Synthetic Studies Toward Complex Polycyclic Natural Products

by

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Synthetic Studies Toward Complex Polycyclic Natural Products

Liming Cao, PhD

University of Pittsburgh, 2018

The first chapter of this dissertation describes the use of an intramolecular Staudinger/*aza*-Wittig reaction in the synthesis of 1,2,5,6-tetrahydro-1,2,4-triazines, a structural motif of the natural product noelaquinone. The DEF ring system of noelaquinone was prepared in 13 steps and 2% overall yield with key steps featuring a Cu(I)-catalyzed C-arylation and the controlled acidic hydrolysis of the PMB protective group.

The second chapter describes the investigation of reactions between methyl 3-oxo-2-oxabicyclo[2.2.0]hexane-6-carboxylate and an indolo-indoline dimer in the presence of BF_3 OEt_2. Two tricyclic-fused heterocyclic products and a diene carboxylic acid have been obtained through a ring opening process, a retro-[2+2] cycloaddition, and a conjugate addition from the indole fragment.

The third chapter describes progress toward the total synthesis of haouamine A. Several routes to the marine alkaloid have been attempted. The challenges associated with the late stage lactam reduction, epoxidation, and aromatization strategy to prepare the necessary tetrahydropyridine and aza-cyclophane moieties are discussed.

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ACKNOWLEDGEMENTS

It has been one of the most unforgettable experiences for me to pursue a Ph.D. degree in organic chemistry at the University of Pittsburgh. I would like to express my most sincere gratitude to Prof. Peter Wipf, whose patience and guidance have benefitted me significantly in both intellectual and emotional ways throughout my graduate studies, as he is devoted to creating a strict but effective educational and research environment that enlightens me. I also wish to thank all my past and present co-workers in the Wipf group and the chemistry department, who have helped me to go through the challenging period.

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I initially acquired my laboratory research experience at Wuhan University under the guidance of Prof. Xiaohai Zhou, and that prepared me for my subsequent graduate studies at the University of Pittsburgh. I am grateful to my Mom and Dad for their unconditional support back in China for all these years as I have been studying in Pittsburgh.

LIST OF ABBREVIATIONS

^{1}H NMR ..... proton nuclear magnetic resonance

^{13}C NMR ..... carbon 13 nuclear magnetic resonance

Ac ..... acetyl

AD-mix-β ..... asymmetric dihydroxylation mixture containing the phthalazine adduct with dihydroquinine

acac ..... acetylacetonate

APCI ..... atmospheric-pressure chemical ionization

Ar ..... aryl

binap ..... 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bn ..... benzyl

Boc ..... *tert*-butyloxycarbonyl

$Bpin_2$ ..... bis(pinacolato)diboron

Bu ..... butyl

calcd ..... calculated

CAN ..... ceric ammonium nitrate

CH_3CN ..... acetonitrile

cod 1,5-cyclooctadiene

Conc. ..... concentrated

dba ..... dibenzylideneacetone

DCE ..... dichloroethane

DCM ..... dichloromethane

DEAD ..... diethyl azodicarboxylate

DIPEA ..... N,N-diisopropylethylamine

DMAP 4-dimethylaminopyridine

DMF ..... N,N-dimethyl foramide

DMDO ..... dimethyldioxirane

DMSO ..... dimethyl sulfoxide

DMP ..... Dess–Martin periodinane

DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone

DPPB ..... 1,4-bis(diphenylphosphino)butane

EDC ..... 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

EI ..... electron ionization

ESI ..... electrospray ionization

Et ..... ethyl

HATU ..... 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

HFIP ..... hexafluoroisopropanol

HRMS ..... high-resolution mass spectrometry

i-Bu ..... *iso*-butyl

IC_{50} ..... the half maximal inhibitory concentration

IR ..... infrared

KHMDS ..... potassium hexamethyldisilazide

LA ..... Lewis acid

LAH ..... lithium aluminum hydride

LiHMDS ..... lithium hexamethyldisilazide

MAD ..... methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)

*m*CPBA ..... *meta*-chloroperoxybenzoic acid

Me ..... methyl

MHz ..... megahertz

min ..... minute

MOM ..... methoxymethyl

Ms ..... methyl sulfonyl

MS..... molecular sieves

NH_2OH..... hydroxylamine

NIS ..... *N*-iodosuccinimide

NMO ..... *N*-methylmorpholine *N*-oxide

NMP..... *N*-methyl-2-pyrrolidone

Ns 4-nitrobenzenesulfonyl

Nu..... nucleophile

o-DCB 1,2-dichlorobenzene

Ph ..... phenyl

PIFA..... iodobenzenebistrifluoroacetate

PMB ..... *para*-methoxybenzyl

PMHS..... polymethylhydrosiloxane

ppm ..... parts per million

PPTS ..... pyridinium *p*-toluenesulfonate

Pr..... propyl

p-TSA..... *para*-toluenesulfonic acid

Red-Al..... sodium bis(2-methoxyethoxy)aluminum hydride

rt ..... room temperature

SAW..... Staudinger/*aza*-Wittig

SM..... starting material

TBAF ..... *tetra*-*n*-butylammonium fluoride

TBDPS ..... *tert*-butyldiphenylsilyl

TBS ..... *tert*-butyldimethylsilyl

t-Bu ..... *tert*-butyl

TC thiophene-2-carboxylate

TES ..... triethylsilyl

TEMPO ..... 2,2,6,6-tetramethylpiperidin-1-yl)oxyl

Tf ..... trifluoromethanesulfonate

TFA ..... trifluoroacetic acid

THF ..... tetrahydrofuran

TIPS ..... triisopropylsilyl

TLC ..... thin layer chromatography

TMDS 1,1,3,3-tetramethyldisiloxane

TMS ..... trimethylsilyl

TPAP ..... tetrapropylammonium perruthenate

TrocCl ..... 2,2,2-Trichlorethoxycarbonyl chloride

Ts ..... toluenesulfonyl

μW ..... microwave

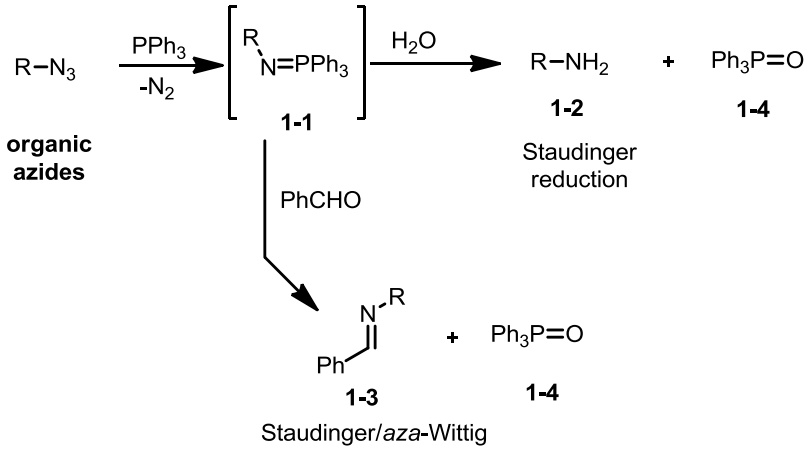
WRAIR ..... Walter Reed Army Institute of Research

1.0 1, 2, 4-TRIAZINE SYNTHESIS USING THE STAUDINGER/AZA-WITTIG REACTION AND ITS APPLICATION TOWARD THE SYNTHESIS OF THE DEF RING SYSTEM OF NOELAQUINONE

1.1 INTRODUCTION

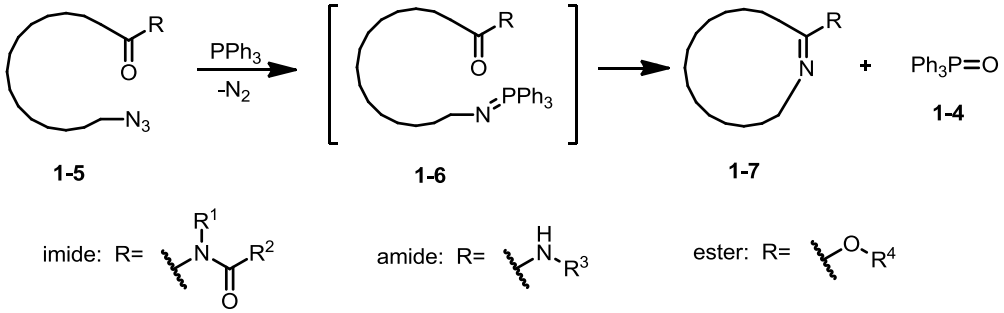
1.1.1 Applications of the Staudinger/*aza*-Wittig (SAW) Reaction

The organic azide is a functional group with versatile applications in organic synthesis.[1,2] In this work, the Staudinger/*aza*-Wittig (SAW) reaction[3] is the relevant transformation involving the organic azide, as shown in Scheme 1-1. In this transformation, the organic azide is treated with trialkyl/triaryl phosphines and phosphites to form iminophosphorane intermediates **1-1**, which can then undergo hydrolysis to the substituted amines **1-2** by subsequent reaction with water (Staudinger reaction), or can be converted to the corresponding imines **1-3** by reaction with carbonyl compounds consisting of aldehydes, ketones, acid halides, or heterocumulenes (Staudinger/*aza*-Wittig reaction). There are several polymer-supported phosphine reagents developed to simplify the removal of phosphine oxide by-products from the desired imine products[4] since phosphine oxide is generally difficult to remove by ordinary purification methods.



Scheme 1-1 Staudinger/*aza*-Wittig reaction

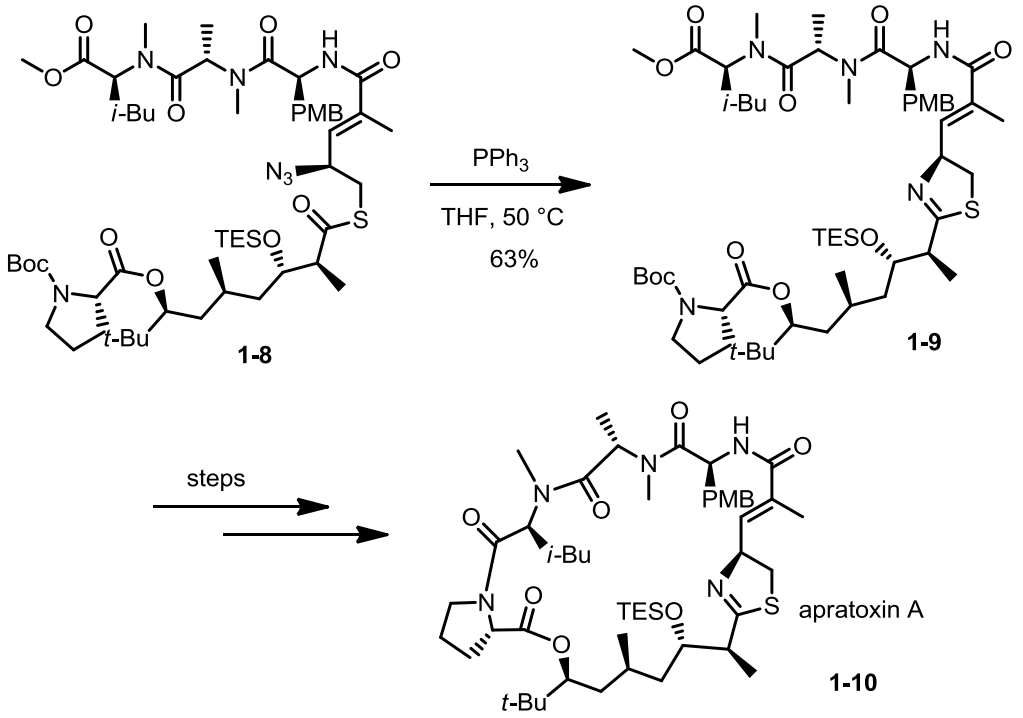
Less reactive carbonyl functionalities of imides, esters, and amides have also been shown to participate in the intramolecular SAW reactions, as shown in Scheme 1-2. [5]



Scheme 1-2 Intramolecular Staudinger/*aza*-Wittig reaction

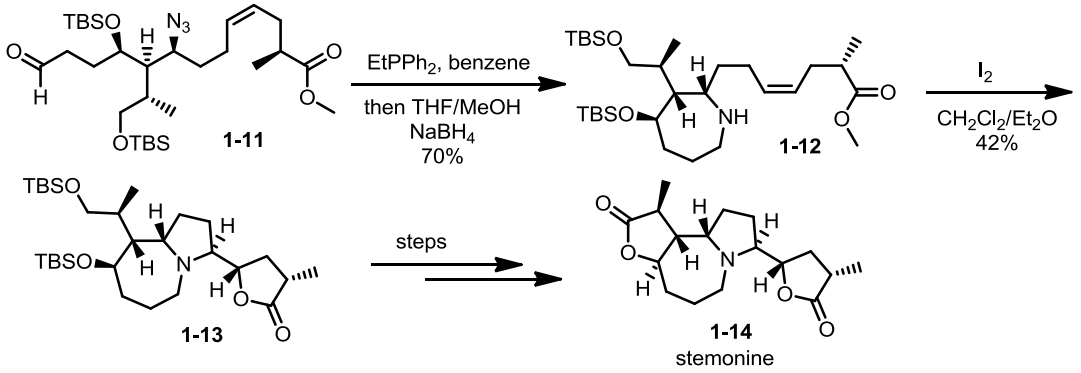
The SAW reaction has been successfully applied toward the construction of complex natural products.

A key step in Forsyth and Chen's total synthesis of the anticancer agent aprotaxin A **1-10** involves a SAW reaction on a thioamide to generate the thiazoline-containing intermediate **1-9** (Scheme 1-3).[6]



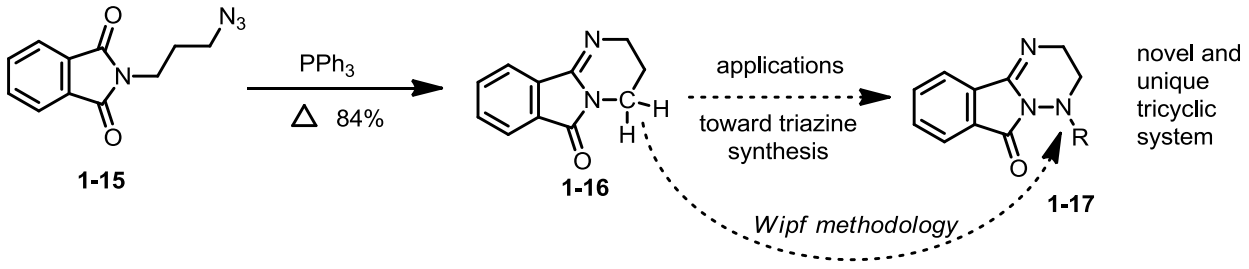
Scheme 1-3 Thiazoline formation in Forsyth and Chen's preparation of apratoxin A **1-10**

The Williams' approach to the stemona alkaloid (-)-stemonine **1-14** involves an azepane formation via a SAW reaction, followed by a $NaBH_4$ reduction of the resulting imine (Scheme 1-4).[7]



Scheme 1-4 Williams preparation of stemonine **1-14**

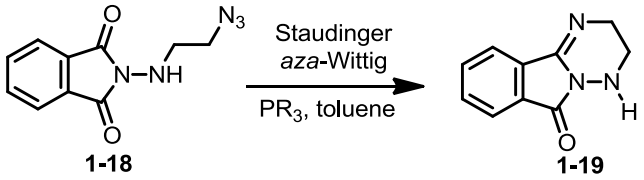
Eguchi *et al.* have described a versatile strategy that prepares iminolactam derivatives **1-16** through SAW reaction by treatment of azides **1-15** with PPh_3 in refluxing toluene.[8] This interesting transformation serves as a precedent for the *aza*-Wittig reaction using phthalimides, which extends the scope of the methodology to the preparation of structurally unique 1,2,4-triazine derivatives such as **1-17** (Scheme 1-5).



Scheme 1-5 Eguchi's Staudinger/*aza*-Wittig reaction to form iminolactam derivatives **1-17**

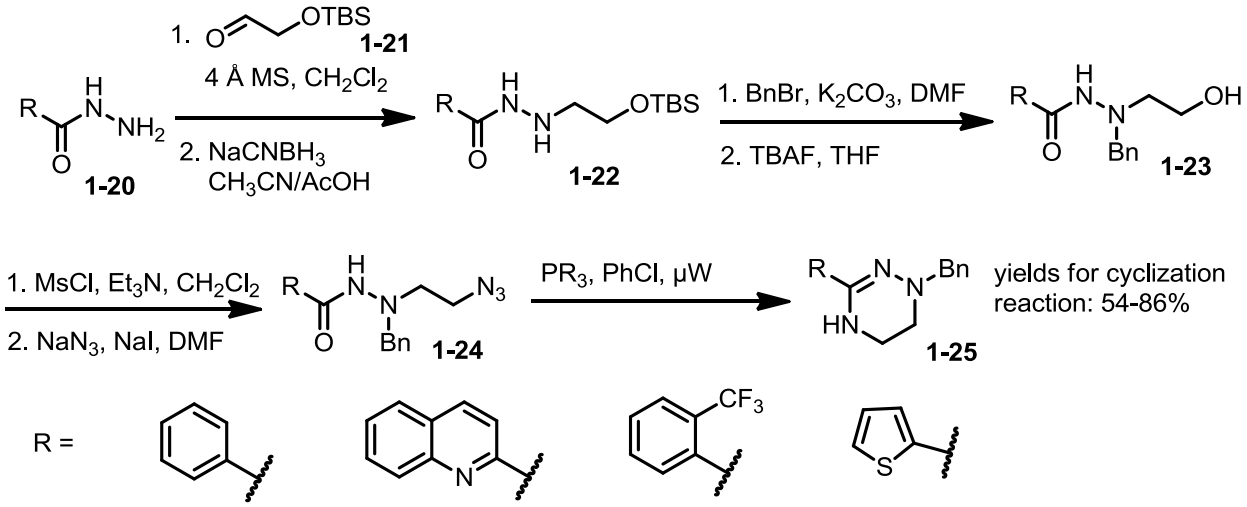
1.1.2 Wipf Group Methodology: 1,2,4-Triazine Synthesis

Previous work in the Wipf group has shown that 1,2,4-triazines such as **1-19** can be prepared from alkyl azides such as **1-18** by treatment with trialkyl/aryl phosphines (Scheme 1-6).[9] With this methodology, a series of substituted triazines of this class has been successfully synthesized.



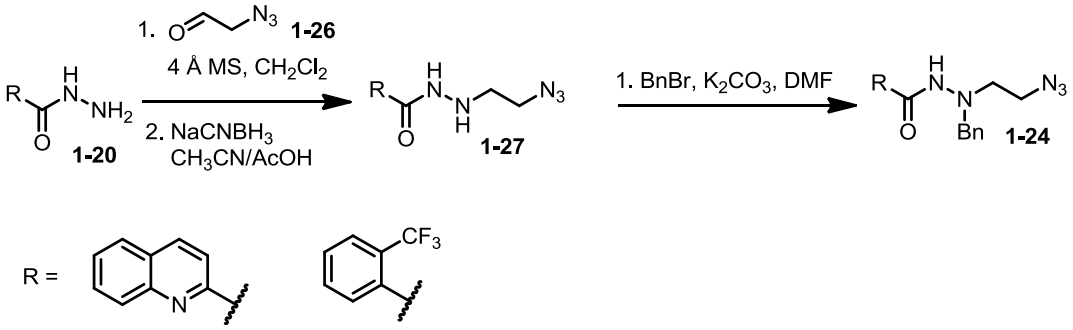
Scheme 1-6 Staudinger/*aza*-Wittig reaction to prepare 1,2,4-triazines

Amantini *et al.* have shown that hydrazide derivatives such as **1-22** can be prepared by reductive amination of aryl hydrazides **1-20**. Subsequent *N*-alkylation and TBS group deprotection afforded **1-23**. Conversion to azides **1-24** using standard conditions followed by treatment with trialkylphosphines under microwave irradiation provided the corresponding cyclic azides **1-25** (54-86%). Representative triazines are depicted in Scheme 1-7.[9]



Scheme 1-7 Preparation of substituted 1,2,4-triazines **1-25**

Alternatively, the azide-containing hydrazides can be initially installed through reductive amination followed by *N*-alkylation to the requisite cyclization precursor **1-24** (Scheme 1-8).[9]

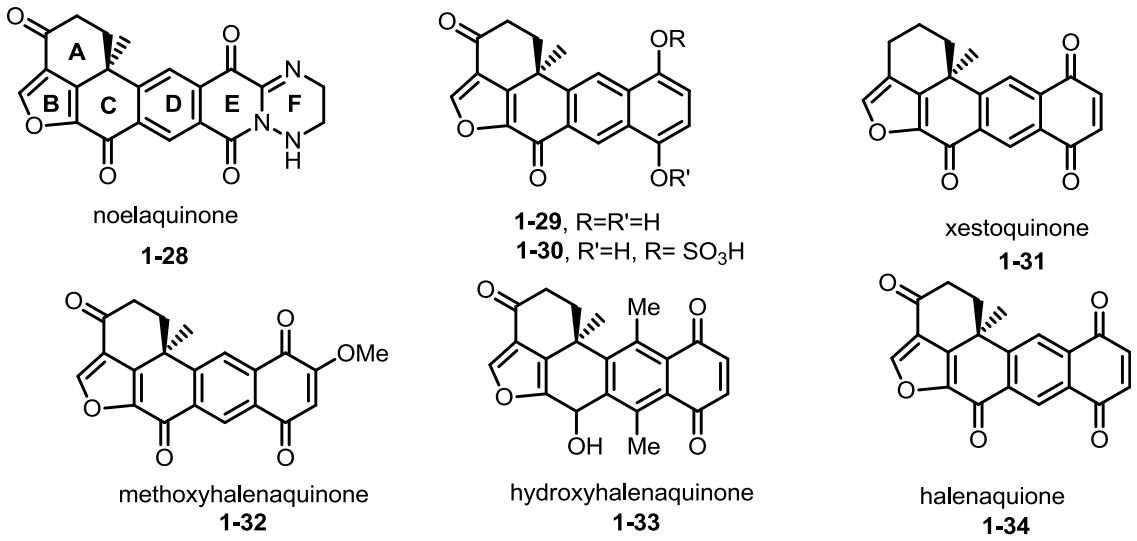


Scheme 1-8 Alternative method for preparing hydrazide **1-24**

1.1.3 Xestospongia Metabolites: Noelaquinone and Related Structures

The triazine-containing moiety of the natural product noelaquinone **1-28** can be constructed through the use of an intramolecular SAW reaction. Noelaquinone **1-28** was first isolated in 1996 from an unidentified *Xestospongia* sp. at Derawan Island, Indonesia, by Paul Scheuer and co-workers (Scheme 1-9).[10] At present, the potential biological activities of noelaquinone **1-28** are unclear, but structurally

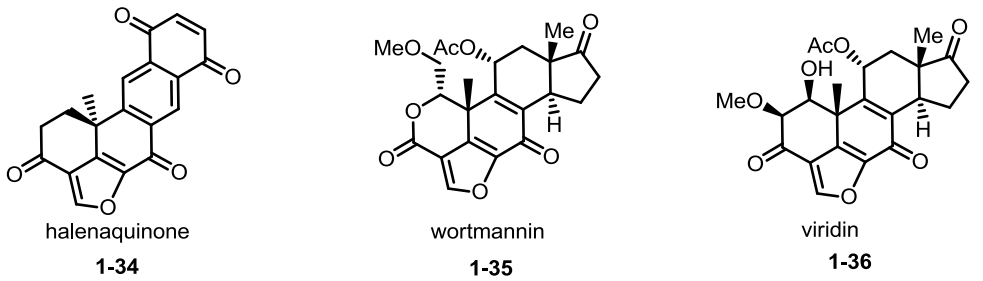
related compounds such as halenaquinone[11] **1-34**, have antibiotic[11], cytotoxic, and antifungal effects.[12] In addition, halenaquinone **1-34** and xestoquinone[13] **1-31** are potent Pfnek-1 kinase inhibitors.[14] Other natural products isolated from *Xestospongia* sp. include Kitagawa's quinol **1-29** and monosulfate[15] **1-30**, methoxyhalenaquinone **1-32**, and hydroxyhalenaquinone **1-33**.



Scheme 1-9 Noelaquinone and related natural products

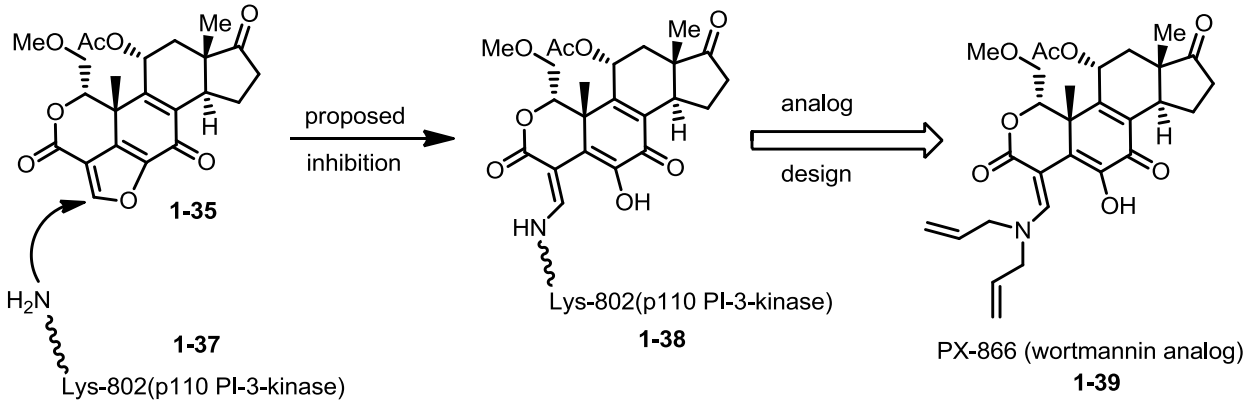
1.1.4 Halenaquinone and Wortmannin Analogs Prepared in the Wipf group

Wortmannin **1-35** and viridin **1-36** are two members of the viridin family that contain a tricyclic furan moiety,[15] which is also present in the structure of halenaquinone **1-34** (Scheme 1-9). As a result of their unselective kinase activities, wortmannin **1-35** and viridin **1-36** are unsuitable therapeutic candidates.[16] However, a research project in the Wipf group involves the design and discovery of protein tyrosine and phosphatidylinositol 3-kinase (PI-3 kinase) inhibitors. [17-19]



Scheme 1-10 Natural products containing the reactive tricyclic furan group

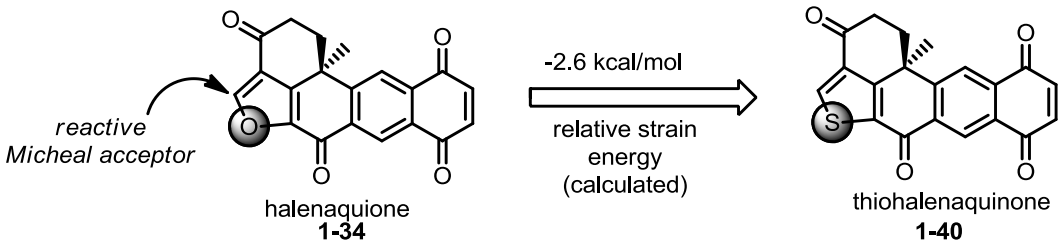
The proposed biological mechanism of action of these molecules involves a Michael addition of the Lys-802 (P110 PI-3-kinase) residue to the tetrahydrofuran group to form covalent adducts such as **1-38** that inactivate protein function.[20,21] This strategy is supported by the diallylamine adduct of wortmannin (PX-866 **1-39**) developed in the Wipf group that is a potent inhibitor of phosphoinositide (PtdIns)-3-kinase (IC_{50} = 0.1 nmol/L)[22], as depicted in Scheme 1-11.



Scheme 1-11 Proposed mechanism of action for kinase inhibition and the design of inhibitor PX-866 **1-39**

The Wipf group has also studied halenaquinone **1-34** and derivatives that target Pfnek-1 protein kinase which is essential to the malaria parasite *Plasmodium falciparum*.[23] Malaria is a disease with three to five hundred million clinical cases and more than two million deaths yearly.[24,25] Its prevention has been the focus of the U.S. Army since the infection of the disease causes a potential health hazard to its worldwide personnel. The Walter Reed Army Institute of Research (WRAIR) supports new treatments for

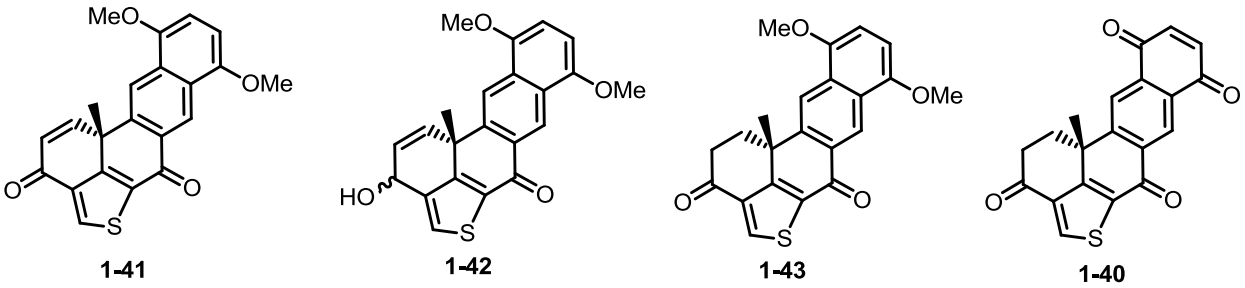
drug-resistant strains of malaria.[26] A more selective Pfnek-1 protein kinase inhibitor was reported by Wipf *et al.*[27,28] that replaces the furan ring with a thiophene. This new analog was designed to attenuate the electrophilic reactivity which was supported by computational calculations indicating a 2.6 kcal/mol lower strain energy for the new thiophene analog (Scheme 1-12).



Scheme 1-12 Proposed analog of halenoquinone **1-34**-thiohalenaquinone **1-40**

In collaboration with the Dow group at WRAIR, several thiohalenoquinone analogs were screened for Pfnek-1 activity and the results are summarized in Table 1-1.[28]

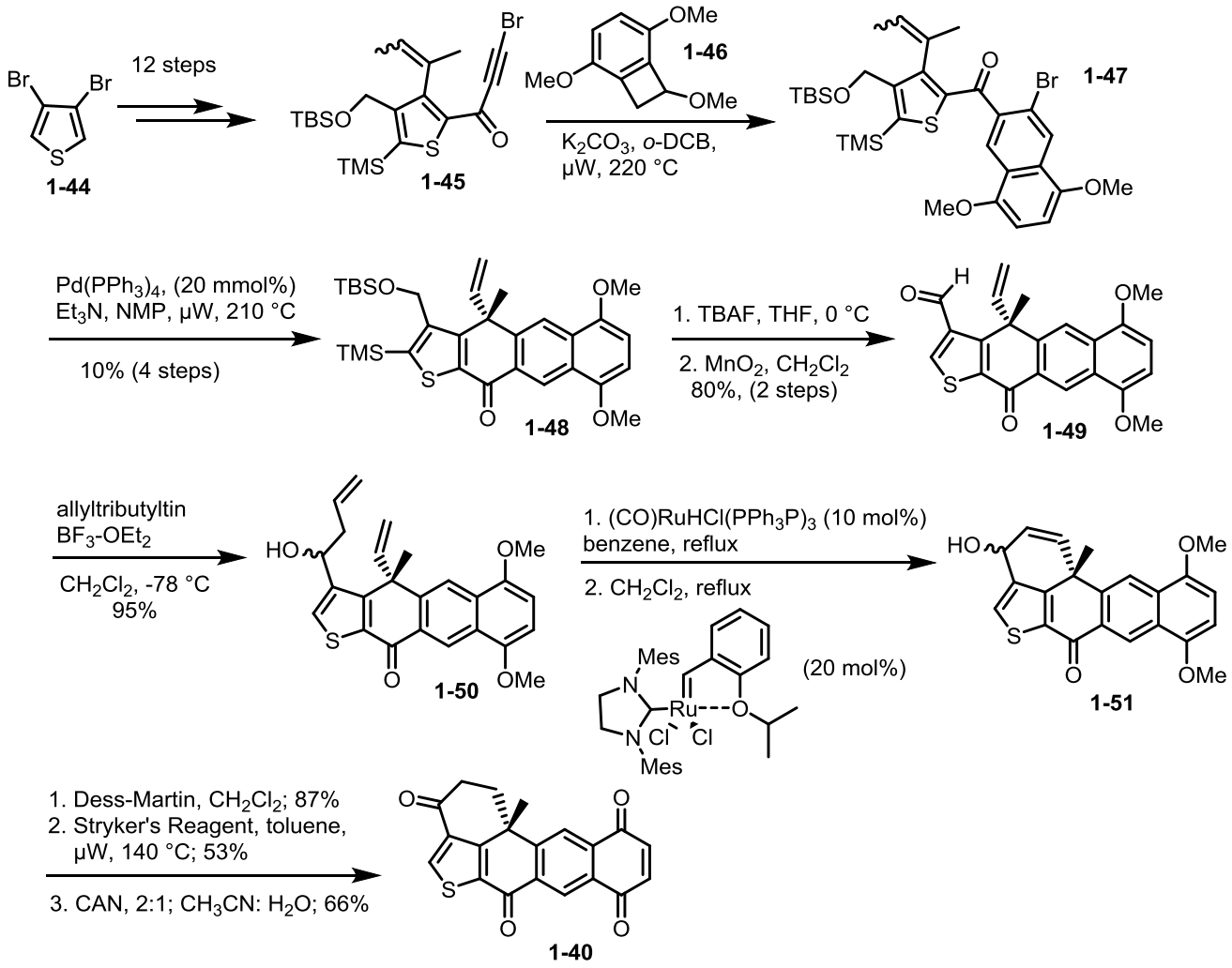
Table 1-1 IC_{50} values of thiohalenoquinone analogs



entry	Thiohalenaquinone analog	IC_{50} (μM)*
1	**1-41**	2.8-3.9
2	**1-42**	>2500
3	**1-43**	>2500
4	**1-40**	4.6-6.7

* Several thiohalenoquinone analogs were screened for Pfnek-1 activity.

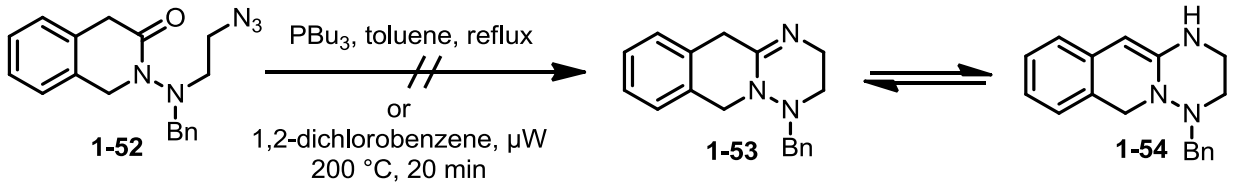
Thiohalenaquinone **1-40** could be obtained by Diels-Alder cycloaddition of diene precursor **1-46** with **1-45** (prepared in 12 linear steps from 2,3-dibromothiophene **1-44**). Intramolecular Heck-cyclization provided **1-48** with 10% overall yield over 4 steps. Deprotection and conversion to aldehyde **1-49** followed by allylation furnished alcohol **1-50** as a mixture of diastereomers. Treatment of **1-50** with Hoveyda-Grubbs 2nd generation ruthenium catalyst proceeded to give the multi-functionalized pentacyclic intermediate **1-51** that was further manipulated into thiohalenaquione **1-40** in a few steps (Scheme 1-13).



Scheme 1-13 Preparation of thiohalenaquinone **1-40**

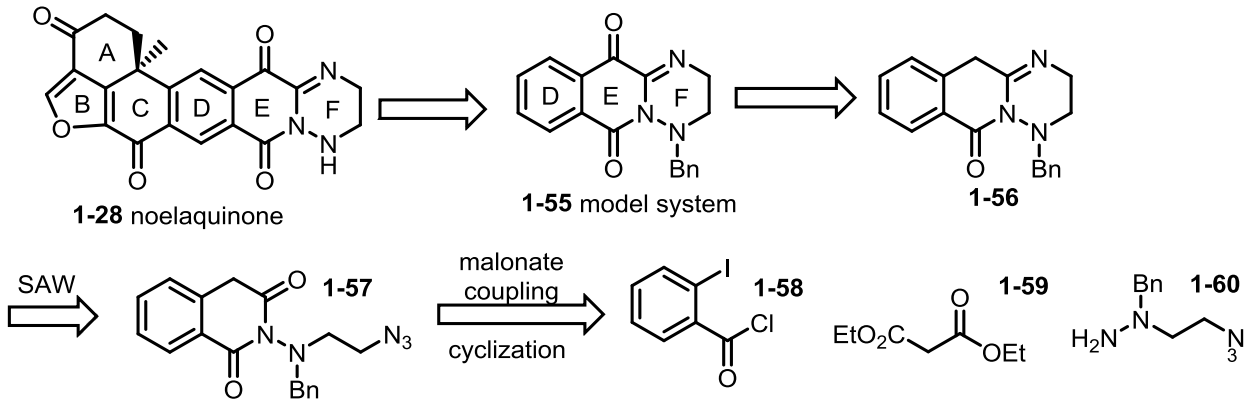
1.1.5 Model Studies toward the DEF Ring System of Noelaquinone

Our initial attempts to construct 1,2,4- triazine-containing scaffolds were unsuccessful using the SAW conditions outlined in Scheme 1-14.[9]



Scheme 1-14 SAW reaction attempts on lactams

A second generation approach to the DEF ring system of noelaquinone **1-28** was developed (Scheme 1-15). The pivotal homophthalimide **1-55** can be prepared from acylation of hydrazine **1-60** and subsequent arylation-cyclization. For this model system, an intramolecular SAW reaction on homophthalimide **1-57** was envisioned to construct the tricyclic ring system.[9,29]

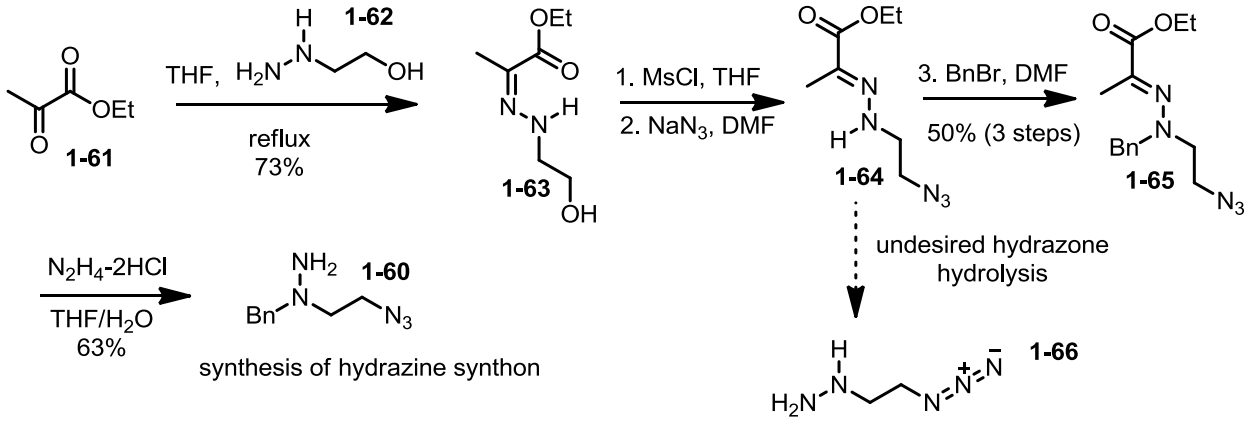


Scheme 1-15 Retrosynthesis of the model system **1-55**

1.1.5.1 Synthesis of Homophthalimide 1-57

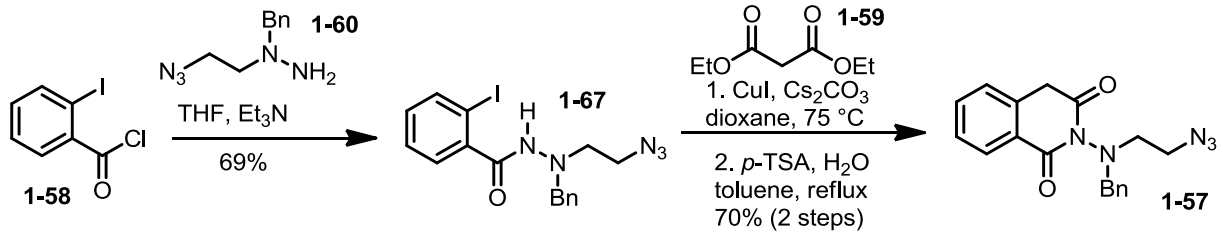
After screening numerous hydrazine protecting groups, it was found that the ethyl pyruvate derived hydrazone was suitable for the proposed transformations.[30]

Thus, condensation of 2-hydroxyethylhydrazine **1-62** with ethyl pyruvate **1-61** gave hydrazone **1-63**, which was readily converted to azide **1-64** via mesylate displacement. The stability of the hydrazone moiety was very important[31] since the undesired hydrolysis could generate the low molecular weight azide **1-66**, which has been shown to be explosive (Scheme 1-16).[1,9,29]



Scheme 1-16 Synthesis of hydrazine **1-60**

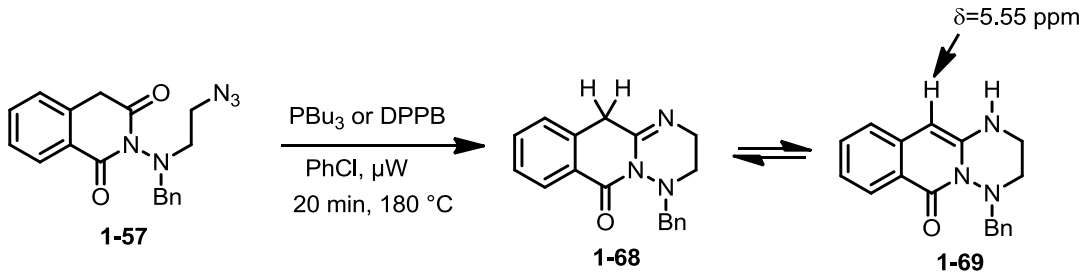
The potentially explosive *N*-benzylhydrazine **1-60**, produced by cleavage of hydrazone **1-65**, was used directly in the next step to provide acyl hydrazide **1-67**.[32] Treatment of **1-67** with CuI, picolinic acid, diethylmalonate **1-59**, and Cs_2CO_3 in dioxane provided an α-arylmalonate intermediate[33,34] (not shown) that was used in the next step following workup (Scheme 1-17). A cyclization/decarboxylation of the α-arylmalonate intermediate was promoted with cat. *p*-TSA to furnish homophthalimide **1-57**.[9,29]



Scheme 1-17 Preparation of homophthalimide **1-57**

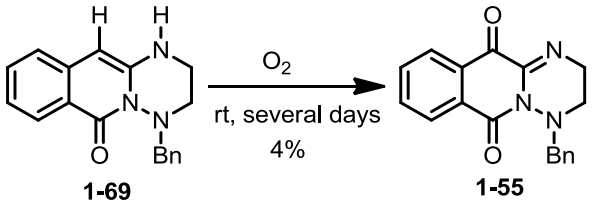
1.1.5.2 Oxidation and Staudinger/*aza* -Wittig Reaction

The initial approach toward the DEF ring model system **1-52** started with the SAW reaction followed by benzylic oxidation of the corresponding intermediate (Scheme 1-18). It was previously shown that treatment of azide substrate **1-57** with either PBu_3 or DPPB using microwave irradiation conditions gave triazine **1-68**. It was also determined that tautomer **1-69** was preferred as indicated by the vinyl-proton peak at 5.55 ppm in the ^1H NMR spectrum.[29]

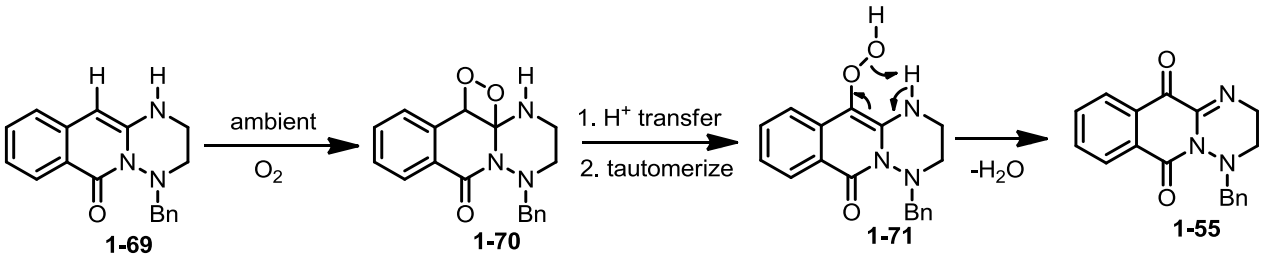


Scheme 1-18 Staudinger/*aza*-Wittig reaction followed by oxidation

Interestingly, enamine **1-69** undergoes a facile oxidation when stored at room temperature for several days (Scheme 1-19). The proposed mechanism involves the formation of a hydroperoxy intermediate **1-70**[35], followed by an opening of the cyclic peroxide and proton transfer to form **1-71**. The desired DEF ring system **1-55** was obtained after dehydration (Scheme 1-20).[29]



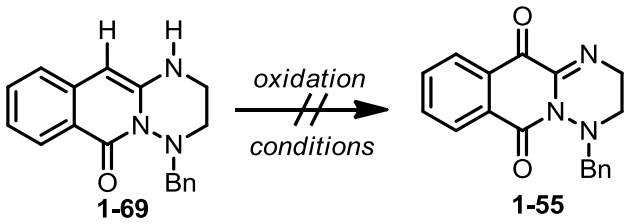
Scheme 1-19 Model system obtained by auto-oxidation



Scheme 1-20 Proposed mechanism for auto-oxidation of enamine **1-69**

However, efforts to identify a controlled conversion of **1-69** to the desired model system **1-55** were not successful, as the conditions mostly resulted in a decomposed material (Table 1-2). The strategy was then redirected toward the oxidation of the benzylic position before performing the SAW reaction.[29]

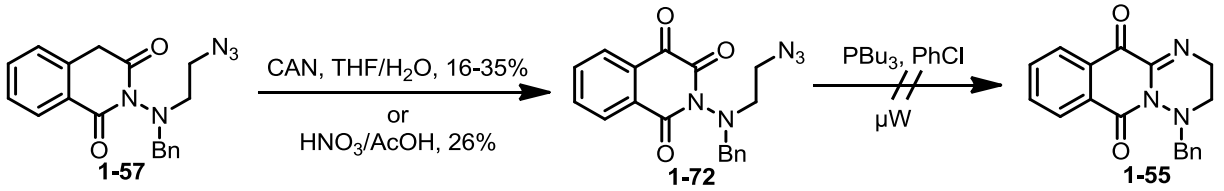
Table 1-2 Oxidation of enamine **1-69**



entry	reagent	solvent	temperature	time	result
1[36]	Fremy's salt	EtOH(aq.)	rt	12 h	SM*
2[37]	CAN	THF (aq.)	rt	24 h	decomposition
3	CAN on alumina	THF (aq.)	rt	12 h	decomposition
4	$K_3Fe(CN)_6$, Cs_2CO_3	THF (aq.)	rt	12 h	decomposition
5	5% CAN, $NaBrO_3$	THF (aq.)	rt	2.5 h	decomposition

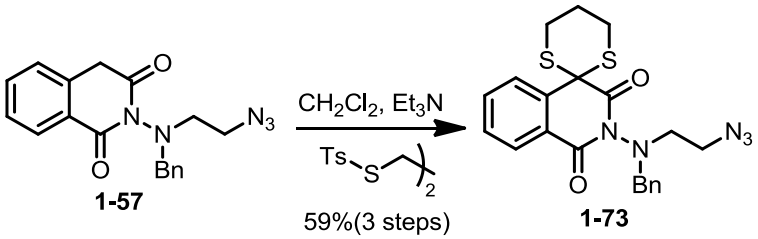
*Starting material was identified by TLC.

Successful benzylic oxidations using CAN in aqueous THF or HNO_3/AcOH gave ketone **1-72** albeit in modest yields. However, subsequent SAW cyclization attempts did not provide the dione **1-55** (Scheme 1-21). At this point, a ketone protecting group strategy was investigated.[29]



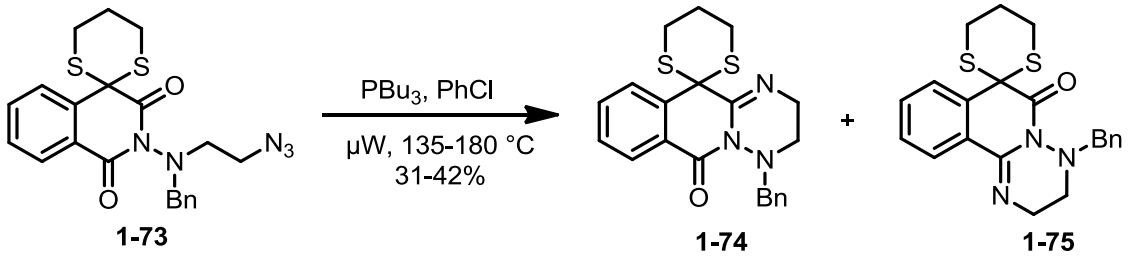
Scheme 1-21 Preparation of model system **1-55** using an oxidation/SAW sequence

A cyclic thioketal was introduced for the incorporation of the necessary benzylic oxidation state (Scheme 1-22) and was anticipated to provide a more compatible substrate for the SAW reaction.[38] The cyclic thioketal **1-73** was obtained in 3 steps from acyl hydrazide **1-57** in 59% yield.[9,29]



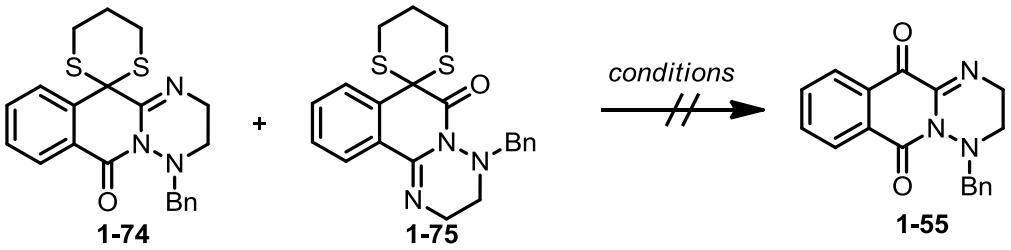
Scheme 1-22 Preparation of cyclic thioketal **1-73**

When subjected to the microwave irradiation SAW conditions, thioketal azide **1-73** was converted to a mixture of inseparable regioisomers **1-74** and **1-75** in low to moderate yields, as shown in Scheme 1-23. Through the use of high-temperature ^{1}H NMR analysis, it was not possible to conclusively determine the composition of the apparent mixture. All attempts to remove the thioketal resulted in either no reaction or decomposition (Table 1-3).[29]



Scheme 1-23 Putative regioisomers from the Staudinger/*aza*-Wittig reaction

Table 1-3 Removal of cyclic thioketal from SAW product **1-74** and **1-75**

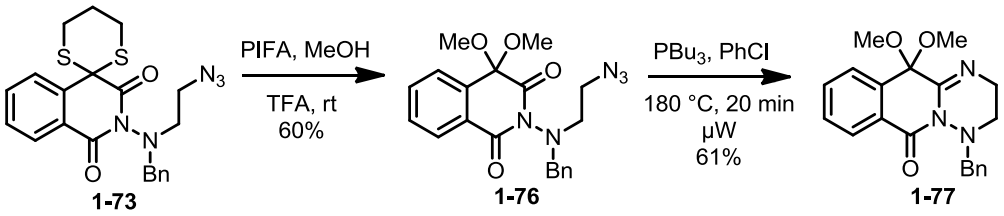


entry	reagent	solvent	temperature	time	result
1[39]	PIFA	CH_3CN/H_2O	rt	40 min	decomposition
2[40]	NBS	acetone/H_2O	0 ℃	5 min	decomposition
3[41]	$CuCl_2$, CuO	acetone/H_2O	rt	6 h	SM*
4[42]	I_2	DMSO	rt; 100 ℃	1.5 h; 1 h	decomposition
5[43]	PIFA	MeOH/H_2O	rt	30 min	decomposition
6	CAN	CH_3CN/H_2O	rt	1 h	decomposition
7	PIFA, AcOH	THF/H_2O	rt	1.5 h	decomposition
8	30% H_2O_2	MeOH	rt	40 min	decomposition
9[44]	$Hg(OAc)_2$	CH_3CN/H_2O	rt	12 h	decomposition
10	$AgNO_3$, NCS	CH_3CN/H_2O	0 ℃	3 h	decomposition

11[45]	Chloramine T	EtOH/H_2O	rt	9.5 h	SM*
12[46]	$NaNO_2$, TFA	H_2O	rt	20 h	decomposition

*Starting material was identified by TLC.

As a result of the difficulties in the removal of the thioketal functionality, an alternative conversion to the dimethoxylketal **1-76** was accomplished using PIFA in dry MeOH in 60% yield.[39] This dethionylation-protecting group exchange proved to be pivotal for the success of the intramolecular SAW reaction to cleanly afford triazine **1-77** in 61% yield (Scheme 1-24).[9,29]



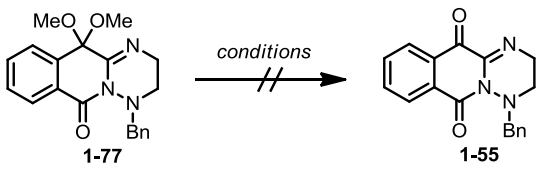
Scheme 1-24 Desulfurization/SAW sequence to arrive at dimethyketal **1-77**

1.2 RESULTS AND DISCUSSION

1.2.1 Hydrolysis of Dimethoxyketal to Ketone

A series of mild ketal hydrolysis conditions were attempted (Table 1-4) and led to either decomposition products or recovery of starting material.

Table 1-4 Mild hydrolysis conditions

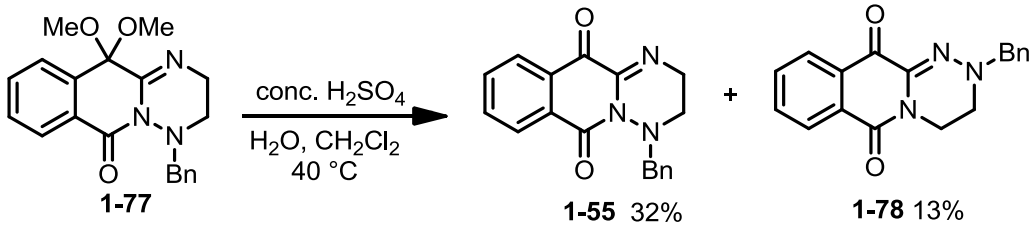


entry	reagent	solvent	temperature	time	result
1	HCl	acetone	50 ℃	12 h	decomposition
2[47]	I_2	acetone	rt	12 h	SM*
3[48]	*p*-TSA	acetone	rt	24 h	SM*
4	HCl	AcOH	rt	24 h	decomposition
5[49]	$Bi(NO_3)_3$ $5H_2O$	CH_2Cl_2	40 ℃	12h	no reaction
6	$BiBr_3$	H_2O	rt; reflux	24h; 2 h	unknown product

*Starting material was identified by TLC.

After substantial reaction optimizations, it was determined that treatment of **1-77** with a mixture of conc. H_2SO_4 in H_2O/CH_2Cl_2 (1/1/2- volume ratio) at 40 ℃ for 12 h could provide the desired triazine-dione **1-55** along with an unexpected regioisomer **1-78** in 32% and 13% yields, respectively (Scheme 1-25).[9]

The structures of both of the triazine regioisomers were unequivocally determined by X-ray crystallographic analysis (Figure 1).[9]



Scheme 1-25 Hydrolysis of dimethyl ketal **1-77**

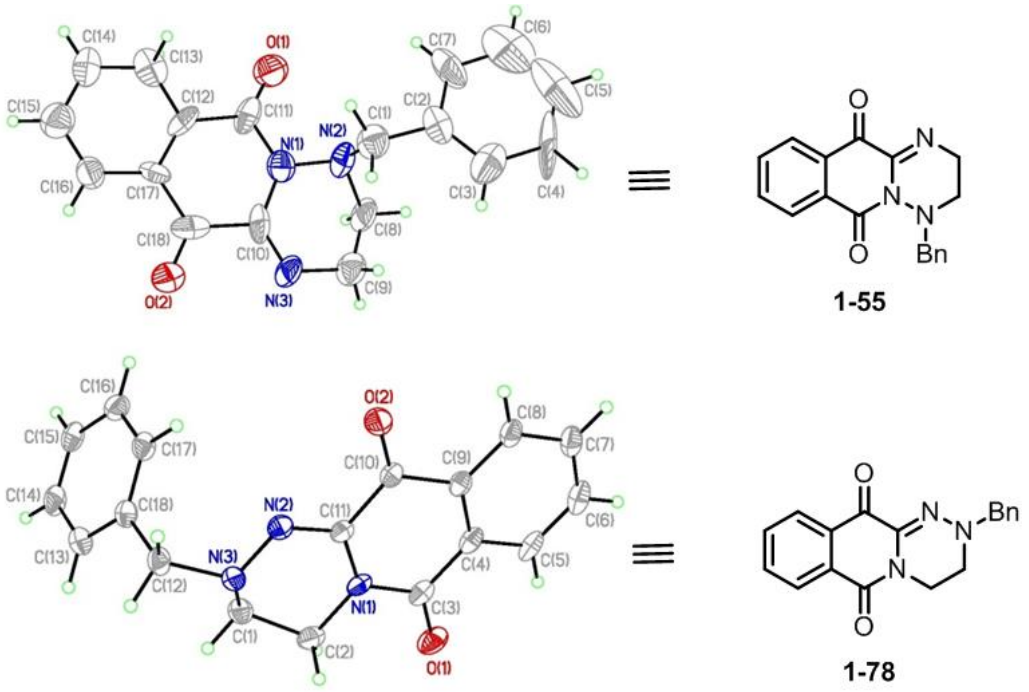
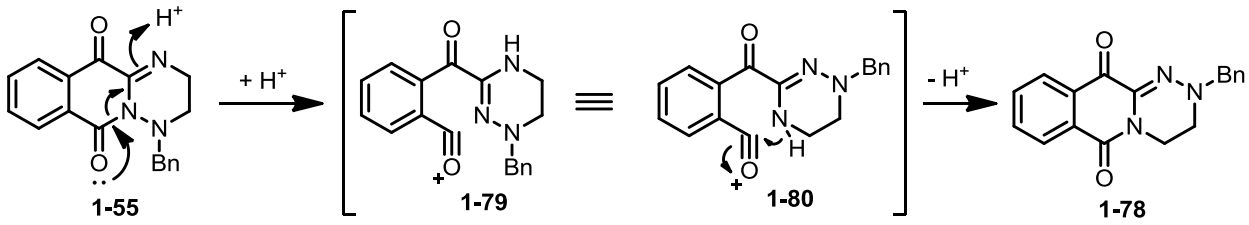


Figure 1 X-ray crystallographic analysis of two regioisomers **1-55** and **1-78**

A plausible mechanism for the conversion of **1-55** into **1-78** under acidic conditions is depicted in Scheme 1-26.[50] An acid-mediated ring opening process presumably gives an initial oxonium ion intermediate **1-79**. Nucleophilic attack of the resulting secondary amine to the oxonium species followed by deprotonation afforded the observed regioisomer **1-78**. Furthermore, it was found that the isomerization products could be formed preferentially through the use of weak acids, such as formic acid.

While this strategy was successful in assembling the DEF rings of a model system, we were unable to identify conditions that avoided the accompanying isomerization.



Scheme 1-26 Proposed mechanism for isomerization of **1-55**

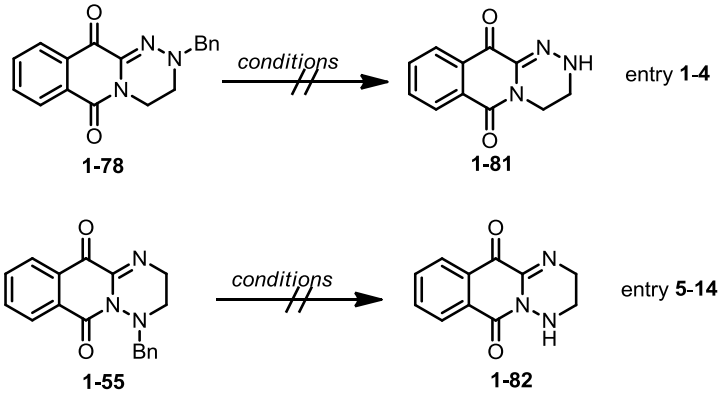
1.2.2 Removal of Benzyl Protecting Group

With the key tricycle **1-55** in hand we turned our attention to the removal of the *N*-benzyl group. A series of conditions were screened including both reductive and oxidative methods depicted in Table 1-5.

Unfortunately, all of these attempts were not productive and either gave decomposition products or recovery of unreacted starting materials (Table 1-5).

The efforts to convert the benzyl group into other functional groups to facilitate removal were also not successful (Table 1-6, entries 1-2). In addition, a complete isomerization of **1-55** into **1-78** was observed under catalytic hydrogenation conditions (Table 1-5, entry 8).

Table 1-5 Conditions to remove benzyl group

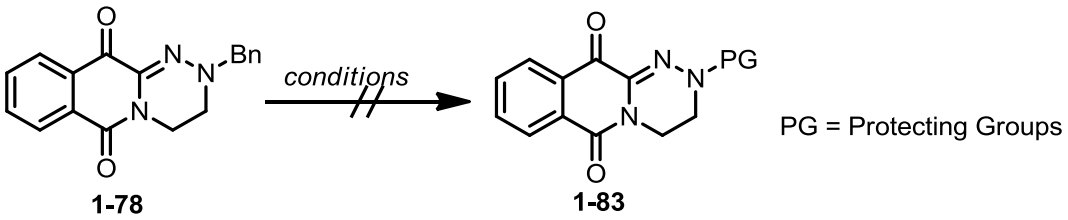


entry	reagent	solvent	temperature	time	result
1[51]	BBr_3	CH_2Cl_2	rt	12 h	decomposition
2[52]	5% Pd/C, H_2	1,1-dichloroethane/MeOH	rt	12 h	unknown product
3[53,54]	$Pd(OH)_2$, H_2	MeOH	rt	12 h	decomposition

4[52]	5% Pd/C, H_2	1,1,2-trichloroethane	rt	5 h	decomposition
5[55]	5% Pd/C, H_2	MeOH	rt	12 h	decomposition
6[56,57]	5% Pd/C, HCOOH	MeOH	rt	12 h	unknown product
7[58]	5% Pd/C, 1,4-cyclohexadiene	MeOH	rt	12 h	decomposition & SM*
8[56,57]	0.2 eq 5% Pd/C, HCOOH	MeOH	rt	12 h	**1-78** (56%)
9[56,57]	2 eq 5% Pd/C, HCOOH	MeOH	rt	12 h	decomposition
10[59]	Zn, ammonium formate	MeOH	rt	12 h	decomposition
11[60]	$FeCl_3$	CH_3CN	rt	12 h	decomposition
12[61]	CAN	CH_3CN/H_2O	rt	12 h	unknown product
13[62]	NIS	CH_2Cl_2	rt	12 h	SM*
14	$NaNO_2$, TFA	CH_2Cl_2/H_2O	rt	12 h	decomposition & SM*

*Starting material was identified by TLC and ^{1}H NMR.

Table 1-6 Conditions to convert benzyl group to other protecting groups



1-78 **1-83**

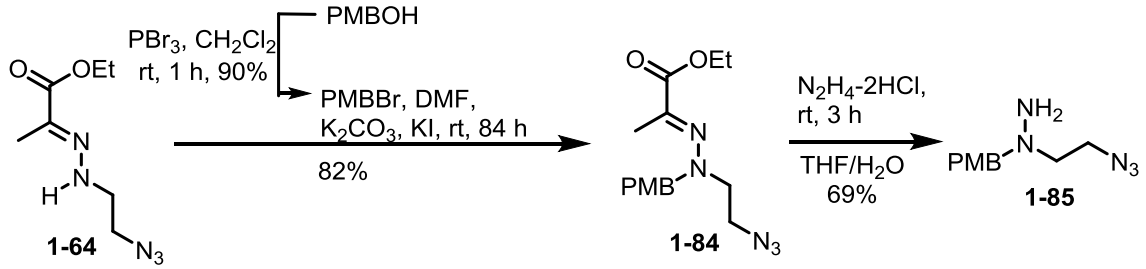
entry	reagents	solvent	temperature	time	results
1[63,64]	TrocCl, $NaHCO_3$	CH_3CN	rt	12 h	SM*
2[65]	$Pd(OH)_2$, PMHS, Boc_2O	EtOH	rt	12 h	decomposition

*Starting material was identified by TLC and ^1H NMR.

Unfortunately, the removal of the *N*-benzyl group proved problematic. An alternative strategy was devised using the *p*-methoxybenzyl (PMB) protecting group from the start of the reaction sequence.

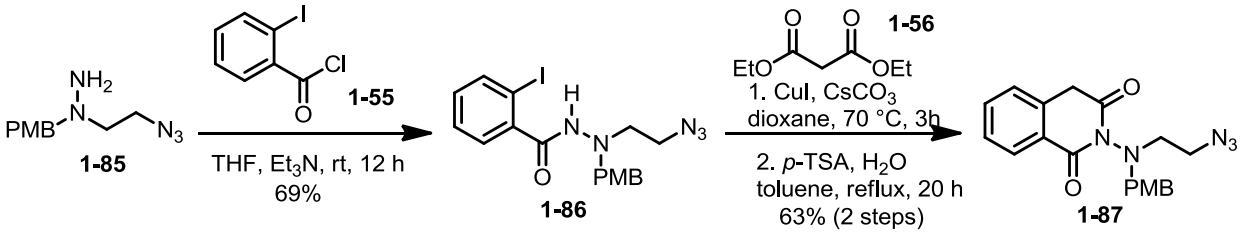
1.2.3 Model Studies for the DEF Ring System of Noelaquinone Using the PMB Protecting Group

The first few steps of this modified approach proceeded according to those previously described. Hydrazone **1-64** was treated with freshly-prepared *p*-methoxybenzyl bromide at room temperature to afford the *N*-PMB-hydrazone **1-84** in 82% yield. This hydrazone was then cleaved with excess hydrazine dihydrochloride in aqueous THF to yield hydrazine **1-85**, which was used immediately following chromatographic purification (Scheme 1-27).[9]



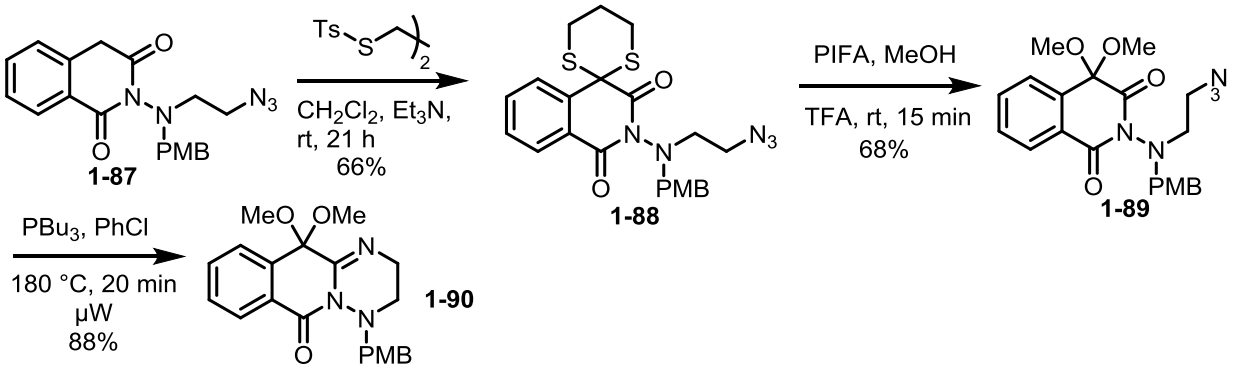
Scheme 1-27 Preparation of hydrazine **1-85**

A similar acylation-arylation-cyclization approach was used to assemble the PMB-containing homophthalimide **1-87** (Scheme 1-28, see Scheme 1-17). Once again, the resulting α-arylmalonate intermediate (not shown) was subjected to cat. *p*-TSA to complete the cyclization/decarboxylation cascade.[9]



Scheme 1-28 Preparation of homophthalimide **1-87**

The cyclic thioketal **1-88** was formed using trimethylene dithiotosylate. Transformation of cyclic thioketal **1-88** to dimethyl ketal **1-89** was accomplished with iodobenzenebistrifluoroacetate (PIFA) in methanol in the presence of trifluoroacetic acid. The subsequent SAW reaction proceeded smoothly under microwave irradiation to afford the desired triazine **1-90** in 88% yield (Scheme 1-29).[9]



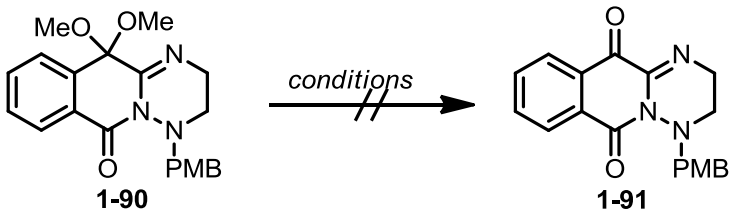
Scheme 1-29 Preparation of triazine **1-90**

1.2.4 Removal of the PMB Protecting Group and Hydrolysis of the Dimethoxyacetal

The remaining steps toward the preparation of the DEF rings of noelaquinone **1-82** involved the hydrolysis of the dimethyl acetal and PMB removal. The application of our previously successful acetal

exchange conditions to **1-90** did not provide dione **1-91**. We speculated that the strongly acidic conditions might be incompatible with the PMB group, which may have contributed to the decomposition. Therefore, several milder conditions were attempted with similarly unproductive results (Table 1-7).[9]

Table 1-7 Conditions to remove dimethyl acetal

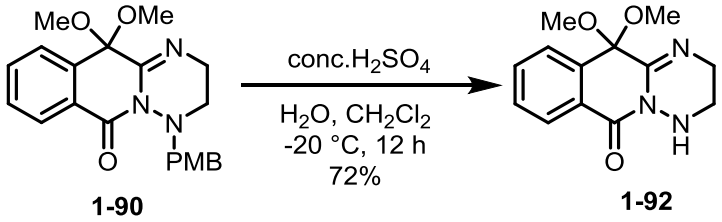


1-90 **1-91**

entry	reagent	solvent	temperature	time	result
1	conc. H_2SO_4	CH_2Cl_2/H_2O	40 ℃	12 h	decomposition
2[66-68]	$LiBF_4$	CH_3CN/H_2O	rt; 55 ℃	8 h; 1 h	SM*
3[69]	amberlyst-15	acetone/H_2O	rt	40 h	SM*
4[70]	PPTS	acetone/H_2O	reflux	18 h	SM*

*Starting material was identified by TLC and 1H NMR.

In order to decrease the presumed acid lability of **1-90**, this compound was treated with a H_2SO_4-H_2O/CH_2Cl_2 mixture at -20 ℃ for 12 h, which instead provided the dimethyl acetal-containing triazine derivative **1-92** in 72% yield (Scheme 1-30).[9]



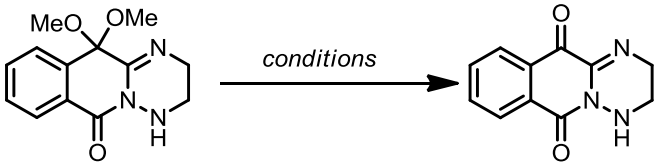
1-90 **1-92**

Scheme 1-30 Removal of the PMB group

Based on this interesting result, our deprotection strategy was reversed. Following extensive reaction optimization conditions (Table 1-8), the final hydrolysis to **1-82** without concomitant isomerization was accomplished by subjecting ketal **1-92** to conc. H_2SO_4 in an H_2O/CH_2Cl_2 mixture at

room temperature for 6.25 h. Interestingly, the different triazine substituents control the isomerization rates (**1-77** and **1-92**). It was rationalized that the oxocarbenium ion formed in the hydrolysis of **1-92** was stabilized to a greater extent due to the smaller lipophilicity of the whole molecule, which largely helps the solvation of **1-92** in the aqueous solution. Therefore, dimethyl ketal **1-92** was found to react at a slightly lower temperature and with no apparent isomerization. The structural assignment of **1-82** was confirmed by X-ray crystallographic analysis (Figure 2).[9]

Table 1-8 Dimethoxyacetal hydrolysis to afford model system **1-82**



1-92 **1-82**

entry	reagent	solvent	temperature	time	result
1[71]	TFA	CH_2Cl_2/H_2O	rt	12 h	SM*
2	HCl	$MeOH/H_2O$	rt	12 h	undetermined product
3	H_2SO_4	$MeOH/H_2O$	rt	12 h	SM*
4[72]	DDQ	CH_3CN/H_2O	rt	18 h	SM*
5	conc. H_2SO_4	THF/H_2O	4 ℃	12 h	SM*
6	conc. H_2SO_4	THF/H_2O	rt	12 h	SM*
7	conc. H_2SO_4	CH_2Cl_2/ H_2O	4 ℃	12 h	SM*
8	conc. H_2SO_4	CH_2Cl_2/H_2O	35 ℃	12 h	decomposition
9	conc. H_2SO_4	CH_2Cl_2/H_2O	rt	6.25 h	62%

*Starting material was identified by TLC and ^1H NMR.

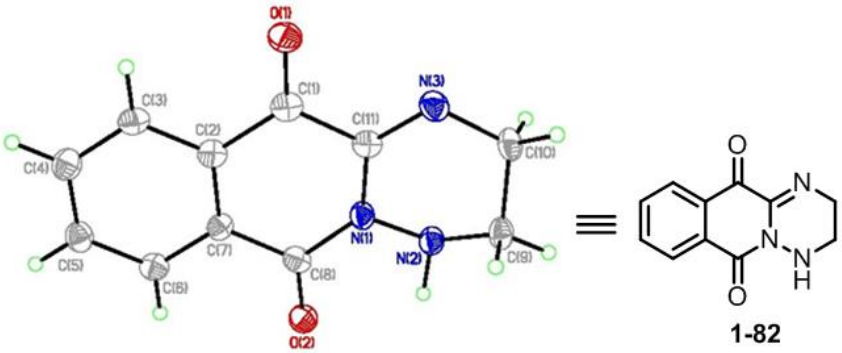


Figure 2 X-ray crystallographic analysis of model system **1-82**

1.3 CONCLUSION

In summary, we have demonstrated a first generation approach toward the preparation of the DEF model system of noelaquinone, in which a Staudinger/*aza*-Wittig (SAW) reaction was utilized to construct the tetrahydro-1,2,4-triazine moiety. In this sequence, homophthalimides **1-57** and **1-85** were accessed via a Cu(I)- catalyzed C-arylation of diethyl malonate followed by cyclization-decarboxylation. Isomerization of **1-55** to **1-78** was observed under acidic hydrolysis conditions when the *N*-benzyl protecting group was used, whereas the use of the PMB protecting group with milder acidic deprotection conditions avoided the isomerization. The DEF ring system of noelaquinone was synthesized in 13 steps and 2% overall yield, and its structure was confirmed by X-ray analysis.[9]

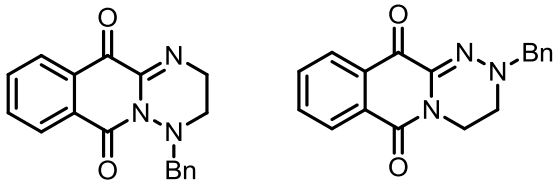
1.4 EXPERIMENTAL PART

General: All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃ employed a CO_2/acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene

were purified using an alumina column filtration system. All other reagents and solvents were used as received unless otherwise noted. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}•4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

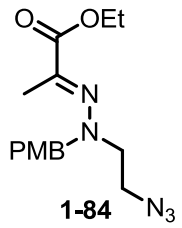
NMR spectra were recorded using XWIN-NMR software. ^{1}H NMR spectra were obtained at 300, 400, 500, 600 or 700 MHz in $CDCl_3$. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak unless otherwise noted. Melting points were determined on a Mel-Temp II and are uncorrected. High-resolution mass spectrometry (HRMS) data (ESI/APCI technique) were recorded using a Waters Q-Tof Ultima API-US instrument. HRMS data (EI technique) were recorded using a Micromass Autospec instrument. Mass spectrometry data were also recorded using an Applied Biosystems MDS SCIEX API 2000 LC/MS/MS system.

All organic azides and azide waste products should be considered toxic as well as potentially explosive and must be handled and stored with care. Avoid using halogenated solvents when performing reactions involving sodium azide, in addition to using halogenated solvents in reaction workup. Avoid quenching/manipulating/treating sodium azide reactions with acid, as the generation of trace amounts of hydrazoic acid (HN_3) may result in an explosion. In general, a safety shield must be used when conducting reactions involving either sodium azide or organic azide derivatives.



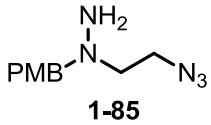
1-55 **1-78**

2-Benzyl-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-*b*]isoquinoline-6,11-dione (1-78); 4-benzyl-3,4-dihydro-2*H*-[1,2,4]triazino[2,3-*b*]isoquinoline-6,11-dione (1-55). After concentrated H_2SO_4 (3.0 mL) was added dropwise into H_2O (3.0 mL), the mixture was stirred for 5 min, cooled to room temperature and treated with a solution of **1-77** (29.8 mg, 0.0848 mmol) in CH_2Cl_2 (6.0 mL). The reaction mixture was stirred at 40 ℃ for 12 h under argon, cooled to 25 ℃, and solid Na_2CO_3 was added until pH>7. The mixture was extracted with CH_2Cl_2 (3×30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexanes:EtOAc, 1:1 with 1% Et_3N) to afford **1-78** (3.5 mg, 0.011 mmol, 13%) as golden needles and **1-52** (8.4 mg, 0.028 mmol, 32%) as yellow crystals. **1-78**: Mp 171.1-174.5 ℃; IR (neat) 2923, 2852, 1659, 1597, 1527, 1453, 1361, 1342, 1314, 1281, 1246, 1079, 1064, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (td, *J* = 7.0, 2.0 Hz, 1 H), 8.32 (t, *J* = 6.5 Hz, 1 H), 7.80 (dtd, *J* = 18, 7.5, 1.5 Hz, 2 H), 7.35-7.33 (m, 5 H), 4.73 (s, 2 H), 4.15 (t, *J* = 5.2 Hz, 2 H), 3.25 (t, *J* = 5.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$; some rearrangement and decomposition occurred during the spectral data collection) δ 173.8, 157.7, 135.6, 134.4, 133.3, 130.3, 129.0, 128.8, 128.4, 127.2, 63.1, 43.8, 38.1; HRMS (ESI) *m/z* calcd for $C_8H_{16}N_3O_2$ ($[M+H]^+$) 306.1243, found 306.1250. **1-55**: Mp 121.1-124.3 ℃; IR (neat) 3068, 2917, 2974, 2924, 2865, 1698, 1597, 1489, 1376, 1355, 1226, 1084, 1070, 984, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.28 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.87 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.79 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.54 (d, *J* = 7.0 Hz, 2 H), 7.4-7.3 (m, 3 H), 4.10 (s, 2 H), 3.97 (t, *J* = 6.5 Hz, 2 H), 3.12 (t, *J* = 6.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$; some rearrangement and decomposition occurred during the spectral data collection) δ 176.0, 157.5, 144.4, 135.6, 135.2, 133.8, 131.4, 130.1, 129.7, 129.5, 128.7, 128.3, 127.7, 58.7, 43.3, 40.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_3O_2$ ($[M+H]^+$) 306.1237, found 306.1243.



1-84

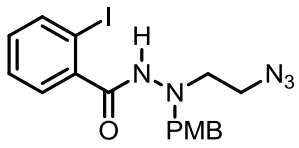
(E)-Ethyl 2-(2-(2-azidoethyl)-2-(4-methoxybenzyl)hydrazono)propanoate (1-84). To a solution of **1-64** (3.93 g, 45.4 mmol) in DMF (50 mL) was added of K_2CO_3 (8.18 g, 59.2 mmol), KI (9.82 g, 59.2 mmol), and 4-methoxybenzyl bromide (9.13 g, 45.4 mmol). The mixture was stirred at room temperature for 84 h, quenched with water (10 mL) and extracted with EtOAc (3×15 ml). The combined organic layers were washed with water (20 mL), brine(20 mL), dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (100% hexanes to hexanes:EtOAc, 1:1 gradient with 1% Et_3N) to afford **1-84** as a yellow oil(5.15 g, 16.1 mmol, 82%): IR(neat) 2954, 2097, 1707, 1610, 1510, 1299, 1245, 1126, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 3.98 (s, 2H), 3.80 (s, 3 H), 3.30 (t, *J* = 6.0 Hz, 2 H), 3.20 (t, *J* = 6.0 Hz, 2 H), 2.21 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 159.2, 153.2, 129.6, 128.6, 114.1, 61.8, 60.3, 55.8, 55.3, 49.7, 16.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_5O_3$ ($[M+H]^+$) 320.1723, found 320.1732.



1-85

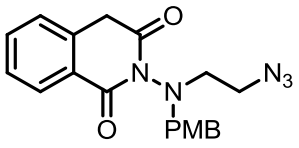
1-(2-Azidoethyl)-1-(4-methoxybenzyl)hydrazine (1-85). To a solution of **1-84** (477 mg, 1.49 mmol) in THF (20 mL) and H_2O (0.5 mL) at 25 ℃ was added hydrazine dihydrochloride (470 mg, 4.48 mmol). This mixture was stirred at 25 ℃ for 3 h, quenched with solid Na_2CO_3, and concentrated *in vacuo*. The resulting oil was immediately purified by chromatography on SiO_2 (hexanes:EtOAc, 1:1 with 1% Et_3N) to **1-85** as an unstable, colorless oil (227 mg, 1.03 mmol, 69%): IR (neat) 3338, 3344, 2934, 2831, 2097, 1610, 1510, 1461, 1243, 1172, 1031, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23(dt, *J* = 9.0, 2.5 Hz, 2

H), 6.86(dt, *J* = 9.0, 2.5 Hz, 2 H), 3.77 (s, 3 H), 3.64 (s, 2H), 3.44 (t, *J* =5.6 Hz, 2H), 2.70 (t, *J* = 2.8 Hz, 2H), 2.69(br s, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ159.0, 130.2, 129.0, 113.8, 66.7, 58.3, 55.1, 48.5; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_5O$ ($[M+H]^+$) 222.1355, found 222.1350.



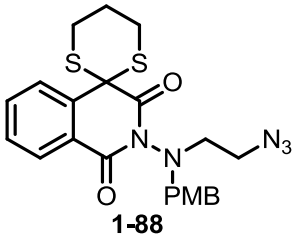
1-86

N'-(2-Azidoethyl)-2-iodo-N'-(4-methoxybenzyl)benzohydrazide (1-86). To a solution of **1-55** (259 mg, 0.972 mmol) in CH_2Cl_2 (20 mL) cooled to 0 ℃ was added a solution of **1-85** (226 mg, 1.02 mmol) in CH_2Cl_2 (5 mL) via syringe, followed by Et_3N (0.20 mL, 1.5 mmol). After addition, the vessel was removed from the ice bath and the solution was allowed to warm to 25 ℃ overnight. After 12 h, the reaction mixture was quenched with satd. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 ×10 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes:EtOAc, 4:1 with 1% Et_3N) to afford **1-86** (304 mg, 0.675 mmol, 69%) as colorless flake-like crystals: IR (neat) 3215.2, 3047.4, 2907.6, 2093.1, 1653.2, 1610.4, 1509.7, 1459.4, 1297.2, 1245.1, 1172.4, 1030.7, 820.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.40 (s, 1 H), 7.28 (dt, *J* = 8.5, 2.0 Hz, 2 H), 7.18 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.97 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.86 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.82 (dt, *J* = 9.0, 2.0 Hz, 2 H), 4.10 (s, 2 H), 3.73 (s, 3 H), 3.44 (t, *J* = 6.0 Hz, 2 H), 3.18 (t, *J* = 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 158.9, 140.3, 139.4, 131.0, 130.4, 128.6, 127.8, 113.6, 92.6, 59.8, 55.1, 54.4, 48.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}IN_5O_2$ ($[M+H]^+$) 452.0584, found 452.0564.



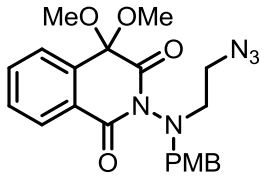
1-87

2-((2-Azidoethyl)(4-methoxybenzyl)amino)isoquinoline-1,3(2H,4H)-dione (1-87). To a flame-dried flask was added **1-86** (215 mg, 0.476 mmol), CuI (9.1 mg, 0.048 mmol), 2-picolinic acid (11.7 mg, 0.0951 mmol) and Cs_2CO_3 (465 mg, 1.43 mmol). The reaction mixture was purged 3x with N_2, and diluted with anhydrous dioxane (19 mL). After addition of **1-56** (94 mg, 0.59 mmol), the reaction flask was placed in a pre-heated oil bath at 70 ℃ under a N_2 atmosphere. TLC analysis (hexanes:EtOAc, 6:1) after 3 h showed that the starting material was consumed. The mixture was cooled to 25 ℃, quenched with satd. NH_4Cl (10 mL), extracted with EtOAc (3×10 mL), washed with brine (20 mL), and concentrated *in vacuo*. The residue was dissolved in toluene (13 mL) and H_2O (3 mL), and *p*-TSA (45.2 mg, 0.238 mmol) was added. The pink colored mixture was heated at reflux for 20 h, cooled to 25 ℃, and quenched with satd. $NaHCO_3$ (20 mL). The biphasic mixture was partitioned and then the aqueous phase was extracted with EtOAc (3x10 mL). The crude mixture showed one spot by TLC (hexanes: EtOAc, 5:1). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes:EtOAc, 10:1 to 5:1) to afford **1-87** (109 mg, 0.297 mmol, 63%) as a bright yellow oil: IR (neat) 3068, 2947, 2097, 1726, 1681, 1609, 1510, 1459, 1342, 1245, 1171, 1033, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.34 (dt, *J* = 8.5, 2.0 Hz, 2 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 6.76 (dt, *J* = 8.5, 2.0 Hz, 2 H), 4.35, 4.30 (AB, *J* = 12.0 Hz, 2 H), 3.96, 3.80 (AB, *J* = 22.0 Hz, 2 H), 3.71 (s, 3 H), 3.43-3.31 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 165.0, 159.1, 133.7, 130.6, 129.2, 128.8, 127.7, 127.0, 125.7, 113.6, 59.2, 55.2, 52.7, 50.1, 37.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_5O_3$ ($[M+H]^+$) 366.1566, found 366.1589.



1-88

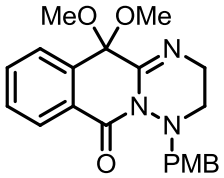
2'-((2-Azidoethyl)(4-methoxybenzyl)amino)-1'H-spiro[[1,3]dithiane-2,4'-isoquinoline]-1',3'(2'H)-dione (1-88). To a solution of **1-87** (109 mg, 0.297 mmol) in CH_2Cl_2 (30 mL) at 25 ℃ was added Et_3N (91.9 μL, 0.654 mmol) followed by trimethylene di(thiotosylate) (156 mg, 0.357 mmol). The green-yellow solution was stirred at 25 ℃ under N_2 for 21 h, quenched with satd. NH_4Cl (10 mL), extracted with CH_2Cl_2 (2×10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexanes:EtOAc, 4:1) to afford **1-88** (92.1 mg, 0.196 mmol, 66%) as a colorless oil: IR (neat) 3009, 2927, 2871, 2097, 1723, 1681, 1611, 1512, 1335, 1243, 1171,751, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.10 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.63 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.48 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.42 (dt, *J* = 8.0, 2.0 Hz, 2 H), 6.81 (dt, *J* = 8.0, 2.0 Hz, 2 H), 4.38, 4.34 (AB, *J* = 7.0 Hz, 2 H), 3.80 (td, *J* = 13.5, 2.0 Hz, 1 H), 3.75 (td, *J* =13.5, 2.0 Hz, 1 H), 3.74 (s, 3 H), 3.45-3.30 (m, 4 H), 2.73 (dt, *J* = 13.5, 3.5 Hz, 1 H), 2.66 (dt, *J* = 13.5, 3.5 Hz, 1 H), 2.32-2.29 (m, 1 H), 2.05-1.97 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 163.1, 159.2, 136.9, 134.2, 130.7, 129.7, 129.5, 129.0, 125.0, 113.7, 59.6, 55.3, 52.2, 49.8, 49.4, 29.0, 28.9, 23.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}N_5O_3S_2Na$ ($[M+Na]^+$) 492.1140, found 492.1170.



1-89

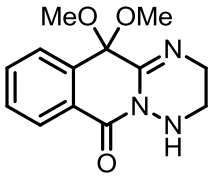
2-((2-Azidoethyl)(4-methoxybenzyl)amino)-4,4-dimethoxyisoquinoline-1,3(2H,4H)-dione (1-89). To a solution **1-88** (92.1 mg, 0.196 mmol) in dry MeOH (8.0 mL) was added TFA (43.7 μL, 0.588 mmol) and PIFA (288 mg, 0.670 mmol) at 23 ℃. The mixture was stirred for 15 min when TLC analysis (hexanes:EtOAc, 4:1) of an aliquot neutralized with Na_2CO_3 showed that the starting material was converted to a slightly more polar spot. After 20 min, the reaction was quenched with solid Na_2CO_3 until pH>7, causing the yellow solution to change to colorless as the pH increased. The mixture was extracted with CH_2Cl_2 (4×10 mL), dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2

(hexanes:EtOAc, 5:1 to 3:1 with 1% Et_3N) to afford **1-89** (56.6 mg, 0.133 mmol, 68%) as a pale yellow oil: IR (neat) 2992, 2936, 2863, 2097, 1739, 1691, 1739, 1512, 1458, 1333, 1282, 1243, 1172, 1083, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 12.0 Hz, 1 H), 7.65 (d, *J* = 4.0 Hz, 2 H), 7.56-7.53 (m, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 8.5 Hz, 2 H), 4.38, 4.29 (AB, *J* = 12.5 Hz, 2 H), 3,71 (s, 3 H), 3.50-3.45 (m, 1 H), 3.37-3.33 (m, 3 H), 3.30 (s, 3 H), 3.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 163.8, 159.3, 135.7, 133.6, 130.9, 130.3, 129.2, 128.6, 126.6, 126.5, 113.7, 95.9, 59.5, 55.3, 52.7, 52.2, 52.1, 49.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_5O_5Na$ ($[M+Na]^+$) 448.1597, found 448.1629.



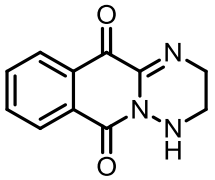
1-90

11,11-Dimethoxy-4-(4-methoxybenzyl)-3,4-dihydro-2*H*-[1,2,4]triazino[2,3-b]isoquinolin-6(11H)-one (1-90). To a flame-dried microwave vial was added a solution of **1-89** (56.6 mg, 0.133 mmol) in distilled PhCl (2.5 mL), followed by a solution of PBu_3 (46.0 mg, 0.228 mmol) in distilled PhCl (580 μL). The green-brown mixture was stirred at room temperature for 10 min then heated at 180 ℃ in the microwave reactor for 20 min. TLC analysis (EtOAc:hexanes, 4:1) showed that the starting material was converted to a much more polar spot. The dark purple solution was concentrated under a stream of N_2 and the residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 4:1 with 1% Et_3N) to produce **1-90** (44.5 mg, 0.117 mmol, 88%) as a dark brown oil: IR (neat) 3096, 3046, 2990, 2936, 2872, 1735, 1692, 1646, 1586, 1512, 1443, 1363, 1351, 1297, 1277, 1234, 1172, 1073, 1033, 938 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.69 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.61 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.42 (dt, *J* = 9.5, 2.5 Hz, 2 H), 6.85 (dt, *J* = 9.5, 2.5 Hz, 2 H), 3.97 (brs, 2 H), 3.76 (s, 3 H), 3.77-3.72 (m, 2 H), 3.35 (brs, 6 H), 3.14 (t, *J* = 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.4, 148.1, 135.6, 132.7, 131.0. 129.8, 129.0, 127.8, 127.3, 126.1, 113.9, 96.2, 57.6, 55.2, 52.4, 45.4, 38.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_3O_4$ (M^+) 381.1689, found 381.1718.



1-92

11,11-Dimethoxy-3,4-dihydro-2H-[1,2,4]triazino[2,3-b]isoquinolin-6(11H)-one (1-92). Concentrated H_2SO_4 (3 mL) was added dropwise into H_2O (3 mL), and the acid mixture was stirred for 5 min and cooled to 4 ℃. A solution of **1-90** (15.5 mg, 0.0406 mmol) in CH_2Cl_2 (10 mL) was added into the acid solution at 4 ℃. The reaction mixture was immediately cooled to -20 ℃, stirred at -20 ℃ for 12 h, and quenched with solid Na_2CO_3 at -20 - 4 ℃ until pH>7. The mixture was diluted with H_2O (20 mL), extracted with CH_2Cl_2 (3×30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc:hexanes, 4:1 with 1% Et_3N) to afford **1-92** (7.6 mg, 0.0291 mmol, 72%) as a light yellow solid: IR (neat) 3276.7, 3271.1, 3066.0, 2926.3, 2849.8, 2875.9, 2831.2, 1675.6, 1638.3, 1584.3, 1552.6, 1364.3, 1284.2, 1237.6, 1036.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.73 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.66 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.52 (br s, 1 H), 3.89 (t, *J* = 5.0 Hz, 2 H), 3.34 (s, 6 H), 3.28 (t, *J* = 5.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.7, 145.5, 136.1, 133.2, 130.0, 128.4, 126.4, 126.1, 96.0, 52.3, 46.5, 43.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}N_3O_3$([M+H]$^+$) 262.1192, found 262.1200.



1-82

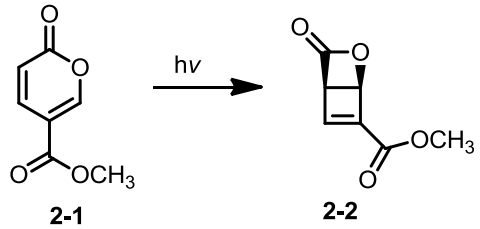
3,4-Dihydro-2H-[1,2,4]triazino[2,3-b]isoquinoline-6,11-dione (1-82). Concentrated H_2SO_4 (3 mL) was added dropwise into H_2O (3 mL), and the acid mixture was stirred for 5 min and cooled to room temperature. A solution of **1-92** (18.0 mg, 0.0689 mmol) in CH_2Cl_2 (10 mL) was added into the acid solution. The reaction mixture was stirred for 6 h 15 min at room temperature, and quenched with solid

Na_2CO_3 to pH>7. The mixture was diluted with H_2O (20 mL), extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude ^{1}HNMR showed that the reaction was complete. The product was purified by chromatography on SiO_2 (EtOAc:hexanes, 4:1 with 1% Et_3N) to afford **1-82** (9.2 mg, 0.0427 mmol, 62%) as yellow powder: IR (neat) 3282, 2924, 2867, 2850, 1694, 1661, 1609, 1596, 1581, 1458, 1437, 1379, 1297, 1241, 1215, 1102, 1010 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.25 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.85 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.76 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.64 (br s, 1 H), 4.05 (td, *J* = 5.0, 1.0 Hz, 2 H), 3.35-3.33 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 156.0, 141.8, 135.7, 133.8, 131.1, 129.2, 128.8, 128.0, 48.1, 42.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}N_3O_2$([M+H]$^+$) 216.0773, found 216.0759.

2.0 REACTIONS INVOLVING METHYL 3-OXO-2-OXABICYCLO[2.2.0]HEXANE-6-CARBOXYLATE

2.1 INTRODUCTION

Methyl 3-oxo-2-oxabicyclo[2.2.0]hexane-6-carboxylate **2-2** is a strained bicycle that contains a fused cyclobutene and a β-propiolactone moiety. This compound has been synthesized through a photochemical 4π-electrocyclization reaction from methyl coumalate **2-1**[73,74] (Scheme 2-1), which adopts a *syn* geometry as predicted by orbital symmetry analysis[75] (Figure 3).



2-1 **2-2**

Scheme 2-1 Electrocyclization of methyl coumalate **2-1** to methyl 3-oxo-2-oxabicyclo[2.2.0]hexane-6-carboxylate **2-2**

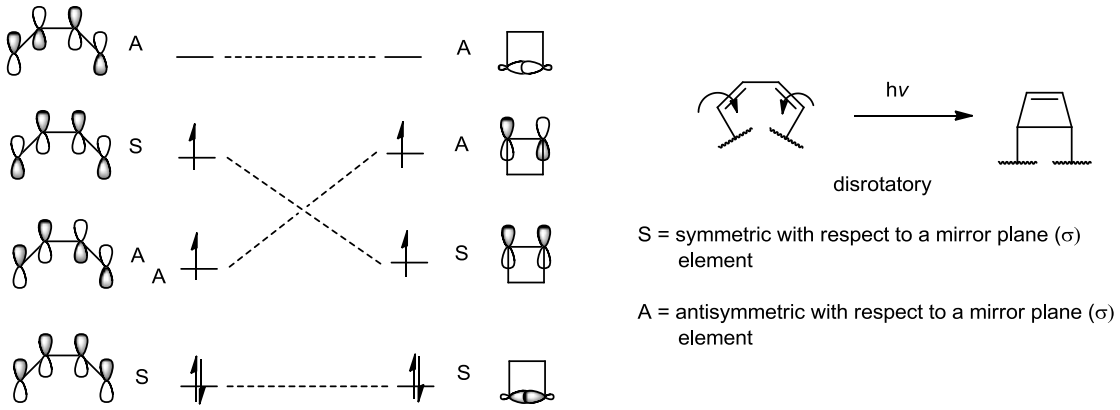
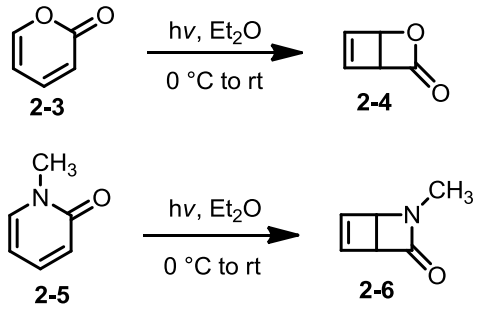


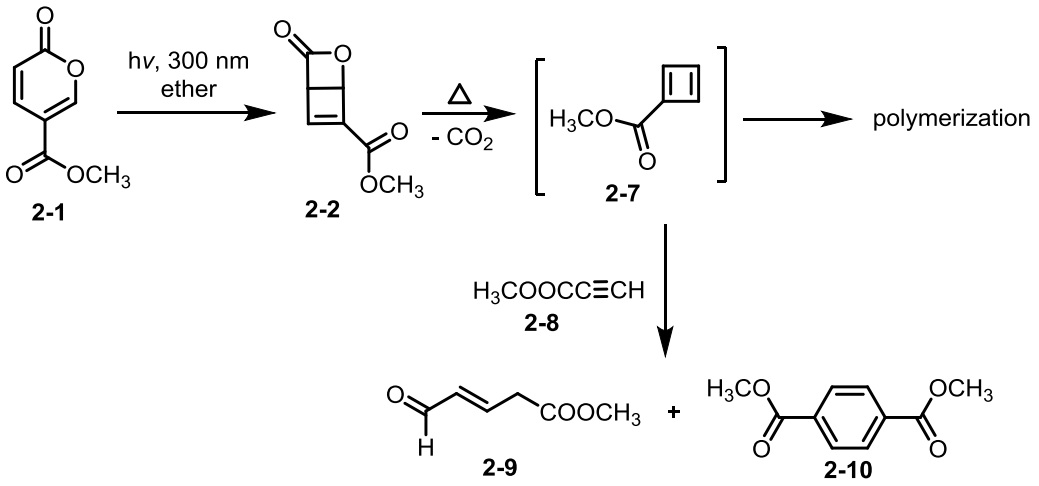
Figure 3 Orbital symmetry analysis of the photochemical 4π-electrocyclization[76]

Photochemical mediated electrocyclizations of this type were first reported by Corey *et al*. in 1964.[77] In these cases, the 2-pyrone **2-3** and *N*-methyl-2-pyridone **2-5** were subjected to UV irradiation to quantitatively afford the corresponding β-propiolactone **2-4** and β-lactam **2-6** (Scheme 2-2).



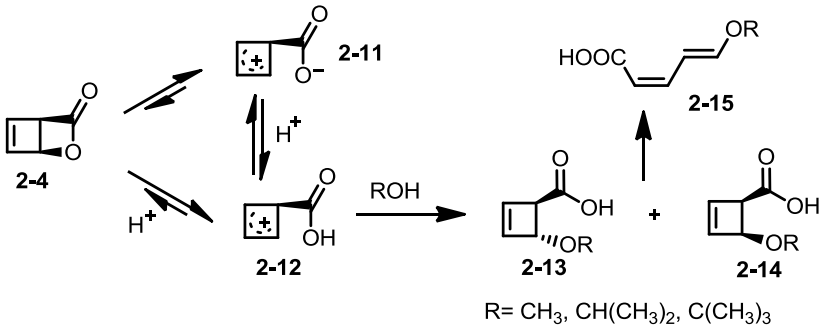
Scheme 2-2 Corey's synthesis of β-propiolactone **2-4** and β-lactam **2-6**

Neckers *et al.*[73] further elaborated this transformation using methyl coumalate **2-1** and irradiation at 300 nm to provide methyl 3-oxo-2-oxabicyclo[2.2.0]hexane-6-carboxylate **2-2** in quantitative yield. This compound underwent a thermal decarboxylation to presumably give a cyclobutadiene intermediate which readily polymerized. Trapping experiments using methyl propiolate **2-8** were used to support the existence of cyclobutene intermediate **2-7**.

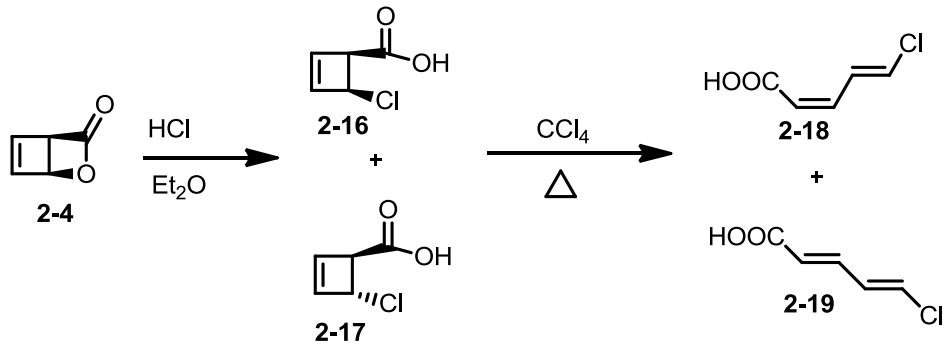


Scheme 2-3 Neckers' transformation of lactone **2-2**

Zwitterion **2-11** or cyclobutenyl cation **2-12** have been postulated as possible reaction intermediates using the photolytic alcoholysis transformation of 2-pyrone **2-4** into 5-alkoxy-2-*cis*-4-*trans*-pentadienoic acids **2-15** (Scheme 2-4).[78] This pathway was supported by treating 2-pyrone **2-4** with anhydrous hydrogen chloride to generate a 1/2.2 mixture of *trans*- and *cis*-chlorocyclobut-2-ene carboxylic acids **2-16** and **2-17**, which were converted to 5-chloro-2-*trans*-4-*trans*-pentadienoic acid **2-19** and 5-chloro-2-*cis*-4-*trans*-pentadienoic acid **2-18** upon heating in CCl_4 (Scheme 2-5).[78]

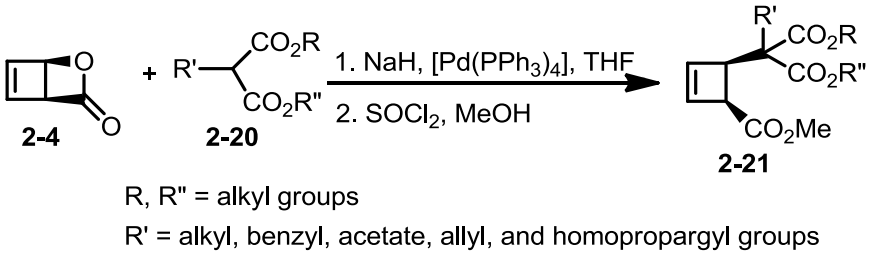


Scheme 2-4 Conversion of 2-pyrone 2-4 to 5-alkoxy-2-cis-4-trans-pentadienoic acids **2-15**



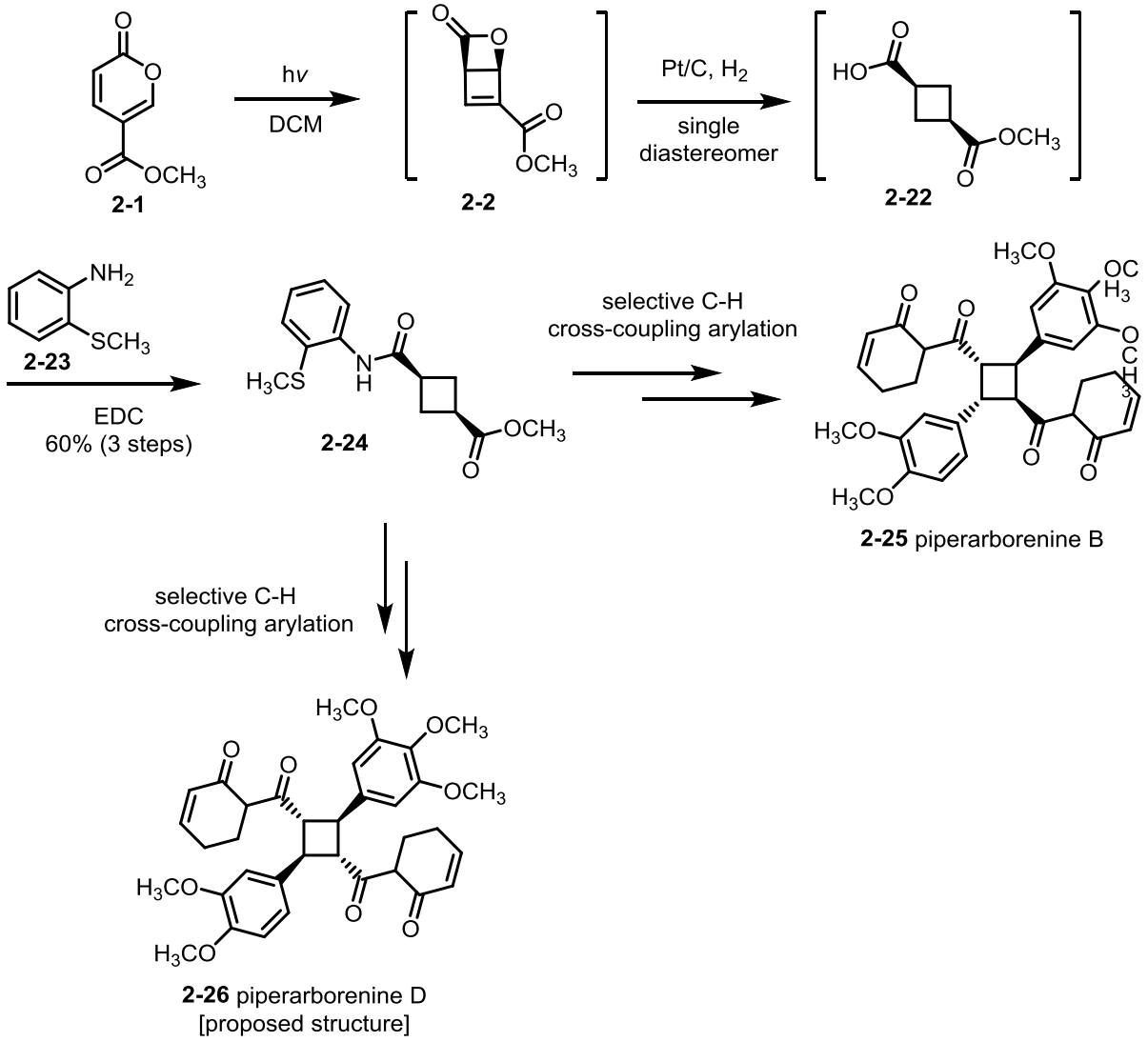
Scheme 2-5 Reaction between lactone **2-2** and anhydrous hydrogen chloride gas

Maulide *et al.* have converted lactone **2-4** into the *cis*-cyclobutene carboxylic acid derivatives **2-21** using a Tsuji-Trost reaction catalyzed by $Pd(PPh_3)_4$ and substituted malonate **2-20**. High diastereoselectivities were observed using numerous nucleophiles (Scheme 2-6).[79]



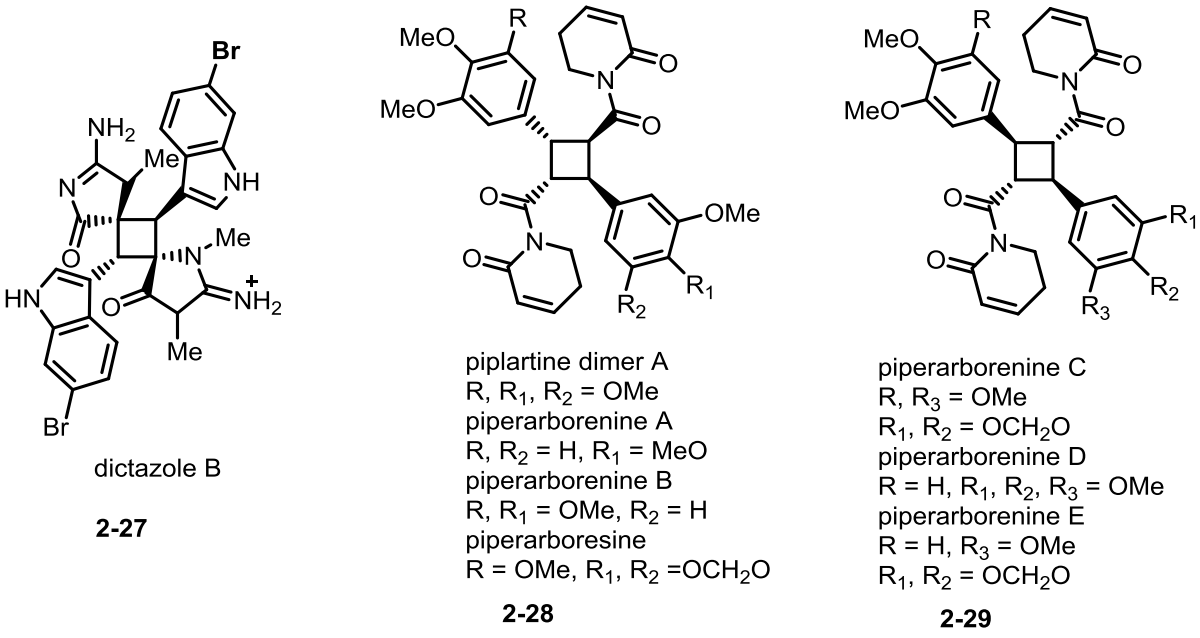
Scheme 2-6 Synthesis of cis-cyclobutene carboxylic acid derivatives **2-21**

In the total synthesis of piperarborenine B **2-25** and the reported structure of piperarborenine D **2-26**, Baran[74] *et al.* demonstrated a C-H functionalization strategy to construct these unsymmetrical cyclobutane-containing natural products starting from methyl coumalate. Pyrone **2-2** was prepared from methyl coumalate **2-1** by a photochemical electrocyclization. Subsequent treatment of pyrone **2-2** with Pt/C generated the *cis*-cyclobutane carboxylate **2-22**. The 2-aminothioanisole **2-23** was installed to direct the requisite C-H arylation reaction. This substrate was then converted to piperarborenine B **2-25** and piperarborenine D (reported structure) **2-26** by selective C-H cross-coupling arylation reactions (Scheme 2-7).

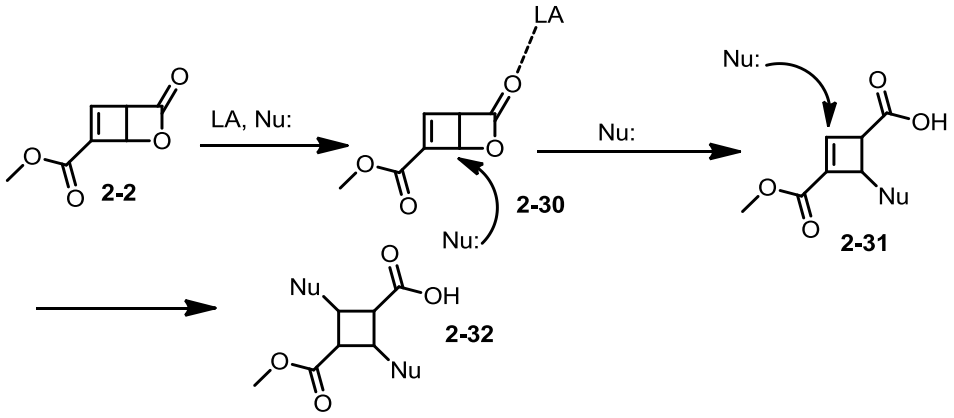


Scheme 2-7 Baran's total synthesis of piperarborenine B **2-25** and the reported structure of piperarborenine D **2-26**

The creative work of Maulide and Baran demonstrated the utility of cyclobutane-containing compounds originating from photocyclization of lactone **2-2**.[74,79] In addition, this approach serves as an inspiration to construct several additional cyclobutane-containing natural products[80-83] (dictazole B, piplartine dimer, piperarboresine, piperarborenine A-E; Scheme 2-8). It was envisioned that lactone **2-2** could undergo a ring opening via treatment with a suitable Lewis acid to give acid **2-32** (Scheme 2-9).



Scheme 2-8 Examples of cyclobutane-containing natural products

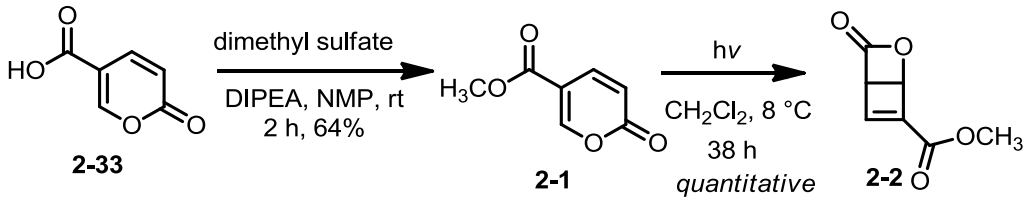


Scheme 2-9 Synthesis of cyclobutane-containing compounds **2-32**

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of Lactone 2-2

Following a well-precedented literature protocol,[73,74] the commercially available coumalic acid **2-33** was first converted to methyl coumalate **2-1** in 64% yield. Lactone **2-2** was obtained quantitatively by irradiation using a 450 W Hanovia lamp for 38 h. A solution of lactone **2-2** (1 mg/mL) could be stored at -20 ℃ for 1 month without noticeable loss of integrity.

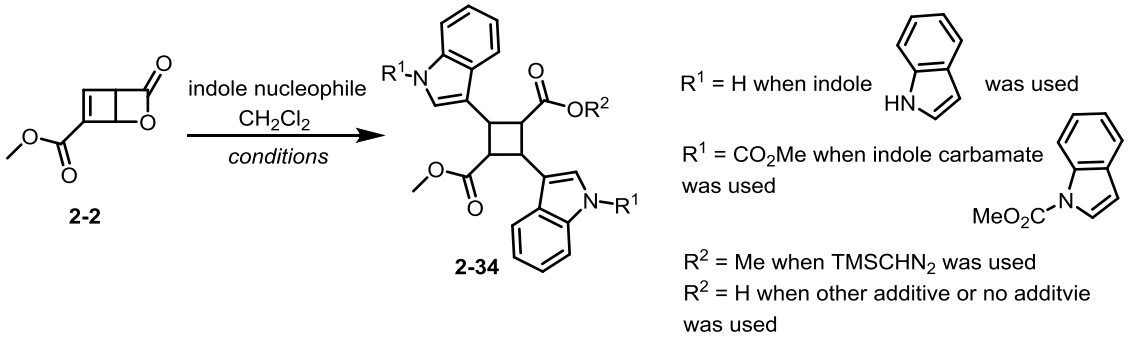


Scheme 2-10 Preparation of lactone **2-2**

2.2.2 Reaction between Lactone 2-2 and Nucleophiles with Lewis Acids

The reaction of lactone **2-2** with several indole-based nucleophiles and a series of Lewis acids was examined with the ultimate goal to prepare dictazole-related natural products. The initial results of these conditions to promote the two-step reaction to substituted cyclobutanes are summarized in Table 2-1.

Table 2-1 Conditions with indole-based nucleophiles

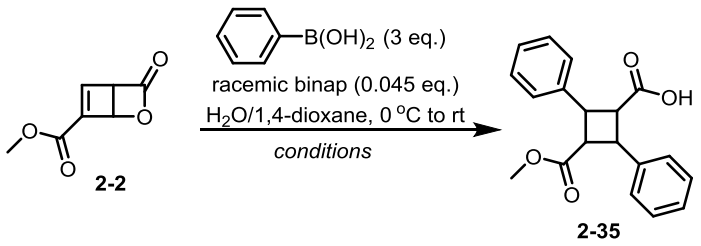


entry	nucleophile	Lewis acid	temperature	additive	time	result
1	3 eq. indole	1.3 eq. $BF_3 \cdot OEt_2$	-78 ℃ to -40 ℃; rt	5 eq. $TMSCHN_2$	5h; 12 h	indolo-indoline dimer (23%)
2[84,85]	3 eq. indole	1.3 eq. MAD	-78 ℃ to -40 ℃; 0 ℃	NA	4h; 36 h	undetermined product
3[84,85]	3 eq. indole carbamate	1.3 eq. MAD	0 ℃ to rt	NA	36 h	SM*
4	3 eq. indole carbamate	0.3 eq. $BF_3 \cdot OEt_2$	0 ℃ to rt	1 eq. 2,6-di-*tert*-butyl-4-methylpyridine	40 h	methyl coumalate* + undetermined product
5[86]	3 eq. indole	2 eq. $BH_3 \cdot THF$, 2 eq. CH_3COOH	0 ℃	2 eq. 1,1'-bi-2-naphthol	30 h	methyl coumalate* + undetermined product
6[86]	3 eq. indole	2 eq. $BH_3 \cdot THF$, 2 eq. CH_3COOH	-20 ℃ to rt	2 eq. 1,1'-bi-2-naphthol	48 h	decomposition
7	3 eq. indole carbamate	0.3 eq. $BF_3 \cdot OEt_2$	0 ℃ to rt	1 eq. 2,6-di-*tert*-butyl-4-methylpyridine	48 h	undetermined product
8	3 eq. indole	0.3 eq. $BF_3 \cdot OEt_2$	-20 ℃ to rt	NA	5 h	decomposition
9[87]	3 eq. indole	1 eq. $SnCl_4$	-20 ℃ to rt	2 eq. 1,1'-bi-2-naphthol, 200 wt% molecular sieves	5 h	decomposition
10[88-90]	3 eq. indole	0.05 eq. AgOAc	-20 ℃	0.1 eq. binaphyl phosphoric acid	48 h	methyl coumalate*

*Starting material and methyl coumalate were identified by TLC.

Several rhodium-catalyzed conjugated additions of phenylboronic acids to lactone **2-2** were also attempted (Table 2-2). Unfortunately, the strong Lewis acids BF_3•OEt_2 and binaphthol-$SnCl_4$ caused only decomposition, with no desired product **2-35** obtained. Rhodium-catalyzed conjugated additions were also not observed.

Table 2-2 Rhodium-catalyzed conjugated additions

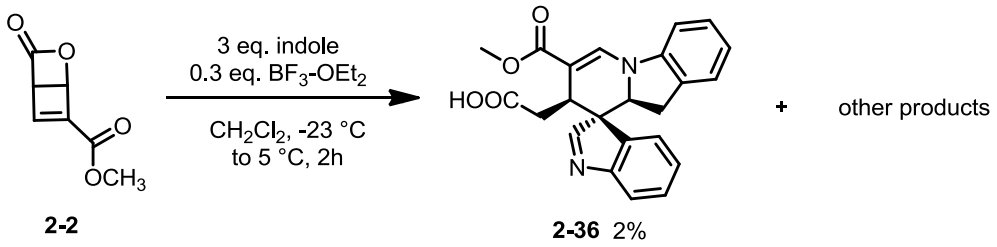


entry	catalyst	time	result
1[91]	0.03 eq. $[Rh(cod)Cl]_2$	24 h	methyl coumalate*
2	0.03 eq. $Rh(acac)(C_2H_4)_2$	48 h	SM*

*Starting material and methyl coumalate were identified by TLC.

2.2.3 Reaction between Lactone 2-2 and Indole with BF_3•OEt_2

The incorporation of an indole nucleophile using the BF_3•OEt_2 catalyzed conditions provided encouraging results as indicated by crude LCMS analysis. Several compounds which were difficult to isolate and fully characterize showed mass correlation to double indole adducts of lactone **2-2**. After considerable effort, one of these products was purified in 2% yield and its unexpected fused ring system **2-36** structure was determined by X-ray crystallographic analysis (Figure 4).



Scheme 2-11 Fused rings **2-36** from lactone **2-2**

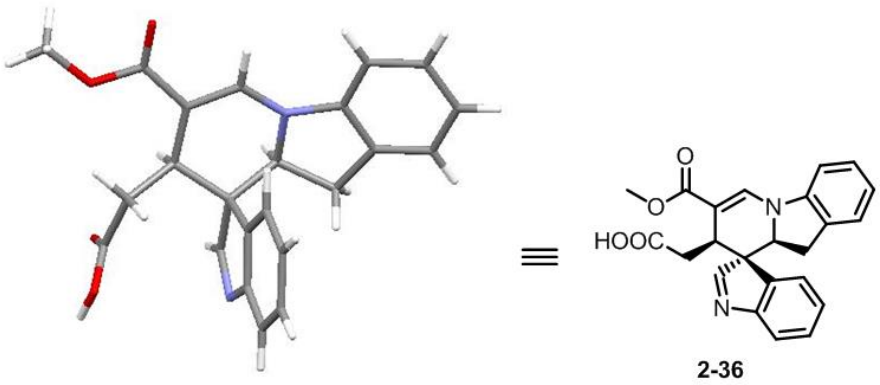
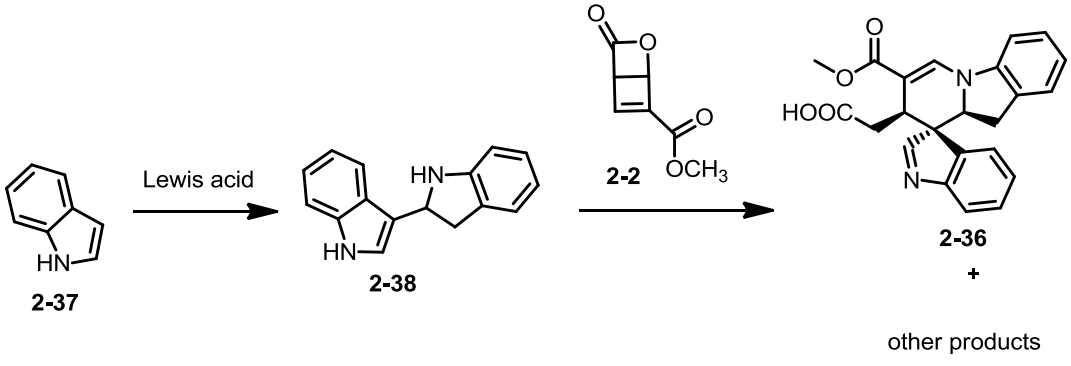


Figure 4 X-ray crystallographic analysis of **2-36**

2.2.4 Reaction between Lactone 2-2 and Indole Dimer 2-38 with BF_3•OEt_2

It was proposed that indolo-indoline dimer **2-38** is formed under the Lewis acid conditions and can then undergo addition and cyclization with lactone **2-2**.

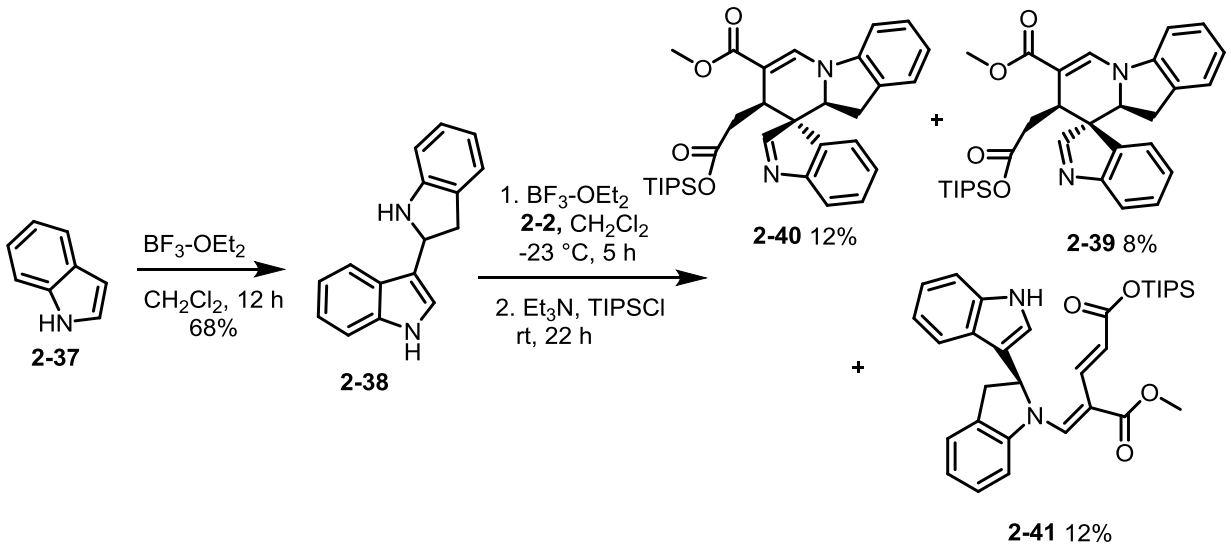


Scheme 2-12 Hypothesis for the generation of indole dimer **2-38**

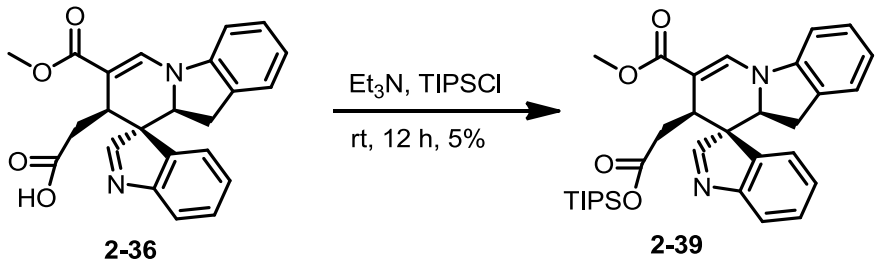
In order to test this hypothesis, indolo-indoline dimer **2-38** was prepared in 68% yield using $BF_3 \cdot OEt_2$. Subsequent treatment of indolo-indoline dimer **2-38** with lactone **2-2** and $BF_3 \cdot OEt_2$ at -23 ℃ for 5 h resulted in three distinct products with identical mass traces corresponding to the adduct according to LCMS. Purification and isolation using Florisil™ provided a clean sample of this mixture containing the three products. Since all of these products contain a carboxylic acid functionality, the mixture was converted to the TIPS-ester by treatment with TIPSCl and triethylamine (Scheme 2-13).

Despite the low yields, we were able to isolate and separate these compounds. One of these adducts **2-39** was found to have an identical ^1H NMR spectrum to that of the TIPS-ester formed in low yield from the X-ray sample of **2-36** (Scheme 2-14).

The remaining products were crystallized and their structures were elucidated by X-ray crystallographic analysis. A diastereomer of **2-40** (Figure 5) was obtained along with a conjugated diene product **2-41** (Figure 6).



Scheme 2-13 Reaction between lactone **2-2** and indolo-indoline dimer **2-38** in the presence of $BF_3 \bullet OEt_2$



Scheme 2-14 Preparation of **2-39**

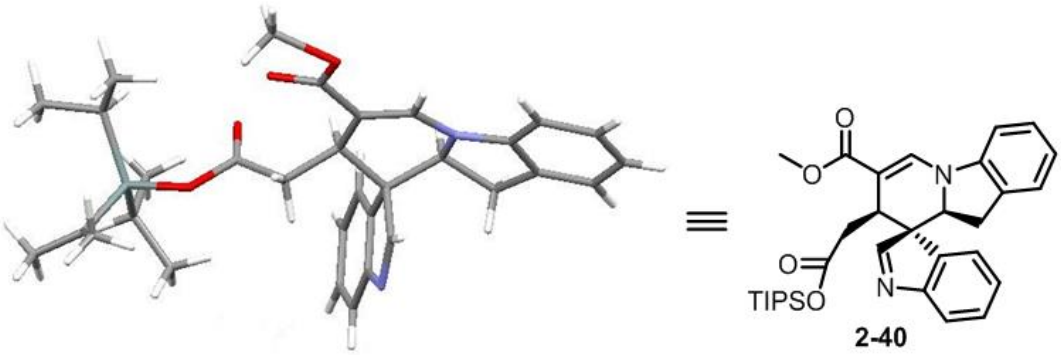


Figure 5 X-ray crystallographic analysis of **2-40**

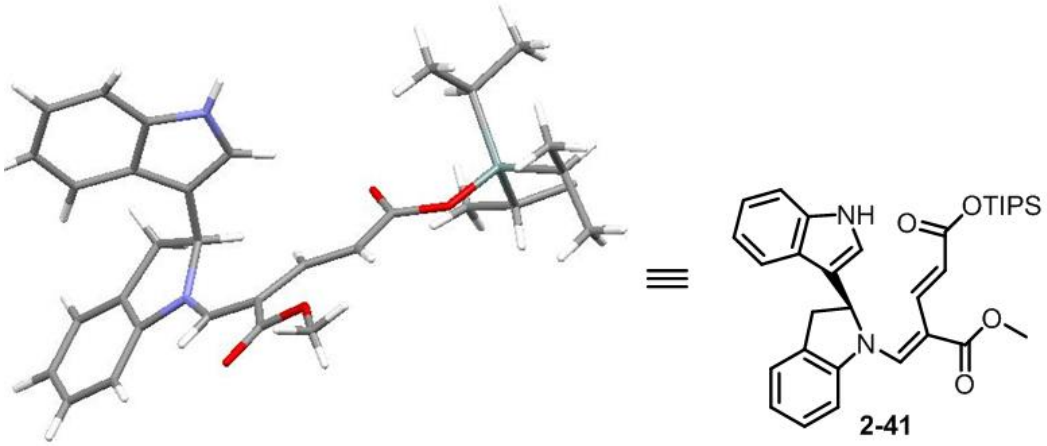
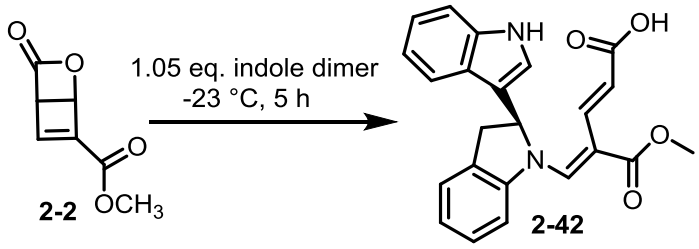


Figure 6 X-ray crystallographic analysis of **2-41**

2.2.5 Reaction between Lactone 2-2 and Indole Dimer 2-38

These preliminary investigations using lactone **2-2** and the indolo-indoline dimer **2-38** suggest an initial reaction through a distinct color change to bright yellow even before the addition of $BF_3 \cdot OEt_2$. Therefore, a series of similar reactions were conducted in the absence of Lewis acid. In addition, 2,4,6-trichlorophenol and 2,6-di-*tert*-butyl pyridine were introduced into the reaction as it was believed that proton transfer may be playing an important role in this process (Table 2-3).

Table 2-3 Reaction between lactone 2-2 and indolo-indoline dimer **2-38**

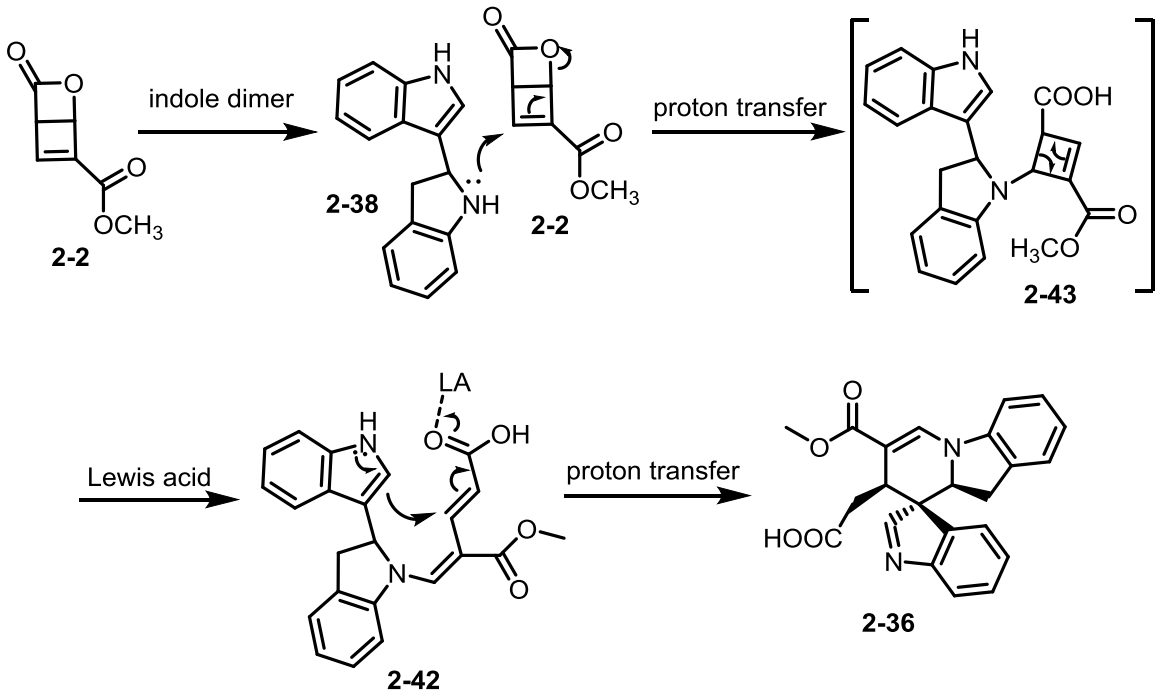


entry	additive	yield
1	none	46%
2	2,4,6-trichlorophenol	52%
3	2,6-di-*tert*-butyl-4-methylpyridine	56%

The reaction without Lewis acids afforded only diene **2-41** in moderate yield. Not much of a difference was observed in the yields of **2-42** when 2,4,6-trichlorophenol and 2,6-di-*tert*-butyl pyridine were introduced into the reaction. At this point, it was rationalized that the role of the Lewis acid such as $BF_3 \cdot OEt_2$ is to catalyze the dimer formation of indole **2-37** and the isomerization of the diene **2-42** when using indole **2-37** as the starting material. When indolo-indoline dimer **2-38** was used, Lewis acid only served to catalyze the isomerization. In this process, strong Lewis acids such as $BF_3 \cdot OEt_2$ may be too harsh, leading to low yields of the product because of substantial decomposition. As no obvious changes

in product yields and reacting rate were observed, the role of proton transfer in this reaction may not be as important.

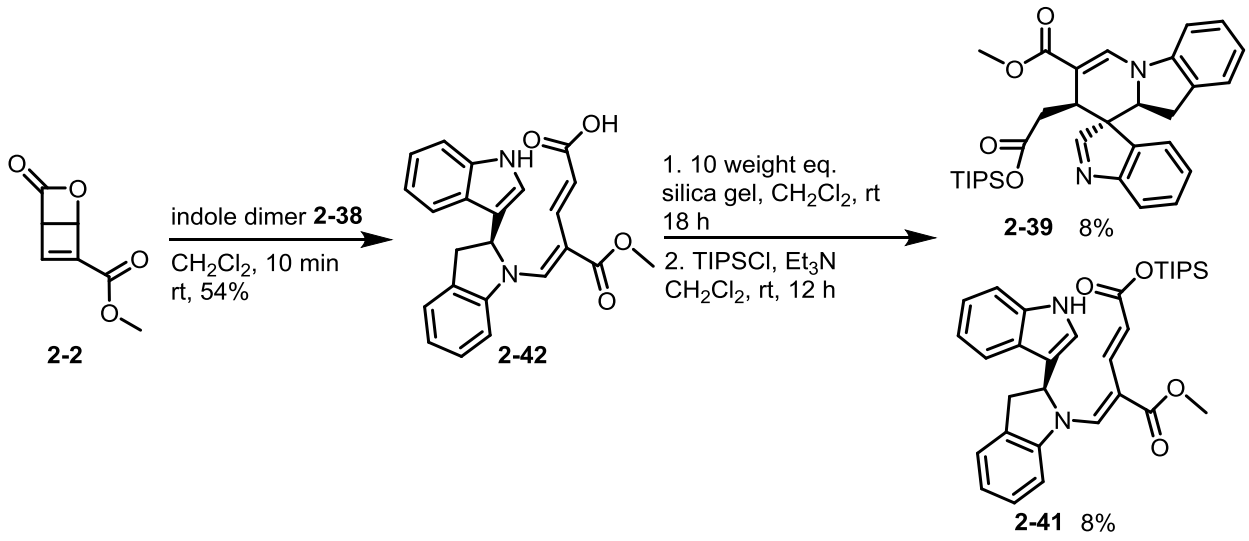
A potential mechanism of the reaction is represented in the Scheme 2-15. Conjugate addition of indolo-indoline dimer **2-38** and tautomerization of the cyclobutene system can open up the lactone to form **2-43** after proton transfer. Conjugate diene **2-42** may be obtained after a retro-[2+2]-cycloaddition of the cyclobutene moiety. Subsequent Lewis catalyzed conjugate-addition can generate fused ring carboxylic acid **2-36** (Scheme 2-15).



Scheme 2-15 Proposed mechanism for the reaction to generate **2-36**

In order to validate this proposed mechanism, lactone **2-2** was treated with indolo-indoline dimer **2-38** at room temperature for 10 min to smoothly obtain diene acid **2-42** in moderate yield. Purification and isolation using Florisil™ provided a clean sample of diene acid **2-42**, and it was subsequently treated with 10 weight equivalents of silica gel in CH_2Cl_2 at room temperature for 18 h. Formation of fused ring system **2-36** was observed according to LCMS characterization of the reaction mixture together with

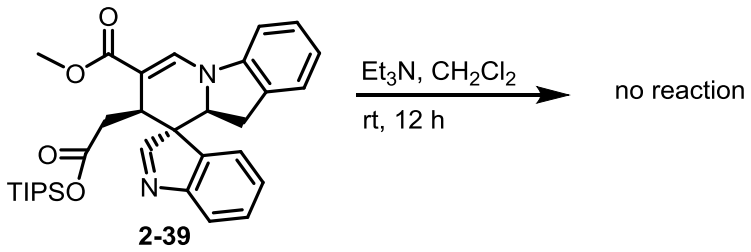
unreacted diene acid **2-42**. The mixture was converted to the TIPS-ester by treatment with TIPSCl and triethylamine (Scheme 2-16). This shows evidence to support the proposed mechanism (Scheme 2-15). When diene acid **2-42** was stirred with 10 weight equivalents of silica gel at room temperature for 18 h, a substantial amount of starting material was observed to have decomposed during this process and therefore low yields for **2-39** and **2-41** were obtained (8%). The protocol could be further optimized by refluxing **2-42** with silica gel in CH_2Cl_2 for 1 h to largely avoid such decomposition.



Scheme 2-16 Conversion of isolated diene acid **2-42** to spiro ring system **2-39** and **2-41**

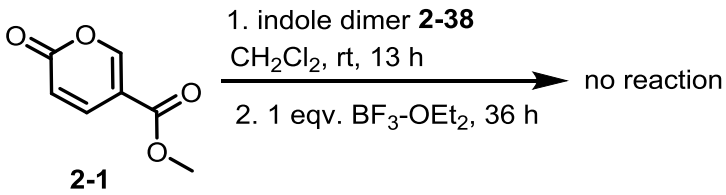
2.2.6 Control Experiments

It is unknown whether the use of triethylamine in the TIPS esterification step will cause the isomerization between **2-39** and **2-40**. In order to clarify the role of triethylamine in the final TIPS esterification step, **2-39** was treated with triethylamine in CH_2Cl_2 at room temperature for 12 h. No isomerization was observed, which indicates triethylamine only serves as a base in the TIPS esterification step (Scheme 2-17).



Scheme 2-17 Clarification of the role of triethylamine

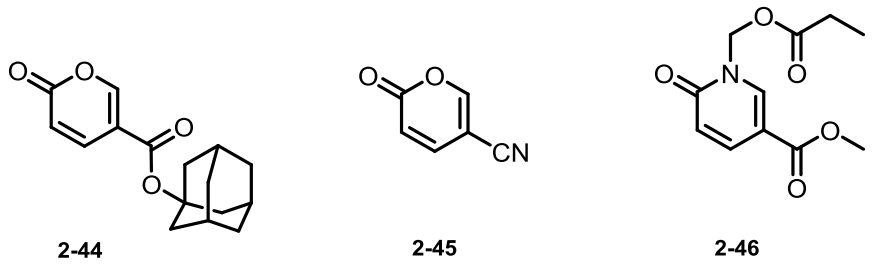
The driving force for the ring opening of lactone **2-2** with indolo-indoline dimer **2-38** to generate diene acid **2-42** is presumed to be its inherent ring strain. In support of this hypothesis, no reaction was observed when methyl coumalate **2-1** was treated with indolo-indoline dimer **2-38** in CH_2Cl_2 at room temperature for 13 h. Addition of 1 equivalent of BF_3 OEt_2 did not affect any transformation over another 36 h (Scheme 2-18).



Scheme 2-18 Control reaction with methyl coumalate **2-1**

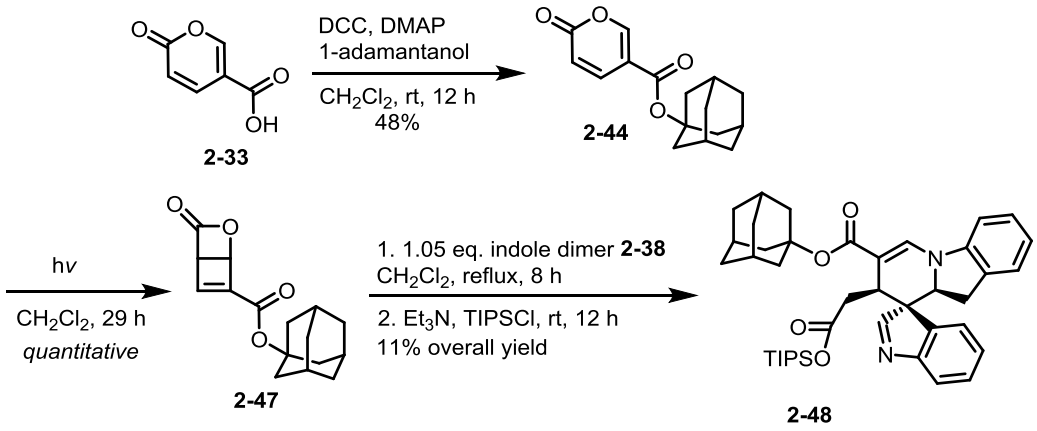
2.2.7 Substrate Scope

Several other starting materials were prepared and tested in order to expand the substrate scope of the established reaction condition, including 1-adamantyl coumalate **2-44**, 2-oxo-2*H*-pyran-5-carbonitrile **2-45**, and methyl 1-(((ethoxycarbonyl)oxy)methyl)-6-oxo-1,6-dihydropyridine-3-carboxylate **2-46** (Scheme 2-19).



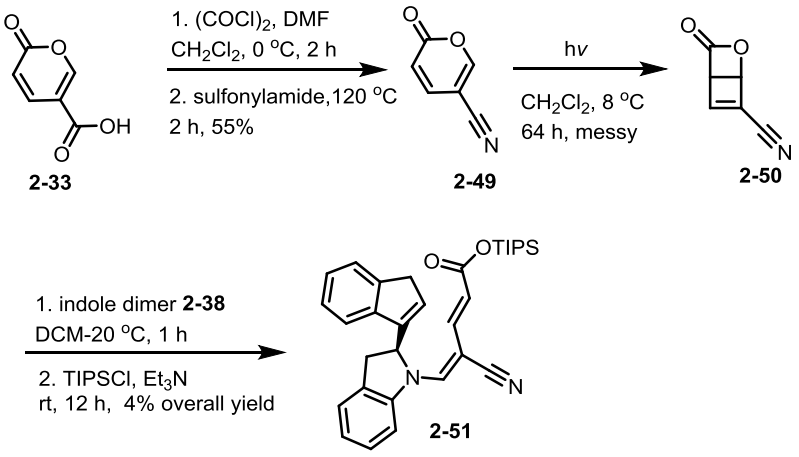
Scheme 2-19 Other starting materials

1-Adamantyl coumalate **2-44** was prepared and explored in the reaction with indole dimer **2-38** to investigate the influence of the bulky adamantyl group on the reaction yield. Commercially available coumalic acid **2-33** was first converted to 1-adamantyl coumalate **2-44** in 48% yield using a Steglich esterification[92]. Lactone **2-47** was obtained quantitatively by irradiation for 29 h. A solution of lactone **2-47** in CH_2Cl_2 (1 mg/mL) was treated with indole dimer **2-38** and was immediately consumed to generate a diene carboxylic acid (not shown) after lactone opening and retro-[2+2] process. The resulting reaction mixture was heated at reflux for 8 h until all diene acid was consumed to cleanly afford its corresponding cyclized acid. The resulting acid with ring fusion was converted to its TIPS-ester **2-48** by treatment with TIPSCl and triethylamine with an overall yield of 11% from **2-47** (Scheme 2-20).



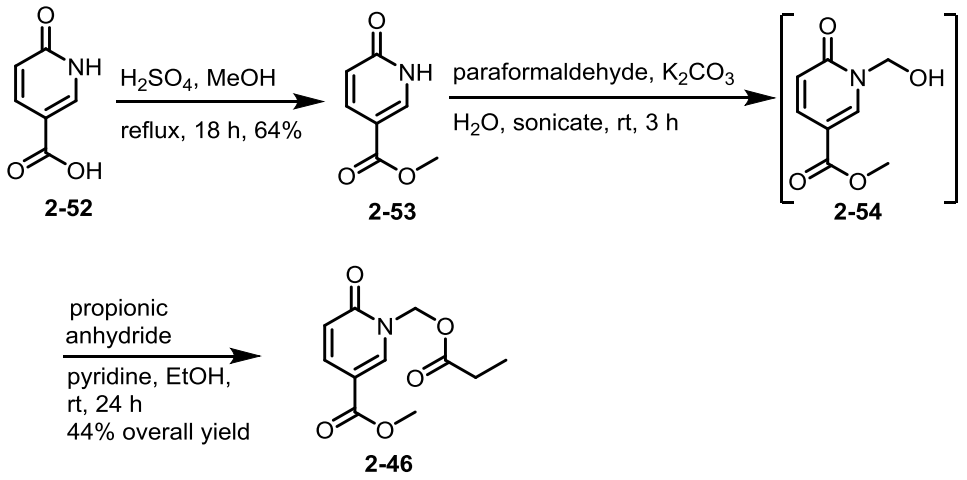
Scheme 2-20 (3*S*,8'*R*,9a'*S*)-(3*S*,5*S*,7*S*)-adamantan-1-yl 8'-(2-oxo-2-((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-7'-carboxylate **2-48**

2-Oxo-2*H*-pyran-5-carbonitrile **2-45** was prepared from **2-33**[93] via an acid chloride (not shown) as a cyano group is similarly electron withdrawing as an ester group in methyl coumalate **2-1**. However, when nitrile **2-49** was irradiated for 64 h, it was converted to a complicated mixture that contained a small amount of desired [2+2] cycloaddition product **2-50** characterized by ^{1}H NMR of the concentrated sample. The complexity of product formation was probably due to the interference of the cyano group during cycloaddition because the cyano group might also absorb energy while it was irradiated. The crude **2-50** was directly used in the following reaction with indole dimer **2-38**. A diene acid (not shown) was immediately generated and was treated with TIPSCl and triethylamine to generate its TIPS ester in 4% yield from nitrile **2-49** (Scheme 2-21).



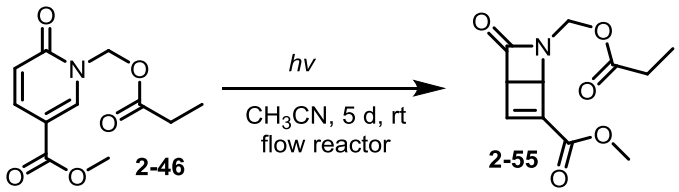
Scheme 2-21 (2*E*,4*E*)-triisopropylsilyl 5-((*S*)-2-(1*H*-inden-3-yl)indolin-1-yl)-4-cyanopenta-2,4-dienoate **2-51**

Lactam **2-46** was prepared as it was envisioned to be more stable than lactone **2-2**, whose instability might be the primary reason why the yield of its reaction with indole dimer **2-38** was always low. Fischer esterification of commercially available acid **2-52** gave methyl ester **2-53**[94], which was treated with paraformaldehyde and K_2CO_3 to generate its hydroxymethyl derivative **2-54**. In situ trapping of **2-54** with propionic anhydride afforded lactam **2-46**[95] in moderate yield (Scheme 2-22).



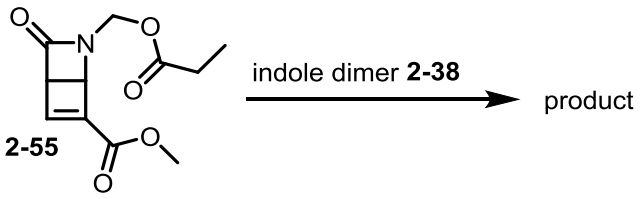
Scheme 2-22 Methyl 1-(((ethoxycarbonyl)oxy)methyl)-6-oxo-1,6-dihydropyridine-3-carboxylate **2-46**

A solution of lactam **2-46** in acetonitrile was irradiated in flow reactor for 5 d and was converted to an inseparable mixture of desired [2+2] cycloaddition product **2-55** and starting material **2-46** in 21% yield (Scheme 2-23). The low yield was probably due to the inherent inactivity of lactam **2-46**. However, when this mixture containing **2-47** was treated with indole dimer **2-38** and a variety of Lewis acids, no reaction was observed (Table 2-4). With these results it was concluded that though **2-55** is considerably more stable than lactone **2-2** in presence of a Lewis acid, it is substantially less reactive than lactone **2-2** when treated with indole dimer **2-38**.



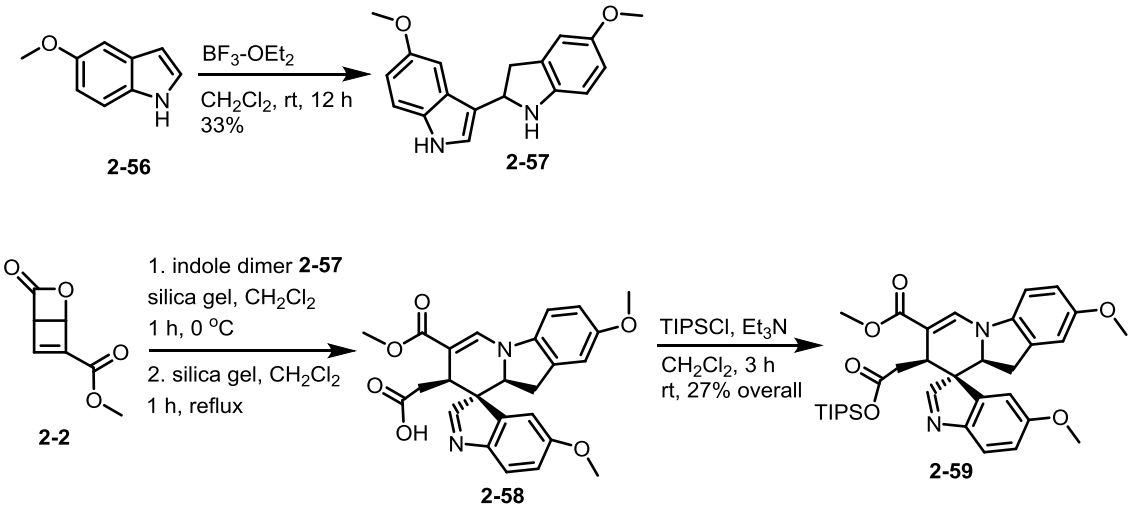
Scheme 2-23 Methyl 3-oxo-2-((propionyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate **2-47**

Table 2-4 Reaction between methyl 3-oxo-2-((propionyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate **2-55** and indole dimer **2-38**



entry	catalyst	solvent	temperature	time	result
1	NA	CH_2Cl_2	rt	4 h	no reaction
2	silica gel	CH_2Cl_2	0 ℃ to rt	26 h	unknown product
3	1 eq. BF_3-OEt_2	CH_2Cl_2	30 ℃ to rt	32 h	no reaction
4	4 eq. BF_3-OEt_2	CH_2Cl_2	30 ℃; rt	1.5 h; 7.5 h	decomposition
5	$ScTf_3$	THF	-30 ℃ to rt	24 h	no reaction
6	$BiCl_3$	THF	0 ℃ to rt	24 h	no reaction
7	$Pd(OAc)_2$	THF	0 ℃ to rt	24 h	no reaction
8	$Pd(PPh_3)_4$	THF	0 ℃ to rt	24 h	no reaction
9	$HNTf_2$	THF	0 ℃ to rt	24 h	no reaction
10	Montmorillonite KSF	CH_2Cl_2	0 ℃ to rt	24 h	no reaction
11	Montmorillonite K10	CH_2Cl_2	0 ℃ to rt	36 h	no reaction
12	NH_4Cl	CH_2Cl_2	rt	27 h	no reaction
13	Alumina	CH_2Cl_2	rt	24 h	no reaction

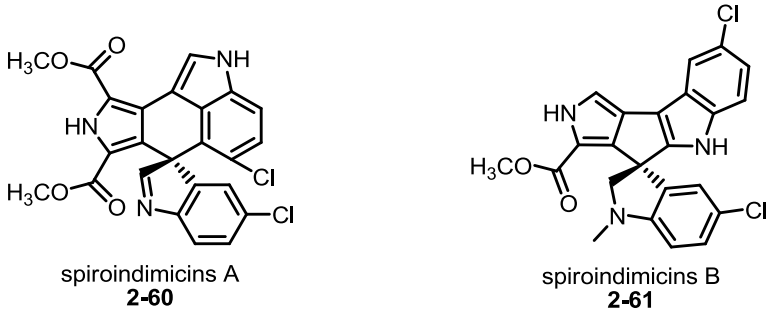
Reactions using a different indole dimer **2-57** with lactone **2-2** were also attempted. Indole dimer **2-57** was prepared from 5-methoxy-1*H*-indole **2-56** in 33% yield using BF_3 OEt_2. Subsequent treatment of indolo-indoline dimer **2-57** with lactone **2-2** in CH_2Cl_2 at 0 ℃ for 1 h resulted in diene acid **2-58**. Purification and isolation using Florisil™ provided a clean sample of **2-58**, which was treated with TIPSCl and triethylamine to afford fused ring compound **2-59** in 27% yield over 3 steps (Scheme 2-24).



Scheme 2-24 Reactions using indole dimer **2-57**

2.2.8 Further Functionalizations

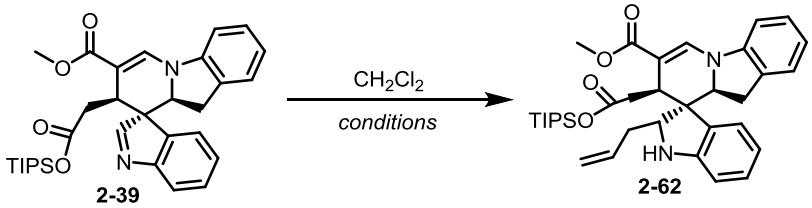
Compounds **2-39** and **2-40** provide interesting scaffolds which can be further modified and used in the total synthesis of related natural products such as spiroindimicins A and B[96] (Scheme 2-25). Therefore, further functionalizations of the obtained spiro compounds **2-39** and **2-40** were attempted, such as the allylation, reduction, and Diels Alder reaction of the imine moiety.

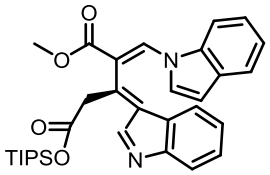


Scheme 2-25 Related natural products

Spiro compound **2-39** was treated with allyltrimethylsilane[97,98] or allyltributyltin[99-101] as allylating reagents in presence of a series of Lewis acids. Unfortunately, the formation of detectable quantities of desired allylation product **2-62** was never observed (Table 2-5).

Table 2-5 (2*S*,3*R*,8'*R*,9a'*S*)-methyl 2-allyl-8'-(2-oxo-2-((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indoline-3,9'-pyrido[1,2-a]indole]-7'-carboxylate **2-62**

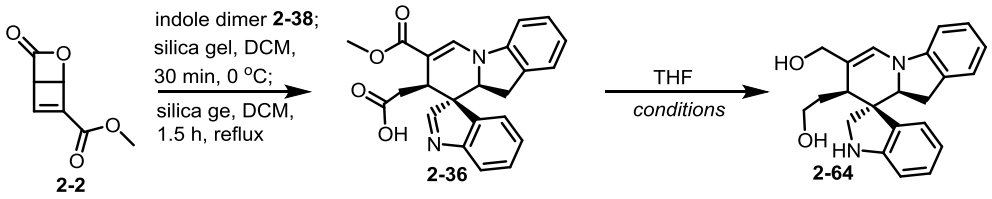




entry	catalyst	reagent	temperature	time	result
1[97]	BF_3-OEt_2	allyltrimethylsilane	-78 ℃ to rt	25 h	trace
2[99,100]	BF_3-OEt_2	allyltributyltin	-78 ℃ to rt	25 h	decomposition
3[101]	$ScTf_3$	allyltributyltin	-78 ℃ to rt	57 h	30% **2-40**, 35% **2-63**, SM mixture
4[98]	$TiCl_4$	allyltributyltin	-78 ℃	24 h	decomposition

Fused ring compound **2-36** was envisioned to be a good substrate toward reduction as its structural features include a methyl ester, a carboxylic acid, and an imine. When **2-36** was generated from the reaction between lactone **2-2** and indole dimer **2-38**, it was purified and isolated using Florisil™ and was immediately treated with strong reducing reagents including BH_3-THF, BH_3-Me_2S, and LAH. Unfortunately, complete decomposition of **2-36** was observed for all experiments conducted (Table 2-6).

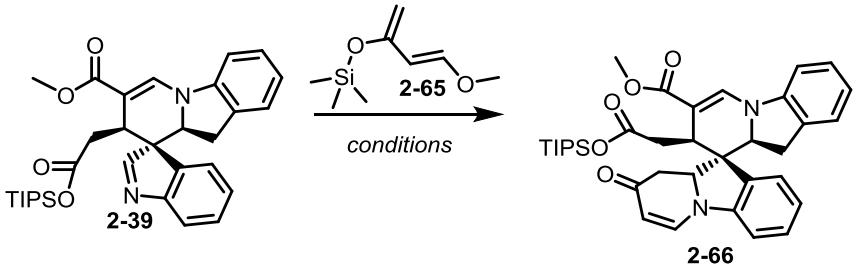
Table 2-6 Reduction of 2-((3*S*,8'*R*,9a'*S*)-7'-(methoxycarbonyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-8'-yl)acetic acid **2-36**



entry	reagent	temperature	time	result
1	BH_3-Me_2S, $B(OMe)_3$	0 ℃ to rt	14 h	decomposition
2	BH_3-THF	rt	12 h	decomposition
3	LAH	-30 ℃ to 0 ℃	12 h	decomposition

The imine functionality in spiro compound **2-39** was envisioned to be a potential dienophile in Diels-Alder reaction with Denishefsky's diene **2-65**[102-105]. Several reaction conditions were attempted with Lewis acids including $Yb(OTf)_3$[102], $AlCl_3$[104] and HBF_4[105], and none of them gave desired cycloaddition product **2-66** (Table 2-7).

Table 2-7 Diels-Alder reaction with Danishefsky' diene **2-65**



entry	catalyst	solvent	temperature	time	yield
1[102]	$Yb(OTf)_3$	CH_2Cl_2	-78 ℃ to rt	22 h	No reaction
2[103]	NA	MeOH	rt	24 h	No reaction
3[104]	$AlCl_3$	MeOH	rt	48 h	No reaction
4[105]	HBF_4	MeOH	rt	24 h	decomposition

2.3 CONCLUSION

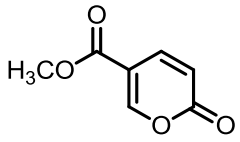
Reactions involving methyl 3-oxo-2-oxabicyclo[2.2.0]hexane-6-carboxylate **2-2** and indole-related nucleophiles have been investigated. The formation of cyclobutane-containing product **2-35** was not observed in the presence of Lewis acids. Instead, tricyclic-fused system **2-36** was isolated. When lactone **2-2** was treated with indolo-indoline **2-38** with $BF_3 \cdot OEt_2$, a mixture of products was isolated in low yields. Diene product **2-42** was obtained in moderate yields when lactone **2-2** was treated with indolo-indoline **2-38** in the absence of Lewis acid and diene **2-42** could be converted to tricyclic-fused system **2-36** by heating at reflux with silica gel in CH_2Cl_2 in low to moderate yield. A potential mechanism has been proposed for the generation of **2-36**, which involves a ring opening process of lactone **2-2**, a retro-[2+2] cycloaddition, and a Lewis acid-catalyzed conjugate addition from the indole fragment.

Expansion of substrate scope was attempted for the reaction between indolo-indoline **2-38** and lactone **2-2** to generate fused ring acid **2-36**, and substrates giving successful results included 1-adamantyl coumalate **2-44** and indolo-indoline dimer **2-57.** Further functionalizations of fused ring product **2-39**, including allylation, reduction, and Diels Alder reaction of the imine moiety, were also attempted. However, none of the products from further functionalization reactions were observed.

2.4 EXPERIMENTAL PART

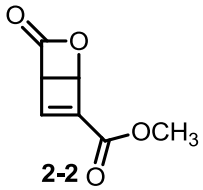
General: All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃ employed a CO_2/acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina column filtration system. All other reagents and solvents were used as received unless otherwise noted. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}•4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

NMR spectra were recorded using XWIN-NMR software. ^{1}H NMR spectra were obtained at 300, 400, 500, 600 or 700 MHz in $CDCl_3$. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak unless otherwise noted. Melting points were determined on a Mel-Temp II and are uncorrected. High-resolution mass spectrometry (HRMS) data (ESI/APCI technique) were recorded using a Waters Q-Tof Ultima API-US instrument. HRMS data (EI technique) were recorded using a Micromass Autospec instrument. Mass spectrometry data were also recorded using an Applied Biosystems MDS SCIEX API 2000 LC/MS/MS system.



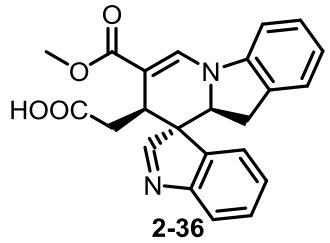
2-1

Methyl coumalate (2-1).[74] With a 100 mL round bottom flask with **2-33** (2.08 g, 14.8 mmol) in NMP (40 mL) was added DIPEA (1.93 g, 15.0 mmol) dropwise over 10 min. The reaction mixture was allowed to stir for 30 minutes at room temperature during which dimethyl sulfate (1.89 g, 15.0 mmol) was slowly added over a period of 15 min. The reaction mixture was allowed to stir for an additional 2 h at room temperature. The reaction was quenched with the dilution of toluene (30 mL) followed by the addition of water (50 mL), and the two layers were allowed to separate. The aqueous layer was extracted with toluene (3×30 mL), The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and water (20 mL). The solution was concentrated *in vacuo*, and the resulting residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:4) to afford **2-1** (1.47 g, 9.52 mmol, 64%) as white flakey crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 2.4, 0.9 Hz, 1 H), 7.64 (dd, *J* = 9.9, 2.7 Hz, 1 H), 6.18 (dd, *J* = 9.9, 0.6 Hz, 1 H), 3.71 (s, 1 H).



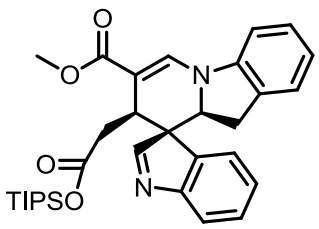
2-2

Methyl 3-oxo-2-oxabicyclo [2.2.0] hex-5-ene-6-carboxylate (2-2). A solution of **2-1** (926 mg, 6.01 mmol) dry CH_2Cl_2 (1.0 L) was transferred to a photoreactor (ACE glass, 1 L jacketed reaction vessel with a quartz immersion well). The reaction mixture was purged with argon. The vessel was irradiated using a 450W Hanovia lamp through a pyrex filter at 15 ℃ for 37 hours while keeping the temperature at 15 ℃. A small aliquot (1 mL) of solution was removed, concentrated afford **2-2** as colorless oil (quantitative yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 4.2, 0.9 Hz, 1 H), 5.51 (dd, *J* = 4.2, 2.1 Hz, 1 H), 4.48 (dd, *J* = 1.8, 1.2 Hz, 1 H), 3.82 (s, 3 H).

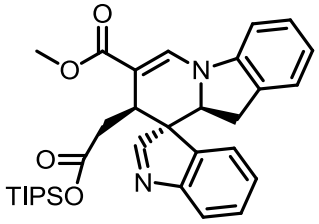


2-36

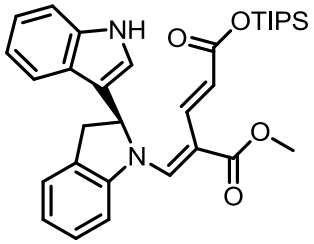
2-((3*S*,8'*R*,9a'*S*)-7'-(Methoxycarbonyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indol]-8'-yl)acetic acid (2-36). To a flame dried 100 mL round bottom flask was added **2-37** (188 mg, 1.60 mmol), and was purged with N_2 (3×). **2-2** (82.4 mg, 0.535 mmol, 50 mL 0.0107 mol/L solution) was added to the flask via syringe. The flask was cooled to -23 ℃ and BF_3•OEt_2 (0.020 μL, 22.8 mg, 0.161 mmol) was added to the flask via syringe. The reaction mixture was stirred at -23 ℃ and was allowed to warm to 5 ℃ for 2 h. The reaction was quenched with sat. $NaHCO_3$ solution (10 mL), and the organic layer was extracted with sat. $NaHCO_3$ solution (3×30 mL). Then the aqueous layer was combined and cooled to 0 ℃. 1 M citric acid was slowly added to the aqueous solution until pH is around 3. The aqueous solution was then extracted with EtOAc (3×50 mL), dried ($NaSO_4$) and concentrated *in vacuo*. The reaction mixture was purified by chromatography on SiO_2 (MeOH: CH_2Cl_2, 1:10) to afford **2-36** as yellow solid (5.0 mg, 0.013 mmol, 2%): (The spectra are not good enough but the X-ray crystallographic analysis suggests the structure of the product.); HRMS (ESI negative) *m/z* calcd for $C_{23}H_{19}N_2O_4$ ($[M-H]^-$) 387.1345, found 387.1340.



2-40



2-39

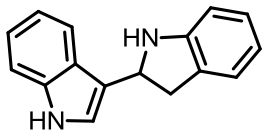


2-41

(3*R*,8'*R*,9a'*S*)-Methyl 8'-(2-oxo-2-((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-7'-carboxylate (2-40); (3*S*,8'*R*,9a'*S*)-methyl 8'-(2-oxo-2-

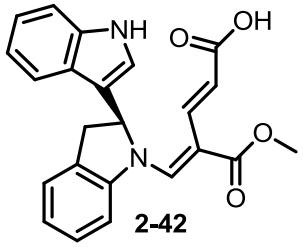
((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-7'-carboxylate (2-39); (2*E*,4*E*)-5-methyl 1-(triisopropylsilyl) 4-(((*S*)-2-(1*H*-indol-3-yl)indolin-1-yl)methylene)pent-2-enedioate (2-41). To a flame dried 100 mL round bottom flask purged with N_2 (3×) was added **2-2** (80.4 mg, 0.533 mmol, 60 mL 0.0087 mol/L CH_2Cl_2 solution)was added via syringe. The reaction mixture was cooled to -23 ℃ and **2-38** (165 mg, 0.702 mmol), $BF_3 \cdot OEt_2$ (19 μL, 0.157 mmol) was added into the flask via syringe. The reaction mixture was stirred at -23 ℃ for 5 h. The reaction was quenched by adding sodium potassium tartrate and the mixture was stirred for 5 min. The solid was filtered and the filtrate was concentrated under vacuum and purified by chromatography on Florisil™ (MeOH: CH_2Cl_2, 1: 10 to remove impurities; MeOH to collect product). The MeOH solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL),treated with TEA (264 mg, 2.61 mmol) and TIPSCl (110 mg, 0.574 mmol). The reaction mixture was stirred for 22 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:4 with 1% TEA) to afford **2-40** (35.4 mg, 0.0650 mmol, 12%) as light yellow solid, **2-39** (22.3 mg, 0.0409 mmol, 8%) as light yellow solid, and **2-41** (33.8 mg, 0.0620 mmol, 12%) as yellow solid. **2-40:** IR (neat) 3441, 2945, 2887, 2869, 1700, 1612, 1586, 1493, 1461, 1385, 1379, 1241, 1191, 1109, 1072, 1027, 1008, 995, 884, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 8.07 (s, 1 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.42 (m, 1 H), 7.33 (d, *J* = 4.2 Hz, 2 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 6.94 (m, 2 H), 6.83 (t, *J* = 7.5 Hz, 1 H), 4.64 (t, *J* = 9.3 Hz, 1 H). 3.94 (s, 1 H), 3.71 (s, 3 H), 2.63 (dd, *J* = 16.5, 9.6 Hz, 1 H), 2.29 (dd, *J* = 18.3, 6.0 Hz, 1 H), 1.98 (dd, *J* = 16.5,9.6 Hz, 1 H), 1.75 (dd, *J* = 18.3, 6.0 Hz, 1 H), 1.25 (m, 3 H), 0.95 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.5, 156.1, 143.0, 137.7, 136.2, 135.3, 129.3, 128.9, 128.2, 127.6, 125.6, 122.5, 122.4, 121.6, 119.7, 107.8, 103.5, 63.2, 51.1, 36.4, 34.4, 29.8, 17.8, 12.4; HRMS (ESI) *m/z* calcd for $C_{32}H_{41}N_2O_4Si$ ($[M+H]^+$) 545.2836, found 545.2848. **2-39:** IR (neat) 3385, 3064, 2945, 2869, 1705, 1612, 1586, 1493, 1467, 1435, 1411, 1366, 1310, 1236, 1103, 1185, 1016, 995, 915, 910, 908, 882, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.09 (br s, 1H), 7.66 (d, *J* = 7.5 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.11 (m, 3 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 7.5 Hz, 1 H), 6.78 (t, *J* = 7.5 Hz, 1 H), 4.77 (t, *J* = 9.0 Hz, 1 H), 4.10 (m, 1 H), 3.71 (s, 3 H), 2.83 (dd, *J* = 16.0, 9.5 Hz,

1 H), 2.44 (dd, *J* = 18.0, 6.0 Hz, 1 H), 1.83 (br s, 2 H), 1.75 (dd, *J* = 16.0, 9.5 Hz, 1 H), 1.34 (dd, *J* = 18.0, 5.0 Hz, 1 H), 1.24 (m, 3 H), 1.04 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 172.8, 157.2, 143.2, 135.5, 129.2, 129.2, 128.0, 127.1, 125.5, 125.1, 122.2, 121.5, 107.4, 101.5, 62.4, 61.2, 51.0, 35.1, 34.6, 29.8, 29.6, 17.8, 12.4; HRMS (ESI) *m/z* calcd for $C_{32}H_{40}N_2O_4SiNa$ ($[M+Na]^+$) 567.2655, found 567.2650. **2-41:** IR (neat) 3359, 3057, 2941, 2889, 2863, 1691, 1609, 1586, 1489, 1459, 1433, 1407, 1359, 1338, 1312, 1271, 1230, 1182, 1109, 1096, 882, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 8.14 (s, 1 H), 7.82 (d, *J* = 15.5 Hz, 1 H), 7.31 (m, 2 H), 7.26 (m, 2 H), 7.13 (m, 3 H), 7.02 (m, 1 H), 6.96 (m, 1 H), 6.22 (d, *J* = 15.5 Hz, 1 H), 6.02 (t, *J* = 4.5 Hz, 1 H), 3.76 (m, 1 H), 3.68 (s, 3 H), 3.42 (m, 1 H), 1.30 (m, 3 H), 1.08 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.2, 145.3, 142.3, 139.3, 137.1, 130.3, 128.2, 125.5, 124.4, 124.1, 124.0, 122.4, 120.0, 119.1, 117.4, 114.8, 111.7, 110.8, 101.7, 60.6, 51.5, 37.7, 18.0, 12.2; δ ; HRMS (ESI) *m/z* calcd for $C_{32}H_{41}N_2O_4Si$ ($[M+H]^+$) 545.2836, found 545.2841.



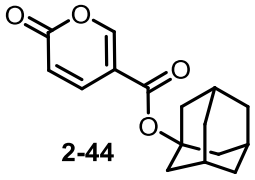
2-38

3-(Indolin-2-yl)-1*H*-indole (2-38). To a solution of **2-37** (1.00 g, 8.54 mmol) in CH_2Cl_2 (50 mL) was added $BF_3 \cdot OEt_2$ (541 μL, 606 mg, 4.27 mmol) dropwise over 30 min at 0 ℃. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo*, and quenched with sat. aqueous $NaHCO_3$. The aqueous solution was back-extracted with EtOAc (3×30 mL). The organic layer was concentrated *in vacuo*, and purified chromatography on SiO_2 (EtOAc:hexanes, 1:3 with 0.5% Et_3N) to afford **2-38** (679 mg, 2.90 mmol, 68%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 6.0 Hz, 2 H), 7.09 (m, 2 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.27 (t, *J* = 8.4 Hz, 1 H), 4.12 (brs, 1 H), 3.49 (dd, *J* = 15.6, 9.2 Hz, 1 H), 3.23 (dd, *J* = 15.6, 9.2 Hz, 1 H).



2-42

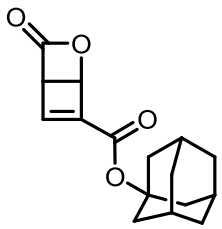
(2*E*,4*E*)-5-((*S*)-2-(1*H*-Indol-3-yl)indolin-1-yl)-4-(methoxycarbonyl)penta-2,4-dienoic acid (2-42). To a flame-dried 250 mL round bottom flask was added **2-2** (114 mg, 0.740 mmol, 50 mL, 0.0148 mol/L) and 2,6-di-*tert*-butyl-4-methyl-pyridine (152 mg, 0.74 mmol), and was cooled to -20 ℃. Then **2-38** (182 mg, 0.777 mmol) was added into the flask via syringe. The reaction mixture immediately turned yellow. The reaction mixture was stirred at -20 ℃ for 2 h and concentrated *in vacuo* and purified by flash chromatography on Florisil^{TM}(100% EtOAc) until the eluent became completely clean by TLC. The yellow fraction remaining on the column was then eluted with MeOH. The product was dissolved in CH_2Cl_2 (100 mL), and filtered through a short plug of celite and concentrated *in vacuo* to give **2-42** (161 mg, 0.416 mmol, 56%) as a brown solid: IR (neat) 3372, 3064, 2951, 2498, 1672, 1614, 1573, 1551, 1525, 1486, 1456, 1434, 1417, 1363, 1355, 1331, 1320, 1290, 1266, 1245, 1221, 1208, 1185, 1167, 1113, 1096, 982, 740 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 7.97 (s, 1 H), 7.37 (d, *J* = 16.0 Hz, 1 H), 7.25 (m, 5 H), 7.00 (m, 3 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.74 (td, *J* = 7.0, 1.0 Hz, 1 H), 6.05 (dd, *J* = 10.5, 4.5 Hz, 1 H), 5.90 (d, *J* = 16.0 Hz, 1 H), 3.73 (m, 2 H), 3.58 (s, 3 H), 3.27 (m, 1 H); ^{13}C NMR (125 MHz, MeOD) δ 176.7, 170.7, 147.1, 140.5, 138.7, 135.7, 131.7, 129.0, 127.0, 126.2, 126.0, 125.6, 124.3, 122.5, 120.0, 119.8, 115.2, 112.6, 110.8, 103.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_2O_4$ ($[M+H]^+$) 389.1501, found 389.1528.



2-44

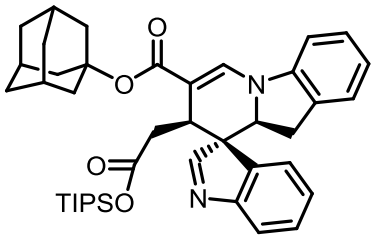
(3*S*,5*S*,7*S*)-Adamantan-1-yl 2-oxo-2H-pyran-5-carboxylate (2-44). To a suspension of coumalic acid **2-33** (600 mg, 4.28 mmol) in CH_2Cl_2 (30 mL) were added 1-adamantanol (685 mg, 4.50 mmol) and

DMAP (52.3 mg, 0.428 mmol), and the mixture was cooled to -20 ℃. DCC (884 mg, 4.28 mmol) was added to the reaction mixture and the mixture was slowly warmed to room temperature and stirred for overnight. The dark brown reaction mixture was concentrated *in vacuo* and purified by chromatography on SiO_2 (EtOAc: hexanes, 1:6) to afford **2-44** (566 mg, 2.06 mmol, 48%) as a white solid: IR (neat) 3055, 2911, 2852, 1750, 1709, 1637, 1553, 1456, 1426, 1333, 1322, 1282, 1266, 1232, 1116, 1103, 1087, 1048, 966, 844, 829, 770, 733, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 2.7, 1.2 Hz, 1 H), 7.71 (dd, *J* = 9.6, 2.4 Hz, 1 H), 6.26 (dd, *J* = 9.6, 1.2 Hz, 1 H), 2.15 (s, 9 H), 1.66 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.2, 157.7, 142.1, 115.0, 113.5, 82.7, 41.4, 36.1, 30.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{19}O_4$ ($[M+H]^+$) 275.1283, found 275.1256.



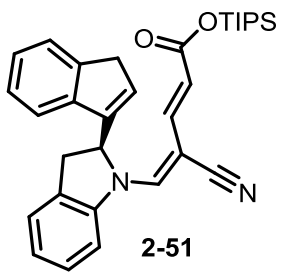
2-47

(3*S*,5*S*,7*S*)-Adamantan-1-yl 3-oxo-2-oxabicyclo[2.2.0]hex-5-ene-6-carboxylate (2-47). A solution of **2-44** (825 mg, 3.01 mmol) dry CH_2Cl_2 (1.0 L) was transferred to a photoreactor (ACE glass, 1 L jacketed reaction vessel with a quartz immersion well). The reaction mixture was purged with argon. The vessel was irradiated using a 450W Hanovia lamp through a pyrex filter at 15 ℃ for 29 hours while keeping the temperature at 15 ℃. A small aliquot (1 mL) of solution was removed, concentrated afford colorless oil **2-47** (quantitative yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 3.9, 0.9 Hz, 1 H), 5.45 (dd, *J* = 4.2, 2.1 Hz, 1 H), 4.40 (dd, *J* = 1.8, 0.9 Hz, 1 H), 2.15 (m, 9 H), 1.68 (s, 6 H).



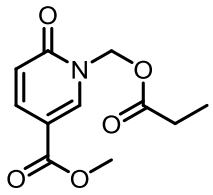
2-48

(3*S*,8'*R*,9a'*S*)-(3*S*,5*S*,7*S*)-Adamantan-1-yl 8'-(2-oxo-2-((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-7'-carboxylate (2-48). To a flame-dried 250 mL round bottom flask was purged with N_2 for 3 times. Then **2-47** (65.8 mg, 0.24 mmol, 30 mL, 0.008 mol/L) was added via syringe and was cooled to -20 ℃. **2-38** (59.0 mg, 0.252 mmol, dissolved in 2 mL of CH_2Cl_2) was added into the flask via syringe. The reaction mixture immediately turned yellow. The reaction mixture was stirred at room temperature for 10 min and then refluxed in CH_2Cl_2 for 8 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography on Florisil™ (EtOAc:hexanes, 1:1) until the eluent became completely clean by TLC. The yellow fraction remaining on the column was then eluted with MeOH. The MeOH solution was concentrated *in vacuo* and redissolved in CH_2Cl_2 (30 mL), and TIPSCl (46.2 mg, 0.24 mmol), TEA (121 mg, 1.2 mmol) were added. The reaction mixture was then stirred at room temperature for 16 h, and concentrated *in vacuo*, purified by chromatography on SiO_2 (EtOAc: hexanes, 1:5 with 0.5% TEA) to afford **2-48** (17.5 mg, 0.0263 mmol, 11%) as light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2 H), 7.64 (s, 1 H), 7.34 (s, 1 H), 7.12 (m, 3 H), 6.88-6.85 (m, 2 H), 6.76 (m, 1 H), 4.73 (t, *J* = 9.2 Hz, 1 H), 4.04 (s, 1 H), 2.83 (dd, *J* = 16.0, 9.2 Hz, 1 H), 2.54 (dd, *J* = 18.0, 4.0 Hz, 1 H), 2.17 (s, 9 H), 1.75 (dd, *J* = 16.0, 9.2 Hz, 1 H), 1.67 (s, 6 H), 1.34 (dd, *J* = 18.0, 5.0 Hz, 1 H), 1.25 (m, 3 H), 1.04 (m, 18 H).



2-51

(2*E*,4*E*)-Triisopropylsilyl 5-((*S*)-2-(1*H*-inden-3-yl)indolin-1-yl)-4-cyanopenta-2,4-dienoate (2-51). To a flame-dried 250 mL round bottom flask was added **2-50** (24.0 mg, 0.198 mmol, 60 mL, 0.0033 mol/L) and was cooled to -20 ℃. Then **2-38** (48.7 mg, 0.0.208 mmol, dissolved in 2 mL of CH_2Cl_2) was added into the flask via syringe. The reaction mixture immediately turned yellow. The reaction mixture was stirred at -20 ℃ for 4 h and was concentrated under vacuum and was purified by flash chromatography on Florisil™ (100% EtOAc) until the eluent became completely clean by TLC. The yellow fraction remained on the column was then washed with MeOH until all yellow fraction on column was washed out. The yellow fraction was collected, concentrated *in vacuo*. The residue was redissolved in 100 mL CH_2Cl_2, added TEA (100 mg, 139 μL, 0.990 mmol) and TIPSCl (84.0 mg, 77.8 μL, 0.436 mmol), and reaction mixture was then stirred for 12 h at room temperature. The reaction mixture was concentrated *in vacuo* and purified by chromatography on SiO_2 (EtOAc:hexanes, 1:5 with 0.5% TEA) to afford **12** (4.1 mg, 0.0080 mmol, 4%) as pale yellow oil: IR (neat) 3346, 3057, 2939, 2922, 2896, 2863, 2199, 1674, 1603, 1579, 1486, 1461, 1376, 1316, 1282, 1271, 1247, 1223, 1178, 1159, 1012, 999, 882, 854, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.43-7.41 (m, 2 H), 7.37-7.29 (m, 3 H), 7.18 (d, *J* = 6.0 Hz, 1 H), 7.15-7.12 (m, 2 H), 7.03-6.98 (m, 1 H), 6.96-6.87 (m, 2 H), 5.88 (d, *J* = 15 Hz), 3.82 (dd, *J* = 16.2, 9.9 Hz, 1 H), 3.31 (dd, *J* = 16.5, 1.8 Hz, 1 H), 1.28-1.25 (m, 3 H), 1.08-1.05 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.6, 142.5, 137.1, 130.7, 128.6, 126.2, 125.0, 124.9, 124.2, 122.6, 120.2, 119.3, 114.9, 114.6, 111.7, 109.2, 58.3, 53.6, 37.6, 29.9, 18.0, 12.2; HRMS (ESI) *m/z* calcd for $C_{31}H_{37}N_3O_2SiNa$ ($[M+Na]^+$) 534.2553, found 534.2555.

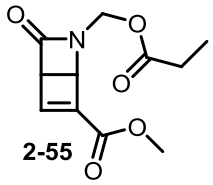


2-46

Methyl 6-oxo-1-((propionyloxy)methyl)-1,6-dihydropyridine-3-carboxylate (2-46). A mixture of **2-53** (1.30 g, 8.49 mmol), paraformaldehyde (1.4 g) and K_2CO_3 (1.73 g, 12.5 mmol) in H_2O (4 mL) was treated

under sonication for 3 h at room temperature. The aqueous solution was then extracted with $CHCl_3$(3×20 mL). The combined organic layer was concentrated in *vacuo* to give a white solid, which was used for the next step.

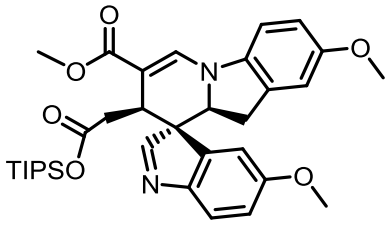
The white solid was dissolved in CH_2Cl_2 (30 mL) and propionic anhydride (1.66 g, 12.7 mmol) and pyridine (1.34 g, 17.0 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 24 h, concentrated in *vacuo*, and the residue was dissovled in CH_2Cl_2 (30 ml). The solution was washed successively with saturated aq. $NaHCO_3$, aq. HCl (1 mol/mL), and brine. The organic layer was dried ($MgSO_4$), concentrated in *vacuo*, and purified with chromatography on SiO_2 (EtOAc:hexanes, 1;1) to a afford **2-46** (900 mg, 3.76 mmol, 44% over two steps) as a white solid: IR (neat) 3081, 2988, 2951, 2248, 1743, 1719, 1666, 1616, 1543, 1441, 1344, 1303, 1294, 1260, 1225, 1191, 1139, 1118, 1107, 1079, 1061, 1044, 1014, 971, 915, 836, 772, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.81 (dd, *J* = 9.2, 1.2 Hz, 1 H), 6.51 (d, *J* = 9.6 Hz, 1 H), 5.84 (s, 2 H), 3.82 (s, 3 H), 2.36 (q, *J* = 7.6 Hz, 2 H), 1.09 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 164.4, 162.0, 143.5, 139.6, 120.5, 110.1, 70.8, 52.2, 27.2, 8.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}NO_5$ ($[M+H]^+$) 240.0872, found 240.0851.



2-55

Methyl 3-oxo-2-((propionyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate (2-55). `**2-46** (884 mg, 3.70 mmol) was dissolved in CH_3CN (20 mL) and sonicated for 15 min. The solution was irradiated (450 W, Hanovia lamp) in a two layer FEP at a flow rate of 1 mL/min in the flow photochemical reactor. The solution was pumped, irradiated for 5 d and the collected solution was concentrated in *vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:2 with 0.5% Et_3N) to afford **2-55** (66.9 mg, 0.280 mmol, 8%) and a mixture of **2-55**

and **2-46** (ratio 4:1, 184 mg, 0.767 mmol, 21%): IR (neat) 3027, 2980, 2949, 2902, 2891, 2882, 2945, 1763, 1720, 1601, 1596, 1435, 1370, 1344, 1312, 1273, 1251, 1219, 1184, 1139, 1079, 1012, 997, 960, 939, 803, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 2.7, 0.9 Hz, 1 H), 5.26, 5.23 (AB, *J* = 11.1 Hz, 1 H), 5.09, 5.05 (AB, *J* = 11.1 Hz, 1 H), 4.66 (t, *J* = 2.4 Hz, 1 H), 4.19 (dd, *J* = 2.1, 0.9 Hz, 1 H), 3.74 (s, 3 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.06 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 167.3, 161.5, 146.0, 144.2, 66.0, 55.5, 53.8, 51.9, 27.2, 8.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO_5Na$ ($[M+Na]^+$) 262.0691, found 262.0702.



2-59

Methyl (3*S*,8'*R*,9a'*S*)-2',5-dimethoxy-8'-(2-oxo-2-((triisopropylsilyl)oxy)ethyl)-9a',10'-dihydro-8'*H*-spiro[indole-3,9'-pyrido[1,2-a]indole]-7'-carboxylate (2-59). To a flame-dried 250 mL round bottom flask was added silica gel (400 mg) and **2-57** (76.4 mg, 0.260 mmol). **2-2** (40.0 mg, 0.260 mmol, 40 mL, 0.00649 mol/L) was added and was cooled to 0 ℃. The reaction mixture immediately turned yellow. The reaction mixture was stirred at 0 ℃ for 1 h and then heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* purified with column chromatography on Florisil™ (EtOAc:hexanes, 1:1) until all impurities and starting material were washed out (characterized by TLC). The Florisil™ column was then washed with MeOH until all yellow fractions on the column were washed out (characterized by TLC). The MeOH solution was concentrated *in vacuo* and redissolved in 1,2-dichloroethane (10 mL).

To this solution was added TIPSCl (50.0 mg, 0.260 mmol) and Et_3N (131 mg, 1.30 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on SiO_2 (EtOAc:hexenes, 1:5 with 0.5% Et_3N) to afford **2-**

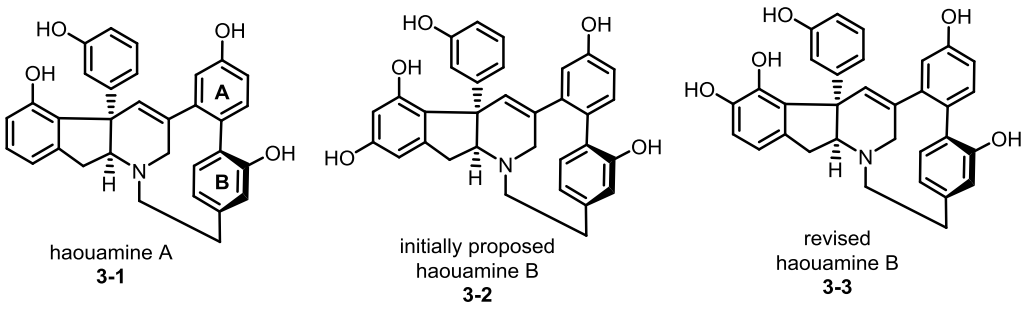
59 (42.0 mg, 0.0694 mmol, 27% over 3 steps) as yellow oil: IR (neat) 2943, 2891, 2865, 2833, 1707, 1685, 1607, 1597, 1555, 1495, 1465, 1433, 1404, 1368, 1355, 1335, 1277, 1225, 1202, 1193, 1180, 1146, 1115, 1085, 1051, 1029, 999, 910, 882, 805, 911, 880 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.93 (s, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 6.88-6.83 (m, 2 H), 6.68-6.65 (m, 2 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 4.74 (t, *J* = 9.6 Hz, 1 H), 4.05-4.02 (m, 1 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 2.82 (dd, *J* = 16.6, 9.2 Hz, 1 H), 2.48 (dd, *J* = 18.0, 6.0 Hz, 1 H), 1.80 (dd, *J* = 16.6, 9.6 Hz, 1 H), 1.35 (dd, *J* = 18.0, 4.8 Hz, 1 H), 1.29-1.21 (m, 3 H), 1.04-1.02 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.9, 172.3, 167.5, 158.9, 155.6, 150.9, 137.3, 137.1, 135.7, 130.7, 121.7, 113.1, 112.9, 112.2, 112.0, 107.7, 99.7, 62.3, 61.3, 55.8, 55.7, 50.9, 35.1, 34.4, 29.8, 17.8, 12.1; HRMS (ESI) m/z calcd for $C_{34}H_{45}N_2O_6Si$ ($[M+H]^+$) 605.30414, found 605.30663.

3.0 TOTAL SYNTHESIS OF HAOUAMINE A

3.1 INTRODUCTION

3.1.1 Haouamines: A Unique Aza-Paracyclophane System

In 2003, Salva *et al.* discovered alkaloids haouamine A **3-1** and B **3-2**/**3-3** (Scheme 3-1) from a tunicate *Aplidium haouarianum* residing off Tarifa Island on the southern coast of Spain.[106] Unique structural features of both natural products include a congested and highly oxygenated indeno-tetrahydropyridine ring system and a highly-strained aza-cyclophane, which was elucidated via NMR spectroscopy. The structure of haouamine A was also confirmed by X-ray crystallographic analysis,[107,108] while the structure of naturally-isolated haouamine B was later revised in comparison with a synthetic sample.[109,110] Haouamine A and B were found to be biologically active. Haouamine A exhibits selective activity in the human colon carcinoma cell line HT-29 (IC_{50} 0.1 μg/mL)[106] and has moderate activity against the human prostate cancer cell line PC3 (IC_{50} 29±2 μM)[107]. The atropisomer of haouamine A, however, shows only moderate activity against human prostate cancer cell line PC3 (IC_{50} 32±3 μM)[107], and haouamine B only shows weak toxicity in MS-1 cell line MS-1 (IC_{50} 5 μg/mL)[106].



Scheme 3-1 Structures of haouamine A and B

The structures of haouamine A and B contain a strained aza-cyclophane-an architecturally-unprecedented feature that makes them fascinating targets for total synthesis. ^{1}H and ^{13}C NMR spectroscopy show typical aromatic chemical shifts for B ring in haouamine A and its carbon-carbon bonds in the ring are around 1.395 Å (Figure 7). These features all match those of planar aromatic systems, despite a strained boat-like conformation in the B ring (Figure 8).[107,108,111]

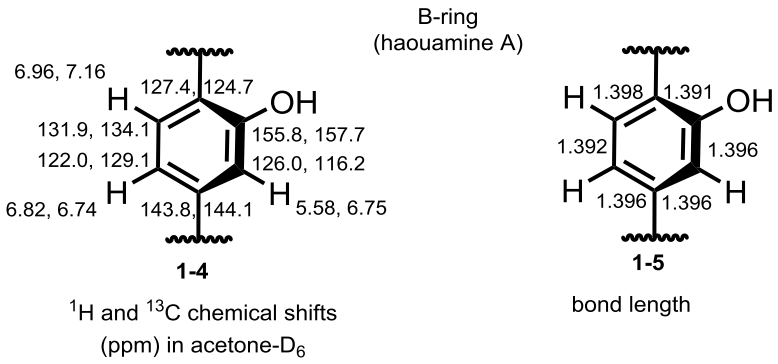


Figure 7 Chemical shifts (ppm) and bond lengths (Å) of B-ring in haouamine A

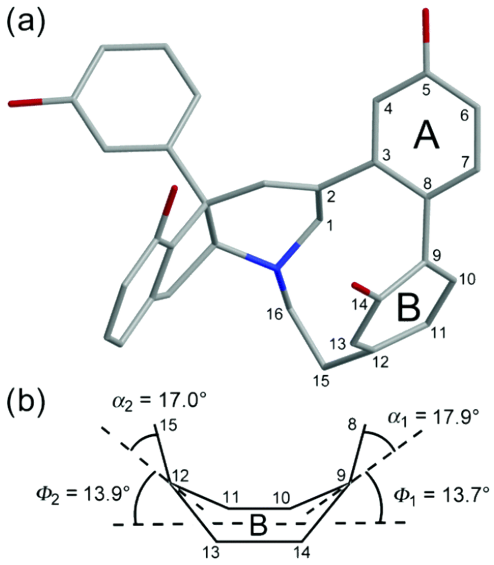


Figure 8 X-ray structure of haouamine A and its boat-like B-ring[107,108]

When dissolved in organic solvent, haouamine A was found to consist of two equilibrating atropisomers which are inseparable by chromatography.[106,112] The ratio of the two atropisomers is solvent dependent (e.g. 1:3 in DMSO-d_6, 2:1 in acetone-d_6), and a mixture of atropisomers were still observed by dissolving a crystal of haouamine A with a single definite molecular geometry in an organic solvent.[106,112] The fact that haouamine A exists as two interconverting atropisomers was rationalized to arise from either rotation of the phenol B ring or from inversion of geometry at the nitrogen center.[106] The latter one was confirmed by Baran *et al.*[107] by synthesizing a pair of separable atropisomers of haouamine A, and additional computational studies supported the rationalization that the N-inversion gives rise to the presence of two atropisomers (Figure 9).[112]

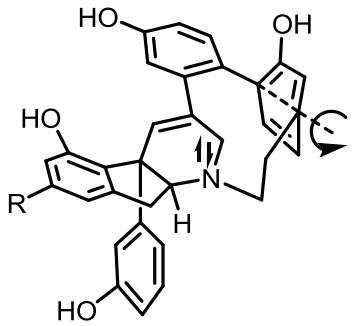
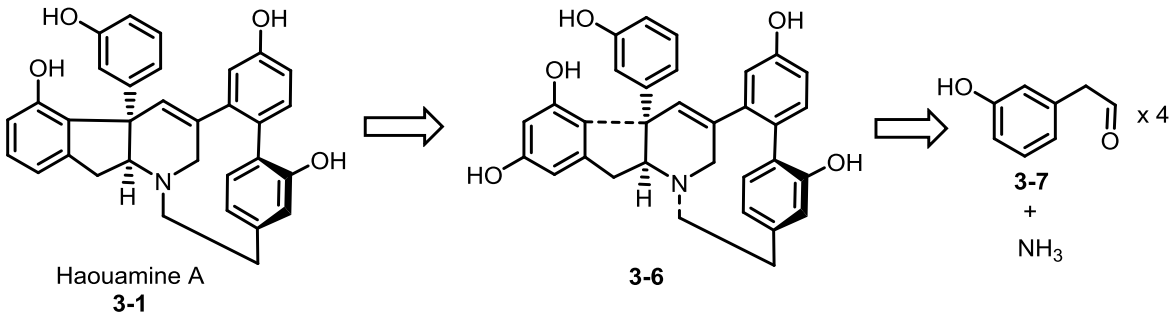


Figure 9 Proposed atropisomerism and N-inversion in haouamines

A biosynthetic pathway of haouamine A was proposed by Baran *et al.* involving a tetramerization route of meta-hydroxylated phenylacetaldehydes **3-7** with ammonia followed by oxidative coupling, though *in vitro* it was ascertained that this route is unlikely to take place without enzymatic intervention (Scheme 3-2).[108,113]

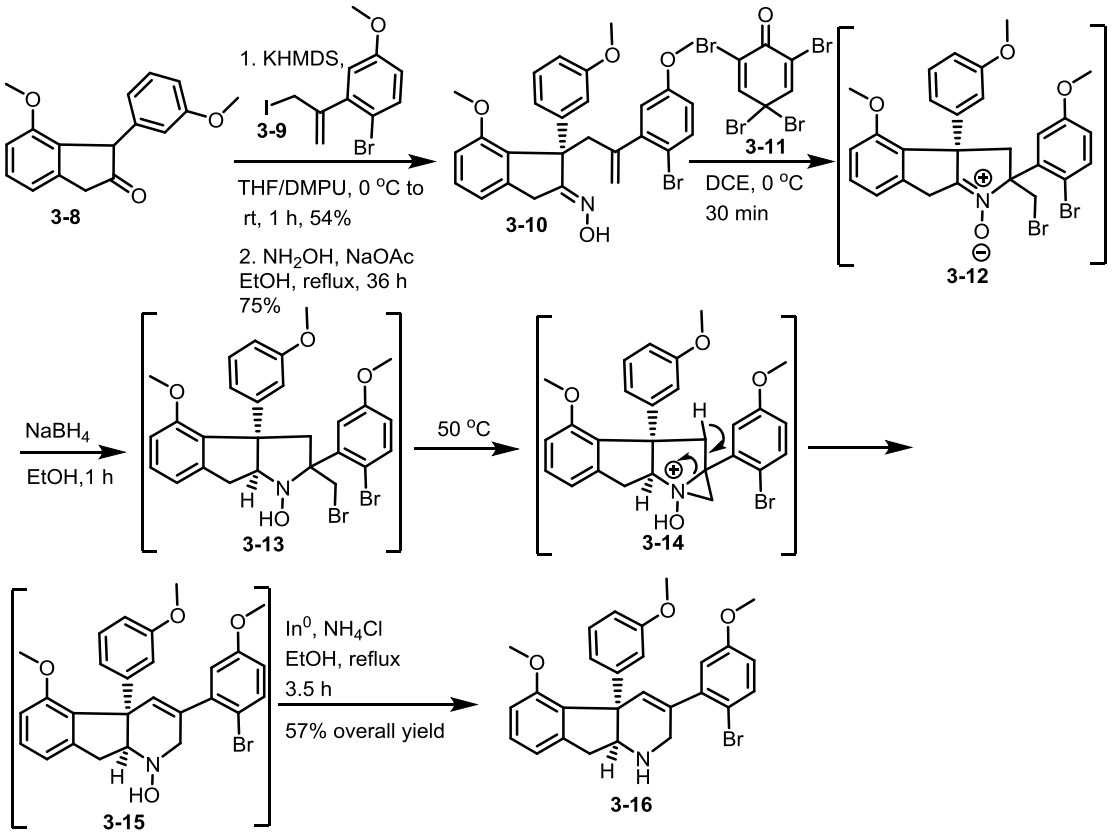


Scheme 3-2 Biosynthesis of haouamine A proposed by Baran *et al.*

3.1.2 Total Synthesis of Haouamine A: Previous Work

3.1.2.1 Previous Work from Other Groups

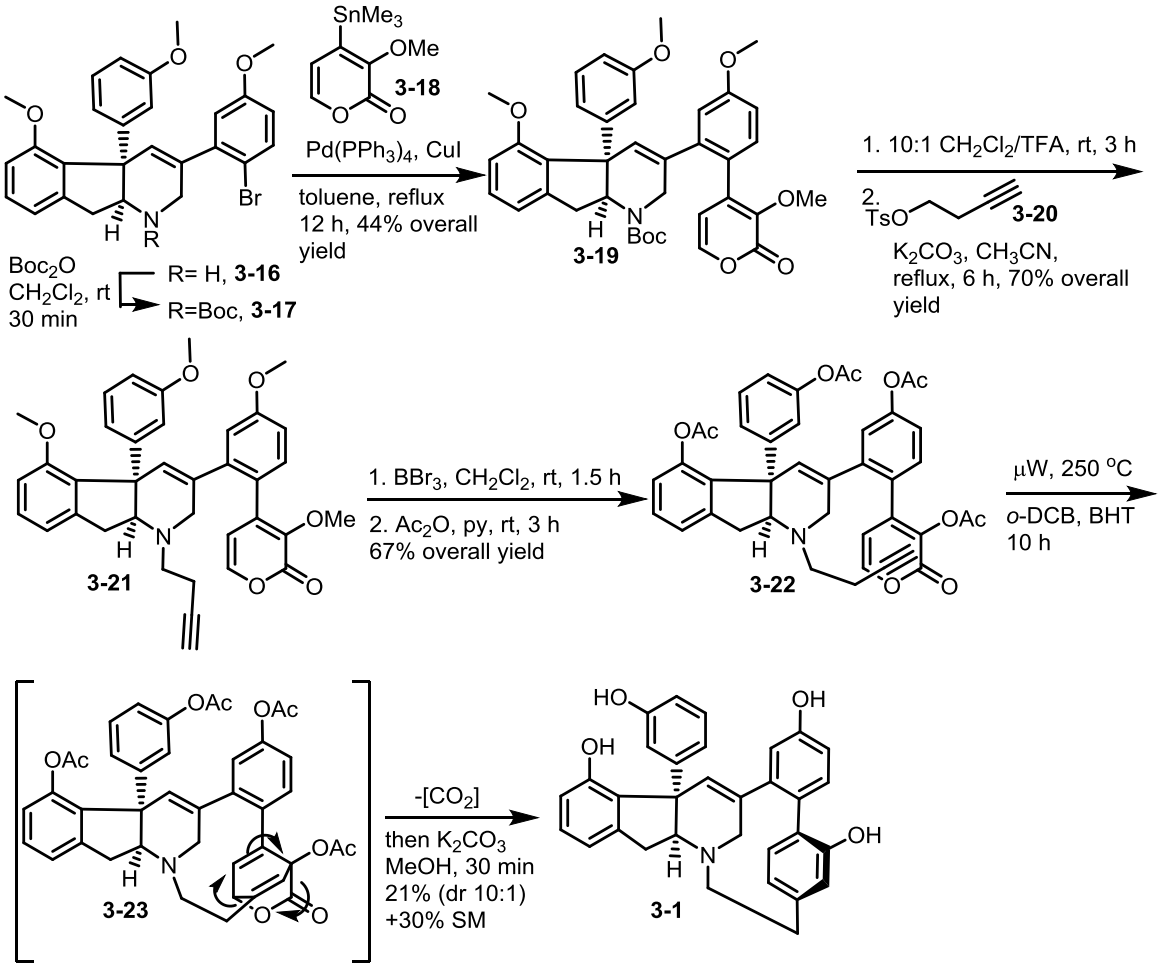
The architectural novelty of haouamine A has aroused the interest of the synthetic community. To date, the most common strategy used in constructing the strained aza-cyclophane in haouamine A was established by Baran *et al.* in 2006, as they reported the first racemic total synthesis of haouamine A.[108]



Scheme 3-3 Baran's total synthesis of haouamine A: preparation of intermediate **3-16**

The synthesis started with allylation of indanone **3-8**, which was prepared in 4 steps from 7-methoxyindanone, with allyl iodide **3-9** and subsequent condensation of the ketone with hydroxylamine. The resulting oxime **3-10** underwent a 5-*exo-trig* cyclization to trap the bromonium ion generated *in situ* when exposed to a bromide source **3-11**. Reduction of nitrone **3-12** using $NaBH_4$ afforded hydroxylamine **3-13**, which upon heating was converted to N-hydroxyl enamine **3-15** via N-hydroxyaziridinium **3-14**. The key piperidine intermediate **3-16** was obtained by selective reduction of N-hydroxylamine **3-15** using In^0 (Scheme 3-3).[108]

Construction of the strained aza-paracyclophane moisty was accomplished exploiting an intramolecular pyrone-alkyne Diels-Alder reaction. It was envisioned that a boat configuration of cyclohexadiene with an embedded CO_2 generated resembles that of the bent aromatic ring in the aza-cyclophane.[108]

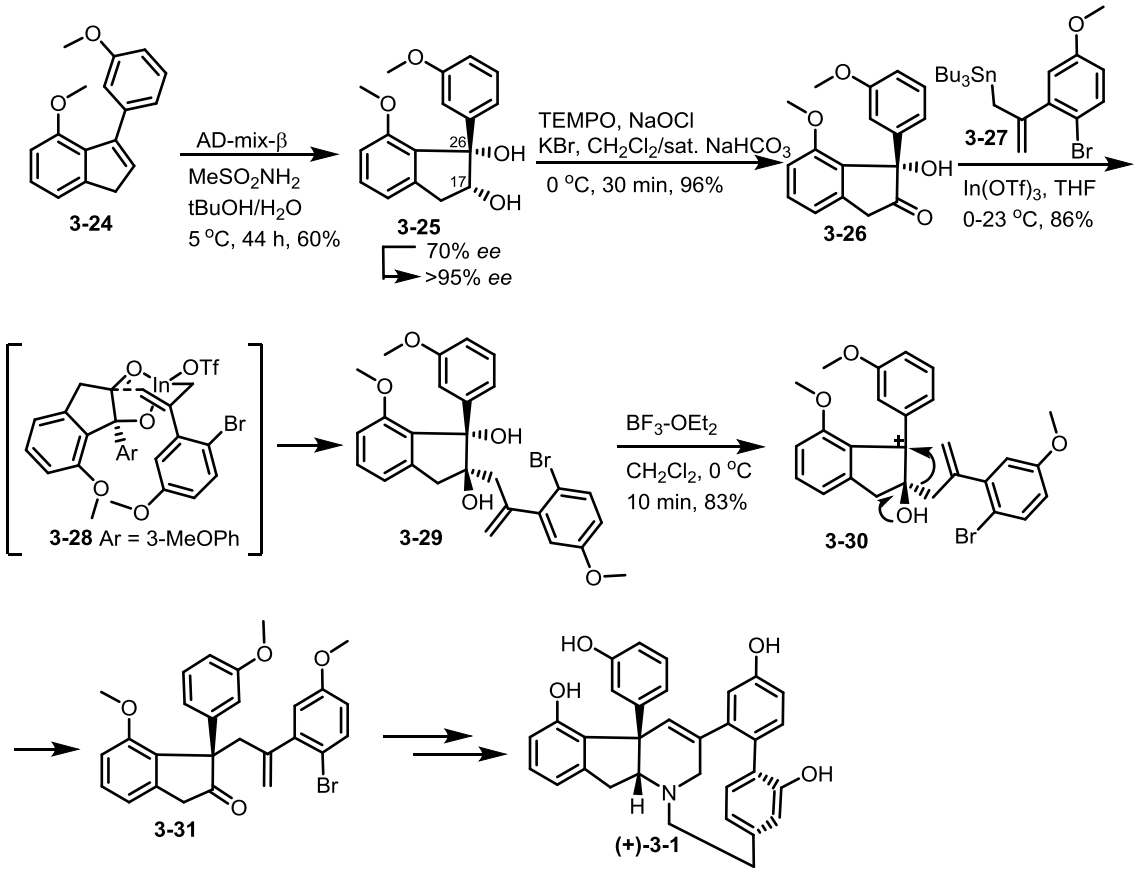


Scheme 3-4 Baran's total synthesis of haouamine A: completion by Diels-Alder reaction

The Diels-Alder precursor **3-21** was prepared from the Boc-protected piperidine **3-17** by Stille coupling with pyrone **3-18**, Boc removal and alkylation with 4-tosyloxybutyne **3-20**. The methyl groups in **3-21** were swapped for acetate groups to increase the thermal stability at elevated temperature, and the resulting alkyne **3-22** was heated at 250 ℃ to effect the Diels-Alder macrocyclization. Acetate removal furnished a mixture of haouamine A **3-1** (*dr* 10:1) and uncyclized staring material (Scheme 3-4).[108]

An asymmetric total synthesis of (+)-haouamine A was later accomplished by Baran *et al.* by establishing the absolute stereochemistry at C-26 (haouamine numbering) in key ketone intermediate **3-31** via a diastereoselective pinacol rearrangement. Diol **3-25** was generated by a Sharpless asymmetric dihydroxylation of aryl indene **3-24.** Enantio-enrichment by crystallization and subsequent oxidation

furnished α-hydroxy ketone **3-26**. Treatment of ketone **3-26** with allyl tributyltin **3-27** in presence of indium triflate afforded allyllation product diol **3-29** via chair-like transition state **3-28**, the diastereoselectivity of allyltin species generated by transmetalation of tributyltin **3-27** with indium triflate. BF_3-OEt_2 initiated pinacol rearrangement of diol **3-29** afforded ketone **3-31** via cation **3-30**, and ketone **3-31** was carried through in steps according to established reaction sequence and was converted to (+)-haouamine A (+)-**3-1**, whose CD spectra were opposite to those of the isolated natural product (Scheme 3-5).[113]

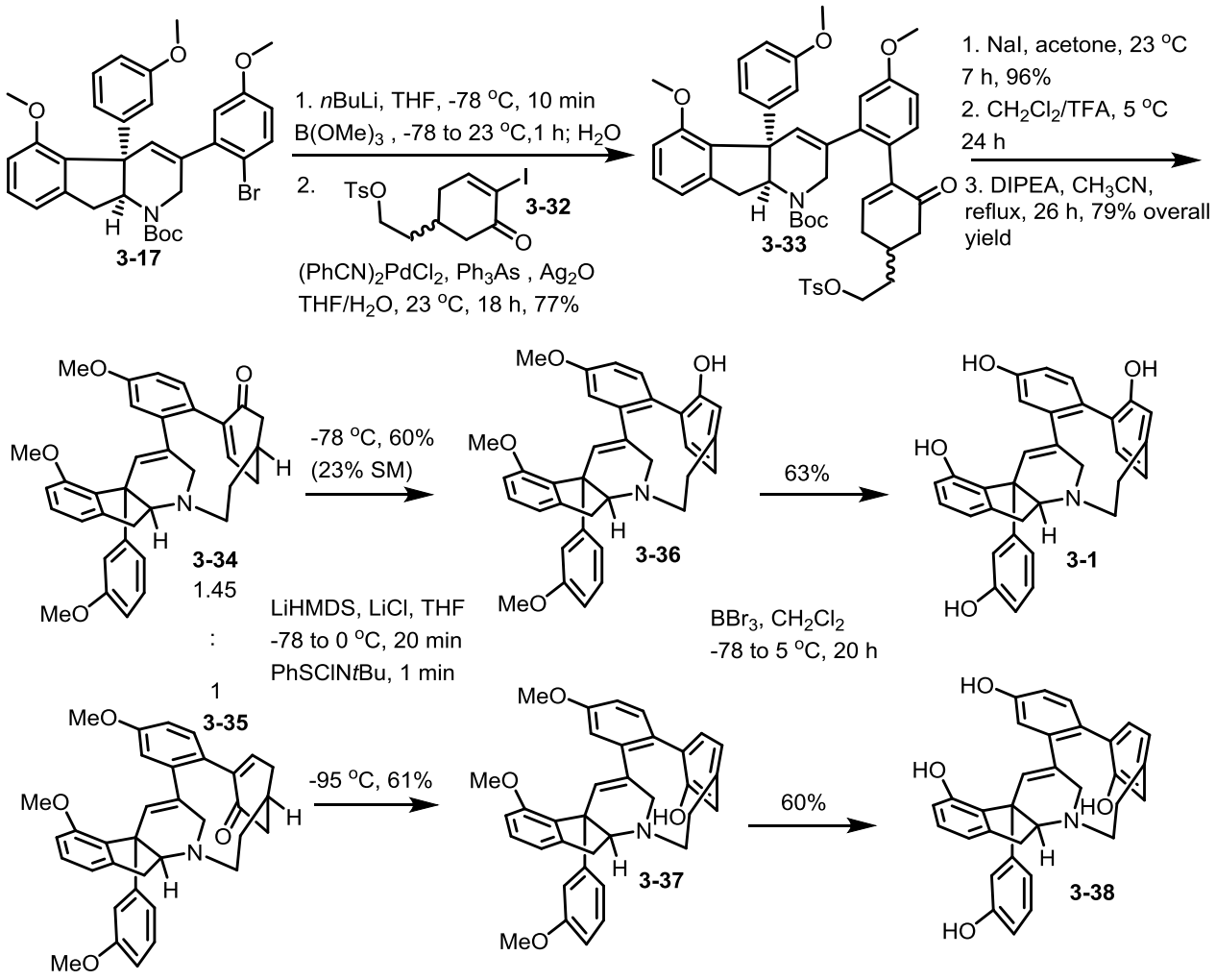


Scheme 3-5 Baran's total synthesis of (+)-haouamine A

Baran *et al.* improved their total synthesis of haouamine A by employing tosylate **3-32**, whose sp^3 tertiary carbon greatly lowers the strain built up in the macrocyclic intermediates **3-34** and **3-35**. In addition, the point chirality of this sp^3 tertiary carbon determines the planar chirality of the cyclophane

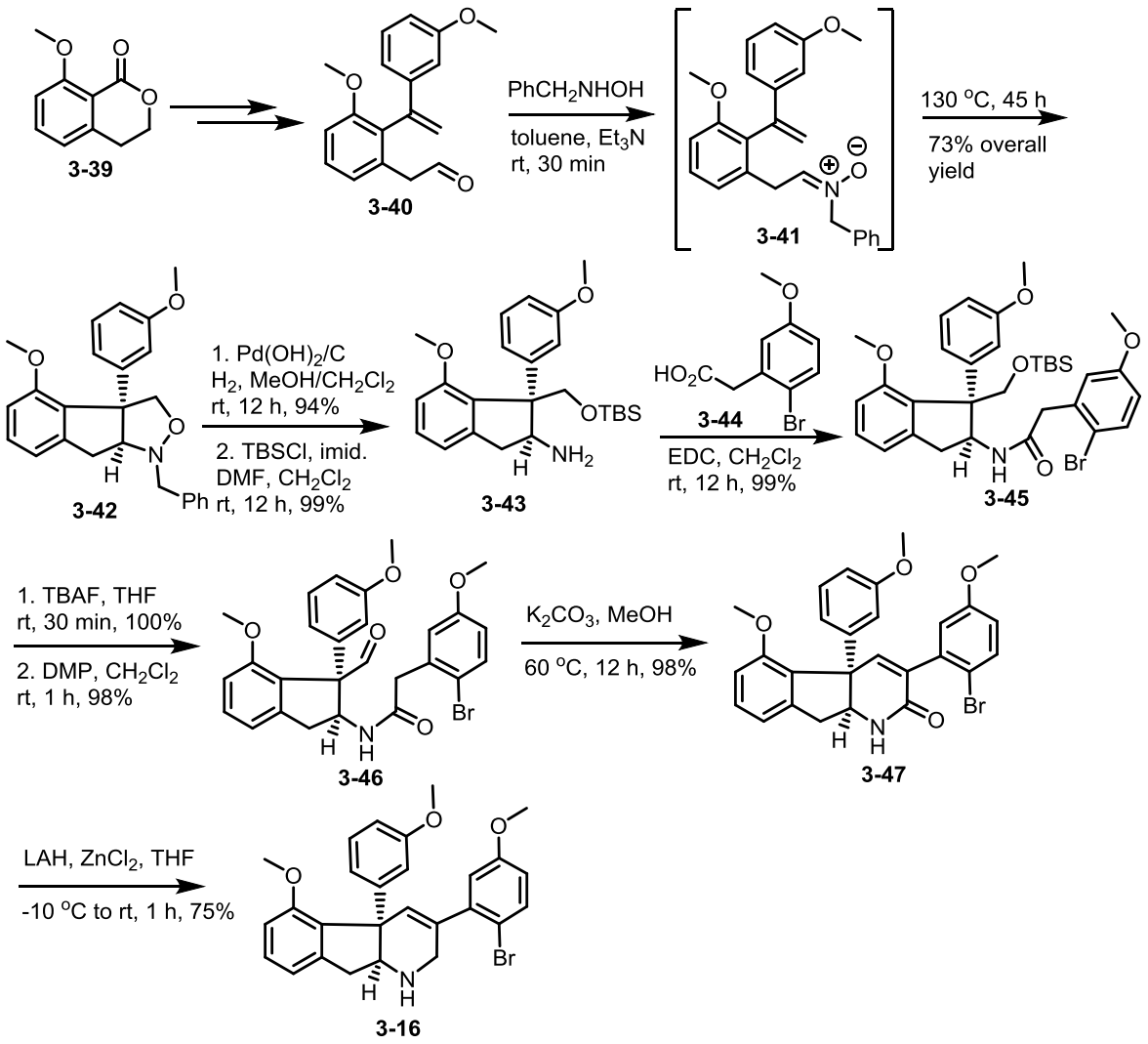
macrocycle in the natural product, which helps eliminate the possibility that the two interconverting isomers in solution are caused by atropisomerism of the boat-like phenol ring.

Their updated total synthesis commenced with borylation of the lithiated aryl bromide **3-17** and palladium-catalyzed cross coupling of the in situ generated aryl borate with enone iodide **3-32**. The coupled product **3-33** was obtained as an inseparable mixture of diastereomers. Conversion to the corresponding iodide and heating in the presence of Hünig's base was effected after N-Boc deprotection. Two macrocycles **3-34** and **3-35** were separated and each of them existed as interconverting isomers in solution, which demonstrates that the two isomers of haouamine A in solution arise from N-inversion of piperidine ring. Subsequent aromatization was accomplished using N-*tert*-butylbenzenesulfinimidoyl chloride followed by removal of methyl ethers afforded haouamine A **3-1** and its atropisomer **3-38** (Scheme 3-6).



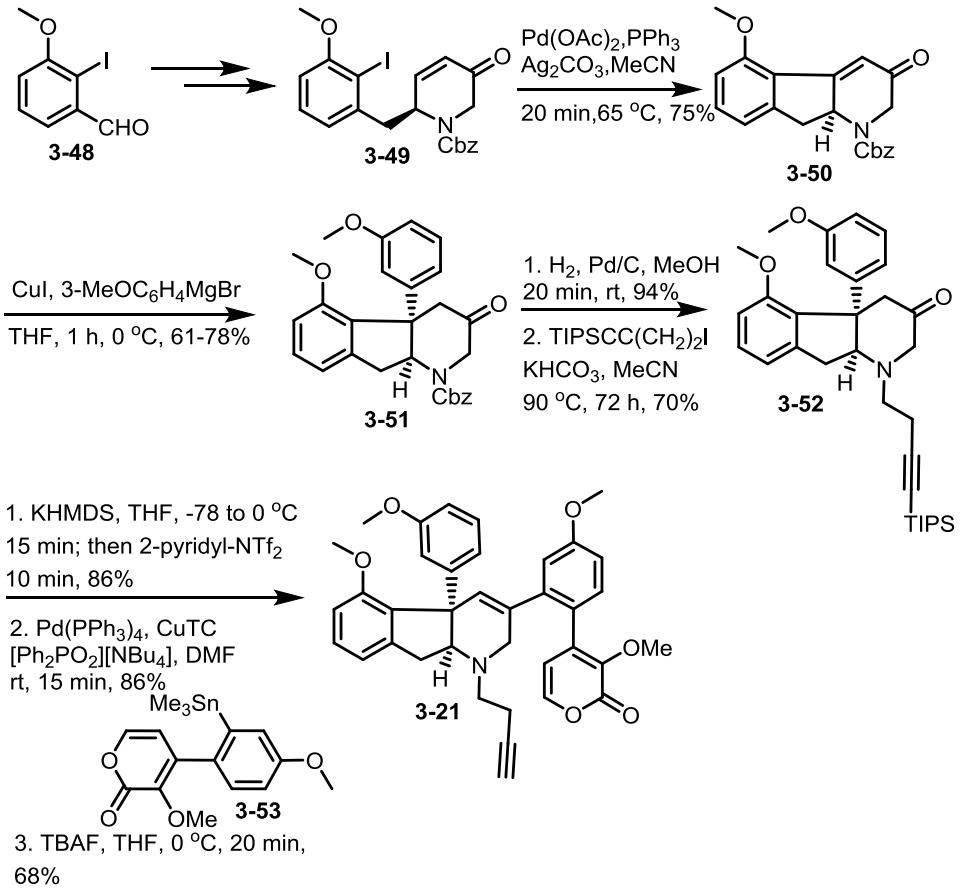
Scheme 3-6 Baran's updated total synthesis of haouamine A

Several formal total syntheses[114-116] of haouamine A have been reported based on the first generation[108] of Baran's total synthesis and two total syntheses of haouamine B[109,110] have been reported based on the second generation[107] of Baran's total synthesis. The targets in the formal total syntheses of haouamine A include key aryl bromide intermediate **3-16** or Diels-Alder precursor **3-21**.



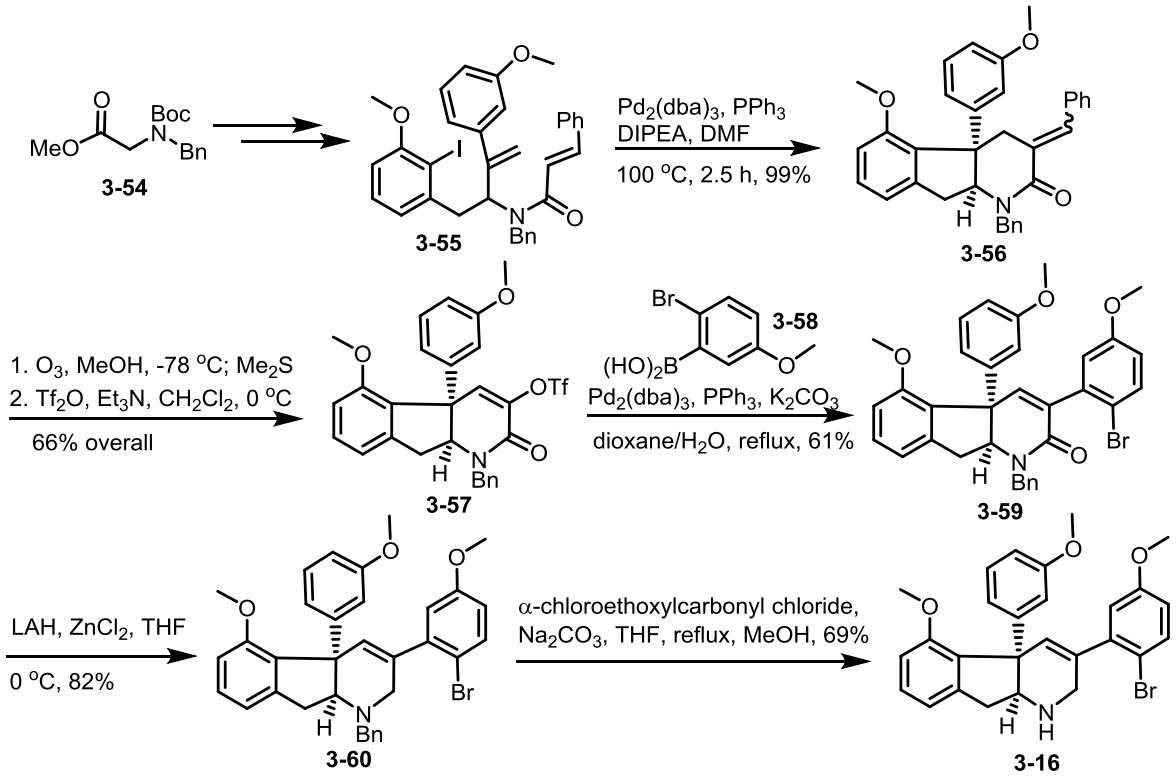
Scheme 3-7 Weinreb's formal total synthesis of haouamine A

The target of Weinreb's formal total synthesis of haouamine A was piperidine **3-16**. The synthesis started with lactone **3-39**[117], which was converted to aldehyde **3-40**. Condensation of aldehyde **3-40** with N-benzylhydroxylamine furnished nitrone **3-41**, which underwent an intramolecular dipolar cycloaddition to generate isoxazolidine **3-42**. This was further elaborated to amine **3-43** by reductive N-O bond cleavage, debenzylation and subsequent silylation of alcohol. Amide coupling of amine **3-43** with acid **3-44** afforded amide **3-45**, whose TBS group was deprotected and the resulting alcohol was oxidized with DMP to provide aldehyde **3-46**. Lactam **3-47** was obtained from aldehyde **3-46** via an intramolecular aldol condensation and was reduced to converge with Baran's intermediate **3-16** (Scheme 3-7).[114]



Scheme 3-8 Fürstner's formal total synthesis of haouamine A

Fürstner *et al.* chose Diels-Alder precursor **3-21** as their target for their formal total synthesis of haouamine A. Enone **3-49**, synthesized from aldehyde **3-48** in a few steps, underwent a Heck cyclization to furnish tricycle **3-50** which was then converted to tetracycle **3-51** via the conjugate addition of an organocuperate. Nitrogen deprotection and alkylation were conducted to form **3-52**. This sequence was necessary to ensure the regioselective formation of an enol triflate in the following step. Stille coupling with trimethyltin **3-53** and desilylation then afforded Baran's Diels-Alder precursor **3-21**. After a protecting group swap, the key Diels-Alder reaction in Baran's total synthesis was attempted but the desired Diels-Alder product was obtained in much lower yields than those reported by the Baran group (Scheme 3-8).[115]

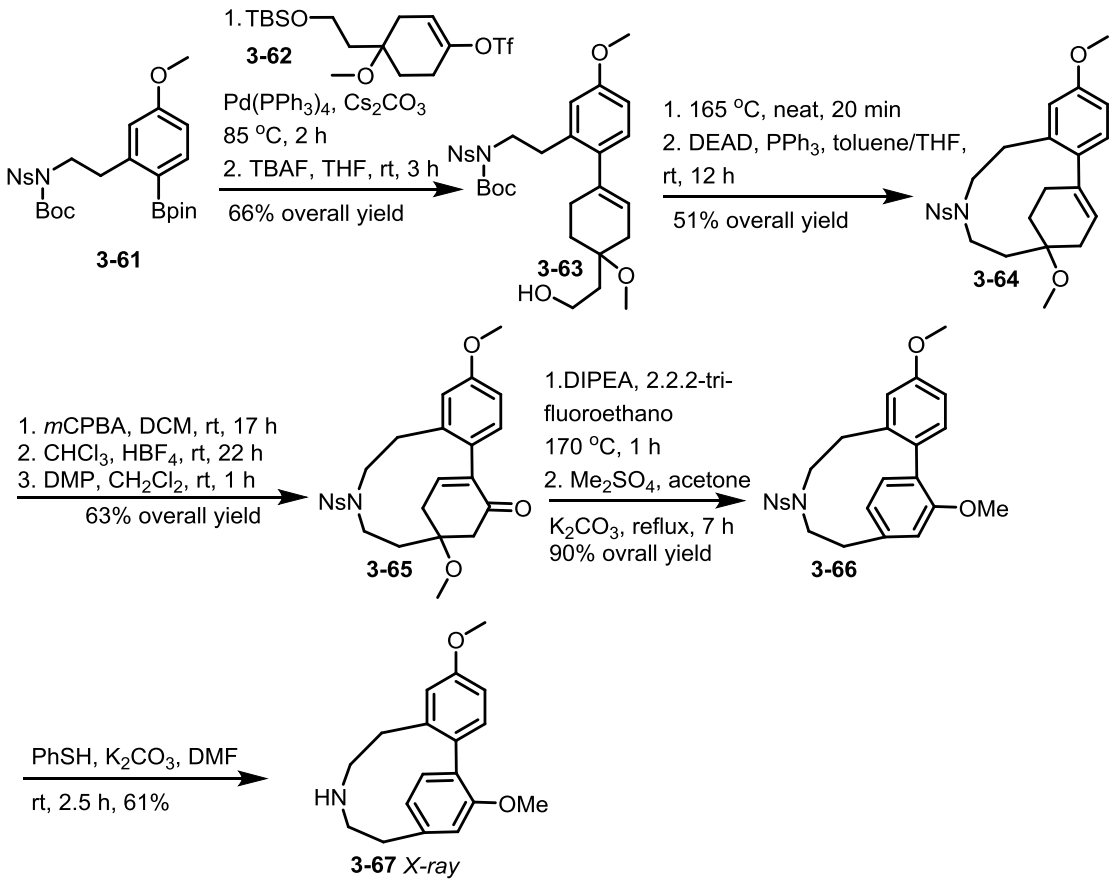


Scheme 3-9 Ishibashi's formal total synthesis of haouamine A

Ishibashi *et al.* completed their formal total synthesis of haouamine A with key aryl bromide intermediate **3-16** as the target. An efficient intramolecular cascade Mizoroki-Heck reaction built up the diaryl quaternary carbon in tetracycle **3-56** from aryl iodide **3-55**. Ozonolysis and enol triflate formation afforded **3-57**, which was subjected to a Suzuki coupling, reduction, and debenzylation to afford **3-16**, the key intermediate in Baran's synthesis (Scheme 3-9).[116]

3.1.2.2 Previous Work from the Wipf Group: a Model System

Initial synthetic work involving haouamine A in the Wipf group was attempted by Dr. Markus Furegati who completed the synthesis of the model 3-aza-[7]-paracyclophane **3-67**. The phenol moiety in the aza-paracyclophane was constructed via a base-promoted aromatization of 5-methoxy-cyclohex-2-en-1-one functionality in intermediate **3-65**. This particular aromatization method of using β-elimination of MeOH was discovered before the oxidative method reported by Baran *et al* to form **3-32**.[107,109,110,113,111]



Scheme 3-10 Wipf's synthesis of **3-67**: the 3-aza-[7]-paracyclophane core of haouamine A

The synthesis of model system **3-67** commenced with a Suzuki-Miyaura coupling of boronic ester **3-61** and enol triflate **3-62**, followed by desilylation to generate alcohol **3-63**. After heat-promoted Boc removal, a Mitsunobu cyclization furnished macrocycle **3-64**. Key enone **3-65** was obtained from **3-64** via a three-step reaction sequence including epoxidation, acid-promoted epoxide opening, and oxidation of the resulting allylic alcohol. Aromatization was effected by heating and afforded model system **3-67**, whose structure was confirmed by X-ray crystallographic analysis of its HCl salt (Scheme 3-10).[111]

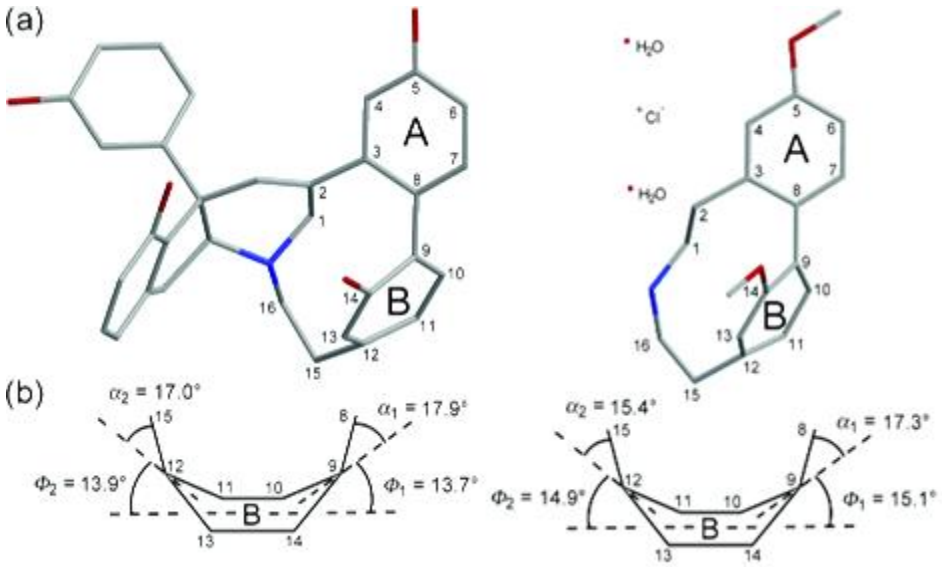


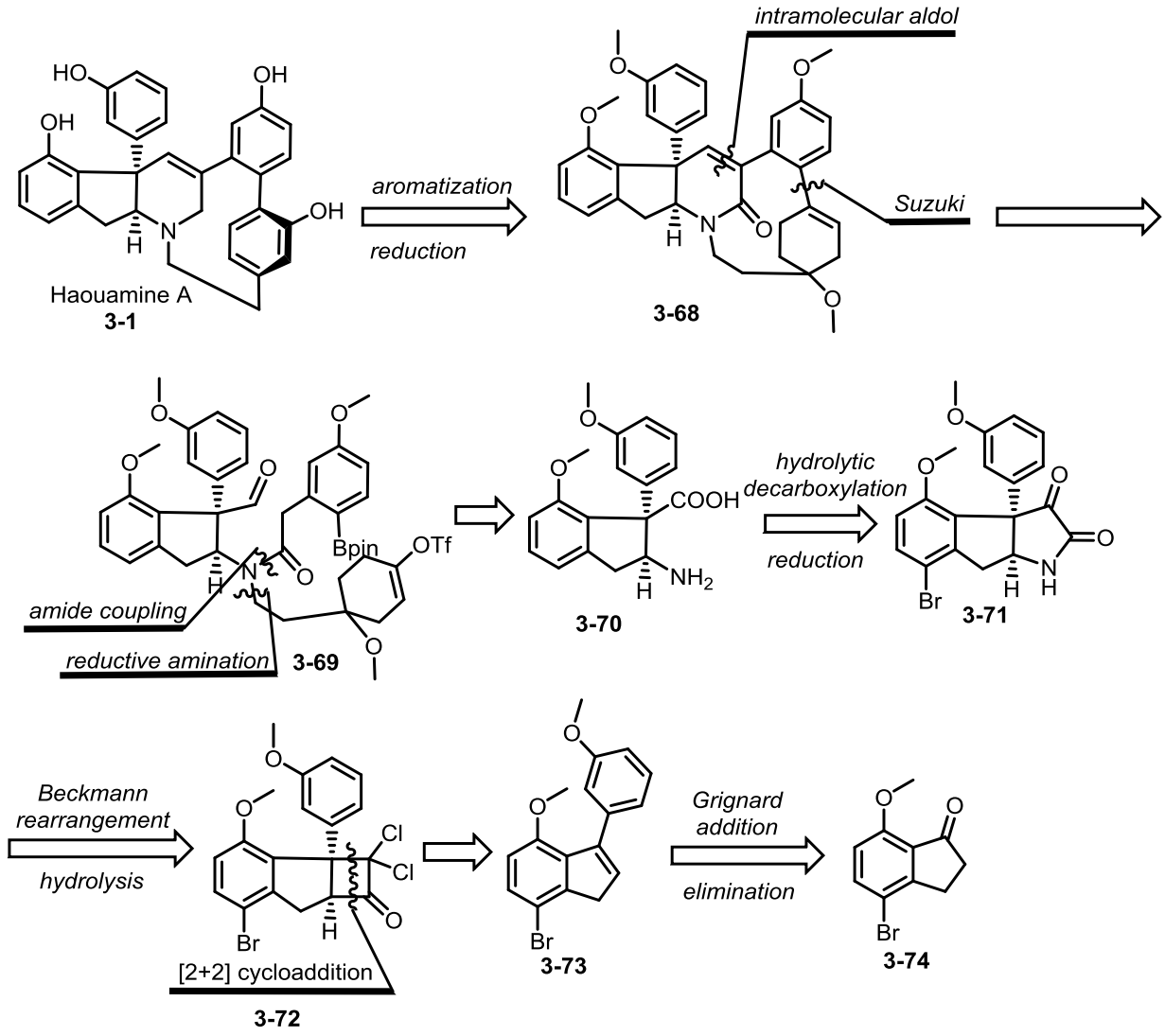
Figure 10 X-ray structure of **3-1** and **3-67-HCl**[107,108,111]

The B ring of haouamine A in model system **3-67** adopts a boat-like conformation (Figure 10, right) as shown in the X-ray structure, which bears a close resemblance to that of the natural product (Figure 10, left). The successful synthesis of model system **3-67** sets a good foundation for the total synthesis of haouamine A, using the unique base-promoted aromatization of enone **3-65**.[111]

3.1.2.3 Previous Work from the Wipf Group: Total Synthesis of Haouamine A

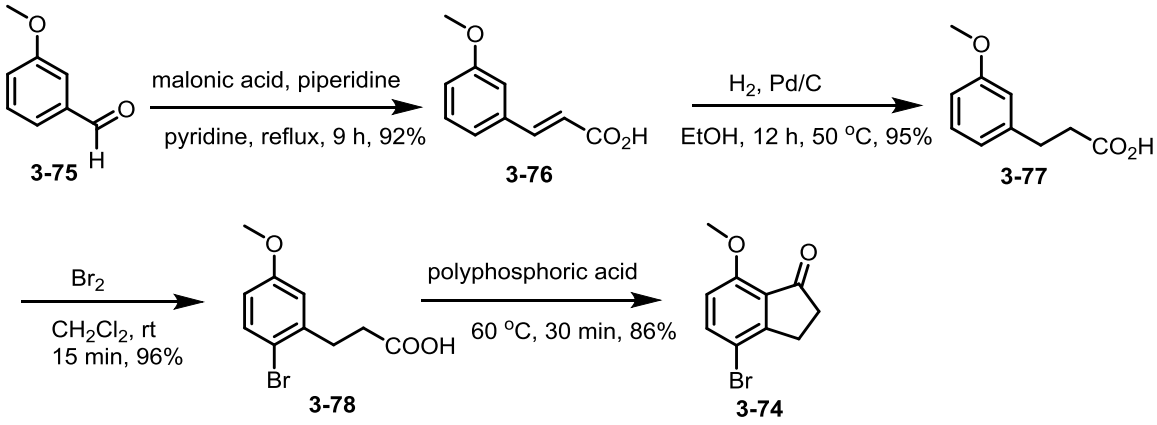
The total synthesis of haouamine A was attempted by Dr. Chenbo Wang in the Wipf group and using the model system as a guide. The distorted B-ring in the aza-paracyclophane would be formed from methoxy cyclohexene **3-68** as it was in the model system **3-67**. The A and B rings of haouamine A could be joined via a Suzuki coupling which to construct the macrocycle. The tetrahydropyridine moiety in haouamine A could be accessible from **3-68** by reduction of the lactam, which is derived from intramolecular aldol condensation of aldehyde **3-69**. The tertiary amide moiety in **3-69** is obtained from amine **3-70** by reductive amination and subsequent amide coupling. The amine and carboxylic acid functionalities in **3-70** would be accessible through hydrolytic decarboxylation and dehalogenation from **3-71**, which should be the product of a Beckmann rearrangement of dichlorocyclobutanone **3-72**. **3-72** would be constructed

via a [2+2] cycloaddition involving indene **3-73**, which could be derived from known dihydroindinone **3-74**[118] via nucleophilic addition of a Grignard reagent and dehydration (Scheme 3-11).[119]



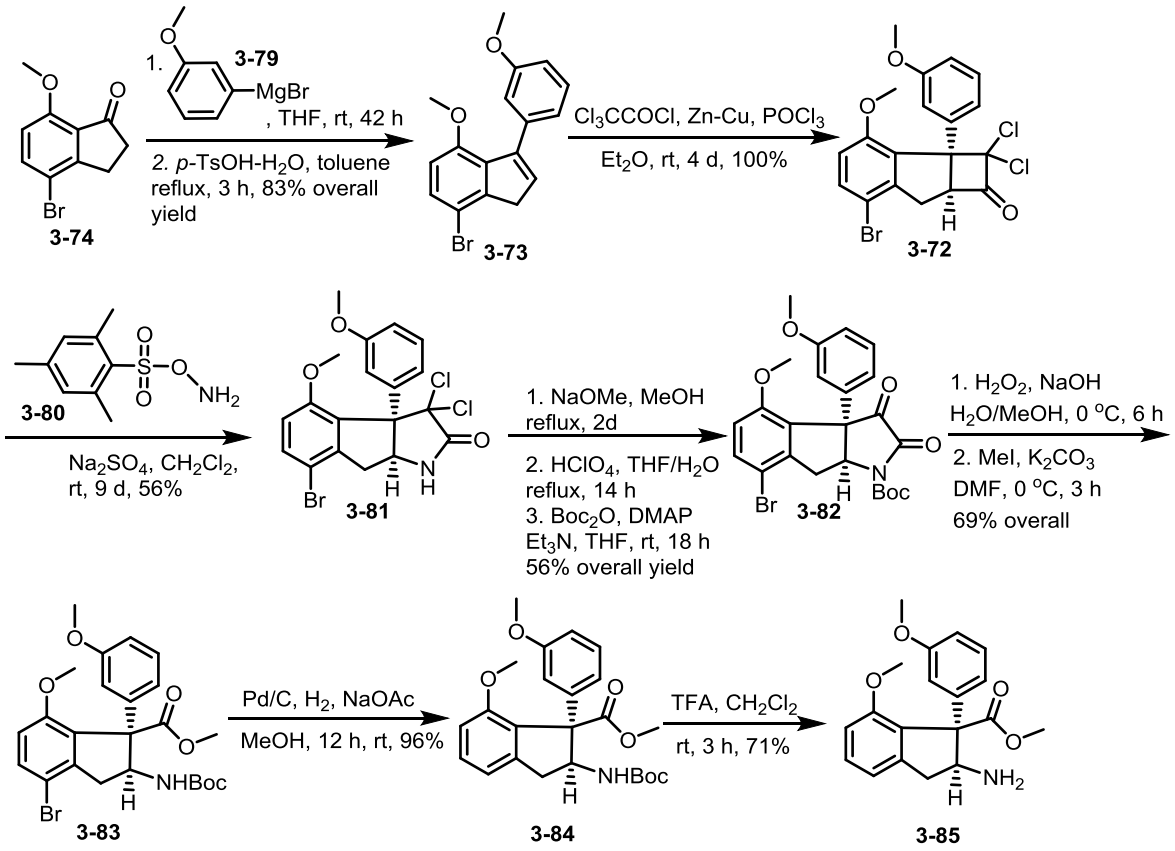
Scheme 3-11 Retrosynthetic analysis of haouamine A

The total synthesis commenced with a Knoevenagel−Doebner condensation[120,121] of commercially available aldehyde **3-75** with malonic acid and piperidine in pyridine at reflux. Catalytic hydrogenation of resulting α, β-unsaturated acid **3-76**, followed by bromination to block the *para*-position, afforded aryl bromo acid **3-78** that underwent a Friedel–Crafts cyclization in hot PPA to furnish indanone **3-74** (Scheme 3-12).[118]



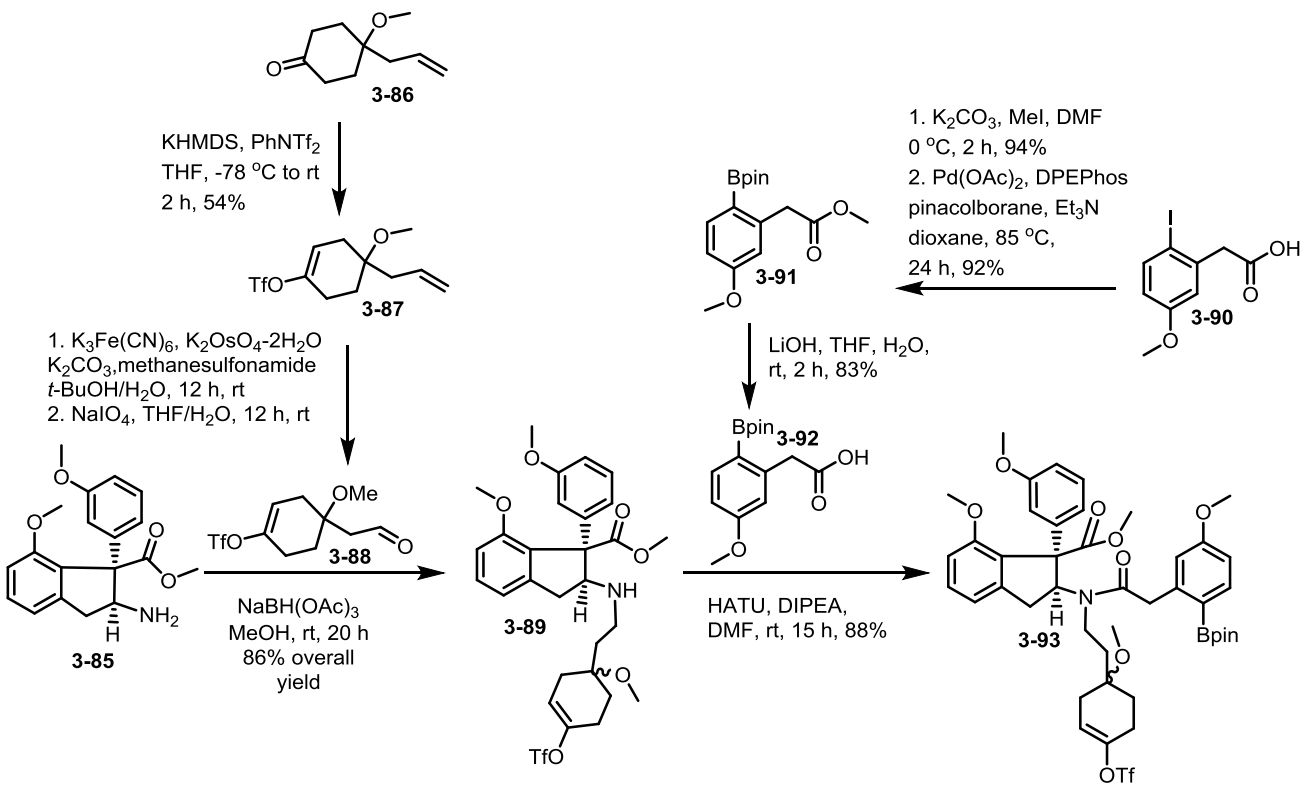
Scheme 3-12 Preparation of indanone **3-74**

Indanone **3-74** was subjected to nucleophilic attack by Grignard reagent **3-79**, and the resulting tertiary alcohol was heated in toluene at reflux with catalytic *p*-TsOH-H_2O to effect dehydration.[122] A [2+2] cycloaddition[123-125] of indene **3-73** with *in situ* generated dichloroketene afforded cyclobutanone **3-72**, which was treated with mesitylene sulfonyl hydroxylamine **3-80**[126-128] to promote a Beckmann rearrangement.[129,130] Regioselective insertion of a nitrogen atom furnished dichlorolactam **3-81** with retention of configuration at the adjacent quaternary carbon. The geminal dichloro moiety was hydrolyzed to a carbonyl using a methanolysis-hydrolysis sequence. Boc-protected α-keto lactam was subjected to oxidative hydrolytic decarboxylation[131-135], and the resulting carboxylate was immediately methylated to give the Boc-amino methyl ester **3-83**. Amine **3-85** was smoothly obtained from **3-83** in two steps including hydrogenative debromination and Boc removal (Scheme 3-13).[119]

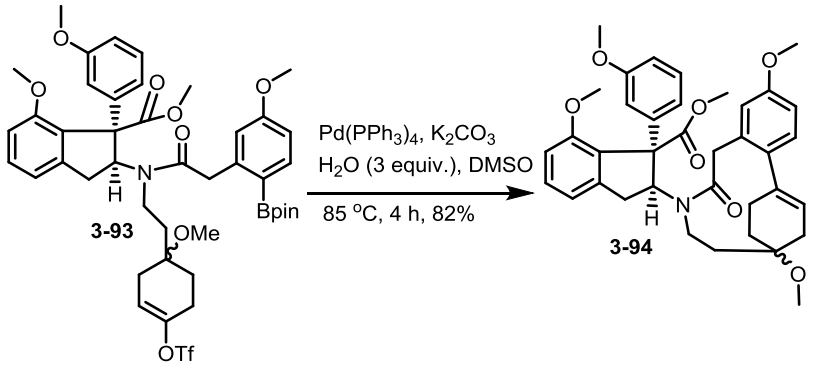


Scheme 3-13 Preparation of amine **3-85**

The secondary amine **3-89** was prepared from **3-85** and aldehyde **3-88** by reductive amination. The inseparable mixture of diastereomers was carried through the subsequent steps. Ketone **3-86**[111] underwent enol triflate formation and dihydroxylation/oxidative cleavage to give aldehyde **3-88**, which was immediately used in a reductive amination due to its instability. Suzuki coupling precursor **3-93** was synthesized from secondary amine **3-89** using peptide coupling conditions with acid **3-92**, which was prepared from known acid **3-90** (Scheme 3-14).[111].[119]



Scheme 3-14 Preparation of amine **3-93** for Suzuki cyclization

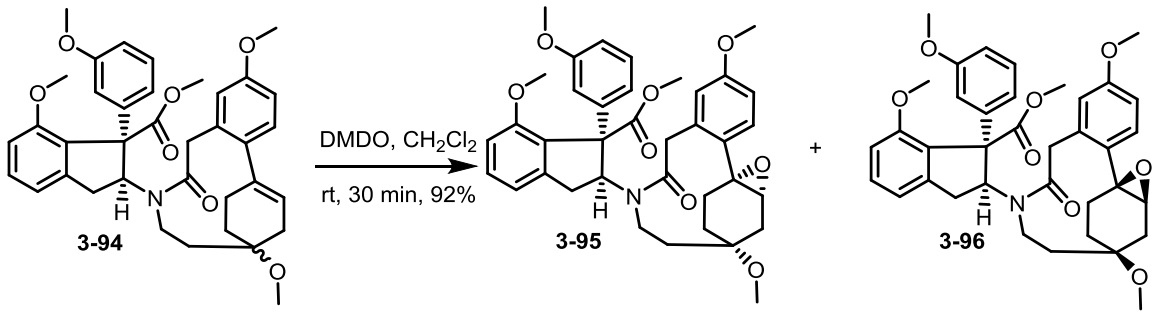


Scheme 3-15 Preparation of macrocycle **3-94** by Suzuki cyclization

The key intramolecular Suzuki coupling to build the macrocycle **3-94** was successfully carried out with great efficiency, reproducibility, and scalability. Addition of three equivalents of water was crucial as it was envisioned to play an important role in promoting the generation of hydroxide ion in

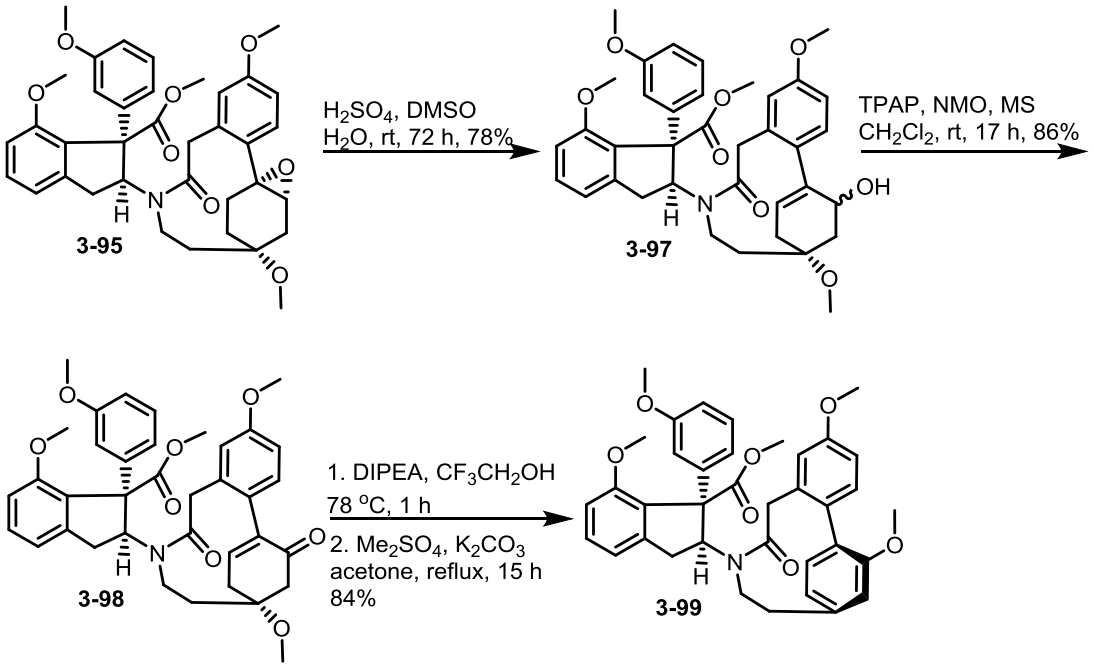
transmetalation process or basic hydrolysis of boronic ester before transmetalation. More water in the reaction led to deboronation that hampered the yield (Scheme 3-15).[119]

However, intramolecular aldol reactions to construct the tetrahydropyridine moiety in haouamine A proved to be difficult. In order to minimize interference from the cyclohexene moiety to possible reactions involved in tetrahydropyridine formation, the methoxyl cyclohexene moiety was aromatized.

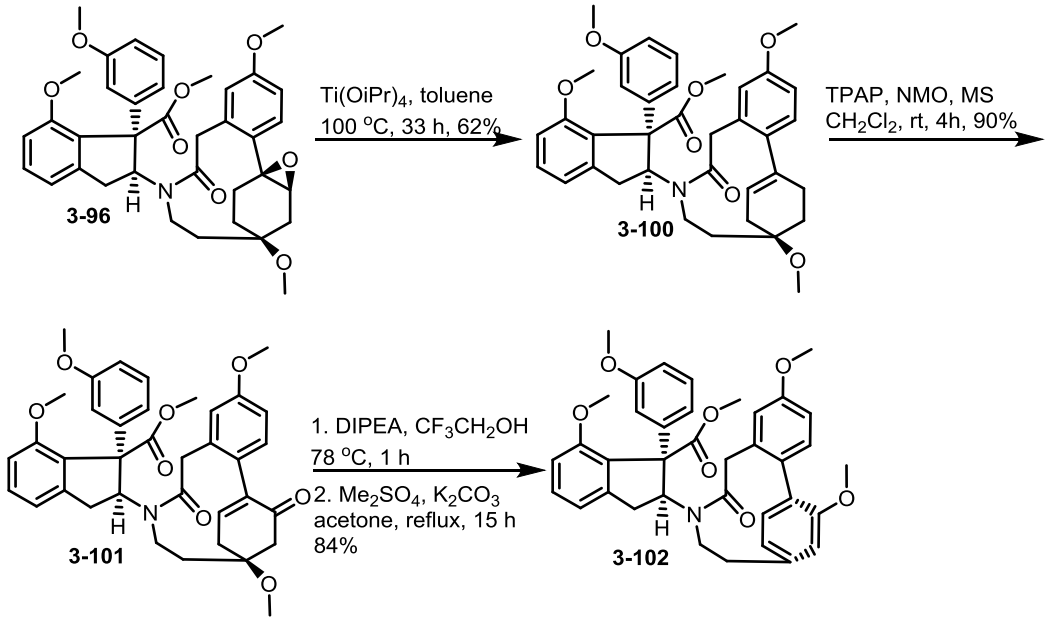


Scheme 3-16 Epoxidation of **3-94** to generate a mixture of diastereomers **3-95** and **3-96**

According to aromatization protocols developed in the model system study, the cyclohexene moiety in **3-91** was epoxidized efficiently to generate a mixture of easily separable diastereomers. Both of them were carried through the following reaction sequence as not much information was known at this stage in terms of stereochemical configuration in comparison with that of haouamine A.[119]



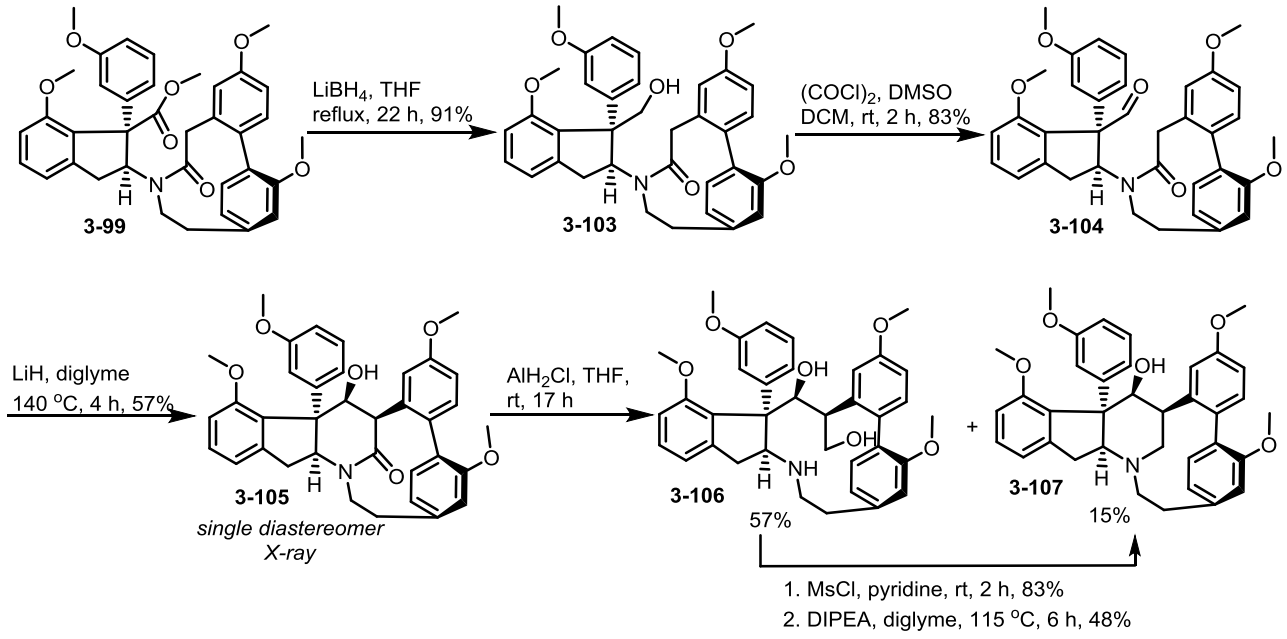
Scheme 3-17 Aromatization sequence from **3-95** to generate **3-99**



Scheme 3-18 Aromatization sequence from **3-96** to generate **3-102**

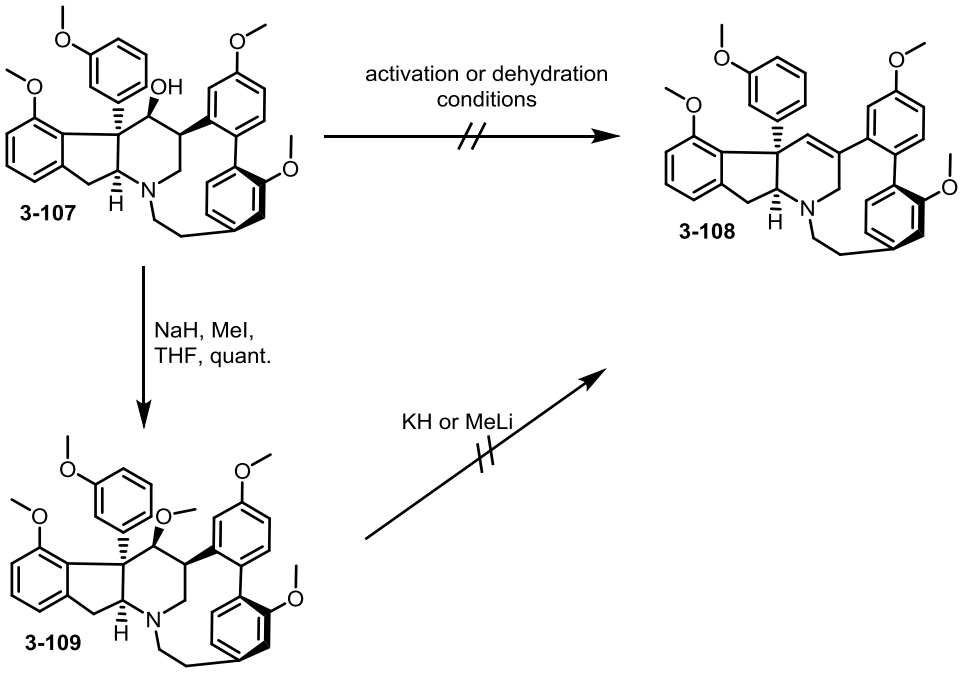
A base-promoted aromatization sequence was carried out separately for **3-95** and **3-96**, including epoxidation (Scheme 3-17), acid-promoted epoxide opening, oxidation of the resulting allylic alcohol and base-promoted aromatization at elevated temperature (Scheme 3-18). Amide **3-99** was later characterized

by X-ray crystallography to confirm the correct atropisomerism to be consistent with haouamine A. This material was used in the final steps of the total synthesis.[119]



Scheme 3-19 Formation of **3-107**

An intramolecular aldol reaction was carried out under relatively harsh conditions with aldehyde **3-101**, which was prepared from aromatized lactam **3-96** in two steps. The aldol product **3-102** was characterized as a single diastereomer by X-ray crystallography. After extensive experimentation, it was discovered that the deeply buried amide moiety **3-105** was reduced, providing amino alcohol **3-106** as the major product and desired tertiary amine **3-107** as the minor product. Activation of the hydroxyl group in amino alcohol **3-106** with mesylate and an intramolecular substitution smoothly furnished desired tertiary amine **3-107** (Scheme 3-19).[119]



Scheme 3-20 Attempted dehydration of alcohol **3-107** to generate **3-108**

However, dehydration of alcohol **3-107** to generate tetrahydropyridine **3-108** proved to be challenging. Numerous conditions including activation of the hydroxyl group (MsCl, $SOCl_2$, $POCl_3$, Tf_2O, $NaH/PhNTf_2$, thiocarbonyldiimidazole, TsOH/PhMe, $DEAD/PPh_3$) and dehydration (Martin's sulfurane, Burgess reagent, P_2O_5/PhMe) were conducted and met with no success. The hydroxyl group was deeply buried in the cavity formed by the aza-cyclophane moiety in **3-107** and it was too hindered to be activated with reagents even as small as mesylate chloride. The structure of **3-107** was also discovered to be rather sensitive as it underwent complete decomposition upon slight heating. Methylation of the hydroxyl group in **3-107** was found to be quantitative using methyl iodide, but the elimination of MeOH from ensuing **3-109** using a sterically less demanding base such as potassium hydride or methyl lithium gave starting material as the proton next to methoxyl group was discovered to be completely shielded. Likewise slight heating of **3-109** with base led to complete decomposition (Scheme 3-20).

Thus, although the late stage intermediate **3-107** was synthesized based on a route featuring intramolecular Suzuki cyclization, aromatization, and intramolecular aldol reaction, the sequence was two steps away from haouamine A **3-1**.

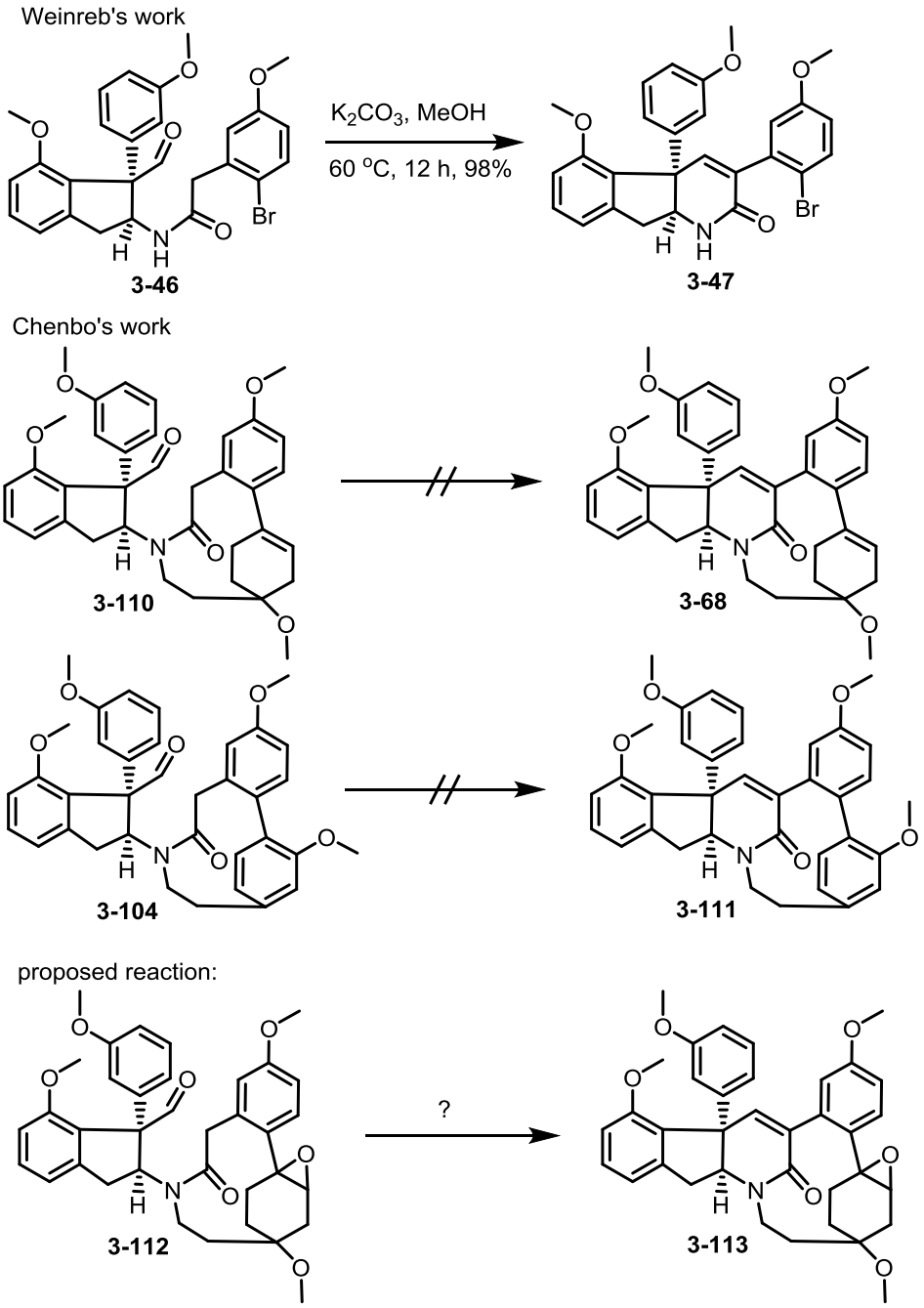
3.2 RESULTS AND DISCUSSION

3.2.1 1st Generation Approach: Intramolecular Aldol Condensation of Epoxide Substrate

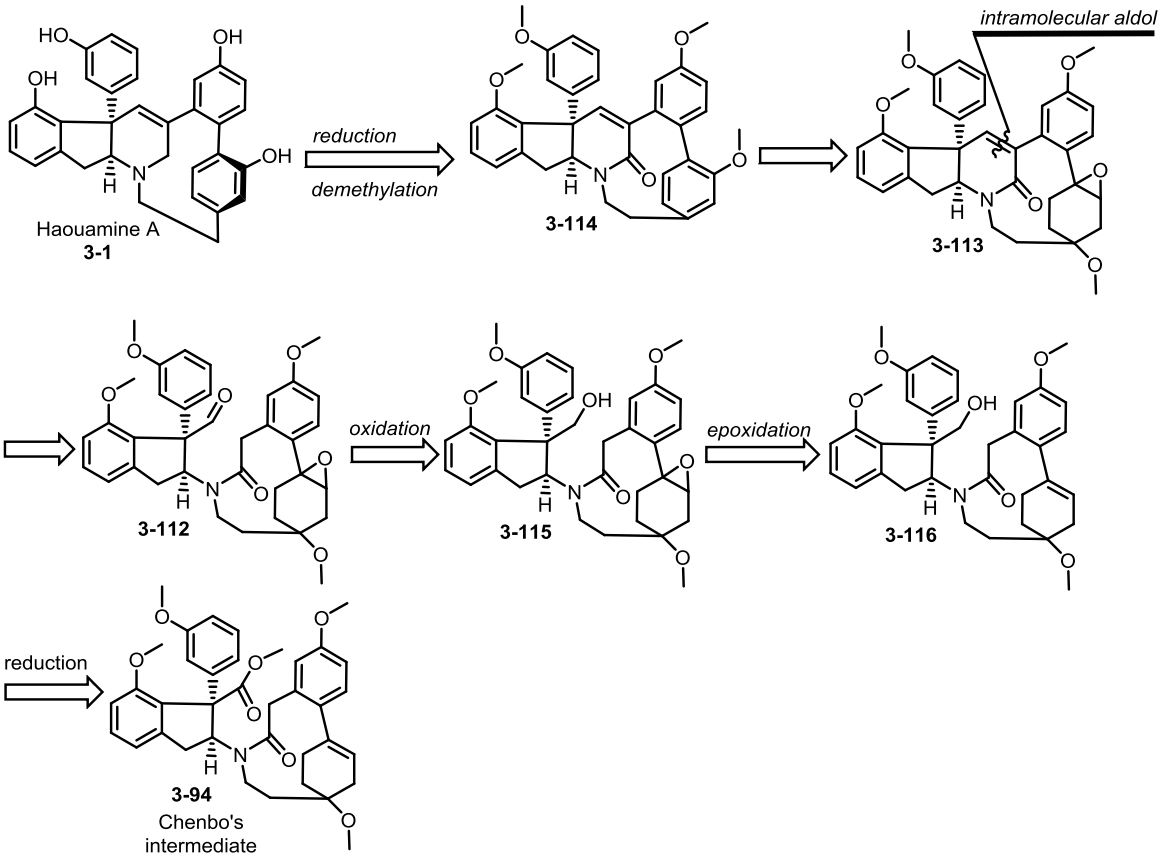
Chenbo's thorough and elaborate work on the total synthesis of haouamine A has shown that the late stage intermediate **3-104** bearing a hindered hydroxyl group formed in the intramolecular aldol reaction was difficult to functionalize. Therefore, it was assumed that the tetrahydropyridine should be formed earlier to avoid manipulations on a rigid aza-paracyclophane intermediate.

It was envisioned that an intramolecular aldol condensation of a less hindered and strained intermediate similar to Weinreb's formal synthesis[114] should be ideal for the direct formation of the tetrahydropyridine moiety. In this way, the challenging dehydration from **3-107** to **3-108** should be bypassed in the early steps. Similar transformations were attempted in Chenbo's work[119] on substrates **3-104** and **3-110** with no success, which was attributed to the rigid nature of both molecules caused by conjugated sp^2 carbons present in the phenol or cyclohexene functionalities (Scheme 3-21).

It was anticipated that the conversion of the sp^2 carbons in **3-110** to sp^3 carbons via epoxidation should greatly reduce the strain present in the pre-formed macrocycle structure, making it more flexible for an intramolecular aldol condensation. Epoxide **3-112** could, therefore, serve as a substrate for intramolecular aldol condensation.

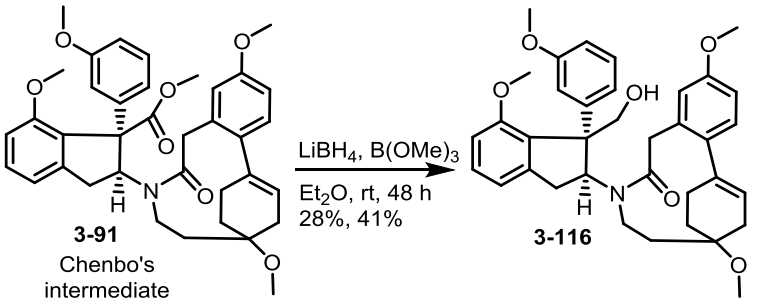


Scheme 3-21 Substrates for intramolecular aldol condensation



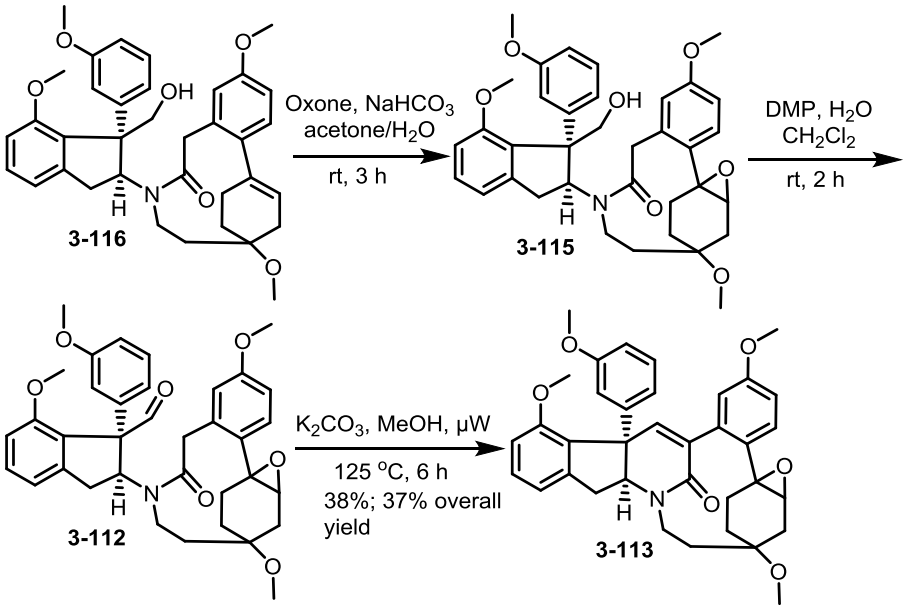
Scheme 3-22 Retrosynthetic analysis based on intramolecular aldol condensation of **3-112**

The tetrahydropyridine moiety in haouamine A **3-1** could be constructed by reduction of lactam **3-111**. Epoxide **3-110** was envisioned to be the precursor of aromatized **3-111** and could be derived from aldehyde **3-109** through an intramolecular aldol condensation. Aldehyde **3-109** could be accessed from Chenbo's key intermediate macrocycle **3-91** after sequential reduction of ester **3-91**, epoxidation of cyclohexene **3-113** and oxidation of ensuing alcohol **3-112** (Scheme 3-22).



Scheme 3-23 Selective reduction of methyl ester **3-91**

The new approach commenced with a selective reduction of sterically-hindered methyl ester **3-91** in the presence of the lactam macrocycle. Although $LiBH_4$ in THF smoothly reduced a similar substrate **3-99** to **3-103**[119], only a trace of desired alcohol **3-116** was obtained. According to literature precedence[136,137], the use of low polarity Et_2O and catalytic $B(OMe)_3$ greatly accelerates the reductions with $LiBH_4$. Therefore, methyl ester **3-91** was exposed to $LiBH_4$ with $B(OMe)_3$ in Et_2O, and the reduction was brought to completion in two days. Formation of two separable diastereomers was observed, each in moderate yields and they could be well separated by chromatography on SiO_2. Both diastereomers were carried through the route individually and their yields for each step were presented separately, as it was not certain as to which diastereomer led to the natural product or its atropisomer at the current stage (Scheme 3-23).

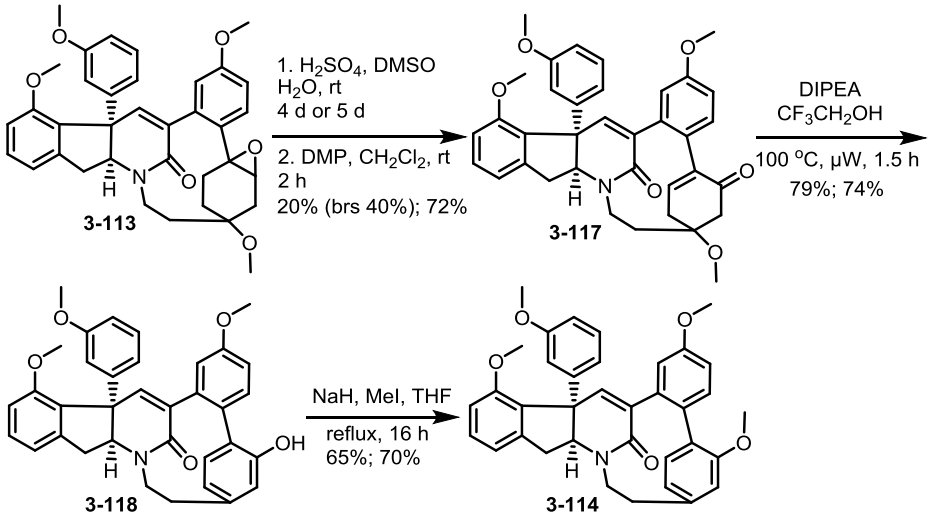


Scheme 3-24 Intramolecular aldol condensation of epoxide **3-112**

As discussed previously, the use of epoxide **3-112** as intramolecular aldol condensation precursor was desirable for the direct formation of lactam **3-113**, as two newly generated sp^3 carbons by the formation of epoxide were envisioned to greatly reduce the strain present in the macrocycle. Therefore, precursor **3-112** was synthesized in two steps from alcohol **3-116** including epoxidation and oxidation of ensuing alcohol **3-115**. Epoxidation was accomplished by *in situ* generated DMDO. Oxidation of **3-115** was accomplished with Dess-Martin periodinane. Intermediate **3-112** was isolated as mixtures of diastereomers, and were directly used without characterization (Scheme 3-24).

For the formation of the lactam moiety in **3-47** in Weinreb's formal total synthesis of haouamine A, aldehyde **3-46** was treated with K_2CO_3 in MeOH heated at 60 ℃. However, aldehyde **3-112** did not react under the same conditions. This may be attributed to the macrocycle present in **3-112**, making it a much more hindered and rigid system than aldehyde **3-46**. The desired condensation product **3-113** was obtained in moderate yields (68%; 46%) when the reaction mixture was stirred for two months at 60 ℃ or 11 days at 100 ℃.[119] Though the reaction time was exceedingly long, this was encouraging because both **3-112** and **3-113** showed good stability at elevated temperature. As a result, a microwave assisted aldol

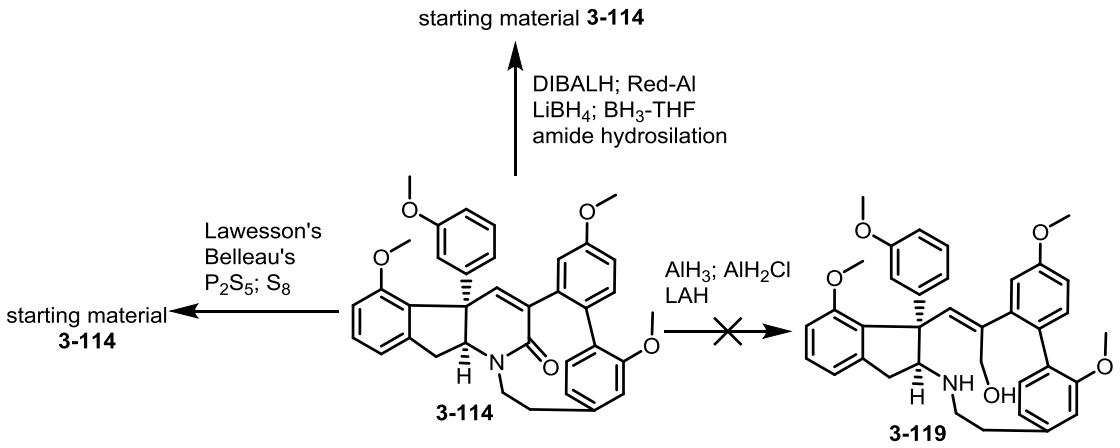
condensation condition was attempted on aldehyde **3-112**. Within 6 hours at 125 ^{o}C aldehyde **3-112** was smoothly converted to lactam **3-113** in a moderate yield over 3 steps (Scheme 3-24).



Scheme 3-25 Aromatization to generate phenol **3-118** and its subsequent methylation

Based on the well-established protocol developed in the model system, epoxide **3-113** was envisioned to be converted to the key aromatization precursor **3-117**. Epoxide **3-113** was anticipated to be considerably more rigid than epoxidation product of **3-64** in model system synthesis or **3-95**/**3-96**, and therefore it showed substantially less reactivity in the acid-induced opening of the epoxide to generate allylic alcohol upon treatment of H_2SO_4 in a mixture of H_2O and DMSO. For one diastereomer, the epoxide was not completely consumed after 4 days, for the other one, the reaction took 5 days to complete. The allylic alcohol products, which existed as a mixture of diastereomers and showed complicated spectra, were oxidized in 2 h with Dess-Martin periodinane to smoothly furnish aromatization precursor **3-117** in 20% (40% brs) and 72% yields over 2 steps (Scheme 3-25).

Aromatization of enone **3-117** was readily accomplished in good yield as previously described as **3-65** or **3-98**/**3-101** under microwave irradiation for 1.5 hours at 100 °C together with Hünig's base in 2,2,2-trifluoroethanol. Phenol moiety formed during aromatization in **3-115** was methylated by refluxing with MeI in presence of NaH, in order to increase the stability of the compound during the subsequent lactam reduction step (Scheme 3-25).

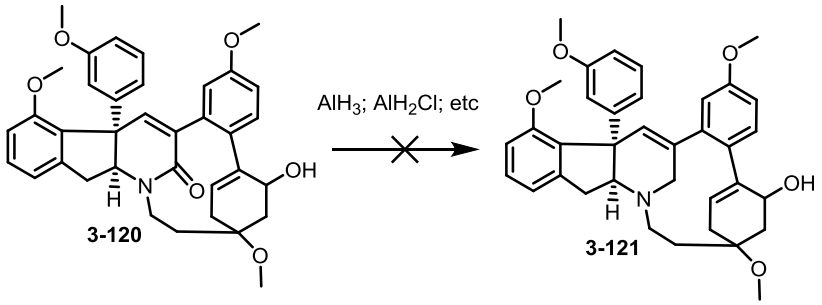


Scheme 3-26 Attempted reduction of lactam **3-114**

Haouamine A **3-1** was anticipated to be accessed from lactam **3-114** via remaining steps including its reduction to tetrahydropyridine and subsequent global demethylation to generate the free phenol. However, the reduction step was confronted with unexpected difficulties which were not present with similar substrates in Chenbo's route. Reduction conditions using AlH_3 or AlH_2Cl in THF at -78 ℃, which smoothly converted lactam **3-105** to amine **3-106**/**3-107**, turned out to be ineffective after considerable experimentation. Though the [M+18] peak indicating the probable presence of amino alcohol **3-119** was often detected by mass spectrometry from the reaction mixture after AlH_3 or AlH_2Cl reduction, its corresponding spot was extremely nonpolar by TLC and the material could not be isolated. If the amino alcohol **3-119** was indeed generated under AlH_3/AlH_2Cl reduction conditions as suggested by mass spectrometry data, it would be merely a trace amount because no available NMR data confirmed it. Extensive optimization was conducted to the reaction time and stoichiometry and no positive result was obtained. It was discovered that the reaction was extremely rapid as the complete disappearance of lactam **3-114** on the TLC plate to generate a nonpolar spot with a mass corresponding to amino alcohol **3-119** happened almost immediately after AlH_3/AlH_2Cl was added into the reaction mixture. Other reduction conditions with aluminum, boron, and silicon-based reagents also generated decomposed material or afforded unreacted starting material. Attempts to convert lactam **3-114** to the corresponding thiolactam were made. However, thionating reagents were not reactive on lactam **3-114** (Scheme 3-26).

The less reactive nature of lactam **3-114** in comparison with its counterpart **3-105** was somewhat expected. The pre-established α, β-unsaturated lactam moiety in **3-114** created a more rigid and hindered environment. This not only prevented most reductive reagents from accessing the carbonyl functionality but was also triggered complete decomposition when the material was treated with AlH_3/AlH_2Cl.

As the lactam moiety in **3-114** was deeply buried and difficult to reduce in the very last step in the proposed route, efforts to reduce it at an earlier stage were attempted under the presumption that early intermediates in this route were not as rigid and sterically hindered as lactam **3-114**. Since the amide carbonyl functionality in intermediates throughout this route is needed, possible intermediates for amide reduction could only be found in the steps following the aldol condensation. Reduction attempts were conducted on allylic alcohol **3-120** using AlH_3/AlH_2Cl and other reducing agents but resulted in a mostly decomposed material (Scheme 3-27).

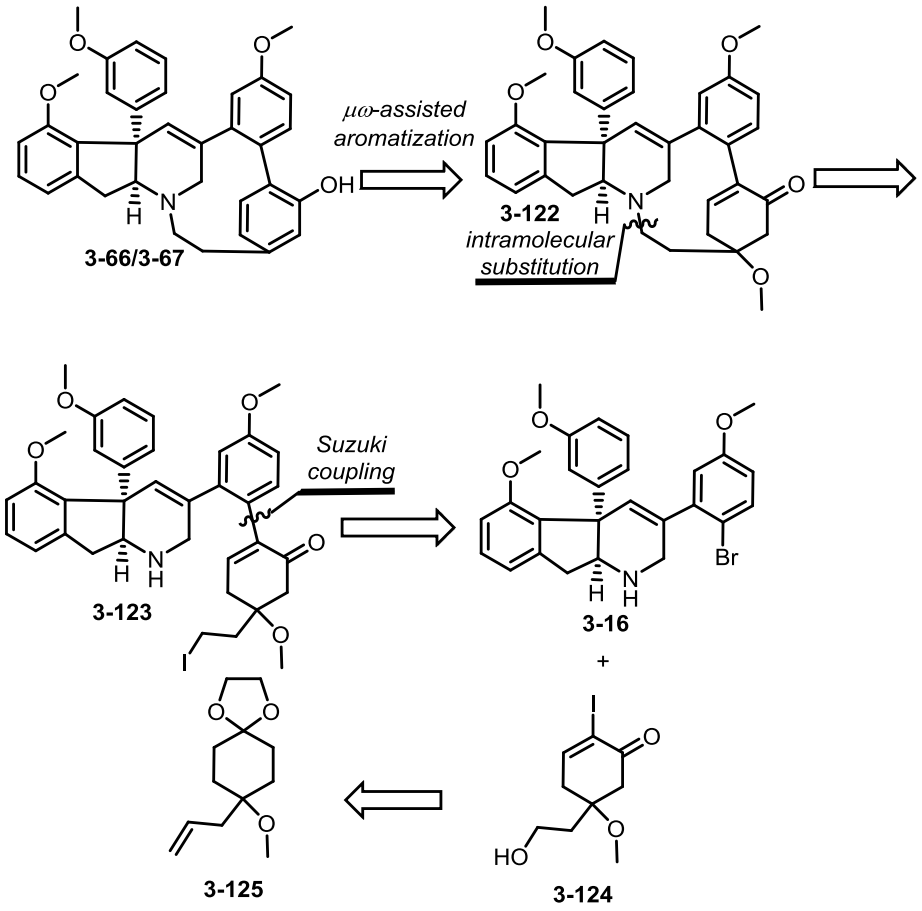


Scheme 3-27 Attempted reduction of lactam **3-117**

At this point, the failure to accomplish the last step in the two routes explored (dehydration in Chenbo's route and reduction in the current route) led to the conclusion that manipulation at central tetrahydropiperidine moiety at the last stage of the total synthesis seemed quite undesirable as the whole molecule is more rigid and sterically hindered. Therefore, an alternative route exploiting Baran's strategy to construct the macrocycle was explored.

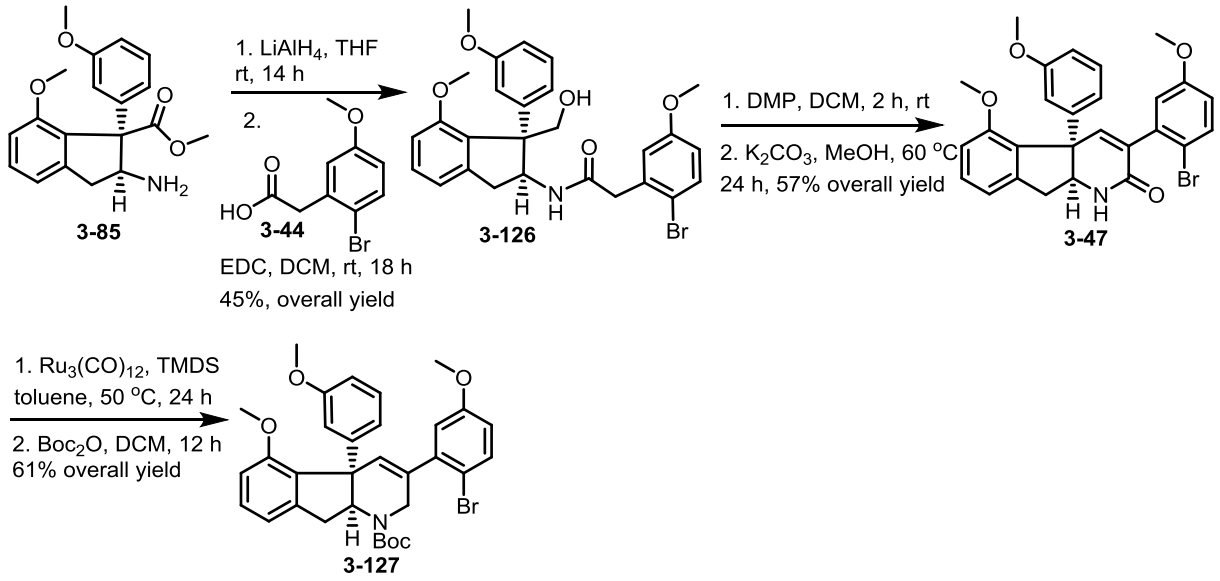
3.2.2 2nd Generation Approach: Intramolecular Substitution

3.2.2.1 Cross-coupling Involving Iodo-enone 3-124



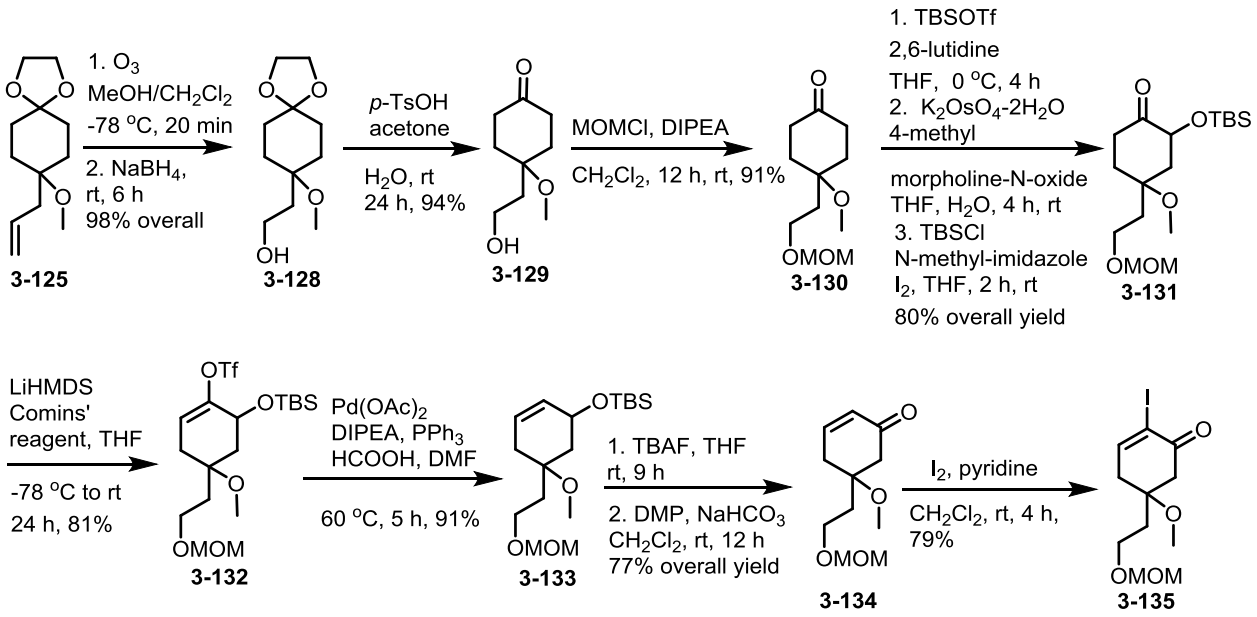
Scheme 3-28 Retrosynthetic analysis exploiting Baran's strategy

Enone **3-122** was envisioned to be the precursor of aromatized late stage intermediate **3-66**/**3-67** in Baran's synthesis[107,113] and could be further derived from amino iodide **3-123** through an intramolecular substitution to construct the macrocycle. Amino iodide **3-123** could be accessed by assembling the two building blocks enone iodide **3-124** which could be synthesized from the known ketal **3-125**[111] and Baran's key intermediate **3-16** via Suzuki coupling[107,108,113] (Scheme 3-28).



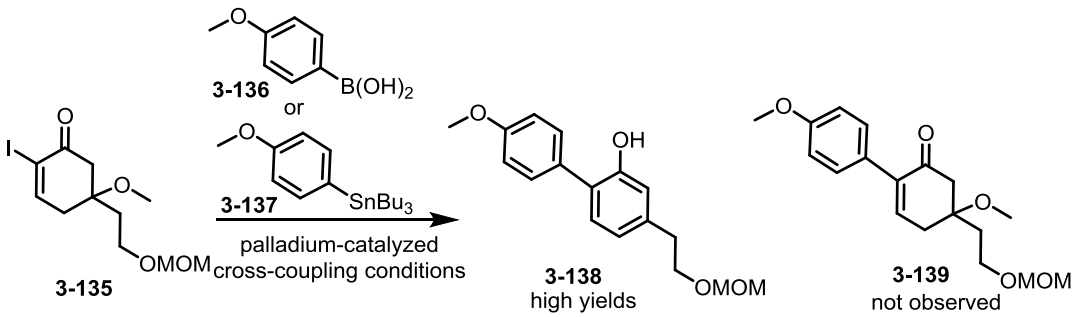
Scheme 3-29 Synthesis of intermediate **3-127**

According to Chenbo's work, amino methyl ester **3-85** was reduced by LAH to generate an alcohol intermediate (not shown), which was coupled with acid **3-44** in presence of EDC in CH_2Cl_2 to smoothly afford amide **3-126**. This approach bypassed the protecting group manipulations in Weinreb's formal total synthesis.[114] Similarly, the resulting alcohol **3-126** was oxidized with DMP to provide aldehyde **3-46**, which was converted to lactam **3-47** via an intramolecular aldol condensation.[114] Reduction of lactam **3-47** with TMDS in presence of $Ru_3(CO)_{12}$ in toluene[138] was found to be superior to previously reported conditions. The resulting amine was then protected to afford **3-127** (Scheme 3-29).



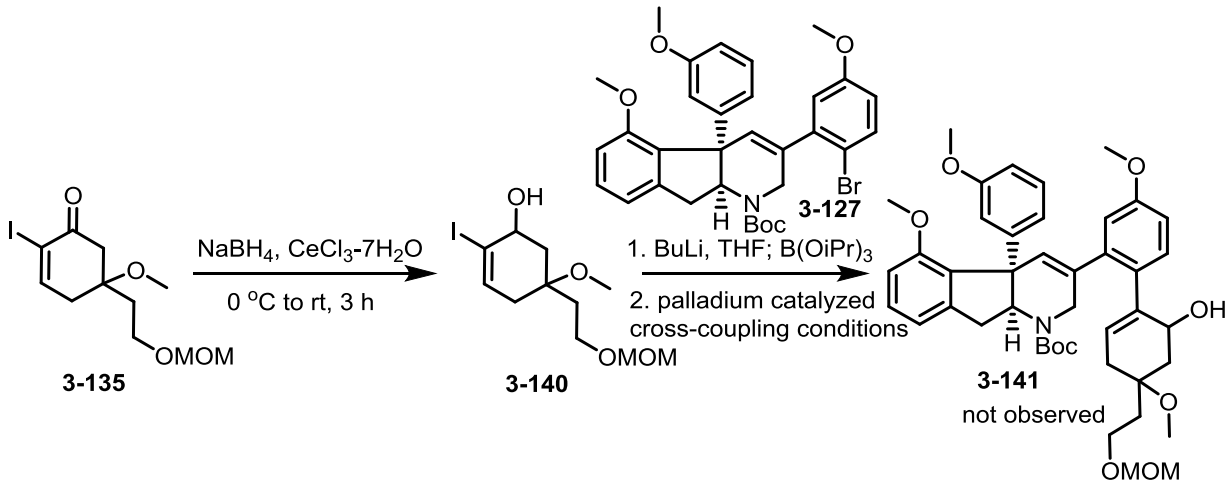
Scheme 3-30 Synthesis of iodo-enone **3-135**

The synthesis of iodo-enone **3-135** commenced with ozonolysis of alkene **3-125** followed by reductive quenching with $NaBH_4$ to furnish a primary alcohol **3-128**. Ketal hydrolysis afforded ketone **3-129** and its hydroxyl group was protected with MOM group. Treatment of ketone **3-130** with TBSOTf and 2.6-lutidine gave a silyl enol ether[139] (not shown), and under osmium-promoted dihydroxylation conditions[140], was converted to a α-hydroxyl ketone which was silylated to generate silyloxy ketone **3-131**. An enol triflate was obtained from silyloxy ketone **3-132** by treating it with LiHMDS and Comins' reagent[141,142], and catalytic hydrogenolysis using formic acid as a hydride source[143] removed the triflate group to furnish **3-133**. Desilylation with TBAF followed by an oxidation with Dess-Martin periodinane[144] provided enone **3-134**, which upon treatment of I_2 and pyridine was iodinated[145] to give iodo-enone **3-135** (Scheme 3-30).



Scheme 3-31 Cross-coupling reactions between iodo-enone **3-135** and model systems

Suzuki or Stille coupling reactions between iodo-enone **3-135** and boronic acid **3-136** or tributyltin **3-137** were attempted to model the coupling needed to form **3-141**. However, the desired cross-coupling product **3-139** was never observed. Instead, the only isolable product was phenol **3-138**. After extensive experimentation, it was realized that it was difficult to avoid such aromatization during the reaction, and therefore iodo-enone **3-135** was not suitable to be engaged in cross-coupling reactions (Scheme 3-31).



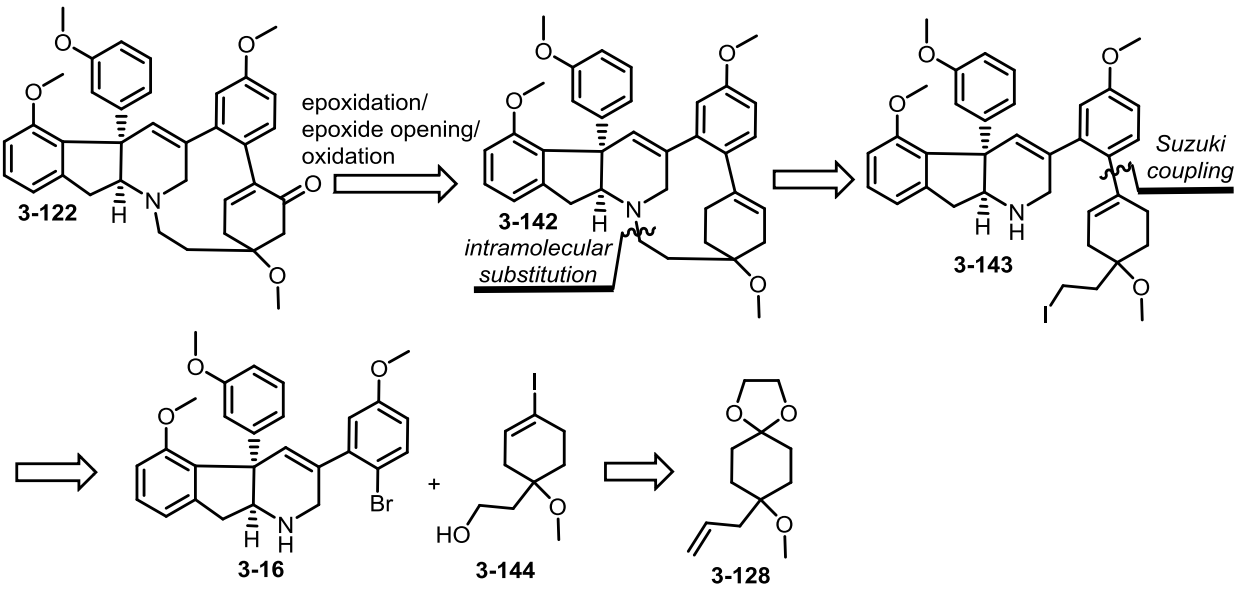
Scheme 3-32 Cross-coupling reaction between iodo-allylic alcohol **3-135** and boronic acid generated from **3-127**

In order to prevent this aromatization during the cross-coupling, iodo-enone **3-135** was reduced to iodo-allylic alcohol **3-140**. However, the reduction was challenging. The iodine was prone to reduction, and the allylic alcohol **3-140** was relatively unstable upon storage. It was discovered that $NaBH_4$ with

$CeCl_3$-$7H_2O$ cleanly reduced iodo-enone **3-135** to allylic alcohol **3-140**, which after purification was immediately treated with the boronic acid generated from **3-127**. No desired cross-coupling product was observed, which could be attributed to the instability of **3-140** or inefficient palladium insertion to allylic alcohol **3-135** (Scheme 3-32).

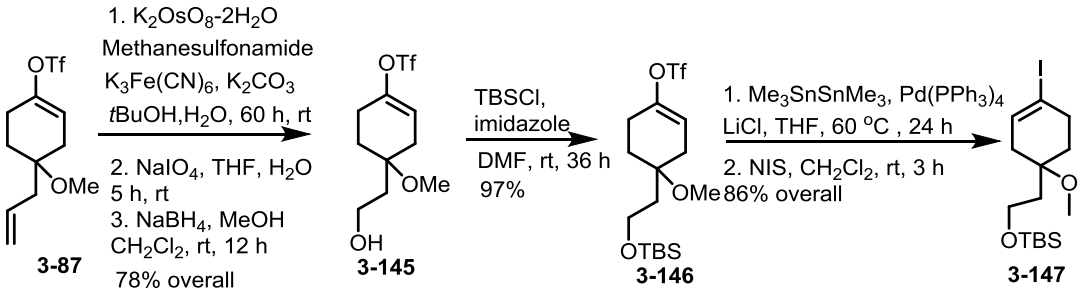
Failures in key cross-coupling reactions that were envisioned to connect the two building blocks **3-127** and **3-140** in the strategy similar to Baran's total synthesis suggested the presence of the hydroxyl group in **3-140** might be undesirable for this process. Therefore, the synthetic plan was further modified as the carbonyl/hydroxyl group in **3-140** was anticipated to be introduced after the cross-coupling reaction.

3.2.2.2 Late-Stage Formation of Enone Functionality



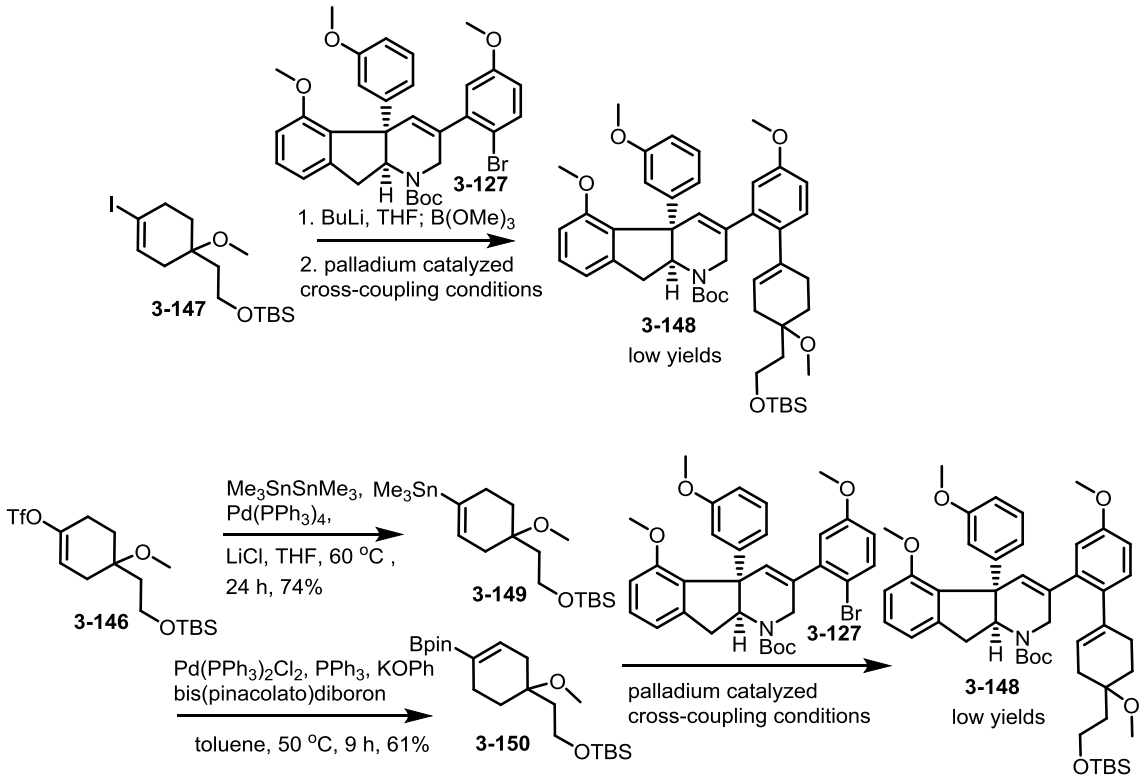
Scheme 3-33 Retrosynthetic analysis with late-stage formation of enone functionality

Macrocycle **3-142** was envisioned to be the precursor of enone **3-122** through an epoxidation, epoxide opening, an oxidation reaction sequence. This could be further derived from amino iodide **3-143** via an intramolecular substitution. Similarly, amino iodide **3-143** was anticipated to be constructed by a cross-coupling reaction between building blocks **3-16** and **3-144** (Scheme 3-33).



Scheme 3-34 Synthesis of alkenyl iodide **3-147**

The synthesis of cross-coupling building block **3-147** commenced with a dihydroxylation and oxidative cleavage, and reduction sequence to smoothly furnish primary alcohol **3-145**. Enol triflate **3-146** was obtained after TBS protection of hydroxyl group and was further converted to alkenyl iodide **3-147** via a stannyl intermediate (Scheme 3-34).

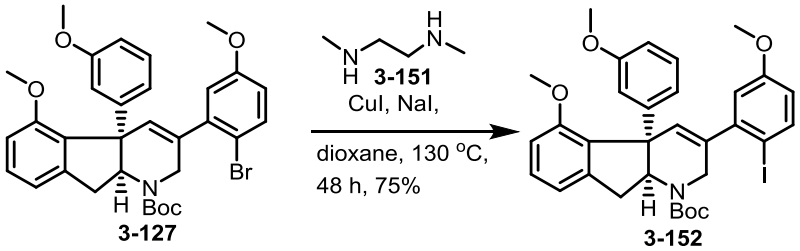


Scheme 3-35 Cross-coupling reactions between **3-149/3-150** and aryl bromide **3-127**

Suzuki cross-coupling reactions were carried out with alkenyl iodide **3-147** and an in situ generated boronic acid from aryl bromide **3-127**. Though the desired coupling product was indeed

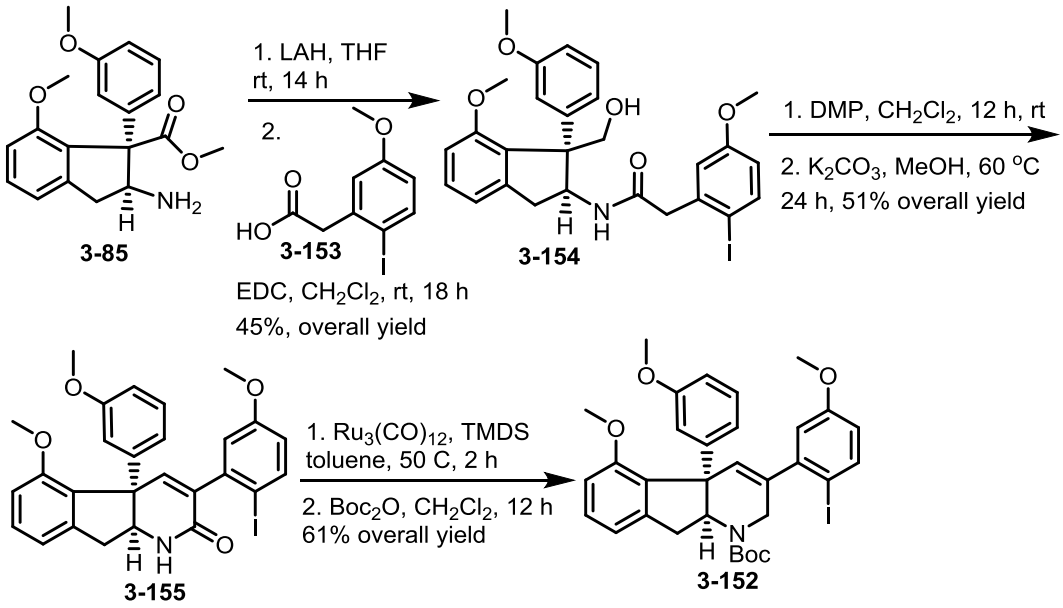
isolated in several attempts, the yield was inconsistent and low, with debromination product from **3-127** as the major side product as well as unreacted alkenyl iodide. Alkenyl iodide **3-147** was presumed to be more electron rich than to iodo-enone **3-32**[107] in Baran's total synthesis and therefore was not considered to be a good cross-coupling component in this reaction (Scheme 3-35).

Stille and Suzuki cross-coupling reactions were also explored using aryl bromide **3-127** and trimethyltin **3-149**/pinacolborate **3-150** generated from enol triflate **3-146**. Though the yield was still low, debromination product from **3-127** was the major species obtained. The formation of debromination product from **3-127** can be rationalized due to the electron-rich *para*-methoxy group and the relative bulky *ortho*-substitution, which might damper its reactivity in cross-coupling reactions.



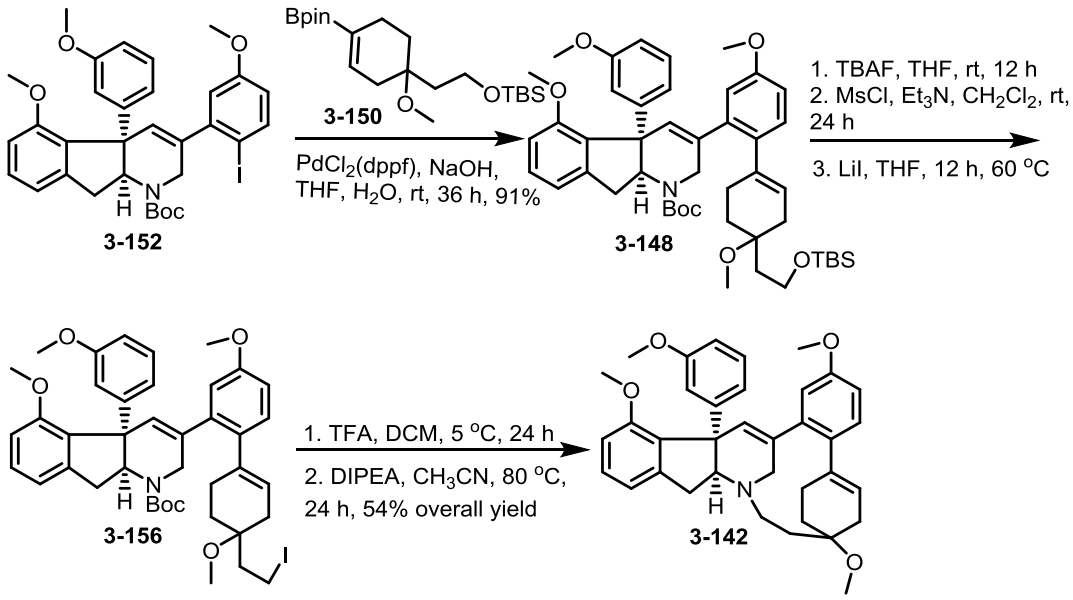
Scheme 3-36 Synthesis of aryl iodide **3-152** via an aromatic Finkelstein reaction from aryl bromide **3-127**

In this regard, aryl iodide **3-152** was envisioned to be more reactive in comparison to aryl bromide **3-123** in cross-coupling reactions. Aryl bromide **3-127** was smoothly converted to iodide **3-152** in good yield when exposed to CuI and NaI in presence of 1,2-dimethyldiamine **3-151** (Scheme 3-36).[146]



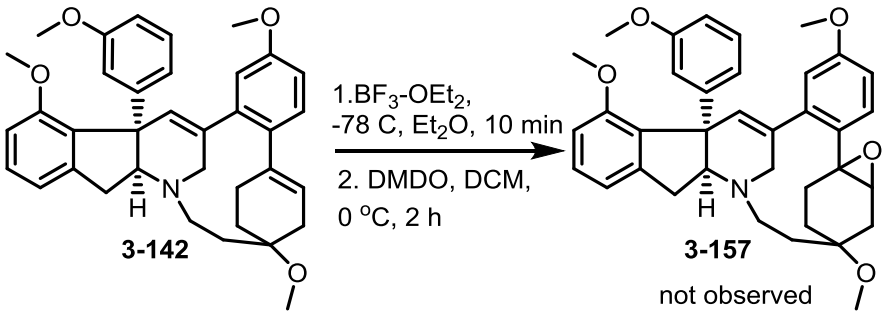
Scheme 3-37 Synthesis of aryl iodide **3-152** from amino ester **3-85**

Aryl iodide **3-152** was synthesized in a similar way to aryl bromide **3-127**. Aminomethyl ester **3-85** was reduced by LAH to generate an alcohol intermediate (not shown), and amide coupling with acid **3-153** in presence of EDC in CH_2Cl_2 to smoothly afford amide **3-154**, which bypassed the protecting group manipulations in Weinreb's formal total synthesis.[114] Similarly, the resulting alcohol **3-154** was oxidized with DMP to provide an aldehyde (not shown), which was converted to lactam **3-155** via an intramolecular aldol condensation.[114] Reduction of lactam **3-155** with TMDS in presence of $Ru_3(CO)_{12}$ in toluene[138] generated the desired tetrahydropyridine (not shown), which was protected to give aryl iodide **3-152** (Scheme 3-37).



Scheme 3-38 Synthesis of macrocycle **3-142**

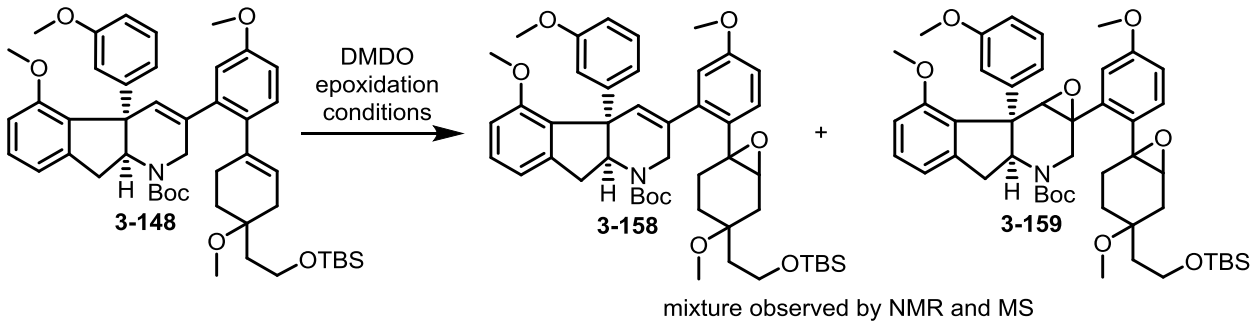
The key Suzuki coupling between aryl iodide **3-152** and pinacolborate **3-150** proceeded smoothly when treated with $PdCl_2$(dppf) in a mixture of THF and 10% aqueous NaOH[147]. Silyl ether **3-148** was converted to iodide **3-156** through desilylation with TBAF, mesylate activation, and iodide substitution.[109] The free amine was generated using TFA, and a cyclization to construct the macrocycle was effected via an intramolecular substitution by heating a dilute solution of the amine in CH_3CN with Hünig's base.[107] Macrocycle **3-142** was isolated in moderate yield over two steps as a mixture of diastereomers (Scheme 3-38).



Scheme 3-39 Attempted epoxidation of **3-142**

Epoxidation of alkenes bearing tertiary amines [148] has been carried out by treating alkenes with boron trifluoride at -78 ℃ to generate a boron trifluoride adduct, followed by epoxidation with DMDO

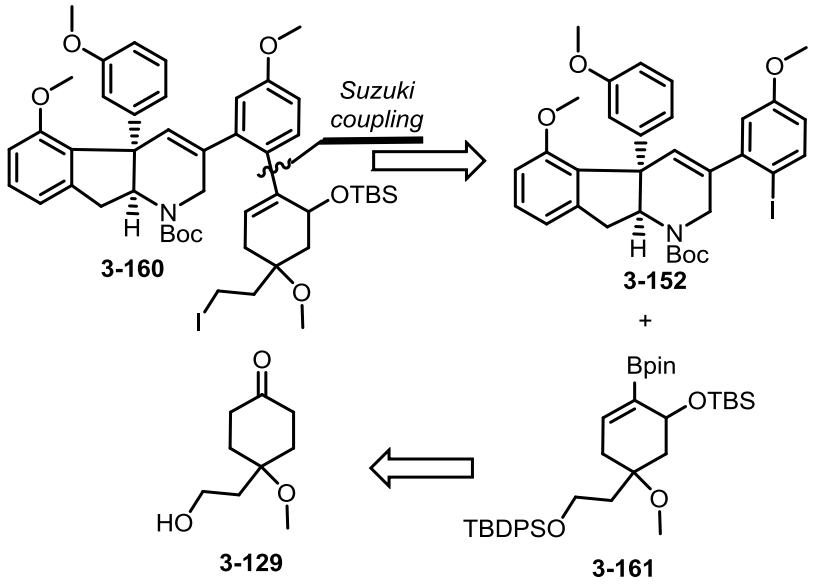
under mild neutral conditions. This particular condition was attempted with alkene **3-142**. Though the adduct formation step of alkene **3-142** with boron trifluoride went smoothly as indicated by TLC, desired epoxidation product **3-157** was never observed upon treatment of DMDO in the second step. Despite the fact that an [M+16] peak was observed by mass spectrometry indicating the probable trace amount of desired epoxide **3-157** formation, it was noticed the boron trifluoride adduct quickly underwent decomposition as soon as DMDO was introduced according to crude ^{1}H NMR characterization (Scheme 3-39).



Scheme 3-40 Attempted epoxidation of **3-148**

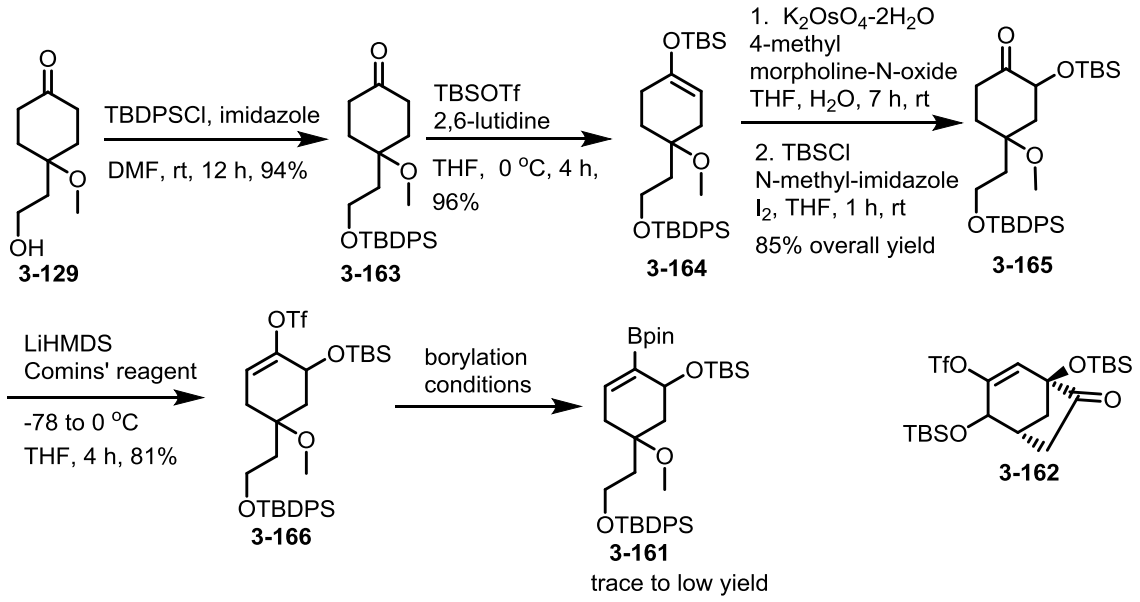
As epoxidation of the delicate and complicated alkene in **3-157** bearing the tertiary amine moiety was found to be unsuccessful, the possibility to conduct epoxidation at an earlier stage when the tertiary amine was still Boc-protected was explored. Therefore, the cross-coupling product was treated with DMDO, only to discover the formation of a mixture of mono- and di-epoxidized products **3-158** and **3-159**, even though the amount of DMDO used was strictly restricted to one equivalent. Considering the open structure of **3-148** compared to **3-142**, the alkene in the tetrahydropyridine moiety was much more accessible to epoxidation reagents (Scheme 3-40).

3.2.2.3 Pinacolborate 3-161 with Preinstalled α-Hydroxyl Group



Scheme 3-41 Retrosynthetic analysis involving pinacolborate **3-161** with preinstalled α-hydroxyl group

Since the epoxidation of cross-coupling product **3-148** or macrocycle **3-142** appeared difficult, it was envisioned that the problematic epoxidation could be avoided by conducting cross-coupling reactions between aryl iodide **3-152** and α-siloxy pinacolborate **3-161.** A preinstalled α-hydroxyl group would provide opportunities for further functionalization to generate the requisite enone required for aromatization (Scheme 3-41).



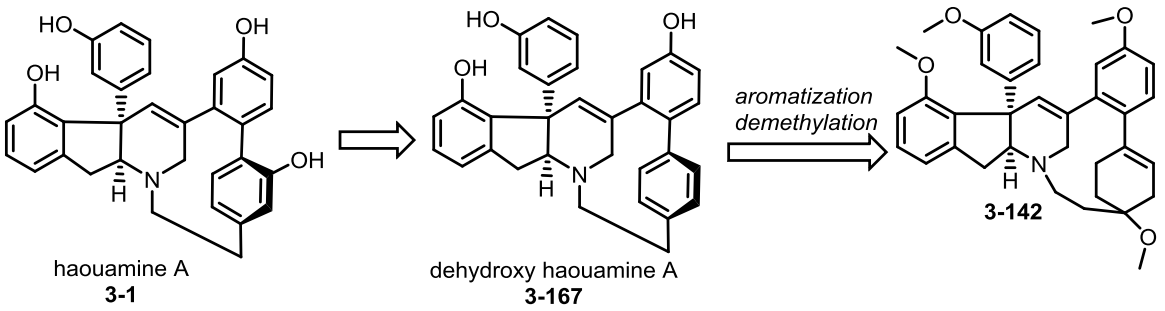
Scheme 3-42 Attempted synthesis of pinacolborate **3-161**

The attempted synthesis of pinacolborate **3-161** commenced with silylation of primary alcohol **3-129** with TBDPS group, leading to ketone **3-163**. Formation of α-silyloxy ketone **3-165** was accomplished from ketone **3-163** after silyl enol ether formation to afford **3-164**, followed by osmium-promoted dihydroxylation to furnish α-hydroxyl ketone functionality, which was protected with a TBS group. α-silyloxy ketone **3-165** was converted efficiently to enol triflate **3-166** by treatment of LiHMDS and Comins' reagent[141,142] in good yield (Scheme 3-42).

However, the borylation step seemed problematic. Literature precedence showed very few examples of palladium-catalyzed borylations of such silyloxy triflates. One closely related silyloxy triflate **3-162**[149] used a condition employing $(PPh_3)_2PdCl_2$, PPh_3 and K_2CO_3 in dioxane at 80 ℃. This condition was applied to **3-166**, and nevertheless only generated the desired pinacolborate **1-161** in trace amounts or extremely low yield with aromatized or base-line material as the side product. Considerable efforts were made to optimize the reaction conditions and no positive results were obtained. Other typical palladium-catalyzed borylation[150] conditions were also attempted with generated similar results (Scheme 3-42).

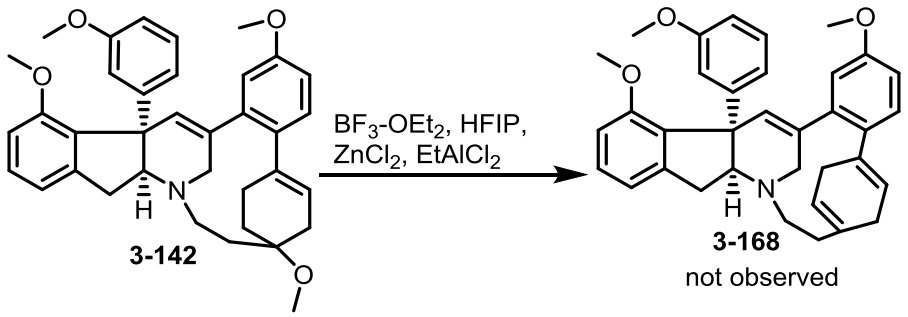
3.2.3 Dehydroxyl Cyclophane

The total synthesis of haouamine A appeared thwarted at this point. If the phenol moiety in aza-paracyclophane had to be constructed via a base-promoted aromatization of 5-methoxy-cyclohex-2-en-1-one (**3-65** in Scheme 3-11), manipulations to generate the central tetrahydropiperidine moiety (dehydration in Chenbo's route or reduction in the aldol condensation route) and phenol B ring in aza-cyclophane (epoxidation or cross-coupling) inevitably interfered.



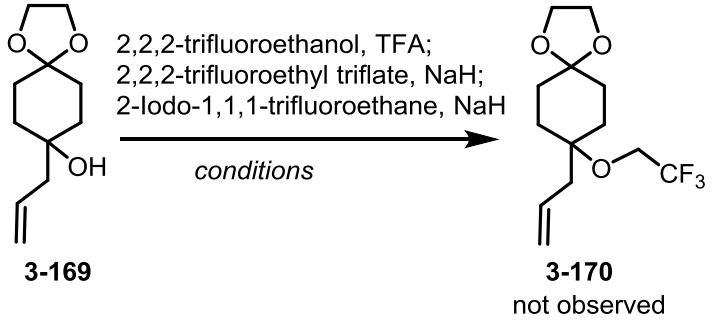
Scheme 3-43 Retrosynthetic analysis of dehydroxy haouamine A

In this regard, the structure of haouamine A was simplified to **3-167** where the B ring phenol in the aza-cyclophane was simplified to a phenyl ring. Readily available macrocycle **3-142** was envisioned to be the precursor of **3-167** through a Lewis acid-catalyzed aromatization and demethylation (Scheme 3-43).



Scheme 3-44 Attempted elimination of MeOH from **3-142** to generate cyclohexadiene **3-168**

Aromatization of methoxy cyclohexene moiety in **3-142** was envisioned to proceed via an auto–oxidation of cyclohexadiene **3-168**, which could be synthesized from **3-142** by a Lewis acid catalyzed-elimination of MeOH. A variety of Lewis acids were screened, including BF_3-OEt_2, hexafluoroisopropanol, $ZnCl_2$, and $EtAlCl_2$, with no desired cyclohexadiene **3-168** formation. In almost all cases, no reaction occurred at room temperature. When the temperature was slightly increased to facilitate any possible elimination, only complete decomposition occurred. The presence of the strained macrocycle in **3-142** likely made it difficult for the methoxy cyclohexene moiety to adopt a conformation to promote elimination (Scheme 3-44).

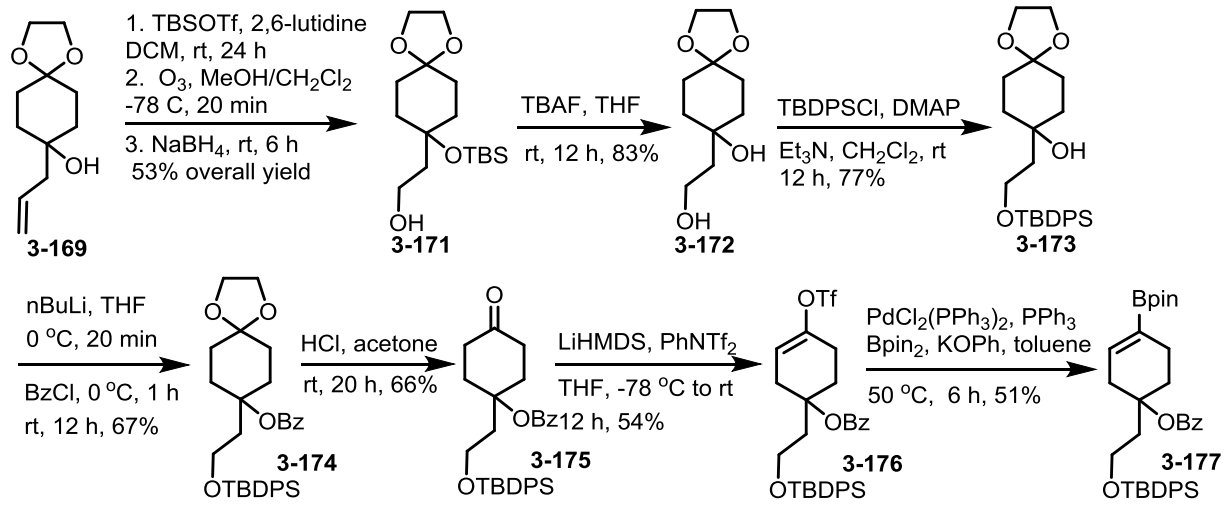


Scheme 3-45 Attempted synthesis of trifluoroethyl ether **3-170**

One of the ways to promote elimination is to use better leaving groups than the methyl ether in **3-142**. A trifluoroethyl group was considered because of it larger electronegativity, rendering it a better leaving group. Therefore attempts were made to form the trifluoroethyl ether of tertiary alcohol **3-169** under acidic conditions (2,2,2-trifluoroethanol in TFA) or basic conditions (2,2,2-trifluoroethyl triflate/2-iodo-1,1,1-trifluoroethane in presence of NaOH). However, no desired ether product was observed, with only clean starting alcohol **3-169** isolated in every case. Lack of reactivity of tertiary alcohol **3-169** in the ether formation probably resulted from dioxolane moiety which further increased the steric hindrance of hydroxyl group (Scheme 3-45).

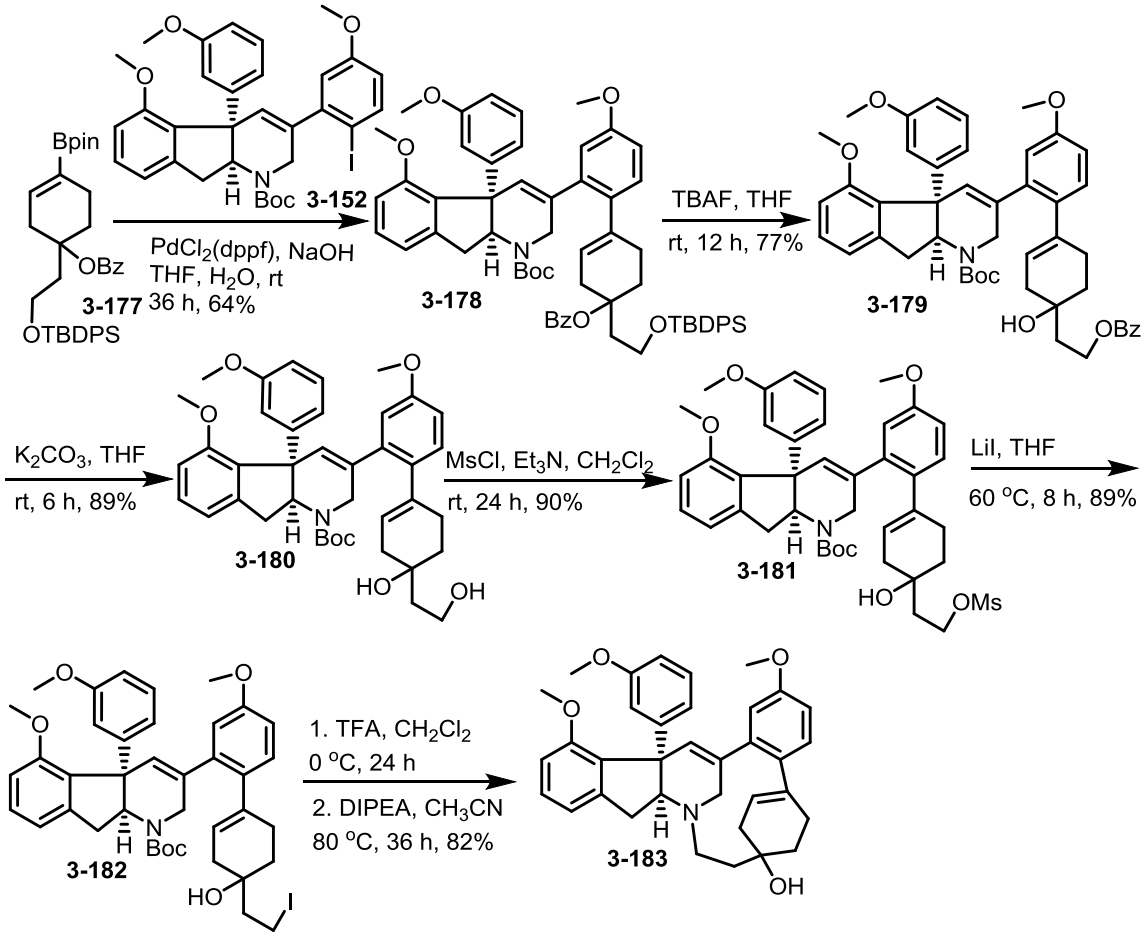
A benzoate was also considered to be a good leaving group to generate cyclohexadiene **3-168**. However, it should be noted that a tertiary benzoate ester with a primary alcohol present may undergo a 1,3-acyl transfer process after ozonolysis and reductive quenching with $NaBH_4$ (similar process as **3-128**

to **3-129**). Therefore, the reaction sequence[109] leading to pinacol borate **3-177** was slightly modified to ensure there was no primary alcohol present when benzoate ester was formed.



Scheme 3-46 Synthesis of pinacol borate **3-177**

The synthesis of pinacol borate **3-177** commenced with the silylation of tertiary alcohol **3-169**, followed by ozonolysis and reductive quenching using $NaBH_4$ to efficiently furnish alcohol **3-171**. Removal of the TBS group on the tertiary alcohol and subsequent selective silylation on primary alcohol with the less acid labile TBDPS group furnished tertiary alcohol **3-173** in good yield. Benzoate ester **3-174** was obtained by treating the lithiated tertiary alcohol **3-173** with benzoyl chloride, which was converted to ketone **3-175** after ketal hydrolysis. Treatment of ketone **3-175** with $PhNTf_2$ in presence of LiHMDS provided enol triflate **3-176**, which was transformed into pinacol boronate **3-177** using palladium catalyzed borylation[150] conditions (Scheme 3-46).

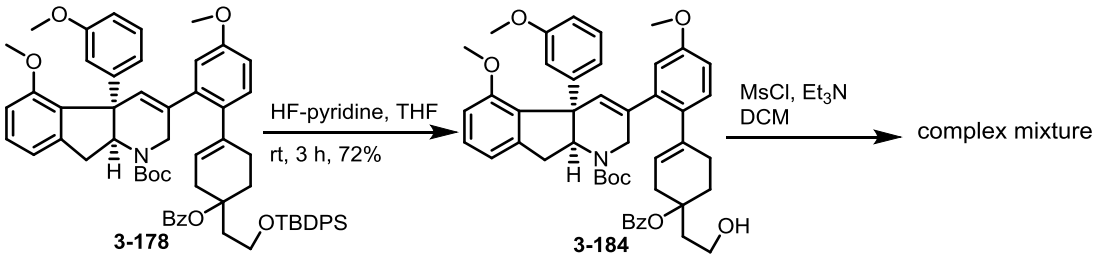


Scheme 3-47 Synthesis of macrocycle **3-183**

Pinacol boronate **3-177** was coupled with aryl iodide **3-152** under the previously established Suzuki conditions to cleanly afford the desired coupling product **3-178**. Silyl group removal, however, furnished the 1, 3-acyl transfer product **3-179**. Despite the fact that the primary benzoate ester **3-179** was undesired, it was still utilized in order to explore whether a tertiary hydroxyl group might facilitate aromatization of the haouamine biphenyl core as the last step of the synthesis. Thus, benzoate ester **3-179** was saponified with K_2CO_3 to provide diol **3-180** and the primary alcohol was selectively mesylated to afford **3-181**. Formation of iodide **3-182** was effected by treating mesylate **3-183** with LiI in THF at 60 ℃. The free amine was generated using TFA, and a cyclization to construct the macrocycle was effected via an intramolecular substitution by heating a dilute solution of the amine in CH_3CN with Hünig's base.

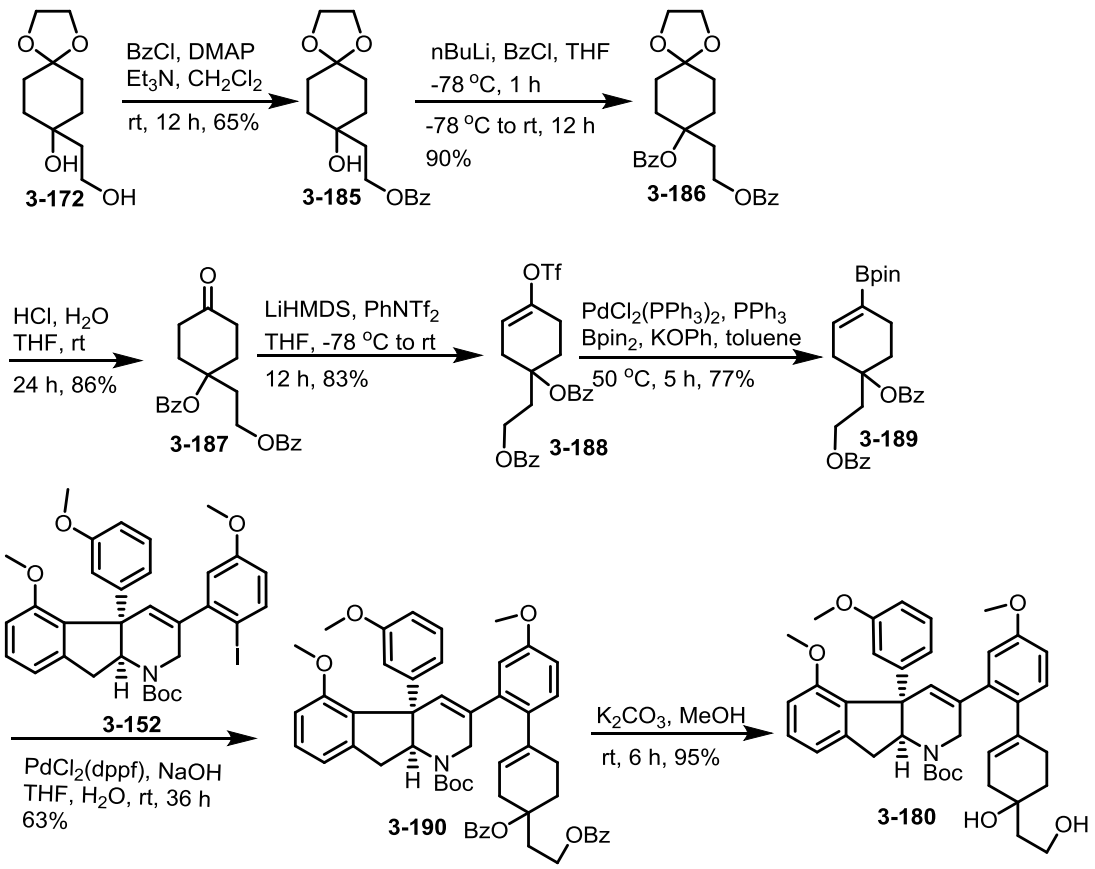
Macrocycle **3-183** was isolated in good yield over two steps as a complex mixture of diastereomers (Scheme 3-47).

Desilylation of **3-178** was also attempted using HF-pyridine in THF in order to avoid 1, 3-acyl transfer of the benzoyl group under basic TBAF conditions (Scheme 3-48). Primary alcohol **3-184** was obtained in good yield. However, activation of alcohol **3-184** with a mesylate group resulted in a complex mixture derived from a 1, 3-acyl transfer of the benzoyl group. This was difficult to avoid since basic triethylamine was inevitably used in mesylation step (Scheme 3-48).



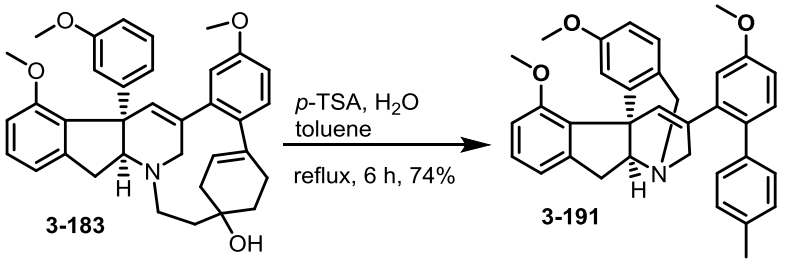
Scheme 3-48 Selective desilylation of **3-178**

Therefore, the reaction sequence leading to diol **3-180** was further optimized to avoid 1, 3-acyl transfer of benzoyl group on intermediates such as **3-184**. In this regard, the primary and the tertiary hydroxyl group in **3-172** were sequentially benzoylated, and acidic hydrolysis of resulting ketal **3-186** gave ketone **3-187**. Treatment of ketone **3-187** with $PhNTf_2$ in presence of LiHMDS provided enol triflate **3-188** and was transformed into pinacol borate **3-189** under palladium catalyzed borylation conditions. Coupling product **3-190** was saponified with K_2CO_3 in MeOH to afford diol **3-180** (Scheme 3-49).



Scheme 3-49 Optimized synthesis of diol **3-180**

The remaining steps toward the preparation of dehydroxy haouamine A **3-167** involved the aromatization of the cyclohexene moiety in **3-183** and global demethylation. When hydroxy cyclohexene **3-183** was heated at reflux with *p*-TSA in toluene (a typical condition for dehydration/aromatization of compounds bearing hydroxy cyclohexene moiety[151]), the unexpected aromatized product **3-191** was generated in good yield. This new product **3-191** was found to have formed a new bond linking the amine nitrogen to the *para*-position of the angular anisole ring (Scheme 3-50). The structural assignment of **3-191** was confirmed by X-ray crystallographic analysis (Figure 11).



Scheme 3-50 Unexpected formation of **3-191**

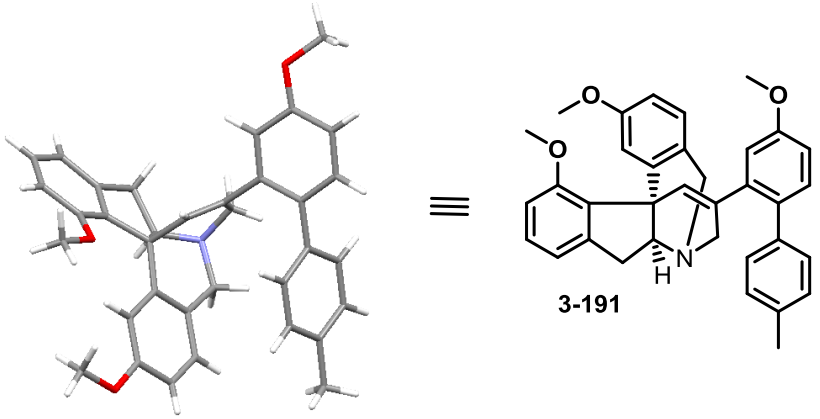
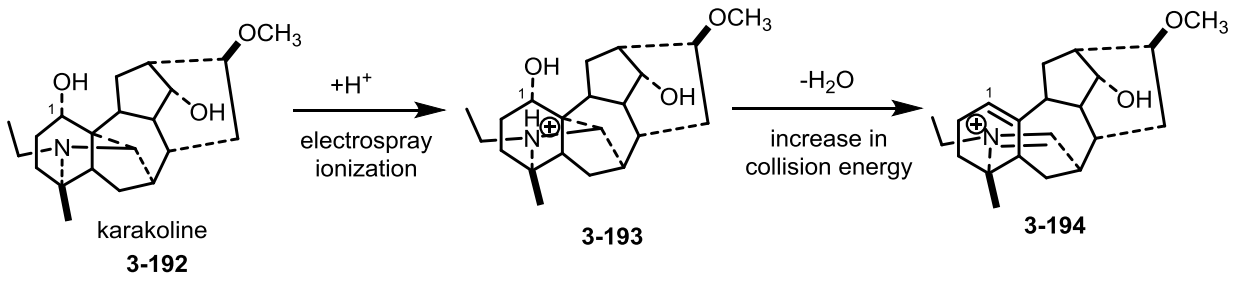


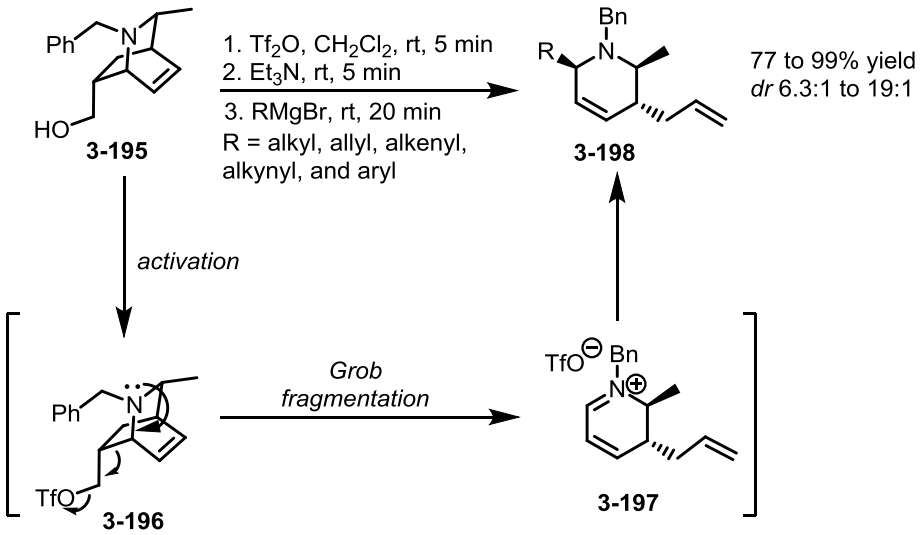
Figure 11 X-ray crystallographic analysis of **3-191**

The formation of the interesting product **3-191** from γ-amino alcohol **3-183** is related to other Grob-fragmentations. Chao[152] *et al.* conducted a mass spectrometry study to elucidate the fragmentation rules of a variety of diterpenoid alkaloids using an electrospray ionization technique. In this study, the firstly-generated protonated molecular ions of alkaloids were further fragmented by collision-induced dissociation and their tandem mass spectrometry MS/MS data provided useful information on fragmentation pathways. For example, the pseudomolecular ion peaks $[M+H]^+$ **3-193** of γ-amino alcohol karakoline **3-192** could be observed under low collision energy. When the collision energy was increased, the $[M+H-H_2O]^+$ ions **3-194** were produced and detected with high intensity. This ion should correspond to the elimination of the hydroxyl group at the C1 position. It was postulated that the elimination was accompanied by a Grob fragmentation, leading to the formation of an iminium and an alkene moiety in the resulting product **3-194** (Scheme 3-51).



Scheme 3-51 Fragmentation pathway of karakoline **3-192**

Charette[153] *et al.* developed a novel methodology to prepare 2,3,6-trisubstituted tetrahydropyridines **3-198** from the aza-bicyclo[2.2.2]octene **3-195** bearing a γ-amino hydroxide moiety. In this methodology, the hydroxyl functionality of the aza-bicyclo[2.2.2]octene **3-195** was activated by conversion to triflate **3-196**. A dihydropyridinium salt **3-197** was immediately generated after addition of triethylamine, which promoted a rapid Grob fragmentation. An array of substituted tetrahydropyridines **3-198** was furnished in high yields and with high diastereoselectivities shortly after the dihydropyridinium salt **3-197** was trapped with a wide variety of Grignard reagents (Scheme 3-52).

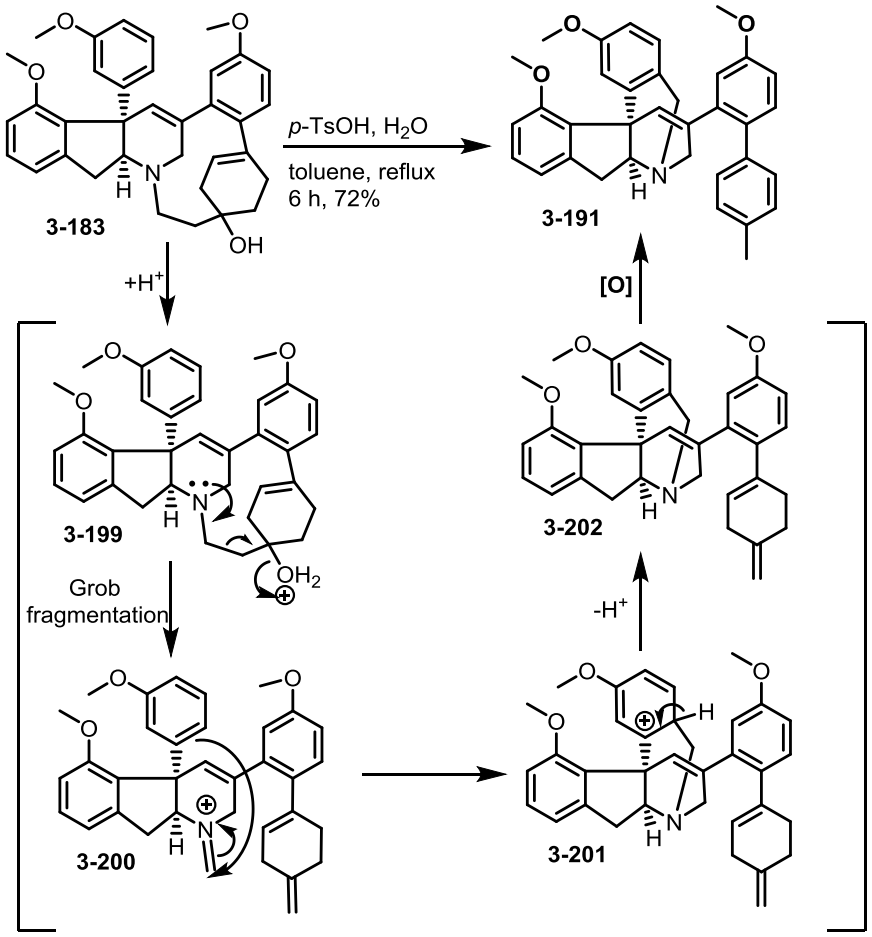


Scheme 3-52 Synthesis of **3-198** via Tf_2O mediated Grob fragmentation

The work from the Chao group and the Charette group supports a similar reaction mechanism to form **3-191** from **3-183**. The benzylic methylene group present in **3-191** suggested a γ-amino hydroxide Grob fragmentation in **3-183** promoted by protonation of the tertiary hydroxy group and subsequent

elimination of H_2O. This led to the breaking of the aliphatic chain in **3-183**, and the formation of an iminium moiety in the intermediate **3-200** (Scheme 3-53).

The anisole substituent trapped the iminium functionality in **3-200** in a Friedel-Crafts manner to construct the new polycyclic system in **3-191** (Scheme 3-53). The methylene-cyclohexene moiety in **3-200** aromatized when exposed to air, and furnished phenyl group in **3-191**.

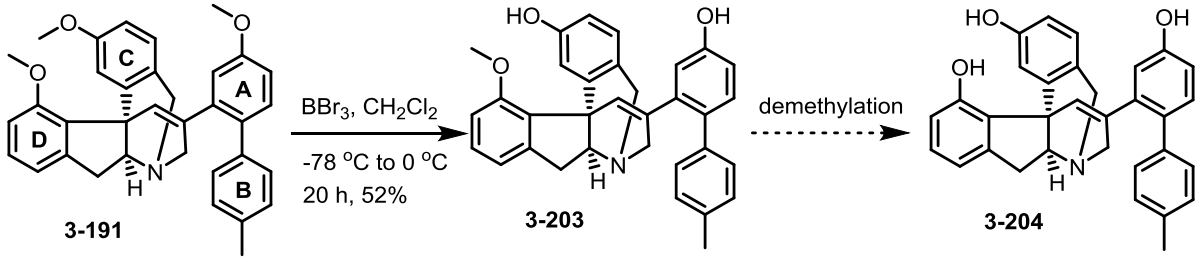


Scheme 3-53 Possible mechanism for the formation of **3-191**

Although **3-191** was not the desired aromatization product that led to dehydroxy haouamine A **3-167**, it was still considered an interesting substrate for demethylation. Thus, **3-191** was treated with excess BBr_3 in CH_2Cl_2 at 0 ℃ in an attempt to remove three methyl groups. Surprisingly, after extended stirring, the clean formation of bis-demethylated product **3-203** was observed. The remaining methyl group was

presumed to be located at the D anisole moiety, because, according to X-ray crystallographic analysis of **3-191**, this methyl group was shielded by the C anisole moiety. Its slightly more downfield chemical shift (3.95 ppm compared to 3.77 ppm and 3.82 ppm for A, C anisole methyl moiety) in ^{1}H NMR supported a subtle deshielding effect from the neighboring C anisole moiety.

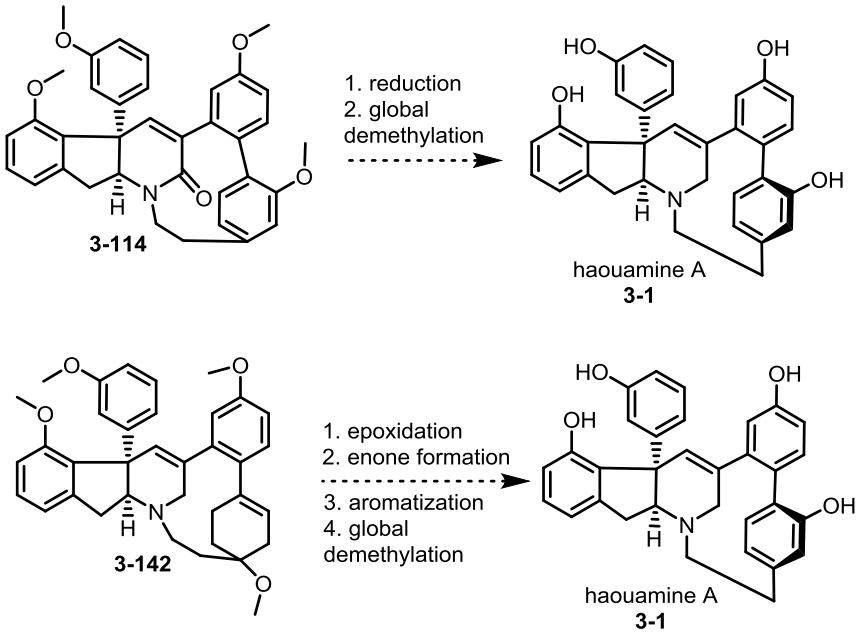
In contrast to haouamine A **3-1** and B **3-2**/**3-3**, **3-191** was a single diastereomer. Increasing the equivalents of BBr_3 used or the reaction temperature did not yield any improvement. At this time, conditions to promote the demethylation of **3-203** to give complete demethylation of **3-191** have not been identified. (Scheme 3-54).



Scheme 3-54 Incomplete removal of methyl groups to generate **3-203**

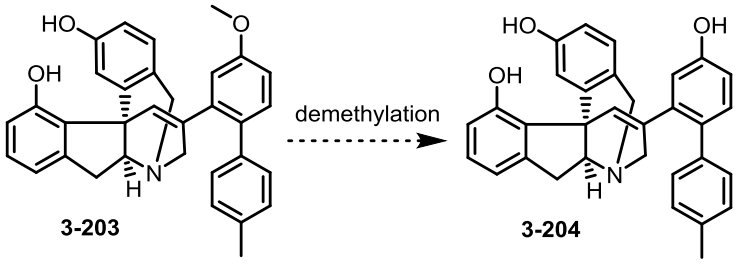
3.3 CONCLUSION

Two approaches towards the total synthesis of haouamine A have been explored. One approach exploited an intramolecular aldol condensation to construct a late stage lactam **3-114**, which was within two synthetic steps of haouamine A (reduction and global methyl deprotection). The other approach employed an intramolecular substitution to build the macrocycle in **3-142** with remaining oxidation/epoxidation steps to generate an enone moiety that could lead to aromatization (Scheme 3-55).



Scheme 3-55 Summary of the remaining synthetic transformations towards haouamine A **3-1**

The synthesis of dehydroxy haouamine A **3-167** was attempted via macrocycle intermediate **3-183**, which rearranged to **3-191** when treated with p-toluenesulfonic acid. Removal of two of the methyl groups occurred with ease, and a procedure needs to be developed to facilitate the deprotection of the remaining methyl ether. If this problem can be solved, we could demonstrate access to the analog **3-204** (Scheme 3-56).

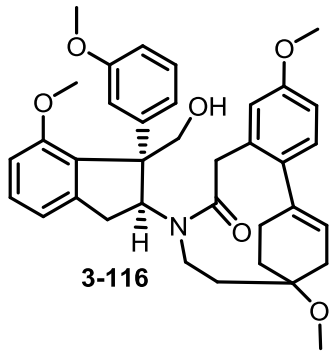


Scheme 3-56 Remaining steps towards **3-204**

3.4 EXPERIMENTAL PART

General: All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃ employed a CO_2/acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina column filtration system. All other reagents and solvents were used as received unless otherwise noted. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}•4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

NMR spectra were recorded using XWIN-NMR software. ^{1}H NMR spectra were obtained at 300, 400, 500, 600 or 700 MHz in $CDCl_3$. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak unless otherwise noted. Melting points were determined on a Mel-Temp II and are uncorrected. High-resolution mass spectrometry (HRMS) data (ESI/APCI technique) were recorded using a Waters Q-Tof Ultima API-US instrument. HRMS data (EI technique) were recorded using a Micromass Autospec instrument. Mass spectrometry data were also recorded using an Applied Biosystems MDS SCIEX API 2000 LC/MS/MS system.



3-116

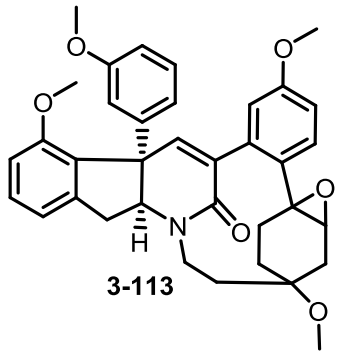
3-((1*R*,2*S*)-1-(Hydroxymethyl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1*H*-inden-2-yl)-6,12-dimethoxy-4,5,6,7-tetrahydro-1*H*-6,9-ethanobenzo[d][1]azacycloundecin-2(3*H*)-one (3-116). 15 dry flasks containing **3-91** (10.0 mg, 0.014 mmol) each were purged with N_2 for three times and was added Et_2O (0.2 mL) each, $LiBH_4$ (5.3 mg, 0.25 mmol, 61 uL 4 M solution in THF) each, and $B(OMe)_3$ (4.2 mg, 0.041 mmol, 4.6 μL) each. The reaction mixture was stirred at room temperature for 48 h. It was noticed that the Et_2O gradually evaporated during this period and it was finally residue stirred at bottom of the flask.

The reaction mixture was quenched with 10% $NaHSO_4$ solution (10 mL), extracted with EtOAc (3x10 mL), washed with brine (10 mL) and dried (Na_2SO_4). The EtOAc solution was concentrated *in vacuo* and purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:2 to 1:1) to afford starting material **3-91** (4.0 mg, 0.065 mmol, 3%), product **3-116** (diastereomer 1) (40.0 mg, 0.0685 mmol, 28%) and (diastereomer 2) (58.2 mg, 0.0997 mmol, 41%) as pale yellow oil:

diastereomer 1: IR (neat) 3377, 3055, 3047, 3038. 2990, 2932, 2852, 2833, 1733, 1717, 1683, 1605, 1586, 1540, 1534, 1497, 1478, 1459, 1437, 1374, 1342, 1290, 1260, 1236, 1219, 1195, 1184, 1152, 1139, 1117, 1077, 1053, 1005, 979, 910, 874, 870, 854, 809, 781, 766, 731, 705 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.7 Hz, 1 H), 7.18 (t, *J* = 7.7 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 7.0 Hz, 1 H), 6.817 (d, *J* = 2.8 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.74 (td, *J* = 7.0, 2.1 Hz, 2 H), 6.71 (dd, *J* = 4.2, 2.8 Hz, 2 H), 5.44 (d, *J* = 4.9 Hz, 1 H), 4.39 (dd, *J* = 9.1, 4.9 Hz, 1 H), 4.32 (dd, *J* = 15.4, 10.5 Hz, 1 H), 4.25-4.20 (m, 1 H), 4.13 (d, *J* = 14.7 Hz, 1 H), 4.08 (t, *J* = 14.0 Hz, 1 H), 3.79 (s, 3 H), 3.78 (d, *J* =

2.1 Hz, 1 H), 3.75 (s, 3 H), 3.74 (m, 2 H), 3.54 (s, 3 H), 3.21 (s, 3 H), 3.03 (dd, *J* = 14.7, 8.4 Hz, 1 H), 2.99 (d, *J* = 14.0 Hz, 1 H), 2.80 (s, 1 H), 2.65 (dt, *J* = 12.6, 2.1 Hz, 1 H), 2.55-2.47 (m, 1 H), 2.47-2.40 (m, 2 H), 2.21 (dd, *J* = 16.1, 5.6 Hz, 1 H), 2.03-1.95 (m, 2 H), 1.95-1.90 (m, 1 H), 1.65 (br s, 1 H), 1.51 (dd, *J* = 15.4, 3.5 Hz, 1 H), 1.25 (s, 2 H), 1.24-1.21 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 159.5, 158.9, 155.8, 149.0, 143.7, 135.7, 135.5, 134.9, 131.5, 129.3, 129.2, 128.8, 127.1, 118.5, 116.9, 116.8, 112.8, 110.7, 109.3, 74.1, 69.9, 63.0, 60.8, 55.3, 55.3, 55.1, 48.8, 48.5, 39.1, 37.8, 34.7, 34.6, 31.2, 29.8; HRMS (ESI) *m/z* calcd for $C_{36}H_{42}NO_6$ ($[M+H]^+$) 584.30066, found 584.30011;

diastereomer 2: IR (neat) 3385, 2992, 2928, 2852, 2835, 1735, 1719, 1702, 1685, 1676, 1670, 1635, 1605, 1588, 1541, 1521, 1495, 1478, 1463, 1437, 1374, 1335, 1290, 1260, 1238, 1217, 1184, 1159, 1079, 1053, 1007, 988, 911, 869, 809, 783, 768, 731, 705 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.0, 1.4 Hz, 1 H), 7.66 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.55 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.46 (td, *J* = 7.7, 3.5 Hz, 2 H), 7.23 (t, *J* = 7.7 Hz, 1 H), 7.18 (t, *J* = 7.7 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 2.8 Hz, 1 H), 6.83 (d, *J* = 7.7 Hz, 1 H), 6.79 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.75 (td, *J* = 7.0, 2.8 Hz, 1 H), 6.73 (t, *J* = 2.1 Hz, 1 H), 6.71 (d, *J* = 7.7 Hz, 1 H), 5.51-5.47 (m, 1 H), 4.53 (dd, *J* = 10.5, 4.9 Hz, 1 H), 4.48 (d, *J* = 13.3 Hz, 1 H), 4.27 (t, *J* = 11.2 Hz, 1 H), 4.24-4.20 (m, 2 H), 4.20-4.14 (m, 1 H), 3.99 (dd, *J* = 14.7, 9.8 Hz, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.74-3.70 (m, 2 H), 3.65 (s, 1 H), 3.60 (s, 1 H), 3.54 (s, 3 H), 3.34 (d, *J* = 18.9 Hz, 1 H), 3.18 (s, 3 H), 3.09 (d, *J* = 14.0 Hz, 1 H), 2.87 (dd, *J* = 15.4, 9.1 Hz, 1 H), 2.66 (dd, *J* = 14.7, 7.7 Hz, 1 H), 2.44 (d, *J* = 17.5 Hz, 1 H), 2.36 (dd, *J* = 18.9, 6.3 Hz, 1 H), 2.20-2.09 (m, 2 H), 2.01-1.95 (m, 1 H), 1.84 (dd, *J* = 15.4, 9.1 Hz, 1 H), 1.78 (dd, *J* = 11.2, 7.0 Hz, 1 H), 1.72 (br s, 1 H), 1.60 (dd, *J* = 16.1, 7.7 Hz, 1 H), 1.39 (d, *J* = 16.1 Hz, 1 H), 1.37-1.31 (m, 1 H), 1.30-1.19 (m, 4 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 174.9, 159.5, 158.7, 155.9, 148.9, 143.4, 139.3, 135.9, 132.8, 132.2, 132.2, 132.2, 132.1, 132.0, 131.3, 129.3, 129.2, 128.6, 128.6, 128.5, 124.0, 118.4, 117.0, 116.8, 113.0, 112.5, 110.6, 109.3, 71.4, 62.9, 60.7, 55.3, 55.1, 49.1, 48.7, 39.3, 38.3, 34.7, 33.7, 32.5, 29.9; HRMS (ESI) *m/z* calcd for $C_{36}H_{42}NO_6$ ($[M+H]^+$) 584.30152, found 584.29945.



3-113

(10*aS*,15*bS*)-2,7,15-Trimethoxy-15*b*-(3-methoxyphenyl)-5*a*,6,7,8,9,10*a*,11,15*b*-octahydro-4*b*,7-ethano-10,17-methanobenzo[*f*]indeno[2,1-*b*]oxireno[2,3-*h*][1]azacyclotridecin-18-one (3-113). (Diastereomer 1) To a flask was added **3-116** (40.0 mg, 0.0685 mmol), Oxone (63.2 mg, 0.103 mmol) and $NaHCO_3$ (23.0 mg, 0.274 mmol). The flask was the cooled to 0 ^oC with ice-water bath and was added acetone (1.6 mL) and H_2O (1.0 mL). The ice-water bath was removed and the reaction mixture was stirred at room temperature for 10 h. The reaction was diluted with H_2O and was extracted with EtOAc (3x5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4) and was concentrated *in vacuo*.

To a solution of the obtained residue in CH_2Cl_2 (1.6 mL) was added Dess-Martin periodinane (87.1 mg, 0.206 mmol) and H_2O (1.2 mg, 0.069 mmol) at 0 ^oC and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding saturated $NaHCO_3$ solution (2 mL) and was extracted with EtOAc (3x5 mL). The EtOAc solution was concentrated *in vacuo* and purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1) to afford a clear oil.

To a solution of the obtained clear oil in MeOH (1.26 mL) in a microwave vial was added K_2CO_3 (94.7 mg, 0.685 mmol). The vial was microwaved at 125 ^oC for 6 h, quenched by pouring into H_2O (20 mL), extracted with EtOAc (3x20 mL), concentrated *in vacuo* and purified by column chromatography on SiO_2 (EtOAc:hexanes, 2:3) to afford **3-113** (15.0 mg, 0.0259 mmol, 38%) as colorless oil: IR (neat) 2993, 2930, 2833, 2240. 1664, 1623, 1603, 1568, 1478, 1463, 1435, 1368, 1349, 1340, 1308, 1290, 1266, 1249, 1215, 1191, 1176, 1154, 1137, 1100, 1077, 1044, 1007, 982, 966, 952, 941, 910, 865, 846, 824, 796, 779, 757, 729 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) not provided because of complex spetrum of mixture of two

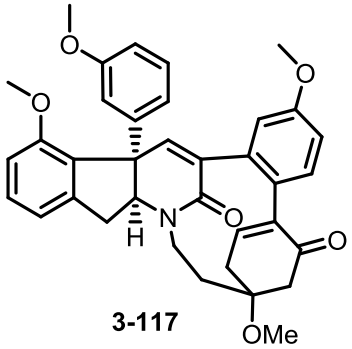
diastereomers; ^{13}C NMR (175 MHz, $CDCl_3$, mixture of two diastereomers) 167.6, 164.4, 159.9, 159.8, 159.3, 159.1, 156.4, 155.9, 146.3, 146.0, 142.5, 141.6, 140.5, 139.4, 137.1, 136.1, 135.7, 131.8, 131.6, 131.5, 131.0, 130.5, 130.2, 129.9, 129.8, 129.5, 126.7, 119.7, 119.0, 117.4, 117.2, 114.6, 114.3, 114.0, 113.9, 112.8, 112.4, 112.0, 111.9, 110.5, 110.3, 74.6, 73.4, 73.4, 67.6, 62.8, 60.8, 59.8, 58.8, 56.3, 56.0, 55.7, 55.5, 55.3, 55.3, 55.2, 48.9, 48.5, 47.2, 39.0, 38.4, 35.8, 35.7; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_6$ ($[M+H]^+$) 584.27005, found 580.26842.

(Diastereomer 2) To a flask was added **3-116** (43.2 mg, 0.0740 mmol), Oxone (136 mg, 0.222 mmol) and $NaHCO_3$ (49.7 mg, 0.592 mmol). The flask was the cooled to 0 ^oC with ice-water bath and was added acetone (1.73 mL) and H_2O (1.08 mL). The ice-water bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction was diluted with H_2O and was extracted with EtOAc (3x5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4) and was concentrated *in vacuo*.

To a solution of the resulting residue in CH_2Cl_2 (1.7 mL) was added Dess-Martin periodinane (94.1 mg, 0.222 mmol) and H_2O (1.3 mg, 0.0.074 mmol) at 0 ^oC and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding saturated $NaHCO_3$ solution (2 mL) and was extracted with EtOAc (3x5 mL). The EtOAc solution was concentrated *in vacuo* and purified by column chromatography on SiO_2 (EtOAc: hexanes, 1:1) to afford a clear oil.

To a solution of the obtained oil in MeOH (1.5 mL) in a microwave vial was added K_2CO_3 (205 mg, 1.48 mmol). The resulting mixture was heated under microwave at 125 ^oC for 6 h. The reaction mixture was poured into water (5 mL) and the mixture was extracted with EtOAc (3x20 mL) and the combined organic layear was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 2:3) to afford **3-113** (16.0 mg, 0.0276 mmol, 37% over 3 steps) as colorless oil: : IR (neat) 3441, 3046, 2999, 2995, 2930, 2855, 2833, 1716, 1700, 1666, 1625, 1603, 1569, 1541, 1478, 1465,

1435, 1374, 1349, 1344, 1290, 1266, 1251, 1215, 1195, 1176, 1154, 1133, 1118, 1103, 1079, 1062, 1040, 1010, 995, 984, 966, 949, 861, 846, 833, 824, 796, 775, 747, 734, 716, 706 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.22 (t, *J* = 7.7 Hz, 1 H), 6.88 (dd, *J* = 8.4, 2.8 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.78 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.73 (d, *J* = 2.8 Hz, 1 H), 6.71 (s, 1 H), 6.56 (d, *J* = 7.7 Hz, 1 H), 6.39 (t, *J* = 2.1 Hz, 1 H), 4.30 (d, *J* = 4.9 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 1 H), 3.79 (s, 1 H), 3.78 (s, 3 H), 3.75 (d, *J* = 6.3 Hz, 1 H), 3.70 (s,3 H), 3.57 (td, *J* = 14.7, 2.8 Hz, 1 H), 3.20 (s, 3 H), 3.18 (d, *J* = 16.8 Hz, 1 H), 3.05 (dd, *J* = 16.1, 4.9 Hz, 1 H), 2.95 (td, *J* = 14.0, 2.1 Hz, 1 H), 2.41 (td, *J* = 12.6, 5.6 Hz, 1 H), 2.33 (dd, *J* = 16.1, 4.9 Hz, 1 H), 2.26 (ddd, *J* = 15.4, 5.6, 2.1 Hz, 1 H), 2.04 (d, *J* = 15.4 Hz, 1 H), 1.71-1.65 (m, 2 H), 1.58 (s, 1 H), 1.43 (dt, *J* = 12.6, 2.8 Hz, 1 H), 1.27-1.23 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 165.2, 159.9, 159.3, 156.3, 145.4, 141.8, 138.1, 138.0, 137.3, 132.1, 130.7, 130.3, 130.0, 129.9, 119.9, 117.4, 114.4, 114.0, 113.7, 111.7, 110.2, 73.6, 73.4, 60.7, 57.0, 55.4, 55.3, 49.1, 46.3, 36.3, 31.3, 30.5, 27.9; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_6$ ($[M+H]^+$) 580.26936, found 580.26876.



3-117

(11*aS*,16*bS*)-2,8,16-Trimethoxy-16*b*-(3-methoxyphenyl)-8,9,10,11*a*,12,16*b*-hexahydro-7*H*-5,8-ethano-11,18-methanobenzo[*f*]indeno[2,1-*b*][1]azacyclotridecine-19,21-dione (3-117).

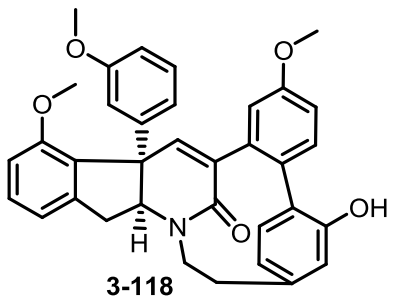
(Diastereomer 1) A solution of **3-113** (10.0 mg, 0.017 mmol) in DMSO (20 mL) was added 10% aqueous H_2SO_4 (3.38 g 10% aqueous solution, 3.45 mmol) at rt. Stirring was continued for 4 d at room temperature. The reaction was quenched by adding Sat. $NaHCO_3$ solution (10 mL) and the mixture was extracted with EtOAc (3x10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$),

concentrated *in vacuo*, and purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1 to 4:1) to afford the desired product allylic alcohol and starting material **3** (5.0 mg, 0.0086 mmol, 50%).

The isolated allylic alcohol was dissolved in CH_2Cl_2 (3 mL) and was added Dess-Marin periodinane (14.6 mg, 0.0345 mmol) and the reaction mixture was stilled at room temperature for 2 h. The reaction was quenched by adding sat. $NaHCO_3$ solution (5 mL), and the resulting mixture was stirred at room temperature for 15 min. The mixture was partitioned in the sep funnel, and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layer was washed with brine (5 mL), dried, and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1) to afford **3-117** (2.0 mg, 0.0035 mmol, 20%) as clear oil: IR (neat) 3068, 2059, 3049, 3042, 3016, 2992, 2936, 2867, 2859, 2833, 2257, 2246, 1743, 1735, 1719, 1700, 1672, 1648, 1623, 1601, 1560, 1480, 1465, 1433, 1420, 1376, 1353, 1292, 1266, 1249, 1238, 1217, 1171, 1156, 1111, 1079, 1062, 1046, 1040, 1008, 997, 911, 898 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.1 Hz, 1 H), 7.23 (dd, *J* = 16.8, 8.4 Hz, 1 H), 7.02 (dd, *J* = 7.0, 2.1 Hz, 1 H), 6.90-6.88 (m, 2 H), 6.84 (d, *J* = 7.0 Hz, 1 H), 6.81-6.77 (m, 3 H), 6.55 (d, *J* = 7.7 Hz, 1 H), 6.44 (t, *J* = 2.1 Hz, 1 H), 4.17 (d, *J* = 4.9 Hz, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.79 (d, *J* = 4.2 Hz, 1 H), 3.72 (s, 3 H), 3.28 (s, 3 H), 3.12-3.06 (m, 2 H), 3.00 (dd, *J* = 16.1 Hz, 1 H), 2.90 (t, *J* = 12.6 Hz, 1 H), 2.80 (dd, *J* = 7.0, 2.1 Hz, 1 H), 2.78 (t, *J* = 2.8 Hz, 1 H), 2.65 (d, *J* = 15.4 Hz, 1 H), 2.56 (ddd, *J* = 18.2, 7.0, 2.8 Hz, 1 H), 1.86 (dd, *J* = 16.8, 4.2 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.7. 165.4, 159.9, 159.3, 156.5, 145.9, 145.8, 141.8, 140.5, 137.9, 137.5, 137.0, 131.9, 131.1, 130.3, 129.9, 126.0, 119.8, 117.4, 115.1, 114.3, 112.4, 111.6, 110.3, 72.8, 56.8, 55.6, 55.4, 55.3, 50.5, 49.6, 44.2, 36.0, 35.0, 30.2; HRMS (ESI) *m/z* calcd for $C_{36}H_{36}NO_6$ ($[M+H]^+$) 578.25368, found 578.25377.

(Diastereomer 2) A solution of **3-113** (10.0 mg, 0.017 mmol) in DMSO (20 mL) was added 10% aqueous H_2SO_4 (3.38 g 10% aqueous solution, 3.45 mmol) at rt. Stirring was continued for 5 d at room temperature. The reaction was quenched by adding Sat. $NaHCO_3$ solution (10 mL) and the mixture was extracted with EtOAc (3x10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$),

concentrated *in vacuo*. The isolated allylic alcohol was dissolved in CH_2Cl_2 (3 mL) and was added Dess-Marin periodinane (14.6 mg, 0.0345 mmol) and the reaction mixture was stilled at room temperature for 2 h. The reaction was quenched by adding sat. $NaHCO_3$ solution (5 mL), and the resulting mixture was stirred at room temperature for 15 min. The mixture was partitioned in the sep funnel, and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layer was washed with brine (5 mL), dried, and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1) to afford **3-117** (7.2 mg, 0.0125 mmol, 72%) as clear oil: IR (neat) 3075, 3066, 3057, 3046, 3023, 2932, 2833, 1750, 1735, 1719, 1676, 1618, 1601, 1560, 1534, 1527, 1523, 1506, 1480, 1465, 1431, 1374, 1351, 1340, 1288, 1266, 1232, 1219, 1176, 1139, 1117, 1081, 1062, 1040, 997, 977, 962, 932, 867, 852, 820, 796, 779, 761, 731, 716, 697 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 7.14 (d, *J* = 2.8 Hz, 1 H), 6.92 (d, *J* = 7.7 Hz, 1 H), 6.88 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.81-6.78 (m, 2 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 6.74 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.52 (dd, *J* = 7.0, 2.1 Hz, 1 H), 6.31 (d, *J* = 1.4 Hz, 1 H), 4.03 (t, *J* = 8.4 Hz, 1 H), 3.97 (ddd, *J* = 14.7, 7.7, 2.8 Hz, 1 H), 3.84 (s, 3 H), 3.80 (d, *J* = 7.7 Hz, 1 H), 3.70 (s, 3 H), 3.57 (dd, *J* = 14.7, 7.7 Hz, 1 H), 3.54 (s, 3 H), 3.29 (s, 3 H), 3.22 (dd, *J* = 14.7, 10.5 Hz, 1 H), 3.01 (ddd, *J* = 16.8, 9.8, 2.8 Hz, 1 H), 2.93 (dd, *J* = 16.1, 2.1 Hz, 1 H), 2.88 (ddd, *J* = 14.0, 9.8, 2.8 Hz, 1 H), 2.79 (ddd, *J* = 17.5, 7.0, 2.1 Hz, 1 H), 2.70 (dd, *J* = 17.5, 2.1 Hz, 1 H), 2.64 (d, *J* = 16.8 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.1, 166.8, 159.6, 159.2, 155.8, 145.8, 142.6, 141.6, 139.7, 138.3, 137.9, 131.7, 131.5, 130.6, 129.7, 129.3, 127.1, 118.9, 117.0, 114.0, 112.9, 112.7, 111.9, 110.5, 73.2, 55.8, 55.6, 55.2, 55.2, 49.3, 49.1, 45.3, 37.3, 35.0, 34.4; HRMS (ESI) *m/z* calcd for $C_{36}H_{36}NO_6$ ($[M+H]^+$) 578.25361, found 578.25387.



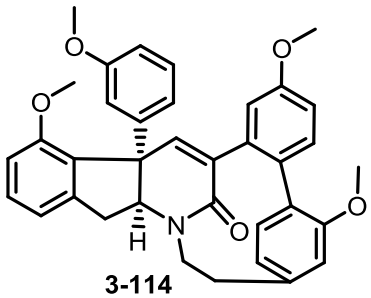
3-118

(11*aS*,16*bS*)-21-Hydroxy-2,16-dimethoxy-16*b*-(3-methoxyphenyl)-10,11*a*,12,16*b*-tetrahydro-9*H*-5,8-etheno-11,18-methanobenzo[*f*]indeno[2,1-*b*][1]azacyclotridecin-19-one (3-118).

(Diastereomer 1) **3-117** (2.0 mg, 0.0035 mmol) was dissolved in a mixture of DIPEA (742 mg, 5.75 mmol, 1.0 mL) and CF_3CH_2OH (1.39 g, 13.9 mmol, 1.0 mL). The reaction mixture was heated in microwave at 100 ^oC for 1.5 h. The reaction mixture was concentrated *in vacuo* and purified with column chromatography on SiO_2 (EtOac:hexanes,1:2) to afford **3-118** (1.5 mg,0.003 mmol, 79%) as pale yellow oil: IR (neat) 3252, 2993, 2923, 2852, 2837, 1733, 1718, 1702, 1691, 1683, 1659, 1597, 1560, 1534, 1523, 1517, 1506, 1478, 1456, 1430, 1418, 1376, 1284, 1266, 1226, 1169, 1158, 1120, 1102, 1079, 1059, 1044, 1021, 997, 951, 870, 861, 824, 802, 772, 757, 734, 718, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz,1 H), 7.22 (td, *J* = 7.8, 1.8 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 6.98-6.95 (m, 2 H), 6.85-6.82 (m,3 H), 6.80 (dd, *J* = 7.8, 1.8 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.62 (s, 1 H), 6.60-6.57 (m, 2 H), 5.32 (br s, 1 H), 4.31 (tdd, *J* = 12.6, 4.8, 1.2 Hz, 1 H), 4.13 (d, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.80-3.77 (m, 1 H), 3.76 (s, 3 H), 3.76 (s, 3 H), 3.05 (dd, *J* = 11.4, 4.2 Hz, 1 H), 3.02 (d, *J* = 9.6 Hz, 1 H), 2.88 (dd, *J* = 16.2, 4.8 Hz, 1 H), 2.81 (dd, *J* = 12.6, 4.8 Hz, 1 H), 2.66 (td, *J* = 13.2, 4.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 159.9, 159.6, 158.5, 156.4, 146.5, 144.0, 142.9, 139.8, 135.4, 133.4, 129.9, 129.7, 128.4, 123.2, 120.8, 119.6, 117.5, 117.4, 113.8, 112.6, 112.2, 110.0, 67.5, 56.6, 55.4, 55.2, 45.0, 35.5, 33.3; HRMS (ESI) *m/z* calcd for $C_{35}H_{32}NO_5$ ($[M+H]^+$) 546.22684, found 546.22754.

(Diastereomer 2) **3-117** (5.0 mg, 0.0087 mmol) was dissolved in a mixture of DIPEA (928 mg, 7.18 mmol, 1.25 mL) and CF_3CH_2OH (1.74 g, 17.3 mmol, 1.25 mL). The reaction mixture was heated in microwave at 100 ^oC for 1.5 h. The reaction mixture was concentrated *in vacuo* and purified with column chromatography on SiO_2 (EtOac:hexanes,1:2) to afford **3-118** (3.5 mg,0.0064 mmol, 74%) as pale yellow oil: IR (neat) 3299, 3066, 3059, 3047, 3021, 3014, 2995, 2988, 2930, 2869, 2857, 2848, 2833, 1683, 1653, 1646, 1597, 1560, 1478, 1465, 1448, 1437, 1420, 1363, 1349, 1323, 1284, 1264, 1226, 1217, 1178, 1137, 1118, 1077, 1044, 1018, 956, 911, 887, 869, 835, 816, 802, 792, 779, 759, 731 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz,1 H), 7.26 (t, *J* = 7.7 Hz,1 H), 7.17 (s,1 H), 7.09 (t, *J* = 8.4 Hz,1 H), 6.97 (d,

J = 8.4 Hz,1 H), 6.95 (d, *J* = 7.0 Hz,1 H), 6.89 (s,1 H), 6.86 (d, *J* = 7.7 Hz,1 H), 6.78 (d, *J* = 7.7 Hz,1 H), 6.72 (d, *J* = 7.7 Hz,1 H), 6.70 (d, *J* = 7.7 Hz,1 H), 6.65 (d, *J* = 8.4 Hz,1 H), 6.62 (s, 1 H), 6.20 (s,1 H), 5.07 (br s,1 H), 4.47 (td, *J* = 13.3, 5.6 Hz,1 H), 3.91 (dd, *J* = 14.0, 10.5 Hz,1 H), 3.86 (s, 3 H), 3.85-3.80 (m, 2 H), 3.75-3.67 (m, 1 H), 3.66 (s, 3 H), 3.50 (s, 3 H), 3.18 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.99 (dd, *J* = 12.6, 5.6 Hz, 1 H), 2.70 (td, *J* = 12.6, 5.6 Hz, 1 H), 2.50 (dd, *J* = 14.0, 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 159.6, 158.3, 156.0, 146.2, 143.2, 142.9, 140.7, 140.0, 133.2, 131.2, 131.1, 129.6, 129.5, 129.4, 129.2, 127.4, 123.6, 122.2, 119.0, 118.3, 117.1, 112.6, 112.4, 111.9, 110.3, 74.2, 56.3, 55.7, 55.3, 55.3, 49.5, 37.0, 36.9; HRMS (ESI) *m/z* calcd for $C_{35}H_{31}NO_5$ ($[M]^+$) 545.2202, found 545.2210.



3-114

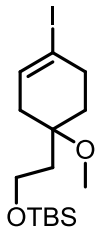
(11*aS*,16*bS*)-2,16,21-Trimethoxy-16*b*-(3-methoxyphenyl)-10,11*a*,12,16*b*-tetrahydro-9*H*-5,8-etheno-11,18-methanobenzo[*f*]indeno[2,1-*b*][1]azacyclotridecin-19-one (114).

(Diastereomer 1) A solution of **3-118** (1.5 mg, 0.0027 mmol) in THF(0.4 mL) is added dropwise at 0 ℃. to a suspension of NaH (1.1 mg 60 wt percent dispersion in mineral oil, prewashed with hexane, 0.027 mmol) in tetrahydrofuran (0.1 mL). The resulting yellow solution is stirred for 10 minutes, and iodomethane (3.9 mg, 0.027 mmol) is added rapidly. The reaction is warmed to ambient temperature and further heated at reflux for 16 h, cooled, diluted with water (20 mL) and extracted with EtOAc (3x5 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:2) to afford **3-114** (1.0 mg, 0.0018 mmol, 65%) as pale yellow oil: IR (neat) 3014, 2995, 2977, 2949, 2936, 2908, 2893, 2869, 2863, 2859, 2855, 2848, 2833, 1661, 1627, 1603, 1592, 1564, 1560, 1478, 1463, 1405, 1322, 1286, 1266, 1245, 1228, 1187, 1169, 1158, 1126, 1079, 1059, 1046, 1034, 1020, 999, 911, 870, 859, 826, 822, 803, 772, 742, 710, 701 cm^{-1};

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1 H), 7.22 (t, *J* = 8.4 Hz, 1 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 7.14 (d, *J* = 7.7 Hz, 1 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.82-6.77 (m, 3 H), 6.76 (s, 1 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 6.62-6.57 (m, 3 H), 4.33 (td, *J* = 13.3, 4.9 Hz, 1 H), 4.10 (d, *J* = 4.2 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.04 (dd, *J* = 13.3, 3.5 Hz, 1 H), 3.01 (d, *J* = 16.1 Hz, 1 H), 2.86 (dd, *J* = 16.1, 3.5 Hz, 1 H), 2.83 (d, *J* = 13.3, 4.9 Hz, 1 H), 2.71 (td, *J* = 12.6, 4.2 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 163.3, 162.2, 159.9, 158.9, 156.4, 146.6, 143.4, 143.0, 141.7, 139.4, 135.9, 133.9, 131.7, 131.3, 129.8, 129.7, 129.6, 125.7, 122.6, 119.6, 117.3, 116.0, 114.2, 113.7, 112.4, 112.2, 110.0, 67.6, 56.5, 55.5, 55.4, 55.2, 44.8, 35.5, 33.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}NO_5$ ($[M+H]^+$) 560.24315, found 560.24410.

(Diastereomer 2) A solution of **3-118** (3.5 mg, 0.0064 mmol) in THF(0.8 mL) is added dropwise at 0 °C. to a suspension of NaH (2.6 mg 60 wt percent dispersion in mineral oil, prewashed with hexane, 0.064 mmol) in tetrahydrofuran (0.4 mL). The resulting yellow solution is stirred for 10 minutes, and iodomethane (9.1 mg, 0.064 mmol) is added rapidly. The reaction is warmed to ambient temperature and further heated at reflux for 16 h, cooled, diluted with water (20 mL) and extracted with EtOAc (3x5 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:2) to afford **3-114** (2.5 mg, 0.0045 mmol, 70%): IR (neat) 3020, 3016, 3005, 2997, 2993, 2988, 2969, 2964, 2956, 2934, 2904, 2896, 2880, 2861, 2854, 2846, 2831, 1657, 1599, 1590, 1560, 1480, 1465, 1439, 1413, 1400, 1325, 1301, 1286, 1277, 1264 1226, 1215, 1200, 1176, 1156, 1137, 1122, 1077, 1036, 1016, 911, 880, 872, 861, 854, 833, 805, 794, 777, 757, 742, 731, 705, 693 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.6 Hz, 1 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.11 (s, 1 H), 7.07 (d, *J* = 6.6 Hz, 1 H), 6.94 (d, *J* = 6.0 Hz, 1 H), 6.88 (d, *J* = 6.6 Hz, 1 H), 6.86 (s, 1 H), 6.81 (d, *J* = 6.6 Hz, 1 H), 6.71 (d, *J* = 7.2 Hz, 1 H), 6.67 (t, *J* = 6.0 Hz, 2 H), 6.63 (s, 1 H), 6.17 (s, 1 H), 4.49 (td, *J* = 10.8, 4.2 Hz, 1 H), 3.91 (t, *J* = 9.6 Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.73 (d, *J* = 4.8 Hz, 1 H), 3.65 (s, 3 H), 3.49 (s, 3 H), 3.17 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.02 (dd, *J* = 10.8, 4.2 Hz, 1 H), 2.75 (td, *J* = 10.8, 4.8 Hz, 1 H), 2.50 (dd, *J* = 12.0, 4.2 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 164.5,

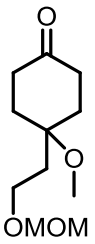
161.9, 159.6, 158.9, 146.3, 142.9, 142.7, 140.5, 139.4, 132.6, 131.6, 131.4, 130.3, 129.5, 129.1, 126.8, 125.5, 119.1, 117.0, 116.9, 115.0, 112.9, 111.5, 110.2, 56.2, 55.7, 55.3, 55.2, 49.4, 37.3, 36.8; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}NO_5$ ($[M+H]^+$) 560.24315, found 560.24461.



3-147

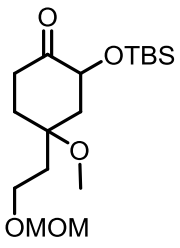
***tert*-Butyl(2-(4-iodo-1-methoxycyclohex-3-en-1-yl)ethoxy)dimethylsilane (3-147).** A stirring solution of **3-146** (200 mg, 0.478 mmol), LiCl (142 mg, 3.34 mmol) and hexamethylditin (172 mg, 526 mmol) in THF (3 mL) was degassed with freeze-pump-thaw cycle for three times. A solution of $Pd(PPh_3)_4$ (11.0 mg, 0.00956 mmol) in THF (4.7 mL, degassed with freeze-pump-thaw cycle for three times) at room temperature was added into the reaction mixture via syringe. The reaction mixture was heated to 60 ℃ for 24 h. TLC showed the starting material was completely consumed. The reaction mixture was subsequently cooled to 0 ℃, and N-iodosuccinimide (161 mg, 0.717 mmol) was added in one portion. After 3 h the reaction was allowed to warm to room temperature, then the mixture was concentrated *in vacuo*. The residue was suspended in Et_2O (2 mL), and a solution of KF (278 mg, 4.78 mmol) MeOH (2 mL) was added. The reaction mixture was stirred at room temperature for 2 h, then was concentrated *in vacuo*. The residue was suspended in Et_2O and filtered through celite. The filtrate was concentrated and purified by silica gel flash chromatography (EtOAc:hexanes, 1:12) to yield **3-147** (162 mg, 0.409 mmol, 86%) as colorless oil: IR (neat) 2926, 2893, 2885, 2882, 2854, 2822, 2242, 1469, 1461, 1439, 1428, 1389, 1359, 1251, 1180, 1048, 1036, 1005, 936, 911, 882, 835, 811, 774, 740, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.17-6.14 (m, 1 H), 3.70 (t, *J* = 7.0 Hz, 2 H), 3.18 (s, 3 H), 2.67-2.56 (m, 1 H), 2.51-2.43 (m, 1 H), 2.16-2.19 (m, 1 H), 2.19-2.04 (m, 1 H), 1.86-1.77 (m, 2 H), 1.77-1.62 (m, 2 H), 1.56 (s, 2 H), 1.25 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ134.2, 95.5, 72.3, 58.5, 49.0, 38.8, 38.0,

36.9, 33.0, 26.1, 26.1, 18.4, 1.2, -5.2; HRMS (ESI) m/z calcd for $C_{15}H_{30}O_2SiI$ ($[M+H]^+$) 397.10543, found 397.10466.



3-130

4-Methoxy-4-(2-(methoxymethoxy)ethyl)cyclohexan-1-one (3-130). To a solution of **3-129** (70.0 mg, 0.406 mmol) in CH_2Cl_2 (2 mL) at 0 ℃ was added DIPEA (68.2 mg, 0.528 mmol, 92.0 μL) and the reaction mixture was stirred at 0 ℃ for 10 min. To this mixture was added MOMCl (49.1 mg, 0.610 mmol, 46.3 μL) at 0 ℃ and the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched by adding sat. NH_4Cl aqueous solution (10 mL) and was extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1) to afford **3-130** (80.0 mg, 0.370 mmol, 91%) as colorless oil: IR (neat) 2941, 2887, 2826, 1713, 1466, 1442, 1415, 1392, 1323, 1232, 1216, 1181, 1149, 1125, 1107, 1067, 1035, 966, 917, 890, 806, 760, 728, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 2 H), 3.59 (t, *J* = 7.1 Hz, 2 H), 3.32 (s, 3 H), 3.23 (s, 3 H), 2.53 (td, *J* = 14.0, 6.0 Hz, 2 H), 2.20-2.04 (m, 4 H), 1.84 (t, *J* = 7.1 Hz, 2 H), 1.67 (td, *J* = 14.4, 5.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 96.6, 73.1, 63.2, 55.3, 49.0, 36.7, 35.3, 33.8; HRMS (ESI) m/z calcd for $C_{11}H_{21}O_4$ ($[M+H]^+$) 217.14344, found 217.14347.



3-131

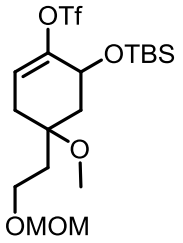
2-((*tert*-Butyldimethylsilyl)oxy)-4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-methoxycyclohexan-1-one (3-131). To a solution **3-130** (80.0 mg, 0.370 mmol) and 2, 6-lutidine (79.2 mg, 0.740 mmol) in THF (1 mL) at 0 ℃ was added TBSOTf (108 mg, 0.407 mmol). The reaction mixture was stirred at 0 ℃ for 4 h. The reaction was quenched by adding sat. NH_4Cl solution (5 mL) and the mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The resulting residue was run through a short pad of silica gel.

To a stirred solution of resulting residue in THF/water (3:1, 3.1 mL in total) were added 4-methylmorpholine-N-oxide (56.3 mg, 0.481 mmol) followed by K_2OsO_4-$2H_2O$ (0.3 mg, 0.0007 mmol). The resulting solution was stirred for 4 h at room temperature. The mixture was diluted with EtOAc (30 mL) and the aqueous layer was extracted with EtOAc (5x5 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified with silica gel column chromatography (EtOAc: hexanes, 1:4) to afford the desired alpha hydroxy ketone as colorless oil.

The resulting oil was dissolved in THF (1.1 mL) and to this solution was added N-methylimidazole (91.1 mg, 1.11 mmol), I_2 (188 mg, 0.740 mmol) and the mixture was stirred at room temperature for 1 min. To this mixture was added TBSCl (61.3 mg, 0.407 mmol) and the mixture was stirred at room temperature for 2 h until TLC showed the hydroxy ketone was completely consumed.

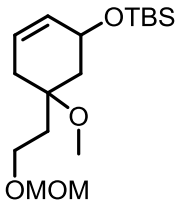
The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc (20 mL), washed with sat. $Na_2S_2O_3$ solution (10 mL), brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by column chromatography on SiO_2 (EtOAc: hexanes, 1:10) to afford **3-131** (91.0 mg, 0.263 mmol, 80% as mixture of diastereomers) as colorless oil: IR (neat, major diastereomer) 2929, 2885, 2856, 2826, 1730, 1464, 1389, 1361, 1299, 1252, 1217, 1150, 1137, 1111, 1068, 1044, 980, 953, 939, 909, 875, 833, 780, 746, 707, 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 4.59 (s, 2 H), 4.42 (ddd, *J* = 11.9, 6.5, 0.6 Hz, 1 H), 3.60 (t, *J* = 7.1 Hz, 2 H), 3.35 (s, 3 H), 3.27 (s, 3 H), 2.57 (tdd, *J* = 14.2, 5.9, 0.8 Hz, 1 H), 2.38 (ddd, *J* = 13.7, 6.6, 3.9 hz, 1 H), 2.24 (ddd,

J = 13.9, 4.4, 2.3 Hz, 1 H), 2.18-2.10 (m, 1 H), 1.85 (t, *J* = 7.4 Hz, 2 H), 1.70 (dd, *J* = 13.6, 12.1 Hz, 1 H), 1.64 (td, *J* = 14.2, 4.5 Hz, 1 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 209.3, 96.7, 75.5, 72.8, 63.2, 55.4, 49.1, 44.4, 35.5, 35.4, 34.4, 25.9, 18.6, -4.5, -5.4; HRMS (ESI) m/z calcd for $C_{17}H_{35}O_5Si$ ($[M+H]^+$) 347.22483, found 347.22310.



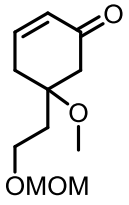
3-132

6-((*tert*-Butyldimethylsilyl)oxy)-4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-methoxycyclohex-1-en-1-yl trifluoromethanesulfonate (3-132). To a stirred solution of **3-131** (470 mg, 1.36 mmol) in THF (3 mL) at -78 ℃ was added LiHMDS (453 mg, 2.71 mmol) in THF (1 mL) via syringe and was stirred at -78 ℃ for 60 min. The reaction mixture was added Comins' reagent (959 mg, 2.44 mmol) in THF (1 mL). The mixture was stirred for 2 h at -78 ℃, and was slowly warmed to room temperature and stirred for 22 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL), and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified with column chromatography on SiO_2 (Et_2O:hexanes, 1:9) to afford **3-132**(528 mg, 1.10 mmol, 81%, mixture of diastereomers) as colorless oil: IR (neat, mixture of diastereomers) 2932, 2887, 2859, 2828, 16877, 1473, 1464, 1419, 1380, 1363, 1248, 1207, 1145, 1095, 1041, 1072, 976, 956, 918, 862, 838, 779, 729, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 5.77-5.63 (m, 1 H), 4.60 (s, 2 H), 4.49 (td, *J* = 6.0, 2.8 Hz, 1 H), 3.69-3.57 (m, 2 H), 3.36 (d, *J* = 1.7 Hz, 3 H), 3.17 (d, *J* = 17.6 Hz, 3 H), 2.52-2.15 (m, 3 H), 1.97-1.69 (m, 4 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of diastereomers) δ 149.4, 148.9, 121.8, 119.7, 117.5, 115.8, 115.4, 96.7, 96.6, 74.8, 74.0, 66.7, 65.4, 63.0, 62.7, 55.4, 55.3, 49.3, 49.2, 41.3, 41.0, 35.4, 34.3, 33.5, 33.4, 25.9, 25.9, 18.1, -4.4, -4.6; HRMS (ESI) m/z calcd for $C_{18}H_{34}O_7SSiF_3$($[M+H]^+$) 479.17411, found 479.17116.



3-133

***tert*-Butyl((5-methoxy-5-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-yl)oxy)dimethylsilane (3-133).** To a suspension of **3-132** (45.0 mg, 0.0940 mmol), DIPEA (97.1 mg, 0.752 mmol, 131 μL), $Pd(OAc)_2$ (4.2 mg, 0.0188 mmol), and PPh_3 (9.9 mg, 0.0376 mmol) in dry DMF (2 mL) was added 99% formic acid (9.5 mg, 0.207 mmol). The resulting pale brown suspension was stirred for 5 h at 60 ℃. The reaction mixture was cooled to room temperature and was diluted with EtOAc (20 mL), washed with brine (5 mL) and concentrated *in vacuo*. The reaction mixture was purified by column chromatography on SiO_2 (Et_2O: hexanes, 1:6) to afford **3-133** (28.2 mg, 0.0853 mmol, 91%) as colorless oil: IR (neat, mixture of diastereomers) 3031, 2929, 2886, 2857, 2824, 1655, 1463, 1389, 1361, 1328, 1253, 1206, 1152, 1110, 1072, 1033, 1006, 917, 879, 856, 836, 775, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 5.57 (dd, *J* = 10.0, 1.1 Hz, 1 Hz), 4.49 (dd, *J* = 10.0, 2.6 Hz, 1 Hz), 4.52 (s, 2 H), 4.34-4.23 (m, 1 H), 3.54-3.44 (m, 2 H), 3.27 (d, *J* = 2.3 Hz, 3 H), 3.11 (d, *J* = 6.2 Hz, 3 H), 2.23-2.00 (m, 2 H), 2.00-1.89 (m, 1 H), 1.89-1.37 (m, 4 H), 0.81 (s. 9 H), 0.00 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 131.3, 130.5, 125.7, 124.6, 96.7, 96.6, 75.2, 67.9, 66.0, 63.3, 63.2, 55.4, 55.3, 49.0, 48.7, 40.5, 39.8, 36.3, 35.1, 35.0, 33.6, 26.0, 18.4, 18.3, -4.5; HRMS (ESI) m/z calcd for $C_{17}H_{35}O_4Si$ ($[M+H]^+$) 331.22991, found 331.23054.

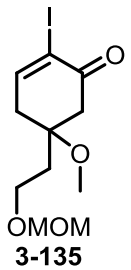


3-134

5-Methoxy-5-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-one (1-134). To a solution of **1-133** (20.0 mg, 0.0605 mmol) in THF (4.0 mL) at 0 ^oC was added TBAF (19.0 mg, 0.0726 mmol, 72.6 μL 1 M solution

in THF) and the reaction mixture was slowly warmed to room temperature. The reaction mixture was stirred for 9 h. The reaction was quenched by adding sat. NH_4Cl solution (10 mL) and was extracted with EtOAc (5x3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (EtOAc: hexanes, 1:1) to afford a mixture of two diastereomers.

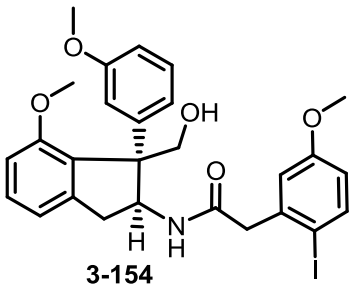
The isolated mixture of diastereomers was dissolved in CH_2Cl_2 (1.2 mL) and was cooled to 0 ^oC and was added $NaHCO_3$ (6.1 mg, 0.073 mmol) and DMP (30.8 mg, 0.0726 mmol). The reaction mixture was slowly warmed to room temperature and was stirred for 12 h. The reaction was quenched by adding sat. $NaCHO_3$ solution (10 mL) and the mixture was stirred at room temperature for 30 min. The mixture was washed with sat. Na_2SO_3 solution (3x5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by column chromatography on SiO_2 (EtOAc: hexanes, 1:1) to afford **1-134** (10.1 mg, 0.0467 mmol, 77%) as colorless oil: IR (neat) 3522, 2939, 2887, 2826, 2124, 1677, 1459, 1388, 1355, 1292, 1267, 1248, 1217, 1182, 1149, 1105, 1046, 1028, 952, 916, 841, 774, 732, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (ddd, *J* = 10.1, 4.9, 3.3 Hz, 1 H), 6.07 (dt, *J* = 10.1, 1.7Hz, 1 H), 4.60 (s, 2 H), 3.62 (td, *J* = 6.7, 1.4 Hz, 2 H), 3.36 (s, 3 H), 3.15 (s, 3 H), 2.74 (dd, *J* = 16.1, 1.1 Hz, 1 H), 2.61 (ddt, *J* = 18.9, 4.9, 1.6 Hz, 1 H), 2.54-2.47 (m, 2 H), 1.96-1.87 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 145.9, 129.6, 96.7, 62.9, 55.5, 49.6, 47.4, 35.5, 35.5; HRMS (ESI) m/z calcd for $C_{11}H_{19}O_4$ ($[M+H]^+$) 215.12779, found 215.12701.



3-135

2-Iodo-5-methoxy-5-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-one (3-135). To a solution of **3-134** (10.1 mg, 0.0471 mmol) in CH_2Cl_2 (130 μL) at 0 ^oC was added pyridine (97.8 mg, 1.24 mmol, 100 μL)

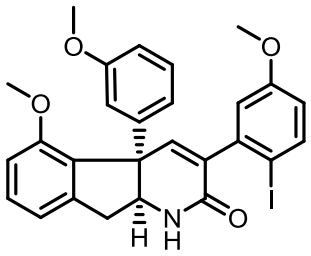
and I_2 (29.9 mg, 0.118 mmol) and the reaction mixture was warmed to room temperature and stirred for 4 h. EtOAc (20 mL) was added, and the organics were washed successively with: sat. aq. $Na_2S_2O_3$ (2 x 5 mL), H_2O (5 mL), 10% aq. $CuSO_4$ (6x5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc: hexanes, 1:2) to afford **3-135** (12.6 mg, 0.0370 mmol, 79%) as pale yellow oil: IR (neat) 3592, 2935, 2886, 2825, 1685, 1599, 1462, 1404, 1328, 1202, 1180, 1149, 1105, 1064, 1046, 1032, 1007, 958, 918, 869, 818, 771, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 5.1, 3.7 Hz, 1 H), 4.59 (s, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.35 (s, 3 H), 3.13 (s, 3 H), 3.02 (dd, *J* = 16.0, 1.6 Hz, 1 H), 2.68 (d, *J* = 16.0 Hz, 1 H), 2.64-2.60 (m, 2 H), 1.93-1.88 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 154.2, 102.6, 96.7, 62.8, 55.5, 49.7, 46.4, 39.4, 35.3; HRMS (ESI) m/z calcd for $C_{11}H_{18}O_4I$ ($[M+H]^+$) 341.02443, found 341.02323.



3-154

N-((1*R*,2*S*)-1-(hydroxymethyl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1*H*-inden-2-yl)-2-(2-iodo-5-methoxyphenyl)acetamide (3-154). To a solution of **3-85** (1.58 g, 4.82 mmol) in dry THF (40 mL) was added $LiALH_4$ (918 mg, 19.3 mmol, 4.83 mL 1 M solution in Et2O) at 0 ℃ and the reaction mixture was stirred at room temperature for 8 h. The reaction was cooled to 0 C and was sequentially added H_2O (918 μL), 15% NaOH aqueous solution (2.75 mL), H_2O (918 μL) and the reaction mixture was stirred at room temperature for 15 min. To this mixture was added $MgSO_4$ (20 mg) and the mixture was stirred for another 15 min and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and directly used in the next step without further purification.

The crude material and **3-153** (987 mg, 3.38 mmol) in CH_2Cl_2 (31 mL) was treated with EDCI (648 mg, 3.38 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h and quenched with water. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water (2x5 mL) and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography on SiO_2 (EtOAc:Hexanes, 1:3) afforded **3-154** (1.54 g, 2.69 mmol, 56%) as a clear oil.: IR (neat) 3308, 3083, 3072, 3062, 3055, 3051, 3033, 3021, 3006, 2997, 2992, 2954, 2036, 2930, 2908, 2872, 2867, 2833, 1653, 1546, 1586, 1568, 1540, 1521, 1476, 1465, 1437, 1431, 1389, 1379, 1359, 1290, 1260, 1238, 1189, 1161, 1148, 1105, 1085, 1079, 1049, 1008, 811, 768, 734, 716, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.7 Hz, 1 H), 7.32 (dd, *J* = 15.4 Hz, 2 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 6.91 (d, *J* = 2.8 Hz, 1 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 6.73 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.64 (d, *J* = 7.7 Hz, 1 H), 6.55 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.53 (d, *J* = 1.8 Hz, 1 H), 4.91 (t, *J* = 6.0 Hz, 1 H), 4.25 (s, 2 H), 3,77 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.65 (s, 2 H), 3.04 (dd, J = 16.3, 6.2 Hz, 1 H), 2.81 (d, *J* = 16.0 Hz, 1 H), 2.58 (br s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 160.2, 159.7, 156.8, 145.5, 144.2, 140.1, 139.4, 130.0, 129.5, 129.4, 119.2, 118.9, 116.7, 115.5, 113.2, 111.7, 109.3, 89.7, 66.3, 62.7, 62.3, 55.5, 55.5, 55.2, 48.9, 39.0 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{27}O_5NI$ ($[M-H]^+$) 572.09284, found 572.09364.

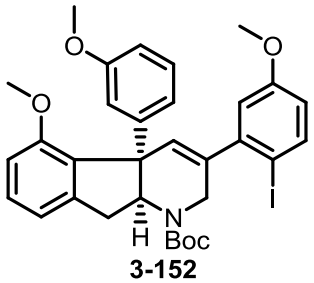


3-155

(4*aS*,9*aS*)-3-(2-Iodo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-1,4a,9,9a-tetrahydro-2*H*-indeno[2,1-b]pyridin-2-one (3-155). To a solution of **3-154** (123 mg, 0.215 mmol) in CH_2Cl_2 (16 mL) was added DMP (182 mg, 0.429 mmol) at room temperature. The reaction mixture was stirred room temperature for 12 h until the starting material was fully consumed (monitored by TLC). The reaction was

quenched by adding sat. $NaHCO_3$ solution (5 mL) and stirred for 10 min. The mixture was partitioned in the sep funnel and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layer was washed with brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:3) to afford the desired aldehyde.

The aldehyde was dissolved in MeOH (5 mL) and was added K_2CO_3 (296 mg, 2.15 mmol). The reaction mixture was heated at room temperature for 24 h and then at 60 ℃ for 24 h. The reaction mixture was concentrated *in vacuo* and dissolved in EtOAc (5 mL). The EtOAc solution was washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1 with 0.5% Et_3N) to afford **3-155** (60.2 mg, 0.109 mmol, 51%) as pale oil: IR (neat) 3208, 3059, 3025, 2999, 2937, 2867, 2854, 2835, 2378, 2347, 2235, 1702, 1670, 1623, 1597, 1586, 1564, 1491, 1478, 1461, 1450, 1405, 1387, 1381, 1308, 1288, 1264, 1240, 1221, 1174, 1137, 1061, 1031, 766, 733, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 1 H), 7.29 (t, J = 7,9 Hz, 1 H), 7.23 (t, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 7.4 Hz, 1 H), 6.83-6.75 (m, 4 H), 6.62 (dd, *J* = 8.7, 3.0 Hz, 1 H), 6.01 (br s, 1 H), 4.24 (brs, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.62 (s, 3 H), 3.50-3.35 (m, 2 H), 1.65 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 159.8, 159.8, 156.6, 145.1, 145.5, 143.1, 139.4, 129.9, 129.8, 129.4, 119.3, 117.6, 117.0, 115.3, 113.2, 112.1, 110.0, 88.4, 64.4, 55.5, 55.4, 55.2, 53.5, 41.0; HRMS (ESI) m/z calcd for $C_{27}H_{25}O_5NI$ ($[M+H]^+$) 554.08228, found 554.08000.

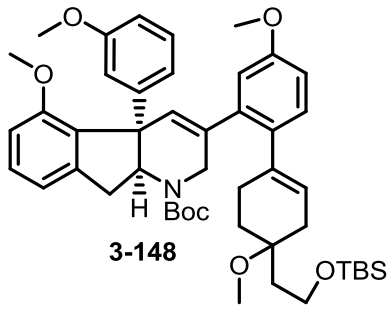


3-152

***tert*-Butyl (4aS,9aS)-3-(2-iodo-5-methoxyphenyl)-5-methoxy-4*a*-(3-methoxyphenyl)-2,4*a*,9,9*a*-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-152).** To a microwave vial was added **3-155**

(230 mg, 0.416 mmol) and $Ru_3(CO)_{12}$ (13.3 mg, 0.0208 mmol). The vial was sealed and purged with N_2. To this vial was added toluene (4.6 mL) and TMDS (880 mg, 6.65 mmol, 1.2 mL) via syringe. The reaction mixture was stirred at room temperature for 30 min, and then heated and stirred at 50 ℃ for 2 h. The reaction mixture was cooled to room temperature and was added 1 M NaOH aqueous solution (2 mL) and CH_2Cl_2 (2 mL). The mixture was vigorously stirred for 30 min and partitioned in the sep funnel. The aqueous layer was extracted with CH_2Cl_2 (3x3 mL) and the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc: hexanes, 1:2) isolate the resulting spot.

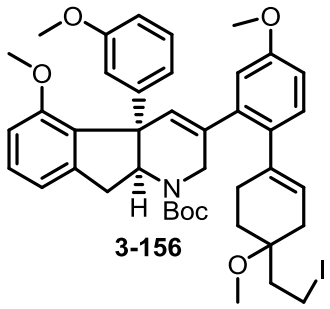
The isolated material was dissolved in CH_2Cl_2 (4.6 mL) and was added Boc_2O (95.2 mg, 0.436 mmol). The reaction mixture was stirred at room temperature for 12 h and was quenched by adding H_2O (5 mL). The mixture was extracted with EtOAc (3x5 mL) and the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:6) to afford the **3-152** (239 mg, 0.374 mmol, 90%) as pale yellow oil: IR (neat) 2934, 2835, 2248, 1691, 1587, 1563, 1480, 1464, 1438, 1416, 1391, 1364, 1343, 1315, 1288, 1255, 1212, 1164, 1112, 1079, 1053, 1024, 1006, 985, 969, 907, 863, 808, 774, 732, 707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75-7.61 (m, 1 H), 7.23 (t, *J* = 7.9 Hz, 1 H), 7.21-7.15 (m, 1 H), 6.95-6.73 (m, 5 H), 6.71 (d, *J* = 8.1 Hz, 1 H), 6.61-6.59 (m, 1 H), 5.92-5.77 (m, 1 H), 5.10-4.94 (m, 1 H), 4.86-4.56 (m, 1 H), 3.90-3.81 (m, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.52 (s, 3 H), 3.42-3.28 (m, 1 H), 3.28-3.13 (m, 1 H), 3.07 (dd, *J* = 15.0, 8.2 Hz, 1 H), 1.44-1.36 (m, 3 H), 1.20-1.07 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.4, 156.2, 154.7, 147.3, 145.9, 142.6, 139.8, 138.4, 131.2, 129.1, 128.7, 127.3, 119.4, 117.3, 115.6, 115.3, 112.6, 111.4, 109.7, 87.0, 79.6, 63.3, 55.5, 55.3, 55.1, 55.0, 42.0, 33.4, 28.4, 28.5, 28.0, 27.5, 27.4; HRMS (ESI) m/z calcd for $C_{32}H_{35}O_5NI$ ($[M+H]^+$) 640.15544, found 640.15629.



3-148

***tert*-Butyl (4*aS*,9*aS*)-3-(4'-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4,4'-dimethoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4*a*-(3-methoxyphenyl)-2,4*a*,9,9*a*-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-148).** To a flask was added **3-152** (86.0 mg, 0.134 mmol), **3-150** (80.0 mg, 0.201 mmol) and $PdCl_2$(dppf) (9.8 mg, 0.0134 mmol) and the flask was purged with N_2. To this flask were added THF (5.0 mL, degassed with freeze pump thaw cycles for three times) and 10% NaOH solution in H_2O (2.0 mL, degassed with freeze pump thaw cycles for three times). The reaction mixture was stirred at room temperature for 36 h. The reaction was quenched by adding H_2O (5 mL). The resulting mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:10) to afford **3-148** (96.0 mg, 0.123 mmol, 91%) as colorless oil: IR (neat) 2933, 2856, 1692, 1600, 1480, 1418, 1390, 1365, 1344, 1317, 1288, 1253, 1210, 1164, 1145, 1079, 954, 896, 836, 810, 774, 733, 707, 695, 663 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.32 (t, *J* = 7.6 Hz, 1 H), 7.26-7.19 (m, 3 H), 7.17 (td, *J* = 7.9, 3.1 Hz, 1 H), 7.03 (d, *J* = 10.3 Hz, 1 H), 6.92-6.86 (m, 2 H), 6.86-6.80 (m, 2 H), 6.80-6.73 (m, 3 H), 6.73-6.69 (m, 1 H), 5.95 (s, 0.5 H), 5.89 (s, 0.5 H), 5.35 (s, 0.5 H), 5.30 (s, 0.5 H), 5.00-4.75 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 1 H), 3.74 (s, 2 H), 3.72 (m, 3 H), 3.52 (m, 3 H), 3.27 (s, 1 H), 3.17 (d, *J* = 10.3 Hz, 3 H), 3.13-2.97 (m, 2 H), 2.57 (td, J = 14.2, 6.1 Hz, 1 H), 2.29-2.10 (m, 2 H), 2.10-1.96 (m, 2 H), 1.96-1.76 (m, 2 H), 1.76-1.57 (m, 2 H), 1.43-1.03 (m, 9 H), 0.92 (d, *J* = 1.62 Hz, 9 H), 0.04 (d, *J* = 0.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) 159.5, 158.2, 154.9, 138.0, 133.5, 132.1, 129.7, 129.5, 129.2, 129.2, 128.8, 126.7, 124.0, 122.9, 119.3, 115.4, 111.1, 109.9, 73.3, 73.2, 58.8, 58.7, 55.7, 55.5, 55.4, 55.2, 55.1, 49.1,

48.9, 38.5, 38.1, 36.8, 35.4, 33.9, 33.1, 28.0, 26.1, 26.0, 18.5, 18.4, 8.4, -5.1, -5.2; HRMS (ESI) m/z calcd for $C_{47}H_{64}O_7NSi([M+H]^+)$ 782.44466, found 782.44470.



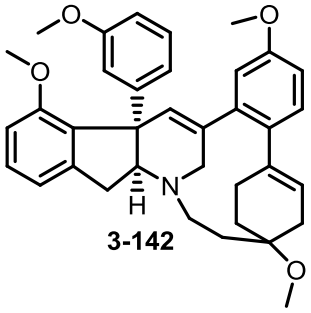
3-156

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-(2-iodoethyl)-4,4'-dimethoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-156).** To a solution of **3-148** (96.0 mg, 0.123 mmol) in THF (3.7 mL) was added TBAF (32.1 mg, 0.246 mmol, 246 μL 1 M solution in THF) under N_2 at 0 ℃. The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 12 h. The reaction was quenched by adding H_2O (5 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

The resulting residue was dissolved in CH_2Cl_2 (1 mL) and was cooled to 0 ℃ and was added Et_3N (62.1 mg, 0.614 mmol) and MsCl (28.1 mg, 0.246 mmol). The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 24 h. The reaction was quenched by adding H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:2) to afford the desired mesylate as a colorless oil.

The resulting oil was dissolved in THF (1 mL) and was added LiI (82.1 mg, 0.614 mmol) and the reaction mixture was heated at 60 ℃ for 12 h. The reaction mixture was cooled to room temperature and was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (6 mL) and was washed with sat. NaS_2O_3 solution (4 mL). The aqueous layer was extracted with EtOAc (3x2 mL) and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting

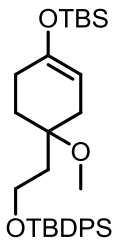
residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:8) to afford **3-156** (75.2 mg, 0.0967 mmol, 79%) as colorless oil: IR (neat) 2935, 2834, 2244, 1689, 1601, 1587, 1563, 1480, 1465, 1435, 1417, 1391, 1364, 1344, 1317, 1288, 1254, 1210, 1165, 1112, 1079, 1045, 1021, 968, 909, 856, 826, 808, 775, 732, 707, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.24 (td, *J* = 7.8, 4.2 Hz, 1 H), 7.16 (td, *J* = 7.9, 3.6 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 6.88 (t, *J* = 6.7 Hz, 1 H), 6.84 (dd, *J* = 12.0, 2.2 Hz, 1 H), 6.80-6.69 (m, 5 H), 5.95 (s, 0.5 H), 5.88 (s, 0.5 H), 5.37 (s, 0.5 H), 5.33 (s, 0.5 H), 4.97-4.78 (m, 2 H), 3.81 (s, 3 H), 3.74 (d, *J* = s. 1.5 H), 3.73 (s, 1.5 H), 3.52 (s, 3 H), 3.17 (s, 2 H), 3.15 (s, 3 H), 3.10-2.95 (m, 2 H), 2.35-2.08 (m, 3 H), 2.08-1.75 (m, 3 H), 1.65-1.50 (m, 2 H), 1.43-1.03 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ159.4, 158.4, 158.2, 156.3, 154.8, 154.8, 147.9, 147.9, 142.5, 139.9, 138.2, 137.2, 135.1, 135.0, 132.1, 129.2, 129.2, 128.8, 122.5, 119.3, 115.2, 111.0, 109.9, 79.6, 79.6, 75.4, 55.5, 55.4, 55.2, 49.0, 49.0, 41.1, 34.5, 34.2, 33.2, 33.1, 29.1, 28.0, 27.9, -1.1; HRMS (ESI) m/z calcd for $C_{41}H_{49}O_6NI([M+H]^+)$ 778.25991, found 778.25669.



3-142

(11a*S*,16b*S*,*E*)-2,8,16-Trimethoxy-16b-(3-methoxyphenyl)-7,9,10,11a,12,16b-hexahydro-8*H*-5,8-ethano-11,18-methanobenzo[f]indeno[2,1-b][1]azacyclotridecine (3-142). To a solution of **3-156** (70.0 mg, 0.0900 mmol) in CH_2Cl_2 (17.7 mL) at 0 ℃ under N_2 was added TFA (1.33 g, 11.7 mmol) and the reaction mixture was stirred at 5 ℃ for 24 h. The reaction mixture was diluted with toluene and the mixture was concentrated *in vacuo*. The resulting residue was added toluene and concentrated *in vacuo* for two more times. The resulting oil was dessolved in CH_3CN (88 mL) and the mixture was added DIPEA (1.16 g, 9.00 mmol). The reaction mixture was degassed with freeze-pump-thaw cycles for three times, and was heated at 80 ℃ for 24 h. The reaction mixture was cooled to room temperature and was

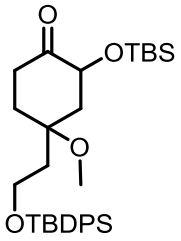
concentrated *in vacuo*. The resulting residue was added sat. $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO2 (EtOAc:hexanes, 1:3 to 1:2 with 0.5% Et3N) to afford **3-142** (26.9 mg, 0.489 mmol, 54%) as pale yellow oil: IR (neat) 2937, 2834, 2240, 1600, 1563, 1480, 1465, 1289, 1263, 1205, 1174, 1114, 1080, 1052, 1022, 982, 911, 874, 810, 776, 732, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 7.23 (dd, *J* = 7.9, 5.2 Hz, 1 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 7.04 (t, *J* = 7.8 Hz, 1 H), 6.93 (dd, J = 7.4, 3.0 Hz, 1 H), 6.81 (d, *J* = 2.7 Hz, 1 H), 6.78-6.65 (m, 6 H), 6.38 (s, 1 H), 5.43 (dd, *J* = 4.0, 2.7 Hz, 1 H), 3.82 (s, 1.5 H), 3.80 (s, 1.5 H), 3.76 (s, 1 H), 3.73 (s, 3 H), 3.67 (td, *J* = 5.4, 2. Hz, 1 H), 3.62 (d, *J* = 14.1 Hz, 3 H), 3.52-3.42 (m, 2 H), 3.25 (d, *J* = 1.5 Hz, 3 H), 3.19-3.10 (m, 2 H), 2.89 (td, *J* = 16.0, 5.1 Hz, 1 H), 2.72-2.65 (m, 1 H), 2.50 (t, *J* = 14.0 Hz, 1 H), 2.17 (td, *J* = 16.2, 4.1 Hz, 1 H), 1.90-1.59 (m, 6 H), 1.53 (dd, *J* = 9.2, 3.2 Hz, 1 H), 1.44 (dd, *J* = 9.8, 4.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 159.7, 159.6, 158.5, 158.5, 157.5, 148.1, 148.0, 145.8, 145.6, 143.6, 141.7, 141.4, 139.6, 133.3, 133.2, 132.8, 132.5, 130.7, 129.5, 129.2, 129.1, 119.5, 119.4, 118.0, 114.9, 113.5, 113.4, 111.9, 111.8, 110.8, 109.7, 83.0, 82.9, 66.6, 60.5, 55.6, 55.4, 55.2, 55.1, 51.3, 51.3, 45.6, 42.3, 40.4, 39.9, 36.0, 34.0, 33.9, 33.2, 33.1, 31.7, 22.8, 14.3, 14.3; HRMS (ESI) m/z calcd for $C_{36}H_{40}O_4N([M+H]^+)$ 550.29519, found 550.29303.



3-164

***tert*-Butyl(2-(4-(*tert*-butyldimethylsilyloxy)-1-methoxycyclohex-3-enyl)ethoxy)diphenylsilane (3-164).** To a solution of **3-163** (2.19 g, 5.33 mmol) and 2,6-lutidine (1.14 g, 10.7 mmol) in THF (28 mL) at 0 ℃ was added TBSOTf (1.83 g, 6.93 mmol). The reaction mixture was stirred at 0 ℃ for 4 h. The reaction was quenched by adding sat. NH_4Cl solution (5 mL) and the mixture was extracted with EtOAc (3x10

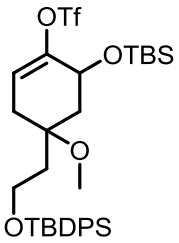
mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (Et_2O:heaxnes, 1:14) to generate **3-164** (2.68 g, 5.11 mmol, 96%) as colorless oil: IR (neat) 3071, 2930, 2857, 2888, 1674, 1590, 1472, 1463, 1428, 1290, 1373, 1361, 1252, 1179, 1196, 1111, 1081, 1007, 939, 877, 838, 799, 778, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 6.6, 1.3 Hz, 4 H), 7.45-7.36 (m, 6 H), 4.68 (t, *J* = 3.6 Hz, 1 H), 3.79 (t, *J* = 7.3 Hz, 2 H), 3.04 (s, 3 H), 2.16-2.06 (m, 2 H), 2.06-1.97 (m, 1 H), 1.97-1.74 (m, 4H), 1.65-1.55 (m, 1 H), 1.06 (s, 9 H), 0.93 (s, 9 H), 0.13 (d, *J* = 0.85 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 135.7, 134.1, 129.7, 127.8, 100.8, 73.5, 59.9, 48.9, 37.3, 33.5, 31.1, 27.4, 27.0, 25.8, 19.3, 18.1, -4.3, -4.3; HRMS (ESI) m/z calcd for $C_{31}H_{49}O_3Si_2$([M+H]$^+$) 525.32147, found 525.32017.



3-165

2-(*tert*-Butyldimethylsilyloxy)-4-(2-(tert-butyldiphenylsilyloxy)ethyl)-4-methoxycyclohexanone (3-165). To a stirred solution of **1-164** (400 mg, 0.762 mmol) in THF/water (3:1, 3.1 mL in total) were added 4-methylmorpholine-N-oxide (134 mg, 1.14 mmol) followed by K_2OsO_4-$2H_2O$ (1.4 mg, 0.0038 mmol). The resulting solution was stirred for 8 h at room temperature. The mixture was diluted with EtOAc (30 mL) and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$) and *concentrated in vacuo*. The residue was purified with silica gel column chromatography (EtOAc:hexanes, 1:4) to afford the desired alpha hydroxy ketone as colorless oil. The resulting oil was dissolved in THF (2.3 mL) and to this solution was added N-methylimidazole (188 mg, 2.29 mmol), I_2 (387 mg, 1.52 mmol) and the mixture was stirred at room temperature for 1 min. To this mixture was added TBSCl (126 mg, 0.838 mmol) and the mixture was stirred at room temperature for 1 h until TLC showed the hydroxy ketone was completely consumed. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc (20 mL),

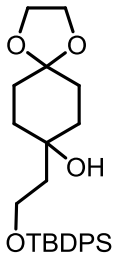
washed with sat. $Na_2S_2O_3$ solution (10 mL), brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 to **3-165** (349 mg, 0.645 mmol, 85%) as a mixture of diastereomers: IR (neat) 3072, 2930, 2886, 2856, 1968, 1730, 1590, 1472, 1463, 1428, 1390, 1361, 1299, 1251, 1159, 1136, 1111, 1075, 1042, 1007, 974, 938, 925, 908, 875, 832, 779, 737, 688, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.67 (d, *J* = 7.5 Hz, 5 H), 7.47 (m, 7 H), 5.63 (t, *J* = 3.8 Hz, 1 H), 4.46 (t, *J* = 6.4 Hz, 1 H), 3.74 (t, *J* = 7.0 Hz, 2 H), 3.02 (s, 3 H), 2.40-2.20 (m, 3 H), 1.97-1.77 (m, 3 H), 1.72 (dd, *J* = 13.5, 8.4 Hz, 1 H), 1.05 (s, 9 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 209.4, 135.7, 133.8, 129.8, 127.8, 72.8, 59.5, 49.0, 44.6, 38.4, 35.5, 34.4, 27.0, 25.9, 19.2, 18.6, -4.5, -5.4; HRMS (ESI) m/z calcd for $C_{31}H_{49}O_4Si_2([M+H]^+)$ 541.31639, found 541.31464.



3-166

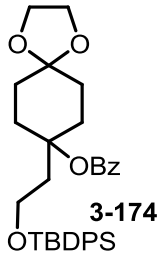
6-(*tert*-Butyldimethylsilyloxy)-4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methoxycyclohex-1-enyl trifluoromethanesulfonate (3-166). To a stirred solution of **3-165** (500 mg, 0.924 mmol) in THF (4.0 mL) at -78 ℃ was added LiHMDS (309 mg, 1.85 mmol) in THF (2.0 mL) via syringe and was stirred at -78 ℃ for 60 min. The reaction mixture was added Comins' reagent (690 mg, 1.76 mmol) in THF (1.6 mL). The mixture was stirred for 2 h at -78 ℃, and for 2 h at 0 ℃. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL), and the whole was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified with column chromatography on SiO_2 (Et_2O:hexanes, 1:40) to afford **3-166** (526 mg, 0.782 mmol, 85%, mixture of diastereomers) as colorless oil: IR (neat, mixture of diastereomers) 3072, 2889, 2932, 2858, 1960, 1685, 1590, 1472, 1463, 1420, 1378, 1362, 1248, 1206, 1144, 1111, 1084, 1007, 973, 914, 864, 837, 778, 738, 702, 688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.67 (d, *J* =

7.2 Hz, 5 H), 7.46-7.36 (m, 7 H), 5.63 (t, *J* = 3.8 Hz, 1 H), 4.46 (t, *J* = 7.4 Hz, 1 H), 3.77-3.68 (m, 2 H), 3.01 (s, 3 H), 2.33-2.21 (m, 3 H), 2.00-1.77 (m, 3 H), 1.72 (dd, *J* = 13.4, 8.5 Hz, 1 H), 1.05 (s, 9 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.3, 135.7, 135.7, 133.7, 133.7, 129.9, 127.8, 119.7, 117.6, 115.9, 74.9, 65.4, 59.4, 49.1, 41.3,38.2, 33.5, 27.0, 26.9, 25.9, 25.8, 19.2, 18.1, -4.5, -4.8; HRMS (ESI) m/z calcd for $C_{32}H_{48}O_6F_3SSi_2$([M+H]$^+$) 673.26567, found 673.26378.



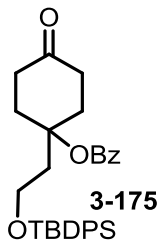
3-173

8-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-1,4-dioxaspiro[4.5]decan-8-ol (3-173). To a solution of **3-172** (282 mg, 1.39 mmol) in CH_2Cl_2 (5.2 mL) was added DMAP (8.5 mg, 0.070 mmol), TBDPSCl (460 mg, 1.67 mmol) and Et_3N (282 mg, 2.79 mmol, 392 μL). The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by adding H_2O (10 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (3 mL), dried (MgSO4) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:4) to afford **3-173** (470 mg, 1.07 mmol, 77%) as colorless oil: IR (neat) 3508, 3072, 2932, 2883, 2858, 2244, 1737, 1590, 1472, 1428, 1391, 1370, 1338, 1265, 1228, 11891166, 1103, 1067, 1038, 1008, 977, 944, 902, 879, 822, 731, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.9, 1.4 Hz, 4 H), 7.47-7.38 (m, 6 H), 3.99-3.91 (m, 4 H), 3.90 (t, J = 5.8 Hz, 2 H), 3.64 (s, 1 H), 2.00 (td, *J* = 13.4, 4.0 Hz, 2 H), 1.83-1.77 (m, 2 H), 1.75 (t, *J* = 5.7 Hz, 2 H), 1.63-1.52 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 132.8, 129.9, 127.8, 109.1, 70.4, 64.3, 64.1, 61.5, 42.0, 35.1, 30.4, 26.9, 19.0; HRMS (ESI) m/z calcd for $C_{26}H_{37}O_4Si$ ([M+H]$^+$) 441.24556, found 441.24590.



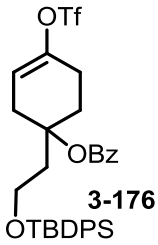
3-174

8-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-1,4-dioxaspiro[4.5]decan-8-yl benzoate (3-174). To a solution of **3-173** (470 mg, 1.07 mmol) in THF (10.1 mL) at 0 ℃ was added *n*BuLi (208 uL 2.0 M solution in hexanes, 1.39 mmol) and the reaction mixture was stirred at 0 ℃ for 20 min. To this mixture at 0 ℃ was added benzoyl chloride (225 mg, 1.60 mmol) and the reaction mixture was stirred at 0 ℃ for 1 h. The reaction mixture was warmed to room temperature and stirred at room temperature for 12 h. The mixture was quenched by the addition of an aqueous saturated solution of NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:20 to 1:15) to afford **3-174** (390 mg, 0.716 mmol, 67%) as colorless oil and starting material 14 (131 mg, 0.297 mmol, 28%): IR (neat) 3071, 2956, 2932, 2884, 2858, 2251, 1791, 1711, 1585, 1473, 1463, 1450, 1428, 1361, 1340, 1315, 1284, 1250, 1093, 1039, 1026, 998, 908, 843, 822, 729, 701, 687, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2 H), 7.64 (dd, *J* = 7.9, 1.2 Hz, 4 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 10.5 Hz, 4 H), 3.96 (s, 4 H), 3.78 (t, *J* = 6.6 Hz, 2 H), 2.62-2.52 (m, 2 H), 2.41 (t, *J* = 6.6 Hz, 2 H), 1.90-1.79 (m, 4 H), 1.71-1.62 (m, 2 H), 1.02 (s, 9 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 135.6, 133.7, 132.7, 131.5, 130.7, 129.6, 129.6, 129.0, 128.4, 127.7, 108.3, 82.8, 64.1, 64.3, 59.9, 53.5, 39.8, 32.8, 30.7, 26.9, 19.1; HRMS (ESI) m/z calcd for $C_{33}H_{41}O_5Si$ ($[M+H]^+$) 545.27178, found 545.27093.



3-175

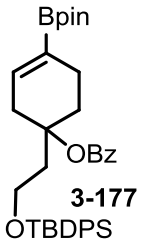
1-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-oxocyclohexyl benzoate (3-175). To a solution of **3-174** (280 mg, 0.514 mmol) in acetone (60 mL) was added *p*-TSA-H_2O (147 mg, 0.771 mmol) and the reaction mixture was heated at 45 ℃ for 24 h. The reaction was concentrated *in vacuo* and quenched by adding sat. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3x5 mL) and the combined organic layers were washed with brine (5 mL) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:10) to afford **3-175** (209 mg, 0.417 mmol, 81%) as colorless oil. IR (neat) 3071, 2958, 2930, 2888, 2856, 1712, 1600, 1588, 1548, 1488, 1462, 1472, 1450, 1390, 1427, 1362, 1313, 1285, 1262, 1220, 1175, 1109, 1095, 1070, 1026, 1007, 999, 909, 848, 821, 735, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.4, 1.4 Hz, 2 H), 7.72 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.61 (dd, *J* = 6.6, 1.5 Hz, 5 H), 7.58-7.53 (m, 1 H), 7.44 (t, *J* = 7.9 Hz, 2 H), 7.41-7.36 (m, 3 H), 7.33 (d, *J* = 7.5 Hz, 3 H), 7.30 (t, *J* = 1.4 Hz, 1 H), 3.80 (t, *J* = 6.4 Hz, 2 H), 2.91-2.82 (m, 2 H), 2.57 (td, *J* = 14.8, 6.0 Hz, 2 H), 2.42 (t, *J* = 6.3 Hz, 2 H), 2.37-2.28 (m, 2 H), 1.96 (td, *J* = 13.8, 4.9 Hz, 2 H), 1.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 165.6, 135.6, 134.9, 133.4, 133.2, 131.0, 129.8, 129.8, 129.6, 128.6, 127.8, 127.8, 127.7, 82.0, 59.8, 39.4, 37.0, 35.0, 26.9, 26.7, 19.2; HRMS (ESI) m/z calcd for $C_{31}H_{37}O_4Si$ ($[M+H]^+$) 501.24556, found 501.24430.



3-176

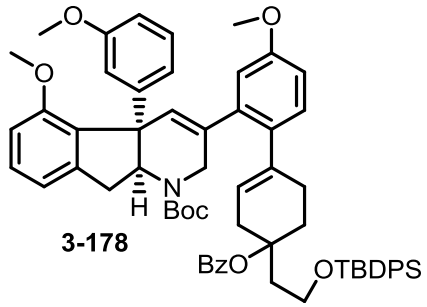
1-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl benzoate (3-176). To a solution of **3-175** (175 mg, 0.350 mmol) in THF (1 mL) at -78 ℃ was added LiHMDS (76.0 mg, 0.454 mmol) in THF (1 mL). The reaction mixture was stirred at -78 ℃ for 30 min and and $PhNTf_2$ (150 mg, 0.419 mmol) in THF (1 mL) was added into the reaction mixture via syringe. The reaction mixture was stirred at -78 ℃ for 1 h allowed to warm to room temperature and stirred at room temperature for 12 h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted

with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:20) to yield **3-176** (120 mg, 0.190 mmol, 54%) as colorless oil: IR (neat) 3072, 2931, 2858, 1713, 1601, 1473, 1451, 1417, 1314, 1284, 1260, 1245, 1207, 1177, 1141, 1111, 1084, 1068, 1026, 969, 938, 864, 823, 738, 702, 687 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.3 Hz, 2 H), 7.63 (d, *J* = 7.7 Hz, 4 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.41 (dt, *J* = 19.9,7.7 Hz, 4 H), 7.33 (t, *J* = 6.4 Hz, 4 H), 5.70 (m, 1 H), 3.80 (td, *J* = 6.1, 1.1 Hz, 2 H), 3.01 (dd, *J* = 18.2, 2.8 Hz, 1 H), 2.77 (m, 2 H), 2.60 (dd, *J* = 18.3, 2.2 Hz, 1 H), 2.51 (dt, *J* = 14.6, 6.2 Hz, 2 H), 2.42-2.31 (m, 2 H), 2.02-1.95 (ddd, *J* = 13.6, 9.9, 6.2 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 148.1, 135.6, 133.4, 133.4, 133.1, 130.9, 129.8, 129.8, 129.6, 128.4, 127.8, 121.8, 119.7, 117.6, 115.4, 115.4, 80.5, 59.8, 38.7, 34.8, 31.3, 26.9, 24.9, 19.1; HRMS (ESI) m/z calcd for $C_{32}H_{36}O_6F_3SSi$ ($[M+H]^+$) 633.19485, found 633.19342.



1-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl benzoate (3-177). To a Schlenk flask with a magnetic stir bar was added **3-176** (45.0 mg, 0.0711 mmol), PPh_3 (1.9 mg, 0.0071 mmol), $Pd(PPh_3)_2Cl_2$ (2.5 mg, 0.0036 mmol), bis(pinacolato)diboron (19.9 mg, 0.0782 mmol), PhOK (9.2 mg, 0.11 mmol) and toluene (710 μL). The reaction mixture was degassed with freeze pump thaw cycles for 3 times. The reaction mixture was stirred at 50 ℃ for 6 h. The reaction was quenched adding H_2O (10 mL). The mixture was extracted with EtOAc (3x10 mL) and the combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (Et_2O:hexanes, 1:40 to EtOAc :hexanes, 1:15) to afford **3-177** (22.3 mg, 0.365 mmol, 51%) as light brown oil: IR (neat) 3071, 2961, 2930, 2891, 2857, 1712, 1637, 1602, 1589, 1472, 1450, 1428, 1388, 1371, 1314, 1285, 1214, 1175, 1144, 1112, 1082, 1026,

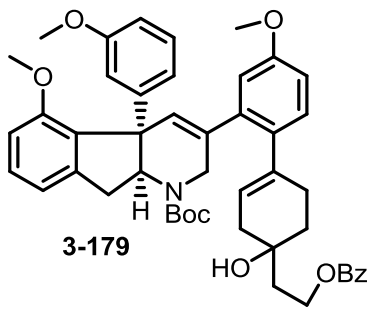
1012, 999, 964, 937, 910, 857, 823, 736, 703, 688, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.1, 1.3 Hz, 2 H), 7.61 (dt, *J* = 8.0, 1.6 Hz, 4 H), 7.51 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.41-7.33 (m, 4 H), 7.33-7.26 (m, 4 H), 6.46 (m, 1 H), 3.78 (t, *J* = 6.6 Hz, 2 H), 2.84 (dd, *J* = 19.0, 2.2 Hz, 1 H), 2.53 (dd, *J* = 19.6, 2.7 Hz, 1 H), 2.48-2.39 (m, 2 H), 2.37-2.27 (m, 1 H), 2.25-2.17 (m, 2 H), 1.85-1.74 (m, 1 H), 1.26 (d, *J* = 1.9 Hz, 12 H), 1.00 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 139.5, 135.6, 135.6, 133.7, 132.6, 131.7, 129.7, 128.3, 127.7, 83.3, 82.3, 59.9, 39.0, 37.7, 31.1, 26.9, 25.0, 24.9, 23.8, 19.2; HRMS (ESI) m/z calcd for $C_{37}H_{47}O_5BSi$ ($[M+H]^+$) 611.33586, found 611.33574.



3-178

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-(benzoyloxy)-4'-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-178).** To a flask was added **3-152** (40.0 mg, 0.0625 mmol), **3-177** (57.3 mg, 0.0938 mmol) and $PdCl_2$(dppf) (2.3 mg, 0.0031 mmol) and the flask was purged with N_2. To this flask was added THF (7.2 mL, degassed with freeze pump thaw cycles for three times) and 10% NaOH solution in H_2O (2.4 mL, degassed with freeze pump thaw cycles for three times). The reaction mixture was stirred at room temperature for 36 h. The reaction was quenched by adding H_2O (5 mL). The resulting mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO2 (EtOAc:hexanes, 1:10) to afford **3-178** (40.1 mg, 0.0402 mmol, 64%) as colorless oil: IR (neat) 2933, 2857, 2835, 1691, 1601, 1587, 1564, 1480, 1450, 1427, 1417, 1391, 1363, 1343, 1314, 1287, 1259, 1211, 1164, 1112, 1079, 1043, 1025, 970, 895, 850, 824, 775, 735, 705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, mixture of diasteromers) δ 7.99 (d, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 7.6 Hz, 1 H),

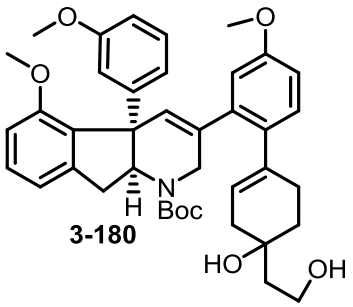
7.67 (d, *J* = 6.5 Hz, 4 H), 7.57-7.52 (m, 1 H), 7.46-7.37 (m, 5 H), 7.37-7.30 (m, 4 H), 7.23-7.09 (m, 2 H), 7.00-6.91 (m, 2 H), 6.90-6.84 (m, 2 H), 6.84-6.71 (m, 4 H), 6.66 (dd, *J* = 19.9, 8.2 Hz, 1 H), 6.00 (s, 0.5 H), 5.90 (s, 0.5 H), 5.40 (s, 0.5 H), 5.37 (s, 0.5 H), 5.12-4.90 (m, 1 H), 4.86 (d, *J* = 18.3 Hz, 1 H), 3.82 (s, 3 H), 3.81-3.75 (m, 3 H), 3.74 (s, 3 H), 3.51 (s, 1.5 H), 3.50 (s, 1.5 H), 3.23-2.85 (m, 2 H), 2.73-2.53 (m, 1 H), 2.53-2.33 (m, 1 H), 2.33-1.95 (m, 5 H), 1.53-1.35 (m, 9 H), 1.18-1.11 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of diastereomers) δ 165.7, 159.4, 158.5, 158.3, 156.3, 156.3, 154.8, 154.7, 147.8, 147.8, 142.4, 139.8, 137.3, 135.9, 135.6, 135.1, 135.0, 133.7, 132.7, 132.6, 132.1, 132.0, 131.7, 130.4, 129.7, 129.6, 129.5, 129.3, 128.8, 128.3, 128.3, 127.7, 126.3, 122.6, 122.4, 119.3, 119.2, 117.7, 117.5, 114.8, 112.7, 111.1, 109.9, 109.9, 81.7, 81.7, 79.3, 79.5, 63.3, 60.0, 59.9, 55.6, 55.5, 55.4, 55.3, 55.2, 55.1, 42.1, 39.0, 36.3, 36.2, 33.2, 33.1, 30.8, 30.6, 28.5, 28.1, 28.0, 26.9, 19.2, 14.2; HRMS (ESI) m/z calcd for $C_{56}H_{64}O_6NSi$ ($[M\text{-}OBz]^+$) 874.44974, found 874.44934.



3-179

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-(2-(benzoyloxy)ethyl)-4'-hydroxy-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-179).** To a solution of **3-178** (89.3 mg, 0.0896 mmol) in THF (3.7 mL) at 0 ℃ was added TBAF (23.4 mg, 0.448 mmol, 448 μL 1 M solution in THF) and the reaction mixture was stirred warmed to room temperature and stirred at room temperature for 12 h. The reaction was quenched by adding sat. $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (3x5 mL) and the combined organic layers were washed with brine (5 mL) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:4) to afford **3-179** (52.4 mg, 0.0691 mmol, 77%) as colorless oil: IR (neat) 3482, 2934, 2835, 1717, 1688, 1601, 1586, 1563, 1480, 1451, 1420, 1364, 1392,

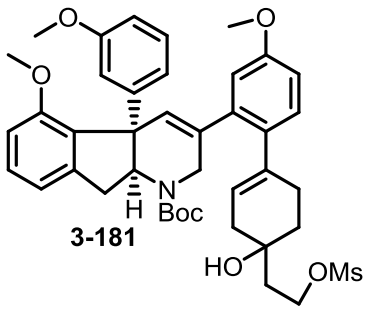
1345, 1315, 1268, 1210, 1164, 1114, 1079, 1043, 1026, 967, 894, 809, 776, 734, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, one of mixture of diastereomers) δ 8.06 (d, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.25-7.18 (m, 1 H), 7.16-7.12 (t, *J* = 7.9 Hz, 1 H), 7.12-7.08 (m, 1 H), 6.86 (t, *J* = 8.0 Hz, 1 H), 6.82-6.66 (m, 6 H), 5.98 (s, 0.5 H), 5.92 (s, 0.5 H), 5.69 (s, 0.5 H),5.48 (s, 0.5 H), 5.00 (d, *J* = 19.4 Hz, 1 H), 4.98-4.92 (m, 1 H), 4.65-4.50 (m, 2 H), 3.80 (s, 1.5 H), 3.77 (s, 1.5 H), 3.73 (s, 1.5 H), 3.71 (s, 1.5 H), 3.64 (t, *J* = 18.5 Hz, 1 H), 3.51 (s, 1.5 H), 3.50 (s, 1.5 H), 3.10 (dd, *J* = 25.5, 10.2 Hz, 1 H), 3.01 (dd, *J* = 15.1, 8.4 Hz, 1 H), 2.57-2.46 (m, 1 H), 2.42-2.21 (m, 2 H), 2.20-2.06 (m, 2 H), 2.06-1.88 (m, 2 H), 1.76 (d, *J* = 11.8 Hz, 0.5 H), 1.56 (d, *J* = 11.8 Hz, 0.5 H), 1.48-1.35 (m, 2 H), 1.15-1.05 (m, 9 H);^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 166.8, 166.7, 159.5, 158.3, 158.2, 156.3, 154.9, 154.8, 148.0, 147.9, 142.5, 139.5, 137.7, 137.1, 136.4, 135.3, 134.7, 133.0, 132.9, 132.2, 132.1, 130.7, 130.6, 129.8, 129.7, 129.6, 129.2, 128.8, 128.7, 128.5, 128.5, 126.8, 126.3 123.7, 123.1, 119.3, 117.6, 116.5, 115.6, 113.1, 112.8, 112.4, 112.2, 111.2, 110.9, 110.0, 80.0, 68.6, 68.0, 63.4, 61.7, 61.6, 55.6, 55.5, 55.2, 55.1, 41.8, 41.1, 40.2, 38.6, 38.1, 34.6, 33.7, 33.0, 32.8, 28.0, 28.0, 27.9, 27.0; HRMS (ESI) m/z calcd for $C_{47}H_{52}O_8N$ ($[M+H]^+$) 758.36929, found 758.37133.



3-180 (from **3-179**)

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-hydroxy-4'-(2-hydroxyethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-181).** To a solution of **3-180** (52.4 mg, 0.0691 mmol) in MeOH (2.0 mL) was added K_2CO_3 (95.5 mg, 0.691 mmol) and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by adding H_2O (5 mL) and the mixture was extracted with EtOAc (3x5 mL) and the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$), and concentrated *in vacuo*.

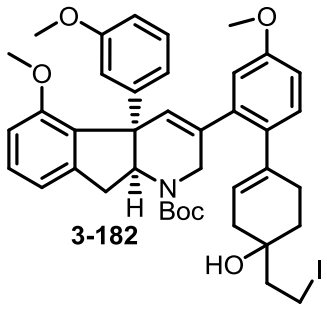
The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1) to afford **3-181** (45.2 mg, 0.0401 mmol, 89%) as colorless oil: IR (neat) 3420, 3002, 2935, 2836, 1676, 1601, 1587, 1563, 1480, 1466, 1420, 1392, 1365, 1345, 1317, 1288, 1257, 1224, 1210, 1164, 1140, 1114, 1080, 1044, 1021, 968, 909, 853, 809, 826, 776, 732, 707, 663 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$, mixture of diastereomers) δ 7.26-7.21 (m, 1 H), 7.19-7.15 (m, 1 H), 7.14 (d, *J* = 8.5 Hz, 0.5 H), 7.05 (d, *J* = 8.3 Hz, 0.5 H), 6.89 (t, *J* = 7.2 Hz, 1 H), 6.82-6.71 (m, 5 H), 6.70 (s, 0.5 H), 6.66 (s, 0.5 H), 5.98 (s, 0.5 H), 5.96 (s, 0.5 H), 5.71 (s, 0.5 H), 5.56 (s, 0.5 H), 5.03-4.92 (m, 2 H), 3.96-3.83 (m, 3 H), 3.78 (s, 1.5 H), 3.77 (s, 1.5 H), 3.61 (dd, *J* = 34.6, 18,5 Hz, 1 H), 3.53 (s, 1.5 H), 3.52 (s, 1.5 H), 3.15-3.07 (m, 1 H), 3.05-2.98 (m, 1 H), 2.61-2.50 (m, 1 H), 2.40 (t, *J* = 16.8 Hz, 1 H), 2.31-2.11 (m, 3 H), 1.91-1.53 (m, 5 H), 1.53-1.36 (m, 2 H), 1.26-1.08 (m, 9 H) ; ^{13}C NMR (175 MHz, $CDCl_3$, mixture of diastereomers) δ159.6, 159.5, 158.4, 158.2, 156.3, 155.1, 154.9, 148.1, 148.0, 142.5, 139.6, 139.3, 138.0, 137.3, 136.9, 136.8, 135.5, 134.7, 132.3, 132.0. 130.1, 129.7, 129.2, 128.8, 126.6, 126.3, 124.0, 119.4, 119.3, 117.6, 116.8, 116.2, 113.4, 112.9, 112.2, 112.2, 110.7, 110.0, 80.2, 80.1, 71.0, 70.7, 63.5, 63.4, 59.6, 55.6, 55.5, 55.2, 43.1, 42.1, 41.6, 41.2, 39.0, 38.4, 34.5, 33.7, 32.9, 32.7, 29.8, 28.0, 28.0, 27.6; HRMS (ESI) m/z calcd for $C_{40}H_{47}O_7NNa$ ($[M+Na]^+$) 676.32447, found 676.32232.



3-181

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-hydroxy-4-methoxy-4'-(2-((methylsulfonyl)oxy)ethyl)-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-181).** To a solution of **3-180** (40.1 mg, 0.0613 mmol) in CH_2Cl_2 (0.6 mL) was added Et_3N (31.0 mg, 0.307 mmol) and MsCl (14.1 mg, 0.123 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by adding H_2O (5 mL) and

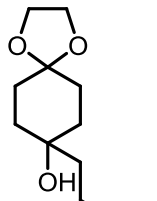
the resulting mixture was extracted with EtOAc (3x4 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 2:3) to afford **3-181** (40.4 mg, 0.0552 mmol, 90%) as colorless oil: IR (neat) 3472, 2937, 2836, 1677, 1601, 1587, 1564, 1480, 1419, 1392, 1357, 1288, 1257, 1224, 1210, 1170, 1140, 1114, 1079, 1043, 1020, 971, 950, 909, 852, 826, 808, 776, 729, 707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.24 (td, *J* = 7.8, 3.7 Hz, 1 H), 7.20-7.12 (m, 1.5 H), 7.04 (d, *J* = 8.4 Hz, 0.5 H), 6.89 (d, *J* = 7.2 Hz, 1 H), 6.82-6.66 (m, 6 H), 5.98 (s, 0.5 H), 5.93 (s, 0.5 H), 5.70 (s, 0.5 H), 5.51 (s, 0.5 H), 5.04-4.93 (m, 2 H), 4.55-4.42 (m, 2 H), 3.79 (s, 1.5 H), 3.77 (s, 1.5 H), 3.74 (s, 3 H), 3.68-3.56 (m, 1 H), 3.53 (s, 1.5 H), 3.51 (s, 1.5 H), 3.13-3.04 (m, 1 H), 3.02 (s, 3 H), 2.58-2.44 (m, 1 H), 2.44-2.33 (m, 1 H), 2.32-2.06 (m, 2 H), 2.06-1.82 (m, 2 H), 1.78-1.21 (m, 4 H), 1.19-1.02 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 159.5, 158.4, 158.2, 156.3, 155.0, 154.8, 148.0, 148.0, 142.5, 139.5, 139.3, 137.9, 137.2, 136.9, 136.5, 135.2, 134.4, 132.2, 132.0, 129.9, 119.7, 129.2, 128.8, 126.8, 126.3, 123.5, 122.9, 119.3, 117.6, 116.8, 115.9, 113.3, 112.9, 112.3, 112.1, 111.1, 110.7, 110.0, 110.0, 80.0, 79.9, 68.2, 67.6, 67.3, 67.1, 63.4, 63.4, 55.6, 55.5, 55.2, 55.2, 41.7, 41.6, 41.1, 40.6, 38.8, 38.1, 37.4, 34.6, 33.7, 32.9, 32.7, 28.0, 27.9, 27.5, 26.7; HRMS (ESI) m/z calcd for $C_{41}H_{50}O_9NS$ ($[M+H]^+$) 732.32063, found 732.31990.



3-182

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-hydroxy-4'-(2-iodoethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridine-1-carboxylate (3-182).** To a solution of **3-181** (6.9 mg, 0.0094 mmol) in THF (0.5 mL) was added LiI (2.5 mg, 0.019 mmol) and the reaction mixture was heated at 60 ℃ for 8 h. The reaction was cooled to room

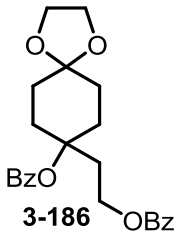
temperature and was quenched by adding 10% aqueous $Na_2S_2O_3$ solution (5 mL). The reaction mixture was extracted with EtOAc (3x5 mL) and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:5) to afford **3-182** (6.4 mg, 0.0084 mmol, 89%) as colorless oil: IR (neat) 3469, 3004, 2934, 2835, 1736, 1674, 1601, 1586, 1563, 1479, 1465, 1438, 1420, 1392, 1363, 1345, 1317, 1287, 1253, 1224, 1210, 1162, 1140, 1115, 1-78, 1043, 969, 907, 855, 825, 808, 774, 728, 706, 664 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.24 (td, *J* = 7.7, 3.4 Hz, 1 H), 7.19-7.11 (m, 1.5 H), 7.04 (d, *J* = 8.3 Hz, 0.5 H), 6.89 (dd, *J* = 7.2, 3.5 Hz, 1 H), 6.82-6.66 (m, 6 H), 5.98 (s, 0.5 H), 5.92 (s, 0.5 H), 5.70 (s, 0.5 H), 5.49 (s, 0.5 H), 5.02-4.92 (m, 2 H), 3.79 (s, 1.5 H), 3.77 (s, 1.5 H), 3.74 (s, 1.5 H), 3.73 (s, 1.5 H), 3.69-3.56 (m, 1 H), 3.53 (s, 1.5 H), 3.52 (s, 1.5 H), 3.43-3.35 (m, 1 H), 3.35-3.28 (m, 2 H), 3.15-3.06 (m, 1 H), 3.05-2.98 (m, 1 H), 2.55-2.45 (m, 1 H), 2.38 (d, *J* = 16.9 Hz, 1 H), 2.25-2.02 (m, 6 H), 1.86-1.61 (m, 1 H), 1.57-1.33 (m, 4 H), 1.20-1.05 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of diastereomers) δ159.5, 159.5, 158.3, 158.2, 156.3, 156.3, 154.9, 154.8, 148.1, 142.5, 139.5, 137.8, 137.3, 137.1, 135.3, 134.5, 132.1, 129.9, 129.6, 129.2, 128.8, 128.8, 126.8, 126.3, 123.4, 122.9, 119.3, 117.6, 117.5, 116.8, 115.8, 113.3, 112.8, 112.3, 112.1, 111.1, 110.7, 110.0, 80.0, 79.9, 63.4, 55.6, 55.5, 55.5, 55.2, 55.2, 48.3, 47.2, 41.7, 41.1, 38.0, 37.5, 34.0, 33.0, 32.9, 32.7, 31.7, 28.0, 28.0, 27.5, 26.8, 14.2, 0.0, -0.3; HRMS (ESI) m/z calcd for $C_{40}H_{47}O_6NI$ ($[M+H]^+$) 764.24426, found 764.24557.



3-185

2-(8-Hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)ethyl benzoate (3-185). To a solution of **3-172** (35 mg, 0.173 mmol) and DMAP (2.1 mg, 0.017 mmol) in CH_2Cl_2 (2.0 mL) at 0 ℃ was added BzCl (122 mg, 865 mmol) and Et_3N (175 mg, 1.73 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Upon completion, saturated $NaHCO_3$ solution (5 mL) was added to the reaction

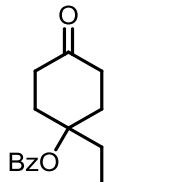
mixture and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography on SiO_2 (EtOAc:hexanes, 1:3) to afford **3-185** (34.2 mg, 0.112 mmol, 65%) as pale yellow oil: IR (neat) 3488, 2929, 2884, 1715, 1602, 1584, 1451, 1370, 1315, 1273, 1170, 1109, 1095, 1035, 1026, 1002, 947, 934, 887, 808, 771, 709, 687, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.5, 1.4 Hz, 2 H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 4.52 (t, *J* = 6.6 Hz, 2 H), 3.98-3.90 (m, 4 H), 1.98 (t, *J* = 6.6 Hz, 2 H), 1.95-1.85 (m, 2 H), 1.79-1.70 (m, 4 H), 1.65-1.57 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 133.1, 130.3, 129.6, 128.5, 108.7, 70.0, 64.4, 64.3, 61.5, 40.7, 35.2, 30.6; HRMS (ESI) m/z calcd for $C_{17}H_{23}O_5$ ($[M+H]^+$) 307.15400, found 307.15530.



3-186

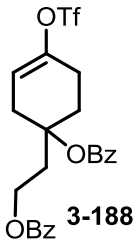
2-(8-(Benzoyloxy)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl benzoate (3-186). To a solution of **3-185** (34.2 mg, 0.112 mmol) in THF (2 mL) under N_2 at -78 ℃ was added *n*BuLi (14.3 mg, 0.223 mmol, 140 μL 1.6 M solution in THF) via syringe. The resulting reaction mixture was stirred at -78 ℃ for 1 h and was added benzoyl chloride (78.5 mg, 0.558 mmol, 65 μL) via syringe and was stirred for 1 h at -78 ℃. The reaction mixture was slowly warmed to room temperature was stirred for 12 h. The reaction was quenched by adding H_2O (5 mL) and the mixture was extracted with EtOAc (3x4 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:6) to afford **3-186** (41.2 mg, 0.100 mmol, 90%) as colorless oil: IR (neat) 3062, 2958, 2935, 2883, 1710, 1601, 1584, 1491, 1450, 1380, 1361, 1316, 1272, 1246, 1176, 1163, 1108, 1094, 1070, 1036, 1026, 1001, 967, 946, 922, 873, 847, 829, 806, 772, 708, 687, 671 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 2 H), 7.91 (d, *J* = 7.2 Hz, 2 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.38 (t, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 7.7

Hz, 2 H), 4.44 (t, *J* = 6.5 Hz, 2 H), 3.95 (s, 3 H), 2.66-2.61 (m, 2 H), 2.60 (t, *J* = 6.5 Hz, 2 H), 1.91-1.80 (m, 4 H), 1.69 (d, *J* = 11.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 165.7, 132.9, 132.9, 131.1, 130.8, 129.6, 129.6, 128.4, 128.3, 108.1 81.9, 64.5, 64.4, 60.9, 36.0, 32.6, 30.6; HRMS (ESI) m/z calcd for $C_{24}H_{26}O_6Na$ ($[M+Na]^+$) 433.12616, found 433.16283.



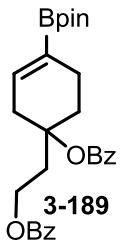
3-187

2-(1-(Benzoyloxy)-4-oxocyclohexyl)ethyl benzoate (3-187). To a solution of **3-186** (41.2 mg, 0.100 mmol) in THF (3 mL) at room temperature was added aqueous HCl (3.7 mg, 3.0 mmol, 1 mL 3 M solution in H_2O). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by adding sat. $NaHCO_3$ (5 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:5) to afford **3-187** (31.6 mg, 0.00862 mmol, 86%) as colorless oil: IR (neat) 3602, 2963, 2931, 1708, 1601, 1584, 1491, 1451, 1393, 1328, 1314, 1268, 1221, 1176, 1144, 1107, 1096, 1070, 1025, 1000, 957, 937, 892, 850, 832, 807, 707, 687, 676 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2 H), 7.90 (d, *J* = 7.2 Hz, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 7.7 Hz, 2 H), 4.49 (t, *J* = 6.4 Hz, 2 H), 2.99-2.92 (m, 2 H), 2.67 (t, *J* = 6.4 Hz, 2 H), 2.61 (td, *J* = 14.5, 5.9 Hz, 2 H), 2.39 (dt, *J* = 15.5, 2.3 Hz, 2 H), 1.98 (td, *J* = 13.7, 4.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 166.5, 165.6, 133.3, 133.0, 130.6, 129.9, 129.6, 129.5, 128.6, 128.4, 81.0, 60.7, 36.8, 35.7, 34.7; HRMS (ESI) m/z calcd for $C_{22}H_{23}O_5$ ($[M+H]^+$) 367.15400, found 367.15585.



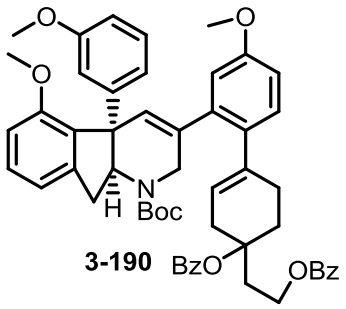
3-188

2-(1-(Benzoyloxy)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)ethyl benzoate (3-188). To a solution of **3-187** (31.6 mg, 0.0862 mmol) in THF (1 mL) at -78 ℃ was added LiHMDS (28.9 mg, 0.172 mmol) in THF (0.2 mL). The reaction mixture was stirred at -78 ℃ for 30 min and $PhNTf_2$ (46.2 mg, 0.129 mmol) in THF (5.0 mL) was added into the reaction mixture via syringe. The reaction mixture was stirred at -78 ℃ for 1 h allowed to warm to room temperature and stirred at room temperature for 12 h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (Et_2O:hexanes, 1:20) to yield **3-188** (35.7 mg, 0.0716 mmol, 83%) as colorless oil: IR (neat) 3185, 3065, 2960, 2924, 2850, 1714, 1695, 1601, 1585, 1495, 1452, 1416, 1379, 1316, 1275, 1245, 1203, 1139, 1112, 1096, 1065, 1026, 978, 945, 866, 819, 752, 709, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, *J* = 7.2 Hz, 4 H), 7.48-7.39 (m, 2 H), 7.31 (t, *J* = 7.8 Hz, 3 H), 7.26 (t, *J* = 7.5 Hz, 3 H), 7.23-1.17 (m, 2 H), 5.67-5.62 (m, 1 H), 4.41 (t, *J* = 6.3 Hz, 2 H), 2.97 (dq, *J* = 17.2, 2.2 Hz, 1 H), 2.81-2.63 (m, 2 H), 2.55-2.39 (m, 3 H), 2.39-2.28 (m, 1 H), 1.91 (ddd, *J* = 15.9, 10.0, 6.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.0, 148.1, 133.9, 133.3, 133.2, 130.5, 129.8, 129.8, 129.6, 129.6, 128.5, 128.4, 127.6, 123.7, 121.5, 120.2, 118.3, 117.0, 115.0, 79.6, 60.6, 35.1, 34.5, 31.2, 24.8; HRMS (ESI) m/z calcd for $C_{23}H_{21}O_7F_3NaS$ ($[M+Na]^+$) 521.08523, found 521.08538.



3-189

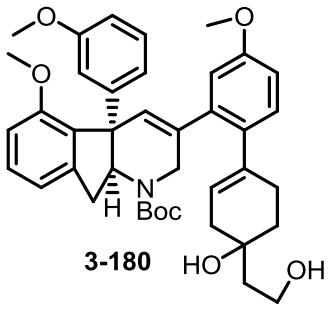
2-(1-(Benzoyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)ethyl benzoate (3-189). To a Schlenk flask with a magnetic stir bar was added **3-188** (60.0 mg, 0.120 mmol), PPh_3 (3.2 mg, 0.012 mmol), $Pd(PPh_3)_2Cl_2$ (4.2 mg, 0.0060 mmol), bis(pinacolato)diboron (42.8 mg, 0.169 mmol), PhOK (47.7 mg, 0.361 mmol) and toluene (1.3 mL). The reaction mixture was degassed with freeze pump thaw cycles for 3 times. The reaction mixture was stirred at 50 ℃ for 5 h. The reaction was quenched adding H_2O (10 mL). The mixture was extracted with EtOAc (3x10 mL) and the combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (Et_2O:hexanes, 1:40 to EtOAc :hexanes, 1:15) to afford **3-189** (44.3 mg, 0.0930 mmol, 77%) as light brown oil: IR (neat) 3003, 2977, 2923, 2849, 1712, 1638, 1602, 1584, 1451, 1417, 1388, 1372, 1314, 1272, 1214, 1176, 1143, 1111, 1070, 1026, 1013, 910, 856, 831, 805, 732, 707, 687, 677, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (td, *J* = 9.8, 1.2 Hz, 4 H), 7.57-7.45 (m, 2 H), 7.39-7.29 (m, 4 H), 6.51-6.46 (m, 1 H), 4.47 (t, *J* = 6.6 Hz, 2 H), 2.89 (d, *J* = 18.9, 2.0 Hz, 1 H), 2.68-2.55 (m, 3H), 2.55-2.43 (m, 1 H), 2.33-2.45 (m, 2 H), 1.96-1.86 (m, 1 H), 1.25 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.9, 139.0, 132.9, 132.8, 131.4, 130.1, 129.7, 129.7, 129.6, 128.3, 83.4, 81.5, 61.0, 37.4, 34.9, 31.0, 24.9, 23.8; HRMS (ESI) m/z calcd for $C_{28}H_{33}O_6BNa$ ($[M+Na]^+$) 499.22624, found 499.22644.



3-190

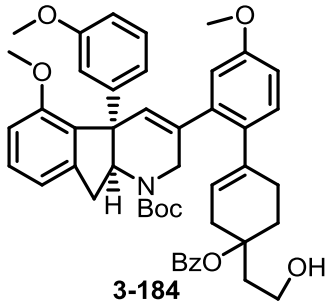
***tert*-Butyl (4a*S*,9a*S*)-3-(4'-(benzoyloxy)-4'-(2-(benzoyloxy)ethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4*a*-(3-methoxyphenyl)-2,4*a*,9,9*a*-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-190).** To a flask was added **3-152** (25.0 mg, 0.0391 mmol), **3-189** (37.2 mg, 0.0782 mmol) and $PdCl_2$(dppf) (2.9 mg, 0.0039 mmol) and the flask was purged with N_2. To this flask

was added THF (3.0 mL, degassed with freeze pump thaw cycles for three times) and 10% NaOH solution in H_2O (1.0 mL, degassed with freeze pump thaw cycles for three times). The reaction mixture was stirred at room temperature for 36 h. The reaction was quenched by adding H_2O (5 mL). The resulting mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:10) to afford **3-190** (21.3 mg, 0.0247 mmol, 63%) as colorless oil: IR (neat) 3062, 3003, 2961, 2931, 2836, 1712, 1689, 1601, 1585, 1564, 1480, 1455, 1450, 1417, 1391, 1364, 1343, 1315, 1266, 1224, 1212, 1165, 1112, 1079, 1070, 1043, 1025, 1001, 968, 909, 875, 852, 825, 808, 785, 777, 731, 710, 688, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.01-7.89 (m, 4 H), 7.57-7.48 (m, 2 H), 7.43-7.31 (m, 5 H), 7.22-7.12 (m, 2 H), 6.96-6.83 (m, 3 H), 6.80-6.64 (m, 5 H), 5.99 (s, 0.5 H), 5.88 (s, 0.5 H), 5.41 (s, 1 H), 5.06-4.82 (m, 2 H), 4.55-4.40 (m, 2 H), 3.81 (s, 1.5 H), 3.80 (s, 1.5 H), 3.73 (s, 1.5 H), 3.72 (s, 1.5 H), 3.50 (s, 1.5 H), 3.49 (s, 1.5 H), 3.16-2.90 (m, 2 H), 2.75-2.55 (m, 3 H), 2.50-2.40 (m, 1 H), 2.39-2.05 (m, 5 H), 1.94 (td, *J* = 13.8, 4.7 Hz, 0.5 H), 1.45-1.20 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 166.6, 165.9, 165.9, 165.7, 159.5, 158.6, 158.3, 156.4, 156.4, 154.9, 154.7, 147.8, 142.5, 139.8, 139.2, 138.3, 137.4, 135.9, 135.0, 134.9, 133.4, 133.1, 132.9, 132.9, 132.8, 132.2, 132.1, 131.5, 131.4, 130.6, 130.4, 130.2, 129.9, 129.6, 129.6, 129.5, 129.5, 129.4, 129.3, 128.8, 128.6, 128.4, 128.4, 128.4, 127.2, 126.4, 122.3, 122.0, 119.3, 119.2, 117.8, 117.5, 115.0, 114.6, 112.9, 112.8, 111.1, 110.0, 110.0, 81.1, 81.1, 81.1, 79.7, 79.6, 63.3, 61.0, 60.7, 55.6, 55.4, 55.4, 55.2, 55.2, 42.1, 41.7, 36.8, 35.9, 35.8, 35.2, 34.8, 33.2, 33.1, 30.6, 30.4, 29.8, 28.5, 28.1, 28.0; HRMS (ESI) m/z calcd for $C_{54}H_{56}O_9N$ ($[M+H]^+$) 862.39496, found 862.39611.



3-180 (from **3-190**)

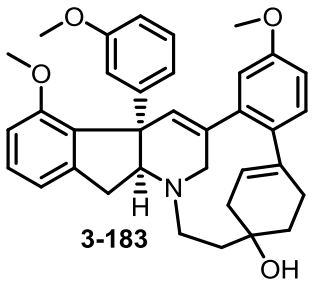
***tert*-Butyl (4a*S*,9a*S*)-3-(4'-hydroxy-4'-(2-hydroxyethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-180).** To a solution of **3-190** (126 mg, 0.146 mmol) in MeOH (2.4 mL) was added K_2CO_3 (202 mg, 1.46 mmol) and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by adding sat. aqueous $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 2:1) to afford **3-180** (90.5 mg, 0.138 mmol, 95%) as colorless oil.



3-184

***tert*-Butyl (4a*S*,9a*S*)-3-(4'-(benzoyloxy)-4'-(2-hydroxyethyl)-4-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-b]pyridine-1-carboxylate (3-184).** To a solution of **3-178** (90.0 mg, 0.0903 mmol) in THF (5.0 mL) at 0 ℃ was added HF-pyridine (1.09 g, 7.77 mmol, 1.0 mL) via syringe and the reaction mixture was warmed to room temperature and stirred at room temperature for 3 h. The reaction mixture was quenched by adding 10% aqueous NaOH solution (3 mL) and the resulting mixture was extracted with EtOAc (3x2 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The

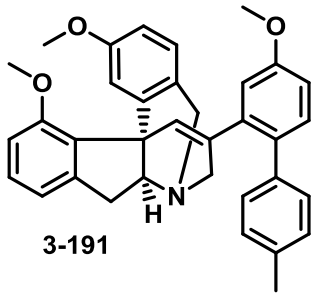
resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:6) to afford **3-184** (49.6 mg, 0.0654 mmol, 72%) as colorless oil: IR (neat) 3472, 2933, 2836, 1736, 1690, 1601, 1586, 1480, 1450, 1418, 1391, 1367, 1344, 1315, 1286, 1247, 1164, 1115, 1078, 1045, 1025, 968, 936, 895, 851, 825, 809, 775, 738, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.5 Hz, 1 H), 7.96 (d, *J* = 7.2 Hz, 1 H), 7.58-7.51 (m, 1 H), 7.46-7.39 (m, 2 H), 7.25-7.13 (m, 2 H), 6.98-6.93 (m, 1 H), 6.90 (d, *J* = 7.4 Hz, 1 H), 6.85 (d, *J* = 2.6 Hz, 1 H), 6.81-6.66 (m, 5 H), 5.98 (s, 0.5 H), 5.88 (s, 0.5 H), 5.48 (s, 0.5 H), 5.44 (s, 0.5 H), 5.07-4.77 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 1.5 H), 3.73 (s, 1.5 H), 3.71-3.64 (m, 1 H), 3.52 (s, 3 H), 3.12-2.90 (m, 2 H), 2.77-2.57 (m, 1 H), 2.57-2.32 (m, 2 H), 2.32-2.06 (m, 4 H), 1.30-1.05 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 159.5, 158.5, 158.2, 156.4, 156.3, 154.9, 154.8, 147.8, 147.6, 142.4, 139.8, 139.2, 138.1, 136.9, 136.2, 135.3, 135.0, 134.9, 132.9, 132.2, 131.9, 131.6, 130.4, 129.5, 129.5, 129.3, 128.8, 128.5, 128.4, 127.0, 126.2, 123.0, 122.6, 119.3, 117.8, 117.5, 115.6, 115.0, 113.0, 112.8, 112.4, 110.9, 110.0, 82.1, 81.8, 79.8, 63.4, 58.7, 55.5, 55.2, 55.2, 55.1, 42.0, 41.7, 39.5, 39.3, 36.1, 33.1, 33.0, 32.0, 30.9, 30.6, 29.8, 28.4, 28.0; HRMS (ESI) m/z calcd for $C_{47}H_{52}O_8N$ ($[M+H]^+$) 758.36874, found 758.37344.



3-183

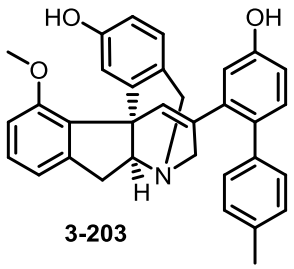
(11a*S*,16b*S*)-2,16-Dimethoxy-16b-(3-methoxyphenyl)-7,9,10,11a,12,16b-hexahydro-8*H*-5,8-ethano-11,18-methanobenzo[*f*]indeno[2,1-*b*][1]azacyclotridecin-8-ol (3-183). To a solution of **3-182** (40.1 mg, 0.0525 mmol) in CH_2Cl_2 (6.5 mL) at 0 ℃ under N_2 was added TFA (838 mg, 7.35 mmol) and the reaction mixture was stirred at 5 ℃ for 24 h. The reaction mixture was diluted with toluene and the mixture was concentrated *in vacuo*. The resulting residue was added toluene and concentrated *in vacuo* for two more times.

The resulting oil was dissolved in CH_3CN (32 mL) and the mixture was added DIPEA (67.8 mg, 0.525 mmol). The reaction mixture was degassed with freeze-pump-thaw cycles for three times, and was heated at 80 ℃ for 36 h. The reaction mixture was cooled to room temperature and was concentrated *in vacuo*. The resulting residue was added sat. $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc:hexanes, 1:1 with 0.5% Et_3N) to afford **3-183** (19.8 mg, 0.0370 mmol, 70%) as pale yellow oil: IR (neat) 3364, 3000, 2934, 2835, 1599, 1562, 1478, 1463, 1437, 1367, 1338, 1288, 1261, 1205, 1172, 1137, 1079, 1040, 1001, 959, 909, 872, 853, 818, 773, 731, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.23 (t, *J* = 7.7 Hz, 1 H), 7.21-7.15 (m, 2 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 7.00 (d, *J* = 2.6 Hz, 1 H), 6.90-6.85 (m, 2 H), 6.80 (ddd, *J* = 14.0, 8.4, 2.7 Hz, 2 H), 6.75-6.69 (m, 3 H), 6.64-6.63 (m, 5 H), 6.56 (d, *J* = 1.8 Hz, 1 H), 5.79 (d, *J* = 6.6 Hz, 1 H), .37 (d, *J* = 6.6 Hz, 1 H), 3.98 (t, *J* = 8.6 Hz, 1 H), 3.85 (s, 2 H), 3.76 (s, 3)H, 3.74 (s, 2 H), 3.73 (s, 3 H), 3.62 (s, 2 H), 3.48 (s, 3 H), 3.26-3.21 (m, 3 H), 3.17-3.11 (m, 1 H), 3.01-2.87 (m, 3 H), 2.87-2.76 (m, 2 H), 2.70-2.63 (m, 1 H), 2.57-2.43 (m, 2 H), 2.43-2.35 (m, 1 H), 2.35-2.26 (m, 2 H), 2.26-2.12 (m, 2 H), 2.05-1.81 (m, 6 H), 1.81-1.67 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 159.7, 159.4, 158.4, 158.4, 158.4, 156.8, 156.4, 152.9, 148.8, 144.3, 143.7, 143.1, 139.1, 135.9, 134.9, 133.9, 133.8, 133.1, 132.1, 129.9, 129.7, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 128.3, 119.4, 119.3, 117.1, 116.8, 115.2, 115.2, 113.3, 112.9, 112.1, 111.9, 110.7, 110.4, 109.9, 109.5, 75.1, 74.4, 72.1, 72.0, 58.9, 55.5, 55.4, 55.1, 53.4, 50.1, 50.0, 54.1, 43.3, 39.2, 38.9, 37.9, 37.5, 36.9, 36.2, 35.4, 34.8, 30.9, 30.7; HRMS (ESI) m/z calcd for $C_{35}H_{38}O_4N$ ($[M+H]^+$) 536.27954, found 536.27879.



3-191

(6a*S*,11b*S*)-2,11-dimethoxy-13-(4-methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-6a,7-dihydro-5*H*-11b,6-prop[1]enoindeno[2,1-*c*]isoquinoline (3-191). To a solution of **3-183** (32.0 mg, 0.0597 mmol) in toluene (18 mL) was added *p*-toluenesulfonic acid monohydrate (160 mg, 0.841 mmol) and H_2O (20.0 mg, 1.11 mmol). The mixture was stirred at reflux for 6 h and was cooled to room temperature. The reaction mixture was diluted with EtOAc (30 mL), washed with 1 M NaOH aqueous solution (10 mL), H_2O (10 mL), brine (5 mL), and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (EtOAc: hexanes, 1:2) to afford **3-191** (22.8 mg, 0.0442 mmol, 74%) as pale yellow oil: IR (neat) 2998, 2926, 2835, 1726, 1676, 1602, 1578, 1478, 1456, 1452, 1352, 1304, 1282, 1262, 1245, 1229, 1206, 1174, 1150, 1129, 1111, 1077, 1046, 1026, 1003, 971, 909, 883, 810, 777, 731, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.5 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz, 2 H), 6.94-6.87 (m, 4 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.79 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.72 (dd, *J* = 8.3, 2.6 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 6.00 (s, 1 H), 4.51 (d, *J* = 17.6 Hz, 1 H), 3.95 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.75-3.66 (m, 1 H), 3.59 (d, *J* = 17.5 Hz, 1 H), 3.57 (dd, *J* = 18.2, 1.4 Hz, 1 H), 2.94 (d, *J* = 18.3 Hz, 1 H), 2.91-2.76 (m, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 157.3, 157.2, 146.1, 144.9, 141.1, 138.3, 136.1, 135.4, 133.1, 131.1, 130.6, 130.3, 129.0, 128.9, 128.7, 126.9, 118.3, 115.1, 112.2, 111.9, 111.2, 109.7, 65.3, 59.3, 55.6, 55.2, 55.0, 53.7, 47.8, 31.8, 29.8, 21.3; HRMS (ESI) m/z calcd for $C_{35}H_{34}O_3N$ ($[M+H]^+$) 516.25332, found 516.25302.



3-203

(6a*S*,11b*S*)-13-(4-hydroxy-4'-methyl-[1,1'-biphenyl]-2-yl)-11-methoxy-6a,7-dihydro-5*H*-11b,6-prop[1]enoindeno[2,1-*c*]isoquinolin-2-ol (3-203). To a solution of **3-191** (21.2 mg, 0.0411 mmol) in CH_2Cl_2 (1.4 mL) at -78 ℃ was added BBr_3 (154 mg, 0.617 mmol, 617 μL 1 M solution in CH_2Cl_2). The flask of the reaction mixture was moved to a 0 ℃ cold bath and the reaction mixture was stirred at 0 ℃ for 20 h. The reaction mixture at 0 ℃ was quenched by adding KH_2PO_4/Na_2HPO_4(pH=7) buffer solution (0.5 mL) followed by EtOAc (2 mL) and MeOH (0.5 mL). The mixture was stirred at 0 ℃ for 20 min and was warmed to room temperature. The resulting mixture was partitioned in sep funnel and the aqueous layer was extracted with a solvent mixture (EtOAc: MeOH, 10:1) (4x2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with column chromatography on SiO_2 (MeOH: CH_2Cl_2, 3:100 to 3.5:100) to afford **3-203** (10.3 mg, 0.0211 mmol, 51%) as white semi-solid: IR (neat) 3250, 2922, 2853, 1671, 1582, 1464, 1264, 1199, 1067, 874, 813, 777, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.2 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 8.3 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 6.87-6.79 (m, 3 H), 6.71 (dd, *J* = 7.5, 2.6 Hz, 1 H), 6.61 (dd, *J* = 8.0, 2.2 Hz, 1 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 5.96 (s, 1 H), 4.48 (d, *J* = 16.1 Hz, 1 H), 3.91 (s, 3 H), 3.67 (t, *J* = 9.6 Hz, 1 H), 3.55 (d, *J* = 17.6 Hz, 2 H), 2.93 (d, *J* = 18.4 Hz, 1 H), 2.88-2.70 (m, 2 H), 2.33 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 157.2, 132.8, 132.6, 131.4, 131.0, 128.9, 128.7, 127.1, 118.2, 116.0, 113.9, 109.9, 68.3, 55.1, 53.6, 38.9, 32.1, 30.5, 29.8, 29.8, 29.5, 29.1, 23.9, 23.1, 22.8; HRMS (ESI) m/z calcd for $C_{33}H_{29}O_3N$ ($[M+H]^+$) 488.22202, found 488.22148.

APPENDIX A

X-RAY DATA

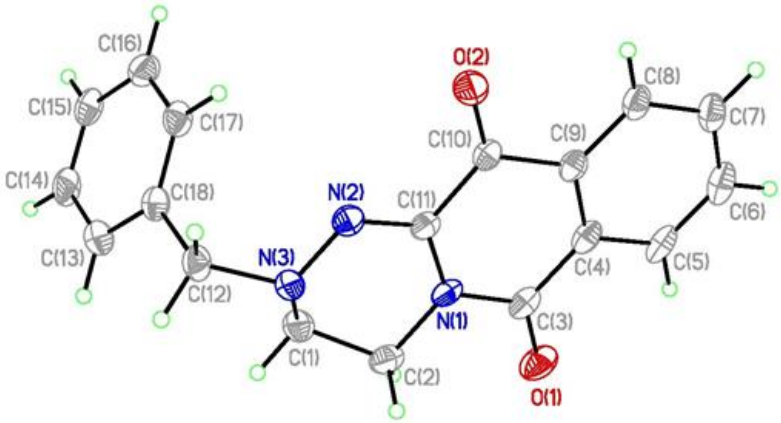


Figure 12 X-ray structure of **1-55**

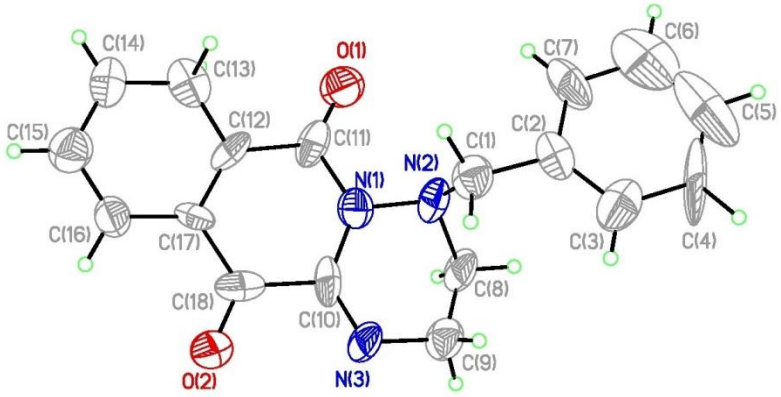


Figure 13 X-ray structure of **1-78**

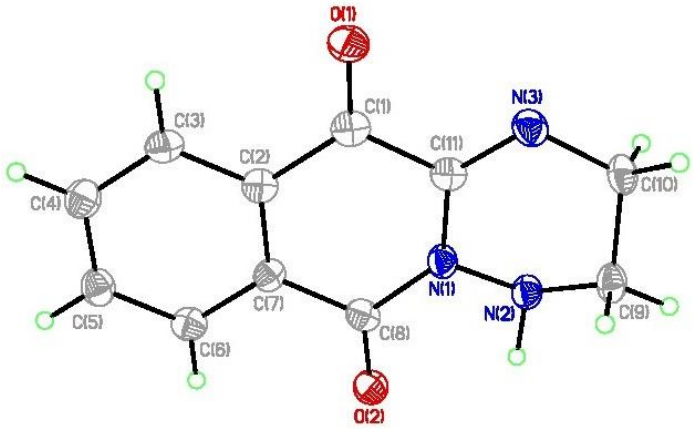


Figure 14 X-ray structure of **1-82**

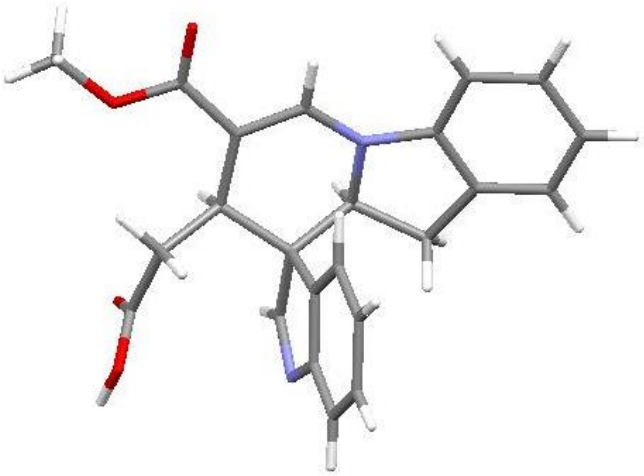


Figure 15 X-ray structure of **2-36**

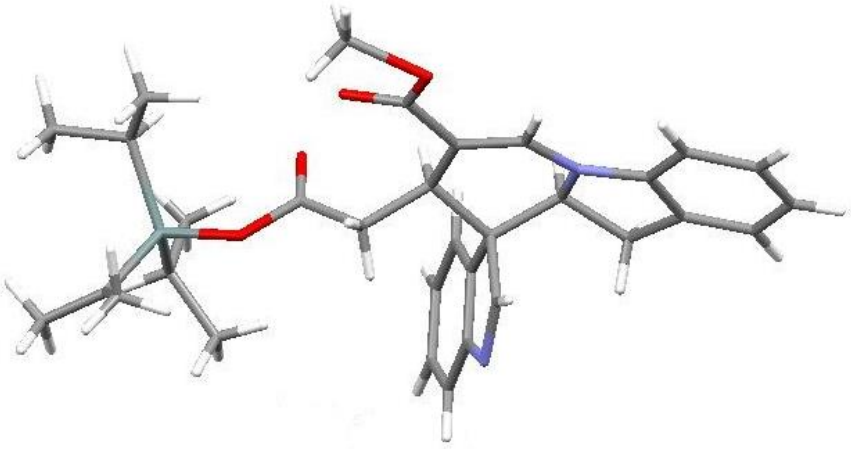


Figure 16 X-ray structure of **2-40**

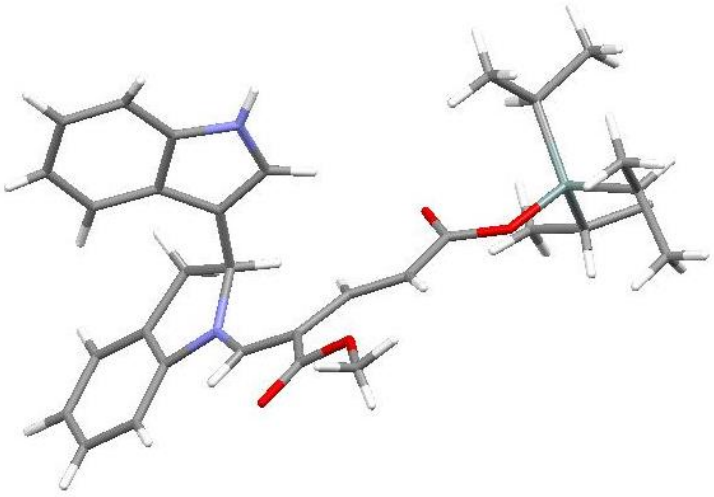


Figure 17 X-ray structure of **2-41**

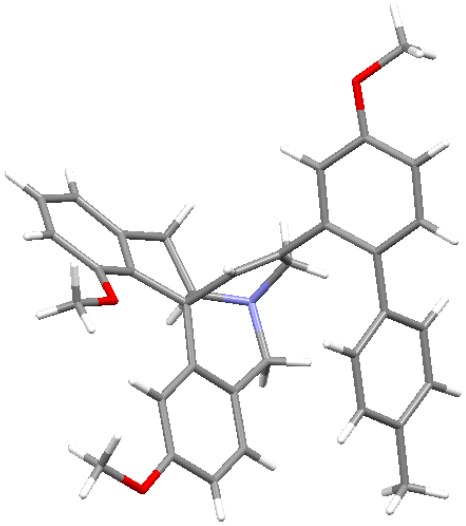
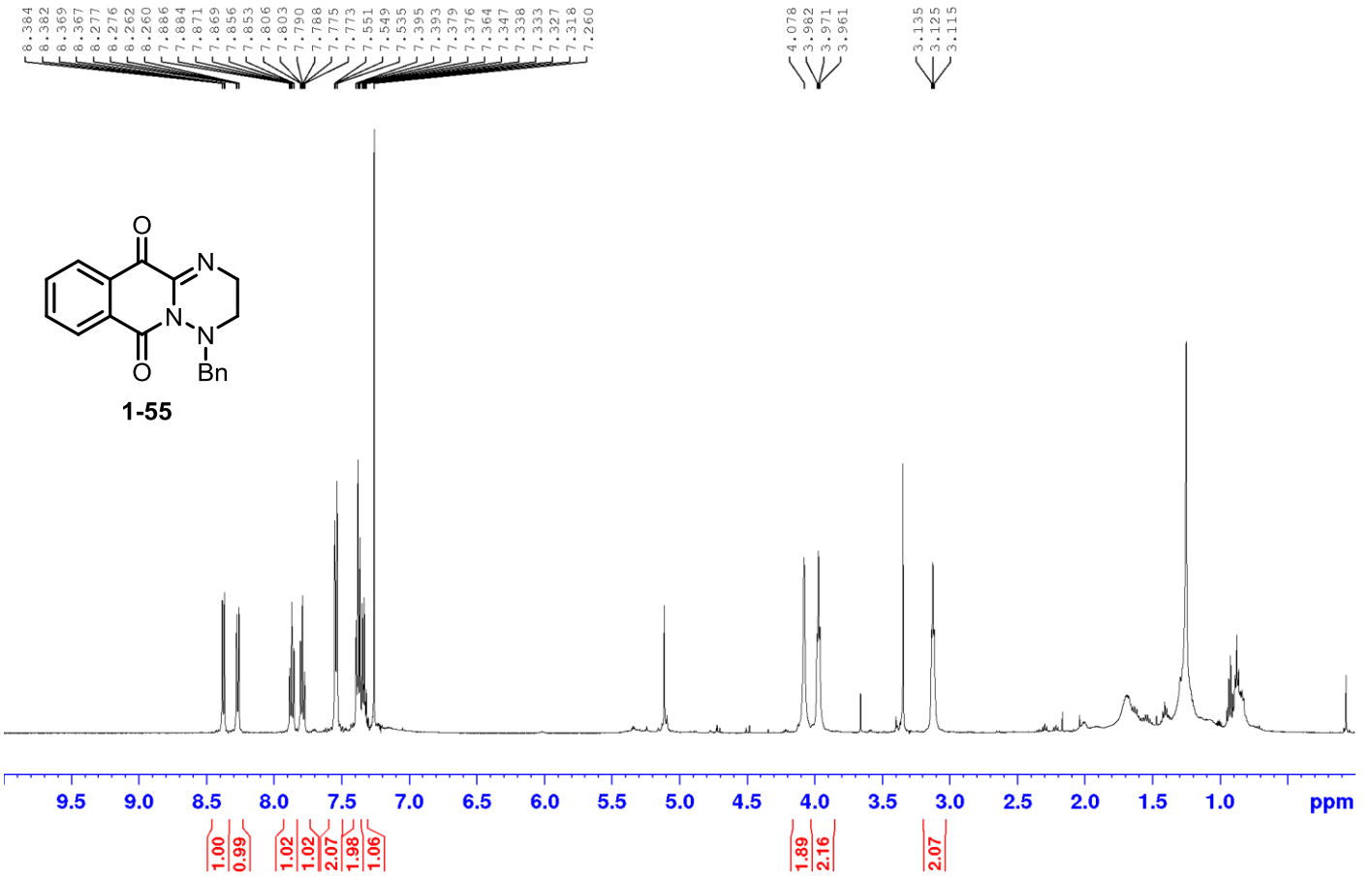


Figure 18 X-ray structure of **3-191**

APPENDIX B

SELECTED NMR DATA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7.856
7.853
7.806
7.803
7.790
7.788
7.775
7.773
7.551
7.549
7.535
7.395
7.393
7.379
7.376
7.364
7.347
7.338
7.333
7.327
7.318
7.260
4.078
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3.971
3.961
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3.125
3.115
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N
N
O
Bn
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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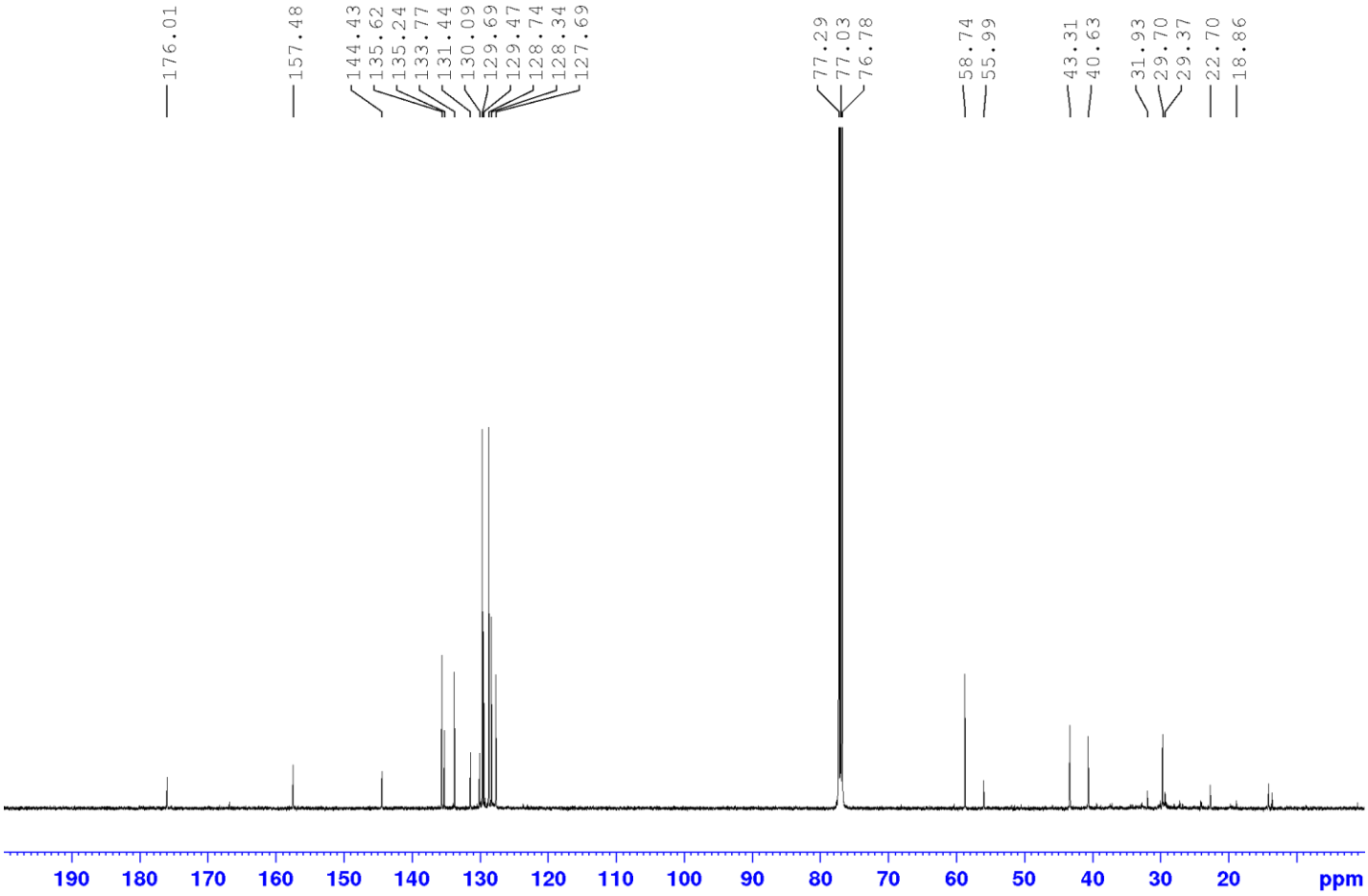
1.89
2.16
2.07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130.09
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77.29
77.03
76.78
58.74
55.99
43.31
40.63
31.93
29.70
29.37
22.70
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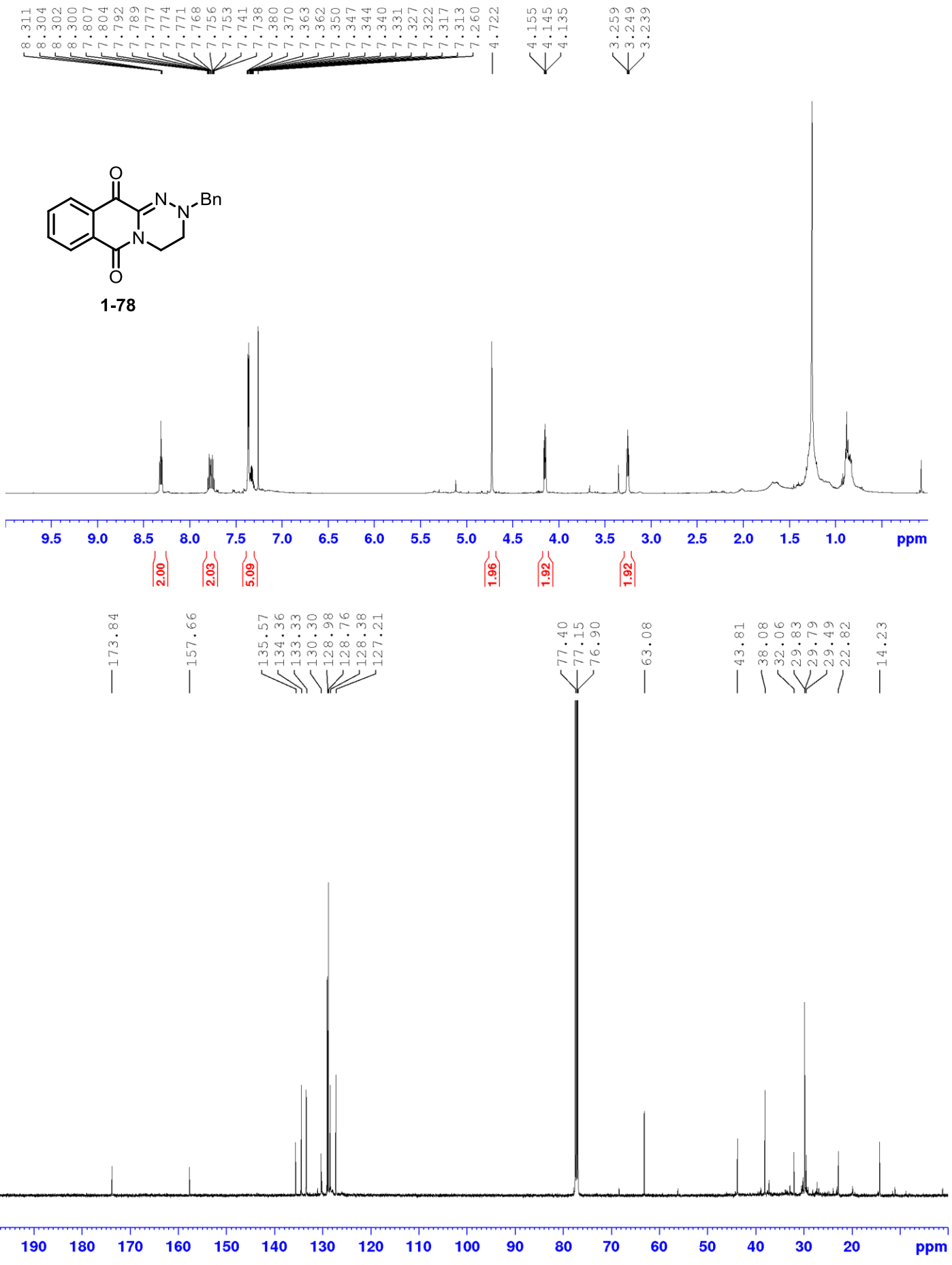
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3.259
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Bn
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1.92
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135.57
134.36
133.33
130.30
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29.49
22.82
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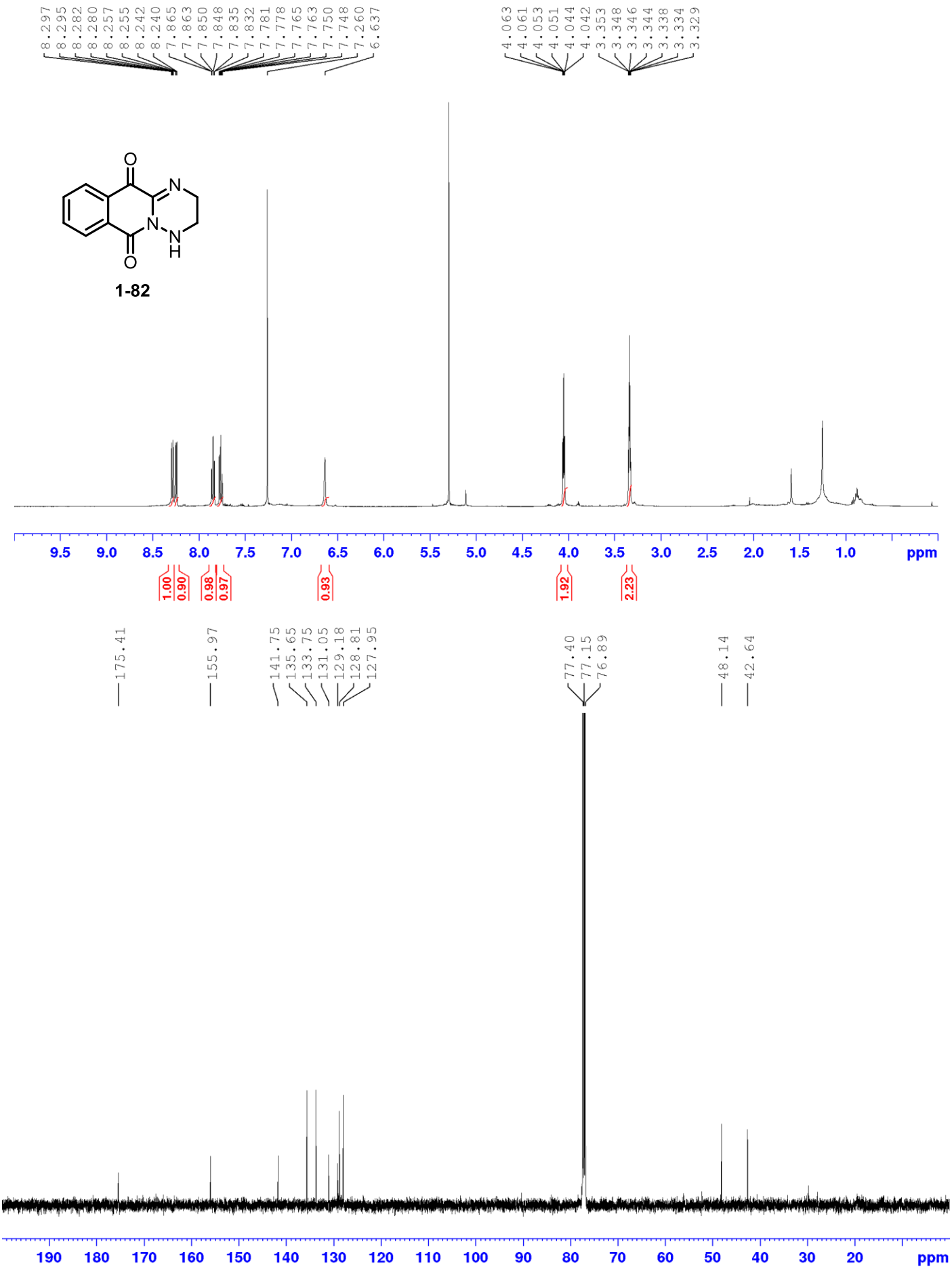
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3.344
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N
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O
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0.90
0.98
0.97
0.93
1.92
2.23
175.41
155.97
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135.65
133.75
131.05
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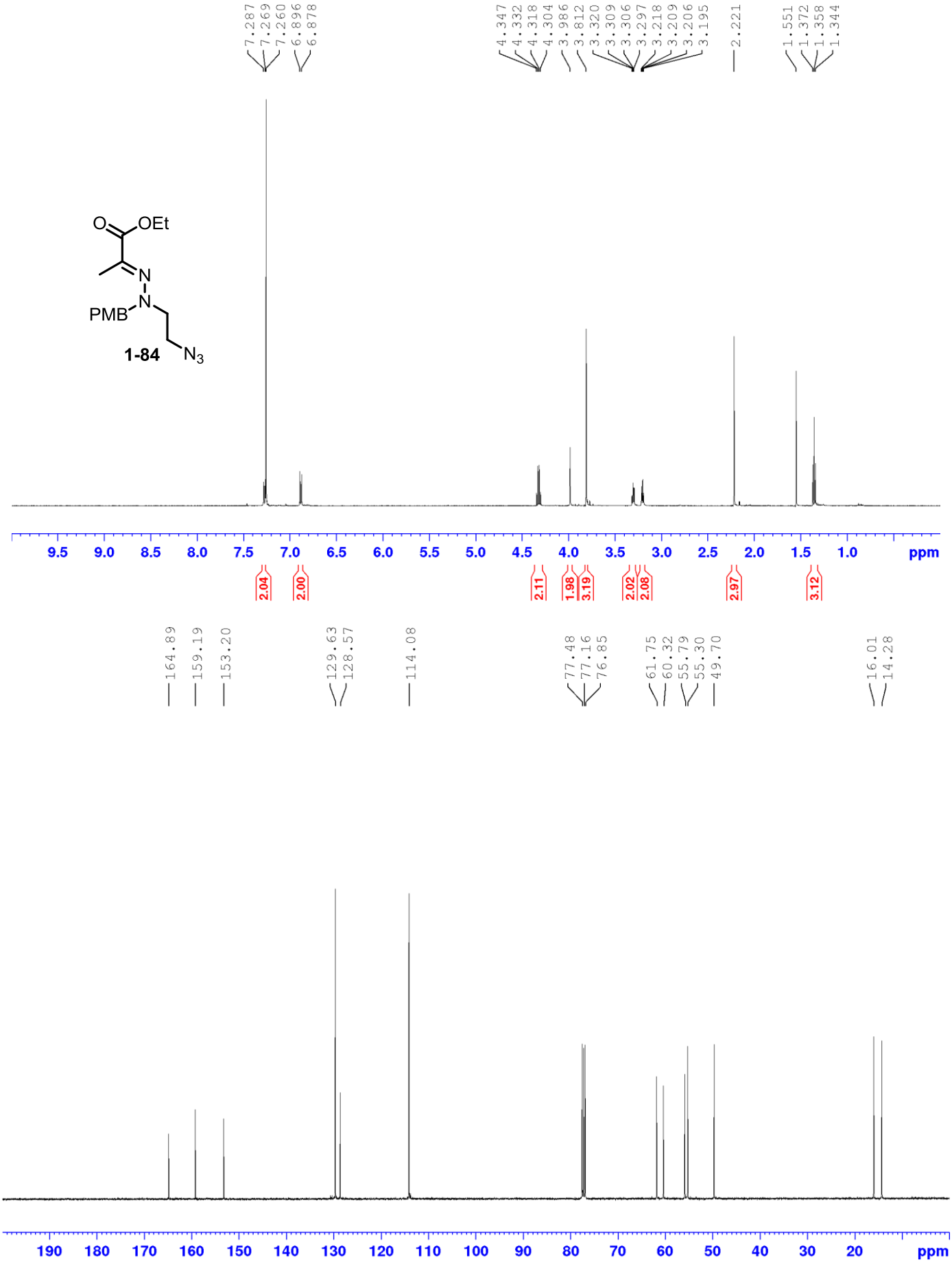
48.14
42.64
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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2.221
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1.372
1.358
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OEt
N
N
PMB
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8.0
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3.0
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ppm
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2.08
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77.16
76.85
61.75
60.32
55.79
55.30
49.70
16.01
14.28
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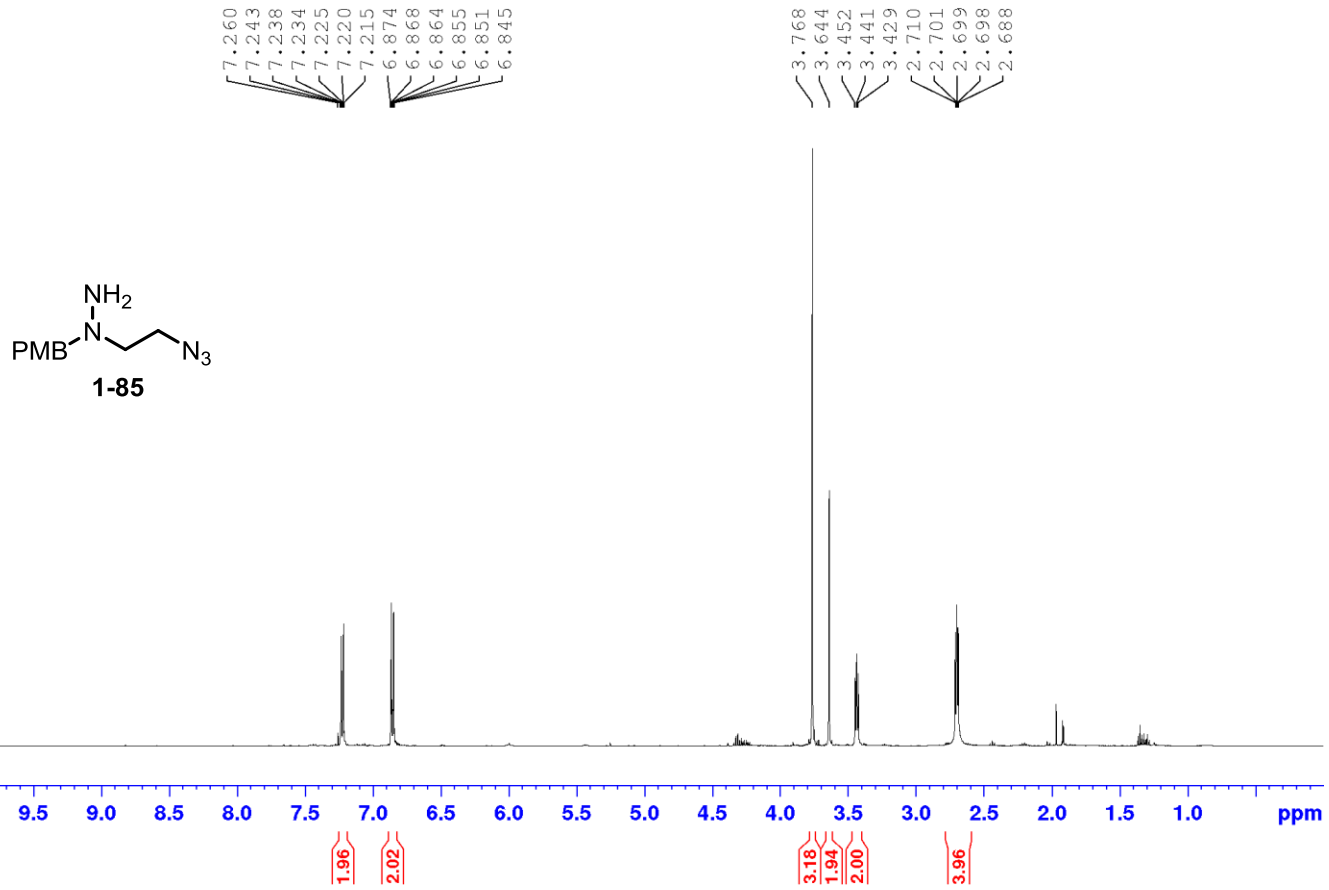
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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6.855
6.851
6.845
3.768
3.644
3.452
3.441
3.429
2.710
2.701
2.699
2.698
2.688
NH2
N
PMB
N3
1-85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
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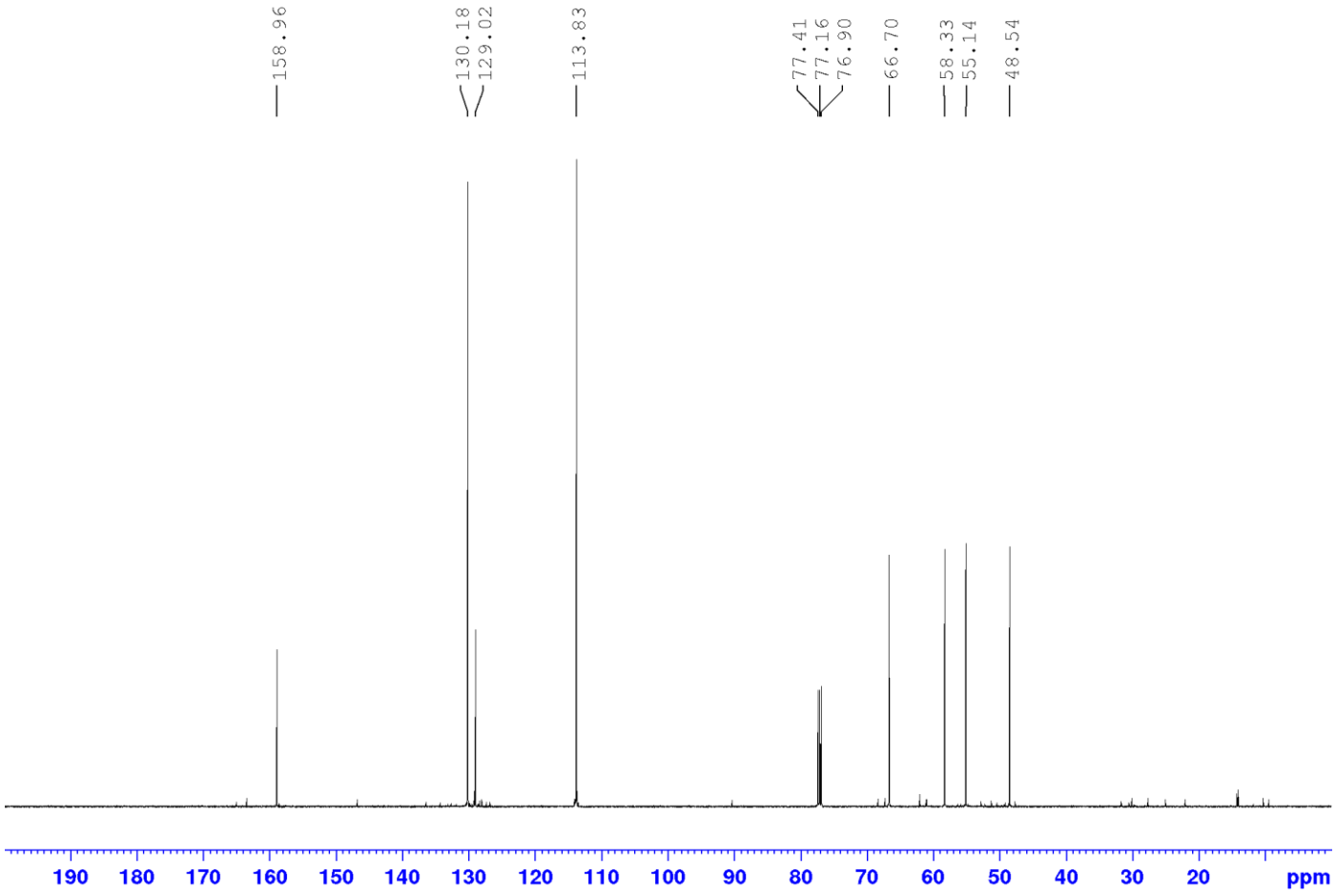
2.02
3.18
1.94
2.00
3.96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129.02
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55.14
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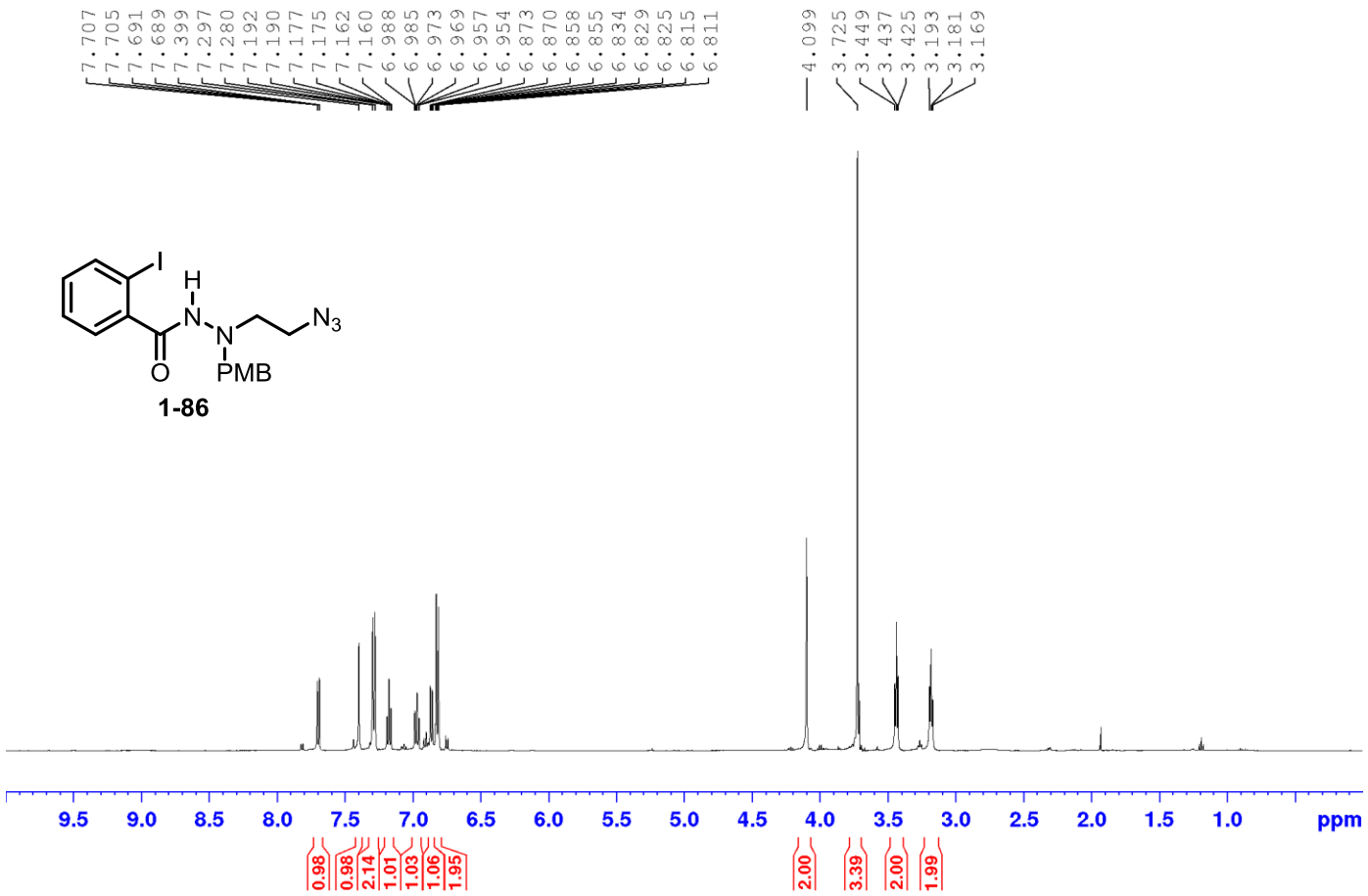
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.705
7.691
7.689
7.399
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7.280
7.192
7.190
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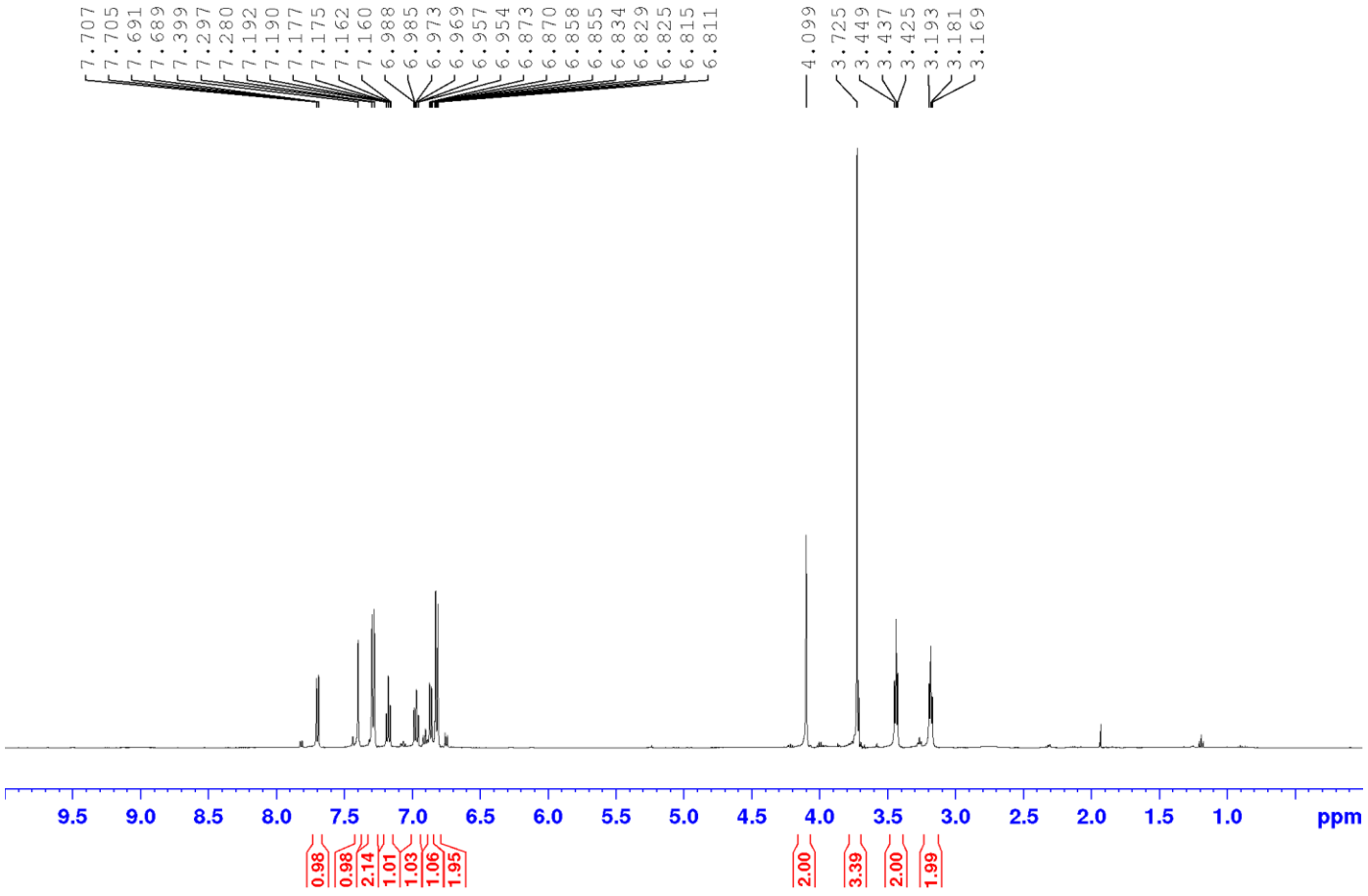
7.175
7.162
7.160
6.988
6.985
6.973
6.969
6.957
6.954
6.873
6.870
6.858
6.855
6.834
6.829
6.825
6.815
6.811
4.099
3.725
3.449
3.437
3.425
3.193
3.181
3.169
I
H
N
N
N3
O
PMB
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.98
0.98
2.14
1.01
1.03
1.06
1.95
2.00
3.39
2.00
1.99

1-86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6.988
6.985
6.973
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6.957
6.954
6.873
6.870
6.858
6.855
6.834
6.829
6.825
6.815
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4.099
3.725
3.449
3.437
3.425
3.193
3.181
3.169
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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2.14
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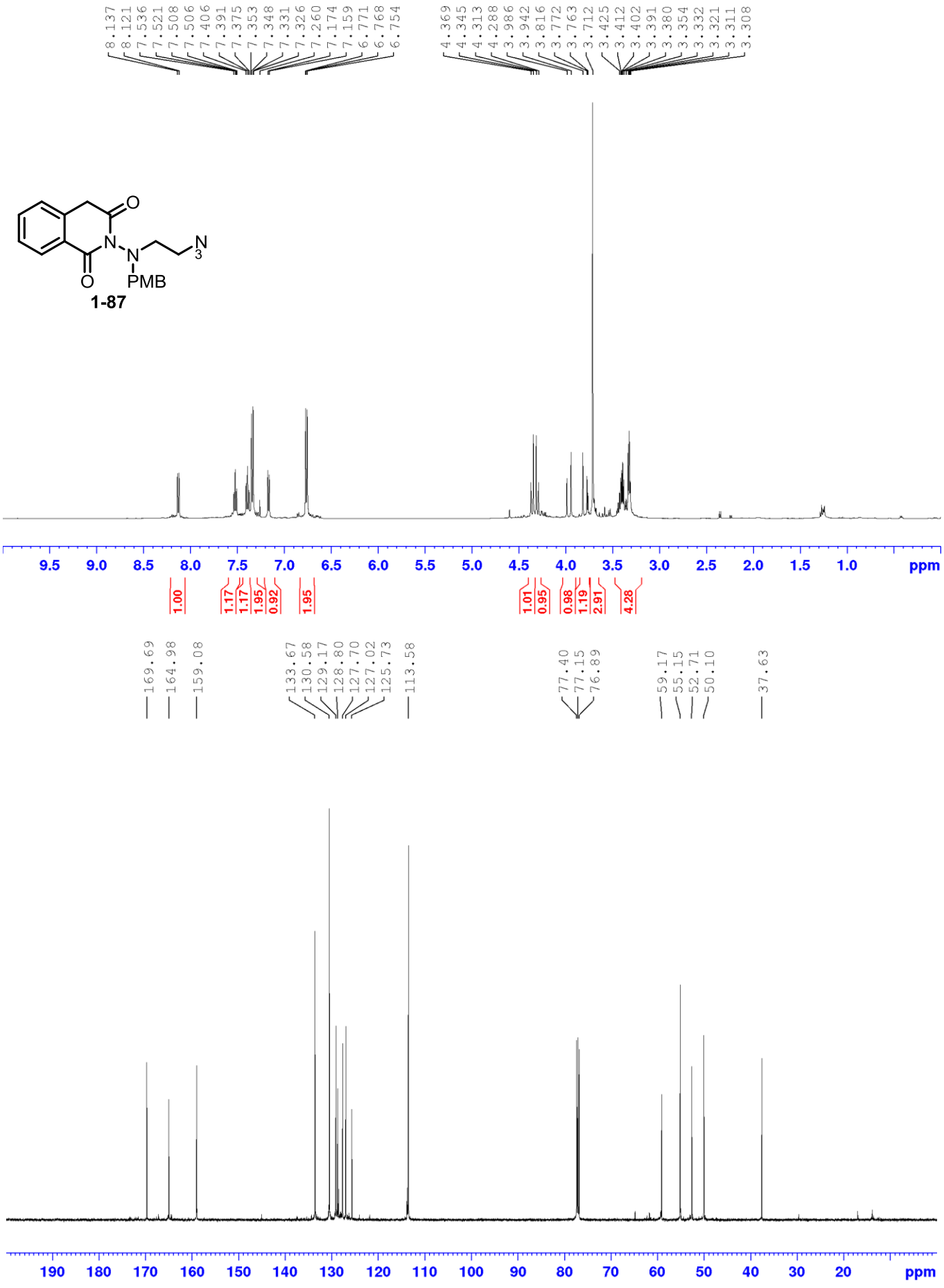
1.03
1.06
1.95
2.00
3.39
2.00
1.99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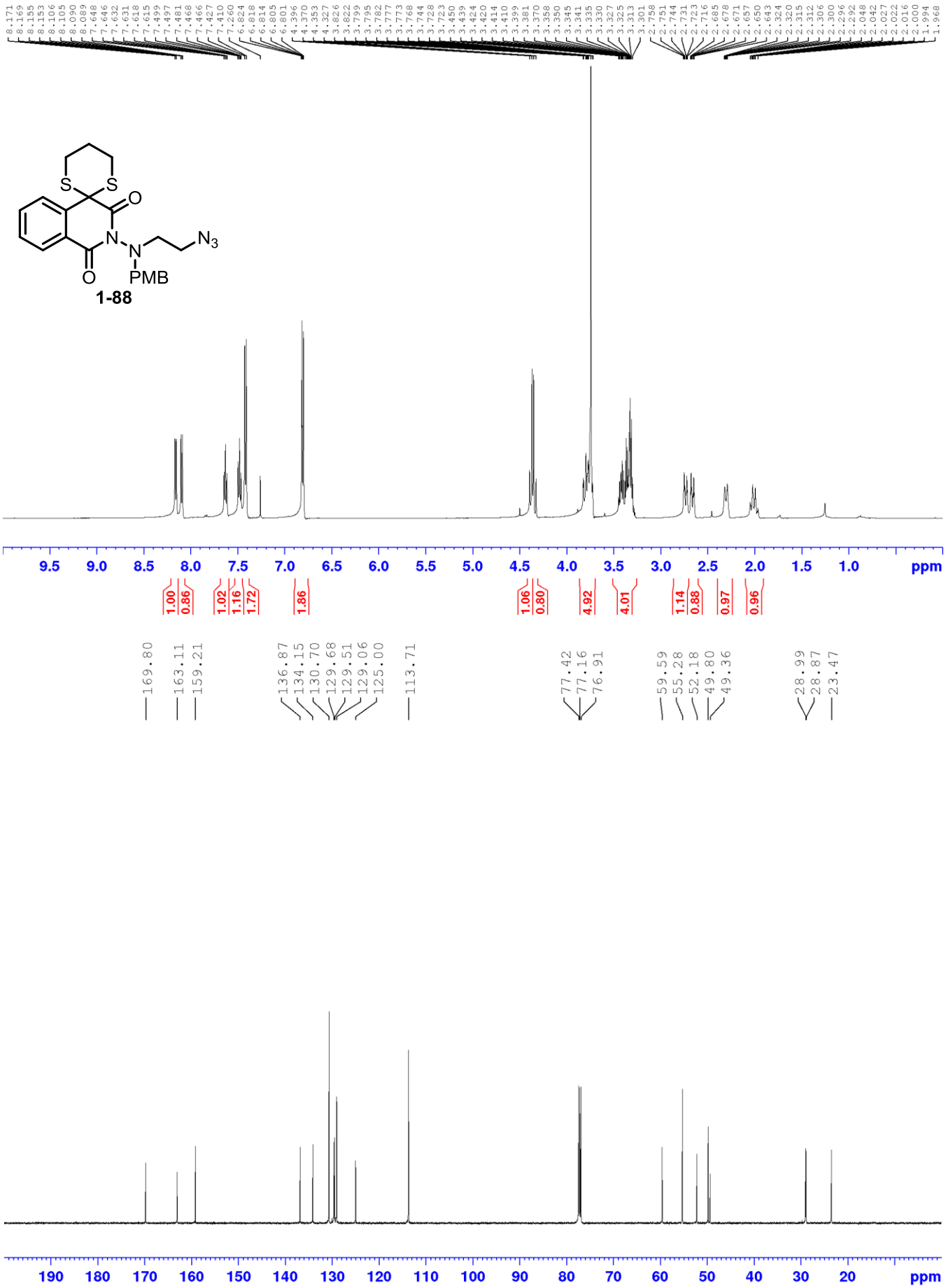
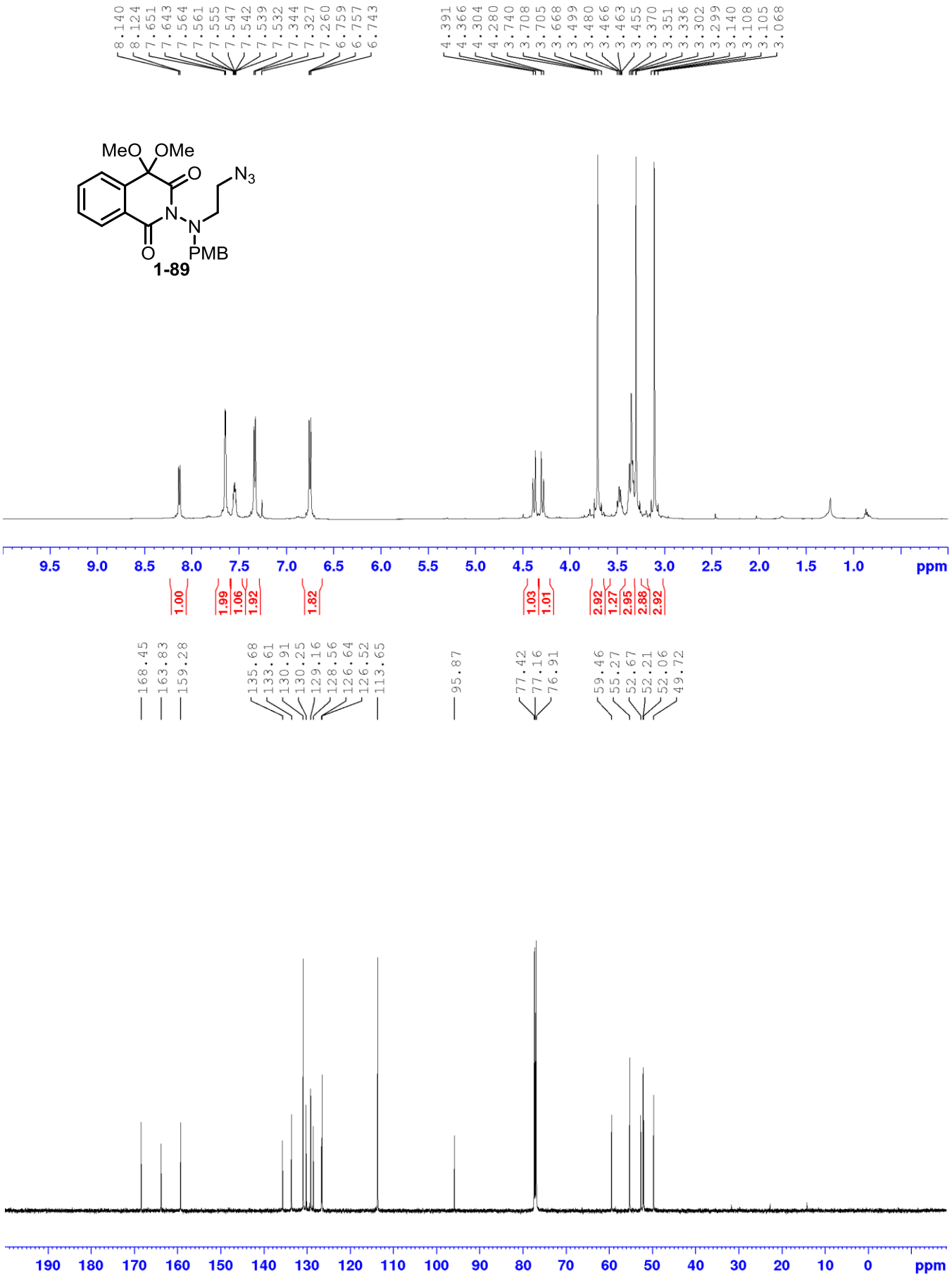
7.391
7.375
7.353
7.348
7.331
7.326
7.260
7.174
7.159
6.771
6.768
6.754
4.369
4.345
4.313
4.288
3.986
3.942
3.816
3.772
3.763
3.712
3.425
3.412
3.402
3.391
3.380
3.354
3.332
3.321
3.311
3.308
O
N
N
N3
PMB
O
1-87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.17
1.17
1.95
0.92
1.95
1.01
0.95
0.98
1.19
2.91
4.28
169.69
164.98
159.08
133.67
130.58
129.17
128.80
127.70
127.02
125.73
113.58
77.40
77.15
76.89
59.17
55.15
52.71
50.10
37.63
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


S
S
O
N
N
N3
O
PMB
1-88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 0.86 1.02 1.16 1.72 1.86 1.06 0.80 4.92 4.01 1.14 0.88 0.97 0.96
169.80 163.11 159.21 136.87 134.15 130.70 129.68 129.51 129.06 125.00 113.71 77.42 77.16 76.91 59.59 55.28 52.18 49.80 49.36 28.99 28.87 23.47
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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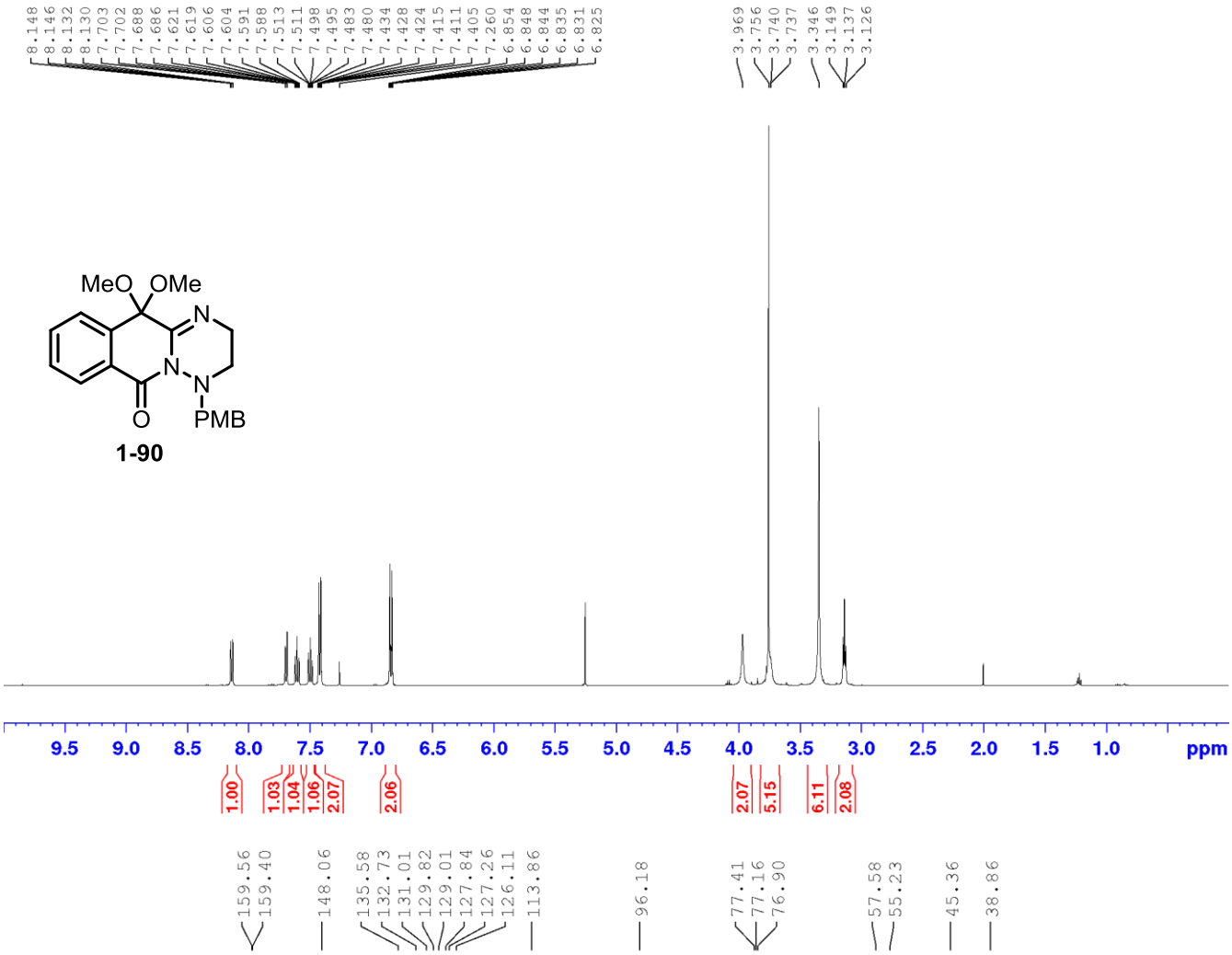
7.547
7.542
7.539
7.532
7.344
7.327
7.260
6.759
6.757
6.743
4.391
4.366
4.304
4.280
3.740
3.708
3.705
3.668
3.499
3.480
3.466
3.463
3.455
3.370
3.351
3.336
3.302
3.299
3.140
3.108
3.105
3.068
MeO
OMe
O
N3
N
N
O
PMB
1-89
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.99
1.06
1.92
1.82
1.03
1.01
2.92
1.27
2.95
2.88
2.92
168.45
163.83
159.28
135.68
133.61
130.91
130.25
129.16
128.56
126.64
126.52
113.65
95.87
77.42
77.16
76.91
59.46
55.27
52.67
52.21
52.06
49.72
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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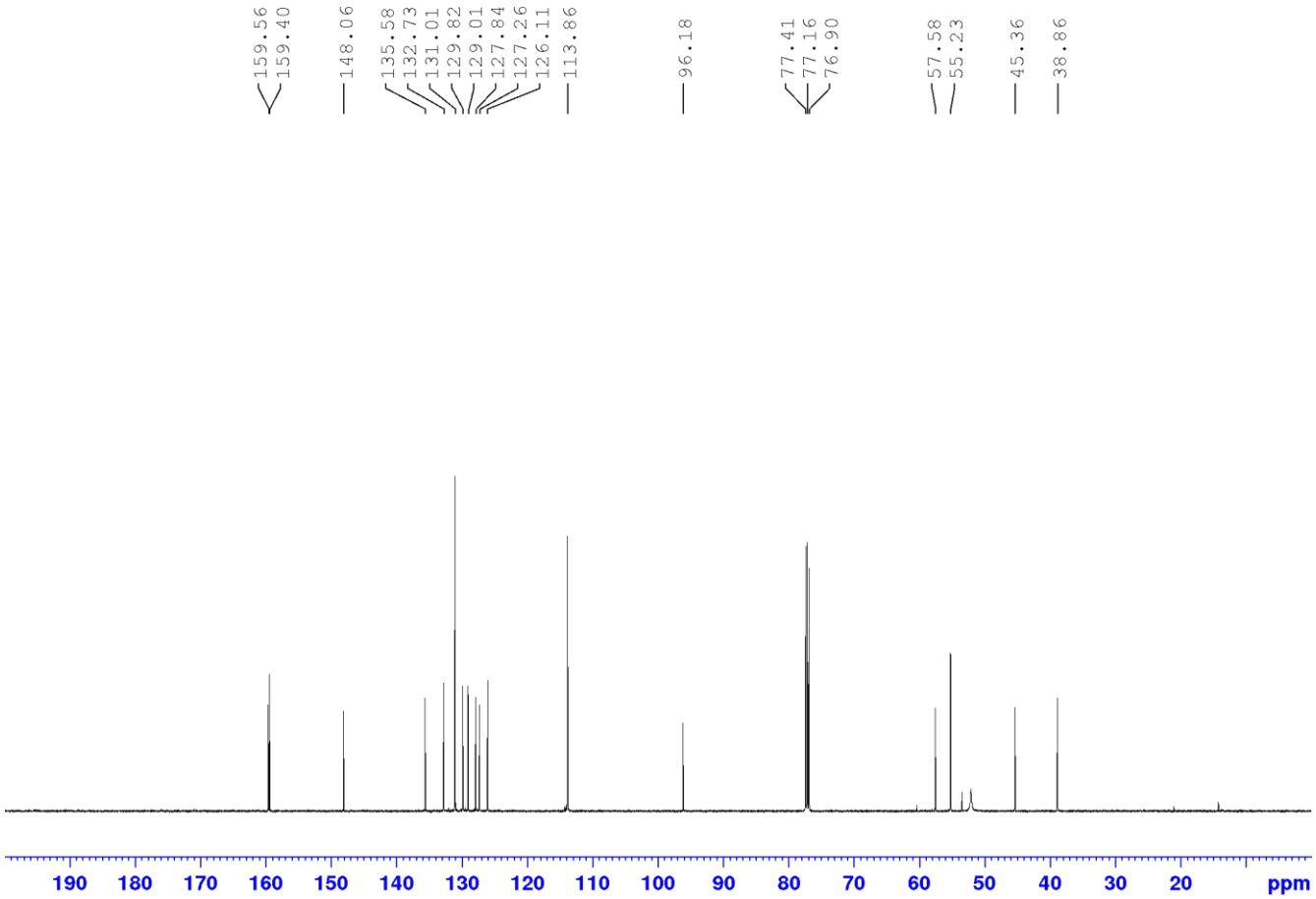
7.686
7.621
7.619
7.606
7.604
7.591
7.588
7.513
7.511
7.498
7.495
7.483
7.480
7.434
7.428
7.424
7.415
7.411
7.405
7.260
6.854
6.848
6.844
6.835
6.831
6.825
3.969
3.756
3.740
3.737
3.346
3.149
3.137
3.126
MeO
OMe
N
N
N
O
PMB
1-90
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.03
1.04
1.06
2.07
2.06
2.07
5.15
6.11
2.08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148.06
135.58
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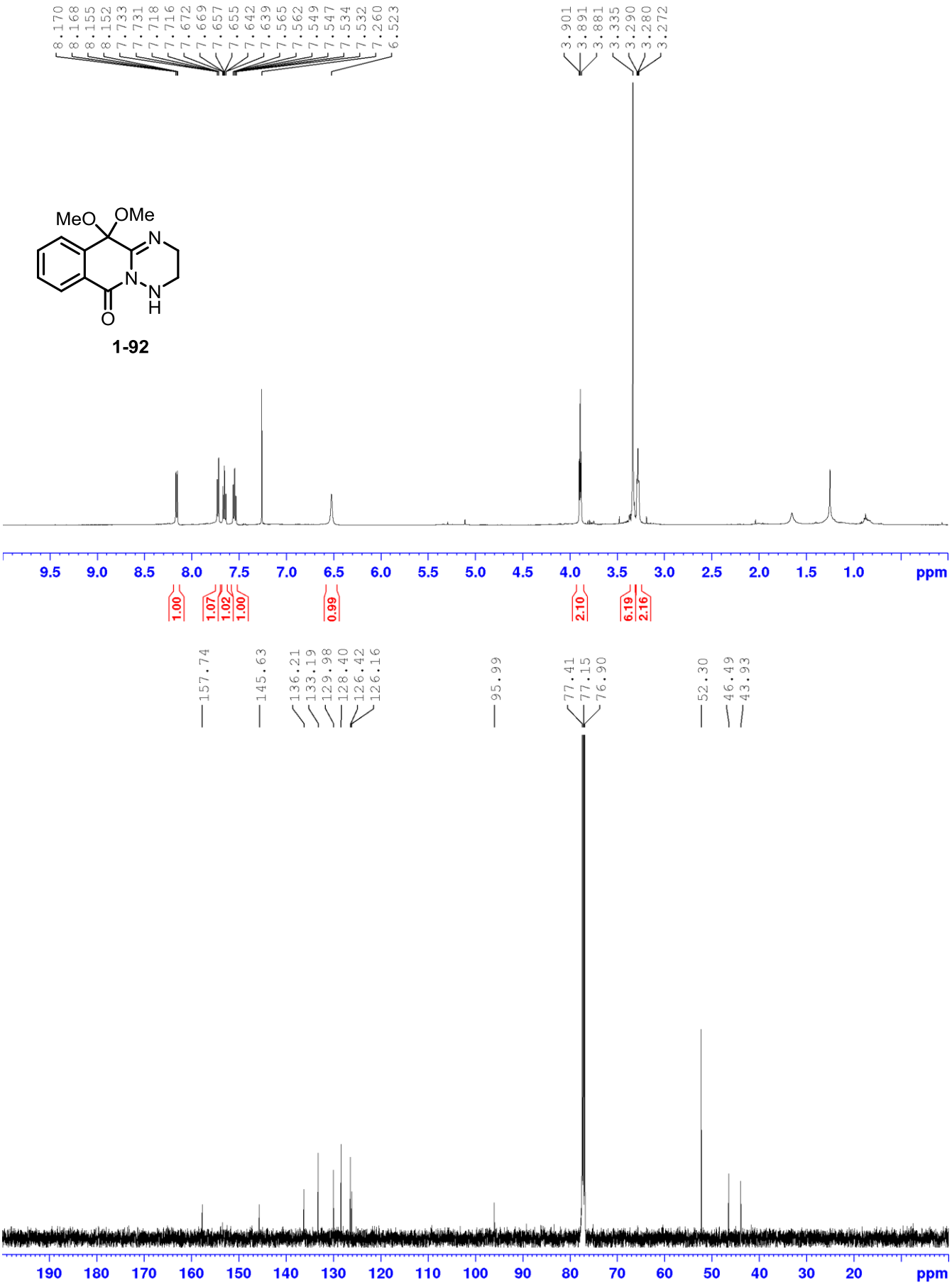
131.01
129.82
129.01
127.84
127.26
126.11
113.86
96.18
77.41
77.16
76.90
57.58
55.23
45.36
38.86
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.731
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7.716
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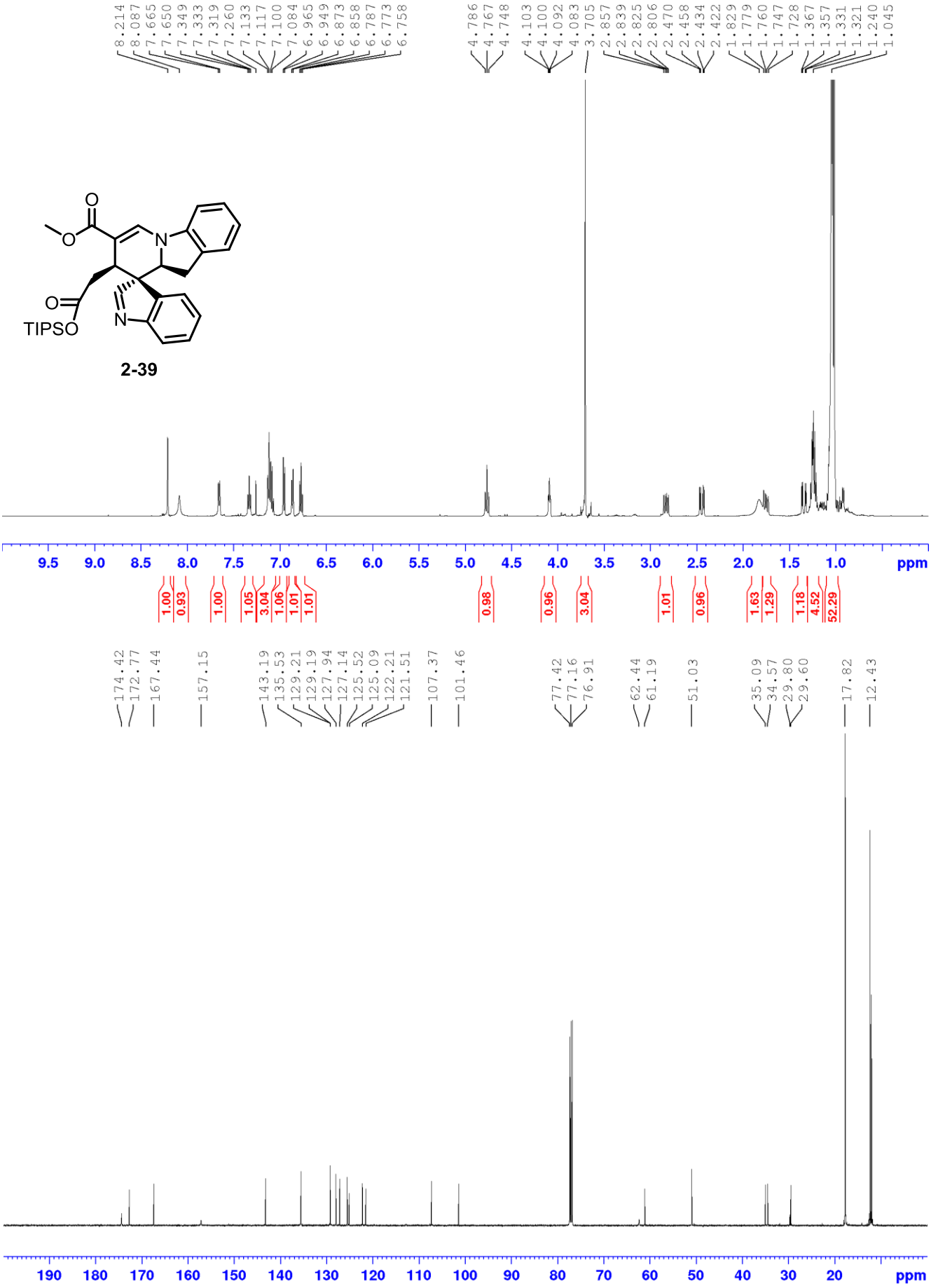
7.669
7.657
7.655
7.642
7.639
7.565
7.562
7.549
7.547
7.534
7.532
7.260
6.523
3.901
3.891
3.881
3.335
3.290
3.280
3.272
MeO
OMe
N
N
N
H
O
1-92
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.07
1.02
1.00
0.99
2.10
6.19
2.16
157.74
145.63
136.21
133.19
129.98
128.40
126.42
126.16
95.99
77.41
77.15
76.90
52.30
46.49
43.93
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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6.965
6.949
6.873
6.858
6.787
6.773
6.758
4.786
4.767
4.748
4.103
4.100
4.092
4.083
3.705
2.857
2.839
2.825
2.806
2.470
2.458
2.434
2.422
1.829
1.779
1.760
1.747
1.728
1.367
1.357
1.331
1.321
1.240
1.045
O
O
N
O
TIPSO
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.93
1.00
1.05
3.04
1.06
1.01
1.01
0.98
0.96
3.04
1.01
0.96
1.63
1.29
1.18
4.52
52.29
174.42
172.77
167.44
157.15
143.19
135.53
129.21
129.19
127.94
127.14
125.52
125.09
122.21
121.51
107.37
101.46
77.42
77.16
76.91
62.44
61.19
51.03
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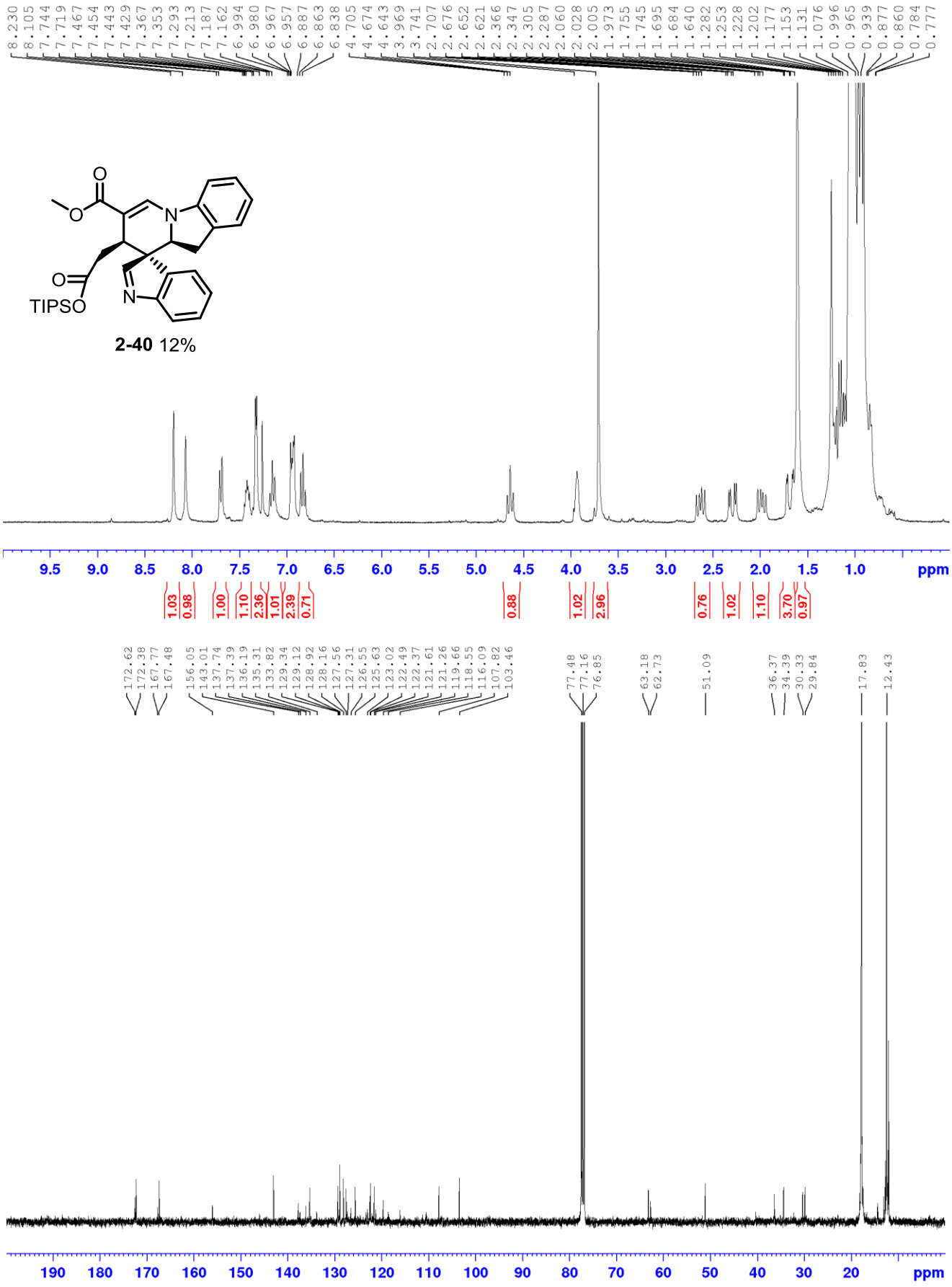
34.57
29.80
29.60
17.82
12.43
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

2-39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7.353
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7.187
7.162
6.994
6.980
6.967
6.957
6.887
6.863
6.838
4.705
4.674
4.643
3.969
3.741
2.707
2.676
2.652
2.621
2.366
2.347
2.305
2.287
2.060
2.028
2.005
1.973
1.755
1.745
1.695
1.684
1.640
1.282
1.253
1.228
1.202
1.177
1.153
1.131
1.076
0.996
0.965
0.939
0.877
0.860
0.784
0.777
O
O
N
O
TIPSO
N
2-40 12%
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.03
0.98
1.00
1.10
2.36
1.01
2.39
0.71
0.88
1.02
2.96
0.76
1.02
1.10
3.70
0.97
172.62
172.38
167.77
167.48
156.05
143.01
137.74
137.39
136.19
135.31
133.82
129.34
129.12
128.92
128.16
127.56
127.31
126.55
125.63
123.02
122.49
122.37
121.61
121.26
119.66
118.55
116.09
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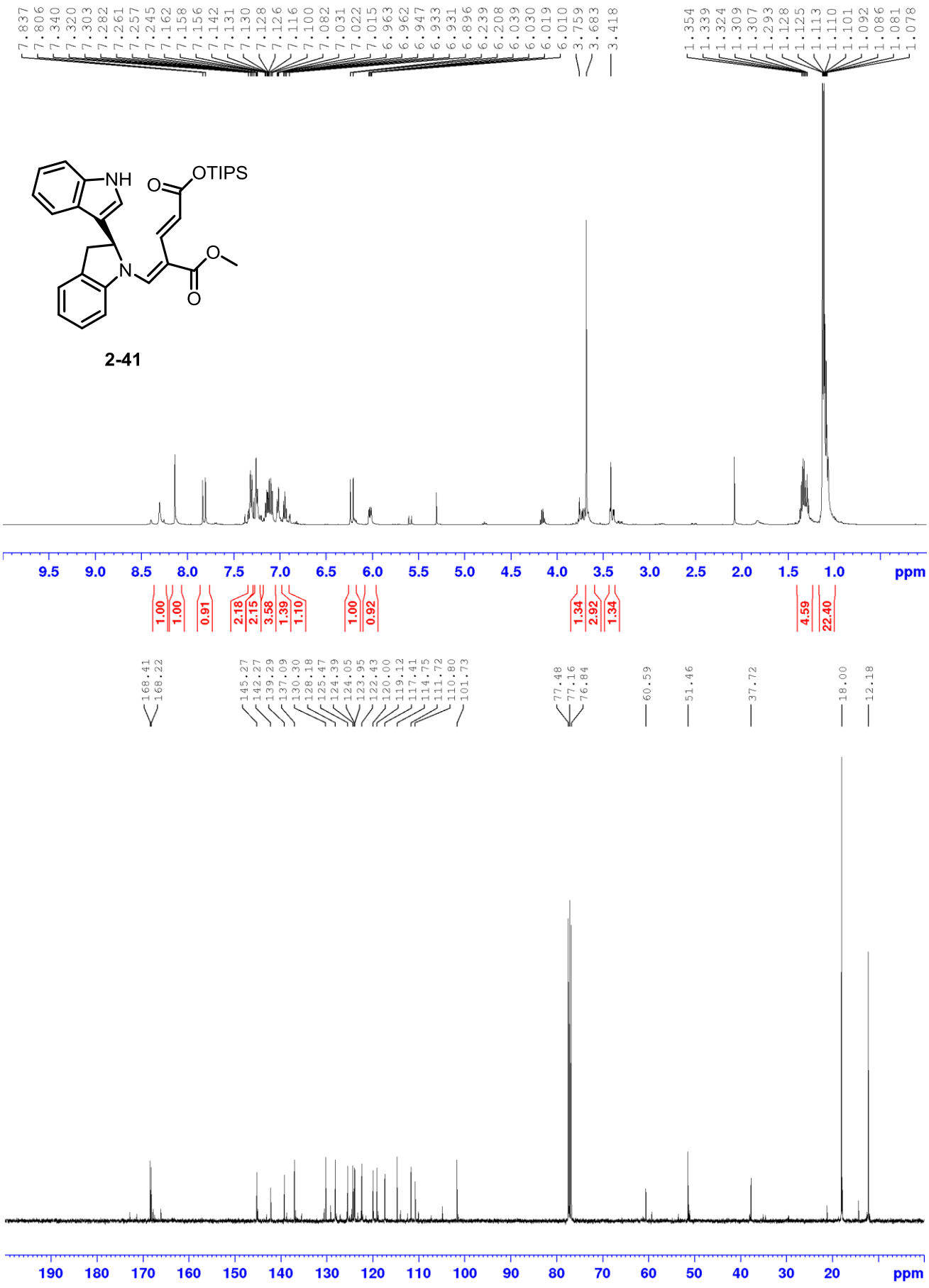
103.46
77.48
77.16
76.85
63.18
62.73
51.09
36.37
34.39
30.33
29.84
17.83
12.43
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.142
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7.130
7.128
7.126
7.116
7.100
7.082
7.031
7.022
7.015
6.963
6.962
6.947
6.933
6.931
6.896
6.239
6.208
6.039
6.030
6.019
6.010
3.759
3.683
3.418
1.354
1.339
1.324
1.309
1.307
1.293
1.128
1.125
1.113
1.110
1.101
1.092
1.086
1.081
1.078
NH
O
OTIPS
O
N
O
2-41
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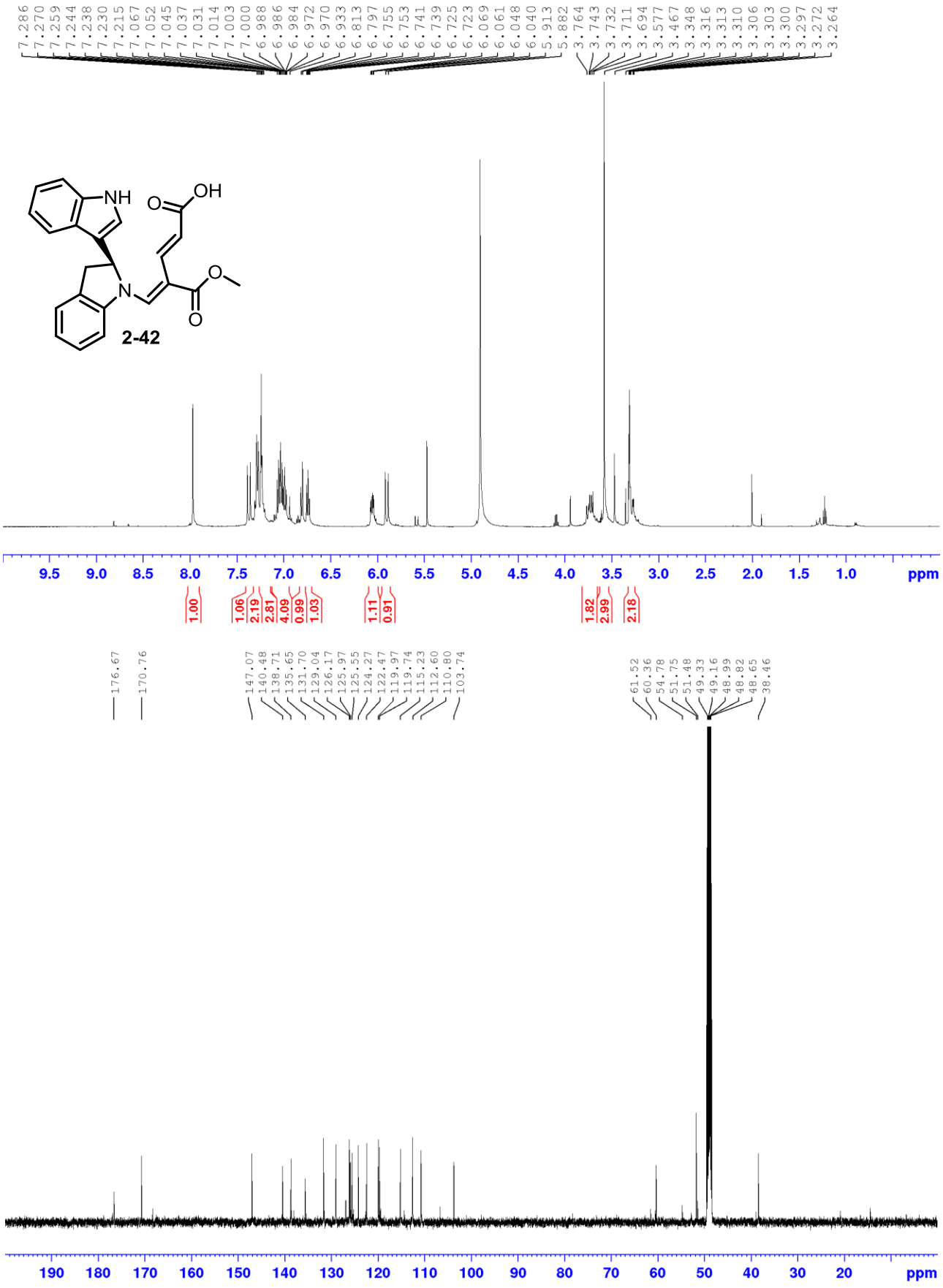
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.00
0.91
2.18
2.15
3.58
1.39
1.10
1.00
0.92
1.34
2.92
1.34
4.59
22.40
168.41
168.22
145.27
142.27
139.29
137.09
130.30
128.18
125.47
124.39
124.05
123.95
122.43
120.00
119.12
117.41
114.75
111.72
110.80
101.73
77.48
77.16
76.84
60.59
51.46
37.72
18.00
12.18
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.037
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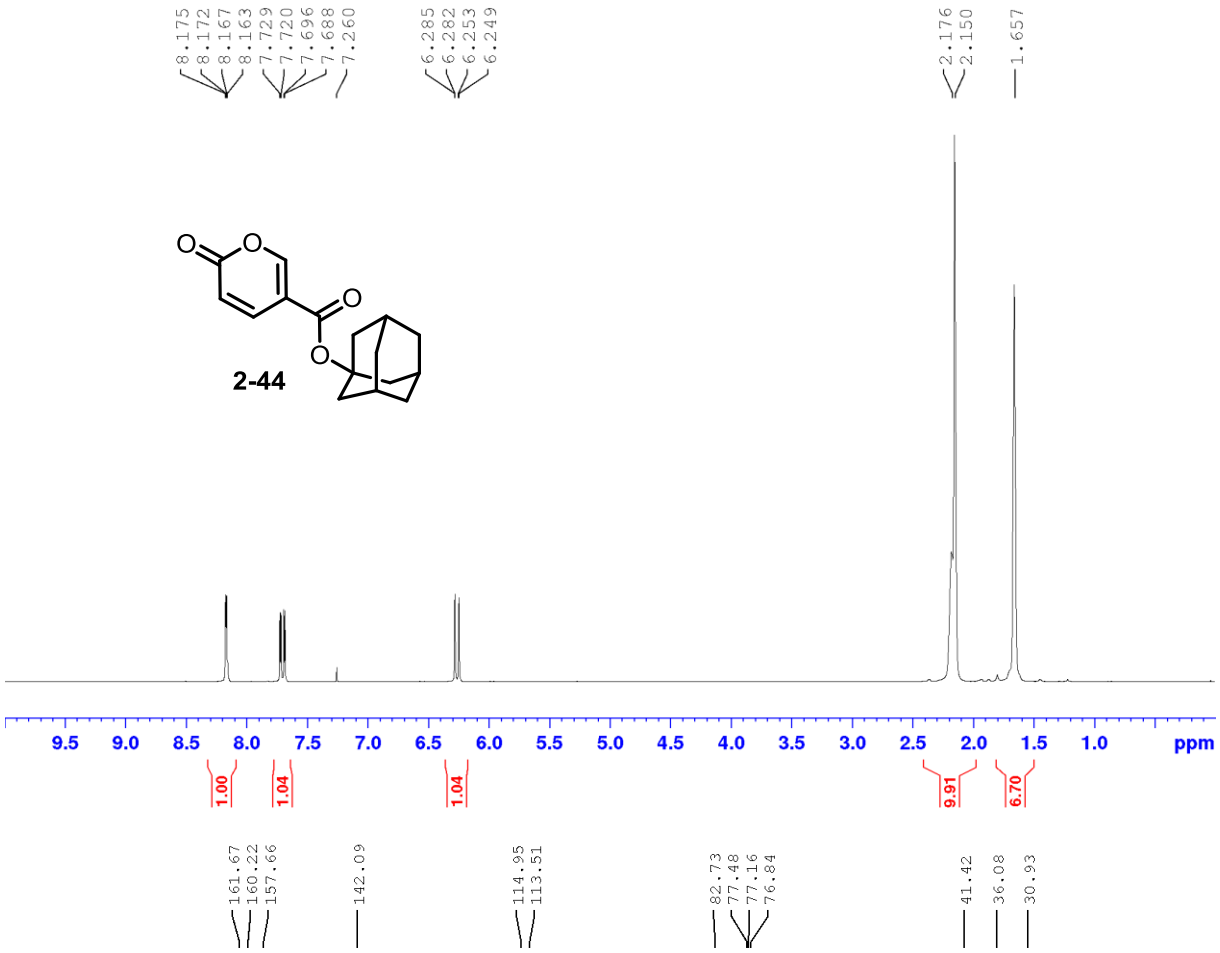
7.014
7.003
7.000
6.988
6.986
6.984
6.972
6.970
6.933
6.813
6.797
6.755
6.753
6.741
6.739
6.725
6.723
6.069
6.061
6.048
6.040
5.913
5.882
3.764
3.743
3.732
3.711
3.694
3.577
3.467
3.348
3.316
3.313
3.310
3.306
3.303
3.300
3.297
3.272
3.264
NH
OH
O
O
O
N
2-42
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.06
2.19
2.81
4.09
0.99
1.03
1.11
0.91
1.82
2.99
2.18
176.67
170.76
147.07
140.48
138.71
135.65
131.70
129.04
126.17
125.97
125.55
124.27
122.47
119.97
119.74
115.23
112.60
110.80
103.74
61.52
60.36
54.78
51.75
51.48
49.33
49.16
48.99
48.82
48.65
38.46
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.696
7.688
7.260
6.285
6.282
6.253
6.249
2.176
2.150
1.657
2-44
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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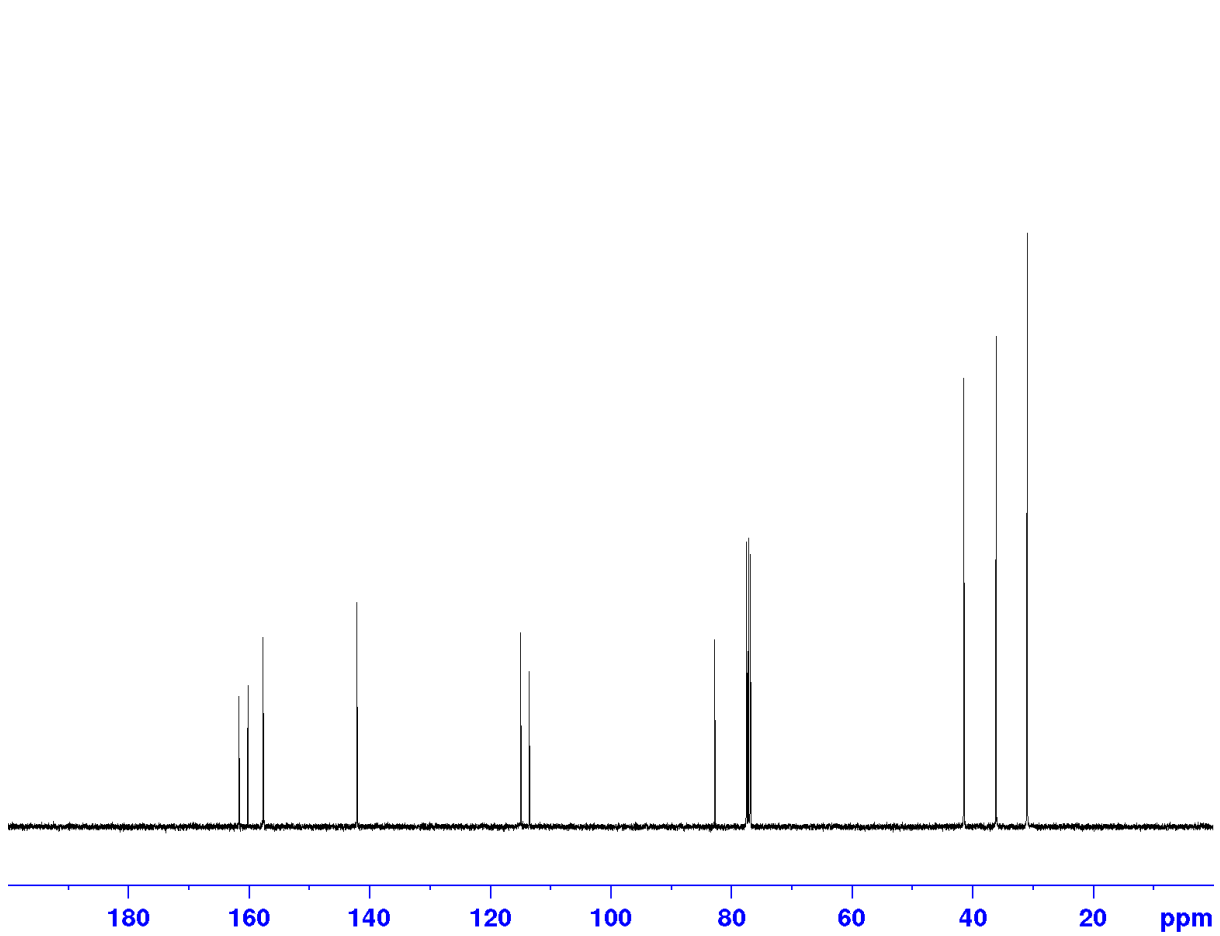
1.04
1.04
9.91
6.70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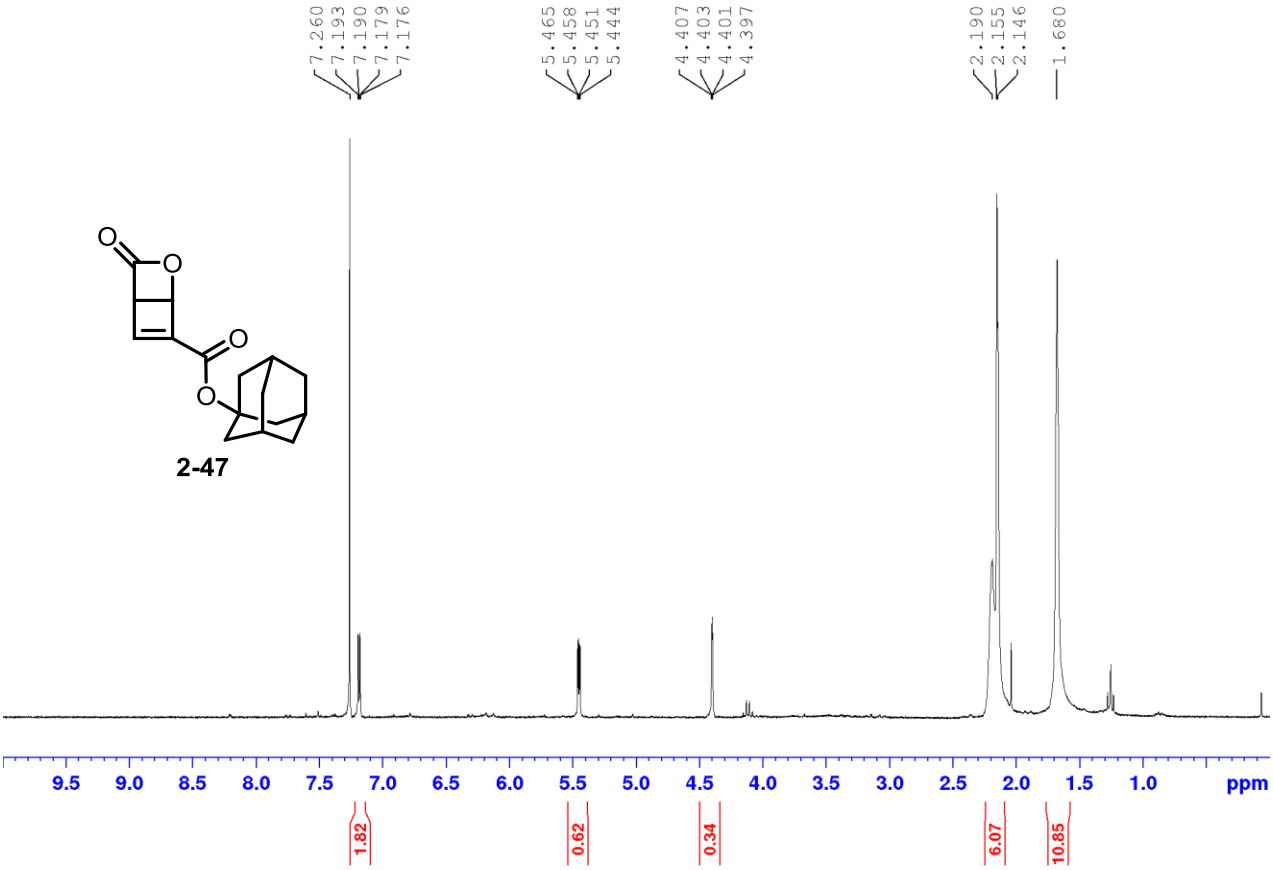
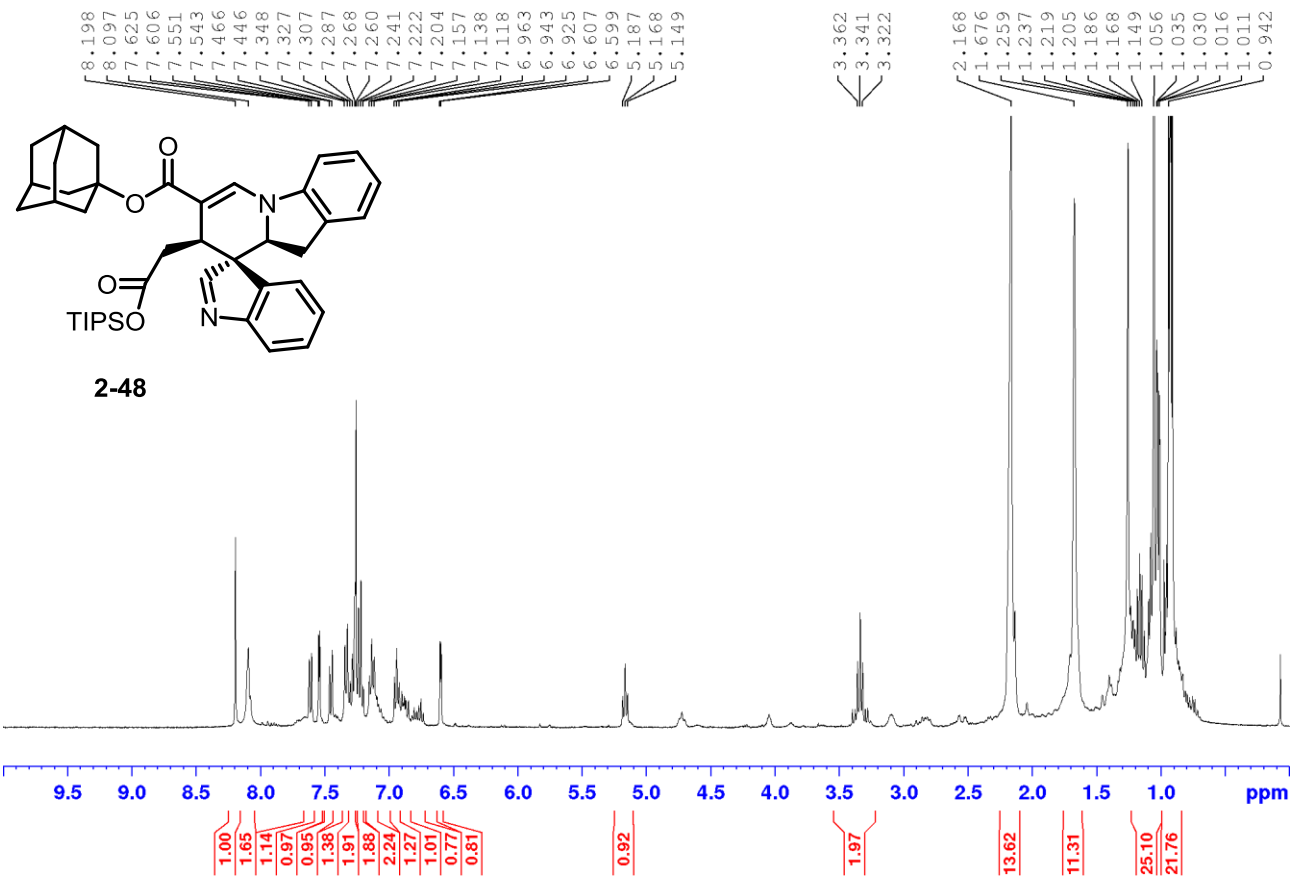
160.22
157.66
142.09
114.95
113.51
82.73
77.48
77.16
76.84
41.42
36.08
30.93
180 160 140 120 100 80 60 40 20 ppm


7.260
7.193
7.190
7.179
7.176
5.465
5.458
5.451
5.444
4.407
4.403
4.401
4.397
2.190
2.155
2.146
1.680
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.82
0.62
0.34
6.07
10.85

2-47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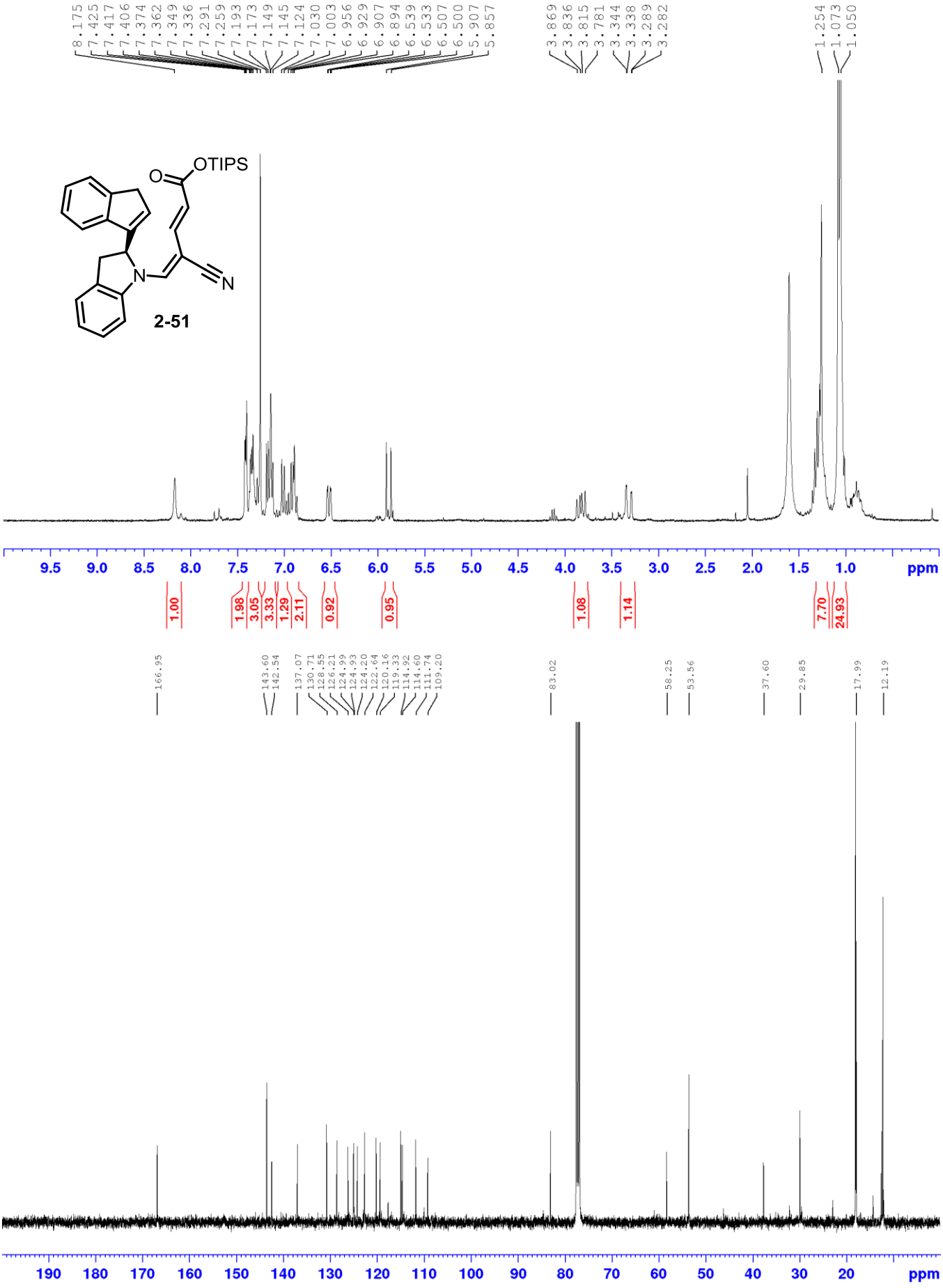
7.543
7.466
7.446
7.348
7.327
7.307
7.287
7.268
7.260
7.241
7.222
7.204
7.157
7.138
7.118
6.963
6.943
6.925
6.607
6.599
5.187
5.168
5.149
3.362
3.341
3.322
2.168
1.676
1.259
1.237
1.219
1.205
1.186
1.168
1.149
1.056
1.035
1.030
1.016
1.011
0.942
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.65
1.14
0.97
0.95
1.38
1.91
1.88
2.24
1.27
1.01
0.77
0.81
0.92
1.97
13.62
11.31
25.10
21.76

2-48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7.425
7.417
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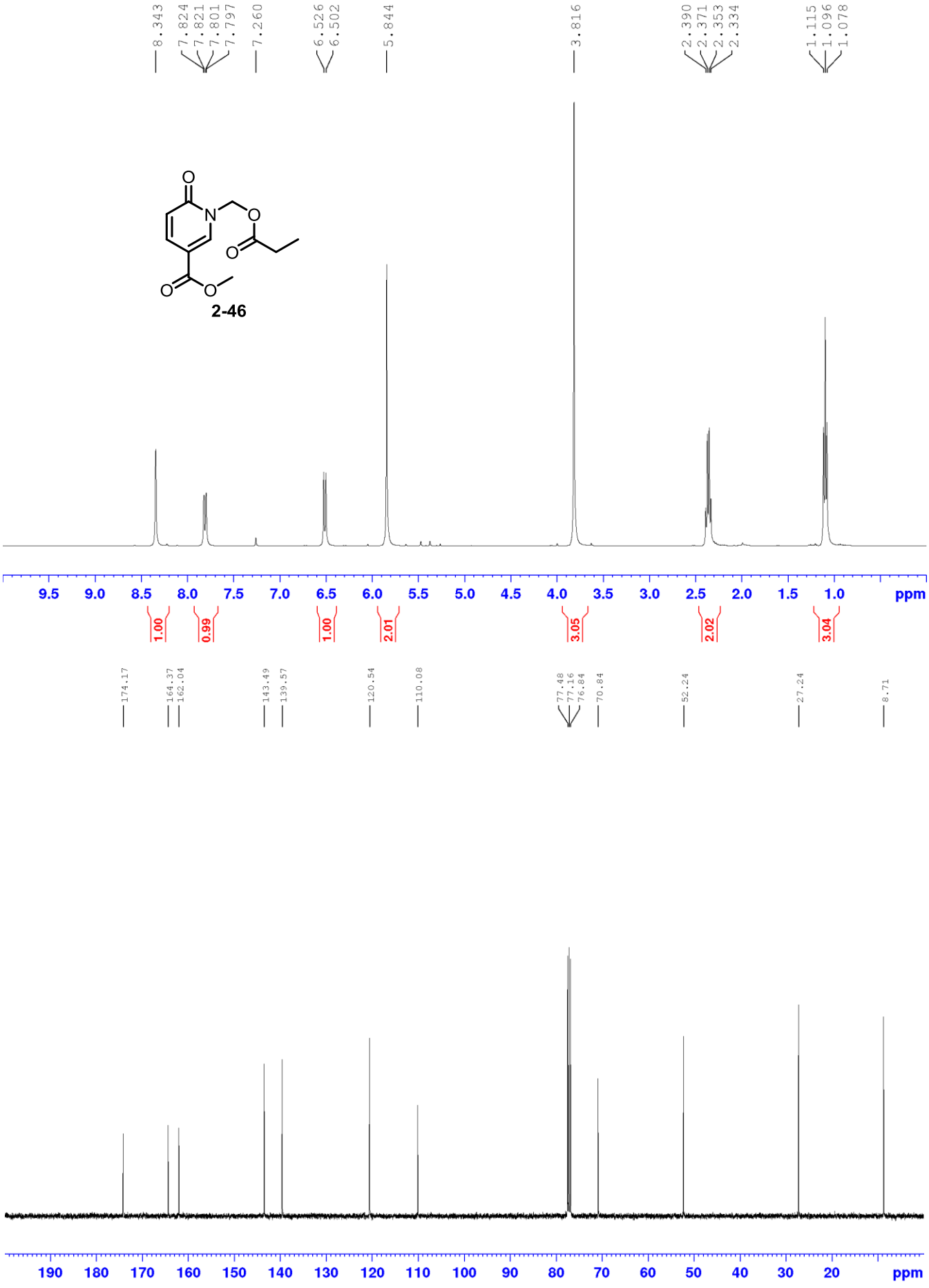
7.349
7.336
7.291
7.259
7.193
7.173
7.149
7.145
7.124
7.030
7.003
6.956
6.929
6.907
6.894
6.539
6.533
6.507
6.500
5.907
5.857
3.869
3.836
3.815
3.781
3.344
3.338
3.289
3.282
1.254
1.073
1.050
OTIPS
O
N
N
2-51
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.98
3.05
3.33
1.29
2.11
0.92
0.95
1.08
1.14
7.70
24.93
166.95
143.60
142.54
137.07
130.71
128.55
126.21
124.99
124.93
124.20
122.64
120.16
119.33
114.92
114.60
111.74
109.20
83.02
58.25
53.56
37.60
29.85
17.99
12.19
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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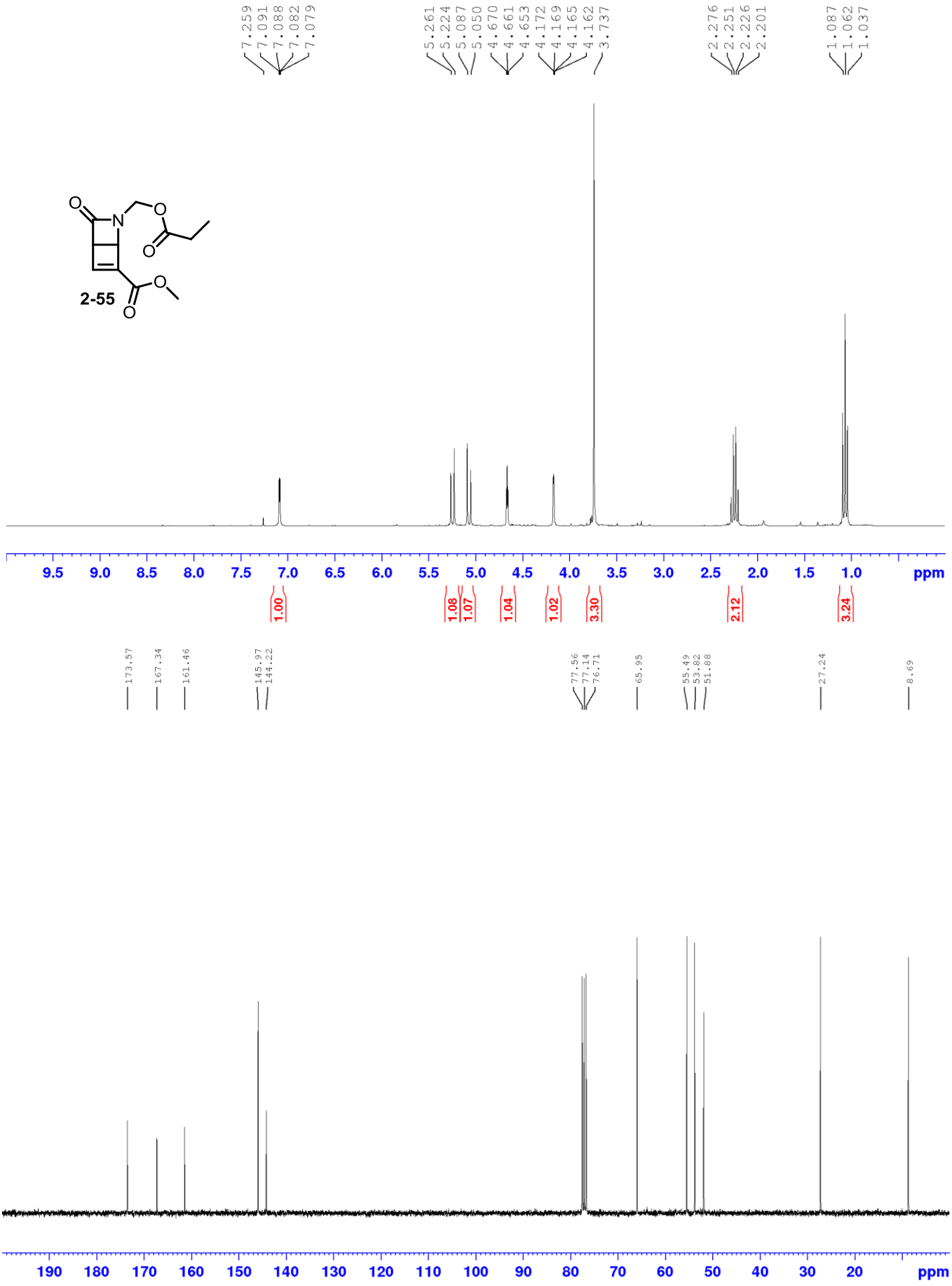
7.824
7.821
7.801
7.797
7.260
6.526
6.502
5.844
3.816
2.390
2.371
2.353
2.334
1.115
1.096
1.078
2-46
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.99
1.00
2.01
3.05
2.02
3.04
174.17
164.37
162.04
143.49
139.57
120.54
110.08
77.48
77.16
76.84
70.84
52.24
27.24
8.71
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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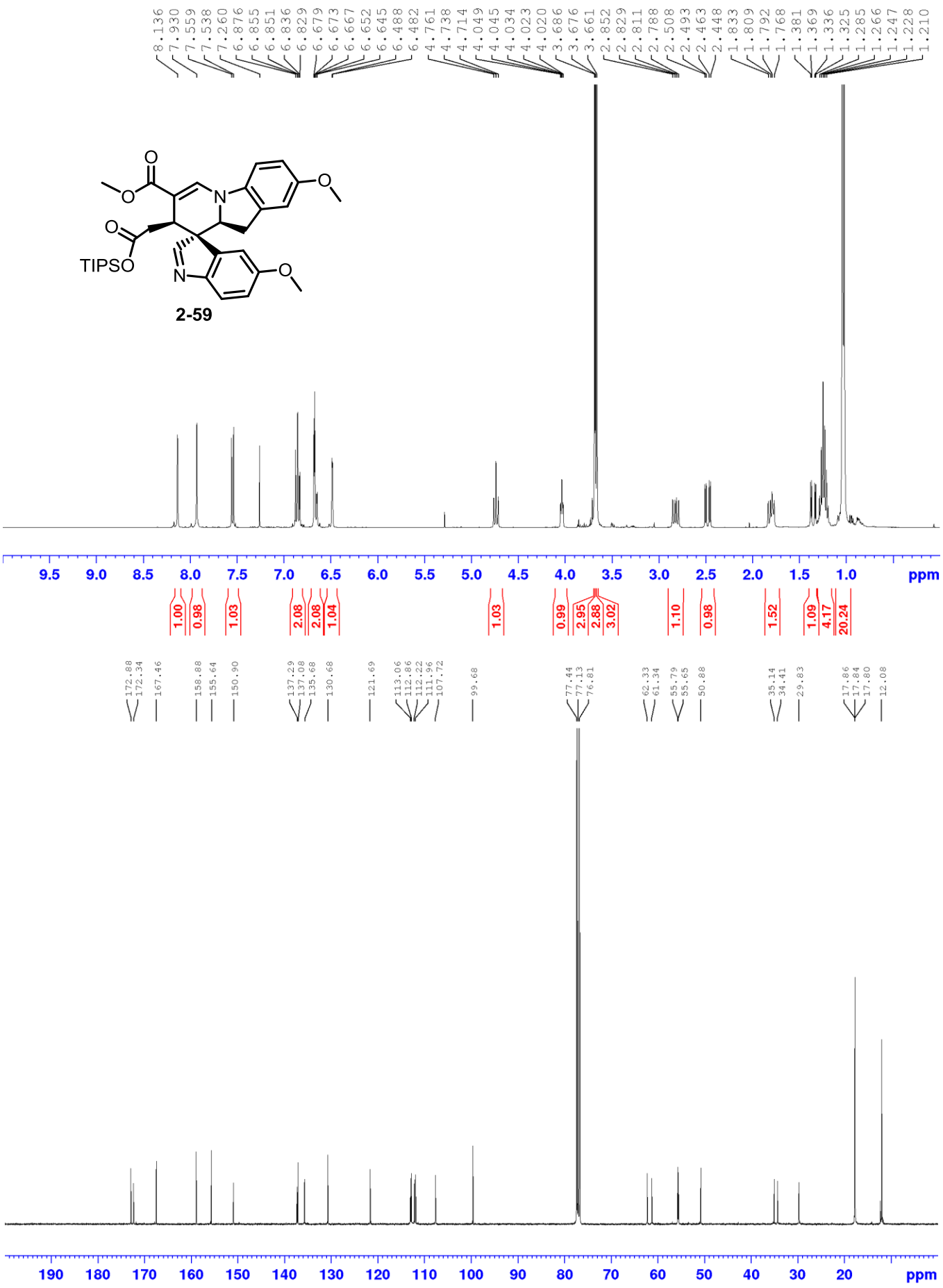
7.088
7.082
7.079
5.261
5.224
5.087
5.050
4.670
4.661
4.653
4.172
4.169
4.165
4.162
3.737
2.276
2.251
2.226
2.201
1.087
1.062
1.037
2-55
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.08
1.07
1.04
1.02
3.30
2.12
3.24
173.57
167.34
161.46
145.97
144.22
77.56
77.14
76.71
65.95
55.49
53.82
51.88
27.24
8.69
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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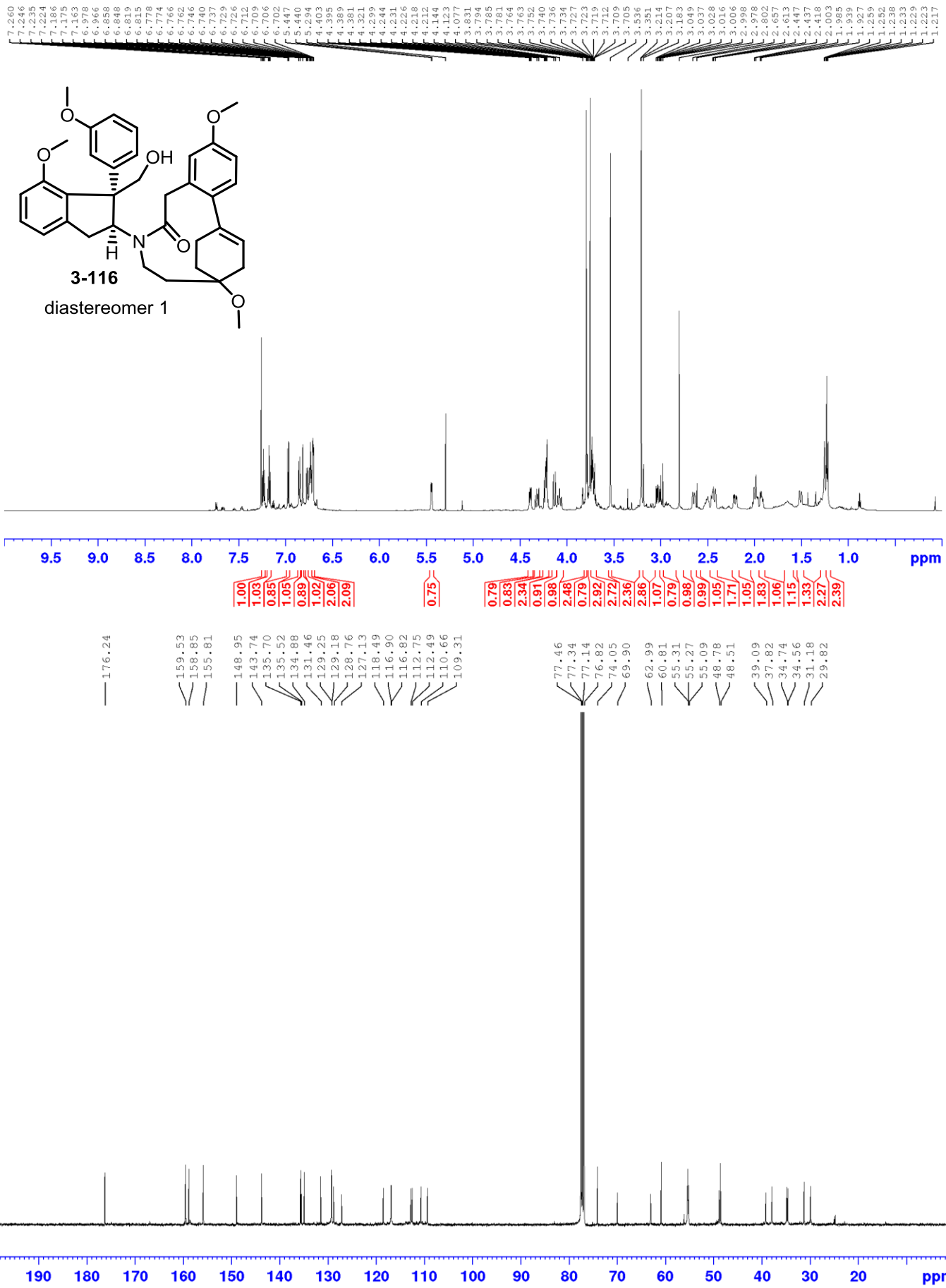
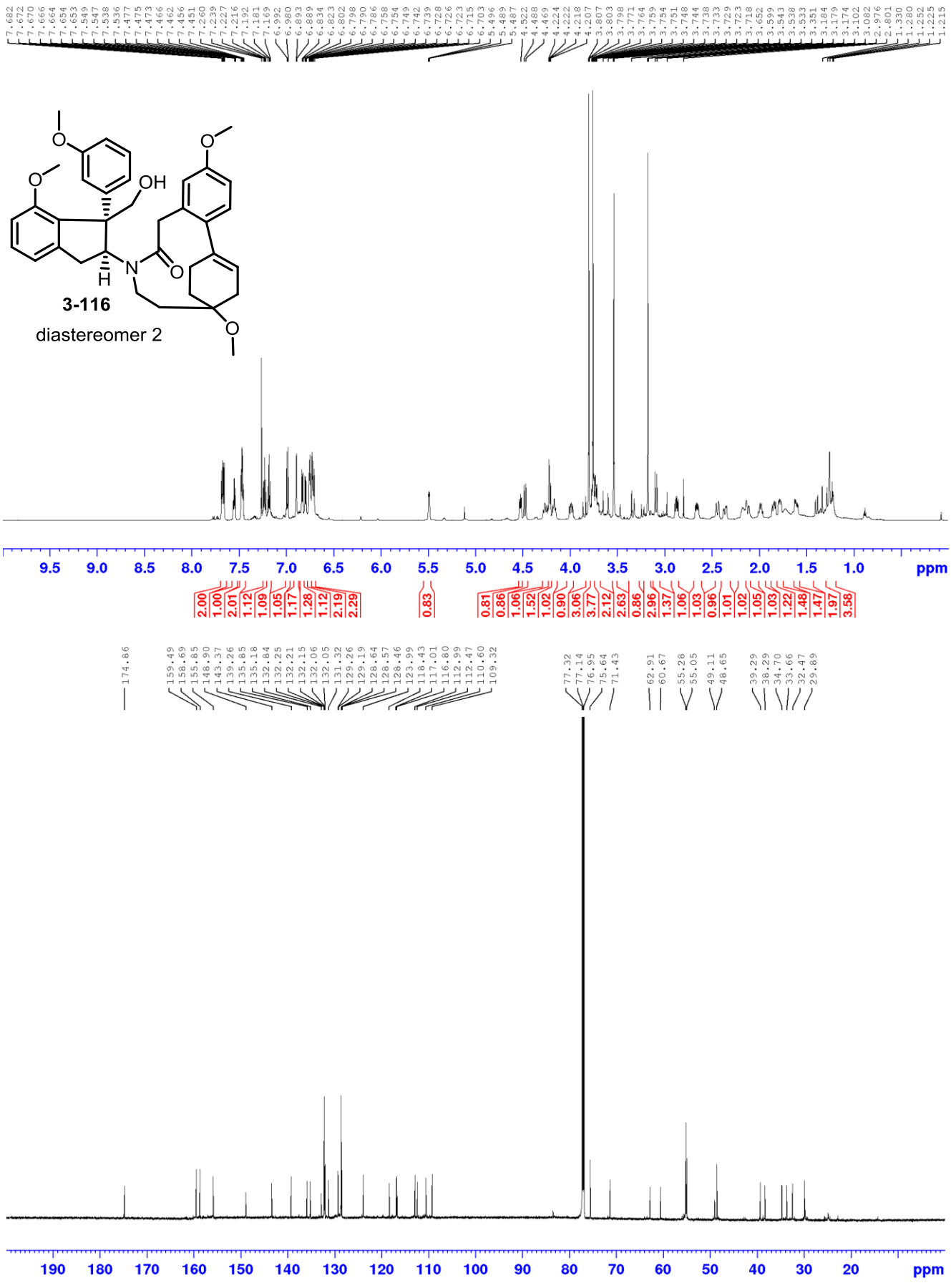
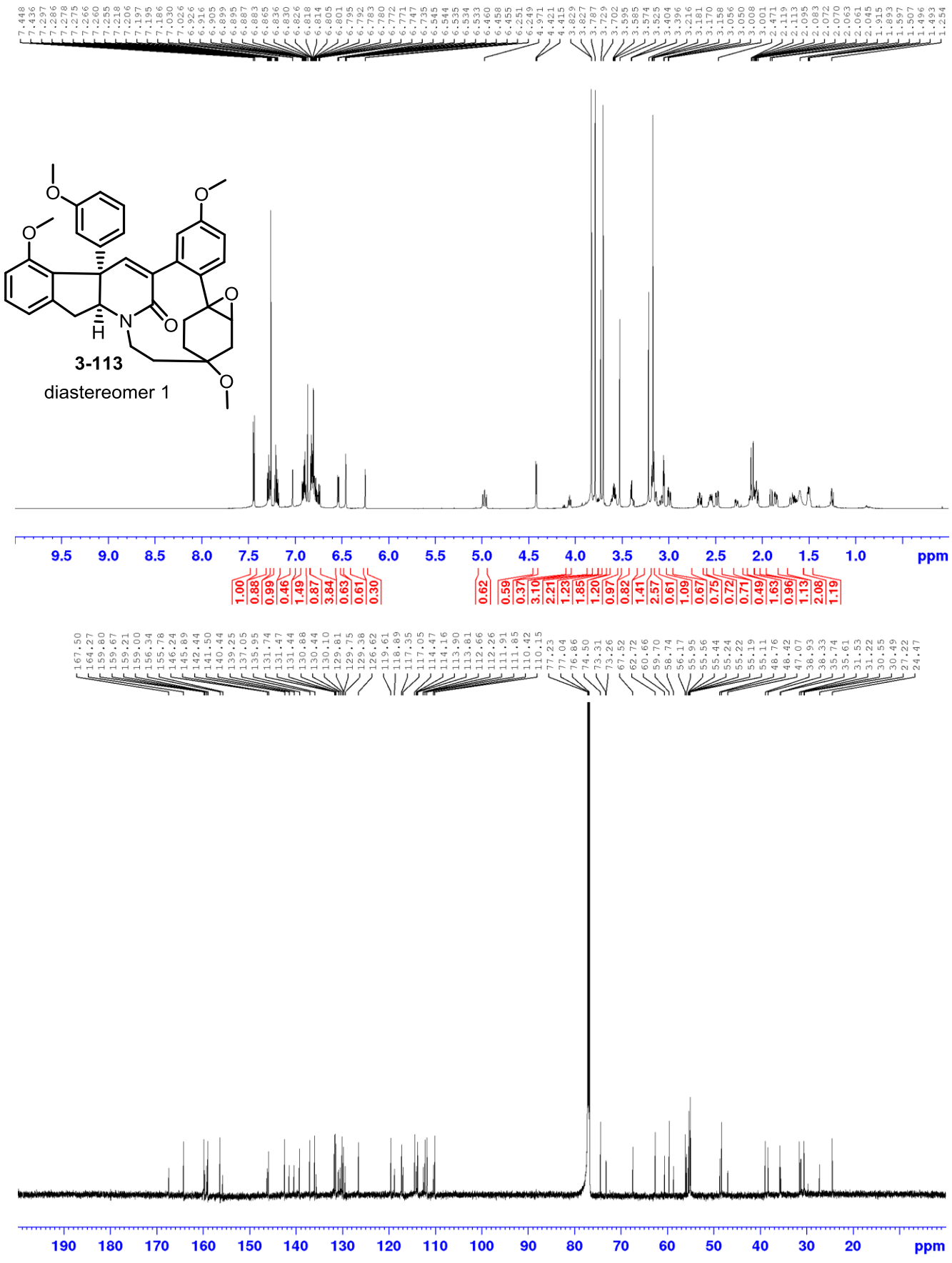
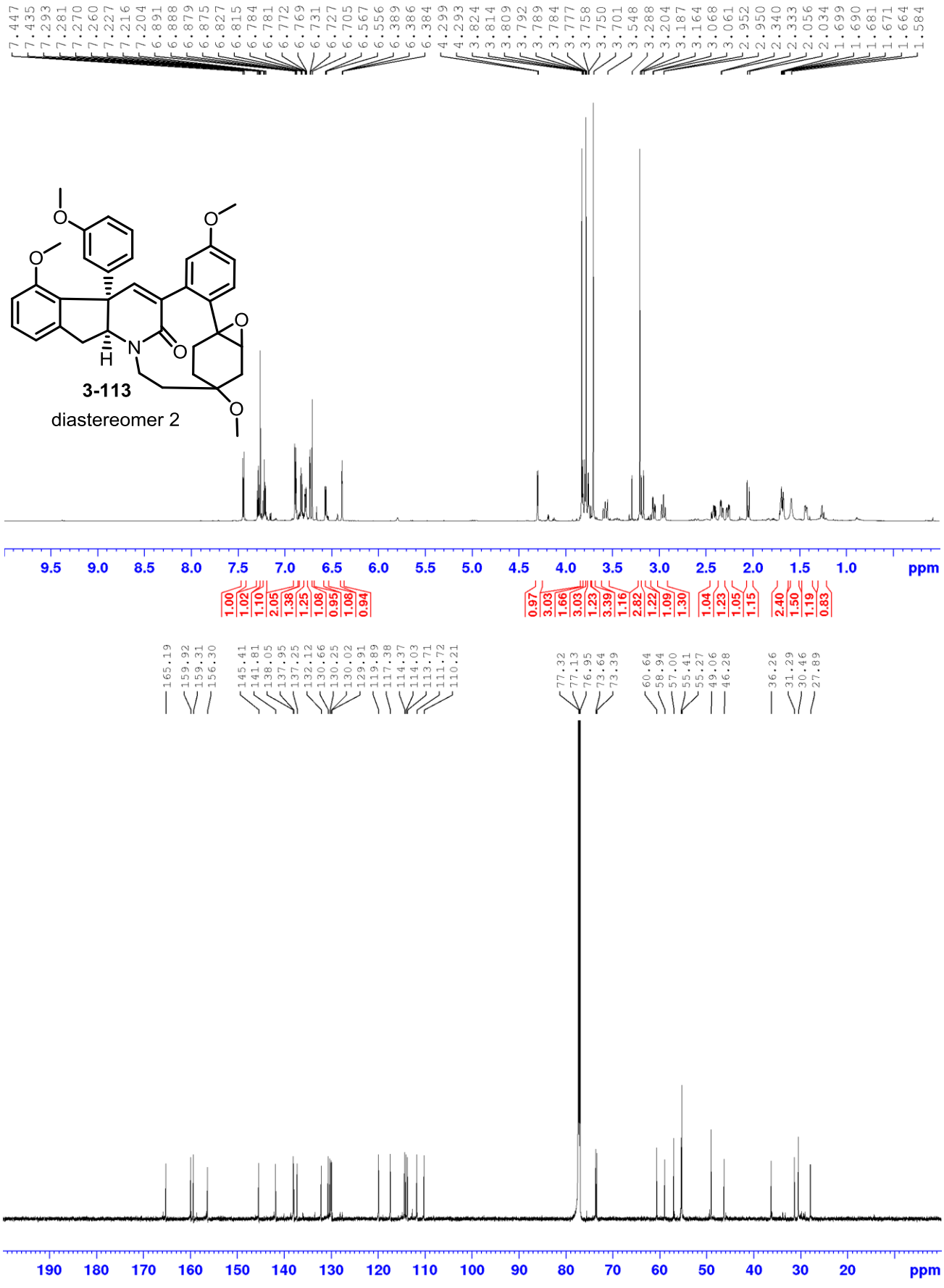
7.930
7.559
7.538
7.260
6.876
6.855
6.851
6.836
6.829
6.679
6.673
6.667
6.652
6.645
6.488
6.482
4.761
4.738
4.714
4.049
4.045
4.034
4.023
4.020
3.686
3.676
3.661
2.852
2.829
2.811
2.788
2.508
2.493
2.463
2.448
1.833
1.809
1.792
1.768
1.381
1.369
1.336
1.325
1.285
1.266
1.247
1.228
1.210
TIPSO
2-59
ppm
1.00
0.98
1.03
2.08
2.08
1.04
1.03
0.99
2.95
2.88
3.02
1.10
0.98
1.52
1.09
4.17
20.24
172.88
172.34
167.46
158.88
155.64
150.90
137.29
137.08
135.68
130.68
121.69
113.06
112.86
112.22
111.96
107.72
99.68
77.44
77.13
76.81
62.33
61.34
55.79
55.65
50.88
35.14
34.41
29.83
17.86
17.84
17.80
12.08
ppm


3-116
diastereomer 1


3-116
diastereomer 2
ppm
ppm


3-113
diastereomer 1
ppm
ppm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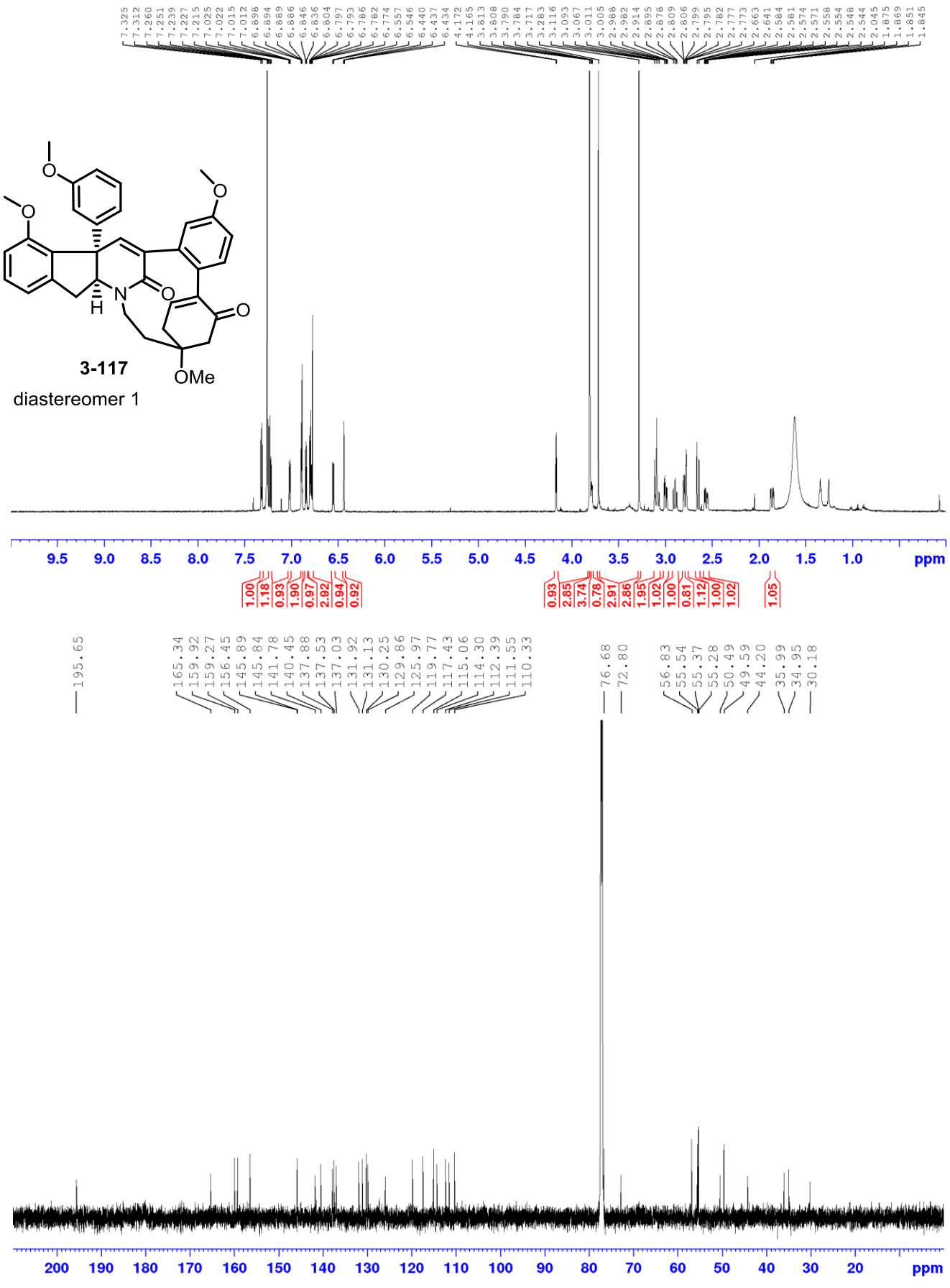
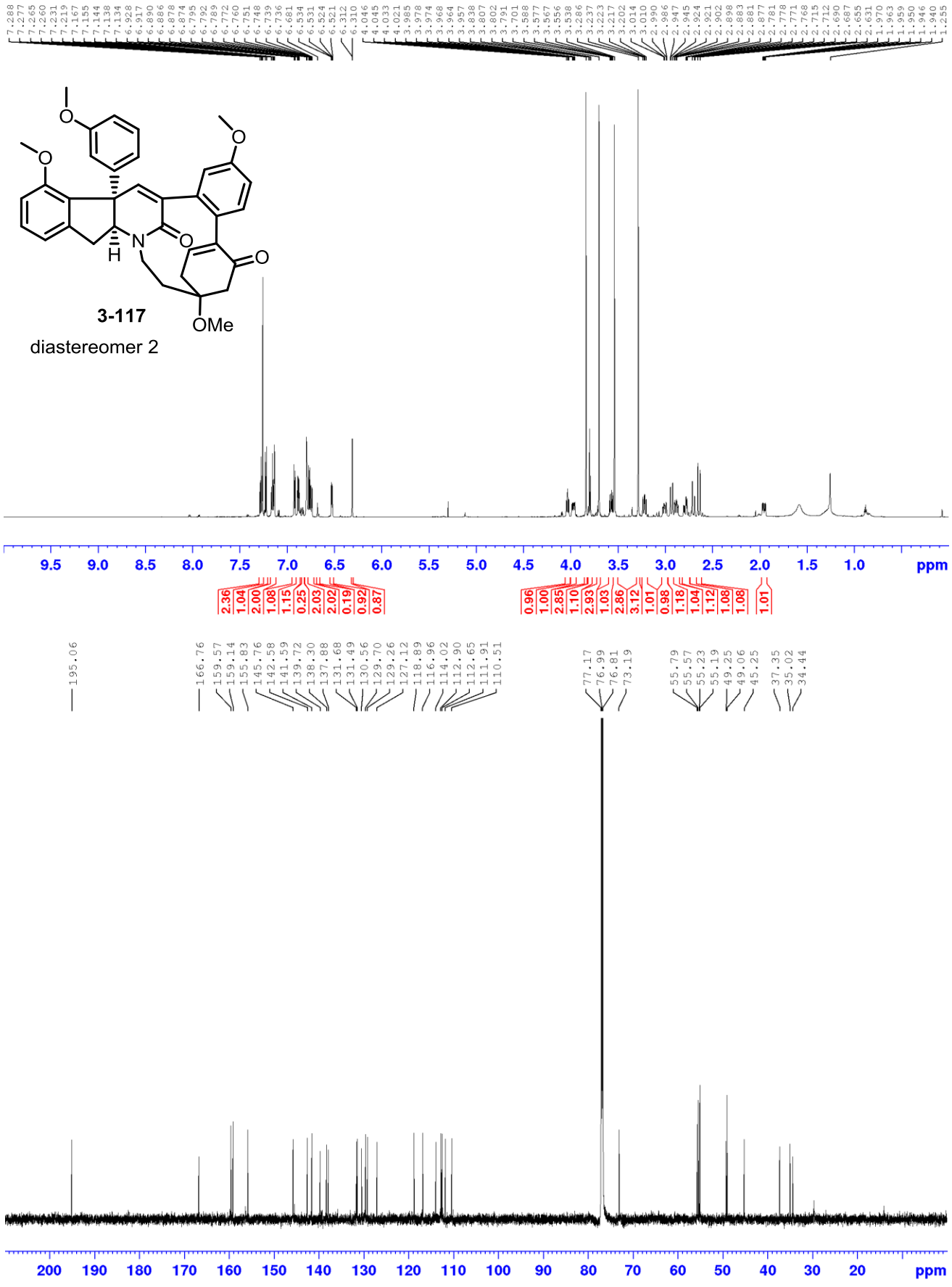
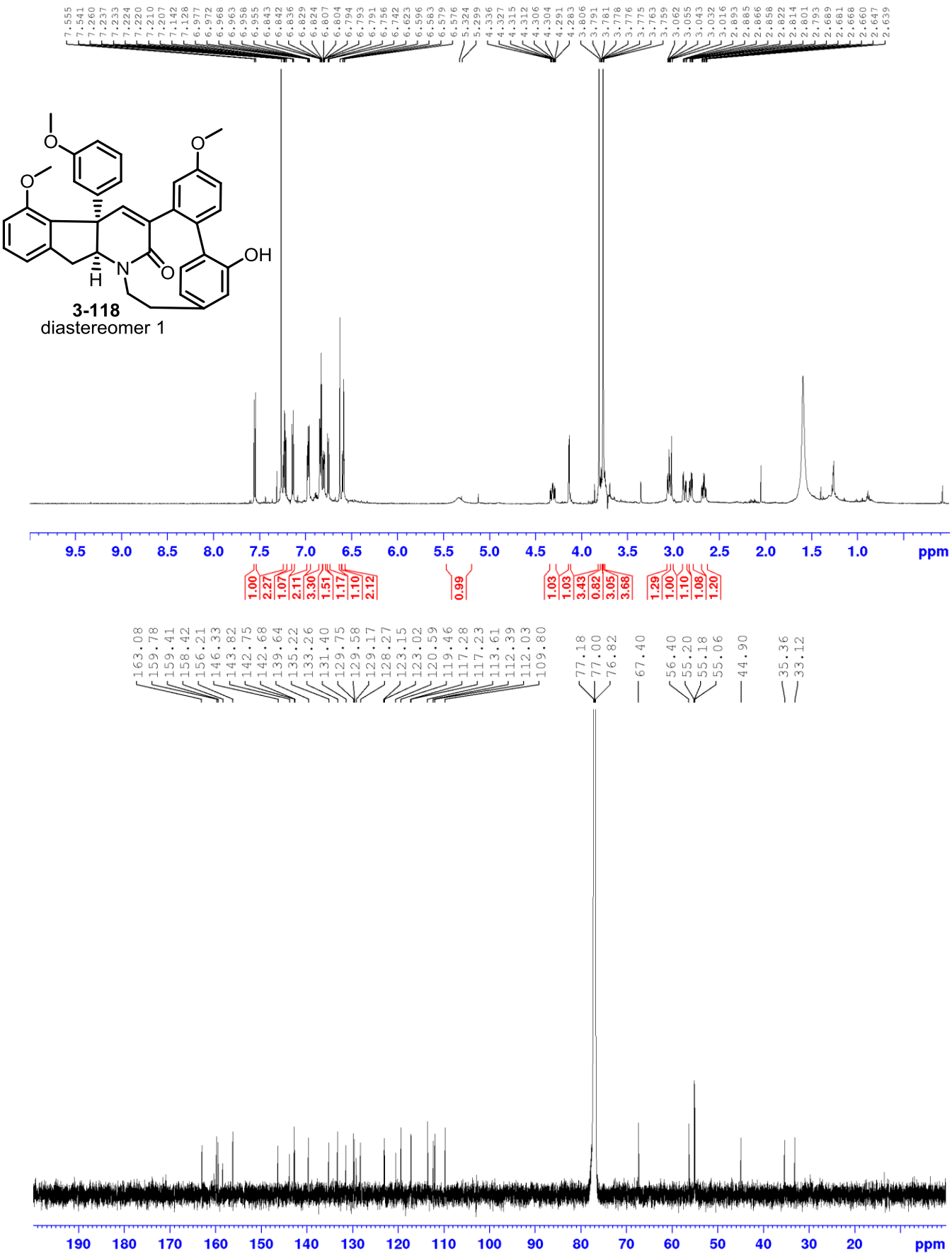
7.260
7.227
7.216
7.204
6.891
6.888
6.879
6.875
6.827
6.815
6.784
6.781
6.772
6.769
6.731
6.727
6.705
6.567
6.556
6.389
6.386
6.384
4.299
4.293
3.824
3.814
3.809
3.792
3.789
3.784
3.777
3.758
3.750
3.701
3.548
3.288
3.204
3.187
3.164
3.068
3.061
2.952
2.950
2.340
2.333
2.056
2.034
1.699
1.690
1.681
1.671
1.664
1.584
3-113
diastereomer 2
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 1.02 1.10 2.05 1.38 1.25 1.08 0.95 1.08 0.94
0.97 3.03 1.66 3.03 1.23 3.39 1.16 2.82 1.22 1.09 1.30 1.04 1.23 1.05 1.15 2.40 1.50 1.19 0.83
165.19
159.92
159.31
156.30
145.41
141.81
138.05
137.95
137.25
132.12
130.66
130.25
130.02
129.91
119.89
117.38
114.37
114.03
113.71
111.72
110.21
77.32
77.13
76.95
73.64
73.39
60.64
58.94
57.00
55.41
55.27
49.06
46.28
36.26
31.29
30.46
27.89
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


3-117
diastereomer 1
OMe
ppm


3-117
diastereomer 2
OMe
ppm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7.233
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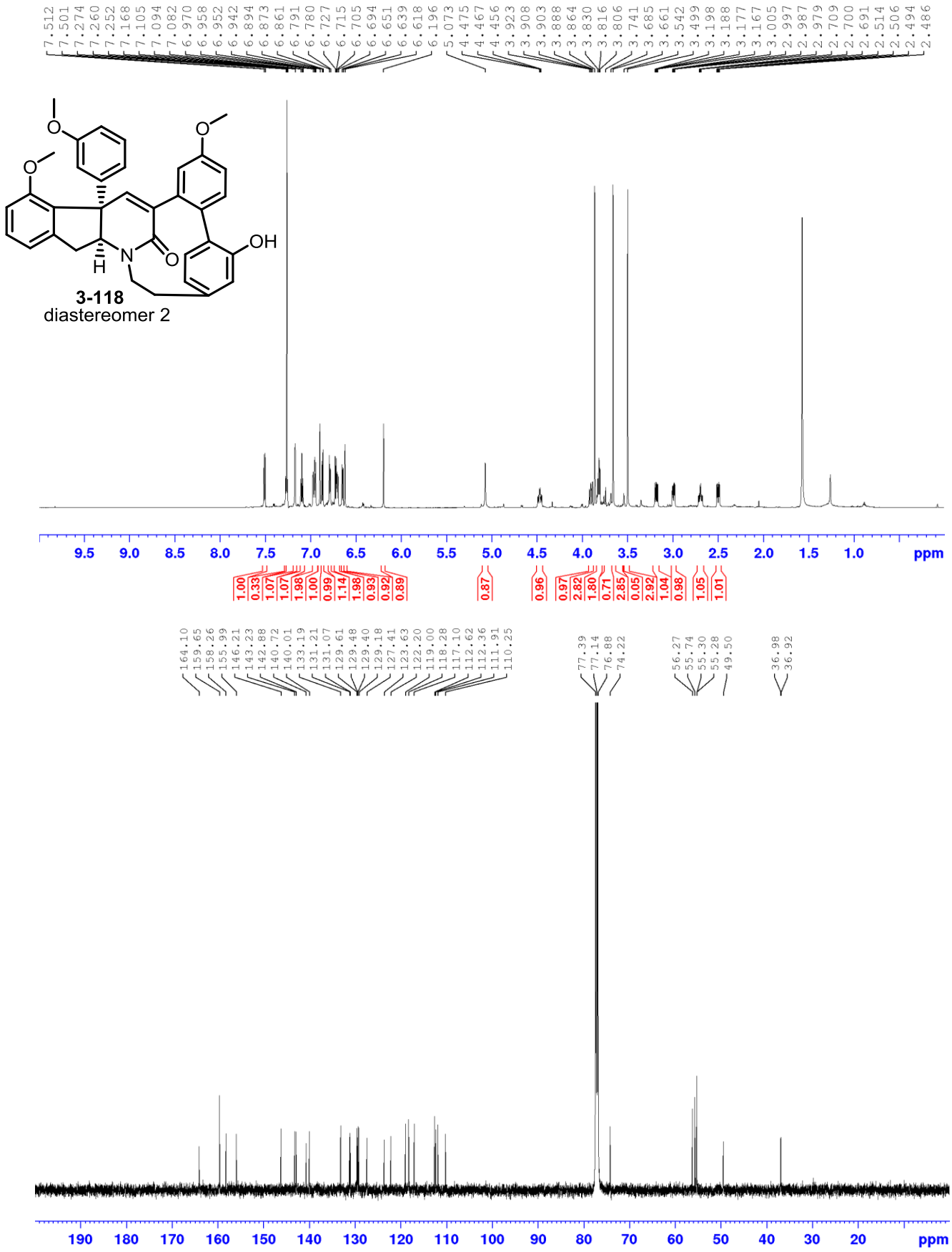
7.220
7.210
7.207
7.142
7.128
6.977
6.972
6.968
6.963
6.958
6.955
6.843
6.842
6.836
6.829
6.824
6.807
6.804
6.794
6.793
6.791
6.756
6.742
6.623
6.596
6.583
6.579
6.576
5.324
5.299
4.336
4.327
4.315
4.312
4.306
4.304
4.291
4.283
3.806
3.791
3.781
3.778
3.776
3.775
3.763
3.759
3.062
3.055
3.043
3.032
3.016
2.893
2.885
2.866
2.858
2.822
2.814
2.801
2.793
2.689
2.681
2.668
2.660
2.647
2.639
O
O
O
OH
N
H
O
3-118
diastereomer 1
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
2.27
1.07
2.11
3.30
1.51
1.17
1.10
2.12
0.99
1.03
1.03
3.43
0.82
3.05
3.68
1.29
1.00
1.10
1.08
1.20
163.08
159.78
159.41
158.42
156.21
146.33
143.82
142.75
142.68
139.64
135.22
133.26
131.40
129.75
129.58
129.17
128.27
123.15
123.02
120.59
119.46
117.28
117.23
113.61
112.39
112.03
109.80
77.18
77.00
76.82
67.40
56.40
55.20
55.18
55.06
44.90
35.36
33.12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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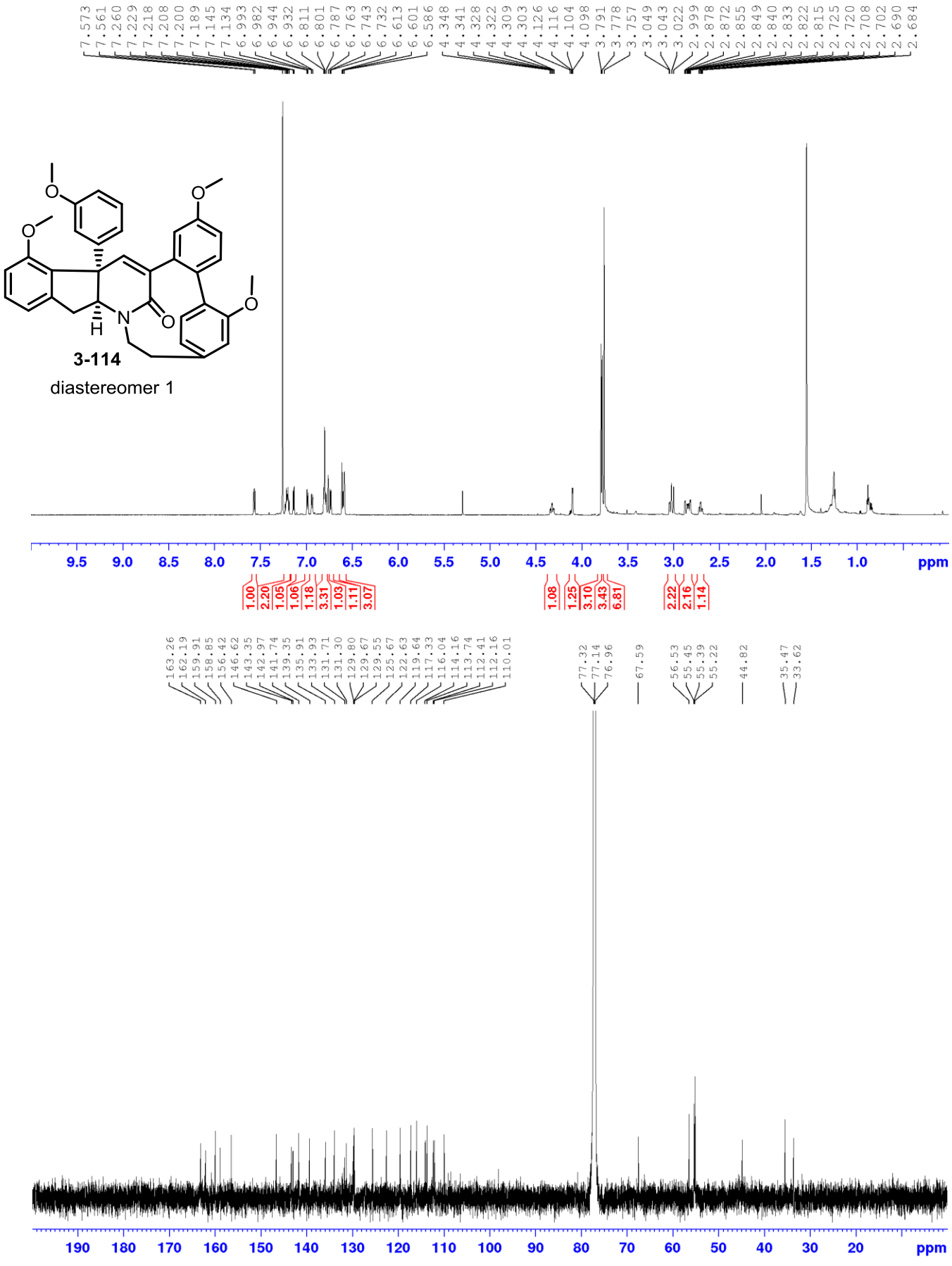
7.274
7.260
7.252
7.168
7.105
7.094
7.082
6.970
6.958
6.952
6.942
6.894
6.873
6.861
6.791
6.780
6.727
6.715
6.705
6.694
6.651
6.639
6.618
6.196
5.073
4.475
4.467
4.456
3.923
3.908
3.903
3.888
3.864
3.830
3.816
3.806
3.741
3.685
3.661
3.542
3.499
3.198
3.188
3.177
3.167
3.005
2.997
2.987
2.979
2.709
2.700
2.691
2.514
2.506
2.494
2.486
O
O
O
OH
N
H
O
3-118
diastereomer 2
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 0.33 1.07 1.07 1.98 1.00 0.99 1.14 1.98 0.93 0.92 0.89 0.87 0.96 0.97 2.82 1.80 0.71 2.85 0.05 2.92 1.04 0.98 1.05 1.01
164.10
159.65
158.26
155.99
146.21
143.23
142.88
140.72
140.01
133.19
131.21
131.07
129.61
129.48
129.40
129.18
127.41
123.63
122.20
119.00
118.28
117.10
112.62
112.36
111.91
110.25
77.39
77.14
76.88
74.22
56.27
55.74
55.30
55.28
49.50
36.98
36.92
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.189
7.145
7.134
6.993
6.982
6.944
6.932
6.811
6.801
6.787
6.763
6.743
6.732
6.613
6.601
6.586
4.348
4.341
4.328
4.322
4.309
4.303
4.126
4.116
4.104
4.098
3.791
3.778
3.757
3.049
3.043
3.022
2.999
2.878
2.872
2.855
2.849
2.840
2.833
2.822
2.815
2.725
2.720
2.708
2.702
2.690
2.684
3-114
diastereomer 1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 2.20 1.05 1.06 1.18 3.31 1.03 1.11 3.07
1.08 1.25 3.10 3.43 6.81
2.22 2.16 1.14
163.26
162.19
159.91
158.85
156.42
146.62
143.35
142.97
141.74
139.35
135.91
133.93
131.71
131.30
129.80
129.67
129.55
125.67
122.63
119.64
117.33
116.04
114.16
113.74
112.41
112.16
110.01
77.32
77.14
76.96
67.59
56.53
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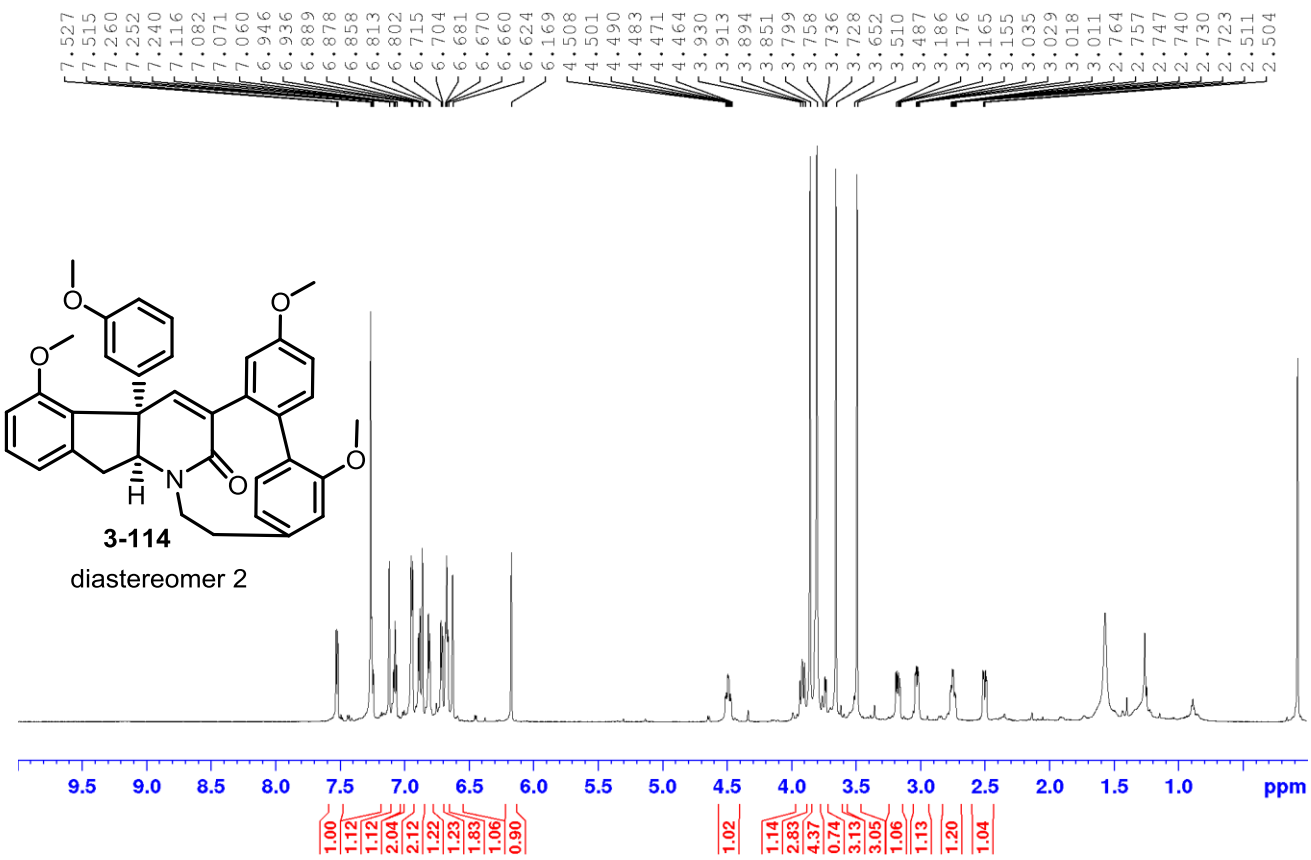
55.39
55.22
44.82
35.47
33.62
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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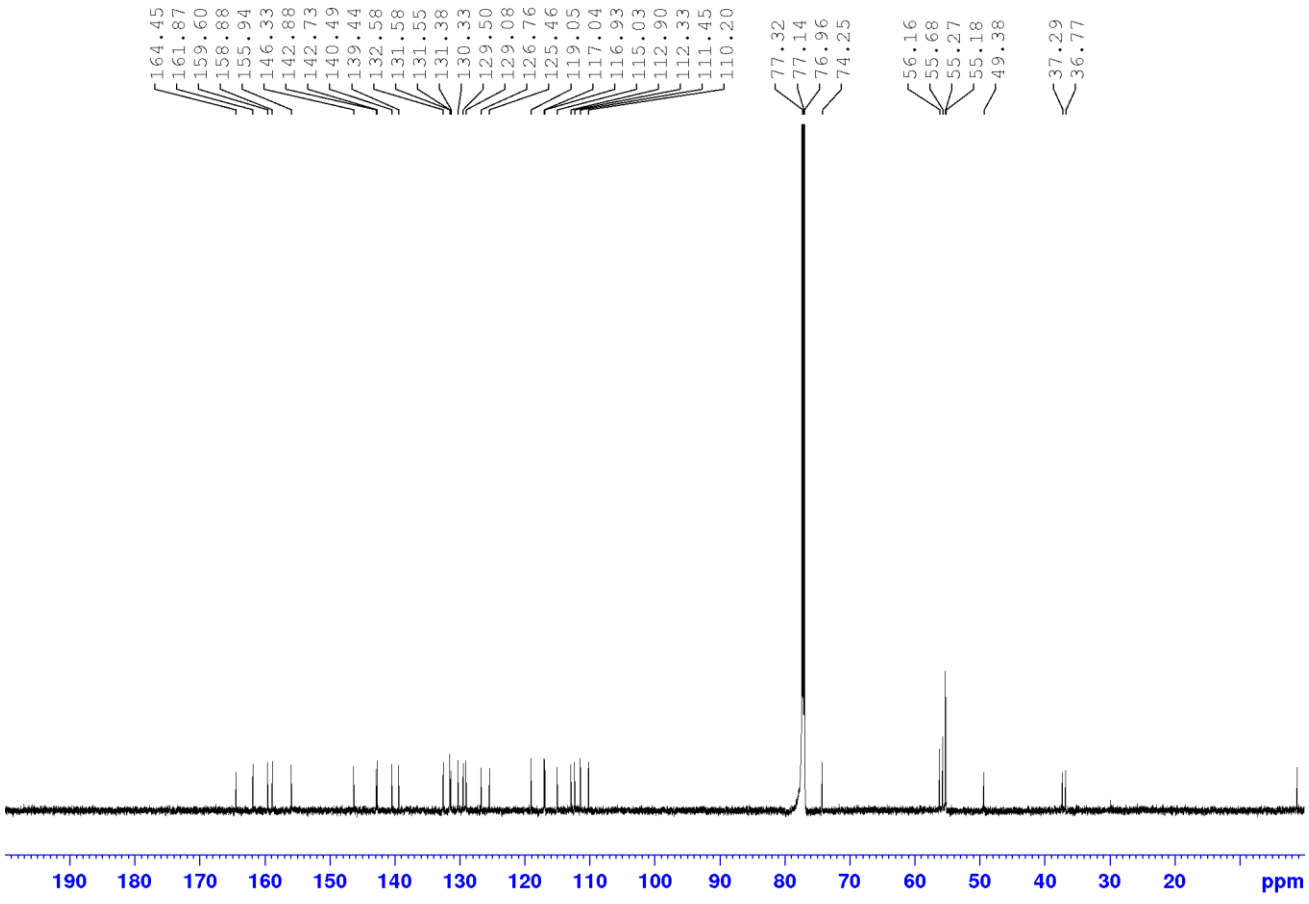
7.252
7.240
7.116
7.082
7.071
7.060
6.946
6.936
6.889
6.878
6.858
6.813
6.802
6.715
6.704
6.681
6.670
6.660
6.624
6.169
4.508
4.501
4.490
4.483
4.471
4.464
3.930
3.913
3.894
3.851
3.799
3.758
3.736
3.728
3.652
3.510
3.487
3.186
3.176
3.165
3.155
3.035
3.029
3.018
3.011
2.764
2.757
2.747
2.740
2.730
2.723
2.511
2.504
O
O
O
O
N
H
O
3-114
diastereomer 2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.12
1.12
2.04
2.12
1.22
1.23
1.83
1.06
0.90
1.02
1.14
2.83
4.37
0.74
3.13
3.05
1.06
1.13
1.20
1.04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131.55
131.38
130.33
129.50
129.08
126.76
125.46
119.05
117.04
116.93
115.03
112.90
112.33
111.45
110.20
77.32
77.14
76.96
74.25
56.16
55.68
55.27
55.18
49.38
37.29
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190
180
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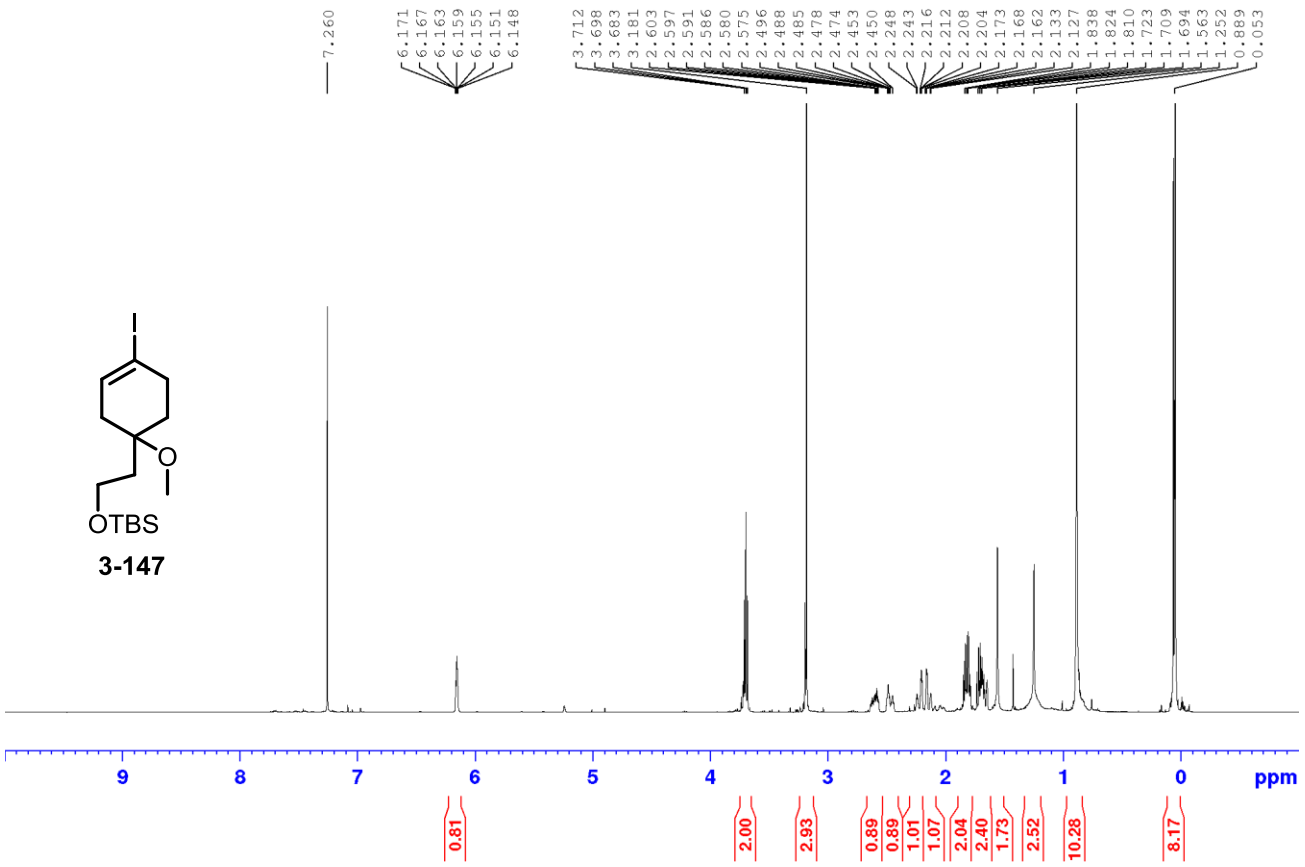
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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6.167
6.163
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6.155
6.151
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2.474
2.453
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2.243
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2.162
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OTBS
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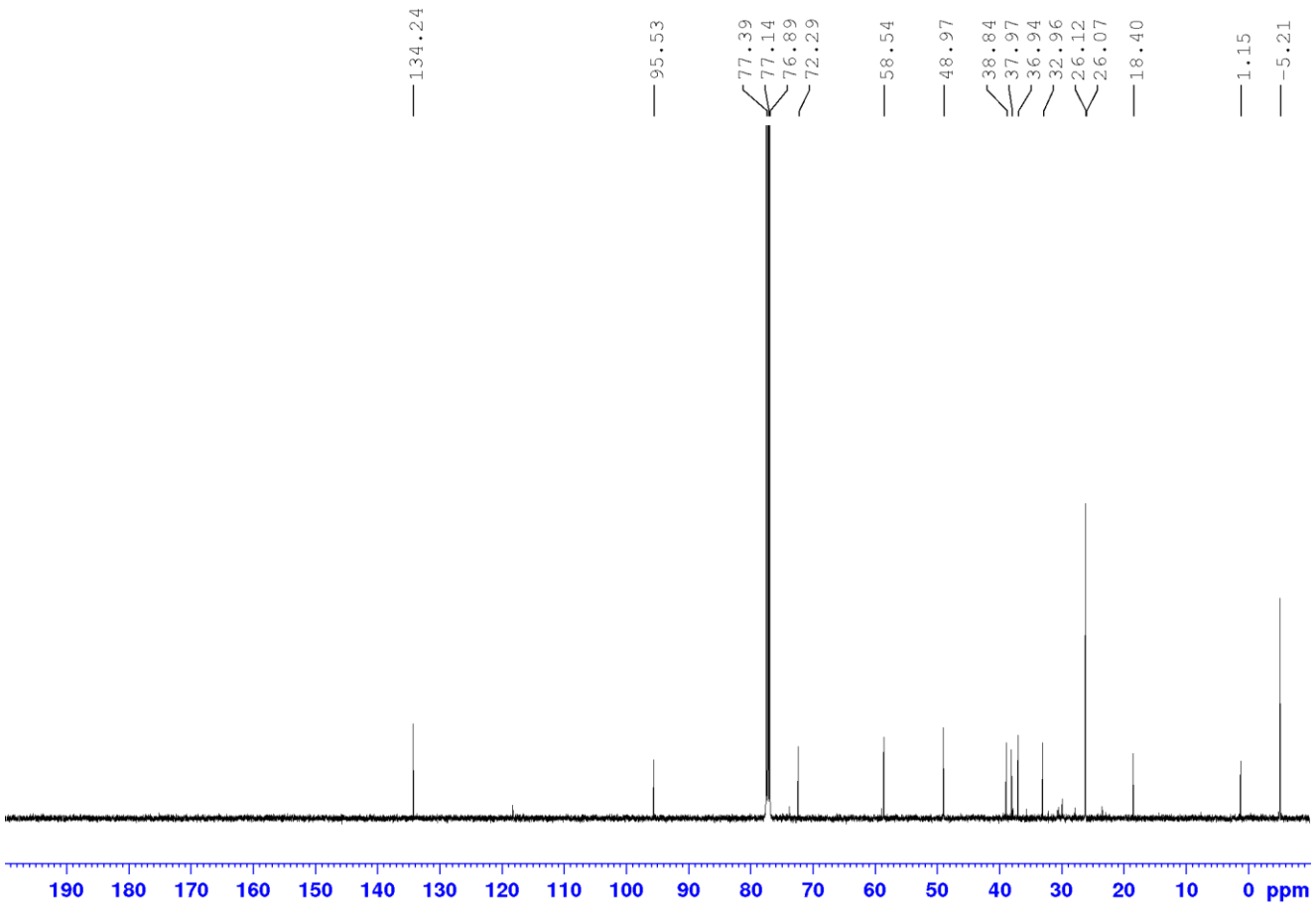
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26.07
18.40
1.15
-5.21
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140
130
120
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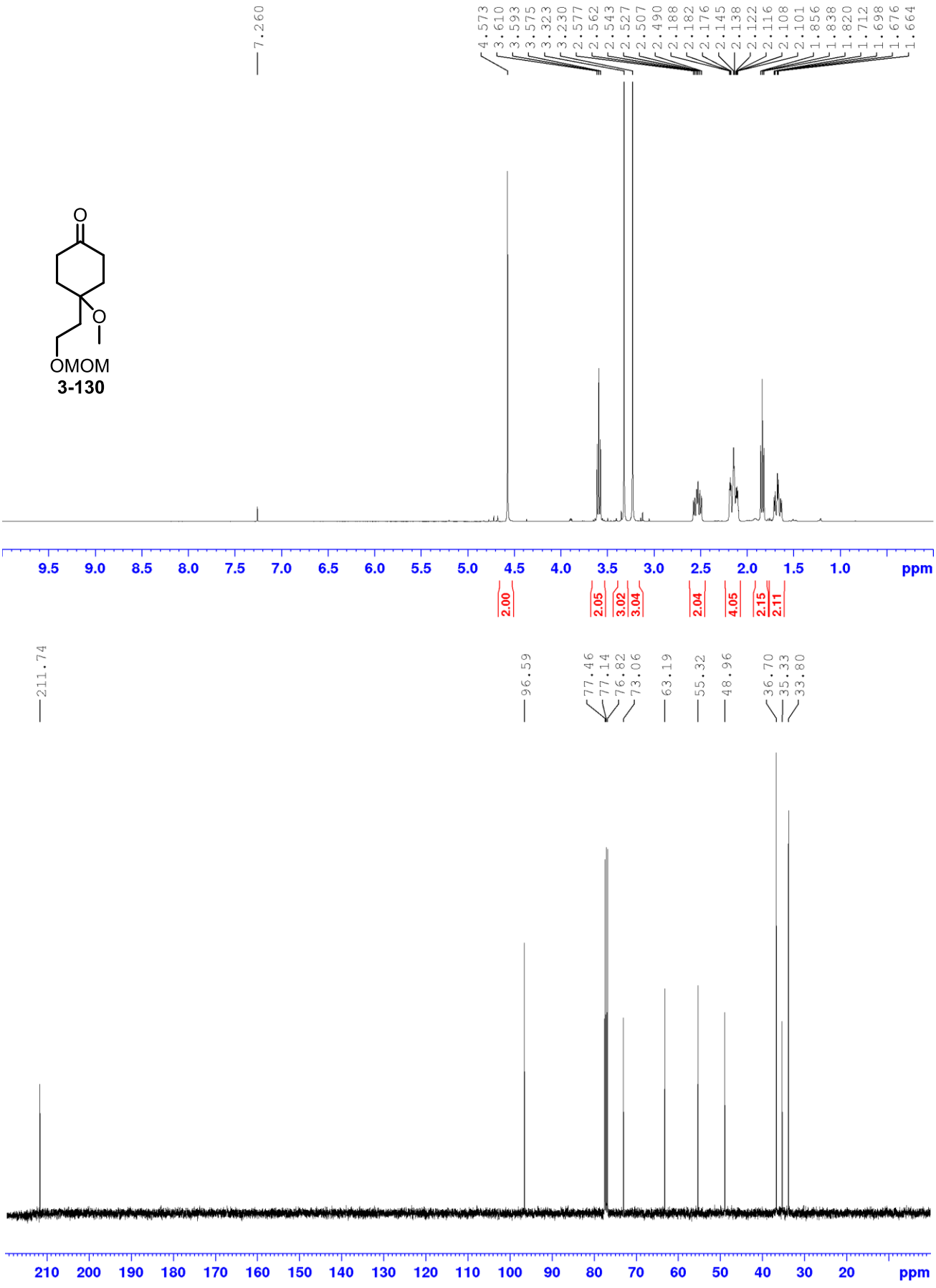
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2.176
2.145
2.138
2.122
2.116
2.108
2.101
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1.820
1.712
1.698
1.676
1.664
O
O
OMOM
3-130
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2.05
3.02
3.04
2.04
4.05
2.15
2.11
211.74
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77.46
77.14
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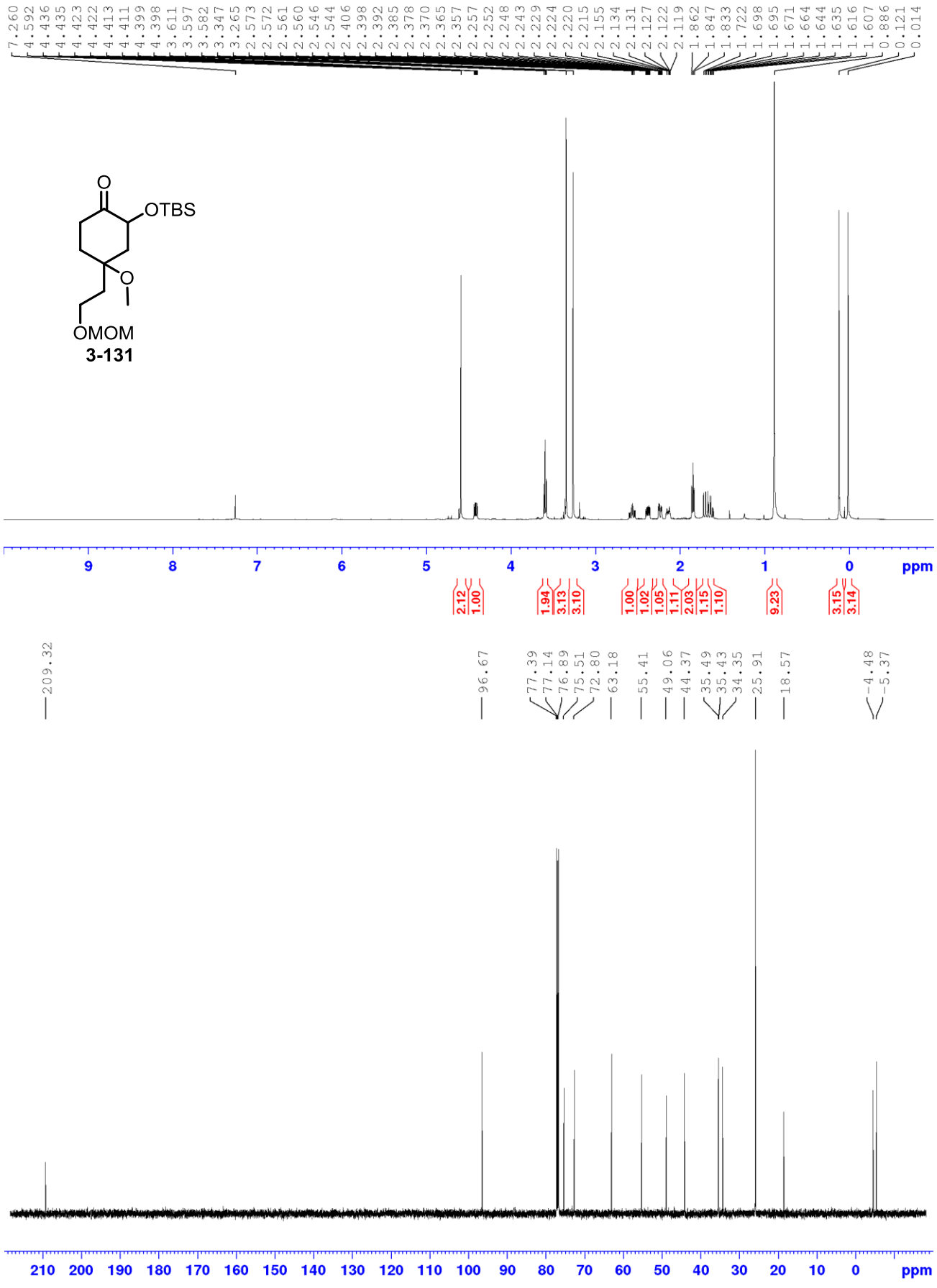
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3.265
2.573
2.572
2.561
2.560
2.546
2.544
2.406
2.398
2.392
2.385
2.378
2.370
2.365
2.357
2.257
2.252
2.248
2.243
2.229
2.224
2.220
2.215
2.155
2.134
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2.127
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2.119
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1.722
1.698
1.695
1.671
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OTBS
O
OMOM
3-131
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4
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1.11
2.03
1.15
1.10
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3.15
3.14
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77.14
76.89
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55.41
49.06
44.37
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35.43
34.35
25.91
18.57
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-5.37
210
200
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60
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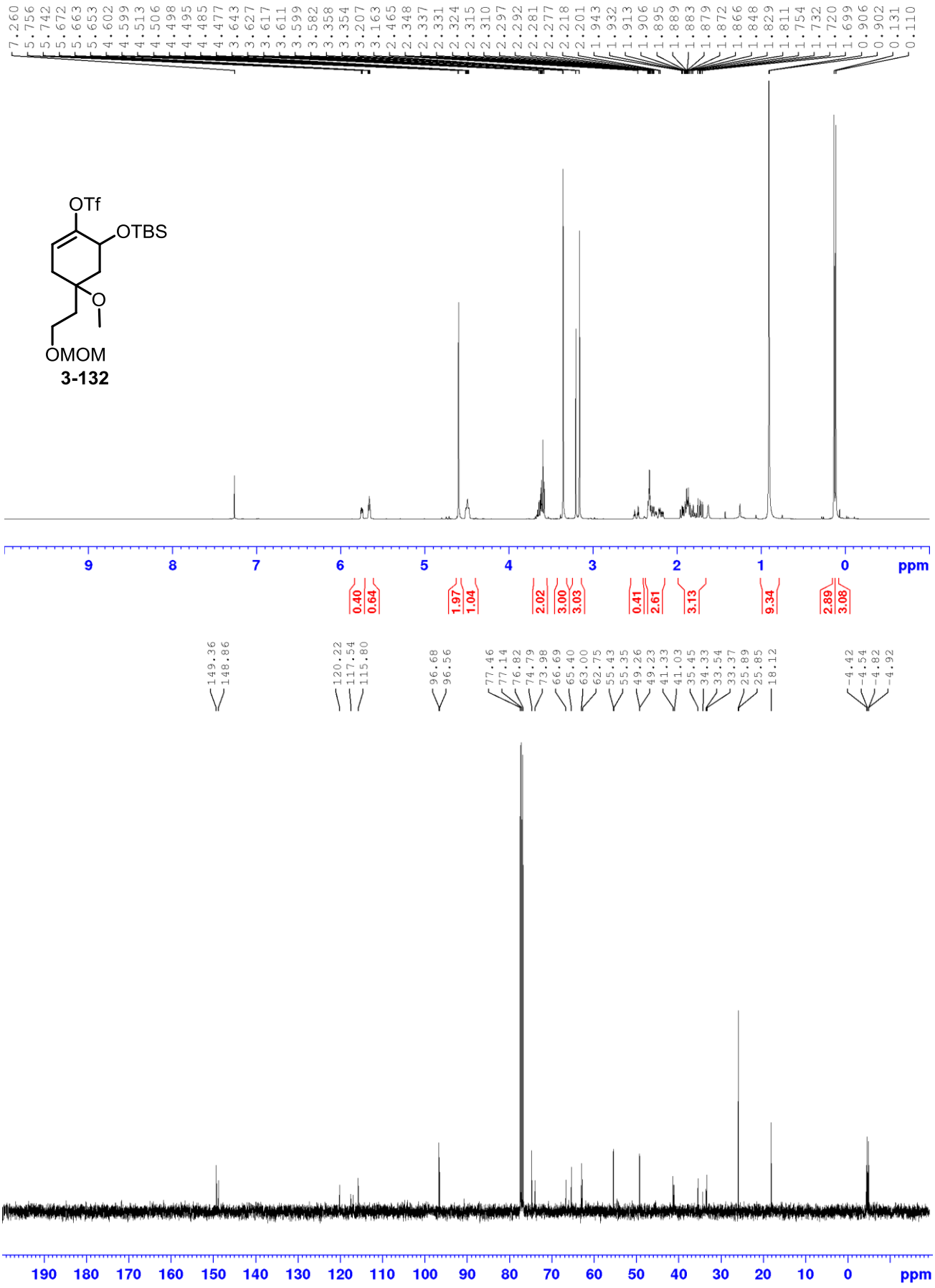
ppm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3.643
3.627
3.617
3.611
3.599
3.582
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2.281
2.277
2.218
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1.932
1.913
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OTf
OTBS
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OMOM
3-132
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3.08
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148.86
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74.79
73.98
66.69
65.40
63.00
62.75
55.43
55.35
49.26
49.23
41.33
41.03
35.45
34.33
33.54
33.37
25.89
25.85
18.12
-4.42
-4.54
-4.82
-4.92
190
180
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150
140
130
120
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100
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80
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60
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20
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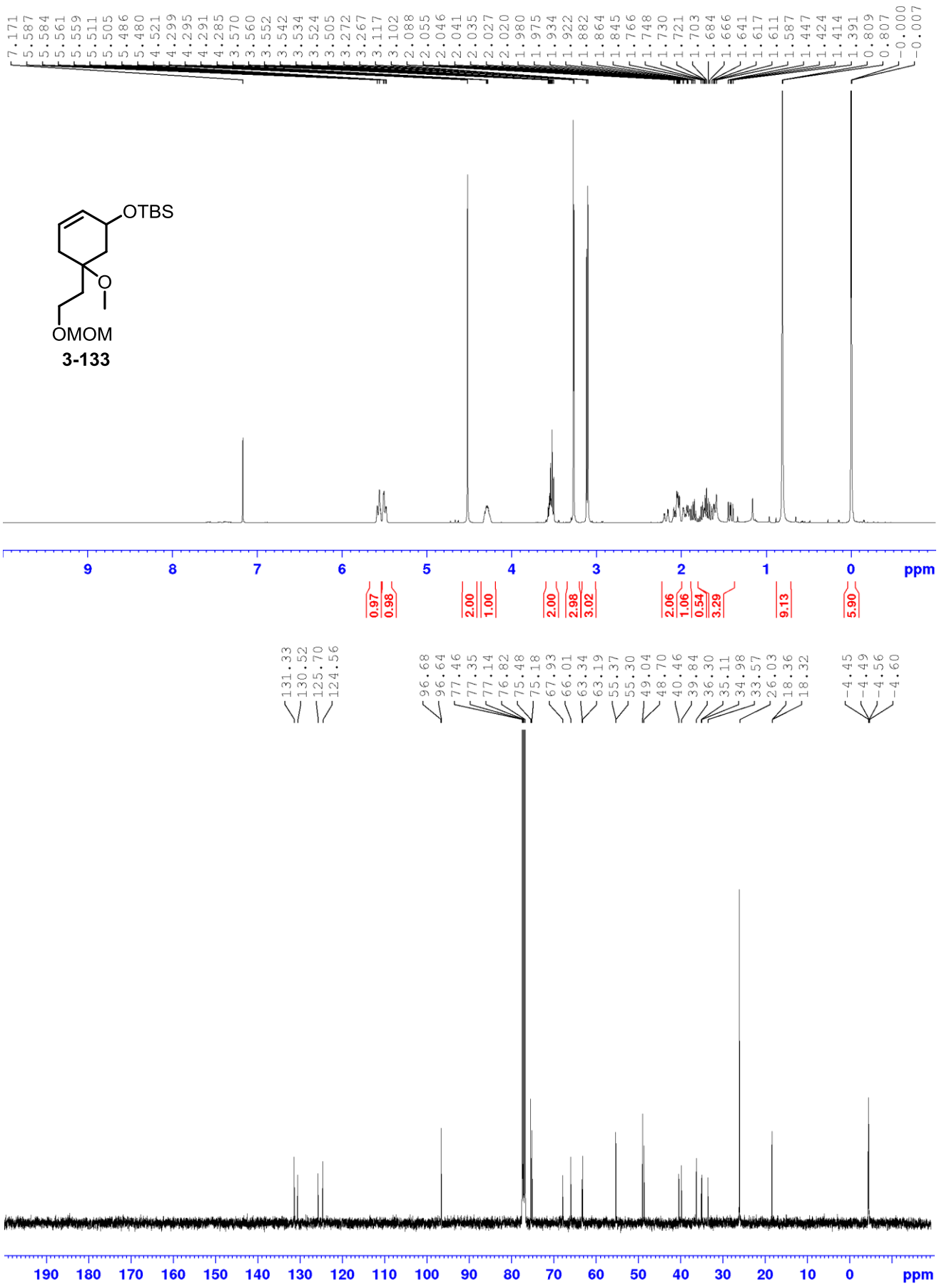
ppm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3.542
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3.524
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2.041
2.035
2.027
2.020
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1.922
1.882
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1.730
1.721
1.703
1.684
1.666
1.641
1.617
1.611
1.587
1.447
1.424
1.414
1.391
0.809
0.807
-0.000
-0.007
OTBS
O
OMOM
3-133
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8
7
6
5
4
3
2
1
0
ppm
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0.98
2.00
1.00
2.00
2.98
3.02
2.06
1.06
0.54
3.29
9.13
5.90
131.33
130.52
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96.64
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77.35
77.14
76.82
75.48
75.18
67.93
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63.34
63.19
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40.46
39.84
36.30
35.11
34.98
33.57
26.03
18.36
18.32
-4.45
-4.49
-4.56
-4.60
190
180
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150
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130
120
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60
50
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30
20
10
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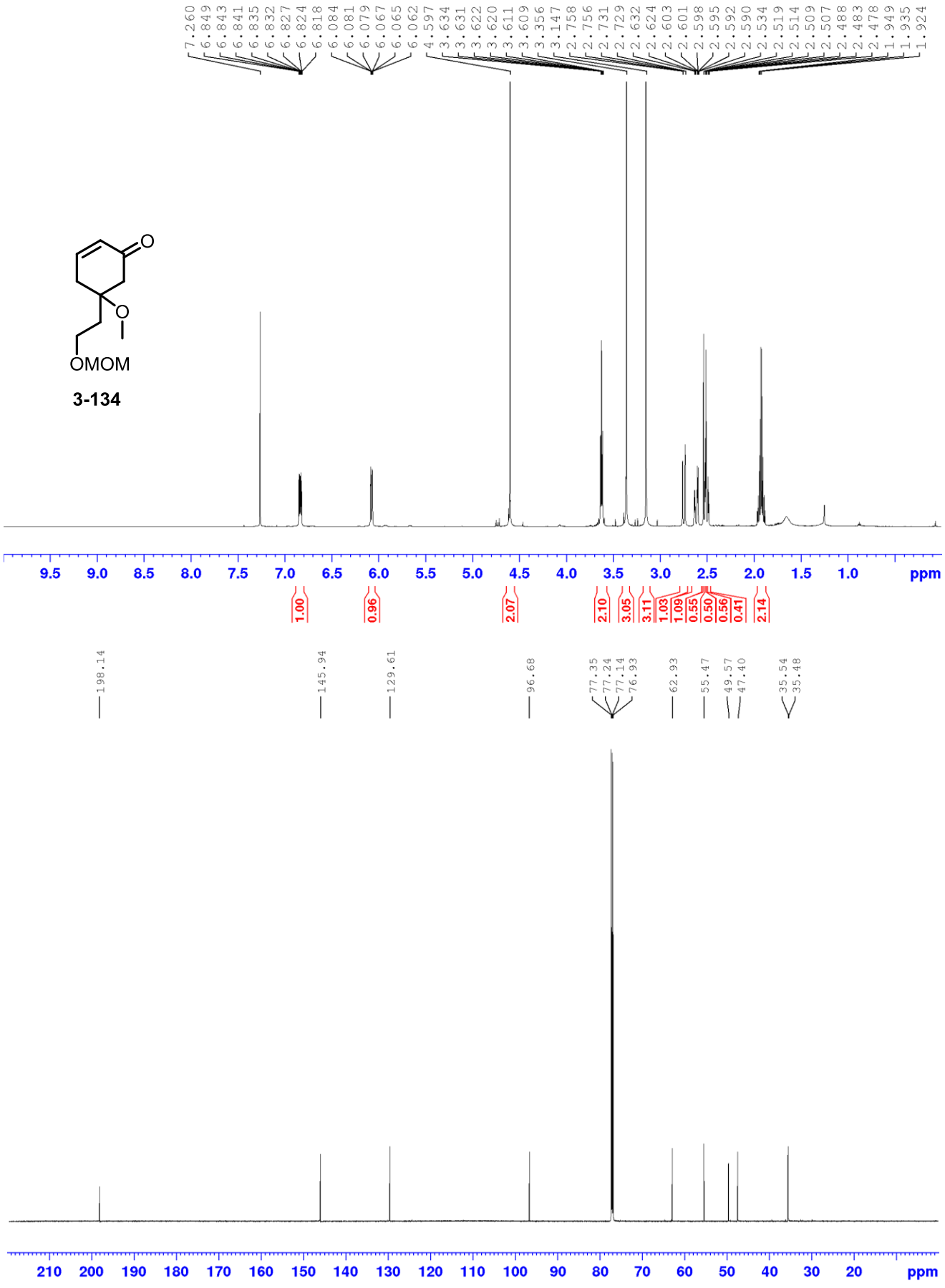
ppm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6.065
6.062
4.597
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3.631
3.622
3.620
3.611
3.609
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3.147
2.758
2.756
2.731
2.729
2.632
2.624
2.603
2.601
2.598
2.595
2.592
2.590
2.534
2.519
2.514
2.509
2.507
2.488
2.483
2.478
1.949
1.935
1.924
O
O
OMOM
3-134
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0.96
2.07
2.10
3.05
3.11
1.03
1.09
0.55
0.50
0.56
0.41
2.14
198.14
145.94
129.61
96.68
77.35
77.24
77.14
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35.54
35.48
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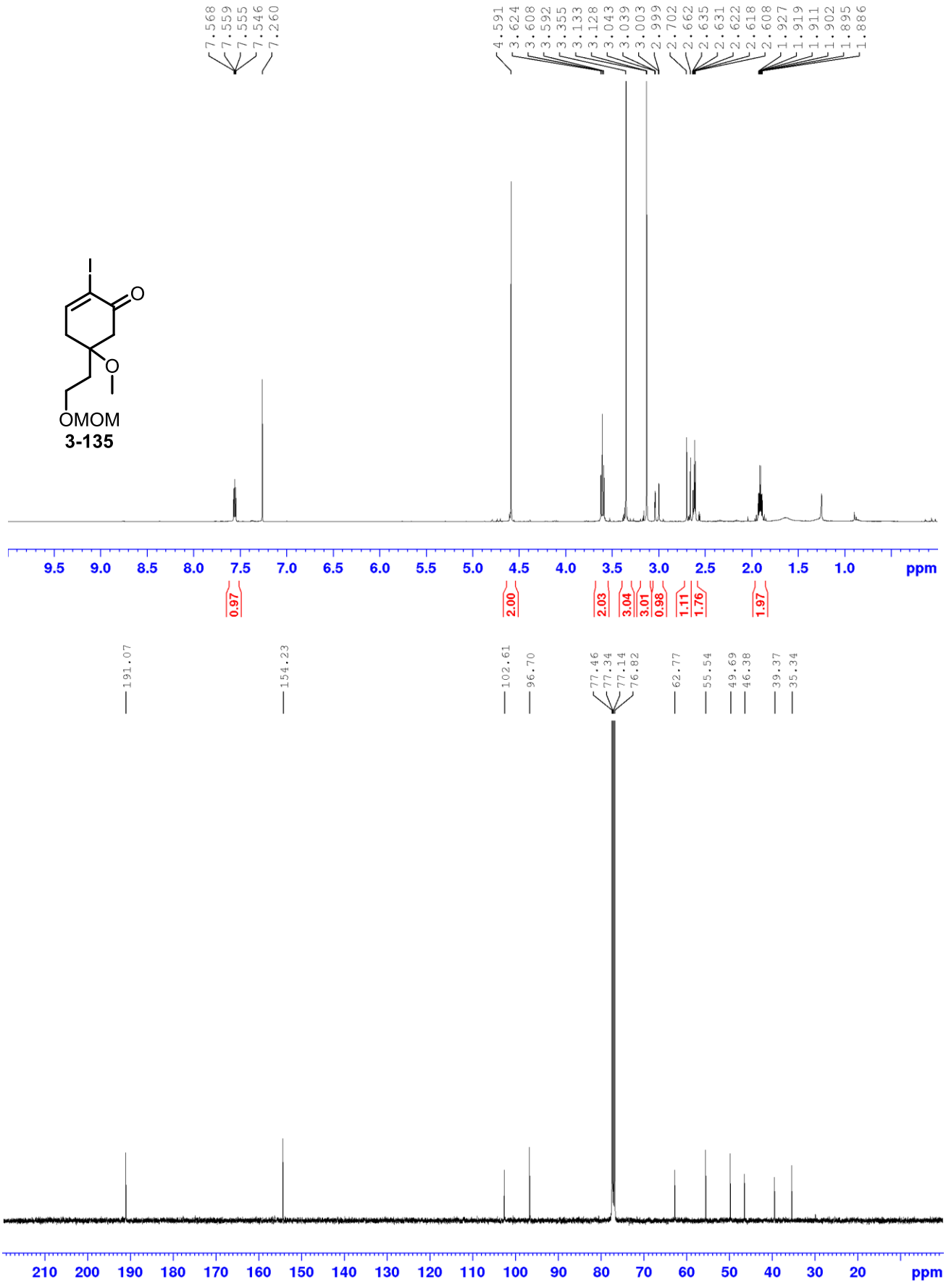
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2.662
2.635
2.631
2.622
2.618
2.608
1.927
1.919
1.911
1.902
1.895
1.886
I
O
O
OMOM
3-135
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2.00
2.03
3.04
3.01
0.98
1.11
1.76
1.97
191.07
154.23
102.61
96.70
77.46
77.34
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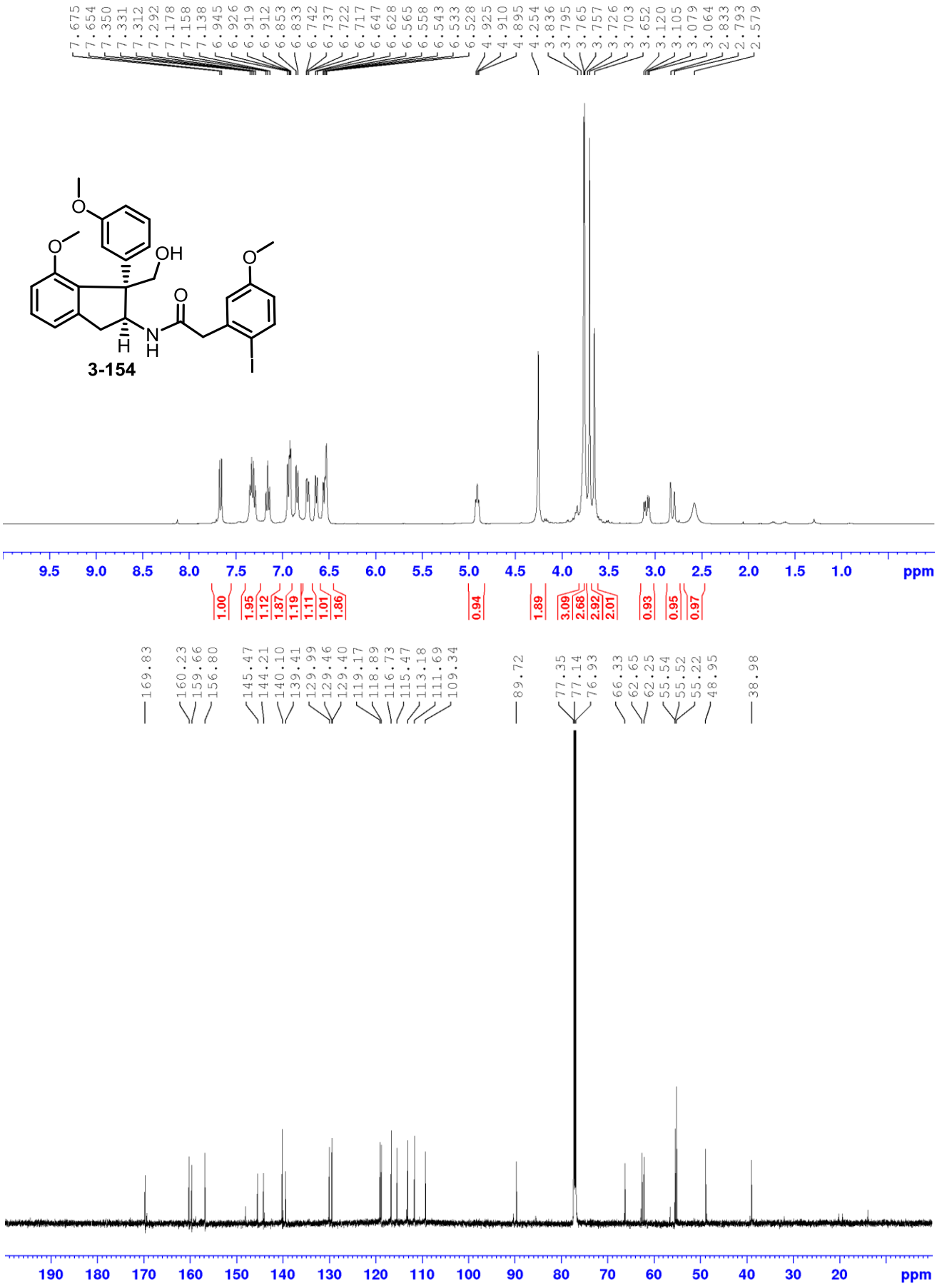
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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6.853
6.833
6.742
6.737
6.722
6.717
6.647
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6.565
6.558
6.543
6.533
6.528
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4.910
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3.726
3.703
3.652
3.120
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3.079
3.064
2.833
2.793
2.579
O
O
OH
O
O
N
H
H
I
3-154
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169.83
160.23
159.66
156.80
145.47
144.21
140.10
139.41
129.99
129.46
129.40
119.17
118.89
116.73
115.47
113.18
111.69
109.34
89.72
77.35
77.14
76.93
66.33
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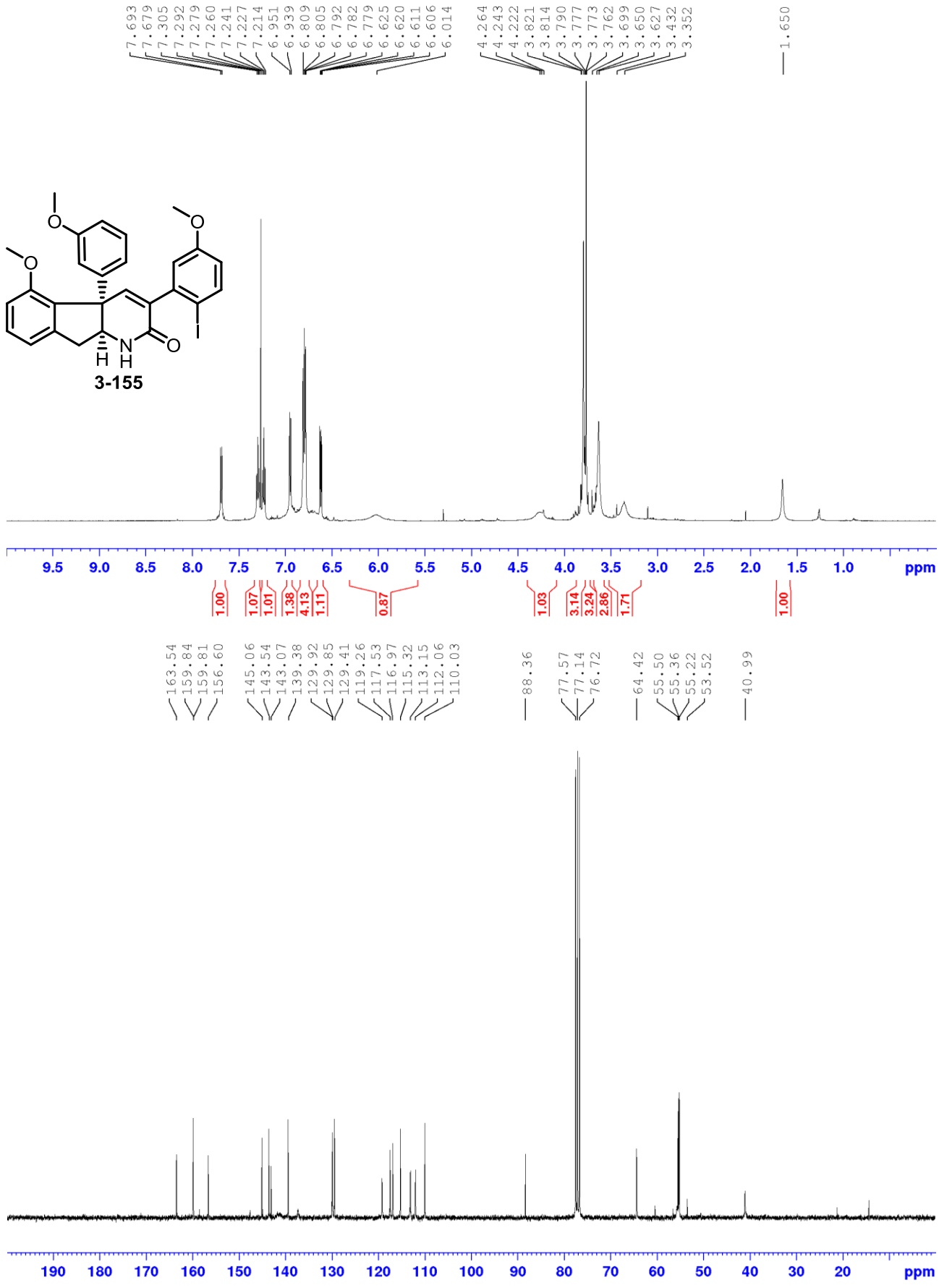
55.54
55.52
55.22
48.95
38.98
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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6.792
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6.625
6.620
6.611
6.606
6.014
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4.243
4.222
3.821
3.814
3.790
3.777
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3.762
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1.650
3-155
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163.54
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159.81
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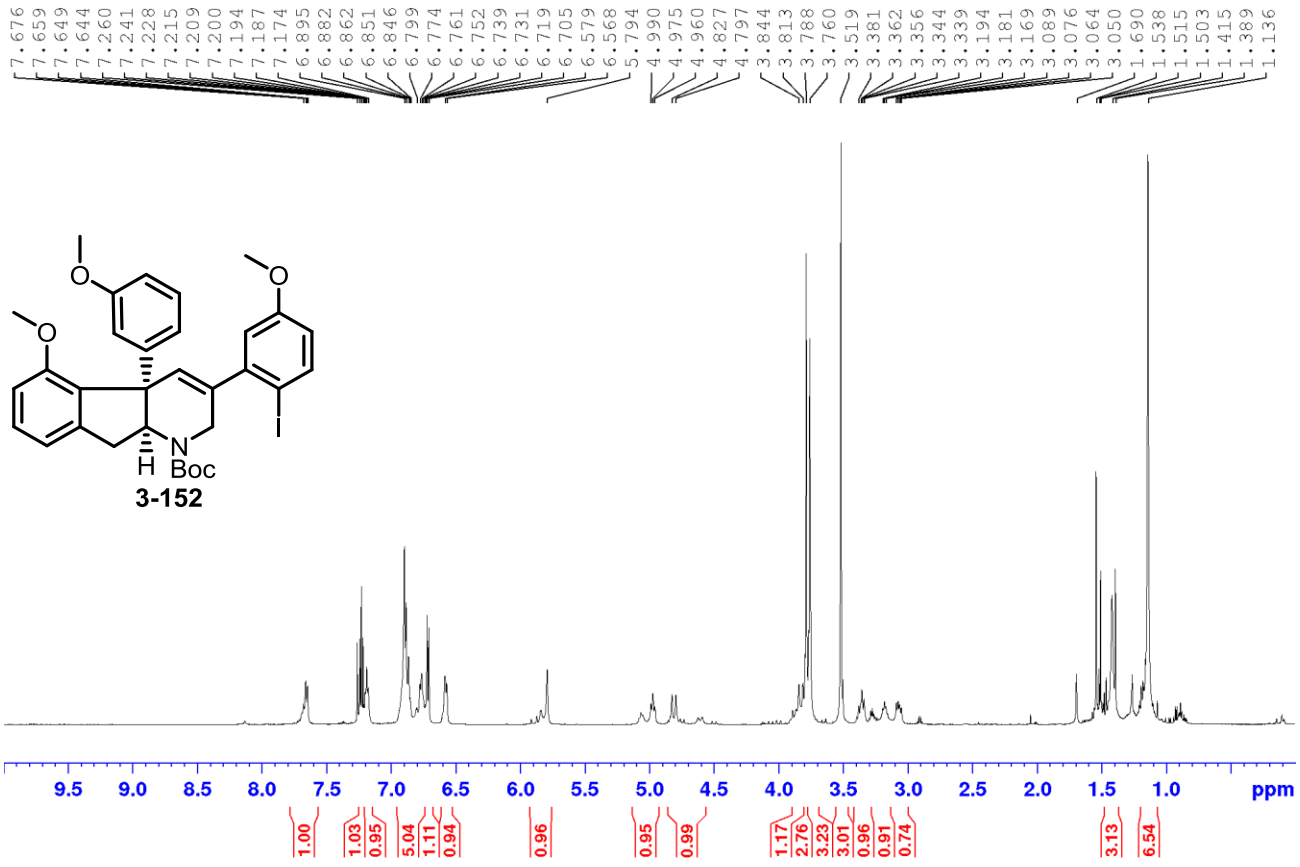
55.36
55.22
53.52
40.99
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.174
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6.882
6.862
6.851
6.846
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6.774
6.761
6.752
6.739
6.731
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O
O
O
I
H
N
Boc
3-152
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6.5
6.0
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ppm
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5.04
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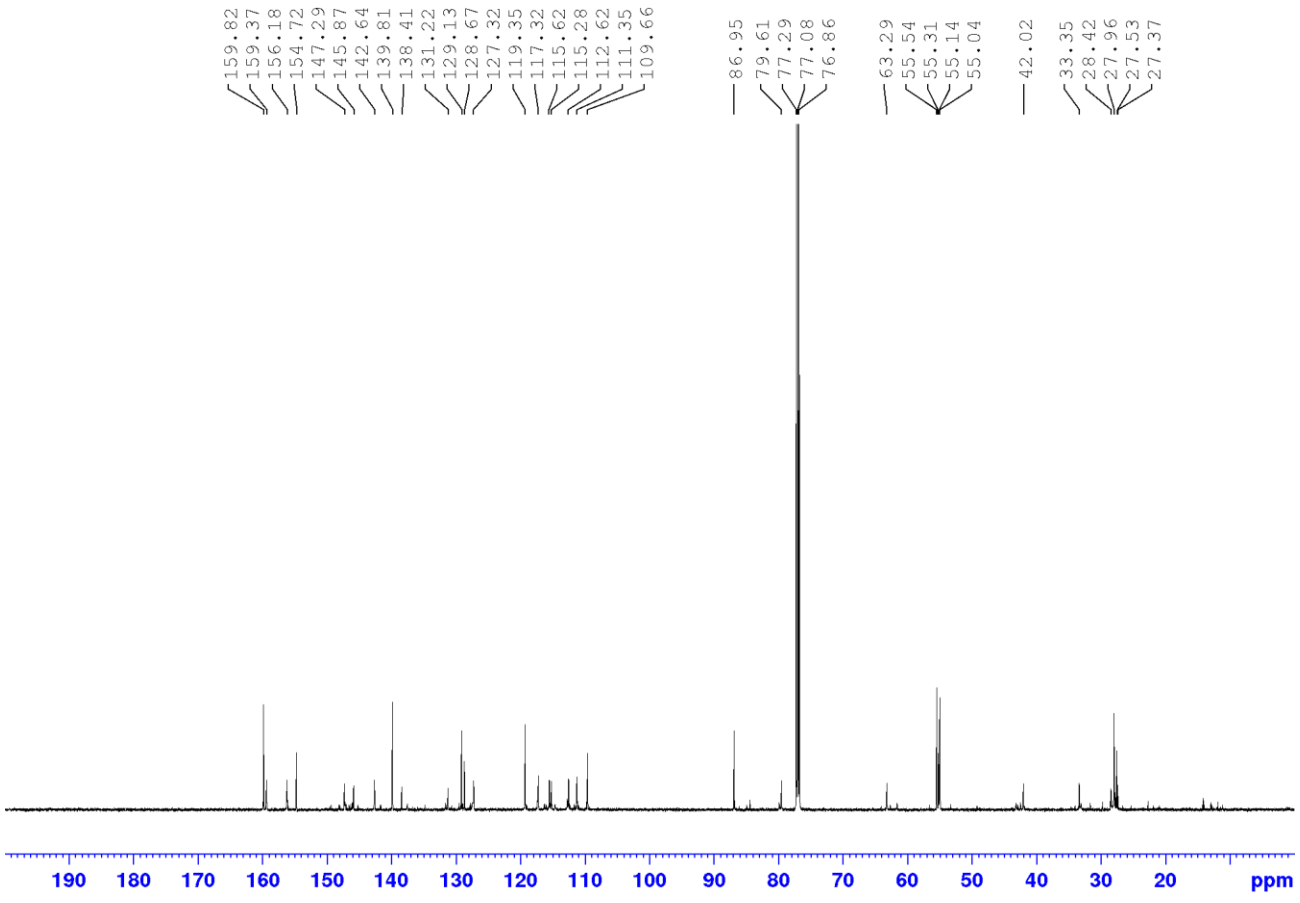
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117.32
115.62
115.28
112.62
111.35
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77.08
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63.29
55.54
55.31
55.14
55.04
42.02
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28.42
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27.53
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150
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120
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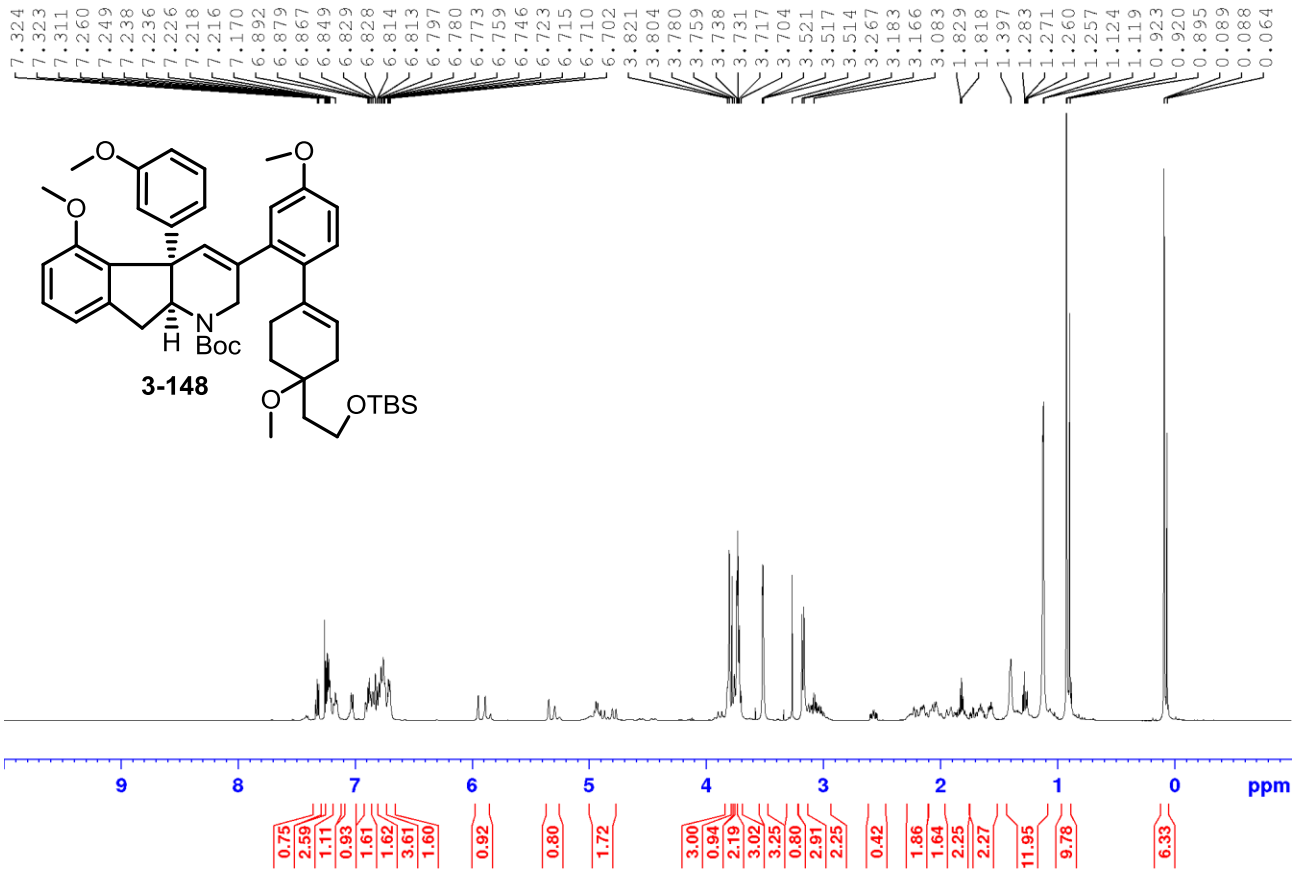
ppm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6.829
6.828
6.814
6.813
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6.780
6.773
6.759
6.746
6.723
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6.702
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3.780
3.759
3.738
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3.704
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1.271
1.260
1.257
1.124
1.119
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0.920
0.895
0.089
0.088
0.064
O
O
O
N
H
Boc
O
OTBS
3-148
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0
ppm
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1.62
3.61
1.60
0.92
0.80
1.72
3.00
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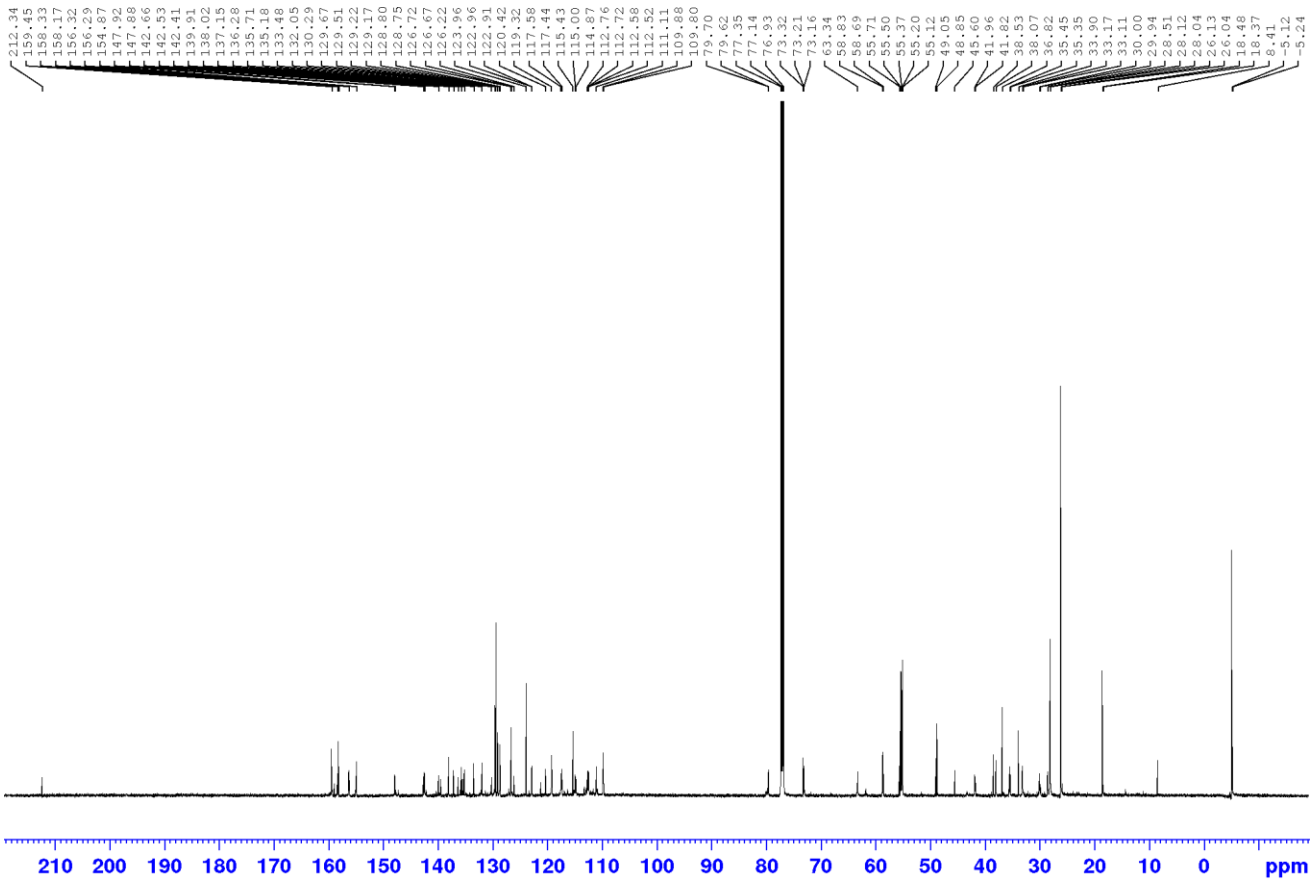
6.33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126.67
126.22
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115.00
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45.60
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38.07
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35.35
33.90
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33.11
30.00
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28.12
28.04
26.13
26.04
18.48
18.37
8.41
-5.12
-5.24
210
200
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140
130
120
110
100
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80
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60
50
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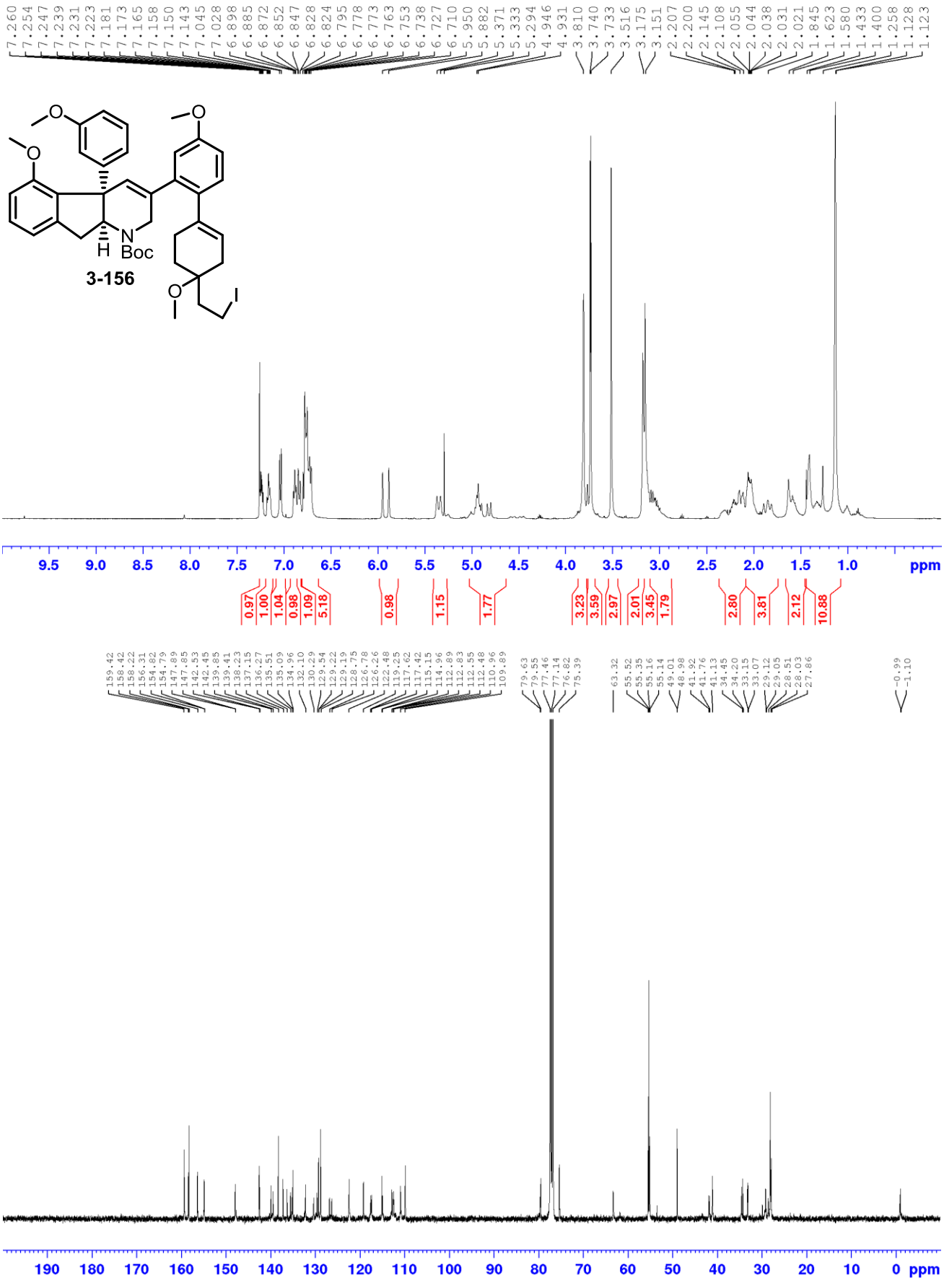
ppm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O
O
N
H
Boc
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33.15
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29.05
28.51
28.03
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-1.10
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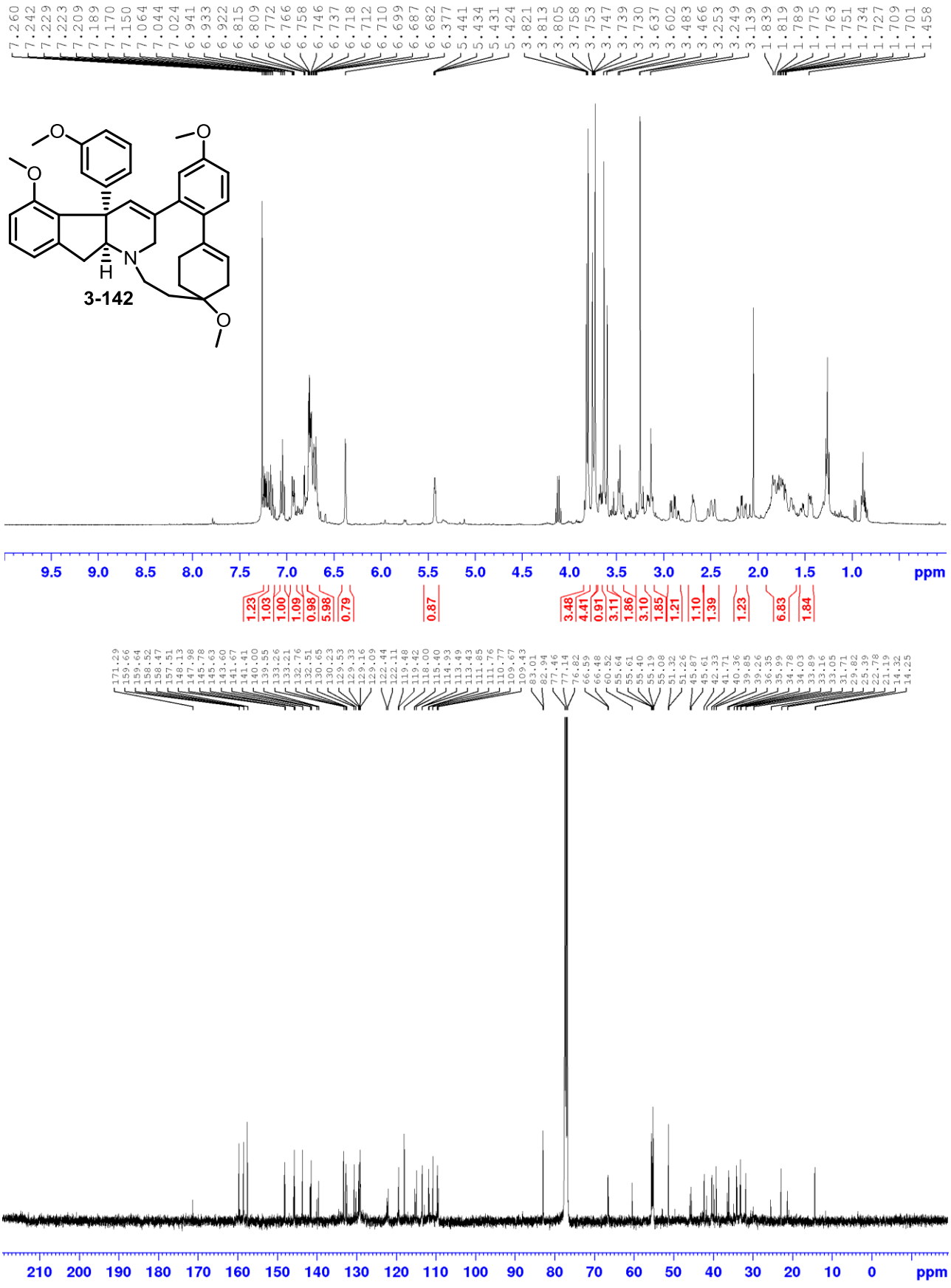
ppm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1.701
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3-142
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1.23 1.03 1.00 1.09 0.98 5.98 0.79 0.87 3.48 4.41 0.91 3.11 1.86 3.10 1.85 1.21 1.10 1.39 1.23 6.83 1.84
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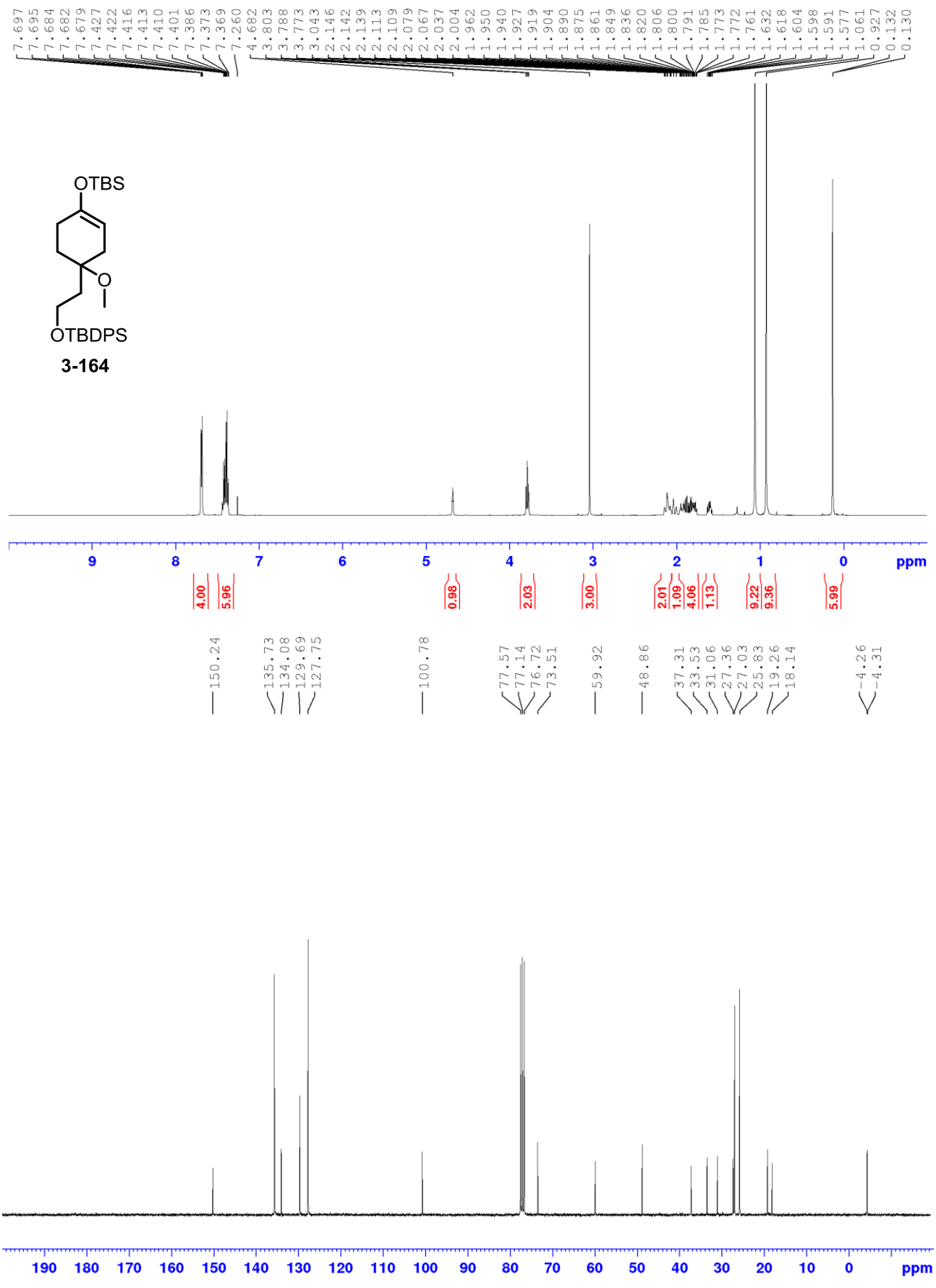
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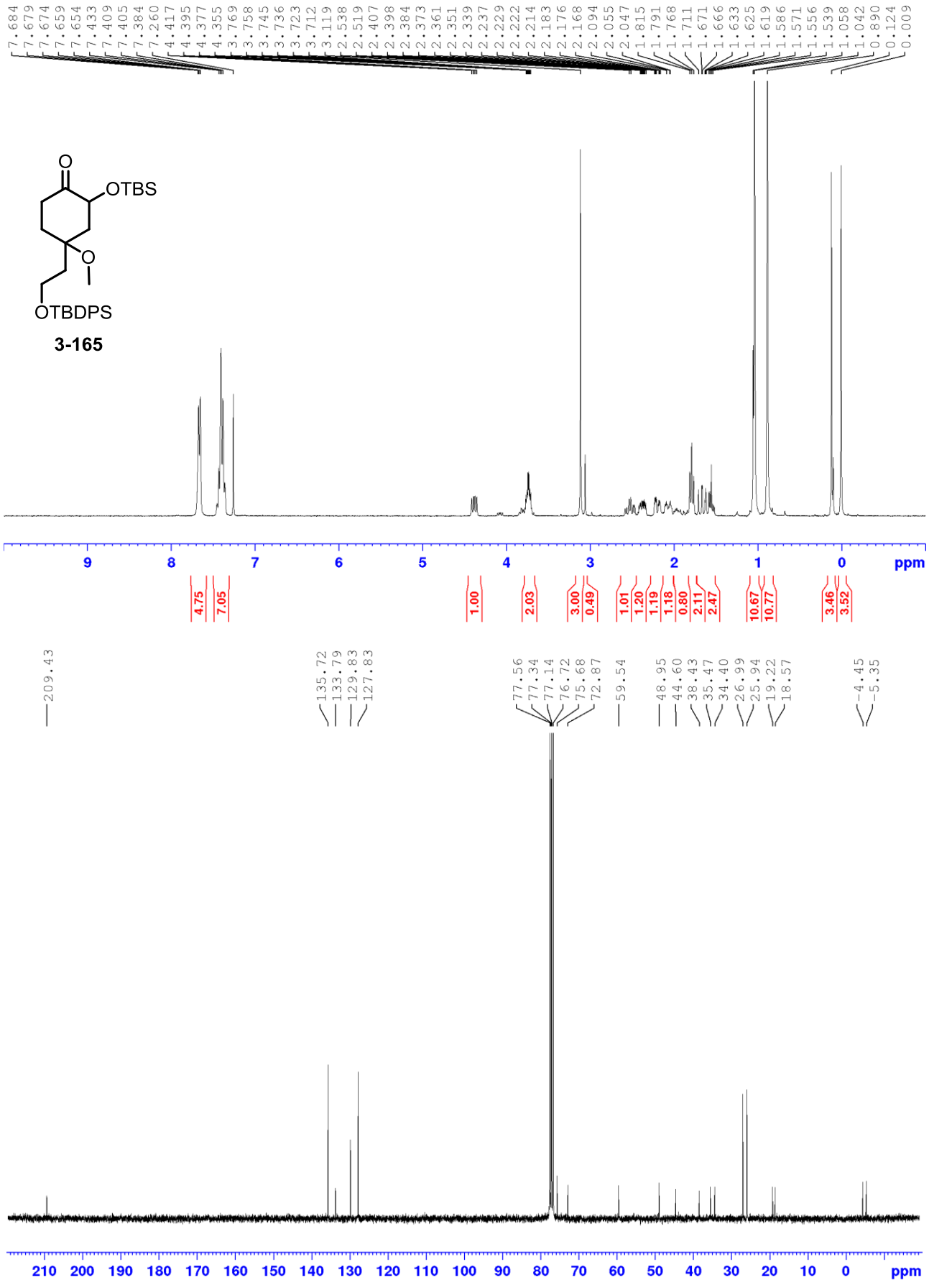
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2.094
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2.047
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O
OTBS
O
OTBDPS
3-165
9
8
7
6
5
4
3
2
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ppm
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1.00
2.03
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1.20
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10.77
3.46
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135.72
133.79
129.83
127.83
77.56
77.34
77.14
76.72
75.68
72.87
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48.95
44.60
38.43
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26.99
25.94
19.22
18.57
-4.45
-5.35
210
200
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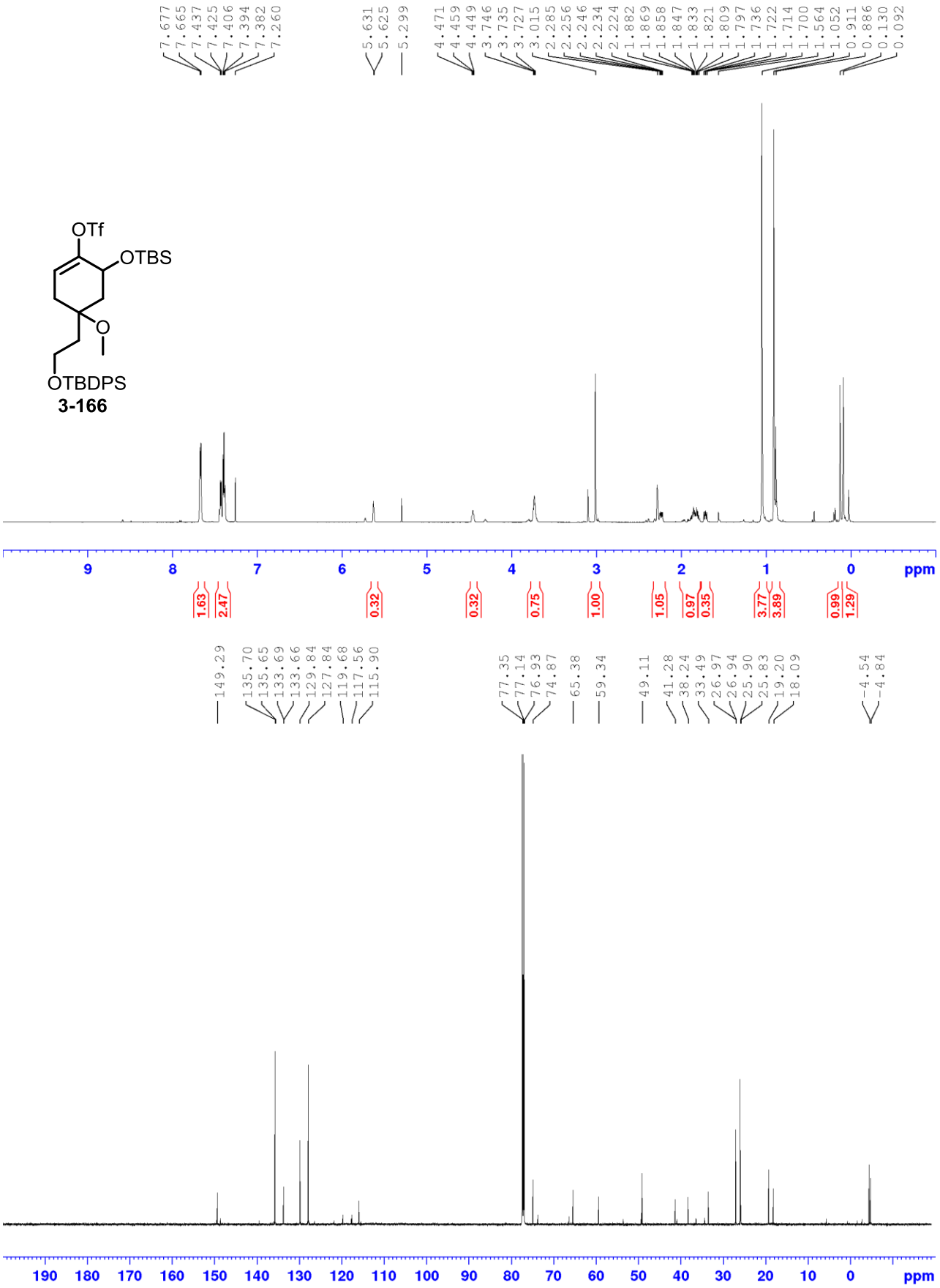
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3.727
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OTBS
O
OTBDPS
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4
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26.94
25.90
25.83
19.20
18.09
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-4.84
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180
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150
140
130
120
110
100
90
80
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60
50
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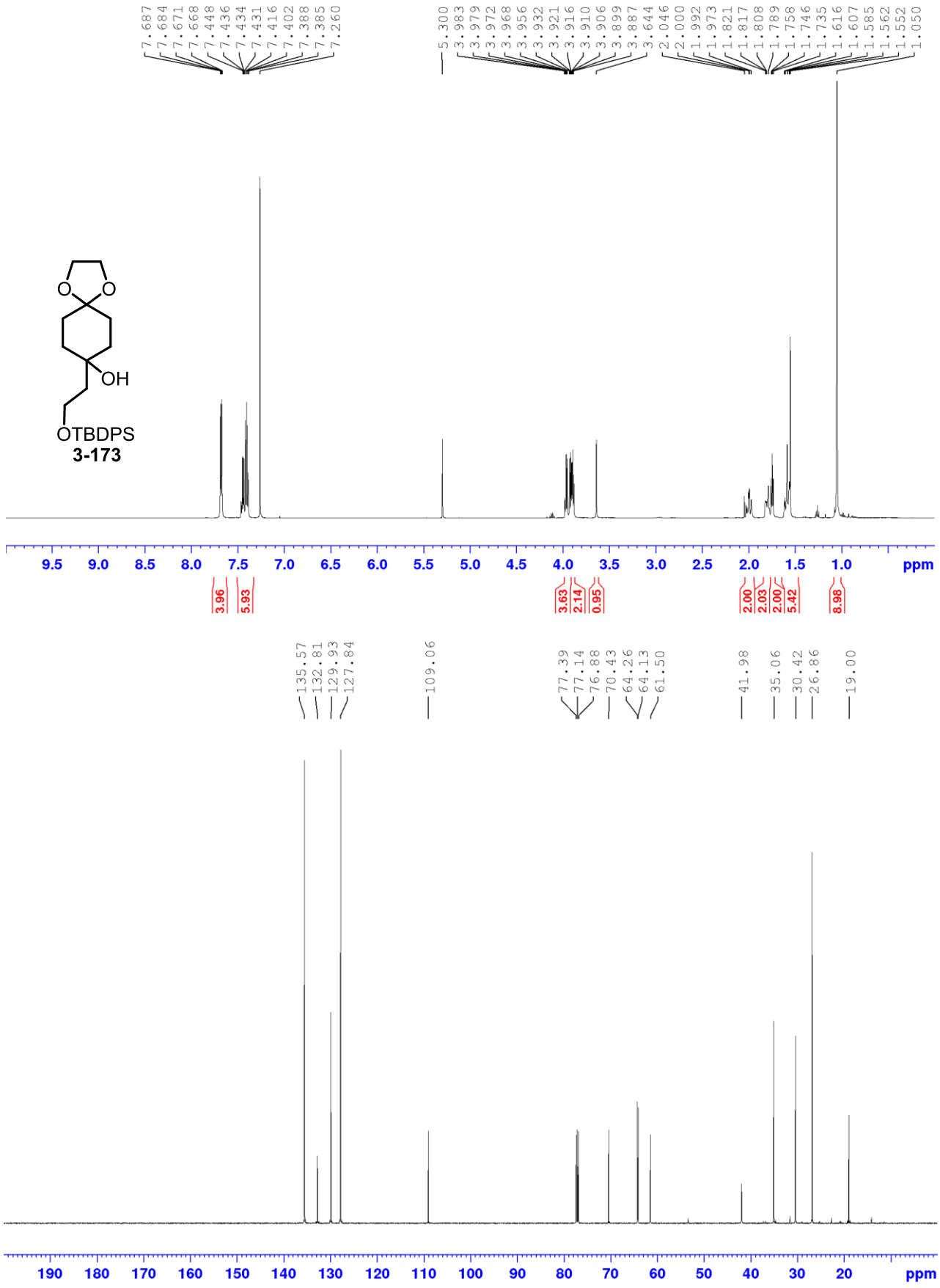
20
10
0
ppm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3.972
3.968
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3.932
3.921
3.916
3.910
3.906
3.899
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3.644
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2.000
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1.808
1.789
1.758
1.746
1.735
1.616
1.607
1.585
1.562
1.552
1.050
O
O
OH
OTBDPS
3-173
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2.00
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77.14
76.88
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26.86
19.00
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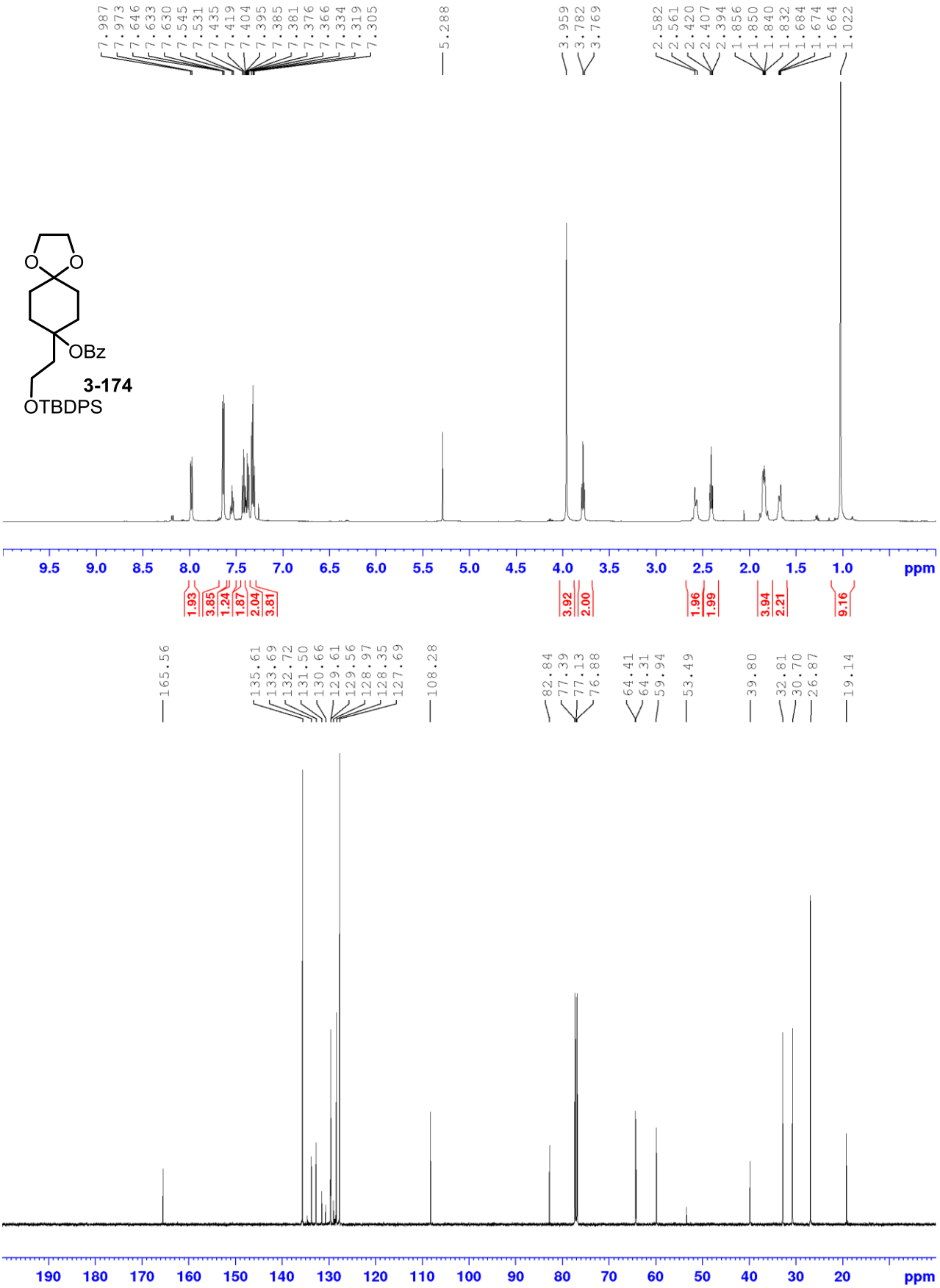
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7.319
7.305
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3.769
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2.561
2.420
2.407
2.394
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1.850
1.840
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1.674
1.664
1.022
O
O
OBz
3-174
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1.24
1.87
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3.81
3.92
2.00
1.96
1.99
3.94
2.21
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129.56
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128.35
127.69
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77.13
76.88
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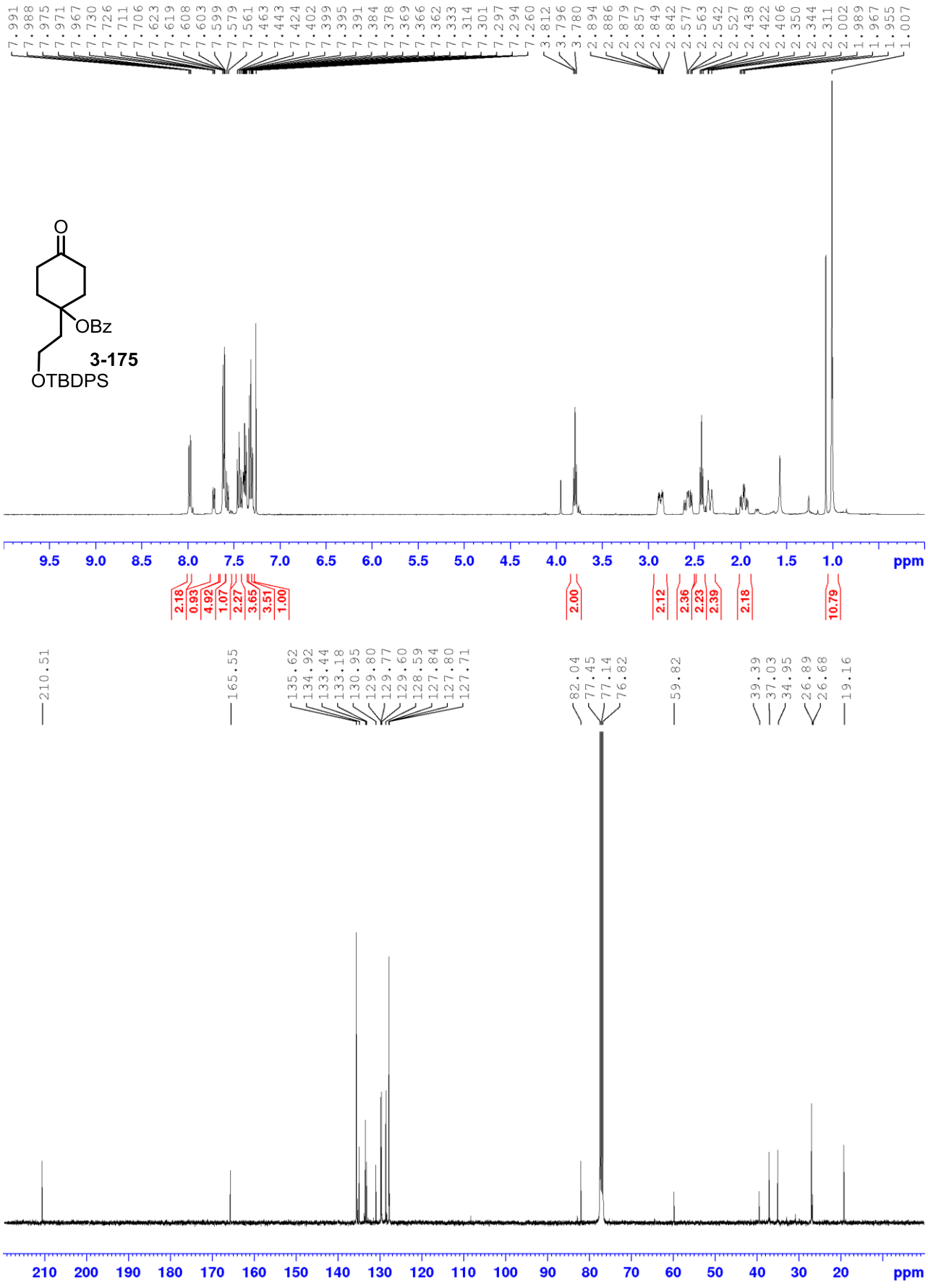
19.14
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.599
7.579
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2.438
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O
OBz
3-175
OTBDPS
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2.00
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2.39
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77.14
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37.03
34.95
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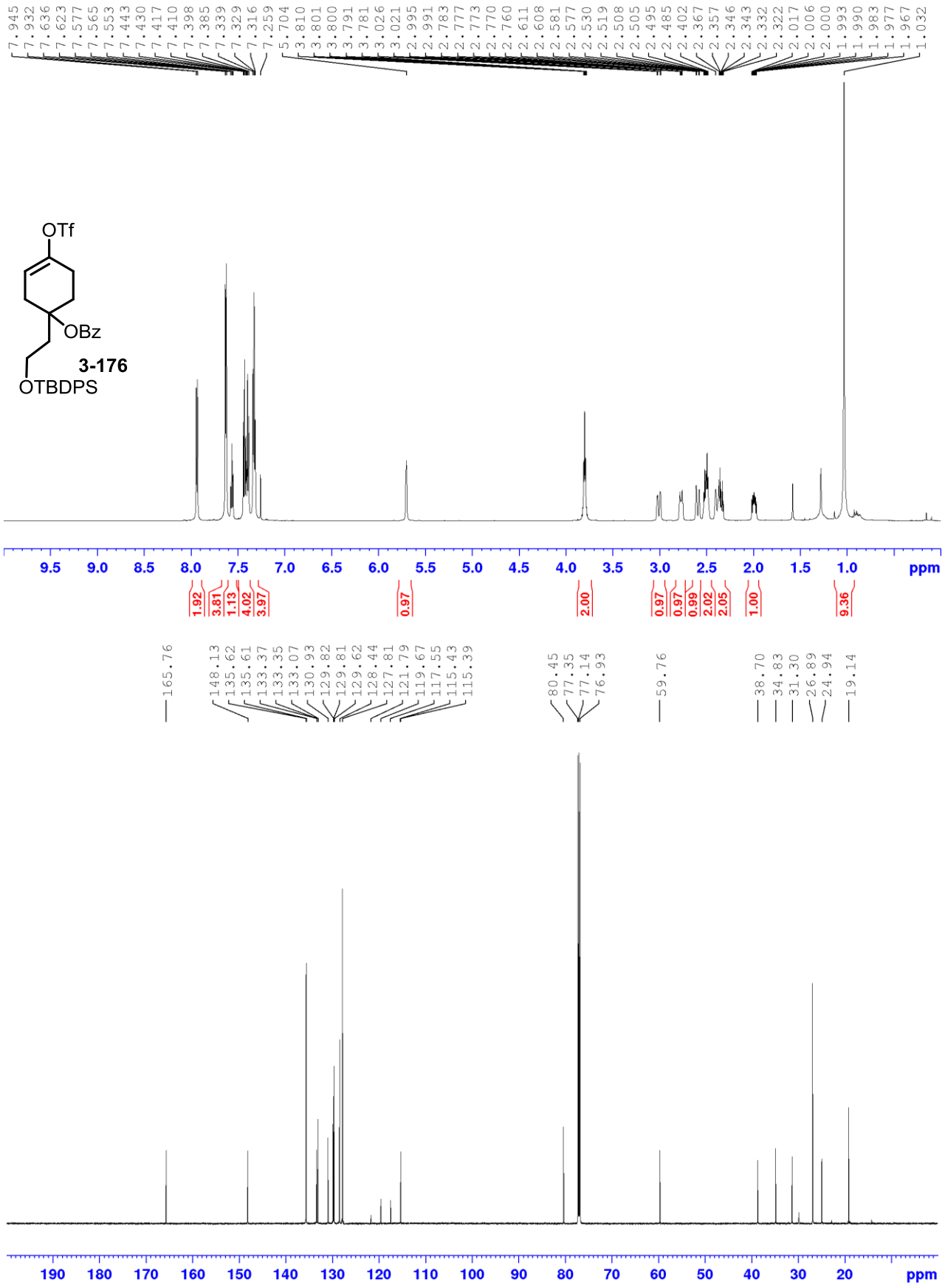
26.68
19.16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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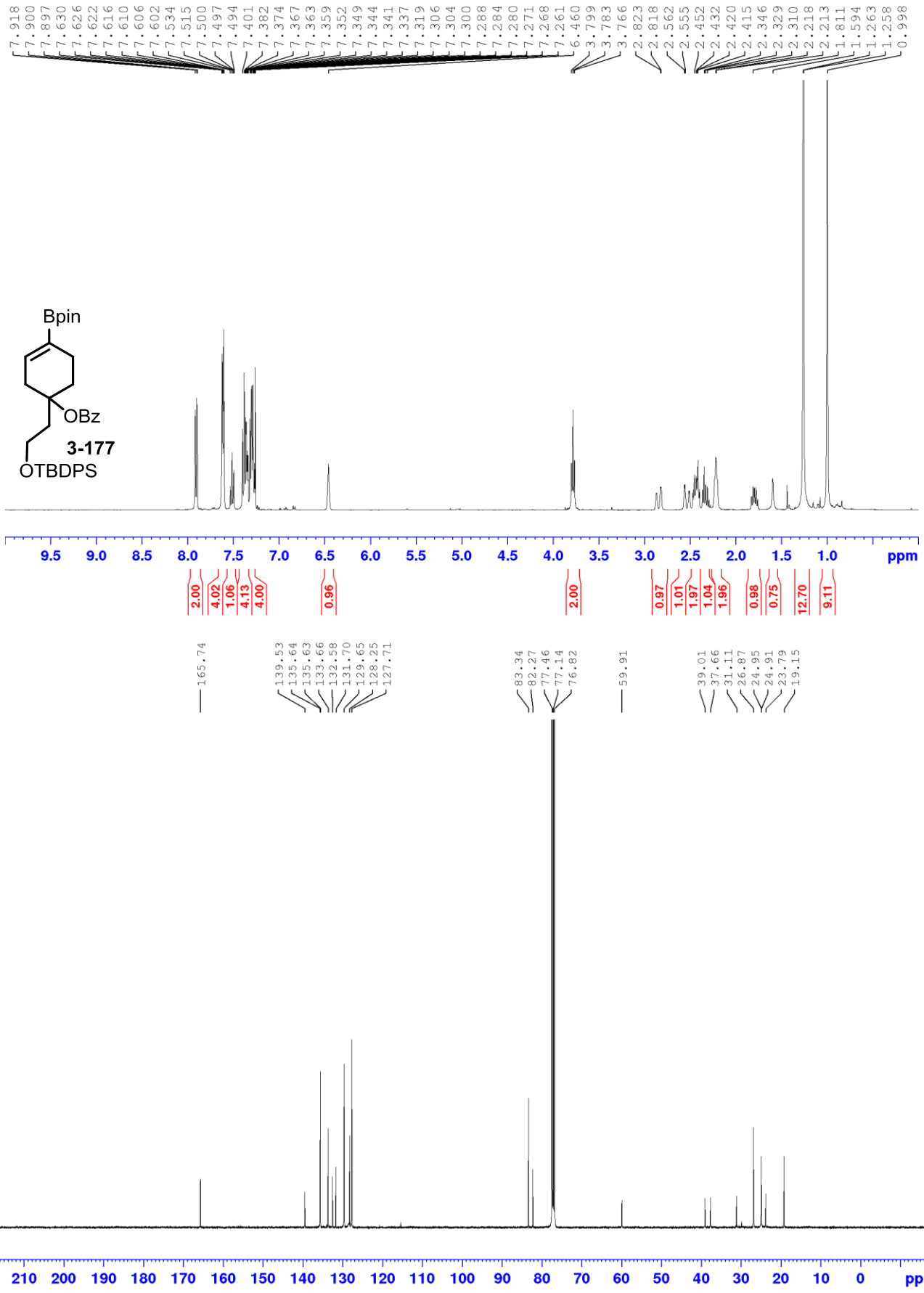
ppm
ppm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Bpin
OBz
3-177
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77.46
77.14
76.82
59.91
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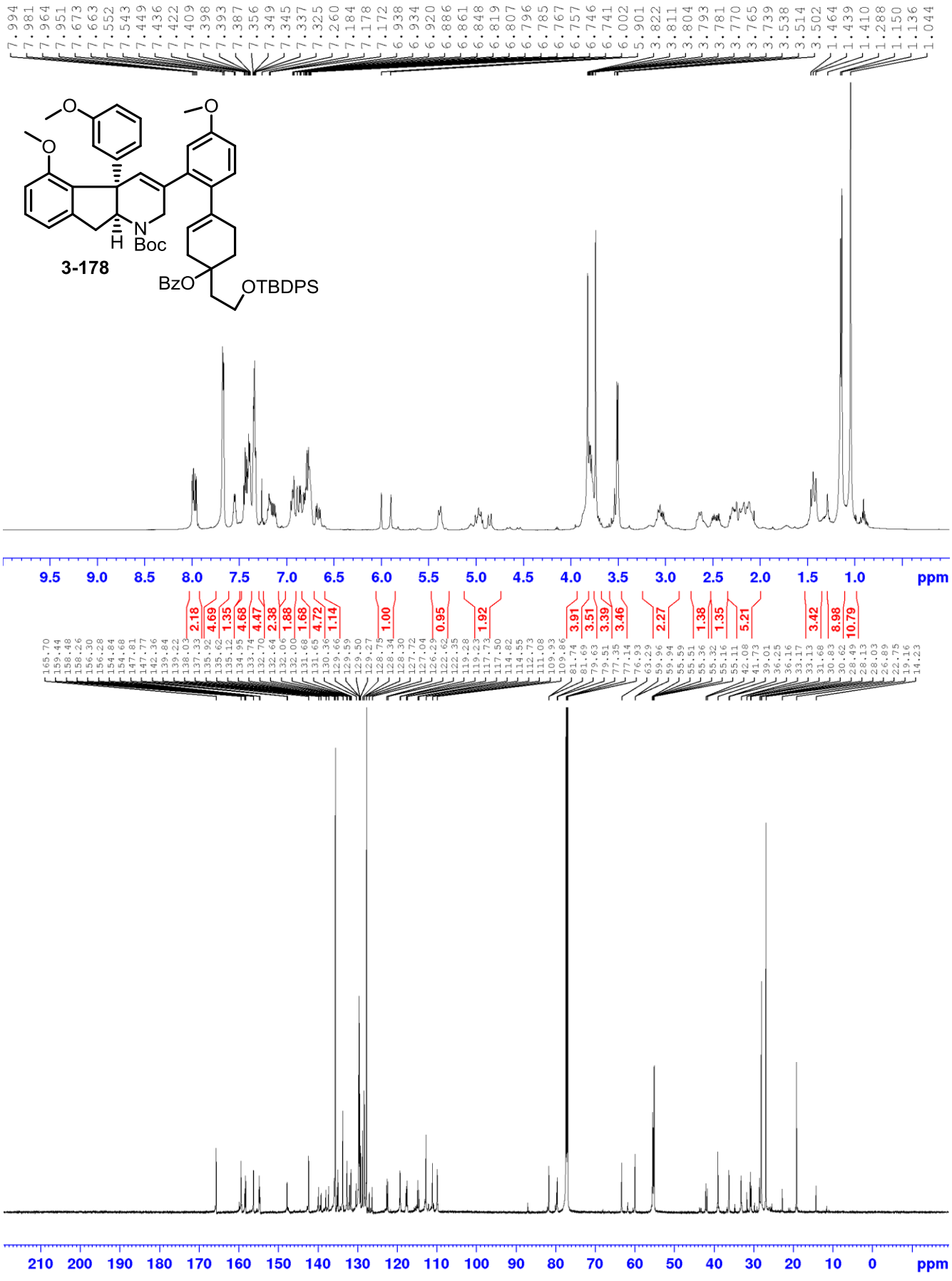
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O
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N
H
Boc
BzO
OTBDPS
3-178
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200
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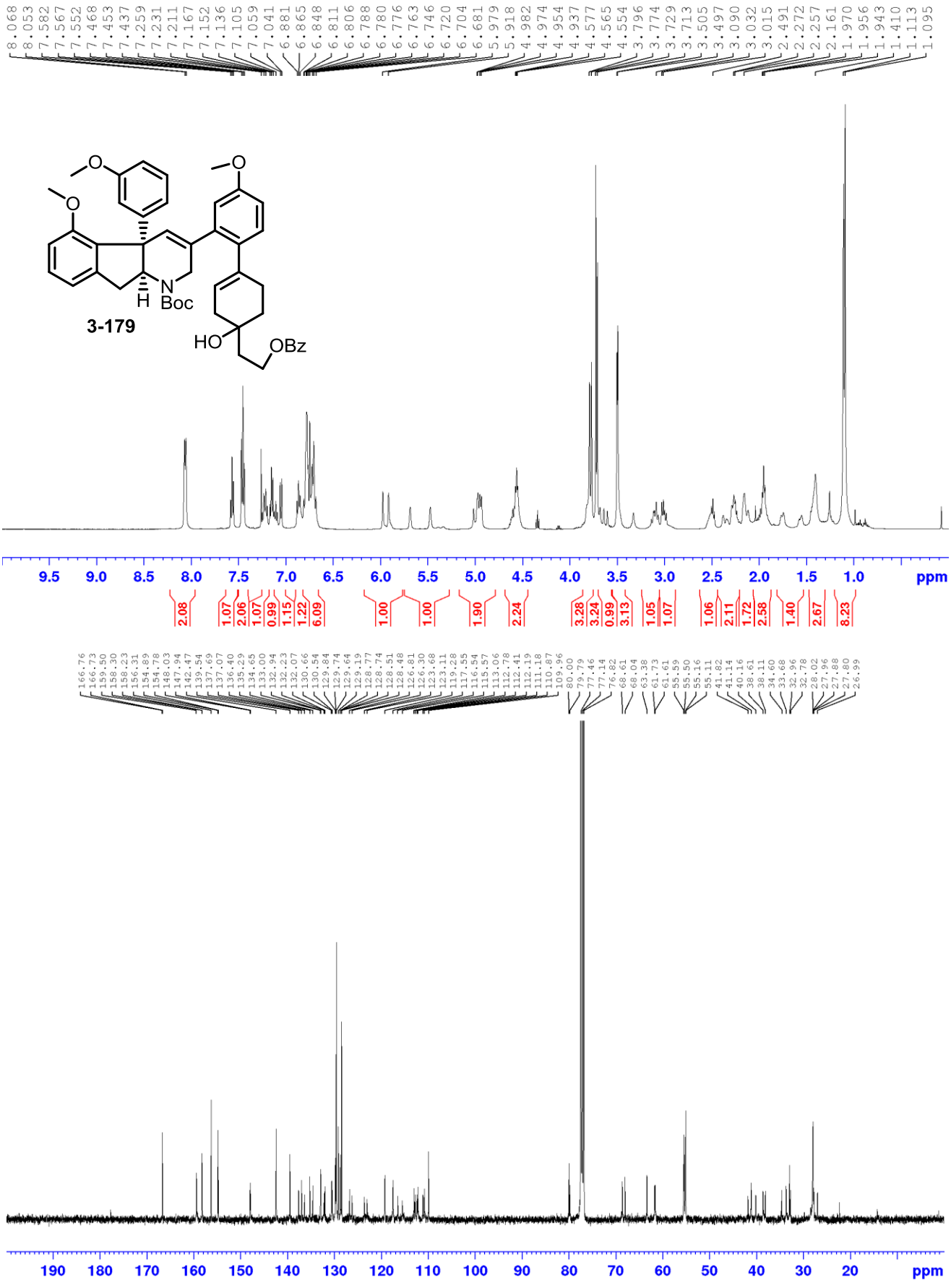
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N
H
Boc
HO
OBz
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30
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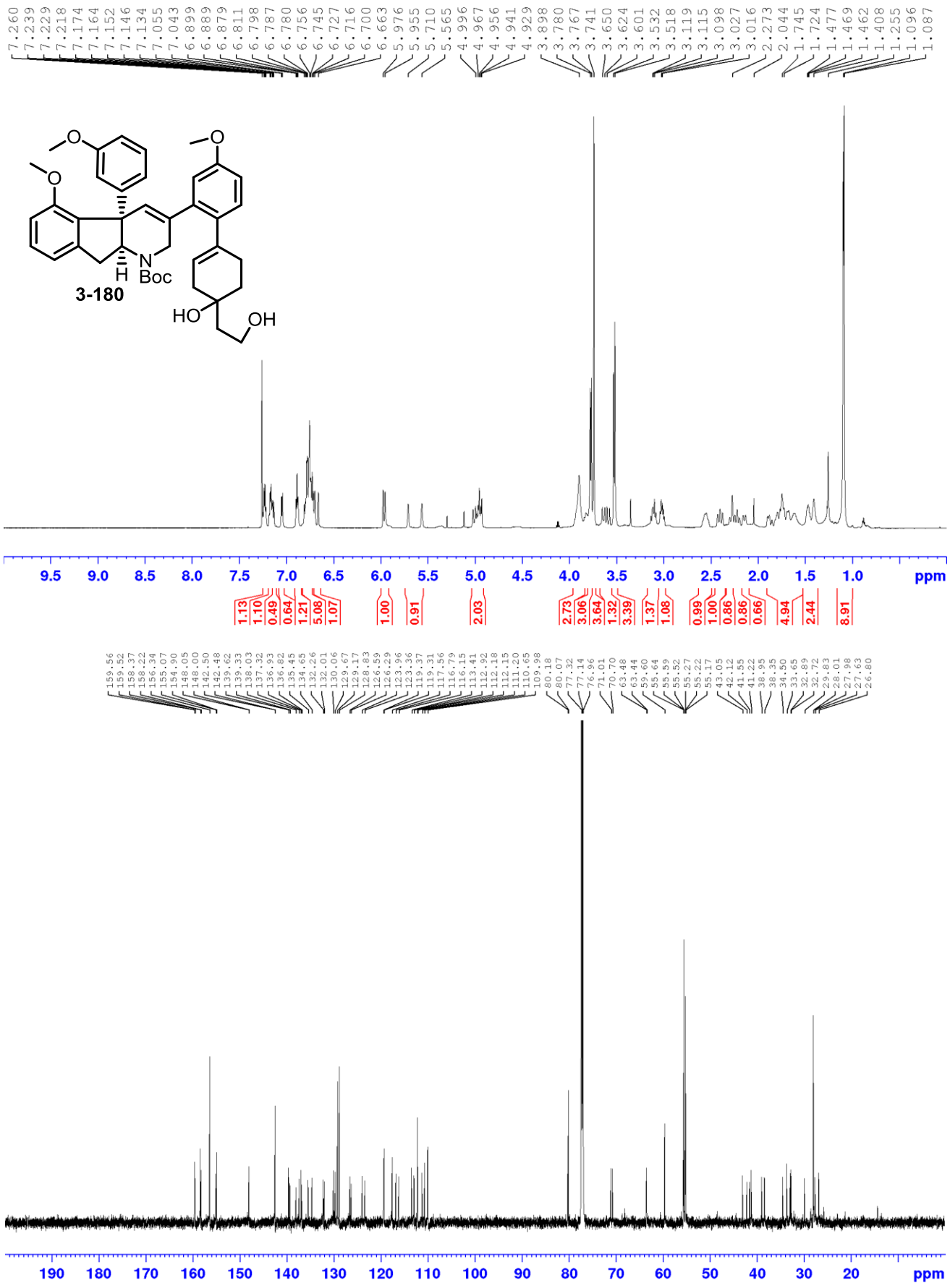
ppm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6.889
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6.811
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6.780
6.756
6.745
6.727
6.716
6.700
6.663
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5.955
5.710
5.565
4.996
4.967
4.956
4.941
4.929
3.898
3.780
3.767
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3.016
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2.044
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1.477
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1.087
O
O
O
N
H
Boc
HO
OH
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1.00
0.91
2.03
2.73
3.06
3.64
1.32
3.39
1.37
1.08
0.99
1.00
0.86
0.86
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132.01
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80.07
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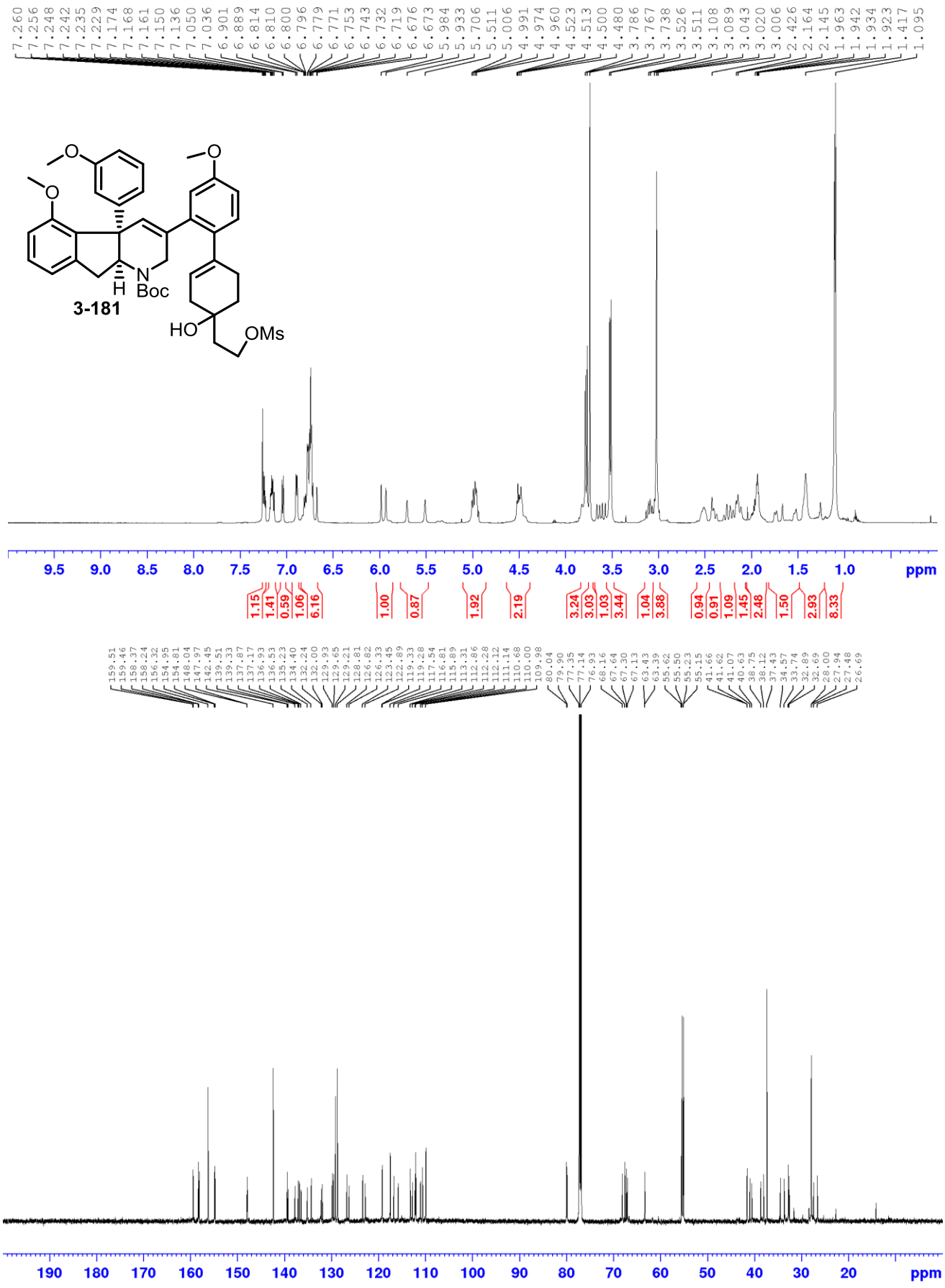
20
ppm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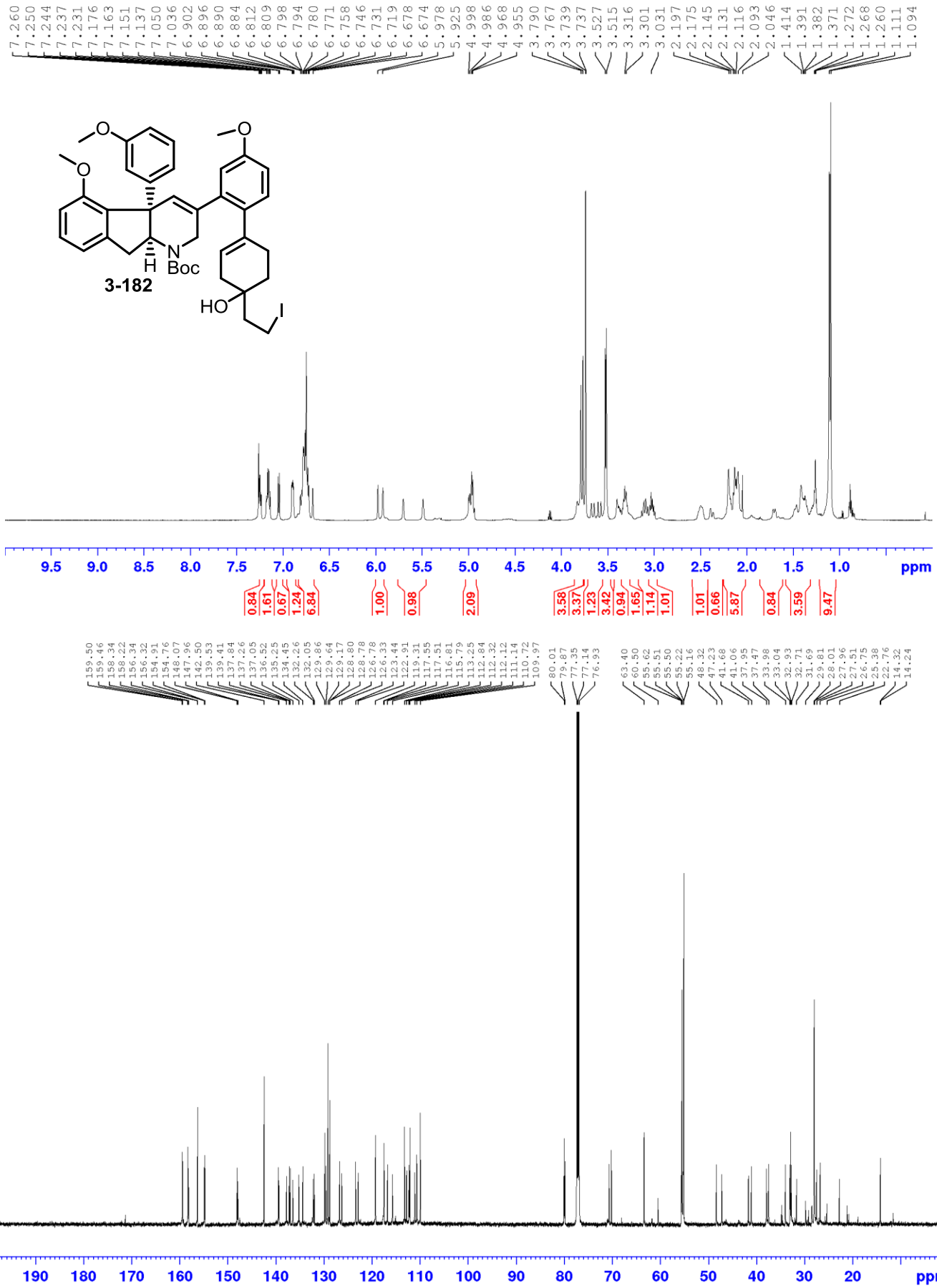
Boc
HO
OMs
ppm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O
O
N
H
Boc
HO
I
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55.51
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27.51
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14.32
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150
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120
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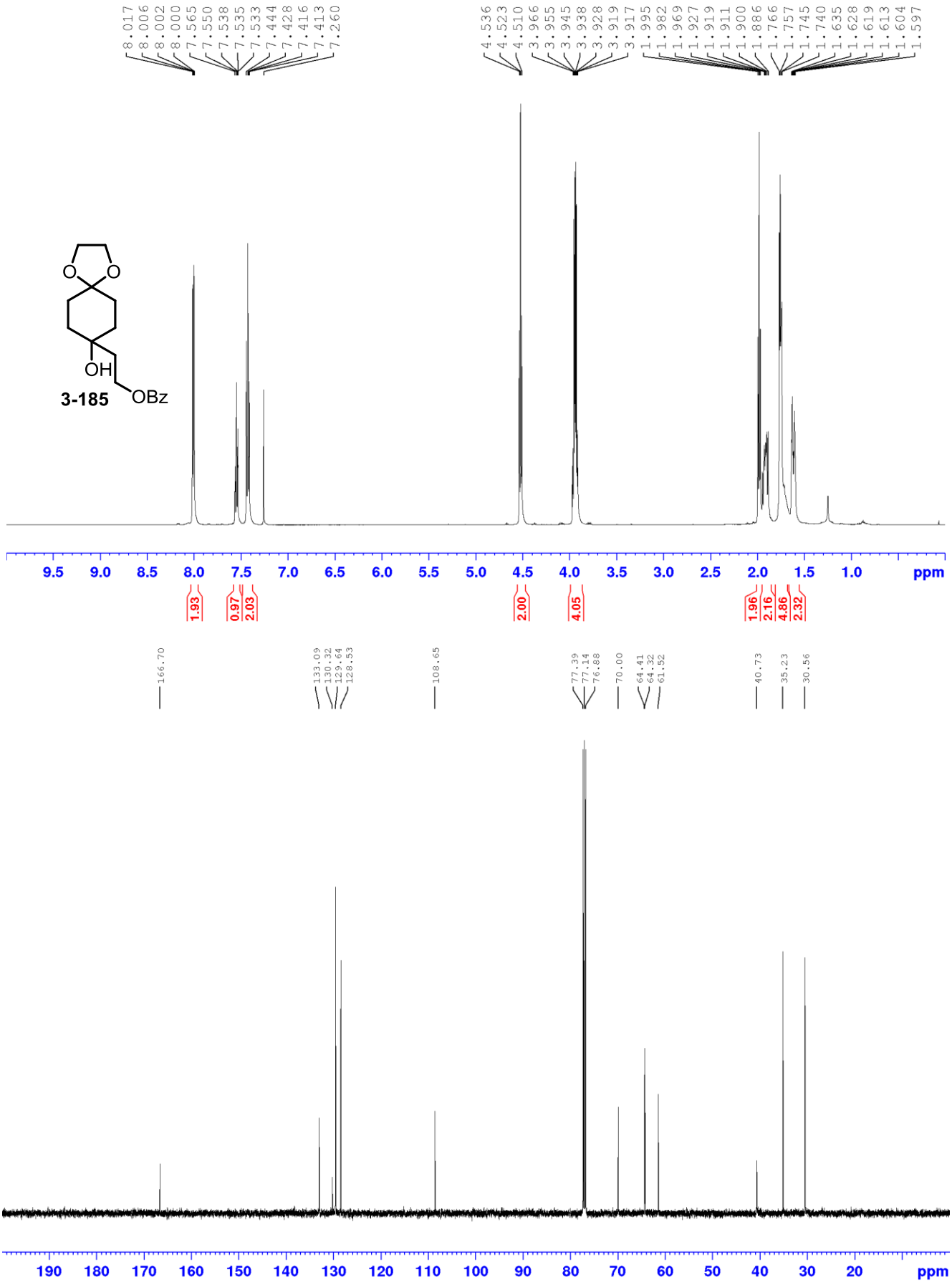
20
ppm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7.260
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4.523
4.510
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3.955
3.945
3.938
3.928
3.919
3.917
1.995
1.982
1.969
1.927
1.919
1.911
1.900
1.886
1.766
1.757
1.745
1.740
1.635
1.628
1.619
1.613
1.604
1.597
OH
OBz
3-185
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0.97
2.03
2.00
4.05
1.96
2.16
4.86
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133.09
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129.64
128.53
108.65
77.39
77.14
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35.23
30.56
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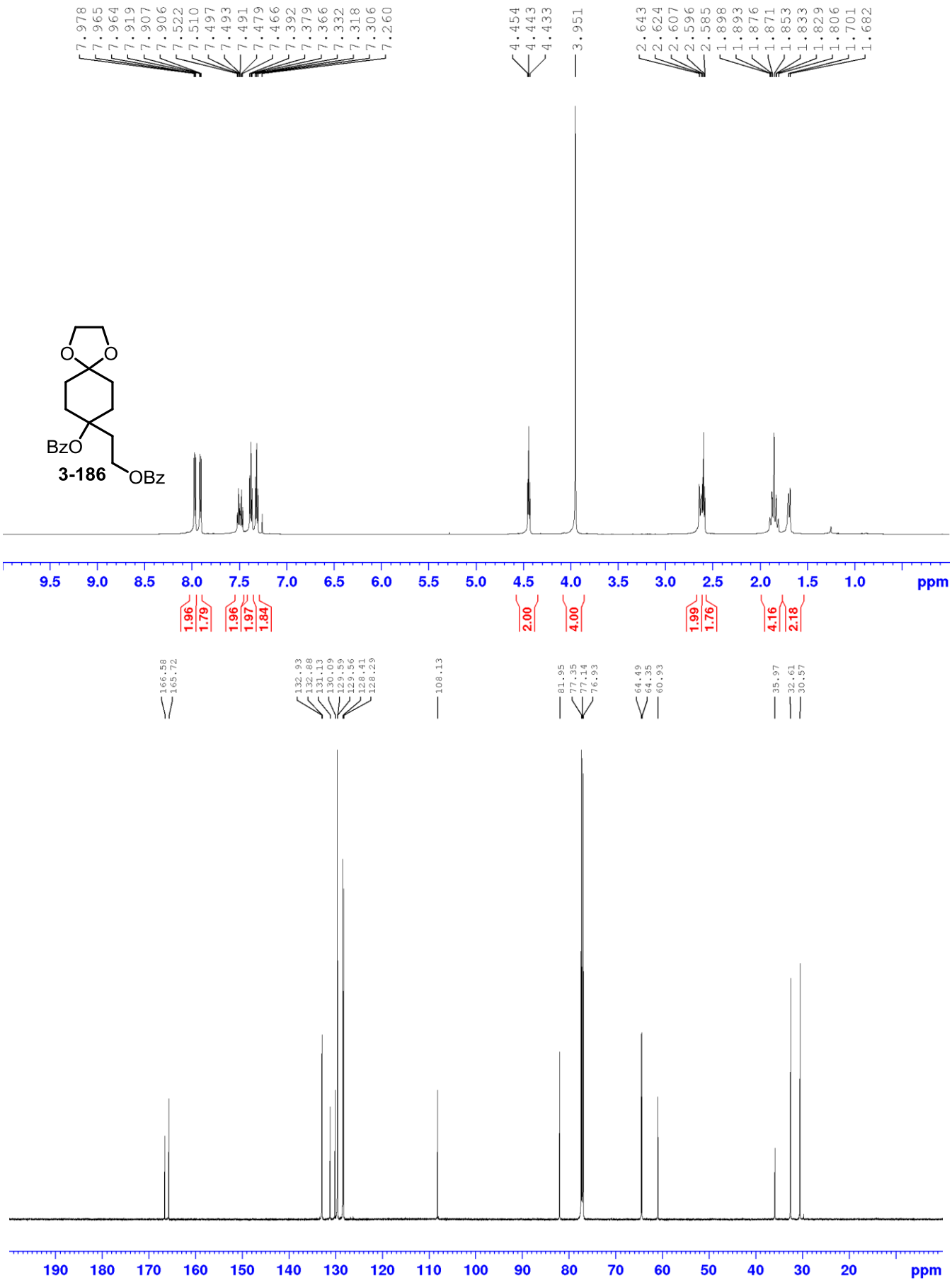
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7.318
7.306
7.260
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4.443
4.433
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2.643
2.624
2.607
2.596
2.585
1.898
1.893
1.876
1.871
1.853
1.833
1.829
1.806
1.701
1.682
BzO
OBz
3-186
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1.96 1.79 1.96 1.97 1.84 2.00 4.00 1.99 1.76 4.16 2.18
166.58
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131.13
130.09
129.59
129.56
128.41
128.29
108.13
81.95
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64.35
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35.97
32.61
30.57
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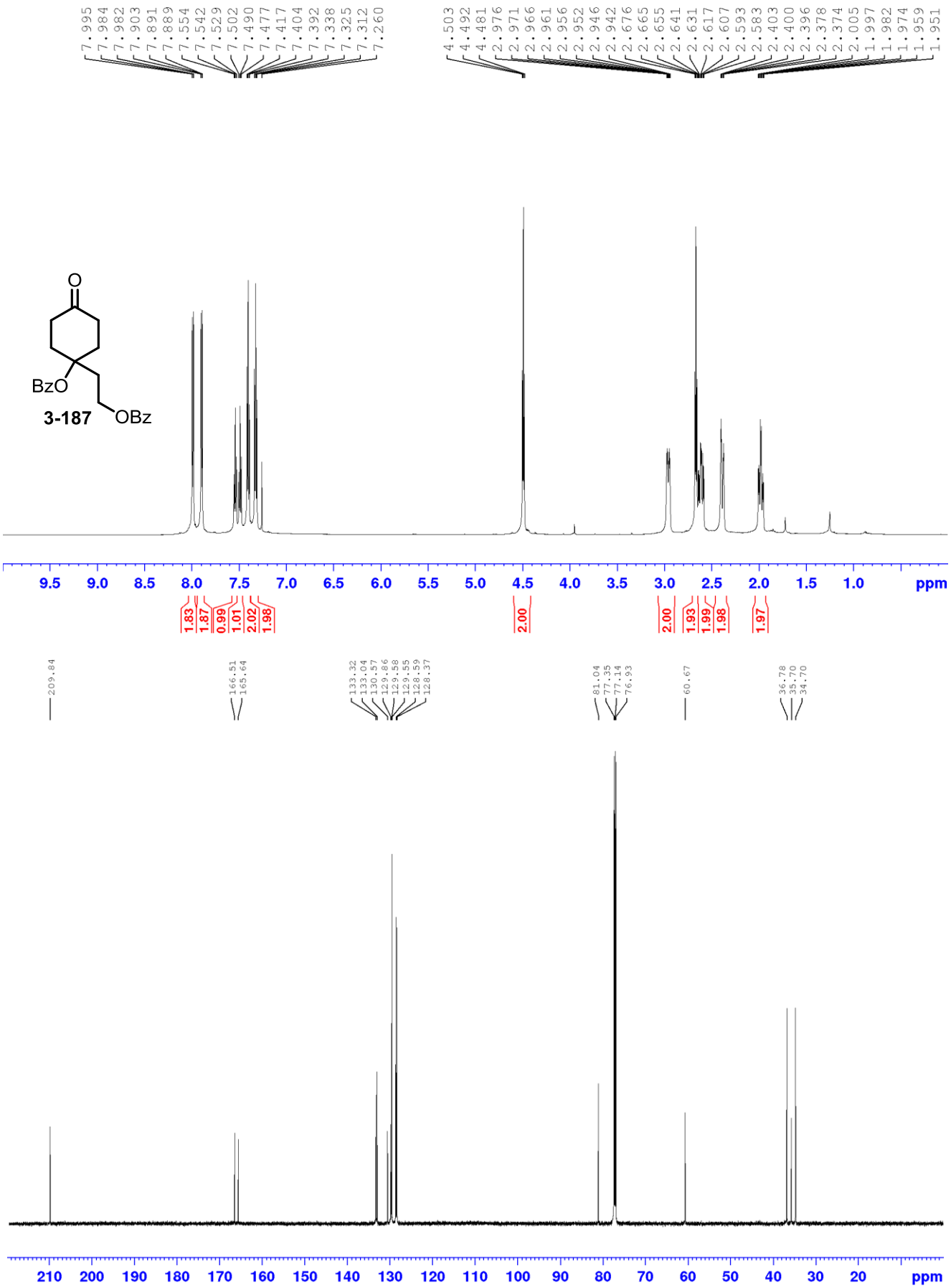
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7.502
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7.477
7.417
7.404
7.392
7.338
7.325
7.312
7.260
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4.492
4.481
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2.971
2.966
2.961
2.956
2.952
2.946
2.942
2.676
2.665
2.655
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2.617
2.607
2.593
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2.400
2.396
2.378
2.374
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1.982
1.974
1.959
1.951
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BzO
3-187
OBz
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2.02
1.98
2.00
2.00
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1.99
1.98
1.97
209.84
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165.64
133.32
133.04
130.57
129.86
129.58
129.55
128.59
128.37
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76.93
60.67
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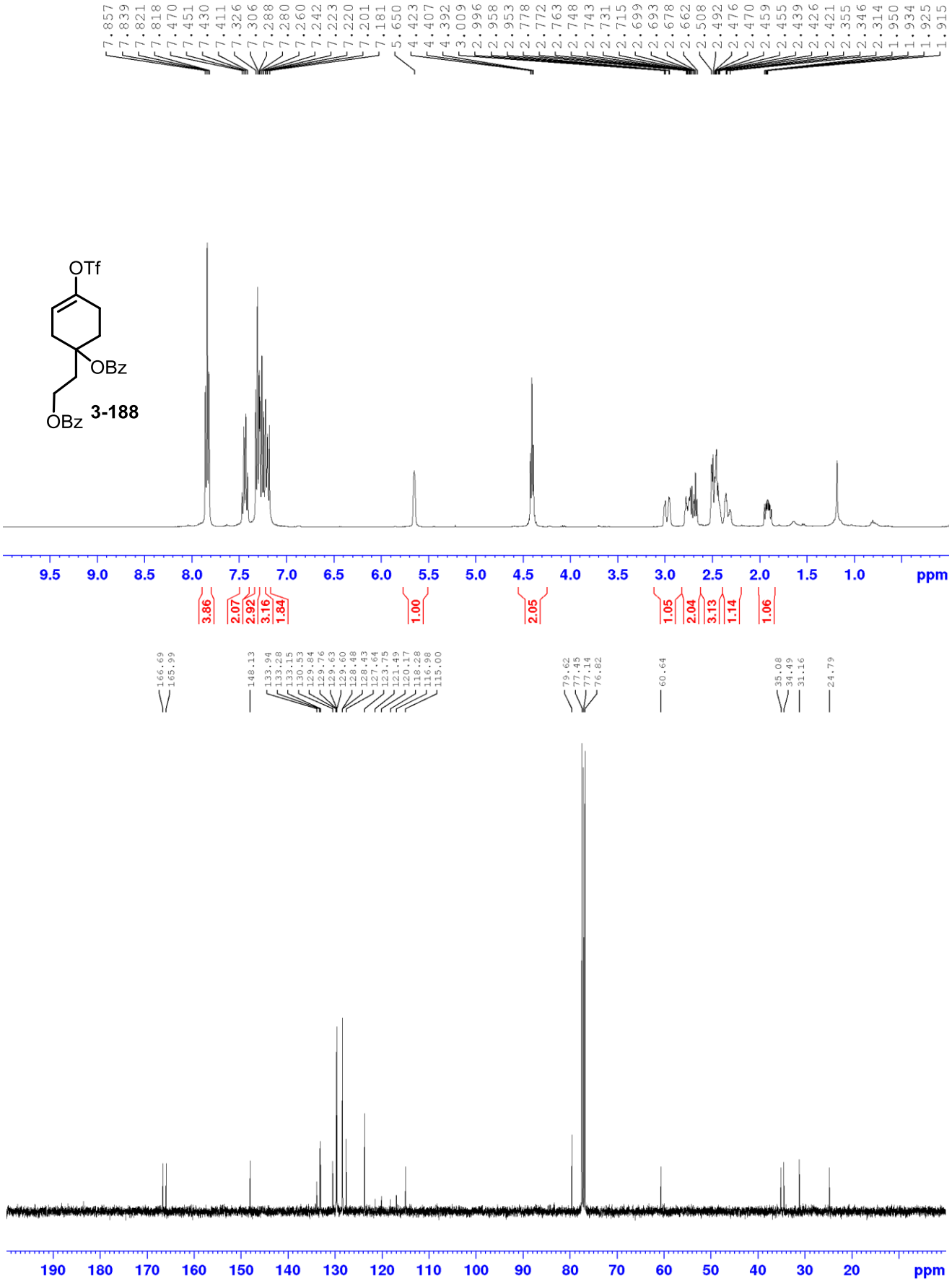
34.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.223
7.220
7.201
7.181
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4.407
4.392
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2.953
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2.772
2.763
2.748
2.743
2.731
2.715
2.699
2.693
2.678
2.662
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2.492
2.476
2.470
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2.455
2.439
2.426
2.421
2.355
2.346
2.314
1.950
1.934
1.925
1.915
OTf
OBz
OBz
3-188
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7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
1.0
ppm
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3.16
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1.00
2.05
1.05
2.04
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1.14
1.06
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133.15
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129.60
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128.43
127.64
123.75
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77.14
76.82
60.64
35.08
34.49
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120
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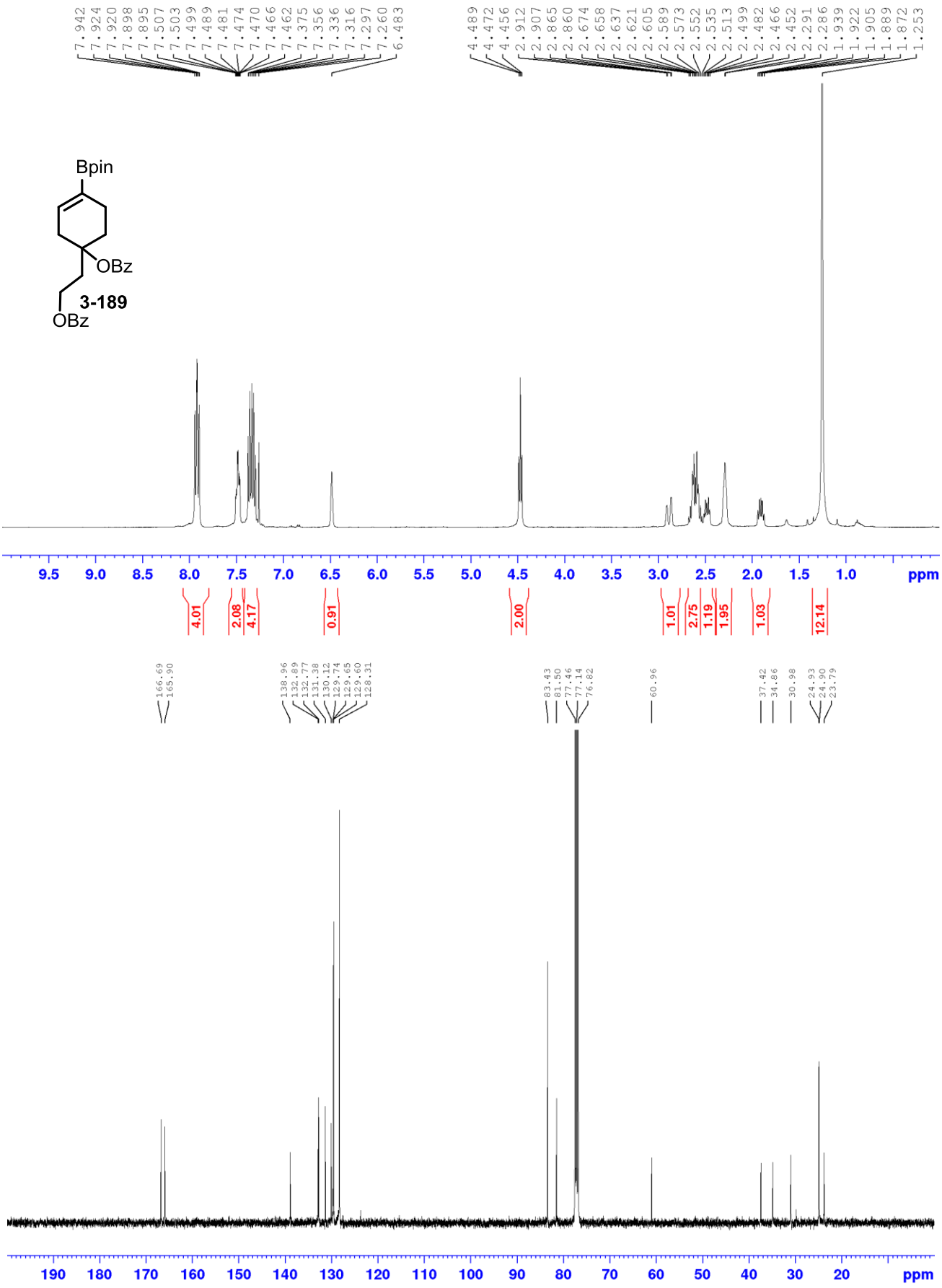
40
30
20
ppm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1.253
Bpin
OBz
3-189
OBz
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76.82
60.96
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24.90
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130
120
110
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80
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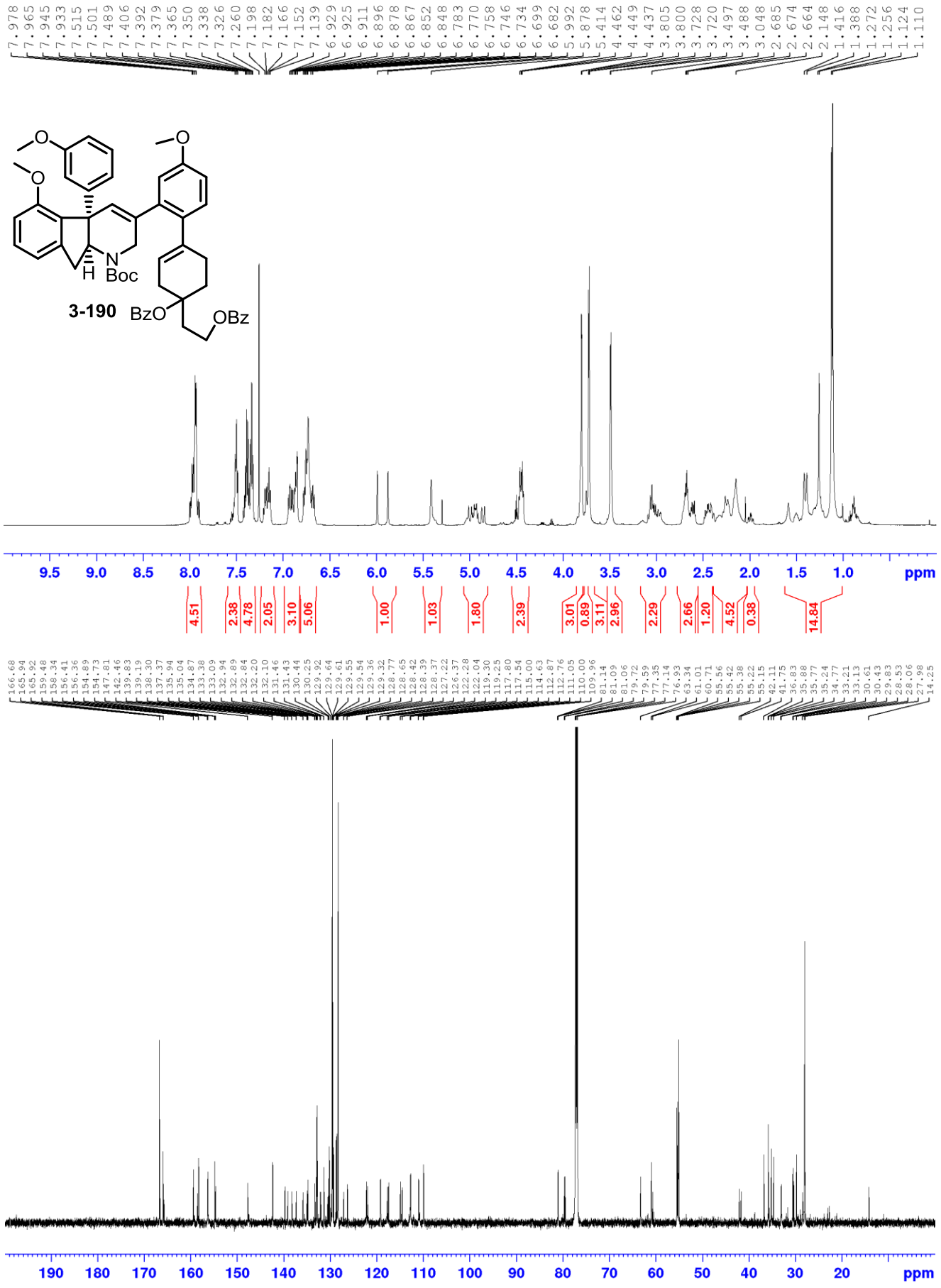
40
30
20
ppm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7.326
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O
O
O
N
H
Boc
3-190
BzO
OBz
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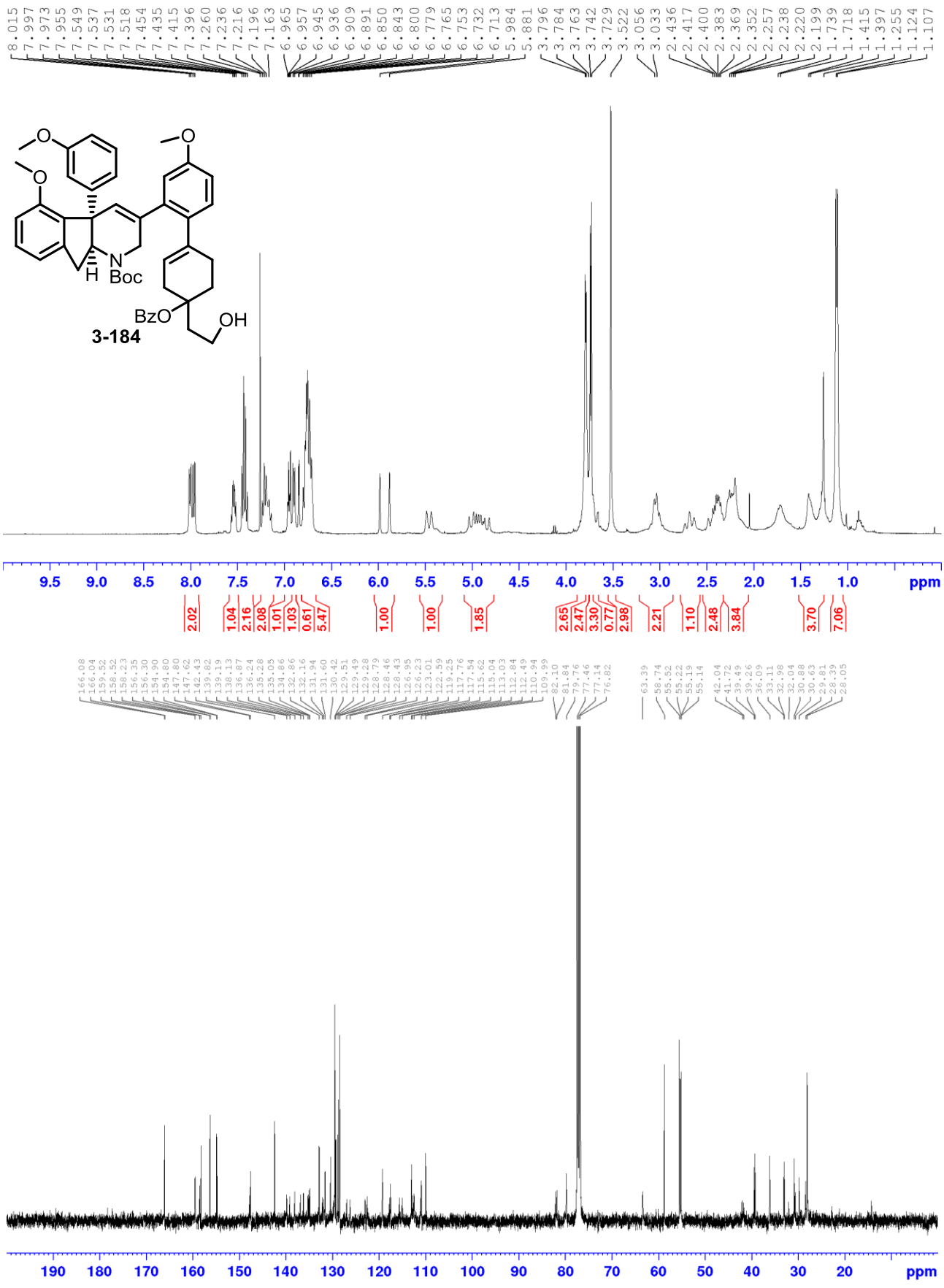
ppm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O
H
N
Boc
BzO
OH
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1.00
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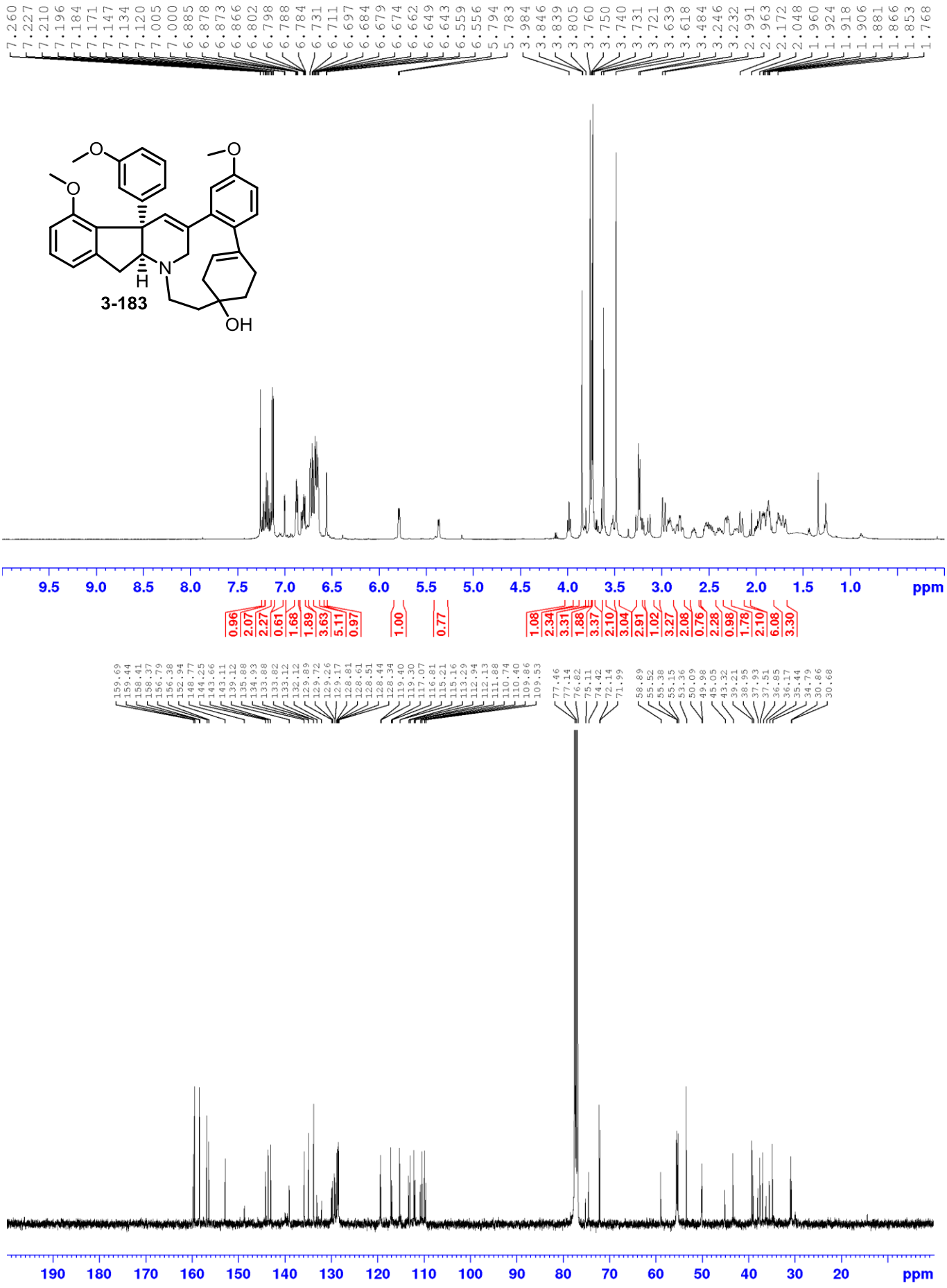
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6.674
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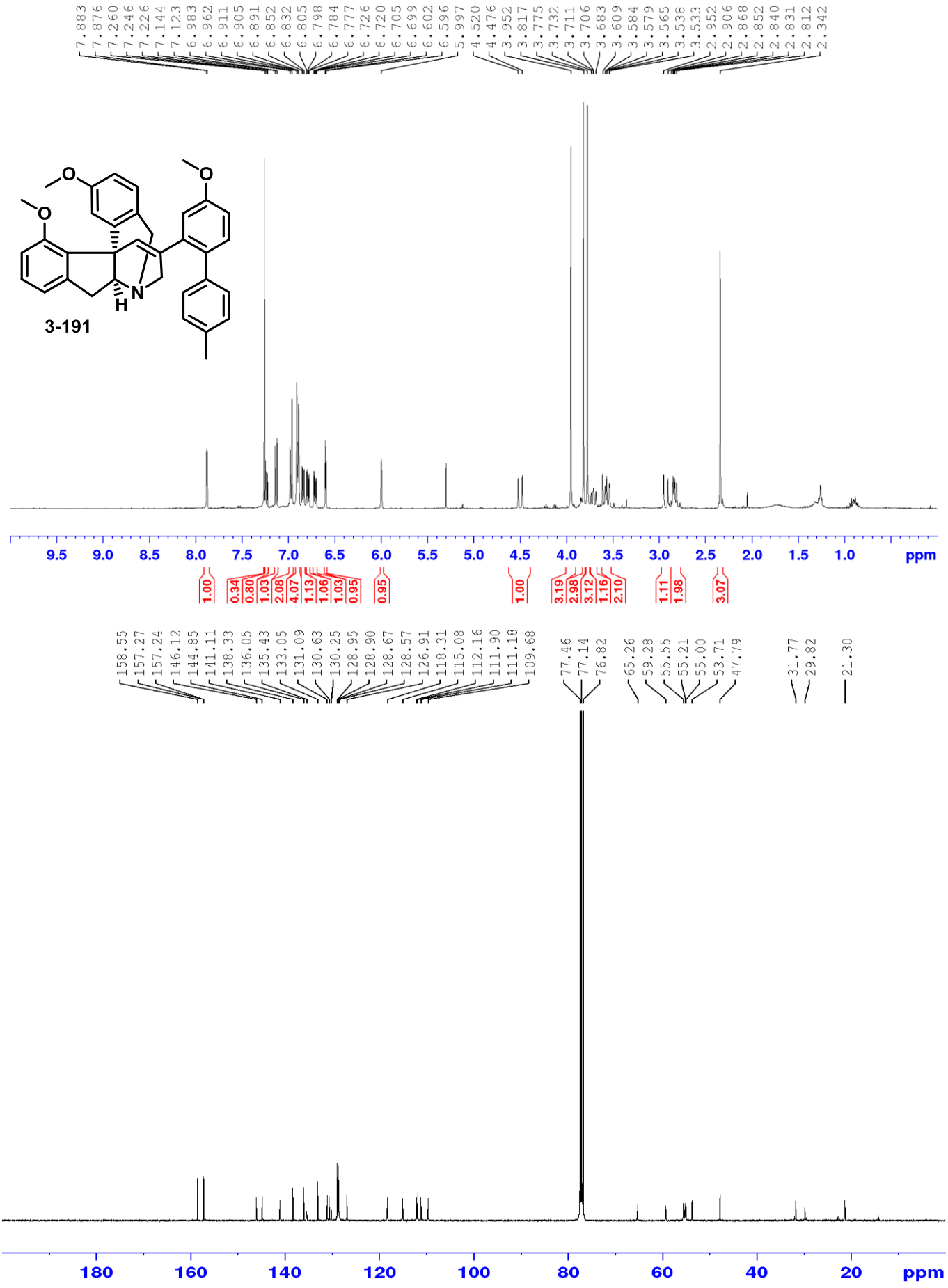
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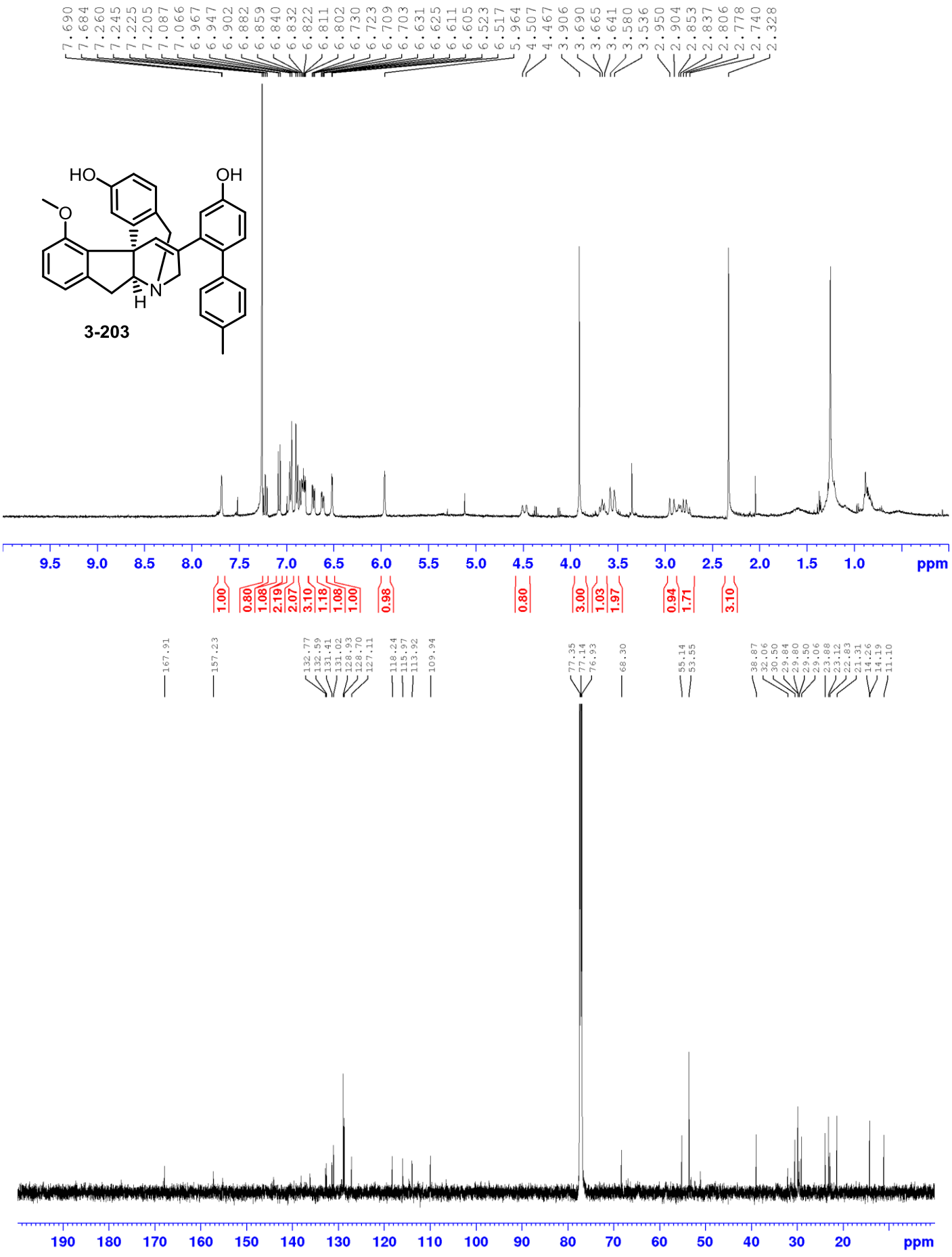
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