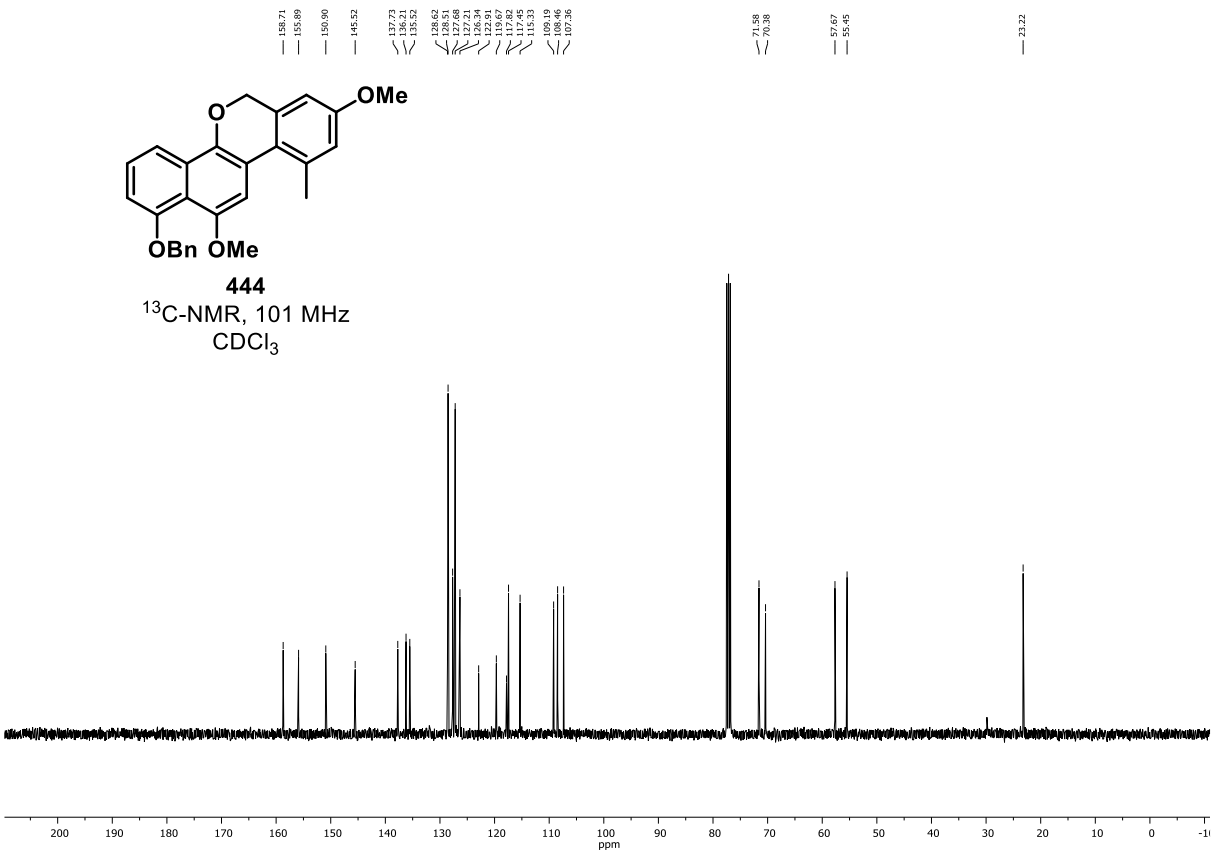

156.71
151.26
150.77
140.15
139.03
132.86
125.90
119.65
116.10
115.57
113.74
108.58
98.28
73.14
63.63
57.83
56.08
22.24
22.22
21.76
15.21
OMe
OMe
O
O
O
443
^{13}C-NMR, 101 MHz
$CDCl_3$
ppm



444

^{1}H-NMR, 400 MHz

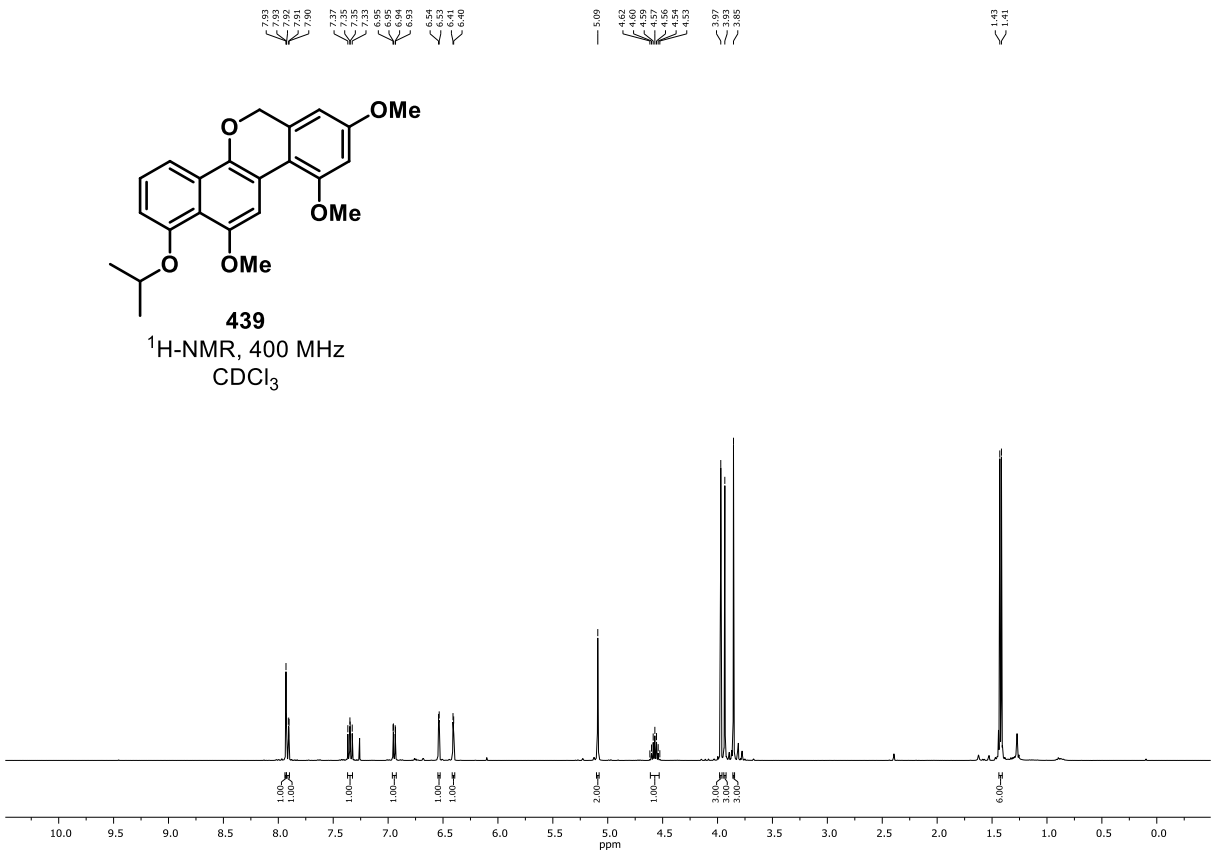
$CDCl_3$



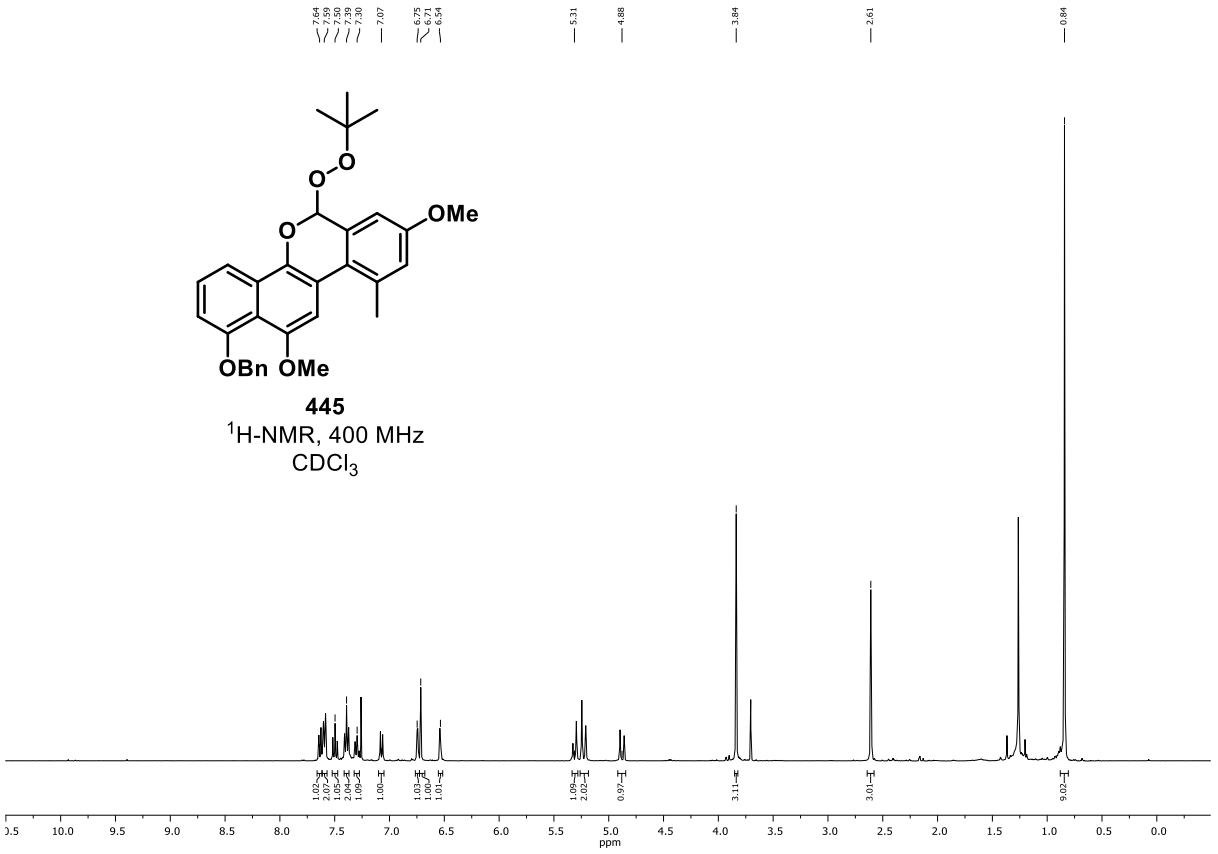
444

^{13}C-NMR, 101 MHz

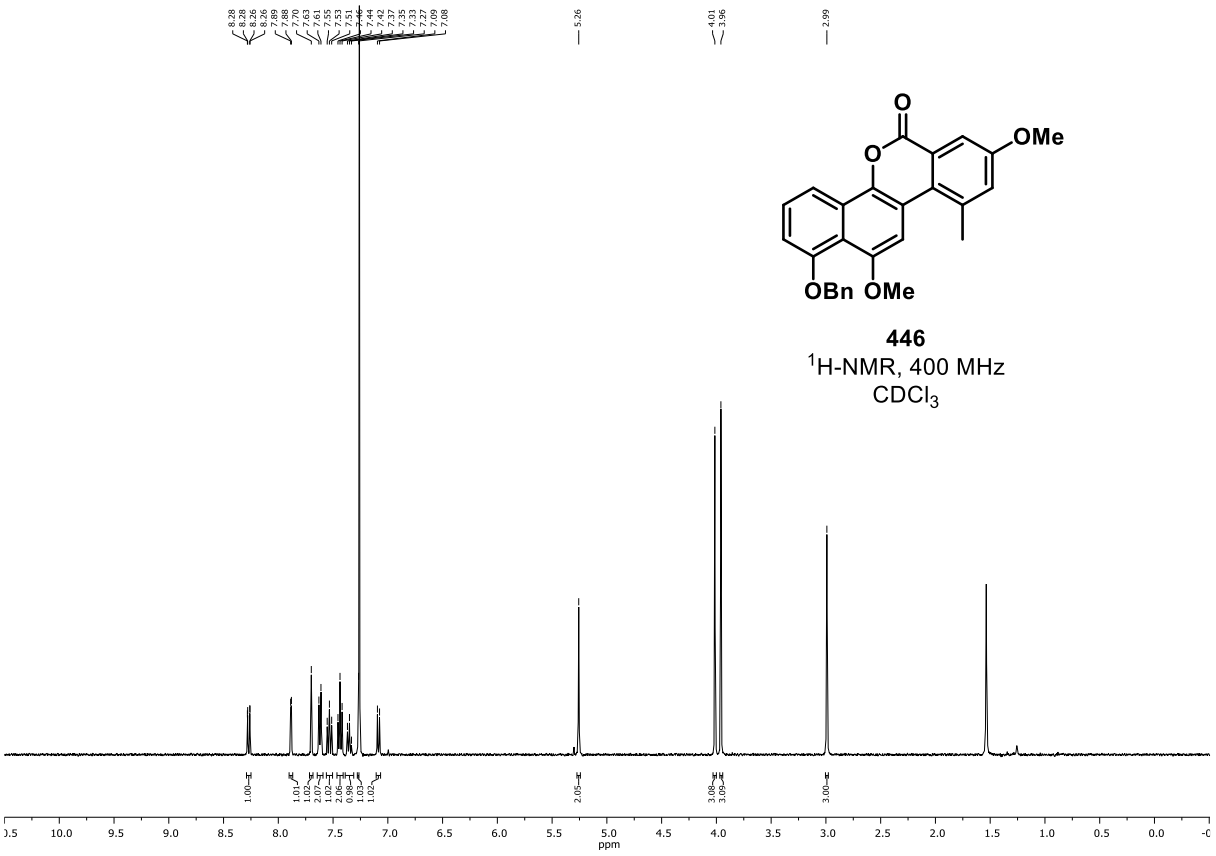
$CDCl_3$



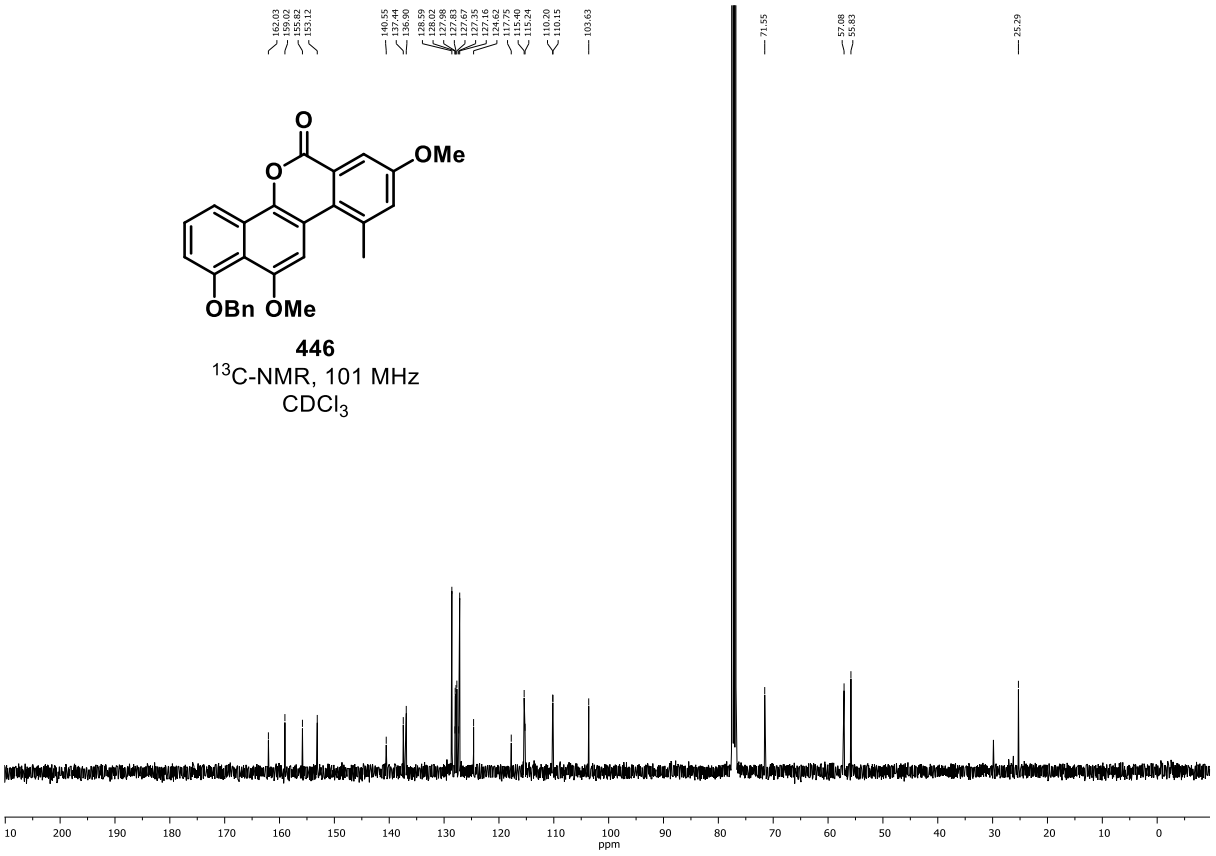
439
^{1}H-NMR, 400 MHz
$CDCl_3$



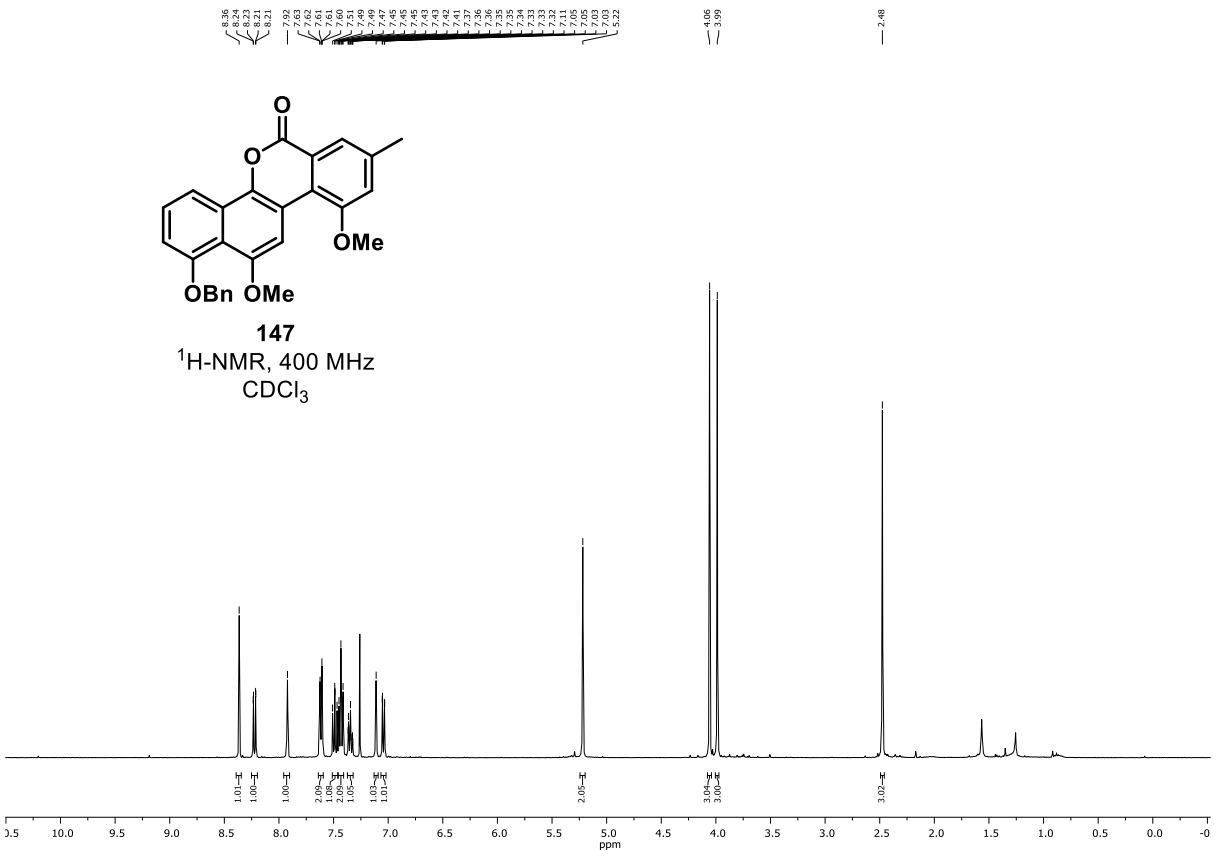
445
^{1}H-NMR, 400 MHz
$CDCl_3$



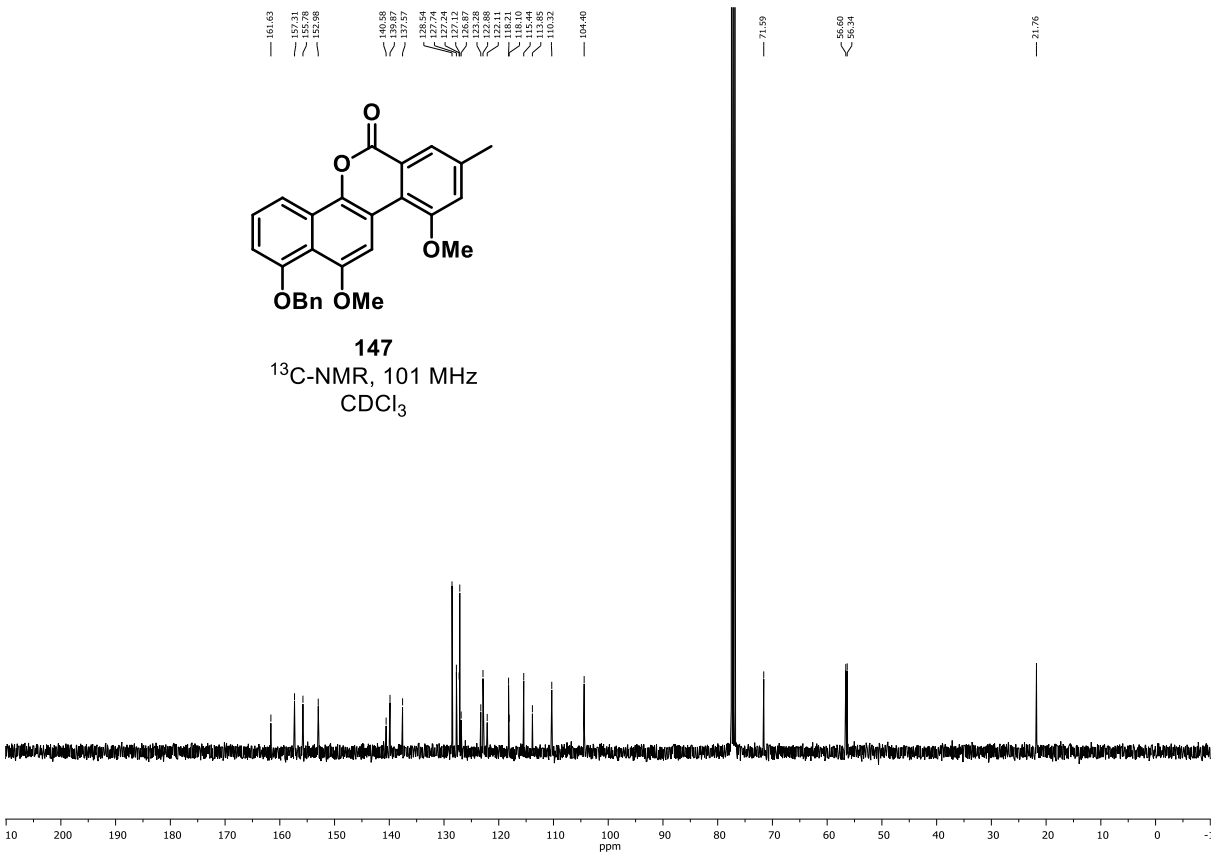
446
^{1}H-NMR, 400 MHz
$CDCl_3$



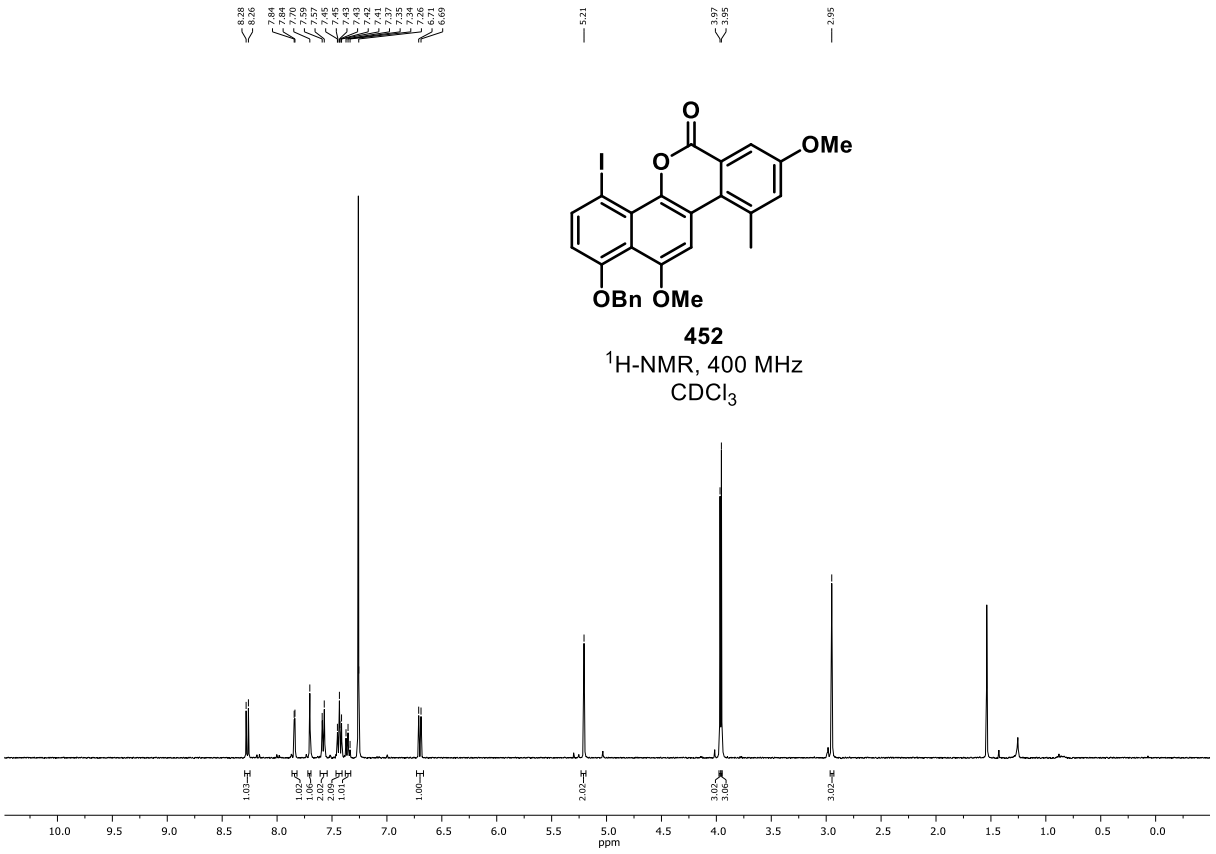
446
^{13}C-NMR, 101 MHz
$CDCl_3$



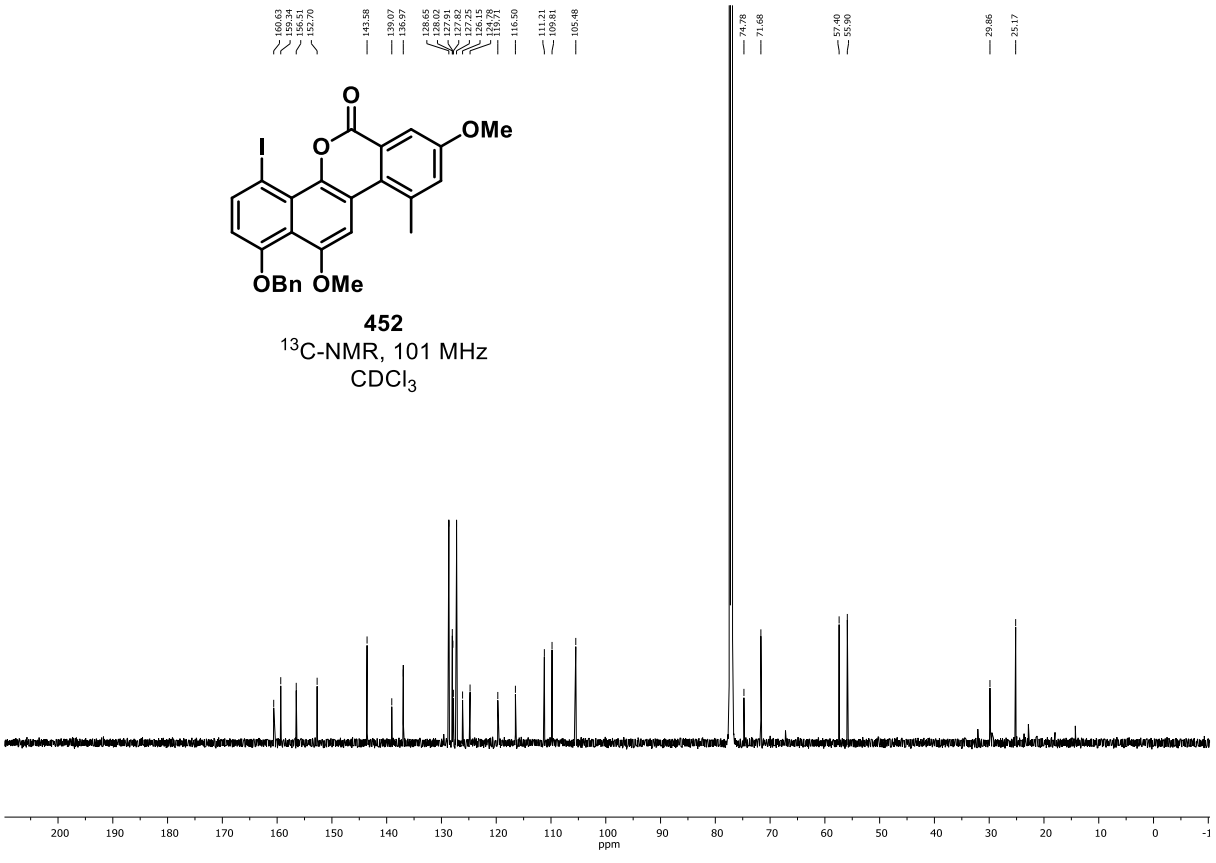
147
^{1}H-NMR, 400 MHz
$CDCl_3$



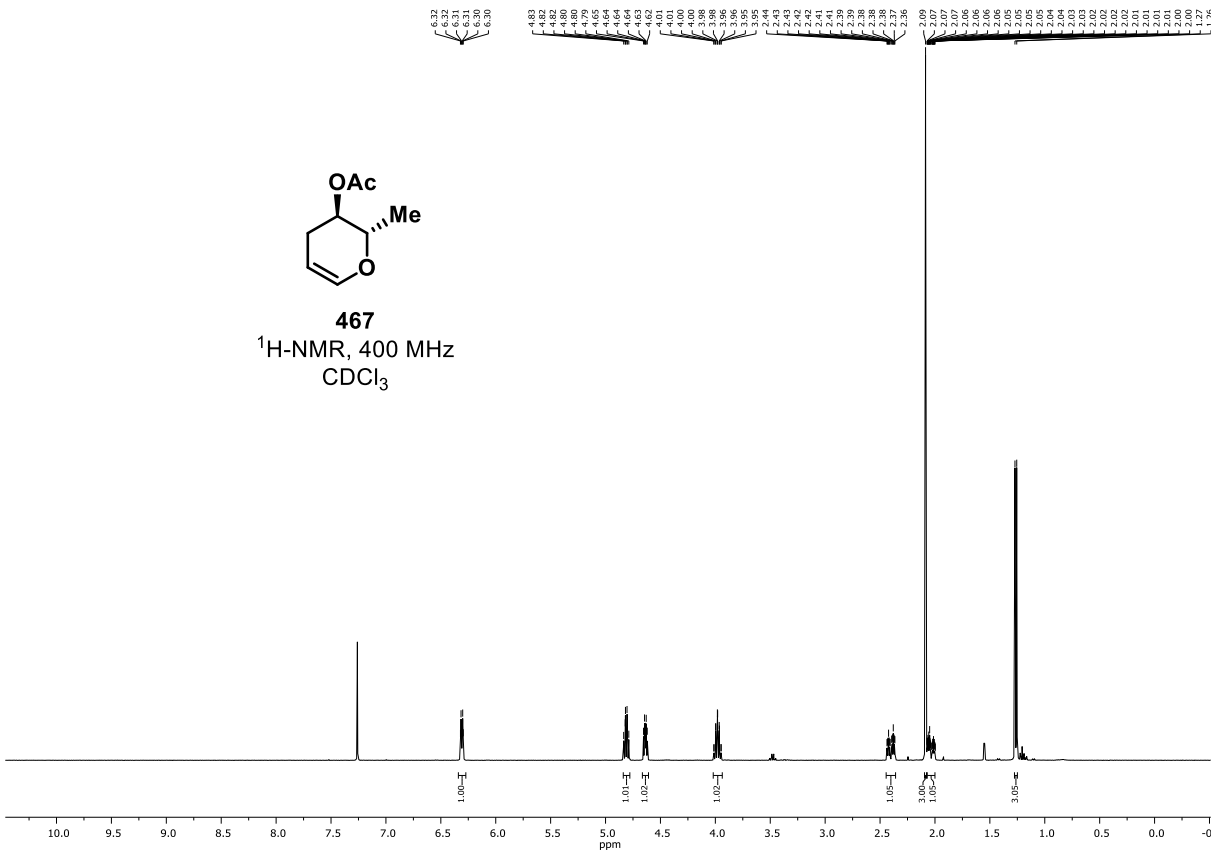
147
^{13}C-NMR, 101 MHz
$CDCl_3$



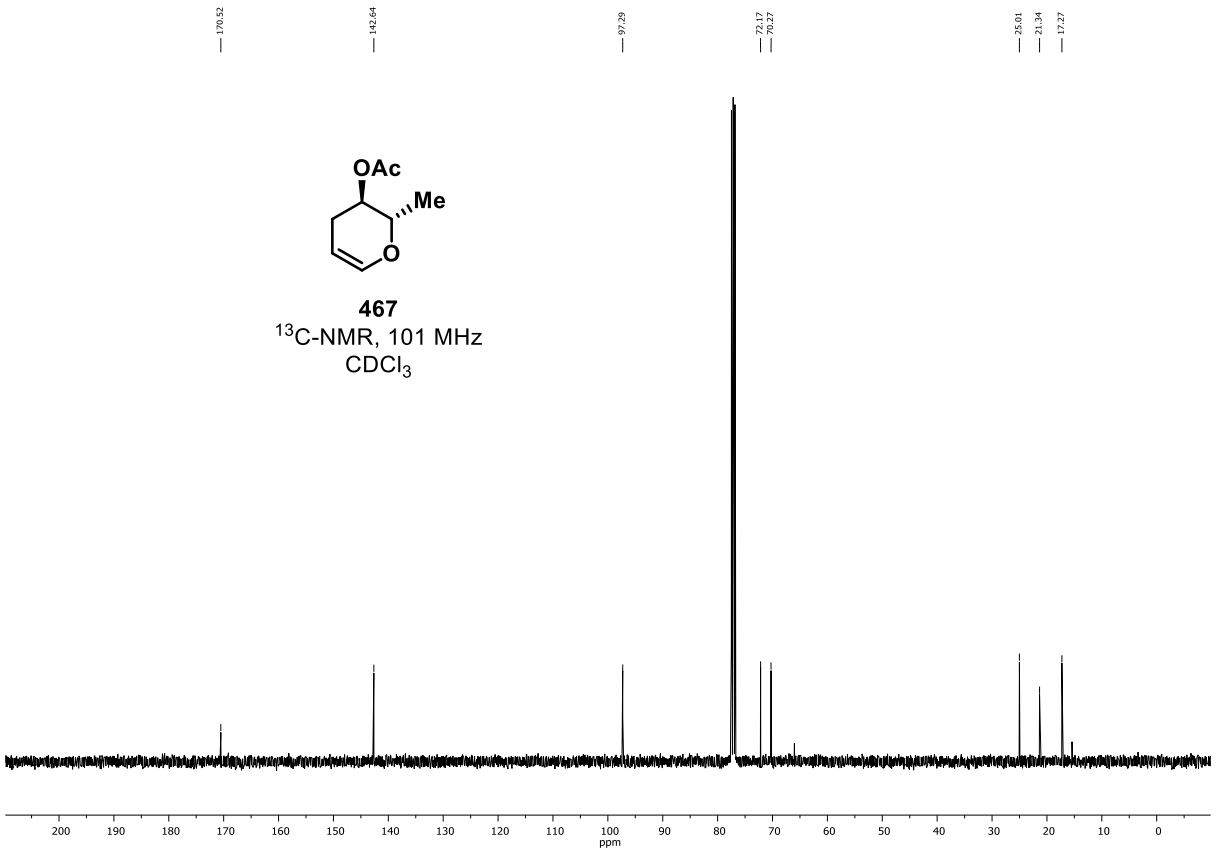
452
^{1}H-NMR, 400 MHz
$CDCl_3$



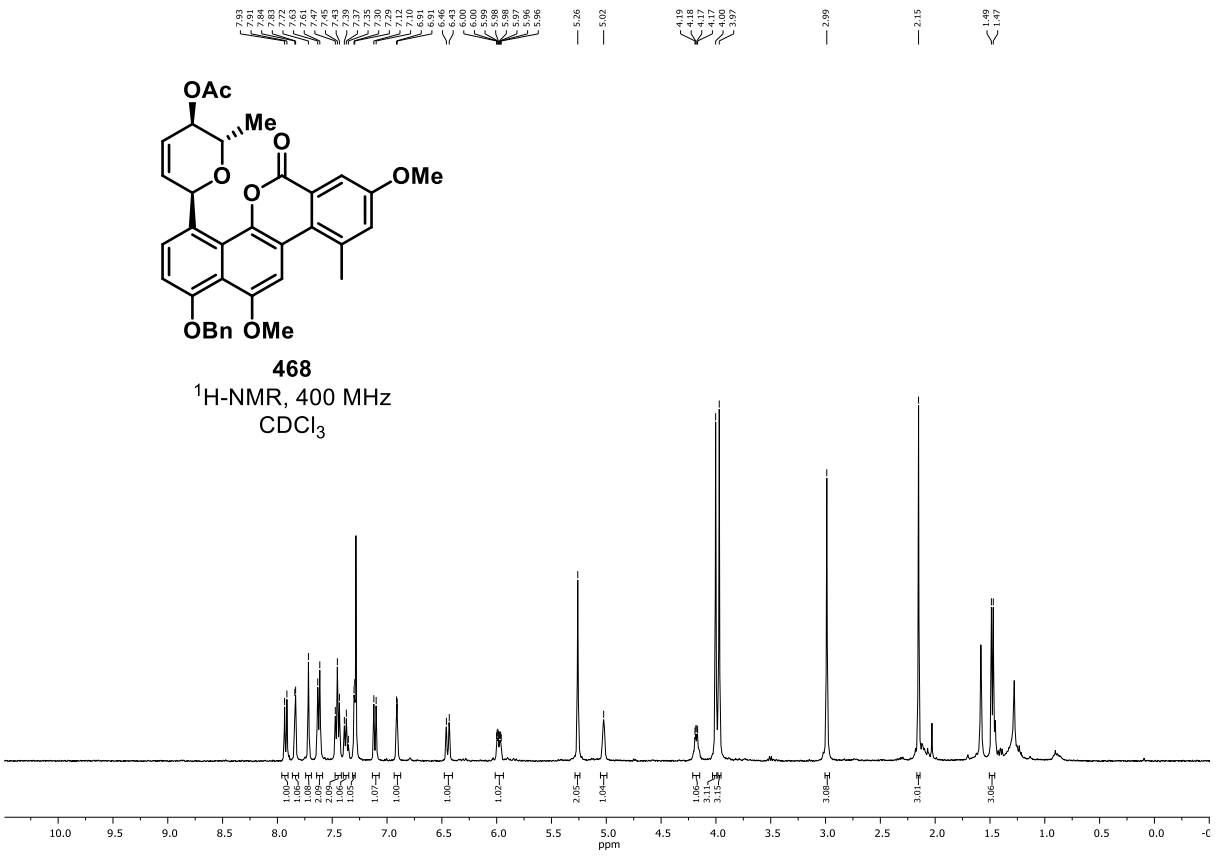
452
^{13}C-NMR, 101 MHz
$CDCl_3$



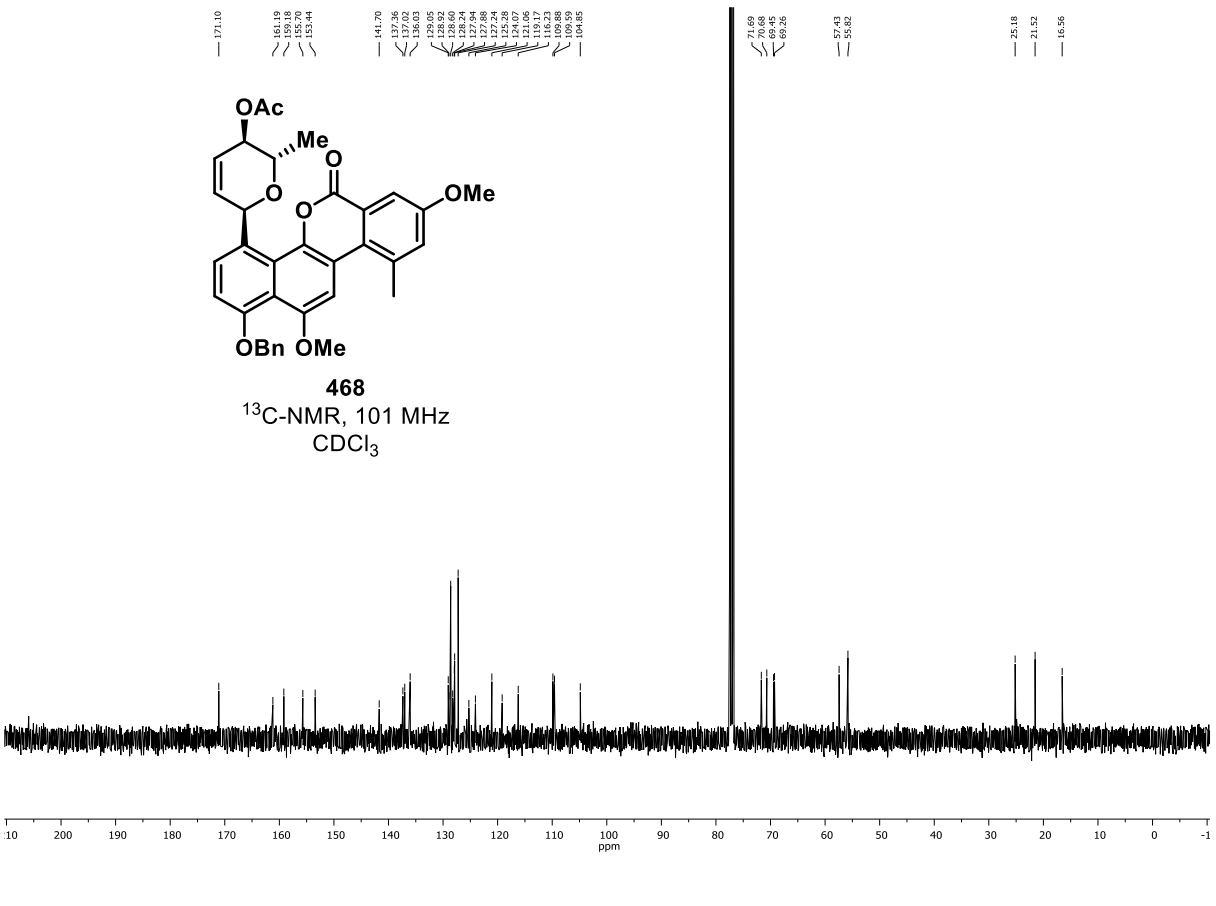
467
^{1}H-NMR, 400 MHz
$CDCl_3$



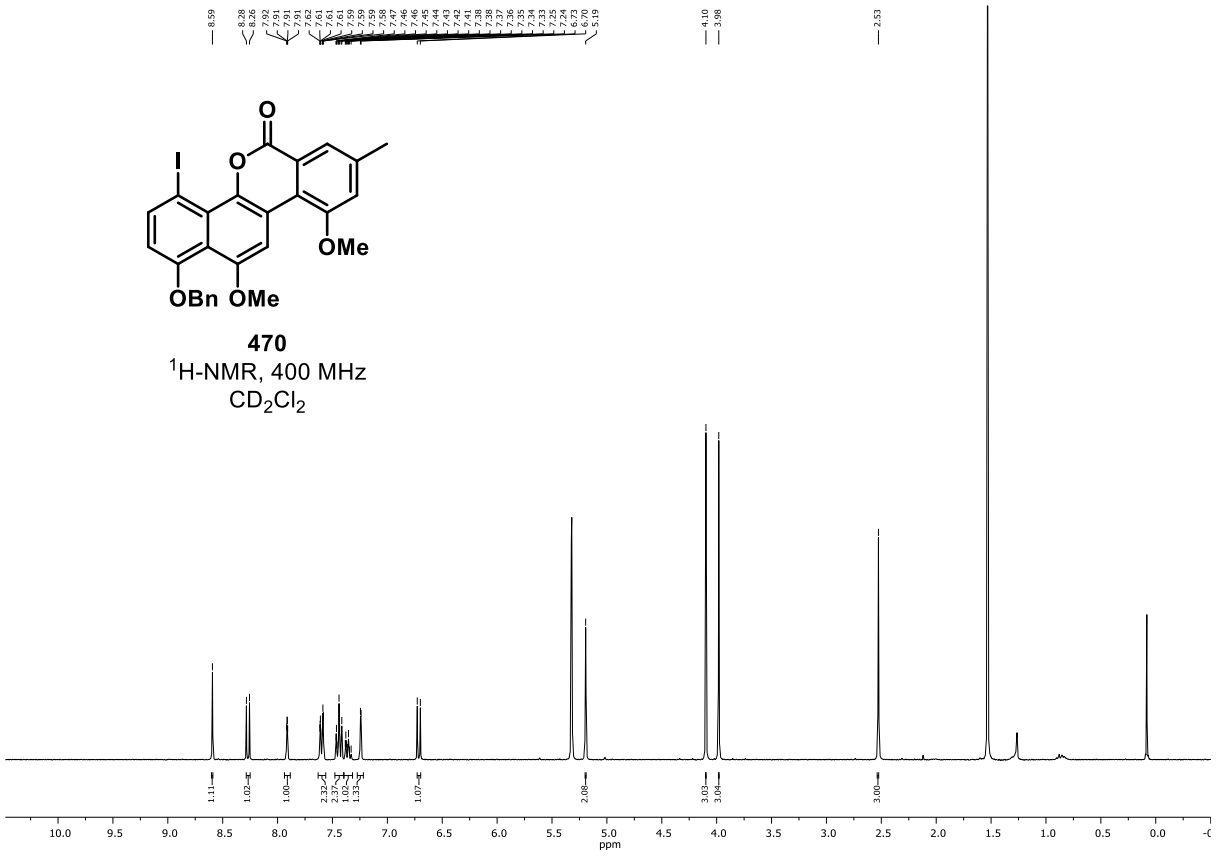
467
^{13}C-NMR, 101 MHz
$CDCl_3$



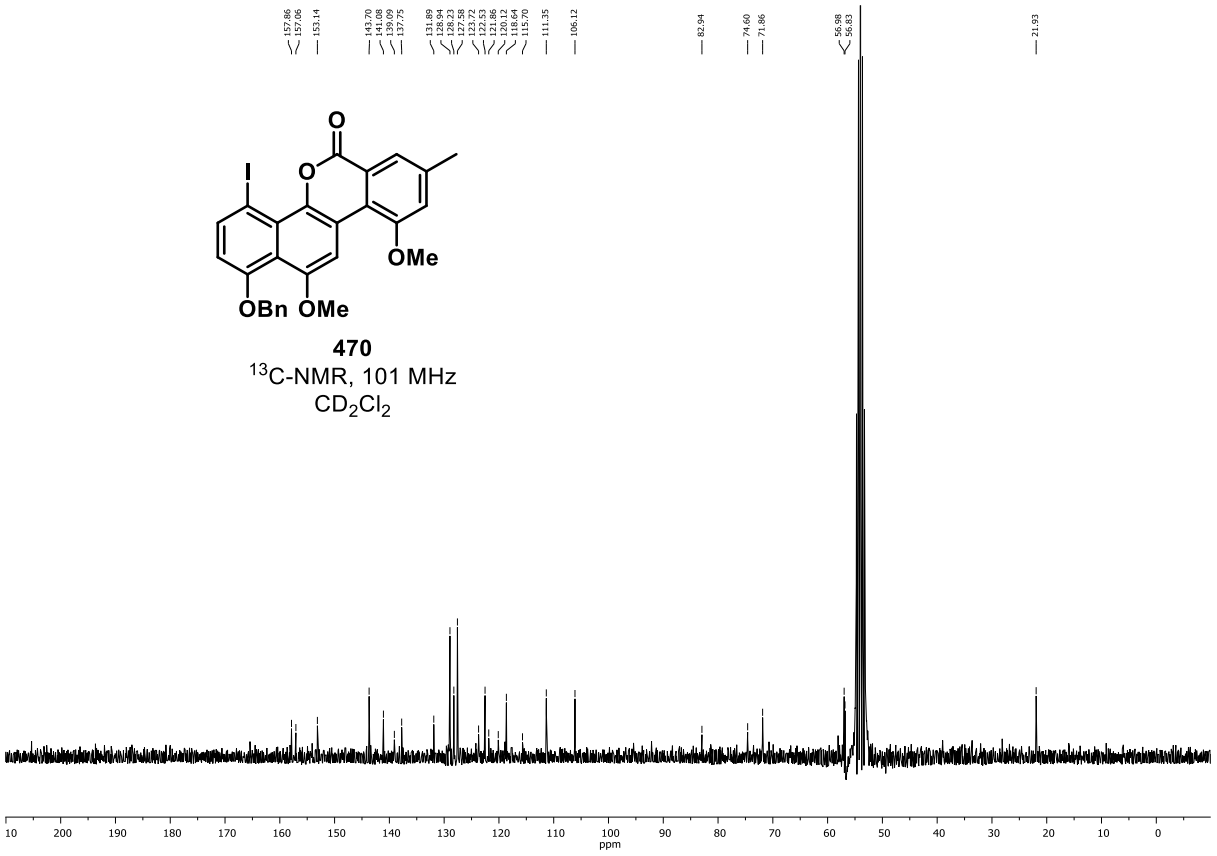
468
^{1}H-NMR, 400 MHz
$CDCl_3$



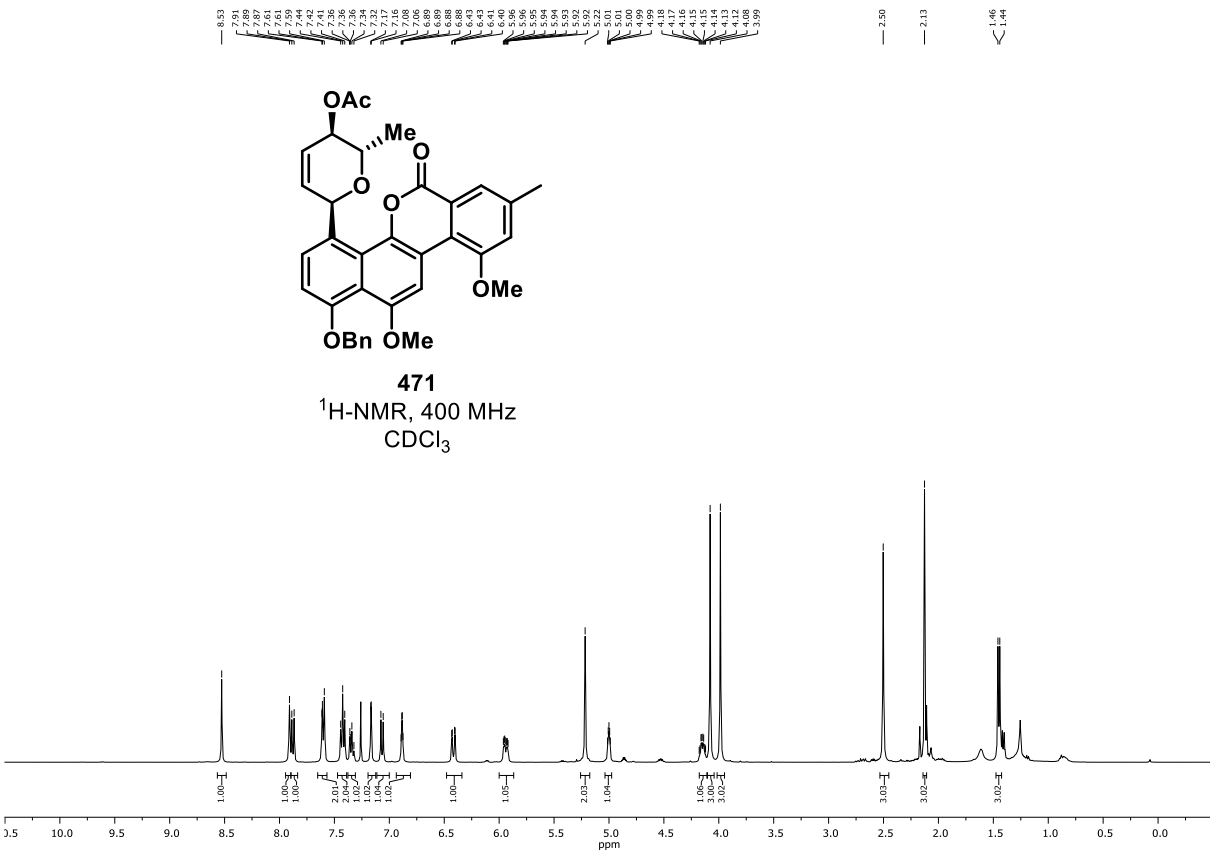
468
^{13}C-NMR, 101 MHz
$CDCl_3$



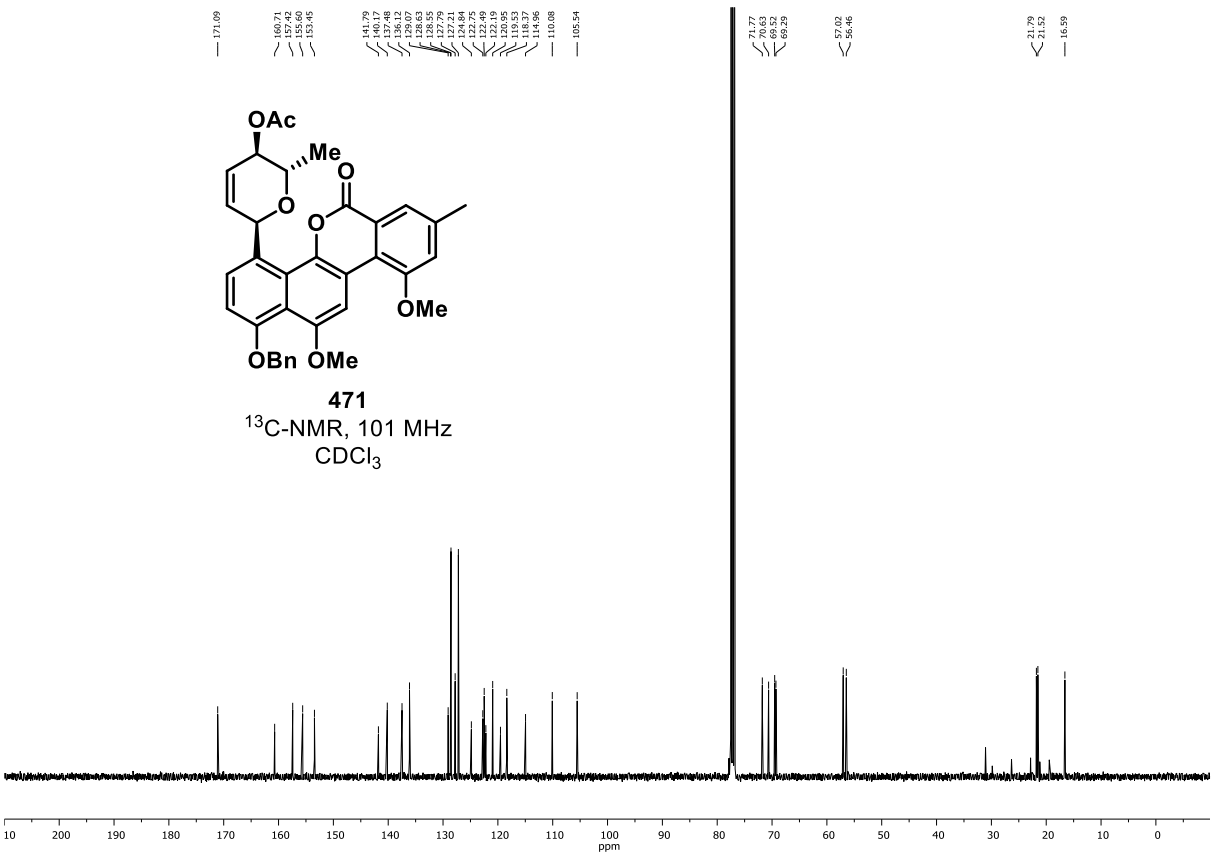
470
^{1}H-NMR, 400 MHz
CD_2Cl_2



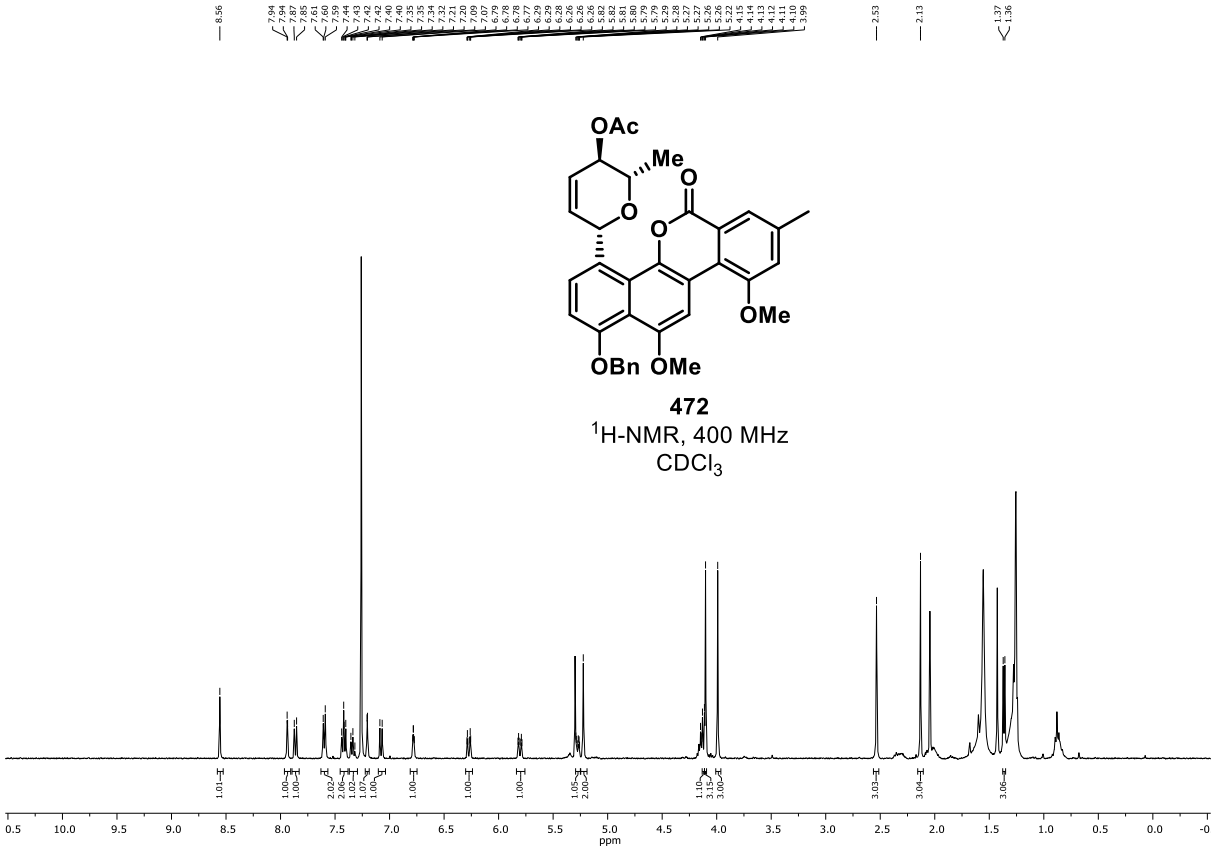
470
^{13}C-NMR, 101 MHz
CD_2Cl_2



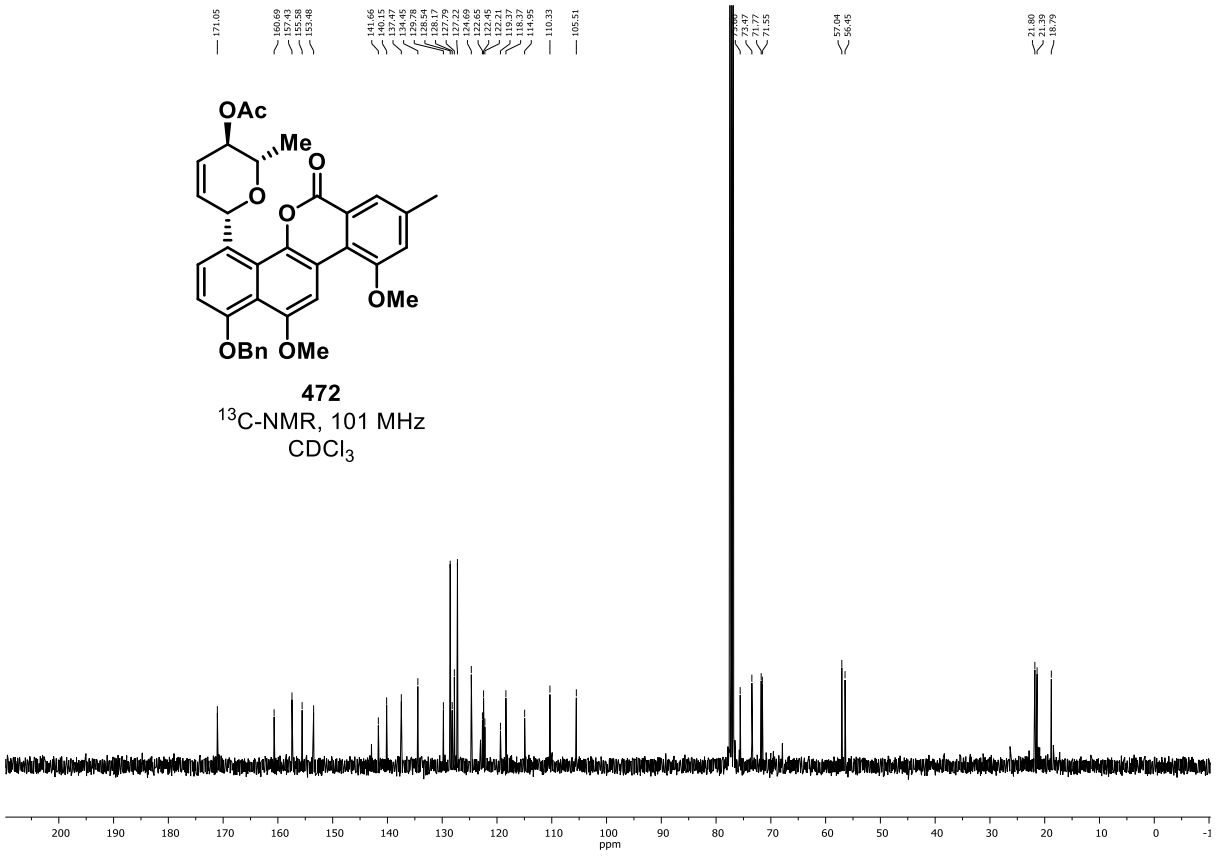
471
^{1}H-NMR, 400 MHz
$CDCl_3$



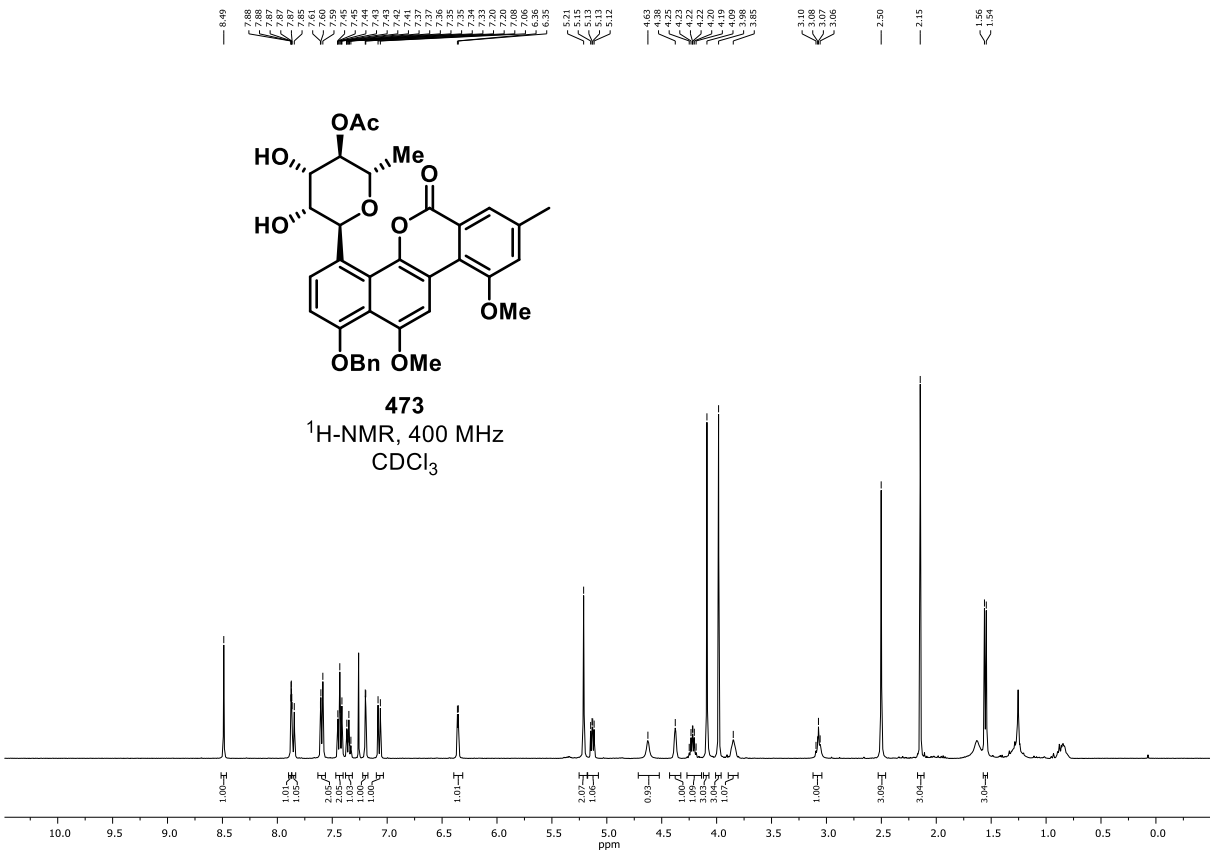
471
^{13}C-NMR, 101 MHz
$CDCl_3$



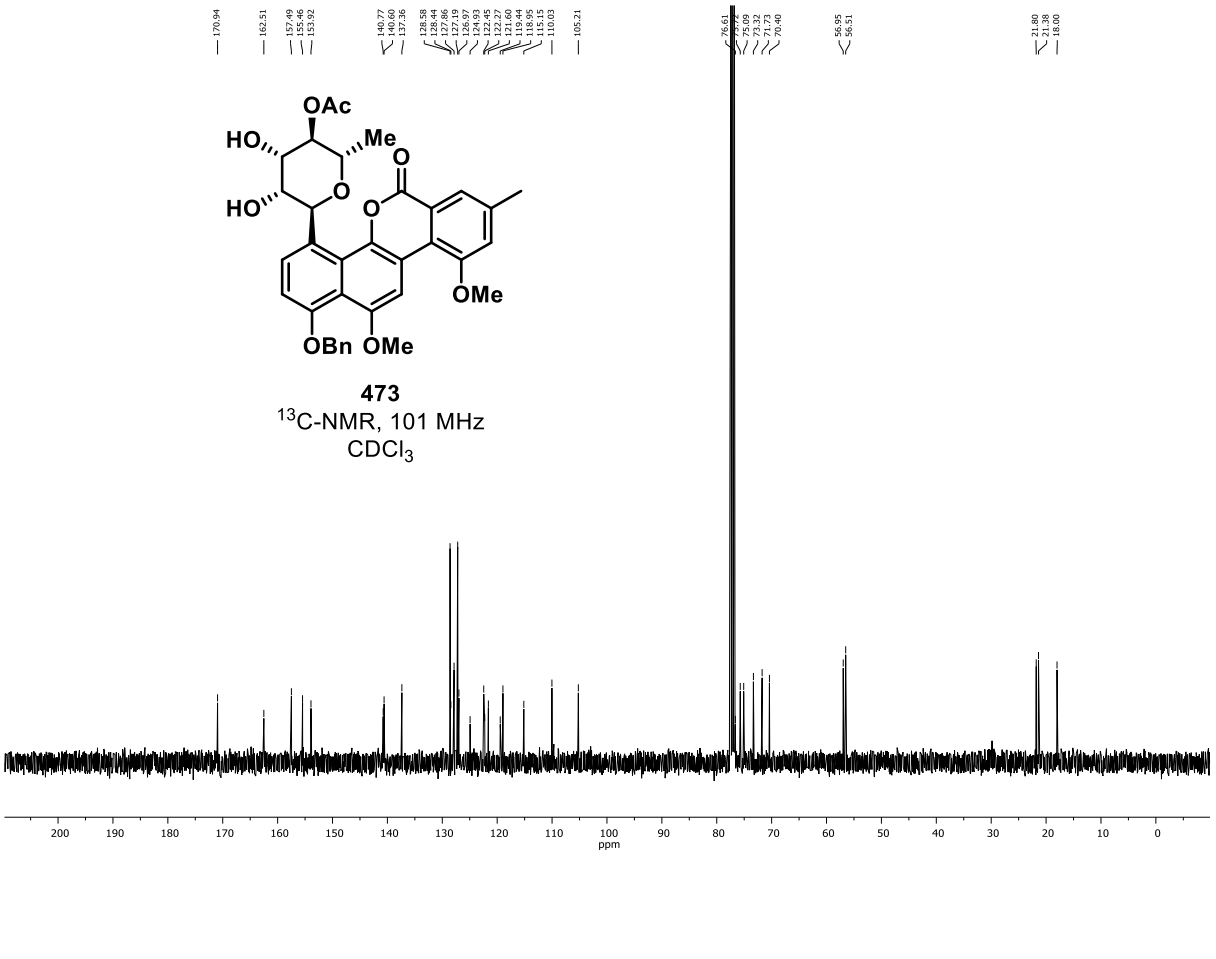
472
^{1}H-NMR, 400 MHz
$CDCl_3$



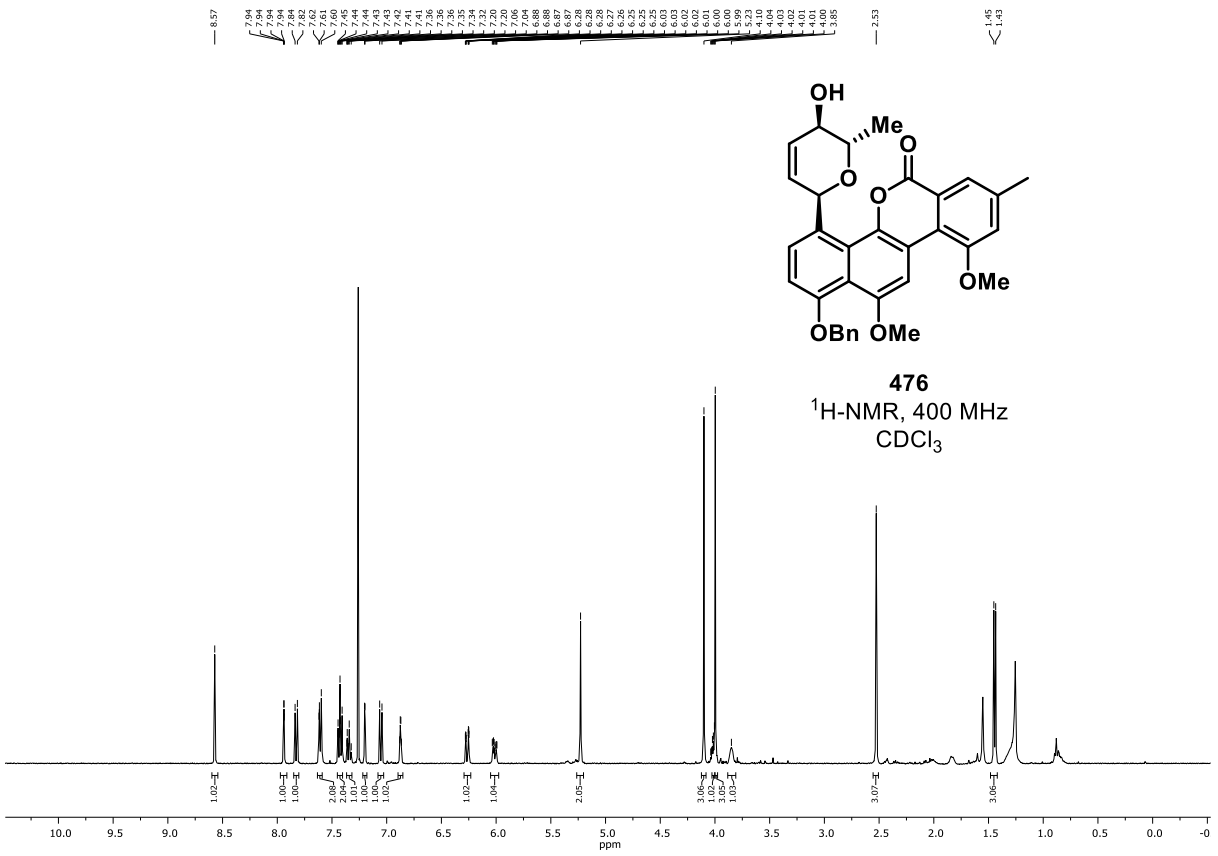
472
^{13}C-NMR, 101 MHz
$CDCl_3$



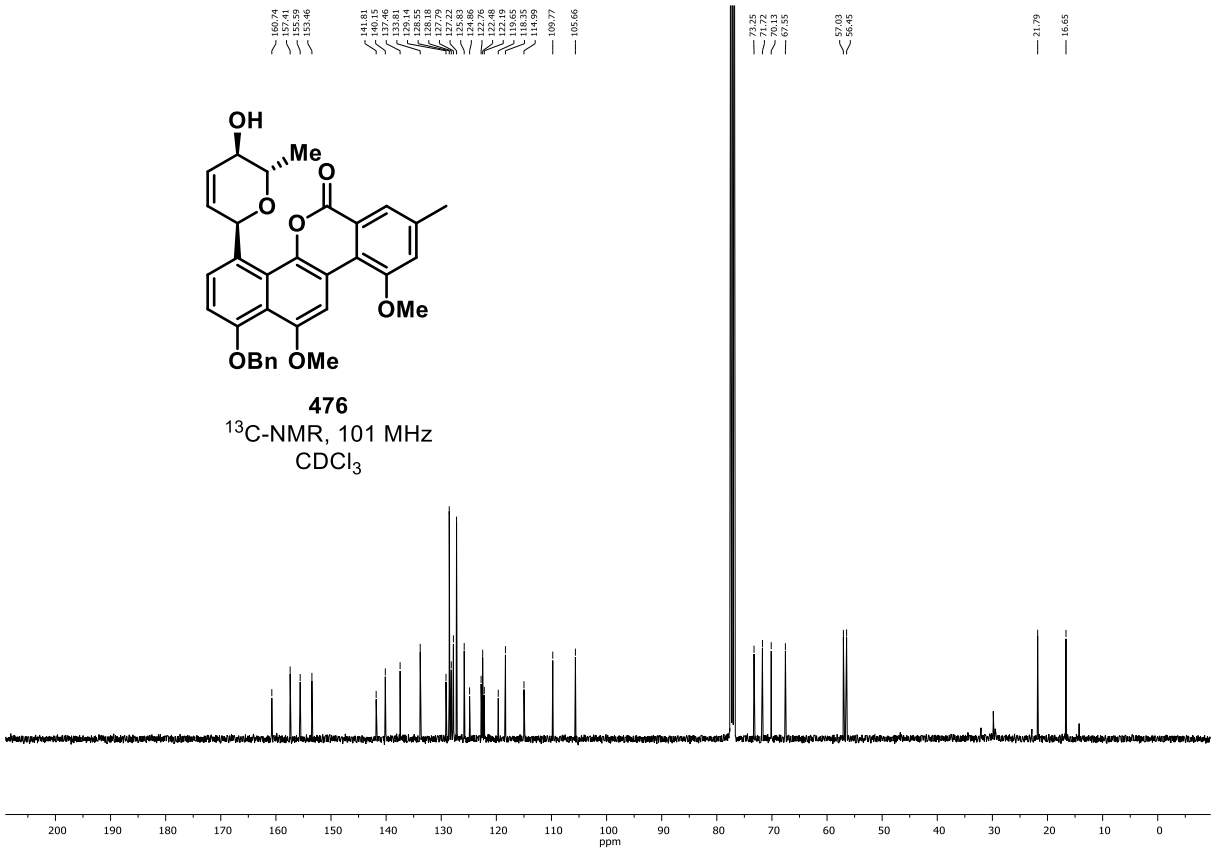
473
^{1}H-NMR, 400 MHz
$CDCl_3$



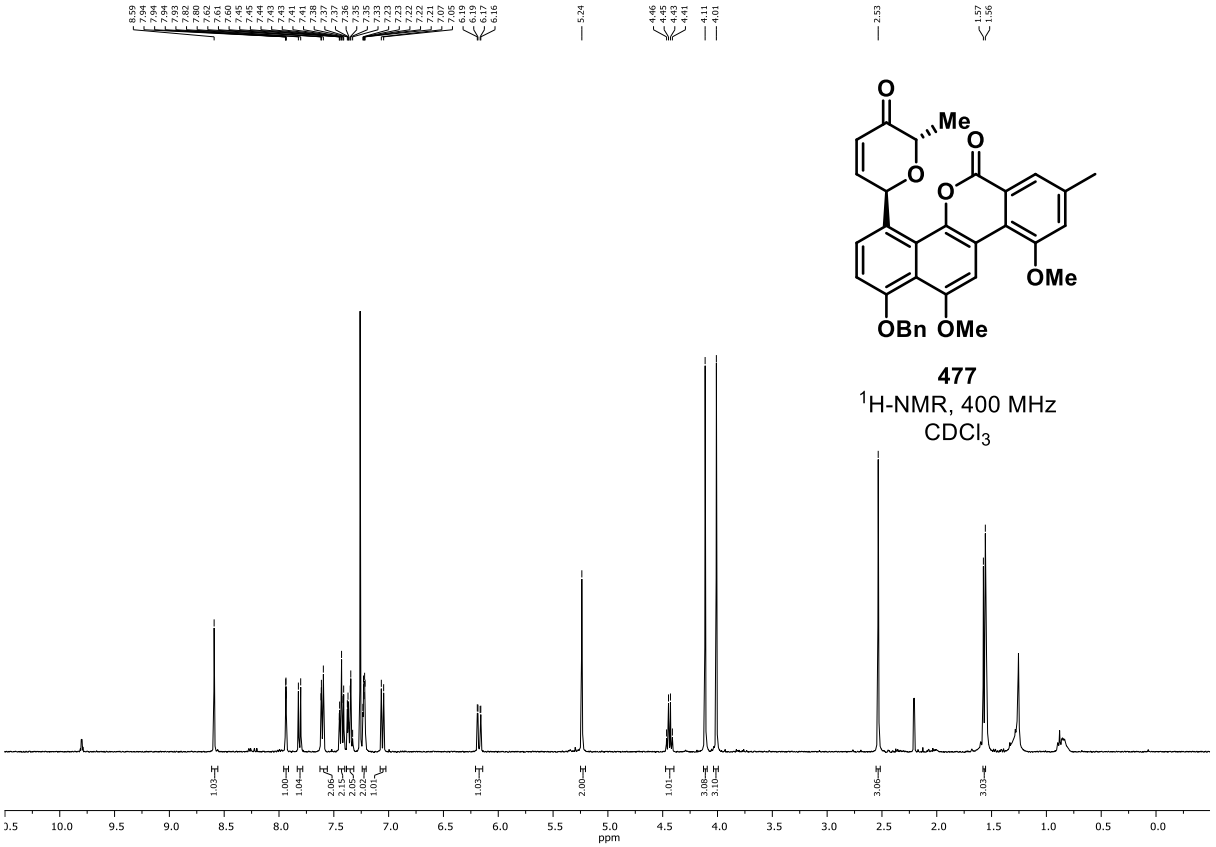
473
^{13}C-NMR, 101 MHz
$CDCl_3$



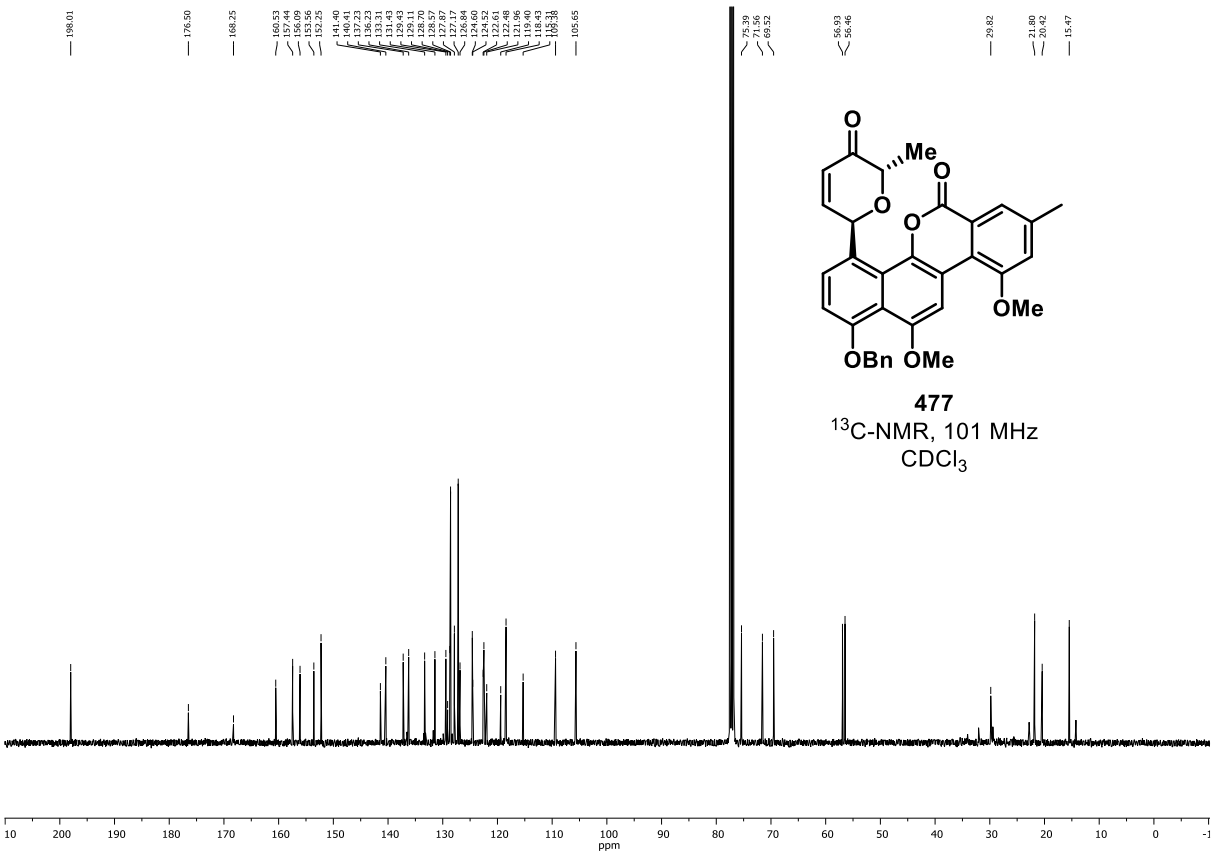
476
^{1}H-NMR, 400 MHz
$CDCl_3$



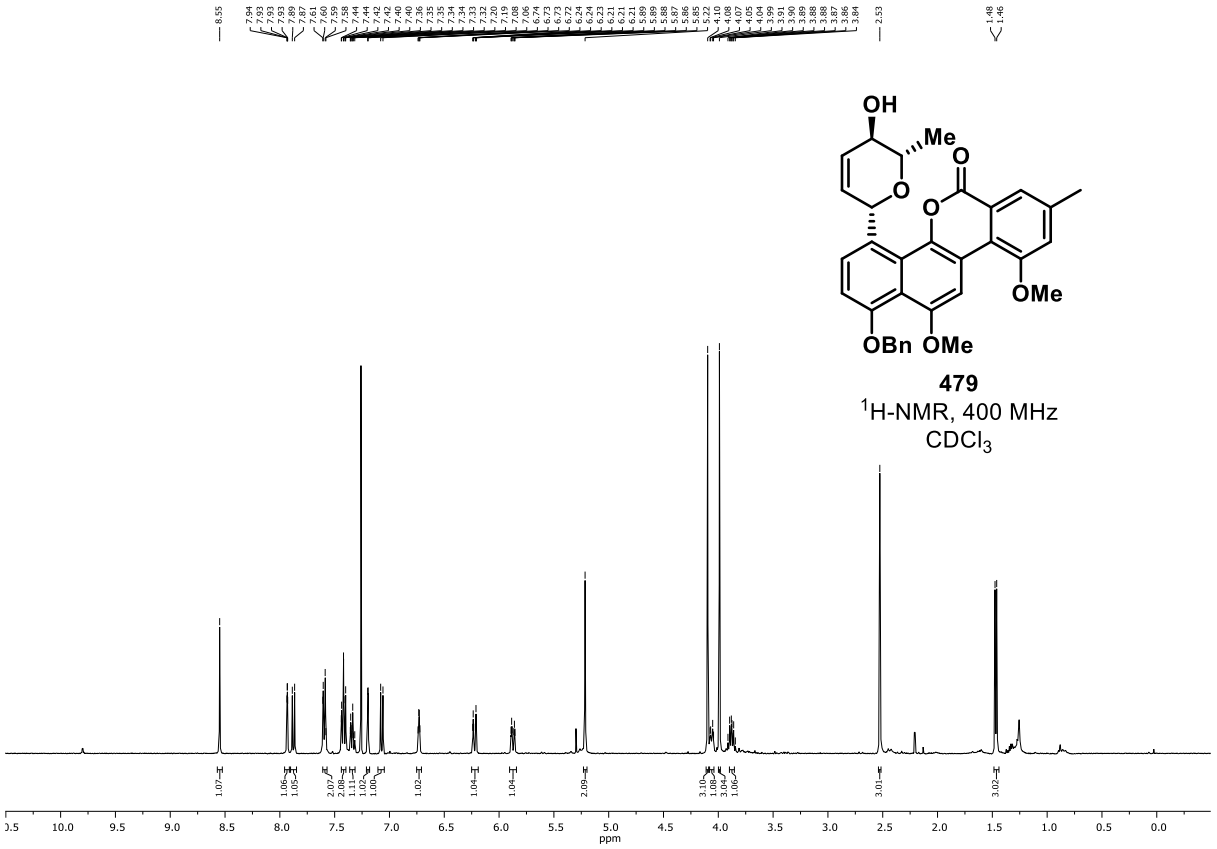
476
^{13}C-NMR, 101 MHz
$CDCl_3$



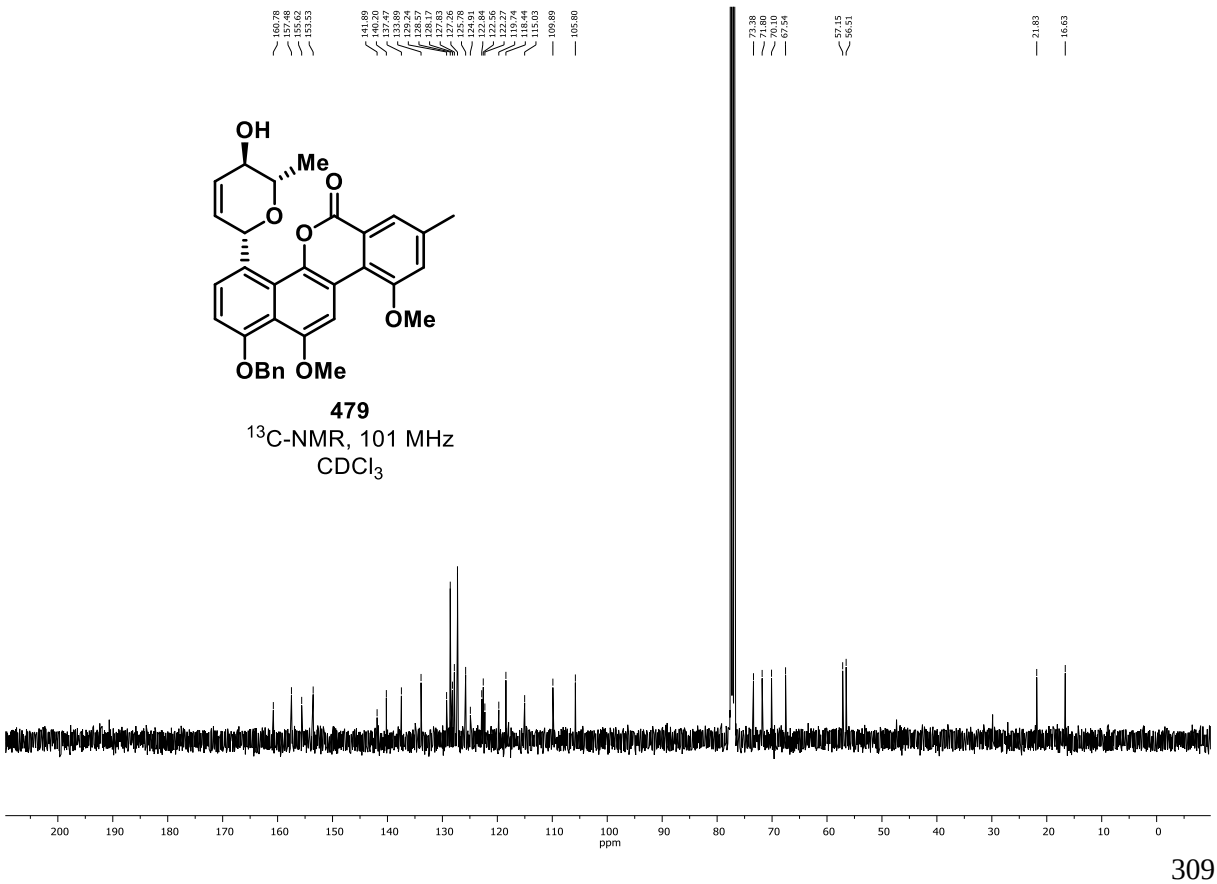
477
^{1}H-NMR, 400 MHz
$CDCl_3$



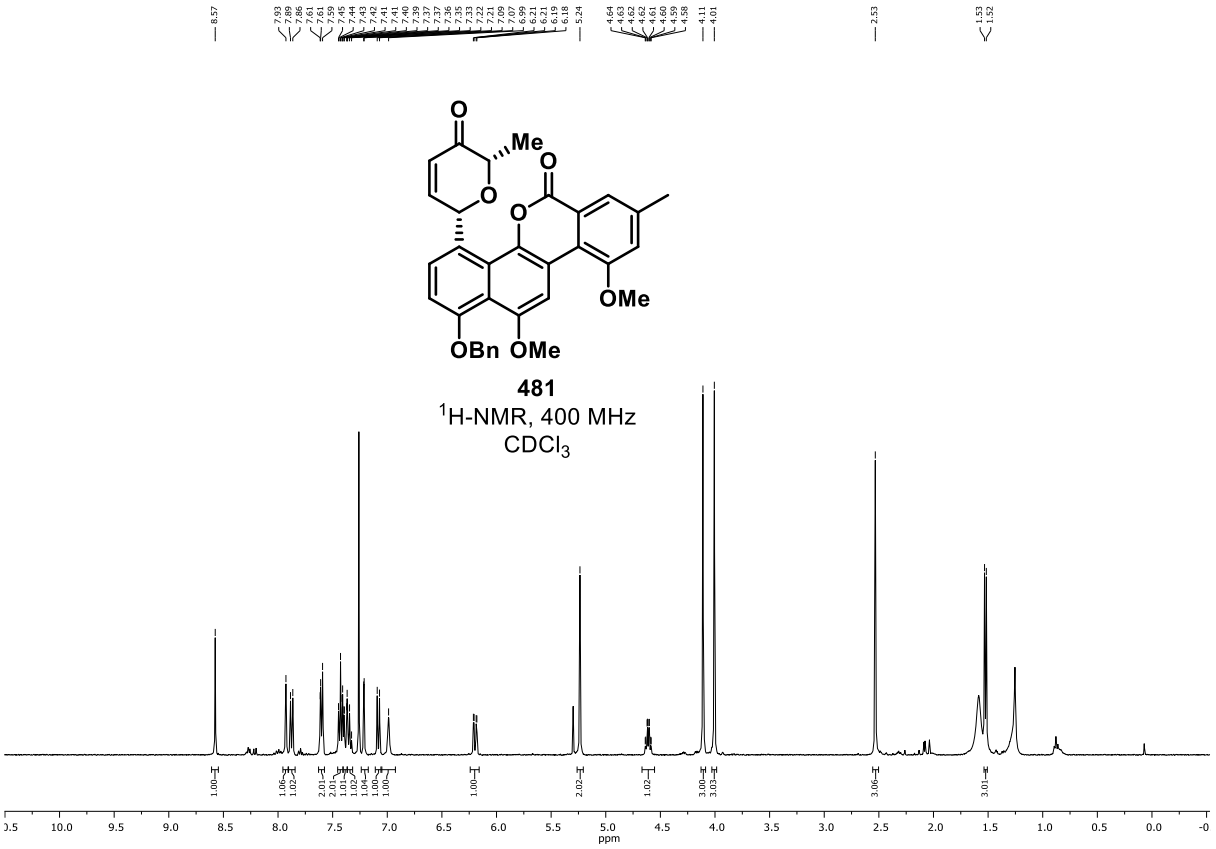
477
^{13}C-NMR, 101 MHz
$CDCl_3$

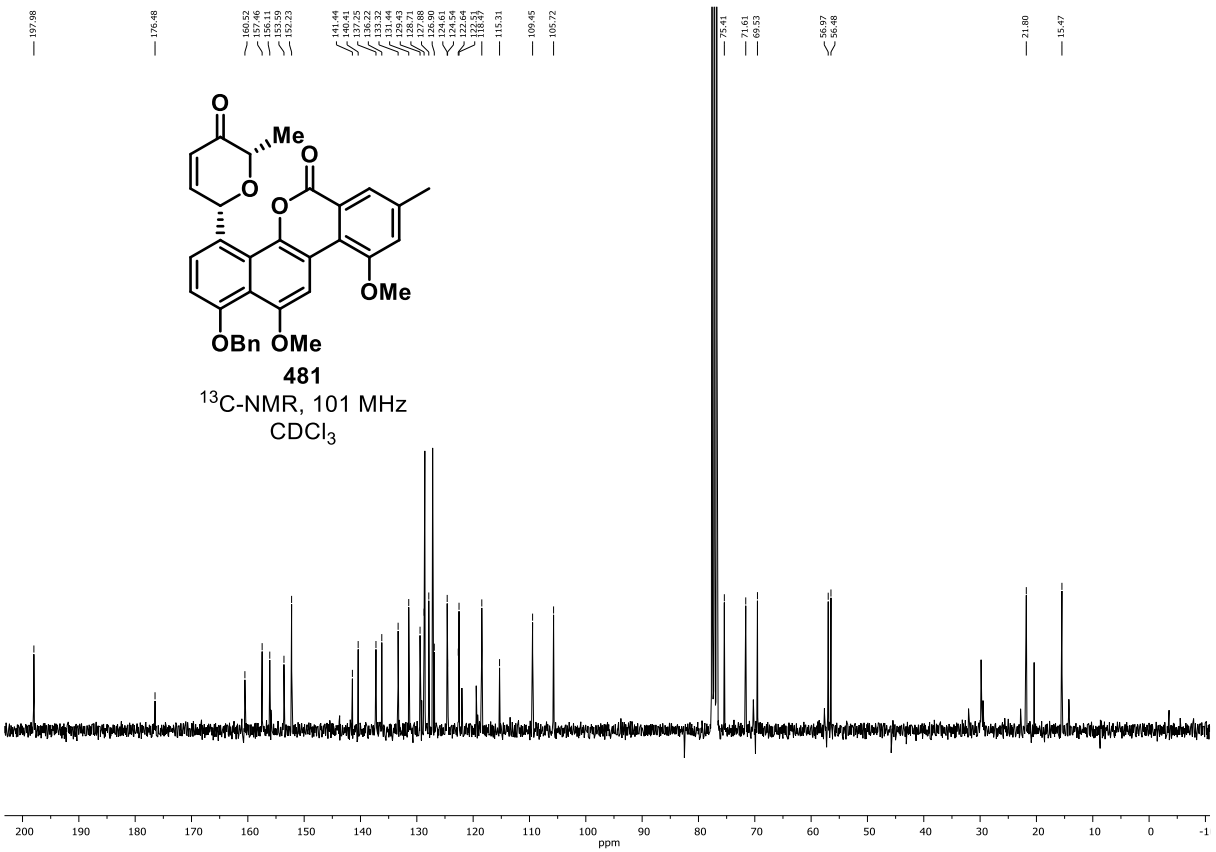


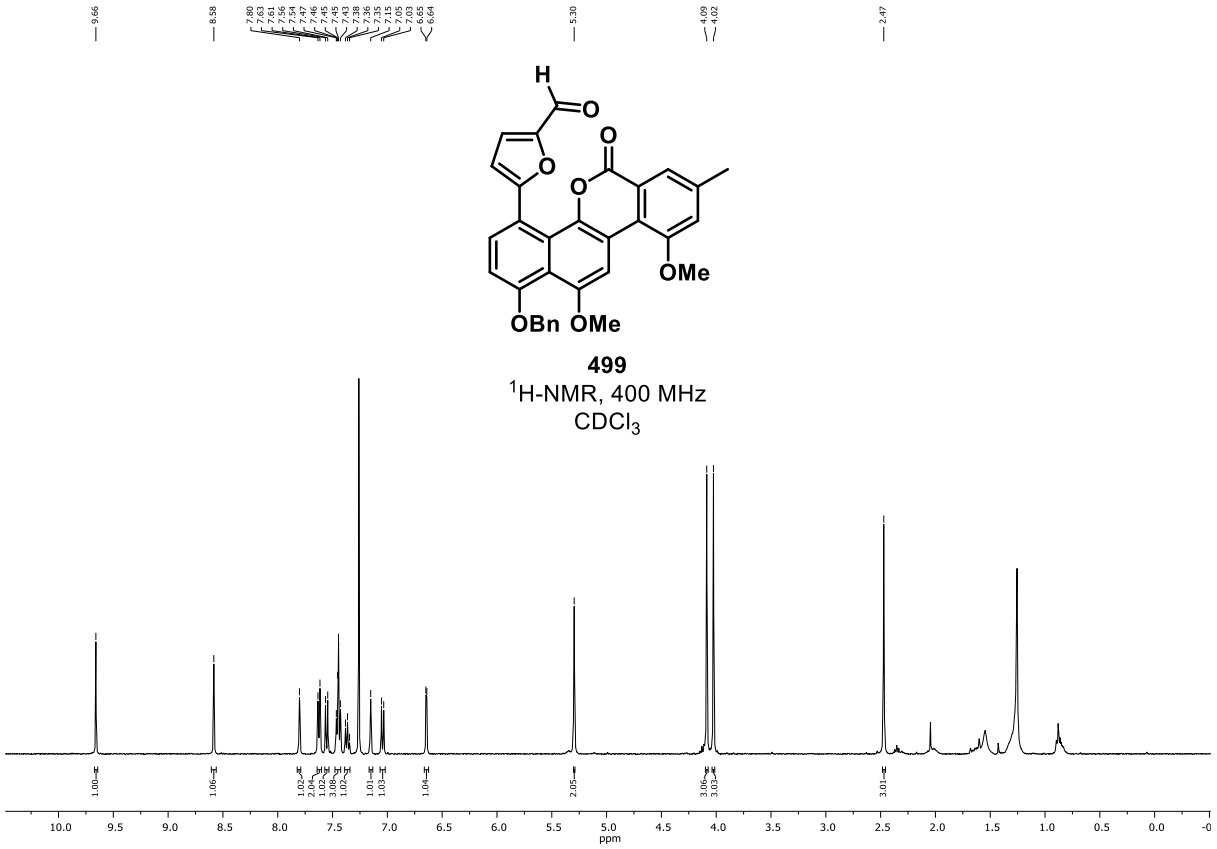
479
^{1}H-NMR, 400 MHz
$CDCl_3$



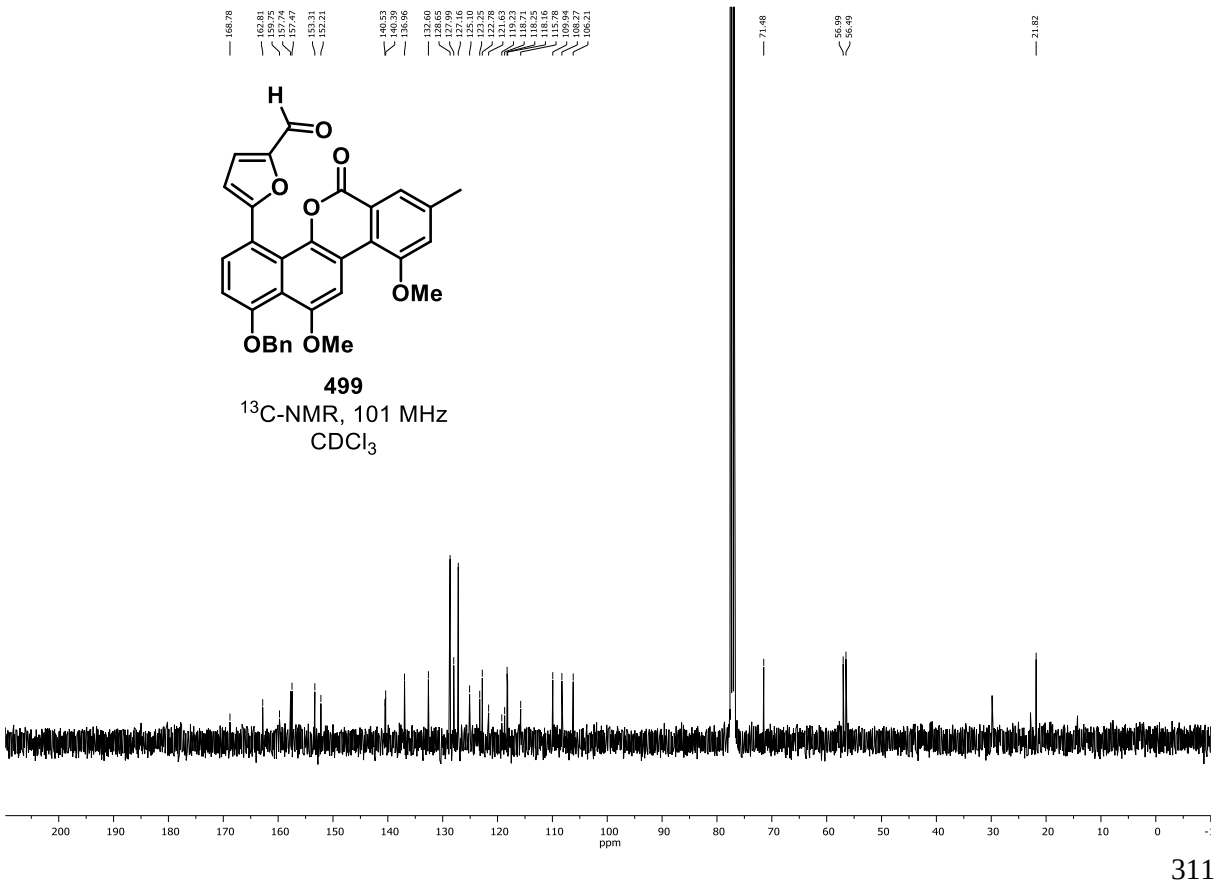
479
^{13}C-NMR, 101 MHz
$CDCl_3$


Me
O
O
O
O
OMe
OBn OMe
481
1H-NMR, 400 MHz
CDCl3
ppm


Me
O
O
O
O
OMe
OBn OMe
481
13C-NMR, 101 MHz
CDCl3
ppm

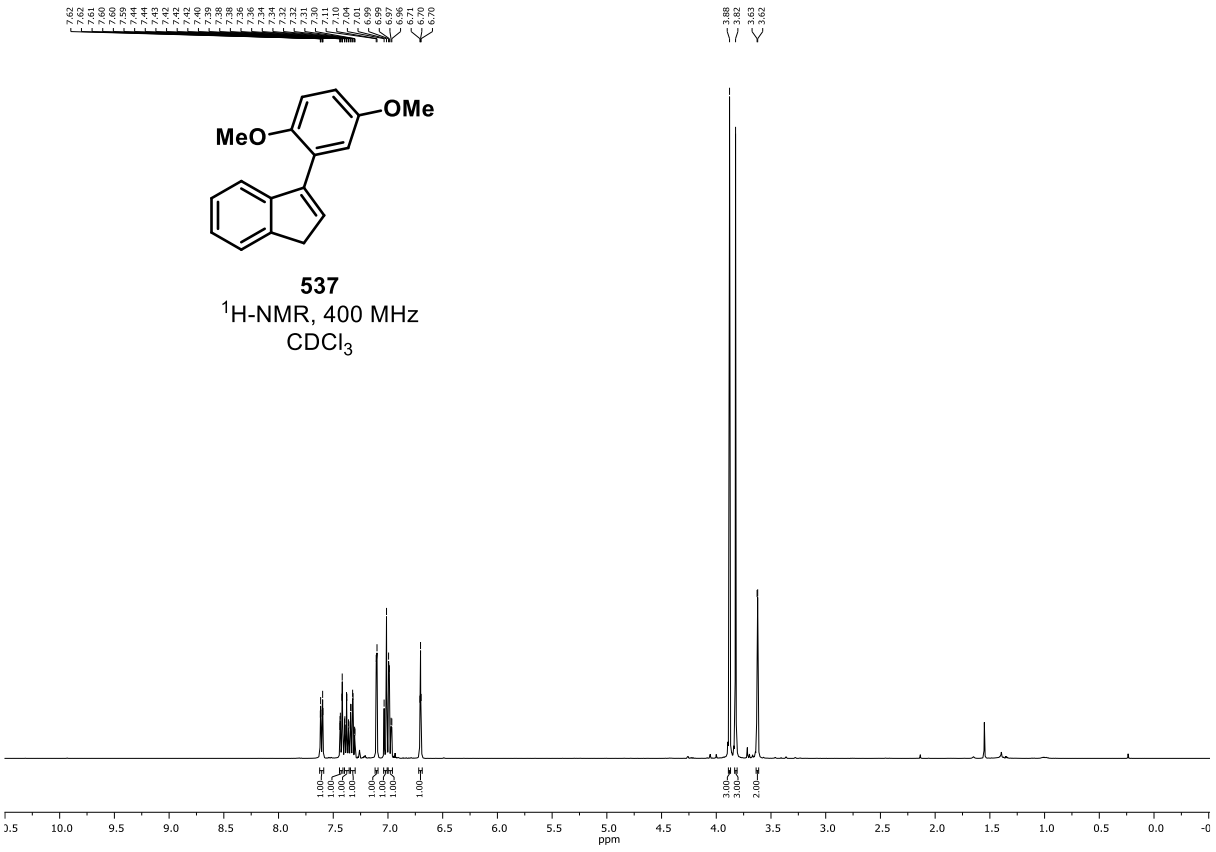


499
^{1}H-NMR, 400 MHz
$CDCl_3$

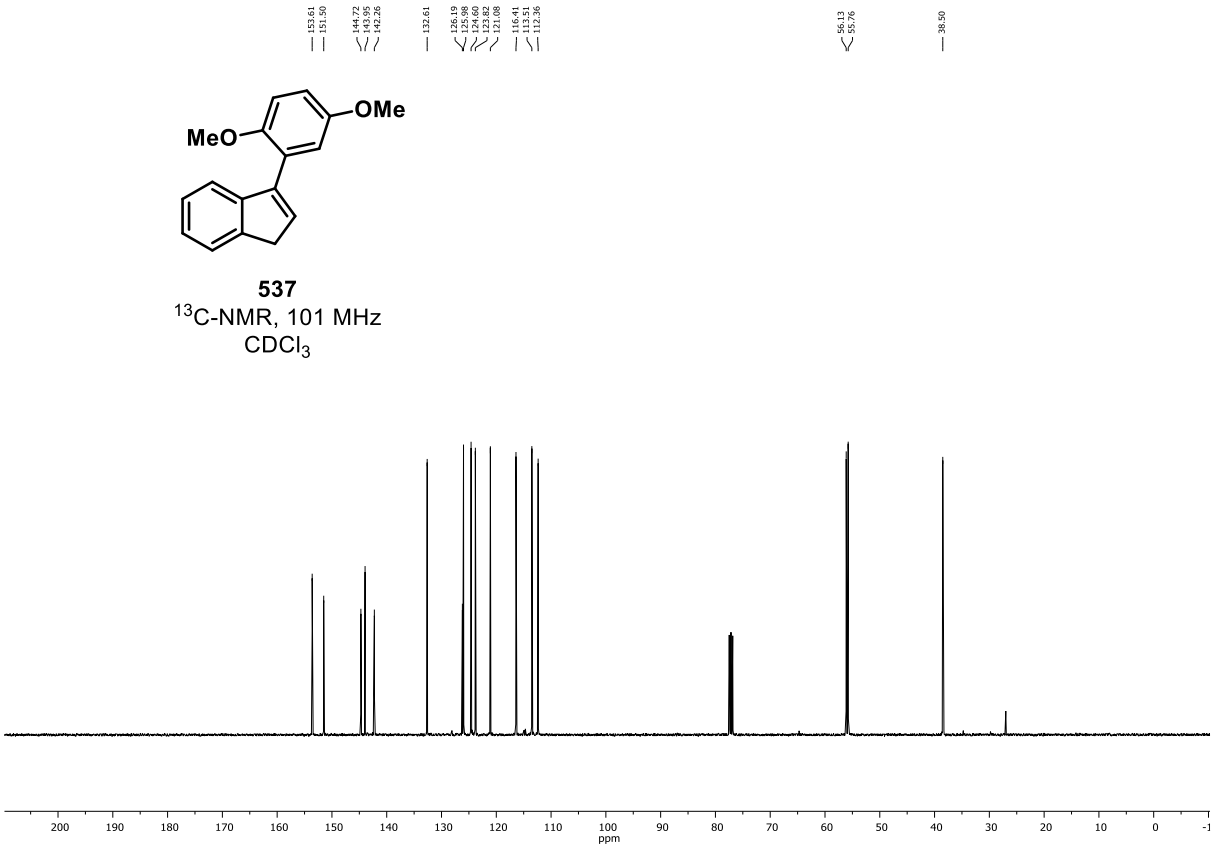


499
^{13}C-NMR, 101 MHz
$CDCl_3$

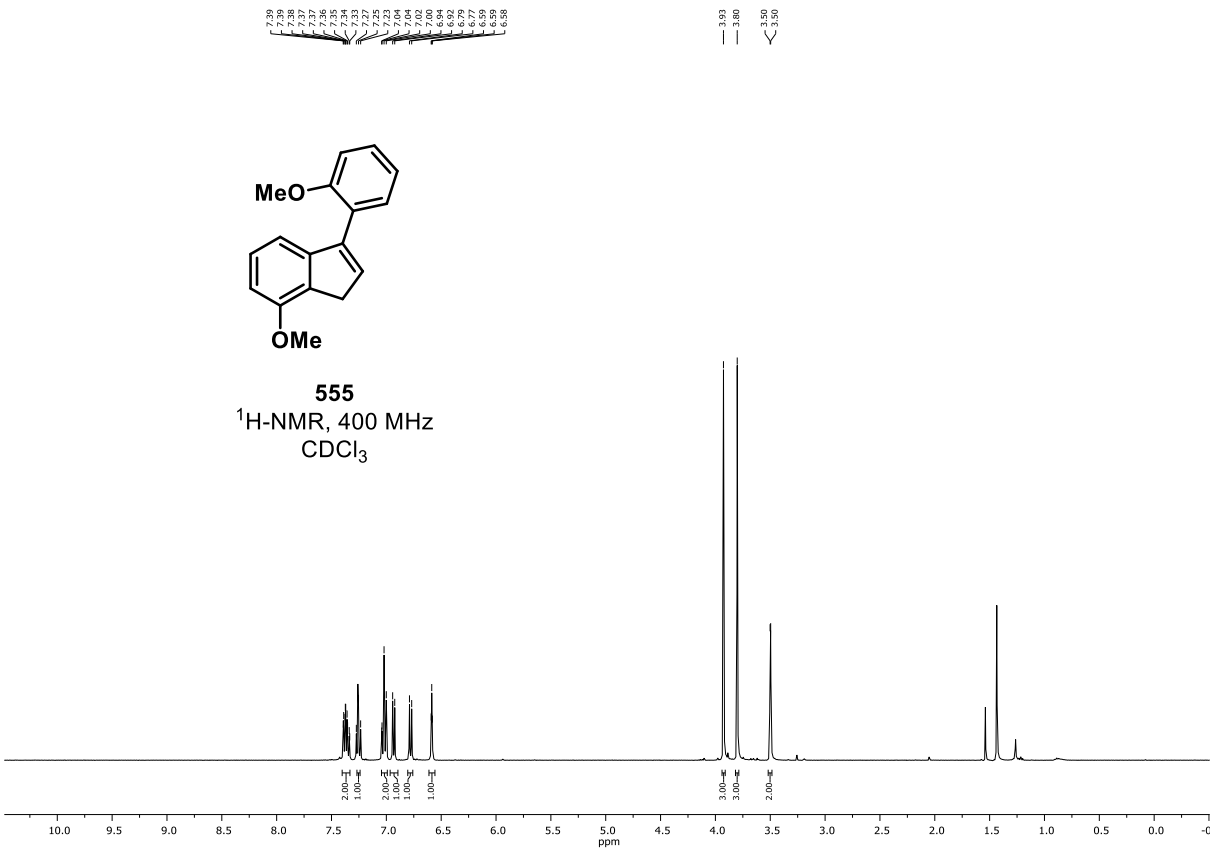
9.3 NMR Spectra for Part II



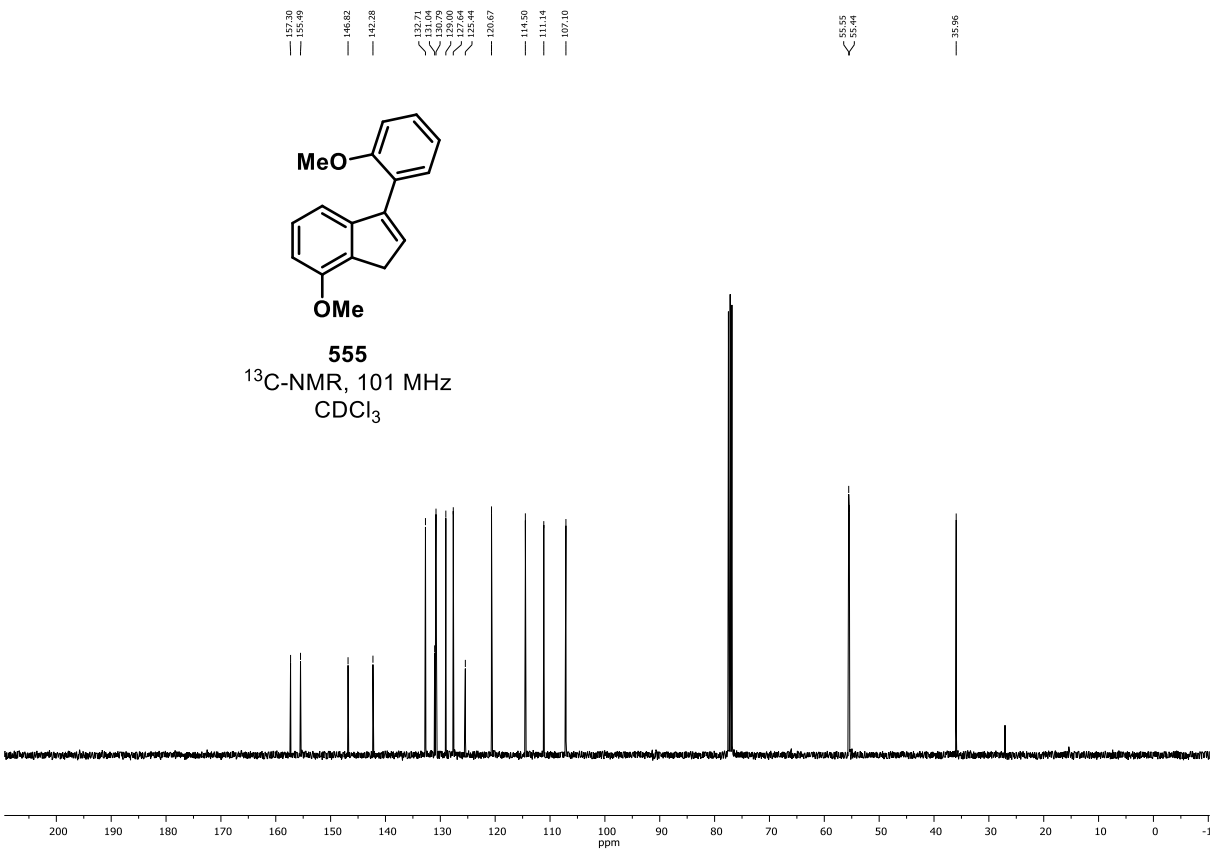
537
^{1}H-NMR, 400 MHz
$CDCl_3$



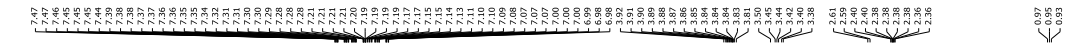
537
^{13}C-NMR, 101 MHz
$CDCl_3$

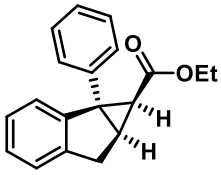


555
^{1}H-NMR, 400 MHz
$CDCl_3$

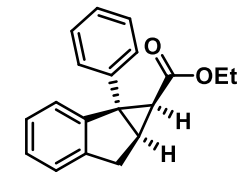


555
^{13}C-NMR, 101 MHz
$CDCl_3$

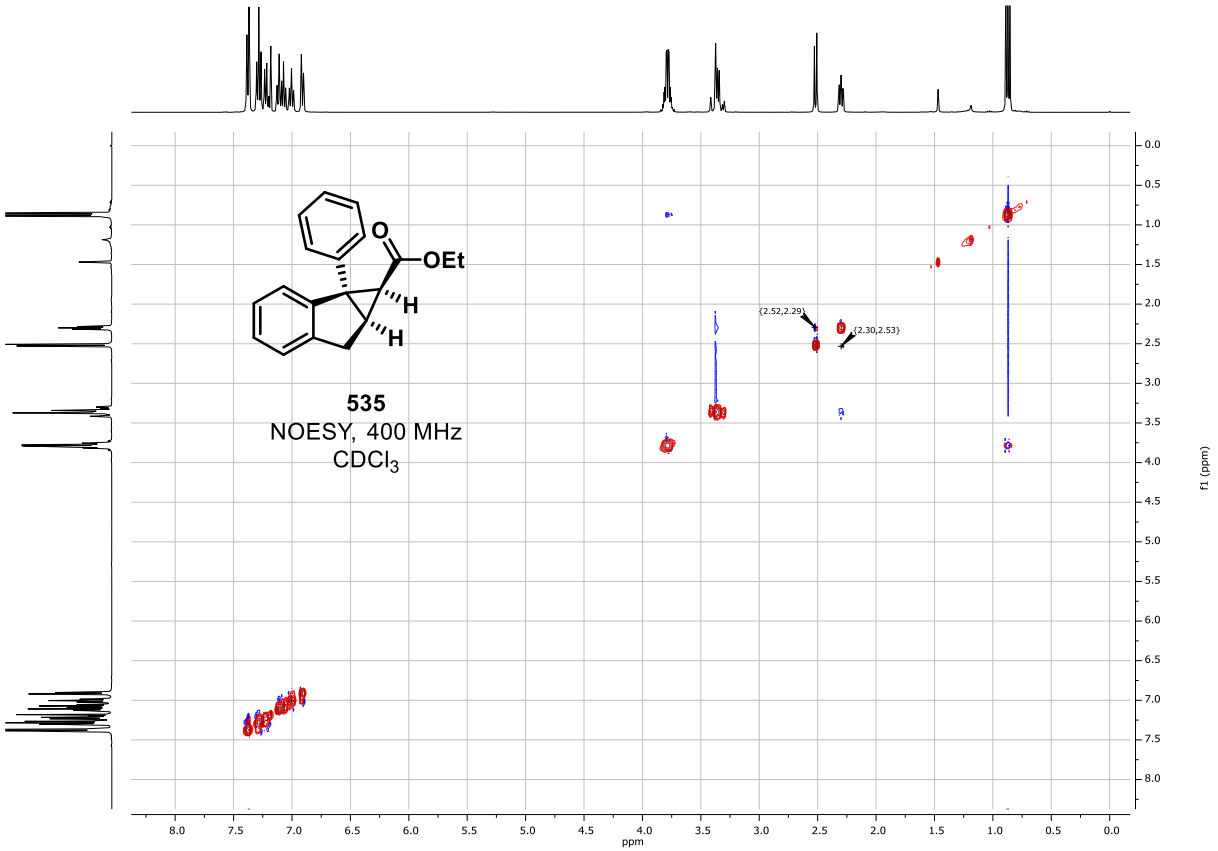


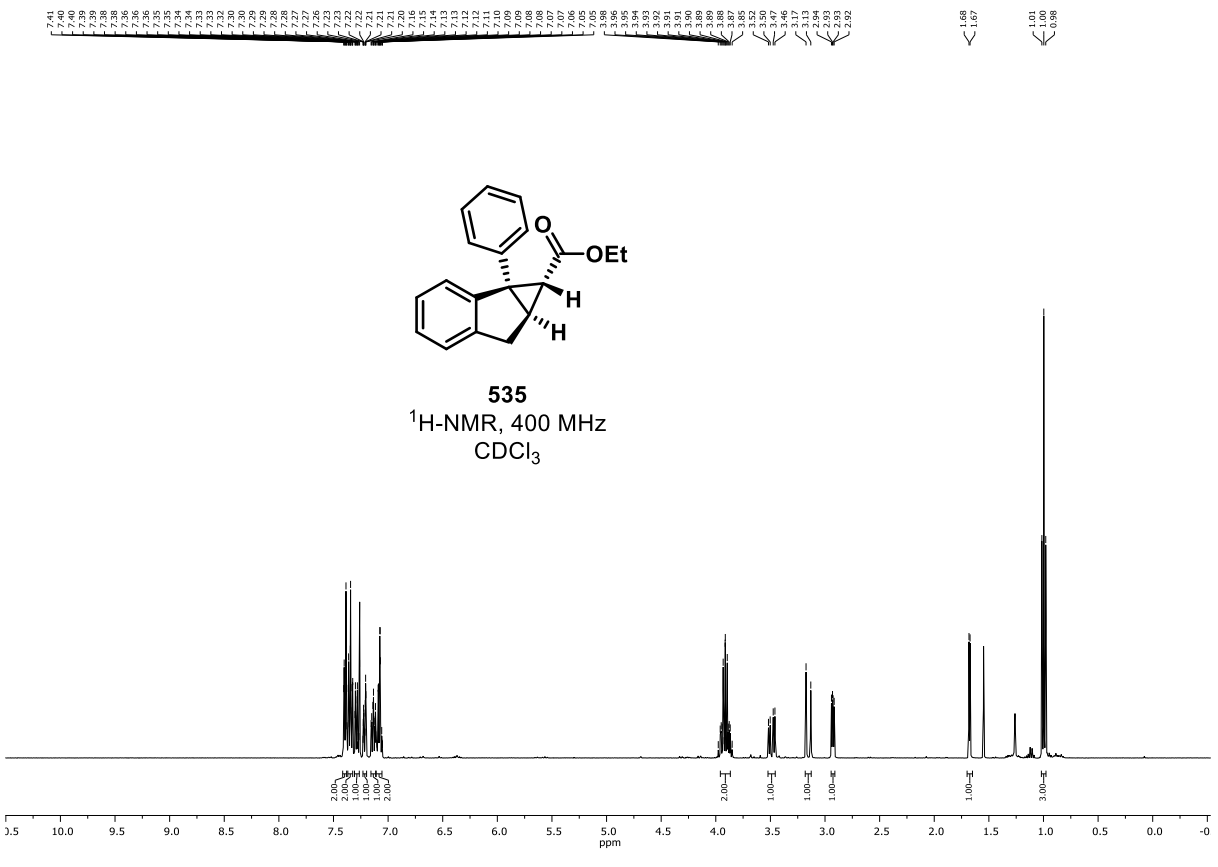


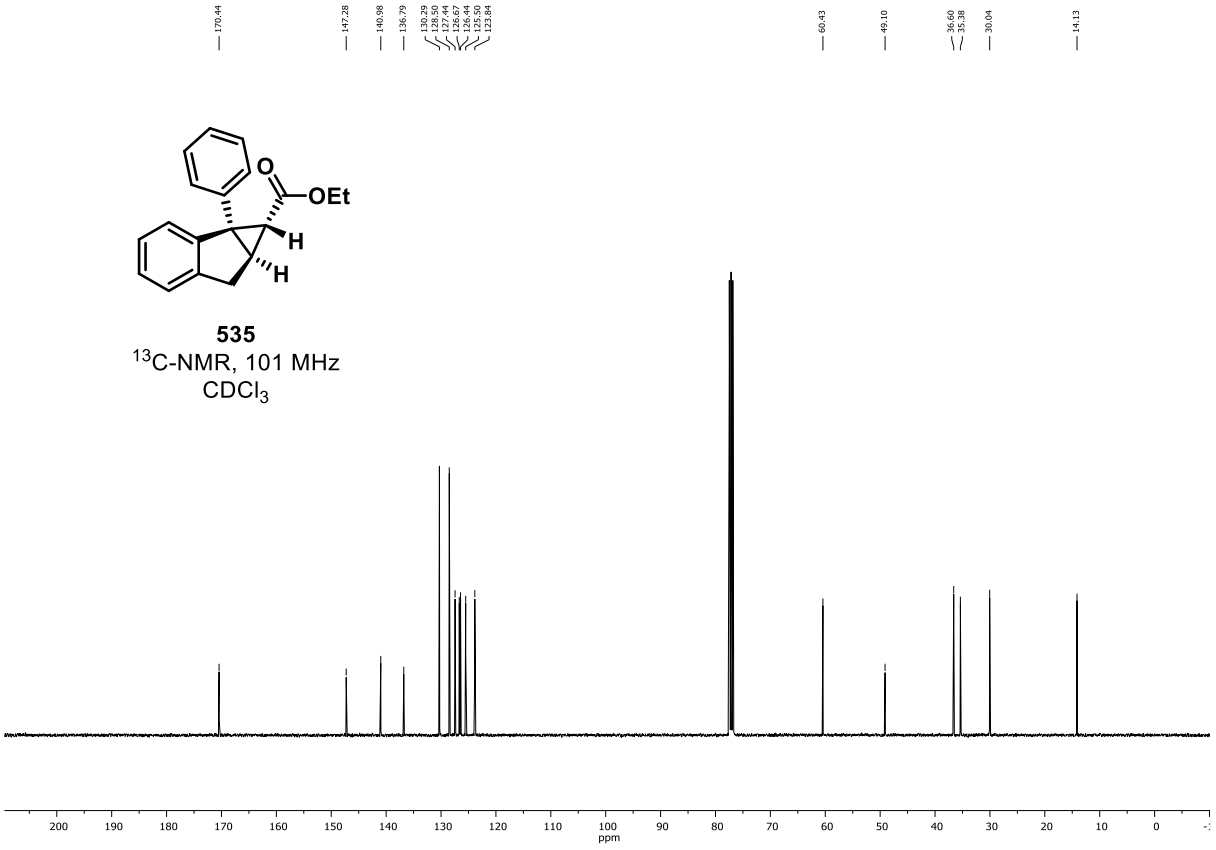
535
^{1}H-NMR, 400 MHz
$CDCl_3$



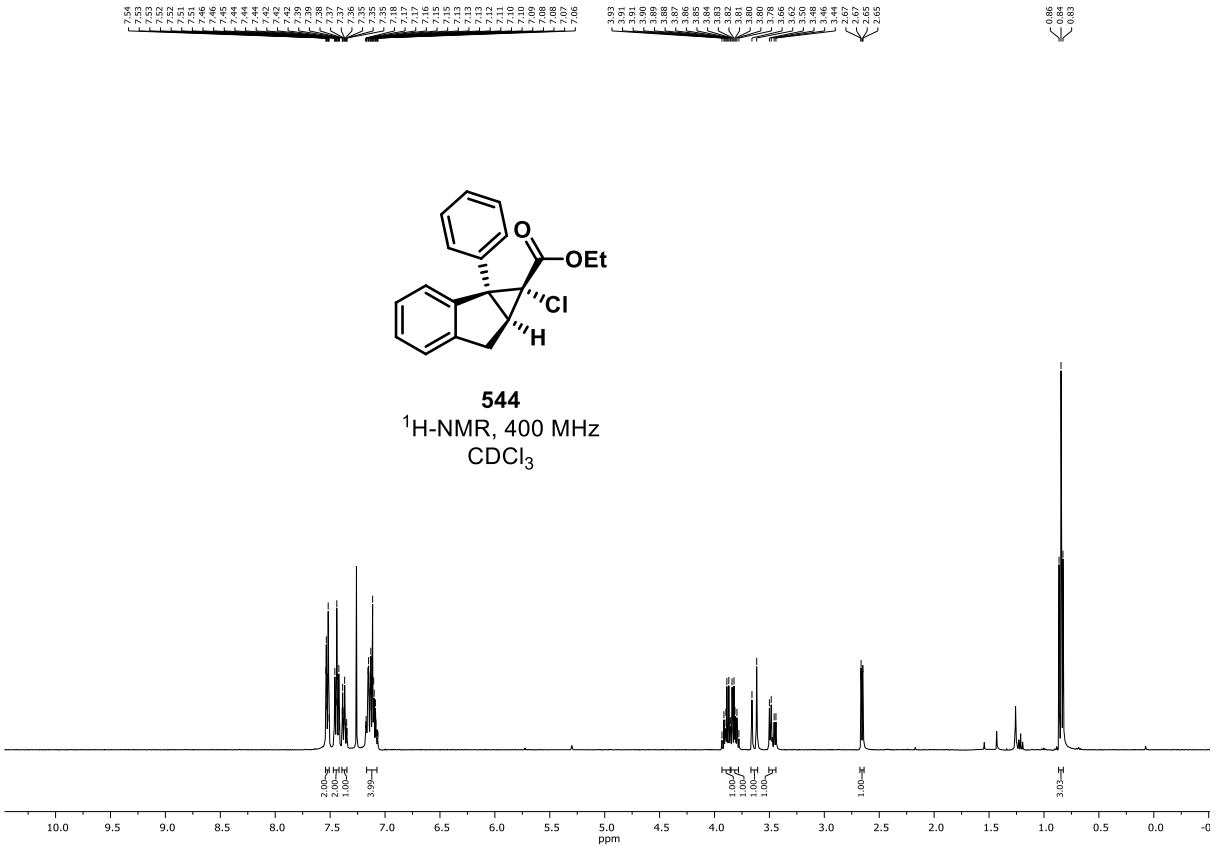
535
^{13}C-NMR, 101 MHz
$CDCl_3$


O
OEt
H
H
535
NOESY, 400 MHz
CDCl3
(2.52,2.29)
(2.30,2.53)
ppm
f1 (ppm)

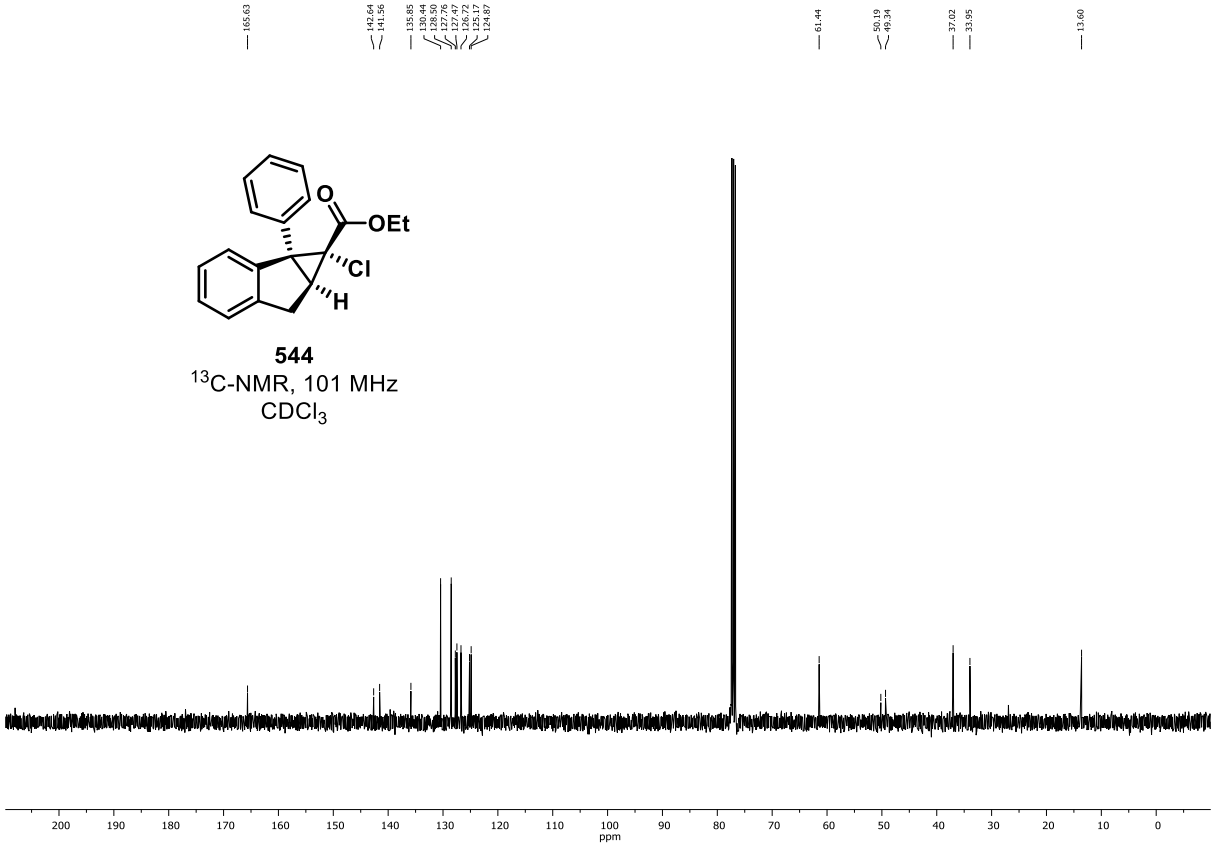

O
OEt
H
H
535
1H-NMR, 400 MHz
CDCl3
ppm



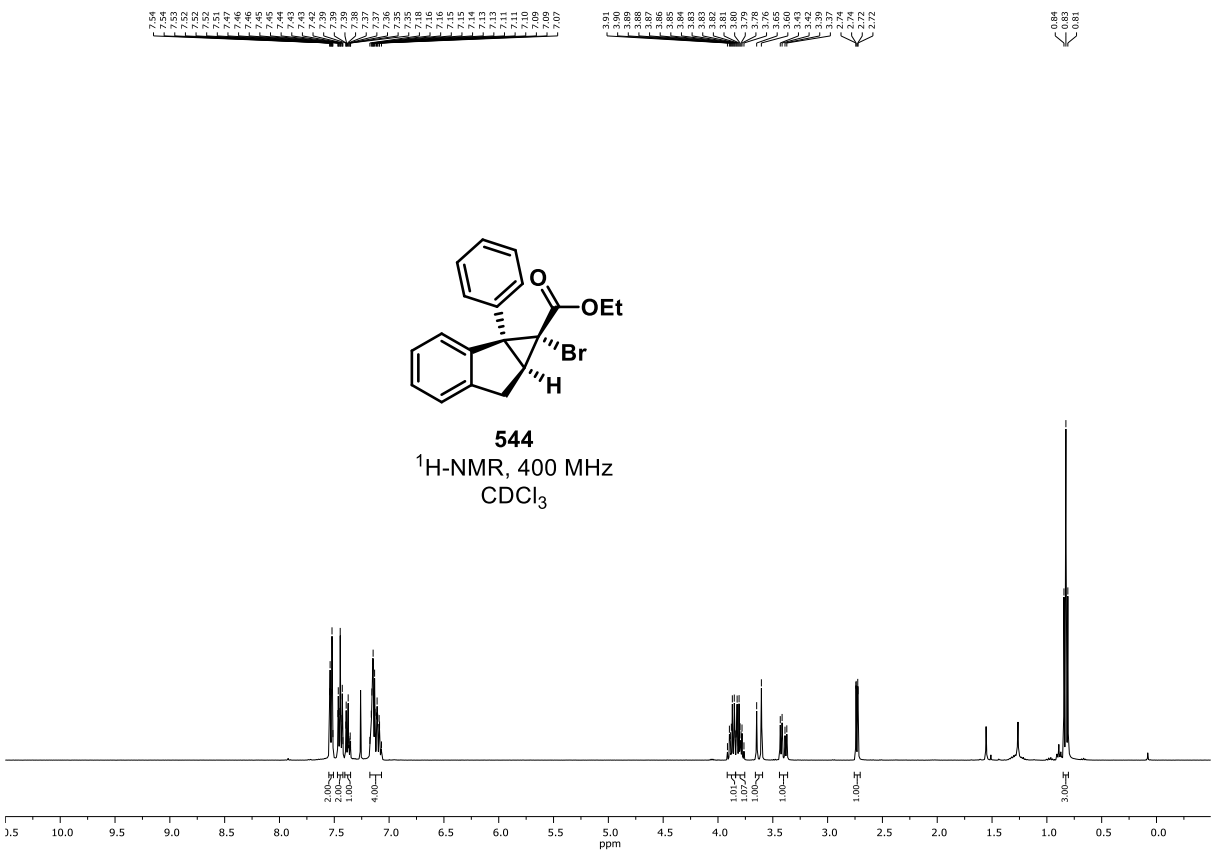
535
^{13}C-NMR, 101 MHz
$CDCl_3$



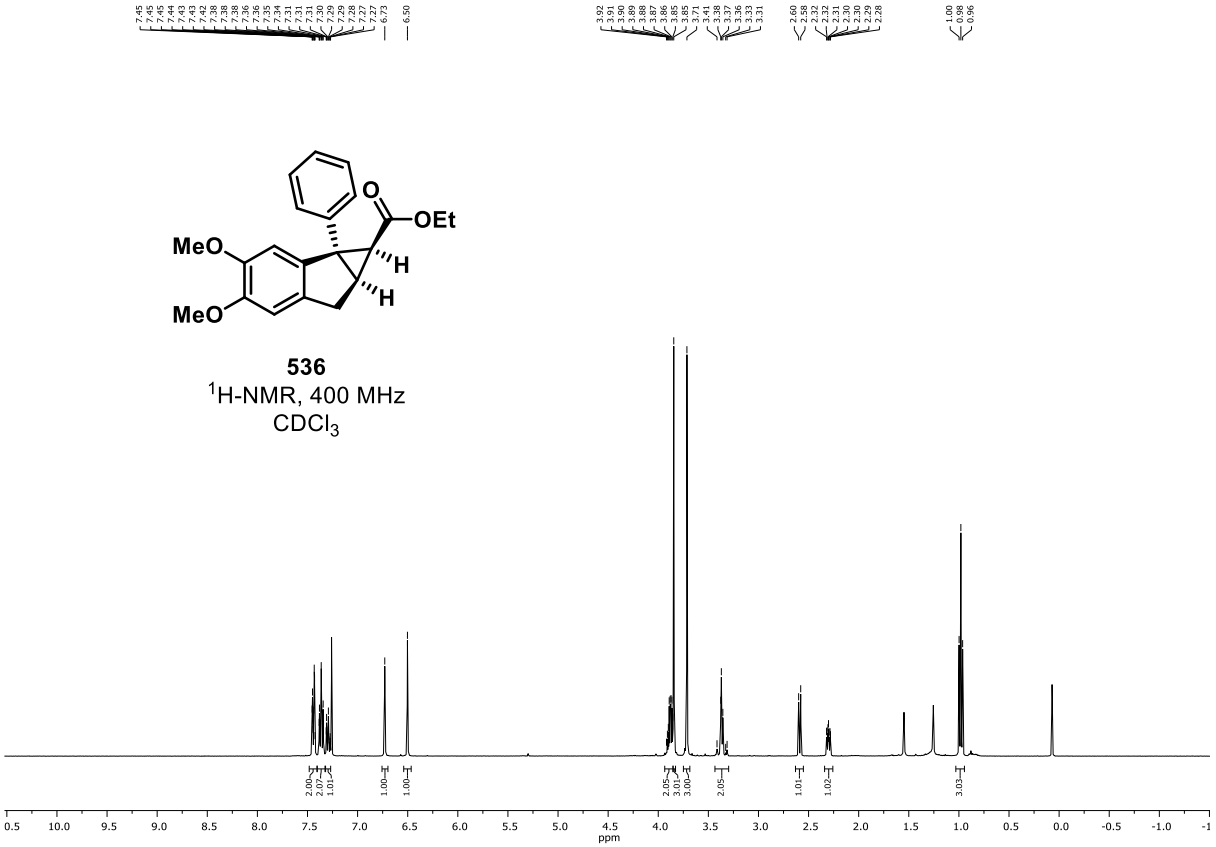
544
^{1}H-NMR, 400 MHz
$CDCl_3$

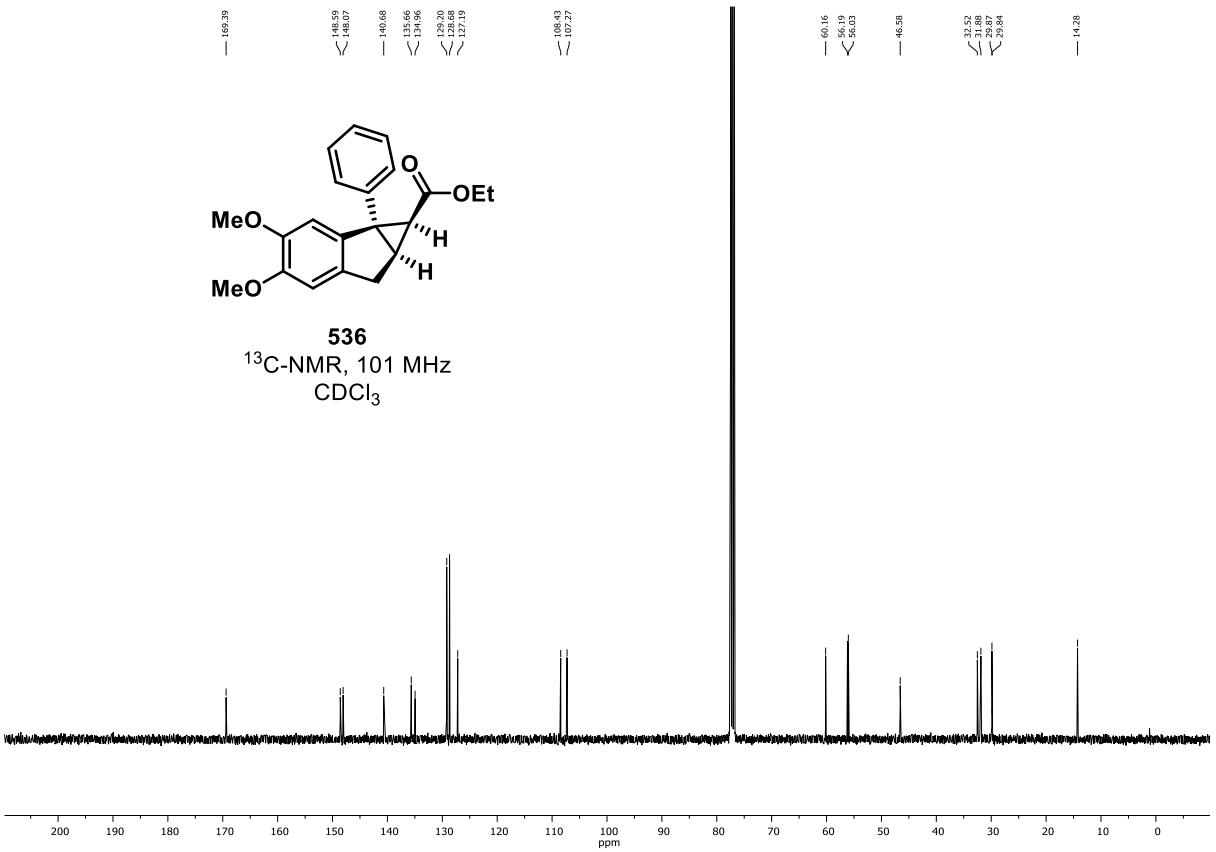


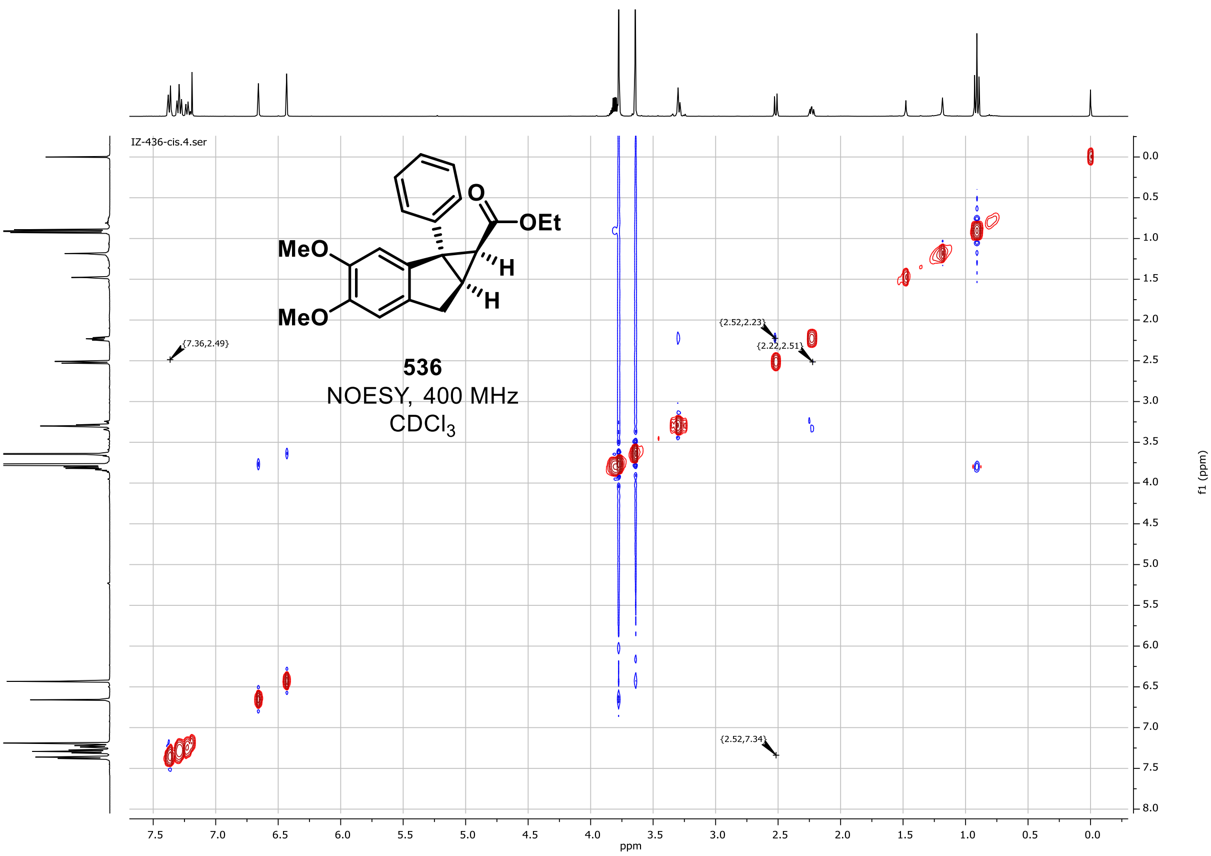
544
^{13}C-NMR, 101 MHz
$CDCl_3$

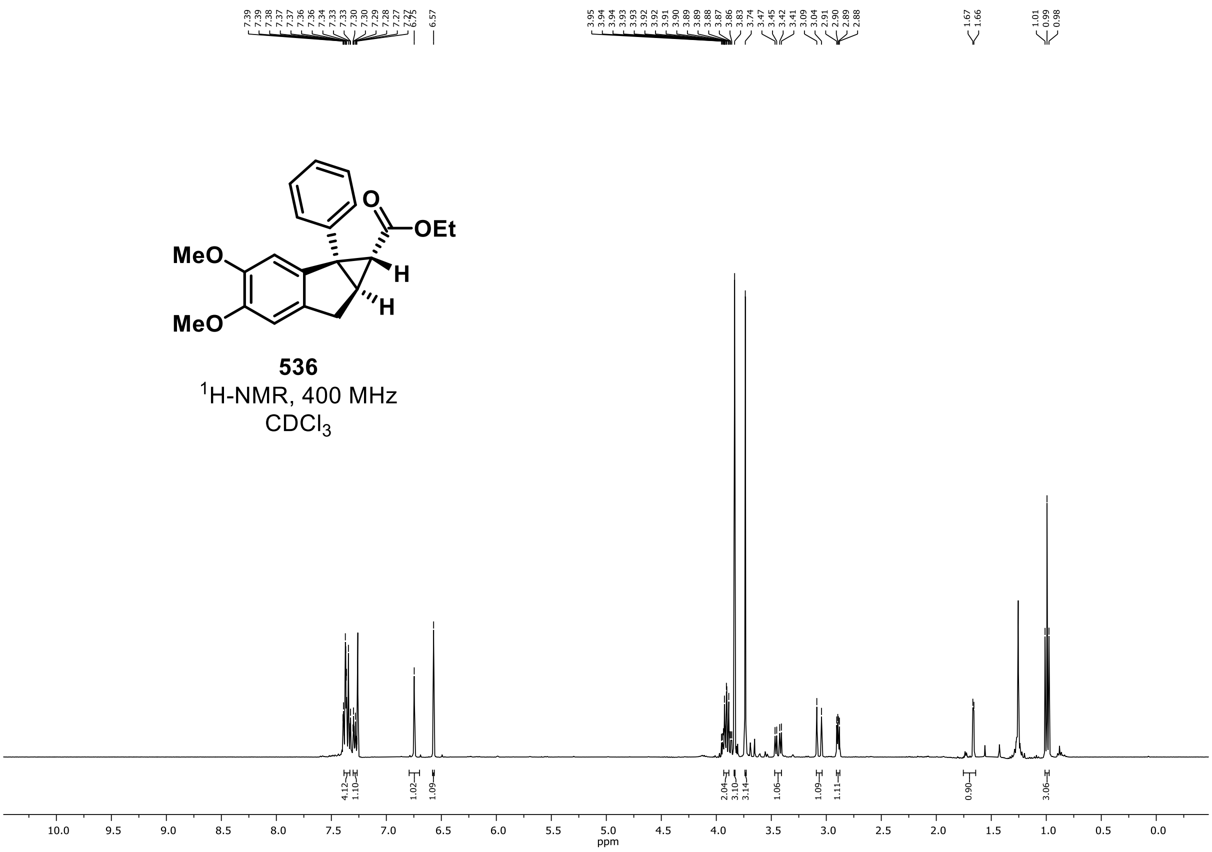


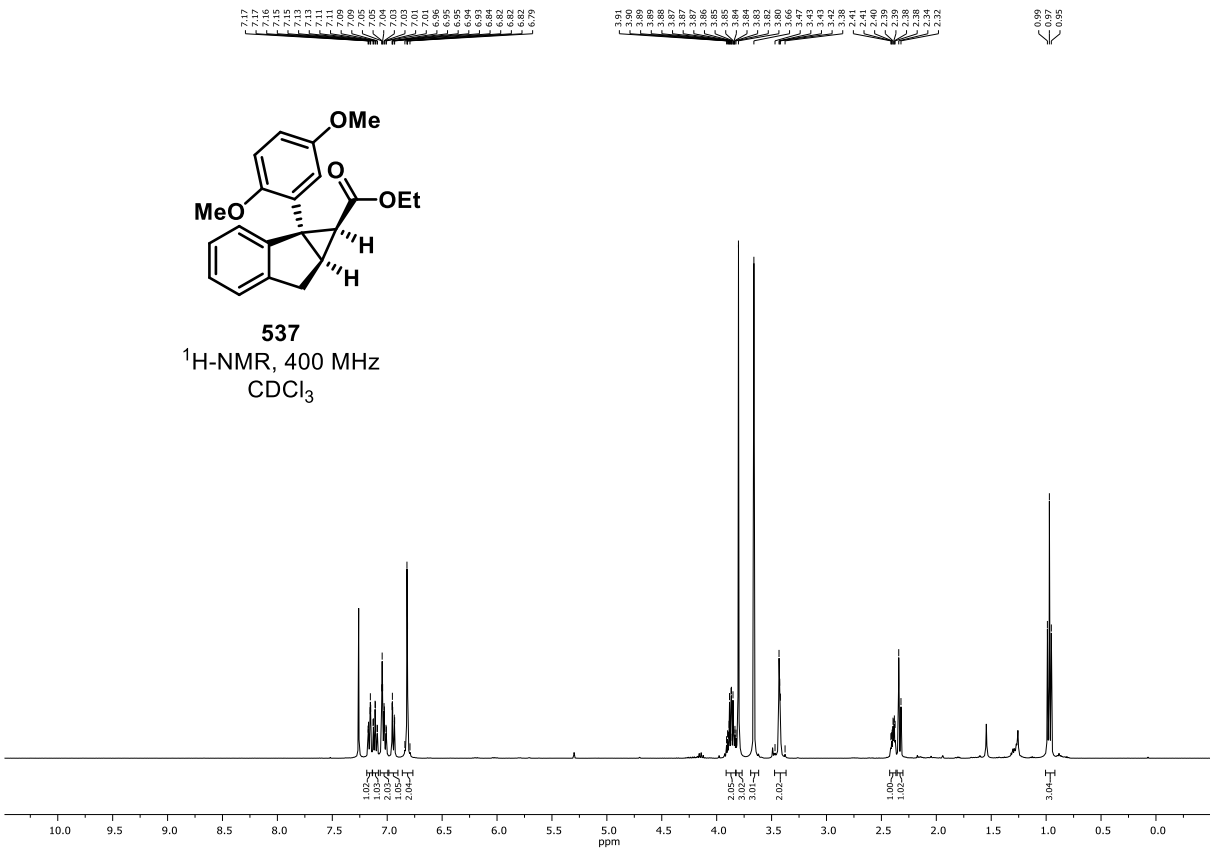
544
^{1}H-NMR, 400 MHz
$CDCl_3$


MeO
MeO
O
OEt
H
H
536
1H-NMR, 400 MHz
CDCl3
ppm

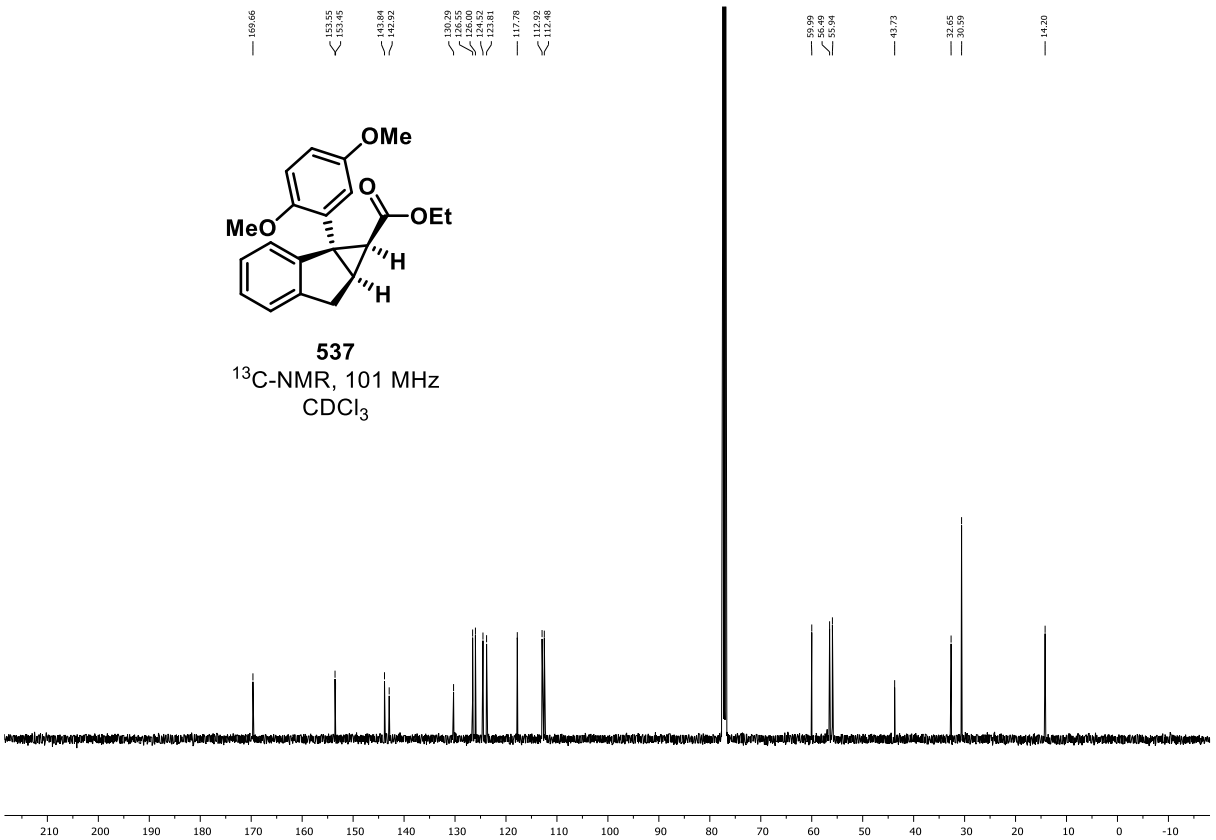

MeO
MeO
O
OEt
H
H
536
13C-NMR, 101 MHz
CDCl3
ppm


IZ-436-cis.4.ser
MeO
MeO
O
OEt
H
H
536
NOESY, 400 MHz
CDCl3
{7.36,2.49}
{2.52,2.23}
{2.22,2.51}
{2.52,7.34}
ppm
f1 (ppm)

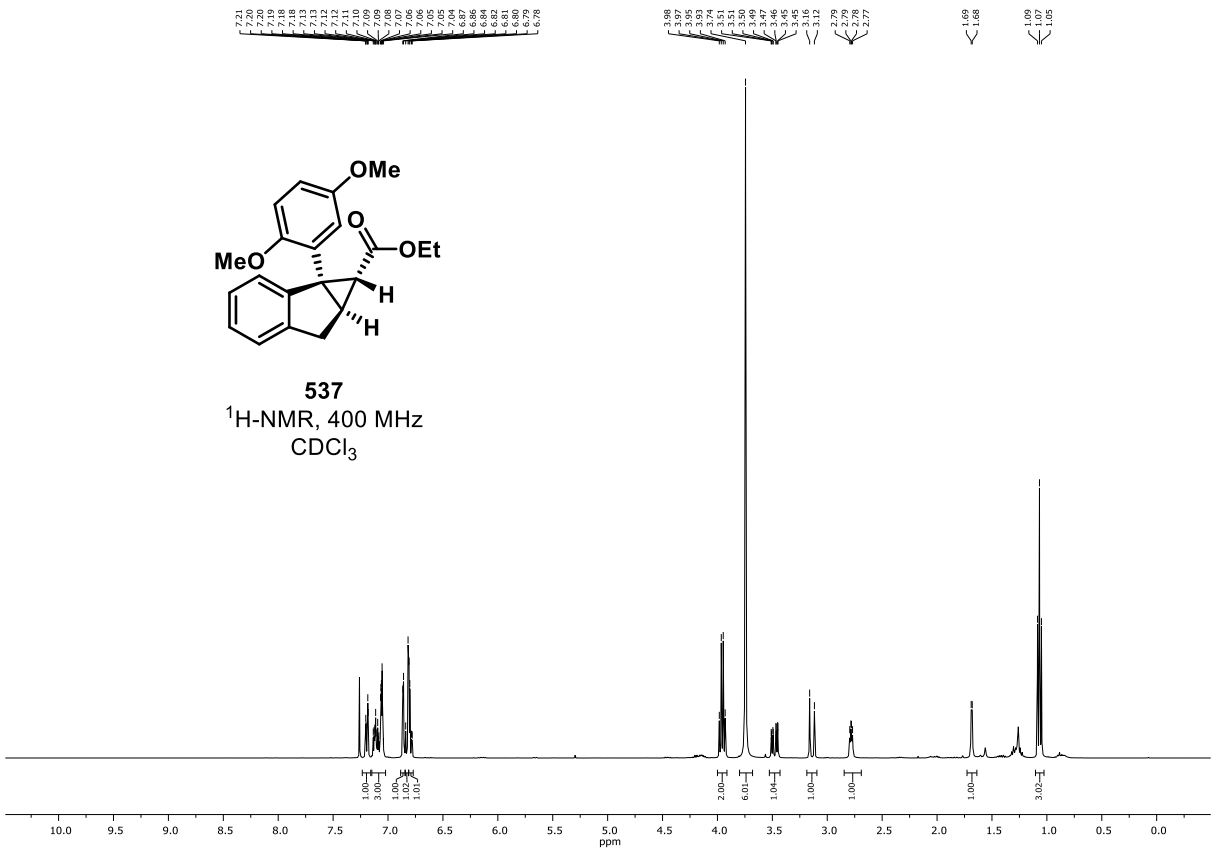

MeO
MeO
O
OEt
H
H
536
1H-NMR, 400 MHz
CDCl3
ppm



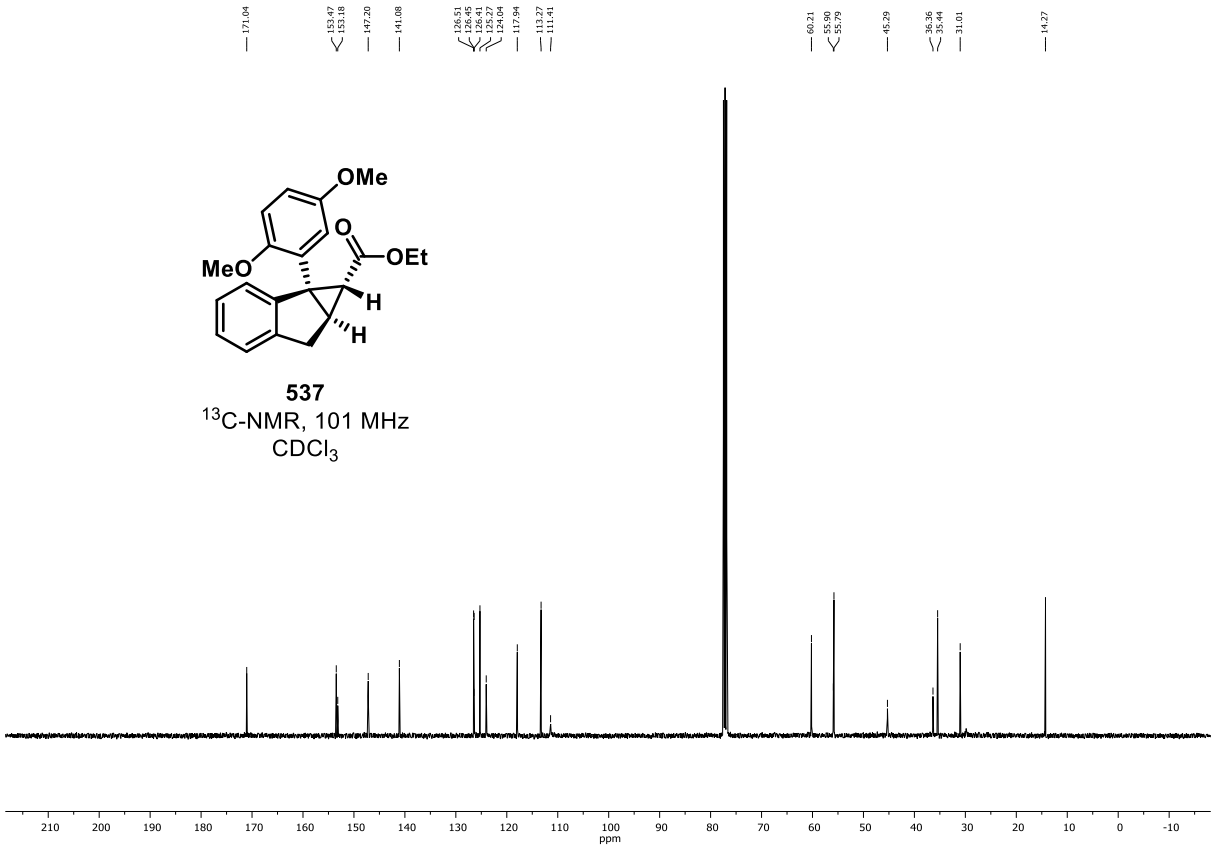
537
^{1}H-NMR, 400 MHz
$CDCl_3$



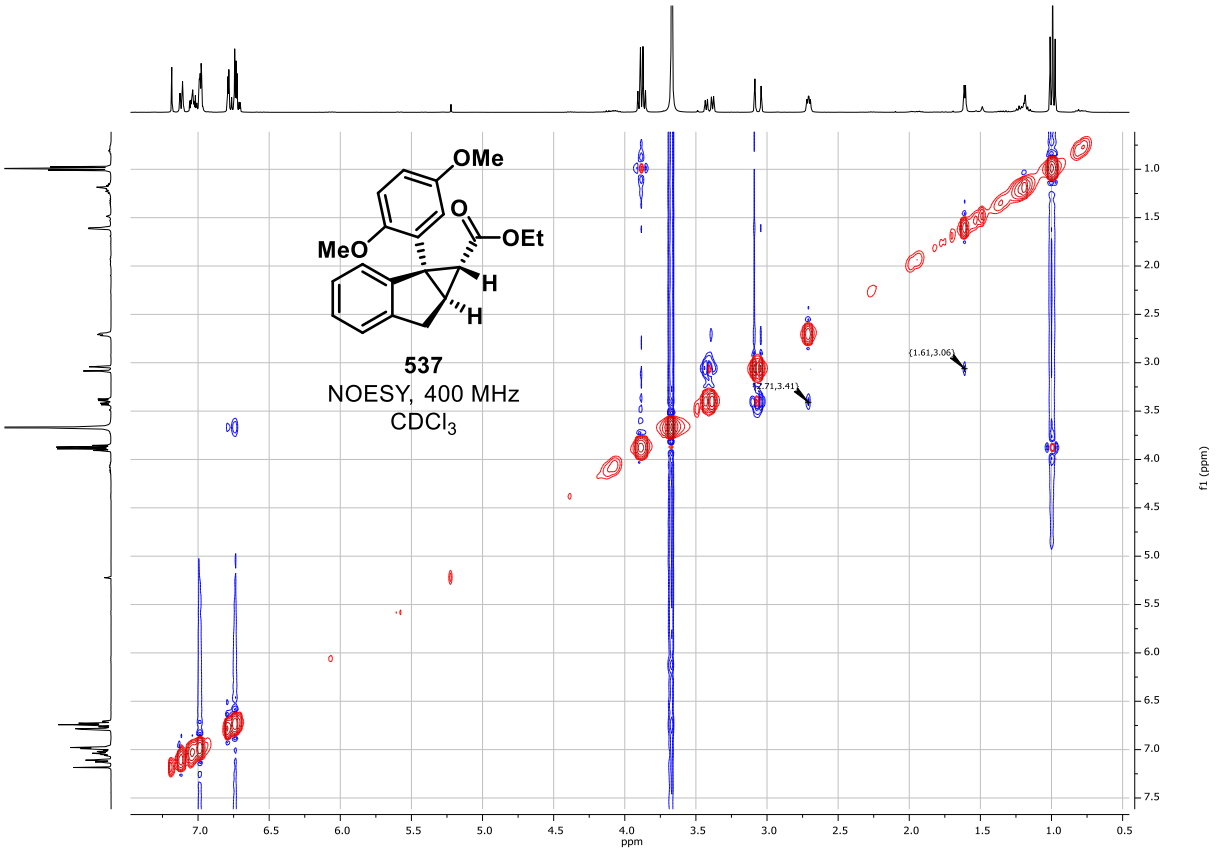
537
^{13}C-NMR, 101 MHz
$CDCl_3$



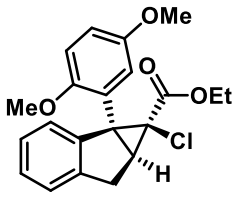
537
^{1}H-NMR, 400 MHz
$CDCl_3$



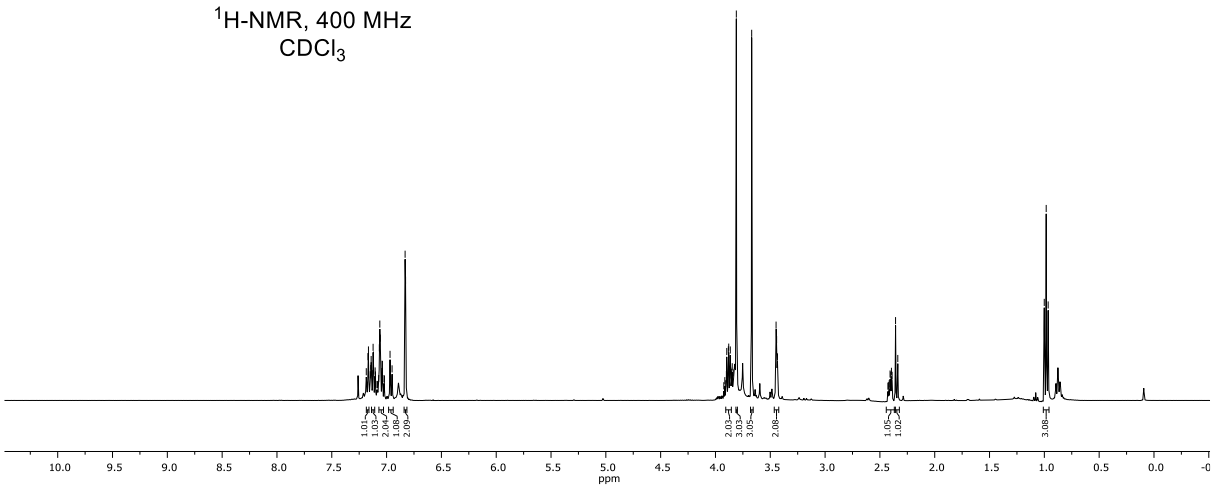
537
^{13}C-NMR, 101 MHz
$CDCl_3$

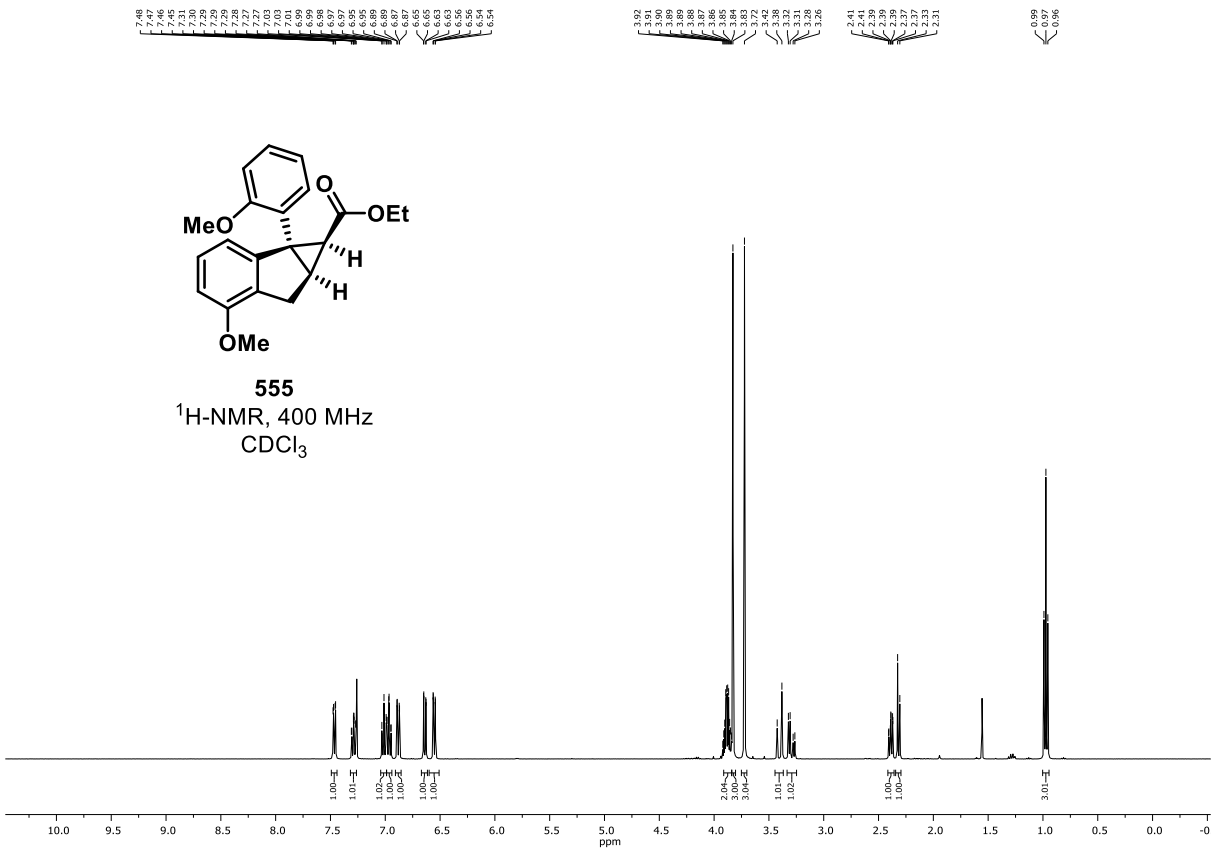


537
NOESY, 400 MHz
$CDCl_3$

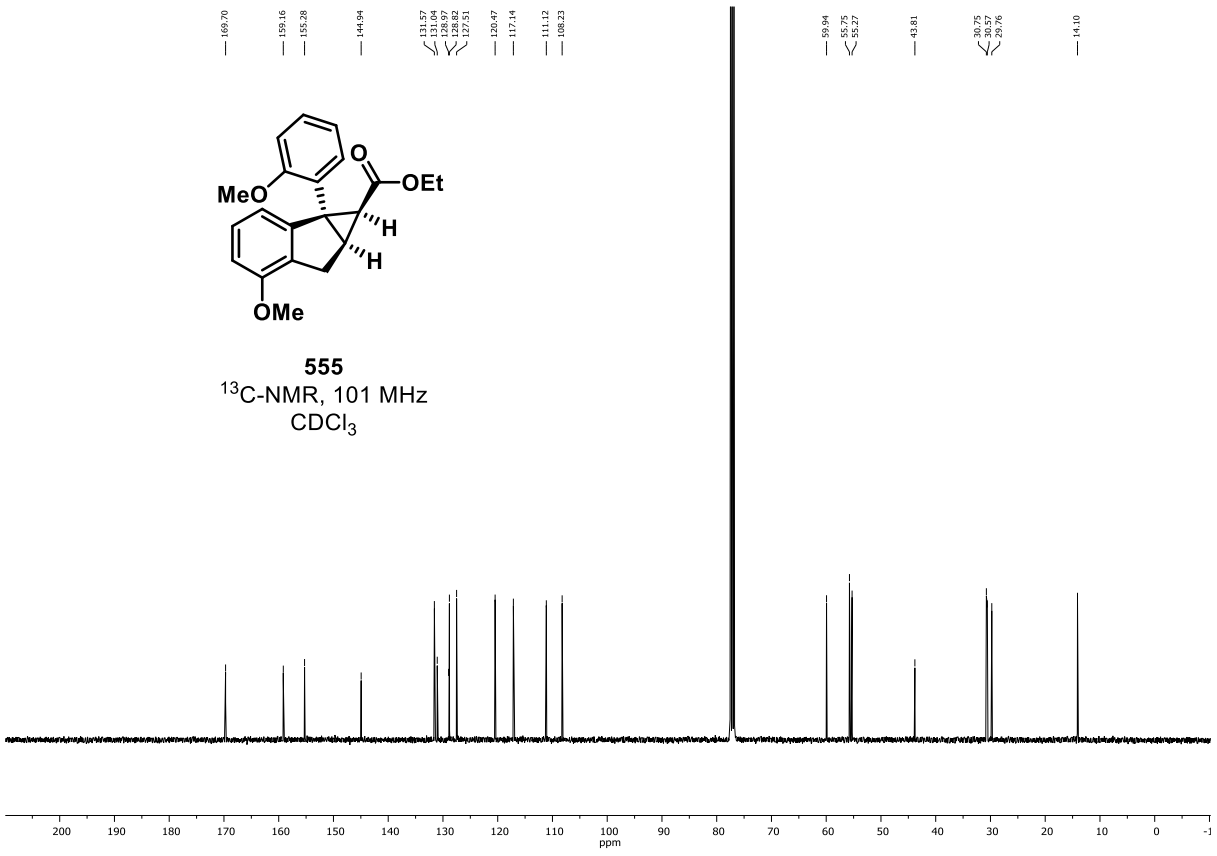


544
^{1}H-NMR, 400 MHz
$CDCl_3$

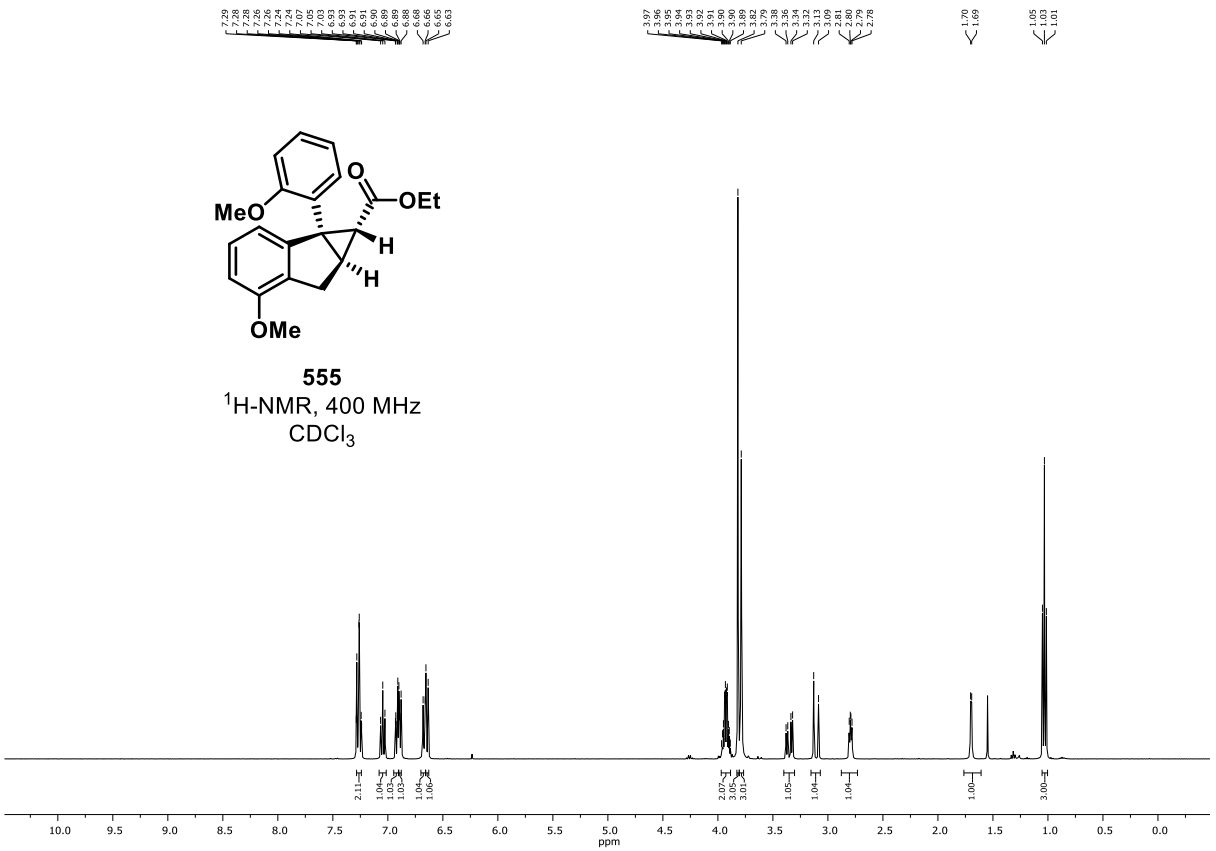




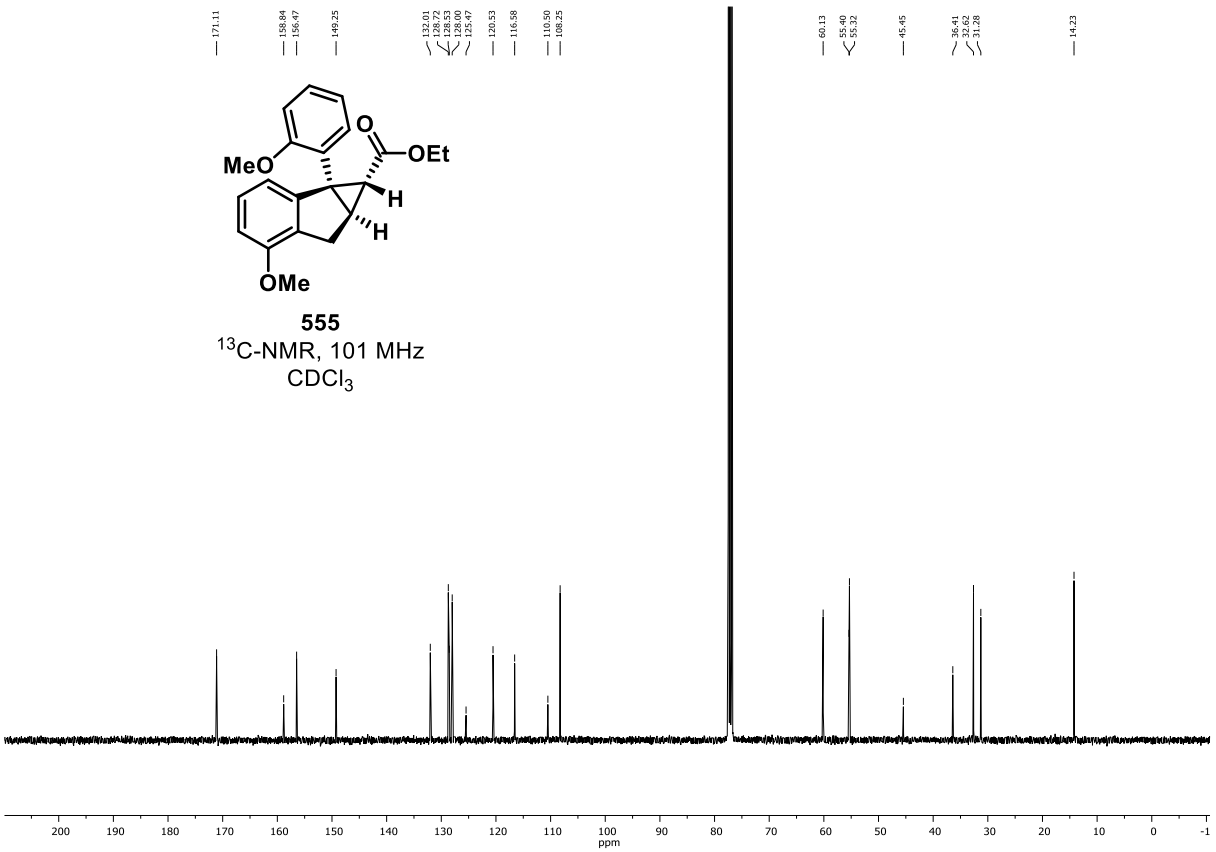
555
^{1}H-NMR, 400 MHz
$CDCl_3$



555
^{13}C-NMR, 101 MHz
$CDCl_3$



555
^{1}H-NMR, 400 MHz
$CDCl_3$



555
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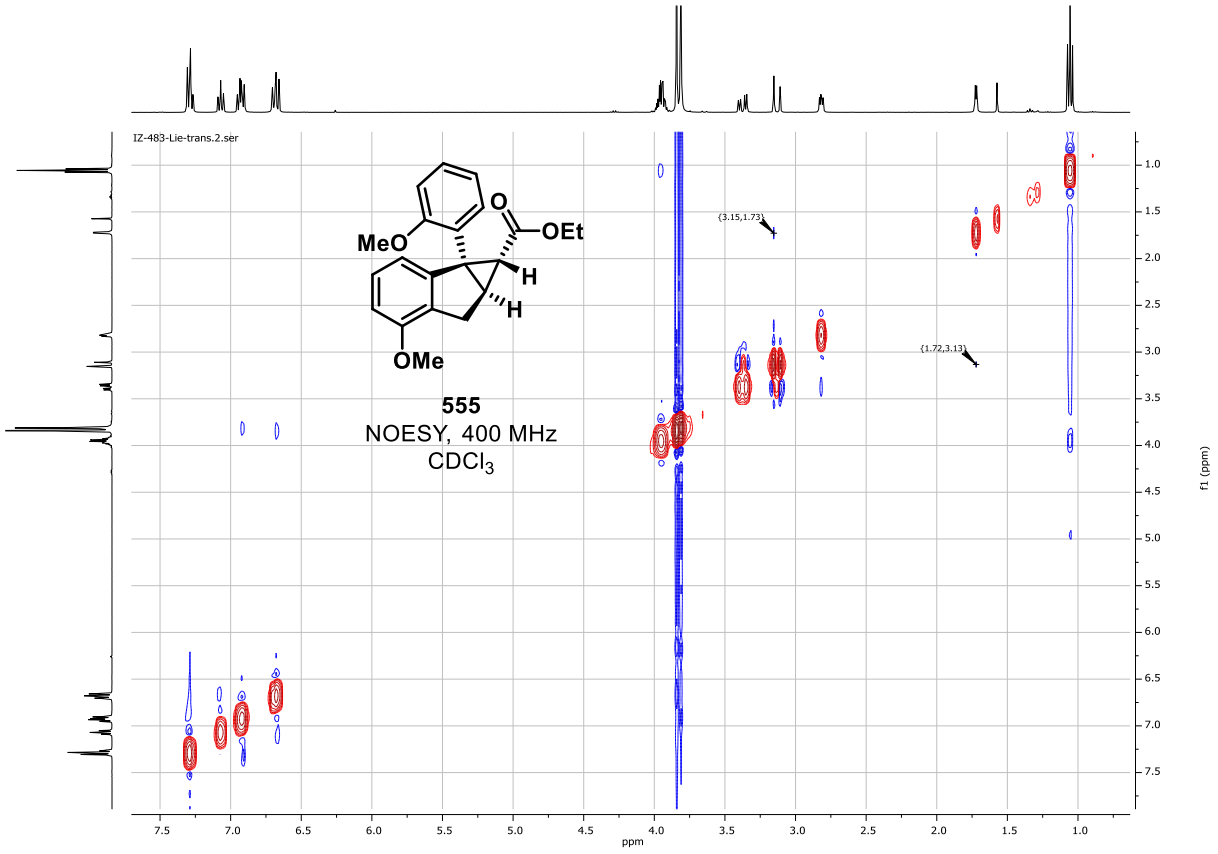
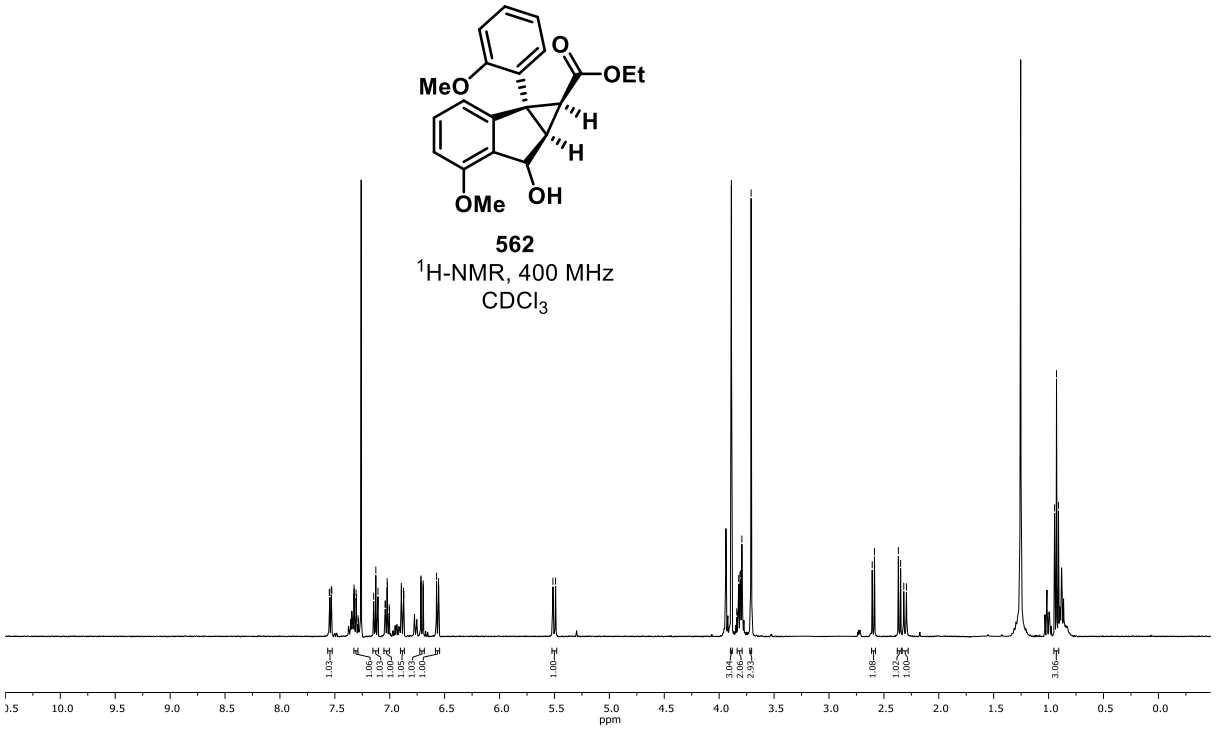
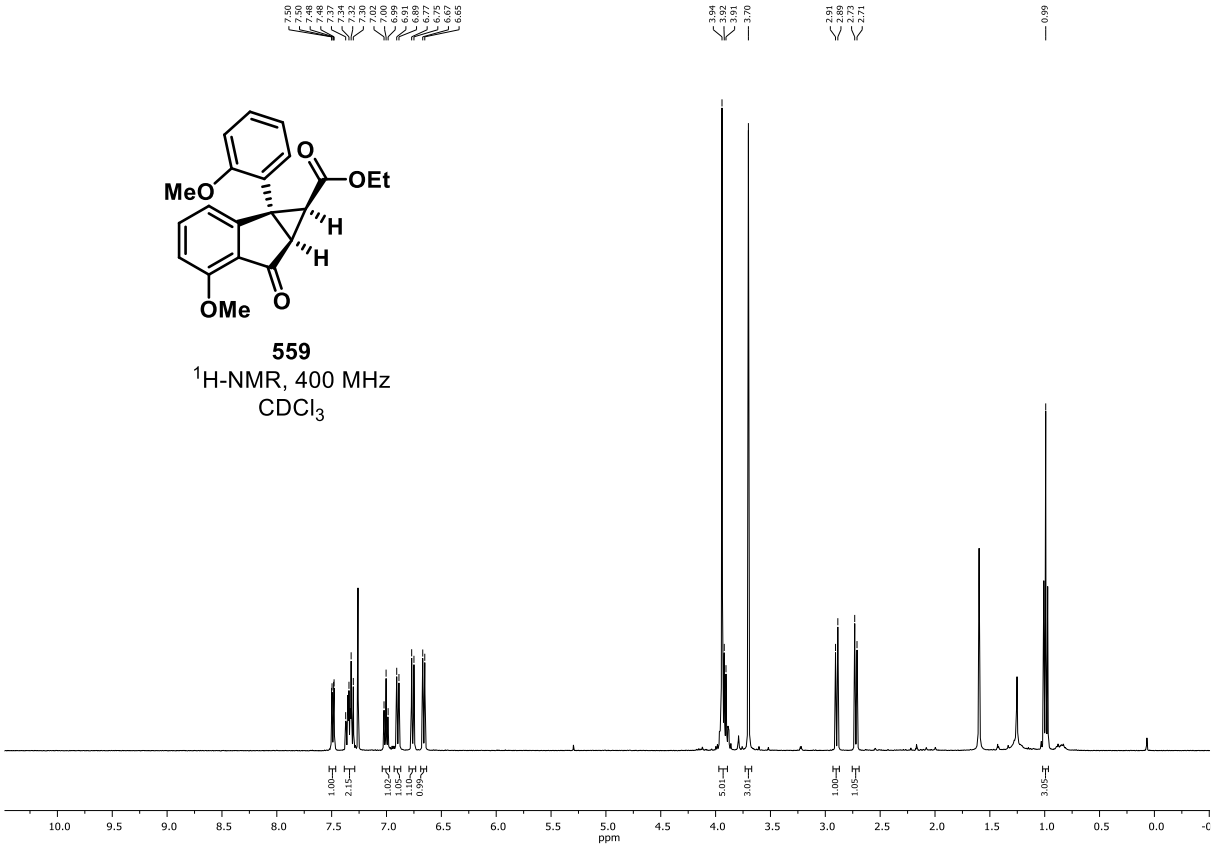
$CDCl_3$

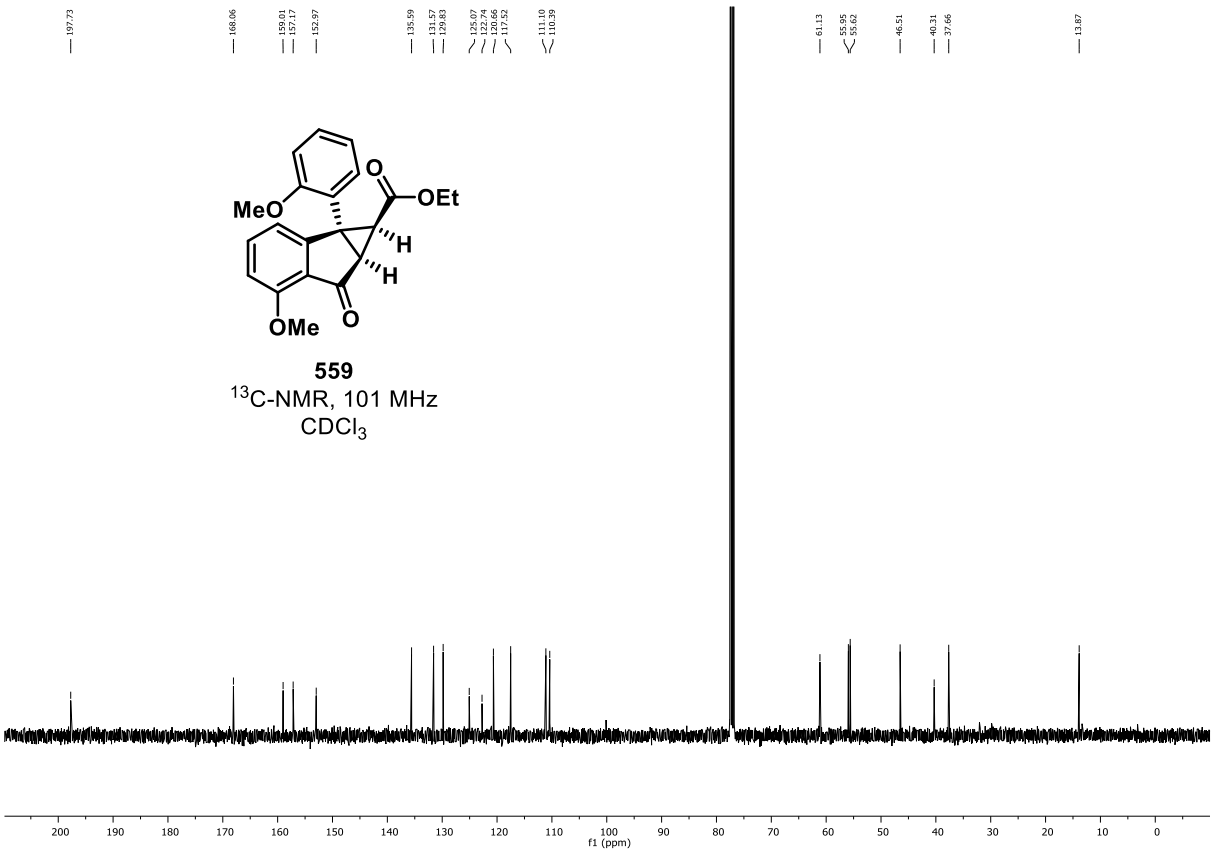


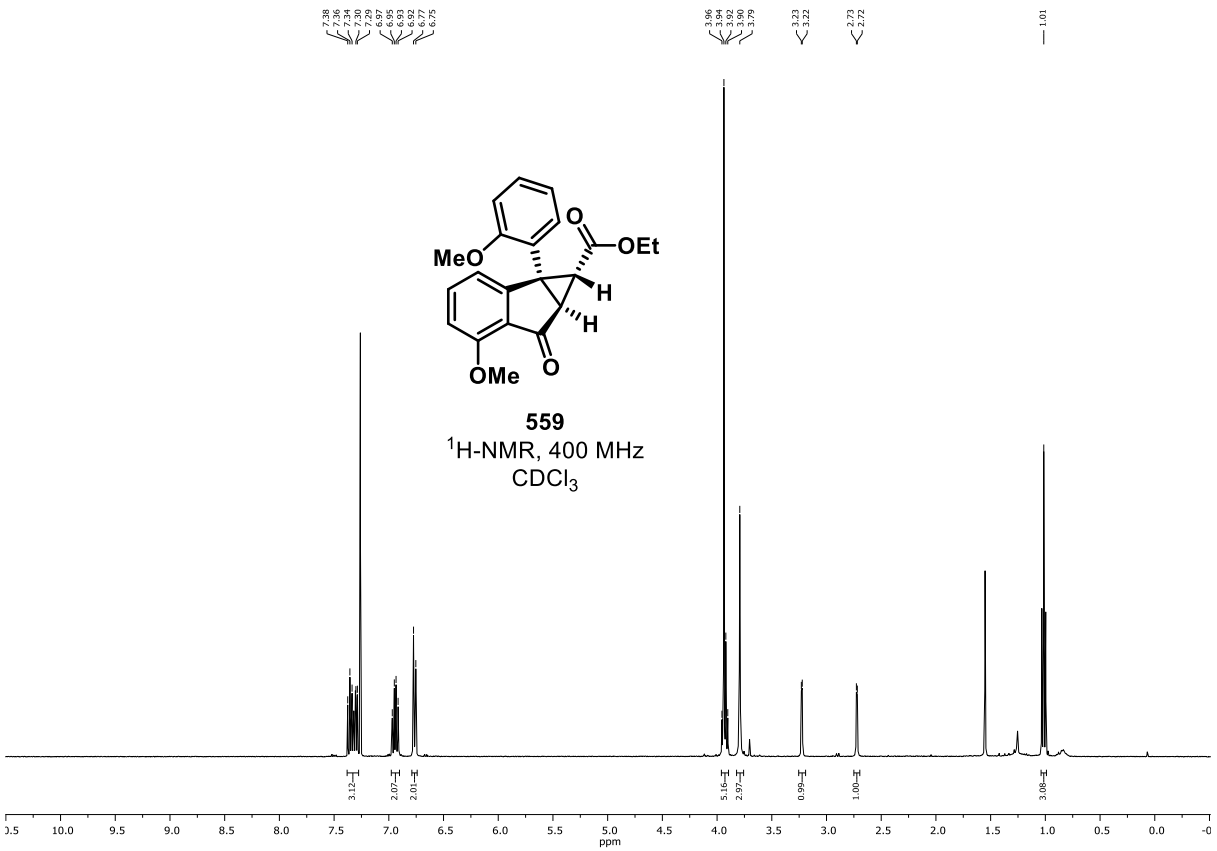
555
NOESY, 400 MHz
$CDCl_3$



562
^{1}H-NMR, 400 MHz
$CDCl_3$


MeO
O
OEt
H
H
O
OMe
559
1H-NMR, 400 MHz
CDCl3
ppm


MeO
O
OEt
H
H
O
OMe
559
13C-NMR, 101 MHz
CDCl3
f1 (ppm)



559
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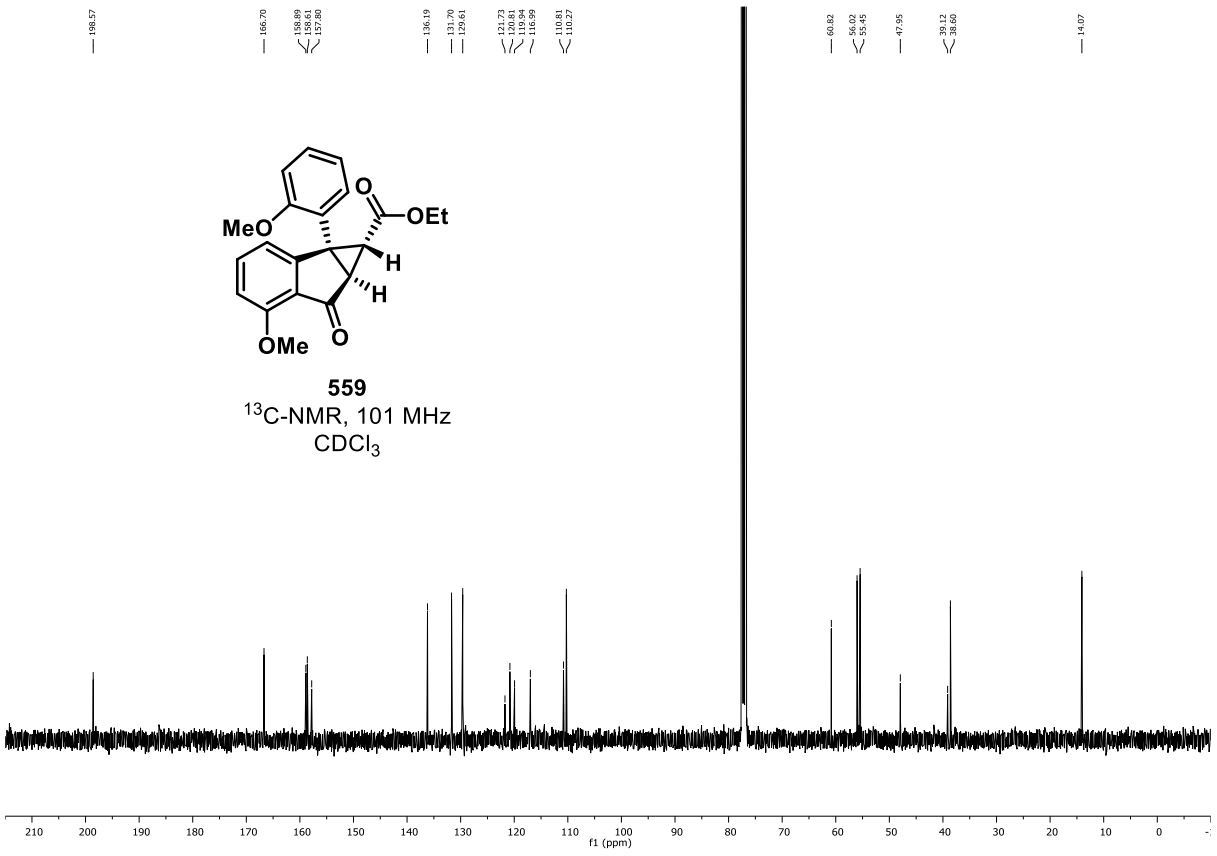

559
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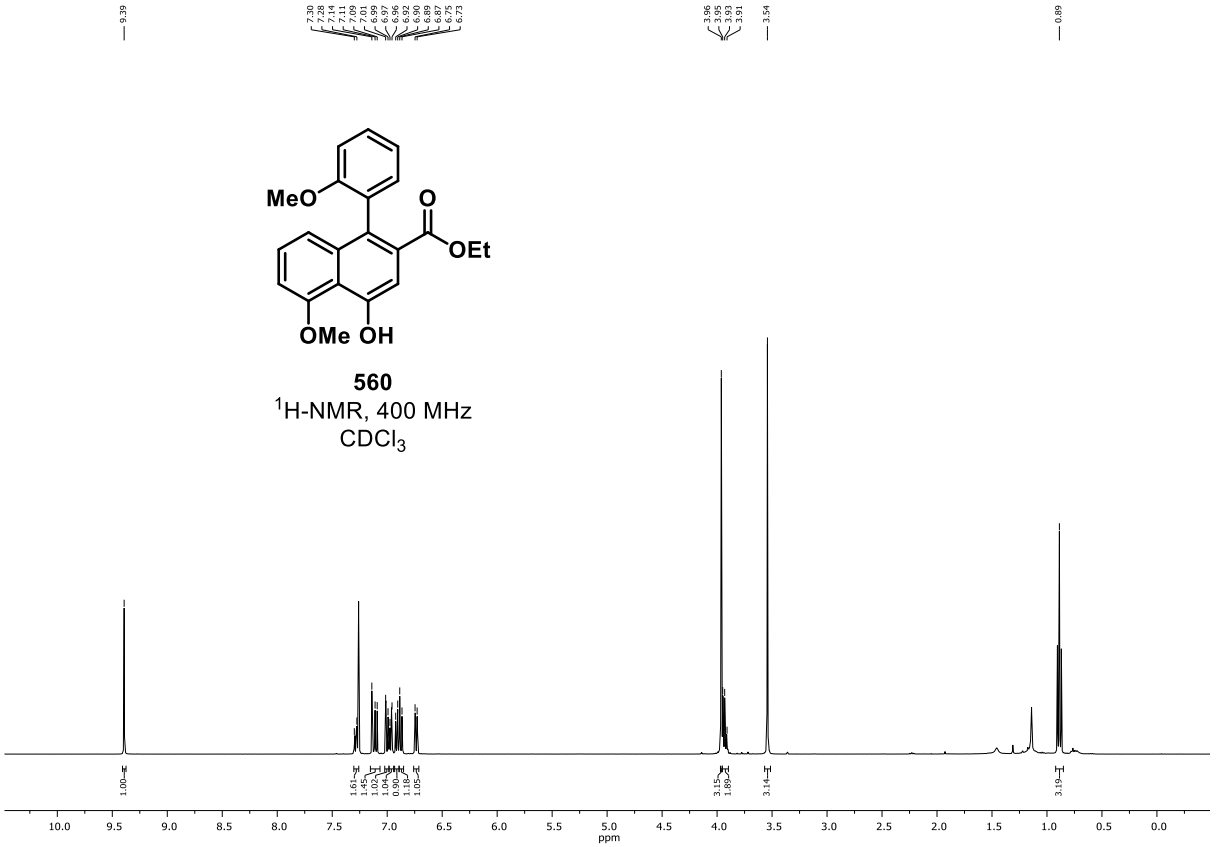
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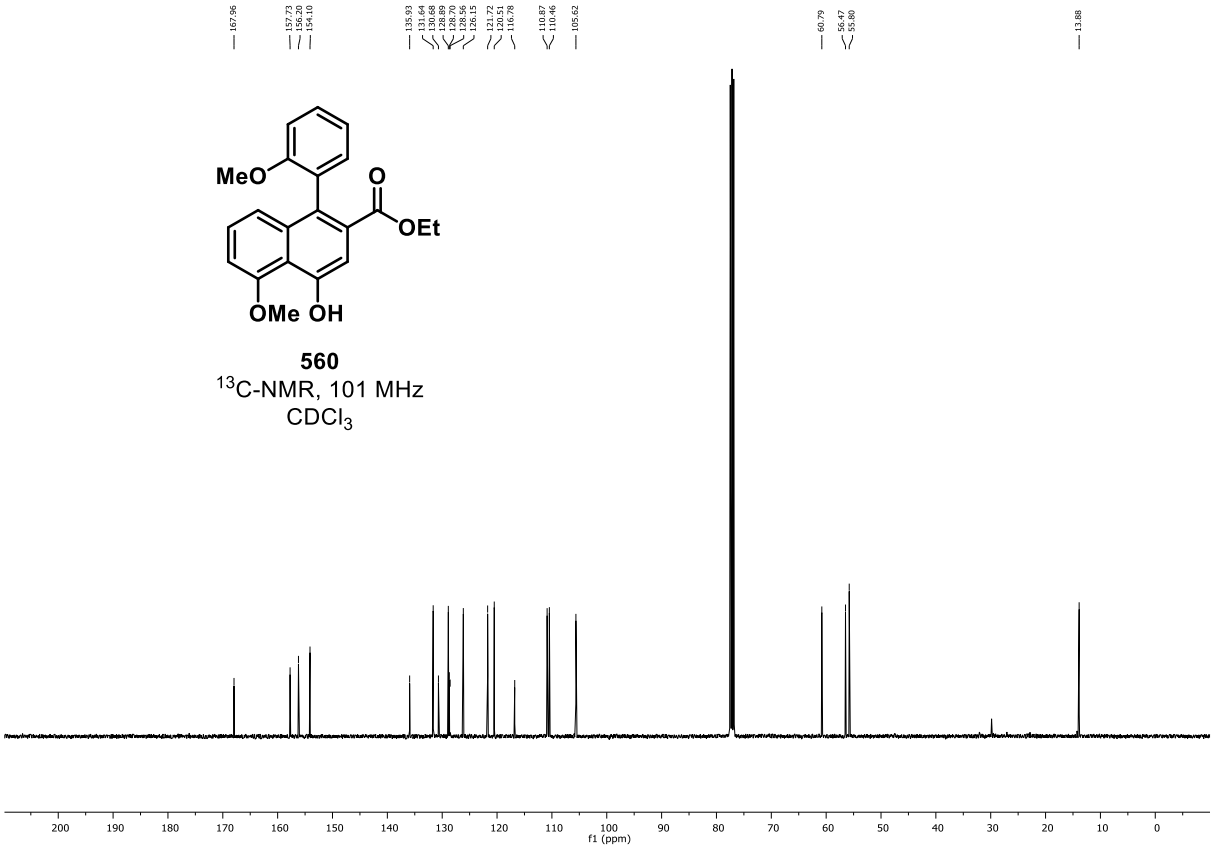
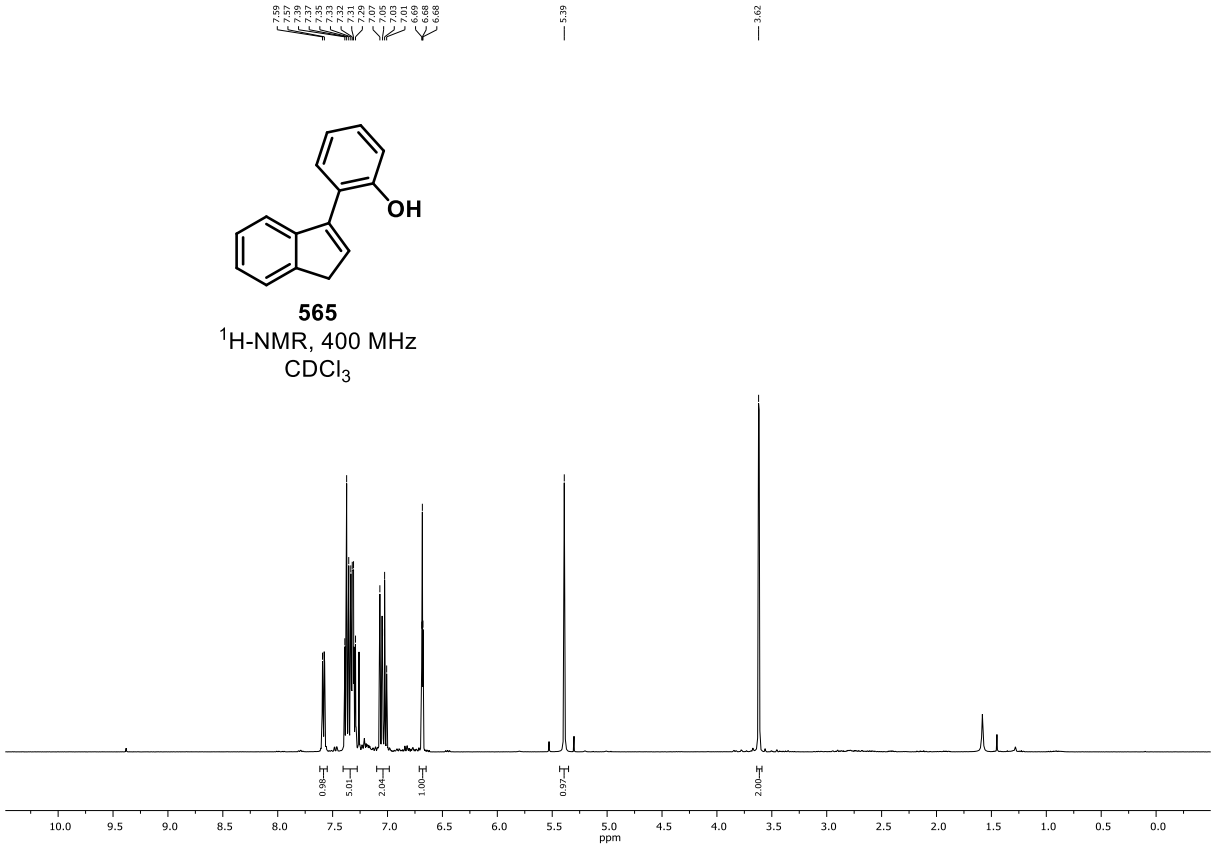
O
OEt
OMe OH
560
1H-NMR, 400 MHz
CDCl3
ppm


MeO
O
OEt
OMe OH
560
13C-NMR, 101 MHz
CDCl3
f1 (ppm)



565
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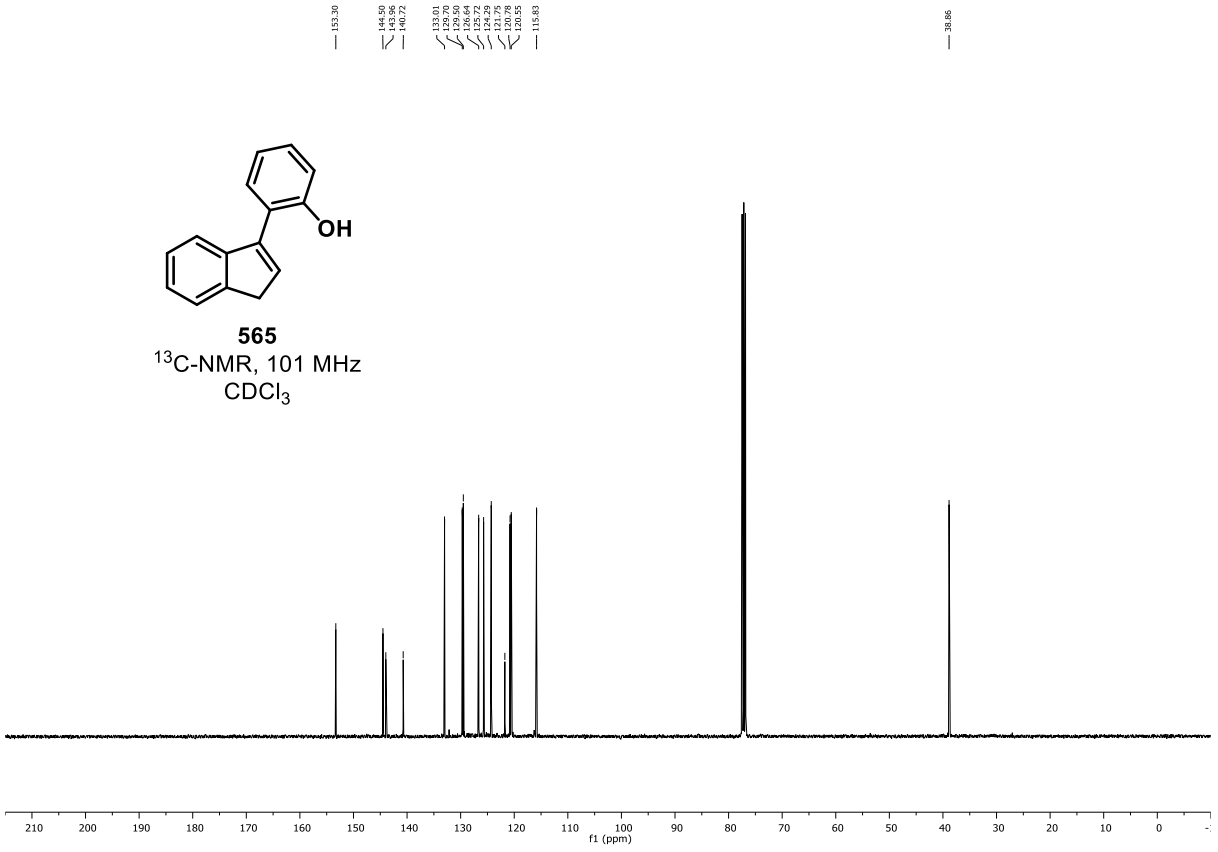
$CDCl_3$



565
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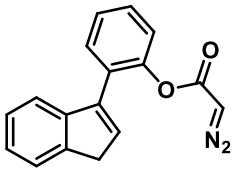
$CDCl_3$



567
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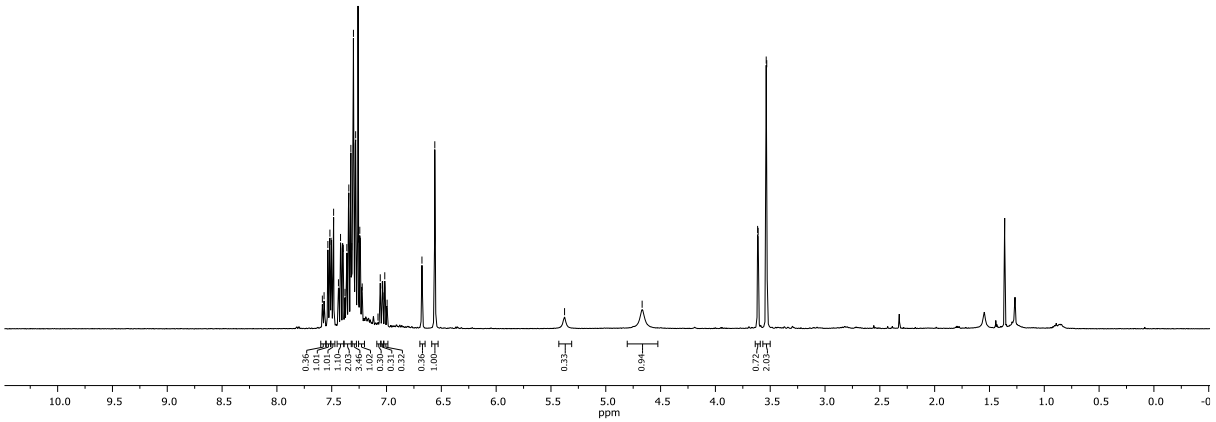
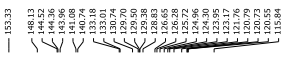
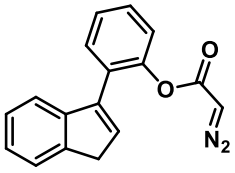
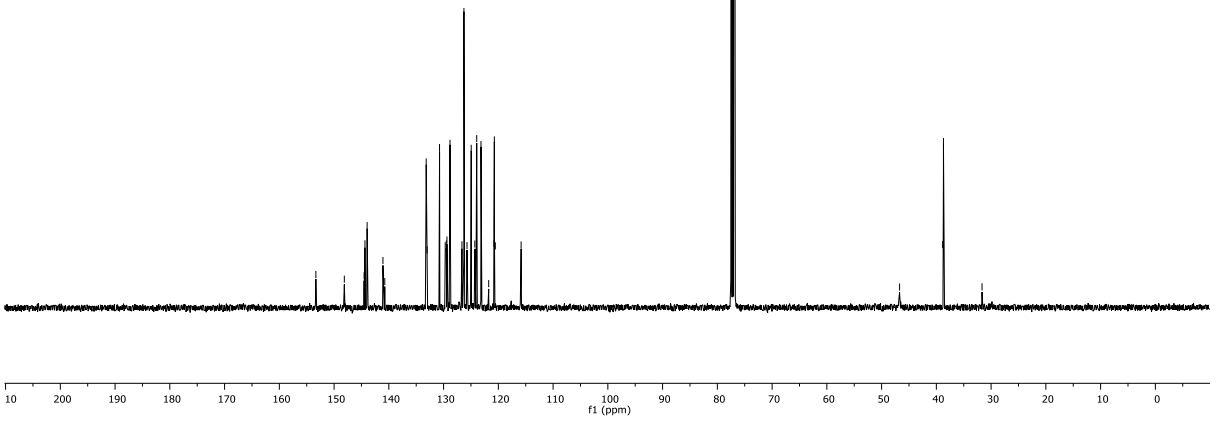
$CDCl_3$

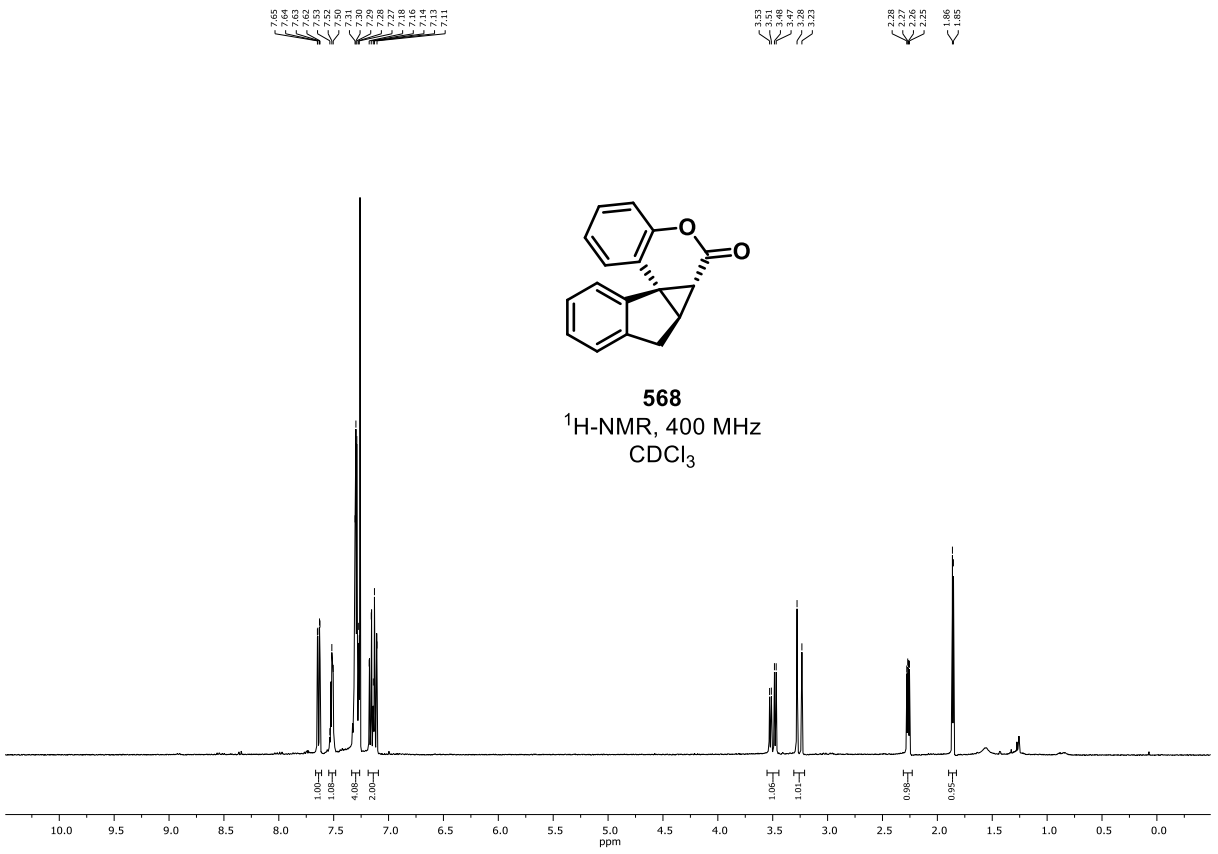






567
^{13}C-NMR, 101 MHz
$CDCl_3$





568
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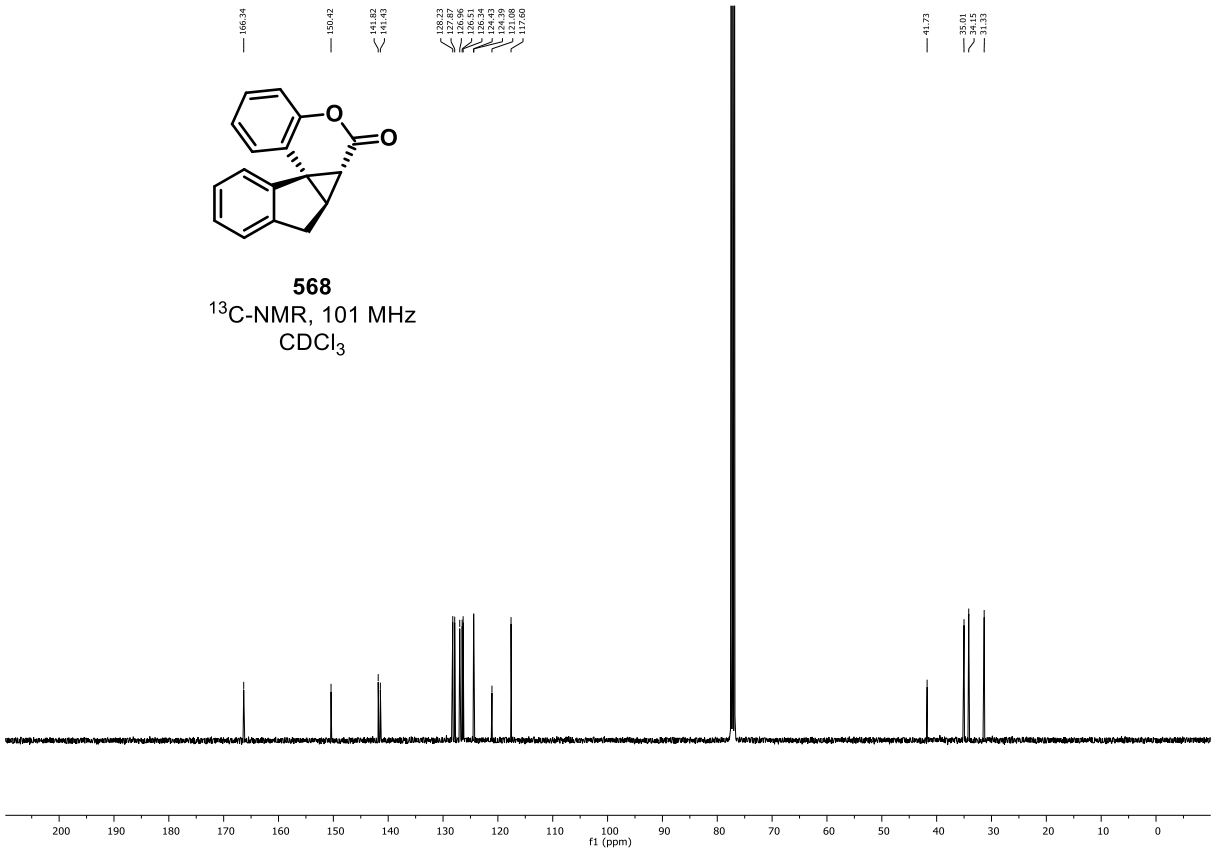
$CDCl_3$



568
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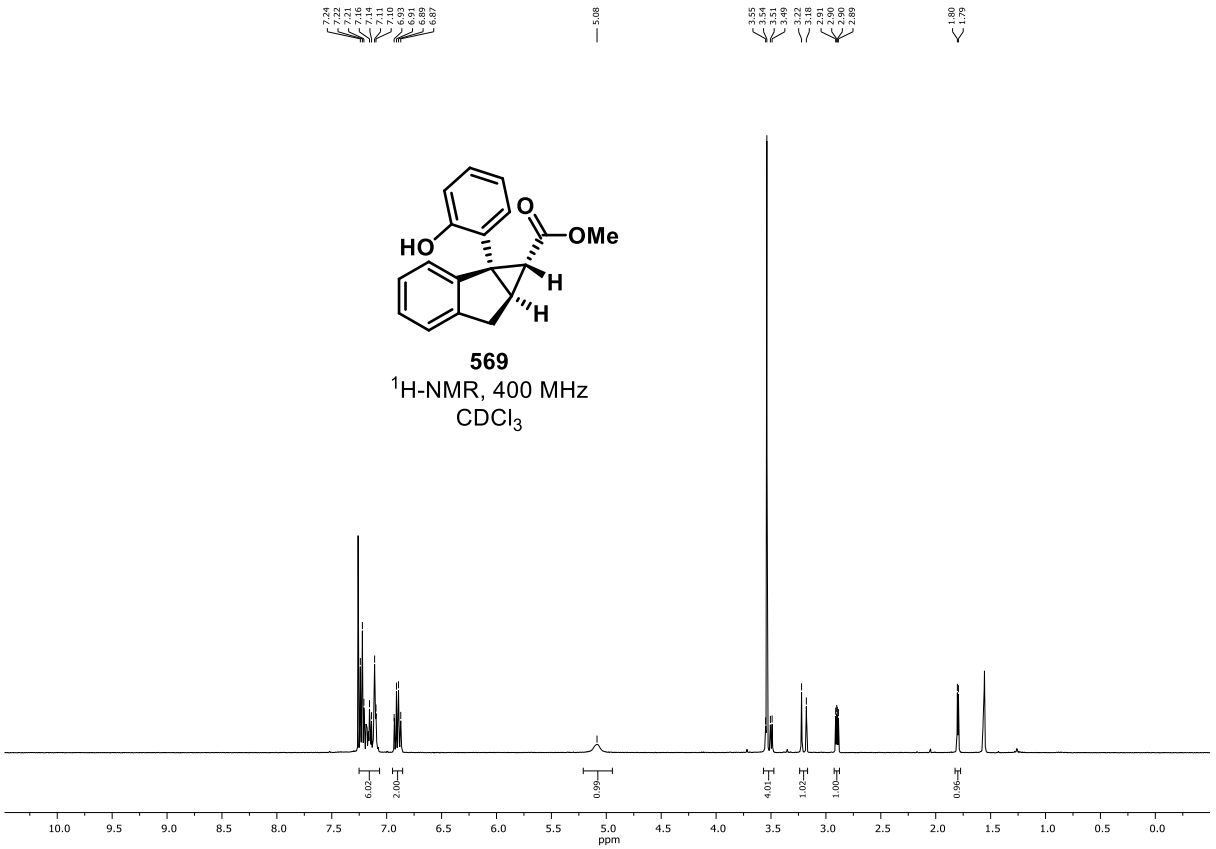
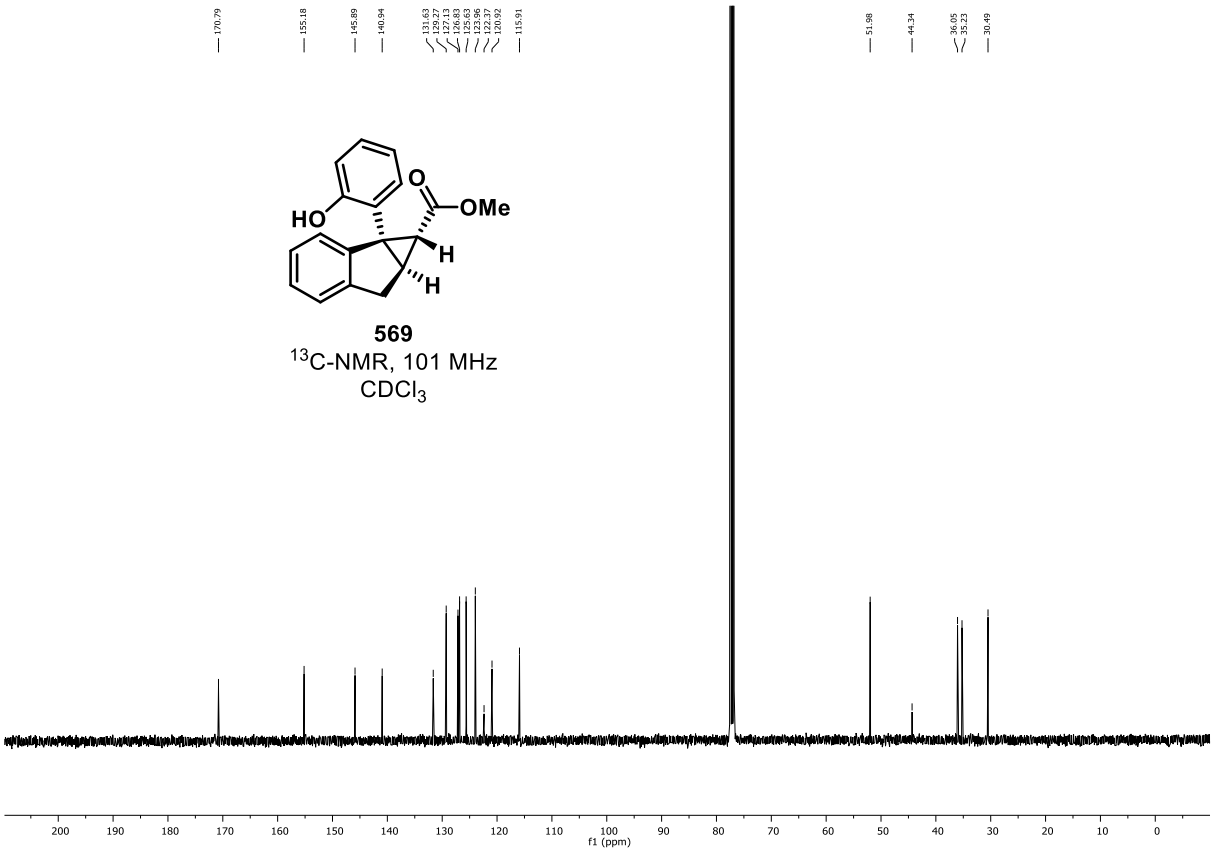
$CDCl_3$



569
^{1}H-NMR, 400 MHz
$CDCl_3$



569
^{13}C-NMR, 101 MHz
$CDCl_3$

10. Literature

[1] A. G. Perkin, *J. Chem. Soc., Trans.* **1898**, 1019.
[2] a) Hori M., Takita T., Koyama G., Tadeuchi T., Umezawa H., *J. Antibiot. (Tokyo)* **1964**, 96-99.; b) S.-A. Wang, Y. Ko, J. Zeng, Y. Geng, D. Ren, Y. Ogasawara, S. Irani, Y. Zhang, H.-W. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 6127.
[3] K. R. Darnall, L. B. Townsend, R. K. Robins, *Proceedings of the National Academy of Sciences of the United States of America* **1967**, *57*, 548.
[4] E. Dietrich, J. Powell, J. R. Taylor, *Drug design, development and therapy* **2013**, *7*, 1399.
[5] A. Cavezza, C. Boulle, A. Guéguiniat, P. Pichaud, S. Trouille, L. Ricard, M. Dalko-Csiba, *Bioorganic & medicinal chemistry letters* **2009**, *19*, 845.
[6] G. Yang, J. Schmieg, M. Tsuji, R. W. Franck, *Angew. Chem. Int. Ed.* **2004**, *43*, 3818.
[7] S. Lemaire, I. N. Houpis, T. Xiao, J. Li, E. Digard, C. Gozlan, R. Liu, A. Gavryushin, C. Diène, Y. Wang et al., *Organic letters* **2012**, *14*, 1480.
[8] M. Hocek, R. Pohl, B. Klepetářová, *Ann. Chem. Pharm.* **2005**, *2005*, 4525.
[9] M. Korb, H. Lang, *Chemical Society reviews* **2019**, *48*, 2829.
[10] T. Kometani, H. Kondo, Y. Fujimori, *Synthesis* **1988**, *1988*, 1005.
[11] T. Matsumoto, M. Katsuki, K. Suzuki, *Tetrahedron Letters* **1988**, *29*, 6935.
[12] D. Y.W. Lee, W.-Y. Zhang, V. V. R. Karnati, *Tetrahedron Letters* **2003**, *44*, 6857.
[13] A. Yepremyan, T. G. Minehan, *Organic & biomolecular chemistry* **2012**, *10*, 5194.
[14] a) B. Aebischer, J. H. Bieri, R. Prewo, A. Vasella, *Helv. Chim. Acta* **1982**, *65*, 2251; b) K. Luthman, M. Orbe, T. Waglund, A. Claesson, *J. Org. Chem.* **1987**, *52*, 3777.
[15] P. Lesimple, J.-M. Beau, P. Sinaÿ, *Carbohydrate Research* **1987**, *171*, 289.
[16] K. Kitamura, Y. Ando, T. Matsumoto, K. Suzuki, *Chem. Rev.* **2018**, *118*, 1495.
[17] a) K. A. Parker, C. A. Coburn, *J. Am. Chem. Soc.* **1991**, *113*, 8516; b) K. A. Parker, C. A. Coburn, P. D. Johnson, P. Aristoff, *J. Org. Chem.* **1992**, *57*, 5547.
[18] A. K. Singh, V. K. Kanaujiya, V. Tiwari, S. Sabiah, J. Kandasamy, *Organic letters* **2020**, *22*, 7650.
[19] J. Ramnauth, O. Poulin, S. Rakhit, S. P. Maddaford, *Organic letters* **2001**, *3*, 2013.
[20] S. N. Thorn, T. Gallagher, *Synlett* **1996**, *1996*, 185.
[21] H.-H. Li, X.-S. Ye, *Organic & biomolecular chemistry* **2009**, *7*, 3855.
[22] R. N. Farr, D. I. Kwok, G. D. Daves, *J. Org. Chem.* **1992**, *57*, 2093.
[23] M. A. Tius, X. Q. Gu, J. Gomez-Galeno, *J. Am. Chem. Soc.* **1990**, *112*, 8188.
[24] R. A. Outten, G. D. Daves, *J. Org. Chem.* **1987**, *52*, 5064.
[25] M. Sezaki, S. Kondo, K. Maeda, H. Umezawa, M. Ohno, *Tetrahedron* **1970**, *26*, 5171.
[26] J. Rohr, R. Thiericke, *Natural product reports* **1992**, *9*, 103.
[27] S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, *Chemical Society reviews* **2015**, *44*, 7591.
[28] T. Bililign, B. R. Griffith, J. S. Thorson, *Natural product reports* **2005**, *22*, 742.
[29] K. Kojiri, H. Arakawa, F. Satoh, K. Kawamura, A. Okura, H. Suda, M. Okanishi, *The Journal of antibiotics* **1991**, *44*, 1054.
[30] S. Nakajima, K. Kojiri, H. Suda, M. Okanishi, *The Journal of antibiotics* **1991**, *44*, 1061.
[31] F. Strelitz, H. Flon, I. N. Asheshov, *J. Bacteriol.* **1955**, *69*, 280.
[32] Philip, J. E., Schenck, J. R., *Antibiot. Chemother.* **1953**, 1218.
[33] K. Hatano, E. Hagashide, Y. Kameda, S. Horii, M. Shibata, *Annual Meeting of the Agricultural Chemical Society. Abstracts of Papers*, **1971**, p. 363.
[34] G. F. Gauze, M. A. Sveshnikova, T. S. Maksimova, O. L. Ol'khovatova, V. S. Bazhanov, *Antibiotiki* **1977**, *22*, 963.

[35] M. G. Brazhnikova, M. K. Kudinova, V. V. Kuliaeva, N. P. Potapova, V. I. Ponomarenko, *Antibiotiki* **1977**, *22*, 967.
[36] Kulyaeva V.V., Kudinova M.K., Potapova N.P., Rubasheva L.M., Brazhnikova M.G., Rozynov B.Y., Bekker A.R., *Bioorg. Khim.* **1978**, 1087-1092.
[37] J. Yoshimura, N. Hong, K.-i. Sato, *Chem. Lett.* **1980**, *9*, 1131.
[38] K. Hatano, E. Higashide, M. Shibata, Y. Kameda, S. Horii, K. Mizuno, *Agric. Biol. Chem.* **1980**, *44*, 1157.
[39] S. Horii, H. Fukase, E. Mizuta, K. Hatano, K. Mizuno, *Chem. Pharm. Bull.* **1980**, *28*, 3601.
[40] H. Nakano, Y. Matsuda, K. Ito, S. Ohkubo, M. Morimoto, F. Tomita, *The Journal of antibiotics* **1981**, *34*, 266.
[41] K. Takahashi, M. Yoshida, F. Tomita, K. Shirahata, *The Journal of antibiotics* **1981**, *34*, 271.
[42] M. Morimoto, S. Okubo, F. Tomita, H. Marumo, *The Journal of antibiotics* **1981**, *34*, 701.
[43] K. Takahashi, F. Tomita, *The Journal of antibiotics* **1983**, *36*, 1531.
[44] N. Hirayama, K. Takahashi, K. Shirahata, Y. Ohashi, Y. Sasada, *BCSJ* **1981**, *54*, 1338.
[45] D. M. Balitz, F. A. O'Herron, J. Bush, D. M. Vyas, D. E. Nettleton, R. E. Grulich, W. T. Bradner, T. W. Doyle, E. Arnold, J. Clardy, *The Journal of antibiotics* **1981**, *34*, 1544.
[46] S. N. Sehgal, H. Czerkawski, A. Kudelski, K. Pandev, R. Saucier, C. Vézina, *The Journal of antibiotics* **1983**, *36*, 355.
[47] J. A. Findlay, J.-S. Liu, L. Radics, S. Rakhit, *Can. J. Chem.* **1981**, *59*, 3018.
[48] U. Weiss, K. Yoshihira, R. J. Highet, R. J. White, T. T. Wei, *The Journal of antibiotics* **1982**, *35*, 1194.
[49] G. T. Carter, A. A. Fantini, J. C. James, D. B. Borders, R. J. White, *The Journal of antibiotics* **1985**, *38*, 242.
[50] M. K. Kudinova, V. V. Kuliaeva, N. P. Potapova, L. M. Rubasheva, T. S. Maksimova, *Antibiotiki.* **1982**, *27*, 507.
[51] M. G. Brazhnikova, M. K. Kudinova, V. V. Kulyaeva, N. P. Potapova, L. M. Rubasheva, B. V. Rozynov, and G. Khorvat, *Antibiotiki.* **1984**, 884.
[52] T. T. Wei, J. A. Chan, P. P. Roller, U. Weiss, R. M. Stroshane, R. J. White, K. M. Byrne, *The Journal of antibiotics* **1982**, *35*, 529.
[53] T. C. Jain, G. C. Simolike, L. M. Jackman, *Tetrahedron* **1983**, *39*, 599.
[54] R. Misra, H. R. Tritch, R. C. Pandey, *The Journal of antibiotics* **1985**, *38*, 1280.
[55] T. Narita, M. Matsumoto, K. Mogi, K. Kukita, R. Kawahara, T. Nakashima, *The Journal of antibiotics* **1989**, *42*, 347.
[56] J. A. Matson, W. C. Rose, J. A. Bush, R. Myllymaki, W. T. Bradner, T. W. Doyle, *The Journal of antibiotics* **1989**, *42*, 1446.
[57] T. Matsumoto, T. Hosoya, K. Suzuki, *J. Am. Chem. Soc.* **1992**, *114*, 3568.
[58] T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *Tetrahedron Letters* **1994**, *35*, 4591.
[59] N. Yamashita, K. Shin-ya, K. Furihata, Y. Hayakawa, H. Seto, *The Journal of antibiotics* **1998**, *51*, 1105.
[60] F. Takashi Nakashima, T. Tadashi Fujii, Y. Kazuya Sakai, F. Tomohiro Sameshima, C. Hiroyuki Kumagai, A. Takeo Yoshioka, **2000**.
[61] S. Futagami, Y. Ohashi, K. Imura, T. Hosoya, K. Ohmori, T. Matsumoto, K. Suzuki, *Tetrahedron Letters* **2000**, *41*, 1063.
[62] M. Arai, H. Tomoda, A. Matsumoto, Y. Takahashi, B. H. Woodruff, N. Ishiguro, S. Kobayashi, S. Omura, *The Journal of antibiotics* **2001**, *54*, 554.
[63] M. Arai, H. Tomoda, N. Tabata, N. Ishiguro, S. Kobayashi, S. Omura, *The Journal of antibiotics* **2001**, *54*, 562.

[64] Y.-q. Li, X.-s. Huang, K. Ishida, A. Maier, G. Kelter, Y. Jiang, G. Peschel, K.-D. Menzel, M.-g. Li, M.-l. Wen et al., *Organic & biomolecular chemistry* **2008**, *6*, 3601.
[65] J. Hou, P. Liu, H. Qu, P. Fu, Y. Wang, Z. Wang, Y. Li, X. Teng, W. Zhu, *The Journal of antibiotics* **2012**, *65*, 523.
[66] S. K. Jain, A. S. Pathania, R. Parshad, C. Raina, A. Ali, A. P. Gupta, M. Kushwaha, S. Aravinda, S. Bhushan, S. B. Bharate et al., *RSC Adv.* **2013**, *3*, 21046.
[67] S.-I. Wada, R. Sawa, F. Iwanami, M. Nagayoshi, Y. Kubota, K. Iijima, C. Hayashi, Y. Shibuya, M. Hatano, M. Igarashi et al., *The Journal of antibiotics* **2017**, *70*, 1078.
[68] X. Cai, K. Ng, H. Panesar, S.-J. Moon, M. Paredes, K. Ishida, C. Hertweck, T. G. Minehan, *Organic letters* **2014**, *16*, 2962.
[69] F. Wu, J. Zhang, F. Song, S. Wang, H. Guo, Q. Wei, H. Dai, X. Chen, X. Xia, X. Liu et al., *ACS central science* **2020**, *6*, 928.
[70] Lei Xiaoguang, Zhang Jing, Wu Fan, Song Fuxing, Zhang Lixin, CN107892680, **2017**.
[71] T. T. Wei, K. M. Byrne, D. Warnick-Pickle, M. Greenstein, *The Journal of antibiotics* **1982**, *35*, 545.
[72] R. K. Elespuru, S. K. Gonda, *Science (New York, N.Y.)* **1984**, *223*, 69.
[73] B. Muralikrishnan, V. M. Dan, J. S. Vinodh, V. Jamsheena, R. Ramachandran, S. Thomas, S. G. Dastager, K. S. Kumar, R. S. Lankalapalli, R. A. Kumar, *RSC Adv.* **2017**, *7*, 36335.
[74] A. Navarrete, E. G. Armitage, M. Musteanu, A. García, A. Mastrangelo, R. Bujak, P. P. López-Casas, M. Hidalgo, C. Barbas, *Pharmacology research & perspectives* **2014**, *2*, e00067.
[75] F. Tomita, K. Takahashi, T. Tamaoki, *The Journal of antibiotics* **1982**, *35*, 1038.
[76] K. E. Price, R. E. Buck, J. Lein, *Applied Microbiology* **1964**, *12*, 428.
[77] R. K. Elespuru, M. B. Yarmolinsky, *Environmental mutagenesis* **1979**, *1*, 65.
[78] B. R. Scott, M. A. Pathak, G. R. Mohn, *Mutation Research/Reviews in Genetic Toxicology* **1976**, *39*, 29.
[79] C. K. Mirabelli, H. Bartus, J. O. Bartus, R. Johnson, S. M. Mong, C. P. Sung, S. T. Crooke, *The Journal of antibiotics* **1985**, *38*, 758.
[80] M. Greenstein, T. Monji, R. Yeung, W. M. Maiese, R. J. White, *Antimicrobial agents and chemotherapy* **1986**, *29*, 861.
[81] S. Rakhit, C. Eng, H. Baker, K. Singh, *The Journal of antibiotics* **1983**, *36*, 1490.
[82] K. Singh, *The Journal of antibiotics* **1984**, *37*, 71.
[83] D. E. Zacharias, J. P. Glusker, P. P. Fu, R. G. Harvey, *J. Am. Chem. Soc.* **1979**, *101*, 4043.
[84] D. A. Steinberg, G. A. Peterson, R. J. White, W. M. Maiese, *The Journal of antibiotics* **1985**, *38*, 1401.
[85] Y.-C. Tse-Dinh, L. R. McGee, *Biochemical and Biophysical Research Communications* **1987**, *143*, 808.
[86] M. J. Peak, J. G. Peak, C. M. Blaumueller, R. K. Elespuru, *Chemico-Biological Interactions* **1988**, *67*, 267.
[87] R. K. Elespuru, S. A. Look in *SPIE Proceedings* (Ed.: D. C. Neckers), SPIE, **1987**, p. 107.
[88] A. Schmoldt, H. F. Benthe, G. Haberland, *Biochemical pharmacology* **1975**, *24*, 1639.
[89] A. Matsumoto, Y. Fujiwara, R. K. Elespuru, P. C. Hanawalt, *Photochemistry and Photobiology* **1994**, *60*, 225.
[90] A. Lorico, B. H. Long, *European Journal of Cancer* **1993**, *29*, 1985.
[91] Akira Matsumoto and Philip C. Hanawalt, *Cancer Research* **2000**, 3921.
[92] J.-M. Chen, M. D. Shepherd, J. Horn, M. Leggas, J. Rohr, *Chembiochem : a European journal of chemical biology* **2014**, *15*, 2729.

[93] A. E. Alegria, C. M. Krishna, R. K. Elespuru, P. Riesz, *Photochemistry and Photobiology* **1989**, *49*, 257.
[94] A. E. Alegría, L. Zayas, N. Guevara, *Photochemistry and Photobiology* **1995**, *62*, 409.
[95] R. Arce, R. Oyola, A. E. Alegría, *Photochemistry and Photobiology* **1998**, *68*, 25.
[96] L. R. McGee, R. Misra, *J. Am. Chem. Soc.* **1990**, *112*, 2386.
[97] O. Kikuchi, T. Eguchi, K. Kakinuma, Y. Koezuka, K. Shindo, N. Otake, *The Journal of antibiotics* **1993**, *46*, 985.
[98] J. R. Brown, M. S. Spring, J. R. Stoker, *Phytochemistry* **1971**, *10*, 2059.
[99] P. Canham, L. C. Vining, *J. Chem. Soc., Chem. Commun.* **1976**, 319.
[100] P. L. Canham, L. C. Vining, A. G. McInnes, J. A. Walter, J. L. C. Wright, *Can. J. Chem.* **1977**, *55*, 2450.
[101] G. T. Carter, A. A. Fantini, J. C. James, D. B. Borders, R. J. White, *Tetrahedron Letters* **1984**, *25*, 255.
[102] K. M. Byrne, M. Greenstein, *The Journal of antibiotics* **1986**, *39*, 594.
[103] C. Fischer, F. Lipata, J. Rohr, *J. Am. Chem. Soc.* **2003**, *125*, 7818.
[104] M. K. Kharel, S. E. Nybo, M. D. Shepherd, J. Rohr, *Chembiochem : a European journal of chemical biology* **2010**, *11*, 523.
[105] G. Wang, J. Chen, H. Zhu, J. Rohr, *Organic letters* **2017**, *19*, 540.
[106] M. D. Shepherd, M. K. Kharel, L. L. Zhu, S. G. van Lanen, J. Rohr, *Organic & biomolecular chemistry* **2010**, *8*, 3851.
[107] M. K. Kharel, L. Zhu, T. Liu, J. Rohr, *J. Am. Chem. Soc.* **2007**, *129*, 3780.
[108] N. Tibrewal, P. Pahari, G. Wang, M. K. Kharel, C. Morris, T. Downey, Y. Hou, T. S. Bugni, J. Rohr, *J. Am. Chem. Soc.* **2012**, *134*, 18181.
[109] N. Tibrewal, T. E. Downey, S. G. van Lanen, E. Ul Sharif, G. A. O'Doherty, J. Rohr, *J. Am. Chem. Soc.* **2012**, *134*, 12402.
[110] M. K. Kharel, P. Pahari, M. D. Shepherd, N. Tibrewal, S. E. Nybo, K. A. Shaaban, J. Rohr, *Natural product reports* **2012**, *29*, 264.
[111] M. K. Kharel, H. Lian, J. Rohr, *Organic & biomolecular chemistry* **2011**, *9*, 1799.
[112] Y. Harigaya, T. Suzuki, M. Onda, *Chem. Pharm. Bull.* **1979**, *27*, 2636.
[113] P. Pahari, M. K. Kharel, M. D. Shepherd, S. G. van Lanen, J. Rohr, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 1216.
[114] J. A. Findlay, A. Daljeet, P. J. Murray, R. N. Rej, *Can. J. Chem.* **1987**, *65*, 427.
[115] S. W. Heinzman, J. R. Grunwell, *Tetrahedron Letters* **1980**, *21*, 4305.
[116] A. I. Meyers, R. Gabel, E. D. Mihelich, *J. Org. Chem.* **1978**, *43*, 1372.
[117] A. D. Patten, N. N. Huy, S. J. Danishefsky, *J. Org. Chem.* **1988**, *53*, 1003.
[118] a) T. C. McKenzie, W. Hassen, *Tetrahedron Letters* **1987**, *28*, 2563; b) T. C. McKenzie, W. Hassen, S. J.F. Macdonald, *Tetrahedron Letters* **1987**, *28*, 5435.
[119] S. J. F. Macdonald, T. C. McKenzie, W. D. Hassen, *J. Chem. Soc., Chem. Commun.* **1987**, 1528.
[120] M. E. Jung, Y. H. Jung, *Tetrahedron Letters* **1988**, *29*, 2517.
[121] L. Claisen, *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 3271.
[122] L. R. McGee, P. N. Confalone, *J. Org. Chem.* **1988**, *53*, 3695.
[123] D. H. Hua, S. Saha, D. Roche, J. C. Maeng, S. Iguchi, C. Baldwin, *J. Org. Chem.* **1992**, *57*, 399.
[124] D. J. Hart, G. H. Merriman, *Tetrahedron Letters* **1989**, *30*, 5093.
[125] K. Maruoka, H. Yamamoto, S. Saito in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, Chichester, UK, **2001**.
[126] P. P. Deshpande, O. R. Martin, *Tetrahedron Letters* **1990**, *31*, 6313.
[127] Ó. d. Frutos, A. M. Echavarren, *Tetrahedron Letters* **1996**, *37*, 8953.
[128] a) C. A. James, V. Snieckus, *Tetrahedron Letters* **1997**, *38*, 8149; b) C. A. James, V. Snieckus, *J. Org. Chem.* **2009**, *74*, 4080.

[129] T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui, T. Matsumoto, K. Suzuki, *Helv. Chim. Acta* **2002**, *85*, 3589.
[130] I. Takemura, K. Imura, T. Matsumoto, K. Suzuki, *Organic letters* **2004**, *6*, 2503.
[131] O. Cortezano-Arellano, A. Cordero-Vargas, *Tetrahedron Letters* **2010**, *51*, 602.
[132] G.-J. M. Gruter, O. S. Akkerman, F. Bickelhaupt, *J. Org. Chem.* **1994**, *59*, 4473.
[133] G. Qabaja, G. B. Jones, *Tetrahedron Letters* **2000**, *41*, 5317.
[134] P. R. Nandaluru, G. J. Bodwell, *J. Org. Chem.* **2012**, *77*, 8028.
[135] Y. Sumida, R. Harada, T. Kato-Sumida, K. Johmoto, H. Uekusa, T. Hosoya, *Organic letters* **2014**, *16*, 6240.
[136] H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758.
[137] T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 7534.
[138] X. Huang, T. Zhu, Z. Huang, Y. Zhang, Z. Jin, G. Zanoni, Y. R. Chi, *Organic letters* **2017**, *19*, 6188.
[139] D. Mal, A. Patra, H. Roy, *Tetrahedron Letters* **2004**, *45*, 7895.
[140] a) G. Hirai, Y. Ogoshi, M. Ohkubo, Y. Tamura, T. Watanabe, T. Shimizu, M. Sodeoka, *Tetrahedron Letters* **2009**, *50*, 3609; b) F. Kaiser, L. Schwink, J. Velder, H.-G. Schmalz, *Tetrahedron* **2003**, *59*, 3201.
[141] a) X.-F. Wang, Y. Koyama, H. Nagae, Y. Yamano, M. Ito, Y. Wada, *Chemical Physics Letters* **2006**, *420*, 309; b) J. Maj, J. W. Morzycki, L. Rárová, G. Wasilewski, A. Wojtkielewicz, *Tetrahedron Letters* **2012**, *53*, 5430.
[142] A. Skrzyńska, P. Drelich, S. Frankowski, Ł. Albrecht, *Chem. Eur. J.* **2018**, *24*, 16543.
[143] R. G. F. Giles, A. B. Hughes, M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1581.
[144] T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004.
[145] K. Suzuki, T. Hosoya, E. Takashiro, Y. Yamamoto, T. Matsumoto, *Heterocycles* **1996**, *42*, 397.
[146] A. Ben, D.-S. Hsu, T. Matsumoto, K. Suzuki, *Tetrahedron* **2011**, *67*, 6460.
[147] O. Meth-Cohn, S. P. Stanforth in *Comprehensive Organic Synthesis*, Elsevier, **1991**, pp. 777–794.
[148] Geuther A., *Ann. Chem. Pharm.* **1862**, *123*, 121.
[149] a) W. P. Weber, G. W. Gokel in *Reactivity and Structure: Concepts in Organic Chemistry* (Eds.: K. Hafner, J.-M. Lehn, C. W. Rees, P. von Ragué Schleyer, B. M. Trost, R. Zahradník, W. P. Weber, G. W. Gokel), Springer Berlin Heidelberg, Berlin, Heidelberg, **1977**, pp. 58–72; b) W. P. Weber, G. W. Gokel in *Reactivity and Structure: Concepts in Organic Chemistry* (Eds.: K. Hafner, J.-M. Lehn, C. W. Rees, P. von Ragué Schleyer, B. M. Trost, R. Zahradník, W. P. Weber, G. W. Gokel), Springer Berlin Heidelberg, Berlin, Heidelberg, **1977**, pp. 18–43; c) A. D. Dilman, V. V. Levin, *Accounts of chemical research* **2018**, *51*, 1272; d) J. P. Oliver, U. V. Rao, *J. Org. Chem.* **1966**, *31*, 2696.
[150] H. Wynberg, *Chem. Rev.* **1960**, *60*, 169.
[151] W. von E. Doering, P. M. LaFlamme, *Tetrahedron* **1958**, *2*, 75.
[152] a) W. E. Parham, H. E. Reiff, *J. Am. Chem. Soc.* **1955**, *77*, 1177; b) W. E. Parham, H. E. Reiff, P. Swartzentruber, *J. Am. Chem. Soc.* **1956**, *78*, 1437.
[153] W. E. Parham, R. R. TWELVES, *J. Org. Chem.* **1957**, *22*, 730.
[154] J. Feierfeil, A. Grossmann, T. Magauer, *Angewandte Chemie (International ed. in English)* **2015**, *54*, 11835.
[155] T. A. Unzner, A. S. Grossmann, T. Magauer, *Angewandte Chemie (International ed. in English)* **2016**, *55*, 9763.
[156] J. Chang, X. Song, W. Huang, D. Zhu, M. Wang, *Chemical communications (Cambridge, England)* **2015**, *51*, 15362.

[157] G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler, *Fortschritte der Chemie organischer Naturstoffe = Progress in the chemistry of organic natural products. Progres dans la chimie des substances organiques naturelles* **2001**, *82*, 1.
[158] C. Morozzi, O. Rosati, M. Curini, D. Lanari, *Synlett* **2018**, *29*, 126.
[159] T. N. Grant, F. G. West, *Organic letters* **2007**, *9*, 3789.
[160] E. Wenkert, T. S. Arrhenius, B. Bookser, M. Guo, P. Mancini, *J. Org. Chem.* **1990**, *55*, 1185.
[161] H. Xu, J.-L. Hu, L. Wang, S. Liao, Y. Tang, *Journal of the American Chemical Society* **2015**, *137*, 8006.
[162] J. Falandysz, A. Fernandes, E. Gregoraszczuk, M. Rose, *Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews* **2014**, *32*, 239.
[163] J. C. DeForest, R. A. Samame, G. Suryn, A. Burtea, S. D. Rychnovsky, *J. Org. Chem.* **2018**, *83*, 8914.
[164] C.-E. Yeom, H. Kim, S. Lee, B. Kim, *Synlett* **2007**, *2007*, 146.
[165] H. Cui, N. G. Akhmedov, J. L. Petersen, K. K. Wang, *J. Org. Chem.* **2010**, *75*, 2050.
[166] B. Wang, H.-X. Sun, B. Chen, Z.-H. Sun, *Green Chem.* **2009**, *11*, 1112.
[167] a) A. J. Allentoff, M. A. Wallace, S. C. Traeger, N. Zheng, Q. Zhang, S. J. Bonacorsi, *Tetrahedron* **2018**, *74*, 6680; b) S. Sasmal, S. Rana, G. K. Lahiri, D. Maiti, *J Chem Sci* **2018**, *130*; c) D. Vagedes, R. Fröhlich, G. Erker, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3362; d) Y. L. Chow, D.-C. Zhao, C. I. Johansson, *Can. J. Chem.* **1988**, *66*, 2556.
[168] S. Sharma, S. K. R. Parumala, R. K. Peddinti, *J. Org. Chem.* **2017**, *82*, 9367.
[169] W. Liu, M. Buck, N. Chen, M. Shang, N. J. Taylor, J. Asoud, X. Wu, B. B. Hasinoff, G. I. Dmitrienko, *Organic letters* **2007**, *9*, 2915.
[170] A. Srikrishna, P. Ravikumar, *Synthesis* **2007**, *2007*, 65.
[171] a) K. Tatsuta, A. Furuyama, T. Yano, Y. Suzuki, T. Ogura, S. Hosokawa, *Tetrahedron Letters* **2008**, *49*, 4036; b) G. Bringmann, M. Ochse, R. Götz, *J. Org. Chem.* **2000**, *65*, 2069.
[172] Á. Gottsegen, M. Nógrádi, B. Vermes, M. Kajtár-Peredy, É. Bihátsi-Karsai, *J. Chem. Soc., Perkin Trans. 1* **1990**, 315.
[173] J. Barluenga, F. J. Fañanás, R. Sanz, Y. Fernández, *Chem. Eur. J.* **2002**, *8*, 2034.
[174] a) T. Tajima, Y. Akagi, T. Kumamoto, N. Suzuki, T. Ishikawa, *Tetrahedron Letters* **2012**, *53*, 383; b) J. W. Lampe, C. K. Biggers, J. M. Defauw, R. J. Foglesong, S. E. Hall, J. M. Heerding, S. P. Hollinshead, H. Hu, P. F. Hughes, G. E. Jagdmann et al., *Journal of medicinal chemistry* **2002**, *45*, 2624.
[175] Ó. d. Frutos, C. Atienza, A. M. Echavarren, *Ann. Chem. Pharm.* **2001**, *2001*, 163.
[176] a) J. Yang, D. Knueppel, B. Cheng, D. Mans, S. F. Martin, *Organic letters* **2015**, *17*, 114; b) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; c) A. G. Schultz, S. J. Kirincich, *J. Org. Chem.* **1996**, *61*, 5631.
[177] P. G. Sammes, *Tetrahedron* **1976**, *32*, 405.
[178] J. L. Charlton, M. M. Alauddin, *Tetrahedron* **1987**, *43*, 2873.
[179] a) K. C. Nicolaou, D. L. F. Gray, J. Tae, *J. Am. Chem. Soc.* **2004**, *126*, 613; b) K. C. Nicolaou, D. Gray, *Angew. Chem. Int. Ed.* **2001**, *40*, 761; c) D. Xue, M. Xu, C. Zheng, B. Yang, M. Hou, H. He, S. Gao, *Chin. J. Chem.* **2019**, *37*, 135.
[180] G. Quinkert, W.-D. Weber, U. Schwartz, H. Stark, H. Baier, G. Dürner, *Liebigs Ann. Chem.* **1981**, *1981*, 2335.
[181] J. L. Charlton, G. L. Plourde, K. Koh, A. S. Secco, *Can. J. Chem.* **1989**, *67*, 574.
[182] a) S. Béarnais-Barbry, R. Bonneau, A. Castellan, *Photochemistry and Photobiology* **2001**, *74*, 542; b) A. I. Ononye, A. R. McIntosh, J. R. Bolton, *J. Phys. Chem.* **1986**, *90*, 6266; c) D. Bryce-Smith, E. H. Evans, A. Gilbert, H. S. McNeill, *J. Chem. Soc., Perkin Trans. 1* **1992**, 485.

[183] E. Rommel, J. Wirz, *Helv. Chim. Acta* **1977**, *60*, 38.
[184] N. P. Gritsan, L.' S. Klimenko, *Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals* **1994**, *246*, 103.
[185] a) J. L. Segura, N. Martín, *Chem. Rev.* **1999**, *99*, 3199; b) B. Yang, S. Gao, *Chemical Society reviews* **2018**, *47*, 7926; c) P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119.
[186] a) K. A. Parker, T. L. Mindt, *Organic letters* **2001**, *3*, 3875; b) K. A. Parker, T. L. Mindt, *Tetrahedron* **2011**, *67*, 9779.
[187] A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727.
[188] P. Beak, R. A. Brown, *J. Org. Chem.* **1982**, *47*, 34.
[189] a) C. B. de Koning, J. P. Michael, A. L. Rousseau, *J. Chem. Soc., Perkin Trans. 1* **2000**, 787; b) Y. Kohyama, T. Murase, M. Fujita, *Chemical communications (Cambridge, England)* **2012**, *48*, 7811.
[190] S. L. MacNeil, O. B. Familoni, V. Snieckus, *J. Org. Chem.* **2001**, *66*, 3662.
[191] Y. He, X. Zhang, L. Cui, J. Wang, X. Fan, *Green Chem.* **2012**, *14*, 3429.
[192] J. Ancerewicz, P. Vogel, *Helv. Chim. Acta* **1996**, *79*, 1393.
[193] a) H. S. Gulbrandsen, H. Serigstad, M. Lovell Read, I. Joos, L.-L. Gundersen, *Eur. J. Org. Chem.* **2019**, *2019*, 6044; b) M. L. Read, L.-L. Gundersen, *J. Org. Chem.* **2013**, *78*, 1311; c) H. S. Gulbrandsen, J. L. D. Alfaro, M. L. Read, L.-L. Gundersen, *Eur. J. Org. Chem.* **2017**, *2017*, 2305; d) H. S. Gulbrandsen, M. Hennum, M. Osheka, M. L. Read, L.-L. Gundersen, *Eur. J. Org. Chem.* **2014**, *2014*, 8182; e) M. L. Read, A. Krapp, P. O. Miranda, L.-L. Gundersen, *Tetrahedron* **2012**, *68*, 1869.
[194] C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nature chemistry* **2010**, *2*, 1044.
[195] G. B. Bajracharya, O. Daugulis, *Organic letters* **2008**, *10*, 4625.
[196] H. Yi, A. Jutand, A. Lei, *Chemical communications (Cambridge, England)* **2015**, *51*, 545.
[197] B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, *Tetrahedron* **1984**, *40*, 5005.
[198] T. Kauffmann, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 291.
[199] B. H. Lipshutz, K. Siegmann, E. Garcia, *J. Am. Chem. Soc.* **1991**, *113*, 8161.
[200] a) B. H. Lipshutz, K. Siegmann, E. Garcia, F. Kayser, *J. Am. Chem. Soc.* **1993**, *115*, 9276; b) B. H. Lipshutz, F. Kayser, Z.-P. Liu, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1842; c) B. H. Lipshutz, Z.-P. Liu, F. Kayser, *Tetrahedron Letters* **1994**, *35*, 5567.
[201] B. H. Lipshutz, F. Kayser, N. Maullin, *Tetrahedron Letters* **1994**, *35*, 815.
[202] a) D. R. Spring, S. Krishnan, S. L. Schreiber, *J. Am. Chem. Soc.* **2000**, *122*, 5656; b) D. R. Spring, S. Krishnan, H. E. Blackwell, S. L. Schreiber, *J. Am. Chem. Soc.* **2002**, *124*, 1354.
[203] X. Wei, P. Johnson, R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109.
[204] a) K. Kong, J. A. Enquist, M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz, J. L. Wood, *J. Am. Chem. Soc.* **2013**, *135*, 10890; b) R. M. Williams, E. Kwast, *Tetrahedron Letters* **1989**, *30*, 451; c) H. Suzuki, A. Tsukuda, M. Kondo, M. Aizawa, Y. Senoo, M. Nakajima, T. Watanabe, Y. Yokoyama, Y. Murakami, *Tetrahedron Letters* **1995**, *36*, 1671.
[205] G. Qabaja, E. M. Perchellet, J.-P. Perchellet, G. B. Jones, *Tetrahedron Letters* **2000**, *41*, 3007.
[206] Y. Wang, Y. Kuang, Y. Wang, *Chemical communications (Cambridge, England)* **2015**, *51*, 5852.
[207] Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton, A. G. M. Barrett, *Organic letters* **2005**, *7*, 4549.
[208] H.-M. Shen, B. Qi, M.-Y. Hu, L. Liu, H.-L. Ye, Y.-B. She, *Catal Lett* **2020**, *150*, 3096.

[209] L. Zhang, H. Yi, J. Wang, A. Lei, *Green Chem.* **2016**, *18*, 5122.
[210] Y. Yoshino, Y. Hayashi, T. Iwahama, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1997**, *62*, 6810.
[211] a) S. Pramanik, M. Jash, D. Mondal, C. Chowdhury, *Adv. Synth. Catal.* **2019**, *361*, 5223; b) C.-L. Sun, Y.-F. Gu, W.-P. Huang, Z.-J. Shi, *Chemical communications (Cambridge, England)* **2011**, *47*, 9813; c) J.-Y. He, Q.-F. Bai, C. Jin, G. Feng, *Synlett* **2018**, *29*, 2311.
[212] Y.-H. Kuo, Y.-L. Lin, *Heterocycles* **1995**, *41*, 1959.
[213] Z.-T. Du, T. Zhang, J. Zhou, P. Han, Y.-M. Xu, *HETEROCYCLES* **2013**, *87*, 1889.
[214] M. C. Ortiz Villamizar, F. I. Zubkov, C. E. Puerto Galvis, L. Y. Vargas Méndez, V. V. Kouznetsov, *Org. Chem. Front.* **2017**, *4*, 1736.
[215] a) M. Nayak, Y. Jung, I. Kim, *Organic & biomolecular chemistry* **2016**, *14*, 8074; b) T. Sasaki, K. Miyagi, K. Moriyama, H. Togo, *Organic letters* **2016**, *18*, 944.
[216] *Synlett* **2000**, *2000*, 1822.
[217] B. M. Trost, T. J. Dietsch, *J. Am. Chem. Soc.* **1973**, *95*, 8200.
[218] B. Fraser-Reid, B. Radatus, *J. Am. Chem. Soc.* **1970**, *92*, 5288.
[219] G. G. Pawar, V. K. Tiwari, H. S. Jena, M. Kapur, *Chem. Eur. J.* **2015**, *21*, 9905.
[220] B. Schmidt, A. Biernat, *Chem. Eur. J.* **2008**, *14*, 6135.
[221] A. Martin, M. Païs, C. Monneret, *Carbohydrate Research* **1983**, *113*, 21.
[222] B.-L. Yin, C.-B. Cai, J.-Q. Lai, Z.-R. Zhang, L. Huang, L.-W. Xu, H.-F. Jiang, *Adv. Synth. Catal.* **2011**, *353*, 3319.
[223] M. D. Shepherd, T. Liu, C. Méndez, J. A. Salas, J. Rohr, *Applied and environmental microbiology* **2011**, *77*, 435.
[224] J. Feierfeil, T. Magauer, *Chem. Eur. J.* **2018**, *24*, 1455.
[225] *Unpublished results.*
[226] H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897.
[227] A. B. Charette, J.-E. Bouchard, *Can. J. Chem.* **2005**, *83*, 533.
[228] S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042.
[229] F. J. Sarabia, E. M. Ferreira, *Organic letters* **2017**, *19*, 2865.
[230] A. Haouas, N. B. Hamadi[], M. Msaddek, *J. Heterocyclic Chem.* **2015**, *52*, 1765.
[231] S. Negretti, C. M. Cohen, J. J. Chang, D. M. Guptill, H. M. L. Davies, *Tetrahedron* **2015**, *71*, 7415.
[232] a) J. D. Moore, K. T. Sprott, A. D. Wrobleski, P. R. Hanson, *Organic letters* **2002**, *4*, 2357; b) D. E. Fuerst, B. M. Stoltz, J. L. Wood, *Organic letters* **2000**, *2*, 3521.
[233] T. T. Nguyen, *Organic & biomolecular chemistry* **2019**, *17*, 6952.
[234] M. Newcomb in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: C. Chatgilialoglu, A. Studer), John Wiley & Sons, Ltd, Chichester, UK, **2012**.