STUDIES TOWARD THE TOTAL SYNTHESIS OF DIDEOXY LOMAIVITICINONE

By

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LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl etherate
Bn	benzyl
Bz	benzoyl
^oC	degrees Celsius
CAN	cerium ammonium nitrate
cat.	catalytic
$CDCl_3$	chloroform-d
$CHCl_3$	chloroform
CH_3CN	acetonitrile
conc	concentrated
δ	chemical shift in ppm
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq.	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
H_2O	water
h	hour
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrum
IBX	o-iodoxybenzoic acid
imH	imidazole
J	coupling constant

KHMDS	potassium bis(trimethylsilyl)amide
L	liter(s)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
μ	micro
m	milli, medium (FTIR), multiplet (NMR)
M	moles per liter
mCPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl ether
Ms	methylsufonyl
NaOH	sodium hydroxide
$NaHCO_3$	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
NBS	N-bromosuccinimide
NH_4Cl	ammonium chloride
NIS	N-iodosuccinimide
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
OAc	acetoxy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	p-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
p-tsa	p-toluenesulfonic acid
pyr	pyridine
q	quartet
s	singlet
SEM	[P-(trimethylsilyl)ethoxy]methyl
TBAF	tetra-n-butylammonium fluoride
TBS	tert-butyldimethylsilyl
TBPDS	tert-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-n-propylammoniumperruthenate
Ts	4-toluenesulfonyl

CHAPTER I

BACKGROUND AND SIGNIFICANCE

Introduction

With the first examples isolated in the 1950`s, the diazo group containing family of secondary metabolites currently consists of more than 30 structures.[1] As opposed to broadly studied synthetic analogs, mostly prepared from hydrazine and its derivatives, diazo compounds and other N-N bond containing natural products (hydrazines, hydrazones, nitramines, nitroamines, azoxy and heterocyclic compounds) have been a subject of limited research. In terms of structural complexity and physical properties, diazo group containing kinamycins and lomaiviticins (diazoparaquinone antibiotics) can be easily depicted as one of the most interesting family of natural products. The following chapter describes recent efforts toward the synthesis, evaluation of biological properties and biosynthetic origin of both the kinamycins and lomaiviticins.

Isolation and Structure Elucidation

The first kinamycins were isolated as orange, crystalline solids from a fermentation culture broth of the soil bacterium *Streptomyces murayamaensis* in 1970.[2-5] A combination of chemical, spectroscopic and crystallographic methods were

used to assign the structure of **1.1a-d** as benzo[b]carbazoloquinone cyanamides with a highly oxygenated D ring (Figure 1.1). Although tentative assignment of the cyanamide functionality could not be fully supported by ^{13}C NMR data, an unexpected resonance at δ 78 ppm instead of the predicted δ 110-120 ppm was tentatively explained by the magnetic influence of the benzo[b]carbazoloquinone ring system. Additionally, the infrared absorbance (2150 cm^{-1}) and detection of ammonia under hydrolytic conditions - were used as evidence in favor of the cyanamide group. Biosynthetic studies and attempts to synthesize biosynthetic precursors to **1.1** revealed poor agreement of collected data with the initial structural assignment.[6] The reexamination of ^{1}H and ^{13}C NMR, IR, high resolution X-ray led to the reevaluation and final identification of the kinamycins as diazobenzo[b]fluorenes **1.2a-d** (i.e. exchange N-CN to C=N=N).[7, 8]

1.1 **a** R^1=H, R^2=Ac, R^3=Ac, R^4=Ac
b R^1=H, R^2=H, R^3=Ac, R^4=H
c R^1=Ac, R^2=Ac, R^3=H, R^4=Ac
d R^1=H, R^2=Ac, R^3=H, R^4=Ac

1.2 **a** R^1=H, R^2=Ac, R^3=Ac, R^4=Ac
b R^1=H, R^2=H, R^3=Ac, R^4=H
c R^1=Ac, R^2=Ac, R^3=H, R^4=Ac
d R^1=H, R^2=Ac, R^3=H, R^4=Ac

Figure 1.1. Benzo[b]carbazolquinone cyanamides and Diazobenzo[b]fluorenes.

Thirty years after isolation of the kinamycins (**1.2a-d**), the fermentation broth of a new species *Micromonospora lomaivitiensis* found in the inner core of a marine ascidian *Polysyncraton lithostrotum*, delivered red, amorphous lomaiviticins A (**1.3a**) and

B (**1.3b**) (Figure 1.2).[9] High-resolution Fourier transform ion cyclotron resonance mass spectrometry was applied to determine the molecular formula of lomaiviticin A as $C_{68}H_{80}N_6O_{24}$ and lomaiviticin B as $C_{54}H_{56}N_6O_{18}$. Analysis of spectroscopic data revealed that the number of carbons and protons corresponded to half of these values suggesting the symmetrical dimeric structure of both metabolites. Further evaluation of two-dimensional spectroscopic experiments led to identification of **1.3a** as a C_2-symmetric diazobenzo[b]fluorene equipped with a highly functionalized central core and four sugars attached to the aglycon – two N,N-dimethyl derivatives of a rare amino sugar pyrrolosamine and two oleandroses. Detailed analysis of the structure of **1.3b** revealed a fused furanol moiety in the central region of the molecule and therefore, the presence of only two N,N-dimethyl pyrrolosamines. The absolute stereochemistry of **1.3a** and **1.3b** was not determined but tentatively assigned based on analogy to the kinamycins.

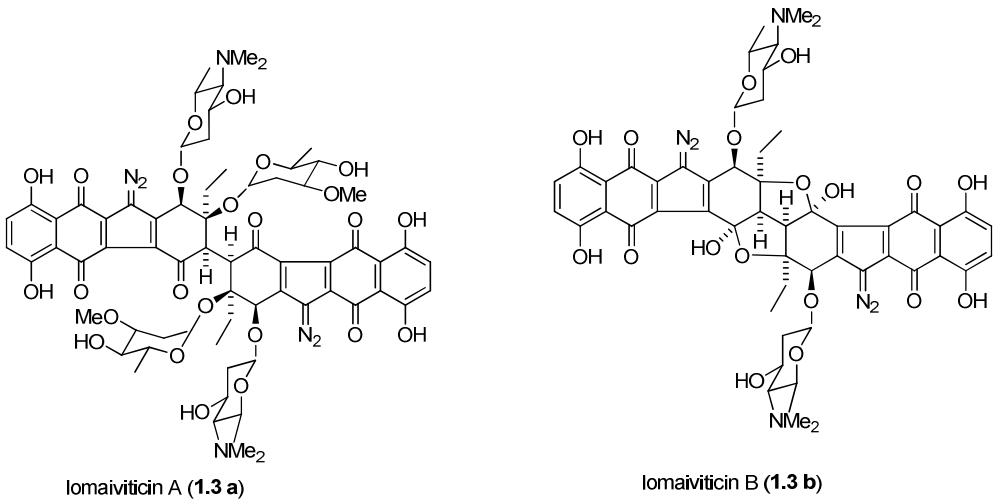


Figure 1.2. Lomaiviticins A (**1.3a**) and B (**1.3b**).

Biosynthesis

The initial incorrect assignment of the structure of the kinamycins as N-cyanamides strongly influenced the first period of biosynthetic studies of **1.2**. At that time a series of isotope experiments revealed that the kinamycins were synthesized from a polyketide synthase.[10,11] Further studies showed that dehydrorabelomycin (**1.4**, Scheme 1.1), identified as a precursor of many other aromatic polyketides (see rebelomycin-like structure, Figure 1.3), is an early intermediate in the biosynthesis of **1.2**.[12]

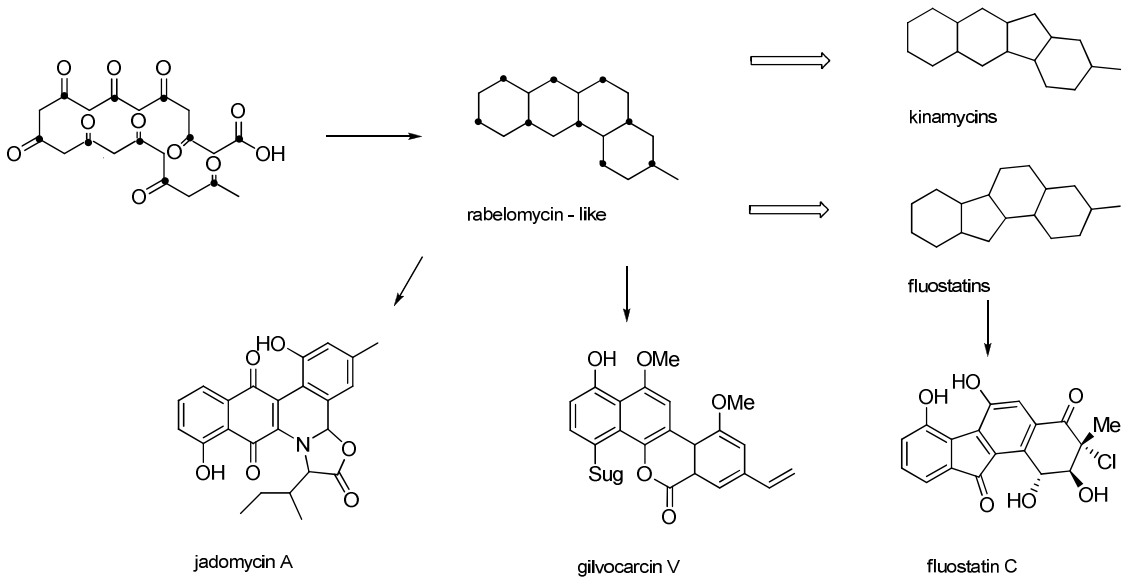
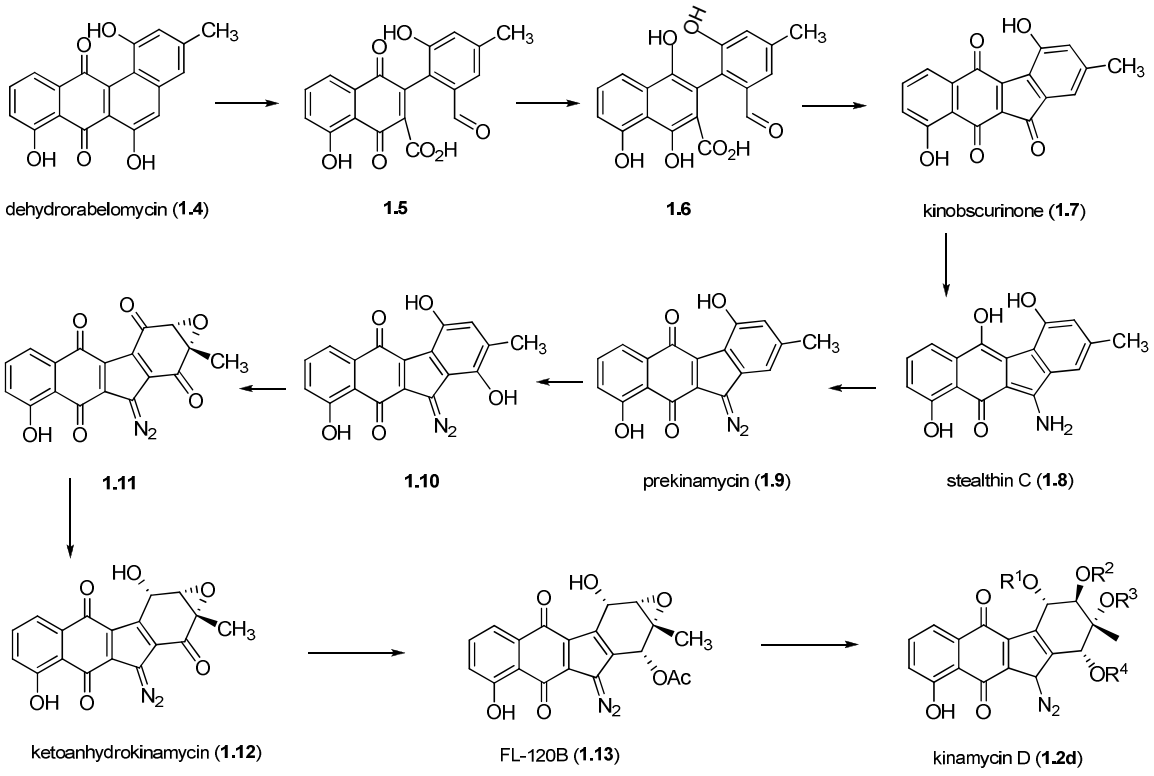


Figure 1.3. Secondary metabolites originated from rabelomycin.

A series of feeding studies and genetic experiments conducted in late 1980`s and early 1990`s led to the isolation of further metabolites and resulted in the proposal of a

plausible biosynthetic pathway for the formation of **1.2** (Scheme 1.1).[13] As suggested, the formation of **1.2** starts with the oxidative ring cleavage of dehydrorabelomycin (**1.4**). Ring contraction then leads to generation of the benzo[b]fluorene skeleton of kinobscurinone (**1.7**). Reductive amination of the carbonyl group of **1.7** provides primary amino group-containing stealthin C (**1.8**). Subsequent diazotization gives prekinamycin (**1.9**), the common precursor to all kinamycins characterized by the presence of a diazo functionality. Finally, a series of oxidative manipulations of the D ring of **1.9** affords different kinamycins.

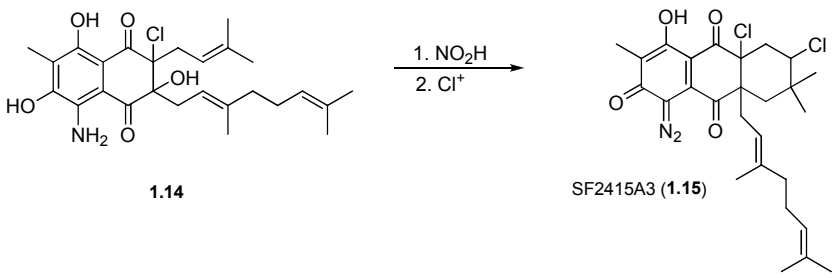


Scheme 1.1. Speculative biosynthesis of kinamycin D (**1.2d**).

Despite being published in 1997, this proposal has not been challenged nor validated. Therefore, the unanswered questions: 1. Of the origin of the diazo group in the structure of prekinamycin and the kinamycins; 2. The source of the second nitrogen for formation of the diazo functionality; and 3. Identification of the enzyme responsible for conversion of the amino group of **1.8** to the diazo group of **1.9**, still await explanation.

Similarly, the question of the biosynthetic origin of lomaiviticins remains to be addressed. Known examples of biosynthetic studies of C_2-symmetric aromatic polyketides seem to suggest that the aglycons of **1.3a** and **1.3b** could be formed via dimerization of two monomeric kinamycin-like units.[14] Identification of an enzyme catalyzing this transformation will enable validation of this hypothesis.

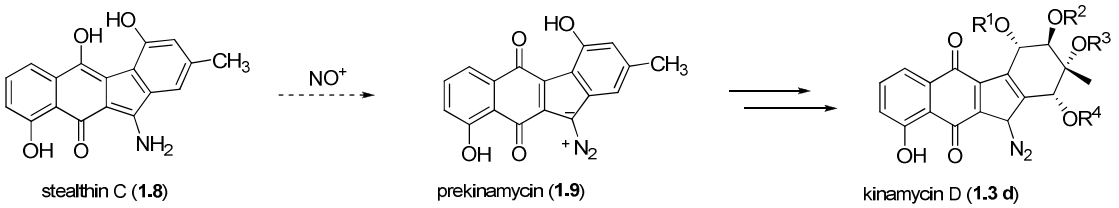
As mentioned previously, the kinamycins and dimeric lomaiviticins are not the only diazo group containing secondary metabolites isolated from bacterial sources.[1] However, the only other biosynthetic study was reported for the diazopyranonaphtoquinone SF2415A3 (**1.15**) a biosynthetic precursor to azamerone (Scheme 1.2).[15] As reported, production of **1.15** involves stepwise introduction of the diazo functionality through formation of an aminodihydroquinone intermediate **1.14**.



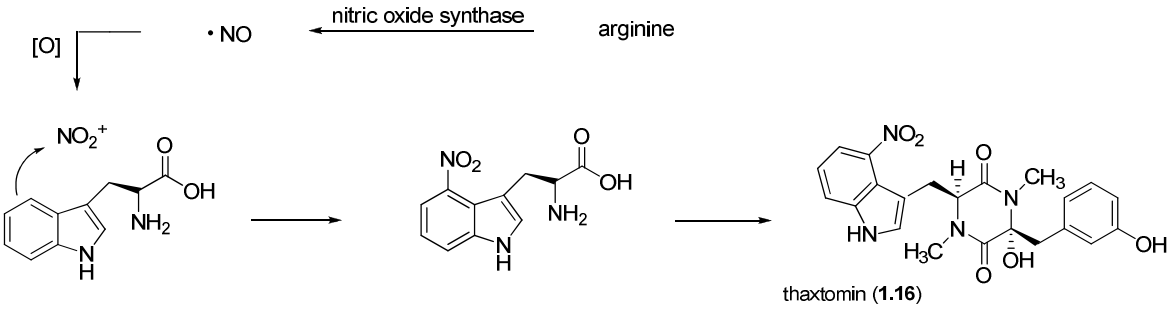
Scheme 1.2. Hypothetical biosynthesis of SF2415A3.

Intrigued by previous findings and even more by unaddressed questions of the biosynthetic origin of **1.2** and **1.3**, we have hypothesized that the formation of the diazo group in the structure of prekinamycin could originate from the reaction of the amino group of stealthin C (**1.8**) with a nitrosonium ion (NO^+) source (Scheme 1.3). This synthetically well-established transformation may be achieved by use of $NaNO_3$ and involves loss of a water molecule.[16] In biological systems NO^+ can be delivered from oxidation of nitric oxide (NO) produced during the conversion of arginine into citrullinic acid catalyzed by the enzyme nitric oxide synthase (NOS). The mammalian NOS and the function of NO have been the subject of intense studies.[17] In contrast, the roles of both bacterial nitric oxide synthase and bacterial NO remain poorly understood.[18] A recent report has shown the contribution of this protein to the production of the secondary metabolite thaxtomin (**1.16**), in which the NOS is responsible for production of NO_2^+ incorporated in the structure of the aromatic dipeptide (Scheme 1.4).[19] NOS was also suggested to be involved in the development of bacterial antibiotic resistance mechanism as a consequence of modification by small molecule antibiotics.[20] It remains to be answered if a similar process is involved in the biosynthetic pathway to **1.2** and

1.3. Observations made during biosynthetic studies of azamerone seem to be in favor of this hypothesis.



Scheme 1.3. Hypothetical formation of prekinamycin (**1.9**).

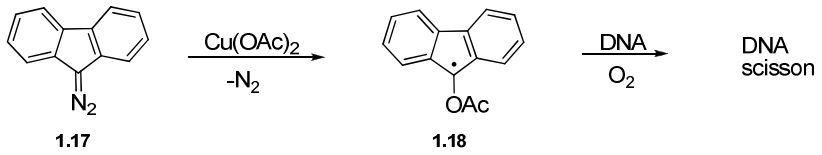


Scheme 1.4. Biosynthetic pathway to thaxtomin.

Reactivity and Biological Activity

Kinamycin isolation was a part of an effort to identify compounds active against Gram-positive bacteria.[2] Subsequent tests revealed antitumor properties of kinamycins (**1.2**).[21] But the cellular mechanistic behavior of the diazofluorene chemotype was not subjected to any studies until the 1990`s, when the first report by Jebaratnam and Arya was published.[22] In this study very simple analogs of diazobenzo[a]fluorenes (**1.17**) were

shown to undergo under reductive conditions formation of radical species (**1.18**) with the ability to nick plasmid DNA in the presence of oxygen. The suggestion was made that similar reactivity could be responsible for the biological properties of kinamycins.

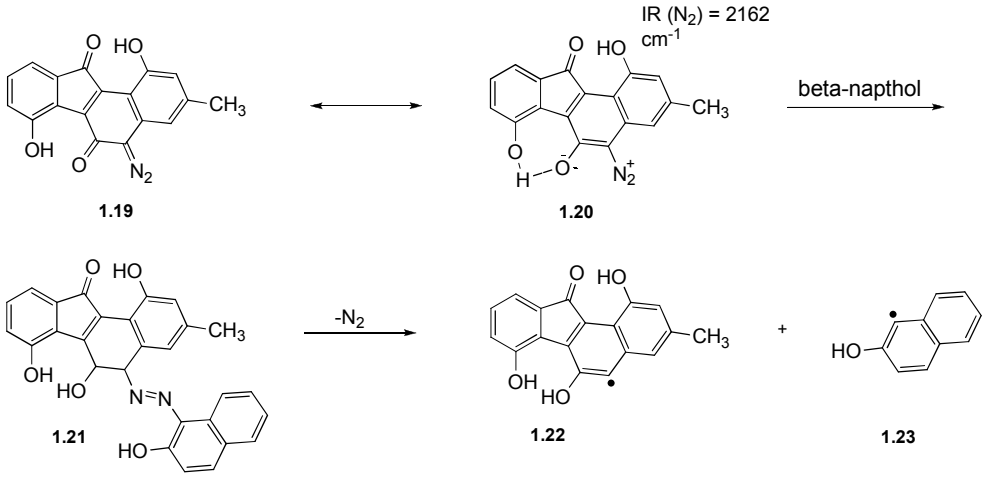


Scheme 1.5. Jebaratnam`s studies.

The lomaivitcin isolation paper, published in 2001, contained information about the potent antibacterial and anticancer properties of **1.3a**.[9] Its activity was tested against Gram-positive bacteria: *Staphylococcus aureus* and *Enterococcus faecium* (MIC`s 6-25 ng/spot in a plate assay). Examination of **1.3a** against panel of 24-cancer cell lines showed potent cytotoxicity with IC_{50} values ranging from pico to nanomolar values (IC_{50} = 0.007 – 72 nM). With use of biochemical induction assay (BIA) lomaiviticin A was demonstrated to possess DNA-damaging properties - compound **1.3a** cleaved double stranded DNA under reducing conditions. Although no follow-up study was reported, the initial report triggered a new wave of interest in the diazobenzo[b]fluorene family of antiobitics.

In 2002, Dmitrienko and coworkers used diazobenzo[a]fluorene-isoprekinamycin (**1.19**) as a model system and tested its reactivity toward nucleophiles.[23] They showed that the enhanced electrophilic properties of the diazo group of **1.19** being, as it was suggested, a result of hydrogen bond formation could lead to greater reactivity of **1.19**

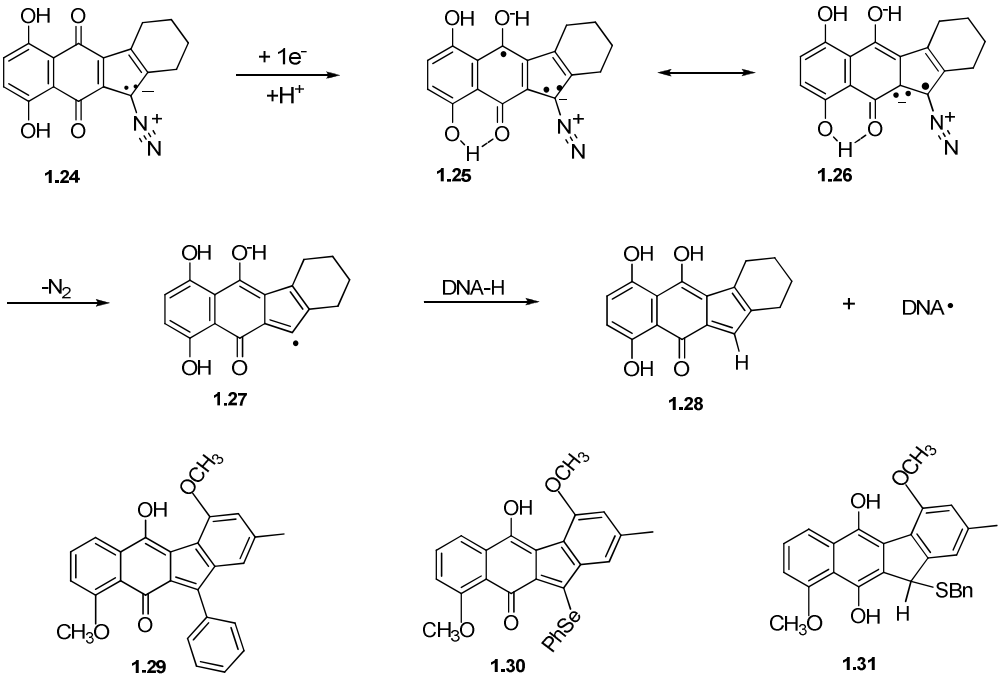
towards nucleophiles. It was proposed that the consequence of greater electrophilicity of **1.19** could be formation of adduct (**1.21**) which would further undergo fragmentation and formation of DNA-damaging radicals (**1.22**).



Scheme 1.6. Dmitrienko`s isoprekinamycin (**1.19**) studies.

The first study which fully took advantage of the diazobenzo[b]fluorene structure was published by Feldman and Eastman in 2005.[24,25] The focus of this work was the examination of reactivity of a model molecule prekinamycin (**1.9**). The study`s starting point was the report that under reducing conditions lomaiviticin A expressed the ability to cleave DNA.[9] As a part of the study, prekinamycin (**1.9**) was treated with Bu_3SnH and AIBN in benzene in the presence of Ph_2Se_2 and $PhCH_2SH$. Formation of different aromatic adducts (compounds **1.29-1.31**) was observed. This finding led to formulation of a proposal for the mechanism of the reactivity of diazobenzo[b]fluorenes (Scheme 1.7). It was suggested that one electron reduction of **1.9** could lead to generation of semiquinone **1.26**. Further loss of the nitrogen moiety could be a consequence of

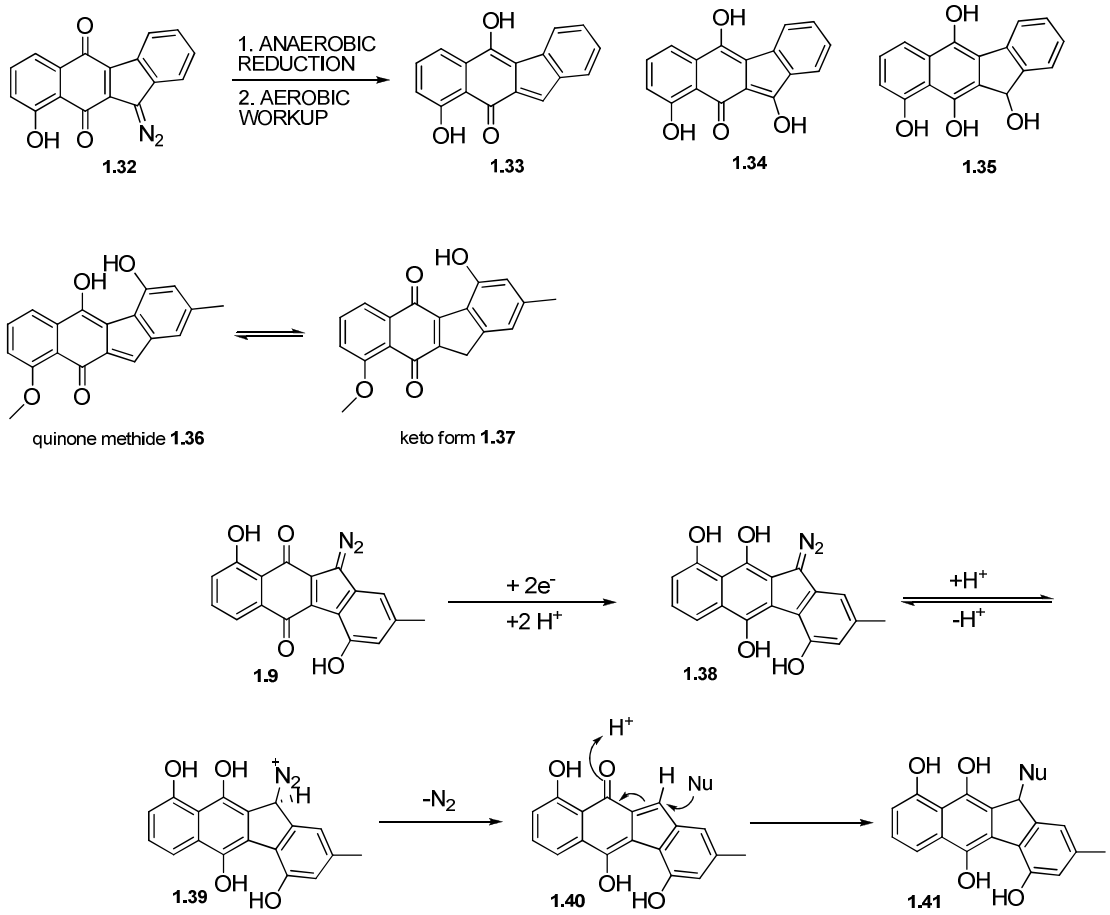
formation of reactive radical species **1.27** possessing DNA-damaging properties. Soon after publication this very general proposal was put into question.[27] The critics highlighted the ambiguity of a mechanism based on one electron reduction in the context of biological systems. In contrast to chemical reagents, known cellular reductants act only via two electron transfer.



Scheme 1.7. Feldman and Eastman`s prekinamycin`s studies.

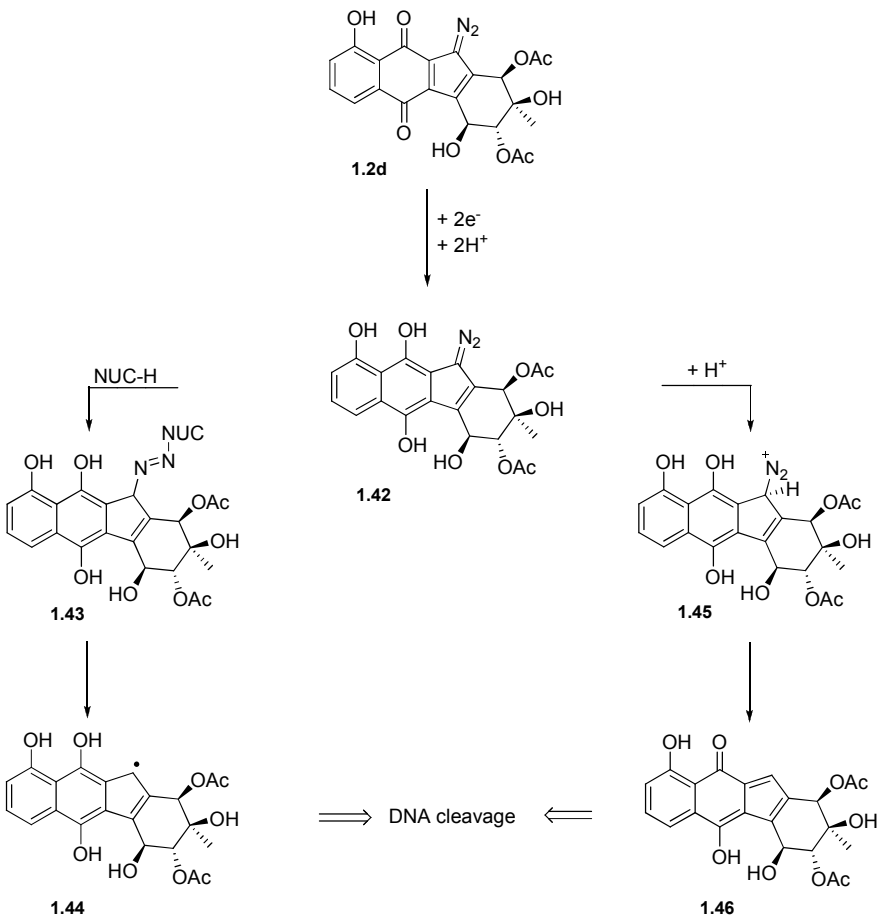
The reactivity of prekinamycin-like compounds was also studied by Khodour and Skibo.[26] In their hands compound **1.32** was subjected to anaerobic reduction followed by aerobic workup (Scheme 1.8). The result of this sequence was isolation of compounds **1.33-1.35**. Consequently, the hypothesis was set that the generation of quinone methide intermediates was required for products **1.33-1.35** to be formed.

Confirmation came with use of spectral global fitting experiments. Additionally, the examination of activity of different prekinamycin derived quinone methides showed that molecules with the more energetically stable keto form **1.37** were less potent against cancer cell lines. In a more general context it was proposed that the reactivity of diazobenzo[b]fluorenes was the consequence of their transformation into hydroquinones **1.38** via 2-electron reduction. Elimination of the nitrogen moiety could lead to formation of electrophilic quinone methides of **1.40** prone to react with cellular nucleophiles (**1.41**).



Scheme 1.8. Skibo`s prekinamycin studies.

The focus of a program led by Christopher Melander has been the DNA-cleavage properties of diazobenzo[b]fluorenes.[27] Initially working with diazo group-containing analogs of kinamycins and later testing properties of kinamycin D (**1.2d**), Melander`s team observed the ability of examined compounds to cleave DNA in the presence of cellular reductants (glutathione, DTT). Kinamycin D (**1.2d**) damaged DNA at physiological temperature, under acidic pH, at a minimal concentration of 1 μM. Not supported by any additional evidence, Melander and coworkers suggested two plausible explanations for the observed behavior of **1.2d**. The first potential route involved 2–electron reduction of the quinone functionality of **1.2d** to hydroquinone **1.42**. Generation of **1.42** could be followed by attack of a nucleophile to form adduct **1.43**. Subsequently, fragmentation of **1.43** would give radical **1.44** with the potential to cleave DNA. A second plausible route also involved formation of hydroquinone **1.42** via the 2-electron reduction process. Protonation of **1.42** could lead to loss of the nitrogen moiety and formation of reactive quinone methide **1.46**. As it was suggested, the second explanation was less valid as a result of lack of evidence for the DNA-cleaving properties of quinone methides.



Scheme 1.9. Melander`s proposal for the mechanism of action of kinamycins.

The laboratories of Gary Dmitrienko and Brian Hasinoff conducted a series of target identification studies of **1.2**.[21,28,29] Although, explicit identification of the cellular target of **1.2** has not been accomplished, several potential targets have been excluded. Additionally, the suggestion was made that kinamycin F could be involved in direct or indirect regulation of activity of cytokine D, a protein involved in cell cycle regulation.

Synthetic approaches toward diazobenzo[b]fluorenes

Total Synthesis of Kinamycins

Inspired by the complex structure and biological properties many research groups have attempted to synthesize compounds kinamycins and lomaiviticins with early efforts leading to the reassignment of the structure of the kinamycins.[6,7,8] However, it took more than 30 years for the first syntheses of a kinamycin to be accomplished. In 2006 Porco`s group along with Nicolaou`s group reported stereoselective syntheses of kinamycin C (**1.2c**) and kinamycins C, F, J. (**1.2c**, **f**, **j**), respectively.[30,31] Their routes were based on the late stage formation of the cyclopentadiene ring of the benzofluorene moiety (Figure 1.4). Shortly after, Ishikawa and coworkers published a synthesis of racemic methyl-kinamycin C.[32] This approach utilized a Diels-Alder reaction to install the highly oxidized D-ring subunit. Most recently, Herzon`s group developed a route for the synthesis of kinamycin F. The strategy involved disconnection of the cyclopentadiene ring of the benzofluorene as well.[33] However, in comparison to the work of Porco and Nicolaou, Herzon`s team based its design of an annulation sequence on a reversed bond formation order.

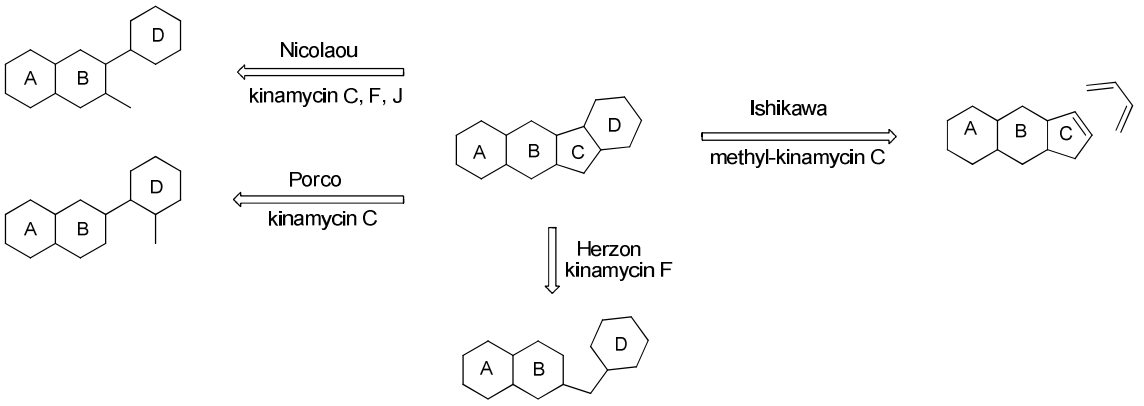
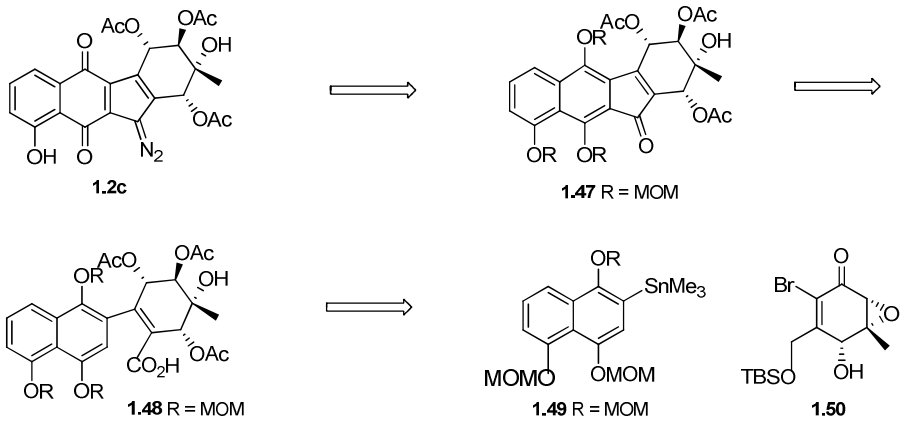


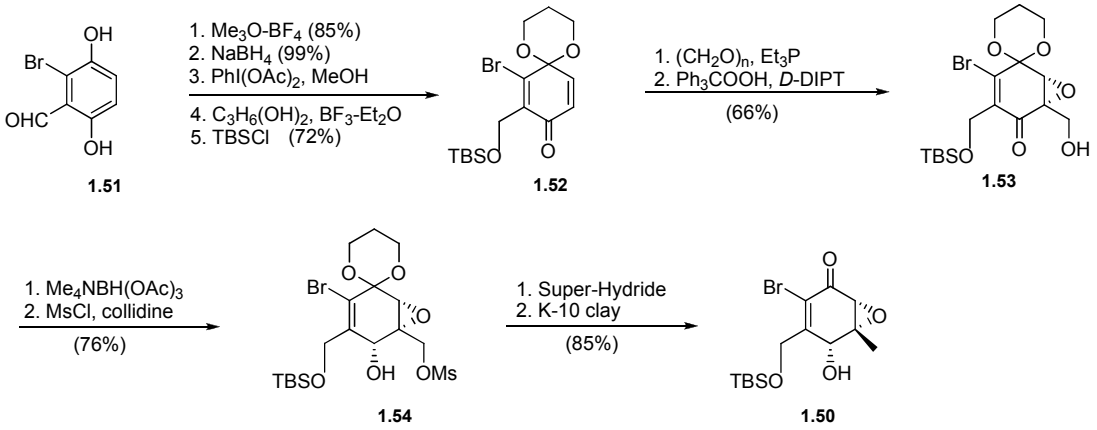
Figure 1.4. Overview of synthetic approaches to the kinamycins.

Recognizing the labile nature of the diazo group, Porco`s group decided to install this functionality at a late stage of the synthesis using ketone **1.47** as an advanced precursor (Scheme 1.10). A Friedel-Crafts cyclization was chosen to complete the cyclopentadienone ring formation and generate the benzofluorene skeleton of **1.2c**. Arylstannane **1.49** and bromoenone **1.50** were designed as two key building blocks to be utilized in an annulation sequence.



Scheme 1.10. Porco`s retrosynthetic analysis of kinamycin C (**1.2c**).

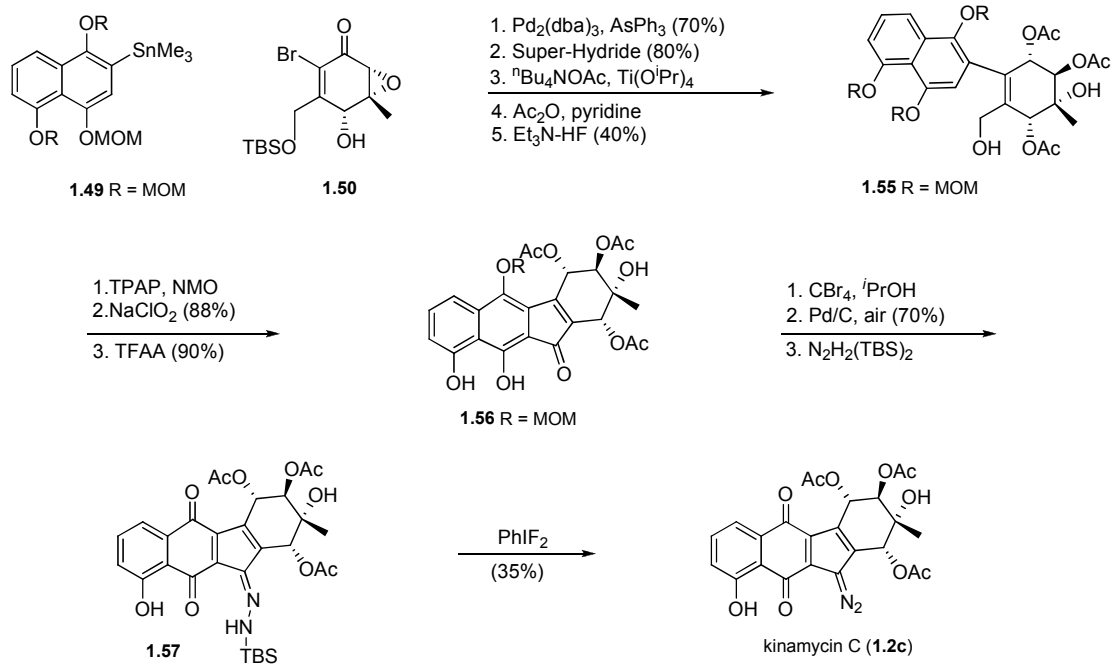
Conversion of known bromodiphenol **1.51** into quinone monoketal **1.52** with a key hypervalent iodine-mediated oxidation and tranketalization was a starting point for the synthesis of α-bromoenone **1.50** (Scheme 1.11). Baylis-Hillman reaction, followed by a carefully optimized tartrate-mediated nucleophilic epoxidation delivered epoxyalcohol **1.53** in 90% ee. A sequence of reductions and selective removal of the cyclic ketal with use of K-10 clay provided bromoenone **1.50**.



Scheme 1.11. Synthesis of bromoenone **1.50**.

Palladium catalyzed Stille coupling between **1.50** and arylstannane **1.49**, delivered in four steps from monobrominated juglone, was used as a first step in the annulation sequence (Scheme 1.12). Following a series of transformations of the complex epoxyketone **1.50** subunit produced a carboxylic acid, which was subsequently subjected to TFAA-mediated Friedel-Crafts cyclisation. As a result enone **1.56** was produced. Introduction of the quinone, followed by condensation with 1,2-bis(*tert*-

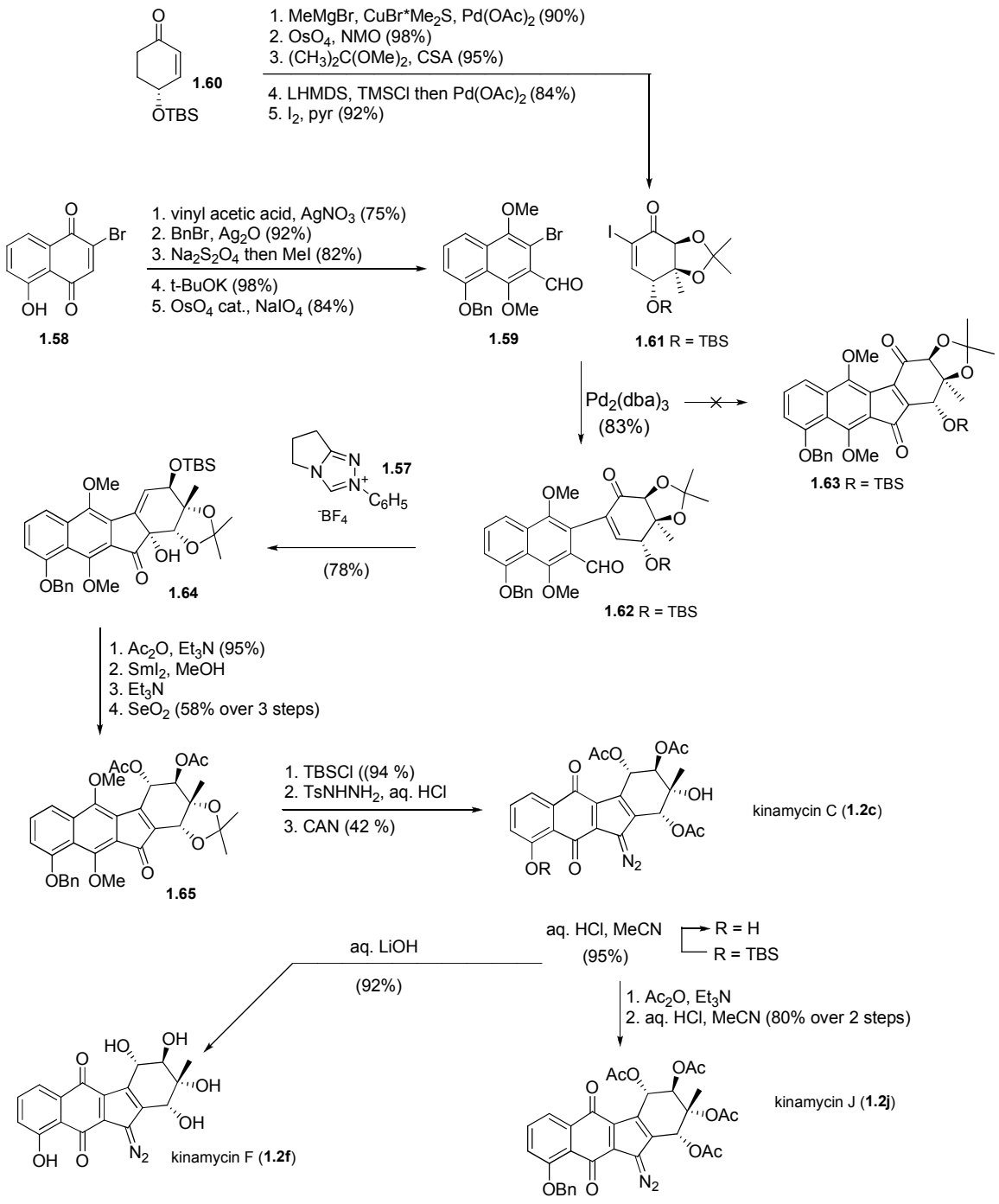
butyldimethylsilyl)hydrazine gave hydrazone **1.57**. Oxidation of **1.57** with $PhIF_2$ and 2-chloropyridine generated kinamycin C (**1.2c**) in 22 steps in the longest linear sequence.



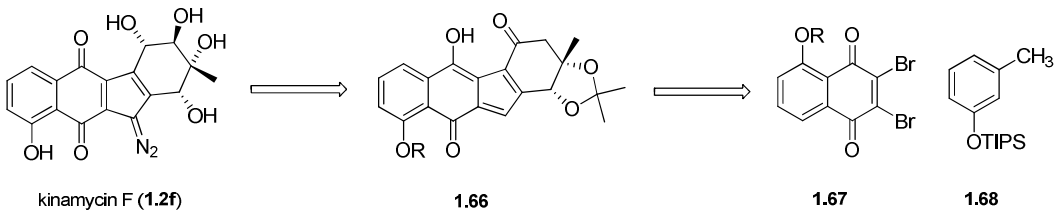
Scheme 1.12. Porco`s synthesis of kinamycin C.

Similar disconnections and late stage introduction of the diazo group were designed and applied by Nicolaou`s group in their syntheses of kinamycins C, F and J (**1.2 c**, **f**, **j**). Synthesis of arylbromide **1.59** and iodoenone **1.61** as key building blocks was followed by the application of a modified Ullmann reaction as a first step of the annulation sequence (Scheme 1.13). Suprisingly, treatment of coupling product **1.62** under Strecker reaction conditions did not produce enone **1.63**, but led to formation of ketone **1.64** as a result of benzoin–type transformation. A series of oxidation state changes on the right portion of the molecule involving base-mediated migration of a

double bond and SeO_2-induced allylic oxidation provided enone **1.65**. Similar to Porco`s approach, introduction of the diazo functionality was performed through the formation of a hydrazone and subsequent oxidation, in this case mediated by CAN. Controlled removal of protecting groups and acetylation produced different kinamycins C, F and J (**1.2c**, **f**, **j**).



Scheme 1.13. Nicolaou`s synthesis of kinamycin C, F, J (**1.2c**, **f**, **j**).

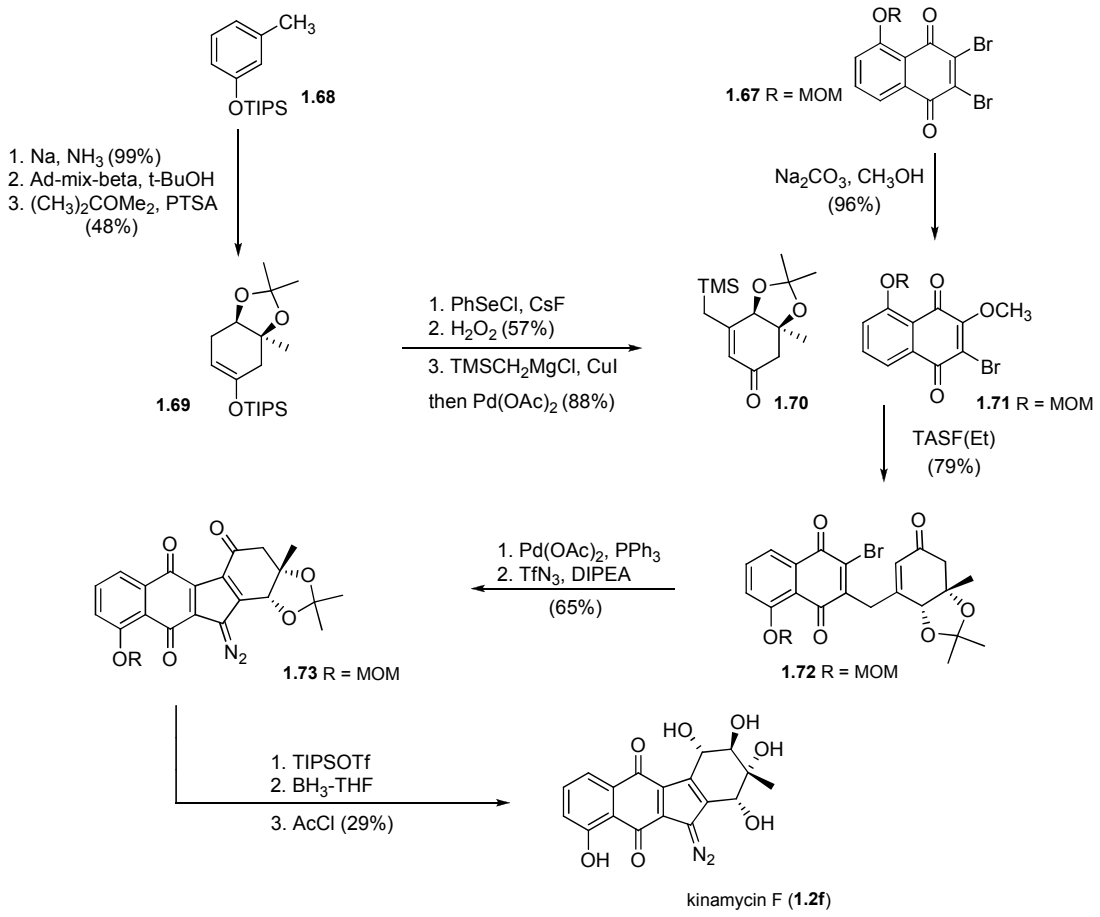


kinamycin F (**1.2f**) **1.66** **1.67** **1.68**

Scheme 1.14. Herzon`s retrosynthetic analysis of kinamycin F (**1.2f**).

The strategy chosen by the Herzon group led to development of a 3-step annulation sequence for the formation of the diazobenzo[b]fluoroene unit and allowed for preparation of kinamycin F (**1.2f**) in only 14 linear steps (Scheme 1.14). The starting point of the synthesis was the formation of acetonide **1.69** via Birch reduction of **1.68**, which was followed by regioselective asymmetric dihydroxylation and protection of the resultant vicinal alcohols (Scheme 1.15). Conversion of **1.69** into enone **1.70** was achieved in four steps involving Michael addition of the *in situ* generated cuprate of trimethylsilylmethamagnesium chloride and Saegusa oxidation. The first step of the annulation sequence was carried out in the presence of tris(diethylamino)sulfonium trimethyldisulforosilicate [TASF(Et)]. Treatment of allylic silane **1.70** with TASF(Et) in the presence of quinone **1.71** provided bromoquinone **1.72**. As reported, use of the methoxy substituted quinone **1.71** was key to the success of this transformation. With use of dibromoquinone **1.67**, formation of a product of 1,2-addition onto carbonyl groups could not be avoided. Completion of the annulation sequence was achieved by utilization of a Pd-mediated intramolecular Heck coupling. Production of quinone methide **1.66** was followed by treatment with azide triflate and Hunigs base. By taking advantage of the nucleophilic character of **1.66**, diazoquinone **1.73** was generated. Only

three more steps - α-oxidation, carbonyl reduction, and global deprotection - were required to generate target molecule kinamycin F (**1.2f**).



Scheme 1.15. Herzon`s synthesis of kinamycin F (**1.2f**).

Total Synthesis of Lomaiviticins

The structural complexity found in the structure of the kinamycins is, in the case of lomaiviticins, magnified by the dimeric nature of both compounds. Challenges associated with C-C bond formation between two monomeric units and the presence of sugars attached to the aglycon further complicate attempted synthesis.

Two general strategies are common for synthesis of molecules with C_2-symmetric character.[34] The first utilizes formation of a monomer followed by dimerization, and the second involves generation and further expansion of a central core. Both strategies were considered in the design of synthetic pathways to lomaiviticins.

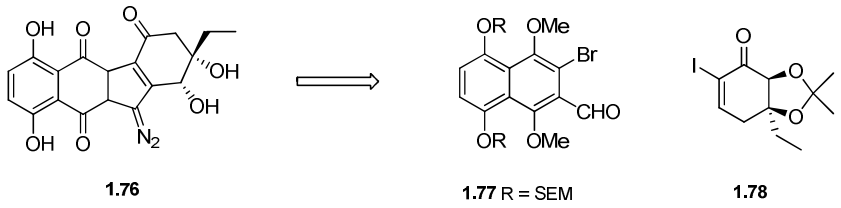
Initial work of Nicolaou`s group toward the preparation of lomaiviticin A was based on the core expansion strategy and involved a 16-step synthesis of bis-ketone **1.75** from enone **1.74** (Scheme 1.16).[35]

1.74 **1.75**

Scheme 1.16. Nicolaou`s lomaiviticin A central core synthesis.

In their most recent report (2010) the same group described generation of a monomer of lomaiviticin A **1.76** through application of a synthetic pathway developed

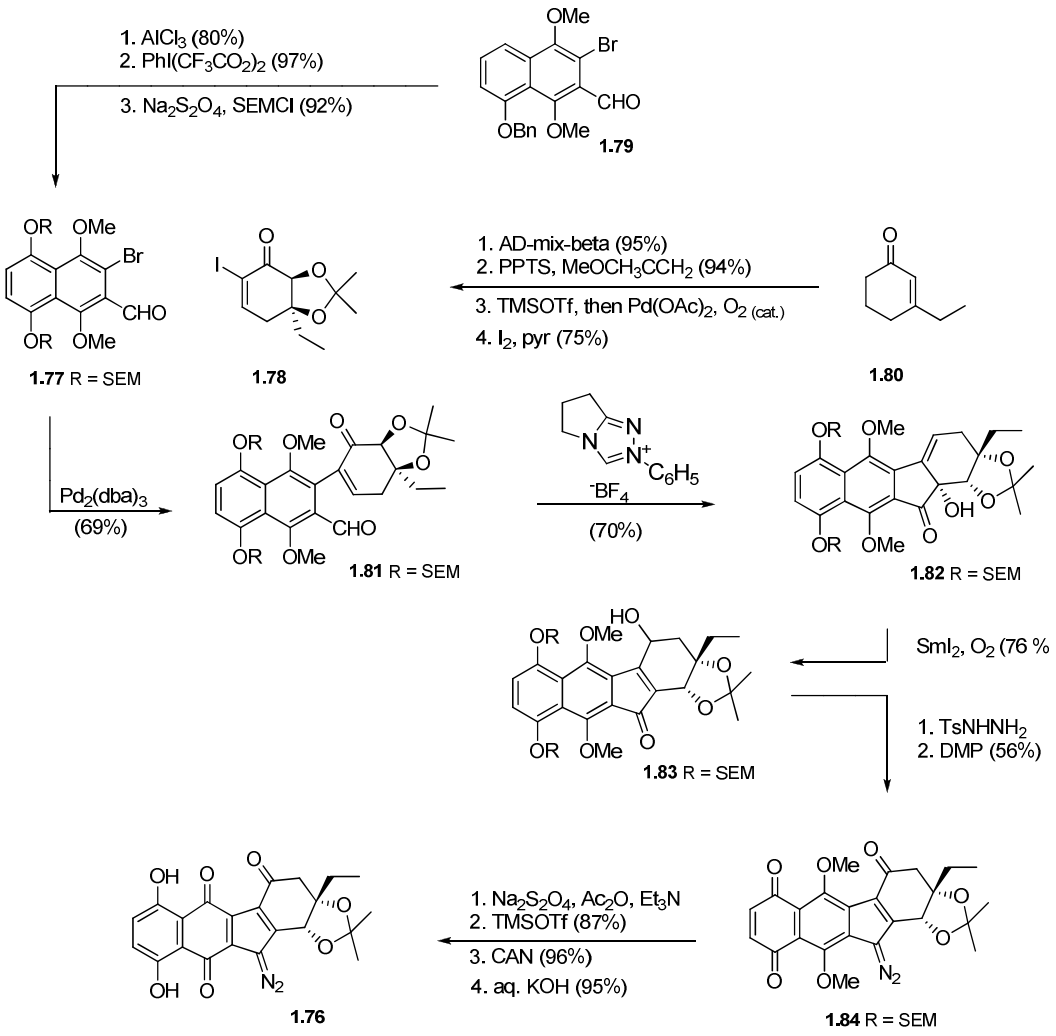
earlier for the synthesis of kinamycins C, F and J.[31,36] Retrosynthetically, compound **1.76** was designed to be generated through coupling of two key building blocks, aryl aldehyde **1.77** and iodoenone **1.78** (Scheme 1.17).



1.76 **1.77** R = SEM **1.78**

Scheme 1.17. Nicolaou`s retrosynthetic analysis of lomaiviticin A monomer.

A hypervalent iodine mediated oxidation of aldehyde **1.79** (previously used in the synthesis of kinamycins) was a key transformation in the synthesis of compound **1.77** (Scheme 1.18), and iodoenone **1.78** was prepared in four steps from enone **1.80**. The fragments were coupled via a palladium catalyzed Ullmann reaction to deliver aldehyde **1.81**. Benzoin-type transformation afforded ketone **1.82**. Treatment of **1.82** with SmI_2, $Na_2S_2O_4$ with O_2 bubbled through the reaction mixture led to formation of allylic alcohol **1.83**. Similar to the previous work, introduction of the diazo group was performed through the formation of a tosylhydrazone and subsequent oxidation. The synthesis of monomer **1.76** was achieved in the longest linear sequence of 9 steps. No attempts to form a dimer of **1.76** were discussed.



Scheme 1.18. Nicolaou`s synthesis of lomaiviticin A monomer (**1.76**).

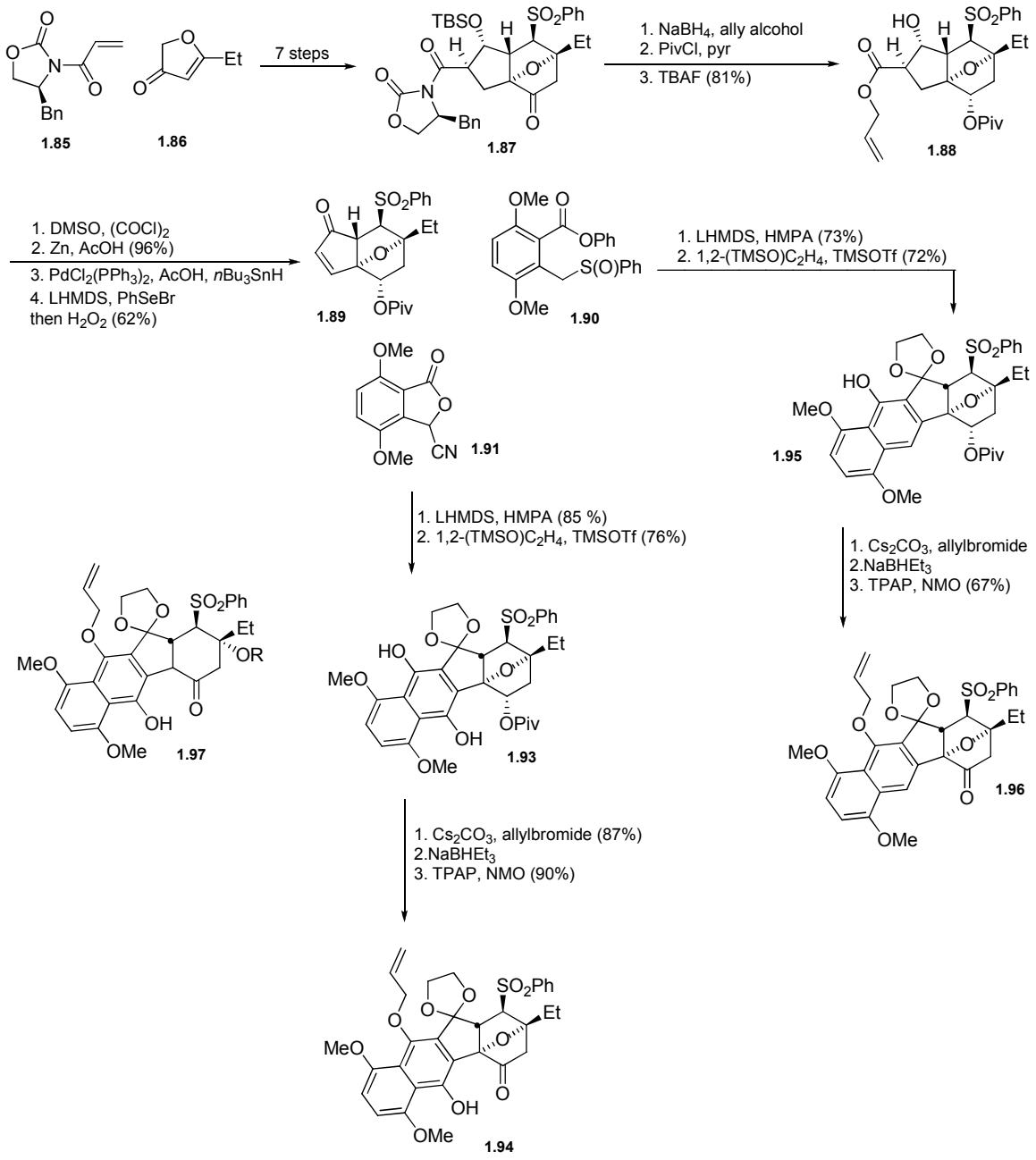
Dimerization as a way to increase efficiency by minimization of double processing (being characteristic of two directional strategy) was chosen by Shair and coworkers.[37,38] 7-oxabornanone **1.94** was designed as an advanced precursor for the key oxidative enolate coupling (Scheme 1.19). According to Shair`s team, application of **1.94** could be beneficial for two reasons: use of **1.94** could lead to dimerization stereoselectivity with central bond formation occurring from the convex faces of the

molecules, and potential β-elimination, which could take place if ketone enolate **1.97** was used could be prevented.

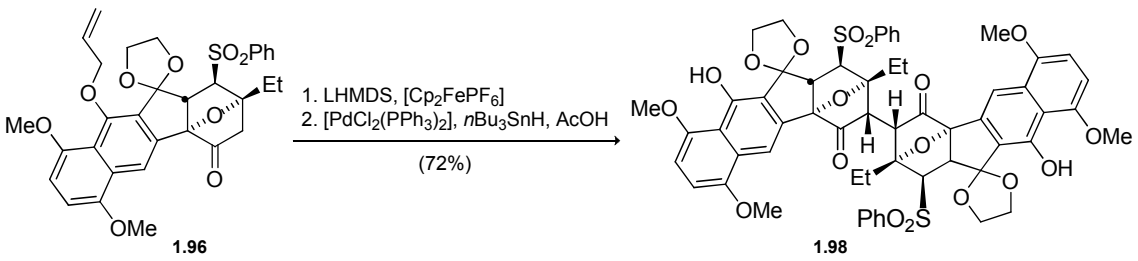
Shair`s initial studies were reported in 2008,[37] and involved generation of the central core of lomaiviticin A with use of $[Cp_2Fe]PF_6$ as a promotor in the coupling step. Two years later the work was expanded to preparation of a full carbon skeleton of the lomaiviticin aglycon (**1.98**) (Scheme 1.20).[38]

Synthesis of the monomeric unit **1.94** began with Michael addition of a lithium enolate of furanone **1.86** to oxazilidinone **1.85**. A six step sequence involving Evans protocol based aldol reaction and intramolecular furan Diels-Alder cycloaddition provided ketone **1.87**. With the goal of generating oxabornanone **1.89**, ketone **1.87** underwent a series of oxidation state changes, removal of protecting groups and introduction of the enone functionality via formation of phenylselenyl derivative and further H_2O_2 oxidation. Use of Kraus`s cyanophthalide method and treatment of **1.89** with the anion of hydroquinone **1.91** resulted in generation of hydroquinone **1.93**. Monoprotection of **1.93** as the allyl ether, reductive removal of pivaloyl group, and oxidation with TPAP provided oxidative enolate precursor ketone **1.94**. Unfortunately, application of previously developed conditions for the oxidative coupling of **1.94** based on the use of LHMDS and $[Cp_2FePF_6]$ did not lead to generation of the desired dimer of **1.94** but resulted only in decomposition or recovery of starting material. Shair`s group rationalized that nonbonded interactions occurring in the transition state could be responsible for inhibition of the dimerization step. To examine this hypothesis, ketone **1.96** was prepared via a Hauser-type annulation between enone **1.89** and sulfoxide

1.90. This time [Cp_2FePF_6] mediated oxidative coupling of **1.96** led to successful formation of phenol **1.98**, obtained as a single diastereoisomer. This result and further analysis of X-ray data confirmed Shair`s group hypothesis. With **1.98** in hand, the full carbon skeleton of lomaiviticin A aglycone was prepared. The challenge of synthesis of the fully oxidized lomaiviticins A aglycone remain to be addressed.



Scheme 1.19. Shair`s lomaiviticin A monomer synthesis.

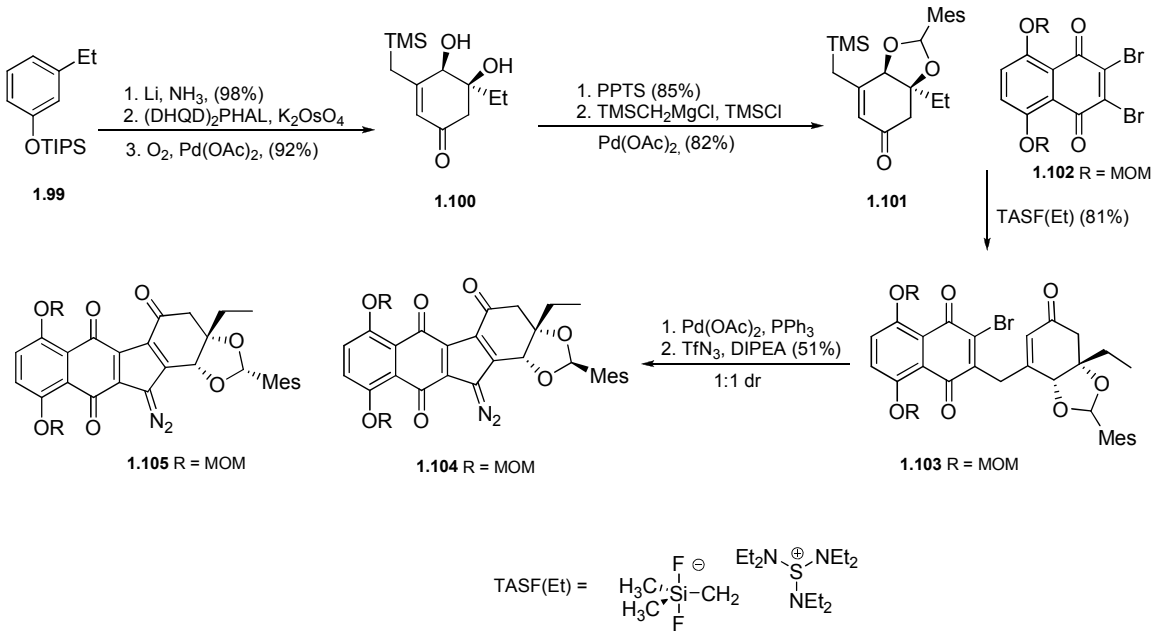


Scheme 1.20. Shair`s dimerization studies.

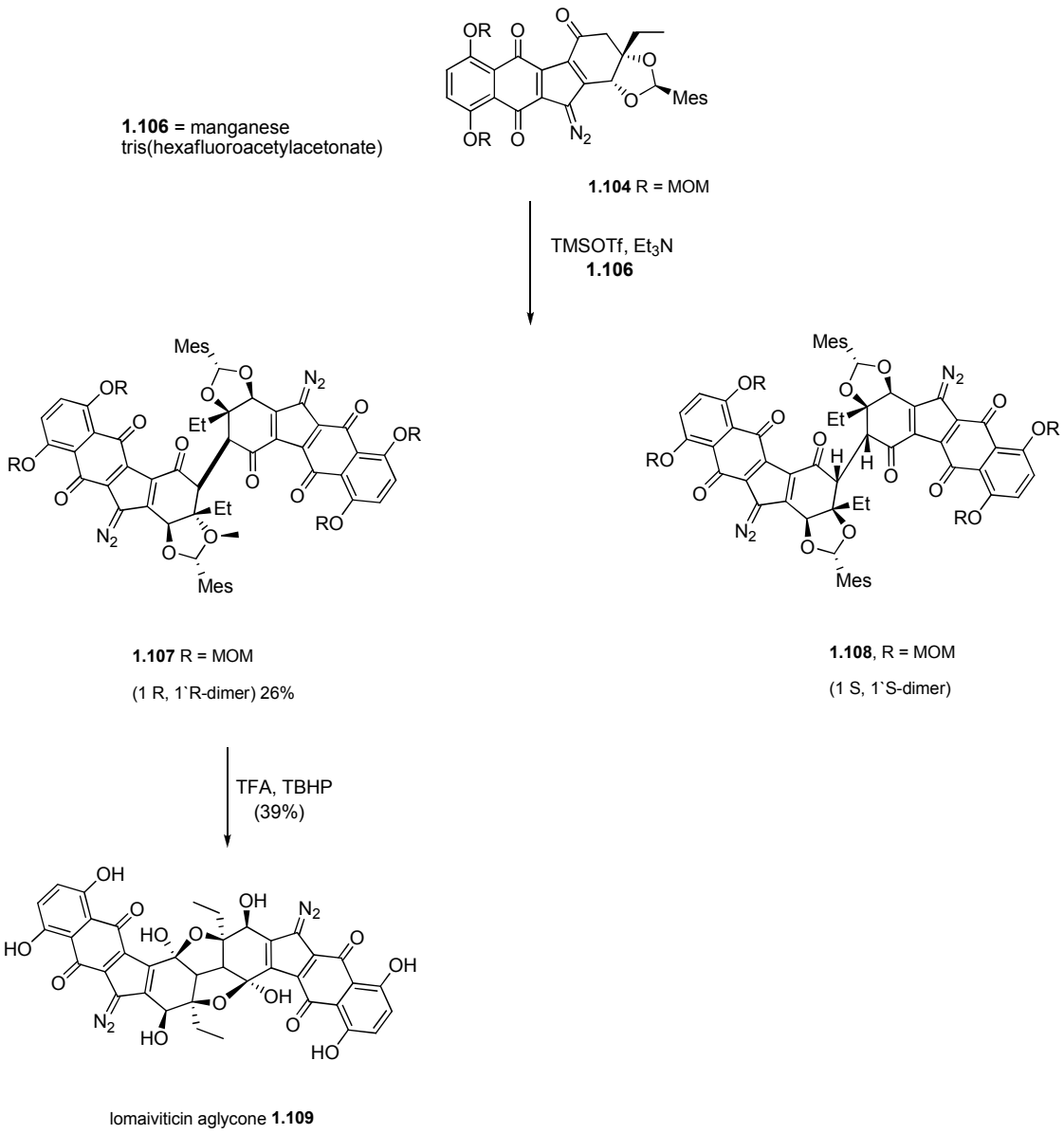
Earlier this year, Herzon and coworkers addressed the long-standing challenge of lomaiviticin B aglycon synthesis.[39] Driven by the assumption that compounds **1.3a** and **1.3b** are formed biosynthetically via oxidative coupling of two monomeric units, Herzon`s group decided to apply this strategy to their approach to **1.3b**. The effort resulted in the report of an 11-step sequence synthesis with many steps successfully executed on a gram scale. The route was based on their pathway developed previously for the preparation of kinamcin F (**1.2f**). The critical modifications resulted from a realization that tertiary alcohols present in compounds such as **1.100** are prone to undergo β-elimination leading to aromatization, a problem previously described and addressed by Shair and coworkers (Scheme 1.21).

The synthesis of **1.109** started with Birch reduction of silylated 3-ethylphenol, stereoselective dihydroxylation and $Pd(OAc)_2$ catalyzed oxidation to deliver enone **1.100**. Protection of the diol of **1.100** prevented β-elimination of the tertriary hydroxy group, and Michael addition of *in situ* formed cuprate of trimethylsilylmethyl group gave enone **1.101**. Coupling of **1.101** and dibromoquinone **1.102** mediated by tris(diethylamino)sulfonium trimethyldifluorosilicate afforded quinone **1.103**. Similarly,

as in the synthesis of kinamycin F (**1.2f**), a Heck coupling was used to produce the cyclopentadienone-containing quinone methide which subsequently was treated with with TfN_3 to generate diazobenzofluorenes **1.104** and **1.105** as a separable mixture of diastereoisomers. Identification of unique reaction conditions for the oxidative coupling, preceded by performing more than 1500 experiments, resulted in conversion of **1.104** into the enoxysilene and further dimerization to produce two diastereoisomers **1.107** and **1.108** (Scheme 1.22). The transformation was mediated by a rarely used manganese tris(hexafluoroacetylacetonate) (in the presence of CAN or $CuCl_2$ the enoxysilane underwent aromatization). Deprotection of the major and desired dimer **1.107** afforded lomaiviticin B aglycon - compound **1.109**.



Scheme 1.21. Herzon`s synthesis of the lomaiviticin monomer (**1.104**).



Scheme 1.22. Herzon`s synthesis of the lomaiviticin B aglycone (**1.109**).

Conclusion

Many years of research devoted to studies of diazobenzofluorene antibiotics resulted in numerous findings and better understanding of this family of compounds. Despite this, the most fascinating questions of the biosynthetic origin of the diazo group, reactivity and cellular target identification still need to be addressed. One can only hope that with recent successes in the field of total synthesis, ergo better access to molecules of interest, our curiosity will be soon satisfied.

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CHAPTER II

SYNTHESIS OF THE CENTRAL CORE OF LOMAIVITICINONE

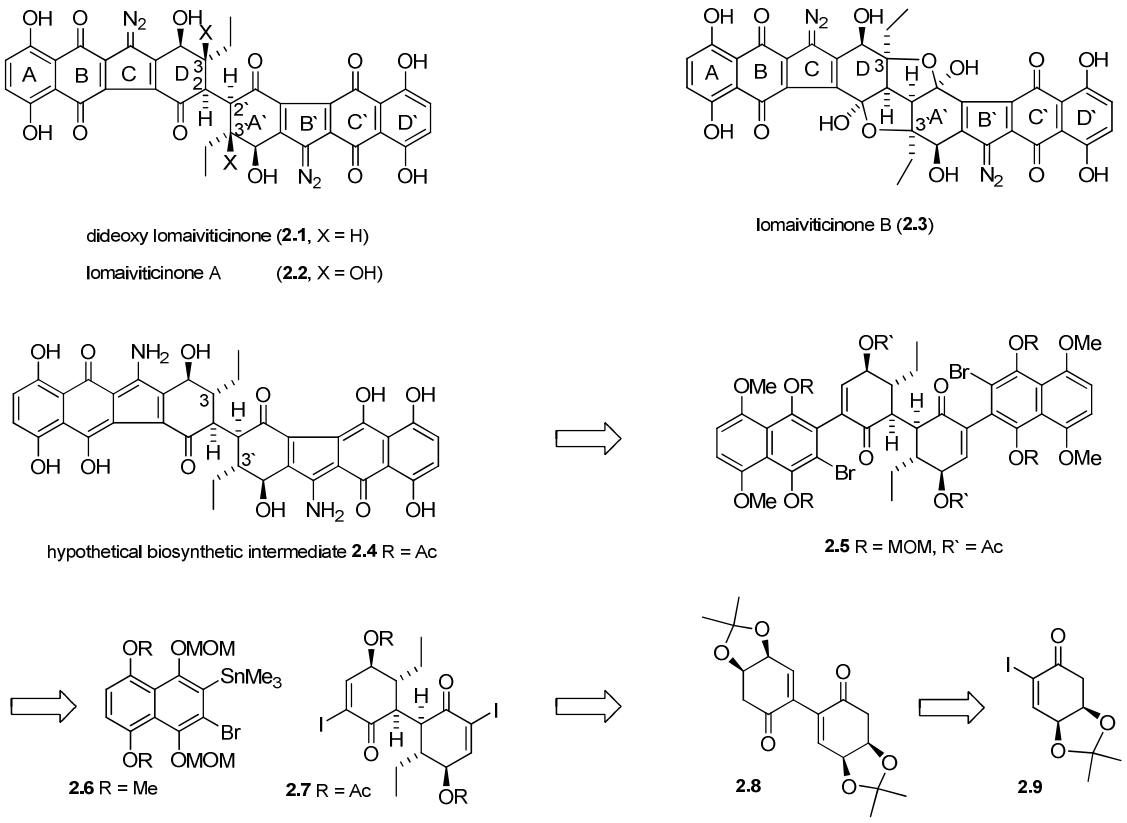
Synthetic analysis

Aromatic polyketides containing a quinone functionality have long been the subject of significant interest due to their complex structure and unique reactivity, which often imparts interesting biological properties.[1] Many members of this family have found clinical use, most often in the role of anticancer agents. Some, too toxic for clinical applications, have been utilized as research tools in mechanistic studies and in the context of biological systems. As a part of a program focused on total synthesis and ultimately biological and mechanistic studies of aromatic secondary metabolites, we set a goal of preparing 3,3`- dideoxy lomaiviticinone **2.1** (Scheme 2.1).

3,3`- Dideoxy lomaiviticinone, as an analog of the aglycone of lomaiviticin A (**2.2**) differs from the latter by the lack of two tertiary hydroxy groups in the central portion of the molecule. The decision to develop a synthetic approach for the preparation of **2.1** was two-fold: generation of **2.1** would be a starting point in an effort to prepare the more structurally challenging lomaiviticin A, and we anticipated that generation of the dideoxy analog of **2.2** could be advantageous in terms of biological studies. The hypothesis was made, later partially confirmed by Herzon`s observations,[2] that the aglycon of **1.3a** did not exist in its open-chained form, but with the lack of sugars

attached to it spontaneously cyclized to form the bis-hemiketal aglycon of lomaviticin B (**2.3**). Consequently, in contrast to the flat aglycone of lomaiviticin A, the aglycone of lomaiviticin B (**2.3**) existed in a bent form. At this point one can only speculate on the influence of these differences on the biological properties of **1.3a** and **1.3b**. We envisioned that the lack of tertiary alcohols in the central core of **2.1** would prevent formation of the bis-hemiketals and resemblance of **2.1** to the aglycone of lomaiviticin A would be ensured.

In contemplating a synthetic pathway to **2.1** we considered several factors: the labile nature of the diazo functionality, reactivity of the quinone ring and high functional density of the central core. In order to address these challenges the decision was made to examine a two-directional strategy involving preparation and further expansion of a central portion of the molecule. We anticipated that early-stage construction of the bis-cyclohexenone unit would have the advantage of stereocontrol about the key C2-C2` bond between two monomeric fragments. Toward preparation of advanced intermediate **2.5**: bis-iodoenone **2.7** would be coupled with arylstannane **2.6** as protected quinone. Inspired by the findings in the biosynthetic studies of kinamycins, we envisioned conversion of bis-enone **2.5** into bis-amine **2.4**. The structure of **2.4** resembled the structure of stealthin C (**1.8**), the biosynthetic precursor to kinamycins (Chapter 1). With preparation of **2.4** we envisioned examination of our biosynthetic hypothesis (Chapter 1) and conversion of **2.4** into **2.1** in a reaction with a nitrosonium ion source (NO^+).

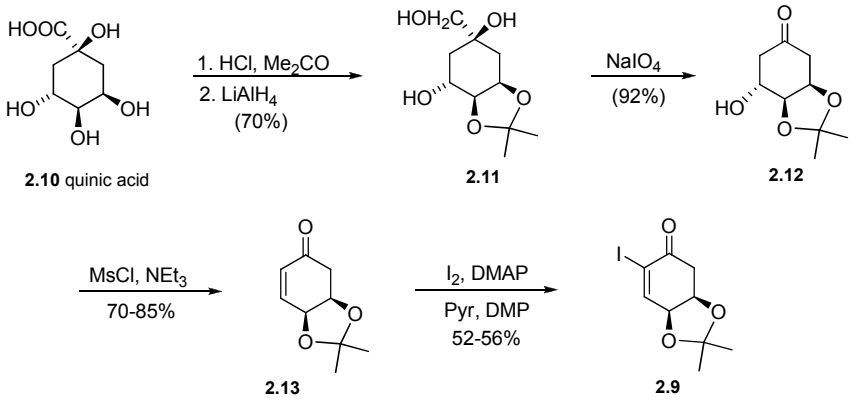


Scheme 2.1. Retrosynthetic analysis.

Construction of the Central Core Skeleton

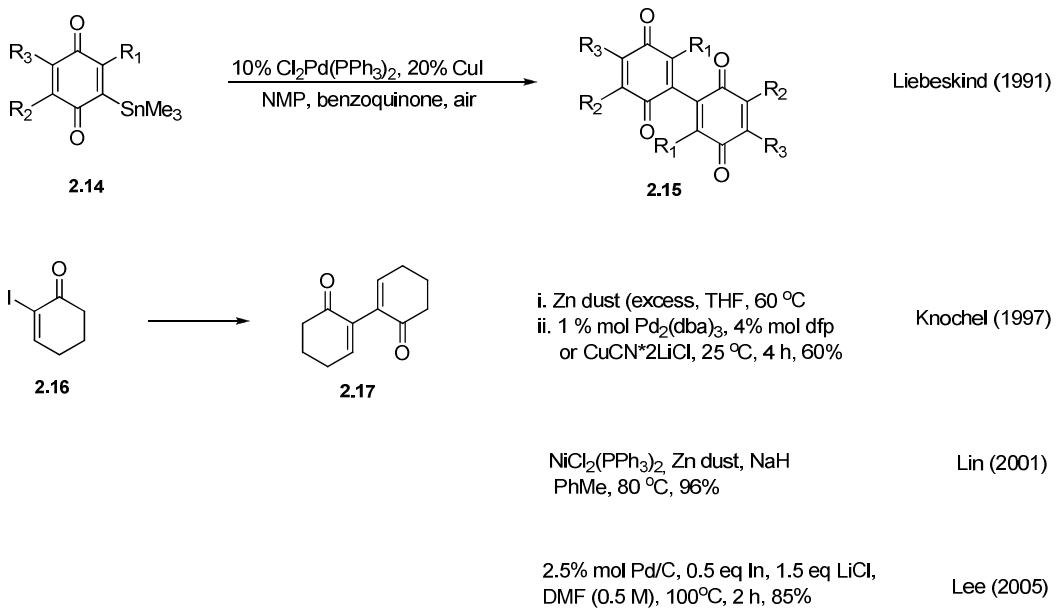
Application of the Danishefsky protocol for preparation of enone **2.13** starting from (-)-quinic acid (**2.10**) was the starting point for the synthesis of the central core of dideoxy lomaiviticinone (Scheme 2.2).[3] Reduction of quinic acid **2.10** into triol **2.11**, followed by $NaIO_4$-mediated oxidative cleavage led to formation of β-hydroxy ketone **2.12**. Treatment of **2.9** with MsCl under basic conditions produced enone **2.13**, and a modification of Johnson`s α-halogenation procedure delivered base-sensitive α-iodo enone **2.9** in yields varying between 50 and 60%.[4,5] With cyclohexanone **2.9** in hand,

identification of appropriate homocoupling conditions was undertaken to generate the skeleton of the central core.



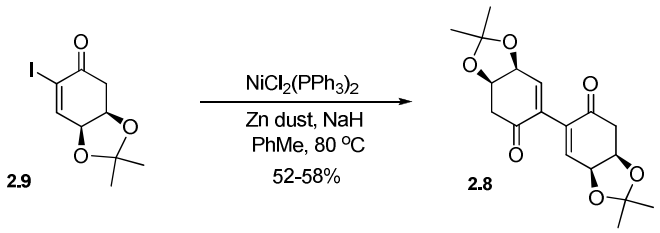
Scheme 2.2. Synthesis of α-iodoenone **2.9**.[3,4,5]

Examples of homocoupling of α-substituted enones and their analogs are rather rare and limited to few reports. In 1991, Liebeskind described successful palladium-catalyzed homocoupling of stannylquinone **2.14** (Scheme 2.3).[6] The first example of a Negishi-type homocoupling of α-iodoenone **2.16** was reported by Knochel, and involved *in situ* generation of the zinc derivative of α-iodoenone **2.16** by the application of excess amount of zinc dust.[7] Subsequent addition of a palladium catalyst or copper reagent resulted in the formation of homocoupling product **2.17**. In 2005, a method based on use of a palladium catalyst and indium as a reducing agent was described.[8] As reported, desired products could be obtained in excellent yields (80-92%).



Scheme 2.3. Methods for homocoupling of α-substituted enones.

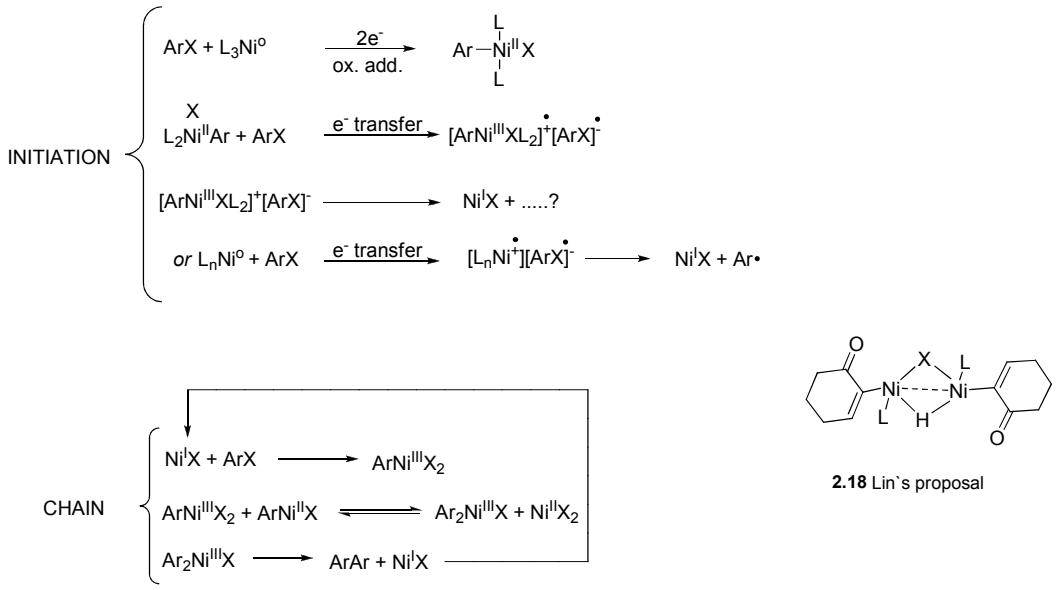
We decided to evaluate an unusual set of conditions developed by Ling and Hong for Ullmann homocoupling of aryl halides and α-iodoenones (Scheme 2.3).[9] Treatment of **2.9** with a nickel catalyst, Zn dust and NaH in toluene, the first example of this specific reductive system led to formation of desired dimer **2.8** (Scheme 2.4).



Scheme 2.4. Formation of bis-enone **2.8**.

Mechanistic aspects of this transformation remain vague. Although literature examples of similar transformations were suggested to involve a free radical mechanism

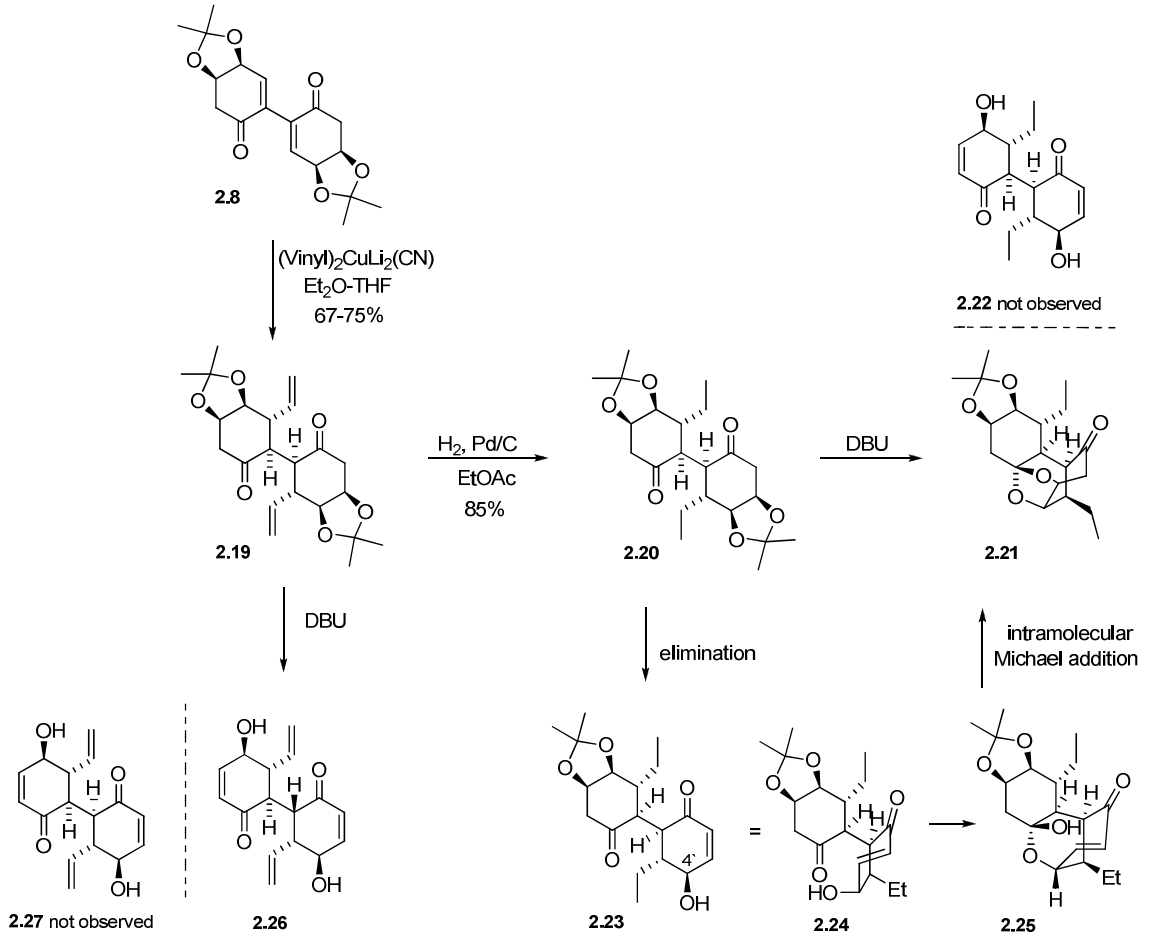
similar to the one shown in Scheme 2.5, experimental observations did not support the generation of radical intermediates.[10] The authors proposed formation of an intermediate complex **2.18** as a part of the mechanistic pathway; however, no further details have been reported.



Scheme 2.5. Proposed mechanistic explanation for Ni-catalyzed couplings.

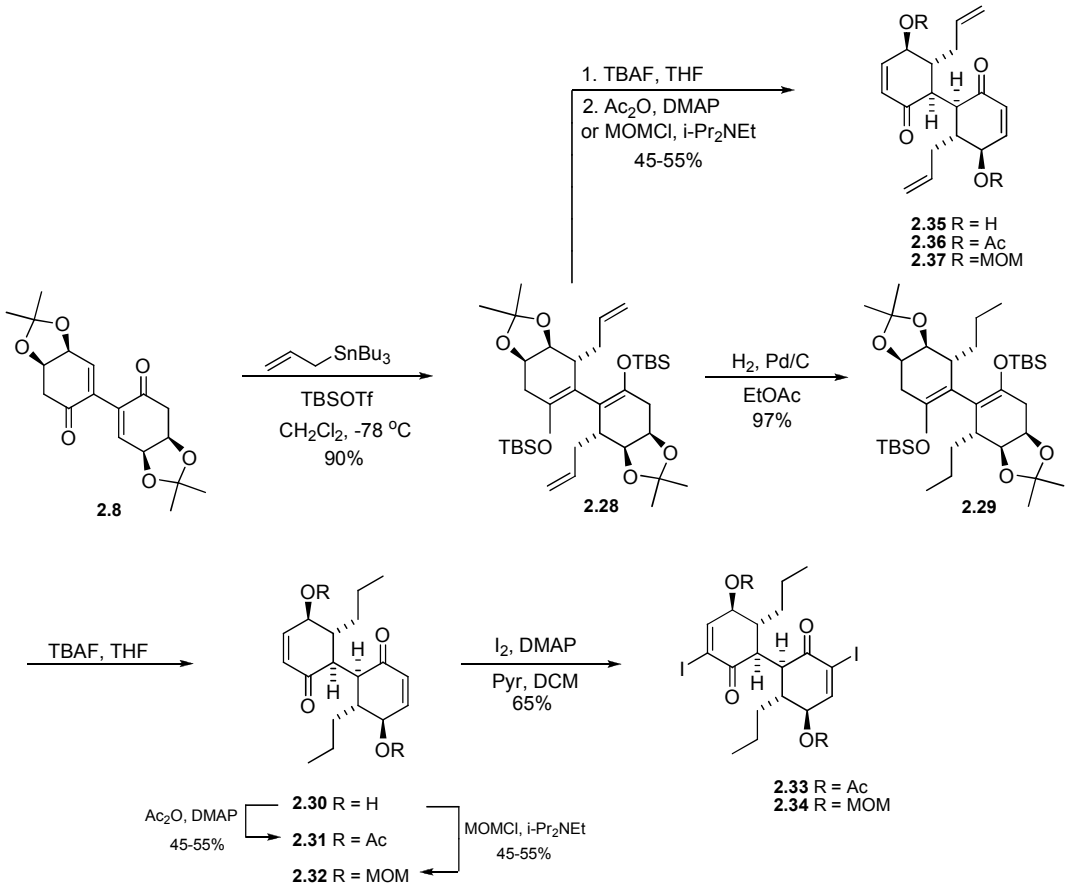
We next turned our attention to introduction of the ethyl groups by treatment of bis-enone **2.8** with vinyl cuprate to stereoselectively deliver ketone **2.19** (Scheme 2.6). Hydrogenation of **2.19** over palladium-carbon completed installation of the ethyl groups to give diketone **2.20**. With the objective to produce bis-alcohol **2.22**, the central core of dideoxy lomaiviticinone, ketone **2.20** was subjected to base-mediated elimination of the acetonide units. Suprisingly, treatment of **2.20** with DBU or aqueous NaOH did not give bis-alcohol **2.22,** but instead led to tetracyclic ketone **2.21** as assigned by extensive 2D-

NMR analysis. Generation of **2.21** could be explained by following reaction pathway. Single elimination of an acetonide ring of **2.20** leads to formation of the unsymmetrical enone **2.23**. The C4` hydroxyl group then adds to neighboring keto group to give hemiketal **2.25**. The addition is followed by addition of the hemiketal group in a 1,4-fashion to the neighboring enone. Examination of the same type of transformation with use of bis-vinyl ketone **2.19** also failed to produce the desired diol **2.27**, but instead formed alcohol **2.26**, the product of epimerisation.



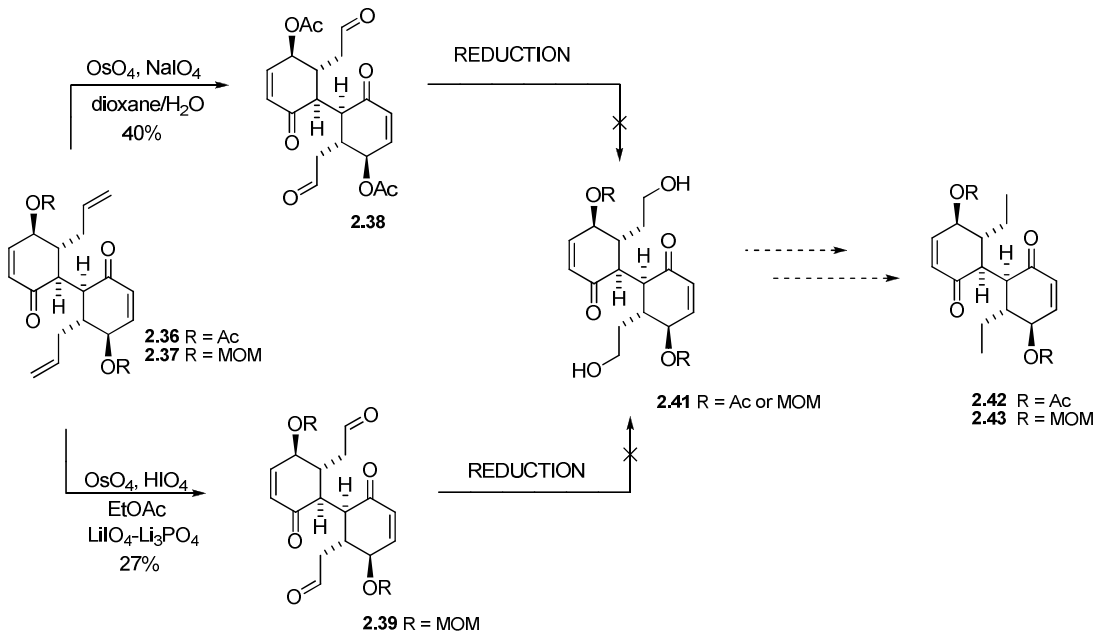
Scheme 2.6. Attempts to synthesize bis-enone **2.22**.

At this stage, formation of the allyl derivative of bis-enone **2.8** was examined in hope of changing the reaction pathway (Scheme 2.7). To this end, bis-enone **2.8** was treated with allyltributylstannane in the presence of TBSOTf to successfully provide bis-silyl enol ether **2.28**.[11] Hydrogenation of **2.28** gave bis-propyl analog **2.29** in near quantitative yield. We were pleased to observe that treatment of **2.29** with TBAF led to formation of diol **2.30** as a result of removal of both silyl and acetonide protecting groups. After protection of the secondary hydroxy groups and double α-iodination, bis-iodoenone **2.33** was produced. X-ray analysis of **2.33** confirmed the desired relative stereochemistry about the C-C bond between two cyclohexenone units of the molecule.[12]



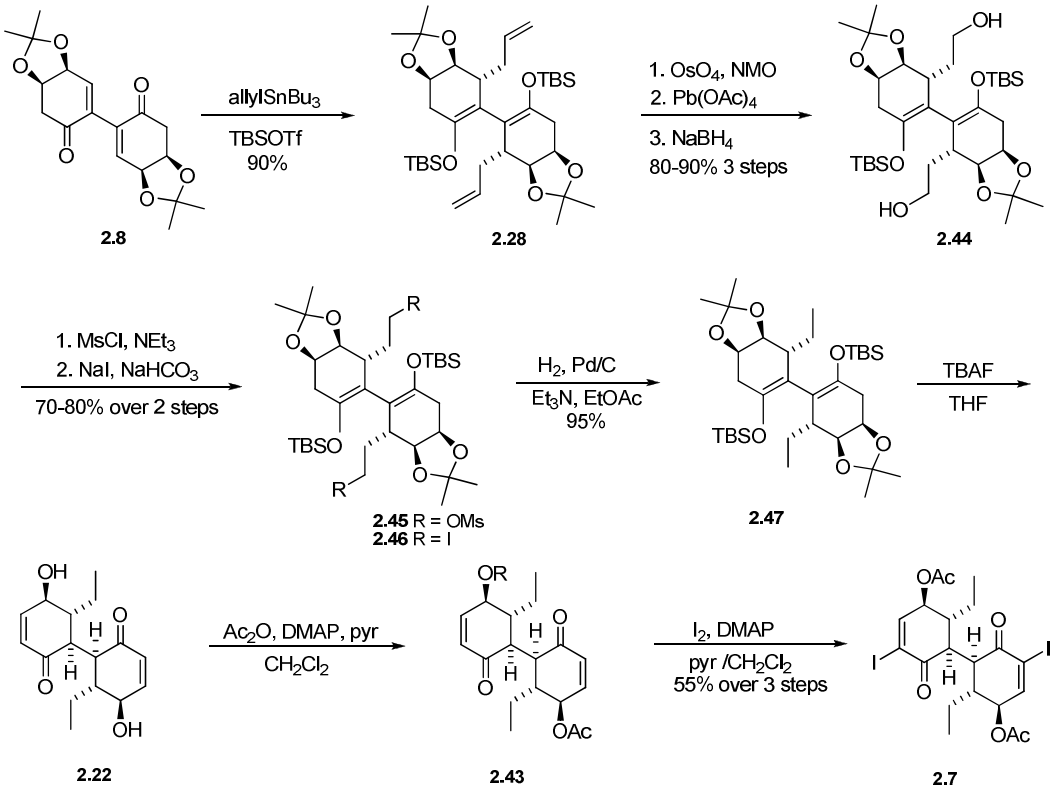
Scheme 2.7. Synthesis of bis-enones **2.33/2.34** and **2.36/2.37**.

Fortunately, we were also able to apply a developed sequence of reactions to provide bis-allylenone **2.36** from silylenol ether **2.28** in ~50% yield (Scheme 2.7). Development of a pathway to produce **2.33** and **2.36** was initially seen as a distraction from our actual studies but turned out to be very helpful in continuation of our effort to prepare bis-ethylenone **2.22**. With **2.36/2.37** in hand, we envisioned that desired **2.42/2.43** could be generated through the formation of bis-aldehyde **2.38/2.39** and its further reduction (Scheme 2.8). After investigation of several different conditions for the oxidative cleavage of terminal olefins, we found that bis-acetyl enone **2.36** could be converted into desired aldehyde **2.38** under Johnson-Lemieux conditions,[13] and bis-MOM aldehyde **2.39** was obtained when treated with a buffered solution of OsO_4 and HIO_4.[14] Unfortunately, none of the aldehydes could be successfully converted into desired alcohol **2.41**. These results prompted us to reexamine our approach.



Scheme 2.8. Early approach to the synthesis of bis-enone **2.42/2.43**.

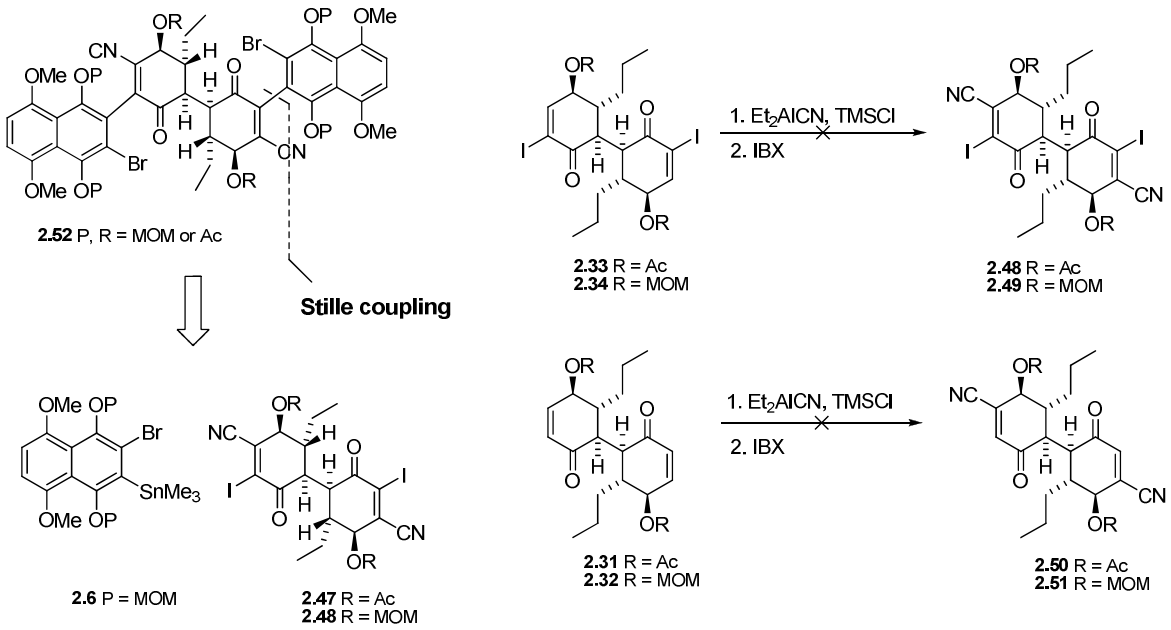
After some consideration, the decision was made to continue our studies with use of silyl enol ether **2.28** as a starting point for the cleavage of the allyl groups and introduction of the ethyl groups. To realize our goal, compound **2.28** was treated with OsO_4 in dioxane–water solution to form the bis-diol (Scheme 2.9). Following oxidative cleavage with $Pb(OAc)_4$ in dichloroethane, $NaBH_4$ reduction of the requisite bisaldehyde generated alcohol **2.43** in 80-90% yield over three steps. Mesylation of diol **2.44**, followed by iodide substitution under Finkelstein conditions gave bis-iodide **2.46** in 70-75%. After examination of several different conditions for the reduction of primary iodides of **2.46** to the desired ethyl groups ($Et_3SiH/PdCl_2$, Bu_3SnH/AIBN, $NaBH_4$) we found that hydrogenation (H_2, (atm), Pd/C, Et_3N) of **2.46** gave **2.47**.[15] The previously examined fragmentation–elimination sequence triggered by treatment of **2.47** with TBAF afforded diol **2.22** as the desired isomer with no epimerisation observed. Protection of the secondary hydroxy groups of **2.22** as MOM ethers provided bis-enone **2.43**. Iodination of **2.43** gave the core of dideoxy lomaiviticinone, bis-iodoenone **2.7**, in 55% yield over three steps.[12]



Scheme 2.9. Synthesis of bis-iodoenone **2.7**.

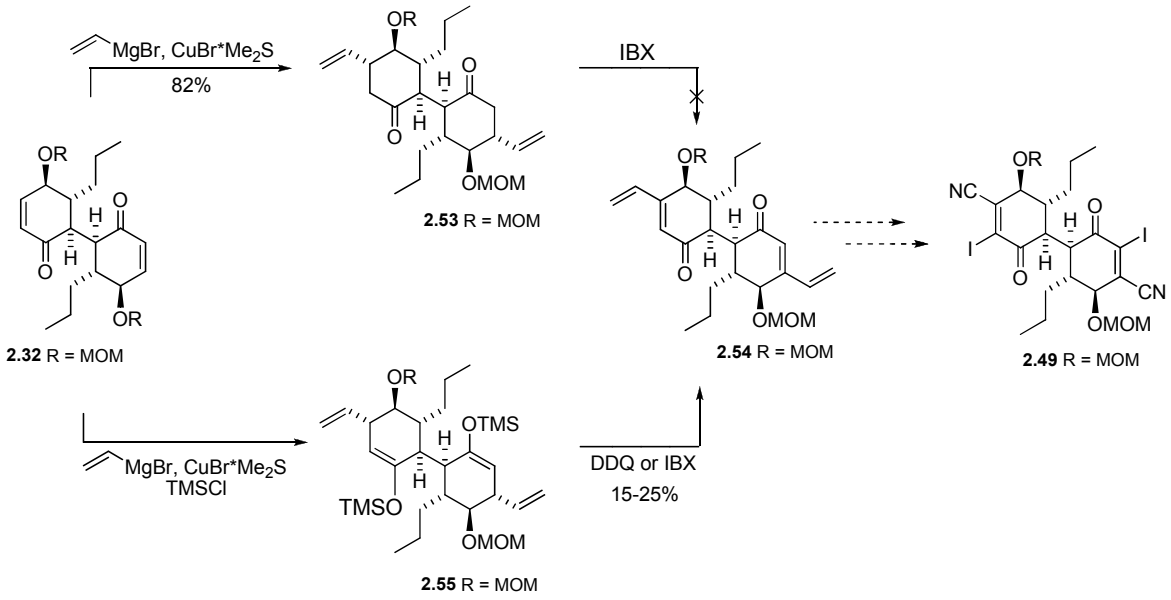
Core Expansion Studies

With successful formation of the central core we turned our attention to its expansion and incorporation of BCD/B`C`D` ring units. We envisioned generation of bis-α-iodo-β-cyano enone **2.48/2.49** which could be coupled to the aromatic portion of the molecule to produce **2.52** (Scheme 2.10). We planned to incorporate the cyano group as the central carbon of the fluorene ring. Disappointingly, application of Nicolaou`s 2-step protocol for the formation of β-cyano enones based on IBX oxidation of the initially formed silyl enol ether did not give desired enones **2.48-2.51** but led to decomposition of substrates **2.31-2.34**.[15]



Scheme 2.10. Failed introduction of cyano group.

At this point, we decided to turn our attention to the synthesis of bis-dienone **2.54** and its further conversion into desired bis-nitrile **2.49** (Scheme 2.11). Michael addition of *in situ* generated vinyl cuprate led to bis-ketone **2.53** in high yield of 80%. Although further attempts to oxidize **2.53** failed to produce **2.54**, the desired bis-enone could be obtained in two steps from enone **2.32** via formation of silylenol ether **2.55**. Unfortunately, unsatisfactory yields, failed α-iodination and unsuccessful oxidative cleavage of terminal olefins led to the termination of this route.



Scheme 2.11. Failed synthesis of bis-iodoenone **2.49**.

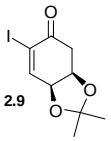
Conclusion

Presented in this chapter is the successful synthesis of the central core of dideoxy lomaiviticinone. The key transformations used to achieve this goal were a Nickel-catalyzed Ullmann coupling to build the skeleton of **2.8** and a TBAF-mediated fragmentation-elimination sequence which produced the stereochemically desired diol **2.22**. The described work set the course for the next chapter of our studies toward the synthesis of dideoxy lomaiviticinone.

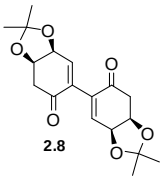
Experimental methods

General. All non-aqueous reactions were conducted under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and, unless otherwise stated, used without further purification. Toluene (CH_3Ph), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) were obtained through purification of commercially available solvents with use of activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was purified by distillation from Na metal with benzophenone indicator. Triethylamine (Et_3N) and N,N-diisopropylethylamine ($i Pr_2NEt$) were distilled from CaH_2 and stored over KOH. Thin-layer chromatography was performed on E.Merck precoated silica gel 60 F524 plates. The plates were visualized with UV light and aqueous stain ($KMnO_4$ or CAM). Liquid chromatography (flash chromatography) was conducted using indicated solvents and Dynamic Adsorbents silica gel 60 (230-240 mesh). Thermo Electron IR100 series instrument was used to record infrared spectra as thin films on NaCl plates. ^1H and ^{13}C NMR were recorded on Bruker 300, 400, 500, 600 spectrometers at ambient temperature and are reported relative to deuterated solvent signals. *n*-BuLi was titrated with use of the Suffert method.

Preparative Procedures

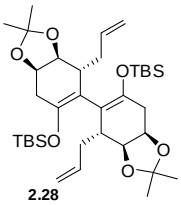

2.9

To a solution of **2.13** (2.0 g, 11.9 mmol) in pyridine/CH_2Cl_2 (1:2, 37.5 mL) at 0 °C was added a solution of iodine (7.55 g, 29.7 mmol) in pyridine/CH_2Cl_2 (1:1, 25.0 mL) over a period of 3 h. Upon complete addition, DMAP (0.29 g, 2.38 mmol) was added and the ice bath was removed. After 3 h the reaction mixture was diluted with Et_2O (500 mL), washed with water (100 mL), 1 N HCl (2 x 100 mL), water (100 mL), 20% $Na_2S_2O_3$ (100 mL), and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to flash chromatography (2:1, hexanes/EtOAc) to afford iodoenone **2.9** (2.2 g, 63%; 74% BRSM) as a pale yellow solid. The ^1H and ^{13}C data for the prepared compounds are fully consistent with those reported in the literature.[4,5]


2.8

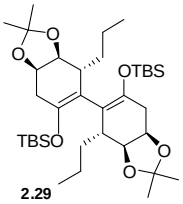
To a suspension of NaH (544 mg, 13.6 mmol, 60% in mineral oil, washed with hexanes prior to use) in toluene (50.0 mL) were added $NiCl_2(PPh_3)_2$ (556 mg, 0.850 mmol), PPh_3 (446 mg, 1.70 mmol), zinc dust (333 mg, 5.10 mmol) and **2.9** (500 mg, 1.70 mmol) simultaneously. The mixture was immediately evacuated and flushed with Ar (4 x). The reaction mixture was placed in 88 °C oil bath. After 4 h the oil bath was removed and the mixture was cooled to 0 °C by ice bath. A solution of 1 N HCl (2 mL) was added to reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). The solvent was concentrated *in vacuo* and the residue was subjected to flash chromatography (1:1,

hexanes/EtOAc) to give dimer **2.8** (182 mg, 64%) as a white solid: $[\alpha]_D^{20}$ –48.7° (c 1.0, $CHCl_3$); IR (neat) ν 1684, 1230, 1060, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 2H), 4.79 (s, 2H), 4.68 (s, 2H), 2.93 (dd, *J* = 2.4, 16.8 Hz, 2H), 2.83 (dd, *J* = 3.3, 16.8 Hz, 2 H), 1.36 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 142.8, 135.9, 109.8, 73.83, 71.28, 39.49, 27.97, 26.50; HRMS (ESI) calcd for $C_{18}H_{22}O_6Li$ [$(M+Li)^+$] 341.1576 found 341.1582.



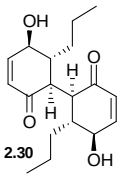
2.28

To a solution of enone **2.19** (200 mg, 0.598 mmol) and allyltributyltin (792 mg, 2.39 mmol) in CH_2Cl_2 (20.0 mL) at –78 °C was added TBSOTf (632 mg, 2.39 mmol) dropwise. After 4 h the 5% aqueous solution of $NaHCO_3$ was added and the cold bath was removed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was concentrated *in vacuo* and the residue was subjected to flash chromatography (10:1, hexanes/EtOAc) to give silylenol ether **2.28** (375 mg, 97%) as a colorless, thick oil: $[\alpha]_D^{20}$ +30.6° (c 1.06, $CHCl_3$); IR (neat) ν 2931, 1373, 1246, 1200, 1043, 835, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.71 (m, 2H), 5.02-4.94 (m, 4H), 4.50-4.43 (m, 2H), 4.25 (d, J = 6.8 Hz, 2H), 2.44 (dd, J = 4.8, 16.0 Hz, 4H), 2.25 (d, J = 14.8 Hz, 4H), 1.88 (q, J = 11.6 Hz, 2H), 1.34 (s, 6H), 1.26 (s, 6H), 0.86 (s, 18H), 0.14 (s, 6H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 137.8, 115.8, 112.1, 107.3, 74.6, 74.0, 40.1, 34.6, 33.5, 26.4, 26.1, 24.2, 18.1, –2.5, –3.4; HRMS (ESI) calcd for $C_{36}H_{62}O_6Si_2Li$ [$(M+Li)^+$] 653.4245, found 653.4222.



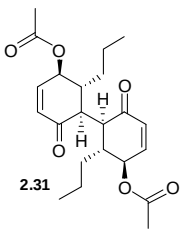
2.29

A mixture of **2.28** (430 mg, 0.665 mmol) and 10% Pd/C (150 mg) in EtOAc (30.0 mL) was applied to the atmosphere of H_2. After 2 h the suspension was filtered through celite pad. The solvent was removed *in vacuo* and the residue was subjected to flash chromatography (10:1, hexanes/EtOAc) to give silylenol ether **2.29** (420 mg, 97%) as a white solid: $[\alpha]_D^{20}$ +30.4° (c 1.04, $CHCl_3$); IR (neat) ν 1370, 1245, 1203, 1046, 901, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53-4.41 (m, 2H), 4.33-4.20 (m, 2H), 2.44 (dd, J = 5.2, 16.8 Hz, 2H), 2.35-2.28 (m, 2H), 2.20 (dd, J = 1.6, 16.4 Hz, 2H), 1.47-1.21 (m, 6H), 1.34 (s, 6H), 1.28 (s, 6H), 1.17-1.07 (m, 2H), 0.83 (t, J = 6.8 Hz, 6H), 0.85 (s, 18H), 0.13 (s, 6H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 113.0, 107.1, 75.4, 74.1, 40.3, 33.4, 32.7, 26.2, 26.1, 24.1, 21.5, 18.1, 14.3, –2.4, –3.5; HRMS (ESI) calcd for $C_{36}H_{66}O_6Si_2Na$ [$(M+Na)^+$] 673.4290, found 673.4283.



2.30

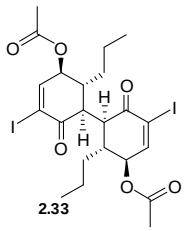
To a solution of enol ether **2.29** (200 mg, 0.31 mmol) in THF (16 mL) at 0 °C was added TBAF (0.92 mL, 1.0 M in THF) dropwise. After 1 h H_2O (15 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (5x 25 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was subjected to flash chromatography (EtOAc) to give diol **2.30** (62 mg) which was taken to the next step.



2.31

To a solution of diol **2.30** (62 mg, 0.20 mmol) and pyridine (80 mg, 1.0 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C were added Ac_2O (103 mg, 1.0 mmol),

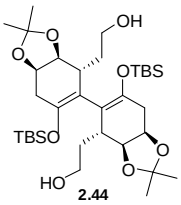
DMAP (cat). The ice bath was removed. After 2 h the solution of 1 N HCl (20 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was subjected to flash chromatography (3:1, hexanes/EtOAc) to give bis-acetate **2.31** (59 mg, 50% for two steps) as a thick oil: $[\alpha]_D^{20}$–141.4° (c 0.73, $CHCl_3$); IR (neat) ν 1739, 1674, 1231, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, J = 2.4, 10.4 Hz, 2H), 6.02 (dd, J = 2.4, 10.4 Hz, 2H), 5.53 (td, J = 2.4, 9.6 Hz, 2H), 2.95-2.83 (m, 2H), 2.75-2.64 (m, 2H), 2.14 (s, 6H), 1.53-1.42 (m, 2H), 1.38-1.20 (m, 6H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 170.5, 146.6, 129.8, 71.6, 47.9, 42.3, 31.6, 21.0, 18.8, 14.4; HRMS (ESI) calcd for $C_{22}H_{30}O_6Li$ [$(M+Li)^+$] 397.2202, found 397.2195.



2.33

To a solution of enone **2.31** (59 mg, 0.15 mmol) in pyridine-CH_2Cl_2 (1:2, 3.0 mL) at ambient temperature was added the solution of iodine (192 mg, 0.756 mmol) in pyridine-CH_2Cl_2 (1:1, 4.0 mL) dropwise. Upon complete addition, DMAP (cat.) was added. After 24 h the reaction mixture was diluted with Et_2O (100 mL), washed with water (30 mL), 1 N HCl (2 x 30 mL), water (30 mL), 20% $Na_2S_2O_3$ (30 mL), and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to flash chromatography (3:1, hexanes/EtOAc) to afford iodoenone **2.33** (61 mg, 63%) as a white solid: $[\alpha]_D^{20}$–140.2° (c 1.29, $CHCl_3$); IR (neat) ν 1739, 1686, 1227, 1031, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.4 Hz, 2H), 5.47 (dd, J = 2.4, 9.6 Hz, 2H), 3.03-2.88 (m, 2H), 2.85-2.71 (m,

2H), 2.14 (s, 6H), 1.54-1.44 (m, 2H), 1.36-1.15 (m, 6H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 170.3, 155.3, 104.3, 72.9, 46.8, 42.4, 31.1, 20.8, 18.4, 14.3; HRMS (ESI) calcd for $C_{22}H_{28}I_2O_6Li$ [$(M+Li)^+$] 649.0135, found 649.0105.



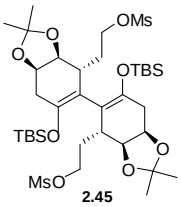
2.44

To a solution of **2.28** (100 mg, 0.15 mmol) in t-BuOH/H_2O (2:1, 22.5 mL) at ambient temperature were added OsO_4 (0.002 mg, 0.0093 mmol), NMO (42.0 mg, 0.31 mmol). After 24 h the solution was transferred to the mixture of Na_2SO_3 (20%) and ethyl acetate (1:1, 20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The organic layers were combined and dried ($MgSO_4$). The solvent was concentrated *in vacuo*.

The crude residue was dissolved in dichloroethane (10 mL) and $Pb(OAc)_4$ (0.14 g, 0.32 mmol) was added. After 30 min the solution was diluted with Et_2O (20 ml). The organic layer was washed with $NaHCO_3$ (15 ml), brine (15ml), dried ($MgSO_4$). The solvent was concentrated *in vacuo* to provide the crude residue - aldehyde that was taken to the next step.

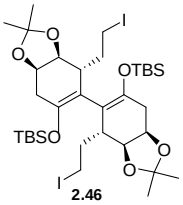
To a solution of the aldehyde in EtOH (10 ml) at 0 $^{\circ}$C was added $NaBH_4$ (12 mg, 0.31 mmol). After 30 min at 0 $^{\circ}$C MeOH was added to the reaction mixture and the ice bath was removed. The solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (1:1, hexanes/EtOAc) to provide the alcohol **2.44** (76 mg, 75% over three steps) as a thick oil: $[\alpha]_D^{20}$-18.6° (c 0.01, $CHCl_3$); IR (neat) ν 3424, 2930, 2856, 1652, 1464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (t, J = 6.1 Hz, 2 H), 4.30 (d, J = 5.5 Hz, 2 H),

3.79 – 3.65 (m, 2 H), 3.62 – 3.51 (m, 2 H), 3.07 – 2.96 (m, 2 H), 2.94 – 2.86 (m, 2 H), 2.55 (dd, J = 16.8 Hz, J = 6 Hz , 2 H), 2.29 (d, J = 16.8 Hz, 2 H), 1.60 – 1.50 (m, 4 H), 1.49 (s, 6 H), 1.36 (s, 6 H), 0.88 (s, 18 H), 0.21 (s, 6 H), 0.19 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8, 110.8, 107.6, 77.6, 73.9, 59.7, 34.5, 34.4, 33.7, 26.1, 25.9, 24.0, 18.0, -2.2, -3.1; HRMS (ESI) calcd for $C_{34}H_{63}O_8Si_2$ [$(M+H)^+$] 655.4062, found 655.4037.

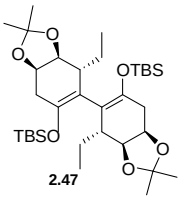


2.45

To a solution of **2.44** (200 mg, 0.30 mmol) in dichloromethane (10 mL) at 0 °C was added Et_3N (106 mg, 1.05 mmol), MsCl (0.90, 100 mg). After 30 min H_2O (2 mL) was added. The ice bath was removed. The aqueous layer was extracted with dichloromethane (3 x 15 mL).The combined organic layers were dried ($MgSO_4$). The solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (1:1, hexanes/EtOAc) to provide the title compound **2.45** (210 mg, 86%) as a thick oil: $[\alpha]_D^{20}$-14.6° (0.01, $CHCl_3$); IR (neat) v 2925, 2851, 1356, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 – 4.33 (m, 4 H), 4.29 (ddd, J = 16.9 Hz, J = 9.6 Hz, J = 7.24 Hz, 2 H), 4.22 – 4.08 (m, 2 H), 2.97 (s, 6 H), 2.62 – 2.43 (m, 2 H), 2.38 – 2.23 (m, 4 H), 2.07 – 1.96 (m, 2 H), 1.8 – 1.65 (m, 2 H), 1.41 (s, 6 H), 1.30 (s, 6 H), 0.87 (s, 18 H), 0.14 (s, 6 H), 0.12 (s, 6 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 110.8, 108.1, 80.1, 73.4, 69.2, 37.8, 37.2, 34.0, 30.6, 26.7, 25.8, 24.2, 17.9, -2.6, -3.4; HRMS (ESI) calcd for $C_{36}H_{66}O_{12}Si_2S_2Na$ [$(M+Na)^+$] 833.3432, found 833.3422.

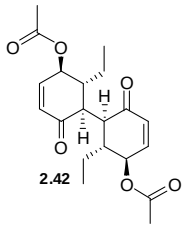


To a solution of **2.46** (193 mg, 0.24 mmol) in acetone (39 mL) were added NaI (572 mg, 3.82 mmol), $NaHCO_3$ (320 mg, 3.82 mmol). The reaction mixture was placed in 50 °C oil bath. After 24 h the oil bath was removed. The mixture was diluted with dichloromethane (50 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$). The solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (9:1, hexanes/EtOAc) to provide the title compound **2.46** (142 mg, 67%) as a thick, yellow oil: $[\alpha]_D^{20}$ +1.74° (0.01, $CHCl_3$); IR (neat): ν 2954, 2922, 2852, 1658, 1462 cm^{-3}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.02 – 4.42 (m, 2 H), 4.28 – 4.18 (m, 2 H), 3.33 – 3.05 (m, 4 H), 2.53 – 2.33 (m, 4 H), 2.30 (dd, J = 16.4 Hz, J = 2.4 Hz, 2 H), 2.12 – 1.99 (m, 2 H), 1.91 – 1.78 (m, 2 H), 1.41 (s, 6 H), 1.32 (s, 6 H), 0.90 (s, 18 H), 0.19 (s, 6 H), 0.18 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 110.7, 107.5, 75.5, 73.6, 42.3, 36.2, 33.4, 26.5, 26.0, 25.6, 18.0, 4.4, -2.3, -3.4; HRMS (ESI) calcd for $C_{34}H_{61}I_2O_6Si_2$ [(M+H)] 875.2096, found 875.2088.



To a solution of **2.46** (112 mg, 0.13 mmol) in EtOH (54 mL) were added Et_3N (28 mg, 0.30 mmol), 5% Pd/C (60 mg). The reaction mixture was applied to the atmosphere of H_2 and placed in 40 °C oil bath. After 24 h the oil bath was removed. The solution was filtrated through the celite pad. The solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (9:1, hexanes/ EtOAc) to provide the title compound **2.47** (81 mg, 95%) as a white solid: $[\alpha]_D^{20}$ +34.0° (c 0.03, $CHCl_3$); IR (neat) ν 2956, 2927, 2857, 1376, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 - 4.40 (m, 2 H), 4.35 - 4.23 (m, 2H), 2.44 (dd, J = 5.2 Hz, J = 16.4 Hz, 2 H),

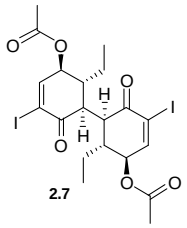
2.29 – 2.20 (m, 4 H), 1.54 – 1.43 (m, 4 H), 1.37 (s, 6 H), 1.31 (s, 6H), 0.95 (t, J = 7.36, 6 H), 0.88 (s, 18 H), 0.15 (s, 6 H), 0.14 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 113.1, 107.2, 75.2, 74.2, 42.1, 33.4, 26.2, 26.0, 24.1, 23.1, 18.1, 12.8, -2.5, -3.5; HRMS (ESI) calcd for $C_{34}H_{63}O_6Si_2$ [$(M+H)^+$] 623.4160, found 623.4163.


2.42

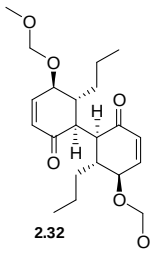
To a solution of **2.47** (18 mg, 0.03 mmol) in THF (1.8 mL) at 0 °C was added TBAF (0.09 mmol, 1.0 M in THF) dropwise. After 30 min H_2O (1 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc) to give diol **2.22** (5.4 mg) which was taken to the next step.

To a solution of **2.22** (8.7 mg, 0.03 mmol) and pyridine (12.3 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added Ac_2O (16 mg, 0.16 mmol), DMAP (cat). The ice bath was removed. After 30 min the reaction mixture was cooled to 0 °C by ice bath and the solution of 1 N HCl (0.2 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography (2:1, hexanes/EtOAc) to provide enone **2.42** (8.6 mg, 76%) as a white solid: $[\alpha]_D^{20}$ -30.7° (0.01, $CHCl_3$); IR (neat) ν 1738, 1675, 1371, 1231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 2.0 Hz, J = 10.4, 2H), 6.02 (dd, J = 2.4, 10.4 Hz, 2H), 5.58 (d, J = 10 Hz, 2 H), 2.94 (s, 2 H), 2.73 (d, J = 9.2 Hz, 2 H) 2.14 (s, 6 H) 1.63-1.58 (m, 2H), 1.44-

1.41 (m, 2H), 0.91 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 170.5, 146.9, 129.8, 71.0, 46.8, 43.1, 21.2, 20.9, 9.5; HRMS (ESI) calcd for $C_{20}H_{26}O_6Na$ [$(M+Na)^+$] 385.1627, found 385.1635.

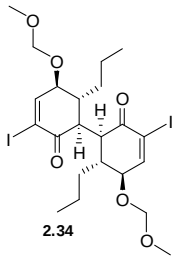

2.7

To a solution of enone **2.42** (13 mg, 0.03 mmol) in pyridine-CH_2Cl_2 (1:2, 0.75 mL) at ambient temperature was added the solution of iodine (45 mg, 0.18 mmol) in pyridine-CH_2Cl_2 (1:1, 0.65 ml) dropwise. Upon complete addition, DMAP (cat.) was added. After 24 h the solution was diluted with Et_2O (10 mL), washed with water (5 mL), 1 N HCl (5 mL), water (10 mL), 20% $Na_2S_2O_3$ (2 x 5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$) and the solvent was concentrated *in vacuo*. The residue was subjected to flash chromatography (3:1, hexanes/EtOAc) to afford iodoenone **2.7** (14 mg, 73%) as a white solid: $[\alpha]_D^{20}$ -22.2° (c 0.01, $CHCl_3$); IR (neat) ν 2919, 2850, 1739, 1686, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.28, 2 H), 5.51 (dd, J = 2.28, J = 9.96, 2 H), 3.09 - 2.97 (m, 2 H), 2.84 - 2.76 (m, 2 H), 2.14 (s, 6 H), 1.70 – 1.57 (m, 4 H), 1.46 – 1.35 (m, 4 H), 0.89 (t, J = 10.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 170.3, 155.5, 104.3, 72.3, 45.9, 43.4, 29.7, 20.8, 9.2; HRMS (ESI) calcd for $C_{20}H_{24}O_6I_2Na$ [$(M+Na)^+$] 636.9560, found 636.9591.


2.32

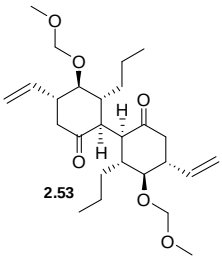
To a solution of enone **2.30** (28 mg, 0.09 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C were added MOMCl (60 mg, 0.74 mmol, 57µL) and Hunig base (144 mg, 1.1 mmol, 195 µL). The ice bath was removed. The mixture was heated up

to 40 °C. After 18 h the solution was cooled to ambient temprature and diluted with CH_2Cl_2. The organic layer was washed with saturated solution of $NaHCO_3$ (x 1), brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide enone **2.32** as a yellow oil (30 mg, 82 %): ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (dd, *J* = 2.5 Hz, 10.5 Hz, 2 H), 5.96 (dd, *J* = 1.5, 10.5 Hz, 2 H), 4.79 (d, *J* = 7.0 Hz, 2 H), 4.73 (d, *J* = 7.0 Hz, 2 H), 4.19 (d, *J* = 7.5 Hz, 2 H), 3.43 (s, 6 H), 2.85 (bs, 2 H), 2.65 (s, bs), 1.55-1.48 (m, 2 H), 1.39-1.24 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.75, 147.48, 128.77, 96.17, 75.11, 55.82, 48.92, 42.05, 32.21, 18.96, 14.28.

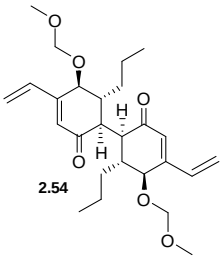

2.34

To a solution of enone **2.32** (38 mg, 0.10 mmol) and DMAP (cat.) in CH_2Cl_2/pyr (2.2 mL/1.1 mL, 2:1) at ambient temperature was added the solution of I_2 (124 mg, 0.49 mmol) in CH_2Cl_2/pyr (0.9 mL/0.9 mL, 1:1) via syringe for 2 h. After 24 h the reaction mixture was diluted with Et_2O. The organic layer was washed with H_2O (x 2), 1M solution of HCl (x 3), H_2O (x 2), aqueous solution of $Na_2S_2O_3$ (20%, x 2) and brine (x 1). The organic layer was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to provide bis-iodoenone **2.34** as a yellow solid (59 mg, 93%): IR (thin film, cm^{-1}): 2956, 2931, 2824, 1681, 1600, 1464; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 2.8 Hz, 2 H), 4.76 (d, *J* = 7.2 Hz, 2 H), 4.69 (d, *J* = 6.8 Hz, 2 H), 4.16 (dd, *J* = 2.8 Hz, 8.0 Hz, 2 H), 3.42 (s, 6 H), 3.00 (bs, 2 H), 2.68 (bs, 2 H), 1.54-1.50 (m, 2 H), 1.32-1.22 (m, 6 H), 0.87 (t, *J* = 16 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.35,

156.81, 103.47, 96.29, 60.30, 56.00, 48.06, 42.46, 31.62, 18.57, 14.25; HRMS (ESI) for $C_{22}H_{32}O_6I_2$ [M] found 646.0250.



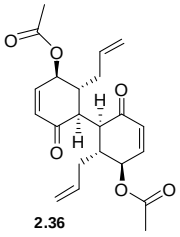
To a solution of vinylmagnesium bromide (0.76 mmol, 0.76 mL, 1 M solution in THF) in THF (0.6 mL) at -50 °C was added CuBr•Me_2S (5.2 mg, 0.025 mmol). After 15 min solution of bis-enone **2.32** (10 mg, 0.025 mmol) in THF (0.6 mL) was added. After 30 min saturated solution of NH_4Cl was added. The aqueous layer was extracted with Et_2O (x 4). The organic layer was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide bis-vinyl ketone **2.53** as a yellow oil (9.5 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.74 (m, 2 H), 5.10 (t, *J* = 18.8, 11.2 Hz, 4 H), 4.74 (d, *J* = 7.2 Hz, 2 H), 4.63 (d, *J* = 7.2 Hz, 2 H), 3.52 (t, *J* = 8.8 Hz, 2 H), 3.4 (s, 6 H), 2.82-2.79 (m, 2 H), 2.51 (dd, *J* = 4.0, 15.6 Hz, 2 H), 2.40-2.31 (m, 4 H), 2.24 (dd, *J* = 12.0, 15.2 Hz, 2 H), 1.66-1.57 (m, 4 H), 1.45-1.36 (m, 4 H), 0.91 (t, *J* = 6.8 Hz, 6 H).



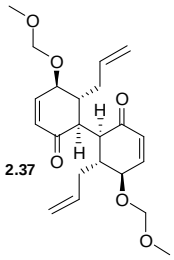
To a solution of vinylmagnesium bromide (0.76 mmol, 0.76 mL, 1 M solution in THF) in THF (0.6 mL) at -78 °C was added CuBr•Me_2S (10 mg, 0.05 mmol). After 30 min TMEDA (88 mg, 0.75 mmol, 0.114 mL), TMSCl (96 mg, 0.88 mmol, 0.112 mL) and solution of enone **2.32** (10 mg, 0.025 mmol) in THF (0.6 mL) were added. After 5 min cold bath was removed. After 30 min saturated solution of NH_4Cl was added. The aqueous layer was extracted with

Et_2O (x 4). The combined organic extracts were washed with H_2O (x 1) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane + 1% Et_3N changed to Hexane/EtOAc, 9:1 + 1% Et_3N) to provide bis-silyl enol ether **2.55** as a yellow oil which was taken to the next step.

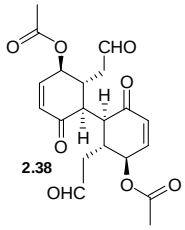
To a solution of bis-silyl enol ether **2.55** in CH_2Cl_2 (1 mL) at ambient temperature were added HMDS (16 mg, 0.1 mmol, 0.21 mL) and DDQ (23 mg, 0.1 mmol). After 1.5 h one more portion of DDQ (46 mg, 0.2 mmol) was added. After 18 h saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with Et_2O (x 4). The organic layer was washed with H_2O (x 2) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to provide bis-enone **2.53** as a pale yellow oil (2.4 mg, 20%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 11.0, 17.5 Hz, 2 H), 5.99 (s, 2 H), 5.90 (d, *J* = 17.5 Hz, 2 H), 5.51 (d, *J* = 11 Hz, 2 H), 4.84 (d, *J* = 7.0 Hz, 2 H), 4.64 (d, *J* = 6.5 Hz, 2 H), 4.39 (s, 2 H), 3.40 (s, 6 H), 3.13 (s, 2 H), 2.53 (t, *J* = 7.0 Hz, 2 H), 1.4-1.18 (m, 8 H), 0.88 (t, *J* = 7.5 Hz, 6 H).


2.36

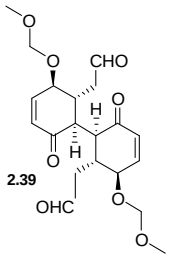
Compound **2.36** was prepared from silyl enol ether **2.35** according to procedures reported for the synthesis of compounds **2.31** and **2.42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 1.6, 10.0 Hz, 2 H), 5.99 (dd, *J* = 2.0, 10.4 Hz, 2), 5.80-5.70 (m, 2 H), 5.49 (d, *J* = 10.4 Hz, 2 H), 5.09-5.01 (m, 4 H), 3.08 (bs, 2 H), 2.79 (d, *J* = 8.4 Hz, 2 H), 2.33-2.27 (m, 2 H), 2.17-2.14 (m, 2 H), 2.10 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.27, 170.48, 147.28, 134.36, 129.79, 117.88, 71.81, 47.35, 42.66, 33.50, 29.69, 20.99.



Compound **2.37** was prepared from silyl enol ether **2.35** according to procedures reported for the synthesis of compounds **2.31** and **2.42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 2.1, 10.5 Hz, 2 H), 5.96 (dd, *J* = 1.8, 10.5 Hz, 2 H), 5.90-5.76 (m, 2 H), 5.08 (dd, *J* = 3.3, 15.0 Hz, 4 H), 4.79 (d, *J* = 7.2 Hz, 2 H), 4.74 (d, *J* = 7.2 Hz, 2 H), 4.18 (d, *J* = 6.6 Hz, 2 H), 3.44 (s, 6 H), 2.88 (s, 4 H), 2.45-2.41 (m, 2 H), 2.24-2.20 (m, 2 H).



To a solution of bis-ketone **2.36** (50 mg, 0.13 mmol) in dioxane/H_2O (4.5 mL/1.5 mL, 3:1) at ambient temperature was added OsO_4 (10 mg, 0.04 mmol). After 15 min $NaIO_4$ (120 mg, 0.54 mmol) was added portionwise for over 30 min. After 1 h 45 min from the completion of addition the reaction mixture was diluted with Et_2O. The aqueous layer was extracted with Et_2O (x 12). The combined organic extracts were dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:2) to provide bis-aldehyde **2.38** as a colorless oil (20 mg, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 2 H), 9.74 (d, *J* = 10.29 Hz, 2 H), 6.05 (d, *J* = 10.32 Hz, 2 H), 4.10-4.00 (m, 2 H), 3.29 (bs, 2 H), 2.96 (d, *J* = 6.5 Hz, 2 H), 2.66-2.51 (m, 4 H), 2.11 (s, 6 H).



To a solution of bis-ketone **2.37** (20 mg, 0.05 mmol) in EtOAc (1.6 mL) at ambient temperature was added 1% solution of OsO_4 in H_2O (80 µL) and buffer solution of $LiIO_4$-Li_3PO_4 (1.6 mL, pH = 6.5). After 5.5 h the reaction mixture was diluted with EtOAc. The layers were separated. The aqueous

layer was extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:5) to provide bis-aldehyde **2.39** as a colourless oil (5.4 mg, 27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 2 H), 7.00 (d, *J* = 10.2 Hz, 2 H), 6.02 (d, *J* = 10.2 Hz, 2 H), 4.73 (d, *J* = 7.2 Hz, 2 H), 4.65 (d, *J* = 7.2 Hz, 2 H), 4.39 (d, *J* = 9.9 Hz, 2 H), 3.41 (s, 6 H), 3.17 (s, 2 H), 2.74 (bs, 4 H), 2.49 (d *J* = 13.5 Hz, 2 H).

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Appendix A1:

Spectra Relevant to Chapter II:

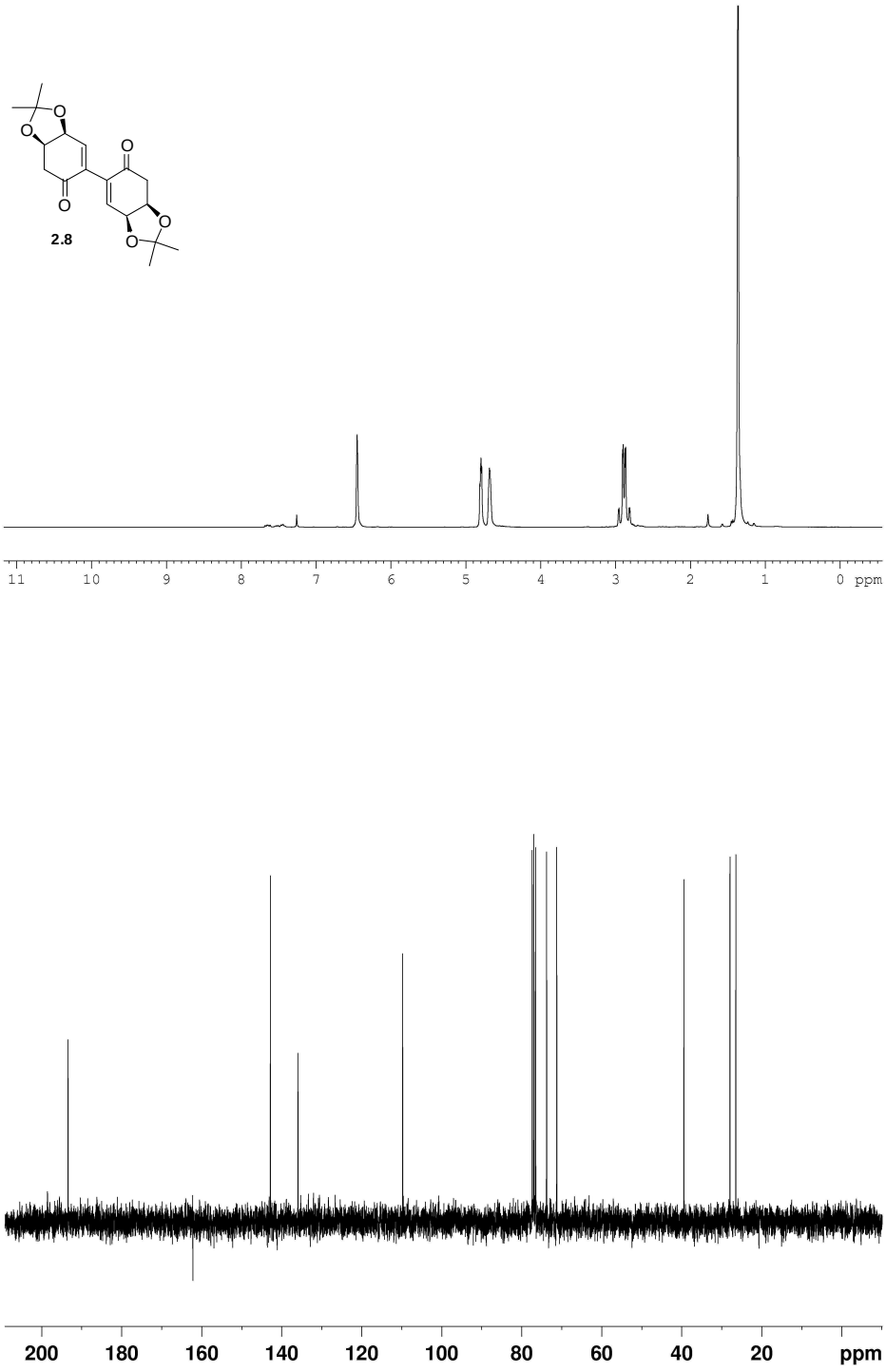


Figure A2.1. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.8**.

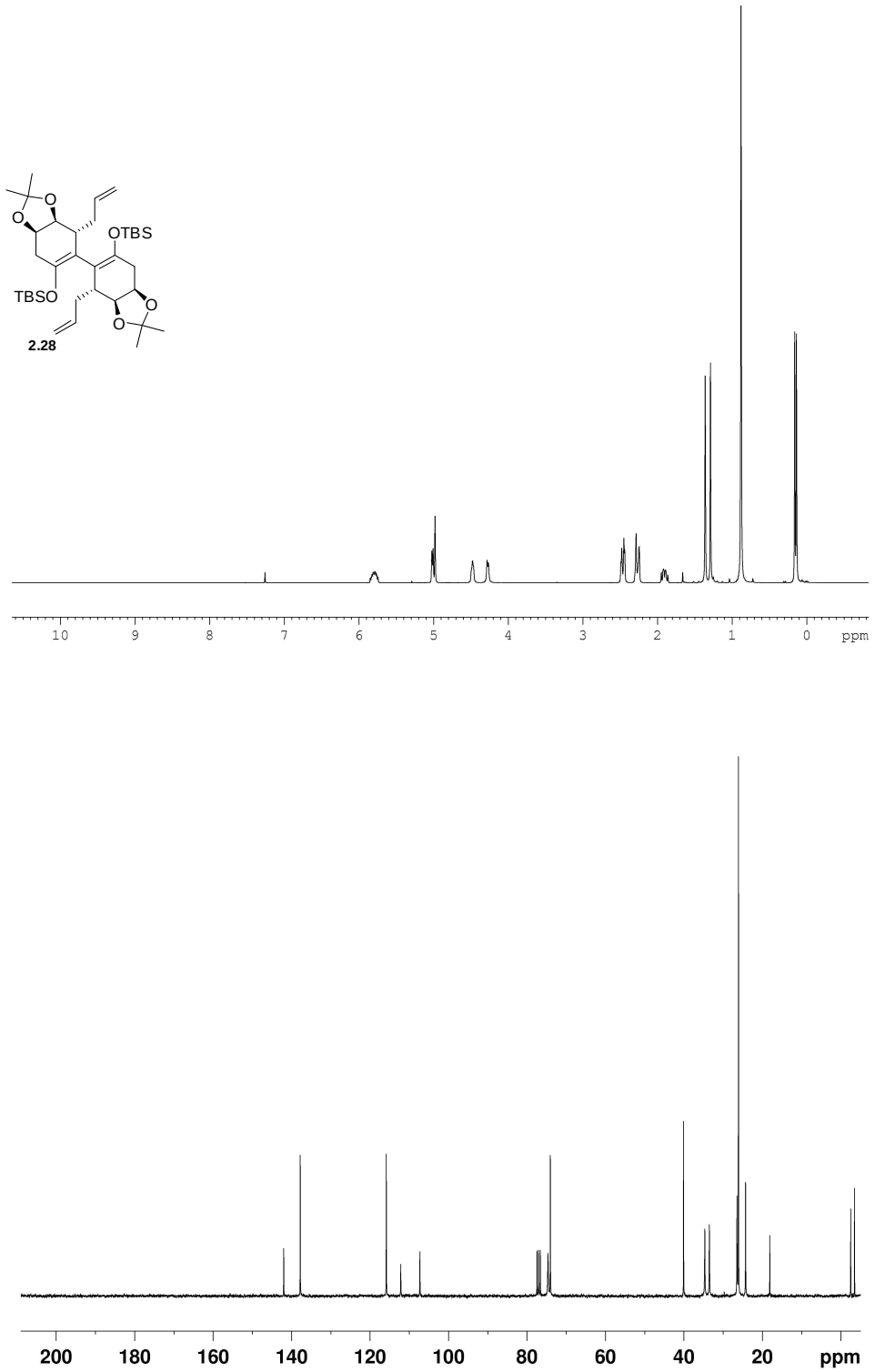


Figure A2.2. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.28**.

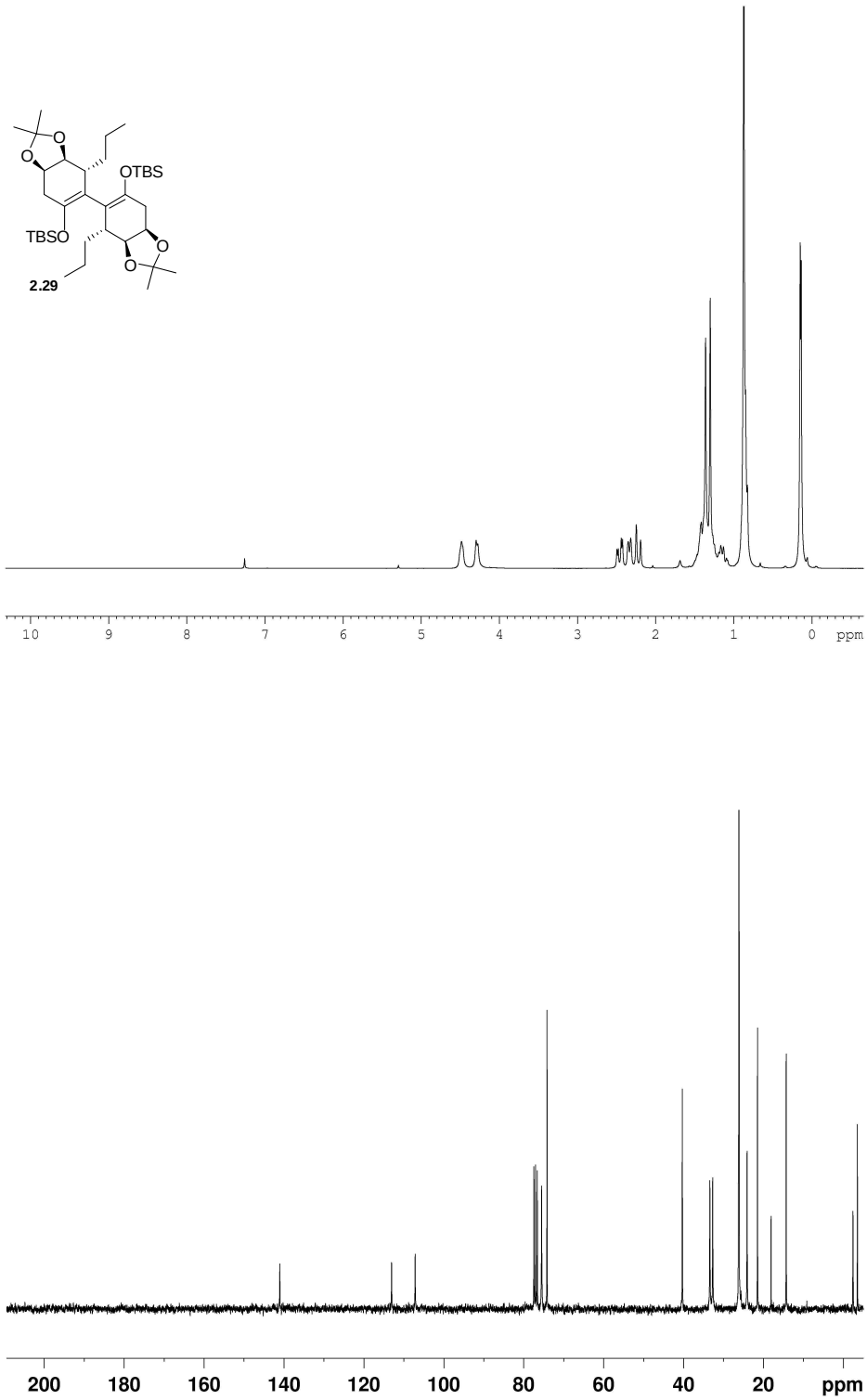


Figure A2.3. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.29**.

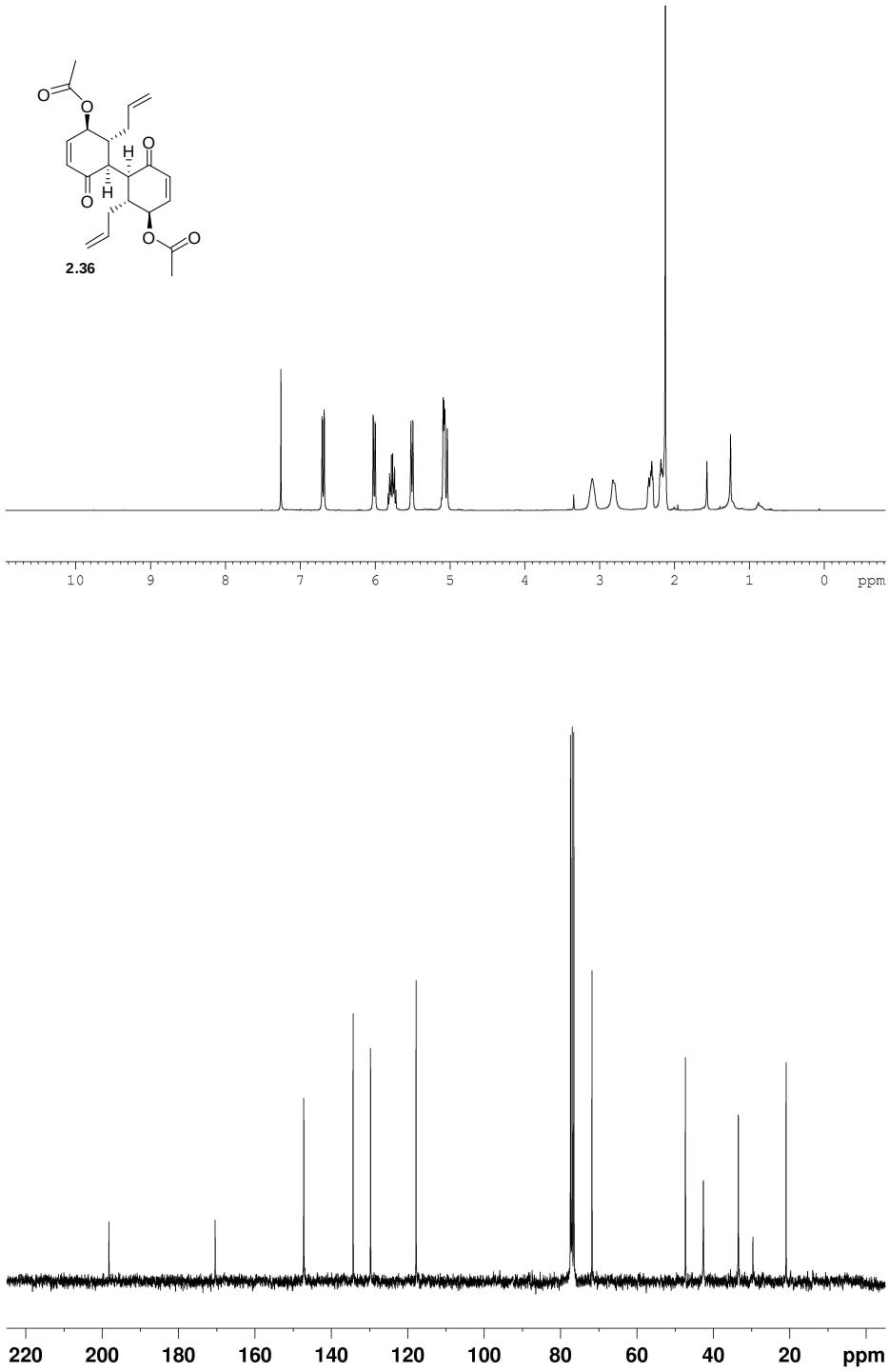


Figure A2.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.36.**

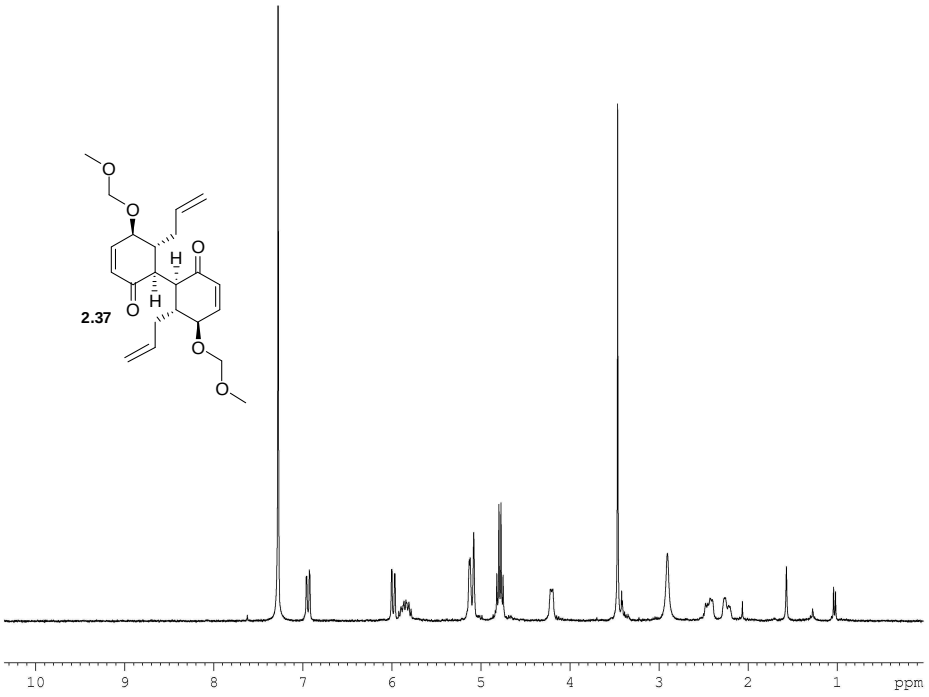


Figure A2.5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **2.37**.

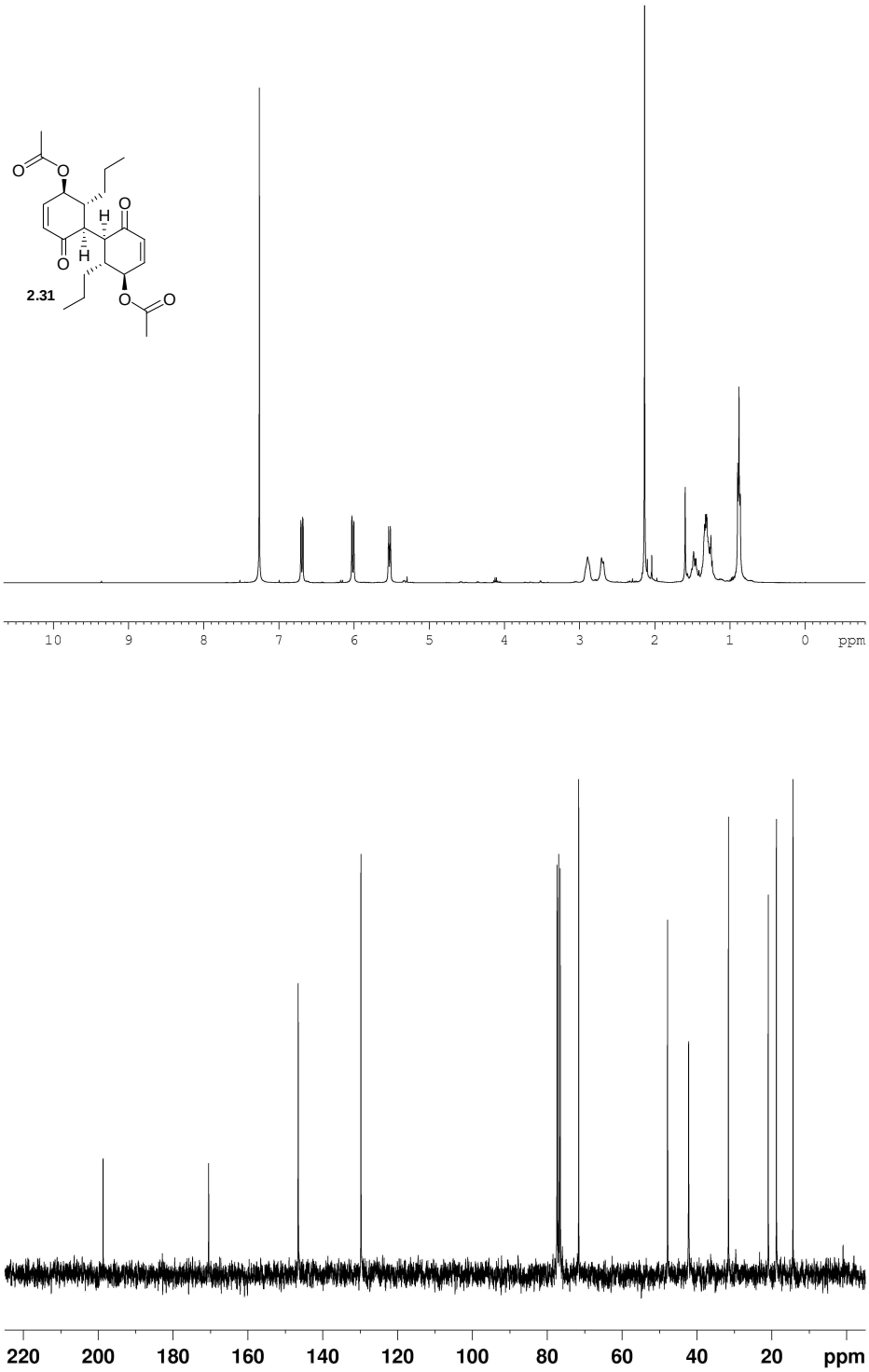


Figure A2.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.31**.

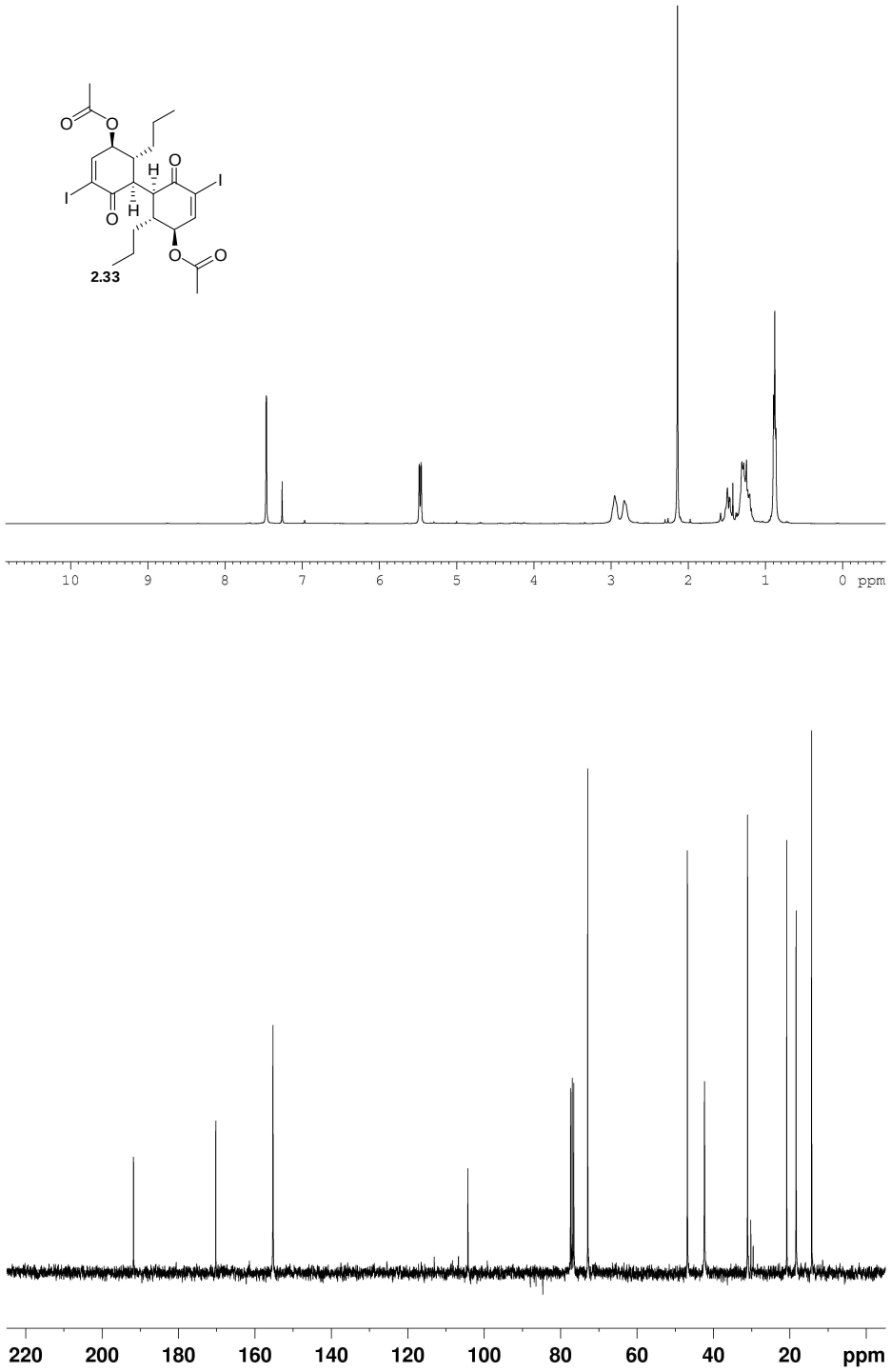


Figure A2.7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.33**.

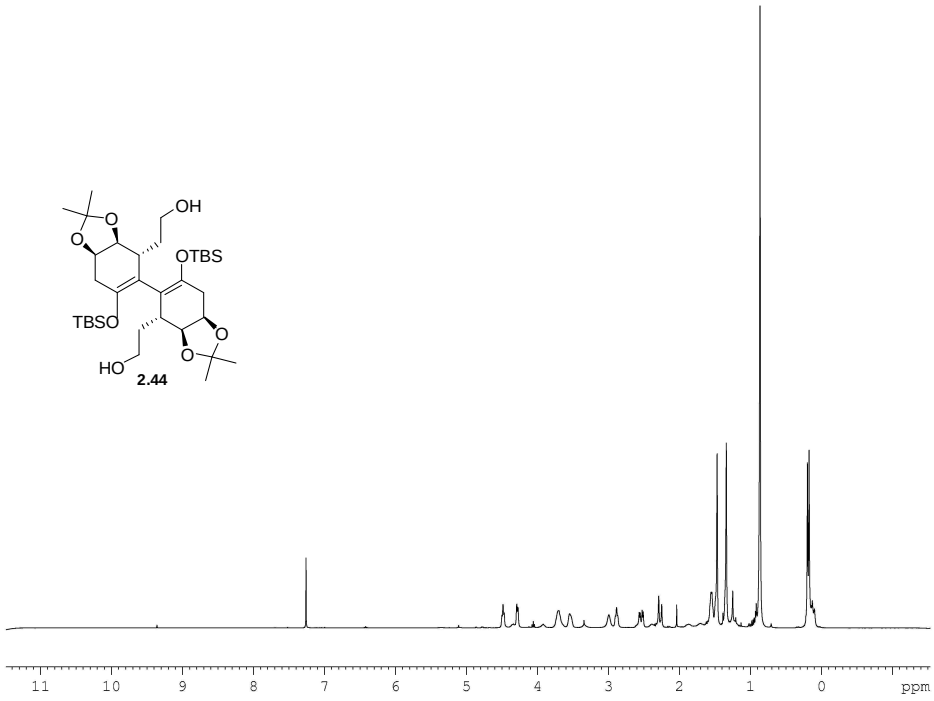


Figure A2.8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2.44**.

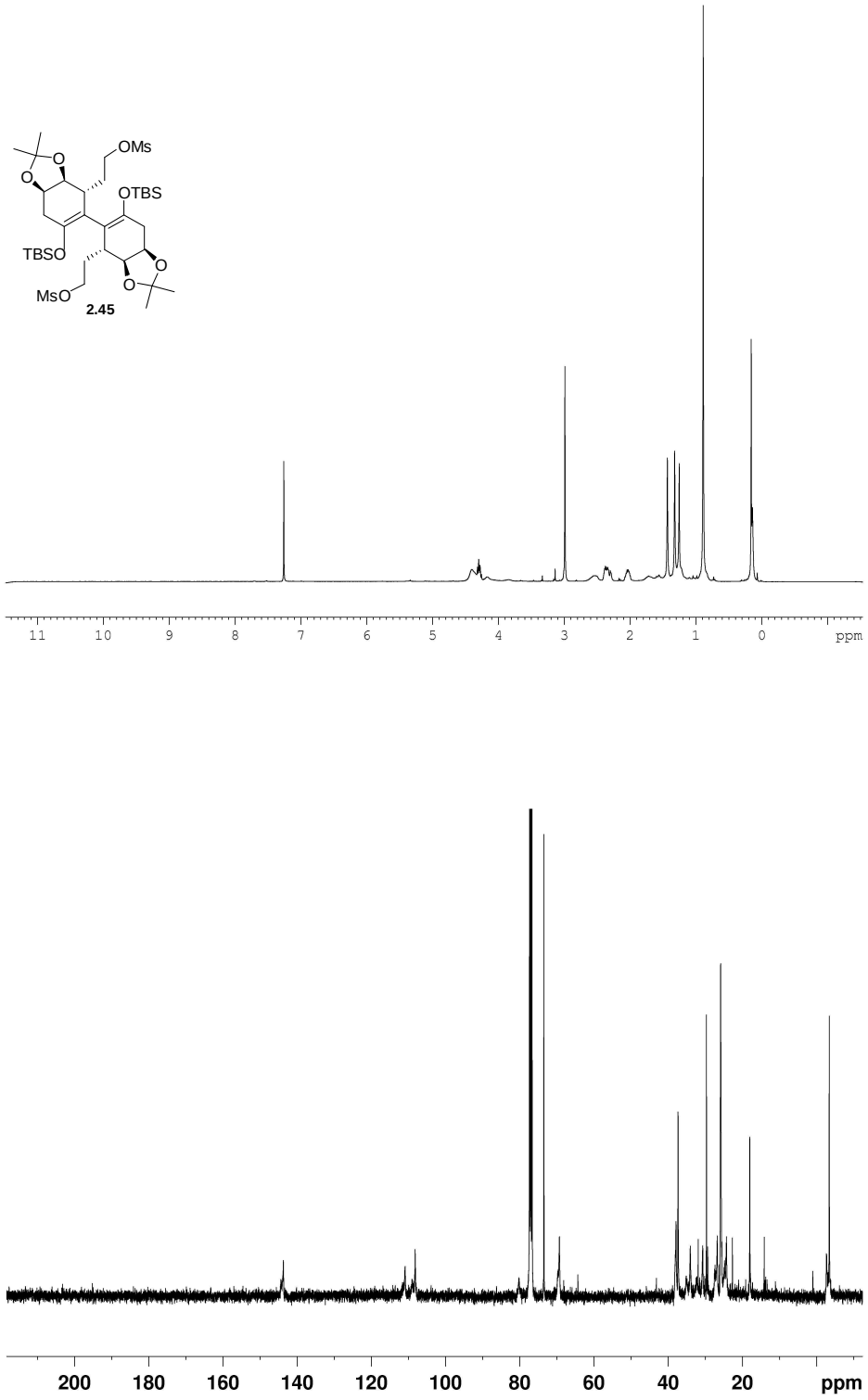


Figure A2.9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2.45**.

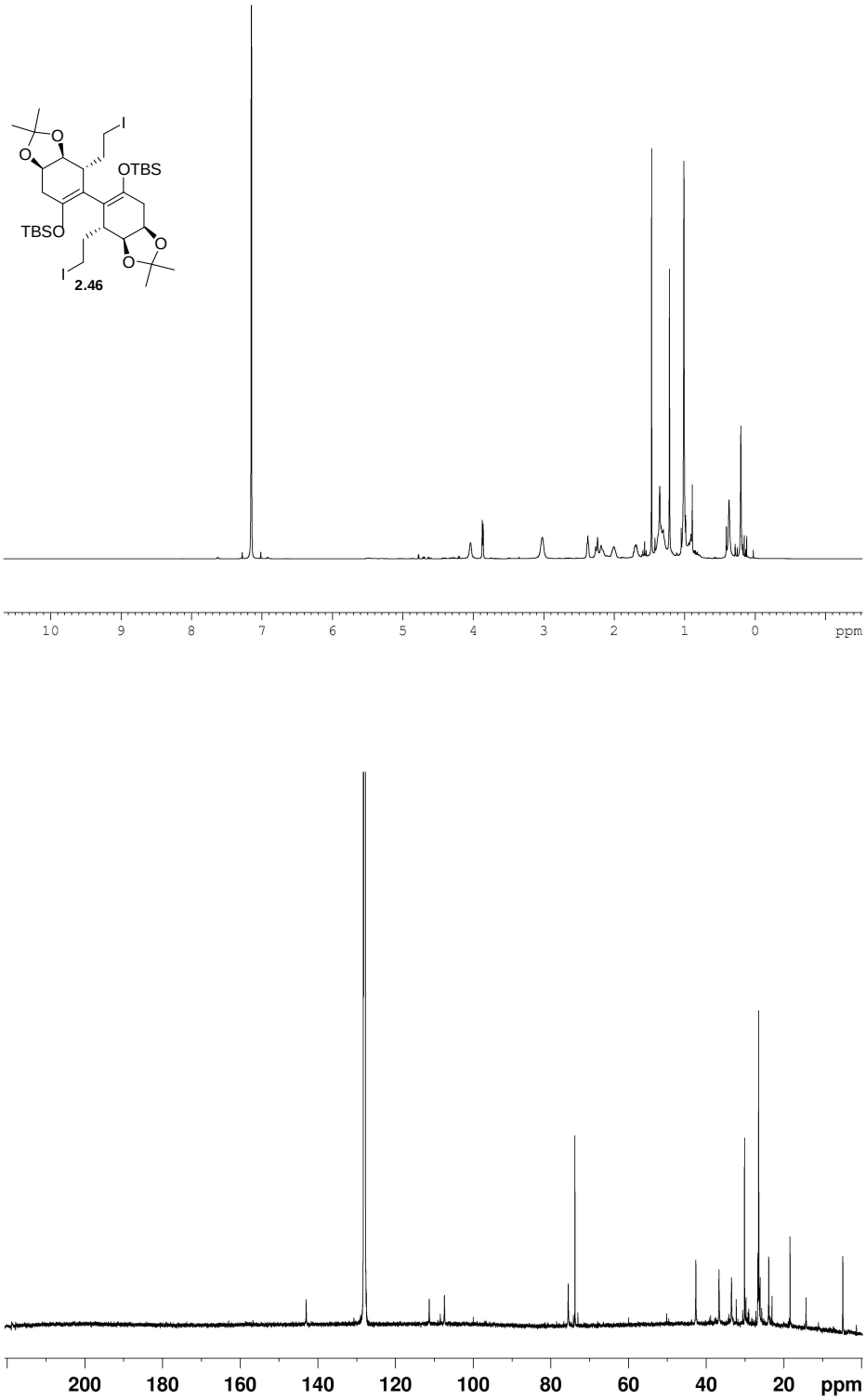


Figure A2.10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2.46**.

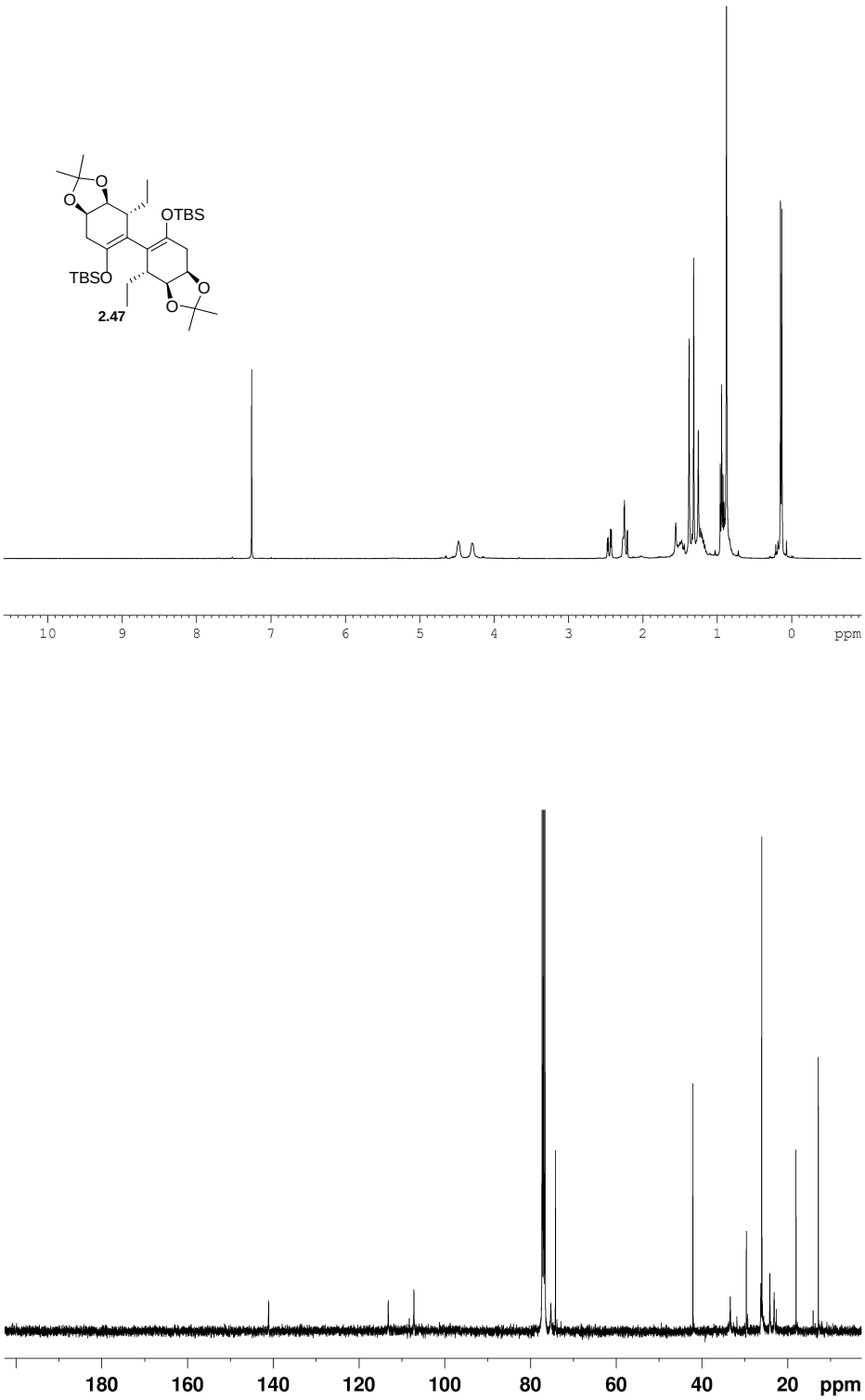


Figure A2.11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2.47**.

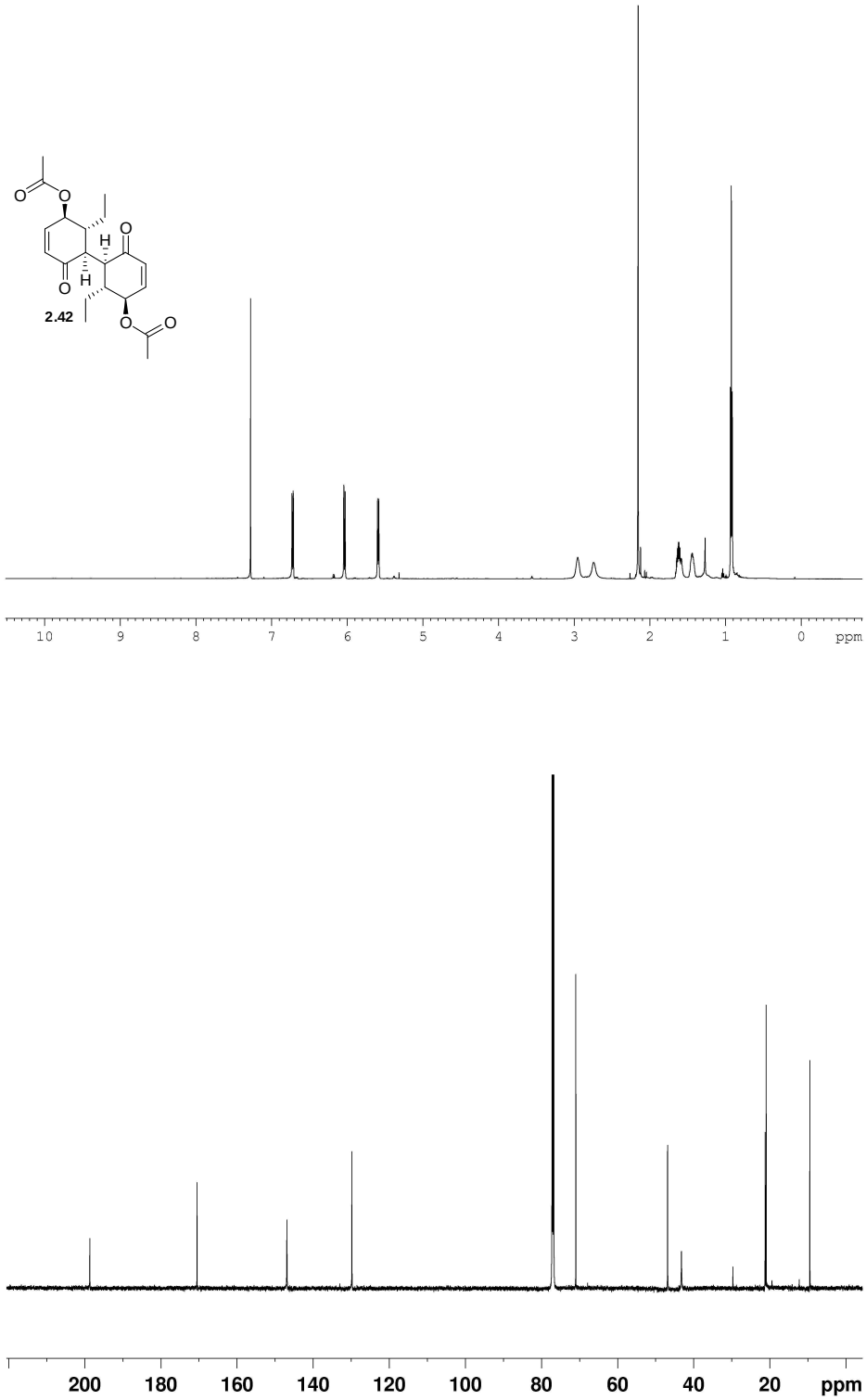


Figure A2.12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **2.42**.

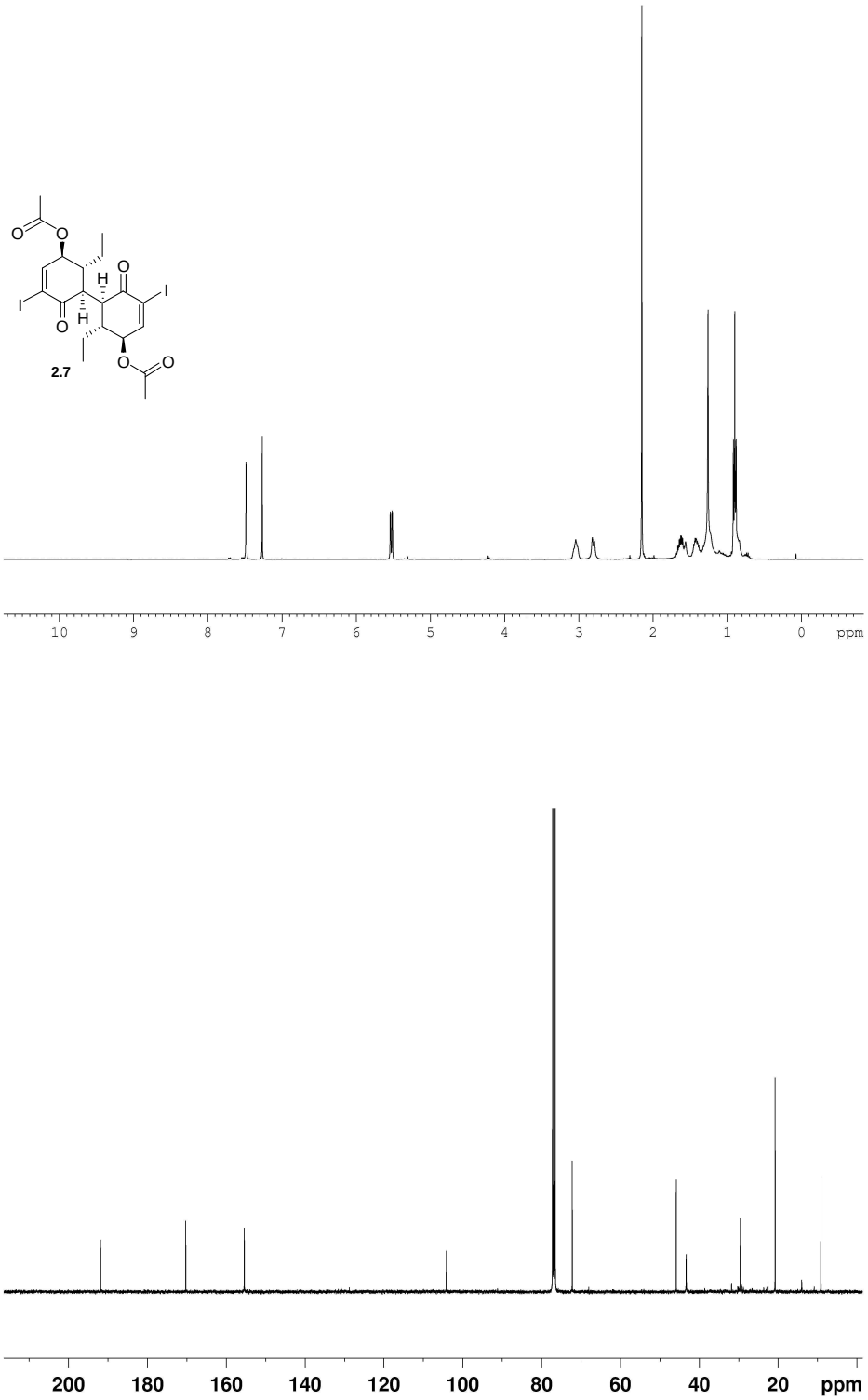


Figure A2.13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2.7**.

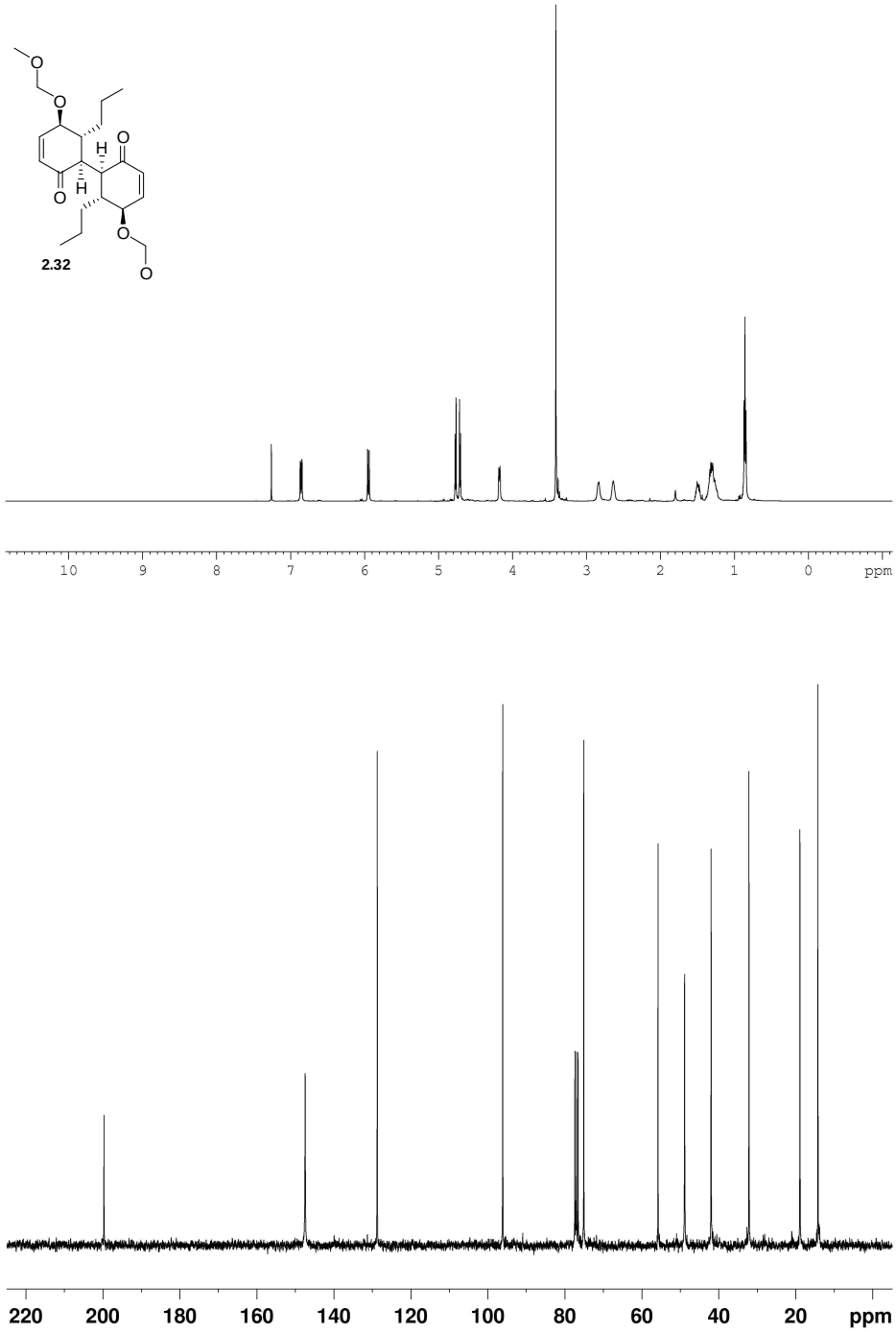


Figure A2.14. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **2.32**.

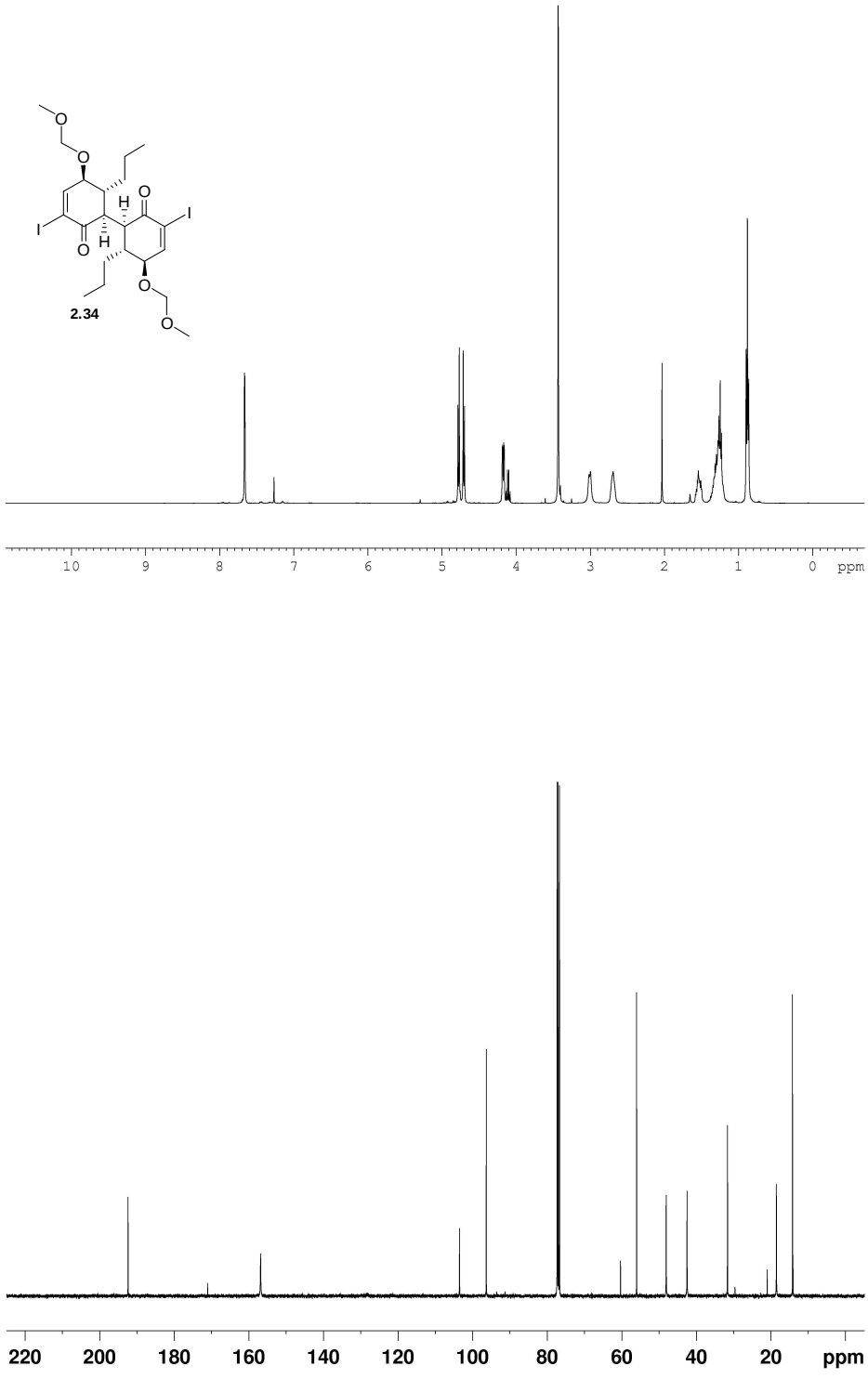


Figure A2.15. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2.34**.

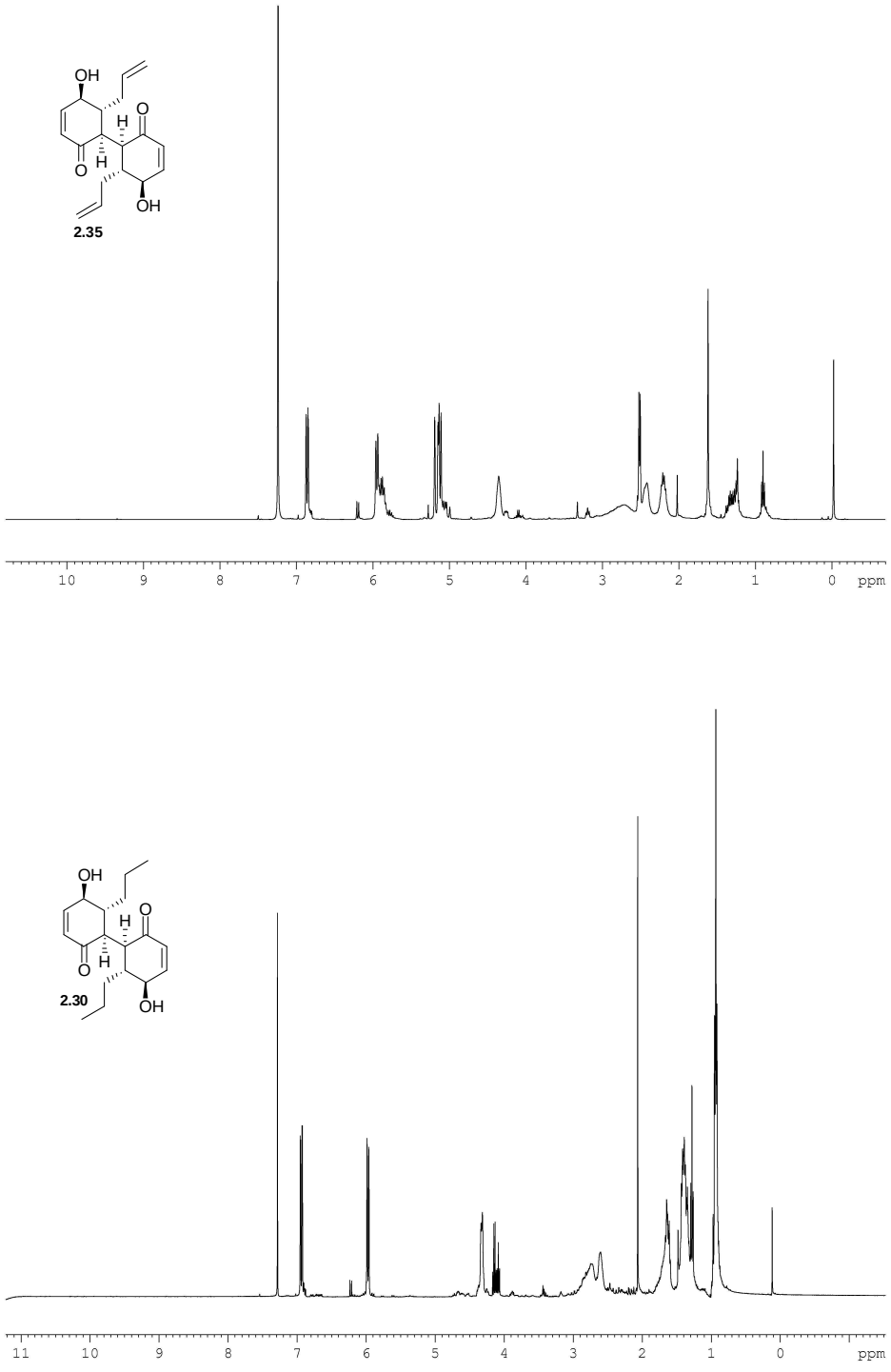


Figure A2.16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2.35** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2.30**.

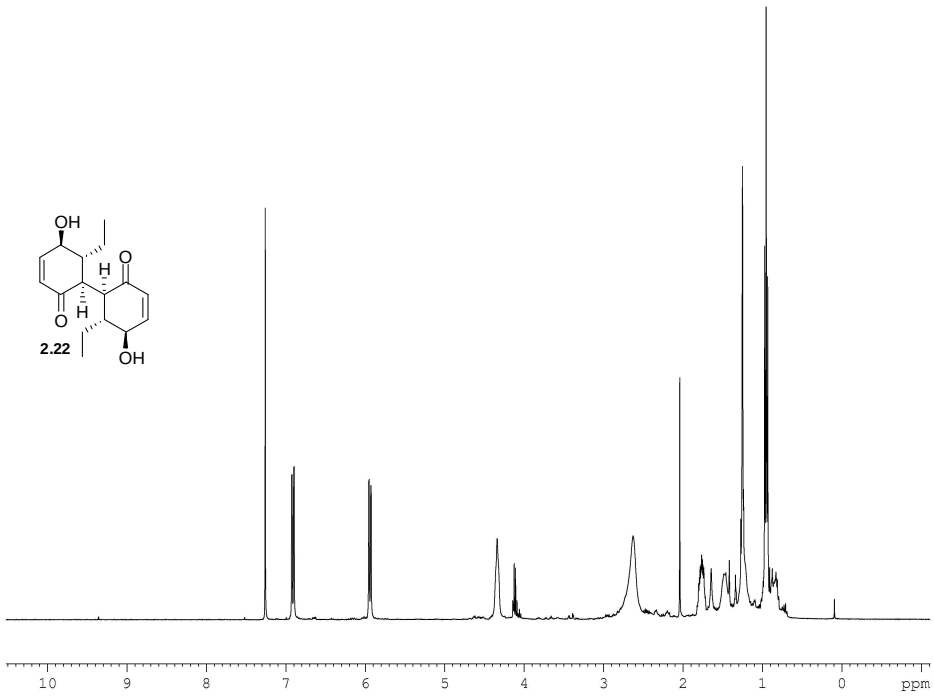


Figure A2.17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2.22**.

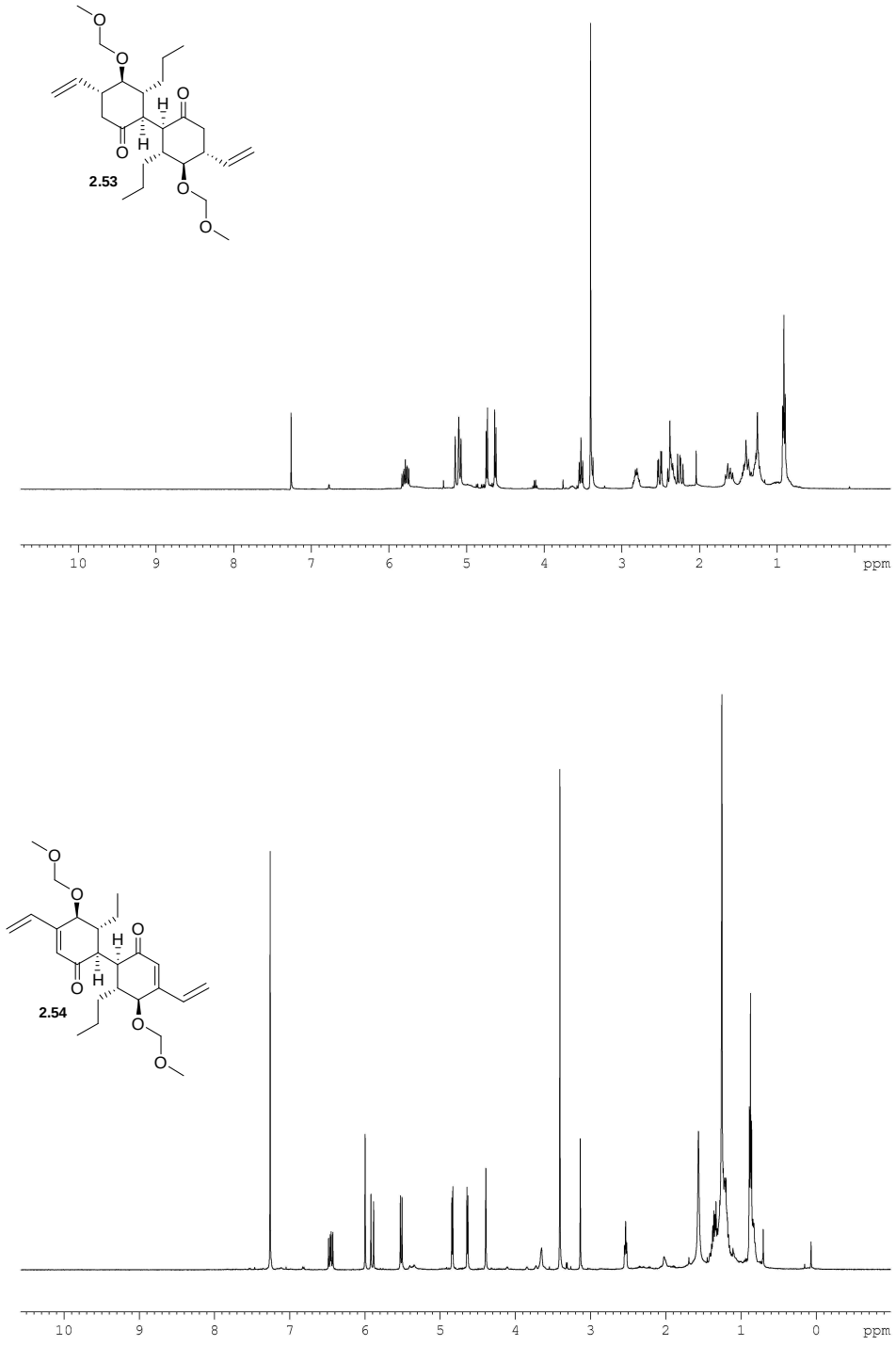
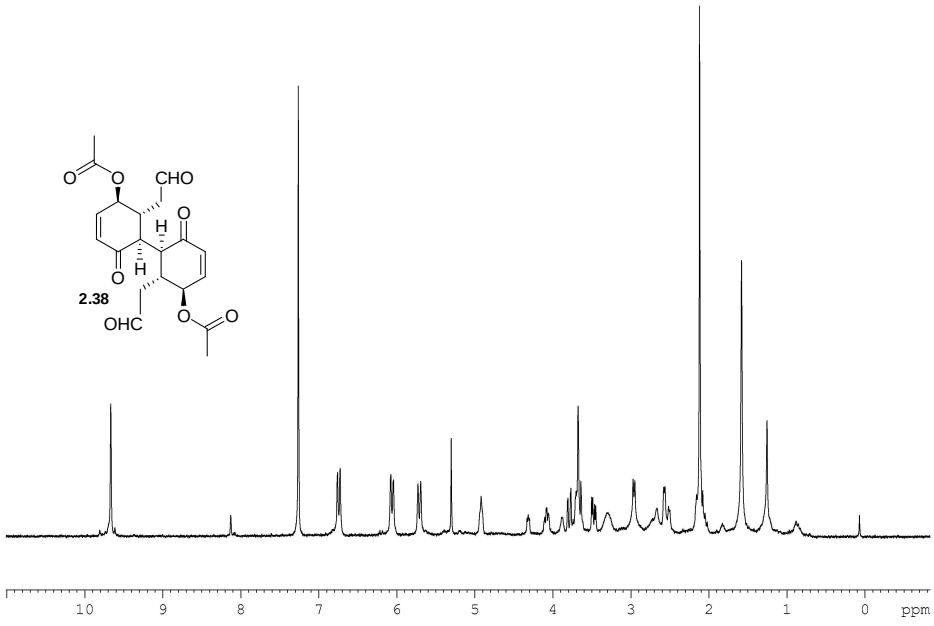


Figure A2.18. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2.53** and ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **2.54**.



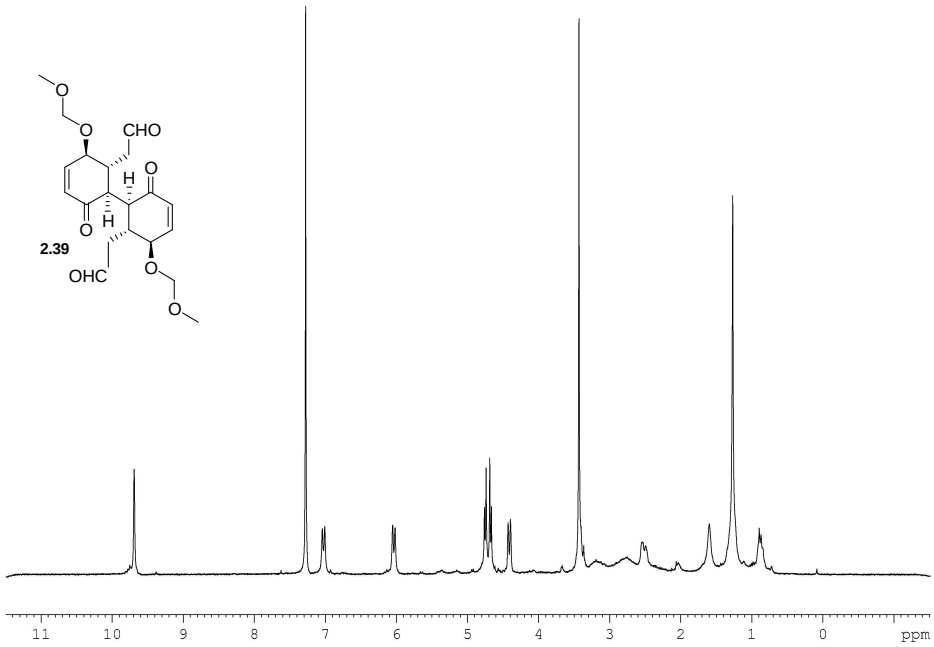


Figure A2.19. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **2.38** and ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **2.39**.

CHAPTER III

FIRST GENERATION APPROACH

Cyano Group Studies

The addition of a carbon radical to a nitrile resulting in ring formation has been employed as key transformation in a number of natural products total syntheses.[1,2] Retrosynthetically, nitriles as compared to alkynes can be considered equivalents of carbonyl radical acceptors (O=C). Nitriles and alkynes have found application in transformations with radical character since the product of the addition, an imine, can be easily hydrolyzed to a ketone. In terms of reactivity, nitriles are less reactive than alkynes, which are even poorer radical acceptors than activated olefins.[2] Simultaneously, application of the cyano group allows fast formation of the desired ketone while use of an alkyne requires a two-step sequence (addition/ozonylsis) to give the same product.

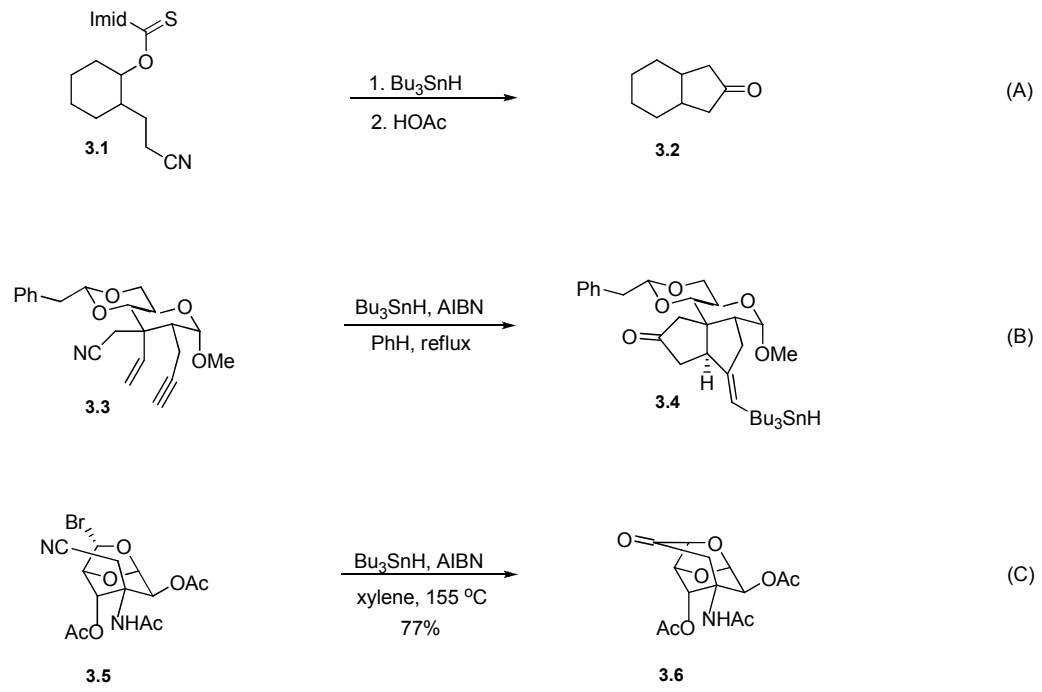
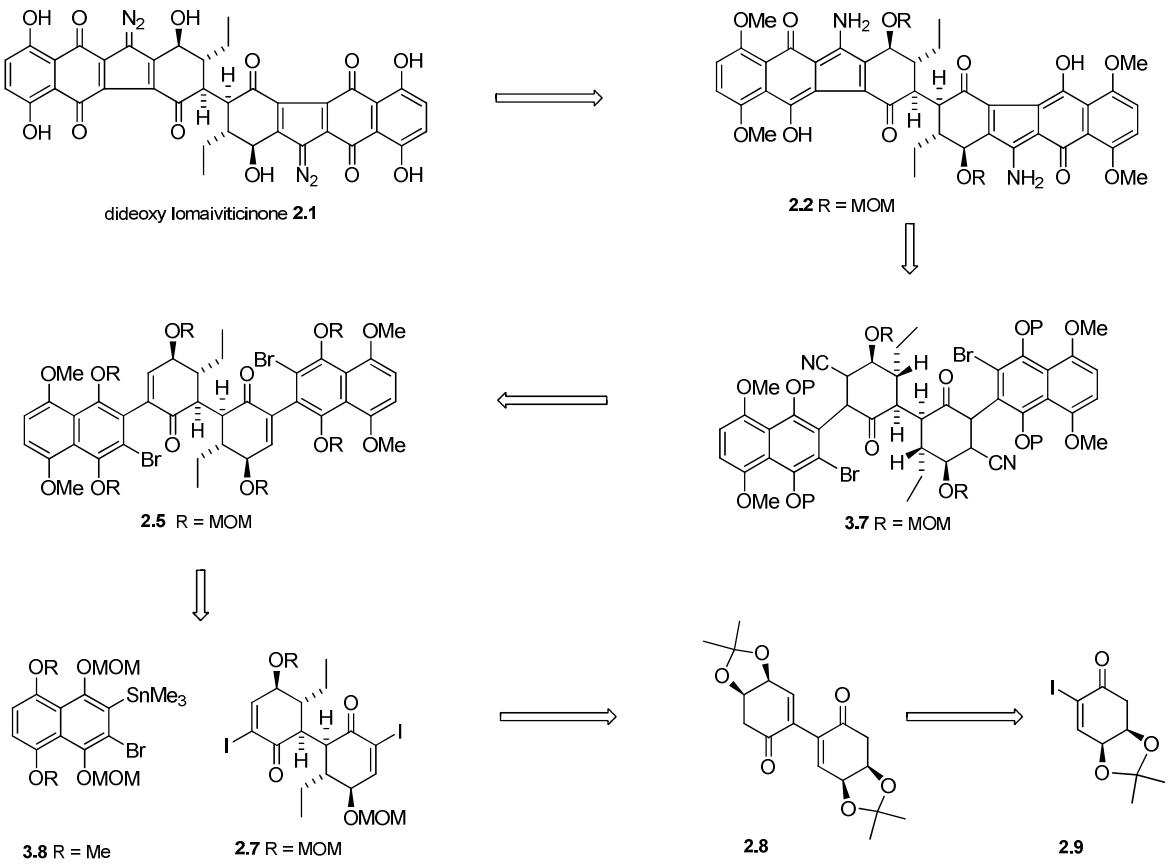


Figure 3.1. Examples of radical cyclizations employing nitriles as radical acceptors.

Radical cylizations onto nitrile groups have been employed mostly as a method for producing cyclopentanone ring systems by way of 5-*exo*-dig cyclizations (Figure 3.1 eqns. A and B). A few examples involve formation of larger rings – in the synthesis of tetrodoxin (Figure 3.1 eqn. C), generation of a cyclohexanone ring was possible due to the favorable rigid structure of bromonitrile **3.5**.[1a]

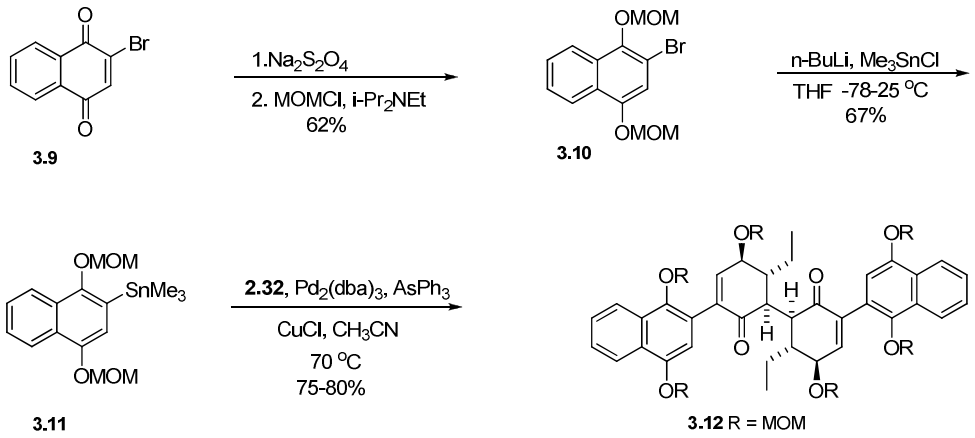


Scheme 3.1. Retrosynthetic analysis.

When designing our synthetic approach to dideoxy lomaiviticinone (**2.1**), we envisioned that an immediate precursor to **2.1**, bis-amine **2.2**, could be generated via intramolecular radical cyclization of nitrile to afford diketone **3.7** (Scheme 3.1). We anticipated that formation of cyclopentyl imines units followed by deprotection would lead to tautomerization to quinone methide **2.2**.

With bis-iodoenone **2.32** in hand (Chapter 2), screening of conditions for the Stille coupling as a first step of an annulation sequence was initiated. Using model system arylstannane **3.11**, quickly prepared (3 steps) from commercially available

bromoquinone **3.9**, we were able to apply a modification of Maier`s conditions based on the application of $Pd_2(dba)_3$ and $AsPh_3$ (Scheme 3.2).[3,4] By this route desired bis-enone **3.12** could be obtained in a reproducable yield of 75-80%.

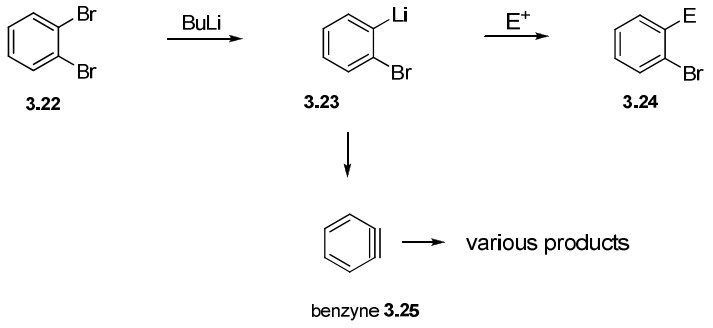


Scheme 3.2. Synthesis of bis-enone **3.12**.

At this point we turned our attention to the synthesis of arylstannane **3.8**, the equivalent of an aromatic portion of dideoxy lomaivitcinone (**2.1**) (Scheme 3.4). We began with the preparation of naphthoquinone **3.16**. In 1971, Brassard reported a method for generation of halogenated and non-halogenated naphthoquinones.[5] The Brassard method employed a mixture of halogenated maleic anhydride derivatives, dimethoxybenzene (**3.15**) and molten $AlCl_3$/NaCl heated to a temperature of 170-190 ^oC. Immediate hydrolysis using an aqueous solution of 4 M HCl produced desired phenol **3.16**. Methyl ether protection of the phenolic groups of **3.16** occurred in the absence of light with the use of a large excess of MeI and Ag_2O.[5] Use of Ag_2O played a key role in the success of this transformation, as treatment of **3.16** with standard bases (K_2CO_3 or

NaOH) resulted exclusively in decomposition of starting material. Reduction of **3.17** with $Na_2S_2O_3$ and subsequent protection of the resulting hydroquinone as MOM-ethers was achieved in ~70% yield over 2 steps. At this point we envisioned preparation of arylstannane **3.8**. Its generation via single lithium-halogen exchange followed by monosubstitution with a trimethyltin group constituted a significant challenge. Early attempts to synthesize **3.8** were rather disappointing as poor yields (20-25% for **3.8**) were accompanied by isolation of multiple by-products (Scheme 3.4, compounds **3.19-3.21**).

In 2007, Yoshida and coworkers described successful (yields between 70-80%) monosubstitution of *ortho*-dibromobenzenes (**3.22**).[6] Although the method employed microreactors, emphasis of the importance of time control for the successful transformation while avoiding formation of the undesired benzyne intermediate (**3.25**) piqued our interest (Scheme 3.3).

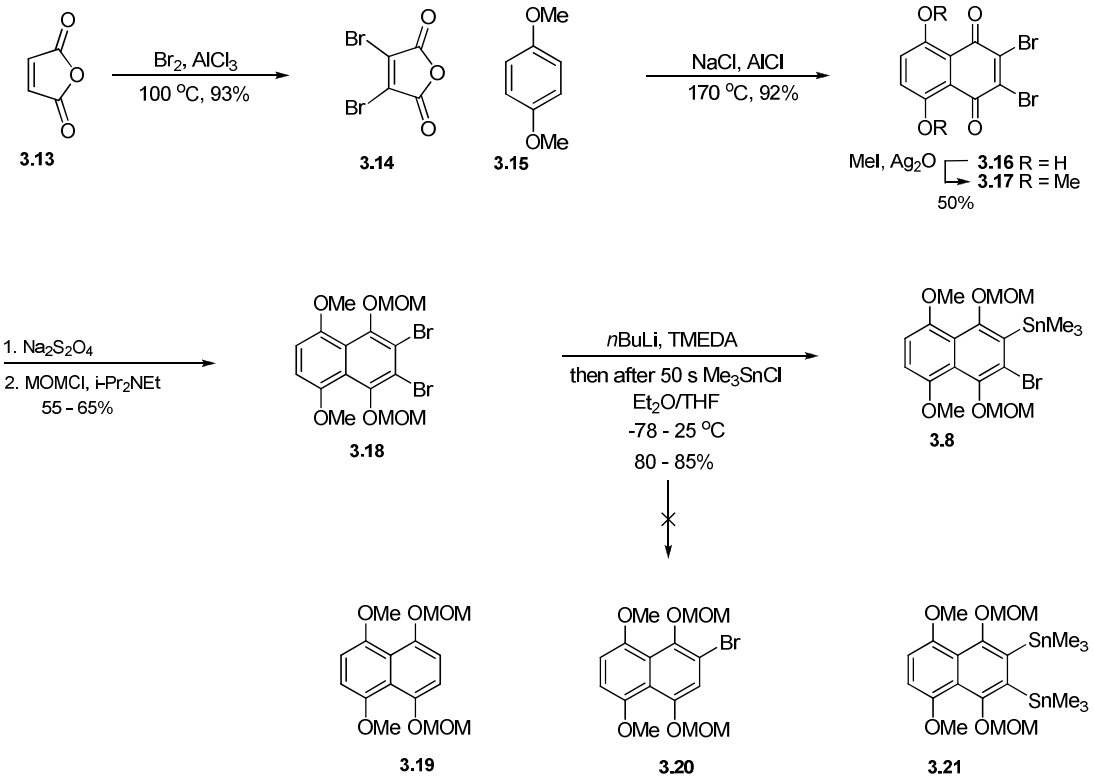


3.22 **3.23** **3.24**

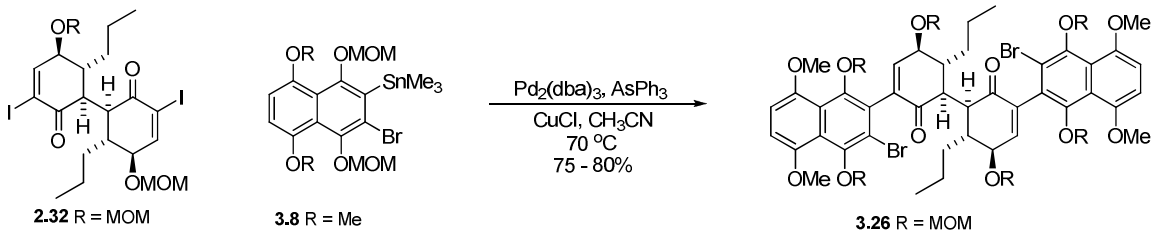
benzyne **3.25**

Scheme 3.3. Lithium-halogen exchange of *ortho*-dibromides.

Applying Yoshida`s observations to our work, we decided to examine addition of Me_3SnCl in a time-controlled manner. We were delighted to observe that addition of n-BuLi followed by a solution of Me_3SnCl in THF after 30-40 s led to best results and compound **3.8** could be delivered in 80-85% yield. Successful application of the previously developed Stille coupling conditions led to generation of C_2-symmetric bis-enone **3.26** (Scheme 3.5).



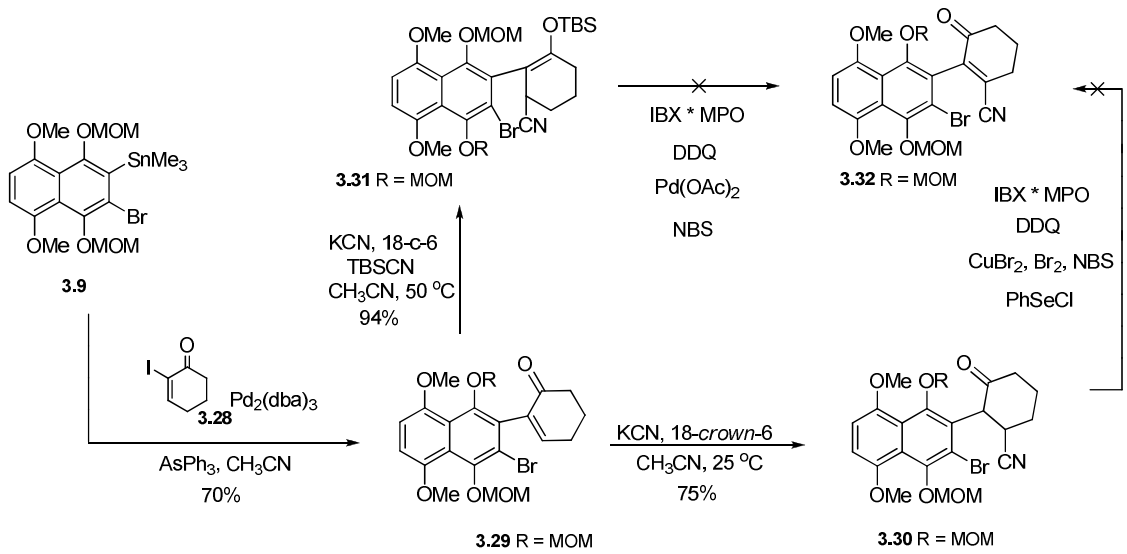
Scheme 3.4. Synthesis of arylstannane **3.8**.



Scheme 3.5. Synthesis of bis-enone **3.26**.

The stage was now set to continue our proposed annulation studies. As an easily prepared monomeric analog of **3.26,** enone **3.29** was generated. We planned to use **3.29** as a model system to develop conditions for nitrile group introduction followed by study of a cyclopentane ring formation by way of radical mediated reaction. After several different reaction conditions were screened, we found that **3.30** could be obtained through reaction with KCN and a catalytic amount of 18-crown-6 in 75% yield.[7] The same cyanoketone **3.30** could also be delivered in 70% yield via treatment of **3.29** with acetone cyanohydrin and NaH in DMF.[8] With cyanide **3.30** in hand, attention shifted towards the key cyclization starting with reintroduction of unsaturation (compound **3.32**) as required for formation of the core of **2.1**. To form enone **3.32** from ketone **3.30**, various oxidations were examined: direct oxidation (IBX, DDQ, CAN, $Pd(OAc)_2$/DMS/TFA), an α-halogenation/elimination sequence ($CuBr_2$/EtOAc, NBS/AIBN, NBS/NaH, Br_2/NaH), α-phenylselenylation/elimination (PhSeCl/NaH, PhSeCl/LDA, PhSeBr/NaH, PhSeBr/NaHMDS, PhSeBr/LDA), formation of a silyl enol ether/oxidation ($TMSCl/Et_3N$, TMSCl/HMDS, $TBSCl/Et_3N$), and application of the Mukaiyama reagent (t-BuPhNSCl/NaH) (Scheme 3.6).[9] Unfortunately, none of the attempts provided the desired product **3.32**. In most experiments, recovery or decomposition of substrate **3.30**

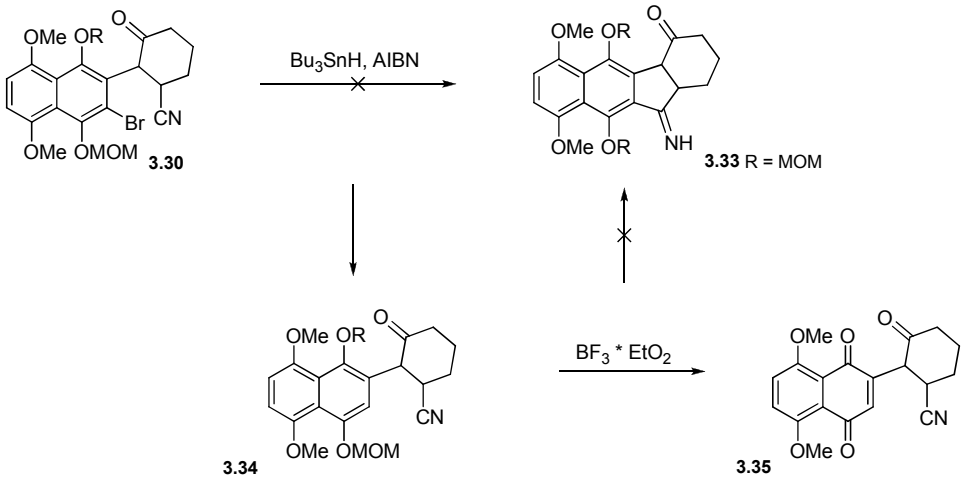
was observed, while some reactions resulted in the deprotection of the hydroquinone unit. Subsequently, silyl enol ether **3.31** as a mixture of diastereoisomers (ratio ~1:1) was generated by treatment of **3.29** with TBSCN, KCN, and a catalytic amount of 18-crown-6 in CH_3CN at 50 ^oC. Again, all attempts to oxidize **3.31** failed to produce enone **3.32**.



Scheme 3.6. Synthesis of cyanomodel **3.30**.

Simultaneously, the possibility of an intramolecular cyclization under radical conditions was examined. Cyanoketone **3.30** was treated with Bu_3SnH and AIBN or Et_3B/O_2 as radical initiators (Scheme 3.7). The experiments were conducted at varying reaction temperatures (25-110 ^oC) employing variety of solvents (THF, C_6H_6, PhMe). Disappointingly, only ketone **3.34** the product of dehalogenation, was isolated. We deduced that hindered rotation around the C-C bond between the aromatic portion and the cyclohexenone unit was likely responsible for the formation of **3.34** instead of **3.33**.

In 2006, Wähälä reported the Lewis acid-mediated synthesis of polyhydroxydeoxybenzoins through electrophilic aromatic substitution of benzilic cyanides.[10] We decided to examine this type of transformation using dehalogenated ketone **3.34** (Scheme 3.7) to effect our desired ring formation. Unfortunately, after treatment of **3.34** with different Lewis acids (BF_3•Et_2O, $TiCl_4$, $ZnCl_2$/HCl, $SnCl_4$), only quinone **3.35** could be isolated. These results prompted us to reexamine our approach.

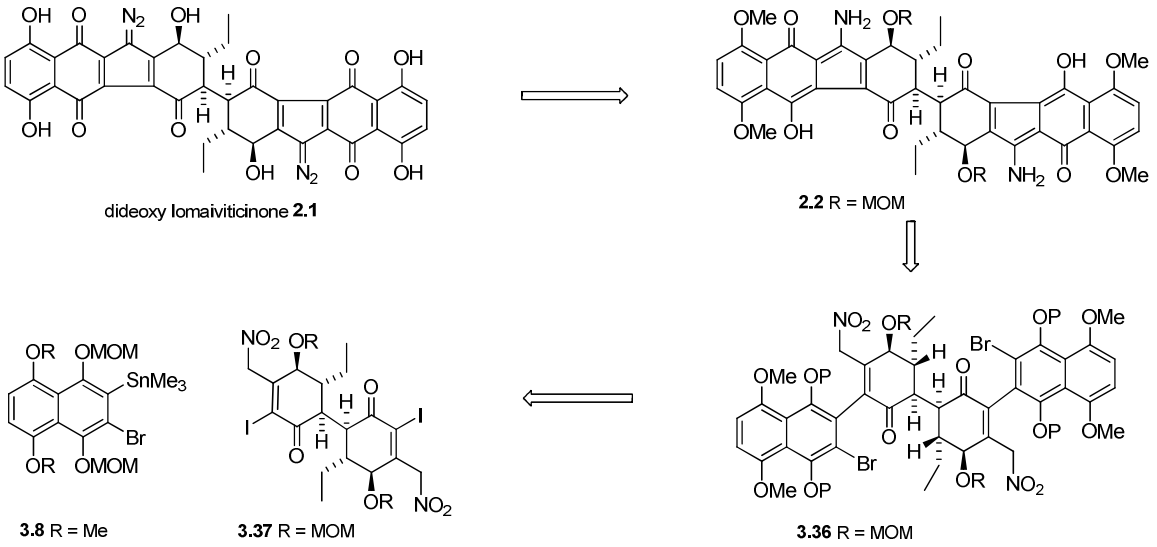


Scheme 3.7. Failed annulation studies.

Nitro Group Studies

On the basis of our previous results, we considered the preparation of bis-α-iodo-β-nitromethylenone **3.37** (Scheme 3.8). We anticipated that **3.37** could be coupled to arylstannane **3.8** to give **3.36**. Since no Michael addition and enone reintroduction would be required after oxidation of **3.36**, the coupling reaction between

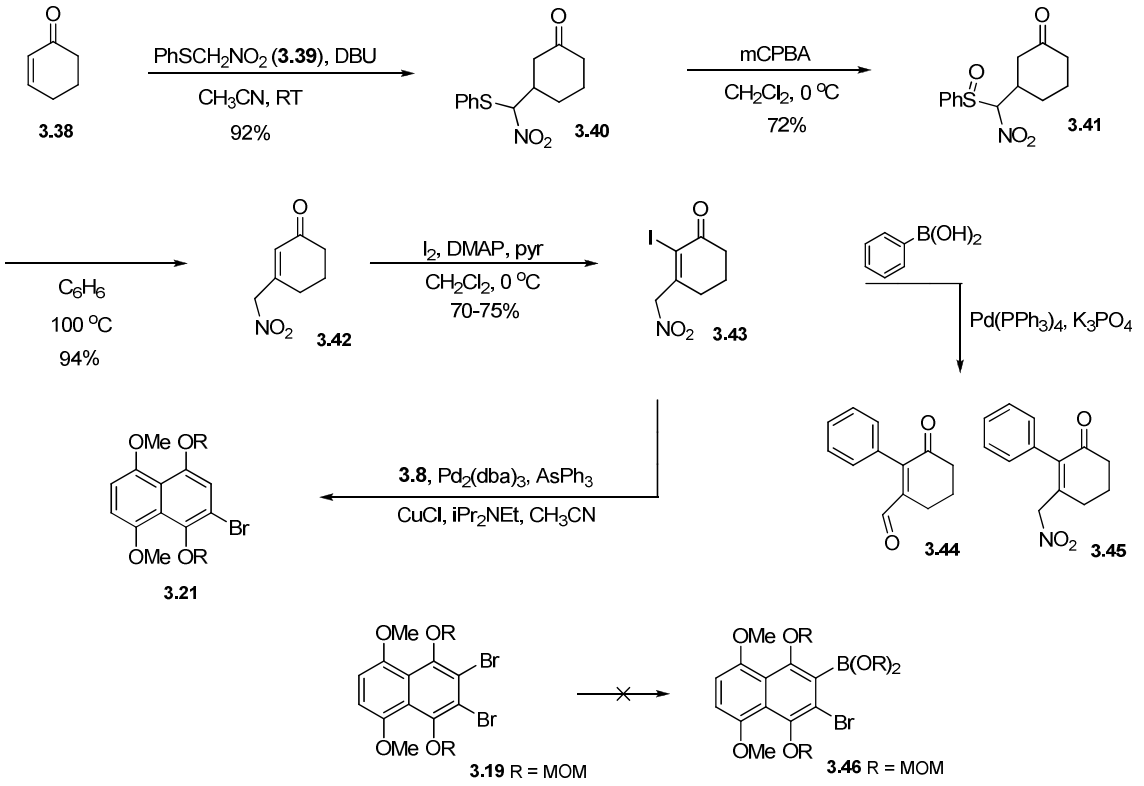
bromoquinone and nitromethane unit could be utilized to form the cyclopentane ring. Reduction of the nitro group would then deliver bis-amine **2.2**.



Scheme 3.8. Retrosynthetic analysis with nitroenone **3.37**.

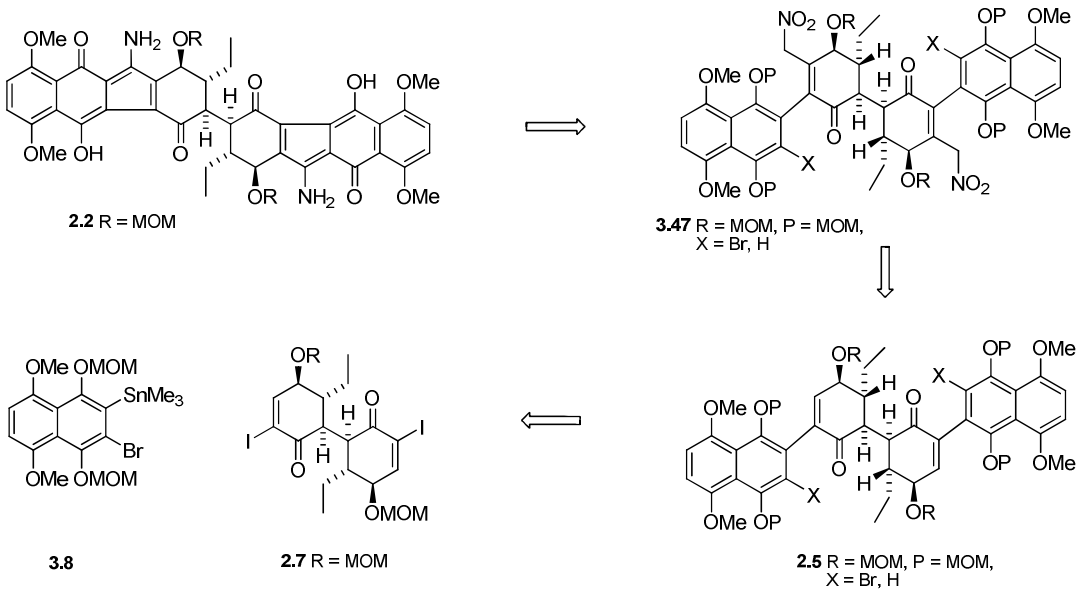
Synthesized for the first time by Seebach, phenyl(thio)nitromethane **3.39** (Scheme 3.9) was available by two-step sequence involving chlorination of benzenethiol followed by chloride displacement by the sodium nitronate of nitromethane.[11] After distillation, the blood red product could be isolated in 90-95% yield. Phenyl(thio)nitromethane **3.39** has been mostly used in Knoevenagel condensations and [2+3] cycloadditions leading the formation of isoxazoles.[12,13] To our surprise, it has never been applied as a Michael donor, a transformation we were eager to test, and we envisioned that **3.39** could be used as a source of the nitromethane unit. After appriopriate manipulation of a sulfur fragment the enone functionality in the cyclohexanone could be reintroduced. Again, we decided to examine our approach with

use of a model system derived from cyclohexenone. Michael addition of **3.39** was achieved by treatment with DBU in CH_2Cl_2 at ambient temperature. We found that the best results were obtained (yields 90-95%) and 1,2-addition was avoided when DBU was applied in large excess (20 eq). Oxidation of **3.40** to sulfoxide **3.41** proceeded smoothly in the presence of *m*CPBA, and careful temperature control prevented over-oxidation to the sulfone. Exposure of **3.41** to heat for ~14 h led to formation of enone **3.42** in ~65% yield making the 3-step sequence a unique method for generation of β-substituted nitromethane-enones. Next formation of iodoenone **3.43** was investigated. Multiple conditions were tested as α-iodination of a nitro group-containing molecule constituted a significant challenge. Finally, the best results were obtained when Johnson`s protocol was applied; however, the desired product **3.43** was obtained in unsatisfactory yields (30-35%) due to the competing Nef reaction – formation of the corresponding aldehyde.[14] Despite this difficulty, we began examination of conditions for coupling of **3.43** to aromatic fragment **3.8**. We quickly learned that compound **3.43** was very unstable to numerous coupling reaction conditions. Examination of the previously developed Stille coupling led exclusively to formation of destannylated naphthalene **3.21**, and very limited success was observed under Suzuki conditions.[15] Two reaction products with phenylboronic acid, aldehyde **3.44** and nitroenone **3.45**, were isolated. Additionally, following attempts to prepare the proper boronic acid or ester derivative of dibromide **3.19** for further examination of Suzuki reaction were met only with failure.



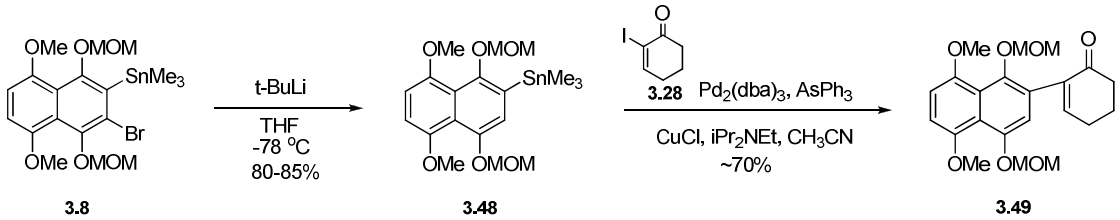
Scheme 3.9. Synthesis and annulation studies of nitroenone **3.43**.

Despite previous failures, we decided to once again evaluate our initial approach based on the use of bis-enone **2.5**. We envisioned conversion of **2.5** into bis-nitroenone **3.47** via Michael addition of nitromethane and reintroduction of the enone functionality (Scheme 3.10). We anticipated that preparation of both halogenated and non-halogenated bis-enone **2.5** would create a wide range of possibilities to achieve cyclopentane ring formations.



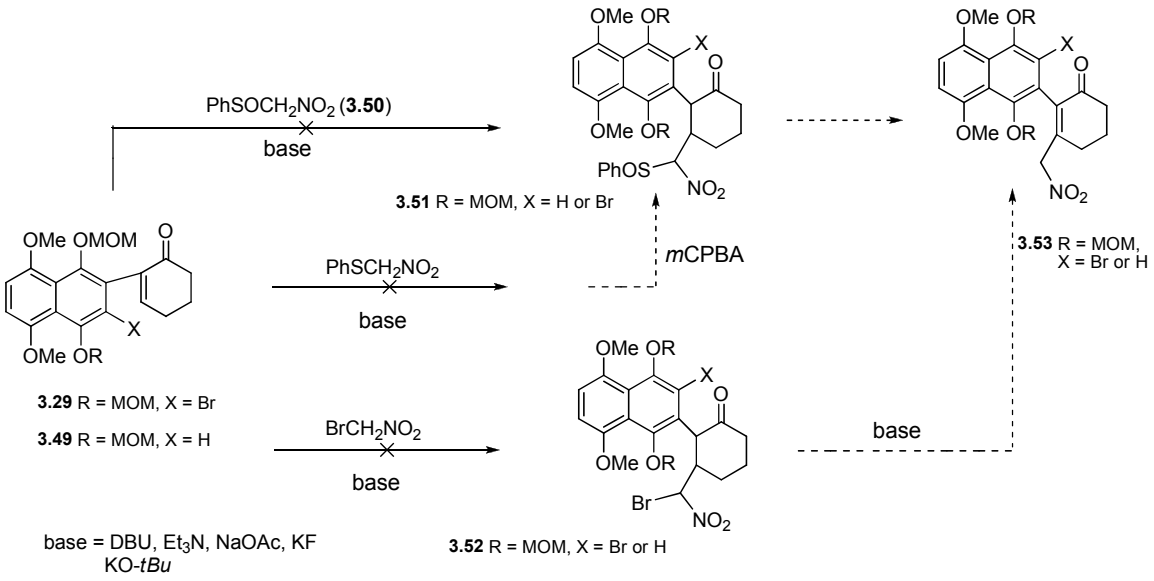
Scheme 3.10. Revised retrosynthetic analysis.

In order to prepare the non-halogenated analog of bis-enone **3.29**, arylstannane **3.48** was constructed (Scheme 3.11). Addition of t-BuLi to the solution of **3.8** in THF at -78ºC followed by quenching with a saturated solution of NH_4Cl delivered **3.48** in excellent yield of 80-85%. Compound **3.48** could be easily coupled to α-iodoenone **3.28** under our standard Stille coupling conditions in an average yield of 70%.



Scheme 3.11. Synthesis of enone **3.49**.

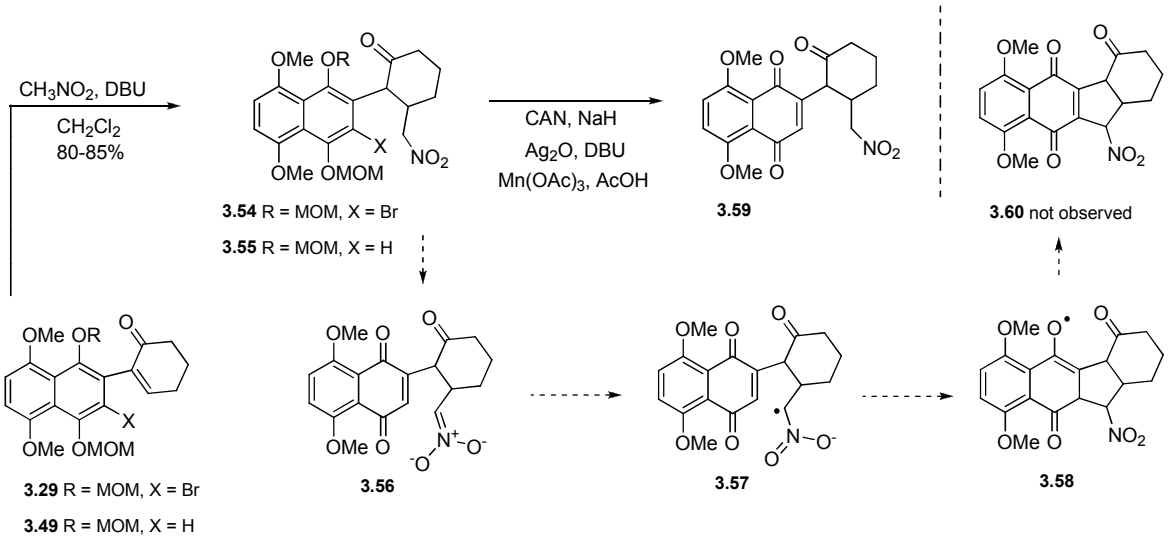
Applying both model systems, halogenated enone **3.29** and non-halogenated enone **3.49**, we subsequently probed conditions for generation of nitroenone **3.53** via synthesis of Michael adducts **3.51** or **3.52** (Scheme 3.12). We hoped that **3.51** could be prepared through Michael addition of nitromethanephenylsulfoxide **3.50** or via Michael addition of phenyl(thio)nitromethane/oxidation sequence. Heat-mediated elimination/isomerisation would then provide **3.53**. Despite significant effort, sulfoxide **3.51** was never obtained. Similarly, addition of bromonitromethane was unsuccessful, and the product of bromine elimination (**3.53**) was never generated.



Scheme 3.12. Failed synthesis of nitroenone **3.53**.

We rationalized that observed reluctancy to conjugate addition were caused by the steric hindrance around the cyclohexenone unit: compounds **3.39**, **3.50** and bromonitromethane were simply too large to undergo Michael addition into the olefin

of **3.29** or **3.49**. Our explanation was later supported by the successful synthesis of nitroketones **3.54** and **3.55** produced through DBU-mediated Michael addition of the sterically less demanding nitromethane (Scheme 3.13). With compounds **3.54** and **3.55** in hand the annulation studies were continued.

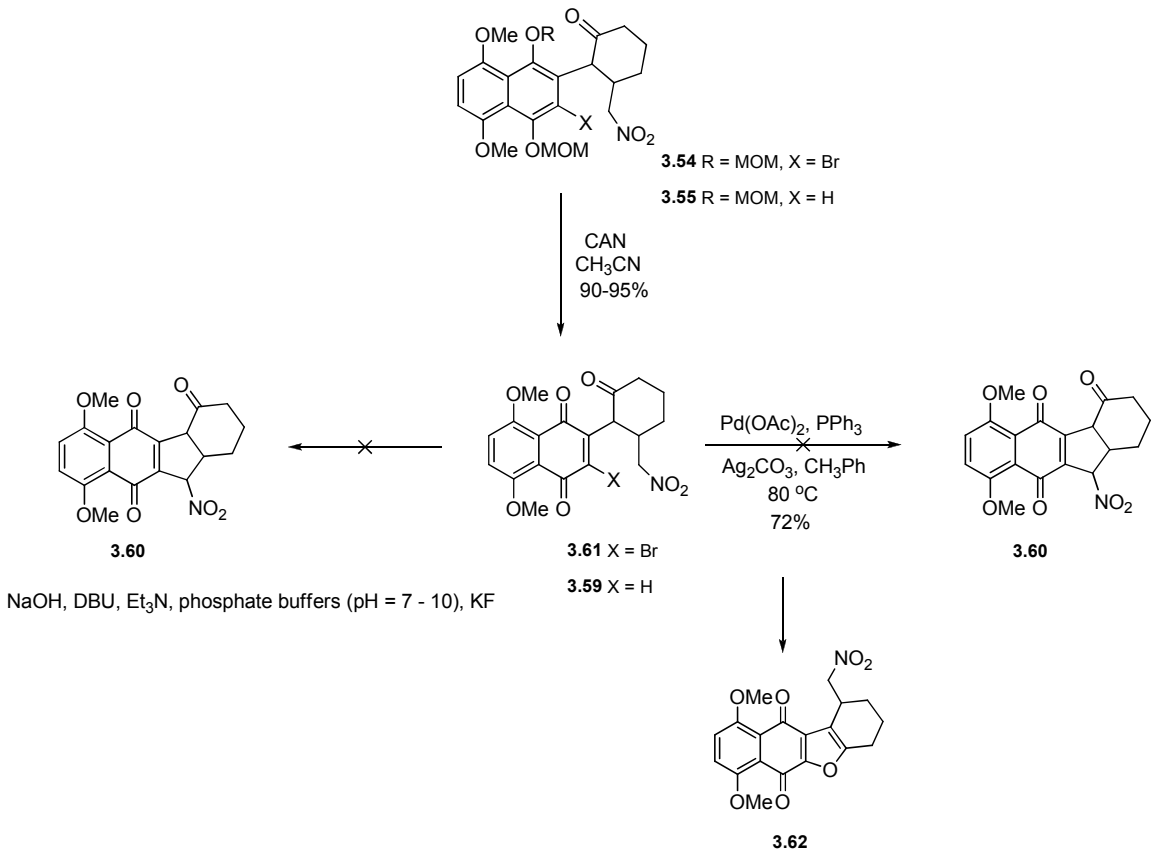


Scheme 3.13. Synthesis of nitroketones **3.54** and **3.55**.

Formation of 1-nitroalkyl radicals as a result of one electron oxidation and their addition onto olefins to form cyclic structures is a well established transformation which has found multiple applications.[16,17,18,19] Following available reports, we envisioned that treatment of **3.55** with an oxidant (CAN, Ag_2O, $K_3Fe(CN)_6$) could lead to removal of the MOM-ethers and generation of quinone-nitronate **3.56** (Scheme 3.13). Oxidation of **3.56** would then afford alkyl radical **3.57**, whose 1,4-addition onto the quinone would produce semiquinone radical **3.58** and after oxidation would be converted into

nitroquinone **3.50**. The combinations of CAN/NaH, Ag_2O/DBU, $Mn(OAc)_3 2H_2O/Ac_2O$, and $K_3Fe(CN)_6$/NaOH were tested to achieve the conversion of **3.55** into **3.60**; however nitroquinone **3.60** was not produced. Only the oxidation product (**3.59**) was isolated.

Our studies were continued with the synthesis of quinones **3.59** and **3.61**, easily prepared by treatment of **3.54** and **3.55** with CAN in CH_3CN (Scheme 3.14). Despite violating Baldwin`s rules (disfavored 5-*endo*-trig ring formation), we decided to evaluate an intramolecular, base induced-cyclization of the nitromethane unit onto the quinone of nitroketone **3.59**.[18] We began this series of experiments using strong bases (DBU, NaOH, Et_3N) but quickly replaced them with KF or phosphate buffers (pH = 7-10) after we learned that compound **3.59** was highly unstable under basic conditions. In the presence of strong base, only decomposition of **3.59** was observed. Phosphate buffer experiments produced trace amounts of a new, yellow compound, but all attempts to identify its structure were met with failure. Disappointed, we were forced to redesign our route.



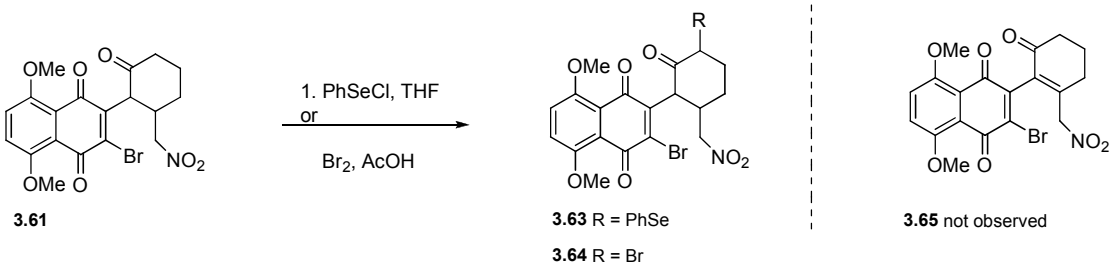
Scheme 3.14. Failed synthesis of nitroquinone **3.60**.

A literature search provided a limited number of metal catalyzed coupling reactions of nitroalkanes. A few examples, demonstrated by Buchwald, involve reaction of simple nitroalkanes (nitromethane, nitroethane) with aromatic halides.[20] Muratake and coworkers reported a method for intramolecular nitroalkane α-arylation.[21] The reactions occur under rather harsh conditions: high temperatures > 100 °C, and use of strong bases (KOt-Bu, NaOt-Bu).

Our choice of conditions for the intramolecular coupling of nitroketone **3.59** was then determined by its reactivity and stability in the presence of base. Employing a procedure developed by Herzon for the synthesis of kinamycin F, we evaluated the

possibility of nitroquinone **3.60** generation through use of Pd-mediated C-C bond formation between the bromoquinone and nitromethane units (Scheme 3.14).[22] Unfortunately, instead of compound **3.60**, furan **3.62** was isolated as a reaction product between the *in situ* formed enol and bromoquinone.

Continually, our attempts to reintroduce the enone functionality in the cyclohexanone portion of **3.61** were unsuccessful (Scheme 3.15). Introduction of an α-substituent which could later undergo elimination was first tested by exposure of **3.61** to NBS/hv, but only compound **3.61** was recovered.[23] Treatment of **3.61** with PhSeCl in THF (no base required) delivered smoothly the undesired regioisomer **3.63**, and a similar product was produced when **3.61** was reacted with Br_2 in AcOH.[24] Further examination of this route was discontinued.



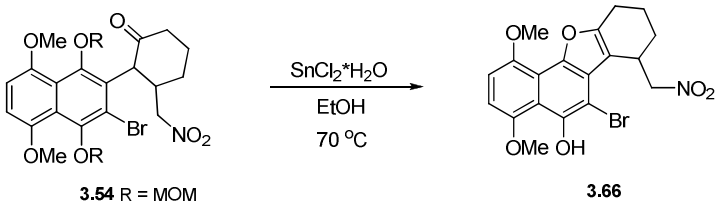
Scheme 3.15. Unsuccessful oxidation of ketone **3.61**.

Nitro Group Derivatives Studies

The value of a nitro group as a synthon in the synthetic route design should not be overlooked. The list of available transformations this functionality can undergo

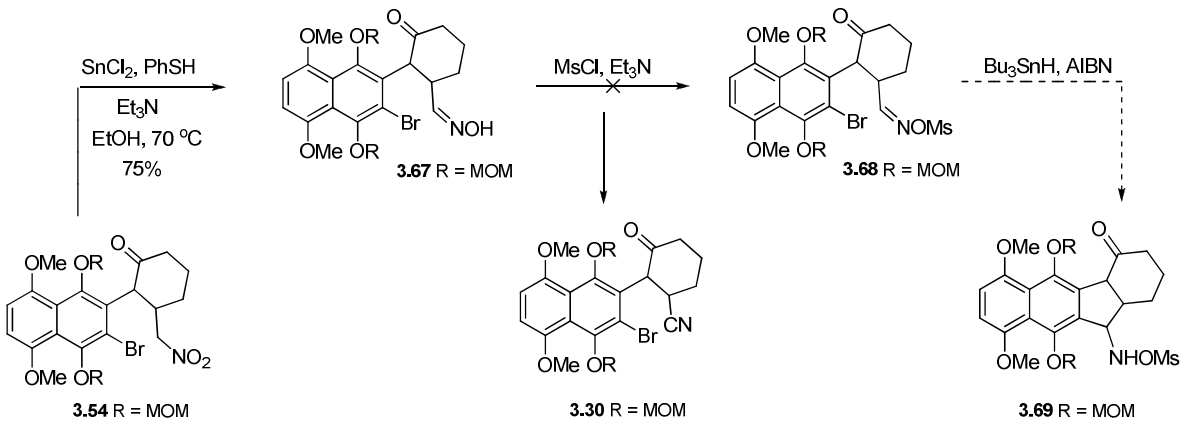
includes formations of aldehydes, ketones, carboxylic acids (Nef reaction), reductions to amines, hydroxylamines or oximes, reductive denitrations, formation of 1,3-dipoles, and finally elimination of nitrous acid to produce olefins.[25]

Taking advantage of the properties of nitroalkanes, we decided to convert compound **3.54** into an oxime and then to an oxime ether which could be subjected to cyclization under radical conditions. Although, our first attempts failed to produce the desired oxime **3.67**, yielding only product resulting from hydroquinone deprotection, 1,2-addition onto the carbonyl group and dehydration (**3.66**, Scheme 3.16), we were pleased to see that a small modification of reaction conditions led to generation of **3.67** (Scheme 3.17).[26,27] Unfortunately, subsequent treatment of **3.67** with MsCl and Et_3N did not give oxime ether **3.68** but delivered previously synthesized cyanoketone **3.30**. Accordingly, plans to examine radical cyclization to produce **3.69** were at this point terminated.



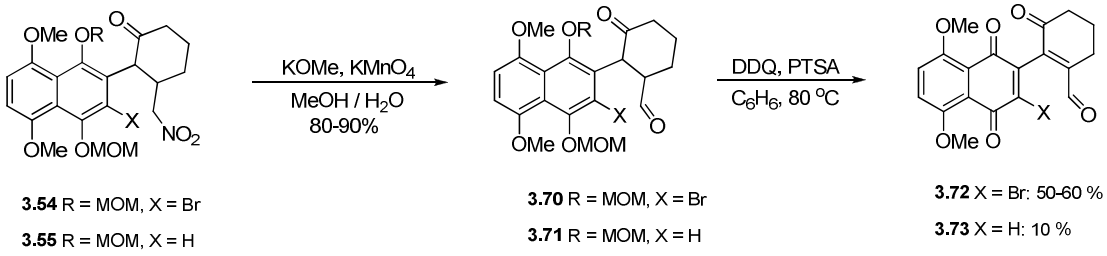
3.54 R = MOM **3.66**

Scheme 3.16. Initial attempts to reduce nitroketone **3.54**.



Scheme 3.17. Failed synthesis of ketone **3.68**.

The study of alternative reactivity modes of nitroalkanes **3.54** and **3.55** was considered next. Applying a method reported by Steliou, both **3.54** and **3.55** were converted into the analogous aldehydes **3.70** and **3.71** (Scheme 3.18).[28] Choice of a Nef reaction conditions was not accidental since deprotection (oxidation) of the hydroquinone fragment needed to be avoided to minimize base-induced decomposition of a potentially formed quinone. Installation of a highly electron withdrawing aldehyde generated an opportunity to examine once again methods for reintroduction of unsaturation. Therefore, both **3.70** and **3.71** were treated with NaH/KOt-Bu/$FeCl_3$, DDQ/C_6H_6 and $CuBr_2$/EtOAc.[29] Eventually it was determined that enone **3.72** could be successfully generated (yields 50-60%) when **3.70** was treated with DDQ in C_6H_6 in the presence of a catalytic amount of PTSA.[30] Unexpectedly, a similar transformation conducted with use of non-halogenated **3.71** provided desired enone **3.73** in only 10% yield.



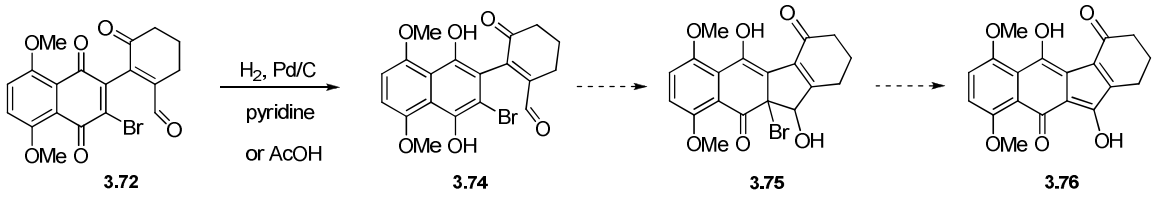
3.54 R = MOM, X = Br
3.55 R = MOM, X = H

3.70 R = MOM, X = Br
3.71 R = MOM, X = H

3.72 X = Br: 50-60 %
3.73 X = H: 10 %

Scheme 3.18. Sythesis of aldehydes **3.72** and **3.73**.

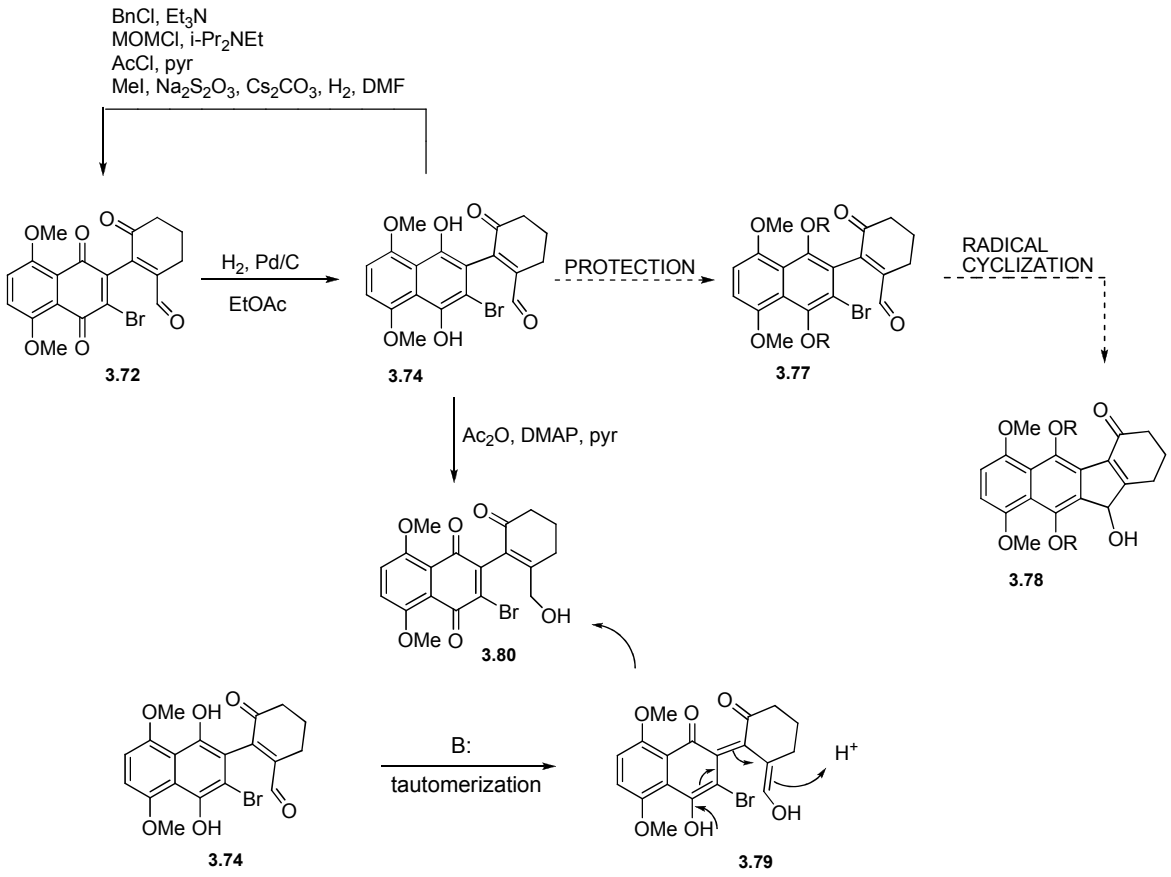
Once the solution to one of our longstanding problems was established, our focus shifted entirely toward the second challenge, cyclopentane ring formation. After several possible transformations were quickly excluded (palladium catalyzed ring formation, cyclization under radical or photochemical conditions), we envisioned conversion of aldehyde **3.72** into hydroquinone **3.74** and its *in situ* based-mediated cyclization onto the carbonyl group to form **3.75** (Scheme 3.19).[21,31] Further elimination of bromine and reintroduction of the quinone functionality would produce the secondary alcohol **3.76**. Disappointingly, both acid and based-induced cyclizations did not occur and compound **3.76** was not produced. Under basic conditions decomposition of **3.72** was observed.



3.72 **3.74** **3.75** **3.76**

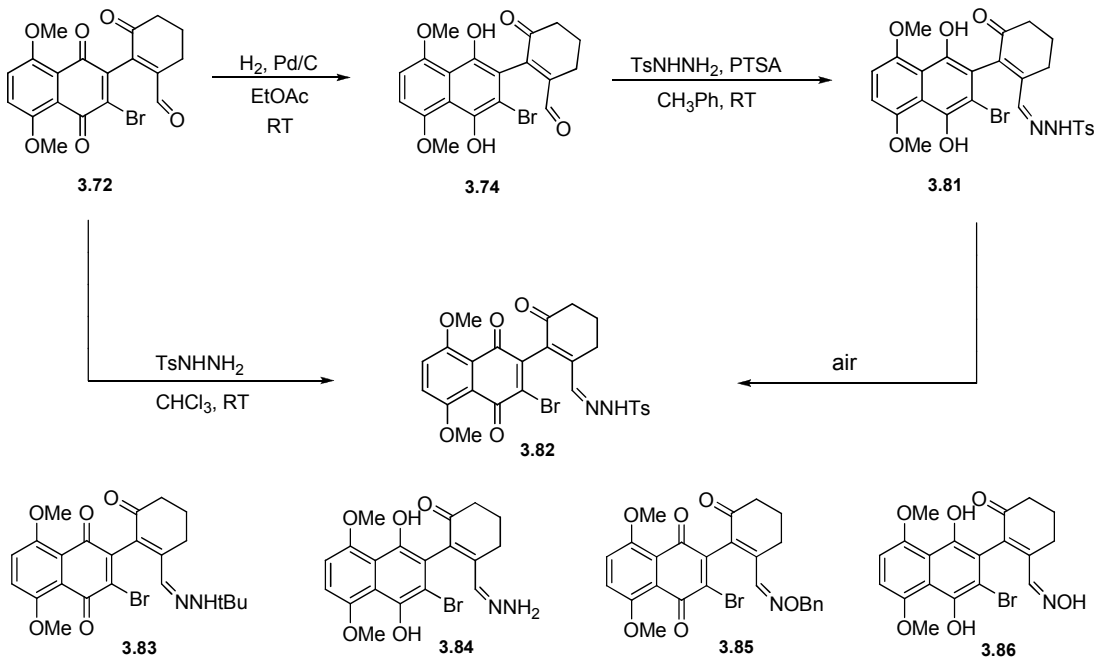
Scheme 3.19. Unsuccessful synthesis of alcohol **3.76**.

Next, we initiated attempts to prepare protected hydroquinone **3.77** to investigate radical-mediated cyclizations with a goal of producing alcohol **3.78** (Scheme 3.20). Interestingly, while treatment of **3.74** under basic conditions led to reintroduction of quinone **3.72**, reaction with Ac_2O, DMAP and pyridine produced alcohol **3.80**. A plausible mechanistic explanation for this transformation is presented in Scheme 3.20. The base-mediated tautomerization of hydroquinone **3.74** to quinone methide **3.79** and subsequent protonation of terminal olefin afforded **3.80**.



Scheme 3.20. Attempts to synthesize alcohol **3.78**.

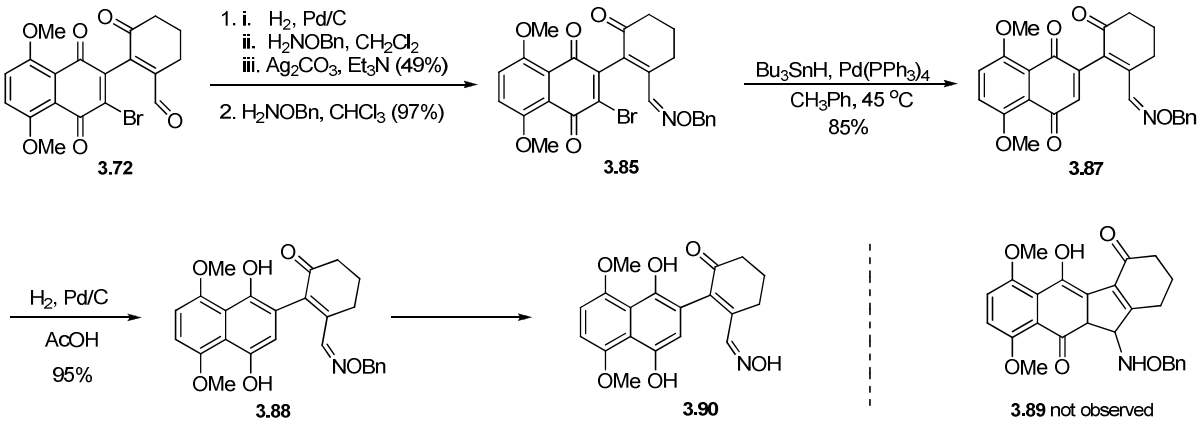
Facing lack of any success with use of aldehyde **3.72**, derivatization studies were continued (Scheme 3.21). Our goal was to identify a method which would allow generation of different nitrogen containing analogs of **3.72**. To better control the regiochemistry of the examined transformations, reduction of **3.72** to hydroquinone **3.74** was conducted under an H_2 atmosphere in the presence of Pd/C, and the generated hydroquinone **3.74** was immediately subjected to condensation. The first experiments were conducted with use of tosylhydrazide, and various solvents were examined (EtOAc, EtOH, $PhCH_3$, CH_2Cl_2), but only treatment of **3.74** with tosylhydrazide and a catalytic amount of *p*-TSA in toluene at ambient temperature provided desired hydrazone **3.81**.[32] Exposure of compound **3.81** to air led to quick oxidation to **3.82**. It was later found that **3.82** could be obtained directly from **3.72** in only one step by reaction with tosylhydrazide in $CHCl_3$ at ambient temperature. Both procedures provided access to different hydrazones, oximes and oxime ethers (compounds **3.82-3.86**).



Scheme 3.21. Synthesis of nitrogenated analogs of aldehyde **3.72**.

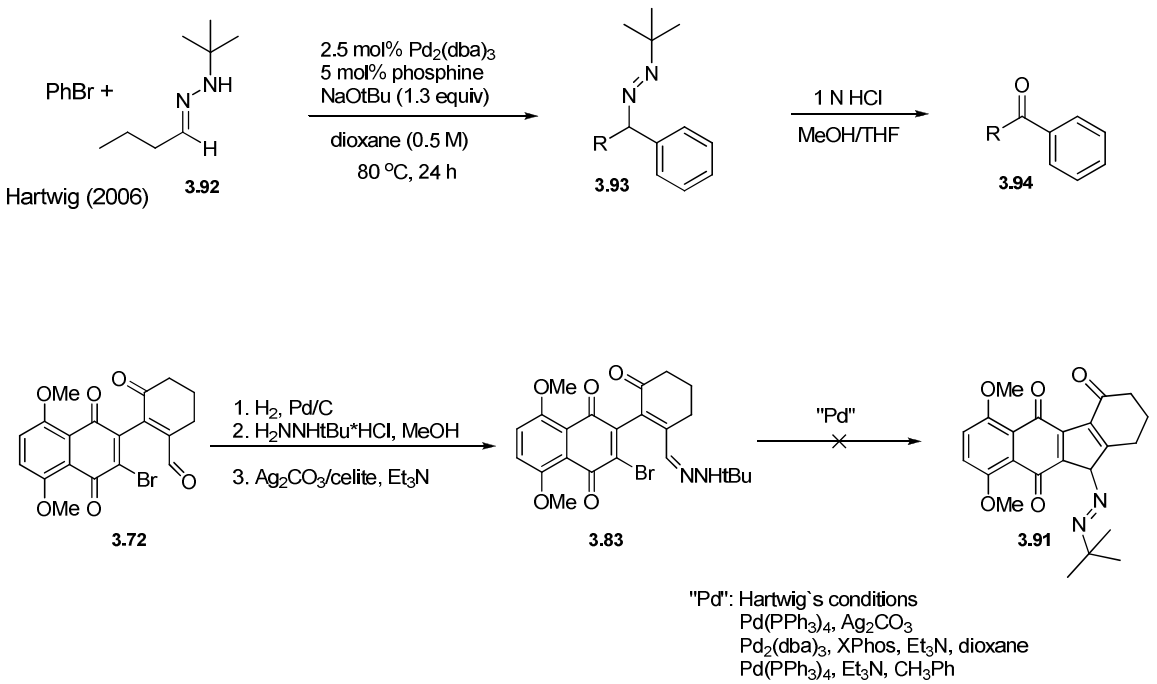
In 1996, Uenishi described a protocol for the reduction of vinyl gem-dibromides to Z-bromoolefins.[33] The reaction catalyzed by $Pd(PPh_3)_4$ occurred in the presence of a stoichiometric amount of Bu_3SnH in benzene at ambient temperature. Catalyst choice played a key role in the success of this transformation as only $Pd(PPh_3)_4$ delivered the desired products while other catalysts promoted exclusive formation of $H_{2(gas)}$. Similar to studies preformed with aldehyde **3.72**, we envisioned formation of the cyclopentane ring of **3.89** through the cyclization of the hydroquinone unit onto the electrophilic oxime ether group (Scheme 3.22). On the basis of our previous results (Scheme 3.19), we anticipated that this transformation would be favored if a sterically bulky bromine atom was removed, and the reaction was tested with use of oxime ether **3.87**. Thus, oxime ether **3.85** was subjected to debromination with the $Bu_3SnH/Pd(PPh_3)_4$ system to

deliver **3.87**. This was the only method which produced **3.87** while attempted debromination with strong base or under radical conditions failed due to the sensitivity of the quinone functionality. Unfortunately, treatment of **3.87** under reductive conditions in acidic media afforded only enone **3.90**. Similarly, reduction of **3.87** to the hydroquinone followed by treatment with $BF_3 \bullet Et_2O$ in CH_2Cl_2 did not give **3.89** but rather decomposition of substrate **3.87** was observed.



Scheme 3.22. Oxime ether **3.87** annulation studies.

The tandem Grignard addition/oxidation sequence has often been utilized to produce aryl ketones. Seeking alternatives to this standard protocol, Hartwig`s group developed a coupling reaction between t-butylhydrazones and aryl halides (Scheme 3.23).[34] The first example of palladium catalyzed C-C bond formation with hydrazones, Hartwig`s method relies on the acyl anion properties of **3.92**. In the described protocol, formation of **3.93** was followed by acid-mediated hydrolysis to give aryl-ketone **3.94**.

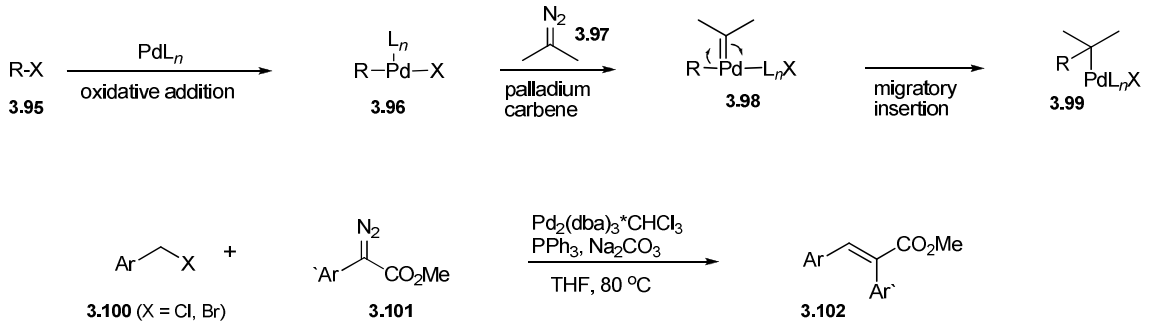


Scheme 3.23. Examination of Hartwig`s method for coupling of *t*-butylhydrazones.

With quick access to hydrazone **3.83**, examination of Hartwig`s method was initiated. Applying reported as well as modified conditions we hoped to generate hydrazone **3.91**; however disappointingly, only decomposition of **3.83** was observed.

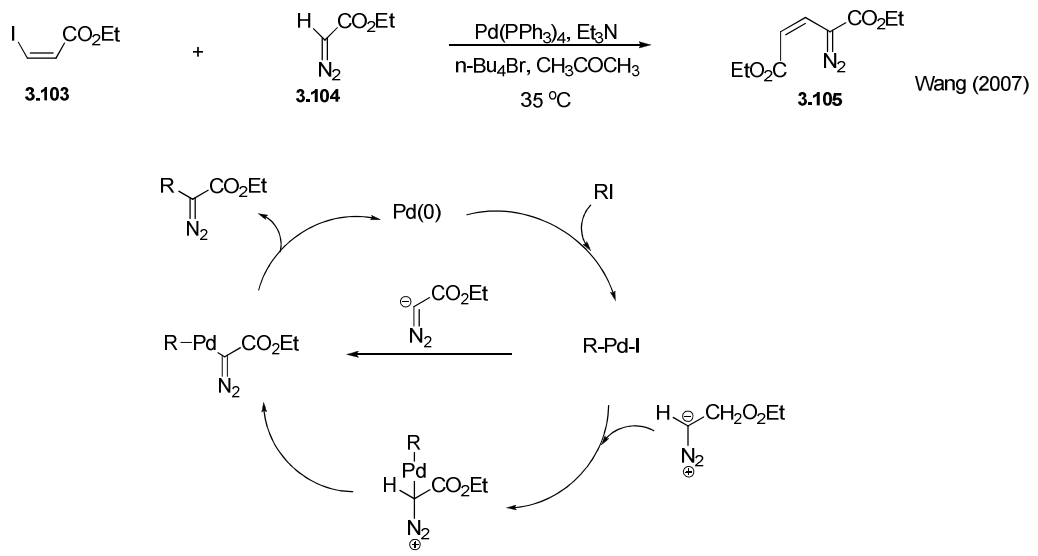
The role of diazo compounds as carbene precursors or metal carbenes is well established. Typically, Rh^{II} or Cu^{I} catalysis is employed to exploit the properties of this reactive functional group. Much less attention has been paid to the application of Pd catalysis as a consequence of its lower efficiency (higher temperatures and longer reaction times are required to promote the similar transformation).[35] Despite this fact, several distinctive reactions have been developed with use of palladium catalysts. Mechanistically, reported transformations have been explained by the sequence of steps presented in Scheme 3.24. Initial transmetallation or oxidative addition produces

Pd intermediate **3.96**, and formation of the Pd carbene **3.98** is then accomplished through the dediazotisation of a stabilized diazo substrate **3.97**. Subsequent migratory insertion leads to the new Pd intermediate **3.99**, which in the majority of described examples undergoes β-elimination to afford olefins. Reported examples include migrations of vinyl, aryl, allyl, acyl and benzyl groups.



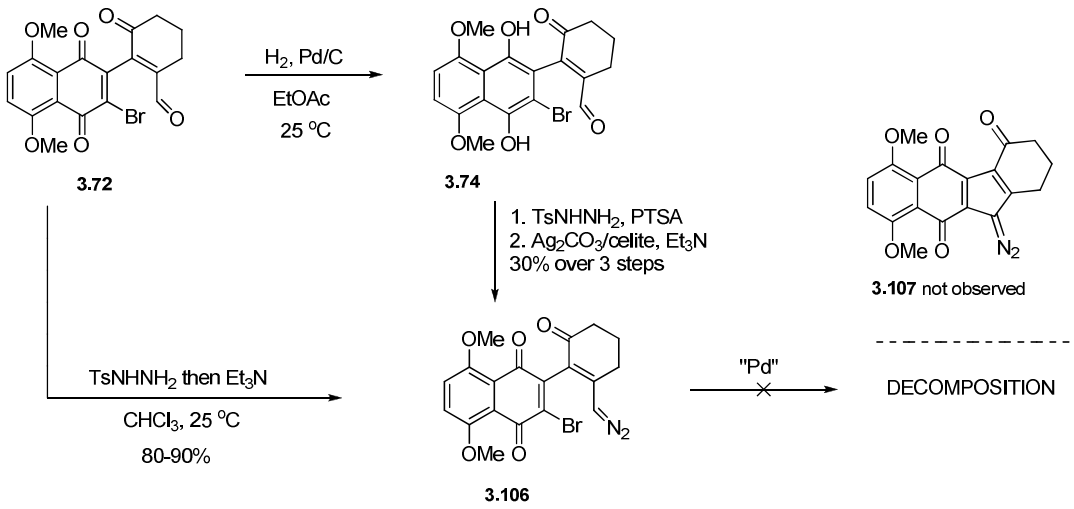
Scheme 3.24. Pd carbene migratory insertion.

In 2007, Wang and coworkers described a very unique Pd-catalyzed coupling reaction between diazoesters and vinyl iodides leading to generation of extended diazoesters (Scheme 3.25).[36] The lack of carbene moiety formation despite the presence of a metal catalyst was striking and previously never reported. The mechanistic explanation provided by the authors included regular oxidative addition with the vinyl halide, transmetallation with the deprotonated diazoester playing the role of a nucleophilic partner, and finally reductive elimination of the metal species to construct C-C bond.



Scheme 3.25. Wang`s method for preparation of extended diazoesters.

Intrigued by this report, we decided to prepare diazoenone **3.106** and test the applicability of Wang`s method to our system (Scheme 3.26), and two pathways with access to **3.106** were developed. Initially, the diazoenone was produced via formation of hydroquinone **3.74**, condensation with $TsNHNH_2$ and oxidation with Ag_2CO_3 and Et_3N. Because this 3-step sequence delivered **3.106** in only 30-40% yield, other conditions were tested. We were delighted to find that **3.106** could be also generated via a one pot condensation/elimination sequence in an excellent yield of 80-90%. Our literature search revealed that **3.106** was a first example of a β-substituted diazocyclohexanone. As a continuation of our studies, compound **3.106** was then subjected to Pd-catalyzed intramolecular coupling to deliver benzo[b]fluorene **3.107**. Unfortunately, none of the examined conditions provided desired **3.107**, only decomposition of substrate **3.106** was observed.

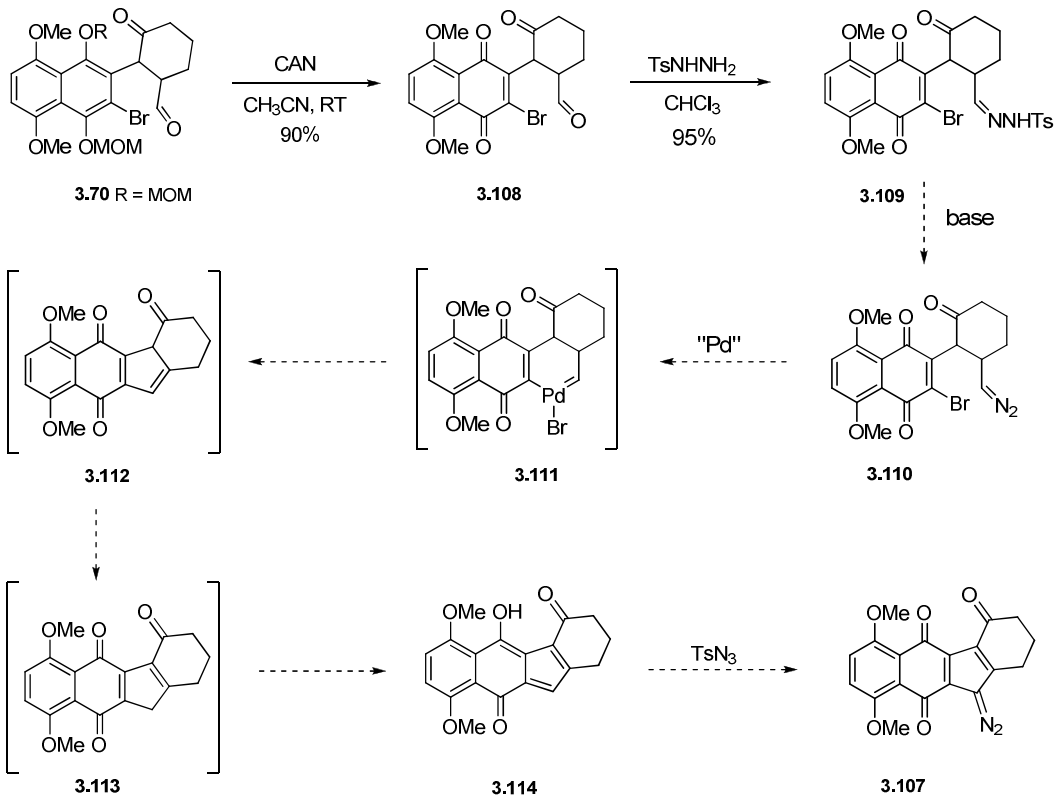


Scheme 3.26. Examination of Wang`s protocol.

While most Pd-catalyzed cross-couplings rely on the application of organometallic nucleophilic components reacting with organic halides, recent efforts have been devoted to development of protocols not based on utilization of stochiometric amounts of organometallic reagents. The list of traditional Pd-catalyzed reactions, which includes the Heck reaction, has been gradually growing, and has been expanded to include direct C-H activation, α-arylation of ketones, esters, and amides, the previously described coupling of diazoesters, or more specific protocols such as Hartwig`s method for generation of arylketones from t-butylhydrazones.[20c,21c,34,35,37] Recently, one more type of a transformation has been added to this list. With first report published in 2007, tosylhydrazones as nucleophilic components have found application in the formation of polysubstituted olefins, silyl enol ethers, enamines and substituted alkynes.[38] In all of these transformations, tosylhydrazone is believed to be converted *in situ* into a diazo derivative which consequently undergoes migratory

insertion to form the C-C bond. Application of tosylhydrazones has enabled coupling of compounds where formation of diazo analogs would be challenging (lack of conjugation associated stabilisation).

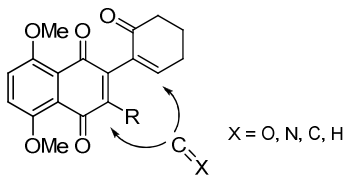
We have envisioned that by application of our protocol for the generation of nitrogenated derivatives, we could quickly prepare tosylhydrazone **3.109** from aldehyde **3.108** (Scheme 3.27). Tosylhydrazone **3.109**, subjected to coupling reaction conditions, could be converted *in situ* into non-stabilized diazoketone **3.110**. Oxidative addition, followed by Pd carbene formation would give intermediate **3.111** which after reductive elimination would produce ketone **3.112**. Double isomerisation could provide quinone methide **3.114**, and following Herzon`s protocol, **3.114** could be converted into diazoquinone **3.107** by reaction with TsN_3. Unfortunately, although hydrazone **3.109** could be easily generated from available materials, its further conversion into **3.107** was unsuccessful and only decomposition was observed. These results led to termination of this route.



Scheme 3.27. Failed synthesis of diazoquinone **3.107**.

Cascade Experiments

With quick access to quinones **3.115** and **3.116**, a number of experiments were examined which could be described as attempts to form the cyclopentadienone ring through cascade C-C bond formations (Figure 3.28). These experiments were not necessarily performed over a specific timeline, rather they were randomly generated ideas which in our opinion should not have been overlooked regardless of whether assumptions of our general synthetic approach to dideoxy lomiaviticinone were not met.

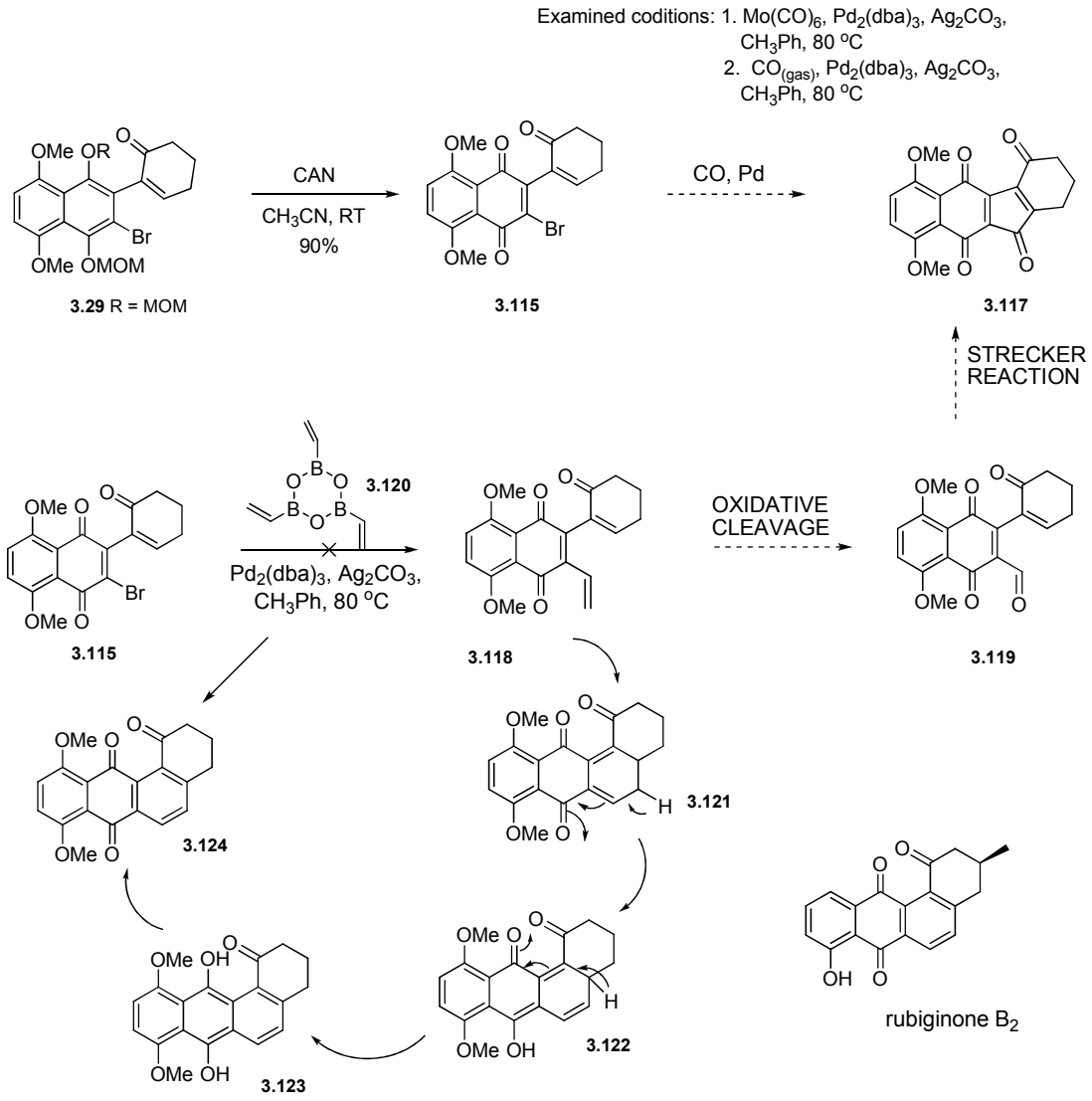


3.115 R = Br

3.116 R = H

Figure 3.2. Cascade annulation.

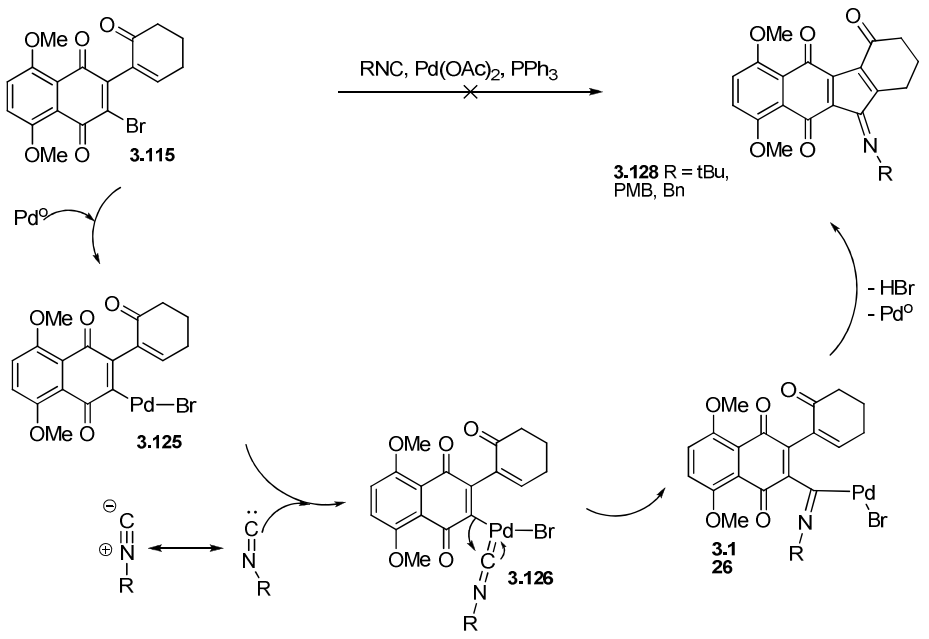
Our first attempt involved examination of Pd-catalyzed carbonylation with the goal of generating enone **3.117** (Scheme 3.29). Several conditions were tested with CO in gaseous form or derived from $Mo(CO)_6$. With no success directly producing **3.117**, a longer route was designed with quinone **3.118**, which was anticipated to be a precursor of aldehyde **3.119**, and we hoped to convert compound **3.119** into **3.117** via a Strecker reaction. In order to deliver **3.118**, bromoquinone **3.115** was subjected to Suzuki coupling with the $(vinyl)_3(BO)_3$ pyridine complex (**3.120**). Although partially successful with no decomposition of starting material, the Suzuki coupling did not produce desired **3.118** but rather delivered quinone **3.124**. We deduced that the initial formation of **3.118** was followed by an unexpected 6π-electrocyclization (**3.121**), double isomerisation (**3.123**) and oxidation of the hydroquinone to afford undesired quinone **3.124**. The carbon skeleton of **3.124** strongly resembled the structure of aglycons of the angucycline family of antibiotics (rubiginone B_1 and rubiginone B_2).[39]



Scheme 3.28. Failed carbonylation and unexpected generation of quinone **3.124**.

Continuing our studies, we envisioned application of an isocyanide as a source of a one carbon unit required for the formation of cyclopentadienone ring from bromoquinone **3.115** (Scheme 3.29). Although, no literature example could be referenced, we anticipated that an isocyanide could be used as a nucleophilic component in a Pd-catalyzed cascade coupling reaction. We envisioned a mechanism involving formation of Pd carbene **3.126** followed by Heck reaction between the

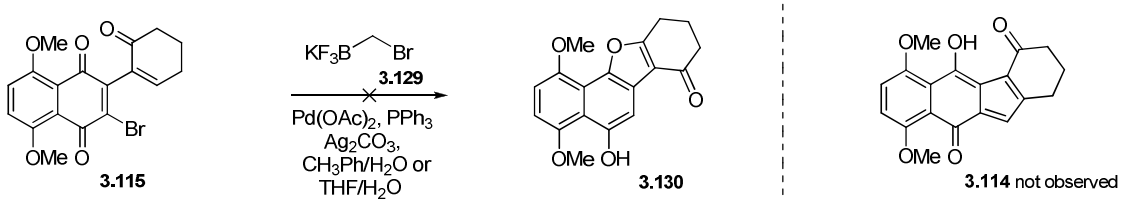
palladium intermediate and enone unit leading to formation of **3.128**. To probe our idea and generate imine **3.128**, three different isocyanides were tested, and the choice of reaction conditions was limited by the character of our model system. Therefore, reagents previously used in the reaction with the $(vinyl)_3(BO)_3$ pyridine complex **3.120** were applied; unfortunately, only decomposition of substrate **3.115** was observed.



Scheme 3.29. Proposed mechanism for coupling of quinone **3.115** with isocyanides.

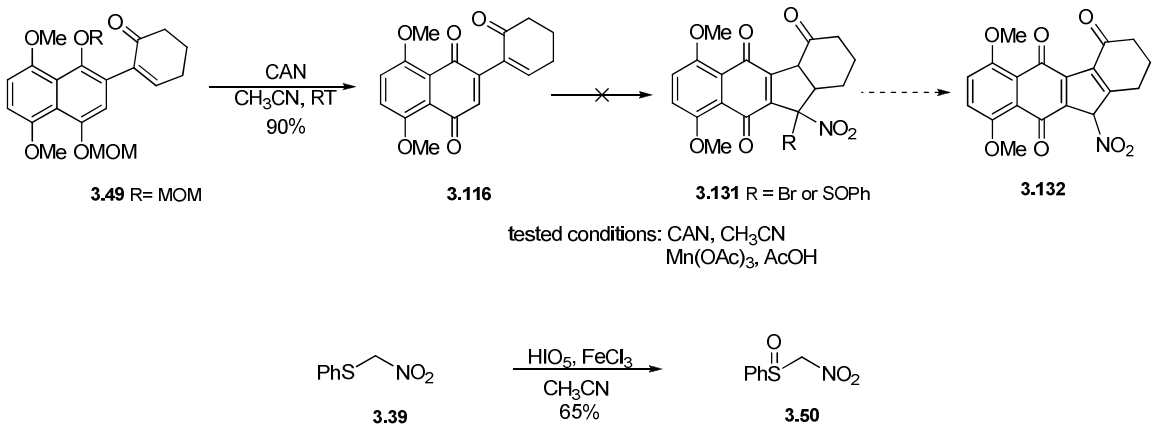
As a part of a program directed toward preparation of air- and moisture-stable organotrifluoroborates, Molander`s group described the synthesis of potassium (bromomethyl)trifluoroborate (**3.129**) (Scheme 3.30).[40] After substitution of the primary bromide with amines, alcohols or an azide, derivatized compound **3.129** served as a coupling components in Suzuki reactions or [2+3] cycloadditions.[41] We envisioned that **3.129** could be used as a source of one carbon unit for the formation of quinone

methide **3.114**. The trifluoroborate fragment, converted *in situ* to the boronic acid, would react with the bromoquinone in a Suzuki reaction, and subsequently the bromide could react with the enone unit in a Heck-type reaction to give **3.114**. Examination of this transformation with use of $Pd(OAc)_2$ as a catalyst, polymer bound PPh_3, Ag_2CO_3 in an aqueous solution of THF or toluene did not produce **3.114** but led to formation of furan **3.130**. Further studies were discontinued.



Scheme 3.30. Coupling of quinone **3.115** with potassium (bromomethyl)trifluoroborate.

Oxidative addition of electrophilic carbon-centered radicals to alkenes mediated by metal salts can be performed inter- or intra-molecularly.[42] $Mn(OAc)_3$ and CAN have been utilized as promoters of these transformations, most efficiently with β-dicarbonyls or β-nitrocarbonyls serving the role of donors. We envisioned that a similar transformation could be achieved with use of bromonitromethane or sulfoxide **3.50** (Scheme 3.31). We hoped that free radical addition of one of these reagents to quinone **3.116** would generate ketone **3.131** which after elimination of bromine or sulfoxide could be converted to enone **3.132**. Unfortunately, treatment of **3.116** with CAN or $Mn(OAc)_3$ did not produced desired product **3.131**, but resulted in recovery of starting material.



Scheme 3.31. Oxidative addition to quinone **3.116**.

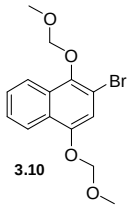
Conclusion

The goal of this chapter was to present the scope of first generation annulation studies conducted in attempts to produce dideoxy lomaiviticinone (**2.1**). Although, our strategy proved to be ineffective, it allowed us to test multiple ideas, expanding our studies far beyond our initial approach. Better understanding of the reactivity of fragments constructed to produce **2.1** should result in the fulfillment of our ultimate goal, the synthesis of dideoxy lomaiviticinone.

Experimental methods

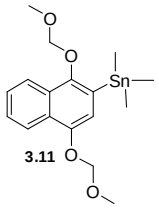
General. All non-aqueous reactions were conducted under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and, unless otherwise stated, used without further purification. Toluene (CH_3Ph), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) were obtained through purification of commercially available solvents with use of activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was purified by distillation from Na metal with benzophenone indicator. Triethylamine (Et_3N) and N,N-diisopropylethylamine ($i Pr_2NEt$) were distilled from CaH_2 and stored over KOH. Thin-layer chromatography was performed on E.Merck precoated silica gel 60 F524 plates. The plates were visualized with UV light and aqueous stain ($KMnO_4$ or CAM). Liquid chromatography (flash chromatography) was conducted using indicated solvents and Dynamic Adsorbents silica gel 60 (230-240 mesh). Thermo Electron IR100 series instrument was used to record infrared spectra as thin films on NaCl plates. ^1H and ^{13}C NMR were recorded on Bruker 300, 400, 500, 600 spectrometers at ambient temperature and are reported relative to deuterated solvent signals. *n*-BuLi was titrated with use of the Suffert method.

Preparative Procedures



3.10

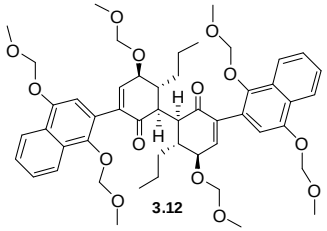
To a solution of bromoquinone **3.9** (1 g, 4.22 mmol) in Et_2O (40 mL) at ambient temperature under argon atmosphere was added the solution of $Na_2S_2O_4$ (5.2 g, 9.3 mmol, 85%) in H_2O (20 mL). After 30 min organic layer was separated and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was cooled to 0 ^oC. MOMCl (4.0 g, 42 mmol, 3.2 mL) and Hunig base (8.18 g, 63 mmol, 11 mL) were added. The solution was heated up to 35 ^oC. After 18 h the reaction mixture was cooled to 25 ^oC, washed with aqueous solution of $NH_4Cl_{(sat.)}$ (x 1), brine (x 1). The organic layer was separated, dried ($MgSO_4$), filtrated, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 9:1) to provide bromide **3.10** as a white solid (0.85 g, 62%): ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.4 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 7.51 (quin, *J* = 8.4 Hz, 14.3 Hz, 2 H), 5.34 (s, 2 H), 5.21 (s, 2 H), 3.73 (s, 3 H), 3.54 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.96, 145.22, 129.79, 127.34, 126.10, 126.04, 122.36, 122.26, 112.23, 112.10, 100.22, 95.10, 58.26, 56.36.



3.11

To a solution (dried prior to use over 4 Å MS for 1 h) of bromide **3.10** (800 mg, 2.4 mmol) in THF (24 mL) at -78 ^oC was added n-BuLi (5.4 mmol, 2.67 mL, 2 M solution in hexanes). After 45 min solution of Me_3SnCl in THF (5.4 mmol, 5.4 mL, dried prior to use over 4 Å MS for 2 h) was added. The cold bath was removed. After 24 h the reaction mixture was diluted with Et_2O. The organic layer was

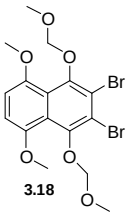
washed with saturated solution of NH_4Cl (x 1) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 15:1) to provide arylstannane **3.11** as a yellow solid (674 mg, 67%): IR (thin film, cm^{-1}): 2954, 2825, 1580, 1450, 1348; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 9.2 Hz, 1 H), 8.12 (d, *J* = 9.2 Hz, 1 H), 7.55-7.47 (m, 2 H), 5.37 (s, 2 H), 5.09 (s, 2 H), 3.64 (s, 3 H), 3.57 (s, 3 H), 0.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.51, 149.58, 130.37, 128.27, 127.73, 126.32, 125.74, 122.38, 122.26, 114.10, 100.87, 95.30, 57.71, 56.30, -8.16; HRMS (ESI) calcd for $C_{17}H_{24}O_4Sn$ [$M+H^+$] 412.0697, found 412.0680.



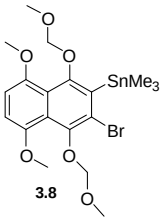
3.12

To a solution of iodoenone **2.32** (15 mg, 0.02 mmol) in dry CH_3CN (2 mL) at ambient temperature were added CuCl (14 mg, 0.14 mmol), $AsPh_3$ (20 mg, 0.07 mmol) and $Pd_2(dba)_3$ (13 mg, 0.02 mmol). The mixture was placed in the oil bath at 70 °C. The solution of arylstannane **3.11** (21 mg, 0.05 mmol) in dry CH_3CN (1 mL) was added. Hunig base (5.6 mg, 0.07 mmol, 5.3 µL) was added. After 20.5 h the reaction mixture was cooled to ambient temperature, filtrated through small pad of celite/SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to provide enone **3.12** as an yellow oil (14 mg, 69%): ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.6 Hz, 2 H), 8.16 (d *J* = 7.6 Hz, 2 H), 7.53-7.45 (m, 4 H), 7.05 (d, *J* = 2.8 Hz, 2 H), 6.85 (s, 2 H), 5.26 (d, *J* = 6.0 Hz, 2 H), 5.20 (d, *J* = 6.0 Hz, 2 H), 4.95 (d, *J* = 5.6 Hz, 2 H), 4.93 (d, *J* = 5.6 Hz, 2 H), 4.83 (d, *J* = 7.2 Hz, 2 H), 4.76 (d, *J* = 6.8 Hz, 2 H), 4.42 (dd, *J* = 3.2 Hz, 6.8 Hz, 2 H), 3.48 (s, 6 H), 3.44 (s, 6 H), 3.40 (s, 6 H), 3.11 (bs, 2 H), 2.91 (bs, 2 H), 1.65-1.44 (m, 8

H), 0.97 (t, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.90, 148.60, 146.08, 145.81, 136.85, 129.23, 129.12, 126.75, 126.39, 125.83, 124.90, 122.65, 122.02, 110.32, 100.34, 95.91, 95.09, 74.93, 57.77, 56.37, 55.92, 50.25, 32.91, 19.55, 14.41; HRMS (ESI) calcd for $C_{50}H_{62}O_{14}$ [M] 886.4507, found 886.4104.

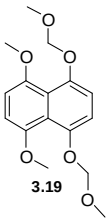

3.18

To a solution of dibromoquinone **3.17** (0.7 g, 1.86 mmol) in CH_2Cl_2 (250 mL) at ambient temperature under argon atmosphere was added Adogen 464 (0.74 g, 0.56 mmol, 0.83 mL). The solution of $Na_2S_2O_4$ (1.9 g, 9.3 mmol, 85 %) in H_2O (100 mL) was added. After 30 min organic layer was separated and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the mixture was cooled to 0 ^{o}C. MOMCl (1.49 g, 18.6 mmol, 1.4 mL) and Hunig base (3.56 g, 27.6 mmol, 4.8 mL) were added. The solution was heated up to 35 ^{o}C. After 24 h the reaction mixture was cooled to 25ºC, washed with aqueous solution of $NH_4Cl_{(sat.)}$ (x 1), brine (x 1). The organic layer was separated, dried ($MgSO_4$), filtrated, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide dibromide **3.18** as a white solid (0.6 g, 69%): IR (thin film, cm^{-1}) 2957, 2930, 2828, 1606, 1540, 1347; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 2 H), 5.03 (s, 4 H), 3.87 (s, 6 H), 3.71 (s. 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.49, 122.01, 119.58, 108.40, 100.82, 58.49, 56.92; HRMS (ESI) calcd for $C_{16}H_{18}Br_2O_6Na$ [M+Na^{+}] 486.9362, found 486.9359.

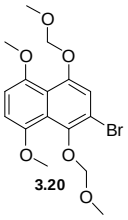

3.8

To a solution (dried over 4Å MS for 2 h prior to the use) of dibromide **3.18** (582 mg, 1.25 mmol) in Et_2O/THF (42 mL/21 mL) at -78 ^{o}C was added

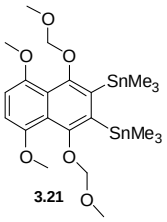
TMEDA (0.218 g, 1.87 mmol, 0.281 mL). The solution of n-BuLi in hexane (1.625 mmol, 0.7 mL, 2.31 M) was added. After 50 sec solution of Me_3SnCl in THF (7.5 mmol, 7.5 mL, 1M, dried over 4Å MS prior to use for 2 h) was added. After 1.5 h cold bath was removed. After additional 2 h saturated solution of NH_4Cl was added dropwise. The mixture was diluted with Et_2O, washed with H_2O (x 3) and brine (x 1). The organic layer was separated, dried ($MgSO_4$), filtrated, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 4:1) to provide arylstannane **3.8** as a yellow oil (600 mg, 88%): IR (thin film, cm^{-1}) 2932, 1605, 1538, 1462; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 4.4 Hz, 2 H), 5.02 (d, *J* = 4.4 Hz, 2 H), 4.91 (s, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.21 (s, 3 H), 0.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.62, 149.62, 145.33, 139.77, 124.86, 123.73, 120.64, 107.98, 107.94, 100.87, 100.51, 58.38, 58.37, 56.99, 56.74; HRMS (ESI) calcd for $C_{19}H_{28}BrO_6Sn$ [$M+H^+$] 551.0078, found 551.0094.



^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 2 H), 6.81, (s, 2 H), 5.14, (4 H), 3.89 (s, 6 H), 3.59 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7, 149.2, 121.9, 116.2, 107.8, 97.9, 57.3, 56.3.

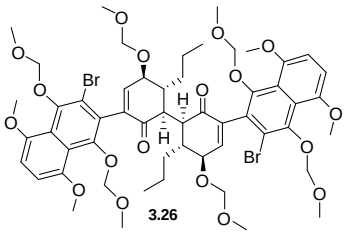


IR (thin film, cm^{-1}): 2937, 2833, 1577, 1454, 1375; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1 H), 6.86-6.81 (m, 2 H), 5.17 (s, 2 H), 5.03 (s, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.72 (s, 3 H), 3.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 150.3, 149.4, 144.7, 123.2, 121.0, 119.0, 115.2, 108.6, 108.2, 100.6, 97.4; HRMS (ESI) calcd for $C_{16}H_{20}BrO_6$ [$M+H^+$] 387.0438, found 387.0422.



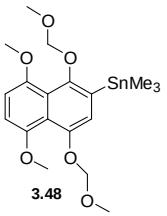
3.21

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2 H), 4.94 (s, 4 H), 3.87 (s, 6 H), 3.50 (s, 6 H), 0.39 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 149.7, 144.2, 121.9, 116.2, 108.4, 101.2, 57.9, 57.4, -4.1.



3.26

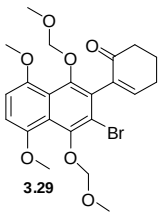
To a solution of bis-iodoenone **2.32** (27 mg, 0.042 mmol) in dry CH_3CN (3 mL) at ambient temperature were added CuCl (10 mg, 0.1 mmol), $AsPh_3$ (15 mg, 0.05 mmol) and $Pd_2(dba)_3$ (11 mg, 0.012 mmol). The mixture was placed in the oil bath at 70 ^{o}C. The solution of arylstannane **3.8** (48 mg, 0.087 mmol) in dry CH_3CN (1 mL) was added. Hunig base (100 mg, 0.10 mmol, 13 µL) was added. After 3 h the reaction mixture was cooled to ambient temperature, filtrated through small pad of celite/SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide enone **3.26** as a yellow solid (37 mg, 77%): HRMS (ESI) calcd for $C_{54}H_{68}Br_2O_{18}Na$ [M+Na^+] 1185.2665, found 1187.2673.



3.48

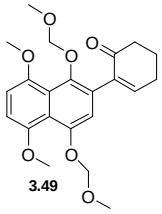
To a solution of arylstannane **3.9** (629 mg, 1.13 mmol) in THF (93 mL) at -78 ^{o}C was added TMEDA (197 mg, 1.7 mmol, 0.254 mL). The solution of t-BuLi in hexane (4.5 mmol, 3.34 mL, 1.35 M) was added. After 10 min saturated solution of $NH_4Cl_{(aq)}$ was added and the cold bath was removed. The mixture was diluted with Et_2O, washed with $NH_4Cl_{(aq)}$ (x 1) and brine (x 1). The organic layer was separated, dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 4:1) to provide arylstannane **3.48** as a yellow

oil (415 mg, 78%): IR (thin film, cm^{-1}) 2933, 2831, 1607, 1564, 1451, 1374; ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1 H), 6.79 (s 2 H), 5.15 (s, 2 H), 4.93 (s, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.61 (s, 3 H), 3.48 (s, 3 H), 0.38 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.71, 150.92, 149.66, 149.50, 133.99, 123.35, 122.57, 121.88, 107.59, 107.18, 100.97, 98.20, 57.82, 57.30, 56.82, 56.40, 8.00.



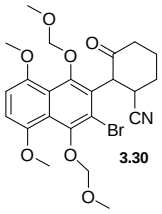
3.29

To a solution of iodocyclohexenone (242 mg, 1.10 mmol) in dry CH_3CN (75 mL) at ambient temperature were added CuCl (129 mg, 1.30 mmol), $AsPh_3$ (240 mg, 0.78 mmol) and $Pd_2(dba)_3$ (150 mg, 0.16 mmol). The mixture was placed in the oil bath at 70 ^oC. The solution of arylstannane **3.9** (600 mg, 1.10 mmol) in dry CH_3CN (15 mL) was added. Hunig base (100 mg, 0.78 mmol, 95 µL) was added. After 2.5 h the reaction mixture was cooled to ambient temperature, filtrated through small pad of celite/SiO_2, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide enone **3.29** as a yellow solid (487 mg, 92%): IR (thin film, cm^{-1}) 2937, 2831, 1679, 1605, 1562, 1345; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (t, *J* = 4 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 5.06 (s, 2 H), 4.94 (d, *J* = 5.6 Hz, 1 H), 4.77 (d, *J* = 5.2 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.70 (s, 3 H), 3.47 (s, 3 H), 2.69-2.57 (m, 4 H), 2.45-2.16 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.13, 150.28, 149.89, 149.47, 147.40, 145.84, 138.84, 130.84, 122.95, 121.93, 118.82, 108.55, 107.28, 100.96, 100.51, 58.40, 57.45, 57.20, 56.64, 38.43, 26.25, 22.71; HRMS (ESI) calcd for $C_{22}H_{26}BrO_7$ [$M+H^+$] 481.0809, found 481.0856.



3.49

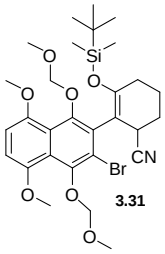
To a solution of iodocyclohexenone (74 mg, 0.33 mmol) in dry CH_3CN (15 mL) at ambient temperature were added CuCl (40 mg, 0.40 mmol), $AsPh_3$ (63 mg, 0.20 mmol, 97%) and $Pd_2(dba)_3$ (37 mg, 0.04 mmol). The mixture was placed in the oil bath at 70 ^oC. The solution of arylstannane **3.48** (157 mg, 0.33 mmol) in dry CH_3CN (5 mL) was added. Hunig base (26 mg, 0.2 mmol, 35 µL) was added. After 2.5 h the reaction mixture was cooled to ambient temperature, filtrated through small pad of celite/SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide enone **3.49** as a yellow solid (126 mg, 94%): IR (thin film, cm^{-1}) 2923, 2831, 1676, 1600, 1453, 1356; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (t, *J* = 4.4 Hz, 1 H), 6.83 (s, 1 H), 6.79 (s, 1 H), 6.79 (s, 1 H), 5.16 (s, 2 H), 4.83 (s, 2 H), 3.85 (s, 6 H), 3.56 (s, 3 H), 3.43 (s, 3 H), 2.60 (t, *J* = 6.4 Hz, 2 H), 2.53 (dd, *J* = 5.6 Hz, 2 H), 2.15-2.12 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.23, 150.88, 150.22, 149.50, 149.45, 145.56, 138.41, 128.62, 122.64, 121.58, 117.28, 108.20, 107.38, 100.71, 97.47, 57.52, 57.33, 56.73, 56.34, 38.51, 26.23, 22.80; HRMS (ESI) calcd for $C_{22}H_{26}O_7Na$ $[M+Na^+]$ 425.1571, found 425.1564.



3.30

To a solution of enone **3.29** (40 mg, 0.08 mmol) in DMF (3 mL) at ambient temperature were added acetone cyanohydrine (21 mg, 0.25 mmol, 23µL), NaH (6 mg, 0.25 mmol). After 3.5 h the mixture was diluted with EtOAc, washed with H_2O (x 6) and brine (x 1), dried ($MgSO_4$), filtrated, concetrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to give cyanoketone **3.30** as a white solid (40 mg, 94%): IR (thin film, cm^{-1}) 2932, 2360, 2241,

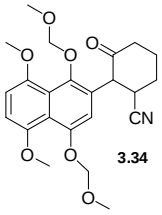
1716, 1606, 1562; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 2 H), 5.08 (d, *J* = 4.8 Hz, 1 H), 5.04 (d, *J* = 5.2 Hz, 1 H), 4.91 (bs, 2 H), 4.02 (bs, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.51 (s, 3 H), 2.75 (d, *J* = 16.8 Hz, 1 H), 2.49-2.41 (m, 2 H), 2.20-2.13 (m, 2 H), 2.11-2.04 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.37, 150.25, 149.95, 127.91, 123.14, 122.18, 120.24, 109.04, 100.83, 58.67, 57.80, 57.32, 40.52, 32.98, 29.49, 22.90; HRMS (ESI) calcd for $C_{23}H_{26}O_7Na$ [M+H$^+$] 508.0965, found 508.0920.



3.31

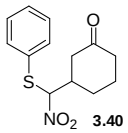
To a solution of enone **3.29** (85 mg, 0.17 mmol) in CH_3CN (8.5 mL) at 50ºC were added KCN (22 mg, (0.34 mmol), 18-*crown*-6 (91 mg, 0.34 mmol), TBSCN (364 mg, 2.6 mmol). After 2 h the mixture was cooled to ambinet temperature, diluted with Et_2O, washed with H_2O (x 1) and brine (x 1), dried ($MgSO_4$), filtrated, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to provide silyl enol ether **3.31** as a mixture of diastereoisomers (ratio ~1:1) (101 mg, 95%): IR (thin film, cm^{-1}): 2932, 2857, 2234, 1668, 1606, 1559, 1345; ^{1}H NMR (400 MHz, C_6D_6): δ 6.58 (d, *J* = 8.8 Hz, 1 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 5.27 (d, *J* = 4.8 Hz, 1 H), 5.25 (d, *J* = 4.4 Hz, 1 H), 5.18 (d, *J* = 4.4 Hz, 1 H), 5.03 (d, *J* = 4.0 Hz, 1 H), 4.00 (s, 1 H), 3.74 (s, 3 H), 3.56 (s, 3 H), 3.55 (s, 3 H), 3.48 (s, 3 H), 2.21-2.14 (m, 1 H), 2.04-1.85 (m, 2 H), 1.82-1.76 (m, 1 H), 1.55-1.46 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6): δ 150.92, 150.52, 150.15, 147.50, 147.08, 132.62, 128.30, 123.88, 123.05, 121.82, 120.70. 109.62, 108.58, 101.10, 100.52, 58.19, 57.49, 57.43, 56.85, 31.43, 29.70, 27.22, 25.50, 20.82, 17.93, -2.85, -3.04; second diastereoisomer: ^{1}H NMR (400 MHz, C_6D_6): δ 6.51 (d, *J* = 8.8 Hz, 1 H), 6.45 (d, *J* = 8.8 Hz, 1 H), 5.44 (d, *J* = 4.0 Hz, 1 H), 5.24 (d, *J* = 4.0

Hz, 1 H), 5.17 (d, *J* = 4.8 Hz, 1 H), 5.14 (d, *J* = 5.2 Hz, 1 H), 3.75 (s, 3 H), 3.65 (s, 3 H), 3.57 (s, 3 H), 3.44 (s, 3 H), 3.39-3.37 (m, 1 H), 2.06-1.84 (m, 3 H), 1.77-1.72 (m, 1 H), 1.62-1.41 (m, 2 H), 0.60 (s, 9 H), 0.02 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6): δ 151.9, 150.8, 150.7, 149.1, 147.5, 131.8, 128.7, 128.4, 128.2, 124.5, 123.8, 121.4, 120.1, 110.9, 110.1, 110.0, 101.4, 101.3, 58.4, 58.4, 57.7, 57.6, 32.0, 30.3, 27.8, 21.1, 18.3, -2.6, -2.9; HRMS (ESI) calcd for $C_{29}H_{41}BrNO_7Si$ [M+H$^+$] 624.1830, found 622.1820.



3.34

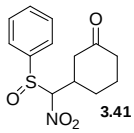
To a solution of cyanoketone **3.30** (8.7 mg, 0.017 mmol) in CH_3Ph was added Bu_3SnH (48 mg, 0.17 mmol, 44 µL). The mixture was heated uo to 40 °C. Et_3B (0.083 mmol, 83 µL) was added. After 1.5 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide cyanoketone **3.34** as a yellow oil (6.8 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1 H), 6.83 (s, 2 H), 5.23 (d, *J* = 6.4 Hz, 1 H), 5.19 (d, *J* = 6.4 Hz, 1 H), 5.02 (d, *J* = 5.6 Hz, 1 H), 4.88 (d, *J* = 5.6 Hz, 1 H), 4.69 (d, *J* = 12.4 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.57 (s, 3 H), 3.48 (s, 3 H), 3.30 (td, *J* = 4.0, 12.4, 16.0 Hz, 1 H), 2.64-2.45 (m, 3 H), 2.28-2.21 (m, 2 H), 1.94-1.86 (m, 1 H).



3.40

To a solution of cyclohexenone **3.38** (273 mg, 2.8 mmol, 0.288 mL) and nitrosulfide **3.39** (1.54 g, 9.1 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added DBU (648 mg, 4.3 mmol). After 24 h the reaction mixure was diluted with CH_2Cl_2. The organic layer was washed with saturated solution of NH_4Cl, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash

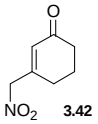
chromatography (Hexane/EtoAc, 3:1) to provide sulfide **3.40** as a mixture of diastereoisomers (ratio ~1:1) in the form of an orange oil (708 mg, 94%): IR (thin film, cm^{-1}): 3060, 2951, 1715, 1552, 1474, 1440; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.45 (m, 4 H), 7.40-7.37 (m, 6 H), 5.40 (d, *J* = 6.8 Hz, 1 H), 5.36 (d, *J* = 8 Hz, 1 H), 2.85-2.80 (m, 1 H), 2.61-2.56 (m, 2 H), 2.48-2.42 (m, 4 H), 2.38-2.87 (m, 4 H), 2.19-2.10 (m, 2 H), 2.09-1.93 (m, 1 H), 1.74-1.72 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.88, 207.69, 133.69, 133.49, 130.48, 130.27, 129.80, 129.73, 99.20, 98.83, 44.02, 43.37, 41.37, 41.08, 40.75, 40.72, 27.95, 27.38, 24.04, 23.91; HRMS (ESI) calcd for $C_{13}H_{15}NO_3SNa$ [$M+Na^+$] 288.0665, found 288.0698.



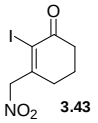
3.41

To a solution of sulfide **3.40** (1.14 g, 4.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added *m*CPBA (700 mg, 4.0 mmol, 77%) portionwise for 1.5 h. After 2 h saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide sulfoxide **3.41** as an inseparable mixture of diastereoisomers (ratio ~2:1) in the form of white solid (922 mg, 77%): IR (thin film, cm^{-1}): 2927, 1714, 1545, 1445, 1344; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (m, 2 H), 7.60-7.53 (m, 8 H), 5.04 (d, *J* = 4 Hz, 1 H), 5.01 (d, *J* = 12 Hz, 1 H), 2.95-2.89 (m, 4 H), 2.47-2.39 (m, 4 H), 2.36-2.25 (m, 2H), 2.19-2.15 (m, 2 H), 2.11-1.90 (m, 2 H), 1.77-1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.89, 206.72, 139.56, 138.28, 133.32, 132.93, 129.84, 129.75, 125.35, 124.25, 107.47, 105.61, 42.58, 42.22,

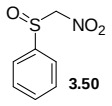
40.83, 40.64, 37.95, 37.18, 27.99, 27.39, 24.20, 23.66; HRMS (ESI) calcd for $C_{13}H_{16}NO_4S$ [M+H$^+$] 282.0795, found 282.0796.


3.42

The solution of sulfoxide **3.41** (422 mg, 1.5 mmol) in C_6H_6 (6 mL) in a sealed tube was heated up to 100 ^{o}C. After 15 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to provide enone **3.42** as a yellow oil (156 mg, 67%): IR (thin film, cm^{-1}): 2924, 2853, 1682, 1557, 1455, 1259; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (s, 1 H), 5.07 (s, 1 H), 2.45-2.41 (m, 4 H), 2.08 (quin, *J* = 14.8, 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.49, 150.05, 131.43, 80.61, 37.02, 27.41, 22.16; HRMS (ESI) calcd for $C_7H_{10}NO_3$ [M+H$^+$] 156.0655, found 156.0667.

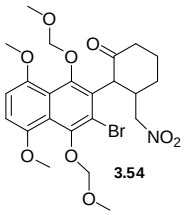

3.43

To a solution of enone **3.42** (30 mg, 0.19 mmol) in CH_2Cl_2 (2 mL, dried prior to use over 4 Å MS for 2.5 h) at 0 ^{o}C were added I_2, (147 mg, 0.58 mmol), DMAP (2.4 mg, 0.02 mmol), pyridine (15 mg, 0.2 mmol, 15 μL). After 25 min the reaction mixture was diluted with Et_2O. The organic layer was washed with saturated solution of NH_4Cl (x 1), 10% solution of $Na_2S_2O_3$ (x 2), brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide iodoenone **3.43** as a yellow solid (14 mg, 27%): IR (thin film, cm^{-1}): 2954, 1688, 1556, 1424, 1370; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (s, 2H), 2.68 (t, *J* = 6.8 Hz, 2 H), 2.61 (t, *J* = 6.0 Hz, 2 H), 2.09 (quin, *J* = 15.6, 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.58, 153.69, 114.48, 86.10, 36.22, 31.29, 21.83.



3.50

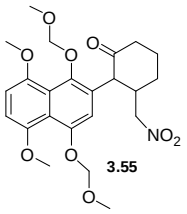
To a solution of sulfide **3.39** (992 mg, 5.8 mmol) in CH_3CN (8 mL) at ambient temperature was added $FeCl_3$ (95 mg, 0.58 mmol). After 5 min H_5IO_6 (1.6 g, 7.0 mmol) was added. After 1 h 15 min saturated solution of $Na_2S_2O_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (x 5). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide sulfoxide **3.50** as a white solid (50 mg, 47%): IR (thin film, cm^{-1}): 3012, 2929, 1556, 1548, 1444; ^1H NMR (400 MHz, C_3D_6O): δ 7.84-7.82 (m, 2 H), 7.66-7.65 (m, 3 H), 5.97 (d, *J* = 12.0, 1 H), 5.67 (d, *J* = 11.6 Hz, 1 H); ^{13}C NMR (100 MHz, C_3D_6O): δ 141.24, 133.45, 130.78, 125.78, 94.71; HRMS (ESI) calcd for $C_7H_{18}NO_3S$ $[M+H^+]$ 186.0219, found 186.0234.



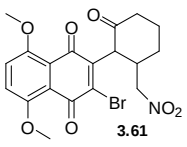
3.54

To a solution of enone **3.29** (15 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) at ambient temperature were added CH_3NO_2 (6.5 mg, 0.10 mmol, 6 µL) and DBU (95 mg, 0.62 mmol, 93 µL). After 20 h the reaction mixture was diluted with CH_2Cl_2 and washed with saturated solution of NH_4Cl. The organic layer was separated, dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide nitroketone **3.54** as a yellow oil (14 mg, 83%): IR (neat) ν 2939, 2833, 1711, 1605, 1552, 1452, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2 H), 5.06 (m, 3 H), 4.79 (bs, 1 H), 4.44 (bs, 1 H), 4.34 (dd, *J* = 10.4, 12.4 Hz, 1 H), 4.14 (d, *J* = 12.0, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.69 (s, 3 H), 3.50 (s, 3 H), 2.77 (d, *J* = 16.8 Hz, 1 H), 2.40 (m, 1 H), 2.20 (d, *J* = 12.4 Hz, 1 H), 2.10 (m, 2 H), 1.67 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 204.7, 150.9, 150.8, 130.0, 123.9, 109.8, 109.4, 102.4,

101.3, 80.1, 58.7, 58.0, 57.5, 54.4, 41.0, 40.5, 29.1, 22.7; HRMS (ESI) calcd for $C_{23}H_{28}O_9BrNNa$ [$(M+Na)^+$] 564.0840, found 564.0826.

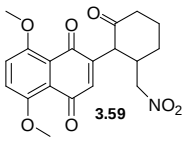

3.55

To a solution of enone **3.49** (210 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) at ambient temperature were added CH_3NO_2 (108 mg, 1.8 mmol, 95 µL) and DBU (1.59 g, 10 mmol, 1.56 mL). After 20 h the reaction mixture was diluted with CH_2Cl_2 and washed with saturated solution of NH_4Cl. The organic layer was separated, dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide nitroketone **3.55** as a yellow oil (166 mg, 69%): IR (neat) ν 2940, 2833, 1716, 1603, 1551, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1 H), 6.82 (s, 2 H), 5.22 (d, *J* = 6.0 Hz, 1 H), 5.18 (d, *J* = 6.4 Hz, 1 H), 4.99 (d, *J* = 6.4 Hz, 1 H), 4.80 (d, *J* = 6.0 Hz, 1 H), 4.41 (d, *J* = 12.8 Hz, 1 H), 4.25 (dd, *J* = 10.8, 12.8 Hz, 1 H), 4.07 (dd, *J* = 3.6, 12.8 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 1 H), 3.58 (s, 3 H), 3.48 (s, 3 H), 2.98-2.87 (m, 1 H), 2.62 (d, *J* = 14.0 Hz, 1 H), 2.51 (td, *J* = 5.6, 13.2, 19.6 Hz, 1 H), 2.25-2.14 (m, 2 H), 1.91-1.86 (m, 1 H), 1.81-1.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 151.1, 150.5, 149.8, 147.2, 125.9, 122.4, 121.4, 114.6, 108.5,107.9, 101.6, 97.5, 79.3, 57.5, 57.0, 56.8, 56.4, 52.7, 42.6, 41.4, 29.5, 24.7; HRMS (ESI) calcd for $C_{23}H_{30}O_9N$ [$(M+H)^+$] 464.1915, found 464.1900.


3.61

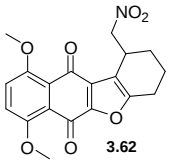
To a solution of nitroketone **3.54** (130 mg, 0.24 mmol) in CH_3CN (8 mL) at ambient temperature was added CAN (263 mg, 0.48 mmol). After 25 min the reaction mixture was diluted with EtOAc. The organic layer was washed with

H_2O (x 2), dried ($MgSO_4$), filtrated and concetrated *in vauo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide bromoquinone **3.61** as a red solid (93 mg, 86%): IR (neat) ν 3583, 2941, 1708, 1662, 1550, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2 H), 4.27 (d, *J* = 6.4 Hz, 2 H), 3.85 (s, 6 H), 3.71 (d, *J* = 10.8 Hz, 1 H), 3.37-3.32 (m, 1 H), 2.71-2.66 (m, 1 H), 2.38-2.29 (m, 1 H), 2.11-2.07 (m, 3 H), 1.63-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 179.8, 175.7, 154.3, 154.2, 146.9, 142.3, 128.2, 120.8, 120.5, 119.8, 119.7, 79.1, 56.8, 40.0, 28.3, 22.1; HRMS (ESI) calcd for $C_{19}H_{19}O_7NBr$ [$(M+H)^+$] 452.0339, found 452.0330.



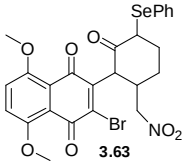
3.59

To a solution of nitroketone **3.55** (34 mg, 0.07 mmol) in CH_3CN (4 mL) at ambient temperature was added CAN (160 mg, 0.3 mmol). After 30 min the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O (x 2), brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide nitroquinone **3.59** as a red solid (28 mg, 94%): IR (neat) ν 2926, 2851, 1712, 1653, 1583, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 2 H), 6.70 (s, 1 H), 4.37-4.27 (m, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.51 (d, *J* = 12.0 Hz, 1 H), 3.06-2.96 (m, 1 H), 2.64 (dt, *J* = 2.0, 15.6 hz, 1 H), 2.36 (td, *J* = 5.6, 13.6, 19.6 Hz, 1 H), 2.16-2.12 (m, 2 H), 2.00-1.89 (m, 1 H), 1.71-1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 183.6, 154.2, 153.7, 144.9, 138.5, 120.7, 120.3, 78.9, 56.9, 56.8, 54.2, 40.6, 40.3, 28.4, 23.3; HRMS (ESI) calcd for $C_{19}H_{20}O_7N$ [$(M+H)^+$] 374.1234, found 374.1258.



3.62

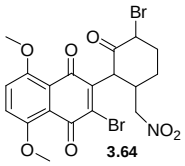
To a solution of nitroketone **3.61** (10 mg, 0.022 mmol) in toluene (1.5 mL) at 80 °C were added as a one portion: $Pd(OAc)_2$ (~5 mg, 0.022 mmol), Ag_2CO_3 (12 mg, 0.044 mmol) and polymer-bound PPh_3 (22 mg, 0.066 mmol, 3mmol/1 g). After 1 h the reaction mixutre was cooled to ambient temperature, filtrated through small celite/SiO_2 pad (washed with EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide nitrofurane **3.62** as a red solid (5.7 mg, 70%): IR (neat) ν 2926, 1770, 1706, 1654, 1548, 1473, 1432, 1379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 2 H), 5.25 (dd, *J* = 2.8, 10.0 Hz, 1 H), 4.53 (dd, *J* = 8.4, 10.0 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.86-3.83 (m, 1 H); 2.77-2.72 (m, 2 H), 1.94-1.91 (m, 3 H), 1.82-1.80 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.6, 173.1, 160.0, 155.1, 154.9, 151.0, 127.6, 121.6, 121.3, 121.1, 121.0, 115.6, 57.0, 56.9, 31.0, 25.2, 23.4, 18.7; HRMS (ESI) calcd for $C_{19}H_{18}O_7N$ [$(M+H)^+$] 372.1078, found 372.1084.



3.63

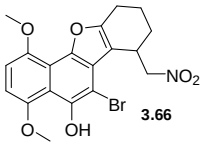
To a solution of nitroketone **3.61** (15 mg, 0.33 mmol) in THF (1.5 mL) at ambient temperature was added phenylselenenyl chloride (63 mg, 0.33 mmol). After 24 h the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide ketone **3.63** as a red solid (20 mg, 98%): IR (neat) ν 2935, 2854, 1695, 1658, 1552, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2 H), 7.34-7.27 (m, 5 H), 4.70-4.55 (bs, 1 H), 4.43-4.34 (m, 2 H), 4.03 (s, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.50-3.44 (m, 1 H), 2.59-2.56 (m, 1 H), 2.38 (dd, *J* = 2.0, 14.8 Hz, 1 H), 2.04-1.93 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.0,

175.7, 175.6, 154.4, 154.3, 135.4, 135.3, 129.3, 129.1, 128.9, 127.9, 127.8, 127.7, 127.6, 120.9, 120.7, 120.6, 120.5, 120.2, 120.1, 120.0, 119.9, 79.0, 56.9, 56.9, 48.3, 28.6, 28.7, 28.6, 25.0; HRMS (ESI) calcd for $C_{25}H_{23}O_7NSeBr$ [$(M+H)^+$] 607.9816, found 607.9820.



3.64

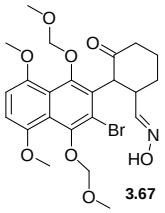
To a solution of nitroketone **3.61** (19 mg, 0.04 mmol) in AcOH (1.5 mL) at ambient temperature was added Br_2 (6.8 mg, 0.04 mmol, 2.19 µL). After 19 h the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with H_2O (x 2) and saturated solution of $NaHCO_3$ (x 2). The organic layer was separated, dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide bromoketone **3.64** as a red solid (14 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 4.59 (d, *J* = 2.56 Hz, 1 H), 4.52 (bs, 1 H), 4.41-4.36 (m, 2 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.44-3.40 (m, 1 H), 2.61-2.50 (m, 1 H), 2.35 (dd, *J* = 2.84, 15.6 Hz, 1 H), 2.22-2.15 (m, 1 H), 2.00 (dd, *J* = 3.52, 13.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, semi-pure sample) δ 197.4, 176.8, 175.6, 154.4, 145.7, 143.1, 120.9, 120.8, 119.8, 119.8, 78.8, 56.9, 49.1, 30.9, 29.5, 21.0.



3.66

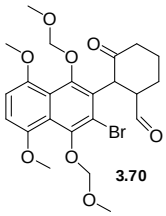
To a solution of nitroketone **3.54** (13.7 mg, 0.0.26 mmol) in EtOH (1.5 mL) at ambient temperature was added $SnCl_2 \bullet 2H_2O$ (29 mg, 0.13 mmol). The reaction mixture was heated up to 70 ^{o}C. After 3 h the solution was cooled to ambient temperature and concentrated *in vauo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide furan **3.66** as a yellow oil (7.5 mg, 66%): IR (neat) ν 3583, 3333, 2932, 1724, 1666, 1607, 1585, 1551, 1450 cm^{-1}; ^{1}H NMR

(600 MHz, $CDCl_3$) 10.12 (s, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 4.96 (dd, *J* = 4.2, 12.6, 1 H), 4.53 (dd, *J* = 10.8, 12.0 Hz, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H), 3.60-3.56 (m, 2 H), 2.96 (d, *J* = 9.6 Hz, 1 H), 2.62 (d, *J* = 13.8 Hz, 1 H), 2.25-2.23 (m, 1 H), 1.88-1.85 (, 1 H), 1.68-1.60 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.9, 149.3, 145.6, 145.3, 129.9, 116.0, 115.3, 111.3, 105.2, 105, 1, 102.9, 79.9, 56.8, 56.7, 29.8, 25.7, 20.3, 15.5.



3.67

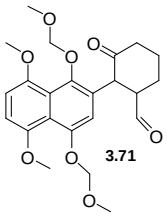
To a solution of nitroketone **3.54** (10 mg, 0.019 mmol) in EtOH (1 mL) at ambient temperature was added mixture of PhSH (9.5 mg, 0.085 mmol, 8.8 µL), Et_3N (8.7 mg, 0.085 mmol, 12 µL), $SnCl_2 \bullet 2H_2O$ (6.5 mg, 0.028 mmol) in EtOH (1 mL). After 2 h 15 min the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/ EtOAc, 1:1) to provide oxime **3.67** as a yellow oil (4.9 mg, 49%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 6.8 Hz, 1 H), 6.83 (s, 2 H), 6.60 (s, 1 H), 5.06-5.02 (m, 3 H), 4.82 (bs, 1 H), 4.64 (bs, 1 H), 3.91 (s, 3 H), 3.85 (s, 2 H), 3.69 (s, 3 H), 3.52 (s, 3 H), 2.74 (d, *J* = 18.4 Hz, 1 H), 2.45-2.40 (m, 1 H), 2.22-2.18 (m, 3 H), 1.87-1.83 (m, 1 H).



3.70

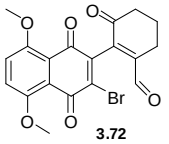
To a solution of nitroketone **3.54** (106 mg, 0.2 mmol) in MeOH (5 mL) at 0 ^oC was added solution of KOH in MeOH (0.215 mL, 0.21 mmol, 1M). After 15 min mixture of $KMnO_4$ (34 mg, 0.21 mmol) and $MgSO_4$ (21 mg, 0.17 mmol) in H_2O (5 mL) was added. The reaction mixture was allowed to warm up to ambient temperature slowly over 1.5 h. After 1.5 h the reaction solution was flitrated through small celite/SiO_2 pad (washed with EtOAc). The filtrate was concentrated *in*

vacuo. The aqueous layer was extraced with EtOAc/Et_2O (x 3). The organic layer was separated, dried ($MgSO_4$), filtrated and concetrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide aldehyde **3.70** as a thick, yellow oil (73 mg, 73%): IR (neat) ν 3423, 2937, 2832, 2723, 2081, 1718, 1605, 1559, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 2.0 Hz, 1 H), 6.83 (s, 2 H), 5.06-5.02 (m, 3 H), 4.92-4.75 (m, 1 H), 3.88 (s, 3 H), 3.85 s, 3 H), 3.67 (s, 3 H), 3.49 (s, 3 H) 2.73 (d, *J* = 16.8 Hz, 1 H), 2.51-2.39 (m, 1 H), 2.24 (d, *J* = 5.4 Hz, 1 H), 2.15-2.11 (m, 2 H), 1.84 (q, *J* = 2.8, 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 201.9, 149.8, 149.5, 129.2, 122.6, 121.7, 108.5, 100.5, 58.4, 57.6, 57.0, 53.3, 40.7, 25.2; HRMS (ESI) calcd for $C_{23}H_{27}O_8NaBr$ $[(M+Na)^+]$ 533.0782, found 533.0780.

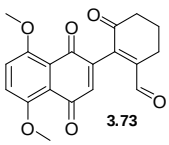

3.71

To a solution of nitroketone **3.55** (122 mg, 0.26 mmol) in MeOH (6 mL) at 0 °C was added solution of KOH in MeOH (0.289 mL, 0.29 mmol, 1M). After 15 min mixture of $KMnO_4$ (46 mg, 0.29 mmol) and $MgSO_4$ (28 mg, 0.23 mmol) in H_2O (6 mL) was added. The reaction mixture was allowed to warm up to ambient temperature slowly over 1.5 h. After 1 h 45 min the reaction solution was flitrated through small celite/SiO_2 pad (washed with EtOAc). The filtrate was concentrated *in vacuo*. The aqueous layer was extraced with EtOAc/Et_2O (x 3). The organic layer was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:2) to provide aldehyde **3.71** as a thick, yellow oil (84 mg, 74%): IR (neat) ν 2937, 2833, 1717, 1603, 1551, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 2.4 Hz, 1 H), 6.87 (s, 1 H), 6.80 (s, 2 H), 5.19 (d, *J* =

6.4 Hz, 1 H), 5.14 (d, *J* = 6.4 Hz, 1 H), 5.00 (d, *J* = 6.0 Hz, 1 H), 4.83 (d, *J* = 6.0 Hz, 1 H), 4.77 (d, *J* = 12.8 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.55 (s, 3 H), 2.47 (s, 3 H), 3.06 (t, *J* =12.0, 1H), 2.58-2.53 (m, 2 H0, 2.31-2.22 (m, 1 H), 2.21-2.13 (m, 1 H), 1.98-1.88 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 201.2, 151.1, 150.3, 149.8, 146.7, 126.6, 122.4, 121.3, 115.3, 114.6, 108.0, 107.8, 101.0, 97.7, 57.5, 57.1, 57.0, 56.5, , 55.6, 50.8, 41.4, 26.0, 25.3; HRMS (ESI) calcd for $C_{23}H_{28}O_8Na$ [$(M+Na)^+$] 455.1676, found 455.1666.

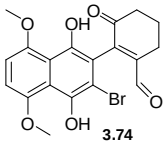

3.72

To a solution of aldehyde **3.70** (238 mg, 0.46 mmol) in CH_3Ph (12 mL) at ambient temeprature were added DDQ (317 mg, 1.4 mmol) and PTSA (16 mg, 0.09 mmol). The mixture was heated up to 80 ^{o}C. After 15 h the reaction solution was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:2) to provide aldehyde **3.72** as a red solid (84 mg, 43%): IR (neat) ν 2941, 2842, 1682, 1665, 1599, 1584, 1562, 1477 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 7.35 (d, *J* = 4.8 Hz, 2 H), 4.09 (s, 3 H), 3.97 (s, 3 H), 2.68-2.62 (m, 4 H), 2.19-2.12 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 192.0, 179.8, 175.6, 154.5, 154.3, 149.3, 143.6, 142.1, 140.7, 120.9, 120.8, 120.1, 120.0, 57.0, 56.8, 38.4, 22.4, 21.2; HRMS (ESI) calcd for $C_{19}H_{16}O_6Br$ [$(M+H)^+$] 419.0125, found 419.0134.


3.73

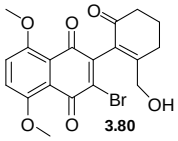
To a solution of aldehyde **3.55** (20 mg, 0.046 mmol) in CH_3Ph (2 mL) at ambient temperature were added DDQ (31.4 mg, 0.14 mmol) and PTSA (1.6 mg, 0.009 mmol). The mixture was heated up to 40 ^{o}C. After 2.5 h the solution was

cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide enone **3.73** as a red solid (1.5 mg, 10%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 7.35 (d, *J* = 2.64 Hz, 2 H), 6.69 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 2.67-2.62 (m, 4 H), 2.13-2.09 (m, 2 H).



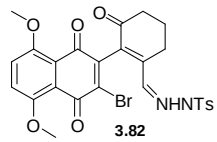
3.74

To a solution of aldehyde **3.72** (11 mg, 0.026 mmol) in EtOAc (1 mL) at ambient temperature under H_2 atmosphere was added Pd/C (5.5 mg, 0.003 mmol, 5%). After 30 min the reaction mixture was filtrated through small celite/SiO_2 pad (washed with EtOAc) and concentrated *in vacuo*. The crude material was immediately used in the next step.



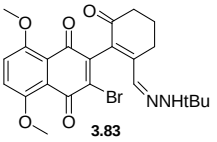
3.80

To a solution of hydroquinone **3.74** (~0.026 mmol) in CH_2Cl_2 (1.5 mL) at 0 ^{o}C were added Ac_2O (10.7 mg, 0.10 mmol, ~10 µL), pyridine (8.3 mg, 0.10 mmol, 8.5 µL) and DMAP (cat.). After 25 min the ice bath was removed. After 4 h the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated solution of $NaHCO_3$ (x 1), brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide alcohol **3.80** as a red solid: ^{1}H NMR (600 MHz, $CDCl_3$) 7.33 (s, 2 H), 4.61 (d, *J* = 3.0 Hz, 2 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 2.57-2.54 (m, 4 H), 2.17-2.09 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195. 2, 179.7, 176.4, 170.2, 155.1, 154.3, 154.2, 146.0, 139.4, 132.7, 120.7, 120.4, 64.4, 57.0, 56.8, 37.5, 29.6, 27.4, 21.7.



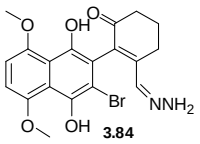
3.82

To a solution of aldehyde **3.72** (10 mg, 0.024 mmol) in $CHCl_3$ (1 mL) at ambient temperature was added H_2NNHTs (4.44 mg, 0.024 mmol). After 30 min the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:2) to provide hydrazone **3.82** as a red solid (12 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.19 (s, 2 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.87-2.81 (m, 2 H), 2.79-2.71 (m, 2 H), 2.44 (s, 3 H), 2.17-2.07 (m, 2 H).



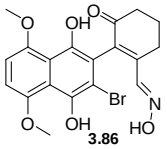
3.83

To a solution of aldehyde **3.72** (15 mg, 0.036 mmol) in EtOAc (1 mL) at ambient temperature under H_2 atmosphere was added Pd/C (7.6 mg, 0.0036 mmol, 5%). After 30 min the solution was filtrated through a small Celite/SiO_2 pad (washed with EtOAc) and concentrated *in vacuo*. The crude material was dissolved in MeOH (1 mL). $H_2NNHtBuHCl$ (13 mg, 0.10 mmol) was added. After 1 h the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide hydroquinone. To the solution of hydroquinone in CH_2Cl_2 (1.5 mL) at ambient temperature were added Ag_2CO_3/celite (30 mg, 0.053 mmol, 50%) and Et_3N (4.3 mg, 0.043 mmol, 6 μL). After 10 min the mixture was filtrated through celite. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide hydrazone **3.83** as a red solid (8.5 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1 H), 7.29 (s, 2 H), 7.03 (s, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.90-2.83 (1 H), 2.61-2.52 (m, 3 H), 2.19-2.02 (m, 1 H), 1.20 (s, 9 H).



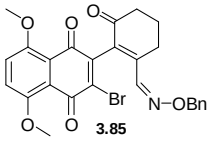
3.84

To a solution of aldehyde **3.72** (8 mg, 0.019 mmol) in EtOAc (1 mL) at ambient temperature under H_2 atmosphere was added Pd/C (4 mg, 0.0019 mmol, 5%). After 30 min the reaction mixture was filtrated through small pad of celite. The filtrate was concentrated *in vacuo.* The crude material was dissolved in CH_3Ph (1 mL). H_2NNH_2 (~2 µL, 0.02 mmol) was added. After 15 min the solution was concentrated *in vacuo* to provide hydrazone **3.84** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1 H), 9.39 (s, 1 H), 7.92 (s, 2 H), 6.72 (d, *J* = 8.8 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 4.01 (s, 3 H), 3.94 (s, 3 H), 2.97-2.91 (m, 2 H), 2.72-2.65 (m, 2 H), 2.30-2.12 (m, 2 H).



3.86

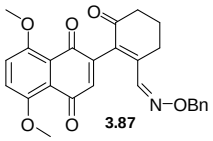
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 9.43 (s, 1 H), 7.66 (s, 1 H), 7.51 (s, 1 H), 6.77-6.70 (m, 2 H), 4.04 (s, 3 H), 3.98 (s, 3 H), 2.91-2.80 (m, 2 H), 2.73-2.69 (m, 2 H), 2.25-2.21 (m, 2 H).



3.85

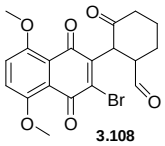
To a solution of aldehyde **3.72** (17.4 mg, 0.04 mmol) in $CHCl_3$ (1.5 mL) at ambient temperature was added O-benzylhydroxylamine (5.4 mg, 0.04 mmol). After 1.5 h the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide oxime **3.85** as a red, amorphous solid (21 mg, 97%): IR (neat) ν 2938, 2358, 1666, 1584, 1563, 1477, 1454, 1433 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) 7.71 (s, 1 H), 7.35-7.30 (m, 7 H), 5.16 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.86-2.79 (, 2 H), 2.61-2.55 (m, 2 H), 2.18-2.05 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$, semi-pure sample) δ 195.7, 180.2, 179.7, 176.1, 154.4, 154.2,

149.5, 149.1, 147.5, 145.3, 144.2, 141.4, 140.2, 136.3, 135.4, 133.4, 128.4, 128.0, 120.9, 120.7, 120.2, 57.0, 56.8, 38.1, 24.46, 21.61.



3.87

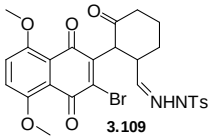
To a solution of of oxime ether **3.85** (15 mg, 0.033 mmol) in CH_3Ph (1.5 mL) at 45 ^oC were added $Pd(PPh_3)_4$ (3.4 mg, 0.003 mmol) and Ag_2CO_3 (8.3 mg, 0.03 mmol). Bu_3SnH (29 mg, 0.10 mmol, 27 µL) was added. After 2 h the reaction mixture was filtrated through small celite/SiO_2 pad (washed with EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide oxime ether **3.87** as a red, amorphous solid (12 mg, 80%): IR (neat) ν 2923, 1654, 1584, 1564, 1476, 1406, 1277 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.36-7.10 (m, 5 H), 6.56 (s, 1 H), 5.16 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.82-2.78 (m, 2 H), 2.61-2.54 (m, 2 H), 2.16-2.00 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 183.8, 183.0, 154.0, 153.6, 149.3, 147.8, 144.2, 138.3, 136.4, 135.0, 128.5, 128.2, 128.2, 121.3, 121.1, 120.9, 120.6, 120.5, 120.4, 56.9, 56.8, 38.0, 24.6, 21.5; HRMS (ESI) calcd for $C_{26}H_{24}O_6N$ [$(M+H)^+$] 446.1598, found 446.1575.



3.108

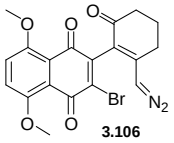
To a solution of aldehyde **3.54** (10 mg, 0.019 mmol) in CH_3CN (1 mL) at ambient temperature was added CAN (32 mg, 0.058 mmol). After 30 min the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O (x 2) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide aldehyde **3.108** as a red solid (7.2 mg, 90%): ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.6 Hz, 1 H), 7.30 (s, 2 H),

4.18 (dd, *J* = 10.8, 16.8 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.57 (td, *J* = 8.8, 3.6 Hz, 1 H), 2.68 (d, *J* = 16.0 Hz, 1 H), 2.39-2.28 (m, 3 H), 2.22-2.16 (m, 2 H).



3.109

To a solution of aldehyde **3.108** (69 mg, 0.16 mmol) in $CHCl_3$ (4 mL) at ambient temperature was added H_2NNHTs (33 mg, 0.18 mmol). After 3.5 h the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:5) to provide hydrazone **3.109** as a red, amorphous solid (77 mg, 81%): IR (neat) ν 3185, 2941, 2362, 2252, 1708, 1657, 1616, 1563, 1477 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (bs, 1 H), 7.61 (t, *J* = 7.8 Hz, 2 H), 7.28 (t, *J* = 3.6 Hz, 2 H), 7.11-7.07 (m, 3 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.37-3.35 (m, 1 H), 2.61 (d, *J* = 16.8 Hz, 1 H), 2.45-2.28 (m, 5 H), 2.07 (d, *J* = 10.2 Hz, 3 H), 1.74-1.68 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.6, 175.7, 154.1, 154.05, 154.0, 150.9, 144.0, 143.3, 135.0, 129.4, 127.6, 120.7, 120.3, 120.2, 119.7, 56.9, 56.8, 40.3, 40.2, 28.2, 22.8, 22.7, 21.4.



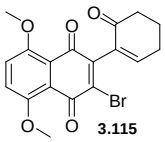
3.106

Method A: To a solution of aldehyde **3.72** (15 mg, 0.035 mmol) in EtOAc (1 mL) at ambient temperature under H_2 atmosphere was added Pd/C (0.4 mg, 0.0035 mmol). After 30 min the reaction mixture was filtrated through small celite/SiO_2 pad (washed with EtOAc). The filtrate was concentrated *in vacuo*. The crude residue was immediately taken to the next step.

To a solution of hydroquinone **3.74** in CH_2Cl_2 (1 mL) at ambient temperature was added NH_2NHTs (14 mg, 0.075 mmol). After 1 h Ag_2CO_3 (19 mg, 0.075 mmol) and Et_3N (3.6 mg, 0.035 mmol, ~5 µL) were added. After 10 min the reaction solution was filtrated through

celite pad (washed with EtOAc). The filtrate was concentrated. The residue was purified by flash chromatography (EtOAc, 100%) to provide diazoenone **3.106** as a red, amorphous solid (5.7 mg, 37%).

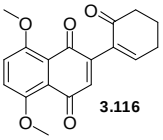
Method B: To a solution of aldehyde **3.72** (38 mg, 0.09 mmol) in $CHCl_3$ (4 mL) at ambient temperature was added H_2NNHTs (17 mg, 0.09 mmol). After 50 min Et_3N (9.1 mg, 0.09 mmol, 12.6 µL) was added. After 10 min the reaction mixture was filtrated through celite/SiO_2 pad (washed with CH_2Cl_2). The filtrate was concetrated *in vacuo* to provide diazoenone **3.106** as a red, amorphous solid (28 mg, 72.5%): IR (neat) ν 3056, 2939, 2841, 2252, 2078, 1734, 1662, 1636, 1585, 1560, 1476 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (s, 2 H), 4.78 (s, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H), 2.57-2.49 (m, 4 H), 2.21-2.11 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$, semi-pure sample) δ 192.2, 192.0, 179.9, 176.8, 154.1, 154.0, 150.0, 149.5, 146.5, 143.2, 142.6, 139.4, 120.5, 120.1, 56.9, 53.4, 36.8, 26.0, 21.5.



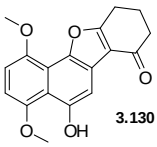
3.115

To a solution of enone **3.29** (57 mg, 0.12 mmol) in CH_3CN (4.5 mL) at ambient temperature was added CAN (131 mg, 0.24 mmol). After 30 min the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O (x 2) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide enone **3.115** as a red solid (42 mg, 90%): IR (neat) ν 2938, 2840, 1665, 1604, 1584, 1562, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2 H), 6.99 (t, *J* = 4.0 Hz, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 2.59-2.54 (m, 4 H), 2.16-2.11 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 180.2, 176.8, 154.0,

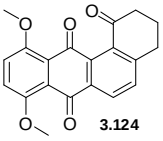
153.9, 151.3, 146.6, 138.4, 135.8, 120.7, 120.5, 120.2, 120.1, 56.9, 56.8, 38.0, 26.0, 22.4; HRMS (ESI) calcd for $C_{18}H_{16}O_5Br$ [$(M+H)^+$] 391.0182, found 391.0176.


3.116

To a solution of enone **3.49** (15 mg, 0.037 mmol) in CH_3CN (1 mL) at ambient temperature was added CAN (61 mg, 0.12 mmol). After 20 min the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O (x 2) and brine (x 1), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:8) to provide enone **3.116** as a red solid (8.7 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2 H), 7.08 (t, *J* = 4.0 Hz, 1 H), 6.93 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 2.58-2.51 (m, 4 H), 2.11 (qnt, 2 H).


3.130

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 7.59 (s, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 4.04 (s, 6 H), 3.14 (t, *J* = 6.6 Hz, 2 H), 2.62 (t, *J* = 6.0 Hz, 2 H), 2.29 (t, *J* = 6.0 Hz, 2 H).


3.124

To a solution of enone **3.115** (10 mg, 0.025 mmol) in THF (1 mL) were added $Pd(OAc)_2$ (2.87 mg, 0.013 mmol), polymer bound PPh_3 (26 mg, 0.077 mmol), Ag_2CO_3 (14 mg, 0.051 mmol), $(vinyl)_3(BO)_3$ pyridine complex **3.120** (12 mg, 0.051 mmol) as a one portion. H_2O (0.1 mL) was added. The mixture was placed in the oil bath at 75 ^{o}C. After 1.5 h the solution was cooled to ambient temperature. The mixture was filtrated through small celite/SiO_2 pad. The filtrate was concentrated *in vacuo*. The residue was purified be flash chromatography (Hexane/EtOAc, 1:4) to

provide ketone **3.124** as a yellow solid (2.5 mg, 29%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 9.6 Hz, 1 H), 7.22 (d, *J* = 9.0 Hz, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 2.95 (t, *J* = 3 H, 2 H), 2.84 (t, *J* = 6.6 Hz, 2 H), 2.21 (t, *J* = 6.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 185.5, 182.2, 153.4, 152.3, 150.2, 138.5, 134.0, 133.9, 131.9, 129.0, 125.8, 122.2, 120.3, 118.3, 57.3, 56.7, 39.0, 30.0, 22.89.

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Appendix A2:

Spectra Relevant to Chapter 3:

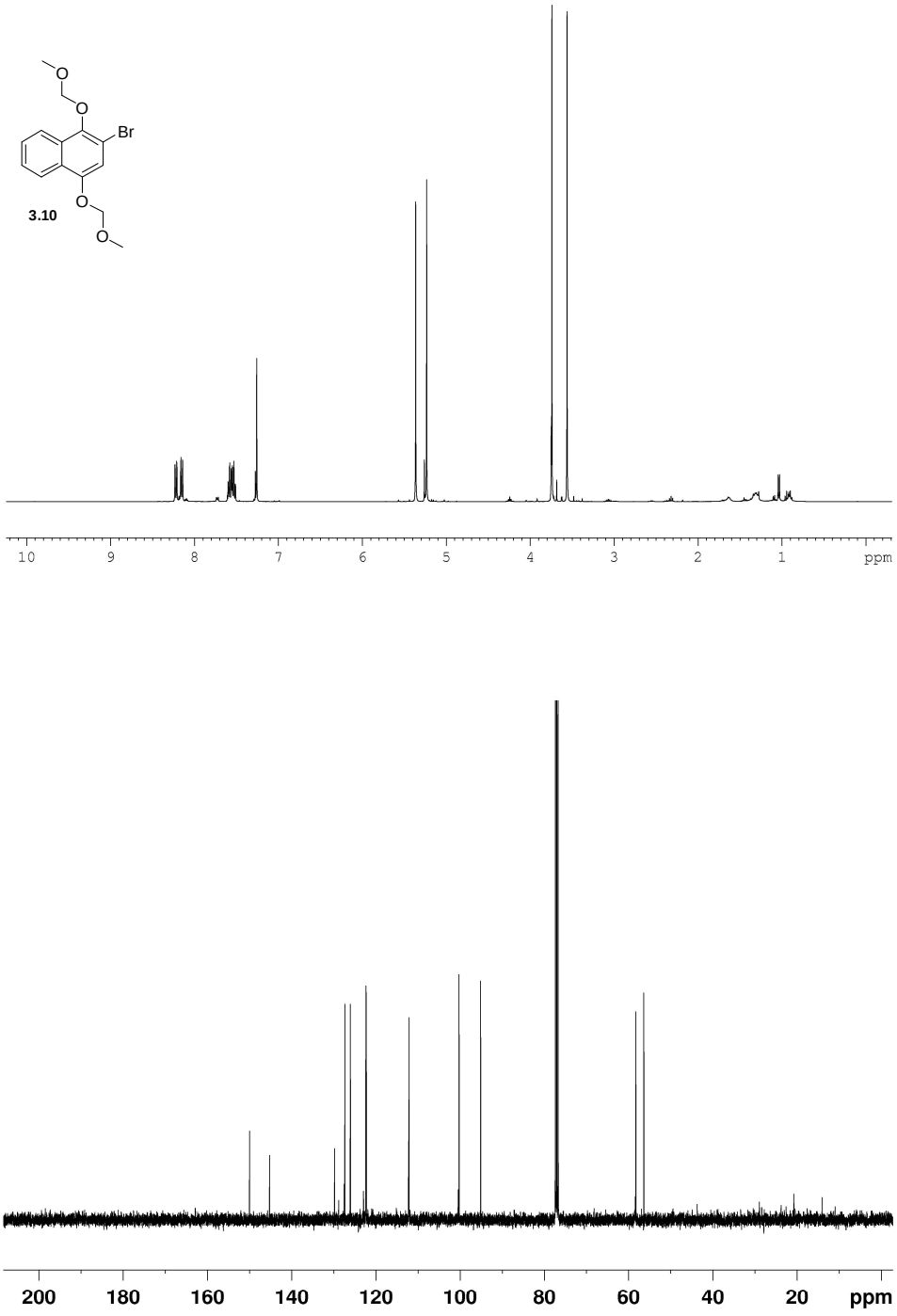


Figure A3.1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.10**.

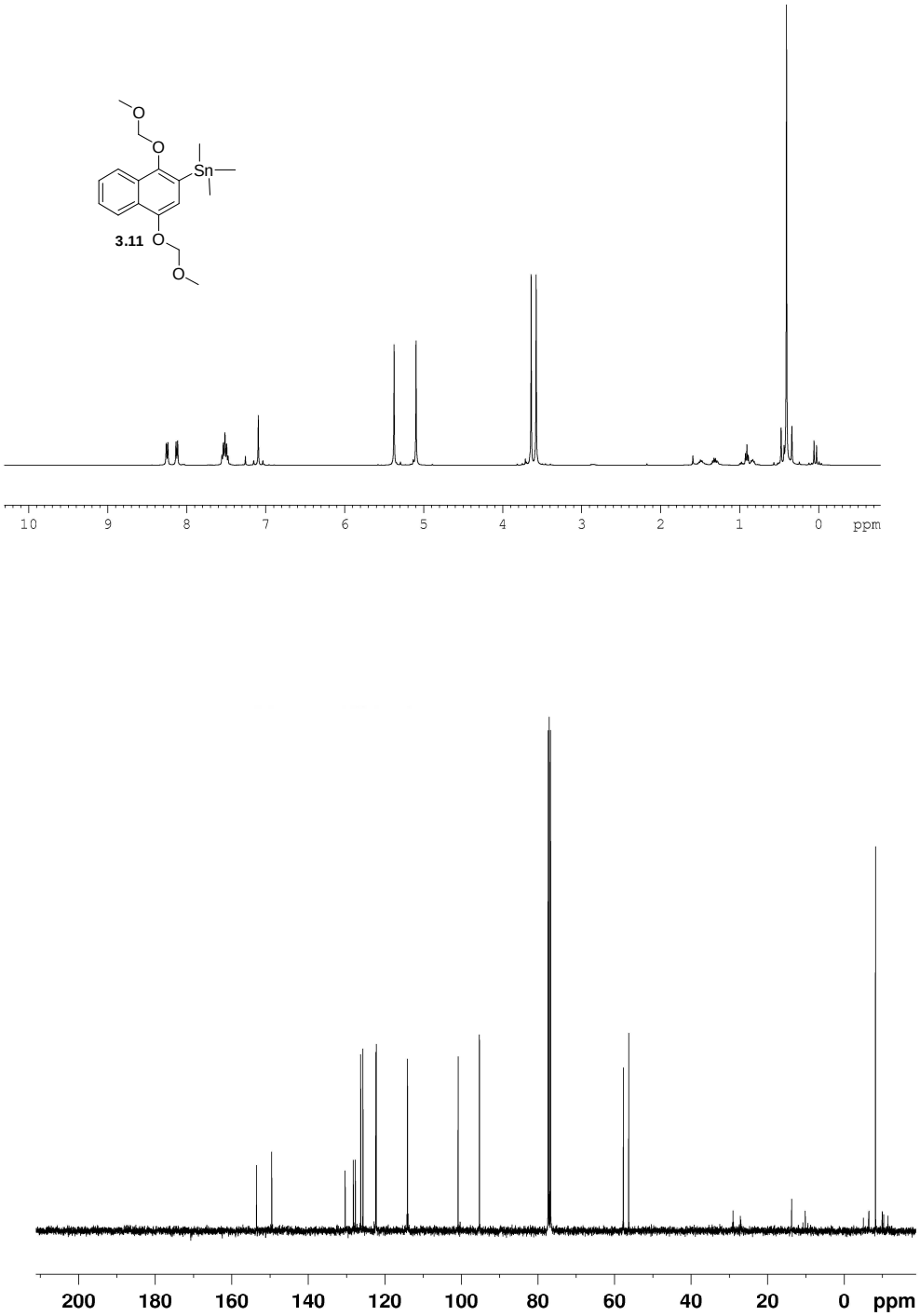


Figure A3.2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.11**.

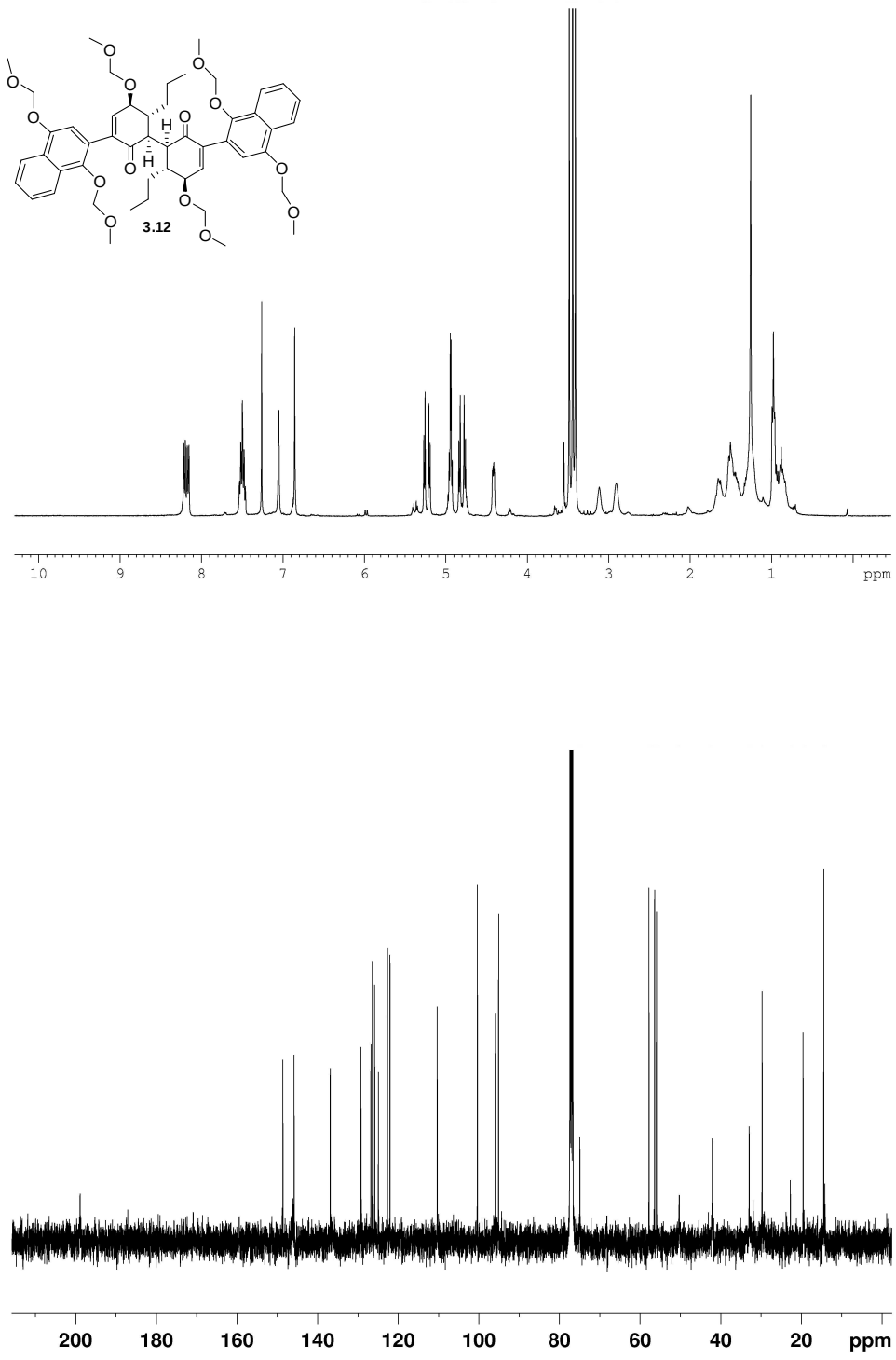


Figure A3.3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.12**.

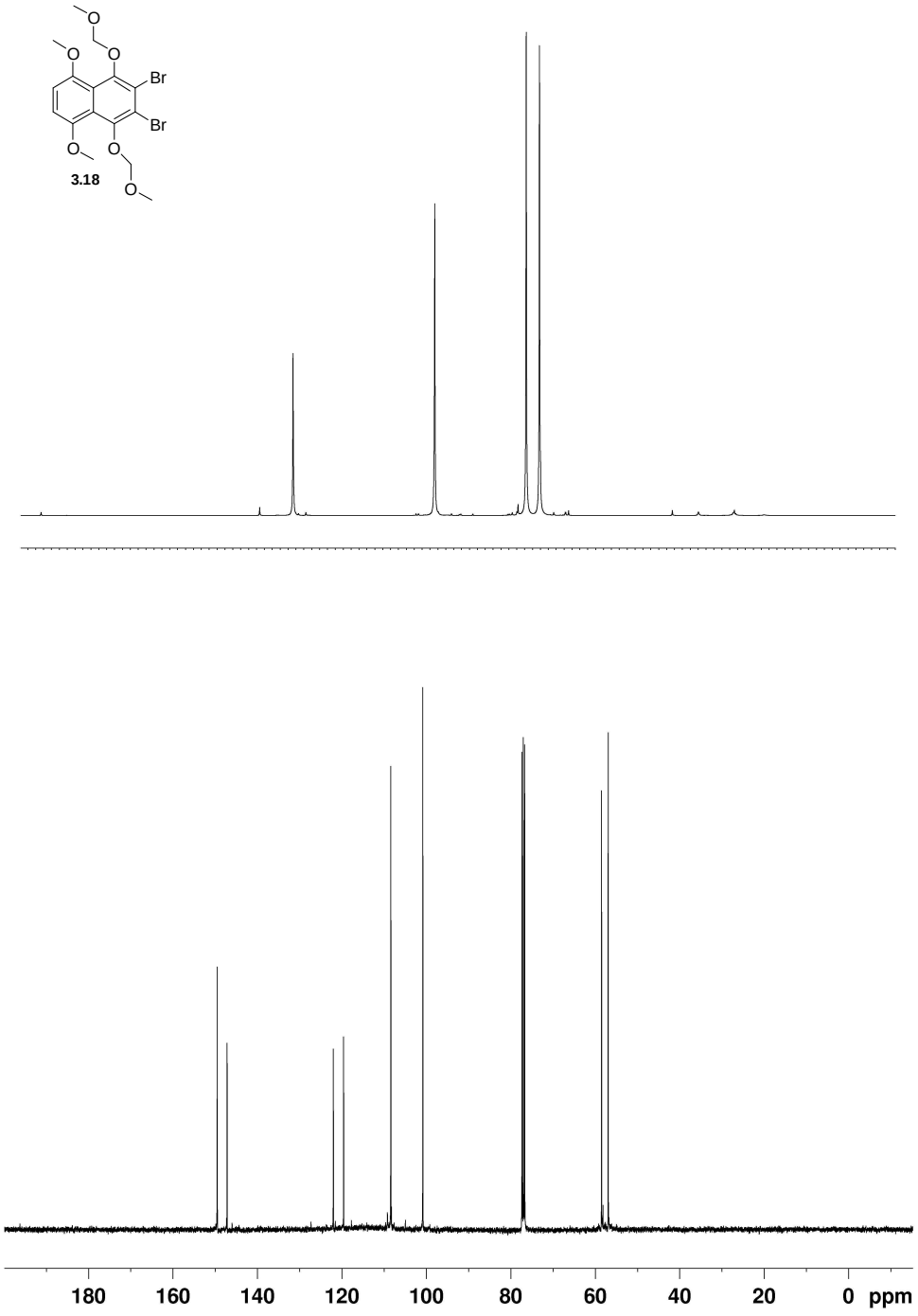


Figure A3.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.18**.

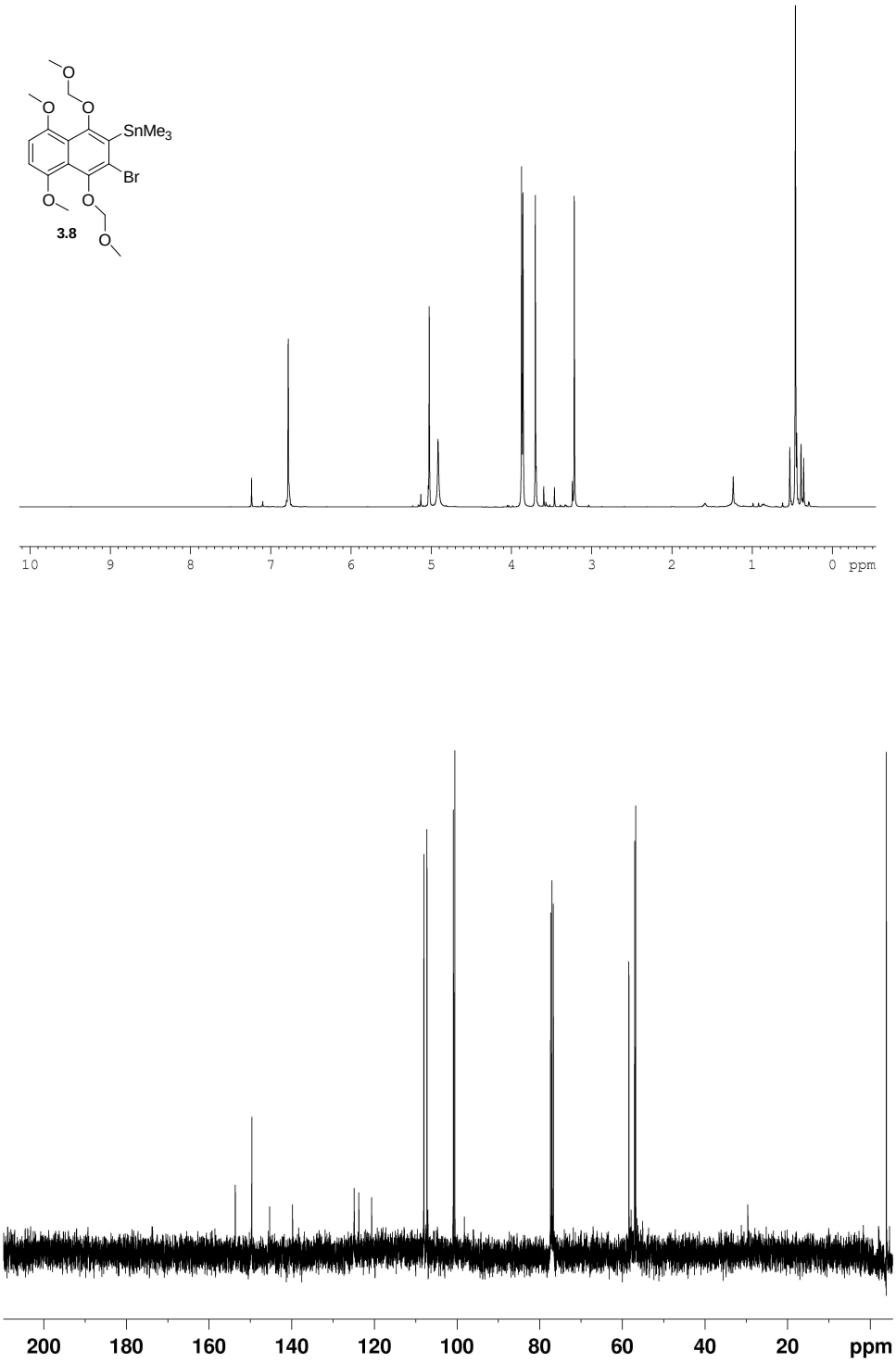


Figure A3.5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.8**.

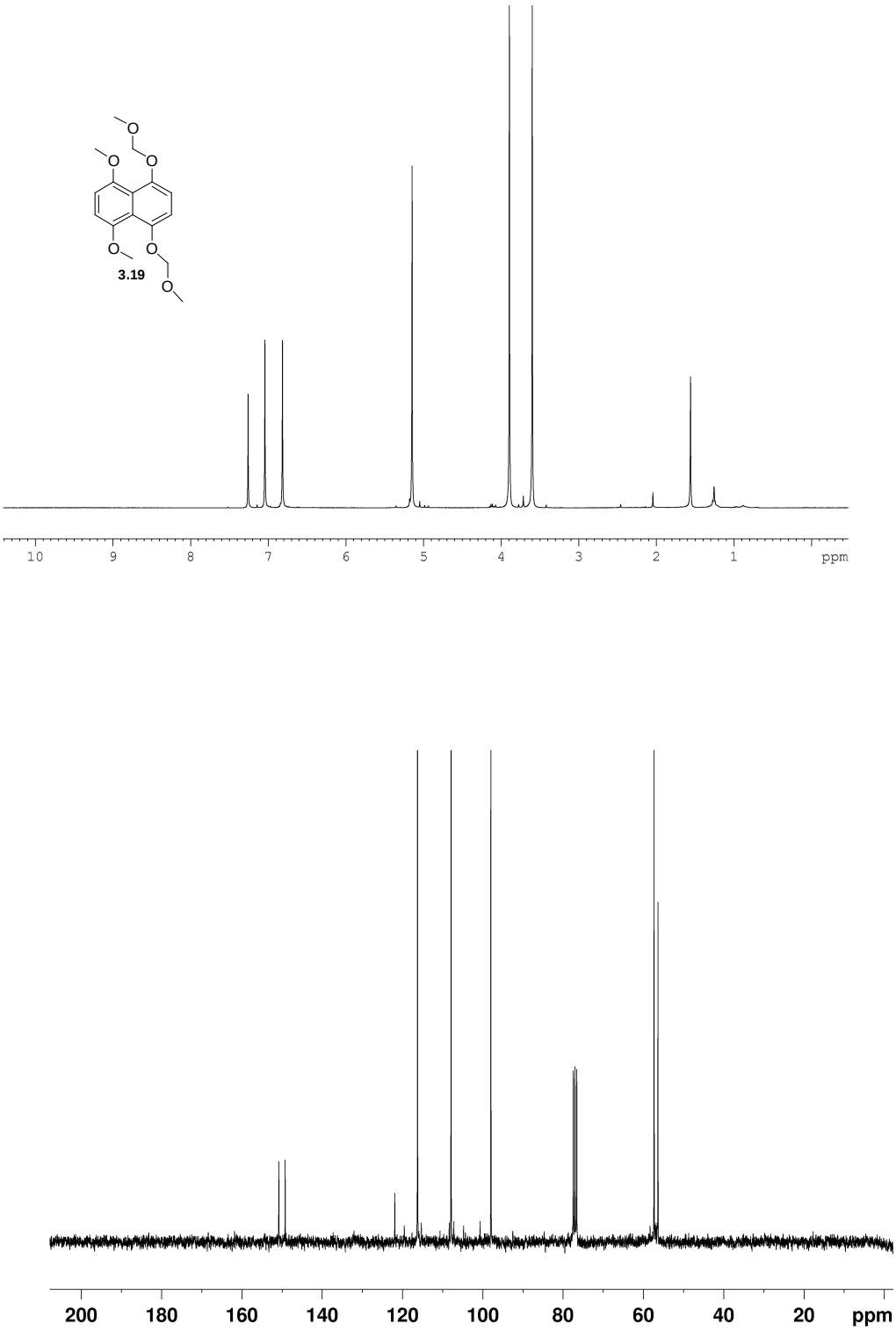


Figure A3.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **3.19**.

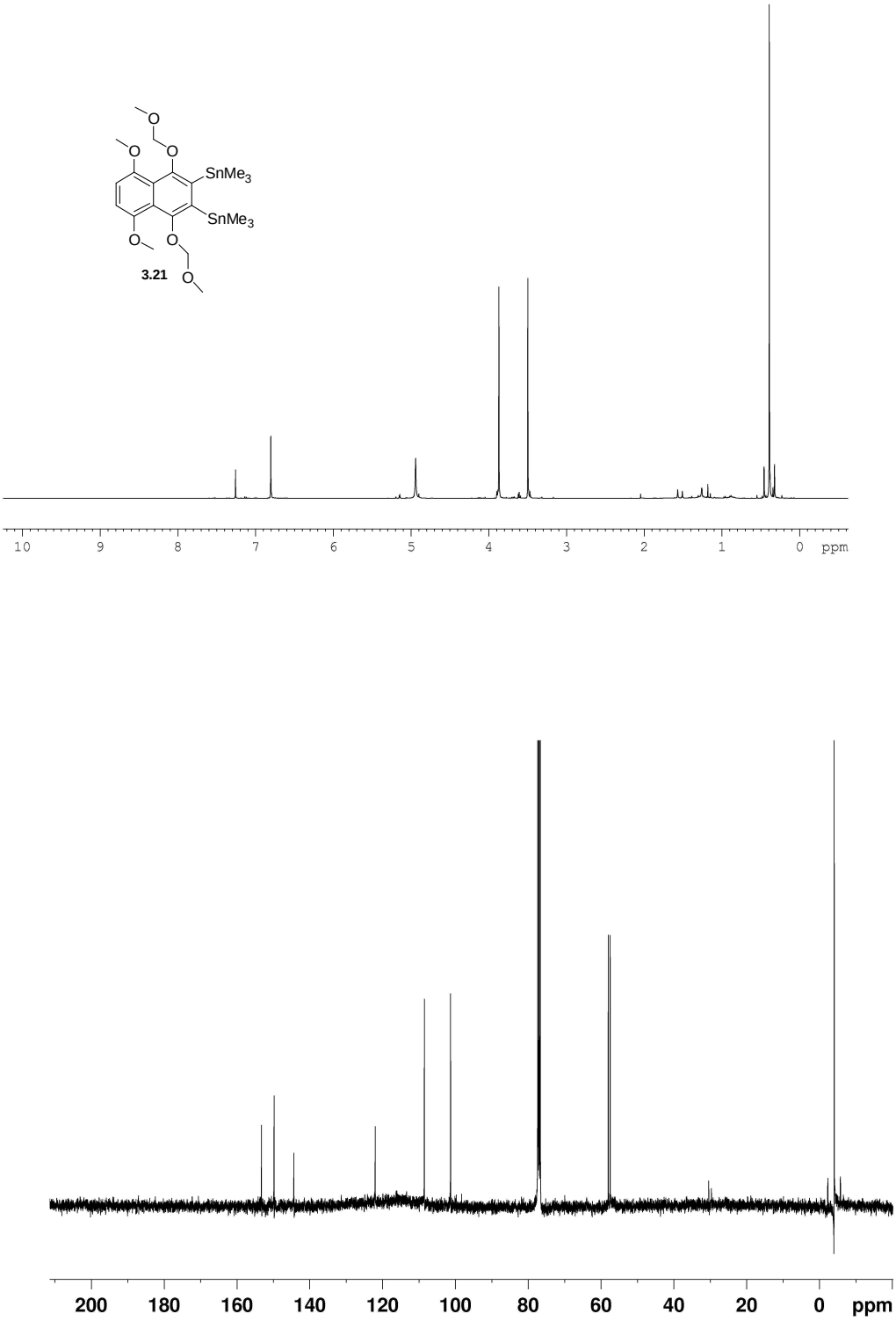


Figure A3.7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.21**.

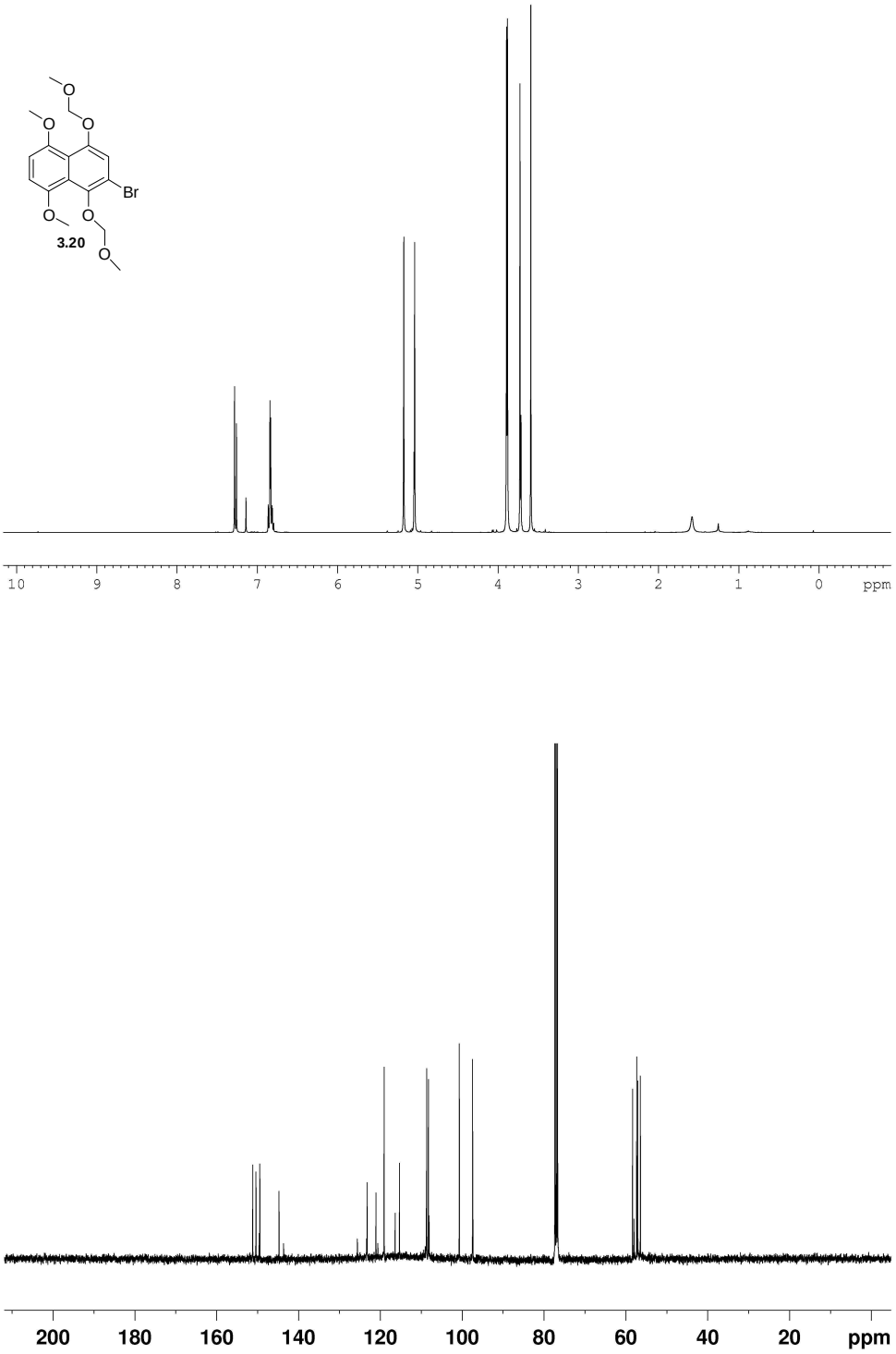


Figure A3.8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.20**.

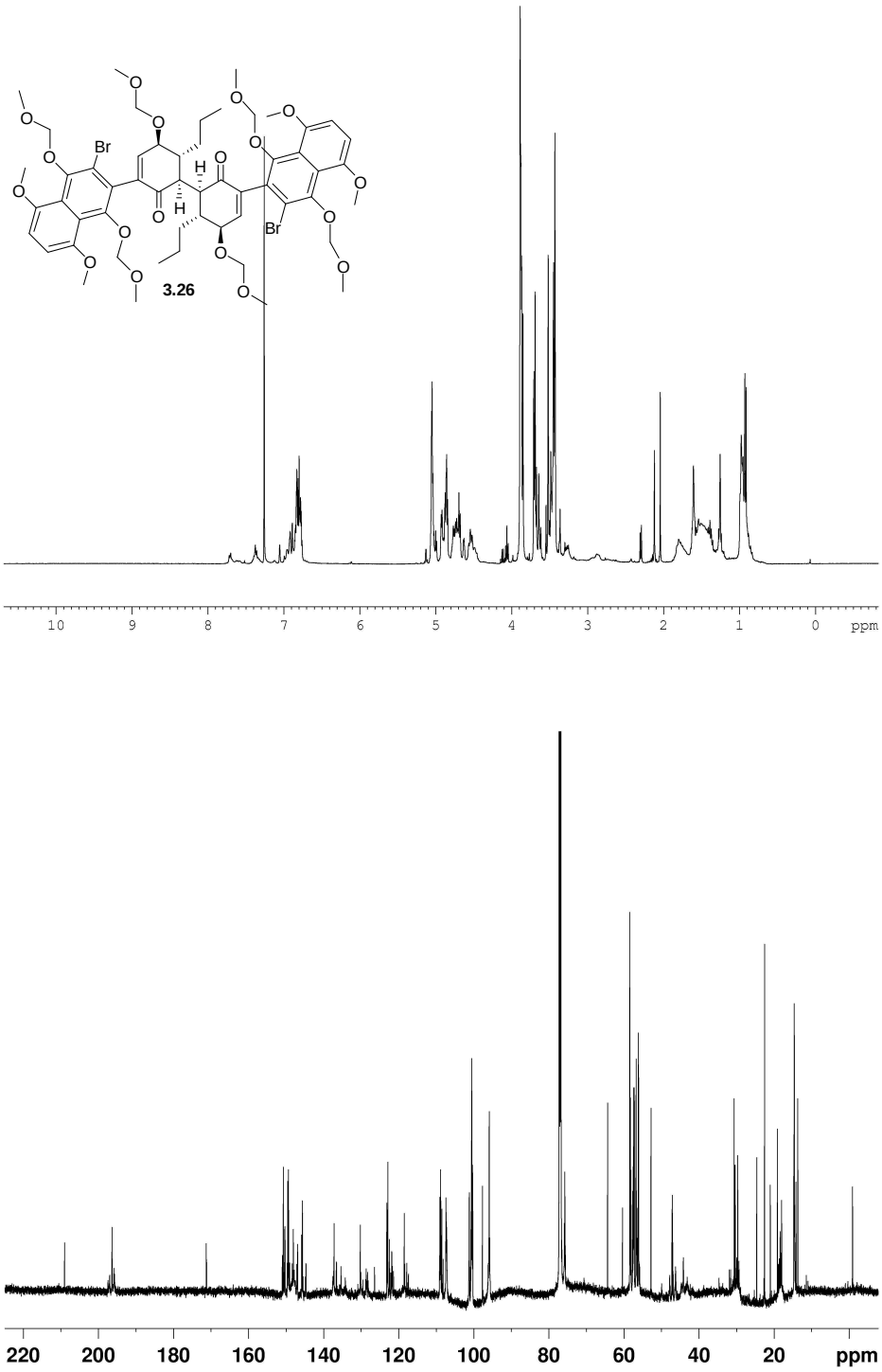


Figure A3.9. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.26**.

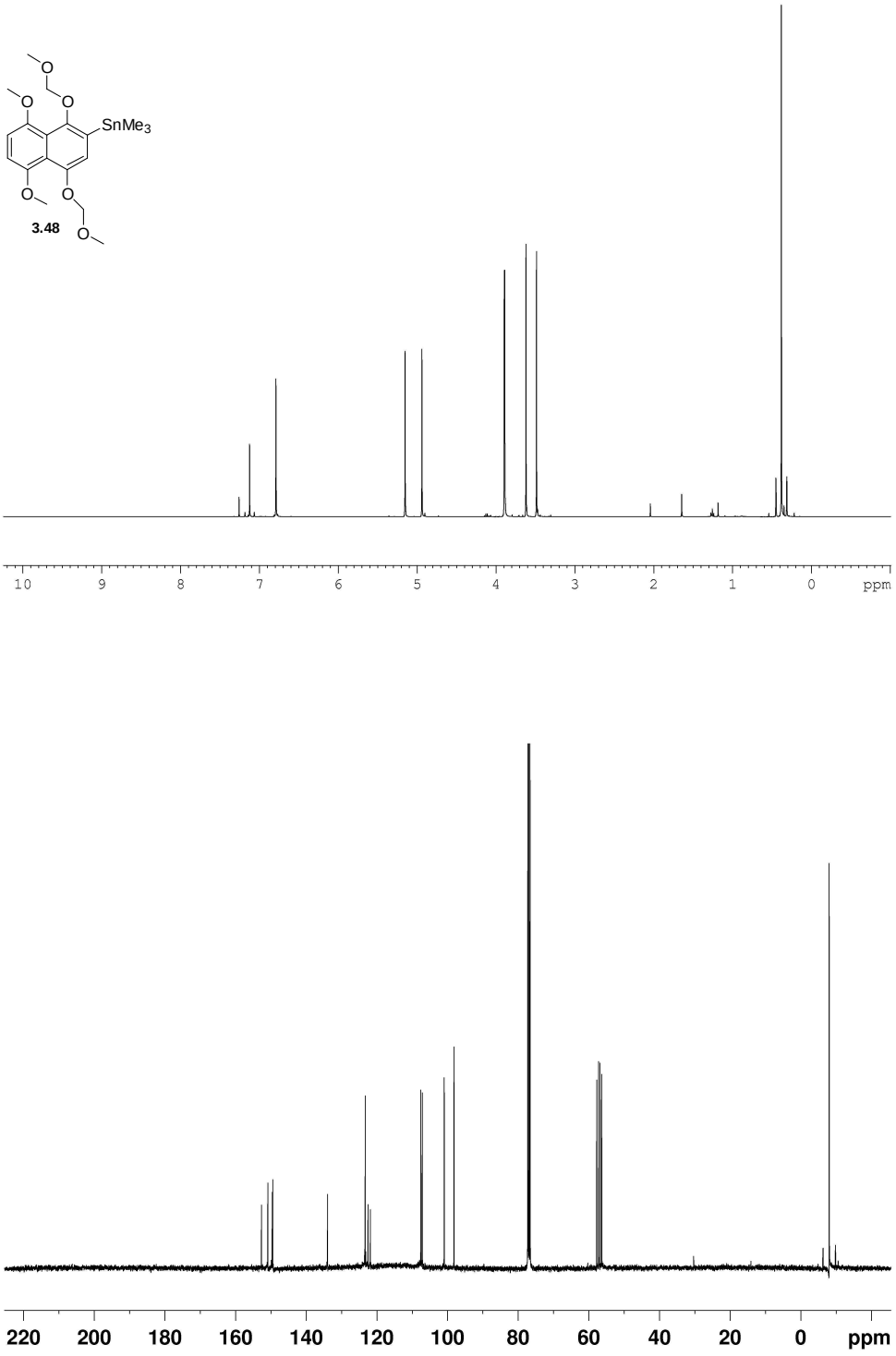


Figure A3.10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.48**.

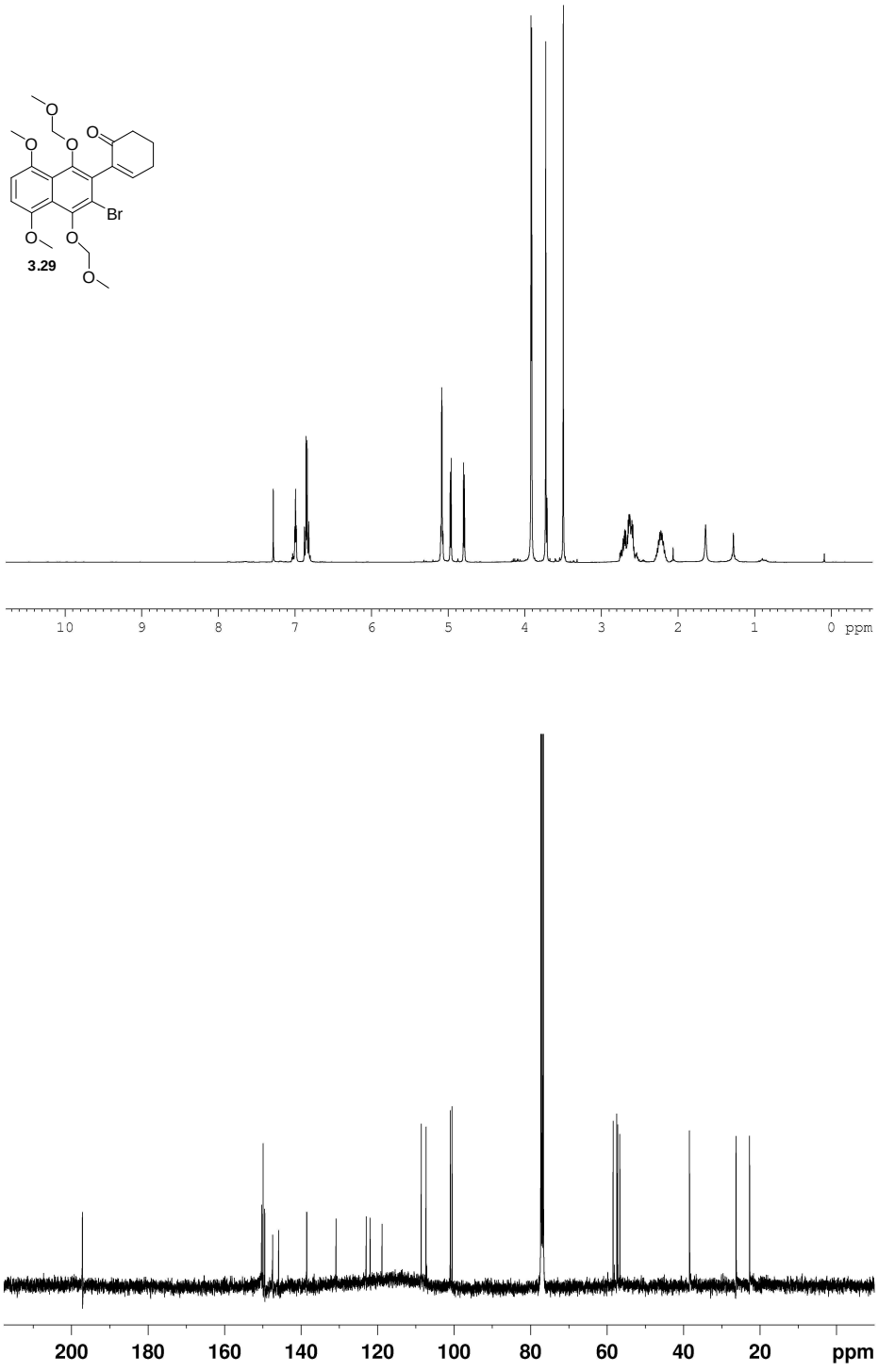


Figure A3.11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.29**.

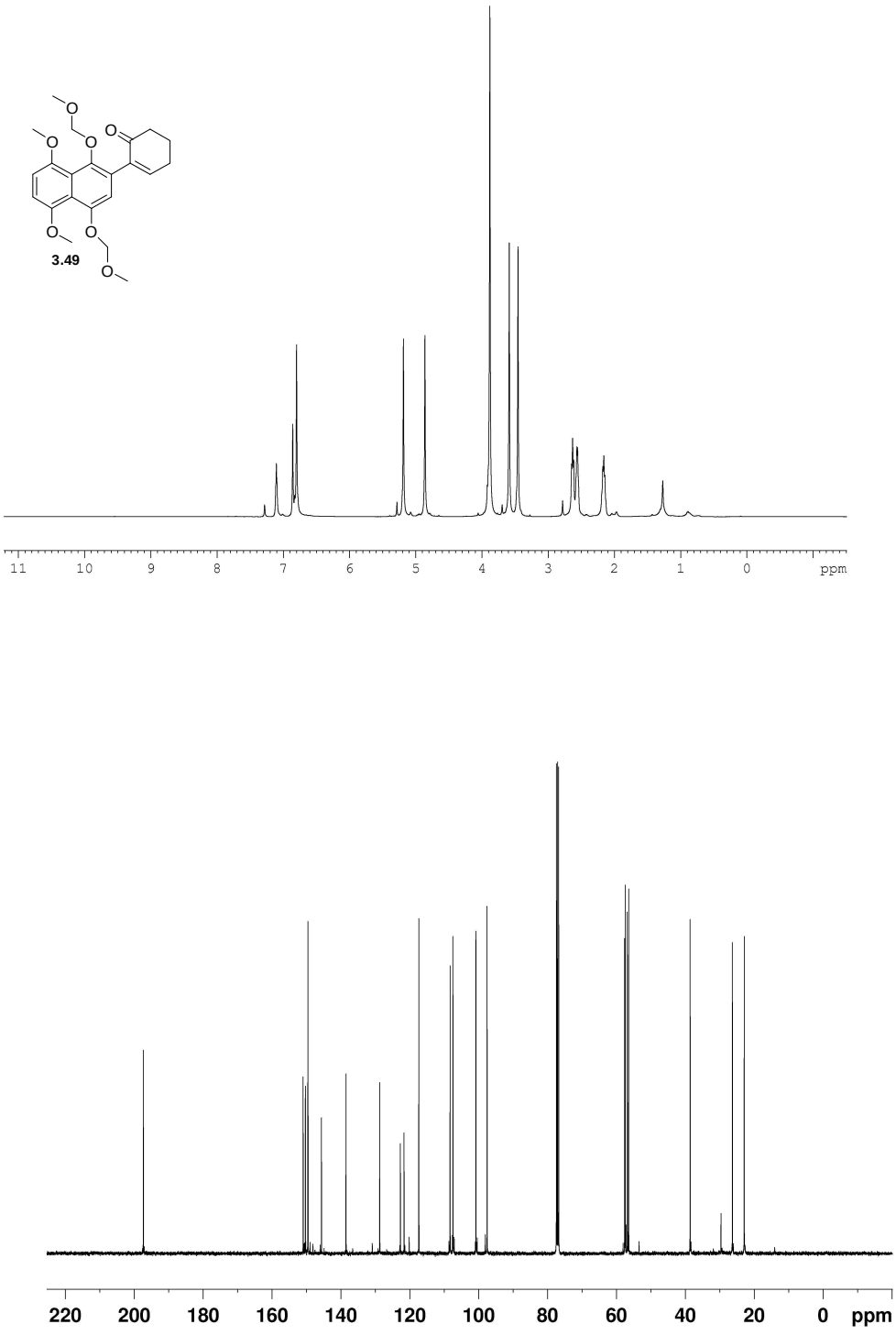


Figure A3.12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.49**.

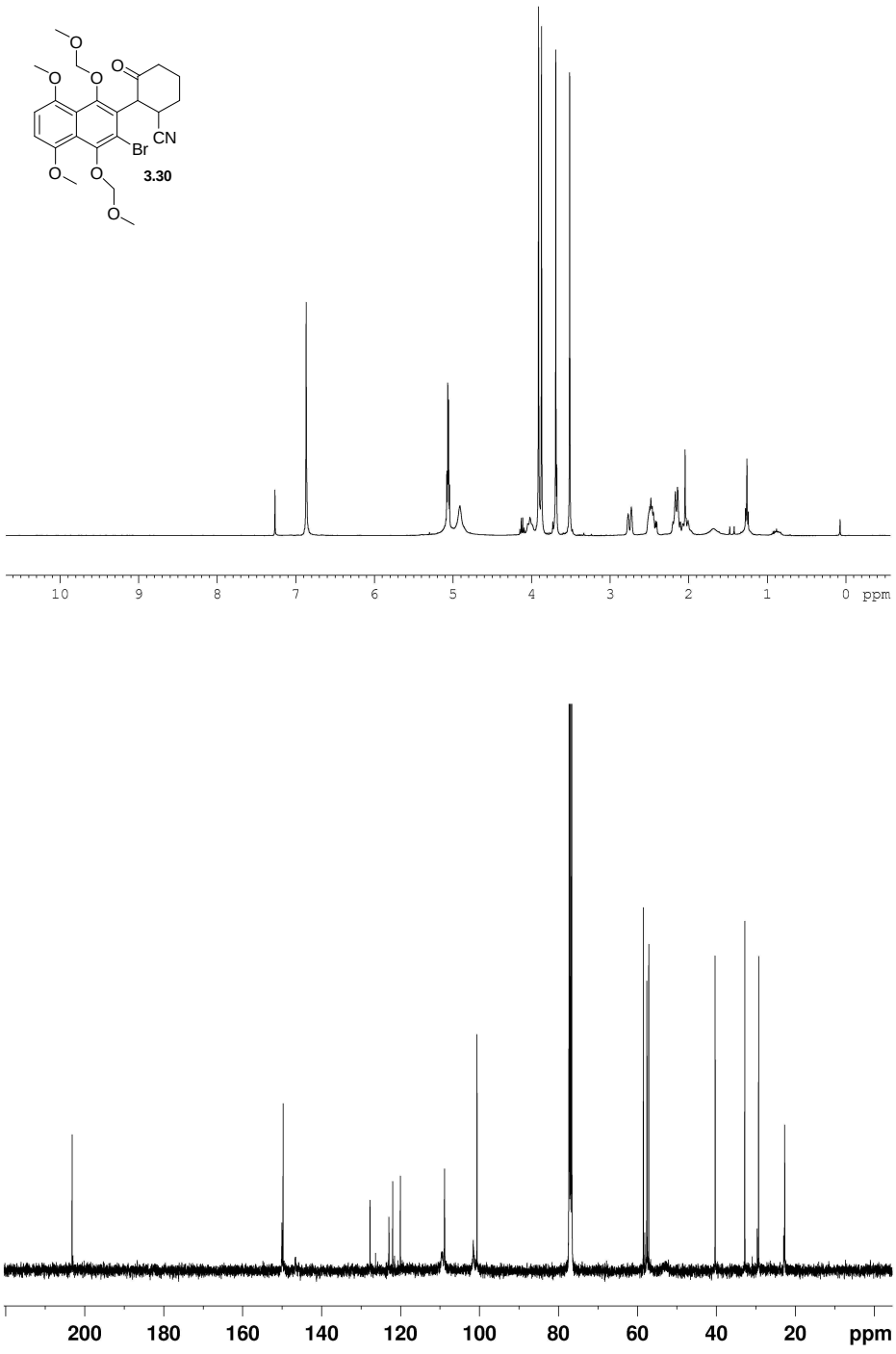


Figure A3.13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.30.**

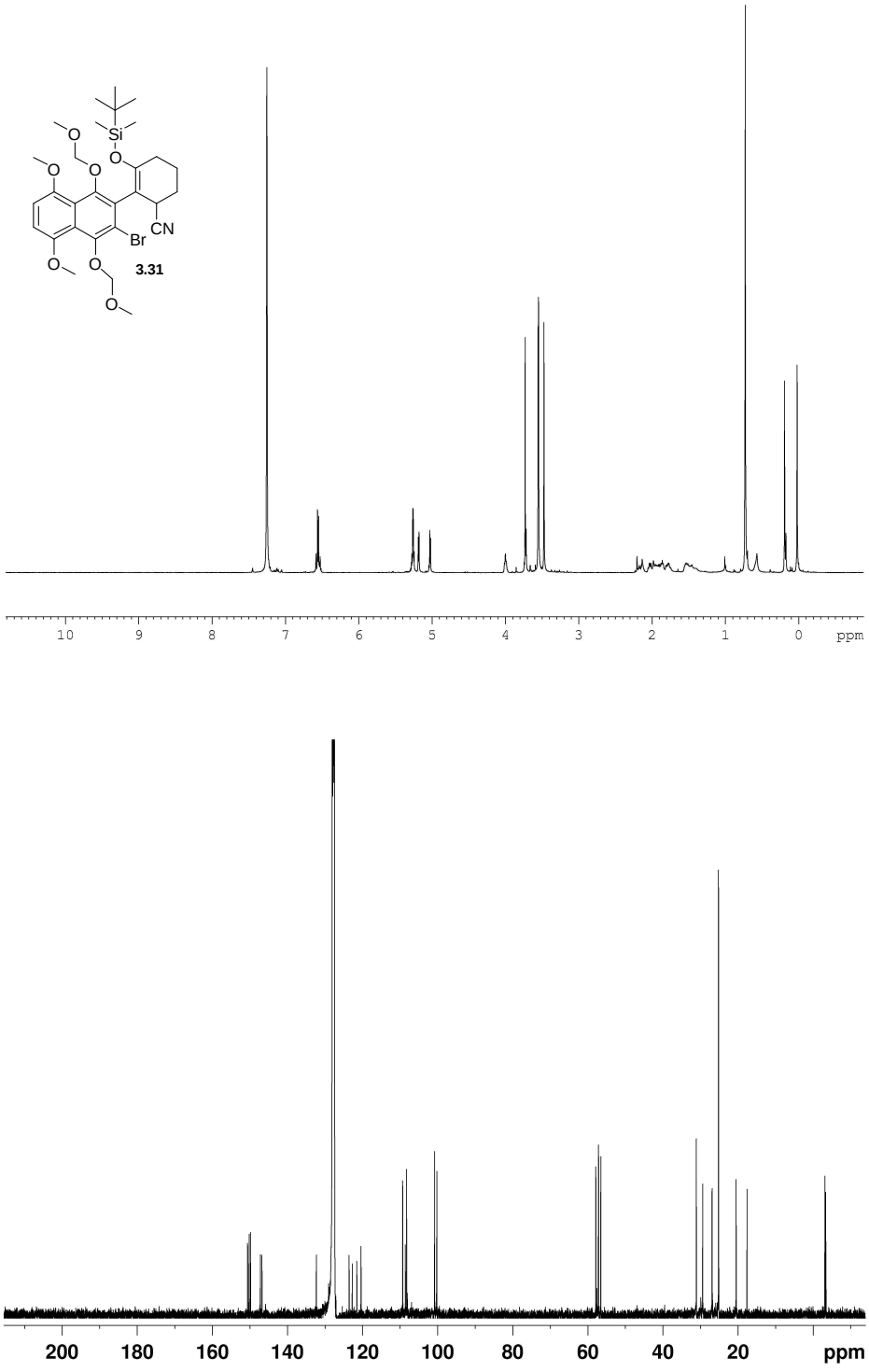


Figure A3.14. ^{1}H NMR spectrum (400 MHz, C_6D_6) and ^{13}C NMR spectrum (100 MHz, C_6D_6) of compound **3.31**.

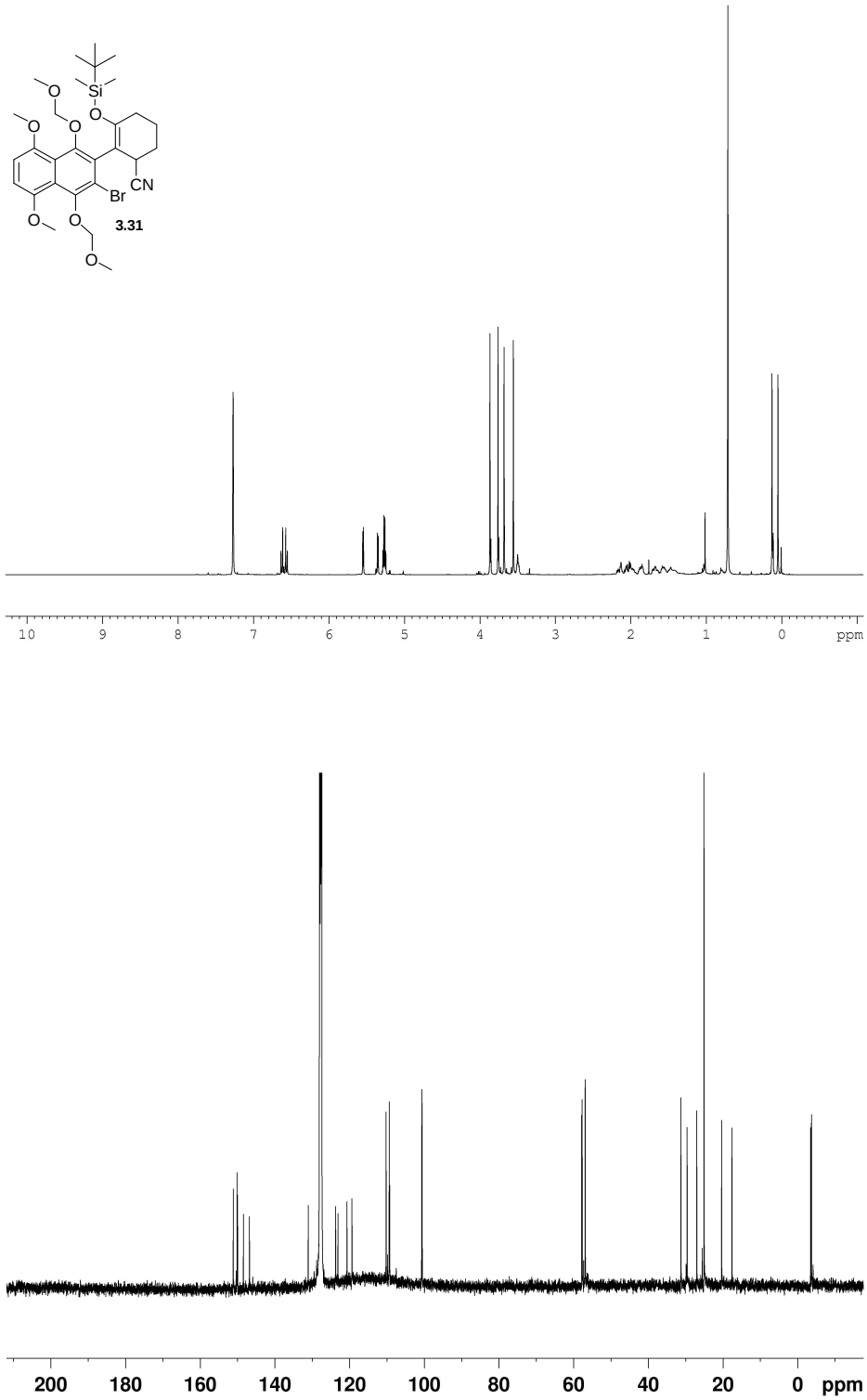


Figure A3.15. ^{1}H NMR spectrum (400 MHz, C_6D_6) and ^{13}C NMR spectrum (100 MHz, C_6D_6) of compound **3.31**.

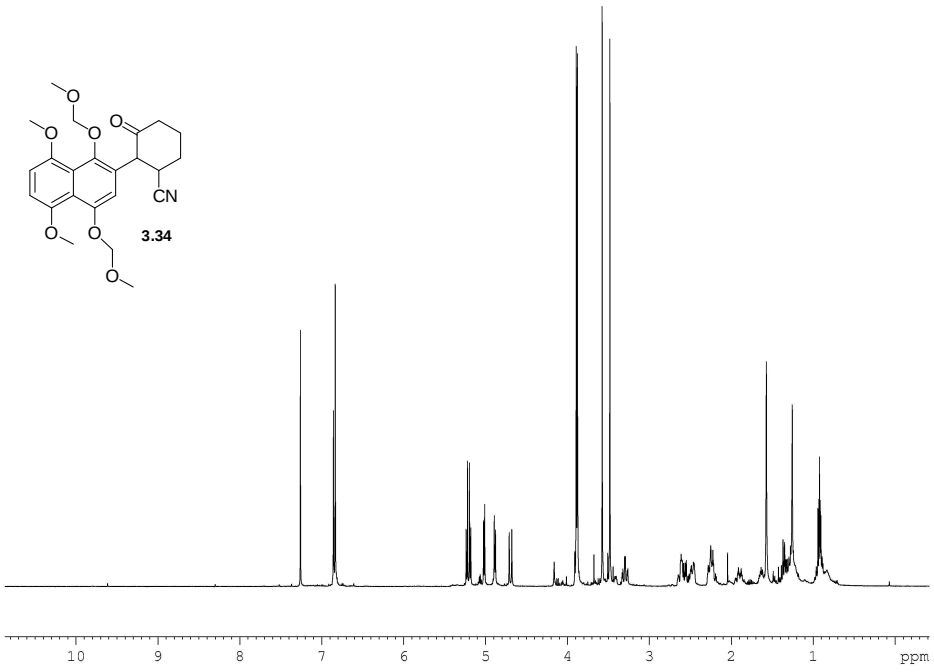


Figure A3.16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.34**.

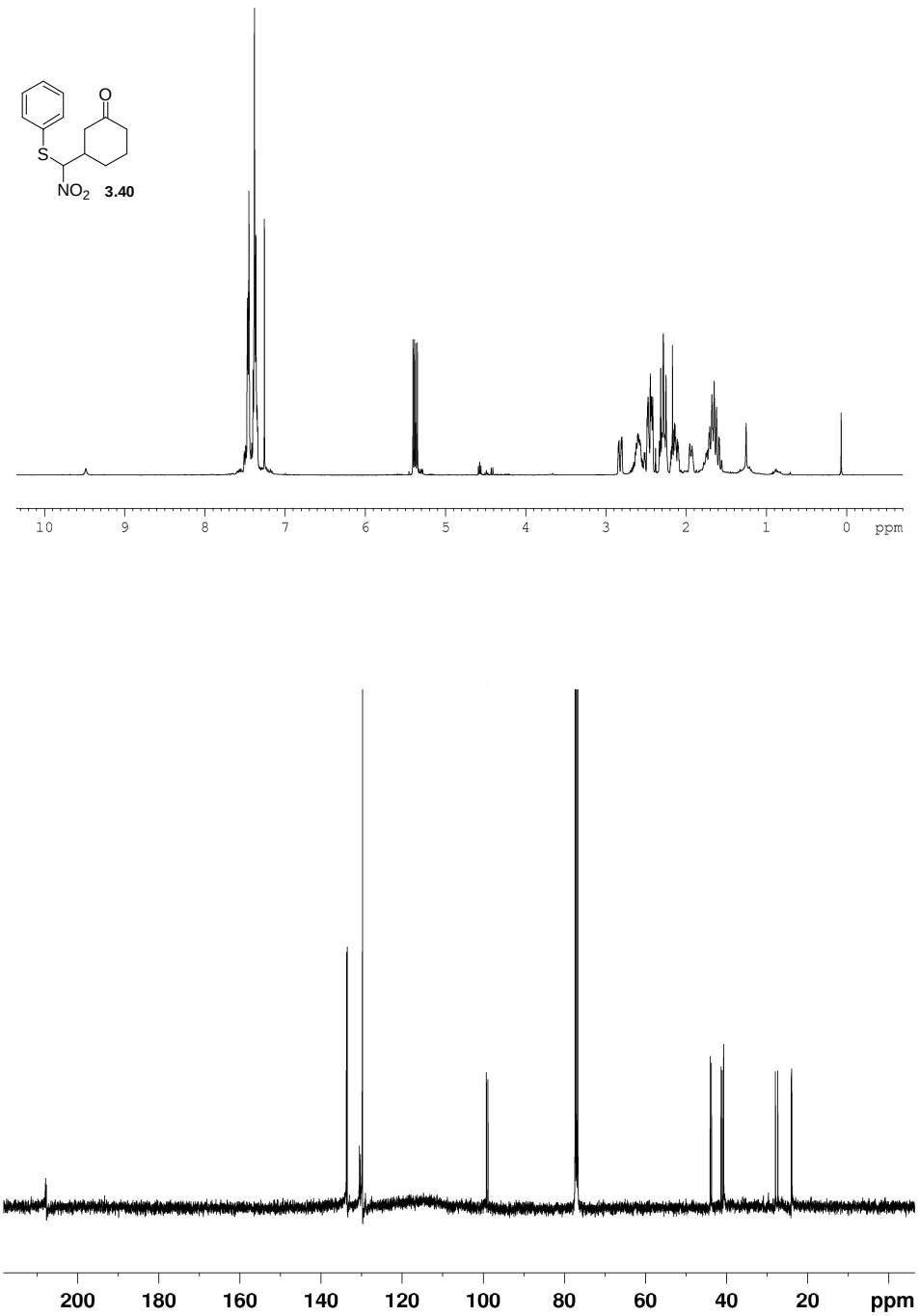


Figure A3.17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.40**.

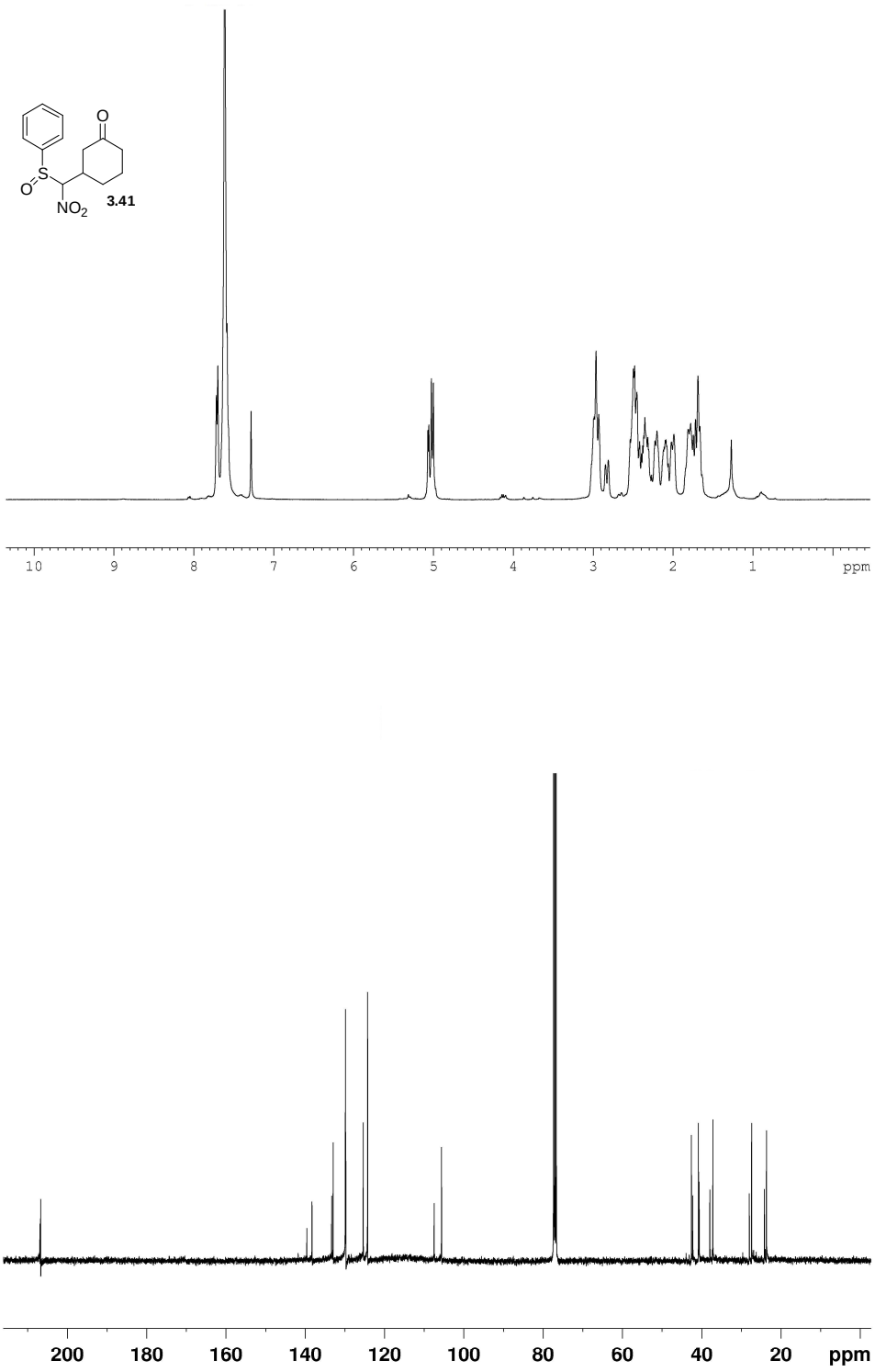


Figure A3.18. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.41**.

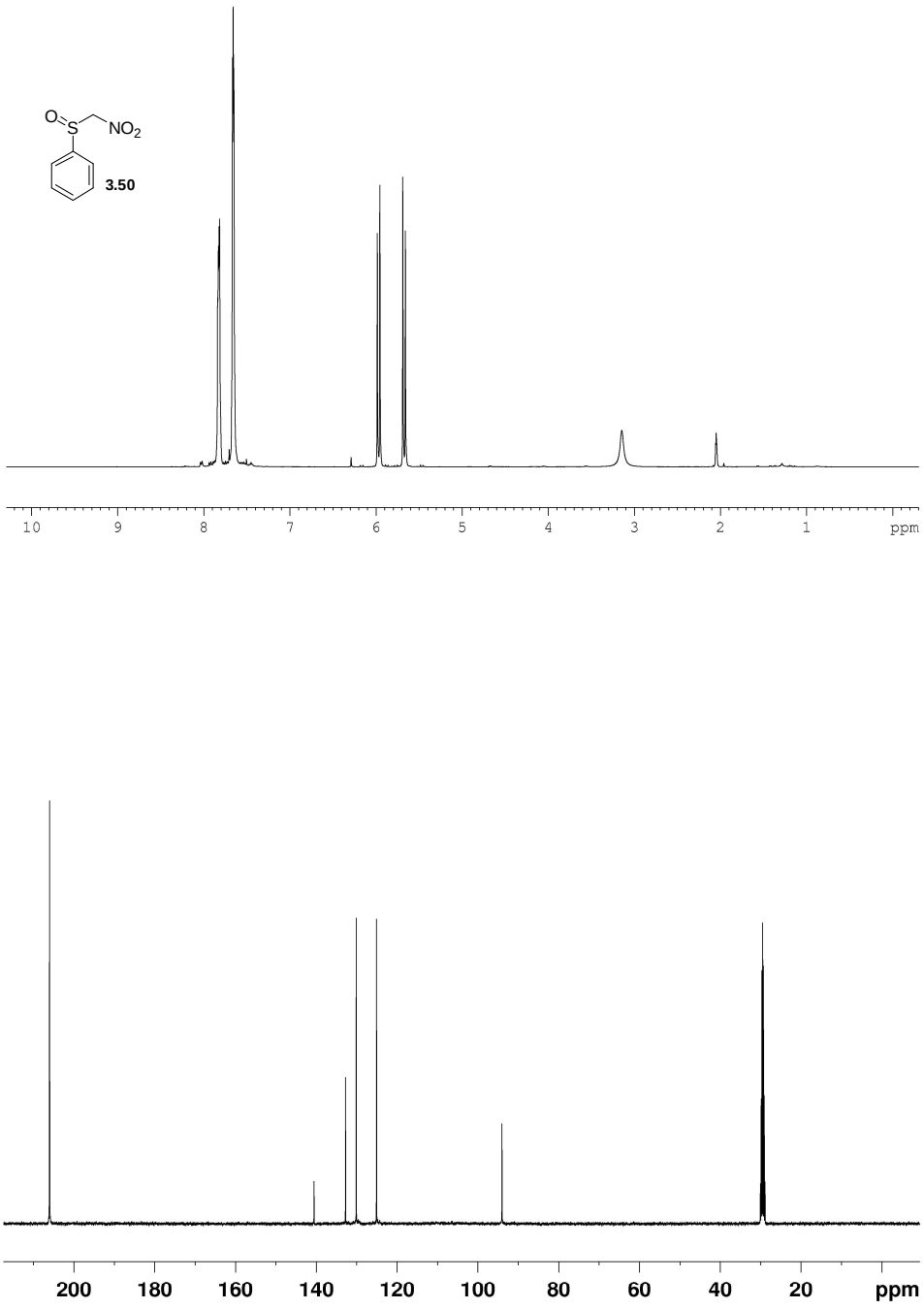


Figure A3.19. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.50**.

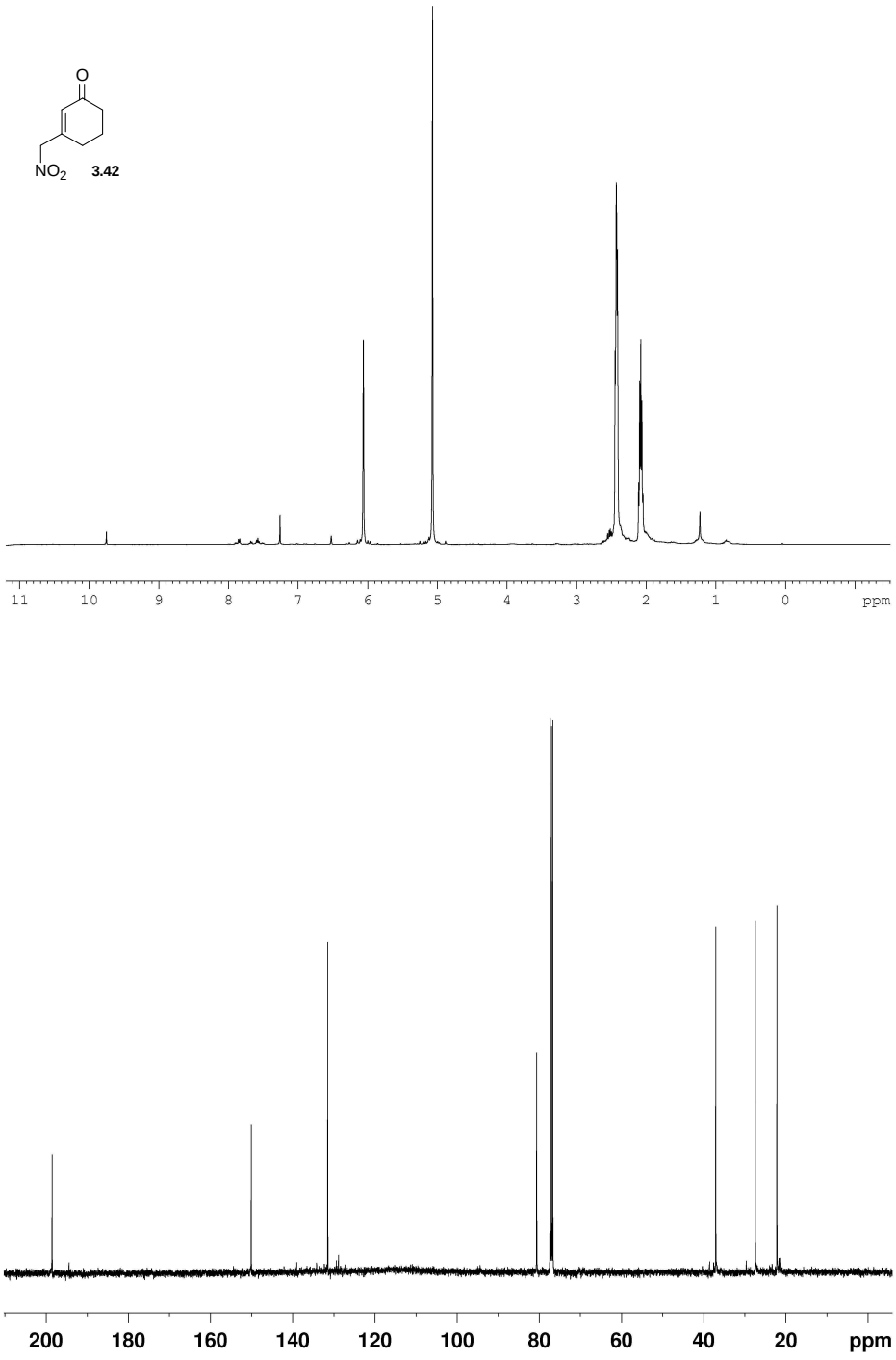


Figure A3.20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.37**.

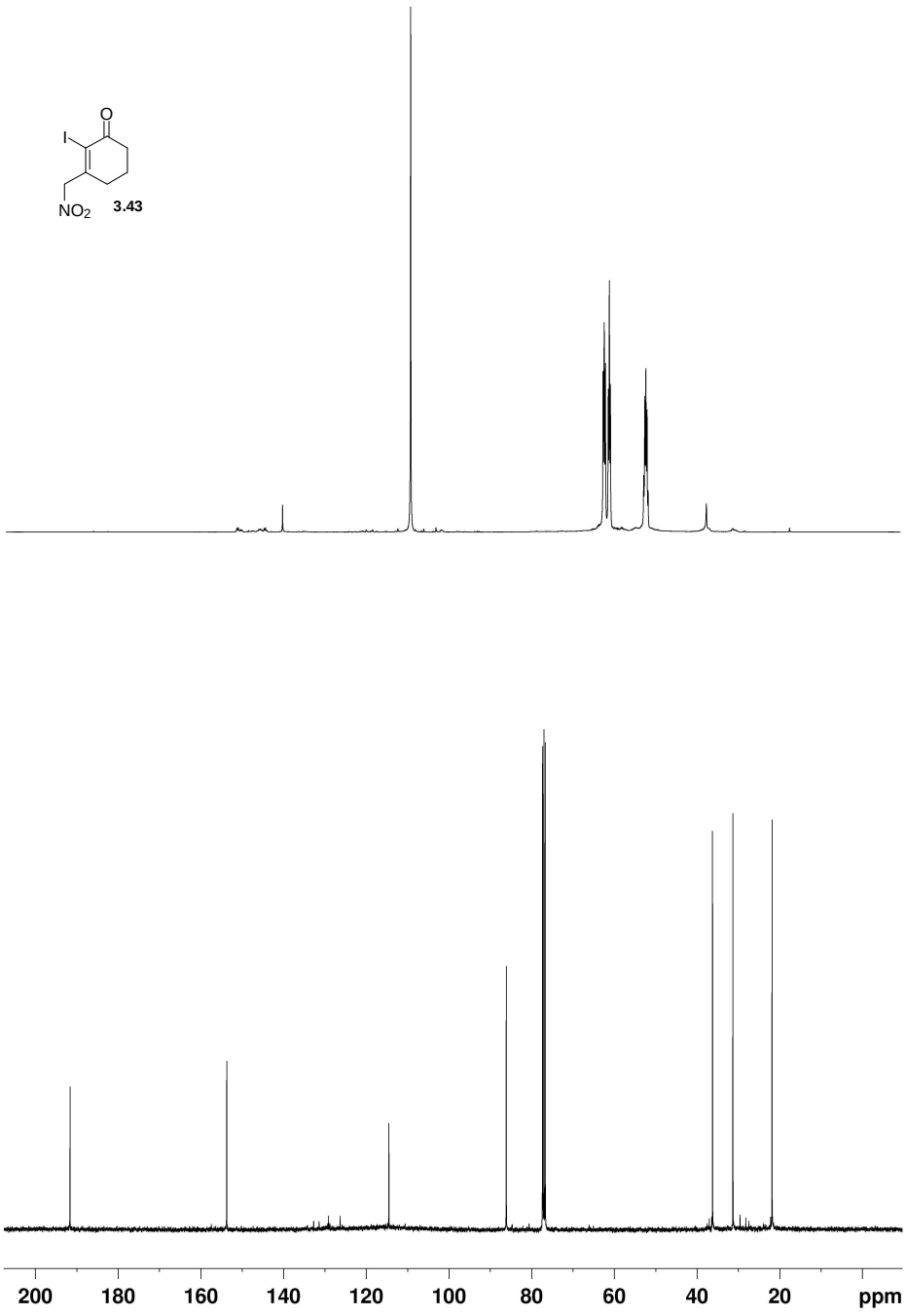


Figure A3.21. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.43**.

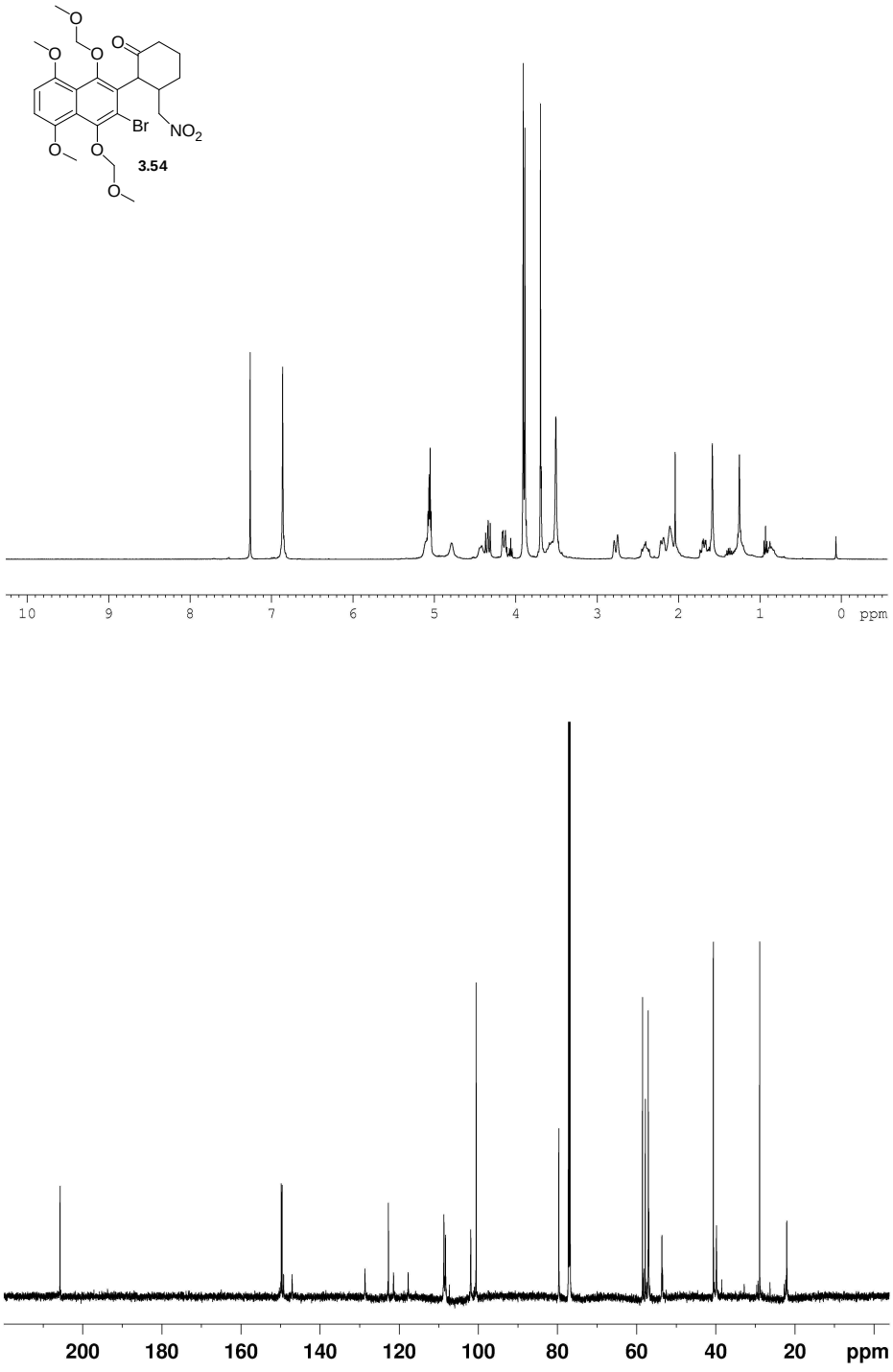


Figure A3.22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.54**.

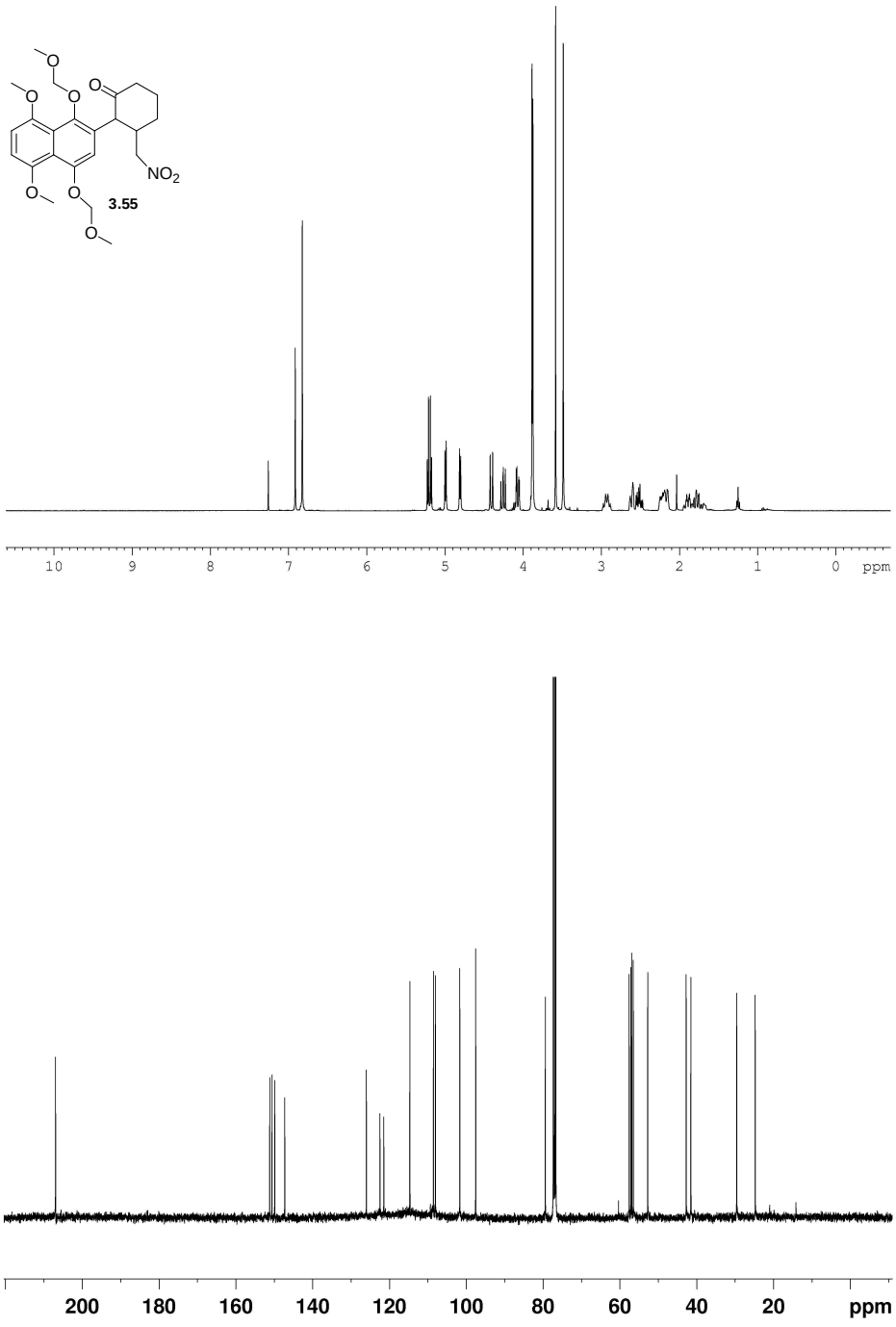


Figure A3.23. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.55**.

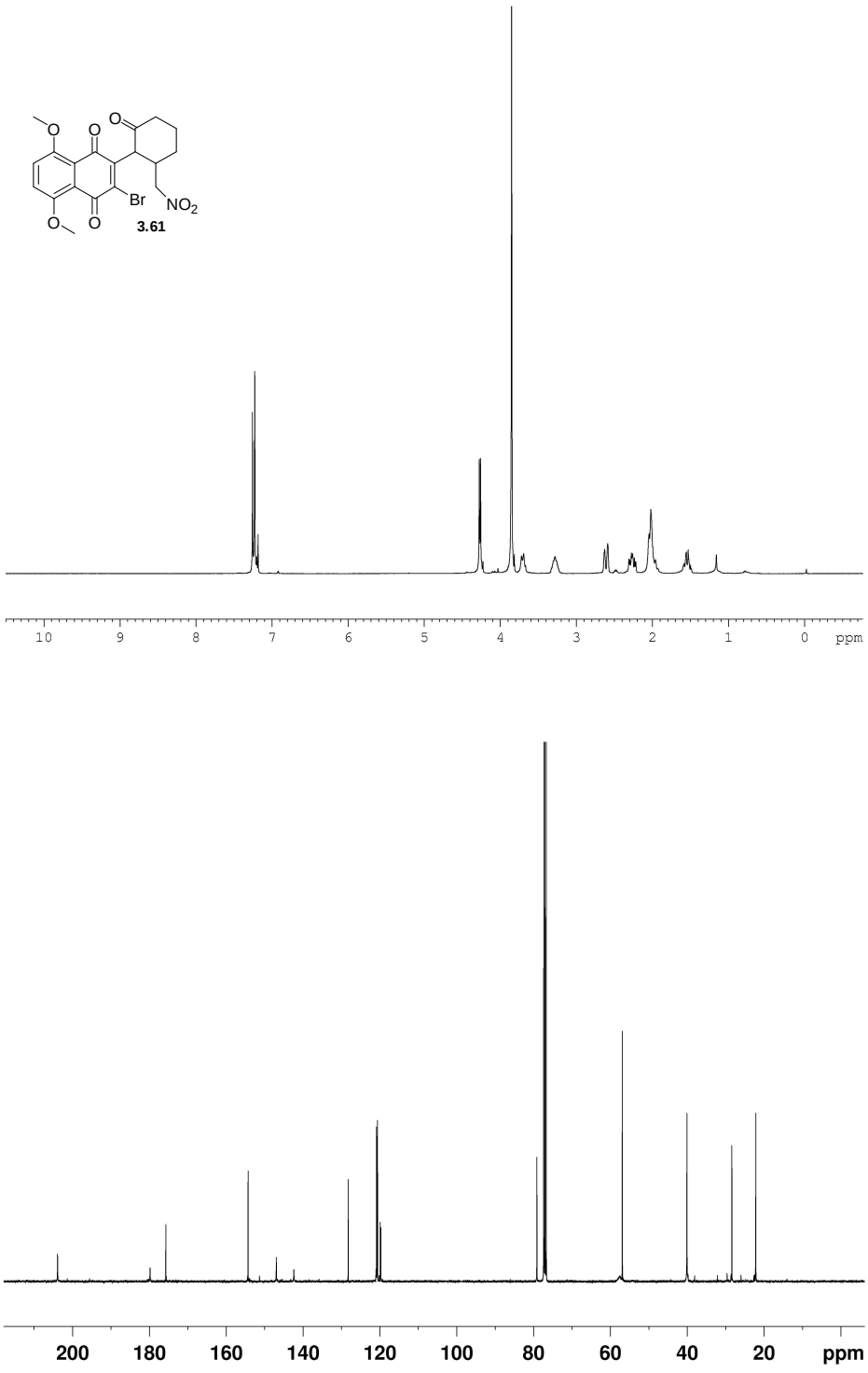


Figure A3.24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.61**

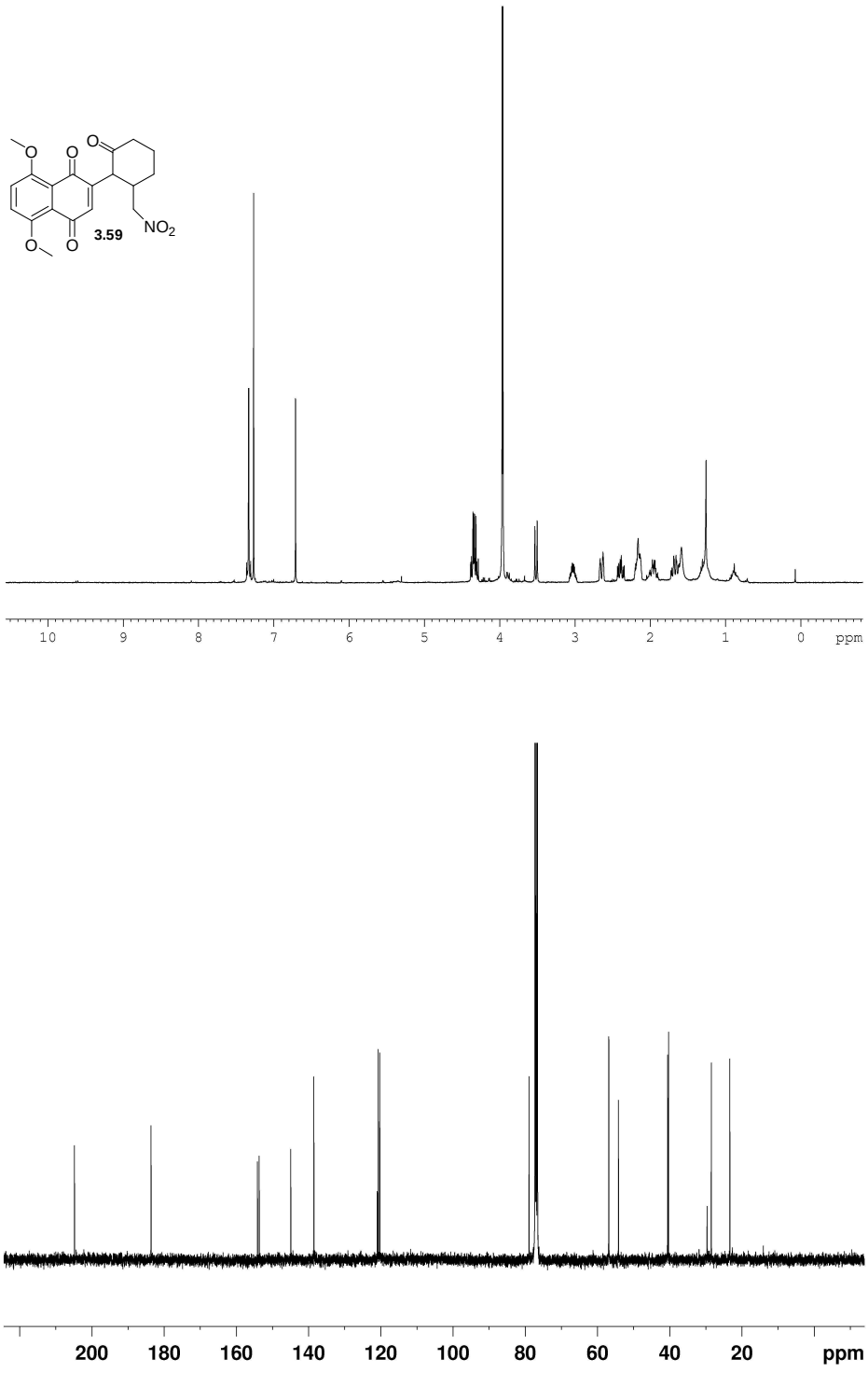


Figure A3.25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.59**.

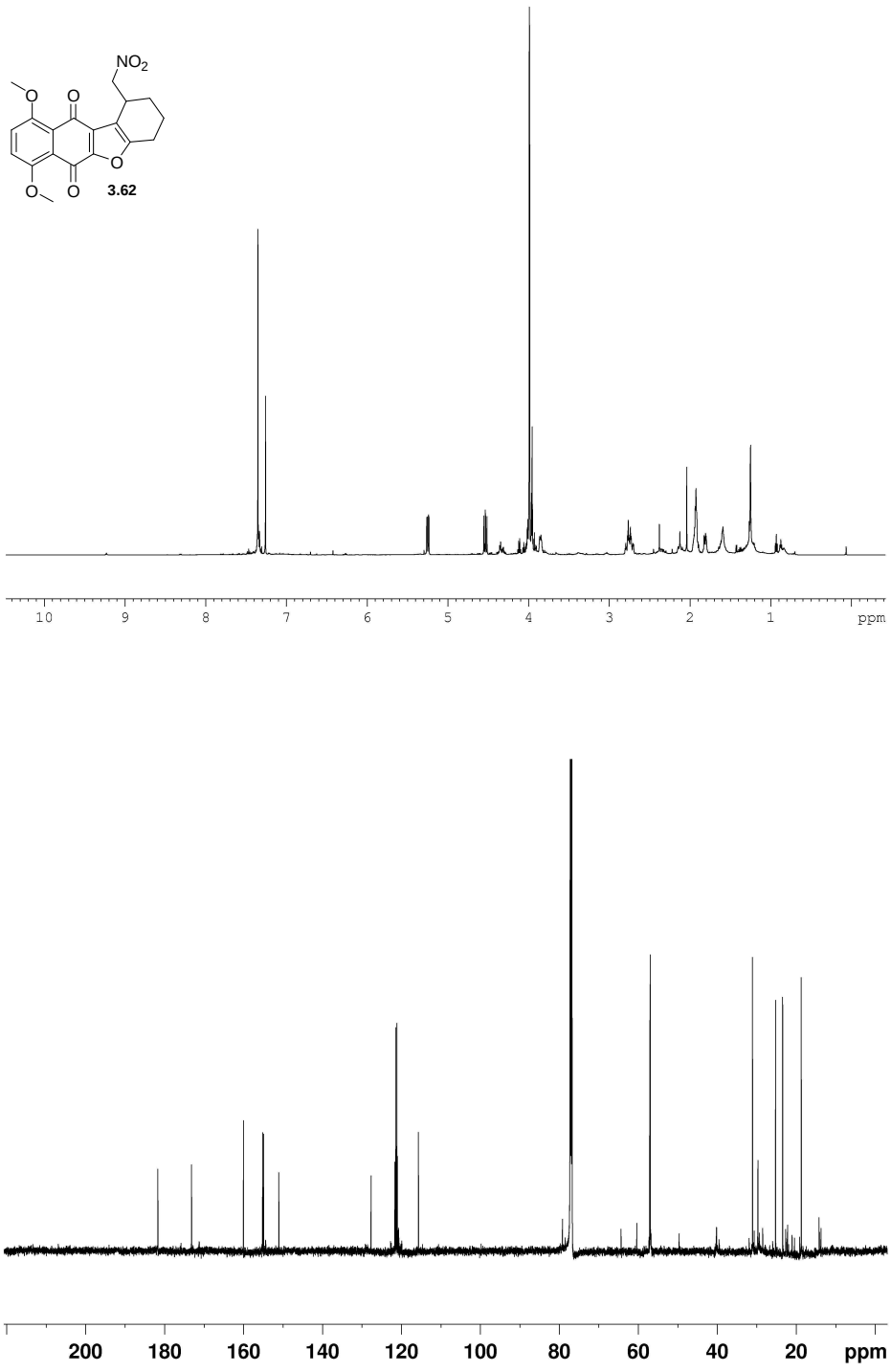


Figure A3.26. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.62.**

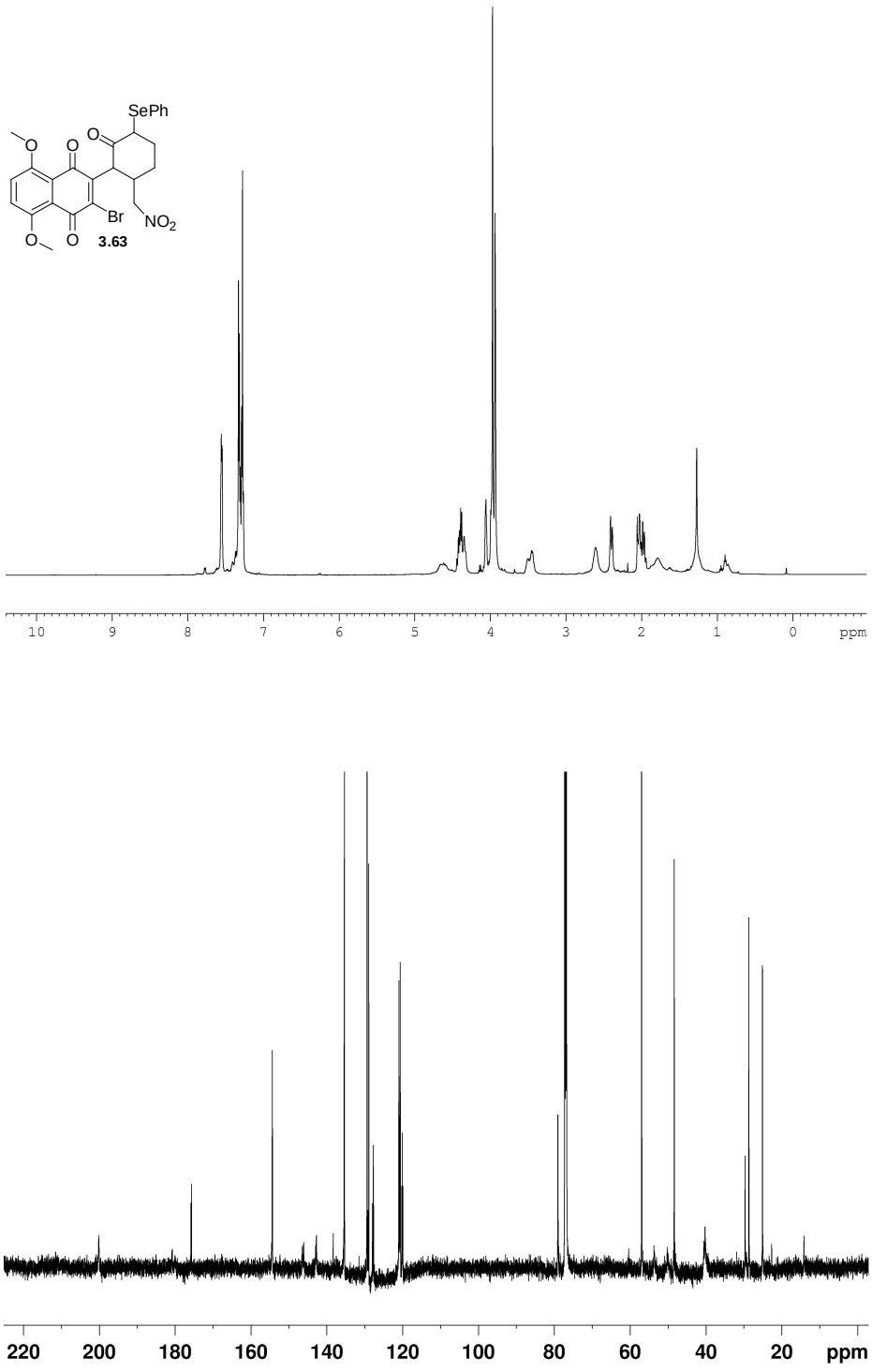


Figure A3.27. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.63**.

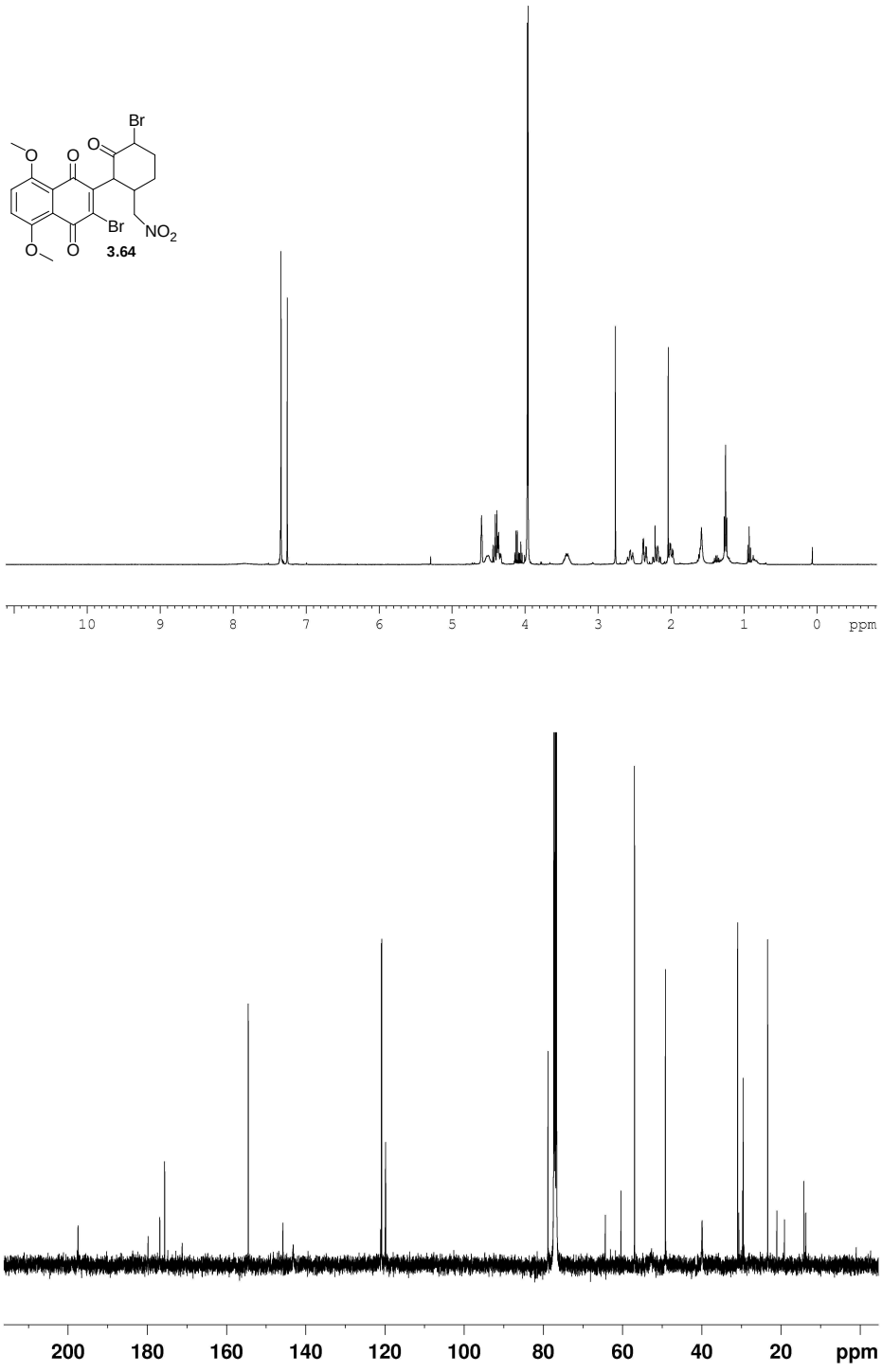


Figure A3.28. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.64**.

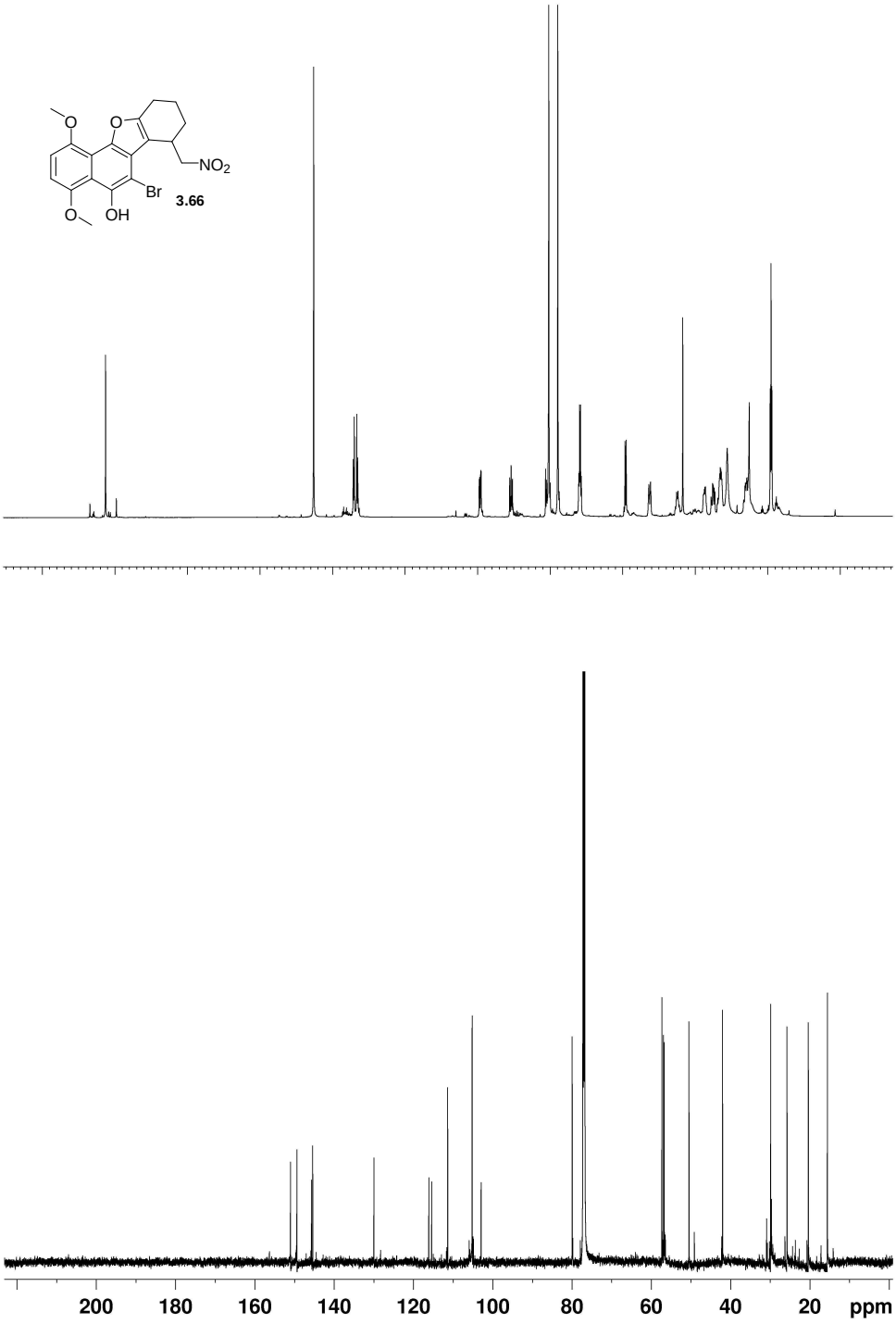


Figure A3.29. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.66**.

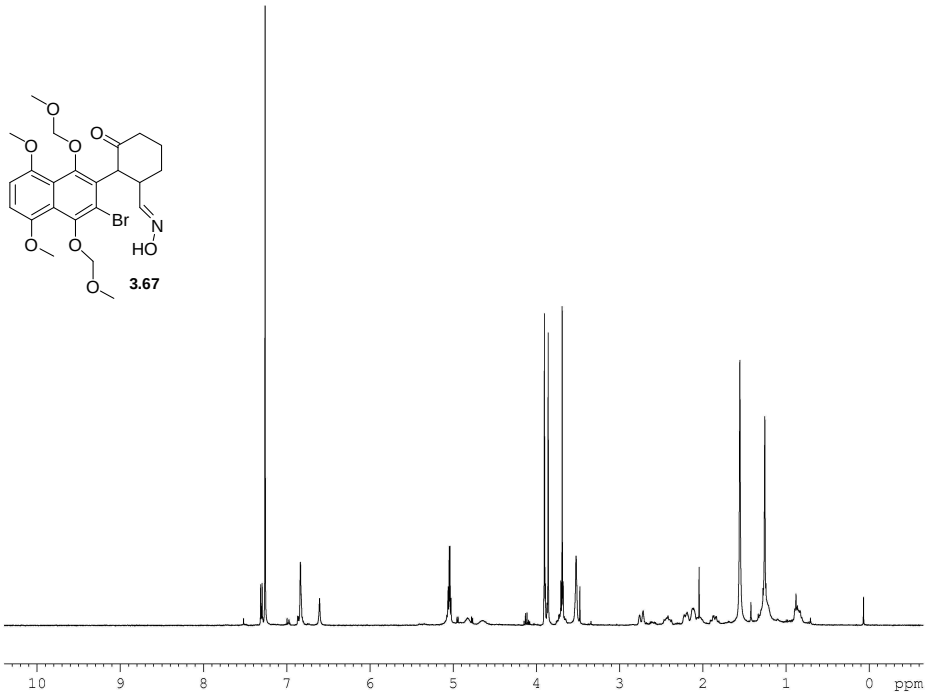


Figure A3.30. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.67**.

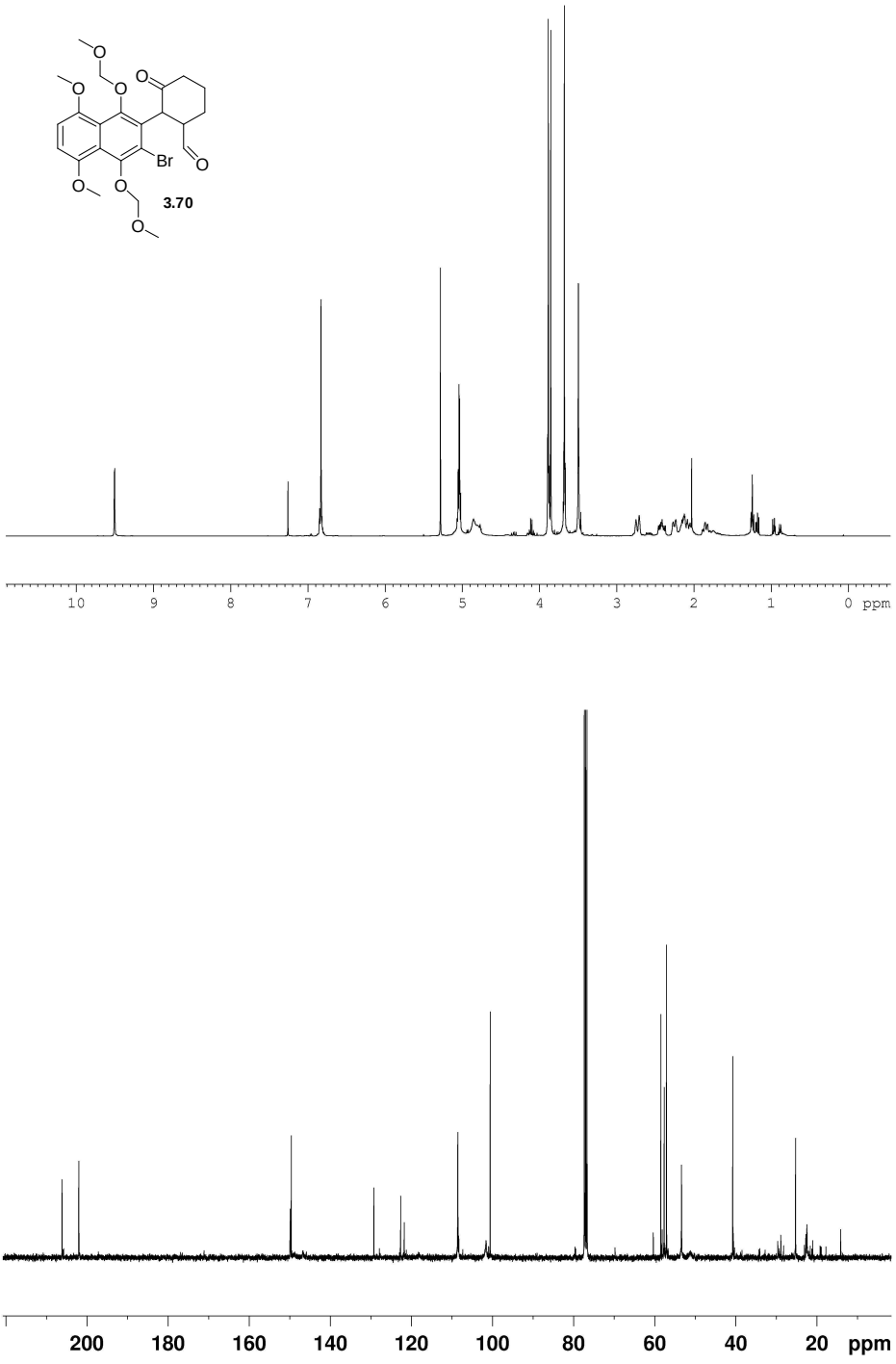


Figure A3.31. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.70**.

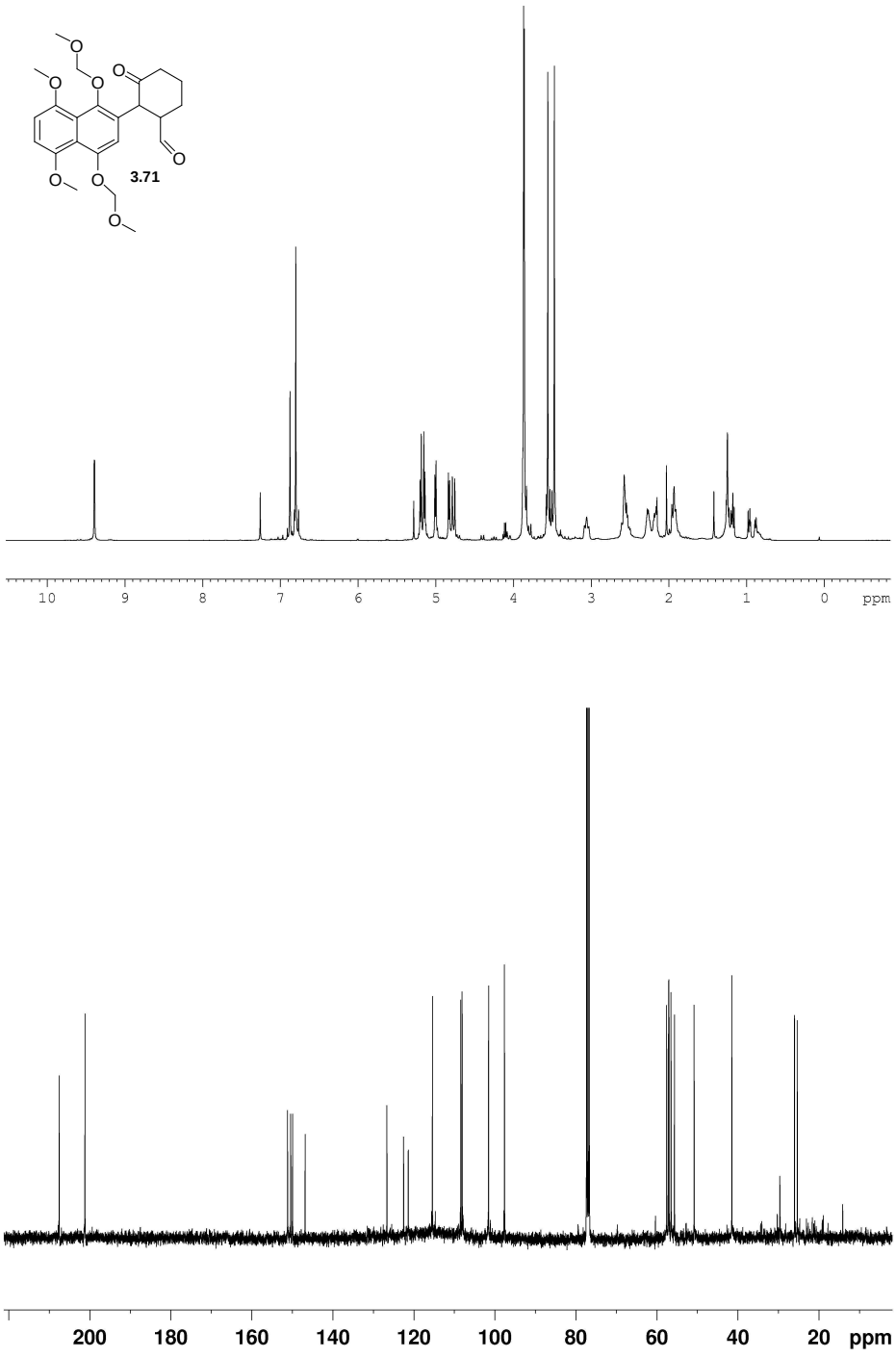


Figure A3.32. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.71**.

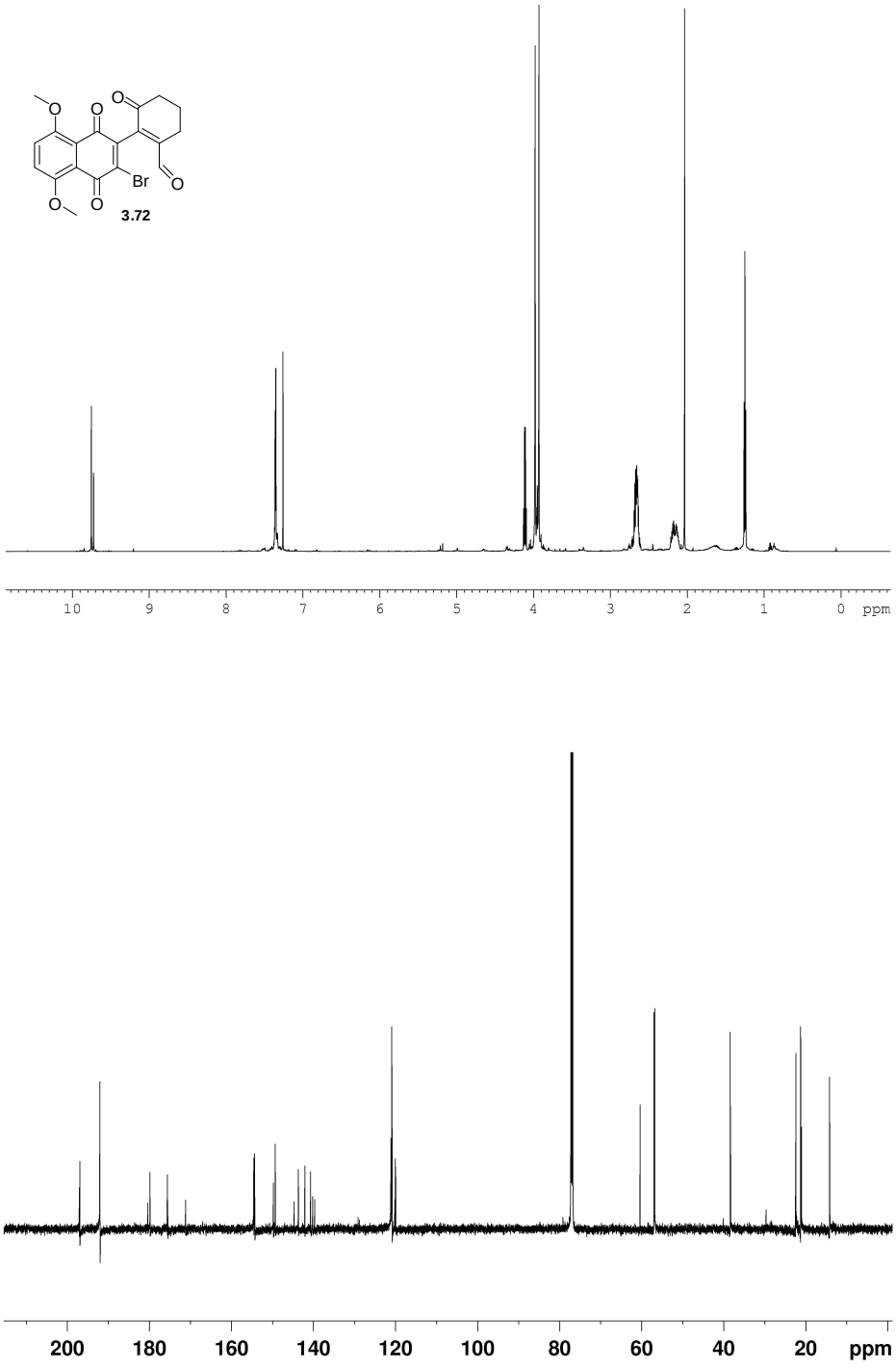


Figure A3.33. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.72**.

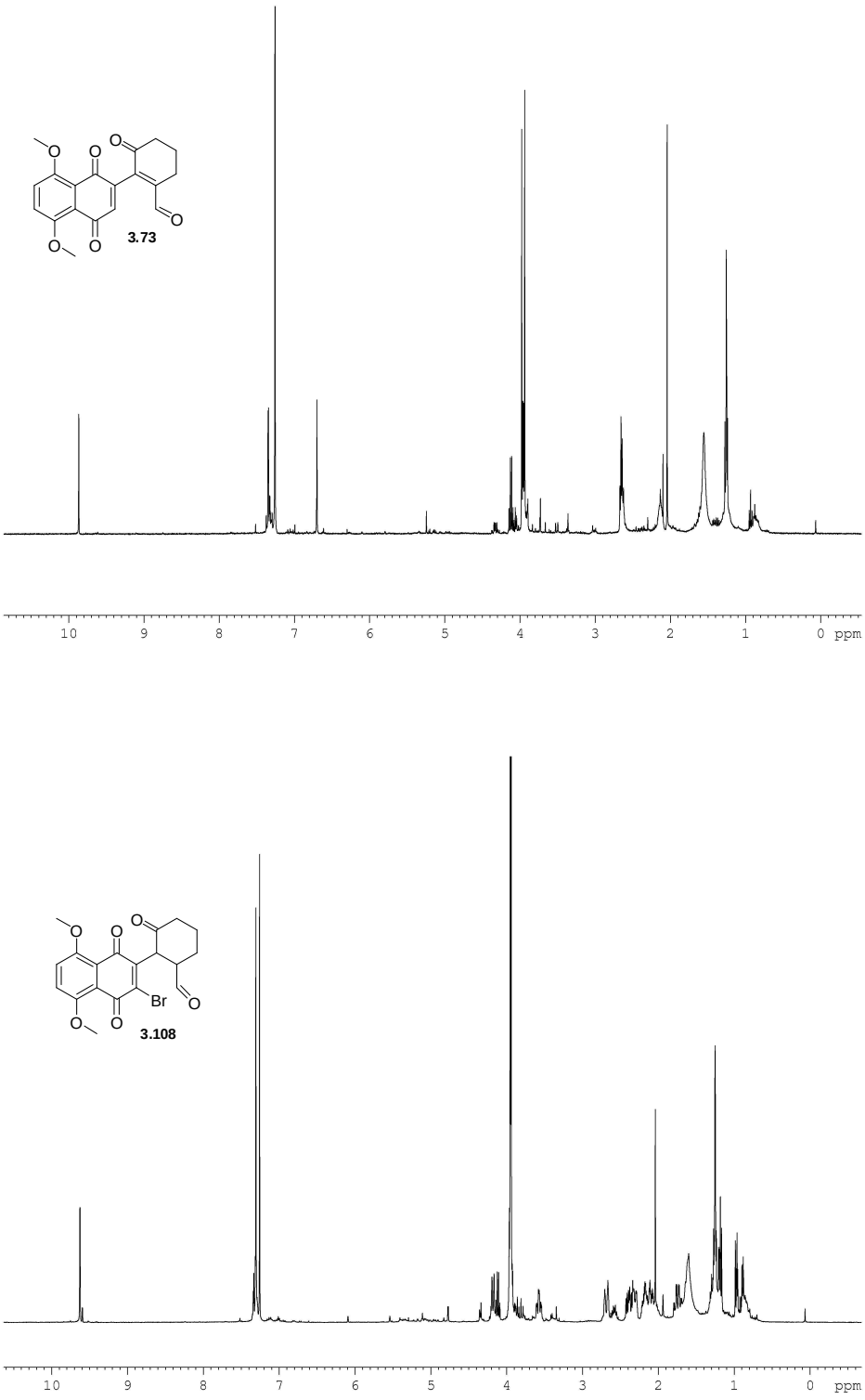


Figure A3.34. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound **3.73** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.108**.

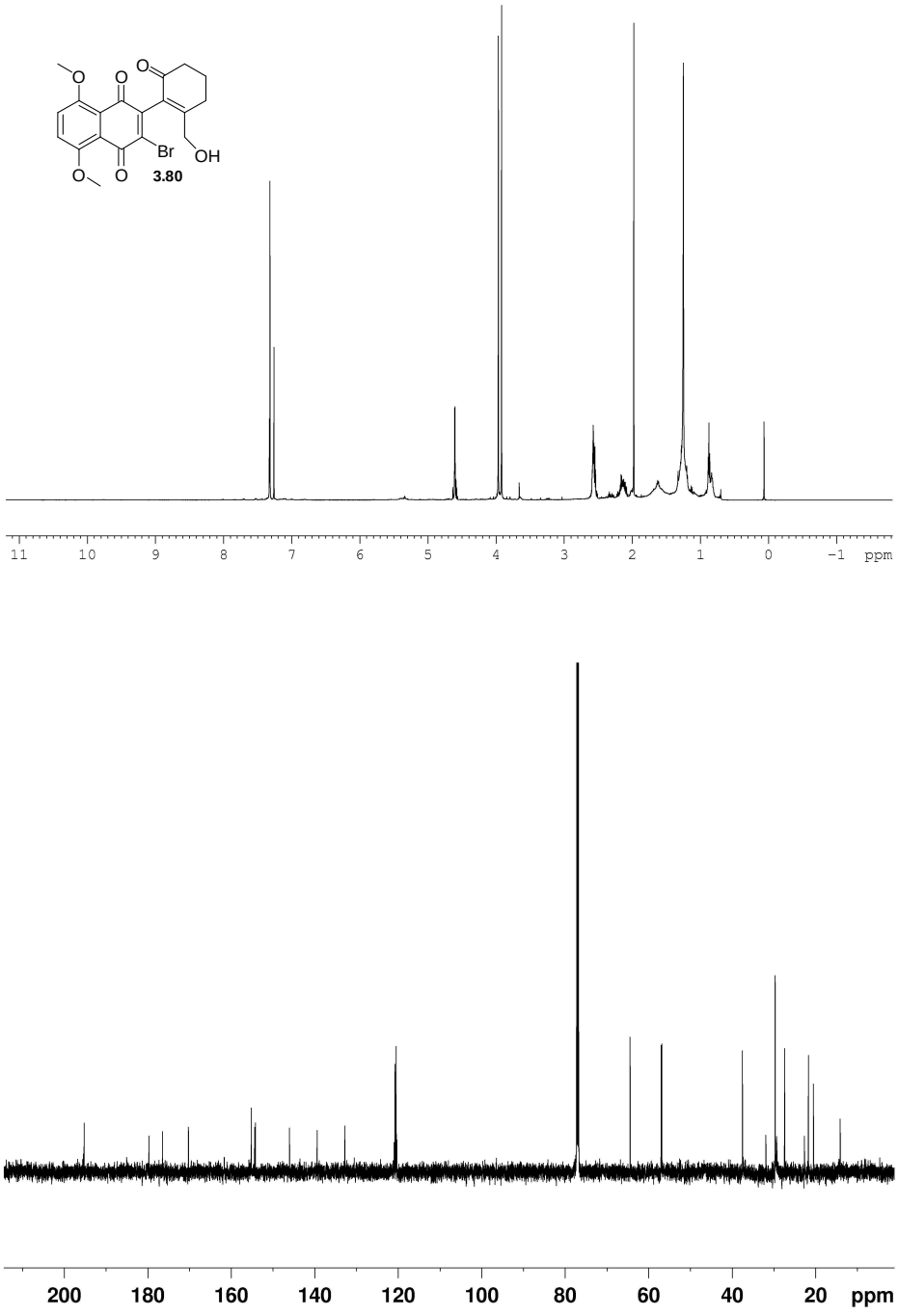
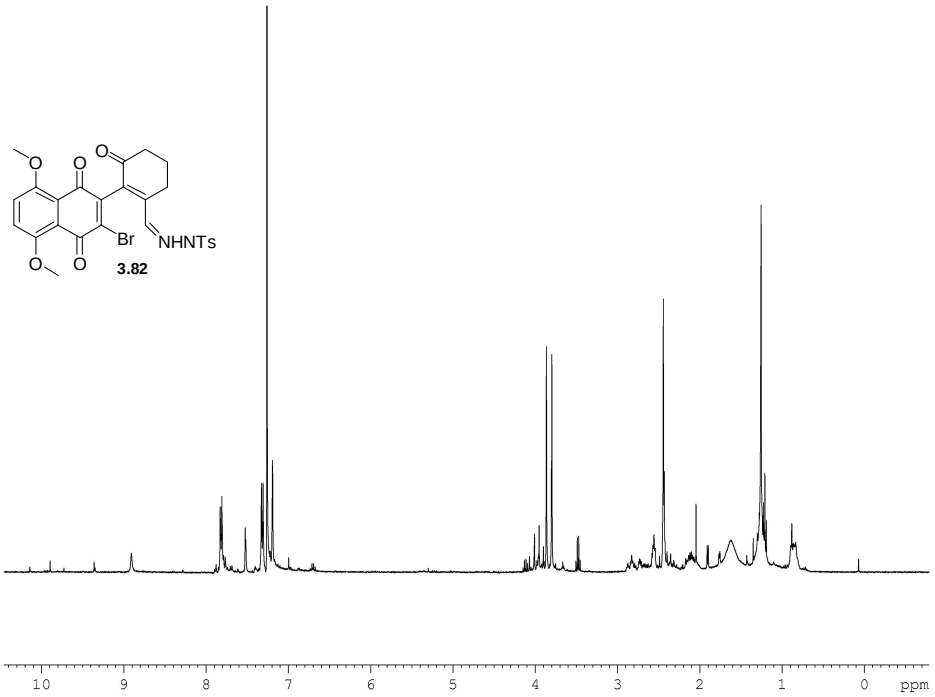


Figure A3.35. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.80**.



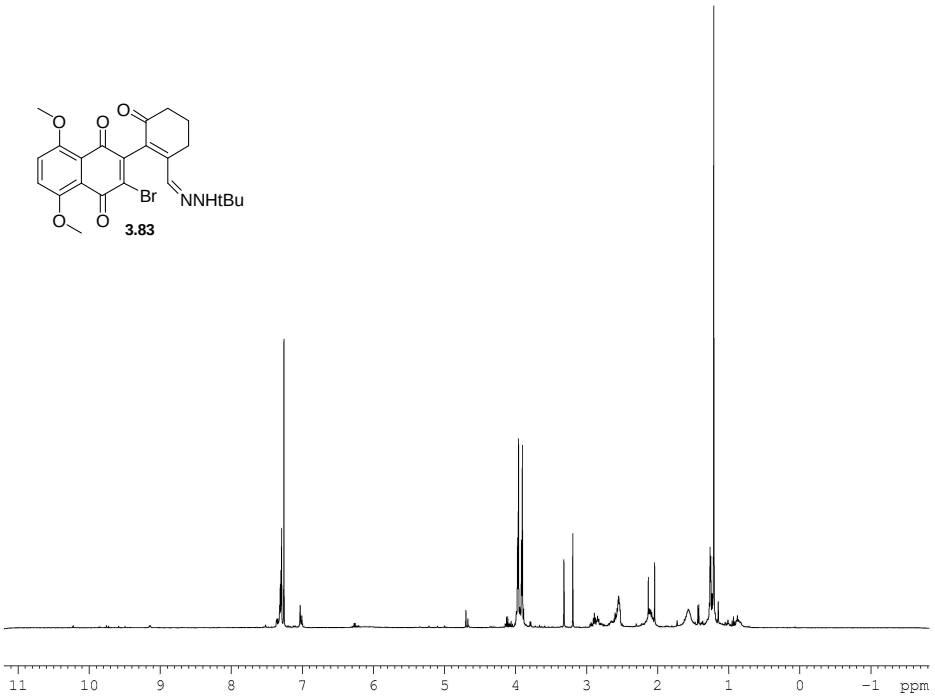


Figure A3.36. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.82** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.83**.

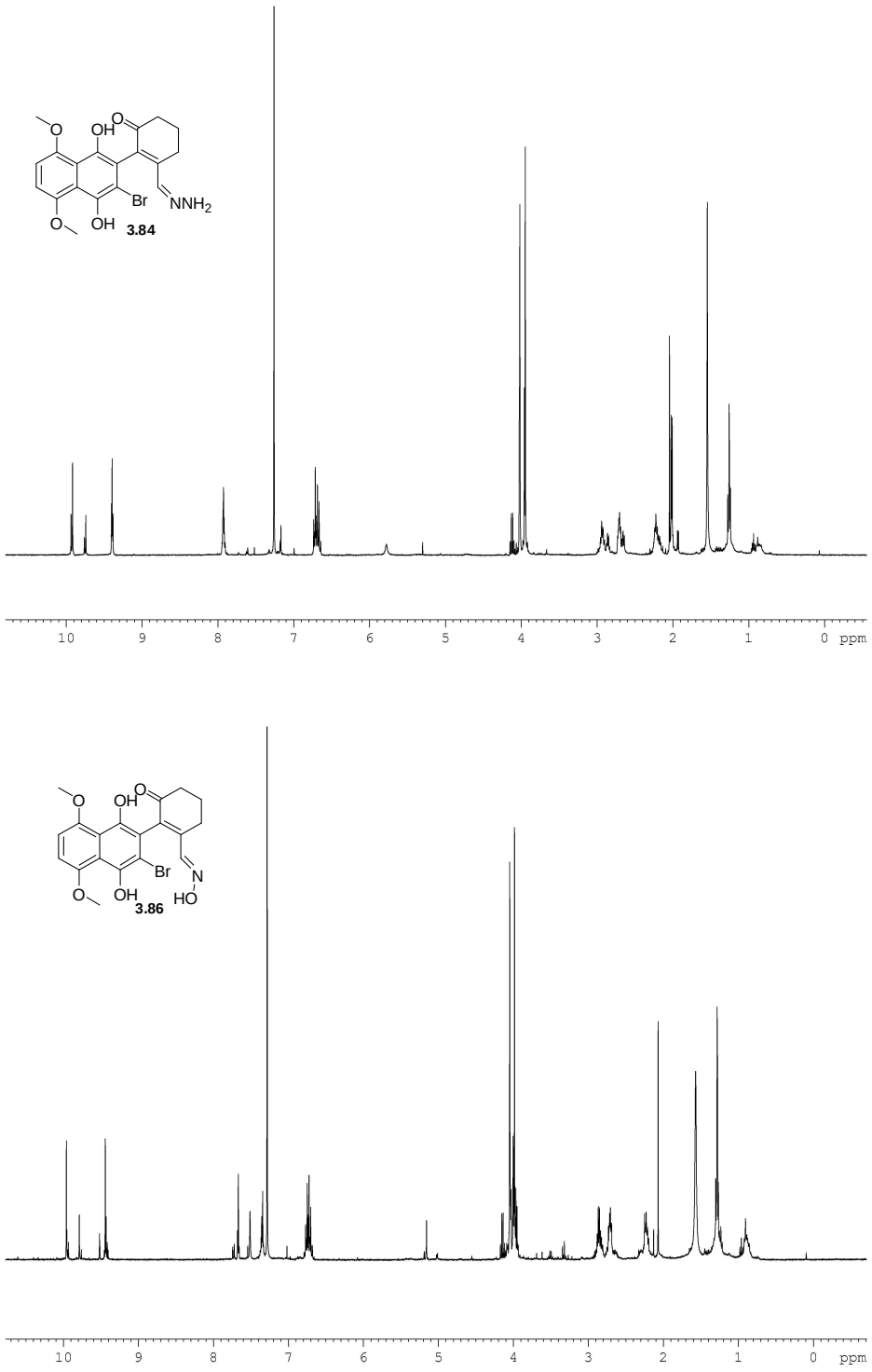


Figure A3.37. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.84** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.86**.

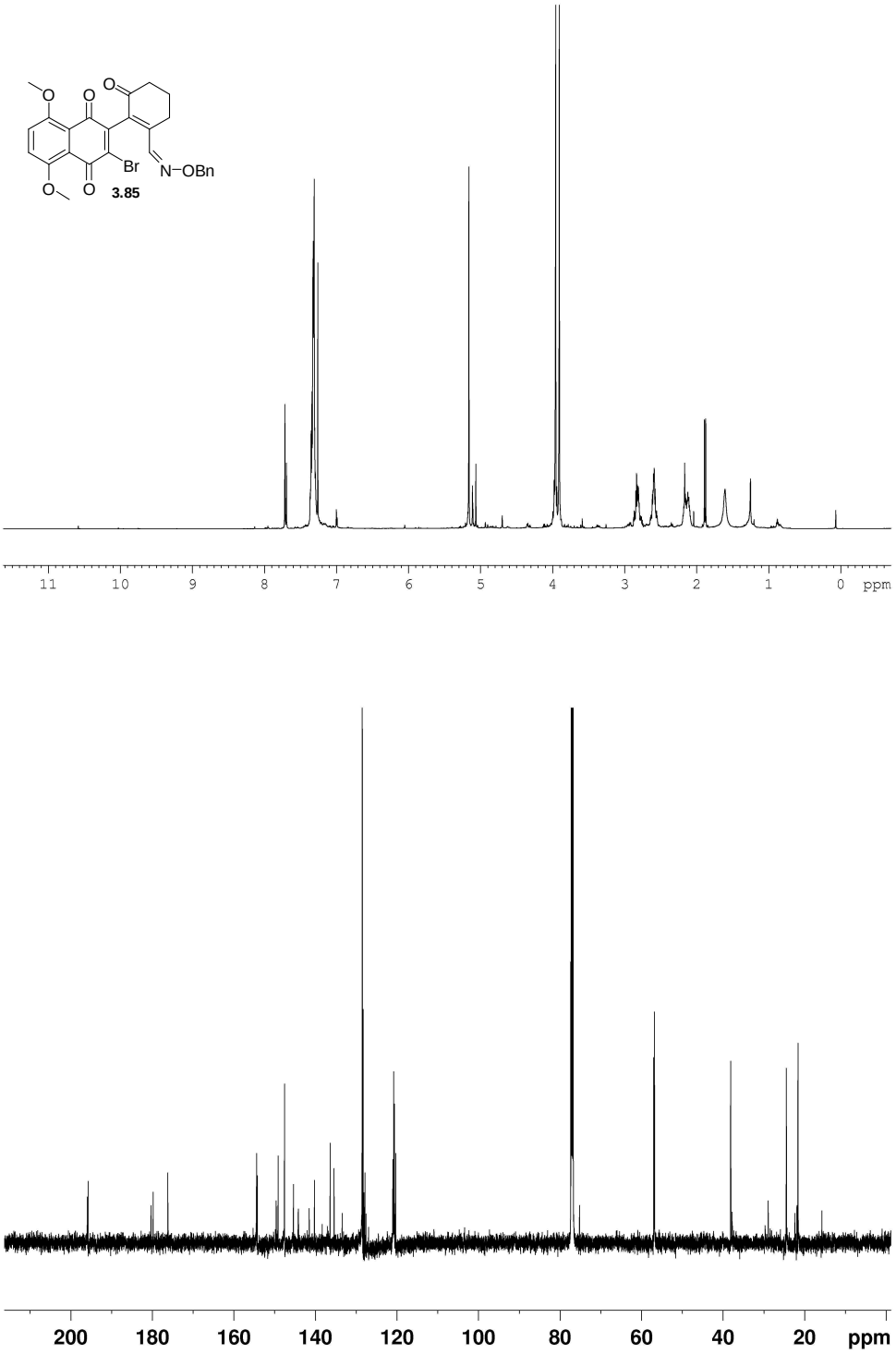


Figure A3.38. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.85**.

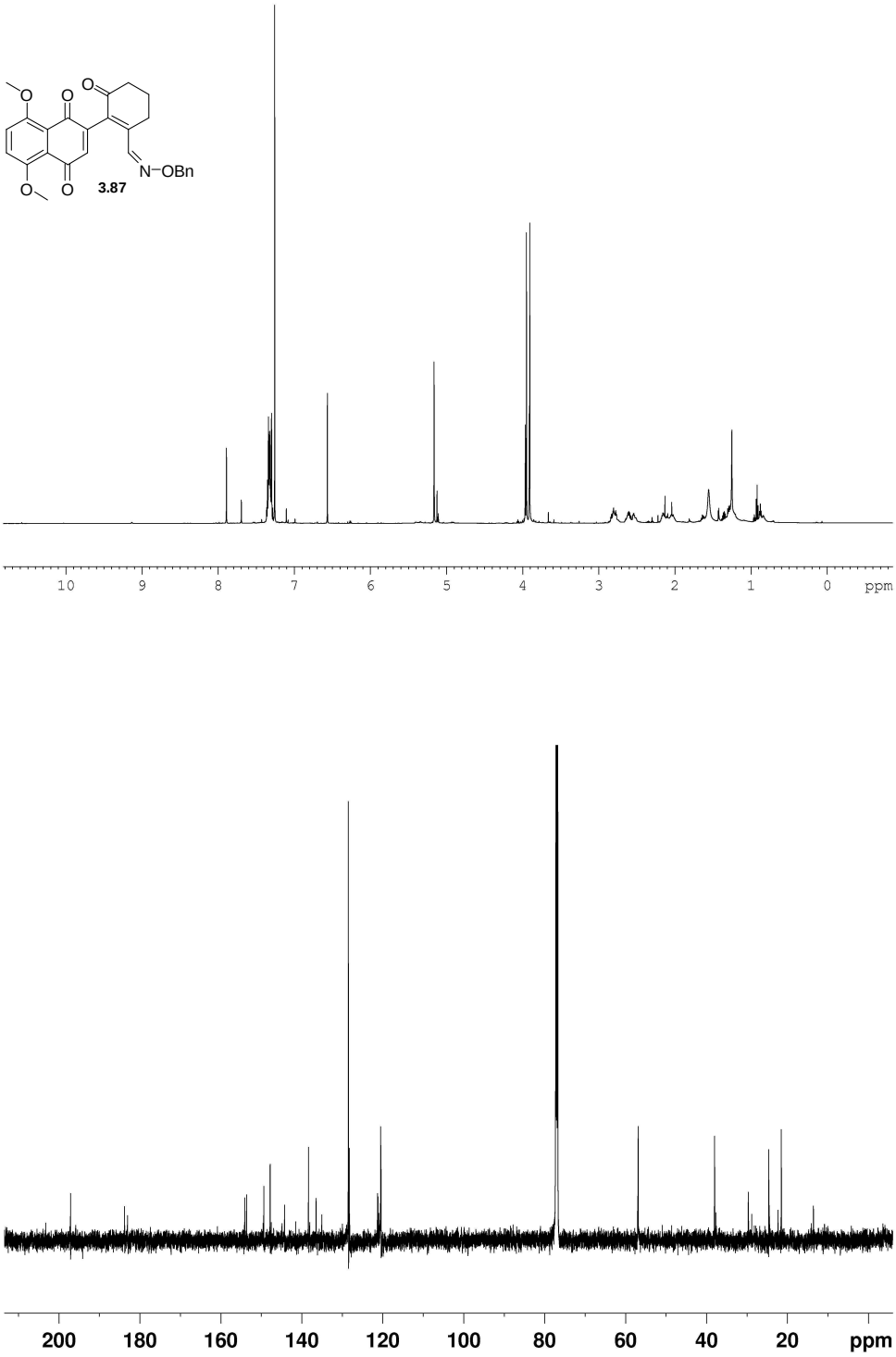


Figure A3.39. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.87**.

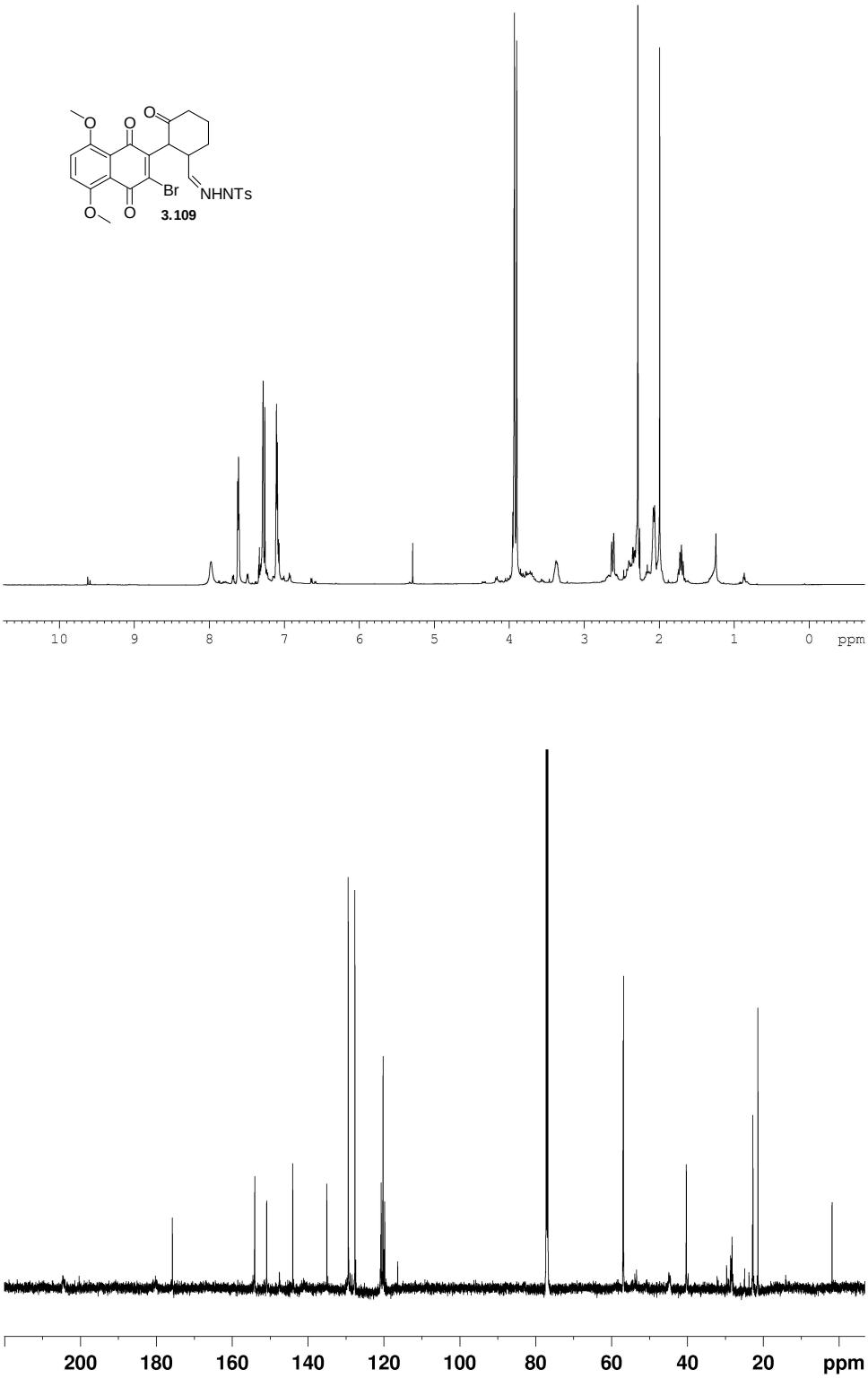


Figure A3.40. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.109**.

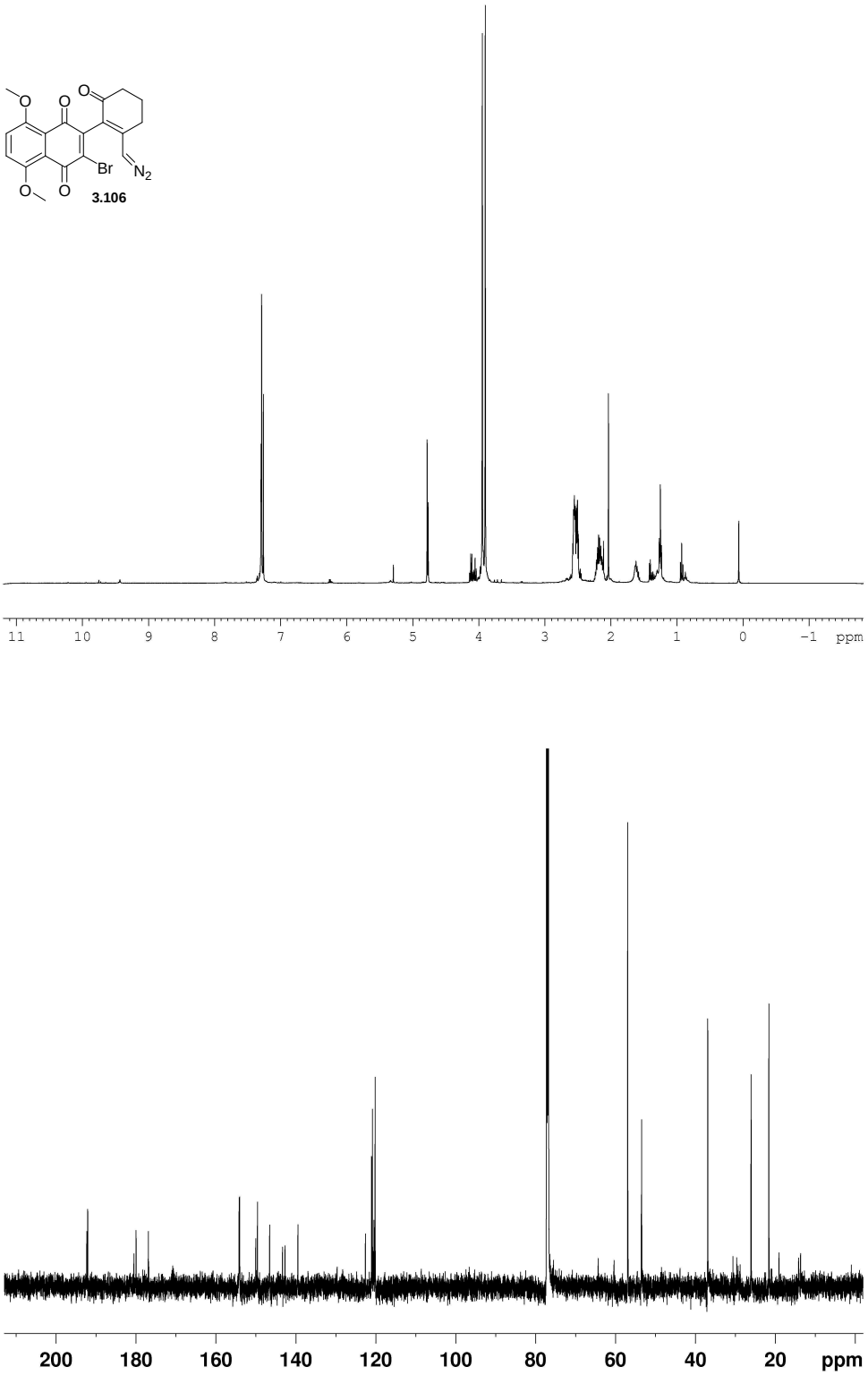


Figure A3.41. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.106**.

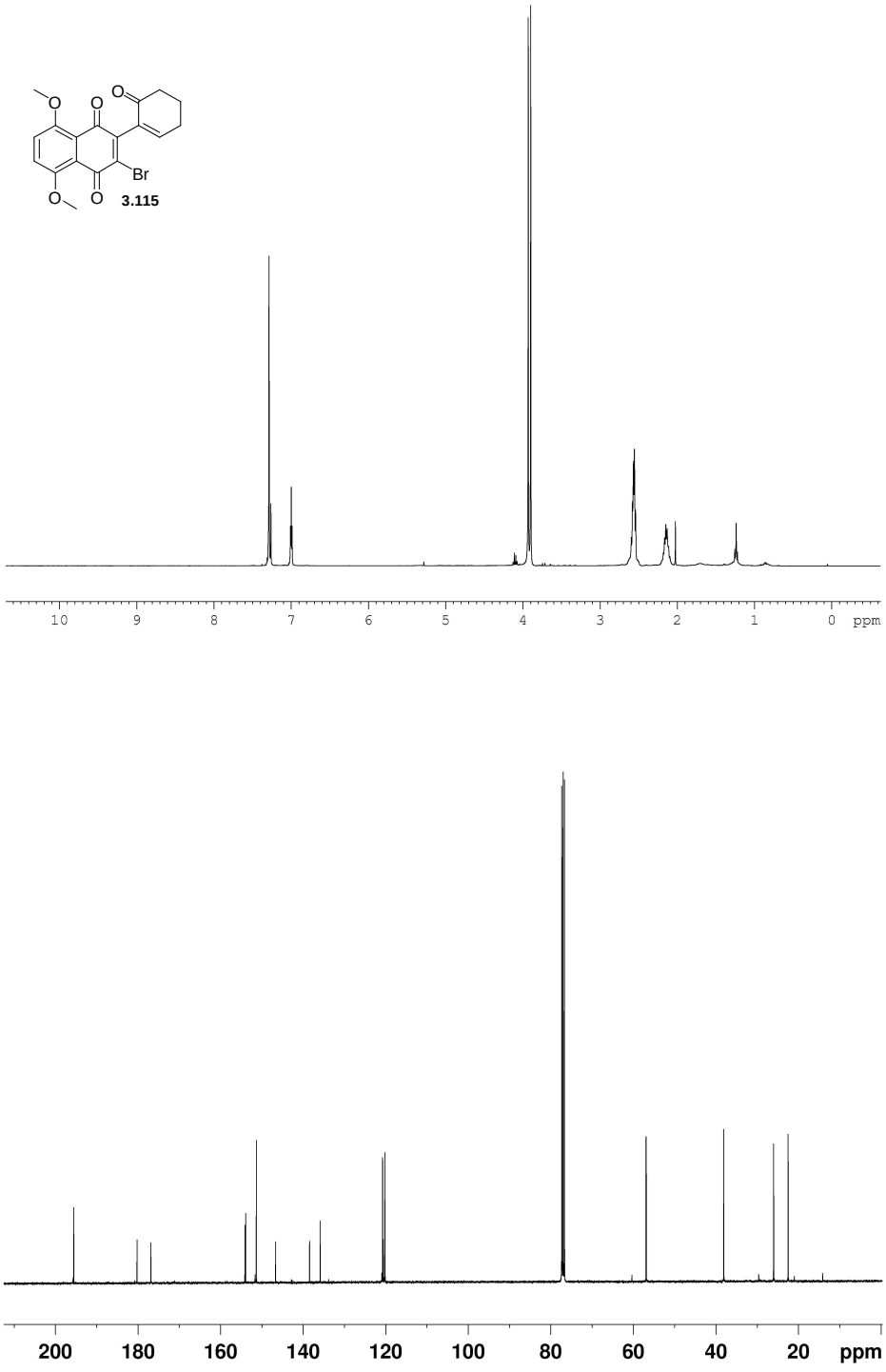
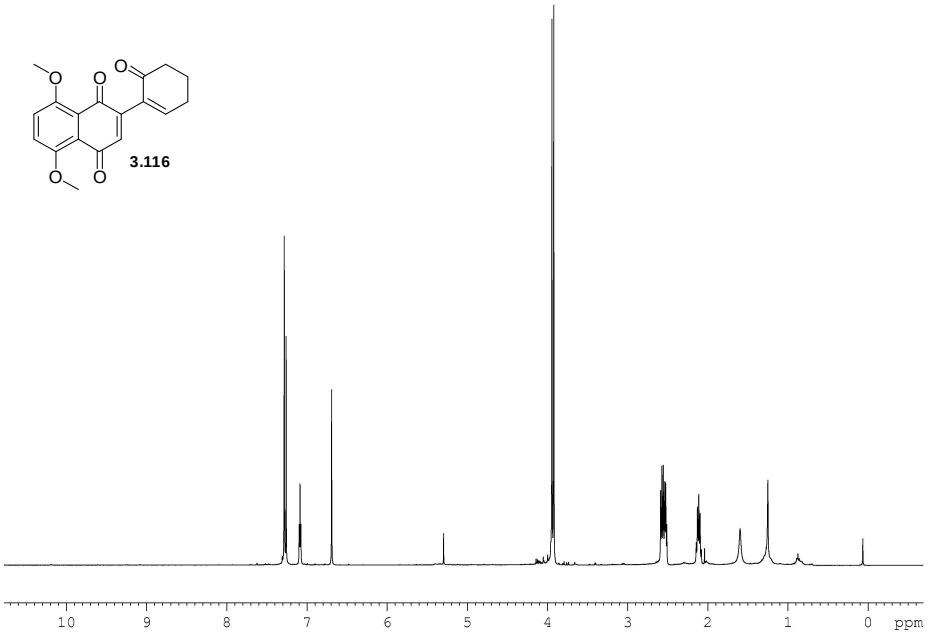


Figure A3.42. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3.115**.



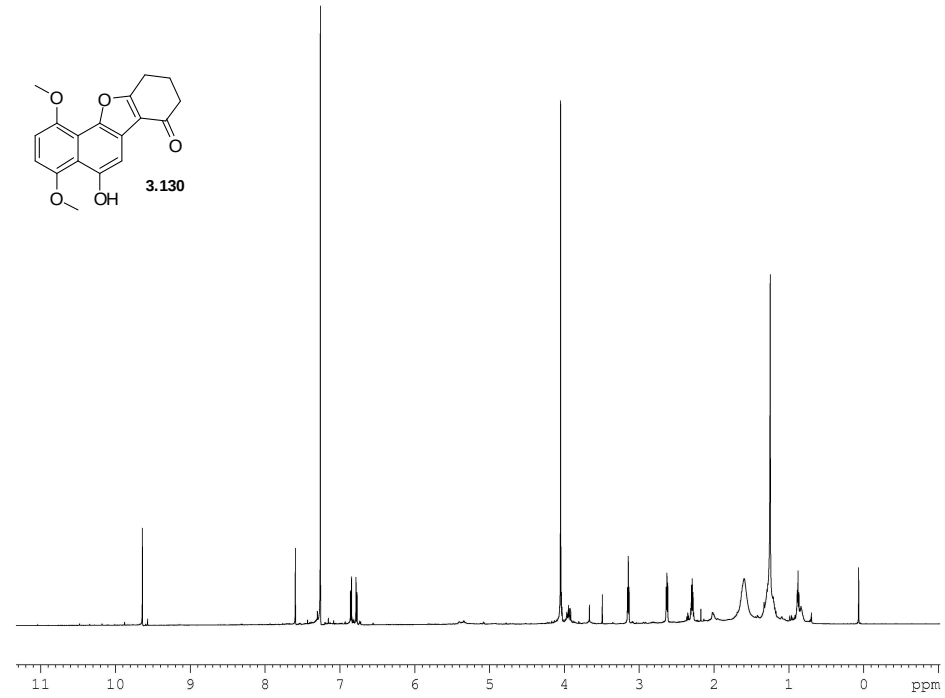


Figure A3.43. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.116** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3.130**.

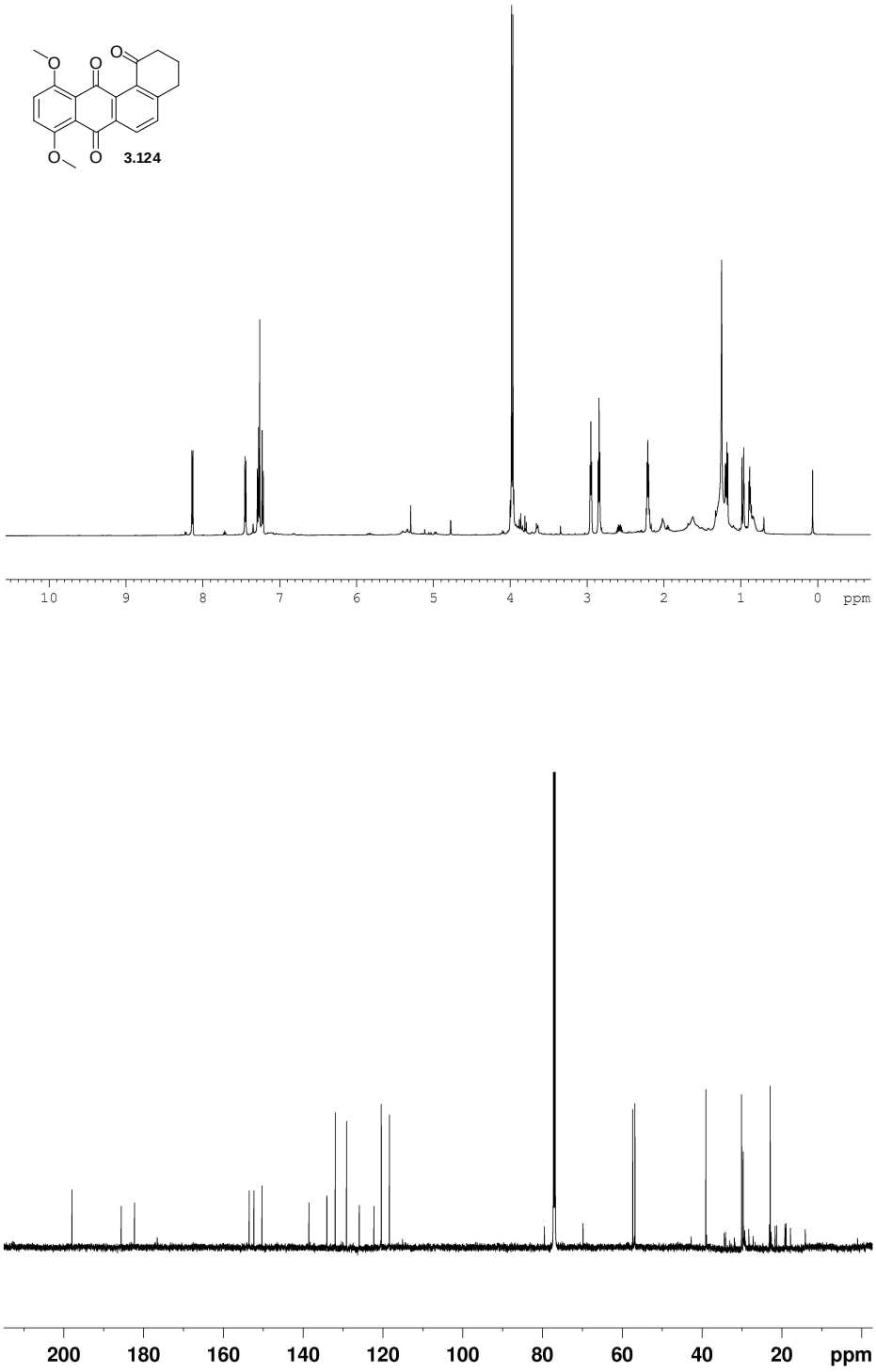


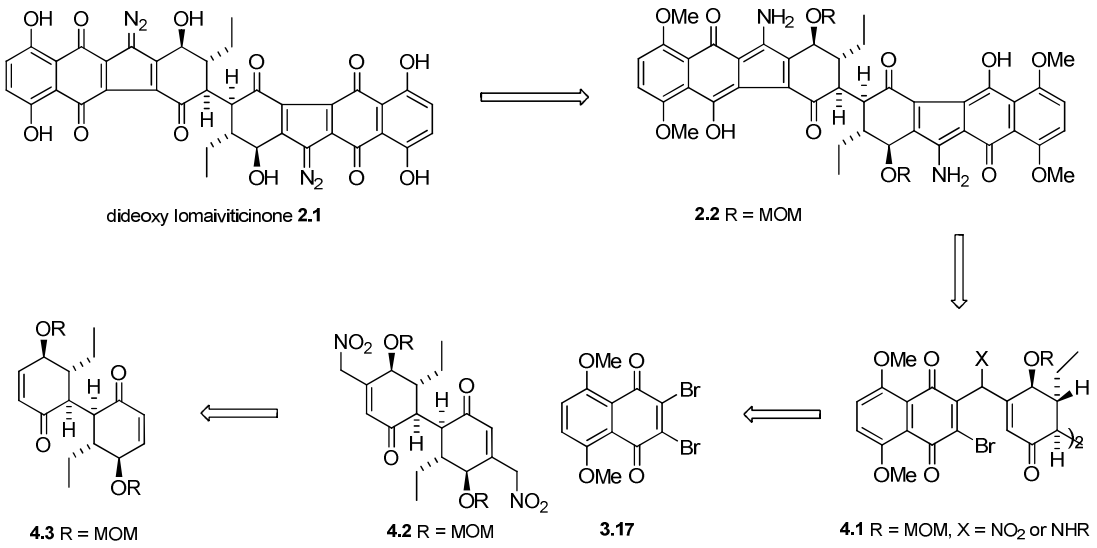
Figure A3.44. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **3.124**.

CHAPTER IV

SECOND GENERATION APPROACH

Introduction

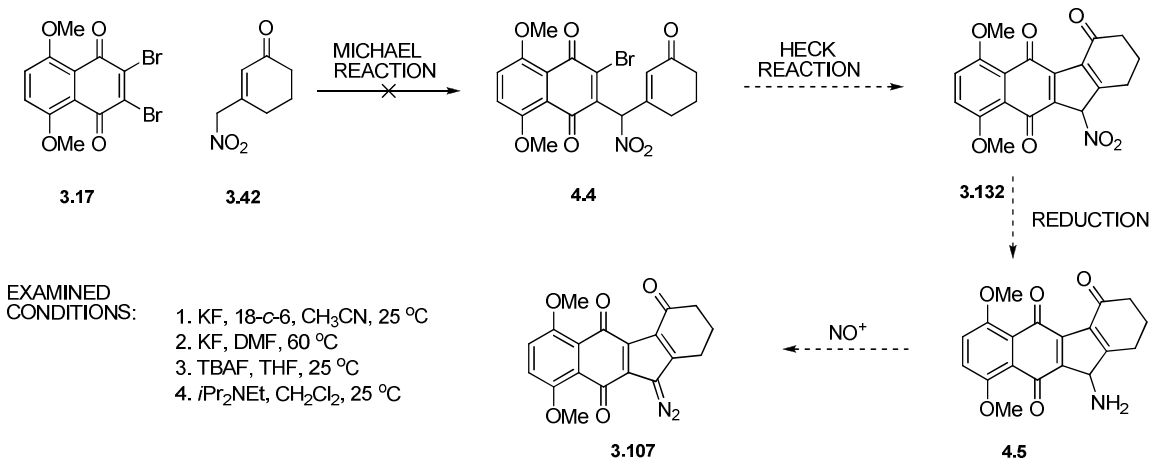
We became convinced that the number of possibilities to achieve the synthesis of dideoxy lomaiviticinone through our first generation approach had been exhausted, and thus we began to design a new route. Simultaneously, we desired to utilize a pathway based on our previously synthesized building blocks bis-enone **4.3** and quinone **3.17** and to continue exploration of a two-directional strategy leading to generation of bis-amine **2.2** (Scheme 4.1). Compared to our initial approach, our new plan established construction of the cyclopentenone ring of dideoxy lomaiviticinone with the order of bond formation reversed. We hoped that with preparation of nitroenone **4.2** we would be able to examine the double Michael addition reaction between **4.2** and dibromoquinone **3.17** with the goal of generating bis-nitroenone **4.1** or an equivalent isomer. A palladium – catalyzed Heck coupling was planned to form the cyclopentenone ring of bis-amine **2.2**. This new strategy had two major advantages: late stage study continuation from previously synthesized material and examination of our biosynthetic hypothesis were ensured.



Scheme 4.1. Second generation approach.

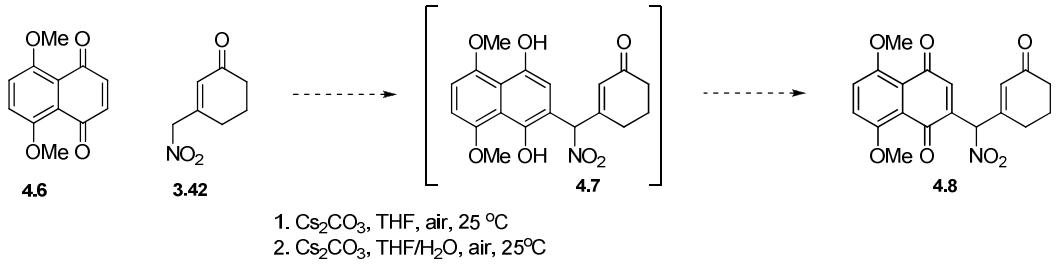
Michael Addition Model Studies

We began this series of experiments using nitroenone **3.42** as a model system (Scheme 4.2). The assumption was made that Michael addition of **3.42** into dibromoquinone **3.17** would result in addition-elimination reaction to give bromoenone **4.4**. A short sequence would then lead to diazoquinone **3.107**. A number of conditions were evaluated, but unfortunately only decomposition of both **3.17** and **3.42** was observed.



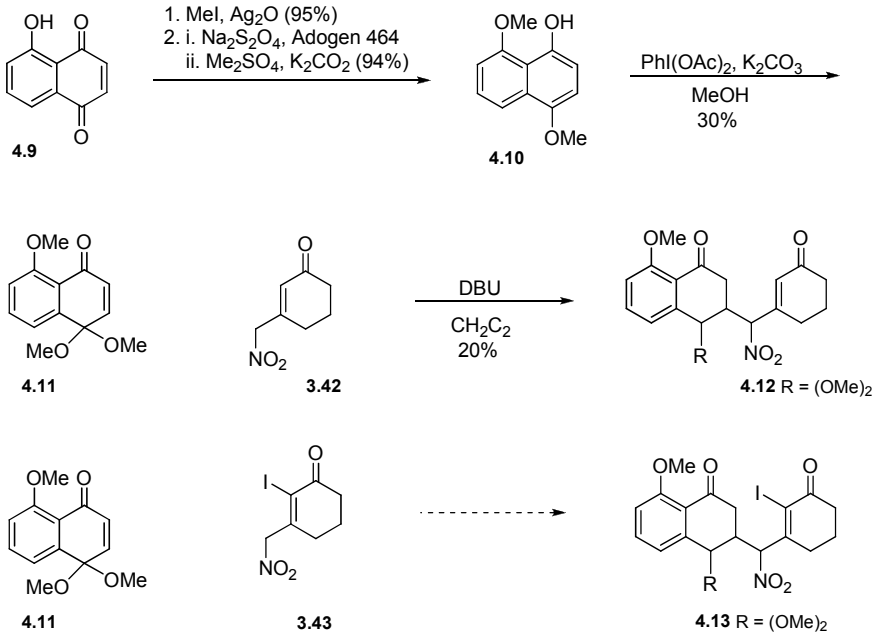
Scheme 4.2. Failed Michael addition.

In an attempt to understand the reason for the unsuccessful Michael reaction shown in Scheme 4.2, a series of experiments aimed at examining base lability were undertaken. First nitroenone **3.42** was treated with known quinone **4.6** (Scheme 4.3), and while bases with high pK_b led to immediate decomposition of both **4.6** and **3.42**, treatment of **4.6** and **3.42** with Cs_2CO_3 resulted in recovery of a small amount of quinone **4.6**.[1]



Scheme 4.3. Michael addition to quinone **4.6**.

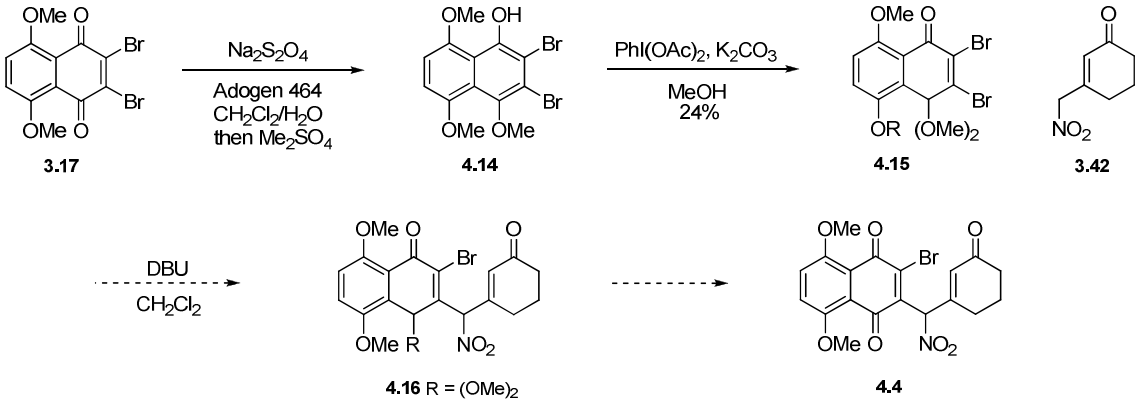
These results showed that more than disfavored steric interactions were likely responsible for the lack of success in generation of **4.8**. Therefore, the masked quinone, dimethylketal juglone **4.11** was prepared (Scheme 4.4),[2,3] and successful DBU- mediated addition of nitroenone **3.42** to **4.11** provided enone **4.12**. Formation of **4.12** in low yield suggested that not only high reactivity and instability of quinones **3.17** and **4.6** or the undesired retro-Michael reaction but also sensitivity of **3.42** under basic conditions were responsible for the failed synthesis of **4.4** and **4.8**. Simultaneously, we rationalized that disfavored steric interactions led to the failed attempt at forming iodoenone **4.13**.



Scheme 4.4. Synthesis of enone **4.12**.

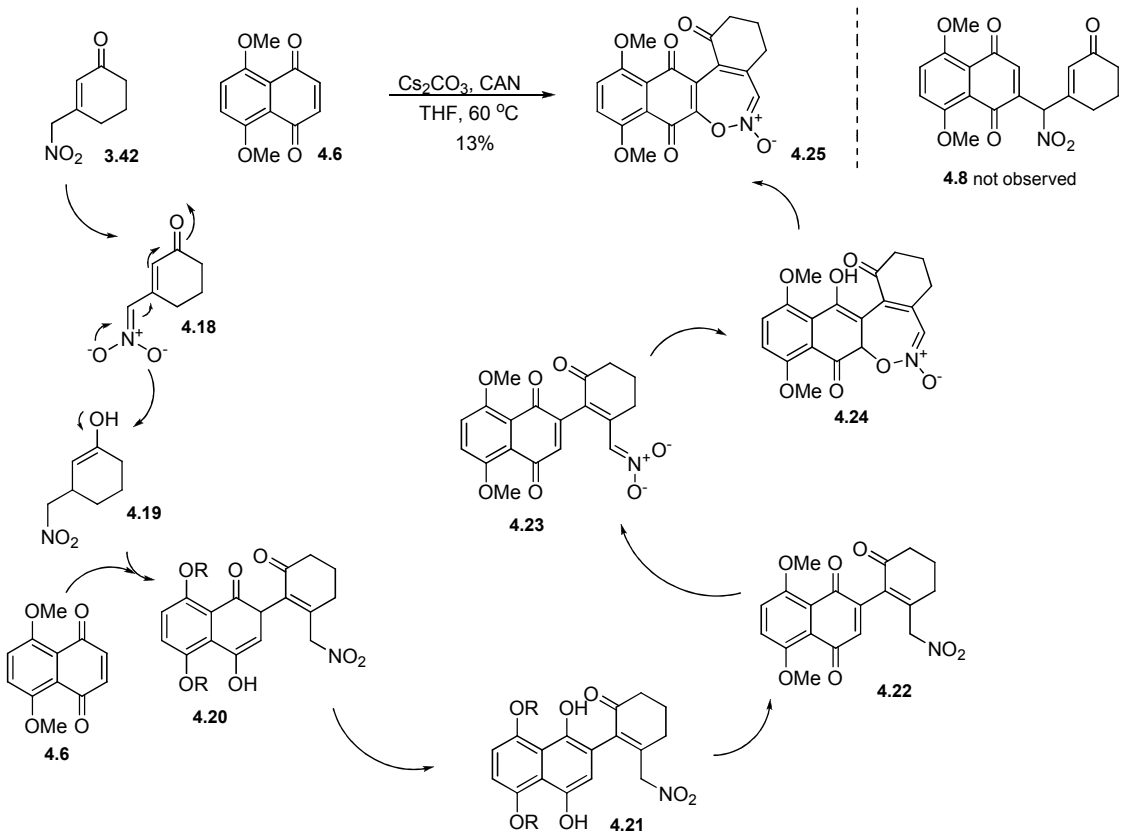
Despite limited success, we attempted to synthesize dibromoketal **4.15** (Scheme 4.5). Although capricious in nature, transformation of **4.14** with $PhI(OAc)_2$ and K_2CO_3 in MeOH (yields between 20-25%) provided the highly unstable product **4.15**.

Disapointigly, Michael addition of **3.42** into **4.15** failed to produce desired enone **4.16** and only small amount of **4.15** was recovered.



Scheme 4.5. Failed attempt to synthesize quinone **4.4**.

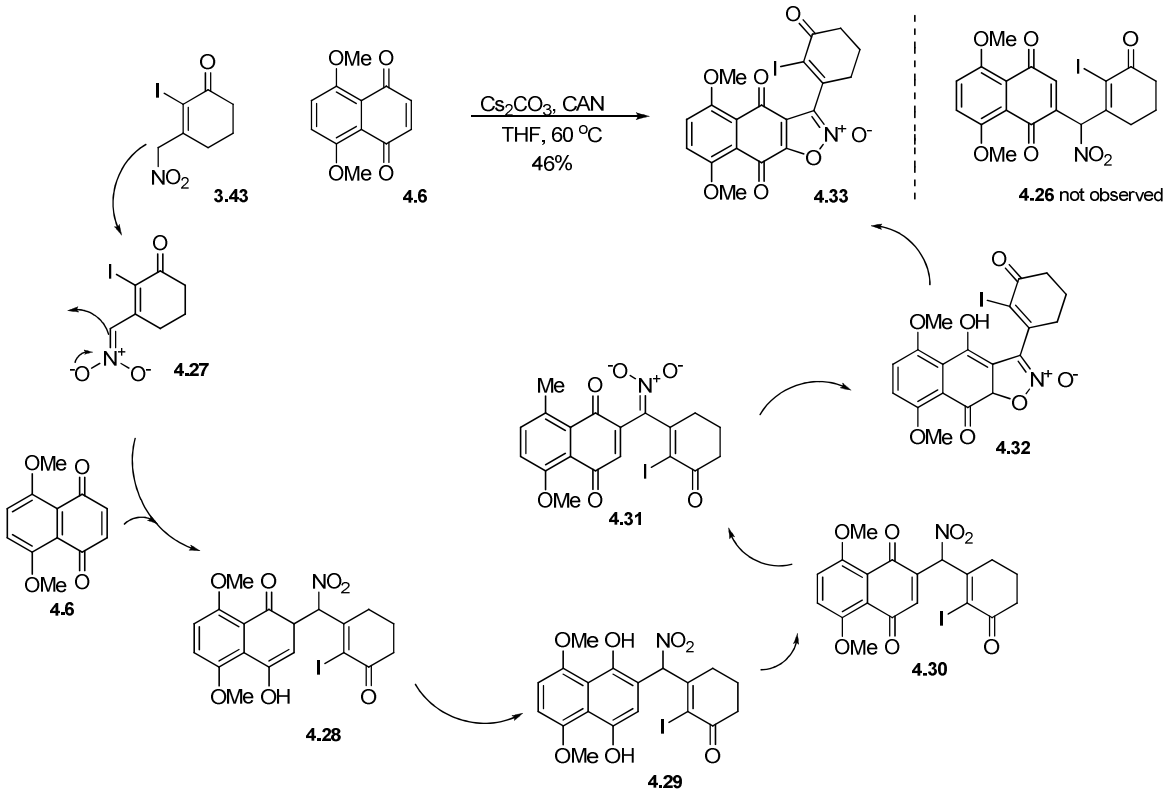
As previously mentioned, the high reactivity of quinones **3.17** and **4.6** (through oxidation state changes) was believed to be partially responsible for the outcomes of experiments shown in Schemes 4.2 and 4.3. To better control its behavior, we decided to react **4.6** with nitroenone **3.42** in the presence of CAN (Scheme 4.6), and unexpectedly we isolated nitronate **4.25**, which contained 6,6,7,6 ring system. A thorough literature analysis revealed no precedence for the synthesis of similar structures. Mechanistically, we believe that formation of **4.25** results from addition of enol **4.19** to quinone **4.6**. Isomerisation of **4.20** to give hydroquinone **4.21** followed by oxidation provides quinone **4.22**. Deprotonation of **4.22**, nitronate formation and 1,4-addition leads to semiquinone **4.24**, and subsequent isomerisation and oxidation affords nitronate **4.25**.



Scheme 4.6. Unexpected formation of nitronate **4.25**.

Analysis of this mechanistic pathway prompted us to examine the same transformation with use of iodoenone **3.43** (Scheme 4.7). We hoped that the presence of a blocking element in the form of an α-iodoenone would prevent formation of the undesired 7-member ring system and iodoquinone **4.26** would be produced. Unfortunately, instead of **4.26**, only nitronate **4.33** was isolated. Similar to the previous mechanistic pathway, we believe that formation of **4.33** starts with base-induced generation of nitronate **4.27**. Michael addition of **4.27** into quinone **4.6**, isomerisation of **4.28** and oxidation of **4.29** gives quinone **4.30**. A second Michael addition into the quinone ring system, this time with an oxygen as the donor, affords semiquinone **4.32**,

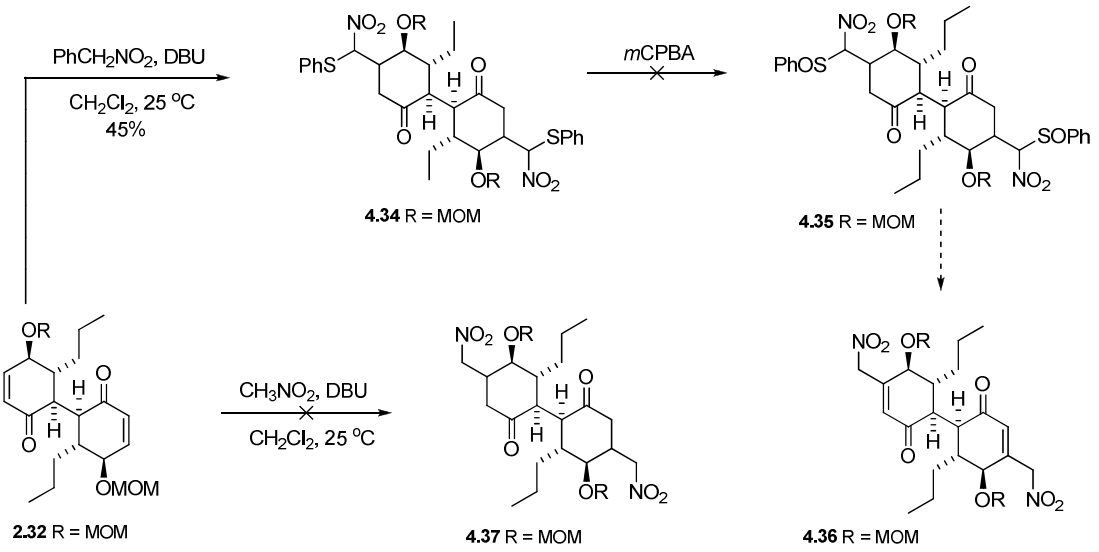
and consequently iodonitronate **4.33** is produced. Again, analysis of available literature data revealed a lack of reports describing similar structures. The only known cyclic 5-member nitronates have been generated via cycloaddition of alkenes which produced saturated systems.[4]



Scheme 4.7. Unexpected formation of nitronate **4.33**.

Simultaneously, formation of bis-nitroenone **4.36** from bis-enone **2.32** was tested (Scheme 4.8). While preparation of bis-sulfide **4.34** proceeded smoothly and desired product could be obtained in relatively satisfactory yield of 45% (without reaction optimization), its oxidation to sulfoxide **4.35** under previously established

conditions was met with failure. Similarly, DBU-mediated addition of nitromethane into bis-enone **2.31** did not produce the desired **4.37**, but rather led to formation of a compound whose structure, despite thorough analysis, could not be assigned. The described results were more than encouraging to discontinue this portion of our studies.

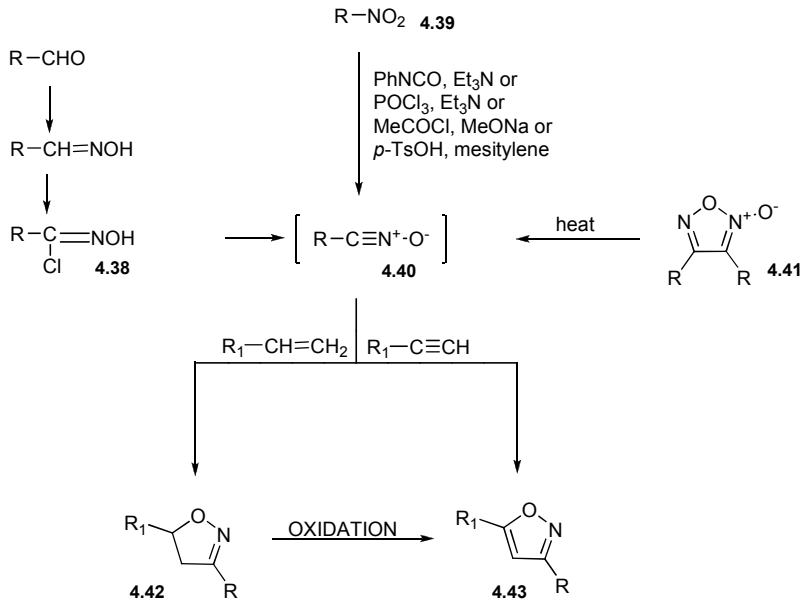


Scheme 4.8. Failed synthesis of nitroketone **4.37** and nitroenone **4.36**.

Isoxazole Model Studies

Isoxazoles as key structural elements in the design of natural product precursors have found numerous applications.[4,5] The choice of this functionality can be attributed to the simplicity of its introduction, inertness to various chemical manipulations and its ability to undergo further modifications leading to a variety of functional motifs (Scheme 4.9). Classically, isoxazoles have been derived *via* 1,3-cycloaddition of alkynes and nitrile oxides which can be formed in three general ways: through dehydration of

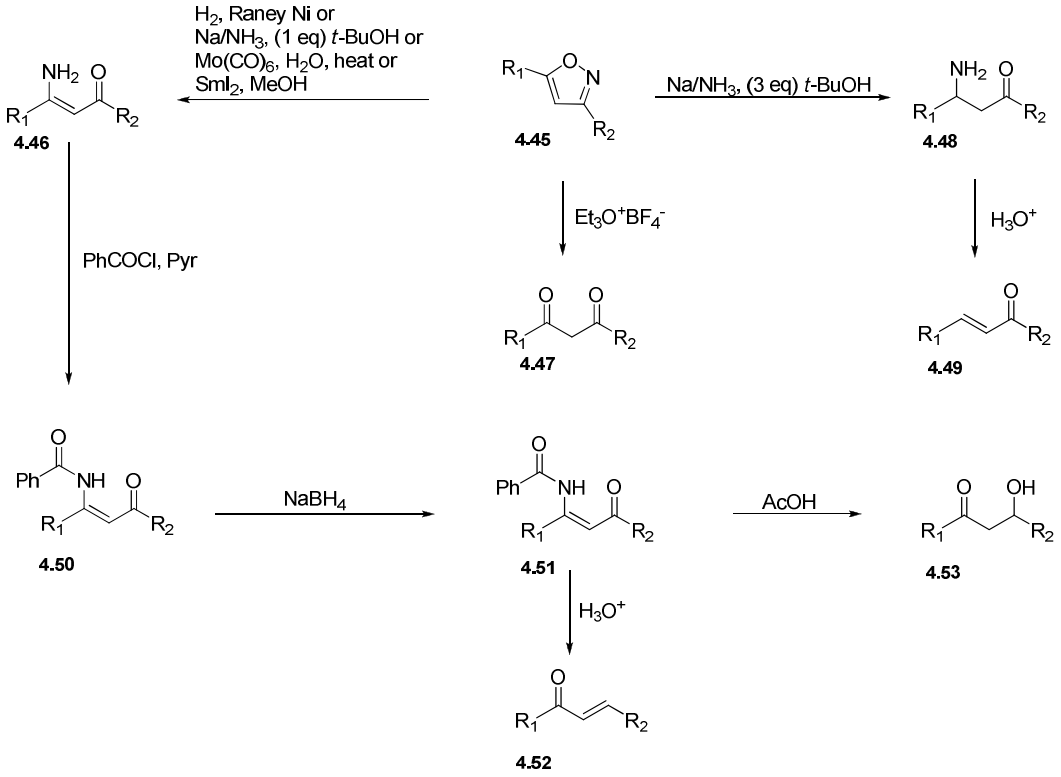
nitroalkanes, dehydrohalogenation of hydroxamoyl halides, or least frequently, thermolysis of furoxans. The less popular method relies on the synthesis of isoxazolines and their further oxidation.[4,5]



Scheme 4.9. Preparation of isoxazoles.

The appropriate choice of reaction conditions for reductive cleavage of the N-O bond enables conversion of isoxazoles into different structural patterns (Scheme 4.10).[5] Treatment of **4.45** with Na/NH_3 and 3 equivalents of *t*-BuOH gives an access to β-aminoketones (**4.48**). When Na/NH_3 and 1 equivalent of *t*-BuOH is used β-enaminoketones (**4.46)** can be obtained. Similar transformation can be achieved with application of H_2/Raney Ni, $Mo(CO)_6/H_2O$ or SmI_2 as a reducing agent. $EtO_3^+BF_4^-$ promoted N-O cleavage of **4.45** leads to formation of 1,3-diketones (**4.47**). Additionally, further modifications can generate β-hydroxyketones (**4.53**) and α,β-unsaturated

ketones (**4.52**). In this context, the isoxazole ring system can be considered a masked form of 1,3-diketone with the ability to undergo selective deprotonation and lack of reactivity toward nucleophiles. Additionally, base-induced opening of an isoxazole ring system can deliver β-ketonitriles.[6] Consequently, in the design of the synthesis of complex molecules, isoxazoles have played the role of masked new heterocyclic rings, masked aromatic rings, masked fused rings or masked aldol reaction products.[5]

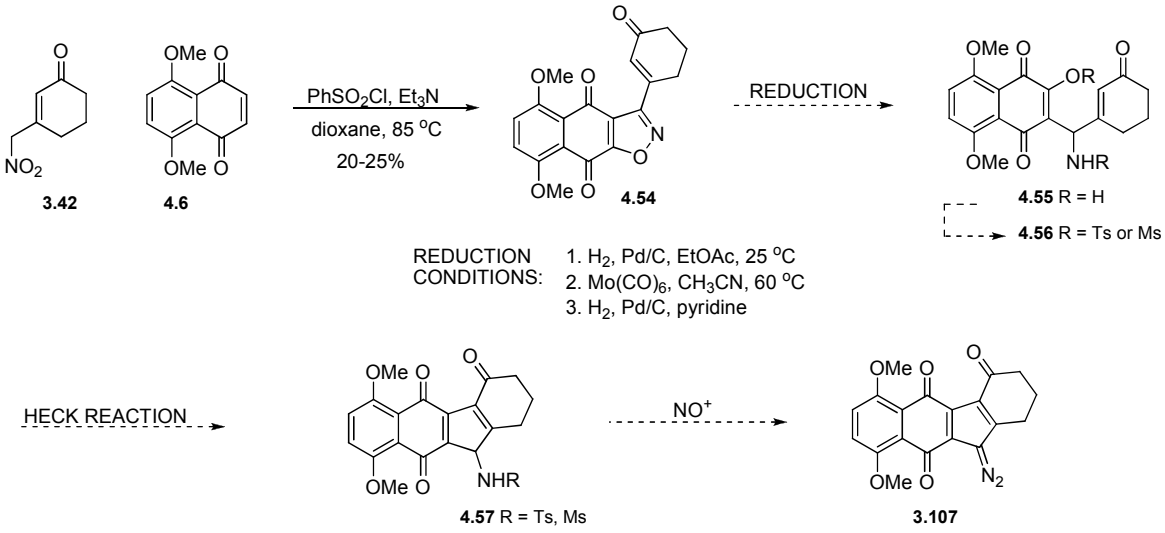


Scheme 4.10. Derivatization of isoxazoles.

Continuing our model annulation studies, we envisioned generation of isoxazole **4.54** which after determination of appropriate N-O bond reducing conditions could be converted into hydroxyquinone **4.55** (Scheme 4.11). Transformation of **4.55** into Heck

reaction precursor **4.56** followed by Pd-promoted intramolecular ring closure reaction conditions could be converted into amine **4.57**. As in our earlier approaches, we anticipated that diazoquinone **3.107** would be generated through reaction with NO^+.

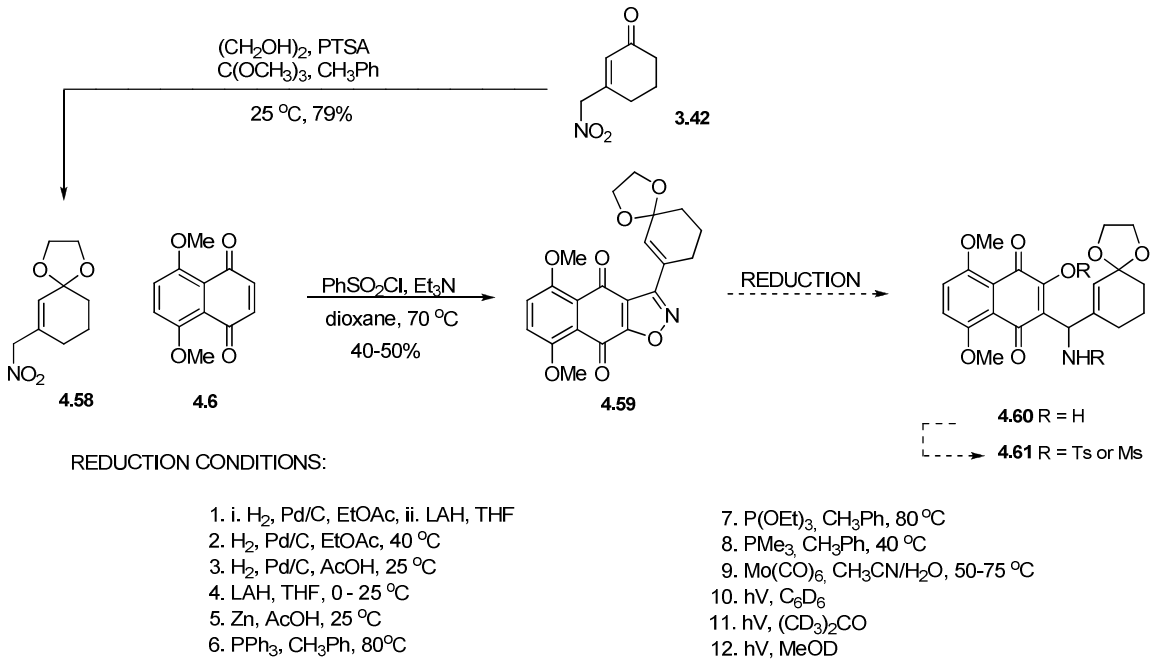
While desired isoxazole **4.54** could be generated when nitroketone **3.42** and quinone **4.6** were treated with benzenesufonyl chloride and Et_3N in dioxane at 85 ^oC (reactions performed in THF, CH_3Ph, $CHCl_3$ failed to produce **4.54**), its reduction under examined conditions proved to be unsuccesful and resulted in complete decomposition.[7]



Scheme 4.11. Preparation and attempted modification of isoxazole **4.54**.

Subsequently, an attempt to generate the less reactive isoxazole **4.59** was undertaken as a way to increase the yield of cycloaddition. Additionally, this approach sought to enable examination of a larger number of N-O reductive bond cleavage reaction conditions since carbonyl group modification could be avoided (Scheme 4.12).

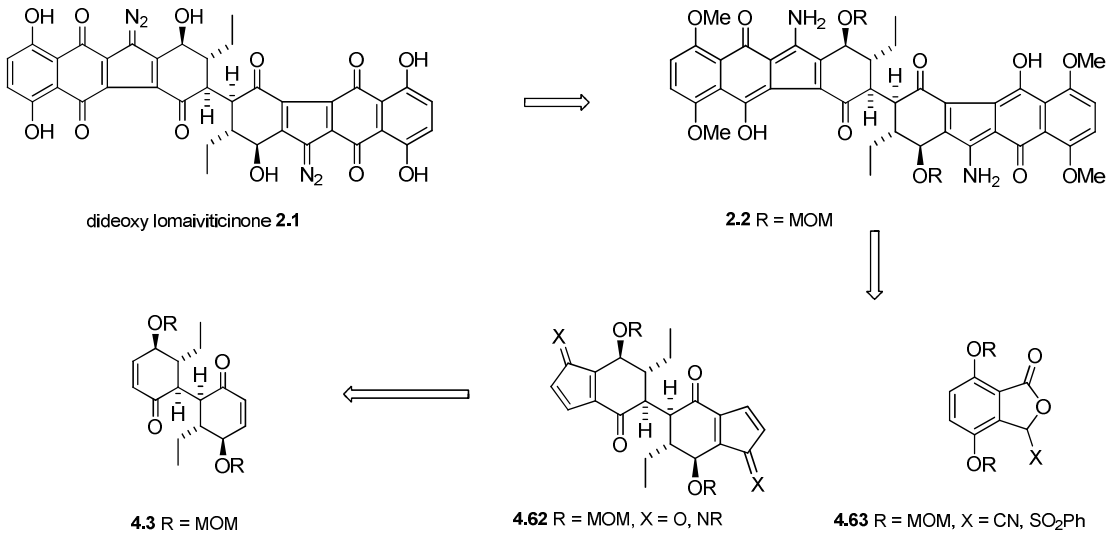
Protection of enone **3.42** occurred smoothly and compound **4.58** could be provided in a very good yield (79%). Treatment of **4.6** and **4.58** under previously developed conditions led to formation of **4.59** with yields varying between 40 and 50%. Consequently, isoxazole **4.59** was subjected to modification with the goal of generating amine **4.60**. Multiple conditions were tested; however, unfortunately, desired product was not formed. Treatment with phosphines and triethylphopshite resulted in recovery of substrate **4.59**. Similarly, exposure of **4.59** to light did not lead to any modification. When **4.59** was reacted with stronger reducing agents (Zn/AcOH, LAH, $Mo(CO)_6$) only decomposition was observed.[8] Further studies were discontinued.



Scheme 4.12. Synthesis and failed reduction of isoxazole **4.59**.

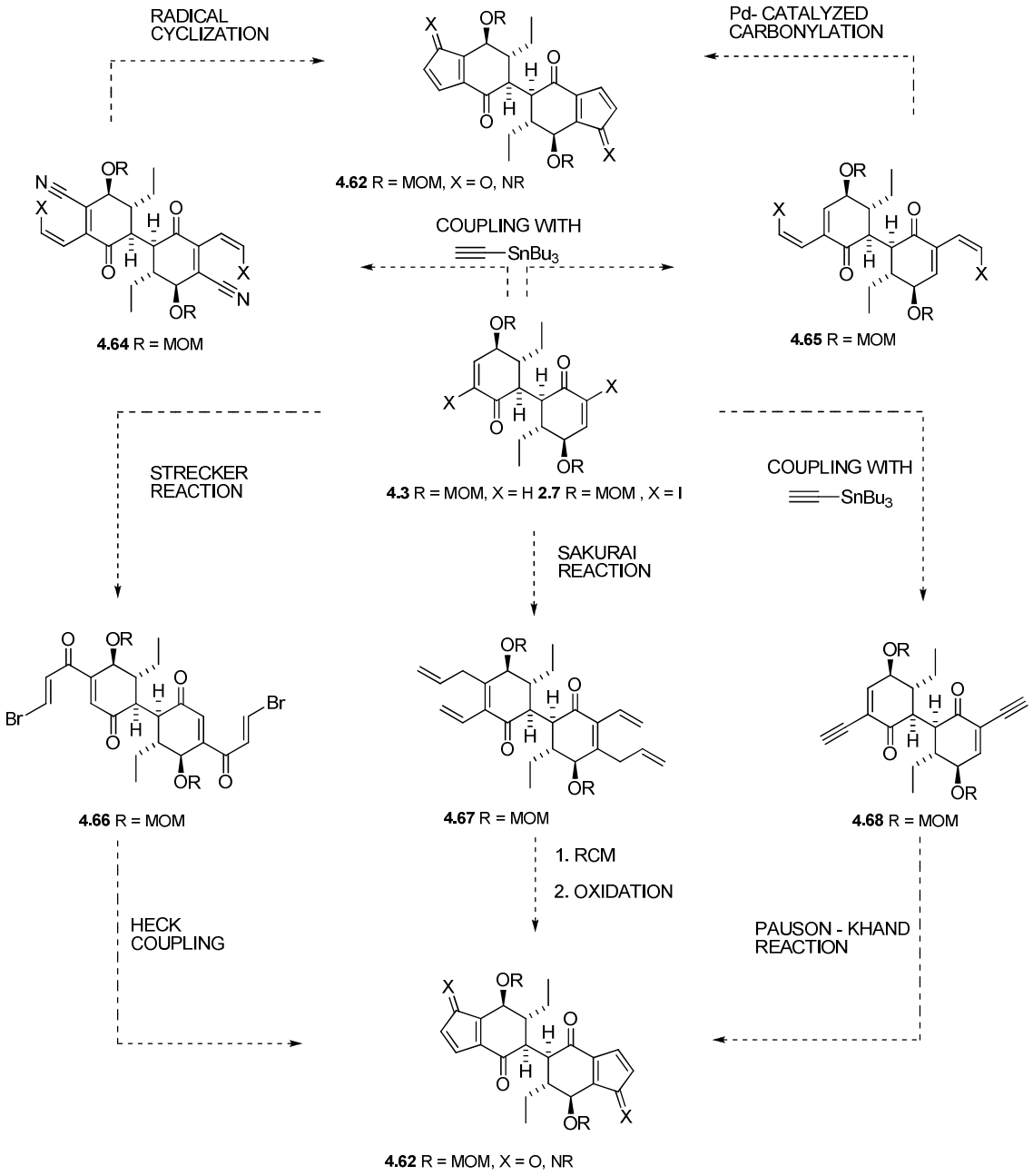
Future Directions

Several conclusions can be drawn from our effort to prepare dideoxy lomaiviticinone. First, we believe that the ineffectiveness of our strategy for generation of **2.1** can be attributed to the sensitivity of fragments we decided to apply in our synthesis. In many cases, high or undesired reactivity of quinones and their capricious nature (inability to undergo protection – Scheme 3.20) prevented further modifications. Numerous times, conducted experiments resulted in decomposition of applied substrates, and too often steric hindrance negatively influenced outcome of our studies (radical cyclization experiments, Michael additions into quinones **3.17**, **4.6**, **3.116**). Taking these considerations into account, we believe that future design of a synthetic route to dideoxy lomaiviticinone should avoid introduction of the two most reactive functionalities - diazo groups and quinone fragments - until the latest possible stage of synthesis. Therefore, with bis-enone **4.3** in hand, its conversion into potentially less reactive bis-cyclopentenone **4.62** could be considered (Scheme 4.13). Generation of the bis-imine version of **4.62** would allow examination of a unique Hauser annulation to introduce the most external portions of the molecule **2.1**. This sequence would allow formation of a desired bis-amine **2.2** and its conversion into **2.1** by treatment with NO^+, ergo examination of our 'biosynthetic hypothesis' would be guaranteed. Additionally, application of the advanced key intermediate **4.3** would ensure continuation of our previous studies.



Scheme 4.13. Proposed synthetic strategy.

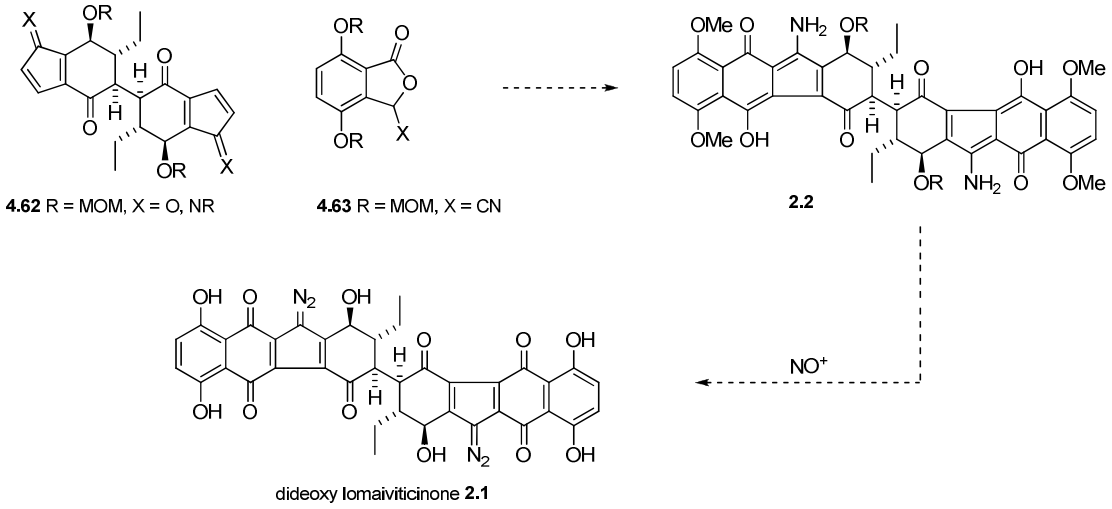
Multiple routes to bis-imine/enone **4.62** can be envisioned (Scheme 4.14). Bis-enone **4.68**, generated through Stille coupling between enone **2.7** and ethynylstannane, could be used as an intermediate in the formation of radical cyclization precursor bis-cyanoenone **4.64**. Generation of compound **4.68** could be followed by preparation of bis-vinyliodide **4.65** with intention of using it in Pd-catalyzed carbonylation. Bis-enone **4.68** could also be applied in a rather risky Pauson-Khand reaction leading directly to bis-enone **4.62**, and additional synthetic pathways could be examined. Formation of Strecker reaction product bis-vinylbromide **4.66** could be followed by a Heck reaction to achieve the bis-cyclopentenone rings construction. Ring-closing methatesis, followed by SeO_2 mediated oxidation could be applied to bis-allyl enone **4.67** delivered *via* a Sakurai reaction.



Scheme 4.14. Possible routes to bis-enone **4.62**.

With preparation of bis-enone **4.62**, the stage would be set for Hauser annulation examination (Scheme 4.15).[9] Application of the MOM-protected analog of known cyanofuranone **4.63** would ensure smooth deprotection in the final steps of the

synthesis.[10] Finally, preparation of a bis-carbonyl version of compound **2.2** would require its condensation with NH_4OAc to provide the precursor for key diazo group formation through the reaction with nitrosonium ion. Unfortunately, the proposed synthetic pathway is not free from risk with the biggest involving requirement of double processing. However, elimination of the presence of most reactive functionalities until the final steps of the synthesis may enable realization of the ultimate goal – synthesis of dideoxy lomaiviticinone.



Scheme 4.15. Final steps.

Conclusion

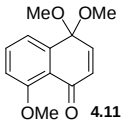
The goal of this work was to describe current knowledge about the diazoparaquinone family of antibiotics (Chapter I), report our solution to the synthesis of advanced dideoxy lomaiviticinone precursors (Chapters II and III) and to offer review

of examined routes within the framework of two generations of strategies we have envisioned (Chapters II, III, IV). Although the outcome of the undertaken effort to prepare dideoxy lomaiviticinone is not fully satisfying, we believe that synthesis of **2.1** and further examination of its properties could be accomplished with the introduction of appriopriate synthetic modifications. At this point one should not underestimate the power of organic chemistry and the number of synthetic tools it has to offer.

Experimental methods

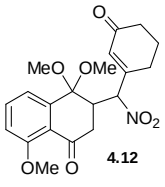
General. All non-aqueous reactions were conducted under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and, unless otherwise stated, used without further purification. Toluene (CH_3Ph), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) were obtained through purification of commercially available solvents with use of activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was purified by distillation from Na metal with benzophenone indicator. Triethylamine (Et_3N) and N,N-diisopropylethylamine ($i Pr_2NEt$) were distilled from CaH_2 and stored over KOH. Thin-layer chromatography was performed on E.Merck precoated silica gel 60 F524 plates. The plates were visualized with UV light and aqueous stain ($KMnO_4$ or CAM). Liquid chromatography (flash chromatography) was conducted using indicated solvents and Dynamic Adsorbents silica gel 60 (230-240 mesh). Thermo Electron IR100 series instrument was used to record infrared spectra as thin films on NaCl plates. ^1H and ^{13}C NMR were recorded on Bruker 300, 400, 500, 600 spectrometers at ambient temperature and are reported relative to deuterated solvent signals. *n*-BuLi was titrated with use of the Suffert method.

Preparative Procedures



4.11

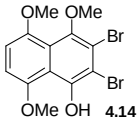
To a solution of phenol **4.10** (100 mg, 0.49 mmol) in MeOH (3.5 mL) at ambient temperature were added $PhI(OAc)_2$ (189 mg, 0.59 mmol) and K_2CO_3 (142 mg, 1.0 mmol). After 30 min the reaction mixture was diluted with Et_2O. The organic layer was washed with $NaHCO_3$ (x 1) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide methylketal **4.11** as a dark solid (35 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 10.4 Hz, 1 H), 6.52 (d, *J* = 10.8 Hz, 1 H), 3.98 (s, 3 H), 3.18 (s, 6 H).



4.12

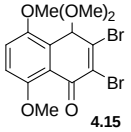
To a solution of methyl ketal **4.11** (15 mg, 0.064 mmol) and nitroenone **3.42** (10 mg, 0.064 mmol) in CH_2Cl_2 (1 mL) at ambient temperature was added DBU (10 mg, 0.067 mmol, 0.01 mL). After 16 h the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated solution of NH_4Cl (x 1) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide enone **4.12** as a yellow oil (5 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 6.08 (d, *J* = 7.2 Hz, 1 H), 5.77 (s, 1 H), 6.85 (d, *J* = 6.4 Hz, 1 H) 3.92 (s, 3 H), 3.74-3.68 (m 1 H), 3.28 (s, 3 H), 3.12

(dd, *J* = 7.2 Hz, 18.8 Hz, 1 H), 2.89 (s, 3 H), 2.47-2.41 (m, 2 H) 2.36-2.27 (m, 2 H), 2.12-1.97 (m, 2 H).



4.14

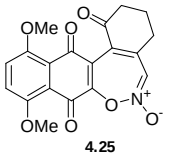
To a solution of quinone **3.17** (50 mg, 0.13 mmol) in CH_2Cl_2 (6 mL) at ambient temperature were added Adogen 464 (27 mg, 0.027 mmol) and solution of $Na_2S_2O_4$ (115 mg, 0.66 mmol) in H_2O (2 mL). The reaction progress was monitored by TLC. After reduction of quinone to hydroquinone was completed, Me_2SO_4 (24 mg, 0.19 mmol) and NaOH (32 mg, 0.8 mmol) were added. The reaction mixture was placed in an oil bath at 35 ^oC. After 50 min the solution was cooled to ambient temperature and diluted with CH_2Cl_2. The organic layer was washed with saturated solution of NH_4Cl (x 1) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide phenol **4.14** as a yellow oil (34 mg, 65%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.6 (s, 1 H), 6.82 (s, 2 H), 4.03 (s, 3 H), 3.93 (s, 3 H), 3.80 (s, 3 H).



4.15

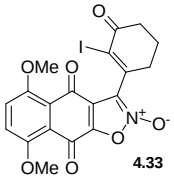
To a solution of phenol **4.14** (34 mg, 0.087 mmol) in MeOH (4 mL) at ambient temperature were added $PhI(OAc)_2$ (30 mg, 0.095 mmol) and K_2CO_3 (26 mg, 0.19 mmol). After 1 h saturated solution of $NaHCO_3$ was added. The aqueous layer was separated. The organic layer was diluted with Et_2O, washed with H_2O (x 1) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:1) to provide methyl

ketal **4.15** as a dark solid (13.5 mg, 24.5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.2 Hz, 1 H), 7.12 (d, *J* = 9.2 Hz, 1 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.06 (s, 6 H).



4.25

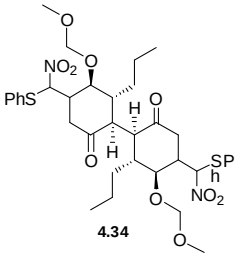
To the solution of nitroenone **3.42** (11 mg, 0.07 mmol) and quinone **4.6** (15 mg, 0.07 mmol) in THF (1.5 mL) at ambient temperature were added CAN (39 mg, 0.07 mmol) and Cs_2CO_3 (6.9 mg, 0.02 mmol).The mixture was heated up to 60 °C. After 4 h the solution was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtoAc, 1:4) to provide quinone **4.25** as a pink solid (3.8 mg, 13%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 9.6 Hz, 1 H), 7.39 (d, *J* = 9.6 Hz, 1 H), 7.16 (s, 1 H), 4.03 (s, 3 H), 3.99 (s, 3 H), 2.93 (t, *J* = 7.6 Hz, 2 H), 2.56 (t, *J* = 6.4 Hz, 2 H), 2.21 (quin, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.15, 177.68, 172.24, 165.24, 160.55, 160.28, 155.62, 155.03, 146.05, 132.45, 123.05, 121.22, 120.74, 119.40, 57.14, 56.90, 37.61, 27.21, 22.45.



4.33

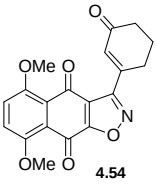
To a solution of nitroenone **3.42** (11 mg, 0.04 mmol) and quinone **4.6** (10 mg, 0.047 mmol) in THF (1 mL) at ambient temperature were added CAN (21 mg, 0.04 mmol) and Cs_2CO_3 (3.8 mg, 0.01 mmol). The mixture was heated up to 60 °C. After 17 h the mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:4) to provide iodoenone **4.33** as a pink/orange solid (8.9 mg, 46%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 9.6 Hz, 1 H), 7.43 (d, *J* = 9.6 Hz, 1 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 2.84-2.80 (m, 4 H), 2.30 (quin, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.25,

177.61, 171.94, 164.40, 161.83, 155.99, 155.10, 153.34, 122.61, 121.42, 121.34, 120.96, 119.01, 110.97, 57.03, 56.98, 36.42, 33.05, 22.51.



4.34

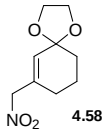
To a solution of bis-enone **2.32** (12 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) at ambient temperature were added $PhSCH_2NO_2$ (36 mg, 0.21 mmol) and DBU (16 mg, 0.01, 16 µL). After 25 h the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated solution of NH_4Cl (x 2) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 4:1) to provide bis-nitrosulfide **4.34** as a yellow oil (10 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 4 H), 7.37-7.35 (m, 6 H), 6.09 (d, *J* = 2.8 Hz, 2 H), 4.83 (d, *J* = 6.4 Hz, 2 H), 4.71 (d, *J* = 6.4 Hz, 2 H), 3.81-3.77 (m, 2 H), 3.30 (s, 6 H), 3.16-3.10 (m, 2 H), 2.78 (dd, *J* = 4.4, 15.6 Hz, 3 H), 2.47-2.40 (m, 4 H), 1.45-1.35 (m, 4 H), 0.97-0.91 (m, 6 H).



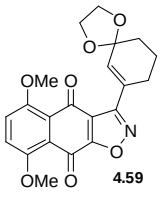
4.54

To a solution of nitroenone **3.42** (10 mg, 0.06 mmol) and quinone **4.6** (14 mg, 0.06 mmol) in dioxane (2 mL) at ambient temperature was added benzenesufonyl chloride (23 mg, 0.13 mmol, 16 µL). The mixture was heated up to 90 ^{o}C. The solution of Et_3N (13 mg, 0.13 mmol, 18 µL) in dioxane (0.3 mL) was added dropwise for 2.5 h. After 3.5 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide isoxazole **4.54** as a pink solid (5.5 mg,

24%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 9.6 Hz, 1 H), 7.40 (d, *J* = 9 Hz, 1 H), 7.16 (s, 1 H), 4.03 (s, 3 H), 4.00 (s, 3 H), 2.93 (t, *J* = 5.4 Hz, 2 H), 2.56 (t, *J* = 6.6 Hz, 2 H), 2.21 (quin, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.30, 177.74, 172.31, 165.23, 160.29, 155.59, 154.99, 146.13, 132.44, 122.99, 122.23, 120.69, 120.21, 119.41, 57.11, 56.90, 37.63, 27.20, 22.46.


4.58

To a solution of nitroenone **3.42** (139 mg, 0.9 mmol) in toluene (5 mL) at ambient temperature were added ethylene glycol (2.23 g, 36 mmol, 2 mL), trimethyl orthoformate (285 mg, 2.7 mmol, 295 mL), PTSA (15.4 mg, 0.09 mmol). After 1.5 h the reaction mixture was diluted with Et_2O/EtOAc. The organic layer was washed with H_2O (x 1), saturated solution of $NaHCO_3$ (x 1) and brine (x 1). The organic extract was dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1) to provide ketal **4.58** as a yellow oil (143 mg, 80%): IR (thin film, cm^{-1}): 3492, 2950, 2886, 1678, 1553, 1372; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (s, 1 H), 4.86 (s, 2 H), 4.01 (td, *J* = 2.0, 4.0, 7.2 Hz, 4 H), 2.13 (t, *J* = 5.2 Hz, 2 H), 1.89-1.84 (m, 2 H), 1.83-1.80 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.43, 131.77, 105.21, 81.35, 64.71, 32.76, 26.57, 20.44.


4.59

To a solution of quinone **4.6** (44 mg, 0.2 mmol) and nitroalkene **4.58** (40 mg, 0.2 mmol) in dioxane (3 mL) under air atmosphere was added benzenesufonyl chloride (71 mg, 0.4 mmol, 51 µL). The mixture was heated up to 70 ^{o}C. Et_3N (40 mg, 0.4 mmol, 56µL) was added. After 1.5 h the reaction

mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 1:3) to provide quinone **4.59** as a pink/orange solid (41 mg, 51%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.6 Hz, 1 H), 7.36 (d, *J* = 9.6 Hz, 1 H), 7.14 (s, 1 H), 4.16 (t, *J* = 3.6 Hz, 2 H), 4.03 (t, *J* = 2.8 Hz, 2 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 2.62 (t, *J* = 4.4, 5.6 Hz, 2 H), 1.97-1.94 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.00, 172.63, 164.95, 161.06, 155.46, 154.82, 133.81, 132.43, 130.18, 123.07, 122.97, 120.78, 120.41, 119.39, 105.40, 64.74, 57.21, 56.88, 33.06, 26.22, 20.58. HRMS (ESI) calcd for $C_{21}H_{20}O_7N$ [$M+H^+$] 398.1234, found 398.1218.

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Appendix A3:

Spectra Relevant to Chapter 4:

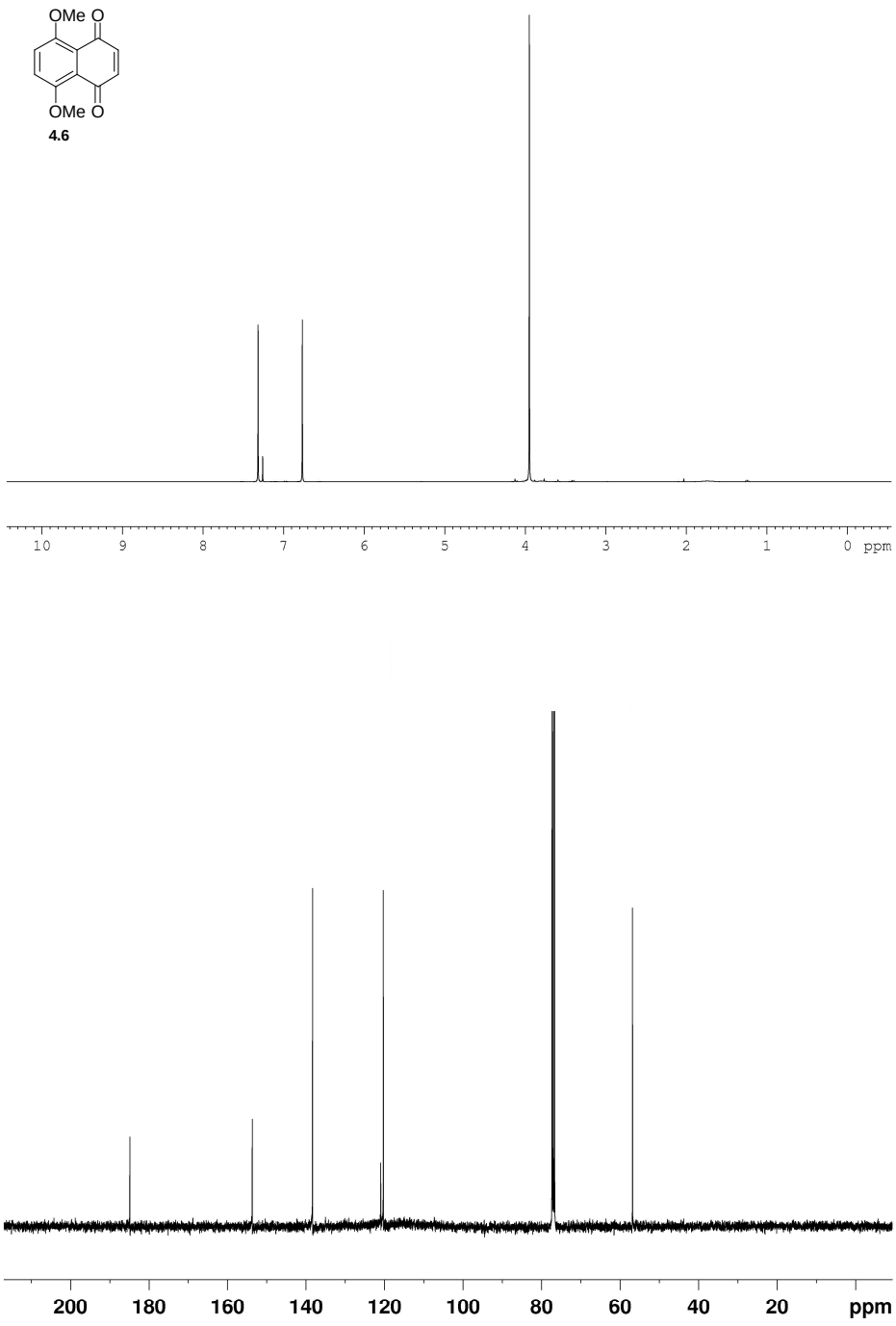
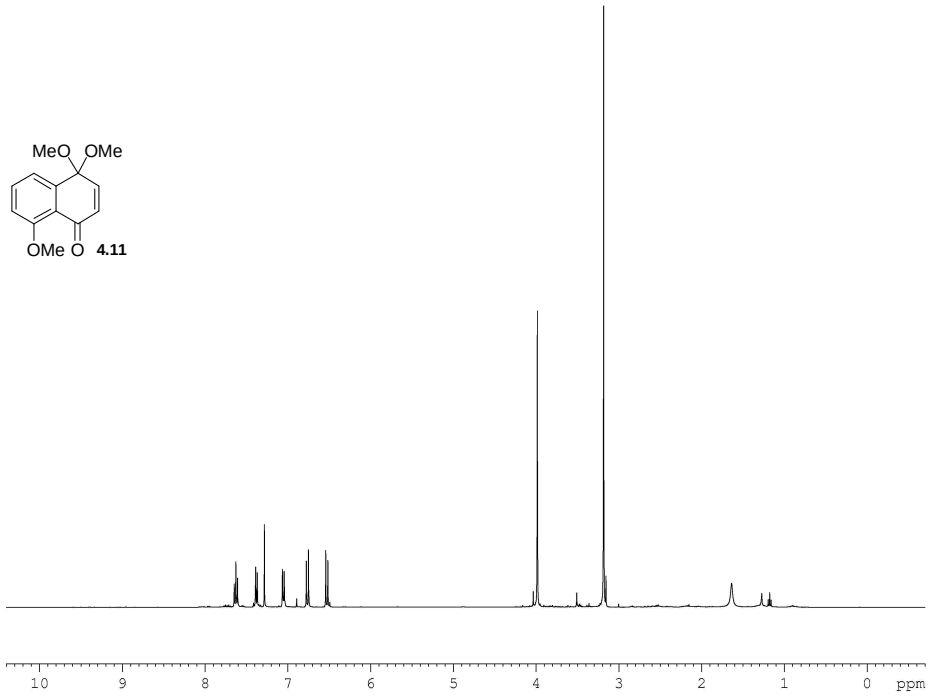


Figure A4.1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4.6**.



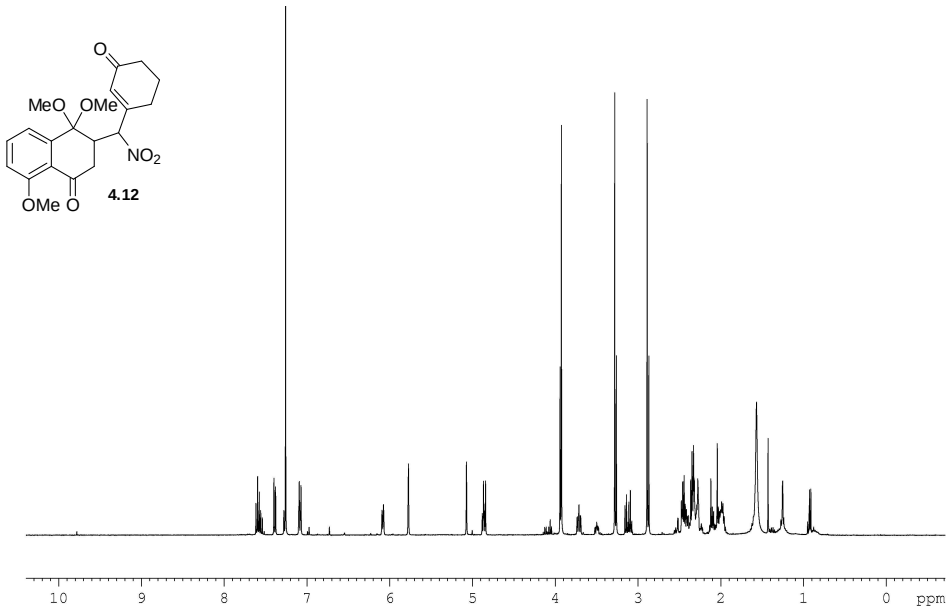
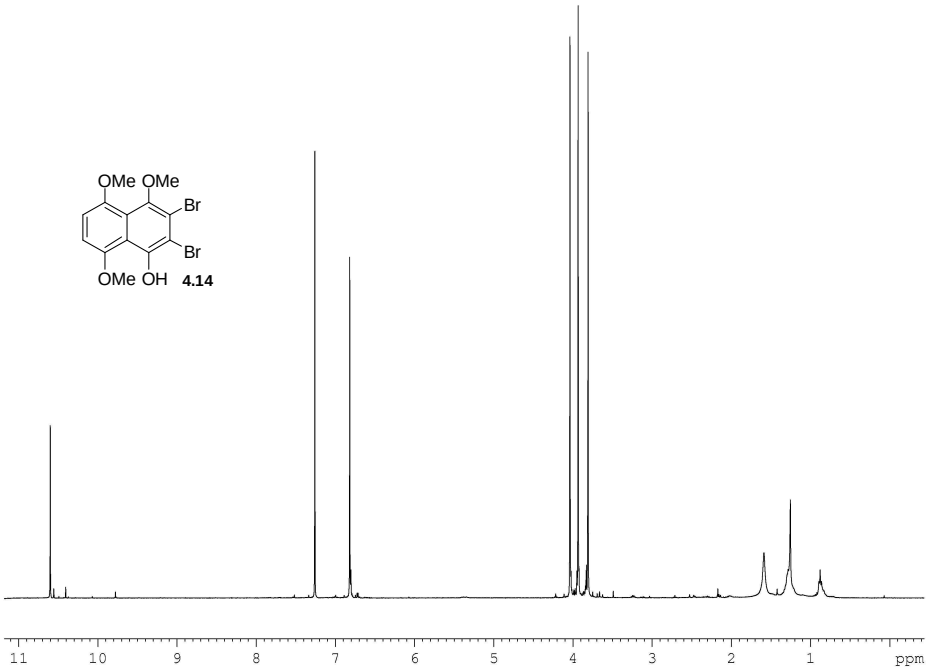


Figure A4.2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4.11** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4.12**.



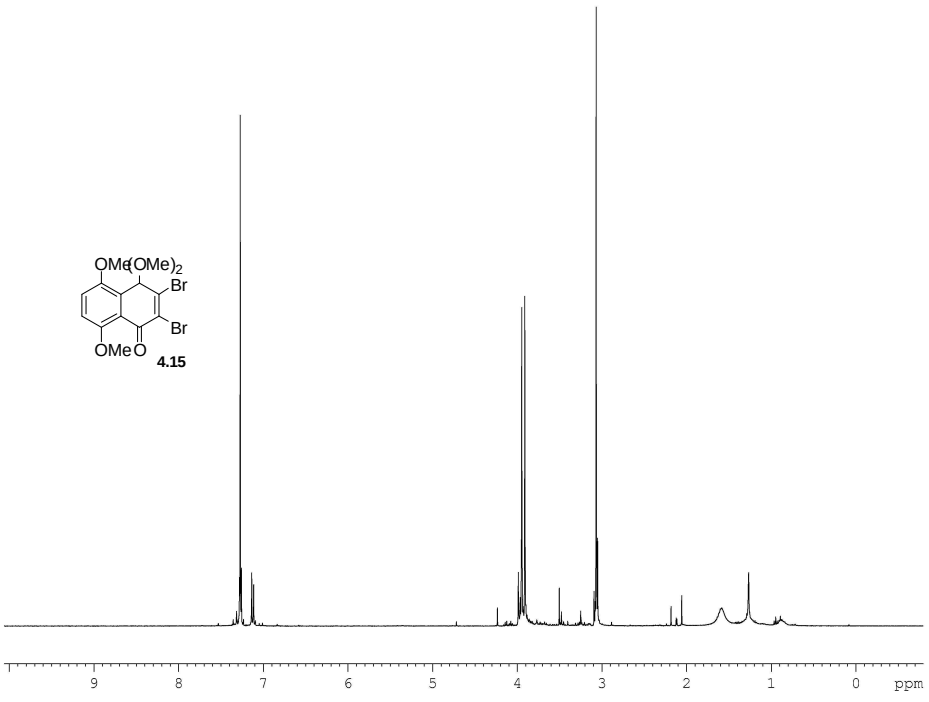


Figure A4.3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4.14** and ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4.15**.

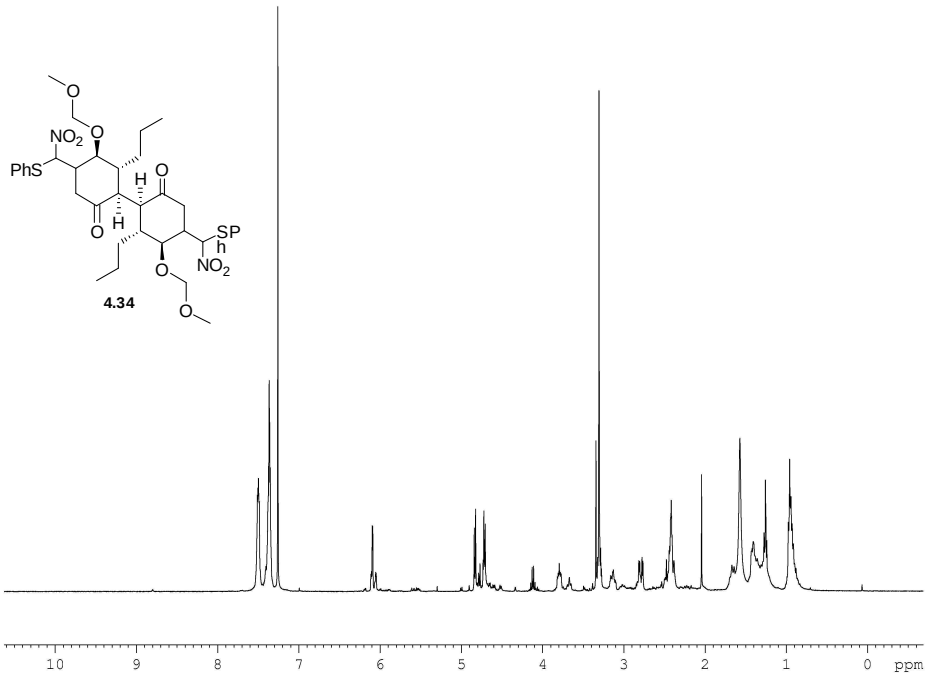


Figure A4.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4.34**.

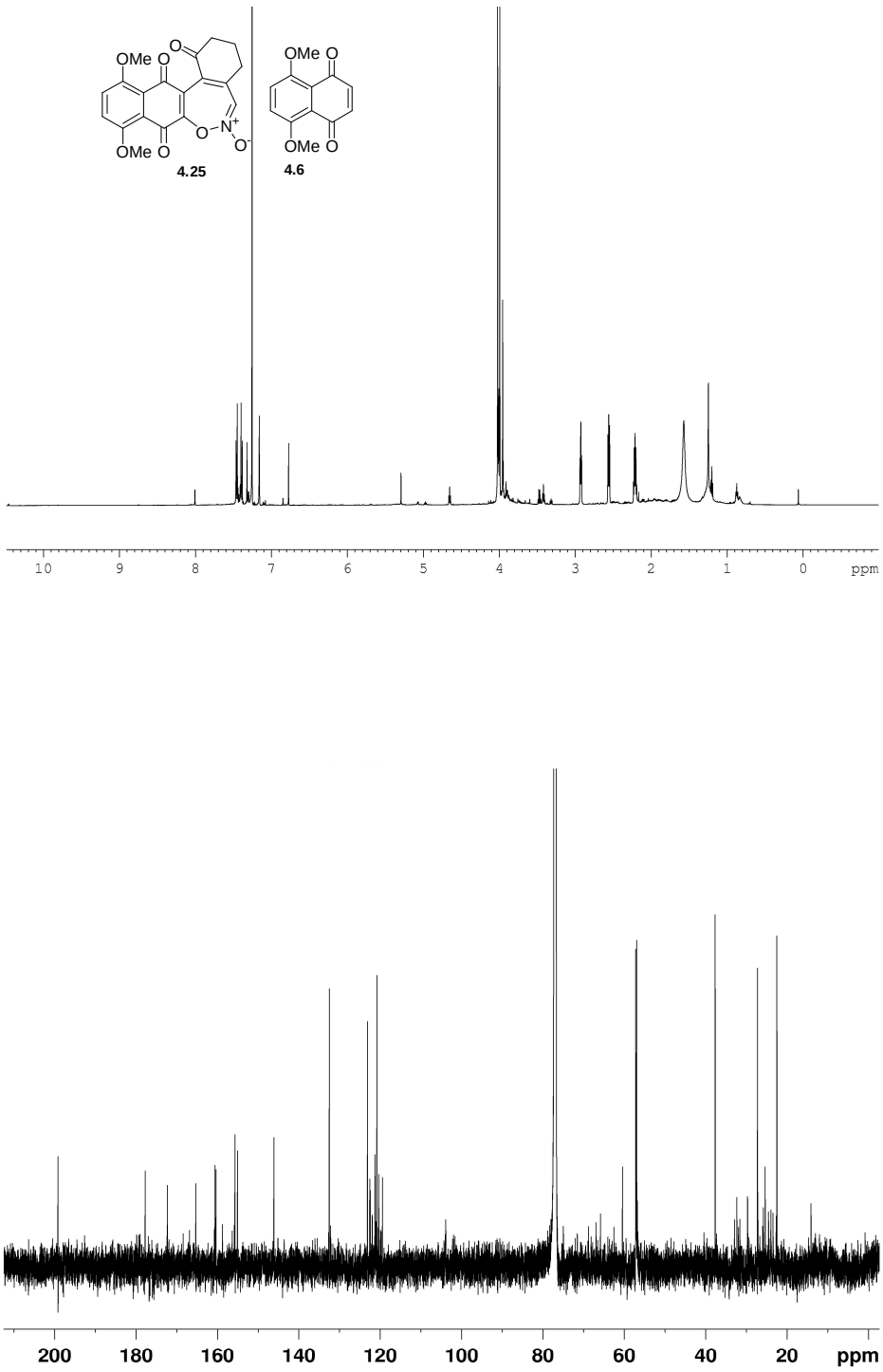


Figure A4.5. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **4.25** and **4.6**.

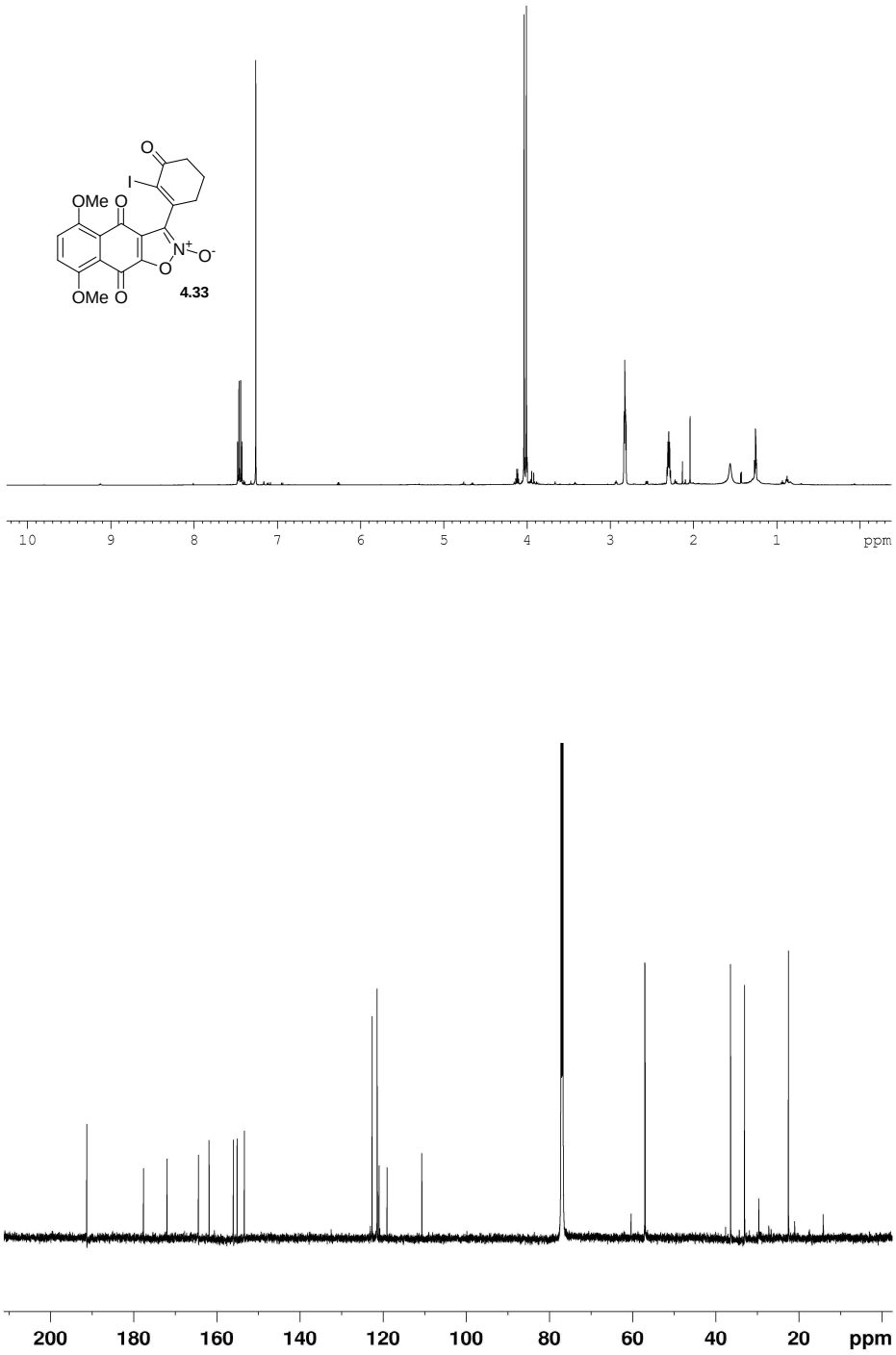


Figure A4.6. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) and ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **4.33**.

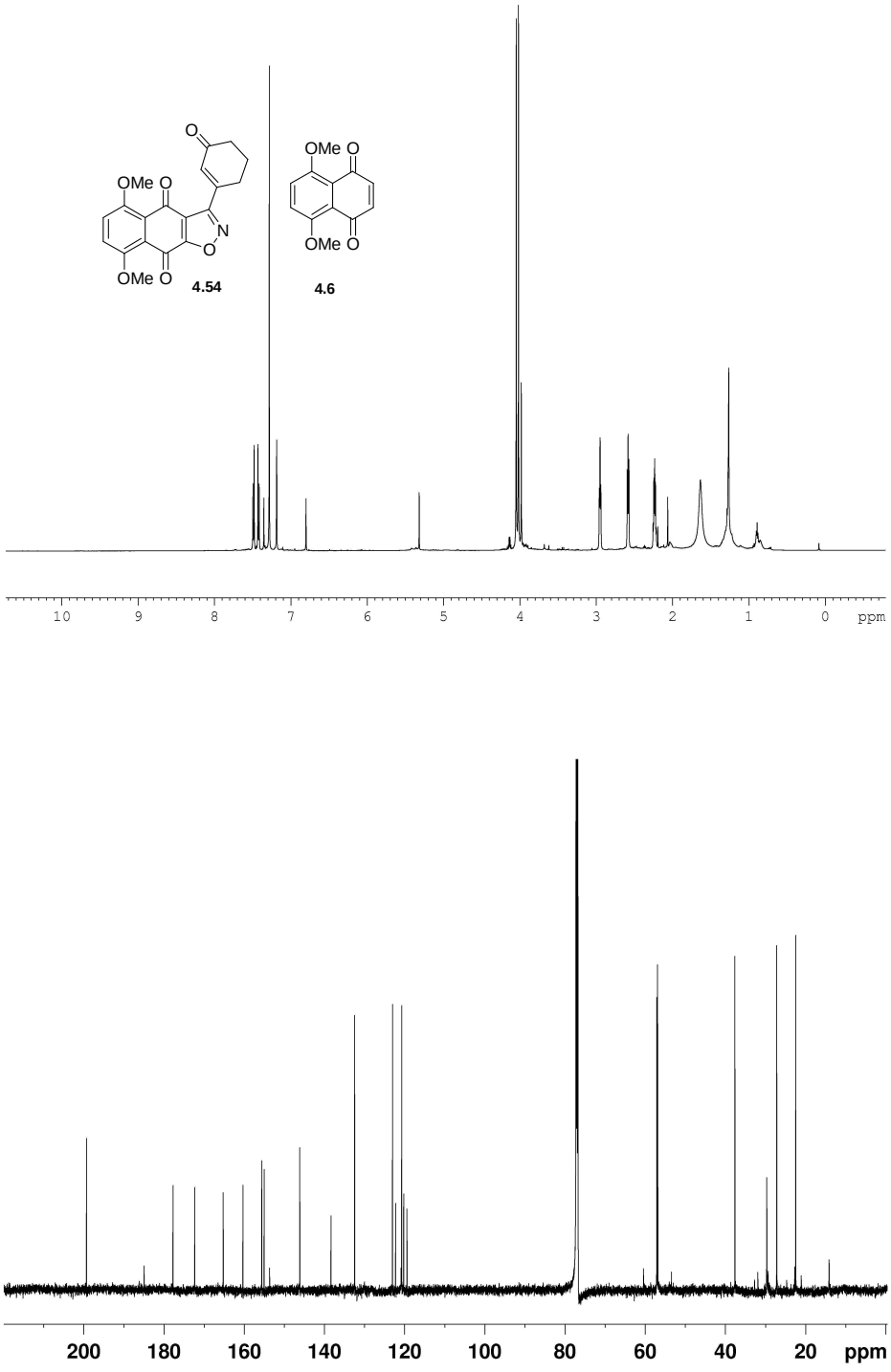


Figure A4.7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4.54** and **4.6**.

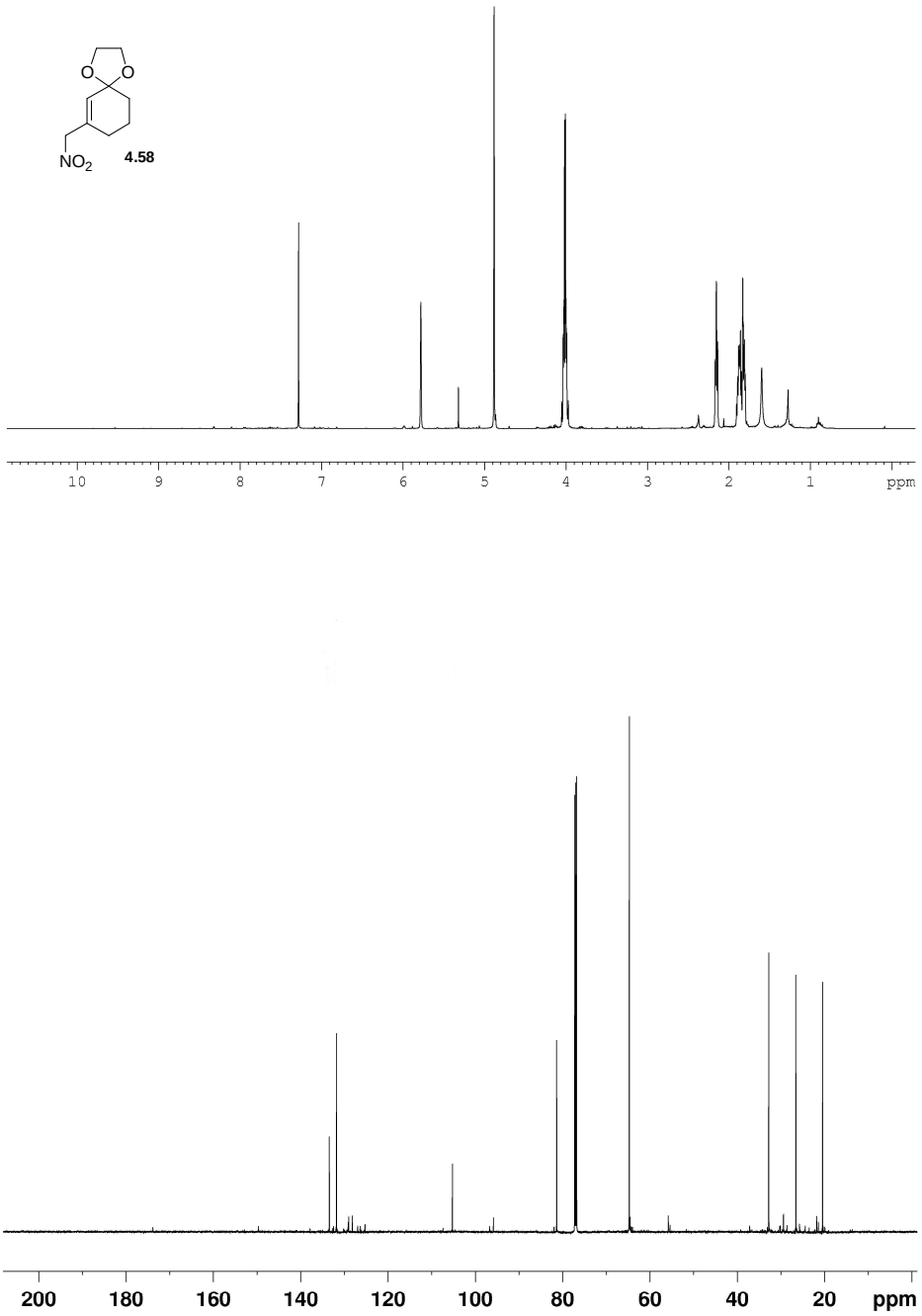


Figure A4.8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4.58**.

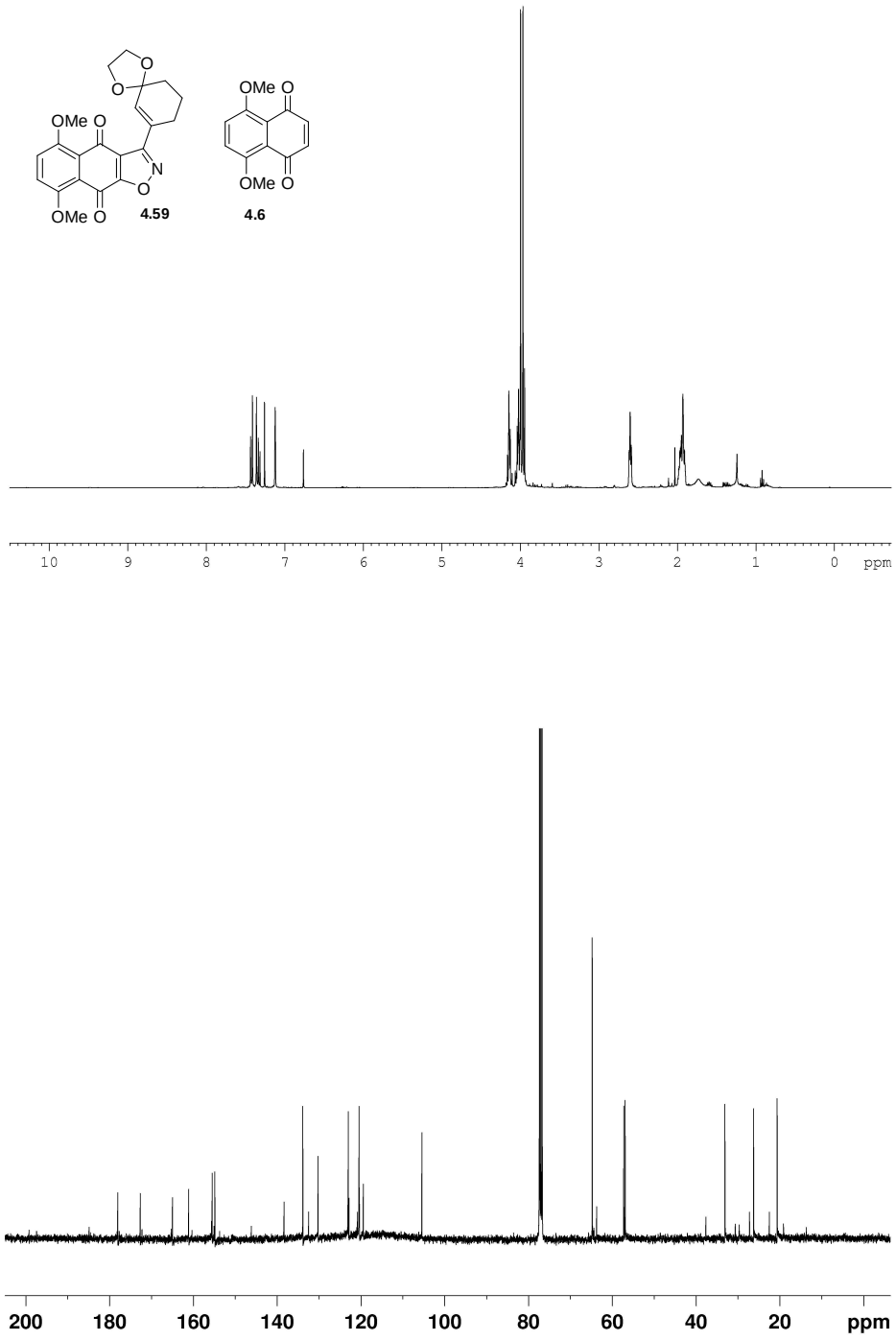


Figure A4.9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) and ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4.59** and **4.6**.